Studies towards a total synthesis of Akuammiline alkaloids

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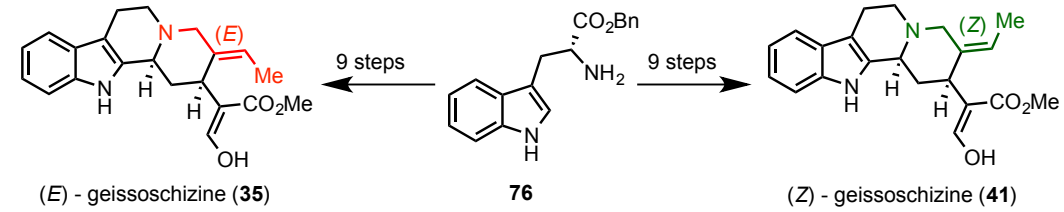
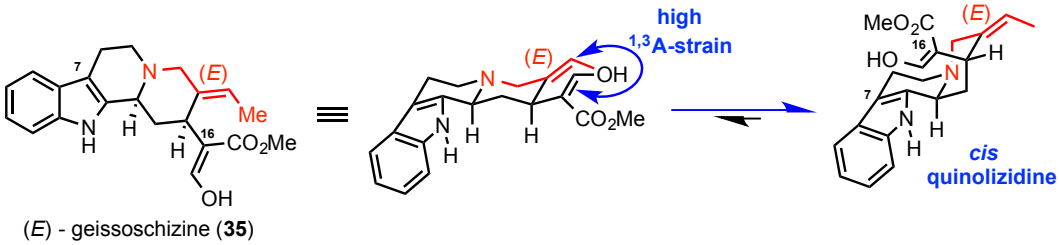
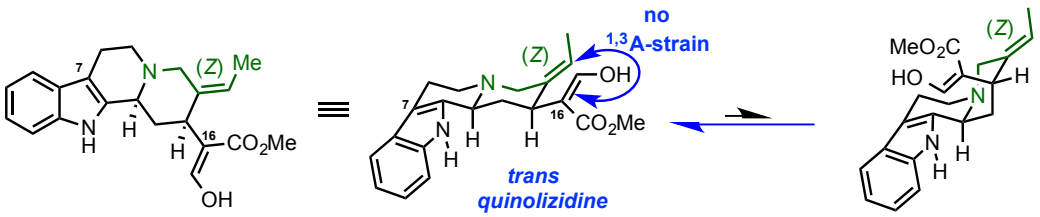
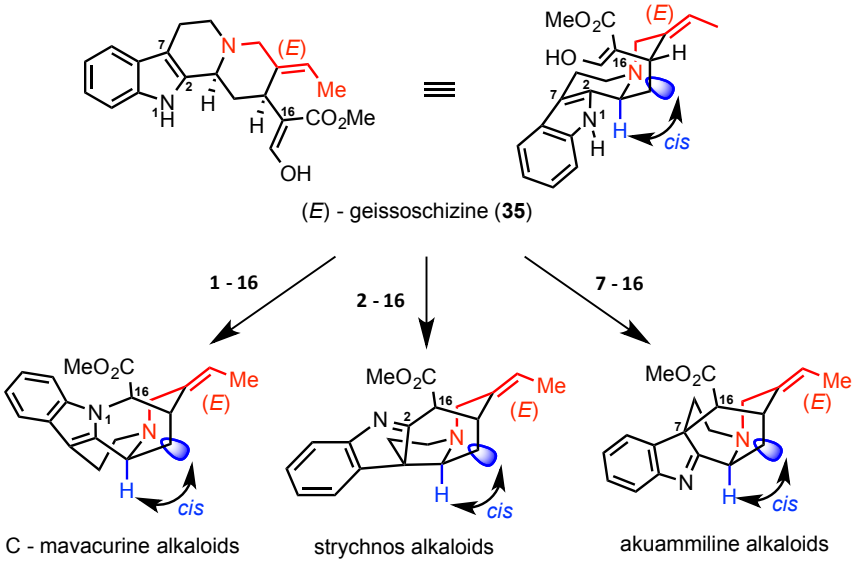
Graphical Abstract

Conformational analysis of geissoschizine derivatives



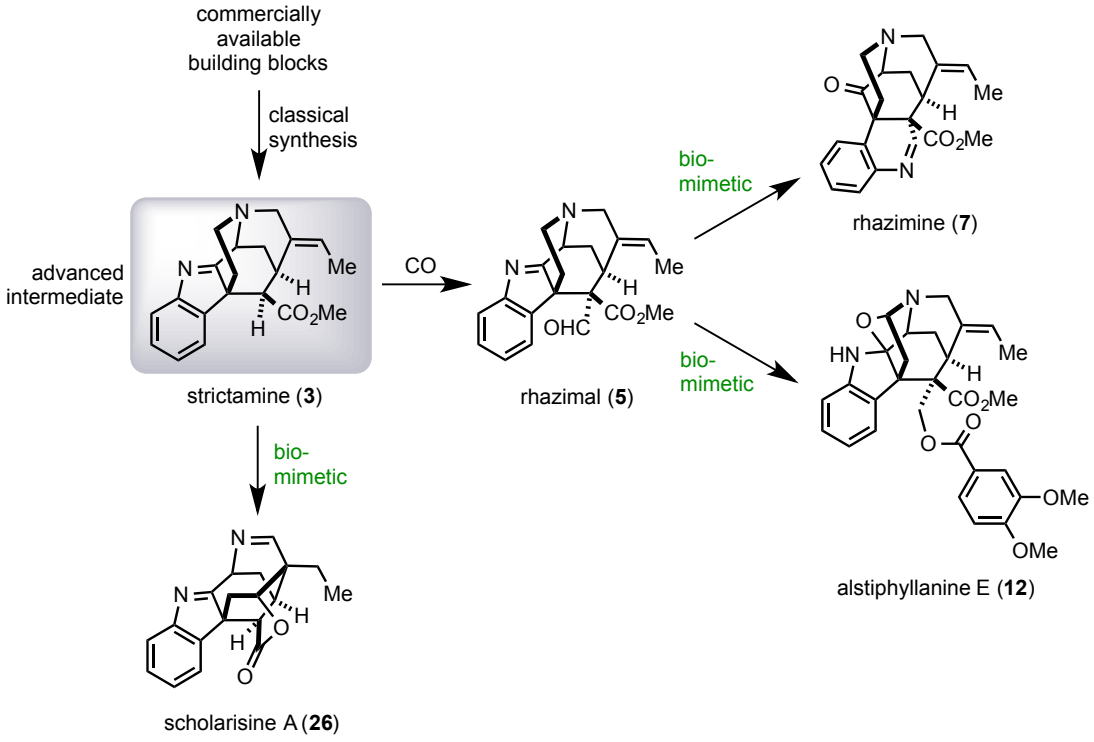




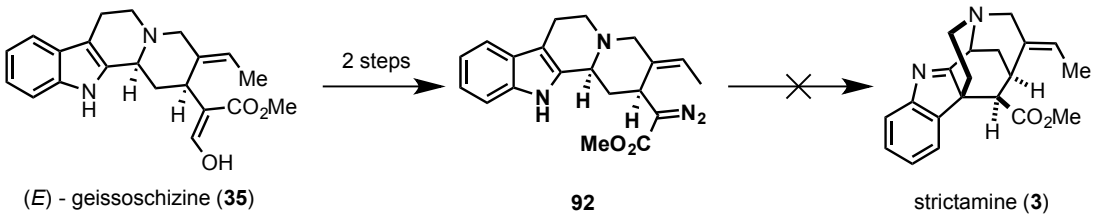


Studies towards a total synthesis of strictamine & biomimetic transformations

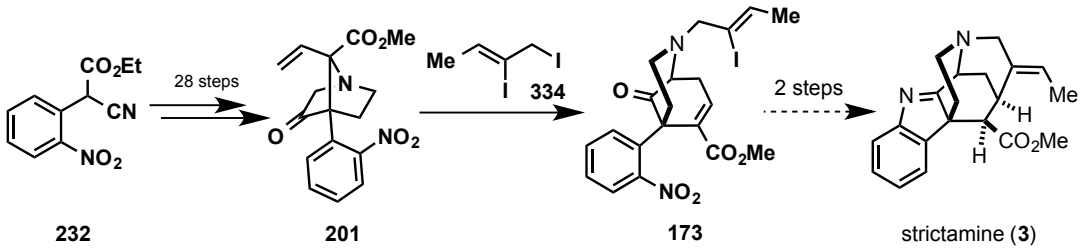
Aim of the project



Biomimetic approach to Strictamine (**3**)



Non-biomimetic approach to Strictamine (**3**)



Abstract

This Ph.D Thesis describes the natural product class of the akuammiline alkaloids. Next to a generalized synthestic access *via* a total synthesis of strictamine the biosynthetic origin of these alkaloids is examined.

Akuammiline alkaloids are monoterpenoid indole alkaloids that represent an indolo[2,3-α]methanoquinolizidine skeleton characterized by an additional bond between carbon atoms C-7 and C-16 compared to the corynanthean alkaloids. This bond leads to a very compact, cage like structure comparable to adamantane. All family members should be synthatically accessible starting from strictamine in a biomimetic fashion. Because of this, strictamine is the key intermediate which is addressed by synthetic efforts in this thesis. Biomimetic transformations to rhazimine, scholarisine A and alstiphyllanine E should be established, compounds showing a therapeutical potential like anti-inflammatory effects, activity against chronic respiratory diseases or an effect against type 2 diabetes.

Biosynthetically the akuammiline alkaloids are derived from *E*-geissoschizine, a monoterpenoid indole alkloid of the corynanthean group. It represents an indolo[2,3-α]quinolizidine skeleton which can exist in two main conformations: *cis*- and *trans*-fused. All akuammiline alkaloids bear a fixed *cis*-fused quinolizidine skeleton due to the additional bond between carbon atoms C-7 and C-16. During this bond formation the biosynthetic precursor should already stay in a *cis*-quinolizidine conformation. The conformational preference of the *cis*-quinolizidine for *E*-geissoschizine is caused by a 1,3-allyl strain of the double bond at C-19-20. This conformational preference is shown by spectroscopical comparison with *Z*-geissoschizine.

The synthetic studies to strictamine are based on two different approaches: a biomimetic synthesis *via E*-geissoschizine and a non-biomimetic synthesis starting from commercially available building blocks. For the biomimetic approach a cyclopropanation strategy was tested including the synthesis of a diazo-geissoschizine derivative. The non-biomimetic approach is composed of

four different retrosyntheses. The most advanced approach is based on a *Stevens* [2,3]-sigmatropic rearrangement generating the azabicyclo-[3.3.1]nonane skeleton present in strictamine. The precursor of the rearrangement is synthesized and transformation to the complex azabicyclo-[3.3.1]nonane skeleton is shown. Nevertheless, the total synthesis of strictamine was not completed due to the lack of two steps.

Keywords: Total synthesis, Akuammiline alkaloids, Conformational analysis

Zusammenfassung

Die vorliegende Dissertation beschreibt die Naturstoffklasse der Akuammilin Alkaloide. Neben der Entwicklung eines allgemeinen synthetischen Zugangs zu dieser Naturstoffklasse mittels einer Totalsynthese von Strictamin, wird der biosynthetische Ursprung näher untersucht.

Akuammilin Alkaloide gehören zur Gruppe der monoterpenen Indolalkaloide. Das Grundgerüst wird beschrieben durch ein Indol[2,3-α]methanoquinolizidin Skelett mit einer charakteristischen Bindung zwischen den Kohlenstoffen C-7 und C-16. Diese zusätzliche Bindung führt zu einer kompakten, käfigartigen Struktur vergleichbar mit der des Adamantans. Alle Mitglieder dieser Naturstoffklasse sind theoretisch zugänglich ausgehend von Strctamin mittels biomimetischer Transformationen. Daher nimmt Strictamin eine Schlüsselposition innerhalb der Akuammilin Alkaloide ein und ist Ziel dieser totalsynthetischen Arbeit. Im Anschluss an die Totalsynthese sollen biomimetische Transformationen ausgehend von Strictamin zu Rhazimin, Scholarisin A und Alstiphyllanin E entwickelt werden. Diese Verbindungen zeigen pharmakologische Eigenschaften wie eine entzündungshemmende Aktivität, Wirkung gegen chronische Atemwegserkrankungen oder Typ 2 Diabetes.

Biosynthetisch werden die Akuammilin Alkaloide ausgehend von *E*-Geissoschizin, einem monoterpenen Indolalkaloid der Corynanthean Gruppe, hergestellt. Das Grundgerüst dieser Naturstoffklasse wird durch ein Indol[2,3-α]quinolizidin Skelett beschrieben. Dieses liegt hauptsächlich in zwei Konformationen vor: *cis*- oder *trans*-verknüpft. Alle Akuammilin Alkaloide hingegen besitzen ein *cis*-verknüpftes Quinolizidin Skelett, fixiert durch die zusätzliche Bindung zwischen Kohlenstoffen C-7 und C-16. Während der Knüpfung dieser Bindung in der Biosynthese muss der Vorläufer, *E*-Geissoschizin, folgerichtig bereits ein *cis*-verknüpftes Quinolizidin Skelett

aufweisen. Die konformationelle Präferenz dieser *cis*-Verknüpfung wird durch eine 1,3-Allylspannung der Doppelbindung zwischen den Kohlenstoffen C-19/20 auf das *trans*-Konformer von *E*-Geissoschizin hervorgerufen. Durch einen Vergleich mit *Z*-Geissoschizin mittels verschiedener spektroskopischer Methoden wird die bevorzugte Konformation beider Isomere aufgeklärt.

Die Studien zur Totalsynthese von Strictamin basieren auf zwei unterschiedlichen Strategien: eine biomimethische Synthese ausgehend von *E*-Geissoschizin und eine "klassische", nicht biomimetische Synthese ausgehend von komerziell erhältlichen Bausteinen sind geplant. Der biomimetische Zugang wird von einer Cyclopropanierung als Strategie bestimmt. Dazu erfolgt eine Synthese von Diazo-Geissoschizoat. Die klassische Synthese lässt sich in vier unterschiedliche Strategien teilen, wovon die vielversprechendste Retrosynthese hier detailierter besprochen werden soll. Schlüsselschritt dieser Synthese ist eine *Stevens* [2,3]-sigmatrope Umlagerung, welche das Azabicyclo[3.3.1]nonan Skelett, charakteristisch für Stictamin, aufbaut. Eine Synthese für den Vorläufer dieser Umlagerung wird vorgestellt und die Transformation zum Azabicyclo[3.3.1]nonan Skelett demonstriert. Nichtsdestotrotz konnte die Totalsynthese von Strictamin innerhalb dieser Arbeit nicht abgeschlossen werden.

Schlagwörter: Totalsynthese, Akuammiline Alkaloide, Konformationsanalyse

Publications and Conferences

Parts of this work were published in the following journals:

"The Akuammiline Alkaloids; Origin and Synthesis" Gaich, T.; Eckermann, R.; *Synthesis*, **2013**, *45* (20), 2813-2823

Parts of this work were presented at the following symposia or conferences:

Stipendiatentreffen FCI 2011 (Münster, Germany)
Lecture title: "Studien zur Totalsynthese von Strictamin"

NTH Bottom up Symposium 2011 (Warberg, Germany)
Lecture title: "Towards a total synthesis of Strictamine"

Hochschule trifft Industrie 2013 (Rheinfelden, Germany)
Lecture title: "Akuammiline Alkaloids - Origin and Synthesis"

26. Irseer Naturstofftage der DECHEMA e.V. 2014 (Irsee, Germany)
Poster title: "Geissoschizine - biosynthetic precursor of the Akuammiline alkaloids?"

2nd MINAS Meeting 2014 (Hannover, Germany)
Lecture title: "Akuammiline alkaloids - Origin and Synthesis"

16th Tetrahedron Symposium 2015 (Berlin, Germany)
Poster title: "Conformational analysis of geissoschizine derivatives"

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1. Introduction

Biological sources like plants, animals or microorganisms are an inexhaustible source of natural products.[1] These compounds produced by different organisms can be differentiated in primary and secondary metabolites. Primary metabolites perform the physiological function like growth or reproduction and are therefore essential for their life. Secondary metabolites are not directly involved in life-sustaining processes but play an important role for the ecology of an organism.[2] For example, a secondary metabolite can be very important for plant defense against a herbivore.[3] A prominent example are the penicillin antibiotics, secondary metabolites produced by *Penicillium* fungi for the defense against bacteria.[4] A lot of drugs acting as antibiotic agents are derived from this penicillin core structure (Figure 1).[5]

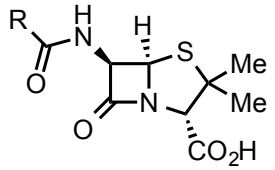


Figure 1: Penicillin core structure.

Natural products are an invaluable source of therapeutic agents. Almost half of the drugs introduced between 1981 and 2006 were of natural origin or inspired by natural products. In case of anticancer and anti-infective agents almost two-thirds are derived from natural products.[6] Often, the isolation of natural compounds from their originator is inefficient due to inaccessibility of the organism or low amounts of the molecule being produced. Hence, the isolation from natural sources can be very expensive or inattractive due to ecologiacl reasons. An alternative way to get a reasonable amount of a natural compound is their total synthesis starting from comercially available building blocks. This can be more efficient than the isolation from a natural source or opens the possibility of chemical modifications during the synthetic process. By this, the analogue of a compound can get more or less potent in

matters of a therapeutical application or undesirable secondary effects can be suppressed. By getting high amounts of a molecule by total synthesis the properties of a natural product can perhaps be examined in a better way and their pharmacological impact can be tested more efficiently. Because of this, total synthesis is essential for the development of new drugs. Another implementation of natural product synthesis is structure elucidation or confirmation.[7]

An important class of natural prducts are alkaloids, cyclic organic compounds containing nitrogen in a negative oxidation state.[8] Alkaloids have diverse and important pharmacological activities on humans like anticancer, analgesic or antimalarial.[9] The akuammiline alkloids belong to the class of monoterpenoid indole alkloids.[10] In addition to their unique and inspirational structure, the akuammiline alkaloids have drawn significant attention from the synthetic community[11] due to their broad range of biological activities.[12]

2. The Akuammiline alkaloids

Akuamma, one of the native names of the tree *Picralima nitida* (family: *Apocinaceae*, synonyms: *Picalima klaineana*, *Picralima macrocarpa*, Figure 2), is a rainforest tree occuring in African forest region from the Ivory coast to Uganda. The plant has diverse applications in traditional medicine by natives in tropical Africa.[13] Extracts from its seeds, fruit rind and stem bark demonstrated antimalarial activity[14], antimicrobial[15] and anti-inflammatory effects.[15b, 16]

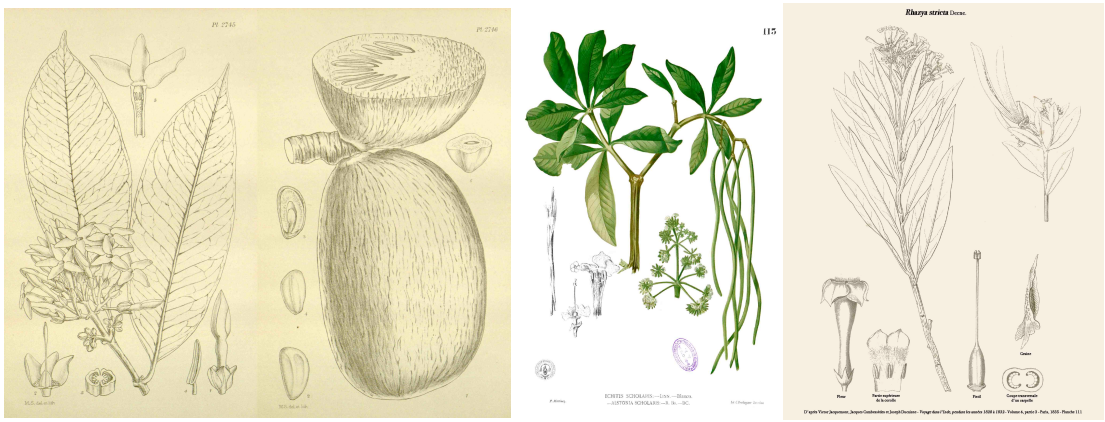


Figure 2: Illustrations of *Picralima nitida* and its seeds[17], *Alstonia scholaris*[18] and *Rhazia stricta*.[19]

Especially the seeds are used as a febrifuge in native medicine. Its alcoholic extracts contain 3.5-4.8% of total alkaloids.[20] Early on, the alkaloids isolated from these seeds were studied as potential sources of pharmaceutical compounds. *Henry* and *Sharp* isolated and characterized four different alkaloids from the akuamma seeds in 1927[13] and named the first structure they elucidated akuammine (**1**) — referring to the akuamma tree. From these seeds, the second indole alkaloid akuammiline (**2**) served as an eponym of a whole natural product family — the akuammiline alkaloids. Akuammiline (**2**) itself was first characterized by *Henry* in 1932[20] (Figure 3).

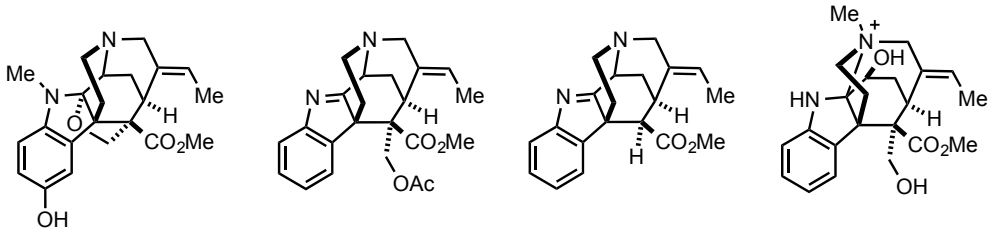


Figure 3: Prominent members of the akuammiline alkaloids.

The class of the akuammiline alkaloids is best represented by strictamine (**3**, Figure 3) which was isolated from the plant *Rhazya Stricta* (family: *Apocinaceae*, Figure 2) in 1966.[21] It bears the least functionalized carbon skeleton of all akuammiline alkaloids without lacking the signature structure motifs.[10] The first akuammiline alkaloid which was isolated and described in literature is echitamine (ditaine, **4**, Figure 3) which was isolated by *Gorup-Besanez* in 1875[22] from the bark of *Alstonia scholaris* (family: *Apocinaceae*, synonyms: *Echites scholaris*, *Pala scholaris*). It was the subject of much controversy between *Hesse* who first described the alkaloid as echitamine (1875)[23] and *Harnack*[24] who described the same alkaloid derived from the dita bark (a native name of for the bark of *A. scholaris*) and called it ditaine in 1878.[25] The correct structure and thereby membership to the akuammiline alkaloids was elucidated much later by *Hamilton* et al. in 1961.[26] The akuammiline alkaloids drew the attention of synthetic chemists due to their broad range of biological activities.[12, 27] Strictamine (**3**) and nareline (**25**) for example show an inhibitory effect of the nuclear factor-kB (NF-kB)[28], which plays an important role in the regulation of gene-expression in immune and inflammatory responses. Alstiphyllanine E (**12**) inhibits the Na^+-glucose cotransporter SGLT1 and SGLT2. An inhibition of SGLT decreases glucose re-absorption causing an increase in urinary sugar excretion. Consequently the blood glucose level decreases opening a therapeutical potential for type 2 diabetes.[29] Corymine (**18**) is a glycine receptor antagonist — an inhibitory receptor in the central nervous system.[30] Echitamine (**4**) shows cytotoxic effects[31] and the reverse of drug resistance in cancer cells is triggered by aspidophylline A (**21**).[32]

Both attributes, diverse biological activity and a unique challenging chemical structure, are reasons for a lively interest concerning a chemical synthesis of akuammiline alkaloids during the last decades.[11]

2. The Akuammiline alkaloids

2.1 Structure analysis

The akuammiline alkaloids belong to the group of monoterpenoid indole alkaloids. Their carbon skeleton consist of a tryptamine, and one monoterpene unit. They are a member of the corynanthean alkaloid group, and are characterized by the presence of a bond between carbon atoms C-7 and C-16, thereby constituting an additional ring D embedded into a methanoquinolizidine system.[10] In contrast, strychnos alkaloids consist of a bond between carbon atoms C-2 and C-16, whereas C-mavacurine alkaloids consists of an additional bond between the N-1 and C-16 (Figure 4).[33]

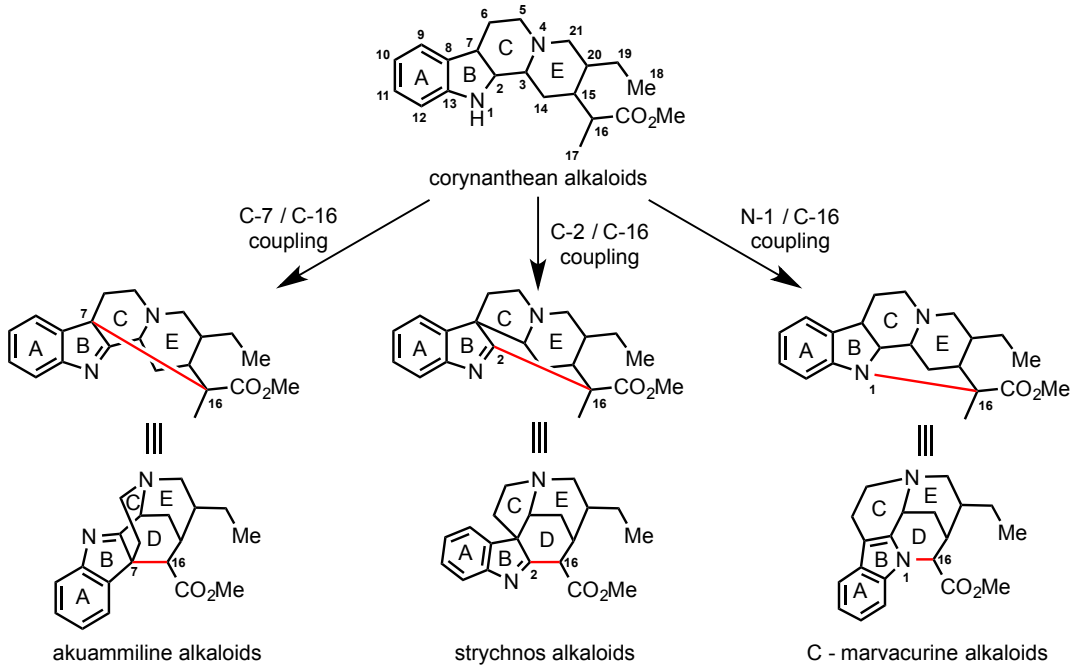


Figure 4: Four classes of monoterpenoid indole alkaloids in comparison.

The connection of carbon atoms C-7 and C-16 in case of the akuammiline alkaloids leads to a very compact, cage like structure comparable to adamantane. The central methanoquinolizidine system highlighted in Figure 5 exhibits a scaffold of three six-membered rings and one eight-membered ring. In contrast, the adamantane system consists of four six-membered rings. The

methanoquinolizidine skeleton has one additional nitrogen atom compared to the adamantane skeleton and a slightly different connectivity. This results in a higher symmetry in case of adamantane illustrated by the fact that all rings exist in a chair conformation, whereas the methanoquinolizinde system consists of two rings (C and E) in a boat conformation (highlighted in red, Figure 5).[10]

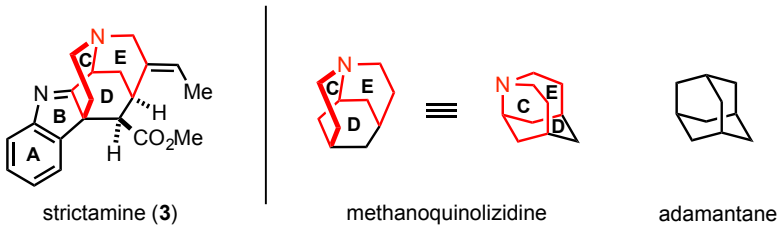


Figure 5: Cage-like structure of the akuammiline alkaloids.

The boat conformation is caused by the connection of carbon atoms C-7 and C-16 — the signature attribute of the akuammiline alkaloids. It heavily influences synthetic planning of akuammiline alkaloids, and comprises one of the major synthetic challenges. This might be a reason why only little congeners have been synthesized up to date, although more then 30 are known in literature.[10] All akuammiline alkaloids consists of an indolo[2,3-α]quinolizidine skeleton that exhibits an *E*-configured ethylidene side chain at carbon atom C-20 and a methyl ester at carbon atom C-16.[10, 33] In some cases the methanoquinolizidine motif can be slightly rearranged or some bonds are cleaved due to oxidative degradation. Some natural products show an oxidation of the prior double bond at carbon atom C-20 or a transformation of the ester at C-16 to a lactone or carboxylic acid. Figures 6-10 summarize some representative akuammiline alkaloids.

2.2 Structure variations, isolated natural products

Natural products containing the unmodified methanoquinolizine motif are shown in Figure 6. Rhazimal (**5**)[34] is the biogenetic precursor of all akuammline alkaloids showing the complete skeleton of a tryptamine unit and the monoterpene unit.

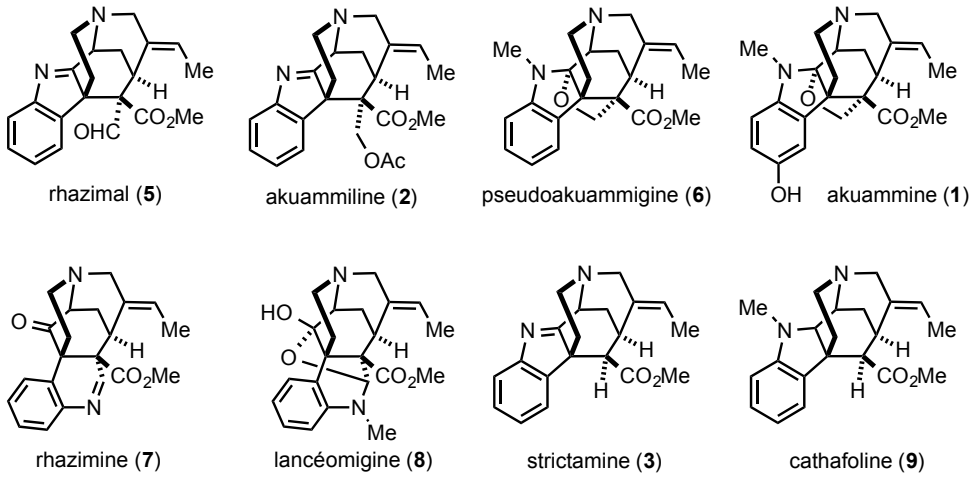


Figure 6: Natural products bearing a normal methanoquinolizidine skeleton.

After reduction of the aldehyde at C-17 the resulting primary alcohol can by acetylated giving akuammiline (**2**)[35] or reacts with the imine at C-2 to pseudoakuammigine (**6**) and akuammine (**1**)[35]. Rhazimine (**7**)[36] is an isomeric form of rhazimal (**5**) where the imine changes from C-2 to C-17 producing a ketone. Water addition to the ketone and methylation of the indole nitrogen results in lancéomigine (**8**).[37] Deformylation at C-16 gives access to strictamine (**3**) and after reduction and methylation of the indolenine nitrogen cathafoline (**9**)[38] is produced.

Figure 7 shows some natural products resulting from an oxidation at carbon atom C-5 and/or C-3. After oxidation at C-5 a secondary alcohol is formed which reacts with the iminine at C-2 building up a hemiaminal and a tetrahydrofurane ring like in vincarinine (**10**)[39] and picraline (**11**).[35] Instead of an acetylation also other carboxylic acids can be reacted with the primary alcohol at C-17 forming different esters like the benzoic acid derivative found

in alstiphyllanine E (**12**).[29] An additional oxidation and *O*-methylation at carbon atom C-3 leads to scholarisin I, III or VII (**13**, **14**, **15**)[15b].

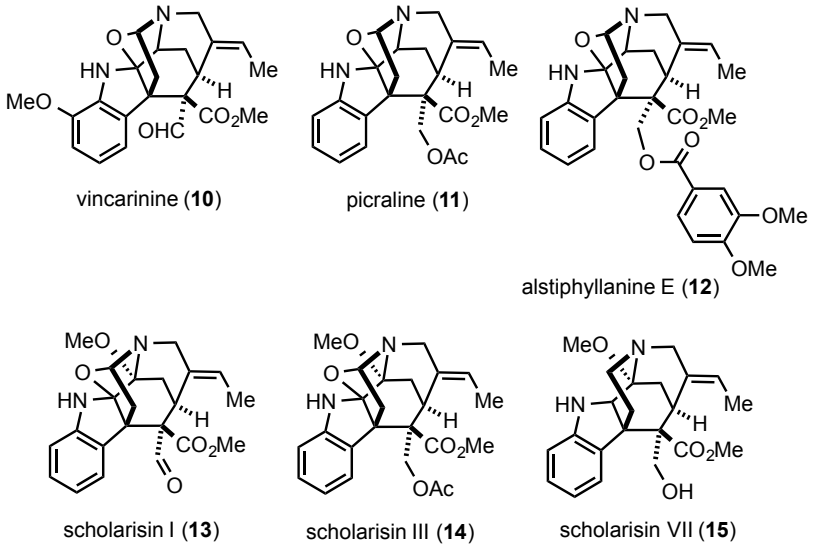


Figure 7: Natural products after oxidation at C-5 and C-3.

Many natural products show a rearranged methanoquinolizinde skeleton where the nitrogen is connected to a different carbon atom than C-3 (Figure 8).

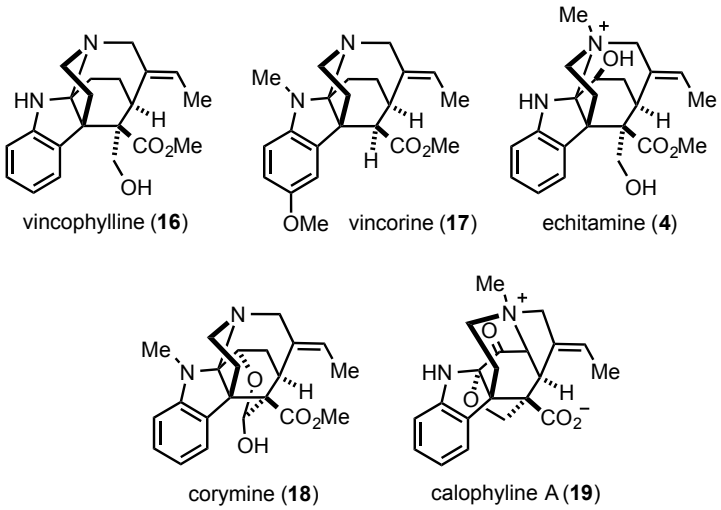


Figure 8: Natural products with a rearranged methanoquinolizidine skeleton.

In the most cases the nitrogen has shifted to position C-2 trapping the indolenine and forming thereby an aminal present in vincophylline (**16**) and vincorine (**17**).[32] This shift is triggered by an oxidation at carbon atom C-3 which is represented by a secondary alcohol in some cases like echitamine (**4**) and corymine (**18**).[40] The nitrogen can also migrate to carbon atom C-14 like in calophyline A (**19**)[41] also triggered by an oxidation at carbon atom C-3. Figure 9 summarizes natural products bearing a broken methanoquinolizidine skeleton due to oxidative degradation. In most cases the bond between nitrogen atom N-4 and carbon atom C-5 is broken up resulting in different oxidation states at N-4 and C-5 represented by aspidodasycarpine (**20**)[42], aspidophylline A (**21**)[32], alschomine (**22**)[43], lanciferine (**23**)[44] and arbophylline (**24**)[45]. Some examples show a new bond formation like in nareline (**25**)[46] between carbon atom C-6 and C-21 or in scholarisine A (**26**)[47] between carbon atom C-5 and C-20.

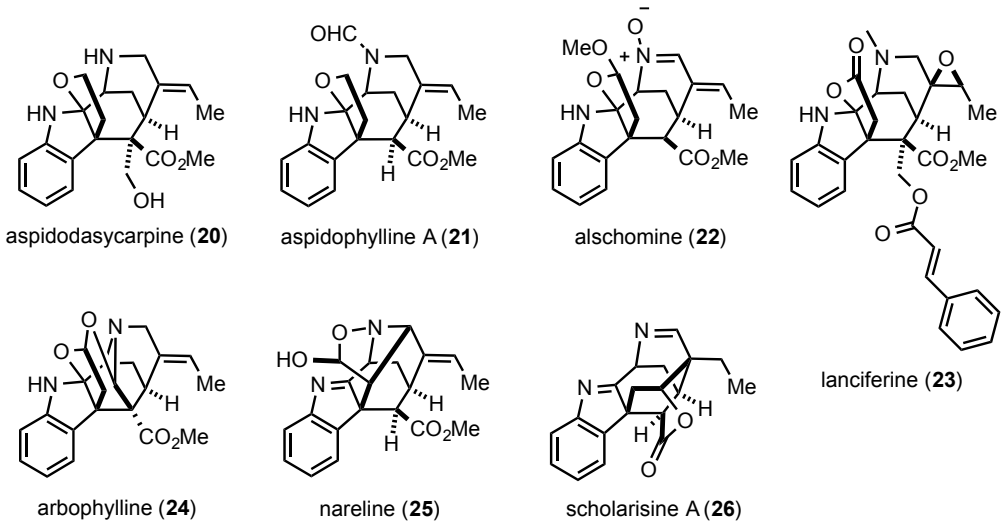


Figure 9: Natural products showing a broken methanoquinolizidine skeleton.

Also natural products consisting of a dimer between an akuammiline alkaloid and another monoterpenoid indole alkaloids are known like ceylanine (**27**)[48] shown in Figure 10.

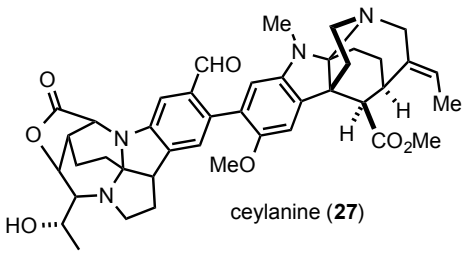
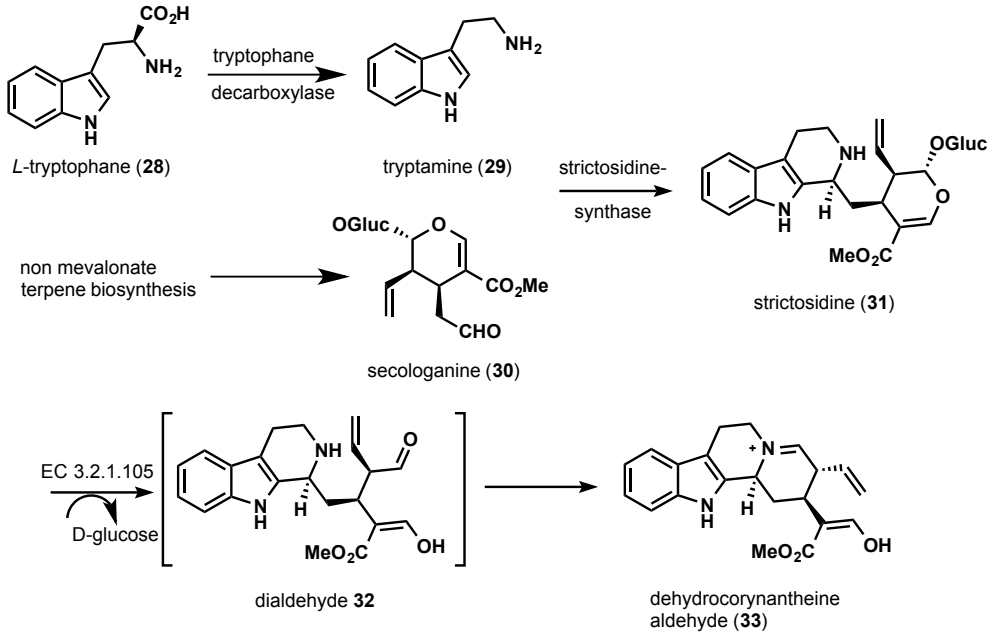


Figure 10: Dimer between an akuammiline alkloid and another monoterpenoid indole alkaloid.

2.3 Biosynthesis of Rhazimal

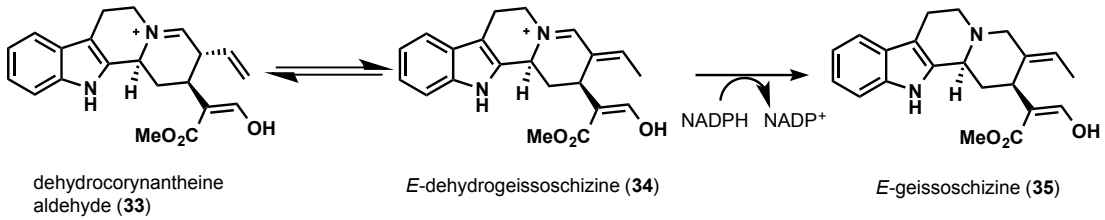
Only three plant families (*Rubiaceae/Naucleaceae, Loganiaceae/Strychnaceae*, and *Apocynaceae)* are the source of the most monoterpenoid indolde alkaloids sharing the same biosynthetic route.[49] Biogenetically the akuammiline alkaloids, next to other monoterpenoid indole alkaloids, are derived from *E*-geissoschizine (**35**)[50] — a key intermediate in the biosynthetic pathway of monoterpenoid indole alkaloids. Therefore all natural products of these class are biogenetically derived from tryptophan and the iridoid terpene secologanin (Scheme 1). Tryptophan decarboxylase converts tryptophan (**28**) to tryptamine (**29**) which reacts in a Pictet-Spengler reaction with secologanin (**30**). Secologanin (**30**) itself is produced by the non-mevalonate terpene biosynthesis. The enzyme stryctosidine synthase catalyses this sterespecific cyclization to strictosidine (**31**).[51]



Scheme 1: *E*-geissoschizine biosynthesis part 1.

The biosynthetic power of strictosidine is revealed after deglucosylation catalyzed by a dedicated β-glucosidase yielding a hemiacetal that opens to dialdehyde **32**. Dialdehyde **32** reacts intramolecularly with the secondary amine to give the iminium ion dehydrocorynantheine aldehyde (**33**).

Dehydrocorynantheine aldehyde (**33**) undergoes an allylic isomerisation resulting in dehydrogeissoschizine (**34**). This is reduced by NADPH to yield *E*-geissoschizine (**35**, Scheme 2).[52]

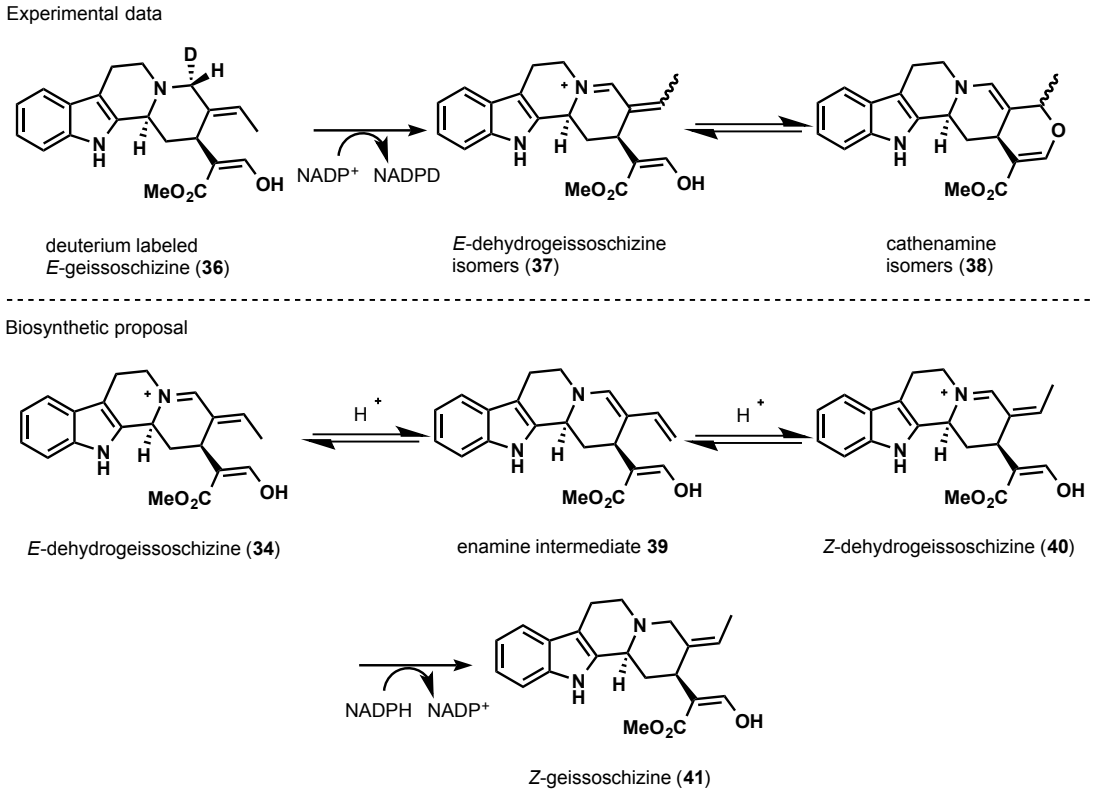


dehydrocorynantheine aldehyde (**33**) | *E*-dehydrogeissoschizine (**34**) | *E*-geissoschizine (**35**)

Scheme 2: *E*-geissoschizine biosynthesis part 2.

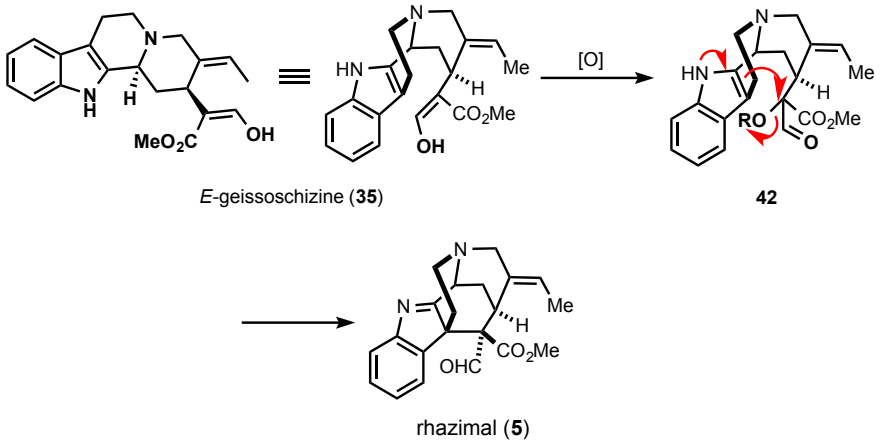
The existence of *Z*-geissoschizine is not proven up to date. In general, an isomerization of the double bond via enamine (**39**) starting from *E*-dehydrogeissoschizine (**34**) to *Z*-dehydrogeissoschizine (**40**) during the biosynthesis of *E*-geissoschizine is plausible. Another possibility is an isomerization independent of the biosynthesis. Stöckigt et al. have shown that deuterium labeled *E*-geissoschizine can be oxidized *in vivo* by $NADP^+$ to dehydrogeissoschizine with an undefined double bond geometry. This can react to cathenamine isomers with both possible stereocenters at carbon atom C-19.[53] This dehydrogeissoschine intermediate (**37**) with an undefined double bond geometry could be reduced either to *E*- or *Z*-geissoschizine (Scheme 3).

The biosynthesis of the akuammiline alkaloids starts from *E*-geissoschizine (**35**). After oxidation of *E*-geissoschizine at carbon atom C-16 a cyclization reaction takes place. This secondary cyclization involves an oxidative dearomatization of the indole ring with an intramolecular attack to the 1,3-dicarbonyl unit to form the crucial C-7/C-16 carbon-carbon bond (Scheme 4).[54]



Scheme 3: Proposed biosynthesis of *Z*-geissoschizine.

Since it is necessary to oxidize the corynanthean alkaloids to get akuammiline alkaloids an oxidative coupling of *E*-geissoschizine (**35**) is predicted. This secondary cyclization leads to the formation of rhazimal (**5**), the central building block from which all other akuammiline alkaloids can be addressed. To the best of our knowledge, the mechanism of the last cyclization from *E*-geissoschizine to rhazimal (**5**) still remains unknown (Scheme 4).[55]

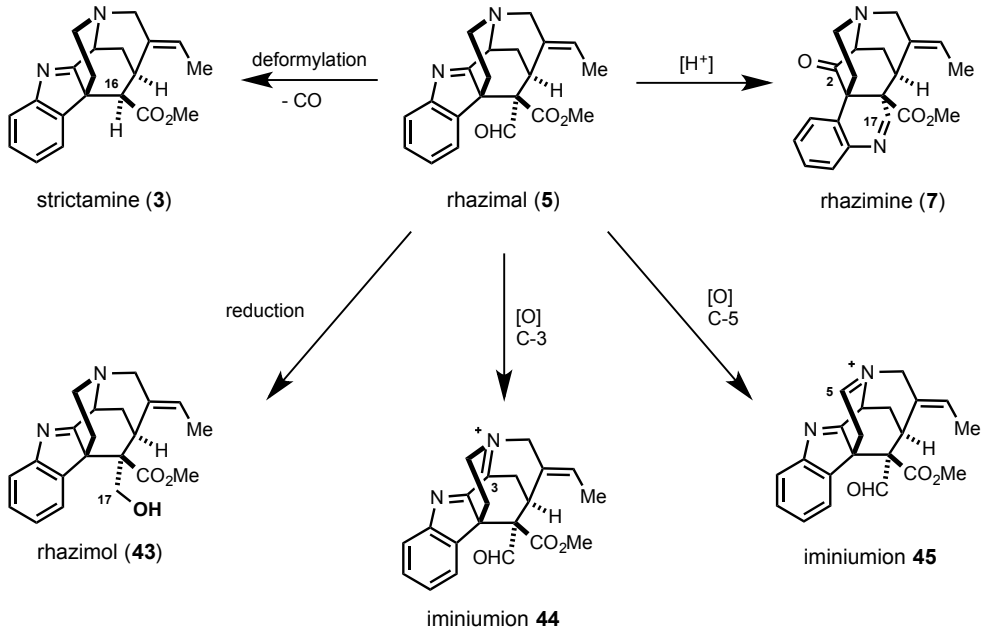


Scheme 4: Transformation of *E*-geissoschizine to rhazimal.

2. The Akuammiline alkaloids

2.4 Biosynthetic transformations

Rhazimal (**5**) is the advanced intermediate nature uses to build up all other akuammiline alkaloids. The most natural products can be devided in five categories depending on the downstream biosynthetic transformations (Scheme 5).



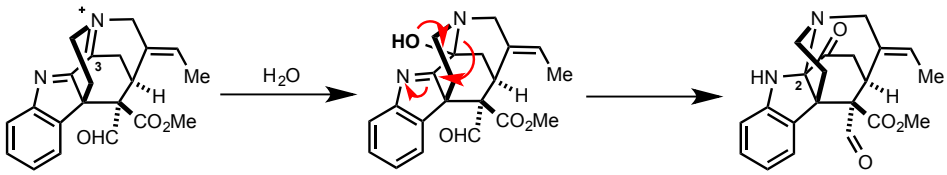
Scheme 5: Biosynthetic transformations from rhazimal (**5**).

Deformylation at carbon atom C-16 yields strictamine (**3**) which can be transformed to cathafoline (**9**) after reduction and *N*-methylation. Acid catalyzed imine isomerization from the ketone at carbon atom C-2 to the aldeyhde at carbon atom C-17 gives access to rhazimine (**7**) and lancéomigine (**8**) after water addition and *N*-methylation.[36-37] Reduction of the aldehyde at C-17 results in rhazimol (**43**)[56] that can be transformed to akuammiline (**2**) by acetylation or to pseudoakuammigine (**6**) after hemiaminal formation and *N*-methylation. Oxidation of the aromatic ring at C-10 gives akuammine (**1**).

Oxidation at carbon atom C-3 gives rise to imminium ion **44** which can be trapped by methanol yielding scholarisin VII (**15**, compare Figure 7) after reduction of the aldehyde at C-17 to the primary alcohol. An additional

oxidation at carbon atom C-5 followed by water addition and hemiaminal formation ends up in scholarisin I (**13**, compare Figure 7). Reduction of the aldehyde at C-17 follwed by acetylation gives scholarisin III (**14**, compare Figure 7).

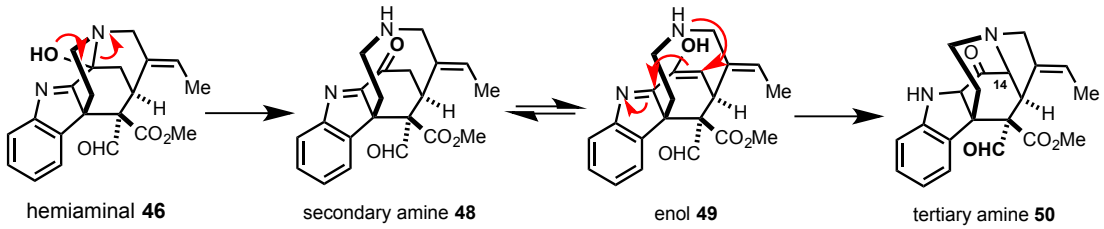
The skeletal rearranged natural products shown in Figure 8 are also a result of an oxidation at carbon atom C-3. Imminium ion **44** is trapped by water building up hemiaminal **46** which reacts to aminal **47** by shifting the nitrogen from carbon atom C-3 to C-2 (Scheme 6).



Scheme 6: Skeletal rearrangement introduced by oxidation at C-3.

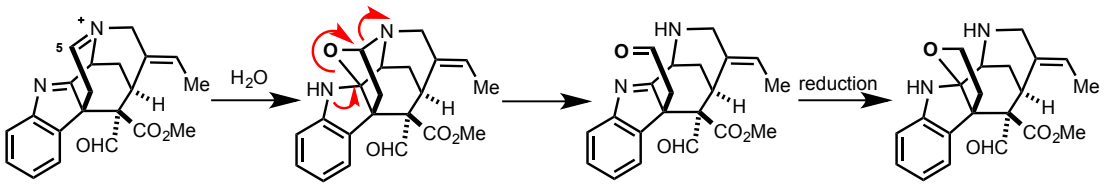
Reduction of the ketone at carbon atom C-3 to the secondary alcohol follwed by hemiacetal formation with the aldehyde at C-17 and indole *N*-methylation gives corymine (**18**, compare Figure 8).[57] Redution of the ketone at C-3 and the aldehyde at C-17 to the corresponding alcohols followed by *N*-methylation to the ammonium salt yields echitamine (**4**, compare Figure 8). Some natural products show a complete reduction of the ketone at carbon atom C-3 like vincorine (**17**) and vincophylline (**16**, compare Figure 8).

The migration of the nitrogen atom to carbon C-14 is also introduced by an oxidation at C-3 to imminium ion **44**. After water addition hemiaminal **46** opens to secondary amine **48**. This secondary amine can undergo a 1,4-addition to enol **49** giving tertiary amine **50** (Scheme 7) representing the skeleton of calophyline A (**19**, compare Figure 8).[58]



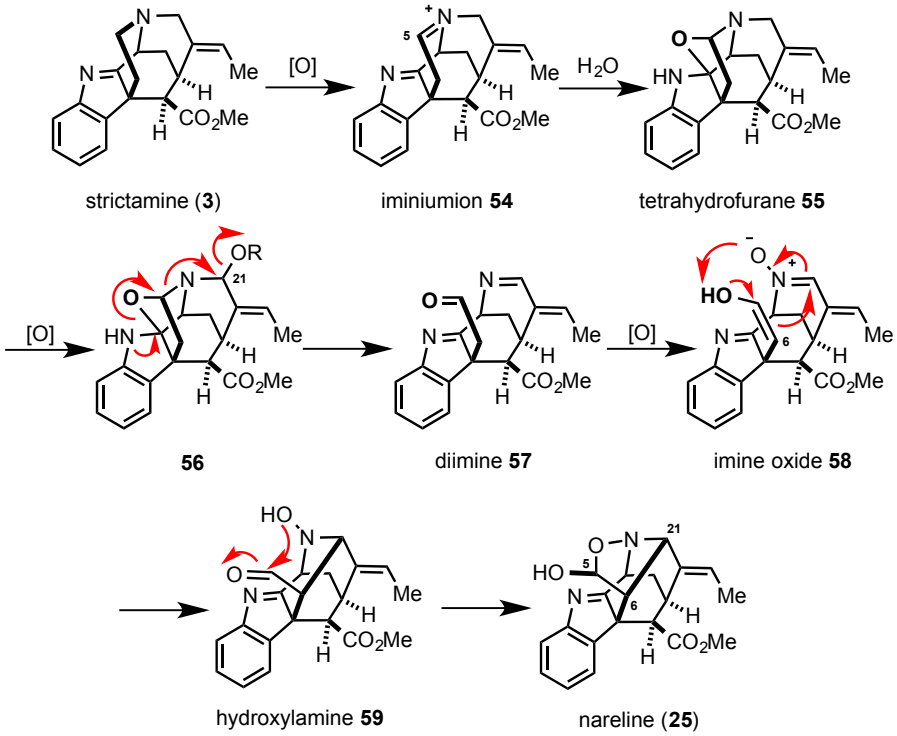
Scheme 7: Alternative skeletal rearrangement introduced by an oxidation at C-3.

Oxidation at carbon atom C-5 results in iminium ion **45** (Scheme 5) which is a precursor for all natural products bearing a tetrahydrofurane ring (see Figure 7) or a broken methanoquinolizidine motif (see Figure 9). Trapping with water results in tetrahydrofurane **51**, a structure motif that is found in scholarisin I (**13**), scholarisin III (**14**), vincarinine (**10**), picraline (**11**) and alstiphyllanine E (**12**, compare Figure 7). An alternative is an opening to the corresponding aldeyhde (**52**). Reduction of the aldehyde to the primary alcohol followed by an addition to the imine builds up hemiaminal **53** (Scheme 8). This structure motif is represented by aspidodasycarpine (**20**), aspidophylline A (**21**), alschomine (**22**), lanciferine (**23**) and arbophylline (**24**, compare Figure 9).[45]



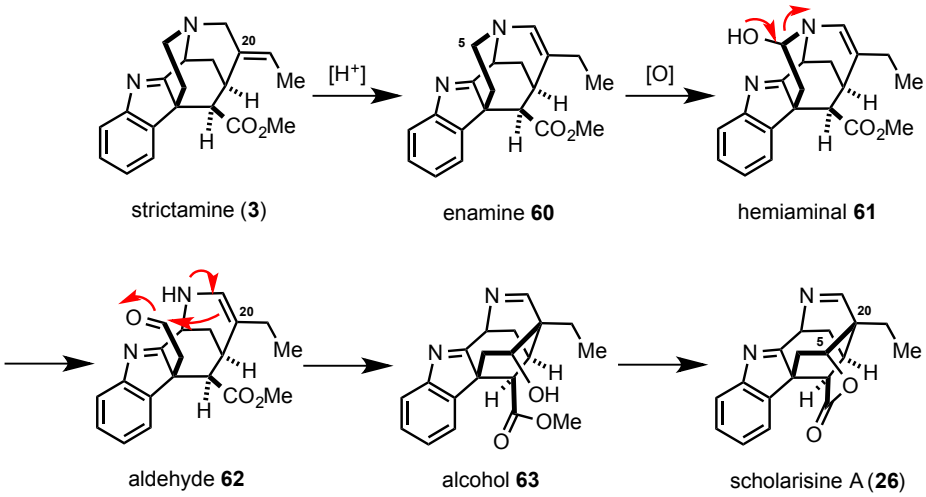
Scheme 8: Tetrahydrofurane formation after oxidation at C-5.

In case of nareline (**25**) and scholarisine A (**26**, compare Figure 9) the biosynthesis gets more complicated due to a higher degradation. However, both biosynthetic transformations start with the oxidation of strictamine (**3**) at carbon atom C-5 resulting in imminium ion **54**, as shown in Scheme 9. Further, they both miss the bond between C-5 and N-4. While in nareline a new bond between C-21 and C-6 is formed, scholarisine A (**26**) bears a bond between C-20 and C-5. Mechanistically, imminium ion **54** is trapped by water building up tetrahydrofurane **55**. A second oxidation takes place at carbon atom C-21 forming an imminium ion which is trapped by an oxygen leaving group (**56**). By an electron push of the indole nitrogen the aminal is opened resulting in an aldehyde and a diimine functionality (**57**). A third oxidation takes place at nitrogen N-4 producing an imine oxide (**58**) which is trapped by the enol at C-6 in an intramolecular *Mannich* reaction. Thereby the new bond between carbon atom C-6 and C-21 is formed. Hydroxylamine **59** reacts with the aldeyhde at C-5 to nareline (**25**).[46]



Scheme 9: Biosynthesis of nareline (**25**).

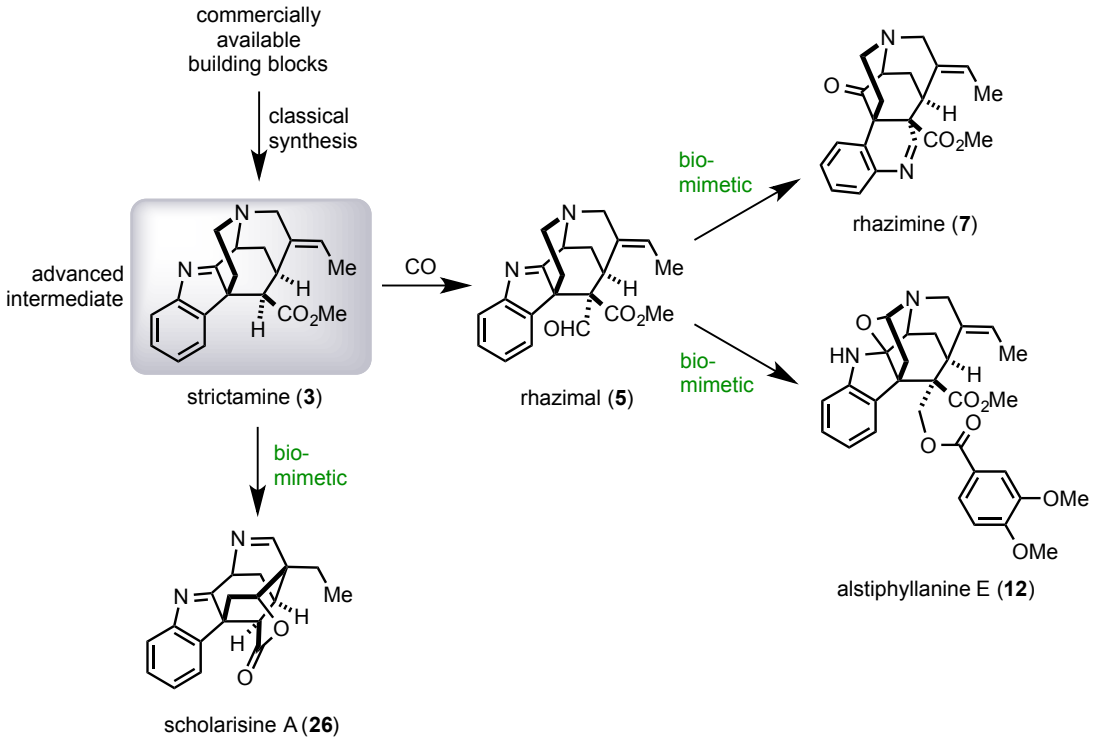
The biosynthesis of scholarisine A (**26**) starts with a double bond isomerization from the ethylidene side chain at carbon atom C-20 in strictamine (**3**) to enamine **60**. An oxidation at carbon atom C-5 takes place building up an imminium ion that is trapped by water resulting in hemiaminal **61**. Opening of the hemiaminal gives access to aldeyhyde **62** which is attacked by the enamine generating the new bond between carbon atoms C-20 and C-5. Alcohol **63** undergoes lactonization with the ester functionality giving scholarisine A (**26**, Scheme 10).[47]



Scheme 10: Biosynthesis of scholarisine A (**26**).

3. Aim of the project

The aim of this work is a generalized approach to the akuammiline alkaloids which allows the synthesis of an advanced intermediate that can be transferred to various akuammiline alkaloids in a biomimetic fashion. Nature uses rhazimal (**5**) as an intermediate from which all other akuammiline alkaloids can be addressed. Instead of rhazimal (**5**) we have choosen strictamine (**3**) as the advanced intermediate. Strictamine (**3**) shows the least functionalized skeleton without lacking the signature structure motifs and can be easily transformed to rhazimal (**5**) by a formylation reaction at carbon atom C-16. Because of this strictamine (**3**) is the ideal congener for an advanced intermediate from a synthetic point of view. To test the biomimetic transformations, three natural products were choosen: rhazimine (**7**), scholarisine A (**26**) and alstiphyllanine E (**12**, Scheme 11).

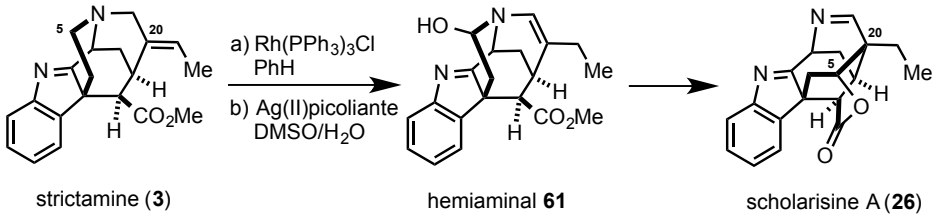


Scheme 11: Biomimetic transformations starting from strictamine (**3**).

This selection is caused by pharmacological reasons. Rhazimine (**7**) shows anti-inflammatory effects[14b], scholarisine A (**26**) activity against chronic

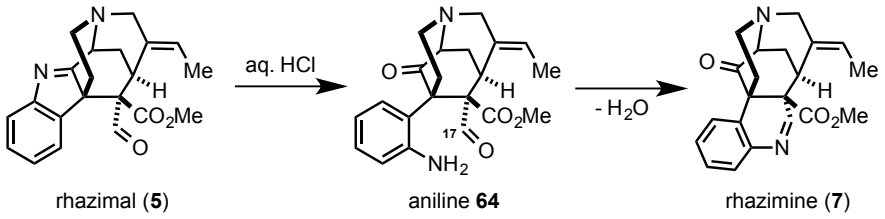
respiratory diseases[47] and alstiphyllanine E (**12**) is a potential drug against type 2 diabetes.[29]

Synthetically, the biomimetic transformations should be realized as follows: the ethylidene side chain at carbon atom C-20 of strictamine (**3**) gets isomerized from an exocyclic double bond to an endocyclic enamine under rhodium catalysis with *Wilkinsons* catalyst. Oxidation of the tertiary amine at C-5 should be performed with silver(II)picolinate resulting in hemiaminal **61** (Scheme 12). The same hemiaminal is an important intermediate during the proposed biosynthesis of scholarisine A (**26**). Once formed, it should open to aldehyde **62** which can be attacked by the enamine resulting in the formation of scholarisine A (**26**, compare with Scheme 10).



Scheme 12: Chemical transformations of strictamine (**3**) to scholarisine A (**26**).

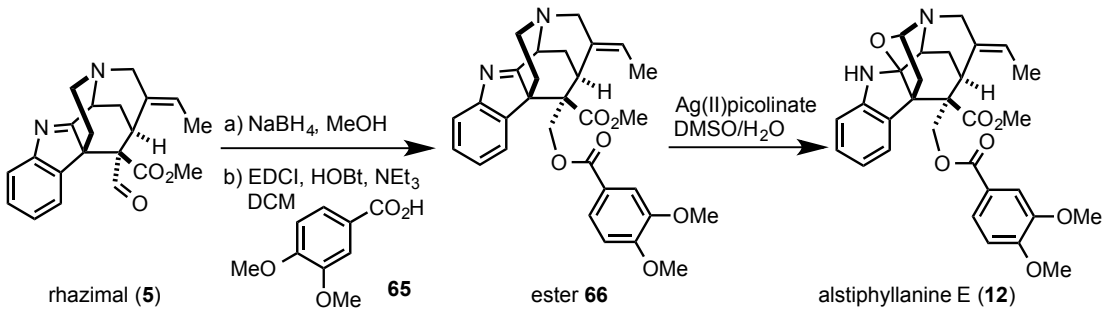
For the biomimetic transformation of rhazimal (**5**) to rhazimine (**7**) the first is treated with an aqueous acidic solution to hydrolize the indolenine to the corresponding aniline **64**. Under loss of water the aniline nitrogen should condensate with the more reactive aldehyde at carbon atom C-17 forming the six-membered imine of rhazimine (**7**, Scheme 13).



Scheme 13: Chemical transformations of rhazimal (**5**) to rhazimine (**7**).

The chemical transformations to alstiphyllanine E (**12**) start with a reduction of the aldehyde at carbon atom C-17 to the primary alcohol. This gets

esterificated with veratric acid (**65**) to the corredsponding ester **66**. Oxidation of the tertiary amine at carbon atom C-5 leads to alstiphyllanine E (**12**, Scheme 14).



Scheme 14: Chemical transformations from rhazimal (**5**) to alstiphyllanine E (**12**).

Two different ways are planned for the synthesis of strictamine (**3**): first a pathway inspired by the postulated biosynthesis *via* *E*-geissoschizine (**35**) and second a non-biogenetic, classical synthesis.

In case of the biomimetic synthesis a conformational analysis of the double bond isomers (*E*)-geissoschizine (**35**) and (*Z*)-geissoschizine (**41**) is planned. We propose that the major conformer of (*Z*)-geissoschizine (**41**) is *trans*-fused referred to the quinolizidine ring system and the major confomer of (*E*)-geissoschizine (**35**) is *cis*-fused because of a 1,3-allylic strain[59] (Figure 11).

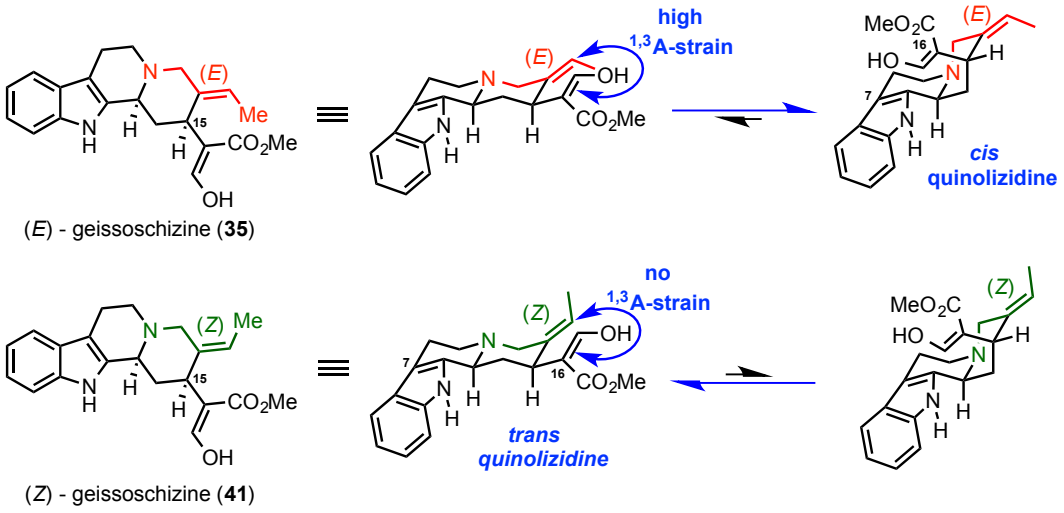


Figure 11: Allyl strain as a rational for the prefered conformations of (*E*) - and (*Z*) -geissoschizine.

In case of the *cis*-isomer carbon atoms C-7 and C-16 are much closer than in case of the *trans*-isomer. This should prefer a bond formation between these two carbon atoms — not only in a chemical synthesis but also in the biosynthesis of the akuammiline alkaloids. To proof this concept both compounds, (*E*)-geissoschizine (**35**) and (*Z*)-geissoschizine (**41**), needs to be synthezied selectively. A detailed conformational analysis including different spectrocopical methods should be performed to clarify the preferred quinolizidine conformations of both compounds.

4. Conformational analysis of Geissoschizine derivatives

4.1 The Indolo[2,3-α]-quinolizidine skeleton

The quinolizidine skeleton incorporating the annulated indolo[2,3-α]-quinolizidine moiety is a prominent structure motif in monoterpenoid indole alkaloids.[60] Such a quinolizidine exists in three main conformations *a*, *b*, and *c* (Figure 12).[61]

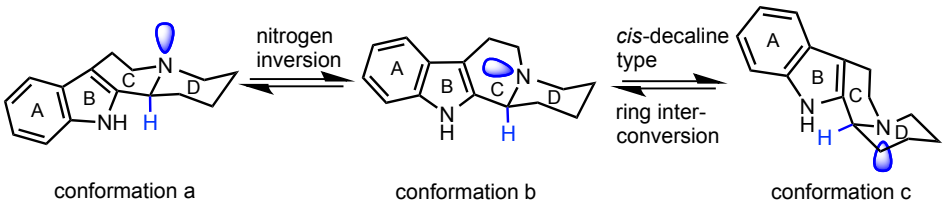


Figure 12: Conformational isomers of indolo[2,3-a]quinolizidine.

Comparison of conformations *a* and *c* shows, that *a* is favored by ~11 kJ/mol (2.6 kcal/mol).[62] Conformation *b* is in general least populated.[63] The conformational equilibrium is strongly influenced by the substituents on rings C and D, and can even be reversed depending on the nature of substituents located at the quinolizidine system.[64]

This quinolizidine system constitutes the core of *Corynanthean* alkaloids[60] with a prominent congener termed geissoschizine (Figure 13) first isolated in 1958[50a] from the plant *Geissospermum vellosii* (family: *Apocynaceae*).

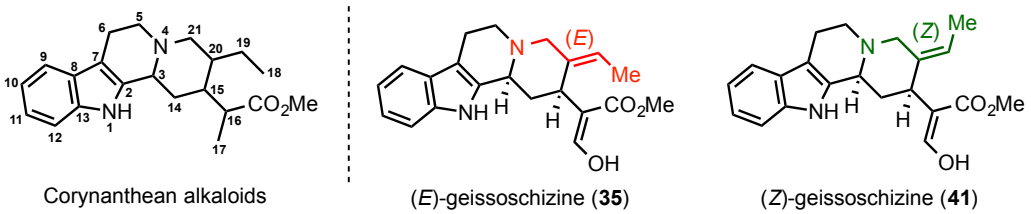


Figure 13: (*E*)- and (*Z*)-geissoschizine (**35** & **41**), members of the Corynanthean alkaloid family.

This natural product displays structure variations with regard to the C19-20 double bond geometry (Figure 14).[65]

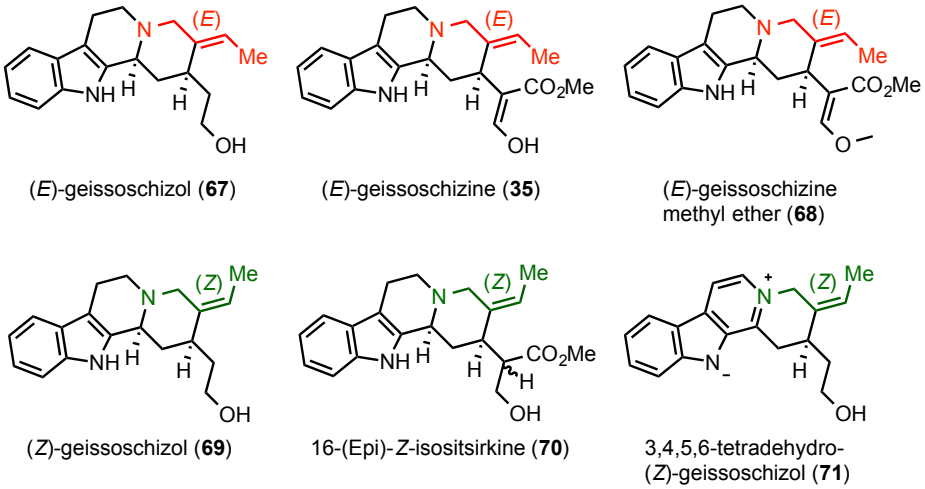


Figure 14: Isolated geissoschizine derivatives with an (*E*)- and (*Z*)-configured double bond.

Its biosynthesis is well known and was extensively studied during the last century (see Schemes 1-3). The *Corynanthean* alkaloids are considered as key intermediates in the biosynthesis of several monoterpenoid indole alkaloids. It is generally agreed upon, that *E*-geissoschizine (**35**) itself is a precursor for biosynthetic "secondary cyclizations", leading to C-mavacurine, strychnos and akuammiline alkaloids (Figure 15).[54]

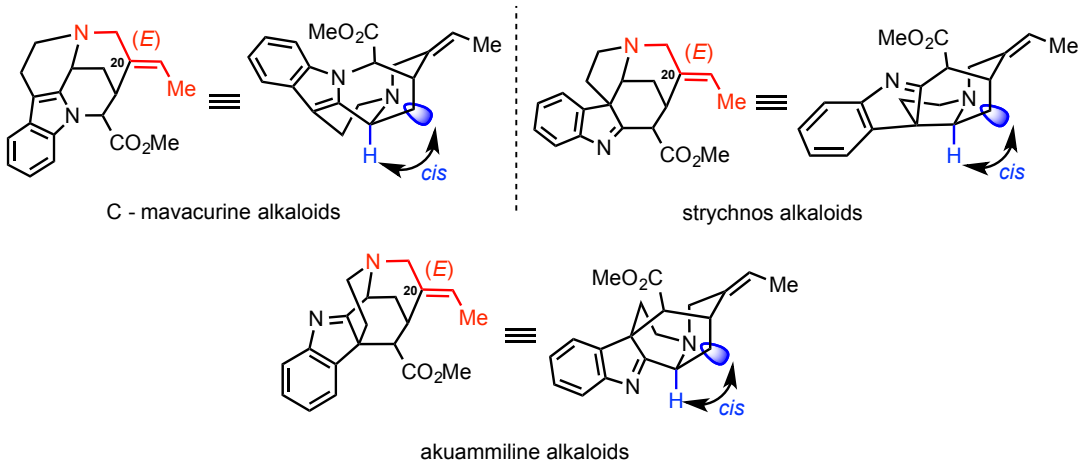


Figure 15: Monoterpenoid indole alkaloids bearing a fixed *cis*-quinolizidine system and an *E*-configured double bond.

These "secondary cyclizations" form the cage-type structure exhibited by these alkaloids, but the mechanisms of these biosynthetic transformations are still on debate.[51, 55b] We propose a correlation between these "secondary cyclizations" and the C19-20 double bond geometry (*E*)- or (*Z*) present in geissoschizine and its derivatives (Figure 14). We started our analysis with a structural comparison of the affore mentioned alkaloids biosynthetically originating from these "secondary cyclizations". Thereby two structural features immediately caught our attention: 1. Whereas geissoschizine and its naturally occurring derivatives display the (*E*)- and the (*Z*)-configured double bond at C19-20 (Figure 14), the alkaloids after "secondary cyclizations" exclusively harbor the (*E*)-configured double bond at this position. 2. These alkaloids all contain a *cis*-quinolizidine system, which is a prior condition for the "secondary cyclizations" to occur and gives the cage-type structure (Figure 4 & Figure 17).[10, 60, 66] The cage-structure in turn precludes isomerization to the thermodynamically favored *trans*-quinolizidine.

By contrast, in geissoschizines **35** and **41** isomerization between the *trans*- and the *cis*-quinolizidine (Figure 16) is still possible.[62] This concludes that the "secondary cyclization" during the biosynthesis requires the *cis*-quinolizidine system of *E*-geissoschizine **35**.

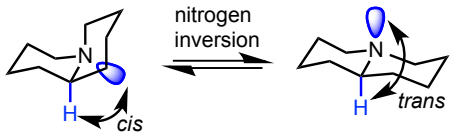


Figure 16: *Cis*- and *trans*-quinolizidine skeleton.

In conclusion, two scenarios for the formation of these cage-structures are conceivable: 1. The "secondary cyclization" of (*E*)- and (*Z*)-geissoschizines **35** & **41** represents a *Curtin-Hammett* situation[67, 68], or 2. The specific structural features of (*E*)-geissoschizine **35** favor the *cis*-quinolizidine, which then preferentially undergoes "secondary cyclizations" to afford the respective alkaloids. Thereby, the configuration of the double bond, and its influence on the conformational equilibrium of geissoschizines **35** and **41** plays a key role to address this question. We propose that the (*E*)-configuration of the C19-20

double bond imposes an 1,3-allylic strain (Figure 11) on *E*-geissoschizine (**35**), rendering the *cis*-quinolizidine thermodynamically favorable and enables the formation of the cage-structure in the secondary cyclizations (Figure 4 & Figure 17). Therefore, these alkaloids exclusively display the (*E*)-configured double bond. This effect is missing in the (*Z*)-derivatives, leaving the system in the *trans*-quinolizidine and prohibiting secondary cyclizations — hence no alkaloids with a C19-20 (*Z*)-configured double bond occur.

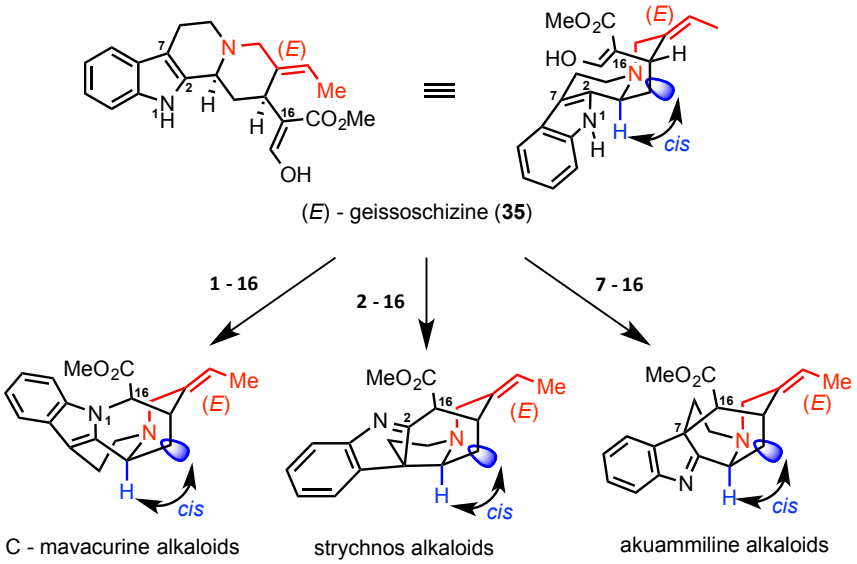
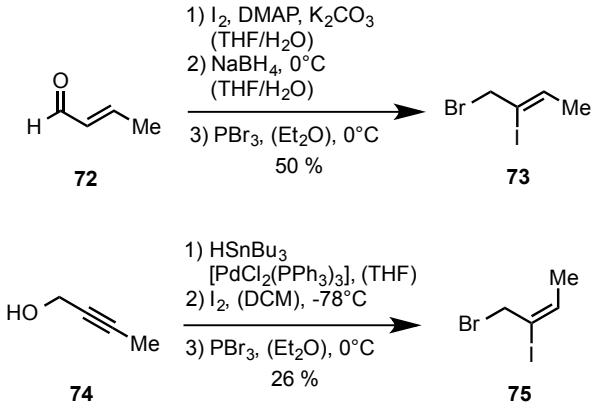


Figure 17: Feasible cyclizations of *E*-geissoschizine (**35**) based on a *cis*-quinolizidine system.

4.2 Synthesis of the Geissoschizine derivatives

To probe our hypothesis we carried out detailed conformational analysis of (*E*)- and (*Z*)-geissoschizine and four derivatives. The synthesis of all derivatives is based on a literature known procedure mainly developed by the group of *James M. Cook*.[69] To get an access to both double bond isomers a selective synthesis for the appropriate vinyl iodides **73** and **75** is neccessary. (*Z*)-1-Bromo-2-iodobut-2-ene (**73**) was synthesized according to a literature kown procedure starting from crotonaldeyhde (**72**).[70] First, the iodine was installed by a *Baylis-Hillman* reaction catalyzed with DMAP. After the reduction of the aldehyde to the primary alcohol by $NaBH_4$ this was transferred to primary bromide **73** by an *Appel* reation with PBr_3. The synthesis of (*E*)-1-bromo-2-iodobut-2-ene (**75**) was realized by a different approach.[71] Starting from 2-butyn-1-ol (**74**) this was transferred to the vinylstannane by a palladium catalyzed hydrostannylation reaction of the triple bond. After a tin iodine exchange the primary alcohol was substituted to primary bromide **75** by an *Appel* reation with PBr_3 (Scheme 15).

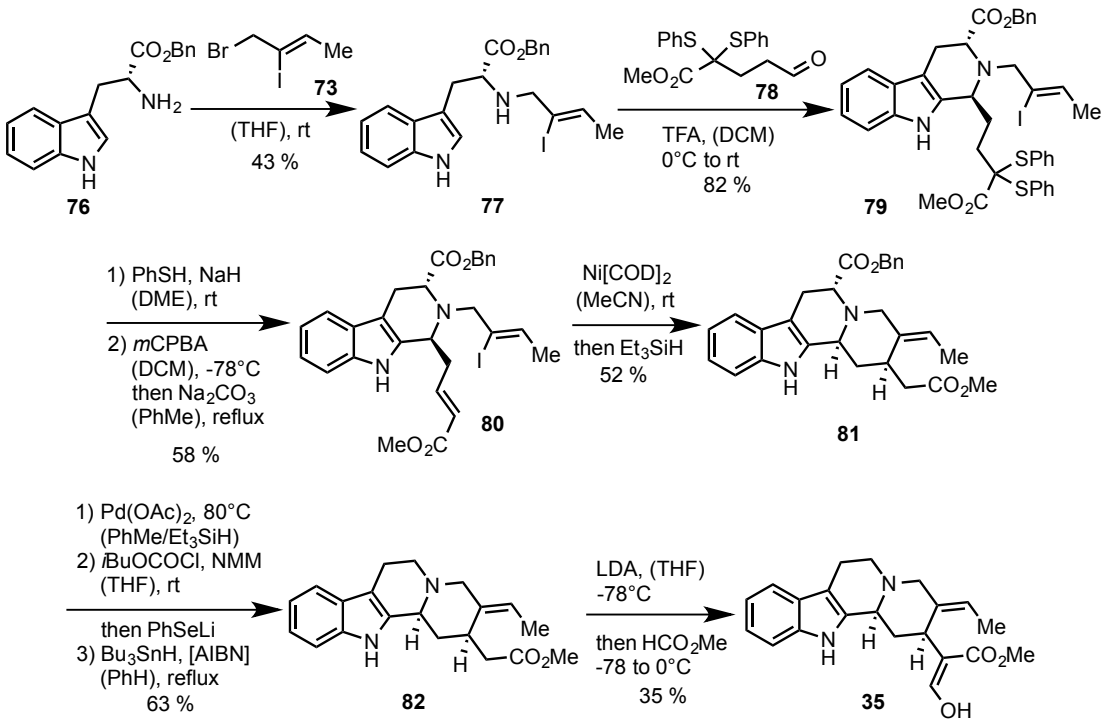


Scheme 15: Selective synthesis regarding to the double bond configuration of both vinyl iodides.

With both vinyl iodides **73** and **75** in hands, a selective synthesis of (*E*)- and (*Z*)-geissoschizine **35** & **41** is possible starting with benzyl protected *D*-tryptophan (**76**).

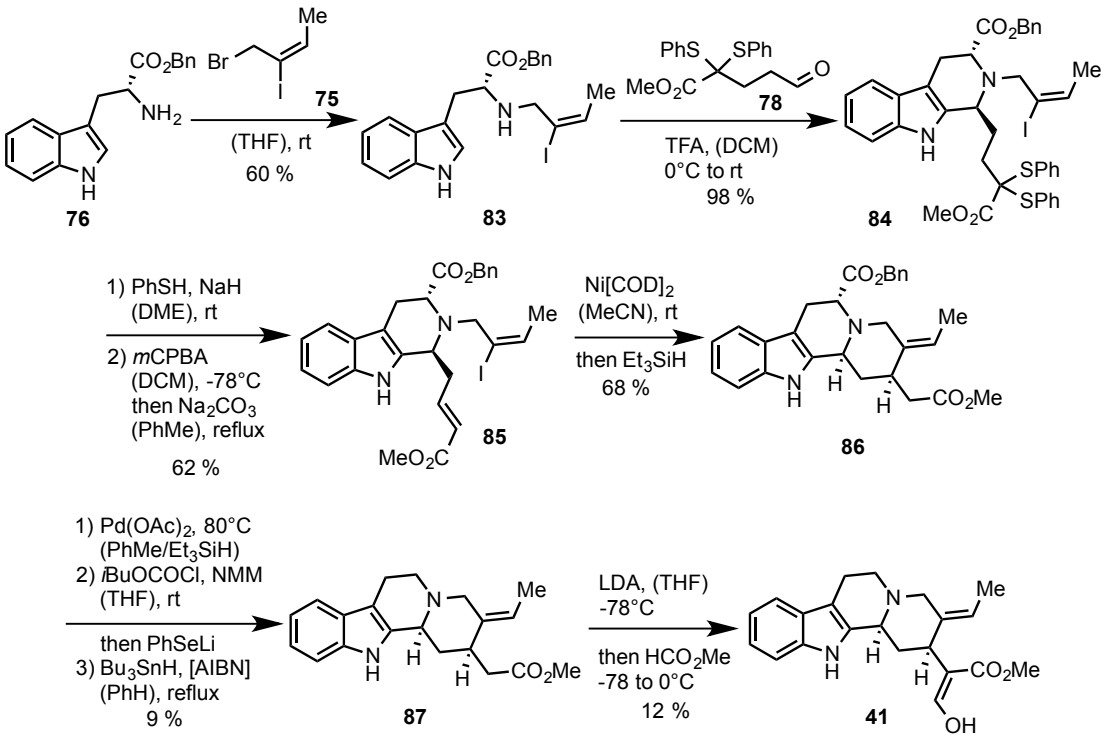
N-Alkylation with bromide **73** yielded secondary amine **77** in a moderate yield of 43%. This was converted to tricycle **79** in a *Pictet-Spengler* reaction with

aldehyde **78**. A sequence of desulfurization using thiophenol follwed by an oxidation of the remaining thioether with *m*-CPBA and elimination of the sulfoxide by heating in refluxing toluene gave access to α,β-unsaturated ester **80**. Ni(0)-promoted 1,4-addition of the vinyl iodide gave the carbon skeleton of (*E*)-geissoschizine represented by benzyl ester **81** in a moderate yield of 52%. Debenzylation under reductive conditions liberated the carboxylic acid which was transferred to the mixed anhydride by *iso*-butyl chloroformate. Conversion to the selenoester opened the possibility of a *Barton-McCombie* defunctionalization giving (*E*)-geissoschizoate **82**. Formylation with methyl formate under the influence of LDA produced (*E*)-geissoschizine **35** in a yield of 35% (Scheme 16).



Scheme 16: Total synthesis of (*E*)-geissoschizine (**35**).

(*Z*)-Geissoschizine (**41**) was synthesized in the same manner using primary bromide **75** in a total of nine steps. In case of (*Z*)-Geissoschizine (**41**) the yield during the defunctionalization steps of the benzyl ester and the formylation step droped dramatically to 9% and 12% respectively (Scheme 17).



Scheme 17: Total synthesis of (*Z*)-geissoschizine (**41**).

Both syntheses resulted six different geissoschizine derivatives **81** & **86**, **82** & **87** and **35** & **41** (Figure 18) that could be analyzed regarding their quinolizidine conformation and the influence of different substituents on a conformational change.

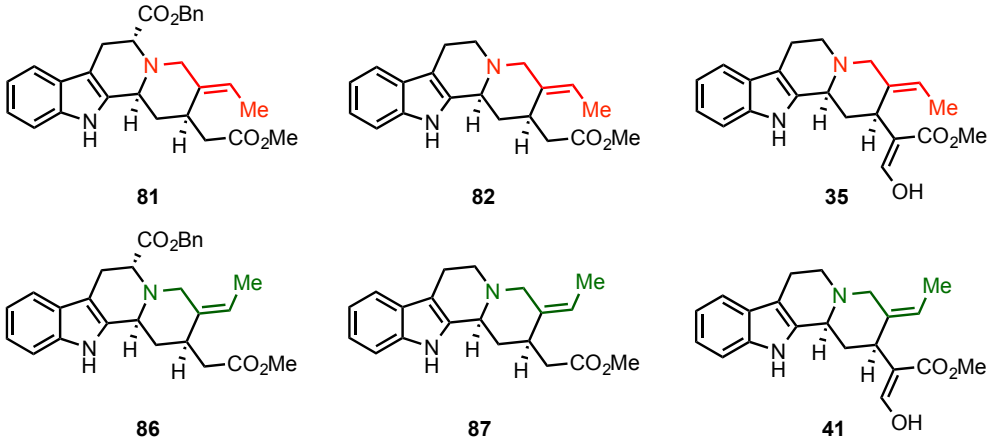


Figure 18: Synthesized geissoschizine derivatives **81** & **86**, **82** & **87** and **35** & **41**.

During the past five decades data on the conformational situation in geissoschizine and derivatives were sporadically published[64, 72], but up to

date no detailed and coherent investigation on this matter exists. Especially the conformation of *E*-geissoschizine (**35**) is not completely clarified.[72f, 72g] In 1976, *Rackur* and *Winterfeldt*[73] were the first to describe the difference of IR- and ^{1}H-NMR spectra of *E*- and *Z*-geissoschizines. The absence of *Bohlmann* bands in the IR-spectra lead them to conclude a *cis*-quinolizidine conformation for *E*-geissoschizine (**35**), and a *trans*-quinolizidine conformation in case of *Z*-geissoschizine (**41**).

4.3 Chemical behaviour of the substrates in comparison

Comparison of the *Z*-configured with their respective *E*-configured compounds **81** & **86**, **82** & **87** and **35** & **41** showed characteristic differences in their chemical behavior. All *E*-compounds exhibited significantly lower R_f-values on TLC than their *Z*-configured counterparts. This feature can be attributed to a *cis*-quinolizidine system in **81**, **82** and **35** for the (*E*)-compounds, in which the lone pair of the nitrogen (tertiary amine) is exposed to the environment, in contrast to the *trans*-quinolizidine in **86**, **87** and **41** present in the (*Z*)-compounds (Figure 19). In *E*-/*Z*-geissoschizines **35** and **41** C-16 is no longer a CH_2-group, but part of the 1,3-dicarbonyl unit, which can therefore exist in the *cis*- (**35**) and in the *trans* enol-form (**41**) (Figure 19). In 1,3-dicarbonyls the *cis*-enol is usually highly favoured. In geissoschizines, this equilibrium is dependent on the quinolizidine conformation and strongly shifted to the *trans*-enol in case of *Z*-geissoschizine (*cis*/*trans*= 5/3 as opposed to 10:1 in *E*-geissoschizine).

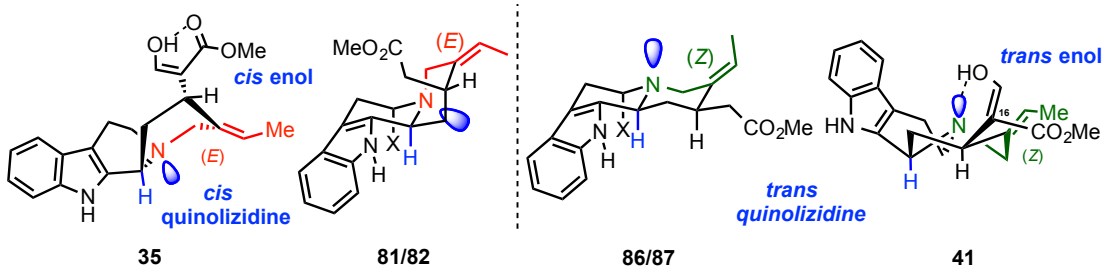


Figure 19: Exposure of the nitrogen lone pair in comparison (X = H, CO_2Bn).

A possible explanation is the formation of a hydrogen bond to the nitrogen lone pair of the *trans*-enol in *Z*-geissoschizine (**41**) when adopting the *trans*-quinolizidine (structure **41**, Figure 19). This hydrogen bond cannot be formed with *E*-geissoschizine (**35**) if adopting the *cis*-quinolizidine, thus the *cis*-enol is maintained (Figure 19; structure **35**).

Quaternization of the tertiary amine in the quinolizidine with *p*-bromobenzyl bromide or methyl iodide proceeded smoothly with (*E*)-compounds **81**, **82** & **35**, due to their greater nucleophilicity, indicating the presence of a *cis*-

quinolizidine system (Figure 20). By contrast, (*Z*)-compounds did not give quaternization products under the same conditions.

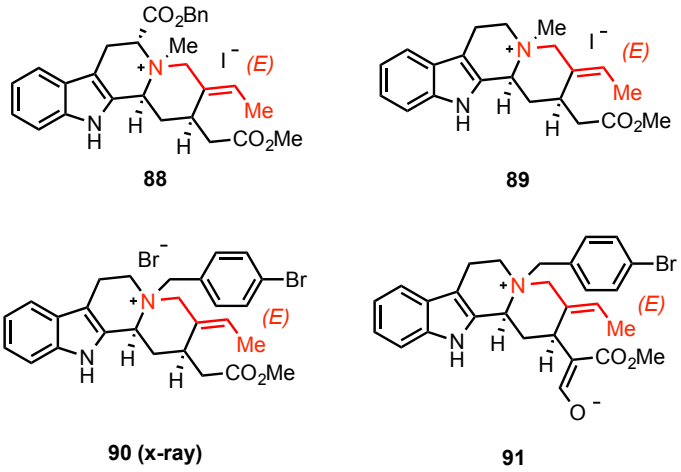


Figure 20: Quaternized geissoschzine derivatives.

With these preliminary characteristics in hands we launched our conformational analysis. For every couple of *E*- and *Z*-compounds the *trans*-quinolizidine system was determined by means of the following seven criteria which can generally be applied: a) Presence of *Bohlmann* bands in the IR-spectra of the *trans*-quinolizidine.[74] b) Consistently lower chemical shifts in the *trans*-quinolizidine of proton at H-3; H-5 (*axial*) and H-21 (*axial*) due to the same stereoelectronic effect causing the *Bohlmann* bands.[75] c) Two *trans diaxial* (*anti*) coupling constants for (H_a)-14 and two *gauche*-like for (H_b)-14. (By contrast, the *cis*-quinolizidine displays exclusively *gauche* interactions at (H_{ab})-14).[76] d) Signal pattern of H-3 is "doublet-like" with J > 10 Hz corresponding to one *anti;* and one very small *gauche* interaction (J ≈ 0) present in the *trans*-quinolizidine, as opposed to a "triplet-like" signal of H-3 in the *cis*-quinolizidine (corresponding to two *gauche* interactions with the same coupling constant J_1=J_2; Figure 21).[75] e) Consistently higher chemical shifts in the ^{13}C-NMR for C-3, 6, 14, 15 and 21 in the *trans*-quinolizidine (3-13 ppm) as stated by *Lounasmaa*.[61b, 63d, 64, 77] f) The reactivity in the salt formation with methyl iodide reflecting the degree of steric hindrance at the quinolizidine nitrogen. *Cis*-quinolizidines are quarternized smoothly whereas *trans*-quinolizidines reluctantly and sluggishly react.[78] g) The presence of the

following characteristic *NOE* signals in the *trans*-quinolizidine: H-16-19 and H-3-21. For ease of comparison the results for each *E*/*Z*-derivative couple are summed up in a table at the end of each chapter.

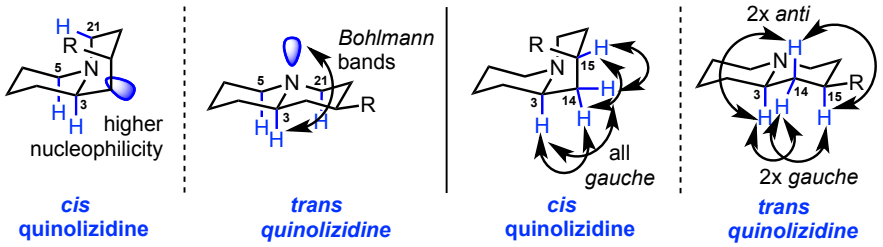


Figure 21: Criteria for distinguishing *cis*-/*trans* quinolizidine conformations.

4. Conformational analysis of Geissoschizine derivatives

4.4 (*E*)- and (*Z*)-Geissoschizoates in comparison

Criterion a (presence of *Bohlmann* bands): Comparison of IR-spectra of *Z*- **87** and *E*-geissoschizoate **82** shows one additional band in the IR-spectrum of the *Z*-compound at 2745 cm^{-1} (Figure 22). This additional band represents the second *Bohlmann* band, which is exclusively present in *trans*-quinolizidines. By contrast, *E*-geissoschizoate **82** is devoid of this second band, suggesting a *cis*-quinolizidine system.

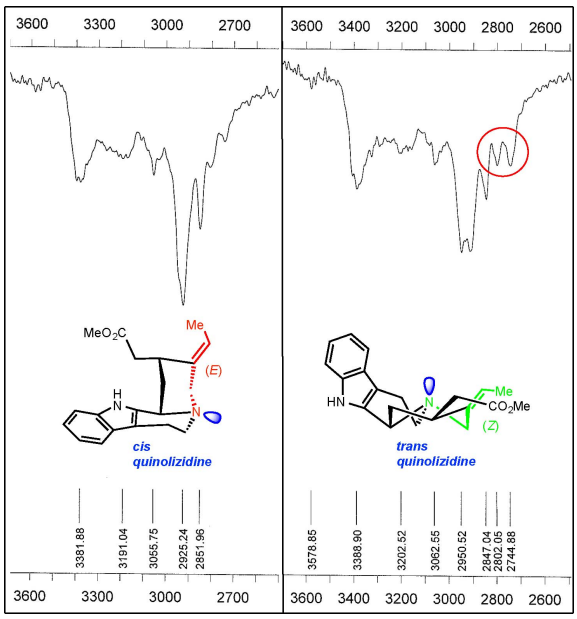
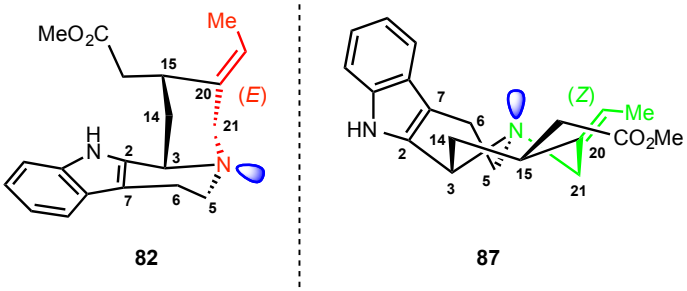


Figure 22: C-H stretching region of the IR-spectra of geissoschizoates in cm^{-1}.

Criterion b (consistently lower chemical shifts of proton at H-3, H-5 and H-21 in the *trans*-quinolizidine system): From Table 1, which lists the chemical shifts for *E*- and *Z*-geissoschizoates **82** and **87**, it can be seen that for the *Z*-compound H-3, one H-5 (*axial*) and one H-21(*axial*) display consistently lower chemical shifts (most significantly at H-3). These high-field shifts in the *Z*-compound **87** originate from *trans diaxial* interactions with the nitrogen lone pair — the same stereoelectronic effect responsible for the *Bohlmann* bands and resembles a *trans*-quinolizidine. The absence of the high-field-shift in *E*-**82** indicates *gauche* interactions of protons H-3, H-5, and H-21 with the nitrogen lone pair. This resembles the *cis*-quinolizidine (Figure 23).

Table 1: Criterion b and e, chemical shifts of the geissoschizoates in comparison.

^{1}H	*E*-isomer **82** (ppm)		*Z*-isomer **87** (ppm)		difference	
3	4,30		3,56		0,74	
5	3,28	3,18	3,16	2,70	0,12	0,48
21	3,56	2,97	3,89	2,81	0,33	0,16
^{13}C						
3	53,4		59,8		6,4	
6	18,0		21,9		3,9	
14	30,6		37,0		6,4	
15	31,2		38,2		7,0	
21	52,9		55,6		2,7	



82 **87**

Figure 23: Numbering of geissoschizoates **82** and **87**.

Criterion c (2 x *trans diaxial* couplings): Coupling constant analysis of (H_a)-14 in *Z*-**87** reveals two identical coupling constants of 11.6 Hz. This corresponds to two t*rans diaxial* interactions (*anti*) with H-3 and H-15. By contrast (H_a)-14 in *E*-**82** displays two *gauche* interactions with H-3 and H-15, and coupling constants of 7.2 and 5.8 Hz.

Criterion d (signal pattern): The coupling pattern of the angular proton H-3 is "doublet-like" in *Z*-**87**, whereas the same proton in *E*-**82** displays a "triplet-like" coupling pattern, therefore indicating a *trans*-quinolizidine system for *Z*-**87**. Application of the *Karplus*[79] equation delivered the approximate dihedral torsion angles for *E*-**82** and *Z*-**87**, and overall concluded a *trans*-quinolizidine for *Z*-**87**, and a *cis*-quinolizidine for *E*-**82** (Figure 24/Figure 25).

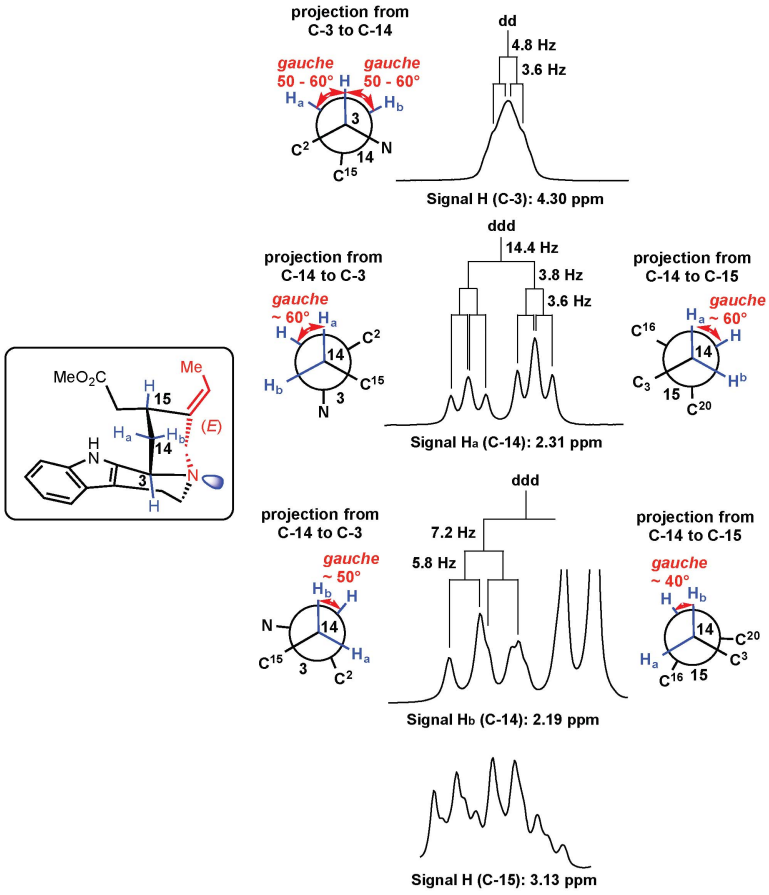


Figure 24: Coupling constant analysis for *E*-Geissoschizoate (**82**).

Criterion e (*Lounasmaa*): Comparison of the ^{13}C-NMR spectra of *Z*-**87** and *E*-**82** reveals significant differences C-3, -6, -14, -15 and -21. Thereby the *Z*-isomer (**87**) displays higher chemical shifts at these carbon atoms, corresponding to a *trans*-conformation of the quinolizidine system (Table 1).

Criterion f (Quarternization kinetics): *E*- and *Z*- geissoschizoates (**82** and **87**) were both reacted to obtain the quaternary ammonium salt. While *E*-**82** reacted smoothly with methyl iodide and *p*-bromobenzyl bromide crystallizing the ammonium bromide, the *Z*-compound did not deliver the desired salt. The X-ray analysis is shown in Figure 26, and clearly displays the *cis*-quinolizidine structure of **90**. This compound was very versatile to test the reliability of our criteria, since it is unambiguously fixed in the *cis*-quinolizidine system.

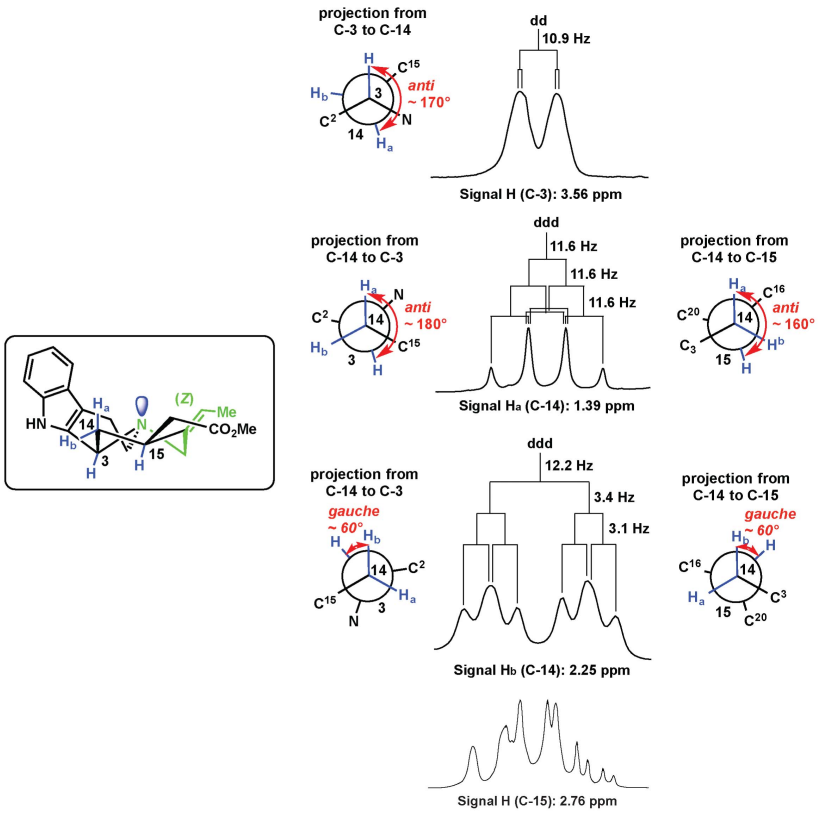


Figure 25: Coupling constant analysis of *Z*-Geissoschizoate (**87**).

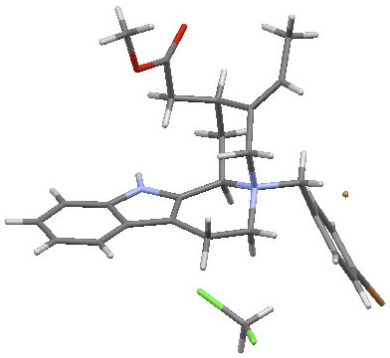


Figure 26: X-Ray structure of ammonium salt **90**.

Coupling constants analysis of this ammonium salt **90** was carried out in the same manner as with *Z*-**87** and *E*-**82**. Comparison reveals close similarities of coupling patterns and constants between ammonium salt **90** and *E*-**82**. Since quaternarized **90** is locked in the *cis*-quinolizidine conformation, this allows the conclusion that *E*-geissoschizoate **82** also prevails in the *cis*-conformation.

Figure 27 summarizes the important coupling constants for comparison with Figure 24.

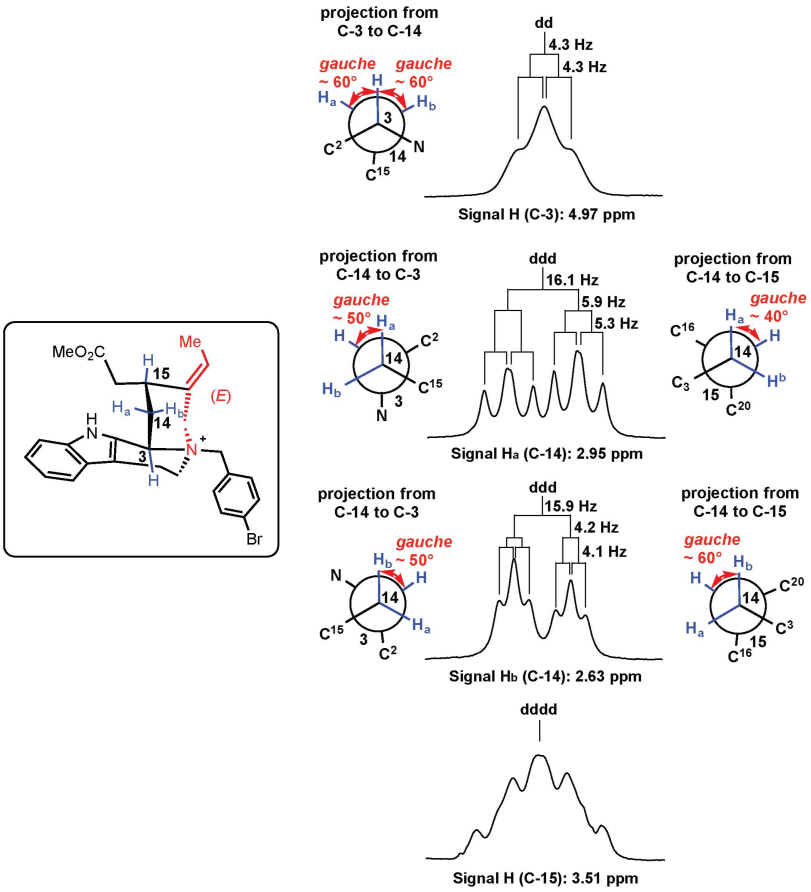


Figure 27: Coupling constants analysis of ammonium salt **90**.

Criterion g (*NOESY*): *NOE*-contacts of *E*- and *Z*-geissoschizoates **82** and **87** and the quaternary ammonium salt **90** are depicted in Figure 28. The *NOE*-contact of H-16 and H-19 confirms the absence of 1,3-allyl strain in *Z*-**87**. By contrast, the *NOE*-contact of H-15 and the methyl-group (H-18) in *E*-**82** and ammonium salt **90** indicate that the system avoids 1,3-allyl-strain with the double bond and flips to the *cis*-quinolizidine system. The contacts between H-3, H-15, and H-21 suggest a *trans*-quinolizidine system for *Z*-geissoschizoate **87**. In *E*-geissoschizoate **82** and quaternary ammonium salt **90** the *NOE*-contacts are identical and were measured between H-6, H-21, and H-16. This is in accordance with a *cis*-quinolizidine system.

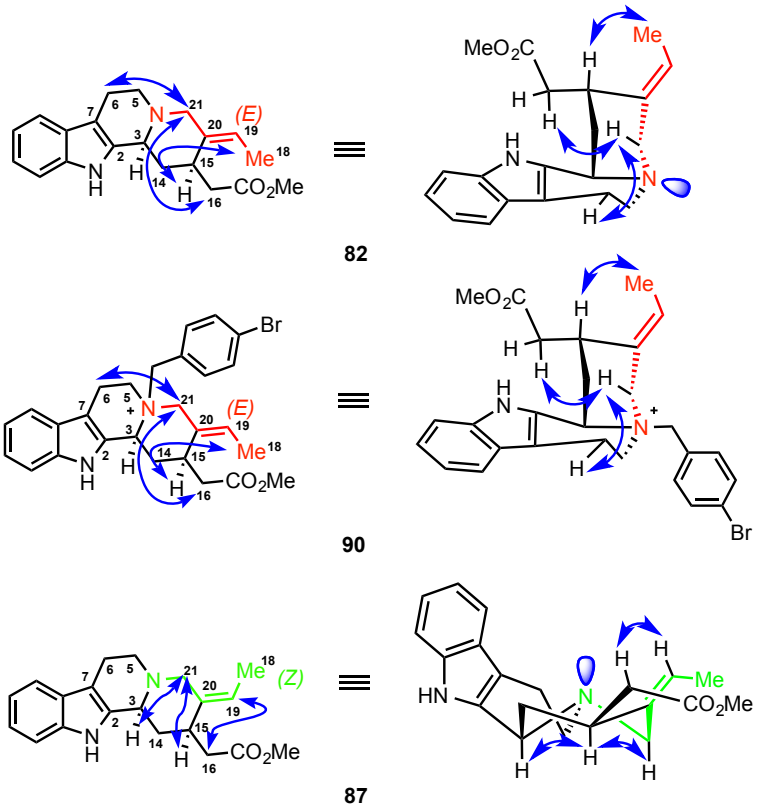


Figure 28: Characteristic *NOE*-contacts of *E*- and *Z*-geissoschizoates.

In summary, all criteria (a-g) for the presence of a *trans*-quinolizidine system are fulfilled in *Z*-geissoschizzoate **87** and none is fulfilled for *E*-geissoschizzoate **82** (Table 2). This strongly supports our hypothesis that the configuration of the C-19-20 double bond is responsible for the equilibrium of *cis*- and *trans* quinolizidine.

Table 2: Comparison of *E*- and *Z*-geissoschizoates (**82**, **87**).

	***E*-comp. 82**	***Z*-comp. 87**
Crit a: *Bohlmann* bands	NO	YES
Crit b: H-3;5;21	higher ppm	lower ppm
Crit c: H(a)-14 coupling const.	2 x *gauche*	2 x *anti*
Crit d: H-3	triplet-like	doublet-like
Crit e: ^{13}C-Lounasmaa	lower ppm	higher ppm
Crit f: Quarternization	YES	NO
Crit g: *NOE* H-16-19 & H-3-21	NO	YES
		trans-quinolizidine

4. Conformational analysis of Geissoschizine derivatives

4.5 (*E*)- and (*Z*)-C-5 Benyzl esters in comparison

In comparison to geissoschizoates *E*-**81** and *Z*-**86**, these two compounds bear an additional substituent (benzyl ester) at C-5 (Figure 30). This introduces an additional stereocenter, with the benzylester incorporated in the *axial* position. To test if this substituent at C-5 perturbates the conformational behaviour of the system both double bond isomers *E*-**81** and *Z*-**86** were analyzed in the same manner as geissoschizoates **82** and **87**. Comparison of IR-spectra (criterion a) of **81** and **86** revealed two *Bohlmann* bands at 2850 cm^{-1} for the *Z*-compound **86**. In the *E*-compound only one band is present indicating a *cis*-quinolizidine system (Figure 29).

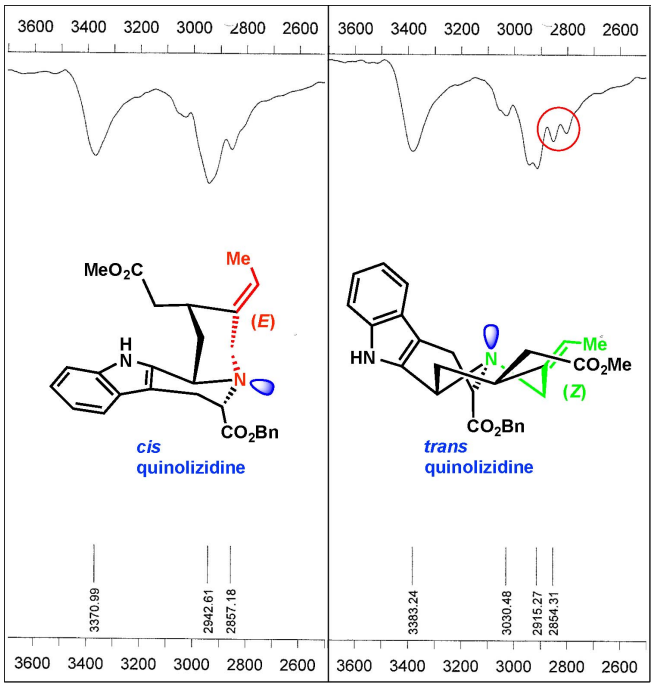


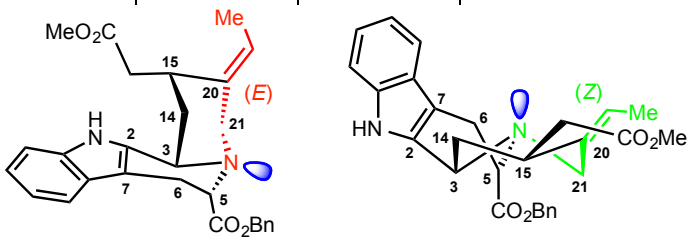
Figure 29: C-H stretching region of the IR-spectra of C-5 benzyl esters **81** and **86** in cm^{-1}.

Criterion b was only fulfilled by H-21 in the *Z*-compound, whereas H-3 and H-5 remained identical in *E*-**81** and *Z*-**86**. This finding is consistent for H-5, which has been substituted by the benzylester in **81** & **86** in the *axial* position. The remaining equatorial H-5 does not qualify for *trans diaxial* interactions with the nitrogen lone pair of the quinolizidine system. In contrast to

geissoschizoates, H-3 does not show any significant high-field shift (Table 3, Figure 30).

Table 3: Criterion b and e, chemical shifts of the C-5 benzyl esters **81** and **86** in comparison.

^{1}H	*E*-isomer **81** (ppm)	*Z*-isomer **86** (ppm)	difference
3	4,58	4,52	0,06
5	3,94	3,97	0,03
21	3,54 3,26	3,83 3,50	0,29 0,24
^{13}C			
3	49,2	55,9	4,7
6	21,8	25,3	3,5
14	32,5	38,4	5,9
15	31,6	38,7	7,1
21	55,2	53,1	2,1



81 **86**

Figure 30: Numbering of C-5 benzyl esters **81** and **86**.

Criterion c is met, as *Z*-compound **86** shows two *trans diaxial* interactions of (H_a)-14 (*anti*) with C-3 and C-15. By contrast, the same proton (H_a)-14 in *E*-**81** displays four *gauche* interactions. Proton H-3 of *Z*-**86** and *E*-**81** fully satisfies criterion d by displaying a "doublet-like" signal pattern in *Z*-**86**, and a "triplet-like" signal pattern in *E*-**81** (Figure 31 and Figure 32).

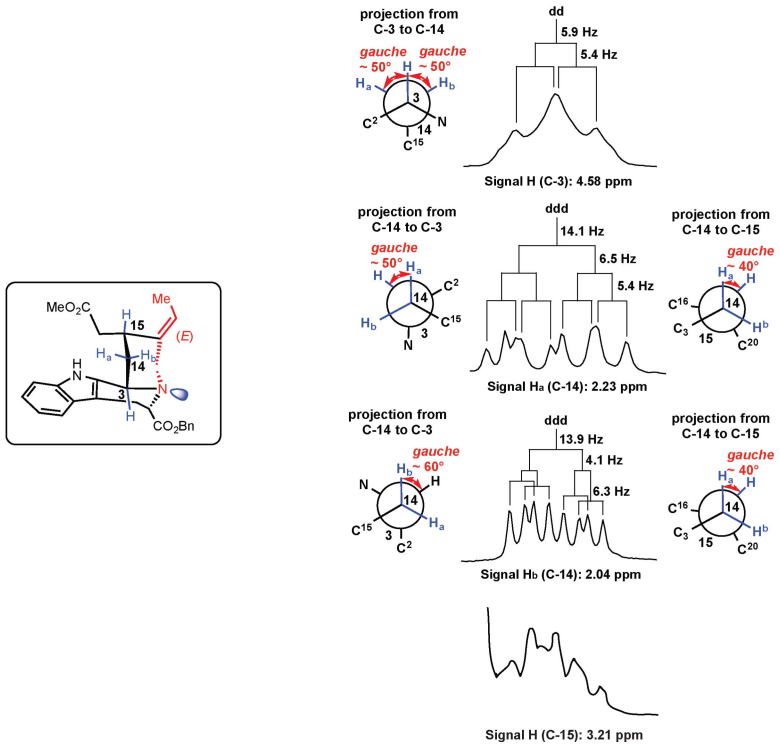


Figure 31: Coupling constant analysis for *E*-C-5 benzyl ester (**81**).

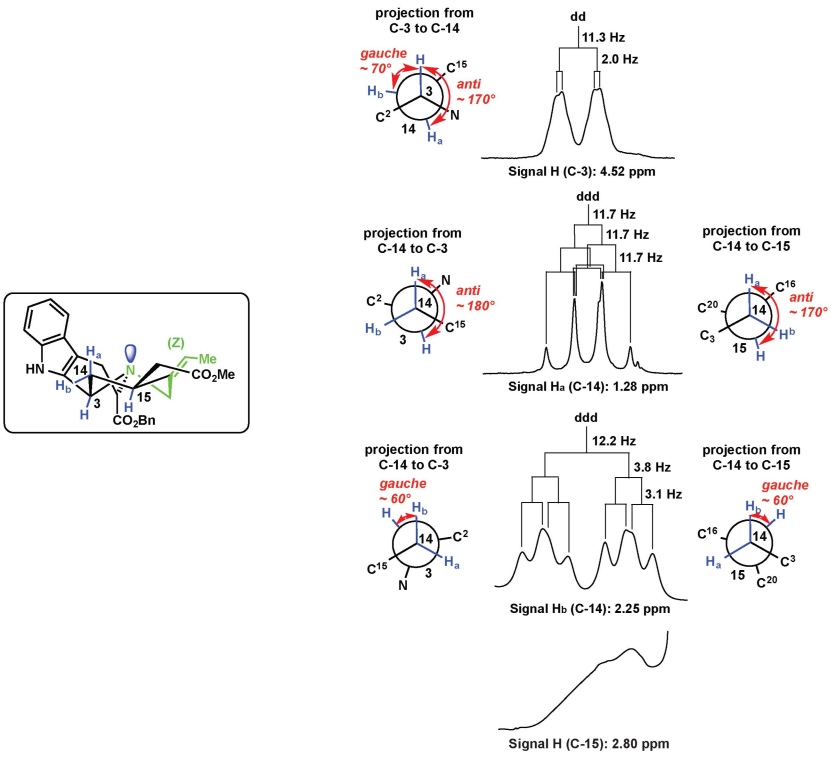


Figure 32: Coupling constant analysis for *Z*-C-5 benzyl ester (**86**).

Lounasmaa's ^{13}C-NMR chemical shift analysis (criterion e) yields consistently higher chemical shifts for the *Z*-compound **86** at carbon atoms C-3, -14, -15, -21 (Table 3). Together with criteria a-e this concludes a *trans*-quinolizidine conformation for *Z*-**86**, and a *cis*-quinolizidine conformation for *E*-**81**.

Criterion f is also fulfilled and quarternization was only observed with the *E*-compound (see Figure 20).

The *NOE*-contacts of criterion g (H-16-19, H-3-21) are present in *Z*-compound **86** and confirm the existence of a *trans*-quinolizidine system. Moreover, *NOE*-contacts between H-6-21, H-6-16 and H-16- N-H (indole) in the *E*-compound clearly indicate a *cis*-quinolizidine in this system (Figure 33).

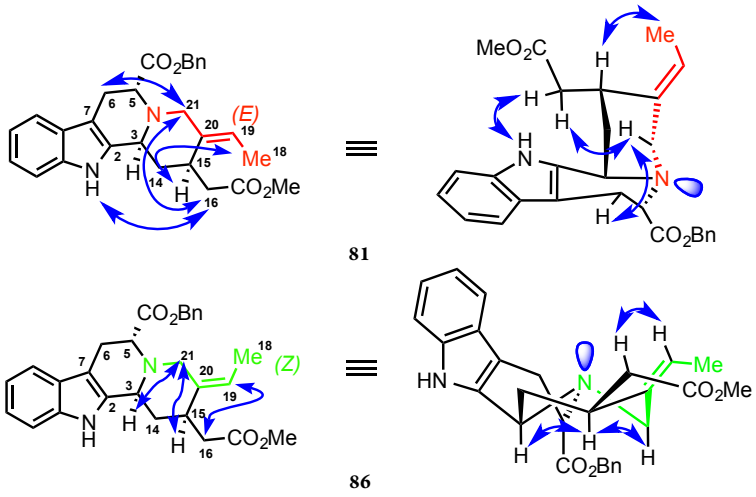


Figure 33: Characteristic *NOE*-contacts of *E*- and *Z*-benzyl esters **81** and **86**.

The benzyl esters **81** and **86** of geissoschizoate support our hypothesis that the *Z*-compound prevails in the *trans*-quinolizidine, which fully meets all criteria except for criteria b (only partly fulfilled). The summary is given in Table 4.

4. Conformational analysis of Geissoschizine derivatives

Table 4: Comparison of *E* - and *Z*-benzyl-geissoschizoates (**81**, **86**).

	***E*-comp. 81**	***Z*-comp. 86**
Crit a: *Bohlmann* bands	NO	YES
Crit b: H-3;5;21		only H-21 lower ppm
Crit c: H(a)-14 coupling const.	2 x *gauche*	2 x *anti*
Crit d: H-3	triplet-like	doublet-like
Crit e: ^{13}C-Lounasmaa	lower ppm	higher ppm
Crit f: Quarternization	YES	NO
Crit g: *NOE* H-16-19 and H-3-21	NO	YES
		trans-quinolizidine

4. Conformational analysis of Geissoschizine derivatives

4.6 (*E*)- and (*Z*)-Geissoschizines in comparison

The IR-spectra of *Z*-**41** and *E*-geissoschizine **35** (criterion a) differ by one additional band in the IR-spectrum of the *Z*-compound at 2743 cm^{-1}, representing the second *Bohlmann* band present in *trans*-quinolizidines (Figure 34).

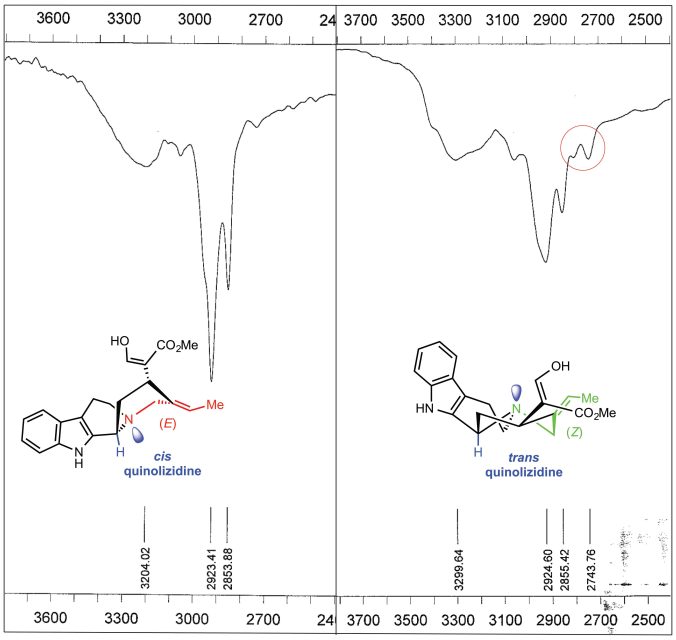


Figure 34: C-H stretching region of the IR-spectra of geissoschizines **35** and **41** in cm^{-1}.

Conformational analysis of *E*- and *Z*-geissoschizines 35 and 41 was exclusively performed with major enol-isomers (mentioned above, Figure 35). For both compounds signal broadening was observed in the ^{1}H-NMR spectra. Criterion b applies for protons H-3 and H-21 of *Z*-geissoschizine 41, thus indicating a *trans*-quinolizidine (Table 5).

Likewise, criterion c is fulfilled in *Z*-geissoschizine with two *trans diaxial* interactions of (H_a)-14 (*anti*) with C-3 and C-15. By contrast, *E*-geissoschizine **35** strongly deviates at (H_a)-14 from the former *E*-derivatives **81** and **82**. This can be attributed to the introduction of the 1,3-dicarbonyl, which strongly pertubates the system.

Table 5: Criterion b and e, chemical shifts of geissoschizines **35** and **41** in comparison.

^{1}H	*E*-isomer **35** (ppm)		*Z*-isomer **41** (ppm)		difference	
3	3,86		3,56		0,30	
5	3,22	2,72	3,19	2,70	0,03	0,02
21	3,95	3,18	3,94	2,87	0,01	0,31
^{13}C						
3	53,7		60,5		6,8	
6	20,6		21,7		1,1	
14	34,0		36,3		2,3	
15	27,8		40,8		13,0	
21	59,3		55,9		3,4	

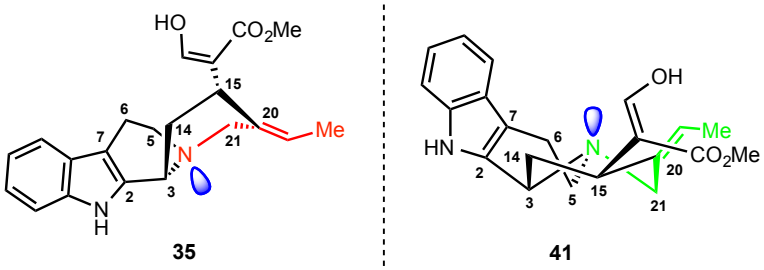


Figure 35: Numbering of geissoschizine **35** and **41**.

Citerion d (signal pattern) is again fulfilled in *Z*-geissoschizine **41** displaying a "doublet-like" signal of H-3. In *E*-geissoschizine (35) H-3 displays a doublet-of-doublet ($J_1 \neq J_2$) instead of a "triplet-like" signal ($J_1 = J_2$). This deviation is still in accordance with a *cis*-quinolizidine system for *E*-geissoschizine (Figure 36/Figure 37). *Lounasmaa*'s ^{13}C-NMR chemical shift analysis (criterion e) is in good accorddance with *Z*-geissoschizine prevailing in the *trans*-quinolizidine (Table 5).

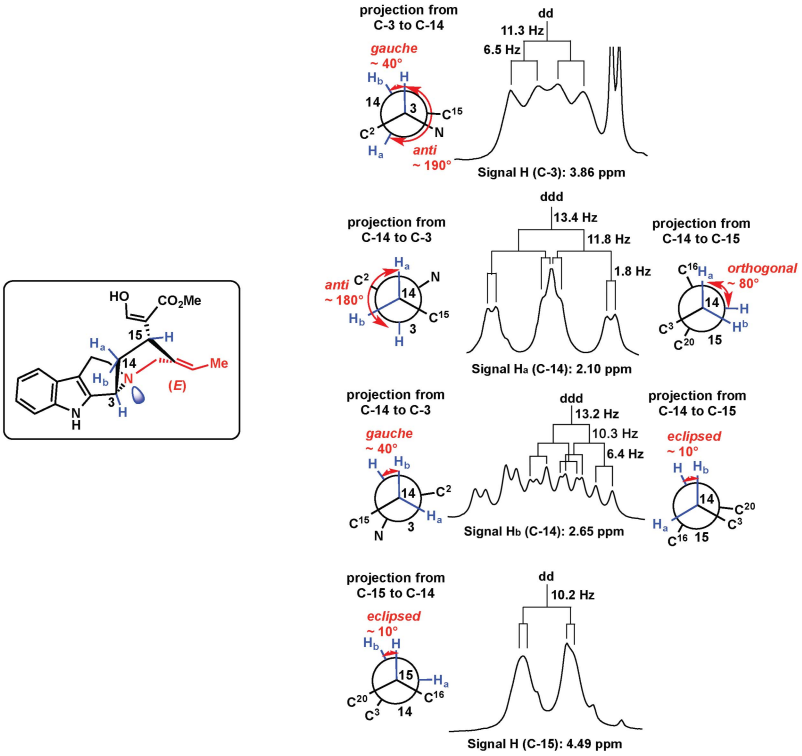


Figure 36: Coupling constant analysis for *E*-geissoschizine (**35**).

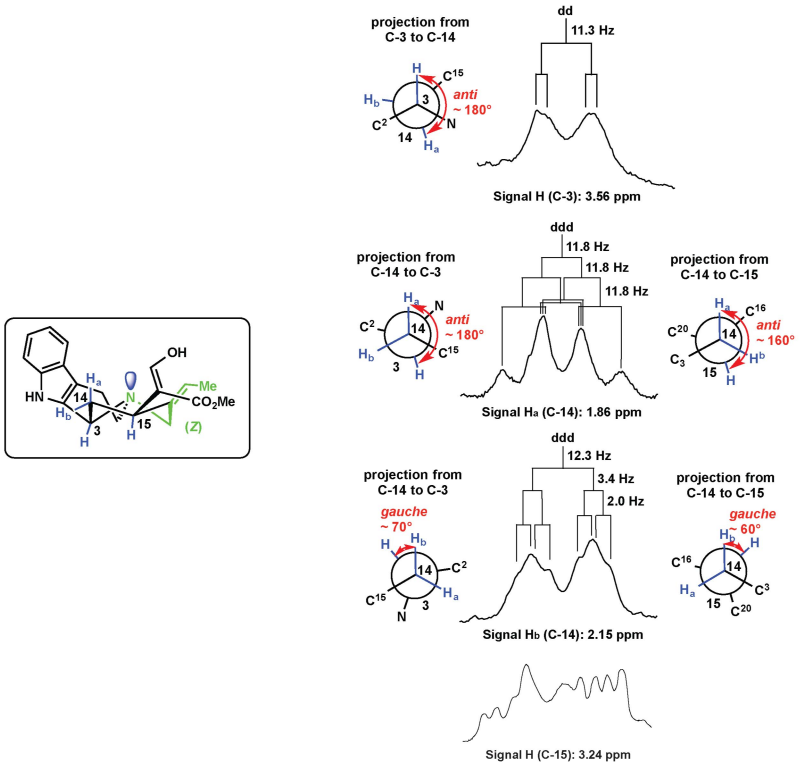


Figure 37: Coupling constant analysis for *Z*-geissoschizine (**41**).

Quarternization of the quinolizidine nitrogen (criterion f) was only observed with the *E*-compound (**35**, see Figure 20).

NOESY analysis (criterion g) revealed the same contacts for *Z*-geissoschizine **41** displayed by the corresponding *Z*-derivatives **86** and **87** (see Figure 38 and Figure 28/Figure 33). In *E*-geissoschizine **35** the *NOE*-contact between H-15 and the methyl-group (H-18) confirms, that the system avoids the 1,3-allyl strain. The *NOE*-contacts in *E*-geissoschizine deviate from the other *NOE*-signals in the *E*-series. This observation is consistent with deviations in criteria c and d, and is assigned to a change of the conformation not only to the *cis*-quinolizidine, but also to the adaption of a boat conformation of ring-D.

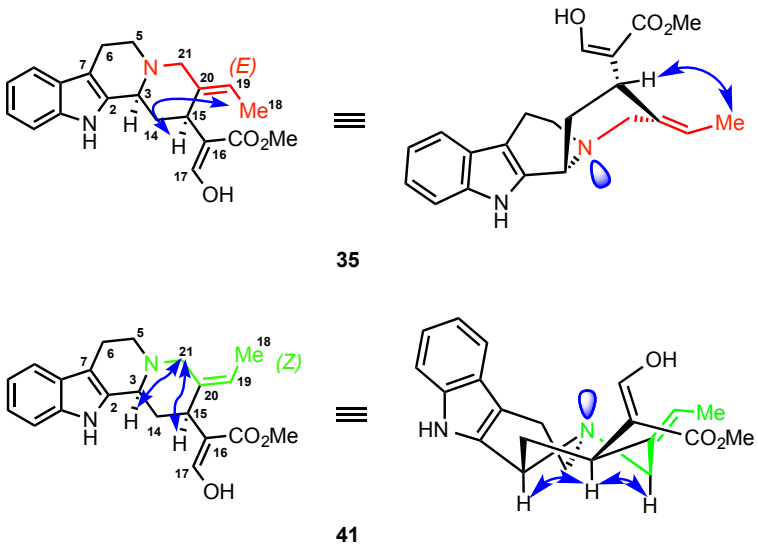


Figure 38: Characteristic *NOE*-contacts of *E*- and *Z*-geissoschizines **35** and **41**.

The summary Table 6 shows, that for *Z*-geissoschizine only two criteria are partly fulfilled and five criteria fully apply, thus suggesting a *trans*-quinolizidine system for this compound. The picture is somewhat more complex when *E*-geissoschizine is analyzed, due to additional conformational changes, but clearly the *NOE*-contact between H-15-18 indicates that the system avoids 1,3-allyl strain.

Table 6: Comparison of *E* - and *Z* -geissoschizines (**35**, **41**).

	***E*-comp. 35**	***Z*-comp. 41**
Crit a: *Bohlmann* bands	NO	YES
Crit b: H-3;5;21		only H-21 and H-3 lower ppm
Crit c: H(a)-14 coupling const.	complex pattern	2 x *anti*
Crit d: H-3	doublet of doublet	doublet-like
Crit e: ^{13}C-Lounasmaa	lower ppm	higher ppm
Crit f: Quarternization	YES	NO
Crit g: *NOE* H-16-19 and H-3-21	NO	only H-3-21
		trans-quinolizidine

Based on our experimental data we conclude, that the double bond geometry definitely is of vital importance for the occurrence of „secondary cyclizations“ in the biosynthesis of C-mavacurine, strychnos and akuammiline alkaloids. As can be seen from every summary Table (2, 4 & 6), the conformational analysis of the respective *Z*-compounds (*Z*-benzylester **86**, *Z*-geissoschizoate **87** and *Z*-geissoschizine **41**) all fulfill the criteria for a *trans*-quinolizidine system. Coupling constants of *E*-compounds conclude a *cis*-quinolizidine, with a more complex picture in *E*-geissoschizine **35**, arising from additional conformational changes in the D-ring, which adopts a boat conformation (absence of 4 x *gauche* interactions in crit. c, Figure 39).

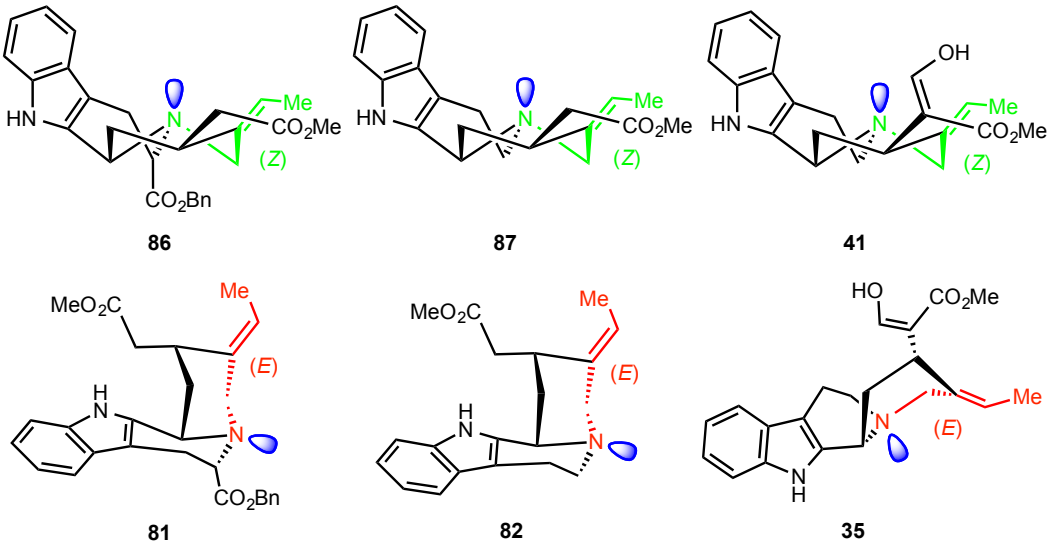


Figure 39: Preferred conformations of all studied geissoschizine derivatives.

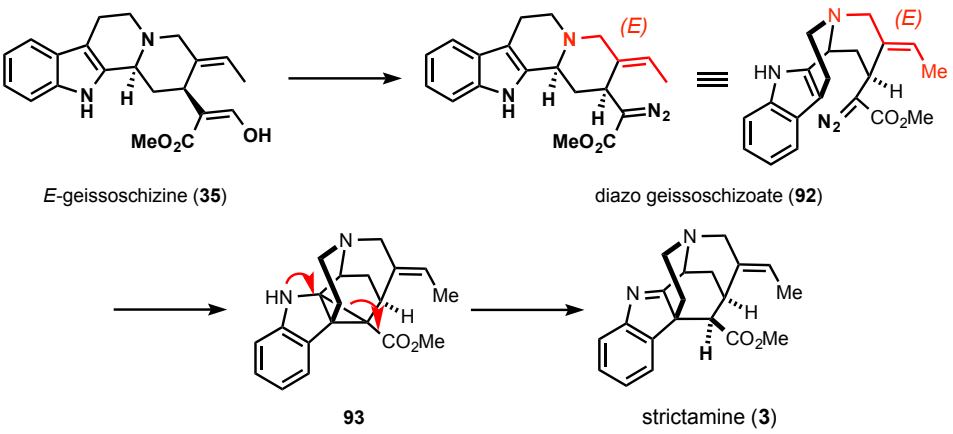
The conformational preference of the *cis*-quinolizidine for *E*-geissoschizine **35**, allows the conclusion that the double bond geometry at C-19-20 is the gateway for "secondary cyclizations" leading to C-mavacurine, strychnos and akuammiline alkaloids, and in parallel explains the exclusive occurence of the *E*-double bond in these biogenetically "downstream" metabolites.

5. Biomimetic synthetic approach to Strictamine

5.1 Introduction

For a biomimetic synthesis of strictamine starting from geissoschizine the double bond configuration is of huge importance. Staying once in the *cis* quinolizidine conformation a formal oxidative coupling between carbon atoms C-7 and C-16 should be more likely to occur. An intramolecular cyclopropanation of the indole double bond is a conceivable strategy to accomplish this bond formation.

A direct approach to strictamine (**3**) starting from *E*-geissoschizine (**35**) is envisioned *via* this cyclopropanation. Introduction of a diazogroup in α–position to the ester at C-16 (**92**) enables a cyclopropanation of the indole double bond under metal catalysis. Cyclopropane **93** could be opened by the indole nitrogen resulting in strictamine (**3**) in one step (Scheme 18).



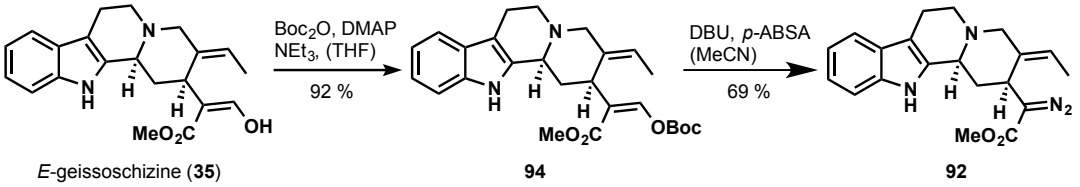
E-geissoschizine (**35**) diazo geissoschizoate (**92**)

93 strictamine (**3**)

Scheme 18: Biomimetic approach *via* cyclopropanation.

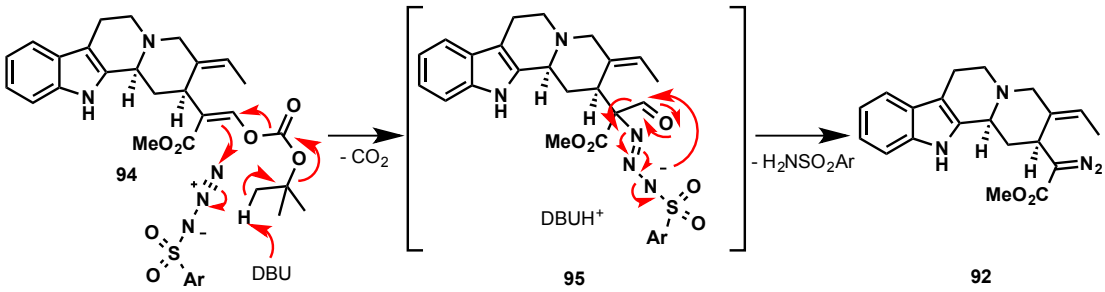
5.2 Results and discussion

A direct diazo transfer from *E*-geissoschizine (**35**) to α-diazo ester **92** with DBU and *p*-ABSA did not work and only leads to decomposition of the starting material. Aprotic basic conditions seem not to be reasonable for the conversion of *E*-geissoschizine (**35**). Instead, diazo transfer did work after transformation of the 1,3-dicarbonyl moiety to the mixed anhydride of the corresponding enolate. Reaction of *E*-geissoschizine (**35**) with Boc_2O resulted in carbonate (**94**) which was transferred to diazo geissoschizoate (**92**) with DBU and *p*-ABSA (Scheme 19).



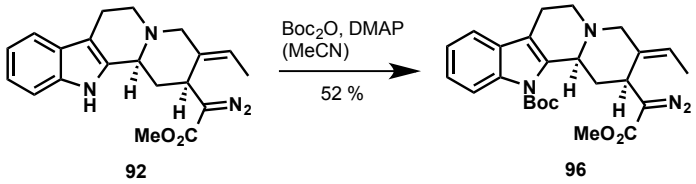
Scheme 19: Synthesis of diazo geissoschizoate (**92**).

The mechanism of this uncommon transformation is given in Scheme 20. Enol **94** reacts with the azide followed by deprotonation of the *tert*-butyl group by DBU under liberation of CO_2 resulting in intermediate **95**. Attack of the aldehyde by the negatively charged nitrogen triggers diazo formation under cleavage of one N-N bond. Diazo geissoschizoate (**92**) and the corresponding formamide are generated.



Scheme 20: Mechanism of the diazo transfer.

Reaction of diazo geissoschizoate (**92**) with Boc_2O resulted in Boc-protected indole **96** (Scheme 21).



Scheme 21: Protection of diazo geissoschizoate (**92**).

Conformational analysis of diazo compounds **92** and **96** shows a disparate picture. The IR spectrum of diazo geissoschizoate **92** shows one additional band at 2742 cm^{-1} (*Bohlmann* band) compared to Boc-protected diazo geissoschizoate **96** (Figure 40). This indicates that the Boc-protected *E*-**96** prefers a *cis*-quinolizidine conformation in contrast to *E*-**92** preferentially stays in a *trans*-quinolizidine conformation.

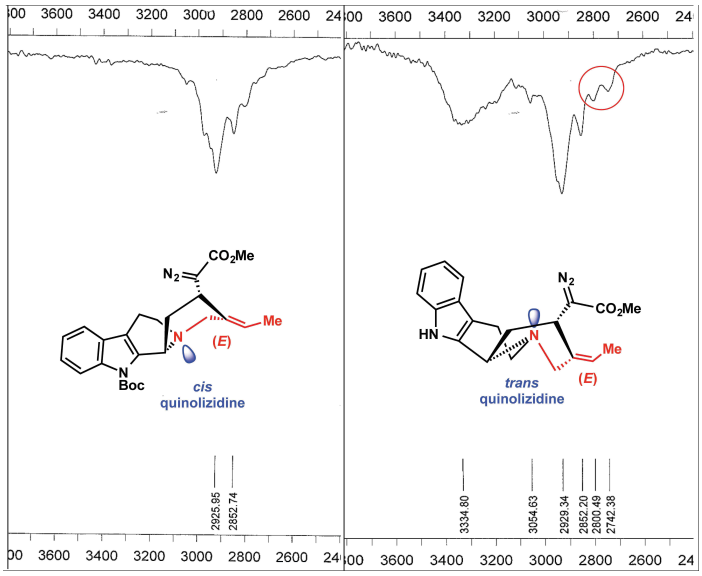


Figure 40: IR-spectra of diazo geissoschizoates **96** and **92**.

Comparison of the ^{1}H- and ^{13}C-NMR shifts strengthen this indication (Table 7, Figure 41). Especially the difference of H-3 (0.51 ppm) with a high-field-shift in *E*-**92** originates from *trans diaxial* interactions with the nitrogen lone pair possible in a *trans*-quinolizidine system.The same is true for the ^{13}C shift of

carbon atom C-21 with a difference of 6.9 ppm which arises from the conformational change at the nitrogen.

Table 7: Chemical shifts of diazo geissoschizoates **96** and **92** in comparison.

^{1}H	Boc *E*-isomer **96** (ppm)	*E*-isomer **92** (ppm)	difference
3	4,41	3,90	0,51
5	3,00 2,80	3,01 2,77	0,01 0,03
21	3,56 3,43	3,49 3,21	0,07 0,22
^{13}C			
3	56,2	56,1	0,1
6	21,7	20,0	1,7
14	32,8	32,8	0
15	32,9	31,5	1,4
21	62,7	59,6	6,9

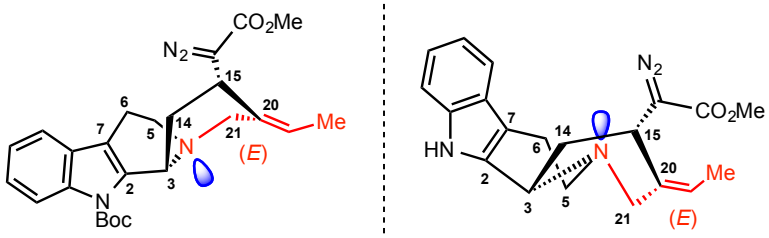


Figure 41: Numbering of diazo geissoschizoates **96** and **92**.

Coupling constant analysis is also in agreement with these results. Although the coupling pattern of the angular proton H-3 is "doublet-like" in Boc-protected *E*-**96**, this is not in objection to a *cis*-quinolizidine system. One *trans-diaxial* interaction (J = 9.9 Hz) between H-3 and H-14 can be explained by ring D adopting a boat conformation. The same proton in *E*-**92** displays a "triplet-like" coupling pattern (bs), therefore indicating a *trans*-quinolizidine system for *E*-**92** with ring D in a boat conformation (only *gauche* interaction). *NOE*-contacts of Boc-protected *E*-**96** and diazo geissoschizoate **92** suggest that the system avoids 1,3-allyl strain (Figure 42).

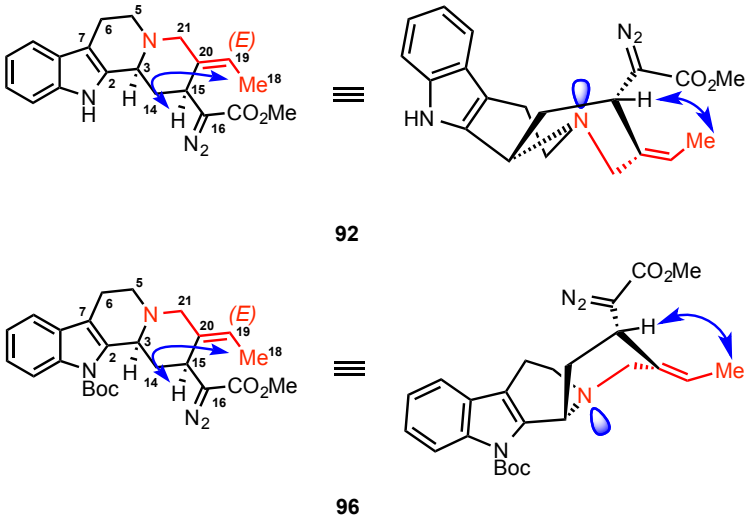
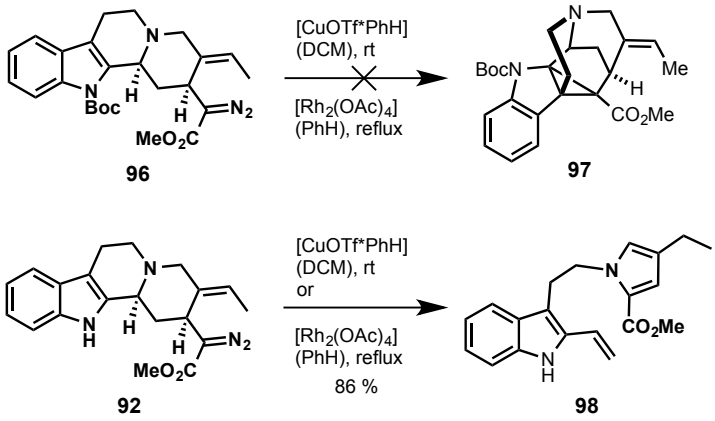


Figure 42: Characteristic *NOE* contacts for diazo geissoschizoates (**92** & **96**).

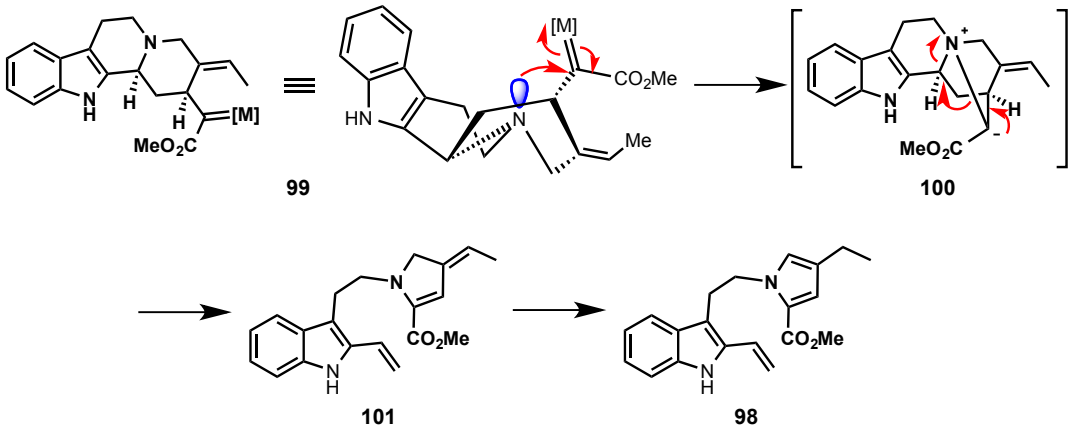
In summary, Boc-protected diazo geissoschizoate (**96**) prefers a *cis*-quinolizidine conformation whereas diazo geissoschizoate (**92**) favors a *trans*-quinolizidine conformation. Probably the bulky *tert*-butyl group at the indole nitrogen forces the system to change from a *trans* to a *cis* conformation.

Both compounds **96** and **92** were subjected to transition metal catalysis trying a cyclopropanation reaction with the indole double bond. As mentioned above, the quinolizidine conformation is of huge importance for a success of this reaction. Only the *cis* conformer should undergo cyclization reaction. The experimental results reflect the outcome of the conformational analysis. Whereas Boc-protected diazo geissoschizoate (**96**) did not react under the conditions, diazo geissoschizoate (**92**) showed a reaction resulting in pyrrole **98** (Scheme 22).



Scheme 22: Reactivity of diazo geissoschizoates **96** and **92**.

The formation of pyrrole **98** can be explained by a reaction of the transition metal carbenoid with the nitrogen lone pair of nitrogen atom N-4. This is only possible for a system staying in a *trans* quinolizidine conformation because the diazo group and the nitrogen lone pair are on the same side. Scheme 23 shows the mechanism of this transformation: Insertion into the nitrogen lone pair results in ylide **100** which undergoes fragmentation reaction to compound **101**. The exocyclic double bond isomerizes to pyrrole **98**.



Scheme 23: Formation of pyrrole **98**.

In case of the Boc-protected geissoschizoate **96** insertion into the nitrogen lone pair of N-4 does not take place. This can be explained by the different conformation: in case of a *cis* quinolizidine system the diazo group and the nitrogen lone pair point to different sides of the molecule. Unfortunately, cyclopropanation with the indole double bond does not occur under the chosen conditions. One possible explanation is the bulkiness of the *tert*-butyl group preventing a reaction of the indole double bond with the carbenoid and the more electron defficient indole double bond.

Quarternization of the nitrogen with benzyl bromide to avoid the insertion into the nitrogen lone pair and prefer cyclopropanation did not work sufficiently. This result is not surprising due to the observation that *trans* quinolizidine systems are not possible to be quarternized efficiently.

Another strategy is the intramolecular substitution of the diazo group by the indole double bond. This can be accomplished under acidic conditions. First, the Boc-protecting group is cleaved followed by a protonation of the diazo group to the diazonium salt. A nucleophilic attack of the indole double bond forms the bond between carbon atoms C-7 and C-16 and yields strictamine (**3**). Acidic conditions (TFA in DCM) at various temperatures only led to decomposition of the starting material and no substitution of the diazo group.

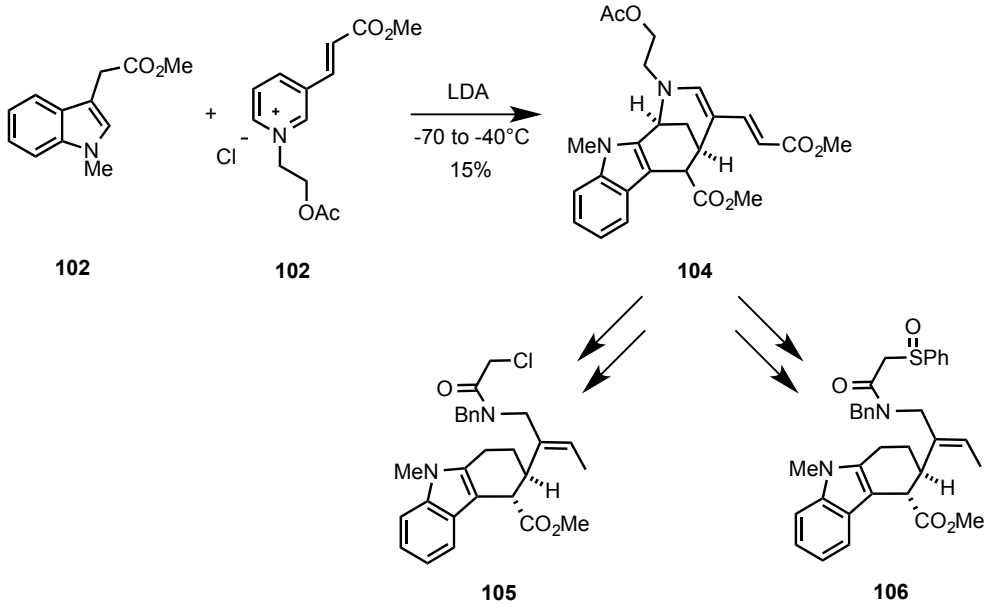
6. Synthetic approaches to Strictamine

6.1 Previous synthetic works

Although strictamine (**3**) was first isolated in 1966 no total synthesis of this natural product is published up to date. Nevertheless, some synthetic attempts towards a total synthesis of strictamine (**3**) are published and will be discussed here briefly.

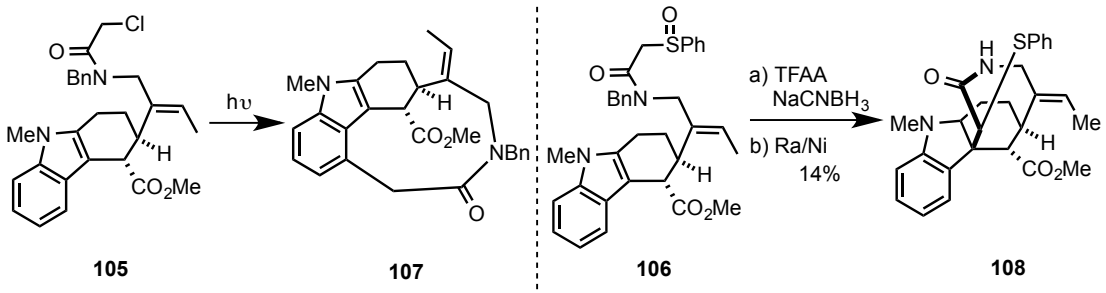
6.1.1 *Bosch*'s approach

First, the group of *Joan Bosch* described in 1996[80] a synthetic approach to strictamine (**3**) via the addition of enolates to pyridinium salt **102** yielding tetracycle **104**. This compound was transferred to sulfoxide **106** and α-chloro amide **105** (Scheme 24). Key steps of the synthesis are a *Pummerer* cyclization or a *Witkop* cyclization, respectively.



Scheme 24: Generation of sulfoxide **106** and α-chloro amide **105**.

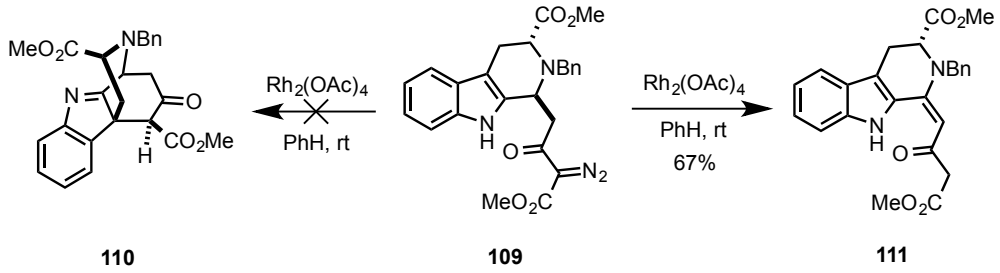
Unfortunately, *Witkop* cyclization led to tetracycle **107** via a cyclization to the indole 4-position instead of the 3-position. *Pummerer* cyclization resulted in a cyclization to the 3-position (**108**) but only in a low yield of 14%. Further transformations of compound **108** to strictamine (**3**) were not successful (Scheme 25).



Scheme 25: *Pummerer* and *Witkop* cyclization approach to strictamine (**3**).

6.1.2 *Cook*'s approach

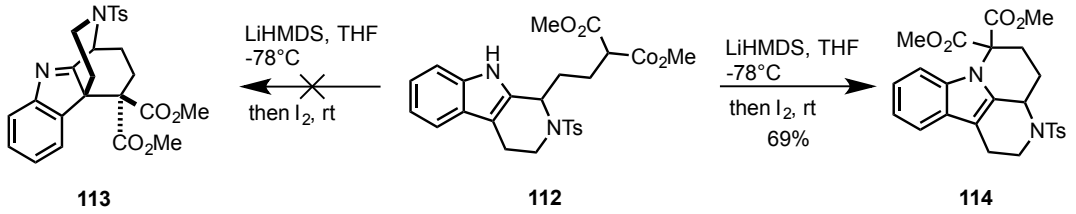
The group of *James M. Cook* investigated a cyclopropanation strategy in 2012.[81] Therefore, they synthezied diazo compound **109** in a few steps. Unfortunately, cyclopropanation attempts did not lead to the strictamine skeleton **110** but to compound **111** instead (Scheme 26).



Scheme 26: Cyclopropanation approach to strictamine (**3**).

6.1.3 *Zhu*'s appraoch

In 2013, the group of *Jieping Zhu*[82] tried to develop an oxidative couling of a dianion for the total synthesis of strictamine (**3**). Therefore, they synthesized key intermediate **112** in a few steps. Deprotonation with LiHMDS followed by the addition of iodine should result in the formation of compound **113**. Instead, cyclization to the indole nitrogen (**114**) occured (Scheme 27).

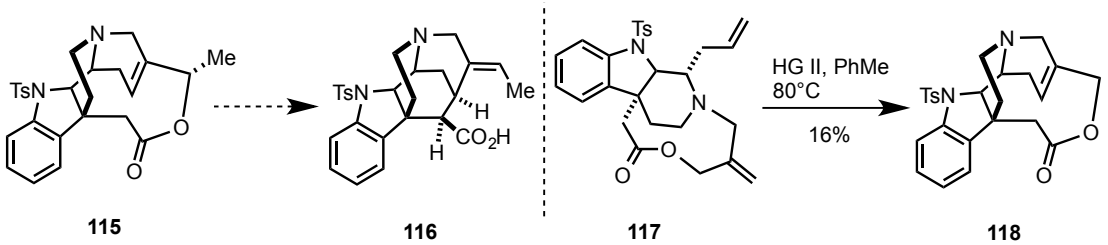


113 **112** **114**

Scheme 27: Oxidative coupling approach to strictamine (**3**).

6.1.4 *Tokuyama*'s approach

The group of *Hidetoshi Tokuyama* tried to develop an *Ireland Claisen* rearangement as a keystep towards the total synthesis of strictamine (**3**) in 2013.[83] Therefore, keyintermediate **115** should be synthesized. Their strategy was based on a ring closing metathesis of compound **117** resulting in the rearrangement precursor **118**. Unfortunately, metathesis reaction only proceeded in a low yield of 16% (Scheme 28). A transformation to strictamine (**3**) is not reported.



115 **116** **117** **118**

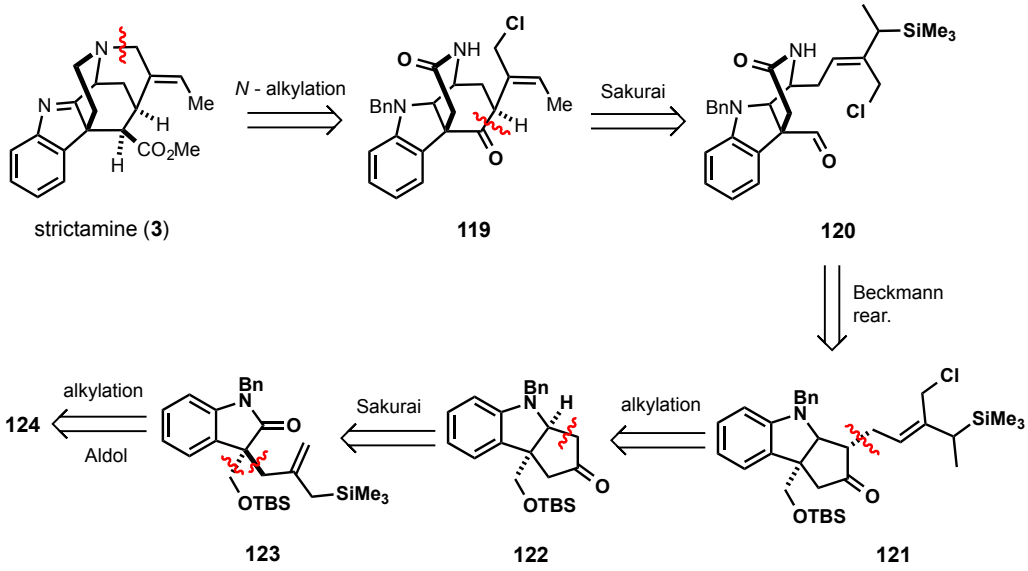
Scheme 28: *Ireland Claisen* approach to strictamine (**3**).

6. Synthetic approaches to Strictamine

6.2 1st Synthetic approach

6.2.1 Retrosynthetic analysis

The first synthetic approach to strictamine (**3**) starts with benzyl protected oxindole (**124**). The keysteps of this synthesis are two *Sakurai* allylations. Scheme 29 shows the reatrosynthesis in detail. Alkylation of oxindole**124** with an allyl silane followed by aldol reaction with formaldehyde gives access to compound **123** with the quarternary carbon center at C-7. Reduction of the amide yields an hemiaminal which can be transformed under *Lewis* acidic conditions *via* an intramolecular *Sakurai* allylation to tricycle **122**. A second alkylation α to the ketone introduces the allyl silane side chain (**121**).

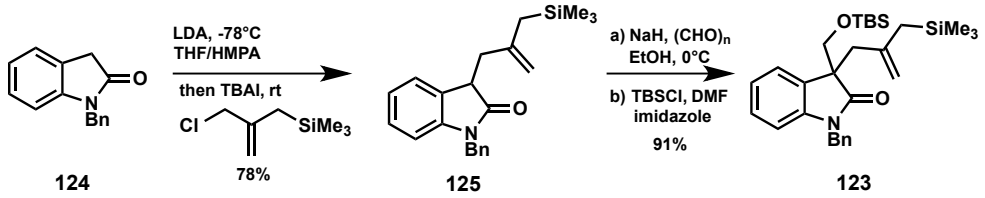


Scheme 29: 1st Generation retrosynthesis of strictamine (**3**).

The alkylation should proceed *cis* relative to the primary alcohol due to the open book effect. The alkylation can procced at two positions relative to the ketone but one of both is a neopentylic position and should therefor be less fevoured. A subsequent Beckmann rearrangement produces the six-membered lactame **120**. A second intramolecular *Sakurai* allylation generates the six-membered carbocycle of compound **119**. *N*-Alkylation of the allyl chloride gives access to the carbon skeleton of strictamine (**3**) which can be accomplished in a few transformations.

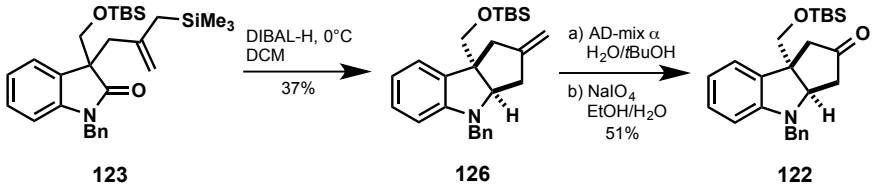
6.2.2 Results and discussion

The synthesis started with an alkylation of oxindole (**124**) with an allyl chloride and LDA in THF/HMPA under the influence of TBAI. Aldol reaction under basic condiditions with paraformaldehyde yielded the primary alcohol which was protected with TBSCl. Thereby the quarternary carbon center at C-7 (**123**) is constructed (Scheme 30).



Scheme 30: Synthesis of quarternary carbon center at C-7.

Reduction of amide **123** yielded a hemiaminal which was *in-situ* converted to tricycle **126** in a *Sakurai* allylation. Various reaction conditions to perform this transformation were tested (Table 8). The best conditions were 1 equivalent DIBAL in DCM at 0°C. However, the yield of this transformation was very low (37%) due to an overreduction of the amide to the amine. Dihydroxylation follwed by periodate cleavage yielded ketone **122** (Scheme 31).

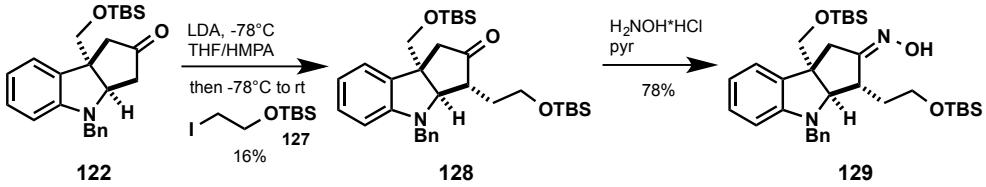


Scheme 31: First *Sakurai* allylation and oxidation of the double bond.

Table 8: Conditions for cyclization of compound **123** to **126**.

eq	reagent	solvent	temp	outcome
1	Red-Al	THF	0°C	25% **126**
1	Red-Al	THF	rt	compl. reduction
1	Red-Al	THF	-78°C	SM
1	DIBAL	DCM	0°C	37% **126**
1	DIBAL	DCM	-78°C	SM
1	DIBAL	DCM	-30°C	SM
1	DIBAL	THF	0°C	33% **126**
1	Me_2AlCl + DIBAL	DCM	0°C	compl. reduction
3	Meerwein salt	DCM	rt	decomposition
1.5	$NaBH_4$	MeOH	rt	SM
1	AlH_3*NMe_2Et	THF	-20°C	compl. reduction
0.3	AlH_3*NMe_2Et	THF	-78°C	SM
1	BH_3	DCM	-78°C	decomposition
1	$HZrCp_2Cl$	THF	0°C	SM
1	$AlEt_3$	DCM	-78°C to rt	SM

Alkylation of ketone **122** with iodide **127**[84] and LDA in THF/HMPA proceedws in a very low yield of 16%. Transformation of ketone **128** to oxime **129** with hydroxylamine hydrochloride in pyridine worked fine (Scheme 32).



Scheme 32: Alkylation of ketone **122** and transformation to the oxime (**129**).

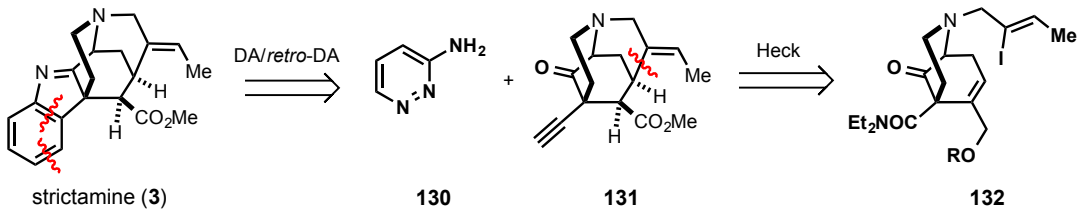
Unfortunately, mesylation of oxime **129** with MsCl and pyridine in DCM did not work and only hydrolysation back to ketone **128** was observed. Due to three inefficient transformations (**123** to **128**, overall yield of 3%) at the beginning of the synthesis this approach was abandened.

6. Synthetic approaches to Strictamine

6.3 2nd Synthetic approach

6.3.1 Retrosynthetic analysis

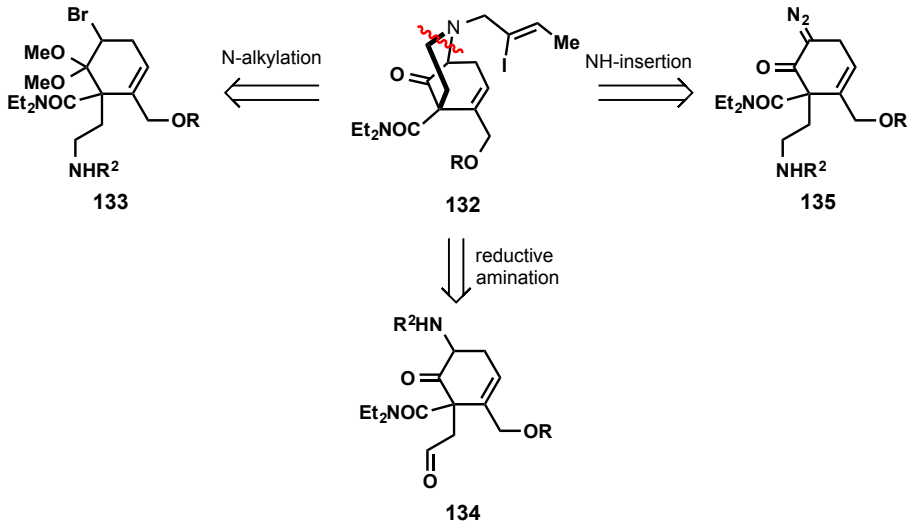
The first strategic step of the second retrosynthesis is a *Diels-Alder*/*retro*-*Diels-Alder* sequence to build up the indolenine core starting with alkine **131** and pyridazine **130**.[85] Condensation of the ketone (**131**) with the primary amine should enable an intramolecular *Diels-Alder* reaction with the alkine followed by a *retro*-*Diels-Alder* reaction under release of nitrogen. The alkine can be synthesized *via* an *Ohira-Bestmann* reaction using the aldehyde that can be derived from amide **132**. A *Heck* cyclization of vinyl iodide **132** yields the piperidine ring of compound **131**. This reaction should also produce an enol ether which can be converted to a methyl ester (Scheme 33).



strictamine (**3**) **130** **131** **132**

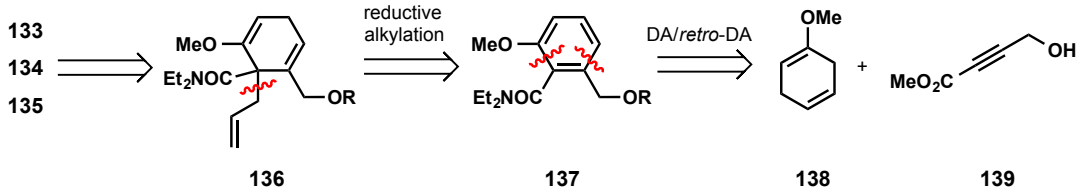
Scheme 33: 2nd Generation retrosynthesis of strictamine (**3**), part 1.

Three different approaches are envisioned to build up bicycle **132**. First approach contains a *N*-alkylation strategy starting from bromide **133** to close the sixmembered ring. Second strategy deals with a *NH*-insertion *via* α-diazo ketone **135**. The third possibility is a reductive amination with aldehyde **134** (Scheme 34).



Scheme 34: 2nd Generation retrosynthesis of strictamine (**3**), part 2.

All three building blocks (**133**-**135**) are accessible from precursor **136** by functional group interconversions. This key intermediate can be synthesized out of enol ether **138** and propargyl alcohol **139** (Scheme 35).



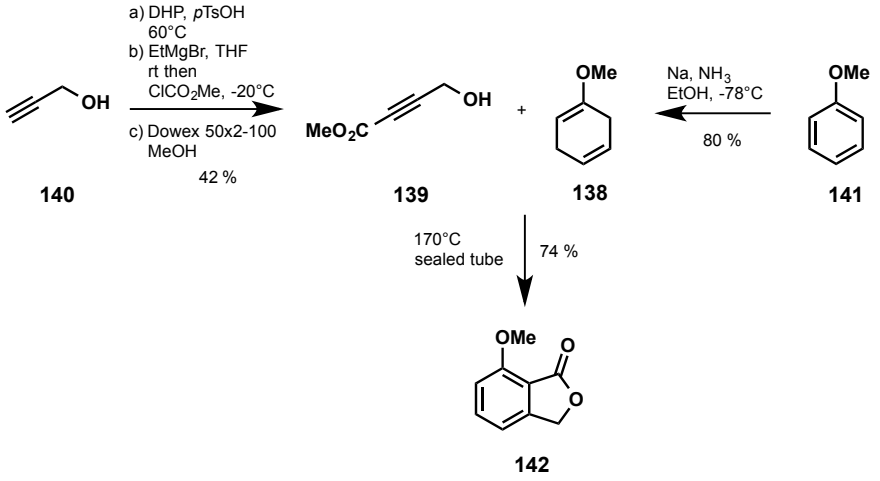
Scheme 35: 2nd Generation retrosynthesis of strictamine (**3**), part 3.

Compound **136** was generated by a reductive alklyation with allyl bromide starting from aromatic compound **137**. The aromatic ring was synthesized *via* a *Diels-Alder*/*retro-Diels-Alder* approach starting from isomerized diene **138** and alkine **139**.

6.3.2 Results and discussion

The synthesis started with the production of both *Diels-Alder* building blocks. *Birch* reduction of anisol (**141**) by the use of sodium in liquid ammonia provided diene **138**.[86] Alkine **139** was synthesized in three steps out of propargyl alcohol (**140**) protected as a tetrahydropyrane followed by

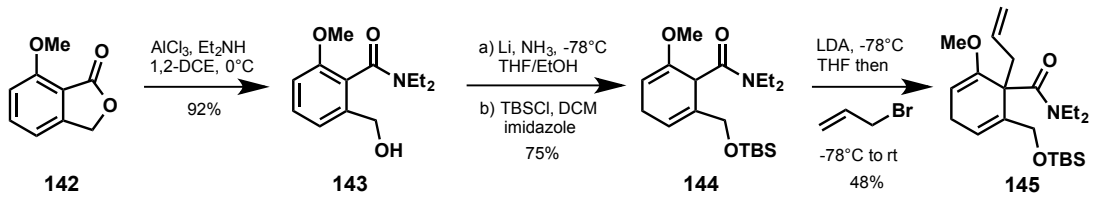
carboxylation of the alkine with methyl chloroformate. A subsequent deprotection of the alcohol with an acidic ion exchange resin in methanol provided the desired product **139**.[87] Mixing diene **138** and alkine **139** in a sealed tube and heating it up to 170°C delivered aromatic lactone **142** (Scheme 36).[88]



Scheme 36: Synthesis of aromatic compound **142**.

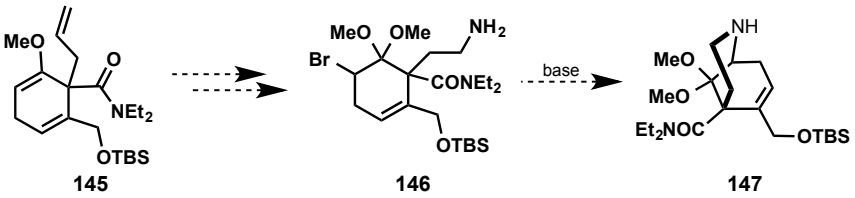
To avoid a defunctionalization of the benzylic alcohol under *Birch* reduction conditions, the lactone has to be opened first due to the fact that the deprotonated alcohol prohibits further alectron transfer to the benzylic position.

Opening of the lactone **142** with diethylamine under *Lewis* acidic conditions gave amide **143**. *Birch* reduction of compound **143** followed by protection of the alcohol with TBSCl provided diene **144**. Unfortunately, allylation proceeded only in 48% yield (Scheme 37).



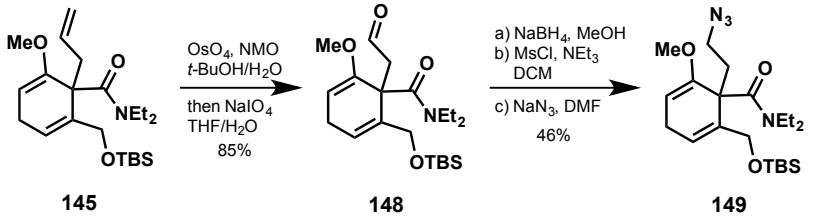
Scheme 37: Reductive alkylation generating the central compound **145**.

With intermediate **145** in hands we were able to address the keystep of our first approach (intramolecular *N*-alkylation, see Scheme 34). Therefore the allyl group was converted to a primary amine and the methyl enol ether to an α-bromo dimethoxyacetal (**146**, Scheme 38).



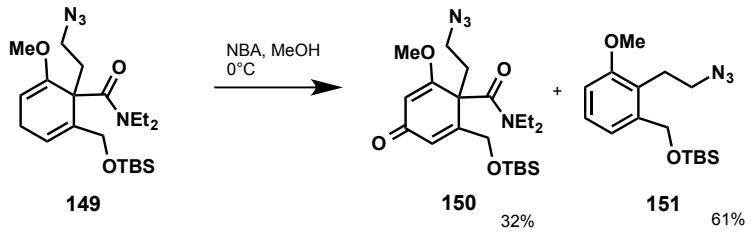
Scheme 38: Intramolecular *N*-alkylation strategy.

Dihydroxylation of the allyl side chain with OsO_4 and NMO followed by a periodate cleavage gave aldehyde **148**. Reduction of the aldehyde by the use of $NaBH_4$ followed by a mesylation - substitution protocol with MsCl and NaN_3 provided azide **149** (Scheme 39).



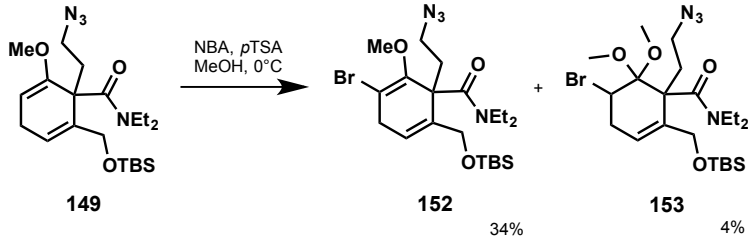
Scheme 39: Transformation of the allyl group to azide **149**.

In principle, the addition of one equivalent NBA to the enol ether in methanol should provide the desired α-bromo dimethoxyacetal **153**. But unfortunately, the use of one equivalent NBA in methanol at 0°C resulted in an oxidation of the bisallylic position to ketone **150** and aromatization to compound **151** (Scheme 40).



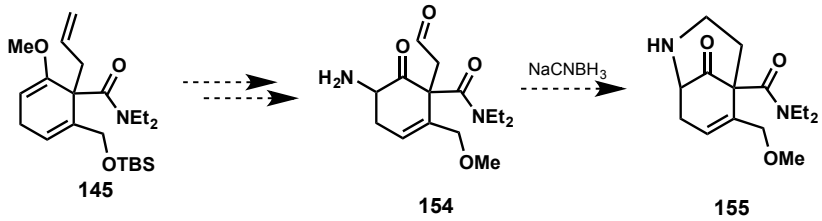
Scheme 40: Oxidation products **150** and **151** with NBA in MeOH.

Moreover, addition of a catalytic amount of *para*-toluenesulfonic acid to suppress the elimination reaction resulted in the generation of α-bromo dimethoxyacetal **153** in only little amounts. Mostly, elimination of methanol to bromo enol ether **152** was observed or a complete decomposition (Scheme 41). Using NBS or NIS instead of NBA gave the same results.



Scheme 41: Formation of α-bromo dimethoxyacetal **153**.

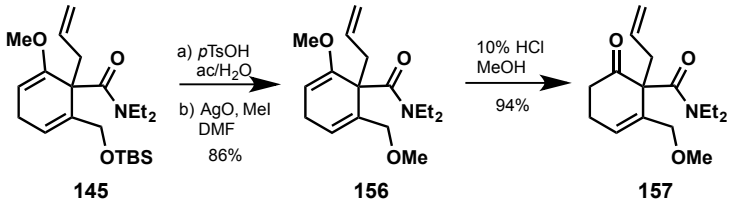
Based on these results, the reductive amination strategy to construct the bicycle **155** was tested. Therefore the allyl group was transformed to an aldehyde and the methyl enol ether to an α-amino ketone (Scheme 42).



Scheme 42: Intramolecular reductive amination strategy.

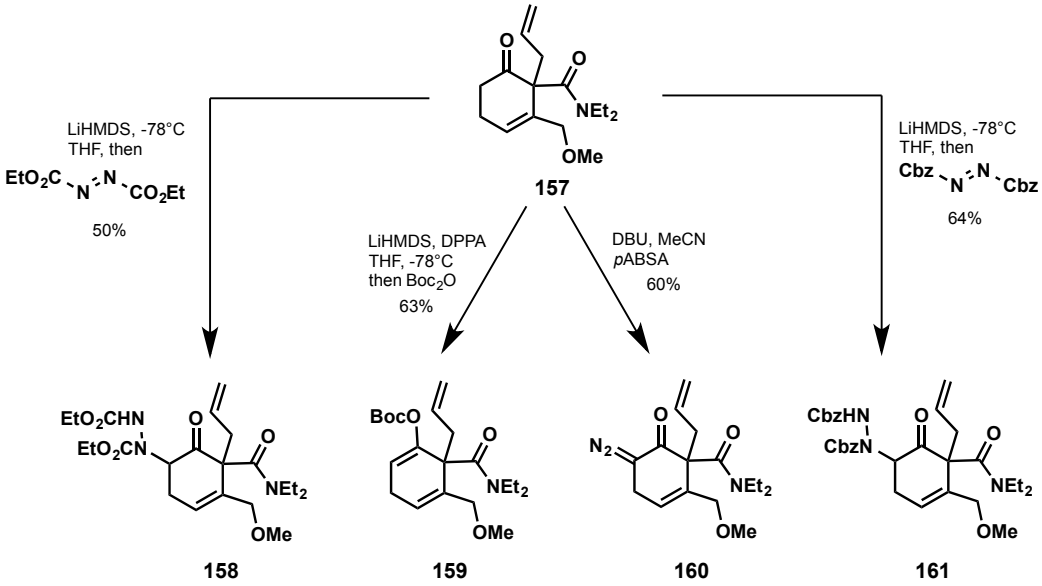
For the hydrolysis of the methyl enol ether to the corresponding ketone aqueous acidic media is neccessary. A deprotection of the TBS-protected allylic alcohol also occured under this conditions. Due to that fact, the allylic

alcohol was selectively deprotected with *para*-toluenesulfonic acid in a mixture of acetone and water and then methylated with methy iodide and silver(II)oxide to methyl ether **156**. Hydrolysis of the enol ether to ketone **157** was achieved by the use of 10% aqueous HCl in methanol (Scheme 43).



Scheme 43: Hydrolysis to ketone **157**.

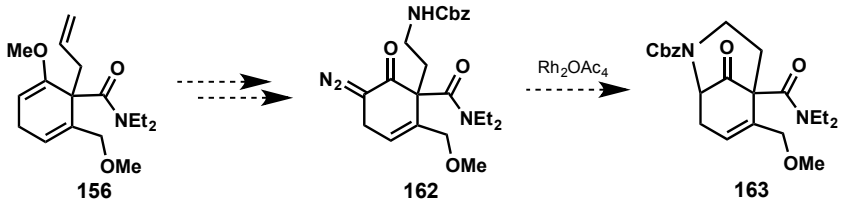
Diazotation with *para*-acetamidosulfonyl azide and DBU to α-diazo ketone **160** worked as well as a 1,4-addition of the enolate to azodicarboxylates (**158**) or (**161**). Addition of the enolate to DPPA followed by the addition of Boc_2O only resulted in the formation of enol ether **159** (Scheme 44).



Scheme 44: α-Functionalization of ketone **157**.

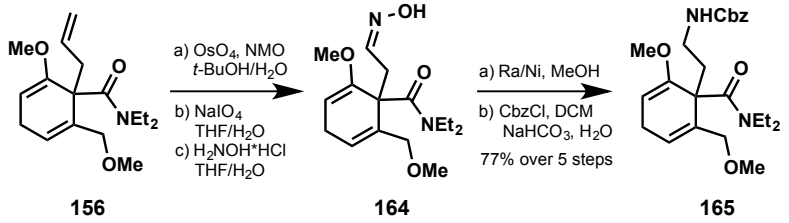
Ozonisation of the allyl group of α-diazo ketone **160** to the corresponding aldehyde only led to decomposition. Moreover, further functionalization attempts of the *Michael*-addition products **158** and **161** only eliminated to the corresponding cyclohexadienone moiety.

At that point we focused on our third strategy to get access to bicycle **163** *via* an intramolecular *NH*-insertion reation of α-diazo ketone **162** (Scheme 45).



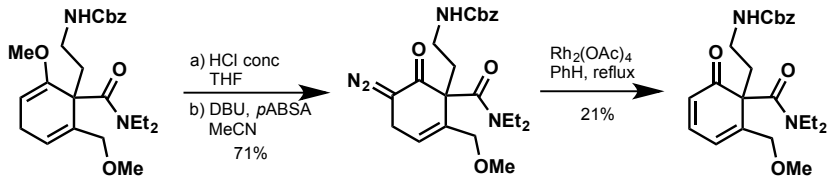
Scheme 45: *NH*-Insertion strategy.

Therefore the allyl group was transformed into a carbamate moiety. This was accomplished by dihydroxylation of the double bond with OsO_4 and NMO followed by a periodate cleavage to the aldehyde. This aldehyde was condensed with hydroxylamie to oxime **164**. Reduction of the oxime to the primary amine with *Raney* nickel and its subsequent protection with CbzCl generated carbamate **165** (Scheme 46).



Scheme 46: Transformation to Cbz-carbamate **165**.

Hydrolysis of the methyl enol ether was performed with concentrated HCl in THF followed by a diazotation with ABSA and DBU to α-diazo ketone **162**. As depicted in Scheme 47 and Table 9 it was not possible to perform a N-H insertion under Rh-catalyis. We only observed the elimination product **166** or no consumption of the starting material. Also the use of CuOTf in DCM did not give the desired product.



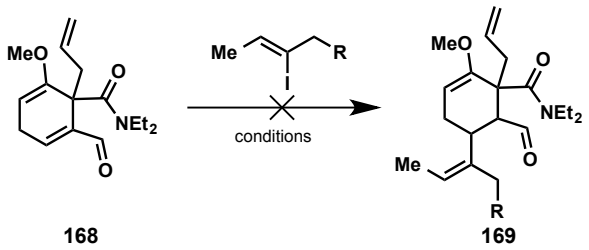
165 **162** **166**

Scheme 47: *NH*-Insertion attempts of α-diazo ketone **162**.

Table 9: Conditions for *NH*-insertion.

eq	catalyst	solvent	temp.	outcome
0.01	$Rh_2(OAc)_4$	PhH	reflux	elimination (**166**)
0.01	$Rh_2(OAc)_4$	DCM	rt	SM
0.01	$Rh_2(OAc)_4$	DCM	reflux	elimination (**166**)
0.02	CuOTf	DCM	rt	SM + elimination (**166**)

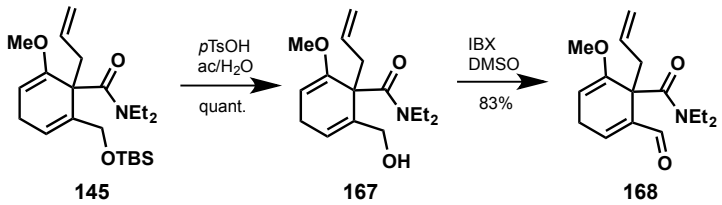
Due to the fact that the bisallylic system (**136**) seemed to oxidize very easily and all α-substituted ketones (**158**, **161** & **162**) tended to eliminate to the corresponding cyclohexadienones, the strategy was changed. We decided to remove the remainig double bond to avoid these products. One possibility is a 1,4-addition of the ethylidene side chain to α,β-unsaturated aldehyde **168** (Scheme 48).



168 **169**

Scheme 48: 1,4-Addition attempts to α,β-unsaturated aldehyde **168**.

Therefore, deprotection of the silyl ether with *para*-toluenesulfonic acid yielded primary allylic alcohol **167** which was oxidized subsequently by IBX to α,β-unsaturated aldehyde **168** (Scheme 49).



Scheme 49: Transformation to α,β-unsaturated aldehyde **168**.

Unfortunately, all attempts to perform a 1,4-addition to compound **168** (Table 10, Scheme 48) with vinyl iodides **170** - **172** were unsuccessful due to the instability of the generated cuprate of the corresponding vinyl iodides **170** - **172** (Figure 43).[70]

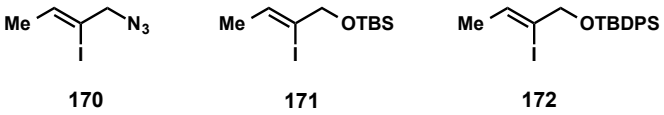


Figure 43: Vinyliodides tested for 1,4-addition.

Table 10: Conditions for the 1,4-addition.

vinyl iodide	reagent	copper-source	solvent	enone	outcome
1	4.2 eq *t*BuLi, -78°C, 15min	1.05 eq CuCN, 0°C, 30min	Et_2O	1 eq, -78°C to 0°C	decomp.
1	4.2 eq *t*BuLi, -78°C, 15min	1.05 eq CuCN, -35°C, 30min	Et_2O	1 eq, -78°C to -35°C	decomp.
1	4.2 eq *t*BuLi, -78°C, 15min	1.05 eq CuCN, -60°C, 30min	Et_2O	1 eq, -78°C to rt	decomp.
1	4.2 eq *t*BuLi, -78°C, 15min	2.1 eq CuI, -40°C, 10min	Et_2O	1 eq, -78°C to rt	decomp.
1	1.1 eq *n*BuLi, -100°C, 15min	1.05 eq CuCN*2LiCl, -78°C, 15min	THF/Et_2O/ hexane	1 eq, -78°C to rt	decomp.
1	1.1 eq *n*BuLi, -78°C, 15min	1.05 eq CuCN*2LiCl, -78°C, 15min	THF/Et_2O/ hexane	1 eq, -78°C to rt	decomp.
1	2.2 eq *t*BuLi,	1.05 eq	Et_2O	1eq,	decomp.

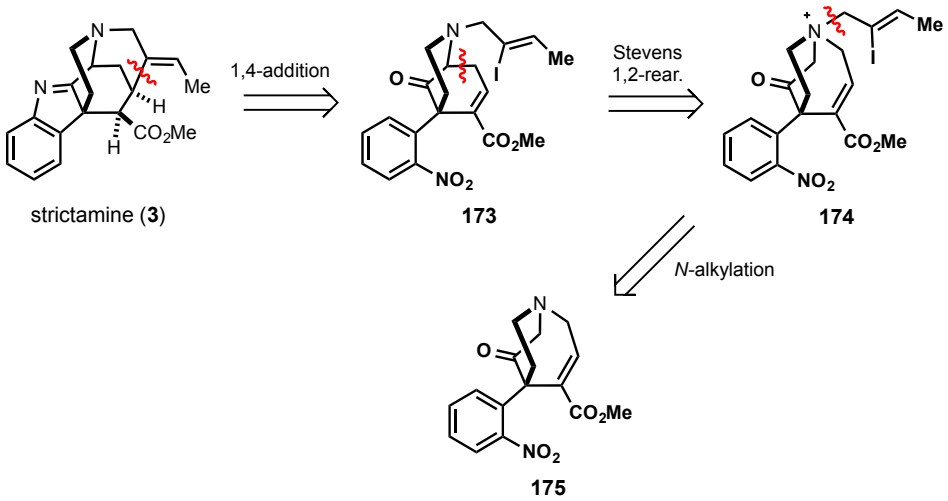
	-78°C, 15min	CuCN*2LiCl, -40°C, 30min		-78°C to rt	
1	3 eq Zn, rt, 3h	1.05 eq CuCN*2LiCl, -40°C, 10min	THF	1eq, -78°C	decomp.
1	1.1 eq *i*PrMgCl*LiCl, -78°C, 2h	1.05 eq CuCN*2LiCl, -40°C, 10min	THF	1eq, -78°C to rt	decomp.
1	1.1 eq *i*PrMgCl*LiCl, 0°C, 2h	1.05 eq CuCN*2LiCl, -40°C, 10min	THF	1eq, -78°C to rt	decomp.
1	1.5 eq Mg, rt	-	Et_2O	1eq, -40°C	decomp.
1	1.5 eq Mg, rt	0.5 eq CuCN, -50°C	Et_2O	1eq, -78°C to rt	decomp.
1	1.2 eq Mg, rt	0.5 eq CuCN, -45°C	THF	1eq, -78°C	decomp.
2	2.2 eq *t*BuLi, -78°C, 15min	1.05 eq CuCN*2LiCl, -40°C, 30min	Et_2O	1eq, -78°C to rt	decomp.
2	1.1 eq *n*BuLi, -100°C, 15min	1.05 eq CuCN*2LiCl, -40°C, 30min	THF/Et_2O/ hexane	1eq, -78°C to rt	decomp.
2	1.1 eq *n*BuLi, -78°C, 15min	1.05 eq CuCN*2LiCl, -40°C, 30min	THF/Et_2O/ hexane	1eq, -78°C to rt	decomp.
2	3 eq Zn, 1.2 eq TMSCl, rt, 3h	1.05 eq CuCN*2LiCl, -40°C, 30min	THF	1 eq, -78°C to 0°C	decomp.
2	1.1 eq *i*PrMgCl*LiCl, 0°C, 2h	1.05 eq CuCN*2LiCl, -78°C, 15min	THF	1 eq, -78°C to 0°C	decomp.
3	2.1 eq *t*BuLi, -100°C, 15min	0.5 eq CuCN, -78°C, 30min	Et_2O	1eq, -78°C	decomp.
3	2.1 eq *t*BuLi, -78°C, 15min	0.5 eq CuCN, -45°C, 30min	Et_2O	1eq, -45°C	decomp.
3	1.2 eq Mg, rt	0.5 eq CuCN, -45°C, 30min	THF	1eq, -78°C to rt	decomp.

In all cases a decomposition of the vinyl iodide was observed in terms of deprotection, S_N2'-displacement or nucleophilic addition to the azide respectively.

6.4 3rd Synthetic approach

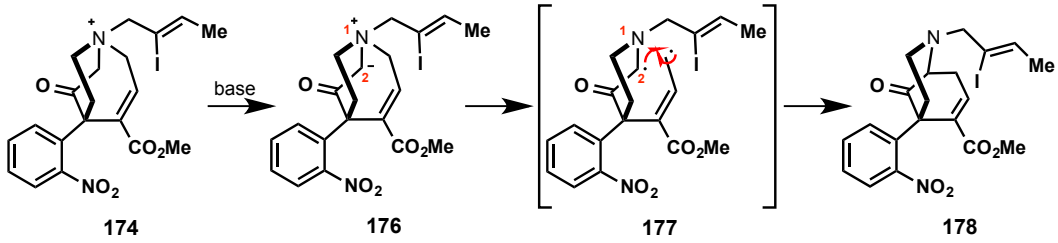
6.4.1 Retrosynthetic analysis

Key step of the 3rd retrosynthesis of strictamine (**3**) is a *Stevens* [1,2]-rearrangement of ammonium salt **174** which establishes the six-membered carbocycle in compound **173**. The ammonium salt is generated by a *N*-alkylation of tertiary amine **175**. The last ring to the strictamine carbon skeleton is closed by a 1,4-addition of vinyl iodide **173** to the α,β-unsaturated methyl ester. Reduction of the nitro group results in the formation of strictamine (**3**, Scheme 50).



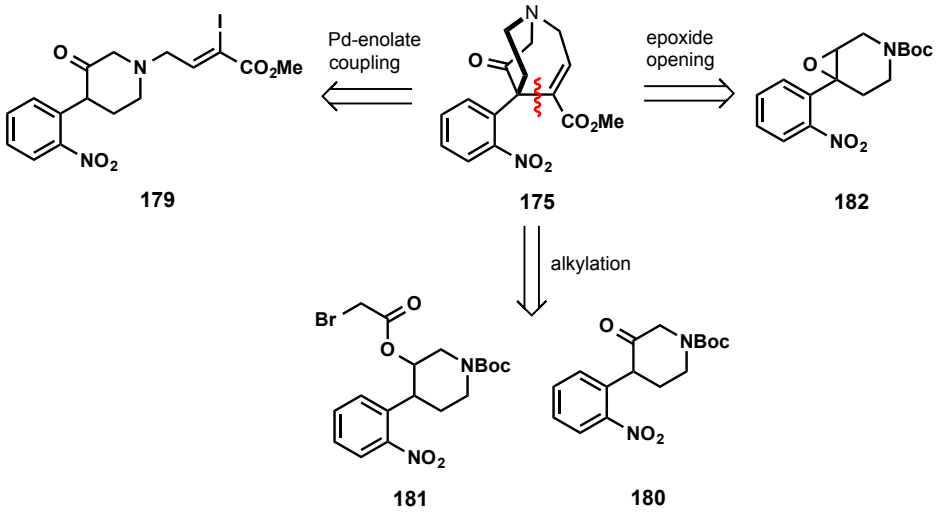
Scheme 50: 3rd Generation retrosynthesis of strictamine (**3**), part 1.

Mechanistically, the *Stevens* 1,2-rearrangement proceeds *via* a radical mechanism. First ammonium salt **174** gets deprotonated to ylide **176** at the most acidic position. The ylide decomposes to biradical **177** which is best stabilized (allylic position).[89] After recombination of the radicals the allylic part did a formal migration from the 1- to the 2-position (Scheme 51).



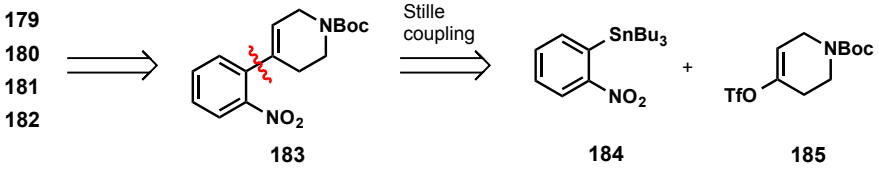
Scheme 51: Mechanism of the *Stevens* 1,2-rearrangement.

The precursor of the *Stevens* 1,2-rearrangement (tertiary amine **175**) could be generated in different ways. A short way is an intramolecular palladium catalyzed enolate coupling of vinyl iodide **179** to generate the quarternary carbon center.[90] This could be also accomplished by an intra- or itermolecular alkylation of ketone **180** or ester **181**. The third strategy is based on a *Lewis* acid triggered epoxide opening followed by a subsequent trapping of the benzylic carbenium ion by a nucleophile (Scheme 52).



Scheme 52: 3rd Generation retrosynthesis of strictamine (**3**), part 2.

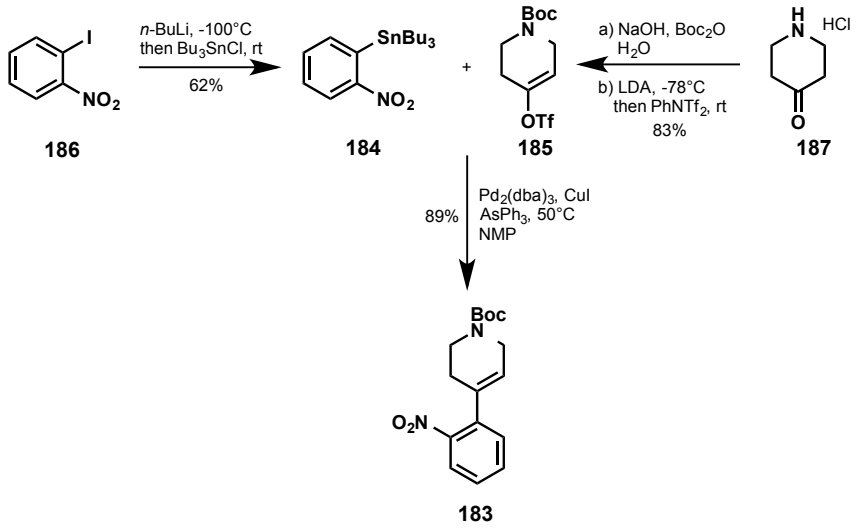
All compounds were synthesized by hydroboration or epoxidation of olefine **183**. This olefinewas produced *via* a *Stille* coupling reaction starting from stannane **184** and vinyl triflate **185** (Scheme 53).



Scheme 53: 3rd Generation retrosynthesis of strictamine (**3**), part 3.

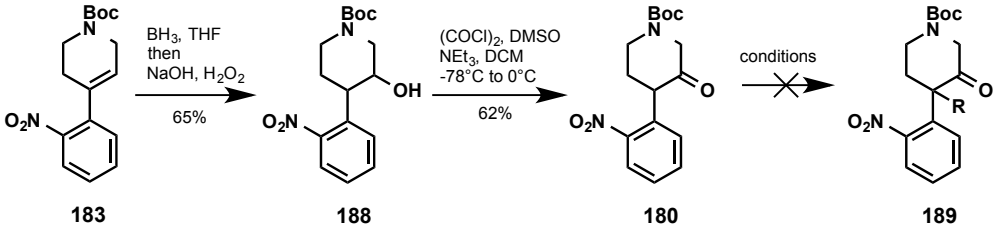
6.4.2 Results and discussion

The synthesis started with the generation of stannane **184** and triflate **185**. 2-Iodo nitrobenzene (**186**) was lithiated with *n*-BuLi at -100°C and then transmetallated to stannane **184** with tributyltin chloride.[91] The synthesis of vinyl triflate **185** started with piperidinone*HCl (**187**). After Boc-protection of the amine[92] the ketone was transferred to the vinyl triflate with LDA and $PhNTf_2$.[93] *Stille* coupling to compound **183** was performed with a catalytic amount of CuI and $Pd_2(dba)_3$ with $AsPh_3$ as a ligand in NMP at 50°C in good yields (Scheme 54).[94]



Scheme 54: *Stille* coupling of vinyl triflate **185** and stanne **184**.

Hydroboration of the benzylic double bond in compound **183** worked fine with borane followed by an oxidative work-up with hydrogen peroxide. *Swern* oxidation yielded ketone **180** in a moderate yield of 62% (Scheme 55).



Scheme 55: Hydroboration and oxidation to ketone **180**.

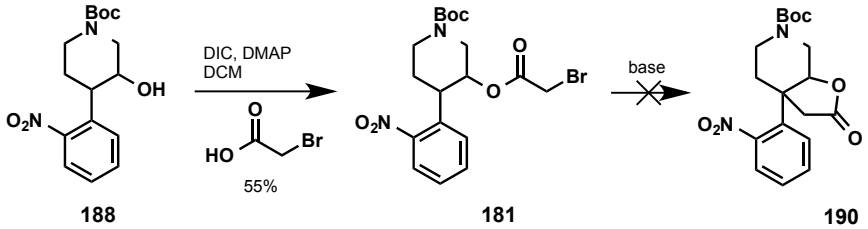
But unfortunately, alkylation or *Aldol* reaction of ketone **180** was not successsful under various conditions (Table 11).

Table 11: Alkylation conditions of ketone **180**.

base	temp.	solvent	cat.	electrophile	temp.	outcome
2.5 eq KO*t*Bu	rt	THF	0.05 eq $Pd(PPh_3)_4$	MeO_2C, I, OTBS, 1.5 eq[95]	reflux	decomp.
1.1 eq KO*t*Bu	rt	THF	0.1 eq $Pd(PPh_3)_4$	MeO_2C, I, OTBS, 1.5 eq	rt	decomp.
1.1 eq KOtBu	rt	THF	0.1 eq $Pd(PPh_3)_4$	I, OTBS, 2 eq[96]	rt	decomp.
1.5 eq NaH	0°C	DMF	-	Br, 10 eq	rt	decomp.
1.5 eq LiHMDS	-78°C	THF	-	Br, 10 eq	-78°C to rt	decomp.
1.5 eq LDA	-78°C	THF	-	Br, 10 eq	-78°C to rt	decomp.
1.5 eq KO*t*Bu	0°C	THF	-	CO_2Me, 2 eq	0°C	decomp.
1.5 eq NaH	0°C	THF	-	O, SPh, 10 eq[97]	rt	decomp.
1.5 eq NaH	0°C	THF	-	O, SPh, 1.5 eq	rt	decomp.

In every case only decomposition of the starting material was observed. Also an intramolecular alkylation with ester **181** was unsuccessful. This ester was generated starting from alcohol **188** and bromoacetic acid under the influence

of DIC. Precursor **181** should be transferred to five-membered lactone **190** under basic conditions (Scheme 56, Table 12). Unfortunately, only the free alcohol **188** was observed.

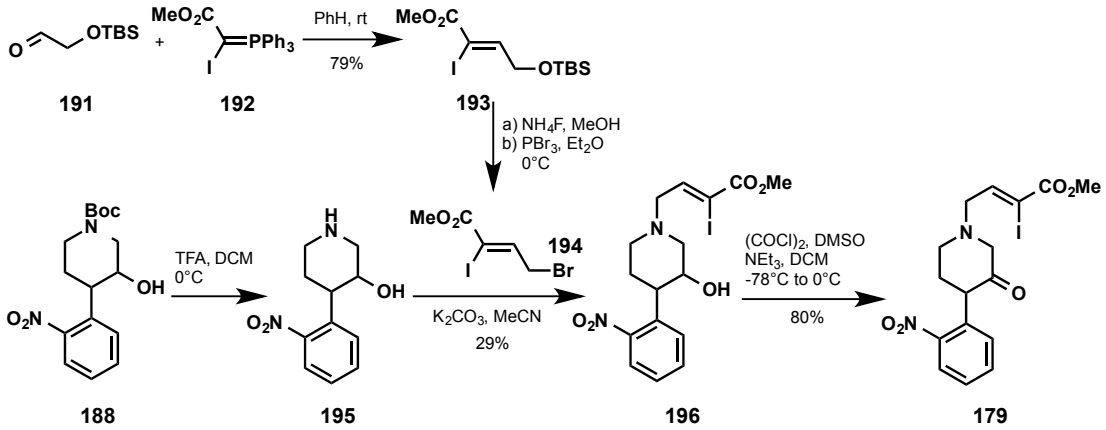


Scheme 56: Intramolecular alkylation of compound **181**.

Table 12: Conditions for intramolecular alkylation of bromo acetate **181**.

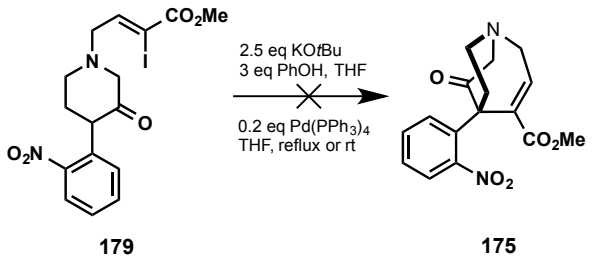
base	temp.	solvent	time	outcome
1.1 eq KO*t*Bu	-78°C	THF	2h	**188**
1.1 eq LiHMDS	-78°C	THF	2h	**188**
2 eq NaH	rt	DMF	30min	**188**

To examine the palladium catalyzed enolate coupling strategy (see Scheme 52), vinyl iodide **179** was generated. First, a *Wittig* reaction of aldehyde **191** and ylide **192** was accomplished in benzene at rt to yield alkene **193**.[95] Deprotection of the TBS-group with NH_4F furnished a primary alcohol which was transferred to bromide **194** by an *Appel* reaction. Cleavage of the Boc-group in compound **188** with TFA yielded secondary amine **195** which was subsequently *N*-alkylated with bromide **194** to tertiary amine **196**. *Swern* oxidation of the alcohol gave access to ketone **179** (Scheme 57).



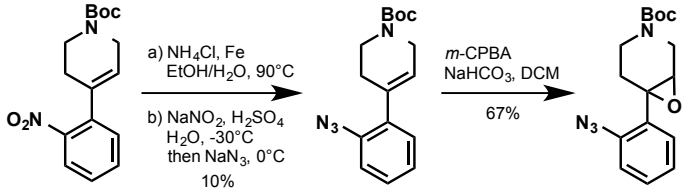
Scheme 57: Substrate synthesis for the palladium enolate coupling.

Also in this case, all attemps to generate the bicyclic system *via* the palladium catalyzed enolate coupling failed (Scheme 58). Only decomposition of the starting material was observed.



Scheme 58: Palladium catalyzed enolate coupling.

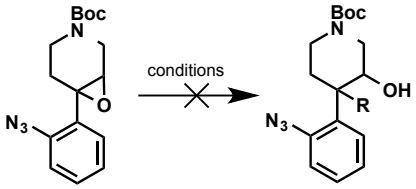
Therefore we envisioned the *Lewis* acid catalyzed epoxide opening strategy to introduce the quarternary carbon center. But unfortunately, epoxidation of nitro compound **183** was not possible due to the electron defficiency of the double bond. For this reason we simply reduced the nitro group (**183**) to the corresponding amine with iron. Transformation of the amine to the diazonium ion by $NaNO_2$ followed by a substitution with NaN_3 furnished azide **197** in a very low yield of 10%. Now, epoxidation of the double bond with *m*-CPBA yielded epoxide **198** (Scheme 59).



183 **197** **198**

Scheme 59: Tranformation to azide **197** and epoxidation.

Epoxide opening under nucleophilic substitution of the benzylic position did not occur under various conditions (Table 13, Scheme 60). Only starting material was observed.



198 **199**

Scheme 60: *Lewis* acid catalyzed epoxide opening.

Table 13: Conditions for *Lewis* acid triggered epoxide opening.

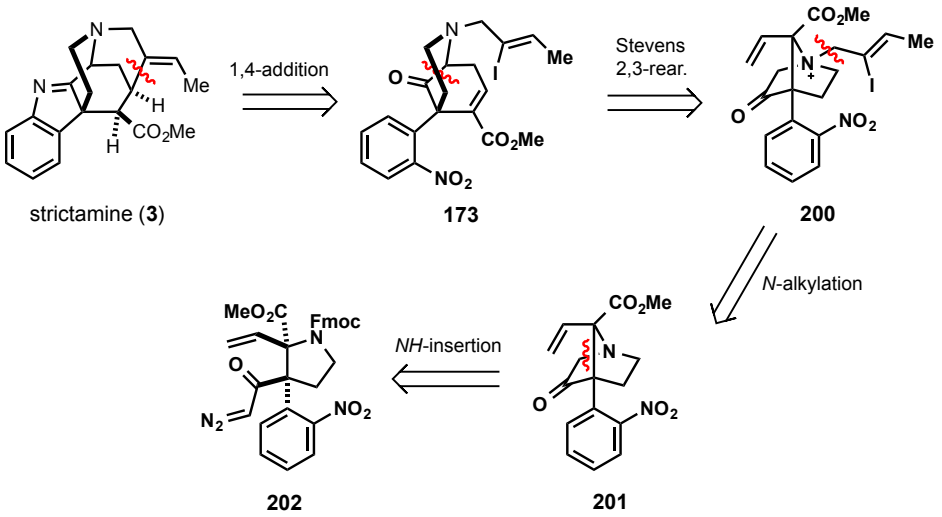
base	nucleophile	temp.	LA	temp.	solv.	epox.	outcome
1.5 eq *n*BuLi	OTBS , 1.5 eq	-78°C, 30min	1.5 eq BF_3*OEt_2	-78°C, 30min	THF	1 eq, -78°C to rt	SM
2 eq *n*BuLi	$SiMe_3$, 2 eq	0°C to rt	2 eq $ClTi(OiPr)_3$	-50 °C, 10min	THF	1 eq, -50°C to rt	SM
2 eq *n*BuLi	$SiMe_3$, 2 eq	0°C to rt	2 eq BF_3*OEt_2	-78°C, 30min	THF	1 eq, -78°C	SM
2 eq *n*BuLi	$SiMe_3$, 2 eq	0°C to rt	2 eq BF_3*OEt_2	-78°C, 30min	THF	1 eq, -78°C to rt	SM

6. Synthetic approaches to Strictamine

6.5 4th Synthetic approach

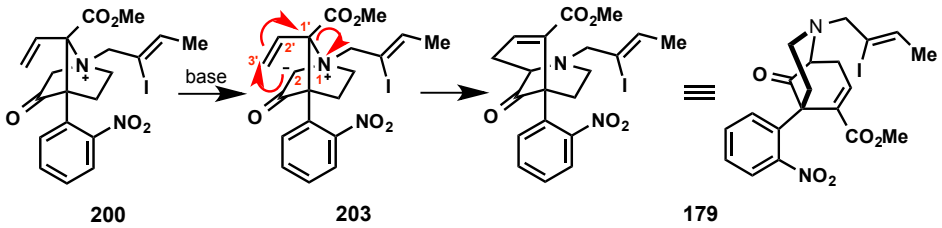
6.5.1 Retrosynthetic analysis

Key step of the 4th synthetic approach to strictamine (**3**) is a *Stevens* [2,3]-sigmatropic rearrangement of ammonium salt **200** which generates the azabicyclo-[3.3.1]nonane structure **173**. A 1,4-addition of vinyl iodide **173** to the α,β-unsaturated methyl ester closes the last cycle and establishes the carbon skeleton of strictamine (**3**). Precursor **200** is generated by a *N*-alkylation of tertiary amine **201**. A formal *NH*-insertion gives access to this tertiary amine (**201**) and leads back to α-diazo ketone **202** (Scheme 61).



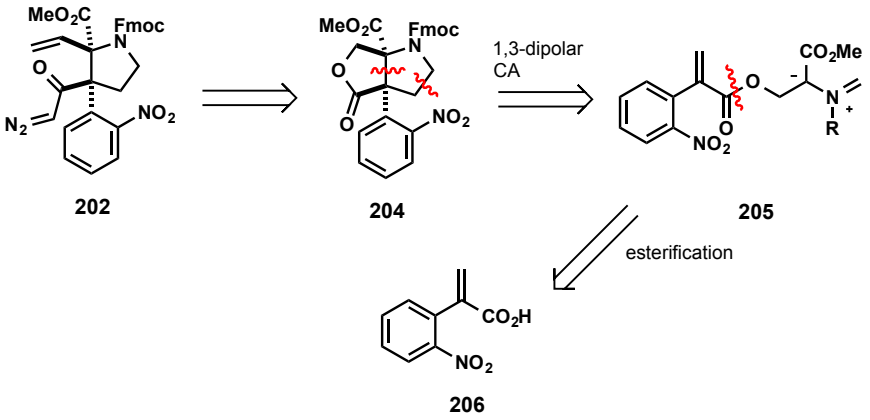
Scheme 61: 4th Generation retrosynthesis of strictamine (**3**), part 1.

Mechanistically the *Stevens* [2,3]-sigmatropic rearrangement works as follows: ammonium salt **200** gets deprotonated by a base forming ylide **203**. In case of an allylic amine the ylide attacks at the allylic position to perform a [2,3]-sigmatropic rearrangement instead of a [1,2]-rearrangement. Thereby the bond between the 1 and 1' position gets broken (Scheme 62).[89, 98]



Scheme 62: Mechanism of the *Stevens* [2,3]-rearrangement.

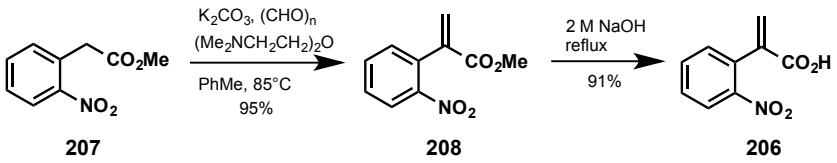
α-Diazo ketone **202** bears a pyrrolidine ring with two neighbouring quarternary centers. The shortest access to the central pyrrolidine ring **202** is probably an intramolecular 1,3-dipolar cycloaddition[99] starting from dipol **205**. This dipol is generated by an esterification of acrylic acid **206** with different corresponding alcohols (Scheme 63).



Scheme 63: 4th Generation retrosynthesis of strictamine (**3**), part 2.

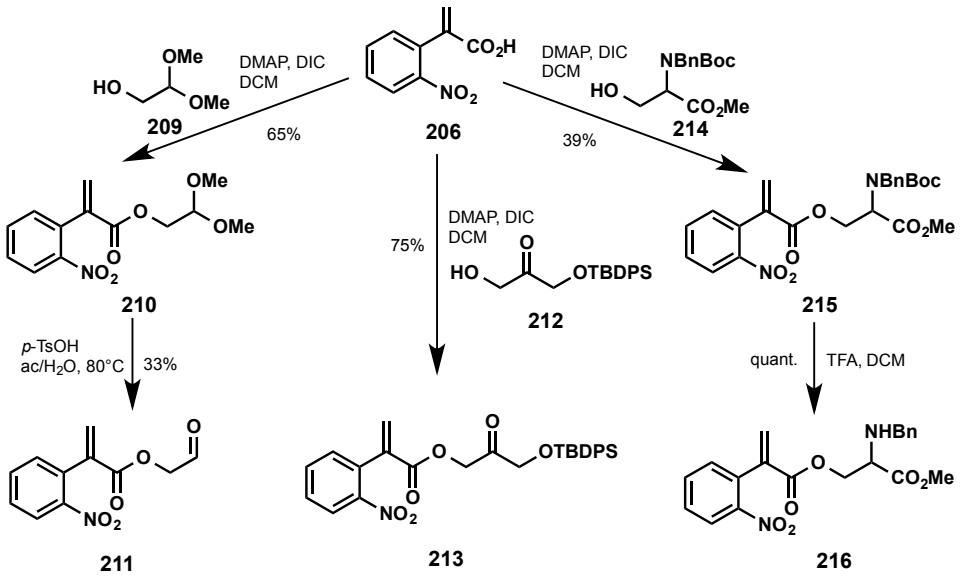
6.5.2 Results and discussion

Different approaches to generate a 1,3-dipol were tested. The synthesis for all dipols started with methyl 2-(2-nitrophenyl)acetate (**207**). Olefination worked fine with paraformaldehyde under basic conditions in toluene at 85°C. Methyl ester **208** was saponificated with 2M NaOH forming acrylic acid derivative **206** (Scheme 64).[100]



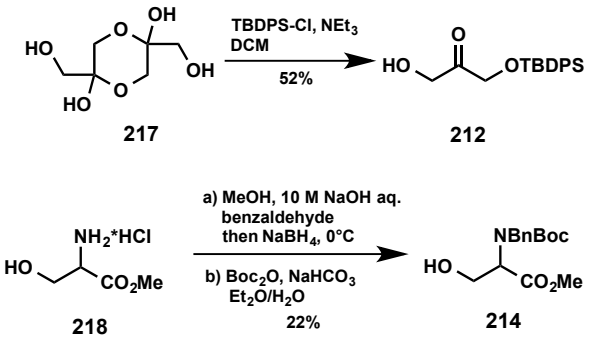
Scheme 64: Synthesis of acrylic acid derivative **206**.

The acrylic acid was esterificated with different alcohols to get suitable precursors for the 1,3-dipols. Esterification with the commercially available dimethyl acetal of glycolaldehyde (**209**) and DIC resulted in ester **210** which libereated subsequently aldehyde **211** under acidic treatment in acetone/water. Esterification with monoprotected dihydroxyacetone (**212**) and DIC yielded ester **213**. Using serine derivative **214** furnished ester **215**. A following Boc-deprotection with TFA resulted in secondary amine **216** (Scheme 65).



Scheme 65: Synthesis of the 1,3-dipol precursors.

The corresponding alcohols were synthesized as follows: dihydroxyacetone dimer (**217**) is splitted under basic conditions and monoprotected with TBDPSCl giving compound **212**.[101] Serine methyl ester hydrochloride (**218**) was double protected by a reductive amination with benzaldehyde follwed by a reaction with *tert*-butyl dicarbonate (Scheme 66).[102]



Scheme 66: Synthesis of alcohols **212** & **214**.

To perform the 1,3-dipolar cycloaddition aldehyde **211** was subjected to different conditions (Table 14).

Table 14: Conditions for 1,3-dipolar cycloaddition of aldehyde **211**.

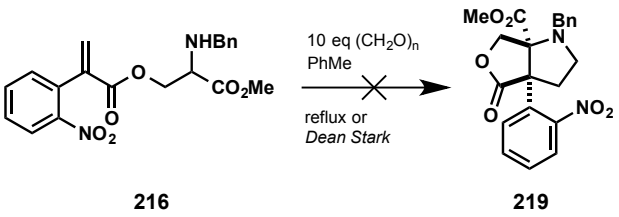
amine	base	metal	solvent	temp.	outcome
H_2N CO_2tBu , 1 eq	1.5 eq DBU	CuI	DCM	rt	decomp.
H_2N CO_2tBu , 1 eq	1.5 eq DBU	AgOTf	DCM	rt	decomp.
H_2N CO_2tBu , 1 eq	1.5 eq DBU	$AgNO_3$	DCM	-20°C	decomp.
H_2N CO_2tBu , 1 eq	1.5 eq DBU	AgOAc	DCM	rt	decomp.
H_2N CO_2tBu , 1 eq	1.5 eq DBU	AgOAc	THF	rt	decomp.

For ketone **213** the following conditions were tested (Table 15):

Table 15: Conditions for 1,3-dipolar cycloaddition of ketone **213**.

amine	base	metal	solvent	temp.	outcome
BnHN CO_2tBu , 2 eq	2 eq Cs_2CO_3	-	MeCN	reflux	decomp.
BnHN $SiMe_3$, 2 eq	2 eq CsF	-	MeCN	rt	decomp.
H_2N CO_2tBu , 1.5 eq	0.2 eq DBU	0.2 eq CuI	$CHCl_3$	rt	decomp.

Serine ester **216** was subjected to the following conditions (Scheme 67):

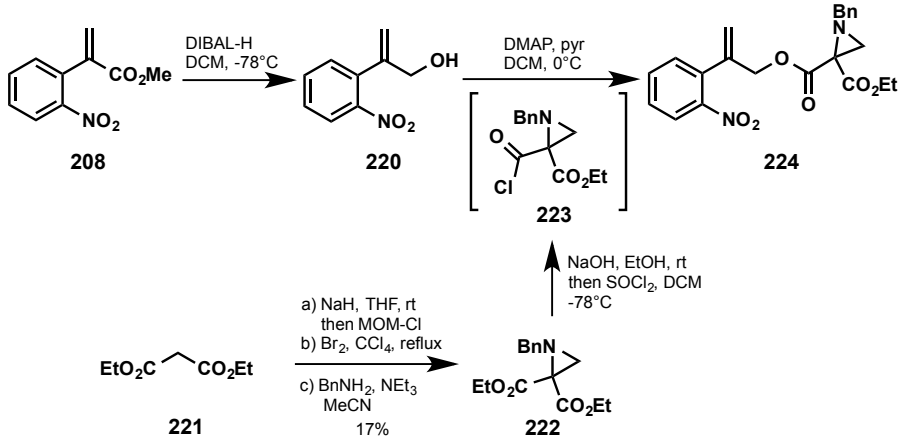


216 **219**

Scheme 67: Conditions for 1,3-dipolar cycloaddition of serine ester **216**.

All tested conditions did not gave any cycloaddition products. Only decomposition of the starting material was observed. One possible reason could be the *Michael* acceptor character of the double bond. All generated dipoles have the opposite polarity neccessary for a productive *Michael* addition. Because of this, the ester was reduced to the corresponding alcohol and esterification was performed in the opposite direction (Scheme 68).

Reduction of methyl ester **208** with DIBAL gave allylic alcohol **220** which was esterificated with carboxylic acid derivative **223** to yield ester **224**. Aziridine **223** was synthesized by a literature known protocol[103]: reaction of diethylmalonate (**221**) with MOMCl and NaH yielded the corresponding substitution product. Elimination of methanol was triggered by refluxing the methyl ether in CCl_4 to produce the olefine which was trapped *in-situ* by bromine. A following double *N*-alkylation with benzylamine resulted in aziridine **222** (Scheme 68).[104]



208 **220** **223** **224**

221 **222**

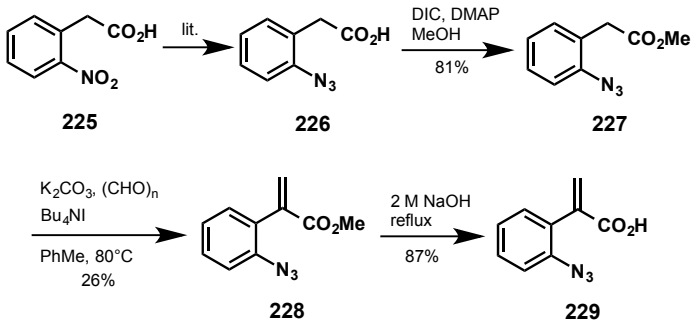
Scheme 68: Synthesis of aziridine derivative **224**.

This aziridine **224** was subjected to the following conditions (Table 16): a bond cleavage of the aziridine moiety has to occur which can be perfromed by high temperatures or irradiation generating the corresponding dipole. Unfortunately, only decomposition of the starting material was observed.

Table 16: Conditions for 1,3-dipolar cycloaddition of aziridine **224**.

temp.	method	solvent	outcome
300 °C	sealed tube	dichlorobenzene	decomp.
350 °C	FVP[104]	-	decomp.
rt	hυ (256 nm)	MeCN	decomp.

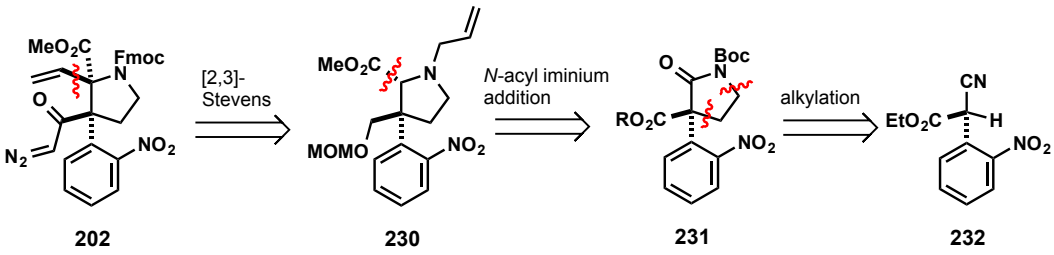
Instead of using the nitrophenylacetic acid derivatives for the 1,3-dipolar cycloadditions the corresponding azidophenylacetic acid derivatives are conceivable. Methylation of carboxylic acid **226**[105] with methanol and DIC yielded methyl ester **227**. Olefination with paraformaldehyde under basic conditions resulted in olefine **228** but only in a low yield of 26%. Saponification with aqueous NaOH worked fine giving acrylic acid derivative **229** (Scheme 69). Because of the low yield during olefination the azido strategy was not accelerated.



Scheme 69: Synthesis of the azide analogues.

6.5.3 Modified retrosynthesis

An alternative strategy to synthesize pyrrolidine **202** is a stepwise sequence. Keysteps are a second *Stevens* [2,3]-sigmatropic rearrangement and a *N*-acyliminium ion addition. Both of these keysteps install an allyl group α to the amine which can be transferred to a methyl ester and a vinyl group respectively. Pyrrolidinone **231** was generated by an alkylation of cyano malonate **232** with dibromoethane (Scheme 70).

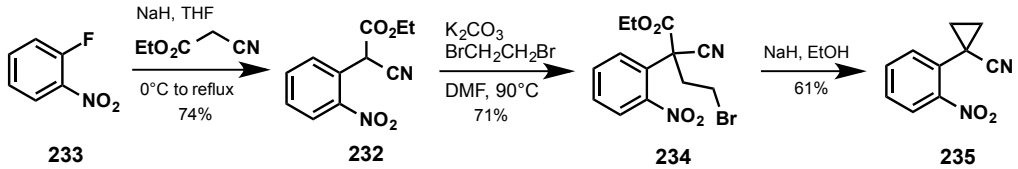


202 **230** **231** **232**

Scheme 70: Changed retrosynthesis of pyrrolidine **202**.

6.5.4 Results and discussion

The synthesis started with a nucleophilic aromatic substitution of 2-fluoro nitrobenzene (**233**).[106] The 1,3-dicarbonyl (**232**) was alkylated with dibromoethane and K_2CO_3 in DMF at 90°C to generate the quarternary carbon center. The structure could be verified by x-ray spectroscopy (Figure 44). This reaction was very sensitive due to decarboxylation under basic conditions. For example, treatment of **234** with NaOEt delivered cyclopropane **235** *via* decarboxylation of the ethyl ester and a following substitution of the primary bromide (Scheme 71).



233 **232** **234** **235**

Scheme 71: Synthesis of the quarternary carbon center.

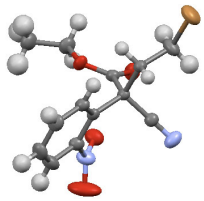
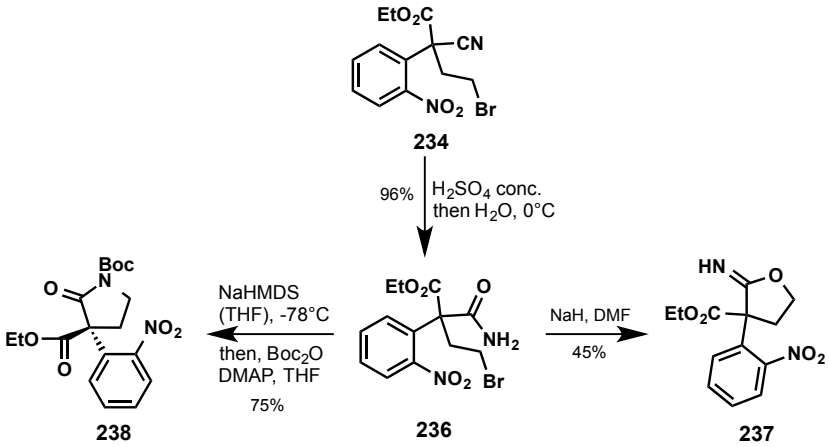


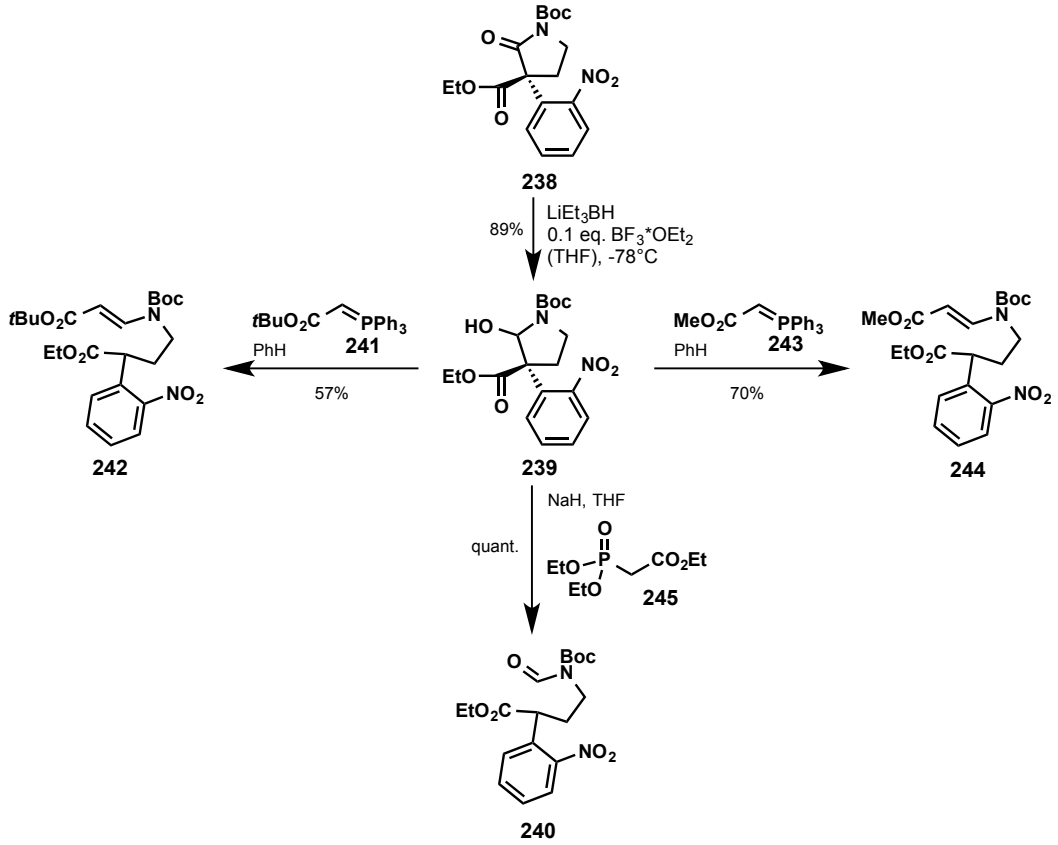
Figure 44: X-Ray structure of compound **234** showing the quarternary carbon.

Nevertheless, under acidic conditions compound **234** was stable and therefore hydrolysis to carboxylic amide **236** worked fine with concentrated sulfuric acid followed by the addition of a ice/water mixture. Deprotonation of the amide with NaH in DMF provided the imidoester **237** instead of the expected lactame. Only NaHMDS at low temperatures (-78°C) gave the five-membered lactame which was protected in a following step with Boc_2O to imide **238** (Scheme 72).



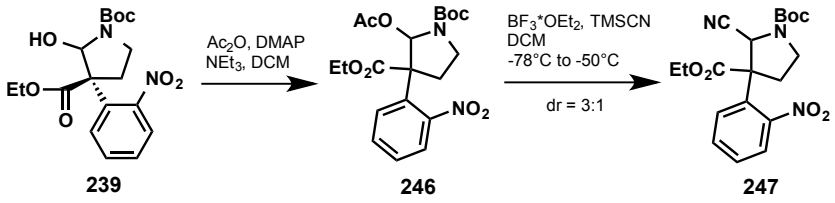
Scheme 72: Lactamisation to pyrrolidinone **238**.

Reduction of imide **238** worked fine with $LiEt_3BH$ under *Lewis* acidic conditions at low temperature and resulted in Boc-protected hemiaminal **239** in a yield of 89%. In contrast, under to basic conditions and higher temperature fragmentation to Boc-protected formamide **240** occured. Due to that reason, the olefination attempts of this hemiaminal failed due to this fragmentation. With *HWE*-reagent **245** the Boc-protected formamide **240** itself was isolated and with *Wittig* reagents **241** and **243** an olefination of this formamide was observed yielding olefins **242** and **244** (Scheme 73).



Scheme 73: Fragmentation of Boc-protected hemiaminal **239**.

However, Boc-protected hemiaminal **239** was converted with acetic anhydride to the acetate which gave access to the *N*-acyl iminiumion chemistry. Following treatment of compound **248** with *Lewis* acid liberated the imminium ion which was trapped by TMSCN to nitrile **247** in a diastereoisomeric ratio of 3:1 (Scheme 74).



Scheme 74: CN-Addition to the *N*-acyl iminiumion.

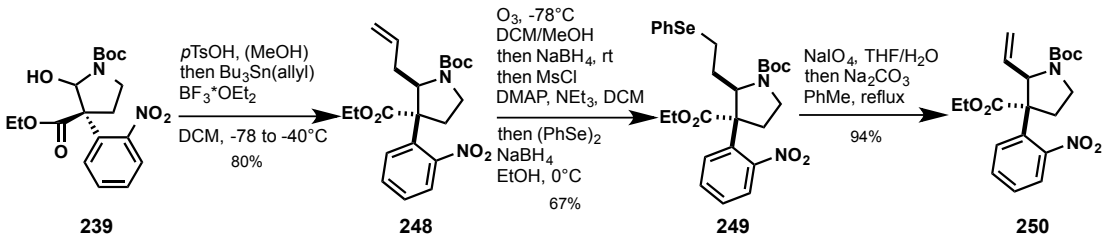
Unfortunately, the subsequent α-Alkylation of the nitrile only delivered starting material under the choosen conditions (Table 17).

Table 17: Alkylation/Aldol conditions for nitrile **247**.

base	solvent	temp.	electrophile	temp.	outcome
1.5 eq LiHMDS	THF	-78°C, 30min	$(CH_2O)_n$, 3 eq	-78°C to rt	SM
1.5 eq NaHMDS	THF	-78°C, 30min	$(CH_2O)_n$, 3 eq	-78°C to rt	SM
1.5 eq KHMDS	THF	-78°C, 30min	$(CH_2O)_n$, 3 eq	-78°C to rt	SM
1 eq NaH	EtOH	rt, 15min	$(CH_2O)_n$, 3 eq	rt	SM
2 eq LDA	THF	-78°C, 30min	$(CH_2O)_n$, 3 eq	-78°C to rt	SM
3.5 eq LDA	THF	-78°C, 30min	BTM, 3 eq	-78°C to rt	SM
3.5 eq KHMDS	THF	-78°C, 30min	BTM, 3 eq	-78°C to rt	SM
1.5 eq LDA	THF	-78°C, 30min	allyl bromide, 5 eq	-78°C to rt	SM
1.5 eq LiHMDS	THF	-78°C, 30min	allyl bromide, 5 eq	-78°C to rt	SM
1.5 eq NaHMDS	THF	-78°C, 30min	allyl bromide, 5 eq	-78°C to rt	SM
1.5 eq KHMDS	THF	-78°C, 30min	allyl bromide, 5 eq	-78°C to rt	SM

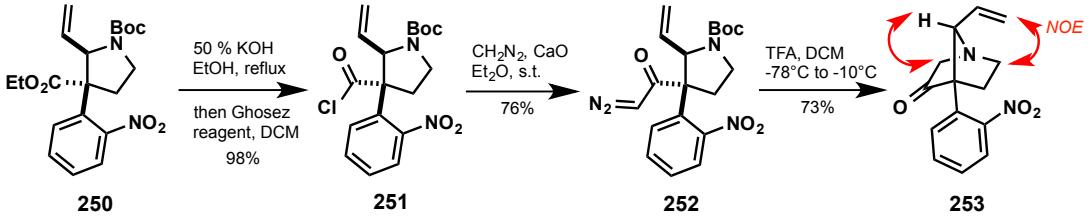
.

Nevertheless, methylation of Boc-protected hemiaminal **239** under *Brønsted* acidic conditiions in methanol proceeded smoothly. A following allylation *via* *N*-acyl iminium ion chemistry to compound **248** delivered only one diastereoisomer. Ozonolysis of the double bond with a reductive work-up giave a primary alcohol which was converted to the corresponding mesylate and then substituted with NaSePh in ethanol to selenoether **249**. Subsequent oxidation of the selenoether with $NaIO_4$ resulted in the selenooxide which eliminated instantly in refluxing toluene to olefine **250** (Scheme 75).



Scheme 75: Allylation and conversion to vinylic compound **250**.

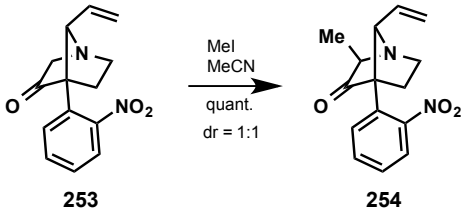
At that point we have to elucidate the stereochemistry of the vinyl group. Further crucial question is the capacibility of the [2,3]-sigmatropic rearrangement to the azabicyclo[2.2.1]heptane skeleton. Therefore, we saponificated ester **250** to the carboxylic acid with 50% aqueous KOH in refluxing ethanol. The free acid was converted to the acid chloride **251** with *Ghosez* reagent which was subsequently treated with diazomethane to give α-diazo ketone **252**. Moreover, the use of trifluoroacetic acid deprotected the secondary amine and substituted the diazo group to the corresponding trifluoroacetate, which underwent an intramolecular substitution by the secondary amine spontaneously resulting in bridged amine **253.** *NOE*-experiments of this compound (**253**) revealed a *cis* relationship between the vinyl group and the CH_2CH_2-moiety. Noteworthy is also the *NOE*-signal of the brigdeg proton to the CH_2-group α to the ketone. Based on this reaults, the [2,3]-sigmatropic rearrangement could not be tested at this system (Scheme 76).



Scheme 76: Synthetic sequence to bridged amine **253**.

An experimental proof of the stereochemistry at the bridgehead carbon atom delivered the methylation of compound **253** with iodomethane α to the ketone (**254**) without using any base in a diastereoisomeric ratio of 1:1. This product outcome leads to the assumption that the reaction pathway proceeds *via* the

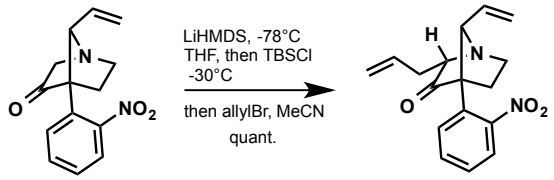
quarternary amine which underwent subsequently a [1,2]-*Stevens* rearrangement (Scheme 77).



253 **254**

Scheme 77: *Stevens* [1,2]-rearrangement.

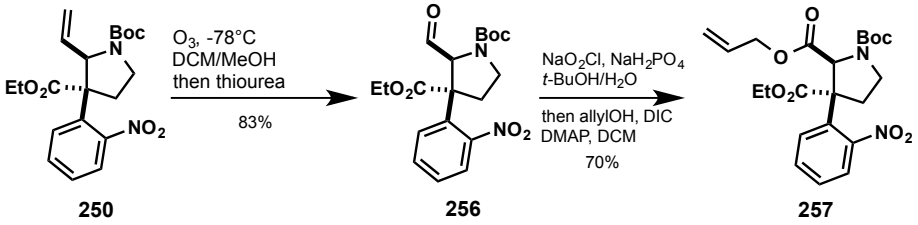
Moreover, treatment with allyl bromide delivered the expected [2,3]-sigmatropic rearrangement product **255** as a single diastereoisomer. In that experiment the ketone was first converted to the silyl enol ehter with LiHMDS and TBSCl and then treated with allyl bromide to quarternize the tertiary amine (Scheme 78).



253 **255**

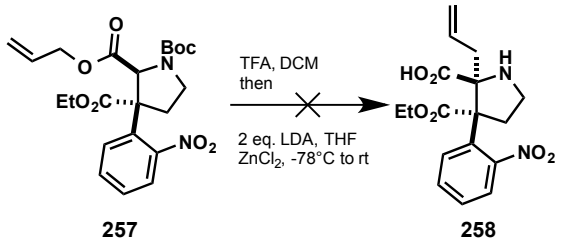
Scheme 78: *Stevens* [2,3]-rearrangement.

To introduce the second substituent α to the nitrogen an *Kazmaier Claisen* reanrrangement is conceivable. Therefore, olefine **250** was ozonolyzed followed by a neutral work-up with thiourea to yield aldeyhde **256**. *Pinnick* oxidation of the aldehyde generated the carboxylic acid which was esterificated in the next step with allylic alcohol and DIC to allylester **257** (Scheme 79).



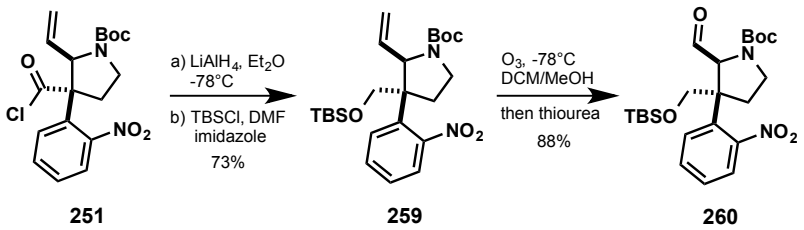
Scheme 79: Transformation to allylester **257**.

Unfortunately, deprotection of the Boc-group and treatment of the secondary amine with 2.5 equivalents of LDA and $ZnCl_2$ at -78°C in THF only gave starting material (Scheme 80).



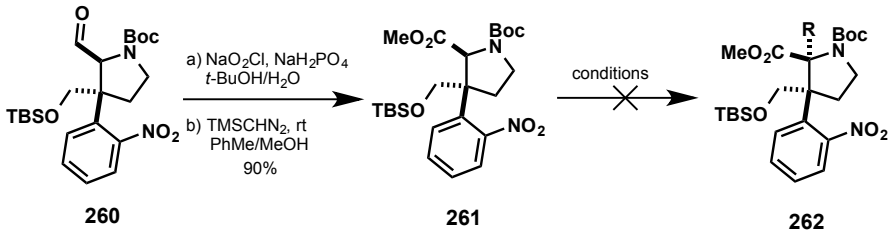
Scheme 80: *Kazmaier Claisen* rearrangement.

Based on this outcome, we have to convert the vinyl group into a methyl ester. Furthermore, we decided to introduce the second substituent *via* alkylation or *Aldol* reaction. To differentiate between both carbonyl functions, first reduction of acid chloride **251** with LAH at -78°C was performed. A following protection of the primary alcohol with TBSCl resulted in TBS-ether **259**. Ozonolysis of the double bond and a subsequent neutral work-up (thiourea) gave aldeyhde **260** in good yields (Scheme 81).



Scheme 81: Redcution to primary alcohol and ozonolysis to aldehyde **260**.

Pinnick oxidation followed by a esterification of the acid moiety with trimethylsilyl diazomethane provided methyl ester **261**. At that point we performed several alkylation or *Aldol* reactions under various conditions (Table 18, Scheme 82). But unfortunately, we only observed starting material.



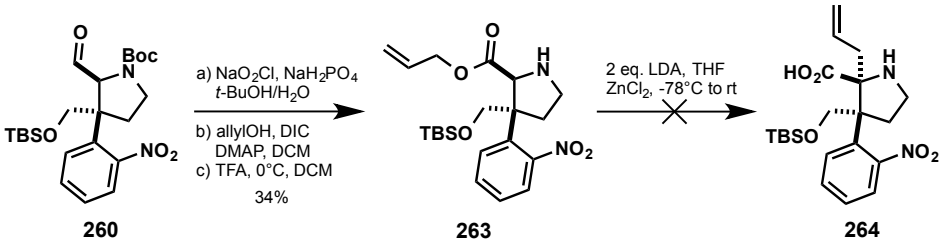
260 **261** **262**

Scheme 82: Conversion of aldehyde **260** to methyl ester **261**.

Table 18: Alkylation/Aldol conditions for compound **261**.

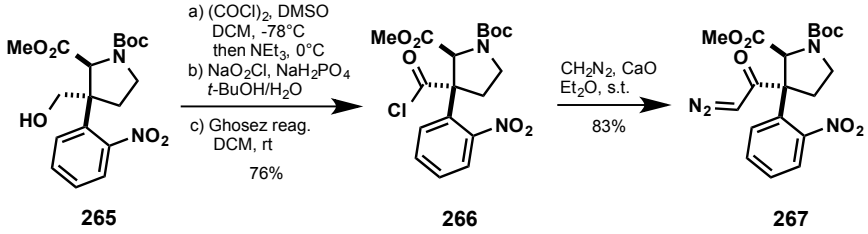
base	solvent	temp.	electrophile	temp.	outcome
1.5 eq LiHMDS	THF	-78°C, 30min	MeO_2CN, 100 eq	-78°C to rt	SM
1.5 eq LiHMDS	THF	-78°C, 30min	MeO_2Cl, 100 eq	-78°C to rt	SM
1.5 eq LiHMDS	THF	-78°C, 30min	allyl bromide, 100 eq	-78°C to rt	SM
1.5 eq *t*BuLi	THF	-78°C, 30min	allyl bromide, 100 eq	-78°C to rt	SM
10 eq LiHMDS	THF	-78 °C, 30min	BTM, 5 eq	-78°C to rt	SM

According to these results, again the *Kazmaier Claisen* rearrangement was tested with allyl ester **263**. Therefore, substrate **263** was synthezied out of aldehyde **260** *via Pinnick* oxidation followed by an esterification of the resulting carboxylic acid with allyl alcohol and DIC to the allyl ester. Cleavage of the Boc-group with TFA in DCM gave secondary amine **263**. A subsequent treatment of this amine with 1.2 equivalents $ZnCl_2$ and 2.4 equivalents LDA in THF at -78°C showed no consumtion of the starting material (Scheme 83).



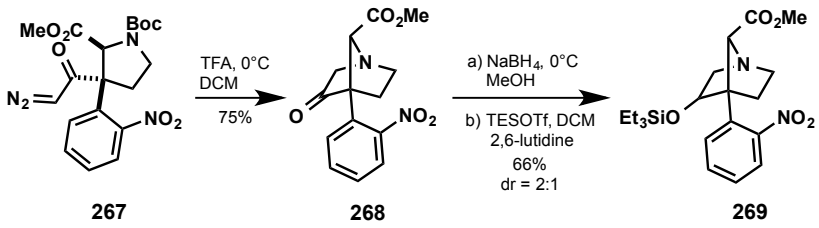
Scheme 83: *Kazmaier Claisen* rearrangement with substrate **263**.

Based on this unexpected behaviour, we decided to introduce the second substituent by the use of a *Stevens* [2,3]-sigmatropic rearrangement *via* intramolecular bridging of the secondary amine to bicycle **268**: primary alcohol **265** was oxidized to the carboxylic acid by a *Swern* oxidation followed by a subsequent *Pinnick* oxidation. The carboxylic acid was converted to acid chloride **266** by *Ghosez* reagent in DCM. Addition of diazomethane in Et_2O in a sealed tube resulted in α-diazo ketone **267** (Scheme 84).



Scheme 84: Transformation to α-diazo ketone **267**.

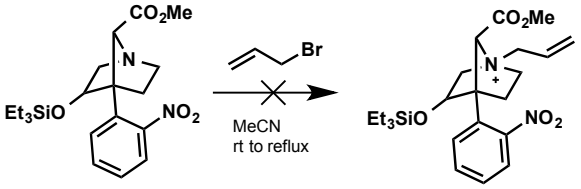
After this, the use of trifluoroacetic acid deprotected the secondary amine and substituted the diazo group to the corresponding trifluoroacetate, which underwent an intramolecular substitution by the secondary amine spontaneously resulting in bridged amine **268**. Reduction of the ketone with $NaBH_4$ followed by a protection of the secondary alcohol with TESOTf gave silyl ether **269** (Scheme 85).



267 **268** **269**

Scheme 85: Acid triggered *NH*-insertion to bridged amine **268**.

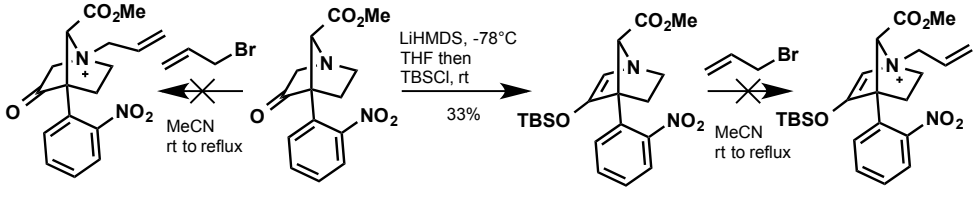
Quarternization attempts of bridged amine **269** to allyl ammonium salt **270** was not successful under the choosen conditions (Scheme 86). Only starting material was observed. Because of this, the *Stevens* rearrangement of compound **269** could not be tested.



269 **270**

Scheme 86: Quarternization attempts of compound **269**.

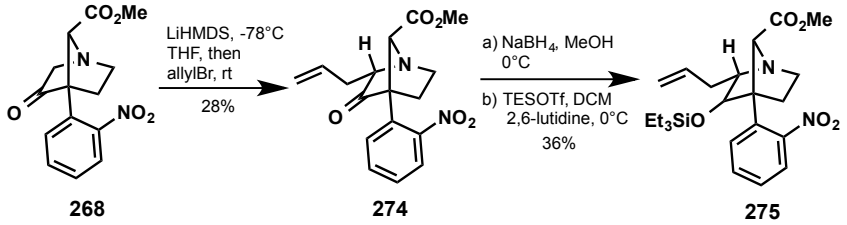
Also a quarternization of ketone **268** or silyl enol ehter **272** did not show any consumption of the starting material (Scheme 87).



271 **268** **272** **273**

Scheme 87: Quarternization attempts of compounds **268** and **272**.

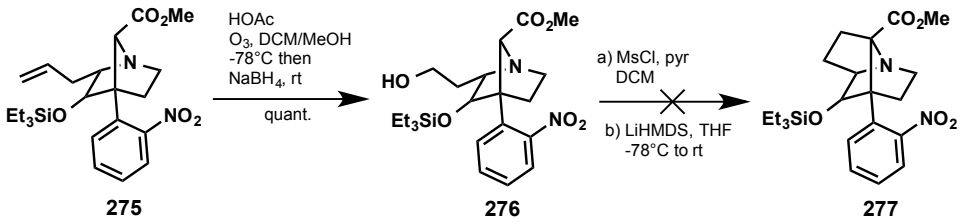
Alkylation of ketone **268** with LiHMDS and allyl bromide resulted in allylic compound **274** in a low yield of 28%. Reduction of the ketone to the secondary alcohol followed by a subsequent protection with TESOTf resulted in silyl ether **275** (Scheme 88).



268 274 275

Scheme 88: Alkylation of ketone **268**.

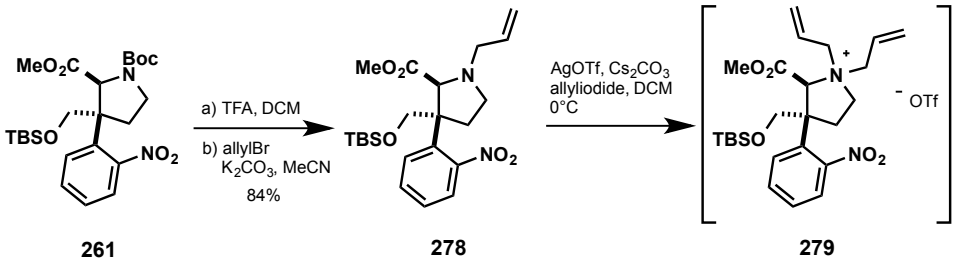
Even an intramolecular alkylation of methyl ester **276** to compound **277** did not work. To test this reaction allylic compound **275** was ozonolyzed followed by a reductive work-up to alcohol **276**. Mesylation of the primary alcohol with MsCl and pyridine followed by an alkylation with LiHMDS only resulted in starting material (Scheme 89).



275 276 277

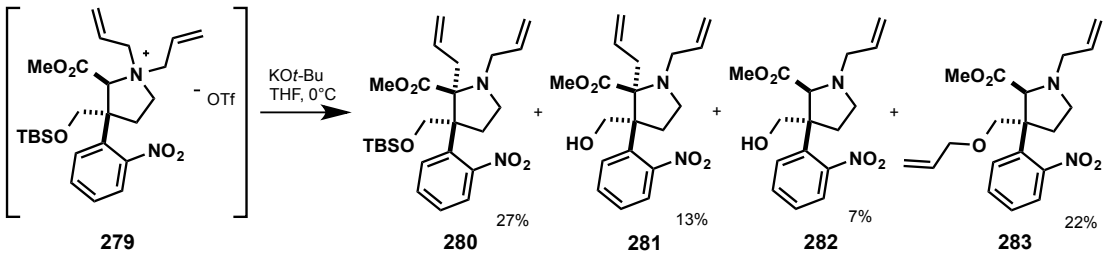
Scheme 89: Intramolecular alkylation attempts to compound **277**.

Based on this unexpected behaviour, we decided to introduce the second substituent by the use of a *Stevens* [2,3]-sigmatropic rearrangement *via* allyl ammonium salt **279**. To get access to the ammonium salt the Boc-protecting group of the secondary amine was removed with trifluoroacetic acid in DCM. The resulting secondary amine was alkylated with allyl bromide and K_2CO_3 in MeCN to allyl amine **278**. It is noteworthy that a second alkylation to ammonium salt **279** was not possible under standard alkylation conditions like allyl bromide/iodide in MeCN. Even under refluxing conditions no reaction was observed. However, successful was a combination of allyl iodide and silver trifluoromethane sulfonate at 0°C in DCM resulting in quarternary ammonium salt **279** (Scheme 90).



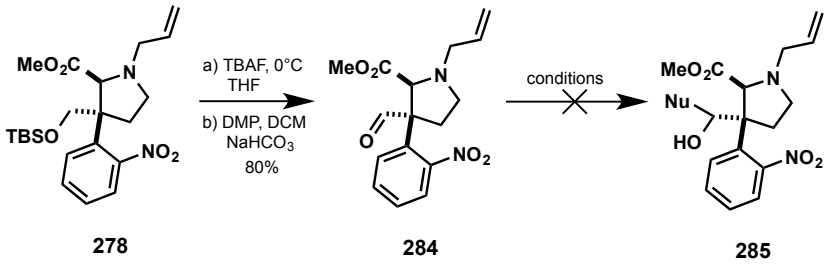
Scheme 90: Qarternization to allyl ammonium salt **279**.

Deprotonation of ammonium salt **279** to the ylide was accomplished with KO*t*Bu in THF at 0°C which resulted in a complex mixture of products: starting material (5%), rearrangement product **280** (27%), deprotected rearrangement product (**281**, 13%), deprotected starting material (**282**, 7%) and allylated alcohol **283** (22%) were observed (Scheme 91).



Scheme 91: *Stevens* rearrangement products of allyl ammonium salt **279**.

Based on this experimental outcome the instability of the TBS-ether seemed to play a crucial role during the reaction. This is probably caused by *Brønsted* acids (HOTf) or *Lewis* acids (AgOTf). To avoid this problem the protecting group was removed and the primary alcohol was oxidized to aldehyde **284** (Scheme 92). Unfortunately, fomation of the ammonium salt with aldehyde **284** was not successful and only leads to decomposition. Even a nuceophilic addition to the aldehyde (Table 19) provided no product formation.

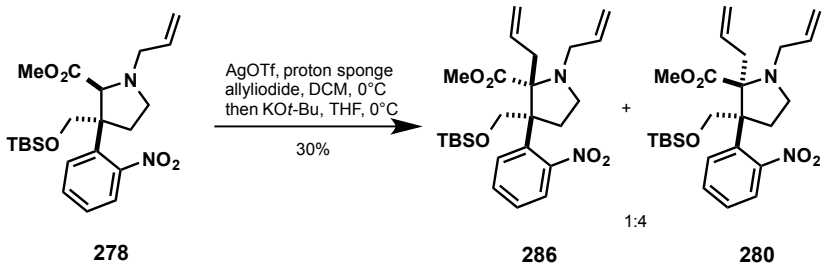


Scheme 92: Conversion to aldehyde **284** and nucleophilic addition.

Table 19: Nuceophilic addition to aldehyde **284**.

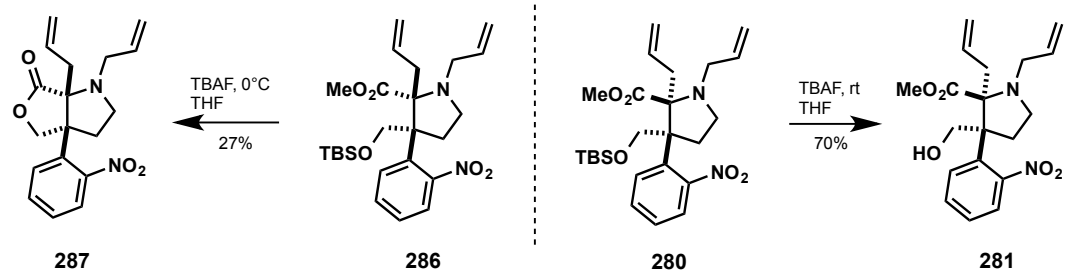
reagent	base	solvent	temp.	outcome
1.5 eq Me_3SOI	1.5 eq NaH	THF/DMSO	0 °C to rt	decomp.
2.2 eq Me_3SOI + 2 eq TMSOTf	2.2 eq NaH	THF	0 °C to rt	decomp.
1.2 eq $TMSCHN_2$	1.2 eq *n*BuLi	THF	-100 to -78 °C	decomp.
1.8 eq CH_2Br_2	1.8 eq MeLi	Et_2O	-78 °C to 0 °C	decomp.

At that point we decided to focus on the TBS-ether approach. Quarternization of compound **278** was optimized by the use of proton sponge instead of Cs_2CO_3 as a base during reaction. These conditions gave better yields and no side products. Probably, the cleavage of the TBS-group was avoided due to a coordination of the Ag^+-ions and thereby reduction of the *Lewis* acidity. Undere these conditions the *Stevens* rearrangement proceeded in a moderate yield of 30% (73% brsm) with a diastereoisomeric ratio of 4:1 (Scheme 93).



Scheme 93: *Stevens* rearranement under optimized conditions.

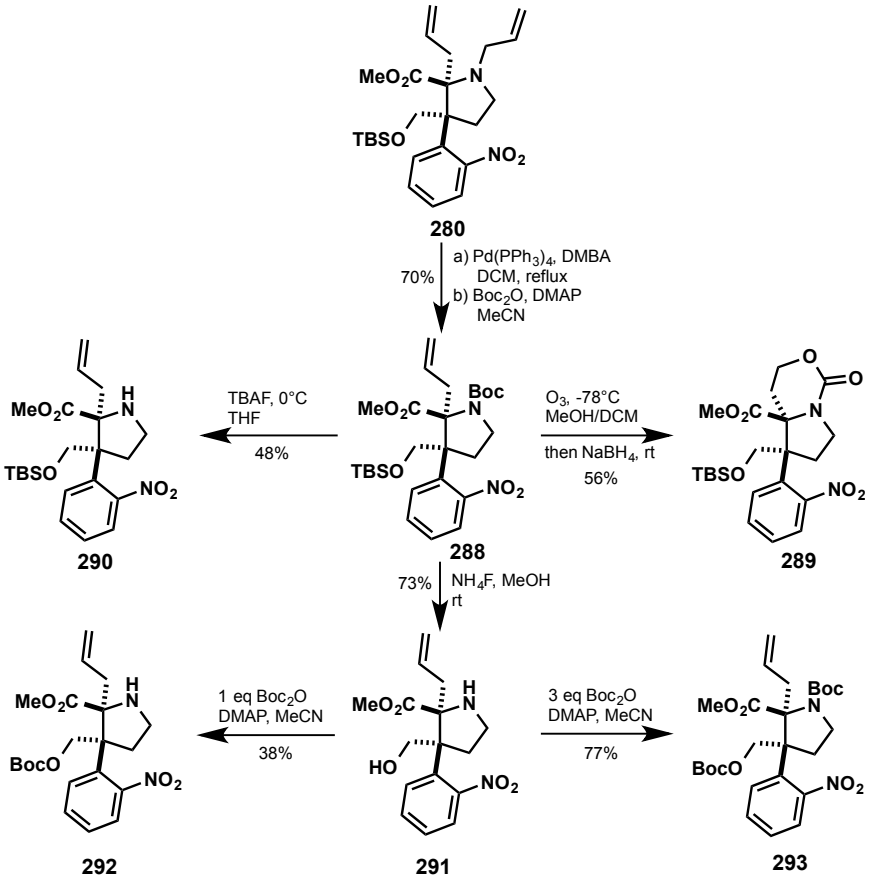
Both diastereoisomers resulting from the *Stevens* rearrangement were seperated by chromatography. To determine the relative stereochemistry the silyl group of the primary alcohol was cleaved. The primary alcohol *cis* to the methyl ester reacted to lactone **287** and the primary alcohol *trans* to the methyl ester stayed (**281**, Scheme 94). By this, both diastereoisomers were identified.



Scheme 94: Determination of the realtive stereochemistry of both rearrangement products.

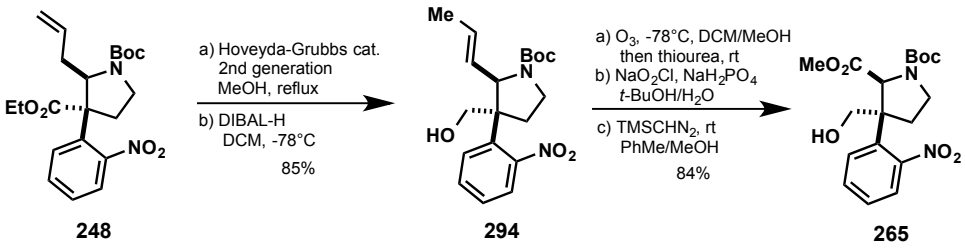
The next step is a deallylation reaction of allyl amine **280** which was accomplished by Pd-catalysis with dimethyl barbituric acid as a nucleophile in refluxing DCM. Boc-protection of the secondary amine resulted in imide **288**. A following reductive ozonolysis with a $NaBH_4$-workup provided cyclic imide **289** instead of the primary alcohol.

At that point we had also problems to cleave the TBS-group of the primary alcohol selectively. With 1 equivalent TBAF in THF at 0°C the Boc-group was selectively removed (**290**) and the TBS-ehter stayed untouched. Moreover, an excess of NH_4F in methanol removed both groups (**291**). Also a selective Boc-protection of the secondray amine in presence of the primary alcohol was not possible. Using 3 equivalents of *tert*-butyl bicarbonate resulted in the double protected compound (**293**). On the other hand, 1 equivalent of *tert*-butyl bicarbonate resulted in the carbonate formation (**292**) selectively (Scheme 95).



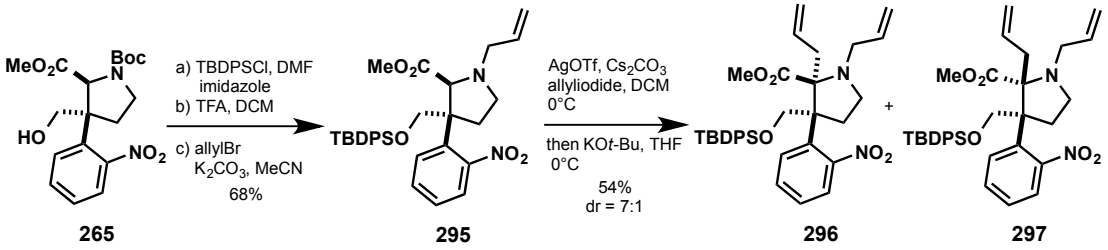
Scheme 95: Selectivity problems between Boc- and TBS-group.

Based on these results, another protecting group for the primary alcohol has to be found. At that point we also have shorten the route by isomerizing the allylic moiety of compound **248** to the higher substituted double bond *via Hoveyda-Grubbs* 2nd generation catalyst. Reduction with DIBAL-H furnished primary alcohol **294**. Ozonolysis of the double bond followed by a work-up with thiourea gave the corresponding aldehyde which was oxidized to the carboxylic acid by a *Pinnick* oxidation and subsequently methylated to ester **265** with $TMSCHN_2$ (Scheme 96).



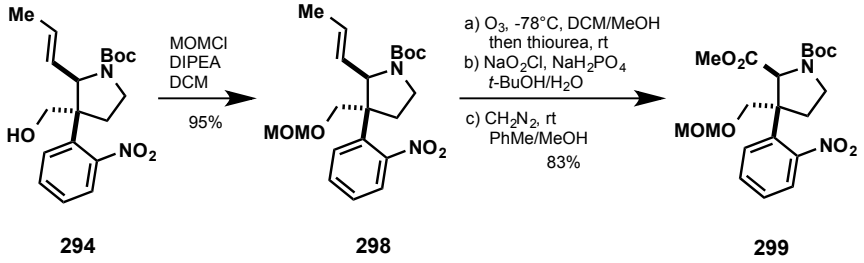
Scheme 96: Isomeriazation with *Hoveyda-Grubbs* 2nd generation catalyst and oxiation of olefine **294**.

Primary alcohol **265** was protected with TBDPSCl in DMF followed by a deprotection of the Boc-group and an alkylation of the corresponding secondary amine to allyl amine **295** with allyl bromide. *Stevens* rearrangement was initiated under the same conditions mentioned above to yield rearrangement products **296** and **297** in a diastereoisomeric ratio of 7:1 (Scheme 97).



Scheme 97: *Stevens* rearrangement with TBDPS-protecting group.

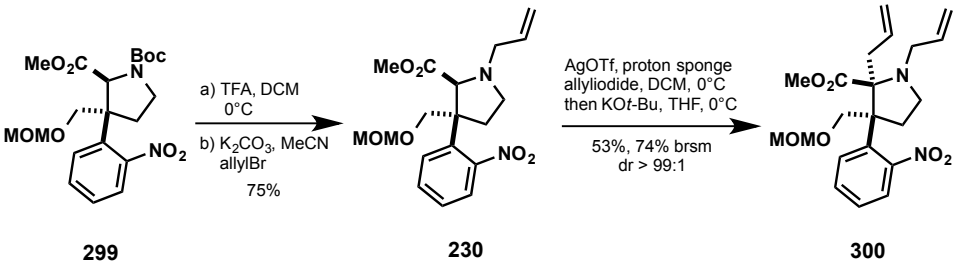
Further extensive research identified the MOM-group as the most suitable protecting group. Therefore, alcohol **294** was protected with MOMCl in the presence of *Hünigs* base resulting in ether **298**. Ozonolysis of the double bond followed by a neutral work-up (thiourea) provided the aldehyde which was further oxidized under *Pinnick* conditions to the carboxylic acid which was subsequently methylated by diazomethane to methyl ester **299** (Scheme 98).



Scheme 98: Ozonolysis of the MOM-protected alcohol **298**.

Deprotection of the Boc-group with trifluoroacetic acid in DCM followed by *N*-alkylation with allyl bromide resulted in allyl amine **230**. *Stevens* rearrangement under the approved conditions gave rearrangement product **300** in a yield of 53% and a diastereoisomeric ratio higher 99:1. Besides starting material (21%) was reisolated. The relative stereochemistry of

compound **300** was determined by x-ray spectroscopy (Scheme 99, Figure 45).



299 **230** **300**

Scheme 99: *Stevens* rearrangement with MOM-protected alcohol **230**.

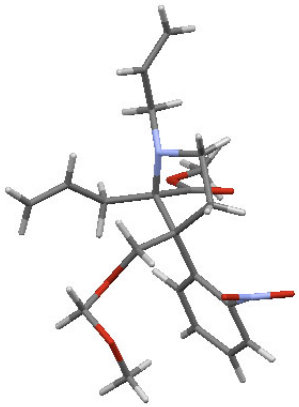
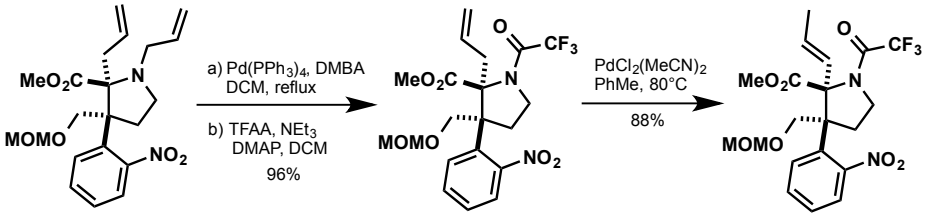


Figure 45: X-Ray structure of compound **300** showing the relative stereochemistry.

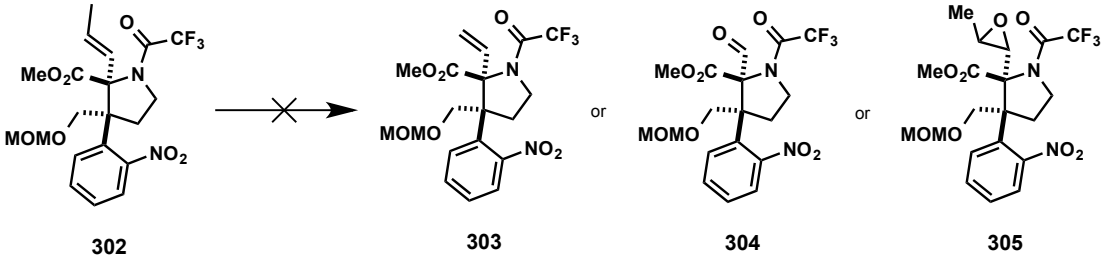
A following deallylation of allyl amine **300** was accomplished under Pd-catalysis with dimethyl barbituric acid. The secondary amine was protected as a trifluoro acetamide (**301**) by reaction with trifluoroacetic anhydride. Isomerization of the allyl moiety to the higher substituted double bond (**302**) was possible with $PdCl_2(MeCN)_2$ in toluene at 80°C (Scheme 100).



300 **301** **302**

Scheme 100: Protection of the secondary amine as a trifluoro acetamide and isomerization.

At that point different attempts were tested to convert the 2-propene substituent of compound **302** to a vinyl group. Ozonolysis, dihydroxylation and epoxidation attempts of compound **302** only resulted in a reisolation of starting material. The same was true for a methatesis reaction under an ethylene atmosphere (Table 20, Scheme 101).



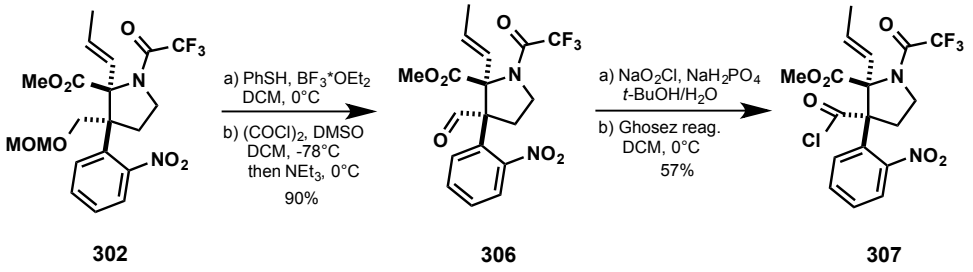
Scheme 101: Derivatisation attempts of compound **302**.

Table 20: Conversion of olefine **302** under different conditions.

reagent	temp.	solvent	outcome
0.1 eq HG II, 1 atm C_2H_4	rt, 20h	DCM	SM
0.1 eq HG II	80 °C, s.t.	1,7-octadiene	SM
0.1 eq G II, 10 bar C_2H_4	rt, 15h	DCM	SM
O_3 then thiourea	-78 °C to rt	DCM/MeOH	SM
O_3 then thiourea	0 °C to rt	DCM/MeOH	decomp.
O_3 then thiourea	-20 °C to rt	DCM/MeOH	decomp.
0.05 eq OsO_4, 1 eq NMO	rt, 24h	*t*BuOH/H_2O	SM
2 eq *m*CPBA	rt, 18h	DCM	SM

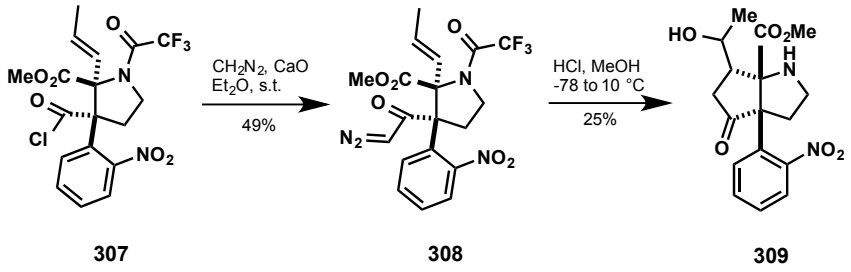
At this stage of the synthesis we also decided to examine the *Stevens* [2,3]-sigmatropic rearranangement to get access to the azabicyclo-[3.3.1]nonane skeleton. Therefore, the MOM-ether **302** was deprotected with thiophenol using trifluoroborane as *Lewis* acid followed by a *Swern* oxidation of the

corresponding primary alcohol to aldehyde **306**. A subsequent *Pinnick* oxidation afforded the carboxylic acid which was converted to the acid chloride (**307**) by the use of *Ghosez* reagent (Scheme 102).



Scheme 102: Transformation to acid chloride **307**.

As depicted in Scheme 103 the acid chloride **307** was converted to α-diazo ketone **308** using diazomethane and CaO in Et_2O under selaed conditions. Unfortunately, deprotection of the trifluoro acetamide to the secondary amine appeared to be very complicated. Either basic or acidic conditions resulted in decomposition or reisolation of the starting material (Table 21). Only the treatment with HCl in MeOH generated annelation product **309** (Scheme 103).

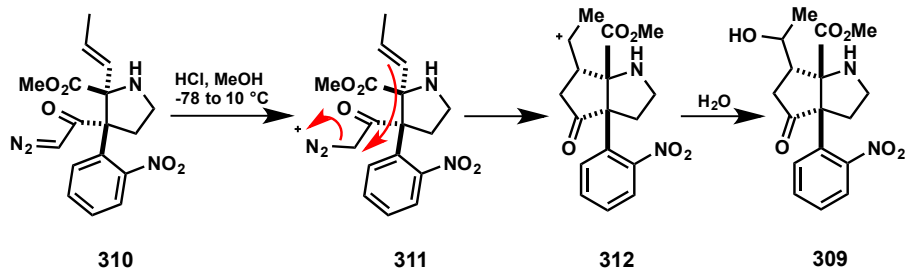


Scheme 103: Transformation to tricycle **309**.

Table 21: Deprotection attempts of TFA-amide **308**.

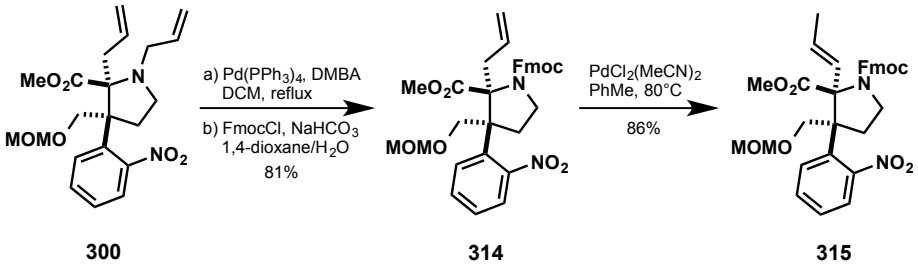
reagent	solvent	temp.	outcome
2 eq K_2CO_3	MeOH	rt, 20h	SM
10 eq Cs_2CO_3	MeOH	rt, 20h	SM
10 eq Cs_2CO_3	MeOH	reflux, 2.5h	decomp.
1 eq NaH	MeOH	rt, 20h	SM
1 M $Ba(OH)_2$	MeOH	rt, 20h	SM
1 M $Ba(OH)_2$	MeOH	reflux, 1h	decomp.
50 % KOH	MeOH	rt, 1h	decomp.
2 M KOH	MeOH	rt, 30h	decomp.
NH_3 conc	MeOH	rt, 20h	SM
NH_3 conc	MeOH	reflux, 1h	decomp.
10 eq Me_3BnNOH	DCM	rt, 22h	decomp.
2 eq Me_3BnNOH	DCM	-78°C, 1h	decomp.
1.2 eq PhSH, 1.2 eq *n*BuLi	THF	rt, 20h	SM
10 eq N_2H_4	DMSO	rt, 40h	SM
5 eq TFA	DCM	-20 °C to rt	SM
10% AcCl	MeOH	rt, 30min	decomp.
48% HBr	THF	0°C , 24h	decomp.
1 eq $NaBH(OAc)_3$	MeOH	rt, 24h	SM
3 eq DIBAL	DCM	-78°C to rt	SM
2 eq $LiBHEt_3$	THF	-78°C, 1h	decomp.

Mechanisstically, the transformation to tricycle **309** proceeds as follows: after deprotection of the TFA-amide the diazo group gets protonated forming diazonium salt **311**. A subsequent nucleophilic attack by the double bond generates carbocation **312** which is trapped by water immediately to provide secondary alcohol **309** (Scheme 104).



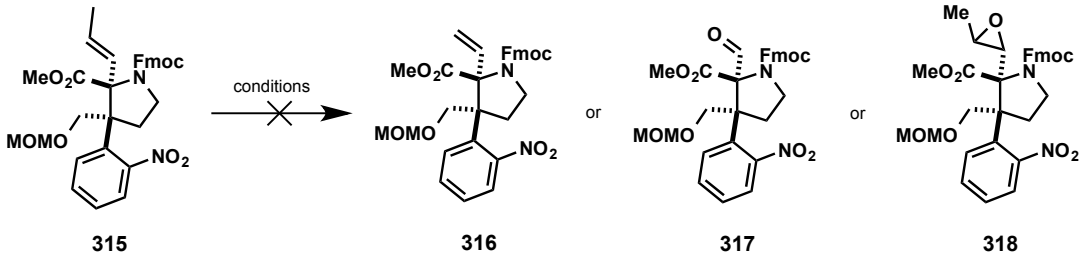
Scheme 104: Mechanism to tricycle **309**.

Due to these deprotection problems (trifluoro acetamide cleavage) another protecting group strategy was neccessary. Therefore, we have choosen the Fmoc-group which is unstable under very mild basic conditions. Based on this considerations, allyl amine **300** was deallylated under Pd-catalysis followed by a protection as a Fmoc-carbamate (**314**) with FmocCl. Isomerization to the higher substituted double bond (**315**) was performed as mentioned above under the influence of $Pd_2Cl_2(MeCN)_2$ (Scheme 105).



Scheme 105: Fmoc-Protection and double bond isomerization.

Similar to compound **302** a conversion of the prop-2-ene substituent to a vinyl group in compound **315** was not achieved. Most of the reaction conditions did not show any conversion (Table 22, Scheme 106).



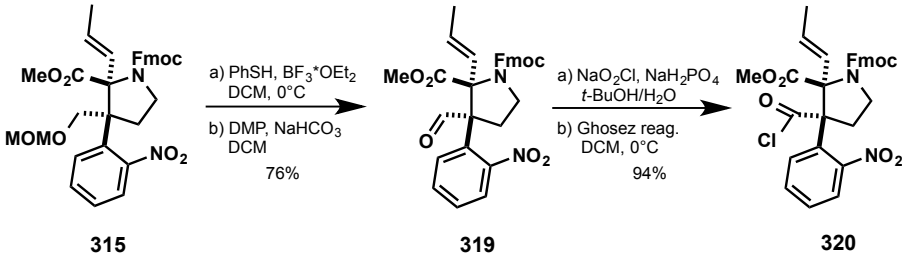
Scheme 106: Derivatisation attempts of compound **315**.

Table 22: Conversion of olefine **315** under different conditions.

reagent	temp.	solvent	outcome
0.1 eq HG II	70 °C, 3h	PhMe/ 1,7-octadiene	SM
0.1 eq G I, 50 bar C_2H_4	rt, 27h	DCM	SM
0.1 eq G II, 50 bar C_2H_4	rt, 27h	DCM	SM
0.1 eq HG II, 50 bar C_2H_4	rt, 27h	DCM	SM
0.1 eq G II, 50 bar C_2H_4	rt, 8d	DCM	SM
0.1 HG II, 10 eq acroleine	50 °C, 13h	DCE	SM
O_3 then thiourea	-78 °C to rt	DCM/MeOH	SM
O_3 then thiourea	-20 °C to rt	DCM/MeOH	decomp.
0.1 eq OsO_4, 1 eq NMO	rt, 24h	*t*BuOH/H_2O	SM
5 eq $KMnO_4$	rt, 24h	MeOH/H2O	SM
5 eq *m*CPBA	rt, 24h	DCM	SM
5 eq *m*CPBA	reflux, 2h	PhMe	SM
5 eq DMDO	0 °C to rt, 24h	acetone/H_2O	SM
3 eq SeO_2	reflux, 3h	PhH	SM
10 eq CrO_3, 10 eq DMP	-20 °C to rt, 15h	DCM	SM
2 eq NBS, 0.1 eq AIBN	reflux, 3h	PhH	decomp.

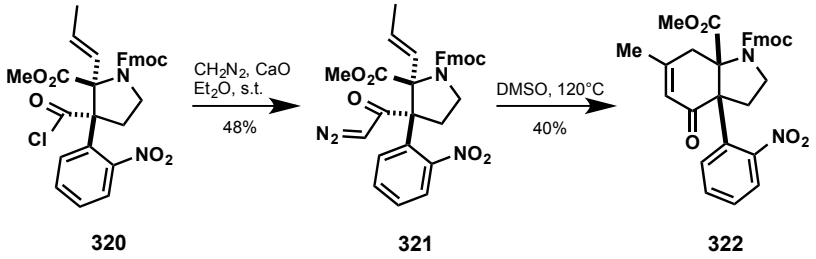
Based on these results, we decided to proceed with the *Stevens* rearrangement problem and adressed the degradation question on a later stage during the synthesis. Therefore, transformation of the MOM-ether **315** to acid chloride **320** proceeded *via* the established protocol. MOM-Deprotection was accomplished with thiophenol and trifluoroborane followed by an oxidation with DMP to aldehyde **319**. *Pinnick* oxidation gave the

carboxylic acid which was converted to the acid chloride (**320**) by the use of *Ghosez* reagent (Scheme 107).



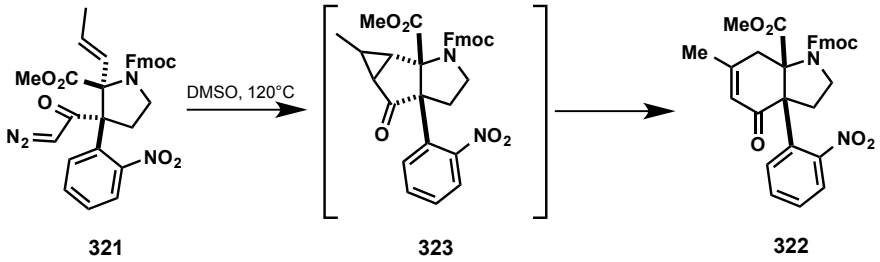
Scheme 107: Transformation to acid chloride **320**.

Acid chloride **320** reacted with diazomethane in Et_2O under sealed conditions to α-diazo ketone **321**. Unfortunately, a deprotection attemp at 120°C in DMSO afforded only the undesired tricycle **322** (Scheme 108).



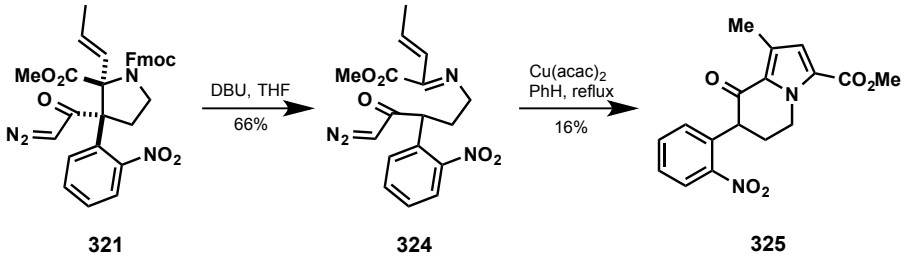
Scheme 108: Transformation to tricyclic compound **322**.

Mechanistically, tricyclic compound **322** was formed *via* cyclopropane **323** which opens spontaniously to α,β-unsatureated ketone **322** in a [2Π] electrocyclic ring opening reaction (Scheme 109).



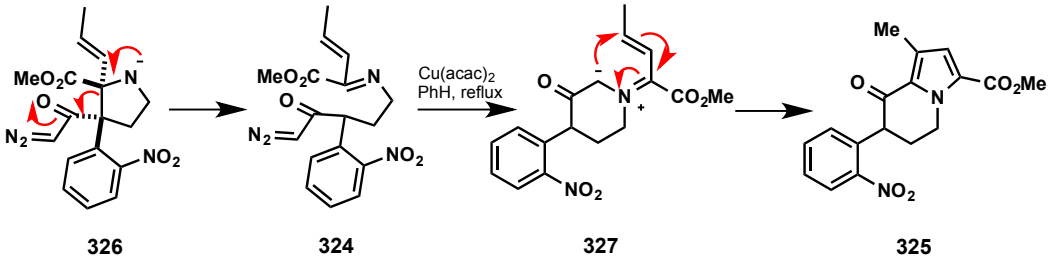
Scheme 109: Mechanism of the formation of tricycle **322**.

Moreover, Fmoc-Deprotection with DBU in THF delivered exclusively fragmentation product **324** instead of the secondary amine. It is also noteworthy that a treatment with $Cu(acac)_2$ in refluxing benzene yielded pyrrole **325** (Scheme 110).



Scheme 110: Fmoc-deprotection under non-protic conditions and transformation to pyrrole **325**.

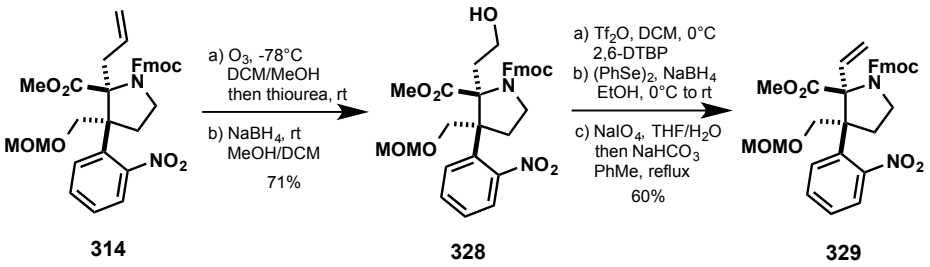
Mechanistaically these transformations proceed as follows: removal of the Fmoc-group under aprotic conditions establishes a negative charge at the nitrogen which initiates a fragmentation to compound **324**. The subsequent release of nitrogen under Cu(II)-catalysis generates the carbenoid which inserts instantly into the imine lone pair to ylide **327**. A following *Michael* addition gives pyrrole **325** (Scheme 111).



Scheme 111: Mechanism to compound **325**.

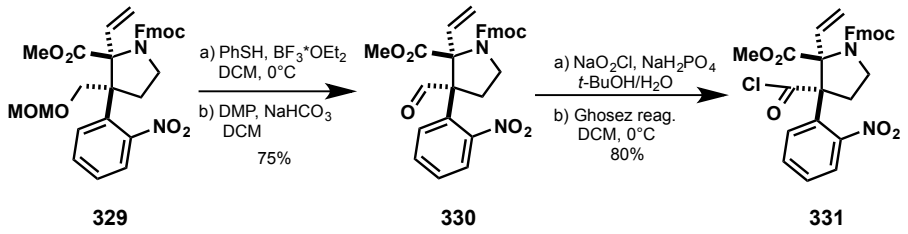
According to these disappointing results, we decided to convert the allyl side chain into the less bulky vinyl group and perform the N-H insertion on a later stage. This transformation was achieved as follows: allylic compound **314** was converveted to the corresponding aldehyde by an ozonolysis. The aldehyde was reduced to primary alcohol **328** with $NaBH_4$ in methanol. It is noteworthy that a direct reductive work-up of the secondary ozonide with $NaBH_4$ only led to decomposition. A following treatment of the primary alcohol with Tf_2O and

2,6-di-*tert*-butyl pyridine in DCM delivered the corresponding leaving group which was substituted by NaSePh to the seleno ether. Oxidation of the seleno ether with sodium periodate provided the seleno oxide which was eliminated by heating in refluxing toluene to vinylic compound **329** (Scheme 112).



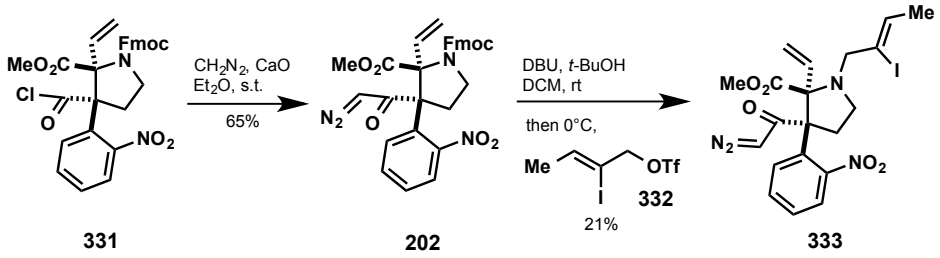
Scheme 112: Transformation to vinylic compound **329**.

Deprotection of the MOM-ether with thiophenol and trifluoroborane gave the primary alcohol which was oxidized with DMP to aldehyde **330**. *Pinnick* oxidation resulted in the carboxylic acid which was converted to acid chloride **331** by using *Ghosez* reagent (Scheme 113).



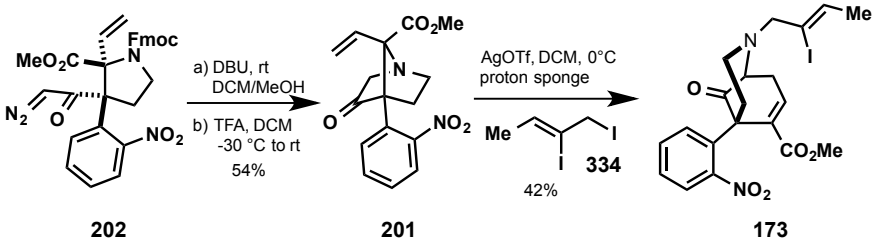
Scheme 113: Transformation to acid chloride **331**.

Reaction of acid chloride **331** with diazomethane yielded α-diazo ketone **202**. Fmoc-Deprotection with DBU in DCM and 10 equivalents *tert*-butanol gave the corresponding secondary amine without any fragmentation product. Unfortunately, *N*-alkylation with triflate **332** only worked in a low yield of 21% and mostly led to decomposition (Scheme 114).



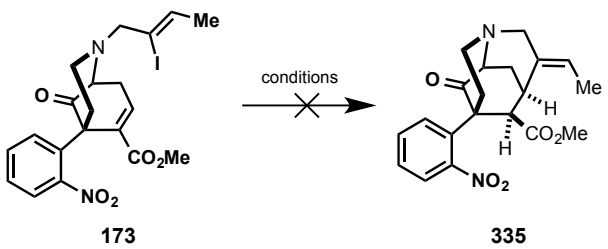
Scheme 114: Transformation to vinyl iodide **333**.

Fmoc-Deprtotection of compound **202** in a mixture of DCM and methanol with DBU followed by an acid-induced *NH*-insertion yielded bridged amine **201**. A subsequent *N*-alkylation with iodide **334** and AgOTf in combination with proton sponge in DCM provided the corresponding ammonium salt which directly underwent a [2,3]-sigmatropic *Stevens* rearrangement to the azabicyclo-[3.3.1]nonane skeleton **173** (Scheme 115).



Scheme 115: *Stevens* rearrangement to the azabicyclo-[3.3.1]nonane skeleton (**173**).

With compound **173** in hands, several attempts were executed to perform an intramolecular 1,4-addition of the vinyl iodide to the α,β-unsaturated ester (**335**). Unfortunately, all conditions led to a reisolation or decomposition of starting material (Table 23, Scheme 116).

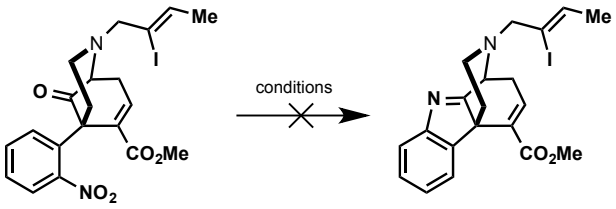


Scheme 116: 1,4-Addition to the strictamine skeleton (**335**).

Table 23: Condition for 1,4-addition of vinyl iodide **173**.

reagent	base	additive	solvent	temp.	outcome
1.5 eq $Ni(COD)_2$	3 eq NEt_3	2 eq Et_3SiH	MeCN	rt, 18h	decomp.
6.6 eq $Ni(COD)_2$	3 eq NEt_3	10 eq LiCN	DMF	rt, 2h	decomp.
6 eq $Ni(COD)_2$	10 eq NEt_3	2 eq BHT	MeCN/ DMF	rt, 30min	decomp.
0.2 eq BEt_3	-	1.2 eq Bu_3SnH	PhMe	rt, 20h	SM
0.1 eq AIBN	-	2 eq Bu_3SnH	PhH	reflux, 1h	decomp.
2,5 eq *t*BuLi	-	-	Et_2O	-78 °C to rt	SM
2,5 eq *t*BuLi	-	3 eq HMPA	Et_2O	-78 °C to rt	SM
0.01 eq $Pd(OAc)_2$	5 eq K_2CO_3	2.5 eq Bu_4NCl, 1.2 eq NaO_2CH	DMF	80 °C, 30min	decomp.
1 eq $Pd(OAc)_2$	-	2 eq PPh_3	NEt_3	reflux, 15min	decomp.
1 eq $Pd(dppf)Cl_2$	3 eq NEt_3	5 eq Et_3SiH	DMF	90 °C, 1h	decomp.

In most cases, a reduction of the nitro group to the amine or imine oxide was observed before complete decomposition. Apparently, a chemoselectivety problem between the 1,4-addition and the reduction of the nitro group occured. Due to this fact, we decided to reduce the nitro group selectively before performing the 1,4-addition (Table 24, Scheme 117).



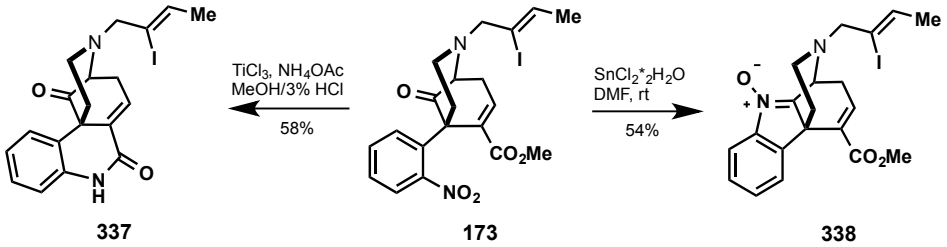
173 **336**

Scheme 117: Reduction of the nitro-group to indolenine **336**.

Table 24: Conditions for the reduction of the nitro group.

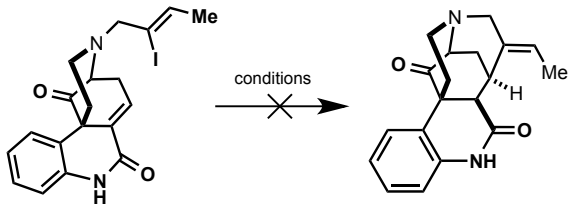
reagent	additive	solvent	temp.	outcome
25 eq Zn	-	HOAc	50 °C, 15min	decomp.
5 eq Fe	10 eq NH_4Cl	EtOH/H_2O	90 °C, 15min	decomp.
70 eq Zn	10 eq $CaCl_2$	MeOH	reflux, 30min	decomp.
cat. PtO_2	1 atm H_2	MeOH	rt, 1h	decomp.
cat Pd/C	1 atm H_2	MeOH	rt, 1h	hydration vinyl iodide
10 eq $SnCl_2$* $2H_2O$	-	DMF	rt, 20h	iminoxide **338**
25 eq $TiCl_3$	3% HCl aq.	MeOH/2.5 M NH_4OAc	rt, 2.5h	α,β-unsaturated lactame **337**

Disappointingly, indolenine **336** was not isolated under the choosen conditions. In most cases the starting material decomposed during reaction. However, treatment of the starting material $SnCl_2$*$2H_2O$ delivered undesired iminoxide **338** as a single product. Moreover, if $TiCl_3$ was used as a reducing agent a smooth conversion to the amine was observed. Unfortunately, the amine performed an unexpected cyclization to α,β-unsaturated lactame **337** under these reaction conditions (Scheme 118).



Scheme 118: Reduction of nitro compound **173**.

Nevertheless, an intramolecular 1,4-addition of the vinyl iodide to α,β-unsaturated lactame (**339**) was examined under different conditions (Table 25, Scheme 119).



337 **339**

Scheme 119: 1,4-Addition of vinyl iodide **337**.

Table 25: Condition for a 1,4-addition of vinyl iodide **337**.

reagent	base	additive	solvent	temp.	outcome
3 eq $Ni(COD)_2$	6 eq NEt_3	1.5 eq Et_3SiH	MeCN	rt, 37h	SM
1 eq $Pd(OAc)_2$	-	2 eq PPh_3	NEt_3	reflux, 10min	decomp.
1 eq $Pd(dppf)Cl_2$	3 eq NEt_3	5 eq Et_3SiH	DMF	rt, 30min	decomp.
0.1 eq AIBN	-	1.5 eq Bu_3SnH	PhH	reflux, 20min	crude mixture

Under Ni-catalysis only starting material was reisolated. Pd-Catalysis led to a complet decomposition of the starting material. Radical conditions seemed to be more promising showing a crude mixture of different products. This is not surprising due to a possible isomarization during radical formation. Due to the fact of less material the product mixture could not be seperated.

7. Conclusions and outlook

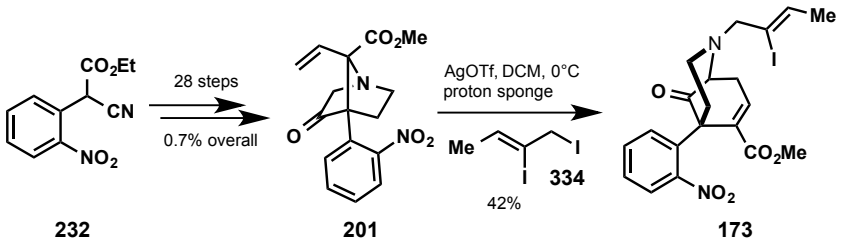
The akuammiline alkaloids, a class of monoterpenoid indole alkaloids, were examined during this work highlighting two different aspects. First, the biosynthetic origin of these alkaloids was studied by a conformational analysis of their proposed biogenetic precursor *E*-geissoschizine (**35**). Second, a general synthetic access to this class of alkaloids should be established by a total synthesis of strictamine (**3**) followed by biomimetic transformations to rhazimine (**7**), scholarisine A (**26**) and alstiphyllanine E (**12**). Therefore, a biomimetic synthesis of strictamine (**3**) starting from *E*-geissoschizine (**35**) and a classical synthesis starting from commercially available building blocks were studied.

The *Corynanthean* alkaloids are considered as key intermediates in the biosynthesis of several monoterpenoid indole alkaloids. It is generally agreed upon, that *E*-geissoschizine (**35**) itself is a precursor for biosynthetic "secondary cyclizations", leading to C-mavacurine, strychnos and akuammiline alkaloids. A correlation between these "secondary cyclizations" and the C19-20 double bond geometry (*E*)- or (*Z*) present in geissoschizine has been shown by a detailed conformational analysis of both compounds and derivatives. The main conformation of (*Z*)-geissoschizine (**41**) comprises a *trans*-quinolizidine system whereas (*E*)-geissoschizine (**35**) comprises a *cis*-quinolizidine system. The C-mavacurine, strychnos and akuammiline alkaloids all contain a *cis*-quinolizidine system, which is a prior condition for the "secondary cyclizations" to occur and gives the typical cage-type structure. The cage-structure in turn precludes isomerization to the thermodynamically favored *trans*-quinolizidine.

Because of this, a biomimetic synthesis of strictamine (**3**) starting from a geissoschizine derivative has only a chance of success if the precursor stays in a *cis*-quinolizidine conformation. For this transformation a cyclopropanation strategy starting from diazo-geissoschizoate **92** was examined. Unfortunately, a cyclopropanation of the indole double bond did not occur but an insertion of the nitrogen lone pair into the carbenoid was observed instead. This is due to

the fact that diazo-geissoschizoate **92** prefers a *trans*-quinolizidine conformation facing the nitrogen lone pair instead of the indole double bond to the carbenoid.

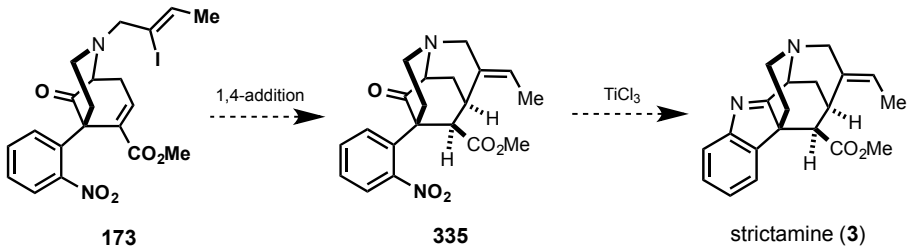
The classical synthesis of strictamine (**3**) starting from commercially available building blocks was based on four different retrosynthetic approaches. The first approach was based on two *Sakurai* allylations generating the carbon skeleton of strictamine (**3**). Due to inefficient steps at the beginning of the synthesis this was skipped. The second approach based on a reductive alklyation and a *Diels Alder* strategy was abandoned due to the reactivity pattern of the examined bisallylic compounds. The third synthetic approach deals with a *Stevens* [1,2]-rearrangement as a key step. Unfortunately, the synthesis of the rearrangement precursor was not successful.
The fourth approach towards a total synthesis of strictamine (**3**) was very promising. Key feature of this synthesis is a *Stevens* [2,3]-sigmatropic rearrangement resulting in the azabicyclo-[3.3.1]nonane skeleton (**173**) present in strictamine (**3**). The precursor of the rearrangement (**201**) was synthesized in 28 consecutive steps starting from literature known[106] compound **232** with an overall yield of 0.7%. The sigmatropic rearrangement giving compound **173** proceeded in a yield of 42% (Scheme 120).



Scheme 120: Key step of the 4th synthetic approach to strictamine (**3**).

Due to the lack of time and material, the missing two steps resulting in a completed total synthesis of stictamine (**3**) were not established. Conditions performing an intramolecular 1,4-addition to compound **335** were tested but did not give any productive results. Further investigations to perform this transformation are neccessary. The last step of the synthesis will be a reduction of the aromatic nitro group to the aniline followed by a subsequent

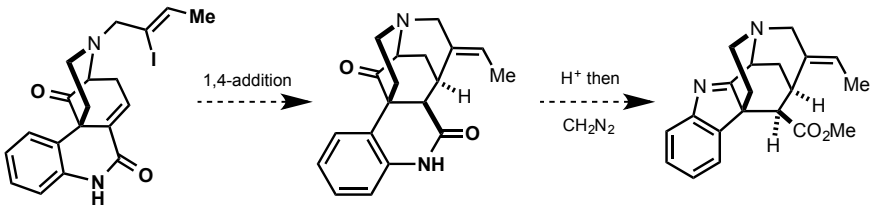
condensation with the ketone closing the indolenine cycle. $TiCl_3$ as a reducing agent seems to be very promising for this transformation (Scheme 121).



173 **335** strictamine (**3**)

Scheme 121: Missing transformations for a completed total synthesis of strictamine (**3**).

A change in order opens the possibility for an alternative strategy. Reduction of the aromatic nitro group in compound **173** under the influence of $TiCl_3$ as reducing agent results in α,β-unsaturated lactame **337**. Again, an intramolecular 1,4-addition to compound **339** is feasible. After this an opening of the lactame and methylation of the corresponding carboxylic acid ends in the formation of strictamine (**3**, Scheme 122).



337 **339** strictamine (**3**)

Scheme 122: Alternative transformations for a completed total synthesis of strictamine (**3**).

8. Experimental Section

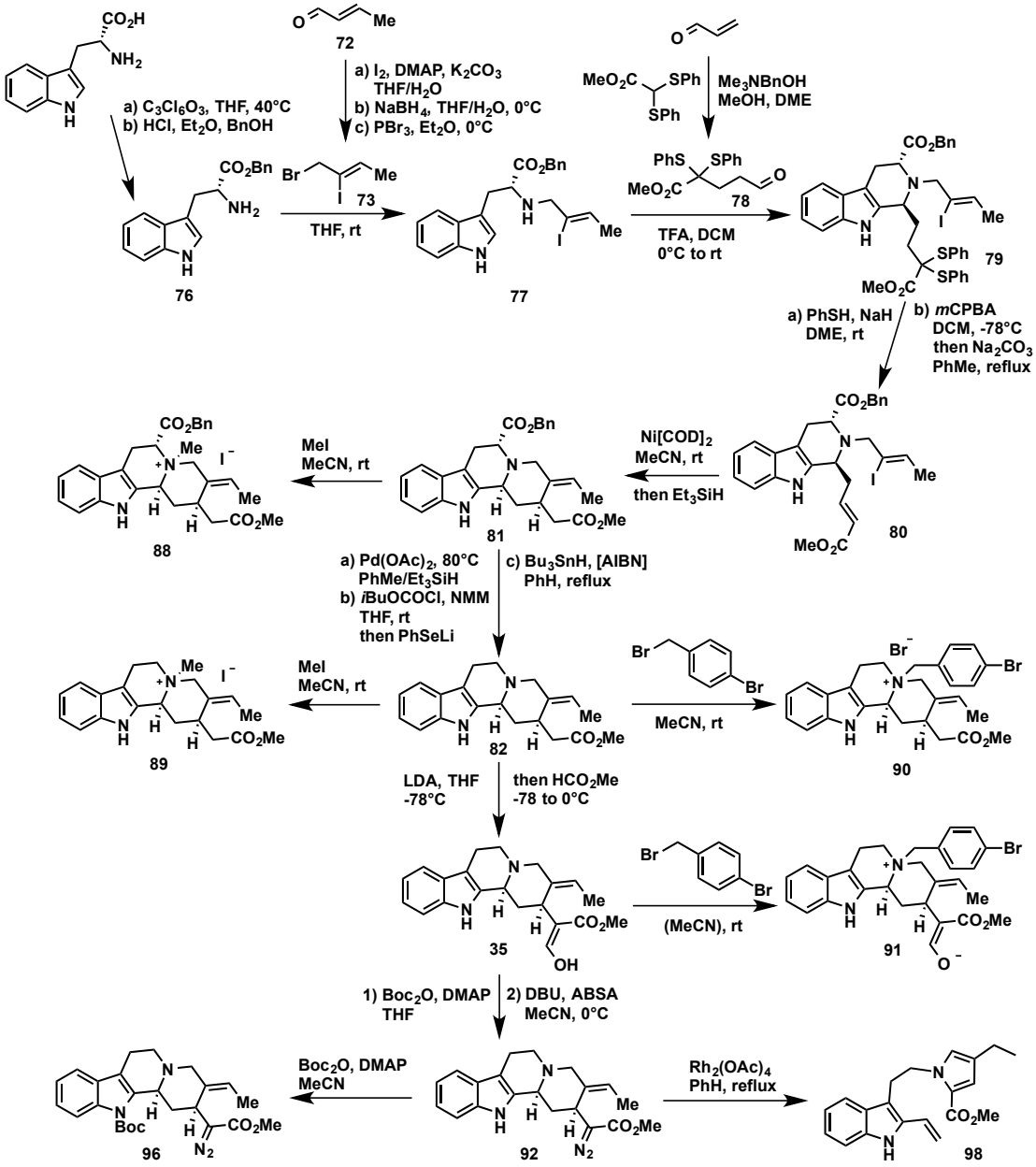
8.1 General

All reactions were carried out in oven-dried glassware. Anhydrous DCM was distilled from CaH_2 under argon and anhydrous THF was distilled from Na and benzophenone under argon atmosphere. Other anhydrous solvents were obtained by filtration through drying columns (Et_2O, DMF, CH_3CN, toluene, benzene, hexane, methanol) on a Glass-Contour system. Reactions were magnetically and mechanically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å of Acros under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer of Bruker. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in ppm (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet, *b* = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy. High resolution mass spectra are obtained with a Micromass LCT via loop-mode injection from a Waters (Alliance 2695) HPLC system. Alternatively a Micromass Q-TOF in combination with a Waters Aquity Ultraperformance LC system is employed. Ionization is achieved by ESI. Modes of ionization, calculated and found mass are given. IR spectra were measured with a Bruker Vector 22 FT-IR spectrometer. Single crystal diffractions were collected on a Bruker X8APEX II CCD or a Bruker SMART X2S diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were placed at calculated positions and refined as riding atoms in the subsequent least squares model refinements. Structure solution and refinement was performed with the SHELX program. Commercially available reagents were used as supplied. Flash chromatography was performed with J.T. Baker brand silica gel (40 -60

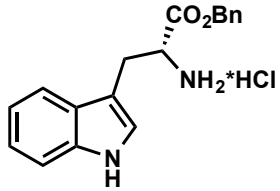
μm, 60 Å pores). Eluents used for flash chromatography were distilled prior to use.

8.2 Experimental procedures

8.2.1 *E*-Geissoschizine



Tryptophan benzylester hydrochloride (76)

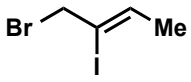


To a suspension of tryptophan (30.6 g, 150 mmol, 1 eq) in absolute THF (350 mL) was added triphosgene (16.9 g, 57.0 mmol, 0.38 eq) at 40°C in one portion. The mixture was stirred at 45°C for 90min and was then allowed to cool down to rt. A saturated etheral solution of HCl was prepared by introducing gaseous anhydrous HCl into absolute Et_2O (600 mL) at -78°C until vigorous bubbling was observed. The mixture was allowed to warm up to rt. During this time benzyl alcohol (33.0 mL, 34.3 g, 317 mmol, 2.1 eq) was added followed by the cooled THF solution. The reaction mixture was stored at rt for 3d. The colourless precipitate was collected and washed with cold Et_2O (3 x 100 mL) to obtain tryptophan benzylester hydrochloride (47.5 g, 144 mmol, 0.96 eq) as a colourless solid. An analytical sample was recrystalized from EtOH.

^{1}H NMR (MeOD, 400 MHz): δ = 7.53 (ddd, J_1 = 7.7 Hz, J_2 = 0.7 Hz, J_3 = 0.7 Hz, 1H), 7.40 (ddd, J_1 = 8.3 Hz, J_2 = 0.8 Hz, J_3 = 0.8 Hz, 1H), 7.36 - 7.32 (m, 3H), 7.27 - 7.22 (m, 2H), 7.15 (ddd, J_1 = 8.1 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.09 (s, 1H), 7.06 (ddd, J_1 = 7.9 Hz, J_2 = 6.9 Hz, J_3 = 0.9 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 4.35 (dd, J_1 = 7.2 Hz, J_2 = 6.1 Hz, 1H), 3.44 (ddd, J_1 = 15.0 Hz, J_2 = 6.2 Hz, J_3 = 0.7 Hz, 1H), 3.36 (dd, J_1 = 15.0 Hz, J_2 = 7.2 Hz, 1H) ppm.

^{13}C NMR (MeOD, 100.6 MHz): δ = 170.4, 138.3, 136.2, 129.7, 129.6, 128.2, 125.5, 123.0, 120.4, 118.8, 112.7, 112.7, 107.4, 69.3, 54.8, 27.8 ppm.

(*Z*)-1-Bromo-2-iodobut-2-ene (73)



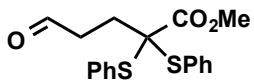
Crotonaldeyhde (11.8 mL, 10.0 g, 143 mmol, 1 eq) was dissolved in THF/H_2O = 1:1 (700 mL). K_2CO_3 (23.7 g, 171 mmol, 1.2 eq), DMAP (3.49 g, 28.5 mmol,

0.2 eq) and iodine (72.4 g, 286 mmol, 2 eq) were sequentially added. The resulting mixture was stirred at rt for 5h. Aqueous $Na_2S_2O_3$ (250 mL) was added and the aqueous phase was extracted with EtOAc (3 x 250 mL). The combined organic phases were concentrated under reduced pressure. The crude vinyl iodide was dissolved in THF/H_2O = 9:1 (600 mL) and cooled to 0°C. $NaBH_4$ (2.70 g, 71.3 mmol, 0.5 eq) was added and the reaction mixture was stirred at 0°C for 1h. H_2O (250 mL) was added and the aqueous phase was extracted with EtOAc (3 x 250 mL). The combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain (*Z*)-2-iodobut-2-en-1-ol (24.1 g, 122 mmol, 0.85 eq) as a colourless liquid.

(*Z*)-2-Iodobut-2-en-1-ol (10.0 g, 50.5 mmol, 1 eq) was dissolved in absolute Et_2O (100 mL) and cooled to 0°C. Phosphorous tribromide (1.92 mL, 5.47 g, 20.2 mmol, 0.4 eq) was added and the resulting mixture was allowed to warm up to rt. After stirring for 19h the organic phase was poured onto aqueous K_2CO_3 (250 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude bromide was purified by flash column chromatography (SiO_2, pentane/Et_2O = 10:1) to obtain (*Z*)-1-bromo-2-iodobut-2-ene (7.70 g, 29.5 mmol, 0.58 eq) as a slightly yellow liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.05 (tq, J_1 = 1.0 Hz, J_2 = 6.4 Hz, 1H), 4.35 (dq, J_1 = 1.9 Hz, J_2 = 0.9 Hz, 2H), 1.80 (dt, J_1 = 6.5 Hz, J_2 = 0.9 Hz, 3H) ppm.

5-Oxo-2,2-bis(phenylthio)pentanoate (78)

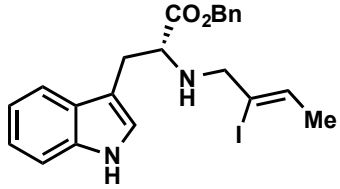


NaH (1.76 g, 44.0 mmol, 2.2 eq, 60% dispersion in mineral oil) was added to MeOH (100 mL) under argon at 0°C. Thiophenol (4.50 mL, 4.85 g, 44.0 mmol, 2.2 eq) was added and the mixture was stirred at 0°C for 30min. Methyl dichloroacetate (2.07 mL, 2.86 g, 20.0 mmol, 1eq) dissolved in MeOH (10 mL)

was added and the mixture was allowed to warm up to rt. After stirring for 1h aqueous NH_4Cl (250 mL) was added. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 100:1 to 20:1 to 10:1) to obtain methyl 2,2-bis(phenylthio)acetate (3.90 g, 13.4 mmol, 0.67 eq) as a colourless fluid.
Methyl 2,2-bis(phenylthio)acetate was dissolved in absolute DME (30 mL). Triton B (300 μL, 670 μmol, 0.05 eq, 40wt% solution in MeOH) was added to the solution. Acroleine (1.08 mL, 904 mg, 16.1 mmol, 0.73 eq) was added dropwise and the resulting mixture was stirred at rt for 2.5d. The solvent was removed under reduced pressure and the crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 2:1) to obtain 5-oxo-2,2-bis(phenylthio)pentanoate (3.08 g, 8.88 mmol, 0.4 eq) as a colourless viscous fluid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.65 (t, *J* = 1.0 Hz, 1H), 7.60 - 7.57 (m, 4H), 7.44 - 7.39 (m, 2H), 7.38 - 7.33 (m, 4H), 3.65 (s, 3H), 2.79 - 2.75 (m, 2H), 2.13 - 2.10 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 200.5, 169.6, 136.6, 130.4, 130.1, 129.1, 68.1, 53.0, 40.1, 27.9 ppm.

N_b-(*Z*-2'-Iodo-2'-butenyl) tryptophan benzylester (77)

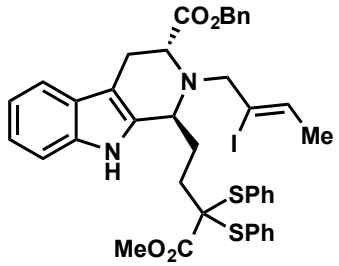


Tryptophan benzyl ester (10.2 g, 34.7 mmol, 1 eq) was dissolved in anhydrous THF (7 mL) and added to a solution of (*Z*)-1-bromo-2-iodobut-2-ene (7.70 g, 29.5 mmol, 0.85 eq) in anhydrous THF (7 mL). The mixture was stirred for 13h at rt. Concentrated aq. ammonia solution (10 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined

organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 2:1, 1:1) to afford N_b-(*Z*-2'-iodo-2'-butenyl) tryptophan benzylester (7.05 g, 14.9 mmol, 0.43 eq).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.05 (bs, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7. 30 - 7.35 (m, 4H), 7.18 - 7.21 (m, 3H), 7.10 - 7.14 (m, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 5.62 (q, *J* = 6.4 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.6 Hz, 1H), 3.67 (t, *J* = 6.6 Hz, 1H), 3.51 (d, *J* = 14.3 Hz, 1H), 3.36 (d, *J* = 14.3 Hz, 1H), 3.23 (dd, J_1 = 6.1 Hz, J_2 = 14.3 Hz, 1H), 3.14 (dd, J_1 = 7.2 Hz, J_2 = 14.3 Hz, 1H), 1.67 (d, *J* = 6.3 Hz, 3H), 2.02 (bs, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 174.4, 136.4, 135.9, 132.1, 128.6, 128.4, 128.3, 127.7, 123.2, 122.2, 119.6, 119.0, 111.3, 111.2, 109.7, 66.6, 59.8, 59.7, 29.4, 21.8 ppm.

trans-3-Benzyloxycarbonyl-2-(_Z_-2'-iodo-2'-butenyl)-1-(3',3'-diphenyl-sulfanyl-3'-methoxycarbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-_b_]indole (79)

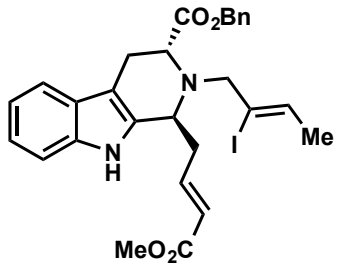


N_b-(*Z*-2'-iodo-2'-butenyl) tryptophan benzylester (2.50 g, 5.27 mmol, 1 eq) and methyl 5-oxo-2,2-bis(phenylthio)pentanoate (2.19 g, 6.34 mmol, 1.2 eq) were dissolved in anhydrous DCM (20 mL) and cooled to 0°C. Trifluoroacetic acid (807 µL, 1.20 g, 10.5 mmol, 2 eq) was added dropwise and the mixture was allowed to warm up to rt. After stirring for 3h water (50 mL) was added and the pH was adjusted to pH = 9 with aqueous ammonia solution. The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organic phases were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and the crude material was purified by flash column

chromatography (SiO_2, PE/EtOAc = 10:1, 5:1, 3:1) to afford *trans*-3-benzyloxycarbonyl-2-(*Z*-2'-iodo-2'-butenyl)-1-(3',3'-diphenylsulfanyl-3'-methoxy-carbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (3.46 g, 4.31 mmol, 0.82 eq).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 - 7.54 (m, 3H), 7.45 - 7.48 (m, 3H), 7.28 - 7.35 (m, 2H), 7.10 - 7.24 (m, 12H), 5.76 (q, J = 6.2 Hz, 1H), 5.05 (s, 2H), 4.18 (bs, 1H), 3.86 (dd, J_1 = 5.4 Hz, J_2 = 5.4 Hz, 1H), 3.58 (s, 3H), 3.55 (d, J = 14.6 Hz, 1H), 3.39 (d, J = 14.6 Hz, 1H), 3.13 (ddd, J_1 = 15.4 Hz, J_2 = 5.5 Hz, J_3 = 0.7 Hz, 1H), 2.94 (ddd, J_1 = 15.4 Hz, J_2 = 5.5 Hz, J_3 = 0.7 Hz, 1H), 2.26 - 2.33 (m, 1H), 2.04 - 2.09 (m, 2H), 1.80 - 1.88 (m, 1H), 1.73 (d, J = 6.1 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.7, 170.2, 136.4, 136.2, 136.0, 134.2, 132.4, 131.4, 131.1, 129.6, 129.5, 128.9, 128.8, 128.5, 128.1, 127.8, 127.1, 121.7, 119.6, 118.1, 111.2, 108.8, 107.8, 69.3, 66.1, 61.5, 56.3, 54.8, 52.9, 31.6, 28.9, 23.4, 21.9 ppm.

trans-3-Benzyloxycarbonyl-2-(_Z_-2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-_b_]indole (80)



trans-3-Benzyloxycarbonyl-2-(*Z*-2'-iodo-2'-butenyl)-1-(3',3'-diphenylsulfanyl-3'-methoxycarbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (1.35 g, 1.68 mmol, 1 eq) was dissolved in anhydrous DME (15 mL). Thiophenol (223 μL, 241 mg, 2.19 mmol, 1.3 eq) and sodium hydride (12.0 mg, 303 μmol, 0.18 eq, 60% dispersion in mineral oil) were sequentially added and the mixture was stirred for 18h at rt. Water (100 mL) was added and the aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The

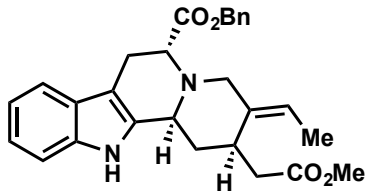
crude material was purified by flash colum chromatography (SiO_2, PE/EtOAc = 5:1, 2:1) to afford the mercaptane (1.05 g, 1.51 mmol, 0.9 eq) as a mixture of diastereoisomers.

This was dissolved in anhydrous DCM (15 mL) and cooled to -78°C. *m*CPBA (276 mg, 1.60 mmol, 0.95 eq) dissolved in anhydrous DCM (5 mL) was added dropwise and the mixture was stirred for 1h at -78 °C. After complete oxidation the reaction mixture was poured into a mixture of aqueous $Na_2S_2O_3$ (100 mL) and DCM (100 mL). The aqueous phase was extracted with DCM (2x100 mL) and the combined organic phases were dried over $MgSO_4$ and filtrated. After removal of the solvent under reduced pressure the crude sulfoxide was dissolved in $CHCl_3$ (10 mL) and added to a refluxing suspension of Na_2CO_3 (233 mg, 2.19 mmol, 1.3 eq) in toluene (30 mL). After 1.5h the mixture was allowed to cool down to rt and was poured into water (300 mL). The aqueous phase was extracted with $CHCl_3$ (3x50 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 5:1, 3:1) to afford *trans*-3-benzyloxycarbonyl-2-(*Z*-2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (573 mg, 980 μmol, 0.58 eq).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.02 - 7.25 (m, 8H), 5.84 - 5.90 (m, 2H), 5.08 (s, 2 H), 4.33 (dd, J_1 = 5.0 Hz, J_2 5.0 Hz, 1H), 4.01(dd, J_1 = 5.6 Hz, J_2 = 5.6 Hz, 1H), 3.69 (s, 3H), 3.65 - 3.67 (m, 1H), 3.54 (d, *J* = 15.0 Hz, 1H), 3.20 (ddd, J_1 = 15.5 Hz, J_2 = 5.8 Hz, 0.7 Hz, 1H), 3.06 (ddd, J_1 = 15.5 Hz, J_2 = 5.3 Hz, J_3 = 1.0 Hz, 1H), 2.69 - 2.82 (m, 2H), 1.76 (d, *J* = 6.49 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.7, 166.8, 145.7, 136.5, 136.0, 133.8, 132.6, 128.6, 128.2, 127.9, 127.0, 123.6, 122.1, 119.8, 118.4, 111.0, 108.7, 107.9, 66.4, 62.4, 57.1, 55.4, 51.6, 37.3, 23.3, 21.9 ppm.

Benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethyl-idene-indolo[2,3-a]quinolizidine-5-carboxylate (81)



$Ni[COD]_2$ (593 mg, 2.16 mmol, 1.5 eq) was dissolved in anhydrous MeCN (60 mL) and put under argon in a Schlenk flask. *trans*-3-Benzyloxycarbonyl-2-(*Z*-2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (840 mg, 1.44 mmol, 1 eq) and triethyl amine (601 μL, 436 mg, 4.31 mmol, 3 eq) were dissolved in anhydrous MeCN (30 mL) and added to the $Ni[COD]_2$ solution. The mixture was stirred for 20min at rt. Triethyl silane (458 μL, 334 mg, 2.87 mmol, 2 eq) was added to each flask and stirred for 2h at rt. The reaction mixture was poured onto a mixture of DCM (200 mL) and saturated aqueous Na_2CO_3 solution (200 mL). Both phases were filtered over a pad of celite and after partitioning, the aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1, 2:1, 1:1) to afford benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidine-5-carboxylate (344 mg, 750 μmol, 0.52 eq).

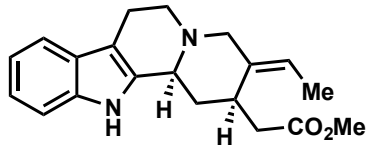
R_f = 0.26 (PE/EtOAc = 2:1) [CAN]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (bs, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.20 - 7.25 (m, 5H), 7.13 - 7.17 (m, 1H), 7.08 - 7.12 (m, 1H), 5.44 (q, *J* = 6.8 Hz, 1H), 5.15 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 12.6 Hz, 1H), 4.58 (dd, J_1 = 5.9 Hz, J_2 = 5.4 Hz, 1H), 3.94 (dd, J_1 = 5.5 Hz, J_2 = 3.1 Hz, 1H), 3.68 (s, 3H), 3.54 (d, *J* = 12.3 Hz, 1H), 3.26 (d, *J* = 12.3 Hz, 1H), 3.15 - 3.24 (m, 2H), 2.36 (dd, J_1 = 14.4 Hz, J_2 = 5.8 Hz, 1H), 2.25 - 2.31 (m, 1H), 2.23 (ddd, J_1 = 14.1 Hz, J_2 = 6.5 Hz, J_3 = 5.4 Hz, 1H), 2.04 (ddd, J_1 = 13.9 Hz, J_2 = 6.3 Hz, J_3 = 4.1 Hz, 1H), 1.64 (dd, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 173.9, 172.3, 136.2, 136.0, 135.6, 134.2, 128.6, 128.2, 128.1, 127.5, 121.6, 121.1, 119.6, 118.1, 111.1, 105.4, 66.4, 61.1, 55.2, 51.9, 49.2, 38.2, 32.5, 31.6, 21.8, 12.9 ppm.

IR (neat): 3370, 2942, 2857, 1727, 1447, 1370, 1316, 1243, 1153, 1043, 1011, 826, 741, 697, 639 cm^{-1}.

***20E*-Geissoschizoate (82)**



Benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidine-5-carboxylate (344 mg, 750 μmol, 1 eq) was dissolved in anhydrous toluene (20 mL) and heated to 80°C. $Pd(OAc)_2$ (42.1 mg, 188 μmol, 0.25 eq) and triethyl silane (14 mL) were added and the mixture was stirred at 80°C for 4h. After cooling down to rt the residue was filtrated over celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1, DCM/MeOH = 10:1; 5:1, 4:1) to afford the carboxylic acid (218 mg, 592 μmol, 0.79 eq) which was dissolved in anhydrous THF (5 mL). *N*-methyl morpholine (75.0 μL, 69.0 mg, 1.15 eq) and *iso*-butyl chloroformate (92.0 μL, 97.0 mg, 681 μmol, 1.2 eq) were sequentially added and the mixture was stirred for 1h at rt.

Phenylselenol (66.0 μL, 98.0 mg, 622 μmol, 1.05 eq) was dissolved in anhydrous THF (500 μL) and *n*-BuLi (249 μL, 622 μmol, 1.05 eq, 2.5 mol/L solution in hexane) was added. After stirring for 5min at rt the mixture was added to the mixed anhydride and was stirred at rt for 30min. Water (50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1, 2:1) to afford the seleno ester (241 mg, 475 μmol, 0.63 eq), which was dissolved in benzene (5 mL). Tri-*n*-butyl stannane (207 μL, 224 mg, 770 μmol, 1.3 eq) and AIBN (10.0 mg, 59.0 μmol,

0.1 eq) were added and the mixture was heated to reflux for 1h. After cooling down to rt the mixture was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1, DCM/MeOH = 20:1, 10:1) to afford 20*E*-geissoschizoate (152 mg, 469 μmol, 0.63 eq).

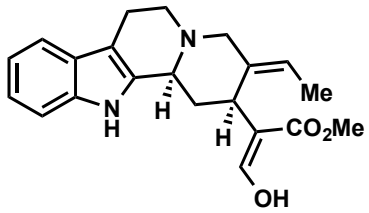
R_f = 0.26 (DCM/MeOH = 10:1) [CAN]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.61 (bs, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.13 - 7.17 (m, 1H), 7.10 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, 1H), 5.49 (q, *J* = 6.8 Hz, 1H), 4.30 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H), 3.69 (s, 3H), 3.56 (d, *J* = 12.3 Hz, 1H), 3.28 (ddd, J_1 = 13.0 Hz, J_2 = 5.8 Hz, J_3 = 1.4 Hz, 1H), 3.09 - 3.20 (m, 2H), 3.00 - 3.07 (m, 1H), 2.97 (d, *J* = 12.3 Hz, 1H), 2.62 - 2.68 (m, 1H), 2.31 (ddd, J_1 = 14.4 Hz, J_2 = 3.8 Hz, J_3 = 3.6 Hz, 1H), 2.10 - 2.23 (m, 3H), 1.64 (dd, J_1 = 6.8 Hz, J_2 = 1.7 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 174.2, 136.2, 136.0, 133.8, 127.8, 121.6, 121.0, 119.6, 118.2, 111.3, 107.7, 53.4, 52.9, 52.0, 51.5, 37.3, 31.2, 30.6, 18.0, 12.8 ppm.

IR (film): 3194, 3057, 2926, 2854, 1733, 1621, 1554, 1451, 1321, 1162, 1010, 742 cm^{-1}.

20-*E*-Geissoschizine (35)



Diisopropylamine (300 μL, 214 mg, 2.11 mmol, 3.7 eq) was dissolved in anhydrous THF (1 mL) and cooled to -78°C. *n*-Butyllithium (850 μL, 2.11 mmol, 3.7 eq, 2.5 mol/L solution in hexane) was added dropwise and the mixture was stirred at 0°C for 30min. 20*E*-Geissoschizoate (185 mg, 570 μmol, 1 eq) dissolved in anhydrous THF (5 mL) was added to the LDA solution at -78°C and stirred for 1h. Methyl formate (2.90 mL, 2.88 g, 47.9 mmol, 84 eq) was added and the mixture was allowed to warm up to 0°C during a period of 5.5h. The reaction mixture was poured onto water (100 mL)

and 1 M aqueous NaOH was added until pH = 12. The starting material was extracted with Et_2O (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield 20*E*-geissoschizoate (85.0 mg, 262 μmol, 0.46 eq). The aqueous phase was acidified to pH = 5 with citric acid and extracted with DCM (3x100 mL). The combined organic phases were abolished. Addition of 1 M aqueous NaOH until pH = 7 was followed by extraction with DCM (5x10 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield 20*E*-geissoschizine (70.0 mg, 199 μmol, 0.35 eq).

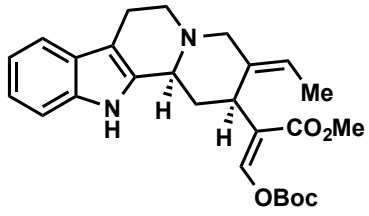
R_f = 0.17 (DCM/MeOH = 10:1) [CAN]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.07 (bs, 1H), 7.86 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.14 - 7.18 (m, 1H), 7.08 - 7.12 (m, 1H), 5.41 (q, *J* = 6.7 Hz, 1H), 4.49 (bd, *J* = 10.2 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 3.86 (dd, J_1 = 11.3 Hz, J_2 = 6.5 Hz, 1H), 3.69 (s, 3H), 3.20 - 3.24 (m, 1H), 3.18 (d, *J* = 14.0 Hz, 1H), 3.03 - 3.11 (m, 1H), 2.80 - 2.85 (m, 1H), 2.72 (ddd, J_1 = 11.6 Hz, J_2 = 11.6 Hz, J_3 = 3.8 Hz, 1H), 2.65 (ddd, J_1 = 13.2 Hz, J_2 = 10.3 Hz, J_3 = 6.4 Hz, 1H), 2.10 (ddd, J_1 = 13.4 Hz, J_2 = 11.8 Hz, J_3 = 1.8 Hz, 1H), 1.82 (d, *J* = 5.5 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 170.6, 161.5, 136.6, 133.3, 133.0, 126.6, 122.2, 121.9, 119.9, 118.4, 111.1, 108.3, 107.8, 59.3, 53.7, 51.3, 50.7, 34.0, 27.8, 20.6, 13.3 ppm.

IR (film): 3204, 2923, 2854, 1684, 1446, 1373, 1331, 1233, 1181, 1081, 1026, 808, 742 cm^{-1}.

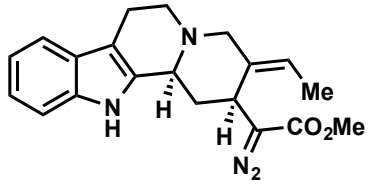
Methyl (*Z*)-3-((*tert*-butoxycarbonyl)oxy)-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)acrylate (94)



20*E*-Geissoschizine (70.0 mg, 199 μmol, 1 eq) was dissolved in absolute THF (5 mL). DMAP (2.40 mg, 20.0 μmol, 0.1 eq), NEt_3 (55.0 μL, 40.0 mg, 397 μmol, 2 eq) and di-*tert*-butyl dicarbonate (65.0 mg, 298 μmol, 1.5 eq) were sequentially added. The reaction mixture was stirred at rt for 24h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain methyl (*Z*)-3-((*tert*-butoxycarbonyl)oxy)-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)acrylate (83.0 mg, 183 μmol, 0.92 eq) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.13 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.30 (s, *J* = 7.5 Hz, 1H), 7.15 - 7.06 (m, 2H), 5.47 (q, *J* = 6.8 Hz, 1H), 3.86 - 3.79 (m, 1H), 3.76 - 3.70 (m, 4H), 3.57 (bd, *J* = 12.6 Hz, 1H), 3.29 (bd, *J* = 12.3 Hz, 1H), 3.14 - 3.09 (m, 1H), 2.99 - 2.93 (m, 1H), 2.85 - 2.75 (m, 2H), 2.00 - 1.94 (m, 1H), 1.55 (s, 9H), 1.50 (d, *J* = 6.8 Hz, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 167.3, 149.9, 146.7, 136.3, 132.3, 132.2, 128.7, 128.6, 127.3, 121.6, 119.5, 118.3, 110.9, 108.5, 85.3, 63.6, 58.0, 52.0, 51.0, 36.4, 33.9, 27.7, 21.3, 13.3 ppm.
HRMS (ESI): calc. for $C_{26}H_{33}N_2O_5^+$: 453.2389; found 453.2383

Methyl 2-diazo-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]-quinolizin-2-yl)acetate (92)

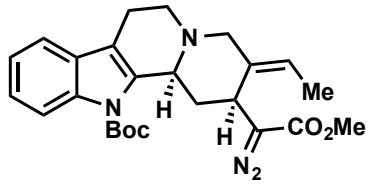


Methyl (*Z*)-3-((*tert*-butoxycarbonyl)oxy)-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)acrylate (83.0 mg, 183 μmol, 1 eq) was dissolved in absolute MeCN (5 mL) and cooled to 0°C. 4-Acetamidobenzene sulfonylazide (72.0 mg, 298 μmol, 1.6 eq) and DBU (90.0 μL, 91.0 mg, 596 μmol, 3.2 eq) were added. The resulting mixture was stirred at 0°C for 19h and was allowed to warm up to rt during this time. H_2O (50 mL) was added

and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, DCM/MeOH = 30:1 to 20:1) to obtain methyl 2-diazo-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizin-2-yl)acetate (44.0 mg, 126 μmol, 0.69 eq) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): d = 7.45 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.14 (ddd, J_1 = 7.9 Hz, J_2 = 7.2 Hz, J_3 = 1.0 Hz, 1H), 7.08 (ddd, J_1 = 7.4 Hz, J_2 = 7.3 Hz, J_3 = 1.1 Hz, 1H), 5.63 (q, *J* = 6.6 Hz, 1H), 3.90 (bs, 1H), 3.76 (s, 3H), 3.64 - 3.59 (m, 1H), 3.53 - 3.45 (m, 1H), 3.23 - 3.15 (m, 2H), 3.12 - 2.97 (m, 2H), 2.93 - 2.86 (m, 1H), 2.80 - 2.74 (m, 1H), 2.42 - 2.36 (m, 1H), 2.23 - 2.19 (m, 1H), 1.69 - 1.62 (m, 3H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 168.0, 136.3, 132.9, 131.9, 127.2, 122.0, 121.9, 119.7, 118.3, 111.0, 108.0, 59.6, 56.1, 52.1, 51.4, 37.3, 32.8, 31.5, 20.0, 12.5 ppm.
IR (film): 3334, 3054, 2929, 2852, 2800, 2742, 2084, 1690, 1611, 1593, 1495, 1437, 1356, 1294, 1275, 1250, 1181, 1159, 1142, 1118, 1088, 1067, 1014, 960, 909, 838, 797, 772, 732, 675, 643, 619 cm^{-1}.

tert-Butyl (*E*)-2-(1-diazo-2-methoxy-2-oxoethyl)-3-ethylidene-1,3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (96)

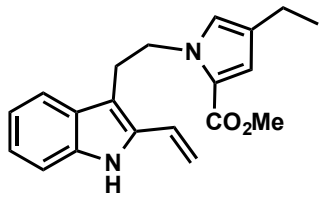


Methyl 2-diazo-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizin-2-yl)acetate (6.00 mg, 17.0 μmol, 1 eq) was dissolved in absolute MeCN (1 mL). DMAP (200 μg, 1.70 μmol, 0.1 eq) and di-*tert*-butyl dicarbonate (7.50 mg, 34.0 μmol, 2 eq) were added. The reaction mixture was stirred at rt for 1.5 h and then directly subjected to flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain *tert*-butyl (*E*)-2-(1-diazo-2-methoxy-2-

oxoethyl)-3-ethylidene-1,3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine-12(2*H*)-carboxylate (4.00 mg, 8.88 μmol, 0.52 eq) as a yellow foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.08 (d, *J* = 7.9 Hz, 1H), 7.41 (dd, J_1 = 7.3 Hz, J_2 = 1.2 Hz, 1H), 7.29 - 7.24 (m, 1H), 7.22 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, 1H), 5.51 (q, *J* = 7.2 Hz, 1H), 4.42 (bd, *J* = 9.9 Hz, 1H), 3.78 (s, 3H), 3.64 (dd, J_1 = 9.6 Hz, J_2 = 6.5 Hz, 1H), 3.56 (bd, *J* = 13.3 Hz, 1H), 3.43 (bd, *J* = 13.6 Hz, 1H), 3.03 - 2.98 (m, 1H), 2.84 - 2.70 (m, 3H), 2.45 (ddd, J_1 = 13.1 Hz, J_2 = 6.1 Hz, J_3 = 3.5 Hz, 1H), 1.83 - 1.75 (m, 1H), 1.73 (dd, J_1 = 7.2 Hz, J_2 = 0.7 Hz, 3H), 1.68 (s, 9H) ppm.
^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 171.1, 150.3, 141.5, 136.7, 132.6, 129.2, 124.3, 122.8, 121.8, 118.2, 116.4, 115.8, 115.7, 84.1, 62.7, 56.2, 52.1, 46.2, 32.9, 32.8, 28.4, 21.7, 12.5 ppm.
IR (film): 2925, 2852, 2082, 1727, 1692, 1615, 1476, 1455, 1435, 1412, 1355, 1307, 1245, 1208, 1147, 1113, 1065, 1045, 1009, 968, 910, 838, 766, 742, 661 cm^{-1}.
HRMS (ESI): calc. for $C_{25}H_{31}N_4O_4^+$: 451.2345; found 451.2344

Methyl 4-ethyl-1-(2-(2-vinyl-1*H*-indol-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate (98)



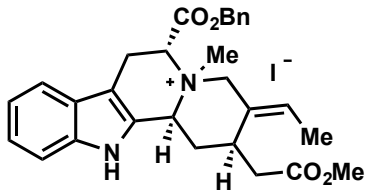
Methyl 2-diazo-2-((*E*)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizin-2-yl)acetate (3.00 mg, 7.00 μmol, 1 eq) was dissolved in benzene (2 mL). $Rh_2(OAc)_4$ (150 μg, 0.30 μmol, 0.05 eq) was added and the resulting mixture was heated to reflux for 30min. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain methyl 4-ethyl-1-(2-(2-vinyl-1*H*-indol-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate (2.00 mg, 6.00 μmol, 0.86 eq) as a colourless foam.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (bs, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.31 (ddd, J_1 = 8.0 Hz, J_2 = 0.7 Hz, J_3 = 0.7 Hz, 1H), 7.20 (ddd, J_1 = 8.1 Hz, J_2 = 7.1 Hz, J_3 = 1.0 Hz, 1H), 7.10 (ddd, J_1 = 7.9 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, J_1 = 17.9 Hz, J_2 = 11.3 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 17.8 Hz, 1H), 5.20 (d, *J* = 11.4 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 3.83 (s, 3H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.37 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 161.7, 136.3, 133.4, 128.8, 126.9, 125.8, 125.3, 123.3, 120.8, 119.9, 119.1, 117.6, 112.6, 111.5, 110.7, 51.1, 49.8, 29.9, 19.8, 15.4 ppm.

IR (film): 3344, 2953, 2924, 2852, 1697, 1448, 1400, 1367, 1317, 1251, 1201, 1132, 1093, 1010, 943, 798, 750, 667, 420 cm^{-1}.

Benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-*N*-methyl-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidinium-5-carboxylate iodide (88)



Benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidine-5-carboxylate (10.0 mg, 21.8 μmol, 1 eq) was dissolved in anhydrous MeCN (200 μL) and iodomethane (2.72 μL, 6.2 mg, 43.6 μmol, 2 eq) was added. After stirring at rt for 2d the mixture was concentrated under reduced pressure to afford benzyl-20*E*-3,4,5,6,14,15,21-heptahydro-*N*-methyl-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidinium-5-carboxylate iodide (13.1 mg, 21.8 μmol, 1 eq) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.6 (bs, 1H), 7.50 (d, *J* = 8.5 Hz), 7.40 (bs, 5H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.19 (dd, J_1 = 7.1 Hz, J_2 = 7.1 Hz, 1H), 7.09 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, 1H), 5.96 (q, *J* = 6.6 Hz, 1H), 5.34 (s, 2H), 5.14 (d, *J*

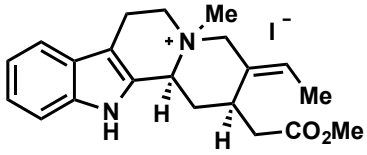
= 9.7 Hz), 4.52 (bd, *J* = 9.9 Hz, 1H), 3.79 - 4.09 (m, 2H), 3.61 (s, 3H), 3.48 (bd, *J* = 16.7 Hz, 1H), 3.28 (s, 3H), 3.14 - 3.21 (m, 1H), 2.87 - 3.03 (m, 1H), 2.36 - 2.63 (bm, 3H), 1.84 (d, *J* = 1.8 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 123.5, 120.3, 118.0, 112.7, 102.4, 77.4, 69.1, 66.6, 59.0, 52.0, 44.7, 36.4, 31.3, 29.8, 22.9, 14.2 ppm.

IR (film): 3181, 2926, 2855, 1732, 1624, 1528, 1455, 1392, 1367, 1349, 1272, 1177, 1136, 1019, 904, 853, 745, 702 cm^{-1}.

HRMS (ESI): calc. for $C_{29}H_{33}N_2O_4^+$: 473.2435; found 473.2459

20*E*-Geissoschizoate-*N*-methyl iodide (89)



20*E*-geissoschizoate (5.00 mg, 15.4 μmol, 1 eq) was dissolved in anhydrous MeCN (100 μL). Iodomethane (4.38 mg, 30.8 μmol, 2 eq) was added and the mixture was stirred at rt for 3d. The solvent and the excess of iodomethane were removed under reduced pressure to afford 20*E*-geissoschizoate-*N*-methyl iodide (7.20 mg, 15.4 μmol, 1 eq) as a colourless oil.

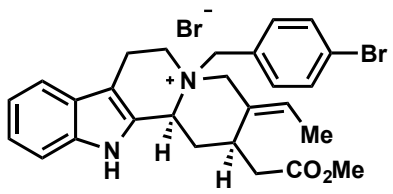
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.40 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H), 7.11 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H), 5.91 (q, *J* = 7.0 Hz, 1H), 4.65 (dd, J_1 = 4.6 Hz, J_2 = 4.6 Hz, 1H), 4.29 (d, *J* = 13.0 Hz, 1H), 3.73 - 3.86 (m, 3H), 3.59 (s, 3H), 3.42 - 3.49 (m, 1H), 3.10 (s, 3H), 3.04 (ddd, J_1 = 17.5 Hz, J_2 = 5.7 Hz, J_3 = 5.7 Hz, 1H), 2.93 (ddd, J_1 = 17.6 Hz, J_2 = 5.5 Hz, J_3 = 5.5 Hz, 1H), 2.55 - 2.71 (m, 2H), 2.46 (dd, J_1 = 15.4 Hz, J_2 = 7.2 Hz, 1H), 2.08 (dd, J_1 = 15.3 Hz, J_2 = 6.3 Hz, 1H), 1.74 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.0, 136.9, 133.8, 127.1, 127.0, 125.5, 123.4, 120.4, 118.5, 112.3, 104.1, 64.8, 52.1, 49.1, 36.9, 30.3, 29.8, 26.9, 17.6, 13.9, 13.7 ppm.

IR (film): 3195, 2947, 2861, 1729, 1625, 1548, 1447, 1371, 1332, 1245, 1166, 1013, 917, 741, 669 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{27}N_2O_2^+$; 339.2067; found 339.2076

20*E*-Geissoschizoate-*N*-4-bromobenzyl bromide (90)



20*E*-geissoschizoate (26.0 mg, 80.0 μmol, 1 eq) was dissolved in anhydrous MeCN (1 mL) and 4-bromo benzylbromide (20.0 mg, 80.0 μmol, 1 eq) was added. The mixture was stirred for 3d at rt and during that time a colourless precipitate was formed. After filtration the precipitate was washed with MeCN (5 mL) to afford 20*E*-geissoschizoate-*N*-4-bromobenzyl bromide (18.0 mg, 31.3 μmol, 0.39 eq).

MP: decomp. >240°C

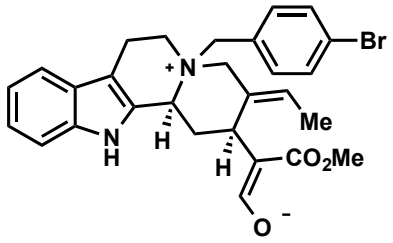
^{1}H NMR (MeOD, 400 MHz): δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.17 - 7.21 (m, 1H), 7.07 - 7.11 (m, 1H), 5.90 (q, *J* = 6.7 Hz, 1H), 4.97 (dd, J_1 = 4.3 Hz, J_2 = 4.3 Hz, 1H), 4.85 - 4.89 (m, 1H), 4.69 (d, *J* = 13.3 Hz, 1H), 4.42 (d, *J* = 13.7 Hz, 1H), 3.91 (ddd, J_1 = 12.4 Hz, J_2 = 4.9 Hz, J_3 = 4.6 Hz, 1H), 3.86 (d, *J* = 13.6 Hz, 1H), 3.66 (ddd, J_1 = 12.7 Hz, J_2 = 8.3 Hz, J_3 = 5.9 Hz, 1H), 3.61 (s, 3H), 3.48 - 3.54 (m, 1H), 3.23 - 3.30 (m, 1H), 3.18 (ddd, J_1 = 17.3 Hz, J_2 = 4.4 Hz, J_3 = 4.2 Hz, 1H), 2.95 (ddd, J_1 = 16.1 Hz, J_2 = 5.9 Hz, J_3 = 5.3 Hz, 1H), 2.63 (ddd, J_1 = 15.9 Hz, J_2 = 4.2 Hz, J_3 = 4.1 Hz, 1H), 2.26 (dd, J_1 = 15.9 Hz, 8.0 Hz, 1H), 2.04 (dd, J_1 = 15.9 Hz, J_2 = 7.3 Hz, 1H), 1.78 (dd, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 3H) ppm.

^{13}C NMR (MeOD, 100.6 MHz): δ = 173.4, 138.6, 136.2, 133.7, 133.5, 128.8, 128.5, 127.9, 127.2, 126.5, 124.0, 121.0, 119.4, 112.6, 105.6, 63.7, 62.3, 59.7, 58.8, 52.2, 37.7, 30.8, 29.3, 18.4, 13.6 ppm.

IR (film): 3385, 3163, 2954, 2365, 1730, 1592, 1489, 1440, 1386, 1327, 1261, 1162, 1073, 1050, 1011, 850, 805, 742, 698, 673, 631 cm^{-1}.

HRMS (ESI): calc. for $C_{27}H_{30}N_2O_2Br^+$: 493.1485; found 493.1392

20-*E*-Geissoschizine-*N*-4-bromobenzyl enolate (91)



20*E*-Geissoschizine (15.0 mg, 43.0 μmol, 1 eq) was dissolved in anhydrous MeCN (3 mL) and 4-bromo benzylbromide (11.0 mg, 43.0 μmol, 1 eq) was added. The mixture was refluxed for 6h. After cooling down to rt the mixture was concentrated under reduced pressure and purified by preparative TLC (SiO_2, DCM/MeOH = 10:1) to afford 20-*E*-geissoschizine-*N*-4-bromobenzyl enolate (17.0 mg, 32.6 μmol, 0.76 eq) as a colourless oil.

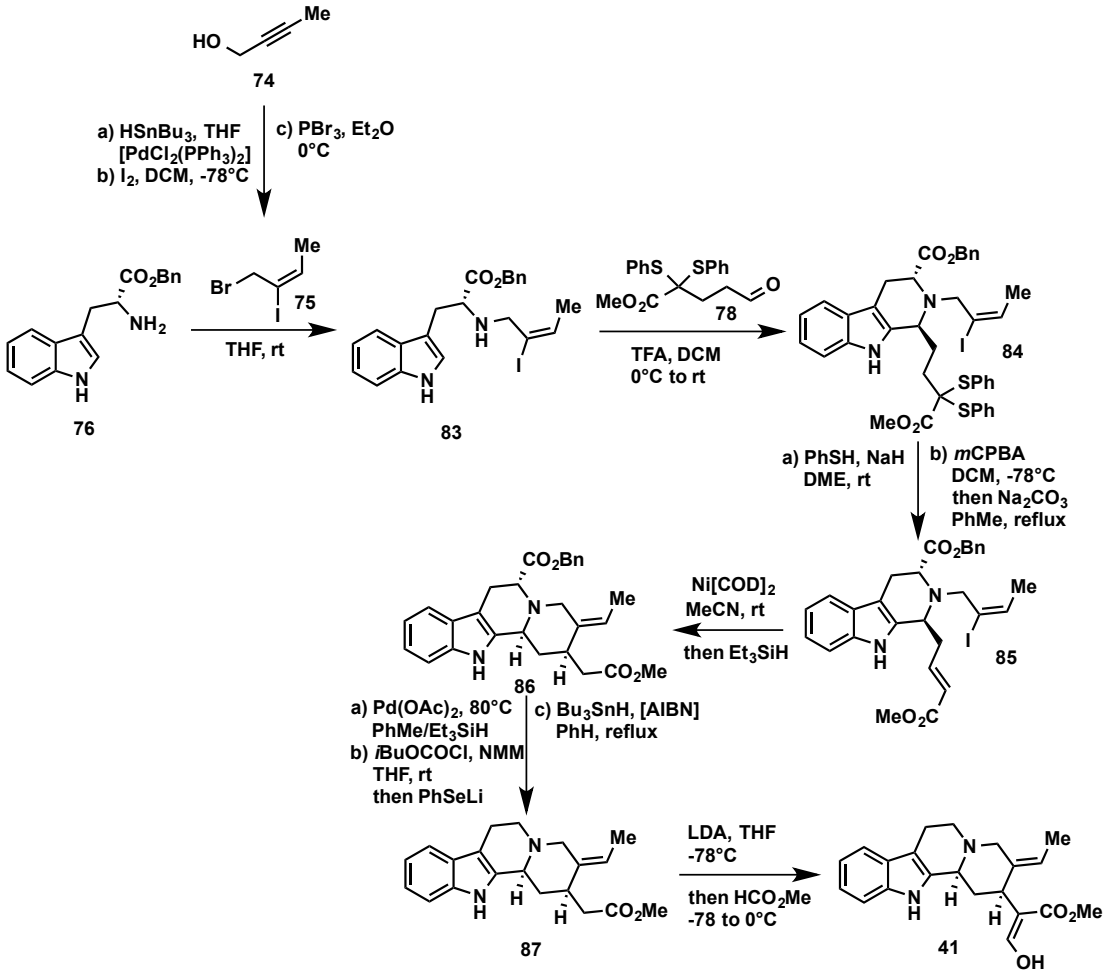
^{1}H NMR (MeOD, 400 MHz): δ = 8.66 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H), 7.09 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 5.45 (q, *J* = 6.4 Hz, 1H), 4.70 (d, *J* = 13.2 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.56 (bs, 2H), 4.16 (d, *J* = 13.4 Hz, 1H), 3.95 - 4.00 (m, 1H), 3.94 (dd, J_1 = 12.3 Hz, J_2 = 5.0 Hz, 1H), 3.74 - 3.79 (m, 1H), 3.53 (s, 3H), 3.36 - 3.45 (m, 1H), 3.20 (bdd, J_1 = 17.5 Hz, J_2 = 4.9 Hz, 1H), 2.53 (ddd, J_1 = 15.0 Hz, J_2 = 11.8 Hz, J_3 = 12.2 Hz, 1H), 2.13 (bdd, J_1 = 14.9 Hz, J_2 = 6.4 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (MeOD, 100.6 MHz): δ = 174.9, 173.5, 138.8, 136.4, 133.5, 132.5, 131.9, 129.1, 128.3, 127.0, 126.2, 123.8, 120.7, 119.4, 112.5, 104.9, 102.8, 68.3, 66.0, 63.6, 61.3, 57.3, 33.6, 33.5, 30.8, 19.0, 13.9 ppm.

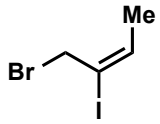
IR (film): 3382, 2923, 2852, 2501, 2358, 1640, 1546, 1490, 1439, 1354, 1302, 1235, 1183, 1108, 1075, 743 cm^{-1}.

HRMS (ESI): calc. for $C_{28}H_{30}N_2O_3Br^+$: 521.1434; found 521.1455

8.2.2 *Z*-Geissoschizine



(*E*)-1-Bromo-2-iodobut-2-ene (75)



$PdCl_2(PPh_3)_2$ (931 mg, 1.33 mmol, 0.02 eq) was put under argon in a Schlenk tube. But-2-yn-1-ol (5.00 mL, 4.65 g, 66.3 mmol, 1 eq) dissolved in degassed absolute THF (100 mL) was added. Tributyltin hydride (19.7 mL, 21.2 g, 73.0 mmol, 1.1 eq) was added dropwise at rt and the resulting mixture was stirred at 40 °C for 12h. The solvent was removed under reduced pressure and the crude vinyl stannane was purified by flash column chromatography (SiO_2, PE) to obtain (*E*)-2-(tributylstannyl)but-2-en-1-ol (6.61 a, 18.3 mmol, 0.28 eq) as a colourless liquid.

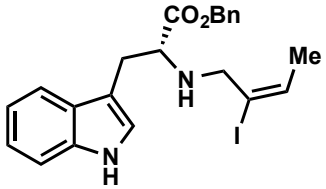
The vinyl stannane was dissolved in DCM (100 mL) and cooled to -78°C. Iodine (5.57 g, 22.0 mmol, 0.33 eq) dissolved in DCM (100 mL) was added dropwise and the resulting mixture was stirred at -78°C for 15min. The mixture was allowed to warm up to rt. The organic phase was washed with aqueous $Na_2S_2O_3$ (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude vinyl iodide was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain (*E*)-2-iodobut-2-en-1-ol (3.56 g, 18.0 mmol, 0.27 eq) as a colourless liquid.

The vinyl iodide was dissolved in absolute Et_2O (50 mL) and cooled to 0°C. Phosphorous tribromide (700 μL, 1.98 g, 7.32 mmol, 0.11 eq) was added and the resulting mixture was stirred at 0°C for 21h. The reaction mixture was allowed to warm up to rt during this time and was then poured onto aqueous K_2CO_3 (100 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concnetrated under reduced pressure to obtain (*E*)-1-bromo-2-iodobut-2-ene (4.52 g, 17.3 mmol, 0.26 eq) as a yellow fluid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.39 (q, *J* = 7.2 Hz, 1H), 4.29 (s, 2H), 1.71 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 141.6, 94.6, 37.0, 16.6 ppm.

N_b-(*E*-2'-Iodo-2'-butenyl) tryptophan benzylester (83)



Tryptophan benzyl ester (6.00 g, 20.4 mmol, 1 eq) was dissolved in anhydrous THF (5 mL) and added to a solution of (*E*)-1-bromo-2-iodobut-2-ene (4.52 g, 17.3 mmol, 0.85 eq) in anhydrous THF (5 mL). The mixture was stirred for 24h at rt. Additional anhydrous THF (10 mL) were added and the mixture was stirred for 2d at rt. Aqueous ammonia solution (30 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 , 2:1, 1:1) to afford N_b-(*E*-2'-iodo-2'-butenyl) tryptophan benzylester (5.78 g, 12.2 mmol, 0.6 eq) as a colourless oil.

R_f = 0.33 (PE/EtOAc = 1:1) [CAN]

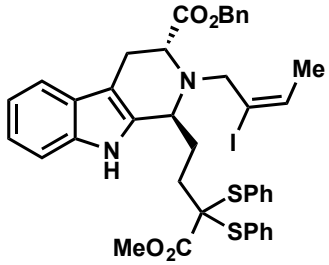
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.01 (bs, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.29 - 7.31 (m, 3H), 7.18 - 7.22 (m, 3H), 7.12 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.30 (q, *J* = 7.0 Hz, 1H), 5.08 (s, 2H), 3.65 (t, *J* = 6.7 Hz, 1H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.33 (d, *J* = 14.4 Hz, 1H), 3.24 (dd, J_1 = 14.4 Hz, J_2 = 6.3 Hz, 1H), 3.16 (dd, J_1 = 14.4 Hz, J_2 = 7.1 Hz, 1H), 2.00 (bs, 1H), 1.50 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 174.5, 138.6, 136.4, 135.8, 128.6, 128.6, 128.4, 127.7, 123.2, 122.2, 119.6, 119.1, 111.3, 111.2, 103.0, 66.7, 59.9, 52.0, 29.6, 16.5 ppm.

IR (film): 3407, 3034, 2918, 1728, 1620, 1495, 1455, 1341, 1171, 1109, 987, 907, 820, 738, 697 cm^{-1}.

HRMS (ESI): calc. for $C_{22}H_{24}N_2O_2I^+$: 475.0883; found $C_{22}H_{24}N_2O_2I^+$ 475.0880

***trans*-3-Benzyloxycarbonyl-2-(*E*-2'-iodo-2'-butenyl)-1-(3',3'-diphenyl-sulfanyl-3'-methoxycarbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (84)**



N_b-(*E*-2'-iodo-2'-butenyl) tryptophan benzylester (5.78 g, 12.2 mmol, 1 eq) and methyl 5-oxo-2,2-bis(phenylthio)pentanoate (5.07 g, 14.6 mmol, 1.2 eq) were dissolved in anhydrous DCM (50 mL) and cooled to 0°C. Trifluoroacetic acid (1.90 mL, 2.78 g, 24.4 mmol, 2 eq) was added dropwise and the mixture was allowed to warm up to rt. After stirring for 5h water (50 mL) was added and the pH was adjusted to pH = 9 with aq. ammonia solution. The aqueous phase was extracted with DCM (3x50 mL) and the combined organic phases were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1, 3:1) to afford *trans*-3-benzyloxycarbonyl-2-(*E*-2'-iodo-2'-butenyl)-1-(3',3'-diphenylsulfanyl-3'-methoxy-carbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (9.54 g, 11.9 mmol, 0.98 eq) as a colourless oil.

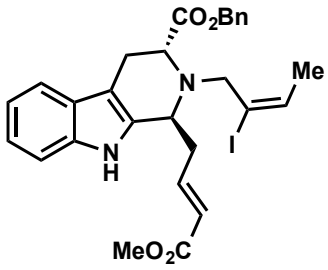
R_f = 0.42 (PE/EtOAc = 2:1) [CAN]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52 - 7.54 (m, 2H), 7.46 - 7.49 (m, 4H), 7.28 - 7.33 (m, 2H), 7.09 - 7.25 (m, 12H), 6.38 (q, *J* = 7.2 Hz, 1H), 5.02 (s, 2H), 4.21 (bs, 1H), 3.87 (dd, J_1 = 5.3 Hz, J_2 = 5.3 Hz, 1H), 3.59 (s, 3H), 3.55 (d, *J* = 13.4 Hz, 1H), 3.19 (d, *J* = 11.9 Hz, 1H), 3.13 - 3.17 (m, 1H), 2.97 (ddd, J_1 = 15.5 Hz, J_2 = 5.5 Hz, J_3 = 1.2 Hz, 1H), 2.34 - 2.42 (m, 1H), 2.02 - 2.15 (m, 1H), 1.82 - 1.89 (m, 1H), 1.45 (d, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.9, 170.2, 139.8, 136.4, 136.2, 136.0, 135.9, 134.1, 131.4, 131.1, 129.6, 129.5, 128.9, 128.8, 128.5, 128.1, 128.0, 127.2, 121.7, 119.6, 118.2, 111.2, 107.9, 101.8, 69.4, 66.1, 55.9, 54.6, 53.2, 52.9, 31.6, 28.7, 23.6, 16.9 ppm.

IR (film): 3386, 3057, 2948, 2850, 1724, 1582, 1470, 1452, 1437, 1325, 1306, 1236, 1170, 1138, 1115, 1067, 1024, 1002, 916, 825, 738, 693 cm^{-1}.
HRMS (ESI): calc. for $C_{40}H_{40}N_2O_4IS_2^+$: 803.1474; found $C_{40}H_{40}N_2O_4IS_2^+$ 803.1475

trans-3-Benzyloxycarbonyl-2-(_E_-2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-_b_]indole (85)



trans-3-Benzyloxycarbonyl-2-(_E_-2'-iodo-2'-butenyl)-1-(3',3'-diphenylsulfanyl-3'-methoxycarbonylpropyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-_b_]indole (9.54 g, 11.9 mmol, 1 eq) was dissolved in anhydrous DME (120 mL). Thiophenol (1.60 mL, 1.70 g, 15.4 mmol, 1.3 eq) and sodium hydride (86.0 mg, 2.14 mmol, 0.18 eq, 60% dispersion in mineral oil) were sequentially added and the mixture was stirred for 24h at rt. Water (300 mL) was added and the aqueous phase was extracted with EtOAc (3x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash colum chromatography (SiO_2, PE/EtOAc = 5:1, 2:1, 1:1) to afford the mercaptane (7.22 g, 10.4 mmol, 0.87 eq) as a mixture of diastereoisomers. This was dissolved in anhydrous DCM (150 mL) and cooled to -78°C. _m_CPBA (2.93 g, 11.9 mmol, 1 eq, 70%) dissolved in anhydrous DCM (50 mL) was added dropwise and the mixture was stirred for 2h at -78 °C. After complete oxidation the reaction mixture was poured into a mixture of aqueous $Na_2S_2O_3$ (100 mL) and DCM (100 mL). The aqueous phase was extracted with DCM (2x200 mL) and the combined organic phases were dried over $MgSO_4$ and filtrated. After removal of the solvent under reduced pressure the crude sulfoxide was dissolved in $CHCl_3$ (80 mL) and added to a refluxing suspension of Na_2CO_3 (1.64 g, 15.4 mmol, 1.3 eq) in toluene (300 mL). After refluxing for 2h the mixture was allowed to

cool down to rt and was concentrated under reduced pressure. The residue was poured into water (300 mL) and the aqueous phase was extracted with Et_2O (3x50 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 5:1, 3:1, 2:1) to afford *trans*-3-benzyloxycarbonyl-2-(*E*-2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (4.32 g, 7.40 mmol, 0.62 eq) as a colourless oil.

R_f = 0.36 (PE/EtOAc = 2:1) [CAN]

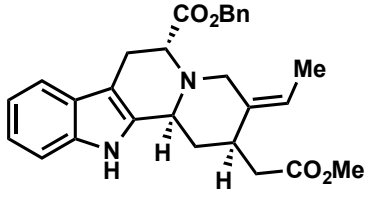
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.08 - 7.25 (m, 8H), 6.45 (q, *J* = 7.3 Hz, 1H), 5.87 (d, *J* = 15.7 Hz, 1H), 5.07 (s, 2H), 4.38 (dd, J_1 = 5.2 Hz, J_2 = 5.2 Hz, 1H), 4.03 (dd, J_1 = 5.2 Hz, J_2 = 5.2 Hz, 1H), 3.68 - 3.71 (m, 1H), 3.68 (s, 3H), 3.43 (d, *J* = 14.0 Hz, 1H), 3.23 (ddd, J_1 = 15.2 Hz, J_2 = 5.5 Hz, J_3 = 0.7 Hz, 1H), 3.09 (ddd, J_1 = 15.4 Hz, J_2 = 5.3 Hz, J_3 = 1.2 Hz, 1H), 2.71 - 2.85 (m, 2H), 1.51 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 172.8, 166.8, 145.7, 139.9, 136.5, 135.8, 133.8, 128.6, 128.2, 128.1, 127.0, 123.5, 122.0, 119.8, 118.4, 111.0, 107.9, 101.6, 66.4, 56.6, 55.1, 54.1, 51.6, 37.0, 23.5, 16.9 ppm.

IR (film): 3364, 3031, 2947, 2851, 2179, 2129, 1722, 1705, 1655, 1495, 1452, 1437, 1323, 1272, 1211, 1168, 1139, 1114, 1083, 1005, 828, 740, 698 cm^{-1}.

HRMS (ESI): calc. for $C_{28}H_{30}N_2O_4I^+$: 585.1250; found $C_{28}H_{30}N_2O_4I^+$ 585.1256

Benzyl-20*Z*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethyl-idene-indolo[2,3-a]quinolizidine-5-carboxylate (86)



$Ni[COD]_2$ (1.50 g, 5.44 mmol, 1.5 eq) was dissolved in anhydrous MeCN (150 mL) and put in a Schlenk flask under argon. *trans*-3-Benzyloxycarbonyl-2-(*E*-

2'-iodo-2'-butenyl)-1-(methyl but-2'-enoate-4'-yl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-*b*]indole (2.12 g, 3.63 mmol, 1 eq) and triethyl amine (1.5 mL, 1.10 g, 10.9 mmol, 3 eq) were dissolved in anhydrous MeCN (90 mL) and added to the $Ni[COD]_2$ solution. The mixture was stirred for 20min at rt. Triethyl silane (1.16 mL, 844 mg, 7.25 mmol, 2 eq) was added and the mixture was stirred for 1.5h at rt. The reaction mixture was poured onto a mixture of DCM (200 mL) and saturated aqueous Na_2CO_3 solution (200 mL). Both phases were filtrated over a pad of celite and after partitioning, the aqueous phase was extracted with DCM (2x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1, 2:1) to afford benzyl-20*Z*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizidine-5-carboxylate (1.13 g, 2.46 mmol, 0.68 eq) as a colourless oil.

R_f = 0.45 (PE/EtOAc = 2:1) [CAN]

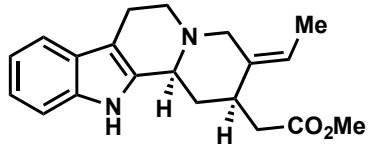
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.76 (bs, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.20 - 7.25 (m, 3H), 7.12 - 7.17 (m, 3H), 7.07 - 7.11 (m, 1H), 5.19 (q, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 4.52 (dd, J_1 = 11.3 Hz, J_2 = 2.0 Hz, 1H), 3.97 (dd, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H), 3.83 (d, *J* = 12.3 Hz, 1H), 3.74 (s, 3H), 3.50 (d, *J* = 12.6 Hz, 1H), 3.27 (ddd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, J_3 = 2.1 Hz, 1H), 3.20 (ddd, J_1 = 15.5 Hz, J_2 = 2.0 Hz, J_3 = 1.7 Hz, 1H), 2.72 - 2.85 (m, 2H), 2.31 (dd, J_1 = 15.2 Hz, J_2 = 8.0 Hz, 1H), 2.25 (ddd, J_1 = 12.2 Hz, J_2 = 3.8 Hz, J_3 = 3.1 Hz, 1H), 1.68 (d, *J* = 6.48 Hz, 3H), 1.28 (ddd, J_1 = 11.7 Hz, J_2 = 11.7 Hz, J_3 = 11.7 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 173.5, 172.5, 136.7, 136.3, 135.9, 134.4, 128.6, 128.2, 127.9, 127.3, 121.6, 119.5, 118.2, 115.8, 110.9, 105.8, 66.1, 61.3, 53.9, 53.1, 51.9, 38.7, 38.4, 36.9, 25.3, 13.3 ppm.

IR (neat): 3383, 3030, 2915, 2854, 1724, 1444, 1331, 1261, 1167, 1139, 1004, 950, 833, 738, 697 cm^{-1}.

HRMS (ESI): calc. for $C_{28}H_{31}N_2O_4^+$: 459.2284; found $C_{28}H_{31}N_2O_4^+$ 459.2283

20-*Z*-Geissoschizoate (87)



Benzyl-20*Z*-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo-[2,3-a]quinolizidine-5-carboxylate (1.13 g, 2.46 mmol, 1 eq) was dissolved in anhydrous toluene (50 mL) and heated up to 80°C. $Pd(OAc)_2$ (138 mg, 616 μmol, 0.25 eq) and triethyl silane (35 mL) were added and the mixture was stirred at 80°C for 6h. After completion of the reaction the mixture was filtrated over a pad of celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, DCM/MeOH = 1:0, 20:1, 10:1, 5:1, 4:1) to afford the carboxylic acid (231 mg, 627 μmol, 0.25 eq) and reisolated starting material (618 mg, 1.35 mmol, 0.55 eq). The carboxylic acid was dissolved in anhydrous THF (8 mL). *N*-methyl morpholine (80.0 μL, 72.0 mg, 715 μmol, 0.29 eq) and *iso*-butyl chloroformate (100 μL, 101 mg, 739 μmol, 0.3 eq) were sequentially added and the mixture was stirred for 2h at rt. Phenylselenol (70.0 μL, 101 mg, 641 μmol, 0.26 eq) was dissolved in anhydrous THF (500 μL) and cooled to 0°C. *n*-BuLi (260 μL, 641 μmol, 0.26 eq, 2.5 mol/L solution in hexane) was added. After stirring for 1min at 0°C the colourless mixture was added to the mixed anhydride and was stirred at rt for 1.5h. Water (30 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1, 2:1) to afford the seleno ester (138 mg, 272 μmol, 0.11 eq) which was dissolved in benzene (5 mL). Tri-*n*-butyl stannane (150 μL, 158 mg, 542 μmol, 0.22 eq) and AIBN (2.40 mg, 15.0 μmol, 0.006 eq) were added and the mixture was heated to reflux for 1h. After cooling down to rt the mixture was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1, 3:1, 2:1, 1:1) to afford 20*Z*-geissoschizoate (70.0 mg, 216 μmol, 0.09 eq) as a colourless oil.

R_f = 0.42 (DCM/MeOH = 10:1) [CAN]

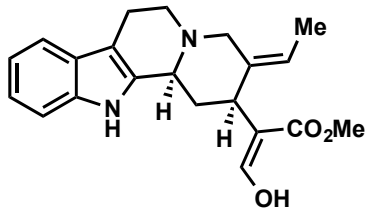
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80 (bs, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.13 (dt, J_1 = 7.4 Hz, J_2 = 1.1 Hz, 1H), 7.08 (dt, J_1 = 7.3 Hz, J_2 = 1.0 Hz, 1H), 5.23 (q, J = 6.5 Hz), 3.89 (d, J = 12.3 Hz, 1H), 3.75 (s, 3H), 3.56 (bd, J = 10.9 Hz, 1H), 3.13 - 3.18 (m, 1H), 2.96 - 3.05 (m, 1H), 2.67 - 2.82 (m, 5H), 2.32 (dd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, 1H), 2.25 (ddd, J_1 = 12.2 Hz, J_2 = 3.4 Hz, J_3 = 3.1 Hz, 1H), 1.71 (d, J = 6.5 Hz, 3H), 1.39 (ddd, J_1 = 11.6 Hz, J_2 = 11.6 Hz, J_3 = 11.6 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 173.6, 136.2, 136.2, 134.4, 127.5, 121.5, 119.5, 118.3, 116.6, 110.9, 108.4, 59.8, 55.6, 52.8, 51.9, 38.2, 37.0, 36.9, 21.9, 13.3 ppm.

IR (film): 3385, 3054, 2916, 2848, 2744, 1731, 1452, 1436, 1322, 1266, 1200, 1163, 1100, 1046, 1008, 830, 739 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{25}N_2O_2^+$: 325.1916; found $C_{20}H_{25}N_2O_2^+$ 325.1919

20-*Z*-Geissoschizine (41)



Diisopropylamine (110 μL, 81.0 mg, 798 μmol, 3.7 eq) was dissolved in anhydrous THF (500 μL) and cooled to -78°C. *n*-Butyllithium (320 μL, 198 μmol, 3.7 eq, 2.5 mol/L solution in hexane) was added dropwise and the mixture was stirred at 0°C for 30min. 20*Z*-Geissoschizoate (70.0 mg, 216 μmol, 1 eq) dissolved in anhydrous THF (3 mL) was added to the LDA solution at -78°C and stirred for 1h. Methyl formate (1.10 mL, 1.09 g, 18.1 mmol, 84 eq) was added and the mixture was allowed to warm up to 10°C during a period of 6h. The reaction mixture was poured onto water (50 mL) and 1 M aqueous NaOH was added until pH = 12. The starting material was extracted with Et_2O (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield 20*Z*-geissoschizoate (60.0 mg, 185 μmol, 0.86 eq). The aqueous phase was acidified to pH = 5 with 1 M aqueous HCl and extracted with Et_2O (3x50 mL).

The combined organic phases were abolished. Addition of 1 M aqueous NaOH until pH = 7 was followed by extraction with DCM (5x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield 20*Z*-geissoschizine (9.00 mg, 26.5 μmol, 0.12 eq) as a colourless oil.

R_f = 0.26 (DCM/MeOH = 10:1) [CAN]

Only the NMR - shifts of the main isomer corresponding to the 1,3 - dicarbonyl unit are listed.

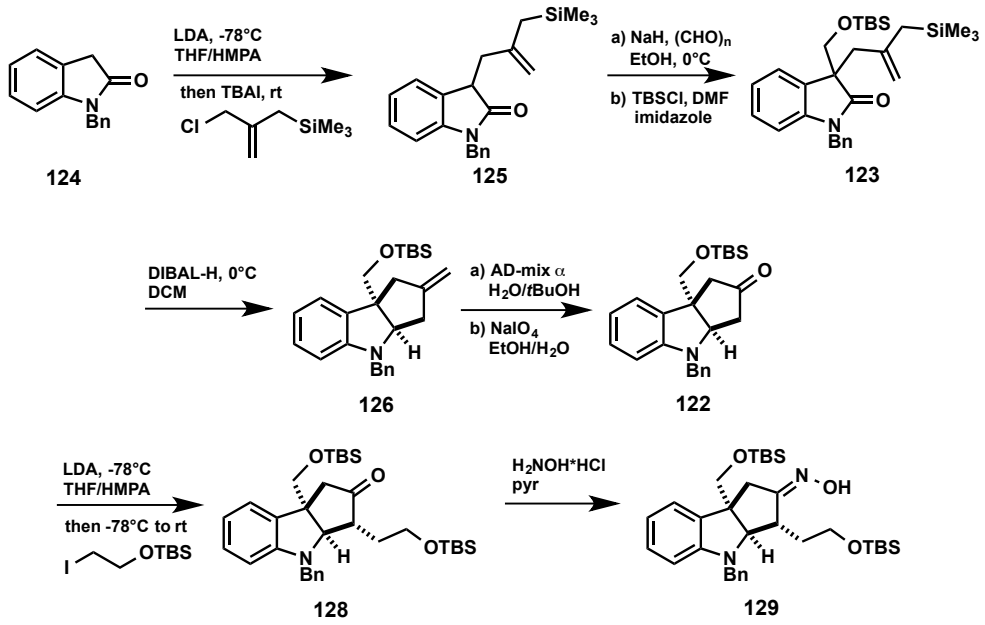
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80 (bs, 1H), 7.72 (s, 1H), 7.48 (dd, J_1 = 6.5 Hz, J_2 = 5.8 Hz, 1H), 7.31 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 7.07 - 7.18 (m, 2H), 5.16 (q, *J* = 6.5 Hz, 1H), 3.95 (d, *J* = 12.7 Hz, 1H), 3.76 (s, 3H), 3.56 (bd, *J* = 11.3 Hz, 1H), 3.15 - 3.30 (m, 2H), 2.99 - 3.08 (m, 1H), 2.87 (d, *J* = 11.4 Hz, 1H), 2.65 - 2.82 (m, 2H), 2.15 (ddd, J_1 = 12.3 Hz, J_2 = 3.4 Hz, J_3 = 2.0 Hz, 1H), 1.86 (ddd, J_1 = 11.8 Hz, J_2 = 11.8 Hz, J_3 = 11.8 Hz, 1H), 1.67 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 173.0, 163.5, 136.6, 136.2, 134.2, 127.4, 121.7, 119.6, 118.5, 118.4, 111.0, 108.4, 104.7, 60.5, 55.9, 52.7, 51.9, 40.8, 36.3, 21.7, 13.2 ppm.

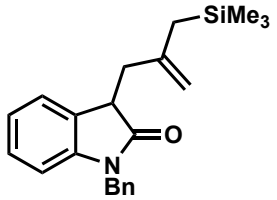
IR (film): 3232, 3055, 2924, 2854, 2749, 1659, 1552, 1445, 1327, 1233, 1188, 1111, 743 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{25}N_2O_3^+$: 353.1865; found $C_{21}H_{25}N_2O_3^+$ 353.1866

8.2.3 1st Synthetic approach



1-Benzyl-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one (125)



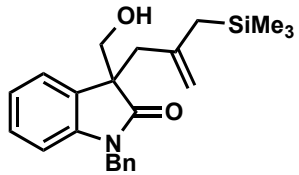
(2-(Chloromethyl)allyl)trimethylsilane (1.80 mL, 1.63 g, 10.0 mmol, 1 eq) was dissolved in absoulte THF (20 mL) and tetrabutylammonium iodide (3.70 g, 10.0 mmol, 1 eq) was added. The mixture was stirred at rt. Diisopropylamine (8.48 mL, 6.08 g, 60.0 mmol, 6 eq) was dissolved in absolute THF (40 mL) and cooled to -78°C. *n*-Butyllithium (24.0 mL, 60.0 mmol, 6 eq, 2.5 mol/L solution in hexane) was added dropswise and the resulting mixture was stirred at -78°C for 15min. The mixture was allowed to warm up to 0°C and was stirred for 30min. After this the LDA solution was recooled to -78°C. 1-Benzylindolin-2-one (13.4 g, 60.0 mmo, 6 eq) was dissolved in absolute THF (60 mL) and absolute HMPA (20 mL) and was slowly transfered to the LDA solution *via* canula. The resulting mixture was stirred at -78°C for 30min and was then transferred to the (2-(chloromethyl)allyl)trimethylsilane solution *via* canula dropwise. The reaction mixture was stirred at rt for 24h and was then poured onto an aqueous NH_4Cl solution (500 mL). The aqueous phase was extracted with EtOAc (3x250mL). The combined organic phases were washed with brin (300 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 30:1 to 10:1 to 2:1 to 1:1) to obtain 1-benzyl-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one (2.71 g, 7.75 mmol, 0.78 eq) as a colourless foam. 1-Benzylindolin-2-one (11.3 g, 50.6 mmo, 5.06 eq) could be reisolated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 - 7.28 (m, 5H), 7.27 - 7.23 (m, 1H), 6.97 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 0.8 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 4.95 (d, J = 15.6 Hz, 1H), 4.89 (d, J = 15.8 Hz, 1H), 4.72 (bs, 1H), 4.70 (bs, 1H), 3.67 (dd, J_1 = 10.1 Hz, J_2 = 4.1 Hz, 1H), 2.86 (dd, J_1 = 14.3 Hz, J_2 = 4.1 Hz, 1H), 2.29 (dd, J_1 = 14.5 Hz, J_2 = 10.1 Hz, 1H), 1.65 (d, J = 13.3 Hz, 1H), 1.60 (d, J = 13.4 Hz, 1H), 0.07 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.9, 144.0, 143.4, 136.1, 129.3, 128.9, 127.9, 127.7, 127.5, 124.9, 122.2, 110.6, 109.0, 43.9, 43.9, 39.7, 26.6, -1.2 ppm.

IR (film): 3381, 2954, 2916, 1716, 1614, 1489, 1467, 1456, 1363, 1247, 1178, 1080, 858, 840, 752, 696 cm^{-1}.

1-Benzyl-3-(hydroxymethyl)-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one (125b)

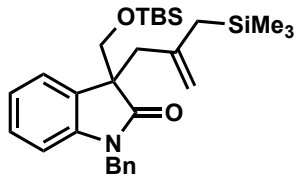


1-Benzyl-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one (2.71 g, 7.75 mmol, 1 eq) was dissolved in EtOH (20 mL) and cooled to 0°C. Paraformaldehyde (698 mg, 23.3 mmol, 3 eq) and NaH (57.5 mg, 1.94 mmol, 0.25 eq, 80% dispersion in mineral oil) were sequentially added and the resulting mixture was stirred at 0°C for 30min. Aqueous NH_4Cl solution (100 mL) was added and the aqueous phase was extracted with EtOAc (3x200 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 4:1:0.001 to 1:1:0.001) to obtain the alcohol as a colourless foam. The material was used for the next step without further purifications.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 - 7.27 (m, 4H), 7.26 - 7.22 (m, 2H), 7.17 (ddd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, J_3 = 1.1 Hz, 1H), 7.04 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.7 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 5.00 (d, J = 15.7 Hz, 1H), 4.83 (d, J = 15.7 Hz, 1H), 4.10 (bs, 1H), 4.40 (bs, 1H), 3.91 (dd, J_1 = 10.1 Hz, J_2 = 10.1 Hz, 1H), 3.76 (dd, J_1 = 10.9 Hz, J_2 2.7 Hz, 1H), 2.81 (d, J = 13.7 Hz, 1H), 2.55 (d, J = 13.3 Hz, 1H), 2.52 (bs, 1H), 1.28 (d, J = 13.6 Hz, 1H), 1.11 (d, J = 13.3 Hz, 1H), -0.03 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179.2, 143.6, 142.0, 135.8, 129.9, 128.8, 128.4, 127.6, 127.4, 123.7, 122.5, 111.7, 109.5, 67.8, 54.7, 43.8, 40.4, 28.1, -1.3 ppm.

1-Benzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-((trimethylsilyl)-methyl)-allyl)indolin-2-one (123)



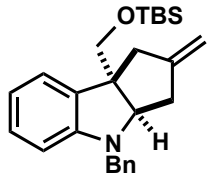
The crude 1-benzyl-3-(hydroxymethyl)-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one was dissolved in absolute DMF (8 mL). Imidazole (3.44 g, 50.5 mmol, 6eq) and *tert*-butyldimethylsilyl chloride (3.81 g, 25.3 mmol, 3 eq) were sequentially added. The reaction mixture was stirred at rt for 3h and was then poured onto water (250 mL). The aqueous phase was extracted with EtOAc (3x250 mL). The combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 60:1:0.001) to obtain 1-benzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-((trimethylsilyl)methyl)allyl)indolin-2-one (3.48 g, 7.05 mmol, 0.91 eq) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 - 7.24 (m, 5H), 7.08 - 7.04 (m, 2H), 6.64 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 6.46 (d, J = 7.5 Hz, 1H), 4.59 (d, J = 2.4 Hz, 1H), 4.50 (d, J = 2.0 Hz, 1H), 4.32 (d, J = 15.3 Hz, 1H), 4.23 (d, J = 15.3 Hz, 1H), 3.62 (d, J = 9.5 Hz, 1H), 3.59 (d, J = 9.6 Hz, 1H), 3.28 (d, J = 9.2 Hz, 1H), 3.17 (d, J = 9.2 Hz, 1H), 2.50 (d, J = 13.6 Hz, 1H), 2.38 (d, J = 13.3 Hz, 1H), 1.44 (d, J = 13.0 Hz, 1H), 1.36 (d, J = 13.3 Hz, 1H), 0.88 (s, 9H), -0.02 (s, 9H), -0.03 (s, 3H), -0.05 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.1, 144.5, 138.8, 134.0, 128.6, 128.1, 127.8, 127.1, 124.5, 117.1, 111.3, 106.7, 67.8, 60.8, 53.0, 49.8, 42.0, 28.3, 26.1, 18.4, -1.2, -5.3, -5.5 ppm.

IR (film): 2953, 2927, 2897, 2856, 1712, 1612, 1489, 1465, 1382, 1354, 1247, 1172, 1107, 1004, 835, 775, 750, 696, 665, 634, 551 cm^{-1}.
HRMS (ESI): calc. for $C_{29}H_{43}NO_2Si_2Na^+$: 516.2730, found: 516.2730

4-Benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylene-1,2,3,3a,4,8b-hexyhydrocyclopenta[b]indole (126)



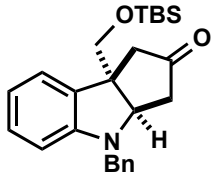
1-Benzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-((trimethylsilyl)methyl)allyl)-indolin-2-one (459 mg, 929 μmol, 1 eq) was dissolved in absolute DCM (5 mL) and cooled to 0°C. Diisobutylaluminium hydride (929 μL, 929 μmol, 1 eq, 1 mol/L solution in hexane) was added and the mixture was stirred for 2h at 0°C. Aqueous Na/K - tartrate (50 mL) was added and the mixture was stirred vigourously overnight. The aqoueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed woth brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 60:1:0.001) to obtain 4-benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylene-1,2,3,3a,4,8b-hexyhydrocyclo-penta[b]indole (180 mg, 444 μmol, 0.48 eq) as a colourless oil. 1-Benzyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-((trimethylsilyl)-methyl)allyl)indolin-2-one (170 mg, 344 μmol, 0.37eq) could be reisolated.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 - 7.23 (m, 5H), 7.03 - 6.99 (m, 2H), 6.61 (ddd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, J_3 = 0.8 Hz, 1H), 6.27 (d, J = 7.5 Hz, 1H), 4.81 (d, J = 1.4 Hz, 1H), 4.79 (d, J = 1.4 Hz, 1H), 4.44 (d, J = 16.1 Hz, 1H), 4.26 (d, J = 16.1 Hz, 1H), 3.97 (dd, J_1 = 6.5 Hz, J_2 = 3.1 Hz, 1H), 3.73 (d, J = 9.6 Hz, 1H), 3.68 (d, J = 9.6 Hz, 1H), 2.87 (d, J = 15.4 Hz, 1H), 2.53 - 2.39 (m, 3H), 0.88 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.9, 138.9, 134.0, 129.9, 128.6, 128.3, 127.5, 127.1, 123.5, 117.0, 107.0, 106.1, 72.0, 67.9, 57.9, 50.7, 42.4, 39.4, 26.0, 18.4, -5.3, -5.4 ppm.

HRMS (ESI): calc. for $C_{26}H_{36}NOSi^+$: 406.2566; found: 406.2562

4-Benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3a,4,8b-tetrahydro-cyclo-penta[b]indol-2(1*H*)-one (122)



4-Benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methylene-1,2,3,3a,4,8b-hexyhydrocyclopenta[b]indole (180 mg, 443 μmol, 1 eq) was dissolved in H_2O/*t*BuOH = 1:1 (5 mL). AD-mix α (700 mg) was added and the reaction mixture was stirred at rt for 21h. Aqueous $Na_2S_2O_3$ (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 50mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude diol was dissolved in H_2O/EtOH = 5:1 (6 mL). Na_2HPO_4 (4.00 mg, 27.0 μmol, 0.2 eq) and $NaIO_4$ (35.0 mg, 161 μmol, 1.2 eq) were added and the mixture was stirred at rt for 18h. The aqueous phase was extracted with EtOAc (3 x 25mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The material was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 10:1:0.001) to obtain 4-benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3a,4,8b-tetrahydrocyclo-penta[b]indol-2(1*H*)-one (96.0 mg, 226 μmol, 0.51 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 - 7.24 (m, 5H), 7.07 (ddd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, J_3 = 1.3 Hz, 1H), 7.01 (dd, J_1 = 7.3 Hz, J_2 = 0.9 Hz, 1H), 6.69 (ddd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, J_3 = 0.9 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 4.42 (d, J = 15.7 Hz, 1H), 4.21 (d, J = 15.7 Hz, 1H), 4.11 (dd, J_1 = 6.7 Hz, J_2 = 2.9 Hz,

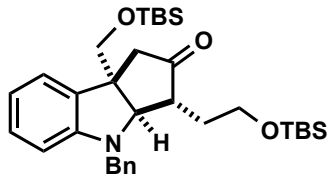
1H), 3.90 (d, *J* = 9.9 Hz, 1H), 3.80 (d, *J* = 9.9 Hz, 1H), 2.74 (dd, J_1 = 18.6 Hz, J_2 = 1.2 Hz, 1H), 2.57 - 2.41 (m, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 216.9, 151.4, 138.0, 132.5, 128.9, 128.8, 127.6, 127.5, 123.2, 118.2, 107.9, 70.3, 68.1, 54.1, 51.1, 46.7, 43.8, 26.0, 18.4, -5.5, -5.5 ppm.

IR (film): 2953, 2926, 2854, 1743, 1602, 1481, 1460, 1388, 1361, 1253, 1186, 1099, 837, 777, 748, 439 cm^{-1}.

HRMS (ESI): calc. for $C_{25}H_{34}NO_2Si^+$: 408.2359; found: 408.2350

4-Benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8b-(((*tert*-butyldimethyl-silyl)-oxy)methyl)-3,3a,4,8b-tetrahydrocyclopenta[b]indol-2(1*H*)-one (128)

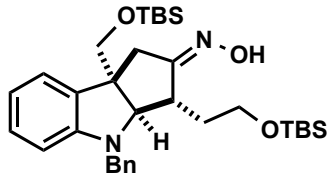


Diisopropylamine (32.0 μL, 23.0 mg, 227 μmol, 1.2 eq) was dissolved in absolute THF (200 μL) and cooled to -78°C. *n*-Butyllithium (91.0 μL, 227 μmol, 1.2 eq, 2.5 mol/L solution in hexane) was added dropwise and the mixture was stirred at -78°C for 15min. The reaction mixture was allowed to warm up to 0°C and was stirred at this temperature for 30min and was then recooled to -78°C. 4-Benzyl-8b-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3a,4,8b-tetrahydrocyclo-penta[b]indol-2(1*H*)-one (80.0 mg, 189 μmol, 1 eq) was dissolved in absolute THF (1 mL) and added to the LDA solution dropwise. The mixture was stirred at -78°C for 15min. *Tert*-butyl(2-iodoethoxy)dimethylsilane (163 mg, 567 μmol, 3 eq) dissolved in absolute HMPA (200 μL) was added and the resulting mixture was stirred for 21h and allowed to warm up to rt during this time slowly. Aqueous NH_4Cl (50 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under redcued pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3

= 60:1:0.001) to obtain 4-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8b-(((*tert*-butyldimethylsilyl)-oxy)methyl)-3,3a,4,8b-tetrahydrocyclopenta[b]indol-2(1*H*)-one (17.0 mg, 30.0 μmol, 0.16 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 - 7.23 (m, 5H), 7.05 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.2 Hz, 1H), 7.01 (dd, J_1 = 7.3 Hz, J_2 = 0.9 Hz, 1H), 6.64 (ddd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, J_3 = 0.9 Hz, 1H), 6.33 (d, *J* = 7.5 Hz, 1H), 4.59 (d, *J* = 16.1 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 1H), 3.99 (d, *J* = 3.4 Hz, 1H), 3.78 (d, *J* = 9.9 Hz, 1H), 3.70 (d, *J* = 9.9 Hz, 1H), 3.68 - 3.60 (m, 2H), 2.84 (d, *J* = 18.4 Hz, 1H), 2.65 - 2.58 (m, 2H), 1.91 - 1.82 (m, 1H), 1.71 - 1.62 (m, 1H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 218.9, 151.2, 138.4, 132.1, 129.1, 128.8, 127.2, 126.8, 123.6, 117.5, 107.0, 74.1, 68.3, 60.8, 53.2, 51.0, 49.8, 46.6, 33.6, 26.1, 26.0, 18.5, 18.4, -5.2, -5.2, -5.4, -5.4 ppm.
IR (film): 2954, 2927, 2856, 1741, 1716, 1604, 1489, 1456, 1375, 1361, 1255, 1228, 1217, 1095, 837, 777, 740, 696, 669 cm^{-1}.
HRMS (ESI): calc. for $C_{33}H_{52}NO_3Si_2^+$: 566.3486, found: 566.3489

4-Benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8b-(((*tert*-butyldimethyl-silyl)-oxy)methyl)-3,3a,4,8b-tetrahydrocyclopenta[b]indol-2(1*H*)-one oxime (129)

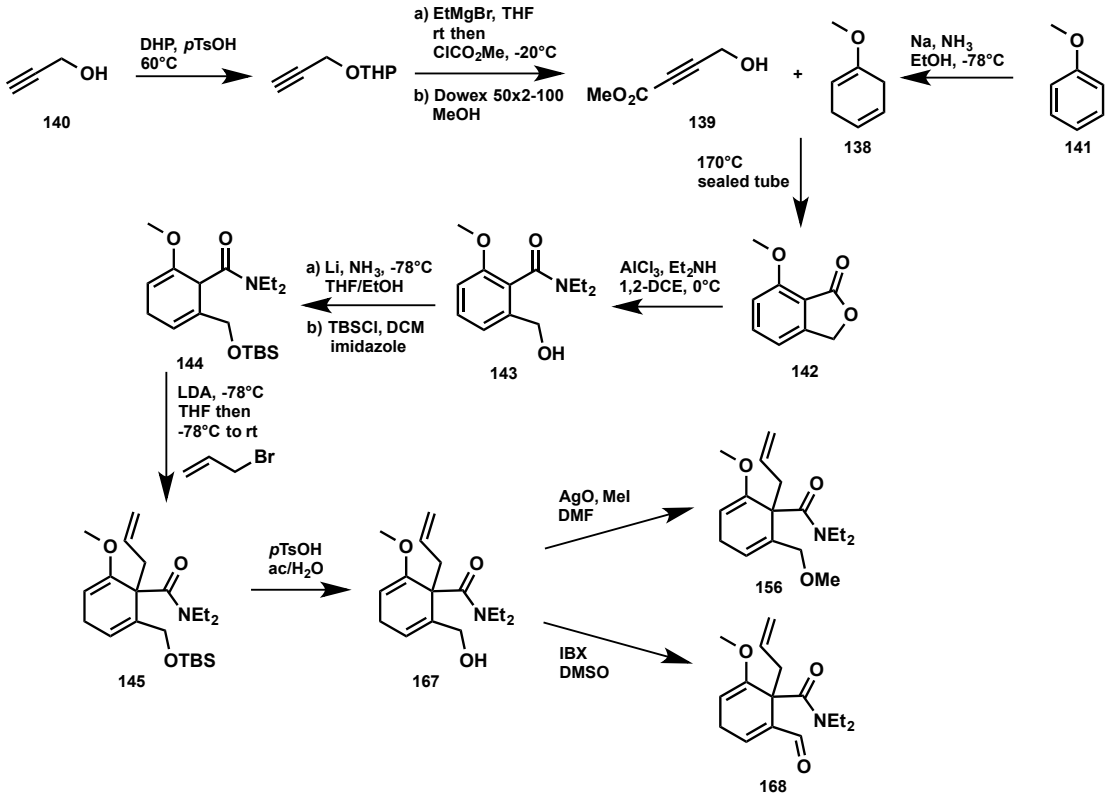


4-Benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8b-(((*tert*-butyldimethylsilyl)-oxy)-methyl)-3,3a,4,8b-tetrahydrocyclopenta[b]indol-2(1*H*)-one (15.0 mg, 26.5 μmol, 1 eq) was dissolved in pyridine (1 mL). Hydroxylamine hydrochloride (9.20 mg, 133 μmol, 5eq) was added and the reaction mixture was stirred at rt for 14h. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 20:1:0.001) to obtain 4-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-8b-

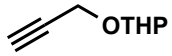
(((*tert*-butyldimethylsilyl)-oxy)methyl)-3,3a,4,8b-tetrahydrocyclopenta[b]indol-2(1*H*)-one oxime (12.0 mg, 20.7 μmol, 0.78 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.31 - 7.22 (m, 5H), 7.04 - 6.95 (m, 2H), 6.73 (bs, 1H), 6.58 (ddd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, J_3 = 0.9 Hz, 1H), 6.25 (d, J = 7.5 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.29 (d, J = 16.2 Hz, 1H), 3.89 (d, J = 1.4 Hz, 1H), 3.71 - 3.58 (m, 4H), 3.36 - 3.29 (m, 1H), 3.13 (dd, J_1 = 16.0 Hz, J_2 = 1.3 Hz, 1H), 2.56 (d, J = 16.5 Hz, 1H), 1.91 - 1.65 (m, 2H), 0.87 (s, 9H), 0.85 (s, 9H), 0.02 (s, 9H), -0.03 (s, 3H) ppm.
IR (film): 3298, 2927, 2856, 1971, 1604, 1489, 1463, 1255, 1099, 1004, 939, 837, 775, 742, 669, 441, 418 cm^{-1}.
HRMS (ESI): calc. for $C_{33}H_{53}N_2O_3Si_2^+$: 581.3595, found: 581.3593

8.2.4 2nd Synthetic approach



2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (140b)



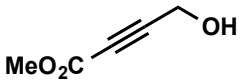
Dihydropyran (73.1 mL, 67.4 g, 802 mmol, 1.07 eq) was placed in a flask. *p*-Toluenesulfonic acid (10.0 mg) was added and the mixture was heated to 60°C. Propargyl alcohol (43.2 mL, 42.0 g, 749 mmol, 1eq) was added *via* dropping funnel without raising the inner temperature above 65°C. After complete addition the reaction mixture was stirred for 1.5h and was allowed to cool down to rt during this time. Solid $NaHCO_3$ (125 mg) was added and the mixture was stirred for 1h. After filtration the crude material was purified by fractional distillation to yield 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (69.9 g, 499 mmol, 0.67 eq) as a colourless fluid.

BP: 106 °C (70 mbar)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.95 - 4.81 (m, 1H), 4.31 - 4.19 (m, 2H), 4.03 - 3.80 (m, 1H), 3.56 - 3.51 (m, 1H), 2.47 - 2.40 (m, 1H), 1.86 - 1.51 (m, 6H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 97.0, 79.9, 74.1, 62.1, 54.2, 30.3, 25.4, 19.1 ppm.

Methyl 4-hydroxybut-2-ynoate (139)



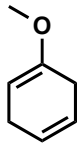
Ethylmagnesium bromide (166 mL, 499 mmol, 1 eq, 3 mol/L solution in Et_2O) was placed in a flask under argon. 2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (69.9 g, 499 mmol, 1 eq) dissolved in absolute THF (500 mL) was placed in a dropping funnel and added to the Grignard solution dropwise under cooling in a water bath. The resulting mixture was stirred at rt for 2h. Methyl chloroformate (42.4 mL, 51.8 g, 549 mmol, 1.1 eq) was dissolved in absolute THF (125 mL), placed in a second flask and cooled to -20°C. The Grignard solution was added via canula in that way that the inner temperature did not rise above -15 °C. After complete addition the mixture was stirred at -15 °C for 30min and afterwards at 0°C for 90min. The flask was placed in a fridge

overnight, all solids were removed by filtration and washed with cold PhMe (3x75 mL). The combined organic phases were concentrated under reduced pressure, washed with brine (5x50 mL), dried over $MgSO_4$ and filtrated. The solvent was removed under reduced pressure. The crude material was dissolved in MeOH (500 mL) and Dowex 50X2-100 ion-exchange resin (50 mg) was added. The mixture was stirred at rt for 12h. After filtration the solvent was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1) to yield methyl 4-hydroxybut-2-ynoate (35.8 g, 314 mmol, 0.63 eq) as a colourless fluid.

BP: 120°C (8 mbar)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.39 (s, 2H), 3.78 (s, 3H), 2.54 (s, 1H) ppm.

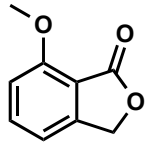
1-Methoxycyclohexa-1,4-diene (138)



Ammonia (800 mL) was condensed in a flask at -78°C. Anisole (43.6 mL, 43.2 g, 400 mmol, 1 eq) dissolved in EtOH (137 mL, 108 g, 2.40 mol, 6 eq) was added followed by sodium pieces (36.8 g, 1.60 mol, 4 eq). The deep blue reaction mixture was stirred at -78°C for 30min with a mechanical stirrer. Solid NH_4Cl was added carefully until the blue colour disappeared. The ammonia was allowed to evaporate overnight. Water was added (1 L) and the aqueous phase was extracted with Et_2O (3x500 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure to yield 1-methoxycyclohexa-1,4-diene (35.3 g, 321 mmol, 0.8 eq). The material was used without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.74 - 5.63 (m, 2H), 4.65 - 4.62 (m, 1H), 3.55 (s, 3H), 2.87 - 2.66 (m, 4H) ppm.

7-Methoxyisobenzofuran-1(3*H*)-one (142)



Methyl 4-hydroxybut-2-ynoate (3.58 g, 31.4 mmol, 1 eq) and 1-methoxycyclohexa-1,4-diene (5.18 g, 47.0 mmol, 1.5 eq) were mixed and put in a sealed tube. The mixure was heated up to 170°C for 5h and was then allowed to cool down to rt. The sealed tube was opened carefully under exhaustion of ethylene. The solid product was recrystalized from EtOAc to yield 7-methoxyisobenzofuran-1(3*H*)-one (3.81 g, 23.2 mmol, 0.74 eq) as a colourless crystaline solid.

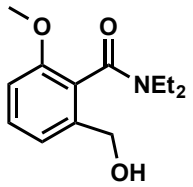
MP: 96.8 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 5.24 (s, 2H), 4.00 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.2, 159.0, 149.6, 136.4, 113.9, 113.4, 110.6, 68.9, 56.1 ppm.

IR (film): 2935, 1743, 1600, 1487, 1456, 1442, 1365, 1317, 1284, 1249, 1199, 1087, 1066, 1028, 1016, 945, 785, 765, 734, 684, 576, 470 cm^{-1}.

***N*,*N*-Diethyl-2-(hydroxymethyl)-6-methoxybenzamide (143)**



$AlCl_3$ (3.97 g, 29.8 mmol, 1.3 eq) was suspended in 1,2-dichloroethane (10 mL) and cooled to 0°C. Diethylamine (5.93 mL, 4.19 g, 57.3 mmol, 2.5 eq) dissolved in 1,2-dichloroethane (10 mL) was added dropwise. After complete addition the mixture was allowed to warm up to rt. 7-Methoxyisobenzofuran-1(3*H*)-one (3.76 g, 22.9 mmol, 1 eq) dissolved in 1,2-dichloroethane (20 mL) was added to the mixture under heat evolution. After stirring at rt for 6h the reaction mixture was poured onto a ice/water mixture (300 mL). The aqueous phase was extracted with DCM (3x100 mL). The combined organic phases

were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The solid product was recrystalized from EtOAc to yield *N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxybenzamide (5.01 g, 21.1 mmol, 0.92 eq) as colourless crystals.

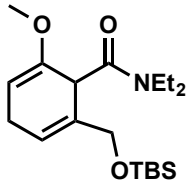
MP: 95.6 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.36 (d, *J* = 12.3 Hz, 1H), 3.81 (s, 3H), 3.68 - 3.52 (m, 2H), 3.22 - 3.08 (m, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.6, 155.2, 139.9, 130.4, 125.9, 122.0, 110.3, 63.8, 55.8, 43.2, 39.3, 14.0, 12.9 ppm.

IR (film): 3392, 2972, 2933, 2873, 2841, 1751, 1597, 1583, 1489, 1469, 1435, 1379, 1363, 1317, 1286, 1263, 1220, 1203, 1082, 1068, 1041, 945, 902, 875, 788, 763, 736, 688, 597 cm^{-1}.

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (144)

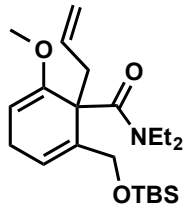


Ammonia (400 mL) was condensed at -78°C. *N*,*N*-Diethyl-2-(hydroxymethyl)-6-methoxybenzamide (5.00 g, 21.1 mmol, 1 eq) and EtOH (3.69 mL, 2.91 g, 63.2 mmol, 3 eq) dissolved in absolute THF (40 mL) were added. Lithium pieces (366 mg, 52.7 mmol, 2.5 eq) were added to the mixture and the deep blue solution was stirred at -78°C for 15min with a mechanical stirrer. Solid NH_4Cl was added carefully until the blue color disappeared. The ammonia was allowed to evaporate overnight. Water (1 L) was added and the aqueous phase was extracted with EtOAc (3x500 mL). The combined organic phases were washed with brine (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Due to reoxidation by air the material has to be further converted rapidly.

The crude alcohol was dissolved in absolute DCM (40 mL) and imidazole (3.44 g, 50.6 mmol, 2.4 eq) followed by *tert*-butyldimethylsilyl chloride (3.81 g, 25.3 mmol, 1.2 eq) were added. The reaction mixture was stirred at rt for 5h. Water was added (250 mL) and the aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (5.58 g, 15.8 mmol, 0.75 eq) as a colourless oil. Due to reoxidation to the aromatic system by air the product has to be further converted rapidly and ^{13}C - NMR analysis was not possible.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.86 - 5.82 (m, 1H), 4.79 (dd, J_1 = 3.6 Hz, J_2 = 3.6 Hz, 1H), 4.20 (dd, J_1 = 6.7 Hz, J_2 = 6.7 Hz, 1H), 4.08 - 3.95 (m, 2H), 3.70 - 3.17 (m, 7H), 3.11 - 2.70 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H) ppm.

1-Allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-cyclohexa-2,5-diene-1-carboxamide (145)

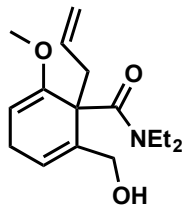


LiHMDS (18.9 mL, 18.9 mmol, 1.2 eq, 1 mol/L solution in THF) was put in a Schlenk tube and cooled to -78°C. 2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (5.58 g, 15.8 mmol, 1 eq) dissolved in absolute THF (40 mL) was added dropwise and the resulting mixture was stirred at -78°C for 1h. Allyl bromide (13.7 mL, 19.1 g, 158 mmol, 10 eq) was added and the resulting mixture was stirred at -78°C for 2h and then allowed to warm up to rt. Water (300 mL) was added and the aqueous phase was extracted with EtOAc (3x300 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtrated and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain 1-allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (3.00 g, 7.63 mmol, 0.48 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.98 - 5.95 (m, 1H), 5.60 (dddd, J_1 = 17.2 Hz, J_2 = 9.9 Hz, J_3 = 7.3 Hz, J_4 = 7.3 Hz, 1H), 4.99 - 4.91 (m, 2H), 4.75 (t, J = 3.4 Hz, 1H), 4.13 - 4.08 (m, 1H), 3.86 (ddd, J_1 = 14.8 Hz, J_2 = 4.5 Hz, J_3 = 2.3 Hz, 1H), 3.70 (dq, J_1 = 14.4 Hz, J_2 = 7.2 Hz, 1H), 3.55 (dq, J_1 = 13.7 Hz, J_2 = 7.0 Hz, 1H), 3.50 (s, 3H), 3.22 (dq, J_1 = 14.4 Hz, J_2 = 7.1 Hz, 1H), 3.09 (dq, J_1 = 13.6 Hz, J_2 = 6.9 Hz, 1H), 2.95 - 2.86 (m, 1H), 2.82 - 2.73 (m, 2H), 2.63 (dd, J_1 = 14.5 Hz, J_2 = 7.3 Hz, 1H), 1.10 (t, J_2 = 7.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.2, 154.0, 136.0, 134.7, 118.8, 116.8, 91.8, 61.5, 54.2, 53.3, 41.1, 40.6, 39.8, 26.3, 26.1, 18.5, 13.2, 12.5, -5.2, -5.3 ppm.
IR (film): 2953, 2929, 2856, 1749, 1734, 1716, 1635, 1558, 1541, 1506, 1489, 1471, 1456, 1375, 1361, 1267, 1217, 1178, 1099, 1062, 1004, 939, 910, 837, 777, 669, 422, 408 cm^{-1}.
HRMS (ESI): calc. for $C_{22}H_{40}NO_3Si^+$: 394.2777, found: 394.2775

1-Allyl-*N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxycyclohexa-2,5-diene-1-carboxamide (167)

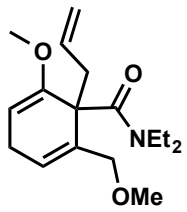


1-Allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (2.90 g, 7.37 mmol, 1 eq) was dissolved in acetone/H_2O = 3:1 (20 mL) and *para*-toluenesulfonic acid (70.0 mg, 369 μmol, 0.05 eq) was added. The mixture was stirred at rt for 5h. Aqueous $NaHCO_3$ (250 mL) was added and the aqueous phase was

extracted with EtOAc (3x250 mL). The combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain 1-allyl-*N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxycyclohexa-2,5-diene-1-carboxamide (2.05 g, 7.34 mmol, 1 eq).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.95 - 5.91 (m, 1H), 5.66 - 5.53 (m, 1H), 4.99 - 4.90 (m, 2H), 4,72 (ddd, J_1 = 17.6 Hz, J_2 = 3.4 Hz, J_3 = 3.4 Hz, 1H), 4.07 - 4.03 (m, 1H), 4.01 - 3.97 (m, 1H), 3.75 - 3.47 (m, 5H), 3.26 - 3.06 (m, 2H), 2.95 - 2.68 (m, 4H), 1.89 (bs, 1H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.6, 154.0, 136.2, 134.8, 121.6, 116.9, 91.5, 62.6, 54.2, 53.5, 41.1, 40.6, 39.9, 26.3, 13.1, 12.3 ppm.
IR (film): 3412, 3070, 2974, 2935, 2875, 2818, 1695, 1614, 1456, 1429, 1379, 1361, 1311, 1271, 1213, 1176, 1149, 1118, 1099, 1068, 1037, 995, 960, 910, 840, 775, 713, 669, 418 cm^{-1}.
HRMS (ESI): calc. for $C_{16}H_{26}NO_3^+$: 280.1913; found 280.1919

1-Allyl-*N*,*N*-diethyl-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamide (156)

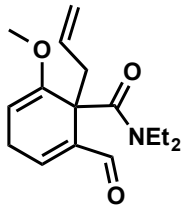


Ag_2O (2.56 g, 11.1 mmol, 1.5 eq) was placed under argon in a flask. 1-Allyl-*N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxycyclohexa-2,5-diene-1-carboxamide (2.05 g, 7.34 mmol, 1 eq) dissolved in absolute DMF (5 mL) was added followed by methyl iodide (1.87 mL, 4.25 g, 22.1 mmol, 3 eq). The resulting suspension was stirred at rt for 21h and was then filtrated over celite. Water (250 mL) was added and the aqueous phase was extracted with EtOAc (3 x 250mL). The combined organic phases were dried over $MgSO_4$, filtrated and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 1-allyl-*N*,*N*-diethyl-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamide (1.85 g, 6.31 mmol, 0.86 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94 - 5.91 (m, 1H), 5.60 (dddd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, J_3 = 7.3 Hz, J_4 = 7.3 Hz, 1H), 4.99 - 4.92 (m, 2H), 4.74 (dd, J_1 = 3.4 Hz, J_2 = 3.4 Hz, 1H), 3.82 - 3.68 (m, 3H), 3.60 (dq, J_1 = 13.7 Hz, J_2 = 6.9 Hz, 1H), 3.50 (s, 3H), 3.31 (s, 3H), 3.16 (dq, J_1 = 14.3 Hz, J_2 = 7.1 Hz, 1H), 3.05 (dq, J_1 = 13.6 Hz, J_2 = 6.9 Hz, 1H), 2.30 - 2.87 (m, 1H), 2.85 - 2.74 (m, 2H), 2.65 (dd, J_1 = 14.7 Hz, J_2 = 7.2 Hz, 1H), 1.09 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.1, 154.1, 134.8, 133.3, 122.0, 116.9, 91.5, 71.7, 58.8, 54.2, 53.5, 40.9, 40.5, 39.8, 26.4, 13.2, 12.3 ppm.
IR (film): 2976, 2933, 2875, 2827, 1732, 1716, 1674, 1558, 1541, 1506, 1471, 1456, 1435, 1379, 1361, 1284, 1267, 1219, 1193, 1170, 1101, 1070, 1004, 947, 877, 840, 804, 765, 669, 422 cm^{-1}.
HRMS (ESI): calc. for $C_{17}H_{28}NO_3^+$: 294.2069, found: 294.2073

1-Allyl-*N*,*N*-diethyl-2-formyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (168)

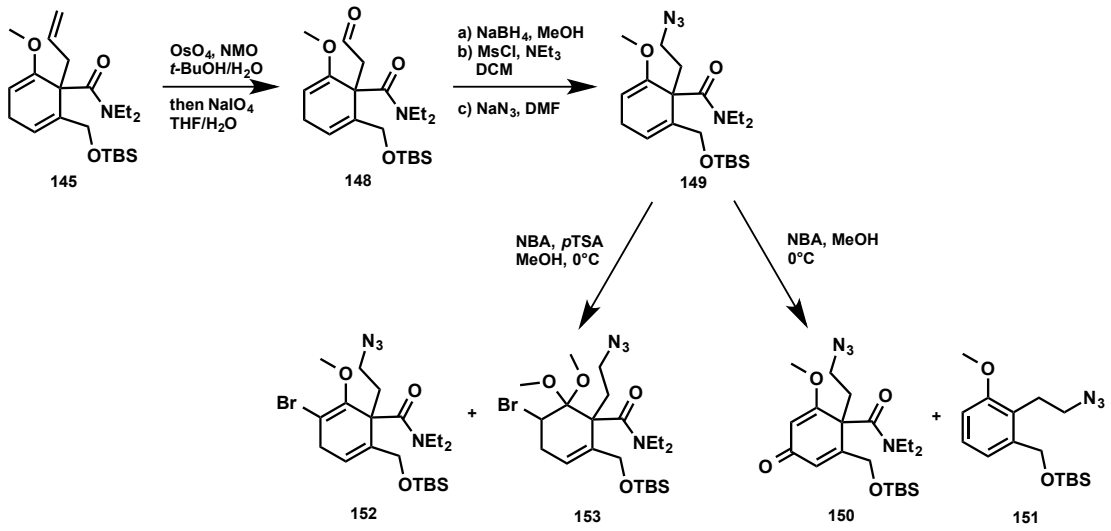


1-Allyl-*N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxycyclohexa-2,5-diene-1-carboxamide (100 mg, 358 μmol, 1 eq) was dissolved in absolute DMSO (4 mL). 2-Iodoxybenzoic acid (110mg, 394 μmol, 1.1 eq) was added and the mixture was stirred at rt for 1h. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). (The combined organic phases were washed with brine (50 mL), dired over $MgSO_4$, filtrated and concnetrated under reduced pressure. The crude aldehyde was purified by flash column

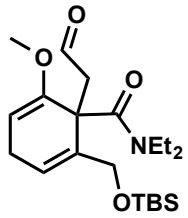
chromatography (SiO_2, PE/EtOAc = 1:2) to obtain 1-allyl-*N*,*N*-diethyl-2-formyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (82.0 mg, 296 μmol, 0.83 eq) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 9.24 (s, 1H), 6.08 (ddd, J_1 = 4.1 Hz, J_2 = 3.4 Hz, J_3 = 0.9 Hz, 1H), 5.67 - 5.57 (m, 1H), 4.96 - 4.93 (m, 1H), 4.91 - 4.90 (m, 1H), 4.14 (dd, J_1 = 3.3 Hz, J_2 = 3.3 Hz, 1H), 3.56 (bs, 1H), 3.47 (dddd, J_1 = 14.6 Hz, J_2 = 6.8 Hz, J_3 = 1.3 Hz, J_4 = 1.3 Hz, 1H), 3.26 - 3.21 (m, 1H), 3.06 - 2.97 (m, 3H), 3.04 (s, 3H), 2.55 (ddd, J_1 = 24.9 Hz, J_2 = 3.1 Hz, J_3 = 3.1 Hz, 1H), 2.36 (ddd, J_1 = 24.9 Hz, J_2 4.1 Hz, J_3 = 4.1 Hz, 1H), 1.11 (bs, 3H), 0.68 (bs, 3H) ppm.

^{13}C-NMR (100 MHz, C_6D_6): δ = 190.0, 167.4, 155.5, 145.8, 141.9, 135.2, 117.5, 89.1, 54.0, 51.6, 41.2, 41.0, 40.5, 27.4, 13.5, 12.7 ppm.


OsO4, NMO
t-BuOH/H2O
then NaIO4
THF/H2O
a) NaBH4, MeOH
b) MsCl, NEt3
DCM
c) NaN3, DMF
NBA, pTSA
MeOH, 0°C
NBA, MeOH
0°C
NEt2
OTBS
Br
N3
145
148
149
152
153
150
151

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-1-(2-oxoethyl)-cyclohexa-2,5-diene-1-carboxamide (148)

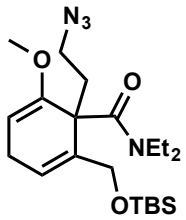


1-Allyl-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxycyclohexa-2,5-diene-1-carboxamide (1.18 g, 3.00 mmol, 1 eq) was dissolved in *t*BuOH/H_2O = 1:1 (30 mL). *N*-Methylmorpholine-*N*-oxide (352 mg, 3.00 mmol, 1 eq) followed by osmium tetroxide (20.0 μL, 15.0 μmol, 0.005 eq, 2.5 wt% solution in *t*BuOH) were added and the resulting mixture was stirred at rt for 24h. Additional *N*-methylmorpholine-*N*-oxide (352 mg, 3.00 mmol, 1 eq) was added and the reaction mixture was stirred at rt for 2d. Aqueous $Na_2S_2O_3$ (250 mL) was added and the aqueous phase was extracted with EtOAc (3x250 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude diol was dissolved in THF/H_2O = 1:1 (30 mL) and sodium periodate (642 mg, 3.00 mmol, 1 eq) was added. After stirring at rt for 1h water (250 mL) was added and the aqueous phase was extracted with EtOAc (3 x 250 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash coloum chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-1-(2-oxoethyl)cyclohexa-2,5-diene-1-carboxamide (1.01 g, 2.55 mmol, 0.85 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.68 (dd, J_1 = 4.1 Hz, J_2 = 2.1 Hz, 1H), 6.00 - 5.97 (m, 1H), 4.79 (dd, J_1 = 3.4 Hz, J_2 = 3.4 Hz, 1H), 4.18 - 4.12 (m, 1H), 3.94 (ddd, J_1 = 14.7 Hz, J_2 = 4.3 Hz, J_3 = 2.2 Hz, 1H), 3.70 - 3.54 (m, 2H), 3.50 (s, 3H), 3.24 - 3.07 (m, 3H), 3.01 - 2.92 (m, 1H), 2.91 - 2.82 (m, 1H), 2.46 (dd, J_1 = 15.0 Hz, J_2 = 3.7 Hz, 1H), 1.12 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.00 Hz, 3H), 0.89 (s, 9), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.6, 168.8, 154.3, 136.1, 119.6, 92.1, 61.8, 54.3, 52.3, 51.5, 41.4, 40.6, 26.1, 26.0, 18.7, 13.4, 12.3, -5.3, -5.4 ppm.
IR (film): 2953, 2929, 2856, 1714, 1631, 1506, 1471, 1460, 1427, 1379, 1361, 1313, 1257, 1217, 1178, 1149, 1105, 1080, 1058, 1006, 960, 939, 837, 777, 732, 667, 420 cm^{-1}.

1-(2-Azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-cyclohexa-2,5-diene-1-carboxamide (149)

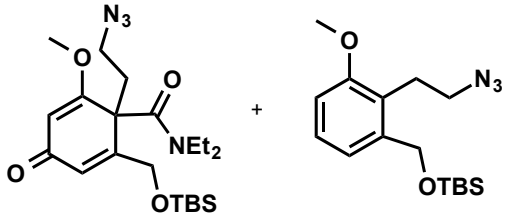


2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-1-(2-oxoethyl)-cyclo-hexa-2,5-diene-1-carboxamide (100 mg, 252 μmol, 1 eq) was dissolved in MeOH (3 mL) and sodium borohydride (10.0 mg, 252 μmol, 1 eq) was added. After stirring at rt for 30min water (50 mL) was added. The aqueous phase was extracted with EtOAc (3x50 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure.
The crude alcohol was dissolved in absolute DCM (1 mL) and cooled to -78°C. Triethylamine (70.0 μL, 51.0 mg, 503 μmol, 2 eq) followed by methanesulfonyl chloride (29.0 μL, 43.0 mg, 378 μmol, 1.5 eq) were added. The resulting mixture was stirred at -78 °C for 1h. Water (10 mL) was added at -78°C, the aqueous was allowed to warm up to rt and was then extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude mesylate was dissovled in absolute DMF (1 mL) and sodium azide (33.0 mg, 503 μmol, 2 eq) was added. The resulting mixture was stirred at rt for 24h. Water was added (25 mL) and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude azide was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1) to obtain 1-(2-azidoethyl)-2-

(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-cyclohexa-2,5-diene-1-carboxamide (49.0 mg, 116 μmol, 0.46 eq) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 6.11 - 6.08 (m, 1H), 4.31 - 4.26 (m, 1H), 4.09 (ddd, J_1 = 14.4 Hz, J_2 = 4.0 Hz, J_3 = 2.0 Hz 1H), 3.54 - 3.41 (m, 2H), 3.10 - 3.04 (m, 2H), 3.02 (s, 3H), 2.99 - 2.90 (m, 2H), 2.80 (ddd, J_1 = 14.8 Hz, J_2 = 7.4 Hz, J_3 = 7.4 Hz, 1H), 2.71 - 2.63 (m, 1H), 2.57 - 2.47 (m, 2H), 1.05 (t, *J* = 6.8 Hz, 3H), 0.98 (s, 9H), 0.75 (t, *J* = 6.8 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H) ppm.
^{13}C-NMR (100 MHz, C_6D_6): δ = 168.7, 154.3, 136.2, 120.0, 91.7, 62.1, 53.8, 52.4, 48.3, 41.4, 40.5, 34.8, 26.2, 26.1, 18.6, 13.4, 12.6, -5.3, -5.4 ppm.
IR (film): 2953, 2929, 2881, 2856, 2090, 1734, 1618, 1541, 1508, 1460, 1423, 1377, 1348, 1317, 1257, 1219, 1176, 1145, 1099, 1066, 1004, 939, 883, 833, 775, 736, 667, 422, 408 cm^{-1}.

1-(2-Azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-4-oxocyclohexa-2,5-diene-1-carboxamide (150) and ((2-(2-azidoethyl)-3-methoxy-benzyl)oxy)(*tert*-butyl)dimethylsilane (151)



1-(2-Azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-cyclo-hexa-2,5-diene-1-carboxamide (15.0 mg, 35.5 μmol, 1 eq) was dissolved in MeOH (500 μL) and cooled to 0°C. *N*-Bromo acetamide (5.00 mg, 35.5 μmol, 1 eq) dissolved in MeOH (300 μL) were added and the resulting mixture was stirred at 0°C for 5h. Aqueous $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with EtOAc (3x25mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1) to obtain ((2-(2-azidoethyl)-3-methoxy-benzyl)oxy)(*tert*-butyl)dimethyl-

silane (7.00 mg, 22.0 μmol, 0.61 eq) and 1-(2-azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-4-oxocyclohexa-2,5-diene-1-carboxamide (5.00 mg, 11.5 μmol, 0.32 eq) as a colourless oil.

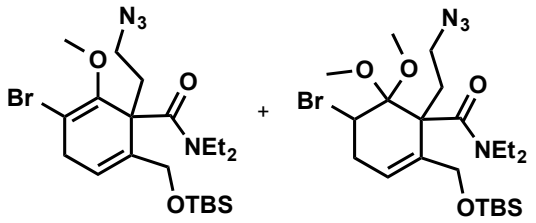
1-(2-Azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-4-oxocyclohexa-2,5-diene-1-carboxamide (150)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.66 (dd, J_1 = 3.4 Hz, J_2 = 1.7 Hz, 1H), 5.76 (d, J = 1.4 Hz, 1H), 4.31 (dd, J_1 = 17.0 Hz, J_2 = 2.0 Hz, 1H), 4.10 (dd, J_1 = 17.1 Hz, J_2 = 2.0 Hz, 1H), 3.77 (s, 3H), 3.54 (ddd, J_1 = 20.5 Hz, J_2 = 7.0 Hz, J_3 = 7.0 Hz, 1H), 3.21 - 3.10 (m, 2H), 3.08 - 2.95 (m, 3H), 2.61 - 2.53 (m, 1H), 2.35 - 2.28 (m, 1H), 1.11 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 186.6, 174.6, 165.5, 156.1, 125.2, 103.6, 60.8, 56.3, 55.3, 46.5, 41.5, 40.2, 37.0, 26.0, 18.4, 13.3, 12.2, -5.4, -5.4 ppm.
IR (film): 2951, 2929, 2885, 2856, 1662, 1635, 1604, 1506, 1458, 1423, 1359, 1311, 1259, 1219, 1128, 1097, 1026, 935, 837, 781, 742, 678, 648, 586, 430 cm^{-1}.

((2-(2-azidoethyl)-3-methoxy-benzyl)oxy)(*tert*-butyl)dimethylsilane (151)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.21 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 7.00 (d, J = 7.7 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.73 (s, 2H), 3.83 (s, 3H), 3.46 - 3.38 (m, 2H), 3.00 - 2.92 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H) ppm.
IR (film): 2953, 2926, 2854, 2092, 1734, 1587, 1471, 1463, 1440, 1375, 1261, 1107, 1068, 1006, 837, 777, 738, 669 cm^{-1}.

1-(2-Azidoethyl)-3-bromo-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-2-methoxycyclohexa-2,5-diene-1-carboxamide (152) and 1-(2-azidoethyl)-5-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6,6-dimethoxycyclohex-2-ene-1-carboxamide (153)



1-(2-Azidoethyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6-methoxy-cyclo-hexa-2,5-diene-1-carboxamide (20.0 mg, 47.0 μmol, 1 eq) was dissolved in MeOH (500 μL) and cooled to 0°C. *para*-Toluenesulfonic acid (800 μg, 5.00 μmol, 0.1 eq) and *N*-bromo acetamide (7.00 mg, 47 μmol, 1 eq) dissolved in MeOH (1 mL) were added and the resulting mixture was stirred at 0°C for 1h. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1) to obtain 1-(2-azidoethyl)-5-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6,6-dimethoxycyclohex-2-ene-1-carboxamide (1.00 mg, 2.00 μmol, 0.04 eq) and 1-(2-Azidoethyl)-3-bromo-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-2-methoxycyclohexa-2,5-diene-1-carboxamide (8.00 mg, 16.0 μmol, 0.34 eq).

1-(2-Azidoethyl)-3-bromo-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-2-methoxycyclohexa-2,5-diene-1-carboxamide (152)

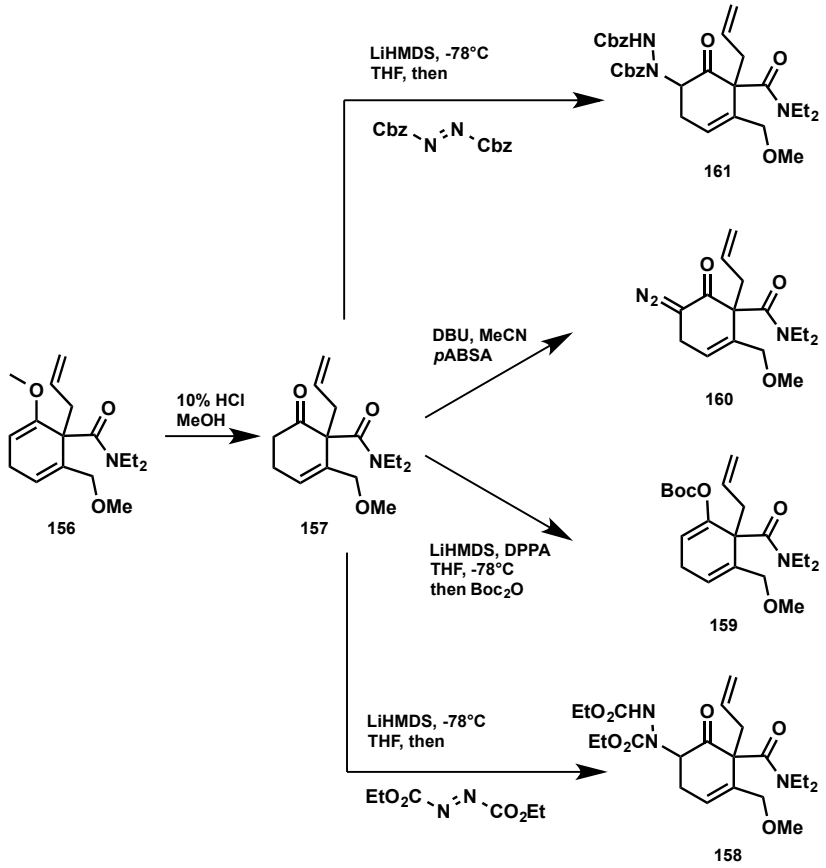
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90 - 5.88 (m, 1H), 4.07 - 4.02 (m, 1H), 3.85 - 3.80 (m, 1H), 3.81 (s, 3H), 3.43 - 3.08 (m, 8H), 2.37 (ddd, J_1 = 14.7 Hz, J_2 = 9.4 Hz, J_3 = 6.1 Hz, 1H), 2.23 (ddd, J_1 = 14.7 Hz, J_2 = 9.7 Hz, J_3 = 6.3 Hz, 1H), 1.12 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 150.6, 136.0, 119.5, 104.9, 61.2, 61.0, 55.8, 47.6, 41.7, 41.3, 37.3, 33.0, 26.0, 18.4, 13.1, 12.5, -5.3, -5.4 ppm.

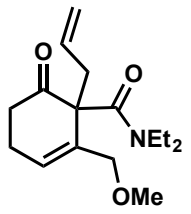
IR (film): 2951, 2929, 2856, 2092, 1780, 1734, 1716, 1683, 1558, 1541, 1508, 1489, 1471, 1458, 1419, 1361, 1338, 1259, 1215, 1099, 1062, 1006, 837, 779, 518, 430, 418 cm^{-1}.

1-(2-Azidoethyl)-5-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*,*N*-diethyl-6,6-dimethoxycyclohex-2-ene-1-carboxamide (153)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.95 - 5.90 (m, 1H), 4.25 (dd, J_1 = 11.9 Hz, J_2 = 5.5 Hz, 1H), 3.86 - 3.85 (m, 2H), 3.64 (s, 3H), 3.63 - 3.54 (m, 1H), 3.46 (s, 3H), 3.44 - 3.37 (m, 3H), 3.28 - 3.21 (m, 2H), 2.83 - 2.69 (m, 2H), 2.52 (ddd, J_1 = 14.9 Hz, J_2 = 10.9 Hz, J_3 = 6.3 Hz, 1H), 1.92 (ddd, J_1 = 14.9 Hz, J_2 = 10.7 Hz, J_3 = 4.2 Hz, 1H), 1.10 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.9, 140.0, 129.3, 122.7, 101.0, 62.9, 62.3, 53.8, 51.9, 51.7, 48.9, 42.7, 41.7, 35.4, 34.5, 26.0, 18.4, 13.5, 12.2, -5.4, -5.4 ppm.
HRMS (ESI): calc. for $C_{22}H_{41}N_4O_4SiBrNa^+$: 555.1978, found: 555.1971


LiHMDS, -78°C
THF, then
Cbz N N Cbz
CbzHN
CbzN
NEt2
OMe
161
DBU, MeCN
pABSA
N2
160
10% HCl
MeOH
156
157
LiHMDS, DPPA
THF, -78°C
then Boc2O
BocO
159
LiHMDS, -78°C
THF, then
EtO2C N N CO2Et
EtO2CHN
EtO2CN
158

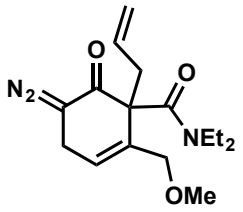
1-Allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (157)



1-Allyl-*N*,*N*-diethyl-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamide (527 mg, 1.80 mmol, 1 eq) was dissolved in MeOH (5 mL). 10 % HCl aq. (5 mL) was added and the reaction mixture was stirred at rt 2.5d. The mixture was poured onto aqueous $NaHCO_3$ (300 mL) and the aqueous phase was extracted with EtOAc (3x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 0:1) to obtain 1-allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (473 mg, 1.69 mmol, 0.94 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.07 - 6.05 (m, 1H), 5.83 - 5.72 (m, 1H), 5.02 - 4.97 (m, 2H), 3.85 - 3.80 (m, 1H), 3.70 - 3.66 (m, 1H), 3.50 - 3.41 (m, 1H), 3.33 (s, 3H), 3.26 - 3.18 (m, 1H), 3.02 - 2.93 (m, 1H), 2.86 (dd, J_1 = 14.0 Hz, J_2 = 7.8 Hz, 1H), 2.72 - 2.63 (m, 2H), 2.54 - 2.50 (m, 2H), 2.46 - 2.36 (m, 1H), 1.10 (bt, J = 6.3 Hz, 3H), 0.98 (bt, J = 6.5 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.2, 168.6, 135.7, 134.6, 123.1, 118.2, 71.9, 62.6, 58.9, 42.8, 41.4, 40.5, 37.0, 24.4, 12.4, 12.3 ppm.
IR (film): 2974, 2931, 2875, 1707, 1631, 1558, 1506, 1458, 1419, 1379, 1361, 1346, 1311, 1265, 1220, 1188, 1141, 1097, 1070, 999, 914, 854, 798, 655, 545, 410 cm^{-1}.
HRMS (ESI): calc. for $C_{16}H_{26}NO_3^+$: 280.1913, found: 280.1913

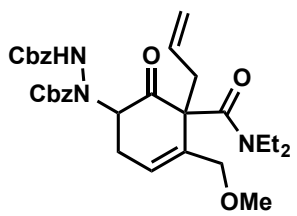
1-Allyl-5-diazo-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (160)



1-Allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (50.0 mg, 179 μmol, 1 eq) were dissolved in absolute MeCN (1 mL). 4-Acetamidobenzenesulfonyl azide (52.0 mg, 215 μmol, 1.2 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (64.0 μL, 65.0 mg, 430 μmol, 2.4 eq) were sequentially added and the resulting mixture was stirred at rt for 2h. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 1-allyl-5-diazo-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (33.0 mg, 108 μmol, 0.6 eq) as a yellow oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 5.79 - 5.68 (m, 2H), 5.06 - 5.01 (m, 1H), 4.94 - 4.91 (m, 1H), 3.77 - 3.66 (m, 2H), 3.47 - 3.38 (m, 1H), 3.33 (dd, J_1 = 14.3 Hz, J_2 = 7.9 Hz, 1H), 3.19 - 2.96 (m, 6H), 2.83 - 2.75 (m, 1H), 2.71 (dq, J_1 = 19.7 Hz, J_2 = 2.7 Hz, 1H), 2.49 - 2.41 (m, 1H), 1.03 (bt, *J* = 6.0 Hz, 3H), 0.80 (bt, *J* = 6.0 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, C_6D_6): δ = 190.8, 167.7, 135.1, 133.5, 118.8, 117.1, 71.4, 60.4, 60.2, 58.5, 43.0, 40.9, 40.7, 23.0, 12.5, 12.4 ppm.

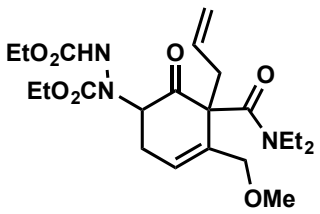
Dibenzyl 1-(5-allyl-5-(diethylcarbamoyl)-4-(methoxymethyl)-6-oxocyclohex-3-en-1-yl)hydrazine-1,2-dicarboxylate (161)



LiHMDS (240 μL, 240 μmol, 1.05 eq, 1 mol/L solution in THF) was placed in a Schlenk tube under argon and cooled to -78°C. 1-Allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (64.0 mg, 229 μmol, 1 eq) dissolved in absolute THF (300 μL) was added and the resulting mixture was stirred at -78°C for 30min. Dibenzyl azodicarboxylate (79.0 mg, 263 μmol, 1.15 eq) dissolved in absolute DCM (600 μL) was added and the resulting mixture was stirred at -78°C for 10min. Water (5 mL) was added at -78°C and the suspension was allowed to warm up to rt. The aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over MgSO4, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 1:1 to 0:1) to obtain dibenzyl 1-(5-allyl-5-(diethylcarbamoyl)-4-(methoxymethyl)-6-oxocyclohex-3-en-1-yl)hydrazine-1,2-dicarboxylate (85.0 mg, 147 μmol, 0.64 eq) as a mixture of diastereoisomers.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.11 - 6.96 (m, 10 H), 6.77 (bs, 1H), 6.03 - 5.65 (m, 3H), 5.41 - 4.64 (m, 10 H), 3.68 - 2.68 (m, 19 H), 0.95 - 0.90 (m, 6H) ppm.
^{13}C-NMR (100 MHz, C_6D_6): δ = 205.6, 205.0, 167.5, 166.7, 166.7, 157.3, 157.1, 156.6, 156.3, 140.7, 136.5, 136.4, 136.4, 136.1, 136.0, 135.3, 134.7, 134.6, 134.3, 134.1, 132.1, 130.4, 128.9, 128.8, 128.6, 128.5, 122.8, 122.0, 119.1, 119.0, 72.0, 71.9, 71.5, 71.2, 69.0, 69.0, 68.5, 67.6, 67.4, 63.7, 63.4, 63.3, 61.5, 60.0, 58.4, 58.3, 55.3, 44.0, 43.6, 43.1, 42.6, 41.6, 40.6, 40.4, 26.1, 25.6, 14.2, 12.5, 12.2, 12.1 ppm.

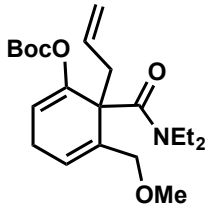
Diethyl 1-(5-allyl-5-(diethylcarbamoyl)-4-(ethoxymethyl)-6-oxocyclohex-3-en-1-yl)hydrazine-1,2-dicarboxylate (158)



LiHMDS (380 μL, 380 μmol, 1.05 eq, 1 mol/L solution in THF) was placed in a Schlenk tube under argon and cooled to -78°C. 1-Allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-carboxamide (100 mg, 358 μmol, 1 eq) dissolved in absolute THF (2 mL) was added and the resulting mixture was stirred at -78°C for 30min. Diethyl azodicarboxylate (65.0 μL, 72.0 mg, 412 μmol, 1.15 eq) was added and the resulting mixture was stirred at -78°C for 2min. Water (5 mL) was added and the mixture was allowed to warm up to rt. The aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1 to 0:1) to obtain diethyl 1-(5-allyl-5-(diethylcarbamoyl)-4-(ethoxymethyl)-6-oxocyclohex-3-en-1-yl)hydrazine-1,2-dicarboxylate (78.0 mg, 177 μmol, 0.5 eq) as a mixture of diastereoisomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.69 - 6.00 (m, 2H), 5.88 - 5.68 (m, 1H), 5.19 - 4.85 (m, 3H), 4.22 - 4.13 (m, 4H), 3.83 - 3.30 (m, 7H), 3.07 - 2.58 (m, 6H), 1.27 - 1.21 (m, 6H), 1.12 - 0.95 (m, 6H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.7, 204.9, 167.0, 156.9, 156.5, 156.2, 136.2, 136.0, 133.9, 133.8, 122.9, 122.2, 119.2, 119.0, 72.0, 71.4, 63.4, 63.2, 63.1, 62.3, 62.2, 61.8, 61.1, 58.9, 58.8, 43.3, 43.0, 42.5, 42.3, 41.6, 40.7, 40.5, 25.8, 25.4, 14.6, 14.5, 14.5, 12.7, 12.2 ppm.

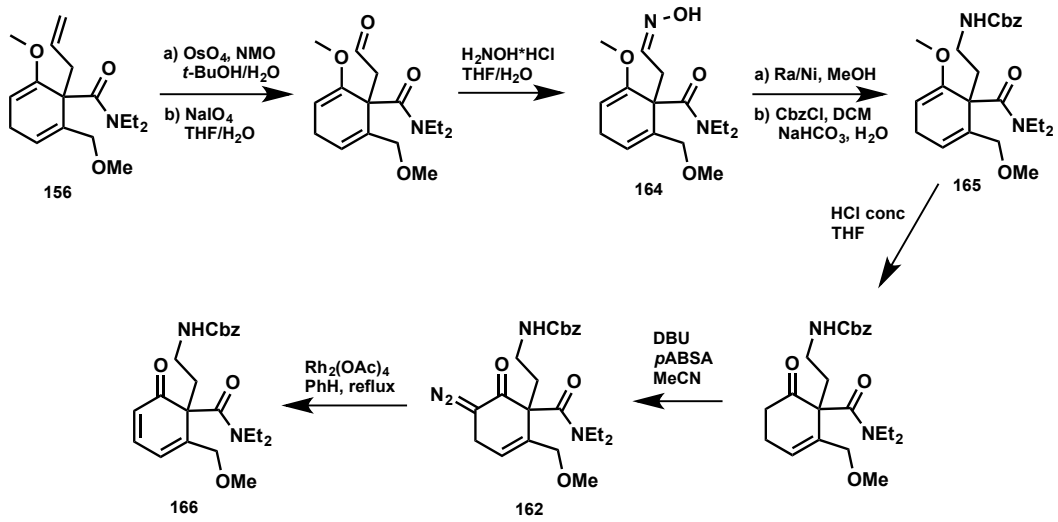
6-Allyl-6-(diethylcarbamoyl)-5-(methoxymethyl)cyclohexa-1,4-dien-1-yl *tert*-butyl carbonate (159)



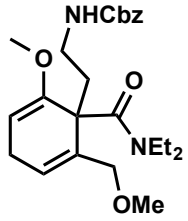
LiHMDS (450 μL, 450 μmol, 2.5 eq, 1 mol/L solution in THF) was dissolved in absolute THF (1 mL), placed in a Schlenk tube under argon and cooled to -78°C. 1-Allyl-*N*,*N*-diethyl-2-(methoxymethyl)-6-oxocyclohex-2-ene-1-

carboxamide (50.0 mg, 179 μmol, 1 eq) dissolved in absolute THF (500 μL) was added and the resulting mixture was stirred at -78°C for 30min. Diphenyl phosphorylazide (100 μL, 123 mg, 450 μmol, 2.5 eq) was added followed by di-*tert*-butyl dicarbonate (100 mg, 450 μmol, 2.5 eq) after 10min. The resulting mixture was stirred at -78°C for 30min. Water (5 mL) was added and the mixture was allowed to warm up to rt. The aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine, dired over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain 6-allyl-6-(diethylcarbamoyl)-5-(methoxymethyl)cyclohexa-1,4-dien-1-yl *tert*-butyl carbonate (43.0 mg, 113 μmol, 0.63 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.89 - 5.86 (m, 1H), 5.62 (dddd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, J_3 = 7.2 Hz, J_4 = 7.2 Hz, 1H), 5.02 - 4.92 (m, 2H), 4.81 (dd, J_1 = 3.4 Hz, J_2 = 3.4 Hz, 1H), 3.81 - 3.76 (m, 1H), 3.70 - 3.65 (m, 1H), 3.61 - 3.52 (m, 1H), 3.50 - 3.42 (m, 1H), 3.41 - 3.33 (m, 1H), 3.31 (s, 3H), 3.26 - 3.17 (m, 1H), 2.91 - 2.83 (m, 1H), 2.78 - 2.69 (m, 2H), 2.64 (dd, J_1 = 15.0 Hz, J_2 = 7.9 Hz, 1H), 1.08 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H), 0.18 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.2, 134.7, 133.7, 121.0, 116.8, 98.5, 71.7, 58.9, 54.0, 41.1, 40.9, 39.1, 26.7, 13.2, 12.4, 0.4 ppm.


a) OsO_4, NMO
t-BuOH/H_2O
b) $NaIO_4$
THF/H_2O
H_2NOH*HCl
THF/H_2O
a) Ra/Ni, MeOH
b) CbzCl, DCM
$NaHCO_3$, H_2O
HCl conc
THF
DBU
*p*ABSA
MeCN
$Rh_2(OAc)_4$
PhH, reflux
NHCbz
NEt2
OMe
N2
OH
156
164
165
162
166

Benzyl (2-(1-(diethylcarbamoyl)-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-dien-1-yl)ethyl)carbamate (165)



1-Allyl-*N*,*N*-diethyl-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamide (277 mg, 944 μmol, 1 eq) was dissolved in H_2O/*t*BuOH = 1:1 (6 mL). *N*-Methylmorpholine-*N*-oxide (111 mg, 944 μmol, 1 eq) followed by osmium tetroxide (62.0 μL, 47.2 μmol, 0.005 eq, 2.5 wt% solution in *t*BuOH) were added and the resulting mixture was stirred at rt for 5h. Aqueous $Na_2S_2O_3$ (25 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude diol was dissolved in THF/H_2O = 1:1 (6 mL) and sodium periodate (202 mg, 944 μmol, 1 eq) was added. The resulting mixture was stirred at rt for 1h followed by the addition of H_2O (25 mL). The aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1) to obtain *N*,*N*-diethyl-2-methoxy-6-(methoxymethyl)-1-(2-oxoethyl)cyclohexa-2,5-diene-1-carboxamide (216 mg, 731 μmol, 0.77 eq) as a colourless oil.

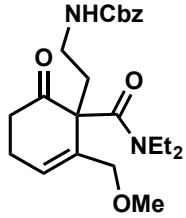
The aldehyde was dissolved in THF (5 mL) and H_2O (200 μL). Na_2CO_3 (47.0 mg, 444 μmol, 0.47 eq) followed by hydroxylamine hydrochloride (61.0 mg, 878 μmol, 0.93 eq) were added and the resulting mixture was stirred at rt for 12h. H_2O (25 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure.

The crude oxime was dissolved in MeOH (10 mL) and Raney-Nickel (300 mg, slurry in H_2O) was added. The resulting slurry was stirred at rt under an atmosphere of hydrogen (1 atm) for 14h. After filtration over celite the solvent was removed under reduced pressure.

The crude primary amine was dissolved in DCM (4 mL) and aqueous $NaHCO_3$ (4 mL) was added. Benzyl chloroformate (400 μL, 483 mg, 2.83 mmol, 3 eq) was added and the resulting suspension was stirred vigorously at rt for 5h. H_2O (25 mL) was added and the aqueous phase was extracted with EtOAc (3x50mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude carbamate was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 0:1) to obtain benzyl (2-(1-(diethylcarbamoyl)-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-dien-1-yl)ethyl)carbamate (171 mg, 397 μmol, 0.42 eq) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.36 - 7.20 (m, 3H), 7.11 - 6.96 (m, 2H), 5.99 - 5.92 (m, 1H), 5.16 - 5.05 (m, 1H), 4.44 - 4.34 (m, 1H), 4.15 - 3.78 (m, 2H), 3.57 - 2.43 (m, 18H), 1.07 - 1.05 (m, 3H), 0.84 - 0.78 (m, 3H) ppm.
^{13}C-NMR (100 MHz, C_6D_6): δ = 169.2, 169.0, 155.9, 154.6, 154.5, 138.2, 134.1, 128.5, 127.6, 121.5, 91.6, 91.2, 71.7, 68.1, 66.8, 66.8, 59.0, 58.5, 58.4, 54.0, 53.8, 52.5, 52.4, 43.8, 43.7, 41.3, 40.5, 34.0, 33.7, 33.3, 33.1, 26.3, 26.3, 13.4, 12.5 ppm.
IR (film): 3523, 2974, 2933, 2875, 1697, 1637, 1591, 1558, 1541, 1506, 1496, 1456, 1423, 1361, 1311, 1263, 1219, 1193, 1176, 1128, 1101, 1080, 1064, 1002, 975, 935, 885, 835, 769, 700, 671, 599, 478, 459, 439, 412 cm^{-1}.

Benzyl (2-(1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (165b)

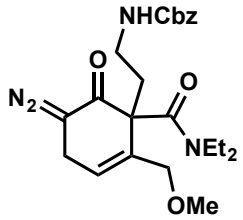


Benzyl (2-(1-(diethylcarbamoyl)-2-methoxy-6-(methoxymethyl)cyclohexa-2,5-dien-1-yl)ethyl)carbamate (171 mg, 397 μmol, 1 eq) was dissolved in THF (5 mL) and concentrated HCl aq. (1 mL) was added. The resulting mixture was stirred at rt for 7d and then poured onto aqueous $NaHCO_3$ (50 mL). The

aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude ketone was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:2) to obtain benzyl (2-(1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (119 mg, 286 μmol, 0.72 eq) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.49 - 7.11 (m, 5H), 5.91 - 5.88 (m, 1H), 5.27 - 5.09 (m, 1H), 4.05 - 3.41 (m, 6H), 3.21 - 3.20 (m, 4H), 3.03 - 1.98 (m, 9H), 1.15 (bs, 3H), 0.85 (bs, 3H) ppm.
^{13}C-NMR (100 MHz, 328 K, C_6D_6): δ = 206.2, 203.4, 168.4, 155.9, 155.8, 138.0, 137.9, 137.9, 128.5, 128.4, 121.8, 71.9, 67.0, 61.6, 61.5, 58.4, 58.3, 41.0, 36.7, 36.2, 30.0, 24.6, 12.4 ppm.

Benzyl (2-(5-diazo-1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (162)



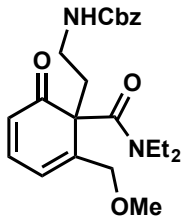
Benzyl (2-(1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (119 mg, 286 μmol, 1 eq) was dissolved in absolute MeCN (3 mL). 4-Acetamido benzenesulfonylazide (103 mg, 429 μmol, 1.5 eq) and 1,8-diazabicyclo[5.4.0]undec-7-ene (128 μL, 130 mg, 857 μmol, 3 eq) were sequentially added and the resulting mixture was stirred at rt for 1h. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:2 to 0:1) to obtain benzyl (2-(5-diazo-1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (124 mg, 280 μmol, 0.98 eq) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 - 6.99 (m, 5H), 6.57 - 5.81 (m, 1H), 5.07 - 4.99 (m, 1H), 4.14 - 2.64 (m, 13H), 2.36 - 1.56 (m, 3H), 1.09 - 1.05 (m, 3H), 1.01 - 0.89 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 190.3, 190.1, 167.8, 167.7, 167.7, 155.8, 155.7, 136.9, 134.8, 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 128.0, 127.9, 117.8, 117.6, 99.6, 71.3, 71.2, 71.0, 67.2, 67.1, 63.3, 61.9, 61.8, 61.5, 60.2, 59.1, 58.9, 58.8, 58.5, 43.1, 42.7, 42.5, 40.9, 40.8, 40.7, 40.3, 40.1, 35.8, 35.7, 35.1, 35.1, 29.8, 29.8, 29.5, 23.4, 23.4, 17.7, 14.1, 12.5, 12.2 ppm.

IR (neat): 2974, 2931, 2875, 2090, 1697, 1621, 1442, 1423, 1379, 1346, 1325, 1265, 1217, 1195, 1128, 1101, 1066, 952, 920, 835, 769, 732, 700, 644, 607, 416 cm^{-1}.

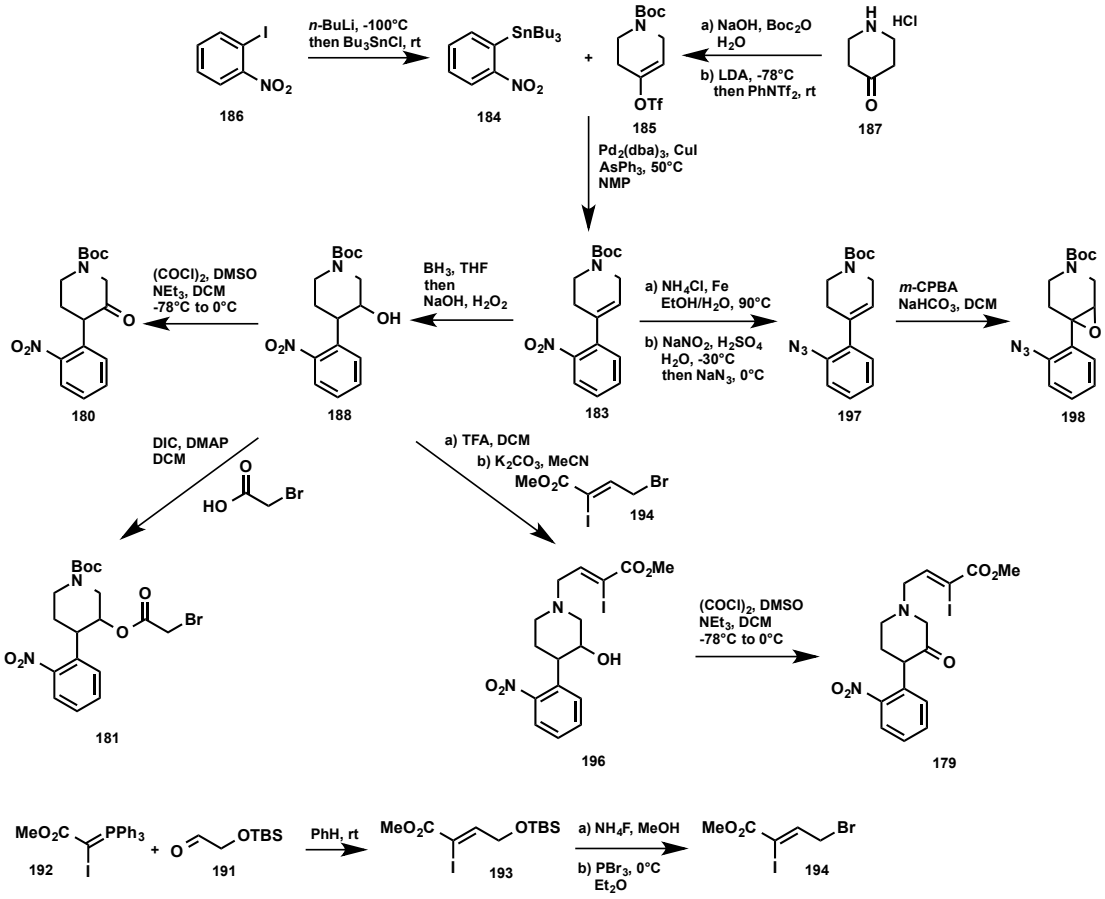
Benzyl (2-(1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohexa-2,4-dien-1-yl)ethyl)carbamate (166)



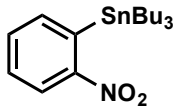
Benzyl (2-(5-diazo-1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohex-2-en-1-yl)ethyl)carbamate (5.00 mg, 11.3 μmol, 1 eq) was dissolved in benzene (3 mL). $Rh_2(OAc)_4$ (500 μg, 0.13 μmol, 0.01 eq) was added and the resulting mixture was heated to reflux for 15min. After cooling down to rt the solvent was removed and the crude product was purified by flash column chromatography (SiO_2, EtOAc) to obtain benzyl (2-(1-(diethylcarbamoyl)-2-(methoxymethyl)-6-oxocyclohexa-2,4-dien-1-yl)ethyl)carbamate (1.00 mg, 2.41 μmol, 0.21 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.87 - 7.62 (m, 1H), 7.36 - 7.28 (m, 4H), 7.14 - 7.06 (m, 1H), 6.58 - 6.46 (m, 1H), 6.20 - 6.07 (m, 1H), 5.06 - 4.89 (m, 2H), 4.15 - 3.75 (m, 2H) 3.46 - 3.09 (m, 7H), 2.92 - 2.64 (m, 3H), 2.28 - 2.16 (m, 2H), 1.10 - 1.07 (m, 3H), 0.93 - 0.88 (m, 3H) ppm.

8.2.5 3rd Synthetic approach



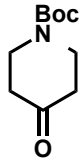
Tributyl(2-nitrophenyl)stannane (184)



1-Iodo-2-nitrobenzene (2.06 g, 8.27 mmol, 1eq) was dissolved in absolute THF (75 mL) and cooled to -100 °C. *n*Butyllithium (3.30 mL, 8.27 mmol, 1 eq, 2.5 mol/L solution in hexane) was added *via* a syringe pump over a period of 10 min. After complete addition the mixture was stirred at -100 °C for 3min. Tributyltin chloride (2.30 mL, 2.70 g, 8.27 mmol, 1 eq) was added dropwise and the reaction mixture was allowed to warm up to rt. After stirring for 1h at rt hexane (100 mL) and Et_2O (50 mL) was added and the resulting mixture was poured onto an ice/H_2O mixture (500 mL). The phases were seperated and the organic phase was washed with brine (250 mL). The organic phase was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Al_2O_3, PE/EtOAc = 50:1) to obtain tributyl(2-nitrophenyl)stannane (2.10 g, 5.10 mmol, 0.62 eq) as a colourless liquid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.33 - 8.28 (m, 1H), 7.70 - 7.64 (m, 1H), 7.63 - 7.56 (m, 1H), 7.52 - 7.43 (m, 1H), 1.57 - 1.08 (m, 18 H), 0.86 (t, *J* = 7.2 Hz, 9H) ppm.

***tert*-Butyl 4-oxopiperidine-1-carboxylate (187b)**

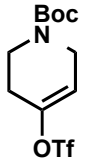


Piperidin-4-one hydrochloride monohydrate (10.0 g, 65.0 mmol, 1 eq) was dissolved in H_2O (100 mL). NaOH (2.90 g, 71.6 mmol, 1.1 eq) and di-*tert*-butyl dicarbonate (14.2 g, 65.0 mmol, 1eq) dissolved in THF (100 mL) were added. The resulting mixture was stirred at rt for 23h. The aqueous phase was extracted with Et_2O (3x250 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude

product was recrystalized from EtOH to obtain *tert*-butyl 4-oxopiperidine-1-carboxylate (11.9 g, 59.7 mmol, 0.92 eq) as colourless crystals.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.69 (t, *J* = 6.5 Hz, 4H), 2.41 (t, *J* = 6.3 Hz, 4H), 1.47 (s, 9H) ppm.

tert-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (185)

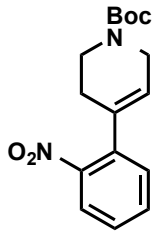


Di-*iso*-propylamine (785 mL, 566 mg, 5.60 mmol, 1.1 eq) was dissolved in absolute THF (5 mL) and cooled to -78°C. *n*Butyllithium (2.40 mL, 5.60 mmol, 1.1 eq, 2.5 mol/L solution in hexane) was added dropwise and the resulting mixture was allowed to stirr at 0°C for 30min. After recooling to -78°C *tert*-Butyl 4-oxopiperidine-1-carboxylate (1.00 g, 5.10 mmol, 1 eq) dissolved in absolute THF (5 mL) was added and the resulting mixture was stirred at -78°C for 30min. *N*-Phenyl-bis(trifluoromethynesulfonimide) (2.00 g, 5.60 mmol, 1.1 eq) dissolved in absolute THF (5 mL) was added dropwise an the reaction mixture was allowed to warm up to 0°C and was stirred for 5h at this temperature. The solvent was removed under reduced pressure and the crude triflate was purified by flash column chromatography (Al_2O_3, PE/EtOAc = 10:1) to obtain *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.24 g, 4.60 mmol, 0.90 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.76 (bs, 1H), 4.04 (dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz, 2H), 3.63 (dd, J_1 = 5.7 Hz, J_2 = 5.7 Hz, 2H), 2.49 - 2.40 (m, 2H), 1.47 (s, 9H) ppm.

IR (film): 2978, 2926, 2854, 1701, 1456, 1417, 1367, 1336, 1282, 1246, 1211, 1166, 1141, 1118, 1064, 1029, 873, 827, 767, 640, 611, 576, 520 cm^{-1}.

***tert*-Butyl 4-(2-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (183)**



$Pd_2(dba)_3$ (212 mg, 232 μmol, 0.05 eq), CuI (9.00 mg, 46.0 μmol, 0.01 eq) and triphenylarsine (28.0 mg, 93.0 μmol, 0.02 eq) were put in a Schlenk tube under argon. *tert*-Butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.24 g, 4.64 mmol, 1 eq) and tributyl(2-nitrophenyl)stannane (1.91 g, 4.64 mmol, 1 eq) dissolved in NMP (15 mL) were added and the resulting mixture was heated to 50°C for 16h. After cooling down to rt DCM (100 mL) was added and the organic phase was washed with NH_4OH solution (100 mL). The organic phase was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain *tert*-butyl 4-(2-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.26 g, 4.14 mmol, 0.89 eq) as a colourless oil.

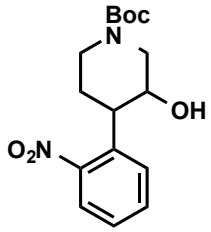
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.56 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.0 Hz, 1H), 7.42 (ddd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, J_3 = 1.5 Hz, 1H), 7.29 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 5.60 (bs, 1H), 4.03 (bs, 2H), 3.65 (dd, J_1 = 5.5 Hz, J_2 = 5.5 Hz, 2H), 2.34 (bs, 2H), 1.50 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.7, 155.1, 138.0, 135.0, 133.1, 131.0, 128.6, 128.3, 124.5, 80.1, 43.8, 39.9, 29.6, 28.7 ppm.

IR (film): 2976, 2931, 2854, 1759, 1697, 1635, 1606, 1570, 1558, 1525, 1471, 1456, 1417, 1390, 1367, 1344, 1321, 1298, 1253, 1224, 1151, 1097, 1076, 1014, 877, 854, 786, 752, 696, 518 cm^{-1}.

HRMS (ESI): calc. for $C_{16}H_{18}N_2O_5Na^+$: 341.1113, found: 341.1115

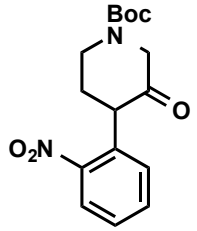
***tert*-Butyl 3-hydroxy-4-(2-nitrophenyl)piperidine-1-carboxylate (188)**



tert-Butyl 4-(2-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (275 mg, 904 μmol, 1 eq) was dissolved in absolute THF (10 mL). Borane (4.50 mL, 4.52 mmol, 5 eq, 1 mol/L solution in THF) was added and the resulting mixture was stirred at rt for 6h. The reaction mixture was cooled to 0°C and H_2O (2 mL) was added followed by 3 M NaOH (2 mL) and 30% H_2O_2 (2 mL). After stirring at 0°C for 90min the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain *tert*-butyl 3-hydroxy-4-(2-nitrophenyl)piperidine-1-carboxylate (190 mg, 589 μmol, 0.65 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 7.63 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.5 Hz, 1H), 1.47 (ddd, J_1 = 8.0 Hz, J_2 = 7.5 Hz, J_3 = 1.6 Hz, 1H), 7.30 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 4.40 (dd, J_1 = 18.3 Hz, J_2 = 1.1 Hz, 1H), 4.22 - 4.10 (m, 2H), 4.00 (d, J = 18.3 Hz, 1H), 3.52 - 3.35 (m, 1H), 3.09 (dd, J_1 = 14.6 Hz, J_2 = 7.3 Hz, 1H), 2.40 - 2.31 (m, 2H), 1.50 (s, 9H) ppm.

***tert*-Butyl 4-(2-nitrophenyl)-3-oxopiperidine-1-carboxylate (180)**

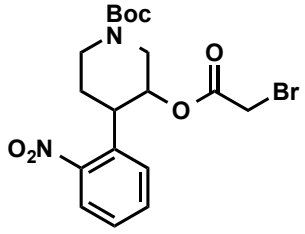


DMSO (257 μL, 282 mg, 3.61 mmol, 6.13 eq) was dissolved in absolute DCM (4 mL) and was cooled to -78°C. Oxalyl chloride (155 μL, 229 mg, 1.81 mmol,

3.07 eq) was added dropwise and the resulting mixture was stirred at -78°C for 15min. *tert*-Butyl 3-hydroxy-4-(2-nitrophenyl)piperidine-1-carboxylate (190 mg, 589 μmol, 1 eq) dissolved in absolute DCM (6 mL) was added and the reaction mixture was stirred at -78°C for 1h. Triethylamine (756 μL, 549 mg, 5.42 mmol, 9.2 eq) was added. The reaction mixture was allowed to warm up to 0°C and was stirred for 2h at this temperature. H_2O (100 mL) was added and the aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude ketone was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain *tert*-butyl 4-(2-nitrophenyl)-3-oxopiperidine-1-carboxylate (117 mg, 365 μmol, 0.62 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.2 Hz, 1H), 7.62 (ddd, J_1 = 7.3 Hz, J_2 = 7.8 Hz, J_3 = 0.9 Hz, 1H), 7.50 - 7.45 (m, 1H), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 4.39 (dd, J_1 = 18.1 Hz, J_2 = 0.7 Hz, 1H), 4.18 (bdd, J_1 = 9.4 Hz, J_2 = 9.4 Hz, 2H), 4.01 (bd, *J* = 17.7 Hz, 1H), 3.45 (bs, 1H), 2.38 - 2.31 (m, 2H), 1.51 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.8, 164.0, 154.6, 133.9, 133.3, 131.6, 128.7, 125.7, 81.0, 59.7, 52.5, 42.4, 30.1, 28.5 ppm.
IR (film): 2976, 2931, 1732, 1687, 1525, 1477, 1456, 1394, 1367, 1346, 1300, 1251, 1151, 991, 854, 779, 748, 704 cm^{-1}.
HRMS (ESI): calc. for $C_{16}H_{20}N_2O_5Na^+$: 343.1270, found: 343.1270

***tert*-Butyl 3-(2-bromoacetoxy)-4-(2-nitrophenyl)piperidine-1-carboxylate (181)**

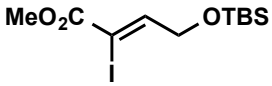


tert-Butyl 3-hydroxy-4-(2-nitrophenyl)piperidine-1-carboxylate (60.0 mg, 186 μmol, 1 eq) was dissolved in absolute DCM (3 mL). DMAP (2.30 mg, 19.0

μmol, 0.1 eq), bromoacetic acid (31.0 mg, 223 μmol, 1.2 eq) and DIC (32.0 μL, 26.0 mg, 205 μmol, 1.1 eq) were sequentially added and the resulting mixture was stirred at rt for 1h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain *tert*-butyl 3-(2-bromoacetoxy)-4-(2-nitrophenyl)piperidine-1-carboxylate (45.0 mg, 102 μmol, 0.55 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.57 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.3 Hz, 1H), 7.45 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.38 (ddd, J_1 = 8.2 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 5.01 (bs, 1H), 4.42 (bs, 1H), 4,25 (bs, 1H), 3.59 (d, J = 12.3 Hz, 1H), 3.55 (d, J = 12.3 Hz, 1H), 3.48 (ddd, J_1 = 11.5 Hz, J_2 = 11.5 Hz, J_3 = 3.3 Hz, 1H), 2.83 (bdd, J_1 = 12.4 Hz, J_2 = 12.4 Hz, 1H), 2.69 (bdd, J_1 = 11.3 Hz, J_2 = 11.3 Hz, 1H), 2.13 - 2.08 (m, 1H), 1.49 (s, 9H) ppm.

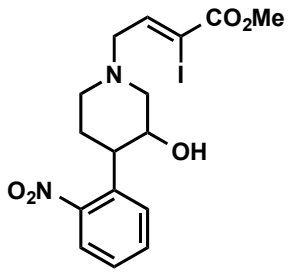
Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodobut-2-enoate (193)



Methyl 2-iodo-2-(triphenylphosphanylidene)acetate (1.30 g, 2.82 mmol, 0.8 eq) and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (615 mg, 3.53 mmol, 1 eq) were dissolved in benzene (30 mL) and stirred at rt for 18h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 20:1 to 20:1) to obtain methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodobut-2-enoate (1.00g, 2.80 mmol, 0.79 eq) as a colourless fluid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.44 (t, J = 4.7 Hz, 1H), 4.33 (d, J = 4.8 Hz, 2H), 3.84 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H) ppm.

Methyl (*Z*)-4-(3-hyroxy-4-(2-nitrophenyl)piperidin-1-yl)-2-iodobut-2-enoate (196)



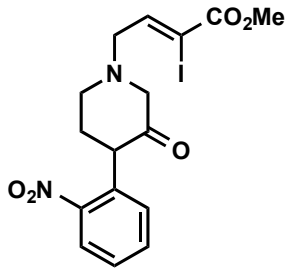
Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-iodobut-2-enoate (140 g, 393 μmol, 1 eq) was dissolved in MeOH (5 mL) and NH_4F (730 mg, 19.6 mmol, 50 eq) was added. The resulting suspension was stirred at rt for 7h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain methyl (*Z*)-4-hydroxy-2-iodobut-2-enoate. The alcohol was dissolved in absolute Et_2O (3 mL) and was cooled to 0°C. PBr_3 (15.0 μL, 43.0 mg, 157 μmol, 0.4 eq) was added and the reaction mixture was allowed to warm up to rt. After stirring for 4h the mixture was poured onto an aqueous $NaHCO_3$ (50 mL) and the aqueous phase was extracted with Et_2O (2x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The bromide was used withouth further purification.

tert-Butyl 3-hydroxy-4-(2-nitrophenyl)piperidine-1-carboxylate (50.0 mg, 155 μmol, 1 eq) was dissolved in DCM (4 mL) and cooled to 0°C. TFA (1 mL) was added and the reaction mixture was allowed to warm up to rt. After stirring for 1h the solvent was removed under reduced pressure and the crude ammonium salt was dissolved in absolute MeCN (2 mL). K_2CO_3 (214 mg, 1.55 mmol, 10 eq) was added followed by the freshly prepared bromide. The reaction mixture was stirred at rt for 12h. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain methyl (*Z*)-4-

(3-hyroxy-4-(2-nitrophenyl)piperidin-1-yl)-2-iodobut-2-enoate (20.0 mg, 45.0 μmol, 0.29 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.40 (t, J = 6.0 Hz, 1H), 7.39 - 7.36 (m, 1H), 3.88 (ddd, J_1 = 9.9 Hz, J_2 = 9.9 Hz, J_3 = 4.4 Hz, 1H), 3.84 (s, 3H), 3.33 (dd, J_1 = 5.8 Hz, J_2 = 1.4 Hz, 1H), 3.23 (ddd, J_1 = 10.6 Hz, J_2 = 4.4 Hz, J_3 = 1.7 Hz, 1H), 3.01 (ddd, J_1 = 12.0 Hz, J_2 = 10.3 Hz, J_3 = 4.0 Hz, 1H), 2.97 - 2.92 (m, 1H), 2.24 (ddd, J_1 = 11.7 Hz, J_2 = 11.7 Hz, J_3 = 2.6 Hz, 1H), 2.12 (dd, J_1 = 10.2 Hz, J_2 = 10.2 Hz, 1H), 2.00 - 1.94 (m, 1H), 1.85 (ddd, J_1 = 12.6 Hz, J_2 = 12.6 Hz, J_3 = 4.1 Hz, 1H) ppm.

Methyl (*Z*)-2-iodo-4-(4-(2-nitrophenyl)-3-oxopiperidin-1-yl)but-2-enoate (179)

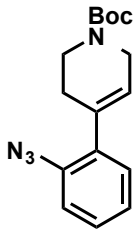


DMSO (25.0 μL, 28.0 mg, 359 μmol, 8 eq) was dissolved in absolute DCM (200 μL) and cooled to -78°C. Oxalyl chloride (15.0 μL, 23.0 mg, 179 μmol, 4 eq) was added dropwise and the resulting mixture was stirred at -78°C for 15min. Methyl (*Z*)-4-(3-hyroxy-4-(2-nitrophenyl)piperidin-1-yl)-2-iodobut-2-enoate (20.0 mg, 45.0 μmol, 1 eq) dissolved in absolute DCM (1 mL) was added and the reaction mixture was stirred at -78°C for 1h. NEt_3 (75.0 μL, 54.0 mg, 538 μmol, 12 eq) was added and the mixture was allowed to warm up to 0°C. After stirring for 1h at 0°C H_2O (10 mL) was added and the aqueous phase was extracted with DCM (3x10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude ketone was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain methyl (*Z*)-2-

iodo-4-(4-(2-nitrophenyl)-3-oxopiperidin-1-yl)but-2-enoate (16.0 mg, 36.0 μmol, 0.8 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.62 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.2 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.38 (t, J_1 = 6.0 Hz, J_2 = 6.0 Hz, 1H), 7.34 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 4.29 (dd, J_1 = 12.3 Hz, J_2 = 6.5 Hz, 1H), 3.86 (s, 3H), 3.46 (dd, J_1 = 14.3 Hz, J_2 = 1.7 Hz, 1H), 3.44 (dd, J_1 = 16.0 Hz, J_2 = 5.8 Hz, 1H), 3.37 (dd, J_1 = 16.0 Hz, J_2 = 5.8 Hz, 1H), 3.18 - 3.10 (m, 2H), 2.79 (ddd, J_1 = 11.3 Hz, J_2 = 11.3 Hz, J_3 = 3.4 Hz, 1H), 2.43 - 2.28 (m, 2H) ppm.
HRMS (ESI): calc. for $C_{16}H_{18}N_2O_5I^+$: 445.0260, found: 445.0258

***tert*-Butyl 4-(2-azidophenyl)-3,6-dihydropyridine-1 (2*H*)-carboxylate (197)**

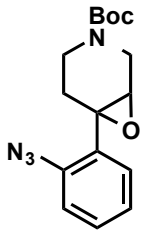


tert-Butyl 4-(2-nitrophenyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (750 mg, 2.46 mmol, 1 eq) was dissolved in EtOH/H_2O = 2:1 (30 mL). NH_4Cl (1.32 g, 24.6 mmol, 10 eq) and iron powder (413 mg, 7.39 mmol, 3 eq) were added and the resulting suspension was heated to 90°C for 3h. After cooling down to rt H_2O (250 mL) was added and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure.
The crude aniline was dissolved EtOH (10 mL) and cooled to -30°C. $NaNO_2$ (180 mg, 2.59 mmol, 1.05 eq) dissolved in H_2O (10 mL) was added followed by H_2SO_4 (220 μL, 4.18 mmol, 1.7 eq). NaN_3 (170 mg, 2.59 mmol, 1.05 eq) was added and the reaction mixture was allowed to warm up to 0°C over a period of 13h. After warming up to rt aqueous $NaHCO_3$ (100 mL) was added and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude azide was purified by

flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1) to obtain *tert*-butyl 4-(2-azidophenyl)-3,6-dihydropyridine-1 (2*H*)-carboxylate (81.0 mg, 270 μmol, 0.1 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.31 (ddd, J_1 = 8.2 Hz, J_2 = 6.6 Hz, J_3 = 2.1 Hz, 1H), 7.19 - 7.06 (m, 3H), 5.70 (bs, 1H), 4.05 (dd, J_1 = 5.7 Hz, J_2 = 2.6 Hz, 1H), 3.61 (dd, J_1 = 5.6 Hz, J_2 = 5.6 Hz, 1H), 2.51 - 2.42 (m, 1H), 1.50 (s, 9H) ppm.
IR (film): 2966, 2927, 2856, 2125, 2090, 1697, 1487, 1456, 1417, 1365, 1292, 1238, 1165, 1112, 1056, 989, 974, 937, 862, 752, 418 cm^{-1}.
HRMS (ESI): calc. for $C_{16}H_{20}N_4O_2Na^+$: 323.1484, found: 323.1482

***tert*-Butyl 6-(2-azidophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (198)**

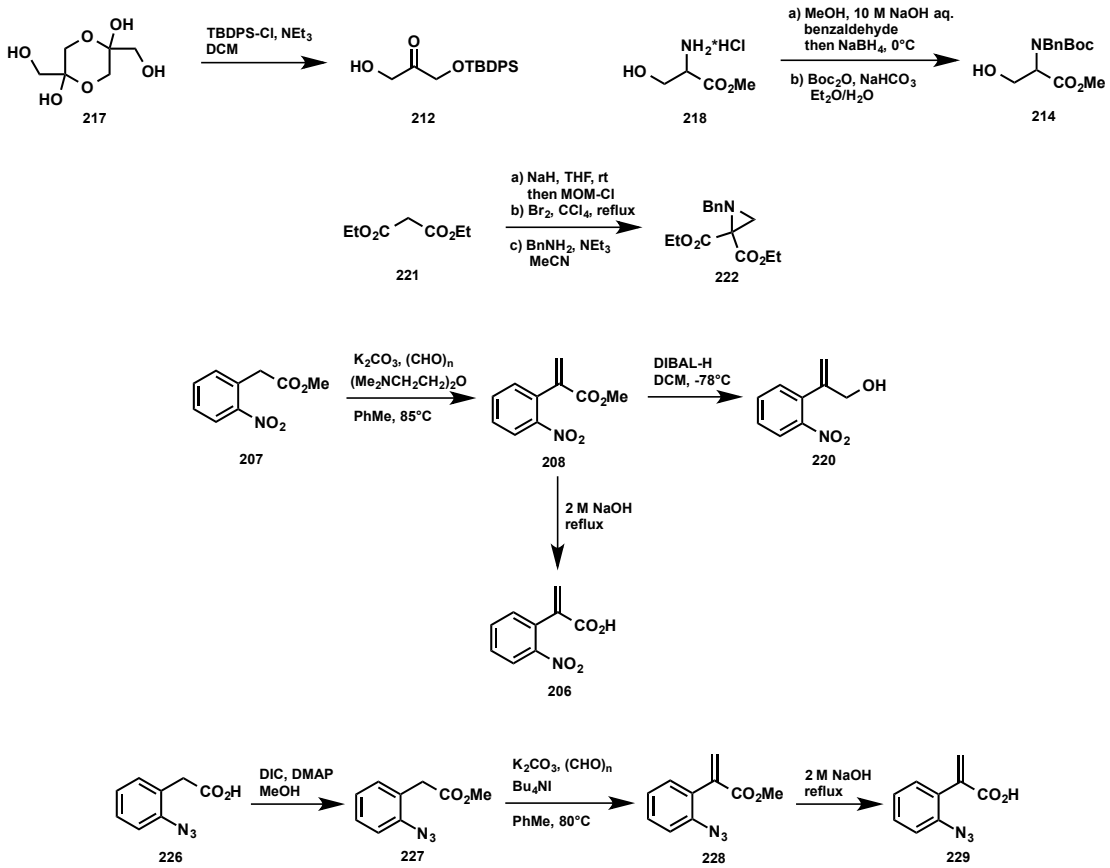


tert-Butyl 4-(2-azidophenyl)-3,6-dihydropyridine-1 (2*H*)-carboxylate (10.0 mg, 33.0 μmol, 1 eq) was dissolved in DCM (1 mL). $NaHCO_3$ (6.00 mg, 66.0 μmol, 2 eq) and *m*CPBA (9.00 mg, 50.0 μmol, 1.5 eq) were added and the resulting mixture was stirred at rt for 14h. Aqueous $NaHCO_3$ (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude epoxide was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain *tert*-butyl 6-(2-azidophenyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (7.00 mg, 22.1 μmol, 0.67 eq) as a colourless foam.

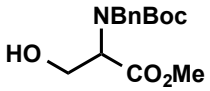
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 7.34 (ddd, J_1 = 8.1 Hz, J_2 = 7.4 Hz, J_3 = 1.6 Hz, 1H), 7.17 - 7.10 (m, 2H), 4.04 - 3.81 (m, 2H), 3.55 - 3.49 (m, 1H), 3.39 - 3.27 (m, 1H), 3.12 (bd, J = 20.5 Hz,

1H), 2.19 (ddd, J_1 = 14.7 Hz, J_2 = 8.2 Hz, J_3 = 5.1 Hz, 1H), 2.11 - 2.00 (m, 1H), 1.49 (s, 9H) ppm.

8.2.6 4th Synthetic approach



Methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)serinate (214)



Methyl serinate hydrochloride (1.00g, 6.43 mmol, 1 eq) was dissolved in MeOH (5 mL) and 10 M aqueous NaOH (640 μL, pH = 8) was added. Benzyaldehyde (721 μL, 750 mg, 7.07 mmol, 1.1 eq) was added and the resulting mixture was stirred at rt for 30min. The mixture was cooled to 0°C and $NaBH_4$ (122 mg, 3.21 mmol, 0.5 eq) was added portionwise. The mixture was allowed to warm up to rt and was stirred for 1h. Solids were removed by filtration and the solvent was concentrated under reduced pressure. Acetone (10 mL) was added followed by filtration and concentration under reduced pressure.

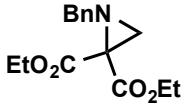
The residue was dissolved in Et_2O (5 mL) and aqueous $NaHCO_3$ (5 mL) was added. Di-*tert*-butyl dicarbonate (1.40 g, 6.43 mmol, 1 eq) was added to the suspension and the mixture was stirred vigourously for 18h. H_2O (50 mL) was added and the aqueous phase was extraceted by EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude carbamate was purified by flash column chropmatography (SiO_2, PE/EtOAc = 2:1) to obtain methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)serinate (438 mg, 1.41 mmol, 0.22eq) as a colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35 - 7.27 (m, 5H), 4.55 - 4.40 (m, 2H), 4.14 - 4.02 (m, 2H), 3.86 - 3.73 (m, 1H), 3.70 (s, 3H), 3.49 - 3.09 (m, 1H), 2.40 (bs, 1H), 1.45 (s, 9H) ppm.

IR (film): 3464, 2976, 2953, 2931, 1739, 1683, 1496, 1456, 1417, 1394, 1365, 1338, 1249, 1205, 1161, 1076, 1045, 900, 862, 775, 738, 700, 457 cm^{-1}.

HRMS (ESI): calc. for $C_{16}H_{23}NO_5Na^+$: 332.1474, found: 332.1474

Diethyl 1-benzylaziridine-2,2-dicarboxylate (222)



Diethyl malonate (11.9 mL, 12.5 g, 78.0 mmol) dissolved in absolute THF (25 mL) was added to a suspension of NaH (3.43 g, 85.8 mmol, 1.1 eq, 60% suspension in mineral oil) in absolute THF (125 mL) dropwise at rt. After complete addition the mixture was stirred at rt for 30min. Chloromethyl methylehter (6.52 mL, 6.91 g, 85.8 mmol, 1.1 eq) dissolved in absolute THF (50 mL) was transferred to the malonate *via* canula dropwise at rt. After complete addition the mixture was stirred at rt for 1h. The reaction mixture was poured onto H_2O (250 mL) and the aqueous phase was extracted with Et_2O (3x250 mL). The combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by distillation (116 °C, 0.1 mbar) to obtain diethyl 2-(methoxymethyl)malonate (7.23 g, 35.4 mmol, 0.45 eq) as a colourless liquid.
This was dissolved in CCl_4 (50 mL) and heated to reflux. Bromine (1.82 mL, 5.66 g, 35.4 mmol, 0.45 eq) dissolved in CCl_4 (10 mL) was added to the refluxing mixture andfurther refluxed for 15min. The mixture was allowed to cool down to rt. Aqueous $Na_2S_3O_3$ (50 mL) was added and the resulting suspension was poured onto aqueous K_2CO_3 (200 mL). The aqueous phase was extracted with DCM (3 x 200 mL). The combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 25:1 to 20:1 to 10:1) to obtain diethyl 2-bromo-2-(bromomethyl)malonate (5.74 g, 17.3 mmol, 0.22 eq) as a colourless fluid.
This was dissolved in absolute MeCN (60 mL). Benzylamine (2.06 mL, 2.02 g, 18.9 mmol, 0.24 eq) and NEt_3 (4.78 mL, 3.47 g, 34.3 mmol, 0.44 eq) were added and the resulting mixture was stirred at rt for 18h under formation of a colourless precipitate. The solvent was removed under reduced pressure. Brine (100 mL) was added and the aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aziridine was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain diethyl 1-benzylaziridine-2,2-dicarboxylate (3.59 g, 12.9 mmol, 0.17 eq) as a colourless liquid.

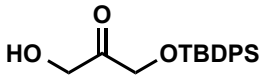
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 - 7.37 (m, 2H), 7.33 - 7.29 (m, 2H), 7.26 - 7.21 (m, 1H), 4.29 - 4.05 (m, 4H), 3.82 (s, 2H), 2.42 - 2.41 (m, 2H), 1.30 - 1.27 (m, 3H), 1.15 - 1.11 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5, 138.0, 128.4, 128.0, 127.3, 61.5, 57.0, 46.9, 39.4, 14.1 ppm.

IR (film): 2981, 2937, 2906, 1728, 1456, 1369, 1282, 1222, 1174, 1134, 1093, 1047, 1014, 918, 860, 732, 696, 599, 457 cm^{-1}.

HRMS (ESI): calc. for $C_{15}H_{20}NO_4^+$: 278.1392, found: 278.1391

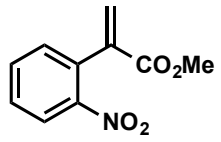
1-((*tert*-Butyldiphenylsilyl)oxy)-3-hydroxypropan-2-one (212)



1,3-Dihydroxyacetone dimer (2.00 g, 11.1 mmol, 1 eq) was dissolved in DCM (20 mL). NEt_3 (3.10 mL, 2.25 g, 22.2 mmol, 2 eq) and *tert*-butyldiphenylsilyl chloride (5.80 mL, 6.10 g, 22.2 mmol, 2 eq) were added and the mixture was stirred at rt for 12h. H_2O (200 mL) was added and the aqueous phase was extracted with DCM (2 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain 1-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxypropan-2-one (1.90 g, 5.78 mmol, 0.52 eq) as a colourless viscous fluid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.67 - 7.41 (m, 10H), 4.61 (d, *J* = 5.0 Hz, 2H), 4.34 (s, 2H), 3.05 (t, *J* = 5.0 Hz, 1H), 1.12 (s, 9H) ppm.

Methyl 2-(2-nitrophenyl)acrylate (208)

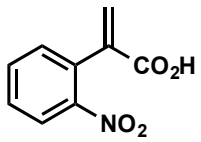


Methyl 2-(2-nitrophenyl)acetate (310 mg, 1.58 mmol, 1 eq) was dissolved in toluene (30 mL). Paraformaldeyhde (477 mg, 15.9 mmol, 10 eq), K_2CO_3 (439

mg, 3.18 mmol, 2 eq) and 2,2'-oxybis(*N*,*N*-dimethylethan-1-amine) (20.0 μL, 17.0 mg, 106 μmol, 0.1 eq) were sequentially added and the resulting mixture was heated to 85°C for 24h. Additional paraformaldeyhde (477 mg, 15.9 mmol, 10 eq) and K_2CO_3 (439 mg, 3.18 mmol, 2 eq) were added and the resulting mixture was stirred at 85°C for additional 24h. H_2O (250 mL) was added and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude acrylate was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1) to obtain methyl 2-(2-nitrophenyl)acrylate (310 mg, 1.50 mmol, 0.95 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 7.65 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.4 Hz, 1H), 7.53 (ddd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, J_3 = 1.4 Hz, 1H), 7.39 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 6.54 (s, 1H), 5.88 (s, 1H), 3.73 (s, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.4, 140.0, 133.9, 133.1, 132.4, 129.5, 127.8, 124.8, 52.4 ppm.
IR (film): 2953, 1720, 1608, 1571, 1521, 1436, 1346, 1321, 1263, 1253, 1205, 1182, 1105, 1070, 991, 956, 879, 854, 812, 788, 763, 713, 692, 642 cm^{-1}.
HRMS (ESI): calc. for $C_{10}H_9NO_4Na^+$: 230.0429, found: 230.0427

2-(2-Nitrophenyl)acrylic acid (206)

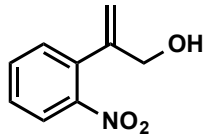


Methyl 2-(2-nitrophenyl)acrylate (310 mg, 1.50 mmol, 1 eq) was added to an aqueous 2 M NaOH (10 mL) and the resulting suspensions was heated to reflux for 11h. After cooling down to rt the aqueous phase was extracted with EtOAc (50 mL). The aqueous phase was acidified to pH = 4 with 1 M HCl and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated

under reduced pressure. The crude carboxylic acid was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain 2-(2-nitrophenyl)acrylic acid (263 mg, 1.36 μmol, 0.91 eq) as colourless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.8 Hz, 1H), 7.66 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.2 Hz, 1H), 7.54 (ddd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, J_3 1.1 Hz, 1H), 7.39 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 6.63 (s, 1H), 5.97 (s, 1H) ppm.
IR (film): 2947, 1734, 1697, 1653, 1606, 1558, 1521, 1508, 1456, 1417, 1346, 1317, 1261, 1213, 1105, 1070, 960, 854, 788, 769, 707, 686, 669, 636, 441, 430, 422, 412 cm^{-1}.

2-(2-Nitrophenyl)prop-2-en-1-ol (220)

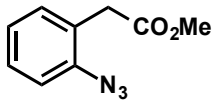


Methyl 2-(2-nitrophenyl)acrylate (100 mg, 483 μmol, 0.95 eq) was dissolved in absolute DCM (5 mL) and cooled to -78°C. DIBAL-H (1.45 mL, 1.45 μmol, 3 eq, 1 mol/L solution in hexane) was added and the mixture was stirred at -78°C for 1h. Aqueous Na-tartrate (50 mL) was added and the suspension was stirred for 1h at rt. The aqueous pahse was extracted with DCM (2 x 50 mL). The combined organic phases were washed with brine (25 mL), dired over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 2-(2-nitrophenyl)prop-2-en-1-ol (59.0 mg, 329 μmol, 0.68 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.94 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.59 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.4 Hz, 1H), 7.46 (ddd, J_1 = 8.0 Hz, J_2 = 7.5 Hz, J_3 = 1.6 Hz, 1H), 7.35 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 5.47 - 5.45 (m, 1H), 5.10 - 5.09 (m, 1H), 4.41 (s, 2H), 1.95 (bs, 1H) ppm.

IR (film): 3365, 3089, 2922, 2864, 1734, 1716, 1606, 1570, 1519, 1456, 1436, 1344, 1301, 1230, 1120, 1076, 1045, 1035, 983, 914, 854, 785, 750, 725, 702, 669, 543 cm^{-1}.

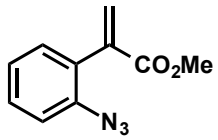
Methyl 2-(2-azidophenyl)acetate (227)



2-(2-Azidophenyl)acetic acid (1.00 g, 5.65 mmol, 1 eq) was dissolved in MeOH (20 mL). DMAP (760 mg, 6.22 mmol, 1.1 eq) and *N*,*N*-dicyclohexyl carbonyldiimide (9.72 mL, 784 mg, 6.21 mmol, 1.1 eq) were sequentially added and the resulting mixture was stirred at rt for 4h. The solvent was removed under reduced pressure and the crude methyl ester was purified by flash column chromatograhy (SiO_2, PE/EtOAc = 5:1) to obtain methyl 2-(2-azidophenyl)acetate (877 mg, 4.59 mmol, 0.81 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): 7.39 - 7.06 (m, 4H), 3.71 (s, 3H), 3.62 (s, 2H) ppm.

Methyl 2(2-azidophenyl)acrylate (228)

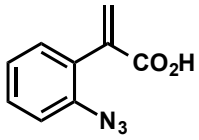


Methyl 2-(2-azidophenyl)acetate (677 mg, 3.49 mmol, 1 eq) was dissolved in absolute toluene (10 mL). Tetrabutylammonium iodide (52.0 mg, 140 μmol, 0.04 eq) K_2CO_3 (2.88 g, 20.9 mmol, 6 eq) and paraformaldeyhde (644 mg, 19.5 mmol, 5.6 eq) were added and the resulting suspension was heated to 80°C for 12h. H_2O (200 mL) was added and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude acrylate was purified by flash column

chromatography (SiO_2, PE/EtOAc = 20:1 to 10:1) to obtain methyl 2(2-azidophenyl)acrylate (187 mg, 920 μmol, 0.26 eq) as a colourless oil.

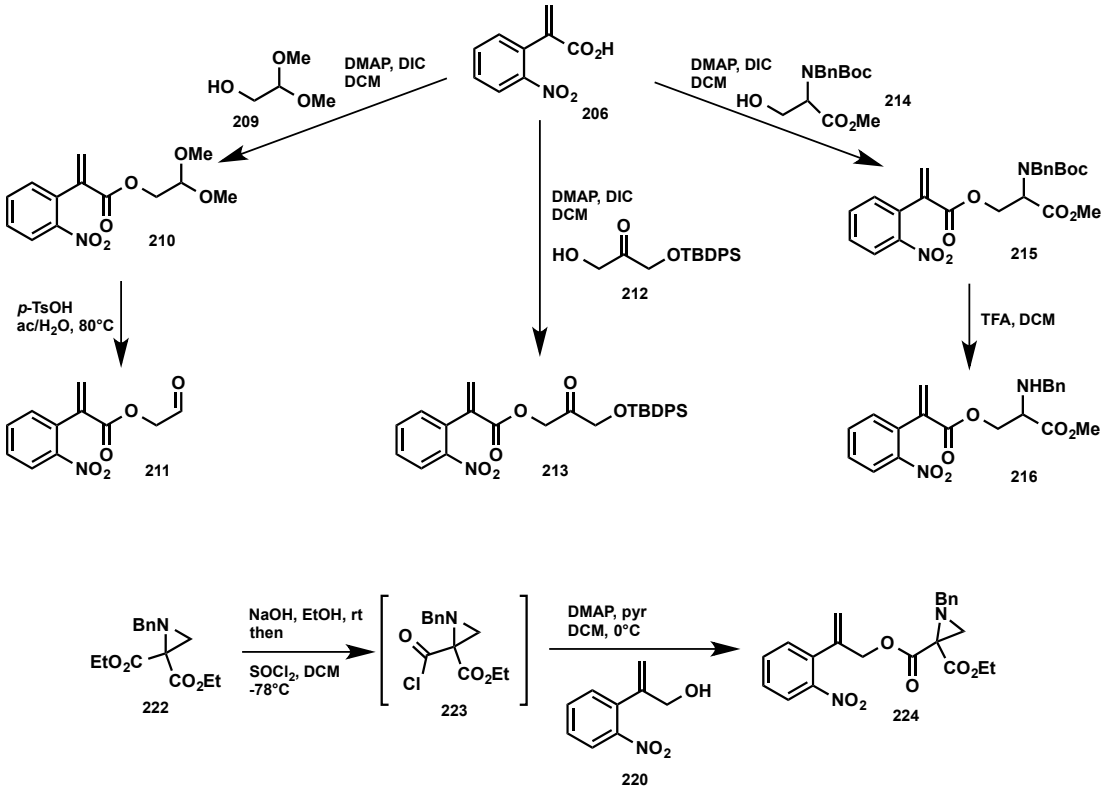
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (ddd, J_1 = 8.1 Hz, J_2 = 7.4 Hz, J_3 = 1.6 Hz, 1H), 7.24 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 7.19 - 7.13 (m, 2H), 6.42 (d, J = 1.4 Hz, 1H), 5.75 (d, J = 1.4 Hz, 1H), 3.80 (1, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.1, 139.4, 138.3, 130.9, 129.9, 129.5, 128.7, 124.9, 118.3, 52.5 ppm.

2-(2-Azidophenyl)acrylic acid (229)



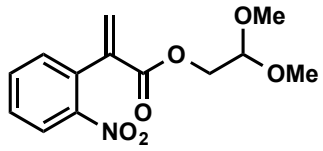
Methyl 2(2-azidophenyl)acrylate (187 mg, 920 μmol, 1 eq) was placed in a flask and aqueous 2 M NaOH (10 mL) was added. The mixture was heated to reflux for 6h. After cooling down to rt the aqueous phase was extracted with Et_2O (2 x 50 mL). The aqueous phase was acidified with 3 M HCl and then extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain 2-(2-azidophenyl)acrylic acid (151 mg, 800 μmol, 0.87 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.41 (ddd, J_1 = 7.9 Hz, J_2 = 7.4 Hz, J_3 = 1.6 Hz, 1H), 7.24 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.20 - 7.14 (m, 2H), 6.57 (d, J = 1.0 Hz, 1H), 5.88 (d, J = 1.0 Hz, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.2, 138.7, 138.5, 131.1, 130.8, 130.1, 128.9, 124.9, 118.3 ppm.


DMAP, DIC
DCM
209
206
214
210
212
215
p-TsOH
ac/H2O, 80°C
TFA, DCM
211
213
216

NaOH, EtOH, rt
then
SOCl2, DCM
-78°C
DMAP, pyr
DCM, 0°C
222
223
220
224

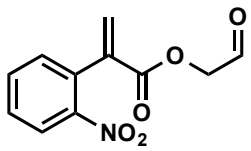
2,2-Dimethoxyethyl 2-(2-nitrophenyl)acrylate (210)



2-(2-Nitrophenyl)acrylic acid (50.0 mg, 260 μmol, 1 eq) was dissolved in DCM (3 mL). DMAP (35.0 mg, 280 μmol, 1.1 eq), 2,2-dimethoxyethan-1-ol (55.0 mg, 520 μmol, 2 eq) and *N*,*N*-dicyclohexyl carbonyldiimide (44.0μL, 36.0 mg, 280 μmol, 1.1 eq) were sequentially added. The resulting mixture was stirred at rt for 3h. The solvent was removed under reduced pressure and the crude ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 2,2-dimethoxyethyl 2-(2-nitrophenyl)acrylate (47.0 mg, 170 μmol, 0.65 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.65 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.4 Hz, 1H), 7.54 (ddd, J_1 = 8.2 Hz, J_2 = 7.5 Hz, J_3 = 1.7 Hz, 1H), 7.40 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 6.57 (d, J = 1.0 Hz, 1H), 5.90 (d, J = 0.7 Hz, 1H), 4.52 (t, J = 5.5 Hz, 1H), 4.16 (d, J = 5.4 Hz, 2H), 3.36 (s, 6H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.6, 139.9, 133.9, 133.1, 132.4, 129.6, 128.0, 124.9, 101.3, 64.0, 54.3 ppm.

2-Oxoethyl 2-(2-nitrophenyl)acrylate (211)

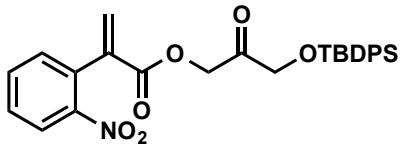


2,2-Dimethoxyethyl 2-(2-nitrophenyl)acrylate (47.0 mg, 170 μmol, 1 eq) was dissolved in acetone/H_2O = 5:1 (1 mL) and *para*-toluenesulfonic acid (18.2 mg, 170 μmol, 1 eq) was added. The mixture was stirred at 80°C for 24h. Aqueous $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography

(SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 2-oxoethyl 2-(2-nitrophenyl)acrylate (13.0 mg, 55.1 μmol, 0.33 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H), 8.16 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.68 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.4 Hz, 1H), 7.57 (ddd, J_1 = 8.2 Hz, J_2 = 7.5 Hz, J_3 = 1.7 Hz, 1H), 7.45 (dd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 6.66 (d, J = 0.7 Hz, 1H), 5.99 (d, J = 0.3 Hz, 1H), 4.69 (s, 2H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 195.8, 166.3, 143.8, 133.9, 132.5, 132.3, 129.8, 128.8, 124.8, 114.2, 69.2 ppm.

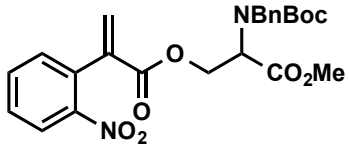
3-((*tert*-Butyldiphenylsilyl)oxy)-2-oxopropyl 2-(2-nitrophenyl)acrylate (212)



2-(2-Nitrophenyl)acrylic acid (932 mg, 4.83 mmol, 1 eq) was dissolved in DCM (50 mL). DMAP (59.0 mg, 483 μmol, 0.1 eq), 1-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxypropan-2-one (1.90 g, 5.78 mmol, 1.2 eq) and *N*,*N*-dicyclohexyl carbonyldiimide (822 μL, 670 mg, 5.31 mmol, 1.1 eq) were sequentially added. The resulting mixture was stirred at rt for 1h. The solvent was removed under reduced pressure and the curde ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 3-((*tert*-butyldiphenylsilyl)oxy)-2-oxopropyl 2-(2-nitrophenyl)acrylate (1.83 g, 3.63 mmol, 0.75 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.12 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.66 - 7.39 (m, 13H), 6.63 (d, J = 0.7 Hz, 1H), 5.94 (d, J = 0.7 Hz, 1H), 5.10 (s, 2H), 4.24 (s, 2H), 1.09 (s, 9H) ppm.

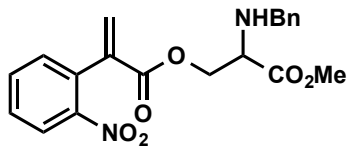
2-(Benzyl(*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 2-(2-nitrophenyl)-acrylate (215)



2-(2-Nitrophenyl)acrylic acid (100 mg, 518 μmol, 1 eq) was dissolved in DCM (5 mL) and cooled to 0°C. DMAP (13.0 mg, 104 μmol, 0.2 eq), methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)serinate (176 mg, 569 μmol, 1.1 eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimid hydrochloride (96.0 mg, 621 μmol, 1.2 eq) were sequentially added and the resulting mixture was allowed to warm up to rt. After stirring at rt for 1.5h H_2O (25 mL) was added. The aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 2-(benzyl(*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 2-(2-nitrophenyl)-acrylate (97.0 mg, 200 μmol, 0.39 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 - 8.12 (m, 1H), 7.69 - 7.62 (m, 1H), 7.58 - 7.51 (m, 1H), 7.40 - 7.34 (m, 1H), 7.32 - 7.19 (m, 5H), 6.45 - 6.44 (m, 1H), 5.87 - 5.83 (m, 1H), 4.75 - 4.44 (m, 4H), 4.07 - 3.84 (m, 2H), 3.65 - 3.61 (m, 3H), 1.45 - 1.36 (m, 9H) ppm.

2-(Benzylamino)-3-methoxy-3-oxopropyl 2-(2-nitrophenyl)acrylate (216)

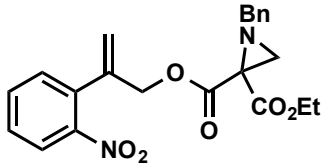


2-(benzyl(*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 2-(2-nitrophenyl)acrylate (10.0 mg, 21.0 μmol, 1 eq) was dissolved in DCM (1 mL). Trifluoroacetic acid (300 μL) were added and the resulting mixture was stirred at rt for 15min. H_2O (25 mL) was added and the aqueous phase was extracted with DCM (25 mL). The aqueous phase was basified with Na_2CO_3

and extracted with DCM (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, Filtrated and concentrated under reduced pressure to obtain 2-(benzylamino)-3-methoxy-3-oxopropyl 2-(2-nitrophenyl)acrylate (8.00 mg, 21.0 μmol, 1 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.64 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 1.4 Hz, 1H), 7.55 - 7.51 (m, 1H), 7.39 - 7.35 (m, 6H), 6.58 (bs, 1H), 6.56 (s, 1H), 5.91 (s, 1H), 4.72 - 4.63 (m, 2H), 4.23 (d, J = 12.6 Hz, 1H), 4.18 - 4.13 (m, 2H), 3.80 (s, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.7, 164.2, 147.5, 138.6, 134.2, 132.5, 132.5, 130.3, 130.2, 130.1, 130.0, 129.8, 129.5, 129.3, 124.8, 61.7, 57.7, 54.1, 50.8 ppm.

2-Ethyl 2-(2-(2-nitrophenyl)allyl) 1-benzylaziridine-2,2-dicarboxylate (224)

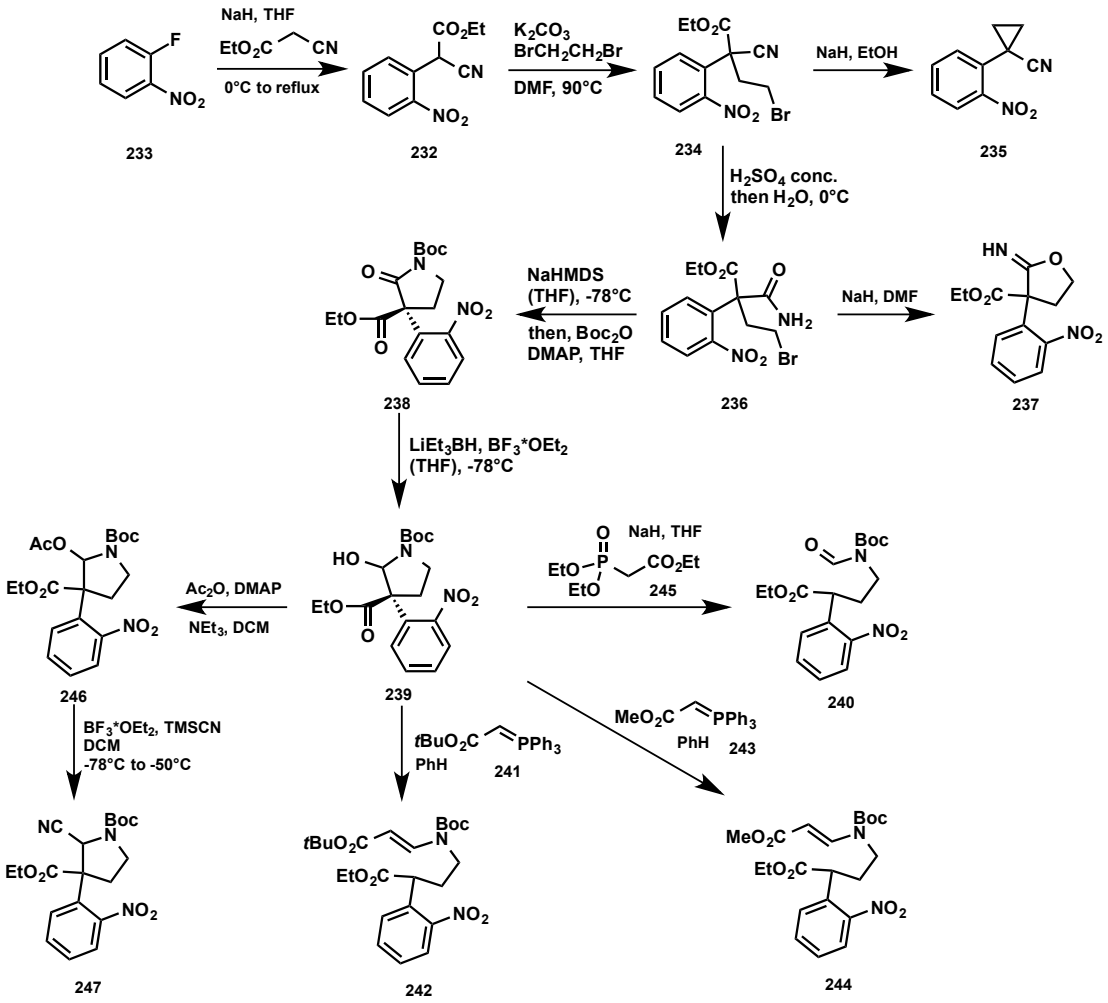


Diethyl 1-benzylaziridine-2,2-dicarboxylate (300 mg, 1.08 mmol, 1eq) was dissolved in EtOH (10 mL). NaOH (45.0 mg, 1.14 mmol, 1.05 eq) was added and the resulting mixture was stirred at rt for 44h. The solvent was removed under reduced pressure. The residue was dissolved in absolute DCM (3 mL) and cooled to -78°C. Thionyl chloride (118 μL, 193 mg, 1.62 mmol, 1.5 eq) was added and the resulting mixture was allowed to warm up to -30°C and then recooled to -78°C.
2-(2-Nitrophenyl)prop-2-en-1-ol (194 mg, 1.08 mmol, 1 eq), DMAP (26.0 mg, 216 μmol, 0.2 eq) and pyridine (174 μL, 171 mg, 2.16 mmol, 2 eq) were dissolved in absolute DCM (2 mL) and cooled to 0°C. The acid chloride was transferred *via* canula to the alcohol solution dropwise. The resulting mixture was allowed to warm up to rt and stirred for 90min at this temperature. Aqueous $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced

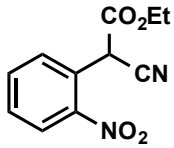
pressure. The crude ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 1:1) to obtain 2-ethyl 2-(2-(2-nitrophenyl)allyl) 1-benzylaziridine-2,2-dicarboxylate (341 mg, 831 μmol, 0.77 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 - 7.95 (m, 1H), 7.62 - 7.55 (m, 1H), 7.53 - 7.44 (m, 1H), 7.41 - 7.08 (m, 3.6 H), 5.54 - 5.49 (m, 1H), 5.22 - 5.15 (m, 1H), 5.11 - 4.90 (m, 0.3 H), 4.81 - 4.69 (m, 1H), 4.65 - 4.54 (m, 1H), 4.47 - 3.27 (m, 2.7 H), 2.50 - 2.35 (m, 0.5 H), 1.36 - 1.05 (m, 2.4 H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.2, 166.9, 148.2, 141.9, 141.6, 138.0, 137.7, 135.8, 134.6, 134.5, 133.3, 133.2, 133.1, 132.3, 132.3, 132.1, 130.8, 129.1, 129.1, 129.1, 128.9, 128.9, 128.8. 128.7, 128.6, 128.4, 128.4, 128.2, 128.0, 127.9, 127.9, 127.7, 127.5, 127.3, 127.2, 127.2, 127.1, 124.5, 124.4, 118.8, 118.4, 64.3, 64.0, 62.5, 62.4, 61.9, 61.6, 58.9, 57.0, 56.9, 56.8, 55.6, 55.4, 54.1, 53.9, 53.4, 52.7, 52.6, 50.1, 48.9, 46.8, 46.6, 46.5, 41.2, 41.1, 39.7, 39.5, 33.9, 33.8, 15.3, 14.5, 14.2, 14.1, 14.0, 13.9 ppm.
IR (film): 2983, 2937, 2860, 1734, 1523, 1456, 1346, 1207, 1006, 962, 918, 856, 786, 754, 702, 665 cm^{-1}.

8.2.7 4th Synthetic approach, modified retrosynthesis



Ethyl 2-cyano-2-(2-nitrophenyl)acetate (232)

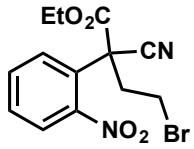


Sodium hydride (33.4 g, 834 mmol, 2.2 eq, 60% dispersion in mineral oil) was put in a 4 L two necked flask and 500 mL absolute THF were added. The mixture was cooled to 0°C. A dropping funnel was connected to the flask and loaded with ethyl cyanoacetate (94.3 g, 89.0 mL, 834 mmol, 2.2 eq) dissolved in 300 mL absolute THF. The ethyl cyano acetate solution was added dropwise at 0°C. After complete addition the mixture was allowed to warm up to rt and stirred until no more gas evolution was observed. 2-Fluoro nitrobenzene (53.5 g, 40.0 mL, 379 mmol, 1 eq) dissolved in 300 mL absolute THF was put to the dropping funnel and added dropwise to the reaction mixture at rt. After complete addition 1 L absolute THF was added and the mixture was heated to reflux for 7h. During the reaction an intensive red colour appeared. After cooling to room temperature the mixture was concentrated under reduced pressure and poured onto water (3 L). The aqueous phase was extracted with Et_2O (3x500 mL). The ether phase was abolished. The aqueous phase was acidified to pH = 6 with 1 M HCl and extracted with DCM (3x1 L). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Ethyl 2-cyano-2-(2-nitrophenyl)acetate (65.7 g, 280 mmol, 0.74 eq) was obtained as a yellow viscous fluid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.23 - 8.21 (m, 1H), 7.79 - 7.74 (m, 2H), 7.66 - 7.62 (m, 1H), 5.66 (s, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.6, 147.5, 134.7, 131.7, 130.9, 126.3, 125.4, 114.6, 64.0, 41.5, 13.9 ppm.

Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (234)



Ethyl 2-cyano-2-(2-nitrophenyl)acetate (65.0 g, 278 mmol, 1 eq) dissolved in 300 mL absolute DMF was put in a 1 L flask. K_2CO_3 (46.0 g, 333 mmol, 1.2 eq) and dibromo ethane (120 mL, 261 g, 1.39 mol, 5 eq) were sequentially added. The solution was heated to 90 °C for 5h. After cooling to room temperature the mixture was poured onto water (3L). The aqueous phase was extracted with Et_2O (3x1 L). The combined organic phases were dried over magnesium sulfate, filtrated und concentrated under reduced pressure. MeOH was added until crystallization of the product was observed. After storage in the frigde overnight the precipitate was collected and washed with MeOH (200 mL). Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (67.3 g, 197 mmol, 0.71 eq) was obtained as colourless crystals.

MP: 85 °C

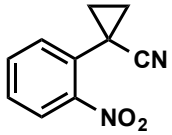
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.17 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.85 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.80 - 7.76 (m, 1H), 7.65 (ddd, J_1 = 8.1 Hz, J_2 = 7.5 Hz, J_3 = 1.5 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 3.56 (ddd, J_1 = 11.0 Hz, J_2 = 10.2 Hz, J_3 = 5.4 Hz, 1H), 3.34 (ddd, J_1 = 11.0 Hz, J_2 = 10.2 Hz, J_3 = 5.2 Hz, 1H), 3.16 (ddd, J_1 = 14.2 Hz, J_2 = 11.1 Hz, J_3 = 5.5 Hz, 1H), 2.97 (ddd, J_1 = 14.2 Hz, J_2 = 11.1 Hz, J_3 = 5.3 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.1, 147.8, 134.3, 130.7, 130.4, 128.4, 126.9, 116.8, 64.2, 52.8, 39.1, 25.7, 13.9 ppm.

IR (neat): 3001, 2987, 2941, 2364, 1735, 1604, 1577, 1527, 1479, 1442, 1396, 1354, 1300, 1278, 1251, 1226, 1176, 1153, 1112, 1085, 1070, 1051, 1029, 1008, 931, 850, 808, 788, 775, 759, 738, 705, 694, 669, 644, 590, 561, 536, 474, 437, 416 cm^{-1}.

CHN: Anal. calc. for $C_{13}H_{13}BrN_2O_4$: C, 45.77; H, 3.84; N, 8.21; found: C, 45.91; H, 3.88; N, 8.09.

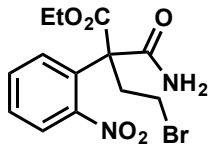
1-(2-Nitrophenyl)cyclopropane-1-caronitrile (235)



Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (50.0 mg, 147 μmol, 1 eq) was dissolved in EtOH (1 mL). NaH (6.00 mg, 147 μmol, 1 eq, 60% dispersion in mineral oil) was added and the resulting mixture was stirred at rt for 10min. Aqueous 1 M HCl (25 mL) was added and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-(2-nitrophenyl)cyclopropane-1-caronitrile (17.0 mg, 90.3 μmol, 0.61 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.65 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 1.4 Hz, 1H), 7.60 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 7.55 (ddd, J_1 = 8.1 Hz, J_2 = 7.1 Hz, J_3 = 1.8 Hz, 1H), 1.80 - 1.78 (m, 2H), 1.30 - 1.27 (m, 2H) ppm.

Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (236)



Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (67.0 g, 196 mmol, 1 eq) was milled by a mortar and dissolved in concentrated sulfuric acid (2 L). After complete dissolution the mixture was transferred to a dropping funnel. A 5L Erlenmeyer flask was packed with ice and water (2 L) and positioned in an ice bath. The reaction mixture was added dropwise under stirring in that way that the inner temperature does not rise about 10 °C. After complete addition the precipitate was collected and washed with water (1L). The precipitate was dissolved in DCM (1 L), transferred to a seperation funnel and washed with saturated NaCl solution (1 L). The organic phase was dried over $MgSO_4$,

filtrated and concentrated under reduced pressure. Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (67.6 g, 188 mmol, 0.96 eq) was obtained as a slightly brown amorphous solid.

MP: 115 °C

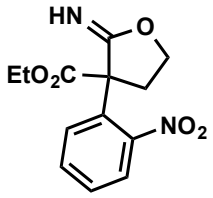
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, J_1 = 8.5 Hz, J_2 = 1.3 Hz, 1H), 8.02 (bs, 1H), 7.73 - 7.69 (m, 1H), 7.55 - 7.50 (m, 2H), 5.81 (bs, 1H), 4.12 (qd, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1H), 4.08 (qd, J_1 = 10.8, J_2 = 7.1 Hz, 1H), 3.43 - 3.30 (m, 2H), 3.02 (ddd, J_1 = 14.0 Hz, J_2 = 11.5 Hz, J_3 = 5.1 Hz, 1H), 2.93 (ddd, J_1 = 14.1 Hz, J_2 = 11.7 Hz, J_3 = 5.9 Hz, 1H), 1.10 (t, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8, 170.2, 148.5, 133.7, 132.6, 129.5, 129.0, 126.1, 62.8, 61.8, 39.8, 26.7, 13.7 ppm.

IR (neat): 3390, 3263, 3170, 2987, 1737, 1714, 1681, 1577, 1523, 1477, 1460, 1442, 1354, 1340, 1301, 1251, 1213, 1178, 1153, 1112, 1082, 1062, 1031, 1012, 977, 960, 914, 854, 808, 788, 738, 705, 690, 669, 655, 623, 590, 536, 516, 472, 433, 416 cm^{-1}.

HRMS (ESI): calc. for $C_{13}H_{16}N_2O_5Br^+$: 359.0243, found: 359.0248

Ethyl 2-imino-3-(2-nitrophenyl)tetrahydrofuran-3-carboxylate (237)

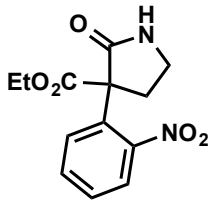


Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (25.0 mg, 69.6 μmol, 1 eq) was dissolved in absolute DMF (1 mL). NaH (3.00 mg, 76.6 μmol, 1.1 eq, 60% dispersion in mineral oil) was added and the reaction mixture was stirred for 10min at rt. Aqueous NH_4Cl (10 mL) and H_2O (50 mL) were added and the aqueous phase was extracted with EtOAc (3x25 mL). The combiend organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude imidoester was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain ethyl 2-

imino-3-(2-nitrophenyl)tetrahydrofuran-3-carboxylate (8.00 mg, 31.2 μmol, 0.45 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.14 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.65 (ddd, J_1 = 7.8 Hz, J_2 = 7.6 Hz, J_3 = 1.1 Hz, 1H), 7.55 - 7.51 (m, 3H), 4.49 (ddd, J_1 = 8.2 Hz, J_2 = 8.2 Hz, J_3 = 3.1 Hz, 1H), 4.27 - 4.10 (m, 3H), 3.64 (ddd, J_1 = 13.7 Hz, J_2 = 8.9 Hz, J_3 = 8.9 Hz, 1H), 2.51 - 2.45 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.8, 162.3, 148.1, 134.1, 134.0, 130.4, 129.3, 126.4, 67.9, 63.0, 37.7, 20.6, 13.9 ppm.

Ethyl 3-(2-nitrophenyl)-2-oxopyrroldine-3-carboxylate (238a)



Ethyl 4-bromo-2-carbamoyl-2-(2-nitrophenyl)butanoate (67.0 g, 187 mmol, 1 eq) was dissolved in absolute THF (9 L) and cooled to -78°C. Sodium bis(trimethylsilyl)amide (94.2 mL, 188 mmol, 1.01 eq, 2 mol/L solution in THF) dissolved in absolute THF (1 L) was put to a dropping funnel and added dropwise to the mixture at -78°C. After complete addition the mixture was poured onto an NH_4Cl solution (10 L) and afterwards allowed to warm up to rt. The organic phase was seperated and the aqueous phase extracted with Et_2O (2x2 L). The combined organic phases were washed with saturated NaCl solution (5 L), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain the lactame as a colourless solid. The material was used for the next step without further purifications.

MP: 116 °C

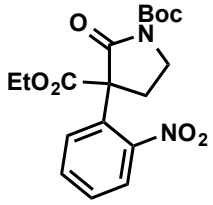
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.67 - 7.62 (m, 2H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.51 - 7.47 (m, 1H), 4.21 (qd, J_1 = 10.6 Hz, J_2 = 7.2 Hz, 1H), 4.15 (qd, J_1 = 10.8 Hz, J_2 = 7.1 Hz, 1H), 3.64 - 3.51 (m, 2H), 3.35 - 3.30 (m, 1H), 2.40 - 2.33 (m, 1H), 1.20 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.6, 169.2, 148.5, 134.4, 134.0, 130.1, 128.8, 126.0, 62.6, 61.5, 39.9, 35.4, 13.9 ppm.

IR (neat): 3196, 3111, 3072, 2989, 2885, 2360, 1734, 1672, 1610, 1577, 1521, 1458, 1350, 1317, 1284, 1226, 1089, 1051, 1014, 954, 850, 769, 752, 707, 661, 653, 603, 569, 536, 507, 416 cm^{-1}.

HRMS (ESI): calc. for $C_{13}H_{14}N_2O_5Na^+$: 301.0800, found: 301.0801

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (238)



The crude lactame was dissolved in absolute THF (1 L). 4-Dimethylaminopyridine (1.14 g, 9.33 mmol, 0.05 eq) and di-*tert*-butyl dicarbonate (48.9 g, 224 mmol, 1.2 eq) were sequentially added and the resulting mixture was stirred at rt for 24 h. The solvent was concentrated under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (53.0 g, 140 mmol, 0.75 eq) as a colourless solid.

MP: 102 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.63 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.5 Hz, 1H), 7.50 (ddd, J_1 = 8.1 Hz, J_2 = 7.6 Hz, J_3 = 1.3 Hz, 1H), 7.41 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 4.17 (qd, J_1 = 7.2 Hz, J_2 = 1.4 Hz, 2H), 4.00 (ddd, J_1 = 10.6 Hz, J_2 = 8.5 Hz, J_3 = 5.5 Hz,

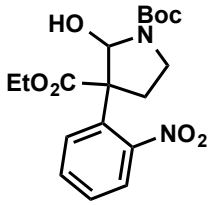
1H), 3.64 (ddd, J_1 = 10.6 Hz, J_2 = 8.4 Hz, J_3 = 6.3 Hz, 1H), 3.39 (ddd, J_1 = 13.7 Hz, J_2 = 8.5 Hz, J_3 = 6.1 Hz, 1H), 2.27 (ddd, J_1 = 13.6 Hz, J_2 = 8.1 Hz, J_3 = 5.4 Hz, 1H), 1.57 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 168.2, 149.8, 148.4, 134.0, 133.9, 130.0, 129.0, 126.2, 84.1, 63.8, 62.9, 44.0, 31.6, 28.1, 13.9 ppm.

IR (neat): 2981, 2081, 1783, 1726, 1608, 1575, 1529, 1479, 1451, 1365, 1293, 1258, 1229, 1147, 1101, 1069, 1009, 922, 850, 780, 738, 704, 674 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{22}N_2O_7Na^+$: 401.1325, found: 401.1322

1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (239)



1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-oxopyrrolidine-1,3-dicarboxylate (49.6 g, 131 mmol, 1 eq) was dissolved in absolute THF (1.5 L) and cooled to -78 °C. Boron trifluoride diethyl etherate (3.50 mL, 13.1 mmol, 0.1 eq, 48% solution) and lithium triethylborohydride (80.8 mL, 137 mmol, 1.05 eq, 1.7 mol/L solution in THF) were rapidly added. The resulting mixture was stirred at -78°C for 30min, then poured onto saturated NH_4Cl solution (1 L) and allowed to warm up to rt. The aqueous phase was extracted with Et_2O (2x500 mL) and the combined organic phases were washed with saturated NaCl solution (1 L), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting colourless solid was collected and washed with EtOAc to obtain 1-(*tert*-butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (31.4 g, 82.5 mmol, 0.63 eq). The residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain additional 1-(*tert*-butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (in total 44.4 g, 117 mmol, 0.89 eq).

MP: 148 °C

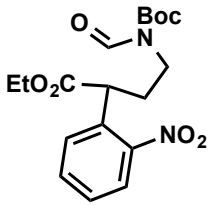
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 - 7.89 (m, 1H), 7.60 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 1H), 7.50 - 7.30 (m, 2H), 5.85 - 5.66 (m, 1H), 4.35 - 3.71 (m, 4H), 3.28 - 3.09 (m, 2H), 2.40 - 2.15 (m, 1H), 1.48 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.6, 154.8, 153.2, 149.0, 148.7, 134.4, 134.0, 133.5, 133.2, 128.8, 128.6, 128.4, 127.9, 126.1, 125.8, 86.3, 86.1, 81.5, 81.3, 62.1, 61.9, 60.6, 60.0, 44.3, 43.7, 31.7, 31.3, 28.5, 14.0 ppm.

IR (neat): 3435 (bs), 2980, 2362, 1679, 1530, 1479, 1390, 1363, 1298, 1246, 1168, 1134, 1068, 893, 854, 781, 742, 668 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{24}N_2O_7Na^+$: 403.1481, found: 403.1477

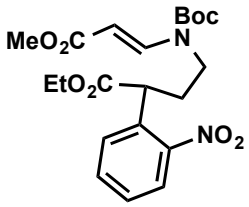
Ethyl 4-(*N*-(*tert*-butoxycarbonyl)formamido)-2-(2-nitrophenyl)butanoate (240)



Ethyl 2-(diethoxyphosphoryl)acetate (12.5 μL, 14.0 mg, 63.0 μmol, 1.2 eq) was dissolved in absolute THF (100 μL). NaH (2.50 mg, 63.0 μmol, 1.2 eq, 60% dispoersion in mineral oil) was added and the resulting mixture was stirred at rt for 10min. 1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (20.0 mg, 53.0 μmol, 1 eq) dissolved in absolute THF (500 μL) was added and the reaction mixture was stirred at rt for 1h. Aqueous NH_4Cl (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were wasehd with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude formamide was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1) to obtain ethyl 4-(*N*-(*tert*-butoxycarbonyl)formamido)-2-(2-nitrophenyl)butanoate (20.0 mg, 52.0 μmol, 1 eq) as a colourless foam.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 9.17 (s, 1H), 7.91 (dd, J_1 = 8.1 Hz, J_2 = 1.3 Hz, 1H), 7.63 - 7.38 (m, 3H), 4.22 - 4.06 (m, 3H), 3.72 - 4.06 (m, 3H), 3.72 - 3.64 (m, 2H), 2.49 - 2.31 (m, 1H), 2.16 - 1.99 (m, 1H), 1.53 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H) ppm.

Ethyl (*E*)-4-((*tert*-butoxycarbonyl)(3-methoxy-3-oxoprop-1-en-1-yl)-amino)-2-(2-nitrophenyl)butanoate (244)



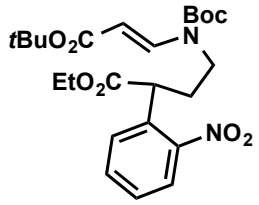
1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (20.0 mg, 53.0 μmol, 1 eq) was dissolved in benzene (2 mL). Methyl 2-(triphenylphosphanylidene)acetate (35.0 mg, 106 μmol, 2 eq) were added and the reaction mixture was stirred at reflux for 3d. After cooling down to rt the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1) to obtain ethyl (*E*)-4-((*tert*-butoxycarbonyl)(3-methoxy-3-oxoprop-1-en-1-yl)amino)-2-(2-nitrophenyl)butanoate (16.0 mg, 37.0 μmol, 0.7 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.18 (bd, *J* = 14.3 Hz, 1H), 7.93 - 7.89 (m, 1H), 7.61 - 7.57 (m, 1H), 7.47 - 7.40 (m, 2H), 5.19 (d, *J* = 14.0 Hz, 1H), 4.23 - 4.10 (m, 4H), 3.72 (s, 3H), 3.65 - 3.60 (m, 2H), 2.46 - 2.36 (m, 1H), 2.10 - 1.54 (m, 1H), 1.51 (s, 9H), 1.20 - 1.26 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9, 168.2, 167.3, 149.2, 142.6, 133.4, 133.2, 129.4, 128.4, 128.2, 125.1, 96.9, 83.4, 61.6, 51.3, 43.8, 28.4, 28.0, 14.0 ppm.

HRMS (ESI): calc. for $C_{21}H_{28}N_2O_8Na^+$: 459.1743, found: 459.1740

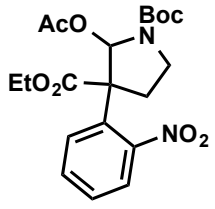
Ethyl (*E*)-4-((3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)(*tert*-butoxycarbonyl)-amino)-2-(2-nitrophenyl)butanoate (242)



1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (1.00 g, 2.63 mmol, 1 eq) was dissolved in absolute toluene (25 mL). *tert*-Butyl 2-(triphenylphosphanylidene)acetate (3.00 g, 7.89 mmol, 3 eq) was added and the reaction mixture was stirred at reflux for 22h. After cooling down to rt the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain ethyl (*E*)-4-((3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)(*tert*-butoxycarbonyl)-amino)-2-(2-nitrophenyl)butanoate (716 mg, 1.50 mmol, 0.57 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.07 (d, J = 14.3 Hz, 1H), 7.92 (dd, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H), 7.60 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.2 Hz, 1H), 7.50 - 7.39 (m, 2H), 5.04 (d, J = 14.3 Hz, 1H), 4.25 - 4.05 (m, 4H), 3.59 (bdd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H), 2.50 - 2.32 (m, 1H), 2.15 - 1.97 (m, 1H), 1.49 (s, 9H), 1.47 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H) ppm.

1-(*tert*-Butyl) 3-ethyl 2-acetoxy-3-(2-nitrophenyl)pyrrolidine-1,3-di-carboxylate (246)

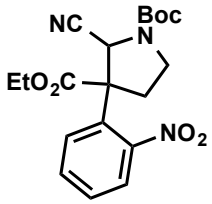


1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (50.0 mg, 132 μmol, 1 eq) was dissolved in absolute DCM (2 mL). DMAP (1.62 mg, 13.2 μmol, 0.1 eq), NEt_3 (55.0 μL, 40.0 mg, 396 μmol, 3 eq) and Ac_2O (25.0 μL, 27.0 mg, 264 μmol, 2 eq) were sequentially added. The

reaction mixture was stirred at rt for 11h. Aqueous $NaHCO_3$ (25 mL) was added and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude acetate was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-acetoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (50.0 mg, 118 μmol, 0.89 eq) as a colourless foam.

^{1}H-NMR (200 MHz, C_6D_6): δ = 7.66 - 7.22 (m, 3H), 6.91 - 6.69 (m, 1H), 6.64 - 6.55 (m, 1H), 4.35 - 3.24 (m, 4H), 2.99 - 2.39 (m, 1H), 2.19 - 2.02 (m, 1H), 1.74 (bs, 3H), 1.44 - 1.35 (m, 9H), 0.94 - 0.86 (m, 3H) ppm.

1-(*tert*-Butyl) 3-ethyl 2-cyano-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (247)



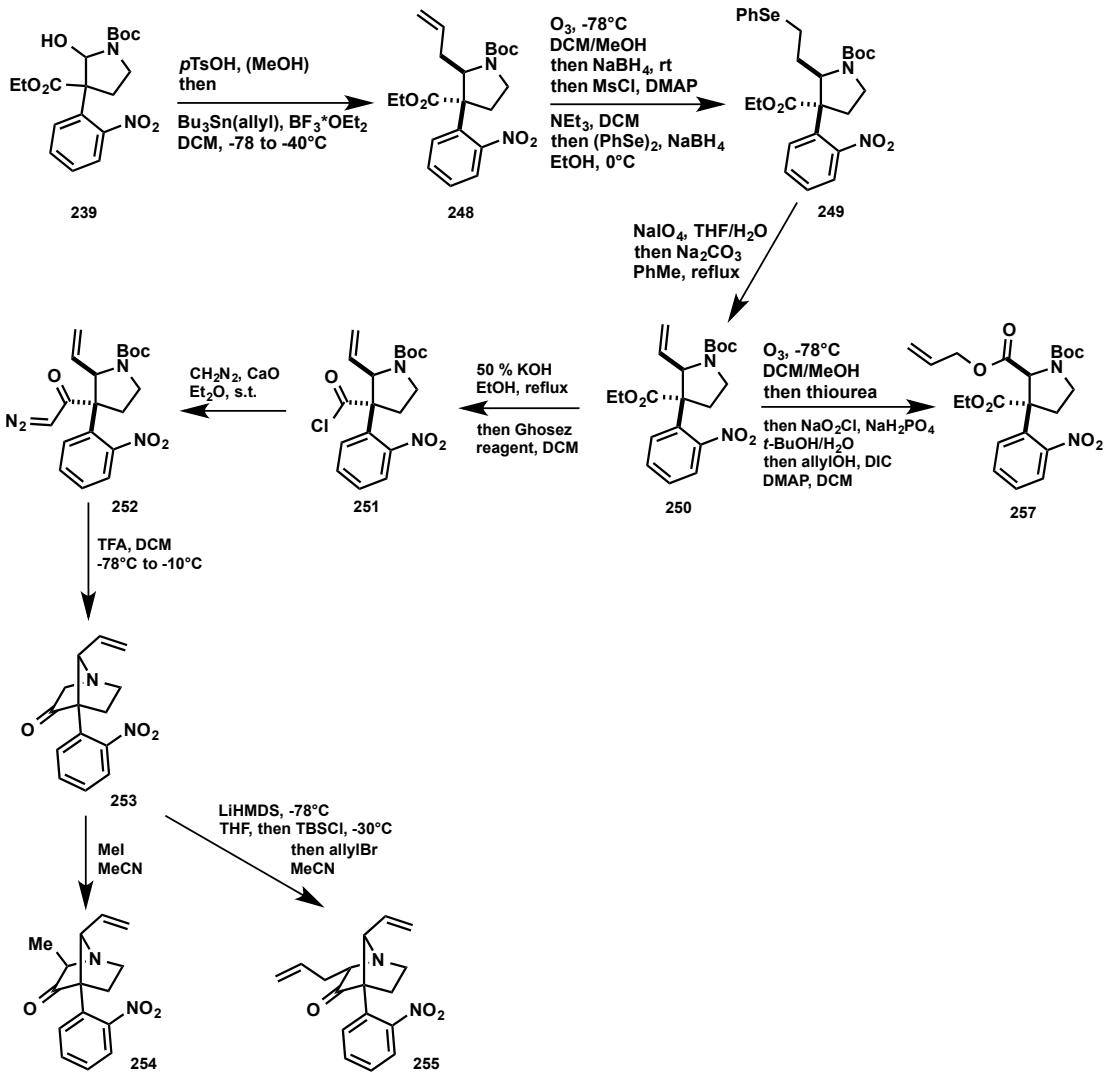
1-(*tert*-Butyl) 3-ethyl 2-acetoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (50.0 mg, 118 μmol, 1 eq) was dissolved in absolute DCM (2 mL) and cooled to -78°C. Trimethylsilyl cyanide (30.0 μL, 24.0 mg, 237 μmol, 2 eq) followed by boron trifluoride diethyl etherate (15.0 μL, 130 μmol, 1.1 eq, 48% solution). The reaction mixture was allowed to warm up to -50°C over a period of 2.5h. Aqueous $NaHCO_3$ (25 mL) was added at -50°C and the mixture was allowed to warm up to rt. The aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude nitrile was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-cyano-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (35.0 mg, 90.0 μmol, 0.76 eq) as a mixture of diastereoisomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 - 8.05 (m, 1H), 7.77 - 7.47 (m, 3H), 6.47 - 5.54 (m, 1H), 4.25 - 4.14 (m, 2H), 3.77 - 3.41 (m, 2H), 3.38 - 2.88 (m, 1H), 2.58 - 2.36 (m, 1H), 1.61 - 1.50 (m, 9H), 1.20 - 1.67 (m, 3H) ppm.

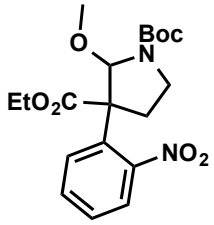
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.9, 171.8, 170.0, 169.1, 153.3, 134.5, 134.0, 134.0, 131.1, 130.2, 130.2, 130.0, 128.8, 126.2, 126.0, 116.5, 82.2, 62.9, 62.9, 62.7, 61.1, 59.5, 54.6, 54.5, 44.2, 43.7, 39.7, 35.5, 34.5, 33.9, 28.4, 28.4, 14.3, 14.0, 13.9 ppm.

IR (film): 2981, 2933, 2902, 1734, 1529, 1475, 1456, 1381, 1367, 1350, 1288, 1238, 1192, 1166, 1153, 1132, 1107, 1020, 987, 927, 898, 852, 785, 731, 713, 690, 634, 534 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{23}N_3O_6Na^+$: 412.1485, found: 412.1488


HO
Boc
N
EtO2C
NO2
239
pTsOH, (MeOH)
then
Bu3Sn(allyl), BF3*OEt2
DCM, -78 to -40°C
248
O3, -78°C
DCM/MeOH
then NaBH4, rt
then MsCl, DMAP
NEt3, DCM
then (PhSe)2, NaBH4
EtOH, 0°C
PhSe
249
NaIO4, THF/H2O
then Na2CO3
PhMe, reflux
250
O3, -78°C
DCM/MeOH
then thiourea
then NaO2Cl, NaH2PO4
t-BuOH/H2O
then allylOH, DIC
DMAP, DCM
257
50 % KOH
EtOH, reflux
then Ghosez
reagent, DCM
251
Cl
CH2N2, CaO
Et2O, s.t.
252
N2
TFA, DCM
-78°C to -10°C
253
MeI
MeCN
LiHMDS, -78°C
THF, then TBSCl, -30°C
then allylBr
MeCN
254
Me
255

1-(*tert*-Butyl) 3-ethyl 2-methoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (239b)



1-(*tert*-Butyl) 3-ethyl 2-hydroxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (44.0 g, 116 mmol, 1 eq) was dissolved in MeOH (500 mL) and *p*-toluenesulfonic acid monohydrate (1.10 g, 5.80 mmol, 0.05 eq) was added. The mixture was stirred at rt for 14h, then poured onto saturated $NaHCO_3$ solution (500 mL) and extracted with Et_2O (3x500 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-methoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate as a colourless viscous fluid. The material was used for the next step without further purifications.

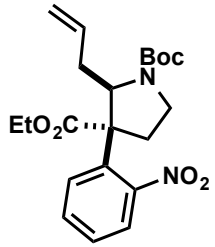
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 - 7.73 (m, 1H), 7.59 - 7.48 (m, 2H), 7.41 - 7.37 (m, 1H), 5.59 - 5.48 (m, 1H), 4.18 - 4.11 (m, 2H), 3.54 - 3.37 (m, 2H), 3.17 - 3.12 (m, 3H), 2.72 - 2.56 (m, 2H), 1.51 - 1.48 (m, 9H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.5, 171.3, 155.6, 155.3, 149.5, 149.3, 133.5, 132.6, 132.4, 131.3, 131.1, 128.1, 124.2, 89.6, 89.6, 80.8, 80.1, 61.8, 60.7, 60.0, 56.3, 55.9, 44.2, 43.6, 33.9, 33.4, 28.4, 14.1, 14.0 ppm.

IR (neat): 2978, 2933, 2900, 2835, 1732, 1697, 1608, 1577, 1525, 1477, 1456, 1363, 1309, 1247, 1228, 1168, 1153, 1128, 1093, 1072, 1022, 991, 979, 925, 896, 852, 781, 769, 731, 717, 690, 636, 599, 538, 511, 487, 459 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{26}N_2O_7Na^+$: 417.1638, found: 417.1643

1-(*tert*-Butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (248)



The crude 1-(*tert*-butyl) 3-ethyl 2-methoxy-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate was dissolved in absolute DCM (600 mL) and cooled to -78 °C. Allyltributylstannane (57.6 g, 53.4 mL, 174 mmol, 1.5 eq) and boron trifluoride diethyl etherate (33.8 mL, 128 mmol, 1.1 eq, 48% solution) were added. The resulting mixture was allowed to warm up to -40°C over a period of 4h, then poured onto saturated $NaHCO_3$ solution (1 L) and allowed to warm up to rt. After seperation of the organic phase the aqueous phase was extracted with DCM (2x500 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1 to 1:1) to obtain 1-(*tert*-butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (42.5 g, 105 mmol, 0.8 eq) as a colourless foam.

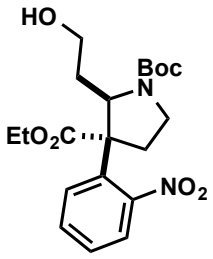
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 - 7.90 (m, 1H), 7.65 - 7.57 (m, 2H), 7.51 - 7.46 (m, 1H), 5.57 - 5.46 (m, 1H), 4.86 - 4.68 (m, 2H), 4.51 - 4.38 (m, 1H), 4.18 - 4.10 (m, 2H), 3.55 - 3.49 (m, 1H), 3.45 - 3.33 (m, 1H), 2.83 - 2.75 (m, 1H), 2.42 - 2.32 (m, 1H), 2.22 - 1.96 (m, 1H), 1.79 - 1.69 (m, 1H), 1.50 - 1.48 (m, 9H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.0, 172.8, 155.3, 154.6, 149.7, 149.5, 134.3, 134.2, 133.1, 132.9, 132.9, 130.7, 130.6, 128.9, 128.9, 125.4, 117.0, 116.8, 80.0, 79.4, 61.8, 61.7, 60.2, 60.1, 59.4, 58.7, 43.9, 43.4, 37.8, 37.2, 33.6, 33.0, 28.6, 14.1, 14.1 ppm.

IR (neat): 2977, 2926, 1785, 1731, 1693, 1530, 1455, 1389, 1364, 1300, 1234, 1174, 1024, 917, 855, 780 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{28}N_2O_6Na^+$: 427.1845, found: 427.1848

1-(*tert*-Butyl) 3-ethyl 2-(2-hydroxyethyl)-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (248b)

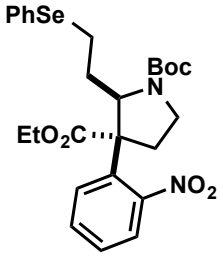


1-(*tert*-Butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (5.73 g, 14.2 mmol, 1 eq) was dissolved in DCM/MeOH = 4:1 (150 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until the blue colour disappeared. MeOH (120 mL) was added followed by $NaBH_4$ (1.61 g, 42.5 mmol, 3 eq) and the resulting mixture was allowed to warm up to rt. After stirring at rt for 18h H_2O (1 L) was added and the aqueous phase was extracted with Et_2O (3x300 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain 1-(*tert*-butyl) 3-ethyl 2-(2-hydroxyethyl)-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (5.38 g, 13.2 mmol, 0.93 eq). The alcohol was used for the next step withour further purifications.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 - 7.87 (m, 1H), 7.66 - 7.60 (m, 1H), 7.58 - 7.54 (m, 1H), 7.51 - 7.47 (m, 1H), 4.98 - 4.79 (m, 1H), 4.48 - 4.10 (m, 3H), 3.66 - 3.38 (m, 4H), 2.79 - 2.70 (m, 1H), 2.51 - 2.41 (m, 1H), 1.49 (s, 9H), 1.22 - 1.18 (m, 3H), 1.15 - 1.07 (m, 1H), 0.87 - 0.78 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.8, 157.0, 149.5, 133.1, 132.7, 130.3, 129.1, 125.6, 80.6, 61.9, 58.8, 58.2, 57.9, 43.9, 36.1, 33.0, 28.5, 14.1 ppm.

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-(2-(phenylselanyl)ethyl)pyrrolidine-1,3-dicarboxylate (249)



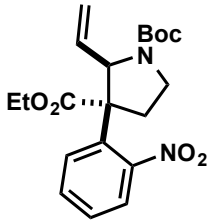
The crude alcohol was dissolved in absolute DCM (150 mL). NEt_3 (3.95 mL, 2.87 g, 28.3 mmol, 1 eq) followed by methanesulfonyl chloride (1.64 mL, 2.43 g, 21.2 mmol, 1.5 eq) was added and the reaction mixture was stirred at rt for 90min. H_2O (500 mL) was added and the aqueous phase was extracted with DCM (2x300 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The mesylate was used without further purification.

Diphenyl diselenide (8.84 g, 28.3 mmol, 2 eq) was dissolved in absolute EtOH (40 mL) and cooled to 0°C. $NaBH_4$ (3.22 g, 85.0 mmol, 6 eq) was added and the resulting mixture was stirred for 15min at 0°C under gas evolution. The mesylate was dissolved in absolute EtOH (50 mL) and was added to the colourless selenide solution dropwise. After complete addition the reaction mixture was allowed to warm up to rt and was stirred for 15h at rt. Aqueous $NaHCO_3$ (500 mL) was added and the aqueous phase was extracted with Et_2O (3x300 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The curde seleno ether was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-(2-(phenylselanyl)ethyl)pyrrolidine-1,3-dicarboxylate (5.20 g, 9.50 mmol, 0.67 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.82 - 7.77 (m, 1H), 7.60 - 7.41 (m, 3H), 7.28 - 7.25 (m, 2H), 7.19 - 7.15 (m, 3H), 4.85 - 4.72 (m, 1H), 4.16 - 4.10 (m, 2H), 3.53 - 3.36 (m, 2H), 2.85 - 2.64 (m, 3H), 2.46 - 2.40 (m, 1H), 1.51 - 1.49 (m, 9H), 1.36 - 1.30 (m, 2H), 1.20 - 1.16 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.5, 155.9, 149.3, 138.4, 133.1, 132.9, 132.6, 132.3, 132.1, 130.6, 130.4, 130.3, 130.1, 129.1, 129.0, 129.0, 128.9, 126.8, 126.6, 125.4, 125.4, 80.4, 79.7, 62.0, 61.9, 61.5, 61.1, 60.5, 59.4, 58.8, 43.9, 43.4, 35.2, 34.6, 33.4, 32.8, 29.8, 28.7, 28.6, 24.0, 21.2, 14.3, 14.2, 14.1 ppm.

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-vinylpyrrolidine-1,3-dicarboxylate (250)

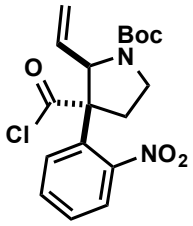


1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-(2-(phenylselanyl)ethyl)pyrrolidine-1,3-dicarboxylate (5.20 g, 9.50 mmol, 1 eq) was dissolved in MeOH/H_2O = 5:2 (175 mL) and $NaIO_4$ (6.10 g, 28.5 mmol, 3 eq) was added. The resulting mixture was stirred at rt for 2h. Toluene (500 mL) was put in a flask, Na_2CO_3 (2.00 g, 19.0 mmol, 2 eq) was added and the mixture was heated to reflux. The seleno oxide solution was added to the refluxing mixture and was stirred after complete addition for 1h at reflux. After cooling down to rt the solvent was concentrated under reduced pressure and H_2O (1 L) was added. The aqueous phase was extracted with Et_2O (3x300 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-vinylpyrrolidine-1,3-dicarboxylate (3.50 g, 9.00 mmol, 0.95 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.55 - 7.51 (m, 1H), 7.48 - 7.45 (m, 1H), 5.17 - 4.99 (m, 3H), 4.92 - 4.85 (m, 1H), 4.23 - 4.12 (m, 2H), 3.65 - 3.56 (m, 1H), 3.46 - 3.37 (m, 1H), 2.72 - 2.64 (m, 1H), 2.50 - 2.42 (m, 1H), 1.48 - 1.46 (m, 9H), 1.21 (t, J = 7.2 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.7, 172.6, 155.0, 149.4, 149.4, 134.3, 134.1, 133.3, 133.2, 133.1, 130.5, 130.4, 128.8, 125.5, 118.0, 117.9, 79.9, 79.6, 63.3, 63.1, 61.9, 61.8, 59.3, 43.9, 43.4, 33.5, 33.0, 28.7, 28.5, 14.1 ppm.
IR (film): 2977, 2898, 1729, 1689, 1606, 1577, 1529, 1477, 1455, 1383, 1362, 1301, 1236, 1172, 1118, 1023, 856, 770, 736, 691 cm^{-1}.
HRMS (ESI): calc. for $C_{20}H_{26}N_2O_6Na^+$: 413.1689, found: 413.1685

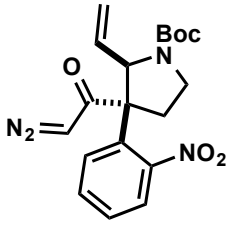
***tert*-Butyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (251)**



1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-vinylpyrrolidine-1,3-dicarboxylate (1.01 g, 2.50 mmol, 1 eq) was dissolved in EtOH (30 mL). Aqueous 50% KOH (30 mL) were added and the resulting mixture was heated to reflux for 5min. After cooling down to rt some ice was added and the aqueous phase was acidified to pH = 4-5 with $NaHSO_4$. The aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the carboxylic acid as a colourless oil. The material was used without further purification.
The crude carboxylic acid was dissolved in absolute DCM (25 mL). 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (660 μL, 667 mg, 5.00 mmol, 2 eq) was added and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure and the crude acid chloride was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain *tert*-butyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (934 mg, 2.45 mmol, 0.98 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.73 - 7.68 (m, 1H), 7.61 - 7.56 (m, 2H), 5.17 - 4.88 (m, 4H), 3.73 - 3.62 (m, 1H), 3.44 - 3.36 (m, 1H), 2.80 - 2.67 (m, 2H), 1.47 - 1.45 (m, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.9, 172.1, 149.2, 134.0, 133.8, 133.6, 131.1, 130.1, 125.8, 119.0, 80.5, 63.2, 42.6, 32.3, 31.1, 28.3 ppm.
IR (film): 3085, 2977, 1792, 1691, 1608, 1577, 1528, 1479, 1454, 1386, 1350, 1287, 1233, 1172, 1126, 980, 934, 891, 854, 811, 784, 737, 711, 680 cm^{-1}.
HRMS (ESI): calc. for $C_{18}H_{21}N_2O_5ClNa^+$: 403.1037, found: 403.1034

***tert*-Butyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (252)**

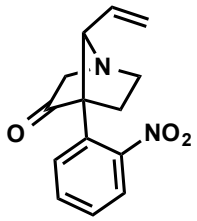


CaO (136 mg, 2.43 mmol, 1.1 eq) was put in a sealed tube and freshly prepared diazomethane in absolute Et_2O (20 mL, solution prepared started from 5.00 g *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide)[107] was added. *tert*-Butyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (840 mg, 2.21 mmol, 1 eq) dissolved in absolute Et_2O (5 mL) was added to the sealed tube. The tube was sealed and the mixture was stirred at rt for 3d. After complete reaction the solids were removed by filtration over celite and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain *tert*-butyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (644 mg, 1.67 mmol, 0.76 eq) as a slightly yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 - 7.82 (m, 1H), 7.66 - 7.60 (m, 1H), 7.55 - 7.46 (m, 2H), 5.21 - 4.89 (m, 5H), 3.67 - 3.54 (m, 1H), 3.39 (ddd, J_1 = 6.2 Hz, J_2 = 11.2 Hz, J_3 = 11.2 Hz, 1H), 2.60 (ddd, J_1 = 8.8 Hz, J_2 = 12.0 Hz, J_3 = 12.0 Hz, 1H), 2.42 (dd, J_1 = 12.6 Hz, J_2 = 6.5 Hz, 1H), 1.48 - 1.45 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.6, 168.6, 154.8, 139.4, 134.2, 133.2, 131.0, 129.3, 126.7, 125.6, 118.3, 80.4, 62.9, 43.3, 35.9, 30.4, 28.6 ppm.
IR (film): 2977, 2932, 2108, 1689, 1642, 1529, 1478, 1385, 1347, 1256, 1171, 1125, 1039, 890, 853, 784, 733, 650 cm^{-1}.
HRMS (ESI): calc. for $C_{19}H_{22}N_4O_5Na^+$: 409.1488, found: 409.1484

4-(2-Nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (253)

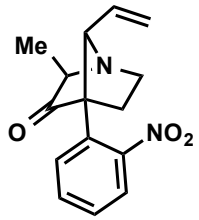


tert-Butyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (529 mg, 1.37 mmol, 1 eq) was dissolved in absolute DCM (100 mL) and cooled to -78°C. Trifluoroacetic acid (524 μL, 780 mg, 6.85 mmol, 5 eq) was added and the resulting mixture was allowed to warm up to -10°C over a period of 7h. Na_2CO_3 (3.63 g, 34.2 mmol, 25 eq) was added at -10°C. After warming up to rt the solids were removed by filtration and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (Al_2O_3, PE/EtOAc = 2:1 to 1:1) to obtain 4-(2-nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (257 mg, 995 μmol, 0.73 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.62 (ddd, J_1 = 8.1 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 7.51 - 7.46 (m, 2H), 5.73 - 5.64 (m, 1H), 5.26 - 5.21 (m, 2H), 4.47 - 4.44 (m, 1H), 3.54 - 3.49 (m, 1H), 3.48 - 3.40 (m, 1H), 3.21 (d, J = 17.0 Hz, 1H), 2.80 - 2.66 (m, 2H), 2.06 - 2.00 (m, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 215.3, 156.5, 133.2, 131.7, 130.6, 129.7, 128.8, 126.0, 121.0, 73.4, 67.5, 63.8, 49.7, 30.3 ppm.
IR (neat): 3074, 2974, 2931, 2899, 1753, 1689, 1639, 1608, 1525, 1477, 1388, 1363, 1348, 1251, 1166, 1122, 1074, 985, 927, 889, 852, 837, 783, 758, 727, 700, 636, 563, 497, 460 cm^{-1}.

HRMS (ESI): calc. for $C_{14}H_{15}N_2O_3^+$: 259.1083, found: 259.1080

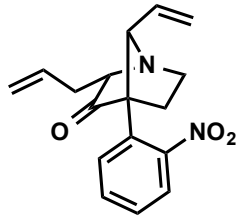
2-Methyl-4-(2-nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (254)



4-(2-Nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (12.0 mg, 46.0 μmol, 1 eq) was dissolved in absolute MeCN (1 mL). Methyl iodide (6.00 μL, 13.0 mg, 93.0 μmol, 2 eq) was added and the mixture was stirred at rt for 90min. The solvent was removed under reduced pressure to obtain 2-methyl-4-(2-nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (13.0 mg, 46.0 μmol, 1 eq) as a mixture of diastereoisomers.

^{1}H-NMR (400 MHz, MeOD): δ = 8.13 - 8.09 (m, 1 H), 7.86 - 7.80 (m, 1H), 7.77 - 7.67 (m, 2H), 6.23 - 6.08 (m, 1H), 5.84 - 5.60 (m, 2H), 5.30 - 5.23 (m, 1H), 4.55 - 4.53 (m, 1H), 4.04 - 3.96 (m, 2H), 3.64 - 3.54 (m, 1H), 3.34 (s, 3H), 2.45 - 2.37 (m, 1H) ppm.
^{13}C-NMR (100 MHz, MeOD): δ = 197.2, 149.6, 134.1, 132.3, 131.5, 130.5, 126.0, 123.8, 122.6, 81.4, 73.5, 62.1, 57.8, 26.8, 18.2 ppm.

2-Allyl-4-(2-nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (255)

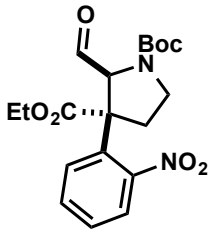


LiHMDS (85.0 μL, 85.0 μmol, 2 eq, 1 mol/L solution in THF) was put in a Schlenk tube under argon and was cooled to -78°C. 4-(2-Nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (11.0 mg, 43.0 μmol, 1 eq) dissolved in absolute THF (1 mL) was added and the resulting solution was stirred for

15min at -78°C. *tert*-Butyldimethylsilyl chloride (19.0 mg, 128 μmol, 3 eq) was added and the reaction mixture was allowed to warm uo to -30°C over a period of 6h. Aqueous $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude silylenol ether was dissolved in absolute MeCN (500 μL). Allyl bromide (37.0 μL, 52.0 mg, 426 μmol, 10 eq) was added and the resulting solution was stirred at rt for 22h. The solvent was removed under reduced pressure to obtain 2-allyl-4-(2-nitrophenyl)-7-vinyl-1-azabicyclo[2.2.1]heptan-3-one (13.0 mg, 43.0 μmol, 1 eq) as a colourless foam.

^{1}H-NMR (400 MHz, MeOD): δ = 8.12 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.83 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.5 Hz, 1H), 7.77 - 7.69 (m, 2H), 6.26 - 6.08 (m, 2H), 5.84 - 5.74 (m, 4H), 5.30 (d, J = 9.6 Hz, 1H), 4.50 - 4.47 (m, 1H), 4.30 (dd, J_1 = 13.1 Hz, J_2 = 7.3 Hz, 1H), 4.15 (dd, J_1 = 13.1 Hz, J_2 = 7.3 Hz, 1H), 4.06 - 3.97 (m, 2H), 3.58 (ddd, J_1 = 13.5 Hz, J_2 = 11.3 Hz, J_3 = 5.6 Hz, 1H), 2.42 - 2.35 (m, 1H) ppm.
^{13}C-NMR (100 MHz, MeOD): δ = 198.3, 150.8, 135.5, 133.4, 133.0, 131.9, 129.4, 129.2, 127.4, 126.0, 124.1, 82.1, 63.1, 59.9, 57.0, 30.9, 27.5 ppm.
HRMS (ESI): calc. for $C_{17}H_{19}N_2O_3^+$: 299.1396, found: 299.1397

1-(*tert*-Butyl) 3-ethyl 2-formyl-3-(2-nitrophenyl)pyrrolidine-1,3-di-carboxylate (250b)

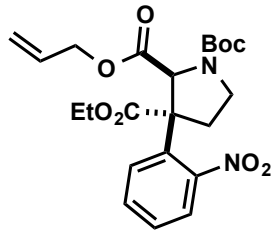


1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-vinylpyrrolidine-1,3-dicarboxylate (600 mg, 1.54 mmol, 1 eq) was dissolved in DCM/MeOH = 5:1 (12 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until the blue colour

disappeared. Thiourea (117 mg, 1.54 mmol, 1 eq) was added and the reaction mixture was allowed to warm up to rt. After stirring at rt for 2h the solvent was concentrated under reduced pressure. The solids were removed by filtration over celite and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain the aldehyde (503 mg, 1.28 mmol, 0.83 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.24 - 9.16 (m, 1H), 8.05 - 7.98 (m, 1H), 7.67 - 7.49 (m, 3H), 5.35 - 5.14 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.87 - 3.83 (m, 1H), 3.62 - 3.50 (m, 1H), 2.83 - 2.72 (m, 1H), 2.49 - 2.40 (m, 1H), 1.48 - 1.43 (m, 9H), 1.22 - 1.17 (m, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.8, 198.3, 171.4, 171.3, 153.9, 149.1, 133.9, 133.7, 133.0, 132.1, 130.9, 130.8, 130.2, 129.7, 129.6, 129.6, 129.5, 129.1, 126.0, 125.9, 125.6, 98.5, 81.2, 80.7, 68.0, 67.9, 65.9, 62.5, 62.4, 62.0, 58.7, 57.3, 54.7, 44.6, 44.2, 43.9, 34.6, 34.1, 29.8, 28.5, 28.4, 14.0 ppm.

2-Allyl 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)pyrrolidine-1,2,3-tricarboxylate (257)



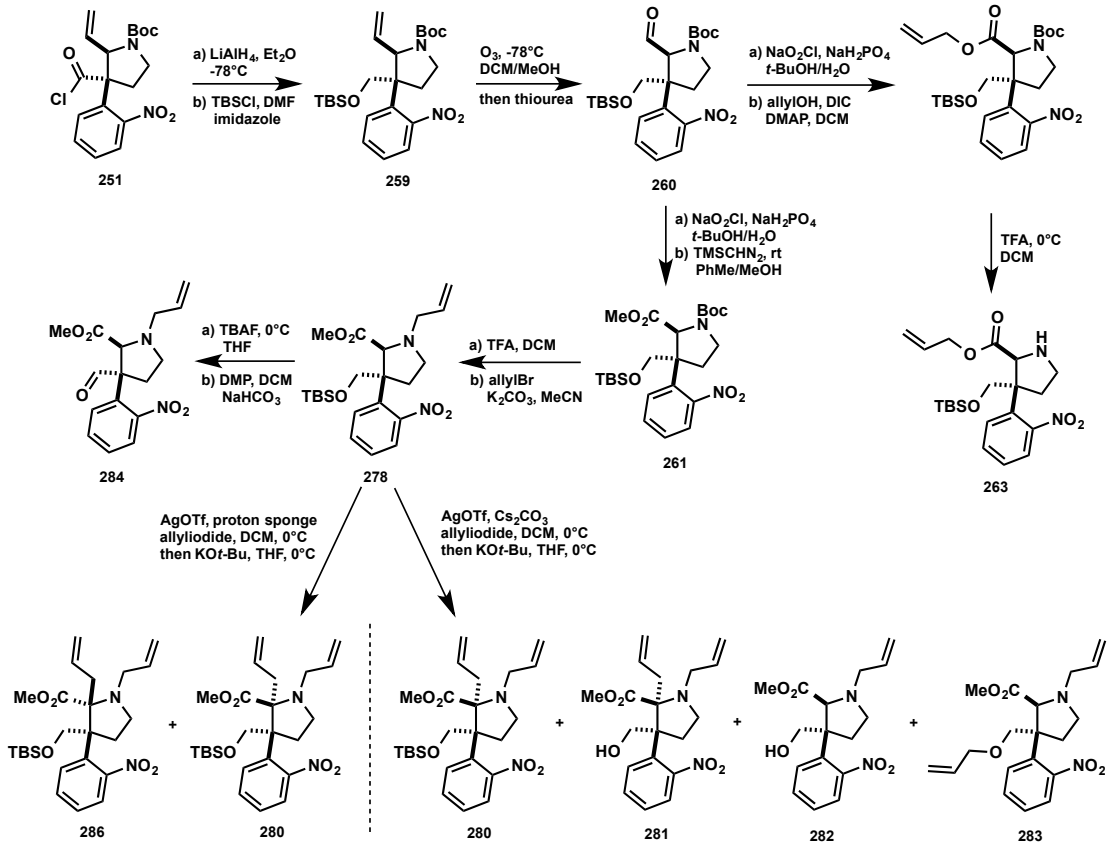
1-(*tert*-Butyl) 3-ethyl 2-formyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (503 mg, 1.28 mmol, 1 eq) was dissolved in *t*BuOH (20 mL) and 2-methyl-2-butene (5 mL) was added. NaO_2Cl (1.75 g, 15.4 mmol, 12 eq, 80%) and NaH_2PO_4*H_2O (1.00 g, 7.25 mmol, 5.7 eq) dissolved in H_2O (5 mL) were added and the resulting mixture was stirred at rt for 1h. Brine (100 mL) was added and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic pahses were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the carboxylic acid as a colourless oil. The acid was used without further purification.

The carboxylic acid was dissolved in DCM (10 mL). DMAP (19.0 mg, 154 μmol, 0.12 eq), allyl alcohol (210 μL, 179 mg, 3.07 mmol, 2.4 eq) and DIC (260 μL, 213 mg, 1.69 mmol, 1.3 eq) were sequentially added. The reaction mixture was stirred at rt for 13h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 2-allyl 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)pyrrolidine-1,2,3-tricarboxylate (402 mg, 896 μmol, 0.7 eq) as a colourless oil.

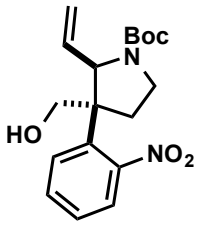
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15 - 8.09 (m, 1H), 7.67 - 7.56 (m, 2H), 7.53 - 7.47 (m, 1H), 5.49 - 4.98 (m, 3H), 4.21 - 4.09 (m, 3H), 3.93 - 3.70 (m, 2H), 3.52 - 3.41 (m, 1H), 3.14 - 3.01 (m, 1H), 2.37 - 2.30 (m, 1H), 1.47 - 1.41 (m, 9H), 1.21 - 1.17 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.6, 171.5, 170.9, 170.8, 170.6, 170.5, 154.0, 153.5, 148.7, 148.3, 133.9, 133.9, 133.7, 133.6, 132.3, 132.2, 132.1, 131.0, 131.0, 130.4, 130.3, 130.2, 130.0, 129.4, 129.3, 129.3, 126.1, 126.1, 125.9, 119.4, 118.9, 80.6, 80.5, 80.3, 80.2, 66.0, 65.9, 63.4, 63.4, 63.2, 62.2, 62.1, 62.1, 62.0, 61.2, 61.0, 60.5, 59.5, 59.4, 58.3, 58.3, 44.0, 43.9, 43.5, 43.5, 33.9, 33.9, 33.3, 33.3, 28.5, 28.4, 14.3, 14.1, 13.6, 13.4 ppm.

HRMS (ESI): calc. for $C_{22}H_{28}N_2O_8Na^+$: 471.1743, found: 471.1736


a) LiAlH4, Et2O -78°C
b) TBSCl, DMF imidazole
O3, -78°C DCM/MeOH
then thiourea
a) NaO2Cl, NaH2PO4 t-BuOH/H2O
b) allylOH, DIC DMAP, DCM
a) NaO2Cl, NaH2PO4 t-BuOH/H2O
b) TMSCHN2, rt PhMe/MeOH
TFA, 0°C DCM
a) TFA, DCM
b) allylBr K2CO3, MeCN
a) TBAF, 0°C THF
b) DMP, DCM NaHCO3
AgOTf, proton sponge allyliodide, DCM, 0°C then KOt-Bu, THF, 0°C
AgOTf, Cs2CO3 allyliodide, DCM, 0°C then KOt-Bu, THF, 0°C
251
259
260
261
263
278
284
286
280
280
281
282
283

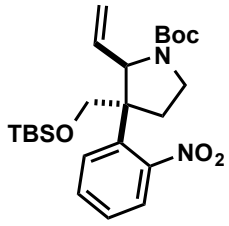
***tert*-Butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (251b)**



tert-Butyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (690 mg, 1.81 mmol, 1 eq) was dissolved in absolute Et_2O (50 mL) and cooled to -78°C. $LiAlH_4$ (1.90 mL, 4.52 mmol, 2.2 eq, 2.4 mol/L solution in THF) was added dropwise and was stirred for 1.5h at -78°C. H_2O (100 mL) was added and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain *tert*-butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (620 mg, 1.78 mmol, 0.98 eq). The alcohol was used without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.71 - 7.34 (m, 4H), 5.46 - 5.25 (m, 1H), 5.19 - 5.00 (m, 2H), 4.91 - 4.58 (m, 1H), 4.19 - 4.04 (m, 1H), 3.74 - 3.68 (m, 1H), 3.54 - 3.42 (m, 2H), 2.78 - 2.47 (m, 1H), 2.26 - 2.07 (m, 1H), 1.46 - 1.42 (m, 9H) ppm.
HRMS (ESI): calc. for $C_{18}H_{24}N_2O_5Na^+$: 371.1583, found: 371.1585

***tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)2-vinyl-pyrrolidine-1-carboxylate (259)**

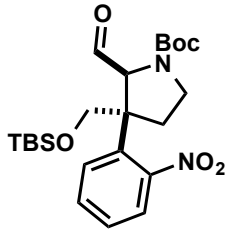


tert-Butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1-carboxylate (544 mg, 1.56 mmol, 1 eq) was dissolved in absolute DMF (5 mL). Imidazole (255 mg, 3.75 mmol, 2.4 eq) and *tert*-butyldimethylsilyl chloride (282 mg, 1.87 mmol, 1.2 eq) were added. The resulting mixture was stirred at rt for 3h. H_2O

(50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1) to obtain *tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)2-vinyl-pyrrolidine-1-carboxylate (535 mg, 1.16 mmol, 0.74 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58 - 7.53 (m, 1H), 7.48 - 7.43 (m, 1H), 7.39 - 7.33 (m, 2H), 5.44 - 5.32 (m, 1H), 5.16 - 4.99 (m, 2H), 4.79 - 4.66 (m, 1H), 4.05 - 4.02 (m, 1H), 3.69 - 3.65 (m, 1H), 3.54 - 3.37 (m, 2H), 2.56 - 2.49 (m, 1H), 2.18 - 2.08 (m, 1H), 1.47 - 1.45 (m, 9H), 0.78 - 0.77 (m, 9H), –0.13 - –0.15 (m, 3H), –0.21 - –0.24 (m, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.7, 154.0, 151.2, 151.0, 134.3, 134.1, 134.1, 133.9, 130.8, 130.7, 127.8, 124.6, 124.5, 118.1, 118.1, 79.9, 79.6, 65.5, 65.2, 62.7, 62.3, 55.8, 55.1, 43.3, 42.7, 28.8, 28.7, 28.6, 28.3, 25.9, 25.9, 25.8, 18.3, 18.2, -3.5, -5.6, -5.8, -5.9 ppm.

tert-Butyl 3-(((_tert_-butyldimethylsilyl)oxy)methyl)-2-formyl-3-(2-nitrophenyl)pyrrolidine-1-carboxylate (260)

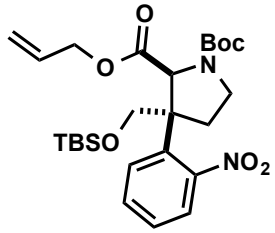


tert-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)2-vinyl-pyrrolidine-1-carboxylate (517 mg, 1.12 mmol, 1 eq) was dissolved in DCM/MeOH = 5:1 (12 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until the blue colour disappeared. Thiourea (94.0 mg, 1.23 mmol, 1.1 eq) was added and the mixture was allowed to warm up to rt. After stirring at rt for 90min all solids were removed by filtration over celite and the solvent was concentrated under reduced pressure. The crude aldehyde was purified

by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain *tert*-butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-formyl-3-(2-nitrophenyl)-pyrrolidine-1-carboxylate (456 mg, 981 μmol, 0.88 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.59 - 9.45 (m, 1H), 7.59 - 7.47 (m, 2H), 7.43 - 7.37 (m, 2H), 5.01 - 4.84 (m, 1H), 3.88 - 3.83 (m, 1H), 3.74 - 3.61 (m, 2H), 3.52 - 3.39 (m, 1H), 2.45 - 2.39 (m, 1H), 2.31 - 2.21 (m, 1H), 1.47 - 1.44 (m, 9H), 0.77 - 0.76 (m, 9H), –0.12 - –0.18 (m, 6H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.5, 198.2, 154.1, 133.0, 132.9, 132.0, 131.3, 131.2, 128.6, 128.5, 124.8, 124.6, 80.9, 80.5, 68.1, 67.5, 66.0, 65.8, 54.7, 44.0, 43.6, 29.5, 28.8, 28.5, 28.5, 25.9, 25.8, 18.2, -5.6, -5.8, -5.8 ppm.
IR (film): 2931, 2889, 2857, 2361, 1730, 1697, 1530, 1469, 1391, 1367, 1254, 1171, 1105, 1003, 943, 839, 776, 671 cm^{-1}.

2-Allyl 1-(*tert*-butyl) 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (263a)



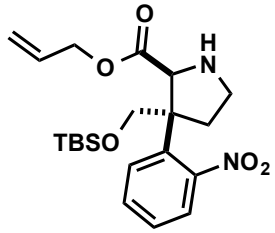
tert-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-formyl-3-(2-nitrophenyl)-pyrrolidine-1-carboxylate (402 mg, 893 μmol, 1 eq) was dissolved in *t*BuOH (20 mL) and 2-methyl-2-butene (4 mL) was added. NaO_2Cl (808 mg, 8.93 mmol, 10 eq) and NaH_2PO_4*H_2O (808 mg, 5.94 mmol, 6.7 eq) dissolved in H_2O (20 mL) was added. The resulting mixture was stirred at rt for 12h. Brine (100 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The carboxylic acid was used without further purification.
The cruce carboxylic acid was dissolved in DCM (20 mL). DMAP (10.9 mg, 89.3 μmol, 0.1 eq), allyl alcohol (122 μL, 104 mg, 1.79 mmol, 2 eq) and DIC

(152 μL, 124mg, 982 μmol, 1.1 eq) were sequentially added and the resulting mixture was stirred at rt for 16h. H_2O (100 mL) was added and the aqueous phase was extracted with DCM (3x50 mL). The ocmbined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude allyl ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1) to obtain 2-allyl 1-(*tert*-butyl) 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (270 mg, 518 μmol, 0.58 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 - 7.33 (m, 4H), 5.64 - 5.50 (m, 1H), 5.16 - 5.04 (m, 2H), 5.02 - 4.87 (m, 1H), 4.36 - 4.17 (m, 2H), 3.99 - 3.93 (m, 1H), 3.81 - 3.77 (m, 1H), 3.71 - 3.60 (m, 1H), 3.54 - 3.45 (m, 1H), 2.59 - 2.48 (m, 1H), 2.40 - 2.33 (m, 1H), 1.46 - 1.43 (m, 9H), 0.80 - 0.79 (m, 9H), –0.14 - –0.16 (m, 6H) ppm.

IR (film): 2931, 2890, 2858, 2289, 2127, 1740, 1702, 1531, 1467, 1393, 1368, 1252, 1177, 1102, 992, 932, 840, 777, 668 cm^{-1}.

Allyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (263)

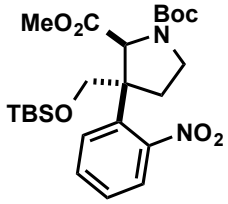


2-Allyl 1-(*tert*-butyl) 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (66.0 mg, 130 μmol, 1 eq) was dissolved in DCM (5 mL) and cooled to 0°C. Trifluoroacetic acid (1.2 mL) was added and the resulting mixture was stirred at 0°C for 1h. Aqueous K_2CO_3 (25 mL) was added and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The secondary amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to obtain allyl 3-(((*tert*-

butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (32.0 mg, 76.1 μmol, 0.59 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 - 7.29 (m, 4H), 5.62 (dddd, J_1 = 16.9 Hz, J_2 = 10.6 Hz, J_3 = 6.2 Hz, J_4 = 6.2 Hz, 1H), 5.17 - 5.09 (m, 2H), 4.49 (s, 1H), 4.37 - 4.27 (m, 2H), 3.87 (d, J = 9.9 Hz, 1H), 3.82 (d, J = 9.9 Hz, 1H), 3.31 - 3.25 (m, 1H), 3.21 - 3.14 (m, 1H), 2.38 (ddd, J_1 = 10.6 Hz, J_2 = 12.3 Hz, J_3 = 6.8 Hz, 1H), 2.11 (ddd, J_1 = 12.3 Hz, J_2 = 8.5 Hz, J_3 = 3.8 Hz, 1H), 0.81 (s, 9H), −0.13 (s, 3H), −0.19 (s, 3H) ppm.
IR (film): 2930, 2857, 1769, 1706, 1607, 1574, 1533, 1466, 1408, 1386, 1348, 1253, 1222, 1102, 1056, 1008, 935, 837, 777, 701, 670 cm^{-1}.

***tert*-Butyl 2-methyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (261)**

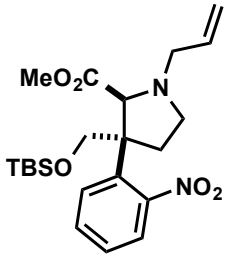


tert-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-formyl-3-(2-nitrophenyl)-pyrrolidine-1-carboxylate (456 mg, 981 mol, 1 eq) was dissolved in *t*-BuOH (20 mL) and 2-methyl-2-butene (5 mL) was added. NaO_2Cl (1.00g, 11.2 mmol, 11.4 eq) and NaH_2PO_4*H_2O (1.00 g, 7.25 mmol, 7.4 eq) dissolved in H_2O (5 mL) were added and the resulting mixture was stirred at rt for 3h. Brine (100 mL) was added and the aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the carboxylic acid as a colourless oil. The acid was used without further purifications.
The carboxylic acid was dissolved in PhMe/MeOH = 4:1 (10 mL). $TMSCHN_2$ (560 μL, 1.12 mmol, 1.14 eq, 2 mol/L solution in hexane) was added and the mixture was stirred at rt for 10min. The solvent was removed under reduced pressure and the crude methyl ester was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain *tert*-butyl 2-methyl 3-

(((*tert*-butyldimethylsilyl)oxy)methyl)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (438 mg, 885 μmol, 0.9 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 - 7.59 (m, 1H), 7.48 - 7.42 (m, 2H), 7.39 - 7.34 (m, 1H), 4.98 - 4.89 (m, 1H), 4.02 - 3.98 (m, 1H), 3.80 - 3.77 (m, 1H), 3.72 - 3.61 (m, 1H), 3.53 - 3.42 (m, 1H), 3.40 (s, 3H), 2.60 - 2.37 (m, 2H), 1.46 - 1.43 (m, 9H), 0.80 (bs, 9H), –0.15 - –0.20 (m, 6H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.2, 171.8, 154.1, 133.6, 133.5, 133.4, 130.8, 130.7, 128.2, 128.1, 124.8, 124.6, 80.6, 80.4, 66.0, 65.7, 63.5, 63.3, 56.3, 55.5, 51.9, 51.8, 44.5, 44.1, 28.7, 28.5, 28.5, 26.0, 25.9, 18.3, 18.3, -5.6, -5.8, -5.9 ppm.

Methyl 1-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (278)

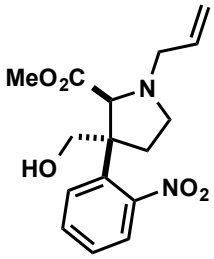


tert-Butyl 2-methyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (200 mg, 404 μmol, 1 eq) was dissolved in DCM (8 mL) and cooled to 0°C. TFA (2 mL) was added and the reaction mixture was allowed to warm up to rt. After stirring for 30min the mixture was poured onto aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the secondary amine which was used in the next step without further purification.
The secondary amine was dissolved in MeCN (4 mL). K_2CO_3 (112 mg, 808 μmol, 2 eq) and allyl bromide (350 μL, 490 mg, 4.04 mmol, 10 eq) were added and the resulting mixture was stirred at rt for 16h. Aqueous $NaHCO_3$ (50 mL) was added and the aqueous ohase was extracted with DCM (3x50 mL). The

combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude allyl amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1) to obtain methyl 1-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (147 mg, 338 μmol, 0.84 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.50 - 7.44 (m, 1H), 7.41 - 7.23 (m, 3H), 5.95 - 5.75 (m, 1H), 5.25 - 5.07 (m, 2H), 4.31 (s, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.86 (d, *J* = 9.7 Hz, 1H), 3.43 (s, 3H), 3.26 (dddd, J_1 = 13.8 Hz, J_2 = 5.8 Hz, J_3 = 1.4 Hz, J_4 = 1.4 Hz, 1H), 3.11 - 2.96 (m, 2H), 2.76 (ddd, J_1 = 10.5 Hz, J_2 = 8.8 Hz, J_3 = 4.4 Hz, 1H), 2.37 (ddd, J_1 = 12.4 Hz, J_2 = 10.5 Hz, J_3 = 5.0 Hz, 1H), 2.00 (ddd, J_1 = 12.6 Hz, J_2 = 8.5 Hz, J_3 = 4.3 Hz, 1H), 0.81 (s, 9H), –0.13 (s, 3H), –0.22 (s, 3H) ppm.

Methyl 1-allyl-3-(hydroxymethyl)3-(2-nitrophenyl)pyrrolidine-2-carboxylate (282)

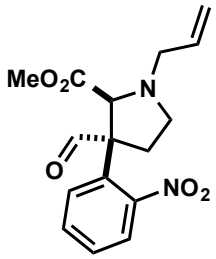


Methyl 1-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (53.0 mg, 122 μmol, 1 eq) was dissolved in absolute THF (10 mL) and cooled to 0°C. TBAF (1.22 mL, 1.22 mmol, 10 eq, 1mol/L solution in THF) was added and the resulting mixture was stirred at 0°C for 2h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain methyl 1-allyl-3-(hydroxymethyl)3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (35.2 mg, 110 μmol, 0.9 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.36 - 7.32 (m, 2H), 5.84 (dddd, J_1 = 17.0 Hz, J_2 = 10.4 Hz, J_3 = 6.5 Hz, J_4 = 6.5 Hz, 1H), 5.22 - 5.14 (m, 2H), 4.32 (s, 1H), 4.01 (d, J = 10.6 Hz, 1H), 3.97 (d, J = 10.6 Hz, 1H), 3.47 (s, 3H), 3.29 - 3.18 (m, 2H), 3.05 - 2.99 (m, 1H), 2.80 (ddd, J_1 = 10.3 Hz, J_2 = 8.9 Hz, J_3 = 5.4 Hz, 1H), 2.53 - 2.39 (m, 2H) ppm.

HRMS (ESI): calc. for $C_{16}H_{21}N_2O_5^+$: 321.1450, found: 321.1456

Methyl 1-allyl-3-formyl-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (284)



Methyl 1-allyl-3-(hydroxymethyl)3-(2-nitrophenyl)pyrrolidine-2-carboxylate (35.2 mg, 110 μmol, 1 eq) was dissolved in DCM (5 mL). $NaHCO_3$ (102 mg, 1.22 mmol, 11 eq) followed by DMP (76.0 mg, 183 μmol, 1.7 eq) was added and the reaction mixture was stirred at rt for 19h. DMP (152 mg, 366 μmol, 3.3 eq) was added and the reaction mixture was stirred at rt for 1h. Aqueous $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain methyl 1-allyl-3-formyl-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (31.0 mg, 97.0 μmol, 0.88 eq) as a colourless oil.

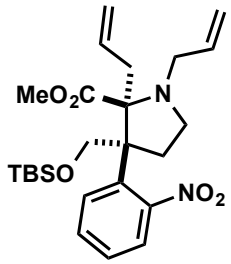
Methyl 1-allyl-3-formyl-3-(2-nitrophenyl)pyrrolidine-2-carboxylate

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H), 7.93 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.65 - 7.57 (m, 2H), 7.47 (ddd, J_1 = 8.2 Hz, J_2 = 7.2 Hz, J_3 = 1.7 Hz, 1H), 5.84 (dddd, J_1 = 17.0 Hz, J_2 = 10.3 Hz, J_3 = 6.6 Hz, J_4 = 6.6 Hz, 1H), 5.22 (ddd, J_1 = 17.0 Hz, J_2 = 3.3 Hz, J_3 = 1.5 Hz, 1H), 5.12 (ddd, J_1 = 9.9 Hz, J_2 =

2.7 Hz, J_3 = 1.0 Hz, 1H), 4.37 (s, 1H), 3.42 - 3.32 (m, 2H), 3.29 (s, 3H), 3.12 (ddd, J_1 = 8.9 Hz, J_2 = 8.9 Hz, J_3 = 2.4 Hz, 1H), 2.94 (ddd, J_1 = 7.2 Hz, J_2 = 8.4 Hz, J_3 = 8.4 Hz, 1H), 2.82 (ddd, J_1 = 12.0 Hz, J_2 = 8.6 Hz, J_3 = 8.6 Hz, 1H), 2.48 (ddd, J_1 = 12.0 Hz, J_2 = 6.9 Hz, J_3 = 2.3 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.3, 171.5, 149.2, 135.1, 133.7, 132.0, 131.3, 129.2, 125.4, 117.9, 67.1, 62.8, 55.6, 51.5, 48.7, 31.9 ppm.

Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (280), procedure 1



Silver trifluoromethanesulfonate (414 mg, 1.61 mmol, 5 eq) and Cs_2CO_3 (1.05 g, 3.22 mmol, 10 eq) were put in a Schlenk tube under argon and protection of light. Absolute DCM (1 mL) was added and cooled to 0°C. Freshly prepared allyl iodide[108] (150 µL, 270 mg, 1.61 mmol, 5 eq) was added and the mixture was stirred for 1min at 0°C. Methyl 1-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (140 mg, 322 µmol, 1 eq) dissolved in absolute DCM (3 mL) was added to the suspension and stirred at 0°C for 1h. The mixture was allowed to warm up to rt. The solids were removed by filtration over celite in a flask containing solid K_2CO_3 (445 mg, 3.22 mmol, 10 eq). The solvent was removed under reduced pressure and the crude ammonium salt was dried under high vacuum for 15min. The ammonium salt was dissolved in absolute THF (10 mL) and cooled to 0°C. KO*t*Bu (390 µL, 390 µmol, 1.2 eq, 1 mol/L solution in *t*BuOH) was added dropwise and the resulting mixture was stirred at 0°C for 30min. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography (SiO_2,

PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (41.0 mg, 87.0 μmol, 0.27 eq) as a colourless oil. Starting material (7.00 mg, 16.1 μmol, 0.05 eq) could be reisolated next to methyl 1,2-diallyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (15.0 mg, 41.9 μmol, 0.13 eq), methyl 1-allyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (8.00 mg, 22.5 μmol, 0.07 eq) and methyl 1-allyl-3-((allyloxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (26.0 mg, 70.9 μmol, 0.22 eq).

Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (280), *trans*-product

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.54 - 7.49 (m, 1H), 7.40 - 7.23 (m, 3H), 6.23 - 6.02 (m, 1H), 5.85 - 5.65 (m, 1H), 5.20 - 5.00 (m, 4H), 4.19 (d, *J* = 10.4 Hz, 1H), 3.97 (d, *J* = 10.5 Hz, 1H), 3.54 - 3.11 (m, 7H), 2.55 - 2.27 (m, 3H), 2.01 - 1.86 (m, 1H), 0.72 (s, 9H), –0.12 (s, 3H), –0.31 (s, 3H) ppm.

HRMS (ESI): calc. for $C_{25}H_{39}N_2O_5Si^+$: 475.2628, found: 475.2631

Methyl 1,2-diallyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (281)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 - 7.48 (m, 1H), 7.41 - 7.36 (m, 2H), 7.34 - 7.30 (m, 1H), 6.24 - 6.13 (m, 1H), 5.81 - 5.71 (m, 1H), 5.36 - 5.31 (m, 1H), 5.21 - 5.14 (m, 2H), 5.11 - 5.08 (m, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.53 - 3.41 (m, 2H), 3.37 (s, 3H), 3.33 - 3.28 (m, 2H), 3.16 (dd, J_1 = 16.2 Hz, J_2 = 8.3 Hz, 1H), 2.60 - 2.52 (m, 2H), 2.48 - 2.34 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.6, 151.7, 135.1, 134.8, 134.5, 130.3, 129.2, 127.8, 125.0, 118.3, 117.2, 77.3, 67.5, 58.1, 53.5, 51.4, 50.8, 37.0, 31.1 ppm.

HRMS (ESI): calc. for $C_{19}H_{25}N_2O_5^+$: 361.1763, found: 361.1769

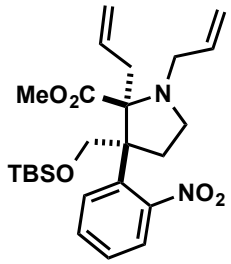
Methyl 1-allyl-3-((allyloxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (283)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.28 (ddd, J_1 = 7.9 Hz, J_2 = 6.9 Hz, J_3 = 1.6 Hz, 1H), 5.90 - 5.71 (m, 2H), 5.22 - 5.06 (m, 4H), 4.36 (s, 1H), 3.90 - 3.84 (m, 3H), 3.74 (d, J = 9.2 Hz, 1H), 3.43 (s, 3H), 3.30 - 3.25 (m, 2H), 3.09 - 3.01 (m, 2H), 2.77 (ddd, J_1 = 10.5 Hz, J_2 = 8.8 Hz, J_3 = 4.4 Hz, 1H), 2.39 (ddd, J_1 = 12.5 Hz, J_2 = 10.6 Hz, J_3 = 5.3 Hz, 1H), 2.06 (ddd, J_1 = 12.6 Hz, J_2 = 8.5 Hz, J_3 = 4.1 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.6, 150.7, 136.1, 135.3, 134.7, 132.4, 130.3, 127.3, 124.1, 116.9, 116.3, 74.1, 72.1, 69.9, 54.7, 54.6, 50.8, 49.4, 30.2 ppm.

HRMS (ESI): calc. for $C_{19}H_{25}N_2O_5^+$: 361.1763, found: 361.1756

Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (280), procedure 2



Silver trifluoromethanesulfonate (1.28 g, 5.00 mmol, 5 eq) was put in a Schlenk tube under argon and protection of light. Absolute DCM (4 mL) was added and cooled to 0°C. Freshly prepared allyl iodide (460 µL, 839 mg, 5.00 mmol, 5 eq) was added and the mixture was stirred at 0°C for 1min. Methyl 1-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (434 mg, 1.00 mmol, 1 eq) and 1,8-bis(dimethylamino)-naphthalene (642 mg, 3.00 mmol, 3 eq) dissolved in absolute DCM (6 mL) were added to the suspension and stirred at 0°C for 1h. The mixture was allowed to warm up to rt. The solids were removed by filtration over celite in a flask containing solid K_2CO_3 (1.38 g, 10.0 mmol, 10 eq). The solvent was removed under reduced pressure and the crude ammonium salt was dried under high vacuum for 15min. The ammonium salt was dissolved in absolute

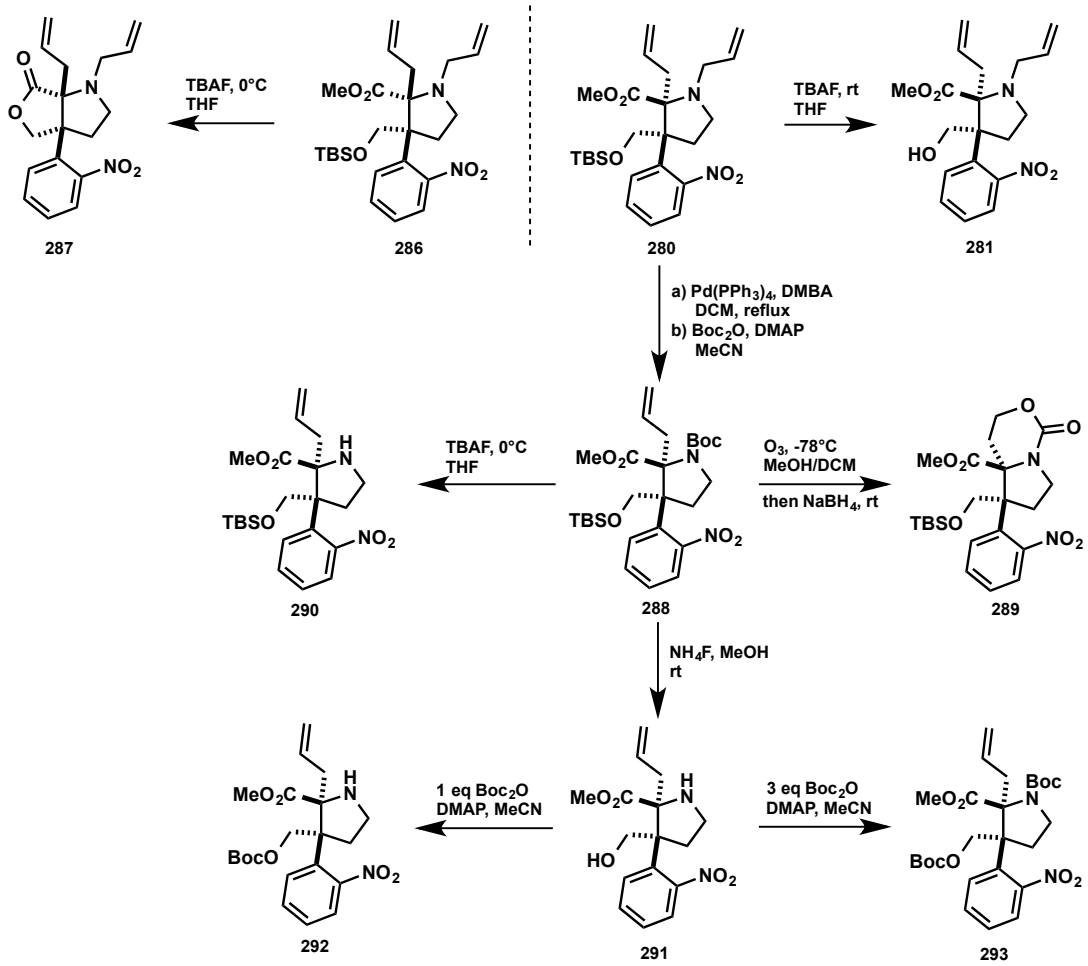
THF (20 mL) and cooled to 0°C. KO*t*Bu (3.00 mL, 3.00 mmol, 3 eq, 1 mol/L solution in *t*BuOH) was added dropwise and the resulting mixture was stirred at 0°C for 1h. H_2O (100 mL) was added and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography (SiO_2, PE/EtOAc = 20:1 to 10:1) to obtain methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (144 mg, 303 μmol, 0.3 eq) as a mixture of diastereoisomers (dr = 4 : 1). Starting material (185 mg, 426 μmol, 0.43 eq) could be reisolated.

Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (286), *cis*-product, minor diastereoisomer

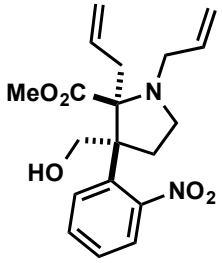
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.8 Hz, 1H), 7.42 (ddd, J_1 = 8.3 Hz, J_2 = 6.7 Hz, J_3 = 1.6 Hz, 1H), 7.33 - 7.28 (m, 2H), 5.80 (dddd, J_1 = 17.0 Hz, J_2 = 10.1 Hz, J_3 = 6.2 Hz, J_4 = 6.2 Hz, 1H), 5.62 - 5.51 (m, 1H), 5.16 (ddd, J_1 = 17.1 Hz, J_2 = 3.3 Hz, J_3 = 1.6 Hz, 1H), 5.06 - 5.03 (m, 1H), 4.76 (bd, *J* = 10.2 Hz, 1H), 4.52 - 4.47 (m, 1H), 4.14 (d, *J* = 9.9 Hz, 1H), 3.78 (s, 3H), 3.70 (d, *J* = 9.9 Hz, 1H), 3.24 (dd, J_1 = 14.2 Hz, J_2 = 6.0 Hz, 1H), 3.13 (dd, J_1 = 14.3 Hz, J_2 = 6.1 Hz, 1H), 3.02 (dd, J_1 = 16.2 Hz, J_2 = 8.0 Hz, 1H), 2.91 - 2.86 (m, 1H), 2.60 - 2.49 (m, 2H), 2.31 - 2.24 (m, 1H), 2.04 (ddd, J_1 = 12.4 Hz, J_2 = 7.7 Hz, J_3 = 2.6 Hz, 1H), 0.74 (s, 9H), –0.22 (s, 3H), –0.36 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4, 152.2, 136.9, 134.5, 134.0, 129.1, 127.4, 125.7, 123.5, 117.8, 115.9, 76.0, 67.7, 60.3, 53.4, 52.3, 48.6, 39.4, 30.5, 26.1, 18.5, -5.5, -6.2 ppm.

HRMS (ESI): calc. for $C_{25}H_{39}N_2O_5Si^+$: 475.2628, found: 475.2628


TBAF, 0°C
THF
TBAF, rt
THF
a) Pd(PPh3)4, DMBA
DCM, reflux
b) Boc2O, DMAP
MeCN
TBAF, 0°C
THF
O3, -78°C
MeOH/DCM
then NaBH4, rt
NH4F, MeOH
rt
1 eq Boc2O
DMAP, MeCN
3 eq Boc2O
DMAP, MeCN
287
286
280
281
290
288
289
292
291
293

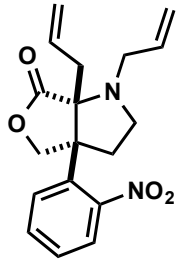
Methyl 1,2-diallyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (281)



Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-, major diastereoisomer (19.0 mg, 40.0 μmol, 1 eq) was dissolved in absolute THF (2 mL). TBAF (200 μL, 200 μmol, 5 eq, 1 mol/L solution in THF) was added dropwise and the resulting mixture was stirred at rt for 9h. H_2O (25 mL) was added and the aqueous pahse was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain methyl 1,2-diallyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (10.0 mg, 28.0 μmol, 0.7 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51 - 7.48 (m, 1H), 7.41 - 7.36 (m, 2H), 7.34 - 7.30 (m, 1H), 6.24 - 6.13 (m, 1H), 5.81 - 5.71 (m, 1H), 5.36 - 5.31 (m, 1H), 5.21 - 5.14 (m, 2H), 5.11 - 5.08 (m, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.53 - 3.41 (m, 2H), 3.37 (s, 3H), 3.33 - 3.28 (m, 2H), 3.16 (dd, J_1 = 16.2 Hz, J_2 = 8.3 Hz, 1H), 2.60 - 2.52 (m, 2H), 2.48 - 2.34 (m, 2H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.6, 151.7, 135.1, 134.8, 134.5, 130.3, 129.2, 127.8, 125.0, 118.3, 117.2, 77.3, 67.5, 58.1, 53.5, 51.4, 50.8, 37.0, 31.1 ppm.
HRMS (ESI): calc. for $C_{19}H_{25}N_2O_5^+$: 361.1763, found: 361.1762

1,6a-Diallyl-3a-(2-nitrophenyl)hexahydro-6*H*-furo[3,4-*b*]pyrrol-6-one (287)



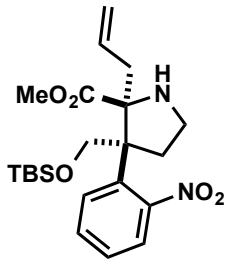
Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate, minor diastereoisomer (26.0 mg, 55.0 μmol, 1 eq) was dissolved in absolute THF (5 mL) and cooled to 0°C. TBAF (274 μL, 274 μmol, 5 eq, 1 mol/L solution in THF) was added dropwise and the resulting mixture was stirred at 0°C for 3h. The reaction mixture was allowed to warm up to rt and was stirred for additional 2h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude lactone was purified by flash column chromatography (SiO_2, PE/EtOAc = 20:1 to 10:1) to obtain 1,6a-diallyl-3a-(2-nitrophenyl)hexahydro-6*H*-furo[3,4-*b*]pyrrol-6-one (5.00 mg, 15.0 μmol, 0.27 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.59 (ddd, J_1 = 8.0 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 7.50 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.41 (ddd, J_1 = 8.2 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 5.94 - 5.84 (m, 1H), 5.30 - 5.13 (m, 3H), 4.89 (bd, J = 10.2 Hz, 1H), 4.52 - 4.45 (m, 2H), 4.22 (d, J = 9.2 Hz, 1H), 3.81 (dddd, J_1 = 14.3 Hz, J_2 = 4.3 Hz, J_3 = 2.1 Hz, J_4 = 2.1 Hz, 1H), 3.37 - 3.29 (m, 2H), 2.68 (bdd, J_1 = 13.8 Hz, J_2 = 7.0 Hz, 1H), 2.56 - 2.45 (m, 2H), 2.41 - 2.33 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.8, 149.8, 136.5, 135.9, 131.7, 130.8, 129.6, 128.1, 124.0, 120.8, 116.8, 75.3, 74.0, 54.9, 51.1, 50.1, 40.5, 35.6 ppm.

HRMS (ESI): calc. for $C_{18}H_{21}N_2O_4^+$: 329.1501, found: 329.1501

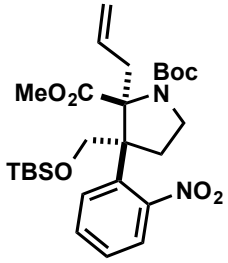
Methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (290)



$Pd(PPh_3)_4$ (20.0 mg, 17.0 μmol, 0.1 eq) and dimethylbarbituric acid (53.0 mg, 337 μmol, 2 eq) were put in a Schlenk tube under argon. Methyl 1,2-diallyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-, major diastereoisomer, (80.0 mg, 169 μmol, 1 eq) dissolved in degassed absolute DCM (8 mL) was added and the reaction mixture was heated to reflux for 40min. After cooling down to rt aqueous NH_4OH (50 mL) was added and the aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The secondary amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (63.0 mg, 145 μmol, 0.86 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, J_1 = 8.0 Hz, J_2 = 0.5 Hz, 1H), 7.41 (ddd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, J_3 = 2.5 Hz, 1H), 7.34 - 7.28 (m, 2H), 6.00 - 5.90 (m, 1H), 5.17 - 5.07 (m, 2H), 4.14 (d, J = 10.2 Hz, 1H), 3.89 (d, J = 10.2 Hz, 1H), 3.32 (s, 3H), 3.29 - 3.24 (m, 1H), 3.19 (ddd, J_1 = 10.2 Hz, J_2 = 10.2 Hz, J_3 = 3.4 Hz, 1H), 3.09 (ddd, J_1 = 9.9 Hz, J_2 = 8.0 Hz, J_3 = 8.0 Hz, 1H), 2.72 (dd, J_1 = 13.6 Hz, J_2 = 8.9 Hz, 1H), 2.46 (ddd, J_1 = 12.5 Hz, J_2 = 10.2 Hz, J_3 = 7.6 Hz, 1H), 2.30 (ddd, J_1 = 12.4 Hz, J_2 = 8.6 Hz, J_3 = 3.5 Hz, 1H), 0.81 (s, 9H), −0.01 (s, 3H), −0.06 (s, 3H) ppm.

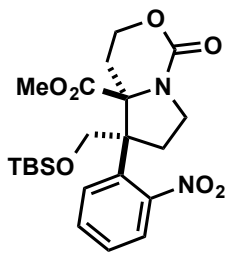
1-(*tert*-Butyl) 2-methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (288)



Methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (63.0 mg, 145 μmol, 1 eq) was dissolved in absolute MeCN (4 mL). DMAP (2.00 mg, 17.0 μmol, 0.12 eq) followed by di-*tert*-butyl dicarbonate (55.0 mg, 253 μmol, 1.7 eq) were added and the reaction mixture was stirred at rt for 20h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain 1-(*tert*-butyl) 2-methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (63.0 mg, 118 μmol, 0.81 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.69 - 7.58 (m, 1H), 7.49 - 7.22 (m, 3H), 6.05 - 5.82 (m, 1H), 5.35 - 5.24 (m, 1H), 5.18 - 5.11 (m, 1H), 4.10 (d, *J* = 10.1 Hz, 1H), 3.95 - 3.82 (m, 2H), 3.70 - 3.38 (m, 2H), 3.29 - 3.28 (m, 3H), 3.19 (bdd, J_1 = 16.1 Hz, J_2 = 7.8 Hz, 1H), 2.73 - 2.56 (m, 1H), 2.32 (dd, J_1 = 12.1 Hz, J_2 = 5.6 Hz, 1H), 1.55 - 1.52 (m, 9H), 0.76 (s, 9H), −0.13 (s, 3H), −0.15 (s, 3H) ppm.

Methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-nitrophenyl)-1-oxo-tetra-hydro-1*H*-pyrrolo[1,2-*c*]oxazine-4a(5*H*)-carboxylate (289)



1-(*tert*-Butyl) 2-methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (21.0 mg, 39.0 μmol, 1 eq) was dissolved in DCM/MeOH = 4:1 (5 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until its blue colour disappeared. MeOH (3 mL) followed by $NaBH_4$ (5.00 mg, 118 μmol, 3 eq) was added and the reaction mixture was allowed to warm up to rt. After stirring at rt for 1h H_2O (25 mL) was added. The aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-nitrophenyl)-1-oxotetra-hydro-1*H*-pyrrolo-[1,2-*c*]oxazine-4a(5*H*)-carboxylate (10.0 mg, 22.0 μmol, 0.56 eq) as a colourless foam.

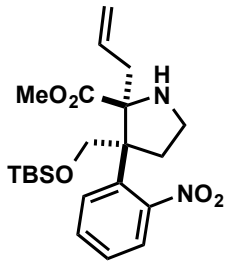
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (bd, *J* = 7.8 Hz, 1H), 7.46 - 7.41 (m, 1H), 7.40 - 7.36 (m, 2H), 4.42 (ddd, J_1 = 11.6 Hz, J_2 = 4.8 Hz, J_3 = 2.1 Hz, 1H), 4.26 - 4.20 (m, 1H), 3.98 (bd, *J* = 10.9 Hz, 1H), 3.86 - 3.78 (m, 2H), 3.65 (ddd, J_1 = 10.8 Hz, J_2 = 10.8 Hz, J_3 = 1.9 Hz, 1H), 3.40 (s, 3H), 2.90 (bd, *J* = 14.0 Hz, 1H), 2.66 - 2.53 (m, 2H), 2.31 - 2.25 (m, 1H), 0.80 (s, 9H), −0.06 (s, 3H), −0.18 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1, 152.0, 151.6, 131.8, 131.4, 129.9, 128.7, 124.3, 72.7, 64.7, 59.3, 52.8, 46.3, 29.9, 28.2, 27.9, 25.9, 18.2, -5.6, -5.8 ppm.

IR (film): 2953, 2927, 2856, 1734, 1693, 1529, 1471, 1421, 1354, 1251, 1211, 1139, 1087, 1006, 987, 939, 835, 775, 752, 682, 667, 555, 418 cm^{-1}.

HRMS (ESI): calc. for $C_{22}H_{33}N_2O_7Si^+$: 465.2057, found: 465.2065

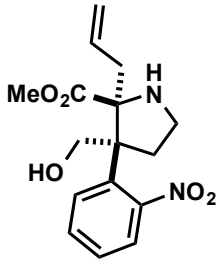
Methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (290)



1-(*tert*-Butyl) 2-methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (25.0 mg, 47.0 μmol, 1 eq) was dissolved in absolute THF (2 mL) and was cooled to 0°C. TBAF (234 μL, 234 μmol, 5 eq, 1mol/L solution in THF) was added dropwise and the resulting mixture was stirred at 0°C for 4.5h. H_2O (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1) to obtain methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (6.00 mg, 14.0 μmol, 0.3 eq) as a colourless foam next to starting material (12.0 mg, 22.4 μmol, 0.48 eq).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, J_1 = 8.0 Hz, J_2 = 0.5 Hz, 1H), 7.41 (ddd, J_1 = 8.1 Hz, J_2 = 6.4 Hz, J_3 = 2.5 Hz, 1H), 7.34 - 7.28 (m, 2H), 6.00 - 5.90 (m, 1H), 5.17 - 5.07 (m, 2H), 4.14 (d, J = 10.2 Hz, 1H), 3.89 (d, J = 10.2 Hz, 1H), 3.32 (s, 3H), 3.29 - 3.24 (m, 1H), 3.19 (ddd, J_1 = 10.2 Hz, J_2 = 10.2 Hz, J_3 = 3.4 Hz, 1H), 3.09 (ddd, J_1 = 9.9 Hz, J_2 = 8.0 Hz, J_3 = 8.0 Hz, 1H), 2.72 (dd, J_1 = 13.6 Hz, J_2 = 8.9 Hz, 1H), 2.46 (ddd, J_1 = 12.5 Hz, J_2 = 10.2 Hz, J_3 = 7.6 Hz, 1H), 2.30 (ddd, J_1 = 12.4 Hz, J_2 = 8.6 Hz, J_3 = 3.5 Hz, 1H), 0.81 (s, 9H), −0.01 (s, 3H), −0.06 (s, 3H) ppm.

Methyl 2-allyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (291)



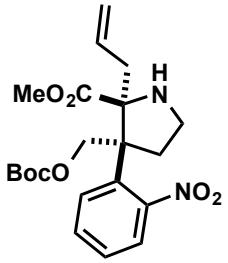
1-(*tert*-Butyl) 2-methyl 2-allyl-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (12.0 mg, 22.0 μmol, 1 eq) was dissolved in MeOH (1 mL). NH_4F (83.0 mg, 2.24 mmol, 100 eq) was added and the resulting mixture was stirred at rt for 18h. H_2O (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain methyl 2-allyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (5.00 mg, 16.0 μmol, 0.73 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.38 - 7.34 (m, 2H), 5.83 - 5.73 (m, 1H), 5.25 - 5.14 (m, 2H), 4.10 (d, *J* = 11.3 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 1H), 3.38 (s, 3H), 3.27 (ddd, J_1 = 9.4 Hz, J_2 = 9.4 Hz, J_3 = 5.1 Hz, 1H), 3.21 - 3.12 (m, 2H), 2.68 (dd, J_1 = 13.0 Hz, J_2 = 8.5 Hz, 1H), 2.50 - 2.39 (m, 2H), ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.6, 151.8, 133.2, 133.0, 130.7, 130.3, 128.2, 124.5, 120.1, 75.2, 68.0, 56.4, 52.1, 42.7, 39.6, 31.8 ppm.

HRMS (ESI): calc. for $C_{16}H_{21}N_2O_5^+$: 321.1450, found: 321.1451

Methyl 2-allyl-3-(((*tert*-butoxycyrbonyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (292)

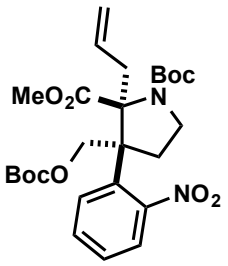


2-Allyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (11.0 mg, 34.0 μmol, 1 eq) was dissolved in MeCN (1 mL). DMAP (500 μg, 4.00 μmol, 0.1 eq) and di-*tert*-butyl dicarbonate (7.40 mg, 34.0 μmol, 1 eq) were added. The reaction mixture was stirred at rt for 3h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 0:1) to obtain methyl 2-allyl-3-(((*tert*-butoxycyrbonyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (6.00 mg, 14.0 μmol, 0.41 eq) as a colourless foam in addition to starting material (4.00 mg, 13.0 μmol, 0.38 eq).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 7.47 (ddd, J_1 = 8.4 Hz, J_2 = 6.6 Hz, J_3 = 1.9 Hz, 1H), 7.37 - 7.30 (m, 2H), 5.81 - 5.70 (m, 1H), 5.16 - 5.08 (m, 2H), 4.73 (dd, J_1 = 11.4 Hz, J_2 = 0.9 Hz, 1H), 4.38 (d, J = 11.3 Hz, 1H), 3.32 (s, 3H), 3.28 (ddd, J_1 = 10.0 Hz, J_2 = 10.0 Hz, J_3 = 3.2 Hz, 1H), 3.18 - 3.10 (m, 2H), 2.52 - 2.40 (m, 2H), 2.32 (ddd, J_1 = 13.1 Hz, J_2 = 8.0 Hz, J_3 = 3.2 Hz, 1H), 1.40 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.6, 153.4, 151.9, 133.8, 132.1, 131.2, 130.1, 128.2, 124.3, 119.2, 82.6, 76.1, 69.5, 56.0, 52.1, 43.4, 38.9, 33.1, 27.8 ppm.

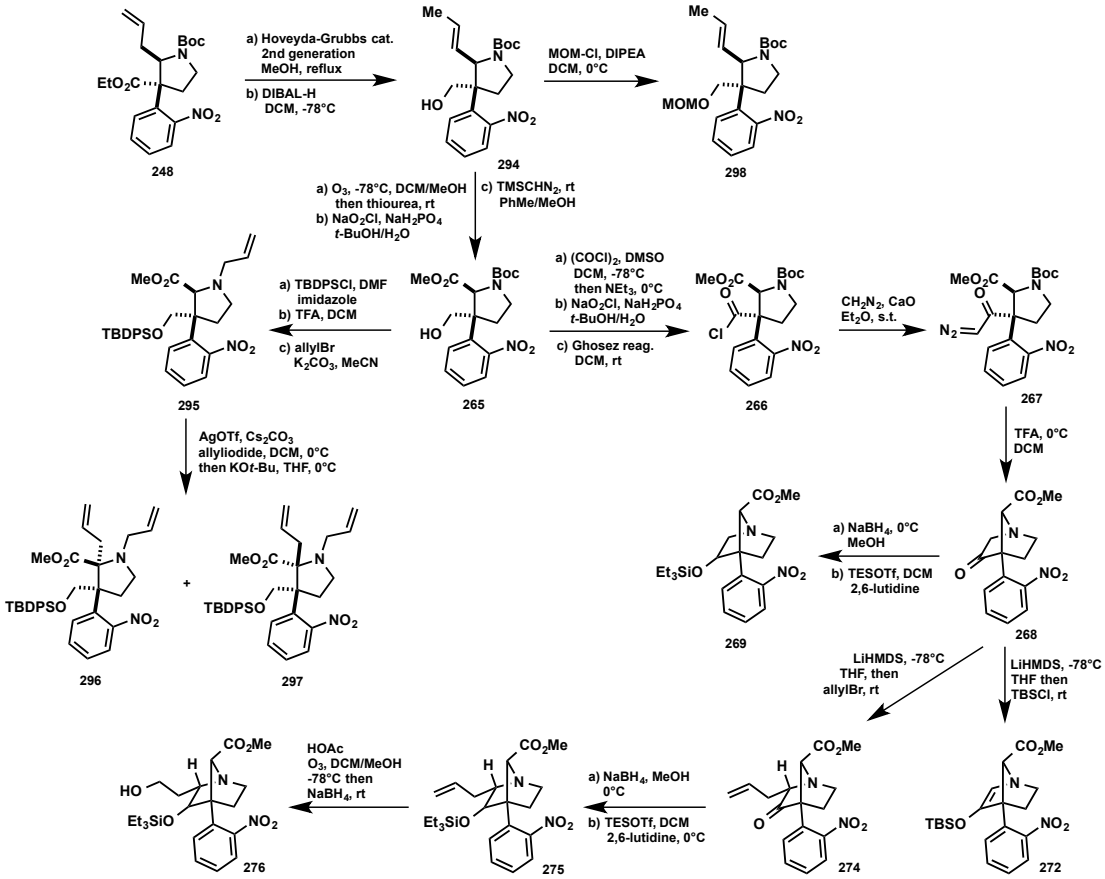
1-(*tert*-Butyl) 2-methyl 2-allyl-3-(((*tert*-butoxycarbonyl)oxy)methyl)-3-(2-nitro-phenyl)pyrrolidine-1,2-dicarboxylate (293)



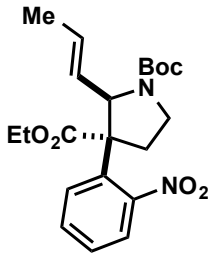
2-Allyl-3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (16.0 mg, 50.0 μmol, 1 eq) was dissolved in MeCN (1 mL). DMAP (500 μg, 4.00 μmol, 0.1 eq) and di-*tert*-butyl dicarbonate (33.0 mg, 150 μmol, 3 eq) were added. The reaction mixture was stirred at rt for 9h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 2-methyl 2-allyl-3-(((*tert*-butoxycarbonyl)oxy)methyl)-3-(2-nitro-phenyl)pyrrolidine-1,2-dicarboxylate (20.0 mg, 38.5 μmol, 0.77 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 - 7.65 (m, 1H), 7.51 - 7.45 (m, 1H), 7.38 (ddd, J_1 = 7.9 Hz, J_2 = 7.4 Hz, J_3 = 1.0 Hz, 1H), 7.29 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 5.94 - 5.80 (m, 1H), 5.37 - 5.32 (m, 1H), 5.22 - 5.17 (m, 1H), 4.60 (dd, J_1 = 11.6 Hz, J_2 = 1.0 Hz, 1H), 4.43 - 4.38 (m, 1H), 4.08 - 3.93 (m, 1H), 3.73 - 3.44 (m, 2H), 3.28 (s, 3H), 3.17 - 3.09 (m, 1H), 2.74 - 2.64 (m, 1H), 2.34 - 2.27 (m, 1H), 1.52 - 1.46 (m, 9H), 1.37 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.7, 153.2, 153.1, 151.4, 147.7, 147.0, 146.2, 132.9, 132.4, 130.9, 130.6, 130.2, 129.9, 129.8, 129.1, 129.1, 124.2, 124.1, 119.6, 119.1, 85.4, 85.3, 82.9, 82.8, 74.9, 74.5, 68.4, 59.6, 58.6, 52.7, 52.6, 46.8, 46.7, 37.2, 35.7, 28.6, 28.0, 27.7, 27.6, 27.5 ppm.


a) Hoveyda-Grubbs cat. 2nd generation MeOH, reflux
b) DIBAL-H DCM, -78°C
MOM-Cl, DIPEA DCM, 0°C
a) O_3, -78°C, DCM/MeOH then thiourea, rt
b) NaO_2Cl, NaH_2PO_4 t-BuOH/H_2O
c) $TMSCHN_2$, rt PhMe/MeOH
a) TBDPSCl, DMF imidazole
b) TFA, DCM
c) allylBr K_2CO_3, MeCN
a) $(COCl)_2$, DMSO DCM, -78°C then NEt_3, 0°C
b) NaO_2Cl, NaH_2PO_4 t-BuOH/H_2O
c) Ghosez reag. DCM, rt
CH_2N_2, CaO Et_2O, s.t.
TFA, 0°C DCM
AgOTf, Cs_2CO_3 allyliodide, DCM, 0°C then KOt-Bu, THF, 0°C
a) $NaBH_4$, 0°C MeOH
b) TESOTf, DCM 2,6-lutidine
LiHMDS, -78°C THF, then allylBr, rt
LiHMDS, -78°C THF then TBSCl, rt
HOAc O_3, DCM/MeOH -78°C then $NaBH_4$, rt
a) $NaBH_4$, MeOH 0°C
b) TESOTf, DCM 2,6-lutidine, 0°C
248
294
298
295
265
266
267
296
297
269
268
276
275
274
272

1-(*tert*-Butyl) 3-ethyl 3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,3-dicarboxylate (294a)



1-(*tert*-Butyl) 3-ethyl 2-allyl-3-(2-nitrophenyl)pyrrolidine-1,3-dicarboxylate (33.6 g, 83.1 mmol, 1 eq) was dissolved in absolute MeOH (800 mL). Hoveyda-Grubbs catalyst 2nd generation (521 mg, 830 μmol, 0.01 eq) was added and the mixture was heated to reflux for 4h. Additional Hoveyda-Grubbs catalyst 2nd generation (521 mg, 830 μmol, 0.01 eq) was added and the mixture was heated to reflux for 8h. After cooling to rt the solvent was removed under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 3-ethyl 3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,3-dicarboxylate as a colourless viscous fluid. The material was used for the next step without further purifications.

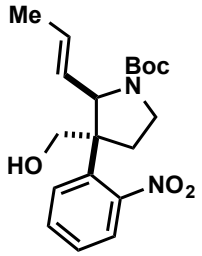
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.64 - 7.58 (m, 1H), 7.55 - 7.50 (m, 1H), 7.44 (dd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, 1H), 5.56 - 5.38 (m, 1H), 5.09 - 4.91 (m, 1H), 4.75 - 4.56 (m, 1H), 4.20 . 4.14 (m, 2H), 3.62 - 3.52 (m, 1H), 3.41 - 3.34 (m, 1H), 2.68 - 2.60 (m, 1H), 2.52 - 2.43 (m, 1H), 1.46 - 1.44 (m, 9H), 1.39 (dd, J_1 = 6.5 Hz, J_2 = 1.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.9, 172.8, 155.0, 154.3, 149.5, 149.3, 133.9, 133.8, 133.3, 133.0, 130.6, 130.6, 130.1, 129.9, 128.6, 127.0, 126.9, 125.3, 79.7, 79.4, 63.0, 62.8, 61.8, 61.7, 59.5, 58.8, 44.0, 43.3, 33.8, 33.4, 28.7, 28.6, 17.7, 17.5, 14.1 ppm.

IR (film): 2976, 2933, 2893, 1732, 1689, 1608, 1575, 1527, 1477, 1454, 1388, 1363, 1352, 1303, 1259, 1217, 1176, 1122, 1082, 1024, 962, 921, 896, 852, 785, 767, 731, 709, 692, 636 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{28}N_2O_6Na^+$: 427.1845, found: 427.1845

***tert*-Butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1-carboxylate (294)**



The crude ethyl ester was dissolved in absolute DCM (1 L) and cooled to -78 °C. Diisobutylaluminium hydride (498 mL, 498 mmol, 6 eq, 1 mol/L solution in hexane) was transferred to a dropping funnel and added dropwise over a period of 2h. The mixture was poured onto a saturated Na/K-tartrate solution (2 L) and was allowed to warm up to rt. Et_2O (2 L) was added and the resulting mixture was vigourously stirred for 48h at rt. The organic phase was seperated and the aqueous phase extrated with Et_2O (2x500 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain *tert*-butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate as a colourless viscous fluid. The material was used for the next step without further purifications.

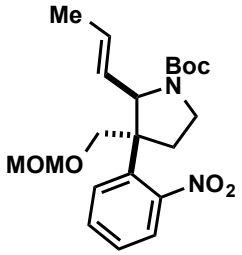
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 - 7.49 (m, 2H), 7.43 - 7.35 (m, 2H), 5.65 - 5.48 (m, 1H), 4.92 - 4.81 (m, 1H), 4.69 - 4.47 (m, 1H), 4.23 - 4.07 (m, 1H), 3.68 (d, J = 10.9 Hz, 1H), 3.53 - 3.38 (m, 2H), 2.70 - 2.54 (m, 1H), 2.17 - 2.08 (m, 1H), 1.95 - 1.70 (m, 1H), 1.49 (dd, J_1 = 6.7 Hz, J_2 = 1.5 Hz, 3H), 1.45 - 1.43 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.7, 154.2, 151.6, 151.3, 134.7, 134.1, 133.6, 133.4, 131.7, 131.3, 131.2, 130.6, 128.1, 128.0, 126.1, 126.1, 125.3, 124.8, 79.9, 79.7, 66.1, 65.5, 62.8, 62.5, 56.0, 55.2, 43.2, 42.5, 29.2, 28.7, 24.0, 18.0, 17.8 ppm.

IR (film): 3419 (bs), 2976, 2933, 2891, 1666, 1604, 1573, 1527, 1477, 1454, 1398, 1365, 1354, 1292, 1257, 1172, 1153, 1126, 1072, 1043, 962, 902, 848, 781, 734, 711, 682, 644 cm^{-1}.

HRMS (ESI): calc. $C_{19}H_{27}N_2O_5^+$: 363.1920, found: 363.1920

***tert*-Butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (298)**



The crude alcohol was dissolved in absolute DCM (500 mL) and cooled to 0°C. *N*,*N*-Diisopropylethylamine (174 mL, 128 g, 997 mmol, 12 eq) and chloromethyl methyl ether (63.1 mL, 66.9 g, 830 mmol, 10 eq) were sequentially added. The mixture was stirred for 20 h and allowed to warm up to rt during this time. Additional *N*,*N*-diisopropylethylamine (58.1 mL, 43.0 g, 332 mmol, 4 eq) and chloromethyl methyl ether (18.9 mL, 20.0 g, 249 mmol, 3 eq) were added at rt and the mixture was stirred for 18h. Water (1 L) was added and the organic phase was seperated. The aqueous phase was extracted with DCM (2x300 mL), the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain *tert*-butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (27.4 g, 67.4 mmol, 0.81 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 - 7.54 (m, 1H), 7.52 - 7.41 (m, 2H), 7.39 - 7.33 (m, 1H), 5.65 - 5.48 (m, 1H), 4.94 - 4.82 (m, 1H), 4.80 - 4.53 (m, 1H), 4.49 - 4.42 (m, 2H), 4.13 - 3.97 (m, 1H), 3.65 - 3.62 (m, 1H), 3.55 - 3.40 (m, 2H), 3.15 - 3.14 (m, 3H), 2.70 - 2.49 (m, 1H), 2.23 - 2.13 (m, 1H), 1.49 (dd, J_1 = 6.6 Hz, J_2 = 1.5 Hz, 3H), 1.46 - 1.44 (m, 9H) ppm.

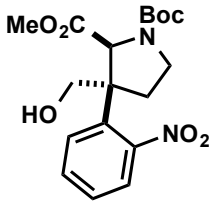
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.6, 153.9, 151.3, 151.0, 135.2, 134.4, 133.8, 133.5, 131.4, 130.9, 130.9, 130.2, 127.9, 127.8, 126.3, 126.1, 125.1,

124.5, 96.5, 79.7, 79.5, 70.1, 69.8, 63.0, 62.5, 55.3, 55.2, 54.4, 53.5, 43.2, 42.5, 29.7, 28.7, 18.0, 17.8 ppm.

IR (film): 2974, 2931, 2887, 2823, 1691, 1529, 1477, 1454, 1394, 1363, 1292, 1255, 1174, 1149, 1111, 1045, 960, 918, 848, 781, 732, 711, 684 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{30}N_2O_5Na^+$: 429.2002, found: 429.2002

1-(*tert*-Butyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (265)



tert-Butyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (7.35 g, 20.3 mmol, 1 eq) was dissolved in DCM/MeOH = 3:1 (160 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until the blue colour disappeared. Thiourea (1.54 g, 20.3 mmol, 1 eq) was added and the reaction mixture was allowed to warm up to rt. After stirring at rt for 2h the mixture was poured onto H_2O (500 mL). The aqueous phase was extracted with DCM (2x200 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure.

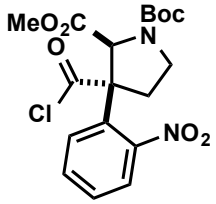
The crude aldehyde was dissolved in *t*BuOH (80 mL) and 2-methyl-2-butene (40 mL) was added. $NaOCl_2$ (18.3 g, 203 mmol, 10 eq) and NaH_2PO_4*H_2O (18.3 g, 133 mmol, 6.55 eq) dissolved in H_2O (80 mL) were added to the mixture. After stirring at rt for 8h the reaction miture was poured onto H_2O (500 mL) and the aqueous phase was extracted with EtOAc (3x200 mL). The combined organic phases were washed with brine (200 mL), dired over $MgSO_4$, filtrated and concentrated under reduced pressure.

The crude carboxylic acid was dissolved in PhMe/MeOH = 3:1 (120 mL). $TMSCHN_2$ (10.1 mL, 20.3 mmol, 1 eq, 2 mol/L solution in hexane) was added dropwise and the resulting mixture was stirred at rt for 10min. The solvent was

removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1 to 0:1) to obtain 1-(*tert*-butyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (6.45 g, 17.0 mmol, 0.84 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.71 - 7.38 (m, 4H), 4.94 - 4.82 (m, 1H), 4.20 - 4.03 (m, 1H), 3.88 - 3.40 (m, 7H), 2.67 - 2.41 (m, 2H), 1.46 - 1.43 (m, 9H) ppm.

1-(*tert*-Butyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (266)



Oxalyl chloride (900 μL, 1.33 g, 10.5 mmol, 2 eq) was dissolved in absolute DCM (20 mL) and was cooled to -78°C. DMSO (1.50 mL, 1.64 g, 21.0 mmol, 4 eq) was added dropwise and was stirred for 15min at -78°C after complete addition. 1-(*tert*-Butyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (2.00 g, 5.26 mmol, 1 eq) dissolved in absolute DCM (30 mL) was added dropwise and the resulting mixture was stirred at -78°C for 75min. NEt_3 (4.40 mL, 3.19 g, 31.5 mmol, 6 eq) was added and the reaction mixture was allowed to warm up to 0°C. After stirring for 1h the reaction mixture was poured onto H_2O (300 mL). The aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1).

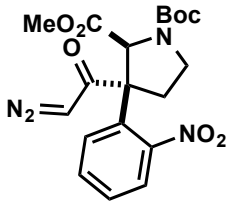
The aldehyde was dissolved in *t*BuOH (50 mL) and 2-metyl-2-butene (10 mL) was added. NaO_2Cl (5.94 g, 52.6 mmol, 10eq, 80%) and NaH_2PO_4*H_2O (5.94 g, 43.0 mmol, 8.2 eq) dissolved in H_2O (50 mL) were added and the resulting mixture was stirred at rt for 25h. The reaction mixture was poured onto H_2O

(250 mL). The aquepous phase was extracted with EtOAc (3x200 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The carboxylic acid was used for the next step without further purification.

The crude carboxylic acid was dissolved in absolute DCM (50 mL). Ghosez reagent (1.40 mL, 1.41 g, 10.5 mmol, 2 eq) was added and the resulting mixture was stirred at rt for 18h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-(*tert*-butyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (1.65 g, 4.00 mmol, 0.76 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.23 - 8.17 (m, 1H), 7.79 - 7.57 (m, 3H), 5.15 - 5.03 (m, 1H), 4.00 - 3.80 (m, 1H), 3.39 (ddd, J_1 = 11.2 Hz, J_2 = 11.2 Hz, J_3 = 5.6 Hz, 1H), 3.19 - 3.18 (m, 3H), 3.07 (ddd, J_1 = 8.5 Hz, J_2 = 11.9 Hz, J_3 = 11.9 Hz, 1H), 2.62 (dd, J_1 = 12.5 Hz, J_2 = 5.1 Hz, 1H), 1.47 - 1.39 (m, 9H) ppm.

1-(*tert*-Butyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (267)

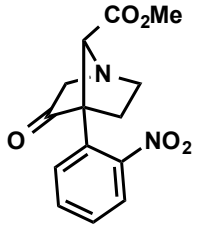


CaO (440 mg, 8.00 mmol, 2 eq) was put in a sealed tube and freshly prepared diazomethane in absolute Et_2O (20 mL, solution prepared started from 5.00 g *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) was added. 1-(*tert*-Butyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (1.65 g, 4.00 mmol, 1 eq) dissolved in absolute Et_2O (5 mL) was added and the tube was sealed. After stirring at rt for 2.5d the solids were removed by filtration over celite and the solvent was removed under reduced pressure. The crude diazo carbonyl was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1

to 1:1 to 0:1) to obtain 1-(*tert*-butyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (1.34 g, 3.32 mmol, 0.83 eq) as a slightly yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.11 - 8.07 (m, 1H), 7.70 - 7.52 (m, 3H), 5.16 - 5.08 (m, 1H), 5.03 - 5.01 (m, 1H), 3.88 - 3.74 (m, 1H), 3.43 - 3.35 (m, 1H), 3.20 - 3.18 (m, 3H), 3.02 - 2.89 (m, 1H), 2.35 - 2.29 (m, 1H), 1.46 - 1.39 (m, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 191.4, 191.1, 171.5, 171.4, 153.9, 153.3, 149.0, 148.7, 134.0, 133.8, 131.7, 131.6, 130.6, 129.9, 129.9, 126.2, 126.1, 80.8, 80.6, 63.2, 62.3, 62.0, 53.6, 53.5, 51.8, 51.7, 43.8, 43.3, 34.1, 33.4, 28.5, 28.4, 14.3 ppm.
IR (film): 3089, 2980, 2895, 2110, 1743, 1689, 1639, 1606, 1575, 1531, 1477, 1454, 1435, 1394, 1342, 1292, 1276, 1236, 1213, 1170, 1151, 1136, 1087, 1053, 1016, 993, 912, 854, 819, 786, 771, 729, 711, 686, 669, 648, 636, 613, 586, 536, 520, 416 cm^{-1}.
HRMS (ESI): calcd for $C_{19}H_{22}N_4O_7Na^+$: 441.1386; found 441.1390

Methyl 4-(2-nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (268)

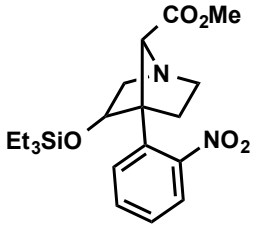


1-(*tert*-Butyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (756 mg, 1.81 mmol, 1 eq) was dissolved in absolute DCM (50 mL) and cooled to 0°C. TFA (4.20 mL, 6.18 g, 45.2 mmol, 30 eq) was added dropwise and the resulting mixture was allowed to warm up to rt and was stirred for 2h. The reaction mixture was poured onto aqueous K_2CO_3 (200 mL). The aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtrated and concetrated under reduced pressure. The crude product was purified by

flash column chromatography (SiO_2, EtOAc) to obtain methyl 4-(2-nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (395 mg, 1.36 mmol, 0.75 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.65 (ddd, J_1 = 7.9 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 7.60 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.51 (ddd, J_1 = 8.2 Hz, J_2 = 7.2 Hz, J_3 = 1.5 Hz, 1H), 4.74 (s, 1H), 3.64 - 3.53 (m, 5H), 3.24 (d, J = 17.1 Hz, 1H), 2.92 - 2.79 (m, 2H), 2.11 - 2.04 (m, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 213.0, 168.4, 149.4, 133.4, 132.1, 129.4, 129.0, 126.1, 72.8, 67.6, 62.8, 52.4, 51.2, 30.3 ppm.
IR (film): 2954, 2926, 2854, 1747, 1683, 1653, 1606, 1525, 1473, 1456, 1436, 1419, 1354, 1265, 1224, 1184, 1134, 1080, 1066, 1014, 948, 852, 788, 758, 729, 698, 565, 491 cm^{-1}.
HRMS (ESI): calc. for $C_{14}H_{15}N_2O_5^+$: 291.0981, found: 291.0979

Methyl 4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo[2.2.1]-heptane-7-carboxylate (269)



4-(2-Nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (12.0 mg, 41.0 μmol, 1 eq) was dissolved in MeOH (1 mL) and cooled to 0°C. $NaBH_4$ (2.00 mg, 50.0 μmol, 1.2 eq) was added and the resulting mixture was stirred at 0°C for 75min. H_2O (25 mL) was added and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure.
The crude alcohol was dissolved in absolute DCM (1 mL). 2,6-Lutidine (30.0 μL, 27.0 mg, 248 μmol, 6 eq) and triethylsilyl trifluoromethanesulfonate (30.0 μL, 33.0 mg, 124 μmol, 3 eq) were sequentially added and the resulting mixture was stirred at rt for 28h. The reaction mixture war poured onto

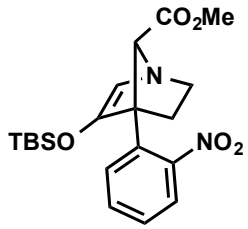
aqueous $NaHCO_3$ (25 mL) and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain methyl 4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo[2.2.1]-heptane-7-carboxylate (11.0 mg, 27.1 μmol, 0.66 eq) as a mixture of diastereoisomers (dr = 2:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 - 7.30 (m, 4H), 4.88 - 4.24 (m, 1H), 4.09 - 4.03 (m, 1H), 3.65 - 3.57 (m, 3H), 3.36 - 3.01 (m, 2H), 2.92 - 2.55 (m, 2H), 2.32 - 2.10 (m, 1H), 1.81 - 1.60 (m, 2H), 0.78 - 0.68 (m, 9H), 0.43 - 0.23 (m, 6H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.7, 169.2, 152.0, 150.5, 133.5, 133.1, 132.1, 131.6, 130.8, 130.3, 127.5, 127.5, 124.2, 123.5, 77.9, 77.8, 71.3, 71.2, 69.5, 69.4, 68.1, 68.1, 64.5, 64.4, 60.2, 60.1, 53.9, 53.7, 52.5, 52.4, 52.2, 52.1, 26.4, 23.6, 4.6, 4.5 ppm.

HRMS (ESI): calc. for $C_{20}H_{31}N_2O_5Si^+$: 407.2002, found: 407.2004

Methyl 3-((*tert*-butyldimethylsilyl)oxy)-4-(2-nitrophenyl)-1-azabicyclo-[2.2.1]hept-2-ene-7-carboxylate (272)

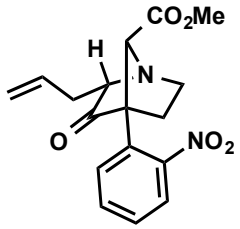


LiHMDS (90.0 μL, 90.0 μmol, 1.2 eq, 1 mol/L solution in THF) was put in a Schlenk tube under argon and cooled to -78°C. 4-(2-Nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (21.0 mg, 72.0 μmol, 1 eq) dissolved in absolute THF (1 mL) was added and the resulting mixture was stirred at -78°C for 15min. *tert*-Butyldimethylsilyl chloride (16.0 mg, 109 μmol, 1.5 eq) was added and the reaction mixture was allowed to warm up to rt over a period of 4h. Aqueous K_2CO_3 (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were dried

over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude silyl enolether was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain methyl 3-((*tert*-butyldimethylsilyl)oxy)-4-(2-nitrophenyl)-1-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (10.0 mg, 25.0 μmol, 0.35 eq) as a colourless foam in addition to starting material (7.00 mg, 24.1 μmol, 0.33 eq).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.83 (bd, *J* = 7.3 Hz, 1H), 7.73 (bd, *J* = 8.0 Hz, 1H), 7.57 (ddd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, J_3 = 1.6 Hz, 1H), 7.42 (ddd, J_1 = 7.9 Hz, J_2 = 7.4 Hz, J_3 = 1.5 Hz, 1H), 5.52 (s, 1H), 4.44 (bs, 1H), 3.59 (s, 3H), 3.48 - 3.36 (m, 1H), 2.70 - 2.57 (m, 2H), 1.91 - 1.76 (m, 1H), 0.67 (s, 9H), 0.10 (s, 3H), 0.01 (s, 3H) ppm.

Methyl 2-allyl-4-(2-nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (274)

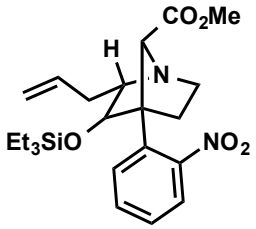


LiHMDS (550 μL, 550 μmol, 1.1 eq, 1 mol/L solution in THF) was dissolved in absolute THF (1 mL) and cooled to -78°C. 4-(2-Nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (146 mg, 503 μmol, 1 eq) dissolved in absolute THF (1.5 mL) was added and the resulting mixture was stirred at -78°C for 30min. Allyl bromide (50.0 μL, 67.0 mg, 553 μmol, 1.1 eq) was added and the reaction mixture was allowed to warm uo to rt over a period of 6h. Aqueous K_2CO_3 (50 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain methyl 2-allyl-4-(2-nitrophenyl)-3-oxo-

1-azabicyclo[2.2.1]heptane-7-carboxylate (12.0 mg, 36.0 μmol, 0.07 eq) as a colourless foam next to starting material (41.0 mg, 141 μmol, 0.28 eq).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 7.66 - 7.61 (m, 2H), 7.52 - 7.47 (m, 1H), 5.95 (dddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.9 Hz, J_4 = 6.9 Hz, 1H), 5.23 (ddd, J_1 = 17.1 Hz, J_2 = 3.1 Hz, J_3 = 1.4 Hz, 1H), 5.16 (ddd, J_1 = 10.2 Hz, J_2 = 2.7 Hz, J_3 = 1.0 Hz, 1H), 4.83 (bs, 1H), 3.67 - 3.60 (m, 4H), 3.16 (dd, J_1 = 9.1 Hz, J_2 = 6.3 Hz, 1H), 2.92 (ddd, J_1 = 12.5 Hz, J_2 = 10.5 Hz, J_3 = 4.9 Hz, 1H), 2.84 (dddd, J_1 = 12.5 Hz, J_2 = 4.6 Hz, J_3 = 8.0 Hz, J_4 = 1.8 Hz, 1H), 2.64 - 2.51 (m, 2H), 2.15 - 2.08 (m, 1H) ppm.

Methyl 2-allyl-4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo[2.2.1]-heptane-7-carboxylate (275)



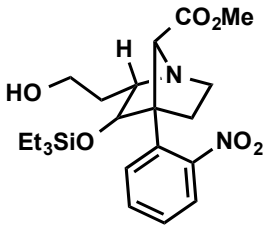
Methyl 2-allyl-4-(2-nitrophenyl)-3-oxo-1-azabicyclo[2.2.1]heptane-7-carboxylate (12.0 mg, 36.0 μmol, 1 eq) was dissolved in MeOH (1 mL) and cooled to 0°C. $NaBH_4$ (1.50 mg, 40 μmol, 1.1 eq) was added and the resulting mixture was stirred at 0°C for 90min. H_2O (25 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure.

The crude alcohol was dissolved in absolute DCM (1 mL) and cooled to 0°C. 2,6-Lutidine (25.0 μL, 23.0 mg, 218 μmol, 6 eq) followed by triethylsilyl trifluoromethanesulfonate (25.0 μL, 29.0 mg, 109 μmol, 3 eq) were added and the resulting mixture was stirred at 0°C for 13h. Aqueous K_2CO_3 (25 mL) was added and the aqueous phase was extracted with DCM (2x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1) to obtain methyl 2-allyl-4-(2-

nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo[2.2.1]heptane-7-carboxylate (6.00 mg, 13.0 μmol, 0.36 eq) as a single diastereoisomer.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.53 (dd, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 7.47 - 7.22 (m, 3H), 6.03 (dddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.8 Hz, J_4 = 6.8 Hz, 1H), 5.19 - 5.06 (m, 2H), 4.25 - 4.13 (m, 2H), 3.62 (s, 3H), 3.16 (ddd, J_1 = 12.3 Hz, J_2 = 10.4 Hz, J_3 = 6.1 Hz, 1H), 2.94 - 2.84 (m, 1H), 2.68 - 2.55 (m, 1H), 2.36 - 2.10 (m, 3H), 1.76 - 1.61 (m, 1H), 0.75 (t, J = 7.9 Hz, 9H), 0.46 - 0.26 (m, 3H), 0.24 - 0.05 (m, 3H) ppm.

Methyl 2-(2-hydroxyethyl)-4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo-[2.2.1]heptane-7-carboxylate (276)

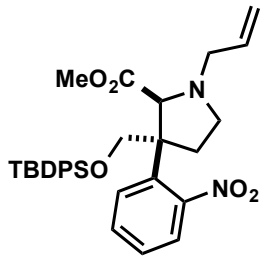


Methyl 2-allyl-4-(2-nitrophenyl)-3-((triethylsilyl)oxy)-1-azabicyclo[2.2.1]-heptane-7-carboxylate (6.00 mg, 13.0 μmol, 1 eq) was dissolved in DCM/MeOH = 3:1 (4 mL). HOAc (0.77 μL, 800 μg, 13.0 μmol, 1 eq) was added and the mixture was cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Then oxygen was passed through the solution until the blue colour disappeared. MeOH (2 mL) was added followed by $NaBH_4$ (2.50 mg, 67.0 μmol, 5 eq). The resulting mixture was allowed to warm up to rt and was stirred for 30min. H_2O (25 mL) was added and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The alcohol was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.43 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.6 Hz, 1H), 7.36 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.5 Hz, 1H), 7.23 (bd, J = 7.5 Hz, 1H), 4.29 - 4.24 (m, 2H), 3.89 - 3.85 (m, 2H), 3.63 (s, 3H), 3.13 - 3.02 (m, 2H), 2.73 - 2.66 (m, 1H), 2.16 (bt, J

= 10.8 Hz, 1H), 2.04 - 1.94 (m, 1H), 1.72 (ddd, J_1 = 12.2 Hz, J_2 = 8.5 Hz, J_3 = 6.6 Hz, 1H), 1.49 - 1.43 (m, 1H), 0.73 (t, J = 8.0 Hz, 9H), 0.39 - 0.29 (m, 3H), 0.20 - 0.10 (m, 3H) ppm.

Methyl 1-allyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (295)



1-(*tert*-Butyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (28.0 mg, 74.0 μmol, 1 eq) was dissolved in absolute DMF (300 μL). Imidazole (15.0 mg, 221 μmol, 3 eq) followed by *tert*-butyldiphenylsilyl chloride (30.0 μL, 30.0 mg, 110 μmol, 1.5 eq) was added and the resulting mixture was stirred at rt for 15h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1) to obtain 1-(*tert*-butyl) 2-methyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (35.0 mg, 57.0 μmol, 0.77 eq) as a colourless oil.

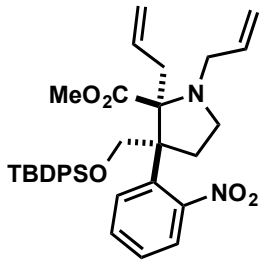
The imide was dissolved in DCM (4 mL) and TFA (1 mL) was added. The resulting mixture was stirred at rt for 90min and was then poured onto aqueous K_2CO_3 (50 mL). The aqueous phase was extracted with DCM (2x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concnetrated under reduced pressure. The secondary amin was used for the next step without further purification.

The crude secondary amine was dissolved in absolute MeCN (1 mL). K_2CO_3 (20.0 mg, 147 μmol, 2 eq) followed by allyl bromide (32.0 μL, 45.0 mg, 368 μmol, 5 eq) was added and the resulting mixture was stirred at rt for 21h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x25

mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude allyl amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1) to obtain methyl 1-allyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (28.0 mg, 50.1 μmol, 0.68 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 - 7.54 (m, 2H), 7.52 - 7.50 (m, 2H), 7.43 - 7.39 (m, 2H), 7.37 - 7.32 (m, 6H), 7.27 - 7.23 (m, 2H), 5.88 - 5.78 (m, 1H), 5.19 (ddd, J_1 = 17.2 Hz, J_2 = 3.3 Hz, J_3 = 1.6 Hz, 1H), 5.12 (ddd, J_1 = 10.3 Hz, J_2 = 2.8 Hz, J_3 = 1.1 Hz, 1H), 4.47 (s, 1H), 4.10 (d, J = 9.6 Hz, 1H), 3.80 (d, J = 9.6 Hz, 1H), 3.47 (s, 3H), 3.28 (dddd, J_1 = 13.8 Hz, J_2 = 5.8 Hz, J_3 = 1.5 Hz, J_4 = 1.5 Hz, 1H), 3.04 - 2.94 (m, 2H), 2.73 (ddd, J_1 = 10.4 Hz, J_2 = 8.9 Hz, J_3 = 4.3 Hz, 1H), 2.35 (ddd, J_1 = 12.6 Hz, J_2 = 10.6 Hz, J_3 = 5.1 Hz, 1H), 1.96 (ddd, J_1 = 12.6 Hz, J_2 = 8.5 Hz, J_3 = 4.1 Hz, 1H), 0.07 (s, 9H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8, 150.8, 136.1, 135.6, 135.5, 135.4, 133.5, 133.1, 133.0, 130.2, 129.7, 129.7, 127.8, 127.7, 127.4, 124.2, 117.0, 69.8, 67.8, 55.9, 54.6, 51.0, 49.4, 30.5, 29.8, 29.7, 26.9, 19.4 ppm.

Methyl 1,2-diallyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (296)



Silver trifluoromethanesulfonate (64.0 mg, 250 μmol, 5 eq) and Cs_2CO_3 (163 mg, 501 μmol, 10 eq) were put in a Schlenk tube under argon and protection of light. Absolute DCM (500 μL) was added and cooled to 0°C. Freshly prepared allyl iodide (23.0 μL, 42.0 mg, 250 μmol, 5 eq) dissolved in absolute DCM (1 mL) was added and the mixture was stirred for 1min at 0°C. 1-Allyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate

(28.0 mg, 50.1 μmol, 1 eq) dissolved in absolute DCM (2 mL) was added to the suspension and stirred at 0°C for 1h. The mixture was allowed to warm up to rt. The solids were removed by filtration over celite in a flask containing solid K_2CO_3 (69.0 mg, 501 μmol, 10 eq). The solvent was removed under reduced pressure and the crude ammonium salt was dried under high vacuum for 15min.

The ammonium salt was dissolved in absolute THF (5 mL) and cooled to 0°C. KO*t*Bu (60.0 μL, 60.0 μmol, 1.2 eq, 1 mol/L solution in *t*BuOH) was added dropwise and the resulting mixture was stirred at 0°C for 1h. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography (SiO_2, PE/EtOAc = 20:1 to 10:1) to obtain methyl 1,2-diallyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (16.0 mg, 27.0 μmol, 0.54 eq) as a mixture of diastereoisomers (dr = 7:1).

Methyl 1,2-diallyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (296), *trans*-product, major

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55 - 7.24 (m, 14H), 5.95 (dddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.8 Hz, J_4 = 6.8 Hz, 1H), 5.75 - 5.65 (m, 1H), 5.10 - 4.98 (m, 3H), 4.90 - 4.87 (m, 1H), 4.22 (d, J = 10.6 Hz, 1H), 3.96 (d, J = 10.6 Hz, 1H), 3.38 - 3.32 (m, 4H), 3.24 - 3.06 (m, 3H),2.65 (dd, J_1 = 13.8 Hz, J_2 = 7.7 Hz, 1H), 2.56 (ddd, J_1 = 10.8 Hz, J_2 = 8.8 Hz, J_3 = 3.2 Hz, 1H), 2.45 - 2.38 (m, 1H), 2.11 (ddd, J_1 = 12.4 Hz, J_2 = 8.6 Hz, J_3 = 3.5 Hz, 1H), 0.92 (s, 9H) ppm.

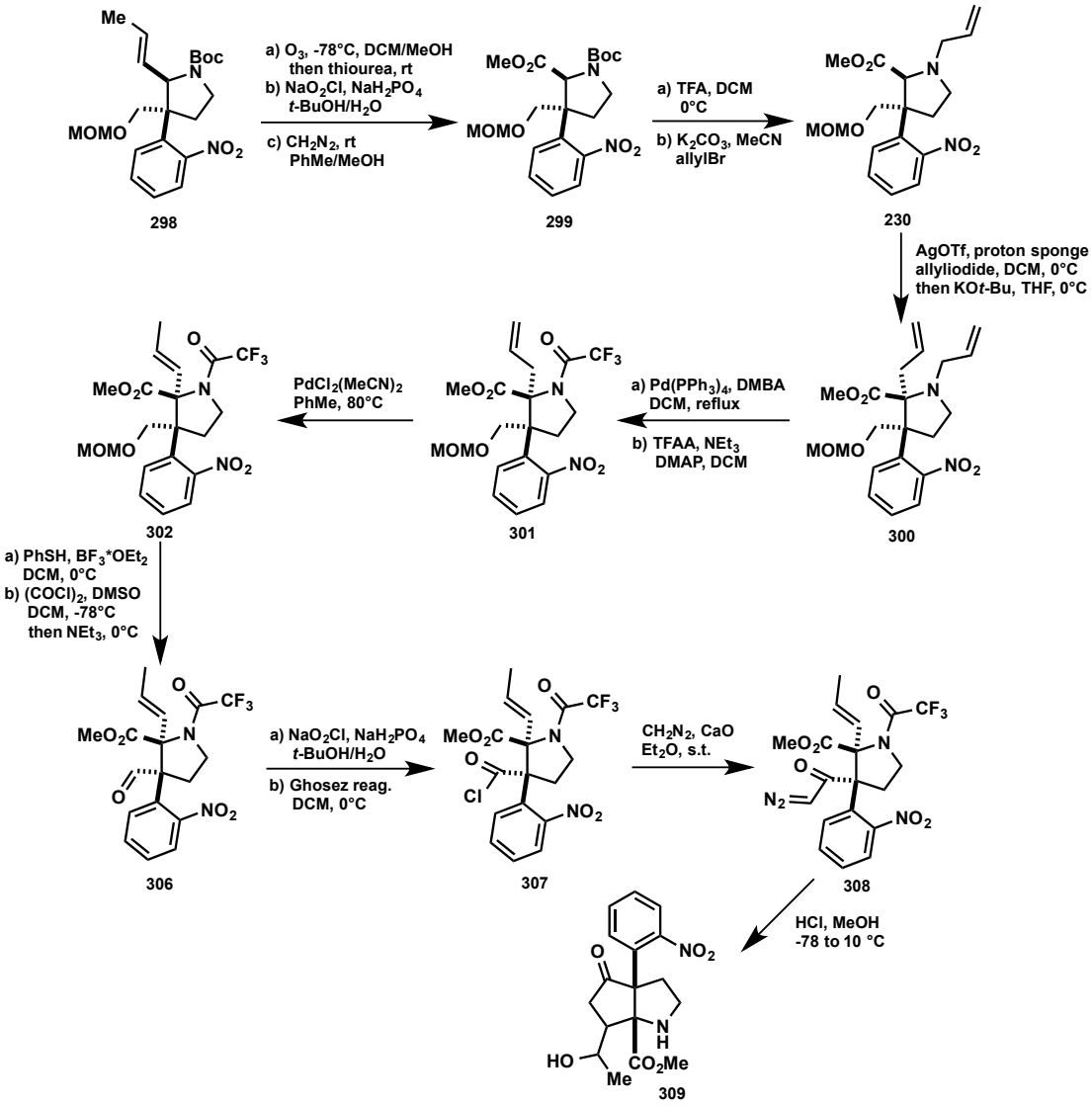
HRMS (ESI): calc. for $C_{35}H_{43}N_2O_5Si^+$: 599.2941, found: 599.2941

Methyl 1,2-diallyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (297), *cis*-product, minor

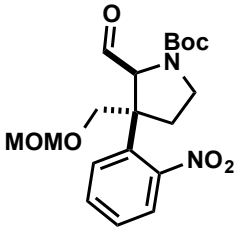
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 - 7.28 (m, 14H), 5.73 (dddd, J_1 = 16.9 Hz, J_2 = 10.4 Hz, J_3 = 6.3 Hz, J_4 = 6.3 Hz, 1H), 5.63 - 5.52 (m, 1H), 5.15 - 5.10 (m, 1H), 5.04 - 5.00 (m, 1H), 4.79 - 4.76 (m, 1H), 4.58 - 4.52 (m, 1H),

3.80 - 3.78 (m, 2H), 3.47 (s, 3H), 3.15 - 3.04 (m, 2H), 2.97 - 2.92 (m, 1H), 2.81 (dd, J_1 = 16.2 Hz, J_2 = 8.0 Hz, 1H), 2.45 - 2.34 (m, 2H), 2.29 - 2.22 (m, 2H), 0.89 (s, 9H) ppm.

HRMS (ESI): calc. for $C_{35}H_{43}N_2O_5Si^+$: 599.2941, found: 599.2941


a) O_3, -78°C, DCM/MeOH
then thiourea, rt
b) NaO_2Cl, NaH_2PO_4
t-BuOH/H_2O
c) CH_2N_2, rt
PhMe/MeOH
a) TFA, DCM
0°C
b) K_2CO_3, MeCN
allylBr
AgOTf, proton sponge
allyliodide, DCM, 0°C
then KO*t*-Bu, THF, 0°C
a) $Pd(PPh_3)_4$, DMBA
DCM, reflux
b) TFAA, NEt_3
DMAP, DCM
$PdCl_2(MeCN)_2$
PhMe, 80°C
a) PhSH, BF_3*OEt_2
DCM, 0°C
b) $(COCl)_2$, DMSO
DCM, -78°C
then NEt_3, 0°C
a) NaO_2Cl, NaH_2PO_4
t-BuOH/H_2O
b) Ghosez reag.
DCM, 0°C
CH_2N_2, CaO
Et_2O, s.t.
HCl, MeOH
-78 to 10 °C
298
299
230
300
301
302
306
307
308
309

***tert*-Butyl 2-formyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1-carboxylate (298b)**



tert-Butyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1-carboxylate (24.0 g, 59.0 mmol, 1 eq) was dissolved in DCM/MeOH = 4:1 (500 mL) and cooled to -78°C. Ozone was passed through the solution until its colour stayed blue. Afterwards oxygen was passed through the solution until its colour turned to slightly yellow. Thiourea (4.50 g, 59.0 mmol, 1 eq) was added and the mixture was allowed to warm up to rt and stirred for 1h. The resulting mixture was poured onto water (1 L). After seperation of the phases the aqueous phase was extracted with DCM (2x300 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain the aldehyde as a colourless foam. The material was used for the next step without further purifications.

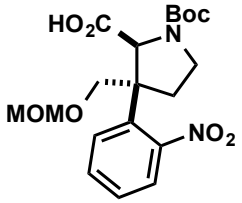
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.58 - 9.48 (m, 1H), 7.61 - 7.38 (m, 4H), 5.11 - 4.90 (m, 1H), 4.47 - 4.45 (m, 2H), 3.82 - 3.77 (m, 1H), 3.74 - 3.58 (m, 2H), 3.52 - 3.41 (m, 1H), 3.15 - 3.14 (m, 3H), 2.45 - 2.31 (m, 2H), 1.46 - 1.42 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.2, 198.3, 154.4, 154.0, 151.2, 151.1, 132.0, 131.9, 131.8, 131.7, 131.6, 128.8, 128.7, 125.0, 124.8, 96.4, 80.8, 80.6, 70.0, 58.3, 67.8, 55.4, 55.4, 52.9, 52.0, 43.8, 43.3, 30.1, 29.7, 28.5, 28.4 ppm.

IR (film): 2976, 2935, 2889, 2825, 1732, 1691, 1604, 1573, 1529, 1477, 1456, 1390, 1365, 1257, 1149, 1136, 1109, 1043, 918, 848, 773, 734, 680, 636, 542, 416, 403 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{27}N_2O_7^+$: 395.1818, found: 395.1818

1-(*tert*-Butoxycarbonyl)-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylic acid (298c)



The crude aldehyde was dissolved in *t*BuOH (200 mL) and 2-methyl 2-butene (50 mL) was added. NaO_2Cl (66.7 g, 590 mmol, 10 eq, 80%) and NaH_2PO_4 (66.7 g) were dissolved in water (200mL) and the resulting solution was added to the first mixture under cooling with an ice bath. The reaction mixture was vigourously stirred for 15h and allowed to warm up to rt during this time. The mixture was poured onto water (1 L) and was extracted with Et_2O (500 mL). 1 M HCl solution (200 mL) was added and the aqoueous phase was extracted with Et_2O (2x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by acid/base wash (1 M NaOH/Et_2O and 1 M HCl/Et_2O) to obtain the carboxylic acid as a colourless solid. The material was used for the next step without further purifications.

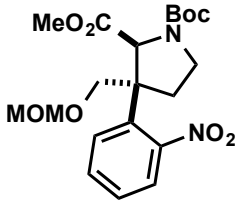
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (bs, 1H), 7.62 - 7.53 (m, 1H), 7.51 - 7.43 (m, 2H), 7.39 - 7.34 (m, 1H), 5.00 - 4.84 (m, 1H), 4.45 (s, 2H), 3.90 - 3.73 (s, 1H), 3.72 - 3.54 (m, 2H), 3.50 - 3.40 (m, 1H), 3.14 - 3.13 (m, 3H), 2.66 - 2.46 (m, 1H), 2.39 - 2.33 (m, 1H), 1.45 - 1.36 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4, 173.1, 155.5, 154.1, 150.6, 150.5, 133.0, 132.7, 132.6, 132.3, 131.3, 131.2, 128.5, 128.2, 124.9, 124.6, 96.5, 96.4, 81.6, 81.1, 70.0, 69.9, 64.1, 64.0, 55.4, 55.3, 54.7, 53.1, 44.3, 44.0, 29.9, 28.9, 28.5, 28.4 ppm.

IR (film): 3062 (bs), 2976, 2935, 2893, 1735, 1697, 1647, 1575, 1531, 1477, 1415, 1392, 1367, 1350, 1244, 1170, 1151, 1111, 1043, 916, 850, 777, 756, 731, 680, 559, 416, 405 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{27}N_2O_8^+$: 411.1767, found: 411.1773

1-(*tert*-Butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-1,2-dicarboxylate (299)



The crude carboxylic acid was dissolved in PhMe/MeOH = 3:1 (400 mL). An freshly prepared ethereal diazomethane solution starting from *N*-methyl-*N*-nitrotoluene-*p*-sulphonamide (37.9 g, 177 mmol, 3eq) was transferred to the solution. The resulting mixture was stirred at rt for 12h in an opened flask. The solvent was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-(*tert*-butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (20.8 g, 49.0 mmol, 0.83 eq) as a colourless viscous fluid.

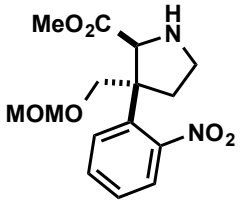
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 - 7.58 (m, 1H), 7.54 - 7.45 (m, 2H), 7.41 - 7.34 (m, 1H), 5.05 - 4.87 (m, 1H), 4.50 - 4.45 (m, 2H), 4.05 - 3.89 (m, 1H), 3.76 - 3.60 (m, 2H), 3.54 - 3.45 (m, 1H), 3.38 - 3.37 (m, 3H), 3.16 - 3.15 (m, 3H), 2.67 - 2.53 (m, 1H), 2.50 - 2.36 (m, 1H), 1.45 - 1.41 (m, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.8, 171.5, 154.4, 154.0, 150.8, 150.5, 133.3, 133.0, 132.8, 132.7, 131.4, 130.9, 128.4, 128.3, 125.1, 124.7, 96.5, 96.5, 80.7, 80.5, 70.0, 69.9, 63.9, 63.8, 55.4, 55.3, 54.8, 53.9, 51.9, 51.8, 44.4, 44.0, 29.6, 29.3, 28.5, 28.4 ppm.

IR (film): 2976, 2951, 2891, 1741, 1697, 1531, 1477, 1456, 1435, 1392, 1365, 1244, 1172, 1151, 1134, 1109, 1043, 981, 918, 850, 777, 725, 561, 462, 408 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{29}N_2O_8^+$: 425.1924, found: 425.1925

Methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (299b)



1-(*tert*-Butyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (20.8 g, 49.0 mmol, 1 eq) was dissolved in DCM (300 mL) and cooled to 0°C. Trifluoroacetic acid (70 mL) was added and the resulting mixture was stirred at 0°C for 5h. The organic phase was washed with 8 M NH_4OH solution (1 L) and after seperation of the phases the aqueous phase was extracted with DCM (2x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by acid/base wash (1 M HCl/Et_2O and 8 M NH_4OH/Et_2O) follwed by flash column chromatography (SiO_2, DCM/MeOH = 50:1 to 40:1 to 30:1 to 20:1) to obtain the secondary amine as a colourless viscous fluid. The material was used for the next step without further purifications.

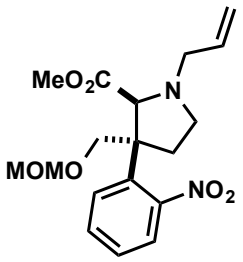
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55 - 7.53 (m, 1H), 7.45 - 7.41 (m, 2H), 7.36 - 7.30 (m, 1H), 4.52 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 6.5 Hz, 1H), 4.46 (s, 1H), 3.82 (s, 2H), 3.44 (s, 3H), 3.28 (ddd, J_1 = 10.3 Hz, J_2 = 10.3 Hz, J_3 = 3.4 Hz, 1H), 3.22 - 3.16 (m, 1H), 3.19 (s, 3H), 2.47 (ddd, J_1 = 12.4 Hz, J_2 = 10.3 Hz, J_3 = 7.4 Hz, 1H), 2.21 (ddd, J_1 = 12.3 Hz, J_2 = 8.5 Hz, J_3 = 3.6 Hz, 1H), 2.12 (bs, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.0, 151.0, 135.7, 132.3, 130.8, 127.7, 124.4, 96.6, 71.7, 66.2, 55.4, 55.1, 51.7, 44.8, 31.2 ppm.

IR (film): 2949, 2885, 1735, 1653, 1527, 1436, 1365, 1244, 1193, 1170, 1149, 1109, 1041, 952, 916, 852, 781, 759, 723, 696, 542 cm^{-1}.

HRMS (ESI): calc. for $C_{15}H_{21}N_2O_6^+$: 325.1400, found: 325.1396

Methyl 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (230)



The crude amine was dissolved in absolute MeCN (50 mL) and K_2CO_3 (13.5 g, 98.0 mml, 2 eq) was added followed by allyl bromide (29.6 g, 21.2 mL, 245 mmol, 5 eq). The resulting mixture was stirred at rt for 18h. The organic phase was poured onto H_2O (500 mL) and the aqueous phase was extracted with Et_2O (3x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain methyl 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (13.4 g, 36.8 mmol, 0.75 eq) as a yellow viscous fluid.

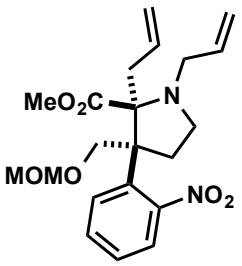
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.30 (ddd, J_1 = 8.0 Hz, J_2 = 6.7 Hz, 1H), 5.85 (dddd, J_1 = 16.9 Hz, J_2 = 10.4 Hz, J_3 = 6.4 Hz, J_4 = 6.4 Hz, 1H), 5.19 (ddd, J_1 = 17.2 Hz, J_2 = 3.2 Hz, J_3 = 1.6 Hz, 1H), 5.11 (ddd, J_1 = 10.1 Hz, J_2 = 2.7 Hz, J_3 = 1.2 Hz, 1H), 4.52 (d, J = 6.5 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.34 (s, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.44 (s, 3H), 3.26 (dddd, J_1 = 13.7 Hz, J_2 = 6.0 Hz, J_3 = 1.3 Hz, J_4 = 1.3 Hz, 1H), 3.17 (s, 3H), 3.11 - 3.04 (m, 2H), 2.79 (ddd, J_1 = 10.6 Hz, J_2 = 8.9 Hz, J_3 = 4.1 Hz, 1H), 2.42 (ddd, J_1 = 12.6 Hz, J_2 = 10.6 Hz, J_3 = 5.5 Hz, 1H), 2.09 (ddd, J_1 = 12.5 Hz, J_2 = 8.4 Hz, J_3 = 4.1 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.7, 150.8, 136.0, 135.4, 132.4, 130.4, 127.5, 124.3, 117.1, 96.5, 71.7, 70.0, 55.2, 54.8, 54.4, 51.0, 49.5, 30.3 ppm.

IR (film): 2949, 2885, 2843, 1732, 1527, 1436, 1363, 1193, 1151, 1109, 1045, 918, 854, 781, 759, 723, 684, 561, 418 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{25}N_2O_6^+$: 365.1713, found: 365.1709

Methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (300)



Silver trifluoromethanesulfonate (46.9 g, 183 mmol, 5eq) was put in a Schlenk tube under argon. Absolute DCM (120mL) was added and the suspension was subjected to ultrasound for 30min. The mixture was cooled to 0°C and freshly prepared allyl iodide (16.7 mL, 30.7 g, 183 mmol, 5 eq) was added. After stirring for 5min 1-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (13.3 g, 36.5 mmol, 1 eq) and 1,8-*bis*(*N,N*-dimethylamio)naphthalene (23.5 g, 110 mmol, 3 eq) dissolved in absolute DCM (200 mL) were added and the resulting mixtured was stirred at 0°C for 1h. After warming up to rt the suspension was filtrated over celite into a flask containing K_2CO_3 (50.4 g, 365 mmol, 10 eq). The solvent was removed under reduced pressure and the crude ammonium salt was dissolved in absolute THF (600 mL) and cooled to 0°C. Potassium *tert*-butoxide (110 mL, 110 mmol, 3 eq, 1mol/L solution in *t*BuOH) was added and the mixtured was stirred at 0°C for 15min. The mixture was poured onto water (2 L) and the aqueous phase was extracted with Et_2O (3x500 mL). The aqueous phase was adjusted to pH = 12 with KOH and extracted with Et_2O (2x500 mL). The combined organic phases were washed with saturated NaCl solution (500 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1 to 3:1) to obtain methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (7.82 g, 19.3 mmol, 0.53 eq, dr > 99:1) as a colourless crystalline solid. An analytical sample for x-ray spectroscopy was crystalized from Et_2O/pentane. Starting material (2.79 g, 7.66 mmol, 0.21 eq) could be recovered and used in a second cycle.

MP: 67.6 °C

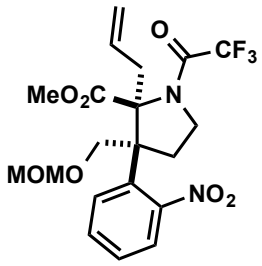
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.35 - 7.27 (m, 2H), 6.07 (dddd, J_1 = 17.1 Hz, J_2 = 10.4 Hz, J_3 = 6.7 Hz, J_4 = 6.7 Hz, 1H), 5.77 (dddd, J_1 = 17.2 Hz, J_2 = 10.0 Hz, J_3 = 7.4 Hz, J_4 = 4.4 Hz, 1H), 5.20 - 5.18 (m, 1H), 5.16 - 5.13 (m, 1H), 5.06 - 5.02 (m, 2H), 4.43 (d, J = 6.5 Hz, 1H), 4.40 (d, J = 6.8 Hz, 1H), 4.06 (d, J = 9.9 Hz, 1H), 3.91 (d, J = 10.2 Hz, 1H), 3.43 - 3.37 (m, 1H), 3.32 (s, 3H), 3.24 (ddd, J_1 = 8.7 Hz, J_2 = 8.7 Hz, J_3 = 5.6 Hz, 1H), 3.20 - 3.14 (m, 2H), 3.08 (s, 3H), 2.69 - 2.58 (m, 2H), 2.53 - 2.46 (m, 1H), 2.09 (ddd, J_1 = 12.5 Hz, J_2 = 8.7 Hz, J_3 = 3.8 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.9, 151.6, 136.0, 135.5, 135.3, 130.7, 129.8, 127.5, 124.3, 116.4, 116.3, 96.5, 77.5, 71.5, 57.7, 55.3, 53.6, 51.2, 49.9, 36.5, 31.6 ppm.

IR (film): 3076, 2978, 2949, 2885, 2843, 1720, 1635, 1529, 1485, 1435, 1365, 1276, 1217, 1151, 1107, 1041, 916, 846, 777, 740, 688, 561 cm^{-1}.

HRMS (ESI): calc. for $C_{21}H_{29}N_2O_6^+$: 405.2026, found: 405.2026

Methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-1-(2,2,2-trifluoro-acetyl)pyrrolidine-2-carboxylate (301)

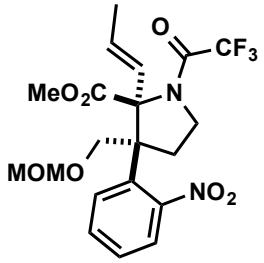


Tetrakis(triphenylphosphine)palladium (157 mg, 136 μmol, 0.1 eq) and 1,3-dimethylbarbituric acid (425 mg, 2.72 mmol, 2 eq) were put in a Schlenk tube under argon. 1,2-Diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (550 mg, 1.36 mmol, 1 eq) was dissolved in degassed absolute DCM (50 mL) and added to the Schlenk tube. The resulting mixture was heated to reflux for 30min. After cooling down to rt the reaction mixture was poured onto 8 M NH_4OH (100 mL) and the aqueous

phase was extracted with DCM (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under redued pressure.
The crude secondary amine was dissolved in DCM (60 mL). DMAP (63.0 mg, 136 μmol, 0.1 eq), NEt_3 (760 μL, 550 mg, 5.44 mmol, 4 eq) and trifluoroacetic anhydride (580 μL, 857 mg, 4.08 mmol, 3 eq) were sequentially added. The resulting mixture was stirred at rt for 4h. H_2O (100 mL) was added and the aqueous phase was extracted with DCM (2x50 mL). The combiend organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude amine was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 1:1) to obtain methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-1-(2,2,2-trifluoro-acetyl)pyrrolidine-2-carboxylate (599 mg, 1.30 mmol, 0.96 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.48 (ddd, J_1 = 8.3 Hz, J_2 = 7.3 Hz, J_3 = 1.5 Hz, 1H), 7.39 (ddd, J_1 = 7.3 Hz, J_2 = 7.9 Hz, J_3 = 0.9 Hz, 1H), 7.29 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 5.75 (dddd, J_1 = 17.0 Hz, J_2 = 9.9 Hz, J_3 = 7.1 Hz, J_4 = 7.1 Hz, 1H), 5.25 - 5.19 (m, 1H), 5.15 - 5.13 (m, 1H), 4.52 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 6.8 Hz, 1H), 4.09 - 4.03 (m, 2H), 3.87 (d, J = 10.2 Hz, 1H), 3.71 - 3.60 (m, 2H), 3.25 (s, 3H), 3.14 - 3.09 (m, 4H), 2.74 (dddd, J_1 = 8.2 Hz, J_2 = 12.2 Hz, J_3 = 12.2 Hz, J_4 = 1.1 Hz, 1H), 2.50 (dd, J_1 = 12.1 Hz, J_2 = 5.3 Hz, 1H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.2, 151.3, 132.6, 130.6, 130.5, 130.0, 128.9, 124.0, 119.8, 117.6, 114.7, 96.7, 76.1, 70.4, 58.0, 55.8, 52.7, 46.4, 35.4, 29.7 ppm.

Methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (302)



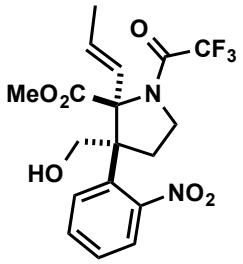
$PdCl_2(MeCN)_2$ (34.0 mg, 130 μmol, 0.1 eq) was put in a Schlenk tube under argon. Methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-1-(2,2,2-trifluoro-acetyl)pyrrolidine-2-carboxylate (599 mg, 1.30 mmol, 1 eq) dissolved in degassed absolute PhMe (40 mL) was added and the reaction mixture was heated to 80°C for 3h. After cooling down to rt the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (525 mg, 1.14 mmol, 0.88 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.51 (ddd, J_1 = 8.1 Hz, J_2 = 7.2 Hz, J_3 = 1.3 Hz, 1H), 7.38 (ddd, J_1 = 7.3 Hz, J_2 = 8.0 Hz, J_3 = 1.0 Hz, 1H), 7.29 - 7.26 (m, 1H), 6.26 (qd, J_1 = 15.7 Hz, J_2 = 1.4 Hz, 1H), 5.60 (dq, J_1 = 15.6 Hz, J_2 = 6.6 Hz, 1H), 4.51 (d, J = 6.8 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.15 - 4.10 (m, 1H), 3.83 (ddd, J_1 = 12.0 Hz, J_2 = 10.8 Hz, J_3 = 5.6 Hz, 1H), 3.74 (dd, J_1 = 10.2 Hz, J_2 = 1.4 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.31 (s, 3H), 3.10 (s, 3H), 2.80 (dddd, J_1 = 8.4 Hz, J_2 = 12.0 Hz, J_3 = 12.0 Hz, J_4 = 1.2 Hz, 1H), 2.62 (dd, J_1 = 12.1 Hz, J_2 = 5.3 Hz, 1H), 1.86 (dd, J_1 = 6.8 Hz, J_2 = 1.7 Hz, 3H) ppm.

IR (film): 2953, 2893, 1747, 1701, 1575, 1533, 1436, 1373, 1251, 1199, 1184, 1147, 1112, 1043, 975, 918, 850, 765, 719, 669, 638, 418 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{23}N_2O_7F_3Na^+$: 483.1355, found: 483.1352

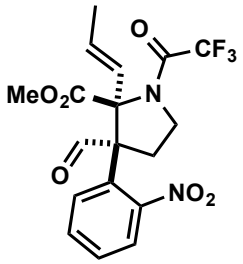
Methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (302b)



Methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (205 mg, 445 μmol, 1 eq) was dissolved in absolute DCM (5 mL) and cooled to 0°C. Thiophenol (50.0 μL, 54.0 mg, 490 μmol, 1.1 eq) followed by BF_3*OEt_2 (130 μL, 490 μmol, 1.1 eq, 48% solution in Et_2O) were added and the resulting mixture was stirred at 0°C for 15h. The reaction mixture was poured onto aqueous K_2CO_3 (50 mL). The aqueous phase was extracted with DCM (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (163 mg, 391 μmol, 0.88 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.63 - 7.50 (m, 2H), 7.47 - 7.39 (m, 1H), 7.35 - 7.30 (m, 1H), 6.29 (qd, J_1 = 15.7 Hz, J_2 = 1.4 Hz, 1H), 5.59 (dq, J_1 = 15.7 Hz, J_2 = 6.5 Hz, 1H), 5.16 - 4.06 (m, 1H), 3.91 - 3.65 (m 3H), 3.28 (s, 3H), 2.85 - 2.53 (m, 2H), 1.87 (dd, J_1 = 6.6 Hz, J_2 = 1.7 Hz, 3H) ppm.

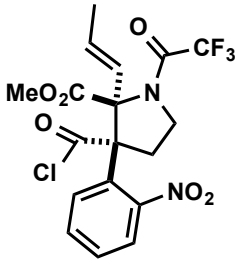
Methyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)-pyrrolidine-2-carboxylate (306)



Oxalyl chloride (70.0 μL, 99.0 mg, 784 μmol, 2 eq) was dissolved in absolute DCM (2 mL) and cooled to -78°C. DMSO (110 μL, 122 mg, 1.57 mmol, 4 eq) was added dropwise and the resulting mixture was stirred at -78°C for 15min. Methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrro-lidine-2-carboxylate (163 mg, 391 μmol, 1 eq) dissolved in absolute DCM (6 mL) was added dropwise and the resulting mixture was stirred at -78°C for 1h. NEt_3 (330 μL, 238 mg, 2.35 mmol, 6 eq) was added and the reaction mixture was allowed to warm up to 0°C. After stirring for 2h the reaction mixture was poured onto H_2O (50 mL). Thr aqueous phase was extracted with DCM (2x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain methyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)-pyrrolidine-2-carboxylate (146 mg, 352 μmol, 0.9 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1H), 7.83 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.67 (ddd, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 7.61 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.54 (ddd, J_1 = 7.8 Hz, J_2 = 7.2 Hz, J_3 = 1.4 Hz, 1H), 6.31 (qd, J_1 = 15.7 Hz, J_2 = 1.5 Hz, 1H), 5.63 (dq, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H), 4.27 - 4.21 (m, 1H), 3.99 (ddd, J_1 = 10.7 Hz, J_2 = 8.9 Hz, J_3 = 6.7 Hz, 1H), 3.31 (s, 3H), 2.82 (ddd, J_1 = 12.8 Hz, J_2 = 8.4 Hz, J_3 = 8.4 Hz, 1H), 2.60 (ddd, J_1 = 12.9 Hz, J_2 = 6.6 Hz, J_3 = 4.0 Hz, 1H), 1.88 (dd, J_1 = 6.5 Hz, J_2 = 1.7 Hz, 3H) ppm.

Methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (307)

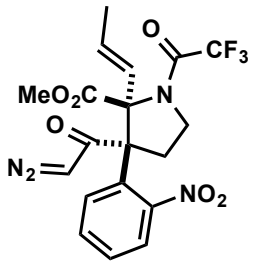


Methyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (166 mg, 401 μmol, 1 eq) was dissolved in *t*BuOH (5 mL) and 2-methyl-2-butene (1 mL) was added. NaO_2Cl (453 mg, 4.01 mmol, 10 eq, 80%) and $NaH_2PO_4*H_2O$ (453 mg, 3.33 mmol, 8.3 eq) dissolved in H_2O (5 mL) were added and the resulting mixture was stirred at rt for 14h. H_2O (50 mL) was added and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The carboxylic acid was used without further purification.

The carboxylic acid was dissolved in absolute DCM (8 mL) and cooled to 0°C. Ghosez reagent (60.0 μL, 59.0 mg, 440 μmol, 1.1 eq) was added and the resulting mixture was stirred at 0°C for 3h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (103 mg, 230 μmol, 0.57 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (bd, *J* = 7.5 Hz, 1H), 7.70 - 7.59 (m, 3H), 5.86 (bd, *J* = 16.0 Hz, 1H), 5.75 (dq, J_1 = 15.3 Hz, J_2 = 6.4 Hz, 1H), 4.23 (bdd, J_1 = 9.4 Hz, J_2 = 9.4 Hz, 1H), 3.99 (ddd, J_1 = 11.2 Hz, J_2 = 11.2 Hz, J_3 = 5.6 Hz, 1H), 3.30 - 3.23 (m, 4H), 2.71 (dd, J_1 = 12.8 Hz, J_2 = 5.3 Hz, 1H), 1.79 (dd, J_1 = 6.5 Hz, J_2 = 1.4 Hz, 3H) ppm.

Methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (308)



CaO (25.0 mg, 450 μmol, 2 eq) was put in a sealed tube and freshly prepared diazomethane in absolute Et_2O (10 mL, solution prepared started from 5.00 g *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) was added. Methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-2-carboxylate (101 mg, 225 μmol, 1 eq) was dissolved in absolute Et_2O (3 mL) and added to the sealed tube. The tube was sealed and the mixture was stirred at rt for 3d. After complete reaction the solids were removed by filtration over celite and the solvent was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)-pyrrolidine-2-carboxylate (50.0 mg, 110 μmol, 0.49 eq) as a slightly yellow foam.

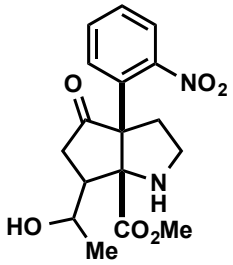
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 - 7.73 (m, 1H), 7.60 - 7.56 (m, 2H), 7.53 - 7.49 (m, 1H), 6.20 (qd, J_1 = 15.6 Hz, J_2 = 1.3 Hz, 1H), 5.73 (dq, J_1 = 15.5 Hz, J_2 = 6.7 Hz, 1H), 4.88 (s, 1H), 4.41 - 4.34 (m, 1H), 4.09 - 4.03 (m, 1H), 3.39 (s, 3H), 2.76 - 2.66 (m, 2H), 1.81 (dd, J_1 = 6.8 Hz, J_2 = 1.7 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 191.8, 169.8, 151.2, 131.3, 131.2, 130.6, 130.1, 130.0, 125.1, 122.4, 117.5, 114.6, 78.1, 67.1, 57.4, 53.1, 47.7, 32.4, 18.6 ppm.

IR (film): 2921, 2209, 1742, 1702, 1635, 1532, 1438, 1352, 1206, 1150, 1013, 960, 855, 785, 738, 639 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{17}N_4O_6F_3Na^+$: 477.0998, found: 477.0999

Methyl 6-(1-hydroxyethyl)-3a-(2-nitrophenyl)-4-oxohexahydrocyclopenta-[*b*]-pyrrole-6a(1*H*)-carboxylate (309)



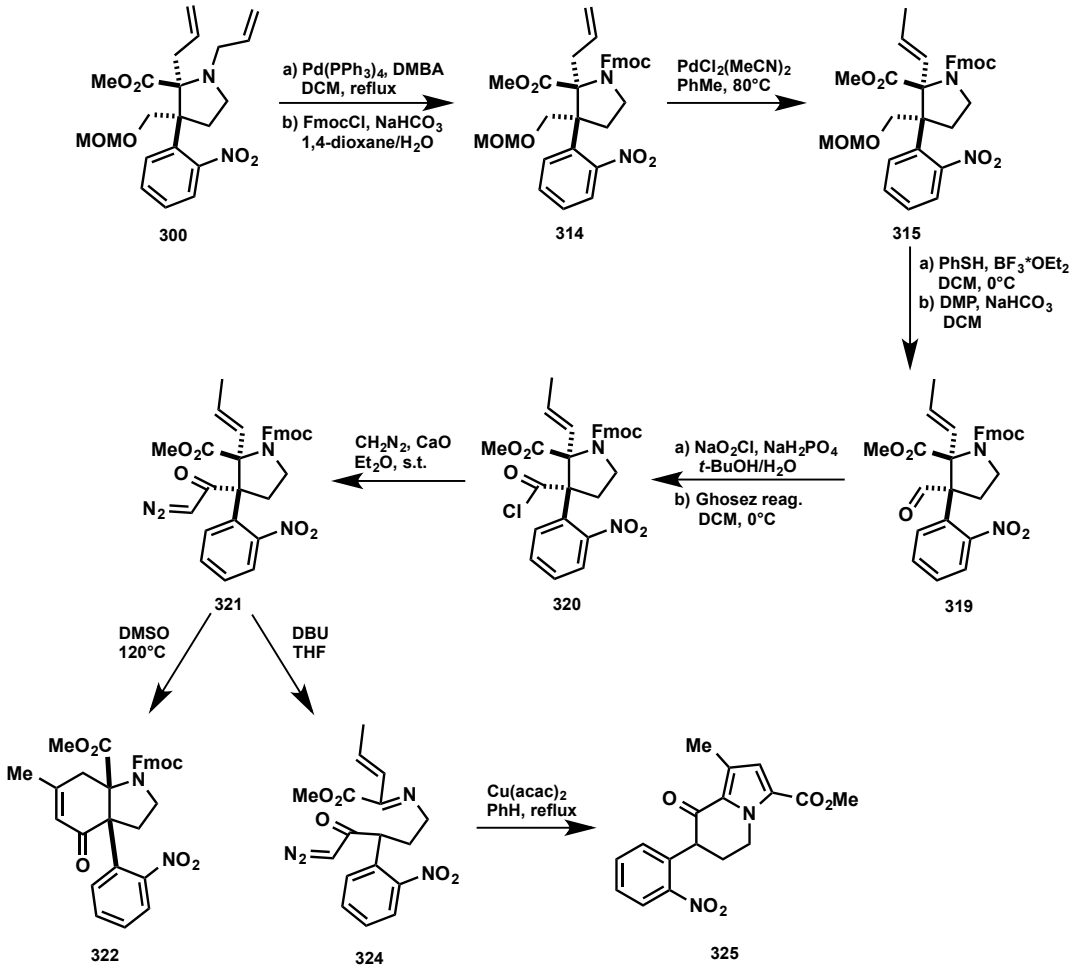
Methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-1-(2,2,2-trifluoroacetyl)-pyrrolidine-2-carboxylate (11.0 mg, 24.0 μmol, 1 eq) was dissolved in MeOH (5 mL) and cooled to -78°C. Acetyl chloride (500 μL) was added dropwise and the reaction mixture was allowed to warm up to 10°C over a period of 6.5h. Aqueous NH_4OH (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatograohy (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1 to 0:1) to obtain methyl 6-(1-hydroxyethyl)-3a-(2-nitrophenyl)-4-oxohexahydrocyclopenta[*b*]pyrrole-6a(1*H*)-carboxylate (2.00 mg, 6.00 μmol, 0.25 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.55 (ddd, J_1 = 8.0 Hz, J_2 = 7.5 Hz, J_3 = 1.5 Hz, 1H), 7.39 (ddd, J_1 = 8.1 Hz, J_2 = 7.4 Hz, J_3 = 1.3 Hz, 1H), 7.34 (dd, J_1 = 8.1 Hz, J_2 = 0.9 Hz, 1H), 4.03 - 3.96 (m, 1H), 3.58 - 3.47 (m, 2H), 3.20 - 3.14 (m, 4H), 2.66 (dd, J_1 = 18.2 Hz, J_2 = 12.5 Hz, 1H), 2.54 - 2.43 (m, 2H), 2.38 - 2.31 (m, 1H), 1.27 (d, J = 6.2 Hz, 3H) ppm.

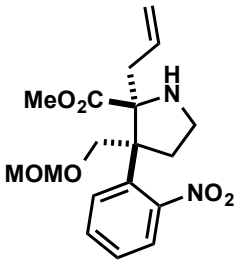
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 214.4, 174.8, 149.3, 134.8, 132.8, 130.3, 128.4, 125.5, 81.6, 68.8, 68.7, 52.3, 48.2, 47.6, 44.7, 40.8, 22.9 ppm.

IR (film): 3352, 2924, 2852, 2358, 2341, 1728, 1606, 1575, 1531, 1458, 1435, 1406, 1359, 1269, 1228, 1192, 1141, 1082, 1066, 1945, 1024, 968, 958, 877, 852, 786, 744, 707, 669, 590, 549, 420 cm^{-1}.

HRMS (ESI): calc. for $C_{17}H_{21}N_2O_6^+$: 349.1400, found: 349.1401


a) Pd(PPh3)4, DMBA
DCM, reflux
b) FmocCl, NaHCO3
1,4-dioxane/H2O
PdCl2(MeCN)2
PhMe, 80°C
a) PhSH, BF3*OEt2
DCM, 0°C
b) DMP, NaHCO3
DCM
a) NaO2Cl, NaH2PO4
t-BuOH/H2O
b) Ghosez reag.
DCM, 0°C
CH2N2, CaO
Et2O, s.t.
DMSO
120°C
DBU
THF
Cu(acac)2
PhH, reflux
300
314
315
319
320
321
322
324
325

Methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (300b)



Tetrakis(triphenylphosphine)palladium(0) (1.13 g, 979 μmol, 0.05 eq) and 1,3-dimethylbarbituric acid (6.11 g, 39.2 mmol, 2 eq) were put in a Schlenk tube under argon. 1,2-Diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-pyrrolidine-2-carboxylate (7.92 g, 19.6 mmol, 1 eq) was dissolved in degassed absolute DCM (200 mL) and added to the Schlenk tube. The resulting mixture was heated to reflux for 1h. After cooling down to rt the reaction mixture was poured onto 8 M NH_4OH (500 mL) and the aqueous phase was extracted with DCM (2x200 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under redued pressure. An analytical sample was purified by acid/base wash (1 M HCl/Et_2O, saturated Na_2CO_3/Et_2O) followed by flash column chromatography (SiO_2, Pe/EtOAc = 1:1 to 0:1). The material was used for the next step without further purifications.

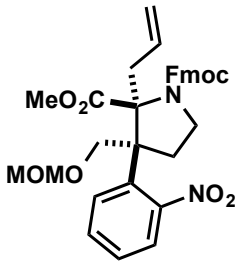
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.2 Hz, 1H), 7.48 - 7.43 (m, 1H), 7.35 - 7.31 (m, 2H), 5.78 (dddd, J_1 = 17.1 Hz, J_2 = 10.1 Hz, J_3 = 8.1 Hz, J_4 = 6.1 Hz, 1H), 5.16 - 5.07 (m, 2H), 4.54 (s, 2H), 4.10 (d, *J* = 9.9 Hz, 1H), 3.8 (d, *J* = 9.9 Hz, 1H), 3.31 (s, 3H), 3.30 - 3.24 (m, 1H), 3.24 (s, 3H), 3.16 - 3.10 (m, 2), 2.52 - 2.44 (m, 2H), 2.37 (ddd, J_1 = 12.9 Hz, J_2 = 8.1 Hz, J_3 = 3.7 Hz, 1H), 2.10 (bs, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.8, 151.9, 134.1, 133.4, 131.1, 130.0, 127.9, 124.2, 118.8, 96.8, 76.0, 71.3, 56.8, 55.7, 52.0, 43.8, 38.9, 34.1 ppm.

IR (film): 3367, 3076, 2949, 2885, 1728, 1639, 1529, 1485, 1435, 1371, 1296, 1217, 1151, 1107, 1041, 999, 918, 848, 773, 678 cm^{-1}.

HRMS (ESI): calc. for $C_{18}H_{25}N_2O_6^+$: 365.1713, found: 365.1711

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (314)



The crude secondary amine was dissolved in 1,4-dioxane (120 mL) and water (30 mL). $NaHCO_3$ (3.46 g, 41.1 mmol, 2.1 eq) and fluorenylmethyloxycarbonyl chloride (5.32 g, 20.6 mmol, 1.05 eq) were sequentially added and the resulting mixture was stirred at rt for 7h. The mixture was poured onto water (1 L) and the aqueous phase was extracted with Et_2O (3x500 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (9.31 g, 15.9 mmol, 0.81 eq) as a colourless foam.

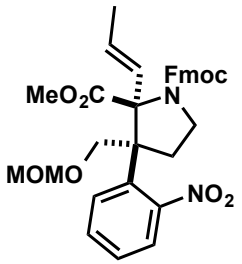
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.71 (m, 3H), 7.63 - 7.58 (m, 2H), 7.50 - 7.26 (m, 7H), 5.86 - 5.46 (m, 1H), 5.27 - 4.98 (m, 2H), 4.60 - 4.23 (m, 5H), 4.10 - 3.83 (m, 3H), 3.71 - 3.52 (m, 1H), 3.52 - 3.39 (m, 1H), 3.27 - 2.76 (m, 7H), 2.72 - 2.50 (m, 1H), 2.41 - 2.28 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.9, 171.4, 154.4, 154.1, 151.6, 151.5, 144.2, 143.9, 143.7, 141.5, 141.4, 134.0, 133.8, 131.4, 130.9, 130.6, 130.4, 129.9, 129.9, 127.9, 127.8, 127.8, 127.7, 127.3, 127.2, 127.2, 127.1, 125.2, 125.1, 124.6, 124.4, 123.9, 120.2, 120.1, 118.2, 117.7, 96.6, 96.5, 74.4, 73.3, 70.5, 67.5, 67.3, 60.2, 59.1, 55.6, 55.5, 52.4, 52.2, 47.4, 47.3, 46.7, 46.0, 36.3, 36.0, 29.0 ppm.

IR (film): 3072, 2949, 2889, 2357, 2341, 1741, 1699, 1529, 1450, 1408, 1355, 1346, 1244, 1213, 1192, 1149, 1109, 1074, 1039, 979, 918, 850, 759, 740, 669, 621, 584, 570, 545 cm^{-1}.

HRMS (ESI): calc. for $C_{33}H_{34}N_2O_8Na^+$: 609.2213, found: 609.2212

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitro-phenyl-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (315)



$PdCl_2(MeCN)_2$ (11.0 mg, 41.0 μmol, 0.05 eq) was put in a Schlenk tube under argon. 1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (481 mg, 820 μmol, 1 eq) dissolved in degassed absolute PhMe (16 mL) was added and the reaction mixture was heated to 90°C for 3h. After cooling down to rt the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitro-phenyl-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (413 mg, 704 μmol, 0.86 eq) as a colourless oil.

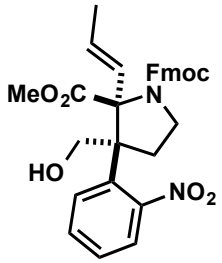
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.70 (m, 2H), 7.64 - 7.47 (m, 4H), 7.44 - 7.24 (m, 6H), 6.34 - 6.22 (m, 1H), 5.80 - 5.58 (m, 1H), 4.53 - 4.50 (m, 1H), 4.46 - 4.43 (m, 1H), 4.42 - 4.07 (m, 3H), 3.98 - 3.91 (m, 1H), 3.73 - 3.53 (m, 3H), 3.33 - 3.25 (m, 3H), 3.10 - 3.08 (m, 3H), 2.76 - 2.66 (m, 1H), 2.51 - 2.46 (m, 1H), 1.86 - 1.83 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.7, 154.8, 154.0, 151.7, 151.6, 144.2, 144.1, 144.0, 143.7, 141.5, 141.5, 141.3, 141.3, 131.1, 131.0, 130.8, 130.0, 129.9, 128.6, 128.5, 128.0, 127.8, 127.8, 127.7, 127.5, 127.2, 127.2, 127.2, 125.8, 125.4, 125.1, 125.0, 124.6, 123.7, 123.7, 120.2, 120.0, 119.9, 96.5, 96.5, 75.6, 75.0, 71.7, 71.7, 68.3, 67.4, 59.4, 58.2, 55.5, 55.4, 52.5, 52.4, 47.4, 47.3, 46.7, 45.8, 31.1, 29.8, 28.2, 27.3, 22.8, 18.3, 18.3, 14.3 ppm.

IR (neat): 2949, 2887, 1739, 1701, 1529, 1450, 1436, 1406, 1373, 1352, 1332, 1232, 1207, 1153, 1109, 1095, 1043, 1020, 989, 977, 918, 848, 779, 761, 740, 723, 671, 621, 605, 588, 567, 545, 428 cm^{-1}.

HRMS (ESI): calc. for $C_{33}H_{34}N_2O_8Na^+$: 609.2213, found: 609.2202

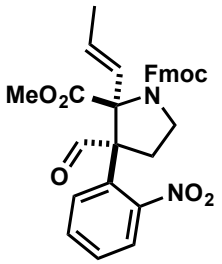
1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (315b)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (413 mg, 704 μmol, 1 eq) was dissolved in absolute DCM (10 mL) and cooled to 0°C. Thiophenol (92.0 μL, 99.0 mg, 902 μmol, 1.1 eq) followed by BF_3*OEt_2 (238 μL, 902 μmol, 1.1 eq, 48% solution in Et_2O) were added and the reaction mixture was stirred at 0°C for 16h. Aqueous $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with DCM (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (355 mg, 654 μmol, 0.93 eq) as a colourless oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.79 - 7.18 (m, 12H), 6.38 - 6.12 (m, 1H), 5.80 - 5.51 (m, 1H), 4.48 - 3.47 (m, 8H), 3.30 - 3.21 (m, 3H), 2.75 - 2.58 (m, 1H), 2.52 - 2.43 (m, 1H), 1.87 - 1.76 (m, 3H) ppm.

1-((9*H*-Fluoren-9-yl) 2-metyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (319)

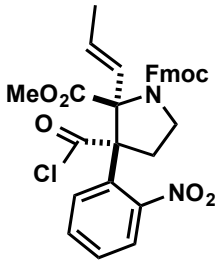


1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (355 mg, 654 μmol, 1 eq) was dissolved in DCM (7 mL). $NaHCO_3$ (330 mg, 3.93 mmol, 6 eq) and DMP (833 mg, 1.96 mmol, 3 eq) were added. The reaction mixture was stirred at rt for 15h and was then poured onto H_2O (100 mL). The aqueous phase was extracted with DCM (3x50 mL). The combined organic phases were washed with brine (25 mL), dired over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude aldehyde was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl) 2-metyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (289 mg, 535 μmol, 0.82 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.81 - 9.73 (m, 1H), 8.27 - 8.19 (m, 1H), 8.02 - 7.88 (m, 2H), 7.81 - 7.28 (m, 9H), 6.48 - 6.34 (m, 1H), 5.80 - 5.46 (m, 1H), 4.56 - 4.17 (m, 3H), 4.00 - 3.65 (m, 2H), 3.34 - 3.21 (m, 3H), 2.63 - 2.39 (m, 2H), 1.90 - 1.86 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.4, 196.2, 176.5, 169.8, 168.3, 167.3, 153.6, 149.0, 144.1, 143.9, 141.5, 136.7, 136.3, 135.5, 133.5, 133.3, 133.1, 132.7, 132.0, 131.8, 131.5, 131.2, 130.6, 129.4, 129.4, 129.1, 128.8, 128.3, 127.9, 127.7, 127.2, 127.2, 127.0, 125.9, 125.7, 125.0, 125.0, 120.1, 118.5, 117.2, 85.6, 83.0, 68.4, 67.3, 65.7, 52.7, 52.5, 47.5, 46.5, 41.2, 41.0, 31.0, 29.8, 28.5, 24.2, 24.0, 20.9, 20.7, 20.6, 20.4, 18.1, 17.7, 17.6, 17.5, 17.4, 14.8 ppm.

1-((9*H*-Fluoren-9-yl)meethyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-(*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (320)

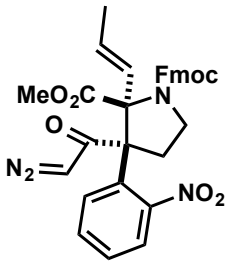


1-((9*H*-Fluoren-9-yl) 2-metyl 3-formyl-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)-pyrrolidine-1,2-dicarboxylate (289 mg, 535 μmol, 1 eq) was dissolved in *t*BuOH (5 mL) and 2-methyl-2-butene (1 mL) was added. NaO_2Cl (610 mg, 5.37 mmol, 10 eq, 80%) and $NaH_2PO_4*H_2O$ (610 mg, 4.49 mmol, 8.4 eq) dissolved in H_2O (5 mL) were added and the resulting mixture was stirred at rt for 7h. H_2O (100 mL) was added and the aqueouy phase was extracted with Et_2O (3x50 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The carboxylic acid was used without further purifications.

The crude carboxylic acid was dissolved in absolute DCM (10 mL) and cooled to 0°C. Ghosez reagent (710 μL, 715 mg, 5.35 mmol, 10 eq) was added and the resutling mixture was stirred at 0°C for 2.5h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-(*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (288 mg, 501 μmol, 0.94 eq) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 - 7.87 (m, 1H), 7.80 - 7.73 (m, 2H), 7.70 - 7.50 (m, 5H), 7.43 - 7.29 (m, 4H), 6.02 - 5.95 (m, 1H), 5.82 - 5.71 (m, 1H), 4.48 - 4.20 (m, 3H), 4.01 - 3.91 (m, 1H), 3.33 - 2.93 (m, 5H), 2.69 - 2.61 (m, 1H), 1.81 - 1.72 (m, 3H) ppm.

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (321)



CaO (56.0 mg, 1.00 mmol, 2 eq) was put in a sealed tube and freshly prepared diazomethane in absolute Et_2O (20 mL, solution prepared started

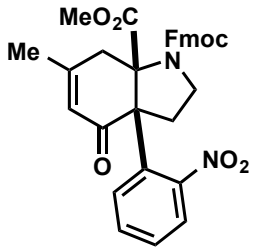
from 5.00 g *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) was added. 1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-(*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (288 mg, 501 μmol, 1 eq) was dissolved in absolute Et_2O (5 mL) and added to the sealed tube. The tube was sealed and the mixture was stirred at rt for 3d. After complete reaction the solids were removed by filtration over celite and the solvent was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (148 mg, 255 μmol, 0.48 eq) as a slightly yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 - 7.75 (m, 3H), 7.62 - 7.52 (m, 4H), 7.47 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.2 Hz, 1H), 7.42 - 7.38 (m, 2H), 7.34 - 7.29 (m, 2H), 6.29 - 6.22 (m, 1H), 5.81 - 5.73 (m, 1H), 4.91 - 4.88 (m, 1H), 4.45 - 4.39 (m, 1H), 4.28 (dd, J_1 = 7.2 Hz, J_2 = 10.6 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.16 - 4.09 (m 1H), 3.89 - 3.79 (m, 1H), 3.41 (bs, 3H), 2.69 - 2.62 (m, 1H), 2.56 (ddd, J_1 = 11.8 Hz, J_2 = 9.6 Hz, J_3 = 9.6 Hz, 1H), 1.80 (dd, J_1 = 6.5 Hz, J_2 = 1.0 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 195.1, 171.1, 154.6, 151.3, 144.2, 143.9, 141.5, 141.4, 131.2, 130.8, 129.6, 129.5, 127.9, 127.8, 127.3, 127.2, 127.2, 125.5, 125.3, 125.2, 125.1, 120.1, 72.3, 72.1, 68.9, 67.5, 62.3, 57.1, 54.9, 52.9, 51.7, 49.2, 48.2, 47.4, 47.3, 43.2, 41.0, 31.8, 28.6, 24.1, 23.1, 21.0, 20.7, 18.6, 17.7, 17.3, 14.8, 14.3 ppm.

HRMS (ESI): calc. for $C_{32}H_{28}N_4O_7Na^+$: 603.1856, found: 603.1854

1-((9*H*-Fluoren-9-yl)methyl) 7a-methyl 6-methyl-3a-(2-nitrophenyl)-4-oxo-3,3a,4,7-tetrahydro-1*H*-indole-1,7a-(2*H*)-dicarboxylate (322)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (5.00 mg, 9.00 μmol, 1 eq) was dissolved in absolute DMSO (1 mL). The mixture was heated to 120 °C for 90min. After cooling down to rt H_2O (25 mL) was added and the aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 7a-methyl 6-methyl-3a-(2-nitrophenyl)-4-oxo-3,3a,4,7-tetrahydro-1*H*-indole-1,7a-(2*H*)-dicarboxylate (2.00 mg, 3.60 μmol, 0.4 eq) as a colourless foam.

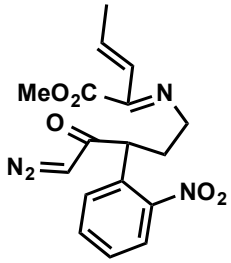
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 - 7.77 (m 3H), 7.66 - 7.57 (m, 3H), 7.54 - 7.51 (m, 1H), 7.48 - 7.40 (m, 3H), 7.36 - 7.31 (m, 2H), 6.03 (bs, 1H), 4.56 (dd, J_1 = 10.7 Hz, J_2 = 6.8 Hz, 1H), 4.46 (dd, J_1 = 10.7 Hz, J_2 = 6.3 Hz, 1H), 4.27 (dd, J_1 = 6.5 Hz, J_2 = 6.5 Hz, 1H), 4.11 - 4.04 (m, 1H), 3.75 - 3.68 (m, 1H), 3.44 (bs, 3H), 2.98 - 2.87 (m, 1H), 2.62 (ddd, J_1 = 14.4 Hz, J_2 = 8.0 Hz, J_3 = 2.8 Hz, 1H), 2.45 - 2.29 (m, 2H), 1.26 - 1.24 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.0, 178.9, 167.4, 156.8, 154.7, 148.9, 144.0, 143.6, 141.6, 141.6, 132.9, 131.7, 130.9, 129.0, 128.0, 127.3, 127.1, 125.2, 125.1, 124.7, 120.3, 120.2, 120.2, 82.4, 76.4, 67.7, 65.9, 63.6, 52.6, 51.2, 49.3, 47.4, 41.0, 29.9, 29.6, 28.6, 24.0, 23.6, 22.9, 21.0, 20.1, 17.9, 17.7, 17.4, 14.8, 14.3, 11.8, 11.6 ppm.

IR (film): 2953, 2924, 2852, 1745, 1705, 1622, 1531, 1450, 1404, 1357, 1330, 1273, 1259, 1213, 1149, 1035, 1020, 869, 754, 742, 678, 669, 650 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{28}N_2O_7Na^+$: 575.1794, found: 575.1792

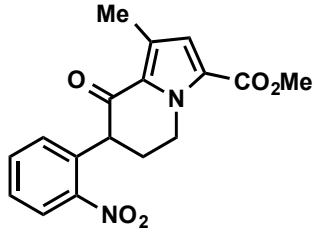
Methyl (2*Z*,3*E*)-2-((5-diazo-3-(2-nitrophenyl)-4-oxopentyl)imino)pent-3-enoate (324)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-((*E*)-prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate (20.0 mg, 34.0 μmol, 1 eq) was dissolved in absolute THF (500 μL). DBU (10.0 μL, 10.0 mg, 69.0 μmol, 2 eq) was added and the resulting mixture was stirred at rt for 10min. The reaction mixture was directly subjected to flash column chromatography (SiO_2, PE/EtOAc/NEt_3 = 5:1:0.001 to 2:1:0.001) to obtain methyl (2*Z*,3*E*)-2-((5-diazo-3-(2-nitrophenyl)-4-oxopentyl)imino)pent-3-enoate (8.00 mg, 22.3 μmol, 0.66 eq) as a mixture of double bond isomers.

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.45 - 7.41 (m, 1H), 7.32 - 7.26 (m, 1H); 6.86 - 6.80 (m, 1H), 6.60 - 6.53 (m, 1H), 6.38 - 6.28 (m, 1H), 6.08 - 5.85 (m, 1H), 4.81 - 4.61 (m, 1H), 4.53 - 4.43 (m, 1H), 3.53 - 3.05 (m, 5H), 2.55 - 2.47 (m, 1H), 2.16 - 2.06 (m, 1H), 1.40 - 1.35 (m, 3H) ppm.

Methyl 1-methyl-7-(2-nitrophenyl)-8-oxo-5,6,7,8-terahydroindolizine-3-carboxylate (325)



(2*Z*,3*E*)-2-((5-Diazo-3-(2-nitrophenyl)-4-oxopentyl)imino)pent-3-enoate as a mixture of double bond isomers (5.00 mg, 13.9 μmol, 1 eq) was dissolved in benzene (4 mL) and $Cu(acac)_2$ (200 μg, 0.90 μmol, 0.05 eq) was added. The resulting mixture was stirred at reflux for 90min. After cooling down to rt the

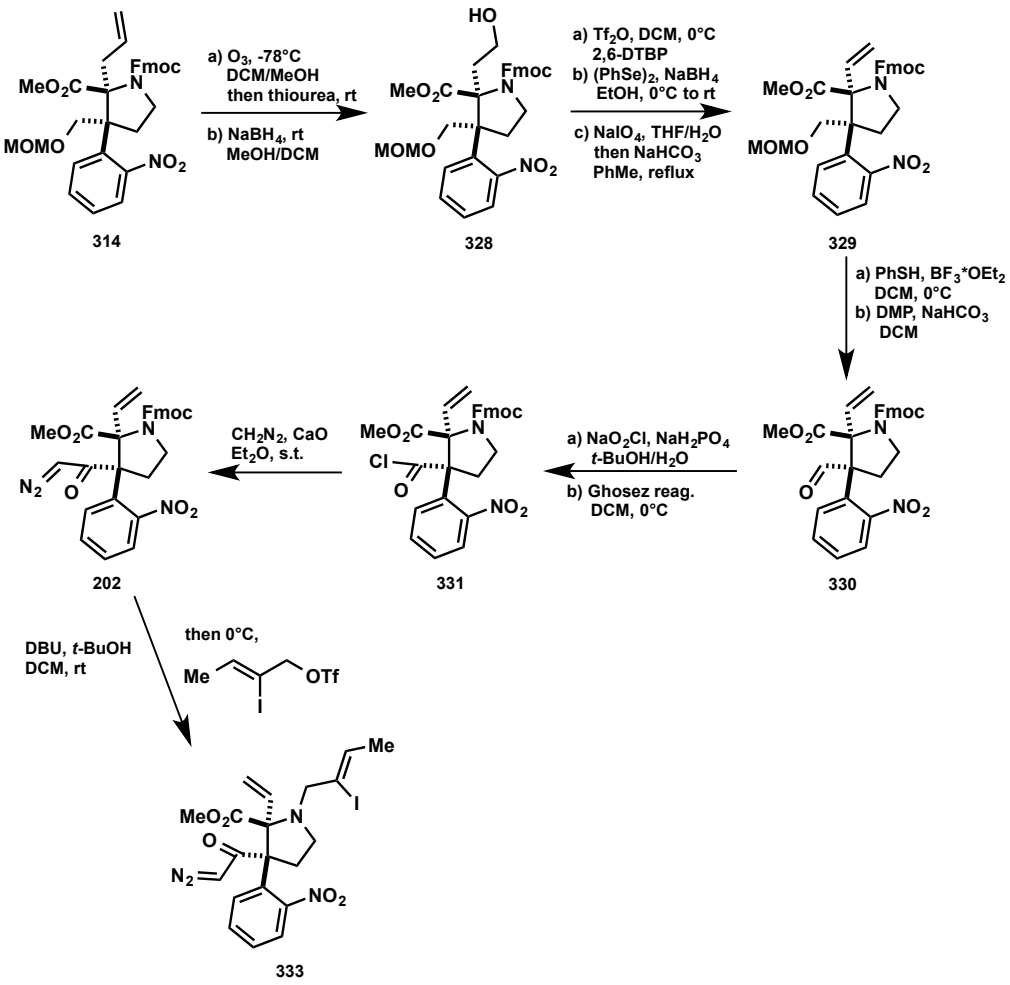
solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (SiO_2 , PE/EtOAc = 2:1) to obtain methyl 1-methyl-7-(2-nitrophenyl)-8-oxo-5,6,7,8-terahydroindolizine-3-carboxylate (1.00 mg, 3.05 μmol, 0.22 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.61 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.4 Hz, 1H), 7.47 (ddd, J_1 = 8.1 Hz, J_2 = 7.4 Hz, J_3 = 1.2 Hz, 1H), 7.34 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 6.77 (s, 1H), 5.18 (ddd, J_1 = 14.1 Hz, J_2 = 4.4 Hz, J_3 = 3.0 Hz, 1H), 4.53 (dd, J_1 = 12.6 Hz, J_2 = 4.4 Hz, 1H), 4.28 (ddd, J_1 = 14.1 Hz, J_2 = 12.0 Hz, J_3 = 3.6 Hz, 1H), 3.88 (s, 3H), 2.78 - 2.68 (m, 1H), 2.60 (ddd, J_1 = 13.6 Hz, J_2 = 7.5 Hz, J_3 = 3.7 Hz, 1H), 2.37 (s, 3H) ppm.

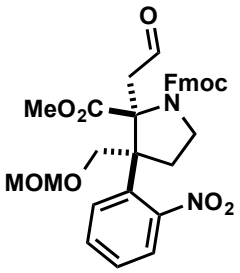
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 187.2, 161.5, 150.2, 133.4, 133.3, 130.8, 130.8, 128.9, 128.4, 125.3, 124.3, 118.8, 51.9, 49.4, 44.8, 30.6, 13.5 ppm.

IR (film): 2954, 2924, 2852, 1734, 1716, 1662, 1558, 1525, 1506, 1456, 1429, 1417, 1386, 1354, 1236, 1211, 1105, 989, 972, 920, 856, 819, 769, 677, 669, 650, 617, 422 cm^{-1}.

HRMS (ESI): calc. for $C_{17}H_{16}N_2O_5Na^+$: 351.0957, found: 351.0959


a) O_3, -78°C
DCM/MeOH
then thiourea, rt
b) $NaBH_4$, rt
MeOH/DCM
a) Tf_2O, DCM, 0°C
2,6-DTBP
b) $(PhSe)_2$, $NaBH_4$
EtOH, 0°C to rt
c) $NaIO_4$, THF/H_2O
then $NaHCO_3$
PhMe, reflux
a) PhSH, BF_3*OEt_2
DCM, 0°C
b) DMP, $NaHCO_3$
DCM
a) NaO_2Cl, NaH_2PO_4
t-BuOH/H_2O
b) Ghosez reag.
DCM, 0°C
CH_2N_2, CaO
Et_2O, s.t.
DBU, *t*-BuOH
DCM, rt
then 0°C,
Fmoc
MeO_2C
MOMO
HO
Cl
N_2
NO_2
Me
OTf
I
314
328
329
330
331
202
333

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (328a)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-allyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (2.09 g, 3.56 mmol, 1 eq) was dissolved in DCM (200 mL) and MeOH (50 mL) and cooled to -78°C. Ozone was passed through the solution until a blue color appears followed by oxygen until the blue color disappears. Thiourea (271 mg, 3.56 mmol, 1 eq) was added and the mixture was allowed to warm up to rt. The reaction mixture was poured onto water (500 mL) and the aqueous phase was extracted with Et_2O (3x300mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain the aldehyde (1.57 g, 2.67 mmol, 0.75 eq) as a colourless foam.

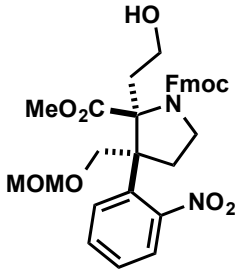
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.64 - 8.91 (m, 1H), 7.78 - 7.76 (m, 2H), 7.66 - 7.30 (m, 10H), 4.93 - 4.21 (m, 5H), 4.12 - 3.73 (m, 4H), 3.66 - 3.46 (m, 1H), 3.29 - 2.85 (m, 7H), 2.78 - 2.54 (m, 1H), 2.42 - 2.22 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 198.7, 198.4, 171.2, 154.7, 151.2, 143.9, 143.7, 141.5, 130.8, 130.3, 130.2, 130.1, 129.0, 128.8, 127.9, 127.2, 125.2, 125.0, 124.3, 124.2, 124.0, 120.5, 120.2, 120.2, 120.1, 96.5, 82.7, 73.2, 70.9, 70.7, 67.7, 66.5, 58.3, 55.9, 55.8, 52.7, 52.4, 47.4, 47.3, 46.5, 46.3, 45.0, 30.3 ppm.

IR (film): 3064, 2951, 2891, 1741, 1695, 1529, 1477, 1450, 1408, 1357, 1336, 1265, 1247, 1217, 1193, 1149, 1107, 1037, 977, 918, 848, 759, 738, 702, 621, 582, 547, 426 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{33}N_2O_9^+$: 589.2186; found: 589.2183

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (328)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-oxoethyl)pyrrolidine-1,2-dicarboxylate (1.57 g, 2.67 mmol, 1 eq) was dissolved in MeOH (150 mL) and DCM (30 mL). Sodium borohydride (112 mg, 2.95 mmol, 1.1 eq) was added and the mixture was stirred at rt for 30 min. Water (50 mL) was added and the mixture was stirred for 5 min at rt. The resulting mixture was poured onto water (500 mL) and the aqueous phase was extracted with Et_2O (3x300 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude alcohol was purified by flash column chromatography (SiO_2, PE/EtOAc = 1:1 to 0:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (1.48 g, 2.51 mmol, 0.94 eq) as a colourless foam.

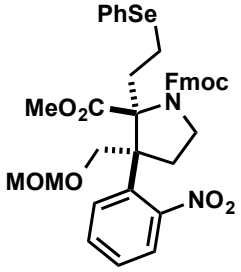
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 - 7.77 (m, 2H), 7.66 - 7.15 (m, 10H), 4.90 - 4.39 (m, 4H), 4.26 - 4.10 (m, 1H), 4.00 - 3.68 (m, 5H), 3.55 - 3.31 (m, 1H), 3.22 - 2.82 (m, 7H), 2.69 - 1.81 (m, 4H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.6, 171.1, 155.4, 154.5, 151.3, 151.2, 143.9, 143.9, 143.8, 142.1, 141.5, 141.4, 131.2, 130.6, 130.4, 130.0, 129.8, 128.6, 128.5, 127.9, 127.9, 127.8, 127.4, 127.2, 127.2, 127.0, 125.1, 125.0, 124.2, 124.0, 123.9, 123.8, 120.4, 120.2, 120.2, 96.7, 96.6, 74.4, 72.5, 71.1, 70.2, 67.7, 66.4, 59.8, 59.6, 59.4, 59.2, 55.7, 55.6, 52.3, 52.2, 47.3, 46.9, 46.4, 36.6, 35.2, 29.8, 27.8 ppm.

IR (film): 3466 (bs), 3064, 2949, 2891, 1739, 1697, 1529, 1450, 1406, 1371, 1344, 1265, 1244, 1213, 1192, 1149, 1105, 1035, 916, 848, 758, 731, 702, 669, 621, 584, 563, 545, 426 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{34}N_2O_9Na^+$: 613.2162; found: 613.2163

1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-phenylselanyl)ethyl)pyrrolidine-1,2-dicarboxylate (328b)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 2-(2-hydroxyethyl)-3-((methoxymethoxy)-methyl)-3-(2-nitrophenyl)pyrrolidine-1,2-dicarboxylate (1.48 g, 2.51 mmol, 1 eq) were dissolved in absolute DCM (50 mL) and cooled to 0°C. 2,6-Di-*tert*-butylpyridine (1.35 mL, 1.15 g, 6.01 mmol, 2.4 eq) and trifluoromethanesulfonic anhydride (505 μL, 848 mg, 3.01 mmol, 1.2 eq) were sequentially added. The mixture was allowed to warm up to rt and was stirred for 1h. The organic phase was washed with saturated $NaHCO_3$ solution (100 mL), dried over $MgSO_4$, filtrated and concentrated under reduced pressure.

Diphenyldiselenid (430 mg, 1.38 mmol, 0.55 eq) was dissolved in absolute EtOH (10 mL) and cooled to 0°C. Sodium borohydride (114 mg, 3.01 mmol, 1.2 eq) was added and the resulting mixture was stirred for 10min at 0°C under gas evolution. The crude triflate was dissolved in absolute EtOH (15 mL) and added to the colourless selenid solution. After beeing allowed to warm up to rt the resulting mixture was stirred for 45min and was then poured onto $NaHCO_3$ solution (300 mL). The aqueous phase was extracted with Et_2O (3x300 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The material was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain the seleno ether (1.54 g, 2.10 mmol, 0.84 eq) as a colourless foam.

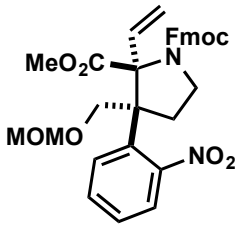
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.75 (m, 2H), 7.63 - 7.20 (m, 15H), 4.53 - 4.21 (m, 5H), 4.02 - 3.64 (m, 3H), 3.53 - 3.38 (m, 1H), 3.20 - 2.40 (m, 11H), 2.34 - 2.22 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.4, 154.9, 151.1, 143.9, 143.9, 141.5, 133.9, 132.9, 131.2, 130.4, 130.2, 129.9, 129.3, 129.2, 128.5, 127.9, 127.7, 127.5, 127.3, 127.2, 127.0, 125.1, 125.0, 125.0, 124.5, 124.5, 123.9, 120.3, 120.2, 96.7, 96.5, 75.2, 70.8, 69.9, 67.5, 67.4, 59.1, 55.8, 55.7, 52.3, 52.3, 47.3, 46.5, 35.1, 30.3, 29.6, 23.4 ppm.

IR (film): 3068, 2949, 2891, 1741, 1699, 1577, 1531, 1477, 1450, 1436, 1404, 1371, 1338, 1244, 1213, 1149, 1109, 1041, 1022, 918, 848, 759, 740, 692 cm^{-1}.

HRMS (ESI): calc. for $C_{38}H_{39}N_2O_8Se^+$: 731.1872; found: 731.1866

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (329)



1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-(2-phenylselanyl)ethyl)pyrrolidine-1,2-dicarboxylate (1.54 g, 2.10 mmol, 1 eq) was dissolved in THF/H_2O = 4:1 (40 mL) and sodium periodate (4.50 g, 21.1 mmol, 10 eq) was added. After stirring at rt for 3h, the colourless suspension was transferred to a refluxing mixture of $NaHCO_3$ (354 mg, 4.21 mmol, 2 eq) in toluene (100 mL) and stirred for 10min. After cooling down to rt the solvent was removed under reduced pressure. H_2O (300 mL) and $Na_2S_2O_3$ solution (50 mL) were added and the aqueous phase was extracted with Et_2O (3x300 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (861 mg, 1.50 mmol, 0.71 eq) as a colourless foam.

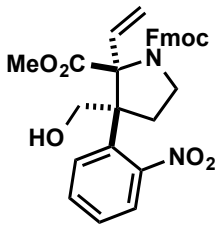
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.71 (m, 2H), 7.62 - 7.58 (m, 2H), 7.54 - 7.21 (m, 6H), 6.68 - 6.39 (m, 1H), 5.44 - 5.15 (m, 2H), 4.52 - 3.94 (m, 6H), 3.76 - 3.56 (m, 3H), 3.32 - 3.17 (m, 3H), 3.10 - 3.06 (m, 3H), 2.79 - 2.62 (m, 1H), 2.52 - 2.44 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.2, 154.7, 151.6, 144.0, 143.9, 143.9, 141.5, 141.5, 141.4, 141.4, 132.3, 131.8, 131.1, 130.7, 130.3, 130.0, 129.9, 128.7, 128.6, 127.9, 127.9, 127.7, 127.2, 127.2, 127.1, 127.0, 125.1, 125.1, 125.0, 124.9, 123.8, 123.7, 120.2, 120.0, 120.0, 117.2, 117.0, 96.5, 96.4, 76.0, 75.3, 71.6, 71.3, 67.7, 67.5, 58.8, 57.9, 55.5, 55.4, 52.6, 52.5, 47.4, 47.3, 46.6, 45.9, 28.2 ppm.

IR (film): 3066, 2951, 2891, 1741, 1705, 1531, 1450, 1408, 1373, 1354, 1340, 1246, 1213, 1193, 1151, 1107, 1087, 1043, 918, 850, 759, 740 cm^{-1}.

HRMS (ESI): calc. for $C_{32}H_{33}N_2O_8^+$: 573.2237; found: 573.2237

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (329b)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (861 mg, 1.50 mmol, 1 eq) was dissolved in absolute DCM (30 mL) and cooled to 0°C. Thiophenol (199 mg, 184 μL, 1.80 mmol, 1.2eq) and BF_3*OEt_2 (476 μL, 1.80 mmol, 1.2 eq, 48% solution in Et_2O) were sequentially added. The reaction mixture was stirred for 13h and was thereby allowed to warm up to rt. $NaHCO_3$ solution (100 mL) was added and the aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO2, PE/EtOAc = 2:1 to 1:1) to obtain the alcohol (715 mg, 1.35 mmol, 0.9 eq) as a colourless foam.

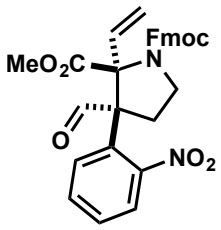
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 - 7.23 (m, 12H), 6.74 - 6.42 (m, 1H), 5.48 - 5.10 (m, 2H), 4.48 - 3.44 (m, 7H), 3.29 - 3.12 (m, 3H), 2.74 - 2.58 (m, 1H), 2.53 - 2.30 (m, 1H), 1.70 - 1.59 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.7, 154.2, 152.1, 144.0, 143.9, 141.5, 141.5, 132.8, 132.8, 132.5, 131.5, 130.5, 130.4, 129.0, 128.9, 127.9, 127.7, 127.3, 127.1, 127.0, 125.1, 125.1. 125.0, 124.9, 124.0, 124.0, 120.2, 120.0, 117.0, 116.8, 116.7, 76.2, 75.5, 67.6, 67.5, 67.4, 67.1, 59.7, 57.9, 52.5, 52.4, 47.4, 47.3, 46.6, 46.0, 28.3 ppm.

IR (film): 3458 (bs), 2951, 2893, 1741, 1701, 1529, 1450, 1409, 1373, 1354, 1340, 1255, 1246, 1209, 1157, 1082, 1066, 1043, 929, 848, 761, 740, 667, 420 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{29}N_2O_7^+$: 529.1975; found: 529.1975

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-1,2-dicarboxylate (330)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(hydroxymethyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (715 mg, 1.35 mmol, 1 eq) was dissolved in absolute DCM (15 mL). $NaHCO_3$ (682 mg, 8.12 mmol, 6 eq) and *Dess-Martin* periodinane (1.72 g, 4.06 mmol, 3 eq) were added at rt and the resulting mixture was stirred for 3h. After that the mixture was poured onto $NaHCO_3$ solution (100 mL) and the aqueous phase was extracted with DCM (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-1,2-dicarboxylate (594 mg, 1.13 mmol, 0.84 eq) as a colourless foam.

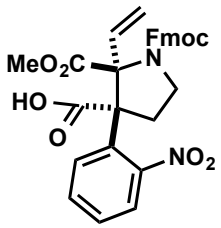
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 7.93 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 7.79 - 7.28 (m, 11H), 6.80 - 6.55 (m, 1H), 5.53 - 5.32 (m, 1H), 5.19 - 5.08 (m, 1H), 4.59 - 4.47 (m, 1H), 4.40 - 4.31 (m, 1H), 4.25 - 4.11 (m, 1H), 4.03 - 3.96 (m, 1H), 3.88 - 3.68 (m, 1H), 3.36 - 3.09 (m, 3H), 2.62 - 2.55 (m, 1H), 2.46 - 2.36 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.0, 169.5, 153.7, 144.0, 143.9, 141.6, 141.5, 136.8, 133.6, 133.3, 133.0, 132.0, 131.9, 130.6, 129.5, 127.9, 127.9, 127.3, 127.2, 127.0, 125.8, 125.1, 125.0, 120.2, 117.5, 67.8, 67.4, 65.4, 52.8, 47.5, 46.5, 31.3 ppm.

IR (film): 3064, 2949, 2897, 1741, 1705, 1606, 1575, 1527, 1477, 1450, 1404, 1340, 1265, 1211, 1155, 1114, 1093, 1058, 1006, 937, 854, 786, 758, 738, 725, 700, 621, 542 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{26}N_2O_7Na^+$: 549.1638; found: 549.1638

1-(((9*H*-Fluoren-9-yl)carbonyl)-2-(methoxycarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-3-carboxylic acid (330b)



1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-formyl-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-1,2-dicarboxylate (448 mg, 851 μmol, 1 eq) was dissolved in *t*BuOH (10 mL) and 2-methyl-2-butene (2 mL) was added. NaO_2Cl (960 mg, 8.51 mmol, 10 eq, 80%) and NaH_2PO_4*H_2O (939 mg, 6.81 mmol, 8 eq) were dissolved in H_2O (10 mL). The aqueous solution was added to the aldehyde and the mixture was vigorously stirred at rt for 22h. The reaction mixture was poured onto H_2O (100 mL) and the aqueous phase was extracted with Et_2O (200 mL). 1M HCl (50 mL) was addded and the aqueous phase was extracted with Et_2O (2x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. An analytical sample was purified by flash column chromatography (SiO_2, EtOAc). The material was used for the next step without further purifications.

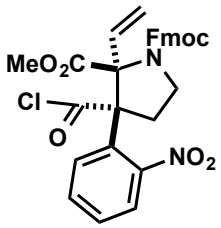
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 3H), 7.63 - 7.49 (m, 4H), 7.43 - 7.37 (m, 3H), 7.30 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H), 6.73 - 6.42 (m, 1H), 5.43 - 5.10 (m, 2H), 4.47 - 4.22 (m, 3H), 4.04 - 3.98 (m, 1H), 3.89 - 3.83 (m, 1H), 3.48 - 3.16 (m, 3H), 2.78 - 2.62 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.2, 170.8, 154.4, 150.2, 144.1, 143.8, 141.5, 141.5, 132.6, 131.7, 131.3, 131.1, 128.9, 127.8, 127.2, 125.2, 125.1, 124.8, 120.1, 117.2, 67.6, 66.9, 52.9, 47.6, 47.3, 31.5, 29.8 ppm.

IR (film): 3064, 2953, 2926, 1735, 1707, 1575, 1529, 1477, 1450, 1408, 1357, 1338, 1247, 1220, 1197, 1157, 1095, 1053, 977, 910, 848, 758, 731, 648, 621, 543 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{26}N_2O_8Na^+$: 565.1587; found: 565.1583

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (331)



The crude carboxylic acid was dissolved in absolute DCM (10 mL) and was cooled to 0°C. Ghosez reagent (560 μL, 568 mg, 4.25 mmol, 5 eq) was added and the mixture was stirred at 0°C for 30min. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 3:1 to 2:1 to 1:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (382 mg, 681 μmol, 0.8 eq) as a colourless foam.

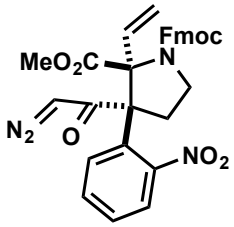
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 - 7.29 (m, 12H), 6.74 - 5.99 (m, 1H), 5.45 - 5.02 (m, 2H), 4.48 - 3.73 (m, 5H), 3.47 - 2.57 (m, 5H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 179.9, 169.8, 154.0, 149.2, 144.1, 143.9, 143.8, 141.5, 133.2, 131.1, 130.4, 130.1, 129.9, 129.0, 127.9, 127.2, 126.0, 125.2, 125.0, 120.1, 119.4, 72.4, 67.6, 52.9, 47.3, 45.4, 32.5, 31.7 ppm.

IR (film): 3064, 2951, 2902, 1797, 1741, 1707, 1606, 1577, 1531, 1450, 1408, 1355, 1342, 1298, 1246, 1219, 1195, 1157, 1095, 1051, 1002, 908, 854, 758, 736, 646, 420 cm^{-1}.

HRMS (ESI): calc. for $C_{30}H_{25}N_2O_7ClNa^+$: 583.1248; found: 583.1248

1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (202)



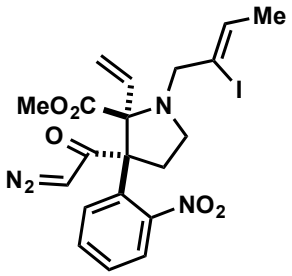
CaO (76.4 mg, 1.36 mmol, 2 eq) was put in a sealed tube and freshly prepared diazomethane in absolute Et_2O (20 mL, solution prepared started from 5.00 g *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) was added. 1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(chlorocarbonyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (382 mg, 681 μmol, 1 eq) was dissolved in absolute Et_2O (5 mL) and added to the sealed tube. The tube was sealed and the mixture was stirred at rt for 2d. After complete reaction the solids were removed by filtration over celite and the solvent was concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, PE/EtOAc = 2:1 to 1:1 to 0:1) to obtain 1-((9*H*-fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (251 mg, 443 μmol, 0.65 eq) as a slightly yellow foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 - 7.70 (m, 3H), 7.61 - 7.46 (m, 5H), 7.41 - 7.38 (m, 2H), 7.34 - 7.29 (m, 2H), 6.66 - 6.31 (m, 1H), 5.46 - 5.07 (m, 2H), 4.90 (s, 1H), 4.47 - 4.43 (m, 1H), 4.29 - 4.08 (m, 3H), 3.93 - 3.85 (m, 1H), 3.41 - 3.15 (m, 3H), 2.65 - 2.58 (, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 191.8, 171.2, 154.5, 151.1, 144.1, 143.9, 141.5, 141.4, 131.9, 131.3, 131.2, 131.0, 127.8, 127.2, 125.3, 125.1, 120.1, 118.7, 68.9, 67.6, 57.3, 52.9, 48.0, 47.4, 47.3, 31.9 ppm.

IR (film): 2953, 2108, 1739, 1706, 1636, 1531, 1449, 1405, 1338, 1244, 1155, 1099, 1051, 911, 853, 739, 649 cm^{-1}.
HRMS (ESI): calc. for $C_{31}H_{27}N_4O_7^+$: 567.1880; found: 567.1878

Methyl 3-(2-diazoacetyl)-1-((*Z*)-2-iodobut-2-en-1-yl)-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-2-carboxylate (333)

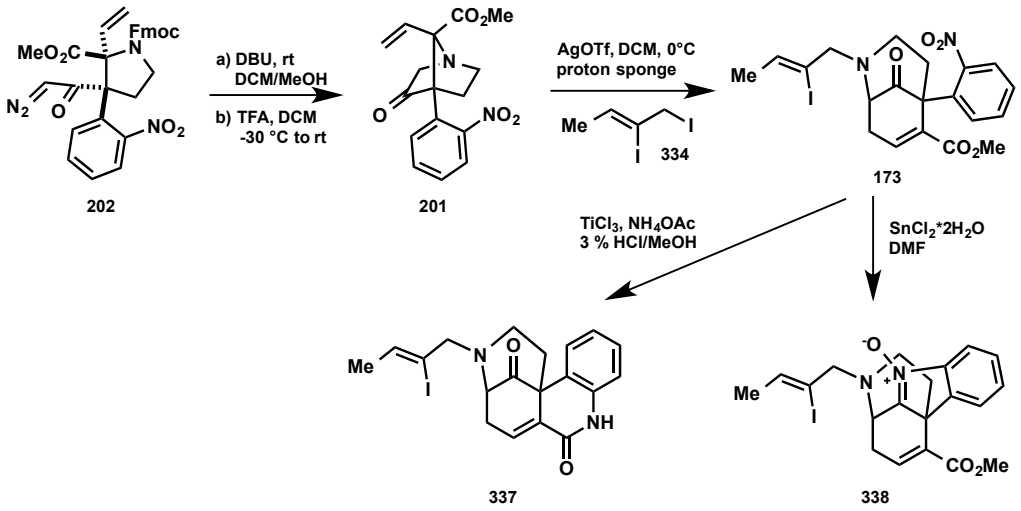


1-((9*H*-Fluoren-9-yl)methyl) 2-methyl 3-(2-diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (11.0 mg, 19.0 μmol, 1 eq) was dissolved in absolute DCM (400 μL). *t*BuOH (18.0 μL, 14.0 mg, 194 μmol, 10 eq) and DBU (5.80 μL, 5.90 mg, 39.0 μmol, 2 eq) were added and the resulting mixture was stirred for 15min at rt. In the meantime (*Z*)-2-iodobut-2-en-1-ol (5.80 mg, 29.0 μmol, 1.5 eq) was dissolved in absolute DCM (100 μL) and cooled to 0°C. 2,6-Di-*tert*-butyl pyridine (13.0 μL, 11.0 mg, 58.0 μmol, 3 eq) and trifluoromethanesulfonic anhydride (4.90 μL, 8.20 mg, 29.0 μmol, 1.5 eq) were added and the resulting mixture was stirred at 0°C for 15min. The triflate was transferred to the secondary amine and the resulting mixture was stirred at rt for 15min. A second portion triflate was prepared in the same manner and was transferred to the secondary amine. The resulting mixture was stirred at rt for 15min. Aqueous $NaHCO_3$ (25 mL) was added and the aqueous phase was extracted with DCM (3x25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude vinyl iodide was purified by flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 3:1 to 2:1) to obtain methyl 3-(2-diazoacetyl)-1-((*Z*)-2-iodobut-2-en-1-yl)-3-(2-nitrophenyl)-2-vinyl-pyrrolidine-2-carboxylate (2.00 mg, 4.00 μmol, 0.21 eq) as a colourless foam.

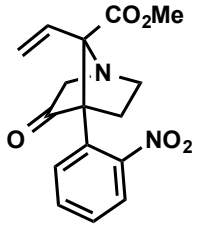
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.5 Hz, 1H), 7.51 - 7.44 (m, 2H), 7.38 (d, J = 8.2 Hz, 1H), 6.38 (dd, J_1 = 17.2 Hz, J_2 = 11.1 Hz, 1H), 6.00 - 5.94 (m, 2H), 5.56 (s, 1H), 5.55 (dd, J_1 = 11.2 Hz, J_2 = 1.4 Hz, 1H), 3.69 (d, J = 13.6 Hz, 1H), 3.50 (s, 3H), 3.30 - 3.25 (m, 1H), 2.83 - 2.76 (m, 1H), 2.66 - 2.57 (m, 2H), 2.39 (ddd, J_1 = 12.9 Hz, J_2 = 10.8 Hz, J_3 = 4.0 Hz, 1H), 1.81 (dd, J_1 = 6.3 Hz, J_2 = 1.9 Hz, 3H) ppm.

IR (film): 2954, 2922, 2850, 2104, 1726, 1635, 1527, 1354, 1226, 1157 cm^{-1}.

HRMS (ESI): calc. for $C_{20}H_{22}N_4O_5I^+$: 525.0635, found: 525.0637


Fmoc
MeO2C
N2
O
NO2
202
a) DBU, rt
DCM/MeOH
b) TFA, DCM
-30 °C to rt
CO2Me
N
O
NO2
201
AgOTf, DCM, 0°C
proton sponge
Me
I
I
334
O2N
O
CO2Me
173
TiCl3, NH4OAc
3 % HCl/MeOH
SnCl2*2H2O
DMF
NH
337
-O
+N
338

Methyl 4-(2-nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (201)



3-(2-Diazoacetyl)-3-(2-nitrophenyl)-2-vinylpyrrolidine-1,2-dicarboxylate (55.0 mg, 97.1 μmol, 1 eq) was dissolved in DCM/MeOH = 1:1 (6 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (29.6 mg, 29.0 μL, 194 μmol, 2 eq) was added and the mixture was stirred for 4.5h at rt. The reaction mixture was poured onto 1 M $NaHSO_4$ (50 mL) and the aqueous phase was extracted with PE (2x50mL). Solid Na_2CO_3 was added to the aqueous phase until no more gas evolution occured followed by solid NaCl until saturation. The aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain the secondary amine as a colourless foam.

The crude secondary amine was dissolved in absolute DCM (6 mL) and cooled to -30°C. Trifluoroacetic acid (110 mg, 73.8 μL, 971 μmol, 10 eq) was added and the mixture was stirred for 23h and was thereby allowed to warm up to rt. Saturated K_2CO_3 solution (50 mL) was added and the aqueous phase was extracted with EtOAc (3x100 mL). The combined organic phases were concentrated under reduced pressure and poured onto 1 M HCl solution (100 mL). The aqueous phase was extracted with EtOAc (2x50 mL). 8 M NH_4OH solution was added to the aqueous phase until pH = 10 followed by extraction with EtOAc (3x100 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain methyl 4-(2-nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (16.6 mg, 52.4 μmol, 0.54 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.63 - 7.56 (m, 2H), 7.48 (ddd, J_1 = 8.2 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz, 1H), 6.01 (dd, J_1 = 17.4 Hz, J_2 = 10.9 Hz, 1H), 5.55 (d, J = 17.4 Hz, 1H), 5.46 (d, J = 11.3 Hz,

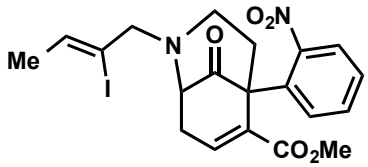
1H), 3.80 - 3.75 (m, 1H), 3.78 (s, 3H), 3.51 - 3.43 (m, 1H), 3.15 (d, *J* = 17.4 Hz, 1H), 2.91 - 2.80 (m, 2H), 2.39 - 2.32 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 212.0, 169.7, 151.3, 133.3, 131.7, 131.6, 129.0, 127.2, 125.8, 121.2, 84.6, 65.0, 63.3, 53.0, 51.5, 33.1 ppm.

IR (film): 2954, 2924, 2852, 1739, 1573, 1529, 1481, 1458, 1436, 1357, 1273, 1255, 1207, 1163, 1139, 1078, 1066, 950, 852, 802, 786, 769, 740, 698 cm^{-1}.

HRMS (ESI): calc. for $C_{16}H_{17}N_2O_5^+$: 317.1137; found: 317.1147

Methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo-[3.3.1]-non-6-ene-6-carboxylate (173)



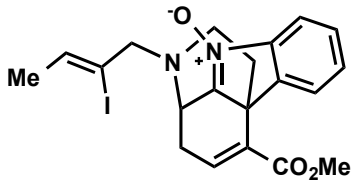
(*Z*)-2-iodobut-2-en-1-ol (500 mg, 2.53 mmol, 1 eq) was dissolved in DCM (10 mL). Triphenylphosphine (629 mg, 2.40 mmol, 0.95 eq) and imidazole (172 mg, 2.53 mmol, 1 eq) were added and the mixture was cooled to 0°C. Iodine (641 mg, 2.53 mmol, 1 eq) was added and the resulting mixture was stirred at 0°C for 2h. Aqueous thiosulfate solution (50 mL) was added and the aqueous phase was extracted with DCM (50 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude iodide was purified by flash column chromatography (SiO_2, pentane/Et_2O = 10:1) to afford (*Z*)-1,2-diiodobut-2-ene (360 mg, 971 μmol, 0.38 eq) as a slightly yellow fluid.

AgOTf (29.2 mg, 114 μmol, 6 eq) was put in a Schlenk tube under argon. Absolute DCM (200 μL) was added and the resulting suspension was cooled to 0°C. Freshly prepared (*Z*)-1,2-diiodobut-2-ene (35.0 mg, 114 μmol, 6 eq) dissolved in absolute DCM (100 μL) was added and the mixture was stirred for 1min at 0°C. 4-(2-Nitrophenyl)-3-oxo-7-vinyl-1-azabicyclo[2.2.1]heptane-7-carboxylate (6.00 mg, 19.0 μmol, 1 eq) and 1,8-bis(*N*,*N*-dimethylamino)naphtalene (24.4 mg, 114 μmol, 6 eq) dissolved in absolute DCM (500 μL) were added to the Schlenk tube and the resulting suspension was stirred at 0°C for 4h. During this time the mixture was allowed to warm up

to rt slowly. The mixture was directly submitted to flash column chromatography (SiO_2, PE/EtOAc = 5:1 to 2:1) to obtain methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (4.00 mg, 8.06 μmol, 0.42 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.45 (ddd, J_1 = 8.3 Hz, J_2 = 6.9 Hz, J_3 = 1.5 Hz, 1H), 7.34 (dd, J_1 = 4.6 Hz, J_2 = 2.9 Hz, 1H), 5.88 (q, *J* = 6.5 Hz, 1H), 3.50 (s, 3H), 3.41 - 3.26 (m, 4H), 2.97 (ddd, J_1 = 20.5 Hz, J_2 = 5.5 Hz, J_3 = 3.1 Hz, 1H), 2.92 - 2.81 (m, 2H), 2.76 - 2.67 (m, 2H), 1.78 (d, *J* = 6.5 Hz, 3H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 205.6, 165.1, 149.2, 139.8, 134.6, 133.9, 132.7, 130.8, 130.2, 128.3, 125.6, 107.8, 65.4, 61.4, 55.7, 51.9, 44.3, 38.4, 29.9, 21.9 ppm.
IR (film): 2954, 2924, 2854, 1716, 1643, 1527, 1462, 1438, 1354, 1284, 1238, 1176, 1118, 1095, 1060, 1014, 964, 852, 783, 732, 574, 474 cm^{-1}.
HRMS (ESI): calc. for $C_{20}H_{22}N_2O_5I^+$: 497.0573; found: 497.0568

(*Z*)-12-(2-Iodobut-2-en-1-yl)-4-(methoxycarbonyl)-1,2-dihydro-1,4a-(epimino-ethano)carbazole 9-oxide (338)

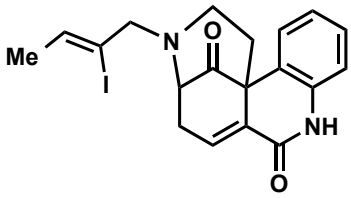


Methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (4.00 mg, 8.06 μmol, 1 eq) was dissolved in absolute DMF (1 mL) under argon. $SnCl_2$*$2H_2O$ (182 mg, 806 μmol, 100 eq) was added and the mixture was stirred at rt for 25h. H_2O (10 mL) was added and the aqueous phase was poured onto aqueous NH_4OH (15 mL). The aqueous phase was extracted with EtOAc (3x25 mL). The combined organic phases were washed with aqueous 1 M HCl (50 mL). The aqueous phase was basified with NH_4OH and extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtrated

and concentrated under reduced pressure to obtain (*Z*)-12-(2-iodobut-2-en-1-yl)-4-(methoxycarbonyl)-1,2-dihydro-1,4a-(epimino-ethano)carbazole 9-oxide (2.00 mg, 4.31 μmol, 0.54 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.45 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.0 Hz, 1H), 7.11 (dd, J_1 = 3.2 Hz, J_2 = 3.2 Hz, 1H), 6.01 (q, *J* = 6.1 Hz, 1H), 4.58 (dd, J_1 = 3.7 Hz, J_2 = 3.7 Hz, 1H), 3.77 (s, 3H), 3.41 (d, *J* = 14.0 Hz, 1H), 3.21 (d, *J* = 14.0 Hz, 1H), 3.09 (ddd, J_1 = 14.3 Hz, J_2 = 12.6 Hz, J_3 = 2.8 Hz, 1H), 2.86 (dd, J_1 = 3.7 Hz, J_2 = 3.7 Hz, 2H), 2.78 - 2.73 (m, 1H), 2.68 - 2.63 (m, 1H), 1.82 (d, *J* = 6.5 Hz, 3H), 1.74 - 1.67 (m, 1H) ppm.

(*Z*)-3-(2-Iodobut-2-en-1-yl)-2,3,4,5-tetrahydro-1*H*-4,12b-methanoazocino-[5,4-*c*]-quinoline-7,13(8*H*)-dione (337)



Methyl (*Z*)-2-(2-iodobut-2-en-1-yl)-5-(2-nitrophenyl)-9-oxo-2-azabicyclo[3.3.1]-non-6-ene-6-carboxylate (2.00 mg, 4.00 μmol, 1 eq) was dissolved in MeOH (400 μL). Aqueous 2.5 mol/L NH_4OAc (600 μL) was added. $TiCl_3$ (20 μL, 1.3 mol/L solution in 3% aqueous HCl, 6.5 eq) was added every 30min over a period of 2.5h at rt (32.5 eq in total). Aqueous K_2CO_3 (25 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure to obtain (*Z*)-3-(2-iodobut-2-en-1-yl)-2,3,4,5-tetrahydro-1*H*-4,12b-methanoazocino[5,4-*c*]-quinoline-7,13(8*H*)-dione (1.00 mg, 2.30 μmol, 0.58 eq) as a colourless foam.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (bs, 1H), 7.54 - 7.50 (m, 1H), 7.46 (dd, J_1 = 3.4 Hz, J_2 = 3.4 Hz, 1H), 7.23 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.4 Hz, 1H), 7.12 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.0 Hz, 1H), 6.71 (dd, J_1 = 7.9

Hz, J_2 = 1.0 Hz, 1H), 5.93 (q, J_1 = 13.0 Hz, J_2 = 6.5 Hz, 1H), 3.50 - 3.42 (m, 2H), 3.37 (d, J = 14.3 Hz, 1H), 3.10 (ddd, J_1 = 12.9 Hz, J_2 = 12.9 Hz, J_3 = 3.2 Hz, 1H), 2.98 (dd, J_1 = 21.0 Hz, J_2 = 3.9 Hz, 1H), 2.81 - 2.68 (m, 2H), 2.33 - 2.28 (m, 1H), 2.01 - 1.97 (m, 1H), 1.81 (d, J = 6.5 Hz, 3H) ppm.

IR (film): 2953, 2924, 2852, 1735, 1676, 1629, 1593, 1489, 1456, 1436, 1375, 1365, 1259, 1228, 1217, 1205, 1091, 1082, 1037, 968, 802, 754, 677, 459, 403 cm^{-1}.

HRMS (ESI): calc. for $C_{19}H_{20}N_2O_2I^+$: 435.0570, found: 435.0569

9. Appendix

9.1 Used abbreviations

^{1,3}A	1,3-Allyl
ABSA	4-Acetamidobenzenesulfonyl azide
Ac	Acetyl
ac	Acetone
acac	Acetylacetone
AD	Asymmetric dihydroxylation
AIBN	Azobisisobutyronitrile
atm	Atmosphere
aq	Aqueous
BHT	Butylated hydroxytoluene
Boc	Butyloxycarbonyl
BP	Boiling point
brsm	Based on recovered starting material
BTM	1*H*-Benzotriazole-1-methanol
Bu	Butyl
CA	Cycloaddition
calc	Calculated
CAN	Cerium ammonium nitrate
cat	Catalyst
Cbz	Carboxybenzyl
COD	1,5-Cyclooctadiene
comp	Complete
conc	Concentrated
Crit	Criterion
d	Days
DA	Diels-Alder
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane

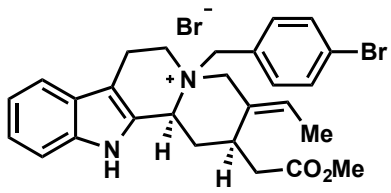
decomp	Decomposition
DHP	Dihydropyran
DIBAL	Diisobutylaluminium hydride
DIC	Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMBA	1,3-Dimethylbarbituric acid
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	Dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereoisomeric ratio
DTBP	2,6-Di-tert-butylpyridine
EC 3.2.1.105	3-Alpha-(S)-strictosidine beta-glucosidase
EDCI	1-Ehtyl-3-(3-dimethylaminopropyl)carbodiimide
eq	Equivalents
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl acetate
Fmoc	Fluorenylmethyloxycarbonyl
FT	Fourier transform
FVP	Flash vacuum pyrolysis
G I	Grubbs' catalyst first generation
G II	Grubbs' catalyst second generation
h	Hours
HOBt	Hydroxybenzotriazole
HG II	Hoveyda Grubbs' second generation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry

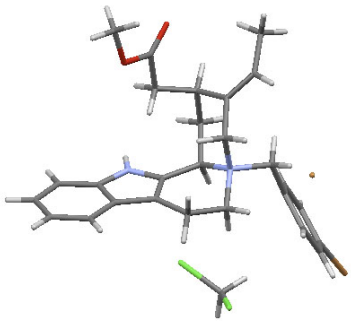
HWE	Horner-Wadsworth-Emmons
i	Iso
IBX	2-Iodoxybenzoic acid
IR	Infrared
LAH	Lithium aluminium hydride
LCT	Liquid chromatography Time of flight
LDA	Lithium diisopropylamide
lit.	Literature
M	Molar
m	Meta
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
MOM	Methoxymethyl
MP	Melting point
Ms	Mesylate
NADP	Nicotinamide adenine dinucleotide phosphate
NBA	*N*-Bromo acetamide
NBS	*N*-Bromo succinimide
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NIS	*N*-Iodo succinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidinone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
[O]	Oxidation step
p	Para
PE	Petroleum ether
Ph	Phenyl
ppm	Parts per million
Pr	Propyl

pyr	Pyridine
Q-TOF	Quadrupole time-of-flight
qunat	Qunatitative
Ra/Ni	Raney Nickel
reag	Reagent
rear	Rearrangement
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
R_f	Retardation factor
rt	Room temperature
sat	Saturated
SGLT	Sodium-glucose linked transporter
SM	Starting material
S_N2	Substitution nucleophili bi-molecular
s.t.	Sealed tube
t	Tert
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	Tertbutyl diphenyl silyl
TBS	Tertbutyl silyl
TES	Triethyl silyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TLC	Thin layer chromatography
TMS	Trimethyl silyl
Ts	Tosyl
X-ray	Röntgen radiation

9.2 Single-crystal diffraction data

20*E*-Geissoschizoate-*N*-4-bromobenzyl bromide (90)





Computing details

Data collection: Bruker *APEX2*; cell refinement: Bruker *SAINT*; data reduction: Bruker *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: Bruker *SHELXTL*; software used to prepare material for publication: Bruker *SHELXTL*.

Crystal data

$C_{27}H_{30}BrN_2O_2 \cdot CH_2Cl_2 \cdot Br$	$F(000)$ = 1336
M_r = 659.28	D_x = 1.539 Mg m^{-3}
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: P 2ac 2ab	Cell parameters from 9409 reflections
a = 10.1326 (4) Å	θ = 2.3–30.0°
b = 16.3094 (7) Å	μ = 3.06 mm^{-1}
c = 17.2211 (8) Å	T = 100 K
V = 2845.9 (2) Å^3	Needle, colourless
Z = 4	0.22 × 0.02 × 0.01 mm

Data collection

Bruker D8 Venture diffractometer	8341 independent reflections
Radiation source: fine-focus sealed tube	7852 reflections with $I > 2\sigma(I)$

Graphite monochromator	R_{int} = 0.049
φ and ω scans	θ_{max} = 30.1°, θ_{min} = 2.3°
Absorption correction: multi-scan *SADABS*	h = −14→14
T_{min} = 0.552, T_{max} = 0.967	k = −22→22
133676 measured reflections	l = −24→24

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.031	H-atom parameters constrained
$wR(F^2)$ = 0.078	$w = 1/[\sigma^2(F_o^2) + (0.039P)^2 + 3.0052P]$ where $P = (F_o^2 + 2F_c^2)/3$
S = 1.06	$(\Delta/\sigma)_{max}$ = 0.001
8341 reflections	$\Delta\rho_{max}$ = 0.78 e Å^{-3}
327 parameters	$\Delta\rho_{min}$ = −0.76 e Å^{-3}
0 restraints	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
Primary atom site location: structure-invariant direct methods	Absolute structure parameter: 0.006 (6)

Special details

Refinement

Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.33196 (3)	0.271372 (17)	0.100483 (14)	0.02124 (6)
O1	0.5699 (2)	0.44997 (13)	0.78844 (12)	0.0294 (5)
O2	0.5624 (2)	0.31257 (14)	0.78055 (12)	0.0315 (5)
N1	0.69708 (18)	0.50551 (12)	0.52056 (12)	0.0148 (4)
H1	0.7628	0.4708	0.5144	0.018*
N2	0.36678 (19)	0.40579 (12)	0.49346 (11)	0.0131 (4)
C1	0.7075 (2)	0.58562 (15)	0.54614 (14)	0.0155 (4)
C2	0.8196 (3)	0.62977 (16)	0.56819 (15)	0.0199 (5)
H2	0.9050	0.6059	0.5663	0.024*
C3	0.8011 (3)	0.70949 (17)	0.59284 (17)	0.0229 (5)
H3	0.8754	0.7414	0.6075	0.027*
C4	0.6736 (3)	0.74450 (16)	0.59662 (16)	0.0226 (5)
H4	0.6638	0.7989	0.6155	0.027*
C5	0.5631 (2)	0.70162 (15)	0.57360 (15)	0.0171 (5)
H5	0.4781	0.7261	0.5756	0.020*
C6	0.5796 (2)	0.62027 (15)	0.54691 (13)	0.0153 (4)
C7	0.4915 (2)	0.55849 (14)	0.51923 (14)	0.0148 (4)
C8	0.3467 (2)	0.56047 (15)	0.50435 (15)	0.0166 (4)
H8A	0.3240	0.6097	0.4735	0.020*
H8B	0.2984	0.5633	0.5543	0.020*
C9	0.3062 (2)	0.48350 (15)	0.46016 (14)	0.0159 (4)
H9A	0.2088	0.4785	0.4614	0.019*
H9B	0.3334	0.4892	0.4052	0.019*
C10	0.5168 (2)	0.40665 (13)	0.48281 (13)	0.0136 (4)
H10	0.5357	0.3996	0.4262	0.016*
C11	0.5655 (2)	0.48953 (15)	0.50643 (13)	0.0141 (4)
C12	0.5814 (2)	0.33498 (14)	0.52639 (14)	0.0141 (4)
H12A	0.6783	0.3419	0.5240	0.017*
H12B	0.5594	0.2835	0.4988	0.017*
C13	0.5408 (2)	0.32540 (15)	0.61274 (13)	0.0157 (4)
H13	0.5725	0.2707	0.6312	0.019*
C14	0.6035 (2)	0.39205 (17)	0.66490 (14)	0.0190 (5)
H14A	0.7002	0.3925	0.6566	0.023*
H14B	0.5687	0.4464	0.6495	0.023*
C15	0.5752 (3)	0.37796 (17)	0.75025 (15)	0.0213 (5)
C16	0.5573 (4)	0.4422 (2)	0.87197 (19)	0.0433 (9)
H16A	0.5656	0.4964	0.8960	0.065*
H16B	0.6269	0.4061	0.8917	0.065*
H16C	0.4708	0.4189	0.8846	0.065*
C17	0.3916 (2)	0.32575 (15)	0.61693 (14)	0.0153 (4)

C18	0.3150 (2)	0.26767 (16)	0.64725 (14)	0.0186 (4)
H18	0.2226	0.2763	0.6429	0.022*
C19	0.3568 (3)	0.19021 (18)	0.68744 (17)	0.0265 (6)
H19A	0.3093	0.1850	0.7368	0.040*
H19B	0.4520	0.1920	0.6975	0.040*
H19C	0.3364	0.1430	0.6543	0.040*
C20	0.3305 (2)	0.39973 (15)	0.57968 (12)	0.0149 (4)
H20A	0.3610	0.4497	0.6069	0.018*
H20B	0.2333	0.3967	0.5850	0.018*
C21	0.3039 (2)	0.33203 (15)	0.45332 (14)	0.0152 (4)
H21A	0.3418	0.2816	0.4763	0.018*
H21B	0.2084	0.3322	0.4653	0.018*
C22	0.3199 (2)	0.32727 (14)	0.36663 (14)	0.0152 (4)
C23	0.2265 (2)	0.36210 (16)	0.31623 (15)	0.0181 (5)
H23	0.1597	0.3967	0.3368	0.022*
C24	0.2300 (2)	0.34705 (16)	0.23712 (16)	0.0193 (5)
H24	0.1653	0.3702	0.2037	0.023*
C25	0.3293 (3)	0.29772 (15)	0.20733 (14)	0.0177 (4)
C26	0.4248 (3)	0.26337 (17)	0.25522 (15)	0.0196 (5)
H26	0.4932	0.2303	0.2341	0.024*
C27	0.4186 (2)	0.27835 (16)	0.33488 (14)	0.0186 (5)
H27	0.4830	0.2547	0.3681	0.022*
Cl1	0.33881 (11)	0.57170 (6)	0.25635 (6)	0.0467 (2)
Cl2	0.60520 (12)	0.52360 (10)	0.29700 (8)	0.0726 (4)
C28	0.4789 (5)	0.5153 (3)	0.2281 (2)	0.0498 (9)
H28A	0.4545	0.4569	0.2218	0.060*
H28B	0.5110	0.5358	0.1774	0.060*
Br2	−0.03270 (2)	0.389646 (15)	0.526873 (15)	0.01861 (6)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.02122 (12)	0.02832 (13)	0.01418 (10)	0.00341 (10)	−0.00121 (9)	−0.00163 (9)
O1	0.0391 (12)	0.0276 (11)	0.0215 (9)	−0.0070 (9)	0.0001 (9)	−0.0052 (8)
O2	0.0457 (14)	0.0274 (10)	0.0214 (10)	−0.0018 (9)	0.0000 (9)	0.0056 (8)
N1	0.0092 (8)	0.0169 (9)	0.0185 (9)	0.0002 (7)	0.0016 (7)	0.0015 (8)
N2	0.0101 (8)	0.0150 (10)	0.0142 (9)	0.0007 (7)	0.0001 (6)	−0.0006 (7)
C1	0.0169 (11)	0.0162 (10)	0.0135 (10)	−0.0022 (8)	0.0027 (8)	0.0015 (8)
C2	0.0151 (11)	0.0236 (12)	0.0209 (11)	−0.0036 (9)	0.0008 (9)	0.0012 (9)
C3	0.0205 (12)	0.0231 (13)	0.0251 (13)	−0.0058 (9)	−0.0016 (10)	−0.0032 (10)
C4	0.0257 (12)	0.0191 (11)	0.0231 (11)	−0.0020 (10)	0.0034 (11)	−0.0025 (9)
C5	0.0162 (11)	0.0151 (11)	0.0199 (11)	0.0000 (8)	0.0030 (8)	0.0014 (9)

C6	0.0161 (10)	0.0161 (11)	0.0137 (10)	−0.0003 (8)	0.0022 (8)	0.0015 (8)
C7	0.0141 (10)	0.0145 (10)	0.0157 (10)	0.0013 (8)	0.0018 (8)	0.0005 (8)
C8	0.0122 (10)	0.0150 (10)	0.0226 (11)	0.0036 (8)	−0.0014 (8)	−0.0022 (8)
C9	0.0130 (10)	0.0165 (10)	0.0181 (11)	0.0005 (8)	−0.0029 (8)	0.0003 (8)
C10	0.0087 (9)	0.0156 (10)	0.0165 (10)	−0.0003 (7)	0.0031 (8)	−0.0009 (8)
C11	0.0112 (10)	0.0160 (11)	0.0150 (10)	−0.0013 (8)	−0.0003 (8)	0.0004 (8)
C12	0.0109 (9)	0.0150 (10)	0.0163 (10)	0.0023 (8)	0.0007 (8)	−0.0008 (9)
C13	0.0146 (10)	0.0167 (10)	0.0159 (11)	0.0011 (9)	−0.0007 (8)	0.0017 (8)
C14	0.0186 (11)	0.0213 (11)	0.0172 (11)	−0.0027 (10)	−0.0027 (8)	0.0022 (10)
C15	0.0189 (11)	0.0247 (13)	0.0204 (12)	−0.0004 (10)	−0.0037 (9)	−0.0001 (10)
C16	0.067 (3)	0.0429 (19)	0.0202 (14)	−0.0177 (18)	0.0052 (15)	−0.0110 (13)
C17	0.0143 (10)	0.0169 (11)	0.0146 (11)	0.0023 (9)	0.0005 (8)	−0.0032 (8)
C18	0.0170 (11)	0.0210 (11)	0.0178 (10)	−0.0019 (10)	0.0025 (9)	−0.0032 (9)
C19	0.0302 (15)	0.0210 (13)	0.0284 (14)	−0.0023 (11)	0.0072 (11)	0.0047 (10)
C20	0.0139 (9)	0.0188 (11)	0.0120 (9)	0.0012 (9)	0.0019 (8)	−0.0004 (8)
C21	0.0152 (10)	0.0160 (10)	0.0143 (10)	−0.0041 (8)	0.0010 (8)	−0.0019 (8)
C22	0.0131 (10)	0.0180 (11)	0.0145 (10)	−0.0020 (9)	−0.0003 (9)	−0.0001 (8)
C23	0.0142 (10)	0.0191 (11)	0.0211 (11)	0.0015 (9)	−0.0018 (9)	−0.0031 (9)
C24	0.0148 (11)	0.0223 (12)	0.0209 (12)	0.0024 (9)	−0.0036 (9)	−0.0021 (10)
C25	0.0180 (11)	0.0203 (11)	0.0148 (10)	−0.0022 (10)	−0.0014 (9)	−0.0003 (8)
C26	0.0175 (11)	0.0227 (12)	0.0187 (11)	0.0065 (10)	0.0011 (9)	−0.0010 (10)
C27	0.0170 (10)	0.0224 (12)	0.0164 (11)	0.0058 (10)	−0.0016 (8)	0.0019 (9)
Cl1	0.0493 (5)	0.0444 (5)	0.0464 (5)	−0.0019 (4)	−0.0075 (4)	0.0174 (4)
Cl2	0.0417 (6)	0.1007 (10)	0.0755 (8)	−0.0154 (6)	−0.0145 (5)	0.0425 (7)
C28	0.052 (2)	0.051 (2)	0.046 (2)	−0.002 (2)	−0.0046 (19)	0.0068 (18)
Br2	0.01179 (9)	0.01952 (11)	0.02452 (11)	0.00263 (9)	0.00047 (9)	0.00214 (10)

Bond lengths (Å)

Br1—C25	1.890 (2)	C13—C17	1.513 (3)
O1—C15	1.347 (3)	C13—C14	1.547 (3)
O1—C16	1.450 (4)	C13—H13	1.0000
O2—C15	1.194 (3)	C14—C15	1.515 (3)
N1—C11	1.380 (3)	C14—H14A	0.9900
N1—C1	1.383 (3)	C14—H14B	0.9900
N1—H1	0.8800	C16—H16A	0.9800
N2—C9	1.521 (3)	C16—H16B	0.9800
N2—C21	1.527 (3)	C16—H16C	0.9800
N2—C10	1.531 (3)	C17—C18	1.331 (4)
N2—C20	1.533 (3)	C17—C20	1.500 (3)
C1—C2	1.397 (3)	C18—C19	1.501 (4)
C1—C6	1.414 (3)	C18—H18	0.9500

C2—C3	1.381 (4)	C19—H19A	0.9800
C2—H2	0.9500	C19—H19B	0.9800
C3—C4	1.414 (4)	C19—H19C	0.9800
C3—H3	0.9500	C20—H20A	0.9900
C4—C5	1.378 (4)	C20—H20B	0.9900
C4—H4	0.9500	C21—C22	1.504 (3)
C5—C6	1.414 (3)	C21—H21A	0.9900
C5—H5	0.9500	C21—H21B	0.9900
C6—C7	1.428 (3)	C22—C27	1.391 (3)
C7—C11	1.370 (3)	C22—C23	1.404 (3)
C7—C8	1.490 (3)	C23—C24	1.385 (4)
C8—C9	1.524 (3)	C23—H23	0.9500
C8—H8A	0.9900	C24—C25	1.387 (4)
C8—H8B	0.9900	C24—H24	0.9500
C9—H9A	0.9900	C25—C26	1.390 (3)
C9—H9B	0.9900	C26—C27	1.395 (3)
C10—C11	1.495 (3)	C26—H26	0.9500
C10—C12	1.536 (3)	C27—H27	0.9500
C10—H10	1.0000	Cl1—C28	1.760 (5)
C12—C13	1.551 (3)	Cl2—C28	1.750 (4)
C12—H12A	0.9900	C28—H28A	0.9900
C12—H12B	0.9900	C28—H28B	0.9900

Bond angles(º)

C15—O1—C16	114.3 (2)	C15—C14—C13	112.3 (2)
C11—N1—C1	108.0 (2)	C15—C14—H14A	109.1
C11—N1—H1	126.0	C13—C14—H14A	109.1
C1—N1—H1	126.0	C15—C14—H14B	109.1
C9—N2—C21	108.51 (18)	C13—C14—H14B	109.1
C9—N2—C10	110.38 (17)	H14A—C14—H14B	107.9
C21—N2—C10	111.54 (17)	O2—C15—O1	124.1 (2)
C9—N2—C20	108.78 (18)	O2—C15—C14	125.4 (3)
C21—N2—C20	106.72 (17)	O1—C15—C14	110.4 (2)
C10—N2—C20	110.79 (17)	O1—C16—H16A	109.5
N1—C1—C2	129.5 (2)	O1—C16—H16B	109.5
N1—C1—C6	108.1 (2)	H16A—C16—H16B	109.5
C2—C1—C6	122.4 (2)	O1—C16—H16C	109.5
C3—C2—C1	117.3 (2)	H16A—C16—H16C	109.5
C3—C2—H2	121.3	H16B—C16—H16C	109.5
C1—C2—H2	121.3	C18—C17—C20	119.9 (2)
C2—C3—C4	121.2 (2)	C18—C17—C13	126.7 (2)

C2—C3—H3	119.4	C20—C17—C13	113.3 (2)
C4—C3—H3	119.4	C17—C18—C19	128.0 (2)
C5—C4—C3	121.6 (2)	C17—C18—H18	116.0
C5—C4—H4	119.2	C19—C18—H18	116.0
C3—C4—H4	119.2	C18—C19—H19A	109.5
C4—C5—C6	118.3 (2)	C18—C19—H19B	109.5
C4—C5—H5	120.9	H19A—C19—H19B	109.5
C6—C5—H5	120.9	C18—C19—H19C	109.5
C5—C6—C1	119.1 (2)	H19A—C19—H19C	109.5
C5—C6—C7	134.2 (2)	H19B—C19—H19C	109.5
C1—C6—C7	106.7 (2)	C17—C20—N2	111.52 (18)
C11—C7—C6	106.9 (2)	C17—C20—H20A	109.3
C11—C7—C8	122.0 (2)	N2—C20—H20A	109.3
C6—C7—C8	131.1 (2)	C17—C20—H20B	109.3
C7—C8—C9	109.47 (19)	N2—C20—H20B	109.3
C7—C8—H8A	109.8	H20A—C20—H20B	108.0
C9—C8—H8A	109.8	C22—C21—N2	116.44 (19)
C7—C8—H8B	109.8	C22—C21—H21A	108.2
C9—C8—H8B	109.8	N2—C21—H21A	108.2
H8A—C8—H8B	108.2	C22—C21—H21B	108.2
N2—C9—C8	112.91 (19)	N2—C21—H21B	108.2
N2—C9—H9A	109.0	H21A—C21—H21B	107.3
C8—C9—H9A	109.0	C27—C22—C23	118.3 (2)
N2—C9—H9B	109.0	C27—C22—C21	119.8 (2)
C8—C9—H9B	109.0	C23—C22—C21	121.4 (2)
H9A—C9—H9B	107.8	C24—C23—C22	121.3 (2)
C11—C10—N2	107.65 (18)	C24—C23—H23	119.3
C11—C10—C12	114.49 (19)	C22—C23—H23	119.3
N2—C10—C12	110.95 (18)	C23—C24—C25	119.0 (2)
C11—C10—H10	107.8	C23—C24—H24	120.5
N2—C10—H10	107.8	C25—C24—H24	120.5
C12—C10—H10	107.8	C24—C25—C26	121.3 (2)
C7—C11—N1	110.2 (2)	C24—C25—Br1	120.17 (19)
C7—C11—C10	127.3 (2)	C26—C25—Br1	118.44 (19)
N1—C11—C10	122.5 (2)	C25—C26—C27	118.8 (2)
C10—C12—C13	115.61 (19)	C25—C26—H26	120.6
C10—C12—H12A	108.4	C27—C26—H26	120.6
C13—C12—H12A	108.4	C22—C27—C26	121.3 (2)
C10—C12—H12B	108.4	C22—C27—H27	119.4
C13—C12—H12B	108.4	C26—C27—H27	119.4
H12A—C12—H12B	107.4	Cl2—C28—Cl1	111.2 (2)
C17—C13—C14	112.3 (2)	Cl2—C28—H28A	109.4
C17—C13—C12	108.09 (19)	Cl1—C28—H28A	109.4
C14—C13—C12	112.1 (2)	Cl2—C28—H28B	109.4
C17—C13—H13	108.0	Cl1—C28—H28B	109.4

C14—C13—H13	108.0	H28A—C28—H28B	108.0
C12—C13—H13	108.0		

Geometric parameters (Å, º)

C11—N1—C1—C2	179.5 (2)	C12—C10—C11—N1	41.3 (3)
C11—N1—C1—C6	−0.7 (3)	C11—C10—C12—C13	71.4 (2)
N1—C1—C2—C3	−179.0 (2)	N2—C10—C12—C13	−50.7 (3)
C6—C1—C2—C3	1.3 (4)	C10—C12—C13—C17	51.0 (3)
C1—C2—C3—C4	0.9 (4)	C10—C12—C13—C14	−73.4 (3)
C2—C3—C4—C5	−2.1 (4)	C17—C13—C14—C15	63.7 (3)
C3—C4—C5—C6	1.0 (4)	C12—C13—C14—C15	−174.3 (2)
C4—C5—C6—C1	1.1 (3)	C16—O1—C15—O2	4.5 (4)
C4—C5—C6—C7	179.9 (3)	C16—O1—C15—C14	−173.7 (3)
N1—C1—C6—C5	177.9 (2)	C13—C14—C15—O2	32.2 (4)
C2—C1—C6—C5	−2.4 (4)	C13—C14—C15—O1	−149.6 (2)
N1—C1—C6—C7	−1.2 (3)	C14—C13—C17—C18	−112.6 (3)
C2—C1—C6—C7	178.6 (2)	C12—C13—C17—C18	123.2 (3)
C5—C6—C7—C11	−176.2 (3)	C14—C13—C17—C20	69.5 (3)
C1—C6—C7—C11	2.6 (3)	C12—C13—C17—C20	−54.7 (3)
C5—C6—C7—C8	4.0 (5)	C20—C17—C18—C19	−179.3 (2)
C1—C6—C7—C8	−177.1 (2)	C13—C17—C18—C19	2.9 (4)
C11—C7—C8—C9	−10.9 (3)	C18—C17—C20—N2	−118.3 (2)
C6—C7—C8—C9	168.9 (2)	C13—C17—C20—N2	59.7 (3)
C21—N2—C9—C8	171.45 (19)	C9—N2—C20—C17	−177.88 (19)
C10—N2—C9—C8	−66.0 (2)	C21—N2—C20—C17	65.2 (2)
C20—N2—C9—C8	55.7 (2)	C10—N2—C20—C17	−56.4 (2)
C7—C8—C9—N2	45.3 (3)	C9—N2—C21—C22	59.6 (3)
C9—N2—C10—C11	45.8 (2)	C10—N2—C21—C22	−62.2 (3)
C21—N2—C10—C11	166.48 (18)	C20—N2—C21—C22	176.7 (2)
C20—N2—C10—C11	−74.8 (2)	N2—C21—C22—C27	98.0 (3)
C9—N2—C10—C12	171.76 (18)	N2—C21—C22—C23	−90.8 (3)
C21—N2—C10—C12	−67.5 (2)	C27—C22—C23—C24	1.4 (4)
C20—N2—C10—C12	51.2 (2)	C21—C22—C23—C24	−169.9 (2)
C6—C7—C11—N1	−3.2 (3)	C22—C23—C24—C25	−1.2 (4)
C8—C7—C11—N1	176.6 (2)	C23—C24—C25—C26	0.0 (4)
C6—C7—C11—C10	175.1 (2)	C23—C24—C25—Br1	176.8 (2)
C8—C7—C11—C10	−5.1 (4)	C24—C25—C26—C27	0.9 (4)
C1—N1—C11—C7	2.5 (3)	Br1—C25—C26—C27	−176.0 (2)
C1—N1—C11—C10	−175.9 (2)	C23—C22—C27—C26	−0.5 (4)
N2—C10—C11—C7	−13.0 (3)	C21—C22—C27—C26	170.9 (2)
C12—C10—C11—C7	−136.9 (2)	C25—C26—C27—C22	−0.6 (4)

N2—C10—C11—N1	165.1 (2)		

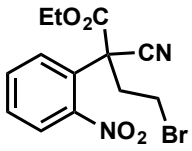
Hydrogen-bond geometry (Å, º)

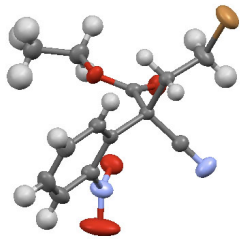
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···Br2^{i}	0.88	2.47	3.3286 (19)	166

Symmetry code: (i) *x*+1, *y*, *z*.

9. Appendix

Ethyl 4-bromo-2-cyano-2-(2-nitrophenyl)butanoate (234)





Computing details

Program(s) used to refine structure: *SHELXL2014*/7 (Sheldrick, 2014).

Crystal data

$C_{13}H_{13}BrN_2O_4$	V = 1408.8 (2) Å^3
M_r = 341.16	Z = 4
Monoclinic, $P2_1/c$	$F(000)$ = 688
a = 9.7123 (9) Å	D_x = 1.609 Mg m^{-3}
b = 10.2252 (10) Å	μ = 2.93 mm^{-1}
c = 14.3238 (12) Å	T = 200 K
β = 97.972 (3)°	0.91 × 0.60 × 0.55 mm

Data collection

8839 measured reflections	θ_{max} = 25.1°, θ_{min} = 2.1°
2495 independent reflections	h = −11→11
1986 reflections with $I > 2\sigma(I)$	k = −12→12
R_{int} = 0.039	l = −15→16

Refinement

Refinement on F^2	0 restraints
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)]$ = 0.039	H-atom parameters constrained
$wR(F^2)$ = 0.104	$w = 1/[\sigma^2(F_o^2) + (0.0457P)^2 + 1.4249P]$ where $P = (F_o^2 + 2F_c^2)/3$

S = 1.04	$(\Delta/\sigma)_{max}$ = 0.001
2495 reflections	$\Delta\rho_{max}$ = 0.48 e Å^{-3}
182 parameters	$\Delta\rho_{min}$ = −0.83 e Å^{-3}

Special details

Geometry

All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	1.36601 (4)	0.06757 (5)	0.37702 (3)	0.06392 (19)
O1	0.6529 (2)	0.0920 (2)	0.22504 (17)	0.0431 (6)
O2	0.8291 (2)	0.16884 (18)	0.40511 (14)	0.0310 (5)
O3	0.8983 (3)	0.2502 (2)	0.27403 (16)	0.0404 (6)
N4	0.9225 (3)	−0.0056 (3)	0.1235 (2)	0.0443 (7)
N1	0.6238 (3)	−0.0230 (3)	0.2252 (2)	0.0417 (7)
C2B	0.8859 (3)	−0.1753 (3)	0.4088 (2)	0.0305 (7)
H2B	0.9802	−0.1672	0.4364	0.037*
C1	0.6941 (3)	−0.1074 (3)	0.3007 (2)	0.0306 (7)
C2	0.8324 (3)	−0.0870 (3)	0.3396 (2)	0.0237 (6)
C3	0.9262 (3)	0.0199 (3)	0.30549 (19)	0.0237 (6)
C4	0.8803 (3)	0.1609 (3)	0.3247 (2)	0.0267 (6)
C5	0.7777 (4)	0.2993 (3)	0.4272 (2)	0.0400 (8)
H5A	0.7213	0.3371	0.3708	0.048*
H5B	0.8569	0.3586	0.4471	0.048*
C6	0.6921 (4)	0.2851 (4)	0.5040 (3)	0.0487 (9)
H6A	0.6176	0.2218	0.4853	0.073*
H6B	0.6515	0.3699	0.5166	0.073*
H6C	0.7504	0.2541	0.561	0.073*

C7	1.0796 (3)	0.0068 (3)	0.3528 (2)	0.0264 (6)
H7A	1.083	0.0178	0.4218	0.032*
H7B	1.1128	−0.0826	0.3414	0.032*
C8	1.1773 (3)	0.1044 (4)	0.3177 (3)	0.0462 (9)
H8A	1.1506	0.1943	0.3336	0.055*
H8B	1.1719	0.0978	0.2484	0.055*
C9	0.8059 (4)	−0.2752 (3)	0.4388 (2)	0.0395 (8)
H9	0.8457	−0.3334	0.4868	0.047*
C10	0.6697 (4)	−0.2906 (3)	0.3996 (3)	0.0443 (9)
H10	0.6148	−0.3583	0.421	0.053*
C11	0.6133 (3)	−0.2070 (3)	0.3290 (3)	0.0421 (8)
H11	0.5198	−0.2177	0.3002	0.051*
O12	0.5382 (4)	−0.0723 (3)	0.1659 (3)	0.0910 (12)
C13	0.9234 (3)	0.0075 (3)	0.2023 (2)	0.0279 (6)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.0313 (2)	0.0784 (3)	0.0809 (4)	−0.00871 (18)	0.00386 (19)	0.0046 (2)
O1	0.0389 (13)	0.0356 (13)	0.0516 (15)	0.0043 (10)	−0.0051 (11)	0.0091 (11)
O2	0.0414 (12)	0.0232 (10)	0.0296 (12)	0.0036 (9)	0.0095 (9)	−0.0038 (9)
O3	0.0585 (15)	0.0228 (11)	0.0426 (14)	−0.0012 (10)	0.0163 (12)	0.0055 (10)
N4	0.0553 (19)	0.0465 (17)	0.0306 (17)	0.0126 (15)	0.0039 (13)	−0.0038 (14)
N1	0.0325 (15)	0.0381 (16)	0.0501 (18)	0.0051 (13)	−0.0094 (13)	0.0012 (14)
C2B	0.0356 (16)	0.0275 (15)	0.0275 (16)	−0.0022 (13)	0.0009 (13)	−0.0002 (13)
C1	0.0308 (16)	0.0256 (15)	0.0340 (17)	0.0025 (12)	−0.0002 (13)	−0.0033 (13)
C2	0.0284 (14)	0.0190 (13)	0.0240 (15)	0.0001 (11)	0.0043 (12)	−0.0031 (12)
C3	0.0270 (14)	0.0222 (14)	0.0214 (15)	−0.0017 (11)	0.0013 (11)	0.0005 (12)
C4	0.0294 (15)	0.0222 (14)	0.0279 (16)	−0.0020 (12)	0.0015 (12)	−0.0014 (13)
C5	0.048 (2)	0.0287 (16)	0.044 (2)	0.0083 (15)	0.0107 (16)	−0.0080 (15)
C6	0.048 (2)	0.049 (2)	0.050 (2)	0.0070 (17)	0.0135 (17)	−0.0100 (18)
C7	0.0284 (15)	0.0266 (15)	0.0238 (15)	−0.0001 (12)	0.0016 (12)	−0.0027 (12)
C8	0.0289 (17)	0.053 (2)	0.055 (2)	−0.0060 (15)	0.0008 (16)	0.0109 (18)
C9	0.056 (2)	0.0287 (16)	0.0350 (19)	−0.0021 (15)	0.0097 (16)	0.0072 (14)
C10	0.048 (2)	0.0305 (17)	0.058 (2)	−0.0115 (15)	0.0188 (17)	0.0009 (16)
C11	0.0321 (17)	0.0330 (17)	0.061 (2)	−0.0067 (14)	0.0043 (16)	−0.0065 (17)
O12	0.089 (2)	0.0603 (19)	0.103 (3)	−0.0097 (17)	−0.062 (2)	0.0012 (18)
C13	0.0314 (16)	0.0232 (14)	0.0287 (18)	0.0039 (12)	0.0029 (13)	0.0012 (13)

Bond lengths (Å)

Br1—C8	1.946 (3)	C5—C6	1.474 (5)
O1—N1	1.209 (4)	C5—H5A	0.99
O2—C4	1.318 (4)	C5—H5B	0.99
O2—C5	1.474 (4)	C6—H6A	0.98
O3—C4	1.195 (3)	C6—H6B	0.98
N4—C13	1.136 (4)	C6—H6C	0.98
N1—O12	1.213 (4)	C7—C8	1.511 (4)
N1—C1	1.475 (4)	C7—H7A	0.99
C2B—C9	1.387 (4)	C7—H7B	0.99
C2B—C2	1.388 (4)	C8—H8A	0.99
C2B—H2B	0.95	C8—H8B	0.99
C1—C11	1.381 (4)	C9—C10	1.372 (5)
C1—C2	1.397 (4)	C9—H9	0.95
C2—C3	1.545 (4)	C10—C11	1.379 (5)
C3—C13	1.480 (4)	C10—H10	0.95
C3—C4	1.545 (4)	C11—H11	0.95
C3—C7	1.555 (4)		

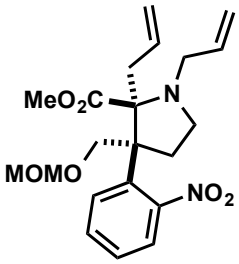
Bond angles(º)

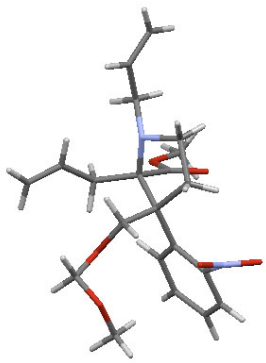
C4—O2—C5	115.0 (2)	C5—C6—H6A	109.5
O1—N1—O12	122.7 (3)	C5—C6—H6B	109.5
O1—N1—C1	119.1 (3)	H6A—C6—H6B	109.5
O12—N1—C1	118.2 (3)	C5—C6—H6C	109.5
C9—C2B—C2	122.0 (3)	H6A—C6—H6C	109.5
C9—C2B—H2B	119.0	H6B—C6—H6C	109.5
C2—C2B—H2B	119.0	C8—C7—C3	114.0 (2)
C11—C1—C2	123.2 (3)	C8—C7—H7A	108.8
C11—C1—N1	115.0 (3)	C3—C7—H7A	108.8
C2—C1—N1	121.8 (3)	C8—C7—H7B	108.8
C2B—C2—C1	115.6 (3)	C3—C7—H7B	108.8
C2B—C2—C3	120.5 (3)	H7A—C7—H7B	107.7
C1—C2—C3	123.8 (3)	C7—C8—Br1	108.9 (2)
C13—C3—C2	109.0 (2)	C7—C8—H8A	109.9
C13—C3—C4	107.0 (2)	Br1—C8—H8A	109.9
C2—C3—C4	114.0 (2)	C7—C8—H8B	109.9
C13—C3—C7	108.2 (2)	Br1—C8—H8B	109.9
C2—C3—C7	111.9 (2)	H8A—C8—H8B	108.3
C4—C3—C7	106.6 (2)	C10—C9—C2B	120.5 (3)
O3—C4—O2	126.1 (3)	C10—C9—H9	119.7
O3—C4—C3	122.3 (3)	C2B—C9—H9	119.7

O2—C4—C3	111.5 (2)	C9—C10—C11	119.4 (3)
O2—C5—C6	108.3 (3)	C9—C10—H10	120.3
O2—C5—H5A	110.0	C11—C10—H10	120.3
C6—C5—H5A	110.0	C10—C11—C1	119.2 (3)
O2—C5—H5B	110.0	C10—C11—H11	120.4
C6—C5—H5B	110.0	C1—C11—H11	120.4
H5A—C5—H5B	108.4	N4—C13—C3	178.1 (3)

9. Appendix

Methyl 1,2-diallyl-3-((methoxymethoxy)methyl)-3-(2-nitrophenyl)pyrrolidine-2-carboxylate (300)





Computing details

Program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014*/7 (Sheldrick, 2014).

Crystal data

$C_{21}H_{28}N_2O_6$	V = 2161.0 (5) Å^3
M_r = 404.45	Z = 4
Monoclinic, $P2_1/n$	F(000) = 864
a = 12.5404 (19) Å	D_x = 1.243 Mg m^{-3}
b = 9.1067 (11) Å	μ = 0.09 mm^{-1}
c = 19.609 (3) Å	T = 200 K
β = 105.204 (5)°	0.50 × 0.30 × 0.20 mm

Data collection

23305 measured reflections	θ_{max} = 25.1°, θ_{min} = 2.5°
3820 independent reflections	h = −14→14
2627 reflections with $I > 2\sigma(I)$	k = −10→8
R_{int} = 0.069	l = −23→23

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map

$R[F^2 > 2\sigma(F^2)] = 0.046$	Hydrogen site location: inferred from neighbouring sites
$wR(F^2) = 0.157$	H-atom parameters constrained
$S = 1.01$	$w = 1/[\sigma^2(F_o^2) + (0.0986P)^2 + 0.0386P]$ where $P = (F_o^2 + 2F_c^2)/3$
3820 reflections	$(\Delta/\sigma)_{max} = 0.011$
264 parameters	$\Delta\rho_{max} = 0.32$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.25$ e Å^{-3}

Special details

Refinement

Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.62440 (16)	0.0340 (2)	0.24763 (10)	0.0758 (5)
O2	0.45543 (13)	0.01682 (14)	0.16261 (7)	0.0482 (4)
O3	0.22066 (14)	0.38788 (16)	0.00065 (8)	0.0549 (4)
O4	0.15943 (15)	0.17662 (17)	−0.05191 (7)	0.0637 (5)
O5	0.5314 (2)	0.60103 (18)	0.16361 (10)	0.0877 (7)
O6	0.54433 (15)	0.40870 (18)	0.22669 (8)	0.0663 (5)
N1	0.15283 (14)	0.21257 (18)	0.11189 (8)	0.0429 (4)
N2	0.53050 (15)	0.4686 (2)	0.16979 (9)	0.0486 (5)
C1	0.6917 (3)	0.0582 (4)	0.2010 (2)	0.1158 (13)
H1A	0.7143	−0.0364	0.1855	0.174*
H1B	0.7574	0.1141	0.2254	0.174*

H1C	0.65	0.1137	0.1598	0.174*
C2	0.5323 (2)	−0.0520 (3)	0.21860 (13)	0.0626 (7)
H2A	0.4955	−0.0769	0.256	0.075*
H2B	0.5567	−0.145	0.2013	0.075*
C3	0.39648 (18)	0.1324 (2)	0.18554 (10)	0.0420 (5)
H3A	0.4473	0.1877	0.2241	0.05*
H3B	0.337	0.0903	0.2042	0.05*
C4	0.34585 (16)	0.23720 (19)	0.12400 (9)	0.0345 (4)
C5	0.23587 (16)	0.1710 (2)	0.07423 (10)	0.0364 (5)
C6	0.03702 (18)	0.1927 (3)	0.07303 (12)	0.0548 (6)
H6A	0.0283	0.0964	0.0488	0.066*
H6B	0.0159	0.27	0.0365	0.066*
C7	−0.0385 (2)	0.1997 (3)	0.12058 (14)	0.0604 (6)
H7	−0.0247	0.1352	0.16	0.072*
C8	−0.1217 (2)	0.2887 (3)	0.11101 (16)	0.0790 (8)
H8A	−0.1374	0.3544	0.072	0.095*
H8B	−0.167	0.2883	0.143	0.095*
C9	0.30196 (18)	0.3750 (2)	0.15534 (11)	0.0433 (5)
H9A	0.3355	0.3806	0.2069	0.052*
H9B	0.3213	0.4655	0.1333	0.052*
C10	0.17770 (19)	0.3602 (2)	0.14013 (12)	0.0506 (6)
H10A	0.1535	0.3728	0.1839	0.061*
H10B	0.1402	0.4346	0.1052	0.061*
C11	0.23229 (18)	0.0010 (2)	0.06295 (10)	0.0431 (5)
H11A	0.1777	−0.0206	0.0176	0.052*
H11B	0.3055	−0.0309	0.0582	0.052*
C12	0.2038 (2)	−0.0907 (2)	0.11969 (14)	0.0606 (7)
H12	0.1479	−0.0536	0.1396	0.073*
C13	0.2468 (4)	−0.2118 (3)	0.14334 (18)	0.1024 (12)
H13A	0.3031	−0.2535	0.1251	0.123*
H13B	0.2229	−0.2612	0.1794	0.123*
C14	0.20787 (17)	0.2578 (2)	0.00396 (10)	0.0417 (5)
C15	0.1214 (3)	0.2569 (4)	−0.11801 (13)	0.1002 (12)
H15A	0.0683	0.3323	−0.1129	0.15*
H15B	0.0856	0.1888	−0.1558	0.15*
H15C	0.1845	0.3037	−0.1299	0.15*
C16	0.43532 (16)	0.27133 (19)	0.08552 (9)	0.0343 (4)
C17	0.44120 (17)	0.1926 (2)	0.02545 (10)	0.0400 (5)
H17	0.3883	0.1174	0.0088	0.048*
C18	0.51975 (18)	0.2183 (2)	−0.01103 (11)	0.0475 (5)
H18	0.5202	0.1604	−0.0512	0.057*
C19	0.59737 (19)	0.3272 (2)	0.01047 (12)	0.0526 (6)
H19	0.651	0.3459	−0.0149	0.063*
C20	0.59590 (18)	0.4086 (2)	0.06935 (12)	0.0499 (5)
H20	0.6484	0.4848	0.0849	0.06*

C21	0.51735 (17)	0.3788 (2)	0.10590 (10)	0.0395 (5)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0687 (12)	0.0743 (12)	0.0703 (11)	0.0030 (10)	−0.0068 (10)	−0.0001 (9)
O2	0.0591 (10)	0.0395 (8)	0.0423 (8)	0.0079 (7)	0.0068 (7)	0.0017 (6)
O3	0.0658 (11)	0.0449 (9)	0.0485 (9)	0.0002 (8)	0.0056 (8)	0.0044 (7)
O4	0.0893 (13)	0.0604 (10)	0.0339 (8)	−0.0056 (9)	0.0029 (8)	−0.0071 (7)
O5	0.140 (2)	0.0410 (10)	0.0720 (12)	−0.0081 (10)	0.0105 (12)	−0.0084 (8)
O6	0.0816 (13)	0.0670 (10)	0.0416 (9)	−0.0157 (9)	0.0007 (8)	−0.0013 (8)
N1	0.0398 (10)	0.0456 (10)	0.0465 (9)	−0.0033 (8)	0.0168 (8)	−0.0122 (8)
N2	0.0484 (11)	0.0434 (10)	0.0477 (11)	−0.0075 (9)	0.0015 (9)	−0.0013 (8)
C1	0.063 (2)	0.150 (3)	0.134 (3)	0.017 (2)	0.024 (2)	0.048 (3)
C2	0.0754 (18)	0.0482 (13)	0.0587 (14)	0.0055 (13)	0.0079 (13)	0.0155 (11)
C3	0.0520 (13)	0.0407 (11)	0.0335 (10)	−0.0016 (10)	0.0117 (9)	−0.0010 (8)
C4	0.0392 (11)	0.0317 (9)	0.0329 (9)	−0.0029 (8)	0.0100 (8)	−0.0048 (8)
C5	0.0385 (11)	0.0367 (10)	0.0364 (10)	−0.0022 (9)	0.0139 (9)	−0.0060 (8)
C6	0.0413 (13)	0.0638 (14)	0.0591 (14)	−0.0061 (11)	0.0128 (11)	−0.0174 (11)
C7	0.0435 (14)	0.0684 (15)	0.0711 (16)	−0.0049 (12)	0.0184 (12)	−0.0088 (13)
C8	0.0484 (16)	0.107 (2)	0.0833 (19)	−0.0007 (16)	0.0206 (14)	−0.0230 (17)
C9	0.0479 (13)	0.0413 (11)	0.0425 (11)	−0.0017 (10)	0.0149 (10)	−0.0111 (9)
C10	0.0486 (14)	0.0516 (13)	0.0545 (12)	−0.0002 (11)	0.0185 (11)	−0.0176 (10)
C11	0.0476 (13)	0.0386 (11)	0.0429 (11)	−0.0082 (9)	0.0117 (10)	−0.0105 (9)
C12	0.0761 (18)	0.0428 (12)	0.0735 (16)	−0.0091 (13)	0.0384 (14)	−0.0047 (12)
C13	0.174 (4)	0.0508 (16)	0.110 (2)	0.0064 (19)	0.087 (3)	0.0082 (16)
C14	0.0394 (12)	0.0476 (13)	0.0379 (10)	0.0012 (10)	0.0098 (9)	−0.0068 (9)
C15	0.153 (3)	0.094 (2)	0.0357 (13)	−0.011 (2)	−0.0074 (17)	0.0022 (13)
C16	0.0360 (11)	0.0319 (9)	0.0341 (9)	0.0025 (8)	0.0076 (8)	0.0025 (8)
C17	0.0413 (12)	0.0393 (10)	0.0400 (10)	0.0013 (9)	0.0118 (9)	−0.0002 (8)
C18	0.0492 (13)	0.0539 (12)	0.0430 (11)	0.0106 (11)	0.0183 (10)	0.0044 (10)
C19	0.0429 (13)	0.0637 (14)	0.0562 (13)	0.0038 (11)	0.0219 (11)	0.0109 (12)
C20	0.0377 (12)	0.0506 (12)	0.0600 (14)	−0.0035 (10)	0.0103 (10)	0.0089 (11)
C21	0.0379 (12)	0.0378 (10)	0.0395 (10)	0.0025 (9)	0.0045 (9)	0.0052 (8)

Bond lengths (Å)

O1—C2	1.388 (3)	C7—C8	1.295 (3)
O1—C1	1.415 (4)	C7—H7	0.95
O2—C2	1.404 (3)	C8—H8A	0.95

O2—C3	1.425 (2)	C8—H8B	0.95
O3—C14	1.199 (2)	C9—C10	1.514 (3)
O4—C14	1.329 (2)	C9—H9A	0.99
O4—C15	1.456 (3)	C9—H9B	0.99
O5—N2	1.212 (2)	C10—H10A	0.99
O6—N2	1.213 (2)	C10—H10B	0.99
N1—C10	1.456 (2)	C11—C12	1.507 (3)
N1—C6	1.464 (3)	C11—H11A	0.99
N1—C5	1.475 (2)	C11—H11B	0.99
N2—C21	1.469 (3)	C12—C13	1.261 (4)
C1—H1A	0.98	C12—H12	0.95
C1—H1B	0.98	C13—H13A	0.95
C1—H1C	0.98	C13—H13B	0.95
C2—H2A	0.99	C15—H15A	0.98
C2—H2B	0.99	C15—H15B	0.98
C3—C4	1.539 (3)	C15—H15C	0.98
C3—H3A	0.99	C16—C17	1.397 (3)
C3—H3B	0.99	C16—C21	1.400 (3)
C4—C16	1.539 (3)	C17—C18	1.381 (3)
C4—C9	1.560 (3)	C17—H17	0.95
C4—C5	1.585 (3)	C18—C19	1.376 (3)
C5—C14	1.547 (3)	C18—H18	0.95
C5—C11	1.562 (3)	C19—C20	1.376 (3)
C6—C7	1.494 (3)	C19—H19	0.95
C6—H6A	0.99	C20—C21	1.389 (3)
C6—H6B	0.99	C20—H20	0.95

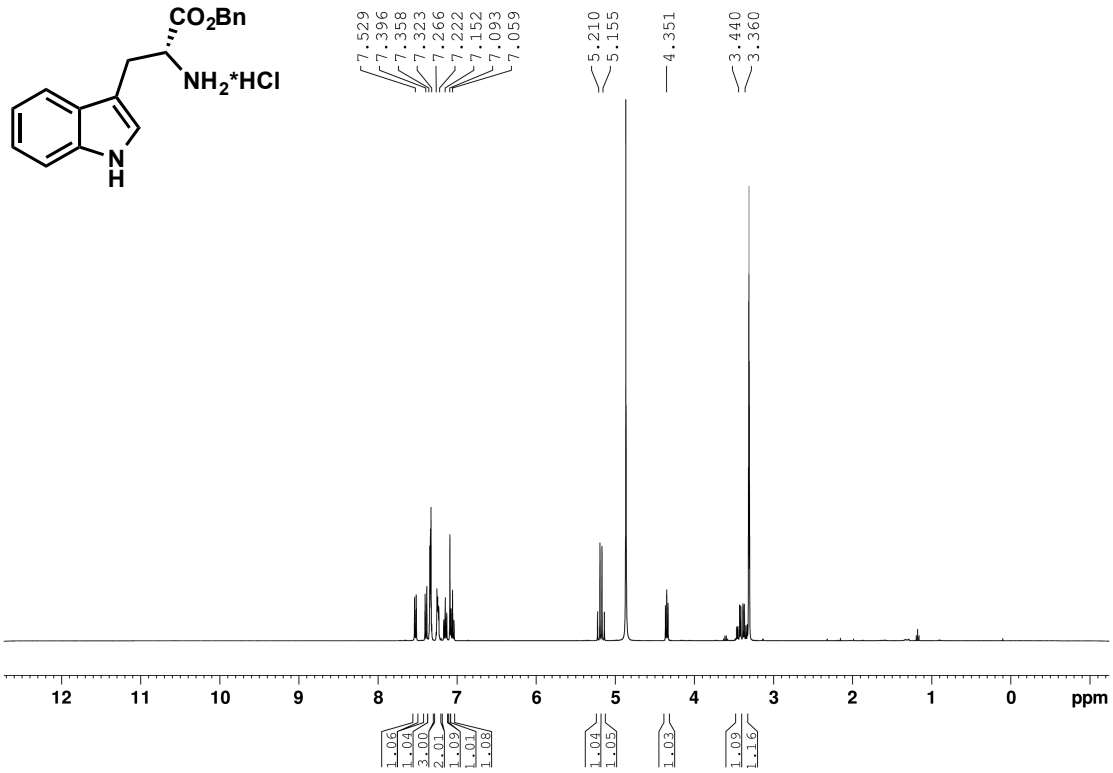
Bond angles(º)

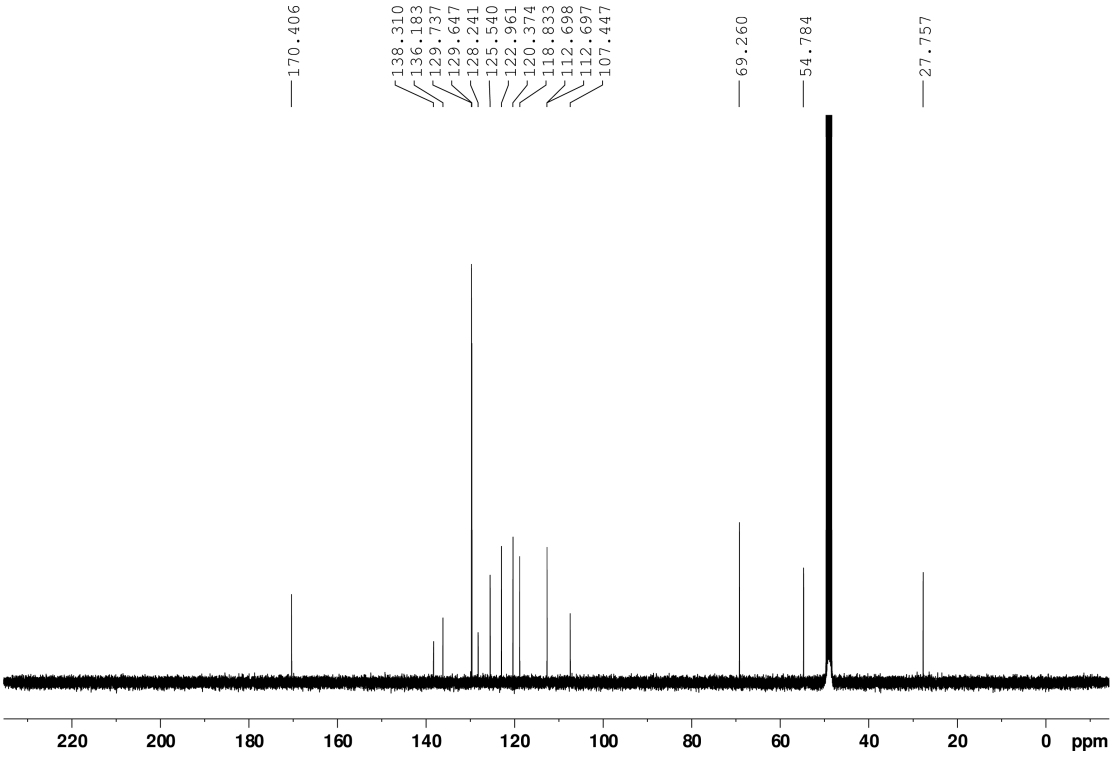
C2—O1—C1	113.3 (2)	C10—C9—C4	107.57 (16)
C2—O2—C3	112.92 (17)	C10—C9—H9A	110.2
C14—O4—C15	115.26 (19)	C4—C9—H9A	110.2
C10—N1—C6	113.35 (16)	C10—C9—H9B	110.2
C10—N1—C5	108.58 (15)	C4—C9—H9B	110.2
C6—N1—C5	116.23 (15)	H9A—C9—H9B	108.5
O5—N2—O6	122.45 (19)	N1—C10—C9	105.31 (16)
O5—N2—C21	118.07 (18)	N1—C10—H10A	110.7
O6—N2—C21	119.41 (17)	C9—C10—H10A	110.7
O1—C1—H1A	109.5	N1—C10—H10B	110.7
O1—C1—H1B	109.5	C9—C10—H10B	110.7
H1A—C1—H1B	109.5	H10A—C10—H10B	108.8
O1—C1—H1C	109.5	C12—C11—C5	116.61 (16)

H1A—C1—H1C	109.5	C12—C11—H11A	108.1
H1B—C1—H1C	109.5	C5—C11—H11A	108.1
O1—C2—O2	113.27 (18)	C12—C11—H11B	108.1
O1—C2—H2A	108.9	C5—C11—H11B	108.1
O2—C2—H2A	108.9	H11A—C11—H11B	107.3
O1—C2—H2B	108.9	C13—C12—C11	126.5 (3)
O2—C2—H2B	108.9	C13—C12—H12	116.8
H2A—C2—H2B	107.7	C11—C12—H12	116.8
O2—C3—C4	110.62 (15)	C12—C13—H13A	120.0
O2—C3—H3A	109.5	C12—C13—H13B	120.0
C4—C3—H3A	109.5	H13A—C13—H13B	120.0
O2—C3—H3B	109.5	O3—C14—O4	122.93 (19)
C4—C3—H3B	109.5	O3—C14—C5	123.42 (17)
H3A—C3—H3B	108.1	O4—C14—C5	113.42 (17)
C16—C4—C3	107.81 (15)	O4—C15—H15A	109.5
C16—C4—C9	114.12 (15)	O4—C15—H15B	109.5
C3—C4—C9	107.80 (15)	H15A—C15—H15B	109.5
C16—C4—C5	113.80 (14)	O4—C15—H15C	109.5
C3—C4—C5	111.11 (15)	H15A—C15—H15C	109.5
C9—C4—C5	102.05 (15)	H15B—C15—H15C	109.5
N1—C5—C14	106.82 (16)	C17—C16—C21	113.71 (17)
N1—C5—C11	109.12 (15)	C17—C16—C4	121.07 (16)
C14—C5—C11	112.89 (15)	C21—C16—C4	125.22 (16)
N1—C5—C4	102.03 (14)	C18—C17—C16	123.53 (19)
C14—C5—C4	108.14 (15)	C18—C17—H17	118.2
C11—C5—C4	116.88 (16)	C16—C17—H17	118.2
N1—C6—C7	112.00 (18)	C19—C18—C17	120.5 (2)
N1—C6—H6A	109.2	C19—C18—H18	119.8
C7—C6—H6A	109.2	C17—C18—H18	119.8
N1—C6—H6B	109.2	C20—C19—C18	118.8 (2)
C7—C6—H6B	109.2	C20—C19—H19	120.6
H6A—C6—H6B	107.9	C18—C19—H19	120.6
C8—C7—C6	123.7 (3)	C19—C20—C21	119.7 (2)
C8—C7—H7	118.2	C19—C20—H20	120.2
C6—C7—H7	118.2	C21—C20—H20	120.2
C7—C8—H8A	120.0	C20—C21—C16	123.84 (19)
C7—C8—H8B	120.0	C20—C21—N2	113.28 (18)
H8A—C8—H8B	120.0	C16—C21—N2	122.86 (18)

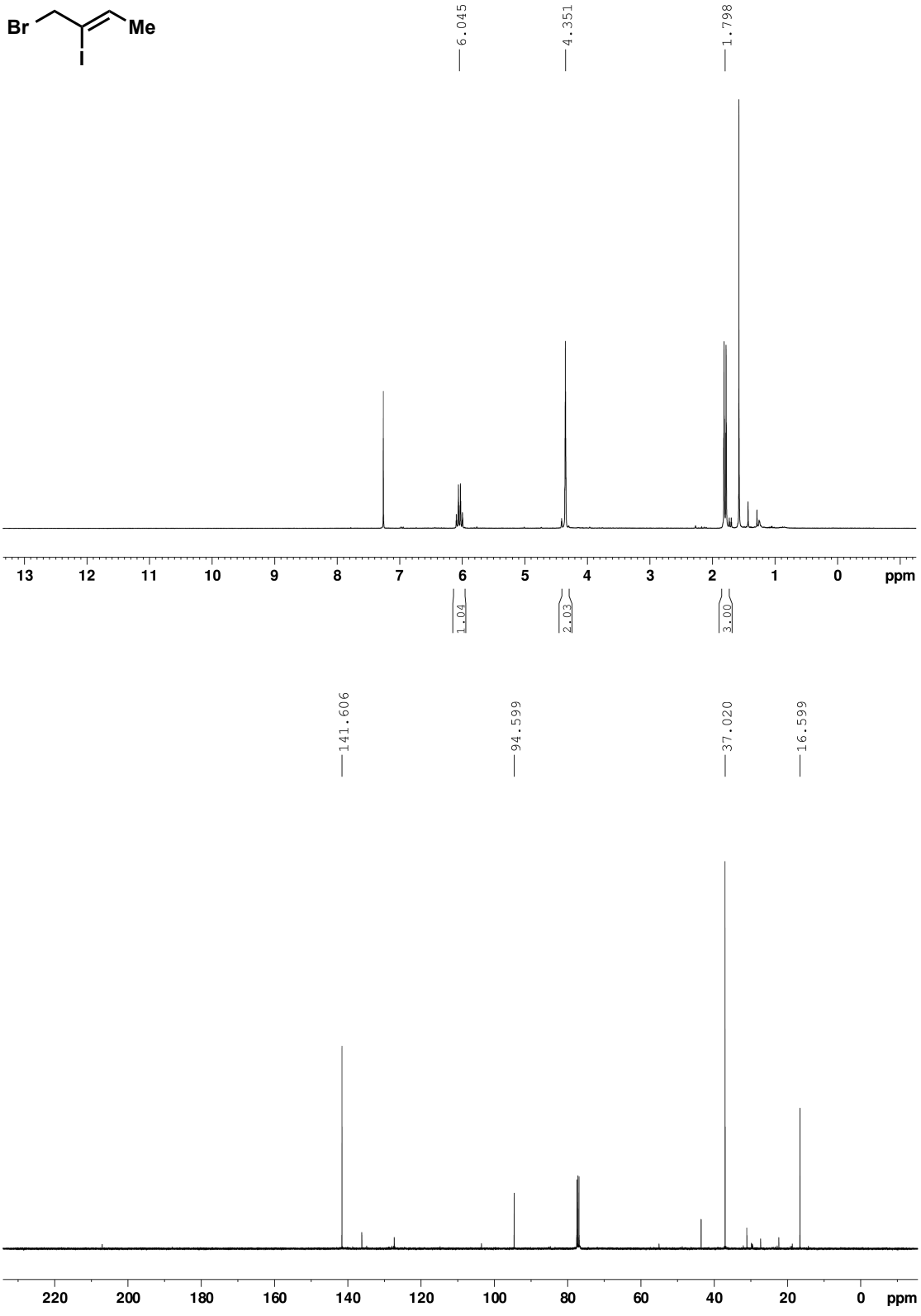
9.3 Spectroscopical data

Compound **76**





Compound **73**


Br
Me
I
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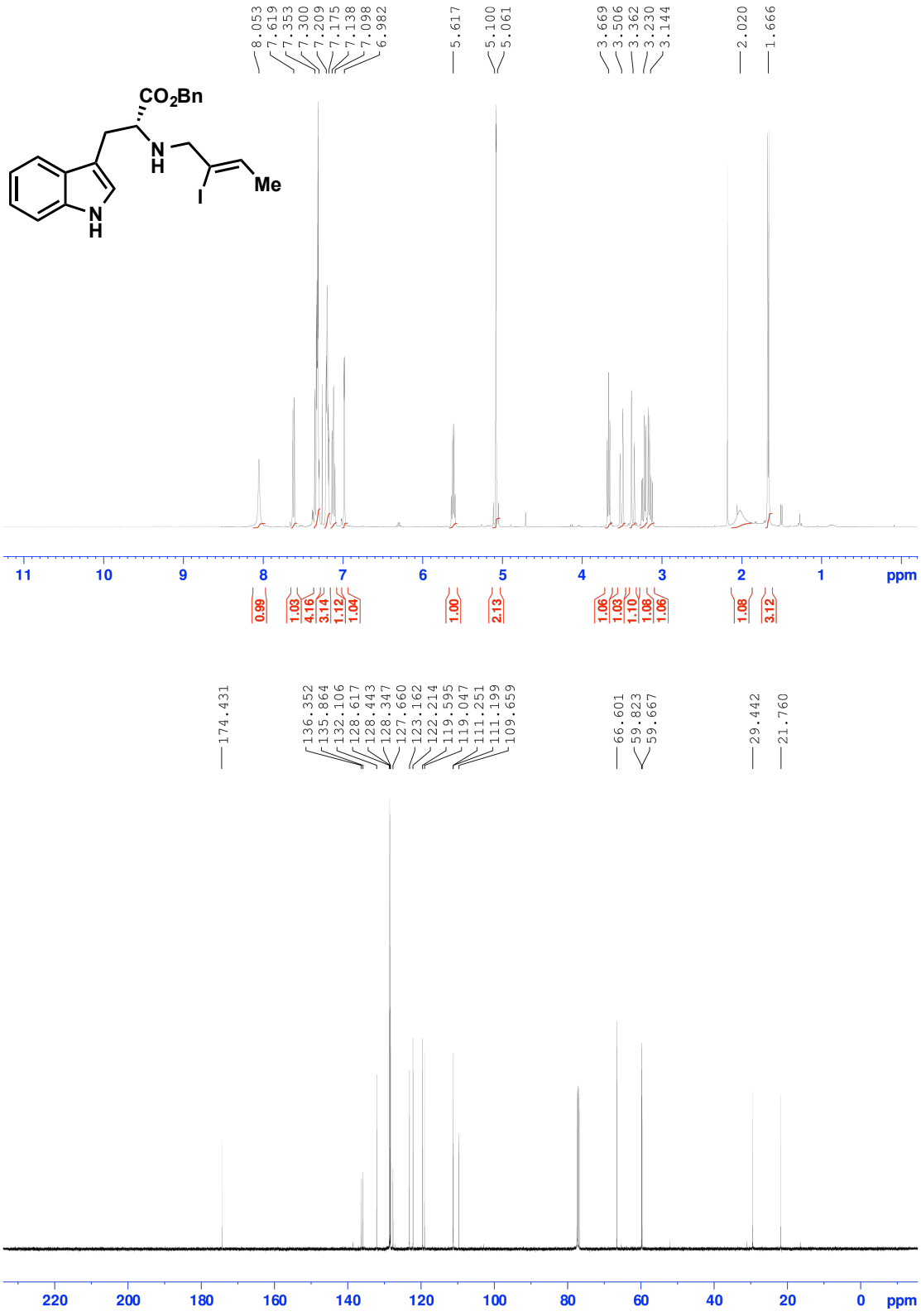
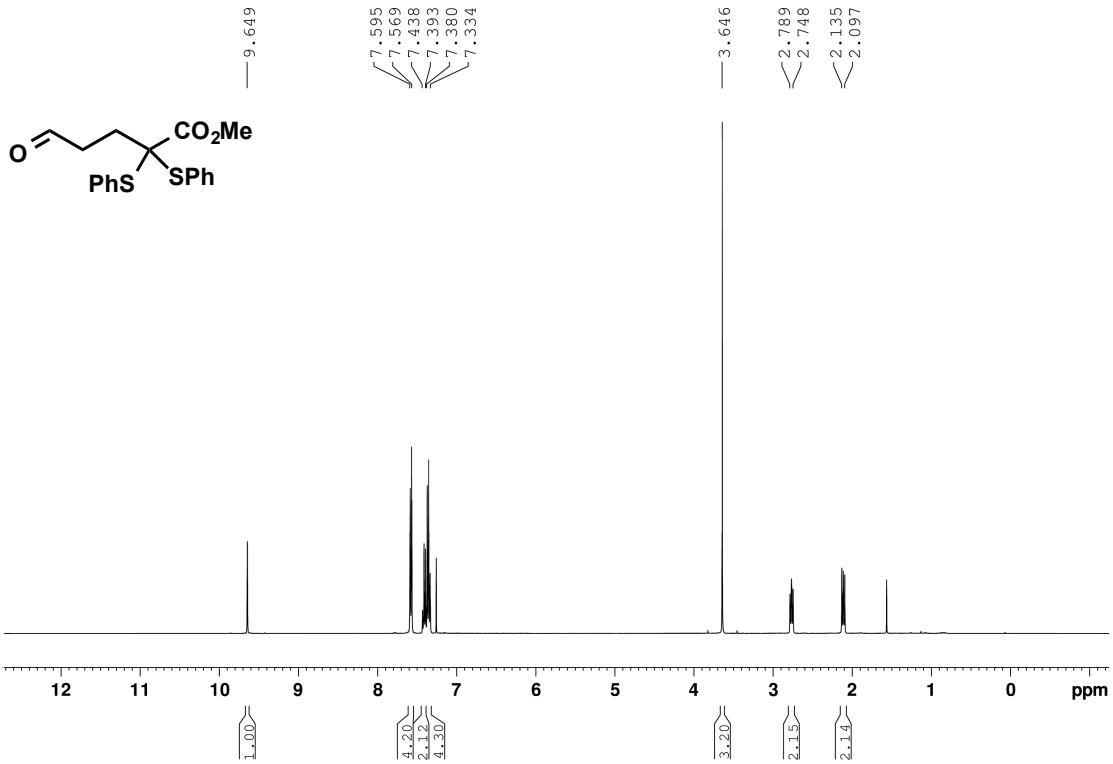
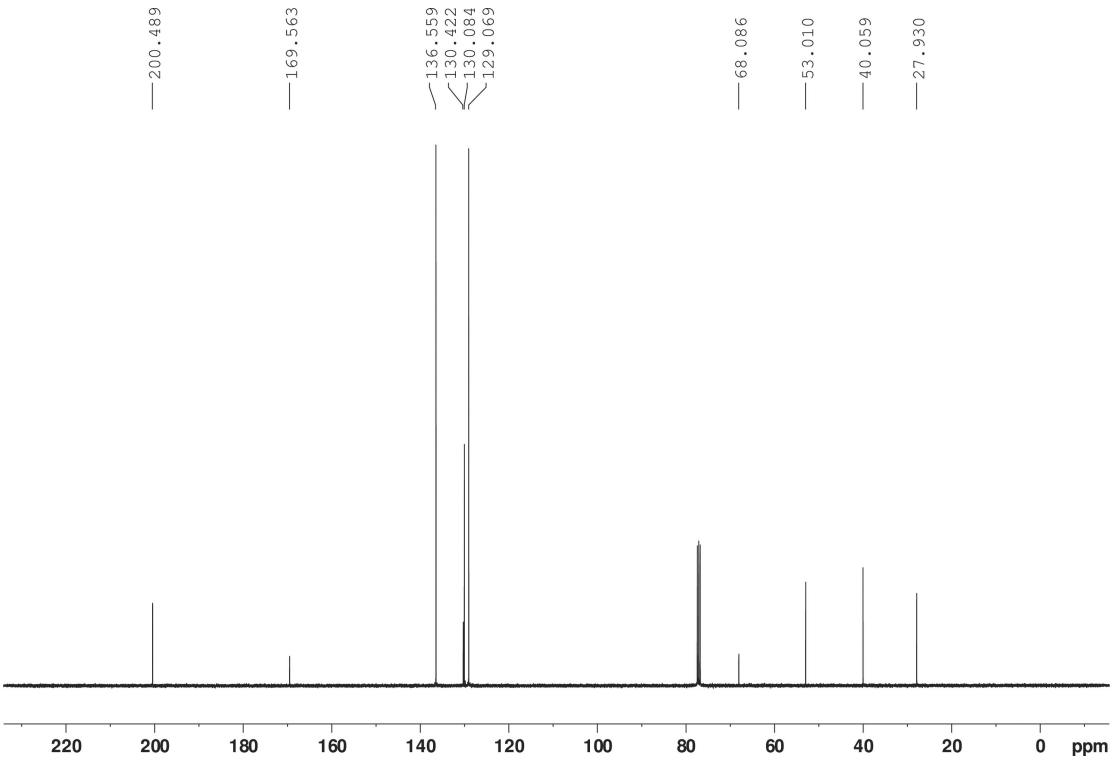
4.351
1.798
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.04
2.03
3.00
141.606
94.599
37.020
16.599
220 200 180 160 140 120 100 80 60 40 20 0 ppm

Compound **77**

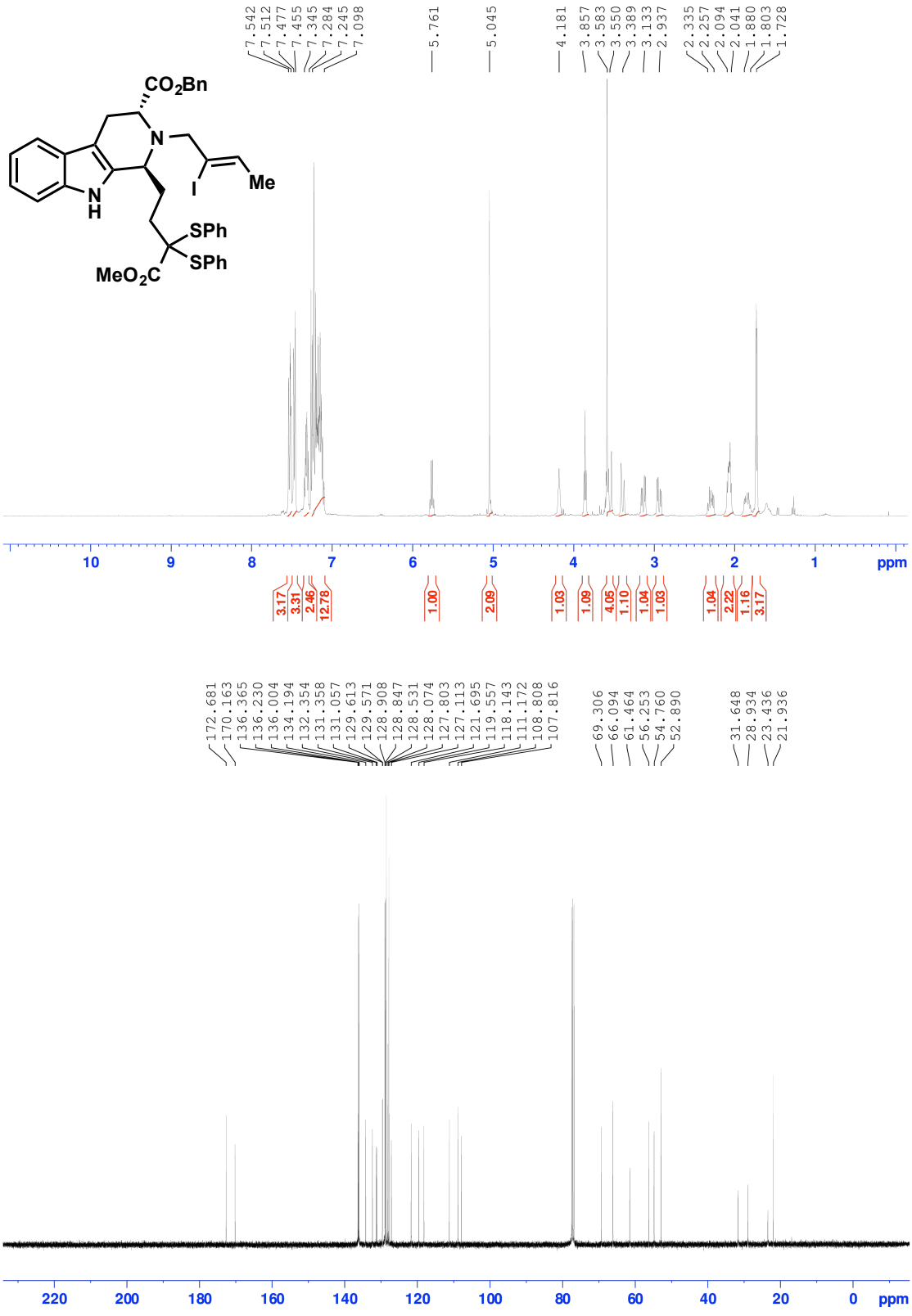

8.053
7.619
7.353
7.300
7.209
7.175
7.138
7.098
6.982
5.617
5.100
5.061
3.669
3.506
3.362
3.230
3.144
2.020
1.666
CO2Bn
N
H
N
H
I
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.03
4.16
3.14
1.12
1.04
1.00
2.13
1.06
1.03
1.10
1.08
1.06
1.08
3.12
174.431
136.352
135.864
132.106
128.617
128.443
128.347
127.660
123.162
122.214
119.595
119.047
111.251
111.199
109.659
66.601
59.823
59.667
29.442
21.760
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **78**

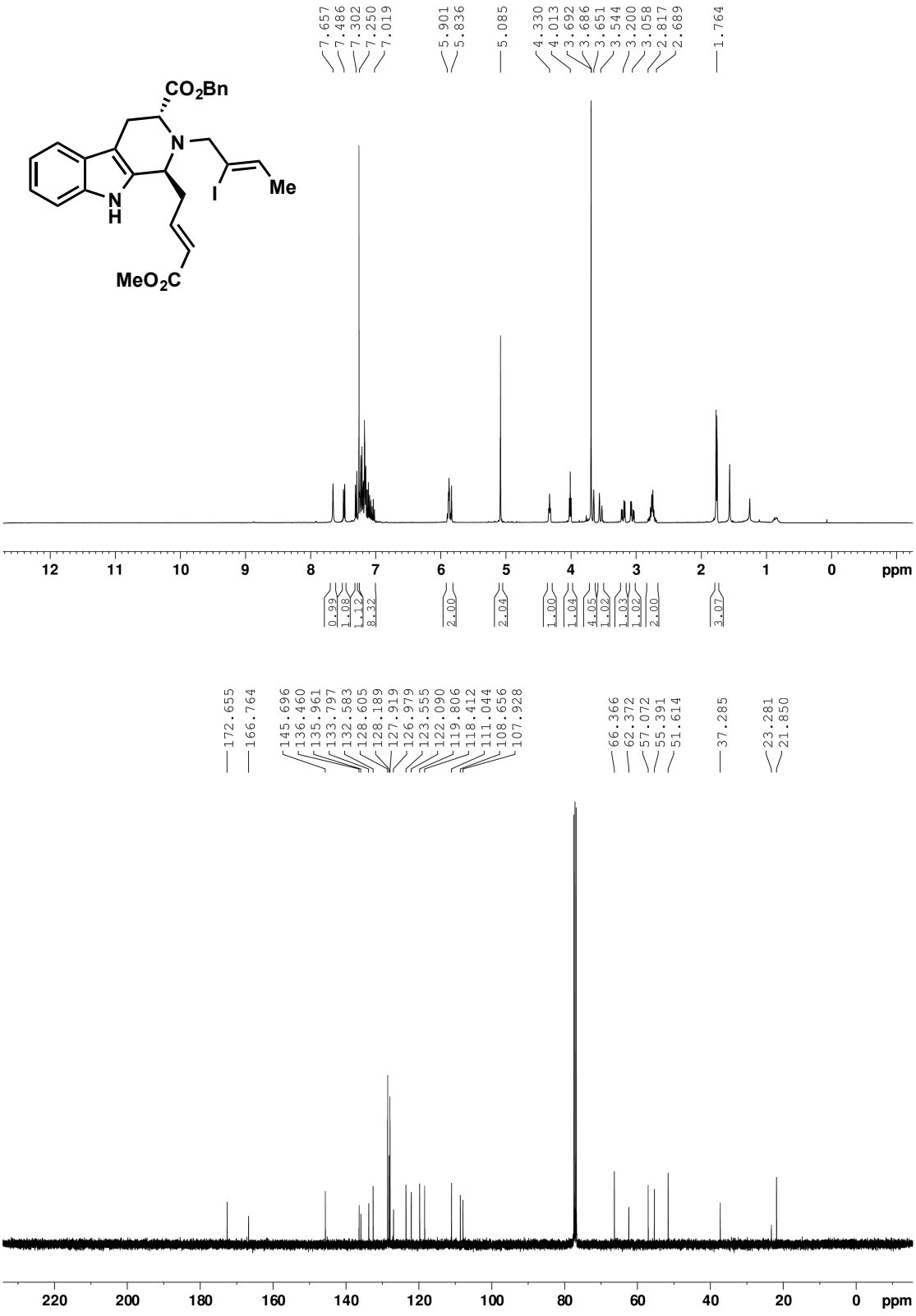

9.649
7.595
7.569
7.438
7.393
7.380
7.334
3.646
2.789
2.748
2.135
2.097
O
CO2Me
PhS
SPh
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
4.20
2.12
4.30
3.20
2.15
2.14


200.489
169.563
136.559
130.422
130.084
129.069
68.086
53.010
40.059
27.930
220
200
180
160
140
120
100
80
60
40
20
0
ppm

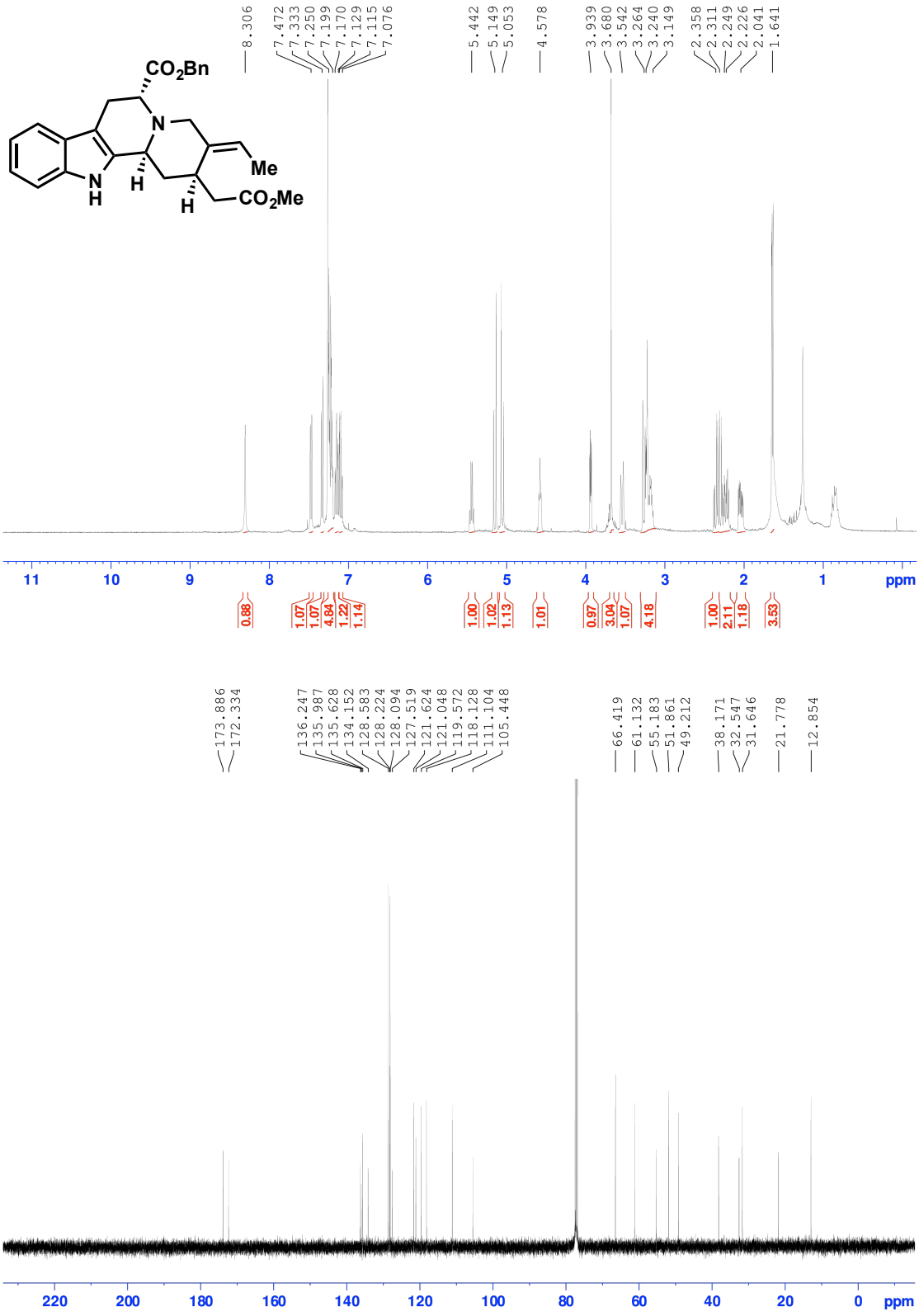
Compound **79**

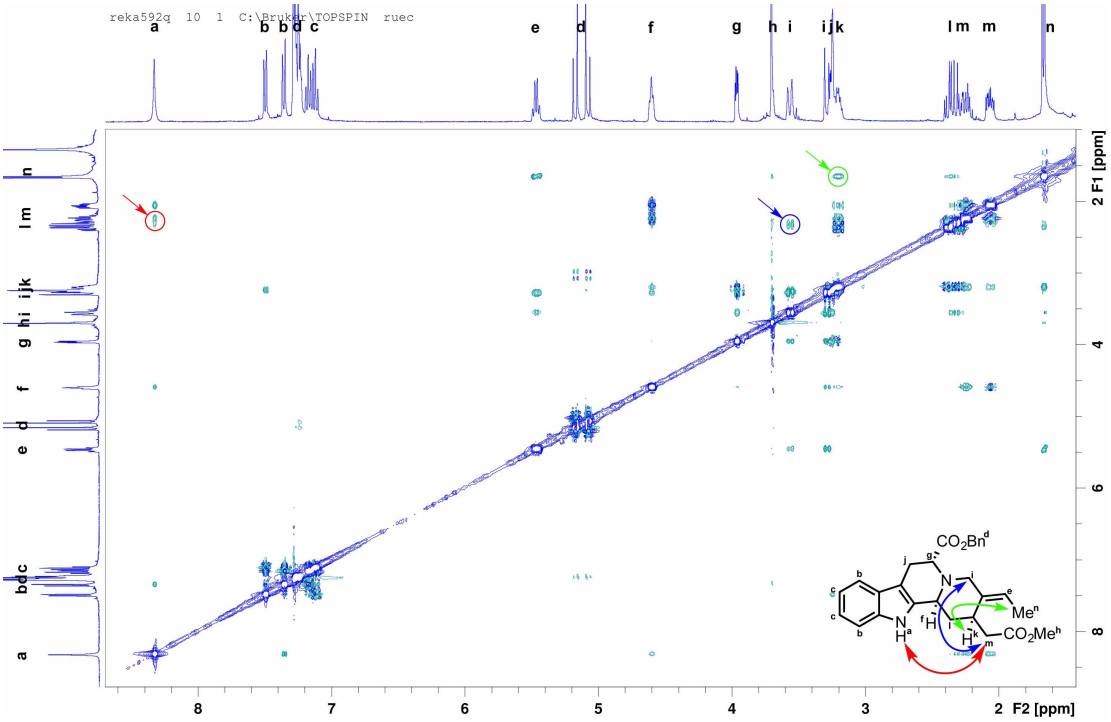

7.542
7.512
7.477
7.455
7.345
7.284
7.245
7.098
5.761
5.045
4.181
3.857
3.583
3.550
3.389
3.133
2.937
2.335
2.257
2.094
2.041
1.880
1.803
1.728
CO2Bn
N
N
H
I
Me
SPh
SPh
MeO2C
10
9
8
7
6
5
4
3
2
1
ppm
3.17
3.31
2.46
12.78
1.00
2.09
1.03
1.09
4.05
1.10
1.04
1.03
1.04
2.22
1.16
3.17
172.681
170.163
136.365
136.230
136.004
134.194
132.354
131.358
131.057
129.613
129.571
128.908
128.847
128.531
128.074
127.803
127.113
121.695
119.557
118.143
111.172
108.808
107.816
69.306
66.094
61.464
56.253
54.760
52.890
31.648
28.934
23.436
21.936
220
200
180
160
140
120
100
80
60
40
20
0
ppm

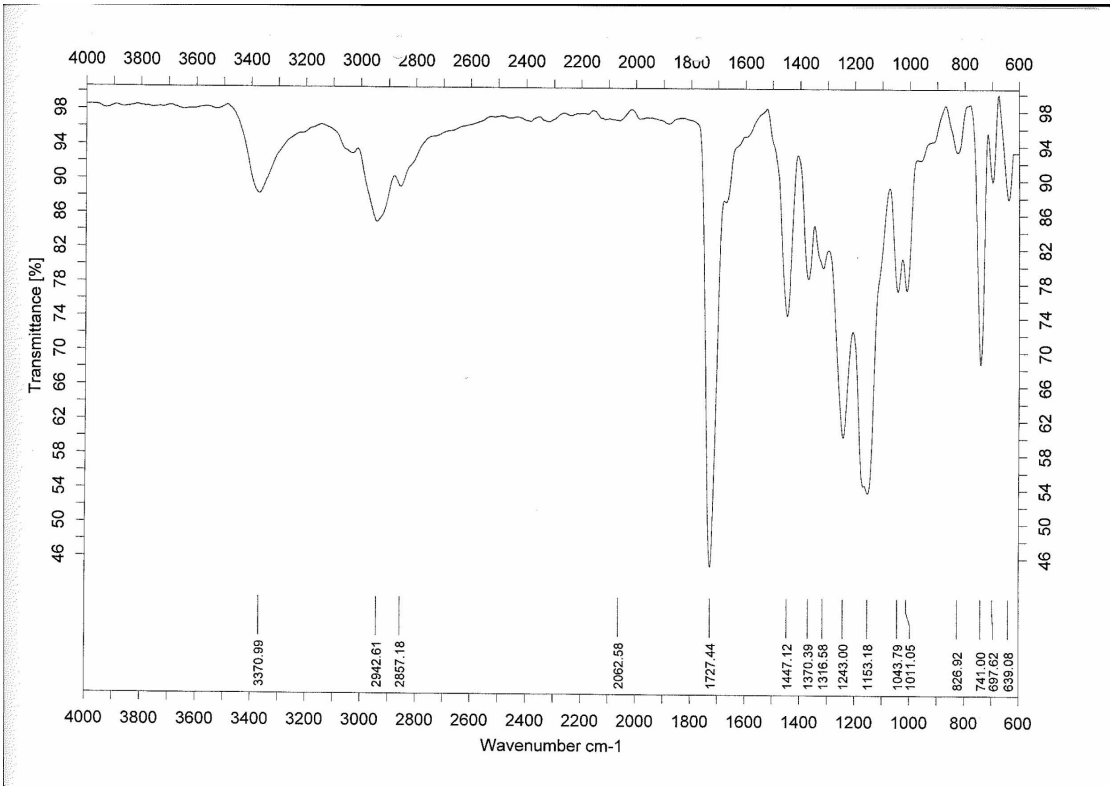
Compound **80**


7.657
7.486
7.302
7.250
7.019
5.901
5.836
5.085
4.330
4.013
3.692
3.686
3.651
3.544
3.200
3.058
2.817
2.689
1.764
CO2Bn
N
I
Me
N
H
MeO2C
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.08
1.12
8.32
2.00
2.04
1.00
1.04
4.05
1.02
1.03
1.02
2.00
3.07
172.655
166.764
145.696
136.460
135.961
133.797
132.583
128.605
128.189
127.919
126.979
123.555
122.090
119.806
118.412
111.044
108.656
107.928
66.366
62.372
57.072
55.391
51.614
37.285
23.281
21.850
220
200
180
160
140
120
100
80
60
40
20
0
ppm

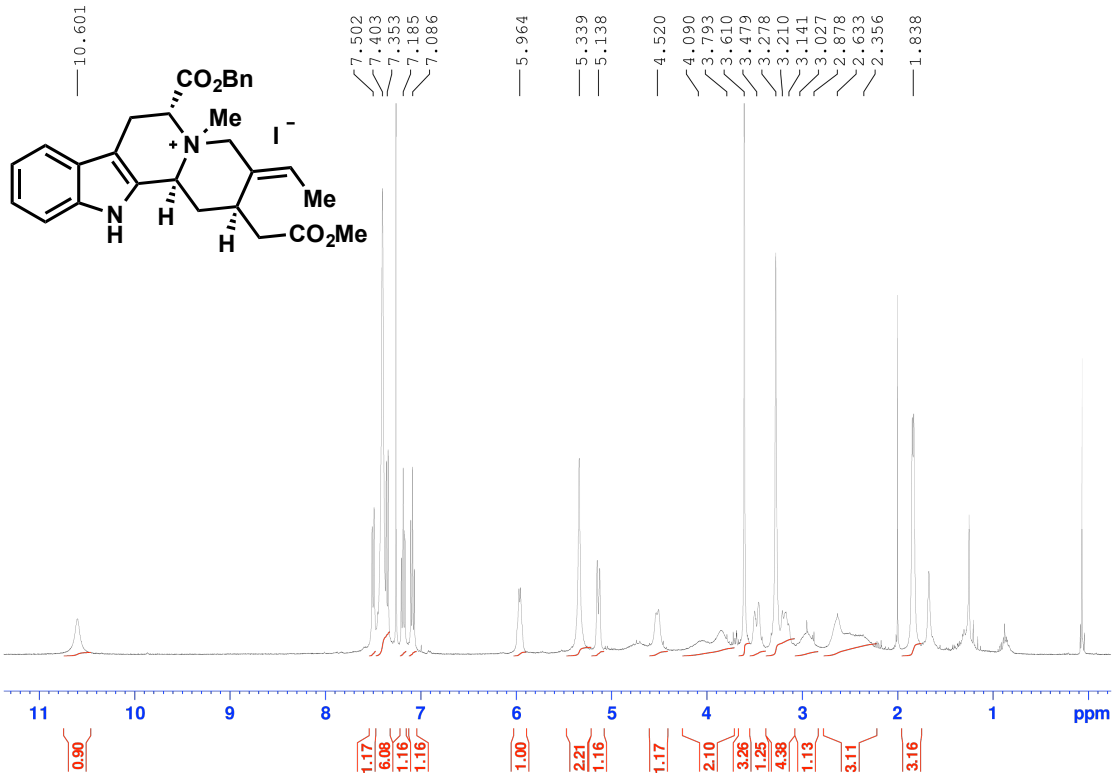
Compound **81**

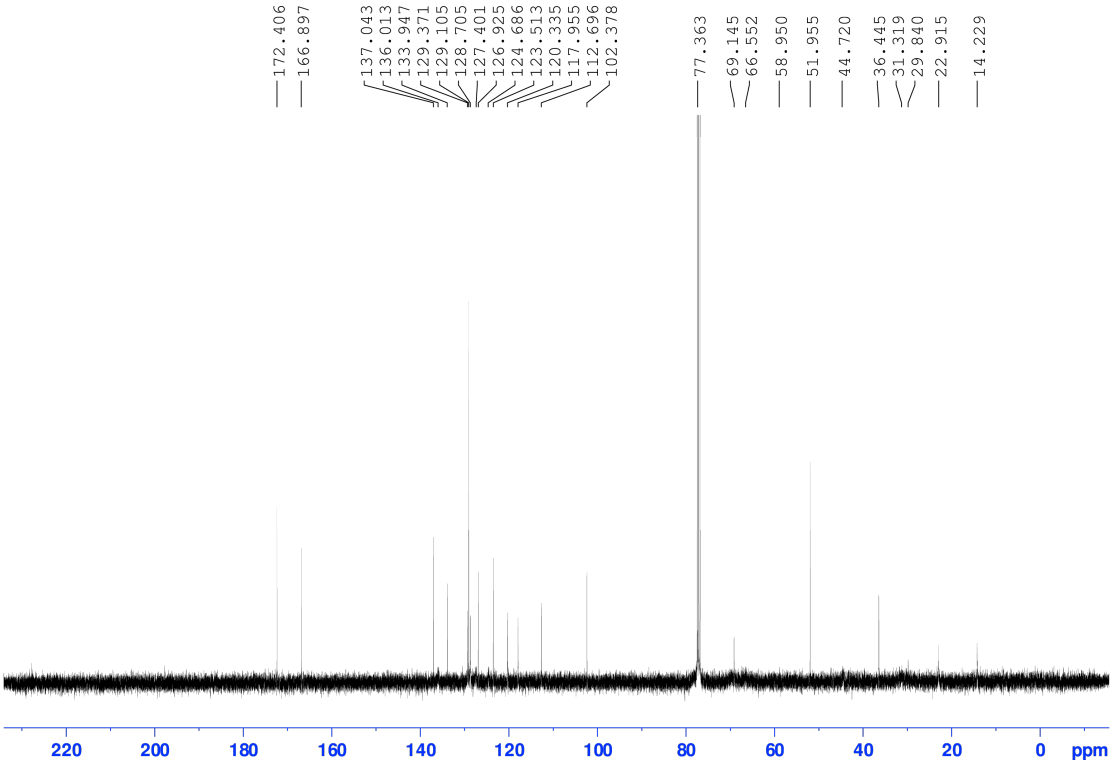

8.306
7.472
7.333
7.250
7.199
7.170
7.129
7.115
7.076
5.442
5.149
5.053
4.578
3.939
3.680
3.542
3.264
3.240
3.149
2.358
2.311
2.249
2.226
2.041
1.641
CO2Bn
N
Me
N
H
H
H
CO2Me
11
10
9
8
7
6
5
4
3
2
1
ppm
0.88
1.07
1.07
4.84
1.22
1.14
1.00
1.02
1.13
1.01
0.97
3.04
1.07
4.18
1.00
2.11
1.18
3.53
173.886
172.334
136.247
135.987
135.628
134.152
128.583
128.224
128.094
127.519
121.624
121.048
119.572
118.128
111.104
105.448
66.419
61.132
55.183
51.861
49.212
38.171
32.547
31.646
21.778
12.854
220
200
180
160
140
120
100
80
60
40
20
0
ppm


reka592q 10 1 C:\Bruker\TOPSPIN ruec
a b b d c e d f g h i ijk lm m n
2 F1 [ppm]
2 F2 [ppm]
CO2Bnd
Mene
CO2Meh

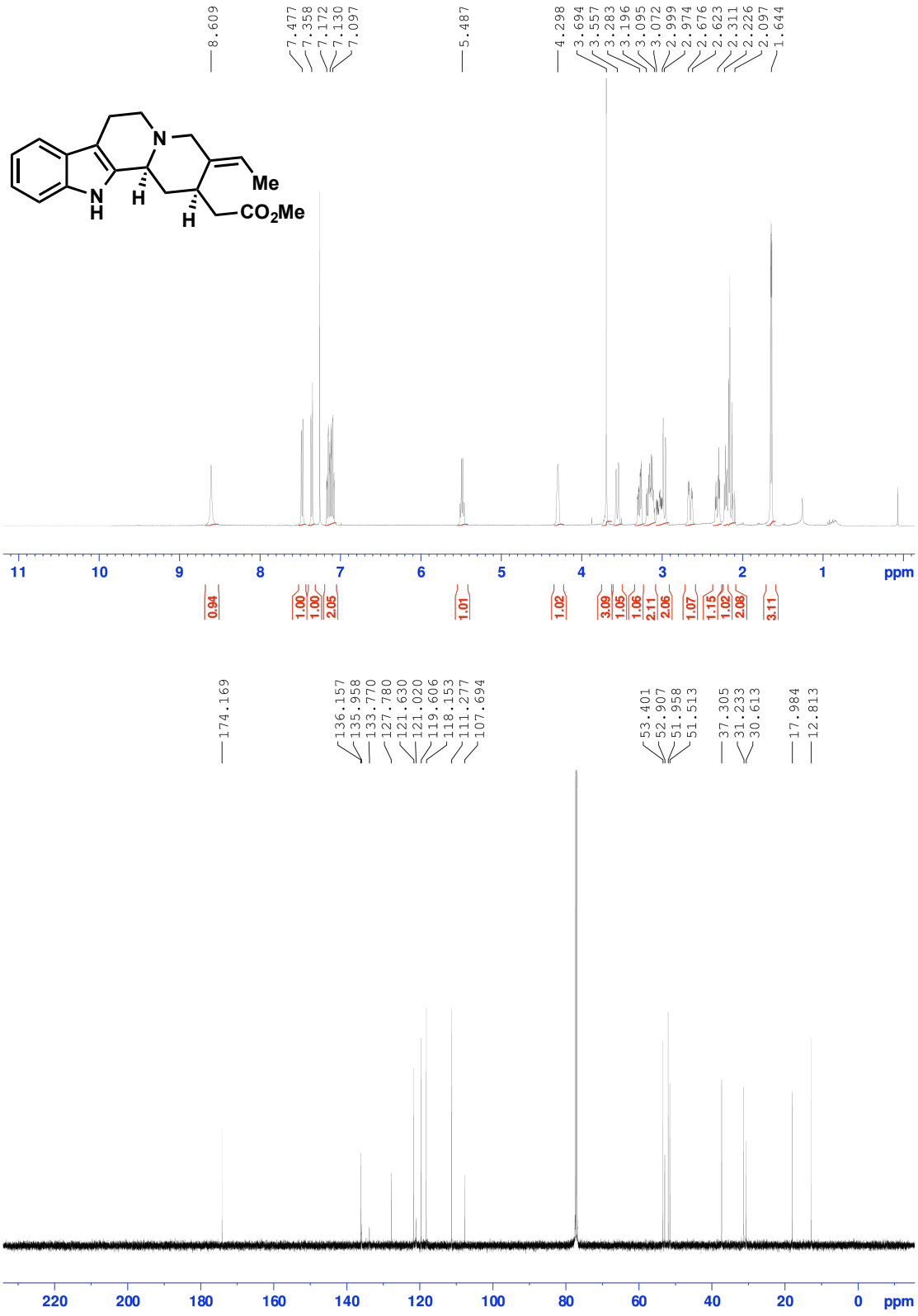

Transmittance [%]
Wavenumber cm-1
3370.99
2942.61
2857.18
2062.58
1727.44
1447.12
1370.39
1316.58
1243.00
1153.18
1043.79
1011.05
826.92
741.00
697.62
639.08

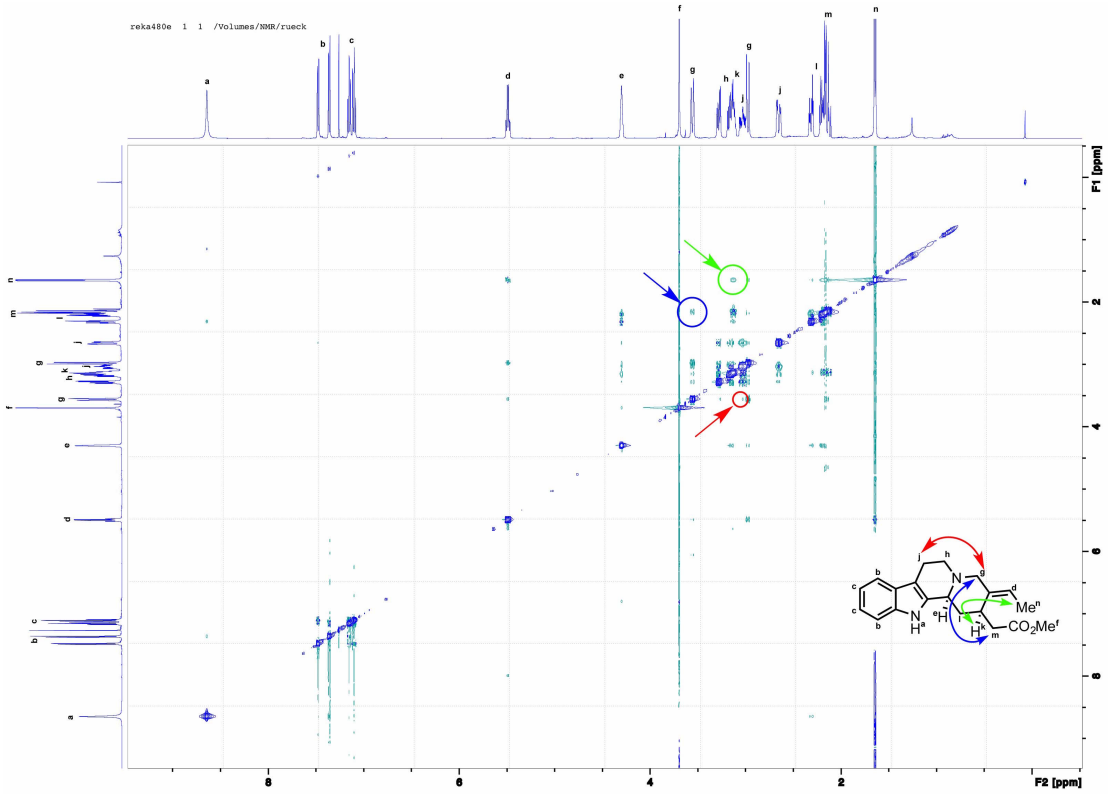
Compound **88**

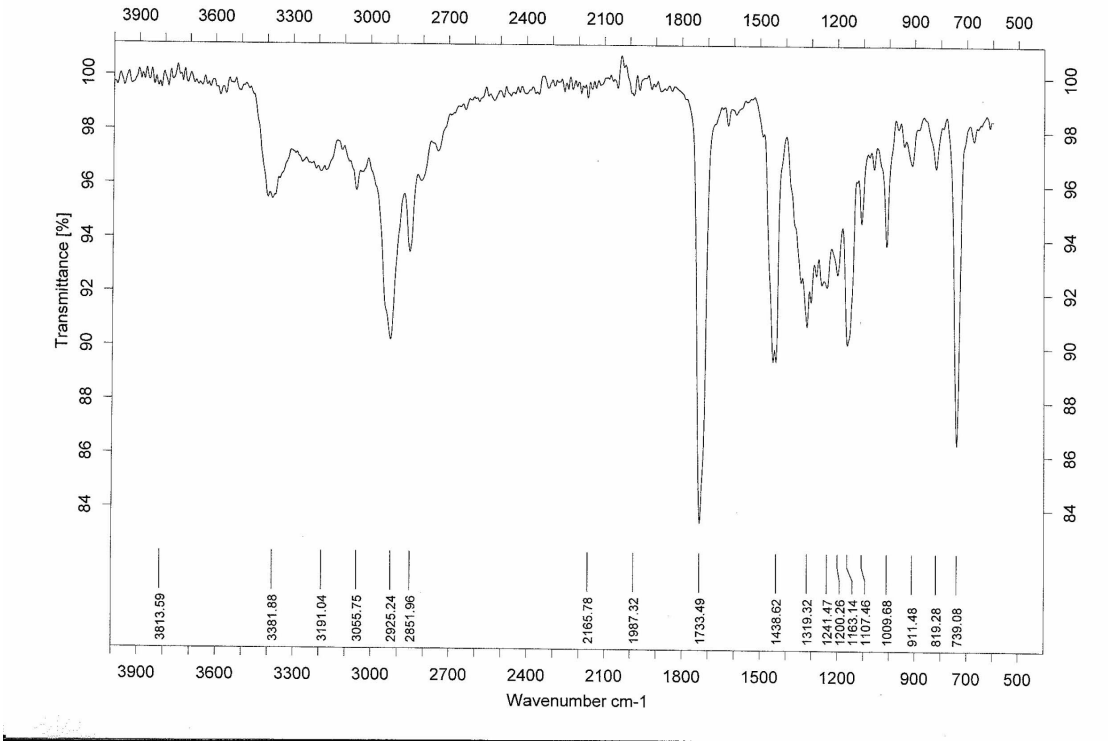

10.601
7.502
7.403
7.353
7.185
7.086
5.964
5.339
5.138
4.520
4.090
3.793
3.610
3.479
3.278
3.210
3.141
3.027
2.878
2.633
2.356
1.838
CO2Bn
Me
N
I -
Me
N
H
H
H
CO2Me
11
10
9
8
7
6
5
4
3
2
1
ppm
0.90
1.17
6.08
1.16
1.16
1.00
2.21
1.16
1.17
2.10
3.26
1.25
4.38
1.13
3.11
3.16


172.406
166.897
137.043
136.013
133.947
129.371
129.105
128.705
127.401
126.925
124.686
123.513
120.335
117.955
112.696
102.378
77.363
69.145
66.552
58.950
51.955
44.720
36.445
31.319
29.840
22.915
14.229
220
200
180
160
140
120
100
80
60
40
20
0
ppm

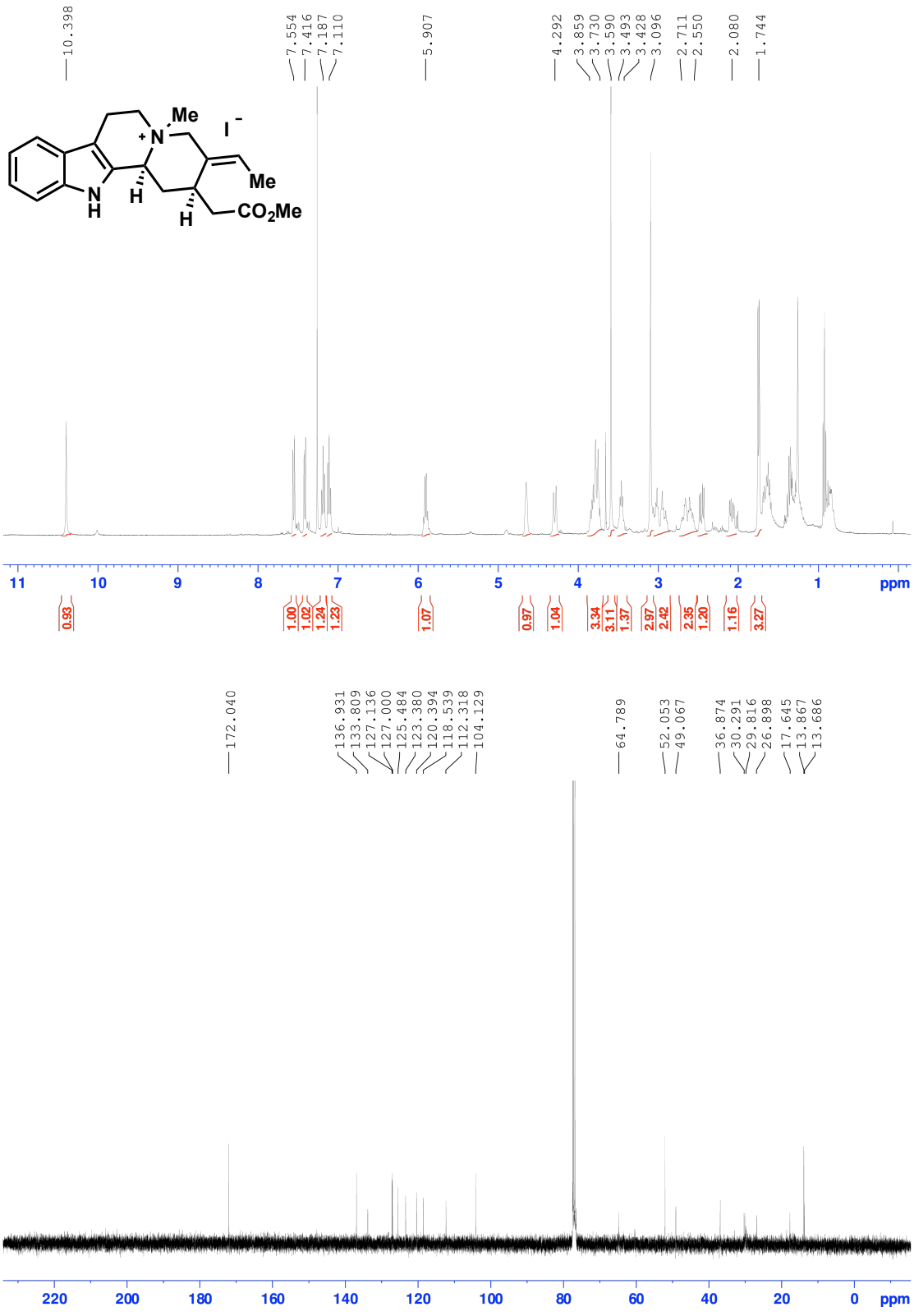
Compound **82**


8.609
7.477
7.358
7.172
7.130
7.097
5.487
4.298
3.694
3.557
3.283
3.196
3.095
3.072
2.999
2.974
2.676
2.623
2.311
2.226
2.097
1.644
N
H
H
H
Me
CO2Me
11
10
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
1.00
2.05
1.01
1.02
3.09
1.05
1.06
2.11
2.06
1.07
1.15
1.02
2.08
3.11
174.169
136.157
135.958
133.770
127.780
121.630
121.020
119.606
118.153
111.277
107.694
53.401
52.907
51.958
51.513
37.305
31.233
30.613
17.984
12.813
220
200
180
160
140
120
100
80
60
40
20
0
ppm

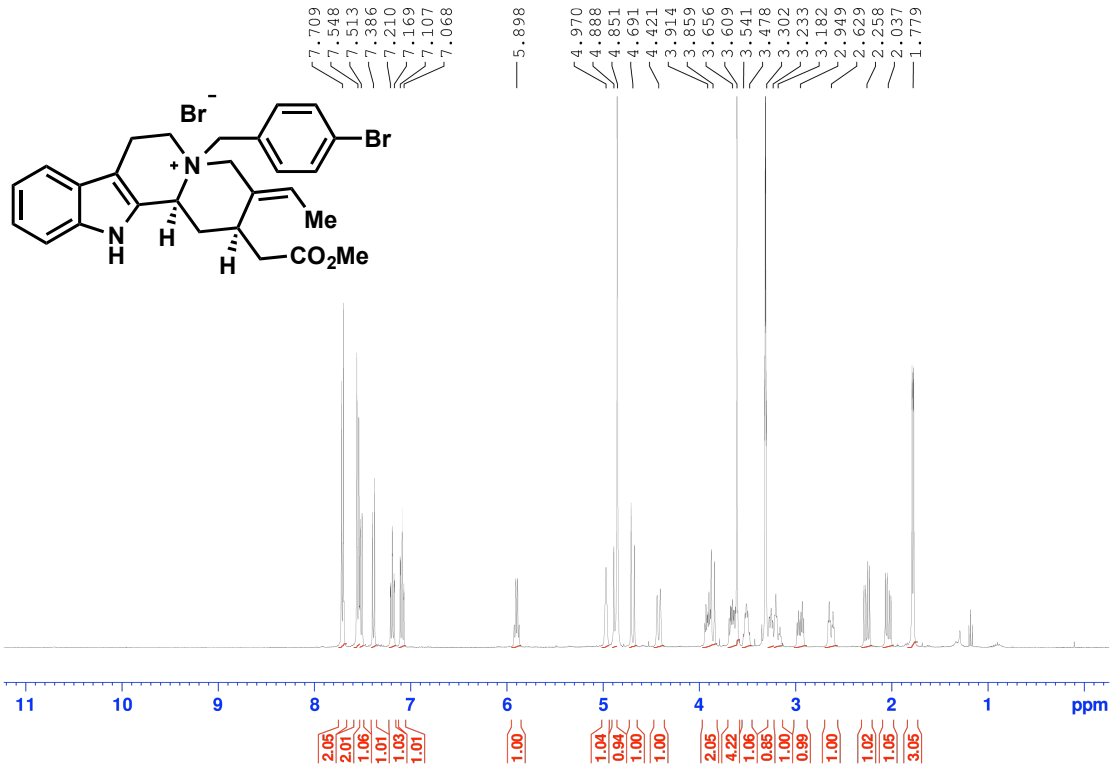

reka480e 1 1 /Volumes/NMR/rueck
F1 [ppm]
F2 [ppm]
Me^n
CO2Me^f

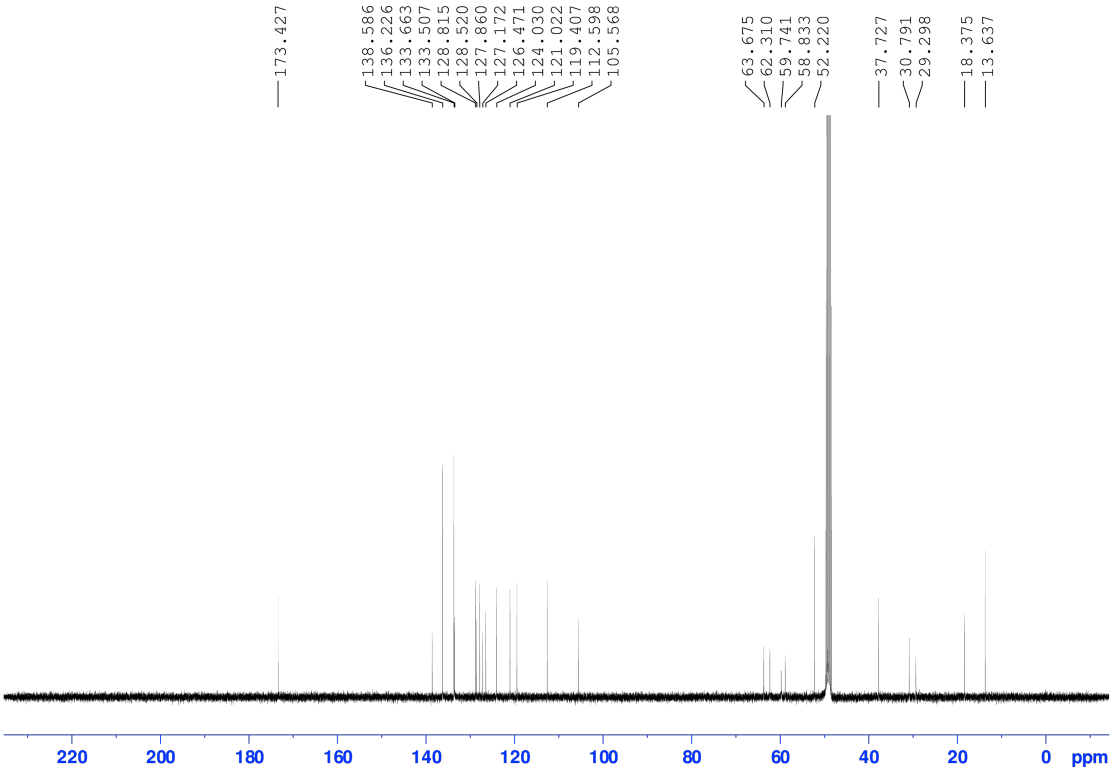

Transmittance [%]
Wavenumber cm-1
3813.59
3381.88
3191.04
3055.75
2925.24
2851.96
2165.78
1987.32
1733.49
1438.62
1319.32
1241.47
1220.26
1163.14
1107.46
1009.68
911.48
819.28
739.08

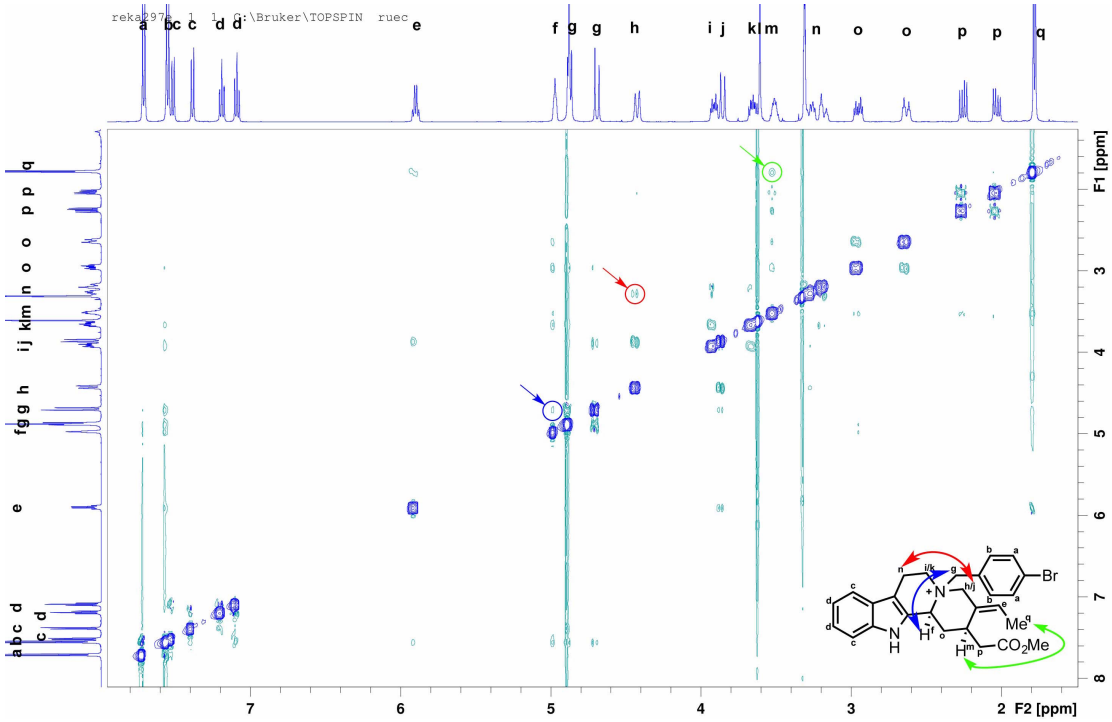
Compound **89**


10.398
7.554
7.416
7.187
7.110
5.907
4.292
3.859
3.730
3.590
3.493
3.428
3.096
2.711
2.550
2.080
1.744
Me
I⁻
N
H
Me
CO2Me
ppm
0.93
1.00
1.02
1.24
1.23
1.07
0.97
1.04
3.34
3.11
1.37
2.97
2.42
2.35
1.20
1.16
3.27
172.040
136.931
133.809
127.136
127.000
125.484
123.380
120.394
118.539
112.318
104.129
64.789
52.053
49.067
36.874
30.291
29.816
26.898
17.645
13.867
13.686
ppm

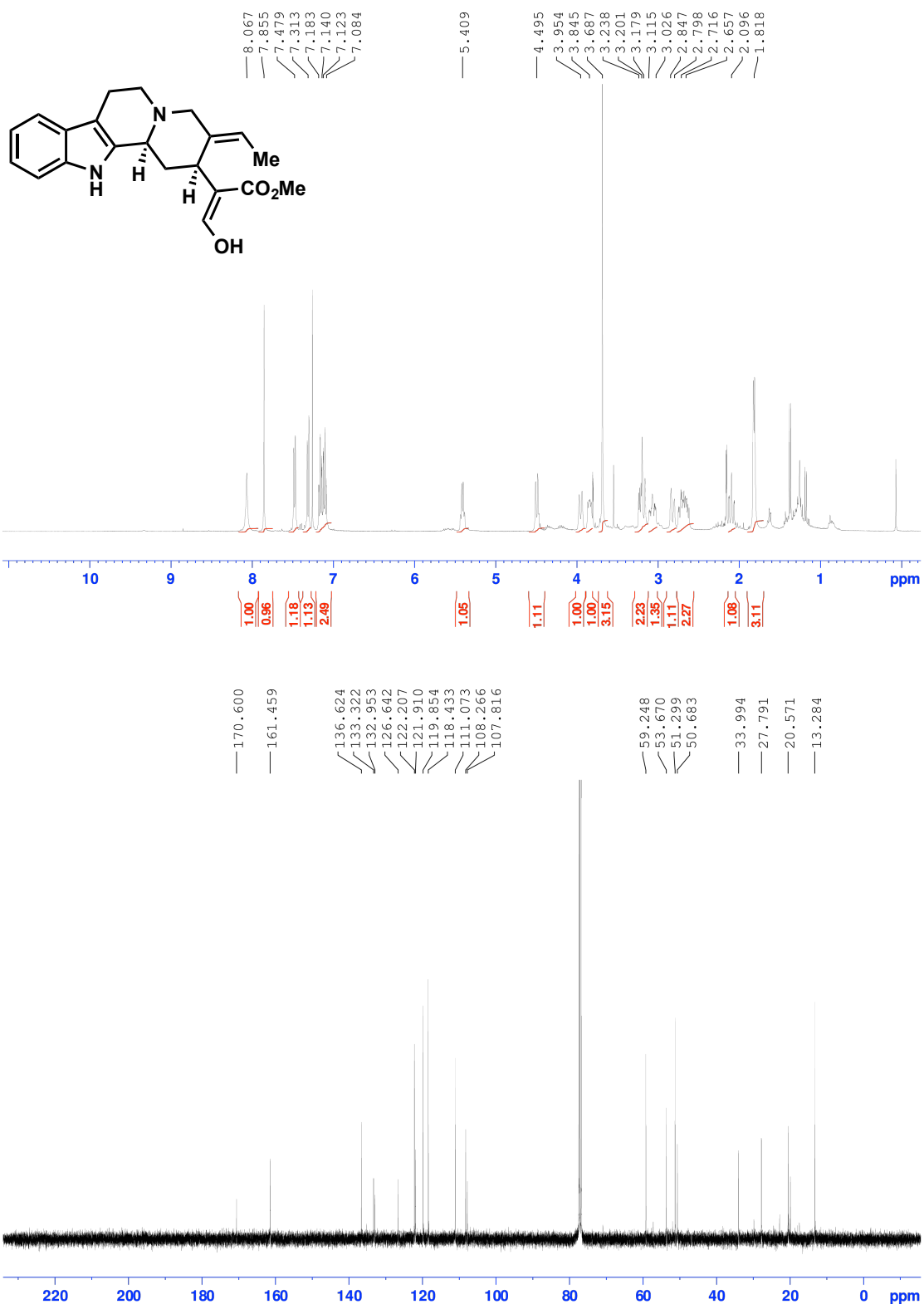
Compound **90**

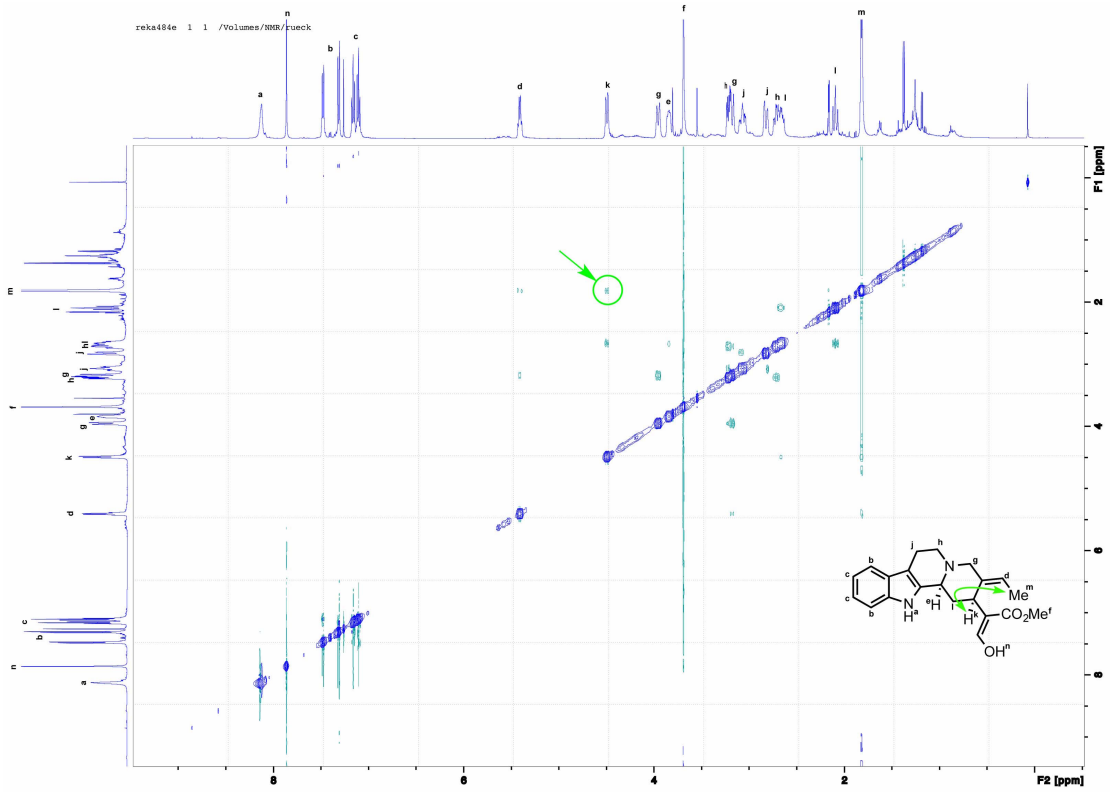

7.709
7.548
7.513
7.386
7.210
7.169
7.107
7.068
5.898
4.970
4.888
4.851
4.691
4.421
3.914
3.859
3.656
3.609
3.541
3.478
3.302
3.233
3.182
2.949
2.629
2.258
2.037
1.779
Br
Br
N
H
H
Me
CO2Me
11
10
9
8
7
6
5
4
3
2
1
ppm
2.05
2.01
1.06
1.01
1.03
1.01
1.00
1.04
0.94
1.00
1.00
2.05
4.22
1.06
0.85
1.00
0.99
1.00
1.02
1.05
3.05

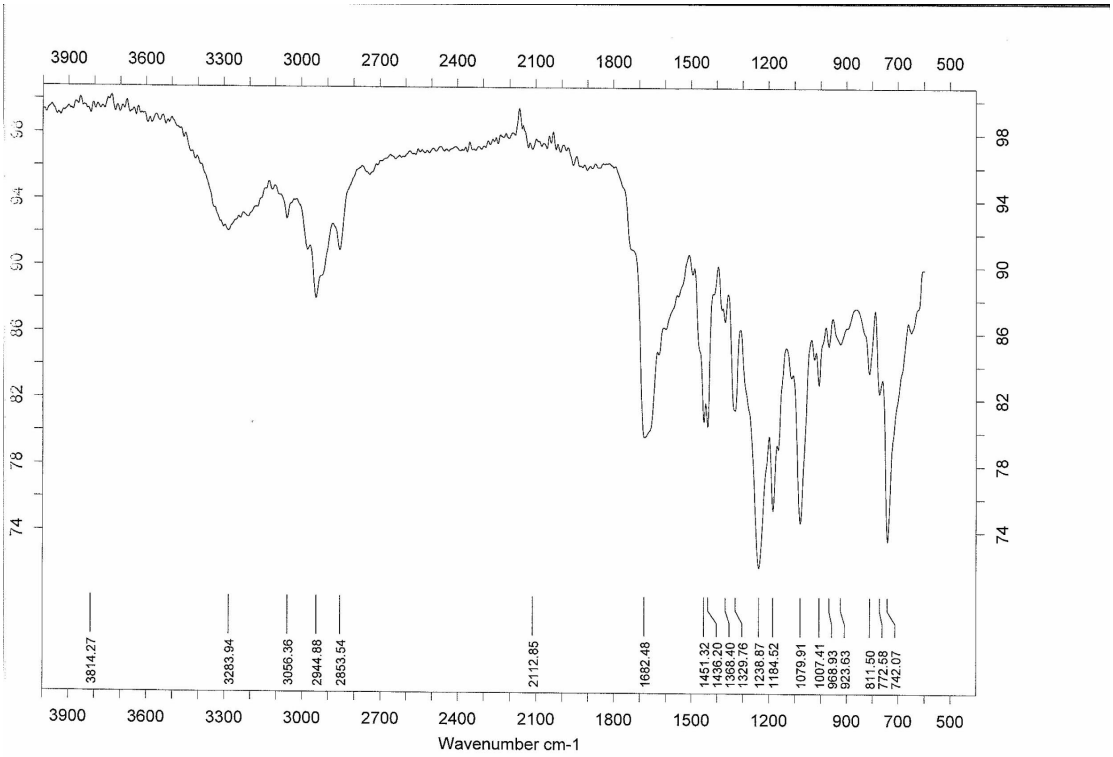

173.427
138.586
136.226
133.663
133.507
128.815
128.520
127.860
127.172
126.471
124.030
121.022
119.407
112.598
105.568
63.675
62.310
59.741
58.833
52.220
37.727
30.791
29.298
18.375
13.637
220
200
180
160
140
120
100
80
60
40
20
0
ppm


F1 [ppm]
F2 [ppm]
Br
Me
CO2Me
N
H

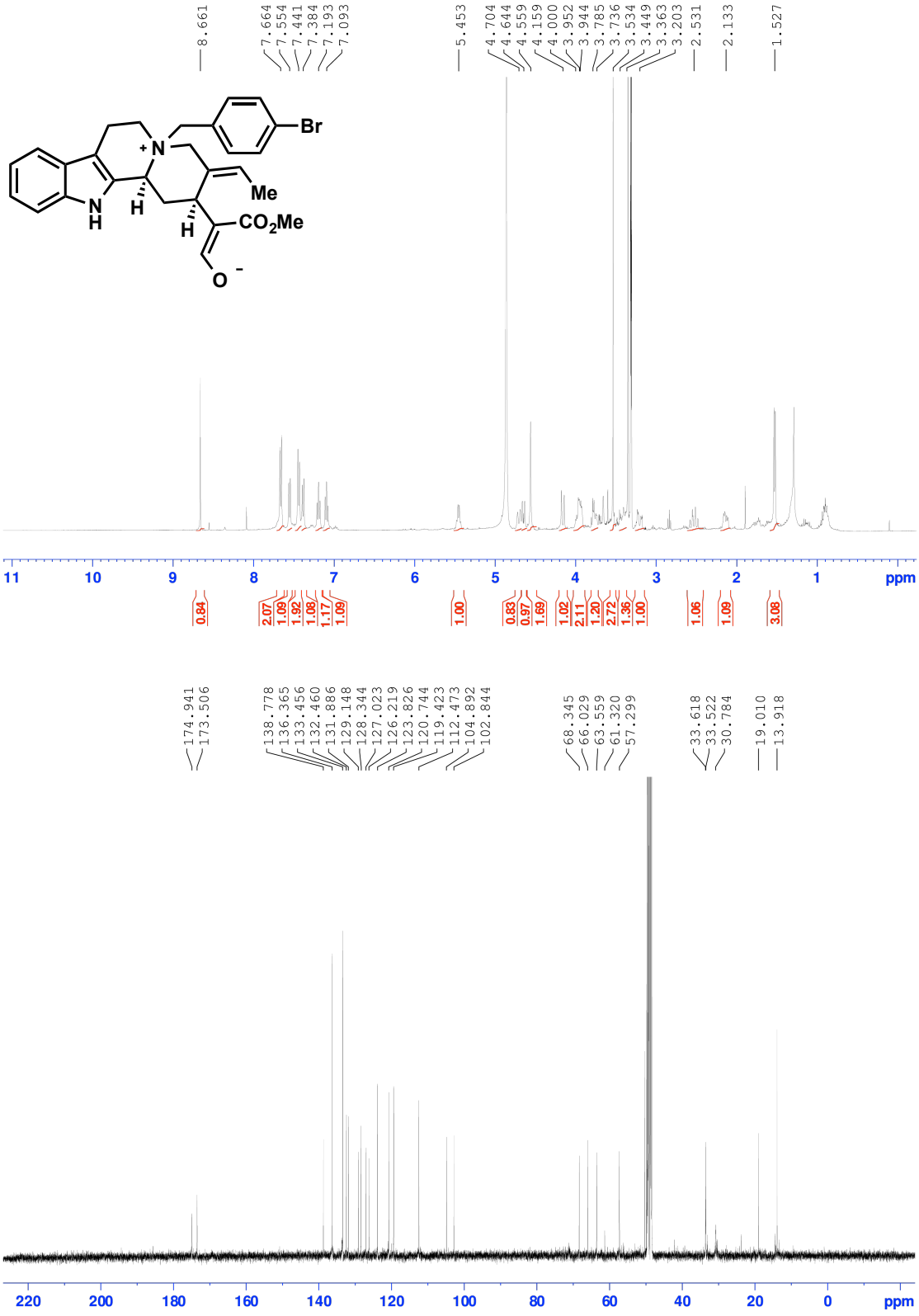
Compound **35**


8.067
7.855
7.479
7.313
7.183
7.140
7.123
7.084
5.409
4.495
3.954
3.845
3.687
3.238
3.201
3.179
3.115
3.026
2.847
2.798
2.716
2.657
2.096
1.818
N
H
N
H
H
Me
CO2Me
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.96
1.18
1.13
2.49
1.05
1.11
1.00
1.00
3.15
2.23
1.35
1.11
2.27
1.08
3.11
170.600
161.459
136.624
133.322
132.953
126.642
122.207
121.910
119.854
118.433
111.073
108.266
107.816
59.248
53.670
51.299
50.683
33.994
27.791
20.571
13.284
220
200
180
160
140
120
100
80
60
40
20
0
ppm

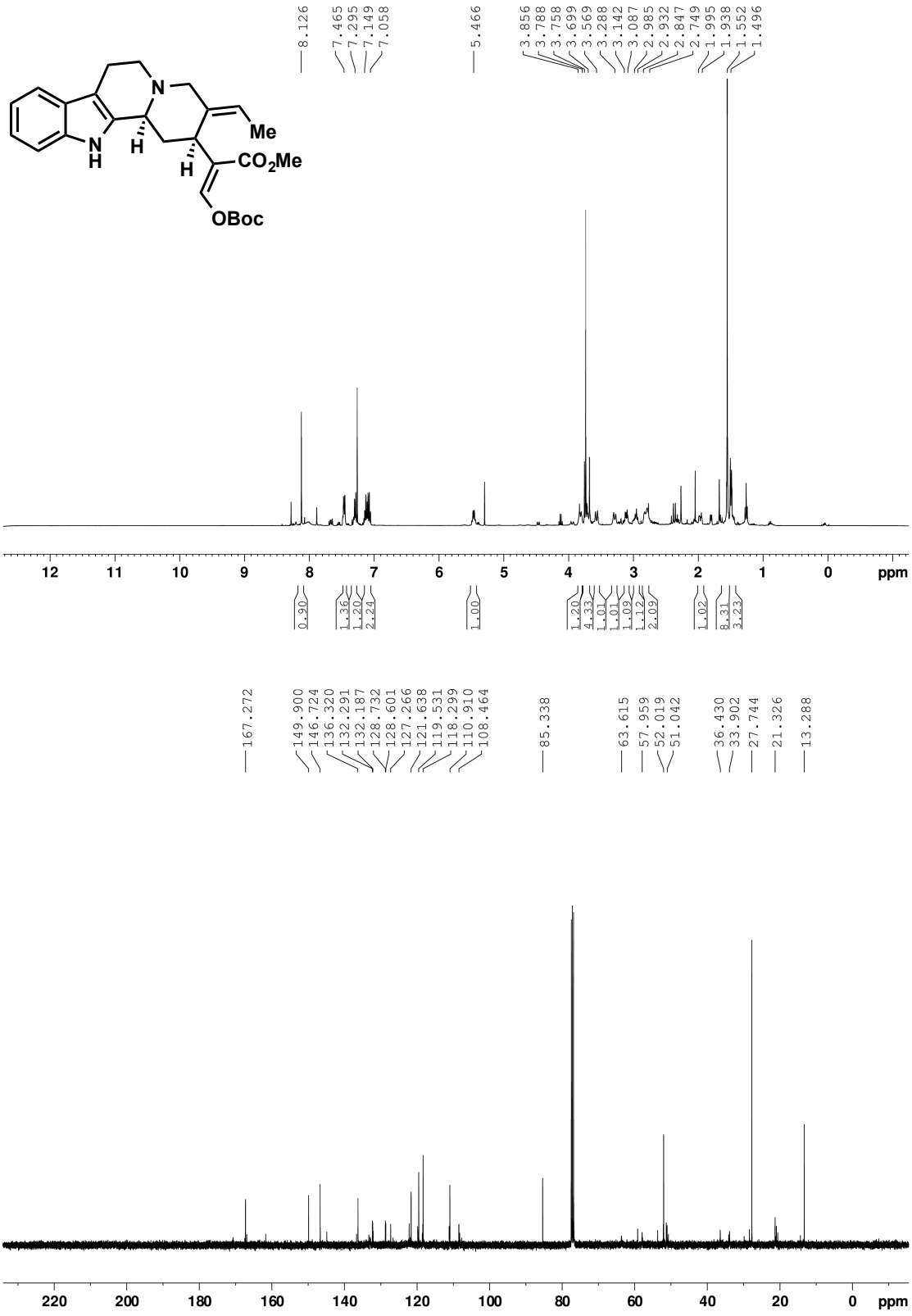

reka484e 1 1 /Volumes/NMR/rueck
F1 [ppm]
F2 [ppm]
Me^m
CO2Me^f
OH^n


3814.27
3283.94
3056.36
2944.88
2853.54
2112.85
1682.48
1451.32
1436.20
1388.40
1329.76
1238.87
1184.52
1079.91
1007.41
968.93
923.63
811.50
772.58
742.07
Wavenumber cm-1

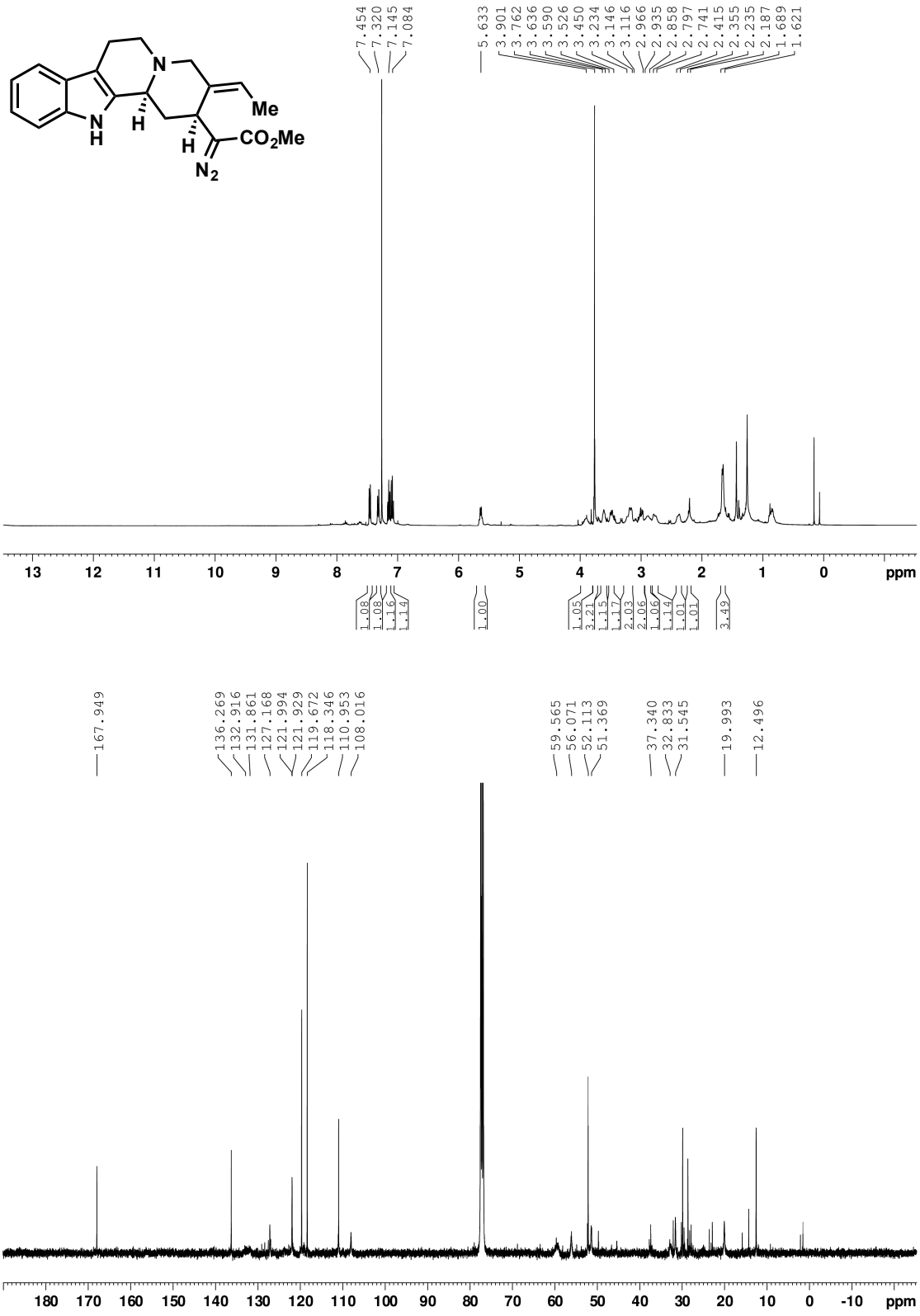
Compound **91**

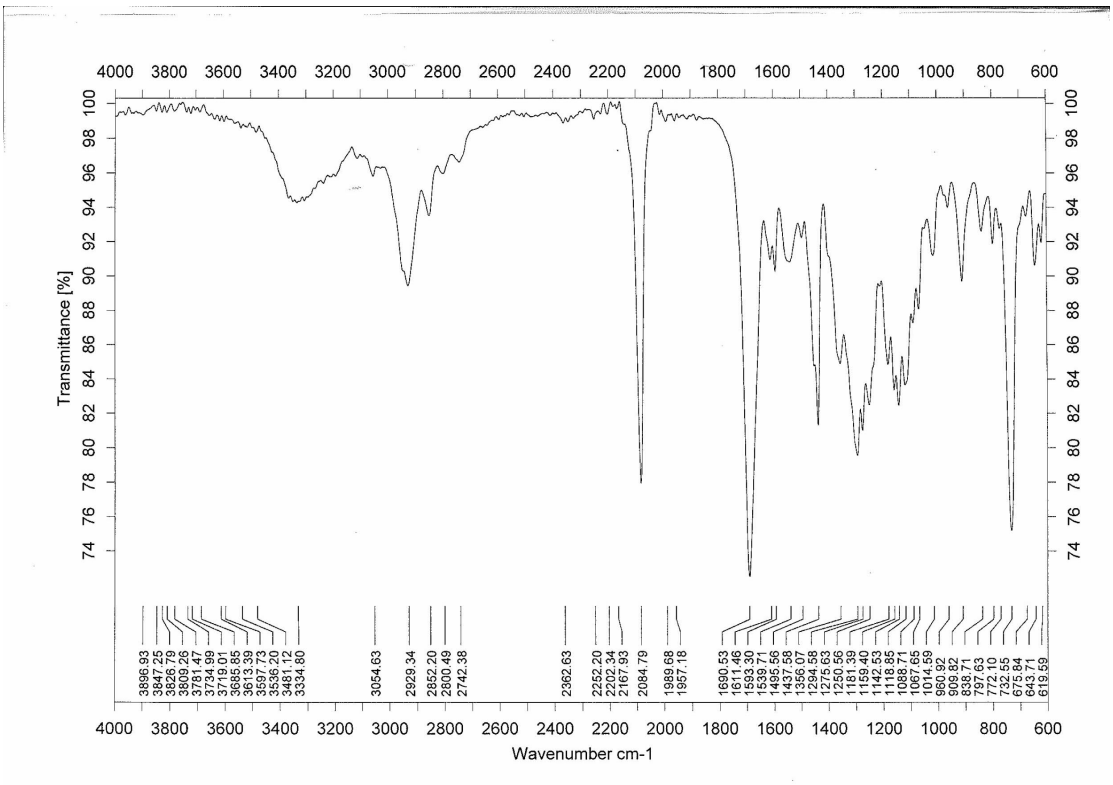

8.661
7.664
7.554
7.441
7.384
7.193
7.093
5.453
4.704
4.644
4.559
4.159
4.000
3.952
3.944
3.785
3.736
3.534
3.449
3.363
3.203
2.531
2.133
1.527
Br
N
H
Me
CO2Me
O
ppm
174.941
173.506
138.778
136.365
133.456
132.460
131.886
129.148
128.344
127.023
126.219
123.826
120.744
119.423
112.473
104.892
102.844
68.345
66.029
63.559
61.320
57.299
33.618
33.522
30.784
19.010
13.918
ppm

Compound **94**

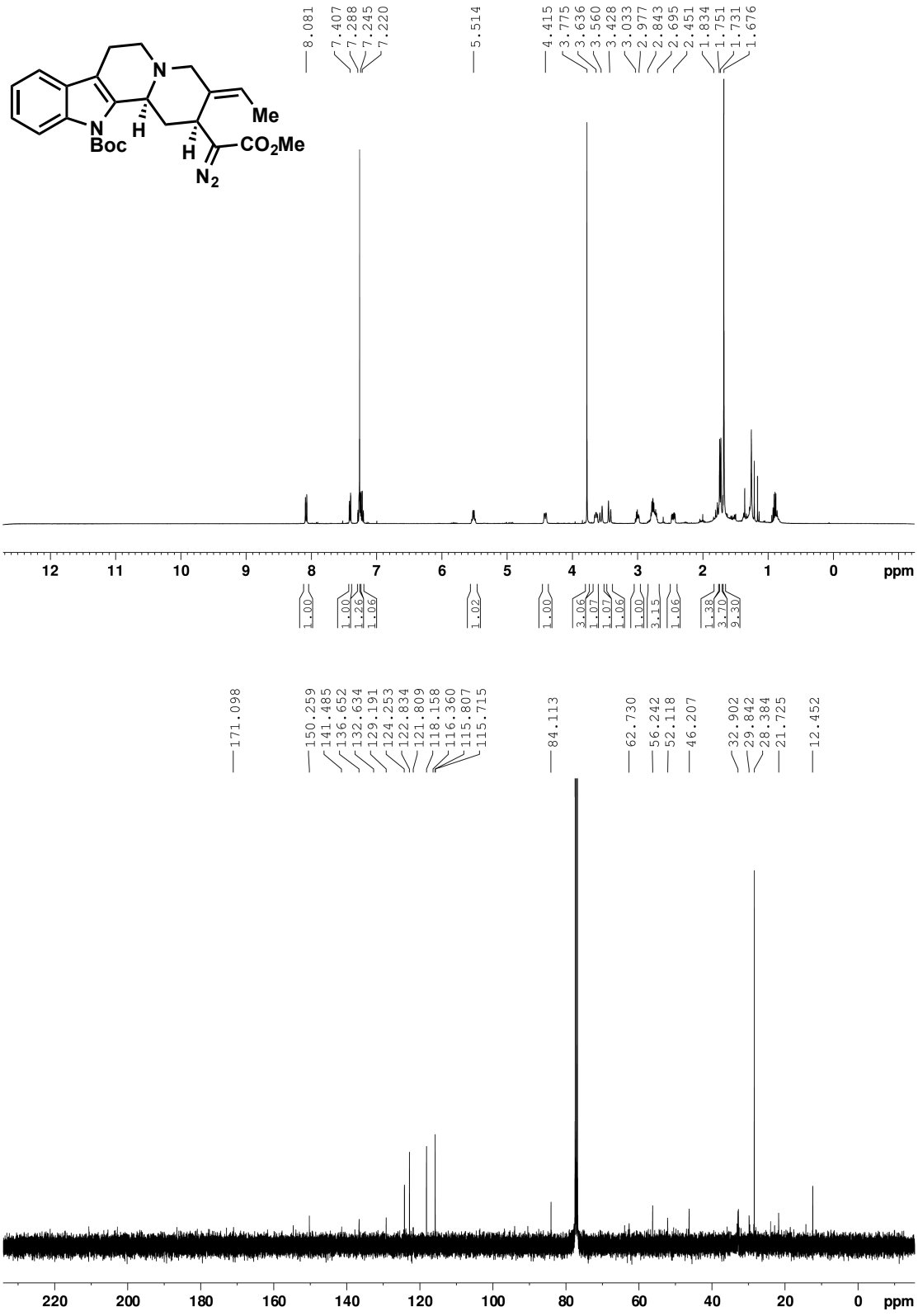

8.126
7.465
7.295
7.149
7.058
5.466
3.856
3.788
3.758
3.699
3.569
3.288
3.142
3.087
2.985
2.932
2.847
2.749
1.995
1.938
1.552
1.496
N
H
H
H
Me
CO2Me
OBoc
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.90 1.36 1.20 2.24 1.00 1.20 4.33 1.01 1.01 1.09 1.12 2.09 1.02 8.31 3.23
167.272
149.900
146.724
136.320
132.291
132.187
128.732
128.601
127.266
121.638
119.531
118.299
110.910
108.464
85.338
63.615
57.959
52.019
51.042
36.430
33.902
27.744
21.326
13.288
220 200 180 160 140 120 100 80 60 40 20 0 ppm

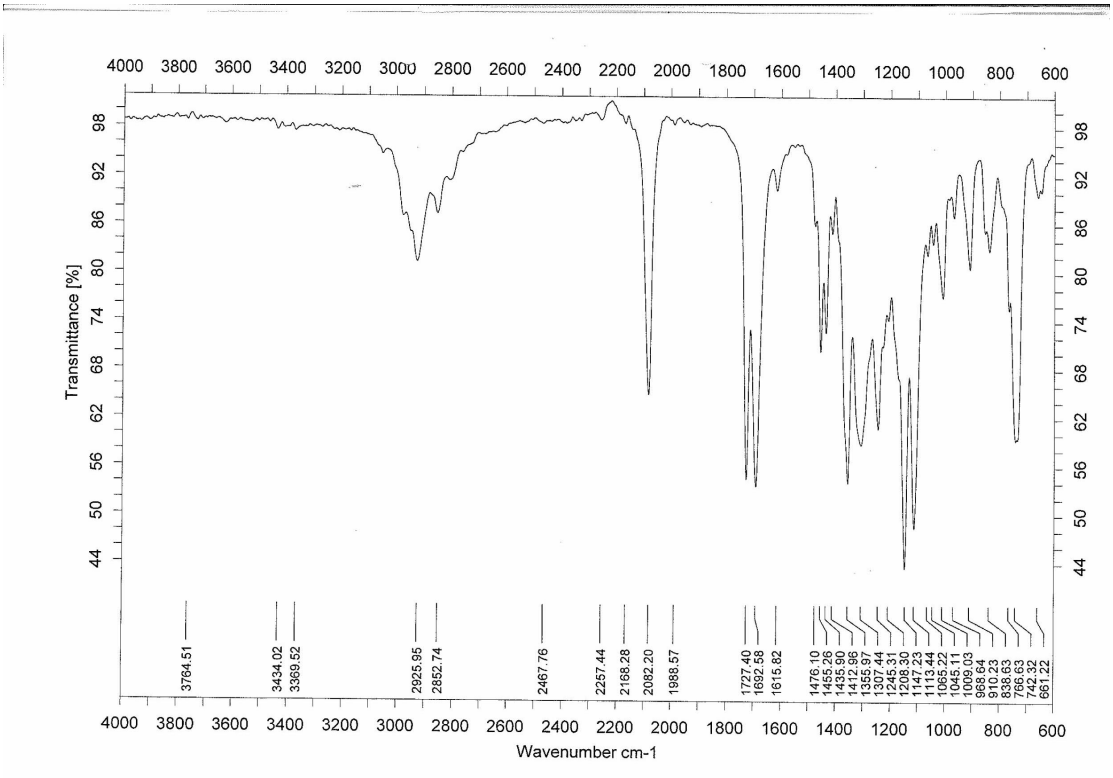
Compound **92**


7.454
7.320
7.145
7.084
5.633
3.901
3.762
3.636
3.590
3.526
3.450
3.234
3.146
3.116
2.966
2.935
2.858
2.797
2.741
2.415
2.355
2.235
2.187
1.689
1.621
Me
CO2Me
N2
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.08
1.08
1.16
1.14
1.00
1.05
3.21
1.15
1.17
2.03
2.06
1.06
1.14
1.01
1.01
3.49
167.949
136.269
132.916
131.861
127.168
121.994
121.929
119.672
118.346
110.953
108.016
59.565
56.071
52.113
51.369
37.340
32.833
31.545
19.993
12.496
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

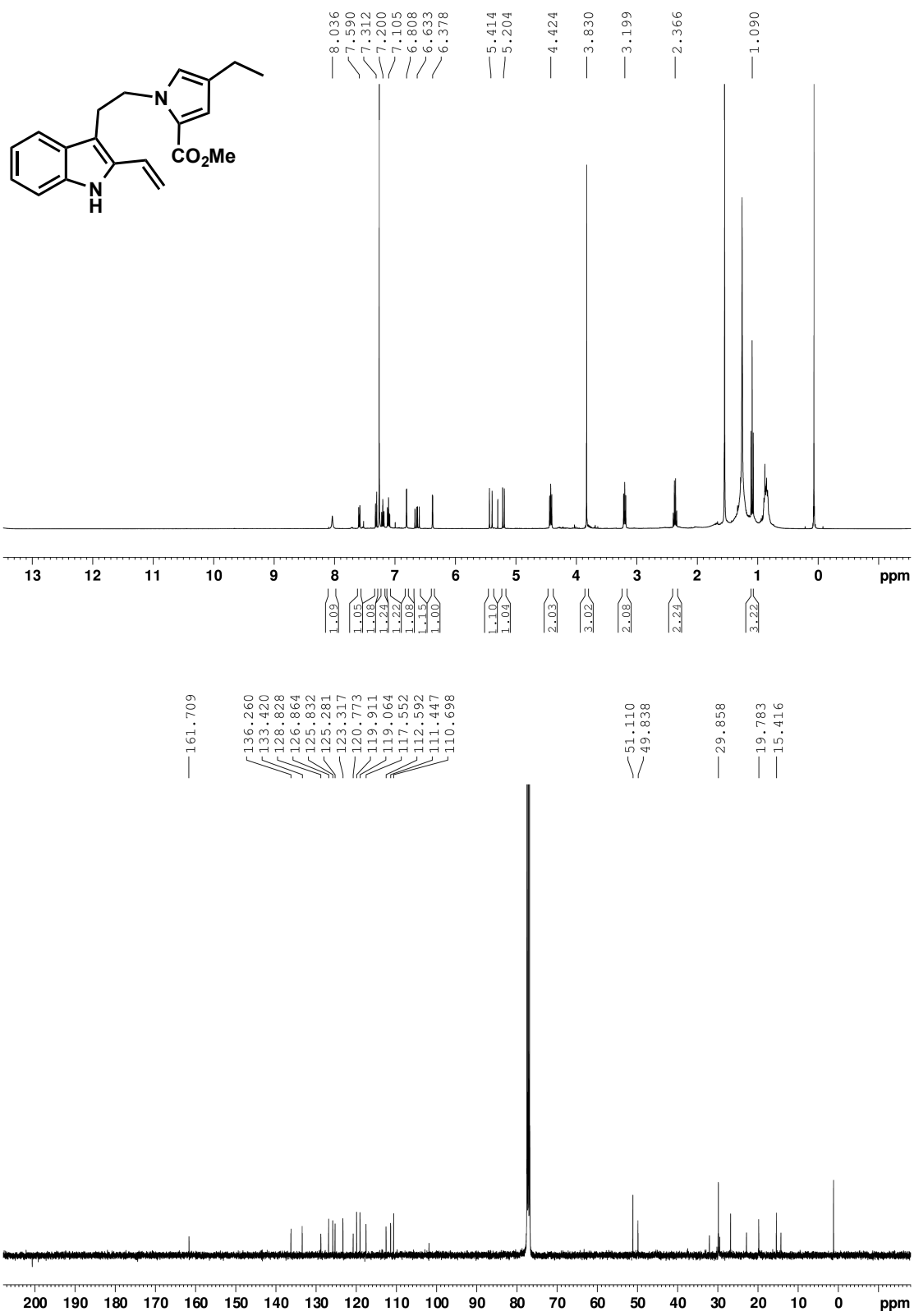

Transmittance [%]
Wavenumber cm-1
3896.93
3847.25
3826.78
3809.29
3781.47
3734.99
3719.01
3685.85
3613.39
3597.73
3536.20
3481.12
3334.80
3054.63
2929.34
2852.20
2800.49
2742.38
2362.63
2252.20
2202.34
2167.93
2084.79
1989.68
1957.18
1690.53
1611.46
1593.30
1539.71
1495.58
1437.59
1396.07
1334.64
1275.63
1250.56
1181.39
1159.40
1142.53
1118.85
1088.71
1067.66
1014.59
960.92
908.82
838.71
797.63
772.10
732.55
675.84
643.71
619.59

Compound **96**

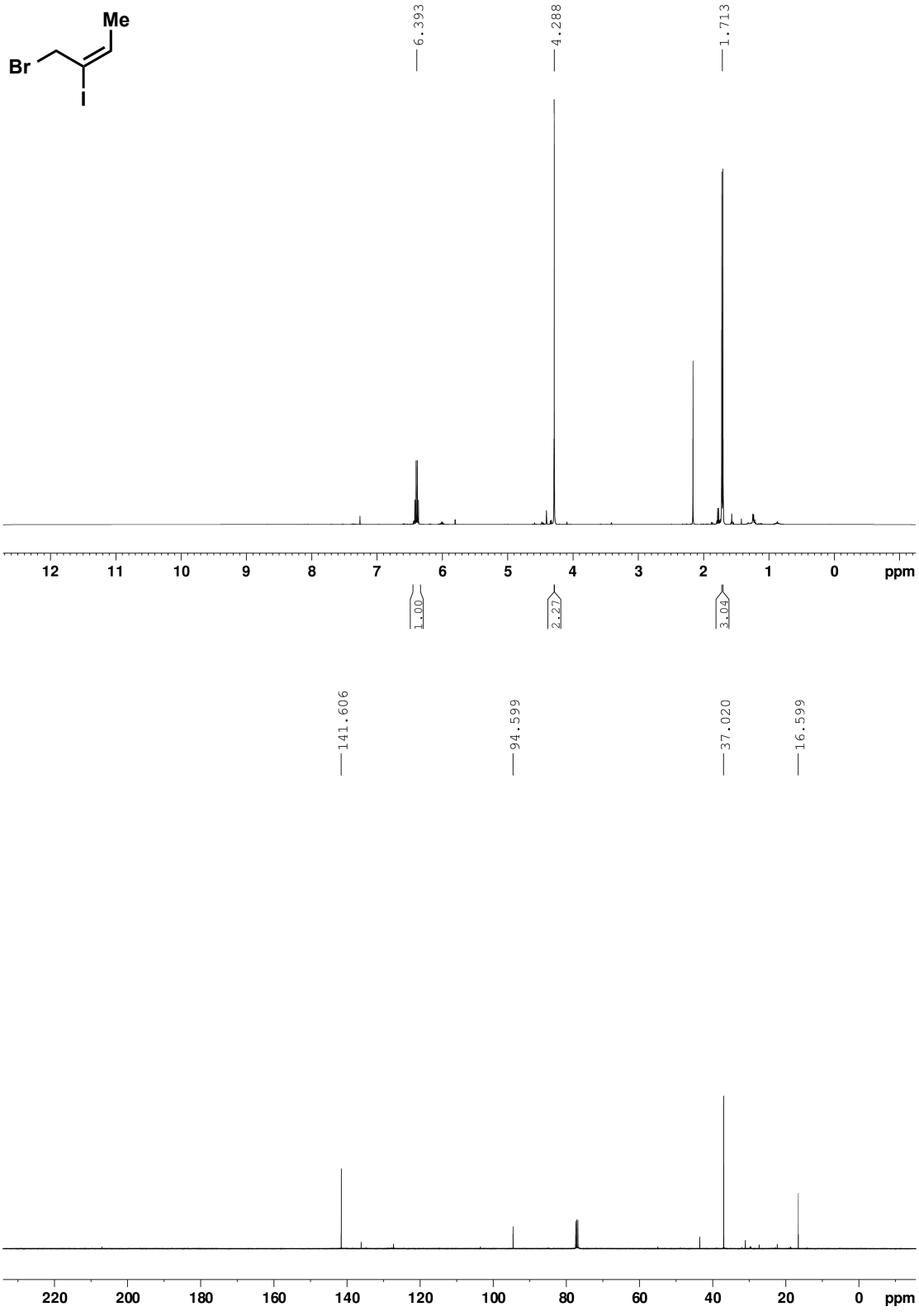

8.081
7.407
7.288
7.245
7.220
5.514
4.415
3.775
3.636
3.560
3.428
3.033
2.977
2.843
2.695
2.451
1.834
1.751
1.731
1.676
N
N
Boc
H
H
Me
CO2Me
N2
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
1.26
1.06
1.02
1.00
3.06
1.07
1.07
1.06
1.00
3.15
1.06
1.38
3.70
9.30
171.098
150.259
141.485
136.652
132.634
129.191
124.253
122.834
121.809
118.158
116.360
115.807
115.715
84.113
62.730
56.242
52.118
46.207
32.902
29.842
28.384
21.725
12.452
220
200
180
160
140
120
100
80
60
40
20
0
ppm


4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600
Transmittance [%]
98 92 86 80 74 68 62 56 50 44
3764.51
3434.02
3369.52
2925.95
2852.74
2467.76
2257.44
2168.28
2082.20
1988.57
1727.40
1692.58
1615.82
1476.10
1455.26
1435.90
1412.96
1355.97
1307.44
1245.31
1208.30
1147.23
1113.44
1065.22
1045.11
1009.03
968.64
910.23
838.63
766.63
742.32
661.22
Wavenumber cm-1

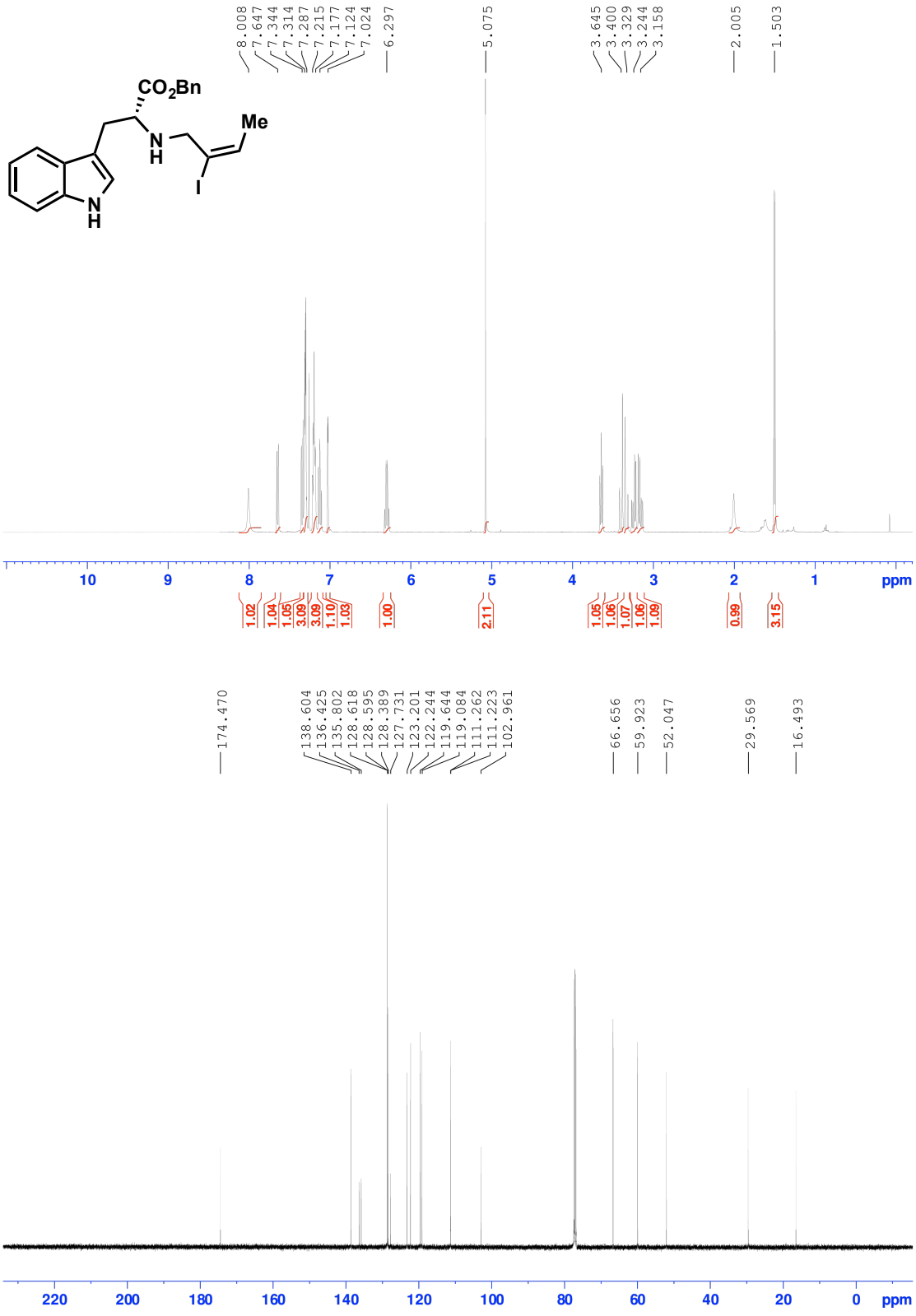
Compound **98**


8.036
7.590
7.312
7.200
7.105
6.808
6.633
6.378
5.414
5.204
4.424
3.830
3.199
2.366
1.090
CO2Me
N
H
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.09 1.05 1.08 1.24 1.22 1.08 1.15 1.00 1.10 1.04 2.03 3.02 2.08 2.24 3.22
161.709
136.260
133.420
128.828
126.864
125.832
125.281
123.317
120.773
119.911
119.064
117.552
112.592
111.447
110.698
51.110
49.838
29.858
19.783
15.416
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

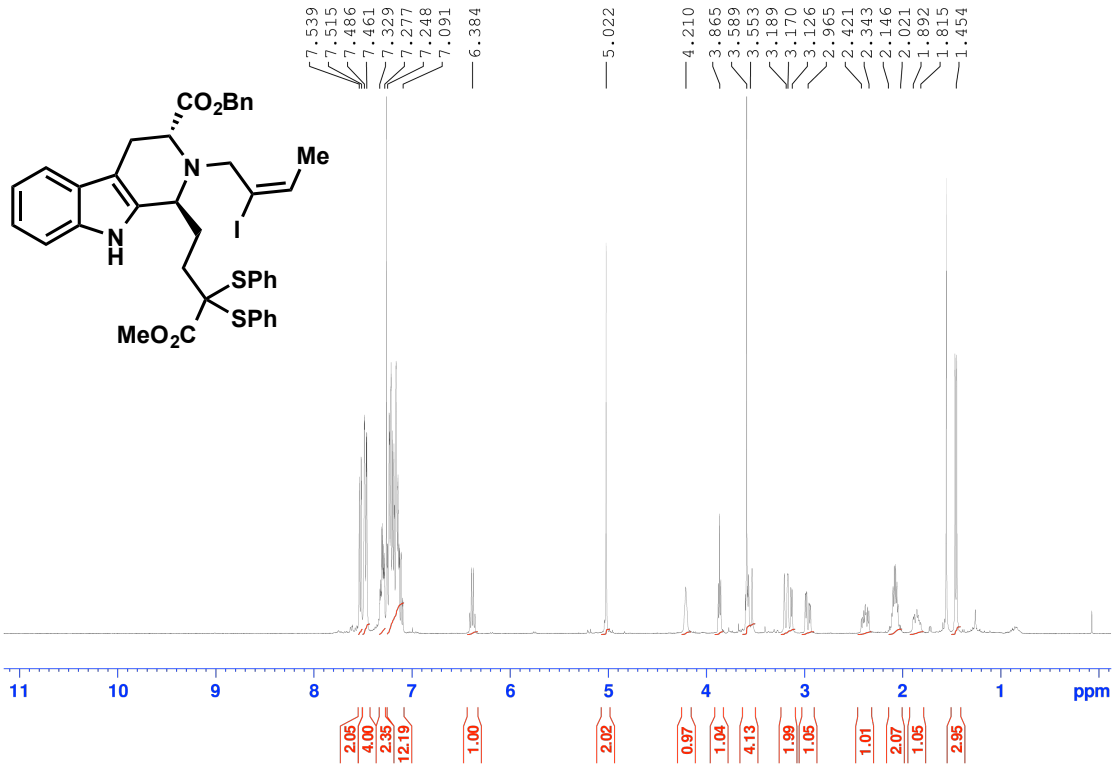
Compound **75**

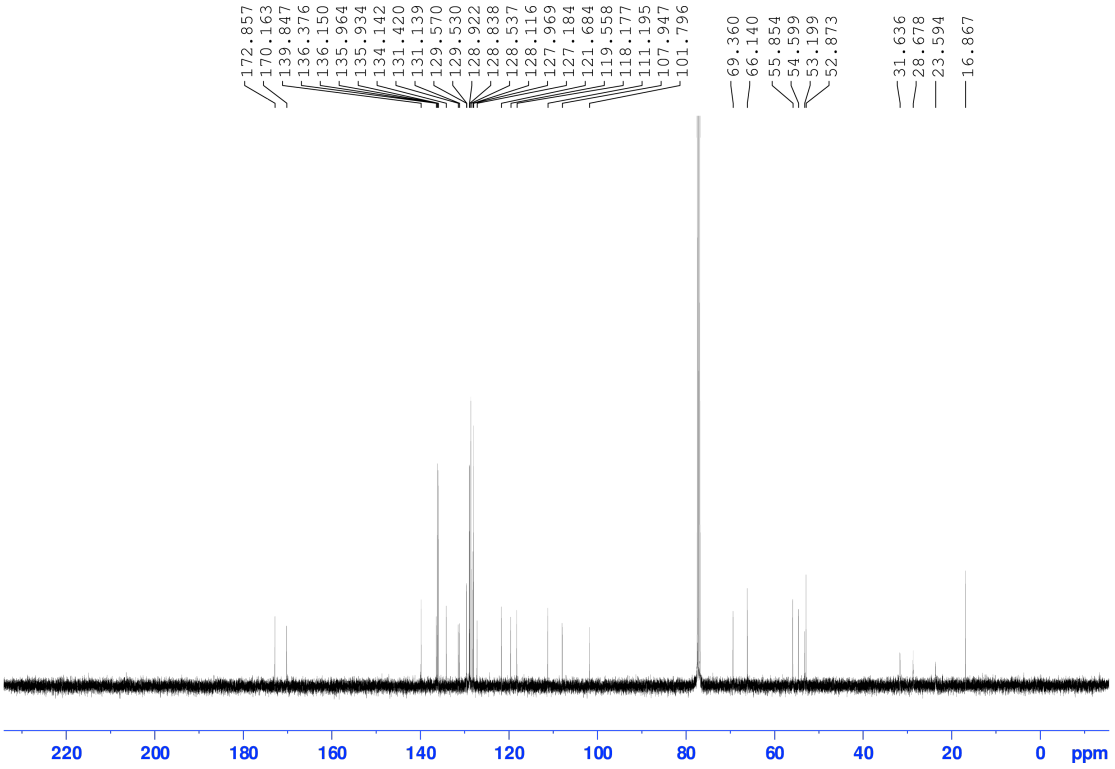

Me
Br
I
6.393
4.288
1.713
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.27
3.04
141.606
94.599
37.020
16.599
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **83**

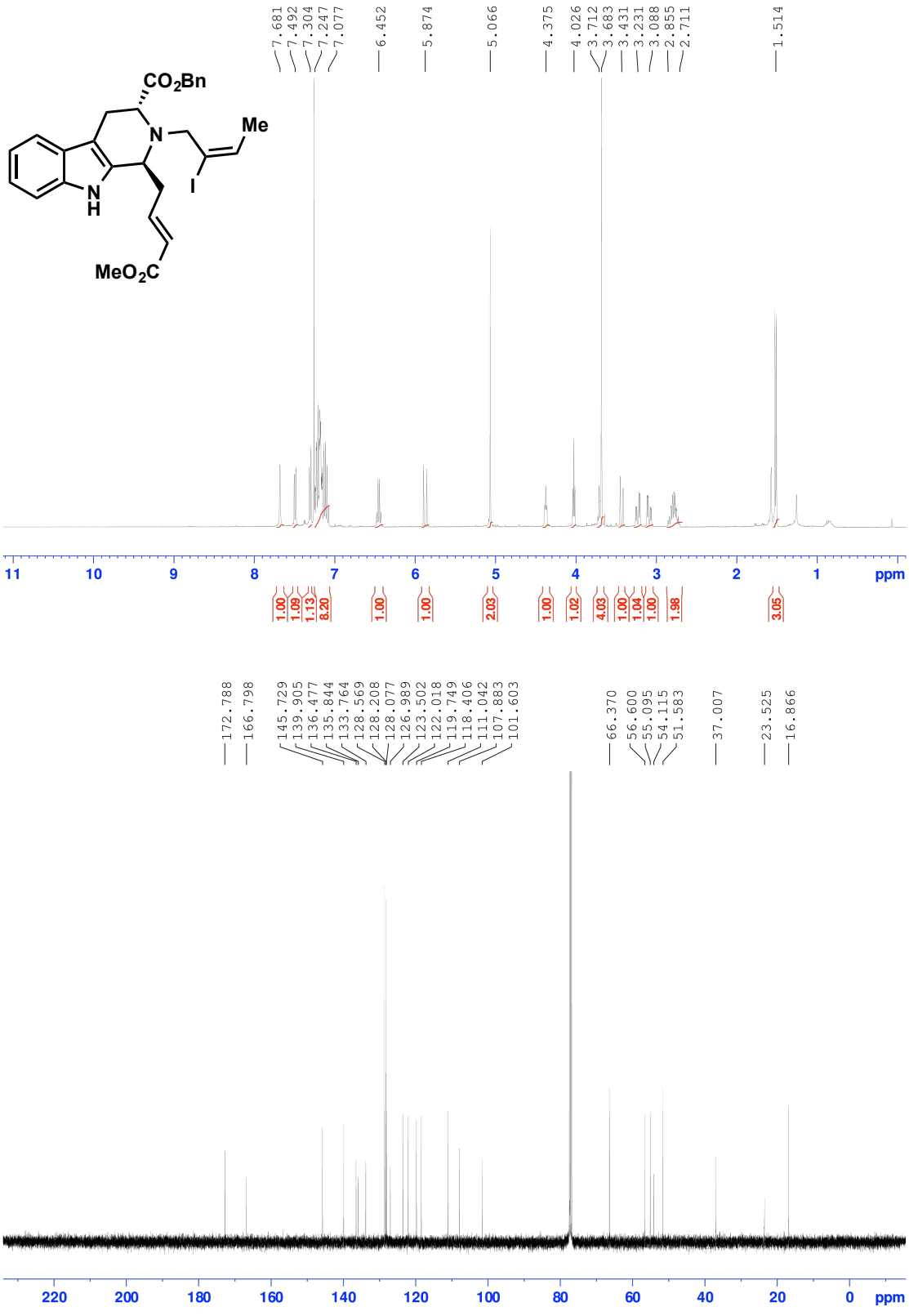

8.008
7.647
7.344
7.314
7.287
7.215
7.177
7.124
7.024
6.297
5.075
3.645
3.400
3.329
3.244
3.158
2.005
1.503
CO2Bn
Me
N
H
I
N
H
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.04
1.05
3.09
3.09
1.10
1.03
1.00
2.11
1.05
1.06
1.07
1.06
1.09
0.99
3.15
174.470
138.604
136.425
135.802
128.618
128.595
128.389
127.731
123.201
122.244
119.644
119.084
111.262
111.223
102.961
66.656
59.923
52.047
29.569
16.493
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **84**

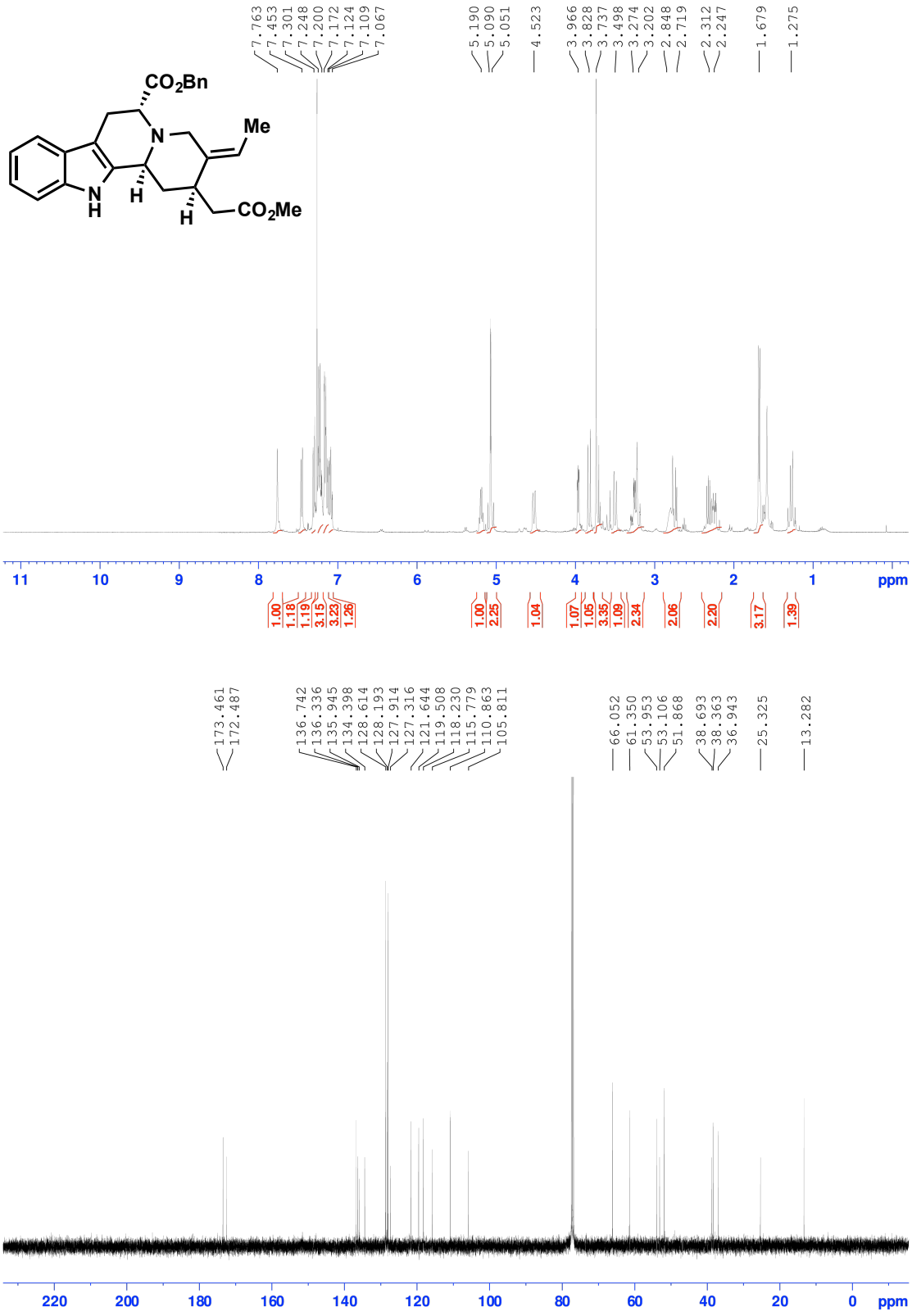

7.539
7.515
7.486
7.461
7.329
7.277
7.248
7.091
6.384
5.022
4.210
3.865
3.589
3.553
3.189
3.170
3.126
2.965
2.421
2.343
2.146
2.021
1.892
1.815
1.454
CO2Bn
N
Me
I
N
H
SPh
SPh
MeO2C
11
10
9
8
7
6
5
4
3
2
1
ppm
2.06
4.00
2.35
12.19
1.00
2.02
0.97
1.04
4.13
1.99
1.05
1.01
2.07
1.05
2.95

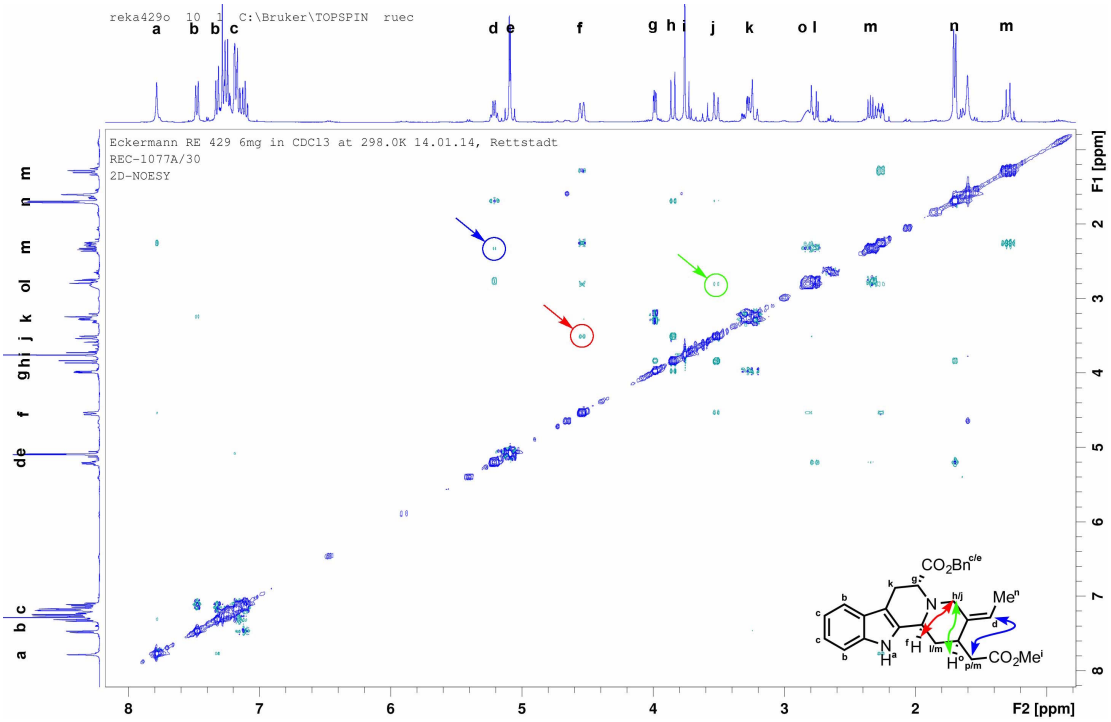

172.857
170.163
139.847
136.376
136.150
135.964
135.934
134.142
131.420
131.139
129.570
129.530
128.922
128.838
128.537
128.116
127.969
127.184
121.684
119.558
118.177
111.195
107.947
101.796
69.360
66.140
55.854
54.599
53.199
52.873
31.636
28.678
23.594
16.867
220
200
180
160
140
120
100
80
60
40
20
0
ppm

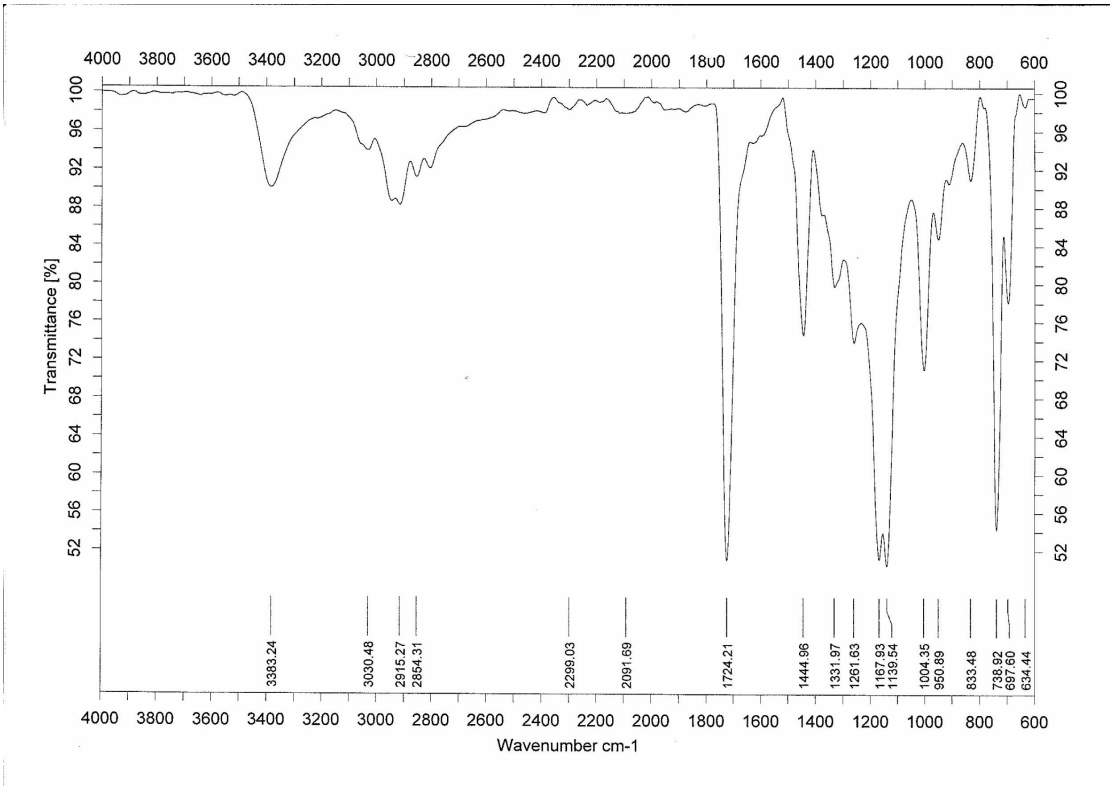
Compound **85**


7.681
7.492
7.304
7.247
7.077
6.452
5.874
5.066
4.375
4.026
3.712
3.683
3.431
3.231
3.088
2.855
2.711
1.514
CO2Bn
N
Me
I
N
H
MeO2C
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.09
1.13
8.20
1.00
1.00
2.03
1.00
1.02
4.03
1.00
1.04
1.00
1.98
3.05
172.788
166.798
145.729
139.905
136.477
135.844
133.764
128.569
128.208
128.077
126.989
123.502
122.018
119.749
118.406
111.042
107.883
101.603
66.370
56.600
55.095
54.115
51.583
37.007
23.525
16.866
220
200
180
160
140
120
100
80
60
40
20
0
ppm

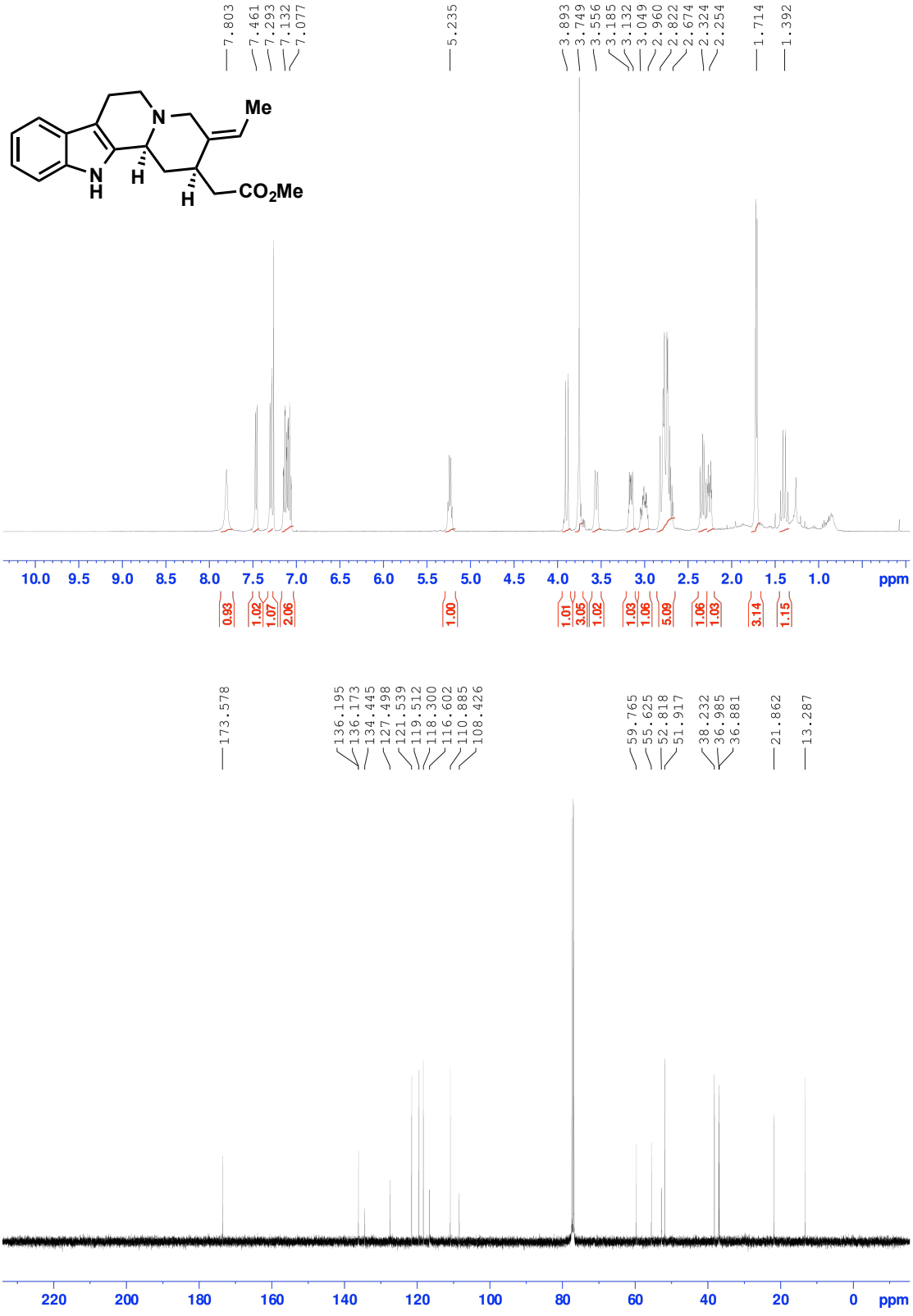
Compound **86**

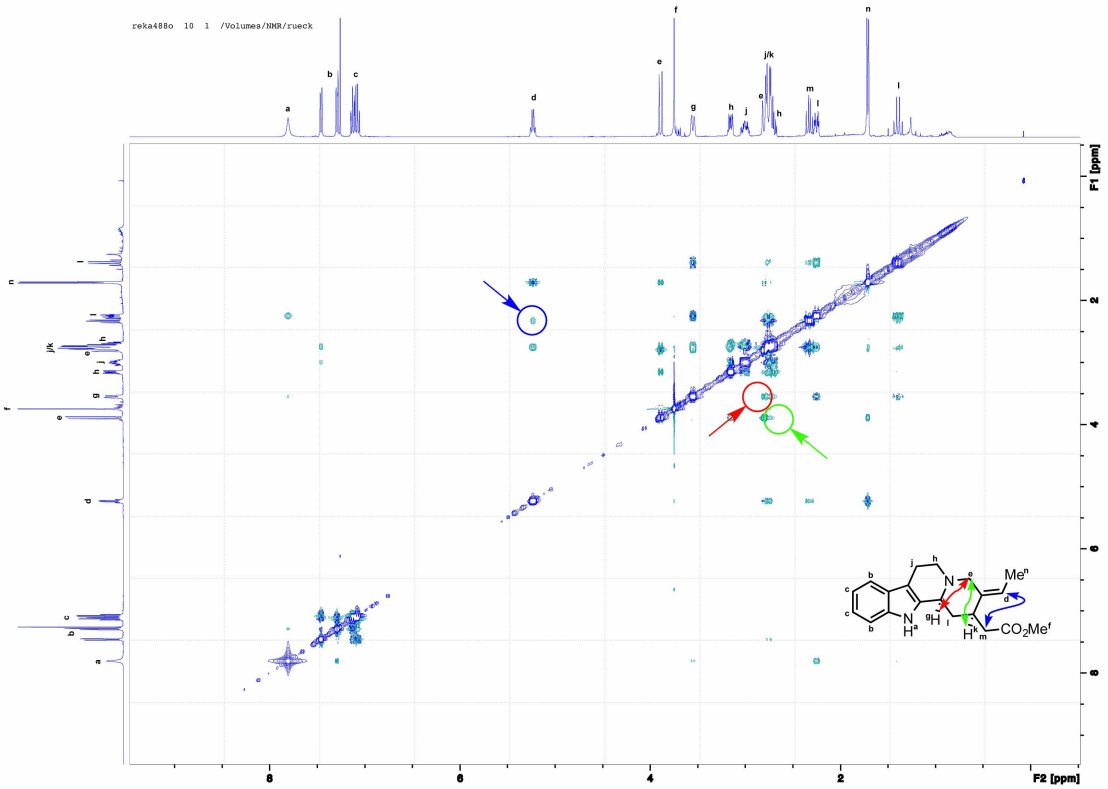

7.763
7.453
7.301
7.248
7.200
7.172
7.124
7.109
7.067
5.190
5.090
5.051
4.523
3.966
3.828
3.737
3.498
3.274
3.202
2.848
2.719
2.312
2.247
1.679
1.275
CO2Bn
N
Me
N
H
H
H
CO2Me
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.18
1.19
3.15
3.22
1.26
1.00
2.25
1.04
1.07
1.05
3.35
1.09
2.34
2.06
2.20
3.17
1.39
173.461
172.487
136.742
136.336
135.945
134.398
128.614
128.193
127.914
127.316
121.644
119.508
118.230
115.779
110.863
105.811
66.052
61.350
53.953
53.106
51.868
38.693
38.363
36.943
25.325
13.282
220
200
180
160
140
120
100
80
60
40
20
0
ppm

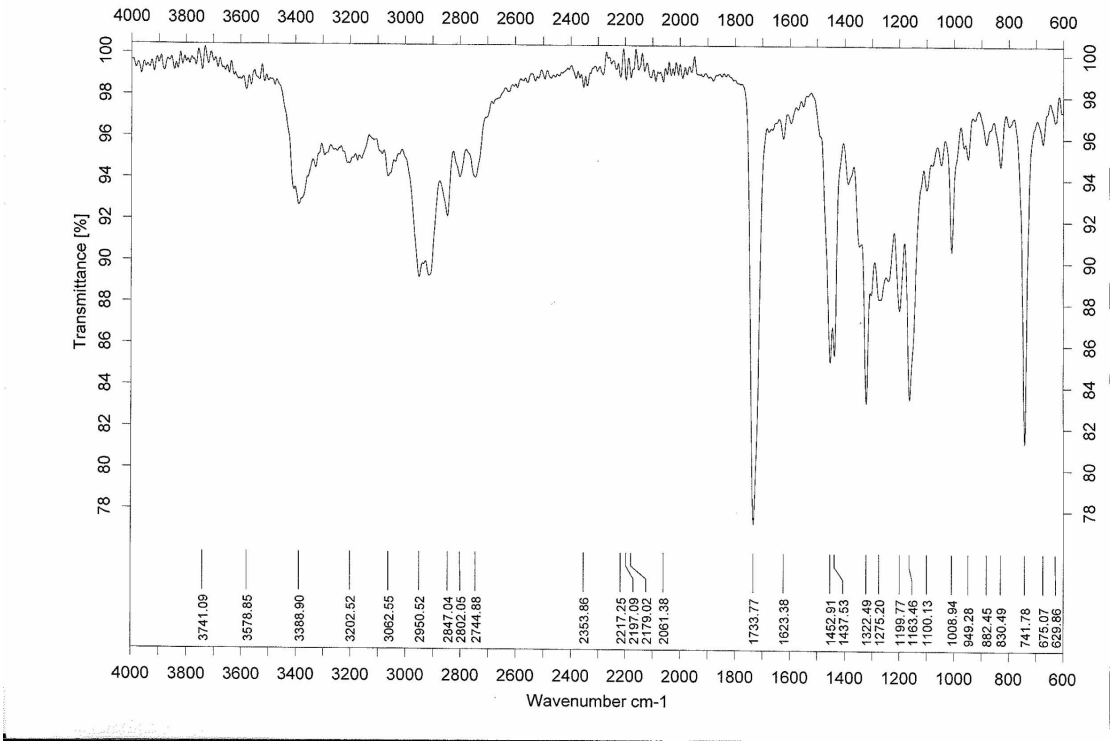

reka429o 10 1 C:\Bruker\TOPSPIN ruec
Eckermann RE 429 6mg in CDCl3 at 298.0K 14.01.14, Rettstadt
REC-1077A/30
2D-NOESY
F1 [ppm]
F2 [ppm]
CO2Bn
Me
CO2Me


Transmittance [%]
Wavenumber cm-1
3383.24
3030.48
2915.27
2854.31
2299.03
2091.69
1724.21
1444.96
1331.97
1261.63
1167.93
1139.54
1004.35
950.89
833.48
738.92
687.60
634.44

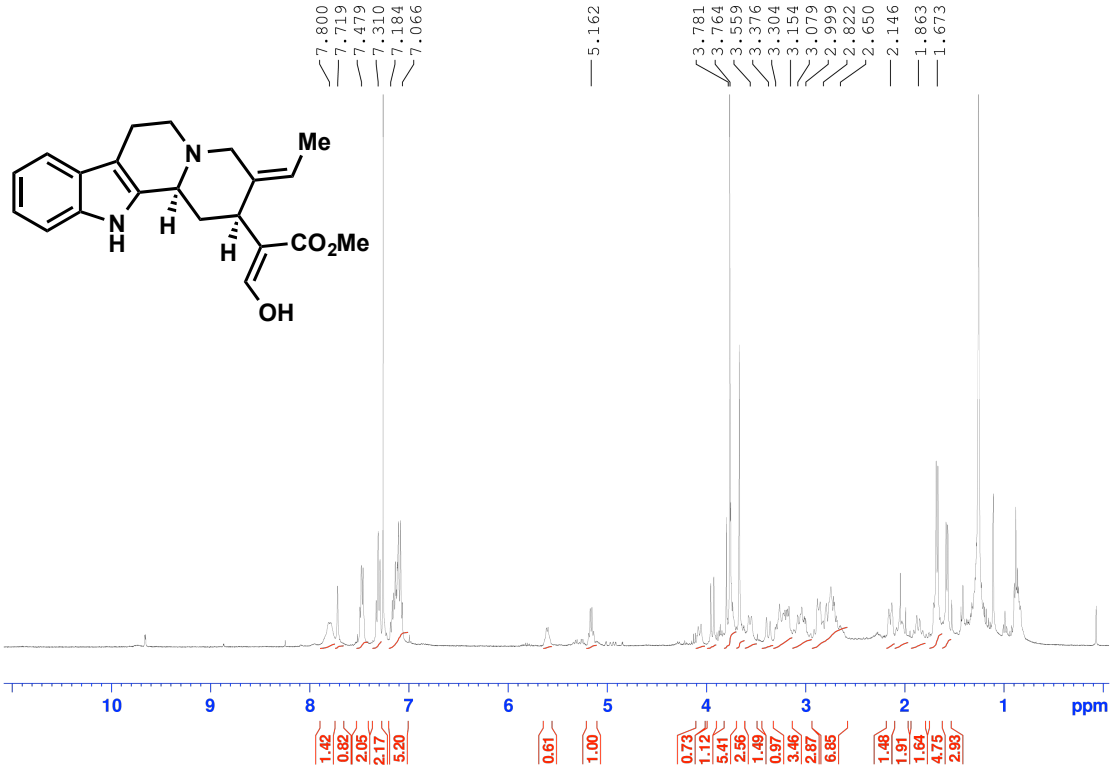
Compound **87**

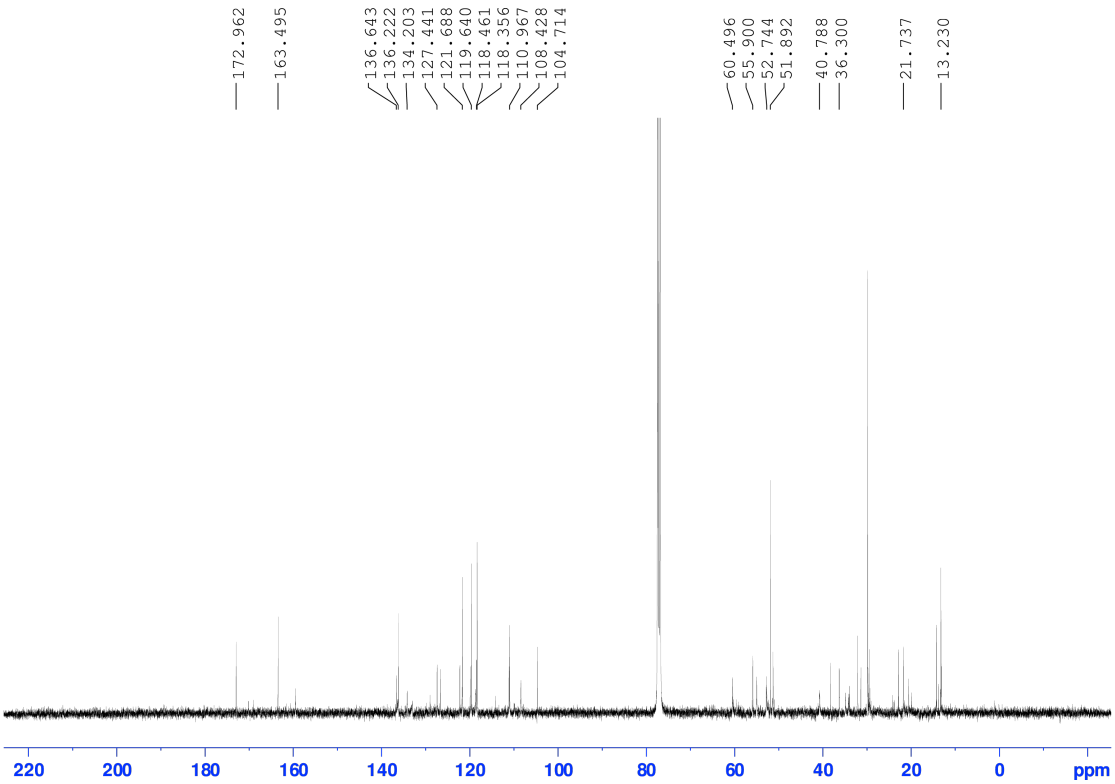

7.803
7.461
7.293
7.132
7.077
5.235
3.893
3.749
3.556
3.185
3.132
3.049
2.960
2.822
2.674
2.324
2.254
1.714
1.392
Me
N
H
N
H
H
CO2Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.93
1.02
1.07
2.06
1.00
1.01
3.05
1.02
1.03
1.06
5.09
1.06
1.03
3.14
1.15
173.578
136.195
136.173
134.445
127.498
121.539
119.512
118.300
116.602
110.885
108.426
59.765
55.625
52.818
51.917
38.232
36.985
36.881
21.862
13.287
220 200 180 160 140 120 100 80 60 40 20 0 ppm

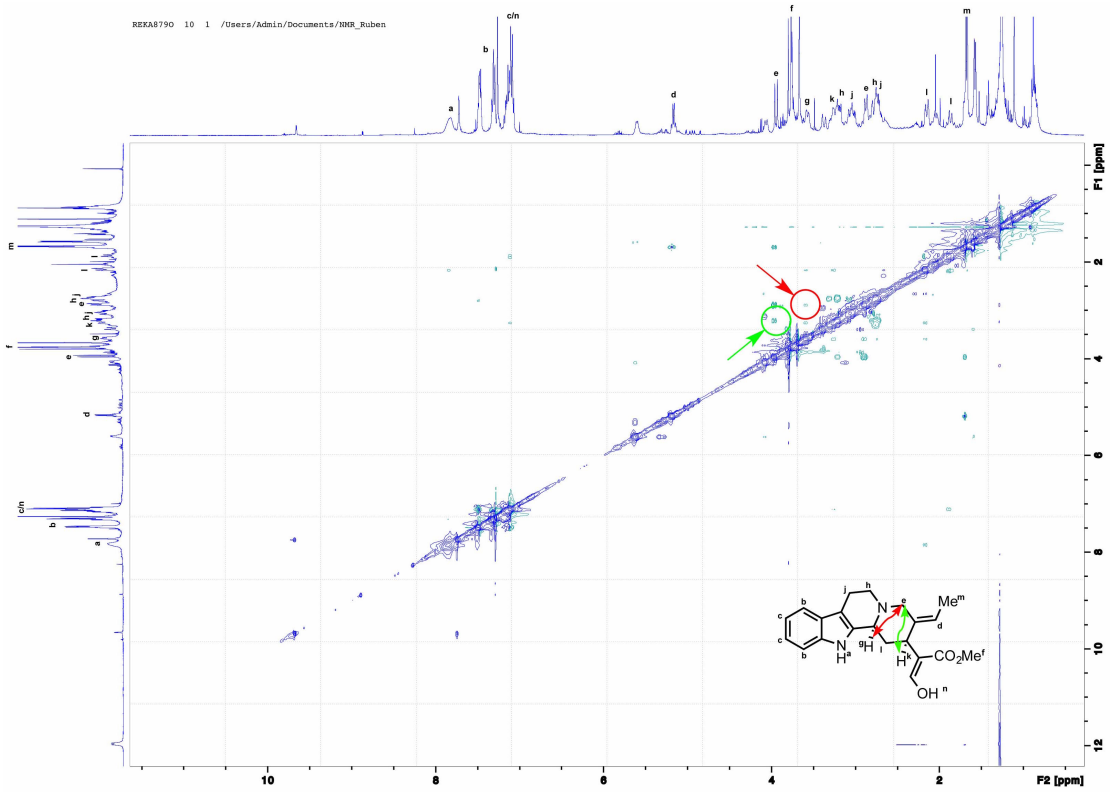

reka488o 10 1 /Volumes/NMR/rueck
F1 [ppm]
F2 [ppm]
Me^n
CO2Me^f


Transmittance [%]
Wavenumber cm-1
3741.09
3578.85
3388.90
3202.52
3062.55
2950.52
2847.04
2802.05
2744.88
2353.86
2217.25
2197.09
2179.02
2061.38
1733.77
1623.38
1452.91
1437.53
1322.49
1275.20
1199.77
1163.46
1100.13
1008.94
949.28
882.45
830.49
741.78
675.07
629.86

Compound **41**

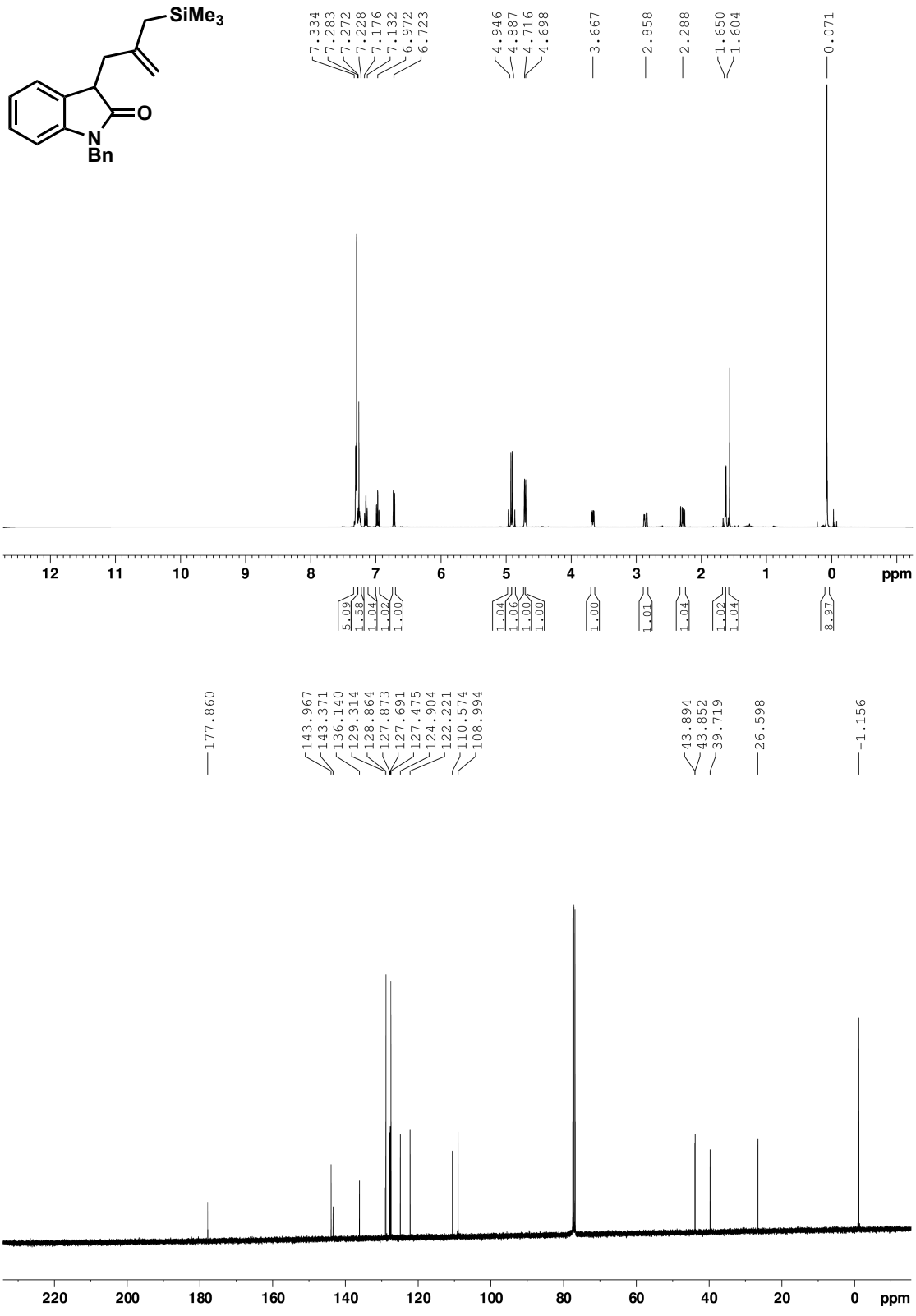

7.800
7.719
7.479
7.310
7.184
7.066
5.162
3.781
3.764
3.559
3.376
3.304
3.154
3.079
2.999
2.822
2.650
2.146
1.863
1.673
Me
N
H
N
H
CO2Me
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.42
0.82
2.05
2.17
5.20
0.61
1.00
0.73
1.12
5.41
2.56
1.49
0.97
3.46
2.87
6.85
1.48
1.91
1.64
4.75
2.93


172.962
163.495
136.643
136.222
134.203
127.441
121.688
119.640
118.461
118.356
110.967
108.428
104.714
60.496
55.900
52.744
51.892
40.788
36.300
21.737
13.230
220
200
180
160
140
120
100
80
60
40
20
0
ppm

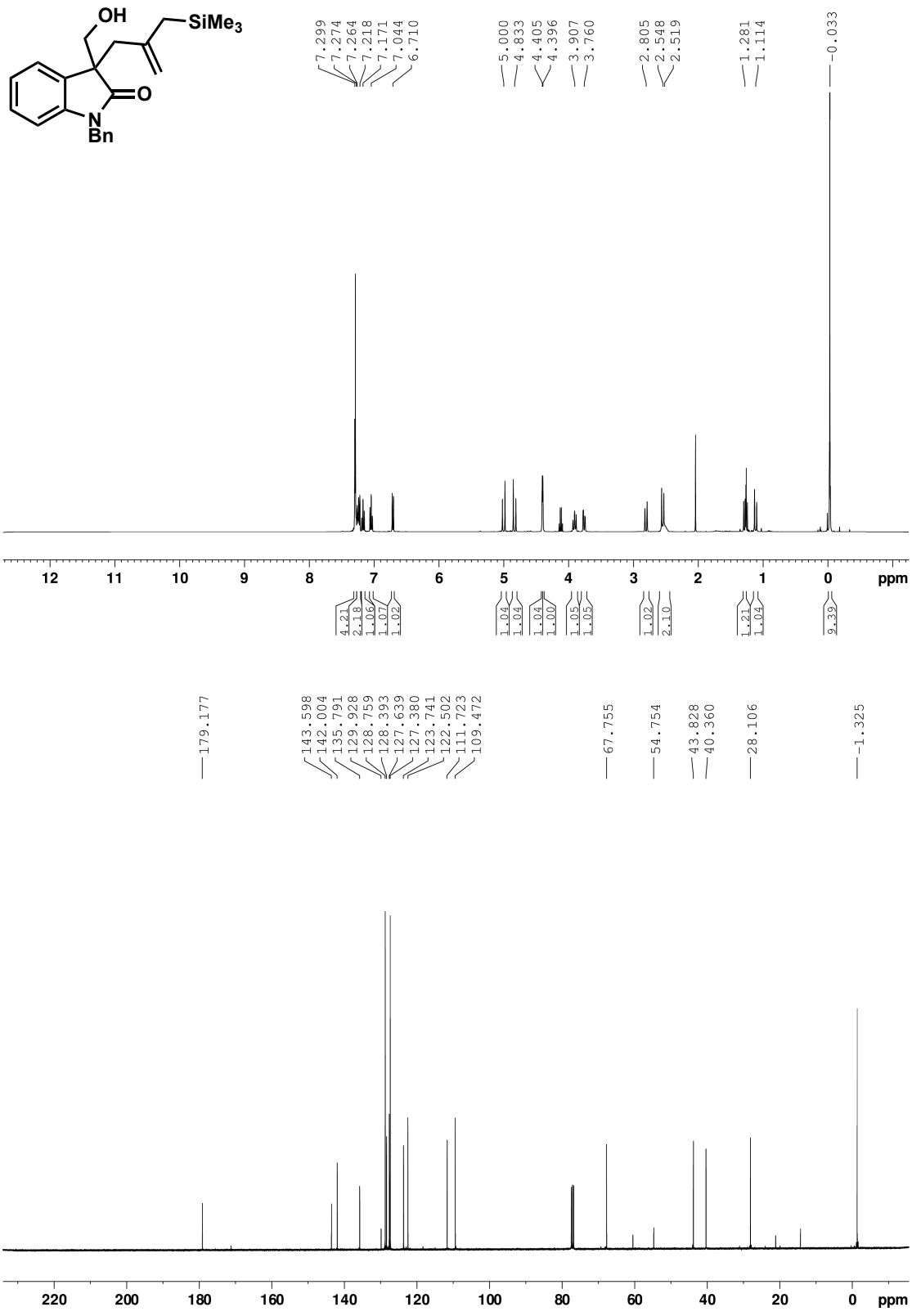

REKA8790 10 1 /Users/Admin/Documents/NMR_Ruben
F1 [ppm]
F2 [ppm]
Me^m
CO2Me^f
OH^n


Transmittance [%]
Wavenumber cm-1
3807.36
3732.22
3232.60
3055.48
2924.15
2854.50
2749.77
2391.63
2189.87
2116.14
2016.56
1900.72
1659.28
1552.81
1445.63
1327.71
1233.90
1188.79
1111.60
836.38
743.76

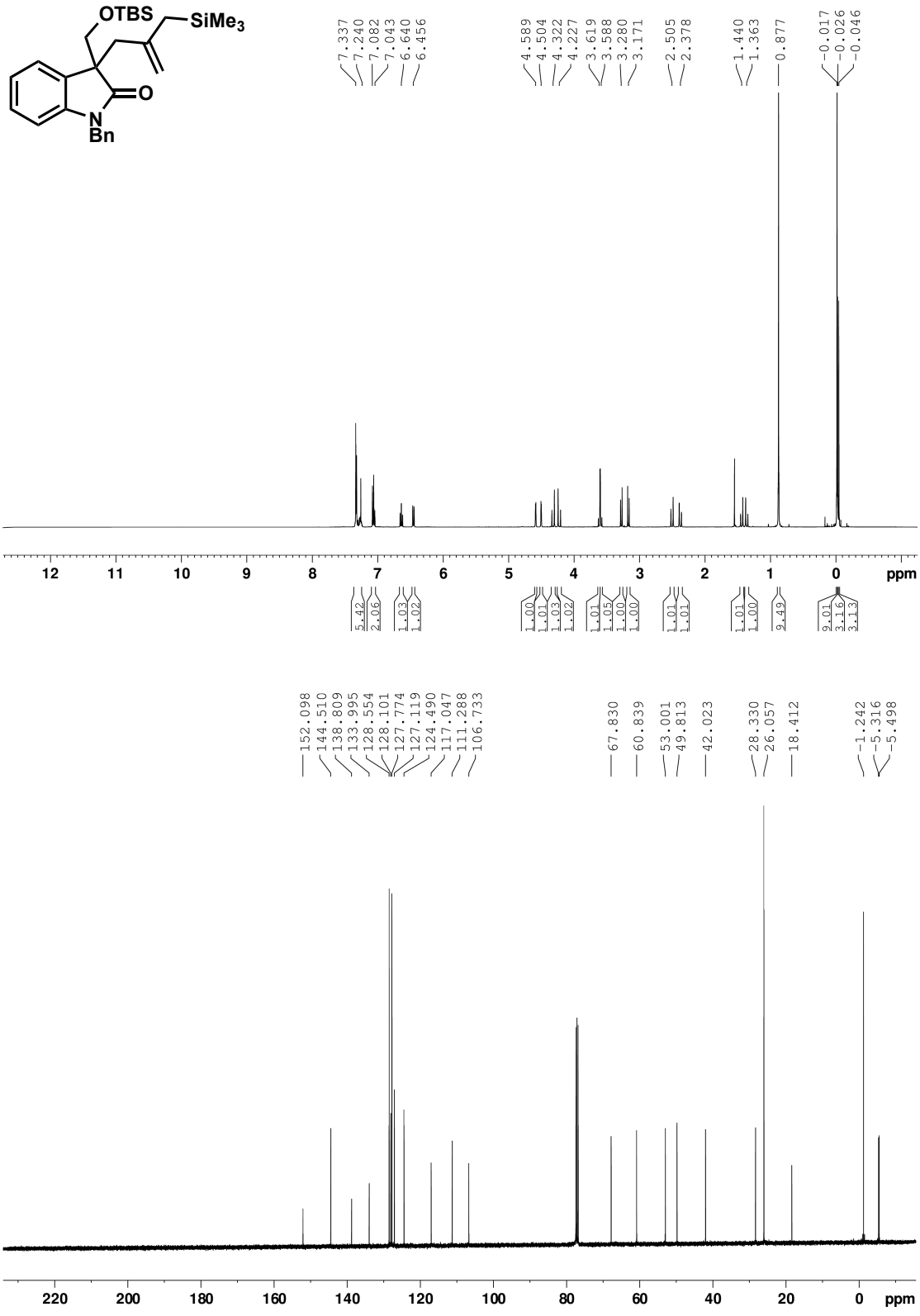
Compound **125**



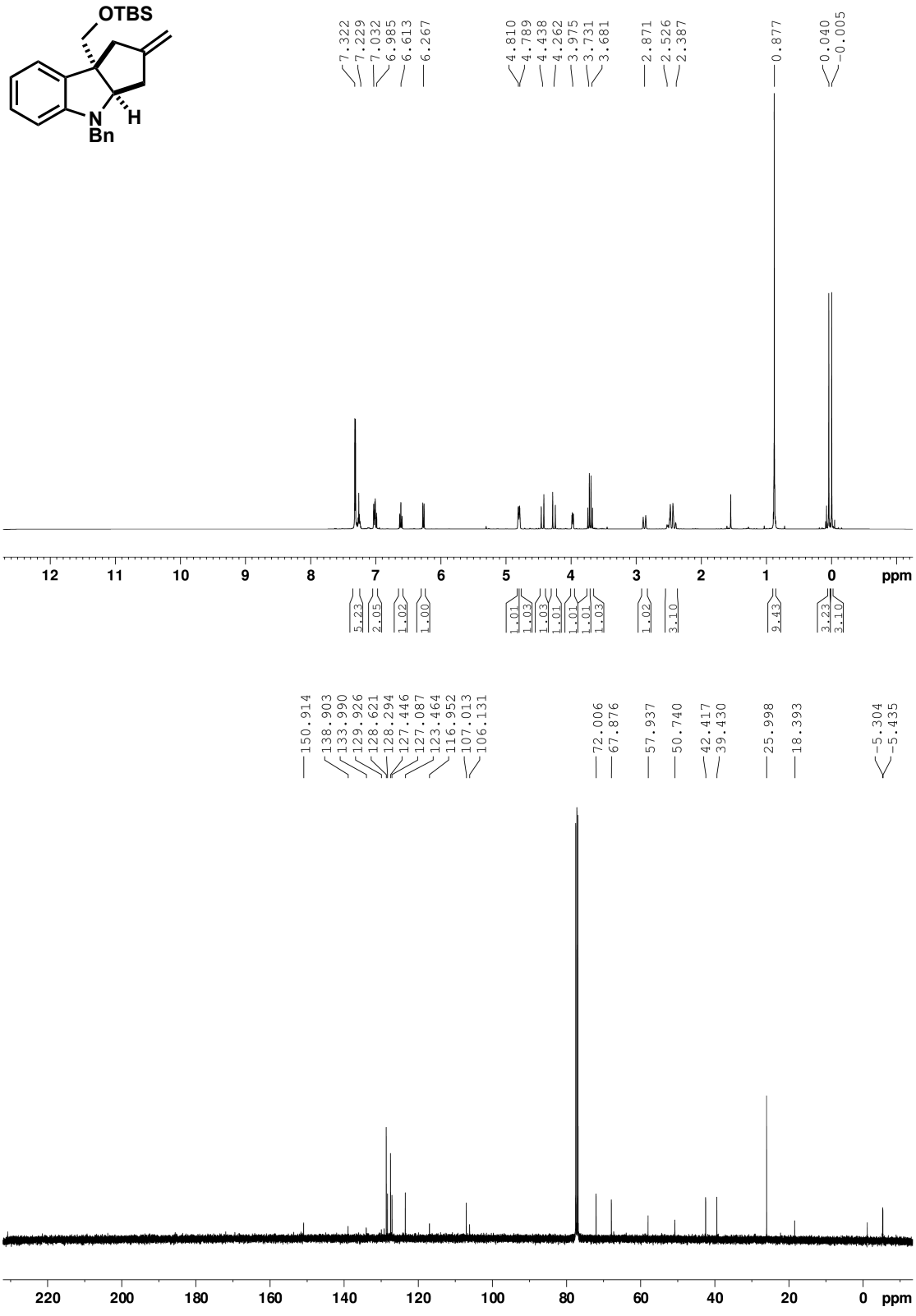
Compound **125b**



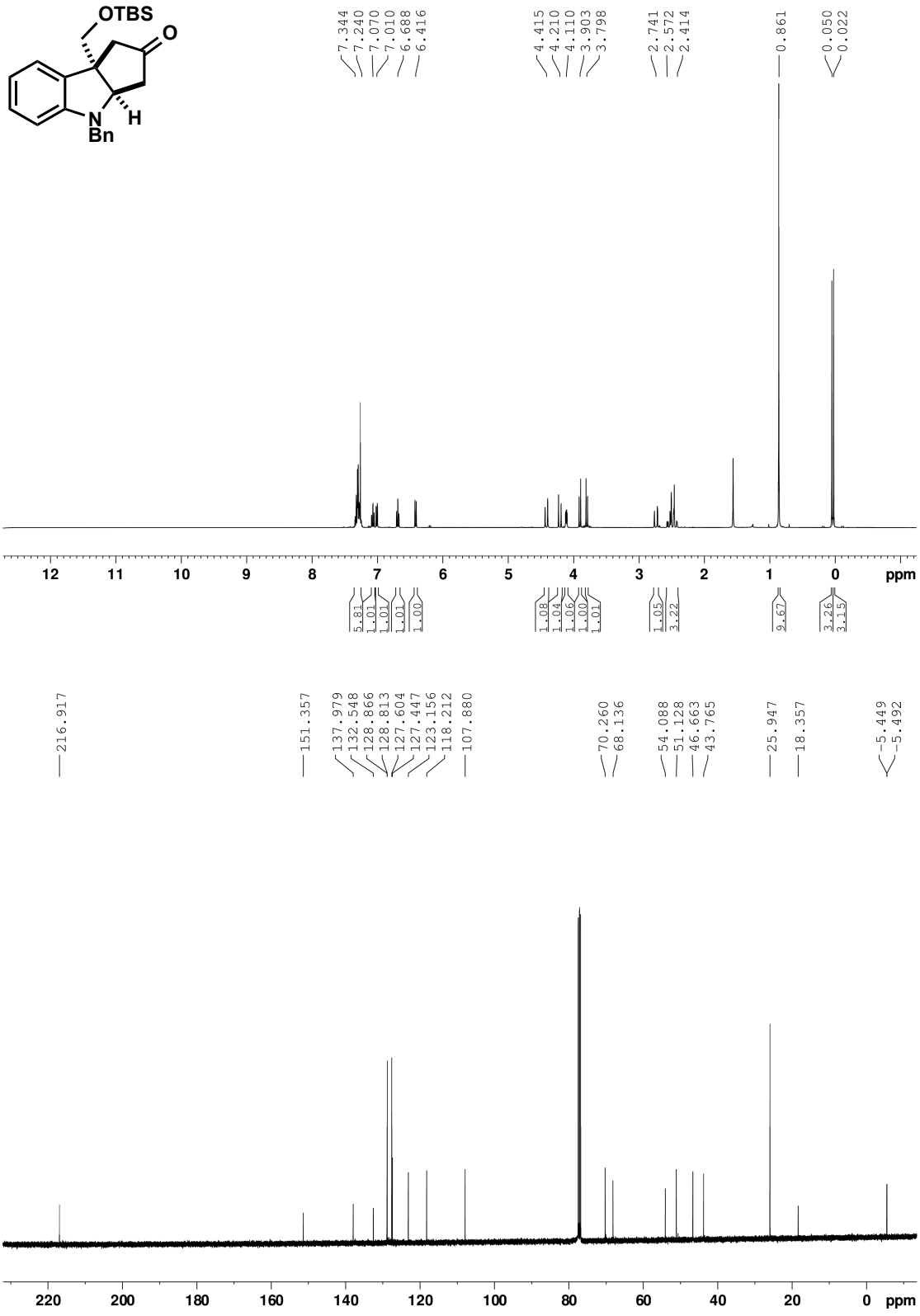
Compound **123**



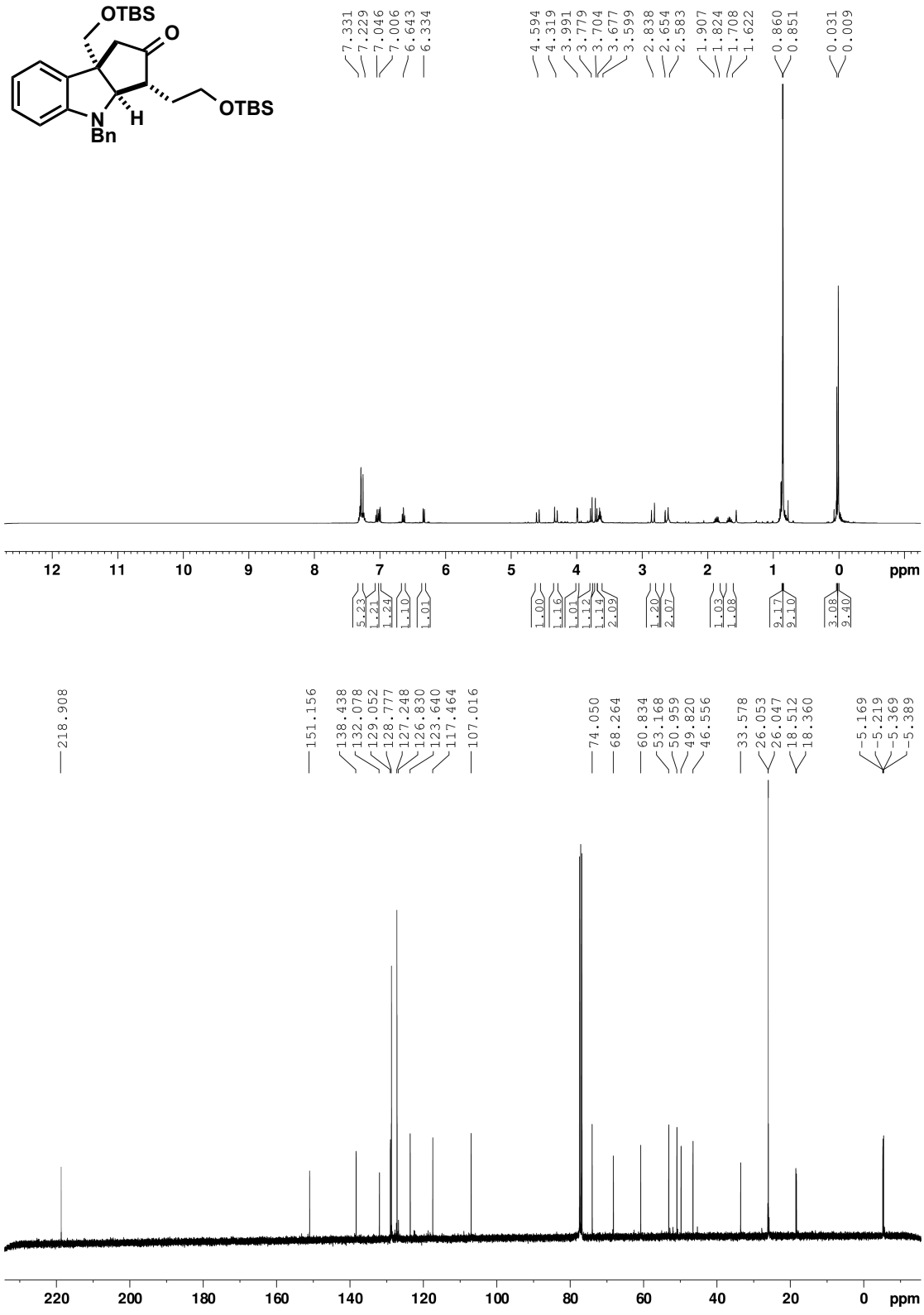
Compound **126**



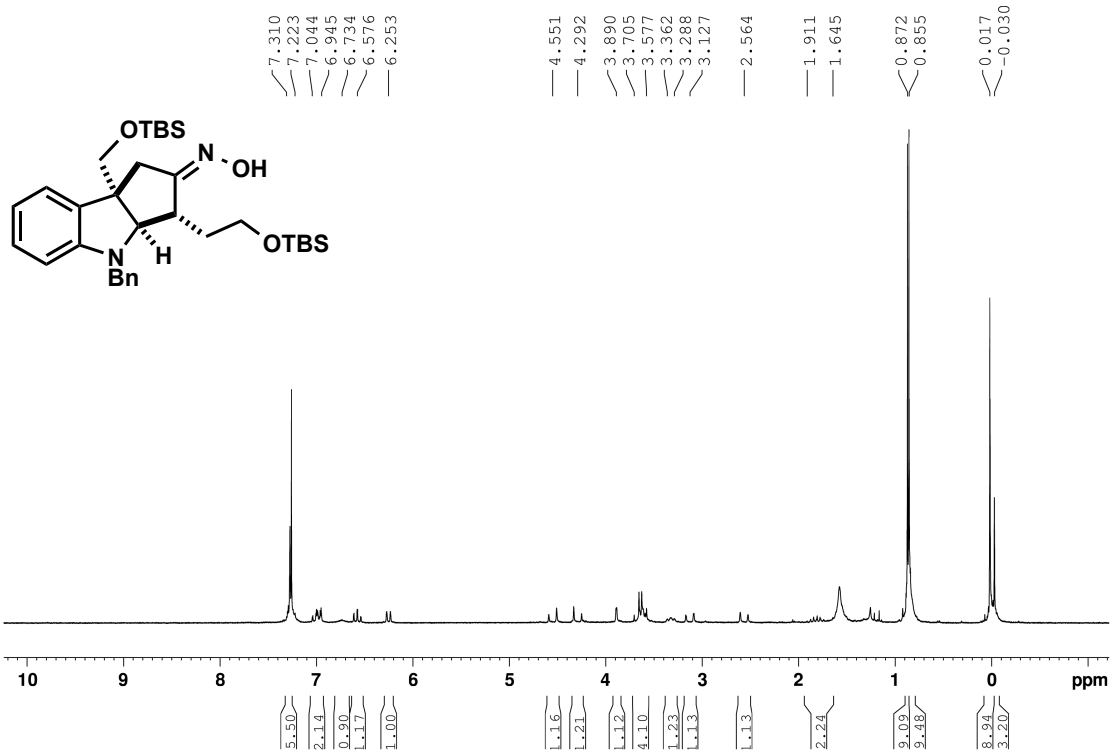
Compound **122**



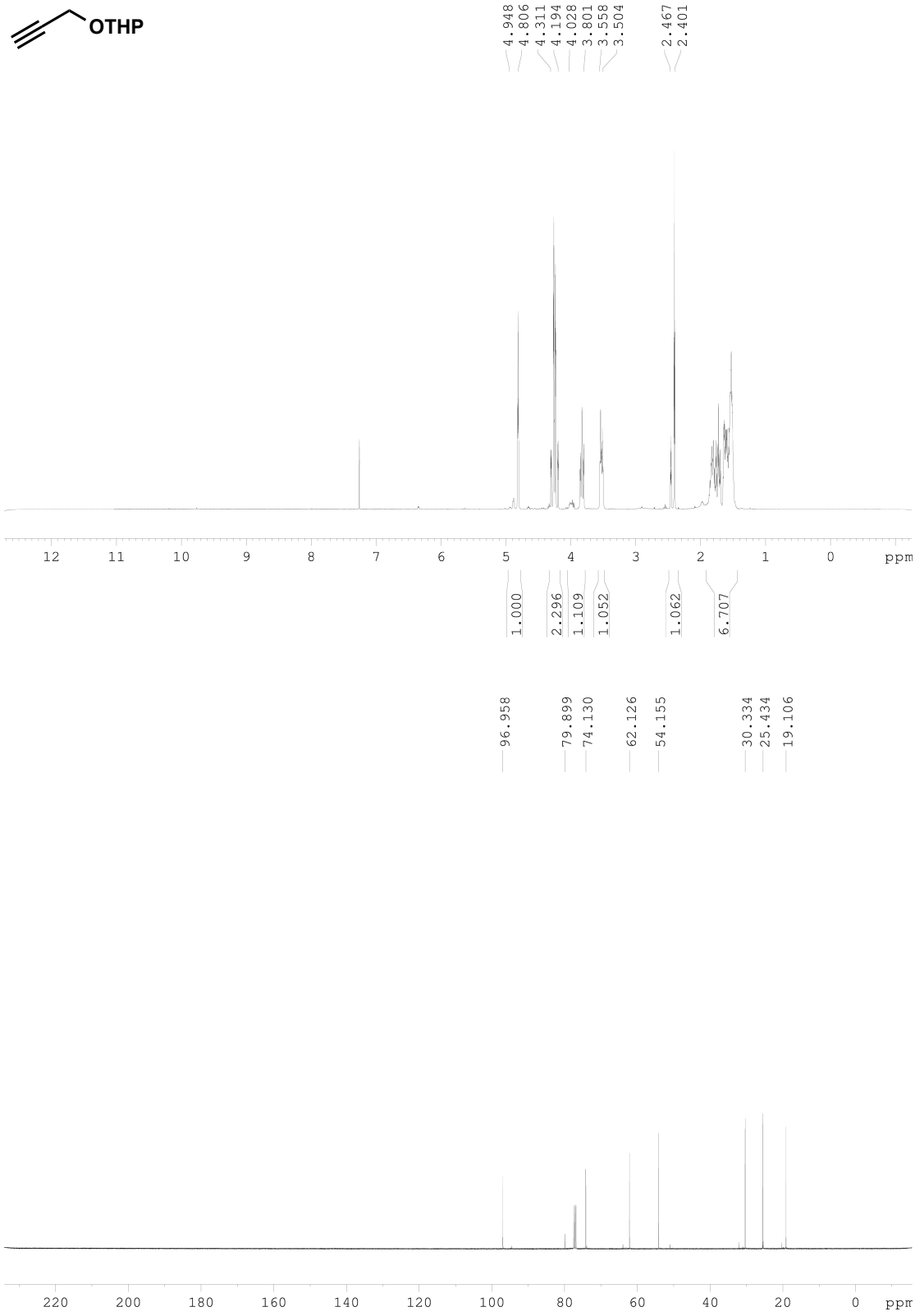
Compound **128**



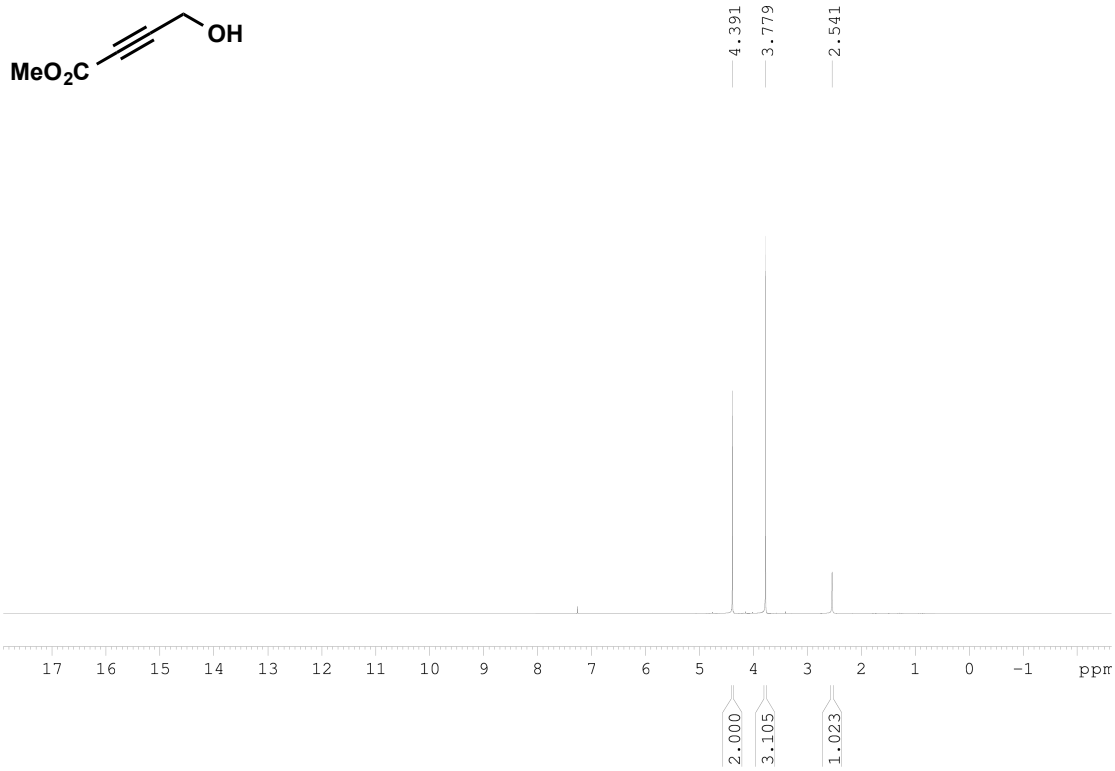
Compound **129**



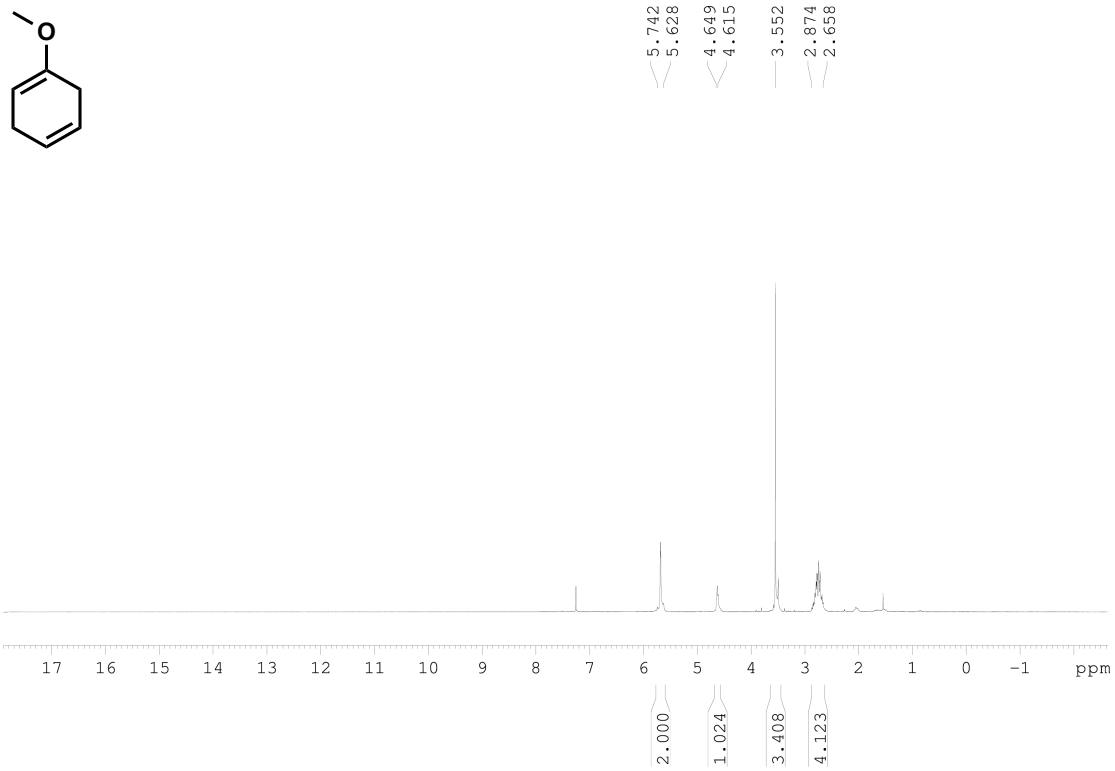
Compound **140b**



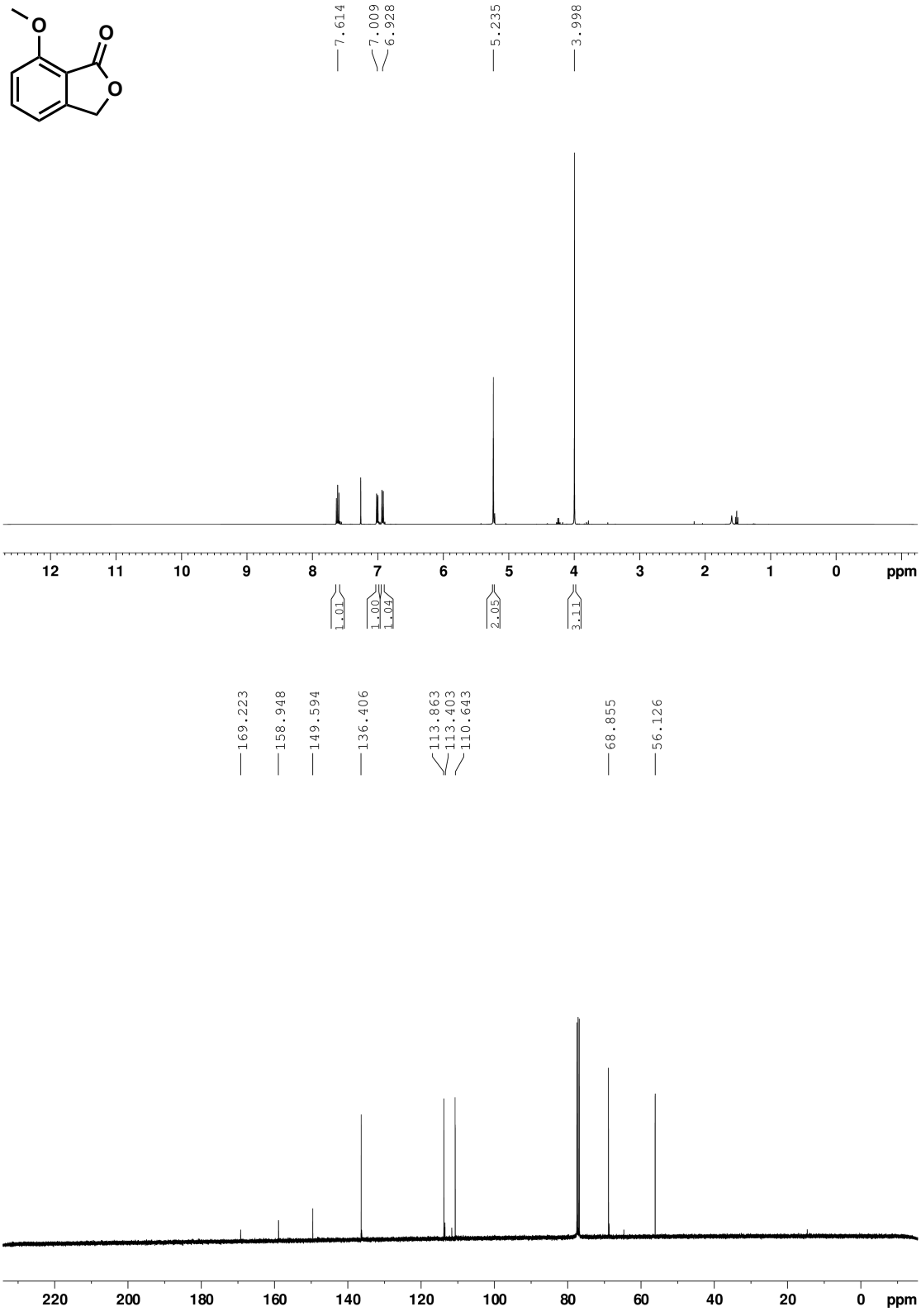
Compound **139**



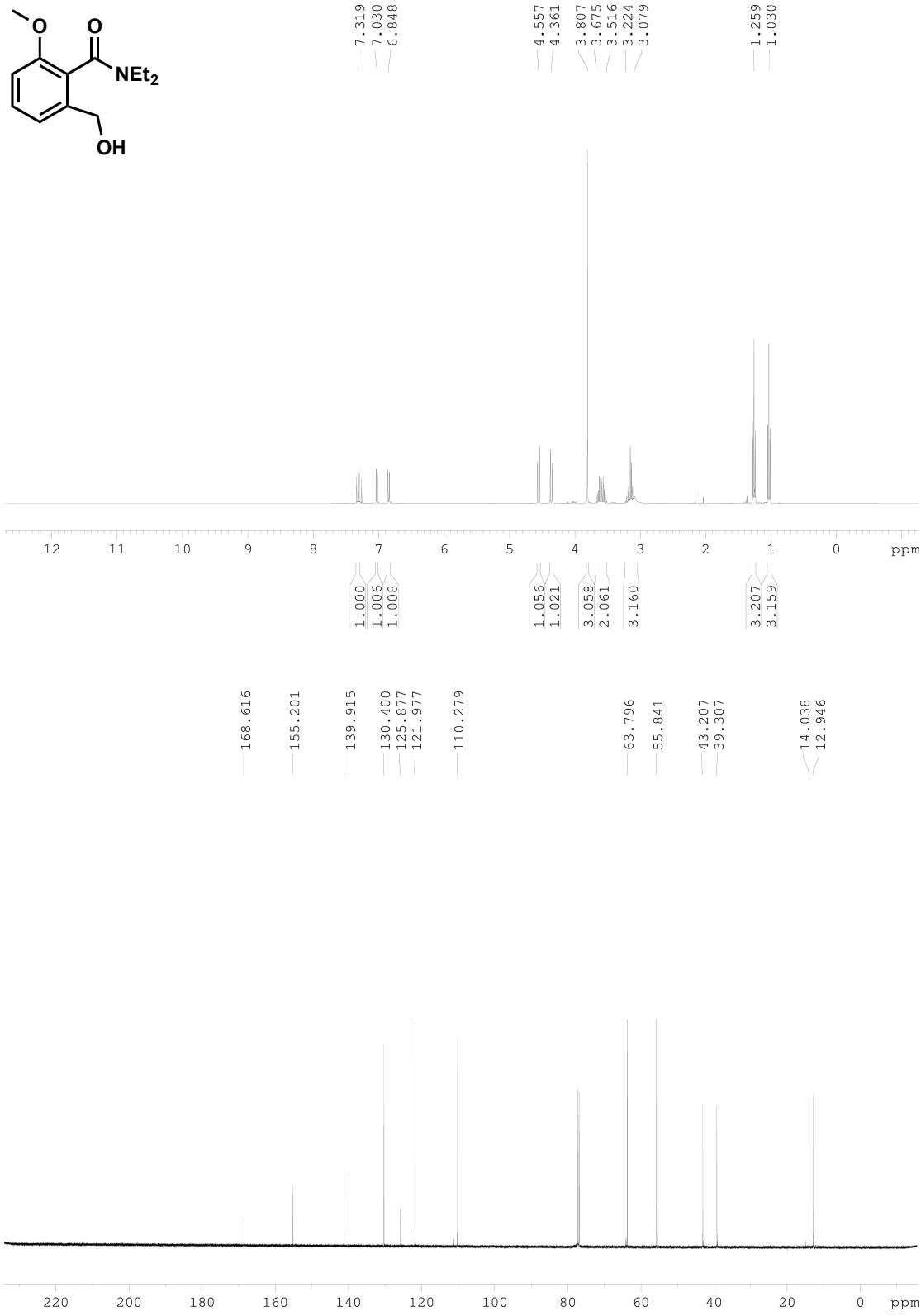
Compound **138**



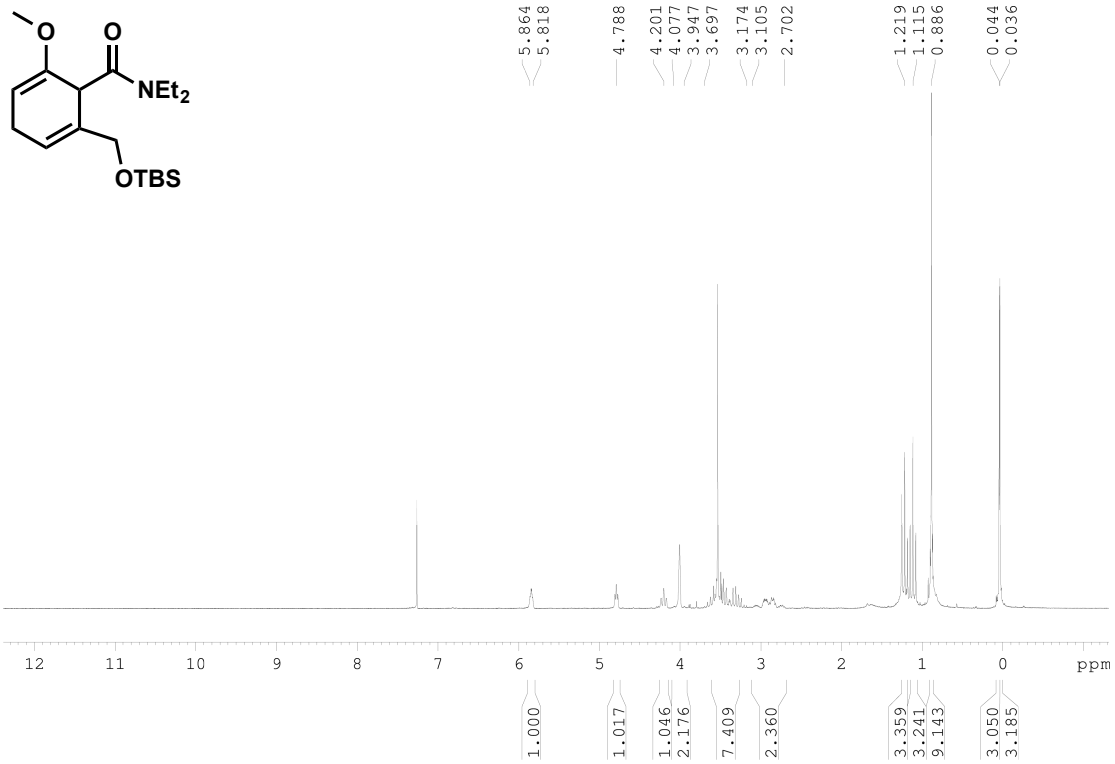
Compound **142**



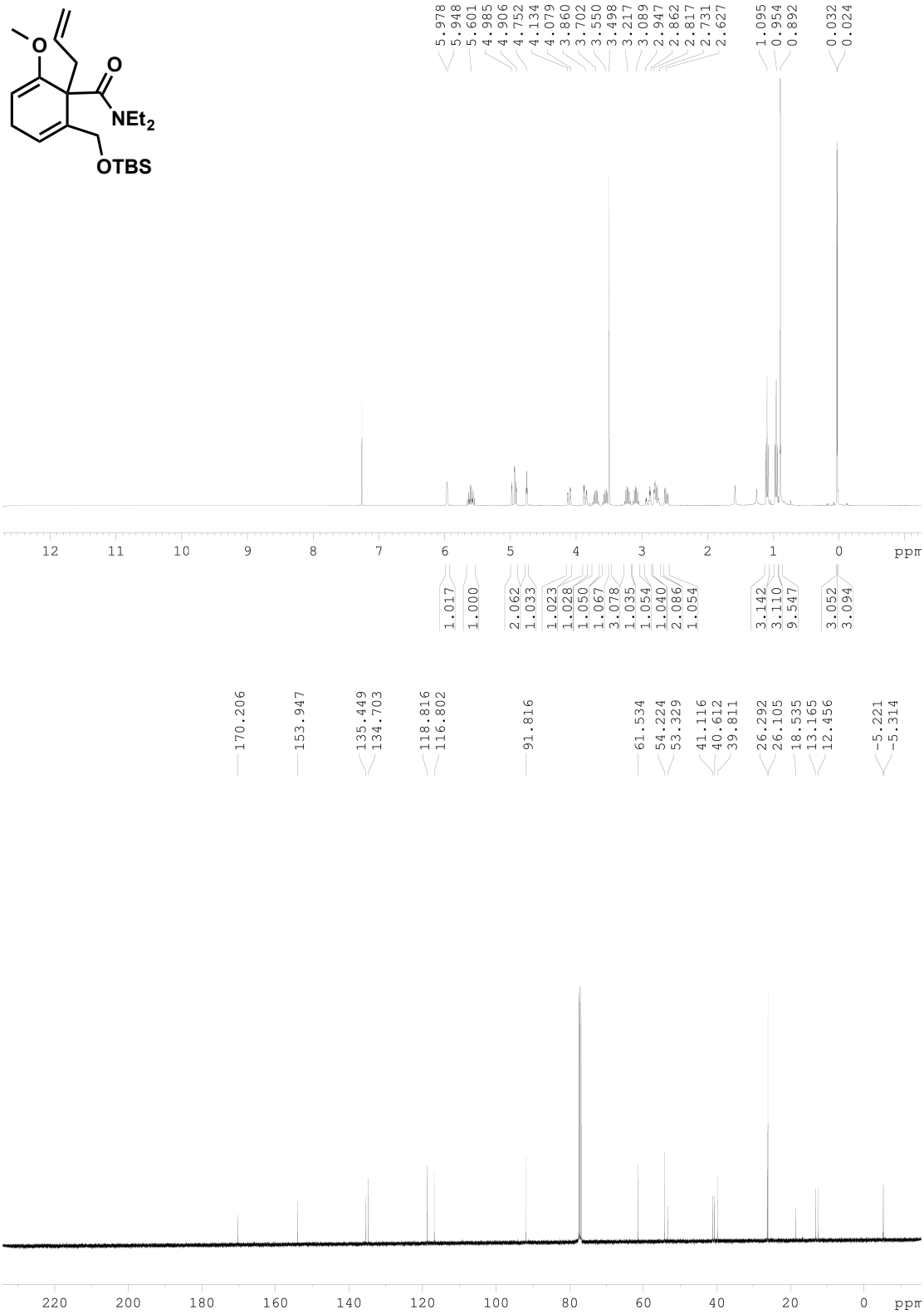
Compound **143**



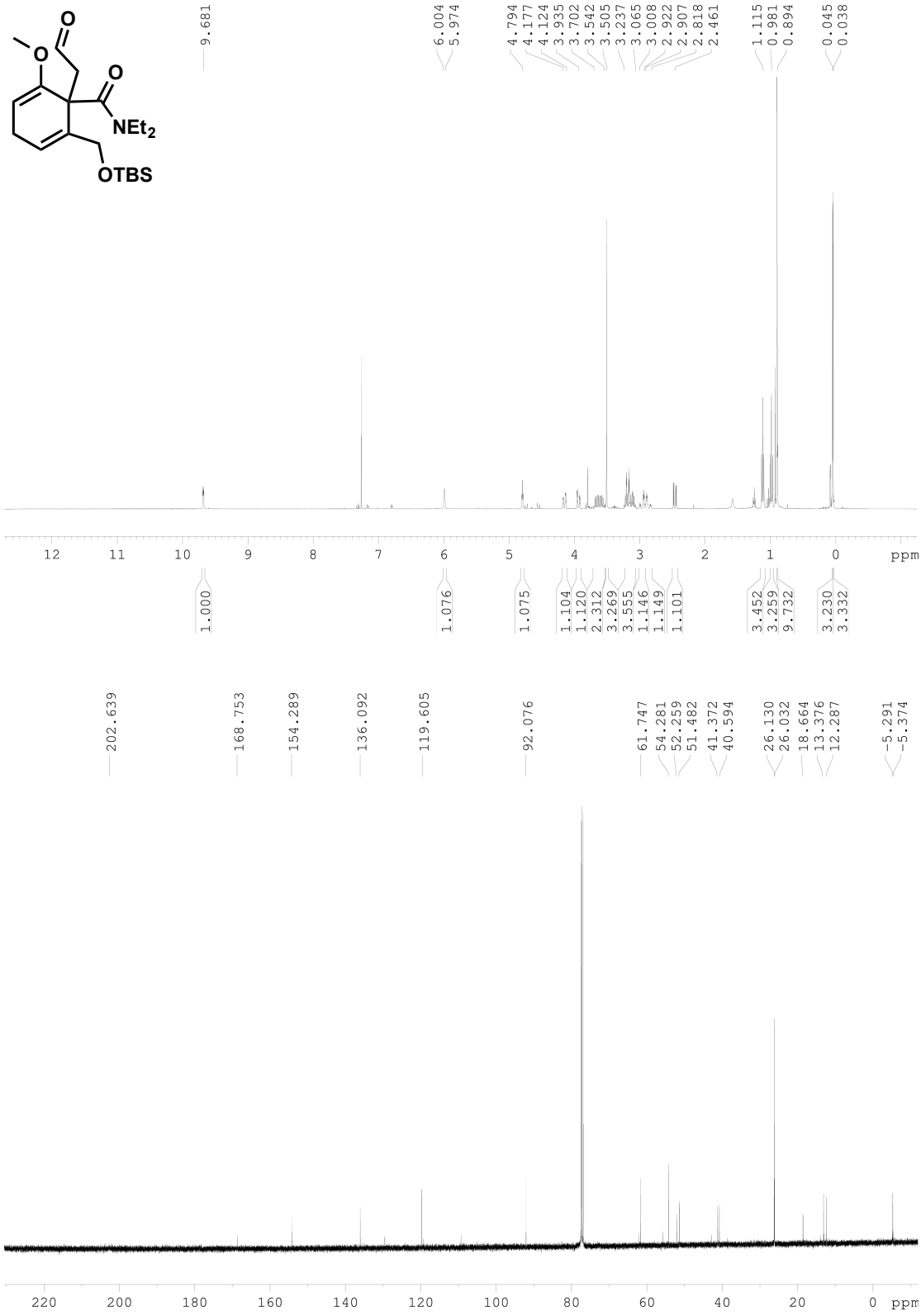
Compound **144**



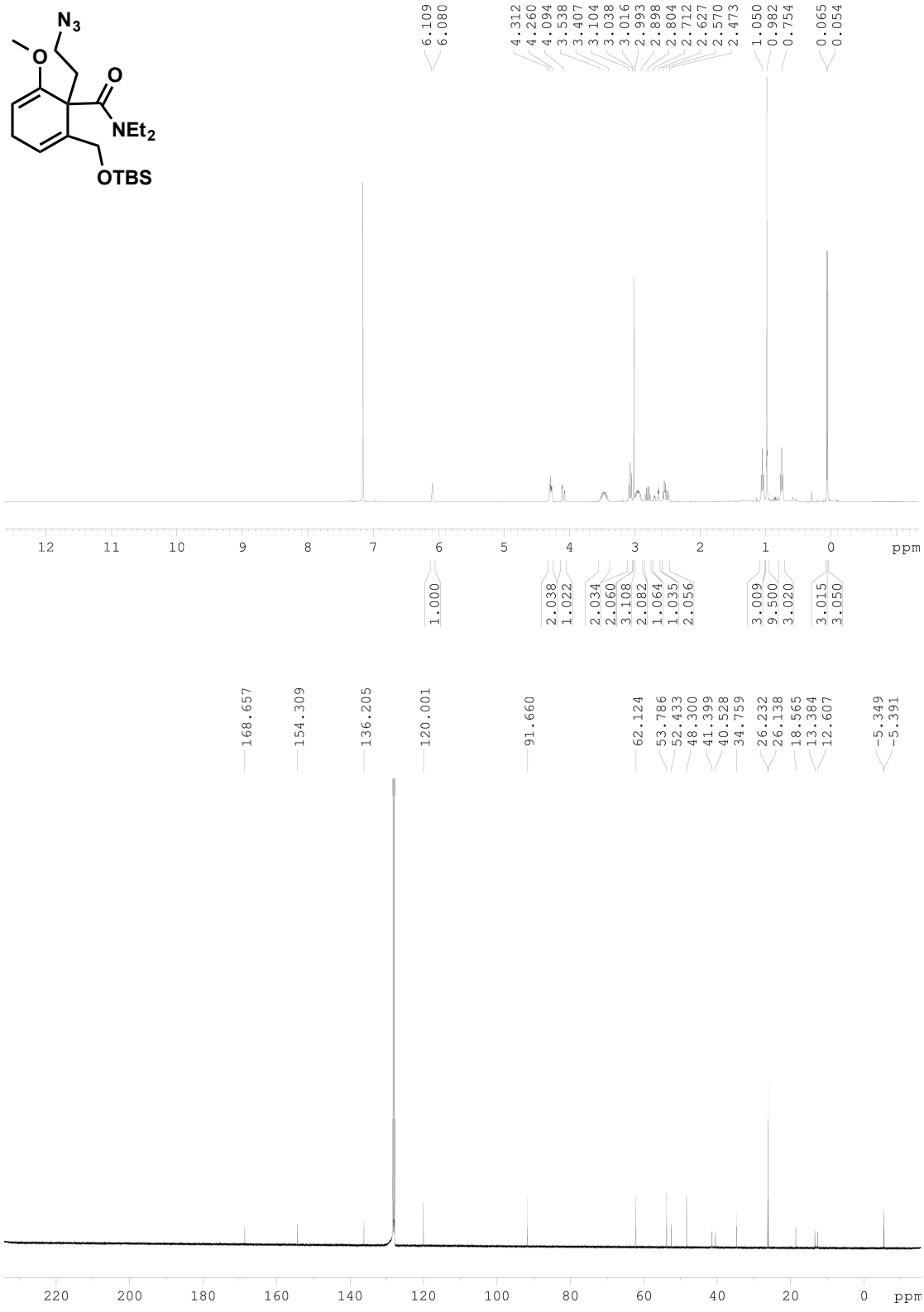
Compound **145**



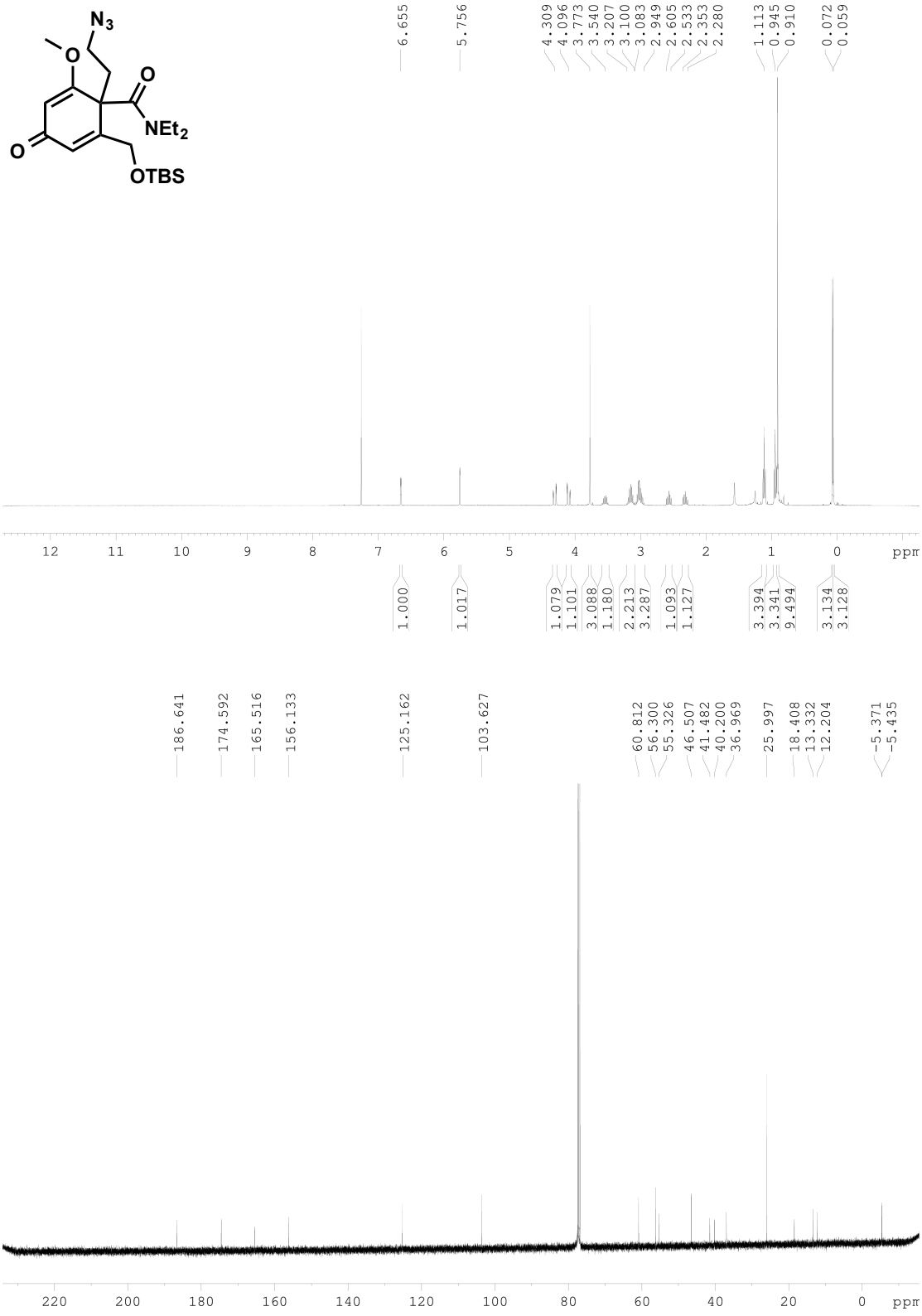
Compound **148**



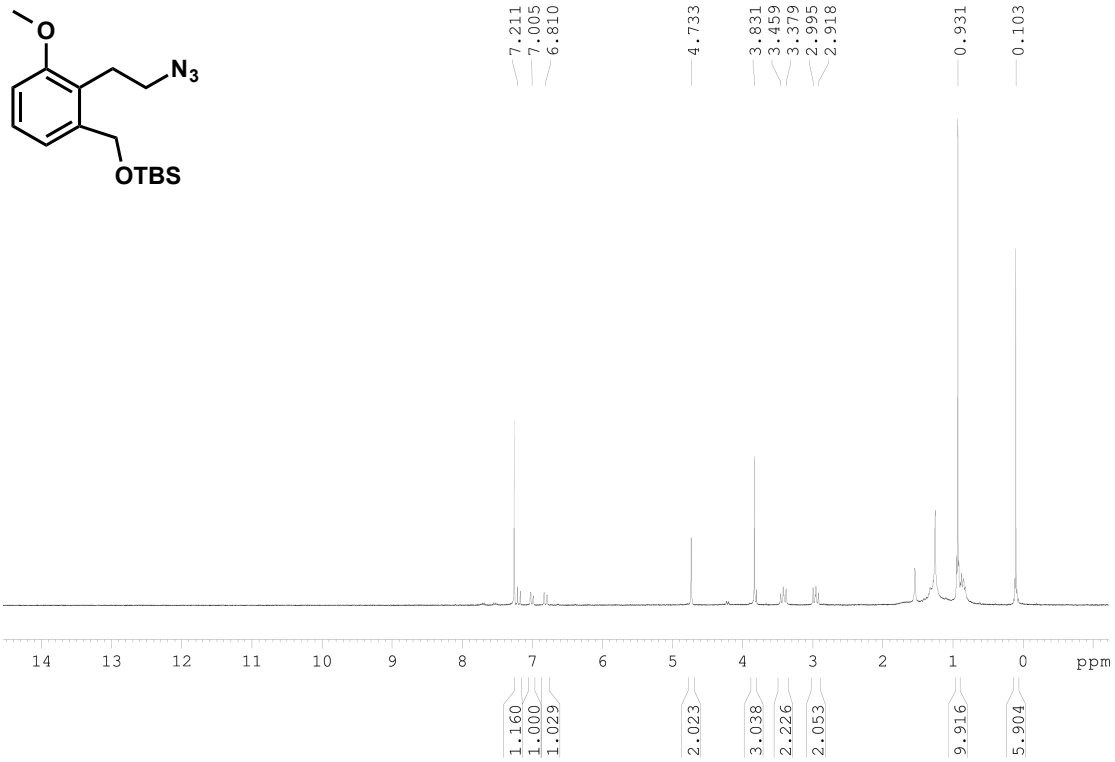
Compound **149**



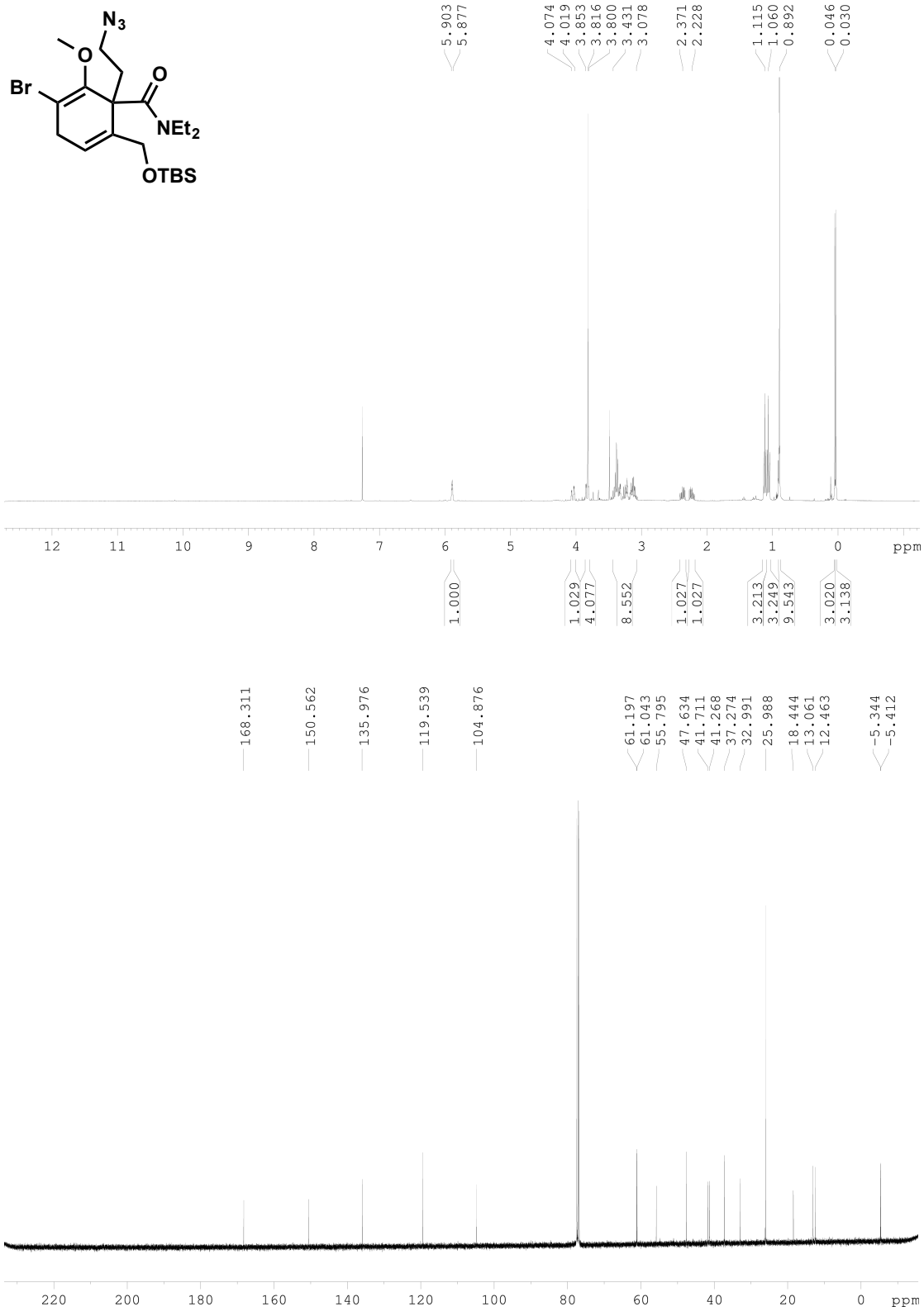
Compound **150**



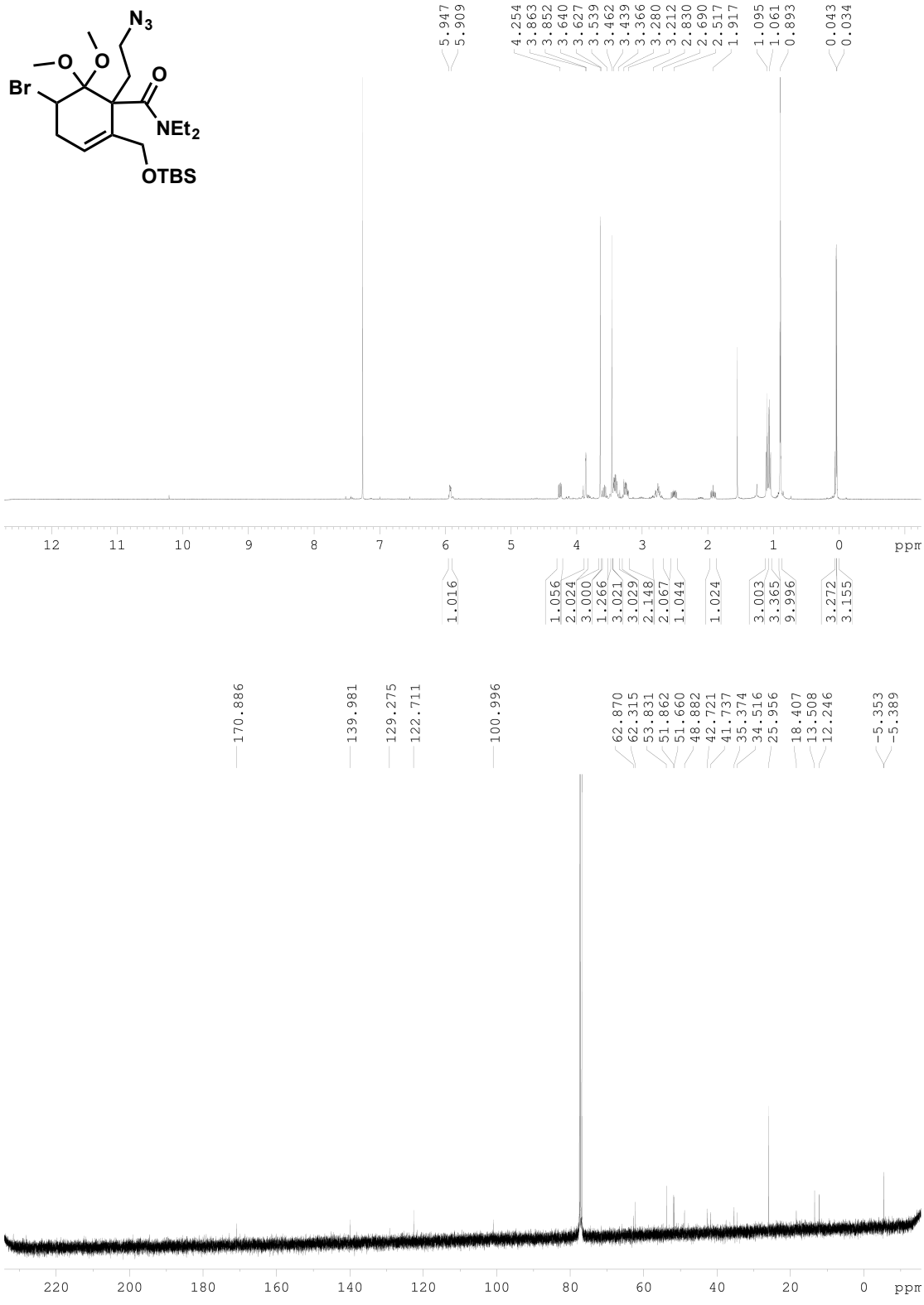
Compound **151**



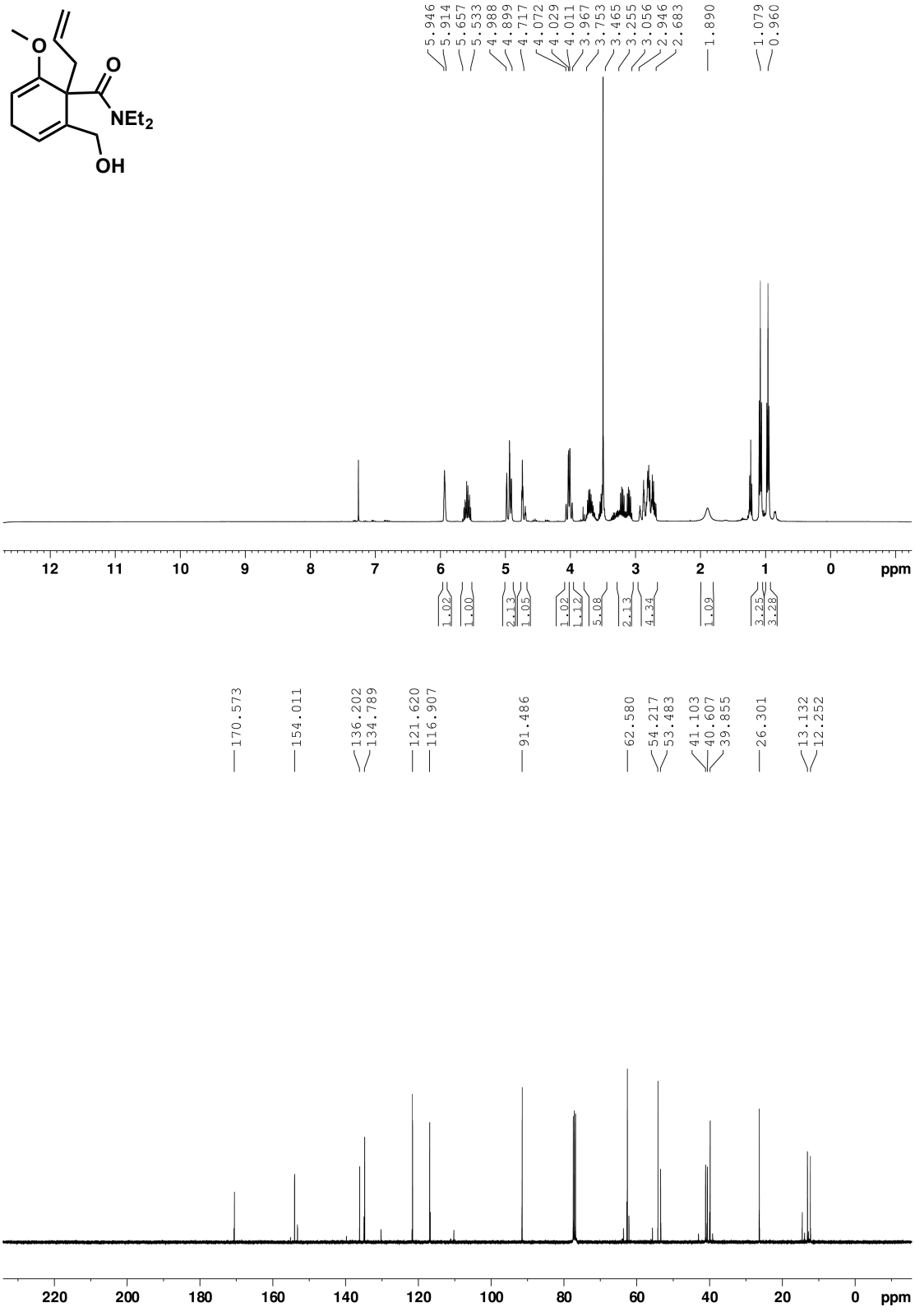
Compound **152**



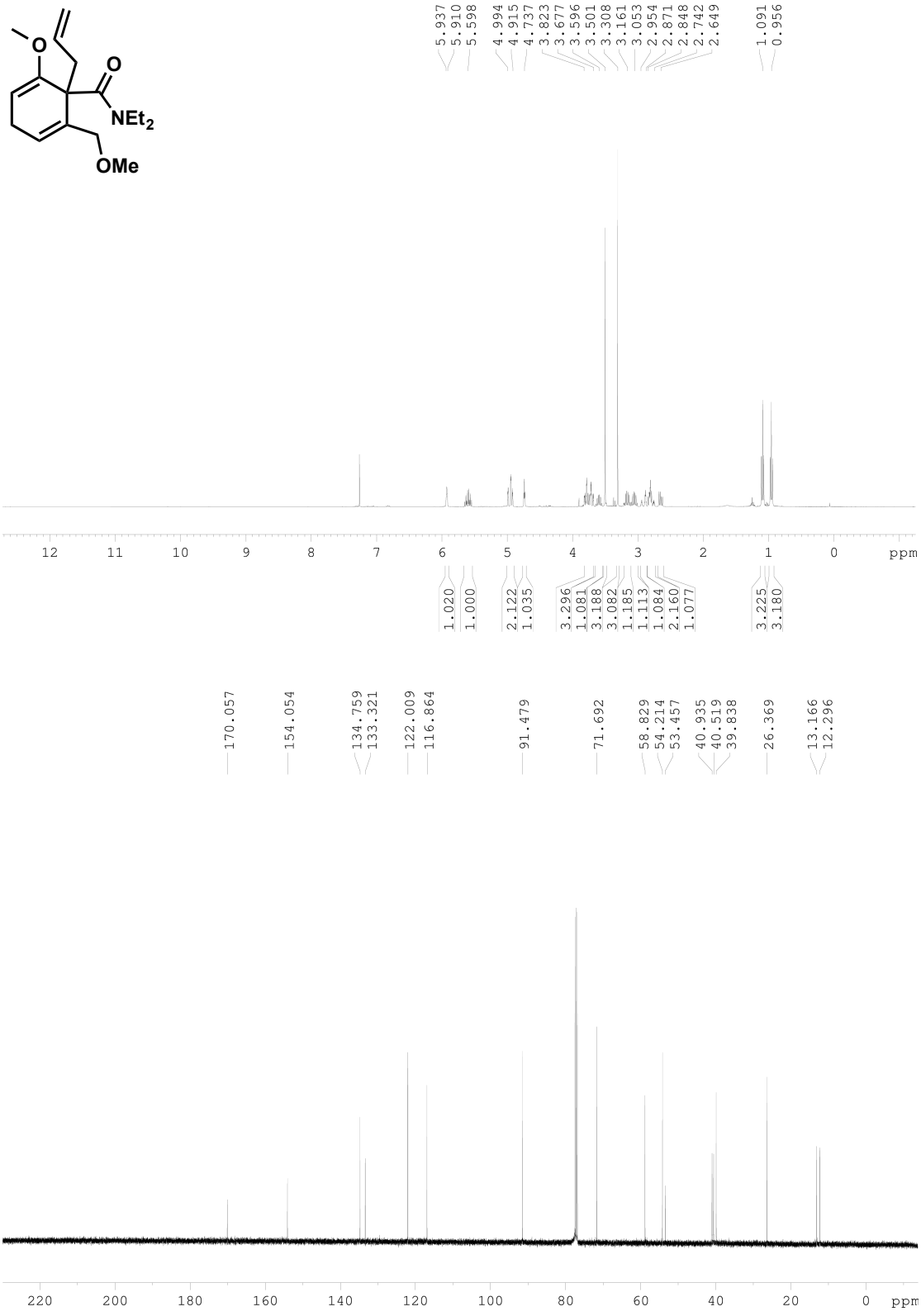
Compound **153**



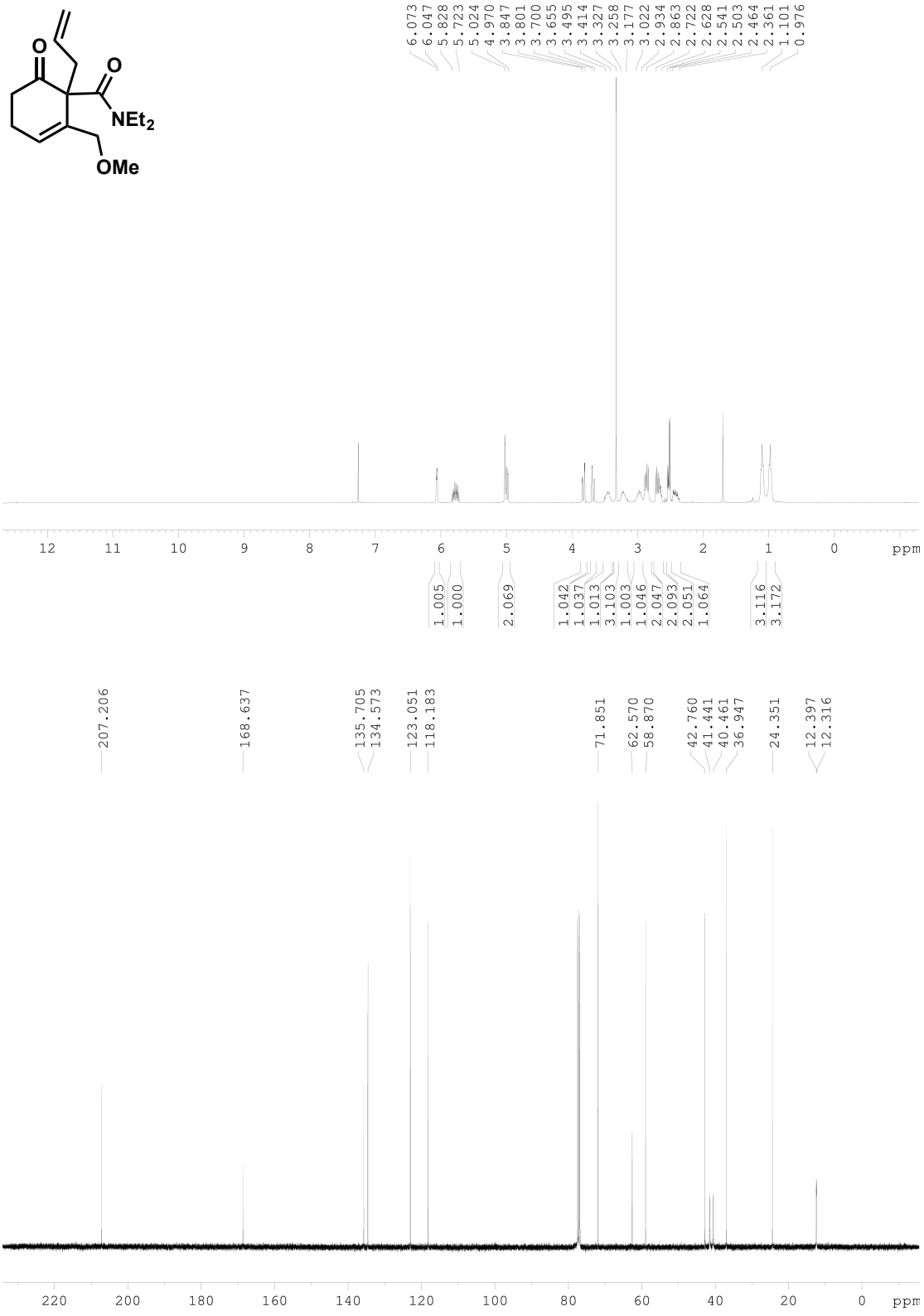
Compound **167**



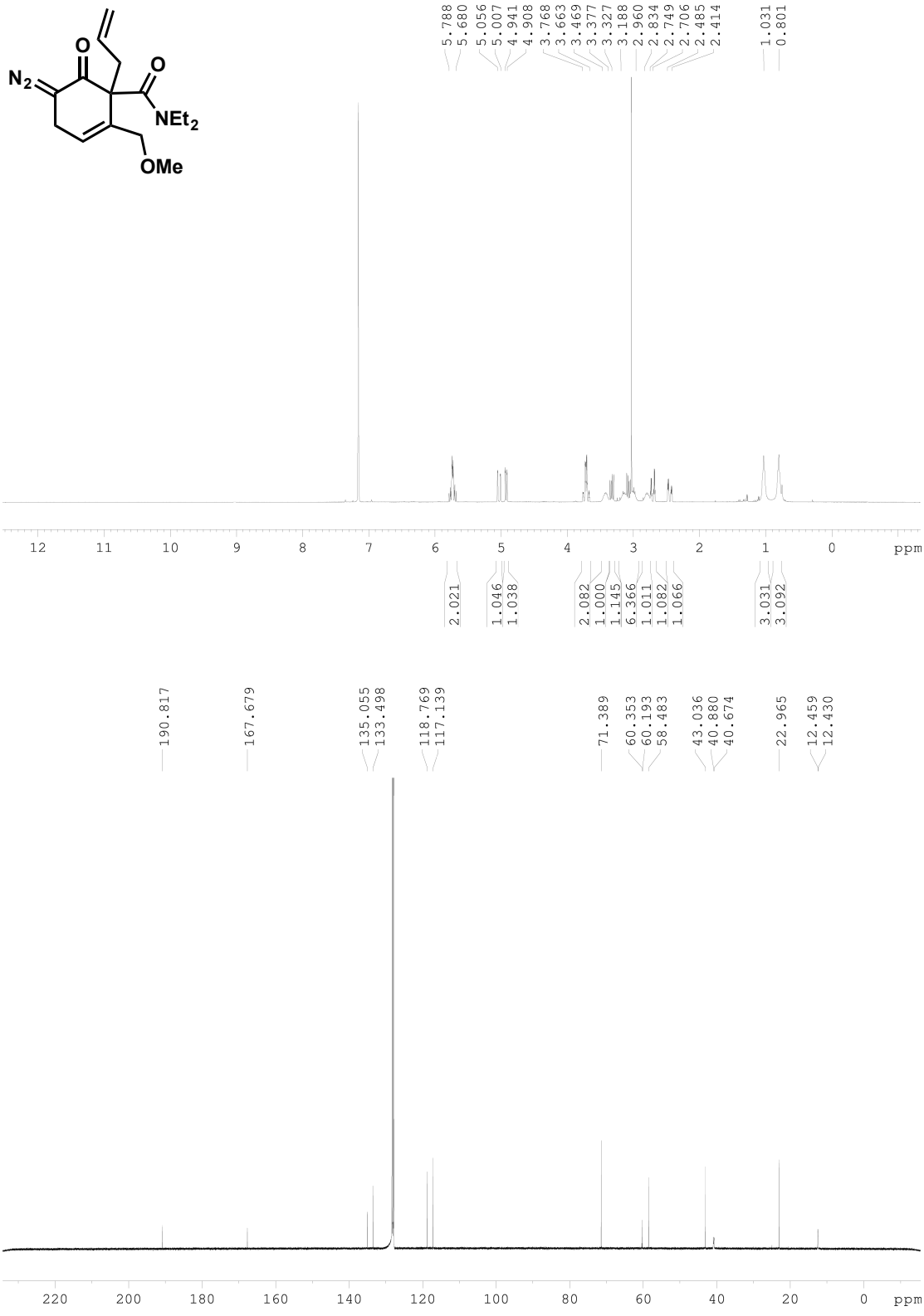
Compound **156**



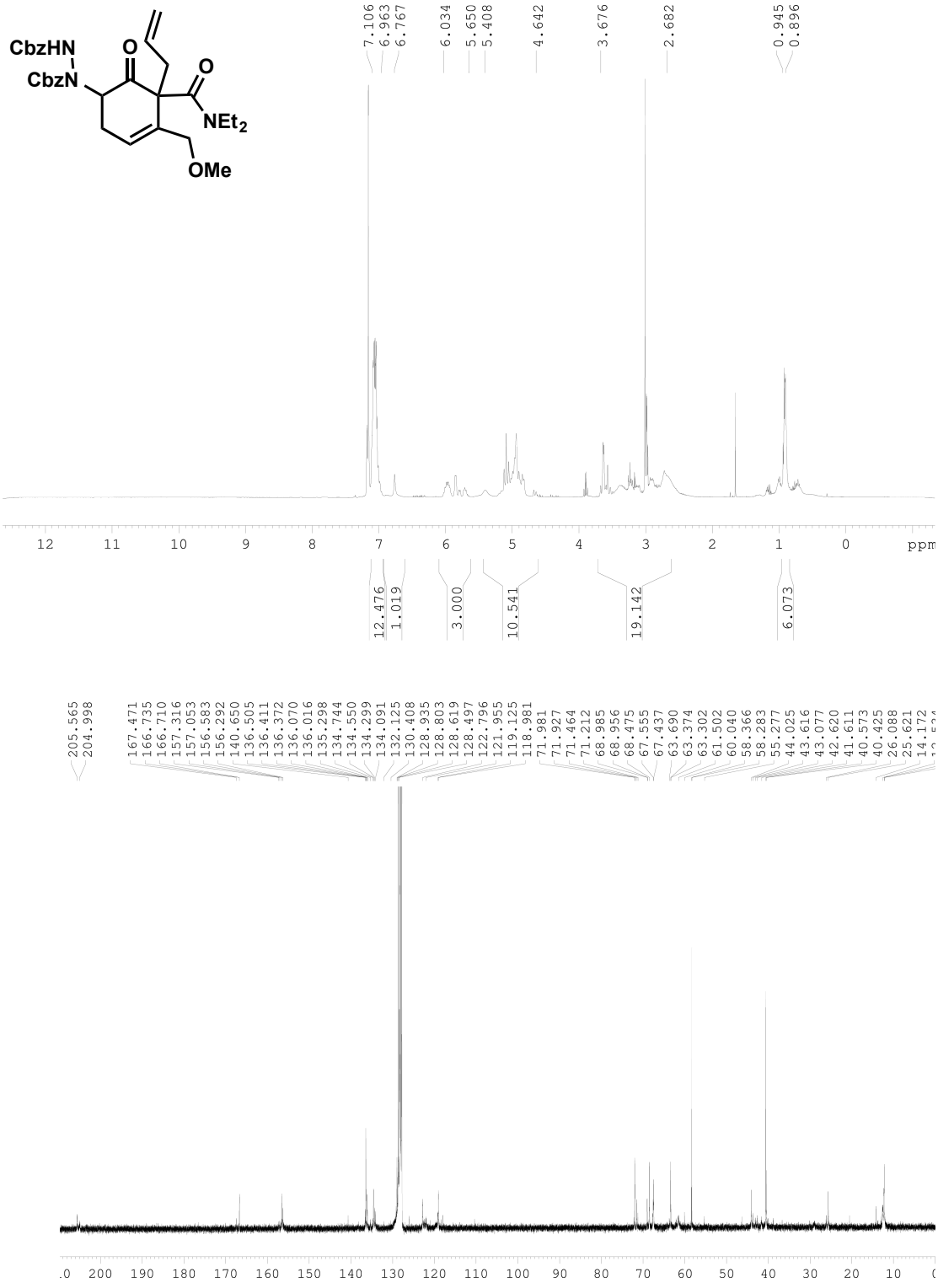
Compound **157**



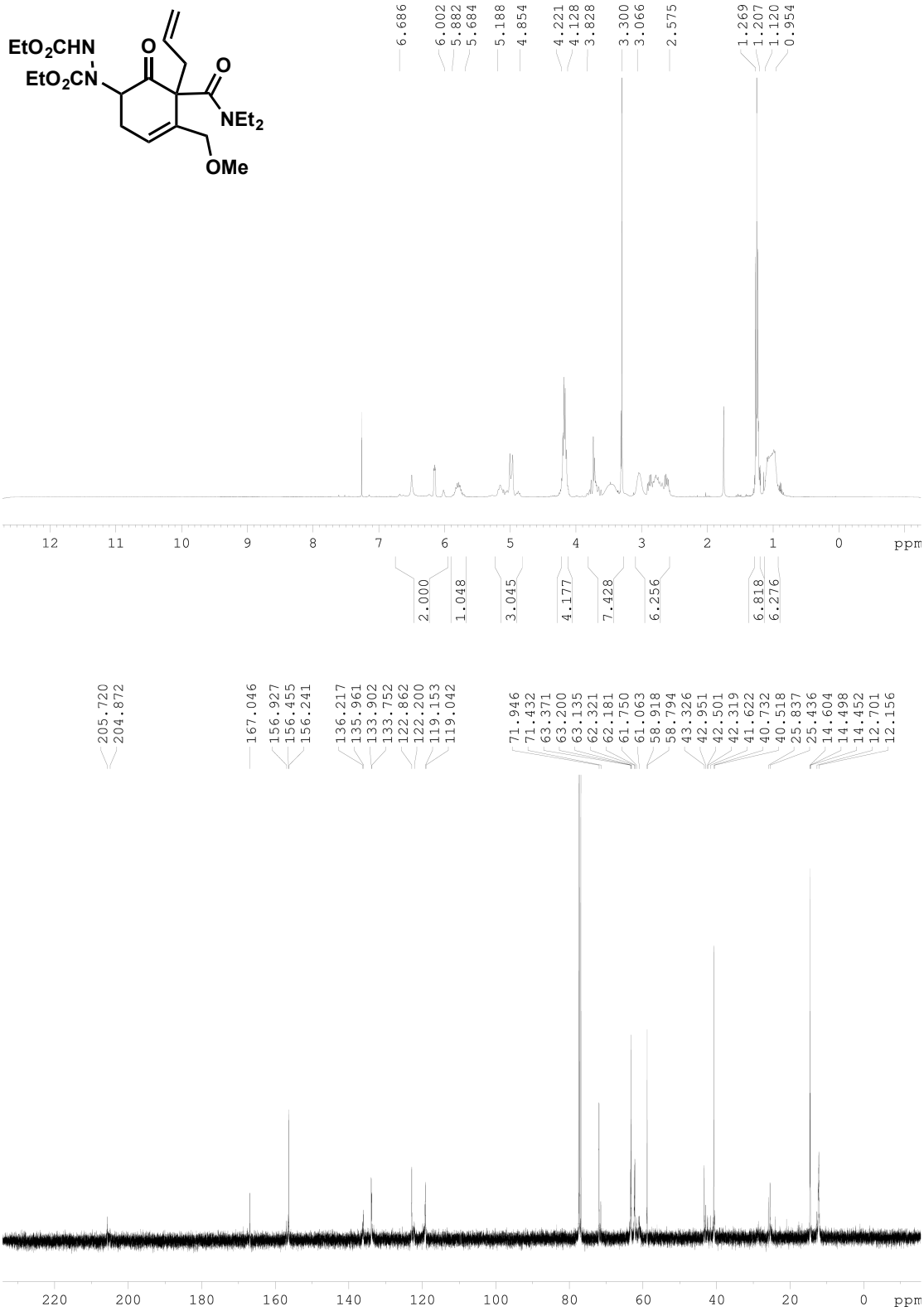
Compound **160**



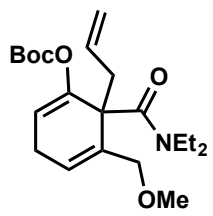
Compound **161**



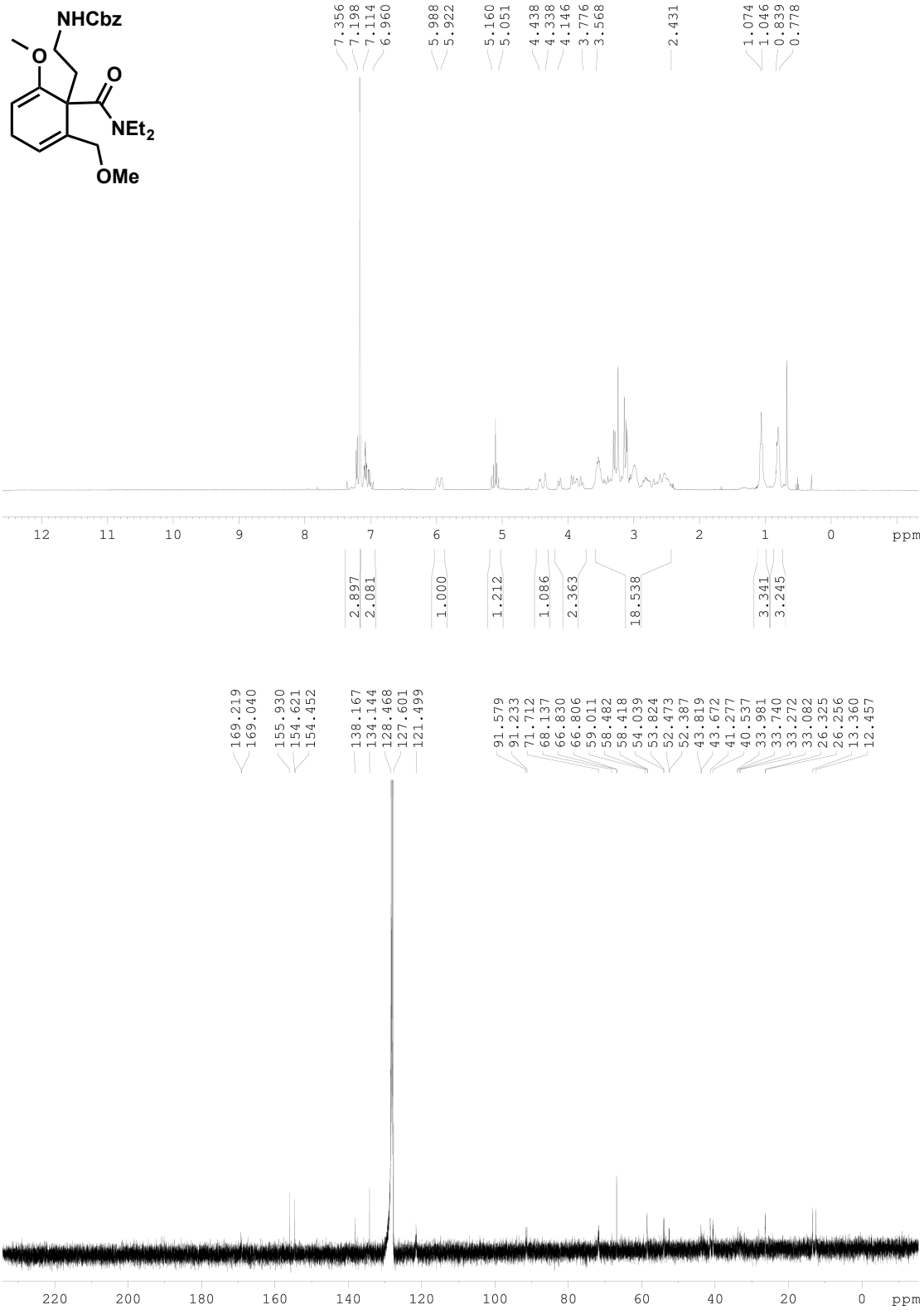
Compound **158**



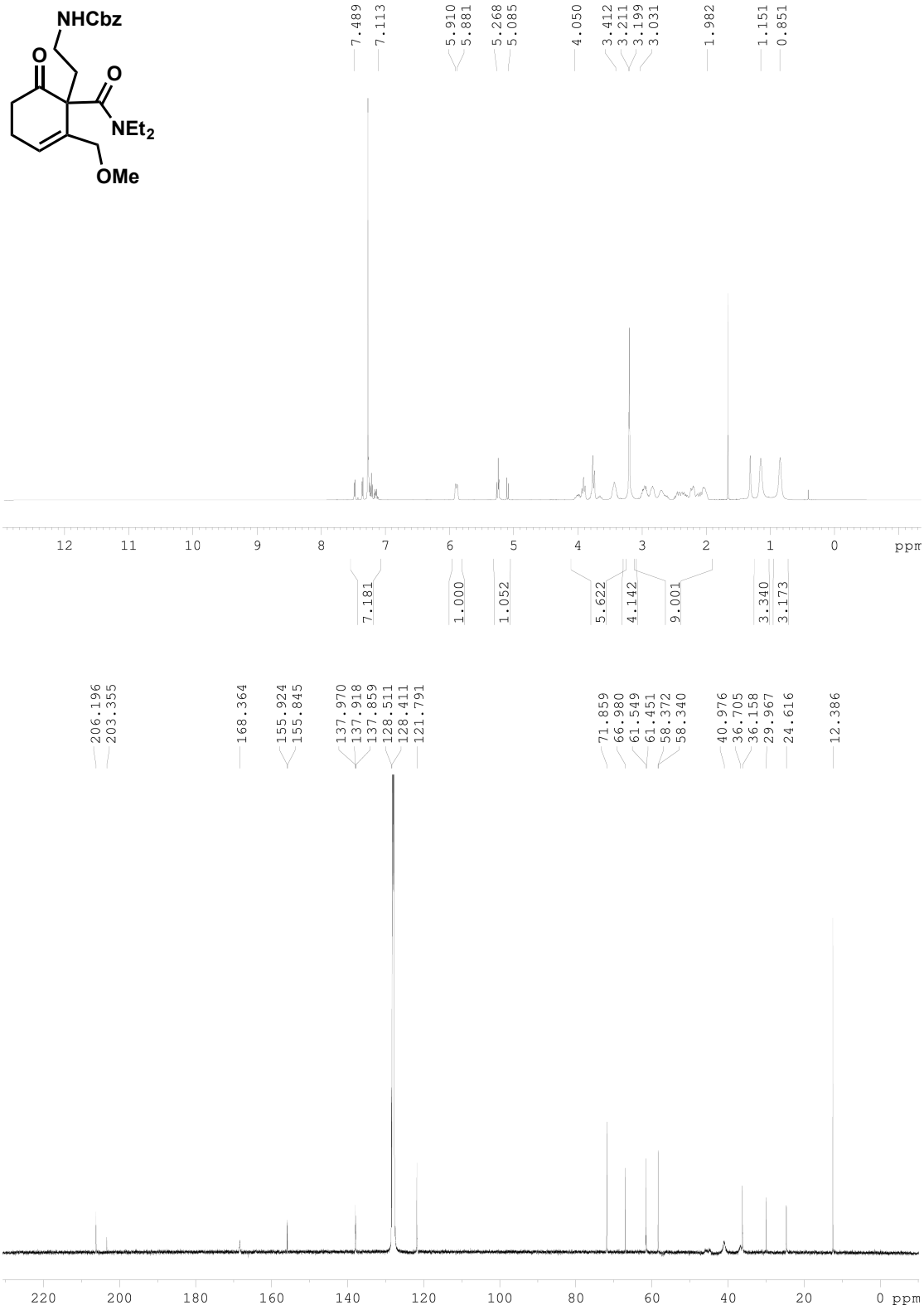
Compound **159**



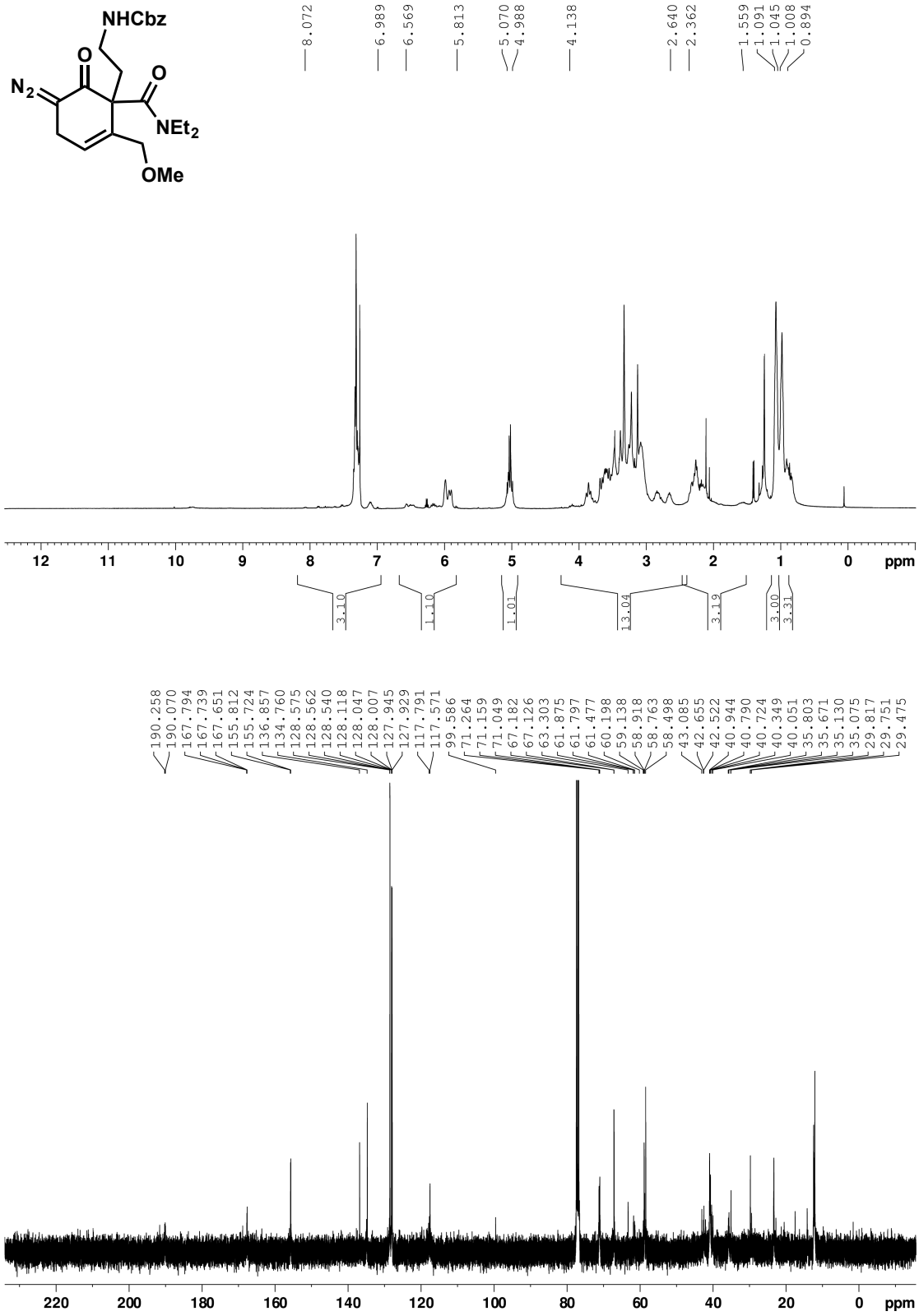
Compound **165**



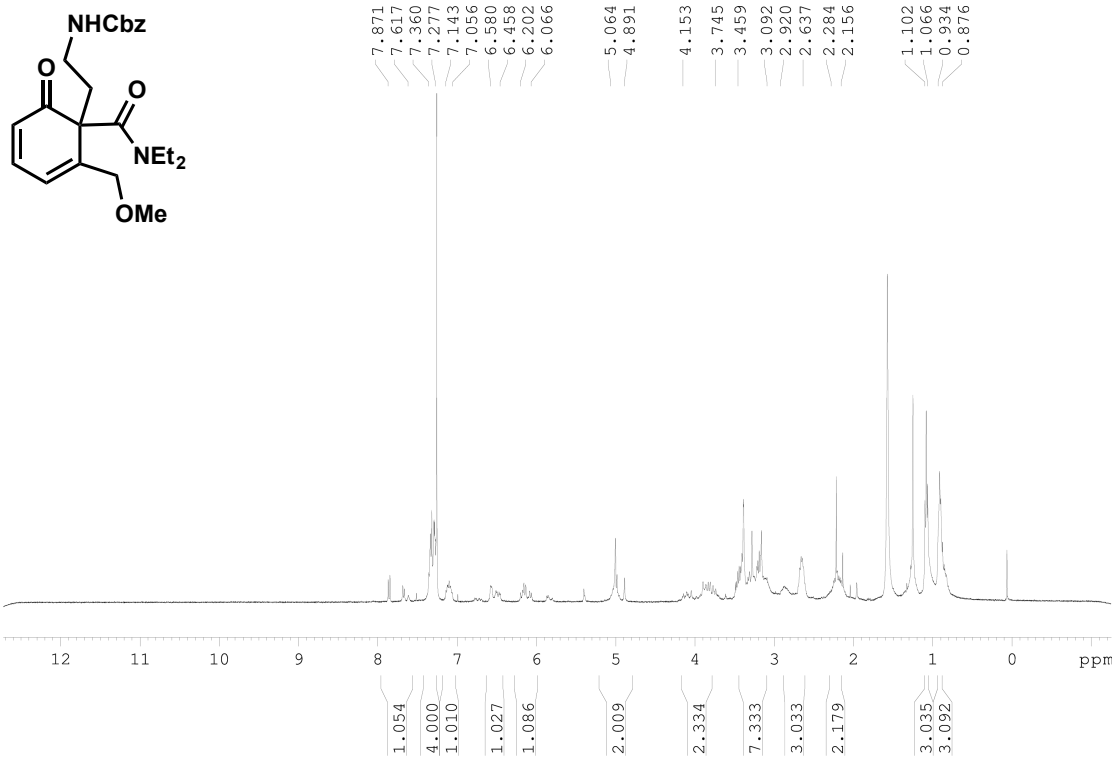
Compound **165b**



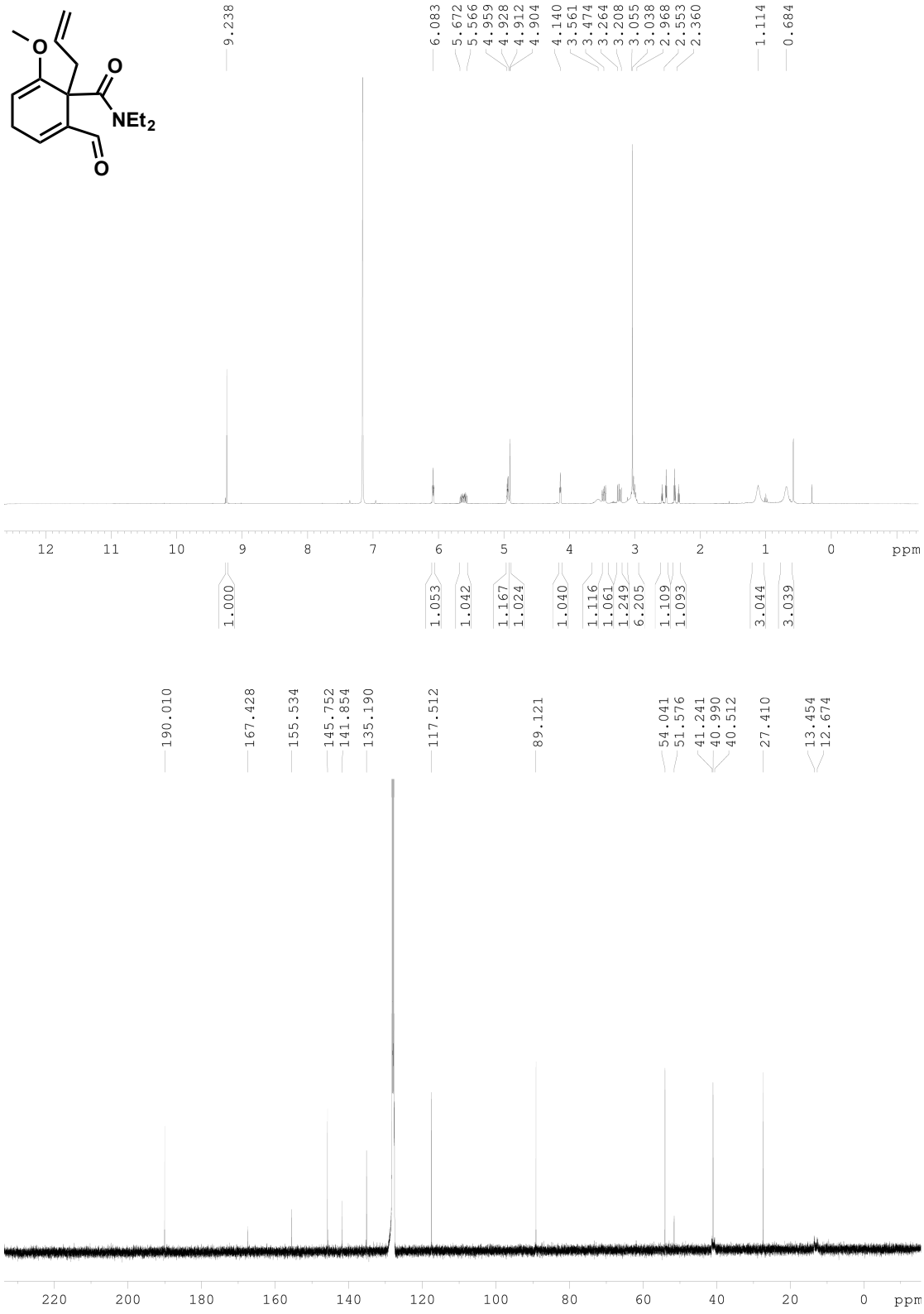
Compound **162**



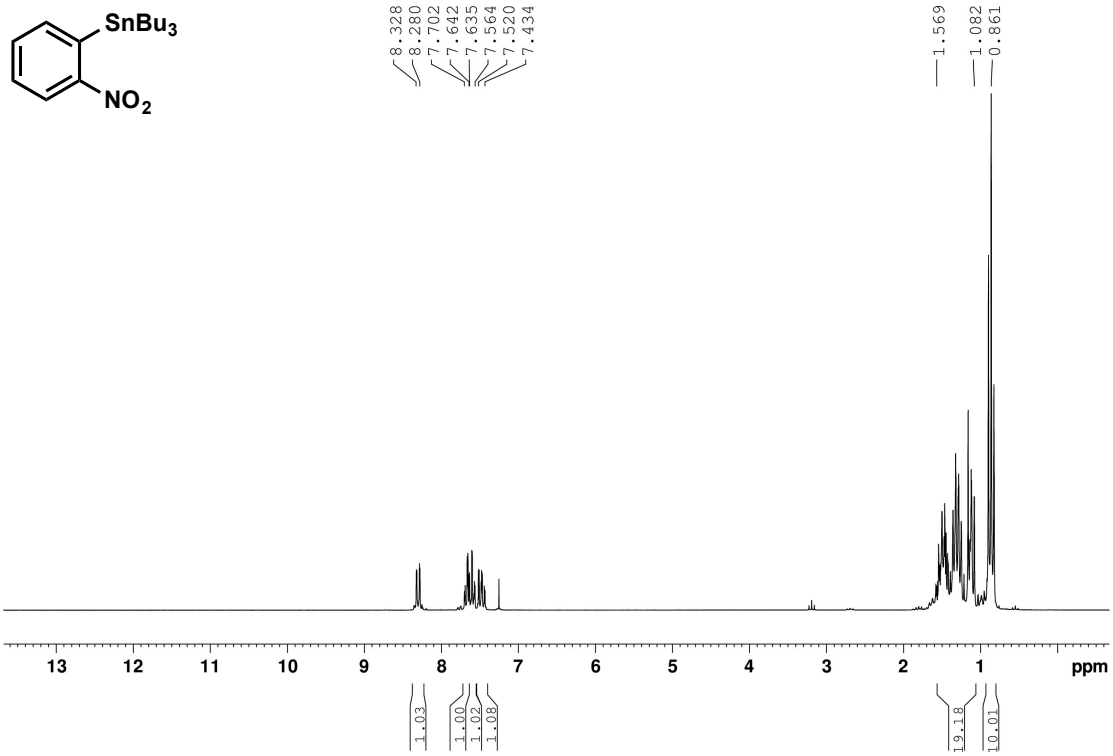
Compound **166**



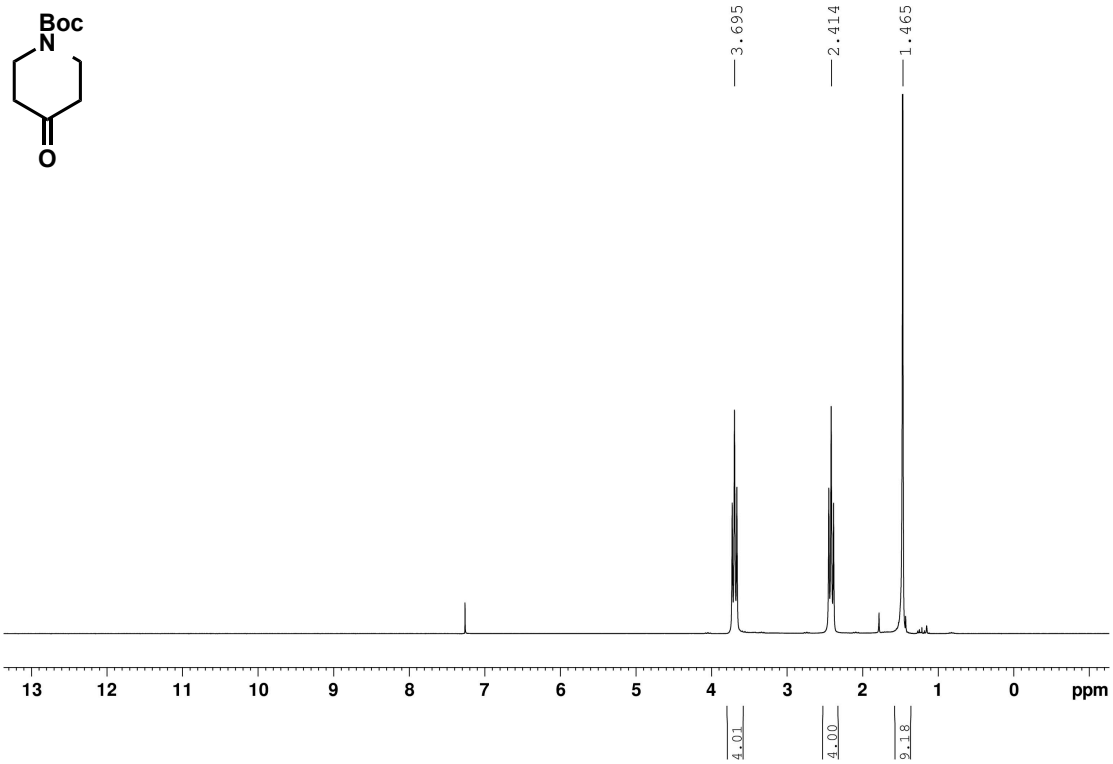
Compound **168**



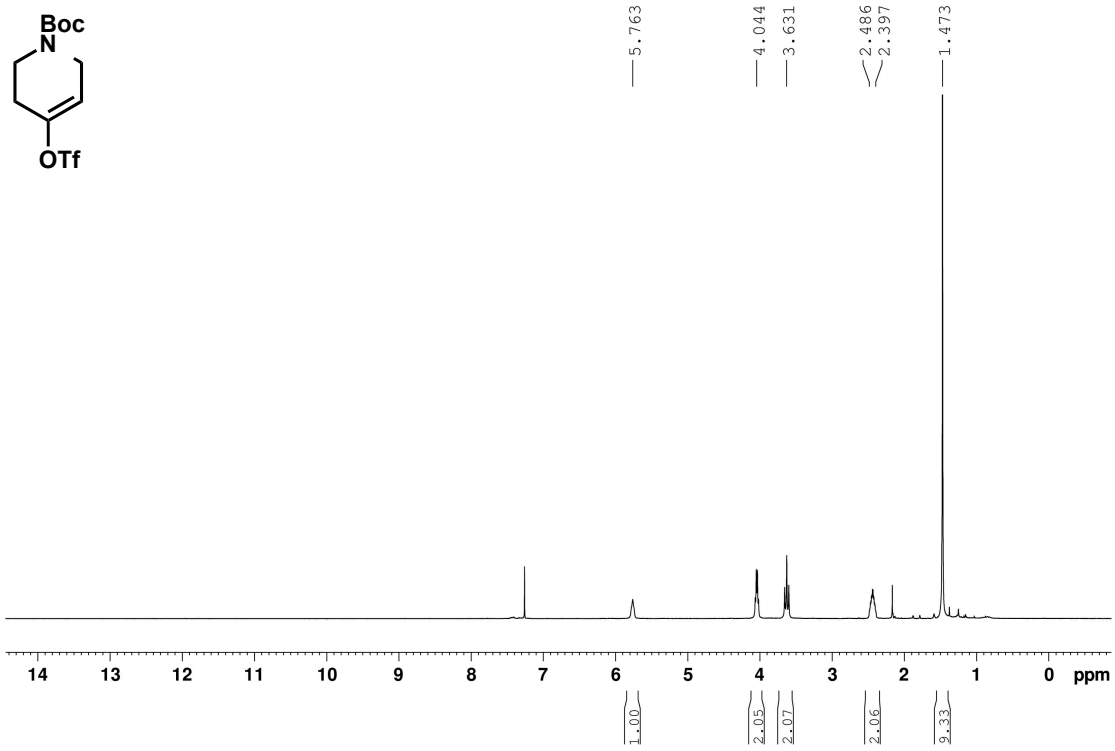
Compound **184**



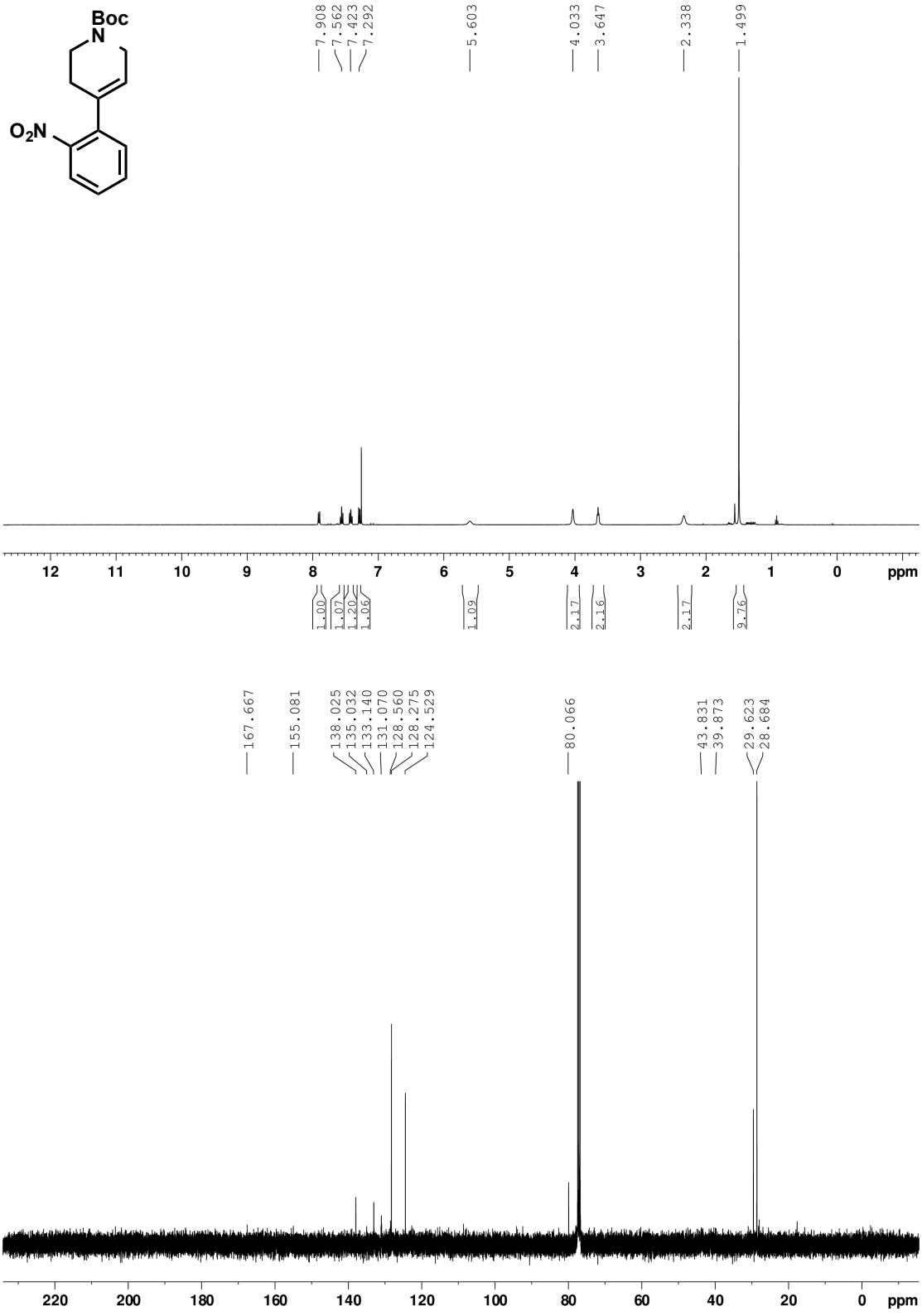
Compound **187b**



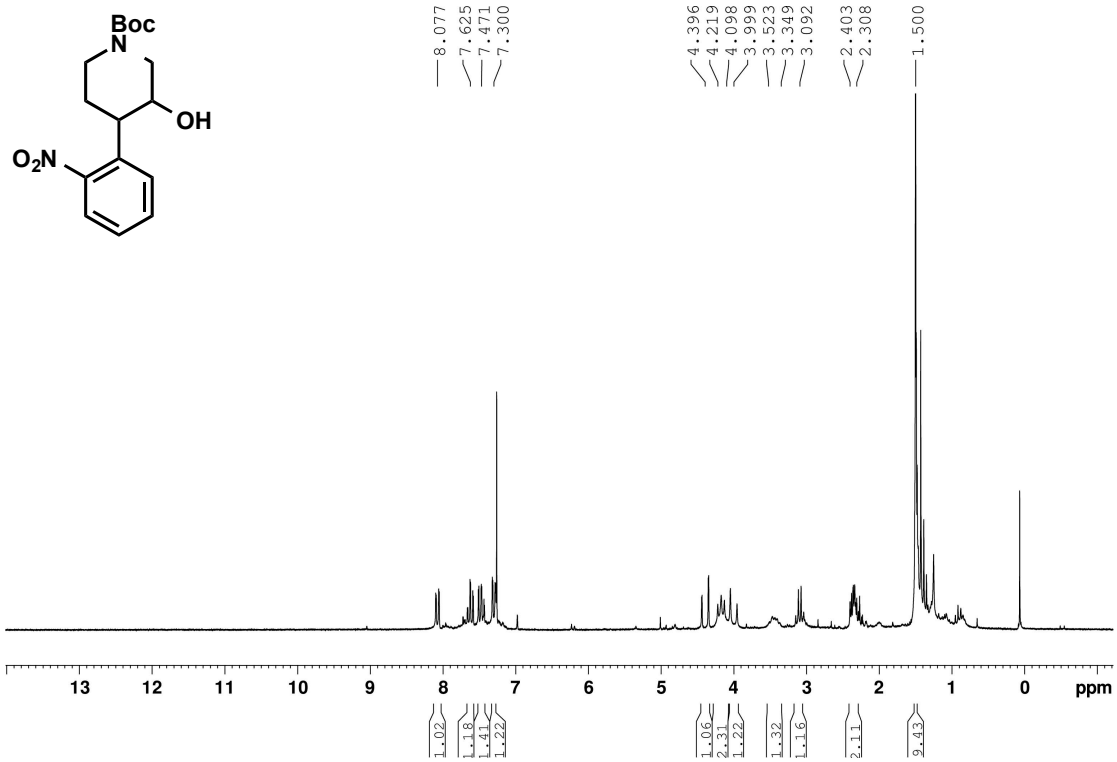
Compound **185**



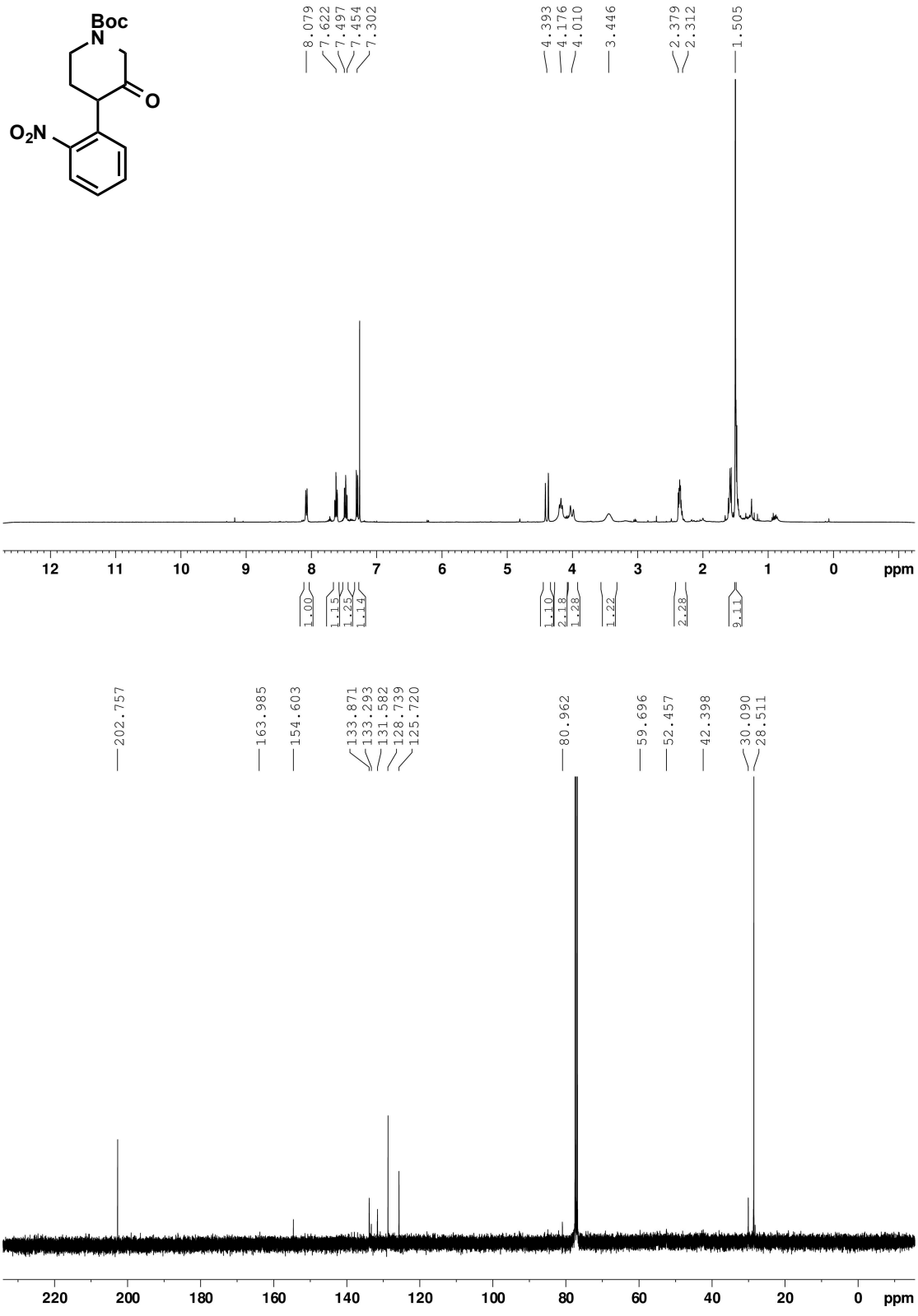
Compound **183**



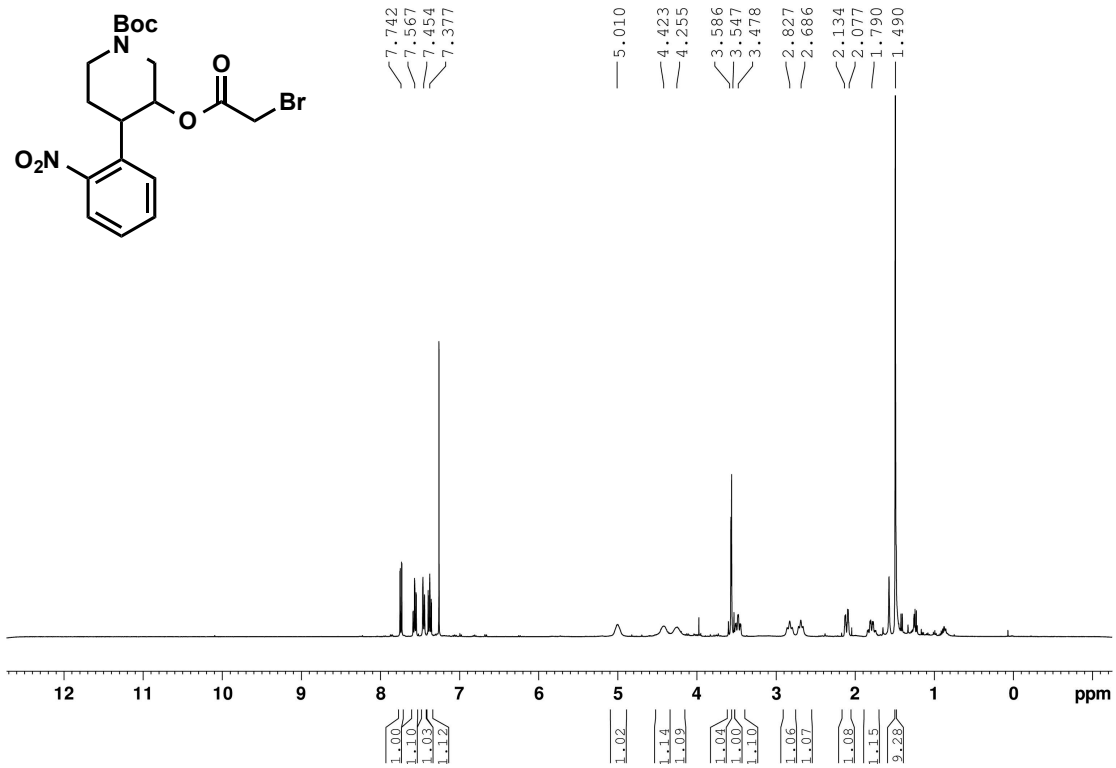
Compound **188**



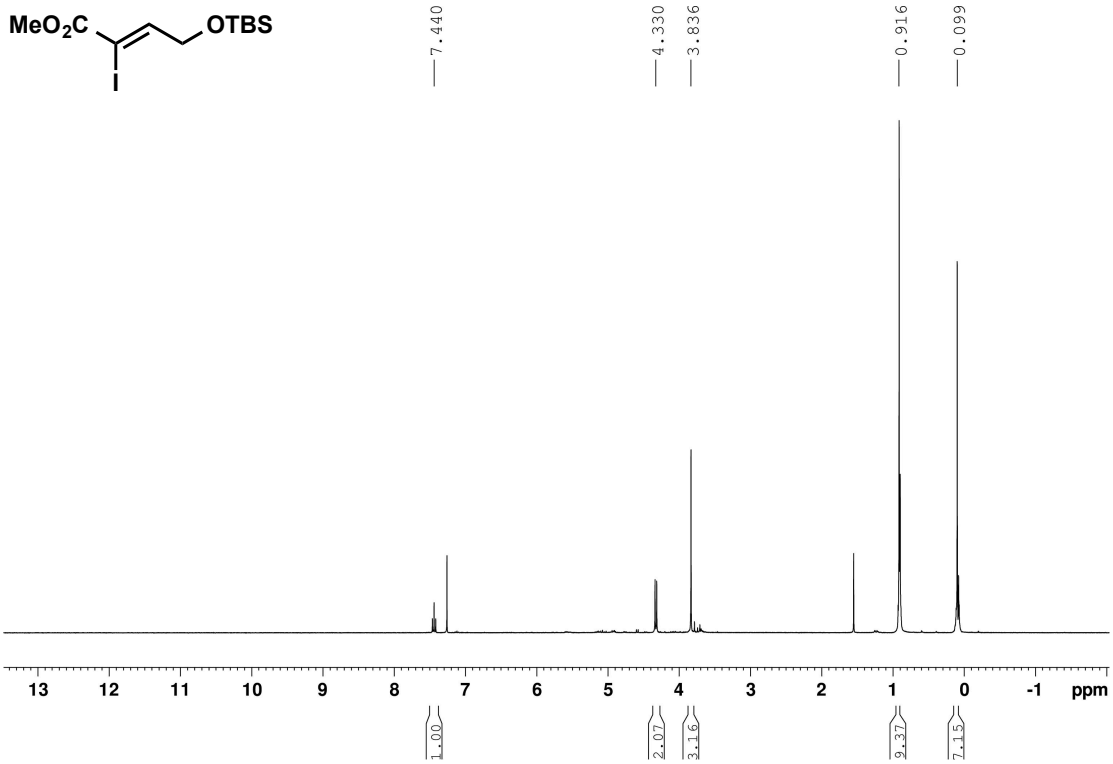
Compound **180**



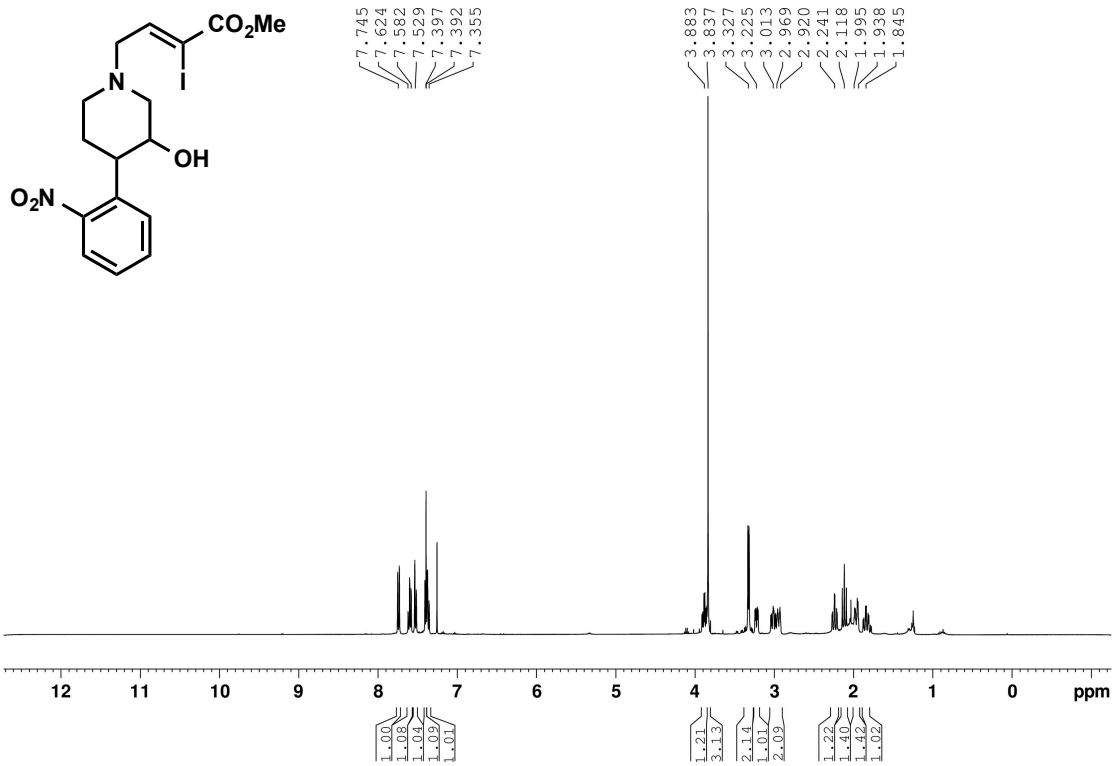
Compound **181**



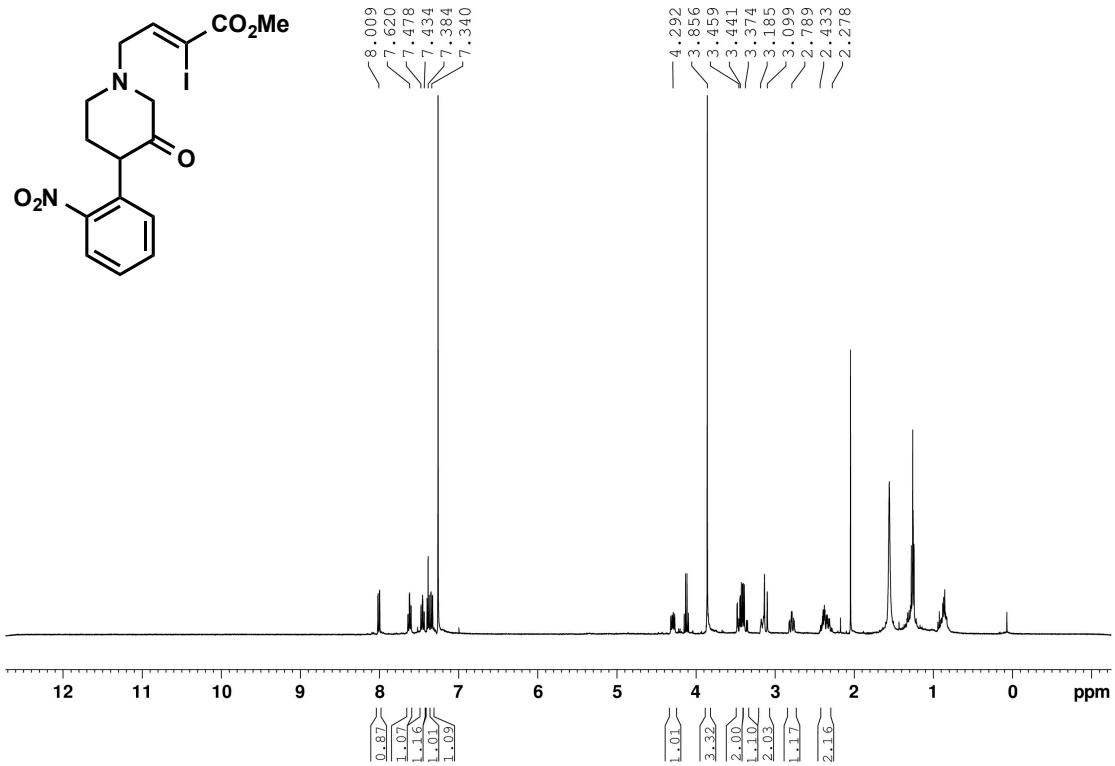
Compound **193**



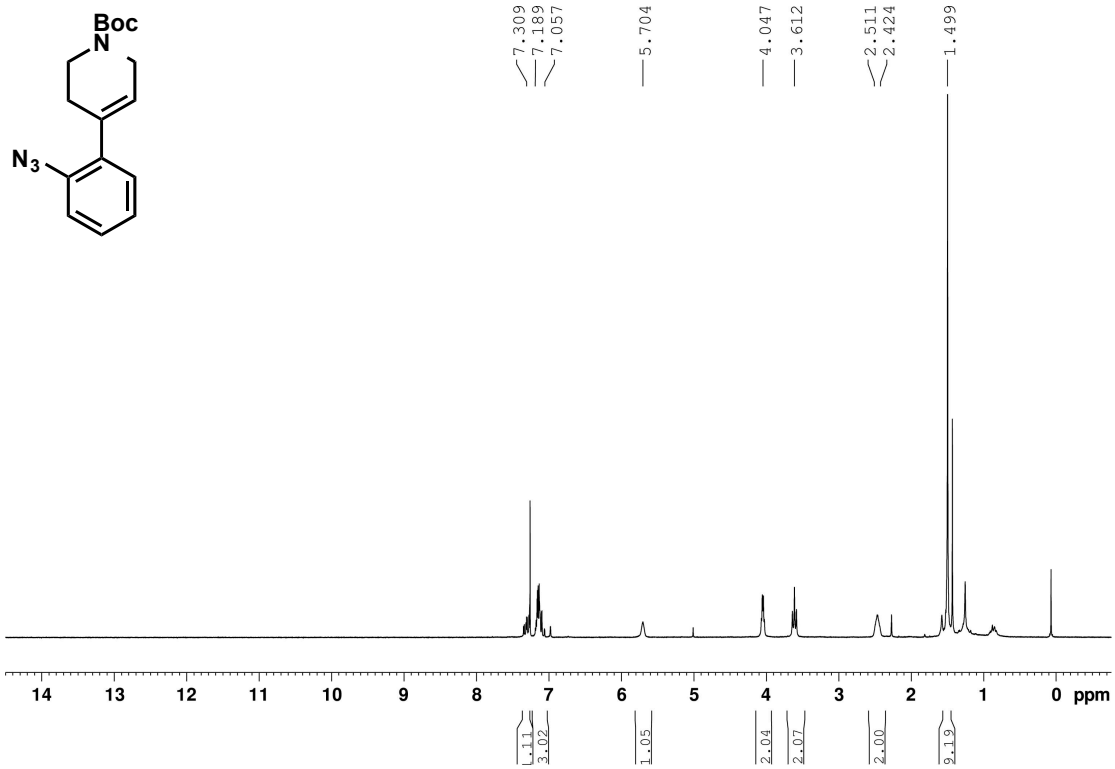
Compound **196**



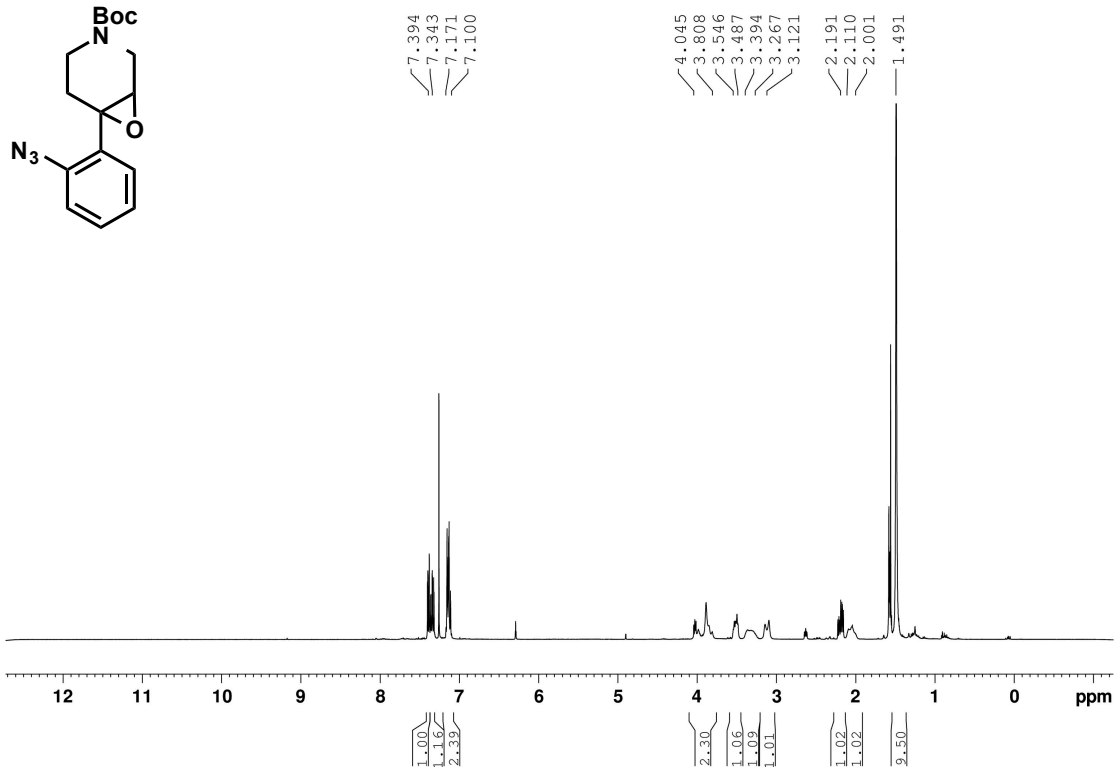
Compound **179**



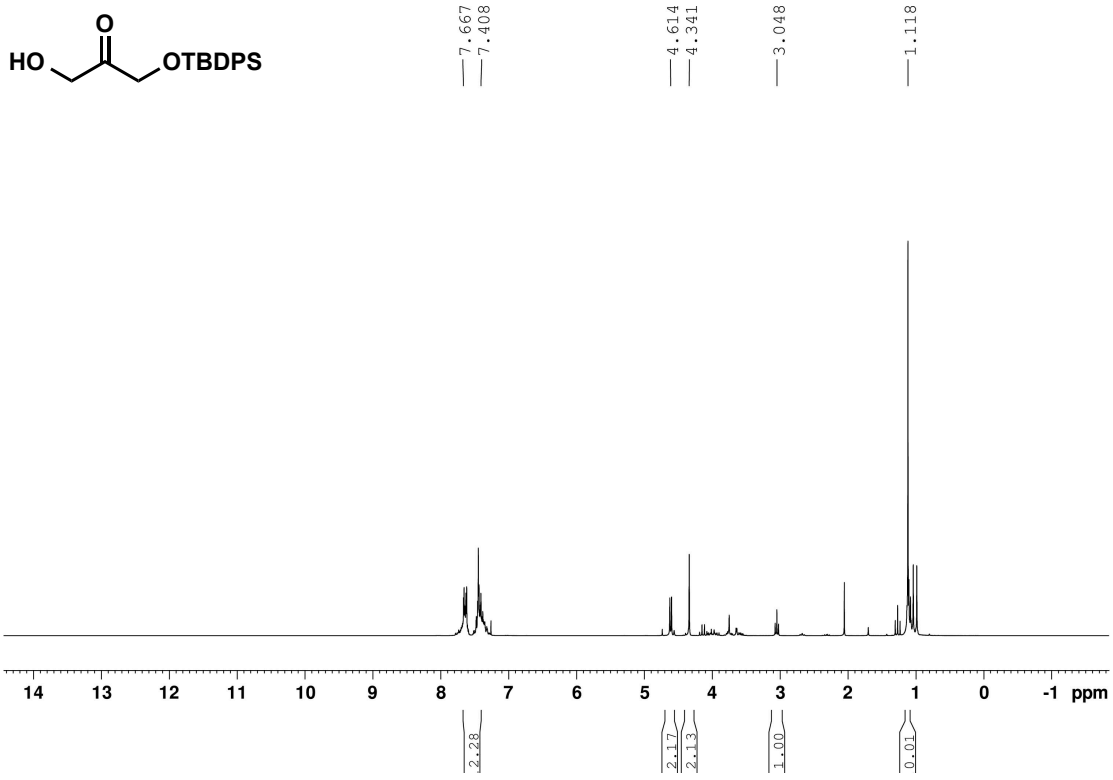
Compound **197**



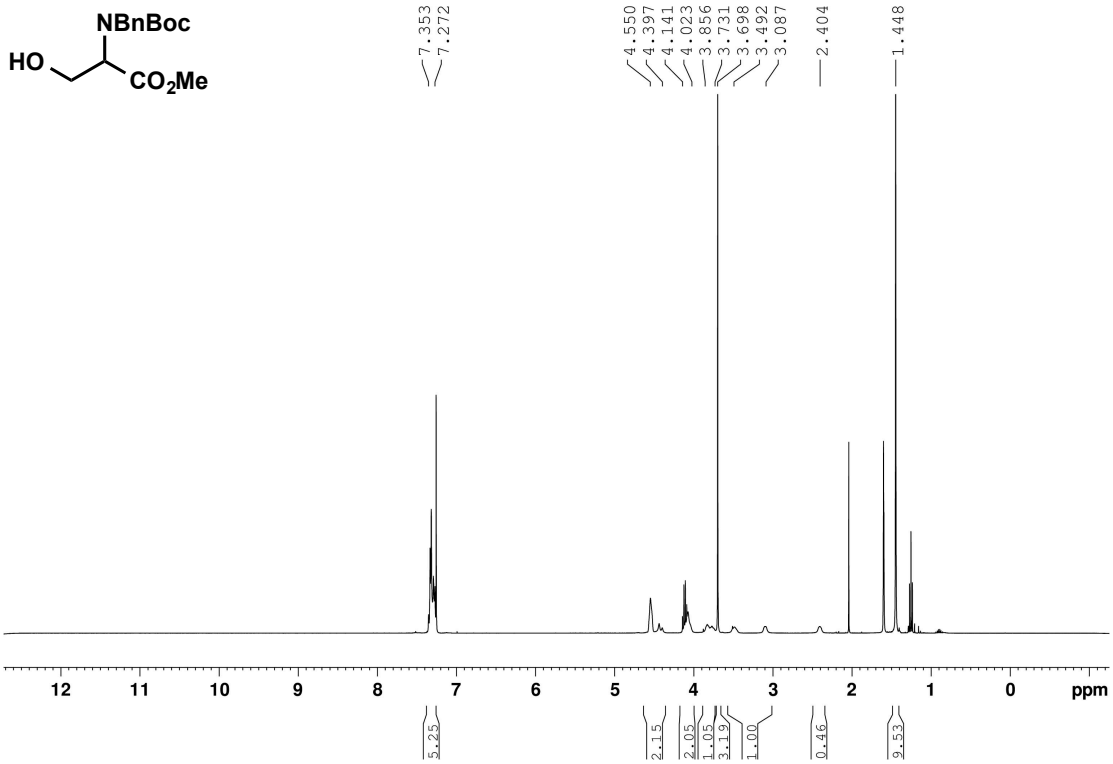
Compound **198**



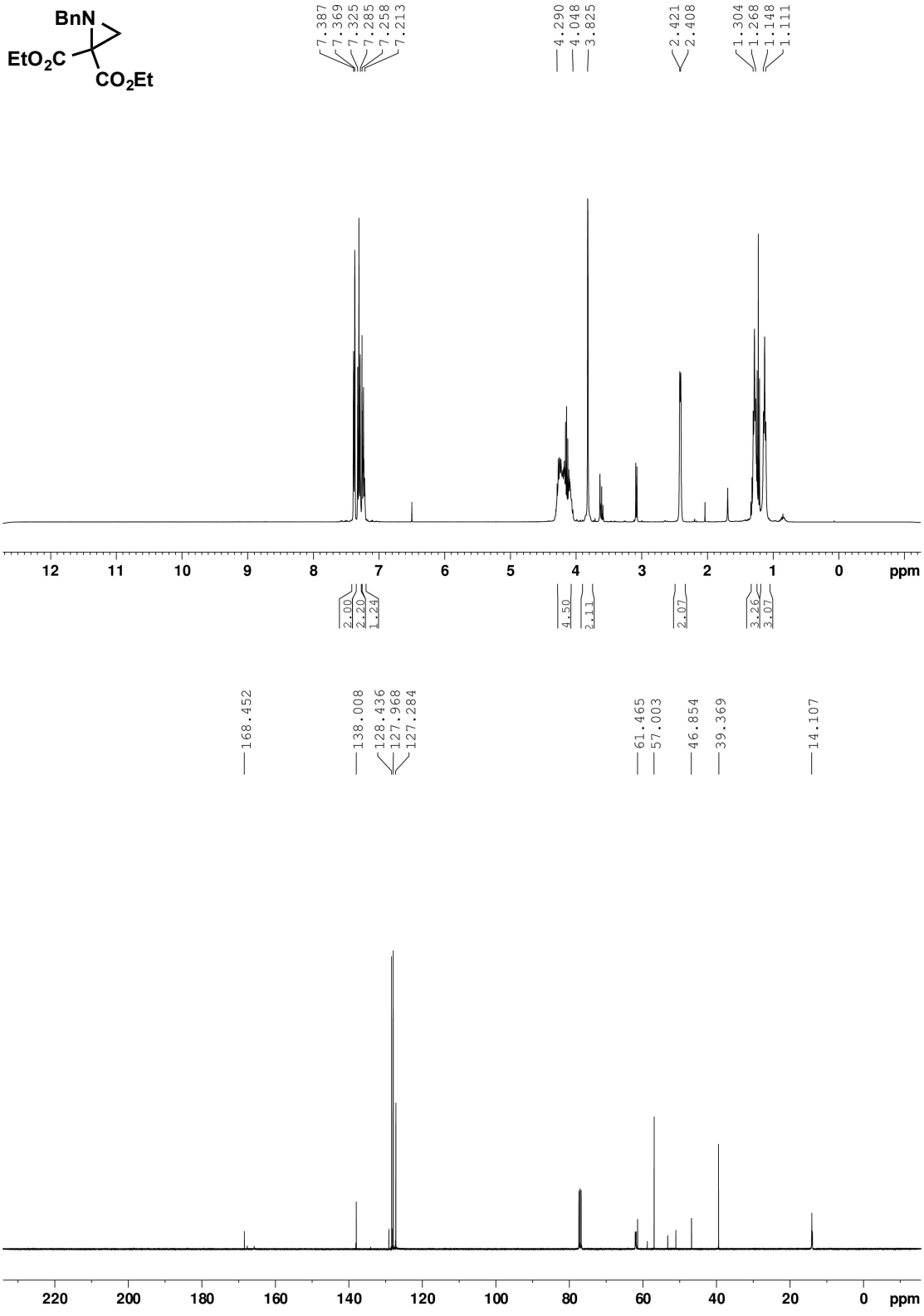
Compound **212**



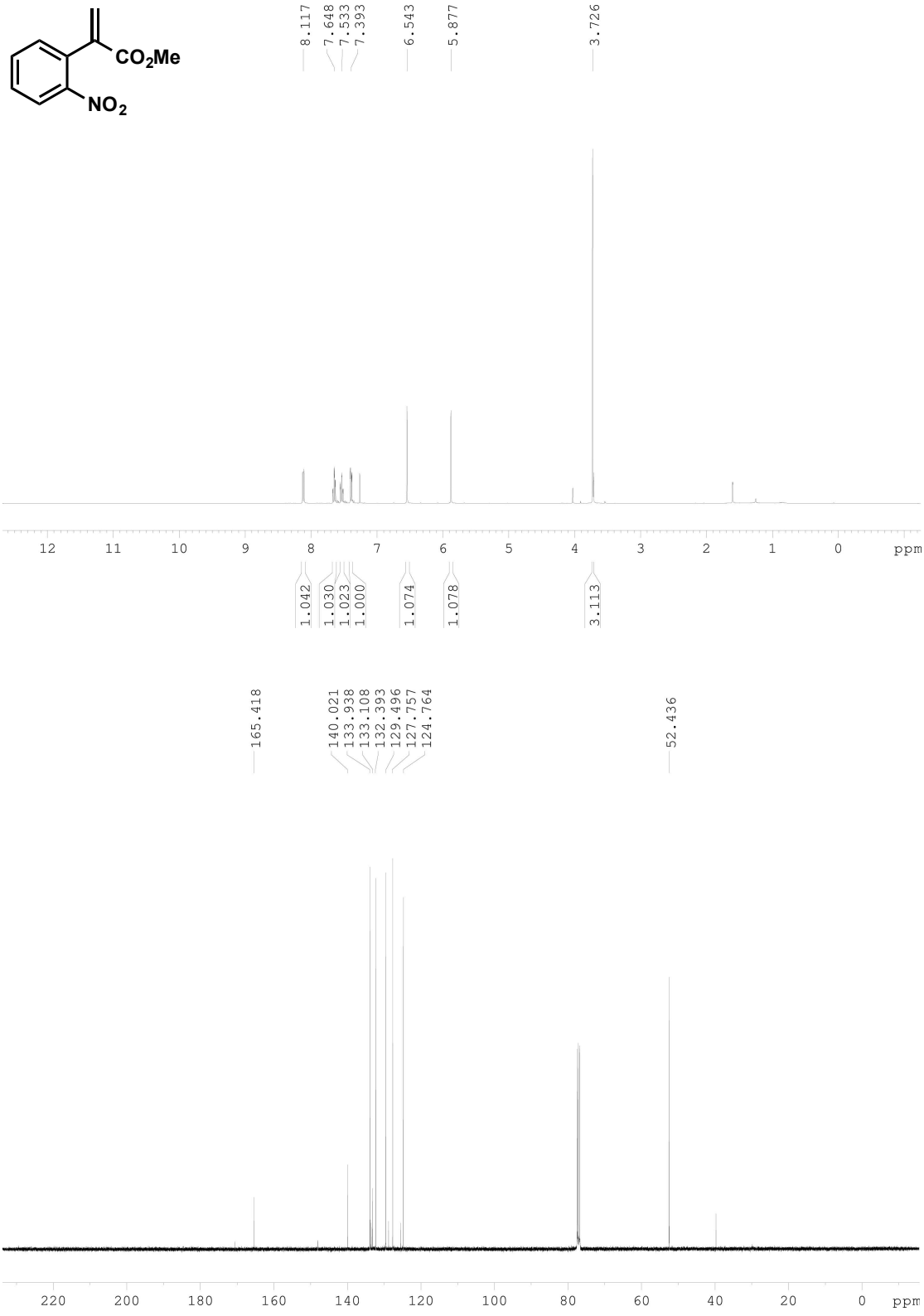
Compound **214**



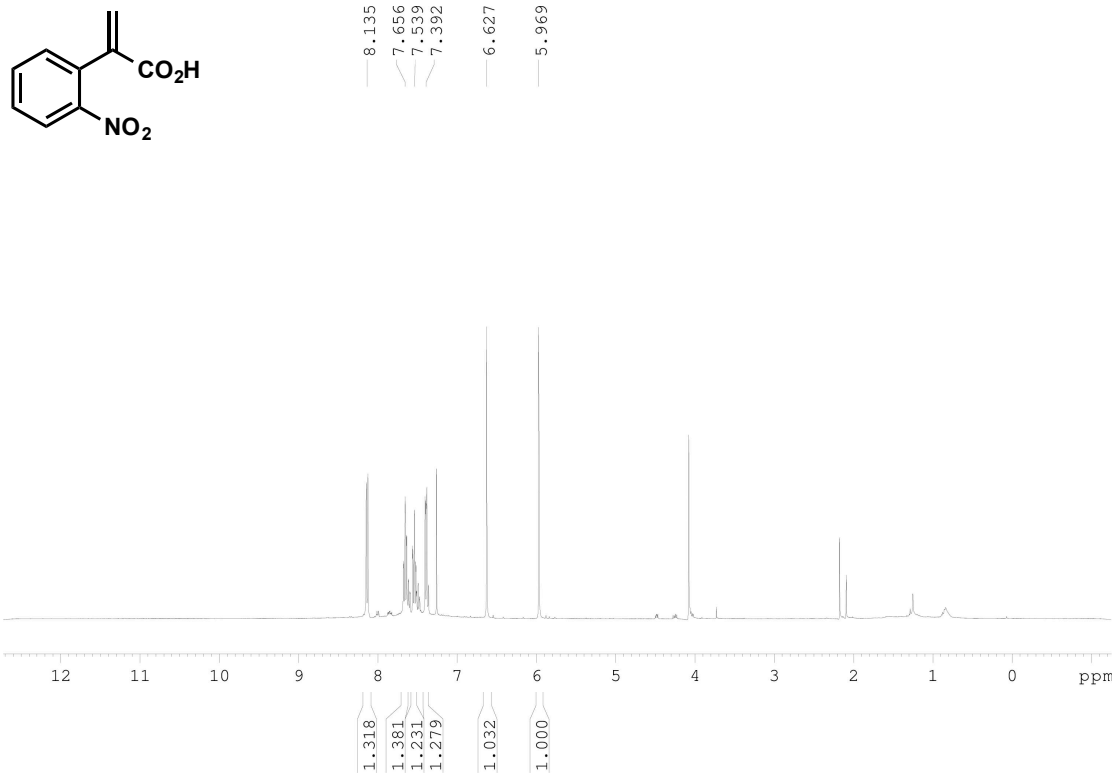
Compound **222**



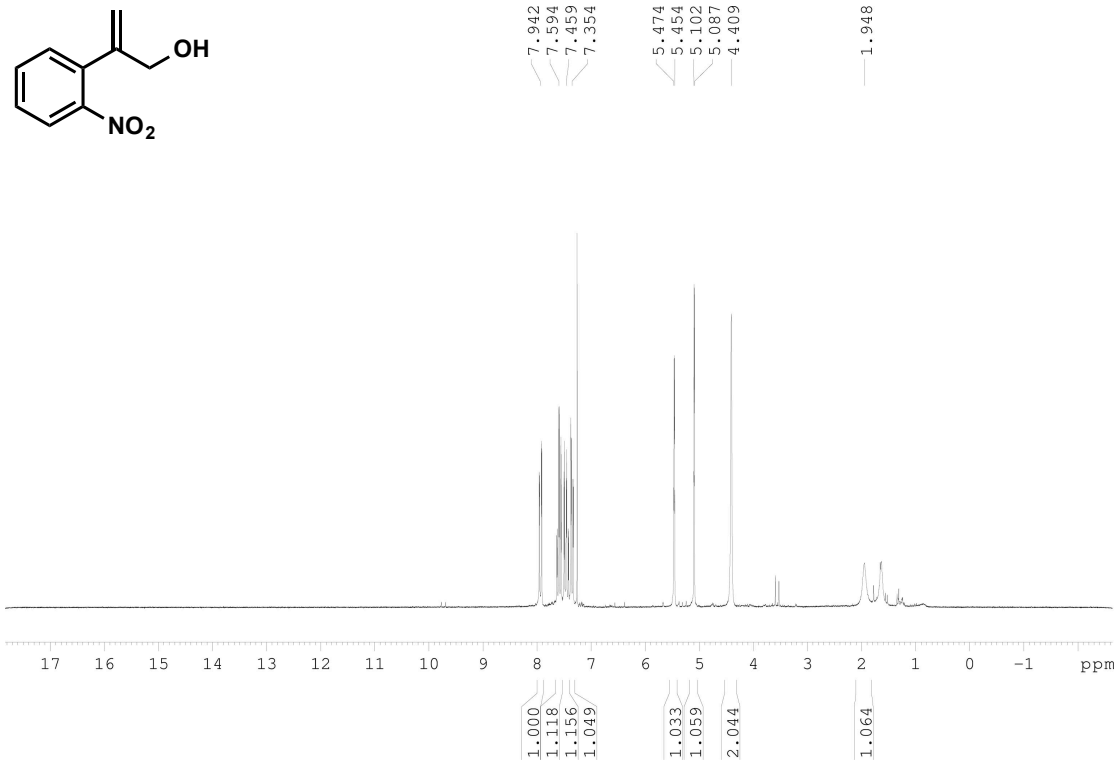
Compound **208**



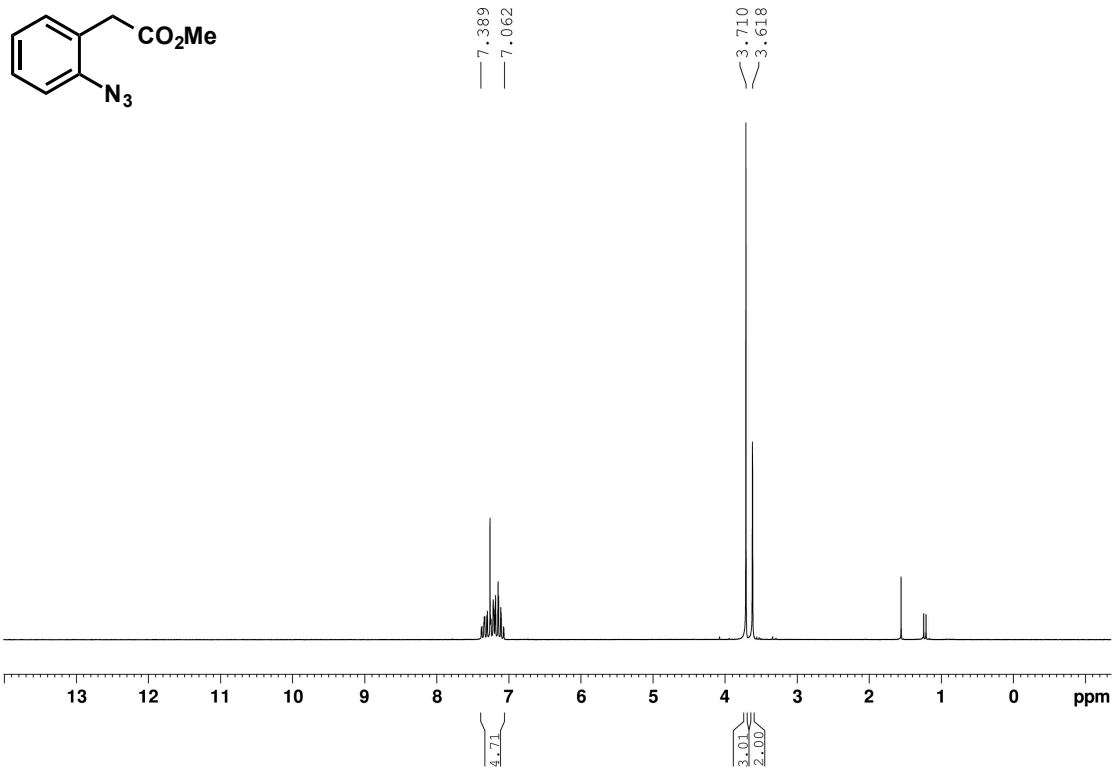
Compound **206**



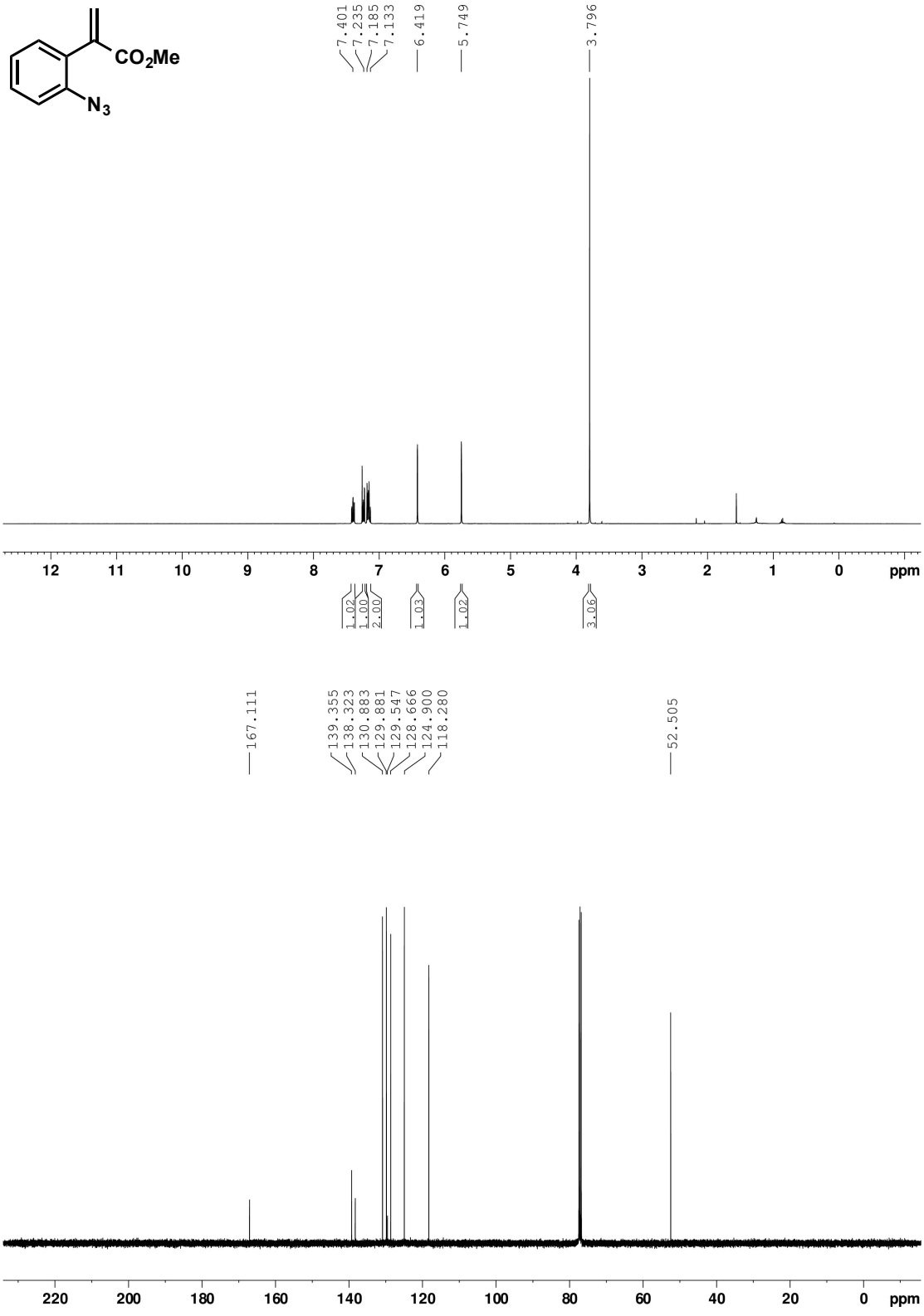
Compound **228**



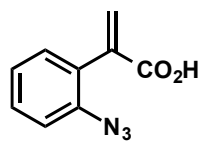
Compound **227**

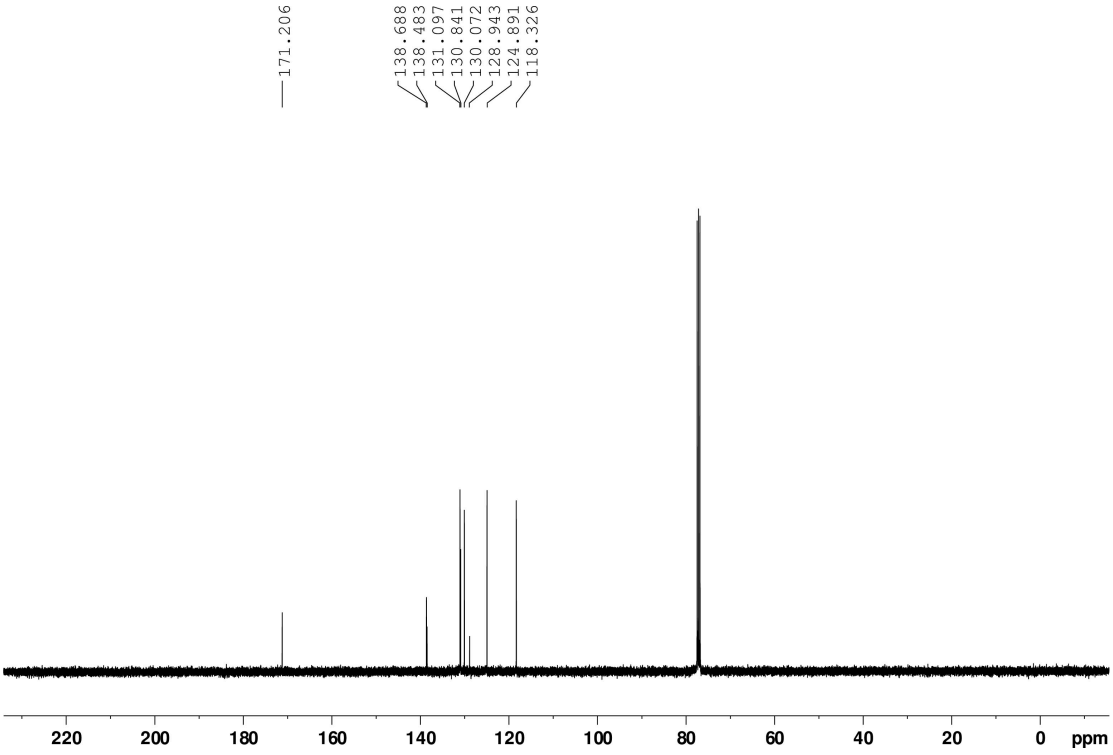


Compound **228**

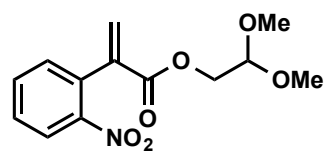


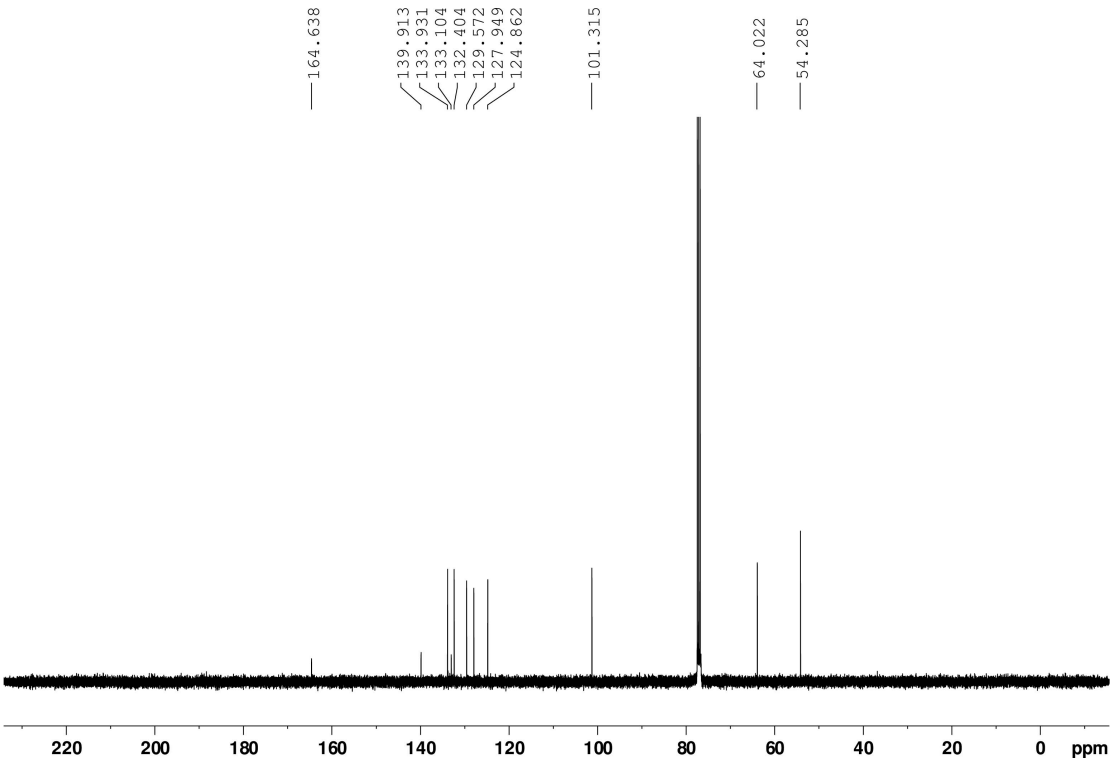
Compound **229**



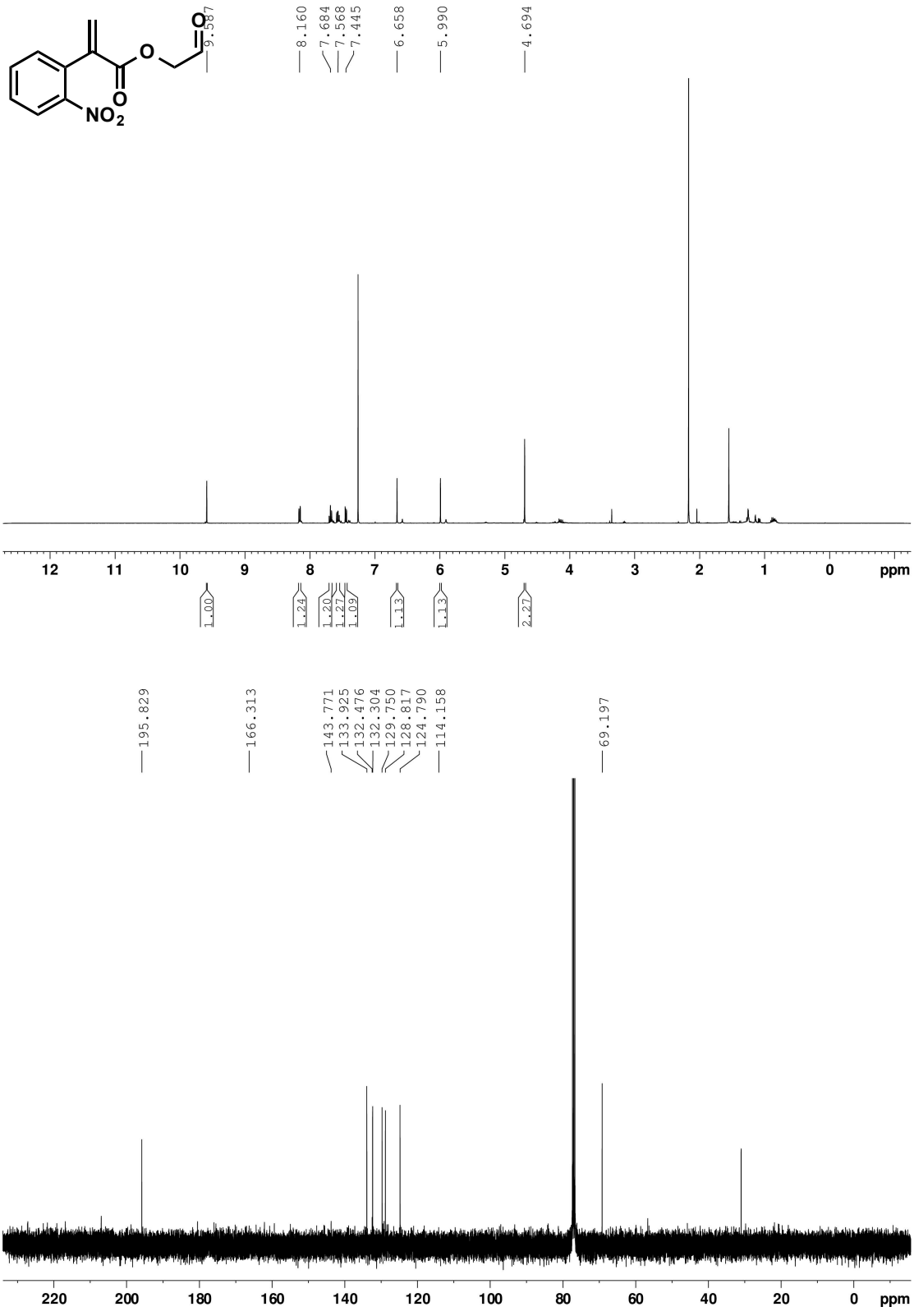


Compound **210**

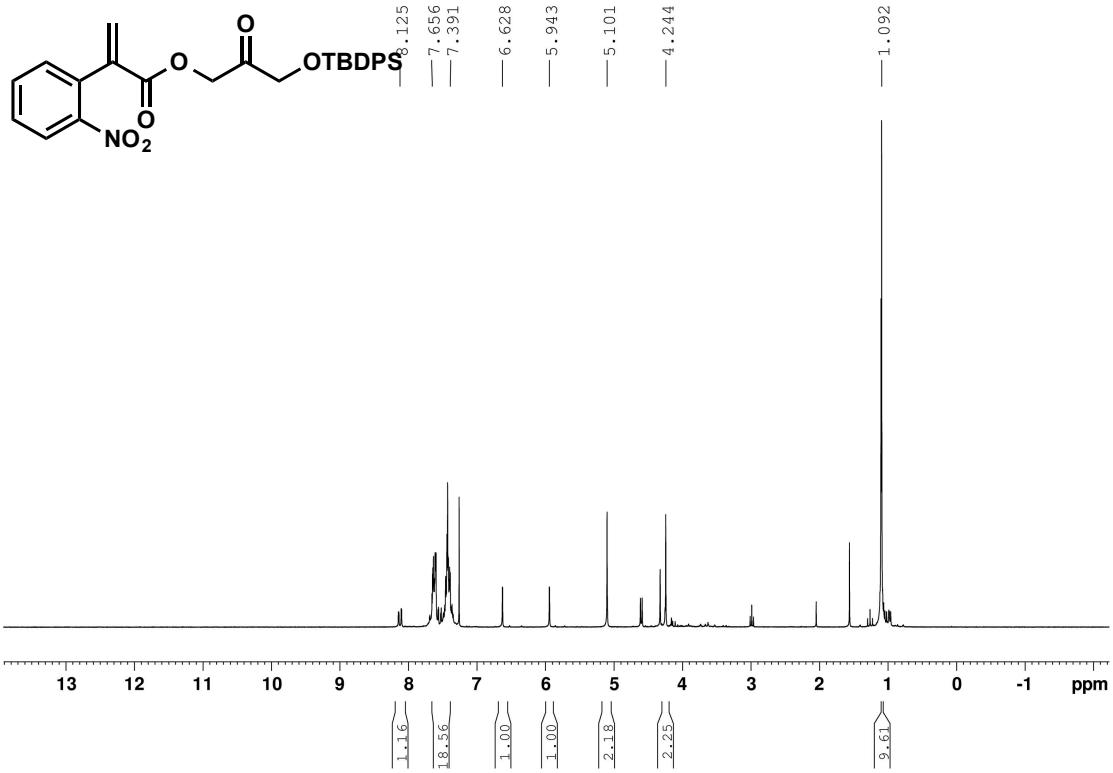




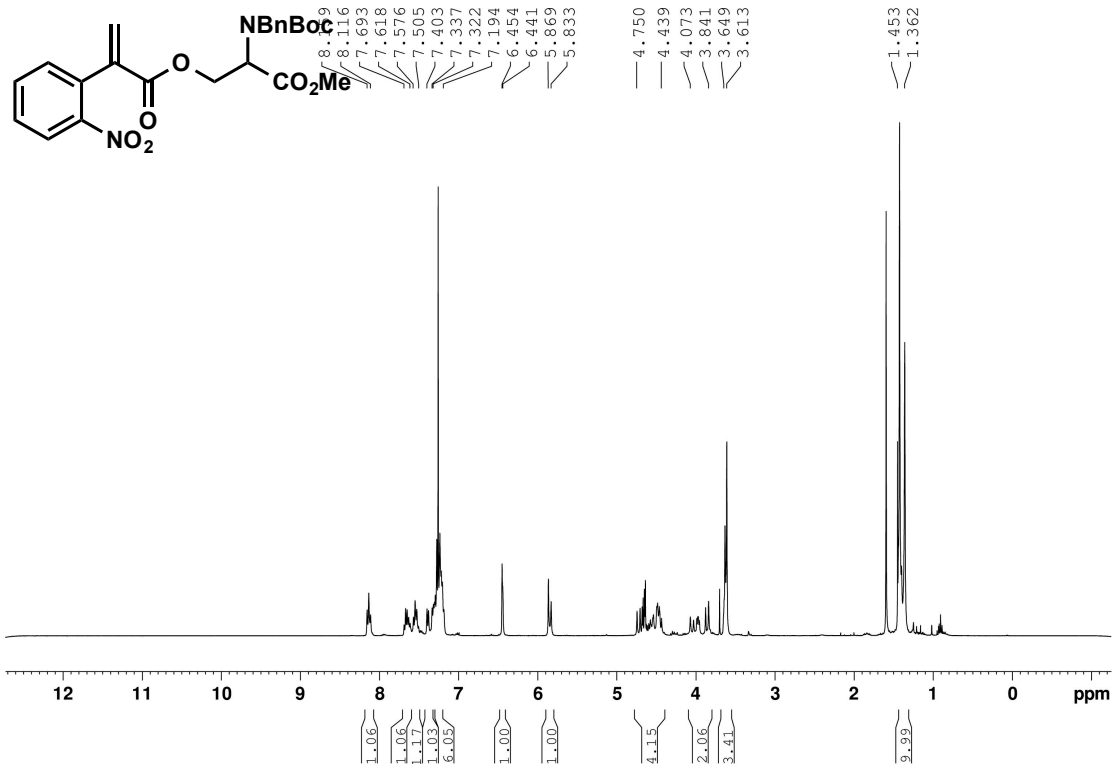
Compound **211**



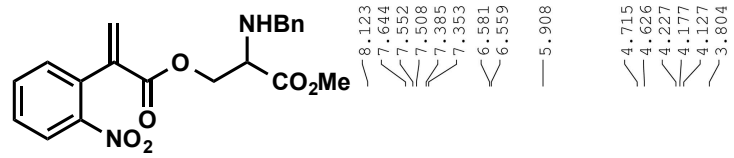
Compound **213**

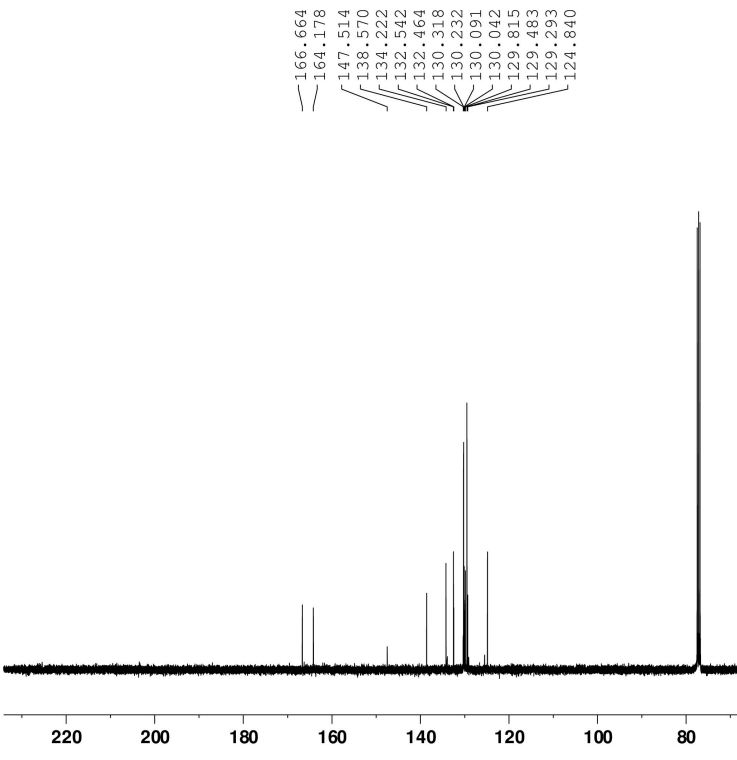


Compound **215**

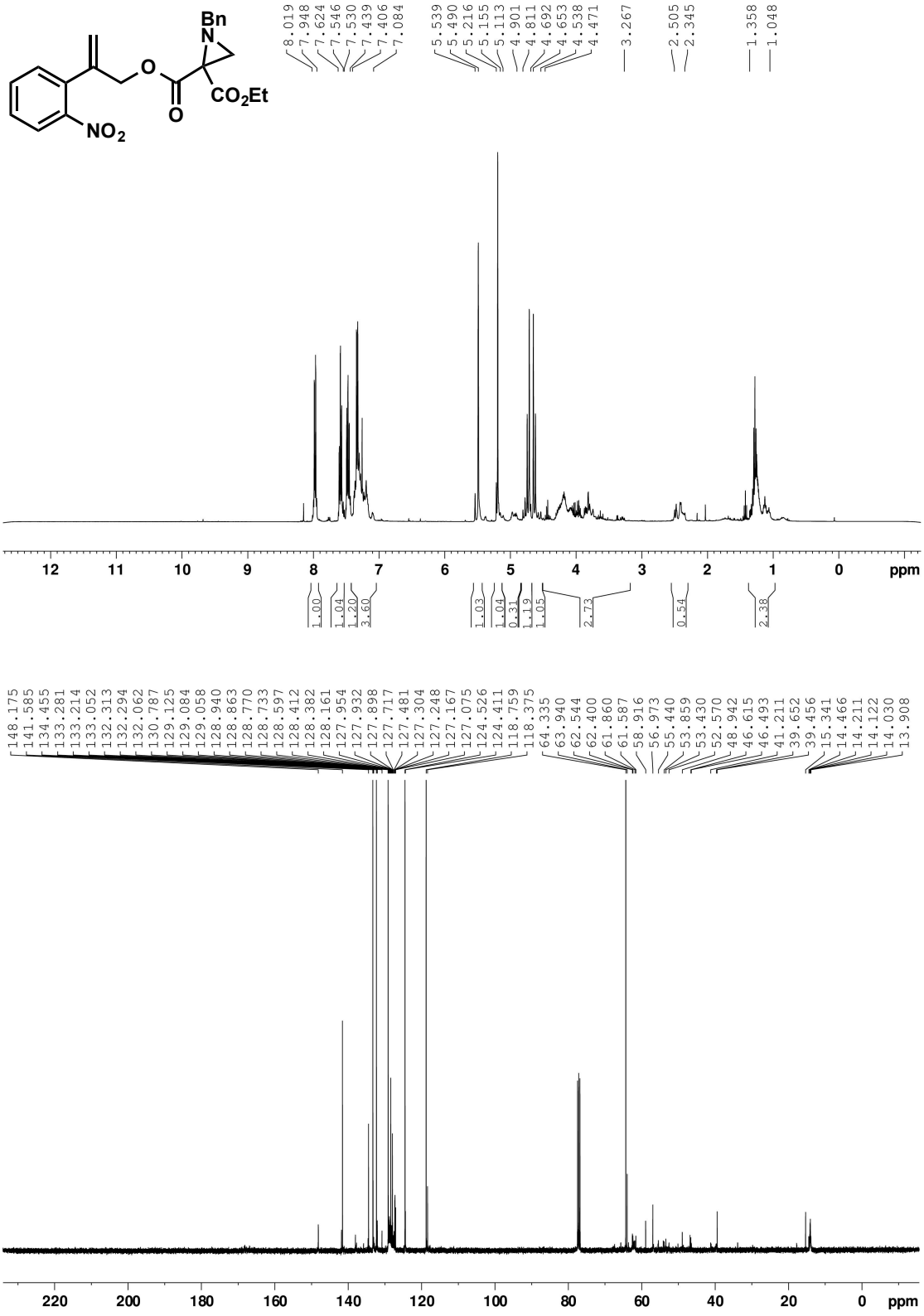


Compound **216**

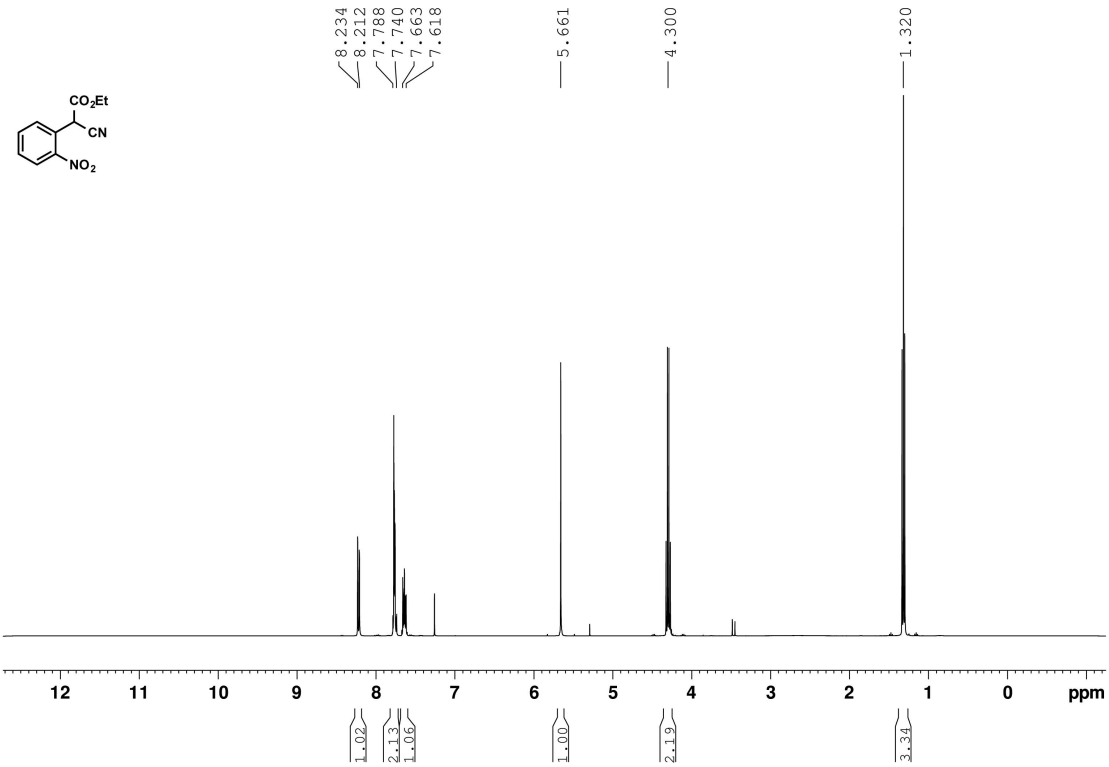


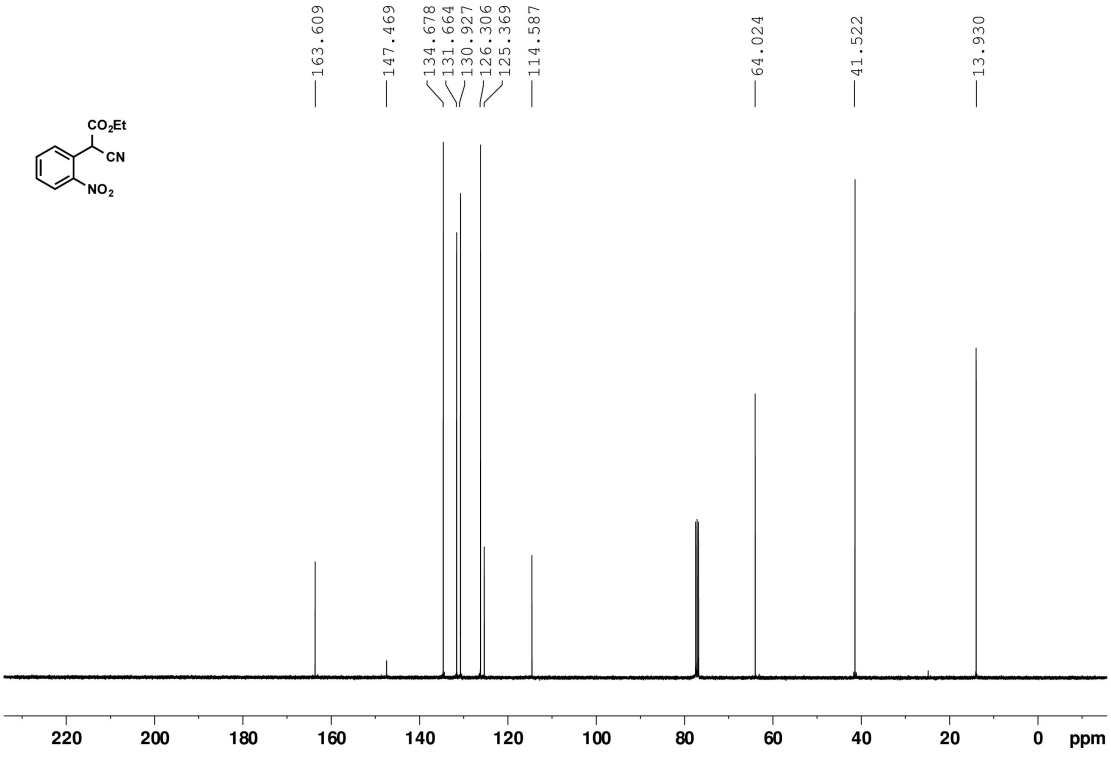


Compound **224**

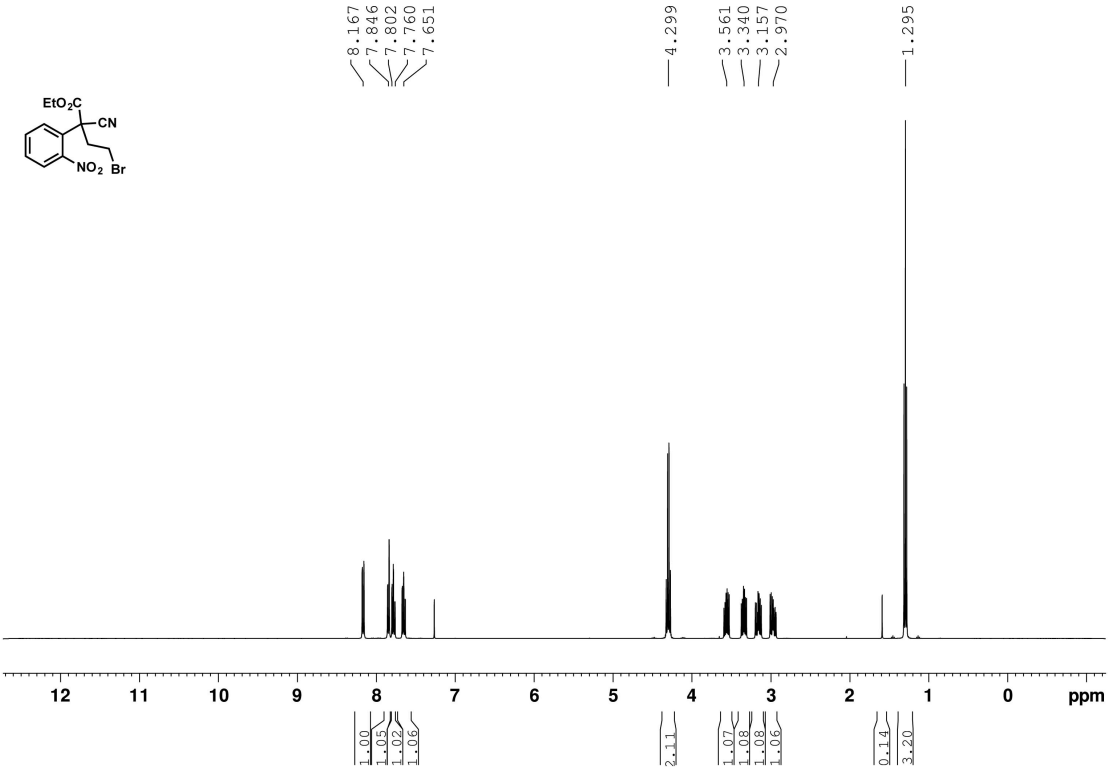


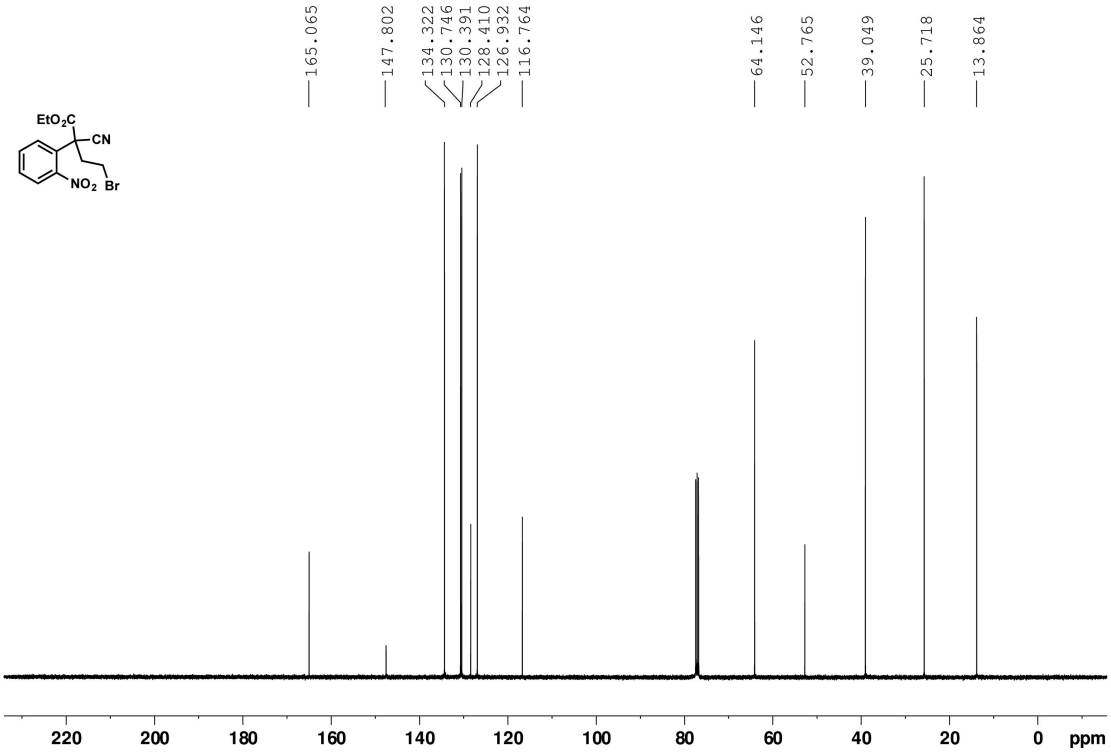
Compound **232**



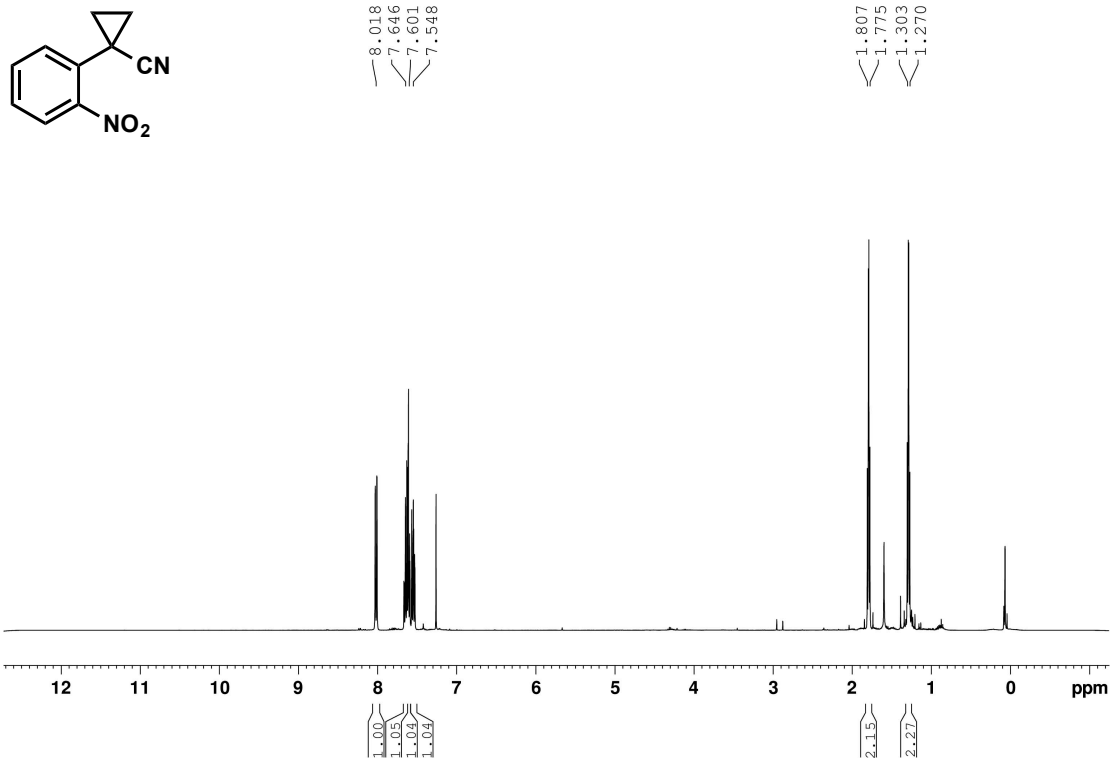


Compound **234**

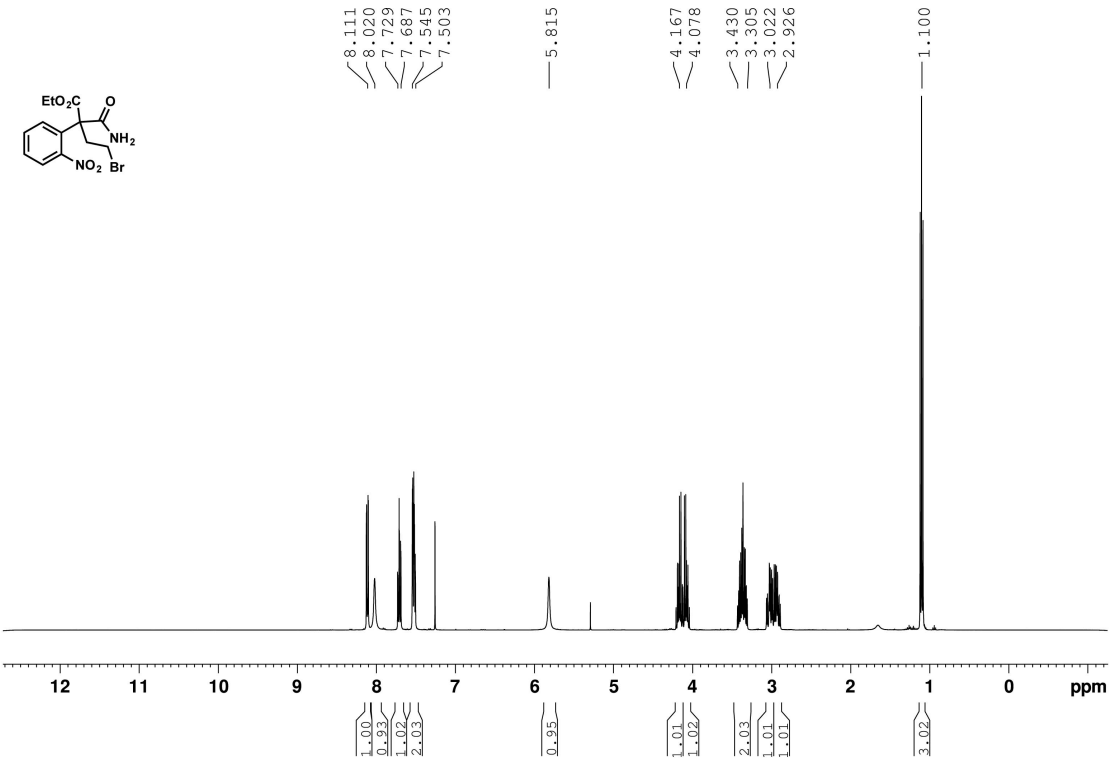


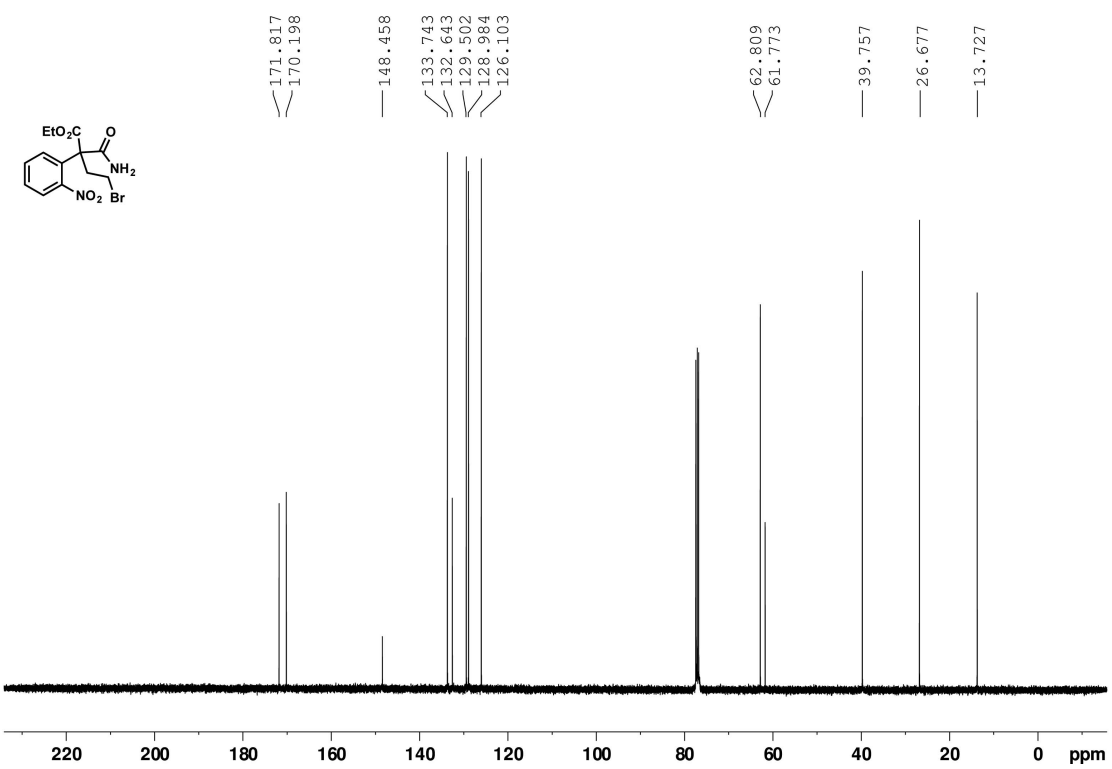


Compound **235**

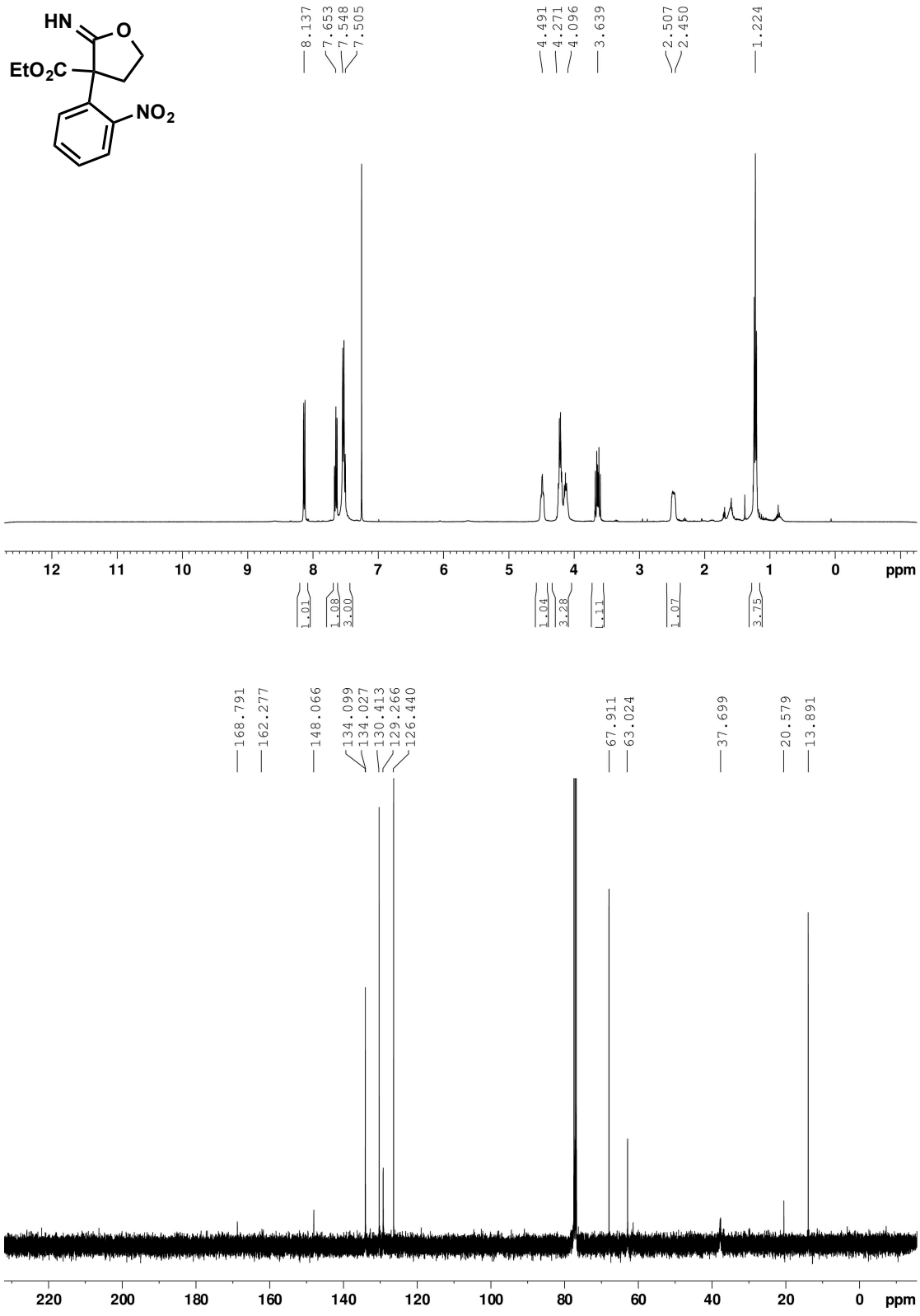


Compound **236**

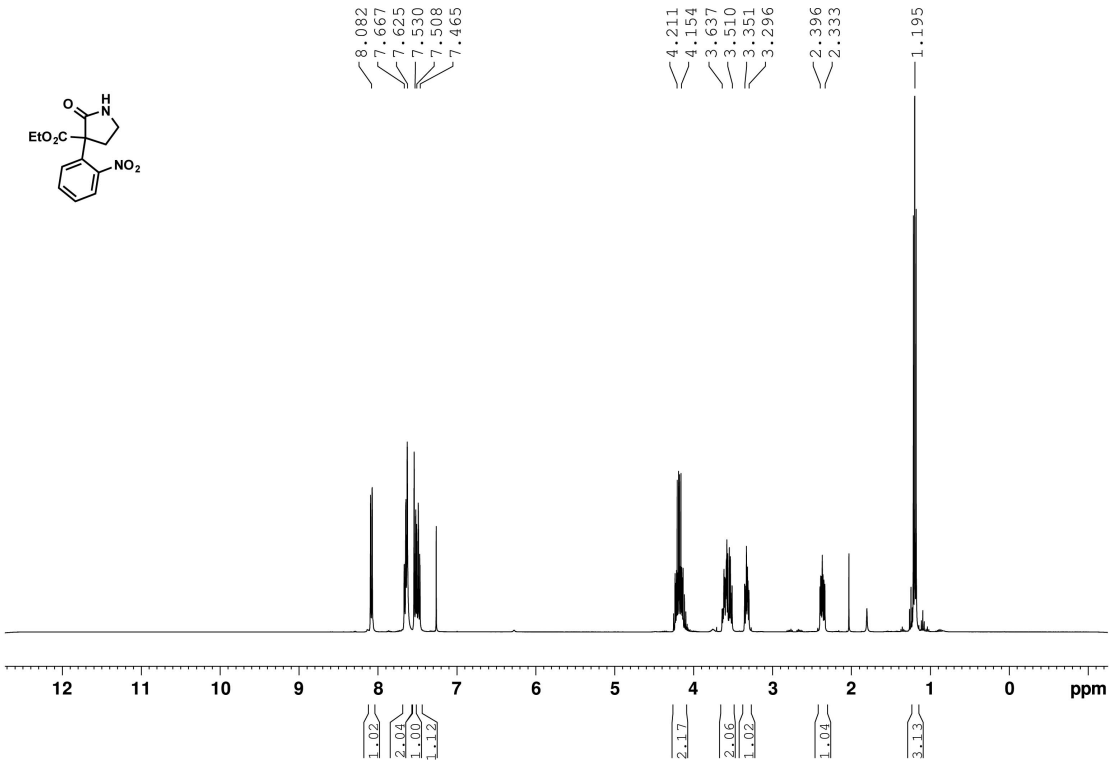


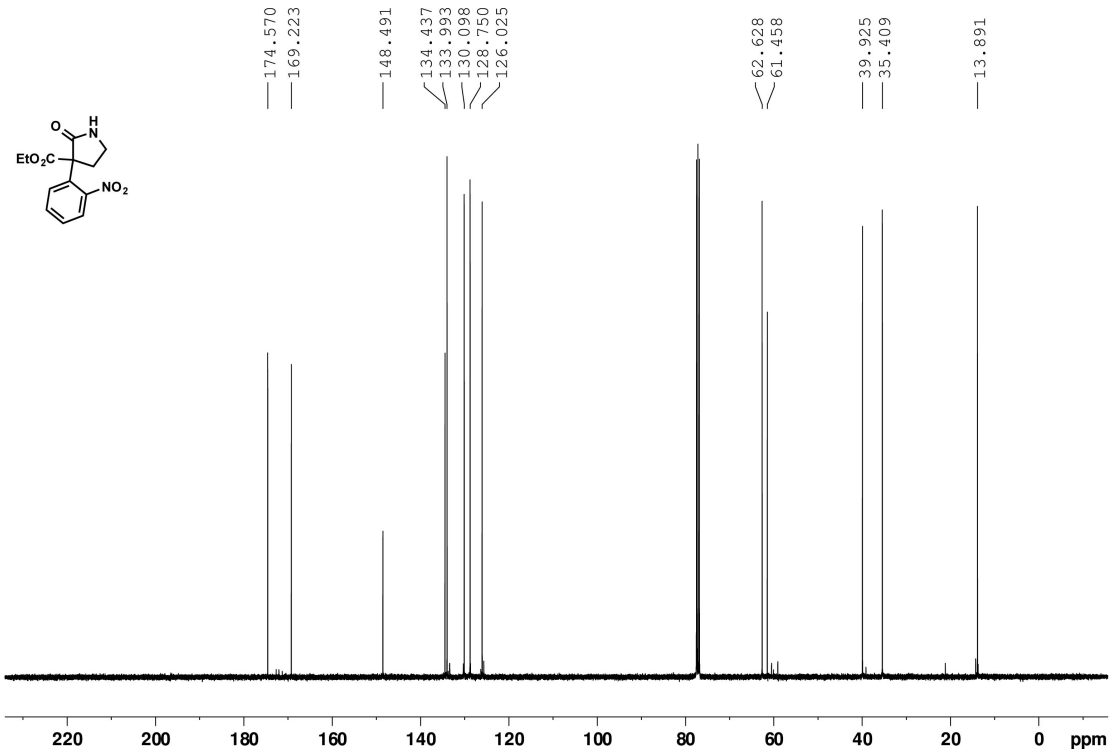


Compound **237**

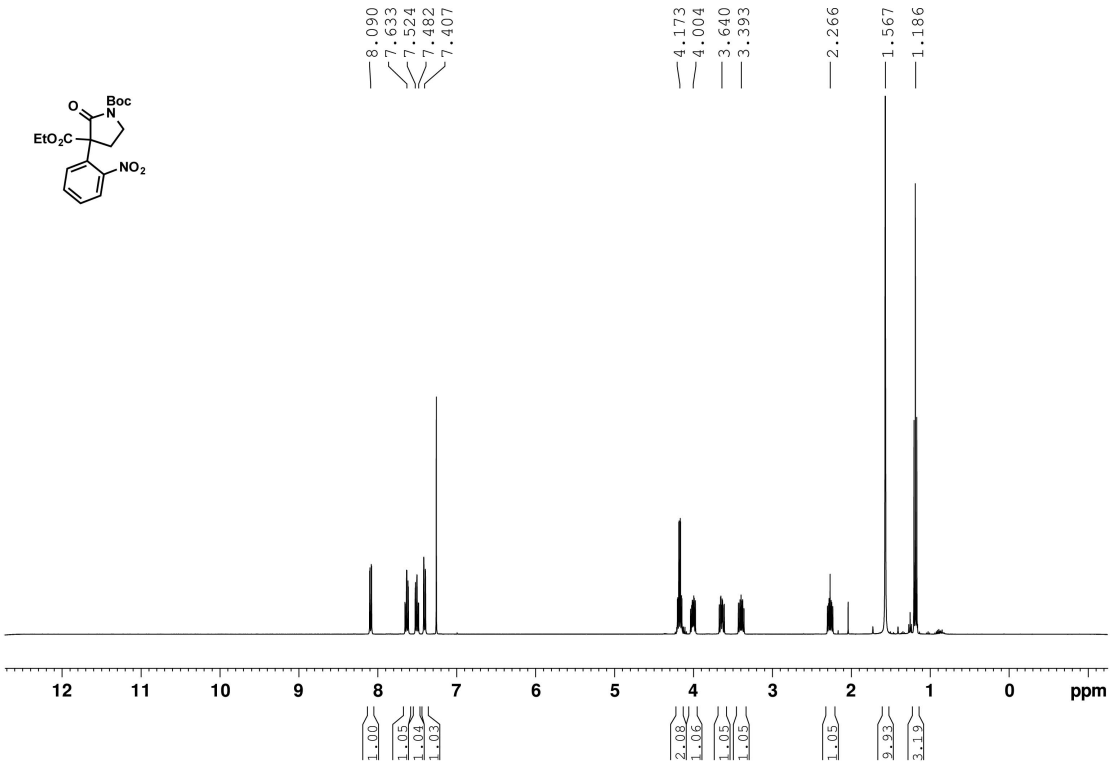


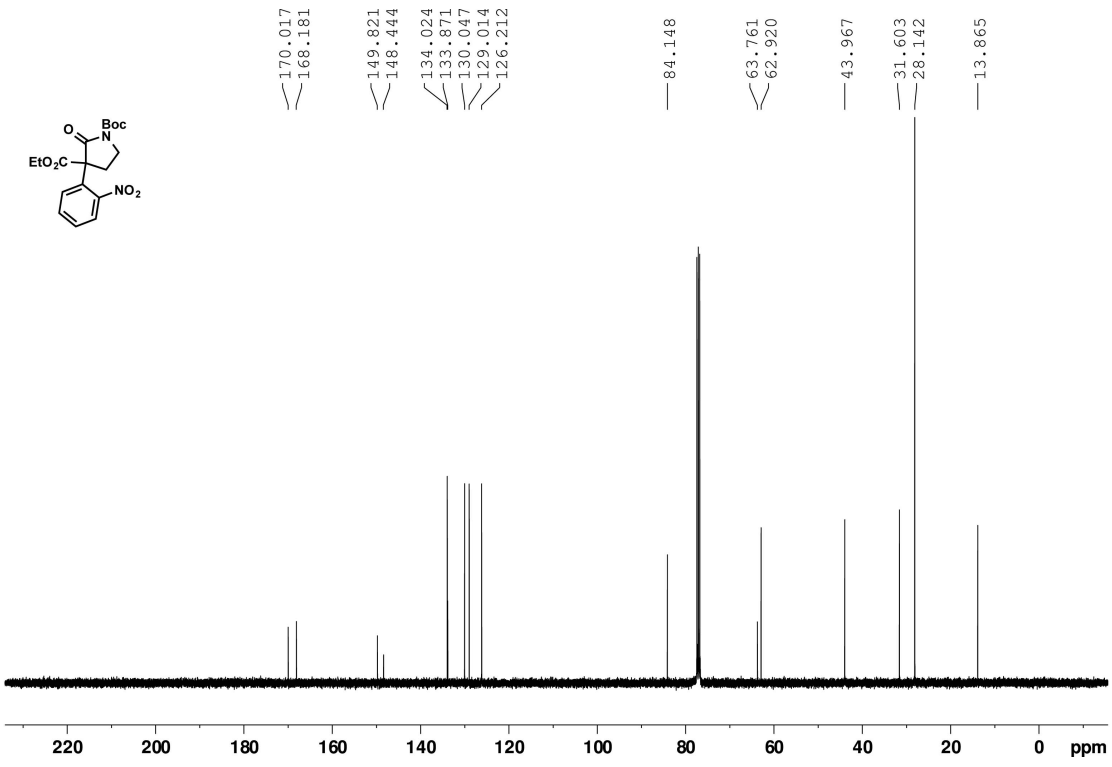
Compound **238a**



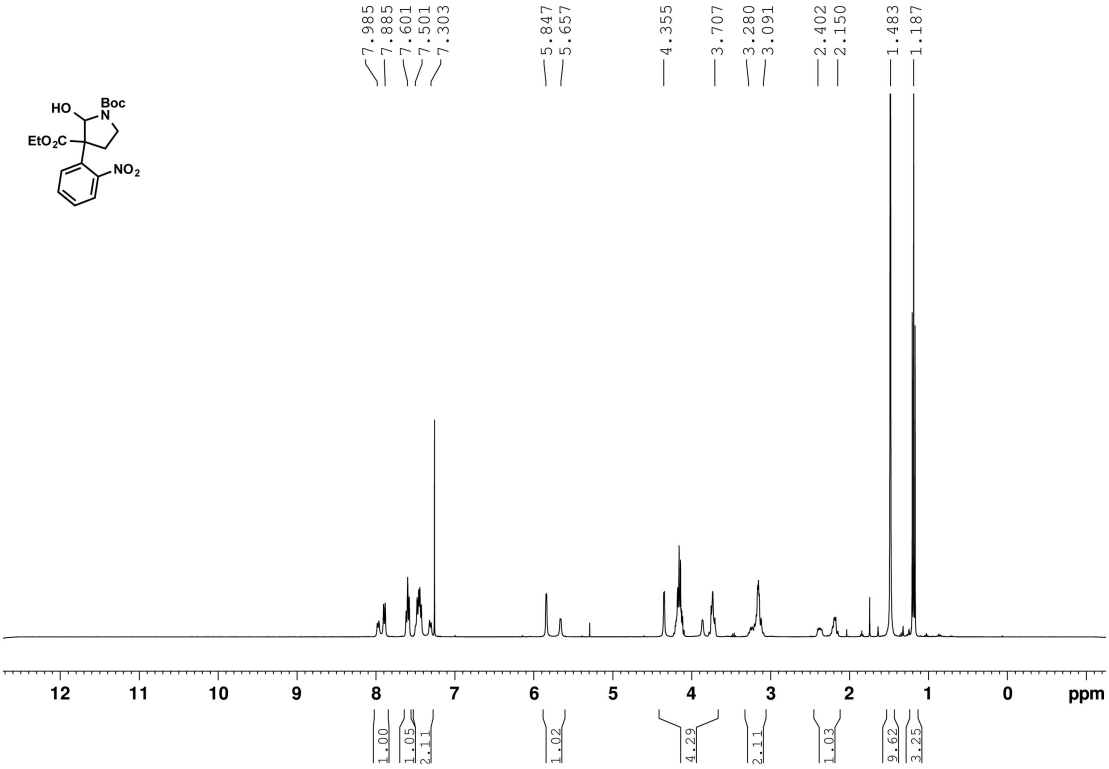


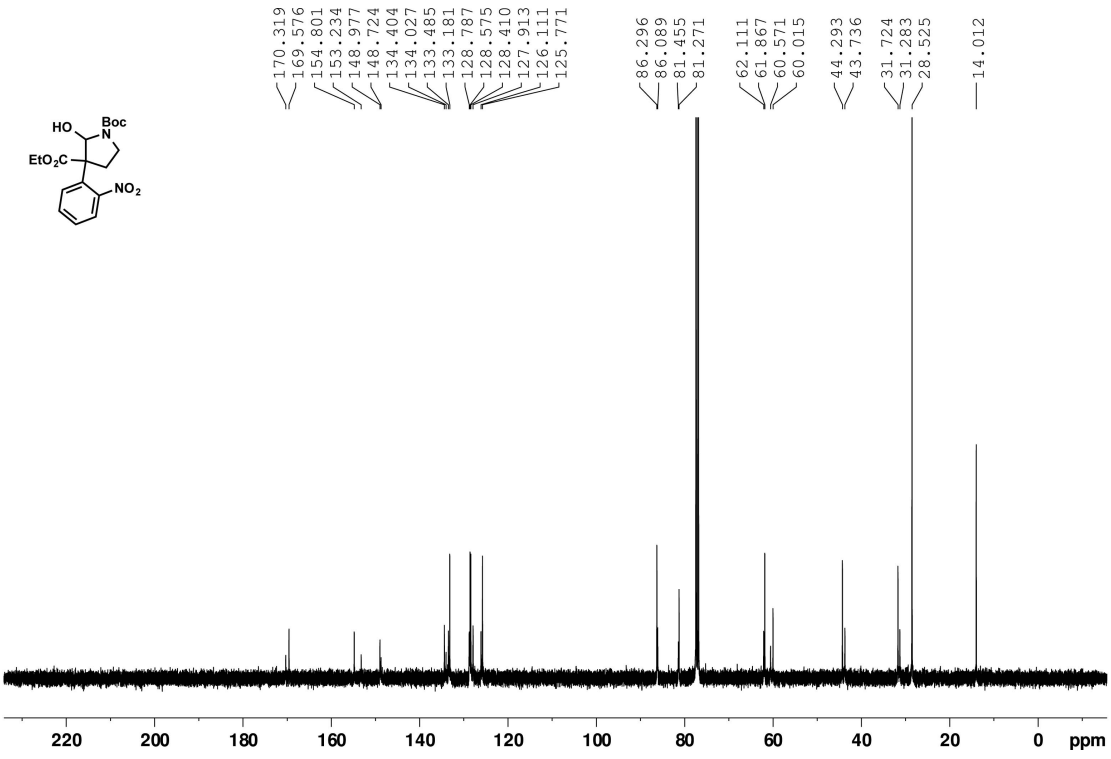
Compound **238**



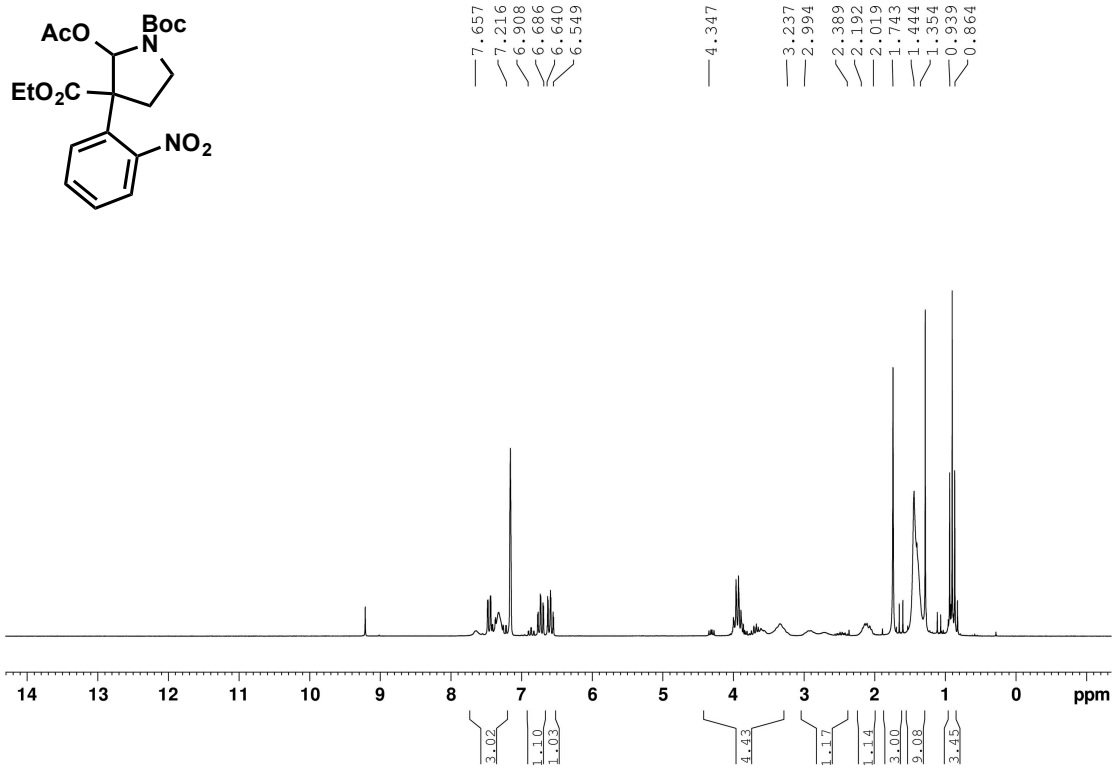


Compound **239**

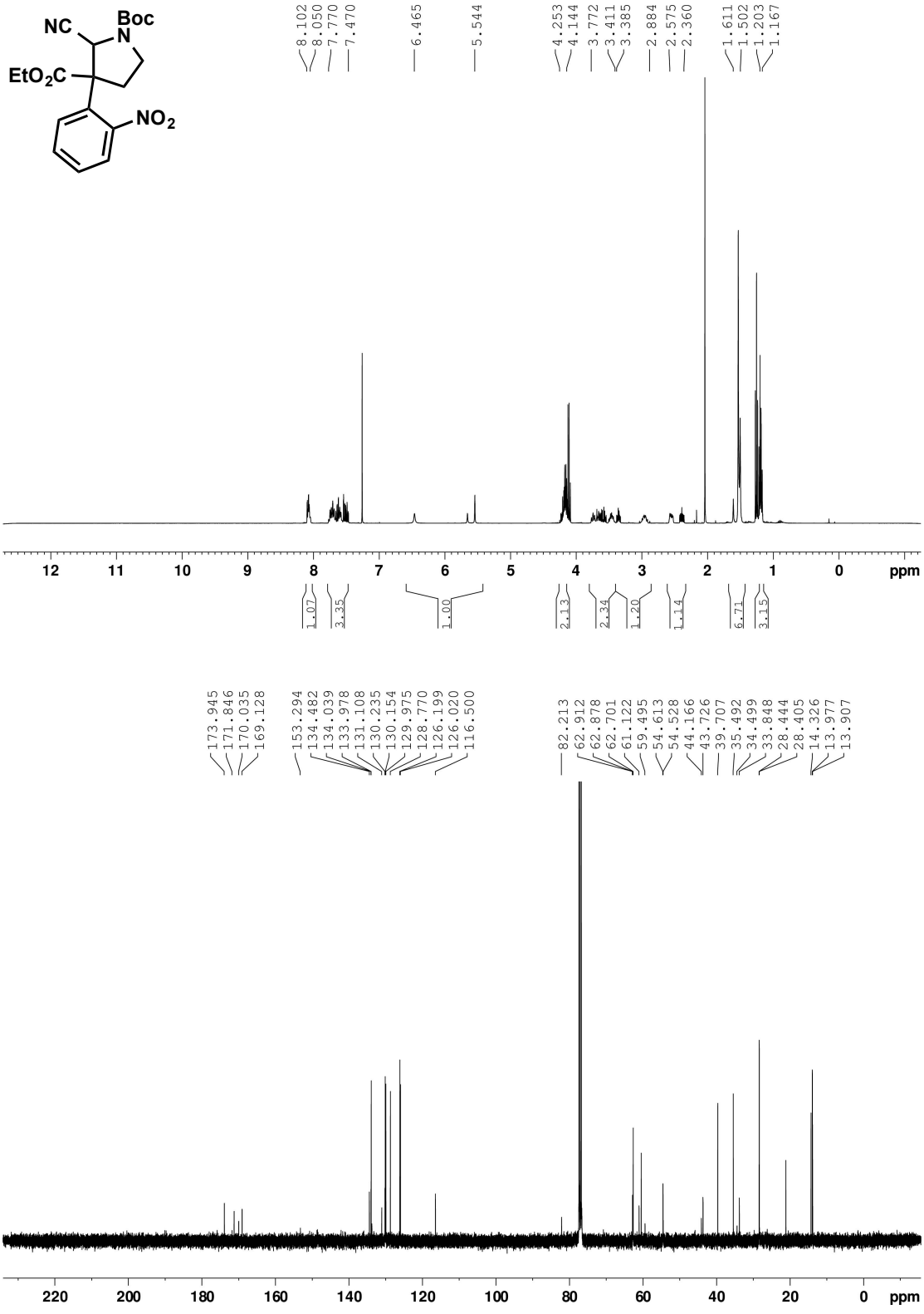




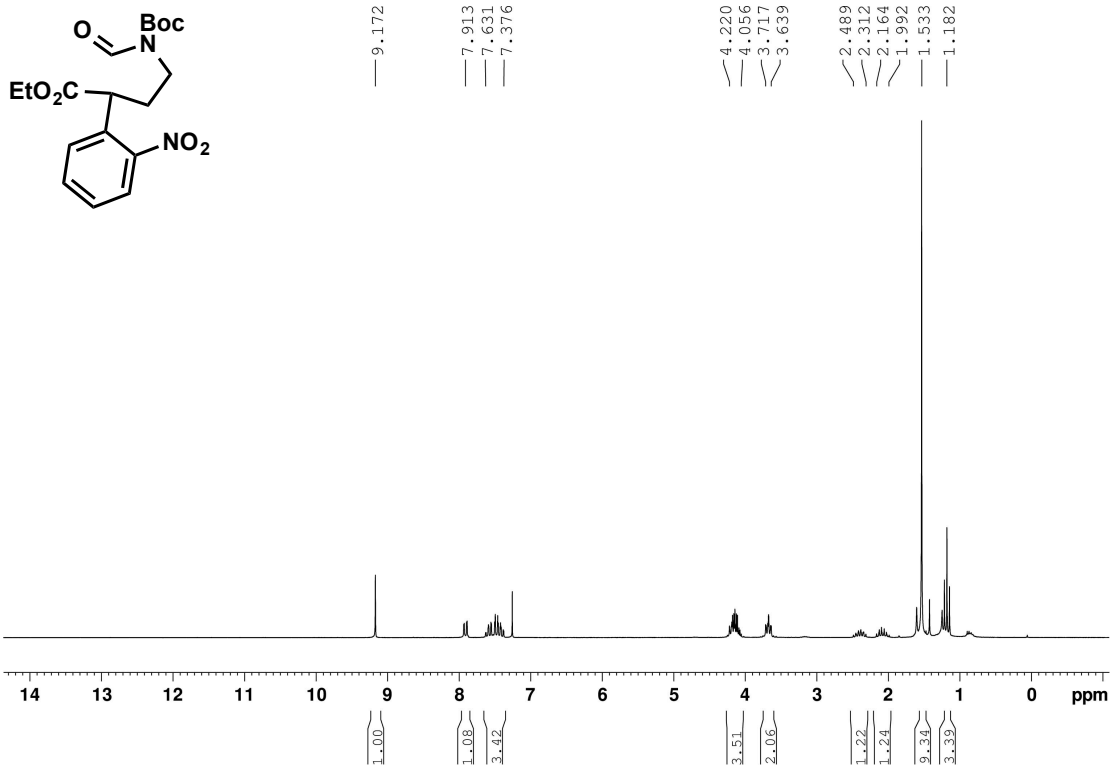
Compound **246**



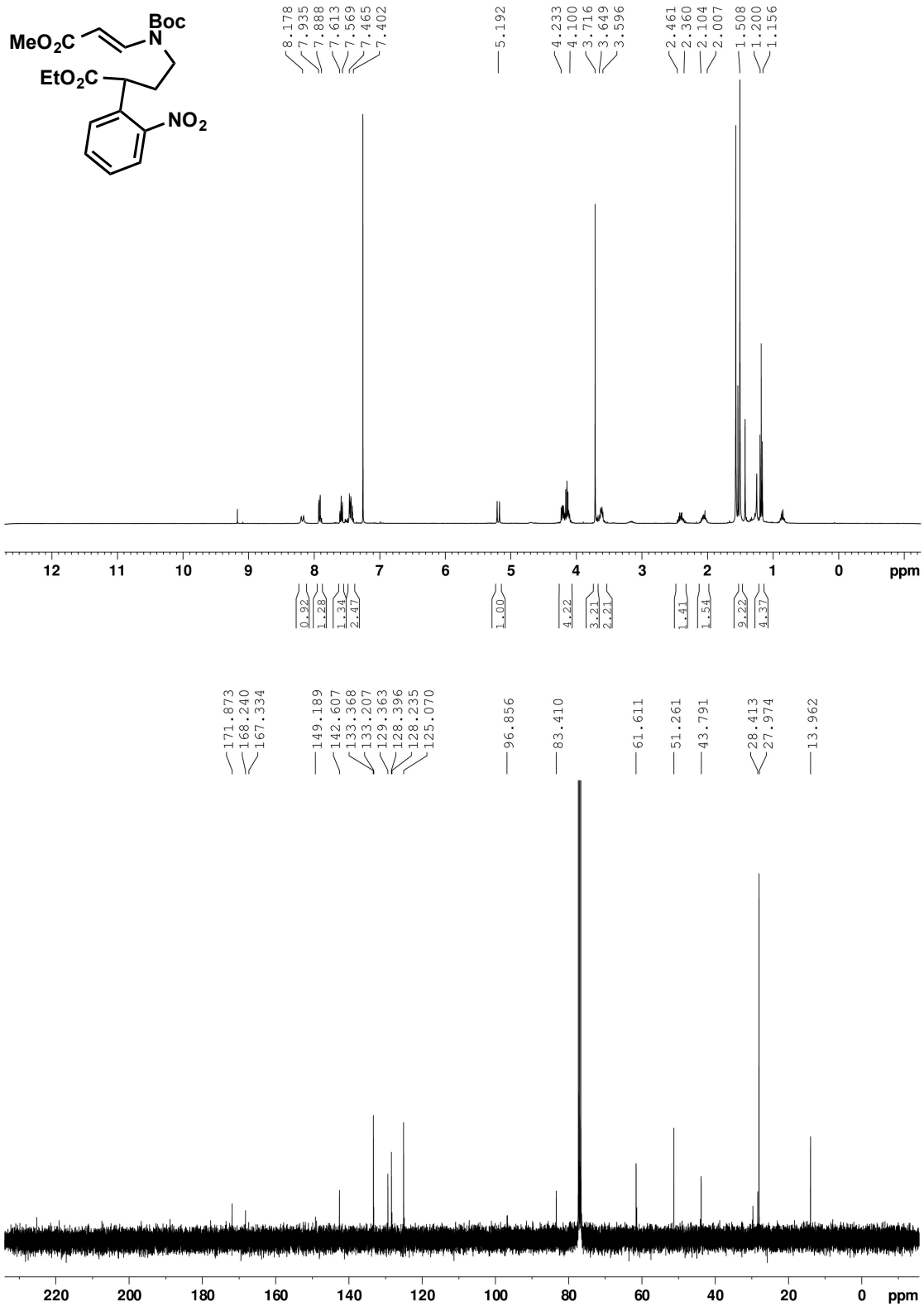
Compound **247**



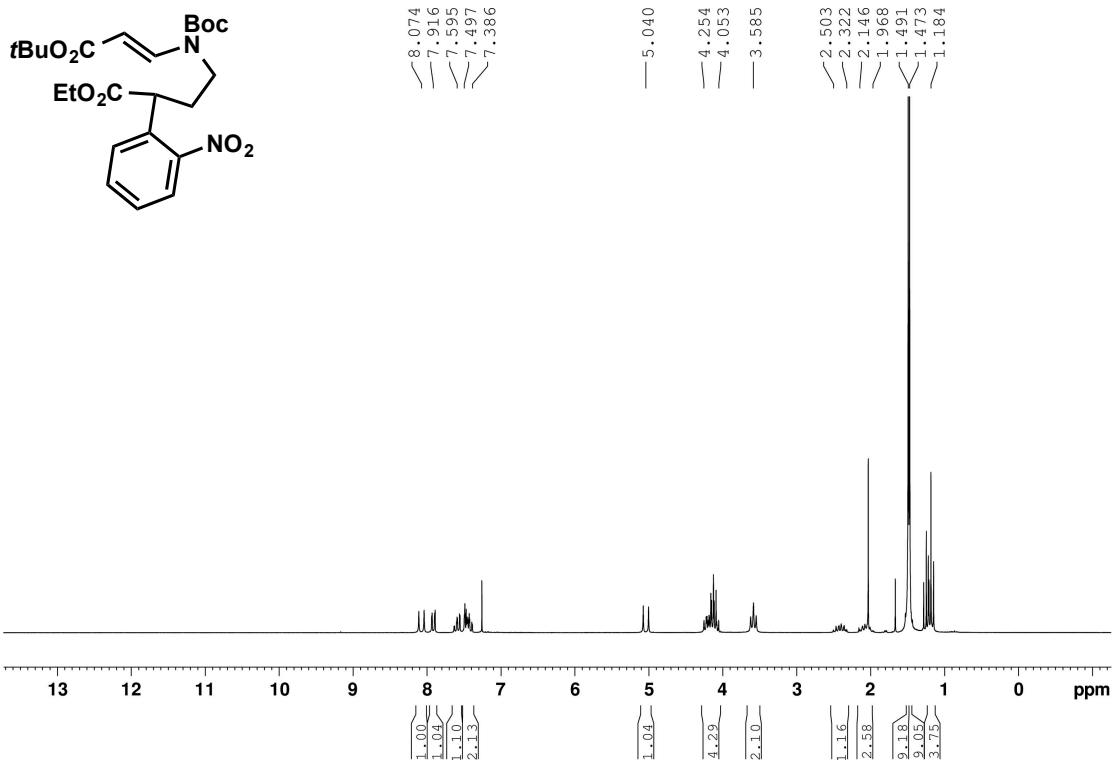
Compound **240**



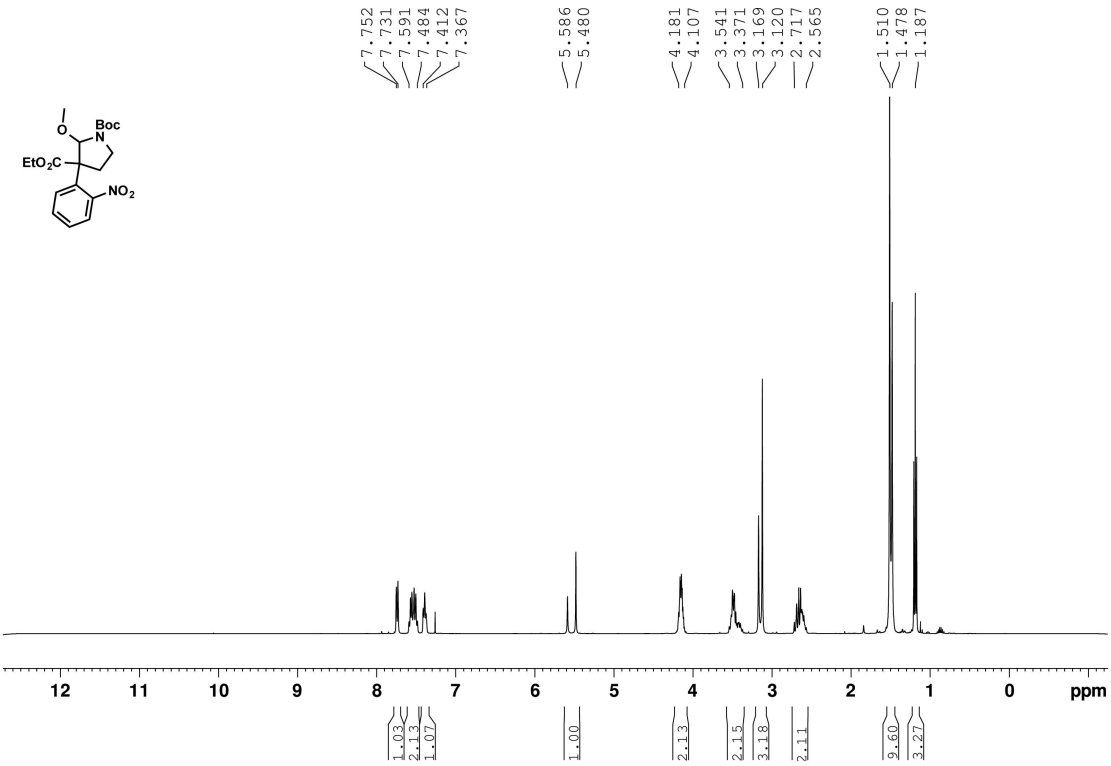
Compound **244**

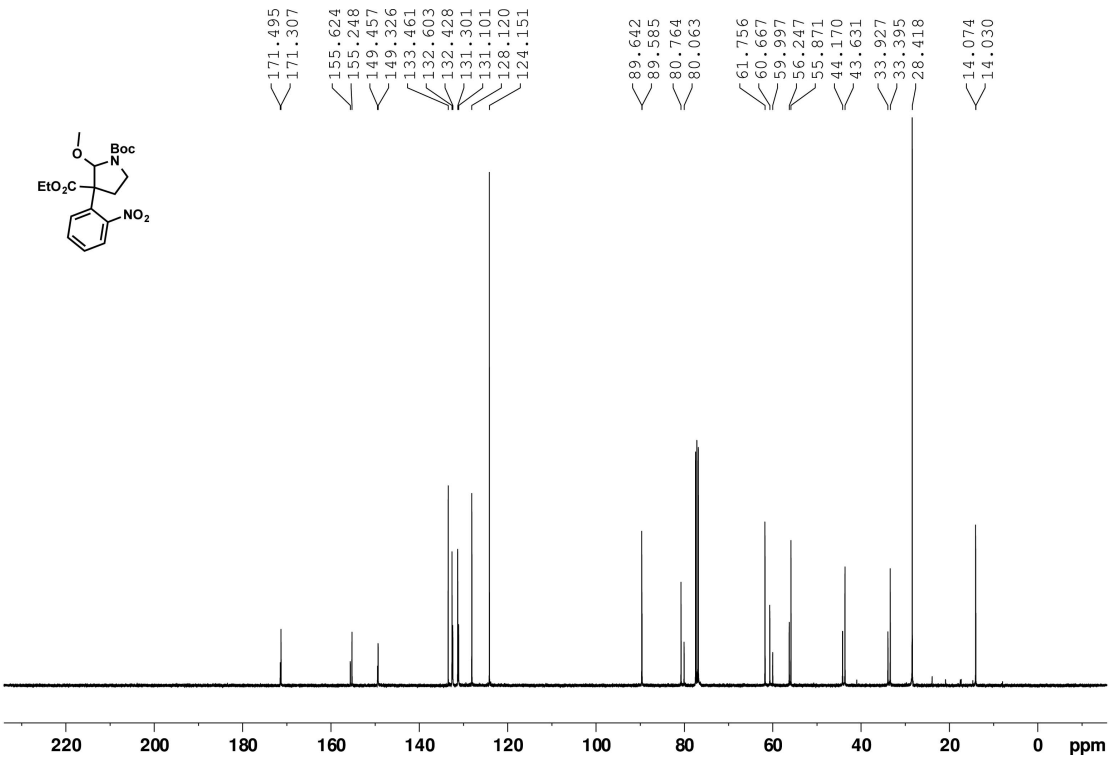


Compound **242**

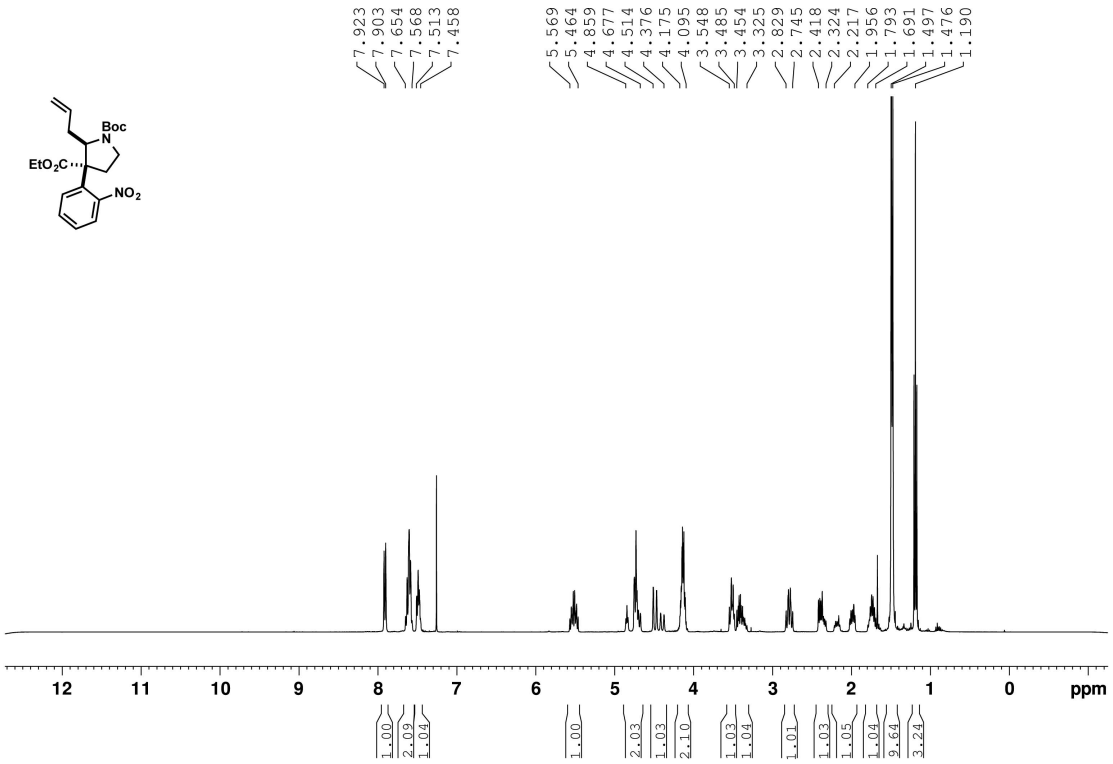


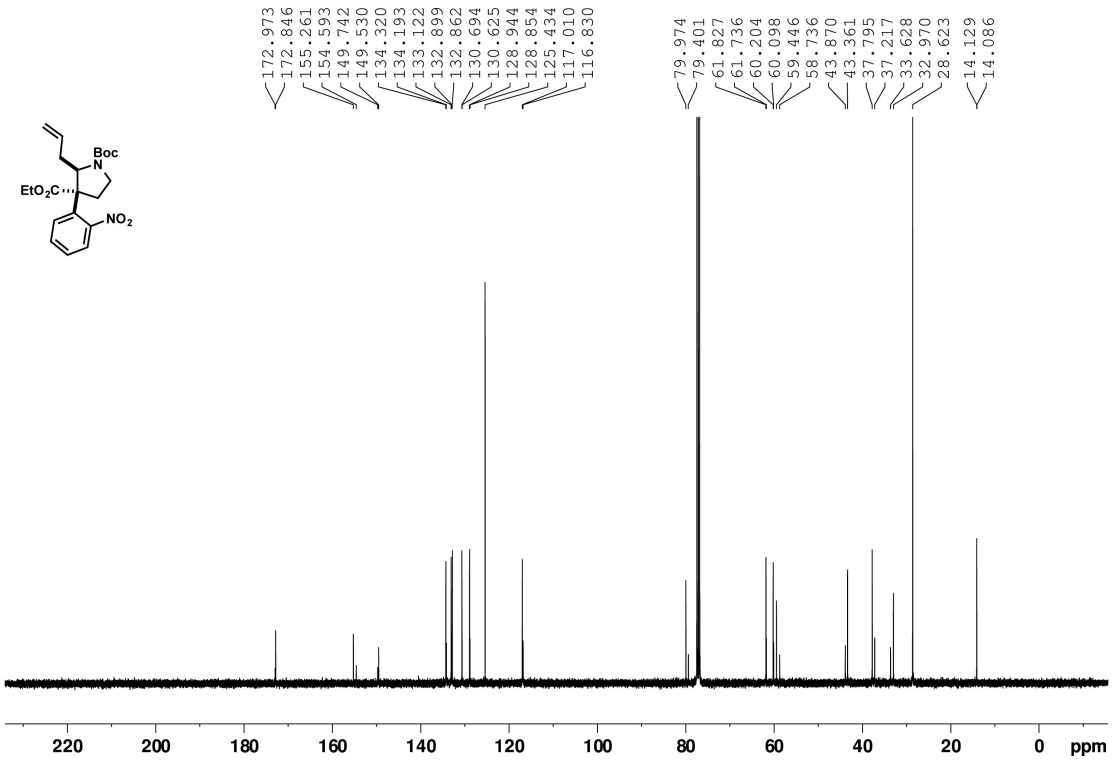
Compound **239b**



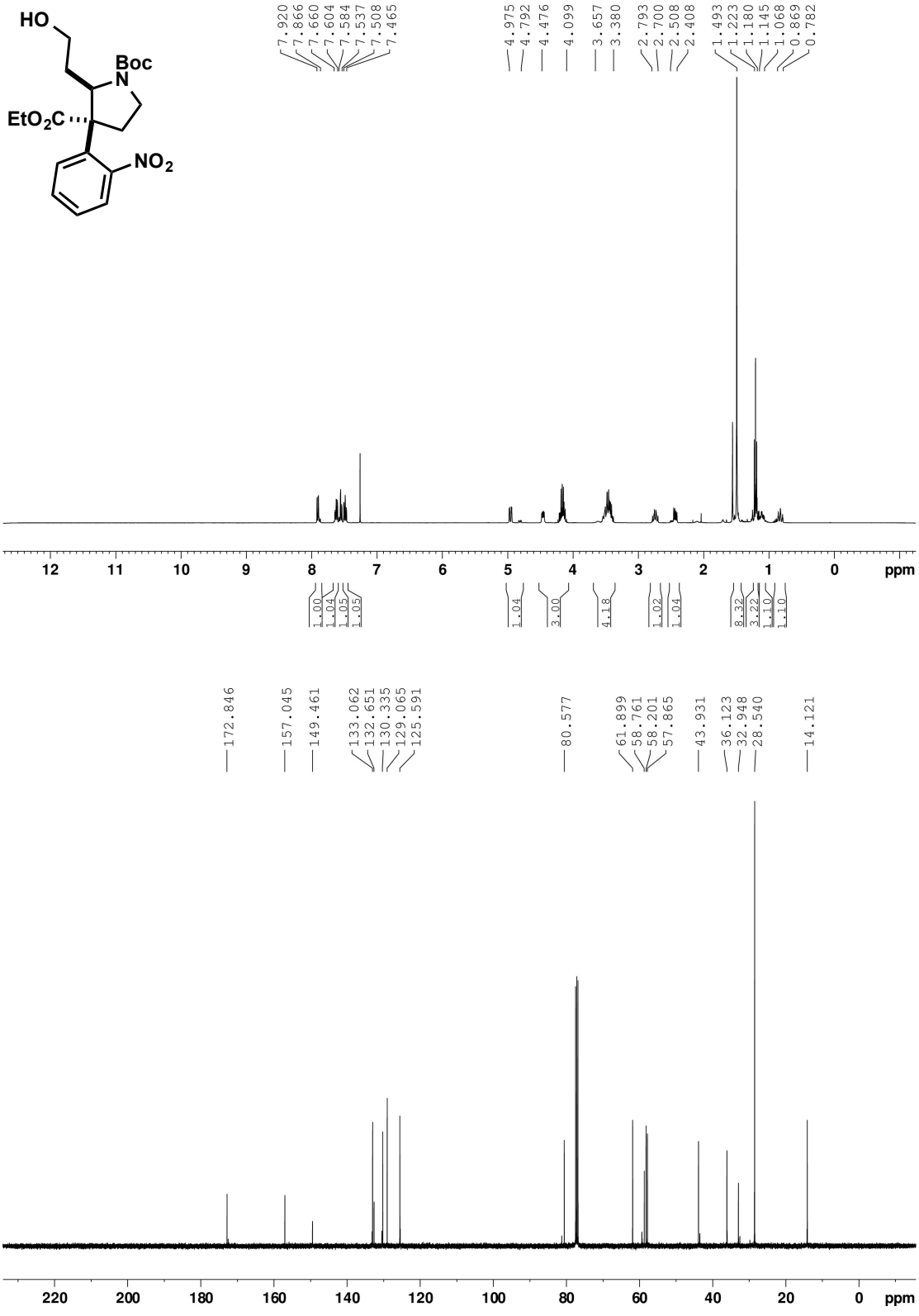


Compound **248**

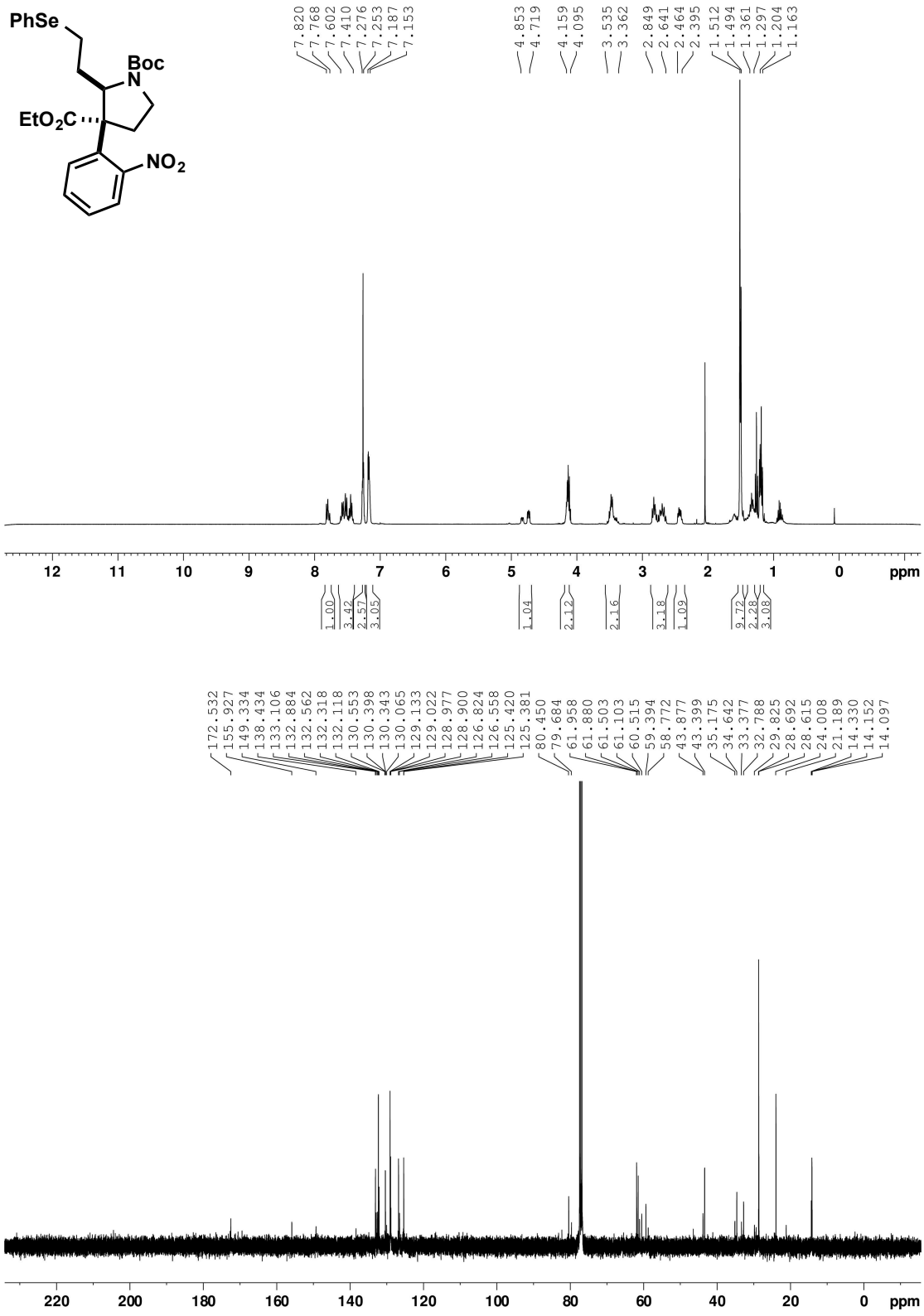




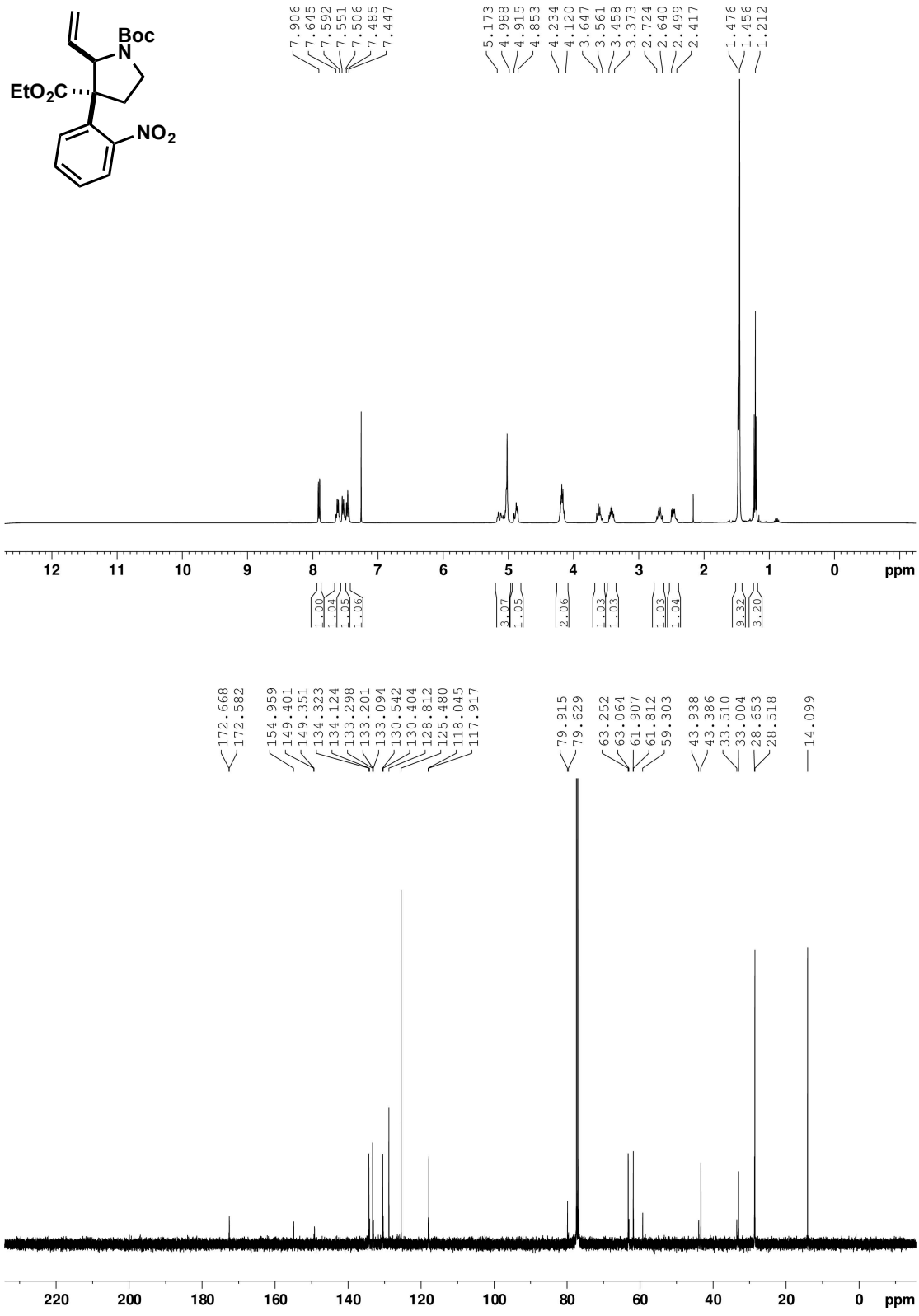
Compound **248b**



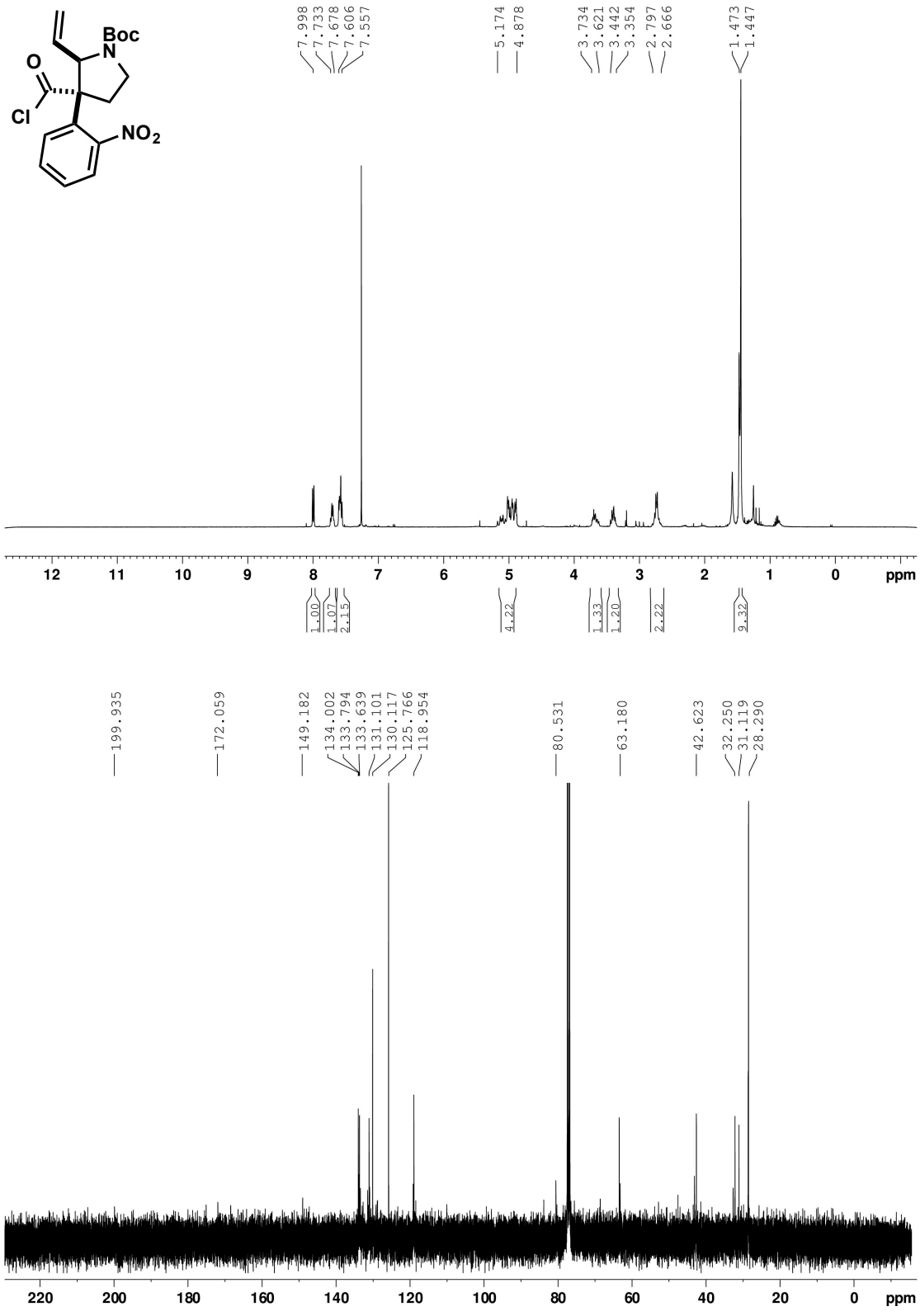
Compound **249**



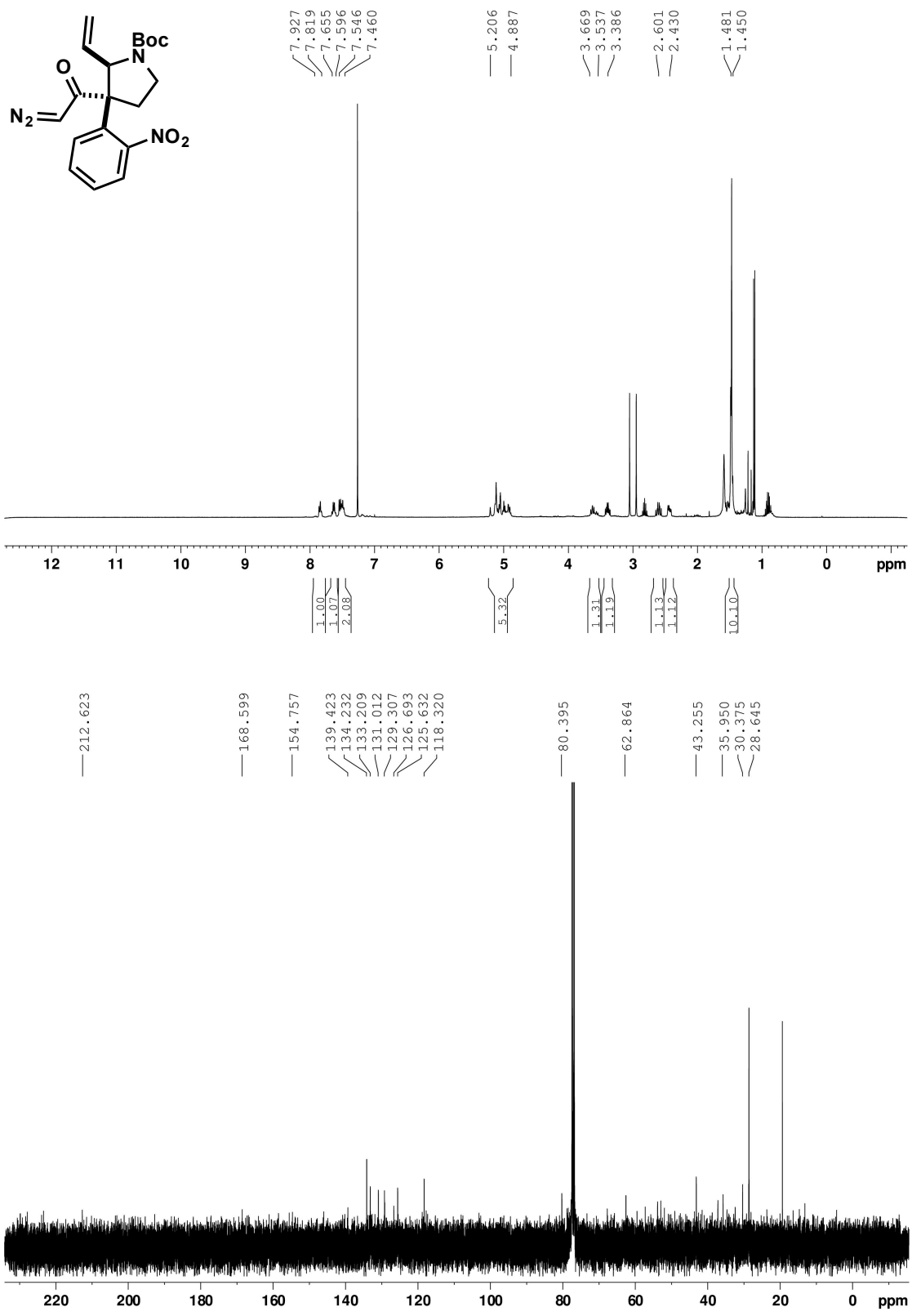
Compound **250**



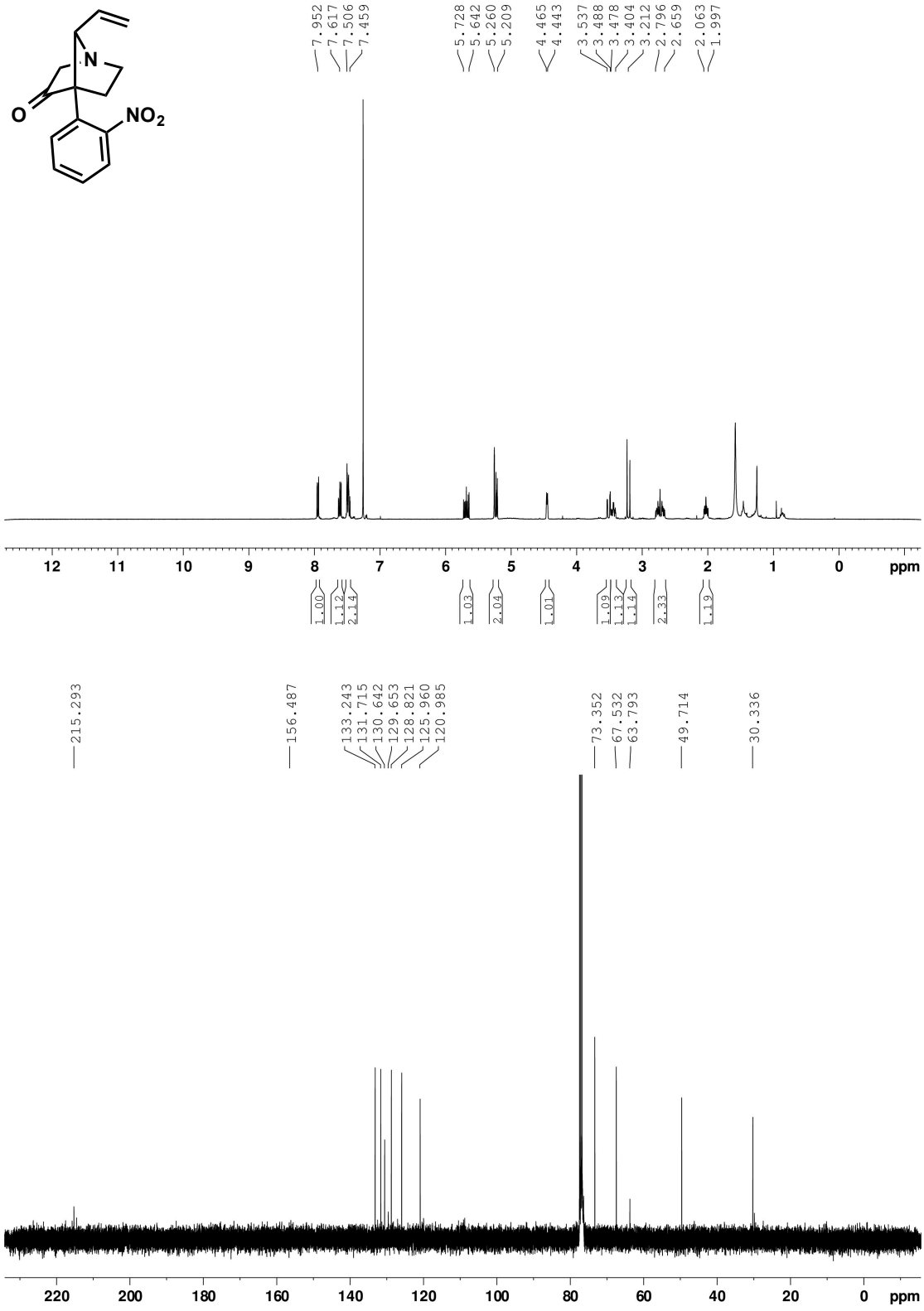
Compound **251**



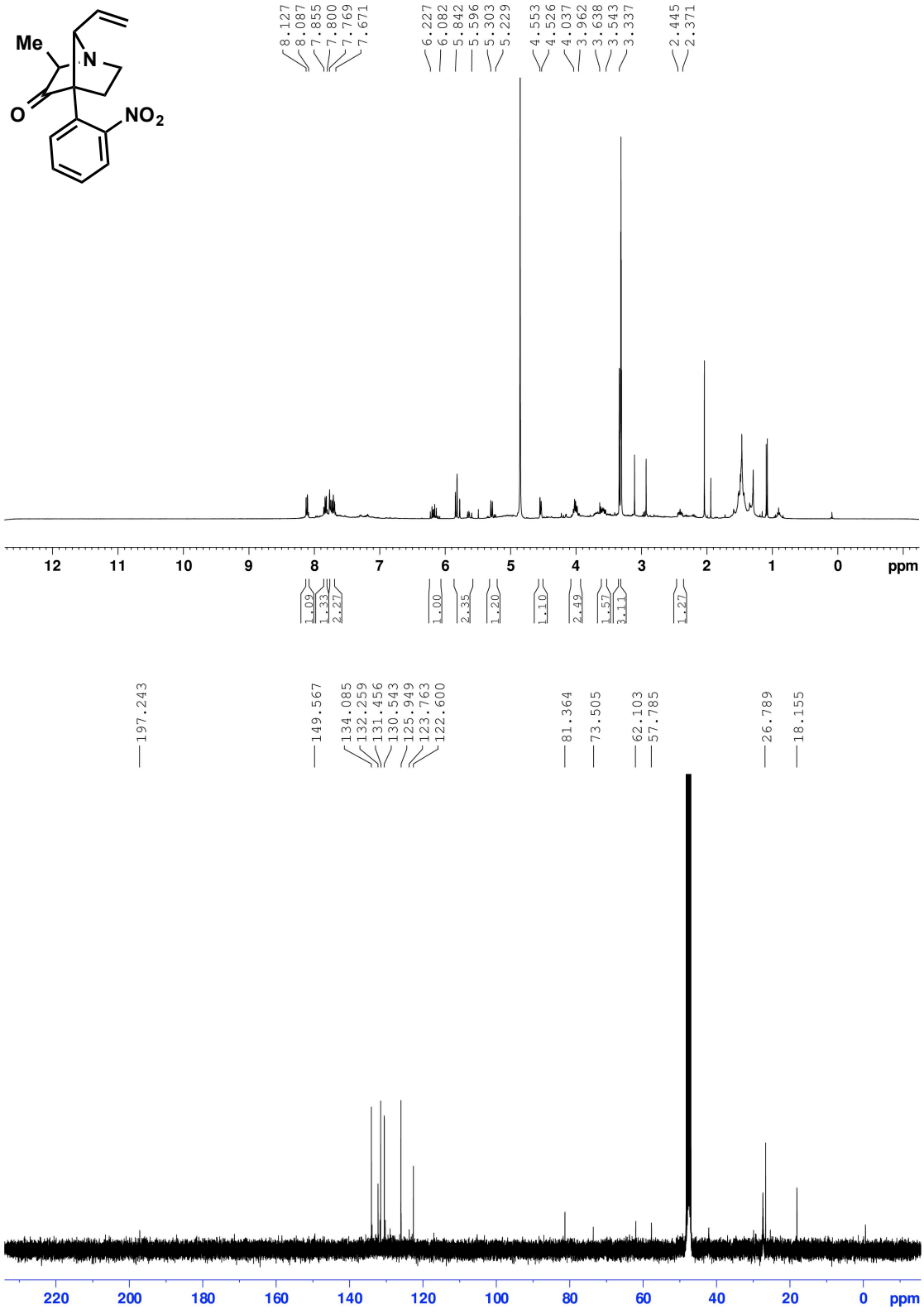
Compound **252**



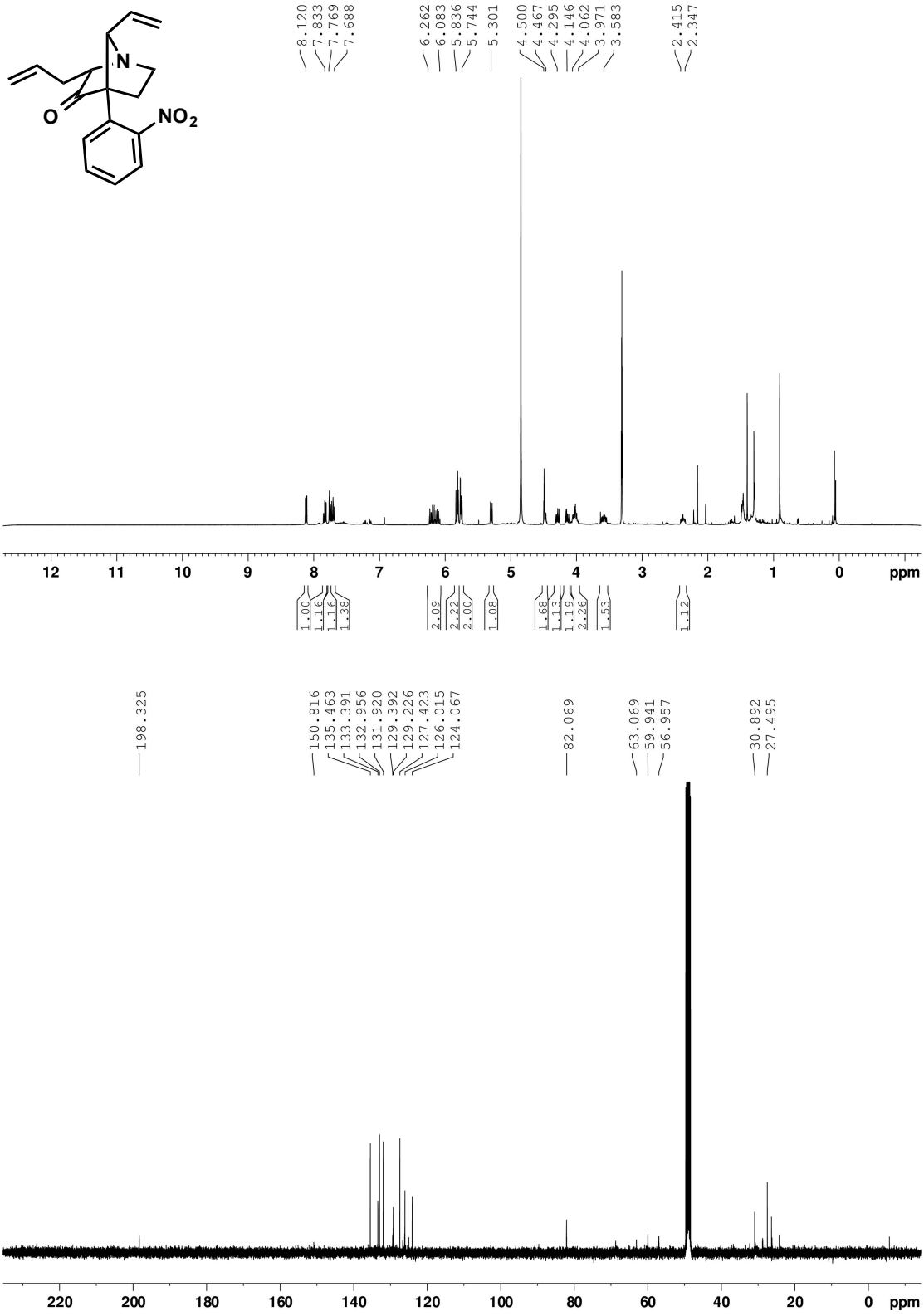
Compound **253**



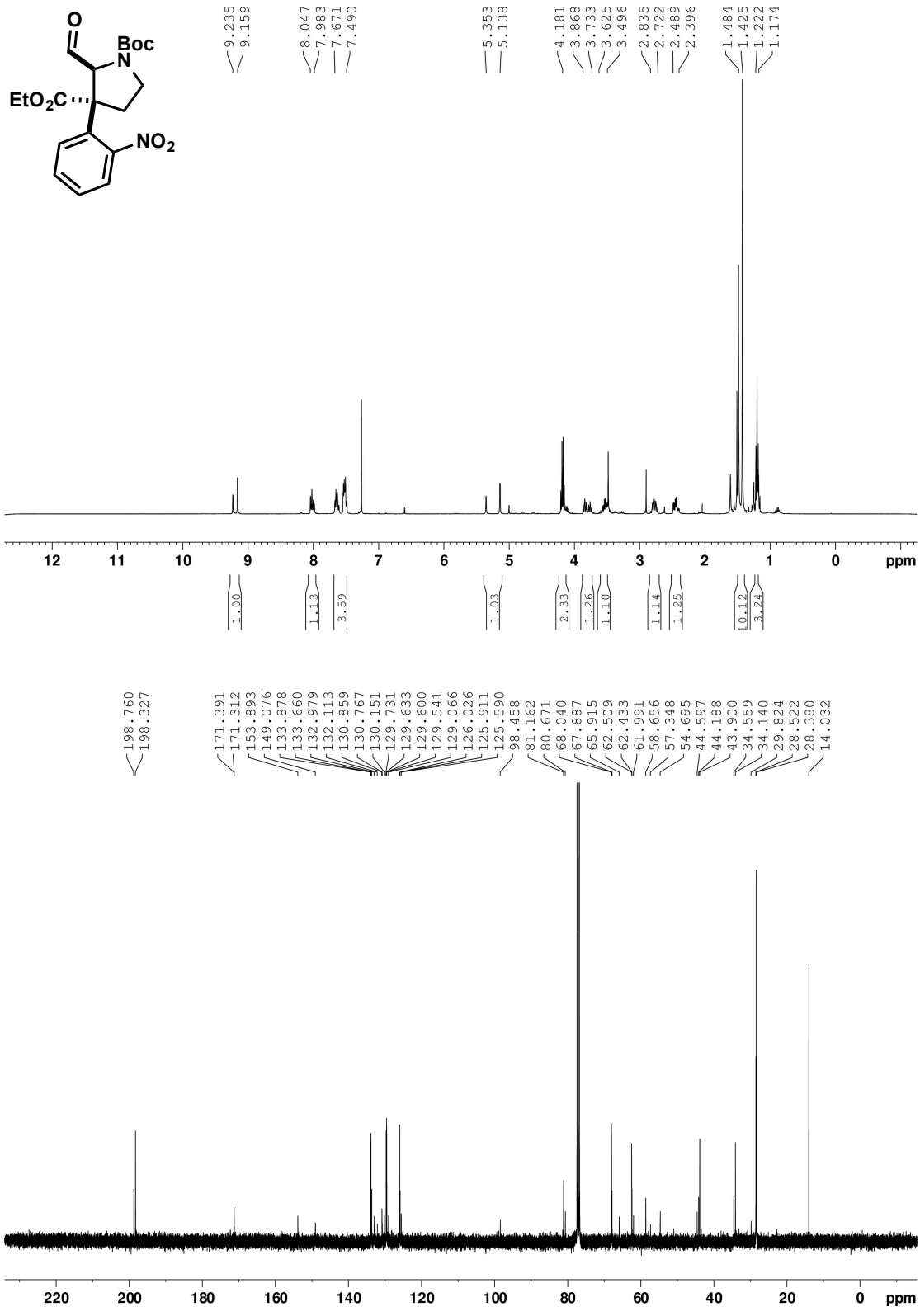
Compound **254**



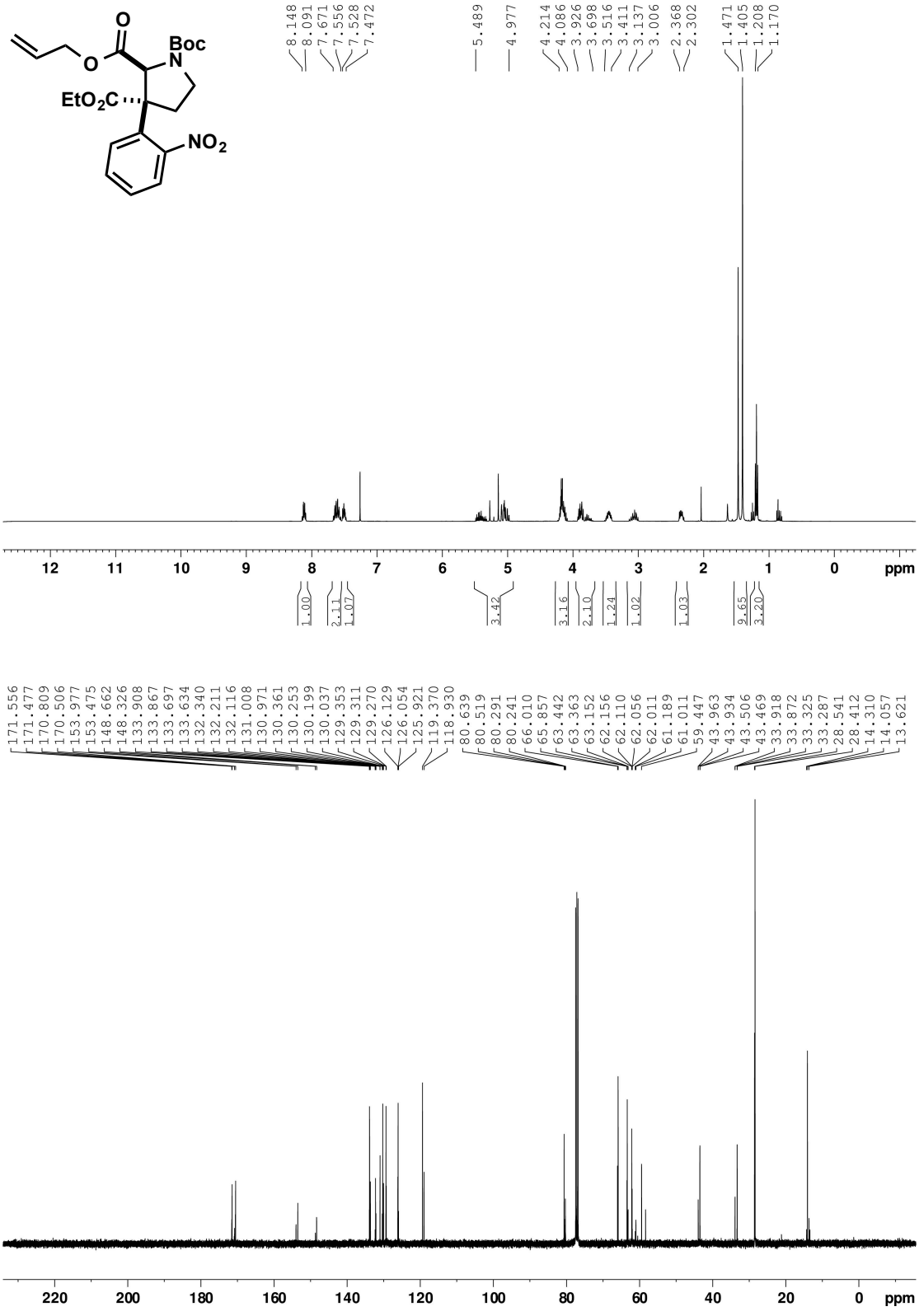
Compound **255**



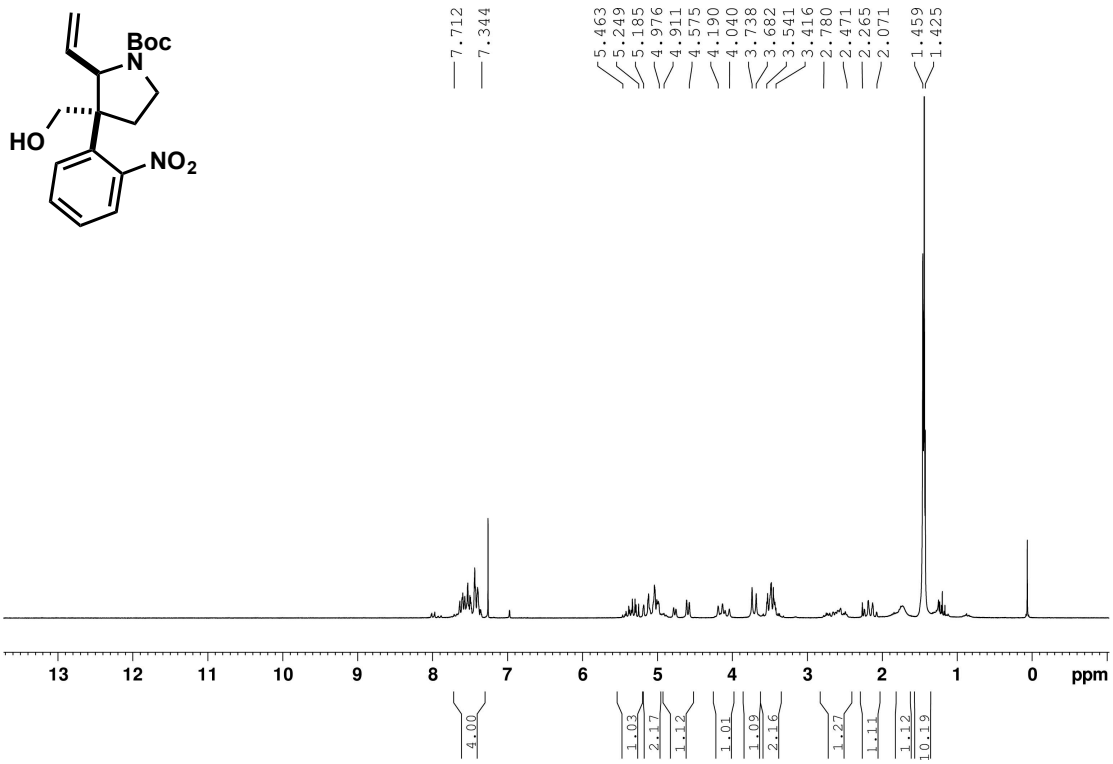
Compound **250b**



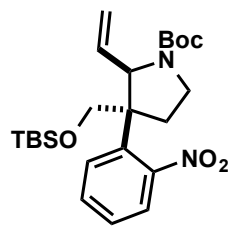
Compound **257**

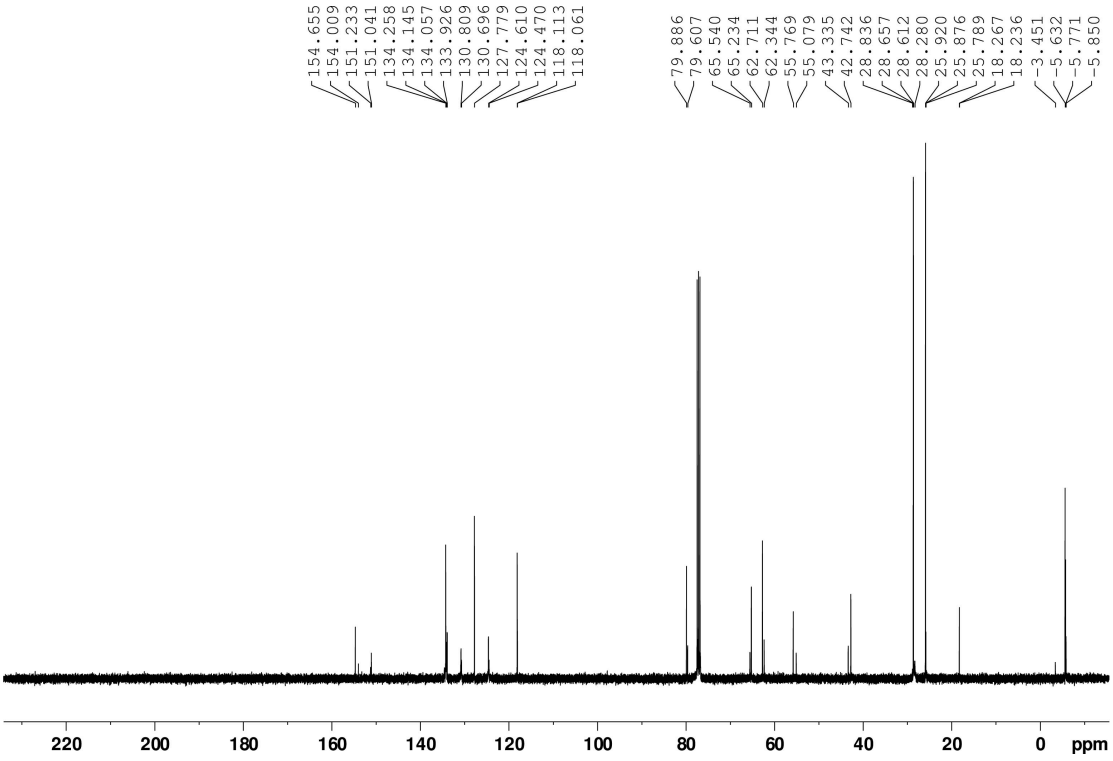


Compound **251b**

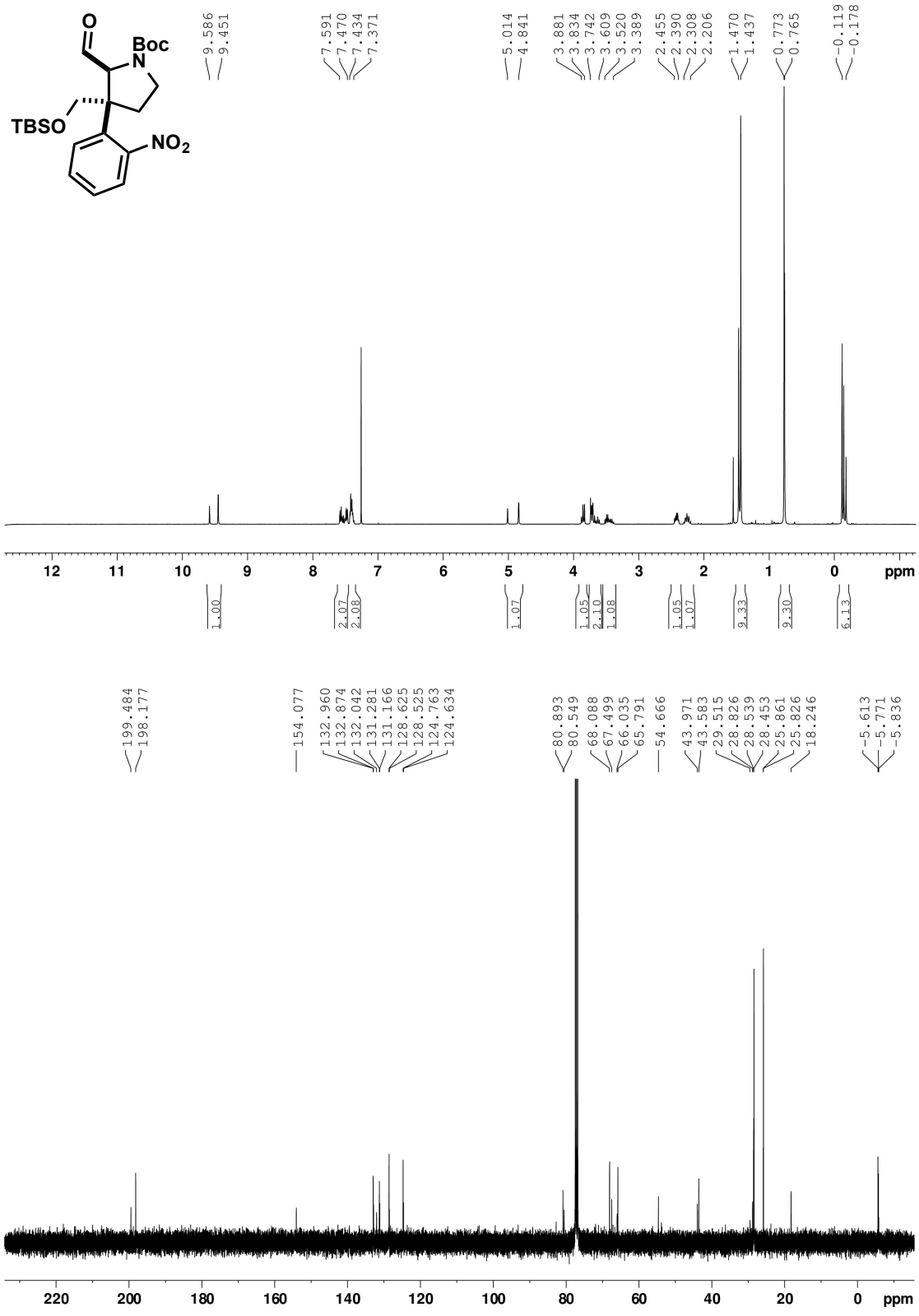


Compound **259**

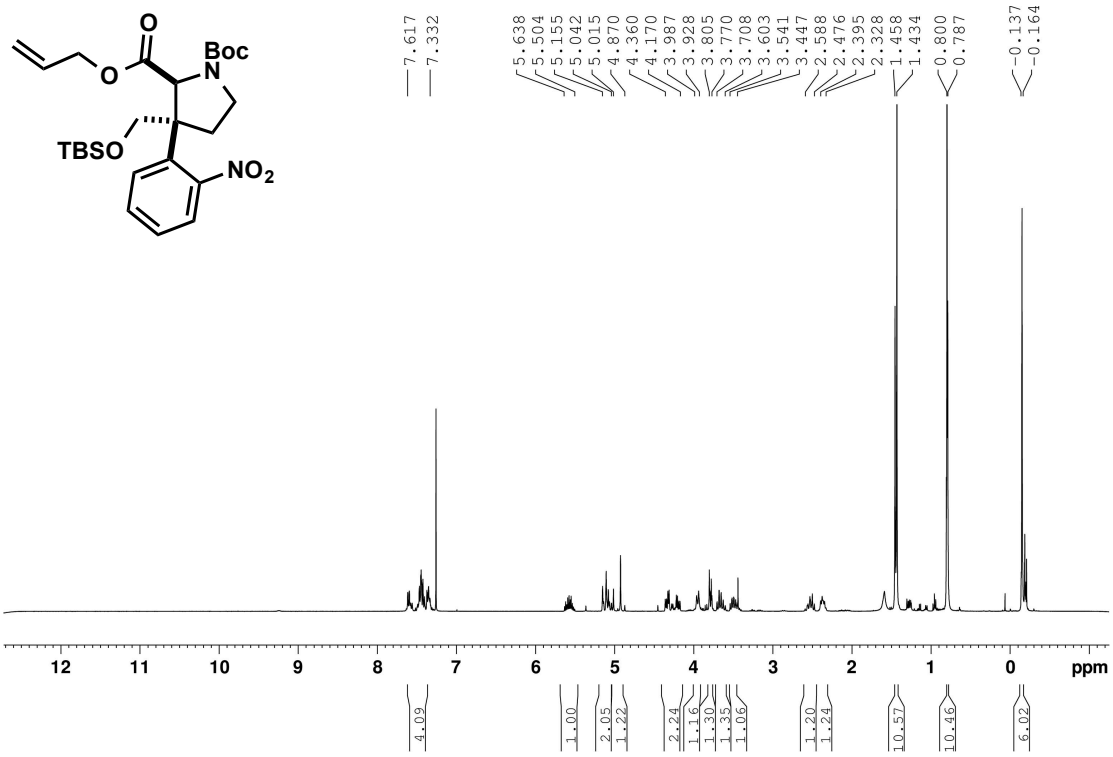




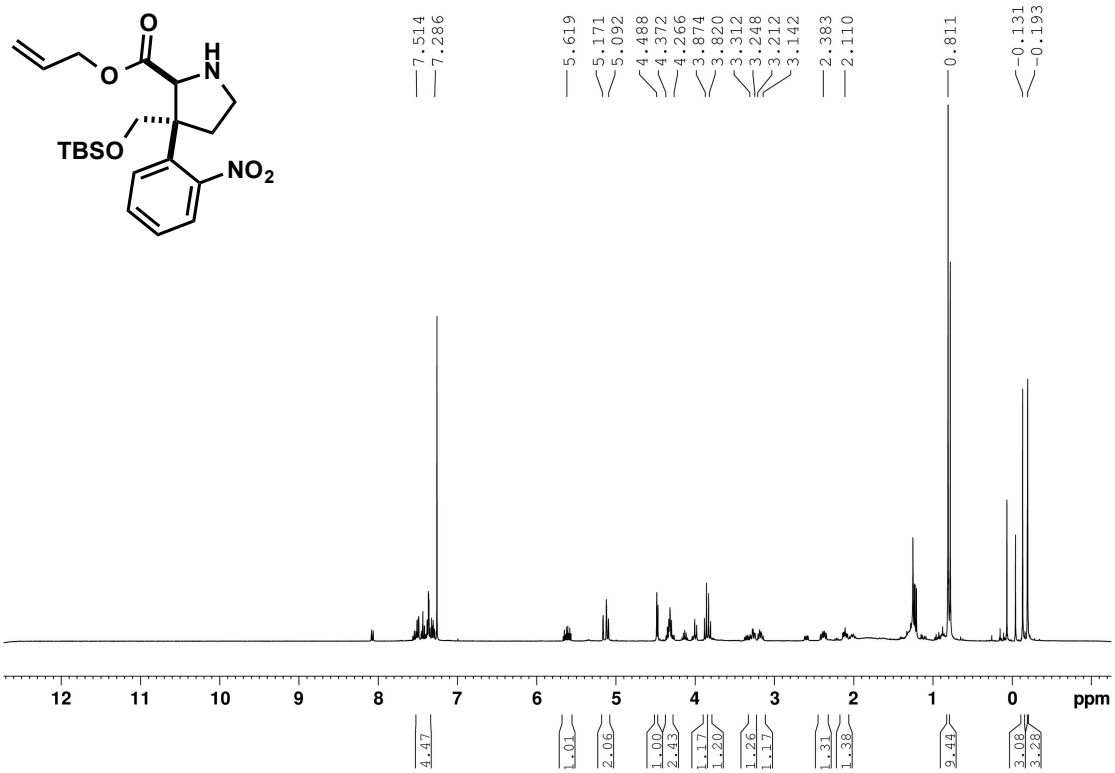
Compound **260**



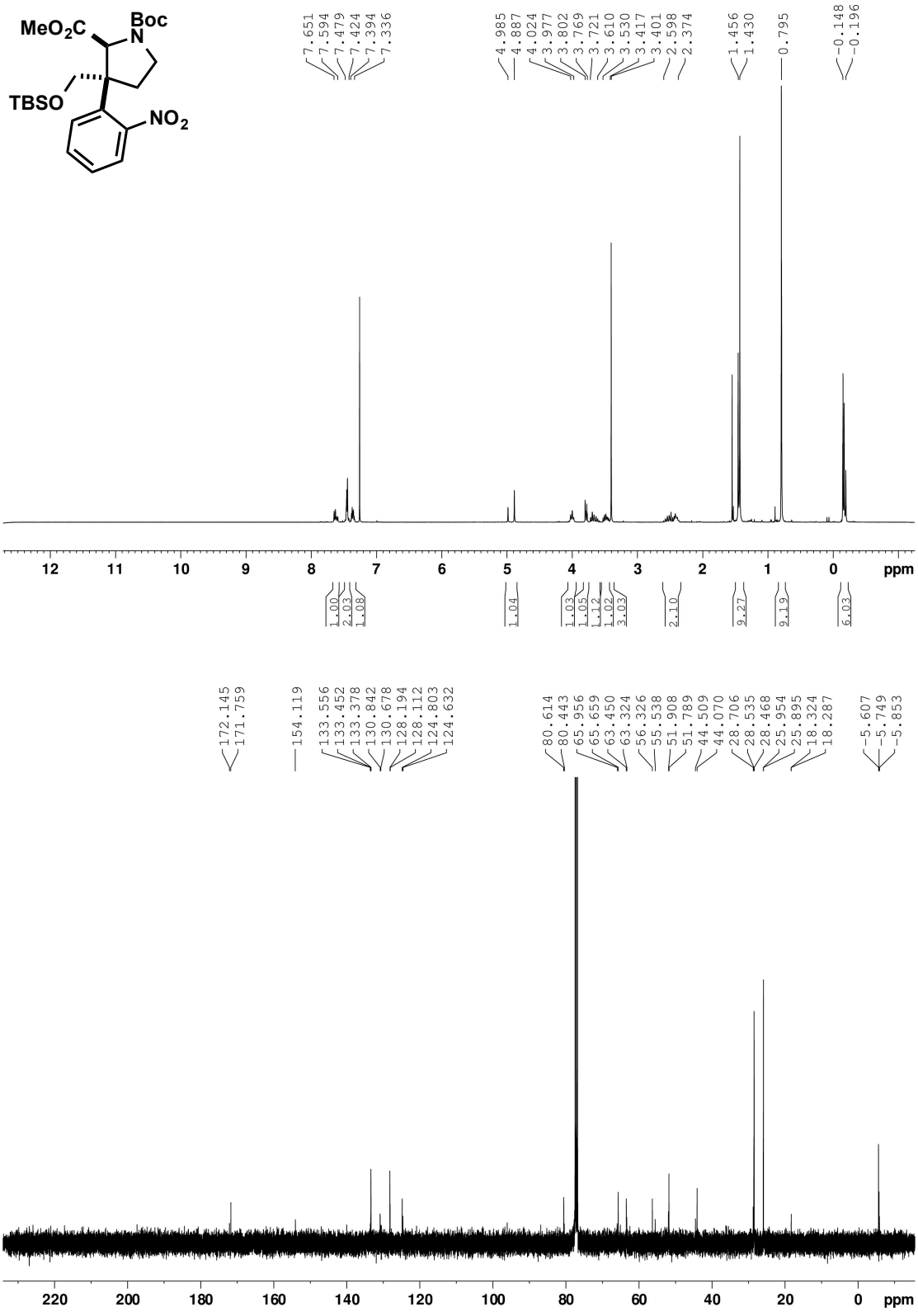
Compound **263a**



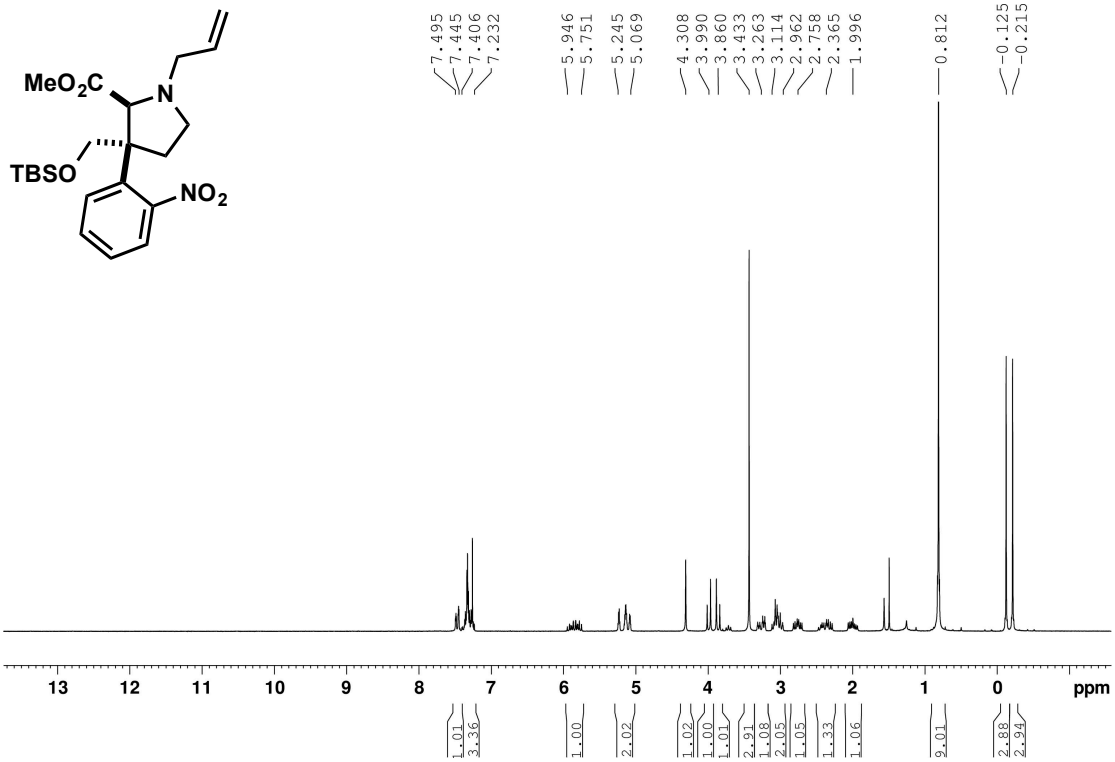
Compound **263**



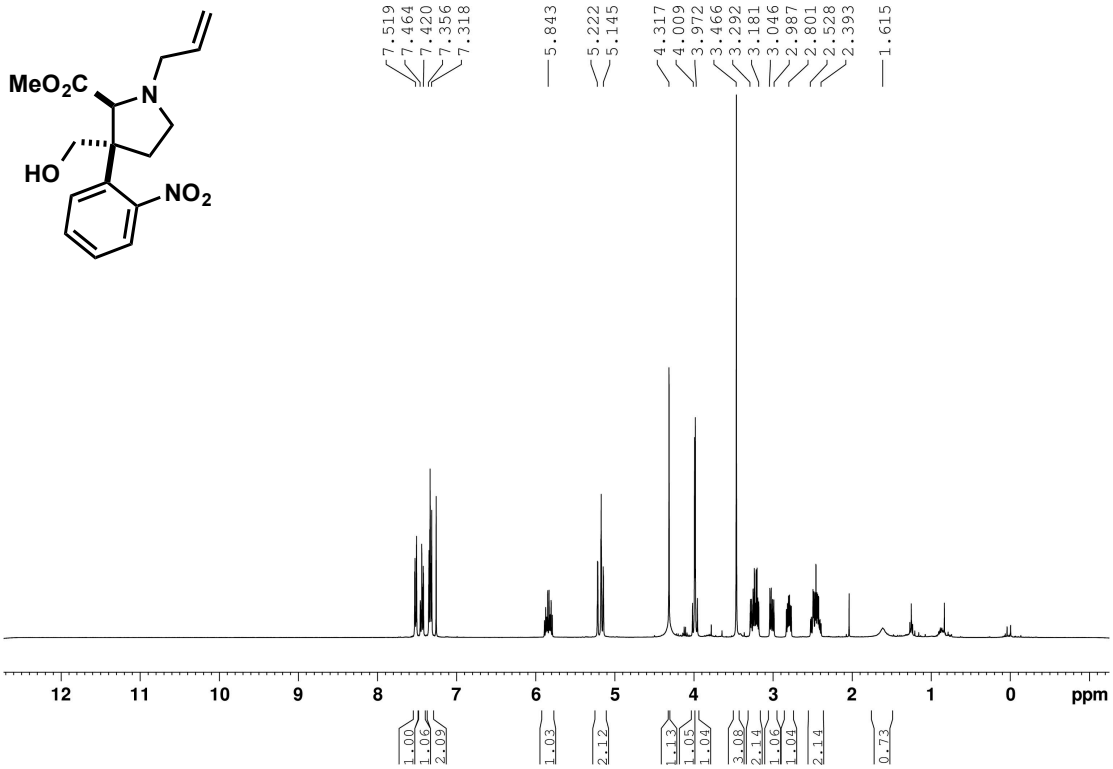
Compound **261**



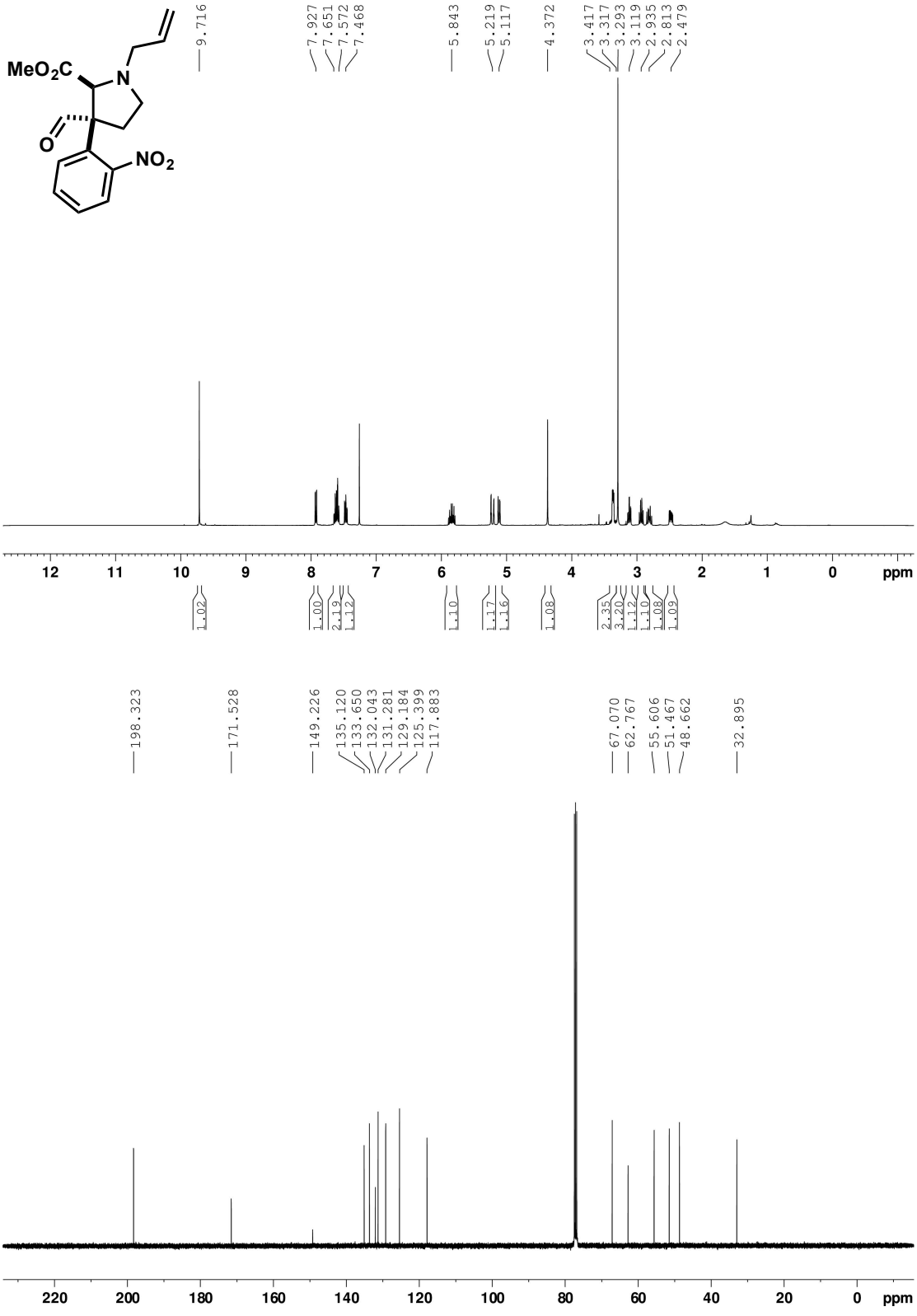
Compound **278**



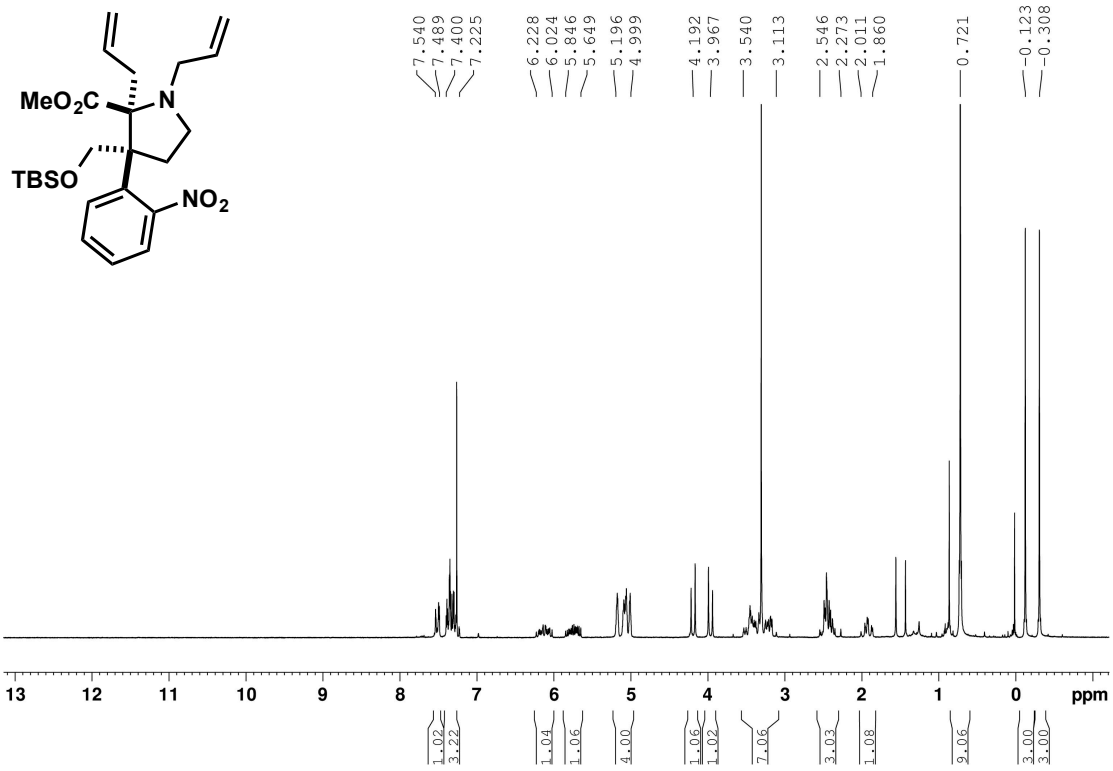
Compound **282**



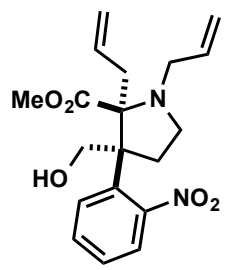
Compound **284**

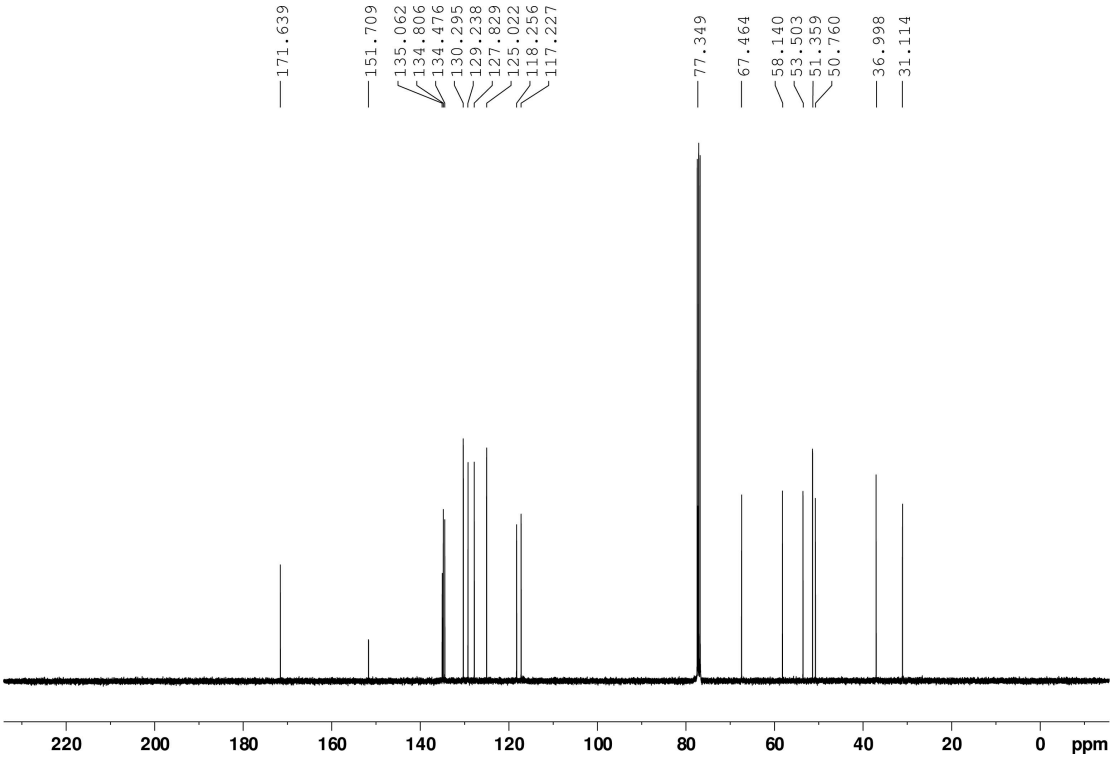


Compound **280**

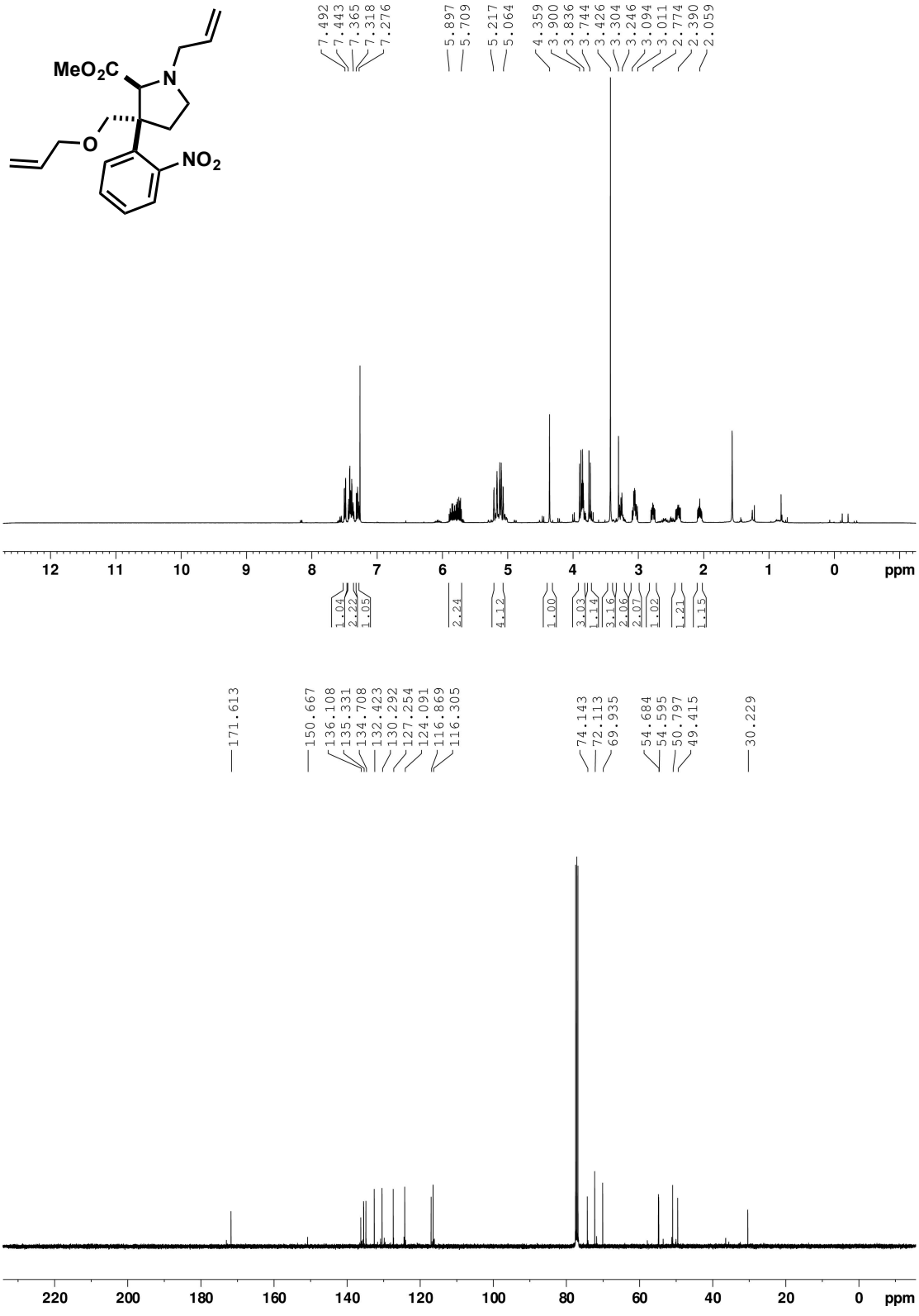


Compound **281**

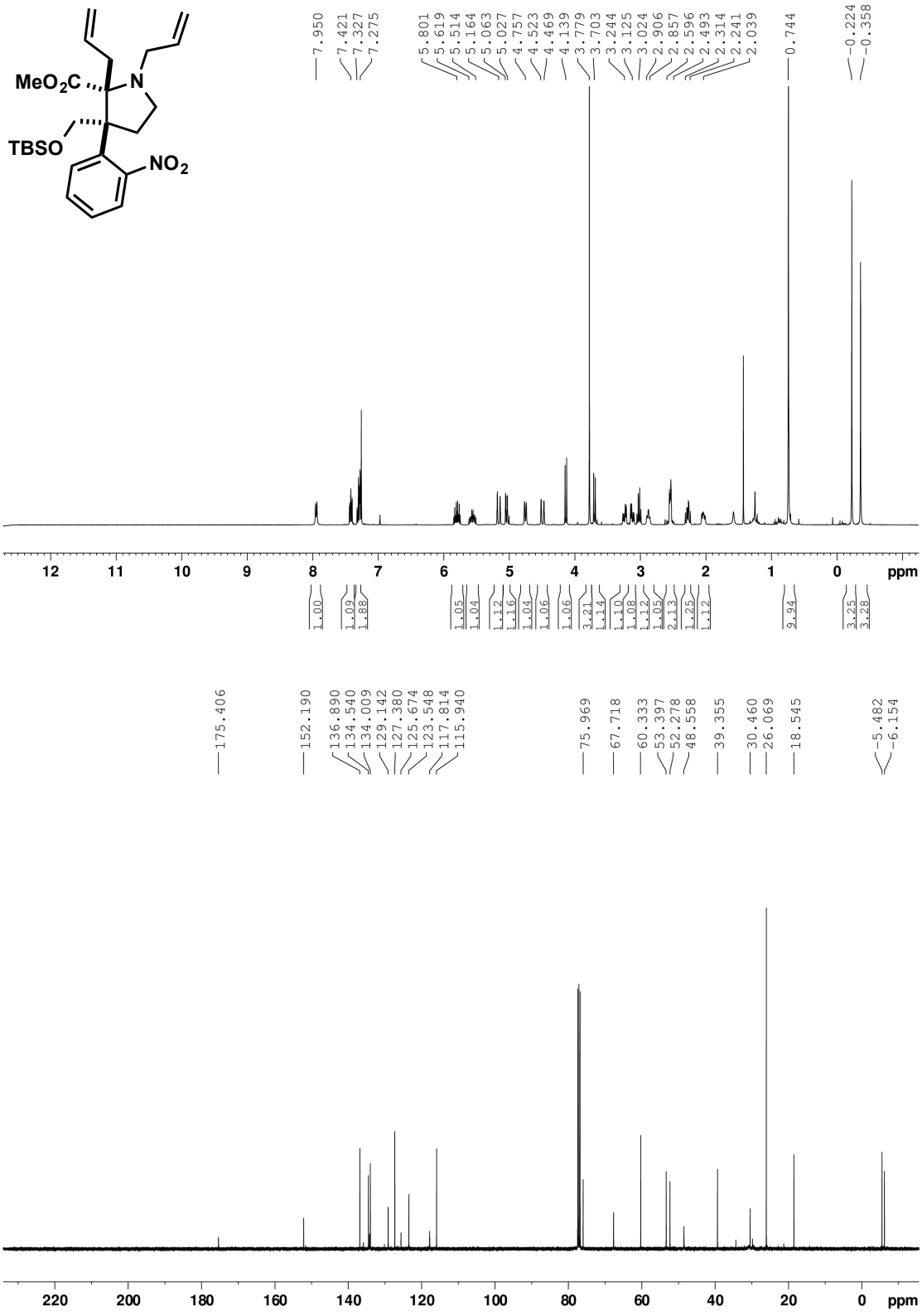




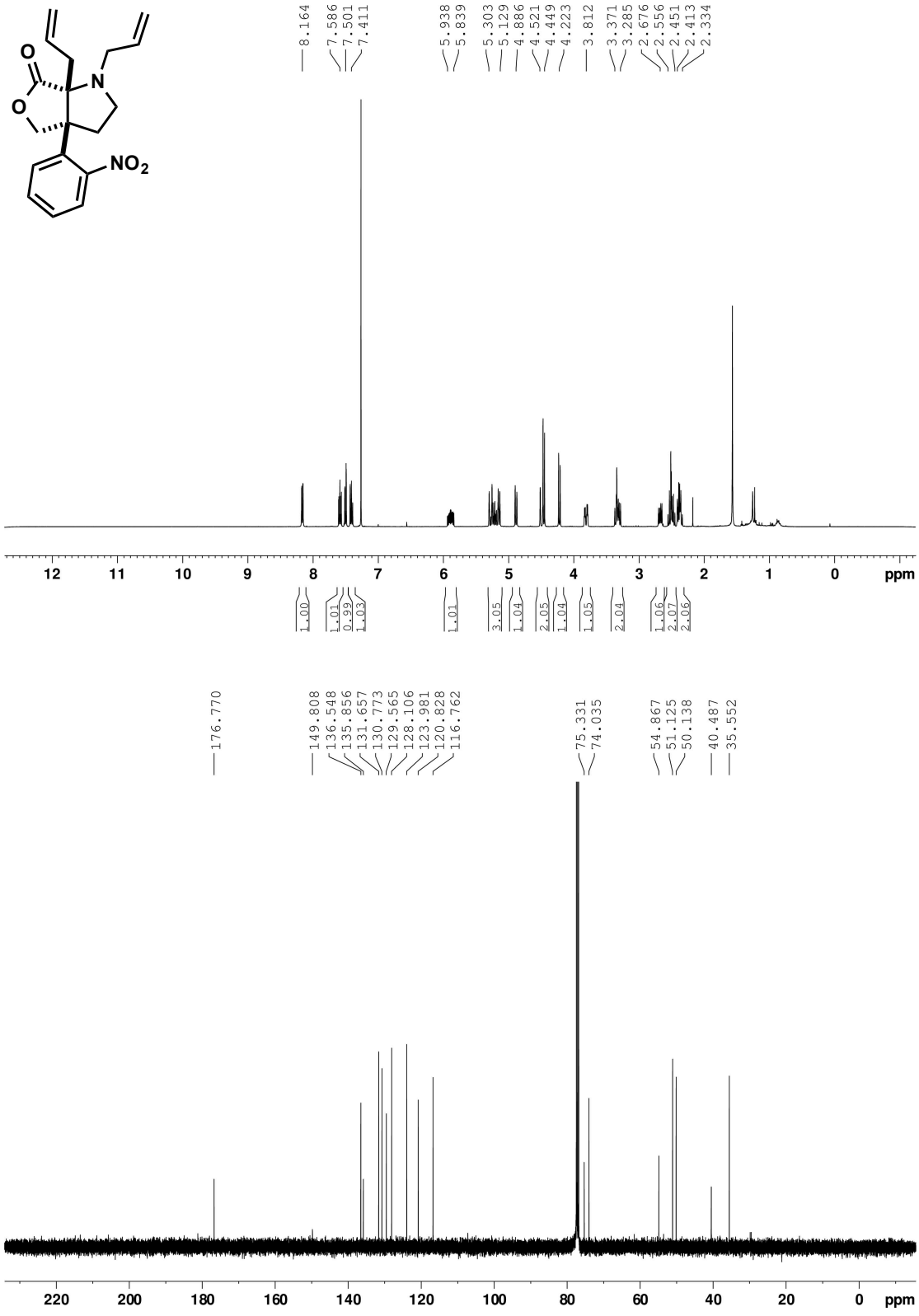
Compound **283**



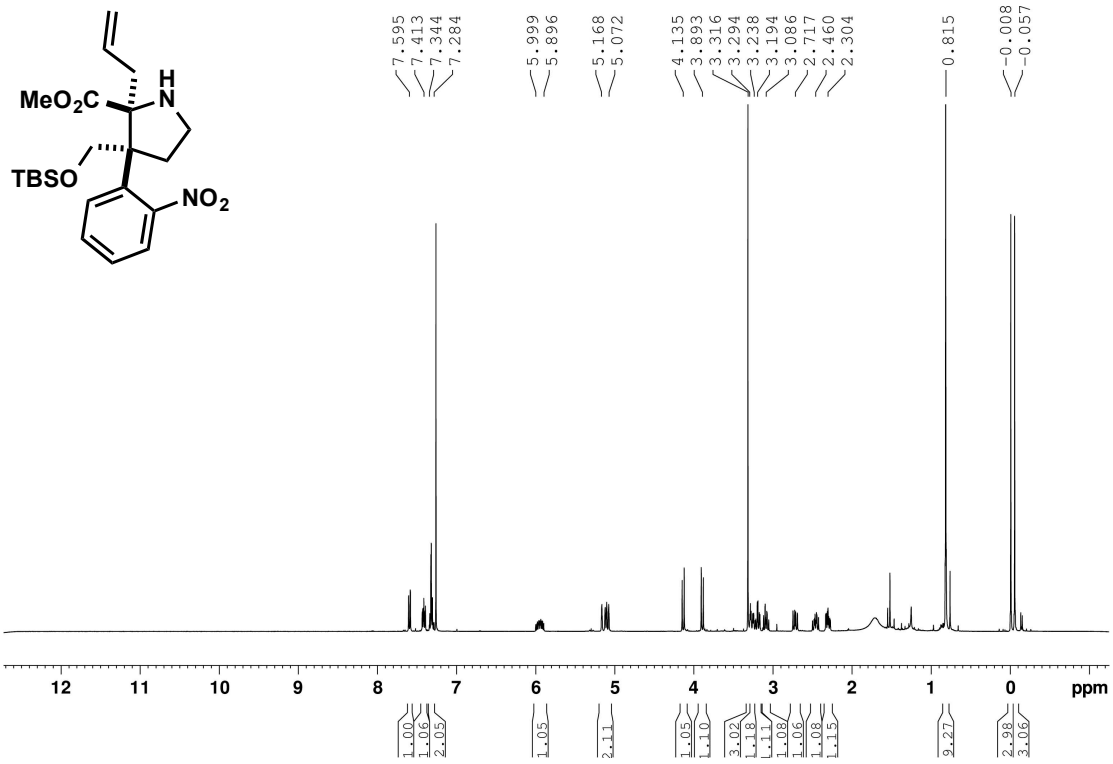
Compound **286**



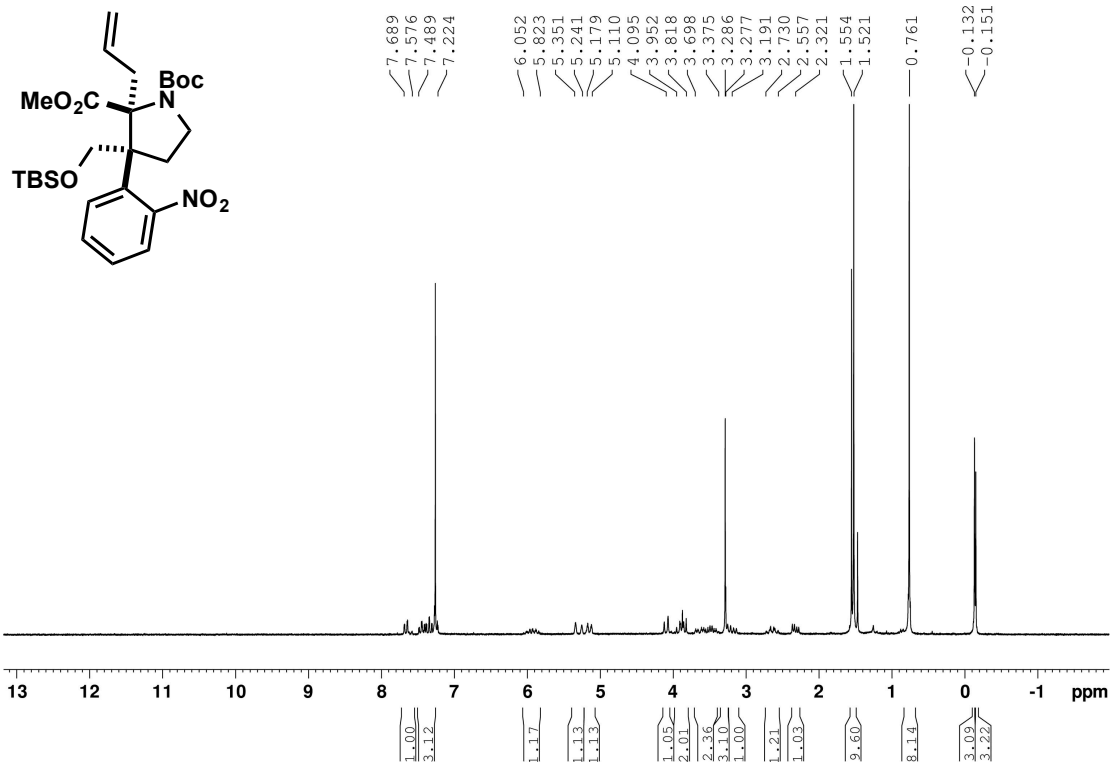
Compound **287**



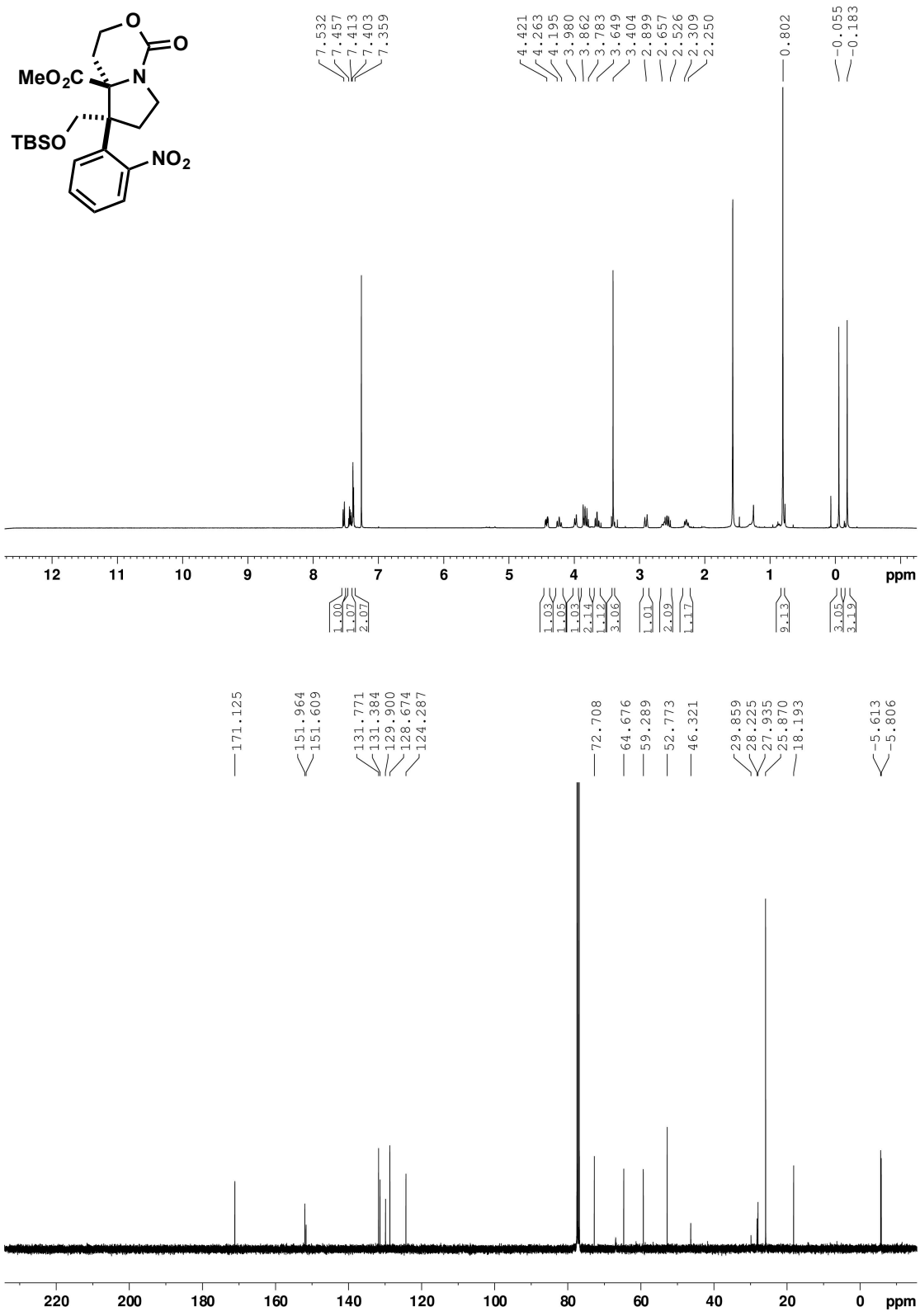
Compound **280b**



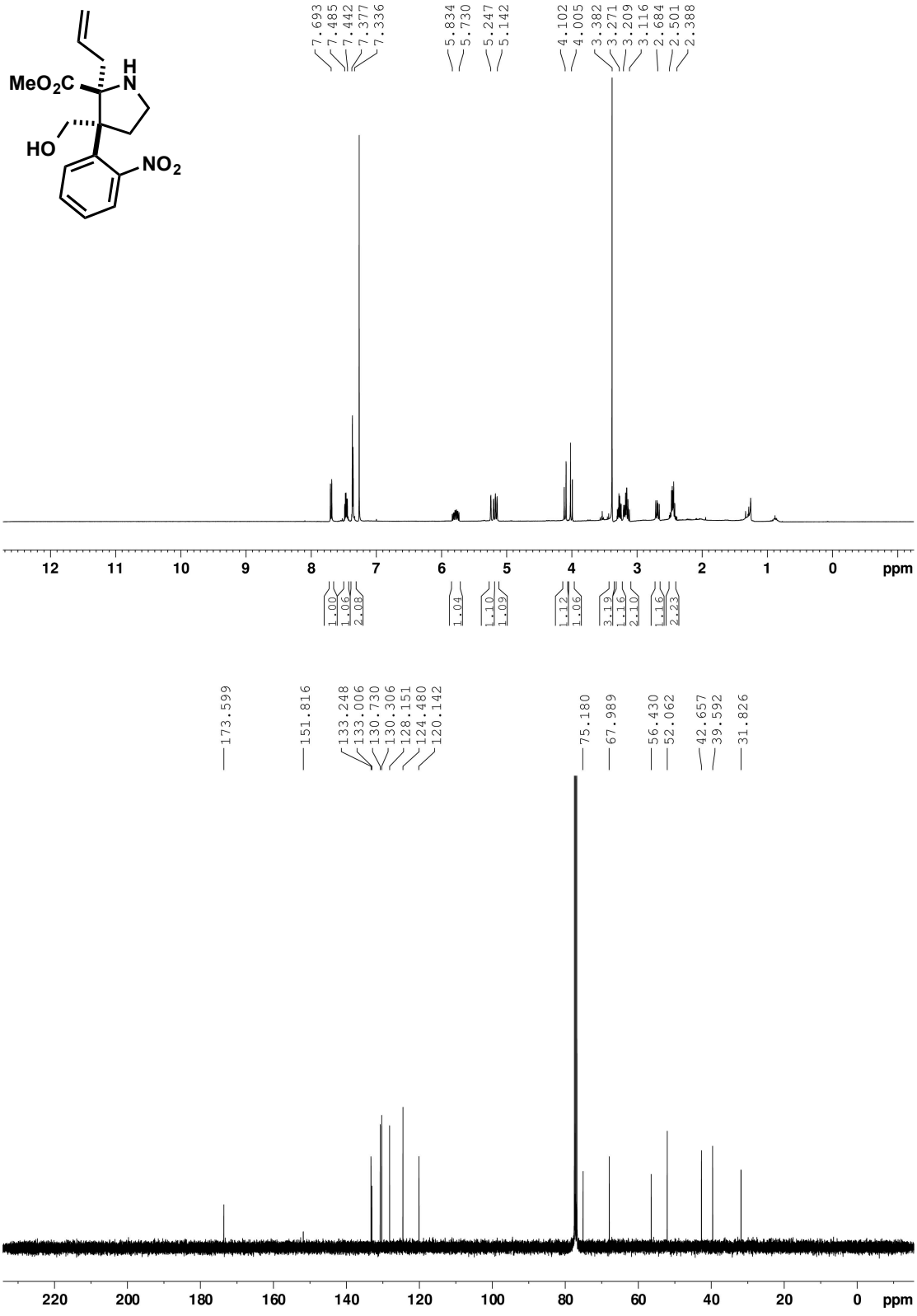
Compound **288**



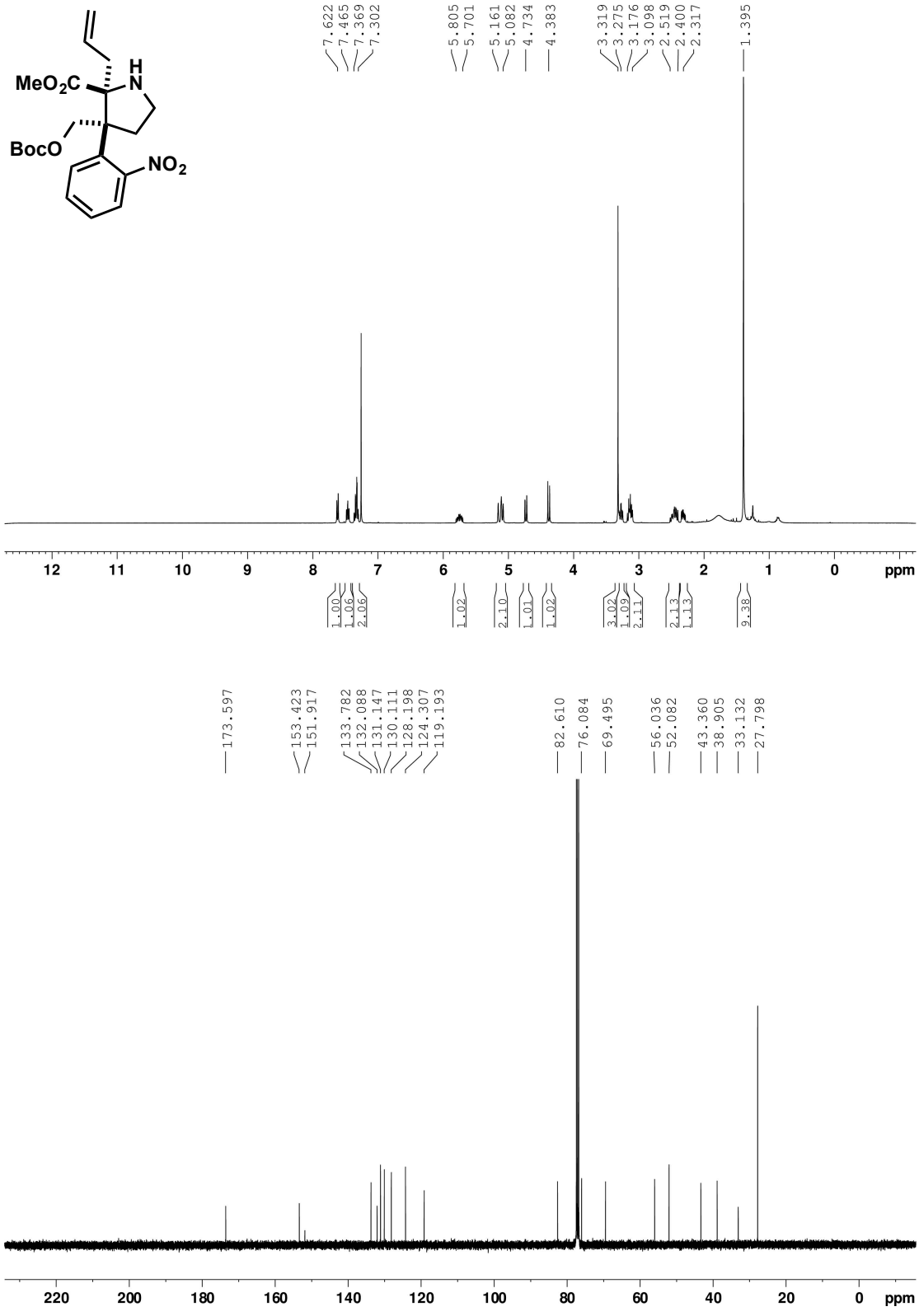
Compound **289**



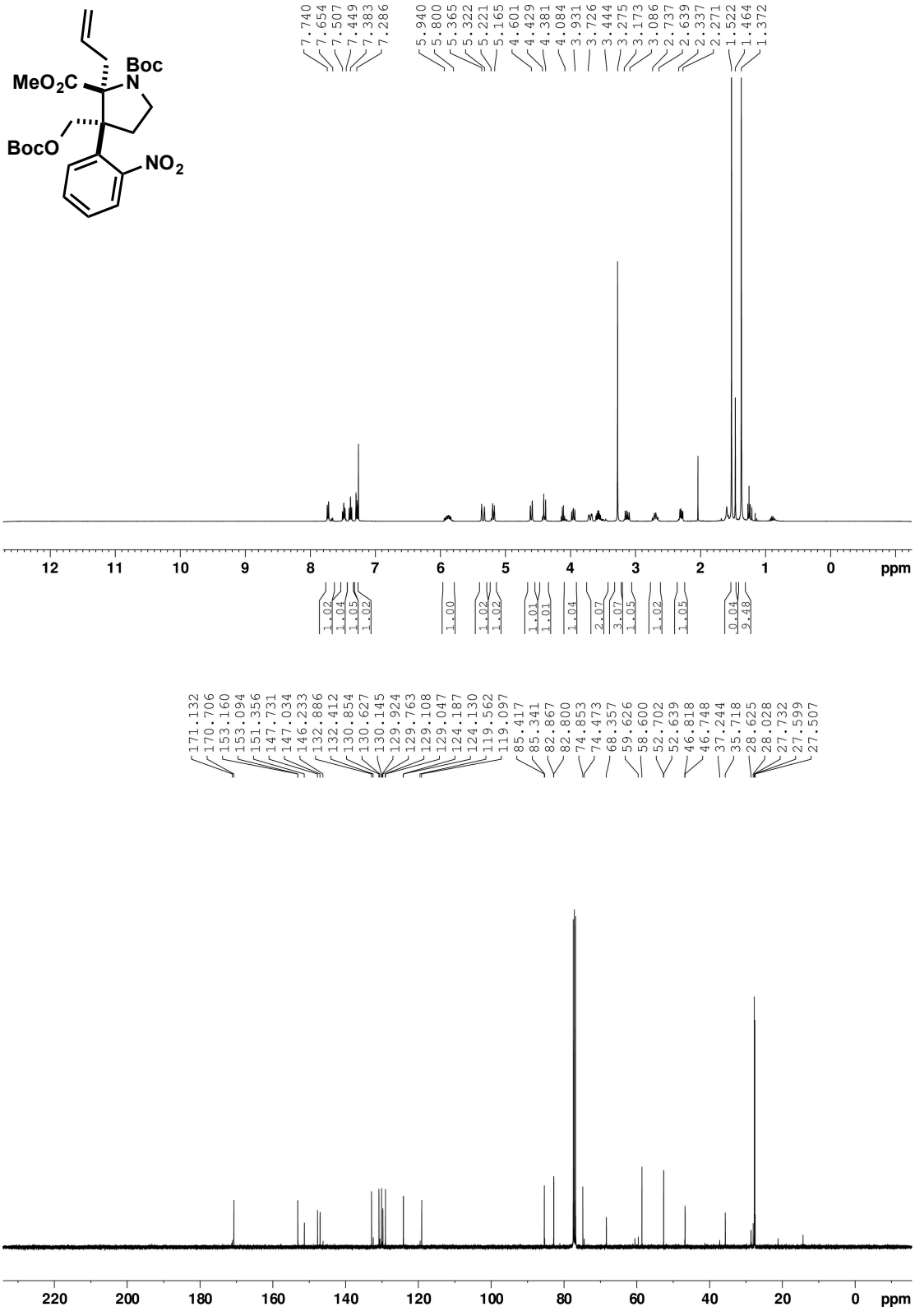
Compound **291**



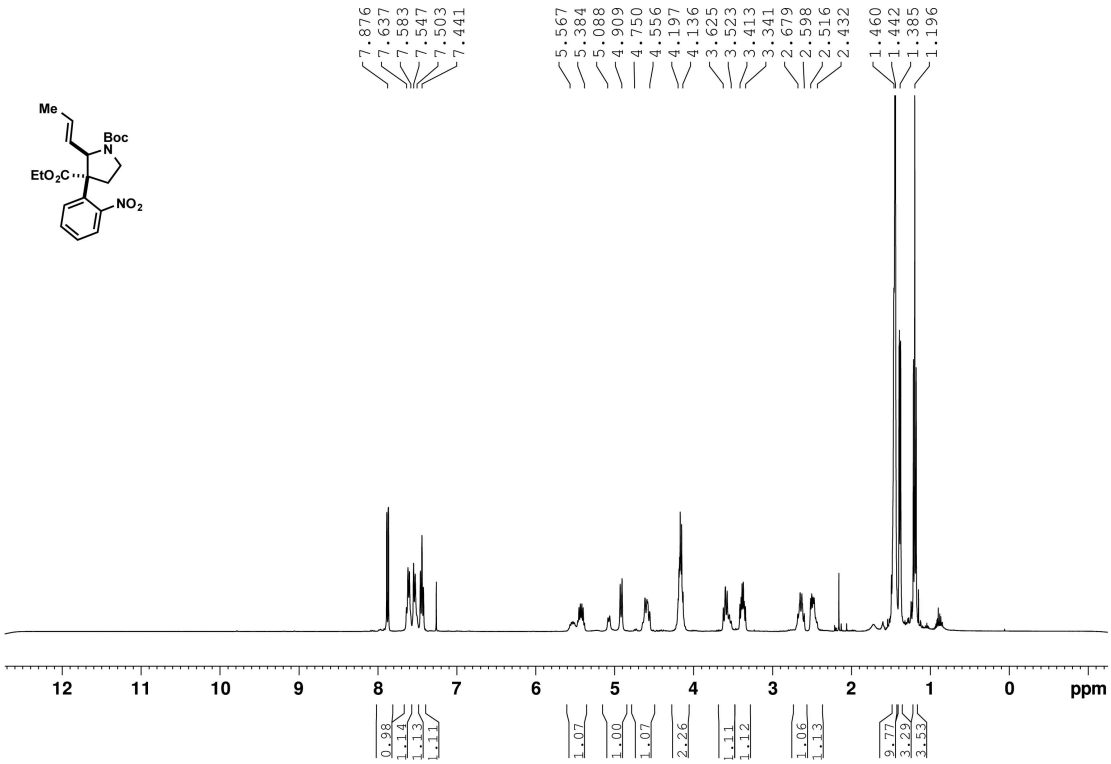
Compound **292**

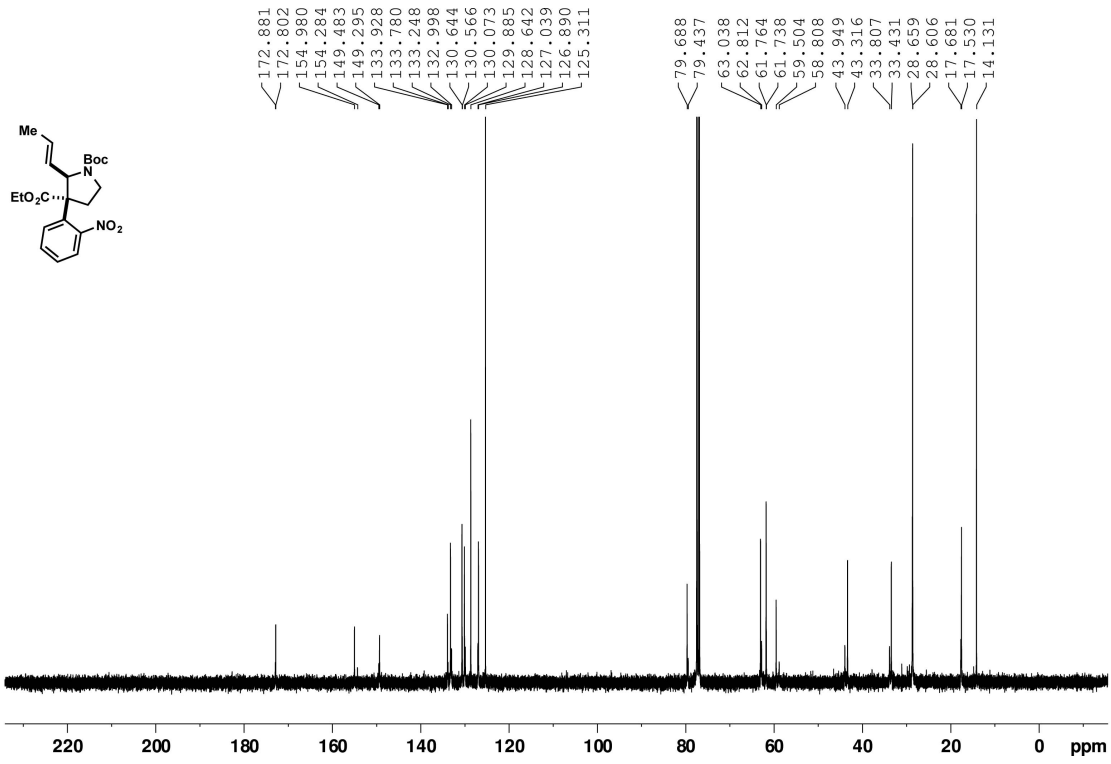


Compound **293**

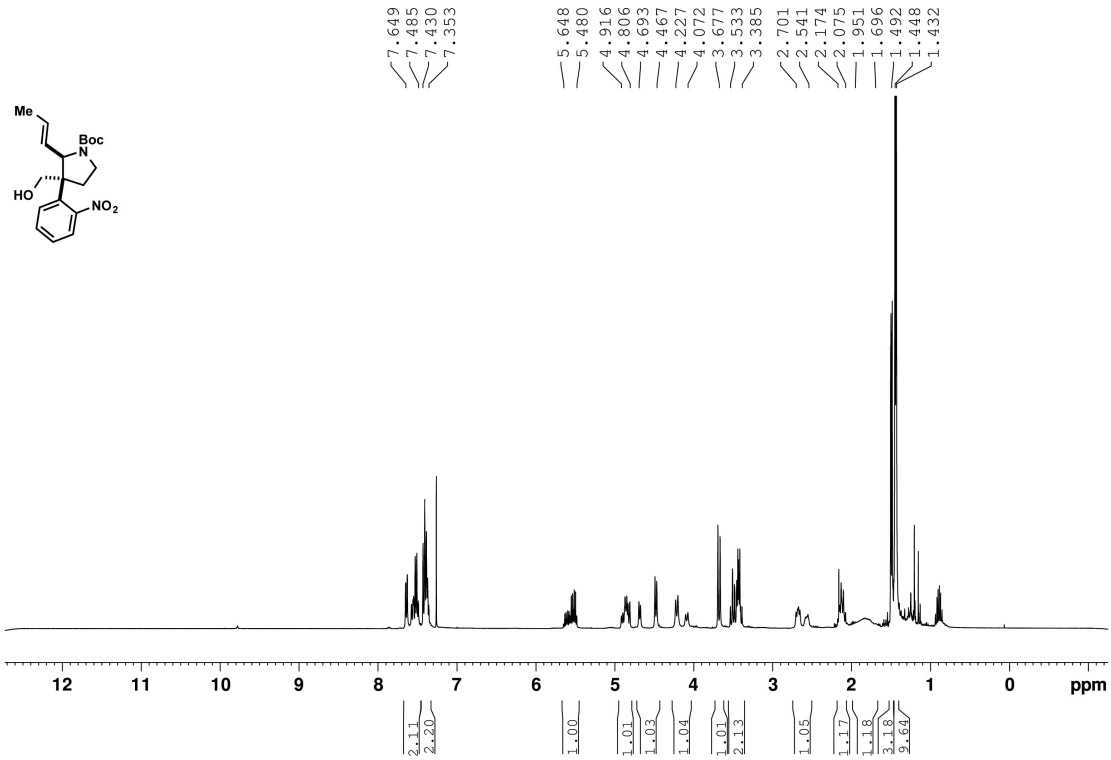


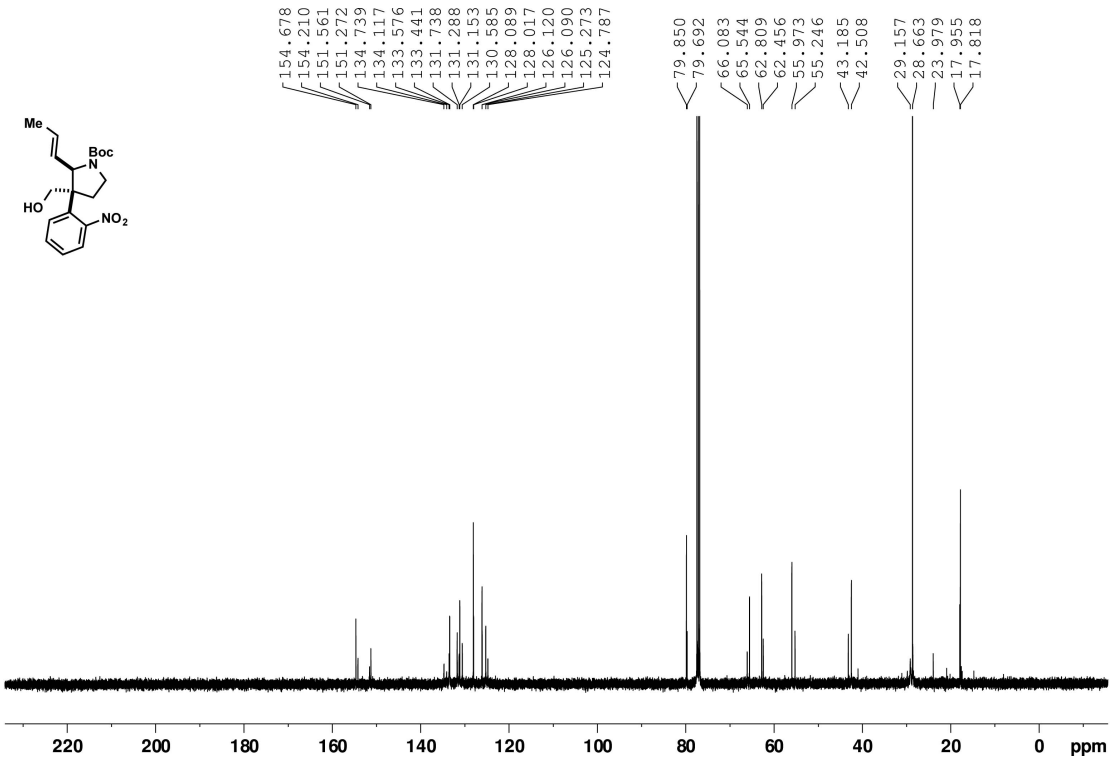
Compound **294a**



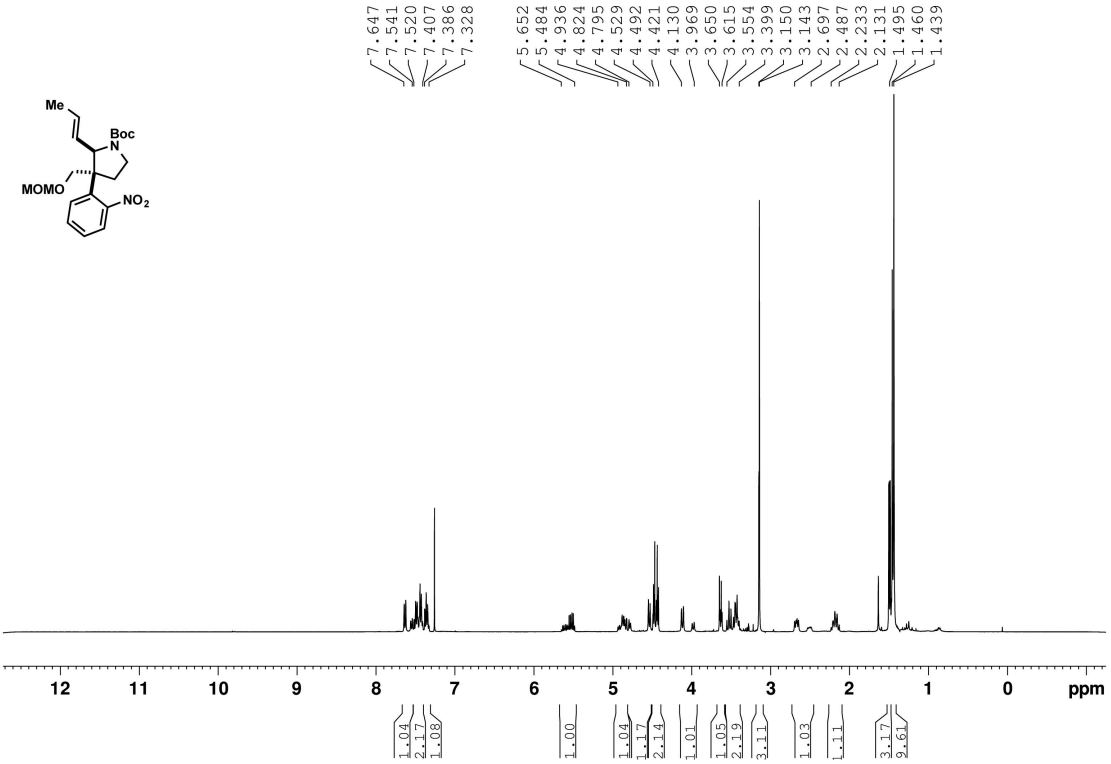


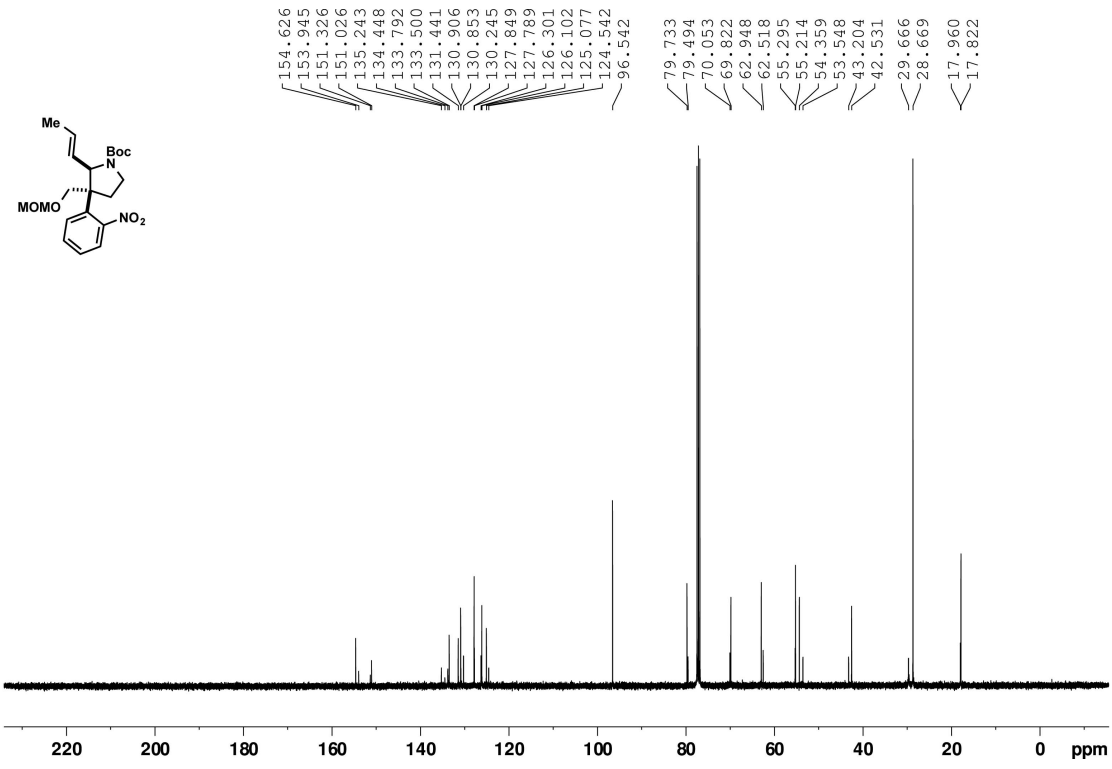
Compound **294**



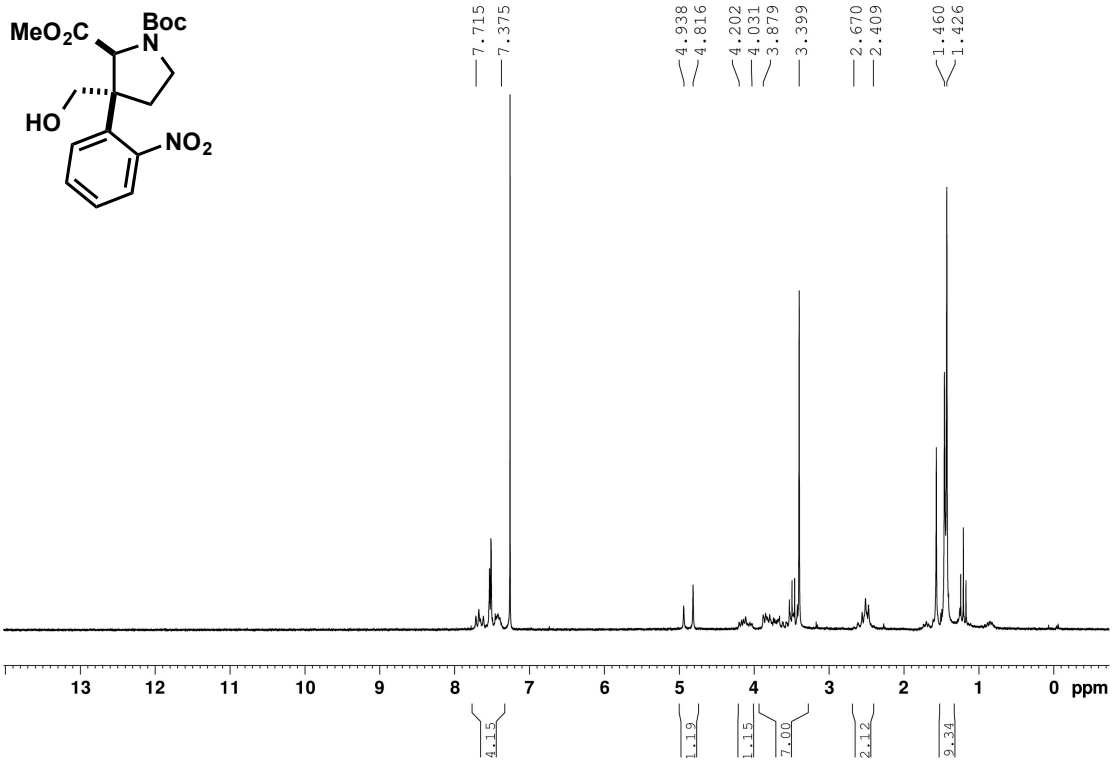


Compound **298**

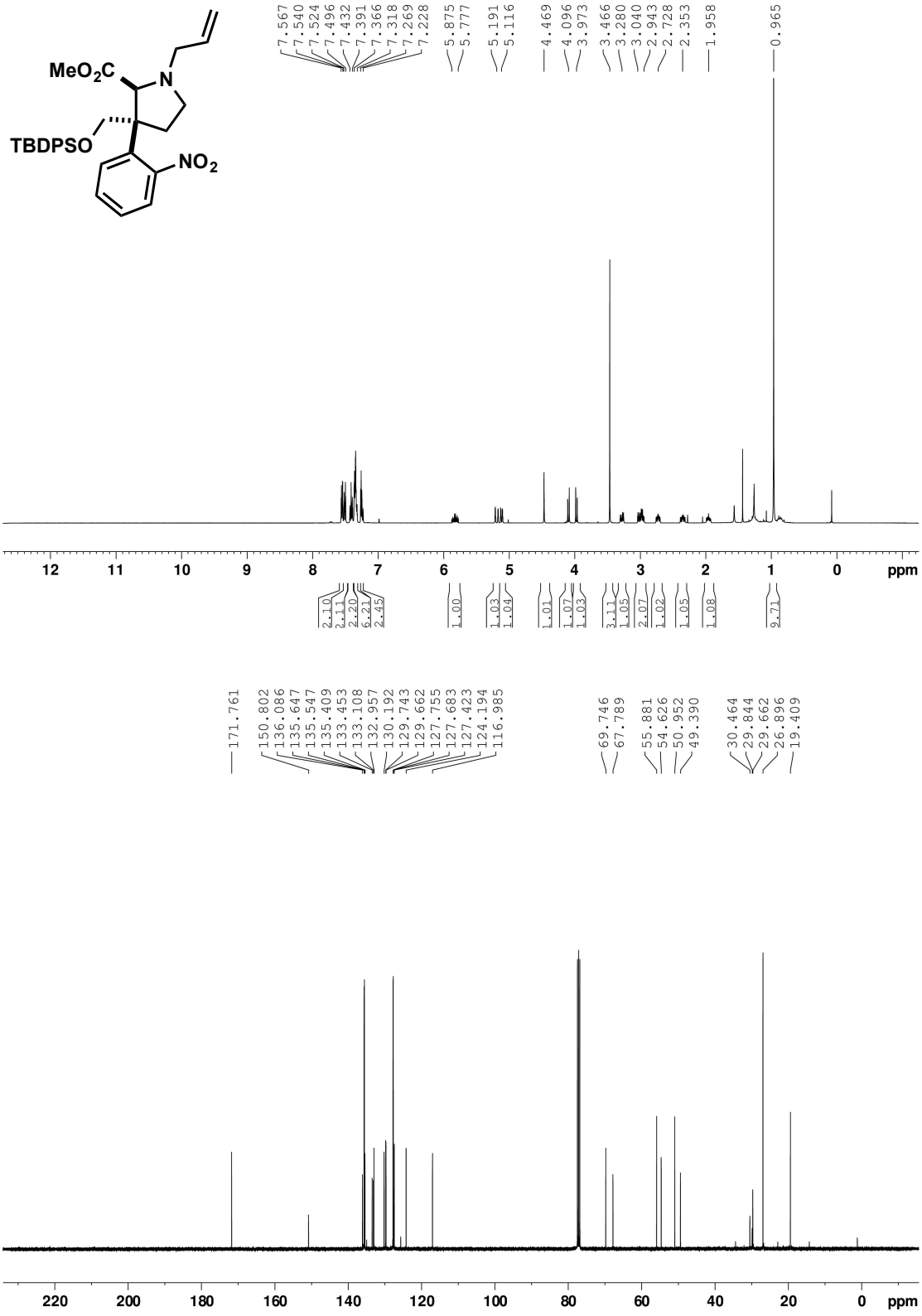




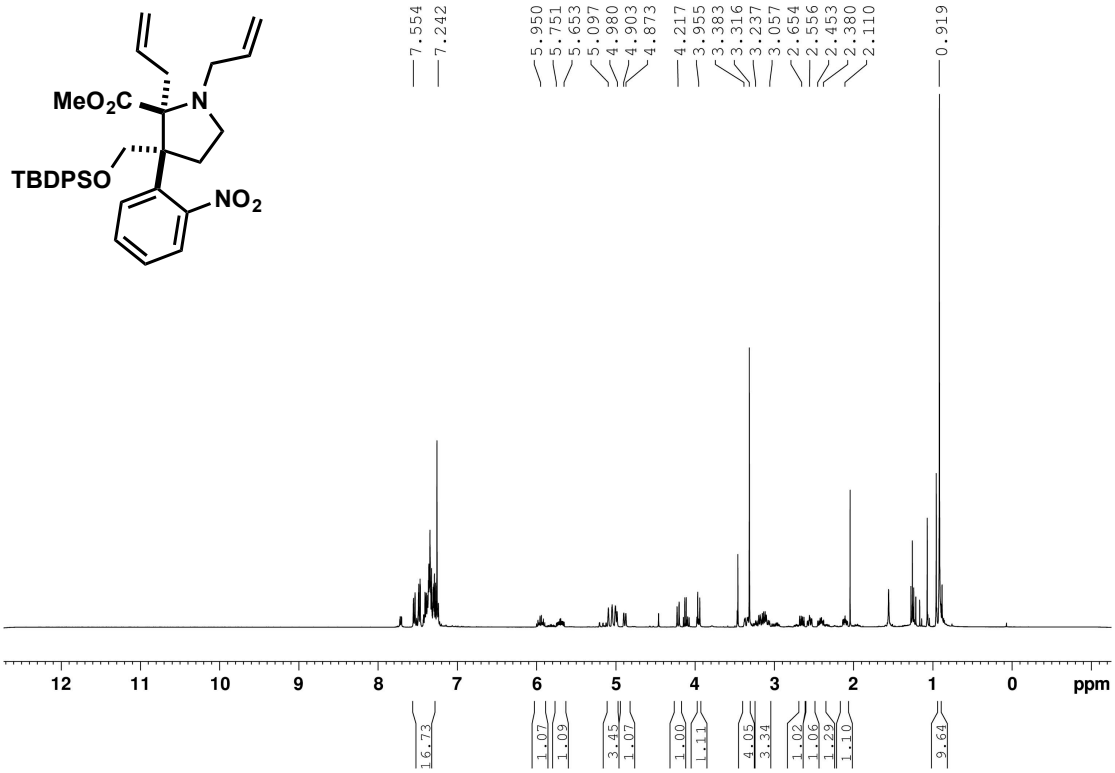
Compound **265**



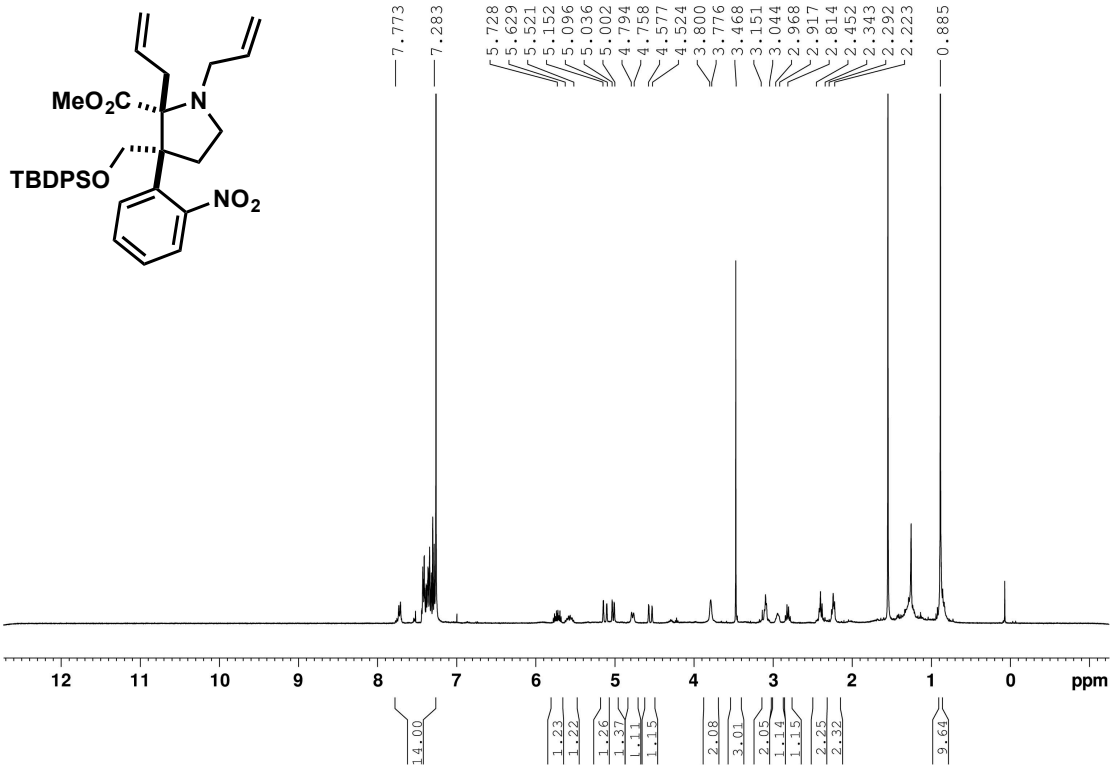
Compound **295**



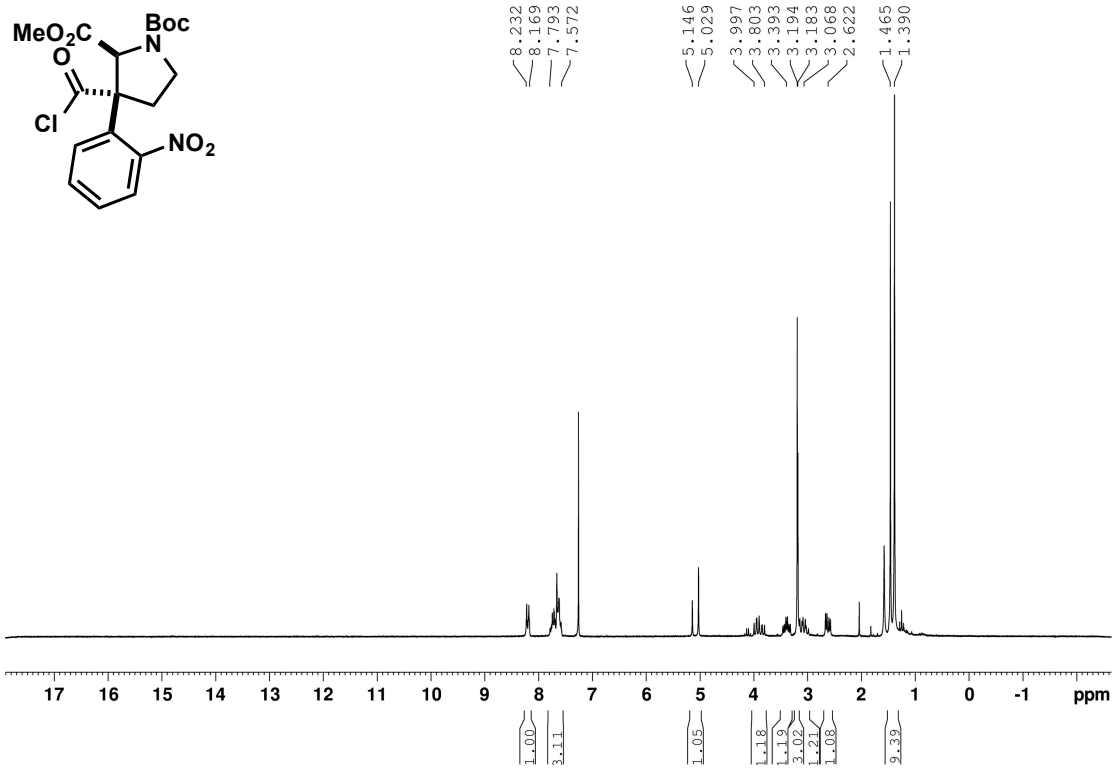
Compound **296**



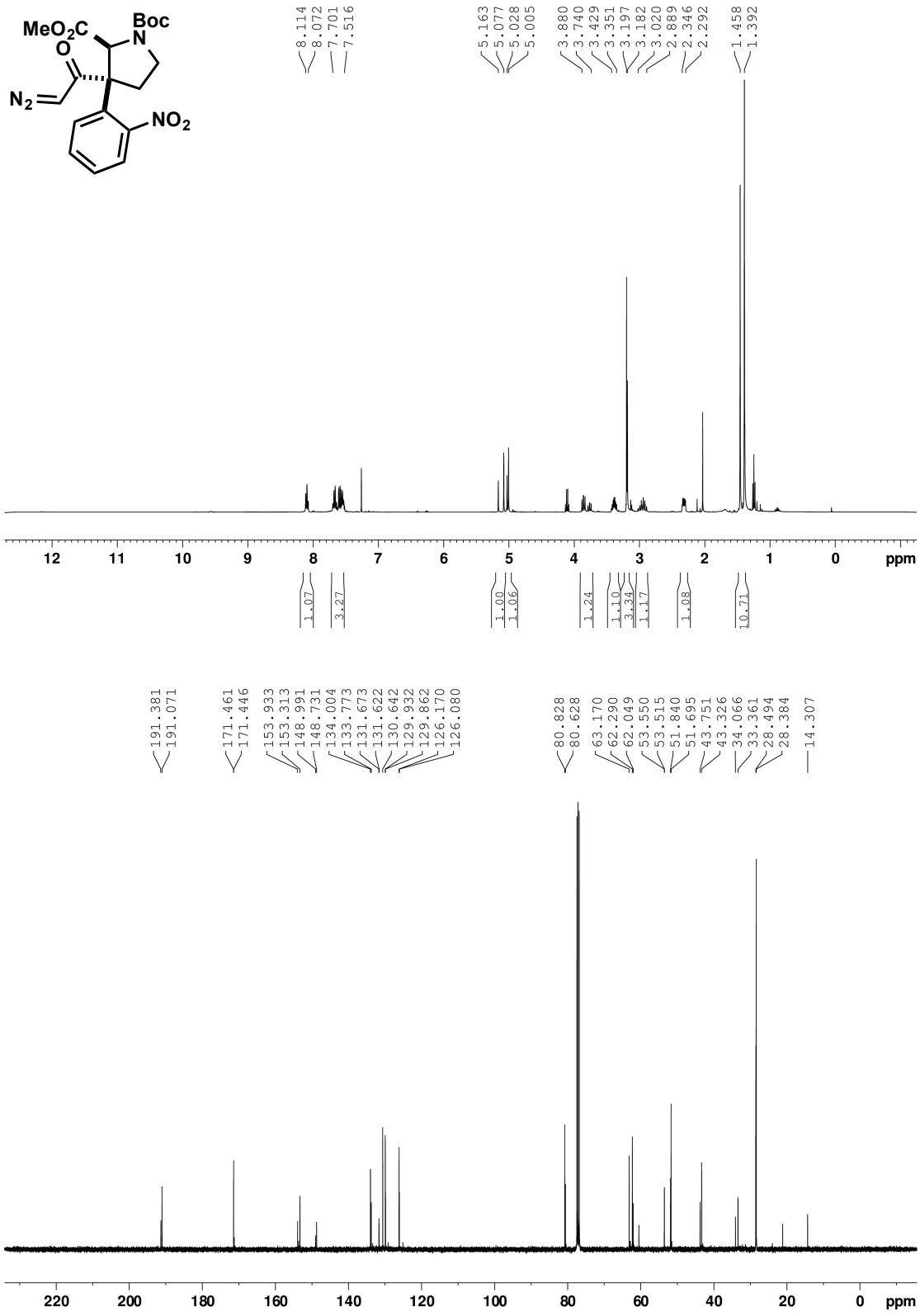
Compound **297**



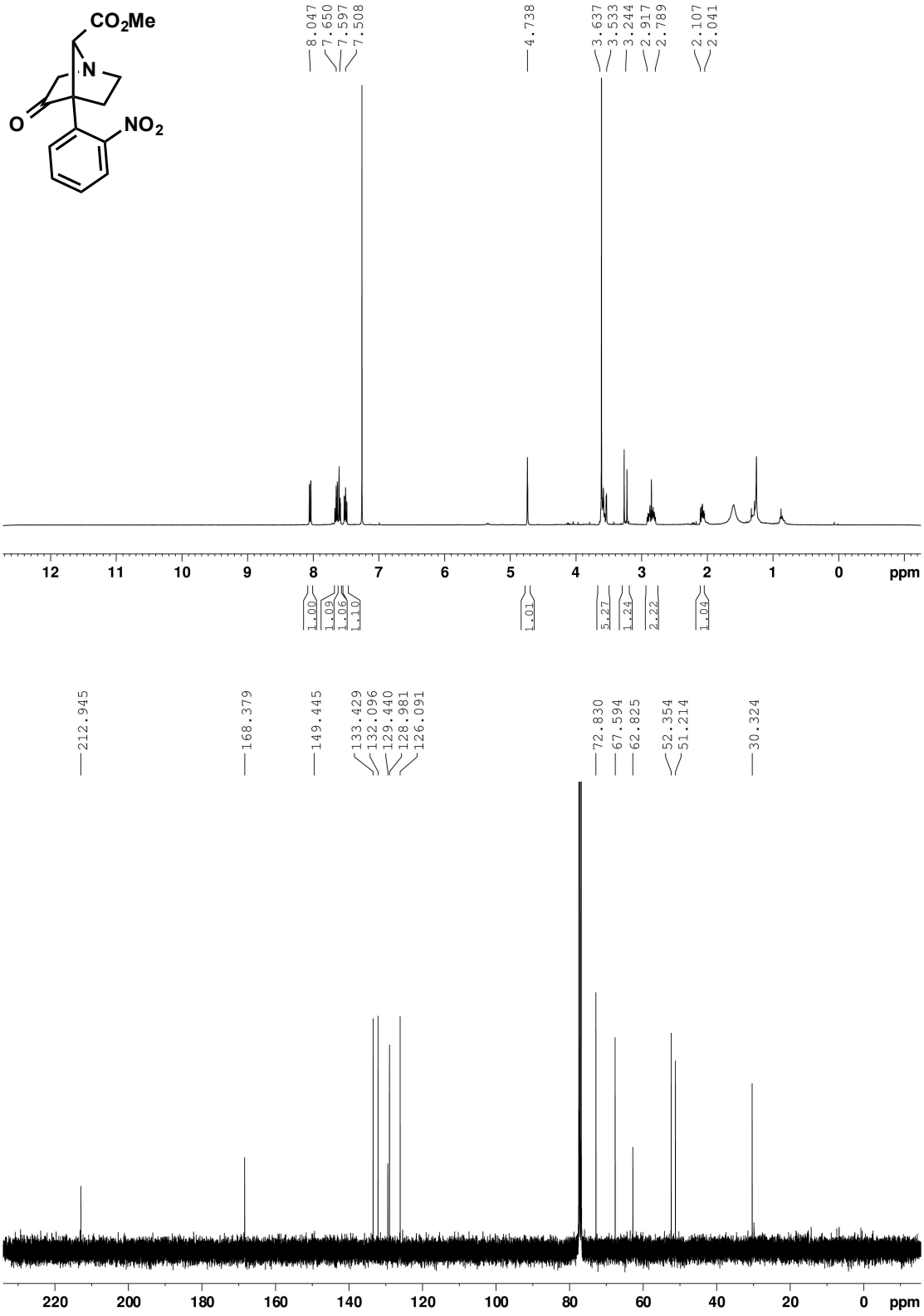
Compound **266**



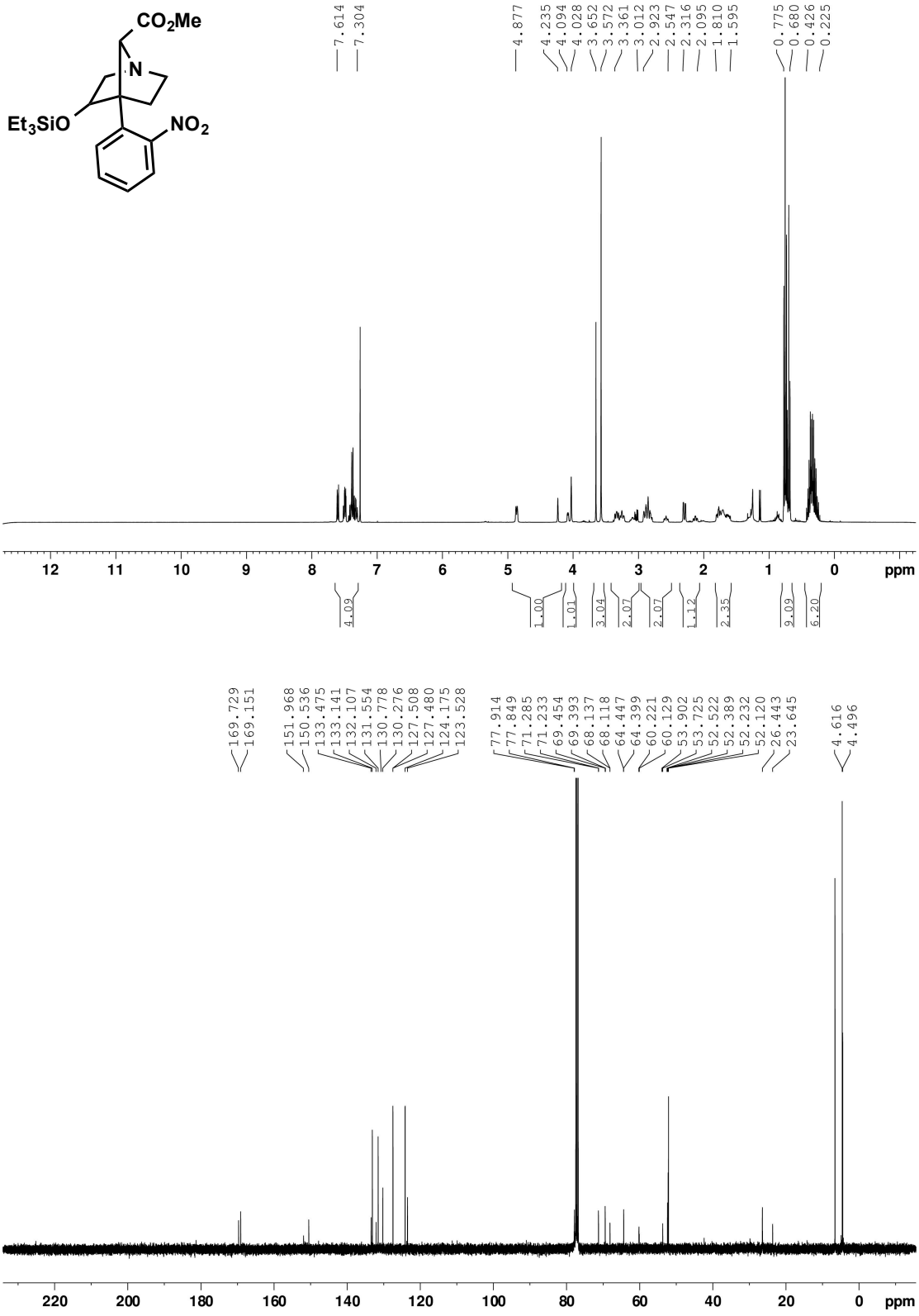
Compound **267**



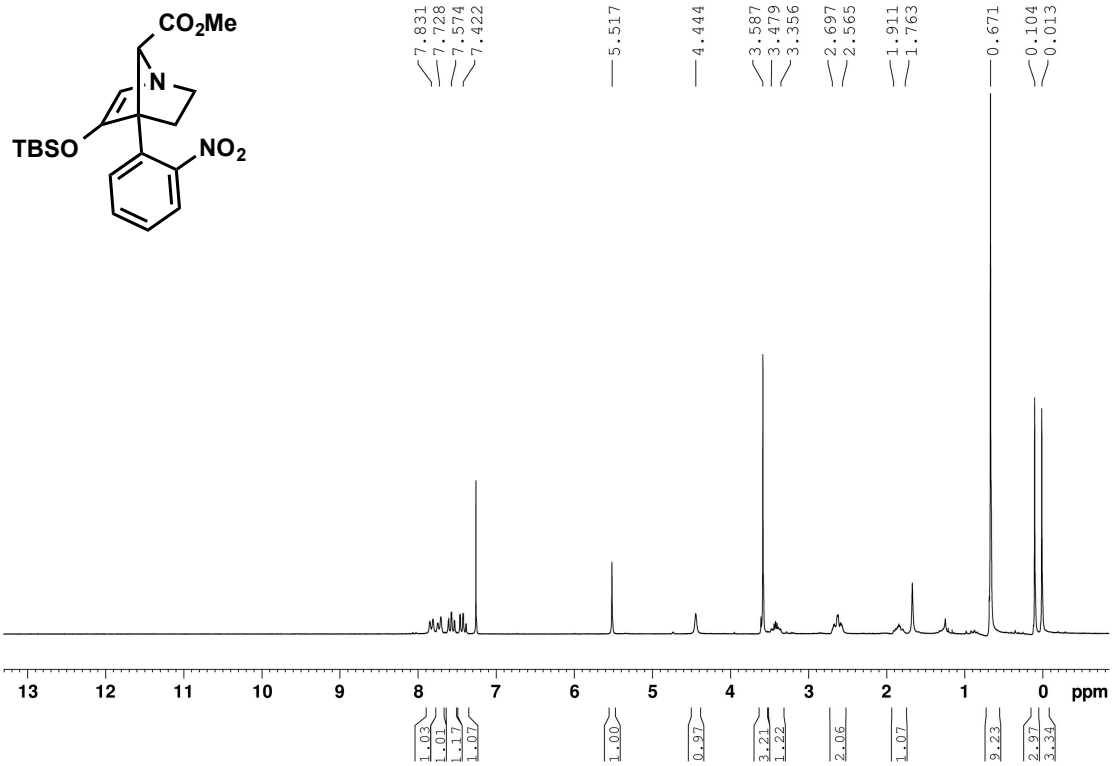
Compound **268**



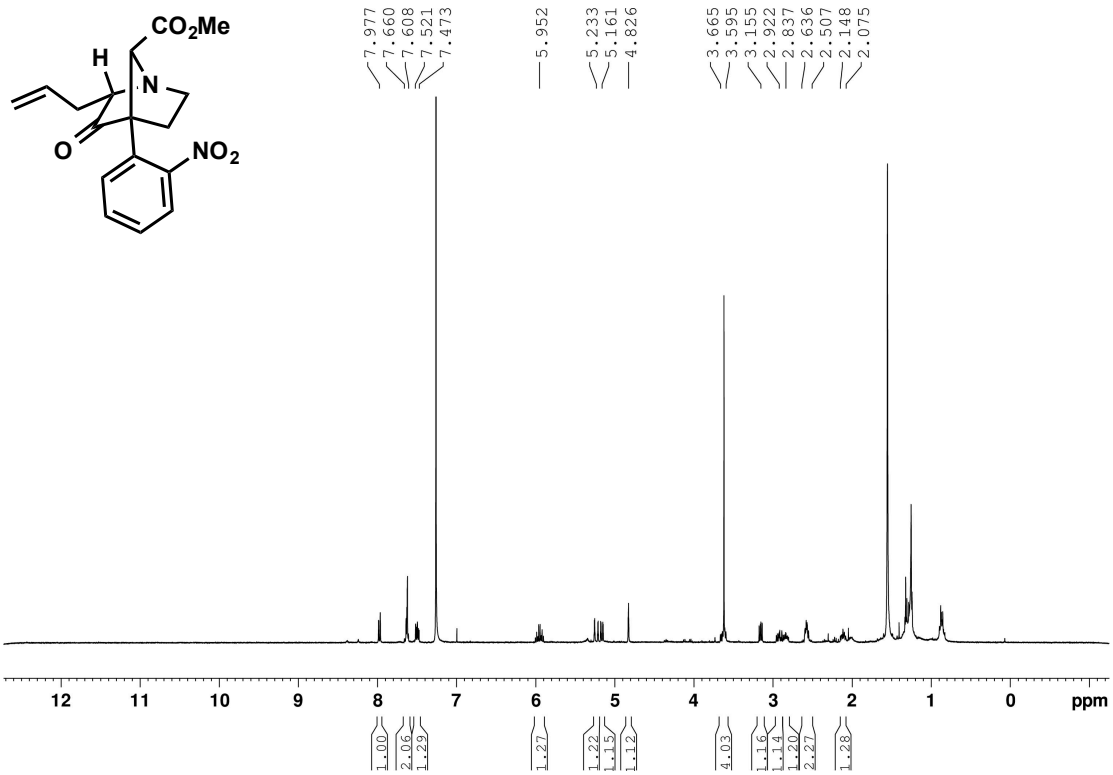
Compound **269**



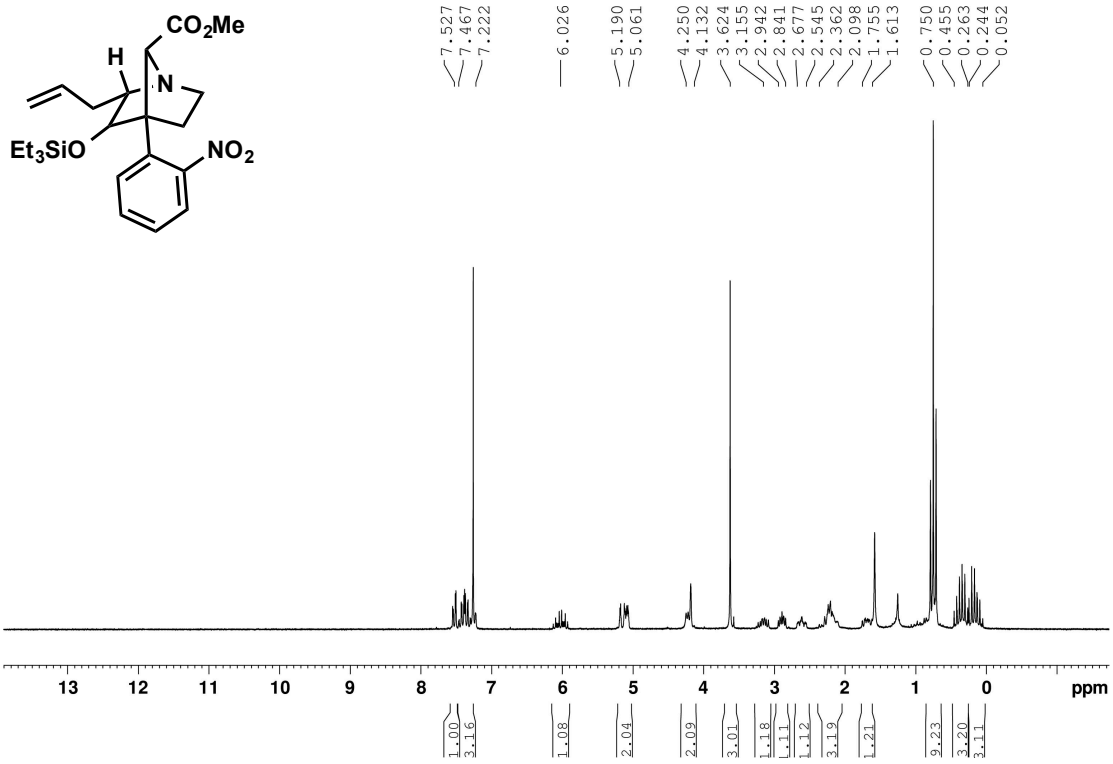
Compound **272**



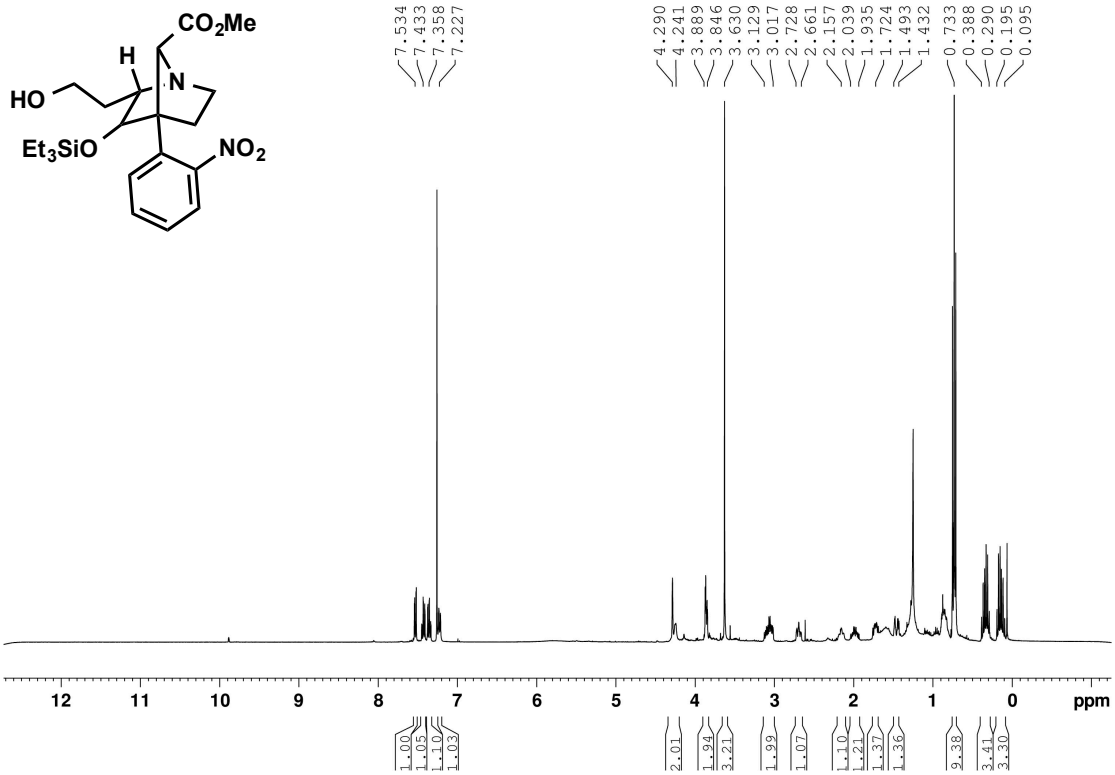
Compound **274**



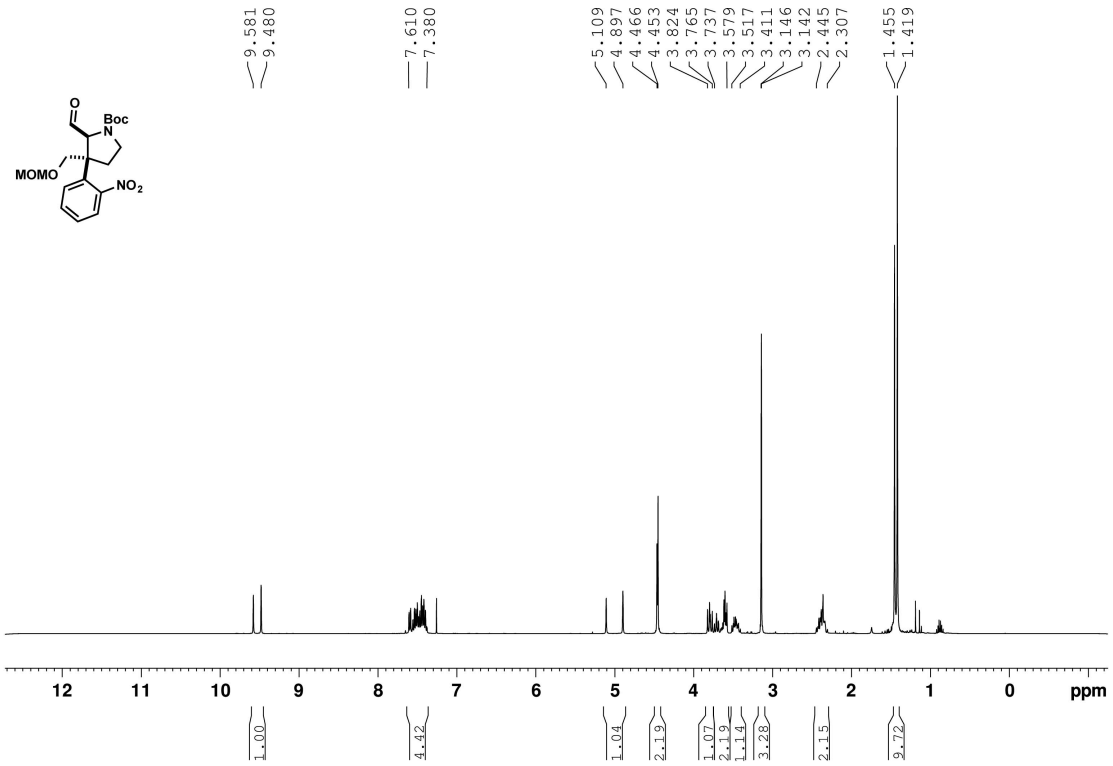
Compound **275**

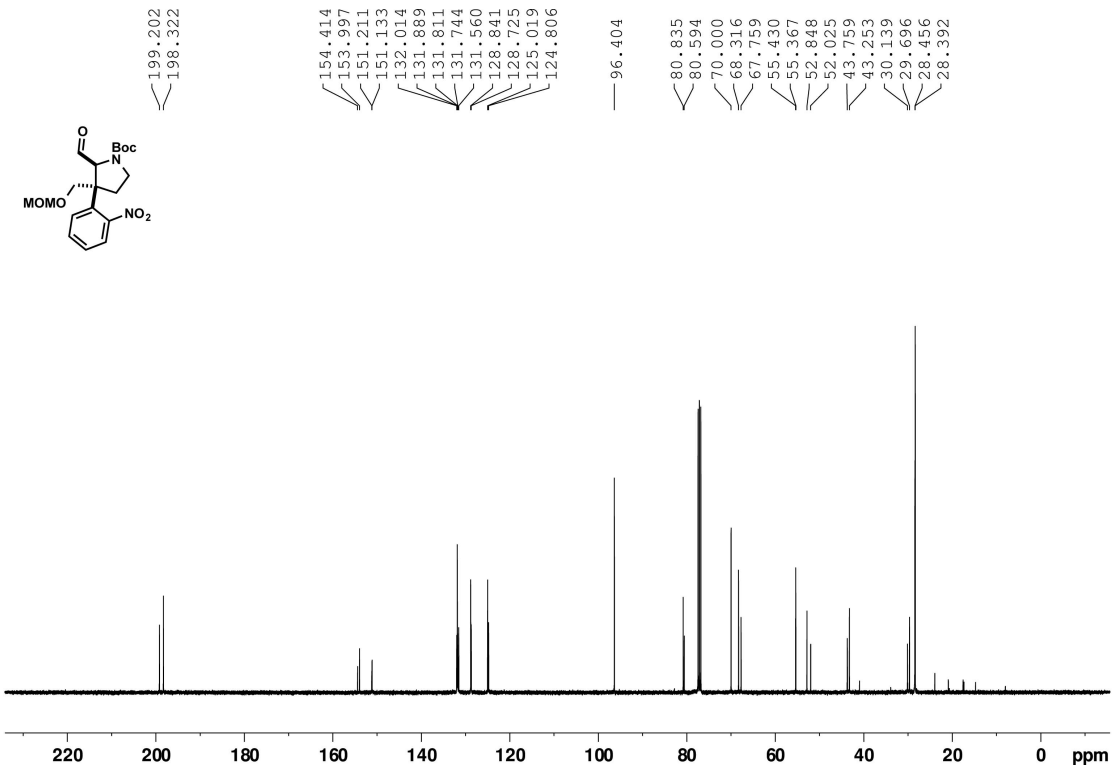


Compound **276**

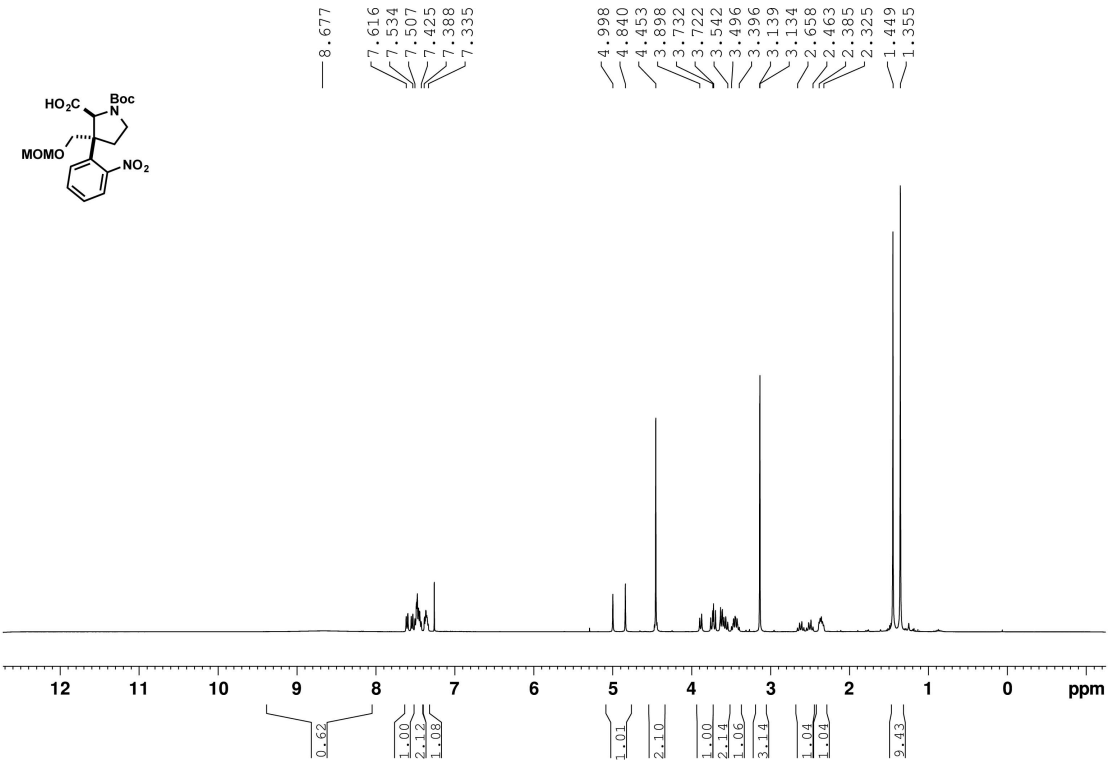


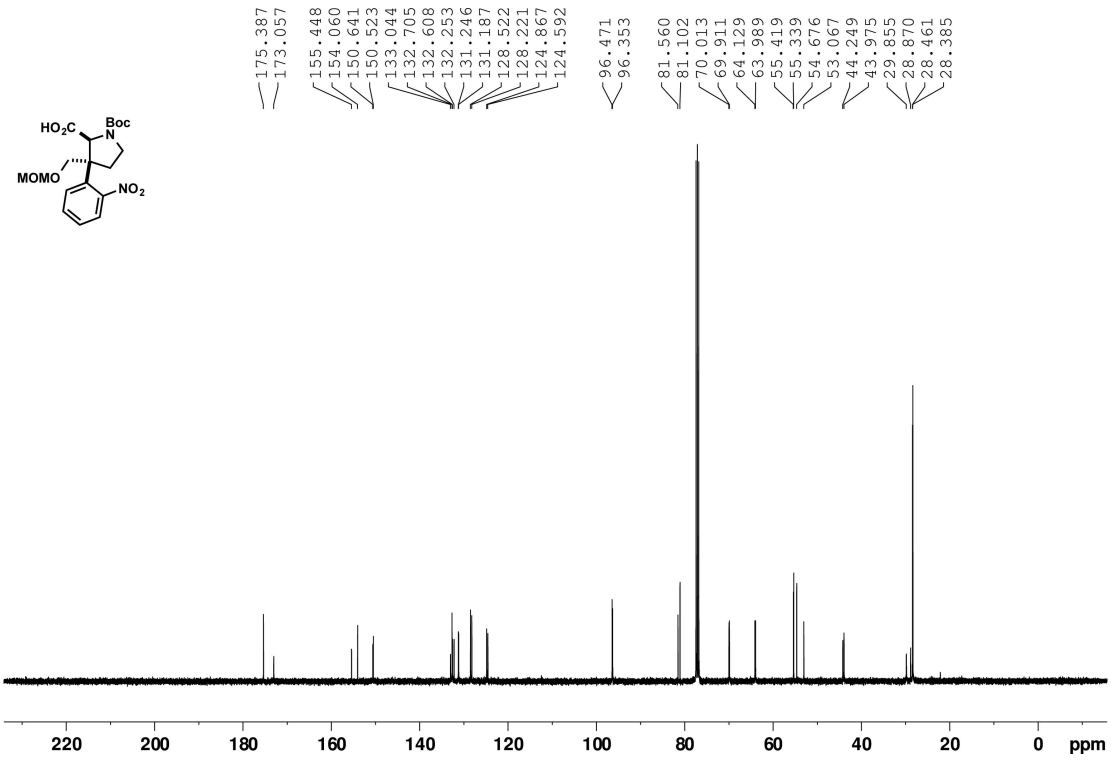
Compound **298b**



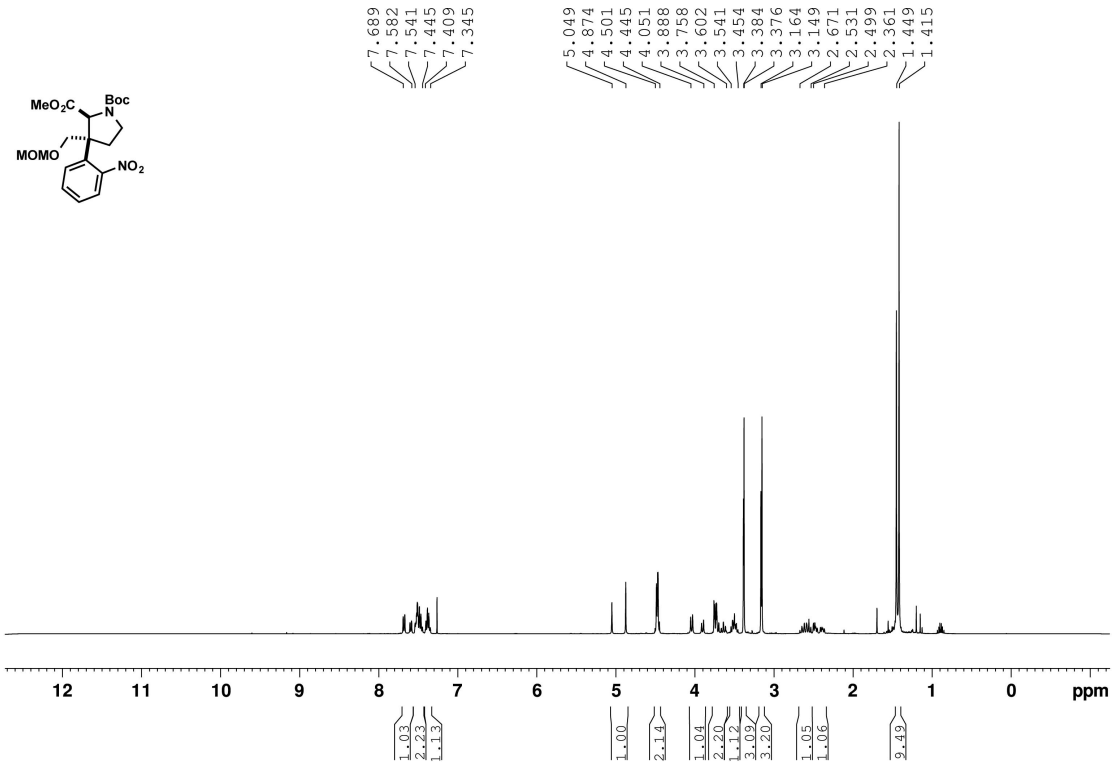


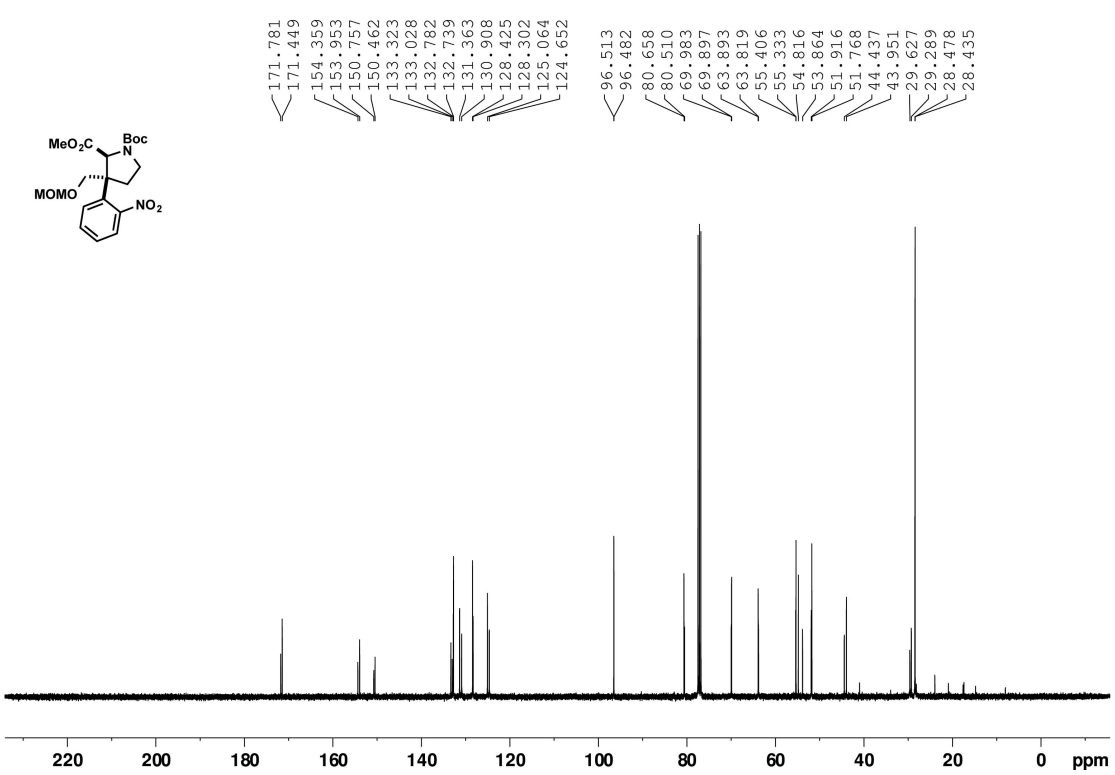
Compound **298c**



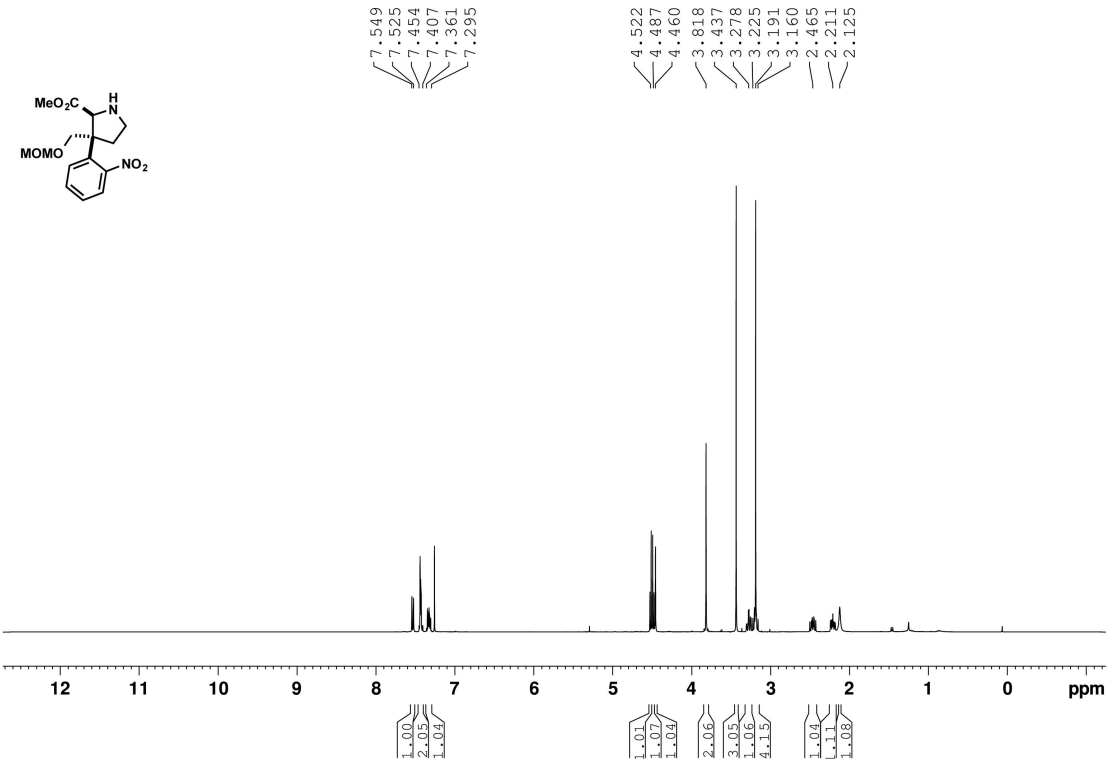


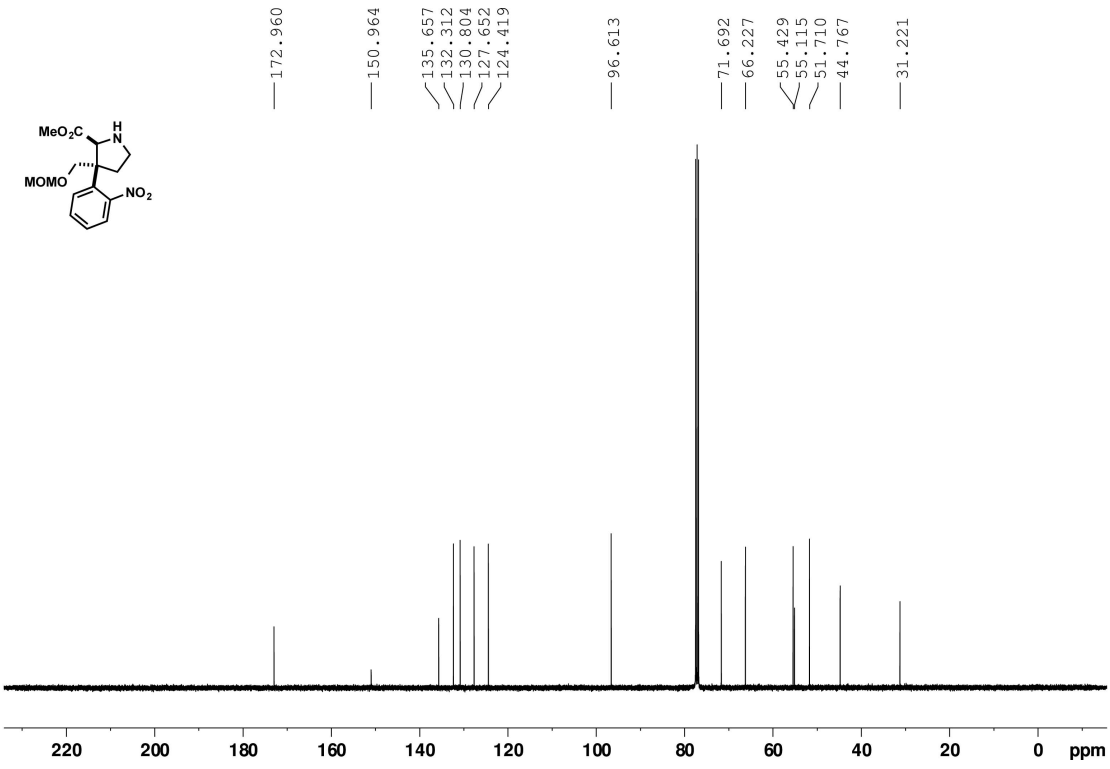
Compound **299**



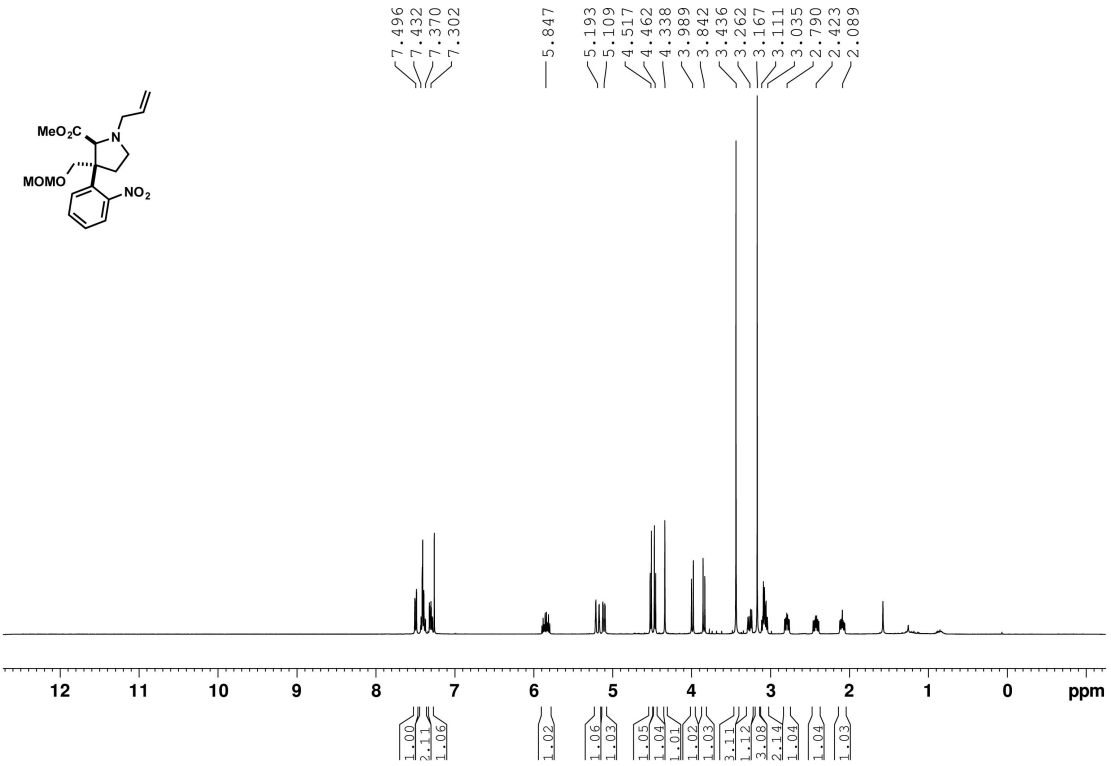


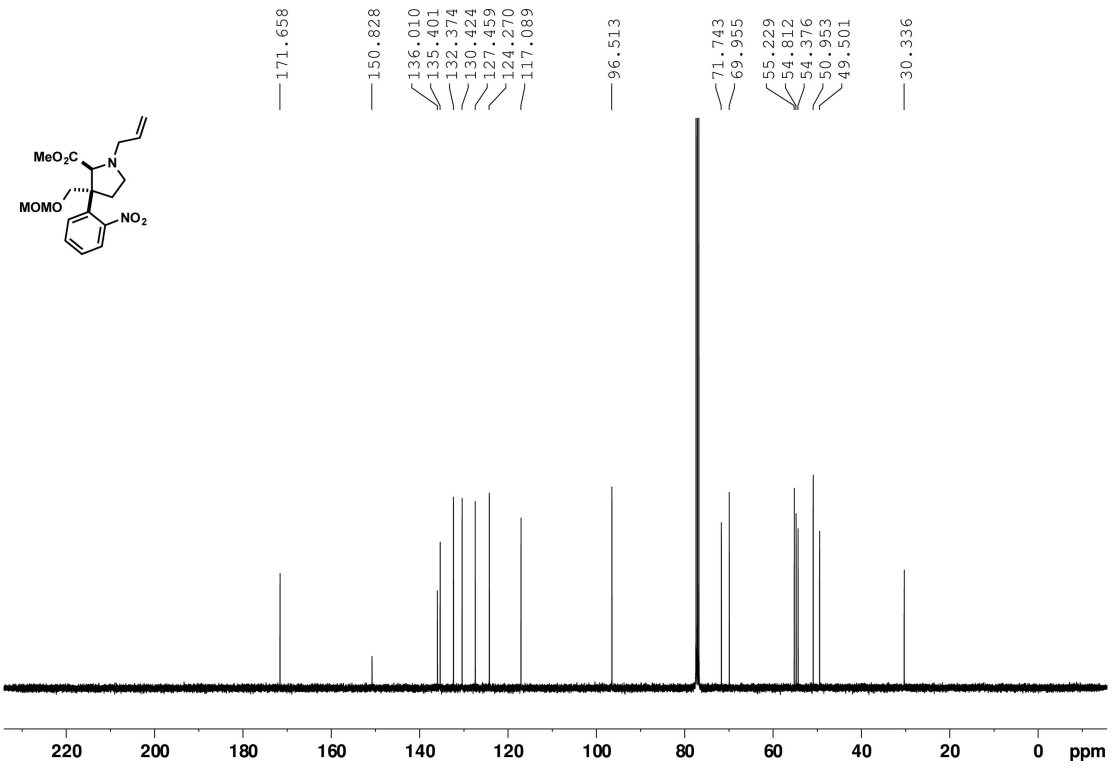
Compound **299b**



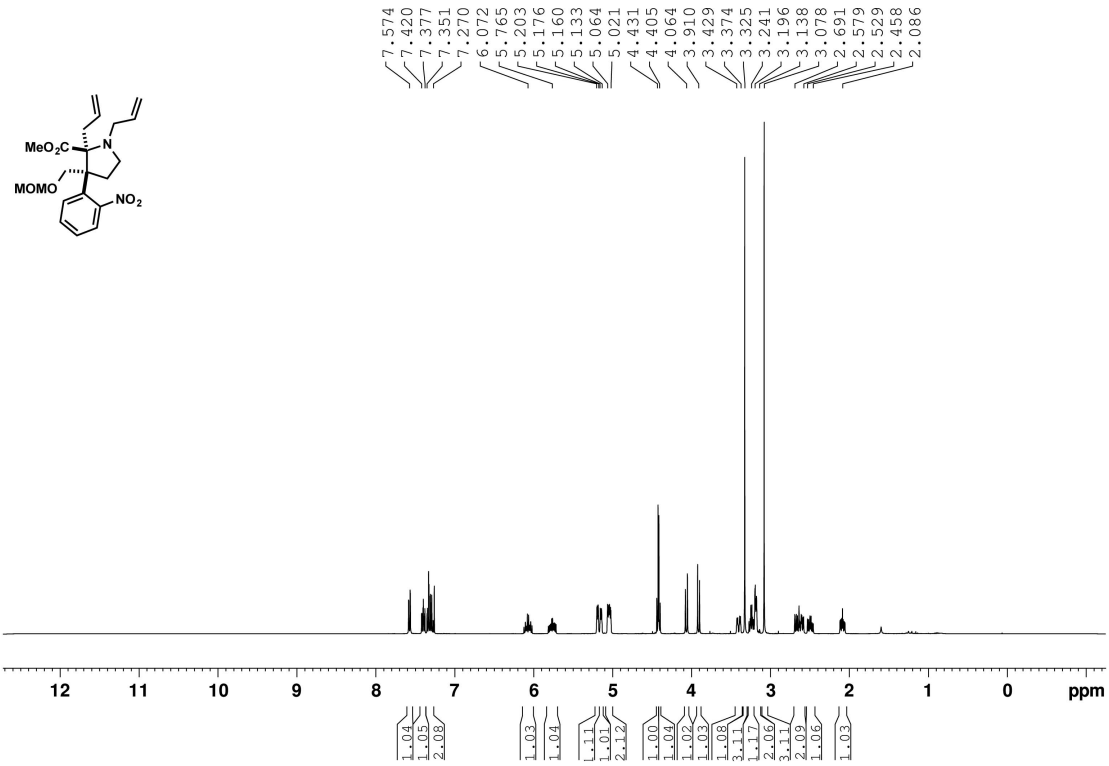


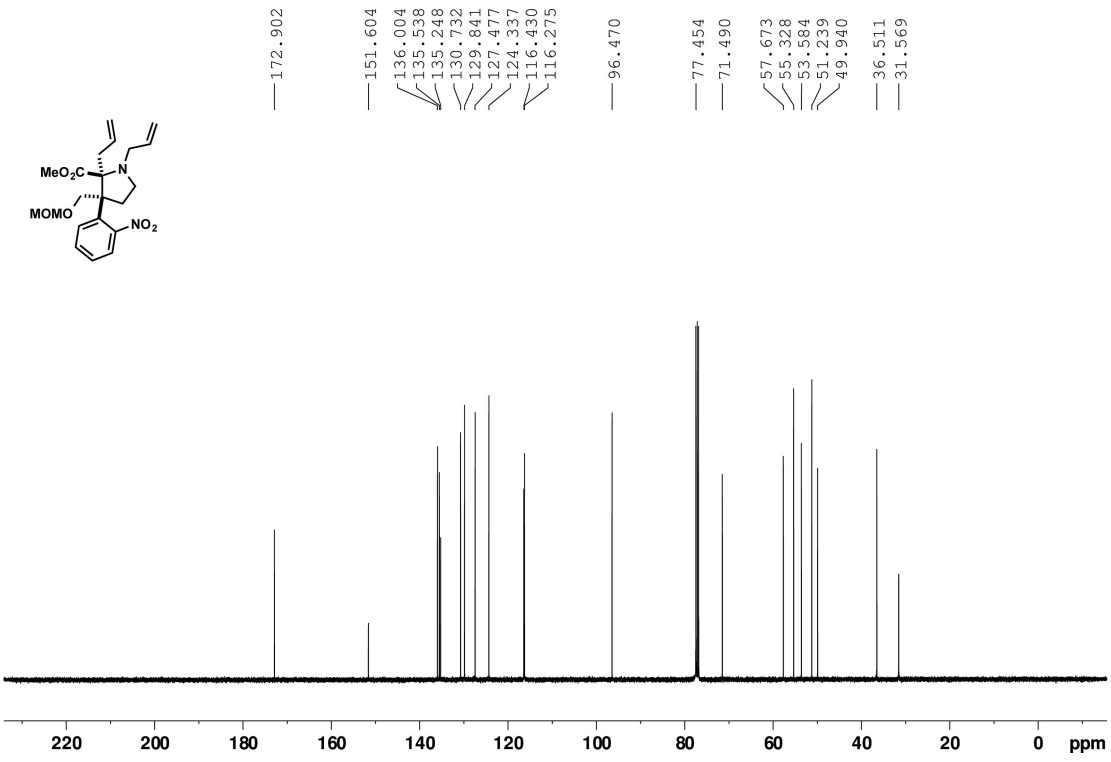
Compound **230**





Compound **300**





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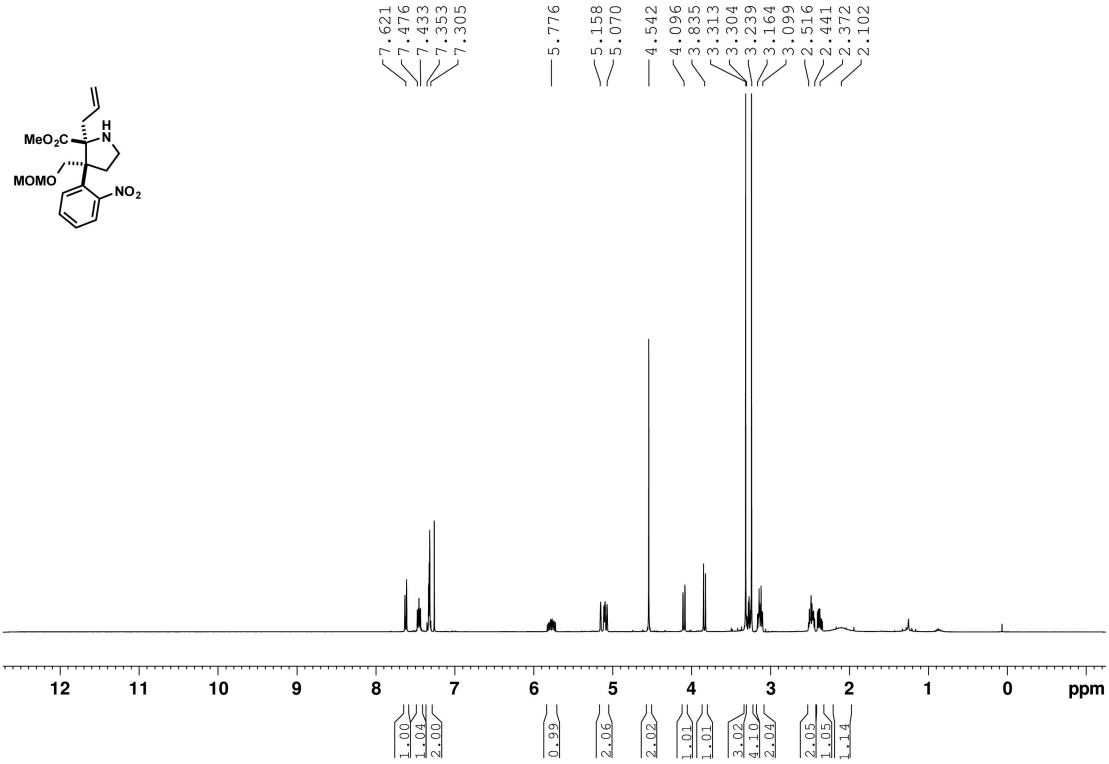

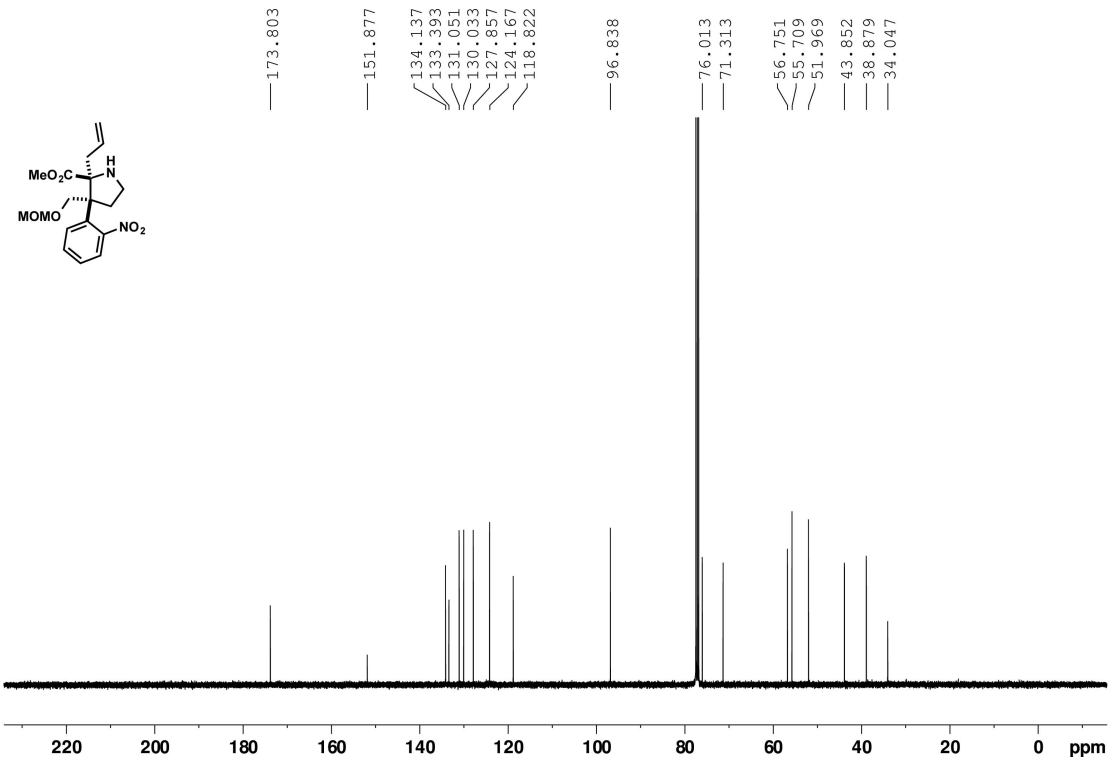

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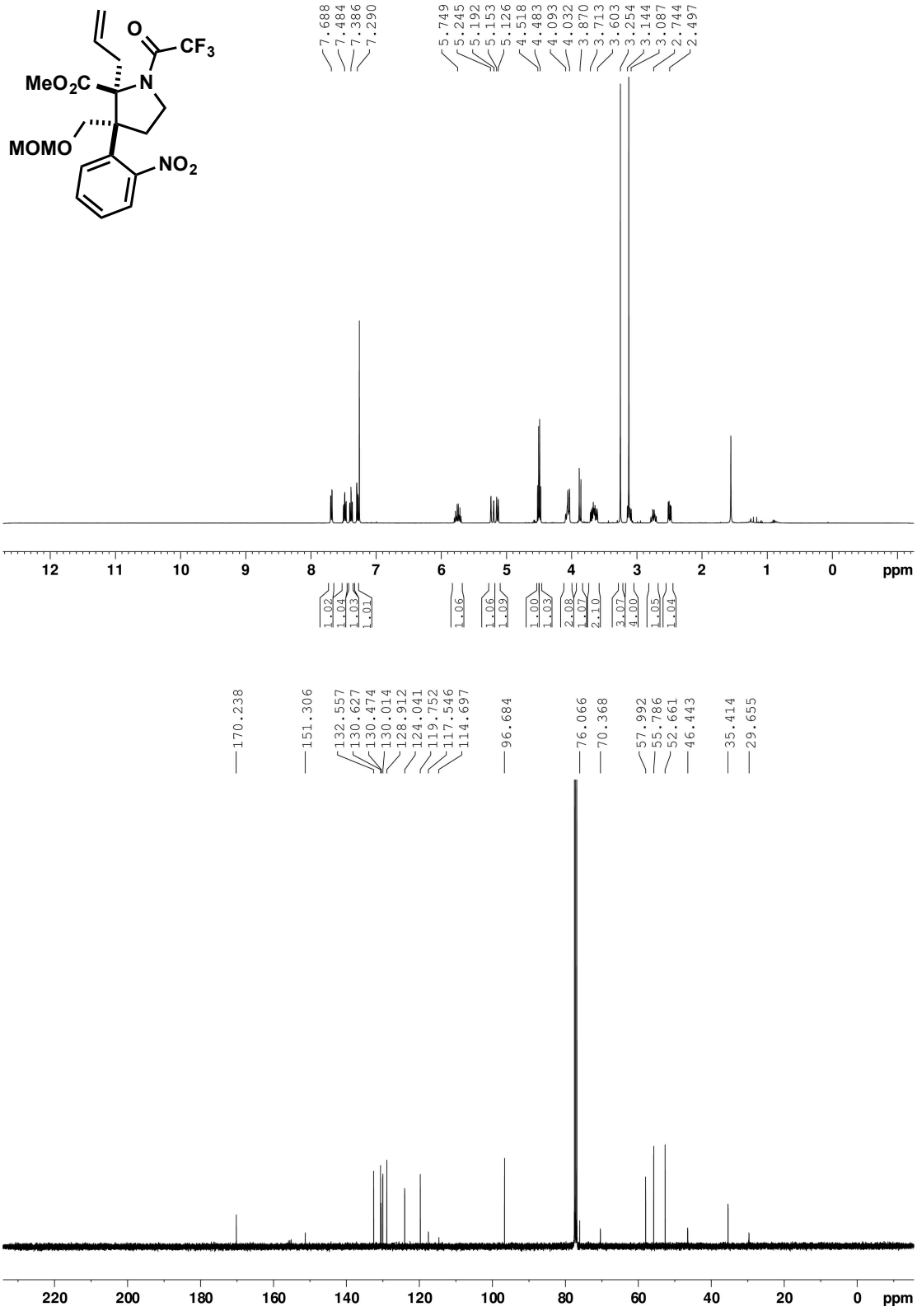

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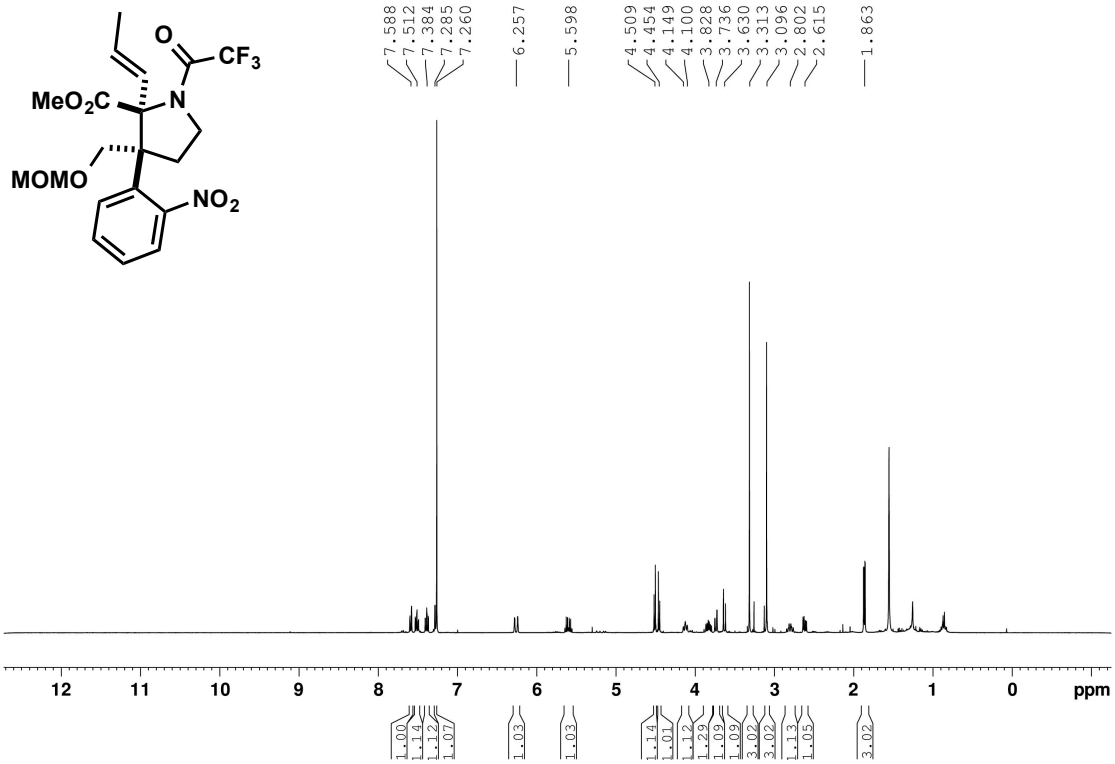

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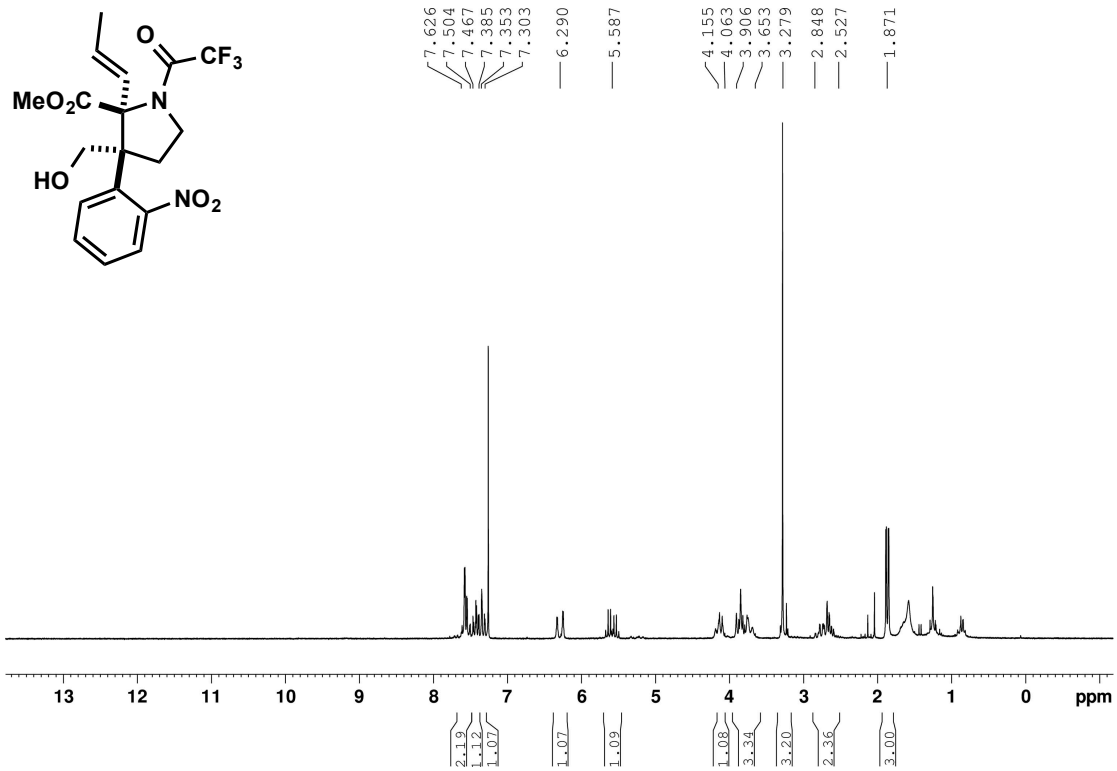

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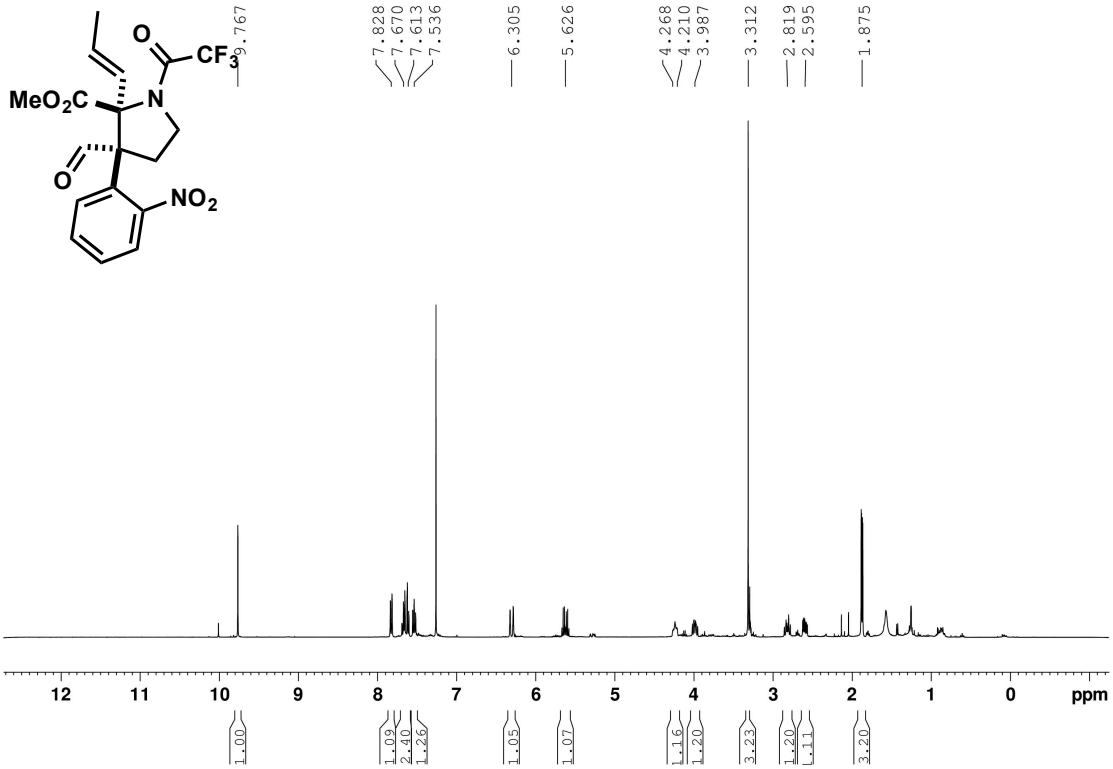
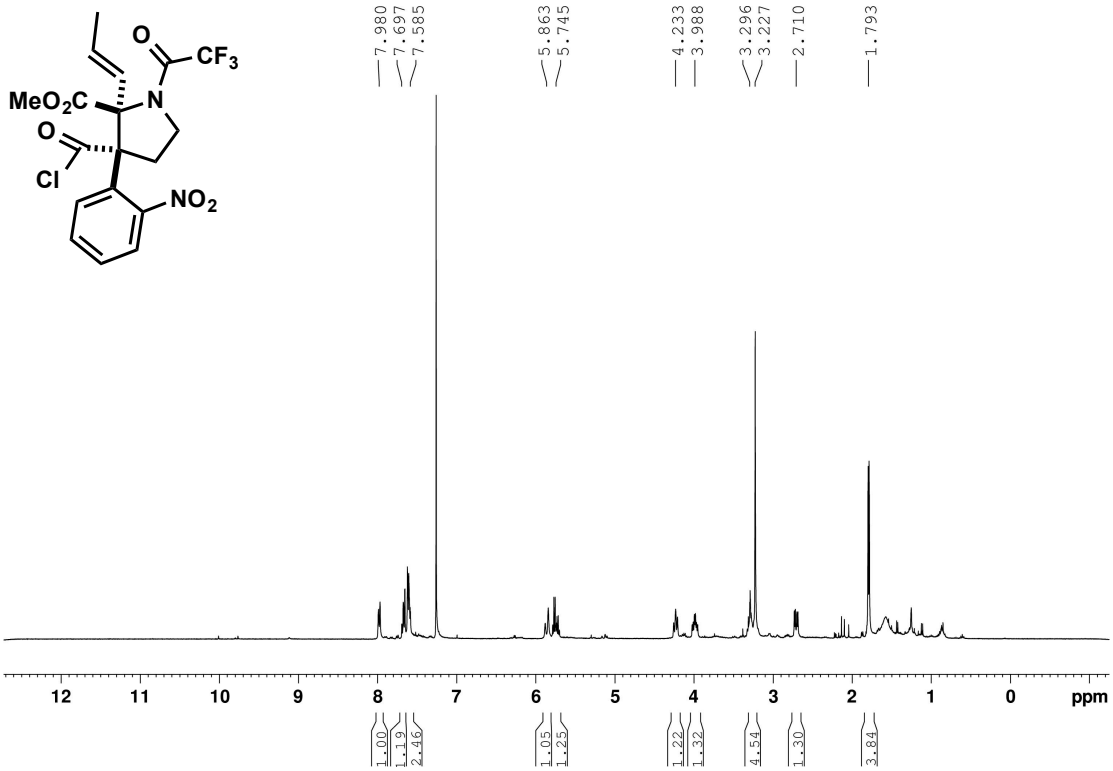


Compound **307**



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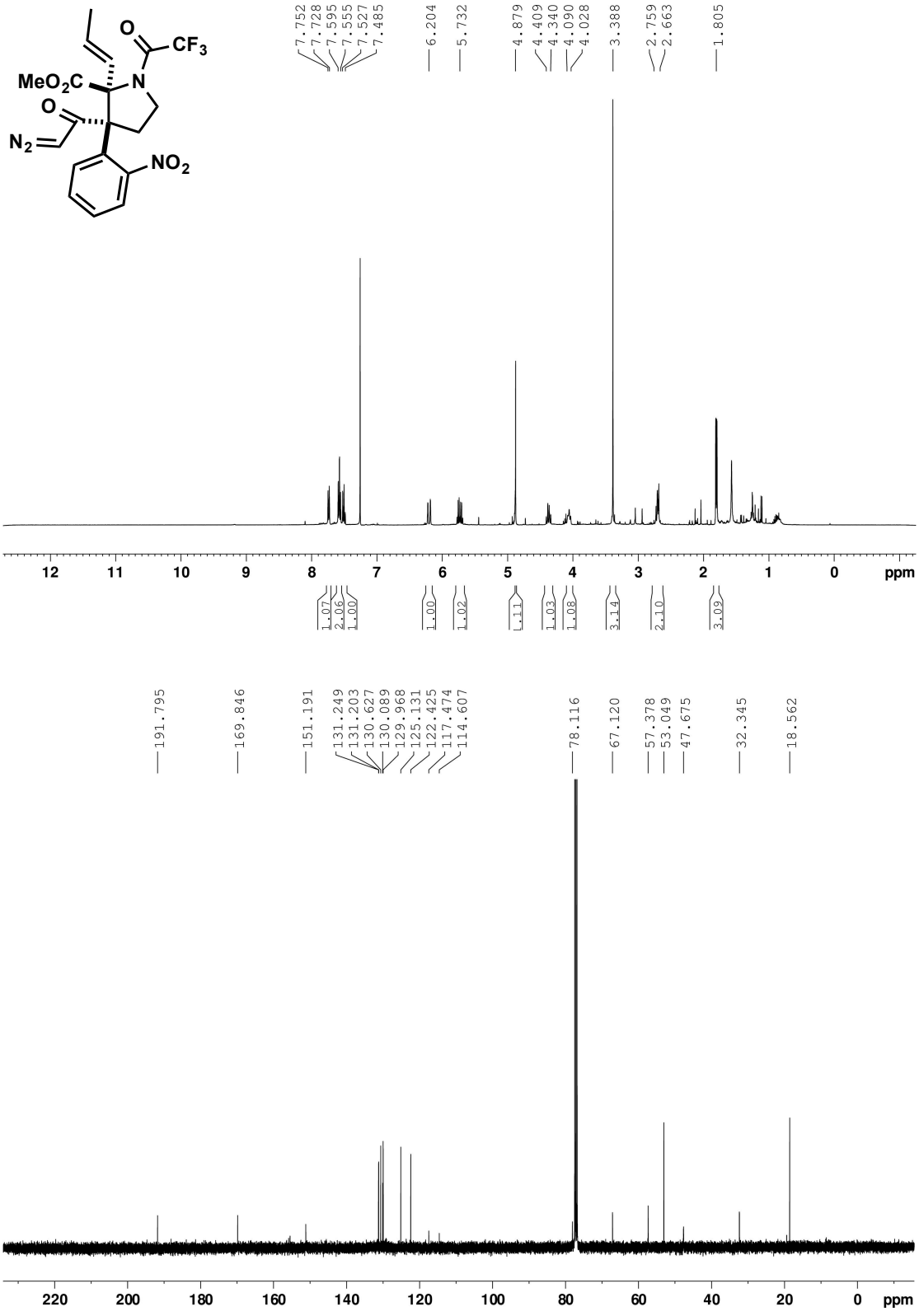

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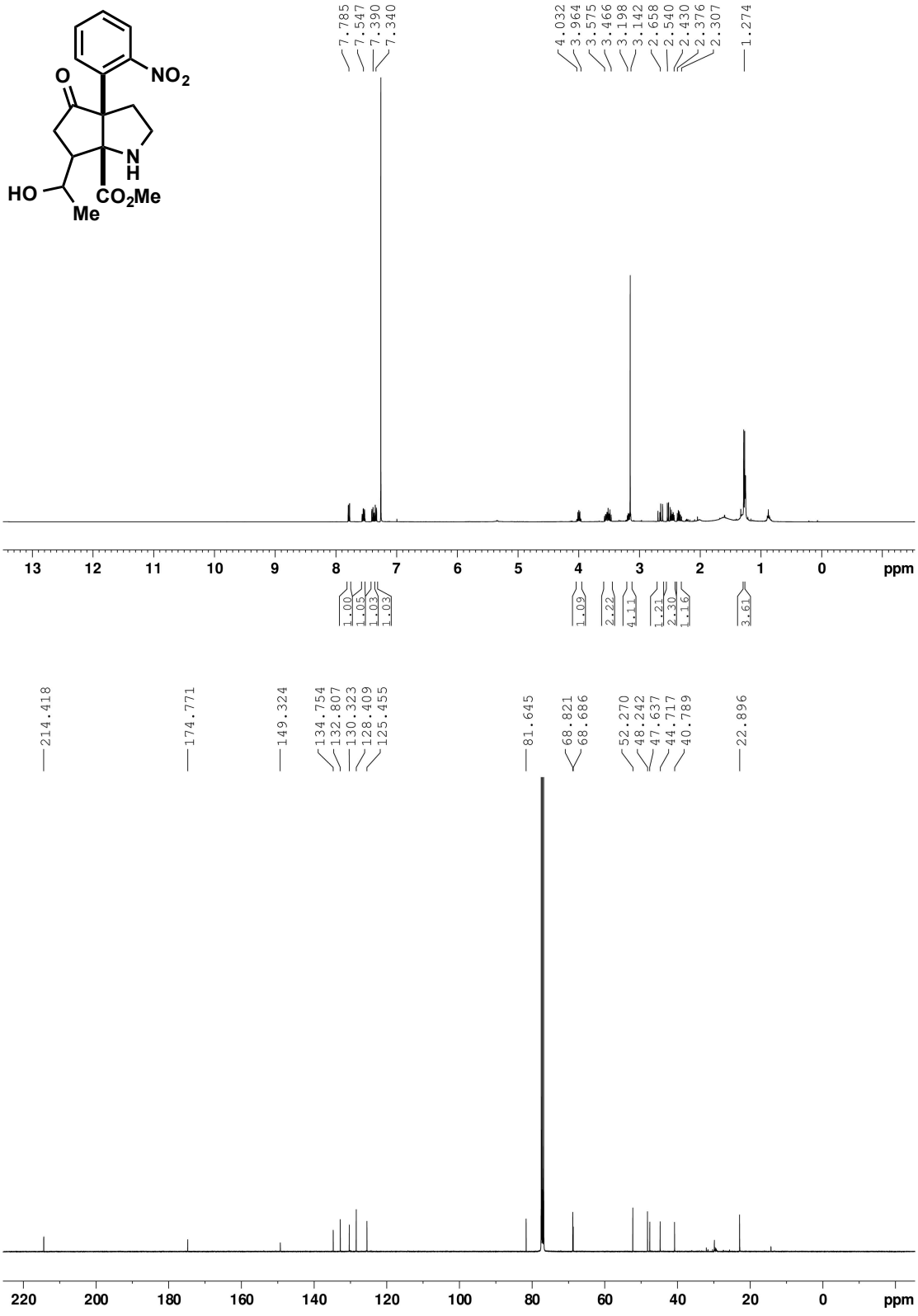

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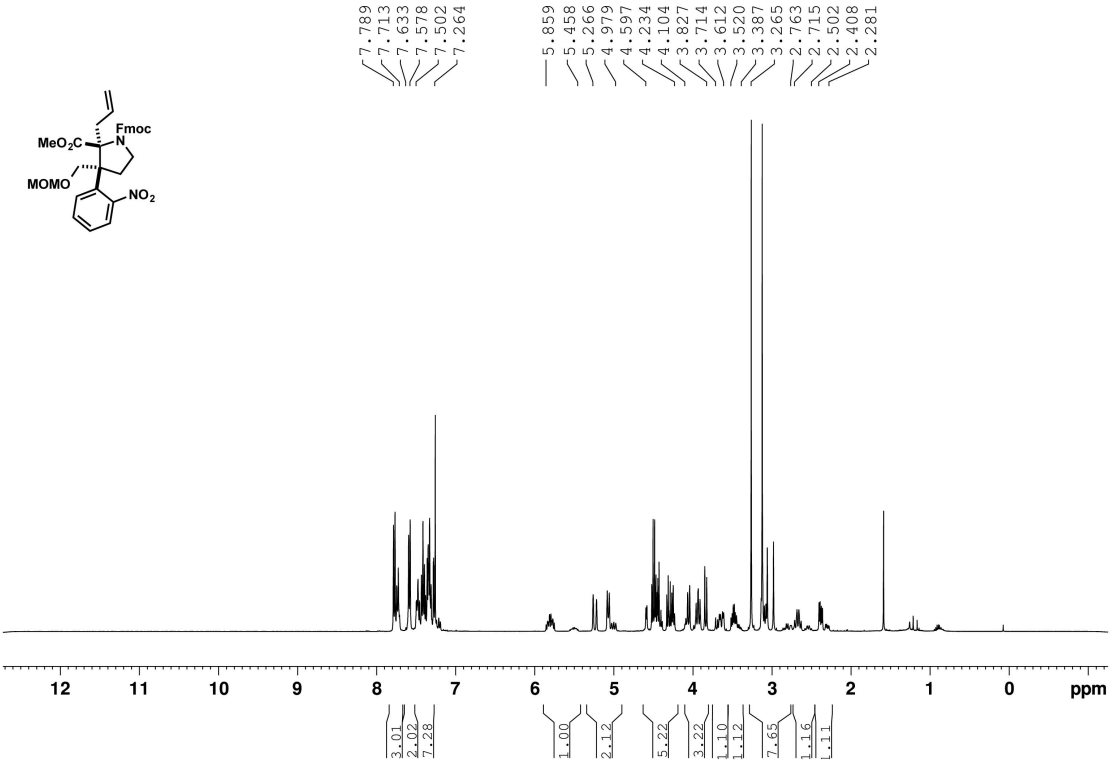

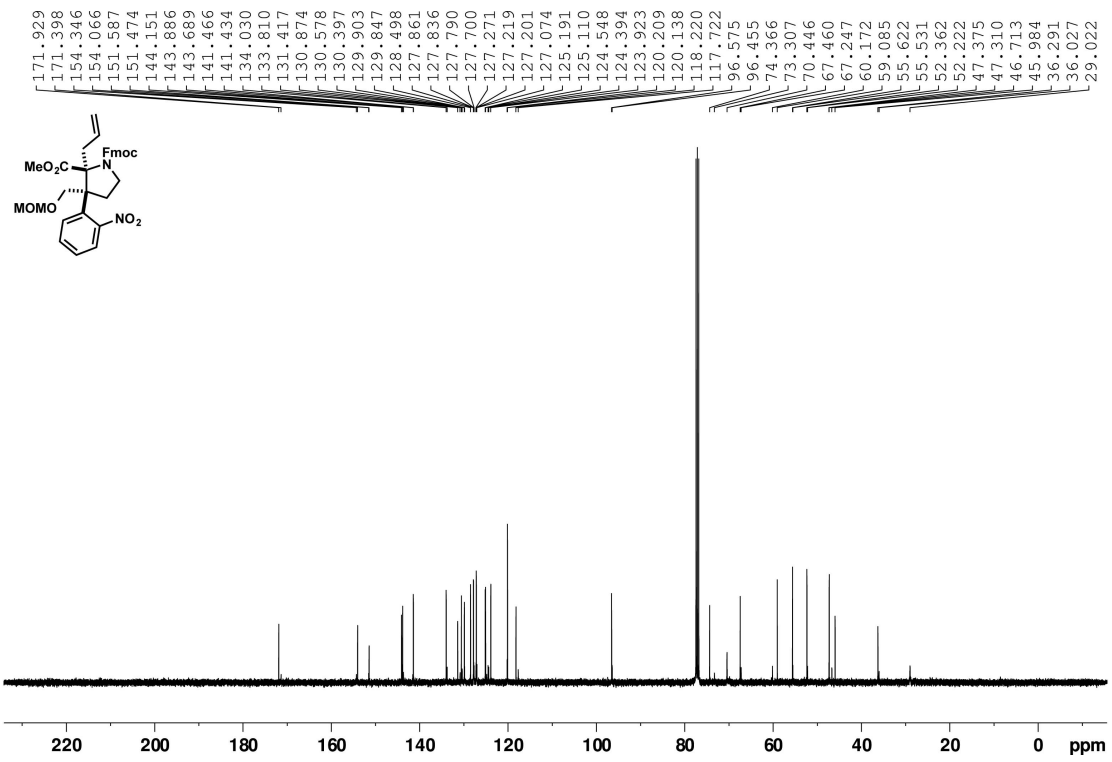

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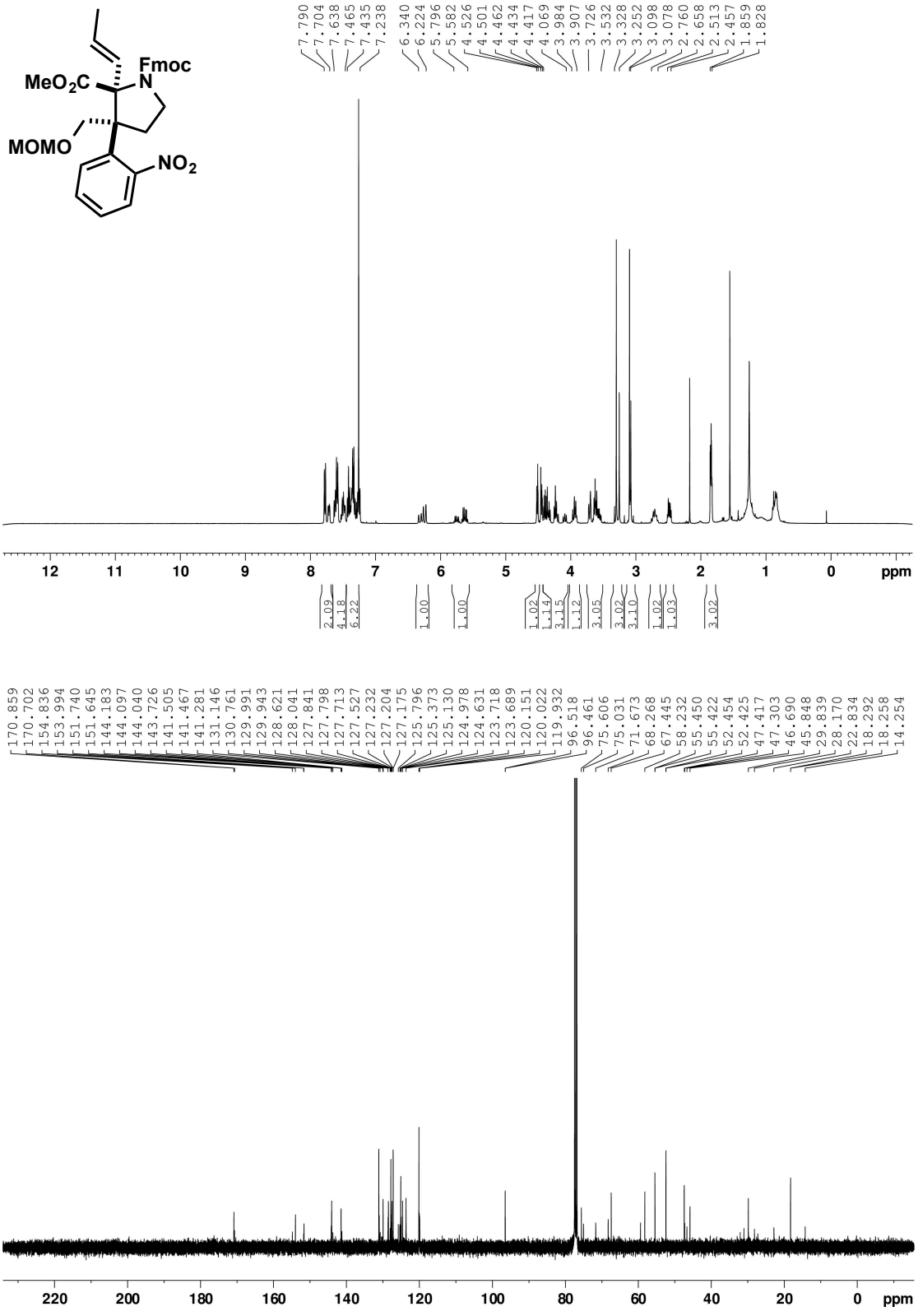

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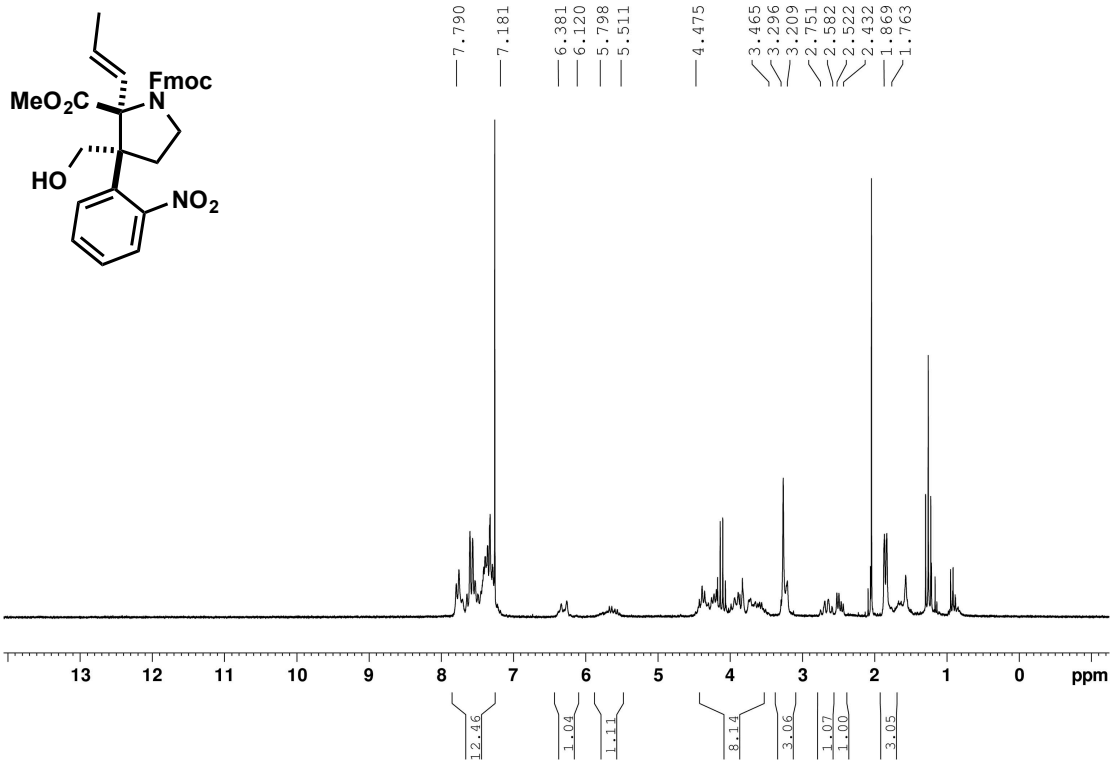

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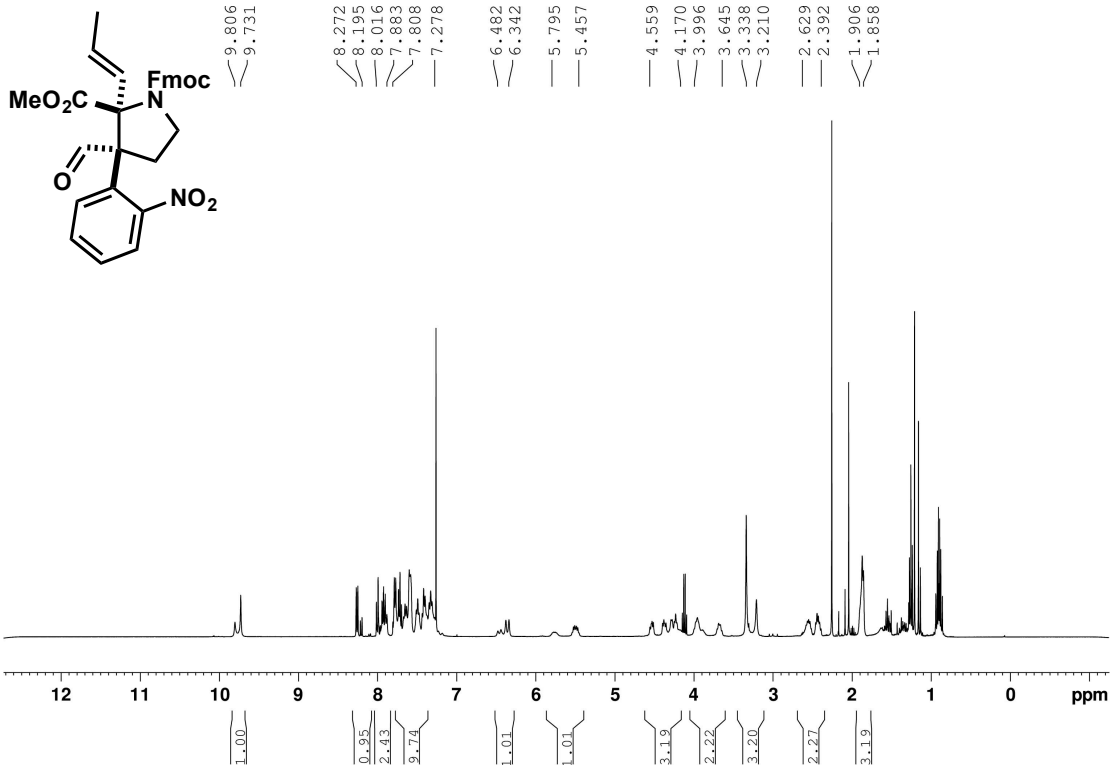

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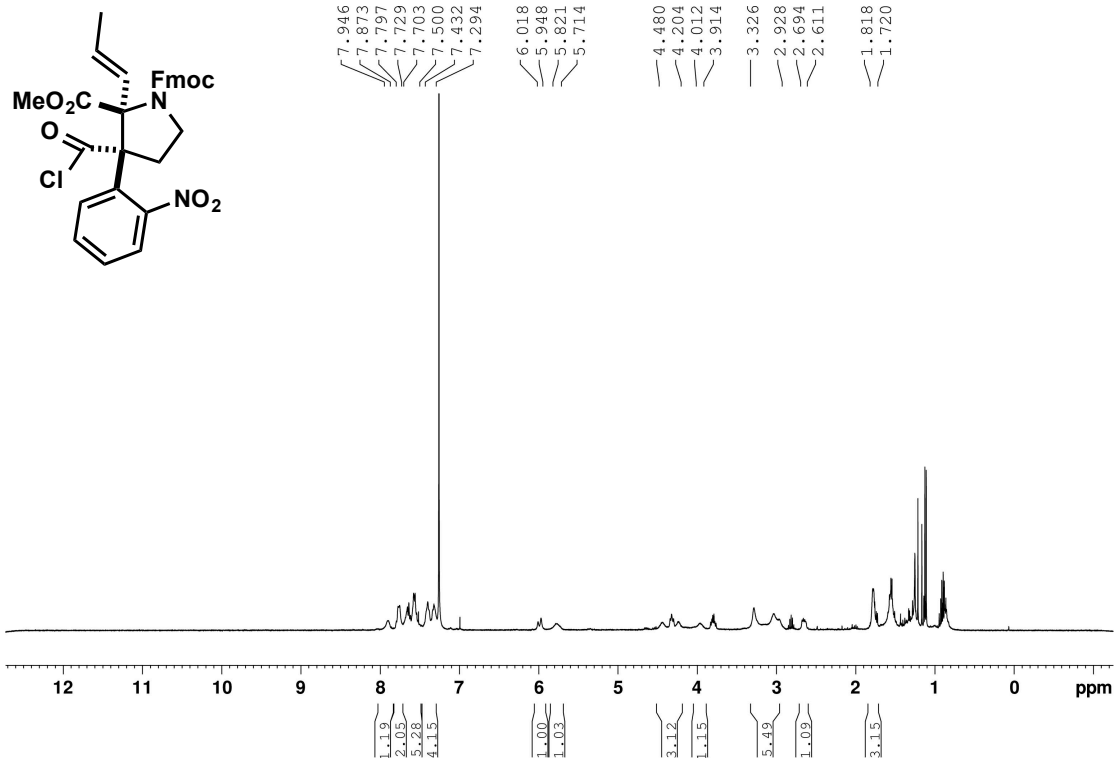

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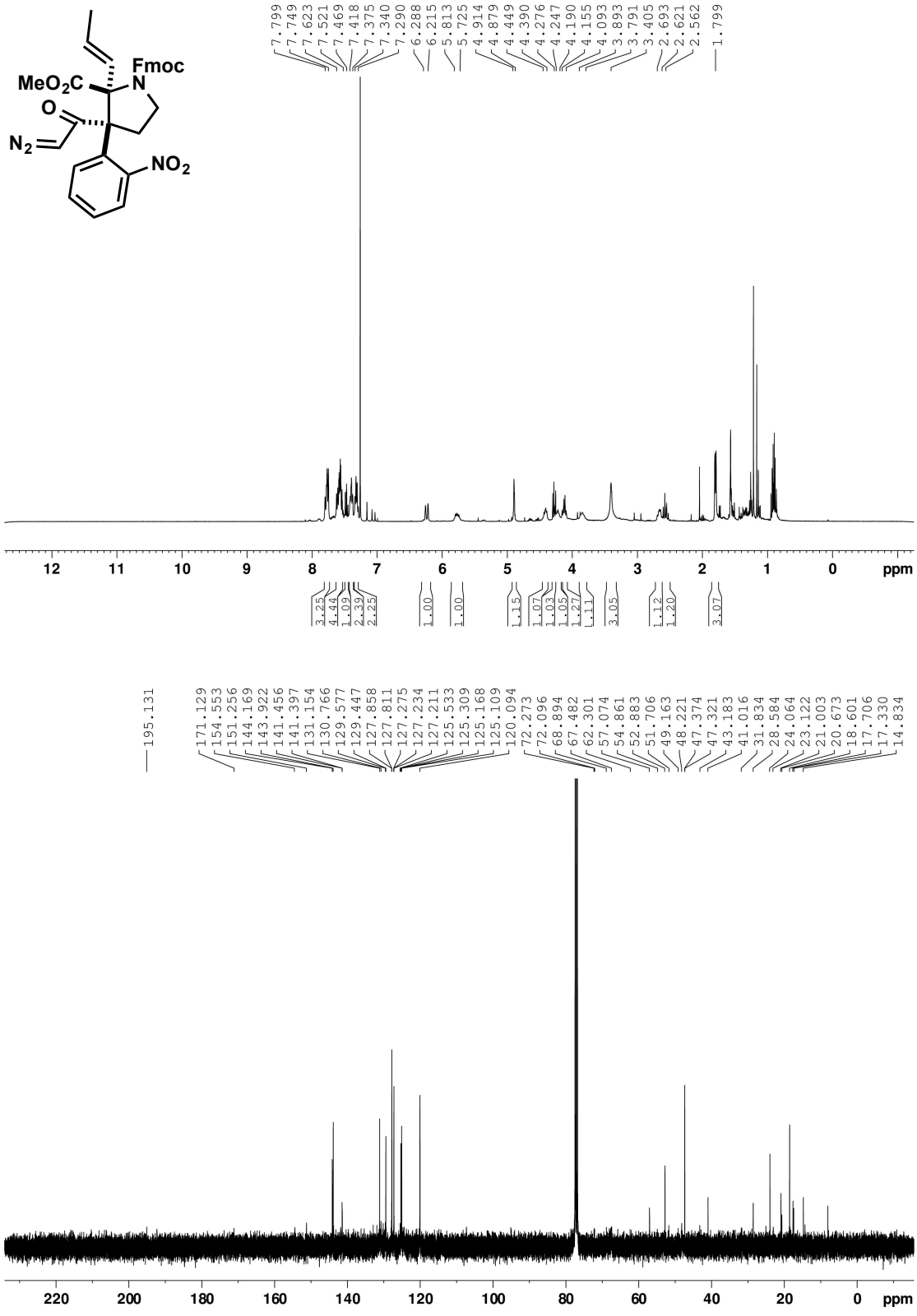

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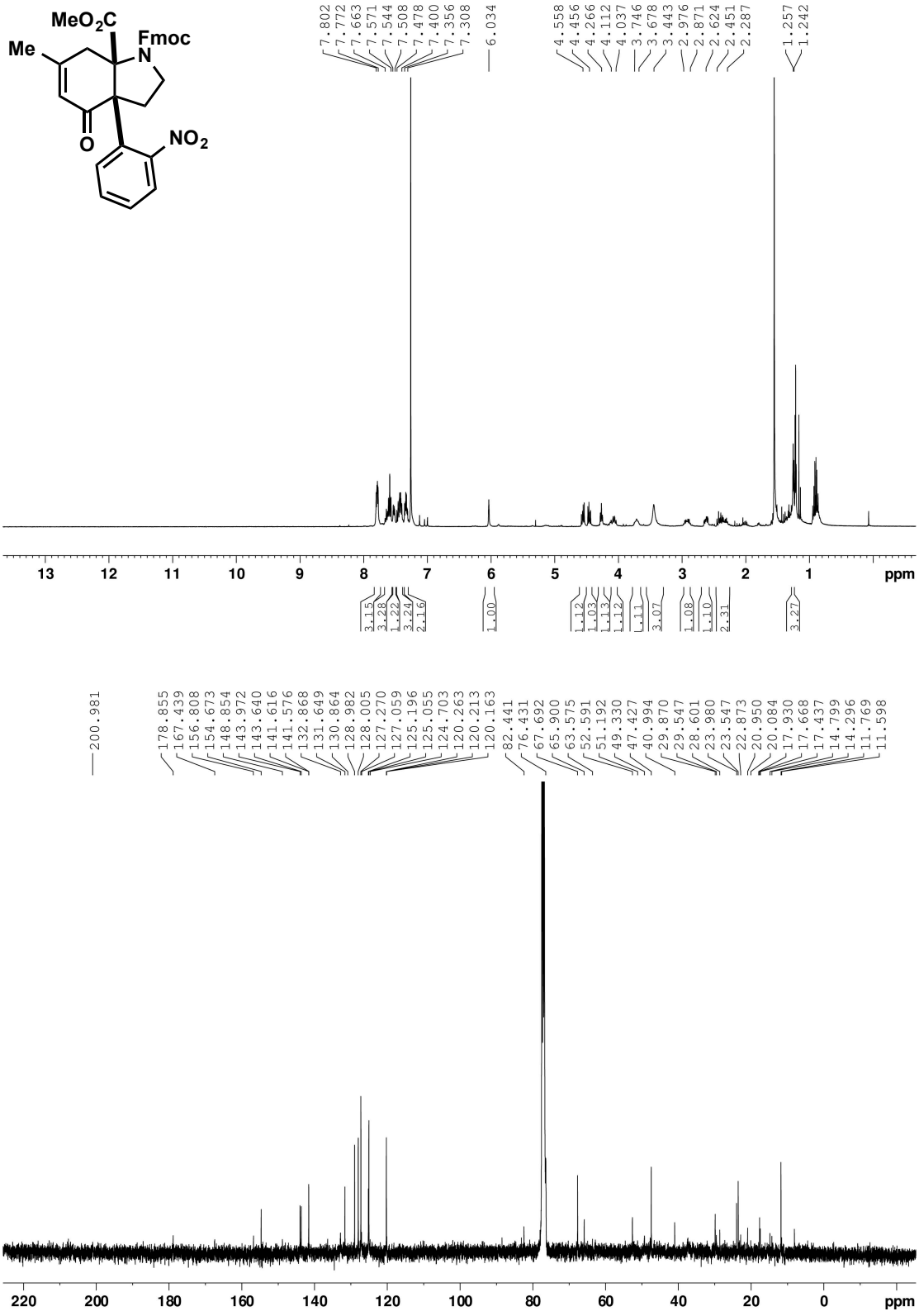

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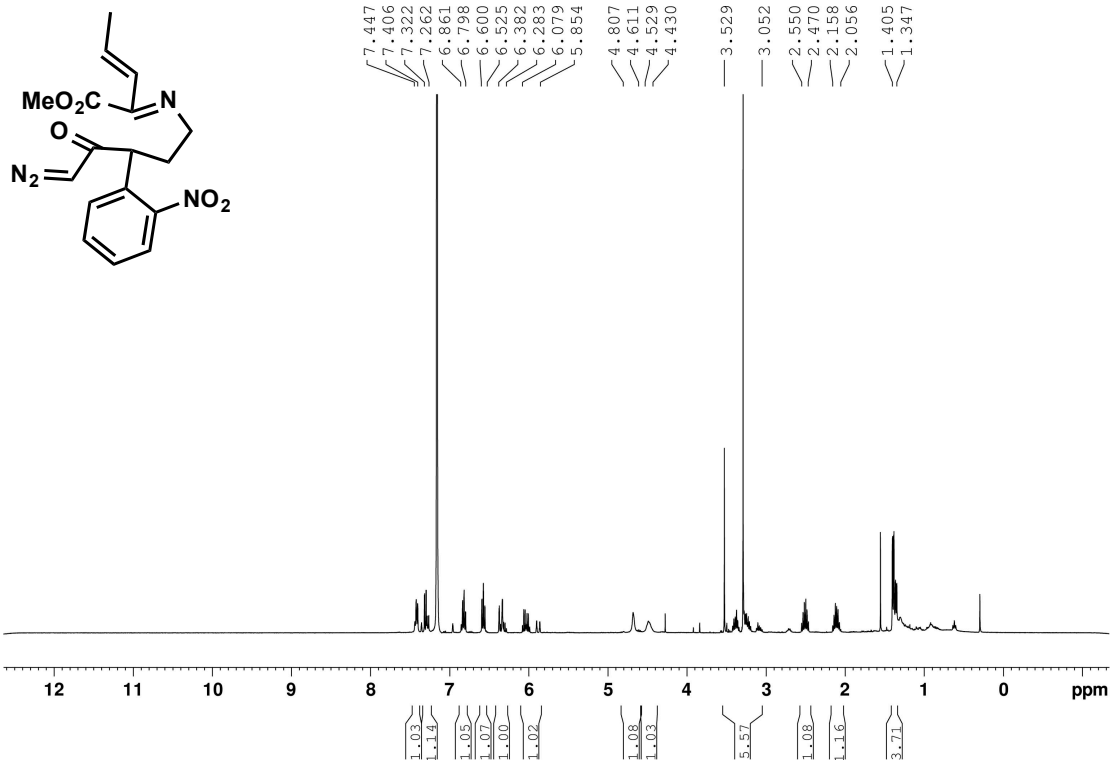

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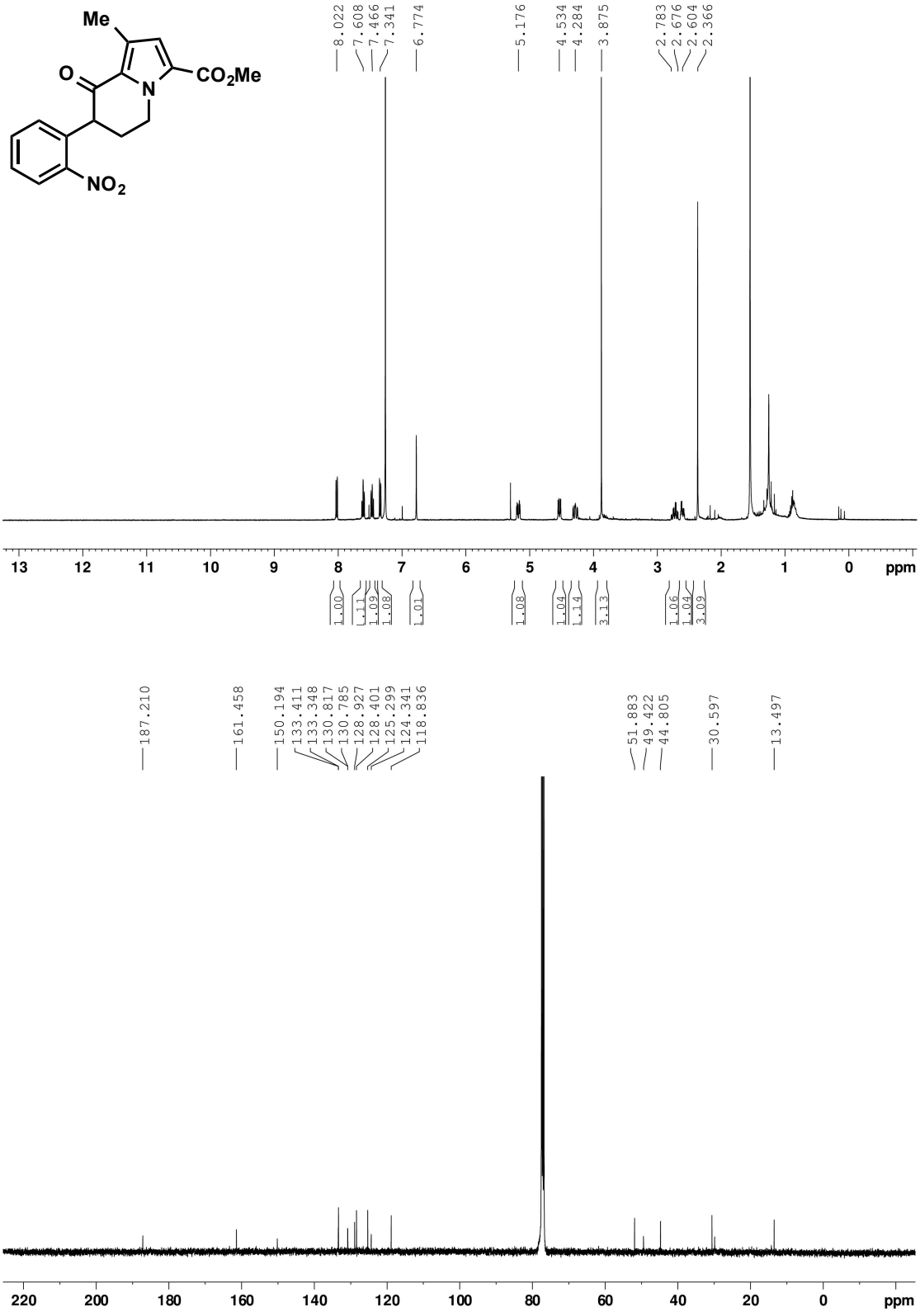

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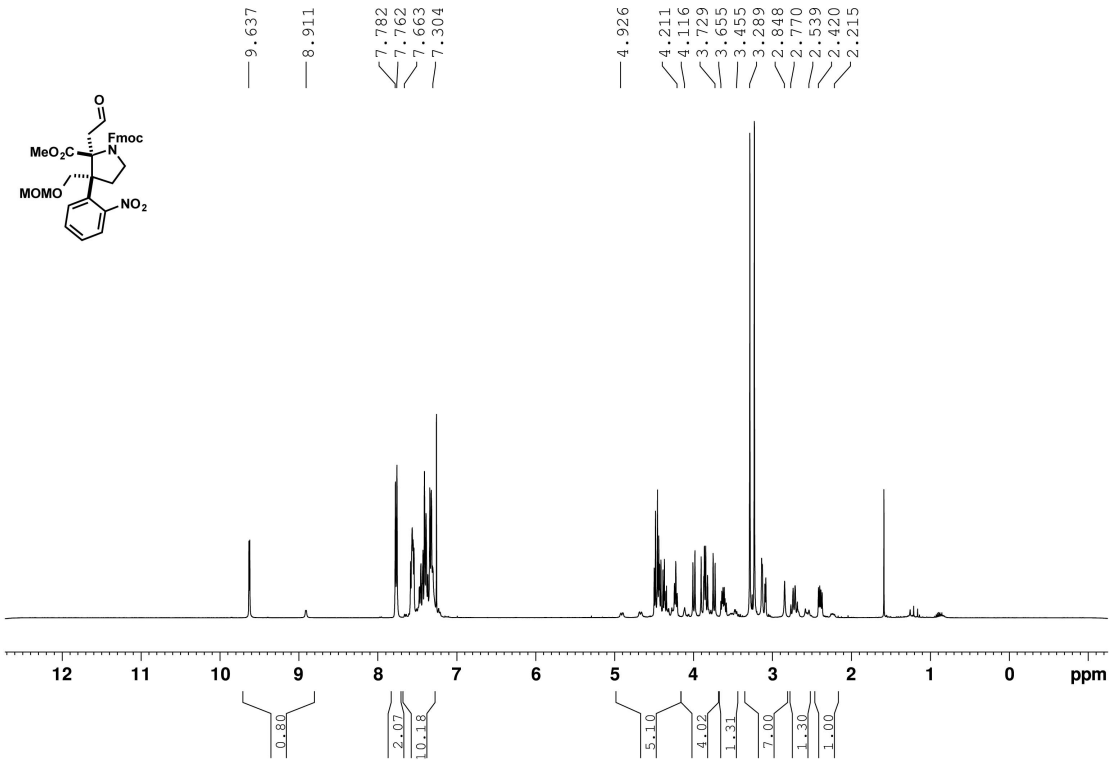

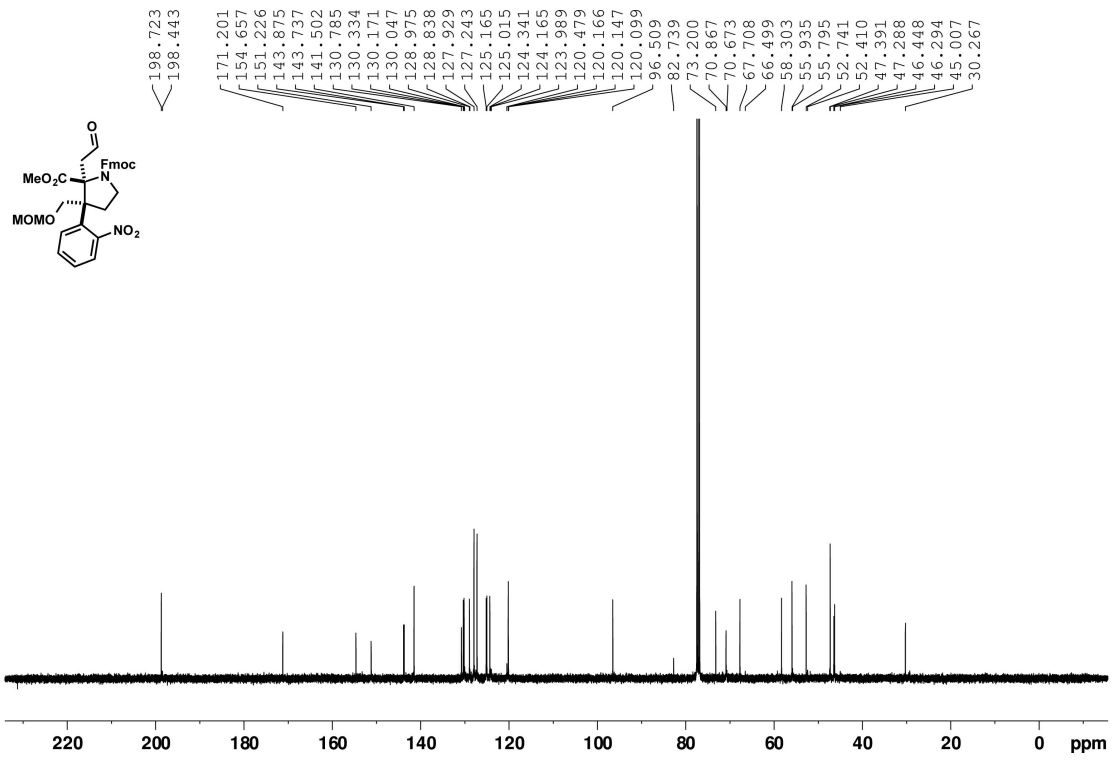

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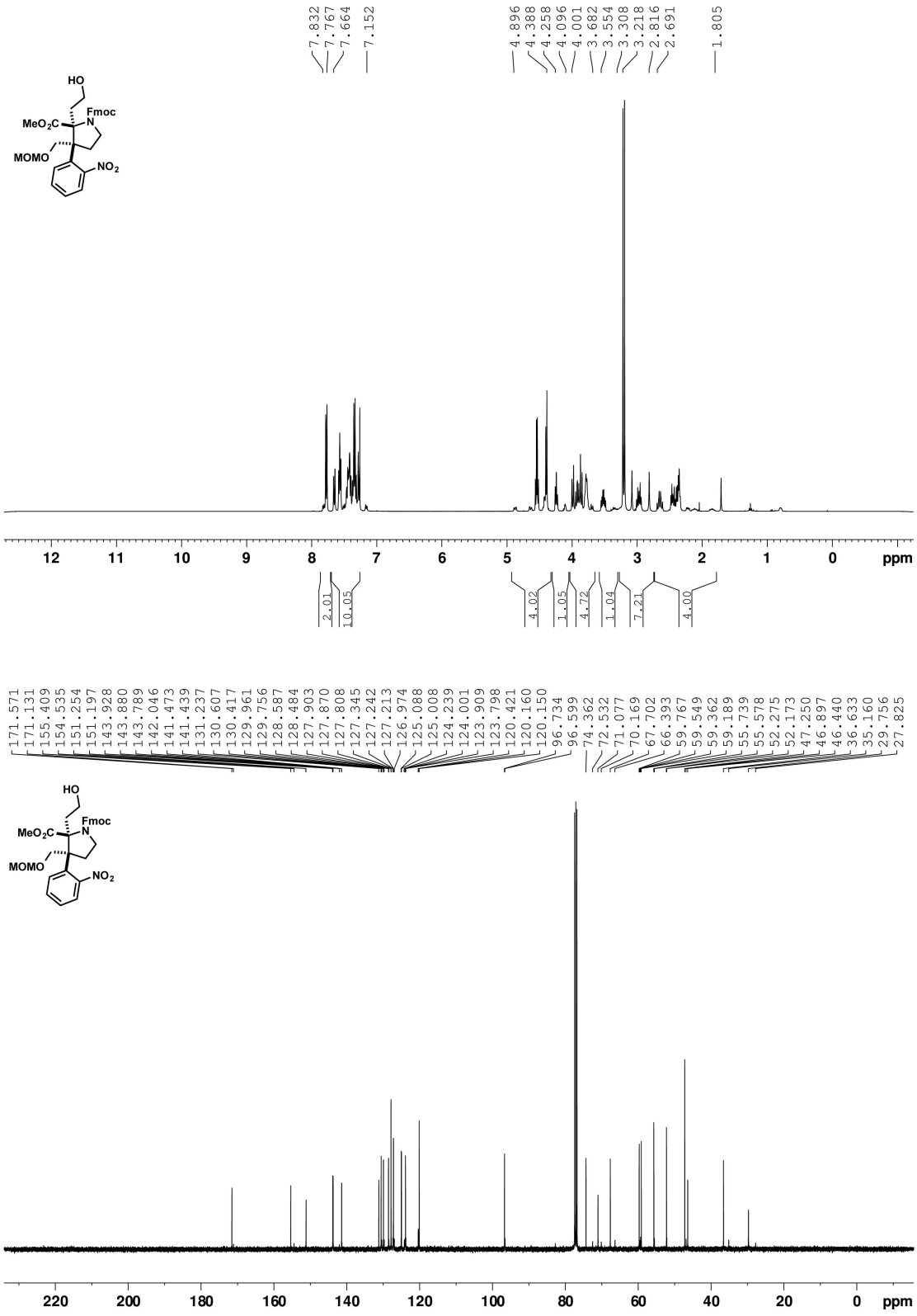

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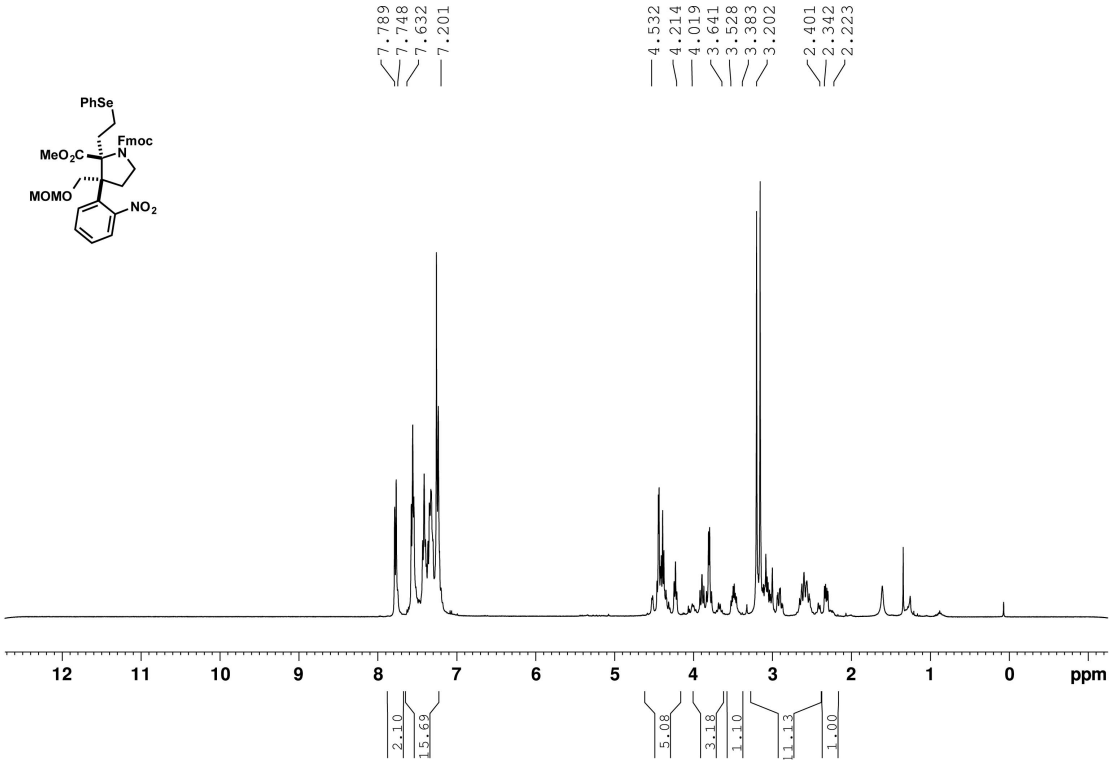

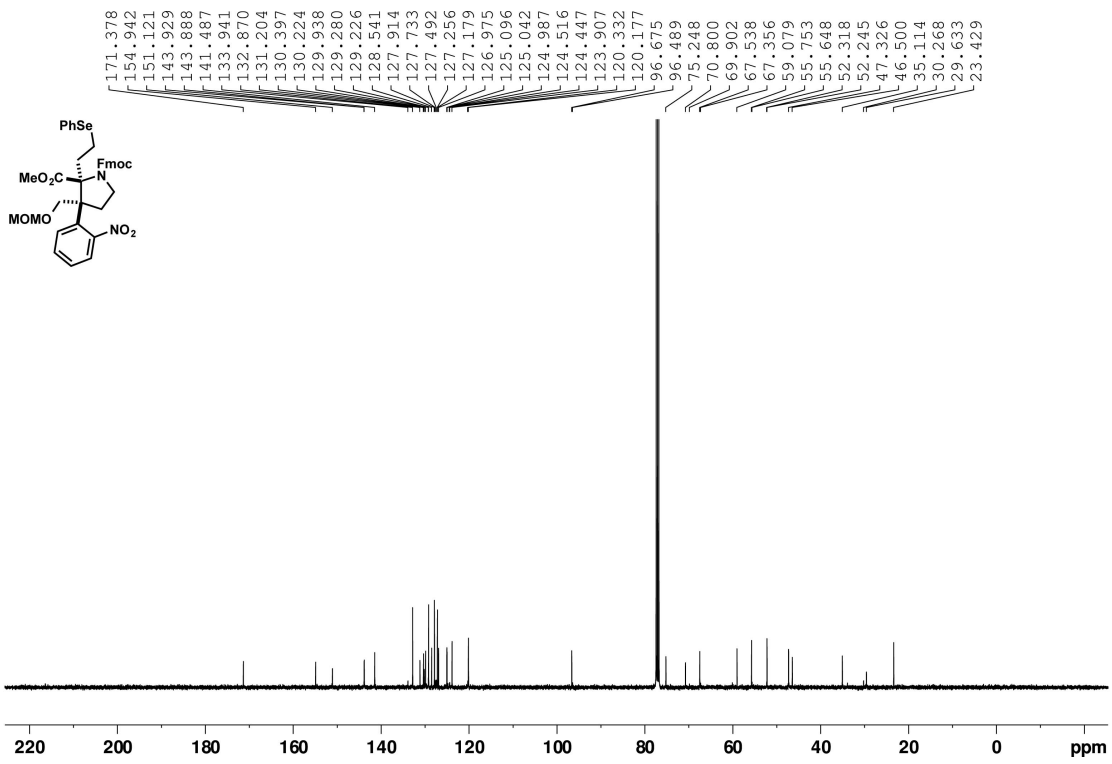

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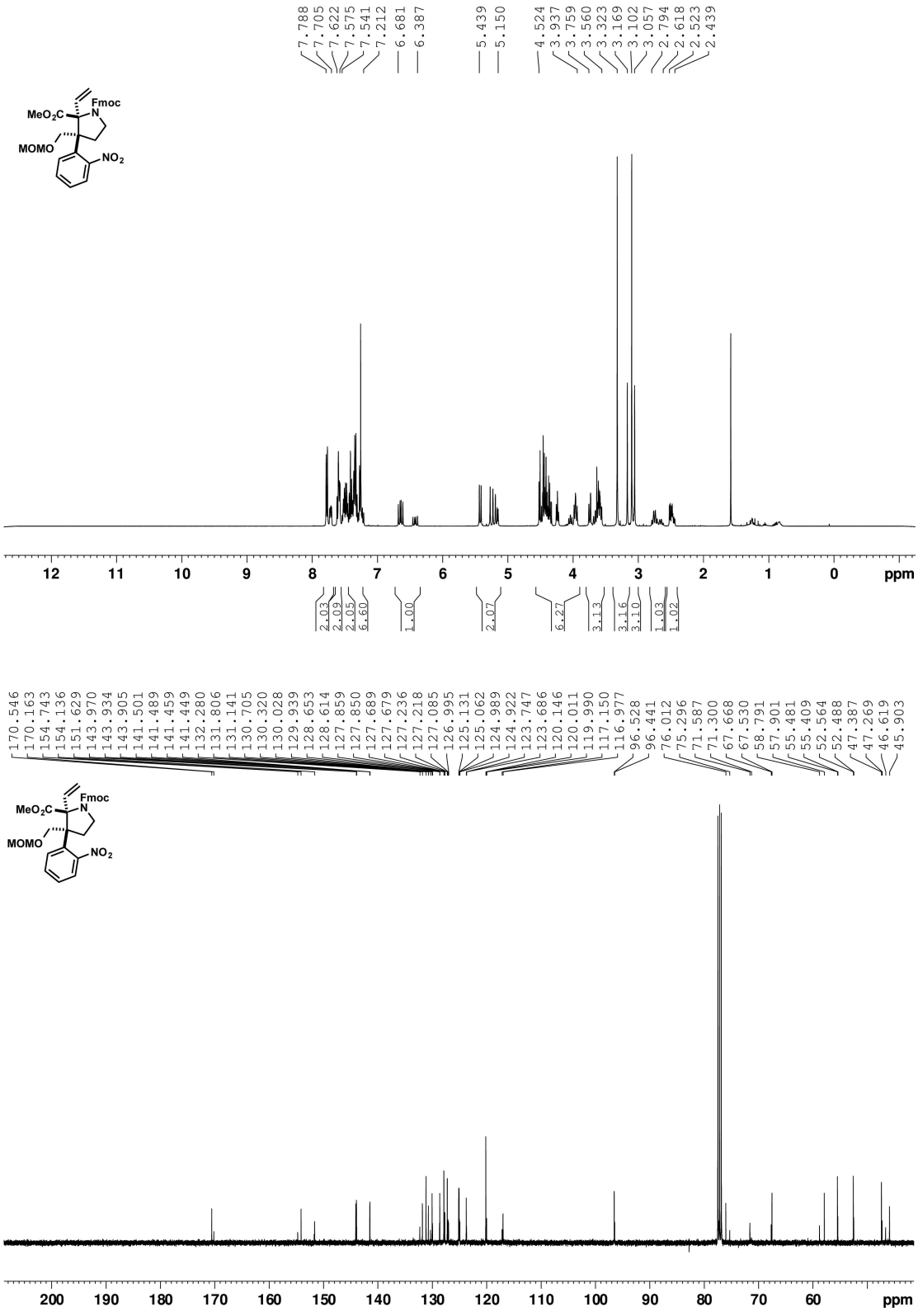

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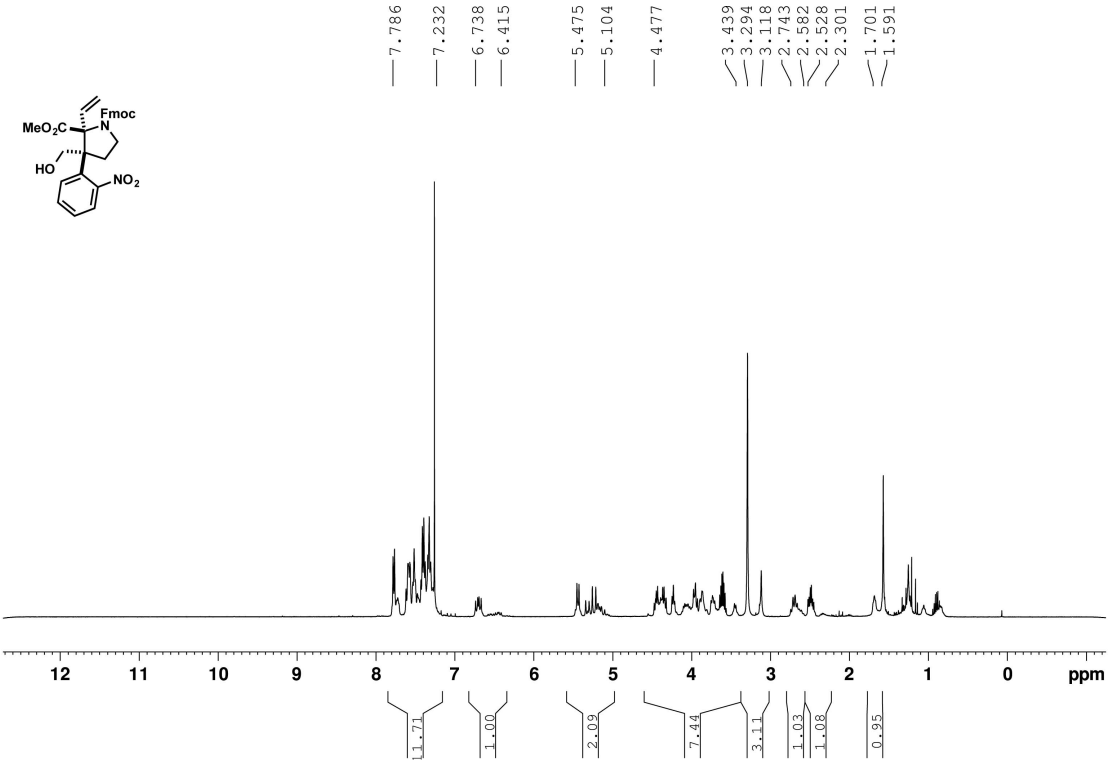

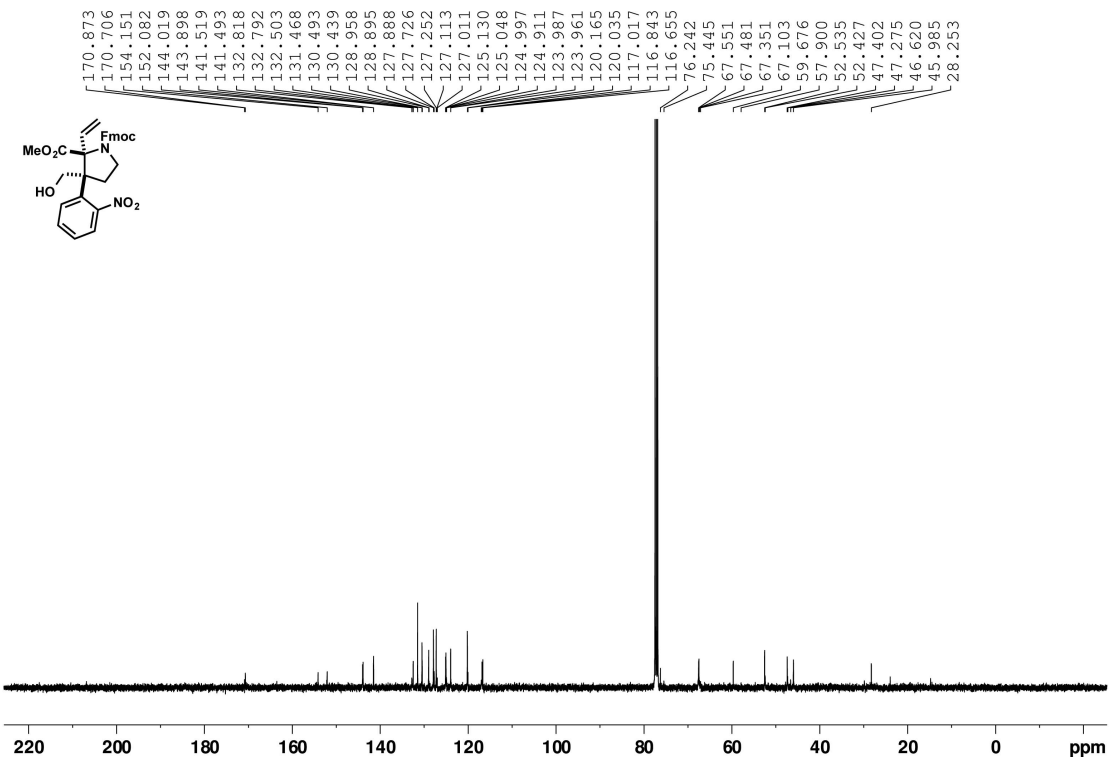

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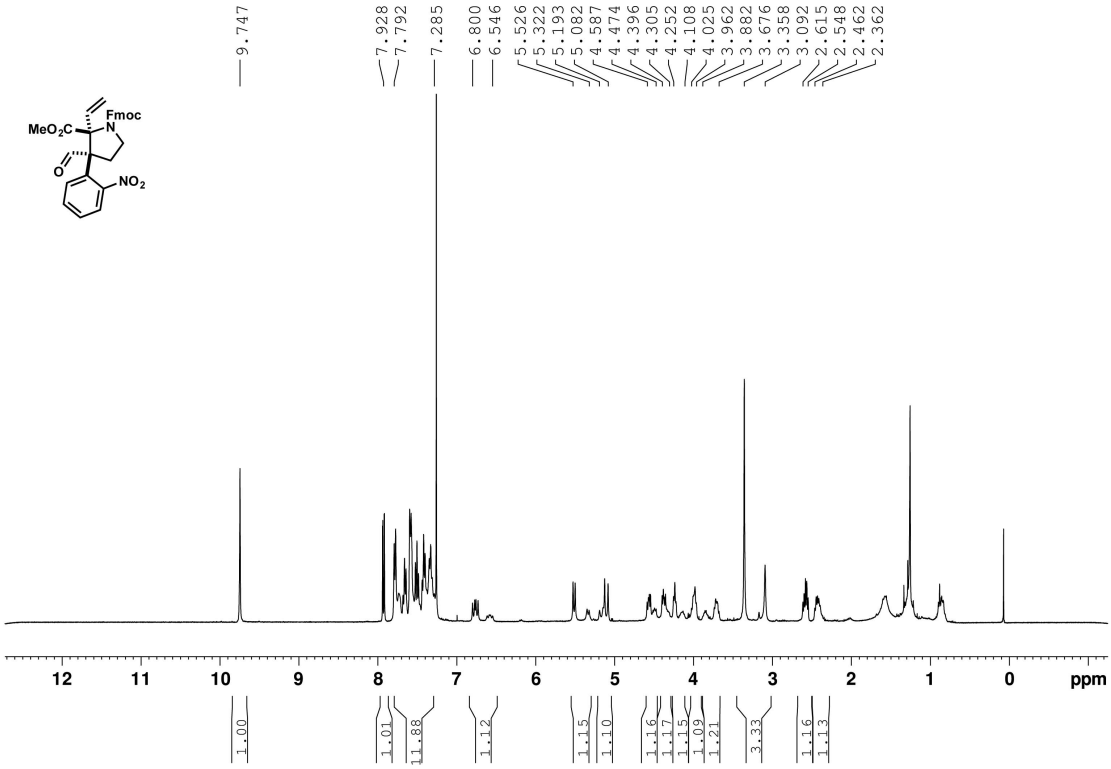

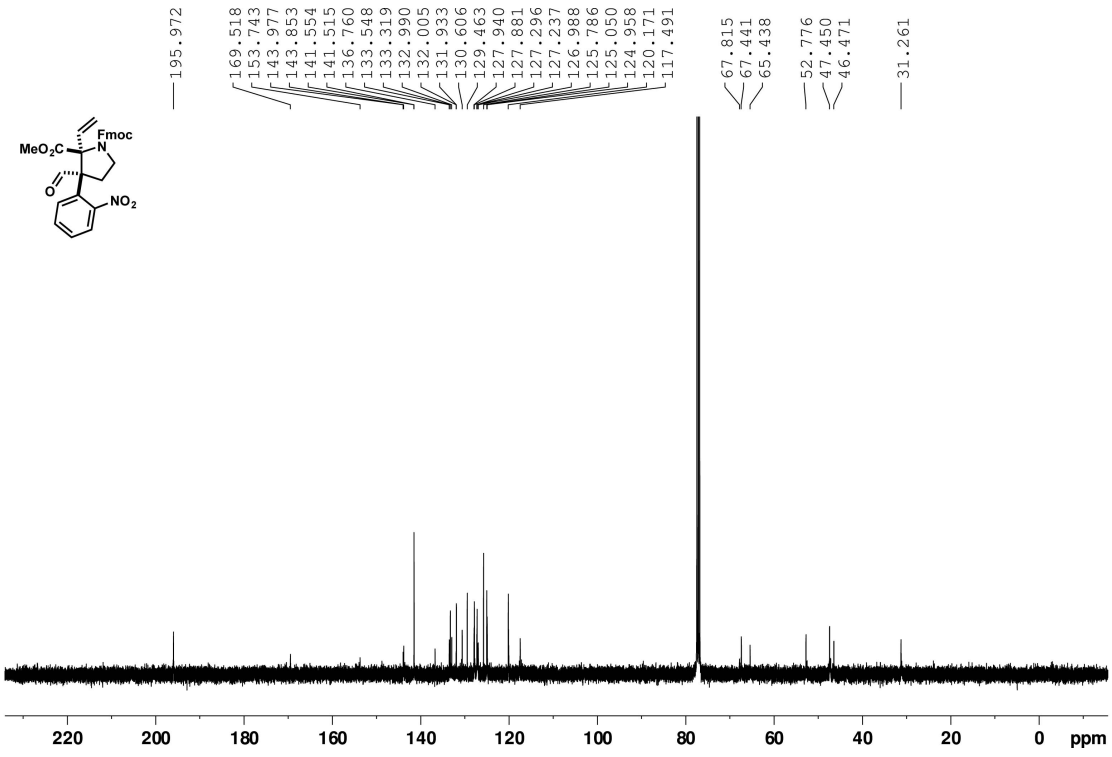

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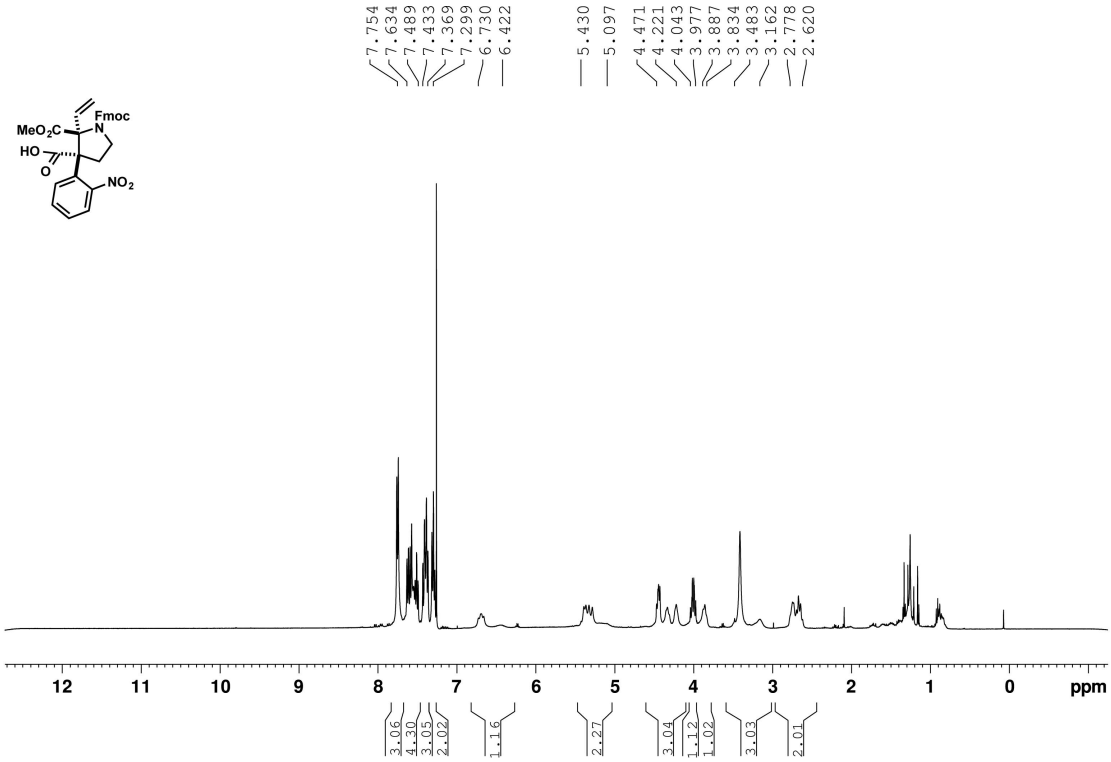

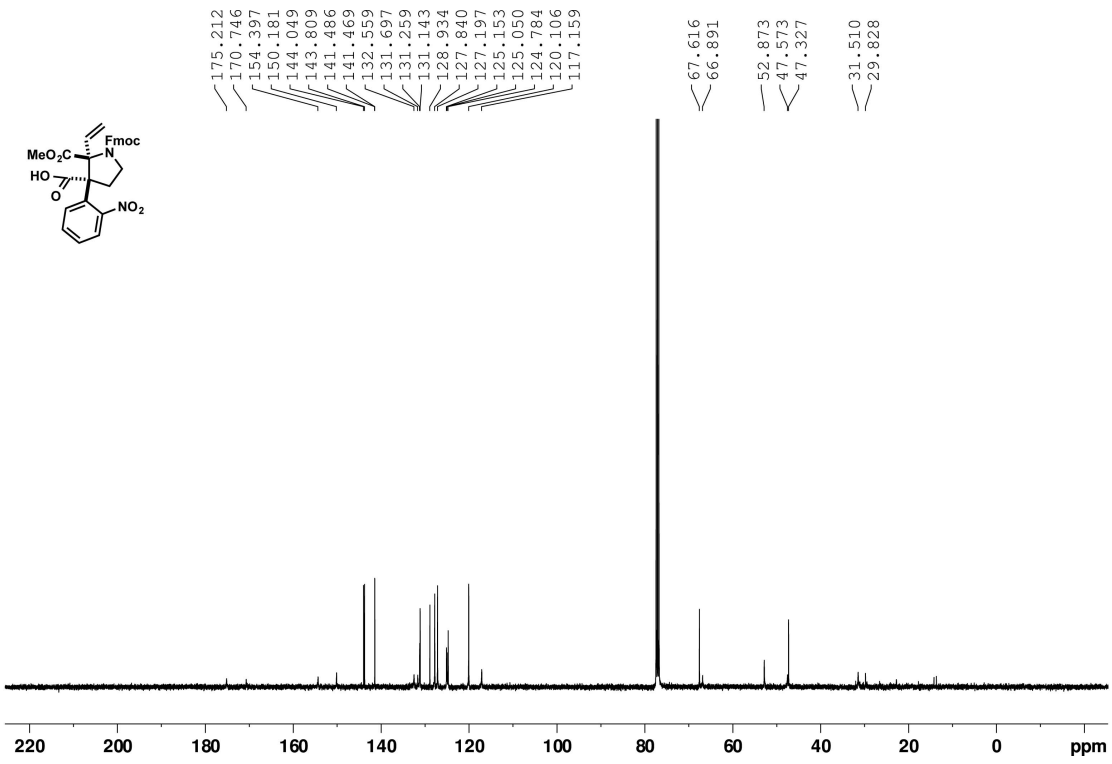

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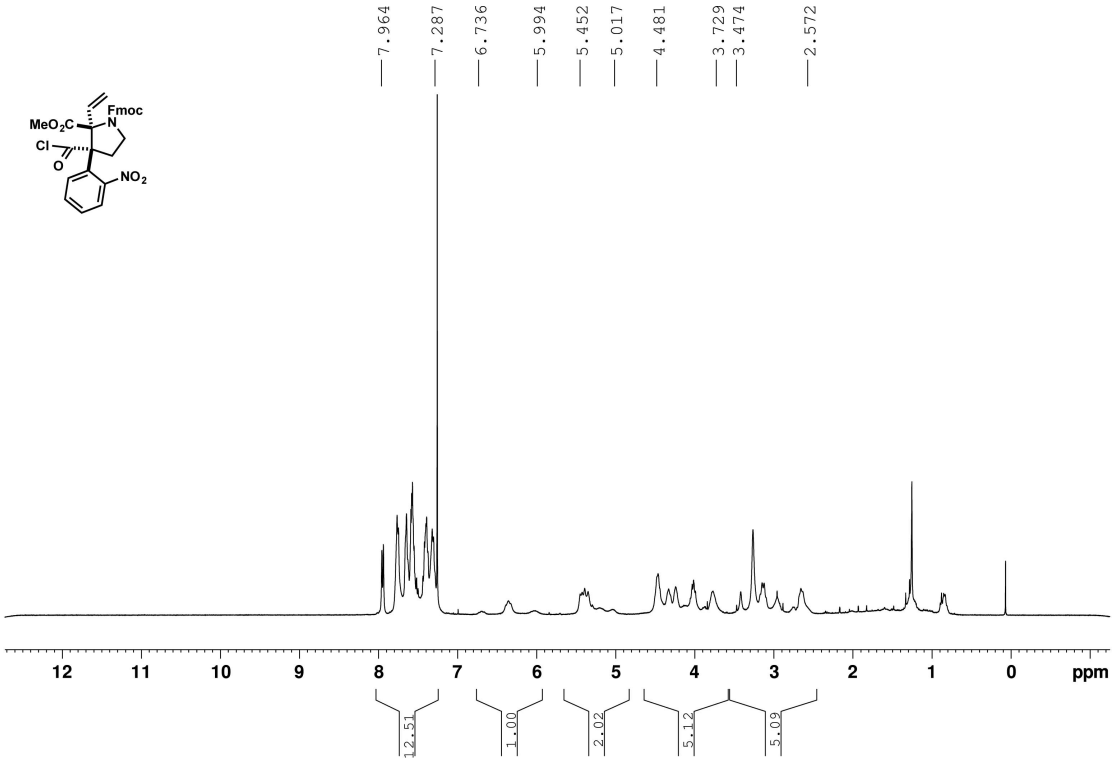

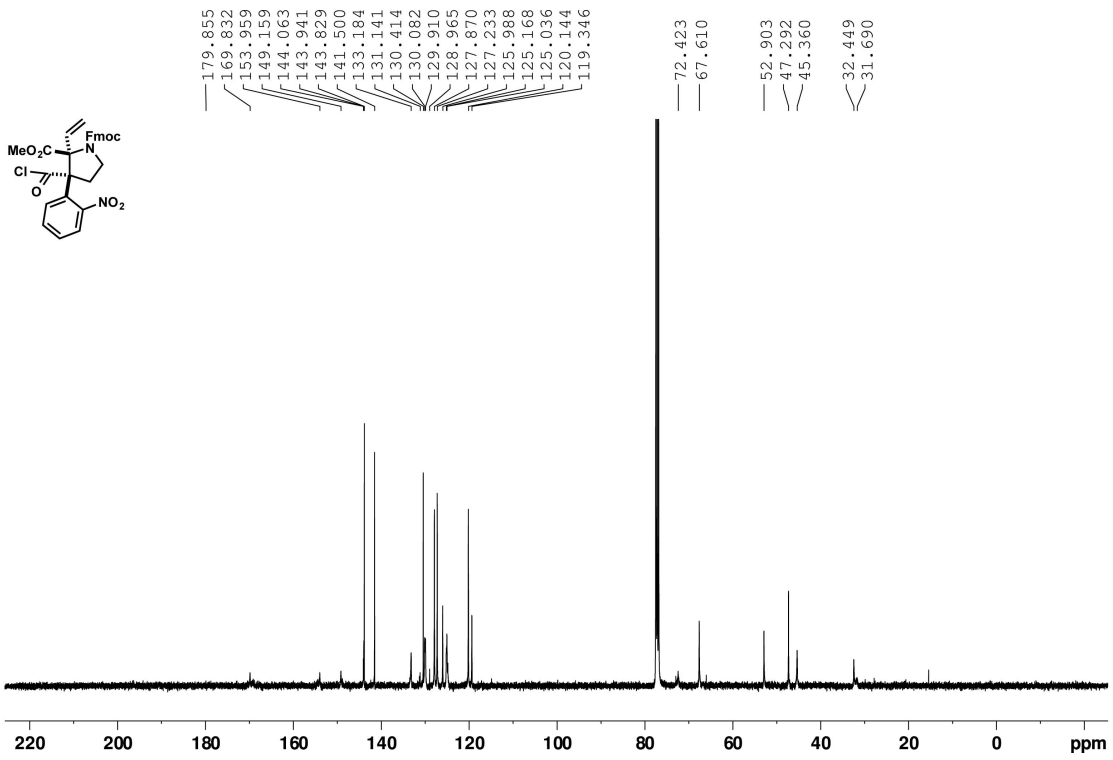

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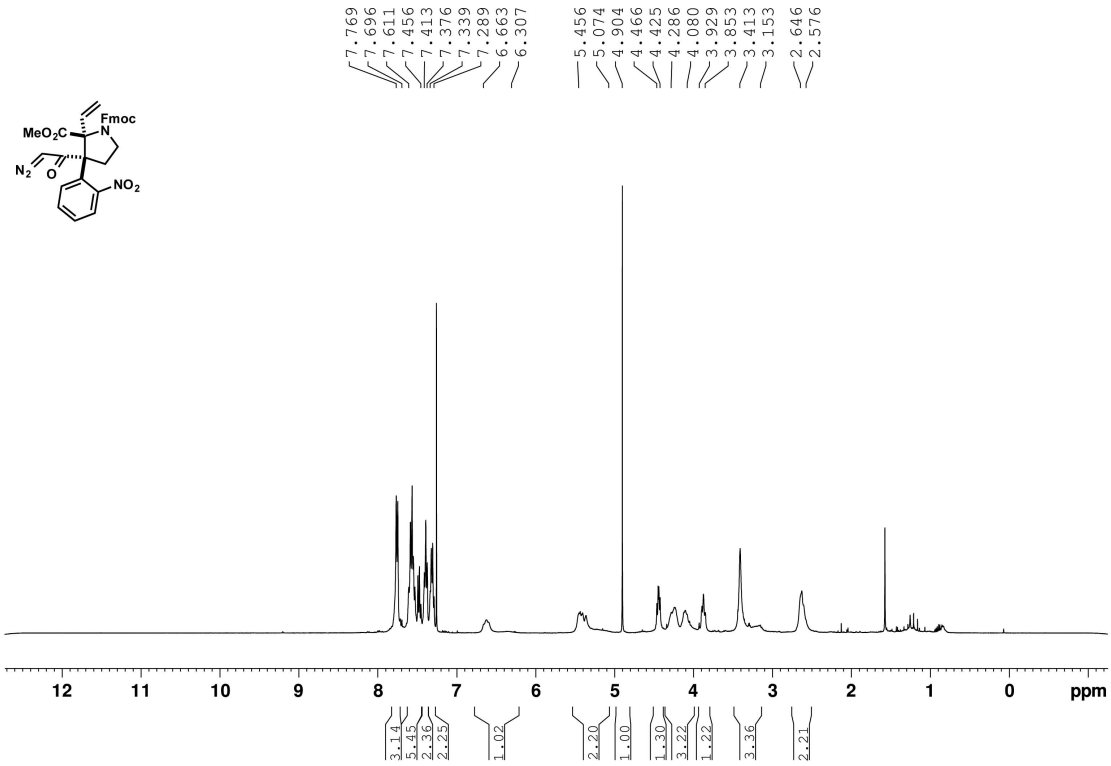

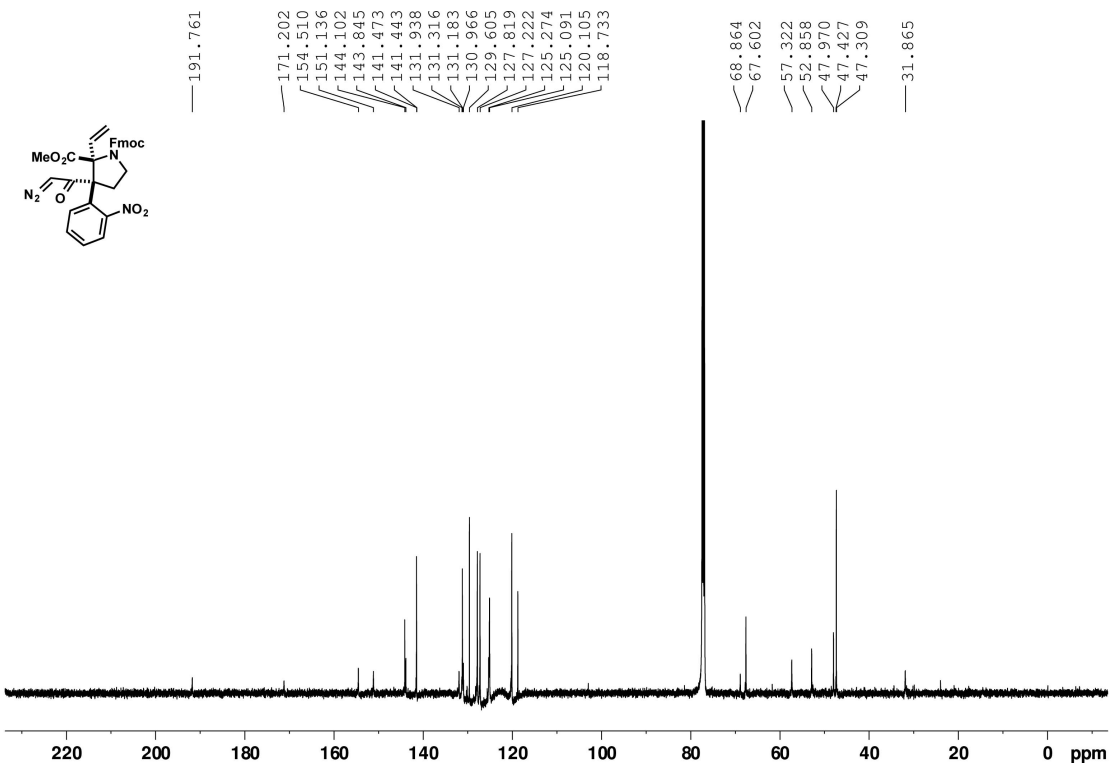

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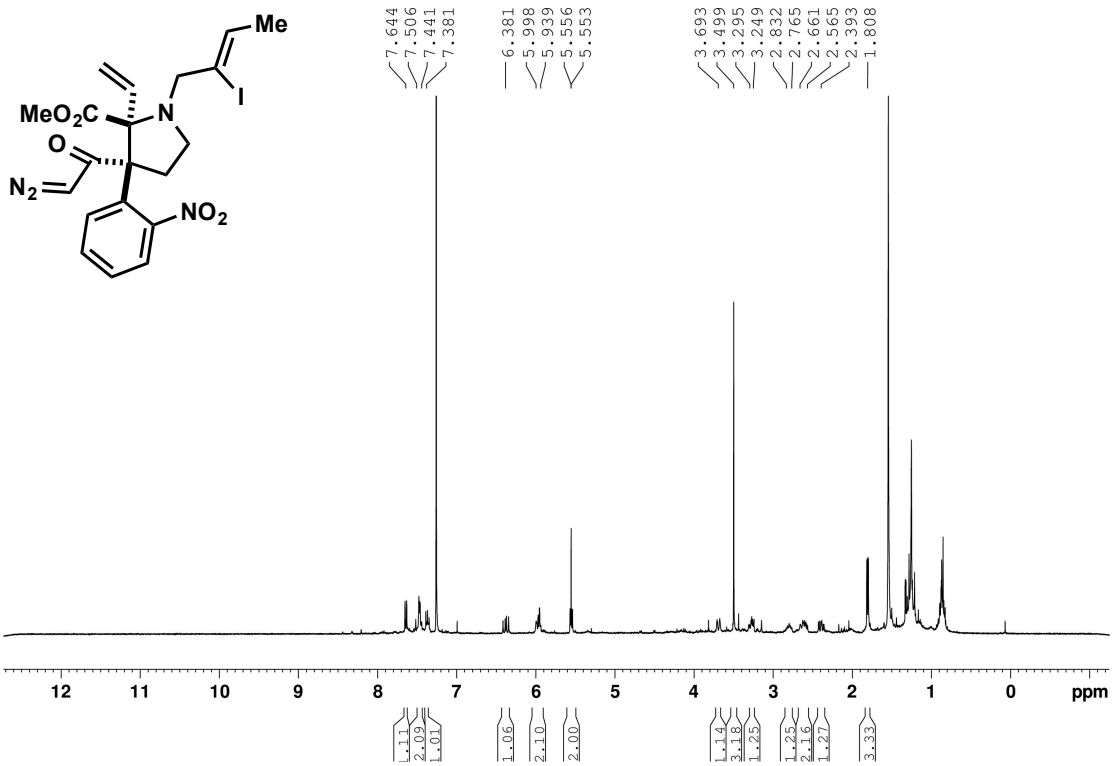

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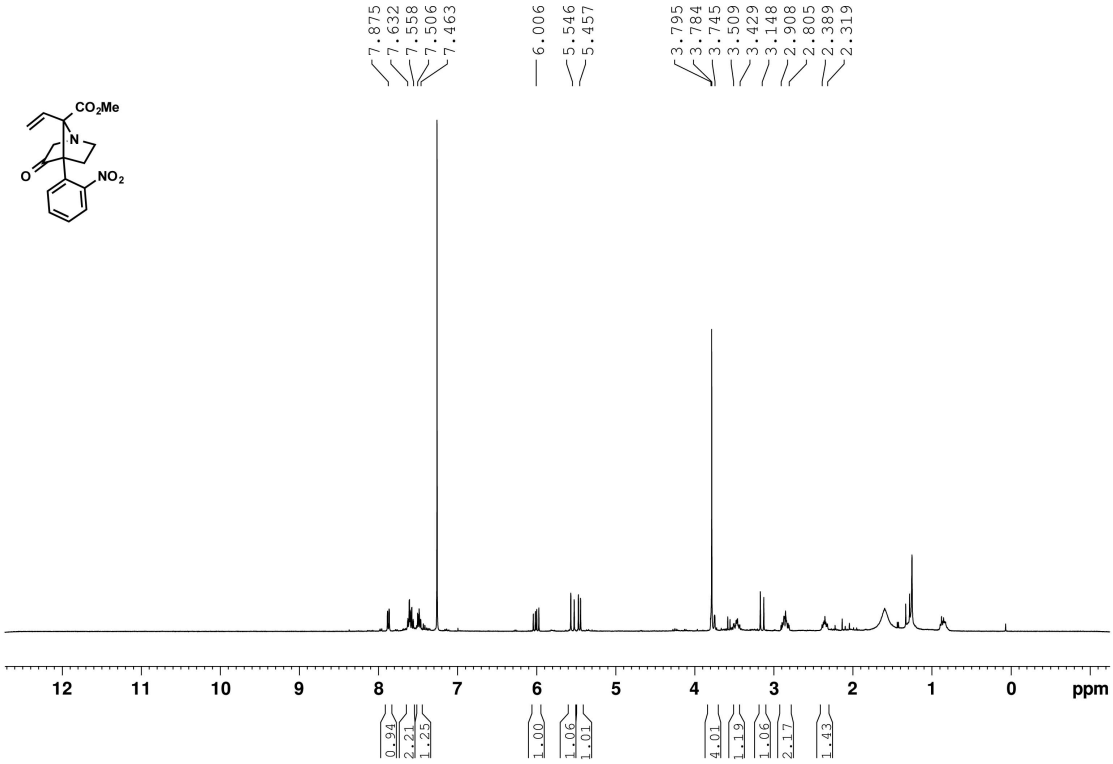

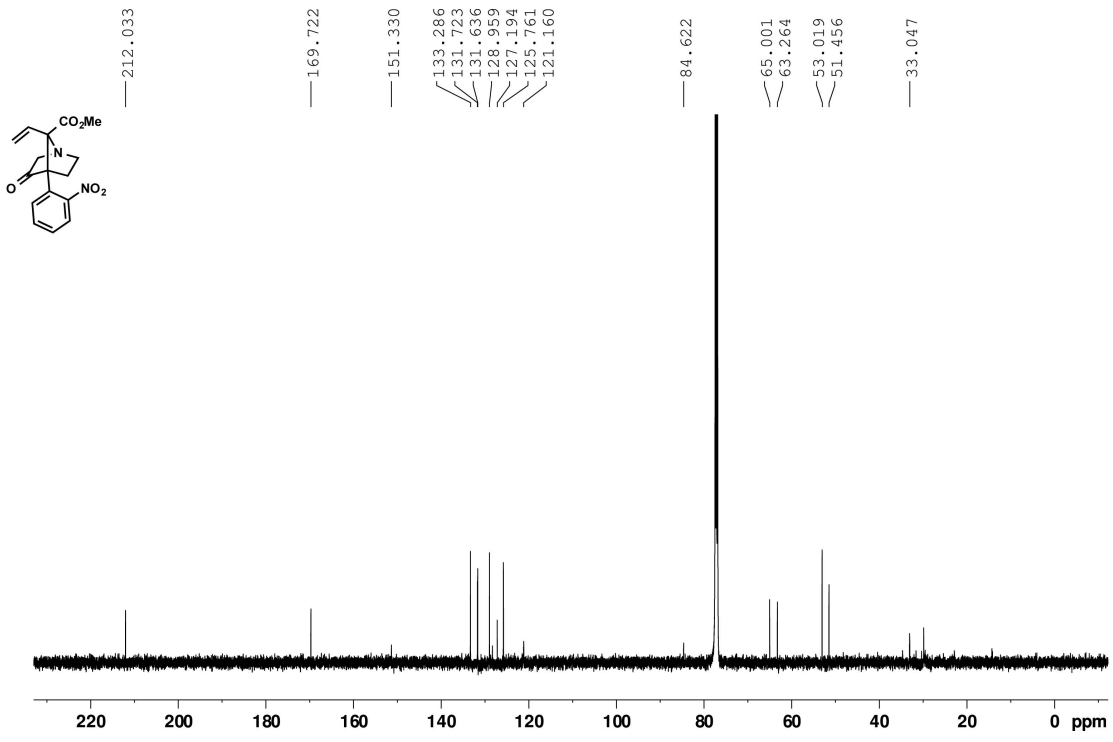

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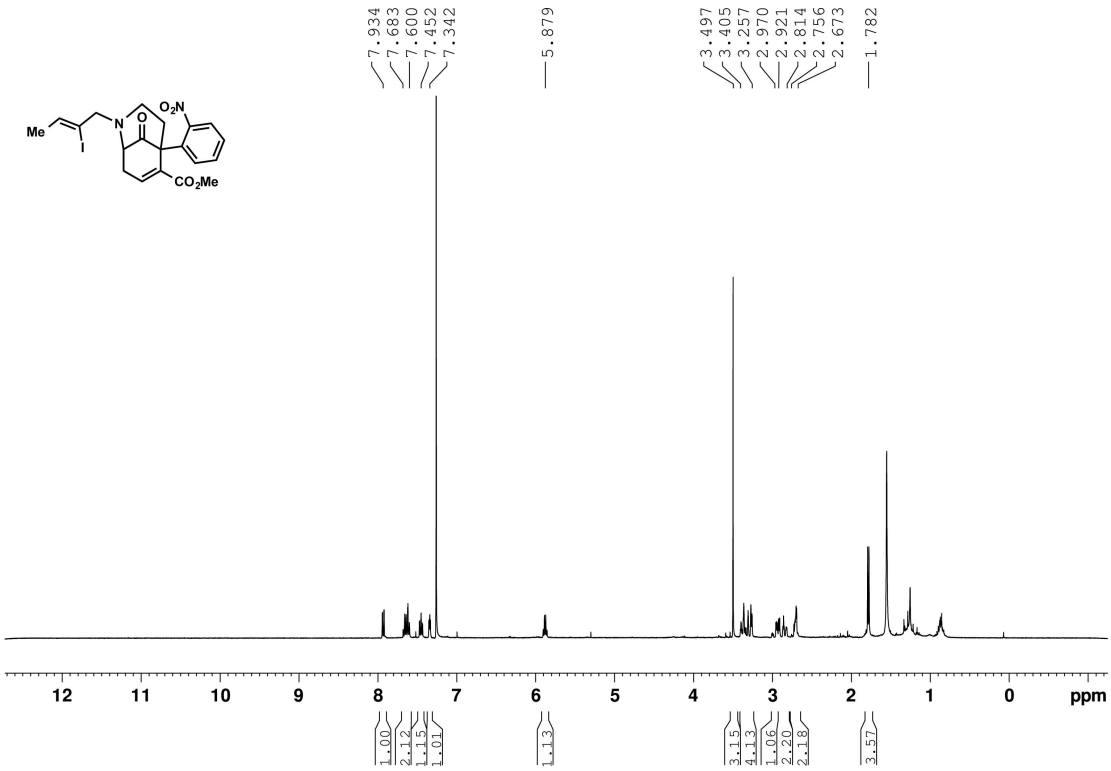

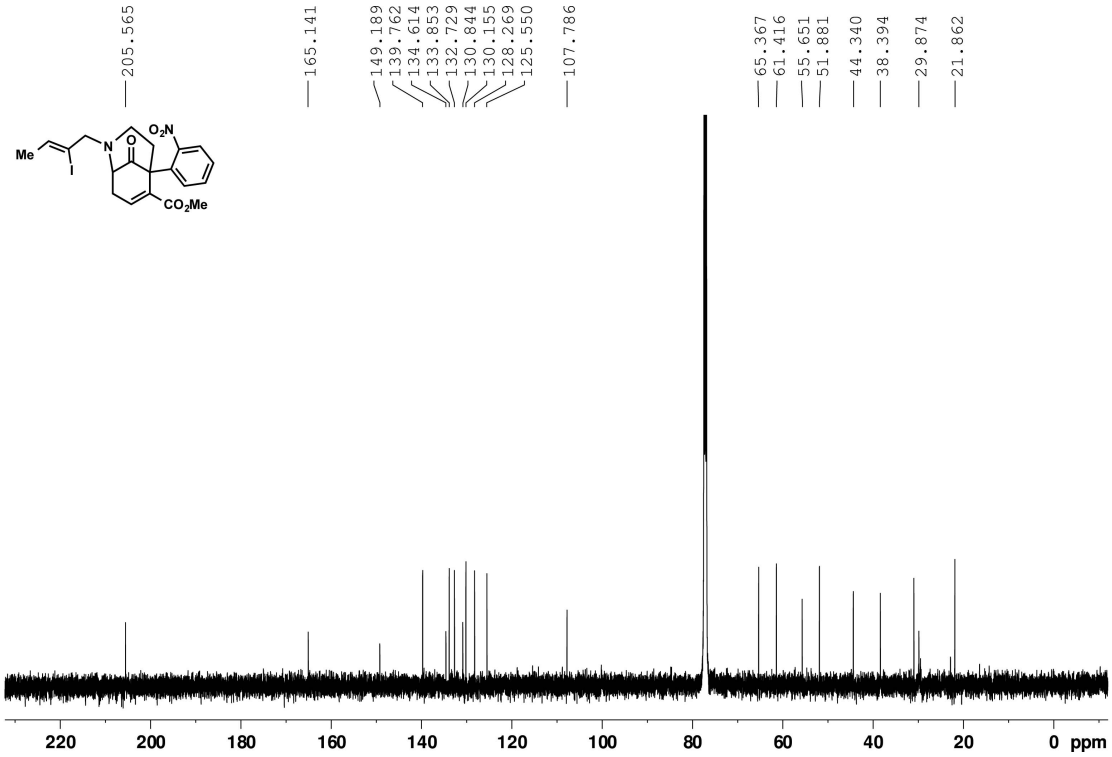

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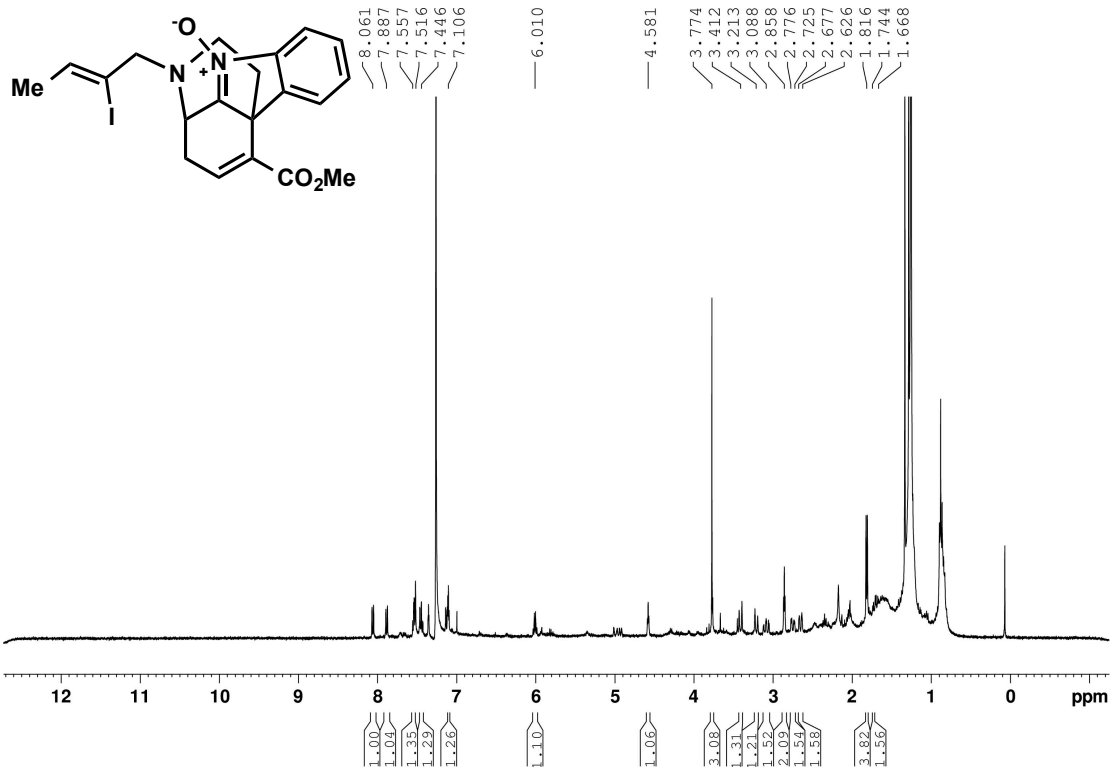

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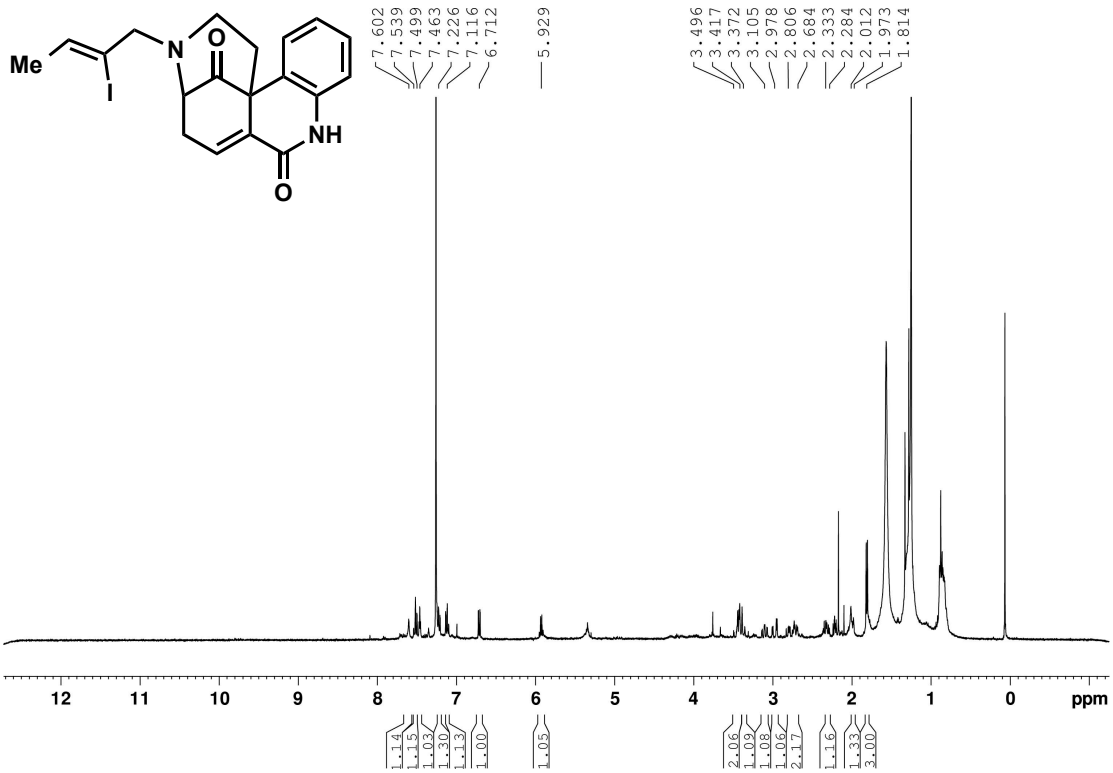

9. Appendix

9.4 Literature

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9.5 Curriculum Vitae

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Education

2011 - 2015	PhD Organic Chemistry, University of Hannover (Supervisor Prof. Dr. Tanja Gaich: *"Studies towards a total synthesis of Akuammiline alkaloids"*)
2011	Voluntary Service at the editorial office of "Nachrichten aus der Chemie"
2008 - 2010	Master of Science, Chemistry, Technical University of Munich (Supervisor Prof. Dr. Thorsten Bach: *"Regioselective radical addition to enones via a photo-induced electron transfer under the influence of chiral catalysts")*
2005 - 2008	Bachelor of Science, Chemistry, Technical University of Munich
2004 - 2005	Military Service
1997 - 2004	Eichsfeld Gymnasium Duderstadt

Fellowships

2011 - 2013	PhD fellowship of the Liebig fellowship by the Stiftung Stipendien-Fonds, Verband der Chemischen Industrie e.V.