Towards a Synthesis of (–)-Actinophyllic Acid:

Applying the Divinylcyclopropane Rearrangement to the Synthesis of Indole Alkaloids

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Inveniam viam aut faciam.

Abstract

This work presents the successful development of a methodology to enantioselectively synthesize cyclohepta[*b*]indoles, molecules where a seven-membered ring is fused to an indole nucleus at the bond between indole C-2 and indole C-3. To showcase the broad applicability of this methodology, a formal total synthesis of actinophyllic acid was also attempted.

Cyclohepta[*b*]indoles, which are also found in natural products, show diverse biological activities and are therefore of great interest. However, prior to this project, no enantioselective and comprehensive methodology to synthesize this structural motive was published in the literature.

To gain access to cyclohepta[*b*]indoles, the application of the divinylcyclopropane rearrangement (DVCPR) in conjunction with the indole nucleus was explored. The DVCPR is a Cope rearrangement where the central σ-bond is replaced by a cyclopropane.

The first approach presented consists of a *spiro*[cyclopropyloxindole] which, was transformed into a divinylcycloprane. During the following rearrangement, the indole nucleus was rearomatized and the desired cyclohepta[*b*]indole was obtained. The scope of this transformation was very limited, as only one example could be obtained. Additionally also a synthesis of cyclohepta[*b,c*]indoles was developed during the study of this approach.

Vinyl-cyclopropanes attached to indole C-2 or indole C-3 then permitted the synthesis of the desired cyclohepta[*b*]indoles with a broad spectrum of functional groups on the seven-membered ring. Depending on the steric demand of the substituents, the rearrangement takes place already at room temperature, although a dearomatization of the indole nucleus occurs. The methodology development culminated in the enantioselective synthesis of biologically active SIRT inhibitor IV.

The synthesis of higher substituted cyclohepta[*b*]indoles was achieved by a 1,4 addition to a propargylic ester, which was attached to an indole C-3 cyclopropane. Selective transformation then permitted the introduction of substituents on all atoms of the seven-membered ring. The correct diastereochemistry for a formal synthesis of actinophyllic acid was achieved in this manner.

Keywords:

Total Synthesis, Alkaloids, Divinylcyclopropane rearrangement

Zusammenfassung

Diese Arbeit präsentiert die erfolgreiche Entwicklung einer Methode für die enantioselektive Synthese von Cyclohepta[*b*]indolen, Moleküle bei denen die Indol C-2 und C-3 Atome teil eines sieben-gliedrigen Rings sind. Um die breite Anwendbarkeit dieser Methode zu demonstrieren wurde eine formale Totalsynthese von (−)-Actinophyllic Acid angestrengt.

Cyclohepta[*b*]indole, die auch in Naturstoffen gefunden werden, zeigen verschiedene biologische Aktivitäten und sind daher von großem Interesse. Bevor dieses Projekt gestartet wurde, war jedoch keine umfassende und enantioselektive Methode für die Synthese von Cyclohepta[*b*]indolen publiziert.

Um Cyclohepta[*b*]indole herzustellen, wurde die Anwendung einer Divinlycyclopropan Umlagerung (divinylcyclopropane rearrangement = DVCPR) im Zusammenhang mit dem Indol-π-system untersucht. Die DVCPR ist eine Cope-Umlagerung bei der die mittlere σ-Bindung durch ein Cyclopropan ersetzt ist.

Der erste Ansatz bestand aus der Synthese eines *spiro*[cyclopropyloxindol], welches in ein Divinylcyclopropan transformiert wurde. Während der Umlagerung kam es zu einer Rearomatisierung des Indols und das gewünschte Cyclohepta[*b*]indole wurde erhalten. Jedoch war die Anwendung auf ein einziges Beispiel beschränkt. Zusätzlich wurde auch ein Zugang zu Cyclohepta[*b*,*c*]indolen entwickelt.

Vinylcyclopropane gebunden an Indol C-2 oder C-3 erlaubten dann die Synthese von Cyclohepta[*b*]indolen mit einem breiten Spektrum an funktionellen Gruppen am 7-gliedrigem Ring. Abhängig von den sterische Eigenschaften der Substituenten findet die Umlagerung schon bei Raumtemperatur statt, währenddem sich jedoch auch eine Dearomatisierung des Indols ereignet. Die Methodenentwicklung gipfelte in der enantioselektiven Synthese von biologischen aktivem SIRT inhibitor IV.

Die Synthese von höher substituierten Cyclohepta[*b*]indolen wurde durch die 1,4-Addition an einen propargylischen Ester, welcher an ein Indol C-3 cyclopropan gebunden war, erreicht. Selektive Transformationen erlaubten dann die Einführung von Substituenten an allen weiteren Atomen des Cycloheptans. Die korrekte Diastereochemie für eine formale Totalsynthese von Actinophyllic Acid konnte so erreicht werden.

Schlagwörter:
Totalsynthese, Alkaloide, Divinylcyclopropanumlagerung

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1 Cyclohepta[*b*]indoles

The term cyclohepta[*b*]indoles describes molecules that consist of a seven-membered ring fused to an indole nucleus at the indole *b*-bond, the bond between C-2 and C-3. The scaffold can be found in natural products, such as methuenine (**3**), ervatamine (**4**), ervitsine (**5**), silicine (**6**) and the ambiguine isonitrile nitrile family (**2**) (Figure 1).[1–3] Additionally, the structural motif has been associated with an array of biological activities: anti-inflammatory[4], LTB_4 inhibitor (**9**), anti-tubercular[5], **10**, gene silencing[6], SIRT IV, (**8**) and anti-aging[7], A-FABP inhibitor (**7**). Of particular interest is actinophyllic acid (**1**), comprised of a complex polycyclic framework found in no other natural product.[8]

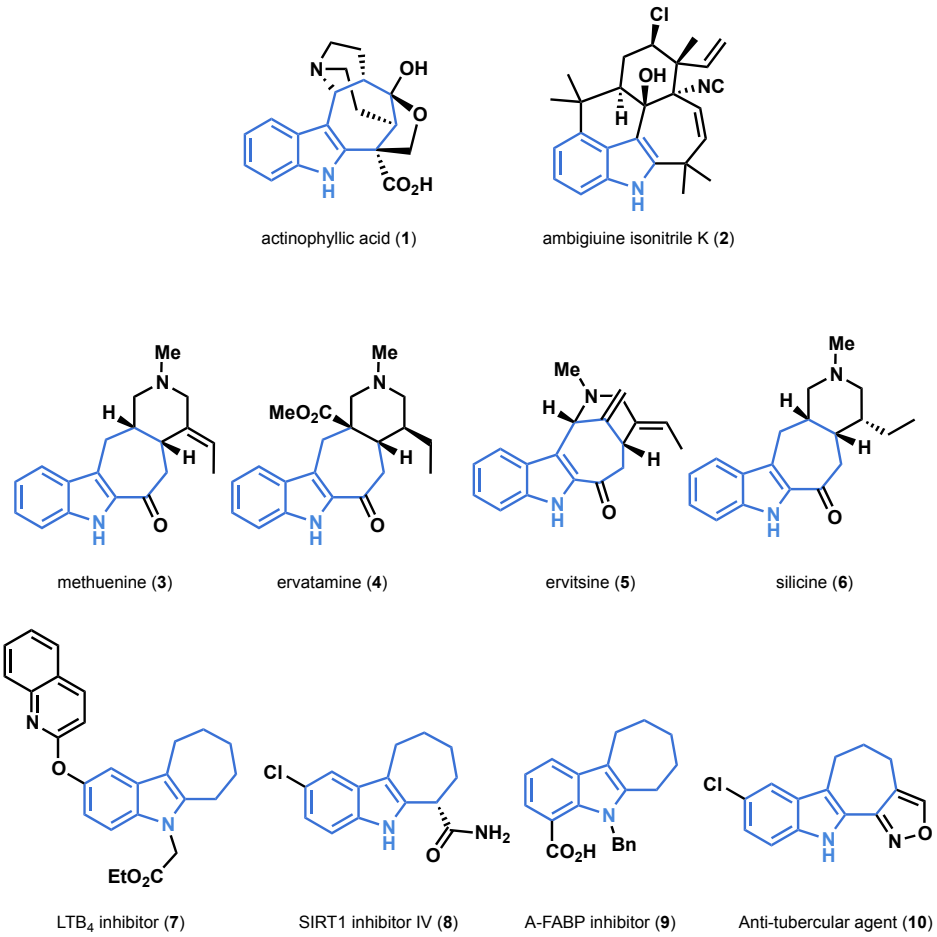


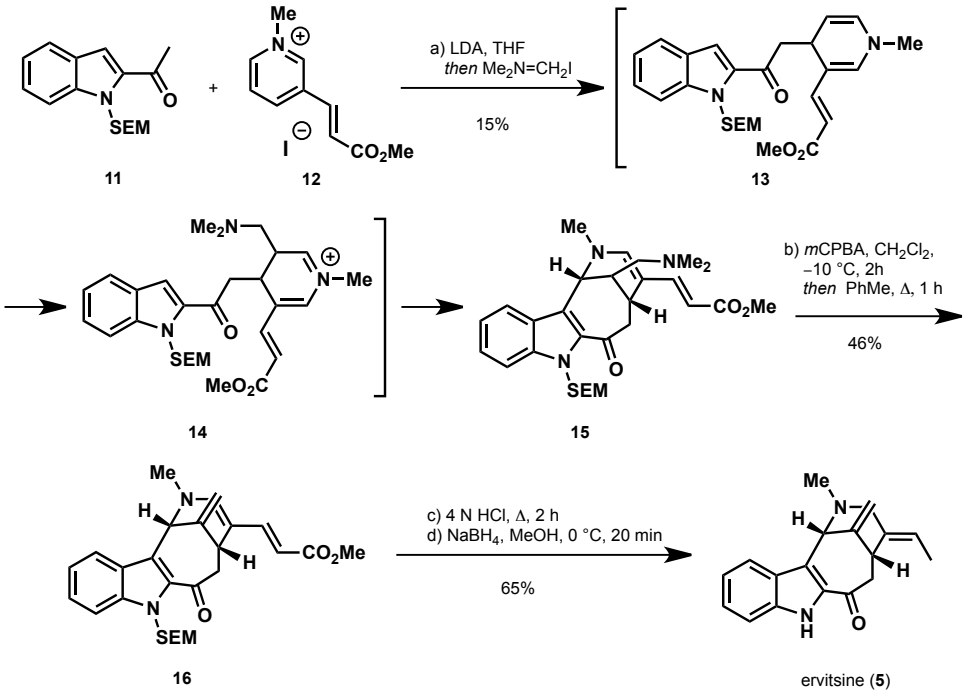
Figure 1 Cyclohepta[*b*]indoles.

1.1 Synthesis of cyclohepta[*b*]indoles in literature

Although cyclohepta[*b*]indoles possess a wide variety of biological activities, their synthesis is often the issue. The applied methodologies generally involve an intramolecular derivatisation of the indole 3-position or the construction of a suitable precursor, already containing a seven membered ring, and as the final step the cyclisation to an indole. Recently also the [4+3]

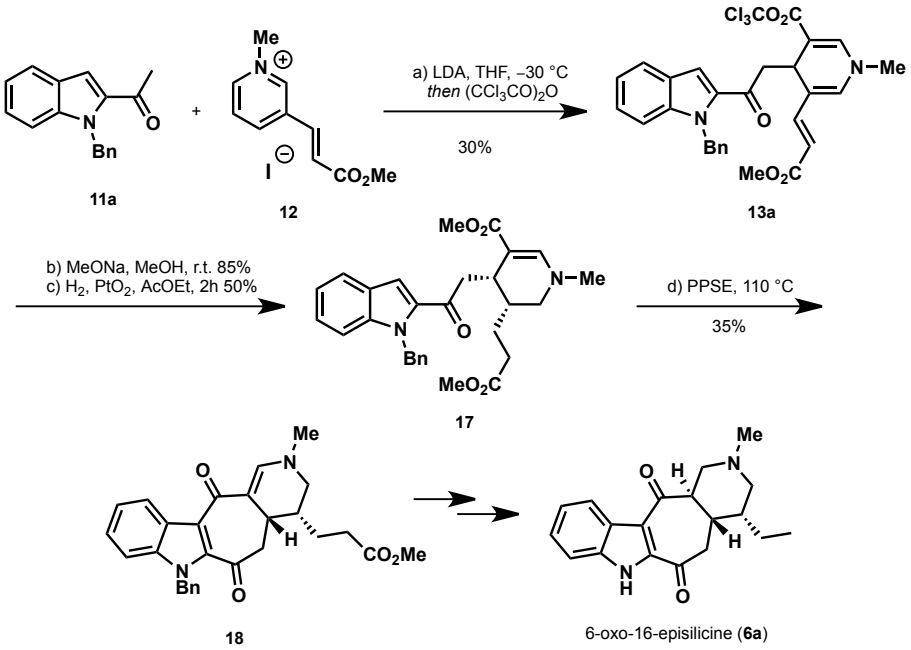
cycloaddition has been successfully employed. The bigger part of reports treating synthesis of cyclohepta[*b*]indoles is presented here but this list is not all-encompassing.

During the first total synthesis of ervitsine, Bennasar, Vidal and Bosch used a biomimetic approach that allowed them to install the desired stereochemistry in a straightforward manner (Scheme 1).[9] Addition of deprotonated ketone **11** to pyridinium iodide **12** was followed by treatment with Eschenmoser's salt, which *in situ* cyclized to tetra cyclic intermediate **15**. *N*-Oxide formation with *meta*-chloroperbenzoic acid was followed by Cope-elimination and subsequent treatment with 4 N hydrochloric acid led to decarboxylation as well as deprotection of the indole nitrogen. Successive elaboration of the double bond with sodium borohydride then gave ervitsine (**5**).



Scheme 1 Synthesis of ervitsine by Bosch *et al.*

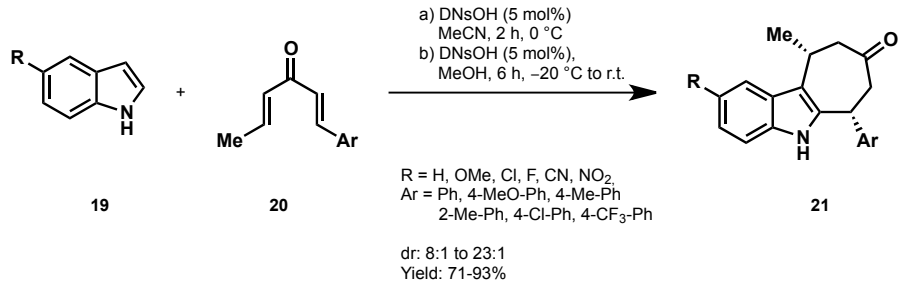
During the synthesis of 6-oxo-16-episilicine by the same group a very similar approach was used (Scheme 2).[10] However in this case, instead of generating an iminium ion, an ester group was attacked by the nucleophilic indole C-3 position mediated by trimethylsilyl polyphosphate. After expulsion of methanol the cyclohepta[*b*]indole **18** was obtained. After three additional steps the desired compound **6a** was obtained.



Scheme 2 Bosch *et al.*'s synthesis of 6-oxo-16-episilicine.

Using these two approaches the group of Bosch synthesized multiple members of the ervatamine alkaloid family.[9–13]

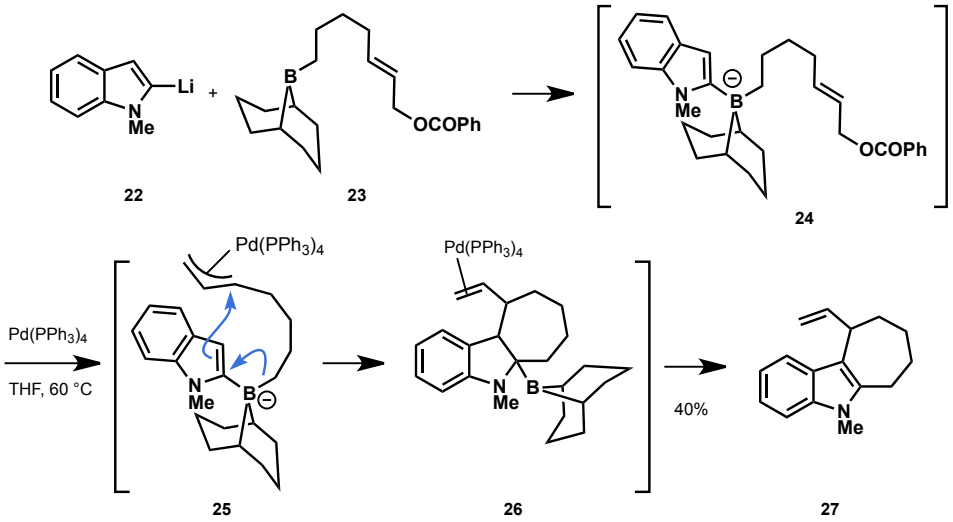
Silvanus *et al.* published an interesting approach, showing a double substitution of the indole C-3 and subsequent migration to obtain stereoselectively cyclohepta[*b*]indoles (Scheme 3).[14]



Scheme 3 Double alkylation of indoles with divinyl ketones.

Starting from indole **19**, treatment under acidic condition with 2,4-dinitro phenylsulfonic acid and a variety of divinyl ketones **20**, the mono-adduct was selectively obtained first. A solvent swap then lead to a second alkylation, presumably first on the indole C-3 postion and followed by a migration and re-aromatisation to yield the desired cyclohepta[*b*]indoles **21**.

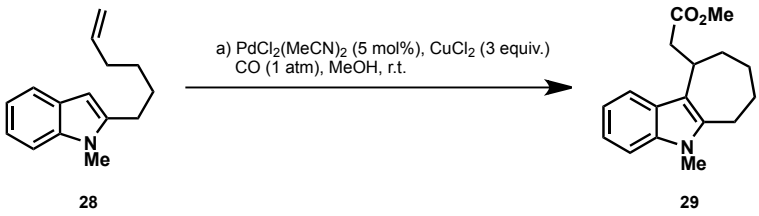
Another methodology to use the indole C-3 nucleophilicity was developed by Ishikura and Kato.[15] Using Aggarwal's boron chemistry, they added lithiated indole **22** to boron reagent **23** forming **24** (Scheme 4).[16]



Scheme 4 Ishikura's and Kato's approach to substituted indoles.

Addition of a palladium (0) species then lead to π-allyl cation **25** which got attacked by the indole core formig **26**. Bond migration and re-aromatisation then furnished the cyclohepta[*b*]indole **27** in 40% yield. As the publication focuses on different-sized rings fused to the indole core, only two more examples are shown where cyclohepta[*b*]indoles are formed.

The approach published by Liu and Widenhoefer seems quite similar, but a palladium (II) species is used (Scheme 5).[17] Indolyl alkenes **28** were treated with palladiumdichlorid, which coordinated to the terminal double bond and acted as Lewis acid. Nucleophilic attack from the indole occured next and the cyclohepta[*b*]indole was formed, where the palladium was bound to the exo-methyl group. This then reacted with carbon monoxide and methanol to form the methyl ester in the product **29**. Again, the publication focuses on making six-membered cycles and therefore this is the only example where a cyclohepta[*b*]indole is formed.

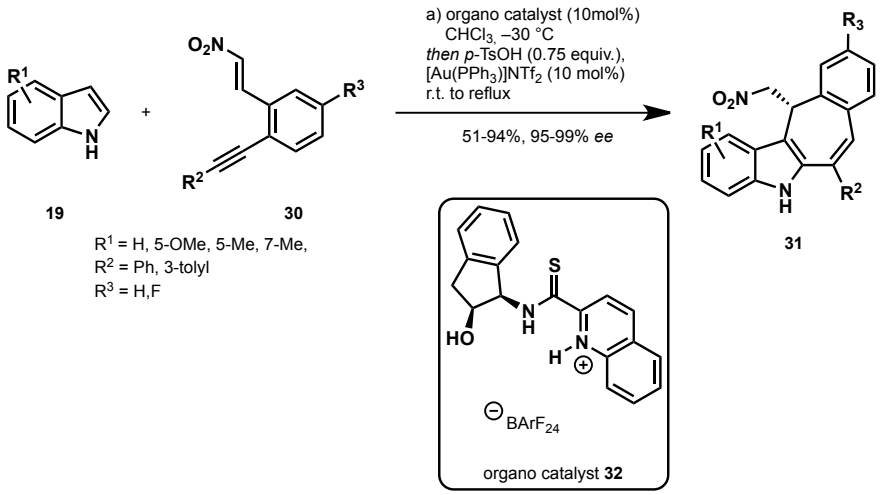


Scheme 5 Liu and Widenhoefer's cyclisation-carbonylation methodology.

An approach used in a variety of ways is to combine a seven-membered ring with appropriate substituents with a benzyl ring and build up the indole core *in situ*. The Fischer indole synthesis is quite useful in this aspect within its known limitations such as regioselectivity of unsymmetrical ketones and the general use of harsh reaction conditions.[18,19]

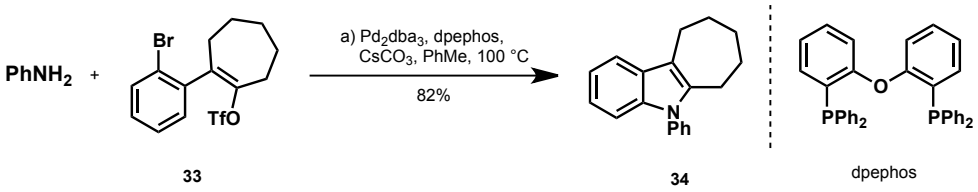
One of the rare examples to synthesize cyclohepta[*b*]indoles enantioselectively was published by the group of Enders (Scheme 6).[20] A one-pot tandem catalysis reaction of indole **19** and

ortho-alkyne substituted nitro styrene **30** gave cyclohepta[*b*]indole **31** with a defined stereochemistry in *α*-position to the nitro substituent. The first step in the reaction is a Michael addition to the nitro-alkene and after protonation of the organocalyst **32**, which renders it inert, gold catalysis furnishes the cyclohepta[*b*]indole. The yields are generally good and the enantionmeric excess excellent, reagarding the scope, the appicability of the methodology is limited.



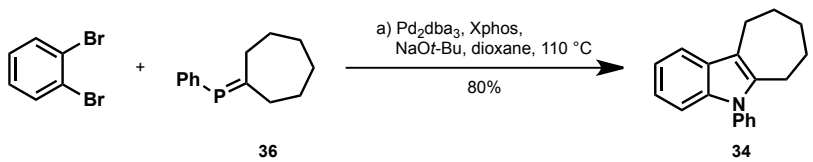
Scheme 6 Enders tandem-one pot reaction.

More recent studies often use metal catalysis to obtain the desired compound. A report by Willis *et al.* used bis-activated arylated ketones **33** to obtain a variety of substituted indoles, among them also a cyclohepta[*b*]indole **34** (Scheme 7).[21]



Scheme 7 Willis *et al.* approach to substituted indoles.

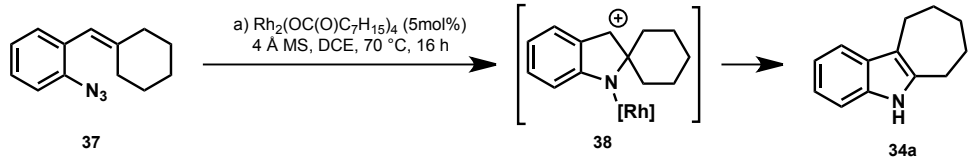
Barlengua *et al.* used dibromo benzene and imine **36** for similar results (Scheme 8).[22] Regioselectivity might become an issue, once a more substituted imine would be used.



Scheme 8 Barlengua *et al.* approach to substituted indoles.

The group around Tom Driver explored *β,β*-disubstituted styryl azides as precursors for disubstituted indoles (Scheme 9).[23] Presumably, the reaction proceeds through an intermediary

cation where migration takes place followed by aromatization. The reported studies focused on different possible ring sizes, however also cyclohepta[*b*]indole with different substituents were synthesized.



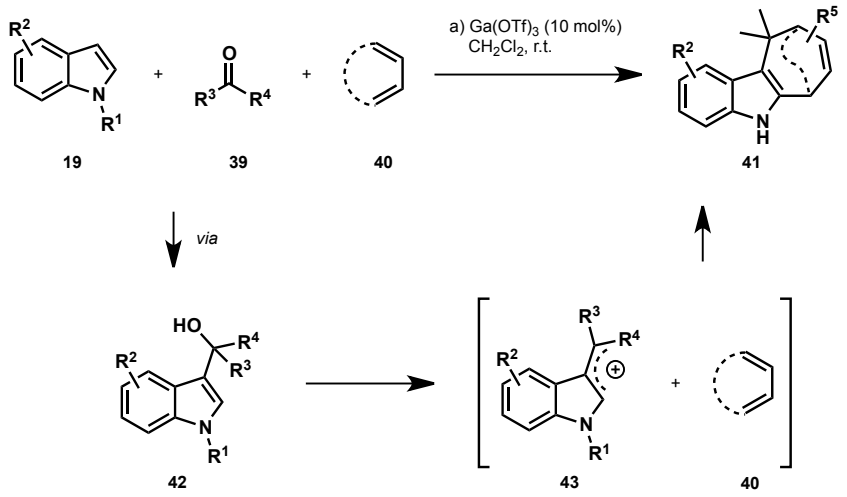
Scheme 9 Approach to disubstituted indoles by Driver and co-workers.

The most recent advances in the synthesis of cyclohepta[*b*]indoles are [4+3]-cycloaddition reactions. The presented methodologies were published at the same time as the research for this thesis was being actively pursued and underline the significance of studying the synthesis of cyclohepta[*b*]indoles.

The [4+3]-cycloaddition reaction requires a 2π unit, which is stretched over three atoms, in this case the indole, and a 4π component, a diene. To create the 2π unit, Lewis acids are often used.

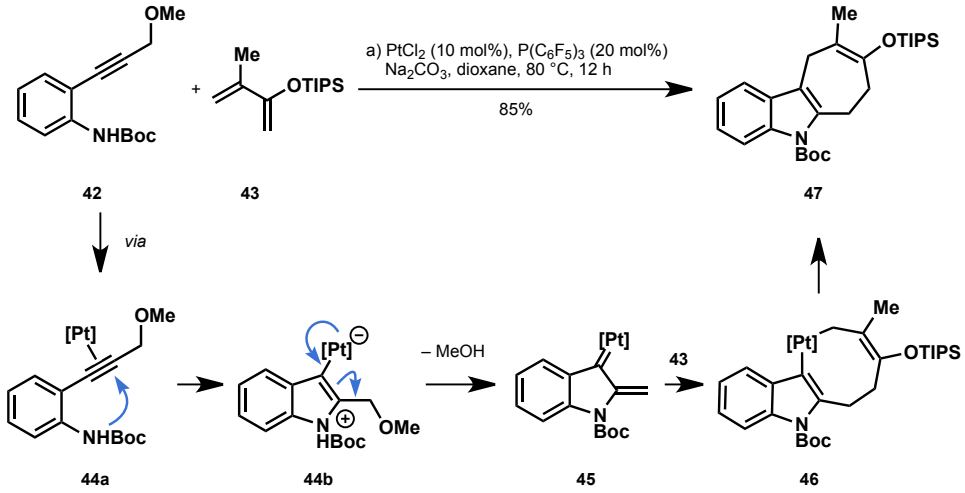
The group of Wu was the first to report a [4+3]-cycloaddition using an unsubstituted indole **19**, an aldehyde or a ketone **39** and a variety of dienes **40** under gallium triflate catalysis (Scheme 10).[24]

The first step in the reaction is the addition of indole to the carbonyle and upon gallium catalyzed elimination of water π-cation **43** is formed. This cation then reacts with the diene to create the cyclohepta[*b*]indole **41**. Wu and co-workers show a broad scope, using aldehydes and ketones and cyclic and acyclic dienes to obtain different cyclohepta[*b*]indole in good to excellent yields.



Scheme 10 Wu *et al.* cycloaddition methodology.

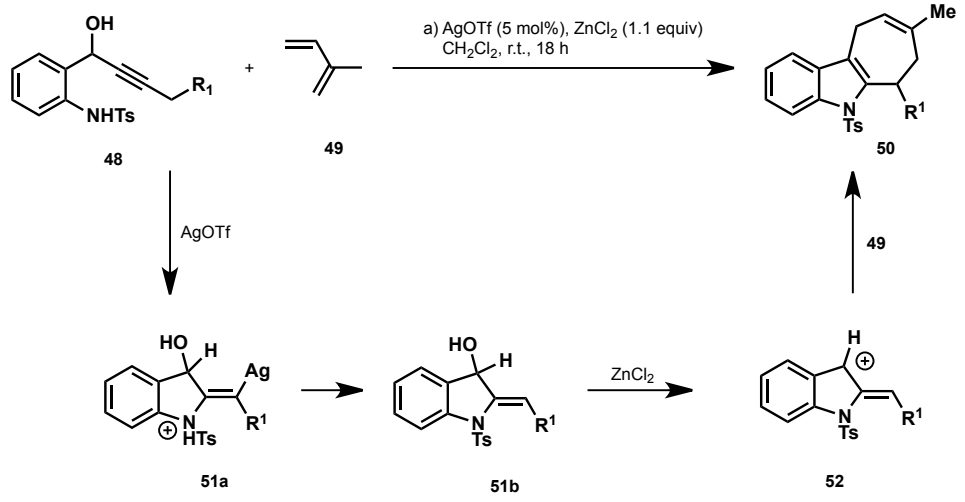
A formal hydroamination-[4+3]-cycloaddition reaction was reported by the group of Tang in 2013.[25] After screening multiple rhodium and platinum catalysts, a combination of platinum and an electron deficient phosphine ligand emerged as the most effective for this reaction. The probable mechanism starts from propargylic ester **42** and by addition of platinum an *endo* cyclisation to **44a** and **44b** takes place and upon loss of methanol, metal carbene **45** is formed.



Scheme 11 Cyclohepta[*b*]indole synthesis by the group of Wang .

Several pathways for the cycloaddition are possible, the most probable is the formation of the metallacycle **46** in a concerted [4+4] fashion given the regioselectivity. The reaction is broadly applicable since linear dienes are converted as well as cyclic dienes such as furans, cyclopentadiene and cyclohexadiene, and yields range from 50 to 90%.

Another example of [4+3]-cycloadditions for the synthesis of cyclohepta[*b*]indoles came from the group of Xue in 2014 (Scheme 12).[26] In this work a hydroamination, catalyzed by silver triflate was combined with a cycloaddition reaction mediated by zinc dichloride.



Scheme 12 [4+3]-cycloaddition published by group of Xue.

In this report the group R^1 can be a variety of different cyclic or linear alkyl substituents as well as ethers. Dienes used are cyclic or linear and yields are between 30 to 90%.

Although an increasing interest, especially in medicinal chemistry, towards fused indoles exists, general methodologies for the synthesis of cyclohepta[*b*]indoles rarely existed at the time the research for this thesis was started. Especially enantioselective synthesis was very little elaborated and challenges were often taken on in a very specific manner and no general methodology was reported.

Regarding a total synthesis of actinophyllic acid (**1**), its framework and other cyclohepta[*b*]indoles it was clear to us that such a general, enantioselective and broadly applicable methology was needed. Such a methodology should ideally allow installing multiple subsitutents on the seven-membered ring in a selective and concise fashion. We turned our attention towards pericyclic reactions and decided, that the divinylcyclopropane rearrangement (DVCPR) would be ideally suited for this challenge.

2 Aim of this project

After surveying literature on cyclohepta[*b*]indoles, it was decided, to develop a methodology that would allow a concise and direct synthesis and the enantioselective installation of substituents of a broad variety on the seven-memered ring. To this end it was planned to develop a variant of the DVCPR in conjunction with the indol nucleus.

To show the applicability of the methodology in a challenging chemical environment, a synthesis of actinophyllic acid (**1**) was envisioned with the DVCPR as keystep to establish the cyclohepta[*b*]indole core.

3 Isolation and biological activity of actinophyllic acid

Actinophyllic acid (**1**) emerged as a promising result from a screening of 40 000 extracts from Australian plants and marine organisms in an effort to find novel useful lead structures for the treatment of cardiovascular disorders. They were screened in a coupled-enzyme assay designed to discover inhibitors of carboxy peptidase U (CPU). Actinophyllic acid was isolated by Carrol *et al*. in 2005 from *Alstonia actinophylla* (Apocynaceae) - a tree indigenous to north-eastern Australia.[8]

In the body's process of removing small blood clots from circulation, fibrinolysis, CPU plays an important role and ultimately inhibits it (Figure 2). During coagulation, the formation of clots, fibrin is formed. Fibrin is degraded by plasmin, a process that leads to exposed carboxy terminals of lysine residues. Plasmin itself is formed during the cleavage of plasminogen, mediated by tissue-type plasminogen activators (t-PA) and urokinase-type plasminogen activators (u-PA). The cleavage of plasminogen is highly activated if plasminogen is bound to carboxy terminals of lysine residues, therefore a positive feedback loop is established.

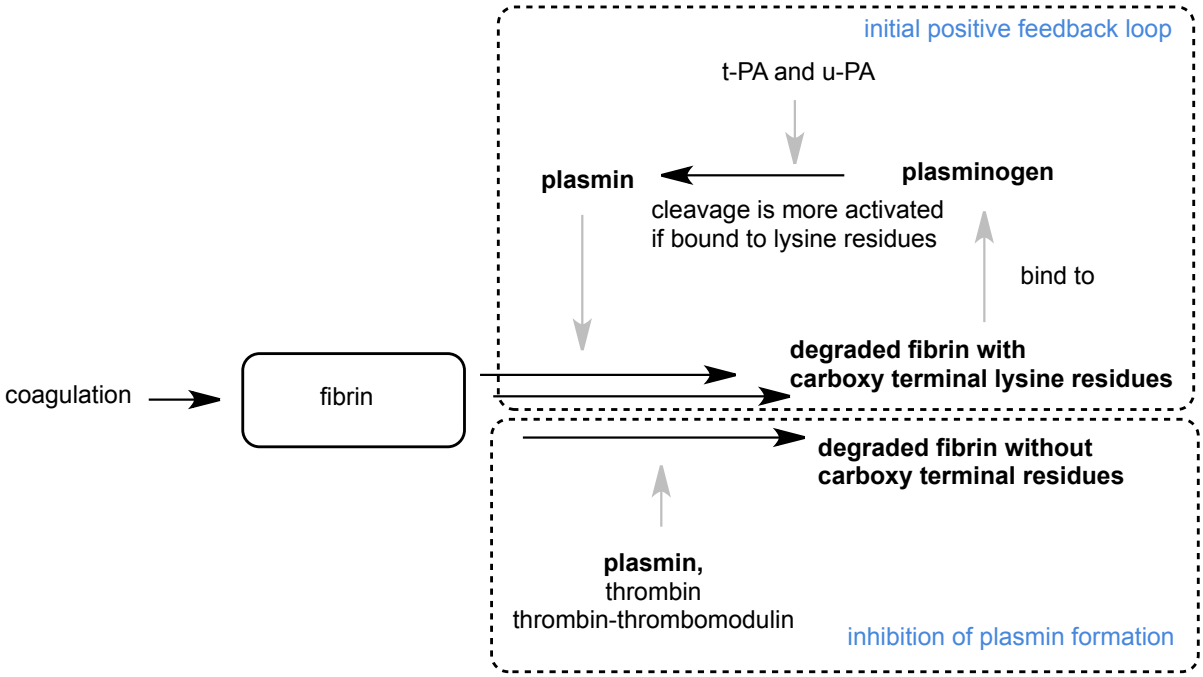


Figure 2 Fibrinolysis and its inhibition.

CPU is also able to degrade fibrin, but it does so by cleaving off carboxy terminal residues, scrambling the positive feedback loop. Moreover, CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolitic enzymes such as thrombin, thrombin-thromdomodulin and more importantly also plasmin. The loss of carboxy terminal lysine residues ultimately leads to an inhibition of fibrinolysis. It follows thus that a compound

that could inhibit CPU and as such facilitate fibrin degradation could potentially be a therapeutic agent in the treatment of cardiovascular diseases.

Prior to the actual structure elucidation, actinophyllic acid was recognized to inhibit a coupled, two-step assay during which it exhibited an IC_{50} of 0.84 μM. The first step of the assay is the enzymatic hydrolysis of *p*-hydroxyhippuric acid arginine amide (**53**) by CPU (Figure 3). The resulting *p* -hydroxyhippuric acid (**54**) is then hydrolyzed by hippuricase to *p*-hydroxybenzoic acid (**55**), which subsequently reacts with 4-aminoantipyrine (**56**) and $NaIO_4$ generating the quinomeine dye (**57**), which is used for quantification.

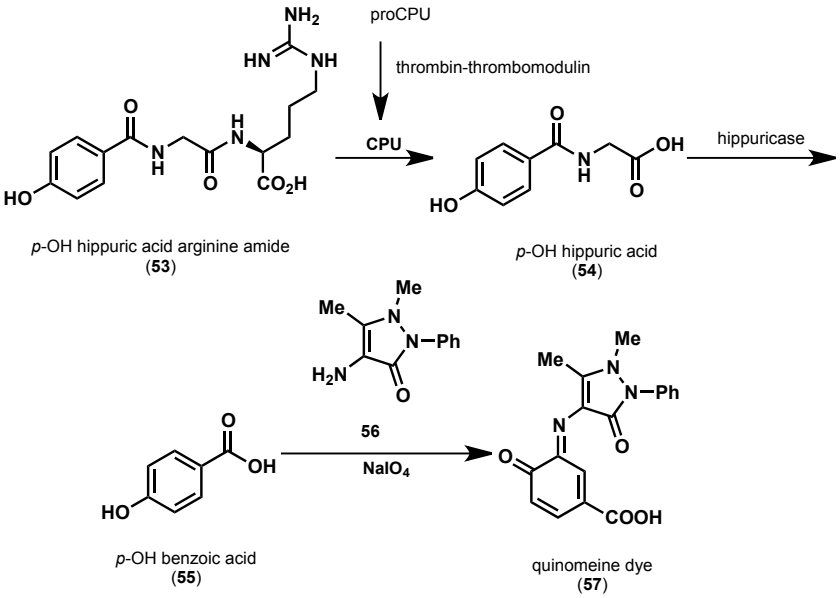


Figure 3 Coupled enzyme assay for the inhibition of CPU.

The results suggested a selective inhibition of CPU by actinophyllic acid. However, subsequent studies, where the starting material and *p*-hydroxybenzoic acid were monitored by HPLC, showed that actinophyllic acid did not inhibit CPU and the cleavage of the amide bond, but that it rather inhibited the formation of the quinomeine dye by reacting with 4-aminoantipyrine and therefore showing a false result.

Nevertheless, the results were interesting enough to prompt a structure elucidation effort and the striking molecular framework of actinophyllic acid was discovered 2005.

4 Structural features of actinophyllic acid

The carbon connectivity and relative configuration of actinophylic acid (**1**) were determined by detailed NMR studies. The absolute configuration of the natural product was put forward based upon a proposed biosynthesis and later Overman and co-workers synthesis of (±)-actinophyllic acid allowed the assignment of the absolute stereochemistry, using spectroscopic analysis and

computational methods.[27] The same group then later confirmed the assignment by enantioselective total synthesis.

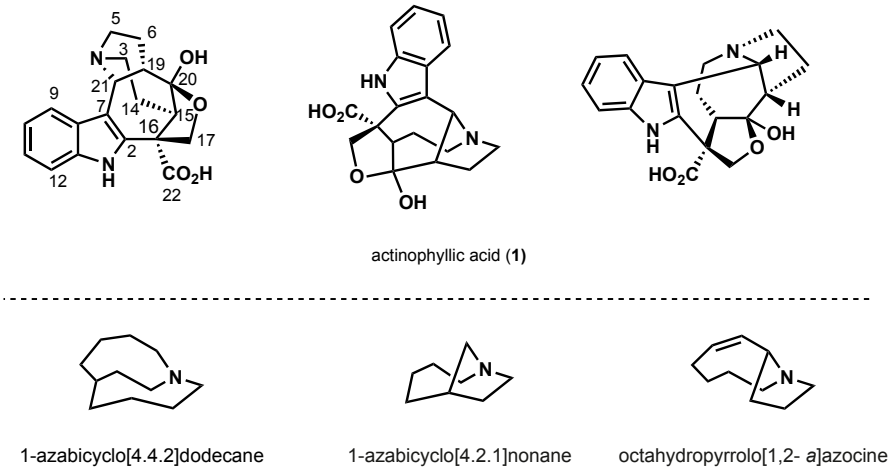


Figure 4 Different representations of actinophyllic acid (1) and its key structural motives.

Actinophyllic acid consists of an indole nucleus which is fused to a seven-membered cycle, making it a cyclohepta[*b*]indole. All of the seven carbon atoms in this cycle bear substitutents, five of which are stereocenters and one is an all-carbon stereocenter. The functional groups are varied; there is a carboxylic acid, a hemi-acetal, a tertiary amine and the indol core.

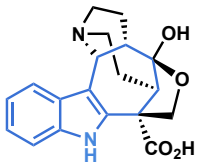


Figure 5 The cyclohepta[*b*]indole of 1.

The most striking characteristic of actinophyllic acid is the complex polycyclic structure. Altogehter it is a hexacyclic scaffold, three belong to the cyclohepta[*b*]indole, to which pyrrolidine is fused (Figure 4). The hemi-acetal bridges over the seven-membered ring, and additionally there is a two-carbon handle, connecting the seven-membered ring and the pyrrolidine nitrogen. Such a framework is unique in the natural products isolated to date and as this novelty made it especially attractive for synthetic chemists. Additinolly, the three bicyclic structures 1-azabicyclo[4.4.2]dodecane, 1-azabicyclo[4.2.1]nonane, octahydropyrrolo[1,2-a]azocine, which make up the polycyclic structure, have also yet to be found in any other natural product.

The central key feature of actinophyllic acid is the central seven-membered ring, which contains all stereocenters of the molecule and its construction is therefore of highest importance for the success of the synthesis.

5 Proposed biosynthesis

Actinophyllic acid is a monoterpenoid indole alkaloid isolated from the family Apocynaceae. As with all monoterpenoid indole alkaloids from this family, the biogenetic precursors are probably tryptamine (**58**) and secologanine glucoside (**59**) (Figure 6).[8] Strictosidine (**60**) formation, catalyzed by strictosidine synthase, would be the first step in the biosynthetic pathway. Subsequently geissoschizine (**62**) could be formed by condensation and concomitant deglucosylation followed by reduction of the resulting iminium ion.

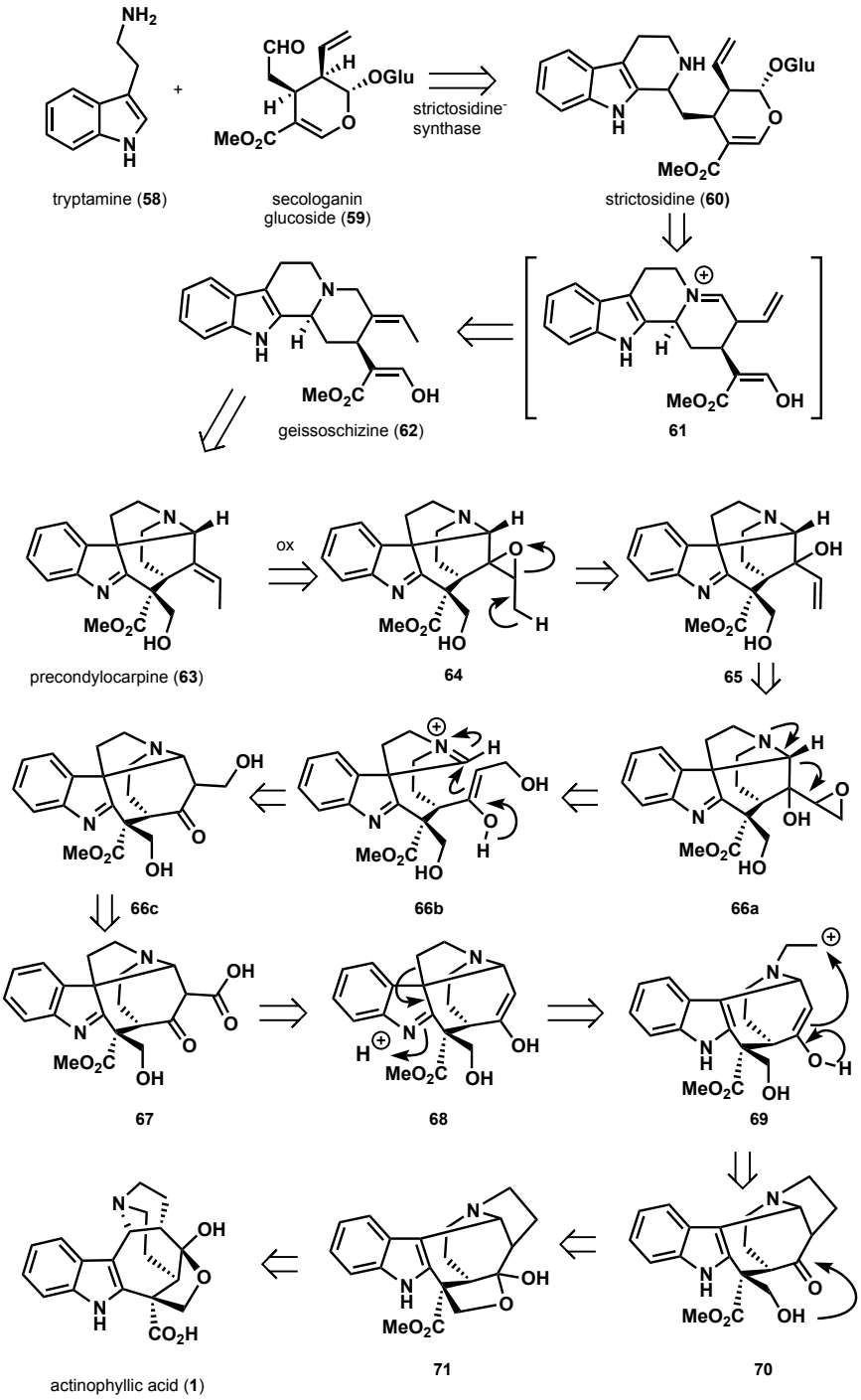


Figure 6 Proposed biosynthesis of actinophyllic acid.

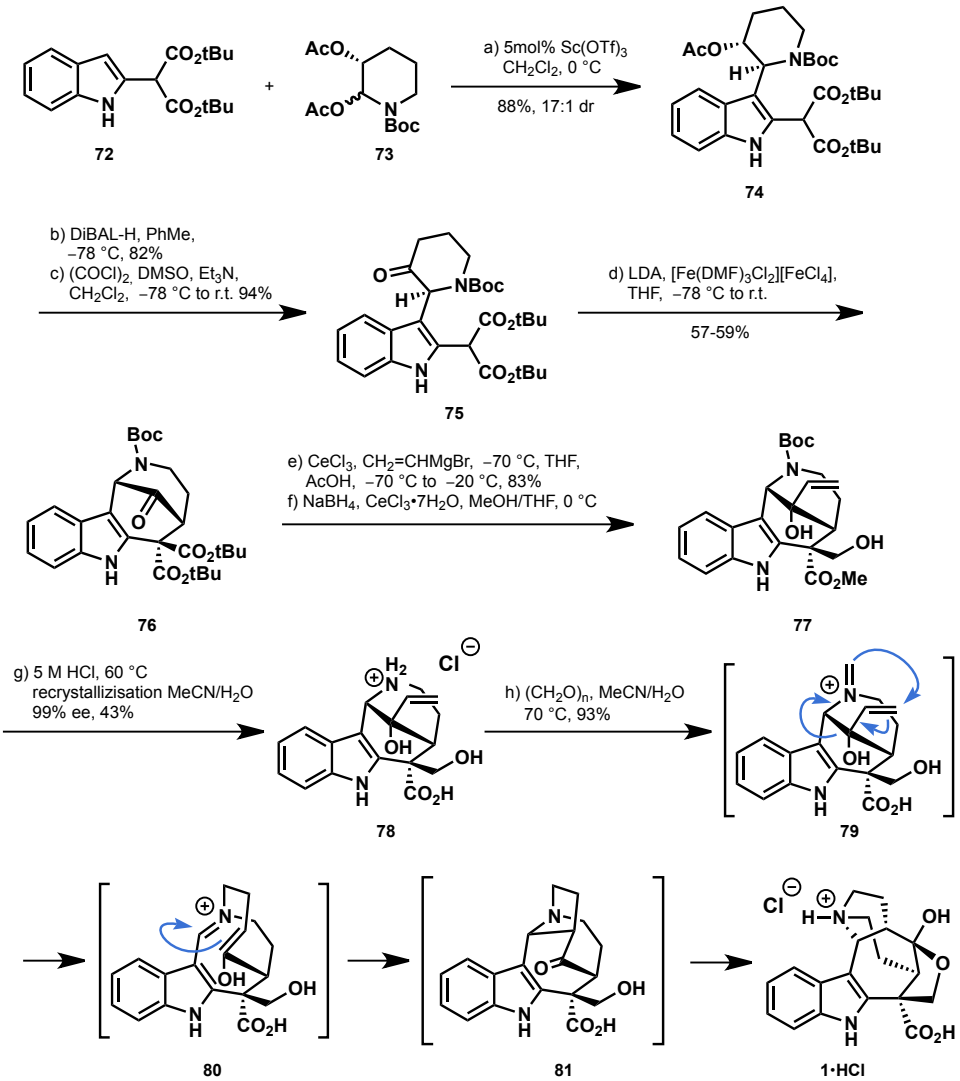
The next step would a rearrangement *via* a stemmadenine imminium ion to form precondylocarpine (**63**). Then an epoxidation of the double bond and subsequent epoxide opening would lead to allylic alcohol **65** that again could be epoxidised to give **66a**. Another epoxide opening initiated by iminium ion formation would be followed by ring closure to give azepan **66c**. Oxidation of the alcohol to the acid **67** followed by decarboxylation would give **68** , which during aromatization would give carbokation **69**. Ketone formation and ring closure would then give **70** and the last steps would be acetalisation to **71** and hydrolysis to yield actinophyllic acid (**1**).

6 Synthetic studies and total syntheses of 1 in the literature

Since the publication of its structure, **1** and its complex and until then unknown carbon framework prompted multiple synthetic endeavours that culminated in two successful syntheses by the groups of Overman and Martin. Overman's work was the only published total synthesis of **1** when this project was started. This chapter will give an overview of the synthetic studies published in literature since 2008.

6.1 Total synthesis of (–)-1 by Overman

The Overman group was the first to report a racemic and later an enantioselective total synthesis in 2008 and in 2010 respectively.[28,29] The key step was a Mannich/aza-Cope cascade, which was initiated by the condensation of paraformaldehyde onto a secondary amine (Scheme 13). The enantioselective synthesis differs from the racemic one only in the utilization of diacetoxy piperidine **73** with defined stereochemistry.



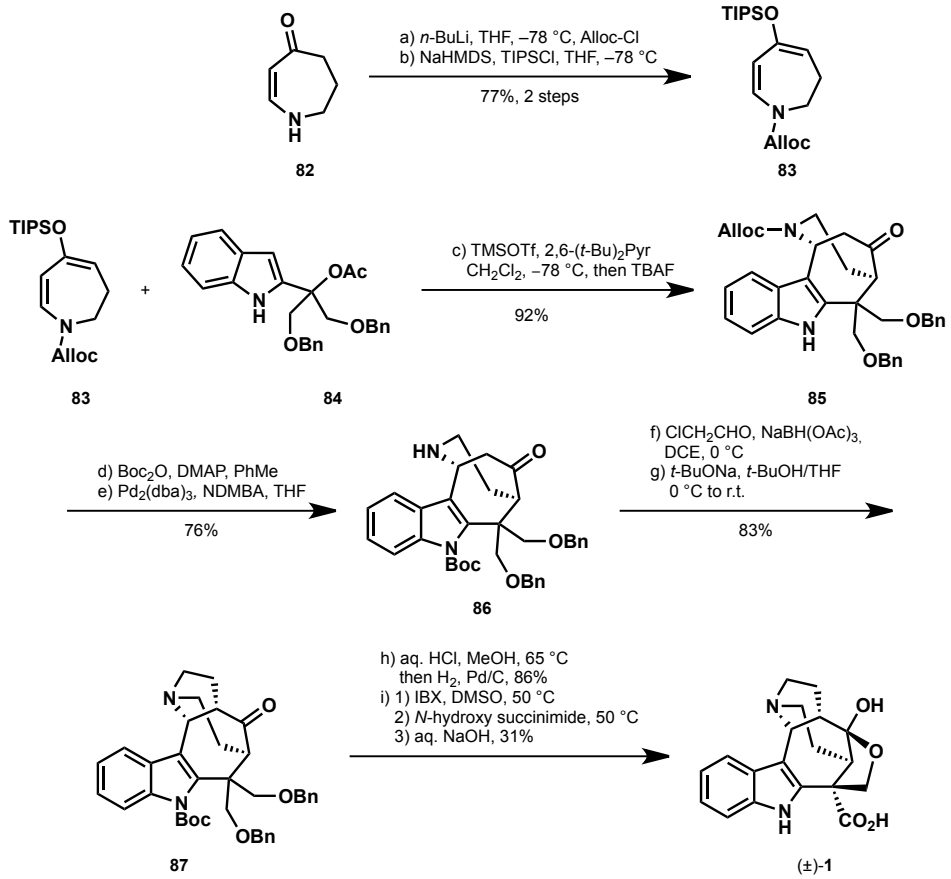
Scheme 13 Overman's enantioselective total synthesis of 1.

In a diastereoselective heteroarylation catalyzed by scandium triflate, diacetoxy piperidine **73** was added to di-*tert*-butyl indole malonate **72** to generate the first chiral center of the synthesis. Employing DiBAL-H, the remaining acetate was cleaved and the resulting alcohol oxidized using Swern conditions to give ketone **75**. An iron mediated reductive coupling then gave tetracyclic intermediate **76**, to which was added a cerium vinyl reagent, that added onto the ketone in a stereoselective way. The resulting alcoxy group reacted intramolecularly with the ester in closer vicinity, forming a 5-membered lactone. This lactone was reduced selectively with sodium borohydride and cerium trichloride in the next step to diol **77**. Treatment with 5 M hydrochloric acid hydrolysed the remaining ester and permitted a recrystallization to yield salt **78** in 99% *ee*. Adding para-formaldehyde set the stage for the Mannich/aza-Cope cascade, which ultimately gave (−)-actinophyllic acid hydrochloride. The total synthesis is accomplished within nine isolated intermediates and in 18% overall yield (91% *ee*, without recrystallisation). The enantiopure actinophyllic acid could be obtained in 8% overall yield.

6.2 Martin's synthesis of (±)-1

Five years later, in 2013, Stephen Martin and his group published their results, based on a cycloaddition reaction of a dihydroazepine and an indole derived *N*-stabilized π-cation.[30] The synthesis (Scheme 14) started with the conversion of known hydroazepinone **82** to dihydroazepine **83** by *N*-acylation and *O*-silylation. Indolyl acetate **84** together with **83** gave in the presence of trimethylsilyl trifate and 2,6 di-*tert* -butyl pyridine, after quenching with tetrabutylammonium fluoride, the tetracyclic intermediate **85**. As **85** was prone to C-N bond cleavage, the indole nitrogen was protected with a Boc-group, followed by palladium catalyzed removal of the Alloc protecting group in the presence of *N*,*N*-dimethylbarbituric acid. Reductive alkylation of the resulting amine **86** with chloroacetaldehyde and intramolecular ring closure after base induced enolisation then furnished the pyrrolidine ring in pentacyclic intermediate **87**. Subsequently the Boc-group was removed under acidic conditions followed by treatment with palladium on charcoal under hydrogen atmosphere to remove the benzyl-protecting groups. Hemi-acetal formation was spontaneous under these conditions and the last step was to be the oxidation of the neopentyl alcohol. This however proved to be challenging. It was discovered that treatment with IBX gave the intermediate aldehyde. Adding *N*-hydroxysuccinimide and excess IBX then gave a succinimide ester, which could be readily saponified under basic conditions upon which (±)-**1** was obtained.

Overall the route devised by Martin and co-workers managed to obtain (±)-**1** by a route that only required 10 chemical operations, the isolation of only nine intermediates and an overall yield of 15%.



Scheme 14. Synthesis of 1 by Martin *et al.*

6.3 Wood's divinylcyclopropane rearrangement approach

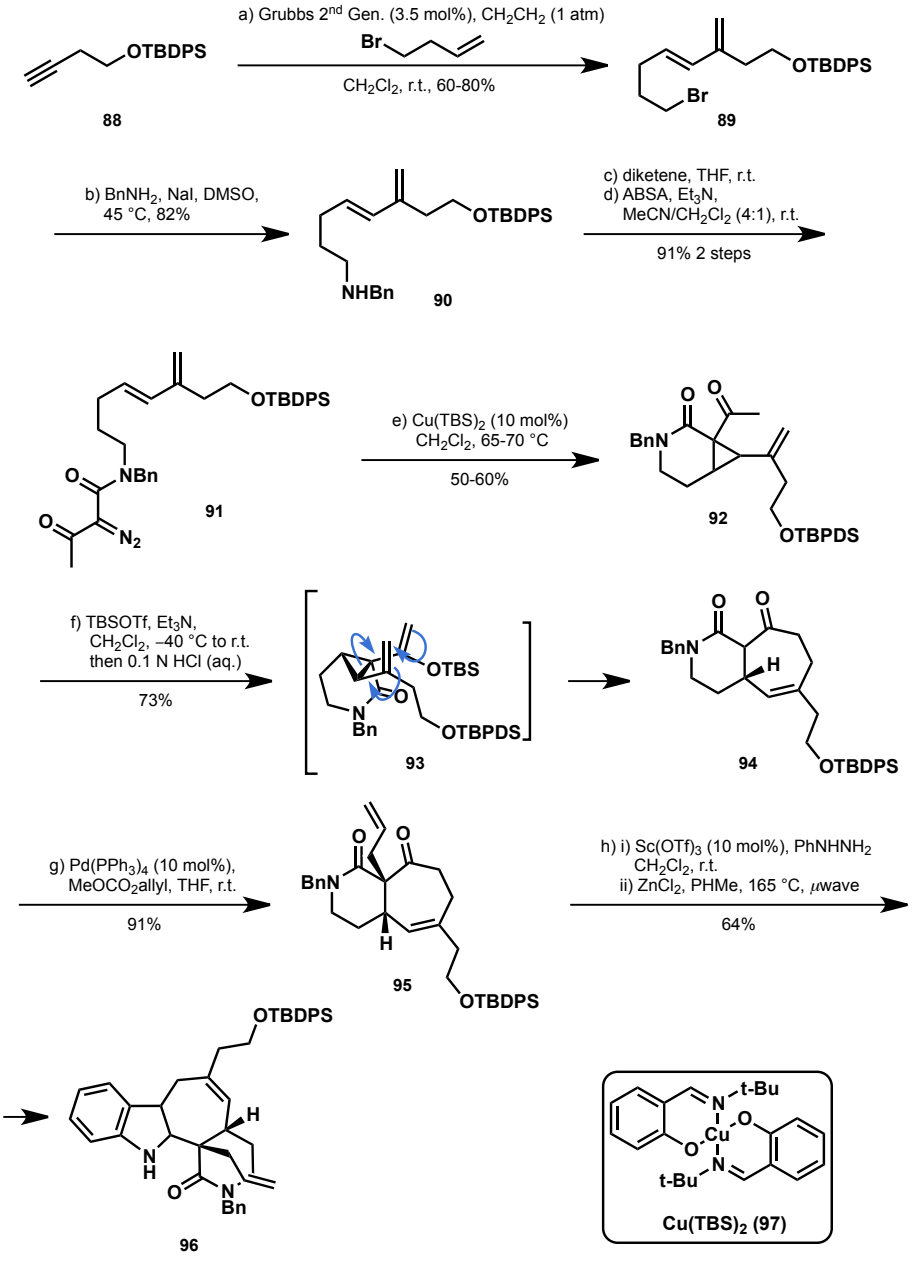
In 2009 the group of Wood published their results on the synthesis of an advanced intermediate for the total synthesis of **1**.[31] It focused on establishing the 7-membered carbocycle first and to be followed at a later stage by a Fischer indol synthesis (Scheme 15).

Starting from protected homopropargylic alcohol **88**, treatment with Grubb's 2nd generation catalyst, 4-bromo-1-butene and ethylene gas, gave, after enyne-cross metathesis, bromo diene **89**. Displacement of the bromide with benzylamine was followed by treatment with diketene to obtain a keto-amide the precursor for diazo **91**, which was obtained after diazo transfer reaction using ABSA and triethyl amine. The intramolecular cyclopropanation was challenging at first, as most common rhodium or copper catalyst known in cyclopropanation chemistry gave only complex mixtures of C-H insertion and propably also cyclopropanation products. After screening a variety of metal catalysts, copper(II)bis(salicylidene-*tert*-butylamine) [$Cu(TBS)_2$] (**97**) was found to effectively promote the cyclopropanation of **91**.

With the cyclopropane in hand, the stage was set for the divinylcyclopropane rearrangement. Enolization of ketone **92** with triethyl amine and TBSOTf at −40 °C led to enoxysilane **93** which at warming to ambient temperature rearranged in a [3,3] sigmatropic process to bicycle **94**. Tsuji-Trost allylation using palladium as catalyst and allyl methylcarbonate provided **95** as a

single diastereomer. Next was a Fischer indole synthesis. Condensation of phenyl hydrazone under scandium triflate catalysis gave the corresponding hydrazine, which upon treatment with zinc chloride and elevated temperatures under microwave irradiation gave tetracycle **96**.

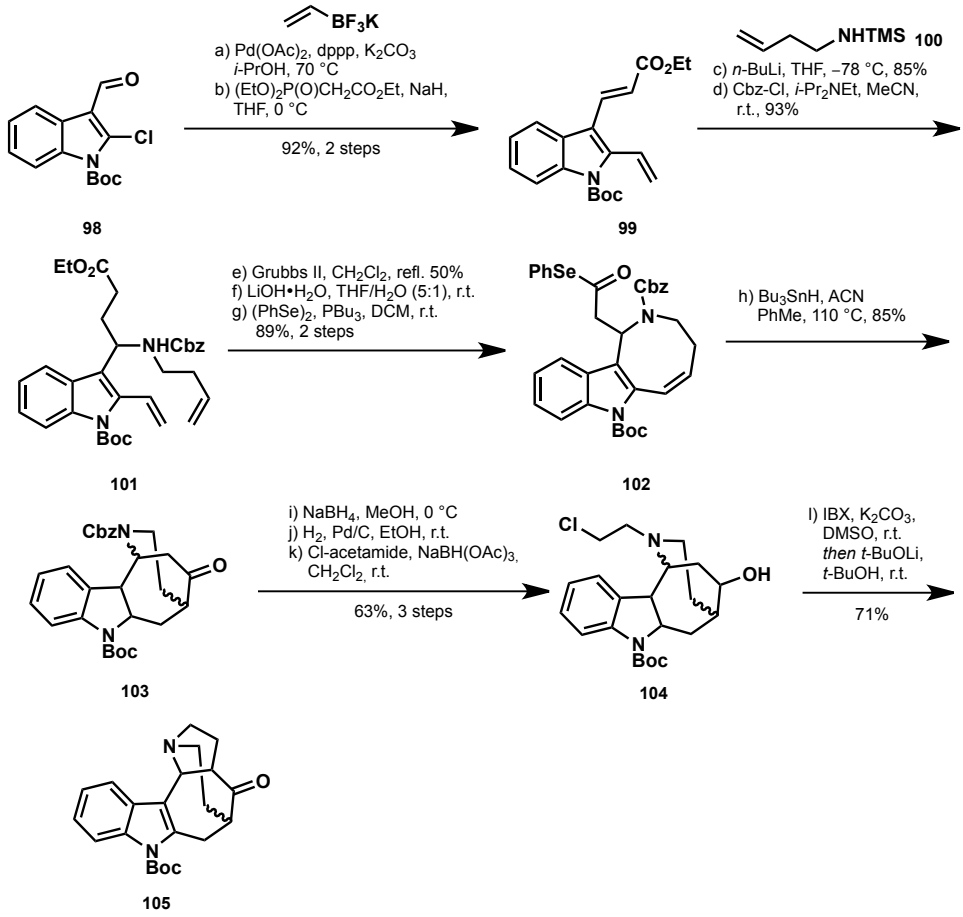
Wood and co-workers disclosed the synthesis of an advanced intermediate with all carbon atoms in place in 8 steps. Some additional steps would have been necessary to finish the synthesis of **1**, but no further results were published.



Scheme 15 Towards 1 by Wood and co-workers.

6.4 Zaimoku et al.'s synthesis of the core of 1

The group of Taniguchi published their approach to the carbon skeleton of **1** in 2012.[32] As key step they envisioned a radical cyclisation in their synthetic study towards the core of **1** (Scheme 16).



Scheme 16 Zaimoku et al.'s synthesis of the core of 1.

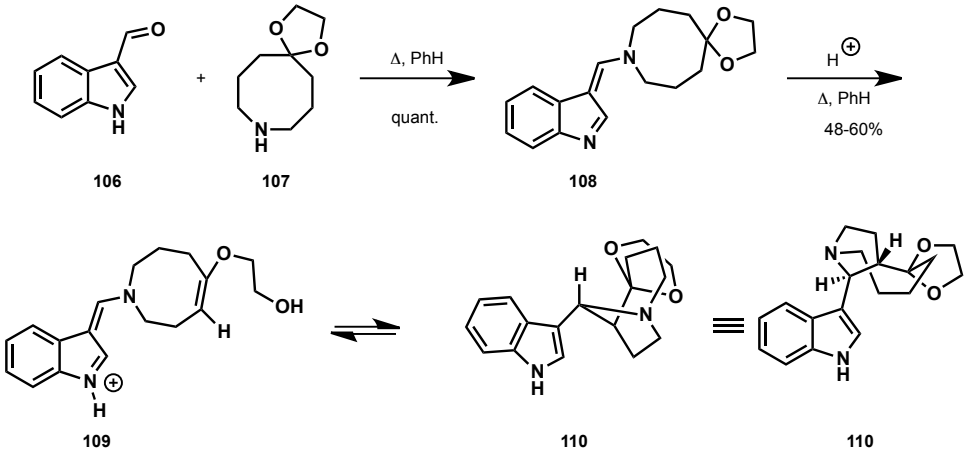
Starting from indole derivative **98**, the chloro-substituent was replaced by a vinyl group in a Suzuki-Miyura coupling with vinyltrifluoroborate under palladium catalysis with bidentate ligand bis(diphenyphosphino)propan (dppp). In a Horner-Wadsworth-Emmond olefination the aldehyde substituent at the indole C-3 position was transformed into *α,β* unsaturated ester **99**. An aza-Michael addition of deprotonated silyl-butenamide **100** introduced a secondary amine, which was protected in the next step with a Cbz-group. Ring-closing metathesis catalyzed by Grubbs II was followed by saponification of the ester and the resulting acid was then transformed into selenoester **102** by using a combination of diphenyldiselenide and tributylphosphine. The stage was now set for the transannular radical cyclisation and upon heating **102** with tributyltin hydride and 1,1'-azobiscyclohexanecarbonitrile (ACN) in toluene the desired tricyclic intermediate **103** was obtained in perfect regioselective manner. The regioselectivity is thermodynamically controlled and therefore formation of **103** *via* a more

stable *α*-indolyl radical is preferred. Before the removal of the Cbz group, the ketone had to be reduced, otherwise a retro-Michael reaction would take place. Therefore treatment with sodium borohydride was followed by hydrogenation with palladium on charcoal. The resulting amine was then reductively alkylated with chloroacetamide to give **104**. The alcohol was re-oxidized and upon treatment with lithium *tert*-butoxide pentacyclic product **105** was obtained.

Zaimoku *et al.* were able to install all but one cycle in their study and to implement an interesting transannular cyclisation. Although no further results were published they managed to build up this complex framework in 12 steps and 14% overall yield.

6.5 Mannich reactions on indol-3-carbaldehyde

Seeing the carbon skeleton of **1**, the group around Maldonado decided to study Mannich reactions using indol-3-carbaldehyde and a suitable amine.[33] The group reasoned that a condensation and an intramolecular attack on an extended iminium ion could be an entry to the core of **1**. Indeed, condensation of indole-3-carbaldehyde **106** and *spiro* 8-membered cyclic amino acetale **107** furnished enamine-imine **108**, which under acidic conditions underwent cyclisation to pentacycle **110**.

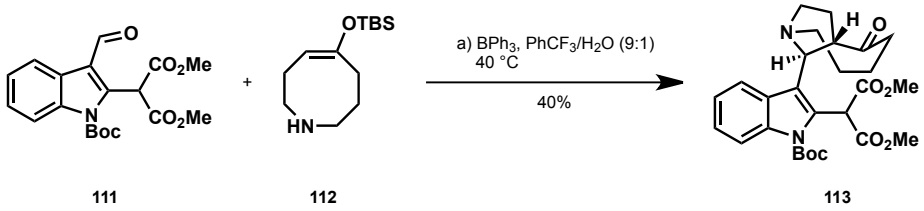


Scheme 17 Galicia and Maldonado's studies towards 1.

Although the reaction went as planned, X-ray analysis showed the obtained product to be the wrong diastereomer. Using the pyrrolidine as reference, the indole and the seven membered ring are positioned *anti* to each other, different from **1**. As this is the thermodynamic product, the researchers were unable to change the selectivity.

A team consisting of Danny Mortimer, Matthew Whiting, Joseph P.A. Harrity, Simon Jones and Iain Coldham from the University of Sheffield and from GlaxoSmithKline initially attempted this Mannich reaction with a series of Brønstead acids as catalysts but without success.[34] After screening multiple Lewis acids, the best result is shown in Scheme 6. The condensation of indolyl aldehyde **111** and cyclic amine **112** led after desilylation to the tetracycle **113** in

40% yield. Again, the product was obtained as a single diastereomer exhibiting the *anti* configuration.



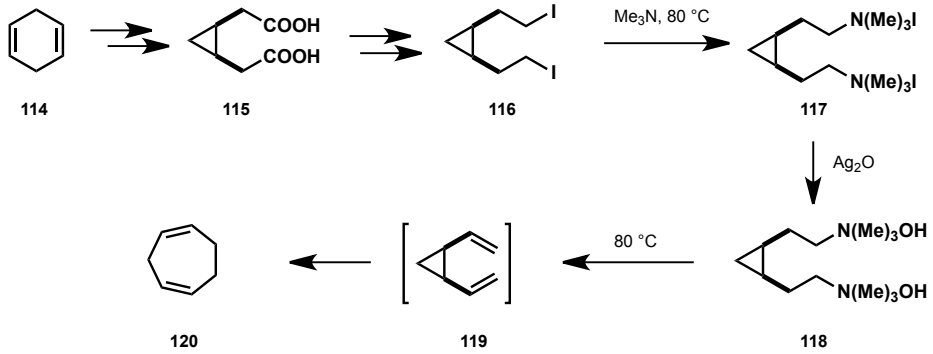
111 112 113

Scheme 18 *Anti*-selective Mannich reaction towards 1.

Building up the carbon framework of **1** is a challenge multiple chemists have sought to overcome. Even after Overman's hallmark synthesis this unique architecture continues to inspire chemists to design new syntheses. Two total syntheses and two advanced approaches published show the attraction of this molecule. Moreover, the fact that there are still challenges to overcome, that not each synthetic effort is successful, displays the room for improvement in organic chemistry and the necessity for research in organic synthesis.

7 The DVCPR and indole alkaloids

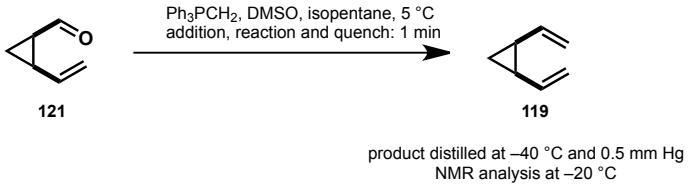
The following chapter heavily relies on Gaich and Krüger's recent and comprehensive review over the DVCPR.[35]



Scheme 19 Vogel and co-workers' rearrangement results.

The DVCPR is essentially a tethered Cope-rearrangement where the central σ-bond is replaced with a cyclopropane and therefore a seven membered ring is obtained. In 1960, Vogel and co-workers reported the first DVCPR during their studies of thermal rearrangement of small rings (Scheme 19).[36] Although *cis*-divinyl cyclopropane **199** could not be isolated by this route, as it readily rearranged under the elimination conditions, the cycloheptadiene **120** was described as well as the rearrangement of the *trans*-divinyl cyclopropane at 200 °C.[37]

Ten years later, Brown *et al.* could isolate the reactive *cis*-cyclopropane **119**. They were able to characterize it by employing a very quick Wittig reaction on aldehyde **121** as well as low temperature NMR analysis (Scheme 20).[38]



Scheme 20 Isolation of *cis*-divinylcyclopropane.

Mechanistically, the DVCPR proceeds differently from the related Cope-rearrangement. Where as the Cope rearrangement of 1,5-hexadiene prefers a chair-like transition state, the DVCPR proceeds through a boat-like transition state.

One can perceive three different transitions states for the DVCPR (Figure 7). However only through the boat transition state (lower row) the product is obtained, as with any other conformation at least one of the resulting double bonds in the cycloheptadiene would be *E* configured which can be considered impossible.

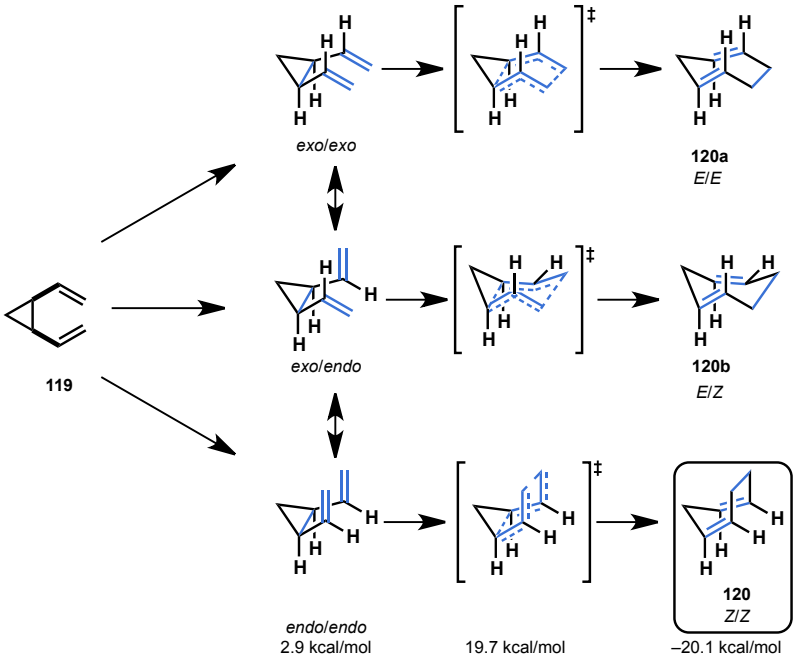


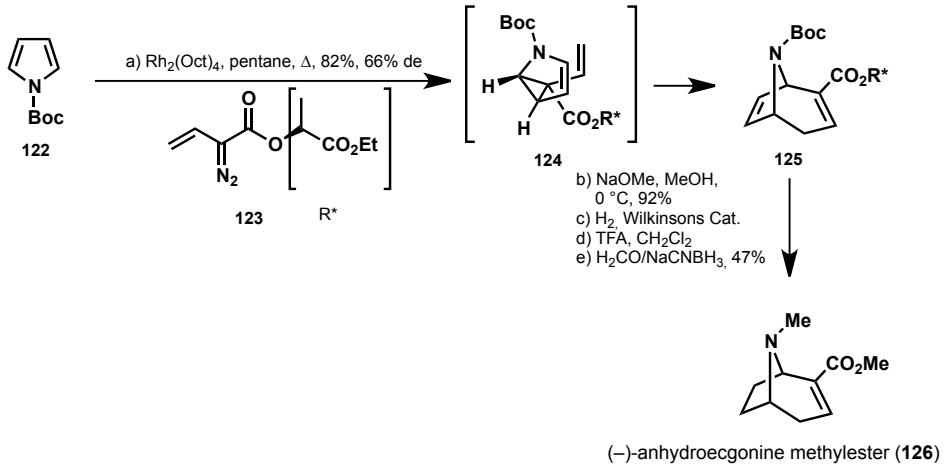
Figure 7 Transition states for the divinylcyclopropane rearrangement.

The *exo*/*exo* conformation (upper row) is energetically preferred as revealed by calculations, rotating one bond into the *endo* position requires 0.8 kcal/mol (central row) and the *endo* position of both vinyl moieties requires 2.9 kcal/mol. The necessary transition state requires 19.7 kcal/mol but the cycloheptadiene **120** is favoured by −20.1 kcal/mol compared to the *cis*-divinylcyclopropane **119**.[35 and cited references]

The DVCPR is a powerful reaction and has been broadly used in total syntheses of natural products. As discussed above, Wood and co-workers used it during their attempt to synthesize **1** (Scheme 15).[31]

However, at the start of the project, the DVCPR was never used in conjunction with an indole nucleus to make cyclohepta[*b*]indoles. Some reports however allowed speculation on the feasibility of such a reaction.

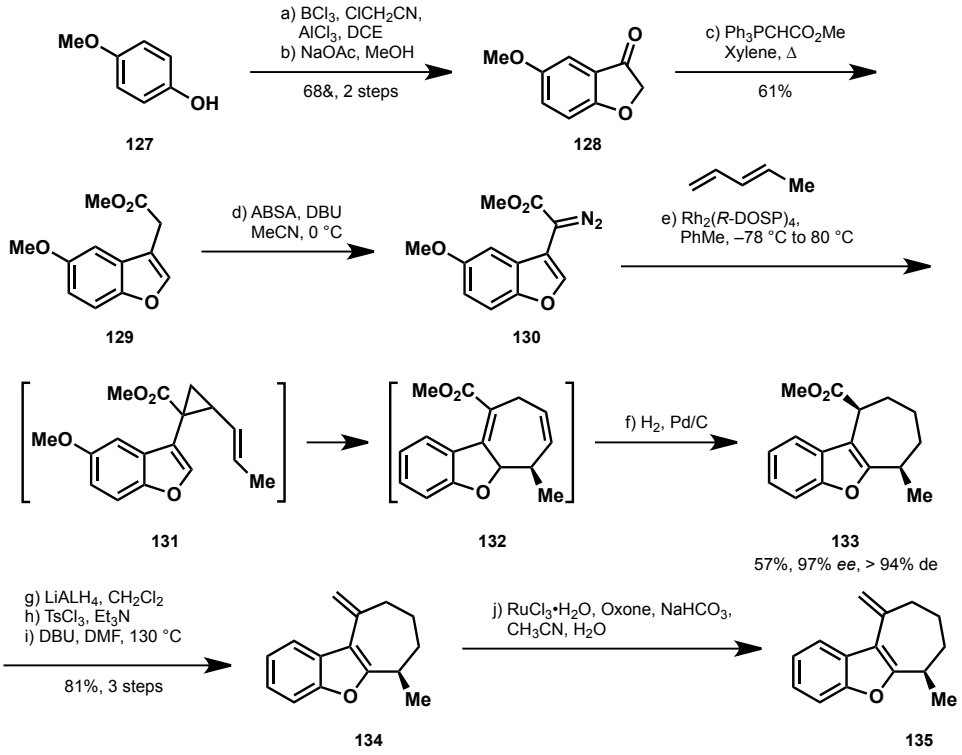
In Davies and co-workers' report on the synthesis (−)-anhydroecgonine methylester (**126**), a DVCPR was used to synthesize the tropane moiety of this alkaloid which is structurally related to cocaine.[39] Boc-protected pyrrole **122** was subjected to vinyldiazo ester **123** bearing a chiral auxiliary and rhodium catalysis. The resulting divinylcyclopropane **124** rearranged under the reaction conditions and the obtained bicycle could be transformed into the desired product in four additional steps.



Scheme 21 Davies use of an enamine substituted cyclopropane for the DVCPR.

The challenges in this synthesis involved the synthesis of a tetrasubstituted cyclopropane with a carbamate in α-position. Isolation of the cyclopropane was not attempted, therefore issues on its stability had not to be addressed. Ultimately the DVCPR-product was obtained in good yield without interference of the nitrogen.

Using a different hetereocycle, Davies was able to use the DVCPR another time for the formal total synthesis of frondosin B (Scheme 22).[40] Starting from 1-methoxy-4-hydroxy benzol **127**, benzofuranyldiazoacetate **130** was synthesized in five steps.



Scheme 22 Davies' formal synthesis of frondosin B.

In a cyclopropanation it was reacted with *E*-piperinene under chiral rhodium catalysis and a mixture of the resulting divinyl cyclopropane **131** and the rearranged seven-membered ring **132** was obtained. Upon heating to 80 °C, the mixture was converted completely to the desired seven-membered ring but the product was unstable, therefore it was immediately hydrogenated, during which it also re-aromatized to **133**. After four additional steps, the formal total synthesis of frondosin B was completed.

Benzofurans and indoles differ substantially in their electronic behavior, just as pyrroles and furans do. Therefore the success of Davies in this case only allowed limited prediction of the behavior of an indole nucleus in a comparable reaction. Nevertheless the results of this DVCPR are encouraging.

Looking at cyclohepta[*b*]indoles one can conceive four different precursors for the DVCPR, given the fact, that there should be a least a single bond between indole C-2 and C-3 in the precursor (Figure 8). The upper two precursors would require the synthesis of a *spiro*[cyclopropylindole] but would have the advantage that not only the release of ring strain would be a driving force for the reaction but also the re-aromatization of the indole core. The lower two precursors may be easier to obtain *via* cyclopropane synthesis, but in the course of the DVCPR, aromatization would be lost and making the reaction more difficult to proceed.

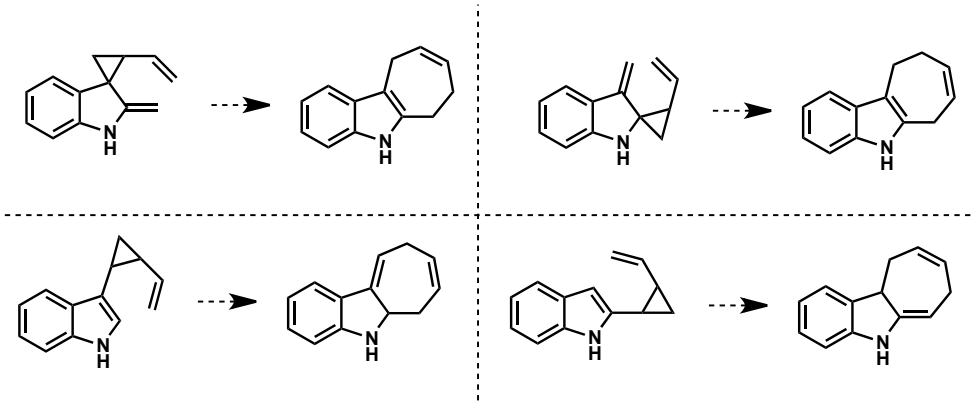


Figure 8 Possible precursors for the DVCPR involfing an indol moiety.

8 Spiro[cyclopropylindole] approach towards the DVCPR

8.1 Initial retrosynthesis of actinophyllic acid

At the time this research project was commenced, only the total synthesis of **1** by Overman was published. Additionally cyclohepta[*b*]indoles themselves were and still are of great interest to medicinal chemists. However as shown in the previous chapters, only a few methodologies to synthesize them exist.

To showcase the applicability of the DVCPR to enantioselectively synthesize complex carbon frameworks, it was decided to use the DVCPR in the keystep to obtain the central cyclohepta[*b*]indole in **1.** To this end, a flexible route for the synthesis of DVCPR precursors had to be developed.

From the four possible DVCPR precursors, the *spiro*[cylcopropylindole], top left in Figure 8, seemed the most promising. Indoles with spiro substituents at C-3 are well known and the synthesis of a *spiro*[cyclopropyloxindole] was published already.[41] Hence the initial retro-synthesis focused on this synthetic proposal (Figure 9).

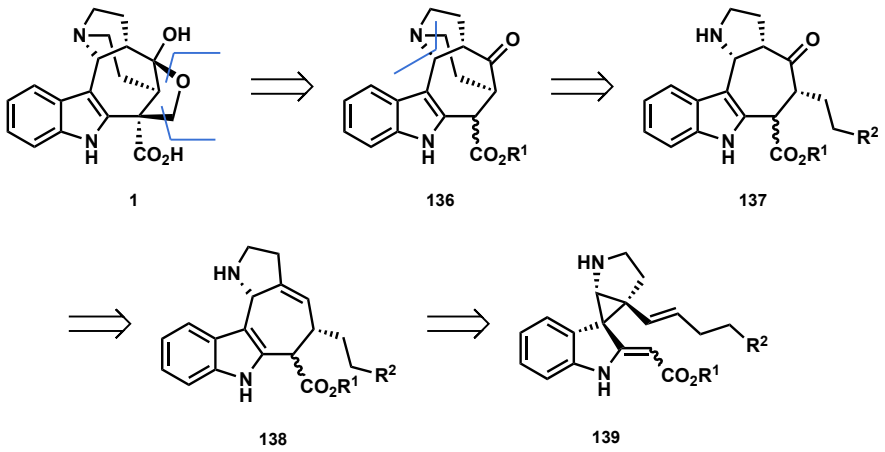


Figure 9 Initial retrosynthesis.

Regarding **1**, it was decided, that the five-membered hemiacetal would be installed in one of the last steps, relying on chemistry that Overman reported.[28] Disconnecting the tertiary amine and the two-carbon handle, spanning the pyrole and the seven membered ring in **136**, reveals tetrameric compound **137**, where R^2 would be an appropriate leaving group such as a halogene or a meslyated alcohol. The ketone in **137** would evolve from a stereo-selective hydroborotation-oxidation sequence of cyclohepta[*b*]indol **138**, which would be the product of a DVCPR starting from *spiro*[cyclopropylindole] **139**.

The proposed transition state for the rearrangement is shown in Figure 10. Mandated by the closed boat transition state, the correct configuration of the cyclopropane and the *E*-double bond would be transferred to the stereo-information of the alkyl chain.

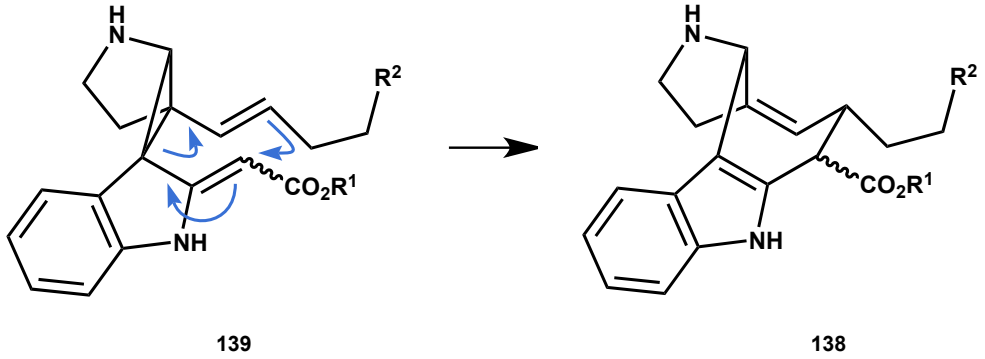


Figure 10 Proposed transition state for the initial retro synthesis.

Overman and co-wokers showed, that the configuration of the ester moiety in **138** would not be of importance because the installation of the acetal proceeded through deprotonation of this exact position followed by addition of *para*-formaldehyde. The selectivity of the planned hydroboration would be greatly enhanced by the fact, that five-membered rings are almost exclusively fused to other rings in a *cis* fashion.

One of the main goals of the retrosynthesis was to incorporate all carbons except the hemi-acetal carbon into the DVCPR precursor. This would provide the advantage that only functional group interconversion would be necessary after the DVCPR. If **139** could be obtained in a concise and selective manner, the synthesis of **1** would be potentially short and convergent. Additionally, a cylopropanation sequence with a broad scope, could establish the DVCPR as a direct means for the synthesis of cyclohepta[*b*]indoles.

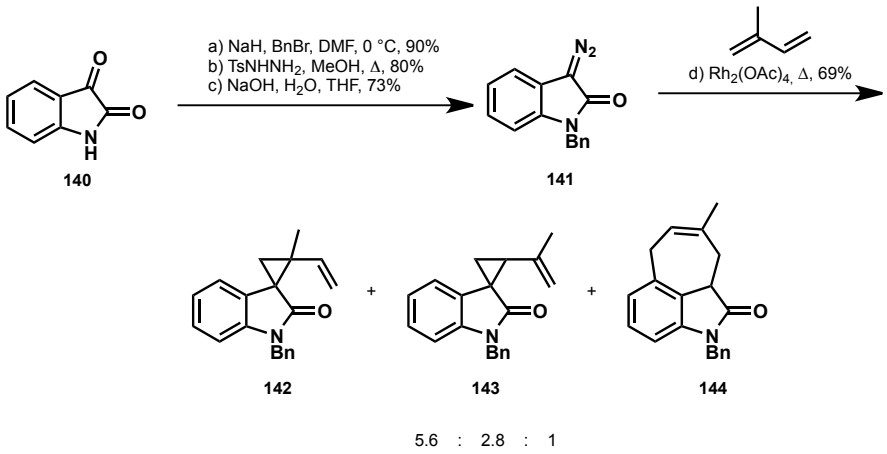
8.2 Intermolecular synthesis of a *spiro*[cyclopropylindole]

As this project was started, two major challenges were identified. One was the selective synthesis of a *spiro*[cyclopropylindole] similar to **139** in Figure 9. In order to be useful for the synthesis of **1**, a penta-substituted cyclopropane would have to be synthesized enantioselectively. Additionally, the conversion of an amide to an enamine would be another synthetic challenge.

A test system with less substituents on the *spiro*[cyclopropylindole] compared to **139**, was synthesized following a published procedure from the group of Eric Carreira.[41]

The synthetic efforts started with commercially available isatine (**140**), which was transformed into diazo-compound **141** in three steps. Benzylation of the nitrogen was followed by condensation of tosyl-hydrazine and under basic conditions the resulting hydrazine was

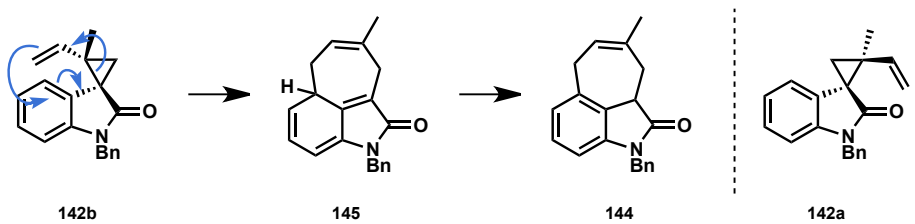
converted to **141**. Using **141**, the cyclopropanation proceeded in refluxing isoprene and catalyzed by rhodium(II) acetate to furnish a mixture of three products in a ratio of 5.6:2.8:1.



Scheme 23 *Spiro*[cyclopropyloxindole] synthesis.

The main products of this reaction were the two region-isomers of the *spiro*[cyclopropyloxindole] **142** and **143**. The major isomer was the higher substituted cyclopropane **42**. As the metal-catalyzed cyclopropanation is an electrophilic process, the more electron rich double bond, which is also the higher-subtituted one, reacted preferentially under the thermodynamical reaction conditions .

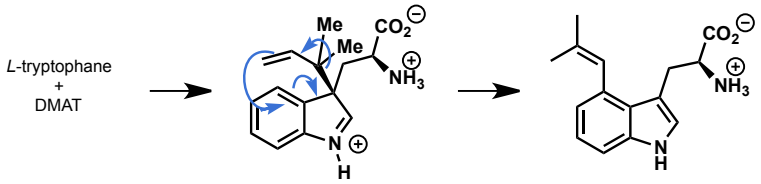
In addition the cyclohepta[*b,c*]indole, **144**, was obtained as well. This product stems from a DVCPR with an aromatic double bond (Scheme 24). In order for this reaction to proceed, the vinyl double bond and the aromatic ring had to be on the same side of the cyclopropane, whereas the other diastereomer should not react. Later it could be shown, that after selective and independent synthesis of both diastereomers, only **142b** would form the cyclohepta[*b,c*]indole **144**. It is also noteworthy that at elevated temperatures **142a** interconverts, probably through diradical pathway, to **142b** and then cyclize to **144**. This result demonstrates clearly the stereochemical demands of the DVCPR.



Scheme 24 Formation of cyclohepta[*b,c*]indole.

Although Cope rearrangements involving aromatic double bonds are known, reaction at the indole C-4 position was unexpected becaus this position is one of the least activated in the indole nucleus. As such this result proved to be twofold fascinating. In contrast to several established methodologies, it allows the installation of substituents on the indole C-4 position without prior

functionalization. Additionally it provides experimental evidence for the biosynthetic hypothesis by Arigoni and Wenkert on the mode of action of 4-prenylation of indoles. They propose an initial reverse prenylation of *L*-tryptophane and dimethylallyl pyrophosphate with the aid of DMAT synthase followed by Cope rearrangement and aromatization.[42–44]



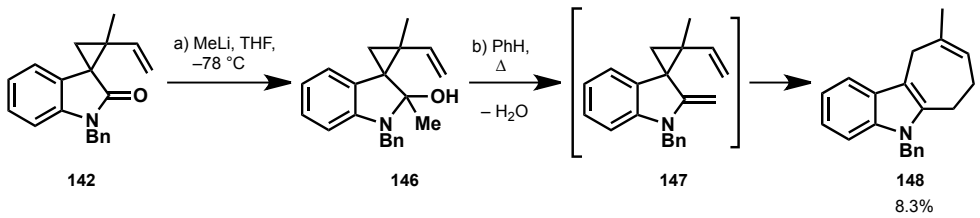
Scheme 25 Arigoni and Wenkert biosynthesis hypothesis.

Further investigations to obtain cyclohepta[*b,c*]indoles was done by Darius D. Schwarzer in this group.[42,45]

The next step towards the DVCPR was the transformation of the amide group in to a double bond. Only the higher substituted cyclopropane **142**, which was the major product in the cyclopropanation reaction, was chosen as substrate to test the hypothesis of a DVCPR on an indole core.

Two strategies were considered: the first was a nucleophilic addition and subsequent elimination of water. The second included the formation of a thioamide and subsequent Ramberg-Bäcklund reaction.[46] In theory both would be complimentary to establish different substituents. To serve as a rapid access to **1** the introduction of an ester was considered. Initial efforts however focused on simple nucleophiles.

Starting with the least sterically demanding reagent, methyl lithium was added to **142** at −78 °C in THF (Scheme 26). After 15 minutes the starting material was consumed and the reaction quenched. After work-up the residue was dissolved in benzene and heated to reflux for 16 hours after which the desired cyclohepta[*b*]indole **148** was obtained albeit in low yield. The reaction worked as planned and the hypothesis was confirmed. However, the low yield proved to be a major drawback.



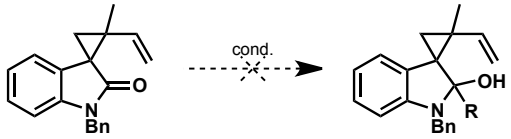
Scheme 26 Methyllithium addition.

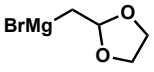
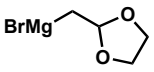
As a matter of fact the amide functionality is innately less reactive towards nuleophiles than esters, ketones and aldehydes and additionally this amide is in a neopentylic position. Therefore

nucleophilic addition proved to be the major challenge to obtain cyclohepta[*b*]indoles by this approach.

Based on these considerations, a variety of nucleophilic additions were studied on this substrate and shown in Table 1. However the activation of the amide using triflic anhydride and di-*tert*butyl pyridine followed by the addition of a lithium- or a cerium-methyl reagent was not successful (entry 1 and 2).[47,48] Unfortunately no product was obtained and reaction monitoring reavealed degradation of starting material during the activation of **142** with triflic anhydride and therefore this approach was discontinued. In an attempt, to study a possible installation of the desired ester group α to indol C-2, an aldol reaction was tested. The rate of success of this reaction was judged quite low due to the fact that an aldol reaction on an amide generally proceeds poorly regarding the low electrophilicity of moiety. But as predicted, starting material could be isolated quantitatively (entry 2). However also the activation of **142** with trifluoroborane dietherate did not improve reactivity or the results of the reaction (entry 3). Next a Grignard addition was tested, but again no addition was observed, even under harsh conditions such as elevated temperatures and activation of the Grignard reagent with lithium chloride (entries 5 and 6). Finally, lithiated ethoxy acetylene, a reagent of very little steric demand was tested as nucleophile. However also in this case, no product could be obtained, but degradation occurred at higher temperatures.

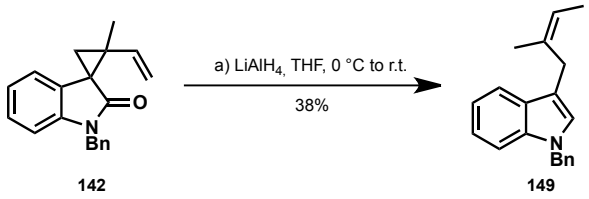
Table 1 Attempted addition to vinyl-*spiro*[cyclopropyloxindole].



entry	conditions	R
1	Tf_2O, D*t*BP, THF −78 °C *then* MeLi, $CeCl_3$	Me
2	Tf_2O, D*t*BP, THF −78 °C *then* MeLi	Me
3	LDA, *t*-BuOAc, THF, −78 °C to r.t.	CH_2CO_2t-Bu
4	LDA, *t*-BuOAc, BF_3•Et_2O THF, −78 °C to r.t.	CH_2CO_2t-Bu
5	 , THF, 0 °C to reflux	2-Methyl(1,3-dioxalanyl)
6	 , THF, LiCl, 0 °C to reflux	2-Methyl(1,3-dioxalanyl)
7	HCCOEt, *n*-BuLi, −78 to r.t.	CCOEt

In summary, nucleophilic addition to amide **142** was not possible apart from small amounts of methyl lithium. The combination of sterical hindrance and unfavorable electronic behavior proved difficult to overcome.

As a step in a different direction, reduction of the amide was studied. Making an aminal might have offered different synthetic pathways. Treating **142** with DiBAl-H and Red-Al™ did not have any effect on the substrate in a temperature range from 0 °C to room temperature. Similarly, treatment with lithium aluminium hydride at −78 °C had no effect on the substrate. At 0 °C however the reduction with lithium aluminium hydride resulted in a 1,6 addition of the hydride to compound **142** followed by reduction of the amide (Scheme 27). This experiment is also a further proof of the poor electrophilicity of amide.

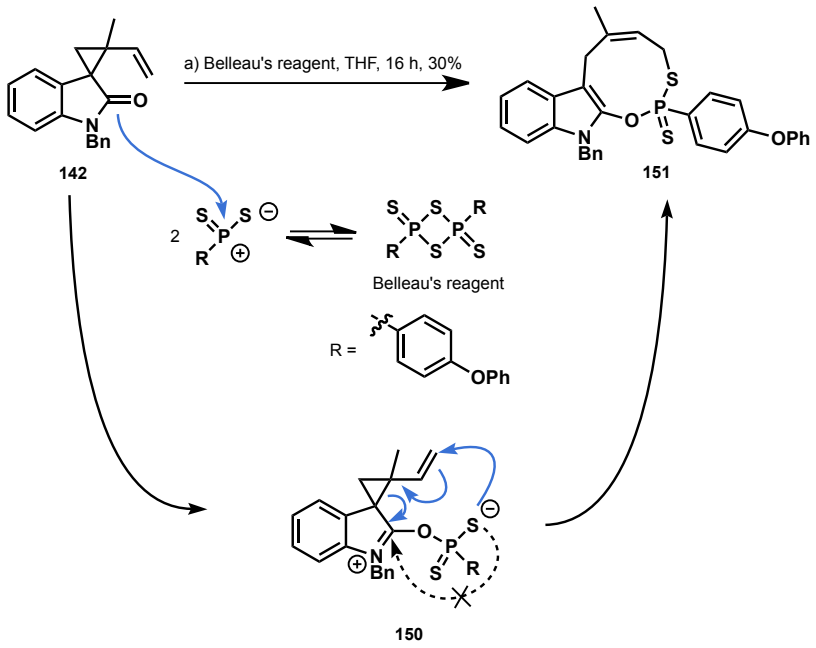


142 149

Scheme 27 1,6 reduction of the cyclopropane.

Based on these results, nucleophilic reagents were not able to react with the amide functionality, the second synthetic concept, the use of a Ramber-Bäcklund reaction, was studied next. This strategy required the transformation of the oxdindole to a thioamide, which would be the precursor for the Ramberg-Bäcklund reaction. The synthetic endeavor was launched by the treating **142** with the Belleau reagent in THF for 16 hours. However under these conditions only the nine-membered heterocycle **151** was generated instead of the desired thioamide (Scheme 28).

Structure elucidation was facilitated by X-ray crystallography and therefore the structure of the product could be unambiguously established.



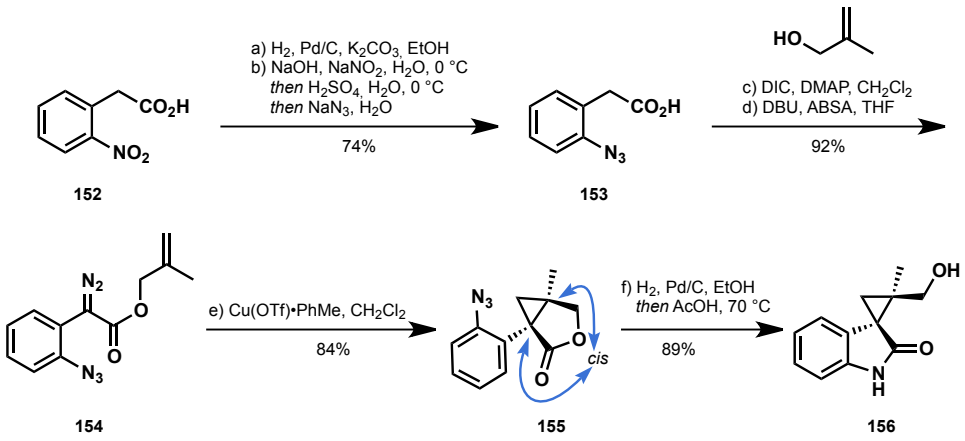
Scheme 28 Attempt to form a thio amide.

As depicted in Scheme 28, the Belleau reagent is in equilibrium between a monomeric, dithiophposphine ylide and the stable, dimeric form in solution. The reaction usually proceeds similar to a Wittig reaction, the first step is the attack of the carbonyl oxygen onto the positively charged phosphorous atom to give **150**. The second step is the addition of the negatively charged sulfur atom onto the former carbonyl carbon (the dashed arrow). However in this case, addition onto the vinylcyclopropane was preferred. Subsequent aromatization of the indole core in the process, which was probably also the driving force of this reaction, furnished compound **151**.

Interestingly, using the related Lawesson reagent no reaction occurred at ambient temperature. At elevated temperatures the product degraded. Using phosphorous pentasulfide did not either produce the desired thioamide. Either no reaction at ambient temperature or degradation at higher temperatures occurred. According to these results, the Ramberg-Bäcklund reaction seemed unattainable.

8.3 Intramolecular synthesis of a *spiro*[cyclopropylindole]

Based on the facts, that the cyclopropanation gave a the multitude of products as well as the low reactivity of the amide group it was decided to develop a new route towards the *spiro*[cyclopropyloxindole]. This diastereoselective approach should allow the formation of the double bond at the indole C-2 position earlier in the synthesis. Due to this strategy the interfering effect of the vinyl group on the cyclopropane could be avoided. An intramolecular cyclopropanation (Scheme 29) offered a solution to these challenges.



Scheme 29 Diastereoselective synthesis of a *spiro*[cyclopropylindole]

Starting from 2-nitrophenylacetic acid **152**, the nitro group was reduced by the use of hydrogen with palladium on charcoal. The resulting amine was transformed into the corresponding diazonium salt, which upon treatment with acid and sodium azide formed 2-azidophenylacetic acid **153**. Esterification with *β*-methallyl alcohol was followed by diazo synthesis using DBU and ABSA to obtain **154**. The following intramolecular cyclopropanation was catalyzed by copper(I) and gave bicyclic lactone **155**.

The diasteroselectivity of this reaction is governed by the size of the generated ring. It is known that a cyclopropane can be compared to a double bond. Therefore a *trans* configutration of the substituents on a cyclopropane is equivalent to an *E*-double bond. Moreover, due to the fact that only *Z*-double bonds can be incorporated into five-membered rings, only the desired *cis*-fused bicycle **155** could be obtained.

The transformation of **155** to the corresponding oxindole **156** was accomplished by reduction of the azide with hydrogen and palladium on charcoal. Subsequent heating to 70 °C for 16h furnished oxindole **156** which maintained the same configuration as bicyclic lactone **155**.

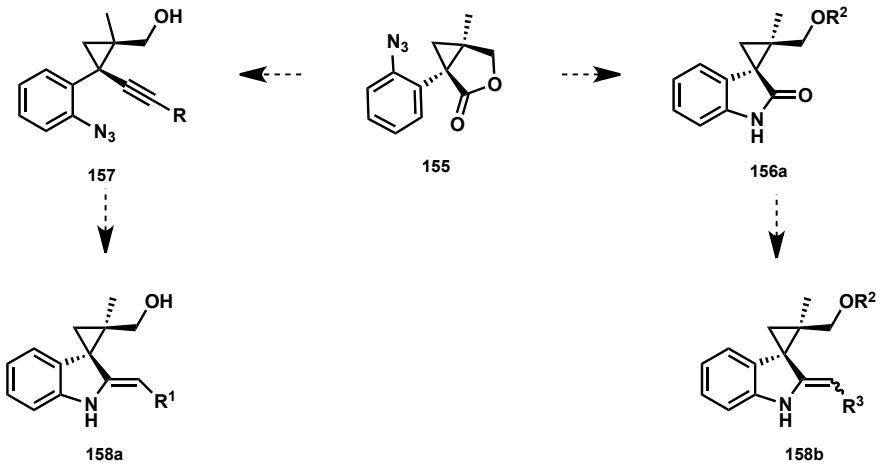


Figure 11 Possible DVCPR precursors.

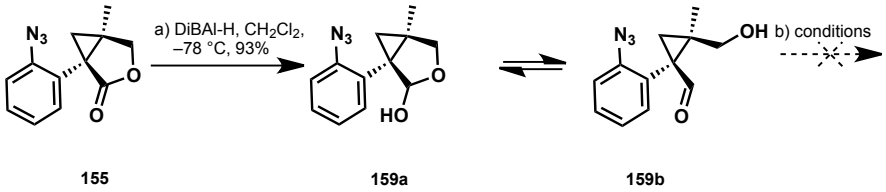
Lactone **155** and oxindole **156a** could both be considered suitable precursors for the DVCPR (Figure 11). One strategy studied was the transformation of the γ lactone **155** to an alkyne **157** before establishing the indole moiety. After cyclisation, the double bond at C-2 would be established. Another strategy tested was to synthesize oxindole **156a** and then convert the amide group to a double bond before building up the second vinyl group on the cyclopropane.

8.3.1 Attempted transformations of lactone 155

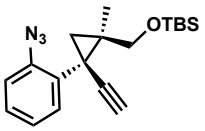
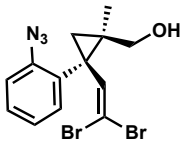
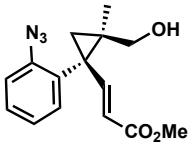
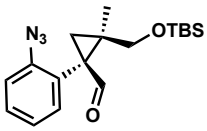
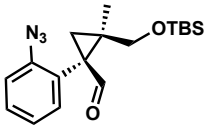
For the transformation of lactone **155** into a DVCPR precursor, the carboxyl functionality had to be transformed first. A suitable transformation into an alkyne or alkene was contemplated and therefore selective reduction to the hemi-acetal with DiBAl-H furnished lactol **159a** in 93% yield. With hemi-acetal **159a** in hand, alkyne synthesis was attempted (Table 2). Neither the Bestmann-Ohira reagent (dimethyl-1-diazo-2-oxopropylphosphonat, B-O reagent) (entry 1-4) nor TMS-diazomethane (entry 5) had any effect on the lactole. In addition the reaction with tetrabromomethane and triphenylphosphine (entry 6), as a first step in the Corey-Fuchs alkyne synthesis failed to give the desired dibrimo alkene.

Where as some cyclic hemi-acetals are in equilibrium to an open chain form with an aldehyde and a free alcohol like **159b**, it seems, this is not the case for lactol **159a**. The cyclopropane is presumably forcing the two groups into close proximity. Therefore, alkyne synthesis that relies on the aldehyde reactivity failed. The same is true for the Wittig reaction with Methyl (triphenylphosphoranylidene)acetate (Table 2, entry 7). The attempt to shift the equilibrium to aldehyde **159b** by trapping the free alcohol with several silyl protecting groups was not successful as well (entry 8 and 9). However, incorporation of the TBS-group occurs, but unfortunately only by forming the silylated lactol.

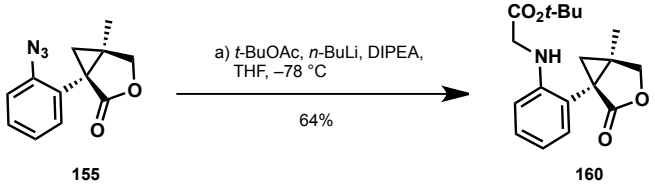
Table 2 Attempted transformation of lactol 159a to an alkyne.



155 159a 159b

entry	conditions	Attempted product
1	B-O reagent, K_2CO_3, MeOH, r.t.	 157b
2	B-O reagent, K_2CO_3, MeOH, 65 °C	**157b**
3	B-O reagent, K_2CO_3, MeOH, r.t., sonification	**157b**
4	B-O reagent, NaH, MeOH, r.t.	**157b**
5	$TMSCH_2N_2$, LDA, THF, −78 °C to r.t.	**157b**
6	CBr_4, PPh_3, DCM, 0 °C to r.t.	
7	$Ph_3PCH_2CO_2Me$, THF, r.t.	
8	TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C	
9	TBSCl, imidazole, DMF, r.t.	

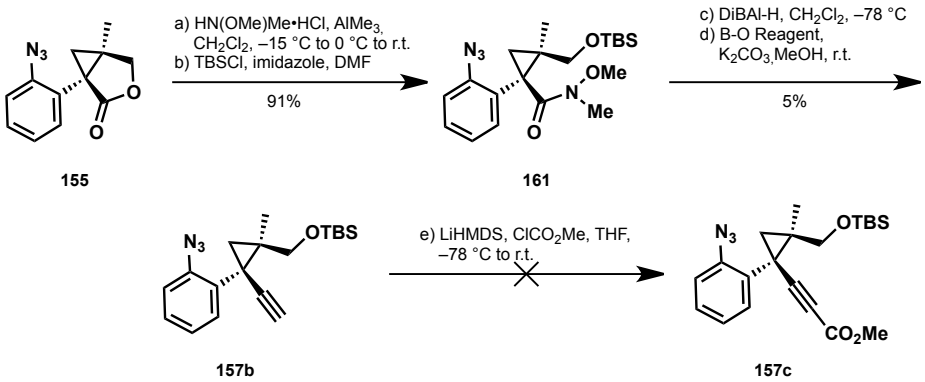
At the same time, nucleophilic addition to lactone **155** was studied (Scheme 30). Addition of deprotonated ethyl or *tert*-butyl acetate to **155** lead to the formation of α-amino compound **160** instead of the desired aldol product.



155 160

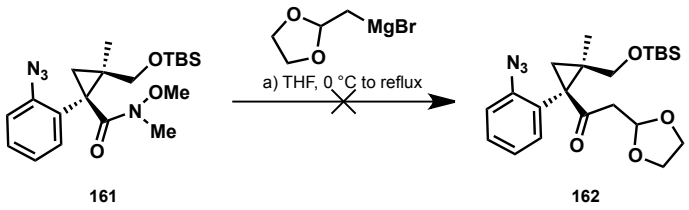
Scheme 30 Aldol reaction on lactone 155.

At this point it was decided, to transform lactone **155** into the corresponding Weinreb amide. After extensive experimentation, it was found that using trimethylaluminium and *N,O*-dimethylhydroxylamine hydrochloride in dichloromethane at 0 °C delivered the corresponding amide. An instant protection of the crude alcohol with TBS-chloride in DMF was essential because the free alcohol showed propensity to cyclize back on to the amide and to form again the starting material.



Scheme 31 Cyclopropyl alkyne synthesis.

In this manner the Weinreb amide **161** could be obtained in very good yield of 91% over two steps. The reduction of **161** with diisobutyl aluminium hydride however was a sluggish reaction, which never could be pushed to full conversion. Nevertheless the desired aldehyde was obtained. It is also noteworthy that the us of lithium aluminium hydride gave no results, presumably the azide was reduced instead of the lactone. The crude aldehyde was directly submitted to alkyne synthesis by using the B-O reagent and potassium carbonate in methanol. In this case the desired alkyne **157b** could be obtained however in very low yield of 5% for the two steps. The little quantities obtained by this route were used to attempt a derivatisation of the alkyne. But unfortunately the formation of propargylic ester **157c** by the use of LiHMDS followed by addition of chloro methylformiat failed.



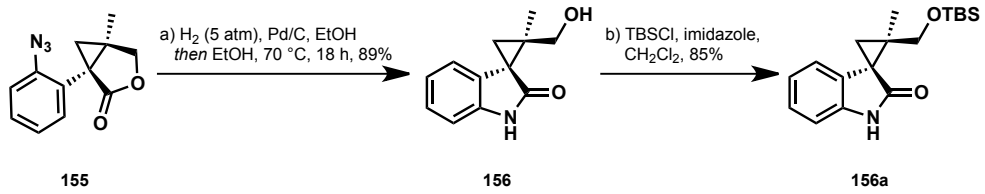
Scheme 32 Attempted addition to Weinreb amide.

In a different approach, Weinrebamide **161** was added to the dioxalan Grignard reagent in THF (Scheme 32). A series of reactions were performed, where the temperature was gradually increased, but no addition onto the Weinreb amide could be obseverd.

At that point, synthetic evidence was convincing that lactone **155** could not be directly transformed into a suitable precursor for the DVCPR as proposed in Figure 11. Neither lactone nor lactol could be derivatized in a satisfying manner. Therefore it was decided to focus on the oxindole approach.

8.3.2 Attempted transformation of *spiro*[cyclopropylindole] 156

In this approach the azido lactone was transformed to *spiro*[cyclopropyloxindole] **156 (**Scheme 33**)**. Reduction of the azide moiety with palladium on charcoal under hydrogen atmosphere was followed by a ring closure reaction with acetic acid at elevated temperature. The free alcohol **156** was subsequently protected with a TBS-group to give amide **156a**.

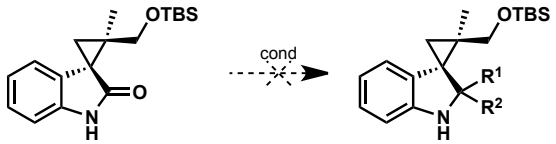


155 156 156a

Scheme 33 Synthesis of OTBS-*spiro*[cyclopropyloxindole].

It was assumed that the lack of the bulky benzyl-protecting group at the amide functionality compared to **142** (Scheme 26) might have a positive impact on the reactivity. With this in mind the nucleophilic addition on amide **156a** was attempted.

Table 3 Additions to OTBS-*spiro*[cyclopropyloxindole].



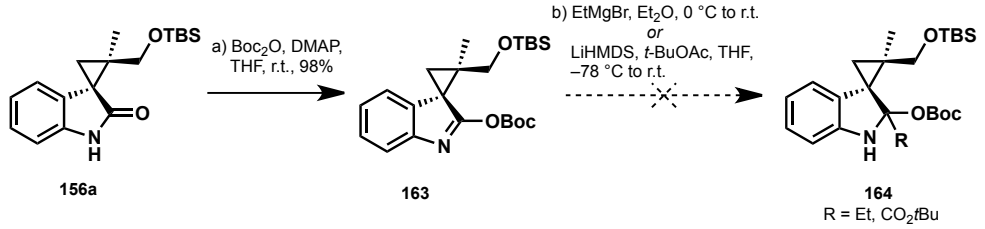
entry	conditions	R^1, R^2
1	1 and 2 equiv. MeLi, THF, −78 °C to r.t.	R^1 = Me, R^2 = OH
2	1 and 2 equiv. EtMgBr, 0 °C to r.t.	R^1 = Et, R^2 = OH
3	1 and 2 equiv. CHCOEt, *n*-BuLi, THF, -78 °C	R^1 = CCOEt, R^2 = OH
4	Zn, $BrCH_2CO_2Et$,	R^1 = CH_2CO_2Et, R^2 = OH
5	Tebbe reagent, CH_2Cl_2	R^1, R^2 = CH_2
6	Lawesson's Reagent, PhMe, refl. 3 h	R^1, R^2 = S
7	Belleau's Reagent, THF, refl. 16 h	R^1, R^2 = S

The addition of lithium or magnesium organyls did not give any product (Table 3, entry 1-3). Responsible for this experimental outcome is probable the free amide. Instead of adding to the

amide, the Grignard reagent must have deprotonated the nitrogen. The Reformatsky reaction (entry 4) was chosen, because this reagent usually adds to a carbonyl group without the danger of abstracting protons.[49] Furthermore, an attempted Tebbe olefination lead to complete decomposition of the starting material (entry 5). Synthesis attempts of the thioamide (entry 6 and 7) were unsuccessful as well. No reaction could be observerd with Lawesson's reagent at ambient temperature. Stepwise elevation of temperature did not show any reaction but at 110 °C for prolonged reaction time, the stargin material degraded. Similar results were obtained with Belleau's reagent.

The unprotected amide did not participate in any attempted reaction and therefore it was concluded that the electronic issue was seemed to be more important than the sterical hinderance.

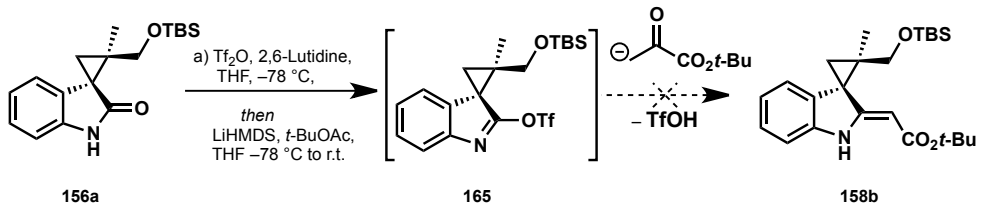
Hence a protection of the nitrogen with a Boc-group, i.e. transforming it into a carbamate was attempted. Treatment of **156a** with di *tert*-butyldicarbonate and dimethylaminopyridine in THF gave however the imidate **163** and not the desired carbamate (Scheme 34).



Scheme 34 Imidate formation and addition attempts.

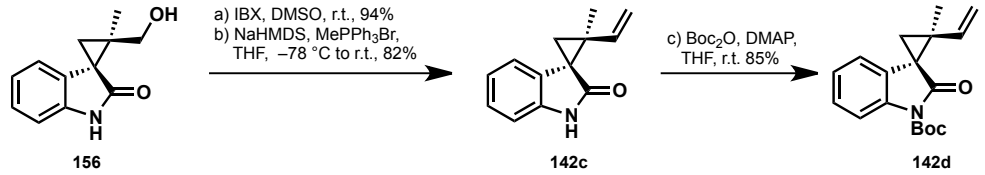
It is literature known that imidates are good electrophiles and therefore the unexpected **163** was used as substrate for attempts to add a nucleophile.[50] However neither ethyl magnesium bromide nor deprotonated *tert*-butyl acetate did react with the product in a satisfying manner.

As a result of the demonstrated propensity for *O*-substitution, an activation of the amide using triflic anhydride was envisioned. Following published procedure, a study was conducted to isolate the *O*-triflated product **165** but unfortunately in this case failed due the stability of the generated imidate.[48] The same reaction was also performed using Comin's reagent and di-*tert*butyl pyridine, however with similar success. As a next step, the reaction was attempted without isolating the apparently unstable intermediate triflate **165** (Scheme 35). Adding deprotonated *tert*-butyl acetat to triflytated **165** lead to a multitude of products.



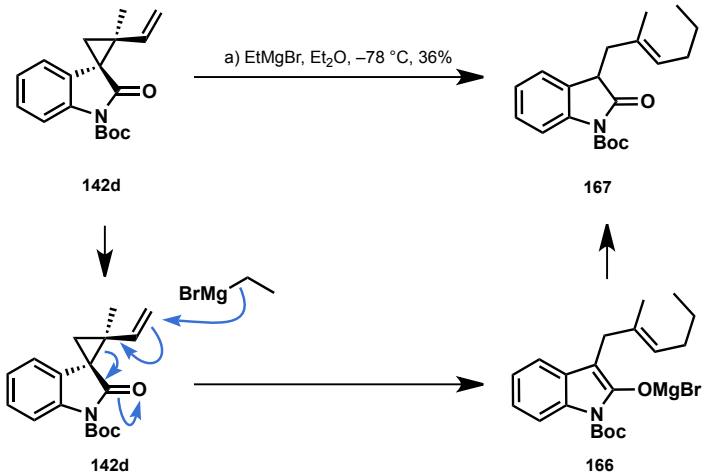
Scheme 35 Activation of OTBS-*spiro*[cyclopropyloxindole]with Tf_2O.

Based on the unsatisfying results it was decided to convert alcohol **156a** to the vinyl cyclopropane **142c** (Scheme 36). This was achieved by oxidation of the alcohol and performing a Wittig reaction on the resulting aldehde. Also the conversion of the amide to the corresponding carbamate **142d** with Boc-anhydride proceeded smoothly.



Scheme 36 Synthesis of vinyl-*spiro*[cyclopropyloxindole].

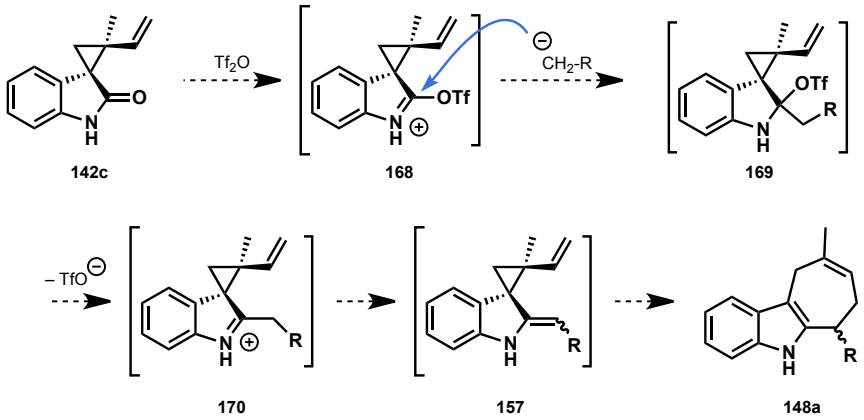
The idea of this approach was to take advantage of the higher electrophilicity of carbamate **142d** to facilitate nucleophilic addition to the carbonyl. Therefore an addition of ethyl magnesium bromide was attempted and indeed, reactivity was more pronounced than with the benzylated oxindole **142**. A single product was isolated, but instead 1,2-addition product, the 1,6 addidtion product **167** was obtained (Scheme 37). Once again, the vinyl substituent interfered with reactions.



Scheme 37 1,6 addition of EtMgBr.

It is also noteworthy that the use of harder nucleophiles such as methyl lithium or lithiated ethoxy acetylene did not give any positive products either.

As a last attempt the activation of unprotected vinyl *spiro*[cyclopropylindole] **142c** was contemplated because the triflic imidate of the OTBS-derivative **156a** appeared to be a promising substrate regarding the amide activation (Scheme 35). In theory a nucleophilic attack on the imidate **168** should initiate a subsequent elimination of the triflate (Scheme 38). The resulting imine **170** could further tautomerize to the corresponding enamine **171**, which then initiate the DVCPR to the desired cyclohepta[*b*]indole **148a**.

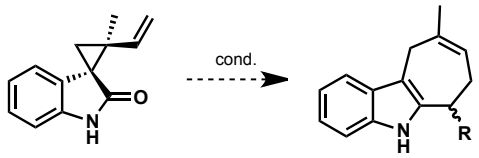


Scheme 38 Proposal for the transformation of triflated oxindole to cyclohepta[*b*]indole.

Therefore **142c** was treated with triflic anhydride at low temperature and subsequently a number of nucleophiles were added. The study commenced with the addition of methyl cerium reagent to compare the results with the first cyclohepta[*b*]indol synthesis (Table 4, entry 1).[51] However it seems, that the cerium reagent destroys the substrate. Next were tested lithium and magnesium reagents (entry 2 and 3) however with the same results.[47]

Activation with triflic anhydride at −78 °C was followed by subsequent addition of deprotonated *tert*-butyl acetate at the same temperature. However no product with incorporated *tert*-butyl group was isolated. Moreover full conversion could not be reached at −78 °C and warming up to 0 °C only resulted in degradation of the starting material.

Table 4 Activation of vinyl-*spiro*[cyclopropyloxindole] with triflic anhydride.

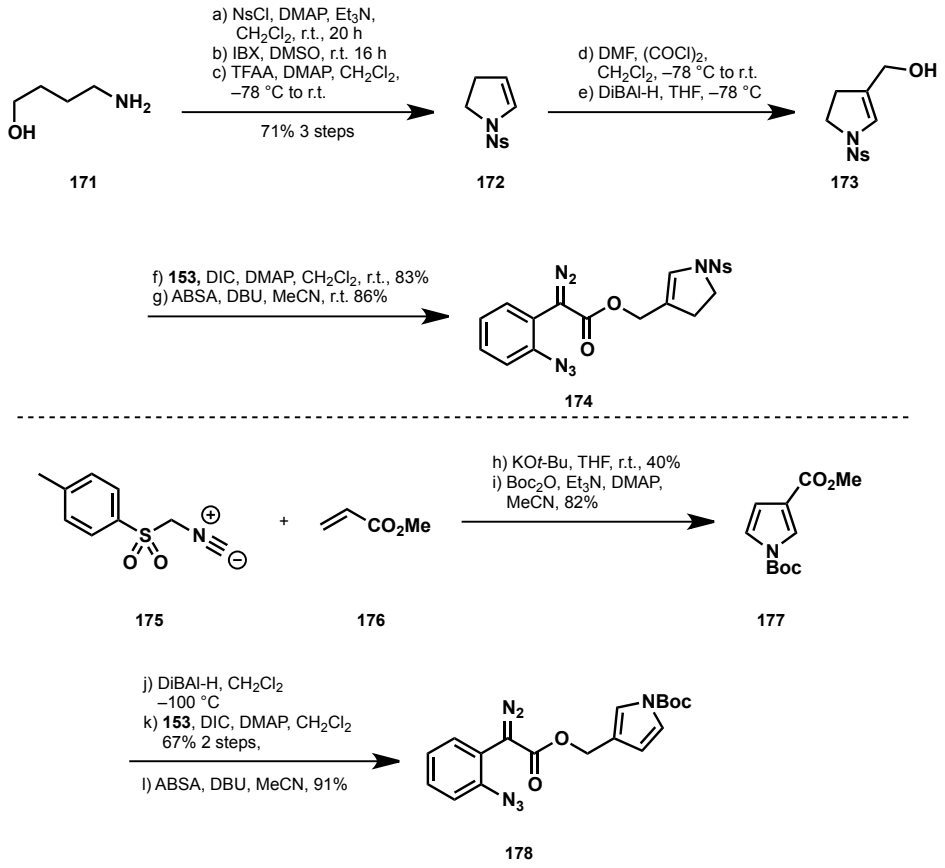


entry	conditions	R
1	Tf_2O, D*t*BP, MeLi, $CeCl_3$, THF, −78 °C to 0 to r.t	R = H
2	Tf_2O, D*t*BP, BuMgBr, THF, −78 °C to 0 to r.t	R = *n*-Pr
3	Tf_2O, D*t*BP, *n*-BuLi, THF, −78 °C to 0 to r.t	R = *n*-Pr
4	Tf_2O, AcO*t*-Bu, LiHMDS THF, activation and reaction at −78 °	R = CO_2*t*-Bu
5	Tf_2O, AcO*t*-Bu, LiHMDS THF, activation and reaction at 0 °C	R = CO_2*t*-Bu

8.3.3 Attempt to synthesize higher substituted cyclopropanes

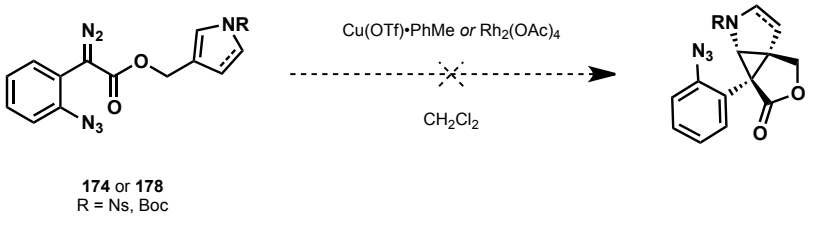
At the same time that the *spiro*[cyclopropyloxindole] was studied as an entry to the DVCPR, a potential synthesis of **1** was developed. It was intended to use the previously applied intramolecular cyclopropanation to synthesize a precursor for the DVCPR.

Two substrates were synthesized, one was a dihydropyrrole the other was a pyrrole substrate (Scheme 39). The dihydropyrrole compound was synthesized, starting from 4-amino butanol **171** which was protected with 4-nitrobenzylsulfonic acid chloride (Nosyl-Chloride or NsCl). The Ns-group had to be used because with the previously synthesized Boc- or Ts-dihydropyrroles were not stable. Obviously a very strong electron-withdrawing group was necessary to avoid undesired sidereactions. Upon oxidation of the alcohol with IBX, intramolecular aminal formation occurred which was treated with trifluoroacetic acid anhydride to afford protected enamine **172**. A following Vilsmeier-Haack reaction using dimethylformamide and oxalylchloride installed an aldehyde which was reduced using di*iso*butylaluminium hydride in CH_2Cl_2 at −78 °C to provide alcohol **173**. Esterification of **173** with acid **153** was accomplished by the use of di*iso*carbonyl diimide and dimethylamino pyridine was followed by a Regitz-diazo transfer reaction employing ABSA and DBU to yield **174**.



Scheme 39 Synthesis of advanced diazo compounds.

The second precursor based on a pyrrole derivative was synthesized *via* a [2+3] dipolar cycloaddition using tosylmethylisocyanat (**175**) and methylacrylate (**176**) in presence of potassium *tert*-butoxide.[52] The resulting pyrrole was protected with Boc anhydride to yield **177** followed by a subsequent reduction of the ester −100 °C with DiBAl-H. The resulting alcohol was transformed to an ester in a coupling reaction with acid **153** mediated by DIC and DMAP. Furthermore the ester was turned into diazo reagent **178** by deprotoantion and treatment with ABSA.



Scheme 40 Attempted intramolecular cyclopropanation.

With **174** and **178** in hand, the cyclopropanation was attempted. Copper (I) triflate and rhodium acetat were chosen as catalysts and dichloromethane as solvent. The cyclopropanation of dihydropyrrole derivative **174** using copper as catalyst proceeded cleanly to give two products.

However both turned out to be undesired. Similar results were obtained, when rhodium was used as a catalyst.

Based on these results, it is very probable, that the lone pair of the nitrogen lead to degradation of the product. The resulting cyclopropane would have been subtstituted with an amine on one side and an ester on the other, making it a potential push-pull system. Although the Nosyl-group acts strongly deactivating towards the electrons of the nitrogen, the cyclopropane is probably too strained to be stable

The reaction of the pyrrole-derivative **178** using either rhodium or copper catalysts lead to a multitude of products which could not be separated with flash chromatography. Although cyclopropanation of pyrroles are known (Scheme 21), the resulting cyclopropanes are usually prone to degradation or are only used *in situ*.

8.4 Summary and conclusion

The *spiro*[cyclopropylindole] approach towards DVCPR gave mixed results. At the beginning a proof of concept of the newly discovered reaction could be demonstrated quickly while further investigations were fruitless.

Moreover during the intermolecular cyclopropanation of diazo oxindole **141** with isoprene, the DVCPR to cyclohepta[*b*]indoles was discovered, a break through for the funcionalistion of the indole C-4 position.

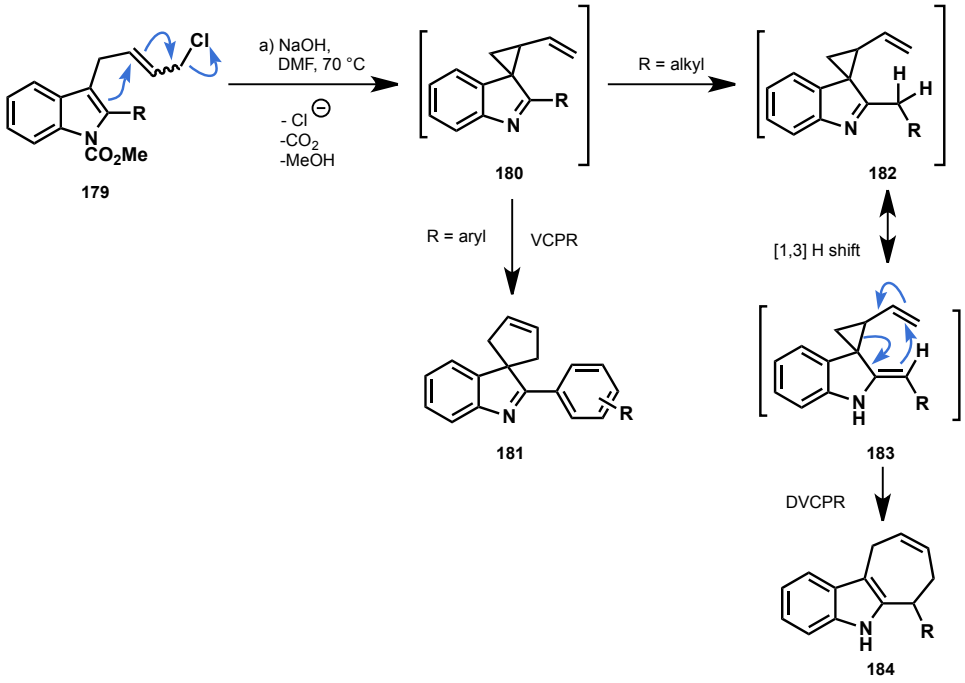
Additionally, after adding methyl lithium to *spiro*[cyclopropyloxindole] the DVCPR occurred *in situ* and, as predicted, cyclohepta[*b*]indol was obtained, albeit in low yield, due to problems with the nucleophilic addition.

Methyllithium however remained the only reagent that could be added onto the oxindole and therefore a broader scope was not possible *via* this route. A new, intramolecular cyclopropanation route was then implemented and as a first attempt, lactone **155** was studied to be transformed into an alkyne of the type of **157**. Later on, oxindole **156a** was synthesized. Again the transformation of the amide to an enamine failed and therefore the OTBS-group was transformed into a vinyl group. This time a Boc group was installed on the nitrogen, but as well as with the unprotected oxindole, no successful transformation of the amide was possible.

The synthesis of **1** would involve a DVCPR precursor with a highly substituted cyclopropane (see Figure 9). It was therefore attempted to synthesize cyclopropanes substituted with pyrrole derivatives (Scheme 40).

Based on disappointing results, it was decided, that although one cyclohepta[*b*]indole could be obtained, this approach would not allow further development of a robust methodology and therefore a different approach was chosen.

During the time the new approach proved to be successful, the group Sinha published their discovery of a DVCPR of *spiro*[cyclopropylindole]. Actually they wanted to synthesize *spiro*[cyclopenteneindoles], but instead they incidentally also synthesized a cyclohepta[*b*]indole.[53]



Scheme 41 DVCPR and cyclohepta[*b*]indole synthesis discovered by Sinha and co-workers.

They report, in the case that in molecule **179** R would be an aryl moiety, the treatment under harsh basic lead to *spiro*[cyclopenteneindoles] *via* a vinylcyclopropan rearrangement (VCPR) (Scheme 41). In contrast if the R-group contained a deprotonable carbon α to indol C-2 a [1,3] H shift would occur and a DVCPR would take place. It is noteworthy that the scope of the publication only focuses on linear alkyl chains and benzyl as R-groups. In principle this methodology could be applied to the synthesis of **1** but regarding the published small scope further investigations to more complex structures would be required.

As the next approach showed positive results, it was decided to not go back to study *spiro*[cyclopropylindoles] as precursors for the DVCPR.

9 Methdology development

The content of this chapter was published as an article together with Erik Stempel and Tanja Gaich.[54]

As the chemical challenges of the *spiro*[cyclopropylindole] approach barred the development of an entry to the cyclohept[*b*]indoles, it was decided, the next approach would entail a DVCPR using the indol double bond between C-2 and C-3 as vinyl-unit. This approach is depicted in the lower row of Figure 8. In cooperation with Tanja Gaich and Erik Stempel the decision was made to approach both DVCPR precursors, in order to see differences in reactivity and to be able to synthesize different substitution patterns. To determine the limits of the DVCPR in regards to the vinyl substituent, it was also decided, to focus on different electronically and sterically different substitutents. Therefore, the cyclopropane was substituted only at two positions, as to minimize interference in the transition state.

As shown in Figure 12, the two approaches would give two differentially substituted cyclohepta[*b*]indoles. If the cyclopropane was attached at indole C-3, **185**, the resulting cyclohepta[*b*]indole **187** would be stutituted α to C-2. Likewise, if the cyclopropane were attached to indole at C-2, **188**, the substitution would end up α to C-3, **190**. Additionally chirality would also transferred to the benzylic position, which otherwise can be difficult to obtain.

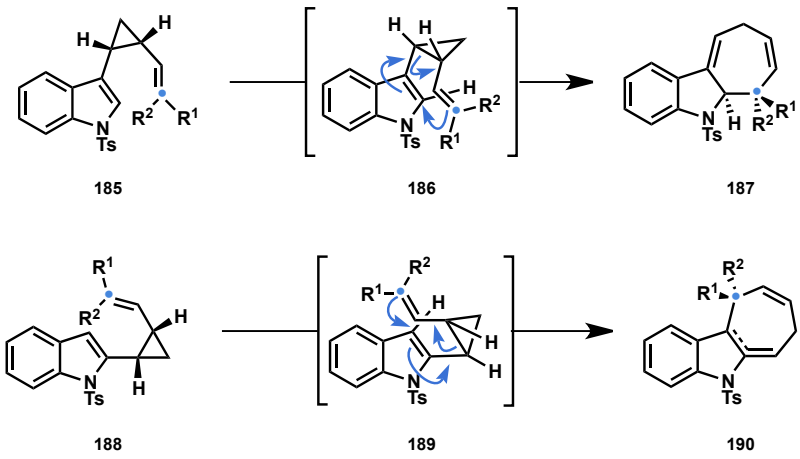
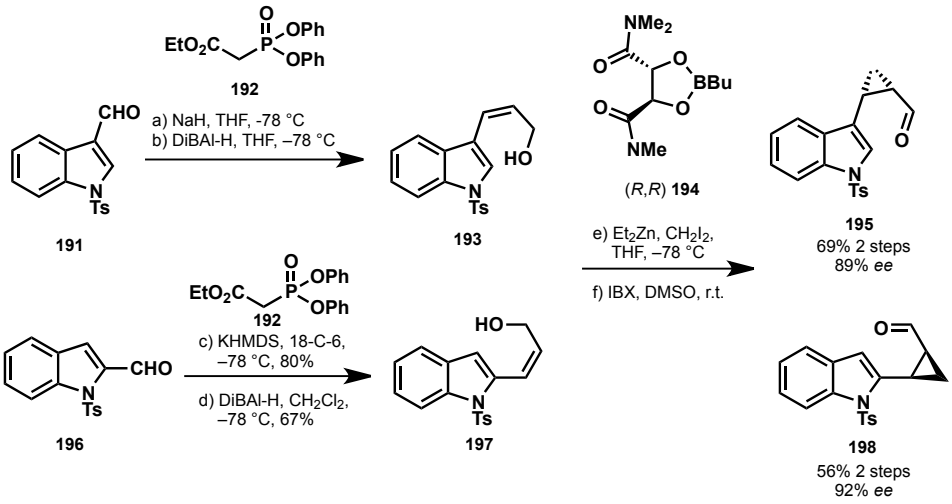


Figure 12 Chirality transfer for DVCPR.

To be able to obtain cyclohepta[*b*]indoles with defined stereochemistry, the cyclopropanation would have to be enantioselective and the olefination would have to give desired double-bond isomers selectively as well. To address these challenges the enantioselective variant of the Simmon-Smith reaction was chosen. Gratifyingly, the Wittig and Horner-Wadsworth-Emmons olefination generally proceeds with high selectivity and therefore, the stereochemical requirements could be met.

Starting either from tosylated indole C-2 **196** or C-3 **191** indole carbaldehyde, the allylic alcohols **193** and **197** were synthesized by reduction of the resulting esters after a *Z*-selective Horner-Wadsworth-Emmons olefination (Scheme 42). Subsequently an enantioselective Simmons-Smith cyclopropanation using dioxaborolanligand **194** furnished the corresponding cyclopropyl alcohosl, which were oxidized to **195** and **198** respectively. Having obtained the desired aldehydes, the DVCPR could be tested

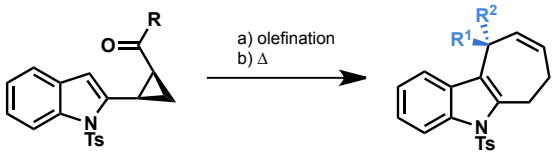


Scheme 42 Cyclopropylaldehyde synthesis.

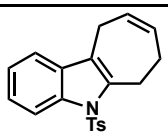
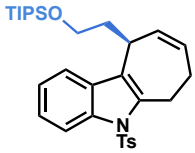
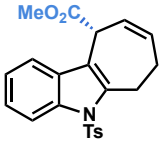
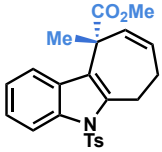
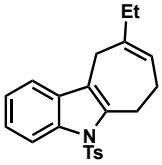
The olefination reaction proceeded as planned and depending on the olefination product cyclization occurred already at room temperature. Additionally cyclisation products retained the stereochemical information and no erosion of *ee* was detected during the reaction (see Table 5 and Table 6).

With both substrates series, C-2 indole-vinyl cyclopropane and C-3 indole-vinyl cyclopropane, dearomatisation occurs during the reaction. With the indole C-2 series, aromatization occurs spontaneously after the DVCPR and so only one stereocenter is retained after the reaction. Table 5 shows the obtained products for the C-2 series. For the substrates with less steric demand on the double bond, the DVCPR takes place at room temperature (entry 1, 2 an 5). For more advanced intermediates, raising the temperature was necessary to obtain full conversion. Nevertheless, even the synthesis of a quaternary carbon was possible (entry 4). To obtain the product of entry 5, first aldehyde **198** was transformed into ketone **198a** by adding ethylmagnesium bromide to **198** followed by oxidation with IBX. Then olefination gave the cyclohepta[*b*]indole.

Table 5 Cyclohepta[*b*]indole synthesis from Indole C-2 vinyl cyclopropane.

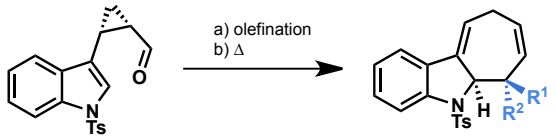


198 R= H
198a R=Et
89 -92% ee

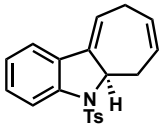
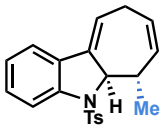
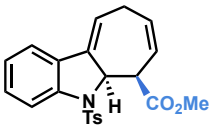
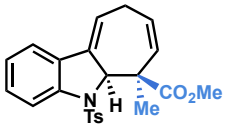
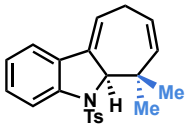
entry	product	*T* / °C	*ee* / %	Yield / %
1		r.t.	N.A.	71
2		r.t.	92	89
3		140	92	89
4		140	89	65
5		r.t.	N.A.	60

Similar results were achieved when the indole C-3 series was studied (Table 6). In this case however, aromatization did not take place deliberately and compounds with two stereocenters could be obtained. Again, the necessary temperature for the rearrangement depended on steric bulk on the vinyl unit. Here as well, alkyl and carboxyl-substituents could be introduced in good yield and quarternary carbons could be built up.

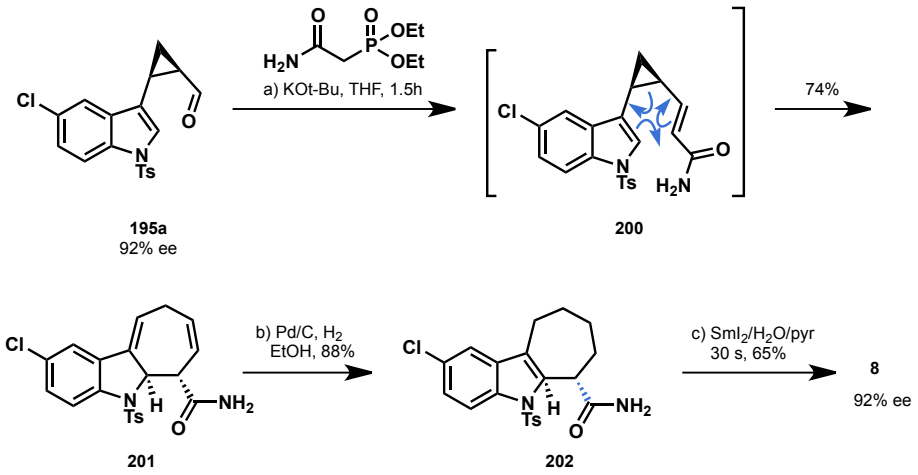
Table 6 Cyclohepta[*b*]indole synthesis from Indole C-3 vinyl cyclopropane.



89% *ee*

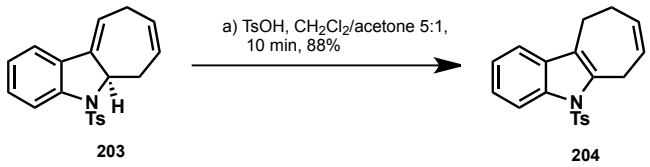
entry	product	*T* / °C	*ee* / %	Yield / %
1		r.t.	89	54
2		80	89	70
3		80	89	76
4		80	89	69
5		80	89	73

To demonstrate the robustness of the methodology it was decided to synthesize the SIRT IV inhibitor (**8**) enantioselectively (Scheme 43). Although the compound contains only one stereocenter it represents a special challenge, as it is prone to racemization. To avoid late stage functional group interconversion at the carboxylic group, the carboxamide group was directly introduced from the beginning. Aldehyde **195a** was synthesized as was **195**, but the cyclopropanation was undertaken with (*S,S*) **194** and so the desired enantiomer could be obtained. Olefination and concomitant rearrangement gave **201**. Hydrogenation of the double bond during which also rearomatisation took place gave cyclohepta[*b*]indole **202**. Removal of the tosyl-group using samarium diiodide then furnished **8** in 42% from the aldehyde without loss of stereoinformation.



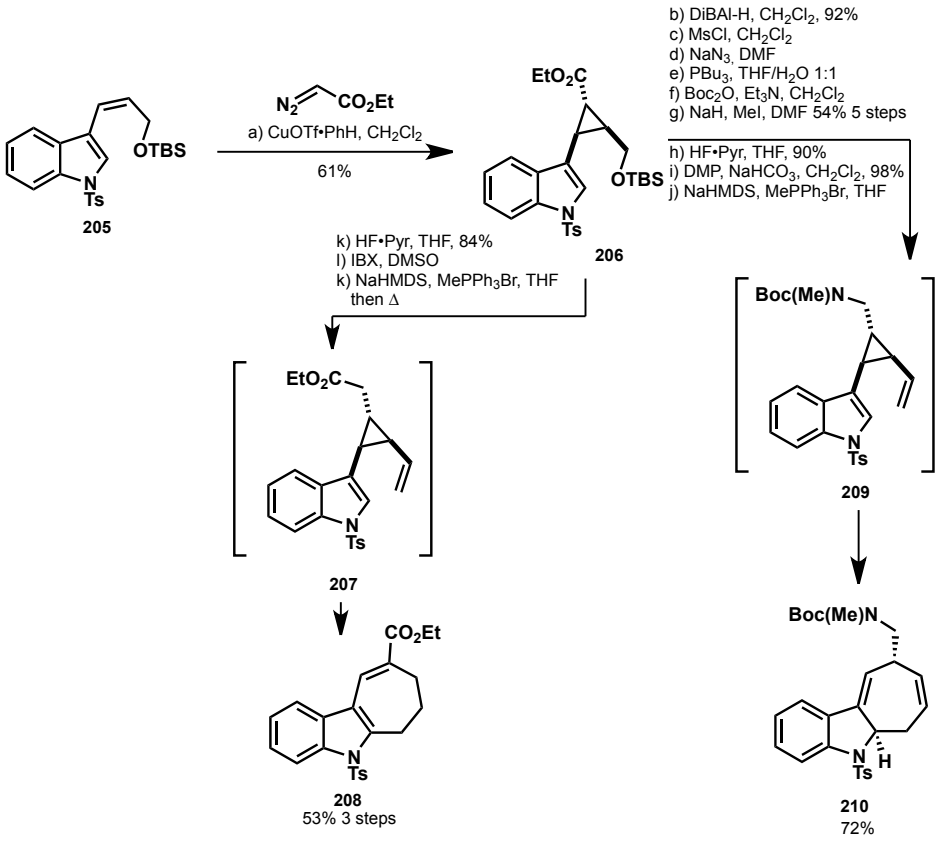
Scheme 43 Enantioselectie Synthesis of *S*-SIRT IV inhibitor (8).

As mentioned, products from the C-3 series do not rearomatise spontaneously. As an example, shown in Scheme 44, **203** was treated with acid and the aromatized product **204** was obtained



Scheme 44 Rearomatisation after DVCPR of indol C-3 vinylcyclopropane.

In a series of reactions Erik Stempel then showed that this methodology could also be extended to the use of transition metal catalysis and higher substituted cycloporpanes (Scheme 45). The cyclopropanation of alkene **205** under copper catalysis and using ethyl diazoacetat furnished cyclopropane **206**. The alcohol was then deprotected, oxidized and after a Wittig reaction cyclohepta[*b*]indole **208** was obtained, where the two double bonds were shifted into conjugation during heating for the cyclisation. Alternatively, conversion of the ester to a Boc-protected amine with subsequent transformation of the alcohol lead to cyclohepta[*b*]indole **210** which could be an intermediate in the synthes is of methuenine (**3)**. The tolerance towards heteroatoms in the system during the DVCPR could be shown this way.



Scheme 45 Extension of scope by Erik Stempel.

In conclusion a robust methodology was developed that uses the a vinyl-cyclopropyl substituent at either C-2 or C-3 of the indole core and allows for the enantioselective cyclohepta[*b*]indoles. Electron rich and electron-poor double bonds are accepted as well as sterically demanding substrates. Additionally the (–)-SIRT IV inhibitor 4 (**8**) was synthesized enantioselectively and an entry to a total synthesis of methuenine (**3**) was demonstrated.

10 Indol C-2 vinylcyclopropane as precursor for the DVCPR

The research discussed in the previous chapter demonstrated that the DVCPR proceeded while dearomatising the indole core. Based on these results, a strategy for the synthesis of **1** was developed. The synthetic plan was designed so that all all carbons present in **1** except the hemiacetal would be incorporated in the molecule before the DVCPR. As such, the cyclopropane would have to bear more than the two substituents. The Simmon-Smith reaction however, which was used with good results in the methodology development, does not furnish 1,2,3 tri- or tetrasubstituted cyclopropanes. Therefore, a transition metal-catalyzed cyclopropanation of a diazo precursor was chosen. For the stabilization of a diazo moiety, an electron-withdrawing group is generally necessary as a substituent. The carboxyl group in **1** could be used for that purpose. Subsequently, this lead to a cyclopropane connected to indole C-2 as a starting point of the synthesis.

10.1 Intramolecular approach

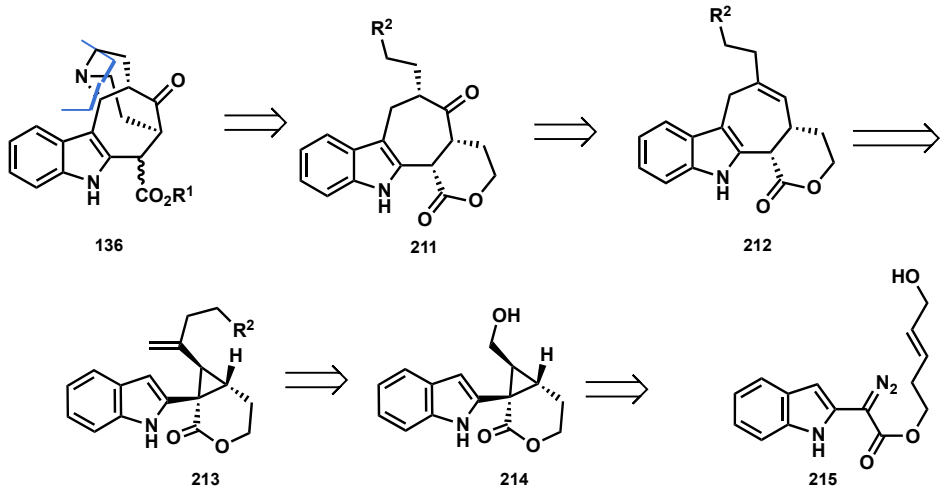


Figure 13 Indole C-2 vinylcyclopropane: intramolecular approach.

The retrosynthetic disconnection of the amine in **136** leads to tetracyclic compound **211** (Figure 13). The two atom handle that spans both the seven-membered and the pyrrole would originate from a hydrolysis of the lactone present in **211**. The ketone would result from a hydroboration-oxidation sequence of the trisubstituted double bond in **212**. The hydroboration would be directed by the lactone, which should block the lower face of the seven-membered ring during the attack of the reagent. Cyclohepta[*b*]indole **212** would come from a DVCPR of vinyl-cyclopropyl indol **213** and subsequent aromatization. To obtain **213** the corresponding cyclopropyl alcohol **214** would have to be derivatised. The cyclopropane moiety would be installed in an intramolecular cyclopropanation reaction of the *E*-double bond present in **215**

and the diazo-group α to indole C-2. The double bond configuration would ensure the correct configuration of the cyclopropane where the indole and the vinyl substituent end up on the same face (Figure 14). Additionally, an intramolecular reaction would lead to only one possible diastereomer, rendering selectivity issues non existent.

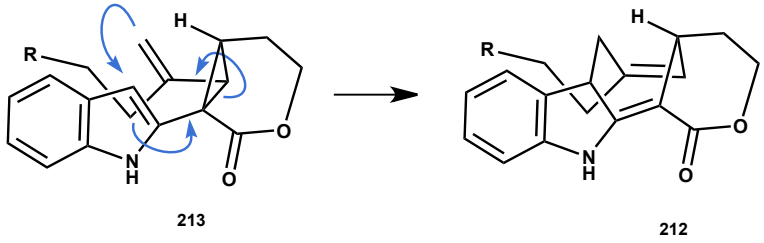


Figure 14 Transition state for the indol C-2 vinylcyclopropane: intramolecular approach.

The transition state depicted in Figure 14 shows the correct configuration of the lactone after the rearrangement and illustrates how the lower face of the seven-membered ring would be shielded during the hydroboration reaction.

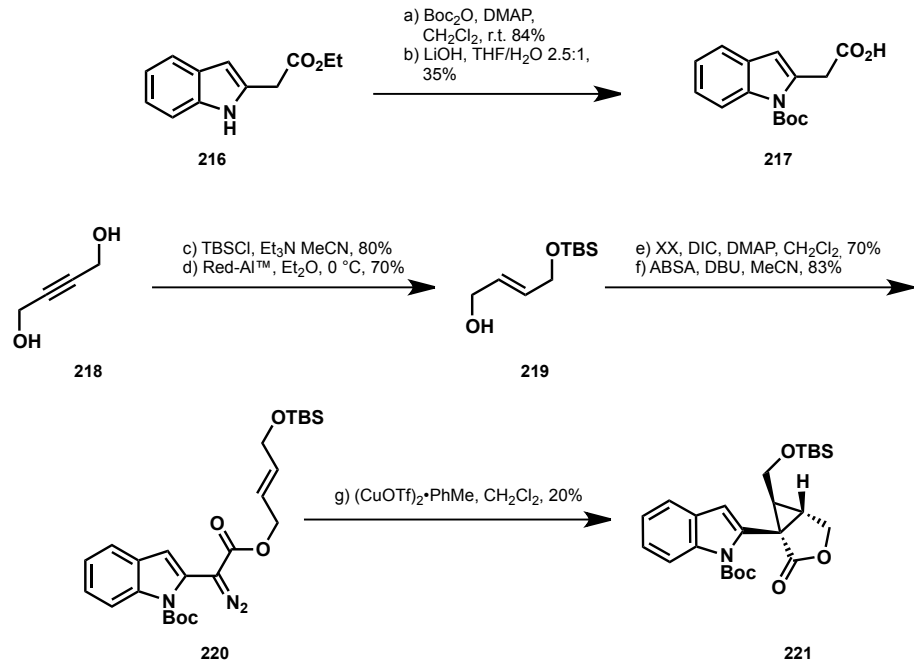
The transition metal-catalyzed intramolecular cyclopropanation is well documented in literature. Wood and coworkers used it in their approach to **1** (Scheme 15) and enantioselective versions have been published as well.[55] Following the cyclopropanation, reactions would involve transforming an alcohol into a methylene group, similar to what has been done during synthesis of **198a**.

Hydroboration of trisubstituted double bonds can be challenging at times but cyclic double bonds are possible to be hydroborated.[56,57] If the steric demand of the substrate does not provide enough directing force, hydroboration using chiral reagents would be an alternative.[58]

The pyrrole present in **1** would be synthesized through a two-step procedure: first R^2 would be converted into a primary amine. Then a benzylic oxidation using reagents such as DDQ, CAN or selenium dioxide as shown in literature[59] with subsequent ring closure would be attempted. It would even be possible to combine both the synthesis of the pyrrole unit with the opening of the lactone and the incorporation of the handle spanning the seven-memberd ring.

Although intramolecular cyclopropanations to give oxabicyclo[4.1.0]heptanons are known,[60] they are more difficult to obtain than their smaller homologues oxabicyclo[3.1.0]hexanones as the formation of five-membered rings is kinetically favored. Additionally, the desired cyclopropane would be tetrasubstituted with a quaternary center as one of the ring atoms. Therefore cyclopropane synthesis would be one of the crucial transformations of this approach. As a proof of concept, a precursor, which would give the 5-membered lactone was synthesized (Scheme 46).

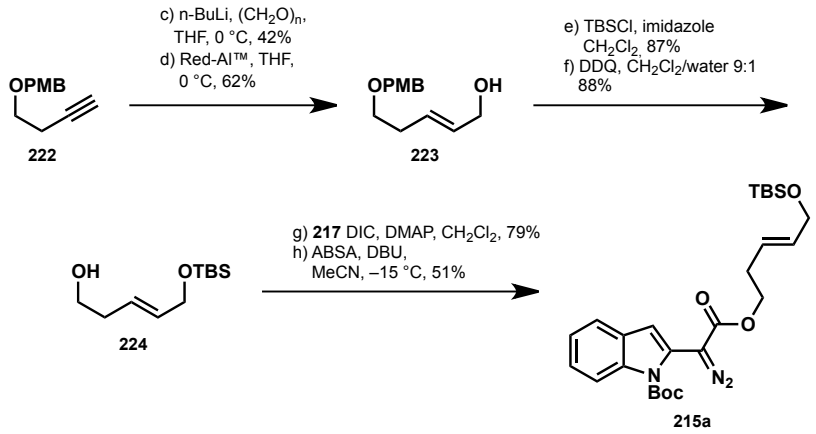
The synthesis of the test system commenced from the literature known compound indole-2-aceticacid ester **216**, which was first protected with a Boc-group and then hydrolyzed to reveal the free acid **217** (Scheme 46). Unfortunately, the hydrolysis did not give satisfying yield however protected ester **216** could be obtained in large quantities. The mono protection of 1,4-but-2-yndiol with a TBS group was followed by the transformation of the alkyne to a double bond using Red-Al™ to give **219**. Esterification of acid **217** and alcohol **219** gave the corresponding ester, which was transformed into diazo-compound **220** using ABSA and DBU in a Regitz-diazo transfer reaction. The cyclopropanation was then tested with copper (I) triflate and gratifyingly gave the desired cyclopropane **221** albeit in low yield of 20%.



Scheme 46 Test system to give 5-membered lactone.

As the unoptimized synthesis of oxabicyclo[3.1.0]hexanones **221** was successful, the attention was turned towards the synthesis of the larger homologue.

Literature known PMB-protected 3-butyn-1-ol (**222**)[61] was transformed by deprotonation with *n*-butyl lithium in THF followed by the addition of *para*-formaldehyde (Scheme 47). Treatment with Red-Al™ reduced the alkyne to the desired *E*-alkene **223** and protection of the free alcohol with a TBS-group followed. Removal of the PMB group with DDQ furnished alcohol **224**, which was then coupled to acid **217** and after a Regitz-diazo transfer reaction **215a** was obtained in a series of 6 steps from literature known PMB-protected 3-butyn-1-ol in generally good yields.



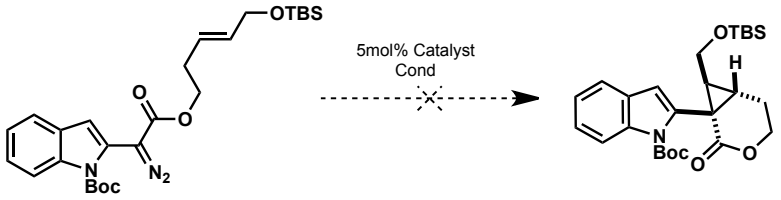
Scheme 47 Diazo 215a synthesis.

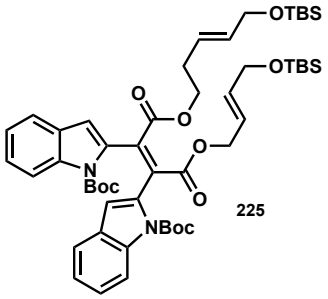
The synthesis of diazo **215a** permitted to study the cyclopropanation reaction to obtain **214** (see Table 7**)**. First copper triflate was tested as catalyst for the cyclopropanation but no reaction occurred at room temperature or at higher temperatures. (entry 1-5). Heating in a sealed tube up to 160 °C lead to degradation of the starting material occurred. The same results were obtained when rhodium acetate was used as catalyst (entry 6).

Switching to Rh_2esp_2, (esp = α,α,α',α' -tetramethyl-1,3-benzenedipropanoate) a more reactive rhodium catalys[62,63], some reactivity was shown (entry 7 and 8). At room temperature some product was isolated, however it turned out no to be the desired compound **214**, instead a dimersation to **225** had occurred. Increasing the temperature up to 40 °C only lead to degradation of the starting material.

Wood mentions in the publication on the studies towards **1**, that only a special copper catalyst, $Cu(TBS)_2$ allowed the synthesis of the desired cyclopropane **92**.[31] Employing this catalyst however did not furnish any product. It failed to react with the diazo-compound as starting material was isolated quantitatively (entry 9).

Table 7 Attempts to cyclopropanate 215a.

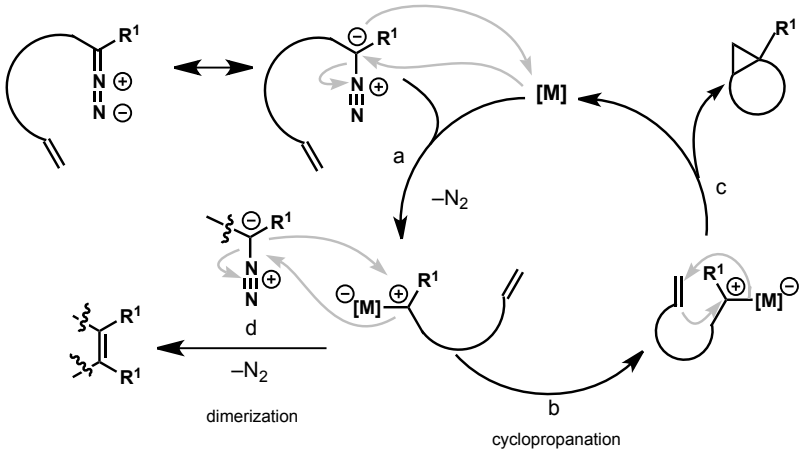


Entry	Catalyst	Solvent	Temp/ °C	Comment
1	$Cu(OTf)_2$•PhMe	CH_2Cl_2	r.t.	No reaction
2	$Cu(OTf)_2$•PhMe	CH_2Cl_2	40	No reaction
3	$Cu(OTf)_2$•PhMe	DCE	90	No reaction
4	$Cu(OTf)_2$•PhMe	PhMe	120	No Reaction
5	$Cu(OTf)_2$•PhMe	PHMe	160	(sealed tube) degradation
6	$Rh_2(OAc)_4$	CH_2Cl_2	r.t.	No reaction
7	Rh_2esp_2	CH_2Cl_2	r.t.	 225 Dimersation, 12%
8	Rh_2esp_2	CH_2Cl_2	40 °C	degradation
9	$Cu(TBS)_2$	CH_2Cl_2	40 °C	No reaction

In summary, it seems that diazo **215a** is a challenging substrate. Neither copper triflate, rhodium acetate nor copper TBS, catalyzed the formation of product and the diazo could be reisolated. The more reactive rhodium-esp_2 catalyzed only the formation of a dimerization product.

This product can be obtained if the alkene is too hindered or cyclisation is electronically unflavored during the metal-catalyzed cyclopropanation.[55] In the catalytic cycle of the transition metal-catalyzed cyclopropanation, shown in Scheme 48, a metal-carbene is formed by the nucleophilic attack of the diazo carbon to the metal center (step a). Backbonding leads to

expulsion of nitrogen and the carbene is formed. However, backbonding is usually weak and therefore leaves the carbon atom positively charged and the carbene overall electrophilic. A chelotropic reaction with the double bond occurs (step b) and a cyclopropane is formed and expulsed from the catalytic cycle (step c). However, if the double bond does not react, a possible side reaction is the addition of an additional diazo compound to the metal carbene (step d). A subsequent loss of nitrogen leads to a diazo dimer.



Scheme 48 Catalytic cycle for the transition metal catalyzed cyclopropanation.

It seems that the energy barrier for the intramolecular cyclopropanation was too high at room temperature. The attempt to overcome the energy barrier by warming the reaction to 40 °C was not met with any success as degradation occurred. This result shows the high hindrance involved in the formation of the highly substituted cyclopropane **214**.

The inability to form **214** from diazo **215a** was a setback. Although the test system could be successfully transformed, an additional carbon atom changed the system drastically and inhibited cyclopropanation. Based on these results it was decided, to focus on an intermolecular cyclopropanation instead of the intramolecular approach.

10.2 Intermolecular approach

The change from an intramolecular to an intermolecular approach demanded an adaption of the retrosynthesis. The new direction would permit a concise synthesis, as two advanced intermediates could be joined and therefore reducing the number of subsequent steps.

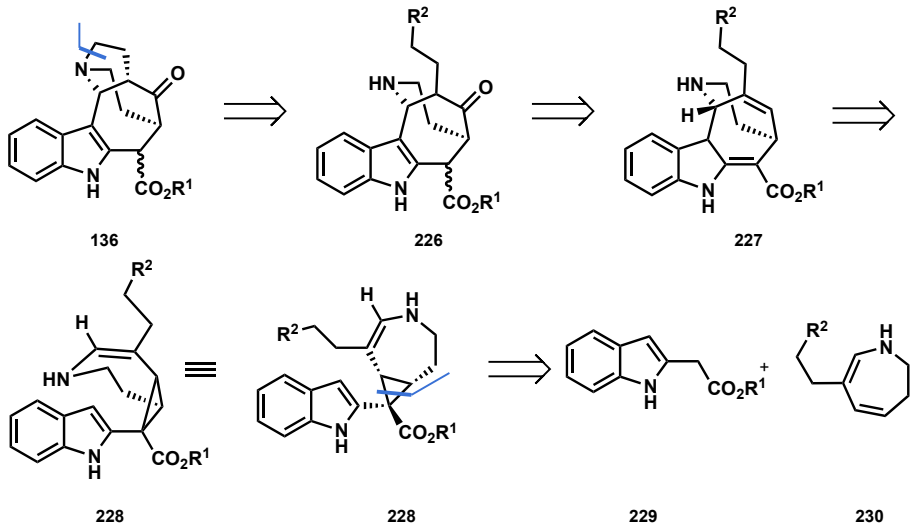


Figure 15 Indol C-2 vinylcyclopropane: intermolecular approach.

Disconnecting the pyrrole in **136** reveals tetracyclic ketone **226**. This could arise from **227**, which would be the product of a DVCPR (Figure 15). The precursor for this DVCPR would then be **228**, consisting of a cyclopropane fused to an azepan moiety and indole-2-acetic acid. Cleaving the cyclopropane reveals that the cyclopropane could be build up from indole-C-2 acetic acid ester **229** and an azepan derivative such as **230**. Provided, that the cyclopropane could be obtained in the right diastereomer, the rearrangenment would proceed through the transition state shown in Figure 16. This approach would install all carbons and would not require any additional C-C bond formation after the DVCPR.

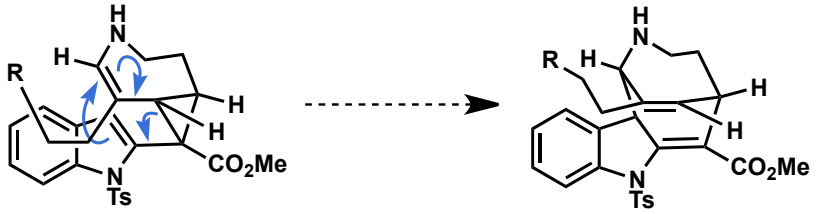


Figure 16 Transition state for indol C-2 vinylcyclopropane: intermolecular approach.

10.2.1 Transition metal catalysis

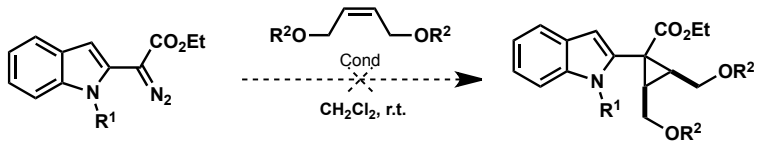
The first approach to obtain a compound similar to **228** was again to use transition-metal catalysis. But the previous chapter demonstrated difficulties involved in the cyclopropanation of indole-2-acetic acid derived diazo compounds. Therefore, the cylopropanation was first tested on a less demanding substrate. The double bond in an azepan is (*Z*)-configured and so silyl protected (*Z*)-1,4 but-2-endiol was chosen as substrate. For the diazo compounds two different protecting groups on the indole nitrogen were chosen and either the ethyl or the methyl ester was studied. To obtain these diazo compounds, literature known indole-2-acetic acid ethyl ester was first protected with tosyl chloride or benzyl chloride and then converted to the corresponding diazo compounds **229a** and **229b** similar to the process shown in Scheme 46.

The results of the cyclopropanation studies with copper, silver and rhodium as catalysts are shown in Table 8. The most important outcome was the incapability to cyclopropanate a (*Z*)-olefin with **229a** or **229b** under the studied conditions.

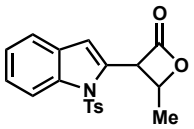
Instead, the cyclopropanation attempt of **229a** gave the interesting CH-insertion product **231** (entries 1-3). This product was formed independently from the catalyst that was chosen and was obtained in an inseparable mixture of two diastereomeres. For **231** be formed, the carbene had to react intramolecularly with the CH_2-group of the ethyl moiety to yield. It was quite unexpected to obtain **231** when silver hexafluoro antimonat was employed since this catalyst was specifically chosen to avoid this side reaction. Davies showed that this catalyst had a very high propensity to cylcopropanate as opposed to mediate C-H insertion.[64] Unfortunately the choice of metal did not influence the outcome of the reaction and neither did the replacement of the TBS-protecting group by the TIPS-groups did not change the outcome of this reaction (entry 5). When the temperature was lowered no reaction occurred at all (entry 4).

The change of the protecting group to Boc did not improve results. Only degradation of starting material could be identified during the reactions (entry 5, 6, 7). Reactions with rhodium acetate or copper triflate lead to degradation already at room temperature. Employing silver-SbF_6 as catalyst had no effect at ambient temperature and warming the reaction to 40 °C quickly destroyed the starting material.

Table 8 Studying the metal-catalyzed intermolecular cylcopropanation of 229a and 229b.



229a R^1 = Ts
229b R^1 = Boc

Entry	Catalyst	R^1	R^2	Result
1	CuOTf•$PhH_{0.5}$	Ts	TIPS	C-H insertion  231 2 diastereomers
2	$AgSbF_6$ (40 °C)	Ts	TIPS	C-H insertion
3	CuOTf•$PhH_{0.5}$	Ts	TBS	C-H insertion
4	CuOTf•$PhH_{0.5}$ (−78 °C to 0 °C)	Ts	TIPS	Isolation of starting material
5	CuOTf•$PhH_{0.5}$	Boc	TBS	degradation
6	Rh_2OAc_4	Boc	TBS	degradation
7	$AgSbF_6$ (40 °C)	Boc	TBS	degradation

Altogether, this study revealed that no intermolecular reaction took place during the attempted cyclopropanations. Therefore, the cyclopropanation to give a compound similar to **228** had to be conducted differently.

10.2.2 Corey-Chaikovsky type cyclopropanation

Literature shows the expansion of the Corey-Chaikovsky reaction and the synthesis of complex cyclopropanes using sulfur-ylides.[65–69] Based on these literature precedents, a cyclopropanation involving the addition of an appropriate sulfur-ylide (**233** in Figure 17) to Michael-acceptor **232** was proposed. The first step would be the formation of enolate **234** and upon re-establishing the carbonyl a C-C bond formation would take place, ejecting diphenyl sulfide and forming the cyclopropane. Although literature references on the addition to triple substituted double bonds are rare[67] and the diastereoselectivity of the reaction remained speculative, an initiative was launched to study the applicability of this reaction for the synthesis of **1.**

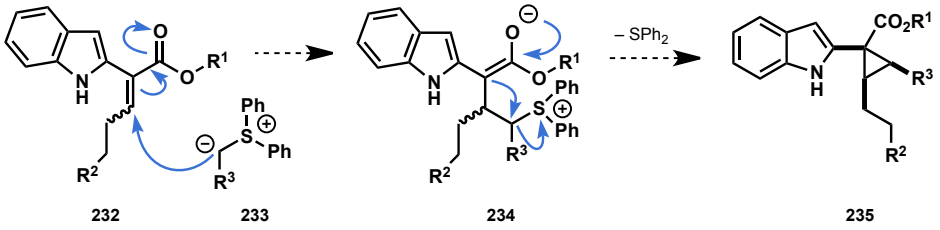
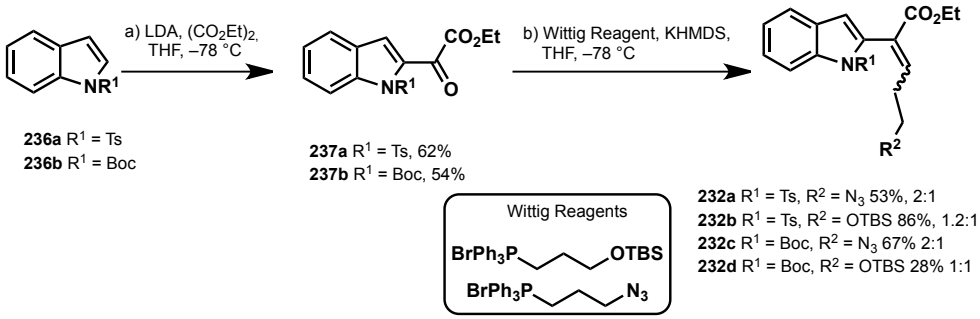


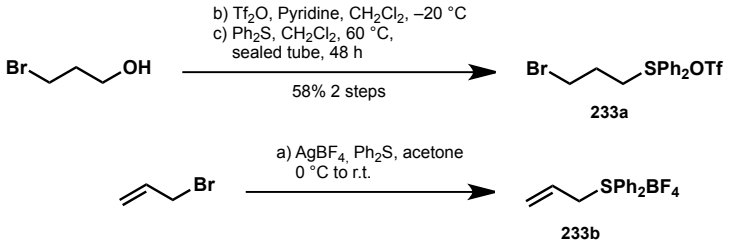
Figure 17 Proposed Corey-Chaikovsky-type cyclopropanation.

The synthesis of the Michael-acceptor started from either tosyl- or Boc-protected indole **236a** and **236b** (Scheme 49). Deprotonation with LDA and subsequent addition of diethyl oxalate furnished keto esters **237a** and **237b**. Those were substrates in the following Wittig-reactions, synthesizing the alkenes **232a** to **232d**. For each olefination both double bonds were obtained in selectivity ranging from 1:1 to 2:1. They were partially separable and used for testing individually. It was planned to use the functional groups introduced by this manner for the synthesis of the azepan-structure.



Scheme 49 Michael-acceptor synthesis.

The sulfur reagents were synthesized from either 3-bromo propanol or allybromide in substitution reactions with diphenyl sulfide. Originally, it was intended to synthesize the dimethylsulfide analogs. However no product could be obtained. Reagent **233a** was synthesized to give rapid access to the proposed azepan moiety by a simple substitution reaction. However, the resulting ylide would also be very reactive, as no stabilizing substituent would be present and therefore sidereaction were more likely to happen. Consequently the allyl-reagent **233b** was also synthesized. The adjacent π electrons would stabilize the ylid during the reaction and the desired reaction outcome was more probable.

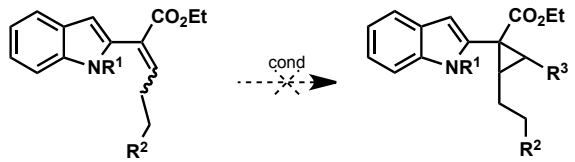


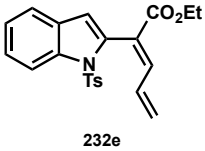
Scheme 50 Synthesis of ylide precursors.

To study the cyclopropanation reaction, the precursors **233a** and **233b** would be deprotonated with a strong base in THF at −78 °C. After 30 minutes and a color change to intense orange, the ylides would be formed and the substrate would be added. The reaction conditions and the results of this study are shown in Table 9. Sulfur reagent **233a** was used once with **232b** as substrate and although the conversion was incomplete, the elimination of the silyloxy group could be identified as the sole reaction (entry 1). The ylide reacted as a base rather then a nucleophile. Switching to the allyl-sulfide reagent and **233a** showed elimination as well, using *n*-butyl lithium or *tert*-butyl lithium (entries 2 and 3). The activation of the substrate with trifluoroboron-etherate and molecular sieves failed to enhance reactivity (entry 4). On the contrary, it led to quantitative reisolation of starting material. When molecular sieves were used, the elimination persisted (entry 5). Addition of trifluoroboron-etherate again resulted in a loss of reactivity (entry 6). It is probable that the Lewis-acid reacts with the ylide resulting in its inactivation. Switching to **233b** as substrate, it was expected to diminish elimination and increase cyclopropanation. At temperatures below 0 °C, no conversion at all was observed (entry 7-9) At 0 °C however, elimination occurred again (entry 10).

Exchanging the tosyl group with a Boc group did not yield better results. At −78 °C, no reaction occurred with the azide incorporated substrate, however warming to −50 °C caused elimination. Replacing the azide moiety with an OTBS revealed an unstable substrate. Already at −78 °C degradation occurred.

Table 9 Corey-Chaikovsky-type cyclopropanation.



Entry	R^1	R^2	R^3	Temp	Base	Additives	Result
1	Ts	OTBS	CH_2CH_2Br	−78 °C	NAHMDS		 232e Partial elimination of OTBS
2	Ts	N_3	$CHCH_2$	−78 °C	*n*-BuLi		Elimination
3	Ts	N_3	$CHCH_2$	−78 °C to r.t.	*t*-BuLi		Elimination
4	Ts	N_3	$CHCH_2$	−78 °C	*n*-BuLi	$BF_3•OEt_2$, MS 3Å	No reaction
5	Ts	N_3	$CHCH_2$	−78 °C	*n*-BuLi	MS 3Å	Elimination
6	Ts	N_3	$CHCH_2$	−78 °C	*n*-BuLi	$BF_3•OEt_2$	No reaction
7	Ts	OTBS	$CHCH_2$	−78 °C	*n*-BuLi		No reaction
8	Ts	OTBS	$CHCH_2$	−50 °C	*n*-BuLi		No reaction
9	Ts	OTBS	$CHCH_2$	−30 °C	*n*-BuLi		No reaction
10	Ts	OTBS	$CHCH_2$	0 °C	*n*-BuLi		elimination
11	Boc	N_3	$CHCH_2$	−78 °C	*n*-BuLi		No reaction
12	Boc	N_3	$CHCH_2$	−50 °C	*n*-BuLi		degradation
11	Boc	OTBS	$CHCH_2$	−78 °C	*n*-BuLi		degradation

Again no indole-2-cyclopropane could be obtained. Either the ylide reagents were more basic than nucleophilic or the Michael acceptors were not electrophilic enough. The Boc-group had a shielding effect on the azide group. However, **232c** did degrade at lower temperature whereas its tosyl-counterpart was stable. Overall, it seems that the steric hindrance of the substrate was too large to allow a Michael-addition.

10.3 Summary and conclusion

Three approaches to the synthesis of indole-2-cyclopropyl –derivatives were studied. An intramolecular approach with a transition metal-catalyzed cyclopropanation was attempted using copper- and rhodium-based catalysts. While a test system involving a

oxabicyclo[3.1.0]hexanon could successfully be obtained, the larger homologue with a six membered lactame remained elusive.

The intramolecular approach necessitated the cyclopropanation of an (*E*)-double bond whereas the retrosynthesis for the intermolecular approach unveiled that a cyclic double bond had to be cyclopropanated. As a test system, the cyclopropanation of double protected (*E*)-1,4-but-2-endiol was attempted, but ultimately failed.

A different approach to the cylcopropanation as a variant of the Corey-Chaikovsky cyclopopranation was investigated. The addition of sulfur ylides to a Michael-acceptor should have led after elimination of diphenylsulfide to the desired cyclopropane. However, no product was isolated besides elimination products. The reagents were too basic and too little nucleophilic for the 1,4-addition.

The synthesis of cyclopropanes became the crucial factor for this approach and finally also the reason why this approach had to be dismissed. The attempt to synthesize tetrasubstituted-cycloropanes failed and probably due to the steric repulsion of the reagents involved. The desired cyclopropane would have combined an ester, the indole and two alkyl substituents on the smallest of all possible rings and was a very ambitious approach.

The necessary cyclopropane for the initial approach comprised a total of five substituents (see Scheme 40). The second approach would have necessitated four substituents. Both desired cyclopropanes were not obtainable by the studied methods. Therefore, it was decided to attempt the synthesis of a cyclopropane with three substituents. Consequently, this also meant to switch approach from indole C-2 to indole C-3.

11 Indole C-3 cyclopropane as precursor for the DVCPR

After attempting to synthesize **1** from an indole substituted at C-2, the next step was to study an indole substituted at C-3. Both are viable precursors for the DVCPR, as was shown during methodology development.

11.1 Retrosynthesis

The goal of a formal total synthesis of **1** is ketone **136** (Figure 18). Disconnecting the pyrrole and the two-atom handle spanning the seven-membered ring reveals **238**. This tricyclic compound could evolve from cyclohepta[*b*]indole **239** after rearomatization of the indole nucleus and a diastereoselective hydroboration-oxydation sequence. To tobtain **239** a DVCPR of cyclopropyl compound **240** would have to take place. The precursor of the DVCPR could be obtained after functional group interconversions of cyclopropane **241**, which would be obtained after cyclopropanation of (*E*)-alkene **242** with commercially available ethyl-diazo acetate.

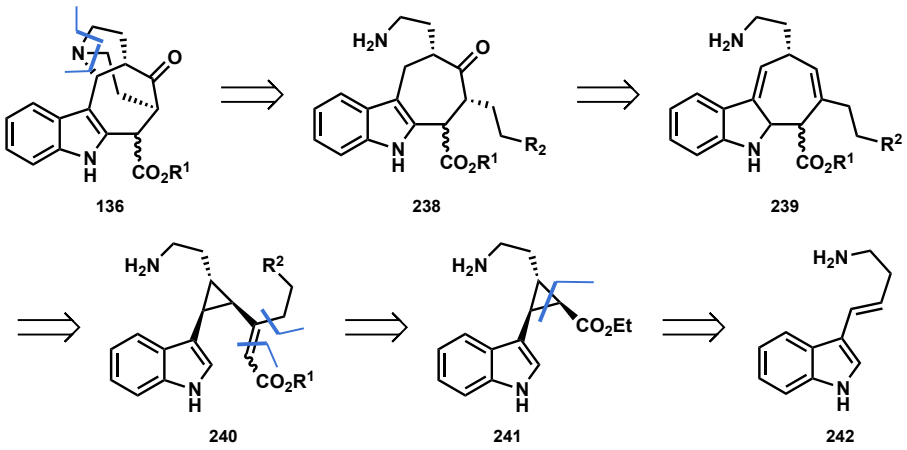


Figure 18 Retrosynthesis for the C-3 substitution approach.

The retrosynthesis relies on a diastereoselective cyclopropanation and on carbonyl chemistry to install the vinyl-cyclopropane. The group R^2 would ideally be a substituent that could be ejected during nucleophilic attack of the nitrogen to form the atom handle. However, R^2 should also be stable under the conditions necessary for the olefination, the DVCPR and the hydroboration sequence. A mesylated or tosylated alcohol was intended for this purpose.

Introducing the nitrogen at an early stage would potentially be more convergent. However, concerns for its interference in reactions, especially the cyclopropanation and the hydroboration, prompted the decision to do otherwise. Thus, a protected hydroxyl group was used. The pyrrole could be build up at during the last stages by benzylic oxidation as described in chapter 10.1.

The hydroboration of **239** would install the necessary stereochemistry for the two-atom handle. It was expected that the conformation of the seven-membered ring in combination with the already established stereochemistry of the ethyl chain pointing down, would direct the boron reagent to come from the upper side of the ring. The regioselectivity would be governed by the substitution pattern of the double bond. To increase selectivity enantioselective reagents such as Ipc-borane could be used.

In the DVCPR, which should proceed through the transition state shown in Figure 19, the central cyclohepta[*b*]indole would be build up. Afterwards, no carbon-carbon bond formation would be required to finish the formal synthesis of **1**. The cyclopropane would have to be synthesized diastereoselectively so that the DVCPR can take place. The ester would have to be on the same site of the cyclopropane, a challenge for the cyclopropanation reaction.

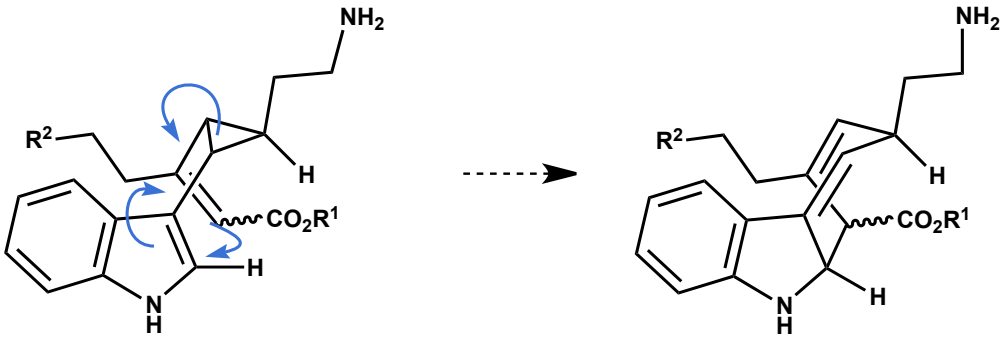
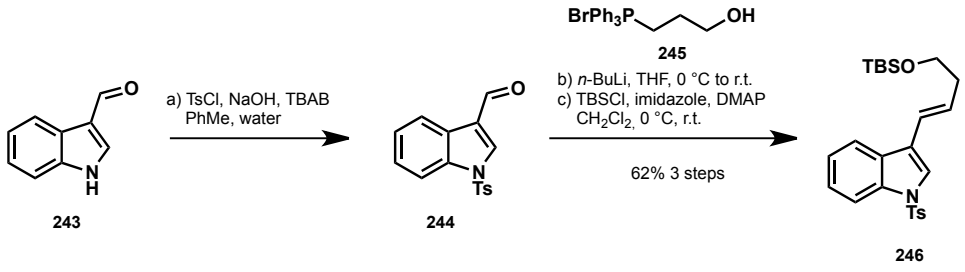


Figure 19 Proposed transition state for DVCPR from C-3 substituted indole.

11.2 Forward synthesis: towards a highly substituted cyclohepta[*b*]indole

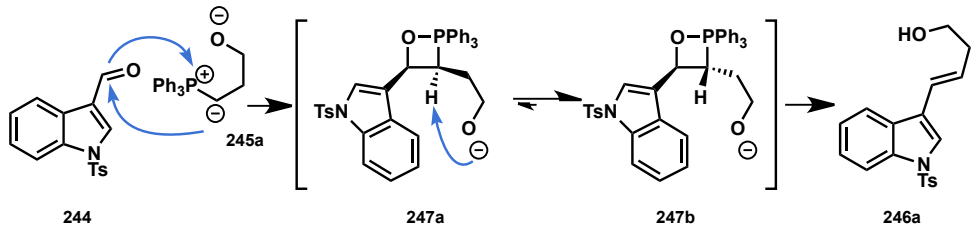
The synthesis started from commercially available indole-3-carbaldehyde **243**. Tosyl protection was followed by a (*E*)-selective olefination reaction with hydroxyl-Wittig reagent **245**.



Scheme 51 Synthesis of olefin 246.

The reaction gave the (*E*)-double bond without detectable isomer. Two equivalents of base are added in this reaction. The first equivalent presumably deprotonates the hydroxyl group, whereas the second equivalent forms the ylide **245a** (Scheme 51). During the olefination, the oxy-anion presumably deprotonates the *cis* configured oxa-phosphatan ring **247a**, which leads

to the *trans* configured oxa-phosphatane **247b** and ultimately to the formation of the (*E*)-configured double bond.[70]



Scheme 52 (*E*)-Selective Wittig reaction.

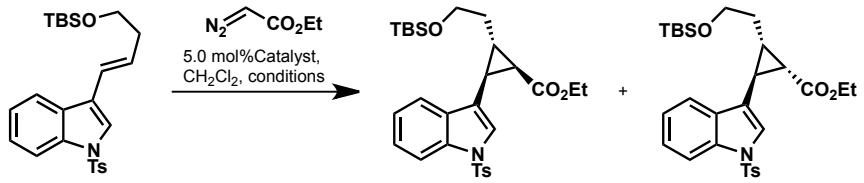
As the resulting primary alcohol **246a** was very polar and purification during flash chromatography was strenuous for large-scale reactions (>20 mmol), the crude alcohol was directly converted to the silyl-protected derivative **246**.

11.2.1 Cyclopropanation studies

With the protected alcohol **246** in hands, the diastereoselective cyclopropanation was studied. Transition metal-catalyzed cyclopropanation reactions are generally performed with an excess of olefin and slow addition of diazo-compound to reduce the possibility of dimerization reactions. However, in this case the olefin was the more valuable substrate and therefore commercially available ethyl diazo acetate was used in excess. By this method, very high conversion of the olefin could be achieved however a large quantity of side products was produced, too.

The cyclopropanation was studied using copper triflate and rhodium acetate as catalysts in dichlormethane or toluene as solvent. The separation from sideproducts of the reaction became arduous since the dimer product, diethyl fumarate, was difficult to separate from the cyclopropane. To determine the yield and the diastereoselectivty, both isomers were isolated together with the dimerization product and then analysed by NMR. The net yield could then be determined by comparison of peak areas as was the diastereoselectivity. Generally a conversion of 90% could be achieved, nevertheless all yield was determined as isolated.

Table 10 Cyclopropanation studies.



246 248 249

Entry	Catalyst	Ligand	Equiv. N_2CHCO_2Et	Yield/%	d.r.	Comment
1	$CuOTf•PhMe_{0.5}$	-	4	60	1.5 :1	-
2	Rh_2OAc_4	-	4	55	1.5:1	-
3	$(CuOTf)_2•PhMe$	-	4	0	-	At 0 °C
4	$(CuOTf)_2•PhMe$	*t*Bu-Box	4	63	2.8 :1	-
5	$(CuOTf)_2•PhMe$	Ph-Box	4	65	3.5-3.0:1	-
6	$(CuOTf)_2•PhMe$	Ph-Box	4	63	3.5-.3.0:1	2.5 mol%
7	$(CuOTf)_2•PhMe$	Ph-Box	3	61	3.5-.3.0:1	2.5 mol% , less dimer
8	$(CuOTf)_2•PhMe$	Ph-Box	2	50	3.5-.3.0:1	Less conversion
9	$(CuOTf)_2•PhMe$	Ph-Box	3	58	3.5-.3.0:1	In PhMe

Copper- and rhodium-based catalysts promoted the synthesis of the desired cyclopropane in acceptable yields. Additionally, little selectivity for the desired diastereomer could be detected (Table 10, entry 1 and 2). As both metals gave similar yields, it was attempted to improve the diastereoselecitivty. To this end, the reaction temperature was lowered, which unfortunately stopped the reaction (entry 3). The next step was to test ligands for the cyclopropanation. The *tert*-butyl bis-oxazoline (Box) ligand gave a selectivity of almost 3:1 (entry 4) while the Ph-Box ligand even gave 3.5-3.0:1 and 65% yield (entry 5).[71–73] Decreasing the catalyst loading did not change selectivity and only slightly decreased yield. Lowering the amount of equivalents of ethyl diazo acetat to three did hardly change yield (entry 7) but decreased the quantity of dimer substiantally, which translated to less waste and facilitated purification. Reducing the number of equivalents of diazo-compound to two however furnished lower conversion and lower yield (entry 8). Changing the solvent to toluene did slightly reduce the yield but did not increase the selectivity (entry 9).

Overall, copper-triflate and in combination with the Ph-Box ligand gave the best results for the cyclopropanation. The Box ligands have been used extensively for the enantioselective cyclopropanation.[55] In this case, enantioselectivity was not the objective. The initial studies towards **1** involved a racemic synthesis, and therefore no measurement of chiral induction was conducted. Nonetheless the diastereoselectivity was increased substantially.

Diastereomeric induction presented a challenge during the cyclopropanation. The olefin is essentially a planar molecule with a linear alkyl chain as one and an aromatic system as the other substituent, both presenting similar steric hindrance adjacent to the alkene (Figure 20). Additionally, the olefin is little polarized and therefore little induction can be gained electronically.

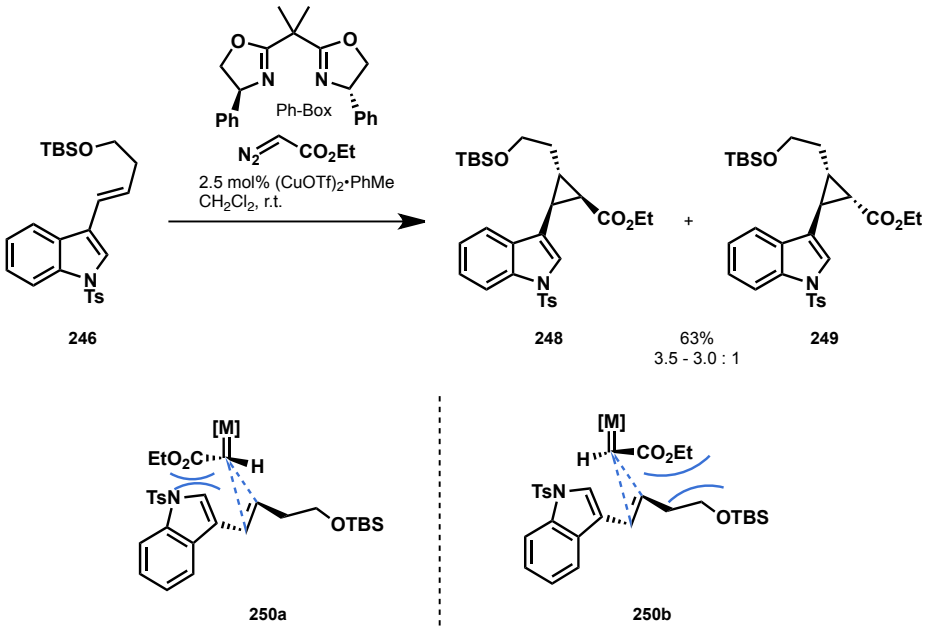


Figure 20 Diastereoselecitivy during the cyclopropanation.

Ultimately, it seems that the flexible alkyl chain represented a larger steric bulk than the indole moiety and a slight selectivity can be observed. The box ligands increased the selectivity by augmenting the steric hindrance. For this challenging substrate a selectivity of 3.5-3.0 : 1 was seen as an optimum and it was decided proceeded with the synthesis.

It is noteworthy that cyclopropane **248** is not a stable at room temperature. Isomerisation of the cyclopropane to **249** occurs spontaneously and therefore it was attempted to transform **248** as soon as possible by reduction of the ester. In some instances both diastereomers were used for transformations to be separated at a later stage in the synthesis.

11.2.2 Synthesis of a vinyl cyclopropane: intermolecular olefination

The next challenge was to transform the ester to a trisubstituted double bond. According to the retro synthesis, a substituent R^2 had to be introduced that could be transformed into an amine in

a substitution reaction. As such, R^2 could be a number of functional groups: tosylated or mesylated alchols, sulfones, halogens, etc. The first concept to obtain **240** was to synthesize a ketone, bearing the requisite substitutent followed by an olefination (Figure 21).

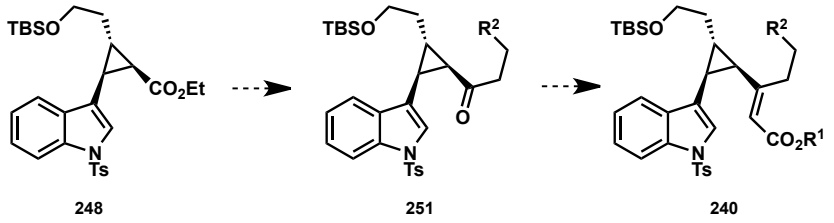
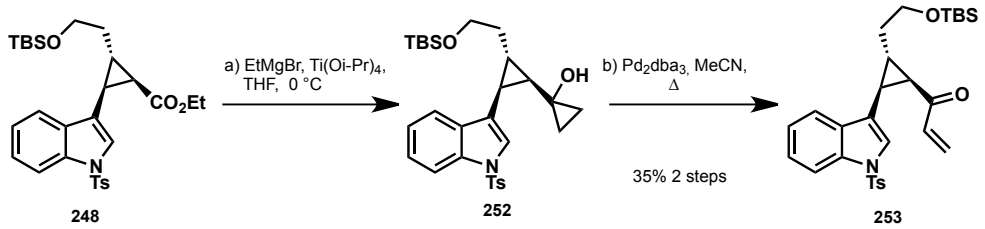


Figure 21 Synthetic plan to obtain 240.

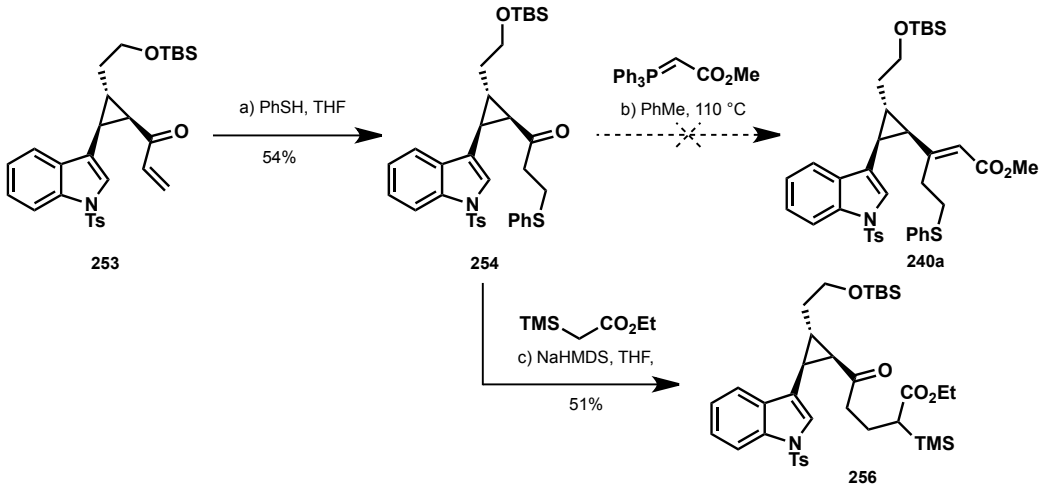
To obtain said ketone a Kulinkovich reaction was performed on cyclopropane **248** (Scheme 53).[74] To this end, the cyclopropane was reacted with titanium *iso*-propoxide and ethyl magnesium bromide and the alcohol **252** was obtained. Submitting **252** to palladium dba in refluxing MeCN, a ring opening took place and vinyl ketone **253** was formed. [75]



Scheme 53 Vinyl ketone 253 formation.

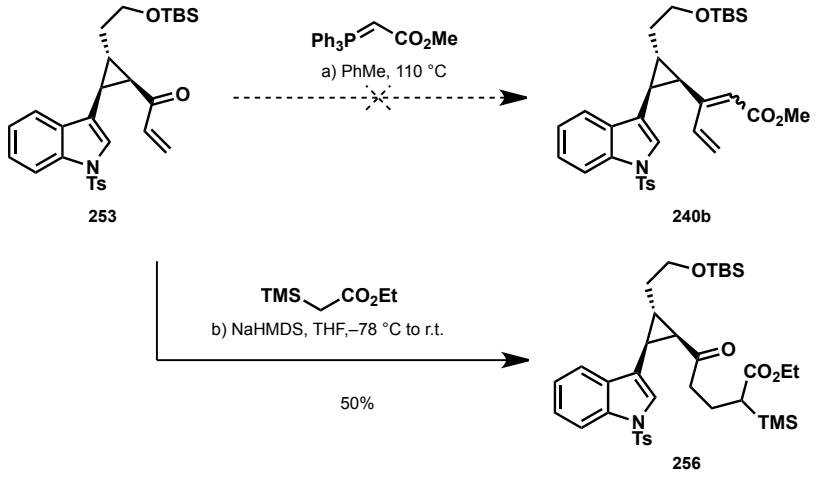
Vinylketone **253** was an advanced intermediate and was used as starting point for the synthesis of the DVCPR precursor **240**.

A 1,4-addition using thiophenol furnished **254** as a possible precursor for **240** (Scheme 54, reaction a). Olefination reaction was then attempted using a Wittig reagent but no reaction took place after prolonged heating in refluxing toluene (Scheme 54, reaction b). It was assumed that no reaction occurred due to steric hindrance. Therefore, a Peterson olefination was attempted, as the reagent is less sterically demanding. However, no olefin was obtained although a transformation took place. Product **256** could be isolated aftera substitution of the thio-ether. More probably, the olefination reagent acted as a base and the thio-ether was eliminated forming *in situ* vinyl ketone **253**. Then a 1,4-addition of still reactive olefination reagent followed (Scheme 54, reaction c).



Scheme 54 Attempted olefination thio derivative.

Unfortunately, thiophenol was also eliminated during the attempt to perform a Horner-Wadsworth-Emmons reaction. Consequently, vinyl ketone **253** was then chosen as substrate for the olefination. In comparison to **254**, steric hindrance would be reduced and no elimination, quenching the reagent, could take place anymore.



Scheme 55 Attempts to olefinate vinyl ketone 253.

Neither a Peterson Olefination using trimethlsilyl ethyl acetat nor a Wittig reaction with an ylide derived from methyl acetate did furnish the desired olefin (Scheme 55). Prolongued heating with the Wittig reagent lead to degradation. The reaction with deprotonated TMS acetate lead to product **256** *via* a 1,4 addition.

The lack of positive results from these reactions showed that ketone **253** was embedded in a sterically demanding environment. Therefore, either a reagent with little steric hindrance had to be used as opposed to olefination reagents with bulky phosphorous containing groups. Another approach would be to generate an environment where the olefination reagent would already be in close proximity to the ketone as for example in an intramolecular reaction.

11.2.3 Synthesis of a vinyl cyclopropane: Nucleophilic addition

Pursuing the concept of a less sterical demanding reagent entailed a nucleophilic addition to **258** (Figure 22). However, most organometallic reagents such as magnesium- or lithium-organyls are basic and would therefore deprotonate between the ketone and the ester opposed to add to the carbonyl functionality. Literature shows that allylstananne reagents like **259** react well with ketones and that these reagents are less basic then Grignard reagents. Examples of carbonyl activation with Lewis acids to enhance reactivity are also known.[76–78]

Allyl-stannannes also possesses the advantage that not the sterically encumbered metal substituted site reacts with the carbonyl atom, but the CH_2 atom in a crotylation-type addition.

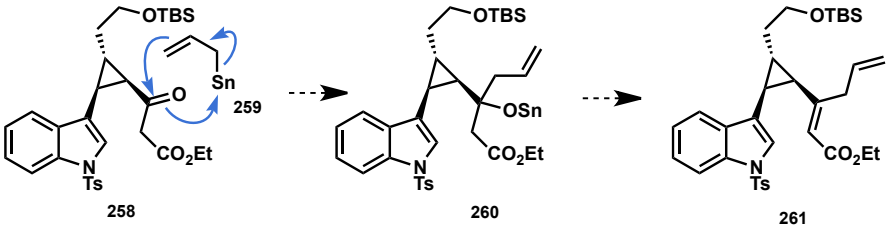
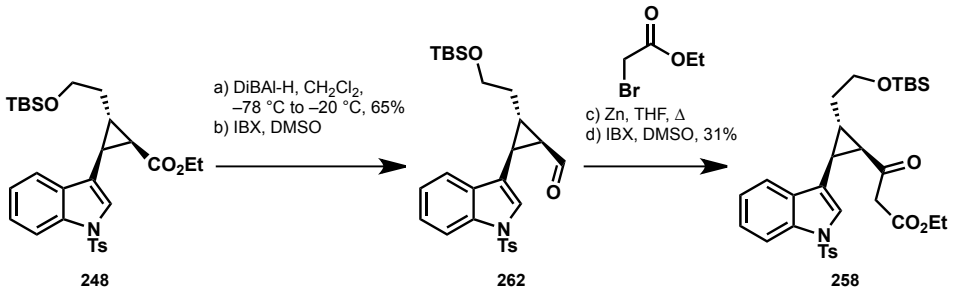


Figure 22 Proposed addition to ketone.

To obtain the precursor for the nucleophilic addition, cyclopropane **248** was reduced to the primary alcohol. Subsequent oxidation gave aldehyde **262**, which was prone to isomerization and degradation. Therefore, the aldehyde was not purified by flash chromatography but used directly in the following Reformatsky reaction with ethyl-bromo acetate. The addition gave a mixture of isomers were obtained which was of no consequence, as direct oxidation with IBX furnished the 1,3 keto ester **258**.

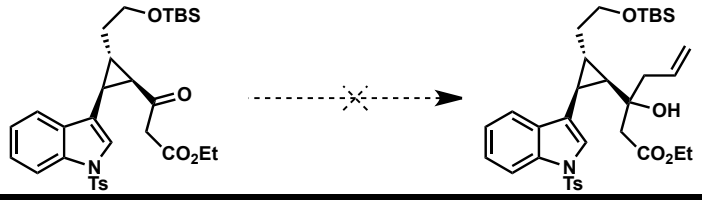


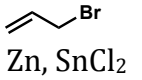
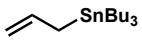
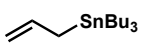
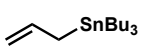
Scheme 56 Synthesis of keto-ester 258.

As described earlier, the cyclopropanation gave a mixture of diastereomers and the separation with flash chromatography was difficult due to little difference in retention time. Transformation of cyclopropane **248** to keto-ester **258** facilitated the separation as the retention time shifted and the different behavior became more pronounced. Therefore diastereomer separation generally was done at a later stage.

With keto ester **258** in hand, the organo-stannane addition was attempted (Table 11). At first, allylbromide was reacted with metallic zinc and tin(II)chloride in an attempt to generate the zinc organyl and subsequent transmetallation should lead to the desired allyl-stananne (entry 1). However, even after repeated trials the conditions failed to promote any reactivity. Therefore, the reagent was changed to allyltributyl stannane. Unfortunately, even at room temperature no reaction between the ketone and the nucleophile occurred (entry 2). Adding Lewis acids only led to a desilylated product and no addition of the nucleophile, which was determined by crude NMR.

Table 11 Organostannane addition.



entry	Reagents	Lewis acid	Cond	Result
1	 Zn, $SnCl_2$	-	THF, r.t.	No reaction
2		-	CH_2Cl_2, −78 °C to r.t.	No reaction
3		BF_3•OEt_2	CH_2Cl_2, −78 °C to r.t.	removal of TBS
4		$TiCl_4$	CH_2Cl_2, −78 °C to r.t.	removal of TBS

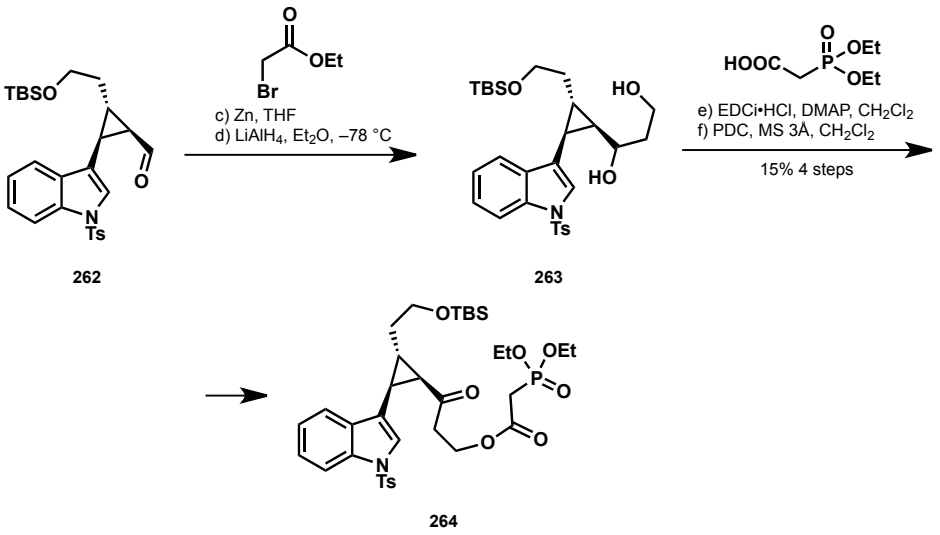
The addition of a stannane reagent to **258** failed probably due to a combination of steric hindrance and insufficient nucleophilicity. A more reactive reagent was not studied, as a deprotonation was more likely than addition. Therefore, the direction was changed and an intramolecular olefination was attempted next.

11.2.4 Synthesis of a vinyl cyclopropane: intramolecular olefination

After several attempts of an intermolecular reaction and a nucleophilic addition to a ketone in α-position to the cyclopropane, an intramolecular olefination was contemplated. The advantage over the intermolecular variant would be that the reagent and the substrate would be in close proximity and therefore reaction would be more probable. However, the steric hindrance would be increased. Reagents and substrates would have to be chosen carefully in order to avoid elimination already observed for the intermolecular case.

The initial strategy was an intramolecular HWE-olefination to obtain an unsaturated γ-lactone. It was presumed that the deprotonation would occur preferentially in α-position to the phosphonate and consequently lead to a minimization of the elimination. The synthesis of the

requisite phosphonate started from cyclopropyl aldehyde **262**. A Reformatsky reaction and a reduction of the resulting ester lead to diol **263** (Scheme 57). Selective mono-esterification with diethylphosphono acetic acid at the terminal alcohol was followed by oxidation. The resulting ketone **264** was obtained in four steps and 15% overall-yield from the crude aldehyde.



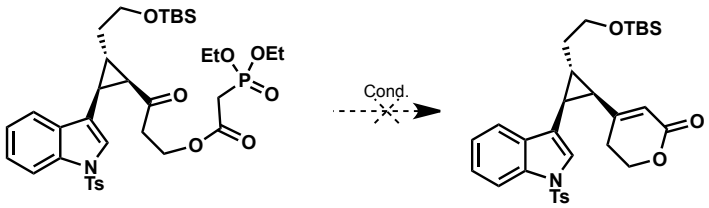
Scheme 57 Synthesis of phosphonate for the intramolecular HWE reaction.

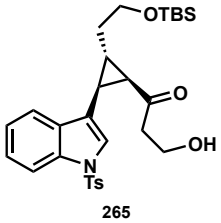
The successful synthesis of ketone **264** permitted to attempt the intramolecular olefination reaction. Classical conditions were used as the first. However, only vinyl ketone **253** was isolated (Subsequently nitrogen based reagents were employed. As elimination occurred with DBU in THF at 0 °C (entry 4), conditions similar to those by Masamune-Roush were studied (entry 5, 6, 7, 8). Hence, the substrate was dissolved and stirred for 30 minutes with the additive and then the base was added in an attempt to activate the phosphonate.[79] The combination of magnesium (II) bromide and DBU did not improve on the previous result (entry 5). When triethylamine and magnesium (II) bromide was used at 0 °C or at room temperature, no reaction could be identified. Warming the reaction for a short time to reflux however caused elimination (entry 6 and 7). The application of lithium chloride and triethylamine was more reactive and caused elimination already at 0 °C (entry 8). Hünig's base in combination with magnesium(II)bromide did not show any reactivity at room temperature only the vinyl ketone was reisolated after heating to reflux (entry 9 and 10). Finally, barium hydroxide was used as base as well and hydrolysis product was obtained in addition to the elimination product.

Table 12, entry 1). Switching to *tert*-butoxy lithium in THF at 0 °C interestingly caused a saponification of the corresponding ester to **265**. At higher temperature also elimination to **253** occured. At lower temperature, ester hydrolysis continued (entry 2 and 3).

Subsequently nitrogen based reagents were employed. As elimination occurred with DBU in THF at 0 °C (entry 4), conditions similar to those by Masamune-Roush were studied (entry 5, 6, 7, 8). Hence, the substrate was dissolved and stirred for 30 minutes with the additive and then the base was added in an attempt to activate the phosphonate.[79] The combination of magnesium (II) bromide and DBU did not improve on the previous result (entry 5). When triethylamine and magnesium (II) bromide was used at 0 °C or at room temperature, no reaction could be identified. Warming the reaction for a short time to reflux however caused elimination (entry 6 and 7). The application of lithium chloride and triethylamine was more reactive and caused elimination already at 0 °C (entry 8). Hünig's base in combination with magnesium(II)bromide did not show any reactivity at room temperature only the vinyl ketone was reisolated after heating to reflux (entry 9 and 10). Finally, barium hydroxide was used as base as well and hydrolysis product was obtained in addition to the elimination product.

Table 12 Intramolecular olefination.



Entry	Base	Cond.	Result
1	NaH	PhMe, 0 °C	Elimination
2	*tert*-BuOLi	THF, 0° C	 265 Ester hydrolysis, at r.t. also elimination
3	*tert*-BuOLi	THF, −20 °C	Ester hydrolysis
4	DBU	THF, 0 °C	Elimination
5	DBU, $MgBr_2$	MeCN, r.t.	Elimination
6	Et_3N, $MgBr_2$	MeCN, 0 °C to r.t.	No reaction
7	Et_3N, $MgBr_2$	MeCN, Δ	Elimination
8	Et_3N, LiCl	MeCN, 0 °C	Mostly elimination
9	DIPEA, $MgBr_2$	MeCN, r.t.	No reaction
10	DIPEA, $MgBr_2$	MeCN, Δ	Degradation
11	$Ba(OH)_2 \bullet 8H_2O$	THF/H_2O 20:1	Hydrolysis and elimination

After studying a multitude of bases no positive result was obtained. The hydrolysis was a surprising product especially as *tert*-butoxy lithium seems too sterically hindered to act as a nucleophile. Given these results, barium hydroxide was chosen over sodium hydroxide, but too no avail.

The most interesting results were obtained when triethyl amine and Hünig's base were used in conjunction with magnesium(II)bromide. These bases are strong enough to deprotonate between the carbonyl and the phosphonate. Unfortunately, no olefination occurred (Figure 23). Presumably, the cyclopropane creates a sterical environment that inhibits olefination. Increasing

the temperature in order to overcome the energy barrier caused a proton switch and concomitant elimination to occur.

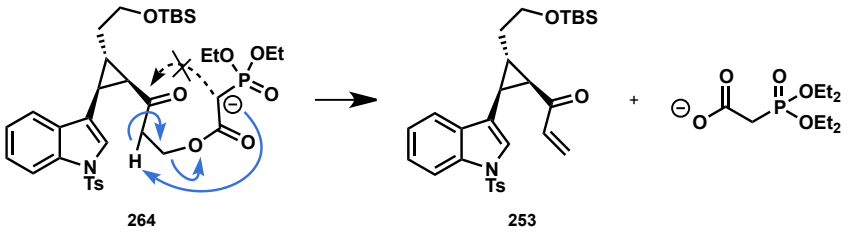
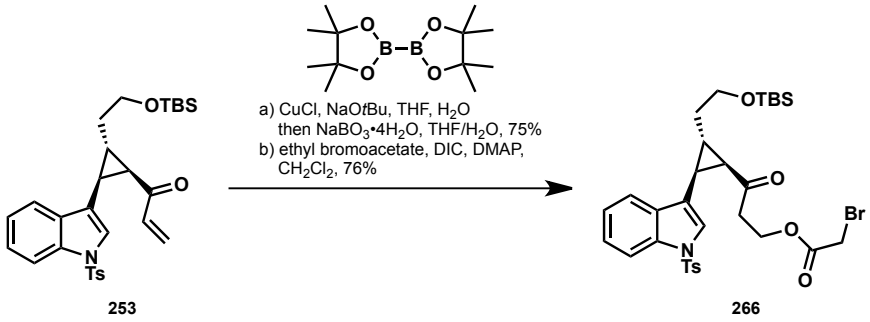


Figure 23 Elimination instead of olefination.

Assuming that the olefination did not occur due to the steric repulsion, meant that the size of the reagent had to decrease. Instead of the bulky posphonate, a reaction involving a radical was conceived. Intramolecular Reformatsky reactions are reported in the literature for the synthesis of five-, six- and even seven-membered lactames employing samarium diiodide.[80]

11.2.5 Synthesis of a vinyl cyclopropane: intramolecular Reformatsky reaction

The Reformatsky-precursor was obtained from vinyl ketone **253**. After a copper catalyzed boronation of the double bond with subsequent oxidation, hydroxyl ketone **265** was obtained.[81] Esterification with ethyl bromoacetate then gave bromo ester **266**.



Scheme 58 Synthesis of the Reformatsky precursor.

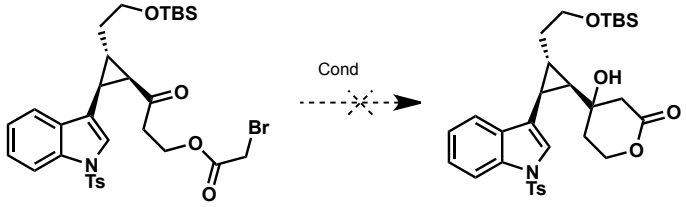
The intramolecular reaction was first attempted with zinc powder, but the reaction would not proceed. The general procedure for a zinc mediated Reformatsky reaction is to mix all reagents and the substrate in a flask and then heat the reaction for a short time. A color change then indicates the insertion of the zinc into the halogen-carbon bond and heating can be stopped. However, in this case no color change occurred and only starting material was obtained (As the initiation of the Reformatsky reaction with metallic zinc was not possible, diethyl zinc and Wilkinson's catalyst were used (entry 5, 6).[82,83] Opposed to zinc powder, reaction occurred but no cyclisation. Instead the debrominated product **266a** was obtained. Warming to room temperature did not improve here (entry 6) and heating to 40 °C lead to degradation. A different approach to create the active species was attempted as well. Premixing metallic zinc and dimethyl aluminium chloride and subsequent addition of the substrateand then heating the

mixture to 50 °C for 12 hours did not lead to the desired product.[84] Again, only the dibrominated product was isolated.

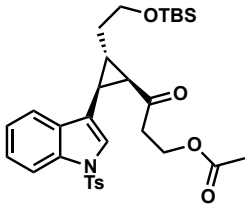
Table 13, entry 1). Therefore, instead of zinc samarium iodide was used. Reaction occurred, but what seemed to be a single product after purification, showed itself to be a multitude of compounds during NMR analysis. The reaction temperature did not influence the outcome of the reaction, as no product was obtained even at lowever temperatures (entry 2, 3 and 4).

As the initiation of the Reformatsky reaction with metallic zinc was not possible, diethyl zinc and Wilkinson's catalyst were used (entry 5, 6).[82,83] Opposed to zinc powder, reaction occurred but no cyclisation. Instead the debrominated product **266a** was obtained. Warming to room temperature did not improve here (entry 6) and heating to 40 °C lead to degradation. A different approach to create the active species was attempted as well. Premixing metallic zinc and dimethyl aluminium chloride and subsequent addition of the substrateand then heating the mixture to 50 °C for 12 hours did not lead to the desired product.[84] Again, only the dibrominated product was isolated.

Table 13 Intramolecular Reformatsky studies.



266

entry	Metal	Cond.	Result
1	Zn	THF, 70 °C then r.t.	No reaction
2	SmI_2	THF, r.t.	degradation
3	SmI_2	THF, 0 °C	degradation
4	SmI_2	THF, −78 °C	degradation
5	Et_2Zn, $RhCl(PPh_3)_3$	THF, 0 °C	 266a debromination
6	Et_2Zn, $RhCl(PPh_3)_3$	THF, 0 °C to r.t. then 40 °C	Debromination, degradation

7	Et_2AlCl, Zn	THF, 50 °C, 12 h	Debromination

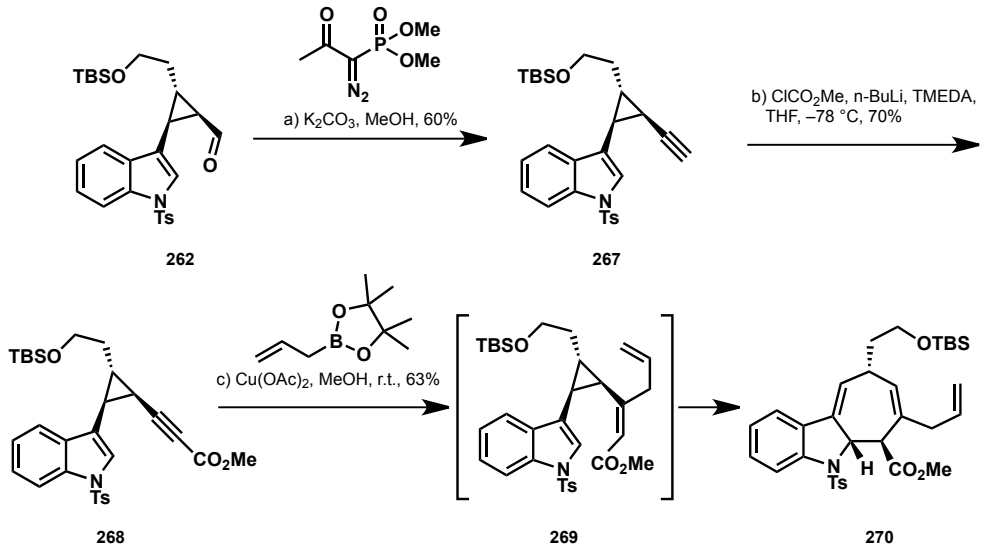
The intramolecular Reformatsky reaction failed to deliver the desired cyclized product. The radical reaction initiated by samarium diiodide was not limited to the cyclisation and could not be controlled. It seems that both Wilkinson's catalyst in combination with diethyl zinc and diethyl aluminium chloride with zinc were able to insert into the bromine-carbon bond. This woud be the first step in the Reformatsky reaction. However, no cyclisation occurred and during work up the reagent was quenched to give the acetat ester. It is difficult to determine whether or not steric or electronic characteristics of the molecule prevented the reaction from happening.. Nevertheless, the intramolecular olefination approach was to the vinyl cyclopropane was a failure.

11.2.6 1-4 addition to synthesize a vinyl cyclopropane

The inter- and intramolecular olefination approaches were both unsuccessful and both suffered from lack of reactivity of the ketone moiety. Ketones **253**, **264** and **266** are in α-position to a tri-subtituted cyclopropane, which dramatically increases the steric demand of those substrates and thererofre lowers their reactivity.

Based on these results a new approach was developed where the electrophilic center had to be as small as possible and very reactive. A copper-catalyzed 1,4-addition of an allylboronate onto an alkyne electron-deficient was selected. A report by Yamamoto *et al.* showed this process to be mild and selective. Most importantly, an example of a very similar system, involving a cyclopropane substituted with an alkyne was described.[85]

Aldehyde **262** was treated with the B-O reagent and potassium carbonate in methanol at room temperature and alkyne **267** was obtained in 60% yield (Scheme 59). Subsequently, the alkyne was deprotonated with *n*-butyl lithium in combination with TMEDA. Addition of methyl chloroformat then delivered **268**. Employing the literature known conditions, pinacol allylboronic ester was added to the alkyne in a copper acetate mediated reaction. Upon work up only one product was isolated which turned out to be cyclohepta[*b*]indole **270**.



Scheme 59 Synthesis of cyclohepta[*b*]indole 270.

Yamamoto *et al.* report their methodology to be exclusively (*E*)-selective in relation to the ester. Given the cyclopropane configuration and the transition state (Figure 19) the product should be **270**. The NMR analysis, more precise the coupling constant between the proton α to the ester and the proton in α to the nitrogen, confirmed this.

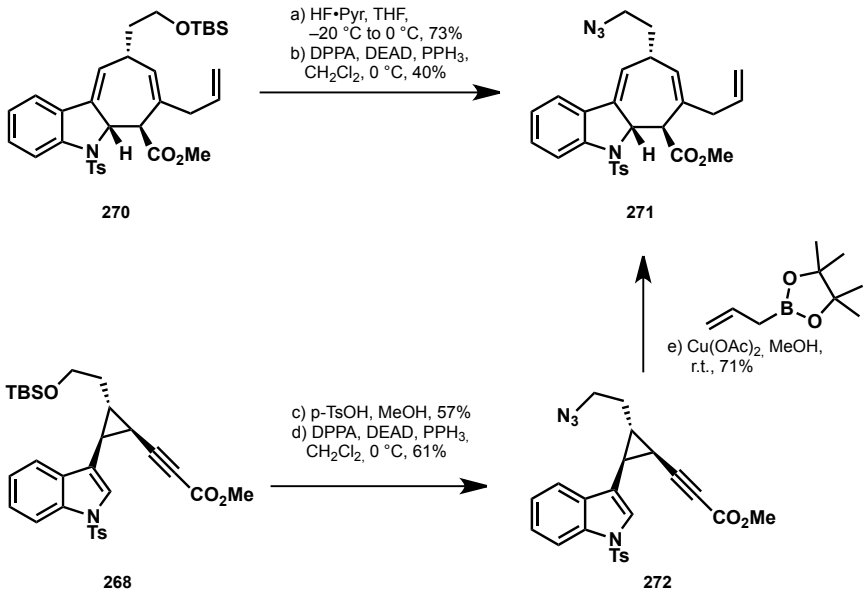
After three futile attempts to synthesize the vinyl cyclopropane, the 1,4-addition to an alkyne provided the desired cyclohepta[*b*]indole. The rearrangement proceeds at room temperature and, similar to an anionic oxy-Cope reaction, probably benefits from charge acceleration. The vinyl-cyclopropane could not be identified or isolated at any stage of the reaction.

12 Studies on the derivatisation of cyclohepta[*b*]indole 270: towards 1

The synthesis of cyclohepta[*b*]indole takes eight steps from literature known compound **244**. Given that the synthesis published by Overman only took nine chemical transformation and Martin's approach necessitated the isolation of only eight intermediates, a formal synthesis of **1** would not be an improvement in terms of yield or step count. Nevertheless, the methodology for the synthesis of cyclohepta[*b*]indoles had been extended to higher substituted cyclohepta[*b*]indoles. Only two carbons of the seven-membered ring were yet unsubtituted and all necessary carbon-carbon bonds for a formal synthesis of **1** were in place. The olefins in **270** present an entry for the necessary functional group interconversions. Three main challenges had to be overcome for a successful formal synthesis: the synthesis of the pyrole ring, transformation of the exo-cyclic allylic chain to an ethyl chain with an appropriate leaving group and a diastereoselective hydroboration.

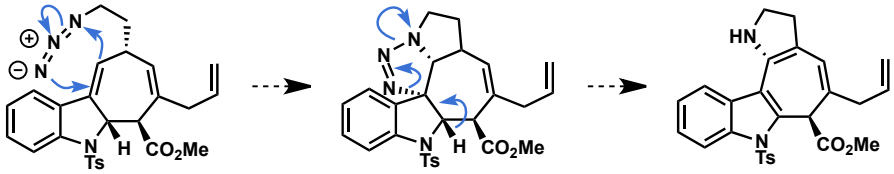
12.1 Derivatisation of the benzylic position

The double bond in conjugation with the aromatic ring was presumed to be the electronically most activated double bond in the system. It was therefore decided to attempt an intramolecular dipolar cycloaddition between an azide and this double bond to synthesize the pyrrole ring. To this end, the TBS group in **270** was removed by treatment with hydrogen fluoride and a subsequent Mitsunobu reaction with diphenylphosphoryl azide installed the azide in **271** (Scheme 60).



Scheme 60 Synthesis of azido cyclohepta[*b*]indole 271.

The same product can be obtained in slightly better yield by treating alkyne **268** with *para*-toluene sulfonic acid in methanol to deprotect the alcohol (Scheme 60, c). A subsequent Mitsunobu reaction employing the same conditions as before installed the azide group and gave **272**. Then followed the addition of pinacol allylboronic ester under copper catalysis, which furnished the desired cyclohepta[*b*]indole, showing the functional group tolerance of the addition-rearrangement reaction. The synthesis of azide **271** permitted to study the 1,3-dipolar cycloaddition.



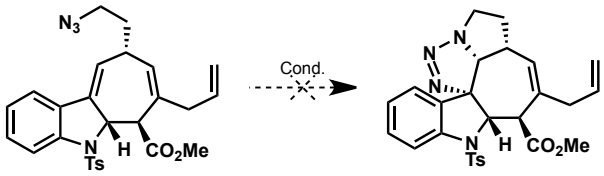
271 273 274

Figure 24 Proposed 1,3-dipolar cycloaddition.

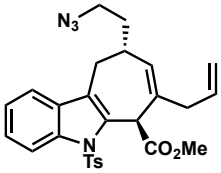
Azides do react with electron rich and electron poor double bonds in dipolar cycloaddition reactions, which usually proceed at elevated temperature. It was envisioned that during prolonged heating, a possible rearomatisation and concomitant elimination of nitrogen could occur, furnishing amine **274** (Figure 24). [86]

The reaction was attempted first in non-poloar solvents like dichloromethane and toluene at room temperature. However, no change was observed (Table 14, entry 1 and 2). Heating the reaction to 90 °C for 90 minutes induced the formation of two new products (entry 3). However, the conversion was sparse and at the same time substantial degradation occurred. Variation of the temperature did improve the conversion rate but tshe two products could not be identified satisfyingly. It was sought to improve results by switching to more polar solvents. Unfortunately, no conversion was seen in refluxing diethyl ether or chloroform. The same was true for dimethyl formamide at room temperature and slowly increasing the temperature up to 150 °C only resulted in degradation (entry 4, 5 and 6). It is literature known, that some dipolar cycloadditions proceed by irradiation and therefore the reaction was also performed under UV light in degassed and dry acetonitrile but this caused degradation in just a few minutes. Finally, the addition of TMS-triflate was attempted.[87] This caused the benzylic double bond to shift and the aromatized cyclohepta[*b*]indole could be isolated.

Table 14 Studies on the dipolar cycloaddition reaction.



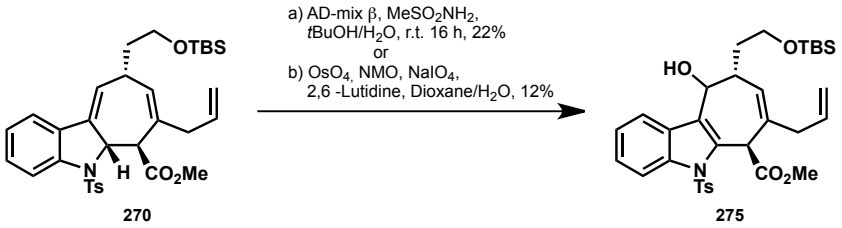
271 273

entry	solvent	Additives	Temp.	Result
1	CH_2Cl_2		r.t.	No reaction
2	PhMe		r.t.	No reaction
3	PhMe		90 °C	Very little conversion, degradation
4	Et_2O		50 °C	No reaction
5	$CHCl_3$		60 °C	No reaction
6	DMF		r.t. to 150 °C	Degradation
7	MeCN	Hν, 254 nm	r.t.	Degradation
8	CH_2Cl_2	TMSOTf	−78 °C to −10 °C	 271a

Most likely, the reaction proceeded in toluene at 90 °C but the degradation at this temperature was faster than the cycloaddition reaction.

Another approach studied was the functionalization of the benzylic double bond by a dihydroxylation reaction. As the benzylic double bond should be the most electron-rich double bond in the system, it was surmised that it would react preferentially.

Employing osmium tetroxide and *N*-methyl morpholine oxide in the dihydroxylation reaction did not show any conversion. Since the AD-mix shows often increased reactivity it was tested as well and a new product was formed. The monohydroxy product **275** was isolated in 22% yield (Scheme 61). The same product was also obtained when sodium periodate and 2,6-lutidine were added to previously tested dihydroxylation conditions using osmium tetroxide.[88] Both conditions were selective for the benzylic position as predicted, but the yield was low.



Scheme 61 Benzylic hydroxylation.

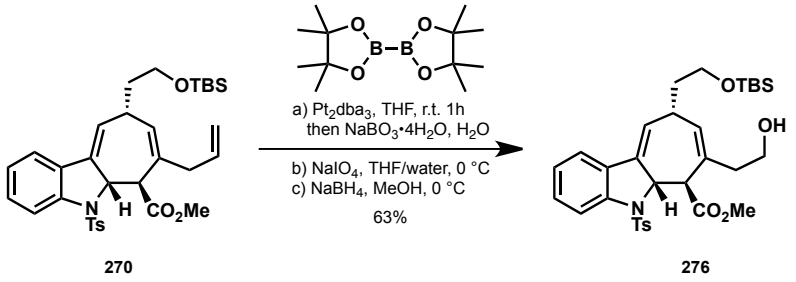
Due to the fact that the benzylic derivatisation gave unsatisfying results, a radical oxidation reaction in α-position to the aromatized indole was considered to as an alternative.[59,89,90] To study this reaction the other two double bonds had to be derivatized first.

12.2 Derivatisation of the allylic chain

Three double bonds are present in **270**. The benzylic double bond could be selectively transformed, although in poor yields. For a formal synthesis of **1** the other two had to be derivatised as well. The cyclic double bond would have to be hydroborated and the allylic chain would have to be shortened by one atom. The hydroboration could only be attempted after derivatisation of the allylic chain. Otherwise, the mono-subtituted double bond would react preferentially in the double bond.

To shorten the allylic chain and to install an appropriate group a dihydroxylation and periodate cleavage would have seemed the optimal methodology. However, the allylic chain was never attacked during the dihydroxylation reaction described previously. The platinum catalyzed 1,2-diboronation of terminal double bonds presented itself as a valuable methodology.[91–93]

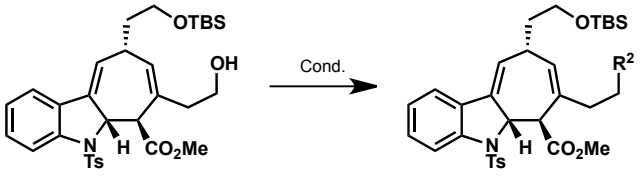
Mixing platinum-dba with *bis*(pinacolato)diboron in THF and then adding **270** gave after one hour a diborylated species, which was oxidized to the corresponding diol with sodium perborate. The diol was then treated with sodium periodate and the resulting aldehyde was subsequently reduced to alcohol **276** with sodium borohydride (Scheme 62). In this manner, the allylic chain could be shortened by one atom in a mild and selective fashion and the desired alcohol could be obtained in 64% yield.



Scheme 62 Derivatisation of the allylic chain.

In order to synthesize **1**, the free alcohol in **276** had to become a leaving group. Therefore a series of derivatisation reactions were studied. It turned out, that once the alcohol was transformed, the product was prone to degradation in most cases (Table 15).

Table 15 Installation of leaving group R^2.



276 277

entry	Cond.	R^2	Result
1	NBS, PPh_3, CH_2Cl_2, 0 °C	Br	Degradation
2	CBr_4, PPh_3, CH_2Cl_2, 0 °C	Br	Degradation
3	PBr_3, Pyridine, THF, r.t.	Br	Degradation
4	ZnBr2, PPh_3, DIAD	Br	Degradation
5	Tf_2O, d*t*BP, CH_2Cl_2, 0 °C	OTf	Degradation during workup
6	MsCl, Et_3N, CH_2Cl_2, 0 °C	OMs	Degradation during purification
7	TsCl, Pyridine, CH_2Cl_2, 0 °C	OTs,	43% yield

Four different variants of the Appel reaction were studied to turn the hydroxyl group into bromine. However, reaction monitoring showed only degradation of material (Table 15, entry 1-4).[94] It is possible that the substitution was successful but the brominated product was not stable. Therefore sulfonic acid esters were then studied as alternatives to bromine. Triflation of the alcohol lead to a product that could be observed during reaction monitoring, but degraded during reaction work-up (entry 5). The mesylated product was stable during aqueous work-up. However, after flash chromatography on silica gel only degraded product was obtained. Tosylation turned out to be the only manner to obtain sufficiently stable product **277** in unoptimized 43 % yield. The objective to transform the allylic chain into an ethyl chain substituted with a leaving group was achieved and attention was turned to the hydroboration reaction.

12.3 Hydroboration studies

The hydroboration of **277** was designed to be a crucial step for the synthesis of **1** *via* a DVCPR. Although numerous reports hydroboration reactions on cyclic double-bonds can be found,

examples on seven-membered rings are rare and diastereoselective examples are even scarcer. The selectivity was expected to be a result of conformational preferences of the seven-membered ring, accordance with its substituents. Figure 25 shows the assumed selectivity during the hydroboration. Forced by the two double bonds and the alkyl chain, the ring would have to adopt a boat-like conformation. However, the depiction in Figure 25 is exaggerated and the conformational freedom of a seven-membered ring is of a higher degree when compared to five- or six-membered ring. Therefore, predictions of the actual conformations were to a certain level presumptuous as were expectations of the outcome of the reaction.

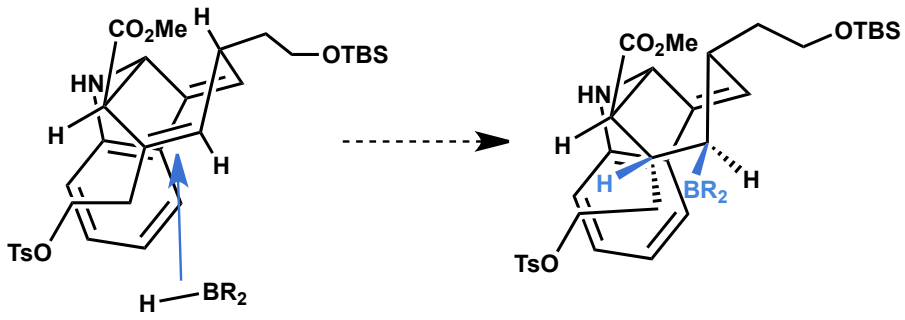
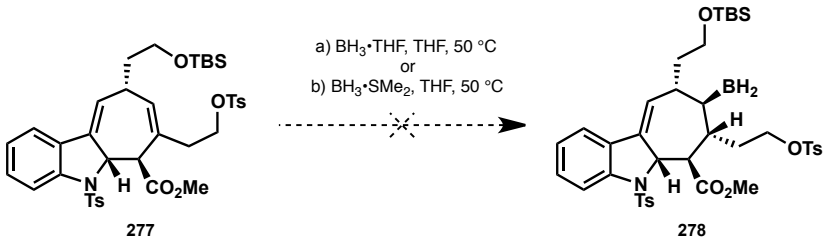


Figure 25 Model for the selectivity of hydroboration reaction.

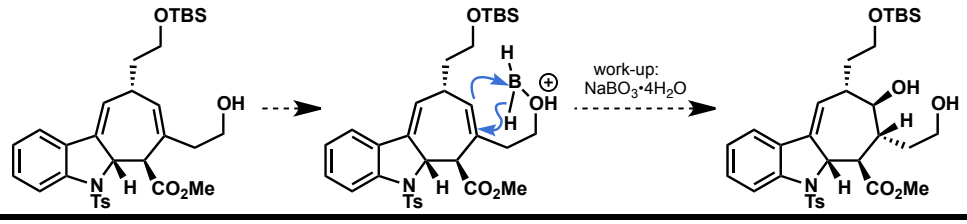
As the attempted reaction involved a tri-substituted double bond it was decided to test the sterically least encumbered boron source available, such as simple borane in THF (Scheme 63). Two different borane reagents were used. Since no reaction occurred at −78 °C the temperature was increased in each experiment. No reaction occurred at 0 °C or room temperature after 16 h. Therefore, the reaction was then heated to 40 °C but at this temperature degradation of the material occurred.



Scheme 63 Attempted studies towards hydroboration reaction.

As the hydroboration reaction could not be effected, it was assumed that steric hindrance was the rationale behind the failure. An intramolecular delivery of the reagent was therefore chosen as a possible alternative. Literature examples show that amines or hydroxyl groups can be used as directing groups for intramolecular hydroboration reactions.[95–97] The homoallylic alcohol present in **276** could be employed as such an anchor and thus effectuate a hydroboration reaction. The reaction was attempted as described in the literature with an oxidative work up. To this end, the product was stirred with sodium perborate before extraction.

Table 16 Directed hydroboration.



entry	Cond.	Result
1	BH_3•THF, THF 0 °C to r.t.	No reaction
2	BH_3•THF, CH_2Cl_2 −78 °C to r.t.	Degradation
3	BH_3•THF, CH_2Cl_2, TfOH, −78 °C to −20 °C.	Desilylation
4	BH_3•SMe_2, CH_2Cl_2,I_2 ,−78 °C to −30 °C.	Degradation
5	Catecholborane, $RhCl(PPh_3)_4$, 0 °C to r.t.	Degradation

First, the reaction was tested without any additives in THF under the same conditions as with tosylated product **277**. Unfortunately, no hydroboration occurred (Table 16, entry 1). Running the reaction in dichloromethane instead of THF at −78 °C did not show any conversion either. Slowly warming the reaction up while monitoring it showed no reactivity until 0 °C. At higher temperatures, no hydroboration product was obtained but rather degradation occurred. Adding triflic acid lead to desilylation of the protected alcohol could be identified during NMR analysis of the crude product, but no other reaction occurred until quench at −20 °C. Adding iodine to the reaction caused degradation of the product after slowly warming the reaction to −30 °C. Presumably, the iodine reacts with the benzylic double bond which then leads to a multitude of reactions. As the literature known examples for coordination of a borane reagent *via* an alcohol failed, a methodology employing the Wilkinson catalyst was applied. However, after hardly any reaction occured at 0 °C, the starting material was degraded while slowly warming to room temperature.

Both attempts of the hydroboration reaction were futile. Based on these results **276** could not be transformed into a precursor to **238**. It was proposed that by rearomatizing the indole core, a change of conformation could be achieved which would permit the hydroboration of the last remaining double bond.

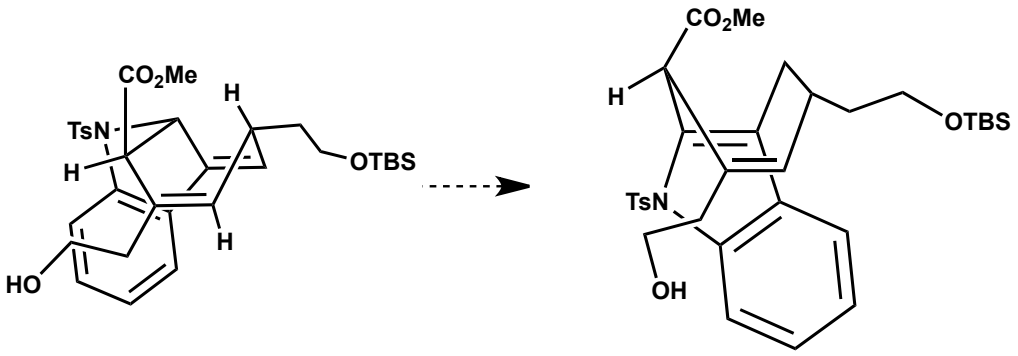
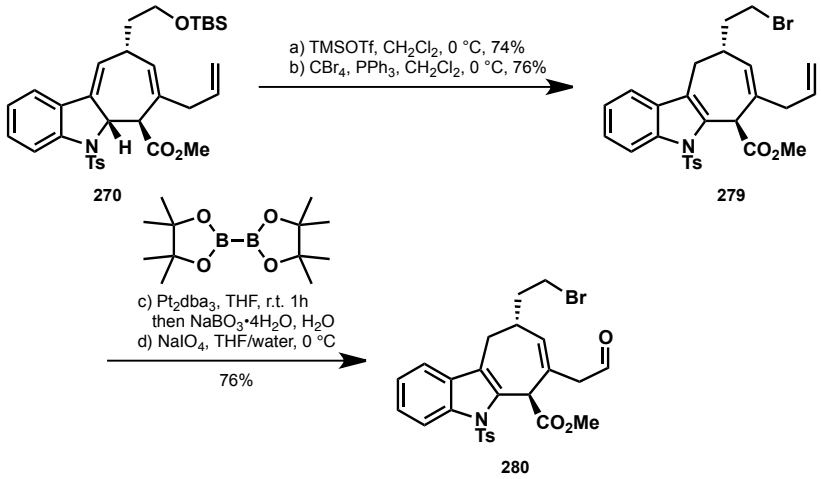


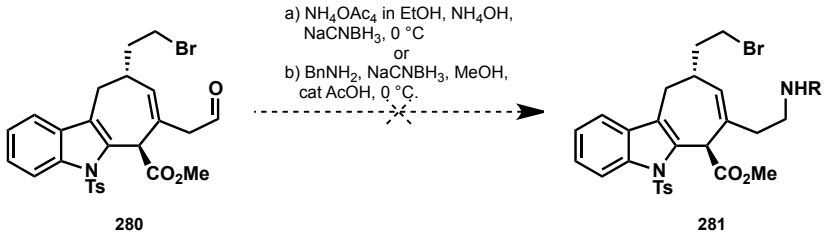
Figure 26 Change of conformation induced by rearomatization.

DVCPR product **270** was therefore treated with TMS-triflate in CH_2Cl_2 at 0 °C and under these conditions the indole rearomatized and the alcohol was desilylated. Rather than reprotecting it, the hydroxyl group was replaced with bromine in an Appel reaction. The subsequent diboronation and oxidation procedure gave a diol which was directly treated with sodium periodate to give aldehyde **280**.



Scheme 64 Aromatization and allyl substituent transformation of 270.

It was intended to transform aldehyde **280** in a reductive amination sequence. However, under the applied conditions (Scheme 65) a slew of reactions occurred.[98] Neither the reaction with ammonium acetate or with benzyl amine furnished the desired product **281**. Instead, NMR analysis of the crude product revealed a shift of the the remaining double bond in conjugation with the ester and the aromatic core.

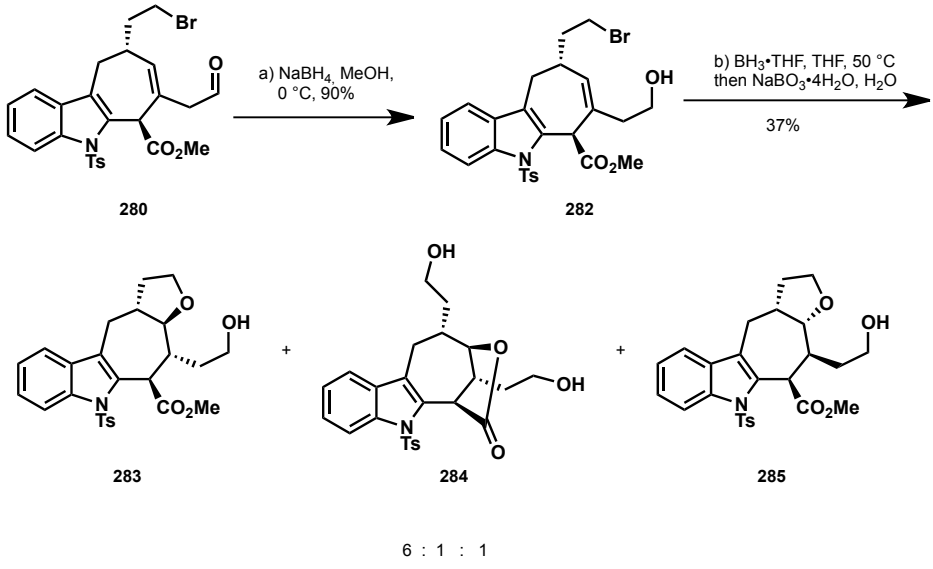


280 281

Scheme 65 Attempted reductive amination of 280.

The aldehyde **280** was then reduced to the respective alcohol **282** and the hydroboration was attempted, investigating whether the rearomatisaion would result in a more pronounced reactivity.

When the hydroboration was attempted in dichloromethane (see Table 16) degradation of starting material occurred. When the solvent was switched to THF, no reaction occurred at −78 °C, 0 ° C or room temperature. Finally, heating the reaction to 50 °C for two hours and subsequent oxidation with sodium perborate furnished 3 products in a ratio of 6:1:1 in 37% yield (unoptimized) (Scheme 66)



280 282 283 284 285

Scheme 66 Hydroboration of homoallylic alcohol 282.

Instead of the expected diol the products showed an additional ring. A tetrahydrofuran was formed in **283** and **285** while a lactonization occurred in **284**. These products were probably formed during the oxidative work up by attack of the newly formed oxygen functionality onto either the *α* bromine carbon or the carbonyl group.

Although the desired product was not obtained the diastereoselectivity did occur as predicted. Both **283** and **284** show the two ethyl chains on the same side of the seven-membered ring. A different functional group instead of the bromine or lower temperature during the oxidation might lead to obtaining the desired diol.

12.4 Results and discussion

A cyclohepta[*b*]indole with five substituents was successfully synthesized by the addition of a copper reagent to an alkyne. The *in-situ* DVCPR occurred at room temperature and gave only one stereoisomer. The product contained three double bonds, which had to be distinguished. An intramolecular 1,3-dipolar cyclo-addition with an azide failed to give positive result while an oxidation with either the AD-mix for dihydroxlation or a combination of osmium tetroxide, NMO and $NaIO_4$ furnished a benzylic alcohol. Unfortunately, the yields were low. Subsequently, the allyic chain was converted into an alcohol and hydrobation was attempted.

After trying a multitude of conditions, rearomatization of the indole and subsequent treatment with borane under forcing conditions gave the hydroboration product. However, these products were not the desired diols. Instead, an intramolecular reaction occurred and therefore a change of direction would have to happen. Nevertheless, the displayed diastereoselectivity was as planned and showed great potential for the formal synthesis of **1**.

The benzylic substitution did not occur as planned. The dipolar cycloaddition would have been an elegant entry. However, probably steric interactions limited the reactivity of the substrate. The results obtained by the dihydroxylation conditions were as desired but in the end the yield was too low. Instead, a radical reaction is planned. Establishing an amine instead of the bromine in **282** and then treating the compound with selenium oxide might form a tetrahydropyrrole, as discussed in chapter 10.1.

The hydroboration was challenging but finally the double bond could be converted as well. The most important result of this study is the displayed diastereoselectivity, which already gives the desired compound. By building up the tetrahydropyrrole before the hydroboration, an increased diastereoselectivity can be expected. Additionally, the formation of the tetrahydrofuran will be evaded.

13 Summary and Outlook

In the course of this project three approaches for the synthesis of cyclohepta[*b*]indoles were studied in detail. The goal was to establish the DVCPR to enantioselectively build-up cyclohepta[*b*]indoles with a broad variety of substituents. Additionally, a total synthesis of actinophyllic acid (**1**) was planned. To this end, effectively three precursors for the DVCPR were investigated.

The first approach entailed the synthesis of a *spiro*[cyclopropyloxindole] and the transformation of an amide into an enamine. An initial positive result was obtained when methyl lithium was used in a nucleophilic addition. However, the yield was low and more importantly no other reagent could be used to add onto the amide.

As a consequence, it was attempted to work around this complication by either changing the functional groups involved, changing the steric hindrance or switching from nucleophilic to electrophilic reagents. However, no further cyclohepta[*b*]indoles were obtained.

During the intermolecular synthesis of the *spiro*[cyclopropyloxindole], an additional product was obtained. The undesired diastereomer of the cyclopropanation underwent a DVCPR with the benzylic core of the oxindole and a cyclohepta[*b,c*]indole was formed. This discovery led to a new research directory and showed potential for the functionalization of the indole C-5 position, which can be applied to the synthesis of molecules such as ambiguine isonitriles (**2**).

The first approach was therefore a partial success, however methodology development was not possible with this initial synthetic entry.

As a consequence of the difficulties encountered during the first approach, it was decided to forego the *spiro*[cyclopropylindole] and to attach the cyclopropane to either C-2 or C-3 of the indole with a carbon-carbon bond.

The DVCPR could then be established as methodology by performing olefination reactions on a cyclopropyl aldehyde. Cyclohepta[*b*]indoles with substituents in α-position either to C-2 or to C-3 were obtained. Since the cyclopropanes were synthesized enantioselectively and the DVCPR is an enantiospecific reaction, the cyclohepta[*b*]indoles were obtained without loss of stereochemical information. Electron-poor and electron-rich vinyl substituents reacted equally and even quaternary carbons could be established with this methodology. An article was published, detailing the scope of the methology and showing the synthesis of the SIRT IV inhibitor in 92% *ee*.

The DVCPR for the synthesis of cyclohepta[*b*]indoles was demonstrated with success, but the synthetic sequence did not allow for the installation of substituents for the total synthesis of **1**.

A higher substituted cyclopropane had to be synthesized as a second approach towards the total synthesis. Therefore, the synthesis of a cyclopropane attached to indole C-2 was studied. The transition metal-catalyzed cyclopropanation of a diazo reagent as well as a variant of the Corey-Chaikovsky cyclopropanation failed to give the desired tetra-substituted cyclopropane and therefore the C-2 approach was abandoned.

Substituting the indole at C-3 was successful and the synthesis of the cyclopropane was diastereomerically selective. The subsequent installation of a triple substituted double bond was challenging and finally achieved by the 1,4 addition to an alkyne. *In-situ* rearrangement gave the cyclohepta[*b*]indole, which had all carbon-carbon bonds in place for the total synthesis of **1**.

The result was a cyclohepta[*b*]indole with only two unsubstituted carbons in the seven-membered ring. The objective of synthesizing highly substituted cyclohepta[*b*]indoles was

achieved and as a last endeavor the selective substitution of the two remaining carbons was studied.

The benzylic position could be substituted selectively with a hydroxyl group, albeit in low yield. After rearomatization, the remaining cyclic, tri-substituted double bond could be hydroborated in a regioselective and diastereoselective fashion.

A total synthesis of **1** could be achieved in five additional steps. Instead of the bromine in **282** an amine would have to be installed. A following tetrahydropyrrole synthesis and subsequent protection with a Boc-group would give **286** (Figure 27). The diastereoselectivity during hydroboration would profit from increased steric hindrance.

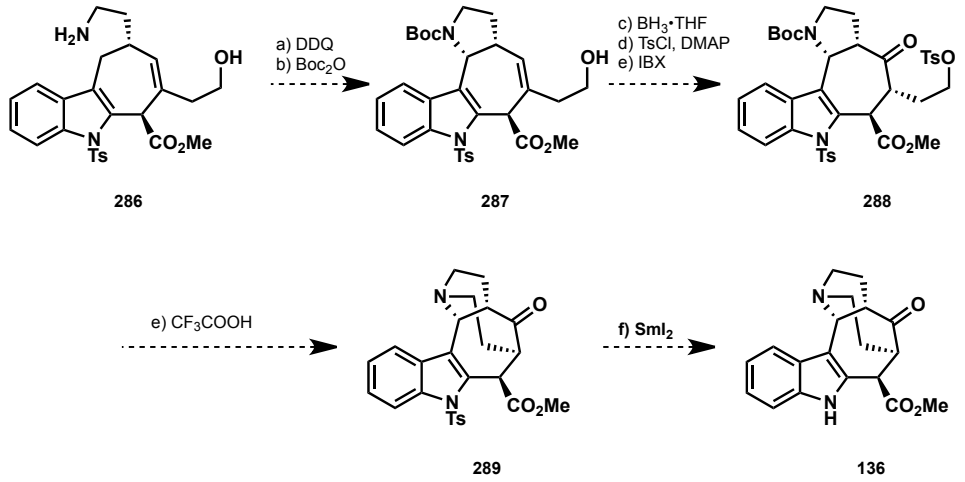


Figure 27 Proposed endgame for the formal synthesis of 1.

The diol from the hydroboration would then be selectively mono-tosylated and the remaining secondary alcohol oxidized to give ketone **288**. By removing the Boc group under treatment with trifluoroacetic acid, a secondary amine would be revealed which should react with the tosylated alcohol to form **289**. Deprotection of the indole nitrogen would then finish the formal synthesis of **1** by synthesizing **136**.

The step-count as crucial point revealed itself to be a issue. As the project progressed, the number of substituents on the cyclopropane decreased and the synthesis became more linear. The combination of low reactivity and the steric hindrance generated by a highly substituted cyclopropane forced to adopt a sequence that allowed to obtain the desired cyclohepta[*b*]indole but failed to do so in a convergent sequence. Intermolecular cyclopropanations or the combinations of large fragments failed to give positive results.

An effort to study in more detail could be the intermolecular synthesis of a cyclopropane like **292** in Figure 28. It is literature known that alkynyldiazocarboxylates like **290** cyclopropanate in high diastereoselectivities with (*Z*)-alkenes to give the desired diastereoselectivity where the alkene substituents are *syn* configured to the alkyne.[99] Therefore reaction of diazo **290** with

azepan **291** could give cyclopropane **292**. Removal of the TMS group and a subsequent Larock indole synthesis could then furnish **293**. Deprotonation of the amide would give the precursor of the DVCPR **294** and cyclohepta[*b*]indole **295** could be obtained in a concise and selective synthesis.

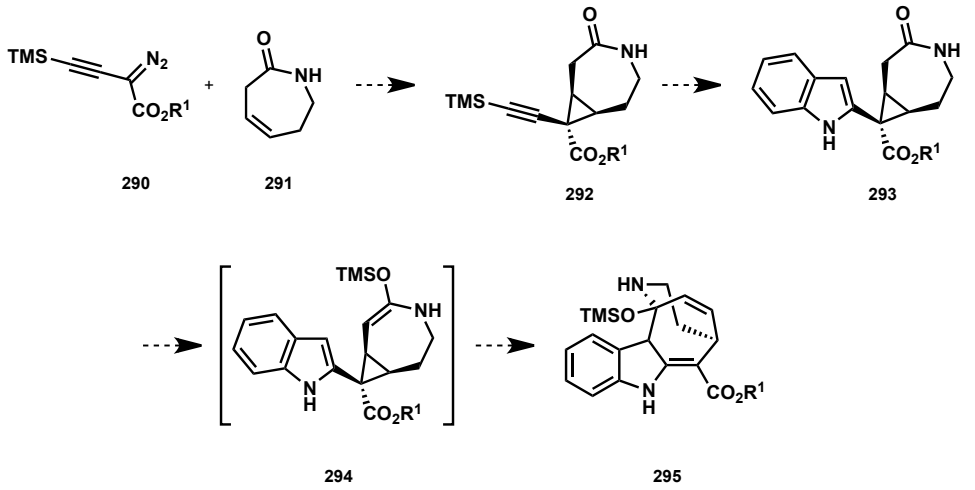


Figure 28 Proposed intermolecular cyclopropanation.

The DVCPR in conjunction with an indole nucleus has been developed and shown to be enantiospecific. Facile installation of functional groups can be achieved as well as the selective derivatisation of the carbons in the resulting cyclohepta[*b*]indole. Although the formal synthesis of **1** was not achieved, the pharmaceutically interesting product SIRT IV inhibitor (**8**) could be obtained enantioselectively.

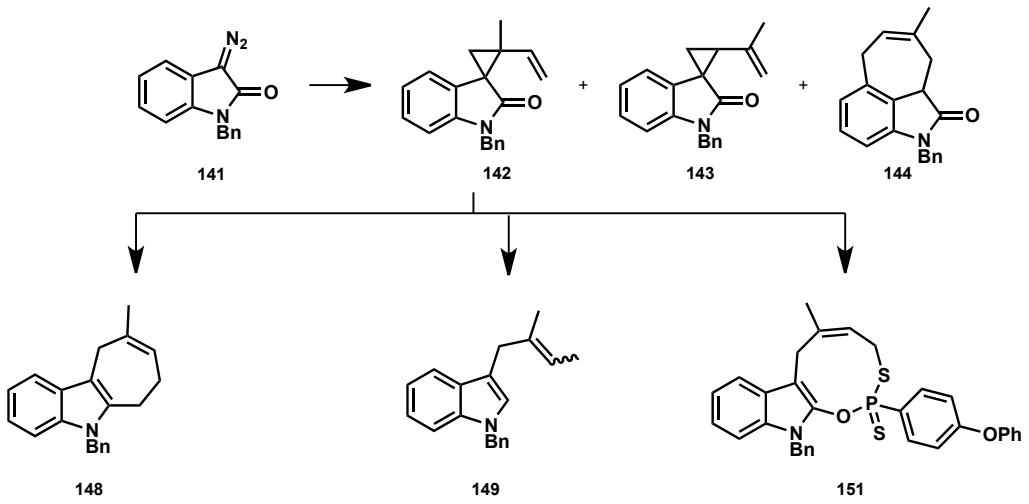
The ongoing research in this research group promises to show more applications of the methodologies developed during these studies.

14 Experimental data

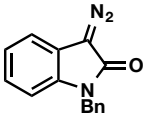
General

All reactions were performed under an inert atmosphere using Argon as the inert gas, using oven-dried glassware unless stated otherwise. Chemicals were used as bought from chemical suppliers. Solvents were used as bought from chemical suppliers or obtained from a dispensory system. THF was used dry after being distilled from Na/benzophenone or as bought from Acros Organics, 99,5 % over molsieves, stabilized. CH_2Cl_2 was used after distillation over CaH_2 or as bought from chemical suppliers. Acetonitrile was used as bought from Acros Organics 99.9 % over molsieves. Acetone was used as bought from Acetone: VMR, technical grade. NEt_3 was used after distillation over CaH_2 or as bought from chemical suppliers. No difference in reactivities/yields was observed using different solvent sources. THF for Pd-catalyzed enolate coupling was used after sparging the solvent with argon for 30 minutes under ultrasonication. TLC was carried put using Macherey-Nagel, ALUGRAM Xtra SIL G/UV254, Aluminium plates, silica 60. Silica gel- NMR-measurements were carried out using Bruker DPX 200 MHz, Bruker AV 400 MHz, Bruker DPX 400 MHz and Bruker DRX 500 MHz. All NMR-spectra are referenced to 7.26 ppm ($CDCl_3$, ^1H) and 77.16 ppm ($CDCl_3$, ^{13}C), 3.31 ppm (methanol-d_4, ^1H) and 49.00 ppm (methanol-d_4, ^{13}C), 7.16 ppm (C_6D_6, ^1H) and 128.06 (C_6D_6, ^{13}C) or 2.50 ppm (DMSO-d_6, ^1H) and 39.52 (DMSO-d_6, ^{13}C). Splitting patterns are reported as such, b = broad, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dddd = doublet of doublets of doublets of doublets, t = triplet, q = quartet, m = multiplet, IR measurements were carried out using Bruker Vector 22. UPLC-MS Spectra were recorded using Waters QTOF-Premier (Waters Aquity Ultra Performance, electron spray ionization). Optical rotations were measured using Perkin Elmer Polarimeter 341.

Graphical Abstract: Intermolecular synthesis of a *spiro*[cyclopropylindole]



1-Benzyl-3-diazo-1,3-dihydro-indol-2-one (141)



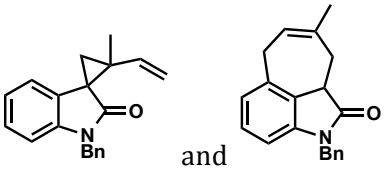
Product was obtained following published procedure (Marti, C.; Carreira, E.M. J. Am. Chem. Soc. **2005**, *127*, 11505-11515).

Yield: 3.25 g (87%)

The spectroscopic data matched the data in the literature.

1'-Benzyl-2-methyl-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (**142**) and

1-Benzyl-4-methyl-2a,3-dihydro-1*H*-cyclohepta[*cd*]indol-2(6*H*)-one (144)



A sealable tube was charged with $Rh_2(OAc)_4$ (40.0 mg, 10.0 µmol, 0.005 equiv.), benzene (2.0 ml) and isoprene (7.00 mL, 70.1 mmol, 35 equiv.). To this mixture was added diazo compound **141** (499 mg, 2.00 mmol, 1 equiv.) in one portion, the tube sealed and stirred at 25 °C for 1.25 h. Subsequently the mixture was concentrated *in vacuo* and purified by flash chromatography (hexanes/EtOAc 5:1). Three products in a ratio of 5.6:2.8:1 were formed during the reaction. Two regiomeric cylcopropanes and cyclohepta[*cd*]indole **144**. Only the higher substituted cyclopropane and the cyclohepta[*cd*]indole were isolated in analytically pure form. The major product is the higher substituted cyclopropane.

Yield combined: 405 mg (69%)

1'-Benzyl-2-methyl-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (142)

^{1}H (400 MHz, $CDCL_3$) δ = 7.36 – 7.24 (m, 5H), 7.16 (dt, J_1 = 11.6 Hz, J_2 = 1.4 Hz, 1H), 7.07 (dd, J_1 = 7.0 Hz, J_2 = 0.8 Hz, 1H), 7.00 (dt, J_1 = 11.3 Hz, J_2 = 1.0 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H) 6.64 (dd, J_1 = 17.1 Hz , J_2 = 10.9, 1H), 5.25 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H), 5.22 (dd, J_1 = 10.1, Hz, J_2 = 1.2 Hz, 1H), 4.99 (dd, J_1 = 45.4 Hz, J_2 = 15.7 Hz, 2H), 2.27 (d, J = 4.8 Hz, 1H), 1.83 (d, J = 5.1 Hz, 1H), 1.56 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 175.1, 143.4, 139.1, 136.3, 128.7, 127.7, 127.5, 127.3, 126.6, 121.9, 121.3, 114.6, 108.8, 44.0, 39.1, 37.0, 31.1, 17.3 ppm.

HRMS (ESI) calculated for $C_{20}H_{11}NO$ 290.1545; found 290.1546.

Rf: 0.5 (hexanes/EtOAc 3:1)

1-Benzyl-4-methyl-2a,3-dihydro-1*H*-cyclohepta[*cd*]indol-2(6*H*)-one (144)

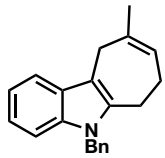
^{1}H (400 MHz, $CDCl_3$) δ = 7.22 – 7.33 (m, 5 H), 7.06 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 1 H), 6.76 (d, J = 7.9Hz, 1H), 6.59 (d, J = 7.5Hz, 1H), 5.53 (d, J= 6.1Hz, 1H), 4.91 (d, J = 2.7Hz, 2H), 3.82 (dd, J_1 = 4.8Hz, J_2 = 13.0Hz, 1H), 3.74–3.78 (m, 1H), 3.19 (dd, J_1 = 7.2Hz, J_2 = 19.1Hz, 1H), 2.78 (ddd, J_1 = 2.9Hz, J_2 = 4.6Hz, J=16.9Hz, 1H), 2.16 (dd, J_1 = 15.4 Hz, J_2 = 15.4 Hz, 1H), 1.79 (s, 3 H) ppm.

^{13}C (100 MHz, CDCl3) δ = 177.6, 142.1, 137.2, 136.0, 134.0, 128.8, 128.6, 127.6, 127.6, 127.3, 122.1, 120.0, 106.8, 43.8, 43.5, 33.6, 32.9, 27.7 ppm.

HRMS (ESI) calculated for $C_{20}H_{11}NO$ 290.1545; found 290.1479.

Rf: 0.7 (hexanes/EtOAc 3:1)

1-Benzyl-9-methyl-5,6,7,10-tetrahydrocyclohepta[*b*]indole (148)



A roundbottom flask was charged with cyclopropane **142** (60.0 mg, 210 µmol, 1 equiv.) and THF (2.1 mL) and then cooled to −78 °C. To this was added MeLi in THF (1.6 M, 140 µL, 224 µmol, 1.05 equiv.). After 15 min. sat. aq. $NaHCO_3$ solution was added and then the reaction was extracted three times with EtOAc. The combined organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in benzene (5 mL) and heated to 80 °C for 16 h. After removal of the solvent the crude products were purified by flash chromatography (hexane/EtOAc 30:1). The product is prone to degradation by oxidation.

Yield (cyclohepta[*b*]indole): 5 mg (8%)

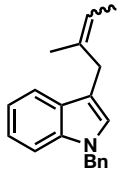
^{1}H (400 MHz, $CDCl_3$) δ = 7.60 – 7.56 (m, 1H), 7.32 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.15 – 7.10 (m, 2H), 7.01 – 6.98 (m, 2H), 5.68 (ddd, J_1 = 7.1 Hz, J_2 = 7.1 Hz, J_3 = 1.3 Hz, 1H), 5.28 (s, 2H), 3.53 (s, 2H), 2.76 (m, 2H), 2.47 (ddd, J_1 = 6.1 Hz, J_2 = 6.1 Hz, J_3 = 6.1 Hz, 1H), 1.92 (s, 3H) ppm.

^{13}C (100 MHz, CDCl3) δ = 141.1, 138.2, 136.5, 135.6, 128.7, 127.1, 126.0, 123.4, 120.8,118.9, 117.4, 108.8, 108.6, 46.1 28.0, 25.6, 24.7, 24.4 ppm

HRMS (ESI) calculated for $C_{21}H_{22}N$ 288.1752; found 288.1757.

Rf: 0.4 (hexane/EtOAc 30:1)

1-Benzyl-3-(2-methylbut-2-en-1-yl)-1*H*-indole (149)



A round bottom flask was charged with 1'-Benzyl-2-methyl-vinylspiro[cyclopropane1,3'-indolin]-2'-one (**142**) (29.0 mg, 100 µmol, 1.0 equiv.) and THF (1 mL) and subsequently cooled to 0 °C. To this was added $LiAlH_4$ in THF (2.4 M, 42.0 µL, 100 µmol, 1 equiv.) and warmed to r.t. over 16 h. The reaction was then poured onto aq. sat. Na/K tartrate solution and stirred vigorously for 2 h. After addition of Et_2O the layers were separated and the aquatic layer was three fold extracted with Et_2O. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexanes/EtOAc 25:1 to 15:1) the product was obtained as colorless liquid.

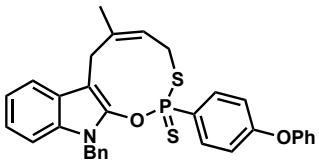
Yield: 11 mg (38%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.63 (d, J = 7.8 Hz, 1H), 7.33 (m, 2), 7.25 (d, J = 7.1 Hz, 1H), 7.18 (ddd, J_1 = 8.0 Hz, J_2 = 7.2 Hz, J_3 = 1.0 Hz, 1H), 7.12 (m, 3H), 6.91 (s, 1H), 5.40 (qq, J_1 = 6.2Hz, J_2 = 0.9 Hz, 1H), 5.31 (s, 2H), 3.52 (s, 2H), 1.80(dd, J_1 = 6.5 Hz, J_2 = 1.4 Hz, 3H), 1.71 (ddt , J_1 =1.5 Hz, J_2 = 1.5 Hz, J_3 = Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 137.9, 136.8, 134.9, 128.7, 128.4, 127.4, 126.6, 126.2, 121.6, 119.5, 119.2, 118.9, 113.6, 109.6, 49.9, 27.2, 23.6, 13.7 ppm.

Rf 0.2 (hexanes/EtOAc 5:1).

(*Z*)-1-Benzyl-6-methyl-2-(4-phenoxyphenyl)-7,12-dihydro-4*H*-[1,3,2]oxathiaphosphonino[9,8-*b*]indole 2-oxide (151)



A roundbottom flask was charged with cyclopropane **142** (200 mg, 690 µmol, 1 equiv.), THF (7 mL) and cooled to 0 °C. Belleau's reagent (220 mg, 420 µmol, 0.6 equiv.) was added and the reaction stirred for 16 h while slowly warming to r.t. The reaction was quenched with sat. aq. $NaHCO_3$ solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and filtered through a short silica plug using a mixture of hexane and EtOAc as eluent (hexane/EtOAc 10:1). The resulting mixture was concentrated and the residue was digerated in hexane/EtOAc 3:1. The resulting solid was the title compound in analytically pure form.

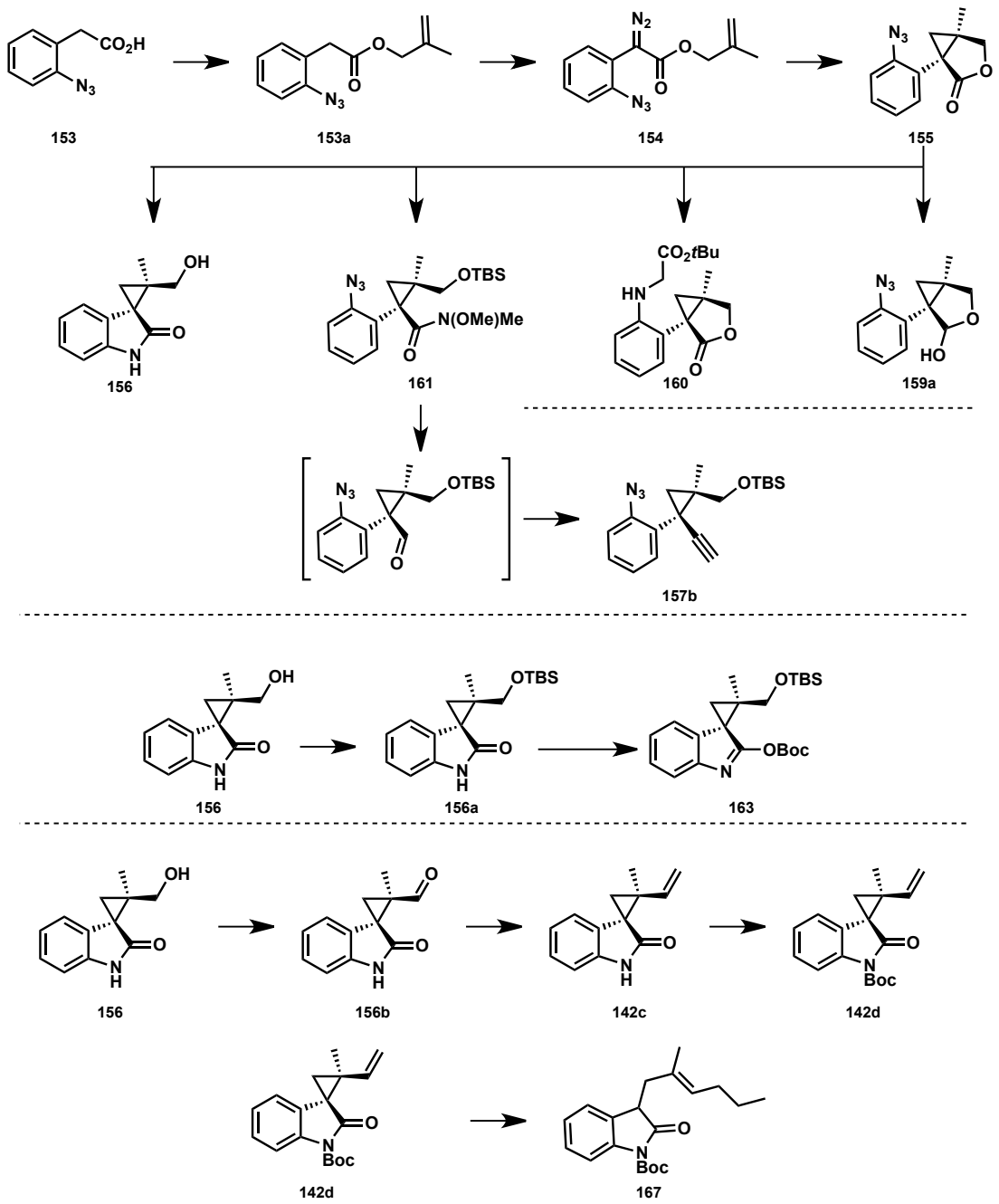
Yield 64 mg (30%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.90 (m, 1H), 7.87 (m, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.43 (m, 2H), 7.24 (dddd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, J_4 = 0.9 Hz, 1H), 7.19-7. 90 (m, 5H), 7.09 - 7.04 (m, 3H), 6.94 (m, 1H), 6.92 (m, 1H), 6.76 (m, 2H), 5.54 (dd, J_1 = 11.1 Hz, J_2 = 5.6 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 4.78 (d, J = 16.7 Hz, 1H), 4.49 (ddd, J_1 = 16.9 Hz, J_2 = 14.2 Hz, J_3 = 11.6 Hz, 1H), 4.14 (dd, J_1 = 14.5 Hz, J_2 = 3.6 Hz, 1H), 3.55 (ddd, J_1 = 26.3 Hz, J_2 = 14.2 Hz, J_3 = 5.6 Hz, 1H), 3.27 (d, J = 14.7 Hz, 1H), 1.72 (s, 3H) ppm.

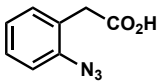
^{13}C (100 MHz, $CDCl_3$) δ = 162.0, 155.3, 139.8, 136.8, 133.2, 133.0, 131.9, 130.1, 123.3, 128.2, 127.0, 126.9, 126.9, 126.0, 124.8, 121.2, 120.4, 120.2, 119.8, 118.1, 117.4, 117.3, 109.4, 99.6, 45.3, 30.5, 25.8, 23.4 ppm.

Rf: 0.15 (hexane/EtOAc 5:1)

Graphical Abstract: Intramolecular synthesis of a *spiro*[cyclopropylindole]



2-Azidophenyl acetic acid (153)

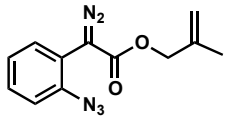


Product was obtained following published procedure (Schwarzer, D.D., Gritsch, P.J.; Gaich, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11514-11516)

The spectroscopic data matches the data in the literature.

Yield: 2.00 g (75%)

2-Methylallyl 2-(2-azidophenyl)-2-diazoacetate (154)

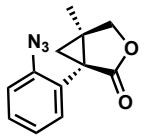


Product was obtained following published procedure (Schwarzer, D.D., Gritsch, P.J.; Gaich, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11514-11516)

The spectroscopic data matches the data in the literature.

Yield: 1.96 g (74%)

1-(2-Azidophenyl)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (155)

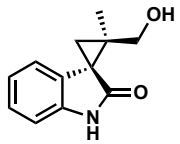


Product was obtained following published procedure (Schwarzer, D.D., Gritsch, P.J.; Gaich, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11514-11516)

The spectroscopic data matches the data in the literature.

Yield: 1.34 g (84%)

2-(Hydroxymethyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (156)

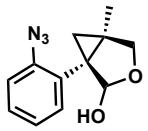


Product was obtained following published procedure (Schwarzer, D.D., Gritsch, P.J.; Gaich, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11514-11516)

The spectroscopic data matches the data in the literature.

Yield: 65 mg (69%)

1-(2-Azidophenyl)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (159a)



Lactone **155** (688 mg, 3.00 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (9 mL) and the resulting solution was cooled to −78 °C. To this was added DiBAL-H in hexane (1 M, 3.5 mL, 3.50 mmol, 1.17 equiv.). After 90 min. TLC showed consumption of starting material and the reaction was quenched by addition of MeOH. Subsequently aq sat. Na/K-tartrate solution was added and the mixture stirred vigorously for 2 h. Three fold extraction with EtOAc, followed by washing with

brine solution and drying over $MgSO_4$ gave after concentration *in vacuo* the crude product which was purified by flash chromatography (hexane/EtOAc 4:1). The product was obtained as a mixture of diastereomers (1.5:1) and used as such.

Yield: 680 mg (93%)

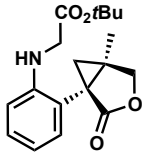
Major diastereomer:

^{1}H (400 MHz, $CDCl_3$) δ = 7.38 - 7.32 (m, 2H), 7.19 - 7.16 (m, 1H), 7.14 (m, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 4.10 (d, *J* = 8.1 Hz, 1H), 3.89, (d, *J* = 8.1 Hz, 1H), 1.21 (s, 3H), 1.09 (d, *J* = 4.3 Hz, 1H), 1.05 (s, 1 H), 0.71 (d, *J* = 4.5 Hz, 1H) ppm.

^{13}C (125 MHz, $CDCl_3$) δ = 134.4, 133.2, 129.0, 128.9, 125.2, 125.1, 118.2, 118.0, 102.2, 82.6, 73.1, 72.0, 29.7, 20.7, 14.7, 14.5, 14.4 ppm.

Rf: 0.5 (hexane/EtOAc 1:1)

Tert-butyl (2-(5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phenyl)glycinate (160)



Di*iso*propylamine (46 µL, 330 µmol, 1.3 equiv.) was dissolved in THF (1 mL) and cooled to −78 °C. To this was added *n*BuLi in hexanes (2.5 M, 130 µL, 330 µmol, 1.3 equiv.) and stirred for 20 min before being warmed to 0 °C. After 20 min. the reaction was again cooled to −78 °C and *t*BuOAc (40 µL, 300 µmol, 1.2 equiv) was added. After 1 h, 1-(2-azidophenyl)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (**155**) was added and the reaction was stirred for an additional hour. Subsequently aq. sat. NH_4Cl solution was added and the reaction was extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified with flash chromatography (hexanes/EtOAc 2:1).

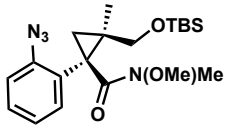
Yield 110 mg (64%).

^{1}H (200 Mhz, $CDCl_3$) δ = 8.37 (b, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, J_1 = 5.8 Hz, J_2 = 3.0 Hz, 1H), 7.33 (m, 1H), 7.29 (m, 1H), 7.25 (m, 1H), 4.43 (d, *J* = 8.9 Hz, 1H), 4.28 (d, *J* = 10.3 Hz, 1H), 4.26 (s, 2H), 1.62 (d, *J* = 4.9 Hz, 1H), 1.54 (s, 9H), 1.42 (d, *J* = 5.1 Hz, 1H), 1.04 (s, 3H) ppm.

IR (ATR): 3294, 3068, 2674, 1741, 1425, 1382, 1282, 1219, 1120, 1082, 1053, 767, 748, 713, 657, 584, 559, 545, 509, 480, 416.

Rf 0.1 (hexanes/EtOAc 2:1).

1-(2-Azidophenyl)-2-(hydroxymethyl)-*N*-methoxy-*N*,2-dimethylcyclopropanecarboxamide (161)



A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (293 mg, 3.00 mmol, 3 equiv.) in CH_2Cl_2 (3 mL) was cooled to −15 °C, $AlMe_3$ in hexanes (2M, 1.45 mL, 2.90 mmol, 2.9 equiv.) was added and the mixture was subsequently warmed to 0 °C over 1 h followed by cooling to −15 °C. Then lactone **155** (230 mg. 1.00 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added. The reaction was warmed to ambient temperature over 12 h and quenched by addition of aq. sat. Na/K tartrate solution. After vigorously stirring for 0.5 h the mixture was extracted three times with EtOAC, the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in DMF (0.7 mL), imidazole (272 mg, 4.00 mmol, 4 equiv.) and TBSCl (301 mg, 2.00 mmol, 2 equiv.) were added and the reaction was stirred for 2 h. The reaction was quenched by addition of water and extracted three times EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was obtained after purification *via* flash chromatography (hexane/EtOAc 7:1 to 5:1)

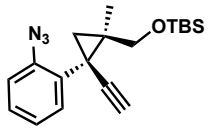
Yield: 370 mg (91%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.50 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.32 (m, 1H), 7.16 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.09 (dt, J_1 = 3.8 Hz, J_2 = 1.1 Hz, 1H), 3.81 (d, *J* 10.6 Hz, 1 H), 3.58 (d, *J* = 10.2 Hz, 1H), 3.31 (s, 3H), 3.16 (s, 3 H), 1.81 (d, *J* = 4.4 Hz, 1H), 1.13 (s, 3H), 0.99 (d, *J* = 5.1 Hz, 1H), 0.93 (s, 9H), 0.84 (s, 3H), 0.72 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 178.3, 140.6, 134.3, 129.5, 128.2, 123.7, 118.4, 67.4, 60.1, 35.6, 34.2, 31.3, 26.0, 25.7, 24.4, 18.4, −5.2, −5.3 ppm.

Rf: 0.7 (hexane/EtOAc 1:1)

((2-(2-Azidophenyl)-2-ethynyl-1-methylcyclopropyl)methoxy)(*tert*-butyl)dimethylsilane (157b)



Weinrebamide **161** (40.0 mg, 99.0 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (500 µL) and cooled to −78 °C. To this was added DiBAL-H in hexanes (1 M, 300 µL, 300 µmol, 3 equiv.) and stirred for 1 h. Subsequently aq. sat. Na/K tartrate solution and Et_2O were added and the reaction stirred vigorously at r.t. for 5 h. The reaction was then extracted three times with Et_2O and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and

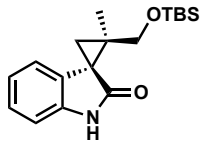
concentrated *in vacuo*. The resulting crude aldehyde (31.0 mg) was taken up in MeOH (500 µL) and dimethyl (1-diazo-2-oxopropyl) phosphonate (38.0 mg, 198 µmol, 2 equiv.) as well as K_2CO_3 (55.0 mg, 399 µmol, 4 equiv.) were added. The reaction was stirred for 3 h at r.t. followed by addition of water. The reaction was then extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The title compound was obtained after flash chromatography (hexane/EtOAc 40:1 to 20:1) as yellow oil.

Yield: 2 mg (5% over two steps)

^{1}H (400 MHz, $CDCl_3$) δ = 7.32 (dd, J_1 = 3.8 Hz, J_2 = 1.5 Hz, 1H), 7.25 (d, J = 6.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.10 (dt, J_1 = 3.8 Hz, J_2 = 1.0 Hz, 1H), 4.06 (d, J = 9.2 Hz, 1 H), 3.82 (d, J = 10.6 Hz, 1H), 2.01 (s, 1H), 1.27 (d, J = 4.12 Hz, 1H), 1.20 (d, J = 4.4 Hz, 1H), 0.98 (s, 9H), 0.86 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H).

Rf: 0.85 (hexane/EtOAc 10:1)

2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (156a)



Alcohol **156** (406 mg, 2.00 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (1 mL), imidazole (327 mg, 4.80 mmol, 2.4 equiv.) and subsequently TBSCl (361 mg, 2.40 mmol, 1.2 equiv.) were added and the reaction was stirred 1 h at r.t. After quenching with water, the reaction was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product was achieved by flash chromatography (hexane/EtOAc 7:1).

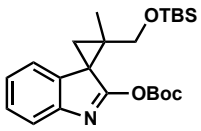
Yield: 541 mg (85%).

^{1}H (400 MHz, C_6D_6) δ = 9.27 (s, 1H), 6.97 (dt, J_1 = 3.84 Hz, J_2 = 1.1 Hz, 1H), 6.79 (dt, J_1 = 3.8 Hz, J_2 = 1.1 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 4.34 (d, J = 10.2 Hz, 1H) 4.03 (d, J = 9.9 Hz, 1H), 1.81 (d, J = 4.8 Hz, 1H), 1.32 (s, 3H), 1.11 (d, J = 4.8 Hz, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C (125 MHz, C_6H_6) δ = 178.2, 142.1, 129.2, 126.4, 121.9, 120.9, 109.6, 64.0, 37.7, 35.9, 28.6, 25.9, 18.4, 17.3, −5.3, −5.4 ppm

Rf: 0.8 (1:1)

Tert-butyl (2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylspiro[cyclopropane-1,3'-indol]-2'-yl) carbonate (163)



Indole **156a** (487 mg, 1.53 mmol, 1 equiv.) was dissolved in THF (7.7 mL), DMAP (39.0 mg, 310 µmol, 0.2 equiv.) and subsequently Boc_2O (402 mg, 1.84 mmol, 1.2 equiv.) were added and the mixture was stirred for 16 h. The solvent was evaporated and the crude product was purified by flash chromatography (hexane/EtOAc 30:1) and obtained as a white solid.

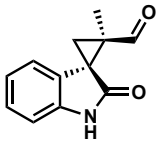
Yield: 630 mg (98%)

^{1}H (400 MHz, C_6D_6) δ = 8.30 (d, J = 8.5 Hz, 1H), 7.05 (dt, J_1 = 4.0 Hz, J_2 = 1.2 Hz, 1H), 6.84 (dt, J_1 = 3.8 Hz, J_2 = 1.1 Hz, 1H), 6.55, (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 4.19 (d, J = 10.2 Hz, 1H), 3.77 (d, J = 10.6 Hz, 1H), 1.70 (d, J = 5.1 Hz, 1H), 1.53 (s, 3H), 1.23 (s, 3H), 1.01 (d, J = 4.8 Hz, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H) ppm.

^{13}C (100 MHz, C_6D_6) δ = 172.5, 150.0, 140.7, 126.8, 122.9, 121.2, 115.0, 82.6, 63.8, 39.5, 35.7, 28. 3, 27.9, 25.9, 18.2, 16.8, −5.3, −5.5 ppm.

Rf: 0.2 (hexane/EtOAc 30:1)

2-Methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (156b)

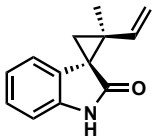


Product was obtained following published procedure (Schwarzer, D.D., Gritsch, P.J.; Gaich, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11514-11516)

The spectroscopic data matches the data in the literature.

Yield: 423 mg (92%)

2-Methyl-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (142c)



A suspension of methyl triphenylphosphonium bromide (3.00 g, 8.41 mmol, 4 equiv.) in THF (10 mL) was cooled −78 °C and NaHMDS in THF (2 M, 4.20 mL, 8.40 mmol, 4equiv.) was added. The reaction was stirred for 10 min at −78 °C and then for 20 min at 0 °C before being cooled back to −78 °C. Then aldehyde **156b** (423 mg, 2.10 mmol, 1 equiv.) dissolved in THF (5 mL) was added and the reaction slowly warmed to ambient temperature over 16 h. Subsequently aq. sat. NH_4Cl solution was added and the reaction three times extracted with EtOAc. The combined

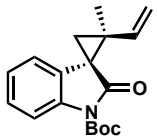
organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was subsequently purified by flash chromatography (hexane/EtOAc 2:1) and the product was obtained as white solid.

Yield 388mg (93%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.14 (b, 1H), 7.19 (ddd, J_1 = 7.8 Hz, J_2 = 6.6 Hz, J_3 = 2.1 Hz, 1H), 7.03 - 6.97 (m, 2H), 6.92 (bd, J = 7.8 Hz, 1H), 6.57 – 6.48 (m, 1H), 5.20 (s, 1H), 5.16 (dd, J_1 = 5.8 Hz, J_2 = 1.4 Hz, 1H), 2.17 (d, J = 5.1Hz, 1H), 1.77 (d, J = 5.1 Hz, 1H), 1.50 (s, 3H) ppm.

^{13}C (125 MHz, $CDCl_3$) δ = 176.9, 141.4, 138.8, 1258.3, 126.7, 122.2, 121.2, 114.6, 109.5, 39.4, 37.1, 31.0, 17.1 ppm.

2-*Tert*-butyl-2-methyl-2'-oxo-2-vinylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (142d)



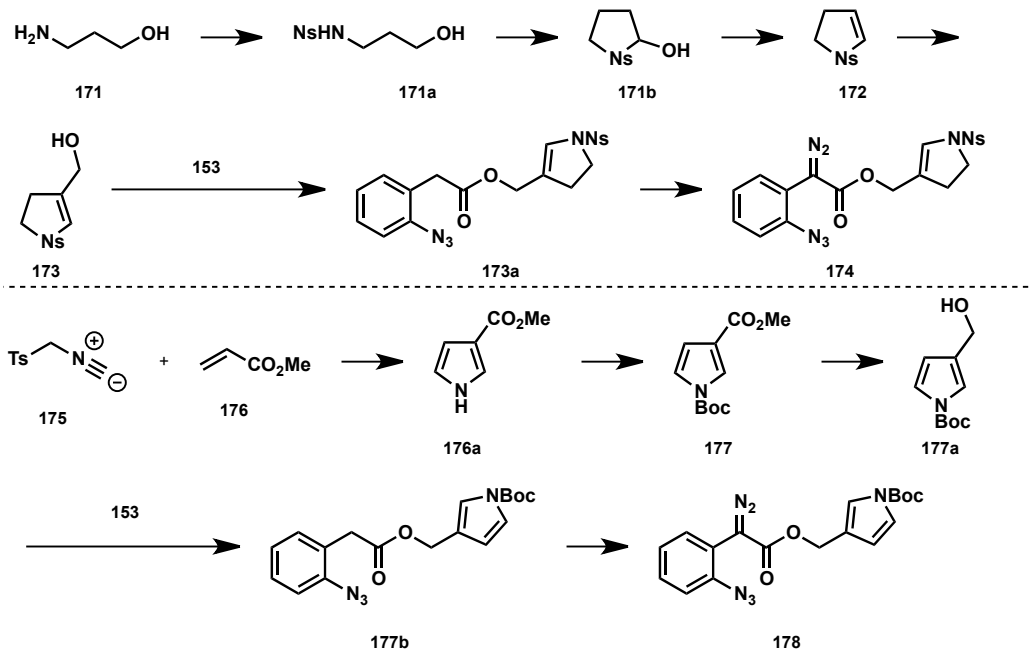
Indole **142c** (100 mg, 500 µmol, 1 equiv.) was dissolved in THF (2.5 mL), DMAP (13 mg, 100 mmol, 0.2 equiv.) and subsequently Boc_2O (131 mg, 600 µmol, 1.2 equiv.) were added and the mixture was stirred for 2.5 h at 20 °C. The solvent was evaporated and the crude product was purified by flash chromatography (hexane/EtOAc 10:1).

Yield: 130 mg (85%)

^{1}H (200 MHz, $CDCl_3$): 7.93 (m, 1H), 7.26 (m, 1H), 7.20 (m, 1H); 7.07 (m, 1H), 6.46 (m, 1H), 5.28 (dd, J_1 = 2.1 Hz, J_2 = 1.2 Hz, 1H), 5.21 (dd, J_1 = 5.1Hz, J_2 = 1.2 Hz, 1H), 2.27 (d, J = 5.5 Hz, 1H), 1.82 (d, J = 5.1 Hz, 1H), 1.69 (s, 9H), 1.51 (s, 3H).

Rf: 0.5 (hexane/EtOAc 1:1)

Graphical abstract: Attempt to synthesize higher substituted cyclopropanes



1-((4-Nitrophenyl)sulfonyl)-2,3-dihydro-1*H*-pyrrole (172)

3-Amino-1-propanol (4.5 mL, 48.8 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (250 mL) and DMAP (1.2 g, 9.80 mmol, 0.2 equiv.), Et_3N (9.5 mL, 68.3 mmol, 1.4 equiv.) and finally 4-nitrophenylsulfonyl chloride (11.36 g, 51.3 mmol, 1.05 equiv.) were added. The reaction was stirred for 24 h at r.t. and then aq. sat. NH_4Cl solution was added. Three-fold extraction with CH_2Cl_2 was followed by washing the combined organic layers with brine solution, drying over $MgSO_4$, filtering and concentrating *in vacuo*. The crude product **171a** was purified by recrystallization (CH_2Cl_2-MeOH 100:1) (crude yield 7.81 g (58%)).

A part of the *N*-protected 3-Amino-1-propanol **171a** (1.41 g, 5.16 mmol, 1 equiv.) was dissolved in DMSO (26 mL) and IBX (2.89 g, 10.31 mmol, 2 equiv.) was added. The reaction was stirred at r.t. for 16 h and subsequently water was added and the reaction was extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **171b**.

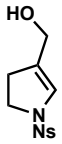
A part of the crude **171b** (750 mg, 2.76 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (50 mL) and cooled to −78 °C. To this was added DMAP (70 mg, 600 µmol, 0.2 equiv.) and TFAA (390 µL, 2.76 mmol, 1 equiv.). The reaction was allowed to warm to r.t. over 16 h and subsequently Et_3N (7.7 mL, 55.2 mmol, 20 equiv.) was added. The mixture was stirred at r.t. for 24 h and then water was added. The reaction was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered concentrated *in vacuo*.

The product was purified *via* flash chromatography (hexane/EtOAc 2.5:1)

Yield: 0.50 g (71%)

^{1}H (400 MHz, , CD_3OD) δ = 8.86 (ddd, J_1 = 8.9 Hz, J_2 = 1.9 Hz, J_3 = 1.7 Hz, 2 H), 8.08 (ddd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, J_3 = 2.0 Hz, 2 H), 6.47 (m, 1H), 5.29 (m, 1H), 3.57 (t, J = 9.0 Hz, 2H), 2.49 (ddd, J_1 = 4.5 Hz, J_2 = 2.4 Hz, J_3 = 2.4 Hz, 2 H) ppm.

(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methanol (173)



DMF (1.94 mL, 25.5 mmol, 13 equiv.) was added to CH_2Cl_2 (9.8 mL), cooled to 0 °C and subsequently $(COCl)_2$ (420 µL, 4.86 mmol, 2.5 equiv.) was added. The reaction was stirred at 0 °C for 30 min. and then dihydro-pyrrole **172** (490 mg, 1.96 mmol, 1 equiv.) dissolved in CH_2Cl_2 (4 mL) was added. The reaction was warmed to r.t. over 16 h and then aq. sat. $NaHCO_3$ solution was added. The mixture was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude product (230 mg, 810 µmol, 1 equiv.) was dissolved in THF (4 mL) and cooled to −78 °C followed by addition of DiBAl-H in hexane (1 M, 980 µL, 980 µmol, 1.2 equiv.). The reaction was stirred at −78 °C for 15 min. and then aq. sat. Na/K tartrate solution was added. The biphasic solution was stirred vigorously for 5 h and then extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

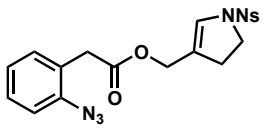
The crude product was purified by flash chromatography (hexane/EtOAc 1:1 to 1:1.5).

Yield: 230 mg (42%)

^{1}H (400 MHz, CD_3OD) δ = 8.44 (ddd, J_1 = 9.2 Hz, J_2 = 2.2 Hz, J_3 = 2.2 Hz, 2 H), 8.06 (ddd, J_1 = 9.4 Hz, J_2 = 2.2 Hz, J_3 = 2.2 Hz, 2 H), 6.38 (m, 1H), 4.04 (d, J = 1.0 Hz, 1H), 4.04 (d, J = 1.0 Hz, 1H), 3.61 (m, 2H), 2.49 (m, 2H) ppm.

Rf: 0.1 (hexane/EtOAc 1:1)

(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methyl 2-(2-azido-phenyl)acetate (173a)



Alcohol **173** (39.0 mg, 140 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (1 mL) followed by acid **153** (25.0 mg, 140 µmol, 1 equiv.), DMAP (300 µg, 28.0 µmol, 0.2 equiv.) and DIC (22 µL, 140 µmol, 1 equiv.). The reaction was stirred for 16 h and then water was added. The mixture was

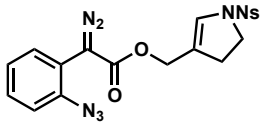
extracted three times with CH_2Cl_2, the combined organic layers washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane/EtOAc 3:1).

Yield 51 mg (83%)

^{1}H (200 MHz, C_6D_6) 7.56 (m, 2H), 7.34 (m, 2H), 6.87 (m, 2H), 6.76 (m, 1H), 6.65 (m, 1H), 6.16 (s, 1H), 4.24 (d, J = 1.1 Hz, 1H) 4.23 (d, J = 1.1 Hz, 1H), 3.34 (s, 2H), 3.04 (dd, J_1 = 9.5 Hz, J_2 = 8.7 Hz, 2H), 1.82 (ddd, J_1 = 9.2 Hz, J_2 = 1.1 Hz, J_3 = 0.8 Hz, 2H) ppm.

Rf: 0.8 (hexane/EtOAc 1:1)

(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methyl 2-(2-azidophenyl)-2-diazoacetate (174)



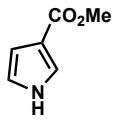
Ester **173a** (39.0 mg, 90.0 µmol, 1 equiv.) was dissolved in MeCN (0.5 mL) followed by the addition of ABSA (30.0 mg, 120 µmol, 1.4 equiv.) and DBU (27 µL, 180 µmol, 2 equiv.). The reaction was stirred for 40 min. and then it was quenched with water. The solution was extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane/EtOAc 3:1).

Yield: 30 mg (71%)

^{1}H (200 MHz, C_6D_6) δ = 7.59 (m, 3H), 7.33 (m, 3H), 6.80 (m, 2H), 6.53 (m, 1H), 6.17 (s, 1H), 4.32 (s, 1H), 3.02 (dt, J_1 = 9.7 Hz, J_2 = 9.3 Hz, 2H), 1.83 (m, 2H) ppm.

Rf 0.5 (hexane/EtOAc 3:1)

Methyl 1*H*-pyrrole-3-carboxylate (176)



Methylacrylate (2.34 mL, 25.9 mmol, 1.01 equiv.) and tosyl-methylisocyanat (5.00 g, 25.6 mmol, 1.0 equiv.) were dissolved in THF (40 mL) and were added dropwise over 12 h to a solution of KO*t*-Bu (3.60 g, 32.0 mmol, 1.25 equiv.) in THF (40 mL). The reaction was subsequently stirred for additional 4 h and then quenched by addition of water. The mixture was extracted three times with EtOAc and the combined organic layers washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography (hexane/EtOAc 4:1).

Yield: 1.26 g (40%)

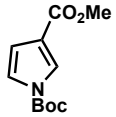
^{1}H (200 MHz, $CDCl_3$) δ = 8.51 (b, 1H), 7.44 (m, 1H), 6.76 (m, 1H), 6.66 (m, 1H), 3.82 (s, 3H)

IR (ATR): 2978, 1726, 1721, 1473, 1423, 1369, 1327, 1269, 1257, 1219, 1157, 1116, 1089, 1024, 968, 938, 908, 812, 769, 740, 613, 472, 433 cm^{-1}.

HRMS (ESI) calculated for $C_6H_7NO_2Na^+$ 148.0374; found 148.0377.

Rf: 0.4 (hexane/EtOAc 1:1)

1-*Tert*-butyl 3-methyl 1*H*-pyrrole-1,3-dicarboxylate (177)



Pyrrole **176** (1.26 g, 10.1 mmol, 1 equiv.) was added to MeCN (20 mL) followed by Boc_2O (2.42 g, 11.1 mmol, 1.1 equiv.), DMAP (1.29 g, 10.6 mmol, 1.05 equiv.) and lastly Et_3N (1.54 mL, 11.08 mmol, 1.1 equiv.). The reaction was stirred for 16 h and then aq. sat. NH_4Cl solution was added. The mixture was extracted three times with EtOAc and the combined organic layers washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by flash chromatography (hexane/EtOAc 25:1).

Yield: 1.86 g (82%)

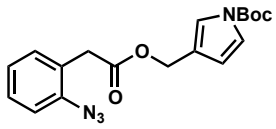
^{1}H (200 MHz, $CDCl_3$) δ = 7.82 (dd, J_1 = 2.0 Hz, J_2 = 1.7 Hz, 1H), 7.20 (dd, J_1 = 3.3 Hz, J_2 = 2.2 Hz, 1H, 6.59 (dd, J_1 = 3.3 Hz, J_2 = 1.6 Hz, 1H), 3.83 (s, 3H), 1.60 (s, 9H) ppm.

IR (ATR): 1739, 1712,1560, 1494, 1477, 1458, 1446, 1402, 1367, 1325, 1282, 1257, 1238, 1195, 1172, 1087, 987, 972, 925 883, 848, 829, 794, 773, 758, 731, 603, 586, 555, 534, 472, 447, 430, 418cm^{-1}.

HRMS (ESI) calculated for $C_{11}H_{16}NO_4$ 226.1079; found 226.1082.

Rf: 0.3 (hexane/EtOAc 20:1)

***Tert*-butyl 3-((2-(2-azidophenyl)acetoxy)methyl)-1*H*-pyrrole-1-carboxylate (177b)**

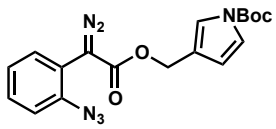


Ester **177** (1.72 g, 7.64 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (40 mL) and cooled with a diethylether-dry ice bath to −100 °C. To this DiBAL-H in hexane (1M, 16.1 mL, 16.1 mmol, 2.1 equiv.) was added over 1 h *via* syringe pump and then stirred for additional 15 min. before being poured onto aq. sat. Na/K tartrate and stirred vigorously for 5 h. The mixture was extracted three times with EtOAc, the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **177a**.

The crude alcohol was dissolved in CH_2Cl_2 (40 mL) followed by the addition of acid **153** (1.35 g, 7.64 mmol, 1 equiv.) and DMAP (0.19 g, 1.53 mmol, 0.2 equiv.). The reaction was cooled to 0 °C

and then DIC (1.20 mL, 7.64 mmol, 1 equiv.) was added. The reaction mixture was allowed to warm to r.t. and was stirred for 16 h. The reaction was then quenched by addition of water and the mixture was extracted three times with CH_2Cl_2 and subsequently the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.
Purification by flash chromatography (hexane/EtOAc 10:1) furnished the title compound.
Yield: 1.83 g (67%)
^{1}H (200 MHz, $CDCl_3$) δ = 7.37 (m, 1H), 7.25-7.03 (m, 5 H), 6.21 (dd, J_1 = 3.2 Hz, J_2 = 1.7 Hz, 1H), 5.01 (s, 2H), 3.62 (s, 2H), 1.59 (s, 9H) ppm.
IR (ATR) 2121, 1735, 1585, 1489, 1452, 1408, 1369, 1350, 1323, 1284, 1247, 1149, 1068, 972, 850, 829, 796, 771, 752, 721, 657, 590, 534, 486, 430, 414 cm^{-1}.
HRMS (ESI) calculated for $C_{18}H_{20}N_4O_4Na^+$ 379.1382; found 379.1385.
Rf: 0.4 (hexane/EtOAc 5:1)

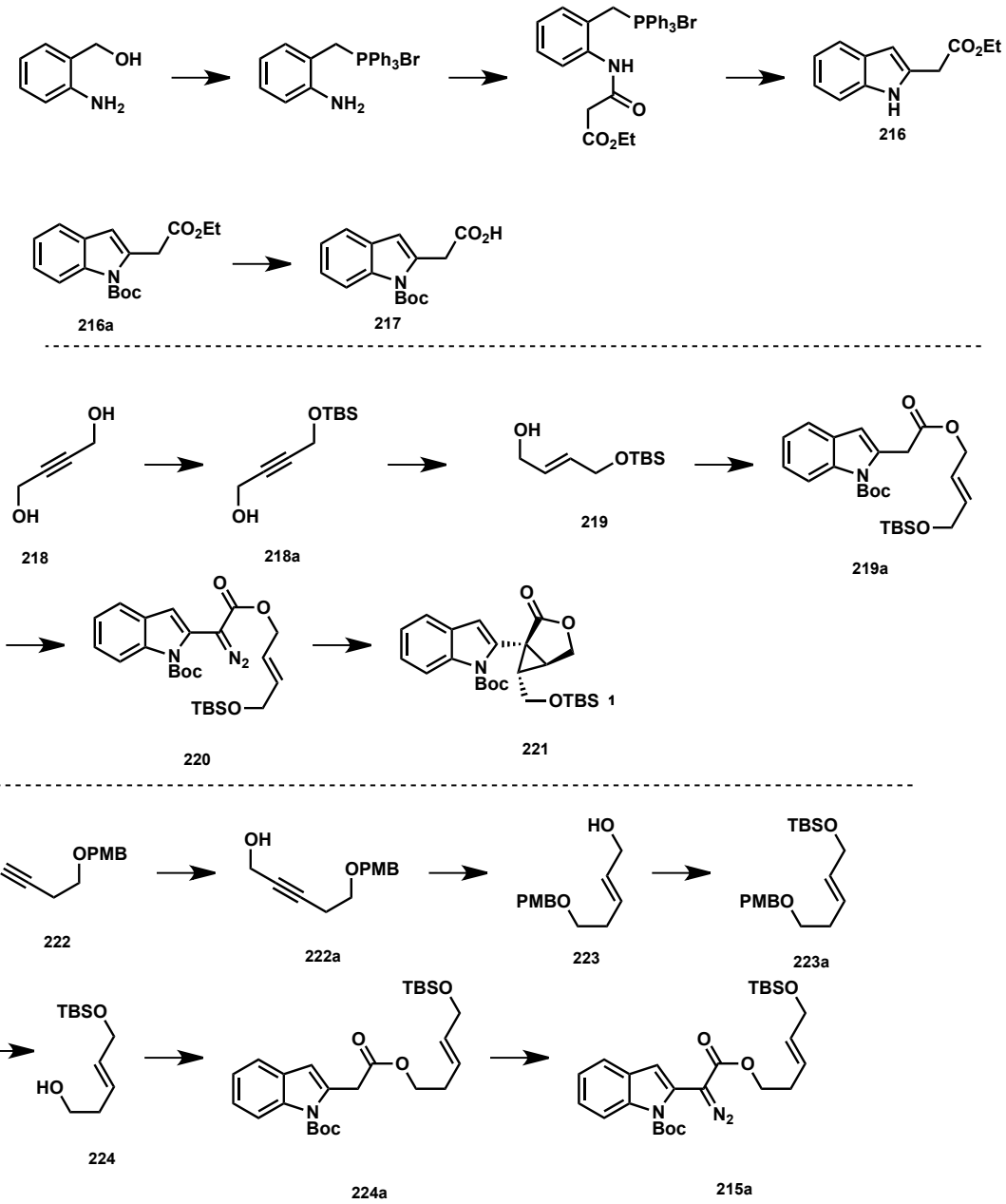
***Tert*-butyl 3-((2-(2-azidophenyl)-2-diazoacetoxy)methyl)-1*H*-pyrrole-1-carboxylate (178)**



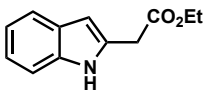
Ester **177b** (240 mg, 670 µmol, 1 equiv.) was dissolved in MeCN (3.4 mL) and to this was added ABSA (372 mg, 1.55 mmol, 2.3 equiv.) and DBU (260 µL, 1.74 mol, 2.6 equiv.). The reaction was stirred for 16 h at 20 °C and then quenched by addition of water. The mixture was extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.
Purification by flash chromatography (hexane/EtOAc 10:1) furnished the title compound.
Yield: 233 mg (91%)
^{1}H (200 MHz, $CDCl_3$) δ = 7.34 (m, 1H), 7.15 – 7.10 (m, 1H); 7.08 (m, 1H), 7.04-6.92 (m, 3H), 6.07 (dd, J_1 = 3.2 Hz, J_2 = 1.7 Hz, 1H); 4.93 (s, 2H), 1.39 (s, 9H) ppm.
IR (ATR): 2125, 2094, 1741, 1697, 1575, 1492, 1448, 1408, 1369, 1354, 1338, 1282, 1249, 1155, 1101, 1070, 1016, 991, 974, 850, 829, 808, 771, 754, 684, 592 cm^{-1}.
HRMS (ESI) calculated for $C_{18}H_{18}N_6O_4Na^+$ 405.1287; found 405.1290.
Rf: 0.4 (Hex 10:1)

Methodolgy Development: see Supplementary Information provided to the article: Gritsch, P.J.; Stempel, E.; Gaich, T. *Org. Lett.* **2013**, *15(21)*, 5472-5475.

Graphical abstract: Indole C-2 vinylcyclopropane: intramolecular approach.



Ethyl 2-(1*H*-indol-2-yl)acetate (216)

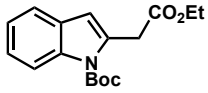


Product was obtained following published procedure (Coulton, S.; Gilchrist, T.L.; Graham, K. *J. Chem. Soc. Perkin Trans.* **1998**, *7*, 1193-1202)

The spectroscopic data matches the data in the literature.

Yield: 1.2 g (20% over 3 steps)

***Tert*-butyl 2-(2-ethoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (216a)**



Indole **216** (58 mg, 280 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (1.4 mL) and DMAP (6.80 mg, 56.0 µmol, 0.2 equiv.) and subsequently Boc_2O (93.0 mg, 430 µmol, 1.5 equiv.) were added. The reaction was stirred at r.t. for 2.5 h and then quenched by addition of water. The reaction was three times extracted with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the pure compound was obtained as a white solid.

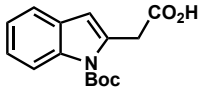
Yield: 71 mg (84%)

^{1}H (400 MHz, $CDCl_3$), δ = 8.09(dd, J_1 = 4.2 Hz, J_2 = 1.7 Hz 1H), 7.49 (m, 1H), 7.27 (m, 1H), 7.20 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.9 Hz 1H), 6.47 (dd, J_1 = 1.5 Hz, J_2 = 0.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.03 (s, 2H), 1.66 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 170.4, 150.5, 136.7, 133.5, 128.9, 123.9, 122.7, 120.2, 115.7, 110.3, 84.2, 60.9, 36.4, 28.2, 14.2 ppm.

Rf: 0.6 (hexane/EtOAc 4:1)

2-(1-(*Tert*-butoxycarbonyl)-1*H*-indol-2-yl)acetic acid (217)



Ester **216a** (3.00 g, 10.4 mmol, 1 equiv.) was dissolved in THF (40 mL) and LiOH (260 mg, 10.4 mmol, 1.05 equiv.) in water (15 mL) was added. The reaction was stirred for 16 h and, although not finished, three times extracted with Et_2O. The aqueous layer was then acidified with aq. sat. NH_4Cl solution and three times extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the acid in analytical pure form.

Yield: 1 .01 g (35%, 70% brsm)

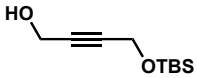
^{1}H (400 MHz, $CDCl_3$) δ = 8.07 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 7.51 Hz, 1H), 7.27 (m, 1H), 7.20 (ddd, J_1 = 7.4 Hz, J_2 = 0.9 Hz, J_3 = 0.1 Hz, 1H), 6.50 (s, 1H), 4.08 (s, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 150.6, 136.4, 128.7, 124.2, 124.0, 122.8, 120.4, 120.3, 115.7, 110.7, 84.6, 28.2 ppm.

HRMS (ESI) calculated for $C_{15}H_{17}NO_4Na^+$ 298.1039; found 298.1053.

Rf: 0.05 (hexane/EtOAc 20:1)

4-((*Tert*-butyldimethylsilyl)oxy)but-2-yn-1-ol (218a)



A round bottom flask was charged with 2-Butin-1,4 diol (17.2 g, 200 mmol, 5 equiv.), triethylamine (6.7 mL, 48 mmol, 1.2 equiv.) and MeCN (400 mL). Subsequently TBSCl (6 g, 40.0 mmol, 1 equiv.) was added. The reaction was stirred for 48 h and then quenched by addition of aq. sat. NH_4Cl solution. The reaction was extracted three times with Et_2O and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. During concentration it was important to not heat the solution above 30 °C.

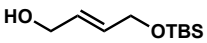
The product was purified with flash chromatography (hexanes/Et_2O 3:1) and obtained as lightly yellow oil.

Yield: 6.4 g (80%)

^{1}H (200 MHz, $CDCl_3$) δ = 4.35 (ddd, J_1 = 3.3 Hz, J_2 = 1.5 Hz, J_3 = 1.5 Hz, 1H), 4.29 (ddd, J_1 = 6.1 Hz, J_2 = 1.8 Hz, J_3 = 1.8 Hz, 1H), 1.80 (t, J = 6.1 Hz, 1H), 0.90 (s, 6H), 0.11 (s, 6H) ppm.

Rf: 0.6 (hexane/EtOAc 2:1)

(*E*)-4-((*Tert*-butyldimethylsilyl)oxy)but-2-en-1-ol (219)



Monoprotected alcohol **218a** (400 mg, 2.00 mmol, 1 equiv.) was dissolved in Et_2O and cooled to 0 °C. Subsequently Red-Al™ in toluene (3.3M, 1.3 mL, 4.40 mmol, 2.2 equiv.) was added drop wise and the reaction was stirred for 45 min. The reaction was then quenched by addition of water and three times extracted with Et_2O. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

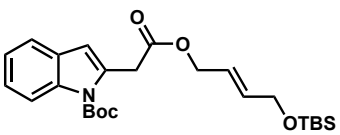
Purification with Kugelrohr distillation (140 °C, 0.13 mbar) gave the compound as clear oil.

Yield: 280 mg (70%)

^{1}H (200 MHz, $CDCl_3$) δ = 5.88 (m, 2H), 4.23 (m, 4H), 1.39 (t, J = 5.83 Hz, 1H), 0.96 (s, 9H), 0.12 (s, 6H) ppm.

Rf: 0.15 (hexane/EtOAc 4:1)

(*E*)-*Tert*-butyl 2-(2-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)-2-oxoethyl)-1*H*-indole-1-carboxylate (219a)



Acid **217** (750 mg, 2.72 mmol, 1 equiv.) and alcohol **219** (551 mg, 2.72 mmol, 1 equiv.) were added to CH_2Cl_2 (14 mL) and DMAP (66.0 mg, 540 µmol, 0.2 equiv.) and stirred at 20 °C.

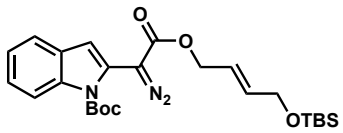
Afterwards DIC (500 µL, 3.26 mmol, 1.2 equiv.) was added and the reaction was stirred for 1.5 h. The reaction was quenched by the addition of water and three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the pure compound was obtained as lightly yellow liquid.

Yield: 980 mg (70%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.08 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 7.48 (m, 1H), 7.25 (m, 1H), 7.19 (dt, J_1 =3.7 Hz, J_2 = 1.0 Hz, 1H), 6.47 (dd, J = 0.7 Hz, 1H), 5.81 (m, 1H), 5.79 (m, 1H), 4.62 (dd, J_1 = 5.8 Hz, J_2 = 1.7 Hz, 2H), 4.15 (m, 2H), 4.05 (s, 2H), 1.65 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C (125 MHz, $CDCl_3$) δ = 170.1, 134.2, 133.7, 133.3, 128.8, 123.9, 123.4, 122.7, 120.2, 115.7, 110.4, 84.2, 65.0, 62.9, 36.3, 28.2, 25.9, 18.4, −5.3 ppm.**Rf**: 0.7 (hexane/EtOAc 5:1)

(*E*)-*Tert*-butyl 2-(2-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)-1-diazo-2-oxoethyl)-1*H*-indole-1-carboxylate (220)



Ester **219a** (547 mg, 1.19 mmol, 1 equiv.) and ABSA (429 mg, 1.79 mmol, 1.5 equiv.) were dissolved in MeCN (6 mL) and cooled to 0 °C. DBU (370 µL, 2.50 mmol, 2.1 equiv.) was added and then the reaction was slowly warmed to r.t. over 16 h followed by concentration. The crude product was then dissolved in CH_2Cl_2 and Et_2O added until a precipitate appeared. This was filtered off and the filtrate was first washed with aq. sat. NH_4Cl solution, then brine solution, dried over $MgSO_4$, filtered and concentrated. This product, a yellow oil, was used without further purification.

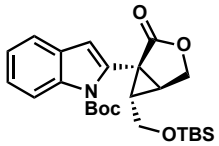
Yield: 478 mg (83%)

^{1}H (200 MHz, $CDCl_3$) δ = 8.18 (m, 1H), 7.82 (m, 1H), 7.54 (m, 1H), 7.23 (m, 1H), 6.81 (m, 1H), 5.82 (m, 1H), 5.80 (m, 1H), 4.71 (m, 2H), 4.17 (d(b), 2H), 1.64 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

IR (ATR): 2947, 2584, 2110, 1734, 1471, 1452, 1452, 1371, 1328, 1253, 1102, 1089, 1060, 1004, 972, 837, 777, 746 cm^{-1}.

Rf: 0.6 (hexane/EtOAc 5:1)

***Tert*-butyl 2-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)-1*H*-indole-1-carboxylate (221)**



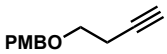
$(CuOTf)_2PhMe$ (1.00 mg, 1.90 µmol, 0.01 equiv.) was dissolved in DCM (5 mL) and diazo **220** (114 mg, 230 µmol, 1 equiv.) dissolved in DCM (15 mL) was added over 3 h at r.t. After the addition was finished the reaction was stirred for additional 12 h and then concentrated. After purification with flash chromatography (hexane/EtOAc 10:1 to 5:1) the pure compound was obtained.

Yield: 21 mg (20%)

^{1}H (200 MHz, $CDCl_3$) δ = 7.99 (m, 1H), 7.55 (m, 1H), 7.35 (m, 1H), 7.25 (m, 1H), 7.09 (m, 1H), 4.68 (m, 1H), 4.36 (m, 1H), 3.93 (m, 1H), 3.72 (m, 1H), 2.21 (m, 1H), 1.19 (m, 1H), 1.73 (s, 9H), 0.96 (s, 9H), 0.14 (s, 6H) ppm.

Rf: 0.3 (hexane/EtOAc 5:1)

1-((But-3-yn-1-yloxy)methyl)-4-methoxybenzene (222)

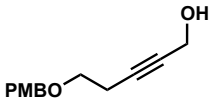


Product was obtained following published procedure (Coffey, D.S.; McDonald, A.I.; Overman, L.E.; Rabinowitz, M.H.; Renhowe, P.A. *J. Am. Chem. Soc.* **2000**, *122*, 4893-4903)

The spectroscopic data matches the data in the literature.

Yield: 1.73 g (57%)

5-((4-Methoxybenzyl)oxy)pent-2-yn-1-ol (222a)



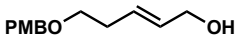
Alkyne **222** (1.73 g, 9.09 mmol, 1 equiv.) was dissolved in THF (23 mL) and cooled to 0 °C. Then *n*BuLi in hexanes (2.5 M, 4 mL, 10.0 mmol, 1.1 equiv.) was added and the reaction stirred for 10 min. at which point paraformaldehyde (1 g, 30.0 mmol, 3.3 equiv.) was added. The reaction was slowly warmed to r.t. over 12 h and quenched by addition of water. The reaction was extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 3:1 to 2:1 to 1:1) gave the compound as a lightly yellow oil.

Yield: 822 mg (42%)

^{1}H (200 MHz, $CDCl_3$) δ = 7.27 (m, 2H), 6.89 (m, 2H), 4.48 (s, 2H), 4.23 (m, 2H), 3.81 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 2.51 (dddd, J_1 = 9.2 Hz, J_2 = 4.7 Hz, J_3 = 2.3 Hz, J_4 = 2.3 Hz, 2H), 1.78 (t, J_1 = 6.0 Hz, 1H) ppm.

Rf: 0.6 (hexane/EtOAc 2:1)

(*E*)-5-((4-Methoxybenzyl)oxy)pent-2-en-1-ol (223)

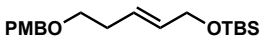


To THF (5 mL) was added Red-Al™ in toluene (3.3 M, 2.12 mL, 7.00 mmol, 3.5 equiv) and cooled to 0 °C. Alcohol **222a** (440 mg, 2.00 mmol, 1 equiv.) dissolved in THF (5 mL) was added and the reaction was stirred for 35 min. at 0 °C and then 3 h at r.t. The mixture was quenched with aq. sat. Na/K tartrate, followed by three times extraction with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 1.5:1 to 1:1) gave the compound as a clear oil.

Yield: 276 mg (62%)

^{1}H (200 MHz, $CDCl_3$) δ = 7.26 (m, 2H), 6.88 (m, 2H), 5.73 (m, 1H), 5.71 (m, 1H), 4.45 (s, 2H), 4.09 (m, 2H), 3.81 (s, 3H), 3.49 (d, *J* = 6.7 Hz, 2H), 2.36 (m, 2H), 1.32 (s, 1H) ppm.

(*E*)-*Tert*-butyl((5-((4-methoxybenzyl)oxy)pent-2-en-1-yl)oxy)dimethylsilane (223a)



Alcohol **223** (276 mg, 1.24 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (1.55 mL) and imidazole (203 mg, 3.00 mmol, 2.4 equiv.) followed by TBSCl (225 mg, 1.49 mmol, 1.2 equiv.) were added. The reaction was stirred for 15 min at r.t. and then quenched by the addition of water. The reaction was extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 10:1) gave the compound as a clear oil.

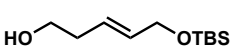
Yield: 361 mg (87%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.25 (m, 2H), 6.87 (m, 2H), 5.65 (m, 1H), 5.64 (m, 1H), 4.45 (s, 2H), 4.13 (m, 2H), 3.80 (s, 3H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.35 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 159.1, 131.2, 130.6, 129.3, 127.4, 113.8, 72.6, 69.6, 63.9, 55.3, 32.7, 26.0, 18.4, −5.1 ppm.

Rf: 0.7 (hexane/EtOAc 2:1)

(*E*)-5-((*Tert*-butyldimethylsilyl)oxy)pent-3-en-1-ol (224)



Protected alcohol **223a** (361 mg, 1.07 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (4.5 mL) and water (500 µL) followed by the addition of DDQ (486 mg, 2.14 mmol, 2 equiv.). The biphasic system was vigorously stirred for 5 h. Then a mixture of aq. sat. $NaHCO_3$ solution and aq. sat.

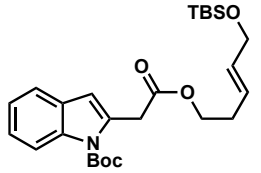
NaS_2O_3 solution (1:1) was added and the reaction was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 2:1) gave the compound as a clear oil.

Yield: 206 mg (88%)

^{1}H (200 MHz, $CDCl_3$) δ = 5.67 (m, 1H), 5.65 (m, 1H), 4.16 (m, 2H), 3.67 (m, 2H), 3.53 (t, *J* = 6.5 Hz, 1H), 2.33 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H) ppm.

Rf: 0.2 (hexane/EtOAc 4:1)

(*E*)-*Tert*-butyl 2-(2-((5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)oxy)-2-oxoethyl)-1*H*-indole-1-carboxylate (224a)



Acid **217** (256 mg, 930 µmol, 1 equiv.) and alcohol **224** (200 mg, 93 µmol, 1 equiv.) were added DMAP (23.0 mg, 190 µmol, 0.2 equiv.) in CH_2Cl_2 (5 mL) and at r.t. Then DIC (173 µL, 1.12 mmol, 1.2 equiv.) was added and the reaction was stirred for 2 h. The reaction was quenched by the addition of water and three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the pure compound was obtained as lightly yellow liquid.

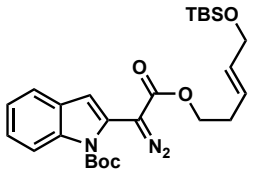
Yield: 346 mg (79%).

^{1}H (400 MHz, $CDCl_3$) δ = 8.10 (ddd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, J_3 = 0.1 Hz, 1H), 7.51 (ddd, J_1 = 7.5 Hz, J_2 = 0.7 Hz, J_3 = 0.1 Hz, 1H), 7.29 (ddd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, J_3 = 0.5 Hz, 1H), 7.22 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.0 Hz, 1H), 6.49 (d, *J* = 1.0 Hz, 1H), 4.16 (ddd, J_1 = 7.1 Hz, J_2 = 7.1 Hz, J_3 = 2.8 Hz, 2H), 4.08 (m, 2H), 4.05 (s. 2H), 2.38 (m, 2H), 1.68 (s, 9H), 0.92 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 170.3, 150.4, 135.5, 133.4, 132.2, 128.8, 125.7, 123.9, 122.7, 120.2, 115.7, 110.3, 84.2, 64.2, 63.6, 36.4, 31.5, 29.7, 28.2, 26.0, −5.2 ppm.

Rf: 0.2 (hexane/EtOAc 10:1).

(*E*)-*Tert*-butyl 2-(2-((5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)oxy)-1-diazo-2-oxoethyl)-1*H*-indole-1-carboxylate (215a)



Ester **224a** (71.0 mg, 150 µmol, 1 equiv.) and ABSA (43.0 mg, 180 µmol, 1.2 equiv.) were dissolved in MeCN (1 mL) and stirred at −15 °C. To this DBU (54 µL, 360 µmol, 2.4 equiv.) was added. The reaction was stirred for 45 min and subsequently quenched with water. The reaction was extracted three times with Et_2O, the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. After purification with flash chromatography using Al_2O_3 (hexane/EtOAc 10:1) the pure product was obtained as a yellow oil.

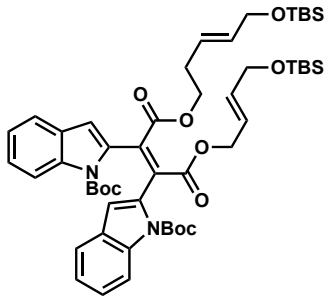
Yield: 39 mg (51%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.05 (ddd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, J_3 = 0.7 Hz, 1H), 7.55 (ddd, J_1 = 7.7 Hz, J_2 = 1.0 Hz, J_3 = 0.7 Hz, 1H), 7.33 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.3 Hz, 1H), 7.24 (ddd, J_1 = 7.2 Hz, J_2 = 7.2 Hz, J_3 = 0.8 Hz, 1H), 6.74 (s, 1H), 5.60 (m, 1H), 5.99 (m, 1H), 4.25 (dt J_1 = 3.5 Hz, J_2 = 1.3 Hz, 2H), 4.05 (m, 2H), 2.41 (m, 2H), 1.69 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 168.2, 150.3, 136.6, 132.8, 128.2, 125.1, 123.2, 121.2, 115.8, 110.6, 85.2, 63.5, 60.6, 32.6, 32.0, 31.4, 29.7, 28.2, 26.0, −5.2 ppm.

Rf: 0.3 (hexane/EtOAc 10:1)

1-((*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl) 4-((*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl) 2,3-bis(1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)maleate (225)



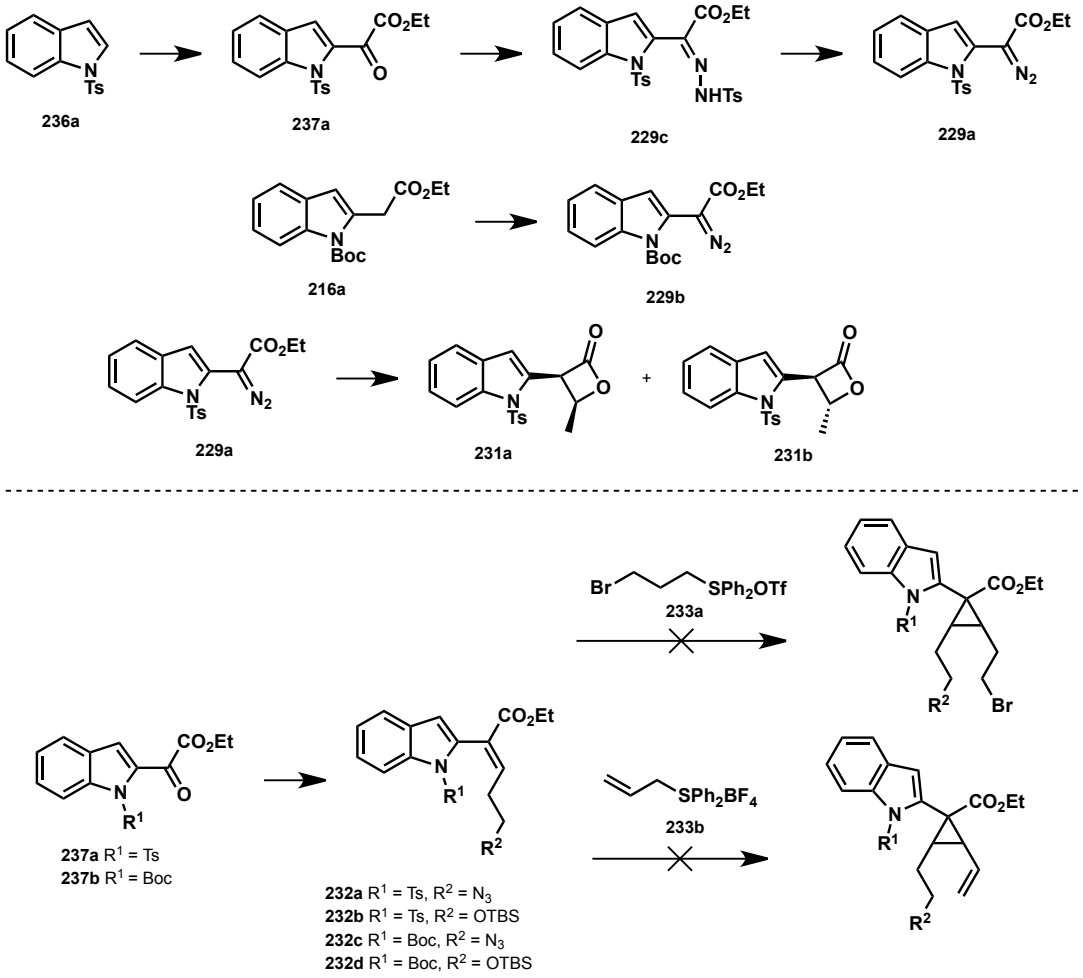
A round bottom flask was charged with bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)] (Rh_2esp_2) (1.1 mg, 1.5 µmol, 0.05 equiv.) and CH_2Cl_2 (1 mL) was added. Subsequently diazo **215a** (16.2 mg, 30 µmol, 1 equiv.), dissolved in CH_2Cl_2 (1 mL) was added dropwise over 5 h. The reaction was then concentrated *in vacuo* at 20 °C and the residue purified with flash chromatography (hexane/EtOAc 10:1 to 3:1).

Yield: 2 mg (14%)

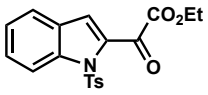
^{1}H (200 MHz, $CDCl_3$) δ = 7.96 (m, 1H), 7.53 (m, 1H), 7.31 (m, 1H), 7.23 (m, 1H), 6.67 (s, 1H), 5.57-5.50 (m, 1H), 5.56 (d, *J* = 9.8Hz, 1H), 4.29 (d, *J* = 9.8 Hz, 1H), 4.18 (t, *J* = 6.9 Hz, 1H), 3.99 (m, 2H), 2.35 (m, 2H), 1.69 (s, 9H), 0.88 (s, 9H), −0.02 (s, 6H) ppm.

Rf: 0.05 (hexane/EtOAc 10:1)

Graphical abstract Indole C-2 vinylcyclopropane: intermolecular approach



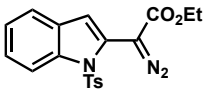
Ethyl 2-oxo-2-(1-tosyl-1*H*-indol-2-yl)acetate (237a)



A round bottom flask was charged with a suspension of powdered KOH (12.0 g, 213 mmol, 5 equiv.) and THF (200 mL) and put in a water bath at r.t. Indole (5.00 g, 42.7 mmol, 1 equiv.) was added and the suspension was stirred vigorously for 30 min during which the solution gradually turned milky blue. Subsequently TsCl (8.95 g, 47.0 mmol, 1.1 equiv.) was added and the reaction turned orange instantly. It was stirred for additional 45 min and then poured into PhMe. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo.* Of the resulting crude product **236a** (9.45 g, 84%) a part (543 mg, 2.00 mmol, 1 equiv.) was taken, dissolved in THF (5 mL) and added to LDA, which was made by adding *n*-BuLi (2.5M, 840 µL, 2.10 mmol, 1.1 equiv) to DIPEA (500 µL; 2.10 mmol, 1.1 equiv.) in THF (5 mL) at −78 °C and stirring for 20 min then warming to 0 °C for 20 min and cooling back to −78 °C. After deprotonating for 1 h at −78 °C, diethyloxalat (410 µL, 3.00 mmol, 1.5 equiv.) in THF (5 mL) was added and the reaction stirred for 3 h before being quenched with aq. sat NH_4Cl solution. The reaction was extracted three times with EtOAc and the combined organic layers washed with

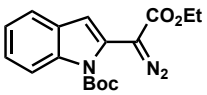
brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 4:1) the pure compound was obtained as off white solid.
Yield 532 mg (62%)
^{1}H (400 MHz, $CDCl_3$) δ = 8.04 (dd, J_1 = 8.6 Hz, J_2 = 0.7 Hz, 1 H), 7.65 (ddd, J_1 = 8.5 Hz, J_2 = 1.4 Hz, J_3 = 1.4 Hz, 2H), 7.58 (ddd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, J_3 = 1.0 Hz, 1H), 7.47 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, 1H), 7.38 (d, J = 1.0 Hz, 1H), 7.28 (ddd, J_1 = 8.1 Hz, J_2 = 7.8 Hz, J_3 = 0.6 Hz, 1H), 7.17 (db, J = 8.2 Hz, 2H), 4.46 (q, 7.2 Hz, 2H), 2.32 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H) ppm.
^{13}C (00 MHz, $CDCl_3$) δ =178.2, 161.2, 145.6, 138.7, 136.3, 134.0, 129.8, 128.9, 128.7, 127.4, 124.9, 123.5, 121.8, 115.5, 63.1, 21.7, 14.1 ppm.
Rf: 0.1 (hexane/EtOAc 4:1)

Ethyl 2-diazo-2-(1-tosyl-1*H*-indol-2-yl)acetate (229a)



Ethyl 2-oxo-2-(1-tosyl-1*H*-indol-2-yl)acetate (**237a)** (183 mg, 510 µmol, 1 equiv.) and tosylhydrazine (100 mg, 540 µmol, 1.05 equiv) were dissolved in MeOH (2.5 mL) and heated to 65 °C for 16 h. Subsequently the solvent was evaporated and the residue taken up in aq. NaOH (0.2 M, 5.1 mL, 1.02 mmol, 2 equiv.). After stirring for 15 min. was added aq. sat NH_4Cl and the reaction extracted with EtOAc three times. The combined organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 4:1) furnished the product as yellow oil.
Yield: 141 mg (75 %)
^{1}H (200 MHz, $CDCl_3$) δ = 8.20 (bd, J = 8.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.49 (m, 1H), 7.36 (m, 1H), 7.28 (m, 1H), 7.15 (d, J = 7.9 Hz, 2H), 6.81 (d, J = 0.7 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.25 (t, J = 6.6 Hz, 3H) ppm.
Rf: 0.2 (hexane/EtOAc 4:1)

***Tert*-butyl 2-(1-diazo-2-ethoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (229b)**



Indole ester **216a** (71.0 mg, 230 µmol, 1 equiv.) was dissolved in MeCN (1 mL) and ABSA (83.0 mg, 350 µmol, 1.5 equiv.) was added. The solution was cooled to 0 °C and DBU (80 µL, 510 µmol, 2.2 equiv.) was added. The reaction was stirred for 1 h at 0 °C and then warmed to r.t. over 2.5 h. Then water was added and the reaction was three times extacted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

After purification with flash chromatography (hexane/EtOAc 10:1) the pure compound was obtained as yellow oil.

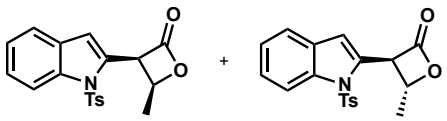
Yield: 53 mg (70%)

^{1}H (200 MHz, $CDCl_3$): 8.06 (m, 1H), 7.55 (m, 1H), 7.31 (m, 1H), 7.25 (m, 1H), 6.75 (m, 1H), 4.29 (q, *J* = 7.2Hz, 2H), 1.70 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

IR (ATR) 2983, 2110,1733, 1454, 1371, 1330, 1253, 1158, 1122, 1090, 1027, 837, 748 cm^{-1}.

Rf: 0.3 (hexane/EtOAc 7:1)

4-Methyl-3-(1-tosyl-1*H*-indol-2-yl)oxetan-2-one (231)



A roundbottom flask was charged with di-TIPS protected (*Z*)-but-2-ene-1,4-diol (146 mg, 36.5 µmol, 5 equiv.) and $(CuOTf)_2PhMe$ (1.84 mg, 3.70 µmol, 0.05 mmol) and CH_2Cl_2 (1 mL). Subsequently ethyl 2-diazo-2-(1-tosyl-1*H*-indol-2-yl)acetate (27.0 mg, 73.0 µmol, 1 equiv.) dissolved in CH_2Cl_2 (1 mL) was added dropwise over 10 h. Then the solvent was evaporated and and the crude product was purified by flash chromatography (hexane/EtOAc 4:1). The product was obtained as 1:1 mixture of isomers.

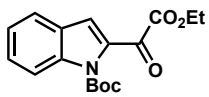
Yield: 8 mg (33%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.15 – 8.07 (m, 2H), 7.67 – 7.60 (m, 4H), 7.57 – 7.50 (m, 2H), 7.39 – 7.31 (m, 2H), 7.30 – 7.22 (m, 6H), 6.88 (s, 1H), 6.84 (s, 1H), 5.42 (dd, J_1 = 6.1 Hz, J_2 = 1.4 Hz, 1H), 5.17 (q, *J* = 6.1 Hz, 1H), 5.00 (dd, J_1 = 6.0 Hz, J_2 = 4.0Hz, 1H), 4.71 (dddd, J_1 = 6.0 Hz, J_2 = 6.0 Hz, J_3 = 6.0 Hz, J_1 = 4.0 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H), 1.86 (d, *J* = 6.2 Hz, 3H), 1.42 (d, *J* = 6.1 Hz, 3H) ppm.

^{13}C (100 MHZ, $CDCl_3$) δ = 168.0, 167.8, 145.6, 145.4, 137.0, 136.8, 135.5, 135.3, 130.2, 130.1, 129.9, 129.4, 129.0, 128.9, 126.3, 126.2, 125.4, 125.3, 124.1, 124.0, 121.4, 121.3, 114.6, 114.3, 112.3, 111.1, 77.9, 74.7, 56.8, 54.0, 21.6, 20.0, 18.0, 16.1 ppm.

Rf: 0.1 (hexane/EtOAc 4:1)

***Tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate (237b)**



Indole (1.87 g, 9.10 mmol, 1 equiv.) was dissolved in THF (24 mL) and DMAP (222 mg, 1.82 mmol, 0.2 equiv.) and finally Boc_2O (2.18 g, 10.0 mmol, 1.1 equiv.) was added. The reaction was stirred at r.t. for 16 h before water was added. The reaction was then extracted three times with Et_2O and the organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Without further purification, a part of the crude product (1 g,

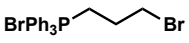
4.60 mmol, 1 equiv.) was dissolved in THF (5 mL) and added to LDA, which was made by adding *n*BuLi in hexanes (2.5M, 2.0 mL, 5.06 mmol, 1.1 equiv) to DIPEA (711 µL; 5.06 mmol, 1.1 equiv.) in THF (15 mL) at −78 °C and stirring for 20 min then warming to 0 °C for 20 min and finally cooling back to −78 °C. After deprotonating for 1 h at −78 °C, diethyloxalat (934 µL, 6.90 mmol, 1.5 equiv.) was added and the reaction kept for 2 h at −78 °C and then warmed to r.t. over 12 h. Addition of aq. sat. NH_4Cl solution was followed by three-fold extraction with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the desired product was obtained.

Yield: 789 mg (54%)

^{1}H (200MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.47 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 7.30 (ddd, J_1 =8.2 Hz, J_2 = 6.6 Hz, J_3 = 0.6 Hz, 1H), 7.30 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.65 (s, 9H), 1.39 (t, *J* = 1.4 Hz, 3 H) ppm.

Rf: 0.4 (hexane/EtOAc 10:1)

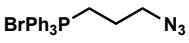
Bromo(3-bromopropyl)triphenylphosphorane (237c)



Product was obtained following published procedure (Corey, E.J.; Desai, M. C. *Tetrahedron Lett.* 1985, *26(47)*, 5747-5748)

Yield: 4.46 g (97%)

(3-Azidopropyl)bromotriphenylphosphorane (237d)



Bromo(3-bromopropyl)triphenylphosphorane (461 mg, 1.00 mmol, 1 equiv.) and NaN_3 (100 mg, 1.50 mmol, 1.5 equiv.) were suspended in water (2.5 mL) and EtOH (2.5 mL) and heated to reflux for 16 h. Then water was added to the clear liquid and the reaction was three times extracted with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. The resulting white solid was used without further purification.

Yield: 363 mg (85%)

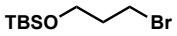
^{1}H (400 MHz, $CDCl_3$) δ = 7.91-7.83 (m, 6H), 7.79 (m, 3H), 7.73-7.66 (m, 6H), 4.19 (m, 2H), 3.85 (ddd, J_1 = 6.4 Hz, J_2 = 6.4 Hz, J_3 = 1.0 Hz, 2H), 1.89 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 135.1, 135.0, 133.8, 133.7, 130.6, 130.5, 118.9, 117.8, 50.9, 50.7, 22.8, 22.7, 20.3, 19.7 ppm.

IR (ATR): 3057, 2357, 2160, 1587, 1558, 1506, 1487, 1438, 1251, 1165, 1112, 995, 738, 732, 690, 532, 509, 462, 445, 432, 418, 408 cm^{-1}.

HRMS (ESI) calculated for $C_{21}H_{21}N_3P^+$ 346.1743; found 346.1475

(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (237e)



3-Bromo-1-propanol (1.18 g, 8.50 mmol, 1 equiv.) and imidazole (1.39 g, 20.4 mmol, 2.4 equiv.) were dissolved in CH_2Cl_2 (8.5 mL) and finally TBSCl (1.33 g, 10.2 mmol, 1.2 equiv.) was added. The reaction was stirred for 1 h before water was added and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. Purification with Kugelrohr distillation gave the desired compound as a clear oil.

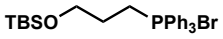
Yield: 2.05 g (95%)

^{1}H (400 MHz, $CDCl_3$) δ = 3.76 (t, *J* = 5.8 Hz, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.06 (ddd, J_1 = 12.0 Hz, J_2 = 6.2 Hz, J_3 = 5.9 Hz, 2H), 0.92 (s, 9H), 0.09 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 60.4, 35.5, 30.7, 25.9, 18.3, −5.4 ppm.

IR (ATR): 2927, 2854, 1734, 1456, 1361, 1257, 1103, 835, 777 cm^{-1}.

Bromo(3-((*tert*-butyldimethylsilyl)oxy)propyl)triphenylphosphorane (237f)



(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (506 mg, 2.00 mmol, 1 equiv.) and PPh_3 (524 mg, 2 mmol, 1 equiv.) were dissolved in PhMe (2 mL) and heated to reflux for 36 h.

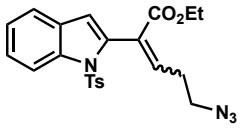
Then the solvent was evaporated giving the desired compound.

Yield: 1.03 g (quant.)

^{1}H (400 MHz, $CDCl_3$) δ = 7.87 (m, 6H), 7.81 (m, 3H), 7.71 (m, 6H), 3.92 (m, 4H), 1.92 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H) ppm.

HRMS (ESI) calculated for $C_{27}H_{36}OPSi^+$ 435.2273; found 435.2232.

Ethyl 5-azido-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232a)



(3-Azidopropyl)bromotriphenylphosphorane (1.48 g, 3.47 mmol, 1.2 equiv.) was suspended in THF (15 mL) and cooled to −78 °C and KHMDS in PhMe (0.7 M, 5.0 mL, 3.57 mmol, 1.2 equiv.) was added. After 1 h, ethyl 2-oxo-2-(1-tosyl-1*H*-indol-2-yl)acetate **237a** (1.03 g, 2.89 mmol, 1 equiv.) in THF (5 mL) was added and the reaction slowly warmed to r.t. over 16 h. Then aq. sat. NH_4Cl solution was added and the reaction was three times extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 7:1 to 5:1) gave two double bond isomers.

Major isomer:

Yield: 429 mg

^{1}H (400 MHz, $CDCl_3$) δ = 8.14(dd, J_1 = 8.5 Hz, J_2 =0.7 Hz, 1H), 7.59 (ddd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, J_3 = 2.0 Hz, 2H), 7.48 (db, J =7.8Hz, 1H), 7.35 (ddd, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_1 = 1.4 Hz, 1H), 7.25 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.7 Hz, 1H), 7.16 (db, J = 8.2 Hz, 2H), 6.57 (s, 1H), 6.33 (t, J = 7.5 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 3.11 (dt, J_1 = 6.9 Hz, J_2 = 6.7 Hz, 2H), 2.33 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 165.1, 144.8, 143.5, 138.8, 136.9, 135.3, 129.7, 129.6, 129.2, 126.7, 125.0, 123.8, 121.0, 115.1, 113.0, 61.0, 50.9, 29.2, 21.5, 14.1 ppm.

IR (ATR): 2926, 2358, 2098, 1715 1645, 1597, 1558, 1494 1450, 1367, 1253, 1228, 1172, 1153, 1122, 1089, 1020, 864, 813, 748, 704, 678, 648, 540, 433 cm^{-1}.

Rf: 0.35 (hexane/EtOAc 5:1)

Minor isomer:

Yield: 253 mg

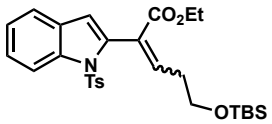
^{1}H (400 MHz, $CDCl_3$) δ = 8.17 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 7.64 (db, J = 8.5 Hz, 2H), 7.54 (d, J = 7.9 Hz, 1H), 7.37 (ddd, J_1 = 8.5 Hz, J_2 = 7.3 Hz, J_3 = 1.3 Hz, 1H), 7.28 (ddd, J_1 = 7.5 Hz, J_2 = 7.2 Hz, J_3 = 0.3 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.15 (db, J = 7.7 Hz, 1H), 6.56 (s, 1H), 4.27 (m, 2H), 3.41 (ddd, J_1 = 6.9 Hz, J_2 = 6.8 Hz, J_3 = 1.5 Hz, 2 H), 2.35 (s, 3H), 2.34 (m, 1H), 2.19 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 165.8, 145.0, 142.3, 136.8, 135.9, 132.8, 129.7, 129.3, 129.2, 126.8, 125.1, 123.7, 121.1, 114.8, 113.0, 61.4, 50.1, 29.6, 21.6, 14.1 ppm.

Rf: 0.25 (hexane/EtOAc 5:1)

HRMS (ESI) calculated for $C_{22}H_{22}N_4O_4NaS^+$ 461.1259; found 461.1259.

Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232b)



Bromo(3-((*tert*-butyldimethylsilyl)oxy)propyl)triphenylphosphorane (7.86 g, 15.3 mmol, 2 equiv.) was suspended in 150 mL and cooled to −78 °C. KHMDS in PhMe (0.7 M, 5 mL, 3.57 mmol, 1.2 equiv.) was added and the reaction was stirred for 30 min. At this point the solid was dissolved and ethyl 2-oxo-2-(1-tosyl-1*H*-indol-2-yl)acetate **237a** (2.80 g, 7.63 mmol, 1.00 equiv.) in THF (150 mL) was added. After 45 min at −78 °C aq. sat. NH_4Cl solution was added and the reaction was subsequently three times extracted with Et_2O. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatograph (hexane/EtOAc 10:1) the product was obtained as a mixture of double bond isomers.

Yield: 3.45 g (86%)

Major diastereomer

Rf: 0.8 and 0.7 (hexane/EtOAc 5:1)

^{1}H (400 Mhz, $CDCl_3$) δ = 8.13 (dd, J_1 = 8.3 Hz, J_2 = 0.9 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.47 (db, J = 7.2 Hz, 1H), 7.33 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 7.24 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 0.8 Hz, 1H), 7.14 (d, J = 7.8Hz, 2H), 6.53 (d, J = 0.7 Hz, 1H), 6.42 (t, J = 7.0 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.84 (t, J = 6.2 Hz, 2H), 3.05 (q, J = 6.5 Hz, 2H), 2.33 (s, 3H), 1.30 (t, J = 9.2 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 166.5, 145.8, 144.6, 136.9, 135.7, 130.4, 129.8, 129.5, 127.8, 126.8, 124.8, 123.7, 120.9, 115.1, 112.6, 62.1, 60.8, 33.3, 29.7, 25.9, 21.5, 14.2, −5.2 ppm.

IR (ATR): 2926, 2854, 2357, 1724, 1452, 1373, 1215, 1174, 1091, 837, 667, 418 cm^{-1}.

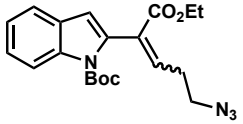
Minor diastereomer

^{1}H (400 Mhz, $CDCl_3$) δ = 8.14 (dd, J_1 =8.5 Hz, J_2 = 0.7 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.47 (ddd, J_1 = 7.8 Hz, J_2 = 1.3 Hz, J_3 = 0.1 Hz, 1H), 7.32 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.3 Hz, 1H), 7.25 (s, 1H), 7.23 (ddd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, J_3 =5.9 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 6.54 (s, 1H), 4.27 (m, 2H), 3.70 (t, J = 6.5 Hz, 2H), 2.30 (s, 3H), 2.28 (m, 1H), 2.11 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 166.2, 144.7, 144.1, 136.8, 135.8, 133.4, 129.6, 129.5, 128.3, 126.9, 124.8, 123.5, 121.0, 114.8, 113.2, 61.8, 61.2, 33.5, 25.9, 21.5, 18.4, 14.2, −5.3 ppm.

HRMS (ESI) calculated for $C_{28}H_{37}NO_5SSiNa^+$ 550.2059; found 550.2056.

Tert-butyl 2-(5-azido-1-ethoxy-1-oxopent-2-en-2-yl)-1*H*-indole-1-carboxylate (232c)



(3-Azidopropyl)bromotriphenylphosphorane (400 mg, 940 µmol, 1.3 equiv.) was suspended in THF (1.8 mL) and cooled to −78 °C and KHMDS in PhMe (0.7 M, 123 µL, 860 µmol, 1.2 equiv.). After 30 min, *tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate **237b** (229 mg, 720 µmol, 1 equiv.) in THF (1.8 mL) was added and the reaction was stirred for 1.5 h at −78 °C and subsequently 30 min at 0 °C. Then aq. sat. NH_4Cl solution was added and the reaction was three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 20:1 to 10:1 to 5:1) gave the product as two double bond isomers.

Major isomer:

Yield: 120 mg

^{1}H (200 MHz, $CDCl_3$) δ = 8.08 (ddd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, J_3 = 0.7 Hz, 1H), 7.53 (ddd, J_1 = 7.4 Hz, J_2 = 1.7 Hz, J_3 = 0.7 Hz, 1H), 7.28 (m, 1H), 7.24 (m, 1H), 6.54 (d, J = 0.7 Hz, 1H), 6.40 (t, J = 7.3 Hz,

1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.51 (t, *J* = 6.7 Hz, 2H), 3.06 (dt, J_1 = 7.0 Hz, J_2 = 6.9 Hz, 2H), 1.62 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm.

Rf: 0.5 (hexane/EtOAc 10:1)

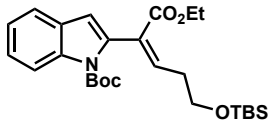
Minor isomer

Yield: 65 mg

^{1}H (200 MHz, $CDCl_3$) δ = 8.16 (ddd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, J_3 = 0.9 Hz, 1H), 7.55 (ddd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, J_3 = 0.7 Hz, 1H), 7.36 (m, 1H), 7.27 (m, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 2.57 (dt, J_1 = 7.2 Hz, J_2 = 6.8 Hz, 2H), 1.60 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm.

Rf: 0.4 (hexane/EtOAc 10:1)

Tert-butyl 2-(5-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxopent-2-en-2-yl)-1*H*-indole-1-carboxylate (232d)



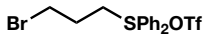
Bromo(3-((*tert*-butyldimethylsilyl)oxy)propyl)triphenylphosphorane (500 mg, 970 µmol, 1.3 equiv.) was suspended in 2.5 mL and cooled to −78 °C. KHMDS in PhMe (0.7 M, 1.05 mL, 730 µmol, 1.2 equiv.) was added and the reaction was stirred for 30 min. At this point the solid was dissolved and *tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate **237b** (238 mg, 750 µmol, 1.0 equiv.) in THF (1.5 mL) was added. After 1 h aq. sat. NH_4Cl solution was added and the reaction was subsequently three times extracted with Et_2O. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the product was obtained as a mixture of double bond isomers, however only the major could be purified enough for NMR analysis.

Yield: 100 mg (28%)

^{1}H (400 Mhz, $CDCl_3$) δ = 8.16 (dd, J_1 = 8.4 Hz, J_2 = 0.9 Hz, 1H), 7.53 (ddd, J_1 = 7.7 Hz, 1.2 Hz, 0.7 Hz, 1H), 7.31 (ddd, J_1 = 8.5 Hz, J_2 = 7.2 Hz, J_3 = 1.4 Hz, 1H), 7.23 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.9 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.50 (d, *J* = 0.7 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 3.73 (t, *J* = 6.7 Hz, 2H), 2.51 (b, 2H), 1.58 (s, 9H) 1.21 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

Rf: 0.8 and 0.7 (hexane/EtOAc 10:1)

(3-Bromopropyl)diphenylsulfonium triflate (233a)



Pyridine (435 µL, 5.40 mmol, 1.05 equiv.) was dissolved in CH_2Cl_2 (5.4 mL) and cooled to −20 °C. Subsequently Tf_2O in DCM (1 M, 5.4 mL, 5.40 mmol, 1.05 equiv.) and after 5 min 3-bromo-1-

propanol (470 µL, 5.14 mmol, 1 equiv.) was added. The reaction was stirred for 1 h at −20 °C and at ambient temperature for 16 h. Subsequently the reaction was filtered and the remaining solid washed with a mixture of CH_2Cl_2 and Et_2O (1:1). The filtrate was concentrated and purified over a short silica plug (Et_2O/DCM 1:1) to yield 1.16 g of a product that was directly used in the next step.

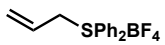
In a sealable tube triflated bromopranol (667 mg, 2.46 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2.50 mL) and diphenylsulfid (410 µL, 2.46 mmol, 1 equiv.) was added. The tube was sealed and heated to 60 °C for 2 d and subsequently concentrated *in vacuo*. The resulting brown solid was taken up in Et_2O and after 5 h the resulting crystals were filtered off and dried *in vauco*.

Yield: 638 mg (58%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.00 (m, 4H), 7.75 (m, 2H), 7.12 (m, 4H), 4.41 (m, 2H), 3.59 (t, J = 6.1 Hz, 2H), 2.35 (dd, J_1 = 14.7 Hz, J_2 = 6.3 Hz, 2H) ppm.

^{13}C (100 Mhz, $CDCl_3$) δ = 135.0, 131.8, 130.7, 123.9, 43.7, 30.0, 27.6 ppm.

Vinyl diphenylsulfonium tetrafluoroborate (233b)

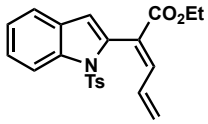


To a solution of $AgBF_4$ (195 mg, 1 mmol, 1 equiv.) in acetone (1 mL) at 0 °C was added diphenyl sulfide (837 µL, 5.00 mmol, 5 equiv.) and to the resulting brown solution was then added allyl bromide (95 µL, 1.10 mmol, 1.1 equiv.). A white solid began to precipitate and after 5 min. the reaction was warmed to ambient temperature. After 2 h of stirring, Et_2O was added to increase crystallization. After additional 2 h the solid was filtered off and then dried *in vacuo.* The product did degrade during ^{13}C spectroscopy.

Yield: 233 mg (74%)

^{1}H (200 MHz, $CDCl_3$) δ = 7.94 (m, 4H), 7.34-7.57 (m, 6H), 5.84 (dddd, J_1 = 17.0 Hz, J_2 = 9.8 Hz, J_3 = 7.2 Hz, J_4 = 7.2 Hz, 1H), 5.55 (dddd, J_1 = 17.0 Hz, J_2 = 0.8 Hz, J_3 = 0.8 Hz, J_4 = 0.8 Hz, 1H), 5.41 (dd, J_1 = 10.0 Hz, J_2 = 0.7 Hz, 1H), 4.80 (d, J = 7.2 Hz, 2H) ppm.

(*E*)-Ethyl 2-(1-tosyl-1*H*-indol-2-yl)penta-2,4-dienoate (232e)



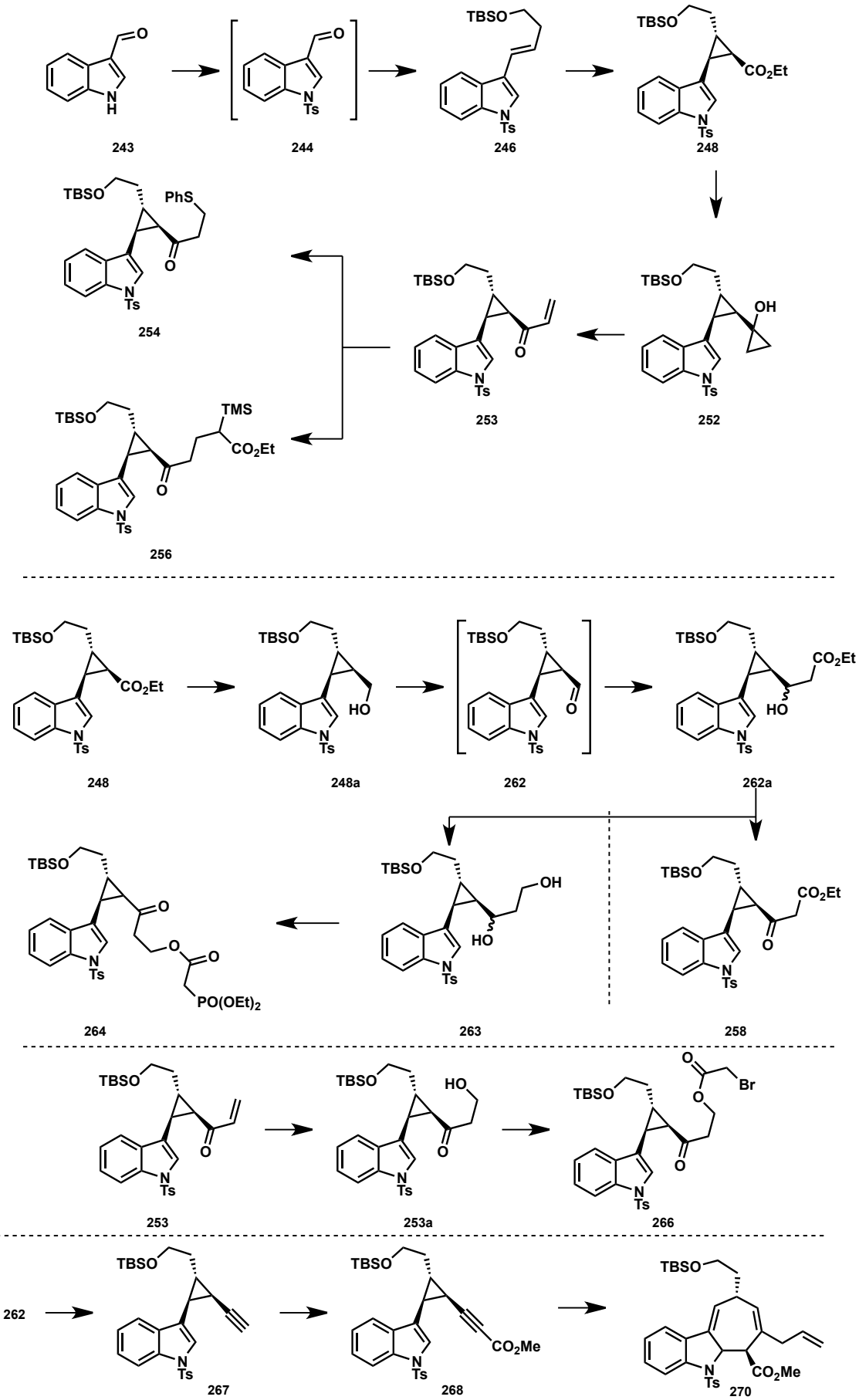
Vinyl diphenylsulfonium tetrafluoroborate (38.0 mg, 120 µmol, 2.4 equiv.) was dissolved in THF (0.2 mL) and cooled to −78 °C. To this was added *n*-BuLi in hexanes (2.5 M, 42.0 µL, 103 µmol, 2.1 equiv.) and the reaction was stirred for 1 h. Then was added ethyl 5-azido-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (22.0 mg, 50.0 µmol, 1.0 equiv.) dissolved in THF (0.2 mL). and the reaction was stirred for 3 h before aq. sat. NH_4Cl solution was added. The reaction was extracted

three times with EtOAc, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification with flash chromatography (hexane/EtOAc 5:1) furnished the product as colorless liquid.

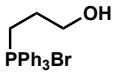
Yield: 6 mg (30%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.19 (m, 1HJ, 7.61 (m, 2H), 7.51 (m, 1H)7.34 (m, 1H), 7.25 (m, 1H), 7.22 (m, 1H) 7.12 (m, 2H), 6.55 (s, 1H), 6.29 (ddd, J_1 =16.9 Hz, J_2 = 10.0 Hz, J_3 = 11.3 Hz, 1H), 5.75 (m, 1H), 5.42 (m, 1H), 4.31 (m, 2H), 2.32 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm.

Graphical abstract: towards a highly substituted cyclohepta[*b*]indole.



3-(Bromotriphenylphosphoranyl)propan-1-ol (243a)

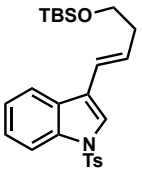


In refluxing PhMe (5 mL) was dissolved PPh_3 (3.02 g, 11.3 mmol, 1 equiv.) and then 3-bromo-1-propanol was added. Soon a precipitate was formed and after refluxing for 5.5 h the reaction was cooled to r.t. and the precipitate was filtered off. After washing with PhMe and drying *in vacuo* the desired product was obtained as a white solid.

Yield: 4.05 g (88%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.84-7.74 (m, 9H), 7.73-7.65 (m, 6H), 3.88 (m, 2H), 3.84 (m, 2H), 1.83 (m, 2H), 1.63 (b, 1H) ppm.

(*E*)-3-(4-((*Tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)-1-tosyl-1*H*-indole (246)



Indole-3-carbaldehyde (5.00 g, 34.4 mmol, 1 equiv.) and TBAB (1.10 g, 3.44 mmol, 0.1 equiv) were added to a mixture of PhMe (120 mL) and 30% NaOH (120 mL). Lastly TsCl (7.20 g, 37.9 mmol, 1.1 equiv.) was added and the reaction stirred vigourously for 3 h. Then the phases were separated and the aqueous layer was three times extracted with PhMe. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product **244** was then used without further purification.

3-(Bromotriphenylphosphoranyl)propan-1-ol (6.22 g, 15.5 mmol, 1.2 equiv) was suspended in THF (40 mL) and cooled to 0 °C. Subsequently *n*-BuLi in hexanes (2.5 M, 12.4 mL, 31.0 mmol, 2.4 equiv.) was added and the resulting dark solution was stirred for 20 min at 0 °C, then for 20 min at r.t. and finally again cooled to 0 °C. Then the crude Ts-protected indol-3-carbaldehyde (3.87 g, 12.9 mmol, 1 equiv.) dissolved in THF (25 mL) was added and the reaction stirred for 5 min at 0 °C before being stirred for 3 h at r.t. The reaction was quenched by addition of aq. sat. NH_4Cl solution and then extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was used without further purification.

(*E*)-4-(1-Tosyl-1*H*-indol-3-yl)but-3-en-1-ol (7.45 g, 21.9 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (44 mL), cooled to 0 °C and imidazole (3.57 g, 52.4 mmol, 2.4 equiv.) and finally TBSCl (3.41 g, 26.2 mmol, 1.2 equiv.) were added and the reaction was stirred and slowly warmed to r.t. over 16 h. Subsequently water was added and the reaction was three times extracted with DCM. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.*

After purification with flash chromatography (hexane/EtOAc 20:1 to 10:1) the product was obtained as slightly yellow oil.

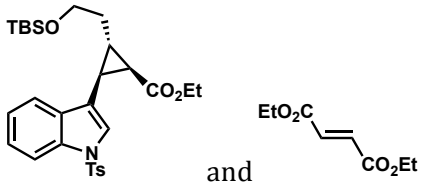
Yield: 7.59 g (62%)

^{1}H (400 MHz, $CDCl_3$) δ = 8.01 (db, *J* = 8.2 Hz, 1H), 7.77 (db, *J* = 8.5 Hz, 2H), 7.70 (m, 1H), 7.54 (s, 1H), 7.49 (m, 1H), 7.34 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.51 (ddd, J_1 = 16.0 Hz, J_2 = 1.7 Hz, J_3 = 1.0 Hz, 1H), 6.30 (dt, J_1 = 16.0 Hz, J_2 = 7.0 Hz, 1H), 3.77 (t, *J* = 6.7 Hz, 2h), 2.48 (dq, J_1 = 6.6 Hz, J_2 = 0.7 Hz, 2H), 2.36 (s, 3H), 0.93 (s, 9H), 0.09 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 144.9, 135.5, 132.2, 129.9, 128.5, 126.8, 124.8, 123.3, 122.9, 122.0, 120.4, 113.8, 62.9, 37.1, 26.0, 21.6, 18.4, −5.2 ppm.

Rf: 0.5 (hexane/EtOAc 10:1)

Ethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl) cyclopropanecarboxylate (248), (249) and **diethyl fumarate**



To $CuOTf(PhMe)_2$ (162 mg, 0.31 mmol, 0.025 equiv.) was added (−)-2,2′-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] (253 mg, 0.76 mmol, 0.06 equiv.) dissolved in CH_2Cl_2 (0.5 mL) and the solution was stirred for 1 h, during which it became dark green. Then alkene **246** (5.74 g, 12.6 mmol, 1 equiv.) dissolved in CH_2Cl_2 (4 mL) was added and finally ethyl-diazoacetat (4.8 mL, 44.1 mmol, 3.5 equiv.) dissolved in CH_2Cl_2 (100 mL) was added dropwise over a period of 8 h. After completion of addition the reaction was stirred additional 12 h and then concentrated. A short filter column enabled to remove most of unreacted starting material and dimerization product of ethlyl diazo compound, diethyl fumarate, and gave the crude cyclopropyl ester.

For analysis purposes a small amount of pure cyclopropylester could be obtained after repeated chromatography. Unfortunately, isomerization occurred during the measurement of the ^{13}C spectrum. It is noteworthy, that the desired isomers exhibits an atropisomeric behavior.

Major diastereomer: **248**

^{1}H (400 MHz, $CDCl_3$) δ = 7.92 (d, 8.2 Hz, 1H), 7.5 (ddd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, J_3 =1.8 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 1.4 Hz, 1H), 7.28 (dd, J_1 = 15.4 Hz, 1.4 Hz, 1H), 7.23 (dd, J_1 = 6.5 Hz, J_2 = 1.0 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.34-4.13 (m, 2H), 3.73 (dddd, J_1 = 18.9 Hz, J_2 = 11.5 Hz, J_3 = 7.2 Hz, J_4 = 4.4 Hz, 2H), 2.34 (s, 3H), 2.28 (ddd, J_1 = 8.7 Hz, J_2 = 6.8 Hz, J_3 = 1.4 Hz, 1H), 2.07 (dt, J_1 = 6.7 Hz, J_2 = 6.7 Hz, J_3 = 5.3 Hz, 1H), 1.99 (dd, J_1 = 8.9 Hz, J_2 = 5.1 Hz, 1H), 1.76 (ddd, J_1 = 6.3 Hz, J_2 = 6.3 Hz, J_3 = 6.3 Hz, 1H), 1.75 (ddd, J_1 = 6.6 Hz, J_2 = 6.6 Hz, J_3 = 6.6 Hz, 1H), 1.33 (m, 3H), 1.26, 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm.

HRMS (ESI) calculated for $C_{29}H_{39}NO_5SiSNa^+$ 564.2216; found 564.2220.

Rf: 0.3 (hexane/EtOAc 10:1)

Minor Diastereomer: **249**

^{1}H (400 MHz, $CDCl_3$) δ = 7.95 (ddd, J_1 = 8.3 Hz, J_2 = 1.0 Hz, J_3 = 0.8 Hz, 1H), 7.73 (ddd. J_1 = 8.5 Hz, J_2 = 2.0 Hz, J_3 = 2.0Hz, 2H), 7.56 (ddd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, J_3 = 0.8 Hz, 1H), 7.31 (ddd, J_1 = 8.4 Hz, J_2 = 7.4 Hz, J_3 =1.2 Hz, 1H), 7.25 (dd, J_1 = 4.3 Hz, J_2 = 0.9 Hz, 1H), 7.23 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 4.19 (tq, J_1 =27.8 Hz, J_2 = 7.1 Hz, 2H), 3.71 (ddt, J_1 = 17,5 Hz, J_2 = 10.2 Hz, J_3 = 6.3 Hz, 2H), 2.44 (ddd, J_1 =6.7 Hz, J_2 = 5.3 Hz, J_3 =1.2 Hz, 1H), 2.33 (s, 3H), 2.02 (dd, J_1 = 13.8 Hz, J_2 = 6.7 Hz, 1H), 1.97 (dd, J_1 =9.4 Hz, J_2 = 4.9 Hz, 1H), 1.90 (ddt, J_1 = 13.7 Hz, J_2 = 6.7 Hz, J_3 = 6.5 Hz, 1H), 1.76 (ddd, J_1 = 14.0, J_2 = 9.0, J_3 = 7.0 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H) 0.88 (s, 9H), 0.04 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 171.8, 144.9, 135.3, 135.2, 130.8, 129.9, 126.8, 126.8, 124.9, 123.2, 122.7, 122.1, 129.6, 113.7, 62.7, 60.7, 30.1, 26.5, 26.5, 26.0, 25.9, 21.8, 21.6, 18.3, 14.3, −5.3, −5.3 ppm.

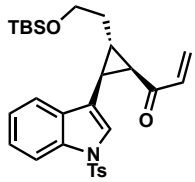
Rf: 0.35 (hexane/EtOAc 10:1)

Diethyl fumarate:

^{1}H (400 MHz, $CDCl_3$) δ = 6.85 (s, 1H), 4.26 (q, J = 7.2Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H) ppm.

Rf: 0.6 (hexane/EtOAc 10:1).

1-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)prop-2-en-1-one (253)



Ethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl) cyclopropane carboxylate (**248**) (254 mg, 470 µmol, 1 equiv.) was dissolved in THF (1.60 mL) and cooled to 0 °C. Then Ti(O*i*Pr)$_4$ (154 µL, 1.05 mmol, 1.1 equiv.) was added and lastly EtMgBr in Et_2O (3 M, 470 µL, 3 equiv.) was added dropwise over 3 h. Subsequently aq. sat. Na/K tartrate solution was added and the mixture stirred for 30 min. Then the reaction was extracted three times with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. After purification with flash chromatography (hexane/EtOAc 5:1) the compound was obtained as a colorless oil.

The resulting alcohol **252** (112 mg, 210 µmol, 1 equiv.) was dissolved in MeCN (3 mL) and Pd_2dba_3 (9.70 mg, 10 µmol, 0.05 equiv) was added. The reaction was heated to reflux for 2 h and then concentrated. Purification by flash chromatography (hexane/EtOAc 20:1 to 10:1) gave the title compound as a white wax-like substance.

Yield: 82 mg (34%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* =8.2 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 1.0 Hz, 1H), 7.25 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 1.0 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.19 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 6.24 (dd, J_1 = 17.6 Hz, J_2 = 10.4 Hz, 1H), 6.09 (dd, J_1 = 17.7 Hz, J_2 = 1.4 Hz, 1H), 5.62 (dd, J_1 = 10.6 Hz, J_2 = 1.4 Hz, 1H), 3.80 (t, *J* = 6,3 Hz, 2H), 2.60 (dd, J_1 = 8.8 Hz, J_2 = 5.1 Hz, 1H), 2.51 (ddd, J_1 = 8.6 Hz, J_2 = 6.9 Hz, J_3 = 0.9 Hz, 1H), 2.34 (s, 3H), 2.26 (qd, J_1 = 6.7, J_2 = 5.5 Hz, 1H), 1.80 (qdd, J_1 = 13.9 Hz, J_2 = 7.0 Hz, J_2 = 7.0 Hz, 2H) 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.

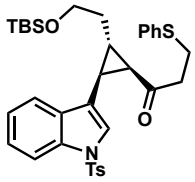
^{13}C (100 MHz, $CDCl_3$) δ = 194.8, 144.5, 137.1, 135.2, 135.0, 131.5, 130.1, 127.0, 126.9, 125.3, 124.4, 123.0, 119.0, 117.6, 113.7, 62.4, 36.1, 33.7, 26.2, 25.9, 23.3, 21.5, 18.3, −5.3, −5.4 ppm.

IR (ATR): 2953, 2926, 2854, 1683, 1446, 1373, 1174, 1122, 1097, 835, 812, 777, 746, 669, 582, 538, 419 cm^{-1}.

HRMS (ESI) calculated for $C_{29}H_{37}NO_4SSiNa^+$ 546.2110; 546.2102.

Rf: 0.5 (hexane/EtOAc 10:1)

1-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-(phenylthio)propan-1-one (254)



Vinylcyclopropane **253** (29.0 mg, 56.0 µmol, 1 equiv.) was dissolved in THF (200 µL) and thiophenol (7 µL, 66.0 µmol, 1.2 equiv.) was added. The reaction was stirred for 1.25 h and subsequently diluted with water. The resulting mixture was three times extracted with EtOAc and the combined organic layers were then washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained after purification with flash chromatography (hexanes/EtOAc 10:1 to 5:1 to 2:1).

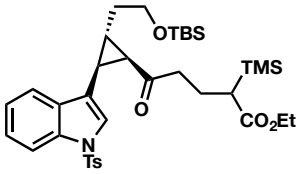
Yield: 19 mg (54%).

^{1}H (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.33 (s, 1H), 7.28 (ddd, J_1 = 7.7 Hz, J_1 = 7.2 Hz, J_3 = 0.7 Hz, 1H), 7.18 (ddd, J_1 = 7.7 Hz, J_2 = 7.3 Hz, J_4 = 0.9 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.12 (m, 2H), 6.94 (m, 2H), 3.74 (t, *J* = 6.3 Hz, 2H), 2.61 (m, 2H), 2.52 (m, 2H), 2.45 (m, 1H), 2.32 (m, 1H), 2.24 (s, 3H), 2.19 (m, 1H), 1.76 (m, 1H), 1.69 (m, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04(s, 3H) ppm.

HRMS (ESI) calculated for $C_{35}H_{43}NO_4S_2SiNa^+$ 656.2301; found 656.2302.

Rf: 0.3 (hexanes/EtOAc 10:1)

Ethyl 5-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-5-oxo-2-(trimethylsilyl)pentanoate (256)



NaHMDS in THF (2 M, 15 µL, 30.0 µmol, 1.5 equi.v) was diluted with THF (50 µL) and cooled to −78 °C before ethyl trimethylsilylacetate (6 µL, 30.0 µmol, 1.5 equiv.) in THF (50 µL) was added. After 1 h vinylcyclopropane **253** was added and the reaction stirred for 45 min. before aq. sat. NH_4Cl solution was added. The reaction was extracted three times with EtOAc and then the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained after flash chromatography (hexanes/EtOAc 10:1 to 5:1).

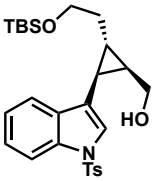
Yield: 7 mg (50%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 7.8 Hz, 1H), 7.76 (dd, J_1 = 8.3 Hz, J_2 = 2.9 Hz, 2H), 7.52 (m, 1H), 7.39 (dd, J_1 =9.7 Hz, J_2 = 0.8 Hz, 1H), 7.25 (ddd, J_1 = 7.9 Hz, J_2 = 7.4 Hz, J_3 = 1.6 Hz, 1H), 7.23 (d, J = 1.0 Hz, 1H), 7.22 (d, J = 9.2 Hz, 2H), 4.07 (m, 2H), 3.77 (t, J = 6.1 Hz, 2), 2.50 (m, 1H), 2.43 (m, 1H), 2.34 (s, 3H), 2.33 (m, 1H), 2.23 (m, 1H), 2.18 (m, 1H), 1.80 (m, 2H), 1.69 (m, 2H), 1.33 (m, 1H), 1.20 (dt, J_1 = 17.9 Hz, J_2 = 6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), −0.08 (d, J = 9.0 Hz, 9H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 204.5, 174.9, 144.4, 135.3, 134.9, 131.4, 129.7, 126.9, 125.4, 125.1, 124.4, 123.2, 123.0, 118.9, 117.4, 113.7, 62.4, 59.7, 44.3, 37.1, 36.8, 36.1, 35.6, 25.9, 25.8, 23.3, 23.2, 21.5, 21.1, 20.9, 18.3, 14.5, −2.9, −5.3 ppm.

Rf 0.5 (hexanes/EtOAc 10:1).

2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methan (248a)



The crude ester **248** was dissolved in CH_2Cl_2 (65 mL) and cooled to −78 °C. DiBAL-H in hexane (1 M, 50.36 mL, 50.36 mmol, 4 equiv.) was added and after 20 min at −78 °C, all the remaining solid dry ice was removed from the aceton-dry ice bath and the bath was warmed to −20 °C over 1 h. Then the solution was poured onto aq. sat. Na/K tartrate solution and Et_2O was added. The biphasic system was stirred vigorously for 12 h and then extracted three times with Et_2O. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and

concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 5:1 to 3:1) the cyclopropyl alcohol was isolated as a mixture of diastereomers. A partial separation for NMR was possible.

Yield: 4.09 g (65%), d.r.: 3.2:1 for the desired *cis* compound

Major diastereomer

^{1}H (400 MHz, $CDCl_3$) δ = 7.99 (ddd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, J_3 = 0.7 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.63 (ddd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, J_3 = 0.7 Hz, 1H), 7.34 (ddd, J_1 = 8.3 Hz, J_2 = 7.2 Hz, J_3 = 1.1 Hz, 1H), 7.30 (d, J = 1.0 Hz, 1H), 7.27 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.0 Hz, 1H), 7.22 (ddd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, J_3 = 2.0 Hz, 2H), 3.8 (t, J = 6.1 Hz, 2H), 3.40 (dd, J_1 = 11.4 Hz, J_2 = 6.6 Hz, 1H), 3.24 (dd, J_1 = 11.6 Hz, J_2 = 8.2 Hz, 1H), 2.35 (s, 3H), 1.91 (ddd, J_1 = 8.5 Hz, J_2 =5.3 Hz, J_3 = 1.2 Hz, 1H), 1.81 (ddd, J_1 = 13.6 Hz, J_2 = 12.6 Hz, J_3 = 6.2 Hz, 1H), 166 (dd, J_1 = 6.8 Hz, J_2 = 6.8 Hz, 1H), 1.61 (dd, J_1 = 6.8 Hz, J_2 = 6.8 Hz, 1H), 1.42 (ddd, J_1 =8.2 Hz, J_2 = 6.5 Hz, J_3 = 3.1 Hz, 1H), 1.21 (ddd, J_1 = 11.9, J_2 = 5.6 Hz, J_2 = 1.2 Hz, 1H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm.

IR (ATR): 2953, 2926, 2854, 1494, 1369, 1172, 1120, 1097, 835, 812, 775, 746, 704, 674, 574, 538, 416 cm^{-1}.

HRMS (ESI) calculated for $C_{27}H_{37}NO_4SiSNa^+$ 522.2110; found 522.2116.

Rf: 0.2 (hexane/EtOAc 3:1)

Minor diastereomer

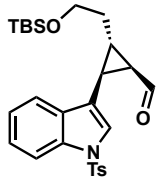
^{1}H (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.5 Hz, 1H), 7.73 (ddd, J_1 = 7.8 Hz, J_2 =1.7 Hz, J_3 = 1.7 Hz, 2H), 7.52 (bd, J = 7.8 Hz, 1H), 7.31 (ddd, J_1 = 8.2 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, 1H), 7.23 (dd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 0.8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.19 (s, 1H), 4.06 (b, 1H), 3.90 (ddd, J_1 = 9.9 Hz, J_2 = 4.1 Hz, J_3 = 4.1 Hz, 1H), 3.75 (ddd, J_1 = 10.2 Hz, J_2 = 10.2 Hz, J_3 = 3.4 Hz, 1H), 3.60 (bd, J = 9.2 Hz, 1H), 3.47 (dd, J_1 =11.4 Hz, J_2 = 10.4 Hz, 1H), 2.33 (s, 3H), 2.07 (ddd, J_1 = 14.7 Hz, J_2 = 6.8 Hz, J_3 = 3.4 Hz, 1H), 1.70 (m, 1H), 1.62 (m, 1H), 1.47 (bt, J = 5.0 Hz, 1H), 1.14 (m, 1H), 1.35 (s, 9H), 0.12 (s, 3H), 0.12 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 144.8, 135.3, 135.2, 131.2, 129.8, 126.8, 124.8, 124.4, 123.1, 121.3, 119.4, 113.8, 64.2, 61.5, 30.5, 27.8, 26.1, 23.5, 21.6, 18.7, 16.4, −5.4, −5.5 ppm.

Rf: 0.21 (hexane/EtOAc 3:1)

HRMS (ESI) calculated for $C_{27}H_{37}NO_4SSiNa^+$ 522.2110; found 522.2112.

2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropanecarbaldehyde (262)



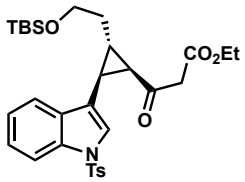
Alcohol **248a** (2.54 g, 5.06 mmol, 1 equiv.) was dissolved in DMSO (25 mL) and IBX (2.13 g, 7.63 mmol, 1.6 equiv.) was added. After stirring for 3 h, water and Et_2O were added and the resulting precipitate was filtered off. The filtrate was three times extracted with EtOAc and the combine organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude aldehyde was used without any further purifications as isomerization and degradation occurred during flash chromatography. The compound forms a very viscous, white gel over time.

Yield: 2.52 g (quant)

Rf major: 0.5 (hexane/EtOAc 3:1)

Rf minor: 0.52 (hexane/EtOAc 3:1)

Ethyl 3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropanoate (258)



Aldehyde **262** (155 mg, 300 µmol, 1 equiv.) and zinc powder (100 mg, 1.50 mmol, 5 equiv.) were added to THF (2 mL). Subsequently ethyl bromoacetate (110 µL, 1.00 mmol, 3.3 equiv.) was added and the reaction briefly heated to reflux with a heat gun. The reaction turned green and was stirred at r.t. for 2 h. Then aq. sat. NH_4Cl solution was added and the reaction three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. A short flash chromatography (hexane/EtOAc 3:1) gave a mixture of four diastereomers which were dissolved in DMSO (1.5 mL) and IBX (208 mg, 0.75 mmol, 2 equiv.) was added. After 2 h water was added and the reaction was three extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

After flash chromatography (hexane/EtOAc 5:1) the two diastereomers could be isolated.

Yield: 56 mg (31% combined, over 3 steps)

Major dia (desired):

^{1}H (400 MHz, $CDCl_3$) δ = 7.86 (bd, J = 8.2 Hz, 1H), 7.72 (ddd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, J_3 = 1.7 Hz, 2H), 7.52 (ddd, J_1 = 7.7 Hz, J_2 = 1.2 Hz, J_3 = 0.7 Hz, 1H), 7.38 (d, J = 0.7 Hz, 1H), 7.23 (dd, J_1 = 8.2 Hz, J_2 = 1.7 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H) 7.19 (ddd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, J_3 = 1.3 Hz, 1H), 3.87 (tdd, J_1 = 15.1 Hz, J_2 = 7.2 Hz, J_3 = 3.1 Hz, 1H), 3.87 (dd, J_1 = 12.3 Hz, J_2 = 7.2 Hz, 1H), 3.76 (t, J = 6.3 Hz, 2H), 3.25 (d, J = 2.7 Hz, 2H), 2.52 (m, 2H), 2.32 (s, 3H), 2.20 (ddd, J_1 = 6.8 Hz, J_2 = 5.7 Hz, J_3 = 3.3 Hz, 1H), 1.80 (ddd, J_1 = 13.4 Hz, J_2 = 13.4 Hz, J_2 = 6.9 Hz, 1H), 1.70 (ddd,

J_1 = 13.7 Hz, J_2 = 13.7 Hz, J_3 = 6.7 Hz, 1H), 0.96 (t, J = 7.2 Hz, 3H), 0.89 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H) ppm.

^{13}C (125 MHz, $CDCl_3$) δ = 196.6, 167.0, 144.6, 135.1, 134.9, 131.3, 129.7, 126.9, 125.4, 124.5, 123.1, 119.0, 117.0, 113.7, 62.2, 31.1, 50.6, 36.0, 15.8, 27.0, 25.9, 24.6, 21.5, 18.2, 13.8, −5.3 ppm.

Rf: 0.5 (hexane/EtOAc 3:1)

Minor dia (undesired):

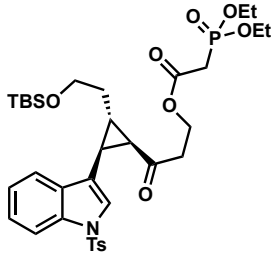
^{1}H (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 1H), 7.32 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 1.2 Hz, 1H), 7.25 (d, J = 0.7 Hz, 1H), 7.23 (m, 1H), 7.22 (d, J = 8.5 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.76 (m, 1H), 3.69 (m, 2H), 3.61 (d, J = 2.1 Hz, 1H), 2.64 (ddd, J_1 = 6.8 Hz, J_2 = 5.1 Hz, J_3 = 1.0 Hz, 1H), 2.34 (s, 3H), 2.32 (m, 1H), 2.05 (dt, J_1 = 15.9 Hz, J_2 = 7.1 Hz, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.88 (s, 6H), 0.05 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 199.8, 167.1, 145.0, 135.3, 135.2, 130.6, 129.9, 126., 125.0, 123.2, 122.4, 122.3, 119.6, 113.7, 62.7, 61.4, 51.1, 34.5 30.6, 29.2, 26 0, 24.1 21.6, 18.3, 14.1, −5.2, −5.3 ppm.

HRMS (ESI) calculated for $C_{31}H_{41}NO_6SSiNa^+$ 606.2322; found 606.2322.

Rf: 0.51 (hexane/EtOAc 3:1)

3-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl 2-(diethoxyphosphoryl)acetate (264)



Aldehyde **262** (1.10 g, 2.21 mmol, 1 equiv.) and zinc powder (760 mg, 11.1 mmol, 5 equiv.) were added to THF (10 mL). Subsequently ethyl bromoacetate (730 µL, 6.63 mmol, 3.3 equiv.) was added and the reaction briefly heated to reflux with a heat gun. The reaction turns green and is then stirred at r.t. for 2 h. Then aq. sat. NH_4Cl solution was added and the reaction three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. A short flash chromatography (hexane/EtOAc 3:1) gave a mixture of four diastereomers of **262a** (1.13 g).

Half of the mixture (565 mg, 970 µmol, 1 equiv.) was dissolved in Et_2O (5 mL) and cooled to −78 °C. To this was added $LiAlH_4$ in THF (2.4 M, 1.21 mL, 2.90 mmol, 3 equiv.) and stirred for 30 min at −78 °C and subsequently for 30 min at −40 °C. Then aq. sat. Na/K tartrate solution was added and the reaction stirred vigorously for 2 h at room temperature. Then the reaction was extracted three times with EtOAc and the combined organic layers were washed with brine

solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. A short flash chromatography (hexane/EtOAc 1:1 to 1:3) gave a mixture of isomers of **263** (319 mg) which were taken directly to the next step.

The crude diol **263** was dissolved in CH_2Cl_2 (2 mL) and diethyl carboxymethylphosphonate (116 mg, 590 µmol, 1 equiv.) as well as DMAP (14 mg, 110 µmol, 0.2 equiv.) were added and cooled to 0 °C. Finally EDCI•HCl (135 mg, 700 µmol, 1.2 equiv.) was added and the reaction slowly warmed to r.t. over 12 h. Then water was added and the reaction was extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 1:2 to 1:4) gave a mixture of isomers (216 mg, 300 µmol), which was used directly for the next reaction. The mixture of isomers was dissolved in CH_2Cl_2 (1.5 mL) and then MS 3Å (300 mg) and PDC (281 mg, 750 µmol, 2.5 equiv.) were added. After stirring for 1.5 h, Et_2O was added and the resulting precipitate was filtered off. The filtrate was concentrated and after purification with flash chromatography (hexane/EtOAc 1:2 to 1:4) gave the title compound as a mixture separable isomers.

Combined yield: 150 mg (15% over 4 steps), d.r.: 2:1

Desired isomer:

^{1}H (400 MHz, $CDCl_3$) δ = 7.87 (d, J = 8.2 Hz, 1H), 7.72 (ddd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, J_3 = 1.8 Hz, 2H), 7.49 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1H), 7.35 (d, J = 0.7 Hz, 1H), 7.24 (dd, J_1 = 8.0 Hz, J_2 =1.5 Hz, 1H), 7.21 (m, 1H), 7.20 (d, J = 8.9 Hz, 2H), 4.15 (m, 1H), 4.10 (ddd, J_1 = 13.8, J_2 = 8.4 Hz, J_3 = 1.5 Hz, 2H), 4.08 (ddd, J_1 = 14.2 Hz, J_2 = 8.2 Hz, J_3 = 1.4 Hz, 2H), 3.94 (dt, J_1 = 11.3 Hz, 6.1 Hz, 1H), 3.75 (t, J = 6.1 Hz, 2H), 2.70 (dt, J_1 = 17.6 Hz, J_2 = 6.2 Hz, 1H), 2.57 (dt, J_1 = 17.4 Hz, J_2 = 6.2 Hz, 1H), 2.48 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 0.8 Hz, 1H), 2.44 (d, J = 21.5 Hz, 2H), 2.34 (dd, J_1 =9.4 Hz, J_2 = 5.6 Hz, 1H), 2.33 (s, 3H), 2.20 (dd, J_1 = 13.5 Hz, J_2 = 7.0 Hz, J_3 = 5.6 Hz, 1H), 1.80 (ddd, J_1 = 20.5 Hz, J_2 = 6.5 Hz, J_3 = 6.5 Hz, 1H), 1.68 (ddd, J_1 = 13.7 Hz, J_2 = 7.2 Hz, J_3 = 6.5 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 130 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 200.9, 165.6, 165.5, 144.8, 135.0, 134.9, 131.4, 129.9, 129.8, 126.7, 125.5, 124.6, 123.2, 118.8, 117.1, 113.8, 62.7, 62.6, 62.2, 60.0, 42.1, 35.9, 34.2, 32.9, 26.2, 25.9, 23.3, 21.5, 18.3, 16.3, −5.3 ppm.

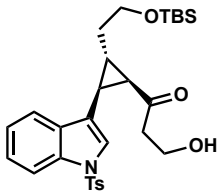
Rf: 0.3 (hexane/EtOAc 1:2

Undesired isomer

^{1}H (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.50 (ddd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, J_3 = 1.0 Hz, 1H), 7.32 (ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 7.25 (s, 1H), 7.23 (m, 1H), 7.22 (d, J = 8.6 Hz, 2H), 4.45 (t, J = 6.6 Hz, 2H), 4.17 (m, 4H), 3.76-3.60 (m, 2H), 3.0 (m, 2H), 2.93 (d, J = 21.5 Hz, 2H), 2.61 (ddd, J_1 = 6.6 Hz, J_2 = 0.9 Hz, J_3 = 0.2 Hz, 1H), 2.34 (s, 3H), 2.27 (dd, J_1 = 8.9 Hz, J_2 = 4.8 Hz, 1H), 1.99 (dq, J_1 = 7.7 Hz, J_2 = 7.3 Hz, 1H), 1.87 (m, 1H), 1.78 (m, 1H), 1.33 (m, 6H), 0.88 (s, 9H), 0.04 (s, 6H) ppm.

Rf: 0.4 (hexane/EtOAc 1:2)

1-((1*R*,2*S*,3*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-hydroxypropan-1-one (253a)



Phosphonate **264** (27.0 mg, 38.0 µmol, 1 equiv.) was dissolved in THF (300 µL) and cooled to −20 °C. To this was added *t*-BuOLi (3.00 mg, 38.0 µmol, 1 equiv.) and the reaction was stirred for 1 h at −20 °C. Then aq. sat. NH_4Cl solution was added and the reaction was three times extracted with EtOAc. The combined organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The curde product was purified *via* flash chromatography (hexane/EtOAc 2:1-1:1).

Yield: 5mg (24%)

The same product was also obtained in another manner

CuCl (3.00 mg, 30.0 µmol, 0.2 equiv.) and NaO*t*Bu (3.00 mg, 30 µmol, 0.2 equiv.) were dissolved in THF (200 µL) and stirred for 10 min before bis(pinacolato)diboron (45.0 mg, 176 µmol, 1.1 equiv.) was added to the reaction and stirred for 10 min. Then enone **253** (82.0 mg, 160 µmol, 1 equiv.) dissolved in THF (600 µL) was added, followed by the addition of water (400 µL). The reaction was stirred for 16 h at r.t. before brine solution was added. The reaction was extracted three times with EtOAc and the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in THF (800 µL) and water (800 µL) followed by the addition of $NaBO_3{\cdot}4H_2O$ (123 mg, 800 µmol, 5 equiv.). The reaction was stirred vigorously for 16 h before being diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After flash chromatography (hexane/EtOAc 2:1 to 1:1) the compound was obtained as a colorless oil.

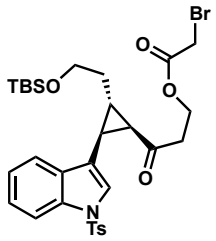
Yield: 65 mg (75%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.91 (bd, *J* = 7.9 Hz, 1H), 7.74 (bd, *J* = 8.2 Hz, 2H), 7.48 (bd, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 1.0 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.23 - 7.17 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.76 (t, *J* = 6.1 Hz, 2H), 3.47 (b, 1H), 3.31 (b, 1H), 2.58 (ddd, J_1 = 17.9 Hz, J_2 = 7.0 Hz, J_3 = 3.8 Hz, 1H), 2.51 - 2.45 (m, 2H), 2.51 – 2.41 (m, 1H), 2.35 (t, *J* = 4.4 Hz, 1H), 2.32 (s, 3H), 2.20 (m, 1H), 1.75 (m, 2H), 0.89 (s,)H), 0.06 (s, 3H), 0.05 (s, 3H) ppm.

^{13}C (100 Mhz, $CDCl_3$) δ = 206.1, 145.0, 135.2, 135.1, 131.4, 129.8, 127.0, 125.5, 124.8, 123.4, 118.9, 117.5, 114.0, 62.4, 57.9, 45.3, 36.1, 36.0, 26.4, 26.1, 23.6, 21.7, 18.4, −5.2 ppm.

Rf: 0.9 (hexane/EtOAc 1:2)

3-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl 2-bromoacetate (266)



Alcohol **253** (56.0 mg, 100 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (0.5 mL) and bromo-acetic acid (19.0 g, 130 µmol, 1.3 equiv.) as well as DMAP (2.50 g, 20.0 µmol, 0.2 equiv.) were added. Subsequently DIC (25 µL, 160 µmol, 1.6 equiv.) was added and the reaction stirred for 45 min. Then water was added and the reaction three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After flash chromatography (hexane/EtOAc 5:1) the compound was obtained as lightly yellow oil.

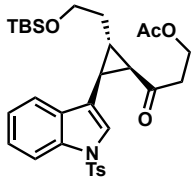
Yield: 50 mg (76%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.50 (dd, J_1 = 6.8 Hz, J_2 = 1.0 Hz, 1H), 7.39 (d, *J* = 1.0 Hz, 1H), 7.34 (d, *J* = 4.8 Hz, 1H), 7.25 (m, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.05 (m, 2H), 3.76 (m, 2H), 2.86 (d, *J* = 13.0 Hz, 1H), 2.76 (d, *J* = 12.6 Hz, 1H), 2.64 (ddd, J_1 = 5.9 Hz, J_2 = 5.9 Hz, J_3 = 2.0 Hz, 2H), 2.51 (ddd, J_1 =8.41 Hz, J_2 = 7.3 Hz, J_3 = 0.7 Hz, 1H), 2.38 (m, 1H), 2.33 (s, 3H), 2.24 (ddd, J_1 = 13.3 Hz, J_2 = 6.3 Hz, J_3 = 5.5 Hz, 1H), 1.79 (dd, J_1 = 13.6 Hz, J_2 = 6.5 Hz, 1H), 1.70 (dd, J_1 = 13.7 Hz, J_2 = 7.2 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm.

HRMS (ESI) calculated for $C_{31}H_{40}BrNO_6SSiNa^+$ 684.1427; found 684.1426.

Rf: 0.2 (hexane/EtOAc 5:1)

3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl acetate (266a)



Bromoacetate **266** (7.00 mg, 10.0 µmol, 1 equiv) and RhCl $(PPh_3)_3$ (10.2 mg, 11.0 µmol, 1.1 equiv.) were dissolved in THF (200 µL). The solution was stirred at 0 °C for 5 min. and subsequently Et_2Zn in hexane (1 M, 22.0 µL, 22.0 µmol, 2.2 equiv.) was added. After 5 min. the reaction was warmed to ambient temperature and stirred for 2h. Then aq. sat. NH_4Cl solution was added and the reaction was three times extracted with EtOAc. The combined organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated. Purification with flash chromatography (hexane/EtOAc 5:1) then gave the title compound.

Yield: 5.8 mg (quant.)

The same product was also obtained in another manner

Hydroxy ketone **253a** (40.0 mg, 74.0 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (400 µL) and cooled to 0 °C. To this was added AcOH (5 µL, 89.0 µmol, 1.2 equiv.), DMAP (16.0 mg, 15.0 µmol, 0.2 equiv.) and finally DIC (16.0 µL, 103 µmol, 1.4 equiv.). The reaction was stirred for 20 min at 0 °C and then warmed to r.t. After 40 min the reaction was diluted with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.* After purification with flash chromatography (hexane/EtOAc 3:1) the product was obtained as a colorless liquid.

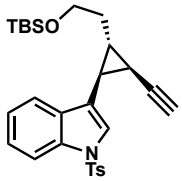
Yield: 33 mg (77%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.86 (d, J = 7.2 Hz, 1H), 7.73 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, J_3 = 1.8 Hz, 2H), 7.50 (dd, J_1 = 6.7 Hz, J_2 = 1.2 Hz, 1H), 7.38 (d, J = 0.7 Hz, 1H), 7.23 (ddd, J_1 = 8.1 Hz, J_2 = 7.9 Hz, J_3 = 1.6 Hz, 1H), 7.20 (d, J = 8.3 Hz, 2H), 7.19 (ddd, J_1 = 7.4 Hz, J_2 = 7.3 Hz, J_3 = 1.3 Hz, 1H), 4.00 (ddd, J_1 = 11.3 Hz, J_2 = 6.2 Hz, J_3 = 5.4 Hz, 1H), 3.92 (ddd, J_1 = 11.4 Hz, J_2 = 6.9 Hz, J_3 = 5.2 Hz, 1H), 3.76 (t, J = 6.3 Hz, 2H), 2.60 (m, 2H), 2.49 (ddd, J_1 = 8.4 Hz, J_2 = 7.2 Hz, J_3 = 0.8 Hz, 1H), 2.36 (dd, J_1 = 8.9 Hz, J_2 = 5.1 Hz, 1H), 2.32 (s, 3H), 2.22 (ddd, J_1 = 13.6 Hz, J_2 = 6.7 Hz, J_3 = 5.5 Hz, 1H), 1.79 (ddd, J_1 = 20.8 Hz, J_2 = 7.0 Hz, J_1 = 7.0 Hz, 1H), 1.70 (ddd, J_1 = 20.5 Hz, J_2 = 6.7 Hz, J_3 = 6.7 Hz, 1H), 1.44 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm.

^{13}C (100 Mz, $CDCl_3$) δ = 201.2, 170.7, 144.8, 134.9, 131.4, 129.9, 129.7, 126.9, 126.7, 125.5, 124.5, 123.1, 118.8, 117.1, 113.8, 62.3, 58.9, 42.2, 36.0, 26.1, 25.9, 23.2, 21.5, 20.1, 18.3, −5.3 ppm.

Rf: 0.9 (hexane/EtOAc 1:1)

3-((1*S*,2*R*,3*R*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-ethynylcyclopropyl)-1-tosyl-1*H*-indole (267)



A mixture of diastereomers of aldehyde **262** (984 mg, 1.98 mmol, 1 equiv.) was dissolved in MeOH (10 mL). Warming the initially formed suspension in a rotavap bath lead to a clear solution. Subsequently dimethyl (1-diazo-2-oxopropyl)phosphonate (951 mg, 4.95 mmol, 2.5 equiv) dissolved in MeOH (1 mL) and finally K_2CO_3 (684 mg, 4.95 mmol, 2.5 equiv.) were added. The reaction was stirred at r.t. for 12 h and then diluted with water followed by three fold extraction with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After flash chromatography (hexane/EtOAc 20:1) both isomers could be separated and obtained as yellow liquids.

Yield: 586 mg (60%)

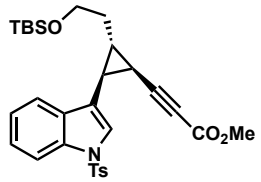
Major dia (Desired)

^{1}H (400 MHz, $CDCl_3$) δ = 7.95 (ddd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, J_2 = 0.7 Hz, 1H), 7.73 (ddd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, J_3 = 1.8 Hz, 2H), 7.61 (ddd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, J_3 = 0.7 Hz, 1H), 7.32 (ddd, J_1 = 8.2 Hz, J_2 = 7.2 Hz, J_3 = 1.4 Hz, 1H), 7.25 (ddd, J_1 = 7.7 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 7.22 (d, J = 1.3 Hz, 1H) 7.21 (d, J = 8.0 Hz, 2H), 3.83 (m, 2H), 2.34 (s, 3H), 1.98 (d, J = 2.1 Hz, 1H), 1.90 (m, 2H), 1.89 (m, 1H), 1.62 (ddd, J_1 = 8.5 Hz, J_2 = 5.0 Hz, J_3 = 2.2 Hz, 1H), 1.48 (ddd, J_1 = 14.2 Hz, J_2 = 7.1 Hz, J_3 = 7.1 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 144.9, 135.3, 135.2, 130.9, 129.9, 126.8, 124.9, 123.2, 123.0, 121.9, 119.7, 113.7, 83.2, 67.5, 62.3, 33.0, 26.0, 25.9, 23.1, 23.0, 21.6, 18.4, 14.1, 1.0, −5.2, −5.3 ppm.

Rf: 0.5 (hexane/EtOAc 10:1)

Methyl 3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (268)



Alkyne **267** (3.24 g, 6.56 mmol, 1 equiv.) was dissolved in THF (35 mL) and cooled to −78 °C. A Solution of *n*-BuLi in hexanes (3.93 mL, 9.84 mmol, 1.5 equiv.) was added followed by TMEDA (1.59 mL, 9.84 mmol, 1.5 equiv.). After 10 min the reaction was warmed to −20 °C and stirred at that temperature for 3 h. Then methyl chloroformate (1.52 mL, 19.68 mmol, 3 equiv.) was added and the reaction stirred for 12 h at −20 °C. Finally aq. sat. NH_4Cl solution was added and the reaction three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 10:1) gave the desired compound as lightly yellow oil.

Yield: 2.55 g (70%)

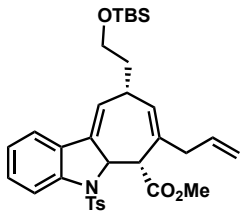
^{1}H (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.59 Hz, 1H), 7.33 (ddd, J_1 =8.2 Hz, J_2 = 7.4 Hz, J_3 = 0.9 Hz, 1H), 7.27 (m, 1H), 7.24 (d, J = 1.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 3.83 (dt, J_1 = 6.0 Hz, J_2 = 5.7 Hz, 2H), 3.77 (s, 3H), 2.34 (s, 3H), 2.13 (ddd, J_1 = 5.4 Hz, J_2 = 5.4 Hz, J_3 = 0.7 Hz, 1H), 1.91 (m, 2H), 1.72 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 154.1, 145.0, 135.2, 130.6, 129.9, 126.8, 125.1, 123.3, 122.3, 121.9, 119.6, 113.7, 89.3, 71.9, 62.1, 52.7, 33.0, 25.9, 24.8, 24.4, 21.6, 18.3, 14.0, −5.3 ppm.

HRMS (ESI) calculated for $C_{30}H_{37}NO_5SSiNa^+$ 574.2059; found 574.2058.

Rf: 0.15 (hexane/EtOAc 10:1)

Methyl 7-allyl-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (270)



To MeOH (0.6 mL) was added $Cu(OAc)_2$ (2.20 mg, 12.0 µmol, 0.05 equiv.) and stirred at r.t. Subsequently ester **268** (130 mg, 240 µmol, 1 equiv.) dissolved in MeOH (0.6 mL) and finally allylboronic acid pinacol ester (125 µL, 480 µmol, 2 equiv.) were added. The reaction was stirred for 2.5 h and then diluted with water. This was followed by three-fold extraction with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 10:1) the cyclohepta[*b*]indole was obtained.

Yield: 90 mg (63%)

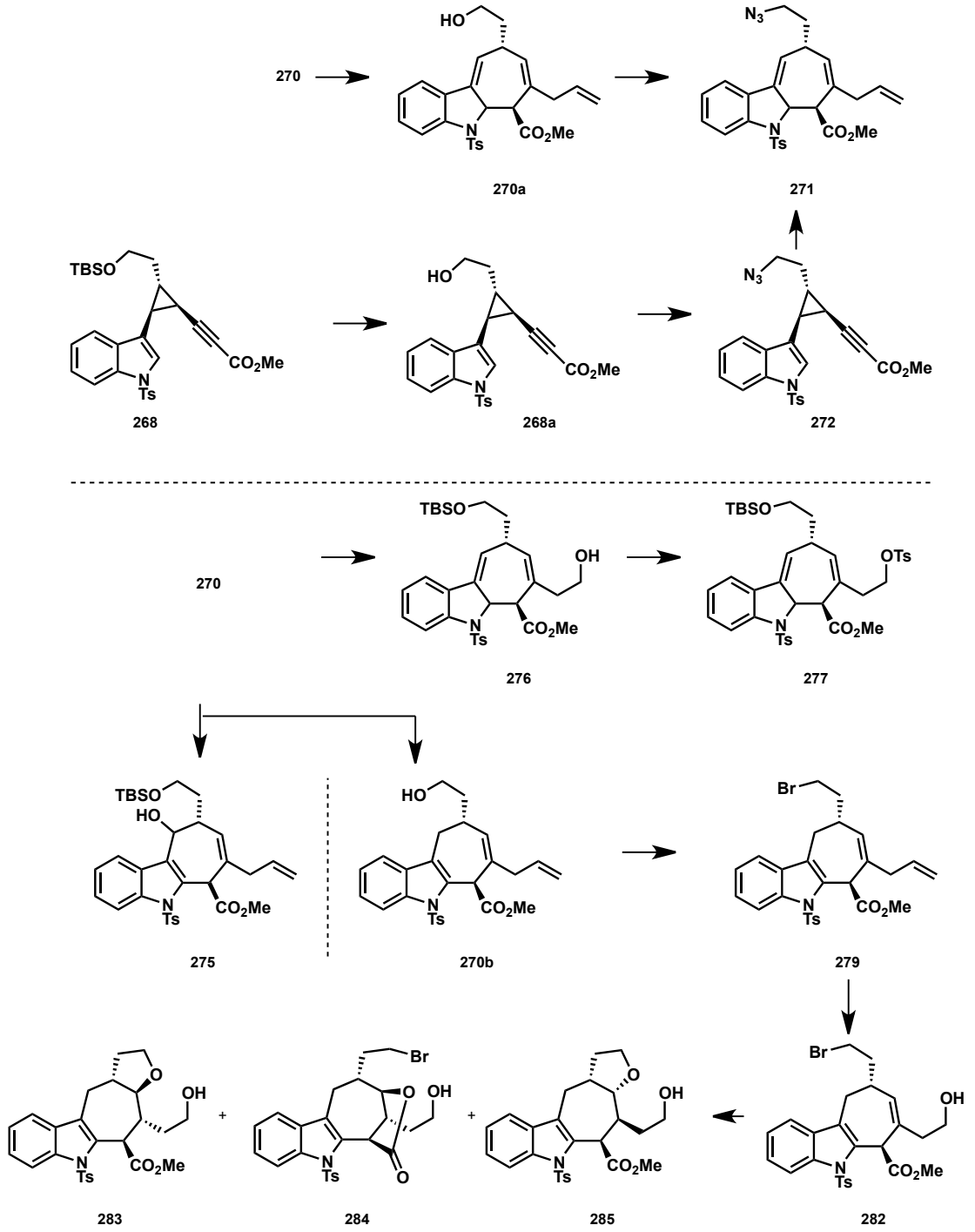
^{1}H (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 9.2 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.22 (ddd, J_1 = 8.2 Hz, J_2 = 7.4 Hz, J_3 = 1.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.03 (J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 0.8 Hz, 1H), 6.10 (dd, J_1 = 5.8 Hz, J_2 = 2.8 Hz, 1H), 5.61 (dddd, J_1 = 17.0, J_2 = 10.4 Hz, J_3 = 7.1 Hz, J_4 = 6.5 Hz, 1H), 5.54 (d, *J* = 3.8 Hz, 1H), 5.50 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1H), 4.96 (m, 1H), 4.94 (m, 1H), 3.89 (s, 3H), 3.64 (ddd, J_1 = 6.3 Hz, J_2 = 6.3 Hz, J_3 = 2.4 Hz, 2H) 3.40 (d, *J* = 8.8 Hz, 1H), 3.15 (m, 1H), 2.68 (ddd, J_1 = 22.0 Hz, J_2 = 15.6 Hz, J_3 = 6.6 Hz, 2H), 2.32 (s, 3H), 1.74 (q, *J* = 6.9 Hz, 2H), 0.88 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.5, 144.1, 143.0, 135.3, 134.9, 133.6, 133.2, 132.0, 129.6, 129.0, 127.8, 127.5, 124.9, 120.1, 117.9, 117.2, 64.8, 61.1, 53.5, 52.6, 42.3, 38.0, 33.2, 25.9, 24.8, 21.6, 18.2, −5.4, −5.4 ppm.

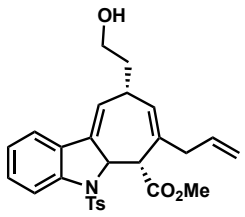
HRMS (ESI) calculated for $C_{33}H_{43}NO_5SSiNa^+$ 616.2529; found 616.2527.

Rf: 0.4 (hexane/EtOAc 5:1)

Graphical abstract: Studies on the derivatisation of cyclohepta[*b*]indole 270



Methyl 7-allyl-9-(2-hydroxyethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (270a)



Protected alcohol **270** (55 mg, 90 µmol, 1 equiv.) was dissolved in THF (450 µL) and cooled to −20 °C. A solution of HF in pyridine (0.2 M, 450 µL, 90 µmol, 1 equiv.) was added and after stirring for 2 h at −20 °C, 1 h at 0 °C and finally 30 min at r.t., the reaction was diluted with aq. sat. $CaCl_2$ solution and extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 1:1) the product was obtained as white solid.

Yield: 32 mg (73%)

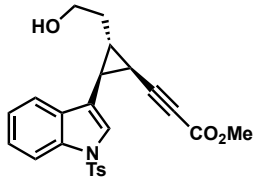
^{1}H (400 MHz, $CDCl_3$) δ = 7.76 (ddd, J_1 = 8.1 Hz, J_2 = 0.7 Hz, J_3 = 0.7 Hz, 1H), 7.55 (ddd, J_1 = 8.5 Hz, J_2 = 1.9 Hz, J_3 = 1.9 Hz, 2H), 7.26 (ddd J_1 = 8.3 Hz, J_2 = 7.6 Hz, J_3 = 0.8 Hz, 1H), 7.22 (dd, J_1 = 7.6 Hz, J_2 = 0.6 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.07 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 7.5 Hz, 1H), 6.10 (dd, J_1 = 6.0 Hz, J_2 = 2.7 Hz, 1H), 5.63 (dddd, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 6.9 Hz, J_4 = 6.5 Hz, 1H), 5.58 (db, J = 5.1 Hz, 1H), 5.54 (ddd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, J_3 = 0.8 Hz, 1H), 4.99 (dddd, J_1 = 10.0 Hz, J_2 = 1.3 Hz, J_3 = 1.3 Hz, J_4 = 1.3 Hz, 1H), 4.97 (dddd, J_1 = 16.9 Hz, J_2 = 1.6 Hz, J_3 = 1.6 Hz, J_4 = 1.6 Hz, 1H), 3.91 (s, 3H), 3.71 (ddd, J_1 = 6.5 Hz, J_2 = 6.5 Hz, J_3 = 1.4 Hz, 2H), 3.44 (d, J = 8.8 Hz, 1H), 3.21 (m, 1H), 2.71 (m, 2H), 2.36 (s, 3H), 1.82 (dddd, J_1 = 7.26 Hz, J_2 = 6.79 Hz, J_3 = 6.79 Hz, J_4 = 0.6 Hz, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.7, 144.2, 143.1, 135.5, 135.1, 133.5, 132.8, 132.5, 129.6, 129.3, 129.1, 127.5, 127.0, 125.0, 120.1, 117.9, 117.3, 64.8, 60.7, 53.4, 52.6, 42.3, 37.7, 32.9, 21.6 pm.

HRMS (ESI) calculated for $C_{27}H_{29}NO_5SNa^+$ 502.1664; found 502.1663.

Rf: 0.15 (hexane/EtOAc 1:1)

Methyl 3-(2-(2-hydroxyethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (268a)



TBS-protected alcohol **268** (710 mg, 1.29 mmol, 1 equiv.) was dissolved in MeOH (7 mL) and *p*TsOH (734 mg, 3.86 mmol, 3 equiv.) was added. After 1 h aq. sat $NaHCO_3$ solution as added and the reaction three times extracted with EtOAc. The combined organic layers were washed with

brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified *via* flash chromatography (hexane/EtOAc 1:1 to 1:2).

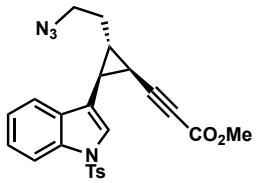
Yield: 323 mg (57%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.90 (ddd, J_1 = 8.0 Hz, J_2 = 0.9 Hz, J_3 = 0.7 Hz, 1H), 7.77 (ddd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, J_3 = 2.0 Hz, 2H), 7.58 (ddd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, J_3 = 0.7 Hz, 1H), 7.51 (d, J = 1.0 Hz, 1H), 7.30 (ddd, J_1 = 8.1 Hz, J_2 = 7.2 H, J_3 = 1.0 Hz, 1H), 7.24 (ddd, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 0.9 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 3.85 (t, J = 6.1 Hz, 2H), 3.68 (s, 3H), 2.33 (s, 3H), 2.25 (ddd, J_1 = 7.8 Hz, J_2 = 6.6 Hz, J_3 = 1.1 Hz, 1H), 1.82 (ddd, J_1 = 14.3 J_2 = 14.3, J_3 = 6.3 Hz, 1H), 1.79 (ddd, J_1 = 14.2 Hz, J_2 = 14.2 Hz, J_3 = 7.1 Hz, 1H), 1.76 (dq, J_1 = 6.9 Hz, J_2 = 6.6 Hz, 1H), 1.69 (dq, J_1 = 6.5 Hz, J_2 = 5.4 Hz, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 153.9, 144.8, 135.2, 134.7, 131.2, 129.9, 126.9, 124.8, 123.2, 123.1, 119.2, 118.5, 113.6, 89.2, 72.7, 61.8 52.5, 36.1, 27.6, 22.1, 21.6, 14.8 ppm.

Rf: 0.2 (hexane/EtOAc 1:1)

Methyl 3-(2-(2-azidoethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (272)



Alcohol **268a** (323 mg, 740 µmol, 1 equiv.) was dissolved in DCM (4 mL) and PPh_3 (388 mg, 1.48 mmol, 2 equiv.) was added. The reaction was cooled to 0 °C and then DEAD (240 µL, 1.55 mmol, 2.1 equiv) and DPPA (240 µL, 1.11 mol, 1.5 equiv.) were added at the same time. After 1 h the reaction was quenched by the addition of water. Subsequently the reaction was extracted three times with DCM and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained after flash chromatography (hexane/EtOAc 5:1 to 3:1) as lightly yellow oil.

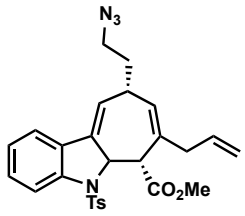
Yield : 210 mg (61%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.93 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 0.7 Hz, 1H), 7.33 (ddd, J_1 = 7.9 Hz, J_2 = 7.5 Hz, J_1 = 1.0 Hz, 1H), 7.27 (ddd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, J_3 = 0.9 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 3.71 (s, 3H), 3.52 (t, J = 6.7 Hz, 2H), 2.35 (s, 3H), 2.27 (ddd, J_1 =7.8 Hz, J_2 = 6.7 Hz, J_3 = 0.9 Hz, 1H), 1.84 (m, 2H), 1.85 (m, 1H), 1.68 (dq, J_1 = 6.6 Hz, J_2 = 5.44, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 153.8, 144.8, 135.2, 134.8, 131.1, 129.9, 127.0, 124.9, 123.1, 119.1, 118.0, 113.6, 88.5, 72.8, 64.3, 52.5, 32.8, 27.7, 22.2, 21.6, 15.0, 14.1 ppm.

Rf: 0.3 (hexane/EtOAc 5:1)

Methyl 7-allyl-9-(2-azidoethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (271)



In THF (500 µL) DEAD (20 µL, 130 µmol, 2 equiv.) and PPh_3 (34.0 mg, 130 µmol, 2 equiv.) were dissolved and cooled to 0 °C. Alcohol **270a** (32.0 mg, 65.0 µmol, 1 equiv.) was added and stirred for 5 min before DPPA (29 µL, 130 µmol, 2 equiv.) was added. After stirring at 0 °C for 2.5 h, water was added and the reaction three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 5:1) the final product was obtained as yellow oil.

Yield: 13 mg (40%)

The product was also obtained via another route.

To a suspension of $Cu(OAc)_2$ (2.10 mg, 12.0 µmol, 0.05 equiv) in MeOH (500 µL) was added alkyne **272** (107 mg, 230 µmol, 1 equiv.) and cooled to 0 °C. To the green solution was added allylboronic acid pinacol ester (120 µL, 460 µmol, 2 equiv.) and the reaction was stirred for 1.5 h during which the color changed to yellow and back to green again. Finally water was added and the reaction was three times extracted with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification (hexane/EtOAc 10:1 to 5:1) the final product was obtained as yellow oil.

Yield: 82 mg (71%)

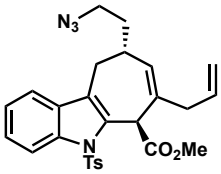
^{1}H (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.26 (ddd, J_1 = 4.9 Hz, J_2 = 4.9 Hz, J_3 = 1.0 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.08 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.7 Hz, 1H), 6.04 (dd, J_1 = 5.8 Hz, J_2 = 2.7 Hz, 1H), 5.63 (dddd, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 6.9 Hz, J_4 = 6.5 Hz, 1H), 5.55 (dd, J_1 = 2.7 Hz, J_2 = 0.7 Hz, 1H), 5.53 (d, J = 3.4 Hz, 1H), 5.00 (dddd, J_1 = 9.4 Hz, J_2 = 1.7 Hz, J_3 = 1.2 Hz, J_4 =1.2 Hz, 1H), 4.97 (dddd, J_1 = 16.7 Hz, J_2 = 1.5 Hz, J_3 = 1.5 Hz, J_4 = 1.5 Hz, 1H), 3.92 (s, 3H), 3.45 (d, J = 8.5 Hz Hz, 1H), 3.34 (ddd, J_1 = 7.0 Hz, J_2 = 7.0 Hz, J_3 = 3.1 Hz, 2H), 3.19 (m, 1H), 2.72 (ddd, J_1 = 14.8 Hz, J_2 = 14.8 Hz, J_3 = 14.8 Hz, 1H), 2.72 (dd, J_1 = 16.0 Hz, J_2 = 16.0 Hz, 1H), 2.34 (s, 3H), 1.82 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.5, 144.3, 136.1, 135.0, 133.4, 133.0, 132.1, 130.1, 130.1, 123.6, 129.3, 129.2, 127.5, 126.1, 125.0, 120.3, 120.2, 118.0, 117.4, 64.7, 53.4, 52.7, 49.3, 42.3, 34.0, 33.7, 21.6 ppm.

IR (ATR): 2949 2095, 1763, 1734, 1449, 1400, 1360 1259, 1169, 1090, 750, 665, 573, 540 cm^{-1}.

Rf: 0.3 (hexane/EtOAc 5:1)

Methyl 7-allyl-9-(2-azidoethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate 271a



In CH_2Cl_2 (200 µL) was dissolved **271** (5 mg, 9.88 µmol, 1 equiv.) and cooled to 0 °C. Subsequently was added TMSOTf (3.60 µL, 19.6 µmol, 2 equiv.) and the reaction was stirred for 30 min. Then aq. sat. $NaHCO_3$ solution was added and the reaction was extracted three times with DCM. The combined organic phase were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 3:1) furnished the product.

Yield: 4 mg (80%)

^{1}H (400 Mhz, $CDCl_3$) δ = 8.00 (bd, *J* = 7.8 Hz, 1H), 7.70 (bd, *J* = 8.2 Hz, 2H), 7.39 (m, 1H), 7.28 – 7.25 (m, 1H), 7.25 – 7.21 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.78 – 5.67 (m, 1H), 5.53 (d, *J* = 6.2 Hz, 1H), 5.20 (s, 1H), 5.06 – 4.98 (m, 2H), 3.76 (s, 3H), 3.46 – 3.31 (m, 2H), 3.07 (m, 1H), 3.01 (m, 2HJ), 2.94 (dd, J_1 = 16.7 Hz, J_2 = 3.1 Hz, 1H), 2.54 (dd, J_1 = 16.7 Hz, J_2 = 12.6 Hz, 1H), 2.34 (s, 3H), 1.75 (ddd, J_1 = 7.1 Hz, J_2 = 7.1 Hz, J_3 = 7.1 Hz, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 171.5, 144.5, 137.7, 136.2, 135.8, 135.0, 132.8, 130.7, 130.3, 129.6, 126.7, 124.9, 123.3, 122.5, 118.3, 117.5 114.8, 52.6, 49.6, 46.9, 43.9, 41.4, 35.1, 31.5, 30.2, 22.6, 21.6 ppm.

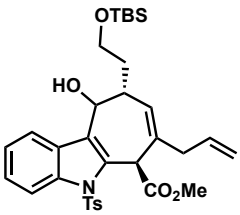
Rf: 0.3 (hexane/EtOAc 3:1)

Diplatinum tribenzylidenaceton

Product was obtained following published procedure (Lewis, L.N.; Krafft, T.A., Huffman, J.C. *Inorg. Chem.* 1992, *31*, 3555-3557)

Yield: 350 mg (65)

Methyl 7-allyl-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-10-hydroxy-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate (275)



To a solution of cyclohepta[*b*]indole **270** (20.0 mg, 30.0 µmol, 1 equiv.) and methyl sulfonamide (10.0 mg, 100 µmol, 3 equiv.) in water (75 µL) and *t*BuOH (75 µL) at 0 °C was added 45 mg AD-mix β and the reaction was stirred for 16 h during which it the reaction was slowly warmed

to r.t. Subsequently the reaction was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 10:1 – 2:1) gave the product.

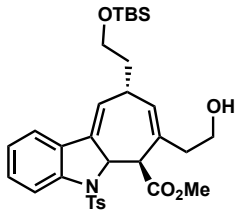
Yield: 4 mg (22%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.96 (m, 1H), 7.77 (m, 1H), 7.67 (bd, *J* = 8.4 Hz, 2H), 7.25-7.17 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.71 (m, 1H), 5.47 (ddd, J_1 = 6.5 Hz, J_2 = 1.0 Hz, J_3 = 1.0 Hz, 1H), 5.30 (s, 1H), 5.02 (m, 2H), 4.70 (dd, J_1 = 9.7 Hz, J_2 = 5.1 Hz, 1H), 3.82-3.67 (m, 2H), 3.72 (s, 3H), 3.45 (b, 1H), 3.11 (m, 1H), 2,96 (m, 2H), 2.31 (s, 3H), 1.93-1.82 (m, 1H), 1.78-168 (m, 1H), 0.92 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 171.6, 144.6, 138.7, 136.2, 135.9, 135.0, 132.1, 130.3, 129.8, 129.6, 126.9, 125.8, 124.8, 123.5, 121.1, 117.6, 114.7, 68.4, 61.0, 52.7, 47.0, 43.7, 40.5, 34.8, 25.9, 21.5, 18.3, −5.4, −5.5 ppm.

MS (ESI) calculated for $C_{33}H_{43}NO_6SSiNa^+$ 632.2473; found 632.2271.

Methyl 9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-7-(2-hydroxyethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (276)



In THF (1 mL) was dissolved Pt_2dba_3 (25.0 mg, 30.0 µmol, 0.05 equiv.) and bis(pinacoloto)diboron (300 mg, , 1.18 mmol, 2 equiv.) was added. After stirring at r.t. for 10 min, **270** (347 mg, 590 µmol, 1 euqiv.) dissolved in THF (4 mL) was added and the reaction stirred for 1h at r.t. Then the reaction was diluted with water (5 mL) and $NaBO_3{\cdot}4H_2O$ (454 mg, 2.95 mmol, 5 equiv.) was added. The reaction was stirred vigorously for 12 h and then the extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated.

The resulting crude diol was dissolved in a THF/water mixture (5:1, 3 mL) and cooled to 0 °C. Subsequently $NaIO_4$ (132 mg, 620 µmol, 1.05 equiv.) was added and the reaction stirred at 0 °C for 2 h followed by dilution with water. The reaction was then three times extracted with EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated.

The residue was taken up in MeOH (3 mL), cooled to 0 °C and $NaBH_4$ (23.0 mg, 620 µmol, 1.05 equiv.) was added. After 15 min the reaction was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over

$MgSO_4$, filtered and concentrated *in vacuo.* After purification with flash chromatography (hexane/EtOAc 2:1 to 1:1) the pure product was obtained as a slightly yellow oil.

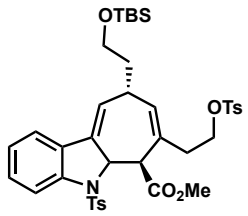
Yield: 122 mg (63%)

^{1}H (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.25 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.07 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.9 Hz, 1H), 6.14 (dd, J_1 = 5.8 Hz, J_2 = 2.7 Hz, 1H), 5.66 (d, *J* = 4.1 Hz, 1H), 5.53 (ddd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, J_3 = 0.6 Hz, 1H), 3.92 (s, 3H), 3.67 (ddd, J_1 = 6.1 Hz, J_2 = 6.1 Hz, J_3 = 0.9 Hz, 2H), 3.59 (m, 2H), 3.45 (d, *J* = 8.5 Hz, 1H), 3.20 (m, 1H), 2.34 (s, 3H), 2.28 (m, 1H), 2.20 (m, 1H), 1.77 (dddd, J_1 = 6.8 Hz, J_2 = 6.5 Hz, J_3 = 6.5 Hz, 0.7 Hz, 2H), 0.91 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.6, 144.2, 143.0, 135.2, 133.5, 130.2, 129.9, 129.6, 129.4, 129.2, 127.5, 126.5, 125.2, 120.2, 118.0, 64.7, 60.1, 53.5, 52.7, 41.3, 37.9, 33.3, 25.9, 21.5, 18.3, −5.4 ppm.

Rf: 0.3 (hexane/EtOAc 1:1)

Methyl 9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-tosyl-7-(2-(tosyloxy)ethyl)-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (277)



Alcohol **276** (80.0 mg, 130 µmol, 1 equiv.) was dissolved in CH_2Cl_2 (600 µL) and cooled to 0 °C. Pyridine (32 µL, 390 µmol, 3 equiv.) and subsequently TsCl (38.0 mg, 200 µL, 1.5 equiv) were added and the reaction stirred for 4 h. Although TLC did not show complete conversion, a side product started to appear. The reaction was quenched by the addition of water. Three fold extraction with EtOAc was followed by the combination of the organic layers, which were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 3:1) then gave the desired product was white wax-like substance.

Yield: 42 mg (43%)

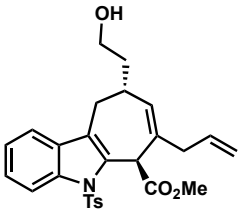
^{1}H (400 MHz, $CDCl_3$) δ= 7.78 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.28 (ddd, J_1 = 7.9 Hz, J_2 = 7.8 Hz, J_3 = 0.9 Hz, 1H), 7.24 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.10 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 0.9 Hz, 1H), 6.11 (dd, J_1 = 5.8 Hz, J_2 = 2.7 Hz, 1H), 5.57 (d, *J* = 4.1 Hz, 1H), 5.47 (ddd, J_1 = 8.6 Hz, J_2 = 2.6 Hz, J_3 = 0.6 Hz, 1H), 3.97 (dddd, J_1 = 36.2 Hz, J_2 = 9.5 Hz, J_3 = 7.3 Hz, J_4 = 5.8 Hz, 2H), 3.85 (s, 3H), 3.65 (ddd, J_1 = 6.2 Hz, J_2 = 6.2 Hz, J_3 = 1.0 Hz, 2H), 3.23 (d, *J* = 8.6 Hz, 1H), 3.15 (m, 1H), 2.43 (s, 3H), 2.34 (s, 3H), 2.32 (m, 2H), 1.73 (ddd, J_1 = 6.8 Hz, J_2 = 6.8 Hz, J_3 = 6.5 Hz, 2H), 0.90 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.0, 144.7, 144.2, 143.0, 135.5, 134.9, 133.4, 132.9, 129.8, 129.6, 129.4, 129.1, 127.9, 127.7, 127.6, 127.4, 125.1, 120.2, 117.8, 68.0, 64.5, 60.9, 53.5, 52.7, 37.8, 37.1, 33.2, 25.9, 21.6, 21.6, 18.2, −5.4, −5.4 pm.

HRMS (ESI) calculated for $C_{39}H_{49}NO_8S_2SiNa^+$ 774.2567; found 774.2565.

Rf: 0.45 (hexane/EtOAc 3:1)

Methyl 7-allyl-9-(2-hydroxyethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*] indole-6-carboxylate (270b)



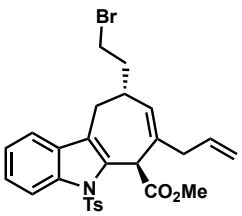
Methyl 7-allyl-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-tosyl-5,5a,6,9-tetrahydro-cyclohepta[*b*]indole-6-carboxylate (**270**) (180 mg, 300 µmol 1 equiv.) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. Subsequently TMSOTf (119 µL, 600 µmol, 2 equiv.) was added and the reaction was stirred for 15 min. Then water was added and the reaction was extracted three times with DCM. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification with flash chromatography (hexane/EtOAc 1:1) the product was obtained as clear oil.

Yield: 106 mg (74 %)

^{1}H (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.40 (dd, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1H), 7.27 (ddd, J_1 = 8.3 Hz, J_2 = 7.1 Hz, J_3 = 1.5 Hz, 1H), 7.23 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 5.72 (dddd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, J_4 = 6.7 Hz, 1H), 5.57 (d, J = 6.1 Hz, 1H), 5.18 (s, 1H), 5.02 (ddd, J_1 = 17.0 Hz, J_2 = 3.2 Hz, J_3 = 1.5 Hz, J_4 = 1.5 Hz, 1H), 4.99 (dddd, J_1 = 7.4 Hz, J_2 = 1.3 Hz, J_3 = 1.3 Hz, J_4 = 1.3 Hz, 1H), 3.74 (s, 3H), 3.06 (m, 1H), 2.99 (d, J = 6.8 Hz, 2H), 2.95 (dd, J_1 = 16.4 Hz, J_2 = 3.1 Hz, 2H), 2.54 (dd, J_1 = 16.4 Hz, J_2 = 12.3 Hz, 1H), 2.34 (s, 3H), 1.74 (dq, J_1 = 6.9 Hz, J_2 = 19 Hz, 2H) ppm.

Rf: 0.15 (hexane/EtOAc 1:1)

Methyl 7-allyl-9-(2-bromoethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate (279)



Alcohol **270b** (162 mg, 0.34 mmol, 1 equiv.) was dissolved in CH_2Cl_2, cooled to 0 °C and then PPh_3 (115 mg, 0.44 mmol, 1.4 equiv.) and CBr_4 (168 mg, 0.51 mmol, 1.5 equiv.) were added. After stirring for 1.5 h, water was added and the reaction three times extracted with CH_2Cl_2. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was obtained after flash chromatography (hexane/EtOAc 10:1).

Yield: 139 mg (76%)

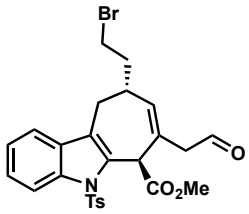
^{1}H (400 MHz, $CDCl_3$) δ = 8.01 (d, J = 7.8 Hz, 1H), 7.71 (ddd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, J_3 = 1.4 Hz, 2H), 7.38 (ddd, J_1 = 7.7 Hz, J_2 = 1.5 Hz, J_3 = 0.7 Hz, 1H), 7.28 (ddd, J_1 = 7.7 Hz, J_2 = 7.5 Hz, J_3 = 1.7 Hz, 1H), 7.23 (ddd, J_1 = 7.3 Hz, J_2 = 7.3 Hz, J_3 = 1.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 5.73 (dddd, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, J_4 = 6.7 Hz, 1H), 5.49 (d, J = 6.2 Hz, 1H), 5.23 (s, 1H), 5.04 (dddd, J_1 = 13.0 Hz, J_2 = 1.5 Hz, J_3 = 1.5 Hz, J_4 = 1.5 Hz, 1H), 5.01 (m, 1H), 3.76 (s, 3H), 3.52 (m, 1H), 3.49 (m, 1H), 3.18 (b, 1H), 3.01 (dd, J_1 = 6.6 Hz, J_2 = 0.8 Hz, 2H), 2.93 (dd, J_1 = 16.5 Hz, J_2 = 2.9 Hz, 1H), 2.55 (dd, J_1 = 16.0 Hz, J_2 = 12.3 Hz, 1H), 2.35 (s, 3H), 2.01 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 171.5, 144.5, 138.2, 136.2, 135.8, 135.0, 132.1, 130.7, 130.4, 129.6, 126.9, 124.9, 123.3, 122.3, 118.3, 117.5, 114.8, 52.7, 46.8, 43.9, 38.9, 32.8, 31.2, 29.9, 21.7 ppm.

HRMS (ESI) calculated for $C_{27}H_{28}BrNO_4SNa^+$ 564.0820; found 564.0182.

Rf 0.45 (hexane/EtOAc 5:1)

Methyl 9-(2-bromoethyl)-7-(2-oxoethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*] indole-6-carboxylate (280)



In THF (200 µL) was dissolved Pt_2dba_3 (6.00 mg, 7.00 µmol, 0.02 equiv.) and bis(pinacoloto)diboron (117 mg, 700 µmol, 2 equiv.) was added. After stirring at r.t. for 20 min, **279** (190 mg, 350 µmol, 1 equiv.) dissolved in THF (500 µL) was added and the reaction stirred for 6 h at r.t. Then the reaction was diluted with water (5 mL) and $NaBO_3{\cdot}4H_2O$ (290 mg, 700 µmol, 2 equiv.) was added. The reaction was stirred vigorously for 12 h and then diluted with brine solution and subsequently extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated.

The resulting crude diol was dissolved in a THF/water mixture (5:1, 1.5 mL) and cooled to 0 °C. Subsequently $NaIO_4$ (112 mg, 525 µmol, 1.5 equiv.) was added and the reaction stirred at 0 °C for 30 min, followed by dilution with water. The reaction was then three times extracted with

EtOAc and the combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated.

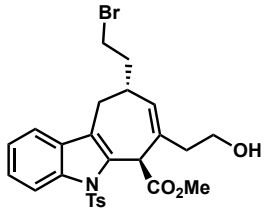
The aldehyde was obtained after flash chromatography (hexane/EtOAc 2:1)

Yield: 130 mg (76%)

^{1}H (400 MHz, $CDCl_3$) δ = 9.65 (t, *J* = 2.2Hz, 1H), 8.02 (1, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.40 (dd, J_1 =7.9 Hz, J_2 = 1.0 Hz, 1H), 7.30 (ddd, J_1 = 8.1 Hz, J_2 = 7.1 Hz, J_3 = 1.5 Hz, 1H) 7.25 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.66 (d, *J* = 6.8 Hz, 1H), 5.28 (s, 1H), 3.76 (s, 3H), 3.53 (m, 1H), 3.43 (m, 1H), 3.25 (dd, J_1 = 16.4 Hz, J_2 = 2.4 Hz, 1H), 2.97 (dd, J_1 = 16.4 Hz, J_2 = 3.1 Hz, 1H), 2.61 (dd, J_1 = 16.4, J_2 = 11.9 Hz, 1H), 2.35 (s, 3H), 2.02 (m, 2H), 1.55 (m, 2H) ppm.

Rf: 0.25 (hexane/EtOAc 2:1)

(6R,9R)-Methyl 9-(2-bromoethyl)-7-(2-hydroxyethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indole-6-carboxylate (282)



Aldehyde **280** (130 mg, 243 µmol, 1 equiv.) was taken up in MeOH (3 mL), cooled to 0 °C and $NaBH_4$ (40.0 mg, 1.05 mmol, 4.32 equiv.) was added. After 15 min the reaction was diluted with water and extracted three times with EtOAc. The combined organic layers were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo.* After purification with flash chromatography (hexane/EtOAc 1:1) the pure product was obtained as a sightly yellow oil.

Yield: 120 mg (90%)

^{1}H (400 MhHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.40 (dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz, 1H), 7.32 (ddd, J_1 = 8.3 Hz, J_2 = 7.2 Hz, J_3 = 1.3 Hz, 1H), 7.26 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 1.0 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.57 (d, *J* = 6.5 Hz, 1H), 5.36 (s, 1H), 3.87 (ddd, J_1 = 11.9 Hz, J_2 = 8.5 Hz, J_3 = 3.7 Hz, 1H), 3.72 (s, 3H), 3.55 (m, 1H), 3.46 (m, 1H), 3.07 (m, 1H), 2.92 (dd, J_1 = 16.6 Hz, J_2 = 3.2 Hz, 1H), 2.54 (dd, J_1 = 16.5 Hz, J_2 = 12.8 Hz, 2H), 2.36 (s, 3H), 2.23 (ddd, J_1 = 14.0 Hz, J_2 = 4.6 Hz, J_3 = 4.6 Hz, 1H), 2.00 (m, 2H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 172.4, 144.8, 137.3, 136.4, 135.9, 134.6, 130.5, 129.9, 129.7, 126.6, 125.1, 123.5, 121.7, 118.3, 114.9, 59.4, 53.1, 45.3, 43.0, 38.5, 32.8, 31.3, 29.6, 21.6 ppm.

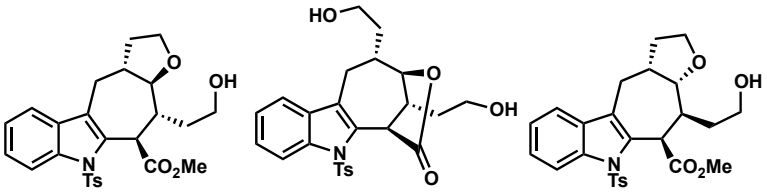
HRMS (ESI) calculated for $C_{26}H_{28}BrNO_5SNa^+$: 568.0769; found 568.0768.

Rf: 0.2 (hexane/EtOAc 1:1)

Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (283)

5,12-Bis(2-hydroxyethyl)-11-tosyl-4,5,6,11-tetrahydro-1,4-methanooxocino[4,5-*b*]indole-2(1*H*)-one (284)

Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (285)



A round bottom flask was charged with **282** (60.0 mg, 110 µmol, 1 equiv) and THF (600 µL) and BH_3•THF (1 M, 330 µL, 330 µmol, 3 equiv.) was added. The reaction was heated to reflux for 4 h. Subsequently water and $NaBO_3$•$4H_2O$ (273 mg, 660 µmol, 6 equiv.) were added and the reaction stirred vigorously for 5 h. This was followed by three times extraction with EtOAc. The combined organic phases were washed with brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification with flash chromatography (hexane/EtOAc 2:1 -1:1 – 1:2) furnished the three products.

Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (283)

Yield: 17 mg (32%)

^{1}H (400 Mhz, $CDCl_3$) δ = 8.22 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.42 (m, 1H), 7.36 (m, 1H), 7.30 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 4.99 (d, *J* =1.0 Hz, 1H), 3.96 (ddd, J_1 = 7.7 Hz, J_2 = 7.7 Hz, J_3 = 7.7 Hz, 1H), 3.88 (ddd, J_1 = 8.4 Hz, J_2 = 8.4 Hz, J_3 = 4.3 Hz, 1H), 3.75 (m, 2H), 3.52 (s, 3H), 3.32 (dd, J_1 =9.9 Hz, J_2 = 7.8 Hz, 1H), 3.18 (dd, J_1 = 16.9 Hz, J_2 = 5.6 Hz, 1H), 2.99 (m, 1H), 2.64 (dd, J_1 = 17.1 Hz, J_2 = 11.3 Hz, 1H), 2.43 (m, 1H), 2.37 (s, 3H), 2.92 (m, 1H), 1.87 (m, 1H), 1.67 – 1.59 (m, 1H) ppm.

^{13}C (100 Mhz, $CDCl_3$) δ = 173.5, 144.8, 136.7, 136.6, 130.7, 130.0, 129.6, 126.6, 125.0, 123.4, 120.3, 118.5, 115.1, 86.3, 67.7, 60.6, 52.5, 44.3, 38.7, 37.0, 34.8, 29.1, 23.9, 21.5 ppm.

HRMS (ESI) calculated for $C_{26}H_{29}NO_6SNa^+$: 506.1613; found 506.1607.

Rf: 0.3 (hexane/EtOAc 1:2)

5,12-Bis(2-hydroxyethyl)-11-tosyl-4,5,6,11-tetrahydro-1,4-methanooxocino[4,5-*b*]indol-2(1*H*)-one (284)

Yield: 3 mg (5%)

^{1}H (400 Mhz, $CDCl_3$) δ = 8.21 (d, *J* = 8.2 Hz, 1H), 7.86 (d *J* = 8.4 Hz, 2H), 7.37 (m, 1H), 7.30 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 5.30 (d, *J* = 7.7 Hz, 1H), 4.93 (dd, J_1 = 6.1 Hz, J_2 = 6.1 Hz, 1H), 3.81 (dd, J_1 = 7.8 Hz, J_2 = 4.9 Hz, 2H), 3.39 – 3.51 (m, 1H), 3.49 – 3.42 (m, 1H), 3.18 (m, 1H), 2.95 (dd,

J_1 = 16.7 Hz, J_2 = 4.8 Hz, 1H), 2.84 (dd, J_1 = 16.5, J_2 = 2.6 Hz, 1H), 2.76 (m, 1H), 2.33 (s, 3H), 1.92 (m, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.33 (m, 1H) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 174.2, 145.2, 136.0, 134.1, 131.4, 130.6, 129.7, 127.1, 125.2, 124.2, 121.7, 118.3, 115.8, 84.7, 60.5, 42.4, 40.9, 39.6, 32.4, 31.5, 29.0, 21.6, 21.3 ppm.

Rf: 0.6 (hexane/EtOAc 1:2)

Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (285)

Yield: 3 mg (5%)

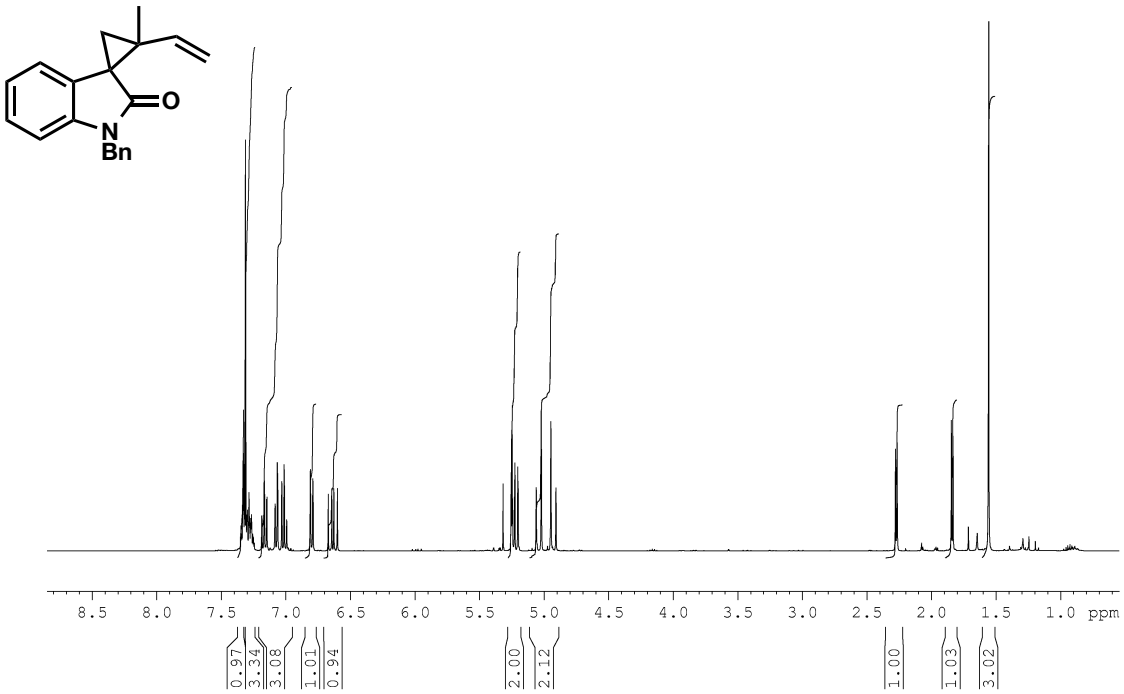
^{1}H (400 Mhz, $CDCl_3$) δ = 8.02 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.43 (m, 1H), 7.26 (m, 1H), 7.24 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 4.68 (s, 1H), 47.06 (ddd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, J_3 = 7.7 Hz, 1H), 3.86 – 3.80 (m, 2H), 3.76 (s, 3H), 3.75 – 3.70 (1H), 3.64 (dd, J_1 = 10.3 Hz, J_2 = 5.0 Hz, 1H), 3.00 – 2.84 (m, 1H), 2.79 (m, 1H), 2.70 (m, 1H), 2.46 (m, 1H), 2.36 (s, 3H), 2.32 – 2.28 (m, 1H), 2.18 – 2.12 (m, 1H), 1.78 (m, 1H) ppm.

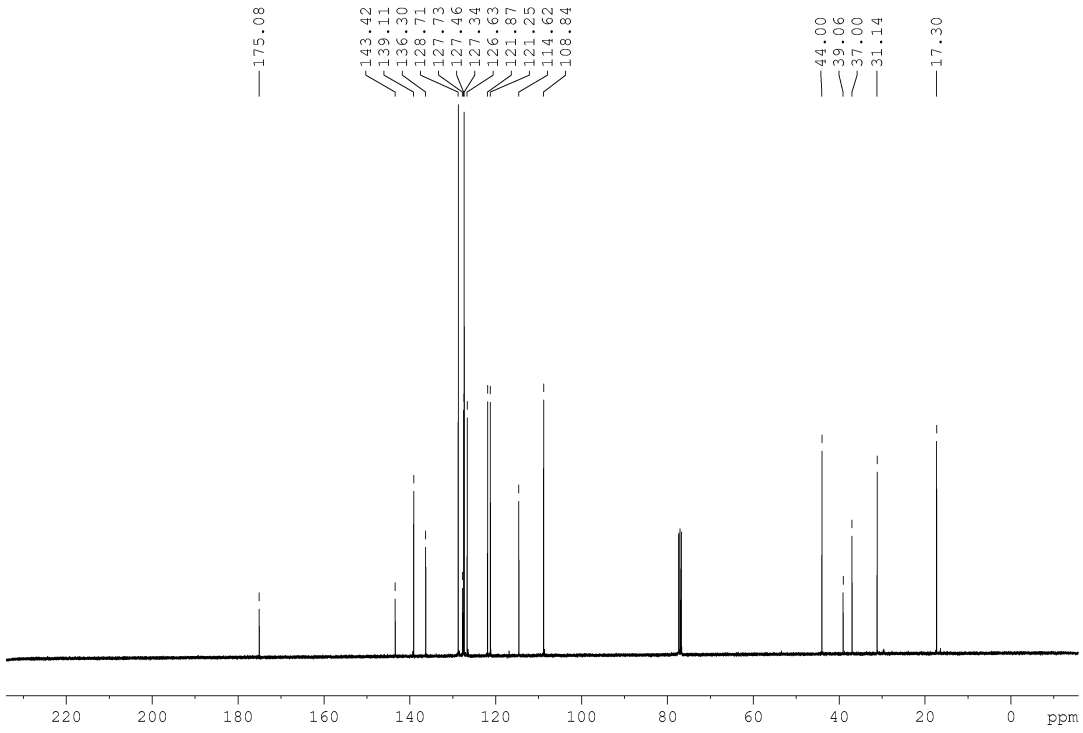
^{13}C (100 MHz, $CDCl_3$) δ = 172.2, 144.7, 136.2, 135.7, 134.21, 130.0, 129.8, 126.6 124.8, 123.3, 122.1, 118.4, 114.6, 84.0, 66.5, 61.6, 52.2, 46.5, 41.9, 39.7, 37.8, 33.9, 26.0, 21.6 ppm.

Rf: 0.5 (hexane/EtOAc 1:2)

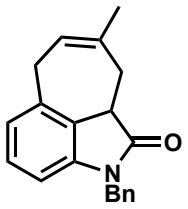
15 NMR spectra

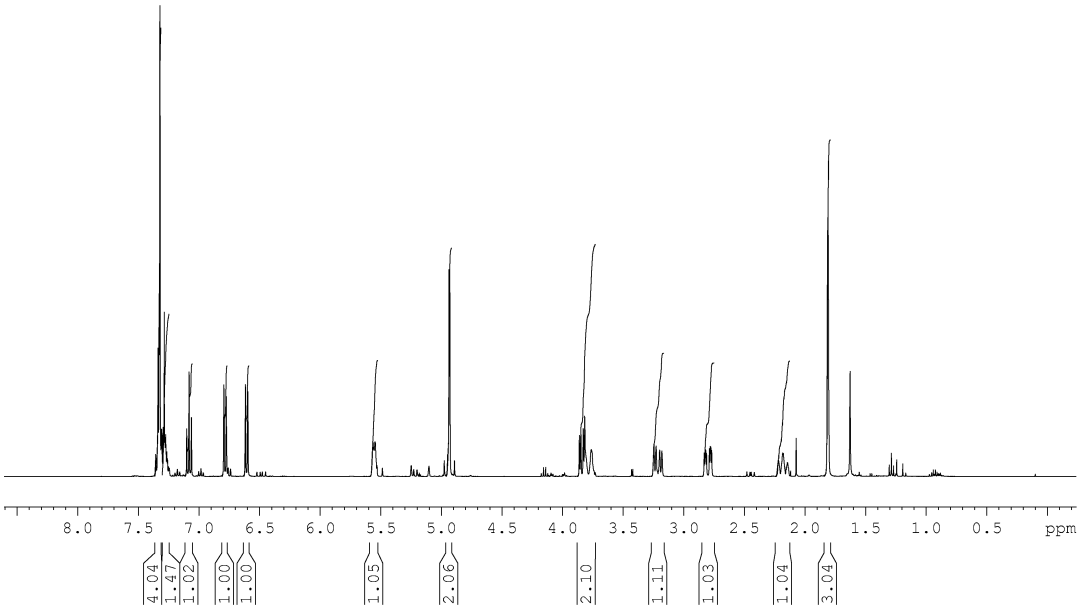
1'-Benzyl-2-methyl-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (142)

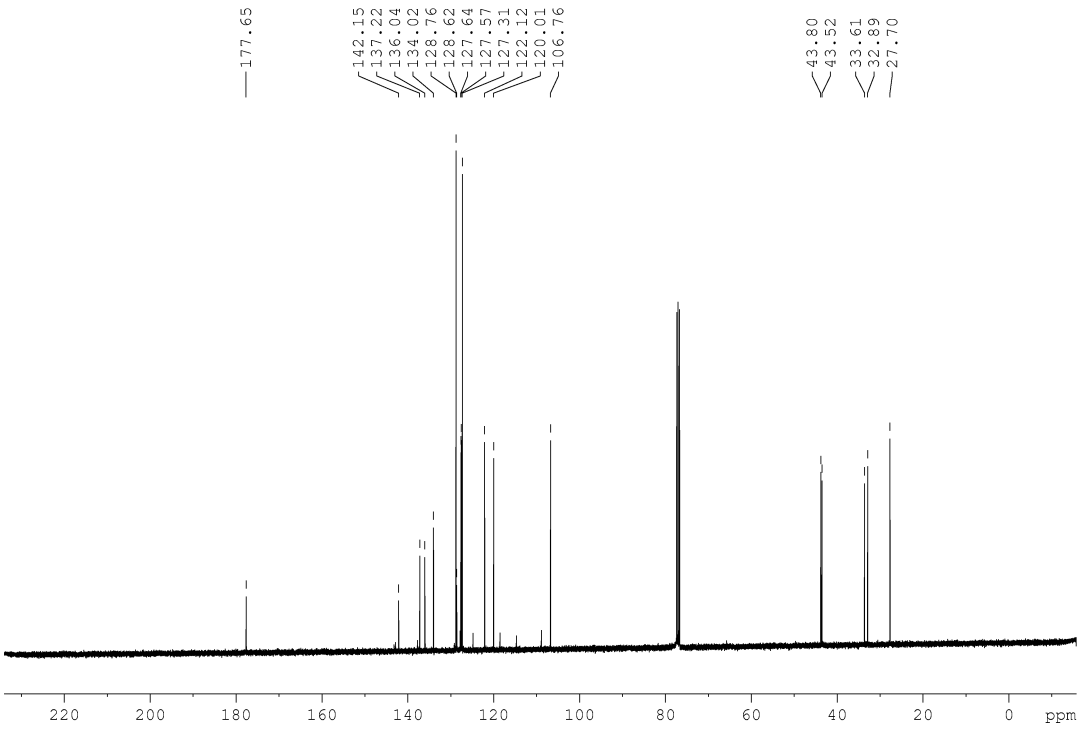




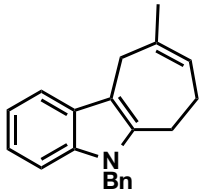
1-Benzyl-4-methyl-2a,3-dihydro-1*H*-cyclohepta[*cd*]indol-2(6*H*)-one (144)

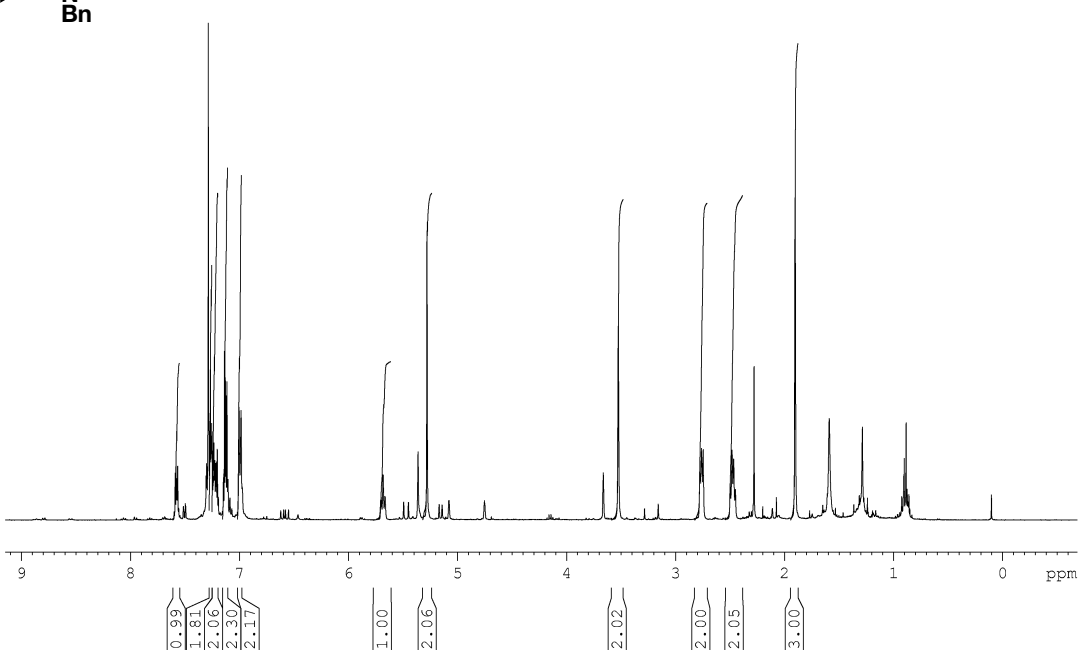


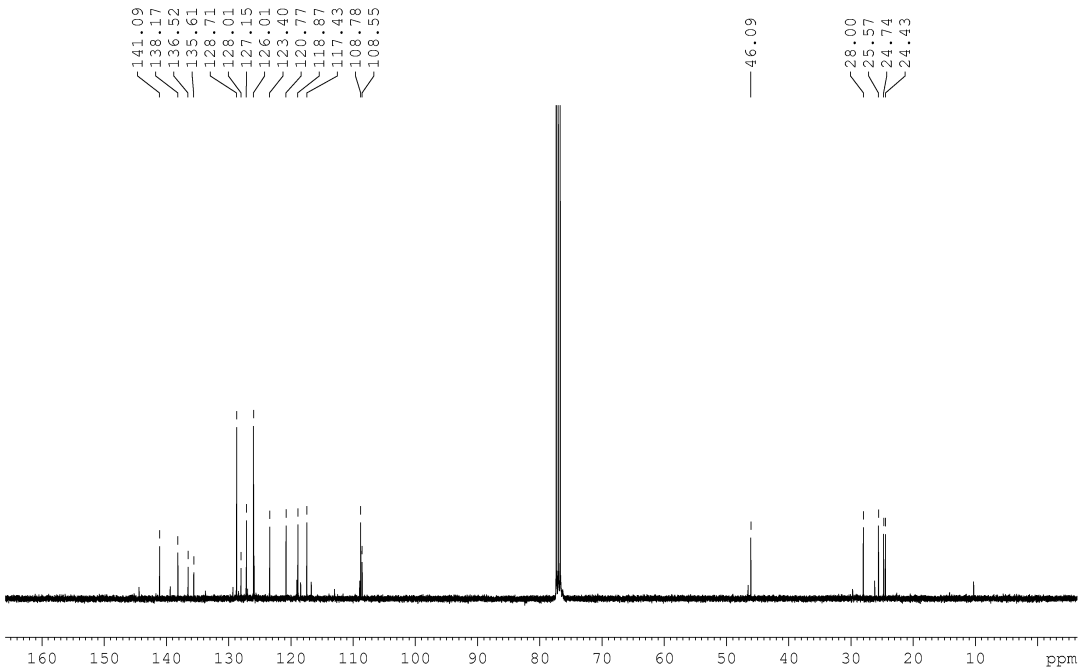




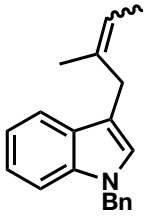
1-Benzyl-9-methyl-5,6,7,10-tetrahydrocyclohepta[*b*]indole (148)

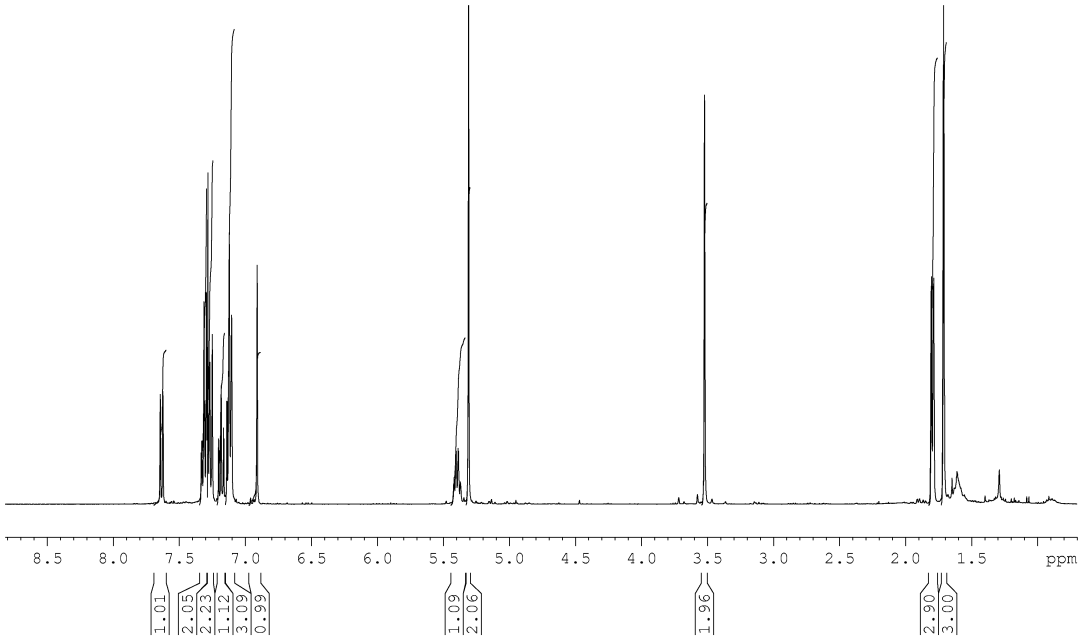


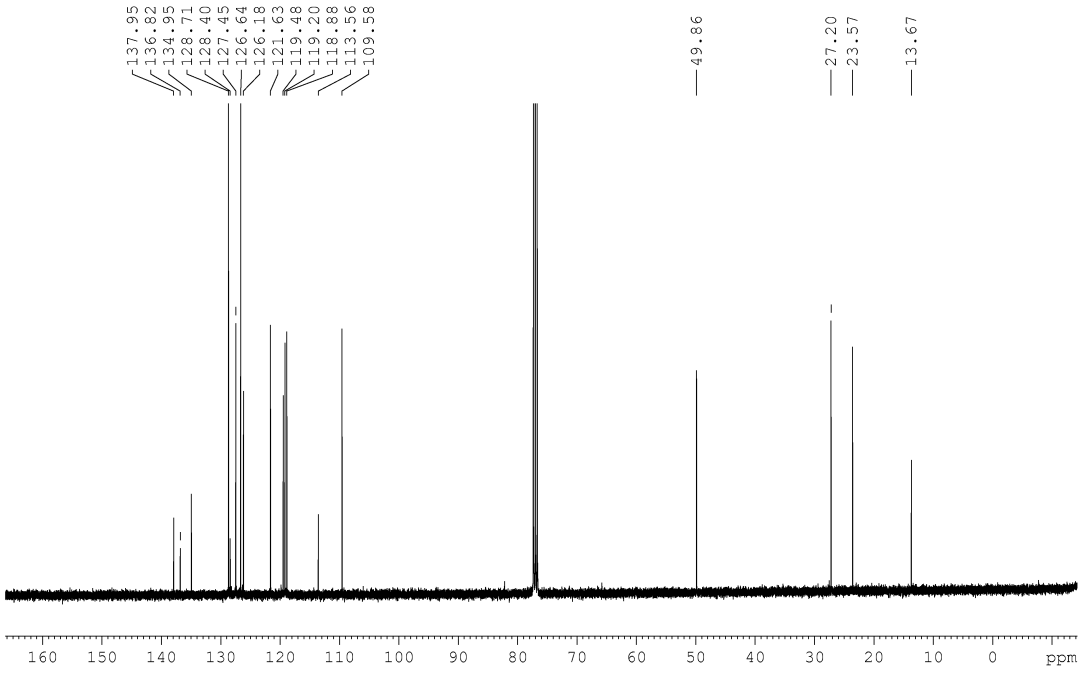




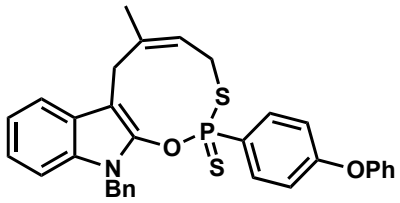
1-Benzyl-3-(2-methylbut-2-en-1-yl)-1*H*-indole (149)

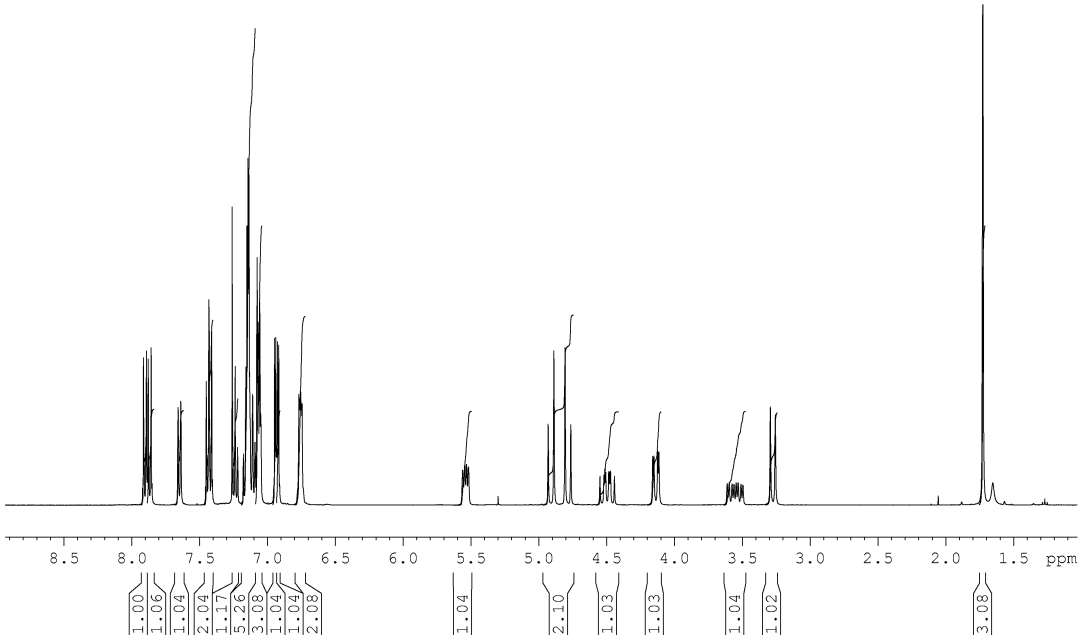


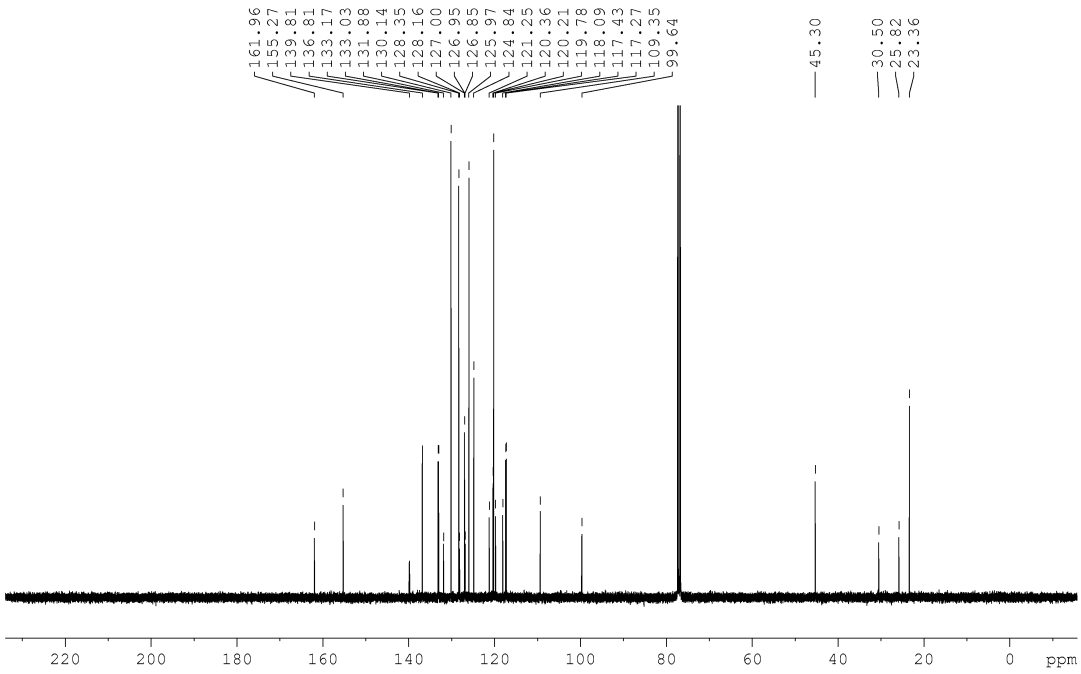




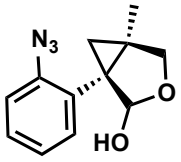
(*Z*)-1-Benzyl-6-methyl-2-(4-phenoxyphenyl)-7,12-dihydro-4*H*-[1,3,2]oxathiaphosphonino[9,8-*b*]indole 2-oxide (151)

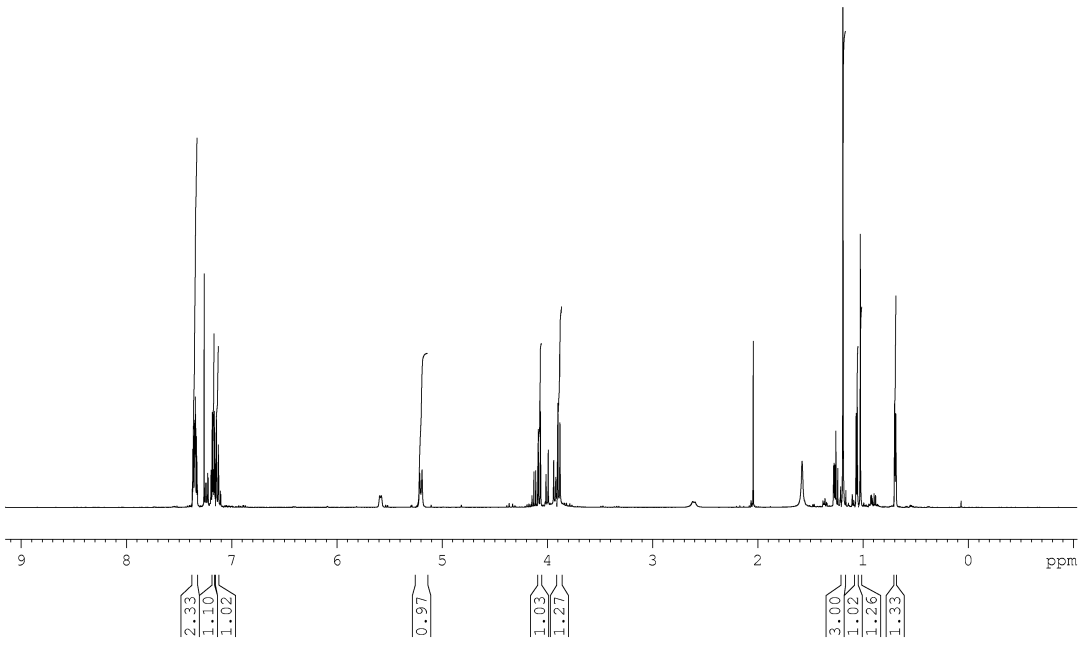




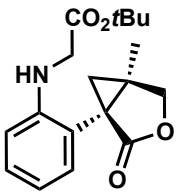


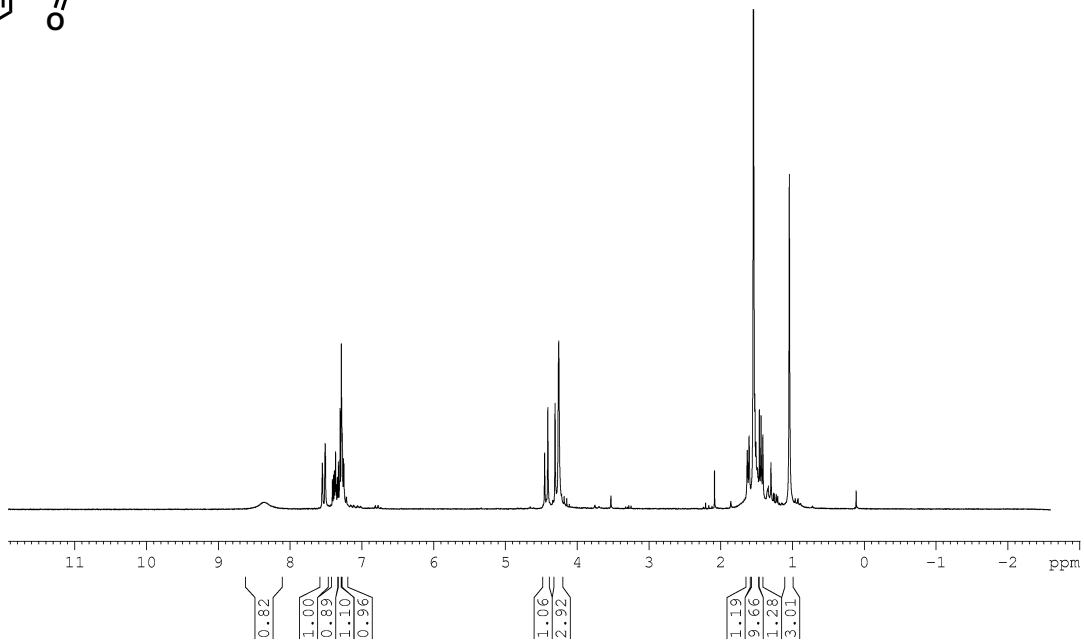
1-(2-Azidophenyl)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-ol (159a)



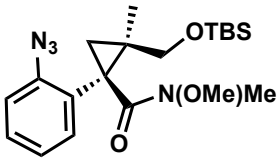


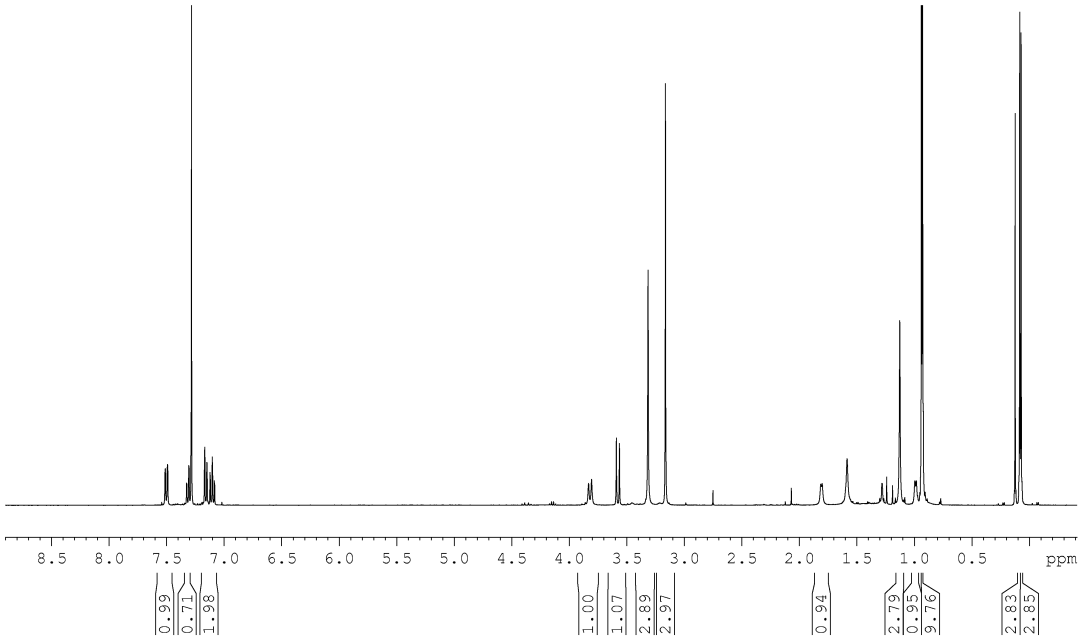
***Tert*-butyl (2-(5-methyl-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)phenyl)glycinate (160)**

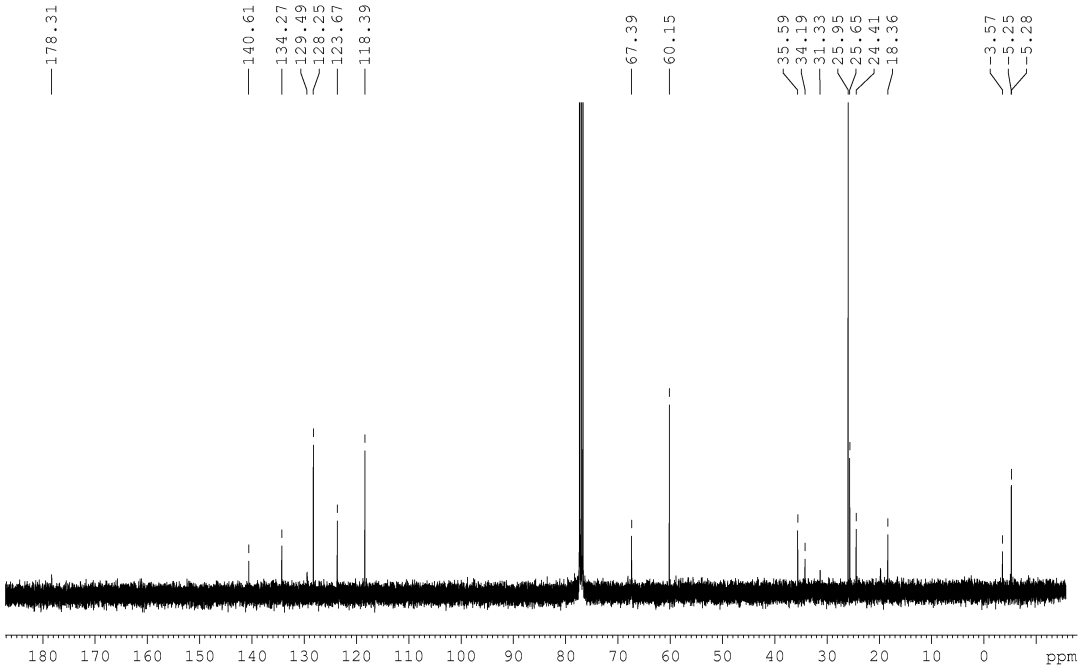




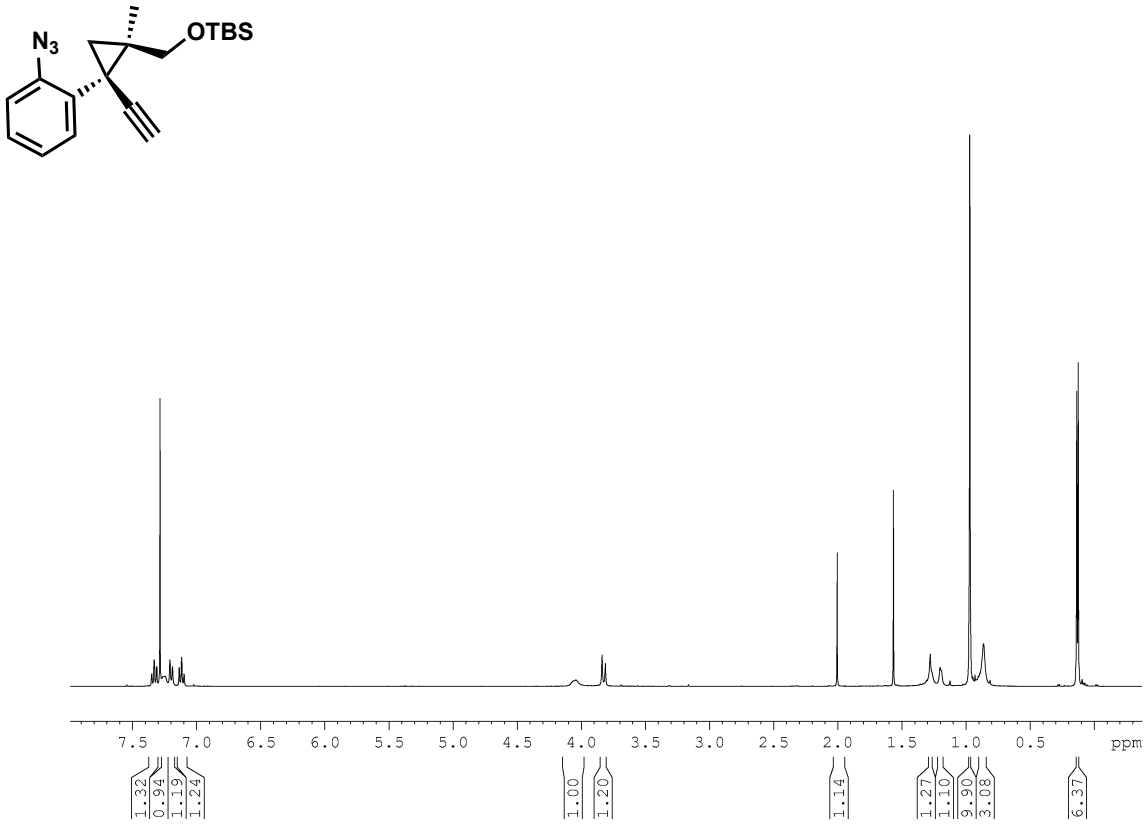
1-(2-Azidophenyl)-2-(hydroxymethyl)-*N*-methoxy-*N*,2-dimethylcyclopropanecarboxamide (161)



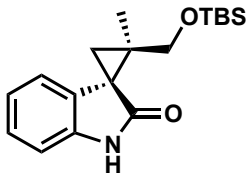


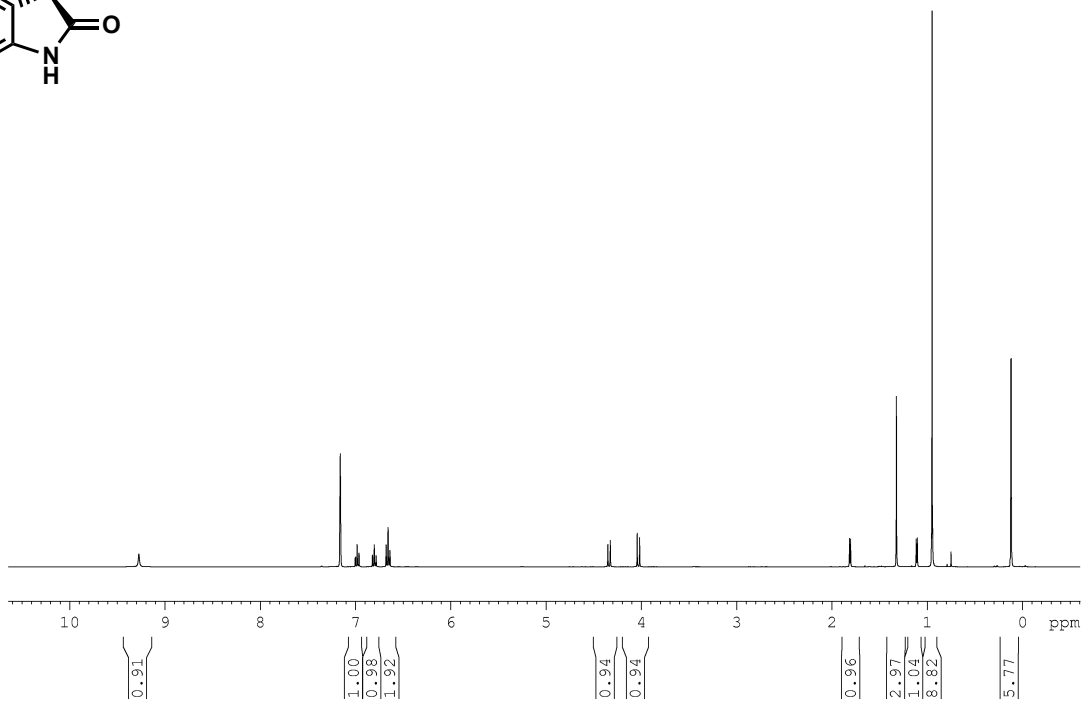


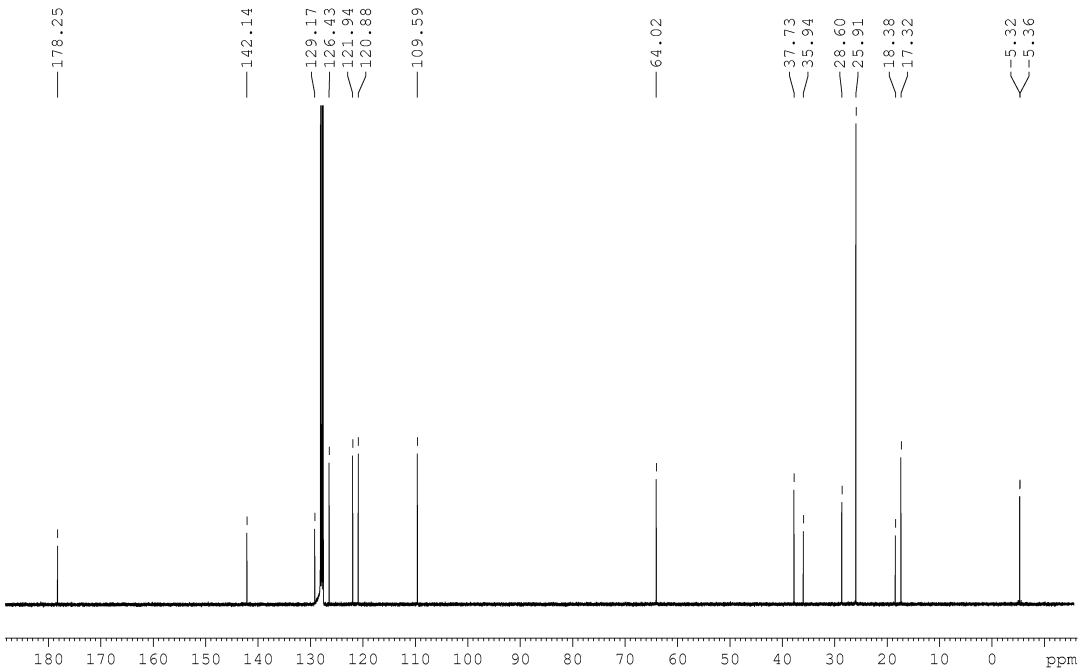
((2-(2-Azidophenyl)-2-ethynyl-1-methylcyclopropyl)methoxy)(*tert*-butyl)dimethylsilane (157b)



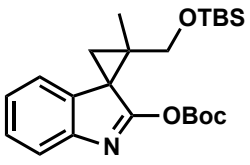
2-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (156a)

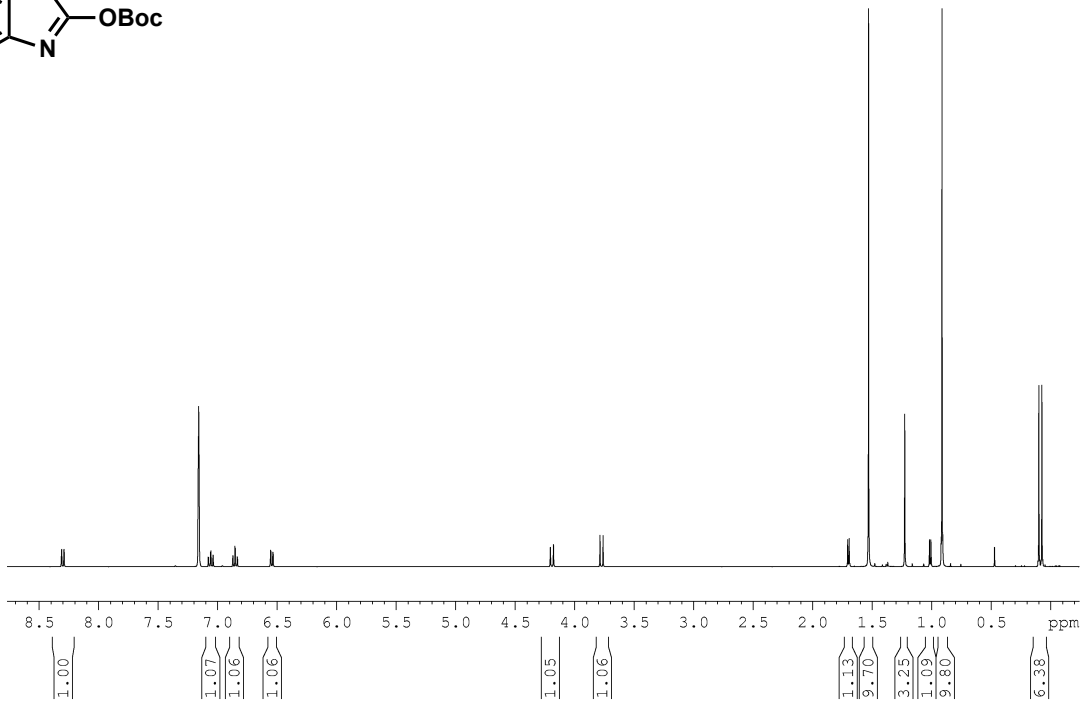


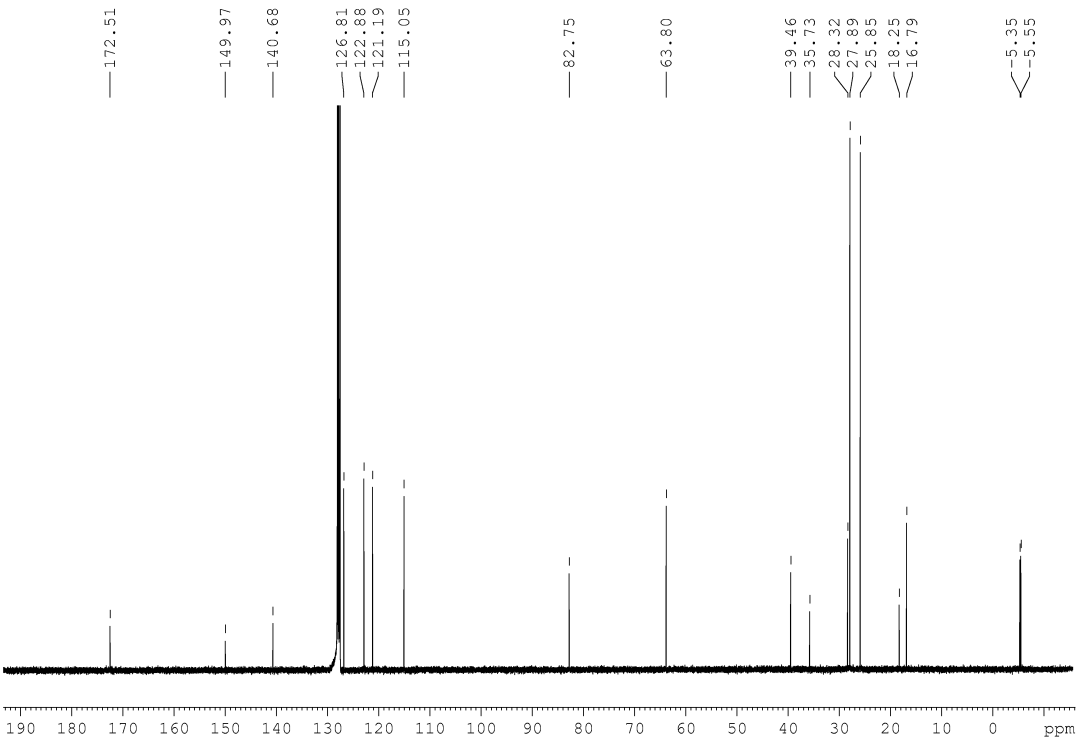




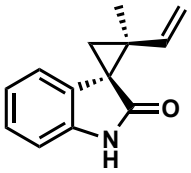
Tert-butyl (2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylspiro[cyclopropane-1,3'-indol]-2'-yl) carbonate (163)

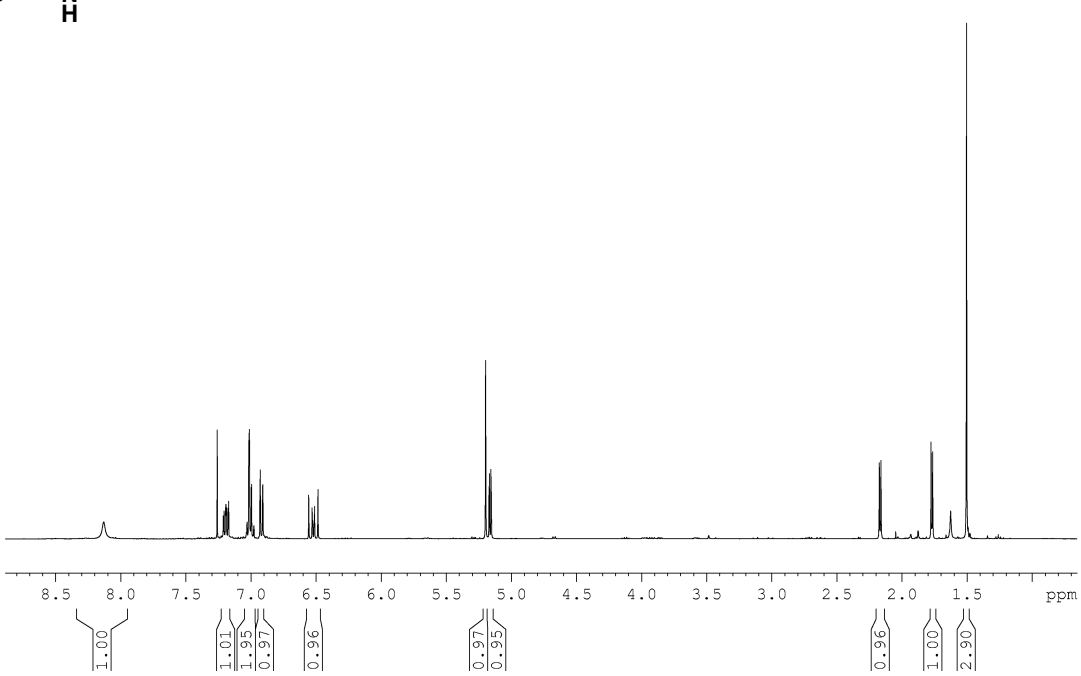


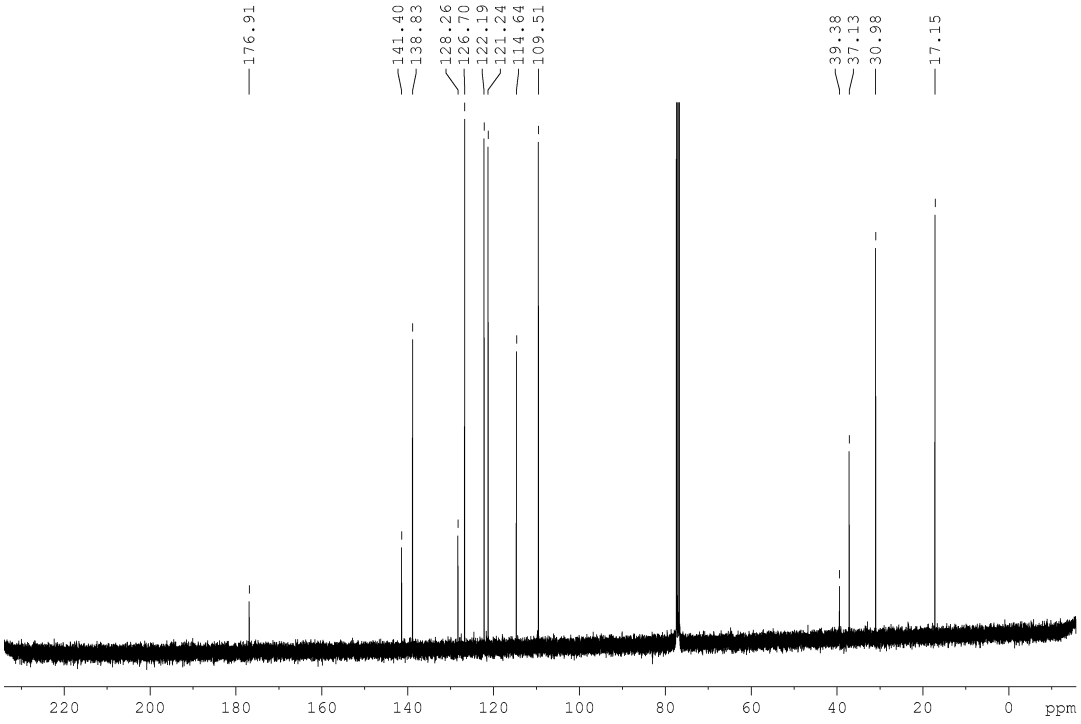




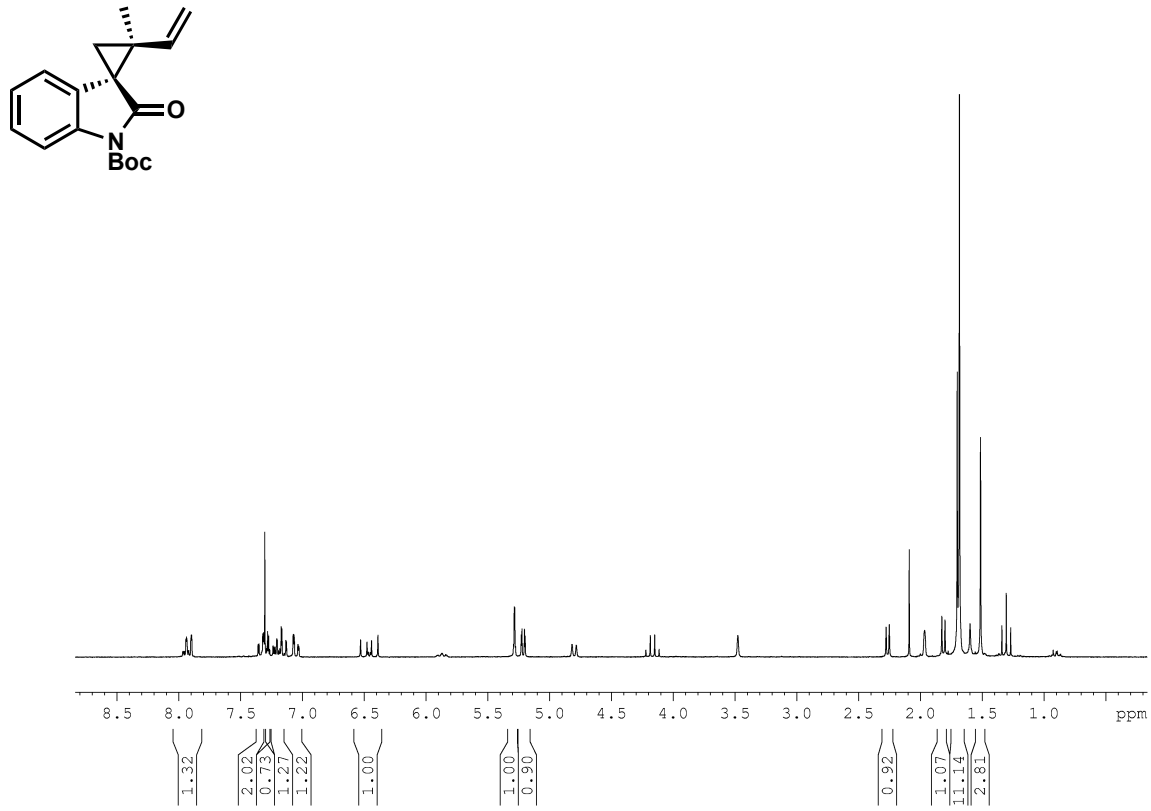
2-Methyl-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (142c)



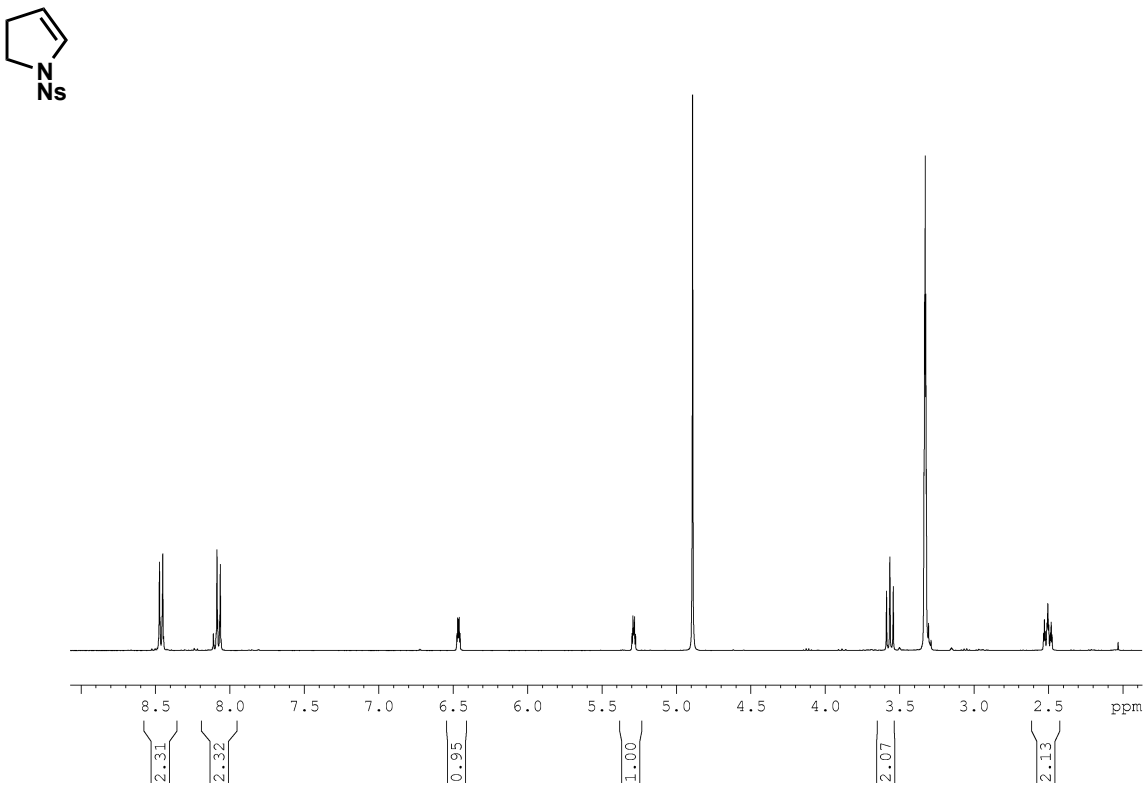




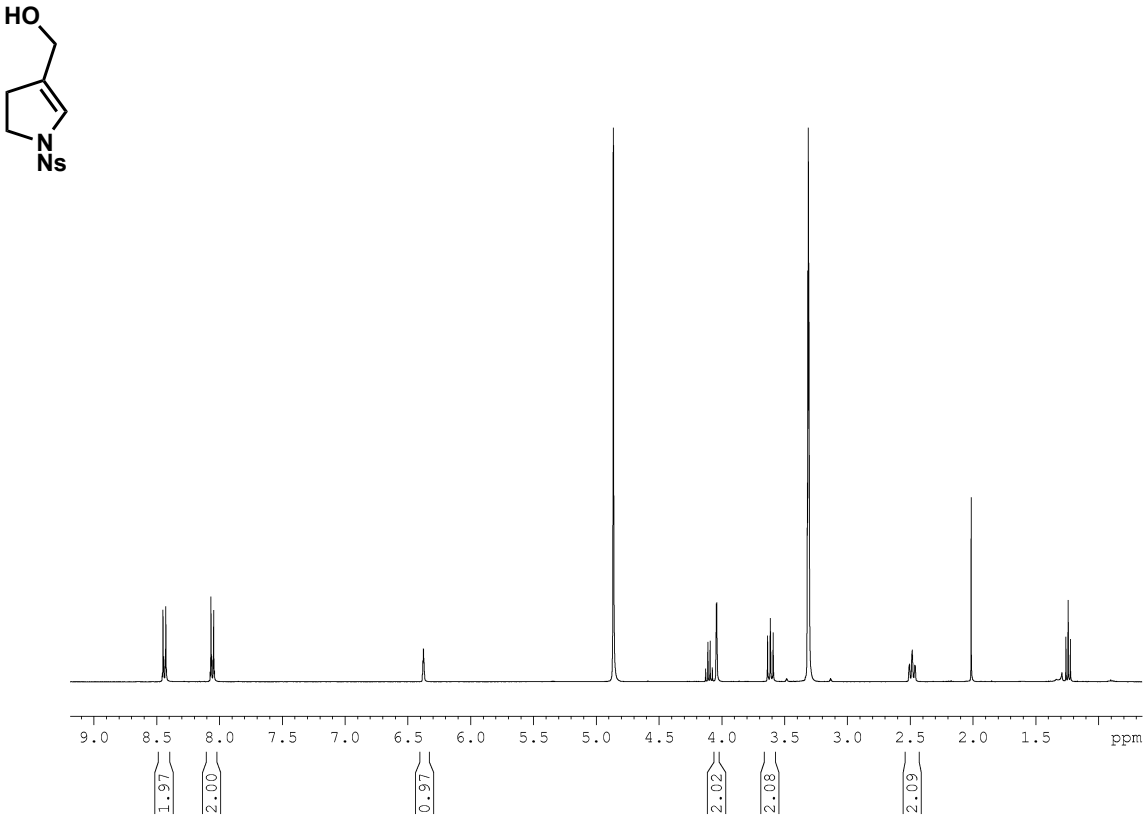
2-*Tert*-butyl-2-methyl-2'-oxo-2-vinylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (142d)



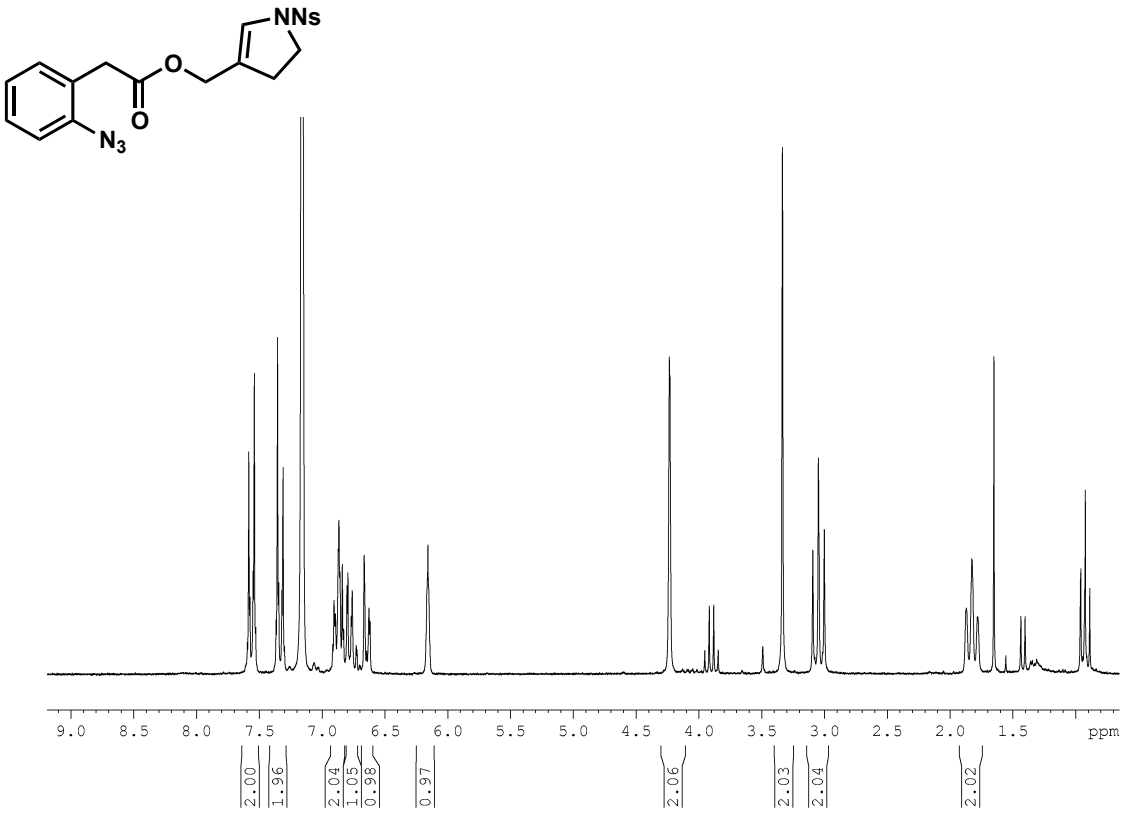
1-((4-Nitrophenyl)sulfonyl)-2,3-dihydro-1*H*-pyrrole (172)



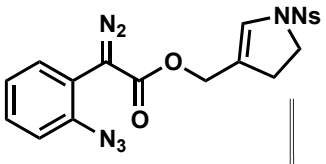
(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methanol (173)

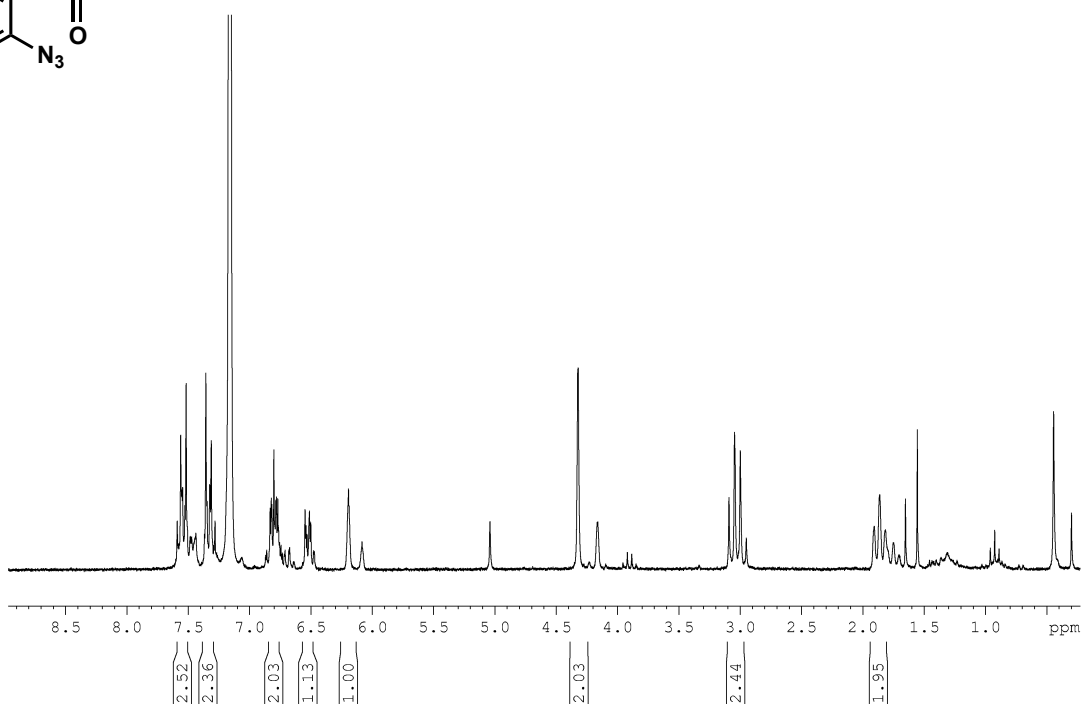


(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methyl 2-(2-azido-phenyl)acetate (173a)

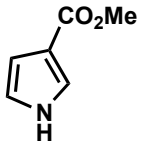


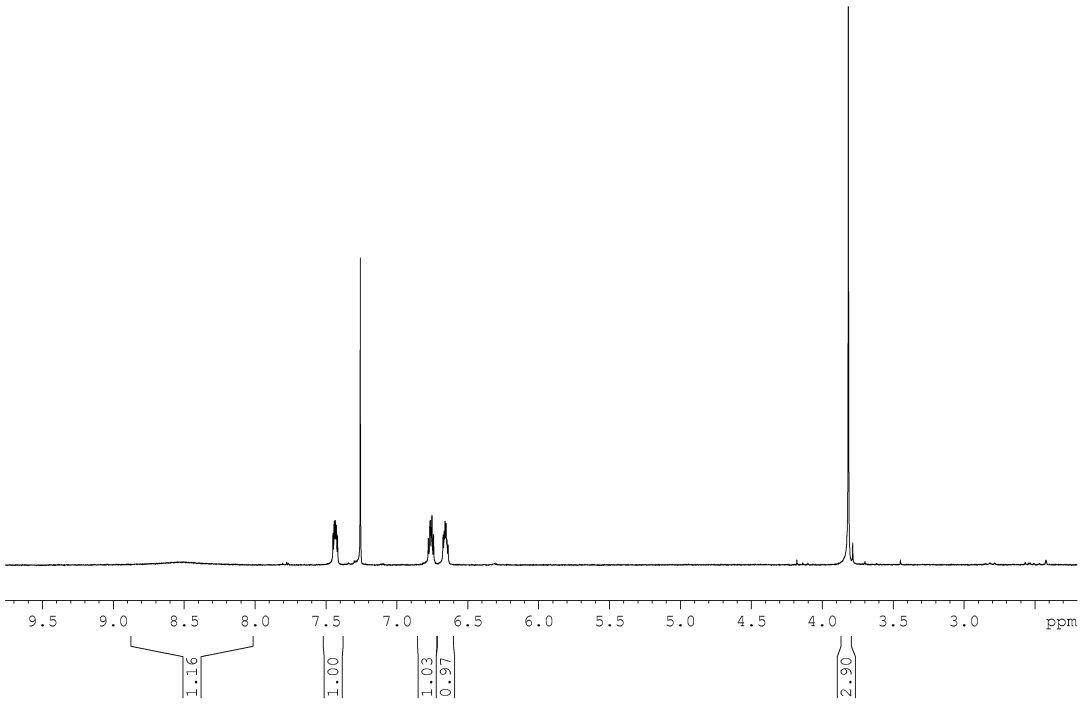
(1-((4-Nitrophenyl)sulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)methyl 2-(2-azidophenyl)-2-diazoacetate (174)



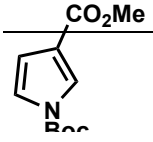


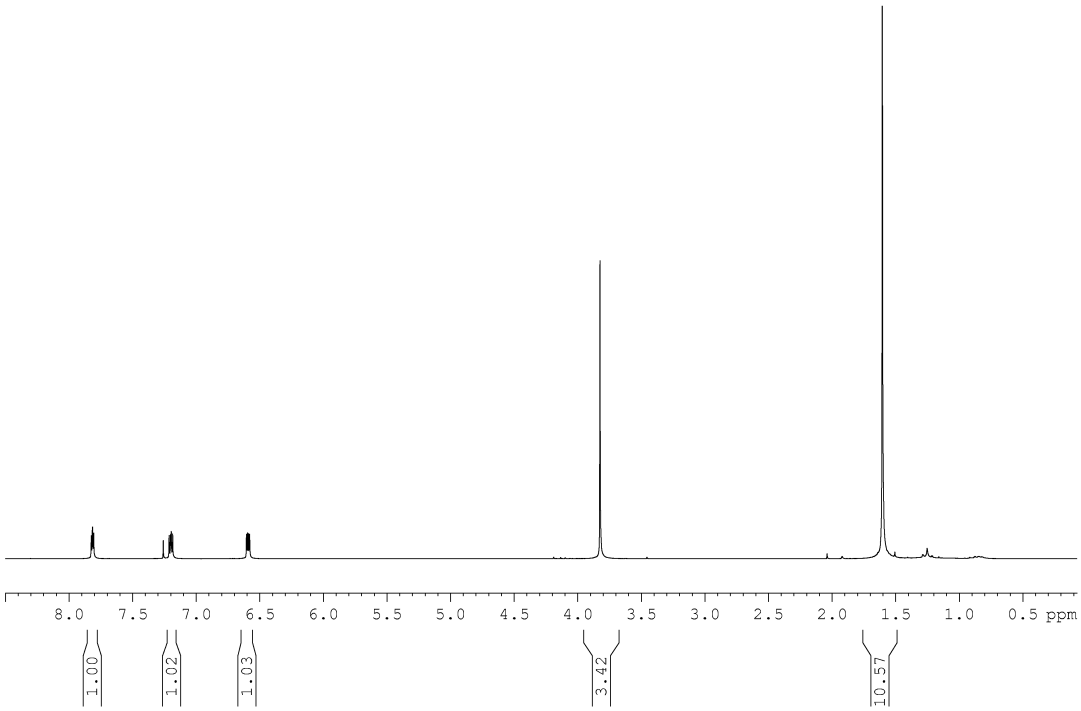
Methyl 1*H*-pyrrole-3-carboxylate (176)



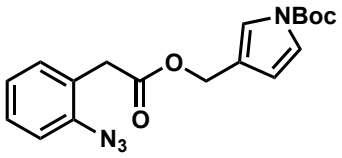


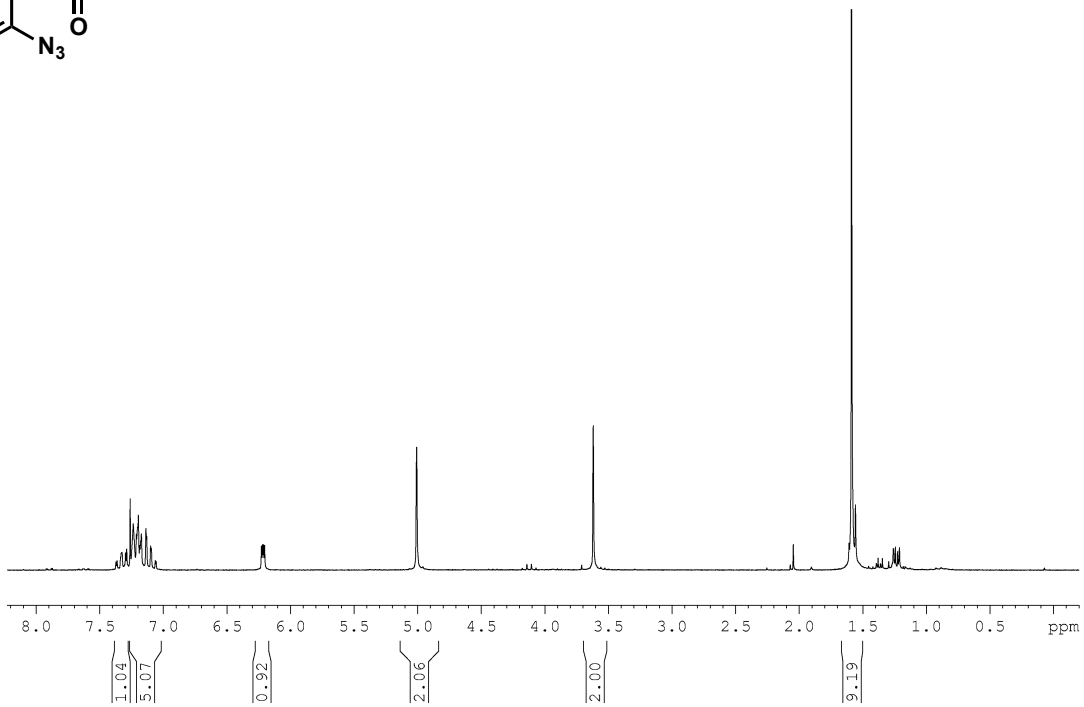
1-*Tert*-butyl 3-methyl 1*H*-pyrrole-1,3-dicarboxylate (177)



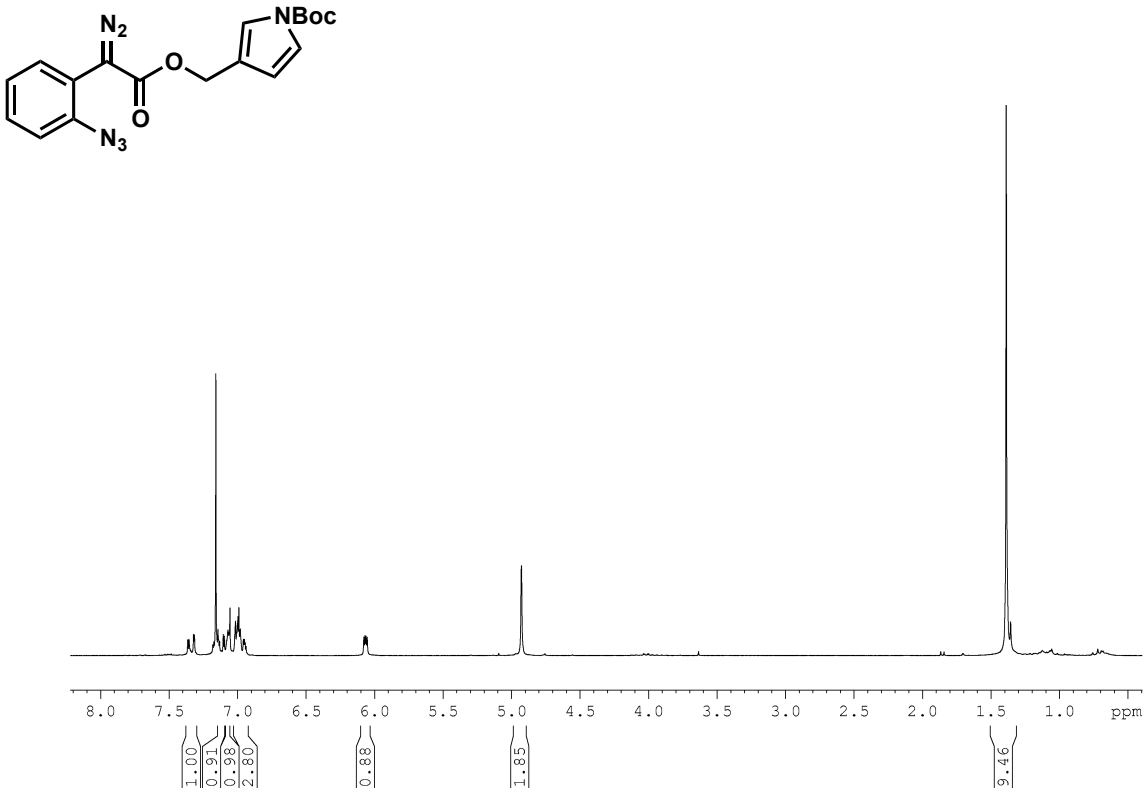


***Tert*-butyl 3-((2-(2-azidophenyl)acetoxy)methyl)-1*H*-pyrrole-1-carboxylate (177b)**

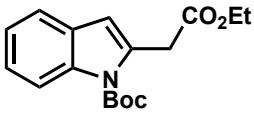


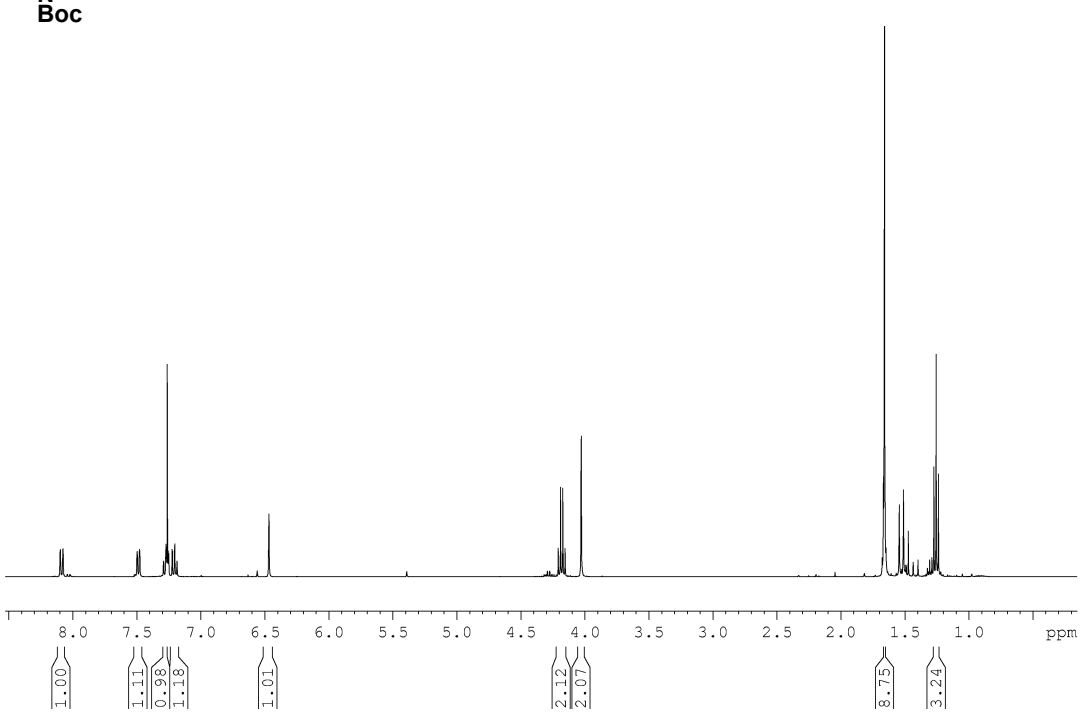


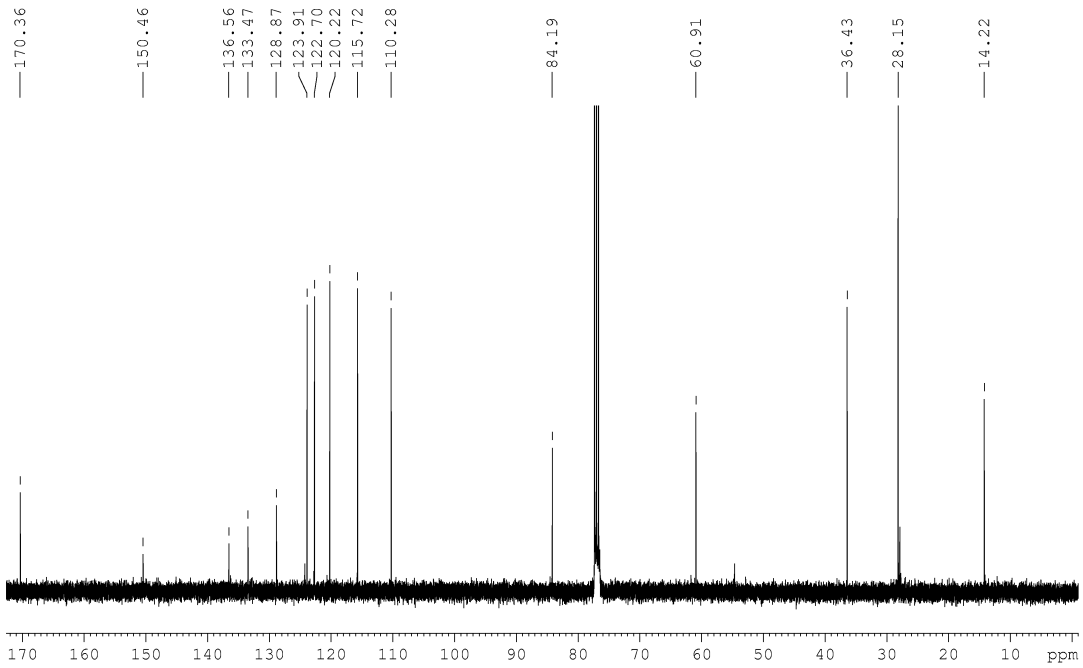
Tert-butyl 3-((2-(2-azidophenyl)-2-diazoacetoxy)methyl)-1_H_-pyrrole-1-carboxylate (178)



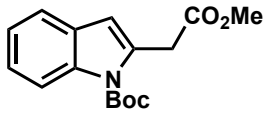
***Tert*-butyl 2-(2-ethoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (216)**

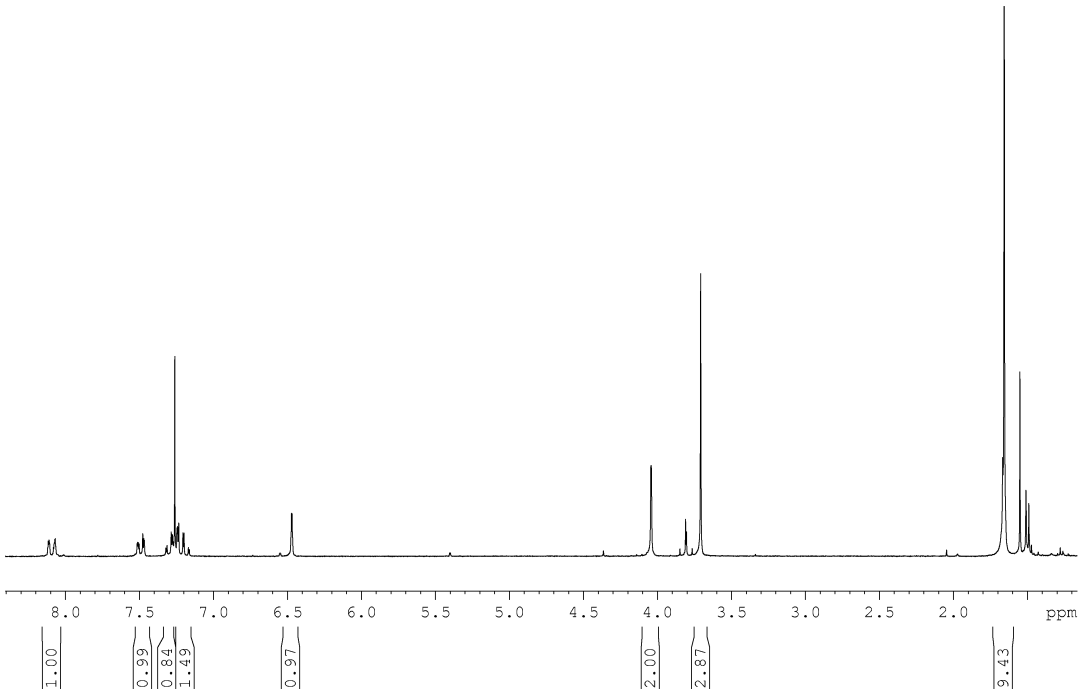




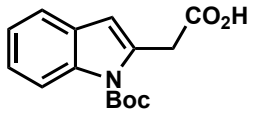


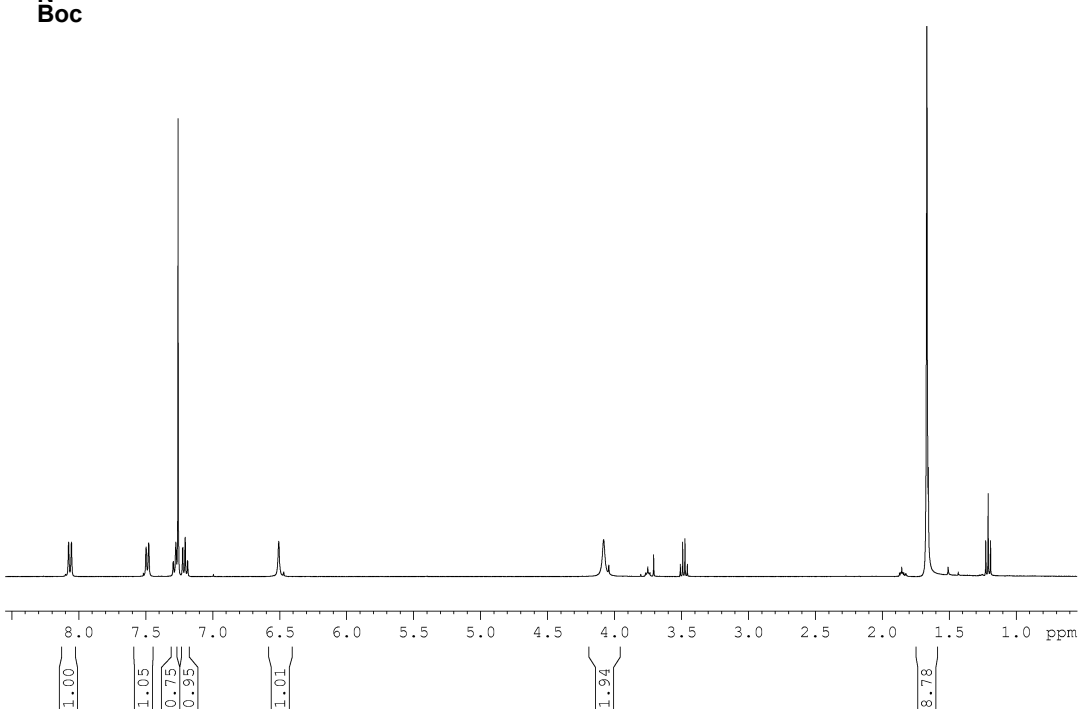
***Tert*-butyl 2-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (216a)**

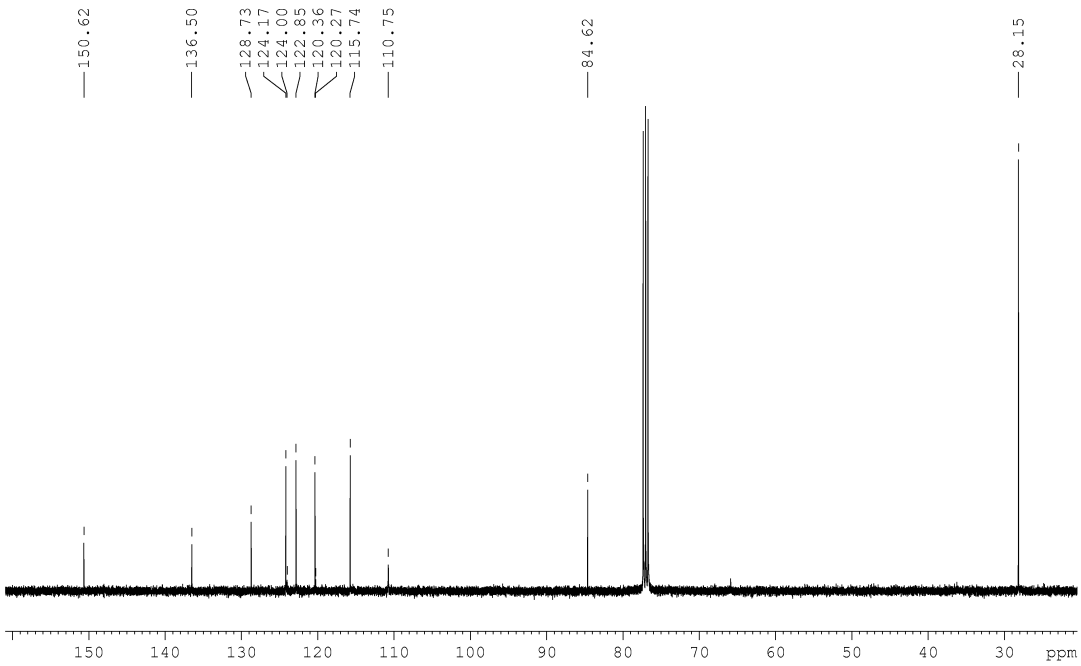




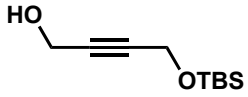
2-(1-(*Tert*-butoxycarbonyl)-1*H*-indol-2-yl)acetic acid (217)

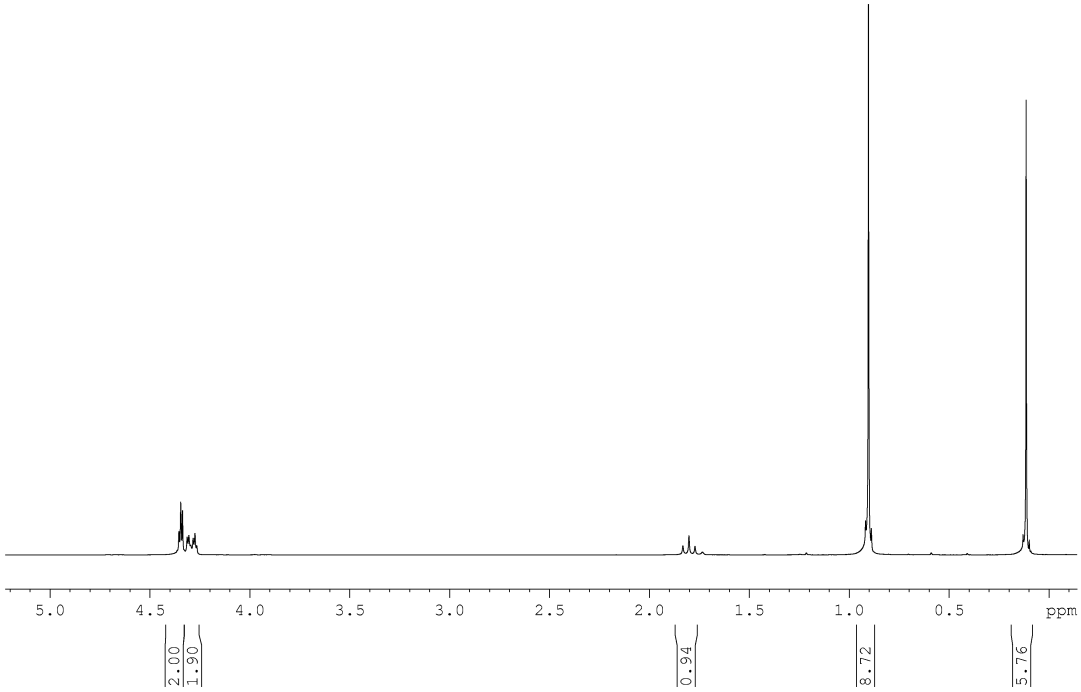




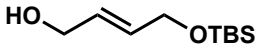


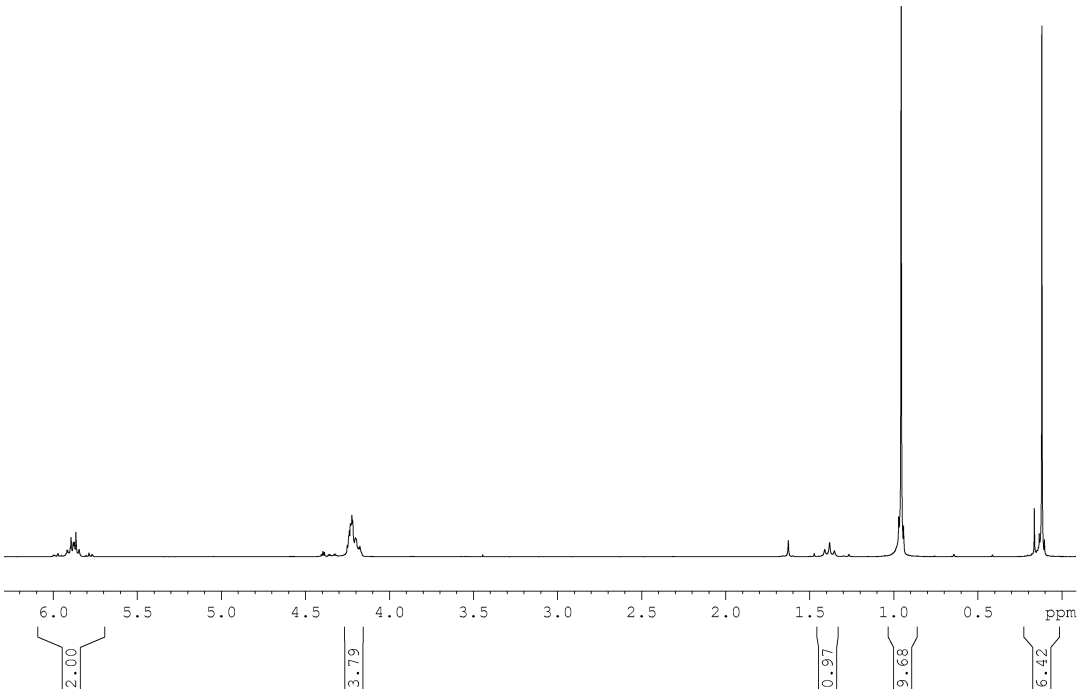
4-((*Tert*-butyldimethylsilyl)oxy)but-2-yn-1-ol (218a)



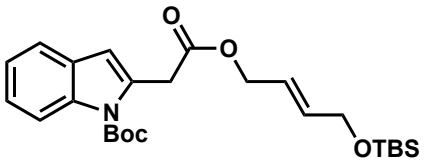


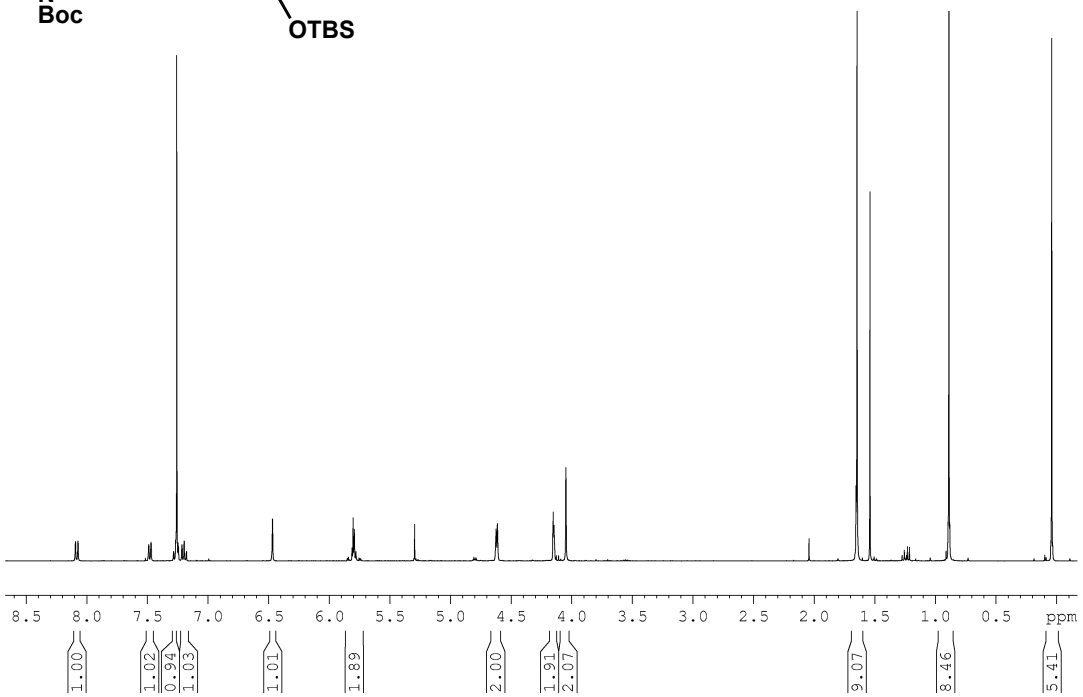
(*E*)-4-((*Tert*-butyldimethylsilyl)oxy)but-2-en-1-ol (219)

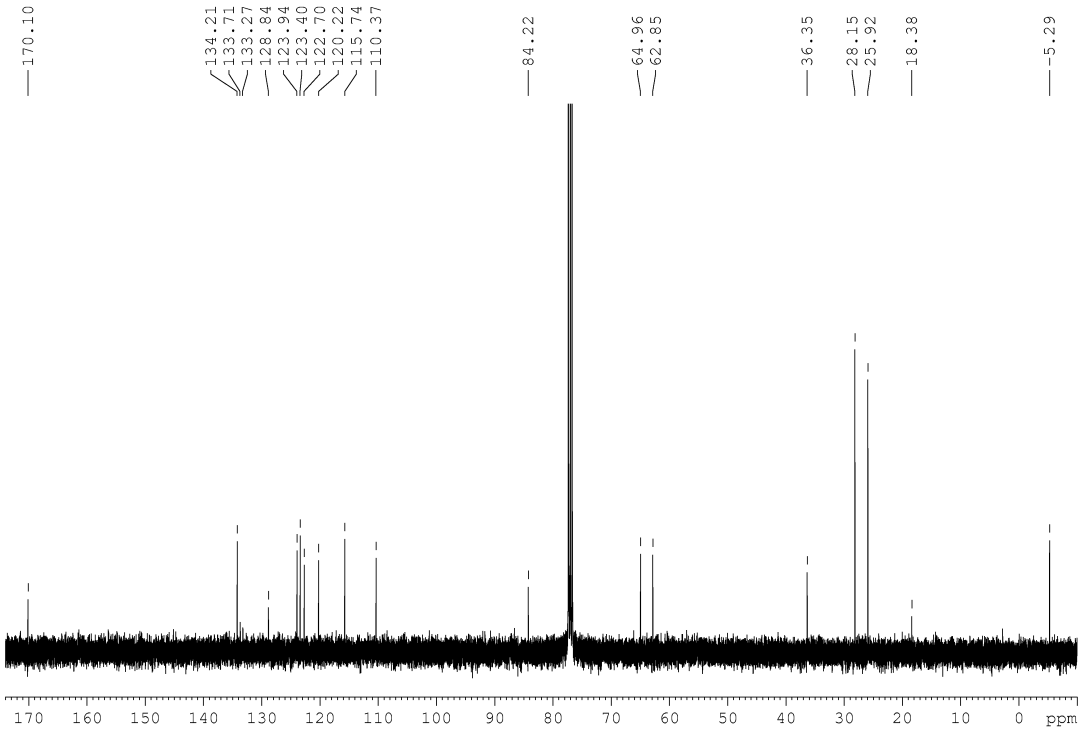



6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
3.79
0.97
9.68
6.42

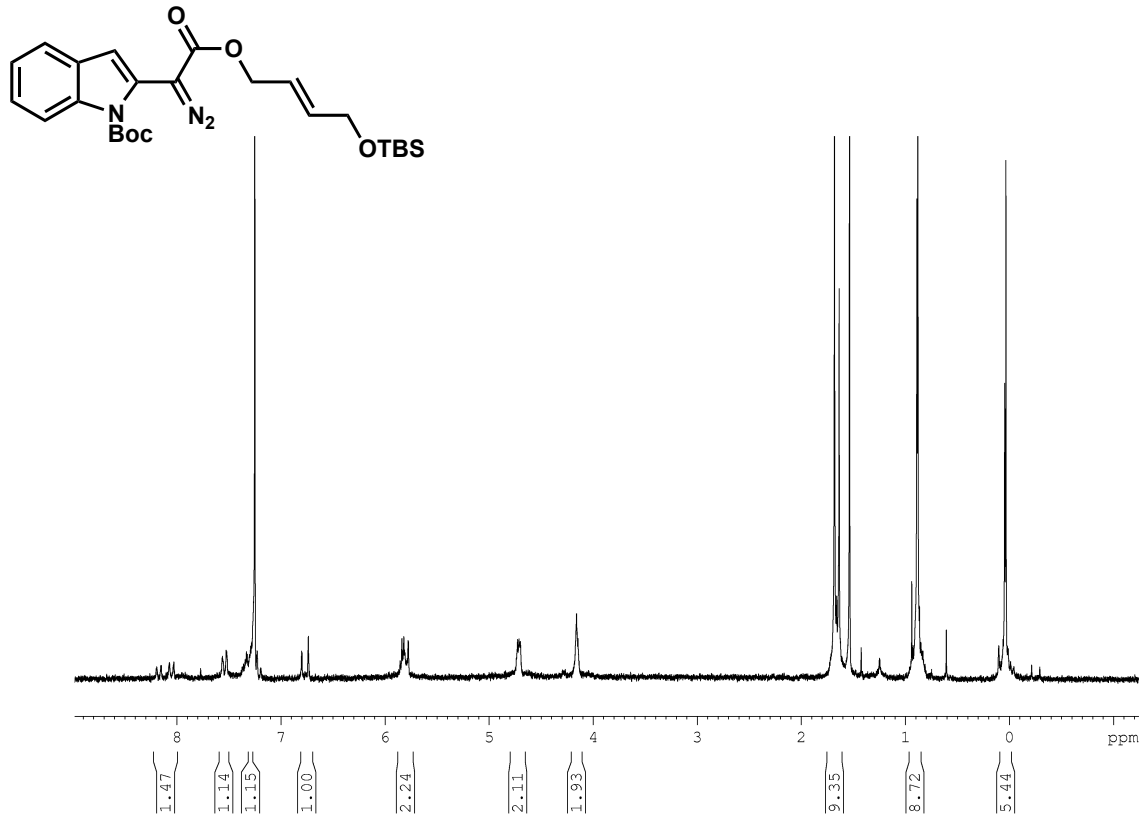
(*E*)-*Tert*-butyl 2-(2-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)-2-oxoethyl)-1*H*-indole-1-carboxylate (219a)



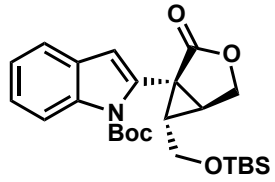


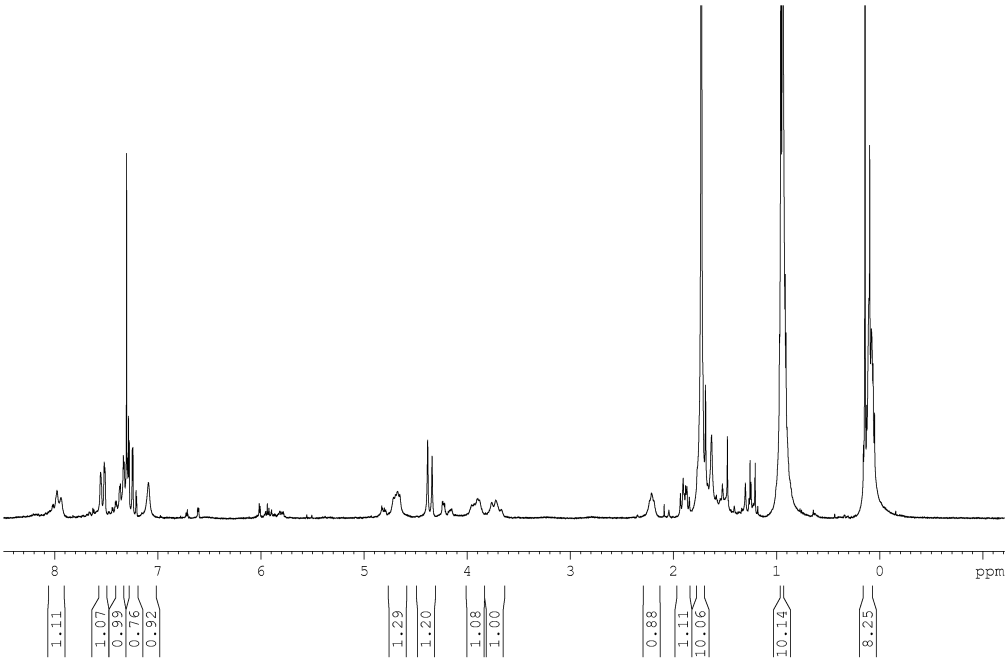


(*E*)-*Tert*-butyl 2-(2-((4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl)oxy)-1-diazo-2-oxoethyl)-1*H*-indole-1-carboxylate (220)

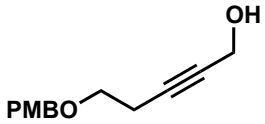


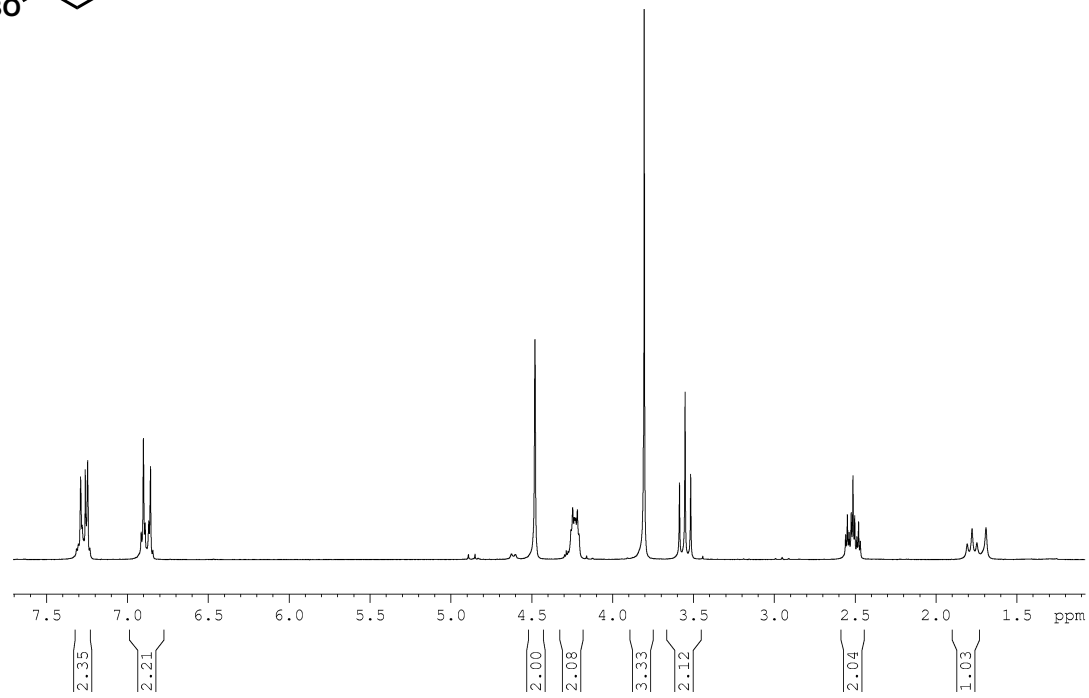
***Tert*-butyl 2-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-3-oxabicyclo[3.1.0]hexan-1-yl)-1*H*-indole-1-carboxylate (221)**



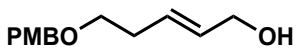


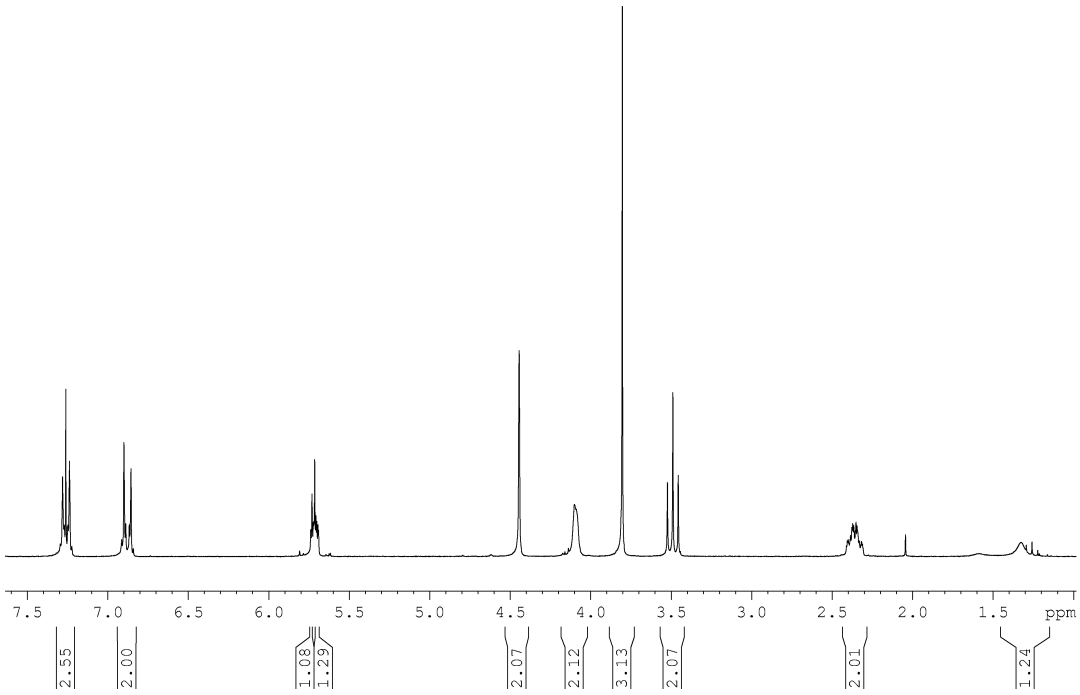
5-((4-Methoxybenzyl)oxy)pent-2-yn-1-ol (222a)



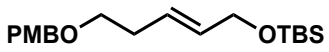


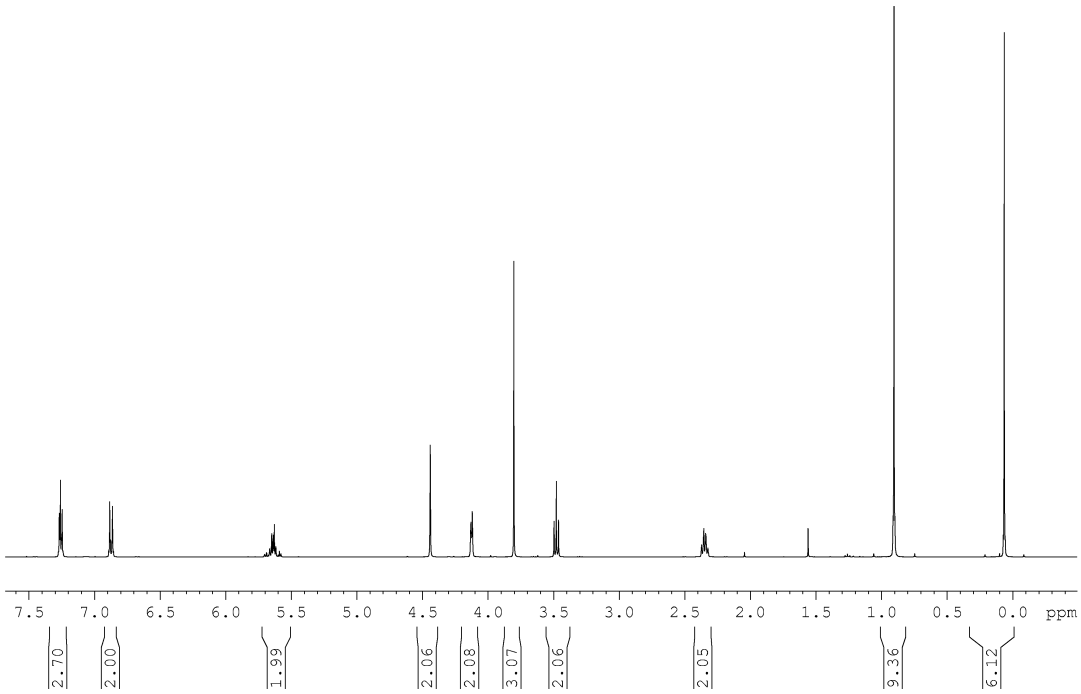
(*E*)-5-((4-Methoxybenzyl)oxy)pent-2-en-1-ol (223)

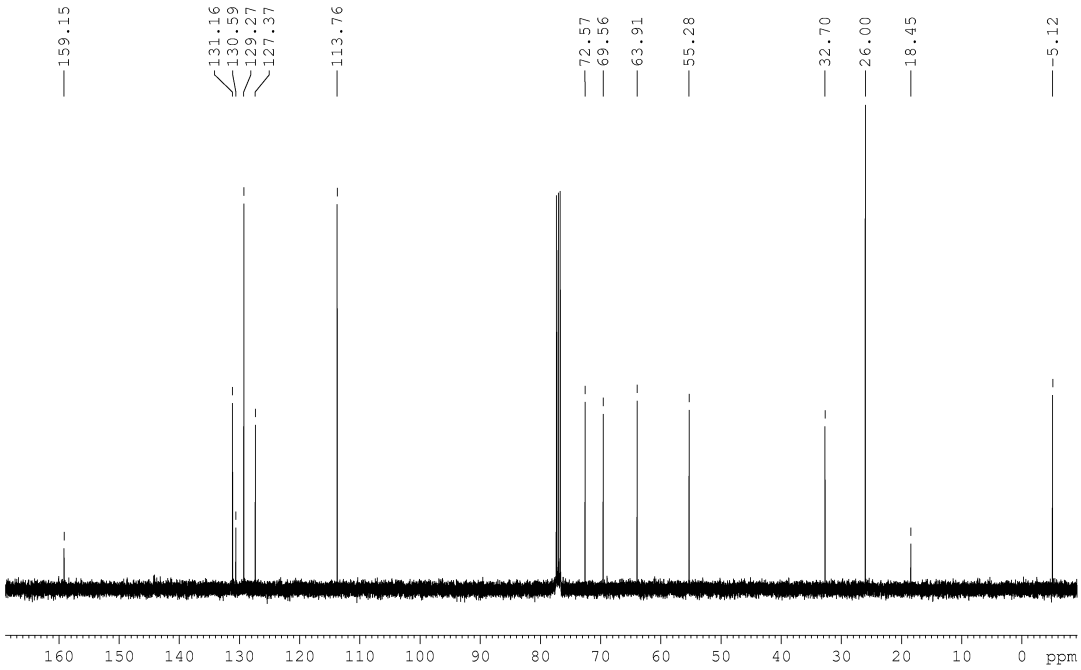

PMBO
OH


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
ppm
2.55
2.00
1.08
1.29
2.07
2.12
3.13
2.07
2.01
1.24

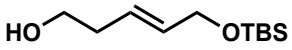
(*E*)-*Tert*-butyl((5-((4-methoxybenzyl)oxy)pent-2-en-1-yl)oxy)dimethylsilane (223a)

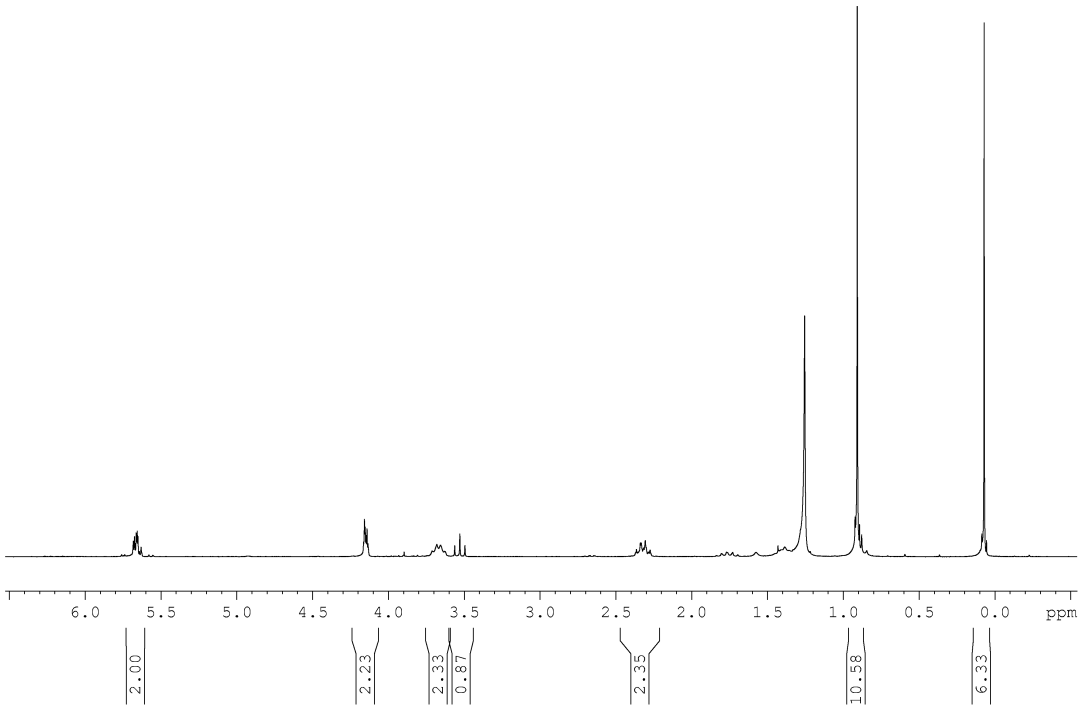




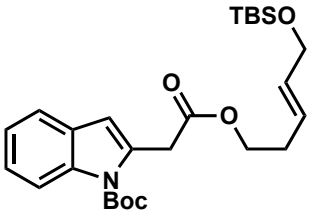


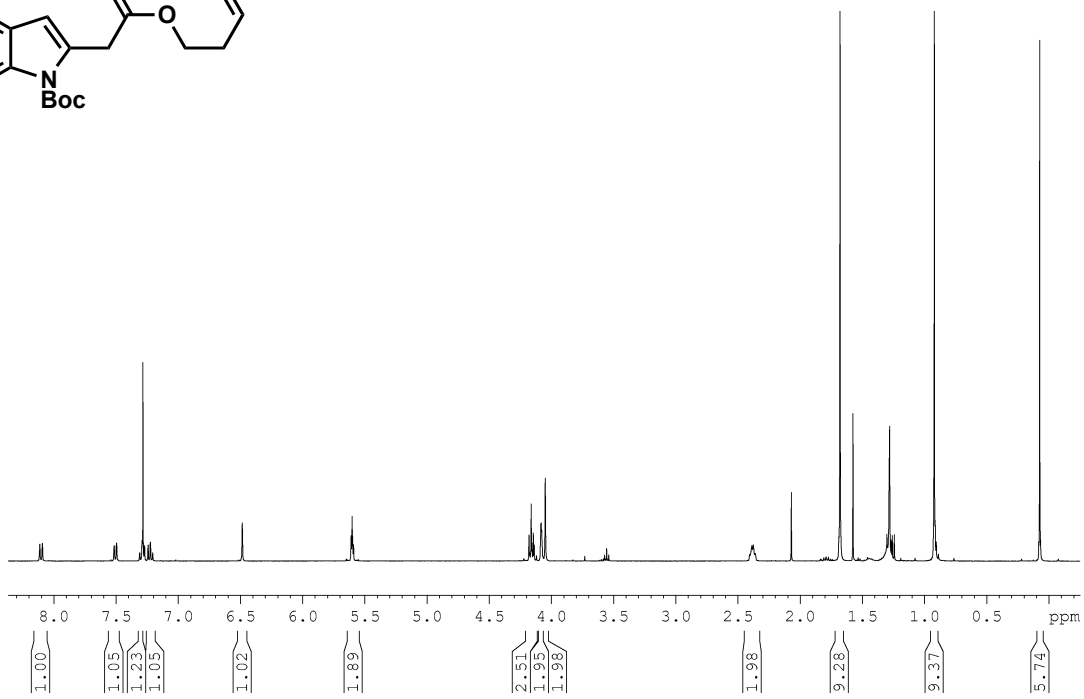
(*E*)-5-((*Tert*-butyldimethylsilyl)oxy)pent-3-en-1-ol (224)

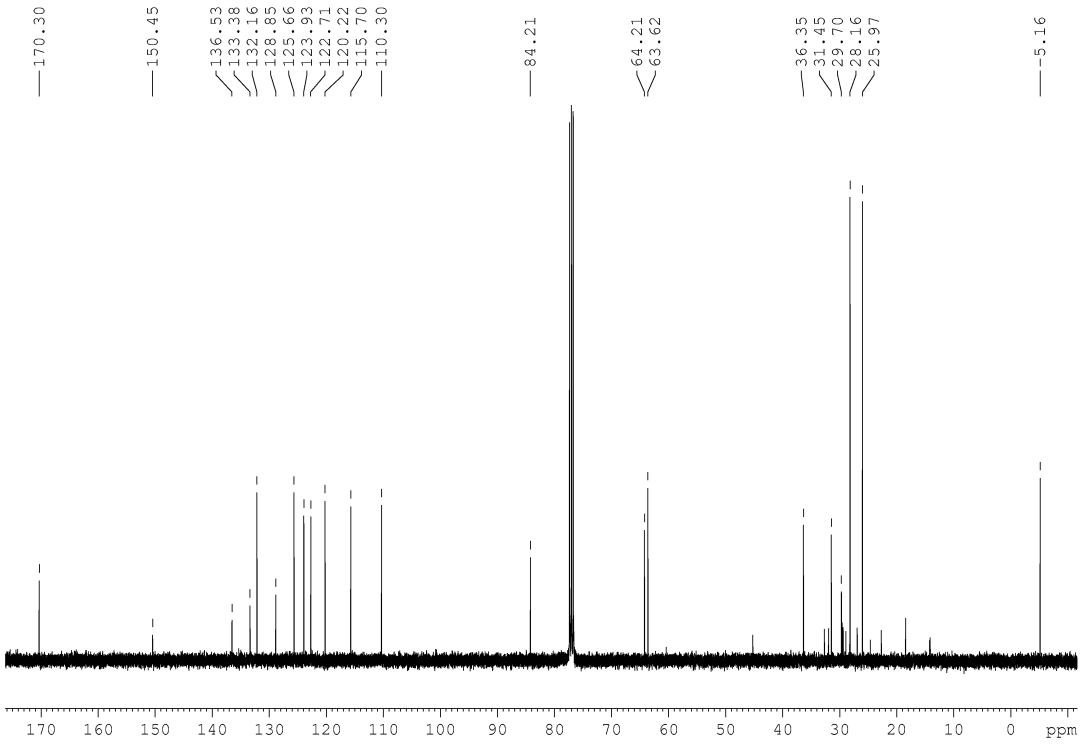




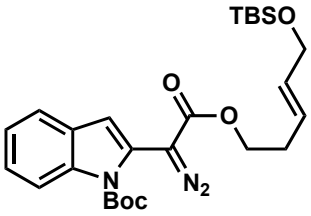
(*E*)-*Tert*-butyl 2-(2-((5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)oxy)-2-oxoethyl)-1*H*-indole-1-carboxylate (224a)

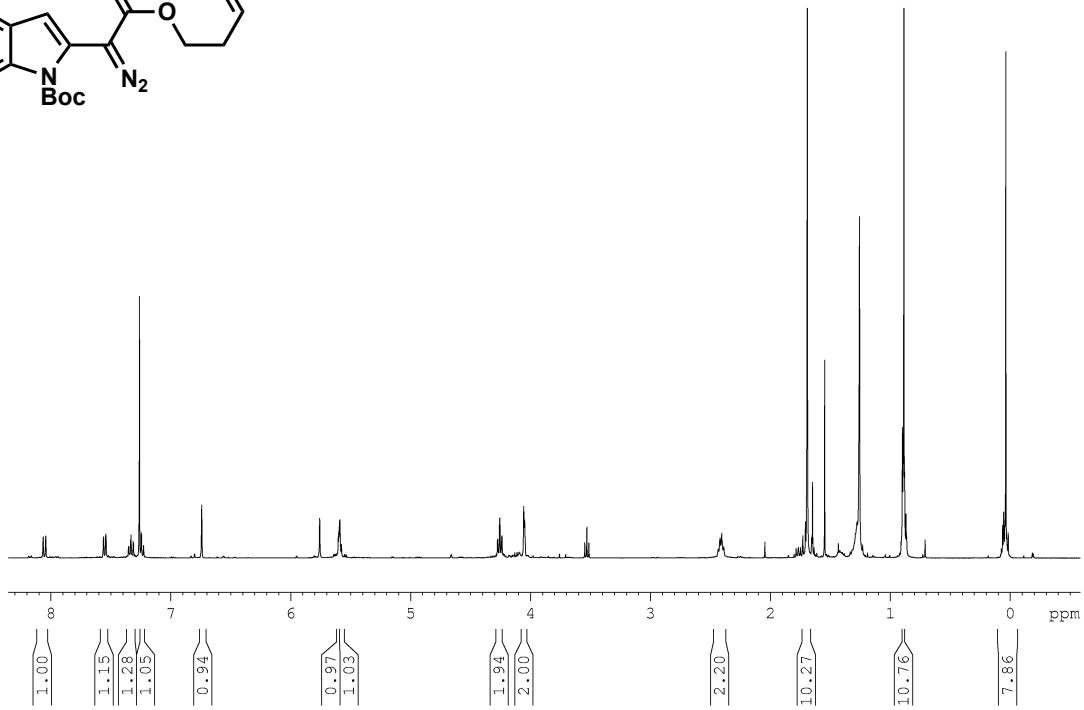


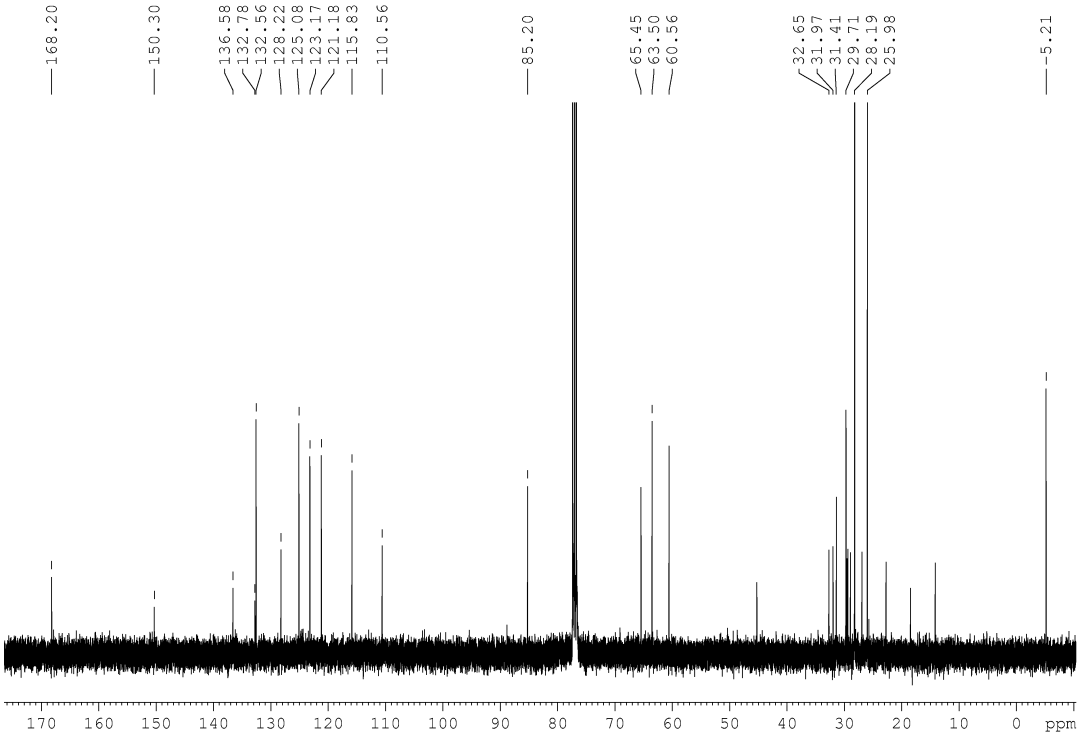




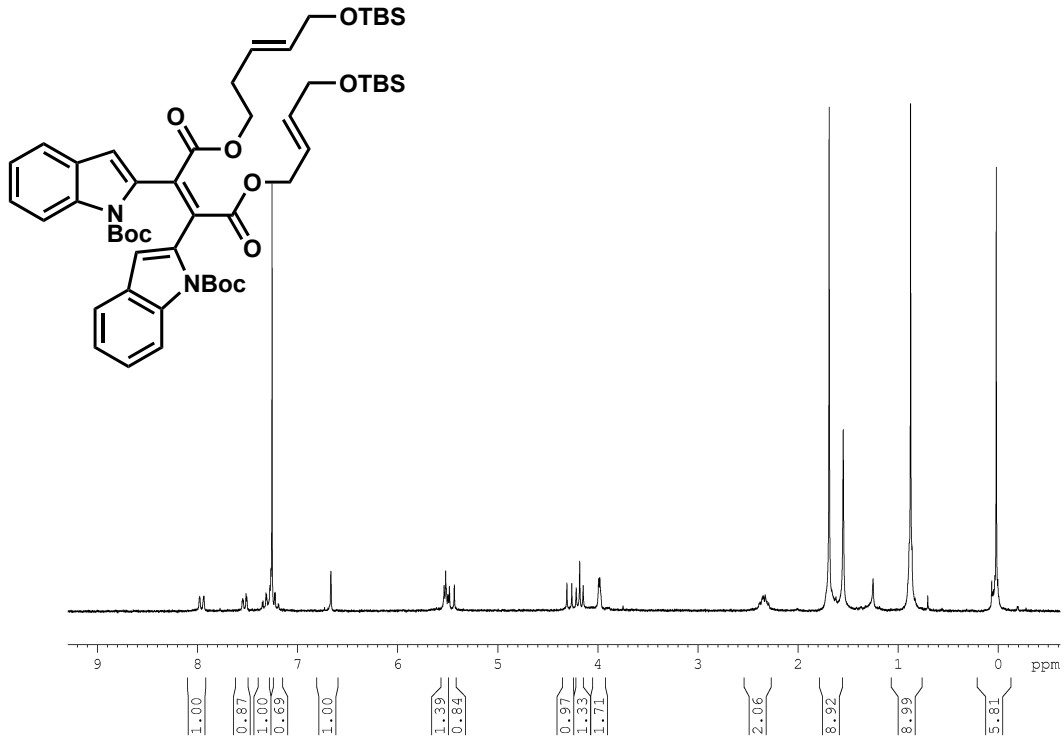
(*E*)-*Tert*-butyl 2-(2-((5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)oxy)-1-diazo-2-oxoethyl)-1*H*-indole-1-carboxylate (215a)



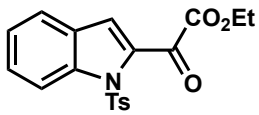


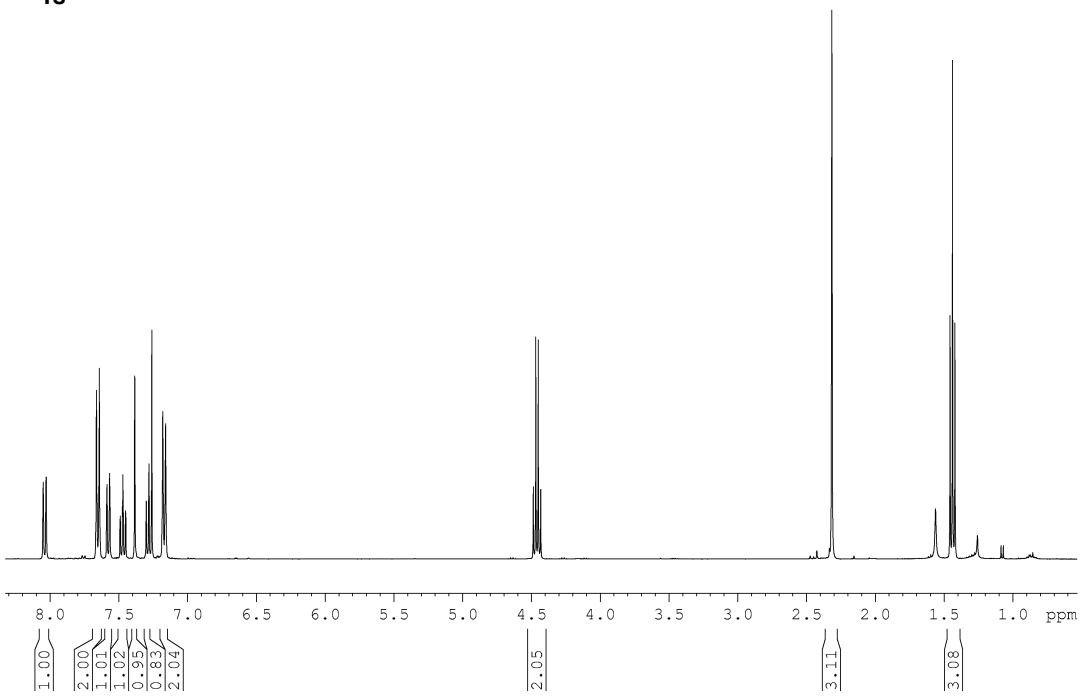


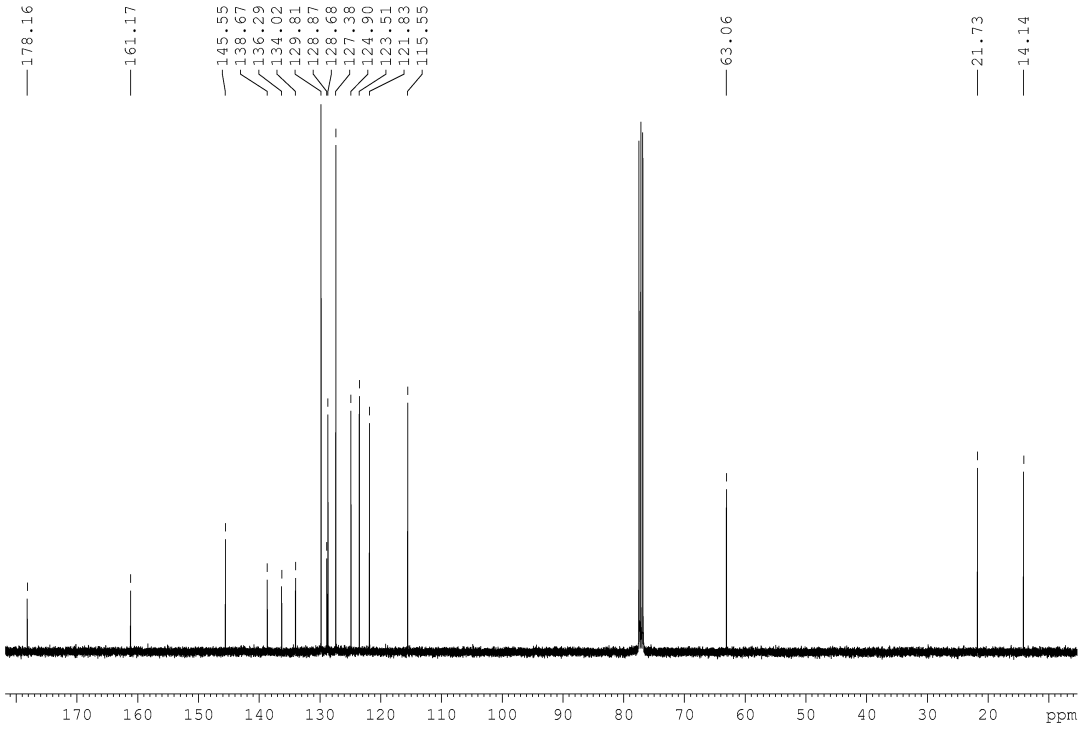
1-((*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-en-1-yl) 4-((*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl) 2,3-bis(1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)maleate (225)



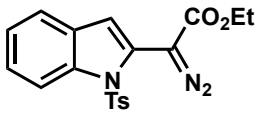
Ethyl 2-oxo-2-(1-tosyl-1*H*-indol-2-yl)acetate (237a)

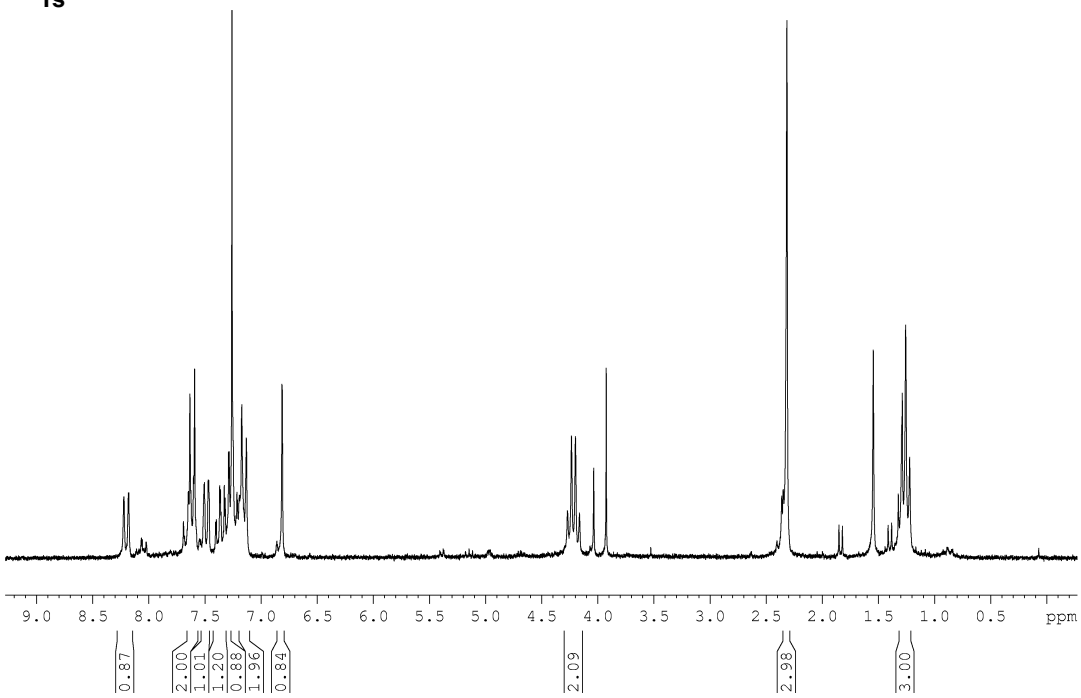




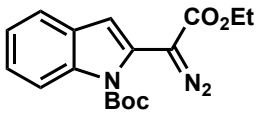


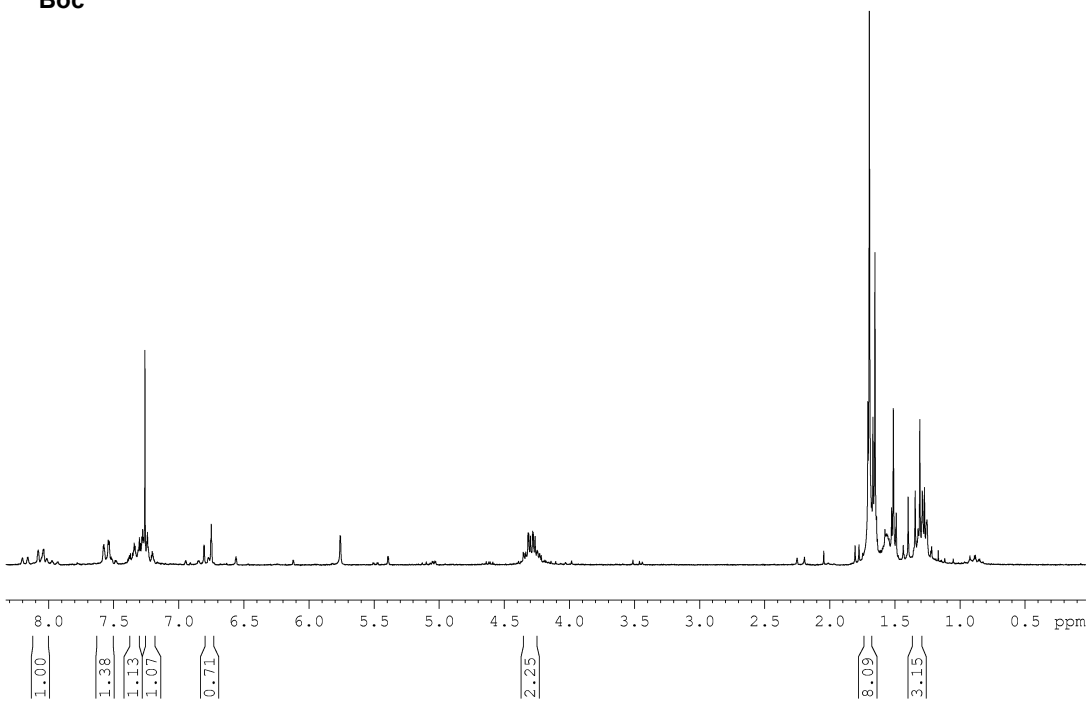
Ethyl 2-diazo-2-(1-tosyl-1*H*-indol-2-yl)acetate (229a)



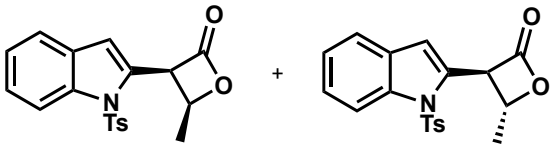


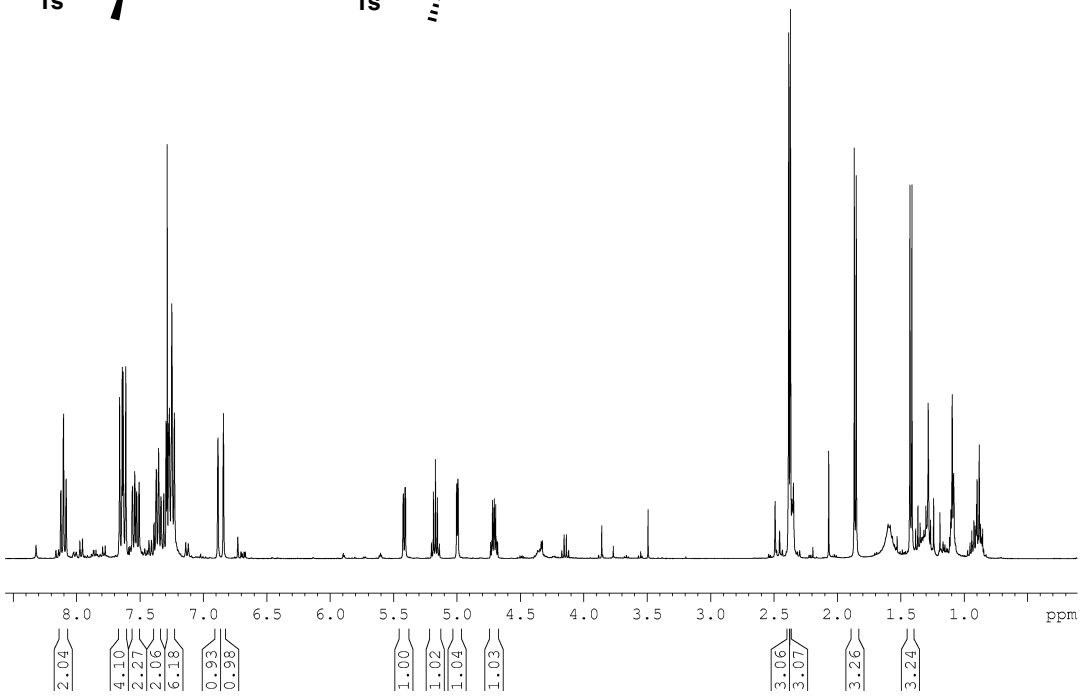
***Tert*-butyl 2-(1-diazo-2-ethoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (229b)**

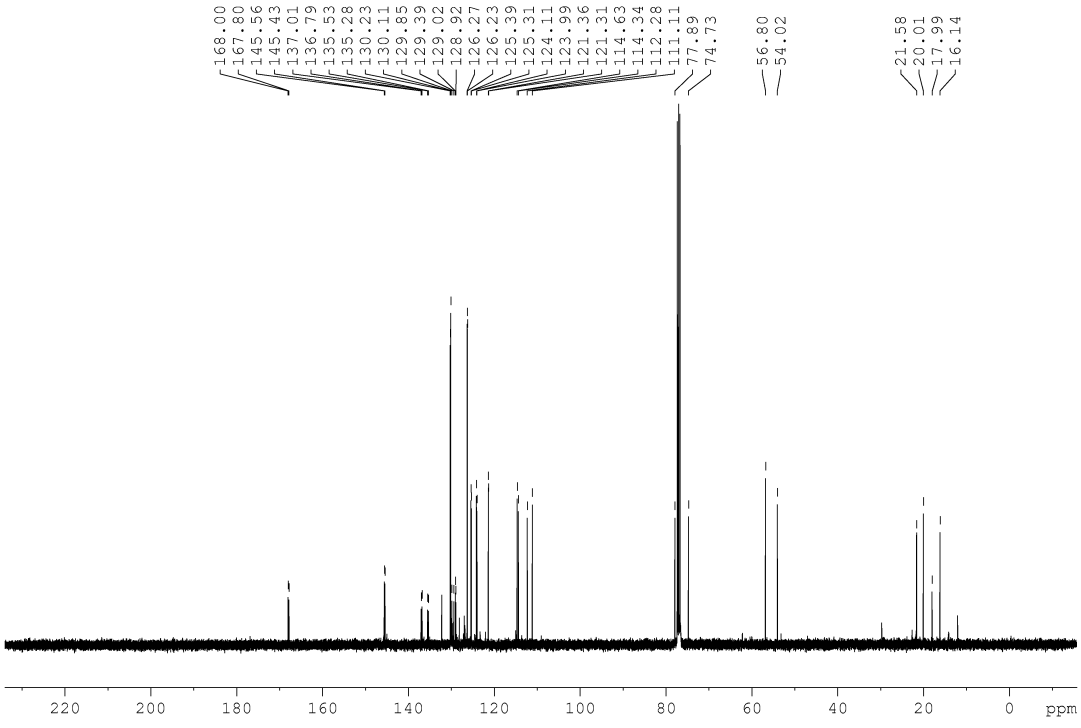




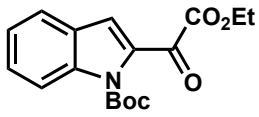
4-Methyl-3-(1-tosyl-1*H*-indol-2-yl)oxetan-2-one (231)

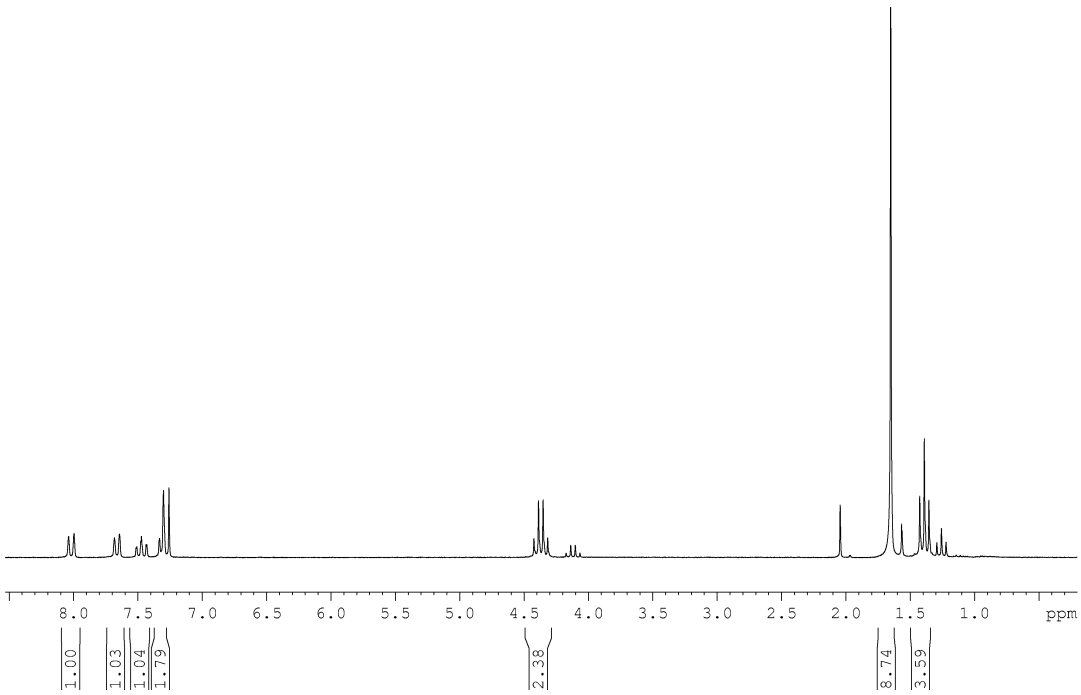




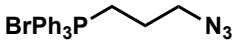


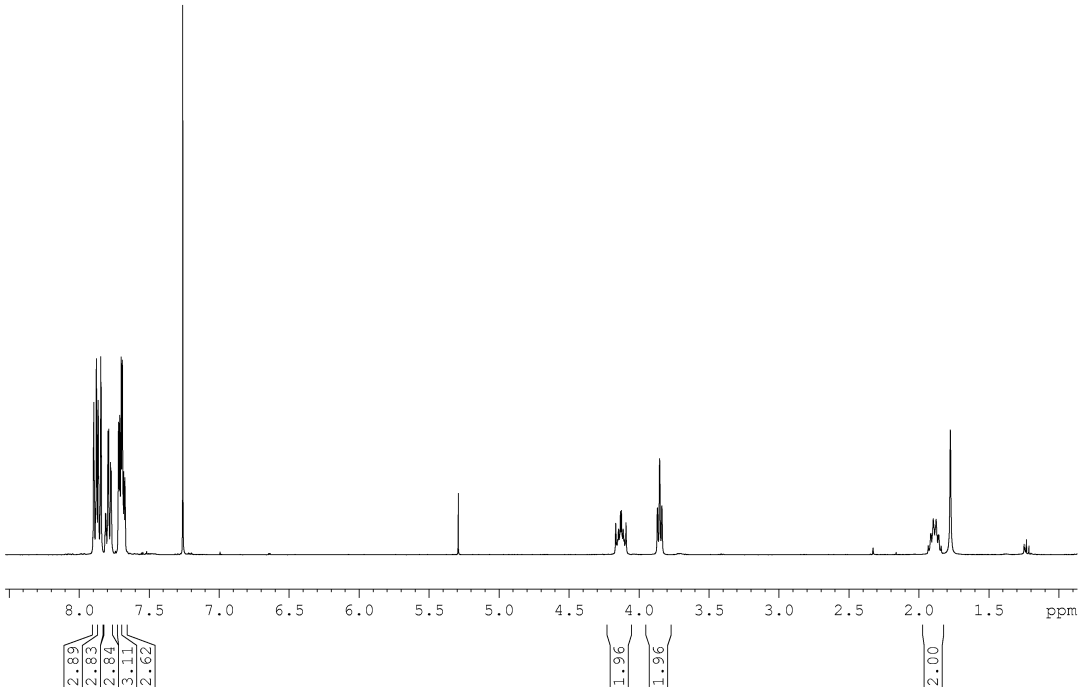
***Tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate (237b)**

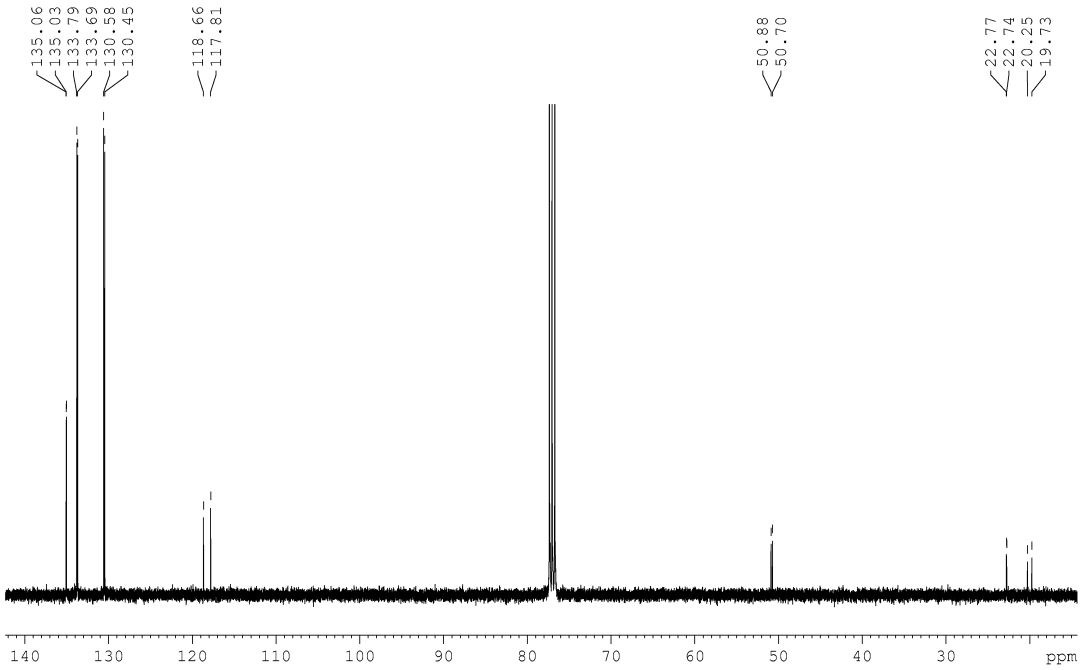




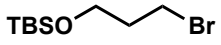
(3-Azidopropyl)bromotriphenylphosphorane (237d)

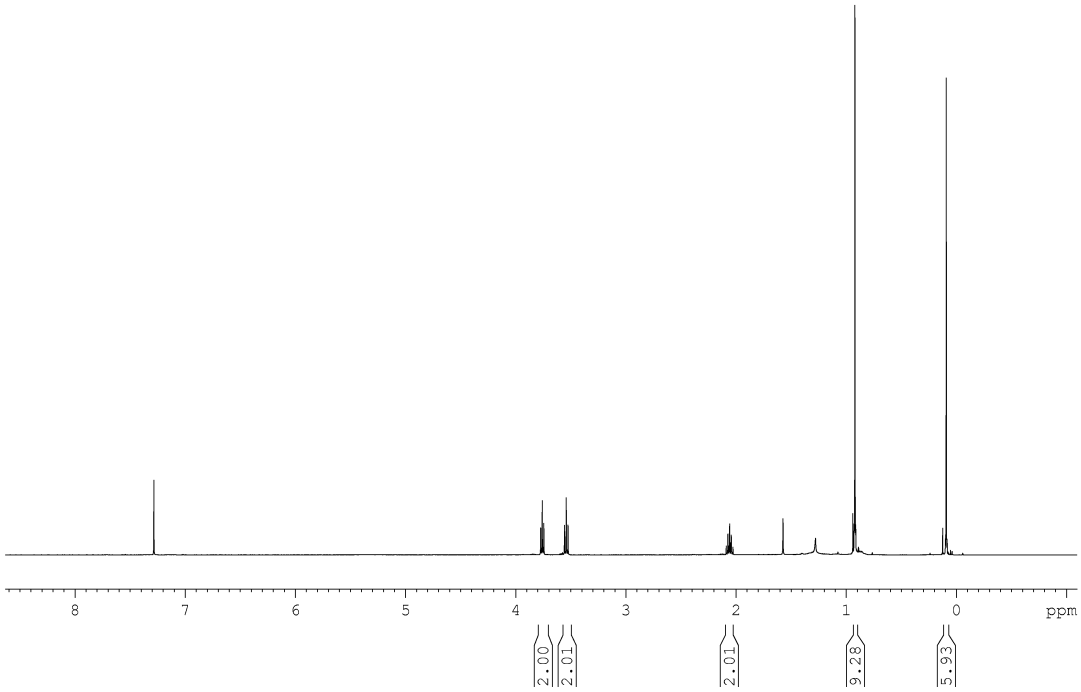


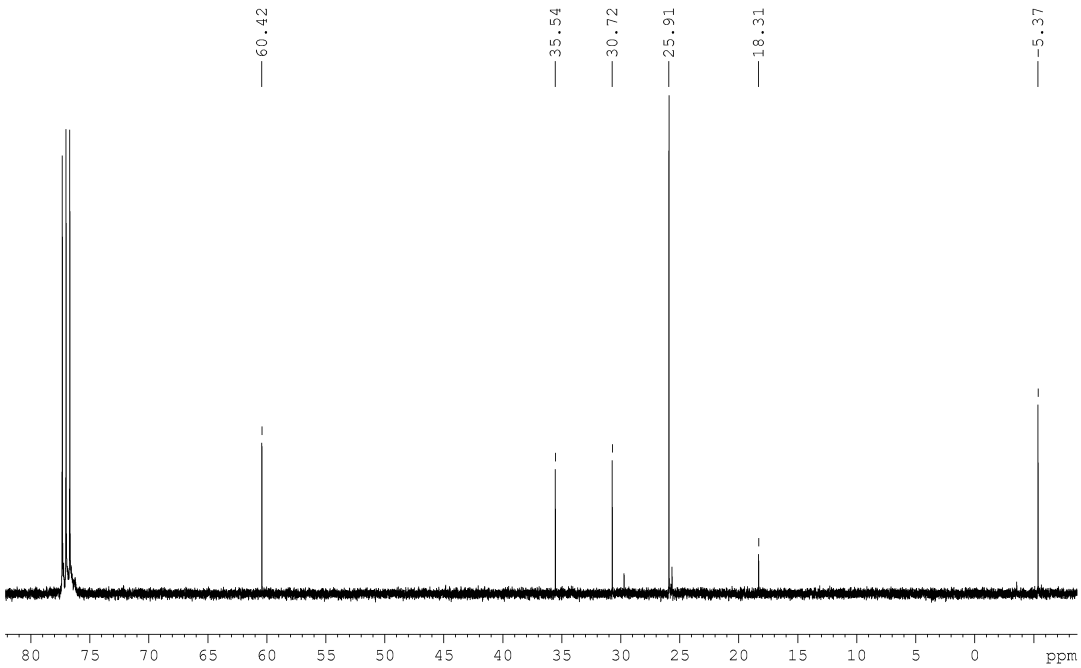




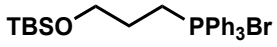
(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (237e)

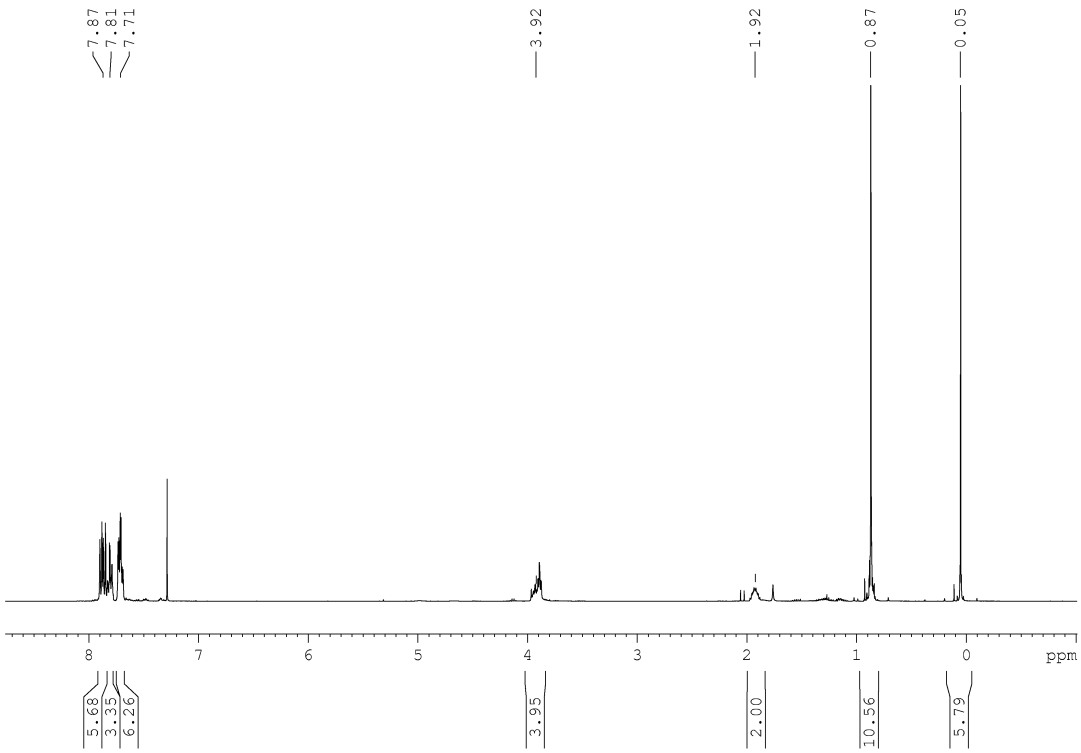




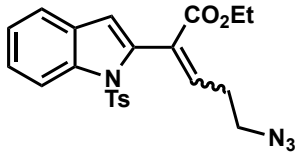


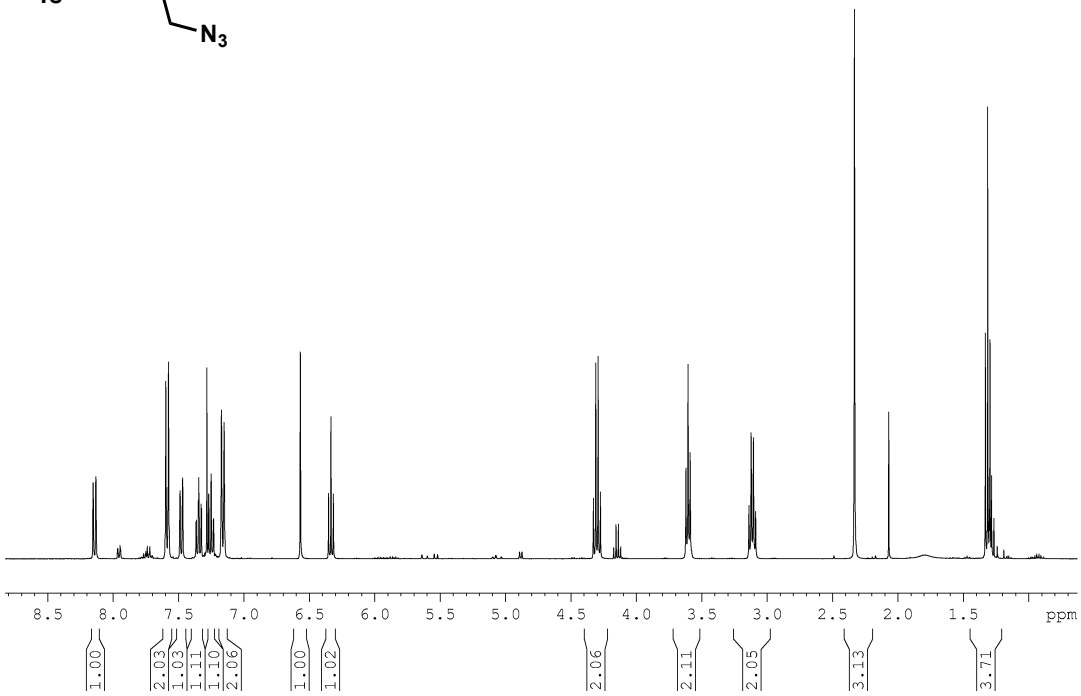
Bromo(3-((*tert*-butyldimethylsilyl)oxy)propyl)triphenylphosphorane (237f)

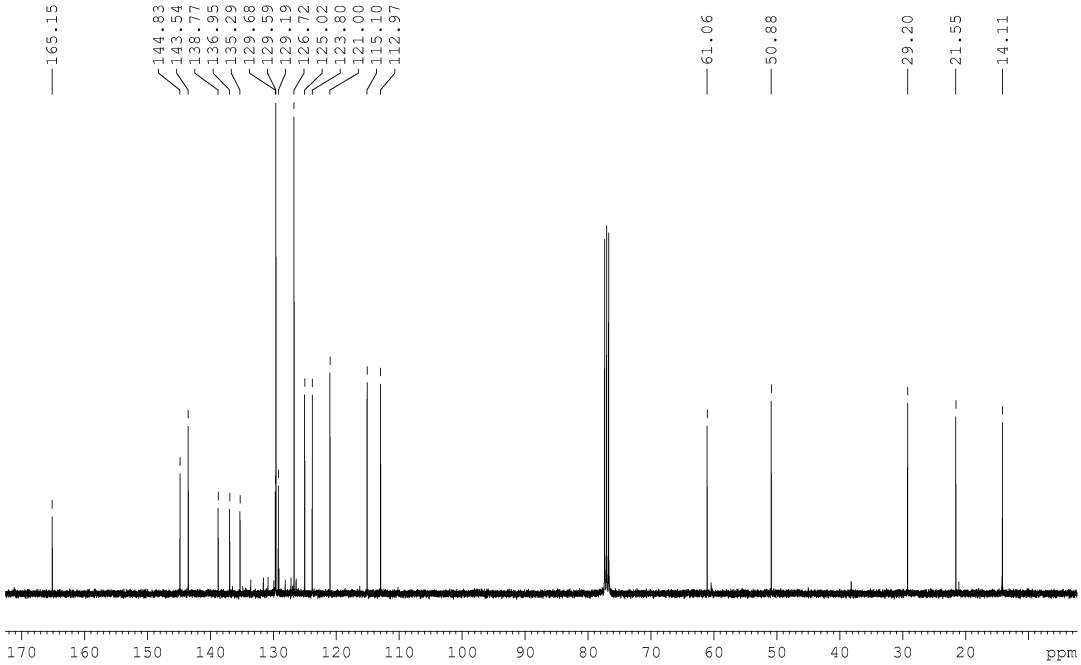




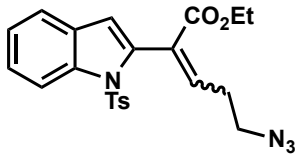
Ethyl 5-azido-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232a)

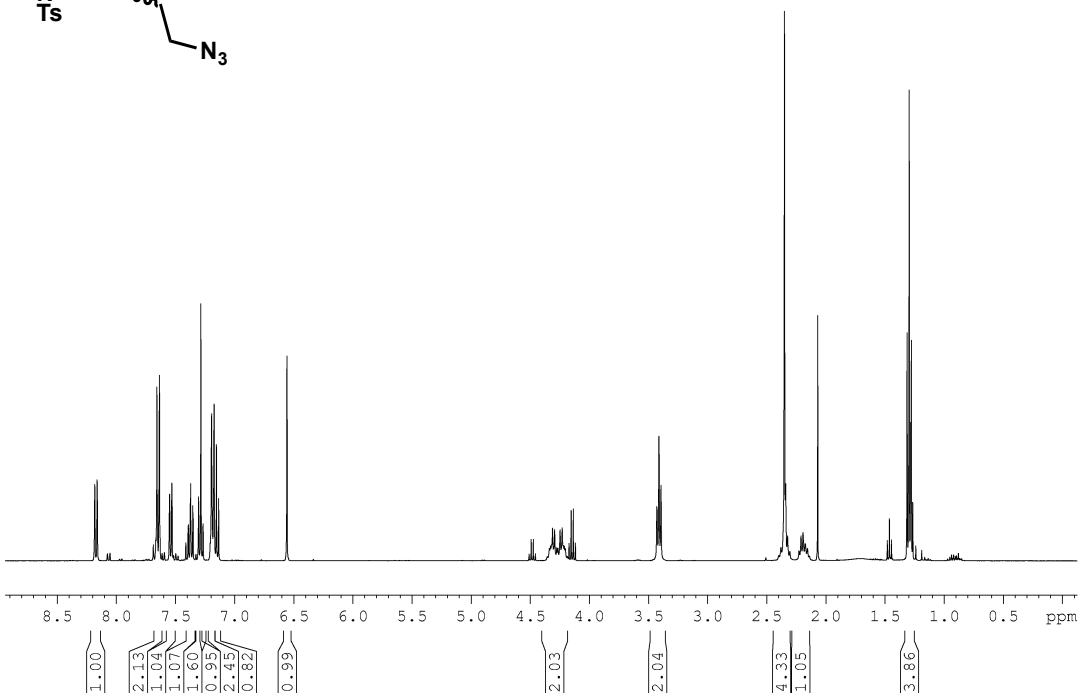


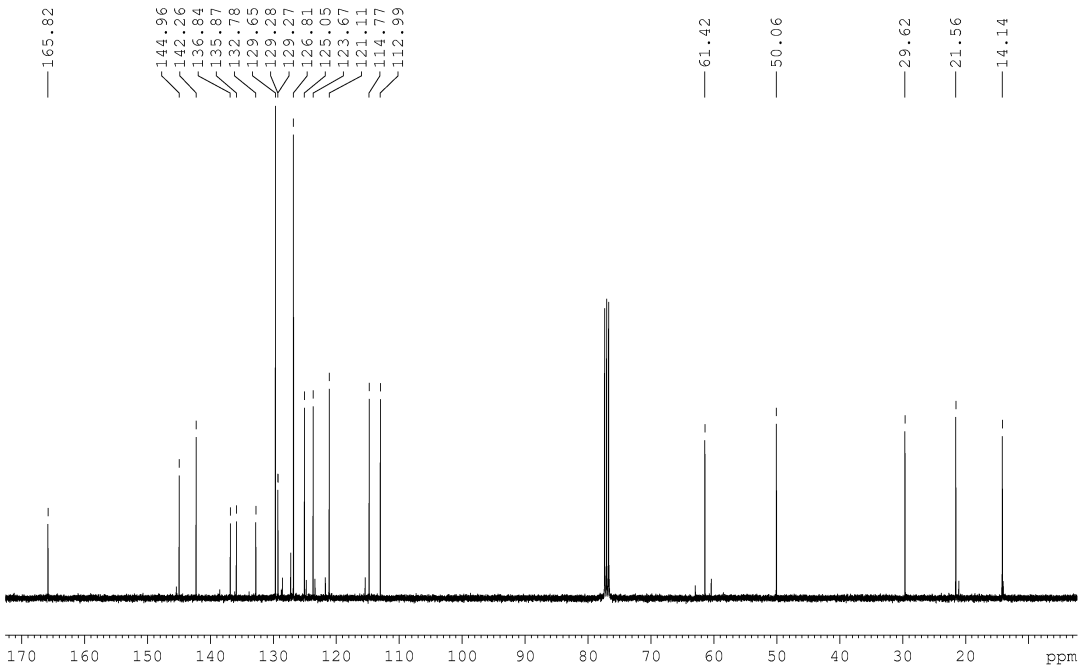




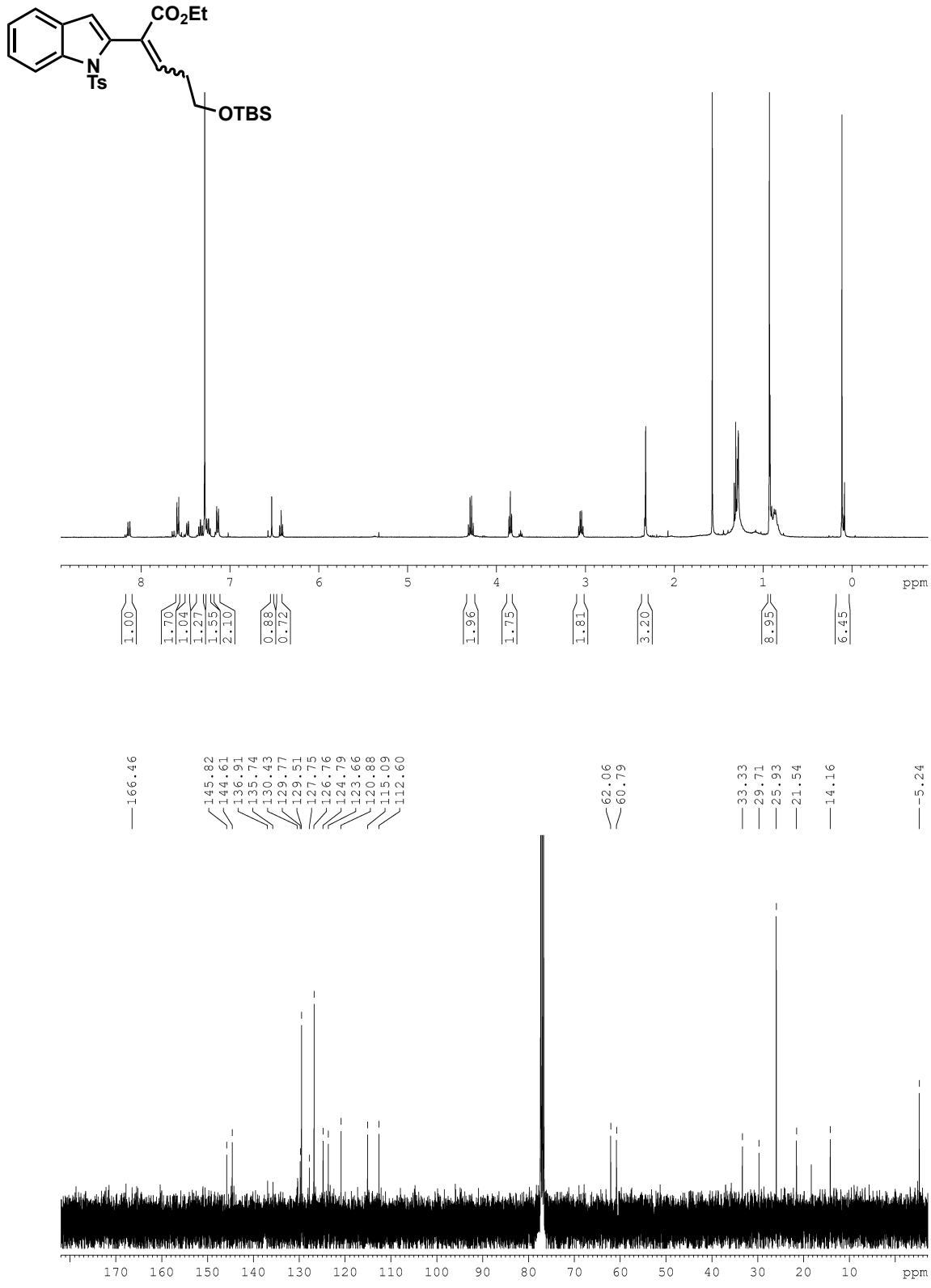
Ethyl 5-azido-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232a)



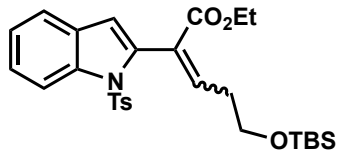


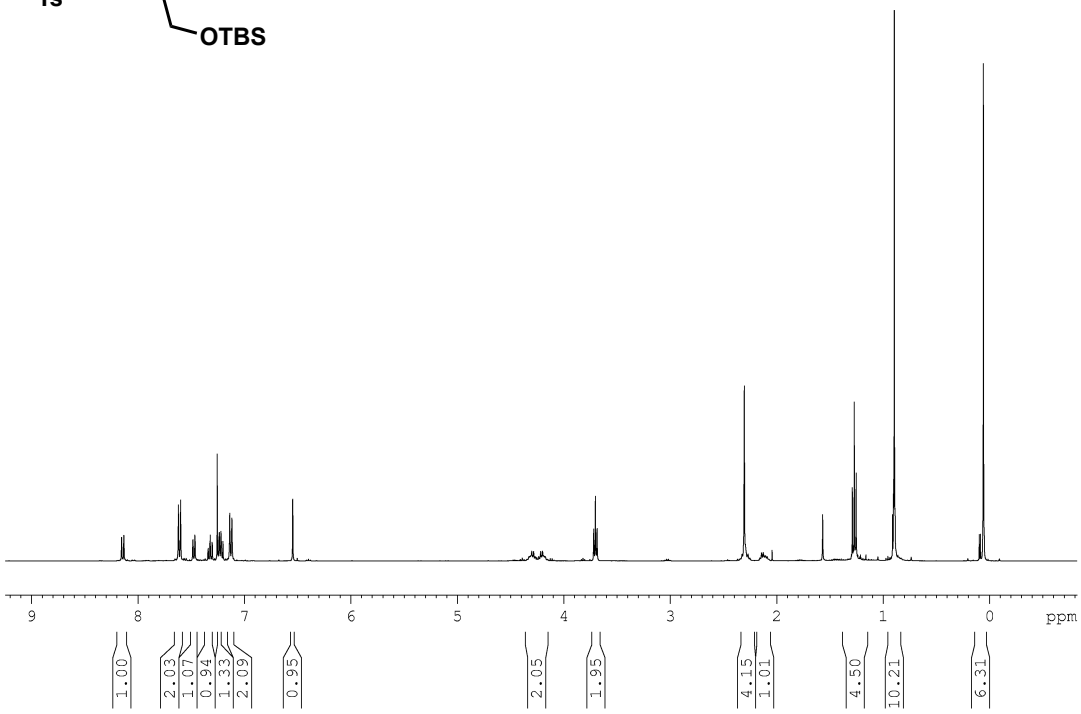


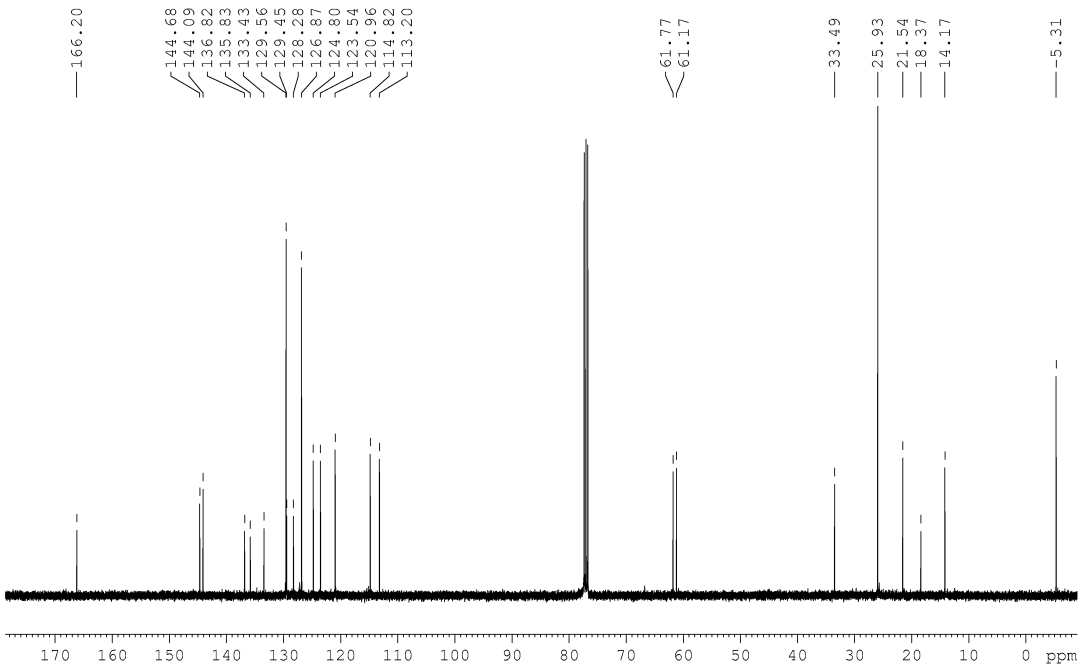
Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232b)



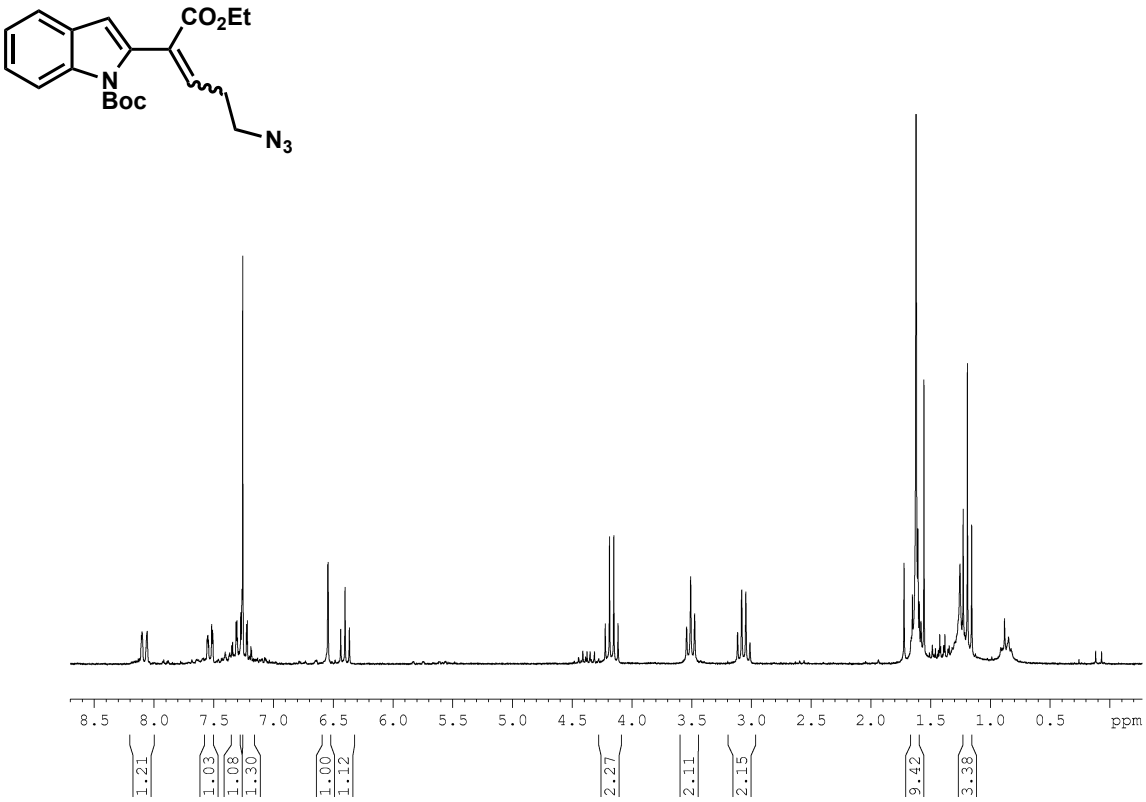
Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2-(1-tosyl-1*H*-indol-2-yl)pent-2-enoate (232b)



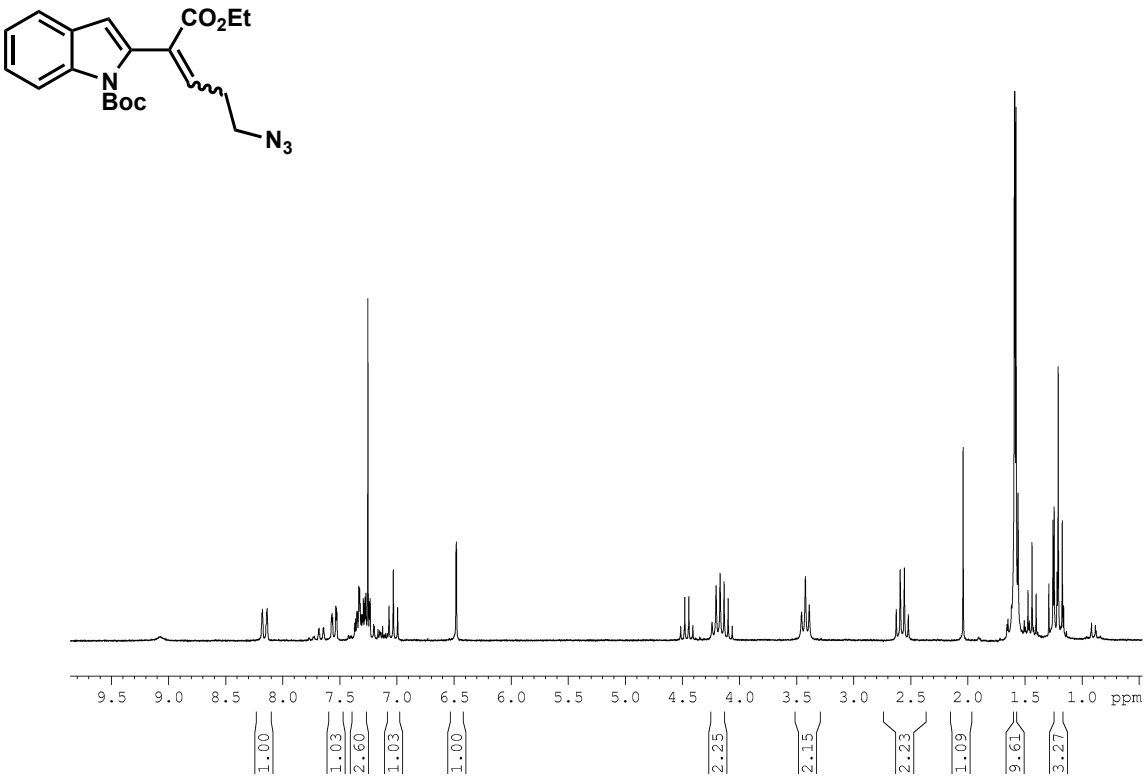




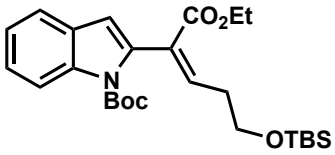
***Tert*-butyl 2-(5-azido-1-ethoxy-1-oxopent-2-en-2-yl)-1*H*-indole-1-carboxylate (232c)**

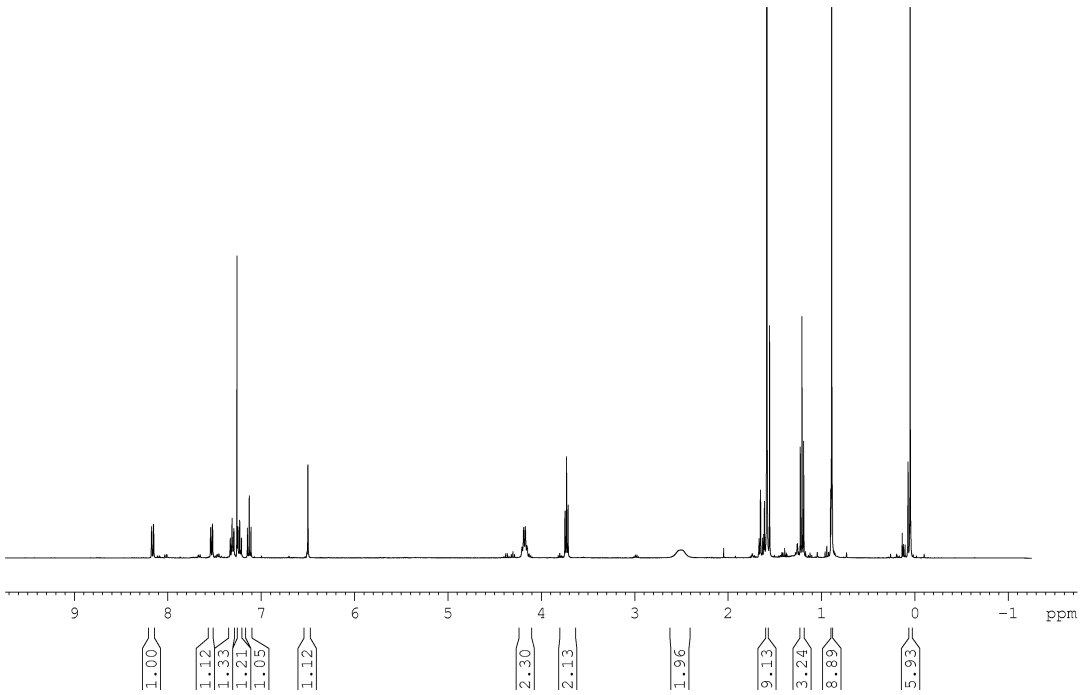


***Tert*-butyl 2-(5-azido-1-ethoxy-1-oxopent-2-en-2-yl)-1*H*-indole-1-carboxylate (232c)**

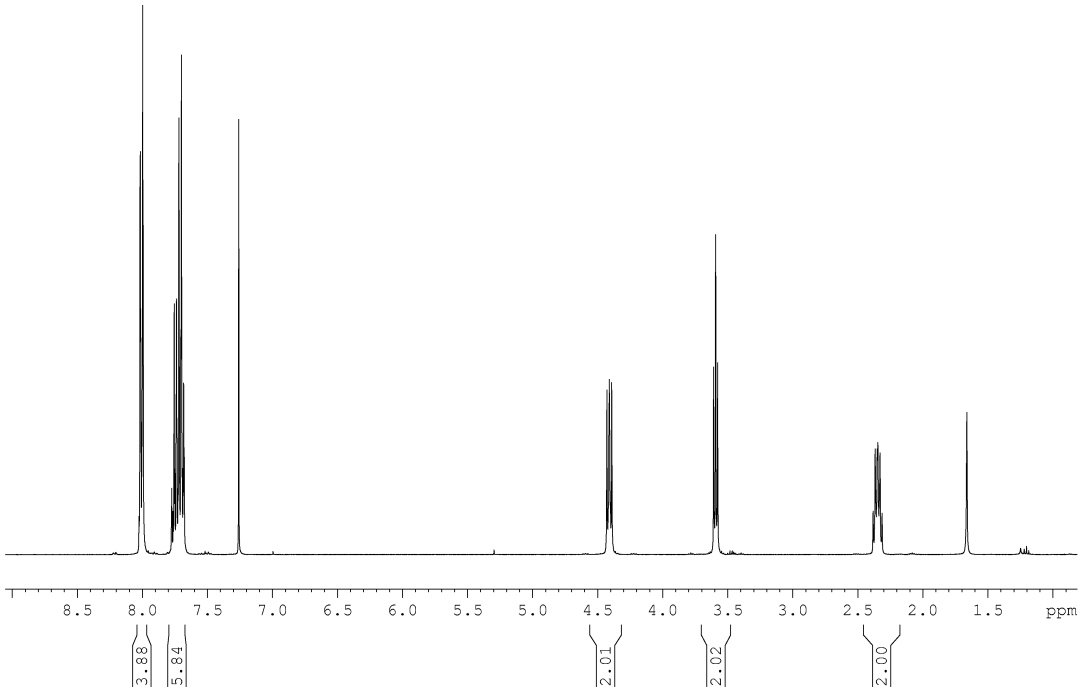


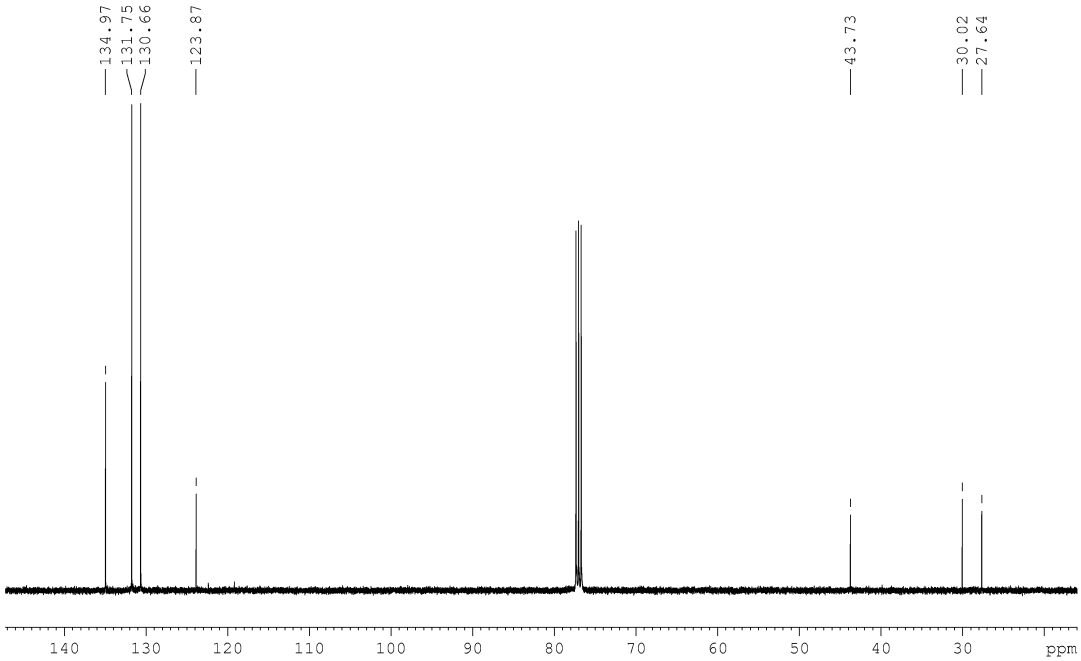
***Tert*-butyl 2-(5-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxopent-2-en-2-yl)-1*H*-indole-1-carboxylate (232d)**



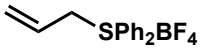


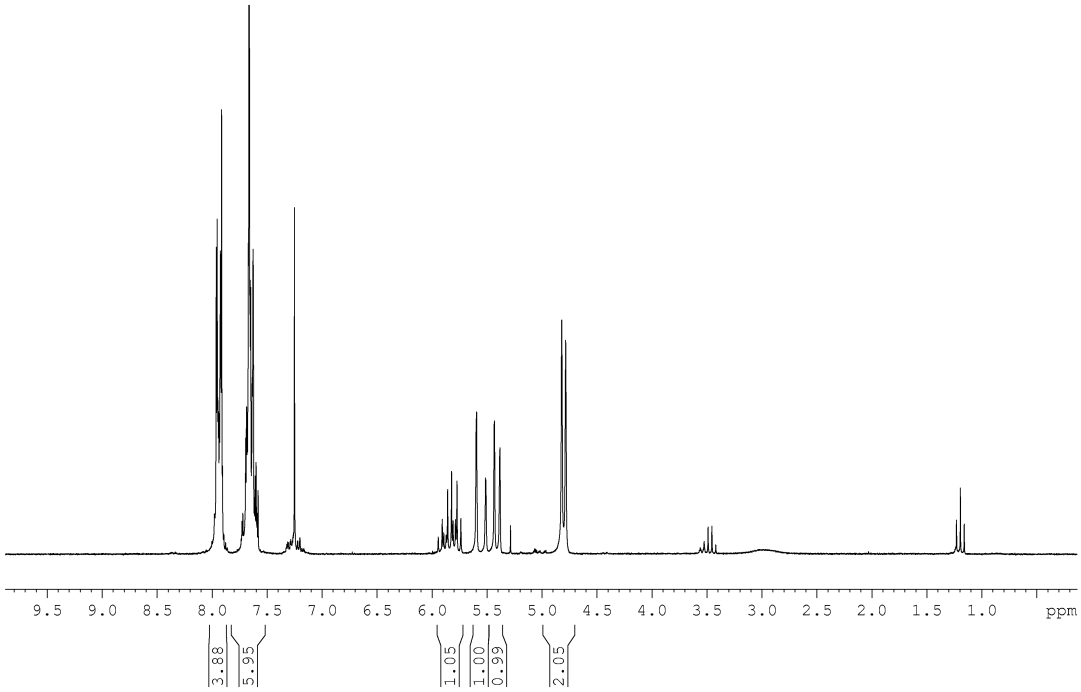
(3-Bromopropyl)diphenylsulfonium triflate (233a)



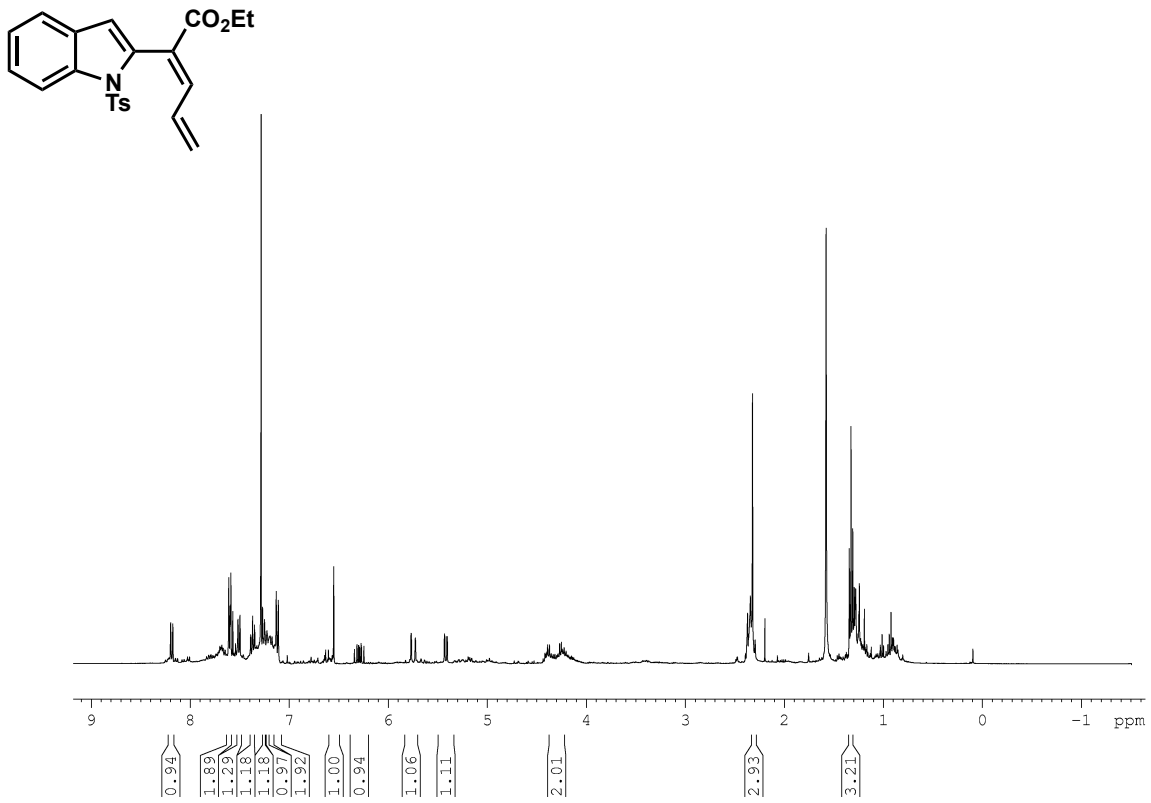


Vinyl diphenylsulfonium tetrafluoroborate (233b)

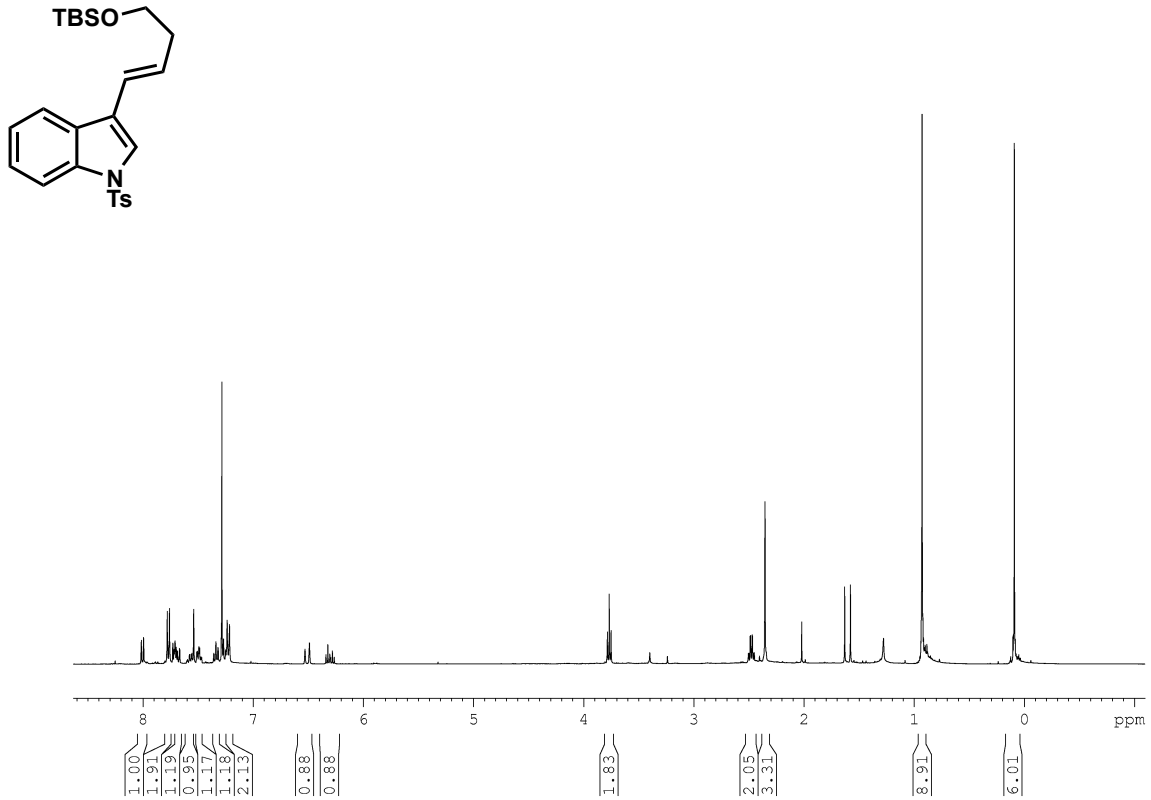


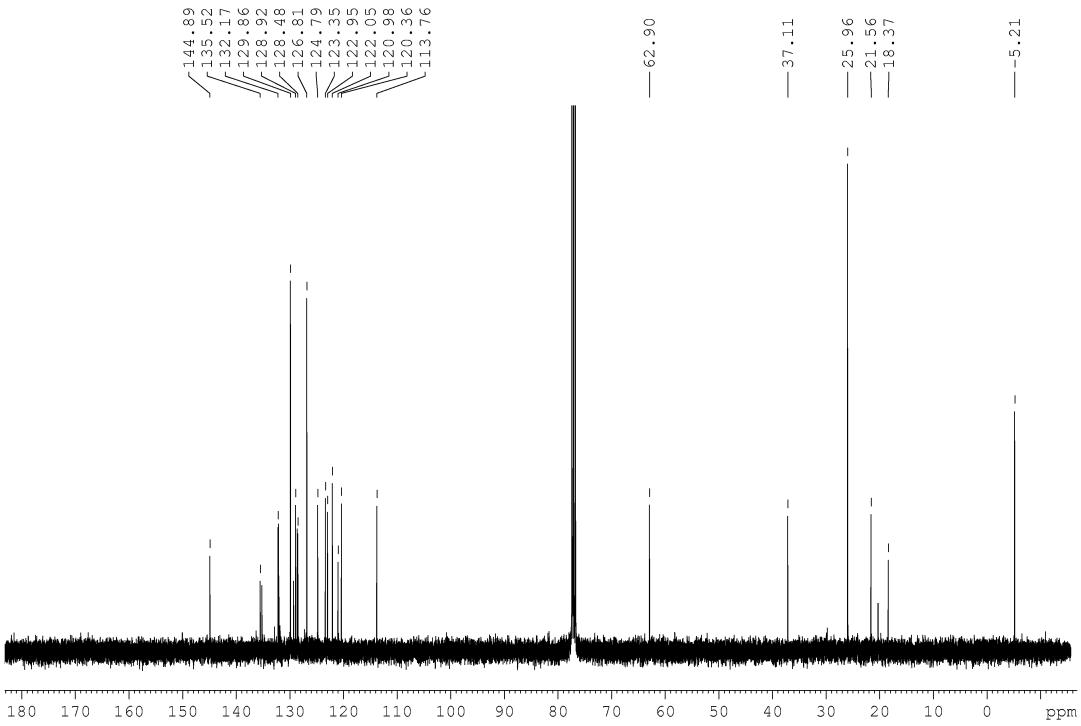


(*E*)-Ethyl 2-(1-tosyl-1*H*-indol-2-yl)penta-2,4-dienoate (232e)

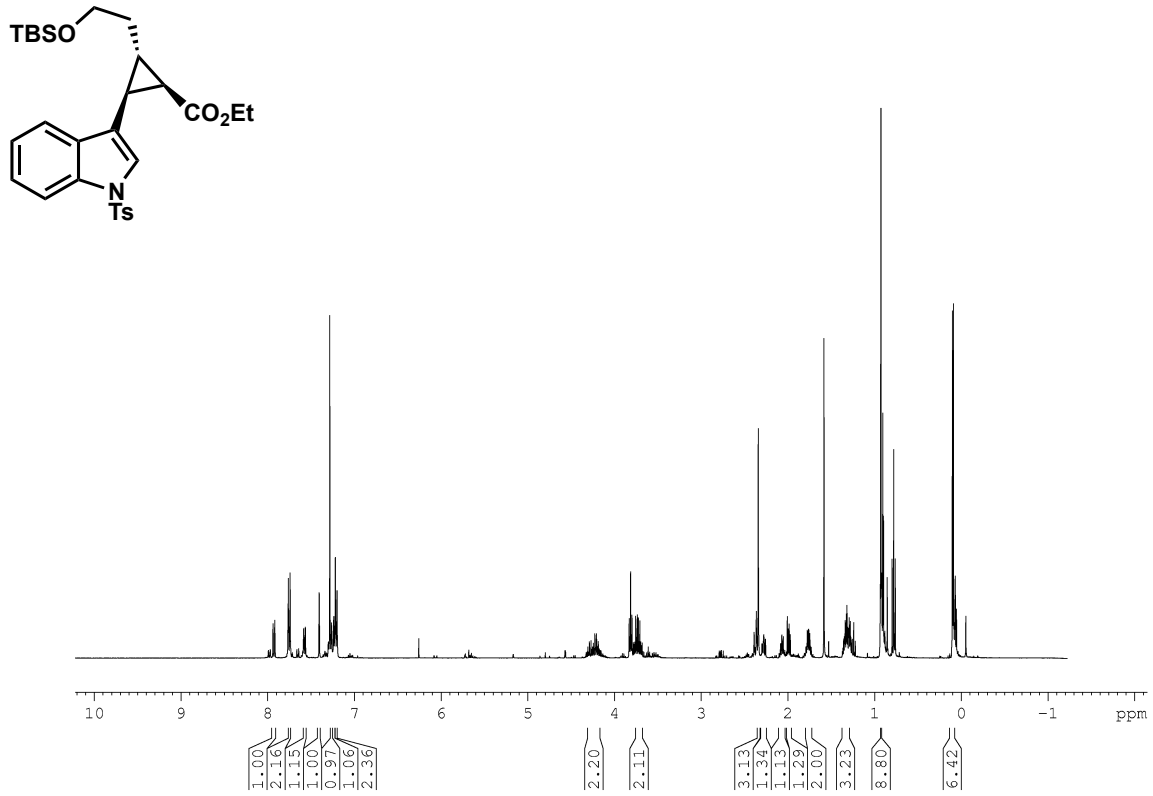


(*E*)-3-(4-((*Tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)-1-tosyl-1*H*-indole (246)

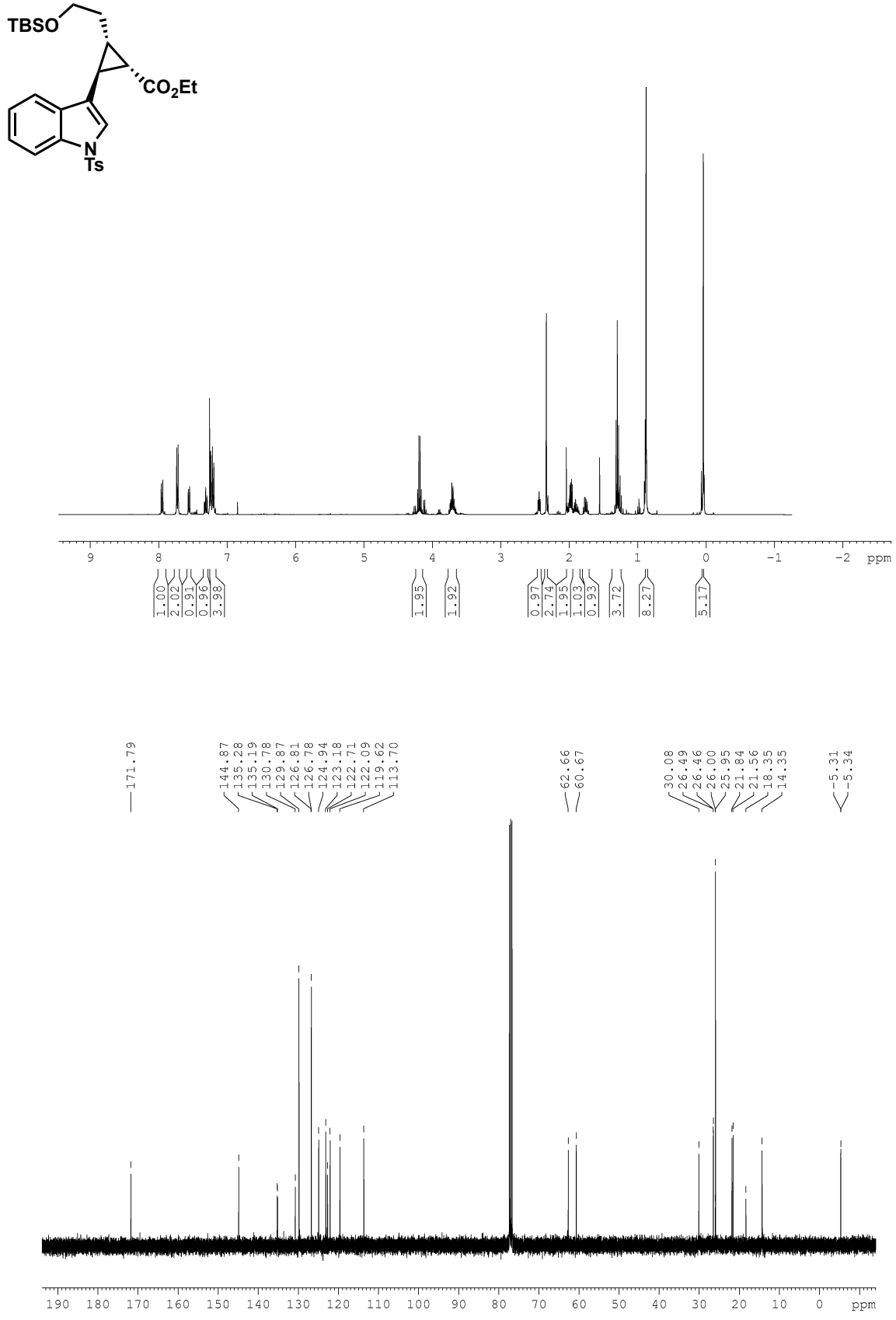



144.89
135.52
132.17
129.86
128.92
128.48
126.81
124.79
123.35
122.95
122.05
120.98
120.36
113.76
62.90
37.11
25.96
21.56
18.37
5.21
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

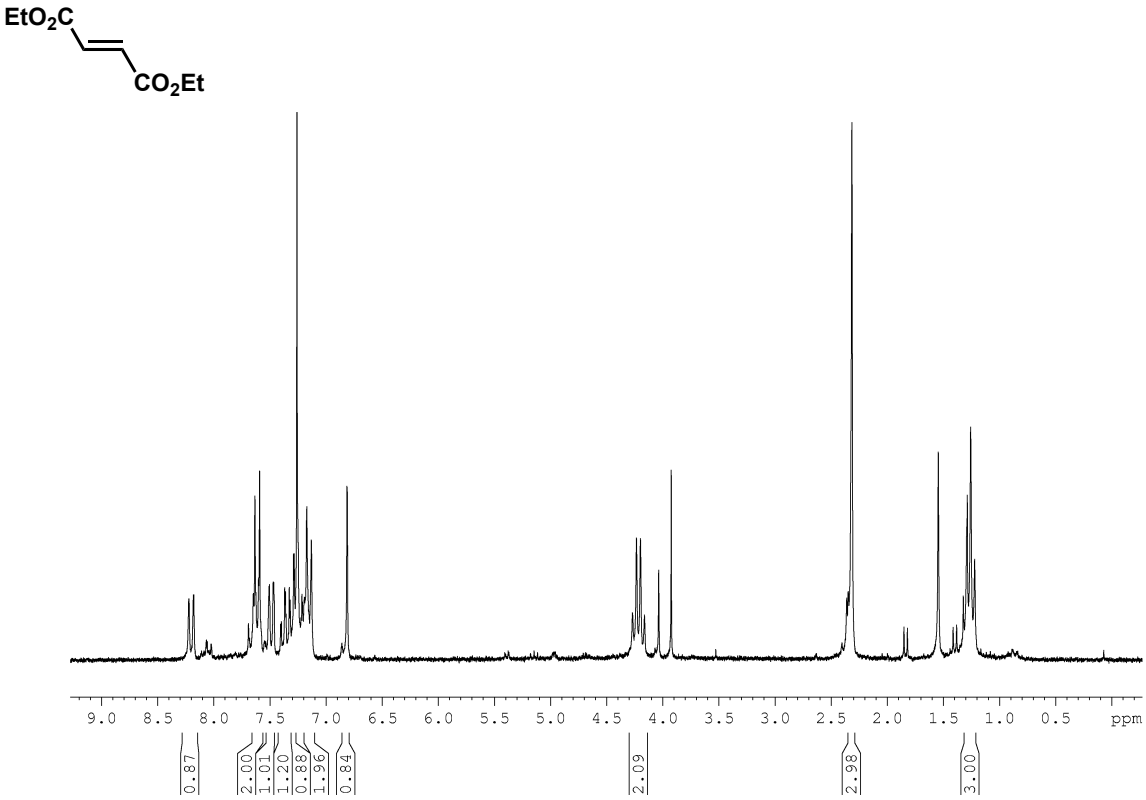
Ethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropanecarboxylate (248)



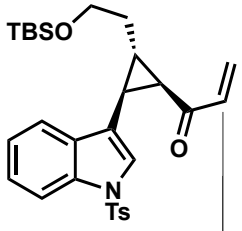
Ethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropanecarboxylate (249)

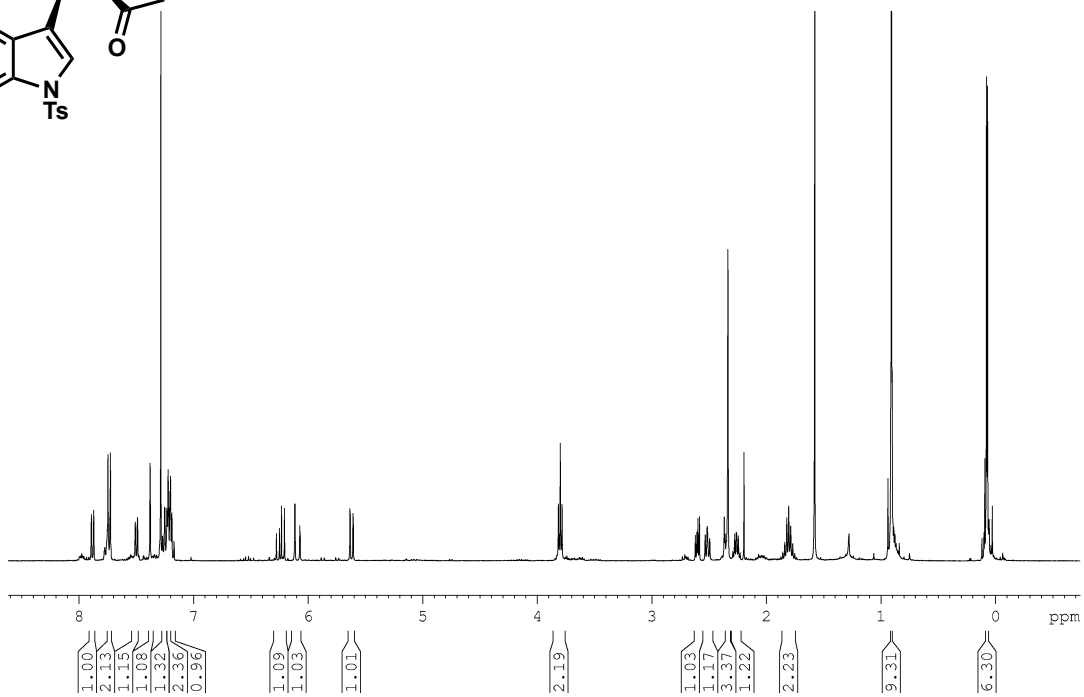


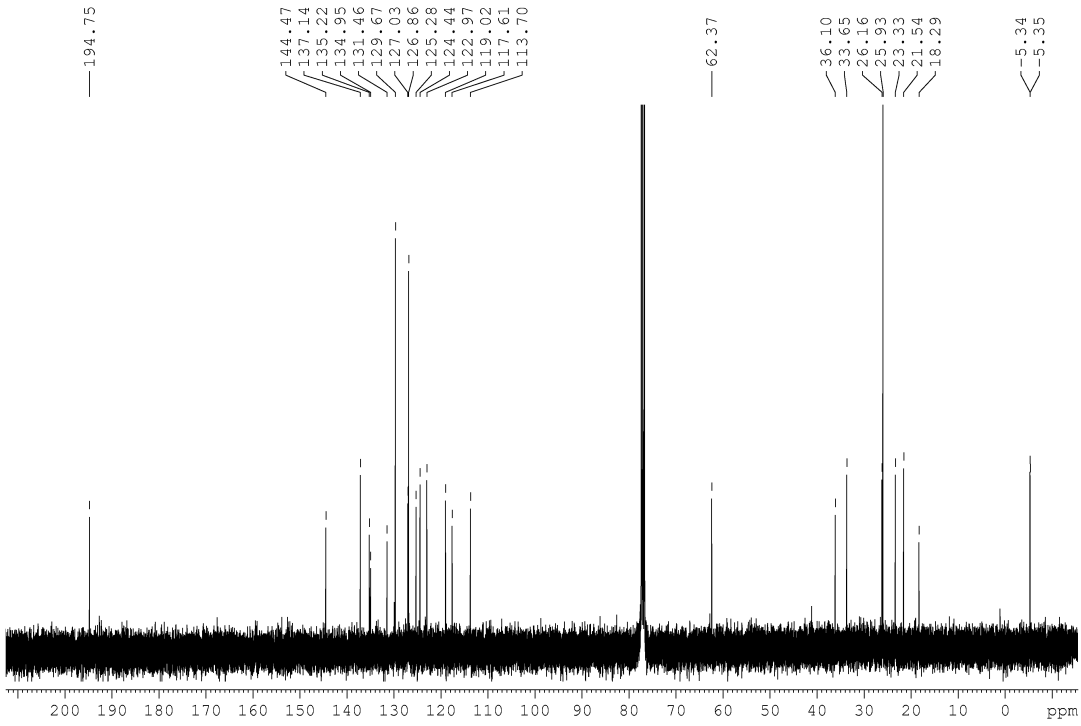
diethyl fumarate



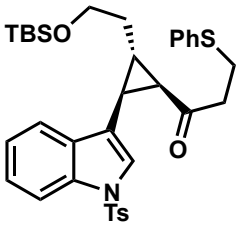
1-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)prop-2-en-1-one (253)

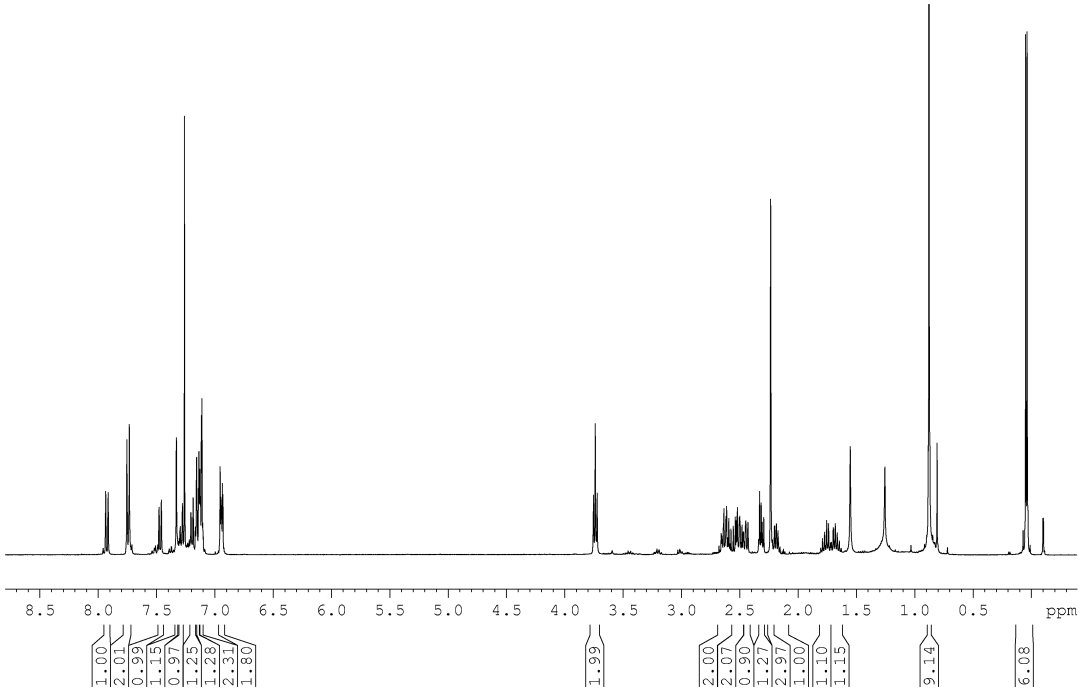




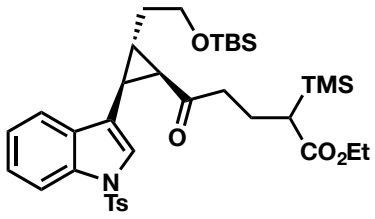


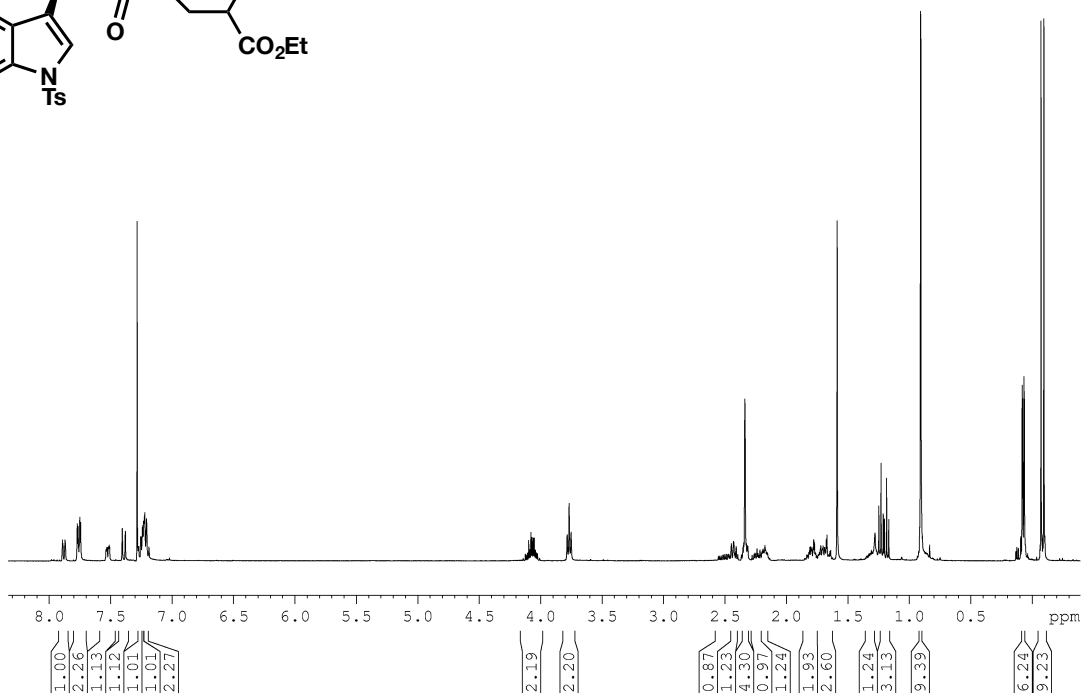
1-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-(phenylthio)propan-1-one (254)

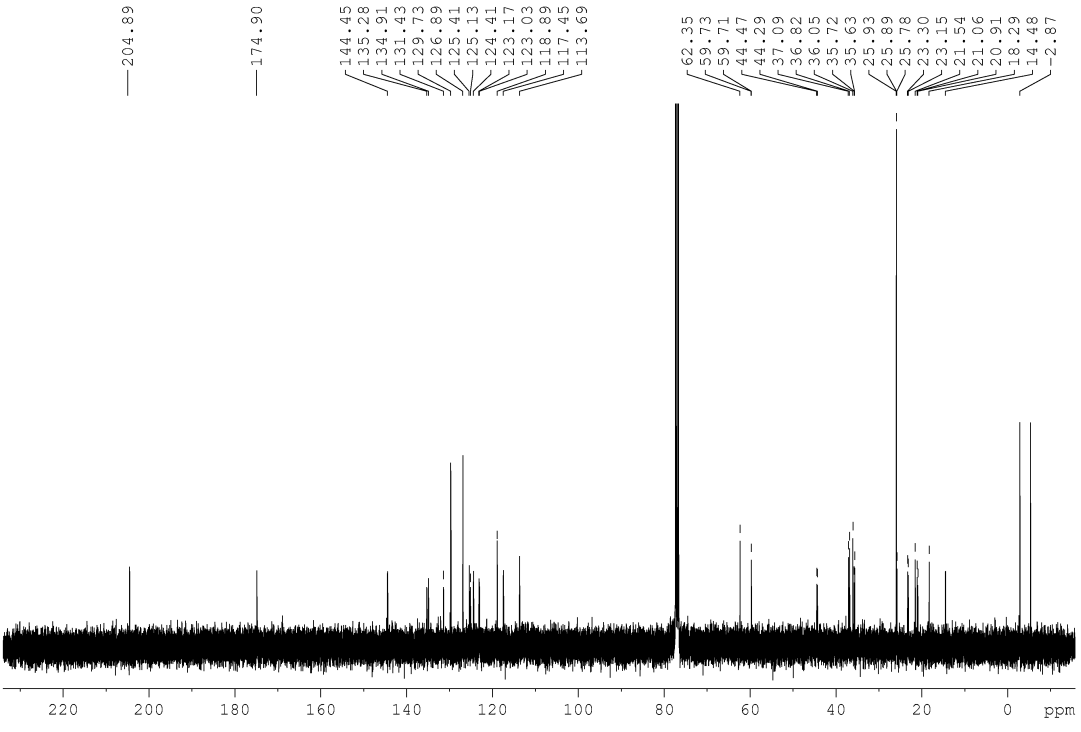




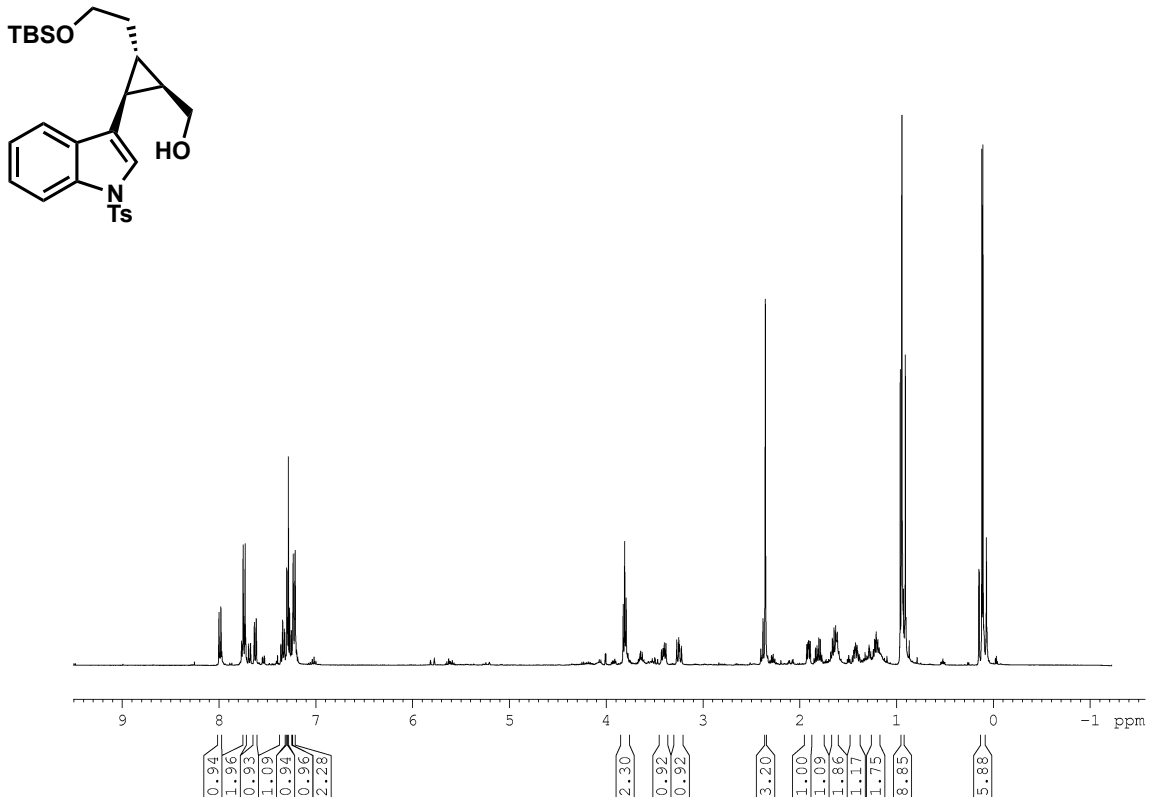
Ethyl 5-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-5-oxo-2-(trimethylsilyl)pentanoate (256)



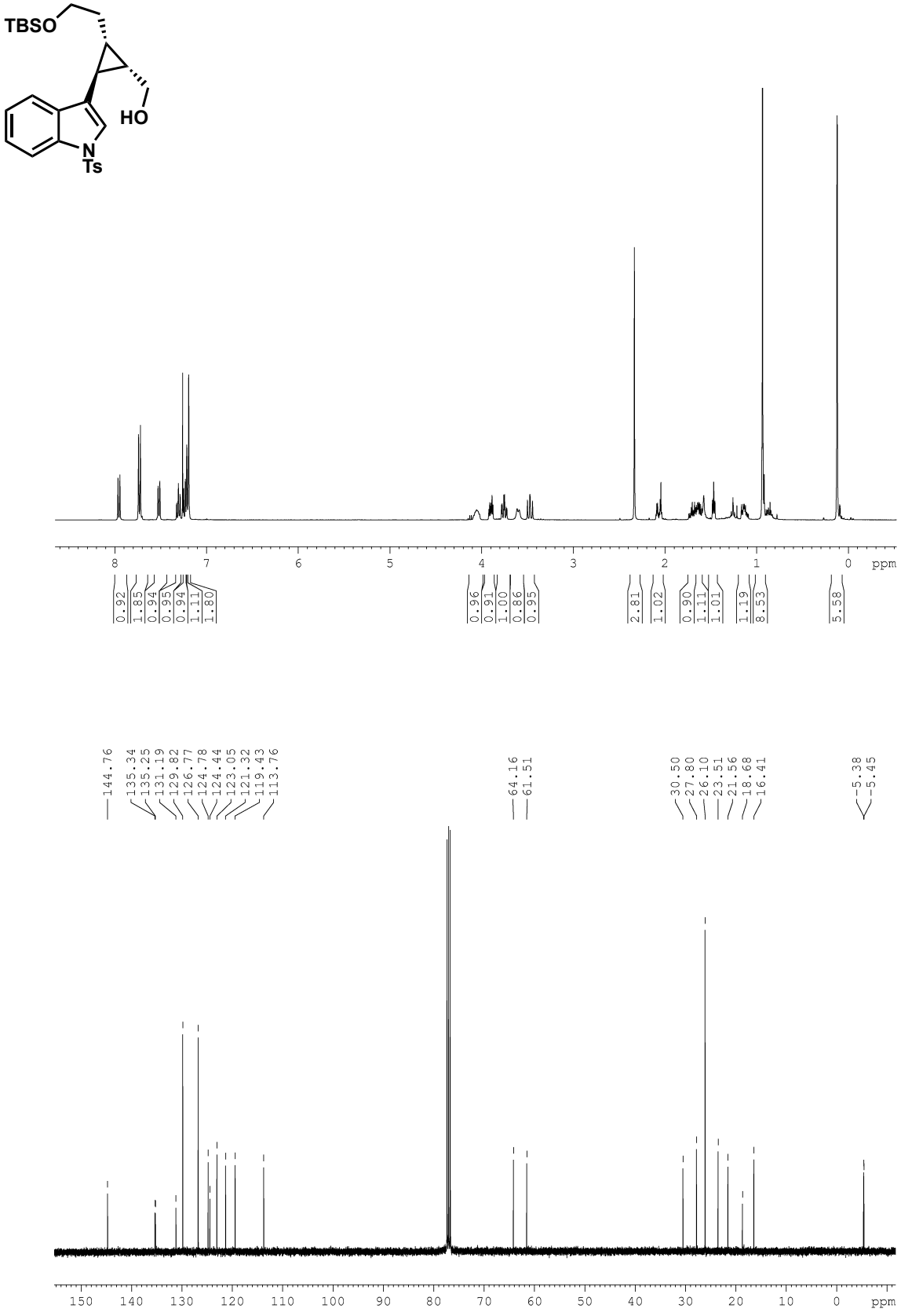




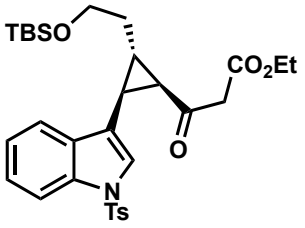
2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methan (248a)

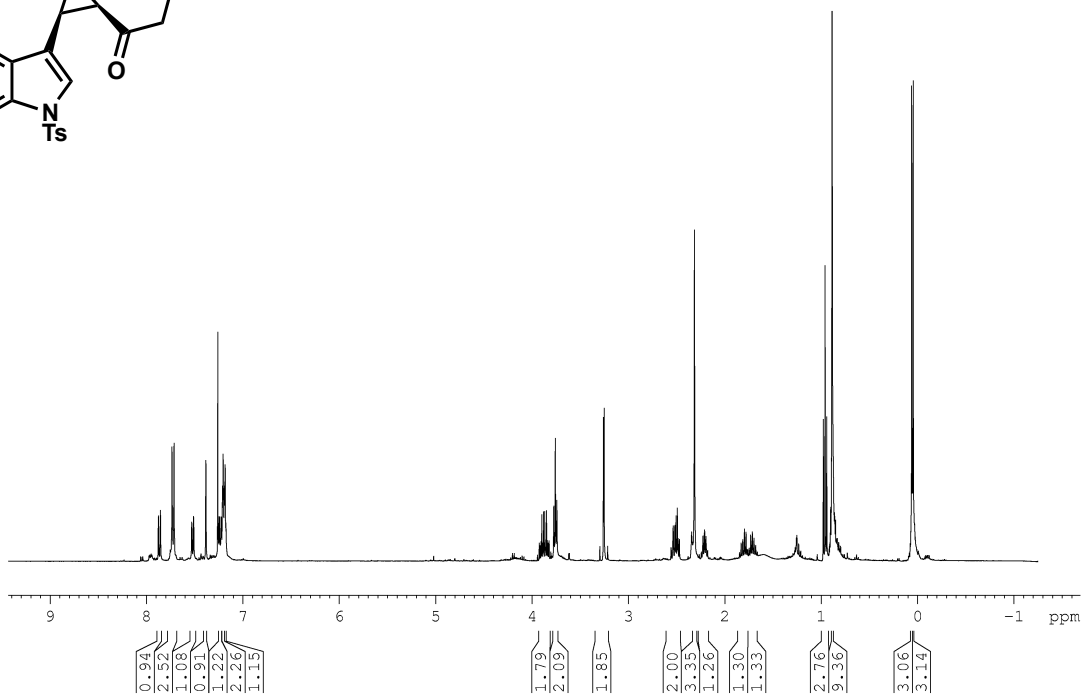


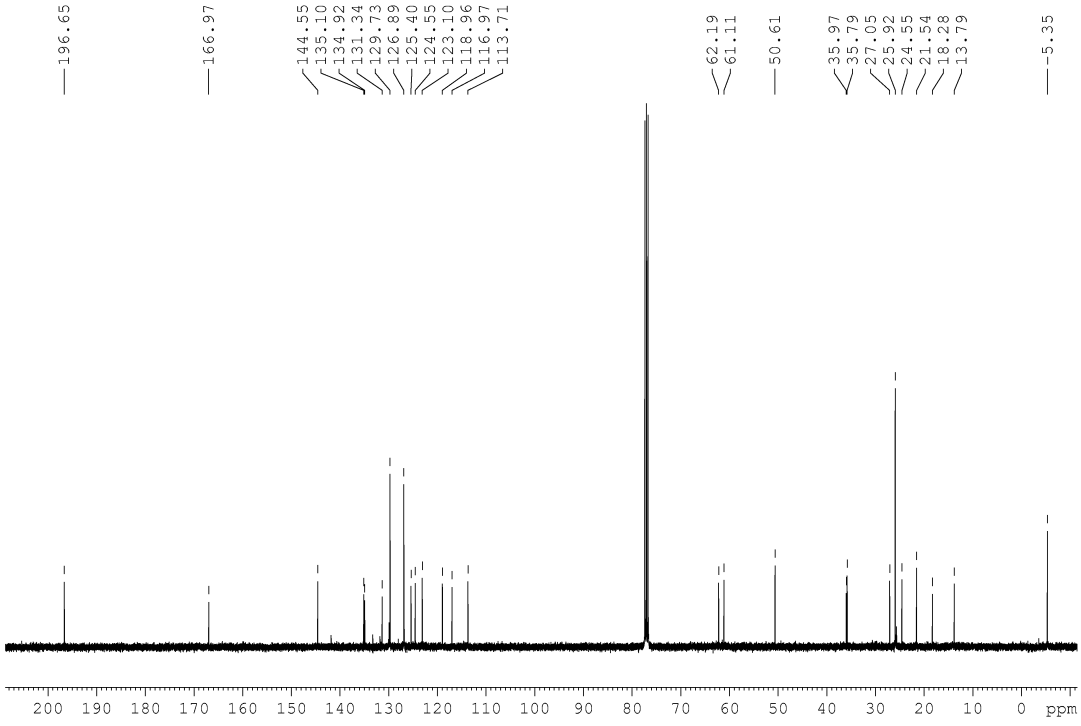
2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methan (248a other dia)



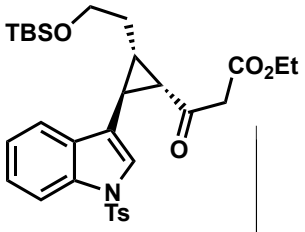
Ethyl 3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropanoate (258)

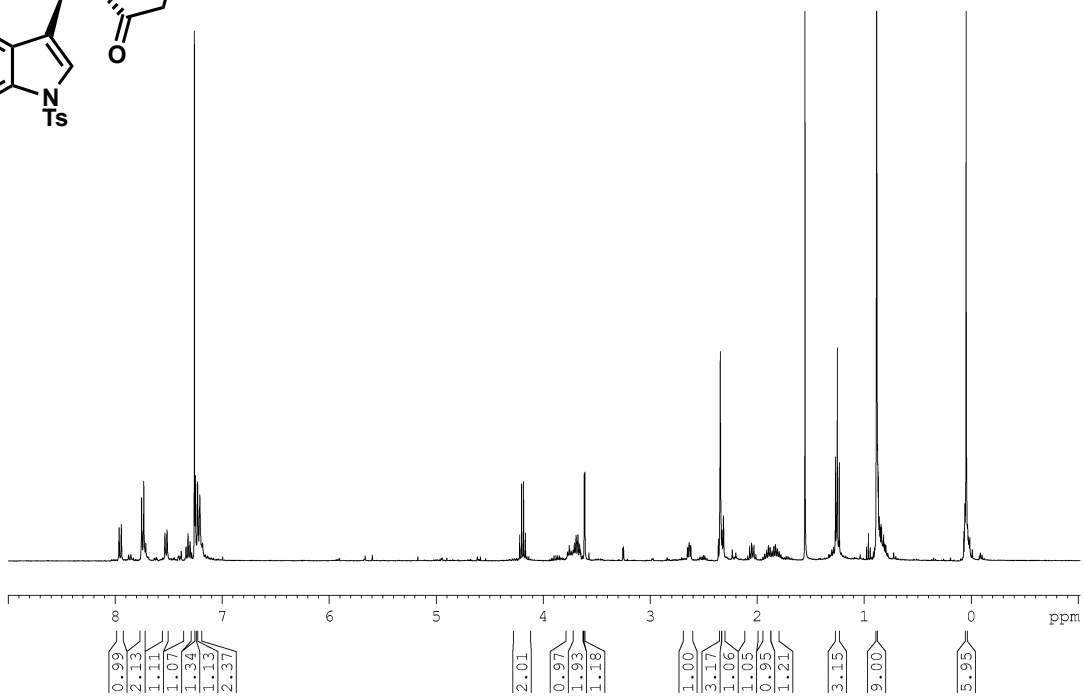


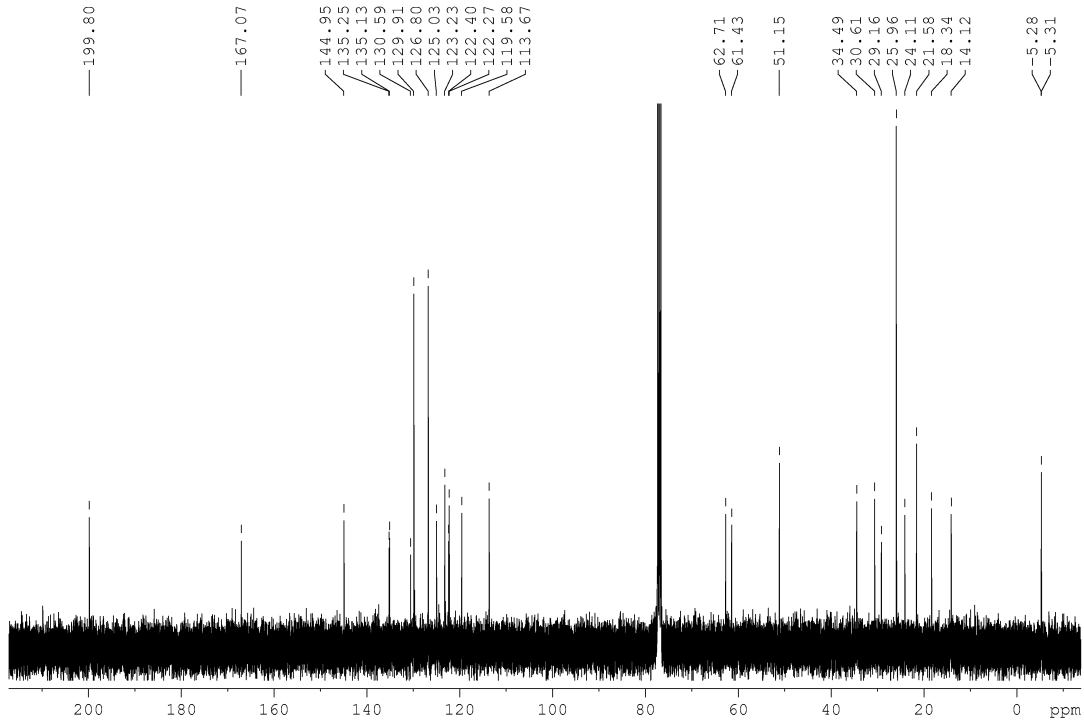




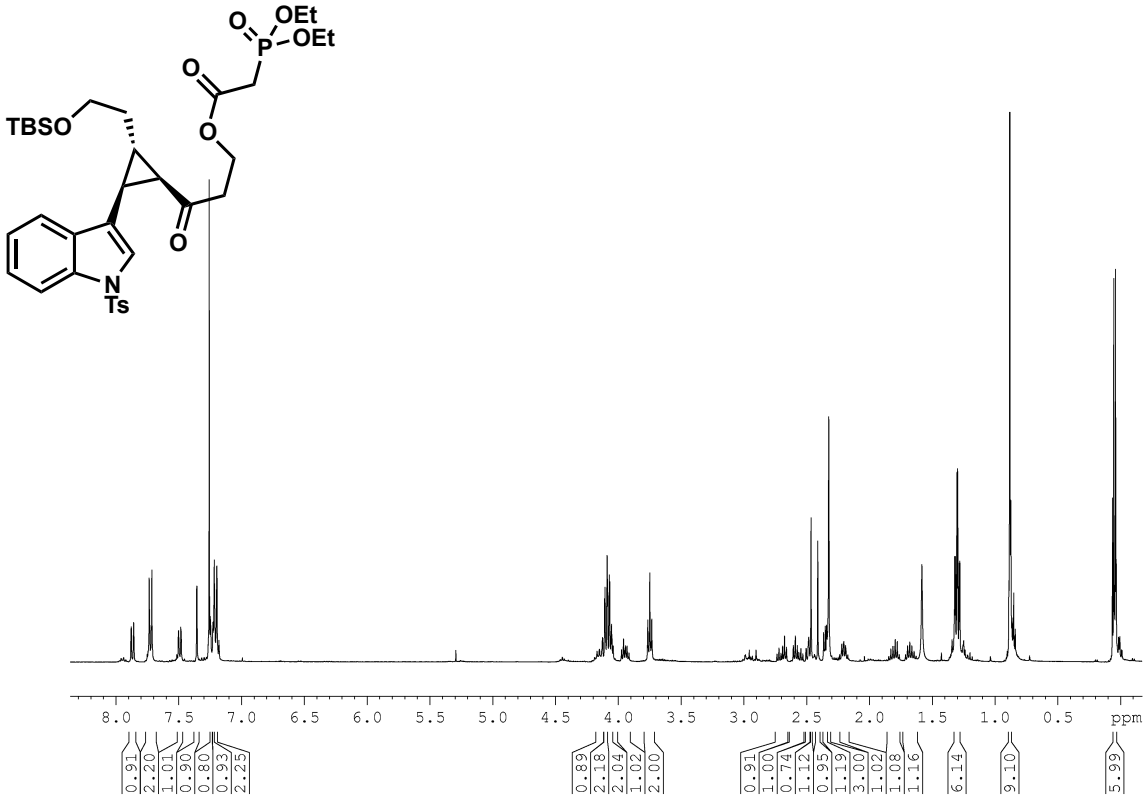
Ethyl 3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropanoate (258 other dia)

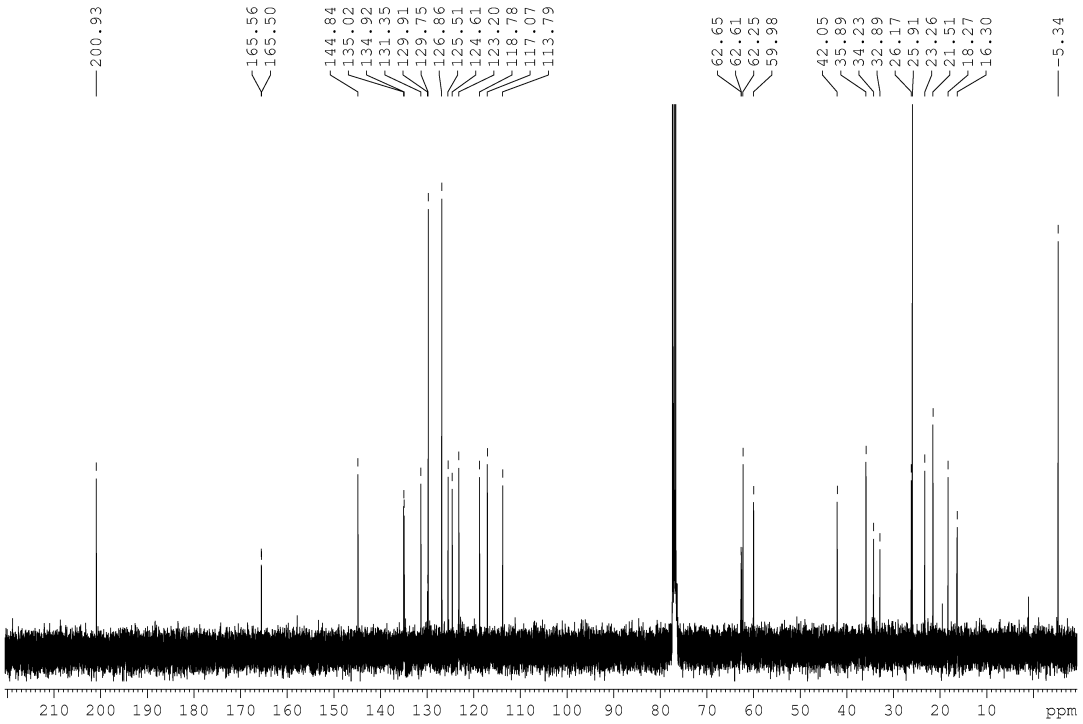




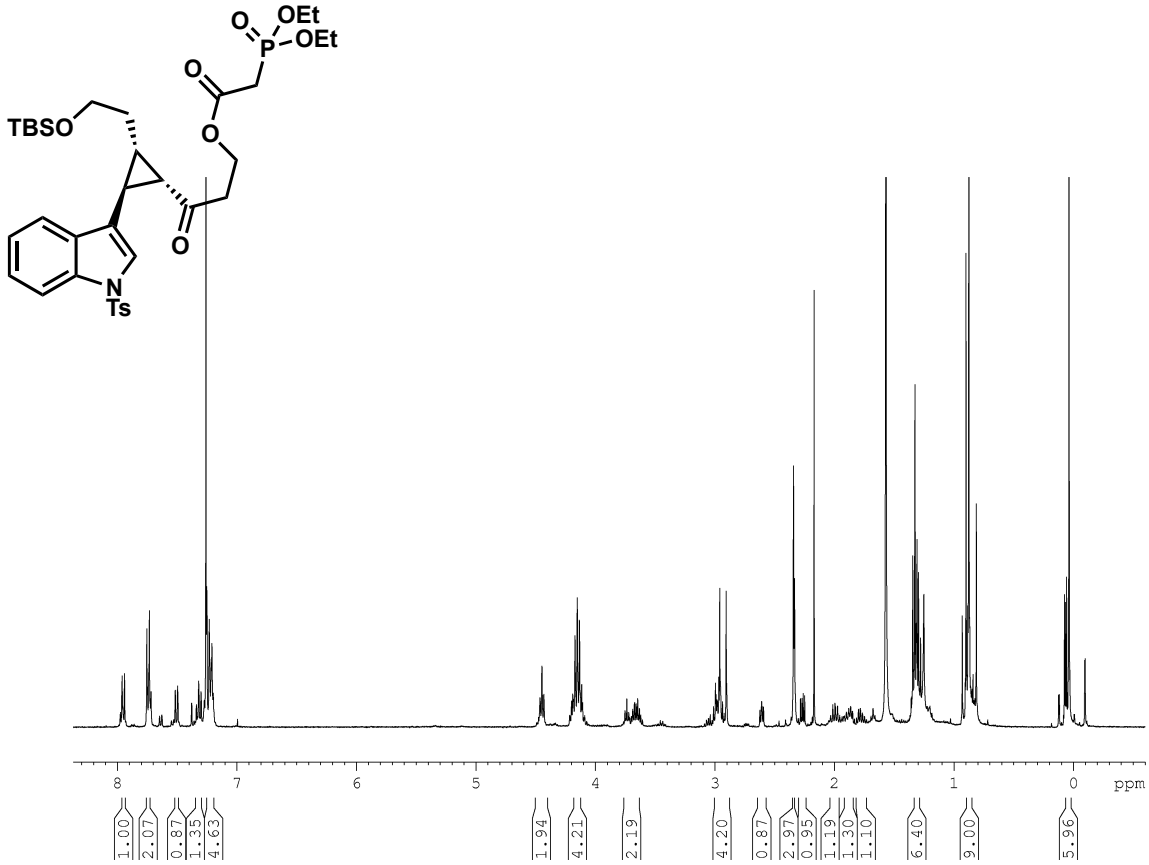


3-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl 2-(diethoxyphosphoryl)acetate (264)

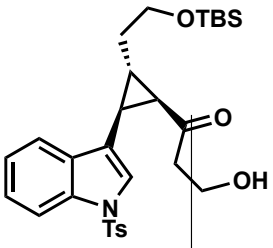


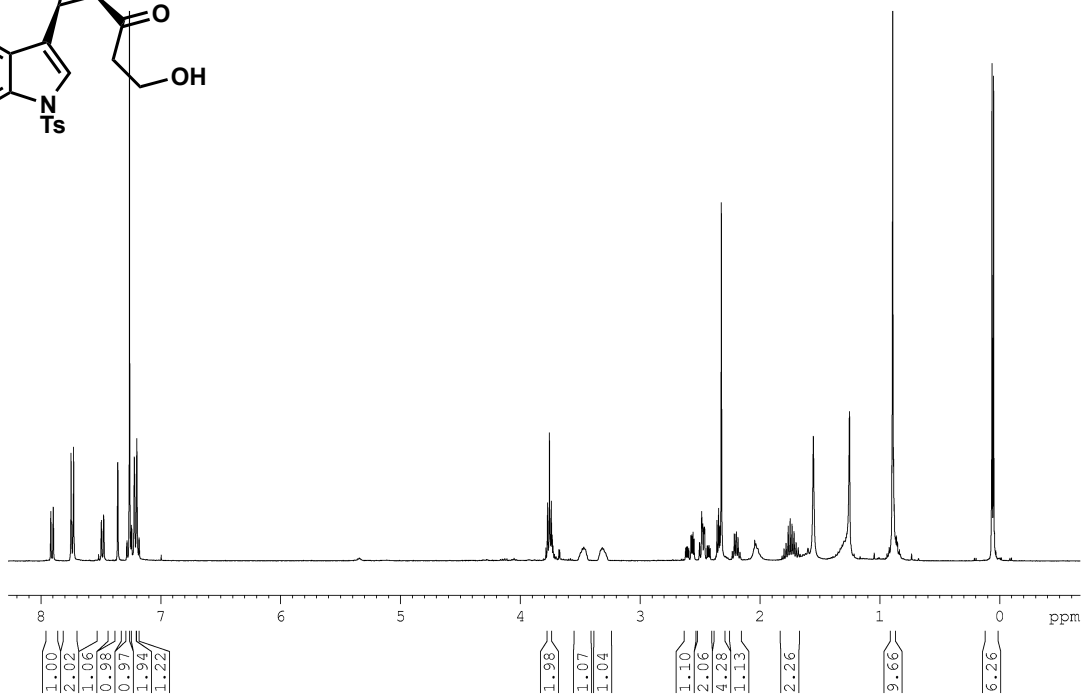


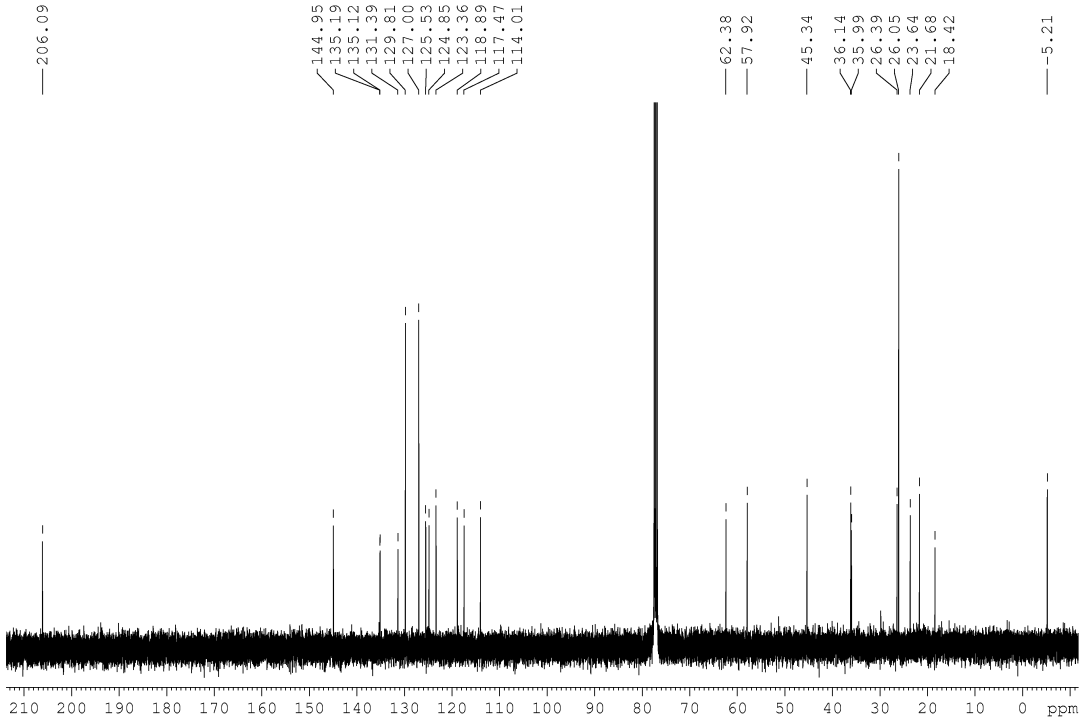
3-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl 2-(diethoxyphosphoryl)acetate (264 undesired dia)



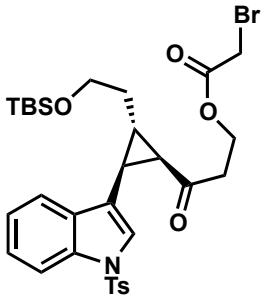
1-((1*R*,2*S*,3*S*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-hydroxypropan-1-one (253a)

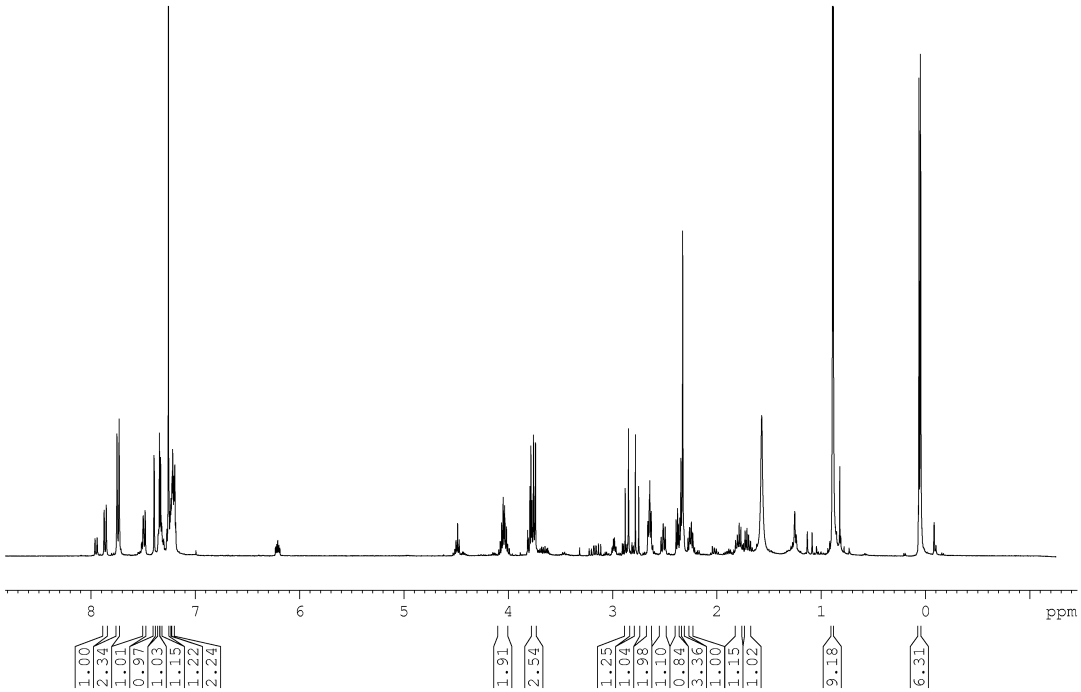




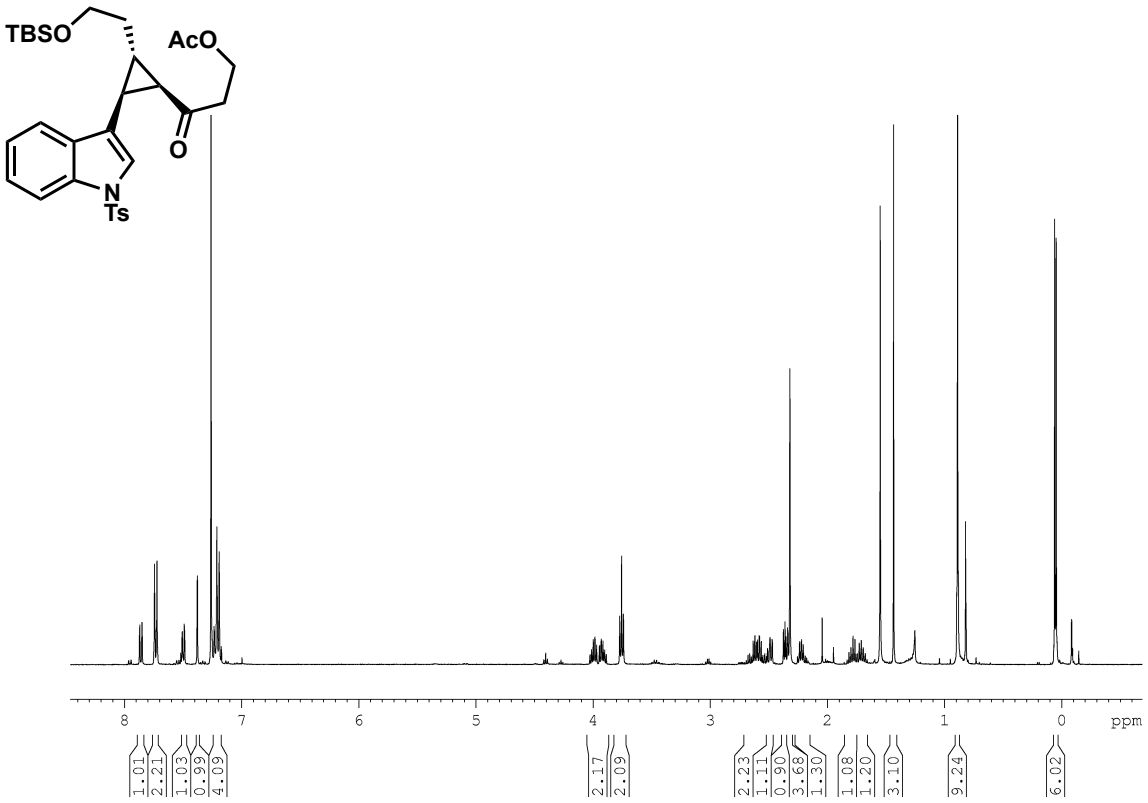


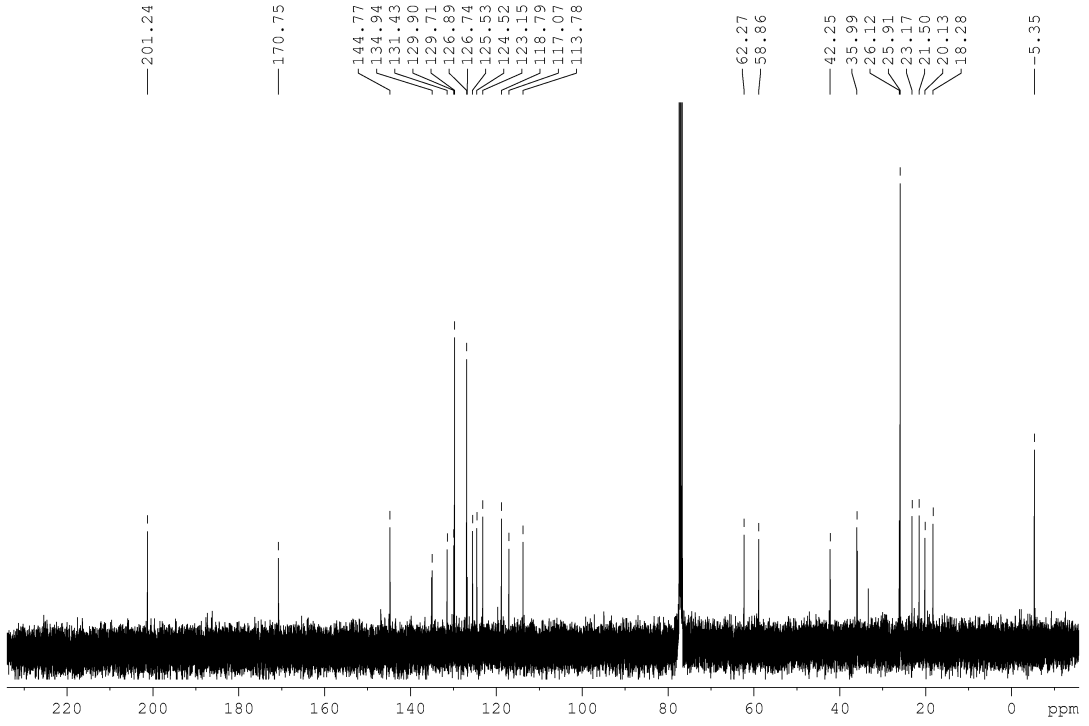
3-(2-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl 2-bromoacetate (266)



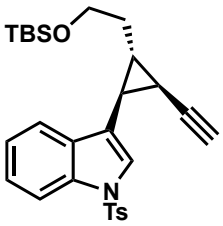


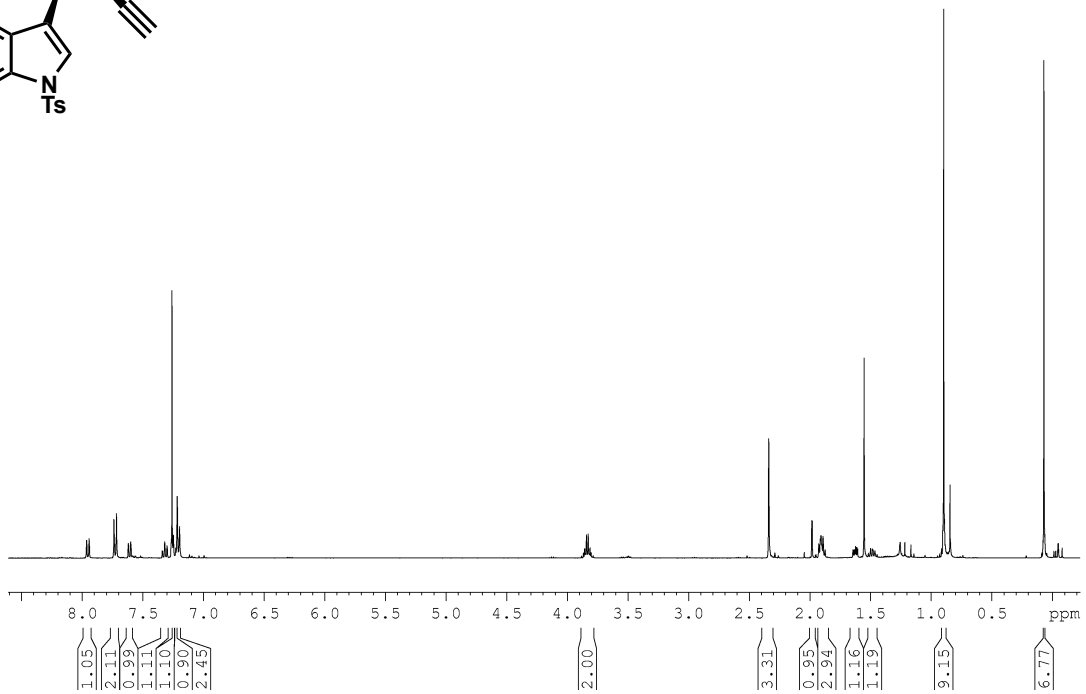
3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-3-oxopropyl acetate (266a)

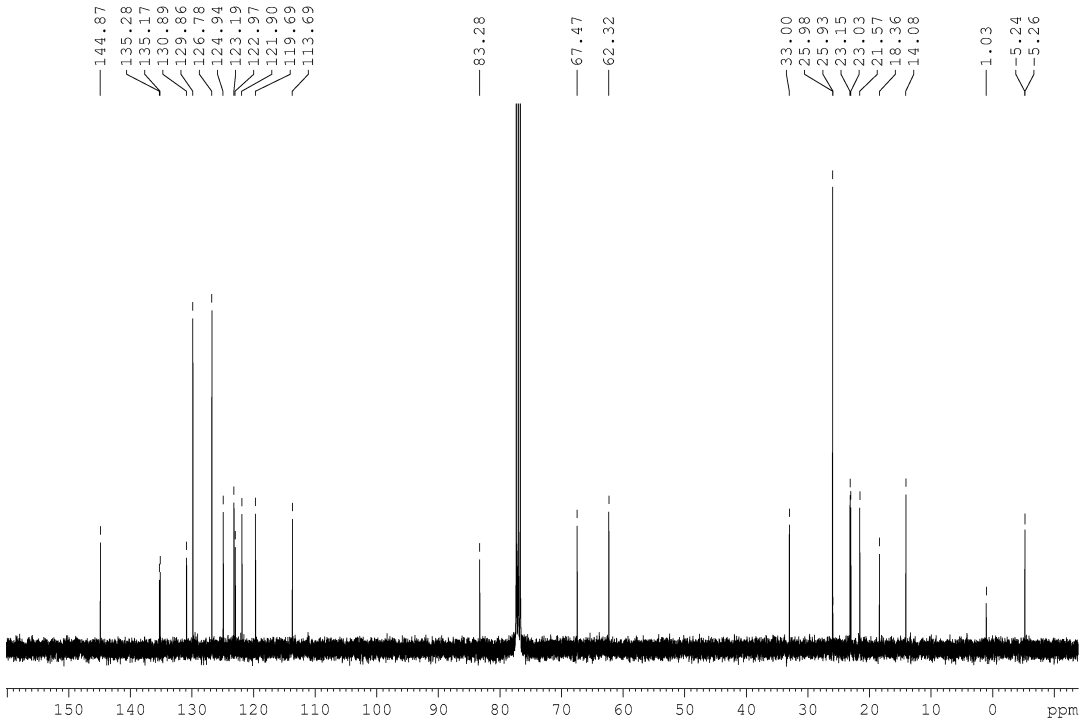




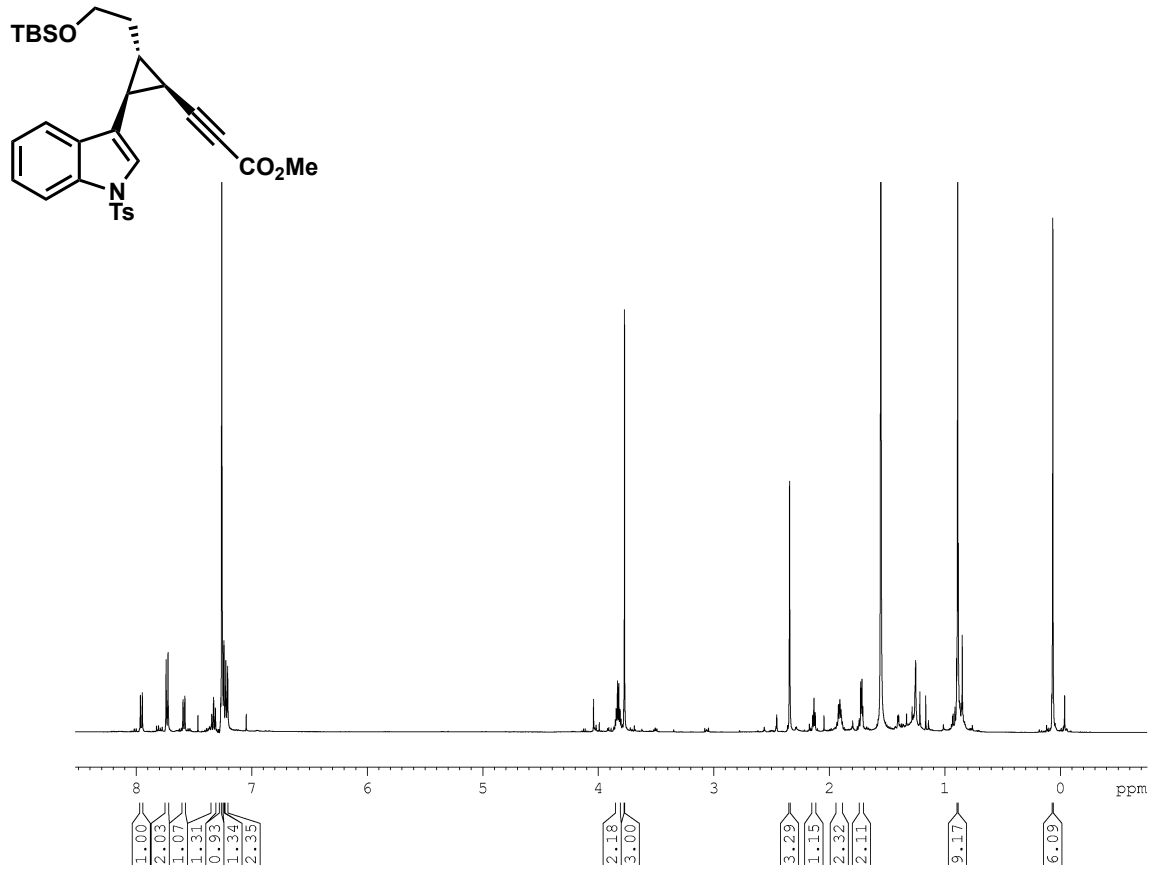
3-((1*S*,2*R*,3*R*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-ethynylcyclopropyl)-1-tosyl-1*H*-indole (267)

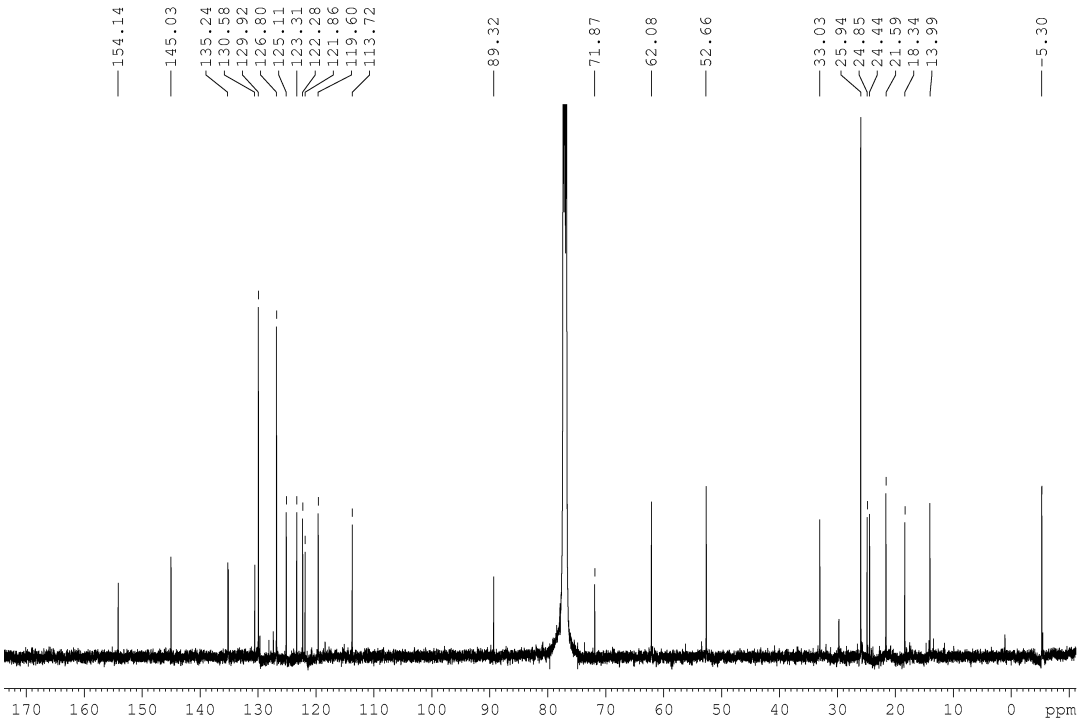




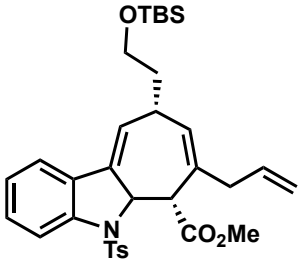


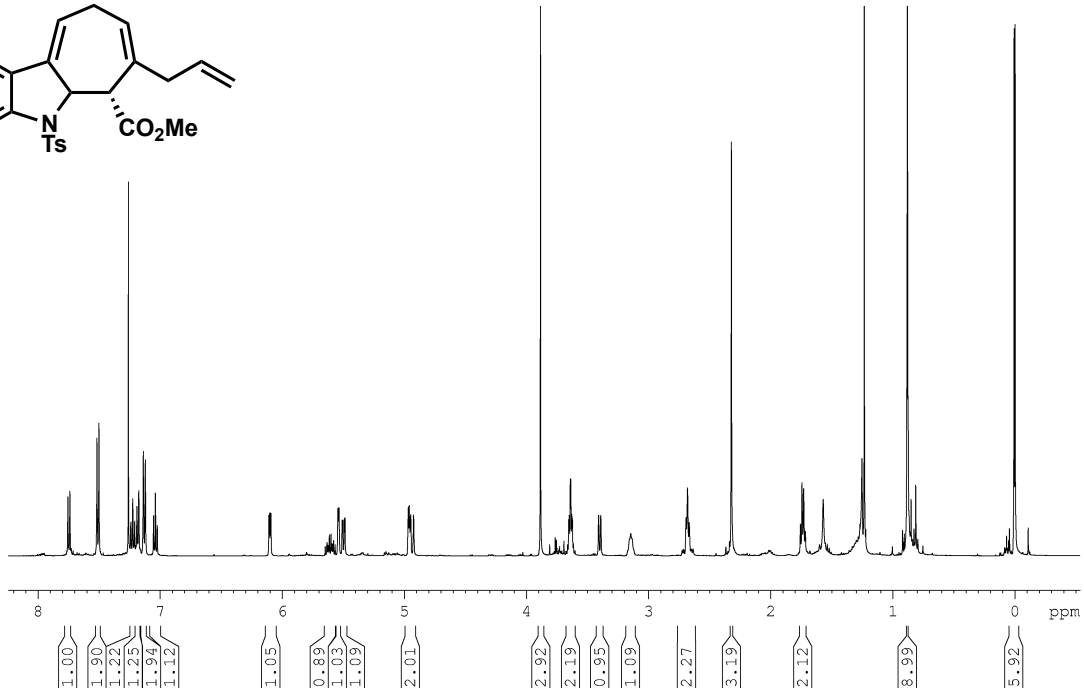
Methyl 3-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (268)

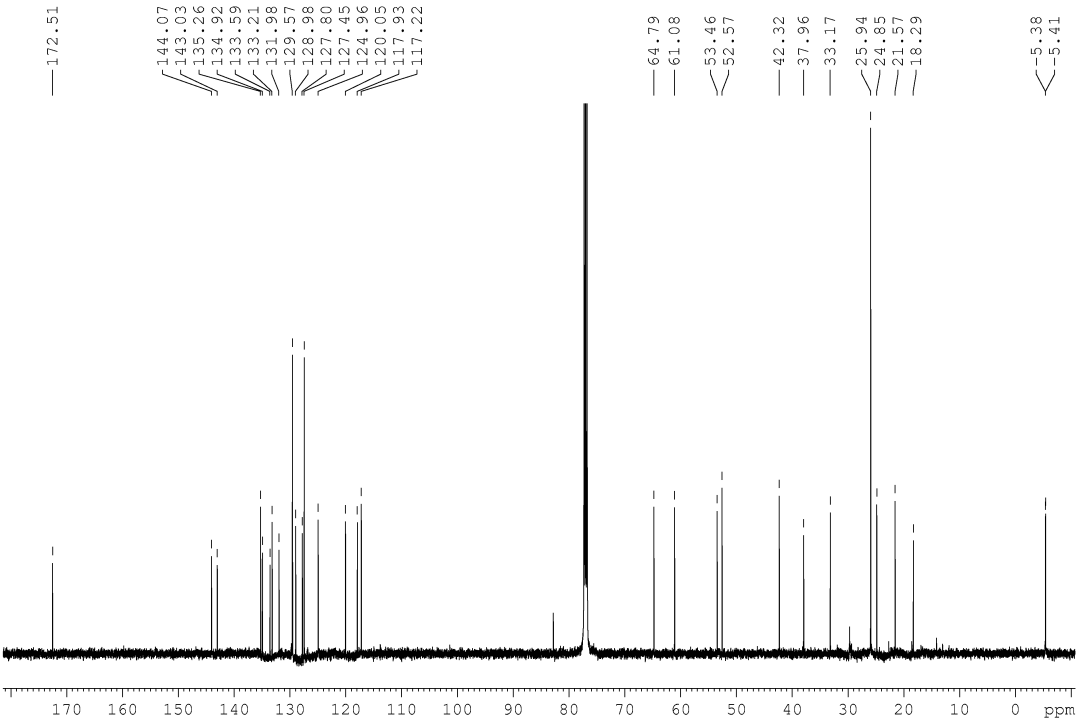




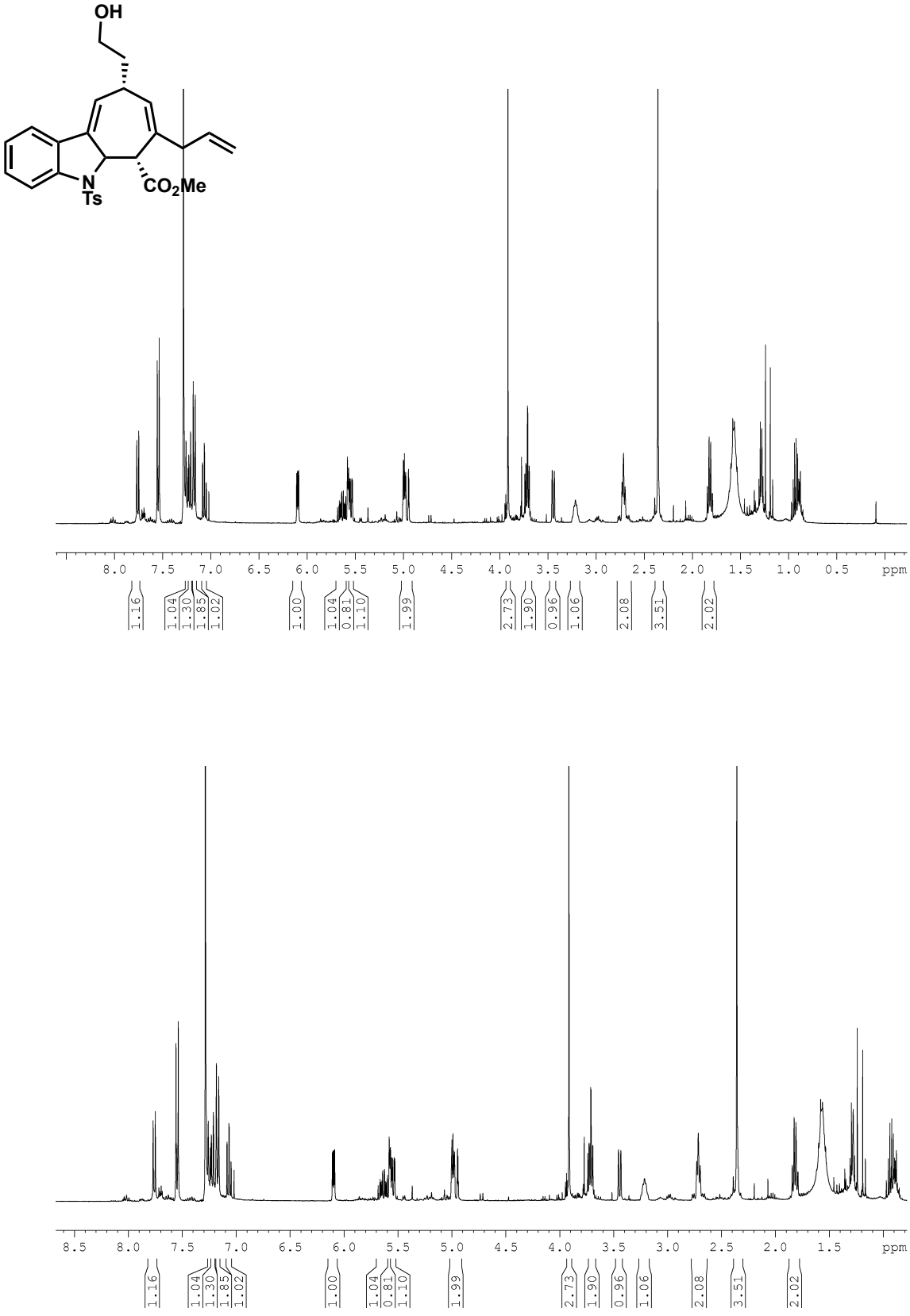
Methyl 7-allyl-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (270)



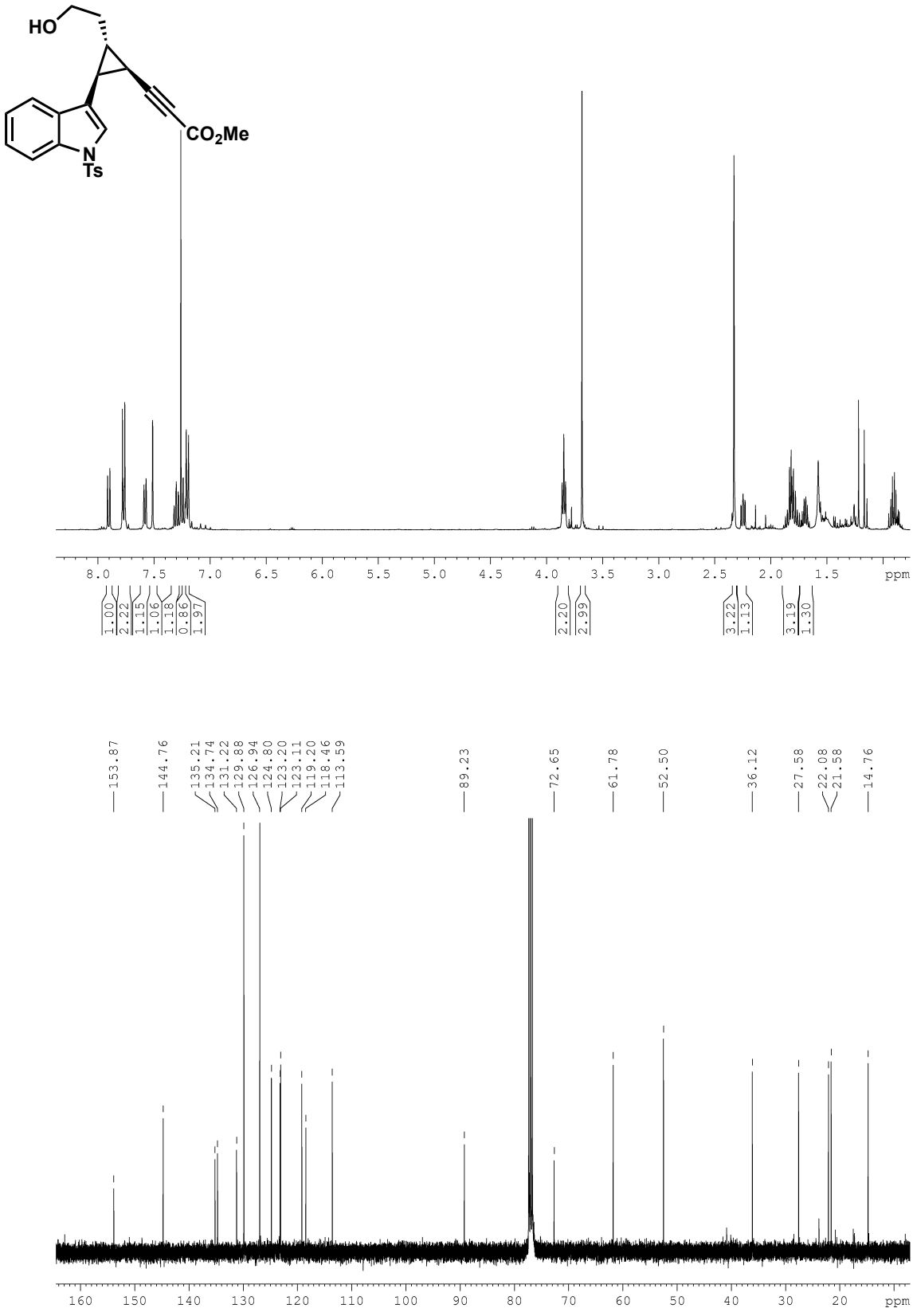




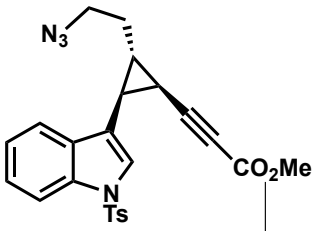
Methyl 7-allyl-9-(2-hydroxyethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (270a)

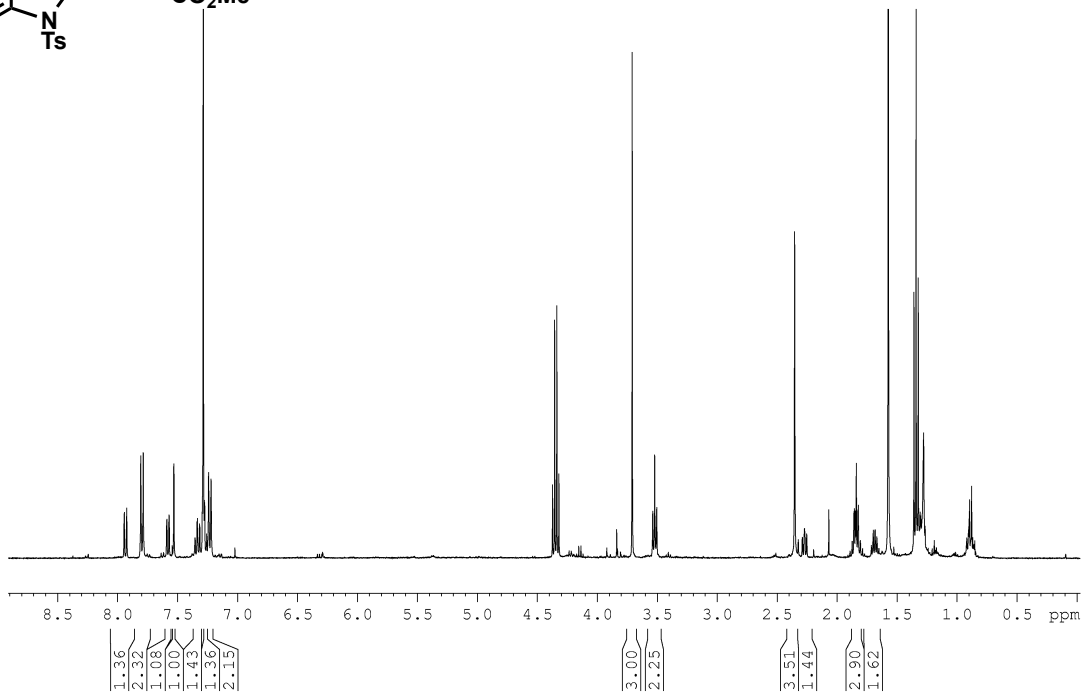


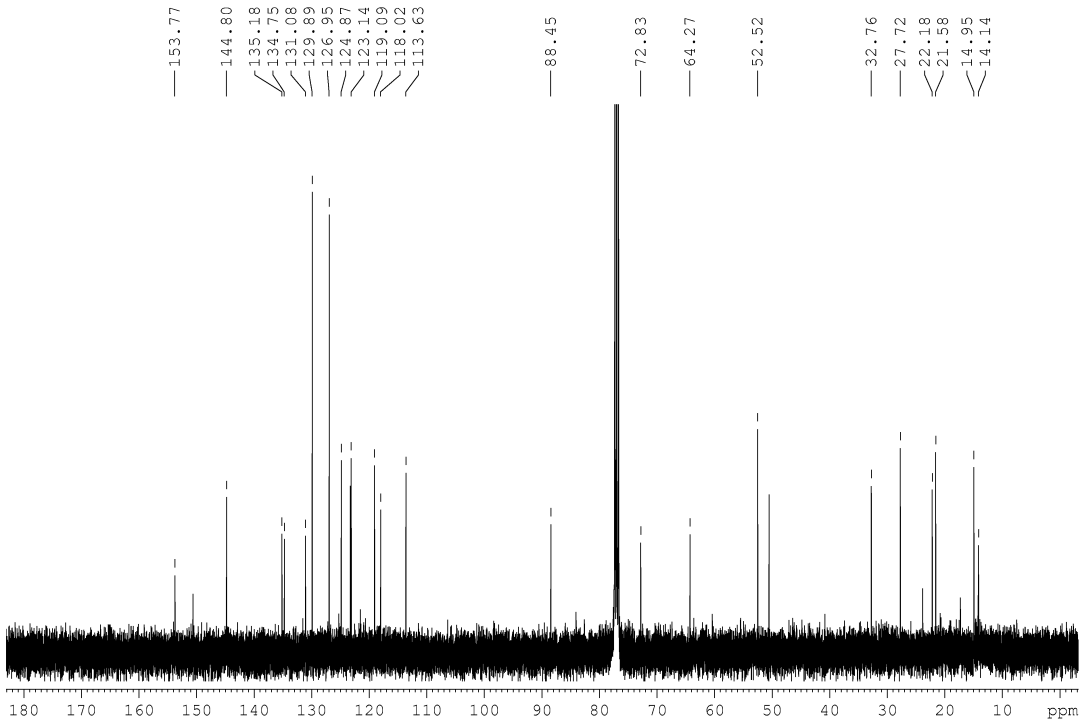
Methyl 3-(2-(2-hydroxyethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (268a)



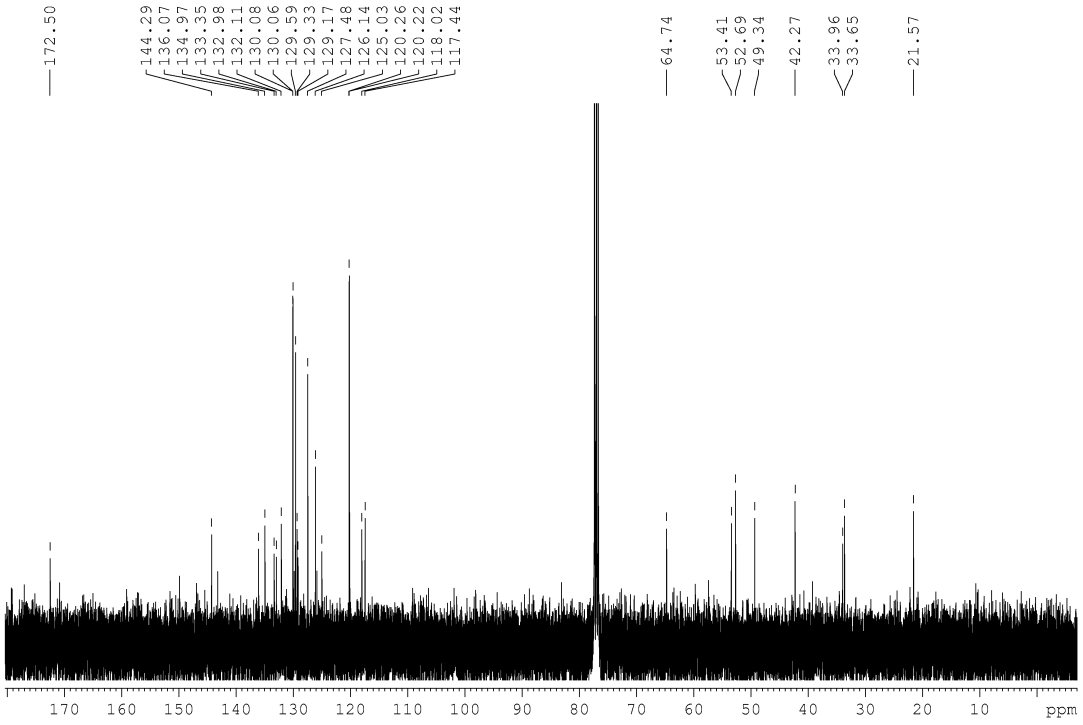
Methyl 3-(2-(2-azidoethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)propiolate (272)



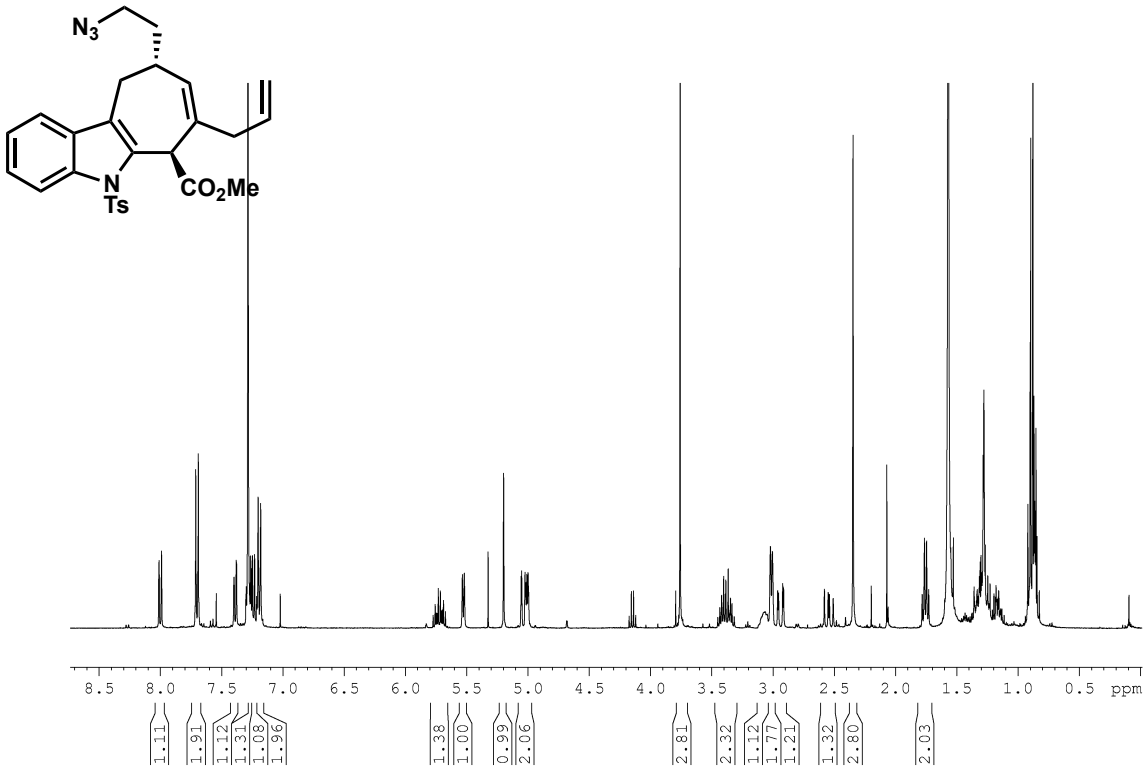


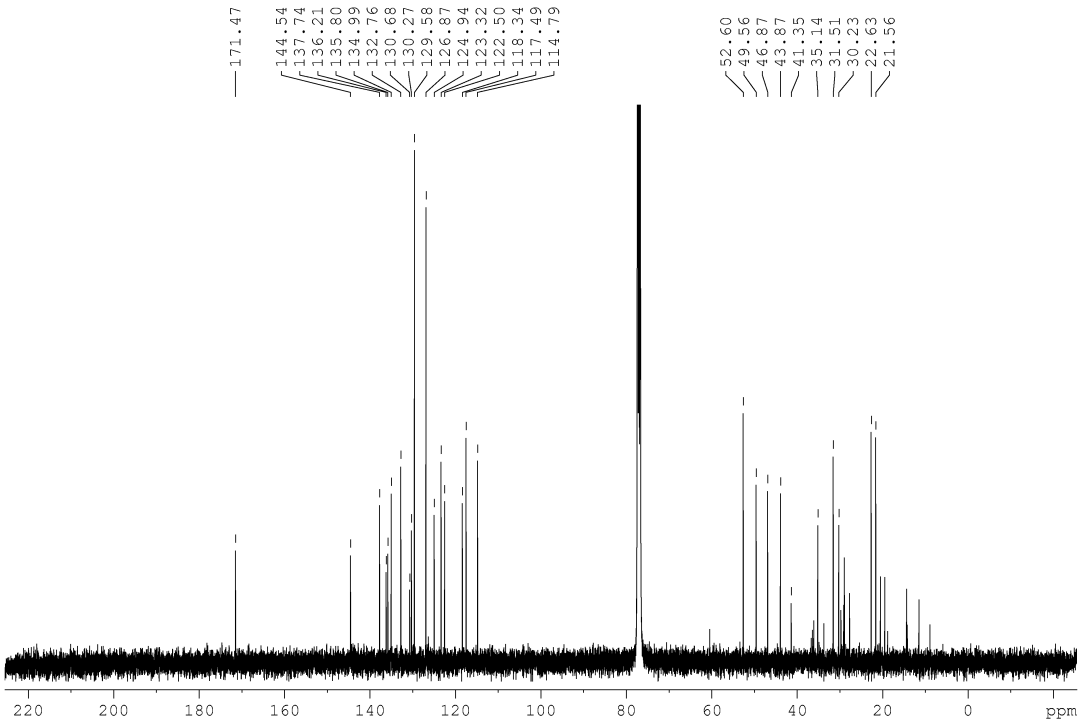


Methyl 7-allyl-9-(2-azidoethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (271)

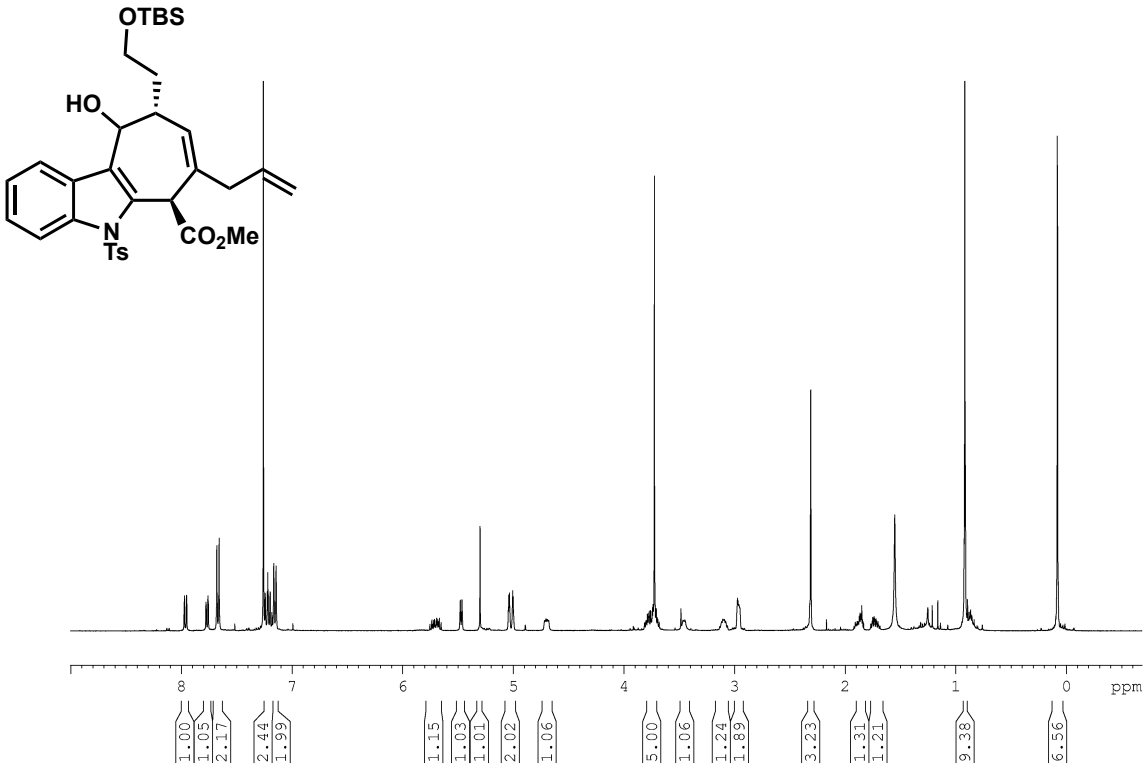


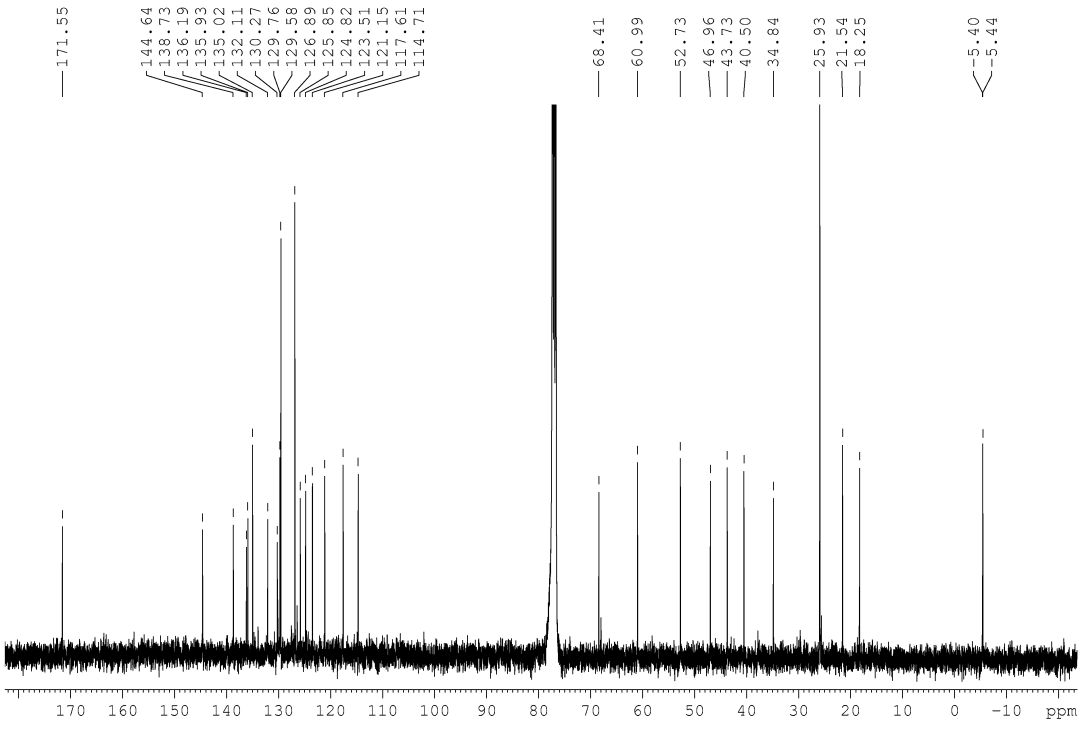
Methyl 7-allyl-9-(2-azidoethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate (271a)



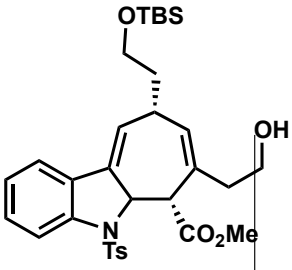


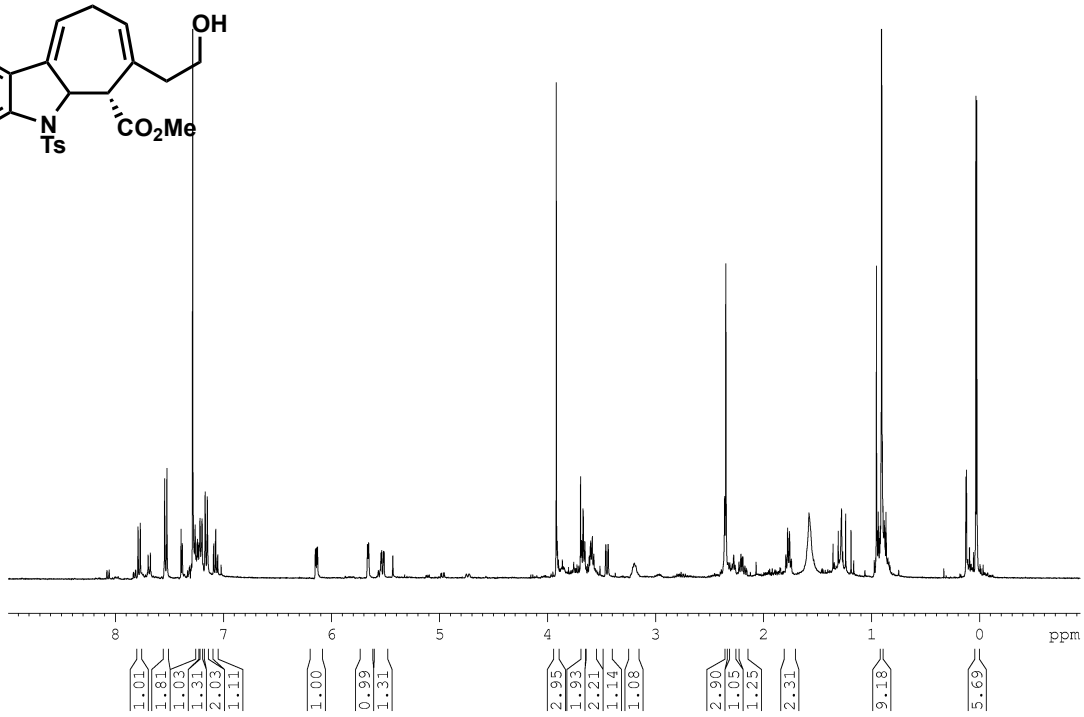
Methyl 7-allyl-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-10-hydroxy-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate (275)

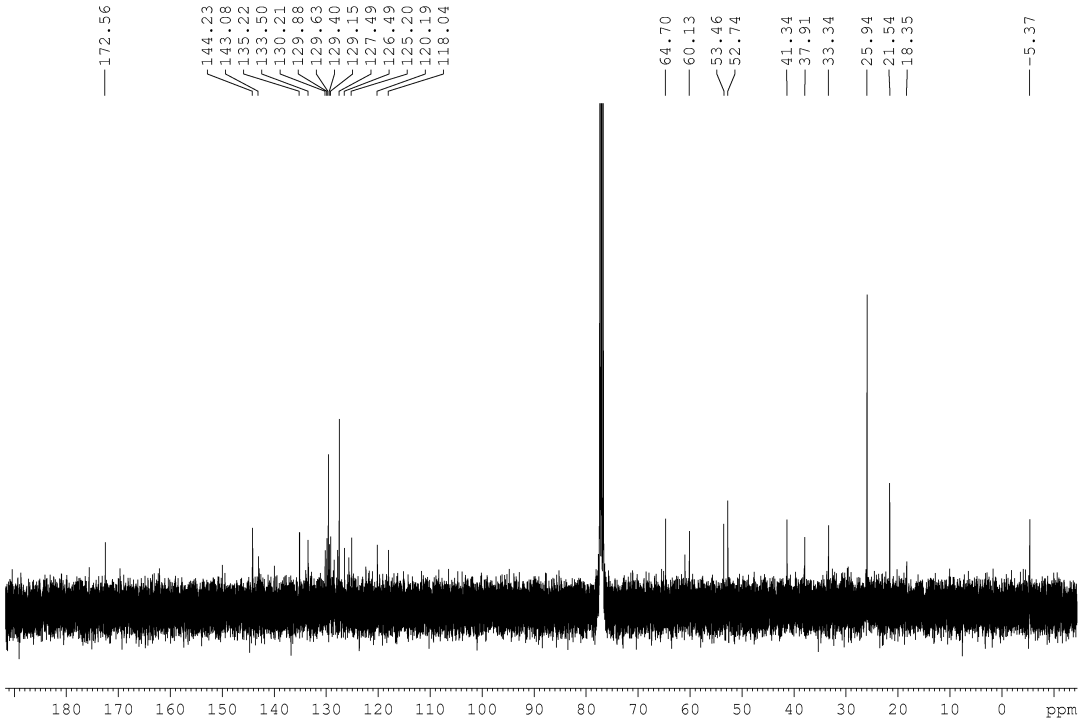




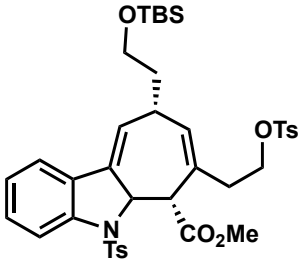
Methyl 9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-7-(2-hydroxyethyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (276)

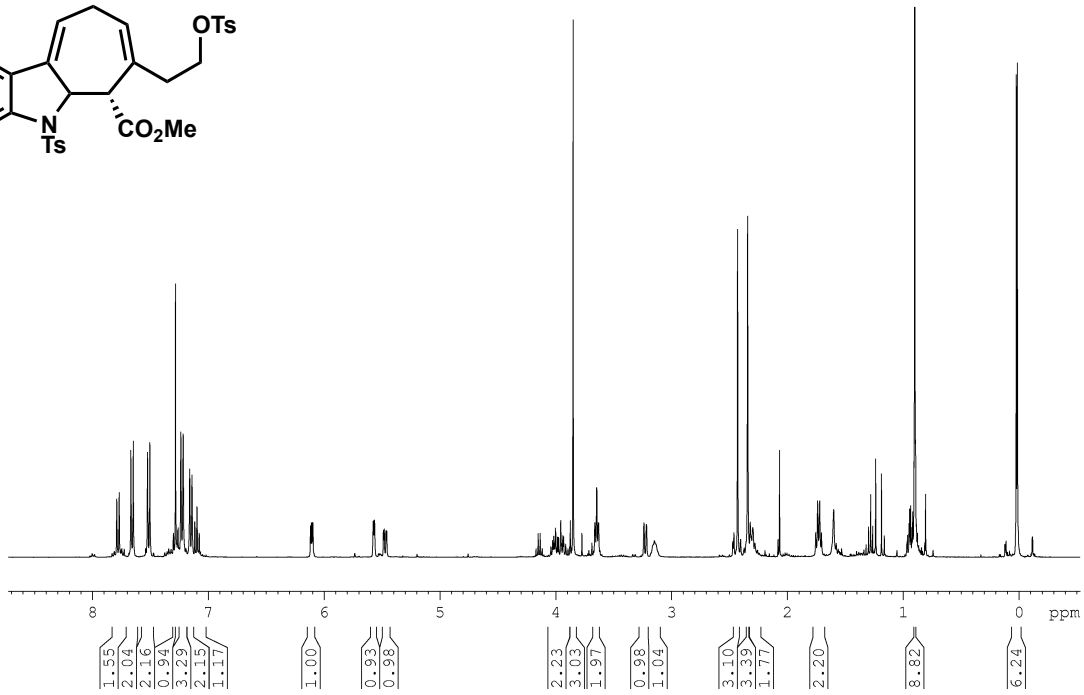


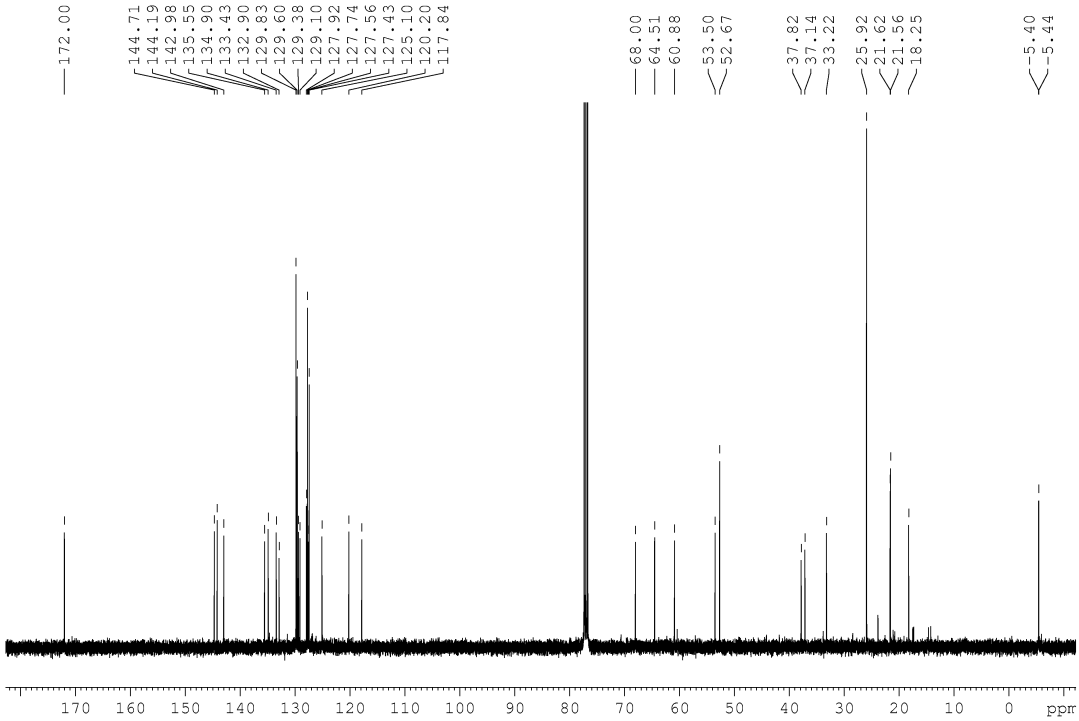




Methyl 9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-tosyl-7-(2-(tosyloxy)ethyl)-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (277)







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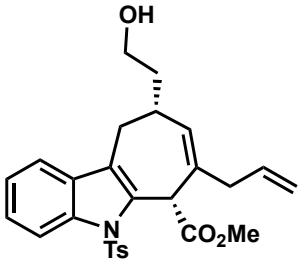
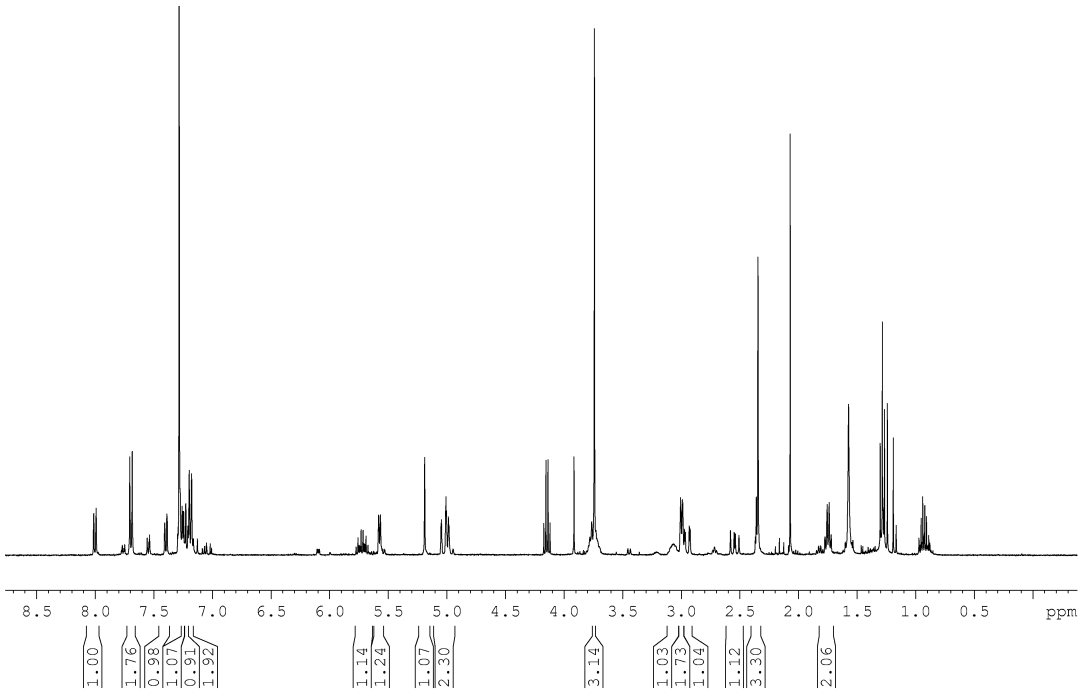
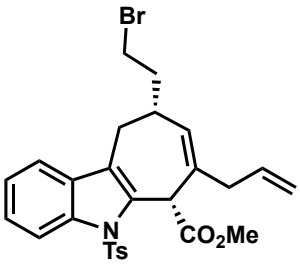
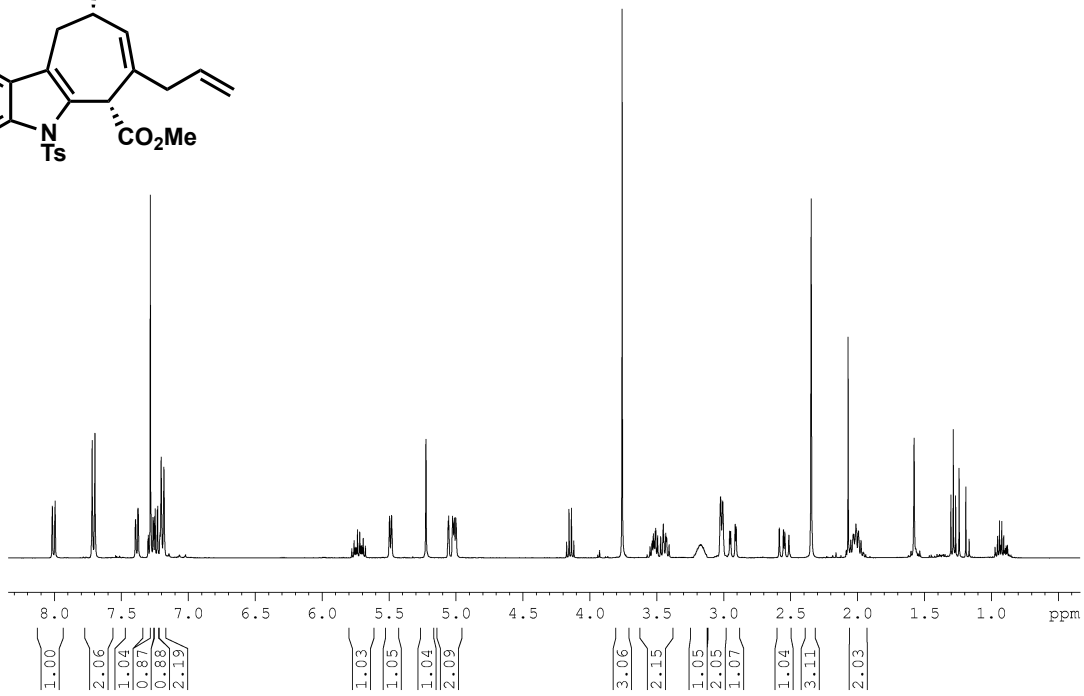
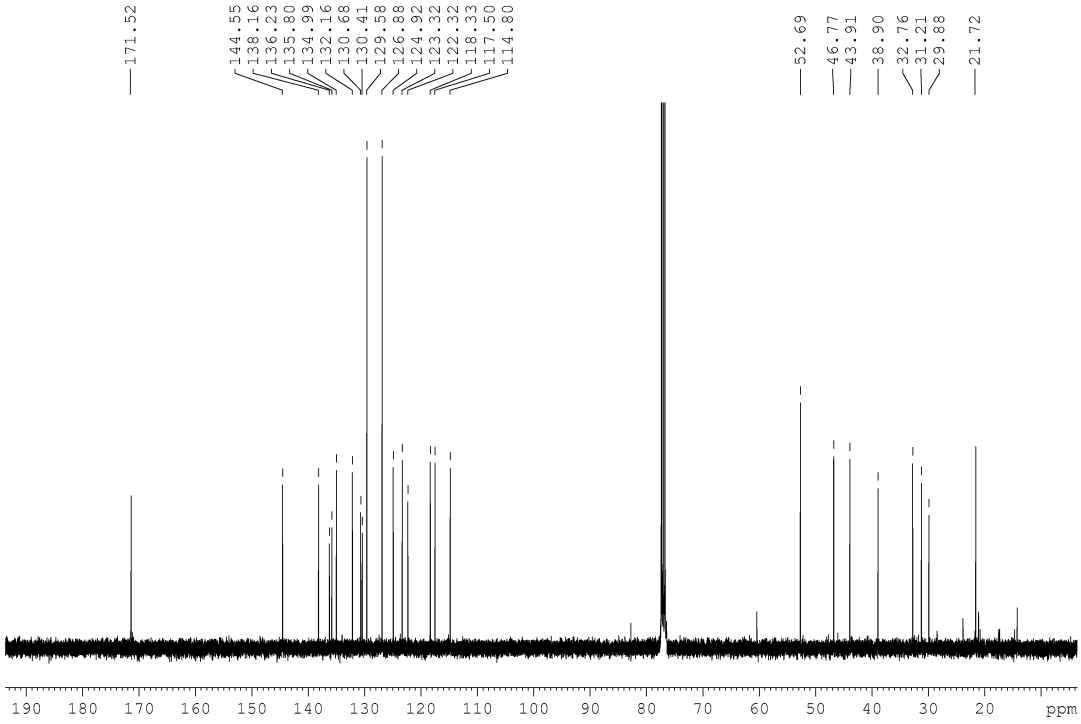




Methyl 7-allyl-9-(2-bromoethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-6-carboxylate (279)







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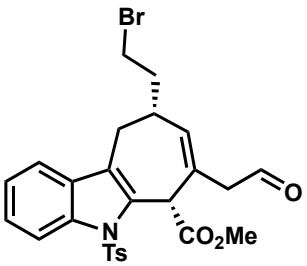
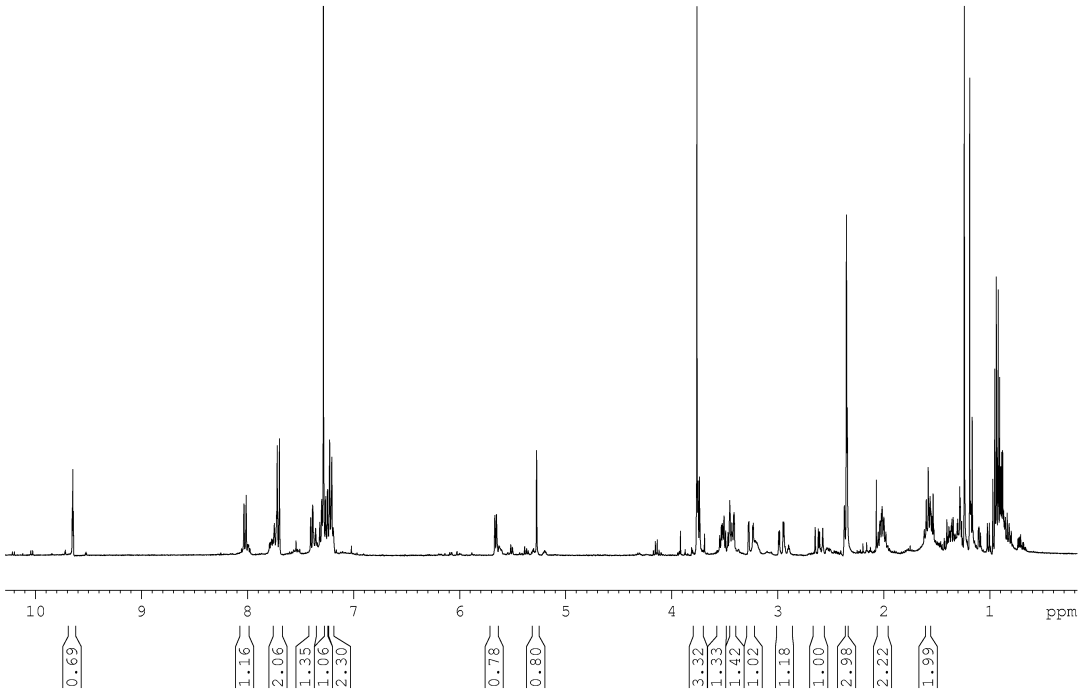
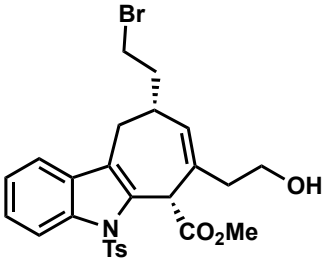
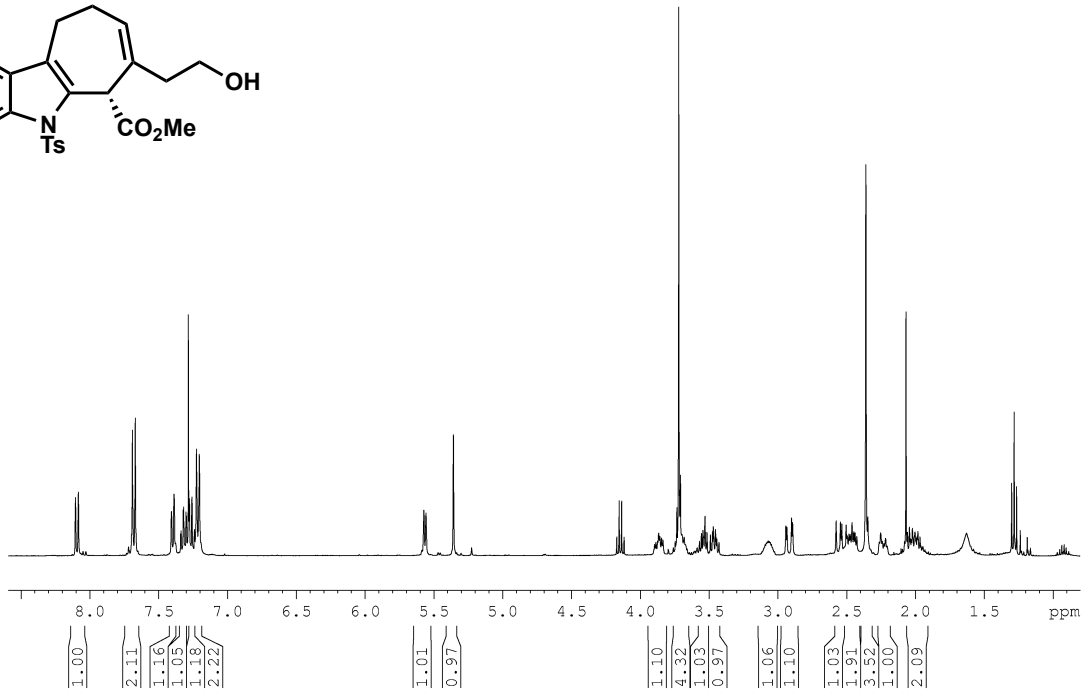
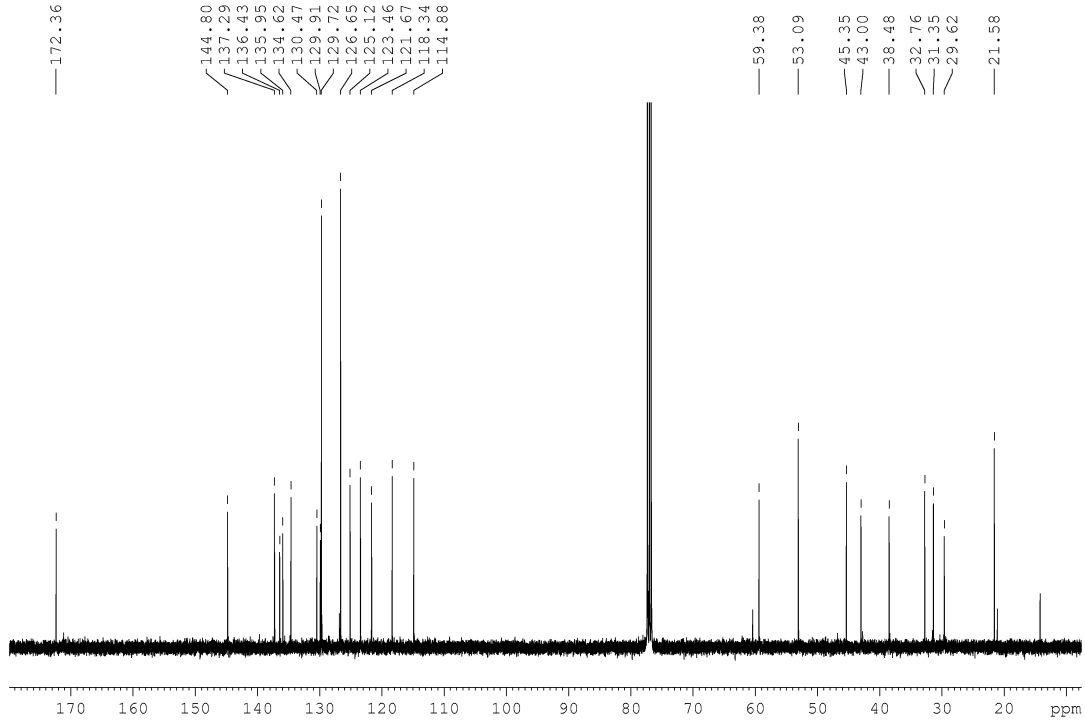




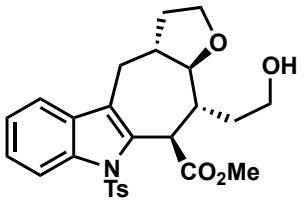
(6R,9R)-Methyl 9-(2-bromoethyl)-7-(2-hydroxyethyl)-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indole-6-carboxylate (282)

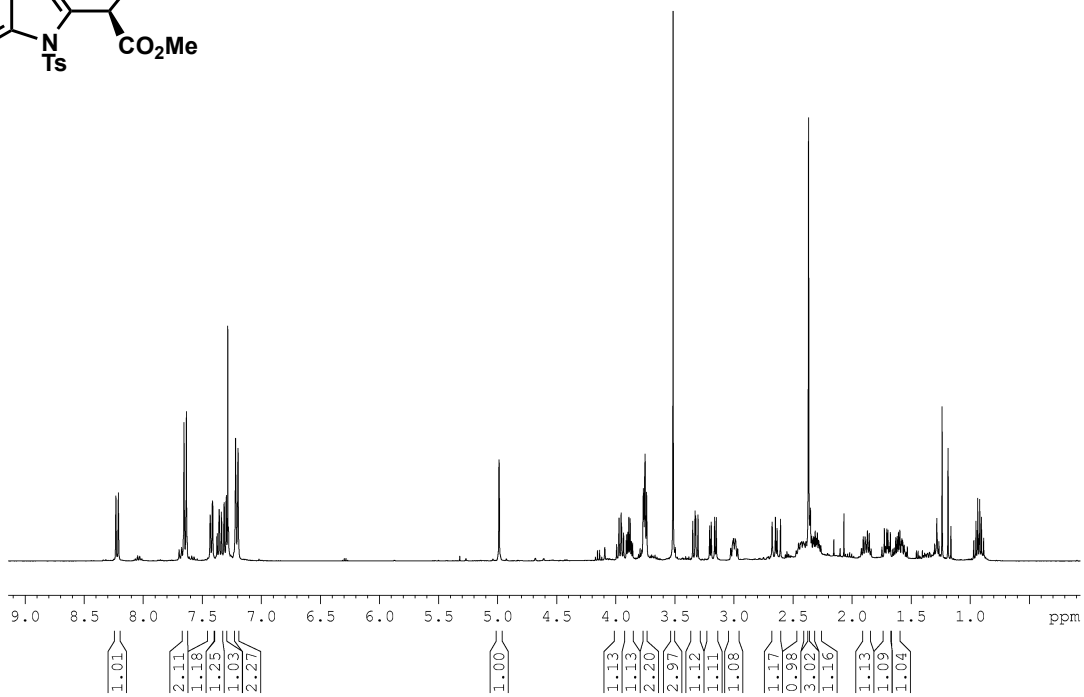


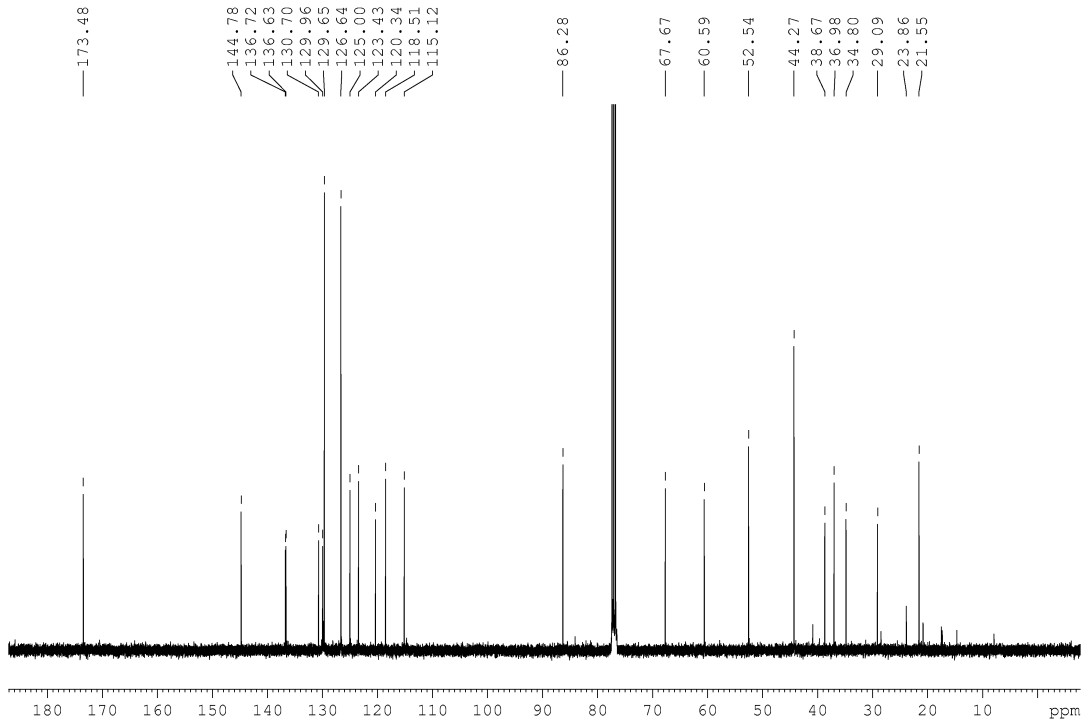




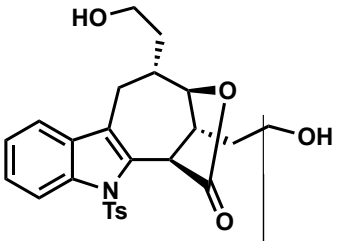
Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (283)

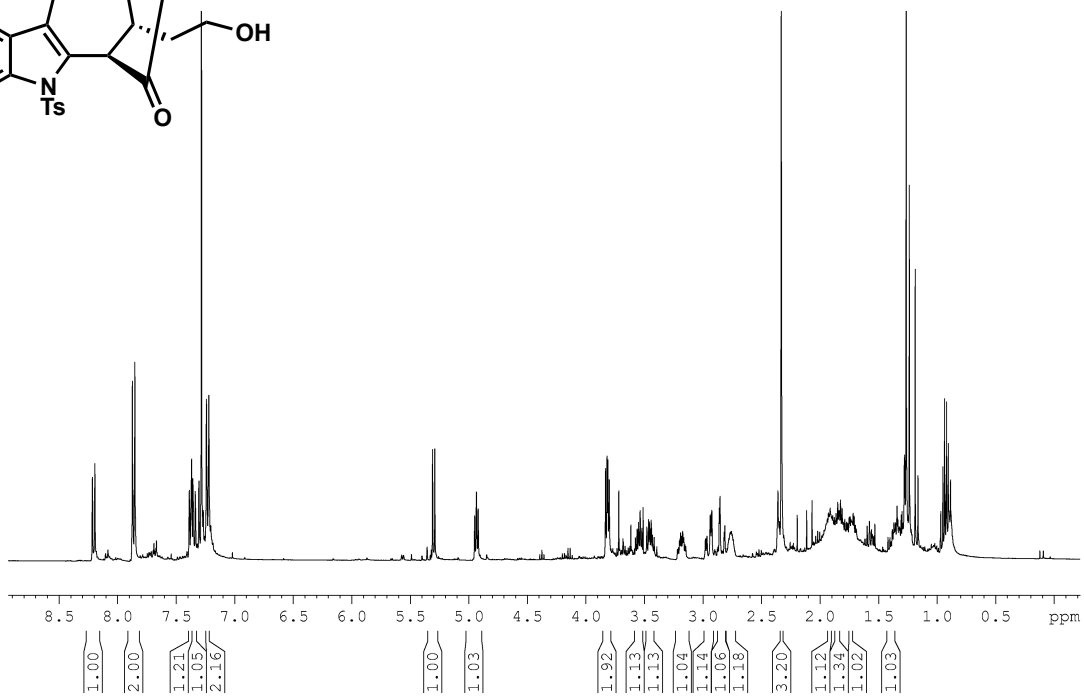


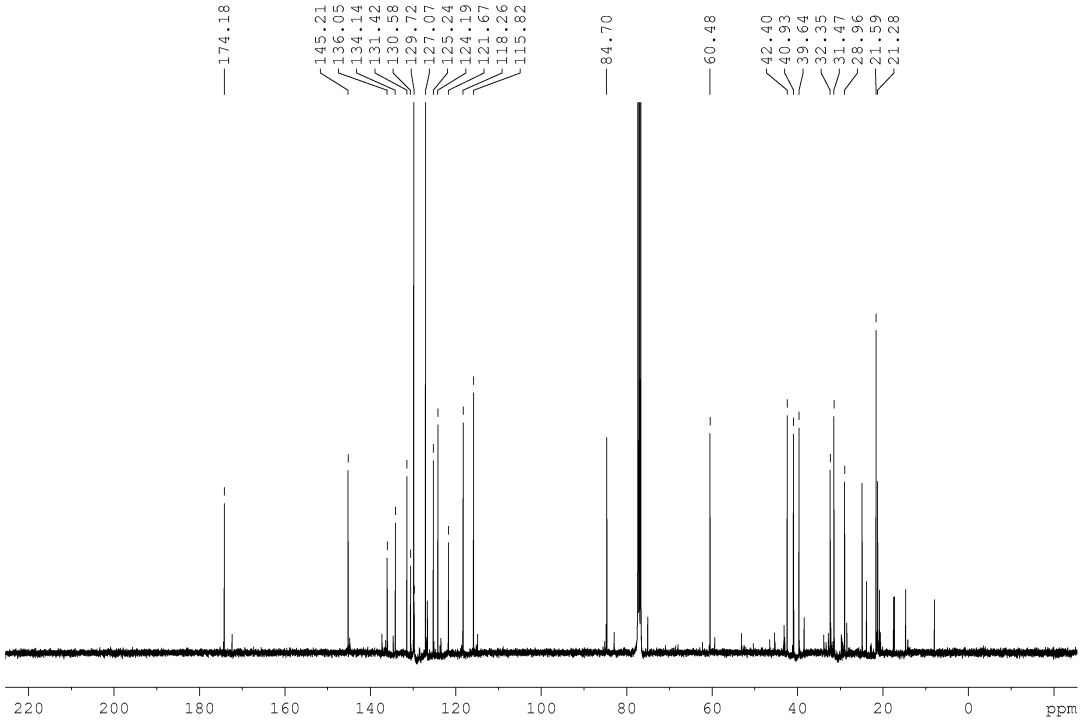




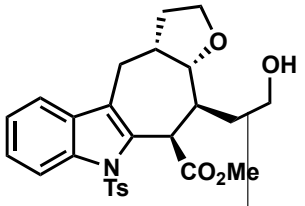
5,12-Bis(2-hydroxyethyl)-11-tosyl-4,5,6,11-tetrahydro-1,4-methanooxocino[4,5-*b*]indol-2(1*H*)-one (284)

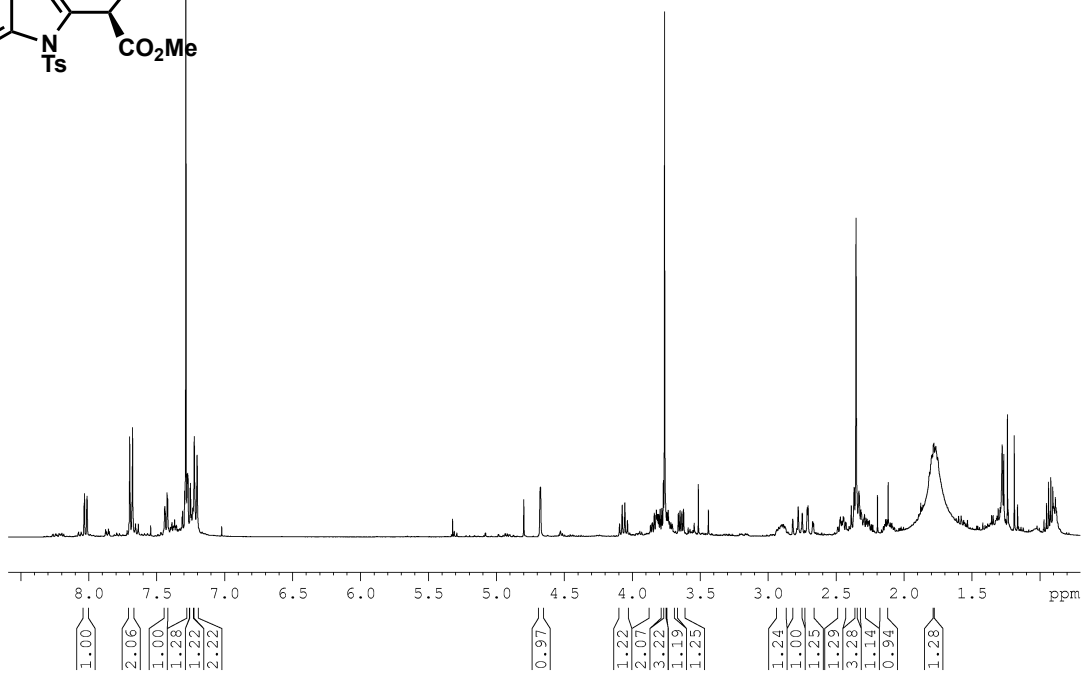


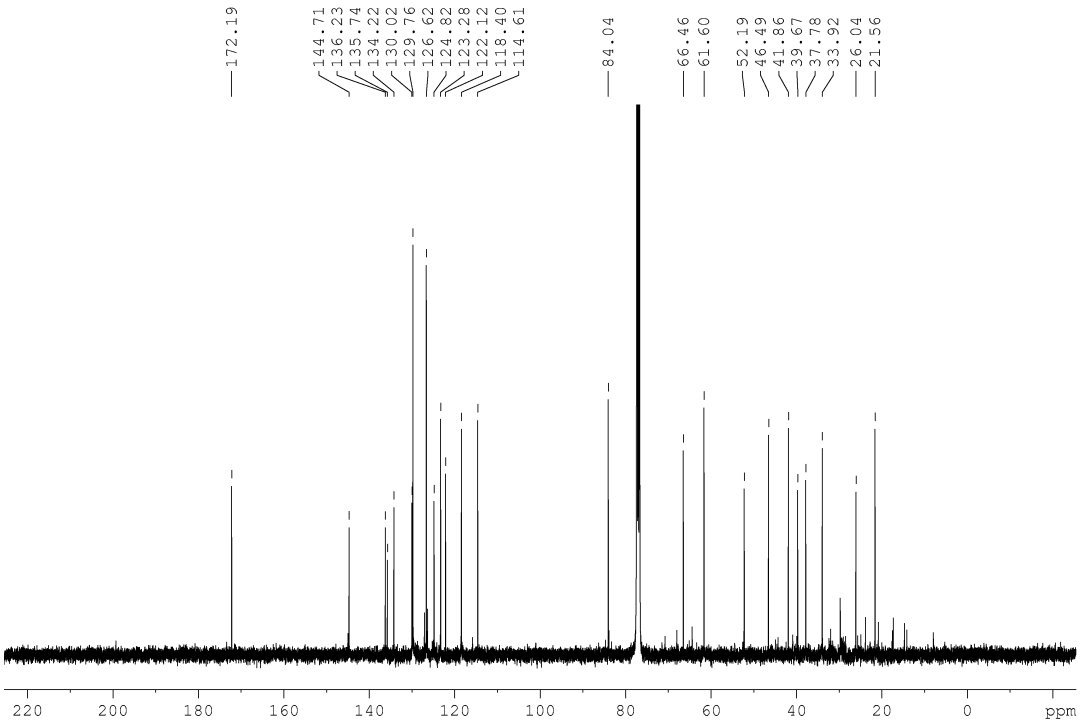




Methyl 11-(2-hydroxyethyl)-9-tosyl-2,3,3a,4,9,10,11,11a-octahydrofuro[3',2':4,5]cyclohepta[1,2-*b*]indole-10-carboxylate (285)







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19 List of abbreviations

ABSA ..... 4-acetamidobenzenesulfonyl azide

Ac ..... acetyl

ACN ..... 1,1'-azobiscyclohexanecarbonitrile

aq..... aqueous

ATR..... attenuated total reflectance

Bn..... benzyl

Boc..... *tert*-butoxycarbonyl

BOX..... bisoxazoline

Bu..... butyl

dba..... dibenzylidene acetone

CAN ..... ammonium cer (IV) nitrate

cat. ..... catalytic

Cbz..... benzylcarbonyl

d.r. ..... diastereomeric ratio

DBU 1,8-Diazabicycloundec-7-ene

DCC..... dicyclohexylcarbodiimide

DDQ..... 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DCE..... 1,2 dichlorethane

de..... diastereomeric excess

DiBAl-H..... di*iso*butyl aluminium hydride

DIC ..... di*iso*propylcarbodiimid

DIPEA ..... di*iso*propylethylamine

DMF..... dimethyl formamide

DMAP..... 4-dimethylaminopyridine

DMSO..... dimethylsulfoxid

DNsOH ..... 2,4-dinitro phenylsulfonic acid

DOSP..... (p-dodecylphenylsulfonyl)prolinato

dppp..... bis(diphenyphosphino)propan

DtBP..... 2,6-di*tert*butyl pyridine

DVCPR..... divinylcyclopropyl rearrangement

ee..... enantiomeric excess

ESI..... electro spray ionization

equiv. . ..... equivalent

Et..... ethyl

FTIR..... fourier transform infrared

GC..... gaseous chromatography

h..... hour

hν..... light

HPLC..... high pressure liquid chromatography

HRMS..... high resolution mass spectrometry

IBX..... 2-iodoxybenzoic acid

IC_{50}..... half maximal inhibitory concentration

KHMDS..... potassium hexamethyldisilazide

Kcal..... kilocalorie

LDA..... lithium di*iso*propyl amine

LiHMDS..... lithium hexamethyldisilazide

*m*CPBA..... *meta*-chloroperbenzoic acid

Me..... methyl

min..... minute

Ms..... mesyl

MS..... mass spectrometry

NAHMDS..... sodium hexamethyldisilazide

N.A. ..... not available

NBS..... *N*-bromo succinimide

NDMBA..... *N*,*N*-dimethylbarbituric acid

NMO ..... *N*-methyl morpholin oxide

NMR ..... nuclear magnetic resonance

Nu ..... nucleophile

Oct ..... octannoate

Ph ..... phenyl

PPSE ..... trimethylsilyl polyphosphate

Pr ..... propyl

Pyr ..... pyridine

r.t. ..... room temperature, ambient temperature

Red-Al™ ..... sodium bis(2-methoxyethoxy)aluminum hydride solution

*s*Bu ..... *sec*-butyl

TBDPS ..... *tert*-butyldiphenylsilyl

TBS ..... *tert*-butyldimethylsilyl

*t*Bu ..... *tert*-butyl

TBAB ..... tetra-*n*-butylamonium bromide

Tf ..... triflyl

TFAA ..... trifluoroaceticacid anhydride

THF ..... tetrahydrofuran

TIPS ..... tri*iso*propylsilyl

TLC ..... thinlayer chromatography

TMS ..... trimethylsilyl

Ts ..... tosyl

Δ ..... heat at reflux

VCPR ..... vinylcyclropropyl rearrangement

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21 Curriculum Vitae

Academics

June 2011-December 2015

PhD with Prof. Tanja Gaich at the Leibniz University Hannover

Sept 2009 - Aug 2010

Research for Master Thesis with Prof. André B. Charette at the University of Montréal.

Sept 2007 – Aug 2008

Student Exchange program at the Université de Montréal (www.umontreal.ca), first internship with Prof. André B. Charette

Oct 2004 – Jan 2011

Diploma Studies: Technical Chemistry at the Vienna University of Technology; Diploma Thesis: "On the enantioselective Synthesis of Cyclopropanes"

Passed Exam with distinction

Education

1991 - 1995	Primary school VS Reisnerstraße 1030 Vienna
1995 - 1999	Secondary School BG Rainergasse 1050 Vienna
1999 - 2003	Secondary School Sir-Karl-Popper Schule, 1040 Vienna

22 List of publications

Scientific Journals

1. The Witkop Cyclization: A Photoinduced C-H Activation of the Indole System*;* Gritsch, P.J.; Leitner, C.; Pfaffenbach, M.; Gaich, T. *Angew. Chem.; Int. Ed.* **2014**, *53(5)*, 1208-1217

2. Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (*S*)-SIRT1-Inhibitor IV;
   Gritsch, P.J.; Stempel, E.; Gaich, T. *Org. Lett* **2013**, *15(21)*, 5472-5475

3. How to "Cope" with the prenylation of the indole C4 position;
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4. Stereoselective Rh_2(*S*-IBAZ)$_4$-Catalyzed Cyclopropanation of Alkenes, Alkynes, and Allenes: Asymmetric Synthesis of Diacceptor Cyclopropylphosphonates and Alkylidenecyclopropanes;
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5. Mimicking Dimethylallyltryptophan Synthase: Experimental Evidence for a Biosynthetic Cope Rearrangement Process;
   Schwarzer, D.D.; Gritsch, P.J.; Gaich, T. *Angew. Chem.; Int. Ed.* **2012**, *51(46)*, 11514-11516.

6. Micellar catalysis in aqueous-ionic liquid systems;
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7. Synthesis of Enantioenriched Allenes from 1,1-Cyclopropanediesters;
   Cerat, P.; Gritsch, P.J.; Goudreau, S. R.; Charette, A.B. *Org. Lett.* **2010**, *12(3)*, 564-567.

Poster Presentations

14th Tetrahedron Symposium: The application of the Divinylcyclopropane Rearrangement to the Synthesis of Cyclohepta[b]indoles;
Gritsch, P.J.; Stempel, E.; Gaich, T.*; Vienna, Austria* 2013-06-25 – 2013-06-28

16th Tetrahedron Symposium: The application of the divinylcyclopropane rearrangement to the total synthesis of indole natural products*;*
Gritsch, P.J.; Stempel, E.; Gaich, T.*; Berlin, Germany* 2015-06-17 – 2015-06-19