Zur Totalsynthese von Hexacyclinsäure

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Hannover, Januar 2007

Kurzfassung

Stelmakh, Andriy

Zur Totalsynthese von Hexacyclinsäure

Schlagwörter: Totalsynthese, Naturstoffchemie, Hexacyclinsäure, FR182877.

Hexacyclinsäure ist ein komplexes Polyketid, welches von *Streptomyces cellulosae* subsp. *griseorubiginosus* (Stamm S1013) produziert wird. Die Isolierung und Strukturaufklärung des Naturstoffs wurde im Jahr 2000 von Zeeck *et al.* veröffentlicht. Aufgrund seiner Komplexität und strukturellen Ähnlichkeit zu (-)-FR182877, einem Naturstoff mit vielversprechenden antineoplastischen Eigenschaften, stellt Hexacyclinsäure eine interessante synthetische Herausforderung dar.

Im Mittelpunkt des ersten Teils dieser Arbeit stand die Untersuchung des stereochemischen Verlaufs der Tandem-Michael-Addition/Aldol-Reaktion als einen Schlüsselschritt im Aufbau des C-Rings von Hexacyclinsäure. Infolge dieser Studien wurde festgestellt, dass die Reaktion unter kinetischen Bedingungen ein Siloxycyclobutan mit einer Selektivität von 7:1 liefert, dessen relative Stereochemie mit dem Naturstoff identisch ist. Die Aufklärung der relativen Stereochemie wurde mit Hilfe von NOE-NMR-Experimenten durchgeführt.

Darauf folgende Untersuchungen der Retroaldol-Reaktion haben gezeigt, dass das kinetische Siloxycyclobutan-Produkt bei tiefen Temperaturen (-30 °C, TBAF) in das gewünschte Methylketon ohne Epimerisierung überführt werden kann. Im Gegenteil dazu lieferte die Reaktion bei Raumtemperatur das epimerisierte Produkt. Dieser Befund erklärt die Tatsache, dass laut der Röntgenstrukturanalyse des vollständig entschützten ABC-Fragments eins von neun Stereozentren die falsche Stereochemie besaß (T. Stellfeld, *Dissertation*, Freie Universität Berlin, 2004). Dies war das Resultat einer Epimerisierung während der Entschützung mit TBAF bei Raumtemperatur.

Die Addition des Grignard-Reagenzes aus 1-(Benzyloxy)-3-brompropan an das Methylketon lieferte das unerwünschte Felkin-Produkt mit einer Selektivität von 1:5. Die Aufklärung der relativen Stereochemie wurde mit Hilfe von ROESY-NMR-Experimenten durchgeführt.

Im zweiten Teil der Arbeit wurden Studien zur Entwicklung eines synthetischen Zugangs zum DEF-Fragment des Naturstoffs durchgeführt. Entsprechend dem synthetischen Plan sollte der Aufbau des DEF-Fragments ausgehend von einem 9-gliedrigen Lacton mit Hilfe einer Dieckmann-Kondensation als Schlüsselschritt erfolgen.

Die zur Synthese des 9-gliedrigen Lactons durchzuführende Ringschluß-Metathese war mit verschiedenen Zyklisierungs-Vorläufern und Katalysatoren nicht erfolgreich. Eine Umstellung des retrosynthetischen Ansatzes führte schließlich zur erfolgreichen Synthese des 9-gliedrigen Lactons mit Hilfe einer Grignard-Reaktion, einer Evans-Aldol-Reaktion und einer Yamaguchi-Macrolactonisierung. Trotz erfolgsversprechender Modellstudien der Dieckmann-Kondensation mit einem Acetat- und Propionat-Vorläufer konnte die Reaktion nicht erfolgreich auf den fortgeschrittenen 9-gliedrigen Lacton-Vorläufer übertragen werden. Eine plausible Erklärung für diese Tatsache wurde vorgeschlagen und die synthetische Strategie zum Aufbau des trizyklischen DEF-Fragments wurde entsprechend überarbeitet.

Abstract

Stelmakh, Andriy

Towards the Total Synthesis of Hexacyclinic Acid

Keywords: Total Synthesis, Chemistry of Natural Products, Hexacyclinic Acid, FR182877.

Hexacyclinic acid is a complex polyketide, produced by the *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013). The isolation of the natural product and elucidation of its structure was reported by Zeeck *et al.* in 2000. Due to the complex structure and similarity to (-)-FR182877, a natural product with promising antineoplastic properties, hexacyclinic acid presents a challenging synthetic target.

In the first part of this work the stereochemical outcome of the Tandem Michael Addition-Aldol reaction as a key step in the construction of the C-ring of hexacyclinic acid was studied. As a result of this investigation it was found that under kinetic conditions the reaction furnishes a siloxycyclobutane product with a selectivity of 7:1, and the relative stereochemistry identical to that of the natural product. Elucidation of the relative stereochemistry was performed using NOE NMR experiments.

The following study of the retroaldol reaction has shown that the kinetic siloxycyclobutane product could be converted into the desired methylketone without epimerization at low temperature (TBAF, -30 °C). In contrast, conducting the reaction at rt afforded epimerized product. This experimental finding explained the wrong stereochemistry of one out of the nine stereocenters in the X-ray structure analysis of the totally deprotected ABC fragment (T. Stellfeld, *Dissertation*, Freie Universität Berlin, 2004). This was a result of the epimerization that took place during deprotection with TBAF at room temperature.

Addition of a Grignard reagent generated from 1-(benzyloxy)-3-brompropane to the methylketone furnished the undesired Felkin product with a selectivity of 1:5. The elucidation of the relative stereochemistry was conducted using ROESY NMR experiments.

In the second part of the thesis the studies were aimed at the elaboration of a synthetic approach towards the DEF fragment of the natural product. According to the synthetic plan the construction of the DEF cyclic fragment had to be straightforward from a 9-membered lactone precursor using the Dieckmann condensation as a key step.

The ring closing olefin metathesis reaction, that we intended to use for the synthesis of the 9-membered lactone, proved to be not successful with a set of catalysts and different substrates. A new, reconsidered retrosynthetic approach, featuring a Grignard reaction, an Evans aldol reaction and a Yamaguchi macrolactonization led to the successful synthesis of the 9-membered lactone. Despite the promising model studies of the Dieckmann condensation with acetate and propionate precursor, the reaction could not be successfully transferred to the advanced 9-membered lactone precursor. A reasonable explanation for this fact has been proposed and the synthetic approach towards the tricyclic DEF fragment has been reconsidered.

Für meine Eltern, Nina und Volodimir Stelmakh

Моїм Батькам, Ніні та Володимиру Стельмах

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If you want to build a ship, don't herd people together to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea.

Antoine de Saint-Exupéry

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List of Abbreviations

Ac	acetyl
AcOEt	ethyl acetate
AcOH	acetic acid
ACP	acetyl carrier protein
Ar	aryl or aromatic
AT	acetyl transferase
atm	Atmosphere (unit); 1 atm = 101325 Pa
Bn	benzyl
bp	boiling point
Bu	butyl
cat.	catalytic
COSY	homonuclear correlation spectroscopy, usually H,H-COSY
CSA	camphorsulfonic acid
dba	dibenzylideneacetone or 1,5-diphenylpenta-1,4-dien-3-one
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DH	dehydratase
DIBAL	diisobutylaluminium hydride (DiBAlH, DIBAL-H or DIBALH)
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
equiv	equivalent(s)
Et	ethyl
GI_{50}	median growth inhibition concentration

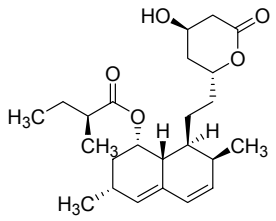
h	hour(s)
hexane	*n*-hexane
HMDS	hexamethyldisilazane, bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide (HMPT, hempa, hexametapol)
HPLC	high performance liquid chromatography
HRMS ESI	high resolution mass spectroscopy (electrospray ionization)
IC_{50}	the half maximal inhibitory concentration
inhib.	inhibitor
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide, potassium hexamethyldisilazide
KR	ketoreductase
KS	ketoacetyl synthase
LA	Lewis acid
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Lit. or lit.	literature
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl, 2,4,6-trimethylphenyl
MOM	methoxymethyl
mp	melting point
MTBE	methyl *tert*-butyl ether
MTM	methylthiomethyl
NAD^+	nicotinamide adenine dinucleotide
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement and exchange spectroscopy
Nu	nucleophiles
PG	protecting group
Ph	phenyl
PKS	polyketide synthase
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl, tosyl
UV	ultraviolet light, usually 254 nm

1 Introduction

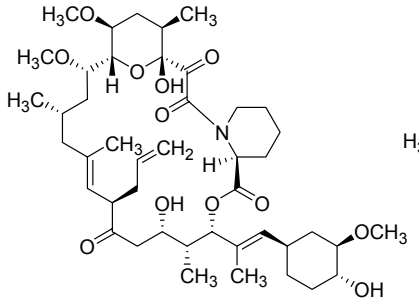
1.1 Natural products in drug discovery

The ability of small organic molecules to interact with specific macromolecules of living organisms makes them useful, both as tools to understand biological processes, and as valuable agents to treat health disorders. The most remarkable feature of natural products is the diversity of chemical structures, which reflects the diversity of enzymes and genes responsible for their biosynthesis. Natural products, which can be identified in screens of extracts, possess useful and often specific macromolecule-perturbing properties. These are reasons why natural products have become the target of new drug discovery. Cholesterol-lowering drugs (**1**), immunosuppressors (**2** and **4**), antibiotics (**3** and **5**) and antitumor agents (**6**) are representative examples (Figure 1).



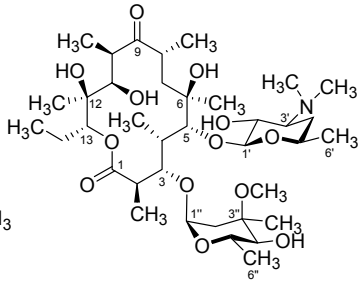
Mevinolin (**1**)

competitive inhibitor of hydroxymethylglutaryl-CoA reductase and cholesterol-lowering agent
Source: *Aspergillus terreus* (fungal cultures)



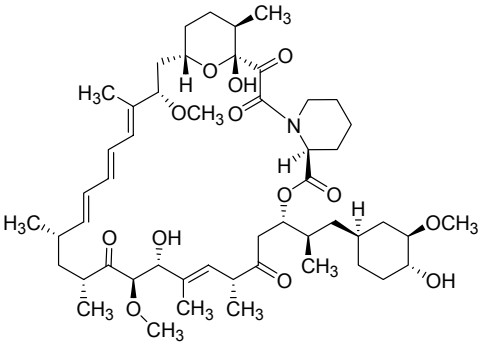
Fujimycin (**2**)

immunosuppressive drug in transplantation surgery
Source: *Streptomyces tsukubaensis* (bacterial)



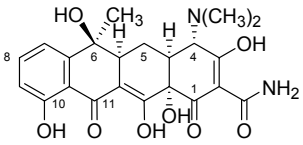
Erythromycin A (**3**)

antibiotic for treatment of respiratory infections, outbreaks of chlamydia, syphilis, acne and gonorrhea
Source: *Actinomyces Saccaropolyspora erythraea* (bacterial)



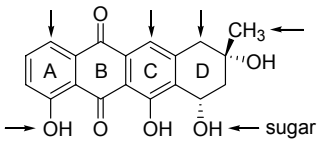
Rapamycin or **Sirolimus** (**4**)

T- and B-cells blocker, immunosuppressant in transplantation surgery
Source: *Streptomyces hygroscopicus* (bacterial)



Tetracyclin (**5**)

broad-spectrum antibiotic
Source: *Streptomyces* (bacterial)



Anthracyclines (**6**)

inhibitor of DNA and RNA synthesis; prevents the replication of growing cells; used to treat a wide range of cancers
Source: *Streptomyces* (bacterial)

Figure 1. Selected polyketides that have found application as medicines

Once an active natural product has been identified, the compound often becomes a target for chemical synthesis. Growing demand for the cost effective synthesis of complex substances results in the development of new synthetic methods and the perfection of spectroscopic and analytical techniques.

1.2 From fatty acids to polyketides

Polyketides (or *acetogenines*) were named in 1890s to refer to a structurally diverse group of natural products that contain carbonyl and alcohol functional groups, separated by methylene groups.[1]

The term "polyketide" may be used in different senses.[2] One covers a wide range of compounds including fatty acids while the other is limited to non-fatty acid natural products, biosynthetically derived from fatty acids. Common fatty acids are *primary metabolites*. Non-fatty acid polyketides are *secondary metabolites* and they are the subject of the study for natural products chemists.

Investigations on the molecular biology of polyketide biosynthesis have demonstrated that genes of fatty acid synthases (FAS) and microbial polyketide synthases (PKSs) have a significant homology and they are recognized to have evolved from the same prototype gene. The chain elongation mechanism in the biosynthesis of such polyketides as erythromycin A (**3**) and rapamycin (**4**) is basically the same as that for FAS. It is therefore reasonable that fatty acids are included within polyketides when their biosynthesis is discussed at the enzyme and gene levels. At the same time there are significant differences in the biosynthesis of polyketides in microorganisms, fungi and plants.

For *E. coli.* bacteria, for example, the synthesis of fatty acids involves eight enzymes. Important for the biosynthesis are coenzyme A (CoA) (**7**) and acyl carrier protein (ACP) (**8**), both possessing a terminal –SH function, crucial for the biosynthetic process (Figure 2).

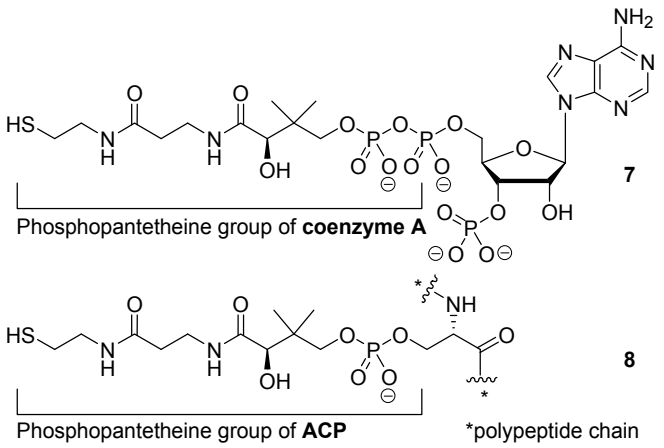
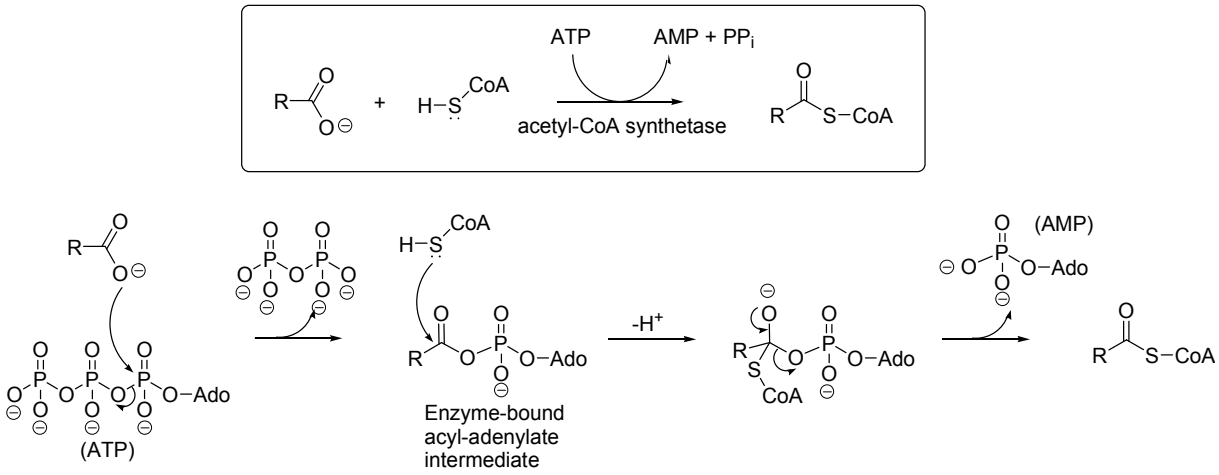


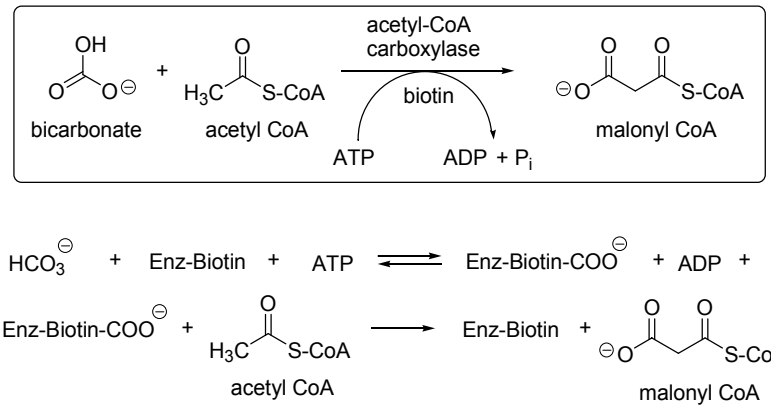
Figure 2. Phosphopantetheine in coenzyme A and acyl carrier protein (ACP)

The CoA activates a carboxylate anion towards nucleophilic substitution by its conversion into a thioester. This process is catalyzed by acyl-CoA synthase and can be considered as the first stage of the fatty acid synthesis (Scheme 1). It is worth to note, that four different acyl-CoA synthases are found in cells, with specificities for fatty acids whose chains are short (<C_6), medium (C_{6-12}), long (C_{12-16}), or very long (>C_{16}).



Scheme 1. Mechanism of the formation of acyl-CoA, catalyzed by acyl-CoA synthase

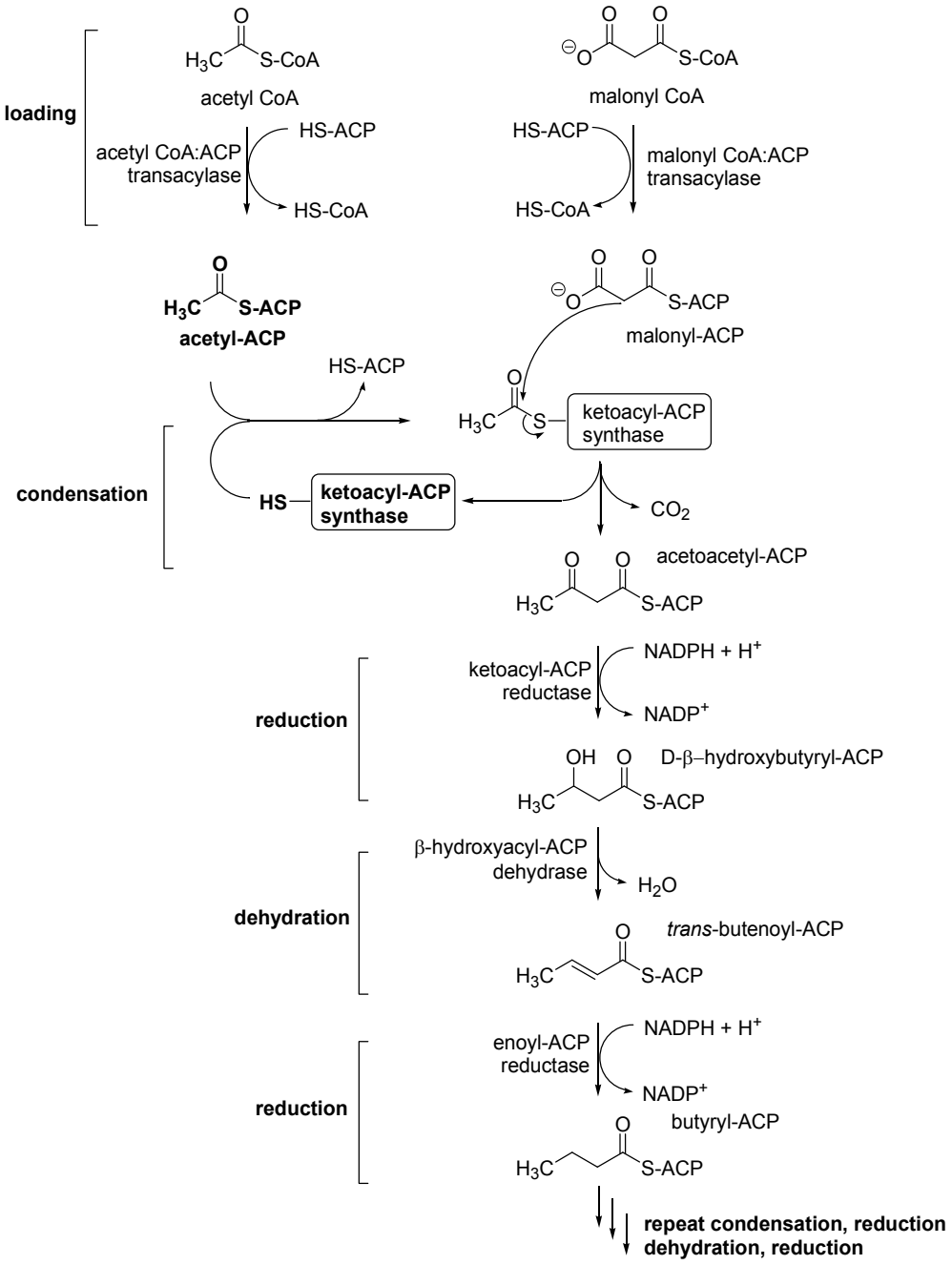
The second stage consists of the carboxylation of acetyl CoA to form malonyl CoA in a reaction catalyzed by the biotin-dependent enzyme acetyl-CoA carboxylase. This process is the key regulatory step of fatty acid synthesis (Scheme 2).



Scheme 2. Mechanism of acetyl-CoA carboxylase

In *Escherichia coli*, three separate protein subunits carry out this transformation: a carrier protein called biotin carboxyl carrier protein (BCCP) and two enzymes, a biotin carboxylase and a transcarboxylase. In animals and yeast, all these functions are combined and performed by a single modular protein.

Assembly of fatty acids may be divided into five stages: (1) loading, (2) condensation, (3) reduction, (4) dehydration and (5) a further reduction (Scheme 3).



Scheme 3. Stages in the biosynthesis of fatty acids from acetyl CoA and malonyl CoA in *E. coli*

1. Loading: two enzymes, acetyl CoA:ACP transacylase and malonyl CoA:ACP transacylase, are required for the loading steps, in which acetyl CoA and malonyl CoA are transesterified with ACP.

2. Condensation: ketoacyl-ACP synthase (KS), also called condensing enzyme, accepts an acetyl group from acetyl-ACP, and ACP-SH is released. KS then catalyzes transfer of the acetyl group to malonyl-ACP, evolving CO_2 and forming acetoacetyl-ACP.

3. Reduction: the ketone of acetoacetyl-ACP is converted to an alcohol, forming D-β-hydroxybutyryl-ACP, in an NADPH-dependent reaction catalyzed by ketoacyl-ACP reductase.

4. Dehydration: a dehydrase catalyzes the removal of water, with formation of a double bond.

5. Further reduction: the product of dehydration, *trans*-butenoyl-ACP, undergoes reduction to form butyryl-ACP, in a reaction catalyzed by NADPH-dependant enoyl-ACP reductase.

Steps **2-5** are repeated until a C_{16} palmitoyl group is formed. A thiolase enzyme catalyzes hydrolytic cleavage of palmitoyl-ACP and furnishes palmitate.

Complex polyketides are synthesized by the essentially the same basic mechanism that was discussed in above**.** A series of decarboxylative condensation reactions between small carboxylic acid units and malonate proceed under enzymatic catalysis with the so called polyketide synthases (PKSs).[a,3]

1.3 Biosynthesis of polyketides by modular synthases

Known PKSs have been classified into three main types.[4] Type I PKSs (or noniterative PKS) are multifunctional enzymes, organized into modules. Each module is responsible for a set of certain non-iteratively acting activities in a single cycle of the chain-elongation sequence, as exemplified in a simplified form by the biosynthesis of erythromycin A (**3**) (Scheme 4).[5] Type II PKSs are multienzyme complexes that carry a single set of iteratively acting activities, as exemplified by the tetracenomycin C (**9**) biosynthesis (Scheme 4). Type III PKSs,[b] are homodimeric enzymes. A single III PKS catalyzes iterative condensation of small fatty acids, as exemplified by the biosynthesis of flavolin (**10**) (Scheme 4).

Type I and II PKSs use acyl carrier protein (ACP) to activate the acyl CoA substrates whereas type III PKSs act directly on the acyl CoA substrates without ACP involvement. Despite these mechanistic differences, biosynthesis catalyzed by any PKSs proceeds through sequential decarboxylative condensation of acyl CoA precursors, and the ketoacetyl synthase (KS) catalyzes the C-C bond-forming step.

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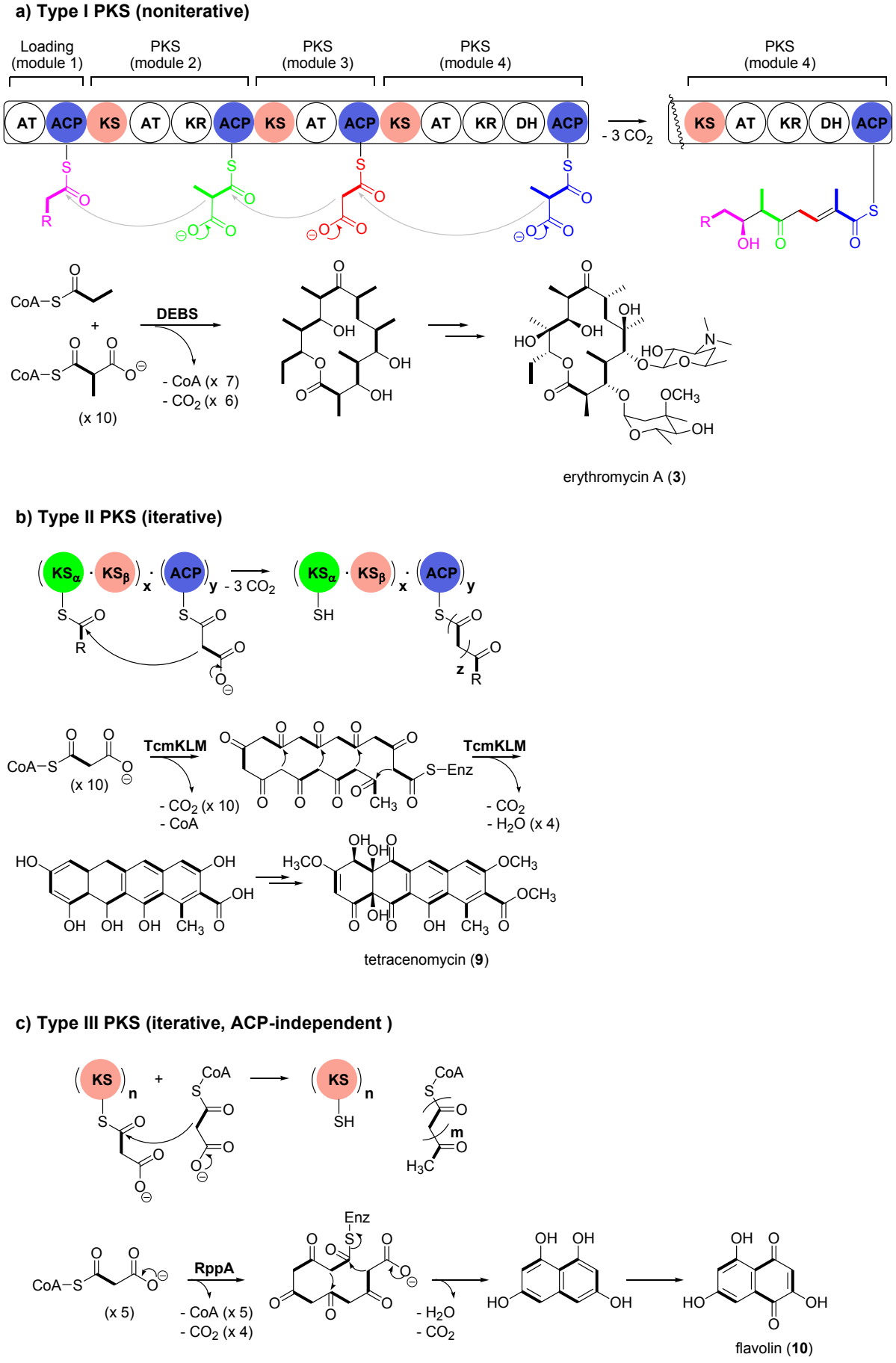
[a]) PKSs are large multienzyme systems (M_r = 100-10000 kDa).

[b]) Also known as chalcone synthase-like PKSs.



Scheme 4. The three types of PKSs in the biosynthesis of polyketides

Since the first reports of bacterial type I PKS in 1990,[5] type II PKS in 1984[6] and type III PKS in 1999[7] the PKS paradigms have helped the scientific community to classify and explain the vast structural diversity observed for polyketide natural products, and the biotechnological platform to produce 'unnatural' natural products by combination of biosynthetic methods with engineered PKSs.[8]

There are about 7,000 identified polyketides, but this represents only a small fraction of what nature is capable of producing.[8] Current and future research on polyketide biosynthesis will be driven by the unparalleled biological activities and commercial value[c] of natural products, which remain the most promising candidates for new drug discovery. Remarkable versatility and amenability of PKSs allow the synthesis of novel compounds, difficult to access by conventional synthetic methods, by *combinatorial biosynthesis*.[8] Integration of biological tools with chemical knowledge will evidently open new frontiers both for science and industry.

1.4 Secondary metabolites and the OSMAC methodology

It has been long known that cultivation conditions have strong influence on the production of microbial products. In nature, a changing environment results into changes in transcriptome, proteome, and finally metabolome. In the course of evolution these changes allow an organism to adapt to the new conditions and to survive. One can speculate on the function of secondary metabolites.[9] Some may bring clear advantage for a living organism, others – not.

In fact, any change of a cultivating parameter may influence every single biosynthetic step. Since there is a huge number of such steps on translational, transcriptional or enzymatic levels, the approach provides an endless number of possible combinations that results into a vast number of microbial products produced in this way. Systematic alteration of cultivating parameters (media composition, pH, temperature, addition of enzyme inhibitors, salts, oxygen supply even the type of culture vessel etc.) is a simple and natural approach to influence the production of secondary metabolites and, probably, to obtain new ones.[10] This way of releasing nature's chemical diversity has been termed by Zeeck *et al.* an OSMAC (**O**ne **S**train – **MA**ny **C**ompounds) approach, which resulted from the observation that small changes in the cultivation conditions can completely shift the metabolic profile of microorganisms.[11,12]

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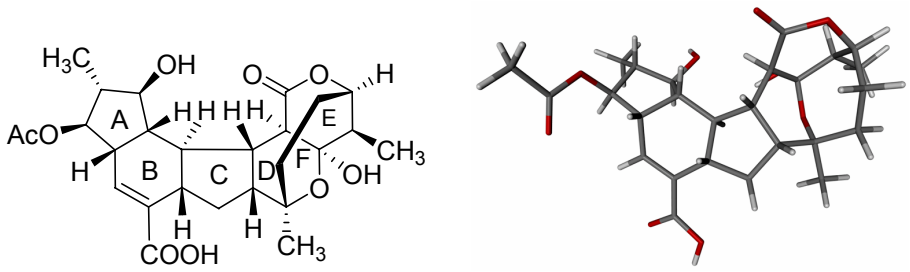
[c]) The market of polyketides is estimated to exceed $10 billion per annum (http://www.bio.cam.ac.uk/~pflgroup/research.htm).

1.5 Hexacyclinic acid - a polyketide from the *Streptomyces*

In 2000 Zeeck *et al.* described the isolation of hexacyclinic acid (**11,** Figure 3), a new natural product with an unusual structure, from *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013).[12]

Following the OSMAC approach strain S1013 has been cultivated in different culture vessels, using a rolled oats medium. In the extract of culture filtrate from a 10 L fermenter a new metabolite has been detected. The substance was identified by TLC (R_f = 0.3 in $CHCl_3$/MeOH 9:1) as an intensive blue spot when anisaldehyde/H_2SO_4 was used as a staining reagent. Unfortunately, low yields obtained did not allow the complete structure elucidation.

Optimization of the fermentation process was conducted. The influence of different alkali metal halides on was investigated. It was found that sodium bromide present in a concentration of 1 g·L^{-1} in the cultivating medium resulted in 10-20 fold increased production of the unknown metabolite. In special fermentation vessels the yield of the compound rose to 13 mg·L^{-1}. Additional optimization of the C-source allowed to obtain up to 56 mg·L^{-1} of the natural product. These efforts allowed the isolation of the substance in reasonable quantities, and structure elucidation using spectroscopic methods (^{1}H and ^{13}C NMR, HRMS ESI, COSY, HSQC, HMBC, NOESY and X-ray structural analysis).[13] Absolute stereochemistry could be defined using advanced Mosher's ester methodology.[14]



hexacyclinic acid (**11**)

Figure 3. Hexacyclinic acid (**11**), a new polyketide from *Streptomyces cellulosae* subsp. *Griseorubiginosus* (strain S1013)[d]

Hexacyclinic acid showed weak cytotoxicity towards three tested cell lines (HM02, HEPG2 and MCF7) with GI_{50} values as low as 14.0 µmol·L^{-1}.

In order get insight into the biosynthesis of **11**, feeding experiments were conducted.[15] Feeding of the growing strain with [1-^{13}C] acetate and comparing ^{13}C NMR of the so obtained

[d]) 3D structure of hexacyclinic acid representing a minimum of potential energy was created and optimized (MM2 method, RMS gradient = 0.01) using Chem3D® software (CambridgeSoft Corp.).

metabolite with the original sample revealed signal enhancement for C-1, C-3, C-8, C-16, C-18 and C-27. The increment of values for specific incorporations of C-5 and C-12 was within the experimental error. Another feeding experiment with [1-^{13}C] propionate showed strong enrichment of C-5, C-10, C-14 an C-22. Combination of these two experiments led to the conclusion that hexacyclinic acid is a polyketide built by seven acetate and four propionate units (Figure 4).

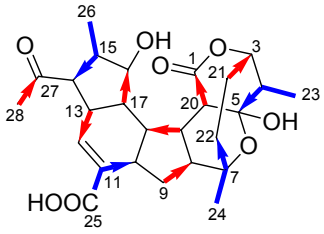
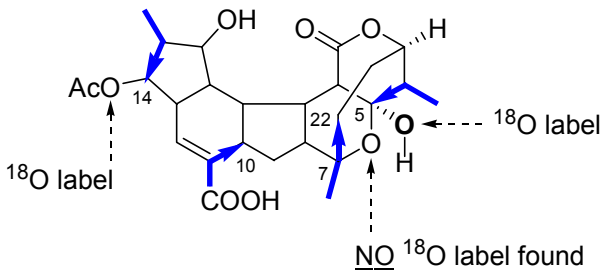


Figure 4. The polyketide nature of hexacyclinic acid was revealed from the labeling pattern

At this stage hexacyclinic acid was believed to arise from a single polyketide chain precursor built by a modular type I polyketide synthase (see Section 1.3). The transformations that could lead from this precursor to **11** were not clear. It was nevertheless proposed that these could be an intramolecular Diels-Alder reaction, aldol reaction, lactonization and ketalization.

Since more understanding of the biosynthetic pathways leading to **11** was desired Zeeck *et al.* conducted advanced feeding experiments.[15] This time the strain was fed with [1-^{13}C, $^{18}O_2$] labelled propionate.

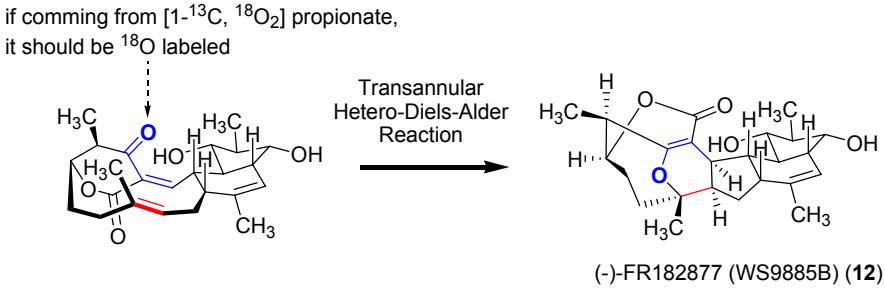


Position	Incorporation ^{13}C (%)	$^{18}O/^{16}O$ (%)
C-5	31.9	70.1
C-10	25.5	-
C-14	32.7	71.3
C-22	22.8	-

Figure 5. Results of the feeding experiments with [1-^{13}C, $^{18}O_2$] propionate

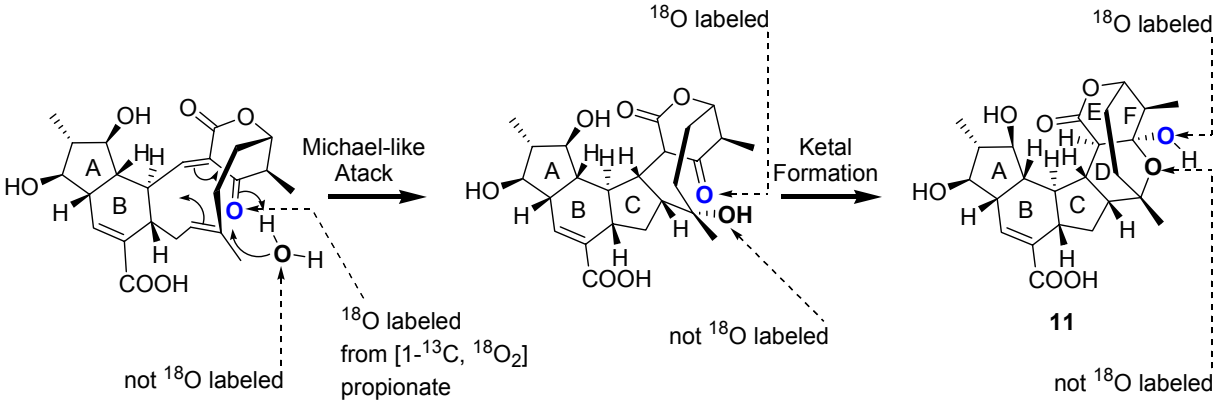
As a result of this experiment, it was found that C-5 and C-14 were directly connected to an ^{18}O enriched oxygen (Figure 5.). Interestingly, no ^{18}O incorporation was found near to C-7 suggesting that hemiketal OH was ^{18}O enriched.

Based on these results Zeeck *et al.* suggested that the D-ring of hexacyclinic acid was probably not formed in a hetero Diels-Alder reaction, as was proposed for a related natural product, (-)-FR182877 (**12**) (Scheme 5),[51a] otherwise there should have been an ^{18}O label at C-7.



Scheme 5. Proposed biosynthetic approach towards (-)-FR182877 (WS9885B) that features transannular hetero Diels-Alder reaction (Sorensen *et al*.)

Zeeck *et al.* proposed a biosynthesis featuring a vinylogous Prins reaction in the formation of the C-ring. In this transformation the trisubstituted alkene acts as a nucleophile adding to the Michael acceptor followed by addition of water (Scheme 6).



Scheme 6. Possible pathway in the biosynthesis of hexacyclinic acid (Zeeck *et al.*)

Especially interesting and valuable for the understanding of the biosyntheses of both (-)-FR182877 (**12**) and hexacyclinic acid (**11**) could be a feeding experiment of the *Streptomyces* strain producing (-)-FR182877 with [1-^{13}C, $^{18}O_2$] labelled propionate. Investigation of the ^{18}O label incorporation could support or reject the proposed biosynthesis of hexacyclinic acid. To the best of our knowledge such experiment has not hitherto been described.

1.6 Structurally related compounds

Bicyclo[4.3.0]nonane structural fragment found in hexacyclinic acid (**11**) and (-)-FR182877 (**12**) is often found in metabolites produced by the *Streptomyces* bacteria. Selected examples are presented in Figure 6.

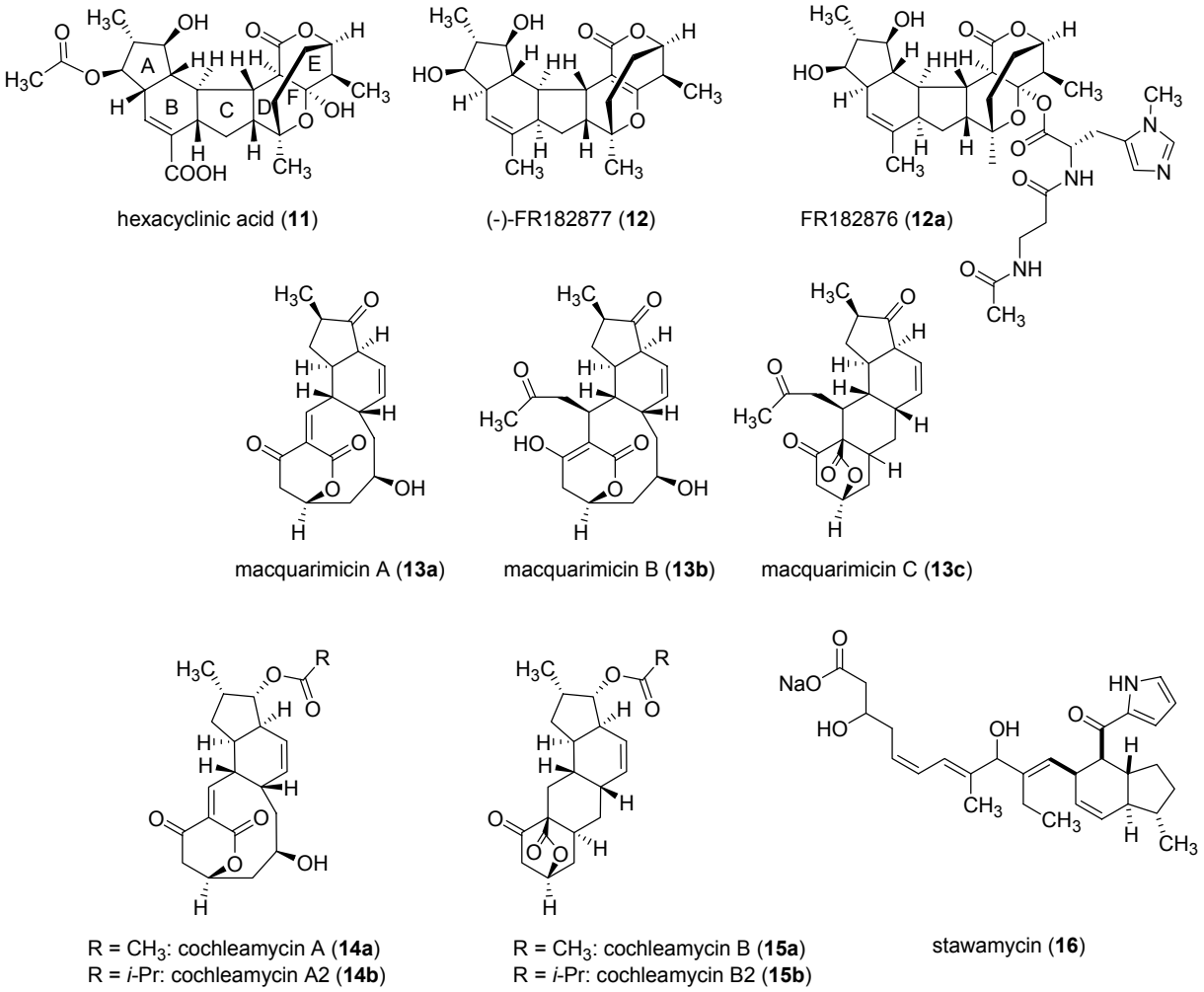


Figure 6. Selected natural products from the *Streptomyces*

The macquarimicins A-C (**13a**-**13c**, Figure 6) were isolated from *Micromonospora chalcea* by researchers at Abbott Laboratories in 1995.[16]

Macquarimicin A (**13a**) was isolated as a very weak antibacterial agent, while macquarimicins B (**13b**) and C (**13c**) were found to exhibit cytotoxicity against the P388 leukemia cell line (IC_{50} is 0.3 and 30.0 μg/mL, respectively).[16a] In 1999, researchers at Sankyo Co. disclosed that **13a** is a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase).[17] An improved understanding of SMase-dependent signaling may provide novel strategies for the treatment of inflammatory and neurodegenerative diseases, as well as cancer. Thus, selective inhibitors of N-SMase are used to gain insight into the enzyme mechanism, which is

currently unknown, and more importantly into the experimental therapy of such diseases. The total synthesis of macquarimicins inspired by a biosynthetic pathway and using an intramolecular Diels-Alder approach was successfully accomplished by Tadano and co-workers.[18]

Another natural product of this family, cochleamycin A (**14a**, Figure 6), was isolated from *Streptomyces* DT136 in 1992 by Shindo and co-workers.[19] In addition to displaying antimicrobial activity against gram-positive bacteria, cochleamycin A is cytotoxic toward a variety of tumor cell lines.[e,20] The total synthesis of the compound was described by the group of W. Roush in 2004.[21]

In 1995, stawamycin (**16**),[22] a new natural product from the pyrroloketoindane family was isolated by Miao *et al.* from a liquid culture of *Streptomyces* sp. and displayed moderate inhibitory activity against the binding of the Epstein-Barr virus[f] BZLF1 transcription factor to DNA with IC_{50} = 50 μM in a DNA binding assay (Figure 6).

(-)-FR182877 or cyclostreptin, a substance formerly known as WS9885B and described by Fujisawa Pharmaceutical Company,[23] has been identified in screens as an agent that binds and stabilizes cellular microtubules.[24] Formation of microtubules involves polymerization of heterodimeric α/β-tubulin subunits which is regulated by several microtubule-associated proteins and involves a hydrolysis of guanosine 5'-triphosphate.[25] Intact microtubule function is required for the formation and functioning of the mitotic spindle. That is why cells treated with agents that bind either tubulin subunits or polymerized microtubules exhibit alterations in spindle formation leading to arrest at the G2/M phase of the cell cycle, which is associated with the induction of apoptosis.[26] Compounds that target microtubules are potent cytotoxic agents, exemplified by a variety of plant and marine natural products. Representative examples are epothilones,[27] discodermolide,[28] eleutherobins,[29] dolastatins,[30] cryptophycins,[31] indanocine,[32] halicondrin B,[33] peloruside A,[34] laulimalide[35] and paclitaxel.[38] Inhibitors of microtubule assembly may also show prominent anti-tumor activities, as exemplified by vinblastine.[36] Important that not all compounds that affect microtubule function are useful as anticancer drugs (e.g., colchicine). Furthermore, recent data suggest that at least a part of the anticancer activity exhibited by this class of drugs involves antiangiogenic effects on tumorassociated endothelial cells.[37]

Preclinical studies indicated that FR182877 binds and stabilizes microtubules in a manner similar but not identical to that of paclitaxel[38] and the epothilones.[39]

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[e]) IC_{50} = 1.6 μg/mL for P388 leukemia cells.

[f]) A human herpes virus that infects lymphocytes and epithelial cells. *See* Dimmock, N. J.; Primrose, S. B. In *Introduction to Modern Virology*, 4th ed.; Blackwell Science: Oxford, **1994**, Chapter 17, p. 266-267.

The molecule of (-)-FR182877 features a strained *anti*-Bredt bridgehead olefin that is believed to be the active site for the covalent binding to tubulin.

In 2004 the scientists from the Fujisawa Pharmaceutical Company, reported on the isolation and structure elucidation of FR182876 (**12a**), a new water soluble natural product, produced by the *Streptomyces*.[40] 3-Methylhistidine moiety found in FR182876, is believed to contribute to both solubility in water and activity in promoting tubulin polymerization. **12a** showed potent cytotoxicity against a panel of cancer cells at concentrations of 28-75 ng/mL.

Natural products **11-16**, possessing bicyclo[4.3.0]nonane skeleton may share a biosynthetic pathway that involves intramolecular Diels-Alder (IMDA) reaction of polyketide intermediates.[19d,50,41]

Oikawa *et al.* proposed that Diels-Alder reactions may be involved in the biosynthesis of more than a hundred of natural products.[41b] However, to date, only three natural enzymes, solanapyrone synthase (SPS),[42] lovastatin nonaketide synthase (LNKS),[43] and macrophomate synthase (MPS),[44] have been shown to catalyze Diels-Alder reactions in purified or partially purified form.[45] At the same time, definitive proof that MPS and the other two enzymes catalyze the Diels-Alder reaction remains somewhat elusive.[46]

In 2003, the group of Tanaka and Oikawa elucidated the structure of Diels-Alderase for the first time by X-ray crystallography of MPS.[47]

Artificial ribozymes that catalyze the Diels-Alder reaction have been described.[48]

Details of the biosyntheses of **11** and **12** are still unclear. Therefore, the development of a synthetic methodology may help to elucidate the details by supplying synthetic probes. This intriguing feature of this class of natural products, combined with biological activities and a formidable molecular architecture, makes them highly attractive targets for synthetic chemists.

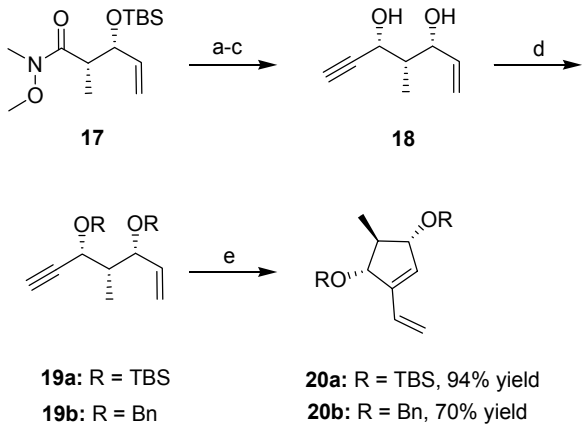
2 Discussion

2.1 Synthetic progress towards hexacyclinic acid and related substances

In 1998 scientists of the Fujisawa Pharmaceutical Company reported on the discovery of a novel microtubulin stabilizing agent, WS9885B (**12**), later called as FR182877.[23] Fujisawa scientists originally incorrectly assigned **12** with the opposite absolute configuration to that shown in Figure 6. Their assignment based on the Mosher ester method was later corrected.[49] In 1999, Sorensen and co-workers reported the first synthetic study towards FR182877 (**12**) and proposed the biosynthetic pathway for the antibiotic.[50] The first total synthesis of FR182877 by Sorensen was actually that of the non-natural enantiomer.[51] Later the group elaborated an optimized synthesis to the naturally occurring enantiomer, (-)-FR182877.[52]
Soon after the synthesis of Sorensen, synthetic investigations towards hexacyclinic acid (**11**) and FR182877 (**12**) were reported by the groups of Evans,[53] Prunet,[55] Armstrong,[61] Nakada,[57] Clarke,[54,59] Roush,[58] Landais[72] and Kalesse.[69] These synthetic contributions will be discussed in this section.

2.2 Synthesis of the A-ring of hexacyclinic acid and (-)-FR182877 by Prunet *et. al.*

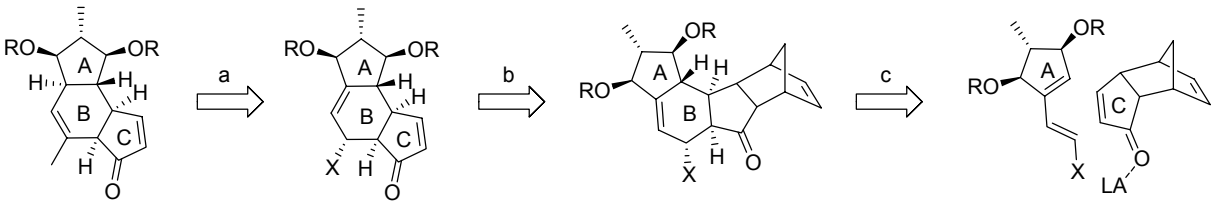
In the course of the studies towards the synthesis of (-)-FR182877 Prunet and co-workers[55] reported on the construction of the A-ring of the natural product exploiting the ring closing olefin metathesis (RCM) (Scheme 7).



(a) CH≡CMgBr, 75%; (b) HF/CH_3CN, 82%; (c) DIBAL, 89%; (d) TBSOTf, 2,6-lutidine, 82% or BnBr, NaH, TBAI, 90%; (e) Grubbs' II catalyst, CH_2Cl_2, 0.03 M, ethylene.

Scheme 7. RCM in the construction of the A-ring of (-)-FR182877 (Prunet *et al*.)

A synthetic approach towards the ABC cyclic fragment of FR182877 featuring a Diels-Alder reaction as the key step was also proposed (Scheme 8).[56]

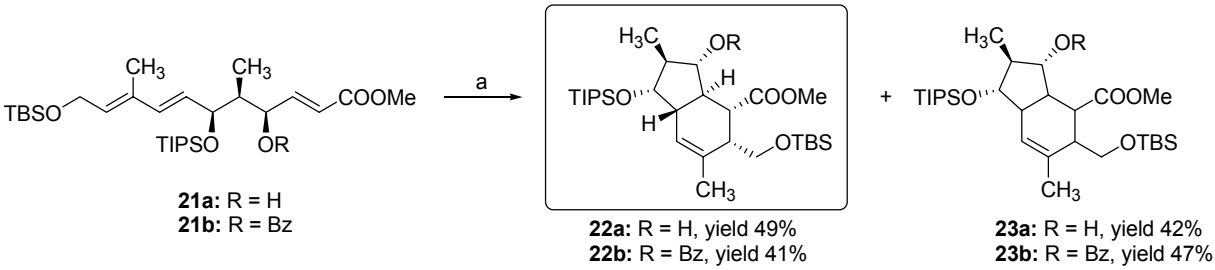


(a) Olefin migration; (b) retro Diels-Alder reaction; (c) Diels-Alder reaction.

Scheme 8. Retrosynthetic approach towards the ABC fragment of (-)-FR182877 (Prunet *et al.*)

2.3 Synthesis of the bicyclic AB-fragment of (+)-FR182877 by Nakada *et al.*

Nakada and co-workers[57] found that the intramolecular Diels-Alder reaction (IMDA) of the all-*trans* substituted precursor **21** proceeds through the *endo*- transition state furnishing the cycloadduct with the relative stereochemistry corresponding to that of the AB cyclic fragment of (+)-FR182877 (Scheme 9).



21a: R = H
21b: R = Bz

22a: R = H, yield 49%
22b: R = Bz, yield 41%

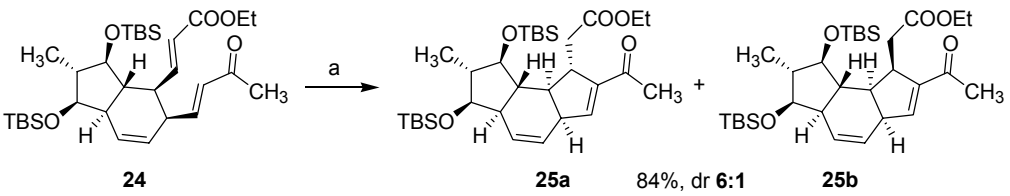
23a: R = H, yield 42%
23b: R = Bz, yield 47%

(a) 2,6-di-*tert*-butyl-4-methylphenol (BHT), 80 °C, 24 h.

Scheme 9. Synthesis of the AB cyclic fragment of (+)-FR182877 (Nakada *et al.*)

2.4 Construction of the C-ring of (-)-FR182877 by Roush *et al.*

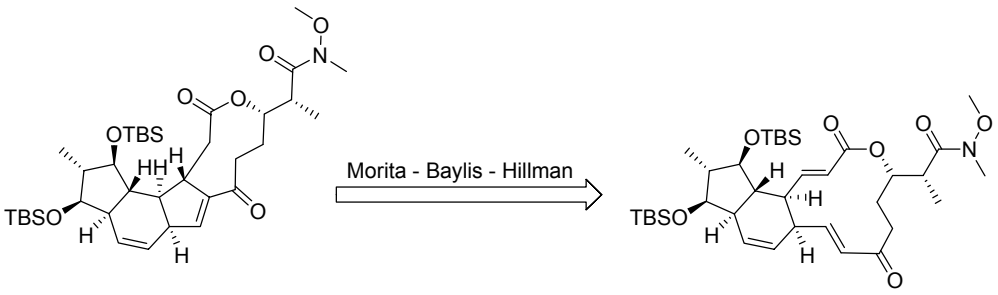
Roush[58] recognized that the C-ring of (-)-FR182877 may be constructed utilizing an intramolecular vinylogous Morita-Baylis-Hillman Reaction. Indeed, treatment of the acrylate **24** with PMe_3 (4 equiv) in THF/H_2O 3:1 resulted in the formation of **25a** and **25b** with 84% yield and 6:1 dr with the desired diastereomer favored (Scheme 10).



(a) 4 equiv PMe_3, 0.03 M *tert*-amyl alcohol, 20 h.

Scheme 10. Intramolecular vinylogous Morita-Baylis-Hillman reaction in the construction of the C-ring of (-)-FR182877 (Roush *et al.*)

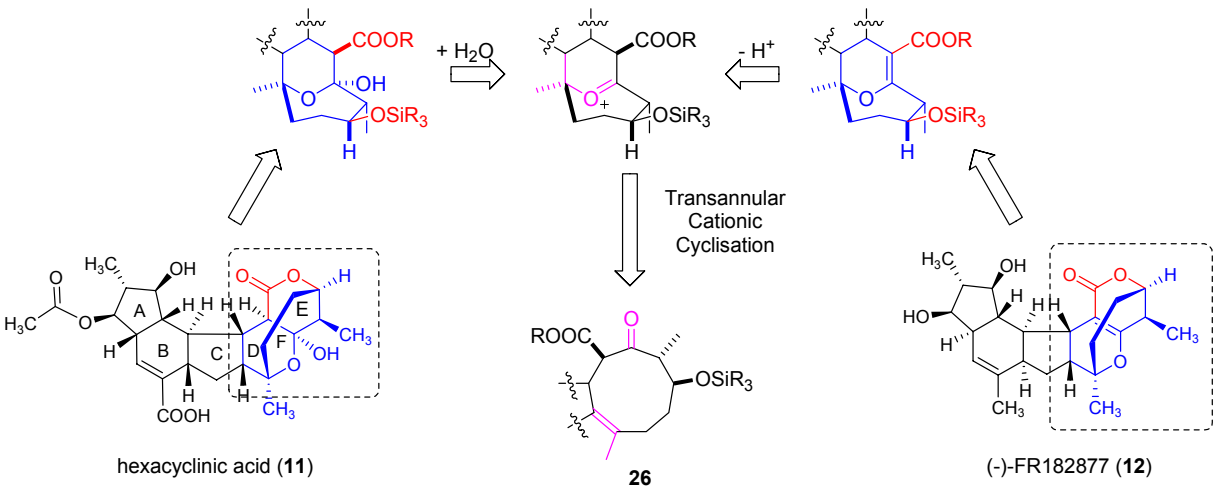
A retrosynthetic approach towards (-)-FR182877 based on the vinylogous Baylis-Hillman reaction has been proposed (Scheme 11).



Scheme 11. Retrosynthetic approach towards the ABC fragment of FR182877 (Roush *et al.*)

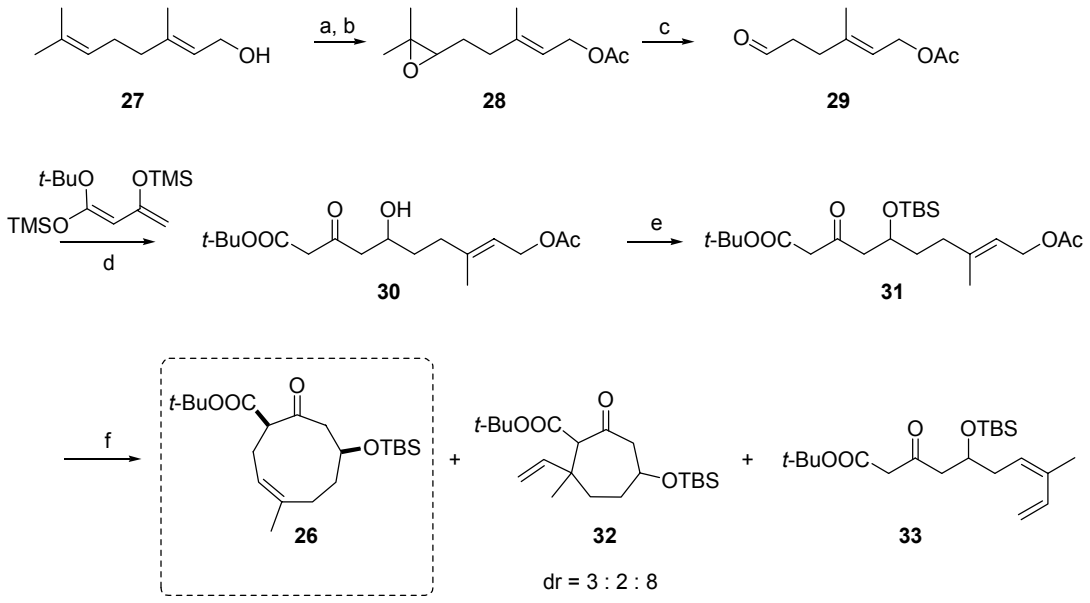
2.5 Synthesis of the DEF-cores of FR182877 and hexacyclinic acid by Clarke *et al.*

Clarke and co-workers proposed a universal approach to the DEF-ring fragments of both FR182877 and hexacyclinic acid utilizing a transannular cationic cyclization of a β-ketoester **26** to an appropriately positioned double bond (Scheme 12).[59]



Scheme 12. Construction of the DEF cores of hexacyclinic acid (**11**) and FR182877 (**12**)

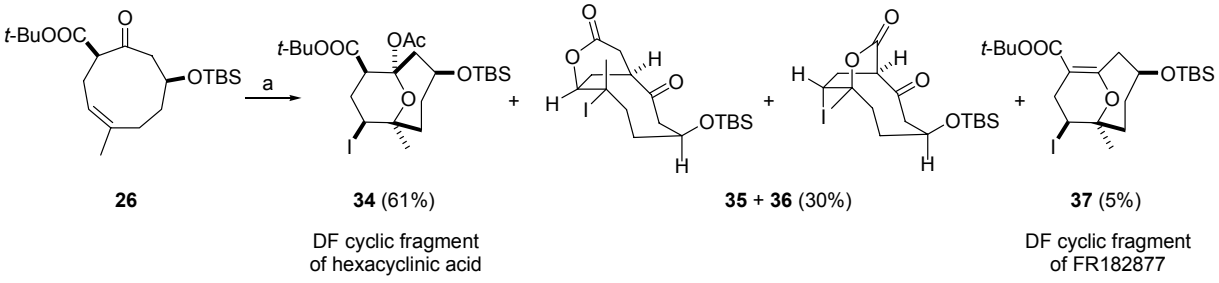
Carbocyclic precursor **26** was synthesized in six steps starting from nerol. The key step in the sequence is the intramolecular C-alkylation of a β-ketoester with a π-allyl Pd-complex.[60]



(a) DMAP, Ac_2O, Py, 18 h 100%; (b) *m*CPBA, 2 h, CH_2Cl_2, 0 °C, 85%; (c) HIO_4, THF/H_2O, 2 h, 0 °C, 81%; (d) $TiCl_4$, CH_2Cl_2, -78 °C, 3 h, 79%; (e) TBSOTf, Py, -35 °C, 8 h, 97%; (f) NaH, 5 mol% $Pd(PPh_3)_4$, 10 mol% dppf, THF, reflux.

Scheme 13. Construction of the nine-membered β-ketoester **26**

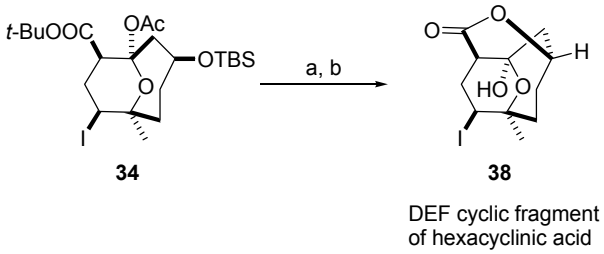
When **26** was treated with iodine and silver acetate in AcOH at rt transannular iodocyclization occurred (Scheme 14). Four products **34**, **35**, **36** and **37** were obtained. It is noteworthy that **34** embodies the DF-ring fragment of hexacyclinic acid whereas **37** – the DF cyclic fragment of FR182877.



(a) Iodine, silver acetate, AcOH, rt, 1 h.

Scheme 14. Transannular iodocyclization of β-ketoester **26**

After the removal of the protecting groups the lactonization was conducted under acidic conditions furnishing the DEF cyclic fragment of hexacyclinic acid (**38**) with excellent yield (Scheme 15).



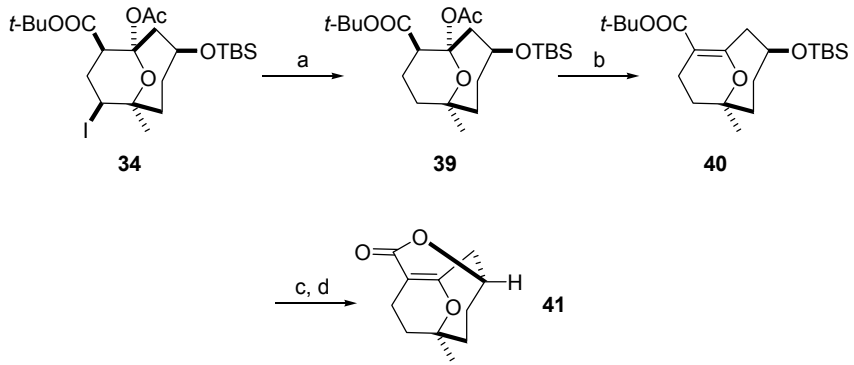
34 **38**

DEF cyclic fragment of hexacyclinic acid

(a) HF, CH_3CN, rt, 18 h, 97%; (b) TFA, CH_2Cl_2, rt, 4 days, 100%.

Scheme 15. Construction of the DEF core of hexacyclinic acid

Though the construction of the DEF core of FR182877 was straightforward from **37**, it was not possible to influence the course of the iodocyclization to favor the formation of **37**. The conversion of **34** into the DEF cyclic fragment of hexacyclinic acid (**41**) required 4 additional synthetic steps (Scheme 16).



34 **39** **40** **41**

DEF cyclic fragment of FR182877

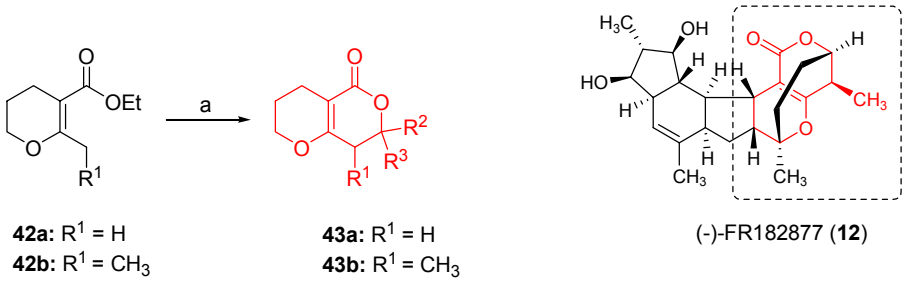
(a) $Pd(PPh_3)_4$, Bu_3N, HCO_2H, DMF, 23%; (b) DBU, CH_3CN, reflux, 93%; (c) 40% aqueous HF, CH_3CN, 100%; (d) TFA, CH_2Cl_2, 100%.

Scheme 16. Construction of the DEF core of FR182877

Though a universal approach towards the DEF-cyclic fragment of both **12** and **11** has been achieved, no synthetic strategy towards these natural products based on the transannular iodocyclization has been proposed.

2.6 Studies towards the DE fragment of FR182877 by Armstrong *et al.*

Armstrong and co-workers envisioned that the synthesis of the DE core of FR182877 may be achieved in one step starting from commercially available compound **42** (Scheme 17).[61]



42a: R^1 = H
42b: R^1 = CH_3

43a: R^1 = H
43b: R^1 = CH_3

(-)-FR182877 (**12**)

(a) LDA, $R^2C(O)R^3$, -22 °C overnight then aqueous workup.

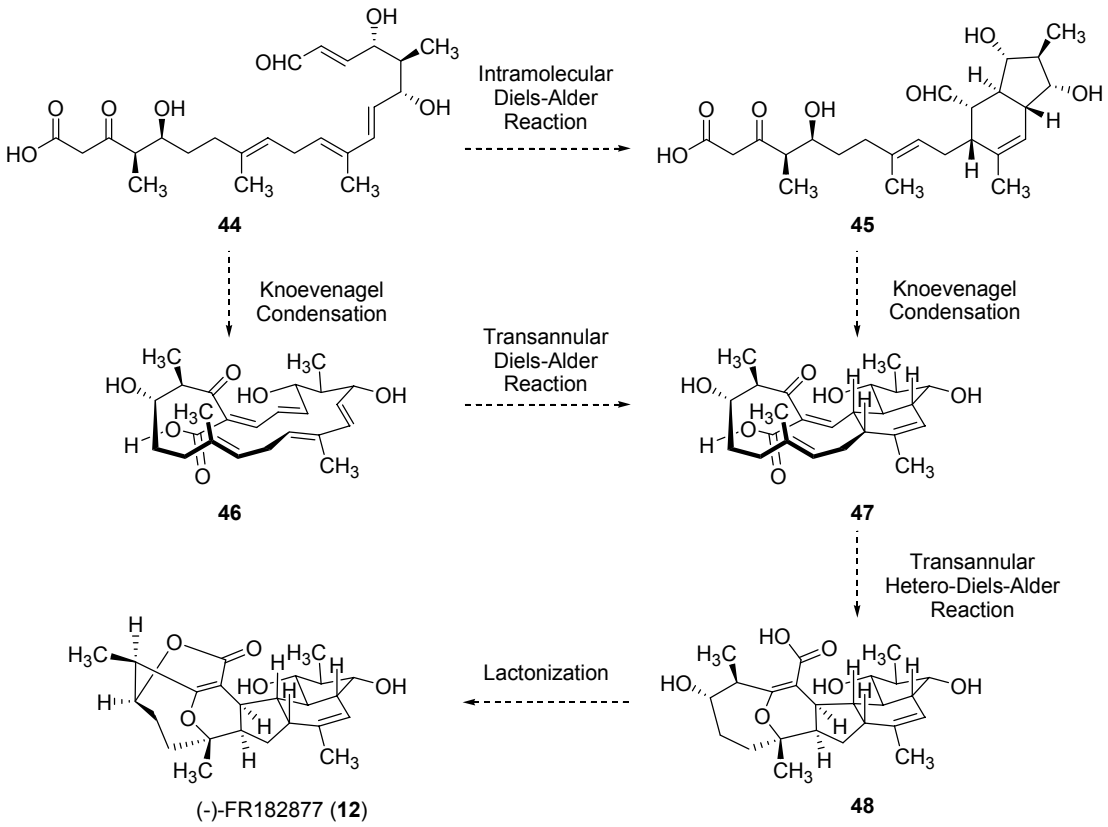
Scheme 17. Synthesis of the DE core of FR182877 by Armstrong and co-workers

Reaction of a carbonyl compound with the γ-enolate generated from **42** furnished the product **43** in a yield of 40-80% after a standard aqueous workup. Aromatic and aliphatic aldehydes, ketones, cyclohexanone, acrolein and diethyl ketomalonate were successfully used as carbonyl components.

No synthetic approach towards the natural product was proposed by Armstrong *et al*.

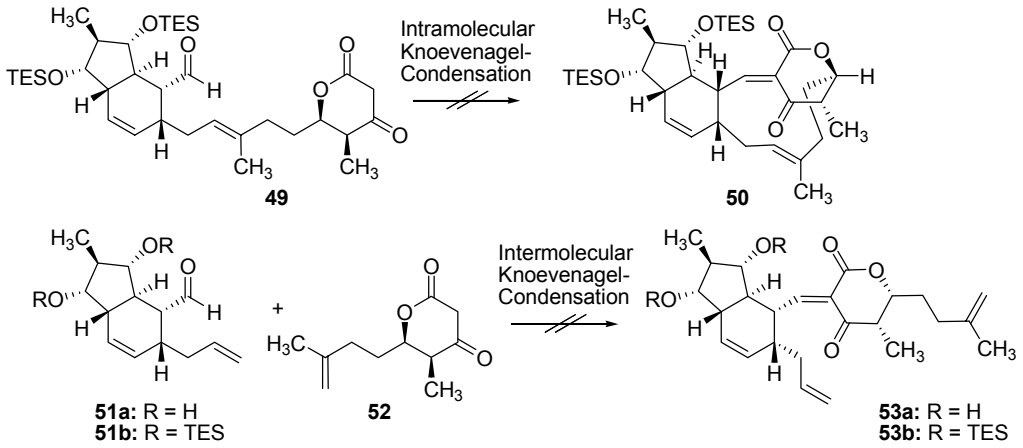
2.7 The total syntheses of (+)-FR182877 and (-)-FR182877 by Sorensen *et al.*

Sorensen *et al.* recognized that four of the six rings of the target molecule and seven of its stereocenters may be constructed in a sequence of two cycloadditions starting form polyunsaturated precursor **44** (Scheme 18). If **44** initially participated in an intramolecular Diels-Alder (IMDA) reaction with *endo*-selectivity to furnish **45**, subsequent intramolecular Knoevenagel condensation could then provide **47**, a substrate suitable for the transannular hetero-Diels-Alder reaction between the enone and the trisubstituted olefin that would provide **48**. Alternatively, **44** could first participate in a Knoevenagel condensation to afford the 19-membered cyclic pentaene **46** poised to undergo a tandem of a transannular Diels-Alder reaction (TADA) and the hetero-Diels-Alder reaction to furnish **48**. In either routes, a final lactonization would complete the target molecule **12**.



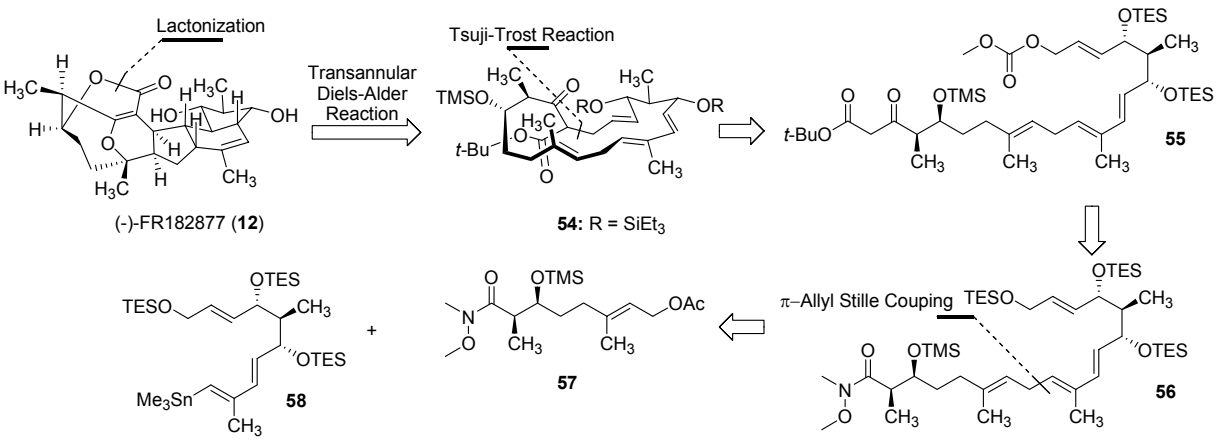
Scheme 18. Biomimetic retrosynthetic approach to (-)-FR182877 by Sorensen *et al.*

Early investigations revealed that compounds such as **45** could, indeed, be synthesized with the help of the intramolecular Diels-Alder reaction. Unfortunately, all attempts to accomplish intramolecular or intermolecular Knoevenagel condensation failed (Scheme 19).[50]



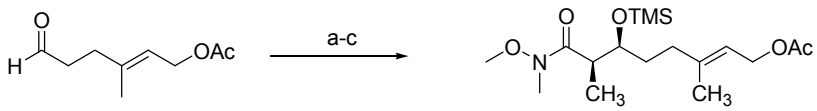
Scheme 19. Attempted intra- and intermolecular Knoevenagel condensation

Sorensen and co-workers decided access the 19-membered pentaene precursor **46** omitting the Knoevenagel condensation.[62] A new retrosynthetic approach to that end has been proposed (Scheme 20).



Scheme 20. Sorensen's retrosynthetic analysis of (-)-FR182877 (12)

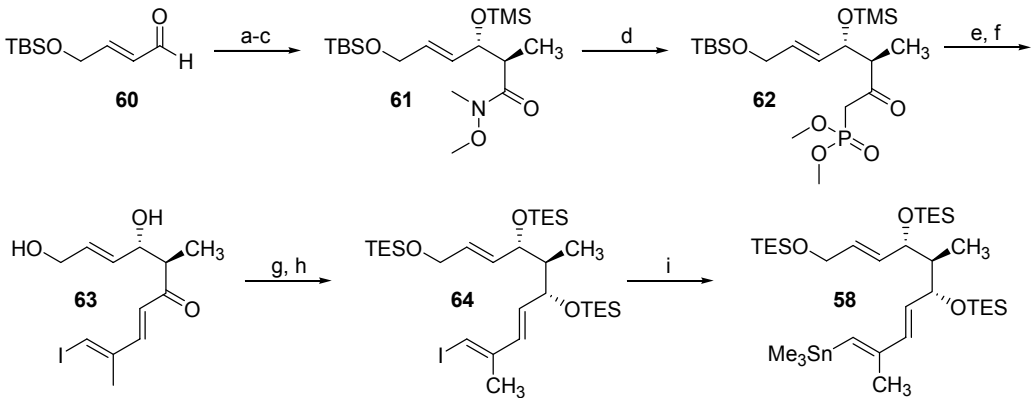
Cyclic tetraene **54** was recognized to be a suitable precursor for the pentaene **46** (Scheme **18**). Sorensen and co-workers expected to introduce the missing double bond via a selenation-elimination sequence.[63] Compound **54** had to be synthesized according to the Tsuji-Trost protocol[64] starting from the acyclic carbonate **55**, which may be accessible from the Weinreb amide **56**. This compound was divided into two precursors **57** and **58** of approximately equal size that have to be merged using the Pd-catalyzed π-allyl Stille reaction.[65] Both **57** and **58** were effectively constructed utilizing the Evans aldol protocol (Scheme 21 and Scheme 22).[66]



59 **57**

(a) (*R*)-4-phenyl-*N*-propionyloxazolidin-2-one, *n*-Bu_2BOTf, *i*-$PrNEt_2$, CH_2Cl_2, -78 °C, 1 h; -25 °C, 18 h; 0 °C, MeOH, 100%; (b) $NH(OCH_3)CH_3 \cdot HCl$, Me_3Al, THF, -15 °C; (c) TMSCl, imidazole, CH_2Cl_2, 25 °C, 25 min; 87% overall yield.

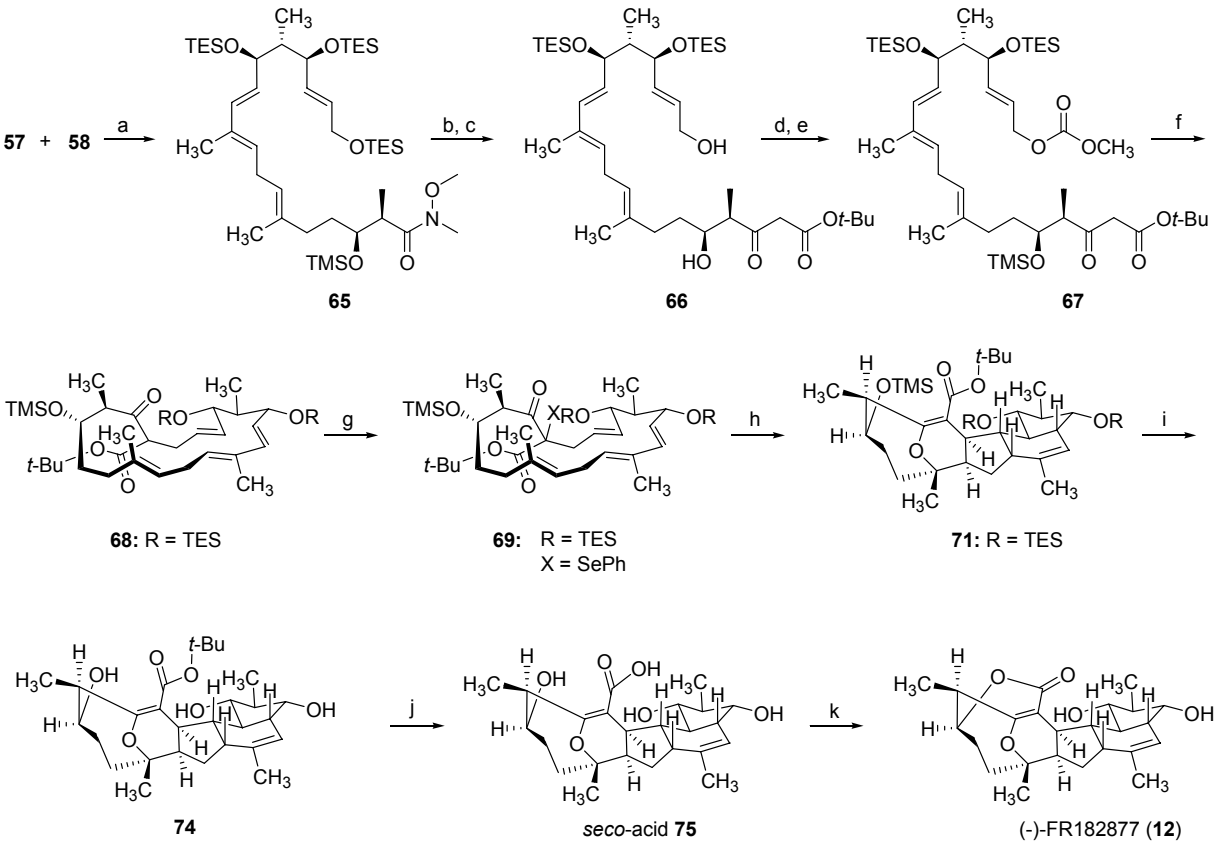
Scheme 21. Synthesis of the Weinreb amide **57**



(a) (*R*)-(-)-4-benzyl-*N*-propionyloxazolidin-2-one, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, -78 → 0 °C, 74%; (b) $NH(OCH_3)CH_3 \cdot HCl$, Me_3Al, THF, 0 °C, 98%; (c) TMSCl, imidazole, DMAP, CH_2Cl_2, 23 °C; (d) $LiCH_2P(O)(OMe)_2$, THF, -78 °C; (e) $Ba(OH)_2$, THF, then (*E*)-β-iodomethacrolein, THF/H_2O, 0 °C; (f) PPTS, MeOH, 23 °C, 83% over four steps; (g) Et_2BOMe, $NaBH_4$, THF/MeOH, -78 → 0 °C; (h) TESCl, imidazole, DMAP, CH_2Cl_2, 90% over two steps; (i) $Me_3SnSnMe_3$, $Pd(Ph_3P)_4$, *i*-Pr_2NEt, PhH, 80 °C, 95%.

Scheme 22. Synthesis of the vinylstannane **58**

According to the retrosynthetic plan the Stille coupling of **57** and **58** proceeded smoothly to provide the product **65** in 91% yield (Scheme 23).



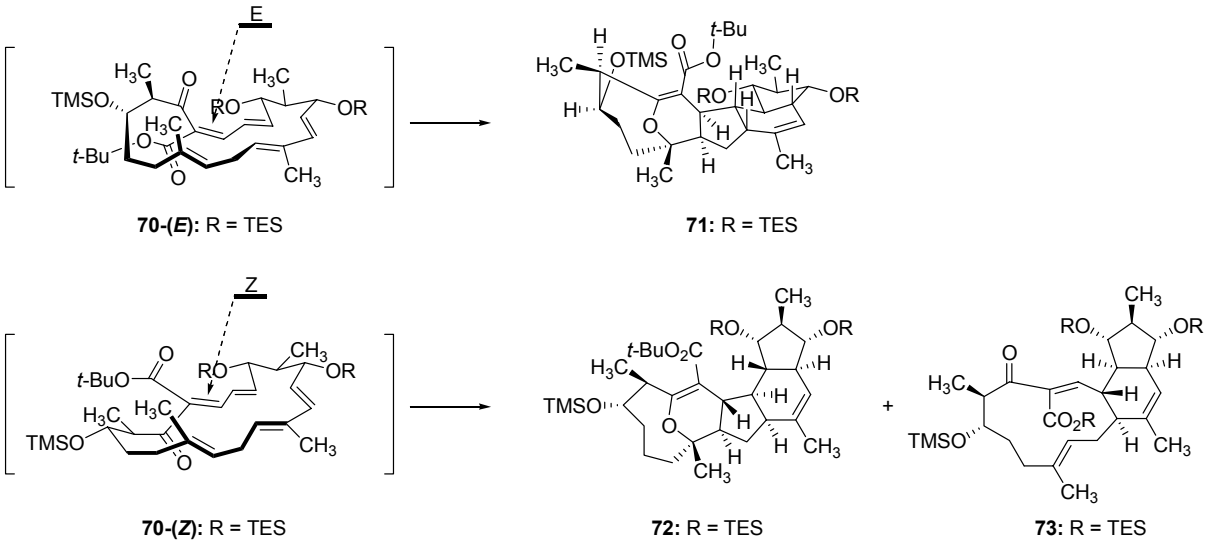
(a) Pd_2dba_3, LiCl, *i*-Pr_2NEt, NMP, 40 °C, 91%; (b) LDA, *t*-BuOAc, THF, -78 → 25 °C, 85%. (c) TBAF, THF, -30 → -10 °C; (d) MeOCOCl, pyridine, CH_2Cl_2, 25 °C; (e) TMSCl, imidazole, CH_2Cl_2, 25 °C, 82% over three steps; (f) 10 mol% Pd_2dba_3, THF (0.05 M), 45 °C, 60-85%; (g) NaHMDS, PhSeBr, Et_2O, 25 °C, < 1 min, 89%, 10:1 dr; (h) *m*CPBA, CH_2Cl_2, -78 °C, 1 min (*E*:*Z* = 2.2 : 1); $NaHCO_3$, CH_3Cl, 45 °C, 4 h, 61-66%; (i) PPTS, MeOH, 0 → 25 °C, 2 h, 100%; (j) TFA/CH_2Cl_2 9:1, 0 °C, 1 h, 96%; (k) Mukaiyama's reagent, Et_3N, CH_2Cl_2/CH_3CN 9:1, 25 °C, 76%.

Scheme 23. Completion of the total synthesis of (-)-FR182877 by Sorensen and co-workers

The Weinreb amide **65** was transferred into the keto ester **66** and the deprotected primary allylic alcohol was converted into carbonate **67** needed for the Tsuji-Trost reaction. Fortunately, when a diluted THF solution of **67** was stirred at 45 °C for 24 h with 10 mol% of Pd_2dba_3, product **68** was obtained in a 60-85% yield.

To introduce the double bond required for the tandem Diels-Alder/hetero-Diels-Alder sequence, **68** was treated with NaHMDS followed by PhSeBr providing a 10:1 diastereomeric mixture of products **69**. When this mixture was treated with *m*CPBA at -78 °C, oxidation-elimination sequence provided a 2.2:1 mixture of (*E*)- and (*Z*)-olefins **70**. Tandem transannular Diels-Alder/hetero-Diels-Alder reaction proceeded when the above diastereomeric mixture was heated in CH_3Cl/aqueous $NaHCO_3$ to furnish the cycloadduct **71**

in 61-66% yield along with **72** (8-15%) and **73** (8-15%) (Scheme 24). Both products are believed to derive from the (*Z*)-olefin obtained after the selenation - elimination sequence.



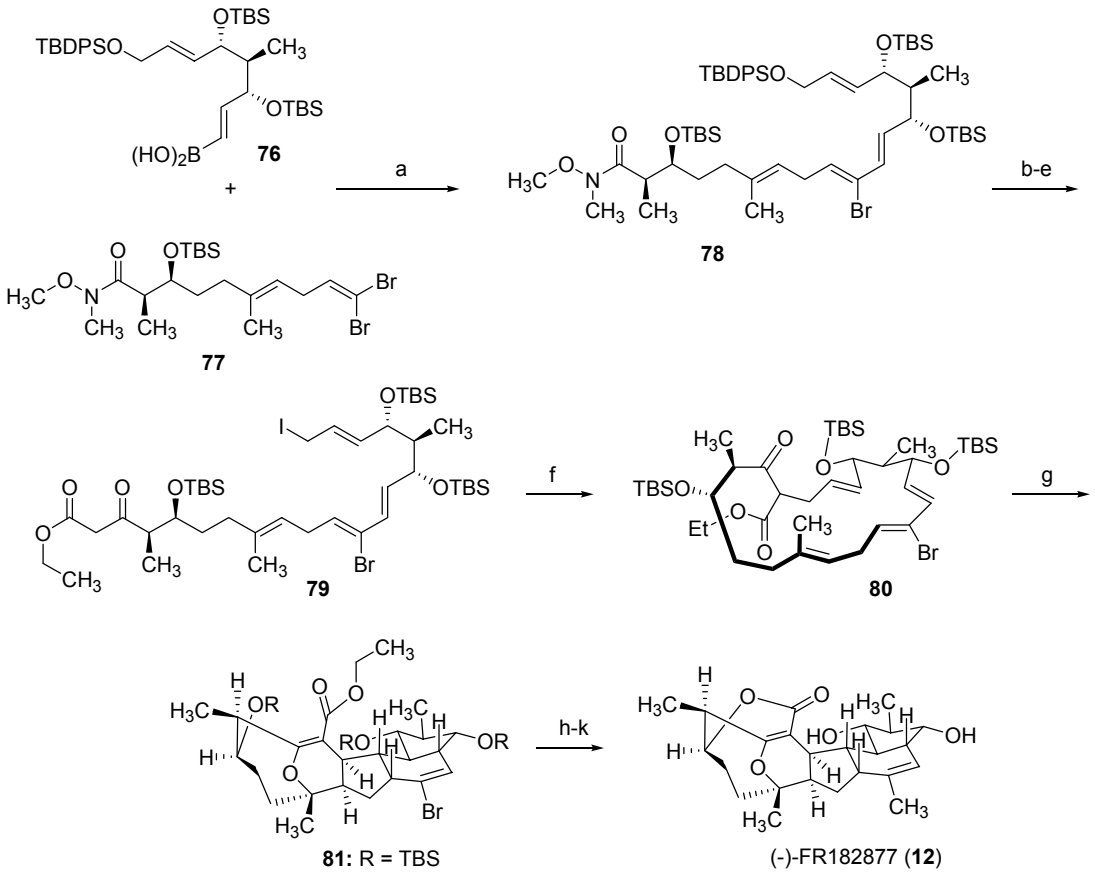
Scheme 24. The tandem transannular Diels-Alder/hetero-Diels-Alder reaction

In order to complete the synthesis, the TMS protected alcohol was deprotected to give **74** and the *tert*-Bu ester was hydrolyzed to furnish the *seco*-acid **75**. The lactonization was accomplished when **75** was treated with the Mukaiyama's reagent to yield the (-)-FR182877 (**12**) (Scheme 23).

2.8 The total synthesis of (-)-FR182877 by Evans *et al.*

In 2002, the Evans group from Harvard university reported a successful completion of the total synthesis of (-)-FR182877. In its strategy the synthesis is similar to that of the Sorensen group, featuring the key sequence of a tandem transannular Diels-Alder/hetero-Diels-Alder reaction.

Instead of the Stille coupling used by Sorensen *et al.* Evans and co-workers utilized Pd-catalyzed Miyaura-Suzuki coupling to merge fragments **76** and **77** (Scheme 25). Weinreb amide **78** was reduced with DIBAL to the aldehyde and converted to the β-ketoester **79** according to the Roskamp protocol.[67] The primary allylic alcohol was deprotected with TBAF and transformed into allyliodide **79**. Intramolecular alkylation of the β-ketoester, promoted by Cs_2CO_3 furnished the 19-membered macrocycle **80**.



(a) $Pd(PPh_3)_4$, Tl_2CO_3, 84%; (b) DIBAL, THF; (c) ethyl diazoacetate, $SnCl_2$ (cat.); (d) TBAF, AcOH; (e) I_2, PPh_3; (f) Cs_2CO_3, 49% over six steps; (g) $(PhSeO)_2O$, SO_3·Py, Et_3N, THF, 25 °C, 2 h, 50 °C, 6 h, 63%; (h) HF/CH_3CN (1:20); (i) $Me_3B_3O_3$, Pd(dppf)Cl_2, Cs_2CO_3, 80 °C; (j) TMSOK, THF; (k) Mukaiyama's reagent, 44% over four steps.

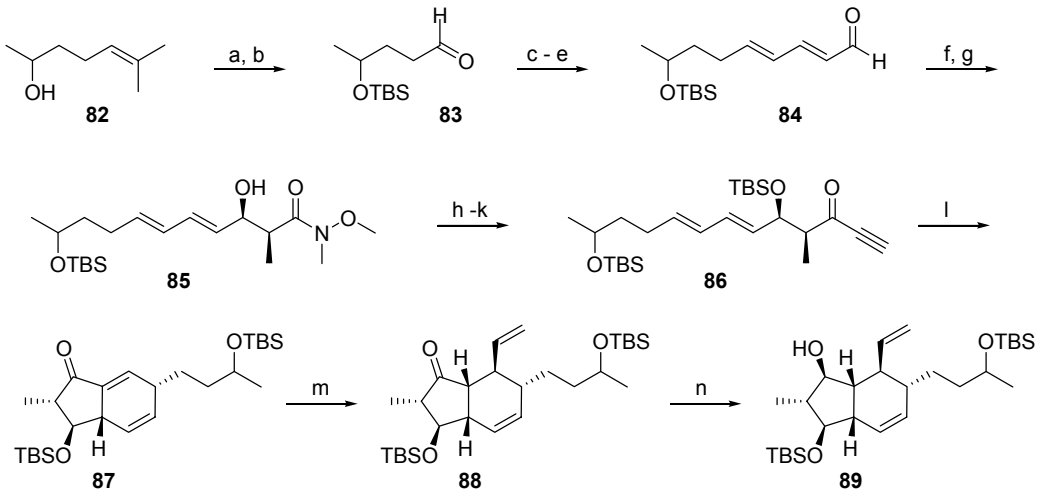
Scheme 25. The synthesis of (-)-FR182877 by Evans *et al.*

To introduce the unsaturation needed for the tandem cycloaddition step, the group of Evans utilized $(PhSeO)_2O$ with SO_3·Py. Remarkably the desired *E*- olefin was obtained exclusively and underwent subsequent tandem transannular Diels-Alder/hetero-Diels-Alder reaction at 50 °C to provide **81** in 63% yield.

The silyl protecting groups were removed with HF in CH_3CN. The vinylic bromine was substituted with a methyl group in a Pd-catalyzed Suzuki reaction with $Me_3B_3O_3$.[68] The ethyl ester was saponificated with TMSOK and the lactonization was successfully effected with the Mukaiyama's reagent to provide (-)-FR182877 (**12**).

2.9 Synthesis of the ABC cyclic fragment of hexacyclinic acid by Kalesse *et al.*

Kalesse *et al.* reported on the synthesis of the ABC cyclic fragment of hexacyclinic acid.[69] The synthesis started with the alcohol **82** (Scheme 26, Scheme 27).

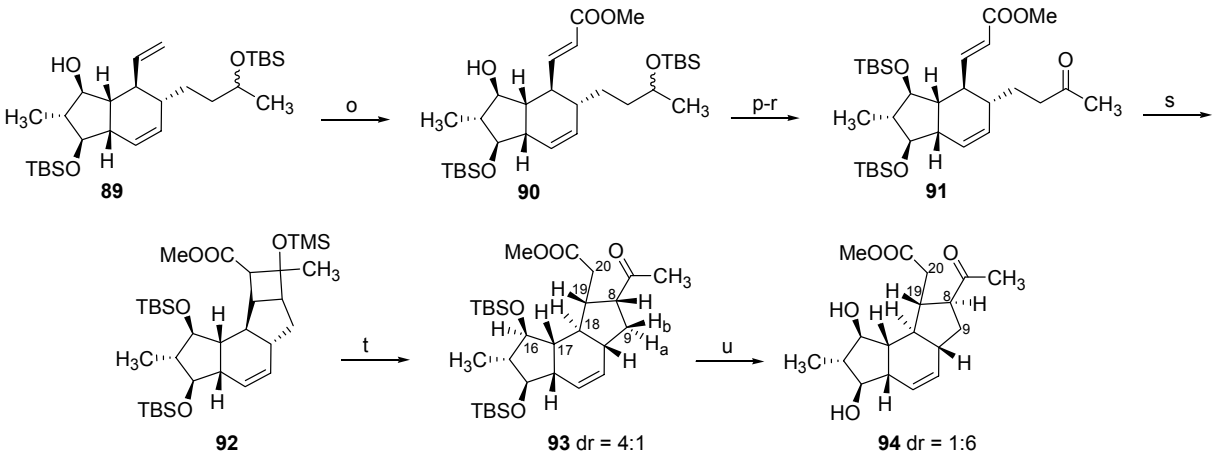


(a) TBSCl, imidazole, DMF; (b) O_3, Me_2S, CH_2Cl_2; (c) (*E*)-$(EtO)_2P(O)CH_2CH$=CHCOOEt, LDA, THF, 0 °C → rt, 70% over three steps; (d) DIBAL, CH_2Cl_2, -78 °C, 98%; (e) MnO_2, CH_2Cl_2, 94%; (f) 4(*S*)-benzyl-3-propionyloxazolidin-2-one, *n*-BuBOTf, Et_3N, CH_2Cl_2, -78 °C, 99%; (g) NHMe(OMe)·HCl, Me_3Al, CH_2Cl_2, 78%; (h) TBSOTf, lutidine, CH_2Cl_2, -78 °C, 86%; (i) DIBAL, THF, -78 °C, 90%; (j) HC≡CMgBr, CH_2Cl_2, -78 °C → rt, 95%; (k) Dess-Martin, CH_2Cl_2, 99%; (l) toluene, 80 °C, 78%; (m) CH_2=CHMgBr, CuBr·Me_2S, THF, Me_2S, -78 °C, 84%; (n) $LiAlH_4$, THF, -100 °C, 96%, dr 20:1.

Scheme 26. The synthesis of the ABC-cyclic fragment of hexacyclinic acid

After TBS protection and ozonolysis, aldehyde **83** was subjected to the HWE olefination with (*E*)-$(EtO)_2P(O)CH_2CH$=CHCOOEt to give the (*E*)-, (*E*)- diene selectively. This was converted to the aldehyde **84** through reduction with DIBAL and reoxidation of the allylic alcohol with MnO_2. The boronate aldol reaction according to the Evans protocol furnished the aldol in 99% yield. This was treated with NMe(OMe)·HCl and Me_3Al to give the Weinreb amide **85**. After the protection of the secondary alcohol as a TBS ether, the amide function was reduced with DIBAL to the aldehyde and reacted with HC≡CMgBr. Reoxidation of the secondary alcohol with the Dess-Martin reagent furnished alkynone **86** (Scheme 26).

The Diels-Alder reaction took place when **86** was heated in toluene to give **87** in 78% yield. Substrate controlled conjugate addition of vinylmagnesium bromide to **87** provided **88**. It was found that the reduction of the ketone functionality in the A-ring with $LiAlH_4$ at -100 °C furnished the desired diastereomeric alcohol **89** with excellent selectivity (Scheme 26).



(o) 4 equiv methyl acrylate, 5 mol% Grubbs II catalyst, CH_2Cl_2, 80%; (p) TBDPSCl, *i*-Pr_2EtN, DMAP, 5d, 98%; (q) CSA, CH_2Cl_2, MeOH, 0 °C, 82%; (r) TPAP, NMO, CH_2Cl_2, 99%; (s) TMSI, HMDS, 1,2-dichloroethane, 30 min, 0 °C then 2 h at rt; (t) TBAF, THF, -20 °C, 10 min, 68%.; (u) TBAF, THF, rt, 3 h.

Scheme 27. The synthesis of the ABC-cyclic fragment of hexacyclinic acid

Alkene cross-metathesis with methyl acrylate gave acrylate **90**. The hydroxy function in the A-ring was protected as a TBS ether. The secondary alcohol in the side chain was deprotected and oxidized to furnish methylketone **91**. When **91** was treated with TMSI and HMDS in 1,2-dichloroethane the tandem Michael-aldol reaction took place to give an inseparable mixture of four diastereomers **92**. When this was treated with TBAF at -20 °C over 10 min at THF a retroaldol reaction took place yielding the methyl ketone **93** as 4:1 diastereomeric mixture (Scheme 27).

The relative stereochemistry of the major diastereomer was determined with the aid of NOESY experiments. A cross peak between H20 and H16 suggested the desired configuration at C19. H_a at C9 was observed as a quartet with $J = 12.2$ Hz in ^{1}H NMR, suggesting that the desired configuration at C8 (Scheme 27).

When **93** was subjected to the action of TBAF (THF, rt, 3 h), total deprotection took place. The diol **94**, which was obtained as 6:1 mixture of diastereomers, was crystalline making it thus possible to obtain an X-ray crystal structure. According to the X-ray structure analysis (Figure 7), eight out of nine stereocenters were constructed correctly, leaving only the configuration at C8 to be opposite to the natural product.[70]

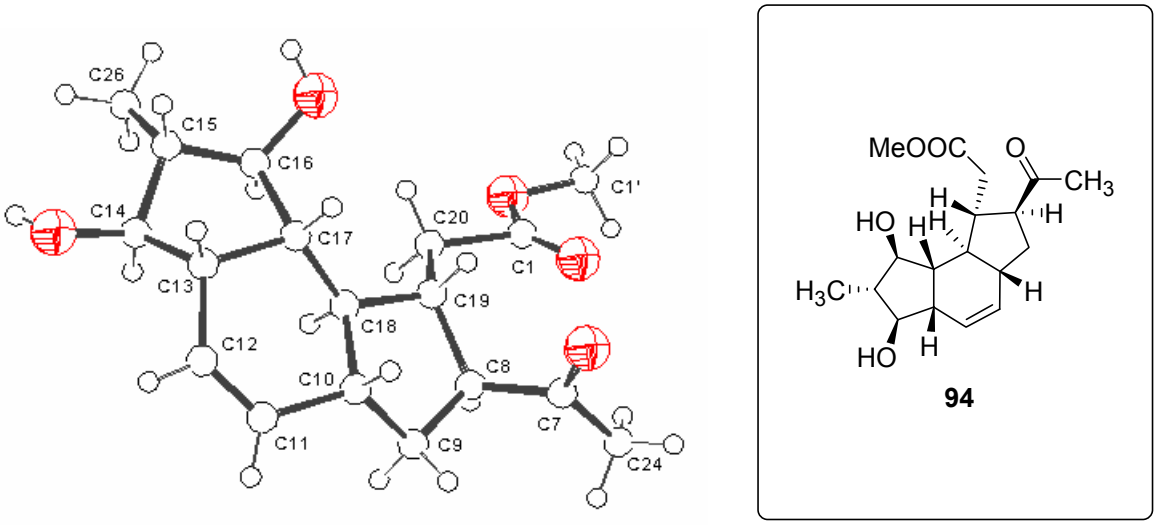
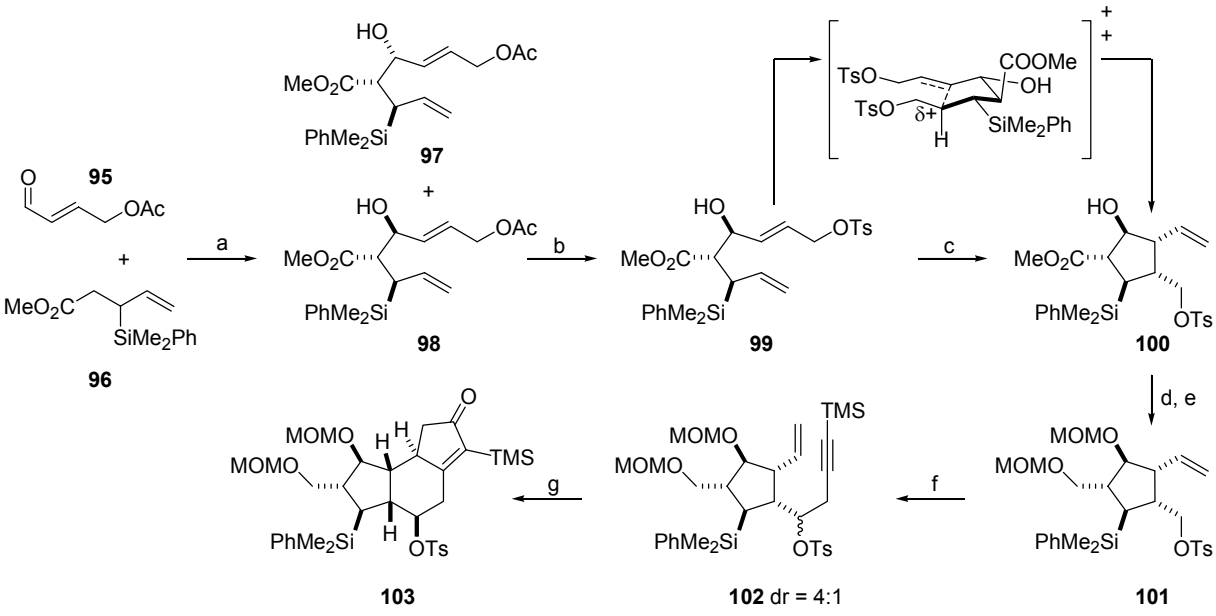


Figure 7. X-ray structure analysis of **94**

2.10 Synthesis of the ABC cyclic fragment of hexacyclinic Acid by Landais *et al.*

Landais *et al.* reported the synthesis of the ABC core of hexacyclinic acid utilizing the free-radical 5-exo-trig cyclization[71] of a chiral 3-silylhepta-1,6-diene **99** (construction of the A-ring) followed by the Pauson-Khand cyclization (construction of rings B and C) (Scheme 28).[72]



(a) LDA, THF, 0.5 h, -78 °C **98**/**97** 65:35, 40%, chromatographic separation; (b) TsONa, $Pd(PPh_3)_4$, *E*/*Z* 95:5, 94%; (c) 0.15 equiv TsSePh, CH_2Cl_2, -25 °C, hν, 2 h, 77%, > 95:5; (d) DIBAL; (e) MOMCl, *i*-Pr_2EtN, 60% over three steps; (f) *n*-BuLi, *t*-BuOK, THF, -78 °C, $TMSC{\equiv}CCH_2Br$, 35% conversion, 65% corrected yield, 4:1; (g) $Co(CO)_8$, TMANO, THF, 74%.

Scheme 28. The synthesis of the ABC core of hexacyclinic acid (Landais *et al.*)

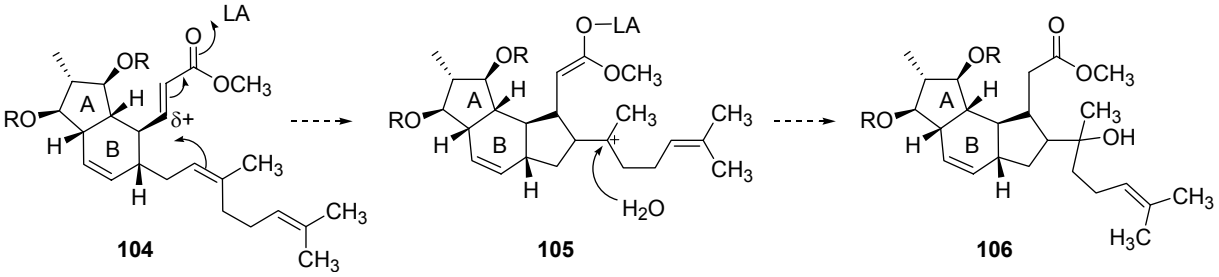
Aldol reaction between **95** and **96** furnished the desired diene **98** along with **97**. Pd-catalyzed allylation of TsONa gave tosylate **99**. Radical 5-*exo*-trig cyclization of **99** was conducted under irradiation with a sun lamp (300W) at -25 °C using catalytic amounts of *p*-TsSePh and AIBN and yielded cyclopentane **100** in 77% yield and > 95:5 dr. After the reduction of the carbomethoxy group with DIBAL and MOM protection of the diol, **101** was obtained. Deprotonation of the sulfonate **101** with Schlosser base and reaction with 1-TMS-3-bromopropyne-1 furnished **102** in 65% corrected yield and 4:1 dr. The Pauson-Khand reaction provided **103** with 74% yield and completed the synthesis of the ABC cyclic core of hexacyclinic acid in seven steps starting from the readily available β-silyl ester **96**.

The strategy towards the natural product based on the elaborated approach (5-*exo*-trig cyclization/alkylation/intramolecular Pauson-Khand reaction) has not been proposed.

2.11 Biomimetic approach in the construction of the C-ring of hexacyclinic acid

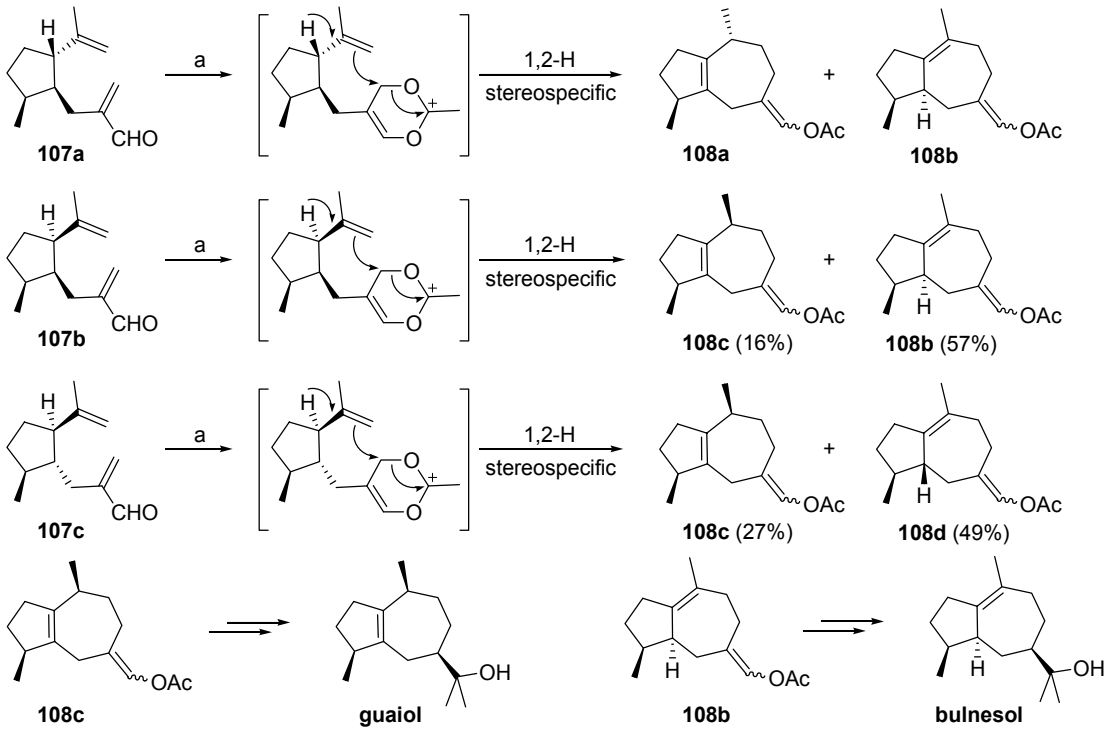
As was discussed in Section 1.2 feeding experiments conducted by Zeeck *et. al.* led to the assumption that the C-ring of hexacyclinic acid may be biosynthetically constructed in a process that mimics cationic π-cyclizations of alkenes.

Inspired by the findings of Zeeck we proposed a biomimetic approach towards the C-ring of hexacyclinic acid (Scheme 29).



Scheme 29. Biomimetic construction of the C-ring of hexacyclinic acid

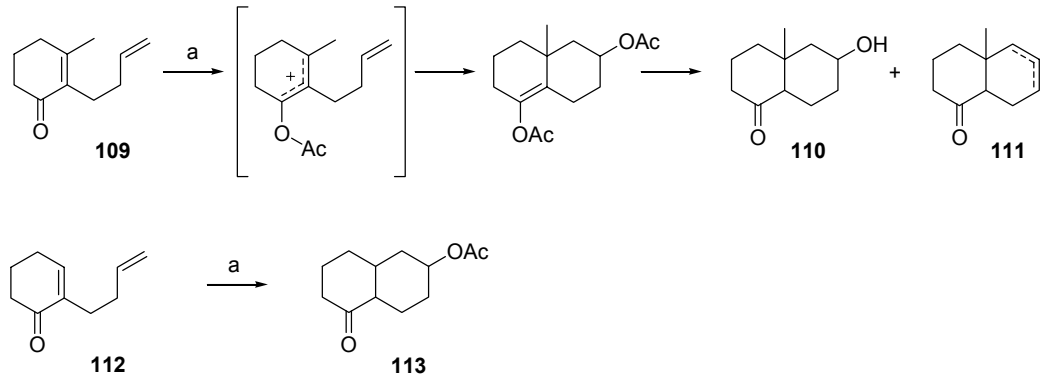
The acid-catalyzed intramolecular reactions of α,β-unsaturated ketones with aromatic rings has been studied by Stork *et. al.*, Dutta *et. al*. in the 1950s and by Ziegler *et al.* in the 1970s.[73] Andersen *et al.* studied the application of cationic cyclizations of α,β-unsaturated aldehydes in the synthesis of hydroazulenic sesquiterpenes (guaiol, bulnesol).[74] It was found that treatment of aldehydes **107a-c** with a mixture of perchloric acid and acetic anhydride in AcOEt[75] at rt resulted into formation of the products of a stereospecific cationic cyclization **108a-d** (Scheme 30).



(a) $HClO_4$, Ac_2O in AcOEt at rt.

Scheme 30. Stereospecific cationic cyclizations of α,β-unsaturated aldehydes (Andersen *et al.*)

The first example of direct cationic olefin cyclization of a simple unsaturated ketone was reported by Cooper and Harding (Scheme 31).[76] When **109** was treated with perchloric acid in a mixture of acetic anhydride and acetic acid, furnished the ketoalcohol **110** in 50% overall yield (*trans*-**110** : *cis*-**110** 4:1) together with the ketone **111** in 12 % yield.



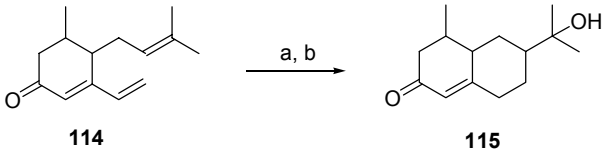
(a) $HClO_4$, AcOH and Ac_2O in AcOEt, 1.5 h at rt; (b) $BF_3 \cdot Et_2O$ in AcOEt, rt.

Scheme 31. Cationic olefin cyclization of an α,β-unsaturated ketones

Interestingly, when treated with a variety of protic and Lewis acids (HCO_2H, CH_3CO_2H, CF_3CO_2H, $HClO_4$ in acetic acid, $SnCl_4$, $BF_3 \cdot Et_2O$ in acetic acid) **109** could be recovered unchanged, and with (*p*-toluene)-sulfonic acid the reaction was sluggish.

Dienone **112** underwent cyclization to keto acetate **113** in good yield when treated with boron trifluoride etherate in AcOH at rt.[77] At the same time **109** was unreactive under same reaction conditions (Scheme 31).

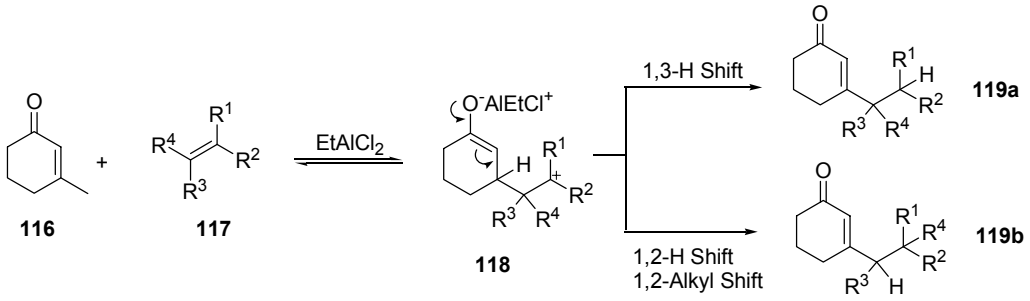
Another example of a cationic cyclization of an α,β-unsaturated ketone was published by Dastur.[78] The cyclization of **114** proceeds at rt in formic acid to furnish **115** (Scheme 32).



(a) HCOOH, rt, 1 h; (b) aqueous NaOH, 50% yield.

Scheme 32. A cationic cyclization of α,β-γ,δ-unsaturated ketone (Dastur *et al.*)

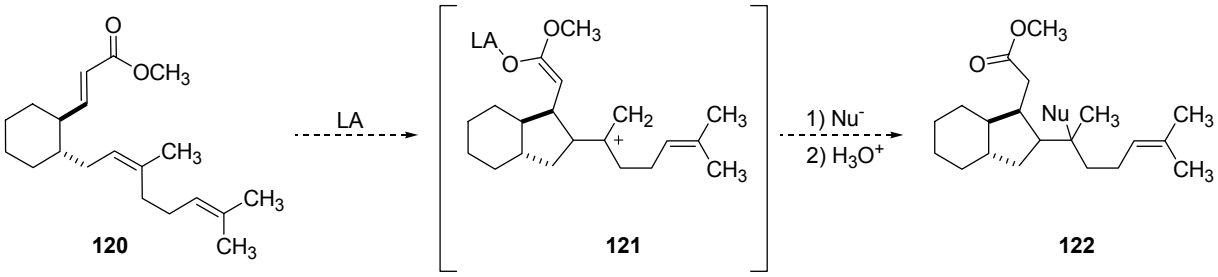
Barry Snider *et al.*[79] investigated Lewis acid catalyzed reactions of alkynyl and alkenyl esters and alkynyl ketones with alkenes **117** (Scheme 33).



Scheme 33. Intermolecular cationic addition of α,β-unsaturated ketones to alkenes (Snider *et al.*)

The first *intermolecular* addition of an enone, as an electrophile, to an alkene was described by the same group. Remarkable are specific termination of the reaction by a series of alkyl and hydride shifts and the absence of polymerization.

In order to investigate cationic alkene cyclizations as a tool for the biomimetic construction of the C-ring of hexacyclinic acid a model compound **120** was proposed and synthesized (Scheme 34).



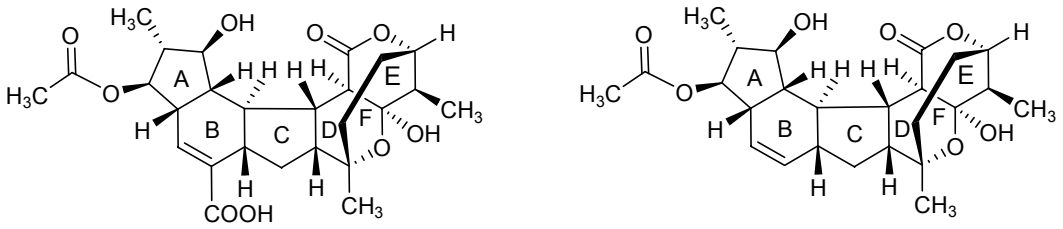
Scheme 34. Investigation of cationic alkene cyclization in the construction of the C-ring on a model compound **120**

Details on the synthesis of **120** and the investigation of cationic alkene cyclizations are discussed in the synthetic part, Section 3.4.

3 Synthetic Part

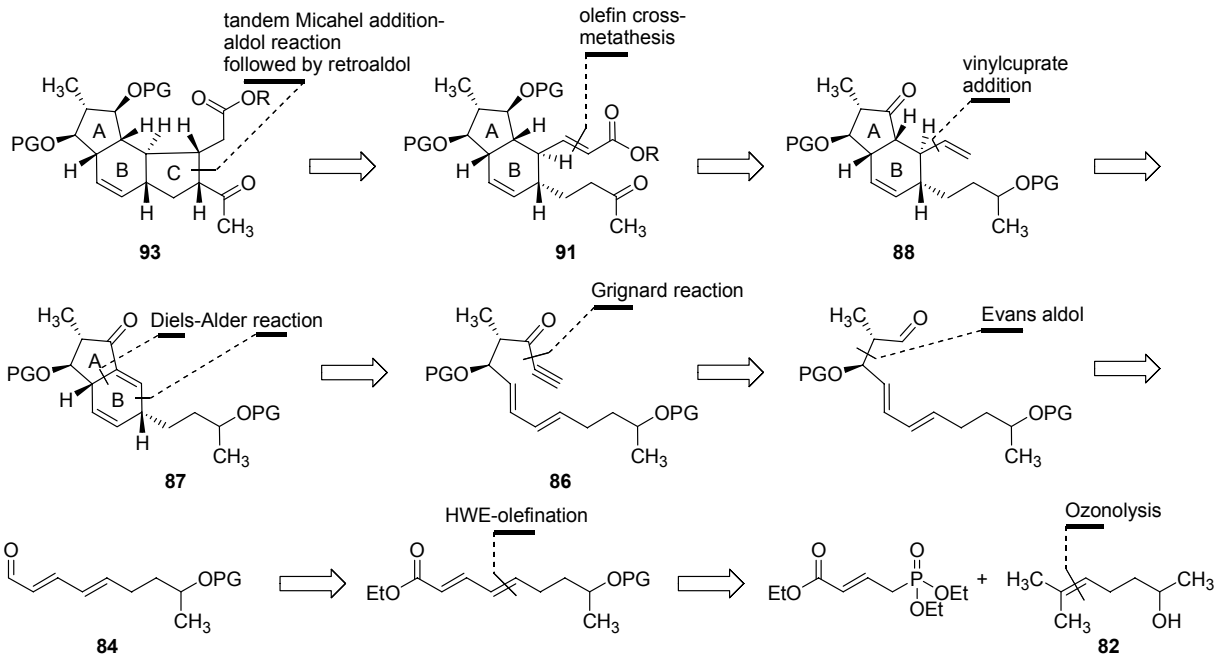
3.1 Retrosynthetic analysis of 25-decarboxy hexacyclinic acid

Remarkable structural features of the target molecule are the combination of 6 fused rings and its 14 stereocenters. To simplify the synthetic target and to focus on the construction of the polycyclic backbone we worked on a synthetic approach towards 25-decarboxy hexacyclinic acid **123** (Scheme 35).



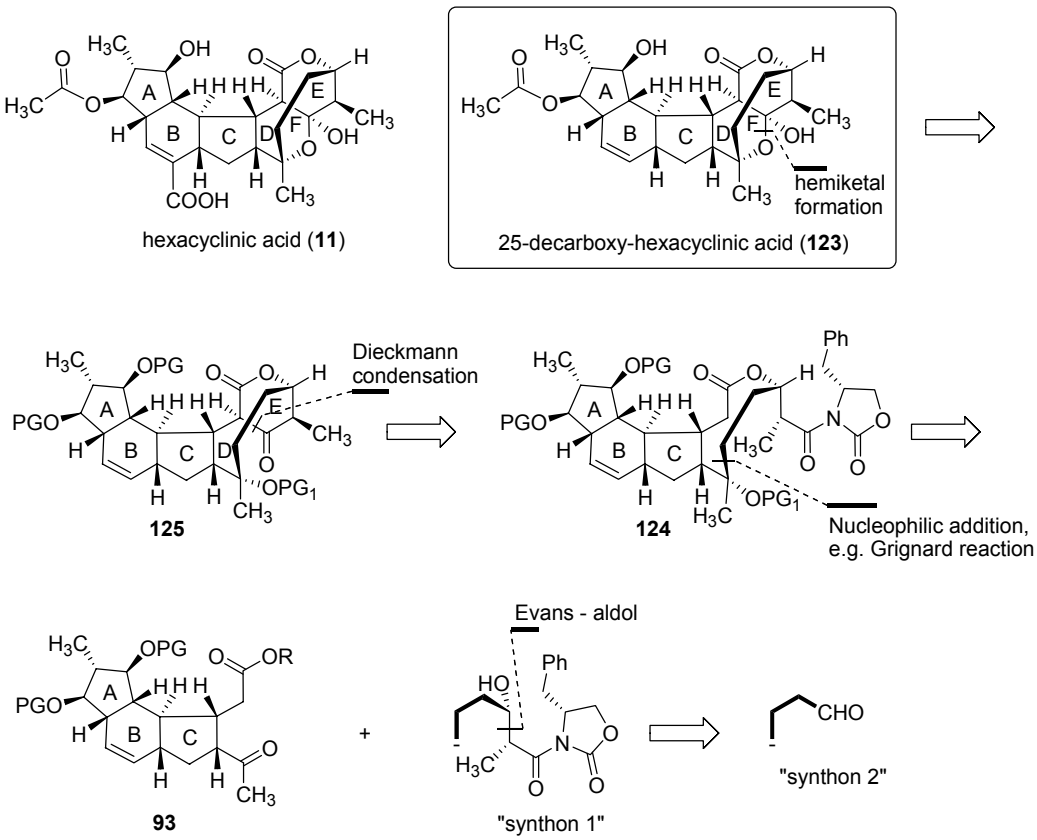
Scheme 35. Hexacyclinic acid (**11**) and 25-decarboxy hexacyclinic acid (**123**)

We divided the molecule into two parts: the ABC and the DEF cyclic fragments. The retrosynthetic analysis of the ABC cyclic fragment has been previously elaborated and supported by a successful synthesis of **93** (Section 2.9) is presented in Scheme 36.



Scheme 36. Retrosynthetic analysis of the ABC cyclic fragment

The strategy for the construction of the DEF cyclic fragment should not only provide access to the target fragment but also be compatible with the previously elaborated approach towards ABC cyclic fragment **93**[69,70] (Scheme 37).



Scheme 37. Retrosynthetic analysis of 25-decarboxy hexacyclinic acid (**123**)

The key step of our approach was the Dieckmann condensation of the imide **124** that would provide access to 1,3-dicarbonyl compound **125**. Subsequent deprotection of the *tert*-alcohol and the formation of the hemiketal should furnish the complete cyclic framework of the natural product.

3.2 Synthetic goals

Though the synthesis of the ABC cyclic fragment was successfully completed, the X-ray structure analysis of the totally deprotected ABC fragment **94** suggested that eight out of nine stereocenters were constructed correctly leaving the configuration at C8 to be opposite to that of the natural product. The following explanations were proposed to explain this observation:[70]

1) formation of a *trans*-fused bicyclo[3.2.0]heptane derivative as the product of the tandem Michael-aldol reaction;

2) epimerization under basic deprotection conditions (4 equiv TBAF, THF, rt);
3) epimerization under storage in $CDCl_3$.

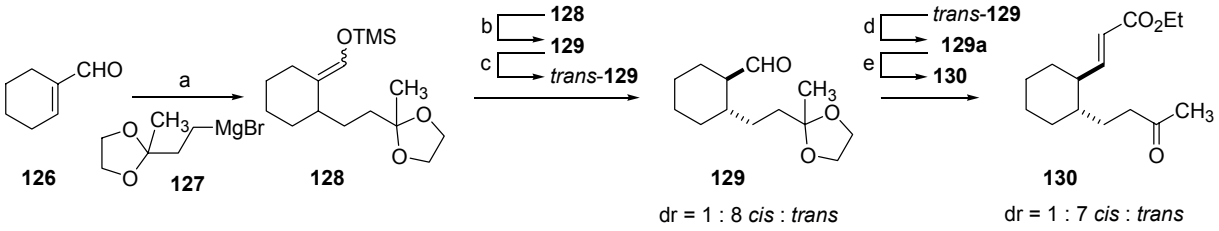
Finding out the reason for the wrong configuration at C8 was a pivotal goal for the further elaboration of the synthesis of the natural product.

Another goal was the elaboration of the synthetic approach towards the DEF cyclic fragment of hexacyclinic acid. Importantly, this approach had to be compatible with our approach for the construction of the ABC cyclic fragment.

3.3 The model study of the tandem Michael-aldol reaction

In order to understand the stereochemical outcome of the tandem Michael-aldol reaction and to establish the conditions of the retro-aldol reaction that avoid epimerization, we studied these transformations on model methyl ketone **130**.

Compound **173** was synthesized in five steps starting from cyclohexene-1-carbaldehyde (**126**) (Scheme 38). Conjugate addition[80,81] of **127**[82] to the aldehyde **126** in the presence of TMSCl and HMPA yielded **128**. Silyl ether **128** was treated with TBAF to give aldehyde **129** which was subjected to equilibration using SiO_2 in hexane/AcOEt 6:1 at rt to establish the desired *trans* substituted cyclohexane derivative with 8:1 selectivity. Subsequently, the α,β–unsaturated ester was introduced according to the Horner-Emmons protocol. The 1,3-dioxolane protecting group was removed in refluxing aqueous acetone with 0.3 equiv of PPTS to provide methyl ketone **130** as mixture of the *cis*- and *trans*-diastereomer (1:7) which were separated by HPLC.[g]



(a) HMPA, $CuBr_2 \cdot Me_2S$, Me_3SiCl, THF, -78 °C, 80%; (b) 1.2 equiv TBAF, THF, 12 h, rt; (c) SiO_2, hexane/AcOEt 6:1, 24 h, rt, 54%; (d) 1.7 equiv $(EtO)_2POCH_2CO_2Et$, NaH, THF, 46%; (e) 0.3 equiv PPTS, 3 h, reflux in aqueous acetone, 92%.

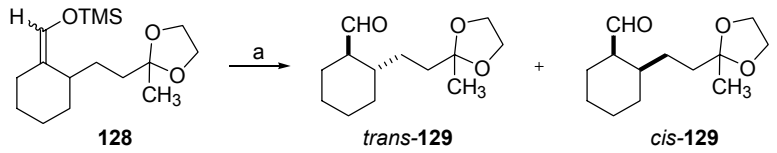
Scheme 38. The synthesis of the model compound **130**

[g]) See Experimental part for the details on the separation.

The key step in the sequence is the conjugated addition[80] of **127**[82,83,84] to the α,β-unsaturated aldehyde in the presence of Me_3SiCl,[81] HMPA and $CuBr \cdot Me_2S$. The reaction proceeded with good yield and no 1,2-addition product isolated.

The deprotection of the TMS-enol ether **128** turned out to be a problematic step. A number of reaction conditions were screened (Table 1). A selectivity of 1:7 (*cis* : *trans*) could be achieved (entries 1, 2, 3, 4, 5).

Table 1. Deprotection of the TMS enol ether **128**.



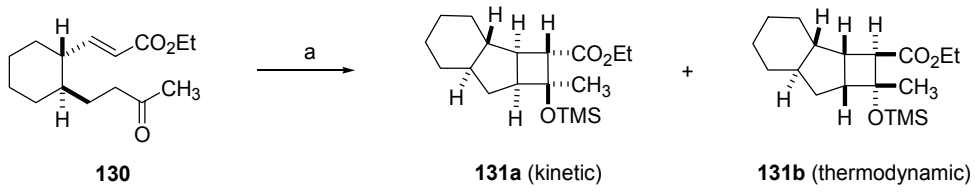
128 *trans*-**129** *cis*-**129**

entry	(a) conditions	Yield, %	*trans*-**129** : *cis*-**129**
1	2.3 equiv TBAF, THF, 5.5 h, rt	54	7:1
2	1.2 equiv TBAF, THF, 30 min, rt	49	7:1
3	1.2 equiv TBAF, THF, 12 h, rt	53	7:1
4	EtONa, EtOH, 1.5 equiv TBAF, THF, 15 h, rt	52	6:1
5	1.2 equiv TBAF, THF, 18 h, rt	49	6:1
6	1.2 equiv TBAF, THF, -10 °C	50	3.4:1
7	1.2 equiv TBAF, MeOH, 2 h, rt	61	1:2
8	10% aqueous H_2SO_4, THF, 5.5 h, rt	15	1:2
9	1.7 equiv KF in MeOH, 8 h, rt	53	1:2.5
10	2.3 equiv TBAF, EtOH, THF, 5.5 h, rt	75	1:3
11	0.6 equiv $H_2C_2O_4$, H_2O, THF, 8 h, rt	34	1:3.2
12	silica gel, hexane/AcOEt 7:3, 5 days, rt	no reaction	
13	37% aqueous HCl/EtOH, 1 min CH_2Cl_2, rt	no reaction	
14	37% aqueous HCl/THF, 1 h, rt	no reaction	

The *trans*-acrylate moiety was introduced according to the Horner-Emmons protocol (Scheme 38). The yield of **129a** appeared to be proportional to the excess of the diethyl ethoxycarbonylmethanephosphonate and NaH used: 38% with 1.05 equiv and 46% with 1.7 equiv of the phosphonate. According to the ^1H NMR the *trans*- olefin was obtained with a selectivity better than 9:1. The Wittig protocol was tested as well. Though the reaction with methoxycarbonyl methylidenetriphenylphosphorane was rather slow at rt, after 100 h 64% of the product could be obtained.

The 1,3-dioxolane protection of the keto functionality was removed by reflux of **129a** in wet acetone in the presence of 30 mol% of PPTS[85] to provide **130** with 92% yield.

With **130** in hands, the diastereoselectivity of the tandem Michael-aldol[86] reaction (Scheme 39) was studied. The results are summarized in Table 2.



130 **131a** (kinetic) **131b** (thermodynamic)

a) 1.5 equiv HMDS, 1.3 equiv TMSI, in $ClCH_2CH_2Cl$, for details see Table 2.

Scheme 39. Tandem Michael-aldol reaction

When the reaction was carried out at 0, -20 or -30 °C the *kinetic* product **131a** was obtained as the major product. On the other hand, when the reaction was performed at rt for more than 1 h, the *thermodynamic* product (**131b**) was formed selectively. In general, longer reaction times favor the *thermodynamic* product with better yields, whereas shorter reaction times favor the *kinetic* product (Table 2).

Table 2. TMSI-HMDS mediated tandem Michael-aldol reaction

entry	conditions[b]	dr **131a** : **131b**[c]	Yield (%)[d]
1	rt, 6 h	1.0 : 17.5	78
2	rt, 3 h	1.0 : 14.3	79
3	rt, 60 min	1.0 : 4.4	82
4	rt, 10 min	1.8 : 1.0	87[a]
5	0 °C, 6 h	1.0 : 1.7	77[a]
6	0 °C, 3 h	1.5 : 1.0	82[a]
7	0 °C, 60 min	5.4 : 1.0	81[a]
8	0 °C, 10 min	8.2 : 1.0	83[a]
9	-20 °C, 6 h	8.2 : 1.0	70[a]
10	-20 °C, 60 min	12.4 : 1.0	81[a]
11	-20 °C, 10 min	16.2 : 1.0	49[a]
12	-30 °C, 3 h	16.2 : 1.0	79[a]
13	-30 °C, 60 min	17.6 : 1.0	71[a]

[a]Incomplete reaction. [b]For all entries in Table 2 the concentration of **130** was 0.1 M. [c]dr was determined by GC. Other products were also detected (up to 6), but not listed in Table 1. Analysis were done on crude products. The composition of crude products was also controlled by the intensity of the signals corresponding to $OSi(CH_3)_3$ group (δ 0.26-0.15 ppm) in ^1H NMR spectra (in C_6D_6). [d]For the mixture of diastereomers after chromatographic purification (hexane-AcOEt 50:1, R_f = 0.10-0.15).

Both **131a** and **131b** were isolated in pure form and analyzed with NOE experiments in order to assign the relative stereochemistry.

NOESY spectra of **131a** support the structure shown in Figure 8 with *cis*-fusion between the cyclopentane and the cyclobutane rings and *trans*-orientation between H5 and H6 as in hexacyclinic acid.

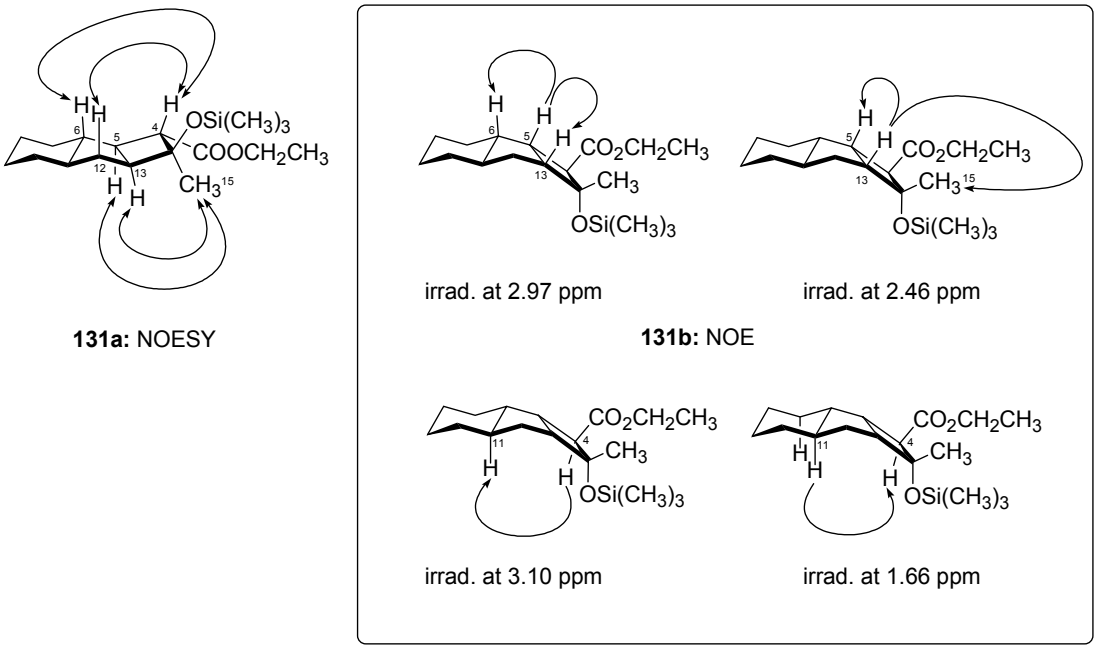
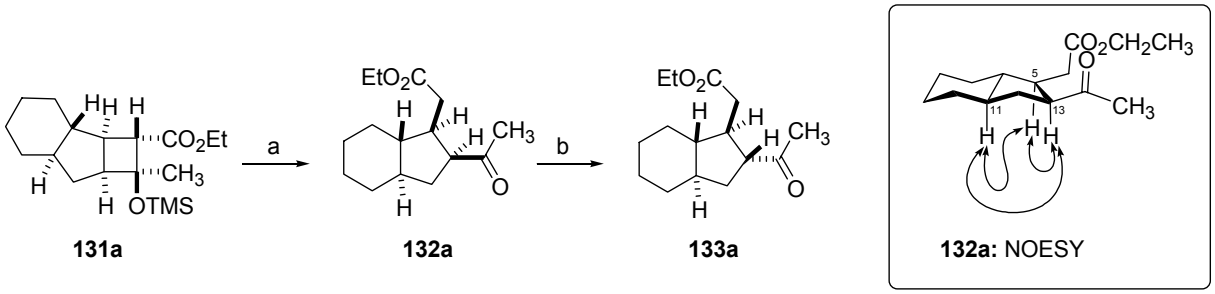


Figure 8. Stereochemistry assignment for **131a** using NOESY and for **131b** with the help of NOE.

In the case of the **131b**, a NOE between H4 and H11 is a strong argument to support the proposed structure (Figure 8).

With **131a** in hand we performed the retro-aldol reaction putting our particular focus on the potential epimerization.

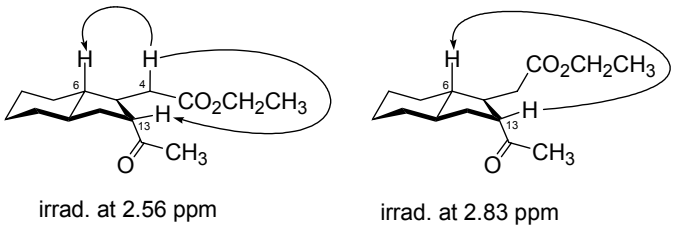
When **131a** was treated with TBAF (1.0 equiv, -30 °C, 30 min), the corresponding methyl ketone **132a** was obtained in 80% yield. The relative stereochemistry of **132a** was assigned using NOESY NMR experiments (Scheme 40).



(a) 1.0 equiv TBAF 30 min, -30 °C; (b) TBAF 3 h, rt.

Scheme 40. Retroaldol reaction of **131a**

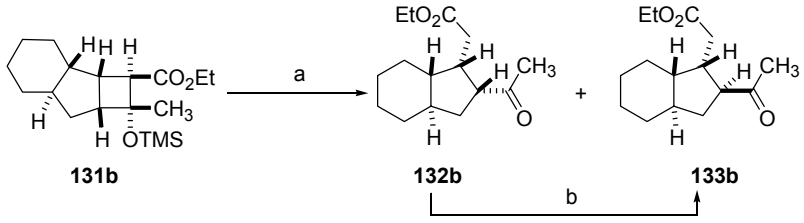
When methyl ketone **132a** was treated with TBAF at rt (Scheme 40), epimerized compound **133a** could be isolated as the sole product. Again, the relative stereochemistry was assigned with the help of NOE NMR experiments (Figure 9).



133a: NOE

Figure 9. Assignment of the relative configuration of **133a** using NOE experiments

When **131b** was treated with TBAF for 30 min at -30 °C, a 2.8:1 diastereomeric mixture of two methyl ketones **132b** and **133b** respectively was isolated. After treatment of this diastereomeric mixture with TBAF at rt (3 equiv, 3 h), only isomer **133b** could be isolated (Scheme 41).

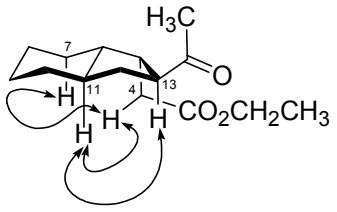


131b **132b** **133b**

(a) 1.0 equiv TBAF, 30 min, -30 °C; (b) TBAF, 3 h, rt.

Scheme 41. Retroaldol reaction of **131b** and epimerization of **132b** into **133b**

The structure of **133b** was studied with the help of ROESY NMR experiments (Figure 10).



133b: ROESY

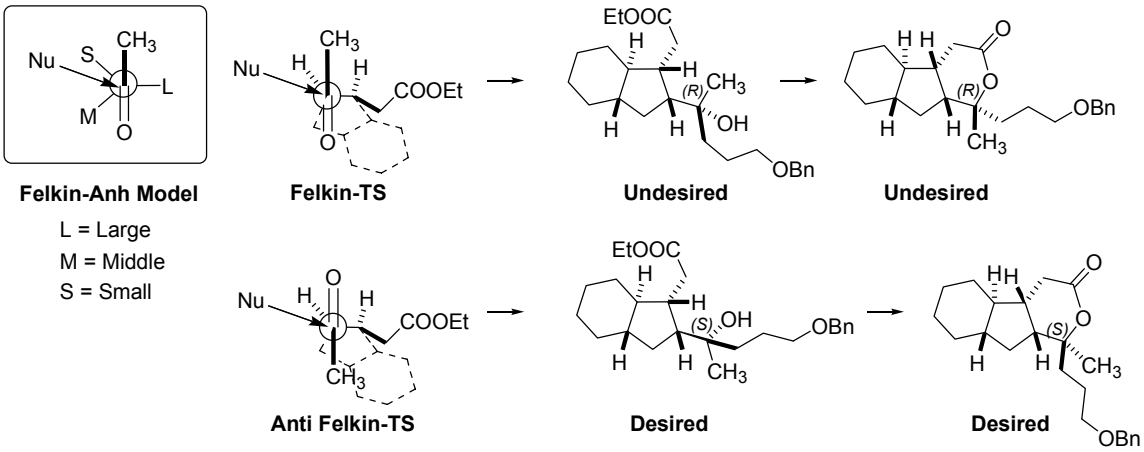
Figure 10. Assignment of the configuration of **133b** by ROESY experiment

With the results obtained, we can explain the unexpected epimerization at C8 center of **93** (Section 2.9) under the conditions for silyl deprotection with TBAF and provide a reliable path for the further elaboration of the total synthesis of hexacyclinic acid. Additionally, we

provided a method which allows the diastereoselective synthesis of 1,2-disubstituted octahydroindene derivatives, with four diastereomers accessible through either the kinetic or thermodynamic product and subsequent epimerization.

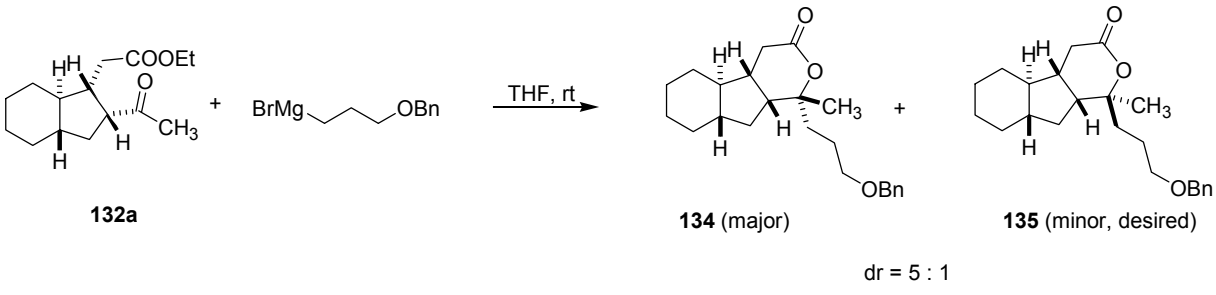
3.3.1 The Grignard reaction with a model methylketone

The selectivity of the Grignard reaction of methyl ketones **93** and **132a** can be predicted[87] in terms of the Felkin-Anh model as shown in Scheme 42. The Felkin transition state will lead to the undesired addition product, whereas the anti-Felkin transition state will furnish the desired *tert*-alcohol.



Scheme 42. Predicting the selectivity of the Grignard reaction of methyl ketones **93** and **132a**

With compound **132a** in our hands its Grignard reaction with (3-(benzyloxy)propyl)magnesium bromide was investigated. When the reaction was conducted at 25 °C the product was obtained as a 5:1 diastereomeric mixture that could be separated by chromatography.



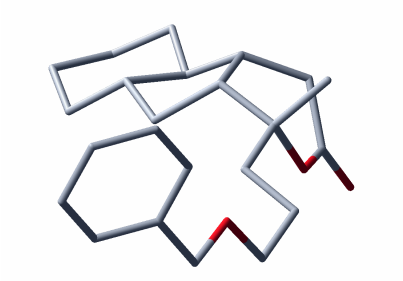
Scheme 43. The Grignard reaction of a model methylketone **132a**

We expected to distinguish between the two products of the Grignard reaction with the help of the ROESY NMR spectra for both compounds. In order to be able to interpret the results of the ROESY experiments, a better understanding of conformational preferences of **134** and **135**

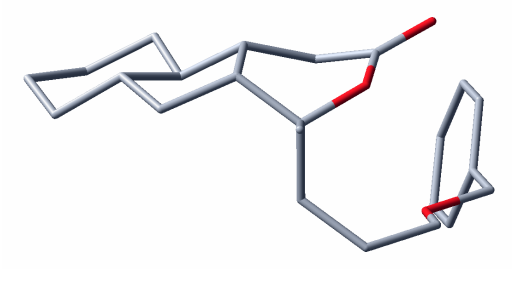
was required. Molecular modeling was conducted using Schrödinger MacroModel (ver. 8.1)[88] and Schrödinger Maestro interface (ver. 5.1.020) under SuSE Linux OS (ver. 10).

Energy minimization was carried out for **134** and **135** by 500 steps of steepest descent until the RMS gradient of the potential energy was less than 0.05 kJ $mol^{-1}Å^{-1}$. The calculation was simulated in $CHCl_3$ as the solvent.

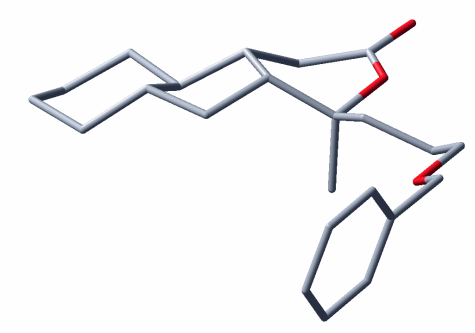
The searching of favorable conformations was conducted using MCMM conformational search protocol. The Monte Carlo Multiple Minimum (MCMM)[89] method implemented in MacroModel is highly efficient in performing global searching, exploring close, as well as distant areas of the potential energy surface. The search proceeds by random changes in torsion angles. Automatic setup of torsions was performed and the calculation was simulated in $CHCl_3$ as above. The method consisted of 1,000 conformational search steps with MMFF94s force field.[90] Other parameters were left by default. Only unique structures within a 50 kJ mol^{-1} energy window above the found global minimum were saved. If a found structure was not converged it was subjected to MMFF94s minimization (in $CHCl_3$) until the RMS of the conjugate gradient was less than 0.05 kJ $mol^{-1}Å^{-1}$. So obtained structures **134a**, **134b**, **135a**, **135b** and their potential MMFF94s energies are presented in Scheme 44.



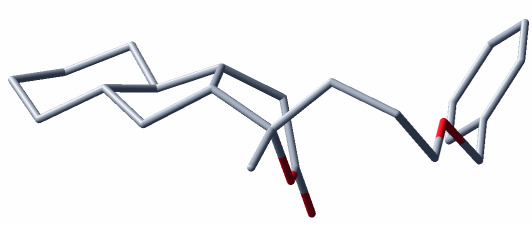
134a, 206.10 kJ mol^{-1}



134b, 204.19 kJ mol^{-1}



135a, 206.06 kJ mol^{-1}

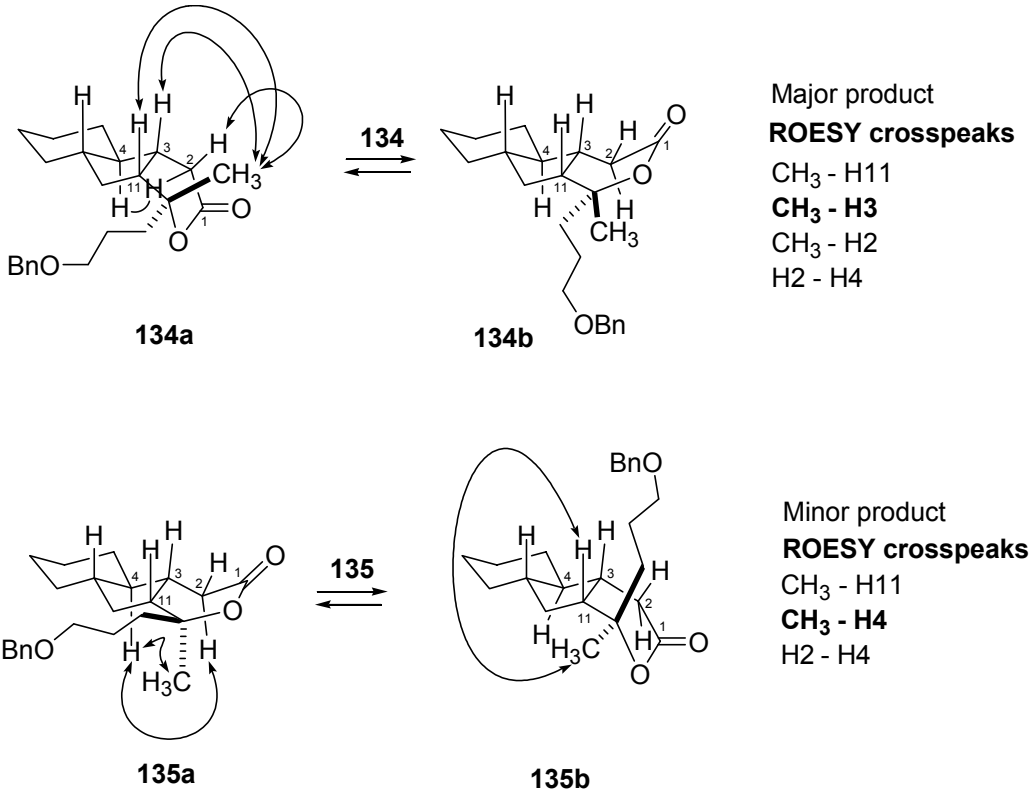


135b, 201.92 kJ mol^{-1}

Scheme 44. Favorable conformations **134a**, **134b**, **135a**, **135b** and their potential energies (hydrogen atoms and bond order are not shown)

It is worth to note that according to the modeling results, conformations with a "bigger" $CH_2CH_2CH_2OCH_2Ph$ substituent in a pseudo-axial position are energetically preferred over those conformations where this substituent takes a pseudo-equatorial position.

Results of molecular modeling and the results of the ROESY experiments were compared (Scheme 45).



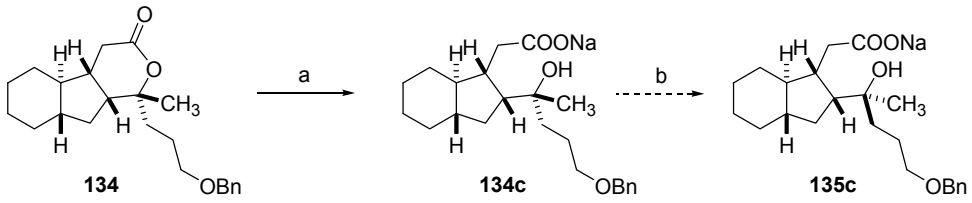
Scheme 45. Elucidation of the relative stereochemistry of **134** and **135** with the help of ROESY

In the ROESY spectrum of the major product **134** a cross peaks between the methyl group and H3 proton (specific for conformation **134a**) strongly supports the proposed structure (Scheme 45). In the ROESY spectrum of the minor diastereomer **135** a cross peak between the methyl group and H4 (specific for the conformation **135a**) support the relative stereochemistry presented in Scheme 45.

The relative stereochemistry of the lactone **135** corresponds to that of hexacyclinic acid (**11**). In agreement with the Felkin-Anh model the Grignard reaction afforded the undesired product **134** selectively.

It is worth to note that unreacted methylketone, isolated after the Grignard reaction was identical with the starting material **132a** according to TLC and 1H NMR, suggesting that no epimerization of **132a** takes place during the Grignard reaction.

Lactone **134** was converted to the corresponding *tert*-alcohol **134c** when treated with NaOMe in MeOH (Scheme 46).



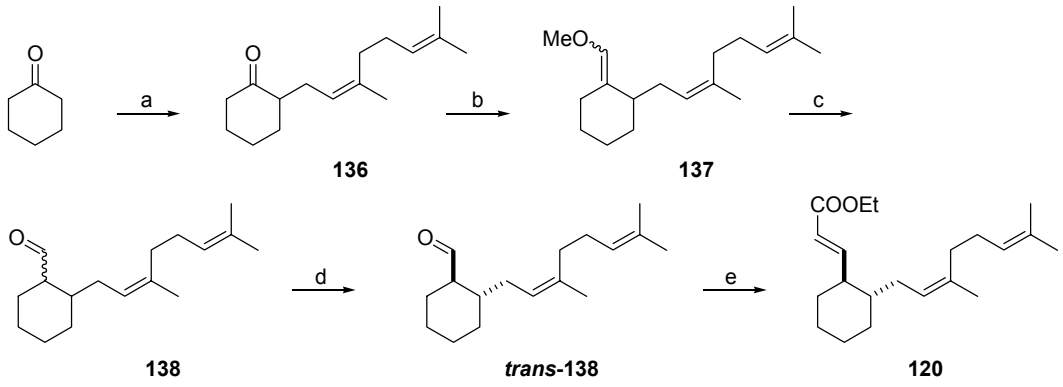
(a) 0.22 M NaOMe in MeOH, 48 h at rt; (b) H_3O^+, PPh_3, DAED, PhCOOH.

Scheme 46. Reaction of lactone **134** with NaOMe in MeOH

It is worth to note that **134c** was prone to undergo spontaneous cyclization (during workup and purification by chromatography) furnishing the starting lactone **134**. One should to point on the possibility to convert the undesired *tert*-alcohol **134c** to the desired **135c** according to the Mitsunobu protocol.[91]

3.4 The C-Ring via a nucleophilic addition of an alkene to the Michael acceptor

In order to investigate cationic alkene cyclizations as a tool for the biomimetic construction of the C-ring of hexacyclinic acid, a model compound **120** was chosen (Scheme 34, Section 2.11). Compound **120** was synthesized in five steps starting from cyclohexanone. Alkylation of the lithium enolate of cyclohexanone with neryl bromide afforded 2-nerylcyclohexnone (**136**). Methylvinylether **137** was prepared according to the Wittig olefination protocol (Scheme 47).



(a) LDA, THF, -78 °C; neryl bromide, 50%; (b) $MeOCH{=}PPh_3$, THF, -78 °C, 68%; (c) 5% HCl/THF 4:1, reflux 10 min, 35%; (d) KOH, MeOH, reflux, 92%; (e) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 52%.

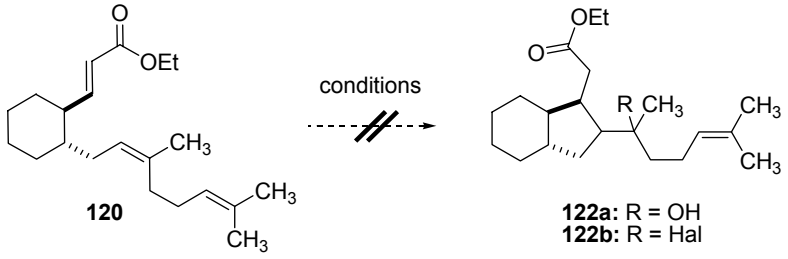
Scheme 47. The synthesis of the model compound **120**

Unfortunately, the acid catalyzed hydrolysis of methylvinylether **137** gave two byproducts together with the desired aldehyde **138** in low yields. In order to optimize the yield of **138** a number of reaction conditions was tested. Best results were obtained when **137** was briefly refluxed (5 min) in a 4:1 mixture of THF and 5% aqueous HCl, furnishing **138** as a 1:1 mixture of the *cis*- and *trans*- isomers as suggested by ^{1}H NMR. The desired *trans*-**138** could be selectively obtained when the 1:1 mixture was subjected to reflux in aqueous KOH/MeOH. A *cis* : *trans* selectivity of 1:7 was achieved.

The HWE olefination and the Wittig protocol were two alternative methods to introduce the required acrylate moiety. Whereas the HWE olefination furnished the *trans*-acrylate with 52% yield, the Wittig olefination afforded the product in 79% yield.

With the compound **120** in hand, we investigated cationic alkene cyclizations. A set of Brønsted and Lewis acids was tested for the ability to induce cationic alkene cyclizations of **120** (Table 3).

Table 3. Investigation of cationic alkene cyclization of **120**



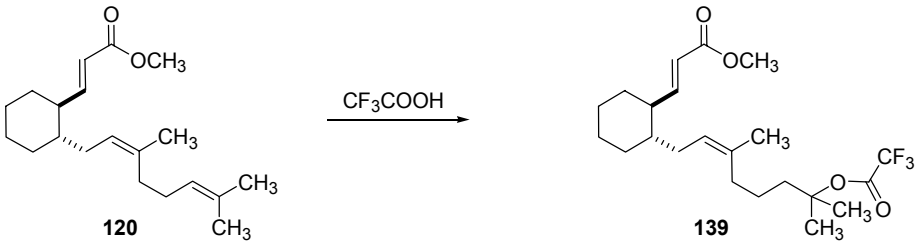
120

122a: R = OH
122b: R = Hal

entry	conditions	notes[h]
1	15 equiv F_3COOH, 50h in CH_2Cl_2, rt	the starting material and a new product, R_f = 0.35-0.31
2	4 equiv $BF_3{\cdot}Et_2O$, 24 h in CH_2Cl_2, -78 °C to rt	starting material
3	2 equiv Me_2AlCl, 24 h in CH_2Cl_2, -78 °C to rt	starting material
4	4 equiv TPPB, H_2O , 24 h in THF, -78 °C to rt	starting material
5	2 equiv $SnCl_4$, 24 h in CH_2Cl_2, -78 °C to rt	starting material
6	4 equiv $Sc(OTf)_3$, 24 h in THF/H_2O 9:1, 0 °C	starting material
7	160 equiv aqueous H_2SO_4, 24 h in THF, 0 °C	starting material
8	4 equiv $TiCl_4$, 18 h in CH_2Cl_2 at -78 °C	products with R_f = 0.40-0.35; R_f = 0.33-0.29, decomp.
9	2.5 equiv $TiCl_4$, 9 h in CH_2Cl_2 at -78 °C	product with R_f = 0.40-0.35
10[i]	2.5 equiv $TiCl_4$, 9 h in CH_2Cl_2 at -78 °C	two products, R_f = 0.40-0.35; R_f = 0.33-0.29
11	1.2 equiv $TiCl_4$, 9 h in CH_2Cl_2 at -78 °C	two products, R_f = 0.40-0.35; R_f = 0.33-0.29

[h]) The progress of the reaction was monitored by TLC in hexane/AcOEt 15:1.
[i]) Reversed addition: the solution of **120** was added to the Lewis acid.

Reaction of **120** with an excess of trifluoroacetic acid was rather slow even at rt (entry 1). A new product, obtained in pure form after chromatographic purification, was assigned a structure of **139** (Scheme 48). According to ^{1}H NMR **139** possessed one olefinic proton less compared to the starting material while both acrylate protons were retained. Strong IR absorption at 1167 (C-F) and 1770 cm^{-1} (CF_3-CO) supported the proposed structure.



Scheme 48. Reaction of **120** with an excess of CF_3COOH

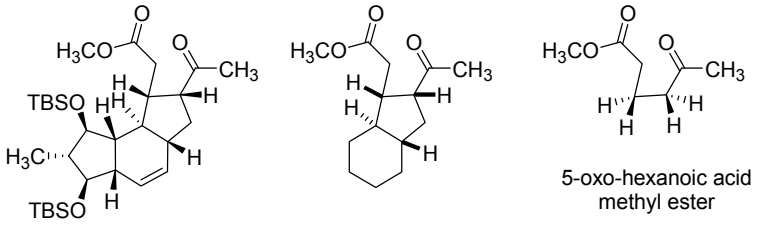
Such Lewis acids as $BF_3{\cdot}Et_2O$, Me_2AlCl, TPPB, $SnCl_4$, $Sc(OTf)_3$ and aqueous H_2SO_4 failed to promote any transformation of **120**. To the contrary, when $TiCl_4$ was used, the formation of up to 4 new products could be observed. Two of these new products were isolated in pure form and analyzed by ^{1}H NMR. In both cases the two acrylate protons could be identified with their usual chemical shifts suggesting that the new compounds are not the result of the desired transformation but are the side-products.

3.5 First generation approach towards the DEF fragment

Compound **93** is accessible in twenty synthetic steps from alcohol **82** with an overall yield of less than 8% (see Scheme 26, Section 2.9). That is why for the elaboration of the synthetic approach towards the DEF-core we decided to start form an easily accessible model compound. This had to have the same arrangement of functional groups as in **93** in order to make the synthesis of the DEF-core applicable to **93** (Scheme 49).

Compound **132a** can be a suitable model as it is structurally closely related to **93** and is accessible in only seven steps from cyclohexene-1-carbaldehyde (**126**) (see Scheme 38, Scheme 39 and Scheme 40, Section 3.3).

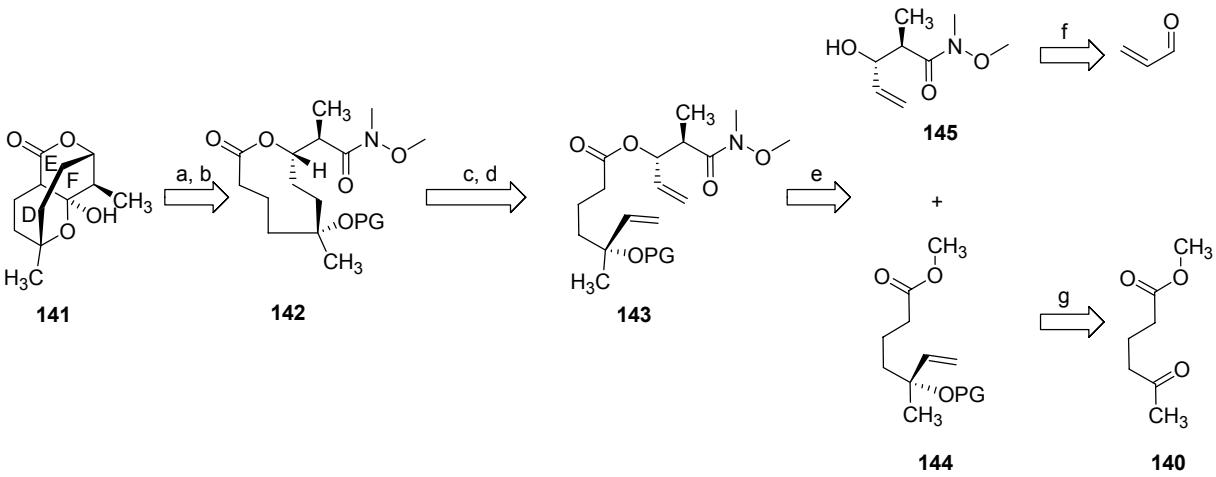
Alternatively, methyl 5-oxohexanoate (**140**) can be a suitable model compound (Scheme 49). It posses the same set of functional groups as **93** does, separated by a chain of three carbon atoms. Importantly, **140** is a commercially available substance that is also available in a single step starting from methyl acrylate and acetylacetone.[126]



93 **132a** **140**

Scheme 49. Model compounds **132a** and **140** for the elaboration of the synthetic approach towards the DEF core of hexacyclinic acid

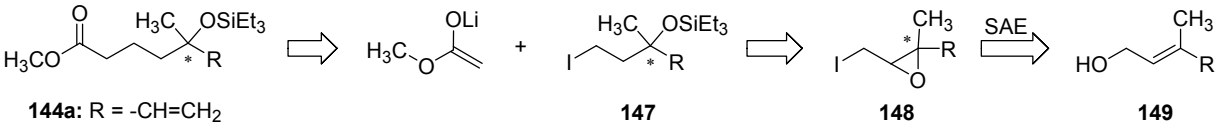
Our first generation approach towards the DEF core of hexacyclinic acid is shown in Scheme 50. We decided to construct the target fragment starting from the readily available **140**. Our retrosynthetic approach features the Grignard reaction (g) furnishing **144**, the Evans aldol reaction (f), esterification (e), the ring closing olefin metathesis (d) the catalytic hydrogenation (c), the Dieckmann condensation (b) and the formation of the hemiketal **141** (a).



141 **142** **143** **145** **144** **140**

Scheme 50. First generation approach towards the DEF core of hexacyclinic acid

We considered an asymmetric synthesis of **144a** using the Sharpless asymmetric epoxidation[92] as the key step (Scheme 51).



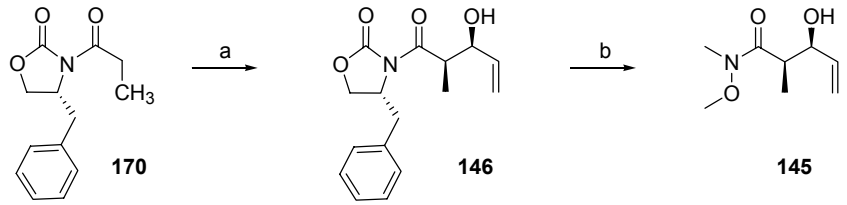
144a: R = -CH=CH$_2$ **147** **148** **149**

Scheme 51. Asymmetric approach to **144a**

The major disadvantage of such synthesis is that it can not be transferred to the ABC fragment **93** (Scheme 49).

A simple addition of common organometallic nucleophiles to **140** will produce racemic mixture of the addition products. The major drawback of conducting the synthesis with racemic **144** is the formation of diastereomeric mixtures e.g. of **143** after the esterification step. This means complication of the spectroscopic characterization by NMR and the need of separation(s) at later synthetic steps. In order to investigate the proposed approach and to reveal the optimal sequence of synthetic transformations we decided to conduct the synthesis with racemic **144**.

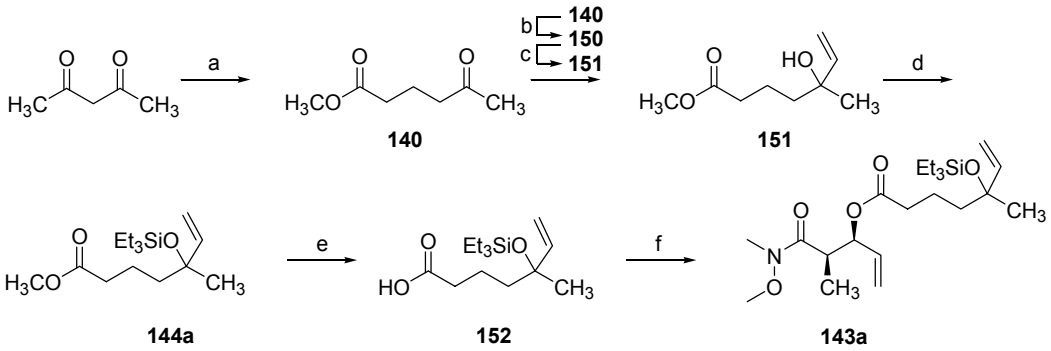
The synthesis of the Weinreb amide **145** was conducted according to a described procedure (Scheme 52).[99]



(a) 1) *n*-Bu_2BOTf, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 2) acrolein, -78 °C → rt, 30 min, 75%; (b) $NH(OCH_3)CH_3 \cdot HCl$, Me_3Al, CH_2Cl_2, -20 °C → rt, 15 h, 87%.

Scheme 52. The synthesis of the Weinreb amide **145**

The Evans aldol reaction with acrolein furnished diastereomerically pure hydroxy imide **146** with a 75% yield. Transamination with *N*,*O*-dimethyl hydroxylamine hydrochloride and Me_3Al afforded **145** in 87% yield. Weinreb amide **145** was used in a 6 step synthesis of **143a** (Scheme 53).



(a) Methylvinylketone, MeONa, 66%; (b) vinylmagnesium bromide, $CeCl_3$, 64%; (c) Et_3N, MeOH, 95%; (d) TESOTf, 2,6-lutidine, 75%; (e) LiOH, 0 °C, THF/MeOH/H_2O, quant.; (f) 2,4,6-trichlorbenzoylchloride, THF, then **152**, 80%.

Scheme 53. Synthesis of the Weinreb amide **143a**

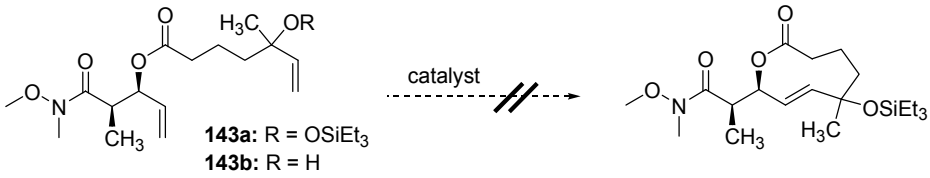
As was mentioned above, methyl-5-oxohexanoate (**140**) was synthesized from methylacrylate and acetylacetone according to a published procedure.[126] With **140** in hand we studied its reactions with organometallic nucleophiles in order to obtain the *tert*-alcohol **151**.

Reaction of **140** with vinylmagnesium bromide afforded a mixture of **151** together with the corresponding lactone **150** in a 42% yield while the reaction with vinyllithium provided the product in 34% yield. The relatively low yields can be explained by the low chemoselectivity of the highly reactive Grignard and organolithium reagents when a keto and a carbomethoxy functions are present in the substrate. Surprisingly, when the reaction was conducted in the presence of equimolar amount of $CeCl_3$, the product was obtained in a 64% yield.[93] After the so obtained lactone-alcohol mixture was treated with Et_3N in MeOH, *tert*-alcohol **151** was obtained in excellent yield. Its hydroxy function was protected as a triethylsilyl ether and the carbomethoxy function was saponificated using LiOH in THF/MeOH/H_2O mixture affording acid **152**. Compound **143a** was obtained according to the Yamaguchi esterification protocol[94] from the acid **152** and the Weinreb amide **145**.

*3.5.2 **RCM in the construction of the 9-membered lactone***

According to the retrosynthetic plan (Scheme 50), the 9-membered lactone **142** should be accessible from a linear precursor **143a** via a ring closing olefin metathesis (RCM) followed by hydrogenation of the double bond. Having **143a** in hand we studied the RCM reaction (Table 4) using different ruthenium catalysts (**153-157**) (Scheme 54).

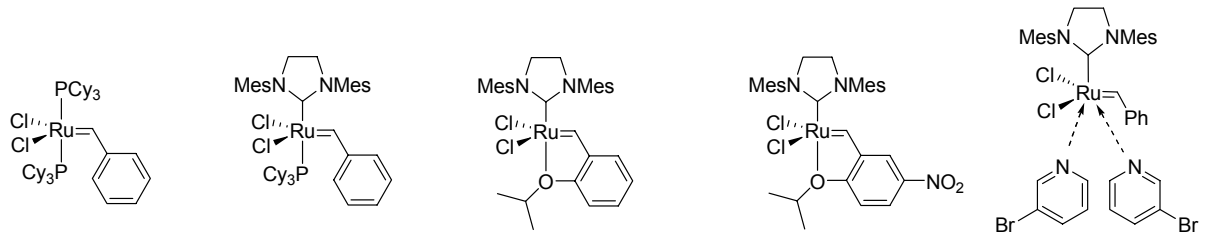
Table 4. Attempted ring closing olefin metathesis of **143a**



143a: R = $OSiEt_3$
143b: R = H

entry	substrate	conditions	notes
1	**143b**	5 mol% **154**, toluene, 80 °C, 24 h (c = 2.9 µmol/mL)	no reaction
2	**143b**	5 mol% **154**, CH_2Cl_2, reflux, 24 h	no reaction
3	**143a**	5 mol% **157**, toluene, 90 °C, 24 h (c = 4.7 µmol/mL)	no reaction
4	**143a**	5 mol% **155**, toluene, 90 °C, 24 h (c = 3.4 µmol/mL)	no reaction
5	**143a**	5 mol% **156**, CH_2Cl_2, rt, 24 h	no reaction
6	**143a**	5 mol% **157**, toluene, reflux, 24 h	no reaction
7	**143a**	10 mol% **157**, toluene, reflux, 24 h	no reaction
8	**143a**	25 mol% **154**, CH_2Cl_2, reflux, 24 h (c = 1.64 µmol/mL)	no reaction
9	**143a**	10 mol% **153**, CH_2Cl_2, reflux, 24 h (c = 1.64 µmol/mL)	no reaction

Unfortunately none of the tested catalysts (Scheme 54) was able to induce the ring closing olefin metathesis of **143a** under the conditions tested. We believed that the proximity of the sterically demanding silyl protecting group to the reacting double bond might prohibit the desired reaction. The triethylsilyl protecting group was removed by treatment **143a** with acetic acid in THF furnishing the *tert*-alcohol **143b**. Attempts to induce the RCM of **143b** using the Grubbs II catalyst were not successful.

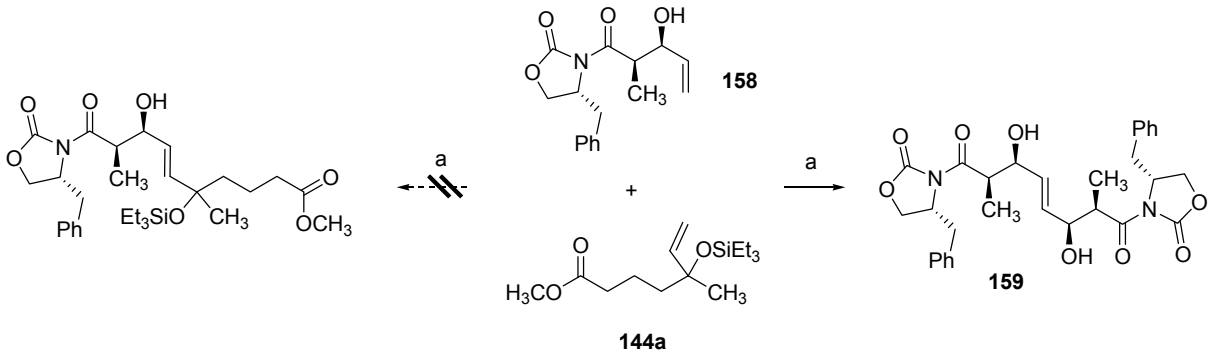


153: Grubbs I catalyst **154:** Grubbs II catalyst **155:** Hoveyda-Grubbs II catalyst **156:** *p*-nitro-Hoveyda-Grubbs II catalyst (Grela catalyst) **157:** Grubbs III

Scheme 54. Ru- catalysts tested for the ring closing olefin metathesis of **143a**

We then reconsidered our approach towards the 9-membered lactone **142** by changing the order of synthetic steps: we expected to be able to conduct a cross metathesis (CM) between **158** and **144a** followed by macrolactonization reaction and hydrogenation.

The CM reaction between **158** and **144a** was studied in the presence of 5-10 mol% of **154**, **155** or **157** as catalysts (Scheme 55). Catalyst **157** was not effective, while **154** and **155** resulted in the consumption of only one of the reaction partners, compound **158**, from the reaction mixture and the formation of a homodimerization product **159**, as suggested by HRMS ESI ($(M + Na)^+$: 573.2195 found).

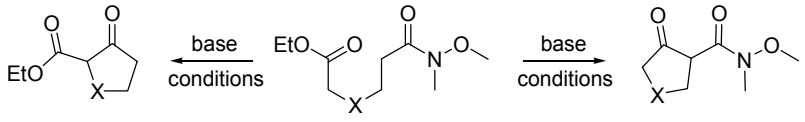


(a) 5 mol% **154** or **155**, $PhCH_3$, reflux 6 h.

Scheme 55. Attempted olefin cross metathesis between **158** and **144a**

*3.5.3 **Dieckmann condensation***

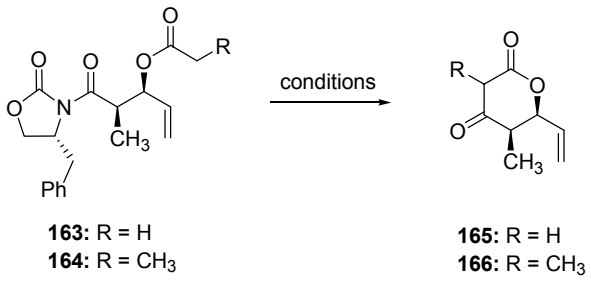
N-methoxy-*N*-methylamides (Weinreb amides) are known to react with C-nucleophiles affording ketones.[95] Enolates derived from ketones, esters, acetonitrile and acetone dimethylhydrazone react with *N*-methoxy-*N*-methylbenzamide to produce β-dicarbonyl compounds in moderate yields.[96] At the same time there are several reports on inefficient condensations of *N*-methoxy-*N*-methylamides with ester enolates.[97] Sibi reported chemoselective Dieckmann-like condensations using *N*-methoxy-*N*-methylamides (Scheme 56).[98]



Scheme 56. Dieckmann condensation of *N*-methoxy-*N*-methylamides **160**.

Depending on the base and the reaction conditions it was possible to selectively obtain one of the two possible reaction products **161** or **162**.

We investigated the Dieckmann condensation of two model substrates, acetate **163** and the propionate **164**, easily and directly available from the aldol product **146**.

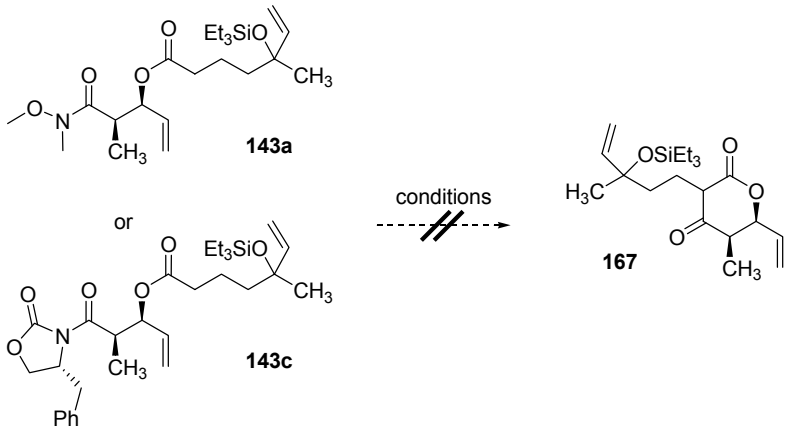


Scheme 57. Dieckmann condensation of **163** and **164**.

The acetate **163** underwent the Dieckmann condensation when 3 equiv of LiHMDS were used as the base and the reaction was conducted for 3 h at -78 °C, furnishing 1,3-diketone **165** in a 19% yield after chromatographic purification. The Dieckmann condensation of **164** furnished **166** as a mixture of diastereomers in 23% yield when the propionate was treated with 4 equiv of KHMDS for 3 h at -78 °C.

With these positive results we expected to conduct the Dieckmann condensation with the more complex substrates **143a** and **143c**. A number of bases was investigated (Table 5).

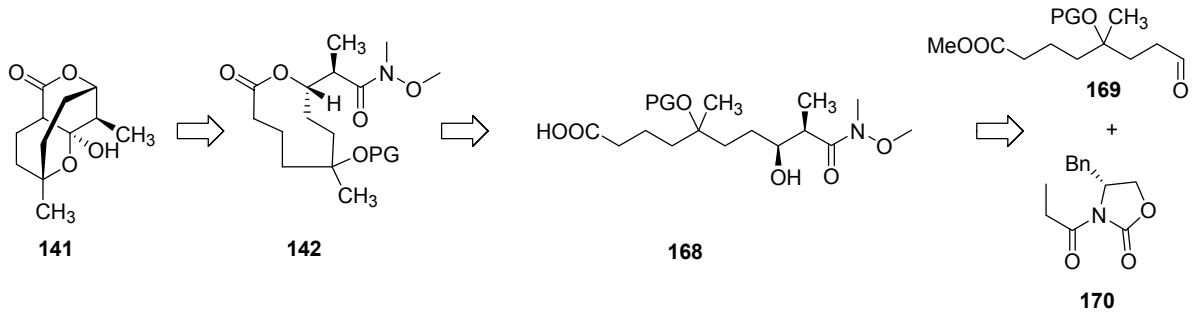
Table 5. The Dieckmann Condensation of **143a**



entry	substrate	conditions	notes
1	**143a**	3.0 equiv LDA, 18 h at -78 °C in THF	no reaction
2	**143a**	1.2 equiv LiHMDS, 16 h at -78 °C, THF	no reaction
3	**143a**	1.2 equiv KHMDS, 16 h at -78 °C, THF	no reaction
4	**143c**	4.0 equiv KHMDS, 16 h at -78 °C, THF	no reaction

3.6 Second generation approach towards the DEF fragment

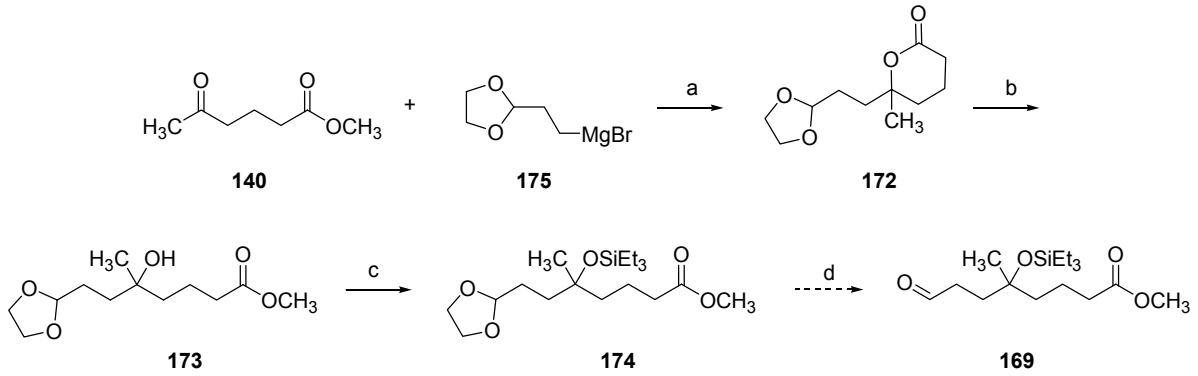
Since the synthesis of the 9-menmbered lactone **142**, required for the construction of the DEF fragment, was not achieved using olefin metathesis, a new synthetic approach was proposed (Scheme 58).



Scheme 58. The second generation approach to the DEF fragment of hexacyclinic acid

Such key steps as the Dieckmann condensation in the construction of the E-ring, the hemiketalization and the macrolactonization of the *seco*-acid **168** to access **142** remained the same. The *seco*-acid **168** should be accessible from the aliphatic aldehyde **169** utilizing the Evans aldol protocol.

To synthesize the aldehyde **169** we started from the precursor, mentioned in Section 3.5, the methyl 5-oxo-hexanoate (**140**) (Scheme 59). The Grignard reaction of **140** with a known organomagnesium reagent **175** followed by the opening of the lactone should provide the methyl ester **173**.



(a) See Table 6 for reaction conditions; (b) Et_3N in MeOH or NaOMe in MeOH; (c) TESOTf, 2,6-lutidine; (d) acetone, PPTS.

Scheme 59. The synthesis of the aldehyde **169**

After the *tert*-alcohol is protected as a triethylsilyl ether the selective removal of the dioxolane protecting group should afford the desired aldehyde **169**. These synthetic transformations will be discussed in this section.

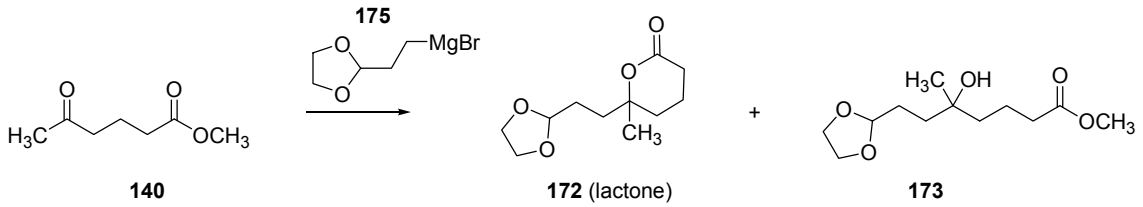
3.6.1 ***Grignard reaction***

The Grignard reagent **175** was prepared from 2-(2-bromoethyl)-1,3-dioxolane[82] (**171**) according to a published procedure. When the reaction of **140** and **175** was conducted under described reaction conditions, only a poor yield of the desired product was obtained, suggesting that an optimization of the reaction conditions was required.

The tested reaction conditions are summarized in Table 6. When THF/Et_2O 1:1 or THF/PhH 2:1 were used as solvent and the reaction was conducted at 0 to -5 °C, yields of 87 and 77% respectively, could be obtained.

Under the conditions of the Grignard reaction, alcohol **173** partly underwent cyclization giving lactone **172**. To obtain the desired *tert*-alcohol **173** the crude reaction product was treated with NaOMe in MeOH at rt.

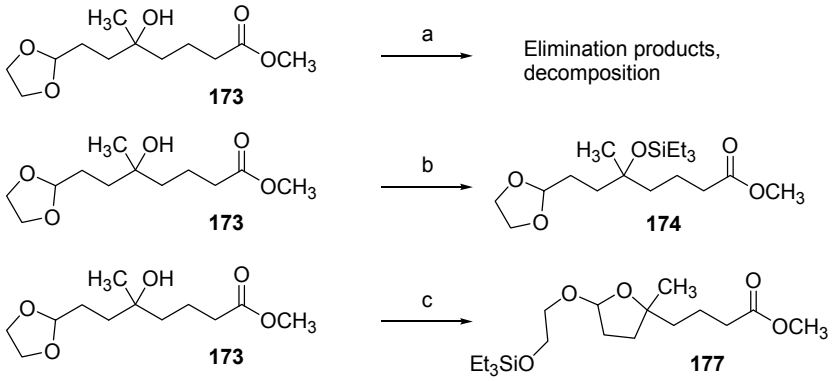
Table 6. Optimization of the Grignard reaction



140 **172** (lactone) **173**

entry	conditions	yield,[j] %	notes
1	1 equiv **175**, THF, -78 °C	20	incomplete reaction
2	2 equiv **175**, THF, -90 °C	30	incomplete reaction
3	2 equiv **175**, THF, -78 °C	37	incomplete reaction
4	2 equiv **175**, THF, 0 - -5 °C	32	complete reaction
5	2 equiv **175**, THF, rt	30	complete reaction
6	1 equiv **175**, rt; then NaOMe in MeOH	60	incomplete reaction
7	1.3 equiv **175**, "One-pot", THF, rt	-	incomplete reaction
8	1.3 equiv **175**, THF/Et_2O 1:1, 0 to -5 °C; then MeOH, NaOMe	87	almost complete reaction
9	1.3 equiv **175**, THF/PhH 2:1, 0 to -5 °C; then MeOH, NaOMe	77	almost complete reaction

The protection of the *tert*-alcohol **173** as a triethylsilyl ether also required the optimization of the reaction conditions (Scheme 60). The temperature control appeared to be important for the desired outcome of the reaction.



(a) 2.0 equiv TESOTf, 3.0 equiv 2,6-lutidine, CH_2Cl_2, rt; (b) 1.5 equiv TESOTf, 2.0 equiv 2,6-lutidine, CH_2Cl_2, -78 °C, quenched while cold, 80% after flash; (c) 2.0 equiv TESOTf, 1.7 equiv 2,6-lutidine, CH_2Cl_2, -78 °C → rt, 30%.

Scheme 60. Reaction of the *tert*-alcohol **173** with TESOTf and 2,6-lutidine

Conducting the reaction at rt resulted in the formation of a complex mixture of products. When the addition of TESOTf was performed at -78 °C followed by warming the reaction

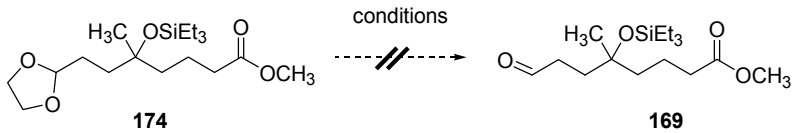
[j]) For the mixture of the lactone **172** and the *tert*-alcohol **173**.

mixture to rt, the undesired product **177** was obtained with 30% yield. The desired silyl ether **174** could be obtained in a yield of 80% when 1.5 equiv of TESOTf and 2.0 equiv of 2,6-lutidine were used and the reaction mixture was stirred for 6 h at -78 °C followed by quenching while cold.

3.6.2 1,3-Dioxolane deprotection

A number of different reagents and reaction conditions was tested in order to selectively cleave the dioxolane protecting group of **174** in the presence of the triethylsiloxy group and to obtain the aldehyde **169** (Table 7).

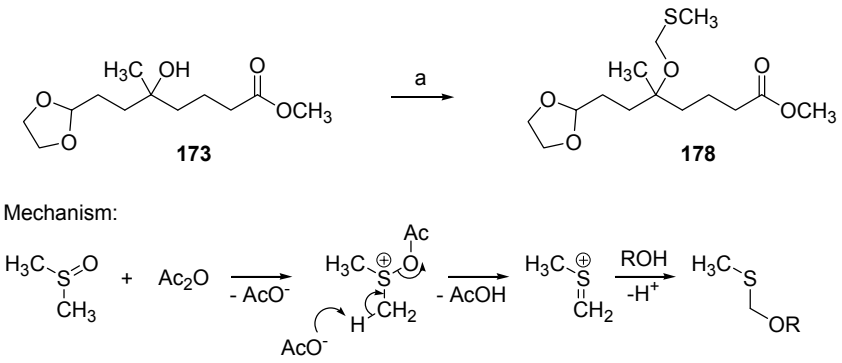
Table 7. Cleavage of the 1,3-dioxolane protection in the presence of the TES-ether



entry	conditions	notes
1	30 mol% PPTS, acetone/H_2O 10:1, reflux, 5 h	no reaction
2	30 mol% PPTS, wet acetone, reflux, 2 h	no reaction
3	1 equiv PPTS, MeOH, rt	deprotection of the TES group
4	cat. *p*-TsOH·H_2O, acetone	simultaneous TES and dioxolane deprotection
5	1.3 equiv *p*-TsOH, acetone/H_2O 15:1, reflux, 4 h	simultaneous TES and dioxolane deprotection
6	3.75 equiv $FeCl_3$, CH_2Cl_2, rt	simultaneous TES and dioxolane deprotection
7	50 mol% $PdCl_2(CH_3CN)_2$, wet acetone, rt, dark, 3d	decomposition

3.6.3 Protection of the tert-alcohol as MTM ether

As it was not possible to find reaction conditions that allowed the deprotection of the aldehyde function leaving the TES group intact, we decided to check if MTM protection of the *tert*-alcohol **173** allow the chemoselective cleavage of the 1,3-dioxolane moiety. To introduce the MTM protecting group, the alcohol **173** was treated with the mixture of DMSO and acetic anhydride at -78 °C to afford the desired MTM ether **178** in an 85% yield. The mechanism of this transformation resembles the Pummerer rearrangement with the difference that in the last mechanistic step the alcohol acts as a nucleophile instead the acetate anion (Scheme 61).



(a) DMSO, Ac_2O, 30 h at 25 °C, 85%.

Scheme 61. MTM protection of the *tert*-alcohol **173**

We tested a set of reaction conditions in order to selectively deprotect the 1,3-dioxolane in the presence of the MTM protecting group (Table 8, compare with Table 7). Unfortunately, the desired aldehyde **169** could not be obtained.

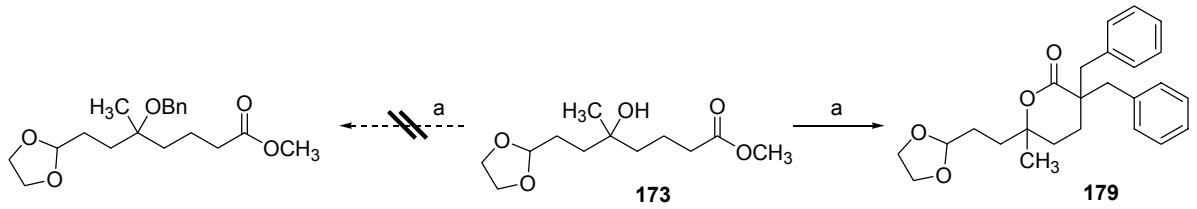
Table 8. Cleavage of the 1,3-dioxolane protection in the presence of the MTM ether

entry	conditions	notes
1	48 mol% TsOH, acetone, 12 h, rt	decomposition
2	3.75 equiv $FeCl_3$, CH_2Cl_2/acetone 4:1, rt, 2 h	decomposition, traces of the product
3	30 mol% PPTS, acetone, 12 h, rt	no reaction
4	45 mol% PPTS, acetone, 48 h, 40-50 °C	decomposition
5	30 mol% PPTS, reflux in wet acetone, 12 h	decomposition
6	conc. AcOH, acetone	no reaction
7	50% aqueous AcOH, acetone	no reaction

3.6.4 Protection of the tert-alcohol as a benzyl ether

It is well known that alkyl ethers are less prone to cleavage under acidic conditions compared to silyl, and especially triethylsilyl ethers. We decided to protect the *tert*-alcohol **173** as a benzyl ether, since that would allow to use strong acids (aq. HCl) for the chemoselective cleavage of the 1,3-dioxolane.

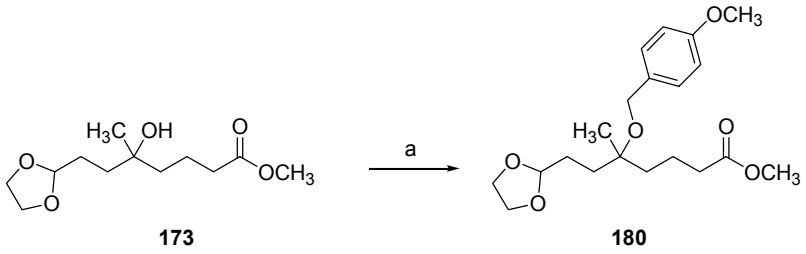
The reaction of **173** with BnBr in the presence of KH unexpectedly gave compound **179** as the product (Scheme 62).



(a) KH, BnBr in THF, 0 °C → rt.

Scheme 62. Reaction of **173** with BnBr and KH

Since the reaction with BnBr under basic conditions led to the formation of the lactone **179** we investigated the possibility to protect alcohol **173** as PMB ether under acidic conditions (Scheme 63).



(a) PMBOC(=NH)CCl_3, 0.3 mol% TfOH, 20 mol% CSA in two portions, Et_2O, 30 h, 88% yield.

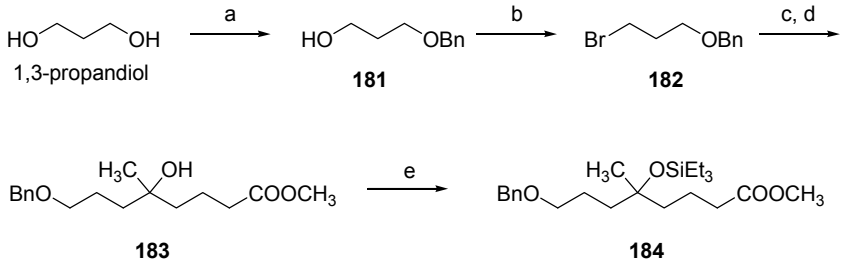
Scheme 63. Protection of the alcohol **173** as a PMB ether

The crude reaction product required extensive chromatographic purification, that resulted in a diminished yield of **180** (36% after two chromatographic separations).

*3.6.5 **Grignard reaction with 3-(benzyloxy)-propylmagnesium bromide***

Having investigated a number of different groups (TES, MTM, Bn and PMB) for the protection of the *tert*-alcohol **173** and have not found a suitable one we considered the possibility of masking the aldehyde group of **169** with such a function which can be removed under neutral conditions that tolerate a *tert*-triethylsilyl ether. For example, aldehyde **169** is directly accessible by the oxidation of the corresponding primary alcohol, which in turn can be temporarily protected as a Bn ether **184** (Scheme 64). Important, that the deprotection of a Bn ether and the oxidation of a primary alcohol can be conducted under neutral conditions, compatible with a TES group.

The synthesis of **184** started from 1,3-propanediol (Scheme 64). Alkylation of one of the two hydroxy groups with BnCl furnished alcohol **181**. This alcohol was converted to the corresponding bromide **182** by treatment with PPh_3 and NBS.



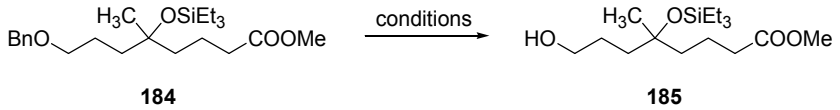
(a) Na, BnCl, *o*-xylene, 65%; (b) NBS, Ph_3P, 64%; (c) 3 equiv Mg, methyl 5-oxo-hexanoate; (d) NaOMe, MeOH, 83%; (e) TESOTf, 2,6-lutidine, 80%.

Scheme 64. Synthesis of the methyl ester **184**

Bromide **182** was required for the synthesis of 3-(benzyloxy)-propylmagnesium bromide,[134] the Grignard reagent, which was reacted with the methyl 5-oxohexanoate (**140**) (compare with Section 3.6.1). The crude product of the Grignard reaction was treated with NaOMe in MeOH affording the *tert*-alcohol **183** in 80% yield. As we did with **173** (see Section 3.6.1), the alcohol **183** was converted to the triethylsilyl ether **184** (Scheme 64) by treatment with a slight excess of TESOTf and 2,6-lutidine at -78 °C.

A number of conditions was tested to selectively cleave the primary Bn-ether of **184** as summarized in Table 9. Catalytic hydrogenation with Pd/C and $Pd/CaCO_3$ catalysts, transfer hydrogenation using 1,4-cyclohexadiene as a hydrogen donor and Pd/C catalyst as well as the Birch reduction protocol did not afford the desired alcohol **185**.

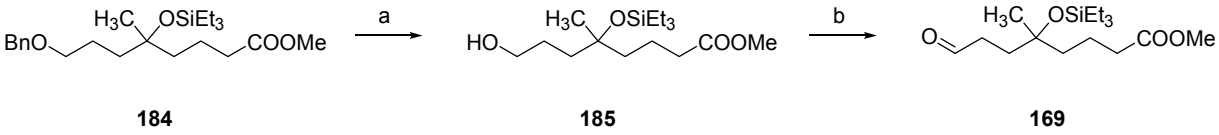
Table 9. Hydrogenolytic cleavage of the Bn-ether **184**



entry	conditions	notes
1	10% Pd/C, H_2, 1 atm, MeOH, rt	cleavage of both Bn and TES groups
2	5% $Pd/CaCO_3$, Et_3N (inhib.), H_2, 1 atm, MeOH, rt	starting material
3	10% Pd/C, 1,4-cyclohexadiene, EtOH, 12 h, rt	cleavage of both Bn and TES groups
4	Na in liquid NH_3	decomposition
5	Ni Raney W2 catalyst, H_2, 1 atm, MeOH, rt	98% yield

Fortunately, **185** was obtained with an excellent yield of 98% when the reaction was conducted using Ni Raney W2 catalyst (Scheme 65).[135]

Oxidation of the primary alcohol **185** was conducted according to the Swern protocol[k] and afforded aldehyde **169** in an 86% yield (Scheme 65).



184 **185** **169**

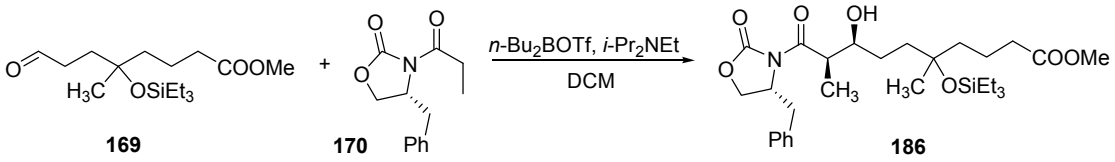
(a) H_2, Raney Ni "W2"; MeOH, rt, 12 h, 98%; (b) DMSO, $(COCl)_2$, -78 °C, CH_2Cl_2, 86%.

Scheme 65. Completion of the synthesis of the aldehyde **169**

3.6.6 The Evans aldol reaction

With the aldehyde **169** in hand the Evans aldol reaction was studied. When the reaction was conducted under the published reaction conditions,[99] no aldol product could be isolated since most of the aldehyde was isolated unchanged. In order to obtain the required aldol product with a suitable yield the reaction conditions were optimized as summarized in Table 10.

Table 10. The optimization of the Evans aldol reaction



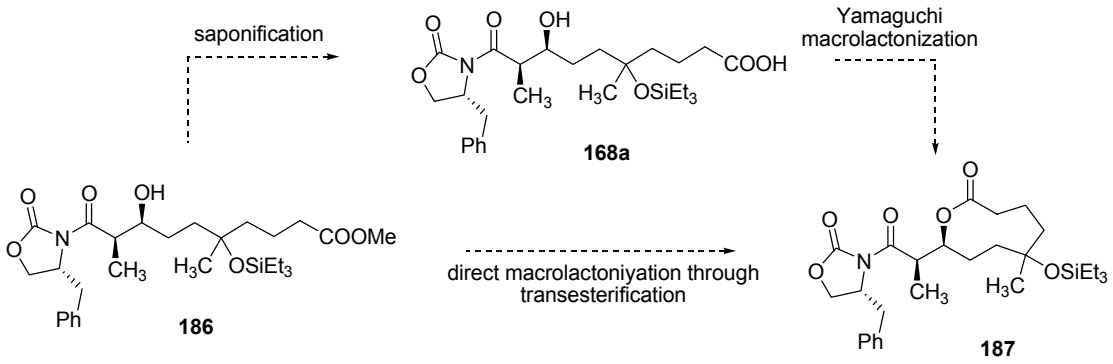
169 **170** **186**

entry	**170**	Bu_2BOTf	*i*-Pr_2EtN	**169**		conditions	yield, %	notes
	equiv			equiv	mmol/L[l]			
1	1	1.2	1.3	0.97	25.8	30 min at -78 °C, then to rt	0	no reaction
2	1	1.2	1.3	0.97	41.8	40 min at -78 °C and 1 h at 0 °C	traces	not reaction
3	1	1.2	1.3	0.97	68.0	2 h at 0 °C and 15 h at rt	40	33% of **169** left, a few side-products
4	2	2.4	2.6	0.97	81.2	2 h at 0 °C and 15 h at rt	44	incomplete, byproducts
5	1	1.2	1.3	0.97	57.1	0 °C, 2 h	< 30	complete, byproducts
6	1	1.2	1.3	0.97	34.8	2 h at 0 °C and 5 h at rt	< 30	incomplete
7	1	1.2	1.3	0.97	57.6	2 h at 0 °C and 15 h at rt	< 30	incomplete, byproduct
8	2	2.2	2.5	0.97	19.8	2 h at -10 to -15 °C	84	complete, little byproduct
9	2	2.2	2.5	0.97	56.8	6 h at -10 to -15 °C and 15 h at rt	60	20% of **169** left, byproduct

[k]) Oxidation with TPAP-NMO was very slow.
[l]) Concentration of the aldehyde **169** in the reaction mixture during the aldol reaction.

It was found that if the aldol reaction was conducted at -78 °C no or little aldol product was formed (entry 1, 2). When the reaction was conducted at 0 °C, the desired product could be isolated in 40% yield together with approx. 30% of the starting aldehyde (entry 3). When 2 equiv of the boron enolate were used, a complex mixture of reaction products was obtained with a little improvement of the yield (entry 4). Fortunately, when the reaction was conducted at -10 to -15 °C with 2 equiv of the boron enolate, the desired aldol product **186** could be isolated with 84% yield. The aldehyde was almost completely consumed and only traces of byproducts were detected by TLC (entry 8).

With the aldol product **186** in hand we considered two possible ways towards the construction of the 9-membered lactone **187**, an analogue of **142** (Scheme 58). One possibility was to exploit the Yamaguchi macrolactonization[94] protocol which required *seco*-acid **168a** as the starting material and the other possibility was to conduct a direct intramolecular transesterification of the aldol product **186** (Scheme 66). We first decided to investigate the formation of the lactone **142** by an intramolecular transesterification since this pathway has the advantage of less synthetic steps.

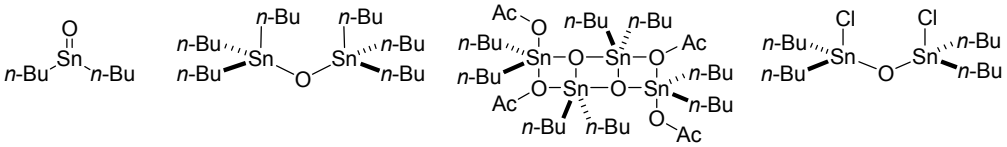


Scheme 66. Two possible ways towards the construction of the 9-membered lactone **187**

*3.6.7 **Macrolactonization through intramolecular transesterification***

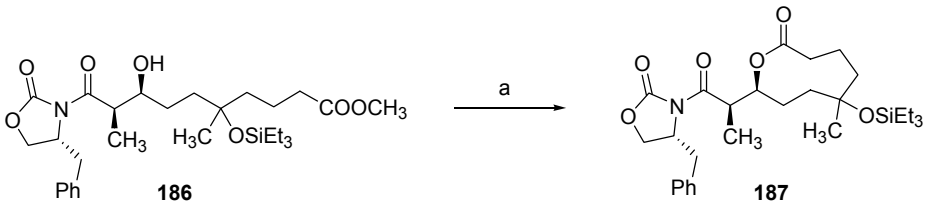
Transesterification has been carried out traditionally and most frequently using acidic or basic catalysts.[100] When the substrate posses no labile functional groups, is cheap and available, strong mineral acids are probably best catalysts. For the substrates, which are not compatible with strong acids or bases, neutral transesterification catalysts are required.

Several organotin compounds, which are neither strong acids nor strong bases, are known to catalyze transesterification reactions (Scheme 67).[100,101] The activity of these catalysts can be attributed to the ability of tin to enhance the nucleophilicity of a heteroatom bound to it, making alcohols more reactive in a transesterification process.



Scheme 67. Organotin transesterification catalysts

The first two catalysts, *n*-Bu_2SnO and (*n*-$Bu_3Sn)_2O$, were tested under conventional reflux conditions. When **186** was refluxed in toluene in the presence of 10 mol% of the catalyst over 48 h, the 9-membered lactone **187** could be obtained with a 20% yield. It is worth to note that (*n*-$Bu_3Sn)_2O$ appeared to be more effective under the specified reaction conditions (Scheme 68).



(a) 10 mol% (*n*-$Bu_3Sn)_2O$, toluene, reflux 48 h, 20%.

Scheme 68. (*n*-$Bu_3Sn)_2O$ catalyzed intramolecular transesterification of **186**

The product **187** was obtained as a mixture of two diastereomers. Chromatographic separation on silica gel using hexane/AcOEt 10:1 proved to be difficult because of close R_f values of the products. Nevertheless each diastereomer of the 9-membered lactone **187** could be obtained in pure form and analyzed with the help of spectroscopic methods. Figure 11 and Figure 12 present the ^1H NMR and ^{13}C spectra of both compounds.

The use of microwave assisted heating allowed conducting the reaction at a temperature exceeding the boiling point of the solvent used. For *n*-Bu_2SnO and (*n*-$Bu_3Sn)_2O$ catalysts there was no yield enhancement when microwave heating was used.

We investigated two other catalysts, [*n*-$Bu_2(OAc)Sn]_2O]_2$ and [*n*-$Bu_2ClSn]_2O$ using a combination of microwave heating and HPLC to analyze the reaction mixture. Results are summarized in Table 11.

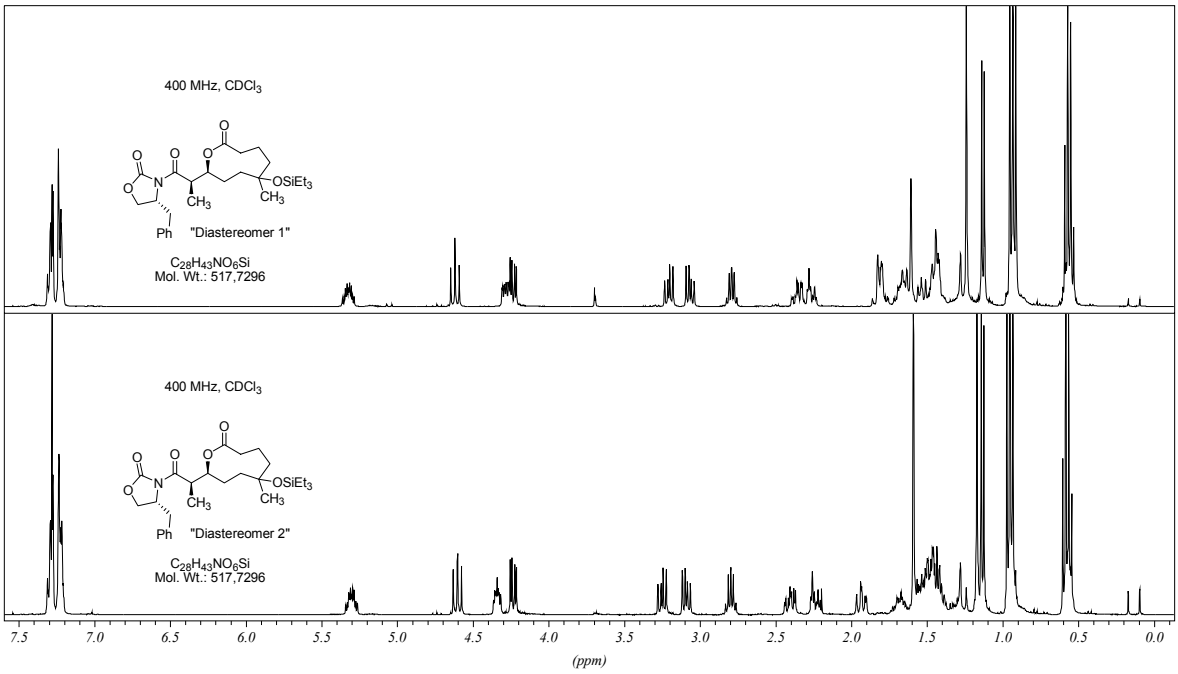


Figure 11. ^{1}H NMR spectra of the diastereomers of **187**

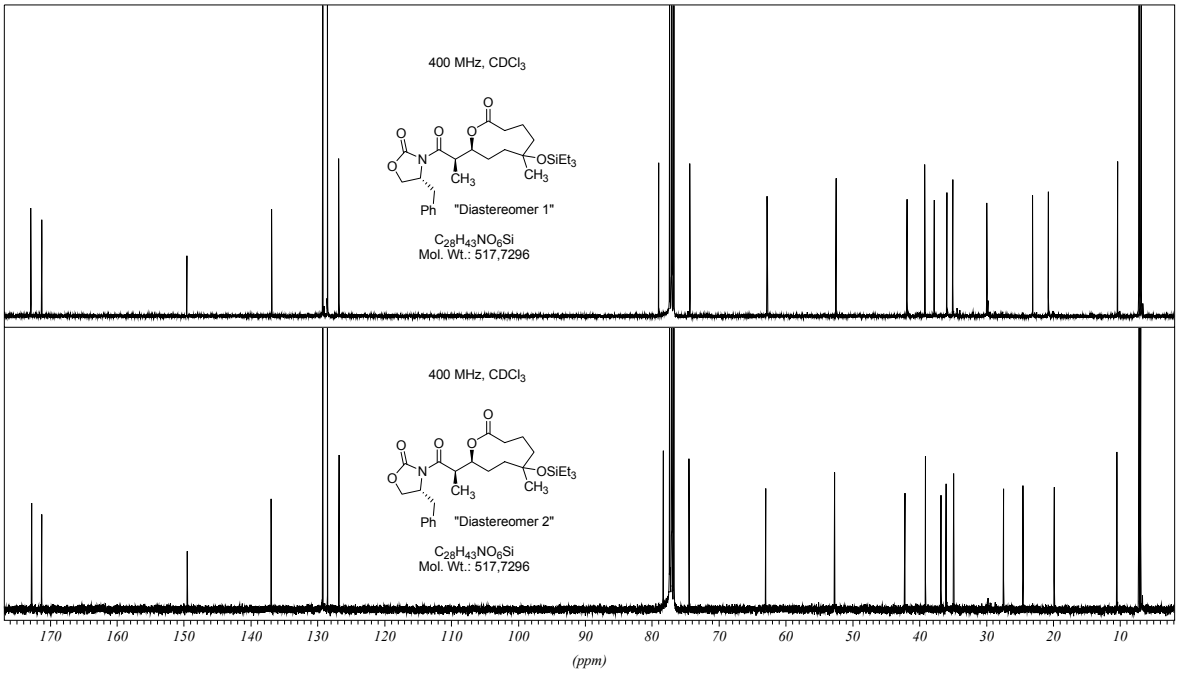
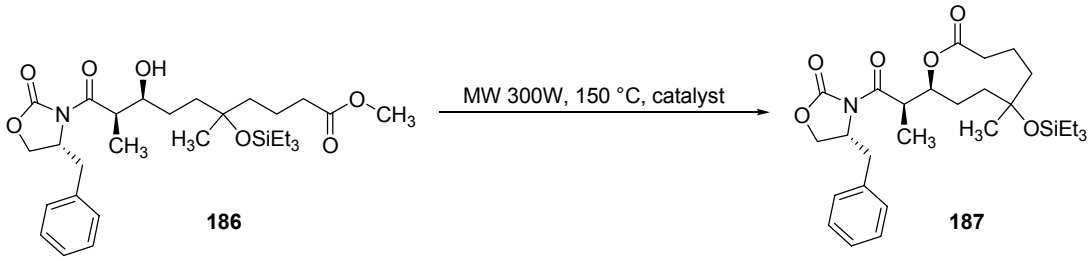


Figure 12. ^{13}C NMR spectra of the diastereomers of **187**

Table 11. Intramolecular transesterification of **186** using organotin catalysts



186 **187**

entry	conditions[m]	**186**, %[n]	**187**, %[o]
1	2.5 mol% {[*n*-Bu_2(OAc)Sn]$_2$O}$_2$, 150 °C, 1 h	61	19
2	2.5 mol% {[*n*-Bu_2(OAc)Sn]$_2$O}$_2$, 150 °C, 2 h	49	21
3	2.5 mol% {[*n*-Bu_2(OAc)Sn]$_2$O}$_2$, 150 °C, 3 h	45	21
4	3.6 mol% [*n*-Bu_2ClSn]$_2$O, 150 °C, 1 h	39	29
5	3.6 mol% [*n*-Bu_2ClSn]$_2$O, 150 °C, 2 h	23	28
6	3.6 mol% [*n*-Bu_2ClSn]$_2$O, 150 °C, 3 h	21	33

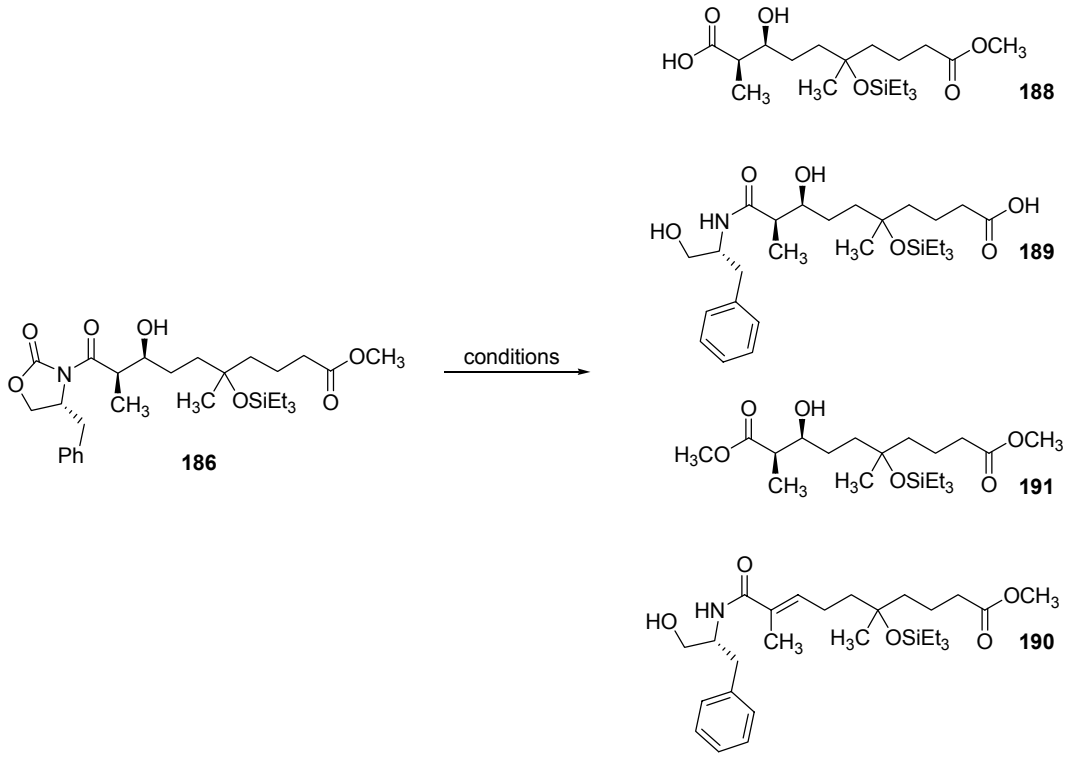
Having investigated a number of catalysts and reaction conditions we were able to obtained the desired 9-membered lactone **187** with yields up to 30%. Though direct transesterification has the advantage of less synthetic steps compared to the saponification/Yamaguchi macrolactonization approach (Scheme 66), we could not be satisfied with the low yields of **187** and investigated the alternative synthetic way.

3.6.8 ***Saponification of the methyl ester***

For the Yamaguchi macrocyclization the *seco*-acid **168a** was required (Scheme 66). In order to selectively saponificate the methyl ester in the presence of the oxazolidine imide a number of reaction conditions was investigated (Table 12).

[m]) 25 mg of **186** were dissolved in $PhCH_3$ (5 mL), $c = 9.1 \cdot 10^{-3}$ M. The catalyst was added and the reaction mixture was irradiated in the microwave oven at 300W for the indicated period of time.
[n]) The yield was determined with the help of HPLC on a LiChrospher 250-4 RP18 (5 µm) column at 1 mL/min flow rate of MeOH/H_2O 85:15. For the aldol **186** a 4-point calibration was conducted. **186** had a $R_t = 10.61$ min.
[o]) As above. For the macrolactone a 5-point calibration was performed. Diastereomers of **187** had a $R_t = 13.01$ min (diastereomer II) and 16.30 min (diastereomer I).

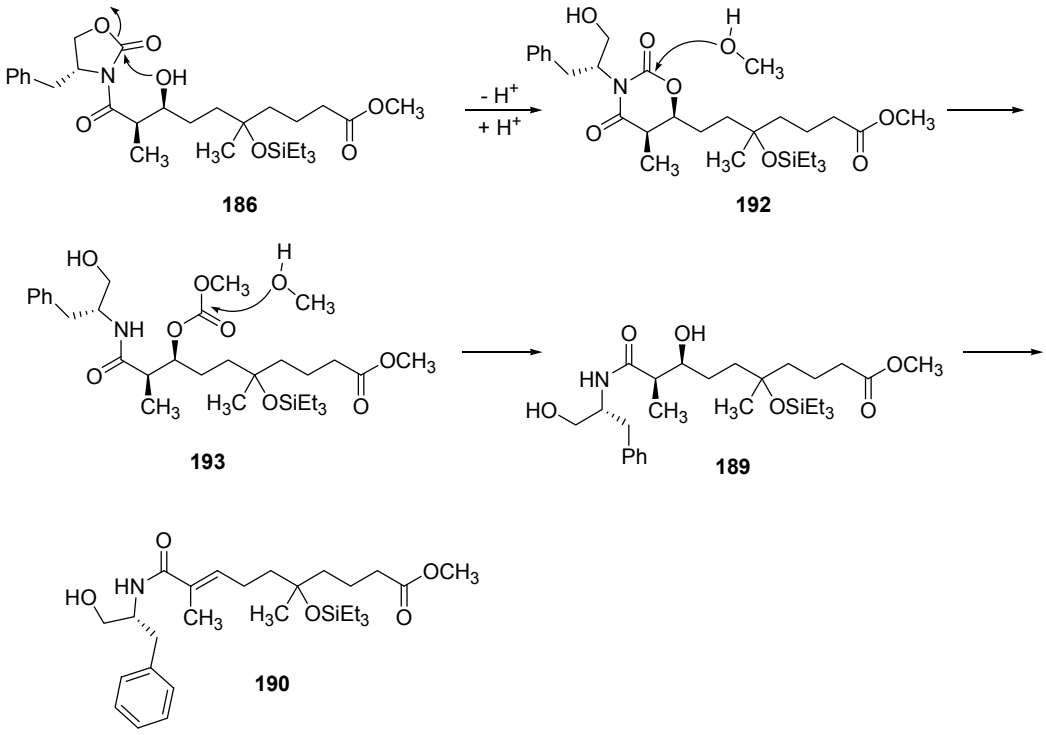
Table 12. Attempted saponification of the methyl ester **186**



entry	Conditions	Product
1	LiOOH, THF-H2O 4:1, 70%	**188**
2	$Ba(OH)_2 \cdot 8H_2O$, MeOH	**189**
3	Me_3SiOK, Et_2O, 25%	**190**
4	LiOH in THF/MeOH/H_2O 2:2:1, rt, 34%	**191**
5	240 units PLE, pH 7.0 phosphate buffer	starting material

None of the tested reaction conditions allowed a chemoselective cleavage of the methyl ester of **186**, leaving the oxazolidine ring intact.

We believe that the secondary hydroxy group of **186** facilities intramolecular cleavage of the Evans auxiliary as shown in the Scheme 69.

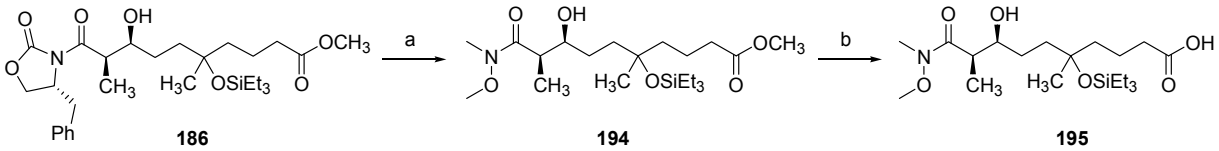


Scheme 69. Anchimerically assisted methanolysis of the oxazolidine auxiliary

The *seco*-acid **168a** was therefore not directly accessible from the aldol product **186**.

*3.6.9 **Synthesis of the seco-acid***

In order to get access to the *seco*-acid required for the Yamaguchi macrocyclization we decided first to convert imide **186** into the Weinreb amide **194** and then to saponificate **194** to the *seco*-acid **195** (Scheme 70).



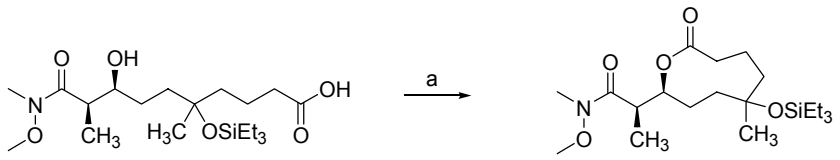
(a) 3.4 equiv $NHCH_3(OCH_3)\cdot HCl$, 3.4 equiv Me_3Al, THF, 0 °C, 2.5 h, 75%; (b) 0.43 M LiOH in THF/MeOH 1:1, 2.5 h at rt, 95%.

Scheme 70. Synthesis of the *seco*-acid **195**

This approach proved to be successful. The transamination furnished the Weinreb amide with a yield of 75% when **186** was treated with $NHCH_3(OCH_3)\cdot HCl$ and Me_3Al. The reaction of **194** with LiOH in THF/MeOH 1:1 afforded the desired *seco*-acid **195** in 95% yield.

3.6.10 ***Yamaguchi macrocyclization***

With the *seco*-acid **195** in hand we could carry out the Yamaguchi macrocyclization.[94,102] First, the solution of the *seco*-acid **195** in THF was treated with 2,4,6-trichlorobenzoyl chloride and Et_3N as the base to afford the mixed anhydride. The macrolactonization took place when the solution of the mixed anhydride was slowly added to a refluxing solution of DMAP in toluene. The 9-membered macrolactone **196** was obtained with yields of 75-90% after a simple extractive workup and a chromatographic purification (Scheme 71).



195 **196**

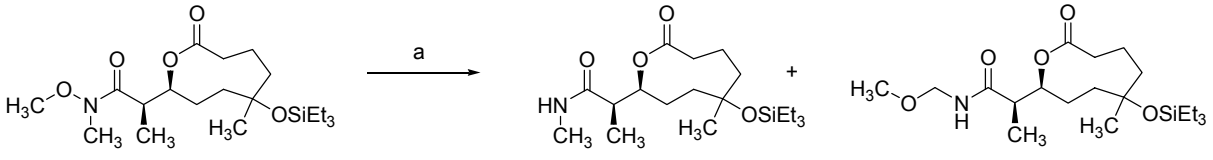
(a) 1) 3 equiv 2,4,6-trichlorobenzoyl chloride, 3 equiv Et_3N, THF; 2) add to 6 equiv of DMAP in toluene over 8 h at reflux, 75-90% yield.

Scheme 71. Yamaguchi macrolactonization of Weinreb amide **195**

3.6.11 ***Dieckmann condensation***

Having achieved some positive results with the Dieckmann condensation of two model substrates (Section 3.5.3) we investigated the reaction of **196** with strong bases. Reactions of **196** with various bases are summarized in Table 13. No reaction took place when the solution of **196** was refluxed with NaH in toluene (entry 2). Also with KHMDS in THF at -78 °C no reaction progress was detected (entry 6). When the addition of KHMDS was done at -78 °C and then the reaction mixture was slowly warmed to rt, the starting material was consumed and a complex mixture of products was obtained (entry 7).

Four new products could be isolated when the reaction was conducted with 2 equiv of LDA at -78 °C (entry 3). After chromatographic separation and thorough analysis using spectroscopic methods two of the products could be assigned structures **198** and **199** (Scheme 72).

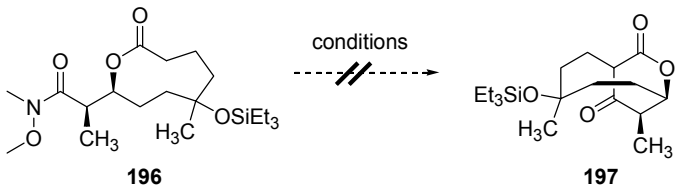


198 **198** **199**

(a) 2 equiv LDA, THF, -78 °C, 1.5 h, 55%.

Scheme 72. Products of the reaction of **185** with LDA

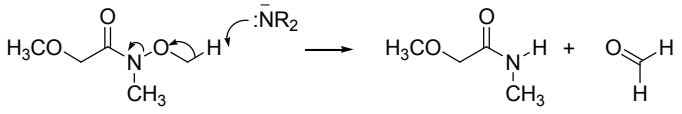
Table 13. Attempted Dieckmann condensation of the Weinreb amide **196**



196 **197**

entry	conditions	notes
1	2 equiv NaHMDS, -78 °C → -30 °C, 12 h	starting material
2	2.5 equiv NaH, reflux in toluene	starting material
3	2 equiv LDA, -78 °C, 30 min	4 new spots, complete reaction
4	4 equiv LiHMDS, -78 °C to rt	starting material
5	4 equiv LiHMDS, 3 equiv TMSI, -78 °C to rt	starting material
6	2 equiv KHMDS, 1 h at -78 °C,	starting material
7	2 equiv KHMDS, -78 °C → rt	decomposition
8	2 equiv, 78 °C → -30 °C then TBAF	decomposition
9	6.5 equiv KHMDS, 3 equiv TMSCl	4 unidentified products
10	4 equiv KHMDS, reversed slow addition, -40 °C	decomposition
11	4 equiv Ph_3CLi, rt, 14 h	starting material, decomposition
12	4 equiv Ph_3CLi, 0 °C → rt, 14 h	starting material

Formation of **198** and **199** from **196** under the action of LDA was neither desired nor expected. Having studied the literature we have found that a similar, rather unusual, transformation of a Weinreb amide has been reported by Graham and Scholz.[103] They observed the fragmentation of a Weinreb amide resulting into formation of an *N*-methylamide and formaldehyde. It was proposed that the reaction involves an E2-elimination (Scheme 73). Two other groups have made similar observations.[104]



200

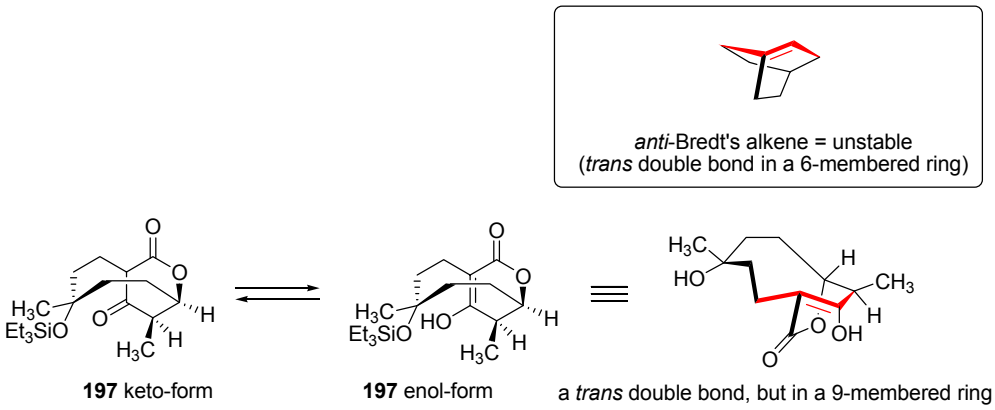
Scheme 73. Fragmentation of Weinreb amides

Unfortunately, it was not possible to find a base and reaction conditions that afforded the desired 1,3-dicarbonyl compound **197**. We attribute the failure of the Dieckmann condensation of **196** to the hampered enolization of the desired 1,3-dicarbonyl compound (Scheme 74).

The ester condensation is a reversible, thermodynamically controlled reaction and the formation of a resonance-stabilized enolate of the 1,3-dicarbonyl compound is its driving force. If the enolization of the 1,3-diketone is not possible, such product is not formed.[105]

The Bredt's rule says that *a bridged bicyclic hydrocarbon cannot have a double bond involving a bridgehead carbon unless one of the rings contains at least eight carbons atoms*. Such a bridged double bond common for the two small ring is equal to a *trans*-double bond in a small ring, what obviously causes severe strain.

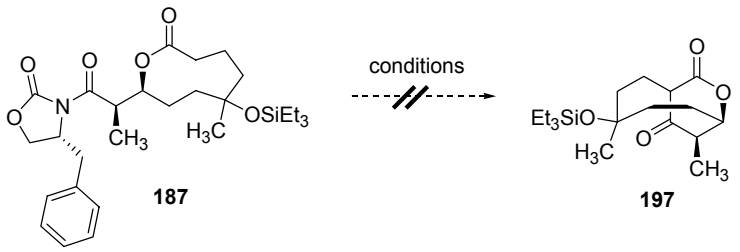
In the case of the ***enol*-197** we have a bridged [2.2.5]bicyclic alkene with a *trans*-double bond in a 9-membered ring (Scheme 74). Therefore, one may expect that ***enol*-197** is higher in its energy compared to ***keto*-197** making enolization unfavorable and resulting in the failure of the Dieckmann condensation.



Scheme 74. The hindered enolization of **197**

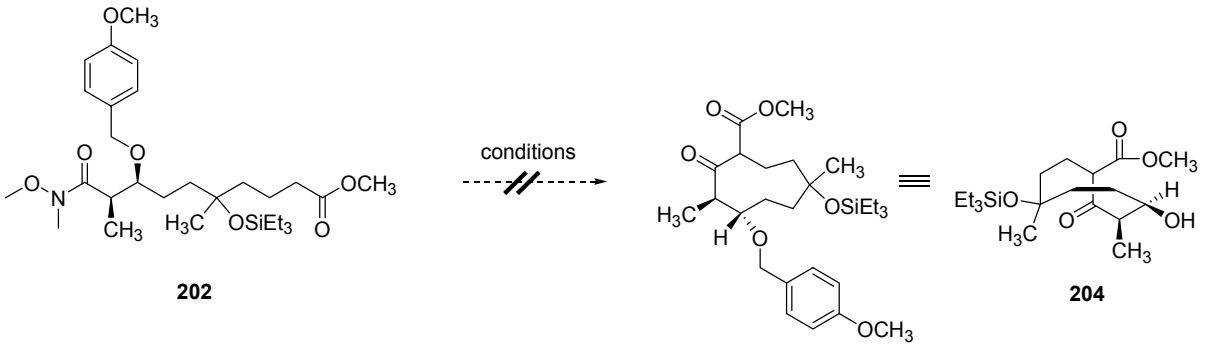
We attempted to carry out the Dieckmann condensation with three another substrates: **187**, **202** and **203**, but, unfortunately, without success (Table 14, Table 15, Table 16).

Table 14. Attempted Dieckmann condensation of the imide **187**



entry	conditions	notes
1	1, 2, 3 equiv LDA, -78 °C → rt, 12 h	starting material
2	2.5 equiv LiHMDS, -78 °C → -30 °C	starting material

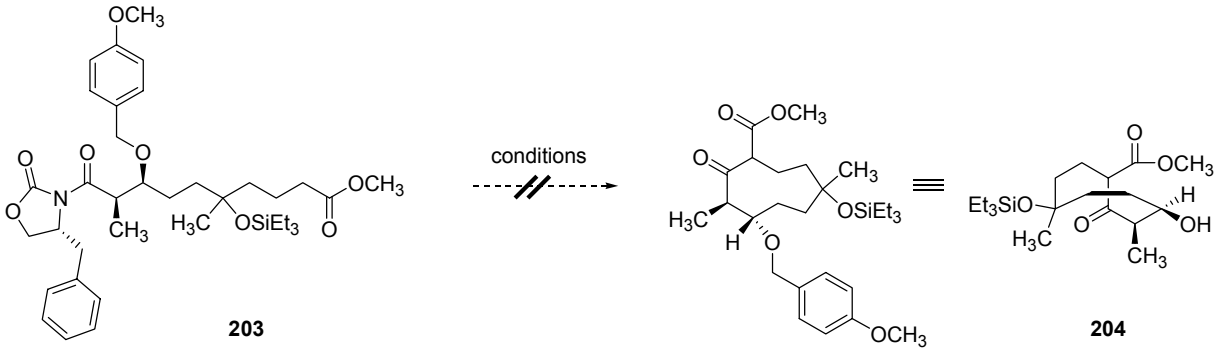
Table 15. Attempted Dieckmann condensation of the Weinreb amide **202**



202 **204**

entry	conditions	notes
1	2.5 equiv *t*-BuOK, toluene, 0 °C, 2 h	No reaction
2	2.5 equiv *t*-BuOK, toluene, rt, 18 h	No reaction
3	5 equiv *t*-BuOK, toluene, reflux, 2 h	No reaction
4	1.2 equiv LDA, -78 °C	No reaction
5	1.2 equiv LDA, -78 °C to rt	No reaction
6	2 equiv LHMDS, -78 °C → rt, 1 h	No reaction
7	2 equiv LHMDS, 0 °C → rt, 1 h	No reaction
8	1 equiv LHMDS, 0 °C → rt, 1 h	No reaction

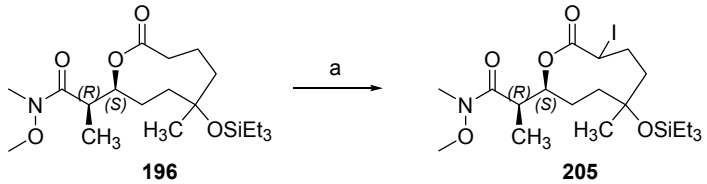
Table 16. Attempted Dieckmann condensation of the imide **203**



203 **204**

entry	Conditions	notes
1	2.5 equiv *t*-BuOK, toluene, 0° C, 2 h	No reaction
2	2.5 equiv *t*-BuOK, toluene, rt, 24 h	No reaction

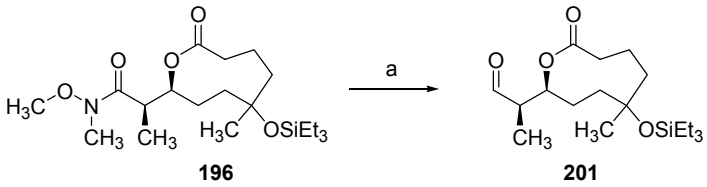
Though the Dieckmann condensation failed to afford **197** it was possible to trap the enolate of **196** with I_2 and to obtain the corresponding iodide (Scheme 75).



(a) 2.7 equiv Ph_3CLi, -78 °C, then 6 equiv I_2, warm to rt.

Scheme 75. Trapping the enolate of **196** with iodine

In addition it was possible to conduct the reduction of the Weinreb amide **196** to the aldehyde **201** with DIBAL (Scheme 76).



(a) 4 equiv DIBAL, THF, -78 °C, 13%.

Scheme 76. Reduction of the Weinreb amide **196**

3.7 Conclusion and outlook

Investigation of the stereochemical outcome of the Tandem Michael Addition - Aldol reaction together with the study of the retroaldol reaction and the epimerization provided insights into the reactions involved in the construction of the C-ring of hexacyclinic acid. It also helped to find the reason for the wrong stereochemistry of a C8 stereocenter in the X-ray structure analysis of the totally deprotected ABC fragment **94**.

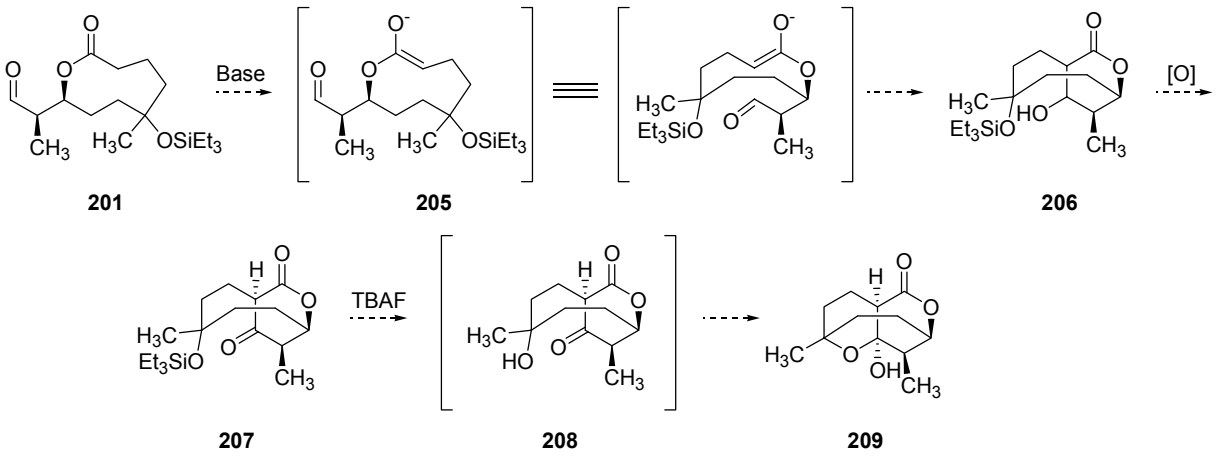
It was shown that the reaction of a Grignard reagent generated from 1-(benzyloxy)-3-brompropane with the methylketone **132a** selectively furnishes the undesired Felkin product **134**. This finding will be of value for the work on the total synthesis of hexacyclinic acid.

Several strategies towards the construction of the DEF core have been studied. The ring closing alkene metathesis using a number of catalysts and different substrates did not prove to be successful in the synthesis of the 9-membered lactone **196**.

A new, reconsidered retrosynthetic approach, featuring a Grignard reaction, an Evans aldol reaction and a Yamaguchi macrolactonization led to the successful synthesis of the 9-membered lactone **196**.

Despite the promising model studies of the Dieckmann condensation with an acetate and a propionate precursor, the reaction could not be successfully transferred to the advanced substrate **196**. The failure of the Dieckmann condensation we attributed to the hindered enolization of the desired product, the 1,3-dicarbonyl compound **197**.

Since the key step of our approach, the Dieckmann condensation, has failed, it is important to propose and to investigate other possibilities to access the DEF cyclic fragment. In this regard an approach featuring an intramolecular aldol reaction[106] could be useful (Scheme 77).

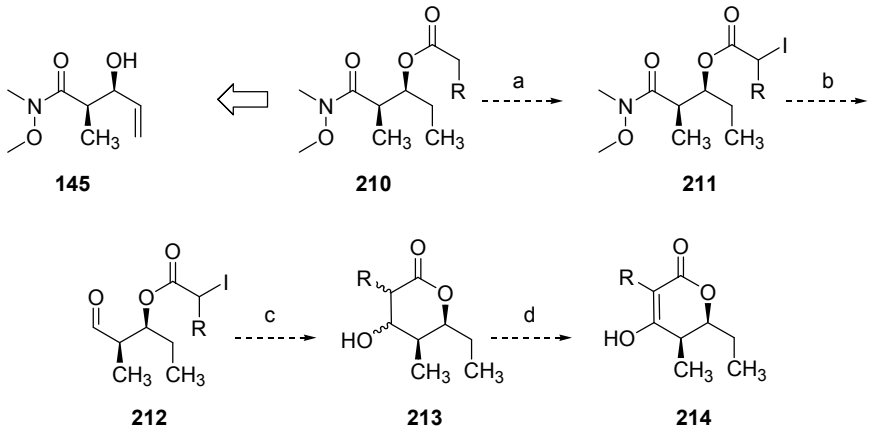


Scheme 77. The construction of the DEF ring fragment via intramolecular aldol reaction

A possible complication associated with this approach may arise from the epimerization of **201** (α-position to aldehyde function) under the conditions of the aldol reaction.

According to another promising approach the construction of the E-ring can be achieved in an intramolecular Reformatsky reaction (Scheme 78). Since the classical method employing zinc dust as a reductant has been established, many improvements and modifications have been reported[107] employing either alternative elemental reductants, such as Cd,[108] Ni,[109] Co,[110] Ce,[111] Mn,[112] Mg,[113] Ge,[114] Sn,[115] In[116] or low-valent organometallic species, such as Cr(II),[117] titanocene(III),[118] $TiCl_2$,[119] and SmI_2.[120,121]

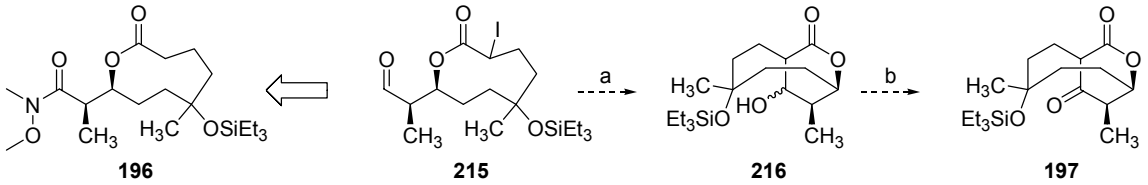
It is worth to note that the reaction may be investigated on an easily accessible model aldehyde **212** as shown in the Scheme 78.



(a) Ph_3CLi, I_2, THF, -78 °C; (b) DIBAL; (c) SmI_2, THF, -78 °C; (d) Dess-Martin oxidation, DCM.

Scheme 78. A model system to investigate the intramolecular Reformatsky reaction in the construction of the E-ring of hexacyclinic acid (**11**).

If the reaction affords the lactone **214** in a diastereomerically pure form (without epimerization), it can be applied to the advanced lactone **215**, furnishing the desired DEF fragment of the natural product (Scheme 79).



(a) SmI_2, THF, -78 °C; (b) Dess-Martin oxidation, DCM.

Scheme 79. Reformatsky reaction in the synthesis of the DEF fragment of hexacyclinic acid

We hope that a reliable strategy for the construction of the DEF cyclic fragment combined with the previously elaborated approach towards the ABC fragment will result in the successful synthesis of the hexacyclinic acid (**11**).

4 Experimental Part

4.1 General Methods

NMR spectra were recorded with Bruker AVS-500, AVS-400 or AM-200 spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm) on δ-scale. Corresponding solvent signal served as an internal standard: for ^{1}H NMR spectra in $CDCl_3$ - the singlet of $CHCl_3$ at δ7.26 ppm, in C_6D_6 - the singlet of C_6D_5H at δ7.16 ppm; for ^{13}C NMR spectra in $CDCl_3$ - the triplet at δ77.00 ppm, in C_6D_6 - the triplet at δ128.40 ppm. Values of the coupling constant, *J*, are given in hertz (Hz). Following abbreviations are used in the experimental section for the description of ^{1}H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of triplet (dt), doublet of quartets (dq), doublet of doublets of doublets (ddd), broad singlet (bs), broad doublet (bd) and broad triplet (bt). The chemical shifts of complex multiplets are given as the range of their occurrence.

^{13}C-Signals were assigned by means of standard DEPT 135 and DEPT 90 experiments and the following abbreviations are used in the experimental part: quaternary (Cq), methyne (CH), methylene (CH_2) and methyl carbon atom (CH_3) respectively. Further assignment of NMR-signals was achieved using two-dimensional NMR experiments when appropriate (H,H-COSY, HMQC and HMBC).

Infrared spectra were recorded with Bruker 580 FT-IR photometer. Samples were solved in dichloromethane or applied neat according to the "Golden-Gate" ATR method.

High-resolution electrospray-mass spectra (HRMS-ESI) were recorded with Waters Micromass LCT spectrometer with a Lock-Spray unit.

Elemental analyses were conducted on an Elementar Vario EL device with acetanilide as a standard.

Optical rotations were determined on a Perkin Elmer PE-241 instrument at 25 °C and using a light with 589 nm (D-line of sodium emission spectrum) and a cuvette of 10 cm length.

Analytical gas chromatography (GC) was performed with HP 6890 device using Macherey-Nagel "Optima 5" capillary column (30 m, 5% phenyl - 95% dimethylpolysiloxan) and a flame ionization detector. Nitrogen served as the carrier gas. According to the standard method used, the column temperature was maintained 50 °C for 1 min then rose to 300 °C at a 20 °C/min rate and was maintained at 300 °C till the end of the run. The overall run time was 20 min.

All air- and moisture sensitive reactions were performed under argon or nitrogen gas in heat gun-dried glassware.

Microwave heating was carried out with a CEM Discover® LabMate™ single-mode device. Reactions were conducted in 10 mL sealed Pyrex vessels, with a maximum operating temperature of 150 °C and a maximum pressure of 8 bar.

All experiments were monitored by thin layer chromatography (TLC) performed on Merck 60 F-254 (0.2 mm thick) silica gel aluminium supported plates. Spots were visualized by exposure to ultraviolet light (254 nm) or by staining with a "Vanillin" (85 mL MeOH, 5 mL H_2SO_4, 10 mL AcOH, 0.5 g vanillin (added last)), "Cer reagent" (10 g $Ce(SO_4)_2$, 25 g molybdophosphoric acid, 80 mL H_2SO_4, H_2O to 1000 mL), followed by heating or by "permanganate reagent" (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5% aqueous NaOH, 300 mL H_2O).

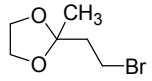
Flash chromatography was performed using J. T. Baker brand silica gel (40-60 µm, 60Å pores). Solvents for chromatography (usually *n*-hexane and ethyl acetate) were distilled prior to use and mixed in volumetric parts.

Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone. Dichloromethane was distilled from calcium hydride under argon.

Commercially available reagents were used as supplied.

4.2 Experimental procedures and spectral data

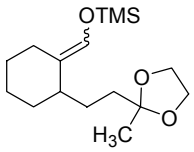
2-(2-Bromo-ethyl)-2-methyl-[1,3]-dioxolane (127)



$C_6H_{11}BrO_2$
Mol. Wt.: 195,05

Method a): **127** was obtained from methylviylketone (10.0 g), bromotrimethylsilane (24.9 g), ethylene glycol (10.6 mL) and *p*-toluenesulfonic acid hydrate (0.7 g) as a catalyst according to the reported procedure[83] to give 17.5 g (57%) of the product after vacuum distillation at 85-90 °C/19-23 mmHg. Lit.[83] yield: 82%, bp 42-46 °C/0.4 mmHg; lit.[122] bp 88-94 °C/27 mmHg.
Method b): **127** was obtained from methylvinylketone (24.7 mL, 0.3 mol), 48% aqueous HBr solution (72 mL, 0.645 mol), ethylene glycol (25 mL, 0.45 mol) and *p*-toluenesulfonic acid hydrate (1.5 g) according to the reported procedure.[83] Modification: 1.5 equiv of ethylene glycol were used; it is not necessary to wash the toluene solution after the addition of HBr to the methylvinylketone; the crude product was distilled under reduced pressure (61-70 °C/15 mmHg) to give 23.9 g (46%) of **127** as a yellow liquid. Lit.[83] yield: 54%, bp 88-94 °C/27 mmHg.
Analytical sample (5.0 g) was obtained by flash chromatographic purification on a 10×2 cm column with hexane/AcOEt 10:1 as eluent. R_f = 0.23-0.25, the spot is UV inactive but visible with "Vanillin" staining reagent.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ4.05-3.90 (m, 4H), 3.50-3.35 (m, 2H), 2.35-2.20 (m, 2H), 1.33 (s. 3H).
HRMS ESI: desired M^+ was not found.

Trimethyl-(2-(2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl)-cyclohexylidene-methoxy)-silane (128)



$C_{16}H_{30}O_3Si$
Mol. Wt.: 298.49

Mg turnings (1.10 g, 46 mmol, 3 equiv) were ground in a mortar and transferred immediately to a Schlenk flask fitted with an argon-filled balloon. THF (3 mL) and 1,2-dibromoethane (200 mg, 1.3 mmol) were added. A solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane

(2.92 g, 15 mmol, 1 equiv) in THF (2 mL) was added dropwise over 2 h to Mg turnings while stirring at 22-24 °C (water bath). After the addition was complete, the reaction mixture was diluted with THF (15 mL) and stirred for 1 h at rt. The resulting grey solution was transferred with a syringe into another 100 mL Schlenk flask fitted with an argon-filled balloon. The flask was cooled to -78 °C and the solution of $CuBr{\cdot}Me_2S$ (0.107 g, 0.5 mmol, 3 mol%) in HMPA (3.8 mL, 22 mmol, 1.5 equiv) was added. After the resulting mixture was stirred for 1 h at -78 °C a mixture of 1-cyclohexene-1-carbaldehyde (929 mg, 8.44 mmol) and TMSCl (2.25 mL, 17 mmol) in THF (10 mL) was added within 8 h to the reaction mixture while stirring at -78 °C. After additional 6 h at -78 °C Et_3N (3 mL) was added followed by hexane (30 mL) and H_2O (30 mL). Organic layer was separated. Aqueous layer was treated with saturated aqueous NH_4Cl solution (20 mL) and extracted with hexane (2×30 mL). Combined hexane extract was washed with water and brine, dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel with hexane/AcOEt/Et_3N 100:10:1 furnished **128** (2.0 g, 80%) as a colorless oil. R_f = 0.55 in hexane/AcOEt 7:3.

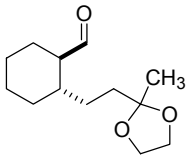
^{1}H-NMR (C_6D_6, 400 MHz): δ6.19 (s, 1H), 3.57 (s, 4H), 2.60-2.45 (m, 1H), 2.20 (m, 1H), 2.00-1.40 (m, 11H), 1.33 (s, 3H), 0.11 (m, 9H).

^{13}C-NMR (C_6D_6, 100 MHz): δ131.93 (CH), 125.03 (Cq), 111.02 (Cq), 65.35 (CH_2), 65.34 (CH_2), 40.35 (CH), 38.66 (CH_2), 34.93 (CH_2), 28.49 (CH_2), 27.13 (CH_2), 24.84 (CH_3), 24.27 (CH_2), 23.77 (CH_2), 0.17 (3×CH_3).

Elemental Analysis: Anal. C, 63.26%; H, 9.94%; calcd. for $C_{16}H_{30}O_3Si$: C, 64.38%; H, 10.13%.

HRMS ESI: desired M^+ was not found.

2-[2-(2-methyl-[1,3]dioxolan-2-yl)-ethyl]-cyclohexane carbaldehyde (129)



$C_{13}H_{22}O_3$
Mol. Wt.: 226.31

1.0 M TBAF solution in THF (1 mL, 1.0 mmol, 2.3 equiv) was added to a solution of **128** (130 mg, 0.44 mmol) in THF (4 mL). After the reaction mixture was stirred for 5 h at rt it was then quenched with H_2O (10 mL) and extracted with MTBE (3×10 mL). Combined organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash

chromatography on silica gel with hexane/AcOEt 7:3 as eluent furnished **129** as a colorless oil (53.2 mg, 54%). R_f = 0.3.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ9.82 (s), 9.55 (d, *J* = 3.9 Hz, 1H), 3.92 (m, 4H), 2.10-0.70 (complex m, 17H). Signals at 9.82 (s) and 9.55 (d, *J* = 3.9 Hz, 1H) ppm correspond to the absorption of the CHO proton of the *cis*- and the *trans*- isomer respectively. According ^{1}H NMR the product was obtained as a 1:7.1 *cis* : *trans* diastereomeric mixture.

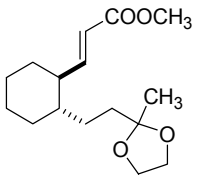
^{13}C-NMR (C_6D_6, 100 MHz): for the *cis* : *trans* mixture: δ204.62 (CH), 204.39 (CH), 110.70 (Cq), 110.69 (Cq), 65.35 (CH_2), 65.32 (CH_2), 56.12 (CH), 52.58 (CH), 38.35 (CH_2), 38.32 (CH_2), 38.18 (CH), 37.14 (CH), 37.06 (CH_2), 37.04 (CH_2), 31.04 (CH_2), 30.06 (CH_2), 29.51 (CH_2), 26.67 (CH_2), 26.33 (CH_2), 25.99 (CH_2), 25.60 (CH_2), 25.17 (CH_2), 24.82 (CH_2), 24.68 (CH_3), 24.67 (CH_3), 24.58 (CH_2).

HRMS ESI: Calcd. for [$C_{13}H_{22}O_3$ + H]: 277.1623; found: 227.1640.

***trans*-129:**

The solution of aldehyde **129** in hexane/AcOEt 6:1 was stirred with silica gel (100 mg) for 24 h at rt. The reaction mixture was filtered through a plug of cotton and concentrated to give the product. According to ^{1}H NMR the *cis* : *trans* ratio was 1:8.

(*E*)-methyl 3-(2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclohexyl)acrylate



$C_{16}H_{26}O_4$
Mol. Wt.: 282,38

A solution of Ph_3P=COOMe (0.502 g, 1.504 mmol, 2 equiv) in CH_2Cl_2 (3 mL) was added at reflux to the solution of the aldehyde **129** (0.168 g 0.743 mmol) in CH_2Cl_2 (3 mL) in a two necked flask fitted with a reflux condenser and an argon balloon.

The mixture was refluxed for 9 h. The solvent was removed under reduced pressure and the rest was triturated with hexane. After the solution was filtered and concentrated, the crude product was purified by flash chromatography to give 134 mg (0.475 mmol, 64%) of the desired acrylate.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ6.85-6.75 (dd, *J* = 9.46, 15.87 Hz, 1H), δ5.80-5.75 (dd, *J* = 0.61, 15.56 Hz, 1H), 3.95-3.83 (m, 4H), 3.71 (s, 3H), 1.90-1.76 (complex m, 2H), 1.75-1.42 (complex m, 7H), 1.28-1.02 (complex m, 9H), 0.98-0.84 (complex m, 1H).

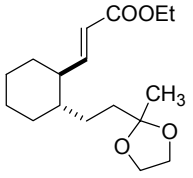
According to the ^{1}H NMR spectrum the product obtained is a 1:7 mixture of diastereomers (*cis*- to *trans*- in relevance to the substituents on the cyclohexane ring). The olefinic protons of the minor (*cis*-) diastereomer are found at: δ7.17-7.09 (dd, *J* = 8.85, 15.56 Hz), δ5.84-5.79 (dd, *J* = 1.22, 15.87 Hz)**.**

^{13}C-NMR (100 MHz, $CDCl_3$): δ167.16 (CO), 153.94 (CH), 120.30 (CH), 110.15 (Cq), 64.56 (CH_2), 64.51 (CH_2), 51.31 (CH_3), 46.93 (CH), 41.07 (CH), 35.66 (CH_2), 32.71 (CH_2), 31.00 (CH_2), 28.69 (CH_2), 25.95 (CH_2), 25.55 (CH_2), 23.64 (CH_3).

Signals from olefinic protons of the *minor* isomer are found at 150.85 and 121.18 ppm.

HRMS ESI: Calcd. for [$C_{16}H_{26}O_4$ + H]: 283.1909, for [$C_{16}H_{26}O_4$ + Na]: 305.1729; found: 283.1921, 305.1742.

(*E*)-ethyl 3-(2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclohexyl)-acrylate (129a)



$C_{17}H_{28}O_4$
Mol. Wt.: 296,40

A solution of diethyl ethoxycarbonylmethanephosphonate (688 mg, 3.01 mmol, 1.7 equiv) in toluene (3 mL) was added to a suspension of NaH in mineral oil (60%, 106 mg, 2.66 mmol, 1.5 equiv) in toluene (4 mL) at rt forming a clear colorless solution which was additionally stirred for 20 min at rt. The solution was cooled to -20 °C and the solution of the aldehyde **129** (400 mg, 1.77 mmol, 1 equiv) in toluene (4 mL) was added dropwise over 20 min. The reaction mixture was stirred for 30 min at -20 °C. When the reaction was complete (TLC with hexane/AcOEt 7:3, product R_f = 0.45, UV), the reaction mixture was diluted with MTBE (10 mL) and H_2O (10 mL). The mixture was extracted with MTBE (3×10 mL) and the combined organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. Chromatographic purification on silica gel using hexane/AcOEt 8:2 as eluent furnished purified **129a** as a colorless oil (240 mg, 46%).

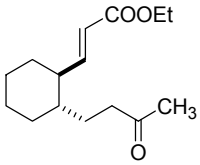
^{1}H-NMR ($CDCl_3$, 400 MHz): δ6.38-6.77 (dd, *J* = 9.5, 15.7 Hz, 1H), 5.78 (d, *J* = 15.7 Hz 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.90 (m, 4H), 1.90-1.40 (m, 8H), 1.30-1.00 (m, 11H), 1.00-0.80 (m, 1H). According ^{1}H NMR the product was obtained as a 1:6.6 *cis* : *trans* mixture of isomers (in respect to the substitution pattern on the cyclohexane ring). Olefinic protons of the minor *cis* isomer are observed at 7.20-7.07 (dd, *J* = 8.9, 15.7 Hz) and 5.82 (d, *J* = 15.7 Hz) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ166.68 (O-C=O), 153.53 (CH), 120.62 (CH), 110.07 (Cq), 64.47 (CH_2), 64.42 (CH_2), 59.99 (CH_2), 46.84 (CH), 40.97 (CH), 35.53 (CH_2), 32.62 (CH_2), 30.92 (CH_2), 28.60 (CH_2), 25.88 (CH_2), 25.48 (CH_2), 23.57 (CH_3), 14.17 (CH_3).

HRMS ESI: Calcd. for [$C_{17}H_{28}O_4$ + H]: 297.2066; found: 297.2070.

IR (cm^{-1}, neat): 2981 (m), 2924 (s), 2854 (m), 1716 (s), 1650, 1447, 1370, 1323, 1263, 1223, 1174, 1039, 987, 947, 859, 720.

(*E*)-3-[2-(3-oxo-butyl)-cyclohexyl]-acrylic acid ethyl ester (173)



$C_{15}H_{24}O_3$
Mol. Wt.: 252,35

A solution of **129a** (253 mg, 0.86 mmol) and PPTS (64 mg, 0.256 mmol, 30 mol%) in aqueous acetone (5 mL, 0.5 mL H_2O) was refluxed for 4 h. When the reaction was complete (TLC with hexane/AcOEt 7:3, product R_f = 0.35, UV) the excess of the solvent was removed under reduced pressure, MTBE (15 mL) was added and the mixture was washed with saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel with hexane/AcOEt 8:2 as eluent to give **173** as colorless oil (199 mg, 92%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ6.80-6.70 (dd, *J* = 9.6, 15.7 Hz, 1H), 5.81-5.72 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.51-2.25 (m, 2H), 2.11 (s, 3H), 1.58 (s, 3H), 1.90-1.60 (m, 5H), 1.35-1.15 (m, 8H), 1.00-0.80 (m, 1H). According to ^{1}H NMR the product was obtained is a 1:6. mixture of isomers (*cis* : *trans*- in respect to the substitution pattern on the cyclohexane ring). Olefinic protons of the minor *cis* isomer are observed at: 7.14-7.08 (dd, *J* = 8.8, 15.7 Hz) and 5.83 (d, *J* = 15.7 Hz) ppm.

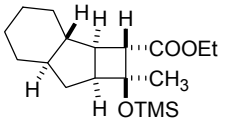
^{13}C-NMR ($CDCl_3$, 100 MHz): δ208.82 (C=O), 166.55 (O-C=O), 153.00 (CH), 120.94 (CH), 60.04 (CH_2), 46.83 (CH), 40.74 (CH_2), 40.48 (CH), 32.56 (CH_2), 30.80 (CH_2), 29.73 (CH_3), 28.33 (CH_2), 25.74 (CH_2), 25.34 (CH_2), 14.14 (CH_3).

HRMS ESI: Calcd. for [$C_{15}H_{24}O_3$ + Na]: 275.1623; found: 275.1628.

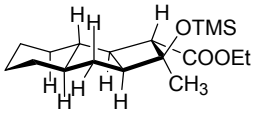
IR (cm^{-1}, neat): 2925 (s), 2854 (m), 1712 (s), 1650 (m), 1447, 1367, 1324, 1266, 1225, 1161, 1133, 1039, 986, 844, 734.

The *cis-trans* mixture was separated using HPLC on a 250×25 mm "Reprosil-Pur 120 C18 AQ 5 μm" column with a 30×20 mm "Reprosil-Pur 120 C18 AQ 10 μm" precolumn and CH_3CN/H_2O 48:52 as eluent at 10 mL/min flow rate. Detection with L-7400 "LaChrome" UV detector at 254 nm. The minor diastereomer had a retention time of 57.0 min. The major one: 59.9 min. In a single run 300 μL of the solution of the diastereomeric mixture in CH_3CN, containing 60 mg of the substance, was injected.

Siloxycyclobutane 131a (*kinetic product*)



$C_{18}H_{32}O_3Si$
Mol. Wt.: 324,53



Rac

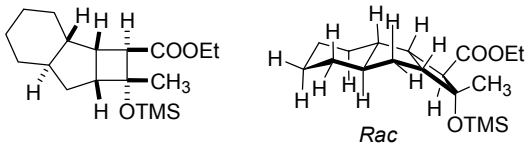
TMSI (58 μL, 0.43 mmol, 1.3 equiv) was dropwise added to a stirred solution of **173** (83.0 mg, 0.33 mmol, 1 equiv) and hexamethyldisilazane (104 μL, 0.49 mmol, 1.5 equiv) in 1,2-dichloroethane (3.5 mL) at -30 °C. After the reaction mixture was stirred at this temperature for 3 h it was diluted with MTBE (10 mL) and saturated aqueous NH_4Cl solution (10 mL) followed by the extraction with MTBE (3×10 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (20×270 mm column) with hexane-Et_2O 50:1 as eluent to give **131a** (56.6 mg, 53%) as a colorless oil. According to the ^1H NMR the product is a 11:1 diastereomeric mixture. R_f = 0.45-0.52 in hexane/AcOEt 10:1; R_f = 0.17-0.13 in hexane-Et_2O 60:1.

^{1}H-NMR (C_6D_6, 400 MHz): δ4.03 (dq, *J* = 3.8, 7.2 Hz, 1H), 3.98 (dq, *J* = 3.6, 7.2 Hz, 1H), 3.05-3.02 (d, *J* = 5.1 Hz, 1H), 2.45-2.31 (m, 2H), 1.98-1.91 (m, 1H), 1.87-1.81 (m, 1H), 1.75-1.62 (m, 4H), 1.43 (s, 3H), 1.14-1.06 (m, 4H), 1.01-0.96 (t, *J* = 7.2 Hz, 3H), 0.21 (s, 9H).

^{13}C-NMR (C_6D_6, 100 MHz): δ172.70 (O-C=O), 74.26 (Cq), 60.12 (CH), 59.99 (CH_2), 55.45 (CH), 50.77 (CH), 49.40 (CH), 37.54 (CH), 32.95 (CH_2), 31.93 (CH_2), 31.92 (CH_2), 27.27 (CH_2), 26.74 (CH_3), 26.62 (CH_2), 14.50 (CH_3), 2.14 (3×CH_3).

HRMS ESI: Calcd. for [$C_{18}H_{32}O_3Si$ + H]: 325.2199, for [$C_{18}H_{32}O_3Si$ + CH_3CN + Na]: 388.2284; found: 325.2394, 388.2424.

Siloxycyclobutane 131b (*thermodynamic product*)



$C_{18}H_{32}O_3Si$
Mol. Wt.: 324,53

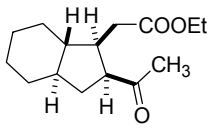
TMSI (52 μL, 0.383 mmol, 1.3 equiv) was added dropwise to a stirred solution of **173** (74.3 mg, 0.294 mmol, 1.0 equiv) and TMS_2NH (93 μL, 0.442 mmol, 1.5 equiv) in 1,2-dichloroethane (3 mL) at 0 °C and the mixture was stirred at this temperature for 24 h. The reaction mixture was diluted with MTBE (5 mL), quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with MTBE (3×10 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (25×400 mm column) with hexane-Et_2O 60:1 as eluent to give **131b** (59 mg, 62%) as a colorless oil. The content of the fractions was judged by the GC. R_f = 0.45-0.50 in hexane/AcOEt 10:1, R_f = 0.15-0.12 in hexane/Et_2O 60:1.

^{1}H-NMR (C_6D_6, 400 MHz): δ4.15 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.08 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.01-2.97 (d, *J* = 6.8 Hz, 1H), 2.89-2.82 (m, 1H), 2.36-2.31 (t, *J* = 8.0 Hz, 1H), 2.20-2.13 (dd, *J* = 12.8, 6.3 Hz, 1H), 1.98-1.91 (m, 1H), 1.71-1.62 (m, 3H), 1.59-1.49 (m, 1H), 1.45 (s, 3H), 1.16-1.12 (m, 5H), 1.02-0.97 (t, *J* = 7.2 Hz, 3H), 0.97-0.87 (m, 1H), 0.24 (s, 9H).

^{13}C-NMR (C_6D_6, 100 MHz): δ172.25 (O-C=O), 74.47 (Cq), 59.95 (CH_2), 50.97 (CH), 48.97 (CH), 48.71 (CH), 43.30 (CH), 37.16 (CH), 32.33 (CH_2), 32.32 (CH_2), 27.05 (CH_2), 26.92 (CH_2), 26.90 (CH_3), 26.58 (CH_2), 14.49 (CH_3), 2.14 (3×CH_3).

HRMS ESI: Calcd. for [$C_{18}H_{32}O_3Si$ + H]: 325.2199, for [$C_{18}H_{32}O_3Si$ + CH_3CN + Na]: 388.2284; found: 325.2191, 388.2304.

Methyl ketone 132a



$C_{15}H_{24}O_3$
Mol. Wt.: 252,35

1.0 M solution of TBAF in THF (0.214 mmol, 0.214 mL) was added to the solution of silyl ether **131a** (69.6 mg, 0.214 mmol) in THF (5 mL) at -30 °C. The reaction mixture was stirred for 30 min at -30 °C, quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted

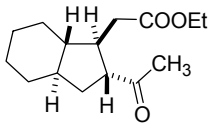
with MTBE (3×10 mL). The combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (20×240 mm column) with hexane/AcOEt 20:1 as eluent to give **132a** (43.2 mg, 80%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ4.07 (q, *J* = 7.1 Hz, 2H), 3.36 (ddd, *J* = 8.7, 8.7 and 8.7 Hz, 1H), 2.56 (dd, *J* = 16.9, 10.8 Hz, 1H), 2.41 (dd, *J* = 16.9, 4.7 Hz, 1H), 2.13 (s, 3H), 2.07 (ddd, *J* = 8.7, 11.7 and 6.0 Hz, 1H), 1.97 (ddd, *J* = 20.7, 11.1 and 4.7 Hz, 1H), 1.86-1.80 (m, 1H), 1.79-1.70 (m, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.27-1.11 (m, 4H), 1.04 (dddd, *J* = 11.3, 11.2, 11.3, 3.1 Hz, 1H), 1.05-0.96 (m, 1H), 0.90-0.81 (m, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ213.38 (Cq), 173.91 (Cq), 60.20 (CH_2), 50.04 (CH), 49.88 (CH), 45.53 (CH), 43.71 (CH), 36.33 (CH_2), 33.40 (CH_2), 32.04 (CH_3), 31.51 (CH_2), 30.09 (CH_2), 26.24 (CH_2), 25.83 (CH_2), 14.18 (CH_3).

HRMS ESI: Calcd. for [$C_{15}H_{24}O_3$ + Na]: 275.1623, for [$C_{15}H_{24}O_3$ + CH_3CN + Na]: 316.1889; found: 275.1636, 316.1883.

Methyl ketone 133a



$C_{15}H_{24}O_3$
Mol. Wt.: 252,35

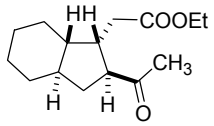
1.0 M solution of TBAF in THF (0.55 mL, 0.55 mmol) was added to the solution of methyl ketone **132a** (27.9 mg, 0.111 mmol) in THF (5 mL) at rt. After 3 h the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with AcOEt (3×10 mL). Combined organic extract was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (160×15 mm column) with hexane/AcOEt 10:1 as eluent to give **133a** (15 mg, 54%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ4.06 (q, *J* = 7.2 Hz, 2H), 2.76 (ddd, *J* = 11.5, 7.6, 3.0 Hz, 1H), 2.49 (dd, *J* = 14.3, 4.3 Hz, 1H), 2.23 (dddd, *J* = 10.9, 7.3, 9.2 and 4.2 Hz, 1H), 2.17 (s, 3H) 2.16 (dd, *J* = 14.4, 9.2 Hz, 1H), 1.85-1.75 (m, 2H), 1.75 (ddd, *J* = 12.7, 7.0 and 2.9 Hz, 1H), 1.75-1.65 (m, 2H), 1.51 (ddd, *J* = 12.3, 12.1, 12.1 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.30-1.20 (m, 1H), 1.20-1.10 (m, 2H), 1.10-1.00 (m, 1H), 0.85-0.99 (m, 1H), 0.83 (dddd, *J* = 11.1, 11.1, 11.1 and 3.3 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ210.76 (Cq), 172.94 (Cq), 60.31 (CH_2), 55.40 (CH), 51.72 (CH), 44.52 (CH), 42.95 (CH), 37.87 (CH_2), 34.71 (CH_2), 31.49 (CH_2), 29.86 (CH_2), 29.07 (CH_3), 25.95 (CH_2), 25.92 (CH_2), 14.15 (CH_3).

HRMS ESI: Calcd. for [$C_{15}H_{24}O_3$ + H]: 253.1798, for [$C_{15}H_{24}O_3$ + Na]: 275.1618, for [$C_{15}H_{24}O_3$ + CH_3CN + Na]: 316.1889; found 253.1742, 275.1669, 316.1901.

Methyl ketone 133b



$C_{15}H_{24}O_3$
Mol. Wt.: 252,35

1.0 M TBAF solution in THF (0.066 mL, 0.066 mmol, 1.0 equiv) was added to the solution of **131b** (21.5 mg, 0.066 mmol) in THF (5 mL) at -30 °C. The reaction mixture was stirred at -30 °C for 30 min, then quenched while cold with saturated aqueous NH_4Cl solution (5 mL), MTBE (5 mL) and H_2O (5 mL), extracted with MTBE (3×10 mL). Combined extract was washed with brine (15 mL), dried over $MgSO_4$, concentrated. After flash chromatographic purification (hexane/AcOEt 8:1, R_f = 0.17-0.20) 13.2 mg (79%) of a colorless oil was obtained. According to ^{1}H NMR the product was a 2.8:1.0 diastereomeric mixture. The signals of the CH_3 group were found at δ1.91 ppm (**132b**) and δ1.93 ppm (**133b**), respectively (in C_6D_6).

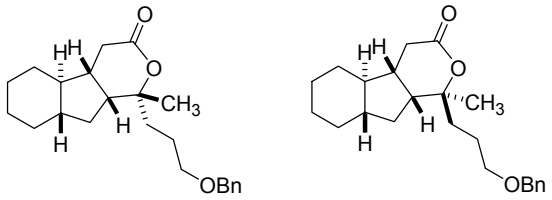
1.0 M TBAF solution in THF (0.13 mL, 0.13 mmol, 3 equiv) was added to the solution of the above 2.8:1.0 diastereomeric mixture (11.0 mg, 0.044 mmol) in THF (9 mL) at rt. After 3 h at rt the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with AcOEt (3×10 mL). Combined extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel with hexane/AcOEt 8:1, R_f = 0.17-0.20 to give **133b** (6.7 mg, 61%) as a colorless oil. According to ^{1}H and ^{13}C NMR the product was diastereomerically pure with the chemical shift of the CH_3 group at δ1.93 ppm (in C_6D_6).

^{1}H-NMR (C_6D_6, 500 MHz): δ3.96 (q, *J* = 7.1 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 1H), 2.88 (dddd, *J* = 2.9, 5.2, 10.9, 8.2 Hz, 1H), 2.49 (ddd, *J* = 3.2, 8.7, 8.7 Hz, 1H), 2.21 (dd, *J* = 5.2, 15.2 Hz, 1H), 1.93 (s, 3H), 1.85 (dd, *J* = 10.9, 15.2 Hz, 1H), 1.73-1.68 (m, 1H), 1.65 (ddd, *J* = 6.2, 8.5, 12.1 Hz, 1H), 1.61-1.53 (m, 2H), 1.48-1.42 (m, 1H), 1.19 (ddd, *J* = 11.8, 11.8, 9.0 Hz, 1H), 1.20-1.13 (m, 1H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.97-0.90 (m, 2H), 0.96-0.88 (m, 1H), 0.81 (m, 1H), 0.75 (dddd, *J* = 2.6, 11.3, 13.0, 12.2 Hz, 1H).

^{13}C-NMR (C_6D_6, 125 MHz): δ208.26 (C=O), 173.12 (O-C=O), 60.54 (CH_2), 56.95 (CH), 48.16 (CH), 43.41 (CH), 39.97 (CH), 36.86 (CH_2), 35.93 (CH_2), 32.49 (CH_2), 29.12 (CH_3), 28.05 (CH_2), 26.80 (CH_2), 26.64 (CH_2), 14.64 (CH_3).

HRMS ESI: Calcd. for [$C_{15}H_{24}O_3$ + Na]: 275.1623, for [$C_{15}H_{24}O_3$ + CH_3CN + Na]: 316.1889; found: 275.1653, 316.1885.

Lactones 134 and 135



134 (major) **135** (minor)

dr = 5 : 1

$C_{23}H_{32}O_3$
Mol. Wt.: 356,50

Preparation of the 0.2 M solution of the Grignard reagent:[134]

The solution of benzyl 3-brompropyl ether (458 mg, 2 mmol, 1.0 equiv) in THF (2 mL) was added over 10 min via a syringe to a suspension of Mg turnings[p] (100 mg, 4 mmol, 2.0 equiv) in THF (1 mL) at rt. The exothermic reaction has an induction period of ca. 10 min, but when the reaction starts, the color of the reaction mixture changes to yellow-green and the temperature may rise up to 40-50 °C. After the reaction mixture was stirred for 45 min at rt it was diluted with THF (7 mL) to provide 0.2 M solution of the Grignard reagent.

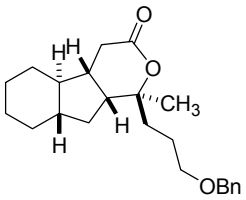
The Grignard reaction:

0.2 M solution (1 mL, 0.2 mmol) of the Grignard reagent was dropwise added to the solution of the methyl ketone **132a** (26.3 mg, 0.10 mmol, 0.5 equiv) in THF (1 mL) at rt. After 1 h at rt EtOH (3 mL) was added and the reaction mixture was stirred for additional 30 min. Solvents were removed under reduced pressure and the rest was diluted with MTBE (10 mL). The grey suspension was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with MTBE (3 × 15 mL) and concentrated to furnish a pale oil. The crude product was purified by flash chromatography on silica gel with hexane/AcOEt 8:2 as eluent giving two fractions: **135**: 3.6 mg (10%) with an R_f = 0.20-0.21 and **134**: 18 mg (48%) with an R_f = 0.17-0.19. **134**

[p]) Ground to generate a fresh surface.

required additional purification by flash chromatography with hexane/MTBE 3:1 (**134**: R_f = 0.21-0.24, impurity R_f = 0.25-0.27, "Vanillin").

Lactone 135 (minor):

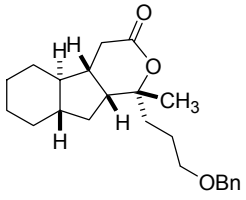


135 (minor)

$C_{23}H_{32}O_3$
Mol. Wt.: 356,50

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.43-7.26 (m, 5H, Ar), 4.48 (s, 2H), 3.54-3.42 (m, 2H), 2.66 (dd, *J* = 16.39, 8.19 Hz, 1H), 2.33 (dd, *J* = 16.56, 4.95 Hz, 1H), 2.30-2.23 (m, 1H), 2.04 (dddd, *J* = 10.84, 10.84, 8.19, 5.04 Hz, 1H), 1.91-1.80 (m, 3H), 1.79-1.59 (m, 6H), 1.32 (s, 3H), 1.23-1.08 (m, 4H), 1.03-0.90 (m, 2H), 0.82 (dddd, *J* = 10.84, 10.84, 10.84, 3.07 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 100 MHz): δ172.90 (Cq, C=O), 138.43 (Cq, Ar), 128.35 (2×CH, Ar), 127.58 (2×CH, Ar), 127.54 (CH, Ar), 84.49 (Cq), 72.84 (CH_2), 70.04 (CH_2), 53.65 (CH), 44.70 (CH), 43.04 (CH), 39.09 (CH), 37.71 (CH_2), 34.40 (CH_2), 32.91 (CH_2), 31.24 (CH_2), 30.25 (CH_2), 26.05 (CH_2), 26.05 (CH_2), 23.78 (CH_2), 23.62 (CH_3).
HRMS ESI: Calcd. for [$C_{23}H_{32}O_3$ + H]: 357.2430, for [$C_{23}H_{32}O_3$ + Na]: 379.2249; found: 357.2445, 379.2262.
IR (cm^{-1}, neat): 2922 (s), 2850 (m), 1737 (s), 1447 (m), 1366 (s), 1274 (w), 1217 (s), 1096 (m), 1028 (w), 988 (w), 953 (w), 737 (m), 698 (m).

Lactone 134 (major):



134 (major)

$C_{23}H_{32}O_3$
Mol. Wt.: 356,50

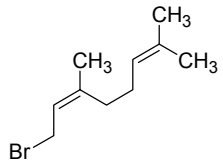
^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.41-7.21 (m, 5H, Ar), 4.50 (s, 2H), 3.57-3.41 (m, 2H), 2.69 (dd, *J* = 16.38, 8.53 Hz, 1H), 2.35 (dd, *J* = 16.73, 2.73 Hz, 1H), 2.23 (ddd, *J* = 10.75, 10.75, 7.17 Hz, 1H), 2.09 (dddd, *J* = 10.58, 10.67, 8.36, 2.39 Hz, 1H), 1.91-1.58 (m, 9H), 1.42 (s, 3H), 1.23-1.05 (m, 4H), 1.02-0.90 (m, 2H), 0.77 (dddd, *J* = 10.80, 10.80, 10.80, 2.86 Hz, 1H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ172.74 (Cq), 138.40 (Cq), 128.30 (2×CH, Ar), 127.52 (2×CH, Ar), 127.48 (CH, Ar), 83.92 (Cq), 72.82 (CH_2), 70.22 (CH_2), 53.40 (CH), 44.37 (CH), 43.81 (CH), 38.39 (CH), 35.88 (CH_2), 33.90 (CH_2), 32.84 (CH_2), 31.07 (CH_2), 30.15 (CH_2), 26.05 (CH_2), 25.98 (CH_2), 25.12 (CH_3), 23.79 (CH_2).

HRMS ESI: Calcd. for [$C_{23}H_{32}O_3$ + H]: 357.2430, for [$C_{23}H_{32}O_3$ + Na]: 379.2249; found: 357.2434, 379.2256.

IR (cm^{-1}, neat): 2921 (s), 2851 (m), 1731 (s), 1453 (m), 1347 (w), 1274 (m), 1213 (w), 1100 (s), 1075 (m), 1014 (w), 971 (w), 950 (w), 737 (m), 698 (m).

Neryl bromide



$C_{10}H_{17}Br$
Mol. Wt.: 217,15

The substance was prepared according to a published procedure.[123] Pyridine (1.0 mL, 12.4 mmol, d = 0.978) was added to a stirred solution of nerol (19.0 g, 21.5 mL, 123 mmol, 1 equiv, d = 0.877) in Et_2O (150 mL) at 0 °C followed by a dropwise addition of a solution of PBr_3 (14.4 g, 52.0 mmol, d = 2.88, 5.0 mL) in hexane (50 mL) at 0 °C, during which a white suspension formed and a weak exothermic effect was observed. The reaction mixture was stirred for 30 min, whereupon the solution had became clear and a pink precipitate of the phosphorous salts [Py·$P(OH)_3$] had formed. TLC analysis indicated incomplete reaction (nerol was left). Additional portion of the solution of PBr_3 (1 mL) in hexane (5 mL) was added so that the nerol was consumed. The yellow solution was decantated from the precipitate onto ice (200 mL), the precipitate was washed with hexane (20 mL) and the washings were combined with the main portion of the product. Organic layer was separated and the aqueous was extracted with MTBE (3×100 mL). Combined organic extract was washed with 5% aqueous $NaHCO_3$ solution (2×100 mL) and brine (100 mL). The extract was dried over $MgSO_4$ and concentrated to give 17.0 g (97%) of yellow oil. TLC (hexane): nerol R_f ca. 0, product R_f = 0.50. Important to note that a sample of the product decomposed during an attempted chromatographic purification on silica gel. The crude product was successfully purified by bulb to bulb distillation at 110-120 °C/0.2 mmHg.

In general, isoprenyl bromides should be stored at 4 °C over Ag threads. In this way the substance may be stored over a month.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ5.65-5.45 (m, 1H), 5.20-5.00 (m. 1H), 4.10-3.90 (d, *J* = 8.4 Hz, 2H), 2.13 (s, 3H), 1.85-1.65 (m, 4H), 1.68 (s, 3H), 1.61 (m, 3H).

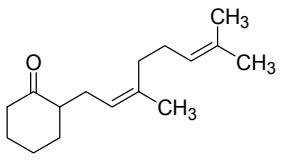
^{13}C-NMR (100 MHz, $CDCl_3$): δ143.31 (Cq), 132.30 (Cq), 123.45 (CH), 121.34 (CH), 31.73 (CH_2), 29.35 (CH_2), 26.18 (CH_2), 25.65 (CH_3), 23.51 (CH_3), 17.65 (CH_3).

The position of the signals corresponding to the CH_3 groups (at δ25.65, 23.51 and 17.65 ppm) in ^{13}C NMR suggests the *cis*- geometry of the double bond.[124]

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 3035 (w), 2968 (s), 2929 (s), 2859 (m), 1655 (m), 1447 (s), 1377 (m), 1200, 1109, 985, 840 (s).

2-(3,7-Dimethyl-octa-2,6-dienyl)-cyclohexanone (136)



$C_{16}H_{26}O$
Mol. Wt.: 234.38

2.5 M solution of *n*-BuLi (3.7 mL, 9.2 mmol) in hexanes was added to the solution of diisopropylamine (1.4 mL, 9.7 mmol) in THF (34 mL), at -78 °C. The so obtained LDA solution was warmed to 0 °C, stirred for 15 min and cooled to -78 °C.

The solution of cyclohexanone (0.9 mL, d = 0.947, 0.903 g, 9.21 mmol) in THF (8 mL) was slowly added to the LDA solution at -78 °C. After 1 h at -78 °C the solution of neryl bromide (1.02 g, 4.61 mmol) in THF (1.6 mL) was dropwise added over 0.5 h at -78 °C.

The reaction mixture was stirred at -78 °C over 12 h, warmed to rt and stirred over 4 h at ambient temperature (TLC with hexane/AcOEt 15:1: neryl bromide R_f = 0.7 (green-blue, "Vanillin"); cyclohexanone R_f = 0.35 (violet, "Vanillin"); product R_f = 0.45 (yellow-brown, "Vanillin"). When there was no starting neryl bromide, the reaction mixture was quenched with 1 M aqueous $NaHSO_4$ solution (50 mL). Organic layer was separated, diluted with MTBE (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL). Aqueous layer was extracted with MTBE (3×15 mL), the extract was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The extract was dried over $MgSO_4$ and concentrated to give 1.15 g of a yellow oil. Crude **136** was purified by flash chromatography with hexane/AcOEt 15:1 (R_f = 0.30-0.35) to furnish 539 mg (50%) of a colorless oil.

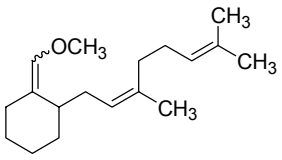
^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.10-5.00 (m, 2H), 2.45-2.32 (m, 2H), 2.30-2.18 (m, 2H), 2.15-2.05 (m, 1H), 2.05-1.95 (m, 4H), 2.00-1.85 (m, 2H), 1.85-1.75 (m, 1H), 1.70-1.50 (m, 11H), 1.35-1.25 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ212.89 (C=O), 136.51 (Cq), 131.37 (Cq), 124.15 (CH), 122.63 (CH), 51.127 (CH), 41.93 (CH_2), 33.39 (CH_2), 31.82 (CH_2), 27.91 (CH_2), 27.44 (CH_2), 26.40 (CH_2), 25.60 (CH_3), 24.94 (CH_2), 23.32 (CH_3), 17.51 (CH_3). The position of the signals corresponding to the CH_3 groups (at δ25.60, 23.32 and 17.51 ppm) in ^{13}C NMR spectrum suggests the *cis*- geometry of the double bond in the neryl rest.[124]

HRMS ESI: Calcd. for [$C_{16}H_{26}O$ + Na]: 257.1881, for [$C_{16}H_{26}O$ + Na + CH_3CN]: 298.2147; found: 257.1890, 298.2151.

IR (cm^{-1}, neat): 2930 (s), 2859 (m), 1712 (m), 1448 (m), 1376, 1313, 1225, 1127, 1068, 960, 831, 740.

1-(3,7-Dimethyl-octa-2,6-dienyl)-2-methoxymethylene-cyclohexane (137)



$C_{18}H_{30}O$
Mol. Wt.: 262.43

2.5 M *n*-BuLi solution in hexanes (5 mL, 12.5 mmol) was dropwise added to the solution of diisopropylamine (2.0 mL, 13.6 mmol) in THF (10 mL) at -60 °C. After 15 min at -60 °C the reaction mixture was warmed to 0 °C and stirred for 30 min.

Methoxymethyl triphenylphosphonium bromide (3.50 g, 10.2 mmol) was added to the above solution of LDA as suspension in THF (60 mL) while stirred at 0 °C forming a red solution. After 30 min at 0 °C the mixture was cooled to -60 °C. The solution of the ketone **136** (1.72 g, 7.34 mmol) in THF (10 mL) was added over 30 min at -60 °C. The reaction mixture was warmed to rt and stirred for 12 h. According to the TLC the reaction was complete (starting material R_f = 0.30-0.35, product has an R_f = 0.7). The reaction mixture was poured into saturated aqueous NH_4Cl solution (50 mL), extracted with MTBE (3×15 mL). Combined extract was washed with brine (25 mL), dried over $MgSO_4$ and concentrated to give the residue of the solid Ph_3PO and the oily product. This was triturated with hexane/AcOEt 15:1 and the cloudy solution was filtered. Evaporation gave 2.35 g of yellow oil. Bulb to bulb distillation (0.2 mm, 120 °C) allows to some extent to separate **137** from the byproduct, Ph_3PO. A portion of **137** (224 mg) was purified by flash chromatography with hexane/AcOEt

100:1 to give 152.5 mg (68%) of the purified product. TLC product R_f = 0.15 (hexane); 0.45 (hexane/AcOEt 50:1); 0.7 (hexane/MTBE 10:1); 0.25 (hexane/AcOEt 100:1).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.80-5.70 (m, 1H), 5.20-5.05 (m, 2H), 3.54 (s, 3H), 2.20-1.15 (complex m, 24H). From the ^{1}H NMR spectra it is clearly seen that the product is a mixture of the two π-diastereomers. Signals at δ7.2-7.3 suggest that Ph_3PO could not be completely separated even after chromatographic purification with hexane/AcOEt 100:1.

^{13}C-NMR (100 MHz, $CDCl_3$): δ139.34 (CH), 138.93 (CH), 137.22 & 137.11 (Cq), 135.46 (Cq), 135.19 (Cq), 133.80 (CH), 133.61 (CH), 131.45 (Cq), 131.33 (Cq), 128.66 (CH), 128.49 (CH), 128.42 (CH), 124.52 (s, CH), 124.39 (CH), 124.27 (CH), 121.26 (Cq), 120.86 (Cq), 59.28 (CH_3), 59.14 (CH_3), 39.86 (CH), 33.38 (CH), 33.18 (CH_2), 32.14 (CH_2), 32.11 (CH_2), 30.40 (CH_2), 30.09 (CH_2), 29.53 (CH_2), 28.35 (CH_2), 27.34 (CH_2), 26.81 (CH_2), 26.65 (CH_2), 26.54 (CH_2), 25.70 (CH_3), 25.69 (CH_3), 24.12 (CH_2), 23.77 (CH_2), 23.42 (CH_3), 23.40 (CH_3), 21.63 (CH_2), 17.62 (CH_3), 17.60 (CH_3).

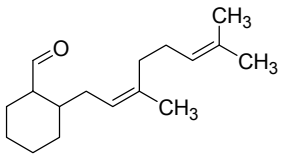
Total are: 12CH, 7×Cq, 14×CH_2, 8×CH_3 = 41 signals. Total need: 8×CH, 6×Cq, 14×CH_2, 8×CH_3 = 36 carbon atoms. The admixture of $OPPh_3$ is the reason for 3 additional CH signals (one of which is a doublet) between δ120-140 and one Cq (137.22 & 137.11, d, J = 11 Hz on P). According to the NMR the product was obtained as E/Z-mixture.

HRMS ESI: Calcd. for [$C_{18}H_{30}O$ + Na]: 285.2194; found: 285.2187.

IR (cm^{-1}, neat): 2926 (s), 2853 (m), 1716 (v), 1680 (m), 1447 (m), 1376, 1234, 1199, 1128 (s), 1089, 995, 834, 743, 697.

GC, R_t, min (intensity): 10.43 (42%), 10.612 (49%).

2-(3,7-Dimethyl-octa-2,6-dienyl)-cyclohexane carbaldehyde (138)



$C_{17}H_{28}O$
Mol. Wt.: 248.40

5% aqueous HCl solution (2 mL) was added at 60 °C to the solution of the methylvinylether **137** (1000 mg) in THF (16 mL). After the reaction mixture was refluxed for 20 min in was cooled to rt and poured into a mixture of ice (10 mL) and saturated aqueous $NaHCO_3$ solution (5 mL), extracted with MTBE (3×15 mL), dried over $MgSO_4$ and concentrated to give a yellow oil of crude **138**. TLC: starting material R_f = 0.6 (hexane/AcOEt 15:1); 0.4 (hexane/AcOEt 50:1). Product R_f = 0.5 (hexane/AcOEt 15:1); 0.3-0.25 (hexane/AcOEt 50:1).

The crude product was purified by flash chromatography with hexane/AcOEt 50:1 to give 0.33 g (35%) of a pale oil of **138**.

The column was gradually washed with hexane/AcOEt 15:1 and 7:3 to obtain the two main byproducts: 0.127 g of a colorless oil (R_f = 0.15 in hexane/AcOEt 15:1) and 0.125 g of a pale oil (R_f = 0.35 in hexane/AcOEt 7:3). According to the IR both are alcohols.

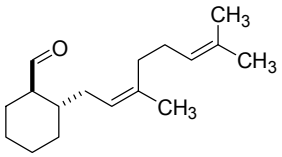
^{1}H-NMR (400 MHz, $CDCl_3$): δ9.77 (s, ½H), 9.52 (d, *J* = 3.92 Hz, ½H), the ratio of the integrals of the aldehyde protons is 1.2:1 (*cis* : *trans*), 5.13-5.05 (m, 2H), 2.41-2.47 (m, ½H), 2.20-1.10 (m, 24H), 1.03-0.92 (m, ½H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ205.52 (CH), 205.17 (CH), 137.02 (Cq), 136.67 (Cq), 131.56 (Cq), 131.51 (Cq), 124.17 (CH), 124.14 (CH), 123.45 (CH), 122.55 (CH), 55.33 (CH), 51.84 (CH), 37.86 (CH), 37.50 (CH), 32.93 (CH_2), 32.01 (CH_2), 31.95 (CH_2), 30.68 (CH_2), 29.29 (CH_2), 26.43 (CH_2), 26.35 (CH_2), 26.10 (CH_2), 25.66 (CH_3), 25.20 (CH_2), 24.72 (CH_2), 24.00 (w, CH_2), 23.75 (CH_2), 23.70 (w, CH_2), 23.37 (CH_3), 23.35 (CH_3), 17.57 (CH_3). Since both diastereomers of **138** are structurarly similar, not all signals in ^{13}C has been resolved. CH_3 and CH_2 groups of the neryl side chain have very close δ values for both diastereomers.

HRMS ESI: Calcd. for [$C_{17}H_{28}O$ + Na]: 271.2038; found: 271.2033.

IR (cm^{-1}, neat): 2926 (s), 2855 (m), 1723 (s), 1448 (m), 1376 (w), 835.

trans-**2-(3,7-Dimethyl-octa-2,6-dienyl)-cyclohexane carbaldehyde (*trans*-138)**



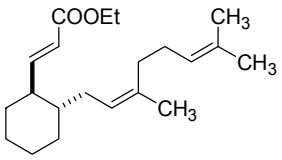
$C_{17}H_{28}O$
Mol. Wt.: 248.40

5% aqueous KOH solution (20 mL) was added to the solution of the aldehyde **138** (0.16 g) in MeOH (20 mL). The mixture was refluxed for 5 h under N_2. The reaction mixture was cooled to rt, extracted with MTBE (3×10 mL), the extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated to give 0.144 g of a yellow oil (92%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ9.79 (s, 1H), 9.54 (d, *J* = 3.88 Hz, 1H), the ratio of the integrals of the aldehyde protons is 1:8.5 (*cis* : *trans*), δ5.20-5.05 (m, 2H), δ2.20-0.80 (m, 25H).

HRMS ESI: Calcd. for [$C_{17}H_{28}O$ + Na]: 271.2038; found: 271.2031.

3-[2-(3,7-Dimethyl-octa-2,6-dienyl)-cyclohexyl]-acrylic acid ethyl ester (120)



$C_{21}H_{34}O_2$
Mol. Wt.: 318.49

The solution of diethyl ethoxycarbonylmethanephosphonate (915 mg, 4.08 mmol, 3.2 equiv) in THF (10 mL) was dropwise added at 0 °C to the suspension of 60% NaH in mineral oil (153.2 mg, 3.83 mmol, 3.0 equiv) in THF (10 mL) to form a clear colorless solution that was additionally stirred for 10 min at 0 °C. The reaction mixture was cooled to -78 °C and the solution of the aldehyde ***trans*-138** (0.317 g, 1.276 mmol, 1.0 equiv) in THF (8 mL) was added over 5 min. The reaction mixture was slowly warmed to rt and stirred over 12 h at ambient temperature, then quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with MTBE (3×15 mL). Combined extract was washed with saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt 50:1 to provide 209.3 mg (52%) of a colorless oil of **120**. The product **120** has an R_f = 0.25-0.3 in hexane/AcOEt 50:1 (permanganate).

^{1}H-NMR (400 MHz, $CDCl_3$): δ7.20-7.05 (dd, *J* = 8.53, 15.69 Hz, 1H), 6.90-6.75 (dd, *J* = 9.47, 15.62 Hz, 1H), 5.85-5.77 (dd, *J* = 15.96, 1.13 Hz, 1H), 5.83-5.75 (d, *J* = 15.69 Hz, 1H), 5.15-5.00 (m, 2H), 4.25-4.10 (q, *J* = 7.04 Hz, 2H), 2.10-1.50 (m, 21H), 1.30-1.20 (t, *J* = 7.04 Hz, 3H), 1.20-1.10 (m, 3H), 0.95-0.80 (m, 1H).

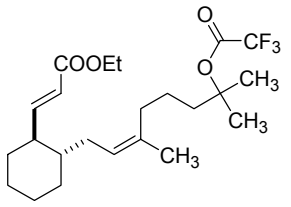
Multiplets: δ7.20-7.05 (dd) and δ5.85-5.77 (dd) correspond to a minor (*cis* on the ring) isomer. Multiplets: δ6.90-6.75 (dd) and δ5.83-5.75 (d) correspond to a major (*trans* on the ring) isomer. The ratio *cis* : *trans* is 1:6.

^{13}C-NMR (100 MHz, $CDCl_3$): δ166.70 (Cq), 153.71 (CH), 136.05 (Cq), 131.33 (Cq), 124.29 (CH), 123.06 (CH), 120.60 (CH), 60.01 (CH_2), 46.63 (CH), 42.03 (CH), 32.77 (CH_2), 32.63 (CH_2), 31.97 (CH_2), 31.27 (CH_2), 26.42 (CH_2), 25.99 (CH_2), 25.62 (CH_2), 25.58 (CH_3), 23.40 (CH_3), 17.52 (CH_3), 14.21 (CH_3).

HRMS ESI: Calcd. for [$C_{21}H_{34}O_2$ + Na]: 341.2456; found: 341.2460.

IR (cm^{-1}, neat): 2925 (s), 2854 (m), 1721 (s), 1651 (m), 1447 (m), 1368, 1323, 1265, 1224, 1163, 1131, 1040, 986, 840, 719.

3-{2-[3,7-Dimethyl-7-(2,2,2-trifluoro-acetoxy)-oct-2-enyl]-cyclohexyl}-acrylic acid ethyl ester (139)



$C_{23}H_{35}F_3O_4$
Mol. Wt.: 432.52

Trifluoroacetic acid (82 µL, 0.942 mmol, 15 equiv, d = 1.48) was added to the solution of the acrylate **120** (20 mg, 0.063 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred over 48 h at rt. The progress of the reaction was controlled by TLC. The starting material has an R_f = 0.25-0.3 in hexane/AcOEt 50:1 (permanganate) and the product an R_f = 0.10 in hexane/AcOEt 50:1 and R_f = 0.3 in hexane/AcOEt 15:1.

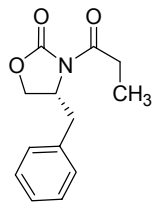
The reaction mixture was quenched with 0.3 M aqueous K_2CO_3 solution (10 mL), stirred for 20 min at rt, then extracted with CH_2Cl_2 (3×10 mL). Combined organic extract was washed with saturated aqueous NaCl solution (10 mL), dried over $MgSO_4$ and concentrated to give a yellow oil of the crude product. Purification by flash chromatography with hexane/AcOEt 30:1 furnished 8.3 mg (30%) of **139**.

^{1}H-NMR (200 MHz, $CDCl_3$): δ6.90-6.70 (dd, *J* = 15.56, 9.03 Hz, 1H), 5.90-5.70 (d, *J* = 15.18 Hz, 1H), 5.35-5.20 (m, 1H), 4.35-4.10 (q, *J* = 7.11 Hz, 2H), 2.20-0.70 (m, 30H).

HRMS ESI: Calcd. for [$C_{23}H_{35}F_3O_4$ + H]: 433.2566, for [$C_{21}H_{34}O_2$ + H]: 319.2632, for [$C_{21}H_{34}O_2$ + Na]: 341.2451, for [$C_{21}H_{34}O_2$ + CH_3CN + Na]: 382.2716; found: 319.2735, 341.2601, 382.2783. Elimination of trifluoroacetic acid took place during the acquisition.

IR (cm^{-1}, neat): 2930 (m), 2856, 2255 (w), 1777 (CF_3-CO, s), 1715 (m), 1651, 1449, 1372, 1270, 1221, 1167 (C-F, s), 1124, 1041, 988, 911 (s), 736 (s), 650.

(*R*)-(-)-4-Benzyl-3-propionyl-oxazolidin-2-one (170)



$C_{13}H_{15}NO_3$
Mol. Wt.: 233.26

2.5 M *n*-BuLi solution (11.4 mL, 28.5 mmol) in hexanes was added over 10 min to a solution of (*R*)-4-benzyl-oxazolidine-2-one (5.00 g, 28.2 mmol) in THF (85 mL) at -78 °C, followed by propionyl chloride (2.8 mL, d = 1.059, 32 mmol) added in one portion while stirring at -78 °C. The reaction mixture was stirred over 30 min at -78 °C then slowly warmed to rt and quenched with saturated aqueous NH_4Cl solution (20 mL). Organic solvent was removed under reduced pressure and the rest was extracted with CH_2Cl_2 (3×20 mL). Combined organic extract was washed with 1 M NaOH solution (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated to give 7.11 g of a yellow oil.

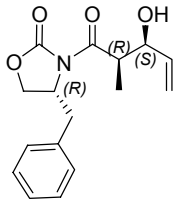
The crude product was cooled with liquid nitrogen and left overnight to crystallize in the refrigerator. The crystals were triturated with cold hexane, filtered off and dried on air to afford 6.42 g (97.6%) of a white solid (mp 42-45 °C). Lit. mp 44-46 °C, 91% yield.[125]

^{1}H-NMR (400 MHz, $CDCl_3$): δ7.45-7.15 (m, 5H, Ar), 4.75-4.60 (dddd, *J* = 9.81, 6.46, 3.51, 3.51 Hz, 1H), 4.30-4.10 (m, 2H), 3.40-3.25 (dd, *J* = 13.30, 3.26 Hz, 1H), 3.10-2.85 (dq, *J* = 2.79, 7.40 Hz, 2H), 2.85-2.70 (dd, *J* = 13.30, 9.66 Hz, 1H), 1.30-1.10 (t, *J* = 7.34 Hz, 3H).

HRMS ESI: Calcd. for $[C_{13}H_{15}NO_3 + Na]$: 256.0950, for $[C_{13}H_{15}NO_3 + CH_3CN + Na]$: 297.1215; found: 256.0956, 297.1220.

$[\alpha]_D^{20}$ (EtOH, *c* = 1.01) = -104° (98% ee).

4(R)-Benzyl-3-(3(S)-hydroxy-2(R)-methyl-pent-4-enoyl)-oxazolidin-2-one (146)[99]



$C_{16}H_{19}NO_4$
Mol. Wt.: 289.33

1.0 M solution of dibutylboryltriflate in CH_2Cl_2 (29.7 mL, 29.7 mmol, 1.1 equiv) was dropwise added to the solution of the imide **170** (6.3 g, 27 mmol, 1 equiv) in CH_2Cl_2 (80 mL,

in a 250 mL flask) at 0 °C. Diisopropylethylamine (5.66 mL, d = 0.742, 32.41 mmol, 1.2 equiv) was added to the reaction mixture at such a rate that internal temperature was bellow 3 °C. After the resulting clear colorless solution was cooled to -78 °C, acrolein (9.01 mL, 135.04 mmol, d = 0.843) was added over 5 min. After being stirred 30 min at -78 °C the solution was allowed to warm to 0 °C and quenched by addition of 1.0 M pH 7.0 phosphate buffer (30 mL) and MeOH (100 mL). A mixture of MeOH (60 mL) and 30% aqueous H_2O_2 (30 mL) was carefully added, so as to keep the internal temperature bellow 5 °C. Volatiles were removed under reduced pressure and water (100 mL) was added. The mixture was extracted with MTBE (3×200 mL). Combined extract was washed with 5% aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give 9.0 g of pale oil.

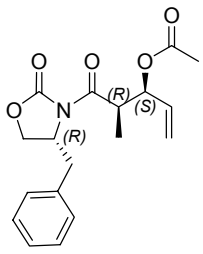
R_f = 0.15-0.20 (hexane/AcOEt 7:3). Flash chromatography with hexane/AcOEt 7:3 on a 6×30 cm column afforded 5.85 g (75%) of **146** as a pale oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ7.40-7.15 (m, 5H, Ar), 5.95-5.75 (ddd, *J* = 17.19, 10.54, 5.14 Hz, 1H), 5.45-5.30 (ddd, *J* = 17.25, 1.57, 1.57 Hz, 1H), 5.30-5.15 (ddd, *J* = 10.51, 1.54, 1.54 Hz, 1H), 4.80-4.60 (dddd, *J* = 9.81, 6.46, 3.39, 3.39 Hz, 1H), 4.60-4.45 (dddd, *J* = 5.02, 1.60, 1.60, 1-2 Hz, 1H), 4.30-4.15 (m, 2H), 3.95-3.80 (dq, *J* = 3.39, 7.03 Hz, 1H), 3.35-3.20 (dd, *J* = 13.36, 3.33 Hz, 1H), 2.95-2.85 (br s, 1H), 2.85-2.70 (dd, *J* = 13.36, 9.47 Hz, 1H), 1.30-1.20 (d, *J* = 7.15 Hz, 3H).

HRMS ESI: Calcd. for [$C_{16}H_{19}NO_4$ + CH_3CN + Na]: 353.1477; found: 353.1470.

α_D^{25} ($CHCl_3$, *c* = 1.42) = -68.6°, α_D^{25} (CH_2Cl_2, *c* = 0.97) = -83.4°.

Acetic acid 1-[2-(4-benzyl-2-oxo-oxazolidin-3-yl)-1-methyl-2-oxo-ethyl]-allyl ester (163)



$C_{18}H_{21}NO_5$
Mol. Wt.: 331.36

Et_3N (0.21 mL, 1.5 mmol, 4.3 equiv) and Ac_2O (0.10 mL, 1.1 mmol, 3.2 equiv) were added to the solution of **146** (100 mg, 0.346 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at rt followed by DMAP (10 mg, 0.081 mmol, 0.23 equiv). After 30 min at rt the reaction mixture was diluted with AcOEt (10 mL), organic layer was washed with 2% aqueous HCl solution (10 mL), by saturated aqueous $NaHCO_3$ solution (15 mL) and brine (15 mL). Aqueous washings were

extracted with AcOEt (20 mL) and washed as before. Combined extract was dried over $MgSO_4$ and concentrated to give a pale oil. The crude product was purified by flash chromatography (hexane/AcOEt 8:2) to afford 97.4 mg (85%) of a colorless oil. The product has an $R_f = 0.20$ in hexane/AcOEt 8:2 and 0.40-0.45 in hexane/AcOEt 7:3; the starting material has an $R_f = 0.20$-0.30 in hexane/AcOEt 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ7.40-7.15 (m, 5H, Ar), 5.84 (ddd, *J* = 17.10, 10.76, 5.87 Hz, 1H), 5.66-5.61 (m, 1H), 5.32 (dt, *J* = 17.23, 1.29 Hz, 1H), 5.23 (dt, *J* = 10.62, 1.19 Hz, 1H), 4.63-4.55 (m, 1H), 4.27-4.21 (m, 1H), 4.19-4.13 (m, 1H), 4.11-4.03 (m, 1H), 3.26 (dd, *J* = 13.30, 3.26 Hz, 1H), 2.77 (dd, *J* = 9.66, 13.43 Hz, 1H), 2.07 (s, 3H), 1.12 (d, *J* = 7.03 Hz, 3H).

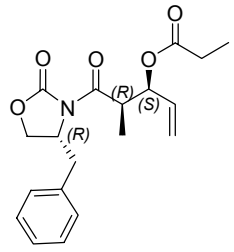
^{13}C-NMR (100 MHz, $CDCl_3$): δ173.41 (Cq), 170.08 (Cq), 153.46 (Cq), 135.23 (Cq), 134.01 (CH), 129.36 (2×CH-Ar), 128.84 (2×CH-Ar), 127.26 (CH), 117.52 (CH_2), 73.97 (CH), 66.25 (CH_2), 55.58 (CH), 41.63 (CH), 37.84 (CH_2), 20.82 (CH_3), 10.93 (CH_3).

HRMS ESI: Calcd. for [$C_{18}H_{21}NO_5$ + Na]: 354.1312, for [$C_{18}H_{21}NO_5$ + CH_3CN + Na]: 395.1583; found: 354.1317, 395.1587.

IR (cm^{-1}, in CH_2Cl_2): 3029 (w), 2986 (w), 2941 (w), 2360 (w), 1777 (s), 1739 (m), 1699 (m), 1647(w), 1605(w), 1498, 1455 (w), 1386 (m), 1371 (m), 1350, 1291, 1230 (s), 1100, 1047, 1020 (m), 973 (m), 945, 841, 763, 742, 704.

α_D^{25} (CH_2Cl_2, *c* = 1.0) = -90.5°.

Propionic acid 1-[2-(4-benzyl-2-oxo-oxazolidin-3-yl)-1-methyl-2-oxo-ethyl]-allyl ester (164)



$C_{19}H_{23}NO_5$
Mol. Wt.: 345.39

Et_3N (0.19 mL, 4 equiv) and propionic acid anhydride (0.18 mL, 1.4 mmol, 4 equiv) were added to the solution of the aldol **146** (100 mg, 0.346 mmol, 1 equiv) and DMAP (8.5 mg, 0.069 mmol, 0.2 equiv) in CH_2Cl_2 (3 mL) at rt. The reaction mixture was stirred for 3 h at rt. The reaction was complete judging by TLC. The reaction mixture was diluted with AcOEt (10 mL), organic layer was washed with 2% aqueous HCl solution (20 mL) then by saturated

aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). Inorganic rests were extracted with AcOEt (20 mL) and washed as before. Combined extract was dried over $MgSO_4$ and concentrated to give a pale oil. Crude product was purified by flash chromatography with hexane/AcOEt 8:2 to afford 116.2 mg of colorless oil (97.2 %). The product has an $R_f = 0.25$ in hexane/AcOEt 8:2 and 0.45-0.50 in hexane/AcOEt 7:3 (permanganate); the starting material has an $R_f = 0.20$-0.30 in hexane/AcOEt 8:2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ7.40-7.15 (m, 5H, Ar), 5.90-5.79 (ddd, *J* = 17.19, 10.67, 5.65 Hz, 1H), 5.68-5.62 (m, 1H), 5.35-5.28 (dt, *J* = 17.23, 1.35 Hz, 1H), 5.25-5.20 (dt, *J* = 10.58, 1.32 Hz, 1H), 4.62-4.55 (m, 1H), 4.28-4.21 (m, 1H), 4.18-4.14 (m, 1H), 4.12-4.04 (m, 1H), 3.26 (dd, *J* = 13.30, 3.26 Hz, 1H), 2.77 (dd, *J* = 9.66, 13.30 Hz, 1H), 2.35 (dq, *J* = 1.69, 7.55 Hz, 3H), 1.21 (d, *J* = 6.90 Hz, 3H), 1.14 (t, *J* = 7.59 Hz, 3H).

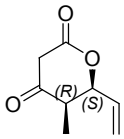
^{13}C-NMR (100 MHz, $CDCl_3$): δ173.46 (Cq), 173.41 (Cq), 153.47 (Cq), 135.25 (Cq), 134.13 (CH), 129.35 (2×CH-Ar), 128.84 (2×CH-Ar), 127.25 (CH), 117.39 (CH_2), 73.65 (CH), 66.25 (CH_2), 55.59 (CH), 41.67 (CH), 37.83 (CH_2), 27.56 (CH_2), 10.89 (CH_3), 9.05 (CH_3).

HRMS ESI: Calcd. for [$C_{19}H_{23}NO_5$ + Na]: 368.1468, for [$C_{19}H_{23}NO_5$ + CH_3CN + Na]: 409.1734; found: 368.1487, 409.1791.

IR (cm^{-1}, in CH_2Cl_2): 3030 (w), 2983 (w), 2944 (w), 2360 (w), 1778 (s), 1735 (m), 1700 (m), 1647(w), 1605(w), 1498, 1456 (w), 1387 (m), 1351 (m), 1269, 1239, 1211, 1182 (s), 1099, 1081, 1010, 982, 935, 807, 762, 743, 704.

α_D^{25} (CH_2Cl_2, *c* = 1.0) = -90.9°.

5-Methyl-6-vinyl-dihydro-pyran-2,4-dione (165)



$C_8H_{10}O_3$
Mol. Wt.: 154.16

A solution of the acetate **163** (50 mg, 0.1509 mmol) in THF (5 mL) was added to a stirred solution of LiHMDS (0.45 mL of 1.0 M solution in hexanes, 3 equiv, 0.453 mmol) in THF (1 mL) at -78 °C. After 3 h at -78 °C the reaction mixture was quenched while cold by addition of saturated aqueous NH_4Cl solution (4 mL), MeOH (3 mL) and H_2O (3 mL). AcOEt (10 mL) and water (10 mL) were added. The organic layer contained the chiral auxiliary. The aqueous basic layer (pH 9-10) was titrated with 0.3 N aqueous HCl solution to pH 2-3 and then extracted with CH_2Cl_2 (3×10 mL). The extract was dried over $MgSO_4$ and concentrated

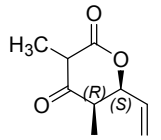
to give 9.4 mg (40%) of the crude product as a yellow oil. The product has an R_f = 0.10-0.15 in hexane/AcOEt 7:3 and R_f = 0.15-0.20 in hexane/AcOEt 1:1 (UV, permanganate, "Vanillin"). Purification by flash chromatography with hexane/AcOEt 1:1 afforded 4.3 mg (18.5%) of a pale solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ5.90-5.70 (ddd, *J* = 17.10, 10.76, 5.30 Hz, 1H), 5.50 (dd, *J* = 0.88, 17.07 Hz), 5.44 (dd, *J* = 0.69, 10.73 Hz), 5.20-5.10 (m, 1H), 3.52 (d, *J* = 20.20 Hz, 1H), 3.42 (d, *J* = 20.33 Hz, 1H), 2.85 (dq, *J* = 4.52, 7.15 Hz, 1H), 1.17 (d, *J* = 7.15 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ201.94 (Cq), 167.11 (Cq), 130.73 (CH), 120.21 (CH_2), 78.78 (CH), 46.46 (CH), 45.45 (CH_2), 9.46 (CH_3).

HRMS ESI: Calcd. for [$C_8H_{10}O_3$ + Na]: 177.0528; found: 177.0537.

3,5-Dimethyl-6-vinyl-dihydro-pyran-2,4-dione (166)



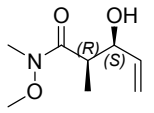
$C_9H_{12}O_3$
Mol. Wt.: 168.19

Freshly prepared solution of KHMDS (1.2 mL of 0.5 M solution in toluene, 0.580 mmol, 4.0 equiv) was added to the solution of the propionate **164** (50 mg, 0.145 mmol) in THF (5 mL) at -78 °C and the reaction mixture was stirred for 3 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (4 mL), MeOH (3 mL) and H_2O (3 mL) while cold. AcOEt (10 mL) and H_2O (10 mL) were added. Aqueous layer was acidified with 1.0 M aqueous HCl solution to pH ca. 2 and extracted with AcOEt (3×15 mL). Combined extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give 13.8 mg of a white solid (57%). Chromatographic purification with hexane/AcOEt 1:1 afforded 5.6 mg (23%) of a white solid. The product has an R_f = 0.10-0.15 in hexane/AcOEt 7:3 and R_f = 0.25-0.30 in hexane/AcOEt 1:1 (UV, permanganate, "Vanillin").

^{1}H-NMR (400 MHz, $CDCl_3$): δ5.91-5.77 (m, 1H), 5.57-5.39 (m, 2H), 5.32-3.24 (m, 1H), 3.59 (q, *J* = 6.73 Hz) & 3.31 (q, *J* = 7.28 Hz) 1H, 2.79-2.70 (m, 1H), 1.44 (d, *J* = 7.15 Hz) + 1.38 (d, *J* = 6.78 Hz) 3H, 1.12 (d, *J* = 7.53 Hz, 3H).

HRMS ESI: Calcd. for [$C_9H_{12}O_3$ + Na]: 191.0684; found: 191.0691.

3(*S*)-Hydroxy-2(*R*)-methyl-pent-4-enoic acid methoxy-methyl-amide (145)[99]



$C_8H_{15}NO_3$
Mol. Wt.: 173.21

2.0 M Me_3Al solution in heptane (5.8 mL, 2 equiv) was added over 20 min to a suspension of *N,O*-dimethyl hydroxylamine hydrochloride (1.304 g, 11.485 mmol, 2 equiv) in CH_2Cl_2 (25 mL) at 0 °C (*caution: gas evolution!*). After the clear reaction mixture was warmed to rt and stirred for 1 h it was cooled to -20 °C, and a solution of the aldol product **146** (1.662 g, 5.744 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added via cannula (*intense gas evolution!*). Clear reaction mixture was slowly warmed to rt and stirred for 15 h at ambient temperature.

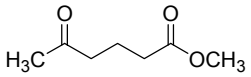
Reaction mixture was cannulated into 1.0 M aqueous tartaric acid solution (50 mL) under vigorous stirring. Organic layer was separated and the aqueous was extracted with CH_2Cl_2 (3×15 mL). Combined extract was washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give the crude product, which was purified by flash chromatography with hexane/MTBE 1:2 to afford 0.861 g (86.5%) of a yellow oil. The product has an $R_f = 0.2$ in hexane/AcOEt 1:1 and 0.20-0.25 in hexane/MTBE 1:2. Evans auxiliary has an $R_f = 0.15$ in hexane/AcOEt 1:1 and 0.10 in hexane/MTBE 1:2.

^{1}H-NMR (200 MHz, $CDCl_3$): δ5.95-5.70 (ddd, *J* = 17.19, 10.54, 5.02 Hz, 1H), 5.45-5.25 (dt, *J* = 17.23, 1.66 Hz, 1H), 5.25-5.15 (dt, *J* = 10.50, 1.69 Hz, 1H), 4.50-4.40 (m, 1H), 3.71 (s, 3H), 3.21 (s, 3H), 3.05-2.85 (m, 1H), 1.20-1.10 (d, *J* = 7.15 Hz, 3H).

Elemental Analysis: Anal. C, 54.13%; H, 8.39%, N, 7.85%; calcd. for $C_8H_{15}NO_3$: C, 55.47%; H, 8.73%; N, 8.09%.

HRMS ESI: Calcd. for [$C_8H_{15}NO_3$ + Na]: 196.0950; found: 196.0937.

5-Oxo-hexanoic acid methyl ester (140)[126]



$C_7H_{12}O_3$
Mol. Wt.: 144.17

Methyl acrylate (45.0 mL, d = 0.956, 500 mmol) and acetylacetone (51.3 mL, 500 mmol, d = 0.975) were added to a solution of sodium methoxide prepared from absolute methanol (200 mL) and sodium metal (0.83 g), and the mixture was refluxed for 3 h. It was left at rt overnight. Glacial acetic acid (2.7 mL, 47.2 mmol) was added and organic solvents were removed under reduced pressure. The rest was solved in MTBE (100 mL), washed with water

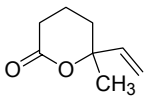
(3×25 mL) and concentrated. The residue was distilled at 93-98 °C/11-12 mmHg) to afford 47.6 g (66%) of **140**.

^{1}H-NMR (200 MHz, $CDCl_3$): δ3.67 (s, 3H), 2.51 (t, *J* = 7.22 Hz, 2H), 2.34 (t, *J* = 7.15 Hz, 2H), 2.14 (s, 3H), 1.89 (qui, *J* = 7.09 Hz, 2H).

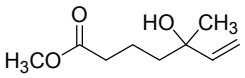
Low resolution MS (M^+ (%)): 28.00 (100.00%), 31.99 (25.32%), 43.02 (29.28%), 55.02 (5.83%), 59.03 (7.04%), 74.04 (8.57%), 85.07(5.33%), 112.05 (10.37%), 113.06 (6.70%).

Elemental Analysis: Anal. C, 57.81%; H, 8.21%; calcd. for $C_7H_{12}O_3$: C, 58.32%; H, 8.39%.

6-Methyl-6-vinyl-tetrahydro-pyran-2-one (150) and 5-hydroxy-5-methyl-hept-6-enoic acid methyl ester (151)



$C_8H_{12}O_2$
Mol. Wt.: 140.18



$C_9H_{16}O_3$
Mol. Wt.: 172.22

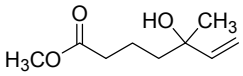
$CeCl_3 \cdot 7H_2O$ (757 mg, 2.03 mmol, 1.5 equiv) was quickly ground in a mortar and placed into a 50 mL Schlenck flask. The flask was heated under vacuum (160 °C/0.01 mmHg) while stirred over 2 h. After the flask was cooled and the inert gas was introduced, THF (5 mL) was added. The flask was cooled to -78 °C and the solution of vinylmagnesium bromide was introduced (2.0 mL of 1.0 M solution, 2.0 mmol, 1.5 equiv). The mixture was stirred over 10 min and the methyl 5-oxo-hexanoate (**140**) (0.195 g, 1.35 mmol, 1.0 equiv) was added as a solution in THF (5 mL). The reaction mixture was stirred for 1 h at -78 °C.

The progress of the reaction was monitored by TLC. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (20 mL), warmed up and the organic layer was separated. The inorganic layer was extracted with MTBE (3×20 mL). Combined extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give 0.276 g of yellow oil. The crude product was purified by flash chromatography with hexane/AcOEt 7:3 to afford 0.148 g (64%) of a pale oil. The product has an R_f = 0.2 in hexane/AcOEt 7:3.

^{1}H-NMR (200 MHz, $CDCl_3$): δ6.00-5.70 (m, 1H), 5.35-5.00 (m, 2H), 3.66 (s, 3H), 2.60-1.50 (m, 6H), 1.46 & 1.28 (s, 3H) (crude product is a mixture of **140**, lactone **150** and alcohol **151**). The product was used in the next step without further purification.

HRMS ESI: desired M^+ was not found.

5-Hydroxy-5-methyl-hept-6-enoic acid methyl ester (151)



$C_9H_{16}O_3$
Mol. Wt.: 172.22

Method a): The solution of the mixture of **150** and **151** (0.1 g, 0.71 mmol) in MeOH (3 mL) was added to the solution of NaOMe obtained from Na metal (22 mg, 0.96 mmol) and MeOH (7 mL) at rt. The reaction mixture was stirred for 40 h at rt.

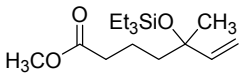
Method b): Et_3N (1 mL) was added to the solution of the mixture of **150** and **151** (0.1 g, 0.71 mmol) in MeOH (5 mL). The reaction mixture was stirred for 40 h at rt.

The workup is the same for both methods: The reaction mixture was quenched by addition of 1.0 M aqueous solution of tartaric acid (20 mL), brine (20 mL) and MTBE (10 mL). Organic layer was separated and the rest was extracted with MTBE (3×20 mL). Combined organic extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give 0.112 g (92% for *Method a)*) and 0.116 g (95% for *Method b)*) of **151** as a pale oil.

^{1}H-NMR (200 MHz, DMSO-d$_6$): δ5.95-5.70 (dd, J = 17.25, 10.73 Hz, 1H), 5.20-5.00 (dd, J = 17.38, 2.07 Hz, 1H), 5.00-4.85 (dd, J = 10.60, 2.07 Hz, 1H), 4.46 (s, 1H), 3.57 (s, 3H), 3.33 (s, 3H), 2.35-2.20 (t, J = 7.59 Hz, 2H), 1.65-1.30 (m, 4H), 1.12 (s, 3H).

HRMS ESI: desired M^+ was not found.

5-Methyl-5-triethylsilanyloxy-hept-6-enoic acid methyl ester (144a)



$C_{15}H_{30}O_3Si$
Mol. Wt.: 286,48

2,6-Lutidune (1.0 mL, 8.71 mmol, 2.2 equiv) and Et_3SiOTf (1.12 mL, 1.31 g, 4.94 mmol, 1.25 equiv) were added at rt to the solution of the alcohol **151** (680 mg, 3.948 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 1.5 h at rt and the progress of the reaction was monitored by TLC. The starting alcohol has an R_f = 0.2 in hexane/AcOEt 7:3 and the product has an R_f = 0.7 in hexane/AcOEt 7:3.

The reaction mixture was quenched with 1.0 M phosphate buffer (25 mL) and the organic layer was separated. The rest was extracted with CH_2Cl_2 (3×15 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated to give the oily

product. The crude product was purified by flash chromatography with hexane/AcOEt 50:1 to afford 0.849 g (75%) of a colorless oil. The product has an R_f = 0.15 in hexane/AcOEt 50:1.

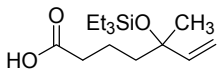
^{1}H-NMR (200 MHz, $CDCl_3$): δ5.90-5.75 (dd, *J* = 17.32, 10.79 Hz, 1H), 5.20-5.05 (dd, *J* = 1.51, 17.07 Hz, 1H), 5.05-4.95 (dd, *J* = 1.51, 10.54 Hz, 1H), 3.65 (s, 3H), 2.28 (t, *J* = 7.28 Hz, 2H), 1.75-1.55 (m, 2H), 1.55-1.40 (m, 2H), 1.29 (s, 3H), 0.93 (t, *J* = 7.78 Hz, 9H), 0.65-0.50 (q, *J* = 7.78 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ174.10 (C=O), 145.24 (CH_2), 111.93 (CH), 76.68 (Cq), 51.34 (CH_3), 43.16 (CH_2), 34.39 (CH_2), 27.27 (CH_3), 19.72 (CH_2), 7.05 (CH_3), 6.76 (CH_2).

HRMS ESI: Calcd. for [$C_{15}H_{30}O_3Si$ + Na]: 309.1862; found: 309.1850.

IR (cm^{-1}, neat): 2954 (s), 2913, 2877, 1743 (s), 1459, 1436, 1415, 1370, 1240, 1173 (s), 1119, 1045 (s), 1008 (s), 921, 873, 725.

5-Methyl-5-triethylsilanyloxy-hept-6-enoic acid (152)



$C_{14}H_{28}O_3Si$
Mol. Wt.: 272,46

Method a): 1.0 M aqueous LiOH solution[q] (0.65 mL, 0.65 mmol, 4 equiv) was added to the solution of the ester **144a** (46.5 mg, 0.163 mmol) in THF (2.5 mL) and MeOH (0.5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred at ambient temperature overnight. The progress of the reaction was monitored by TLC. The starting material has an R_f = 0.7 in hexane/AcOEt 7:3 and the product has an R_f = 0.3-0.4 in hexane/AcOEt 7:3.

The reaction mixture was diluted with MTBE (10 mL) and quenched with 2% aqueous HCl solution (7 mL). Organic layer was separated and the inorganic rest was extracted with MTBE (3×10 mL). Combined extract was washed with saturated aqueous $NaHCO_3$ solution (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated to give 44.3 mg (99.7%) of pale oil.

Method b): Ester **144a** (482 mg, 1.682 mmol, 1 equiv) was refluxed with *n*-Bu_2SnO (335 mg, 1.346 mmol, 0.8 equiv) in toluene (10 mL) for 86 h. The progress of the reaction was monitored by TLC.

[q]) Obtained by the dissolution of $LiOH \cdot H_2O$ (0.42 g) in H_2O (10 mL).

The crude product was purified by flash chromatography with hexane/AcOEt 8:2 to afford 0.296 g (65%) of the acid **152**. The product has an R_f = 0.35-0.4 in hexane/AcOEt 7:3 and 0.20-0.30 in hexane/AcOEt 8:2; the starting material has an R_f = 0.7 in hexane/AcOEt 7:3.

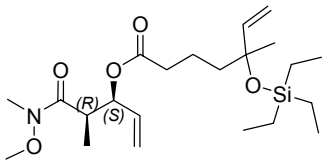
^{1}H-NMR (200 MHz, $CDCl_3$): δ5.90-5.75 (dd, *J* = 10.68, 17.32 Hz, 1H), 5.20-5.10 (dd, *J* = 17.28, 1.48 Hz, 1H), 5.05-4.95 (dd, *J* = 10.64, 1.64 Hz, 1H), 2.40-2.30 (t, *J* = 7.34 Hz, 2H), 1.75-1.55 (m, 2H), 1.55-1.45 (m, 2H), 1.30 (s, 3H), 0.94 (t, *J* = 7.84 Hz, 9H), 0.65-0.55 (q, *J* = 7.91 Hz, 6H). The acidic proton is not seen.

^{13}C-NMR (100 MHz, $CDCl_3$): δ179.81 (COOH), 145.17 (CH), 112.03 (CH_2), 75.20 (Cq), 43.01 (CH_2), 34.29 (CH_2), 27.29 (CH_3), 19.45 (CH_2), 7.05 (CH_3), 6.74 (CH_2).

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 3500-3000 (broad), 2955, 2912, 2877, 1709 (s), 1459, 1413, 1371, 1275, 1236, 1175, 1119, 1045 (s), 1006 (s), 972, 921, 819, 724 (s).

5-Methyl-5-triethylsilanyloxy-hept-6-enoic acid 1-[1-(methoxy-methyl-carbamoyl)-ethyl]-allyl ester (143a)



$C_{22}H_{41}NO_5Si$
Mol. Wt.: 427.65

The reaction is performed according to the general procedure described by Yamaguchi *et al.*[94] 2,4,6-trichlorobenzoylchloride (47µL, 73.2 mg, d = 1.561, 0.3 mmol, 1 equiv) was added to a mixture of the acid **152** (81 mg, 0.3 mmol, 1 equiv) and Et_3N (0.3 mmol, 42 µL) in THF (2 mL) and the mixture was stirred for 1 h at rt. The white precipitate formed was removed by filtration[r] and the filtrate was concentrated under reduced pressure.[s] The mixed anhydride was solved in toluene (2 mL) and treated with the solution of the alcohol (51.9 mg, 0.3 mmol, 1 equiv) in toluene (2 mL) and DMAP (73.3 mg, 0.6 mmol, 2 equiv) in toluene (2 mL). The reaction mixture was allowed to stir at rt for 3 h. The progress of the reaction was monitored by TLC.

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[r]) Triethylammonium chloride started to appear after 10 min. After 1 h the precipitate was filtered off with the help of a 5 mL plastic syringe by placing a piece of cotton that served as a filter between a needle and a syringe.

[s]) THF was removed while stirring at reduced pressure, without letting the solution to get in contact with the air.

The reaction mixture was diluted with MTBE (10 mL) and quenched by water (5 mL). Organic layer was separated, washed successively with 2% aqueous HCl solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). Aqueous layers were collected and extracted with MTBE (2×10 mL). Combined organic extract was dried over $MgSO_4$ and concentrated to give 150.7 mg of a yellow oil. The crude product was purified by flash chromatography with hexane/AcOEt 7:3 to afford 102.45 mg (80%) of **143a** as a colorless oil. The product has an R_f = 0.30-0.35 in hexane/MTBE 7:5 and 0.30-0.35 in hexane/AcOEt 7:3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ5.95-5.75 (m, 2H), 5.47-5.40 (t, *J* = 6.8 Hz, 1H), 5.30-5.20 (dt, *J* = 17.16, < 1 Hz, 1H), 5.20-5.15 (dt, *J* = 10.52, < 1 Hz, 1H), 5.15-5.05 (dd, *J* = 17.28, 1 Hz, 1H), 5.05-4.95 (dd, *J* = 10.68, 1 Hz, 1H), 3.66 (s, 3H), 3.20-3.14 (m, 4H), 2.29 (t, *J* = 7.64 Hz, 2H), 1.75-1.55 (m, 2H), 1.55-1.45 (m, 2H), 1.28 (s, 3H), 1.15-1.12 (d, *J* = 7.03 Hz, 3H), 0.92 (t, *J* = 8.03 Hz, 9H), 0.65-0.45 (q, *J* = 8.03 Hz, 6H).

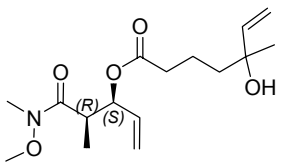
^{13}C-NMR (100 MHz, $CDCl_3$): δ174.30 (w, C=O), 172.57 (C=O), 145.24 & 145.23 (CH), 134.56 (CH), 117.64 (CH_2), 111.90 & 111.89 (CH_2), 75.38 (CH), 75.37 (CH), 75.18 (Cq), 61.43 (CH_3), 43.14 (CH_2), 39.33 (CH), 34.71 (CH_3), 27.18 (CH_3), 26.93 (CH_3), 19.66 (CH_2), 13.43 (CH_3), 7.04 (CH_3), 6.71 (CH_2).

HRMS ESI: Calcd. for [$C_{22}H_{41}NO_5Si$ + Na]: 450.2652; found: 450.2640.

IR (cm^{-1}, neat): 3088 (w), 2957 (s), 2913, 2877(m), 2360 (w), 1739 (s), 1667 (s), 1461 (m) , 1415 (m), 1377 (m), 1239 (m), 1173 (s), 1118 (m), 1047 (m), 1000 (s), 921 (m), 742, 725.

α_D^{25} (CH_2Cl_2, *c* = 0.95) = -10.21°.

5-Hydroxy-5-methyl-hept-6-enoic acid 1-[1-(methoxy-methyl-carbamoyl)-ethyl]-allyl ester (143b)



$C_{16}H_{27}NO_5$
Mol. Wt.: 313.39

Glacial AcOH (1.4 mL) and H_2O (0.6 mL) were added to the solution of the silyl ether **143a** (6.8 mg, 0.0164 mmol) in THF (0.5 mL) and the reaction mixture was stirred for 2 h at rt. The progress of the reaction was monitored by TLC.

The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with AcOEt (3×15 mL). Combined extract was washed with brine (20 mL), dried

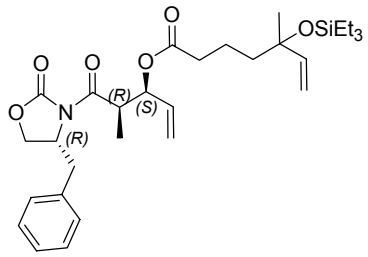
over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt 1:2 to afford 4.7 mg (94%) of a colorless oil. The product has an $R_f = 0.3$ in hexane/AcOEt 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$): δ5.97-5.78 (complex m, 2H), 5.57-5.45 (m, 1H), 5.35-5.15 (m, 3H), 5.10-5.00 (ddd, *J* = 10.79, 4.77, 1.25 Hz, 1H), 3.68 (s, 3H), 3.16 (m, 4H), 2.50-2.25 (m, 2H), 1.80-1.50 (m, 4H), 1.29-1.28 (2×s, 3H), 1.17-1.14 (d, *J* = 7.16 Hz, 3H).

HRMS ESI: Calcd. for [$C_{16}H_{27}NO_5$ + Na]: 336.1787; found: 336.1778.

IR (cm^{-1}, neat): 3447 (broad), 3087 (w), 2923 (s), 2854, 1735 (s), 1651 (s), 1461, 1416, 1378, 1252, 1175 (s), 1116, 1053 (w), 993 (s), 922 (m), 740.

5-Methyl-5-triethylsilanyloxy-hept-6-enoic acid 1-[2-(4-(*R*)-benzyl-2-oxo-oxazolidin-3-yl)-1-(*R*)-methyl-2-(S)-oxo-ethyl]-allyl ester



$C_{30}H_{45}NO_6Si$
Mol. Wt.: 543.77

The reaction is performed according to the general procedure described by Yamaguchi *et al.*[94] 2,4,6-trichlorobenzoylchloride (47μL, 73.2 mg, d = 1.561, 0.3 mmol, 1 equiv) was added to a mixture of the acid **152** (81 mg, 0.3 mmol, 1 equiv) and Et_3N (0.3 mmol, 42 μL) in THF (2 mL) and the mixture was stirred for 1 h at rt.

The white precipitate formed was removed by filtration[t] and the filtrate was concentrated under reduced pressure.[u] The mixed anhydride was solved in toluene (2 mL) and treated with the solution of the aldol **146** (86.8 mg, 0.3 mmol, 1 equiv) in toluene (2 mL) and DMAP (73.3 mg, 0.6 mmol, 2 equiv) in toluene (2 mL). The reaction mixture was allowed to stir at rt for 3 h.

The reaction mixture was diluted with MTBE (10 mL) and quenched with water (5 mL). Organic layer was separated, washed successively with 2% aqueous HCl solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), brine (10 mL). Aqueous layers were collected

[t]) Triethylammonium chloride started to appear after 10 min. After 1 h the precipitate was filtered off with the help of a 5 mL plastic syringe by placing a piece of cotton that served as a filter between a needle and a syringe.

[u]) THF was removed while stirring at reduced pressure, without letting the solution to get in contact with the air.

and extracted with MTBE (2×10 mL). Combined organic extract was dried over $MgSO_4$ and concentrated to give 167 mg of colorless oil. The crude product was purified by flash chromatography with hexane/AcOEt 9:1 to afford 0.114 g (70%) of the product. The product has an R_f = 0.15 in hexane/AcOEt 10:1, 0.20 in hexane/AcOEt 9:1 and 0.45 in hexane/AcOEt 8:2.

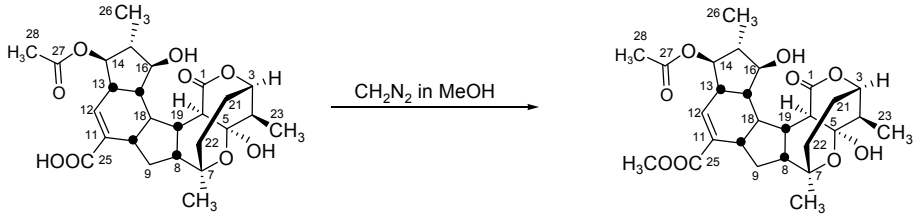
^{1}H-NMR (400 MHz, $CDCl_3$): δ7.40-7.18 (m, 5H, Ar), 5.92-5.80 (m, 2H), 5.70-5.65 (m, 1H), 5.37-5.31 (dt, *J* = 17.23, 1.35 Hz, 1H), 5.27-5.21 (dt, *J* = 10.62, 1.32 Hz, 1H), 5.19-5.12 (ddd, *J* = 17.29, 2.54, 1.60 Hz, 1H), 5.03-4.95 (dt, *J* = 10.71, 1.32 Hz, 1H), 4.65-4.55 (m, 1H), 4.35-4.22 (m, 1H), 4.25-4.15 (dd, *J* = 8.97, 2.45 Hz, 1H), 4.15-4.05 (dq, *J* = 4.55, 6.88 Hz, 1H), 3.35-3.25 (dd, *J* = 13.36, 3.20 Hz, 1H), 2.85-2.75 (dd, *J* = 13.36, 9.73 Hz, 1H), 2.40-2.30 (t, *J* = 7.28 Hz, 2H), 1.75-1.60 (m, 2H), 1.55-1.45 (m, 2H), 1.32 (s, 3H), 1.28-1.20 (d, *J* = 6.90 Hz, 3H), 0.96 (t, *J* = 7.91 Hz, 9H), 0.65-0.55 (q, *J* = 7.91 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ173.36 (Cq), 172.74 (Cq), 153.49 (Cq), 145.23 (CH), 135.29 (Cq, Ar), 134.22 (CH), 129.36 (2×CH, Ar), 128.84 (2×CH, Ar), 127.25 (CH), 117.34 (CH_2), 111.88 (CH_2), 75.15 (Cq), 73.63 (CH), 66.25 (CH_2), 55.65 (CH), 43.04 (CH_2), 41.74 (CH), 37.85 (CH_2), 34.55 (CH_2), 27.21 (CH_3), 19.61 (CH_2), 10.83 (CH_3), 7.02 (CH_3), 6.46 (CH_2).

HRMS ESI: Calcd. for [$C_{30}H_{45}NO_6Si$ + Na]: 566.2914; found: 566.2923.

α_D^{25} (CH_2Cl_2, *c* = 2.25) = -56.33°.

Methyl ester of hexacyclinic acid



$C_{26}H_{34}O_9$
Mol. Wt.: 490.54

$C_{27}H_{36}O_9$
Mol. Wt.: 504.57

The solution of diazomethane in Et_2O was added dropwise to the solution of hexacyclinic acid[v] (5.0 mg) solved in AcOEt (5 mL) until the color of the reaction mixture remained yellow and did not bleach after 3 min. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography with hexane/AcOEt 1:1 to afford 4.3 mg (84%) of the product. Hexacyclinic acid has an R_f = 0.40 in $CHCl_3$/MeOH 9:1; the methyl ester has an R_f = 0.7 in $CHCl_3$/MeOH 9:1, 0.23 in hexane/AcOEt 1:1 and 0.30 in hexane/AcOEt 1:2,

[v]) A sample of hexacyclinic acid was kindly granted by Prof. Zeeck, University of Göttingen.

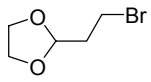
UV. According to the TLC the product is stable over months. Biological tests have shown that the substance posses low or no cytotoxicity against the tested cell lines.

^{1}H-NMR (500 MHz, CD_3OD, 300K): δ6.77-6.74 (t, *J* = 2.64 Hz, 1H), 4.68-4.62 (m, 1H), 4.52-4.48 (m, 1H), 3.70 (s, 3H), 3.70-3.65 (m, 1H), 3.21 (s, 1H), 2.98-2.90 (m, 1H), 2.87-2.81 (t, *J* = 10.74 Hz, 1H), 2.45-2.38 (m, 1H), 2.26-2.14 (m, 3H), 2.12 (s, 3H), 2.08-1.96 (m, 3H), 1.89-1.80 (m, 1H), 1.78-1.71 (m, 1H), 1.55-1.44 (m, 2H), 1.33-1.27 (m, 2H), 1.16 (s, 3H), 1.12-1.08 (d, *J* = 6.87 Hz, 3H), 1.05-1.01 (d, *J* = 6.10 Hz, 3H), 0.93-0.88 (m, 1H).

^{13}C-NMR (125 MHz, CD_3OD, 300K): δ178.87, 172.81, 168.57, 140.67, 135.79, 95.91, 80.88, 80.58, 80.41, 74.05, 53.57, 51.88, 46.84, 46.32, 45.69, 43.36, 42.69, 36.19, 32.75, 32.28, 27.47, 24.21, 23.69, 20.94, 14.53, 14.42, 8.58.

HRMS ESI: Calcd. for [$C_{27}H_{36}O_9$ + Na]: 527.2257; found: 527.2249.

2-(2-Bromoethyl)-1,3-dioxolane (171)



$C_5H_9BrO_2$
Mol. Wt.: 181.03

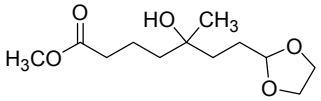
The substance was prepared according to the known procedure[82] using tetralin (0.825 mol), bromine (2.0 mol), acrolein (2.0 mol) and ethylene glycol (2.5 mol). The product was obtained as a pale heavy oil with a yield of 56% (201.67 g) after vacuum distillation (bp 53-63 °C/2 mmHg). Lit. [82b] bp 68-70 °C/5 mmHg; lit. [82a] bp 68-70 °C/8 mmHg.

^{1}H-NMR (200 MHz, $CDCl_3$): δ5.01 (t, *J* = 4.58 Hz, 1H), 4.05-3.80 (m, 4H), 3.47 (t, *J* = 7.09 Hz, 2H), 2.22 (dt, *J* = 4.61 Hz, 7.12 Hz, 2H).

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 2950 (s), 1409 (w), 1363 (m), 1262, 1210, 1030 (m), 877, 822 (w).

Methyl 7-(1,3-dioxolan-2-yl)-5-hydroxy-5-methylheptanoate (173)



$C_{12}H_{22}O_5$
Mol. Wt.: 246,30

Mg turnings (800 mg, 33 mmol, 3 equiv) were ground in a mortar (2-3 min) and transferred into a 50 mL Schlenk flask. The flask was evacuated and heated with the heat gun, the turnings were stirred for 30 min under vacuum. Then the vessel was fitted with an Ar balloon and THF (5 mL) was added.

A solution of **171** (2.00 g, 11.04 mmol, 1.0 equiv) in THF (5 mL) was added over 30 min to the Mg turnings while stirring and maintaining the temperature at 22-24 °C (cold water bath). The reaction has begun after 5 min. After the solution of **171** was added, the reaction mixture was stirred for 30 min at ambient temperature.

The grey-colored solution of the organomagnesium compound (11.04 mmol, 1.0 equiv) in THF (10 mL) was separated from the rest of Mg turnings and dropwise added to the solution of **140** (1.59 g, 11.04 mmol, 1.0 equiv) in THF (10 mL) over 60 min at 0 - -10 °C (ice-salt bath). The reaction mixture was stirred for 4 h at 0 - -5 °C and the progress of the reaction was monitored by TLC. The starting material has an R_f = 0.50 in hexane/AcOEt 2:3; the product has an R_f = 0.20 in hexane/AcOEt 2:3; and the lactone has an R_f = 0.25 in hexane/AcOEt 2:3.

The reaction mixture was diluted with MTBE (30 mL), quenched by saturated aqueous NH_4Cl solution (10 mL) and water (10 mL) and extracted with MTBE (3×20 mL). Combined extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give 1.85 g of pale oil.

The crude product was solved in MeOH (10 mL) and this solution was added to the solution of Na metal (12 mg, 0.5 mmol) in MeOH (10 mL). The reaction mixture was stirred for 15 h at ambient temperature.

The reaction mixture was diluted with MTBE (5 mL) and quenched by saturated aqueous NH_4Cl solution (5 mL). Organic solvents were removed under reduced pressure and the rest was excessively extracted with MTBE (3×50 mL). Combined extract was dried over $MgSO_4$, filtered and concentrated to give 1.91 g (70%) of a yellow-brown oil, which was bulb to bulb distilled to afford 1.64 g (60%) of a pale oil. The product has an R_f = 0.15-0.20 in hexane/AcOEt 1:1.

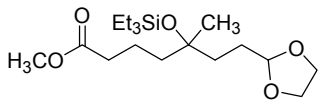
^{1}H-NMR ($CDCl_3$, 400 MHz): δ4.82 (dt, *J* = 1.51, 4.45 Hz, 1H), 4.00-3.90 (m, 2H), 3.85-3.75 (m, 2H), 3.61 (d, *J* = 1.51 Hz, 3H), 2.27 (dt, *J* = 1.05, 7.31 Hz, 2H), 1.75-1.40 (m, 8H), 1.12 (d, *J* = 1.38 Hz, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ173.96 (C=O), 104.49 (CH), 71.66 (d, *J* = 0.58 Hz, Cq), 64.77 (2×CH_2), 51.39 (CH_3), 41.19 (CH_2), 35.22 (CH_2), 34.20 (CH_2), 28.03 (CH_2), 26.46 (CH_3), 19.32 (CH_2).

HRMS ESI: Calcd. for [$C_{12}H_{22}O_5$ + Na]: 269.1365; found: 269.1375.

IR (cm^{-1}, neat): 3600-3400 (br), 2959 (m), 2883 (m), 1784 (w), 1734 (s), 1437, 1417, 1373 (m), 1238, 1207 (m), 1166, 1128 (m), 1039 (s), 1014, 984, 944, 917 (m), 885, 805.

Methyl 7-(1,3-dioxolan-2-yl)-5-methyl-5-(triethylsilyloxy)heptanoate (174)



$C_{18}H_{36}O_5Si$
Mol. Wt.: 360,56

2,6-Lutidune (90 µL, 0.755 mmol, 2.0 equiv) and $Et_3SiOOTf$ (130 µL, 0.566 mmol, 1.5 equiv) were added with a Hamilton syringe to the solution of **173** (93 mg, 0.378 mmol, 1 equiv) in CH_2Cl_2 (5 mL) while stirred at -78 °C. Reaction mixture was stirred at -78 °C for 6 h. The progress of the reaction was monitored by TLC: the starting material has an R_f = 0.10 in hexane/AcOEt 1:1 while the product has an R_f = 0.60 in hexane/AcOEt 1:1.

The reaction mixture was quenched while cold with 1.0 M pH 7.0 phosphate buffer (15 mL), extracted with CH_2Cl_2 (3×10 mL). Combined extract was washed with saturated aqueous NH_4Cl solution (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The crude product was purified by flash chromatography with hexane/AcOEt 5:1 to afford 108.4 mg (80%) of a colorless oil.

The product has an R_f = 0.20-0.25 in hexane/AcOEt 5:1, 0.55-0.60 in hexane/AcOEt 1:1, 0.25-0.30 in hexane/AcOEt 4:1 and 0.15-0.20 in hexane/AcOEt 8:1.

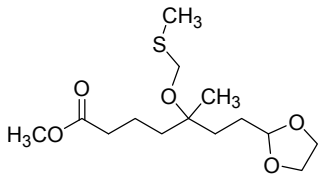
^{1}H-NMR ($CDCl_3$, 400 MHz): δ4.80 (t, *J* = 4.71 Hz, 1H), 4.00-3.90 (m, 2H), 3.85-3.75 (m, 2H), 3.63 (s, 3H), 2.26 (t, *J* = 7.34 Hz, 2H), 1.70-1.35 (m, 8H), 1.16 (s, 3H), 0.90 (t, *J* = 7.97 Hz, 9H), 0.53 (q, *J* = 7.91 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ173.95 (C=O), 104.85 (CH), 74.64 (Cq), 64.77 (2×CH_2), 51.34 (CH_3), 41.67 (CH_2), 35.94 (CH_2), 34.41 (CH_2), 28.65 (CH_2), 27.54 (CH_3), 19.75 (CH_2), 7.07 (CH_3×3), 6.76 (CH_2×3).

HRMS ESI: Calcd. for [$C_{18}H_{36}O_5Si$ + Na]: 383.2230, for [$C_{18}H_{36}O_5Si$ + CH_3CN + Na + H]: 425.2573; found: 383.2235, 425.2451.

IR (cm^{-1}, neat): 2955 (s), 2912, 2876, 1741 (s), 1459, 1437, 1414, 1375, 1237, 1197, 1171, 1139, 1040, 1016, 944 (w), 889 (w), 724 (s).

Methyl 7-(1,3-dioxolan-2-yl)-5-methyl-5-(methylthiomethoxy)heptanoate (178)



$C_{14}H_{26}O_5S$
Mol. Wt.: 306,42

The transformation was conducted according to a published protocol.[127] Ac_2O (92 mL, d = 1.087, 0.9 mol) was added to the solution of the **173** (4.92 g, 19.98 mmol) in DMSO (140.0 mL, d = 1.101, 1.8 mol) at rt and the reaction mixture was stirred for 60 h at ambient temperature. The reaction mixture was poured into 500 mL of mixture of ice and saturated aqueous $NaHCO_3$ solution (1:1 v/v). The emulsion was stirred until the evolution of the gas has ceased and was extracted with MTBE (5×50 mL). Combined extract was washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure (60 °C/up to 10 mar) and the oil obtained was further concentrated under high vacuum (rt/0.5 mmHg) to give 7.48 g of a brown-yellow oil. Bulb to bulb distillation (250 °C/0.5-1 mmHg) afforded a yellow oil with a typical smell, 5.23 g (85%). The product has an R_f = 0.55-0.60 in hexane/AcOEt 1:1 and 0.25-0.30 in hexane/AcOEt 2:3.

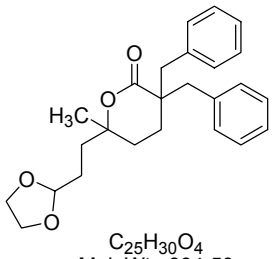
^{1}H-NMR ($CDCl_3$, 400 MHz): δ4.82 (t, *J* = 4.45 Hz, 1H), 4.42 (s, 2H), 4.00-3.90 (m, 2H), 3.85-3.75 (m, 2H), 3.62 (s, 3H), 2.27 (t, *J* = 7.15 Hz, 2H), 2.14 (s, 3H), 1.70-1.40 (m, 8H), 1.14 (m, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ173.76 (C=O), 104.37 (CH), 77.54 (Cq), 66.04 (CH_2), 64.79 (2×CH_2), 51.36 (CH_3), 37.72 (CH_2), 34.06 (CH_2), 31.66 (CH_2), 27.85 (CH_2), 22.87 (CH_3), 18.98 (CH_2), 14.46 (CH_3).

HRMS ESI: Calcd. for [$C_{14}H_{26}O_5S$ + Na]: 329.1412; found: 329.1336.

IR (cm^{-1}, neat): 2953 (s), 2881, 1737 (s), 1437, 1376, 1303, 1257, 1198, 1140, 1039, 946, 911, 761, 688.

6-(2-(1,3-Dioxolan-2-yl)ethyl)-3,3-dibenzyl-6-methyl-tetrahydropyran-2-one (179)



$C_{25}H_{30}O_4$
Mol. Wt.: 394,50

The reaction was conducted according to a published procedure.[128] The solution of the alcohol **173** (1.43 mmol, 352 mg, 1 equiv) in THF (3 mL) was added to the suspension of KH[w] (1.85 mmol, 1.29 equiv, 74 mg) in THF (2 mL) at 0 °C. A solution of BnBr (1.86 mmol, 1.3 equiv, 320 mg) in THF (3 mL) was added. The reaction mixture was warmed to rt and stirred at ambient temperature over 12 h. As the reaction was not complete according to the TLC, additional portion of KH (0.9 mmol, 0.65 equiv, 35 mg) was added and the reaction mixture was stirred at rt for additional 3 h. Reaction mixture was diluted with MTBE (10 mL), quenched with H_2O (10 mL) and extracted with MTBE (3×15 mL). Combined organic extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give 395 mg of a brown emulsion.

The crude product was purified by flash chromatography with hexane/AcOEt 7:3 to afford 119 mg (21%) of a colorless oil that formed white crystals later. The product has an R_f = 0.25-0.30 in hexane/AcOEt 7:3.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.20 (m, 10H, Ar), 4.60 (t, *J* = 4.71 Hz, 1H), 4.95-3.70 (m, 4H), 3.55-3.35 (dd, *J* = 25.47, 13.05 Hz, 2H), 2.70-2.50 (dd, *J* = 39.90, 13.05 Hz, 2H), 1.90-1.70 (m, 2H), 1.50-1.35 (m, 2H), 1.30-1.10 (m, 4H), 0.70 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ175.85 (C=O), 137.02 (Cq, Ar), 136.93 (Cq, Ar), 130.64 (2×CH, Ar), 130.49 (2×CH, Ar), 128.33 (2×CH, Ar), 128.24 (2×CH, Ar), 126.85 (CH, Ar), 126.80 (CH, Ar), 103.98 (CH), 83.50 (Cq), 64.72 (CH_2, dioxolane), 64.67 (CH_2, dioxolane), 47.82 (Cq), 46.67 (CH_2, Bn), 46.12 (CH_2, Bn), 35.27 (CH_2), 29.9 (CH_2), 27.76 (CH_2), 25.42 (CH_3), 22.98 (CH_2).

HRMS ESI: Calcd. for [$C_{25}H_{30}O_4$ + H]: 395.222, for [$C_{25}H_{30}O_4$ + Na]: 417.2042; found: 395.2185, 417.2023.

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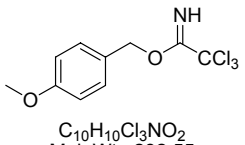
[w]) 35%-suspension of KH in mineral oil (150 mg) was transferred into a weighted Schlenk flask, washed with hexane over N_2, the solvent was removed by a syringe and KH was dried under reduced pressure (0.1 mmHg). The flask was weighted.

IR (cm^{-1}, neat): 3027(w), 2933, 2879, 1705(s), 1602(w), 1494, 1454, 1372, 1278, 1203, 1132(s), 1108(s), 1031(s), 946, 766, 743, 702(s).

4-Methoxybenzyl 2,2,2-trichloroacetimidate

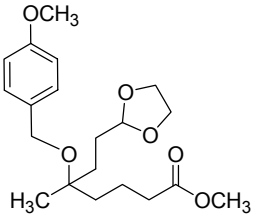


$C_{10}H_{10}Cl_3NO_2$
Mol. Wt.: 282.55

The compound was prepared according to the published procedure.[129] A solution of PMBOH (22.65 g, 163.94 mmol, 1 equiv) in MTBE (25 mL) was added over 30 min to the stirred suspension of NaH (655 mg of 60% suspension in mineral oil, 16.38 mmol, 0.1 equiv) in MTBE (40 mL) at 0 °C. After the addition was complete, the reaction mixture was warmed to rt and stirred for 90 min at ambient temperature. The reaction mixture was cooled to -10 °C, and trichloroacetonitrile (26.0 g, 18.0 mL, 179.51 mmol, 1.1 equiv, d = 1.44) was added over 30 min in small portions so that the temperature stayed bellow 5 °C. When the addition was complete the reaction mixture was stirred additional 15 min at -10 °C, then slowly warmed to rt and stirred for 1 h at ambient temperature. The reaction mixture was concentrated under reduced pressure (30 °C/15 mmHg). Hexane (70 mL), MeOH (1 mL) and celite (5 g) were added. The resulting mixture was stirred for 30 min at rt and filtered. Filtrate was concentrated to afford 47 g (100%) of a brown oil.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ8.36 (br s, 1H), 7.37 (d, J = 8.78 Hz, 2H), 6.91 (d, J = 8.78 Hz, 2H), 5.27 (s, 2H), 3.82 (s, 3H).

Methyl 5-(4-methoxybenzyloxy)-7-(1,3-dioxolan-2-yl)-5-methylheptanoate (180)



$C_{20}H_{30}O_6$
Mol. Wt.: 366.45

4-Methoxybenzyl 2,2,2-trichloroacetimidate (287 mg, 1.015 mmol, 2.5 equiv) and TfOH (0.108 µL, 0.003 equiv, 0.0012 mmol, d = 1.696)[x] were added to the solution of the alcohol **173** (100 mg, 0.4060 mmol) in Et_2O (10 mL) at rt. As there was no reaction progress after 1 h

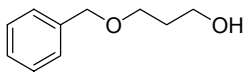
[x]) 10 µL of the TfOH were solved in ether (10 mL). 0.1 mL of this solution was taken.

according to the TLC, additional portion of TfOH (0.216 µL, 0.006 equiv) was added. CSA monohydrate (20 mg, 20 mol%) was added. The reaction mixture was stirred for 15 h at rt.
The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL), followed by extraction with AcOEt (3×15 mL). Combined extract was dried over $MgSO_4$ and concentrated. The crude product was purified twice by flashed chromatography with hexane/AcOEt 7:3 to afford 53.2 mg of a white solid on concentration. The product has an R_f = 0.2-0.3 in hexane/AcOEt 7:3.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ7.25 (d, *J* = 8.64 Hz, 2H), 6.85 (d, *J* = 8.76 Hz, 2H), 4.88 (t, *J* = 4.14 Hz, 1H), 4.30 (s, 2H), 4.00-3.82 (m, 4H), 3.79 (s, 3H), 3.66 (s, 3H), 2.32 (t, *J* = 7.09 Hz, 2H), 1.80-1.50 (m, 8H), 1.21 (s, 3H).

HRMS ESI: Calcd. for [$C_{20}H_{30}O_6$ + CH_3CN + Na]: 430.2206; found: 430.2212.

3-(Benzyloxy)propan-1-ol (181)



$C_{10}H_{14}O_2$
Mol. Wt.: 166.22

3-(Benzyloxy)-1-propanol was prepared according to the published procedure[130]. Sodium (25 g, 1.09 mol) was added in small portions to vigorously stirred solution of 1,3-propanediol (240 mL, 250 g, 3.3 mol) in dry *o*-xylene (100 mL) at 50 °C. The temperature rose by itself up to 120°-140 °C, so that the reaction mixture refluxed. After all the sodium has been dissolved, benzyl chloride (139 mL, 150 g, d = 1.1 g/mL, 1.19 mol) was slowly added with stirring to the hot (120 °C) solution over a period of 2 h. The reaction mixture was heated for 1 h and then cooled to rt. Precipitated NaCl was removed by filtration and washed with toluene. Combined filtrate washings were concentrated under reduced pressure to provide a clear liquid (300 g), which was fractionated under vacuum using a Vigreux column. After a forerun of 1,3-propanediol (185 g), bp 80-85 °C (2 mmHg), the γ-benzyloxopropanol (120 g, 65%) distilled as a clear colorless liquid, bp 95-100 °C (1-2 mmHg). Lit.[130] yield: 65%, bp 95-100 °C (1-2 mmHg), lit.[131] bp 145-150 °C (13 mmHg).

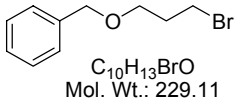
^{1}H-NMR ($CDCl_3$, 400 MHz): (Not calibrated) δ7.36 (m, 5H, Ar), 4.54 (s, 2H), 3.77 (t, *J* = 5.84 Hz, 2H), 3.67 (t, *J* = 5.90 Hz, 2H), 2.82 (br s, 1H), 1.88 (qui, *J* = 5.84 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ137.97 (Cq, Ar), 128.28 (2×CH, Ar), 127.54 (CH, Ar), 127.50 (2×CH, Ar), 73.04 (CH_2), 68.85 (CH_2), 61.18 (CH_2), 32.03 (CH_2).

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 3353 (br, s), 3031 (w), 2932, 2859, 1495, 1454, 1364, 1205, 1072 (s), 1026, 972, 919, 735 (s), 696 (s).

1-(Benzyloxy)-3-brompropane (182)



The substance was prepared according to a described procedure.[132] *N*-bromosuccinimide (38.2 g, 0.215 mol) was added in small portions to the ice-salt cooled mixture of **181** (35.7 g, 0.215 mol) and triphenylphosphine (56.4 g, 0.215 mol) under mechanical stirring[y] and at such a rate that the temperature of the reaction mixture did not exceed 10 °C.[z]

After the reaction mixture was stirred over 20 h at rt it has been diluted with hexane (30 mL), filtered with suction and the precipitate was washed with hexane (2×50 mL) and MTBE (30 mL). The filtrate was concentrated under reduced pressure and the oily rest was diluted with MTBE (30-40 mL), washed with 10% aqueous $Na_2S_2O_3$ solution (3×20 mL), 0.5 M aqueous NaOH solution (30 mL) and brine (30 mL). Inorganic rests were extracted with MTBE (3×30 mL) and the extract was washed as above. Combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure (50 °C/8 mmHg) providing the crude product which was distilled bulb to bulb (150 °C/2 mmHg) to afford 31.31 g (64%) of a colorless liquid.[aa] Lit.[132] yield: 33.2 g (67%), bp 128-130 °C/5 mmHg; lit.[133] bp 159-160 °C/3 mmHg.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.39 (m, 5H, Ar), 4.57 (s, 2H), 3.65 (t, J = 5.90 Hz, 2H), 3.58 (t, J = 6.53 Hz, 2H), 2.19 (qui, J = 6.07 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ138.14 (Cq, Ar), 128.32 (2×CH, Ar), 127.56 (CH, Ar), 127.54 (2×CH, Ar), 73.01 (CH_2), 67.59 (CH_2), 32.81 (CH_2), 30.59 (CH_2).

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 3496 (v, br), 3064, 3030, 2858, 1720 (w), 1495, 1453, 1363, 1255, 1205, 1099 (s), 1069 (s), 1027, 909, 881, 735 (s), 696 (s).

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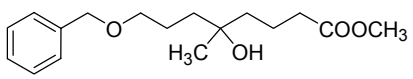
[y]) Good mechanical stirring and inner temperature control are essential.

[z]) The reaction has an induction period of ca. 30 min and is very exothermic! The addition of NBS must be slow enough.

[aa]) The product, obtained after distillation contains an admixture (5%-10%) of the staring alcohol. From that reason it is advised to take 1.1-1.2 equiv of both PPh_3 and NBS.

Methyl 8-(benzyloxy)-5-hydroxy-5-methyloctanoate (183)



$C_{17}H_{26}O_4$
Mol. Wt.: 294.39

3-(Benzyloxy)propylmagnesium bromide was prepared according to the published procedure.[134] A solution of **182** (17.09 g, 74.59 mmol, 1.0 equiv) in THF (10 mL) was added over 30 min to a suspension of Mg turnings[bb] (3.58 g, 149 mmol, 2 equiv) in THF (10 mL) at 22-24 °C (the flask was cooled on a cold water bath). The reaction is exothermic and has an induction period of approx. 15 min. When the reaction starts, the color of the reaction mixture becomes olive-green and the temperature may rise to 50-60 °C.

After the addition of **182** was complete, the reaction mixture was stirred at ambient temperature for 2 h. Green-brown solution of the Grignard reagent was dropwise added to the solution of methyl 5-oxo-hexanoate (**140**) (4.33 g, 30 mmol, 0.4 equiv) in THF (10 mL) over 30 min at rt. An exothermic effect was noticed during the addition.

After the reaction mixture was stirred for 1 h at rt, MeOH (5 mL) was added. Then the reaction mixture was added to MeOH (100 mL) and stirred for 30 min at rt. Solvents were removed under reduced pressure and the rest was diluted with MTBE (50 mL). The grey suspension was filtered through sand and celite and the precipitate was washed with MTBE (2×40 mL) and CH_2Cl_2 (20 mL). 15.5 g of a yellow oil was obtained on concentration.

The crude product was purified by bulb to bulb distillation (150 °C/0.1 mmHg) to afford ***the product*** as a yellow oil, 8.7 g (98.5%) ***as the rest in the distillation flask***, and a colorless distillate. According to the NMR, the product is the mixture of the lactone and the methyl ester. It was used in the next step without further purification.

NaOMe solution obtained from Na metal (220 mg, 9.18 mmol) and MeOH (25 mL) was added to the solution of the crude product (2.39 g, 9.10 mmol) in MeOH (50 mL) at rt. Pale cloudy solution was stirred for 2 h at rt. The reaction mixture was quenched by addition of 2% aqueous HCl solution (16 mL) at 0 °C (pH 2-3) and 1.0 M pH 7.0 phosphate buffer (2 mL). After volatiles were removed under reduced pressure H_2O (20 mL) was added (pH should be neutral) and the mixture was extracted with MTBE (3×40 mL). Combined organic extract was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to afford 2.23 g

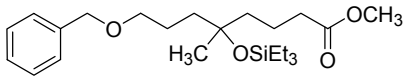
[bb]) Ground to generate a fresh surface.

(83%) of **183** as a yellow oil. The product was used in the next step without further purification. It has an R_f = 0.3 in hexane/AcOEt 1:1.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.20 (m, 5H, Ar), 4.55-4.48 (m, 2H), 3.67 (s, 3H), 3.50 (t, *J* = 6.14 Hz, 2H), 2.33 (t, *J* = 7.34 Hz, 2H), 1.75-1.65 (m, 4H), 1.60-1.54 (m, 2H), 1.51-1.45 (m, 2H), 1.17 (s, 3H).

HRMS ESI: Calcd. for [$C_{17}H_{26}O_4$ + Na]: 317.1729; found: 317.1744.

8-Benzyloxy-5-methyl-5-triethylsilanyloxy-octanoic acid methyl ester (184)



$C_{23}H_{40}O_4Si$
Mol. Wt.: 408,65

2,6-Lutidune (4.7 mL, 4.30 mg, 40.10 mmol, 2.0 equiv) and Et_3SiOTf (6.3 mL, 7.42 g, 28.07 mmol, 1.4 equiv) were added to the solution of the alcohol **183** (5.90 g, 20.05 mmol) in CH_2Cl_2 (40 mL) at -95 °C over 2 min. The reaction mixture was stirred for 2 h at -78 °C until the reaction was complete according to the TLC. Reaction mixture was quenched by the addition of H_2O (10 mL) and saturated aqueous NH_4Cl solution (10 mL) while cold. The mixture was warmed to rt and extracted with CH_2Cl_2 (3×30 mL). The combined organic extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt 10:1 to afford 4.60 g (56%) of **184** as a colorless oil as a product. It has an R_f = 0.55-0.60 in hexane/AcOEt 3:2 and 0.20-0.25 in hexane/AcOEt 10:1.

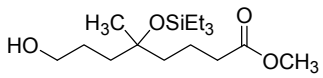
^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.20 (m, 5H, Ar), 4.53 (s, 2H), 3.69 (s, 3H), 3.48 (t, *J* = 6.65 Hz, 2H), 3.32 (t, *J* = 7.47 Hz, 2H), 1.75-1.60 (m, 2H), 1.55-1.40 (m, 2H), 1.22 (s, 3H), 0.97 (t, *J* = 7.91 Hz, 9H), 0.59 (q, *J* = 7.91 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ174.05 (Cq), 138.62 (Cq), 128.27 (2×CH), 127.53 (2×CH), 127.39 (CH), 74.99 (Cq), 72.74 (CH_2), 70.90 (CH_2), 51.37 (CH_3), 41.63 (CH_2), 38.56 (CH_2), 34.47 (CH_2), 27.64 (CH_3), 24.58 (CH_2), 19.78 (CH_2), 7.12 (3×CH_3), 6.83 (3×CH_2).

HRMS ESI: Calcd. for [$C_{23}H_{40}O_4Si$ + Na]: 431.2594; found: 431.2608.

IR (cm^{-1}, neat): 2951 (s), 2911, 2874, 1739 (s), 1496, 1455, 1435, 1415, 1360, 1238, 1196, 1170, 1100, 1008 (s), 722 (s), 697.

8-Hydroxy-5-methyl-5-triethylsilanyloxy-octanoic acid methyl ester (185)



$C_{16}H_{34}O_4Si$
Mol. Wt.: 318.52

The solution of the benzyl ether **184** (1000 mg, 2.45 mmol) in MeOH (5 mL) was added to the suspension of Ni* Raney (W2)[135] catalyst (ca. 4 mL of the sedimented suspension that corresponds to ca. 2.4 g of dry catalyst) in MeOH (5 mL). The flask was evacuated and attached to H_2-line (1 atm). The reaction mixture was vigorously stirred over 6 h while the hydrogenation was controlled by TLC.

When the reaction was complete, the reaction mixture was filtered through celite and concentrated to give 0.768 g (98.5%) of **185** as a colorless oil. The product was used without further purification in the next step. It has an R_f = 0.15-0.20 in hexane/AcOEt 7:3.

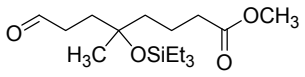
^{1}H-NMR ($CDCl_3$, 400 MHz): δ3.64 (s, 3H), 3.60-3.55 (m, 2H), 2.27 (t, *J* = 7.47 Hz, 2H), 1.99 (s, 1H), 1.70-1.50 (m, 4H), 1.50-1.40 (m, 4H), 1.18 (s, 3H), 0.91 (t, *J* = 7.91 Hz, 9H), 0.54 (q, *J* = 7.99 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ174.09 (CO), 75.14 (Cq), 63.31 (CH_2), 51.41 (CH_3), 41.56 (CH_2), 38.25 (CH_2), 34.36 (CH_2), 27.69 (CH_3), 27.48 (CH_2), 19.80 (CH_2), 7.06 (3×CH_3), 6.76 (3×CH_2).

HRMS ESI: Calcd. for [$C_{16}H_{34}O_4Si$ + Na]: 341.2124; found: 341.2296.

IR (cm^{-1}, neat): 3388 (br), 2951 (s), 2911, 2875, 1740 (s), 1458, 1436, 1415, 1374, 1237, 1196, 1169, 1120, 1053 (s), 1010 (s), 720 (s), 671.

Methyl 5-methyl-8-oxo-5-(triethylsilyloxy)octanoate (169)[136]



$C_{16}H_{34}O_4Si$
Mol. Wt.: 318.52

DMSO (334 µL, 368 mg, 4.71 mmol, 5 equiv, d = 1.101) was added to a solution of oxalylchloride (164 µL, 239 mg, 1.88 mmol, 2.0 equiv, d = 1.455) in CH_2Cl_2 (5 mL) at -78 °C. The reaction mixture was stirred 25 min at -78 °C. Solution of the alcohol **185** (307 mg, 0.942 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was dropwise added over 2 min. The reaction mixture was stirred for 15 min at -78 °C.

Pr_2EtN (1000 µL, 742 mg, 5.74 mmol, 6 equiv, d = 0.742) was added and the reaction mixture was allowed to warm to rt.

After the reaction mixture was stirred for 1.5 h at rt it was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The extract was washed with brine (20 mL), dried over $MgSO_4$ and concentrated to give the oily product.[cc] The crude product was purified by flash chromatography with hexane/AcOEt 5:1 to afford 0.244 g (81%) of a light yellow oil. The product has an R_f = 0.22-0.27 in hexane/AcOEt 5:1 and 0.42 in hexane/AcOEt 7:3.

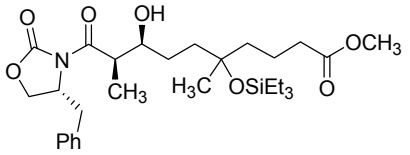
^{1}H-NMR ($CDCl_3$, 400 MHz): δ9.75 (t, *J* = 1.69 Hz, 1H), 3.65 (s, 3H), 2.55-2.40 (m, 2H), 2.29 (t, *J* = 7.28 Hz, 2H), 1.90-1.70 (m, 2H), 1.70-1.55 (m, 2H), 1.50-1.40 (m, 2H), 1.19 (s, 3H), 0.91 (t, *J* = 7.91 Hz, 9H), 0.55 (q, *J* = 7.99 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ202.71 (C=O), 173.83 (C=O), 74.46 (Cq), 51.46 (CH_3), 41.78 (CH_2), 39.10 (CH_2), 34.25 (CH_2), 33.85 (CH_2), 27.45 (CH_3), 19.90 (CH_2), 7.05 (3×CH_3), 6.70 (3×CH_2).

HRMS ESI: desired M^+ was not found.

IR (cm^{-1}, neat): 2954 (s), 2912, 2876 (s), 2719 (w), 1738 (s), 1727 (s), 1459, 1437, 1416, 1377, 1239, 1195, 1170, 1135, 1121, 1043 (s), 1008 (s), 971, 888 (w), 722 (s), 672 (w).

Methyl (8*S*,9*R*)-10-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-8-hydroxy-5,9-dimethyl-10-oxo-5-[(triethylsilyl)oxy]decanoate (186)



$C_{29}H_{47}NO_7Si$
Mol. Wt.: 549.77

1.0 M solution of dibutylboryltriflate (*n*-$Bu_2BOSO_2CF_3$) in CH_2Cl_2 (5.40 mL, 5.40 mmol, 2.2 equiv) and diisopropylethylamine (1.10 mL, 6.13 mmol, 2.5 equiv) were dropwise added to a solution of the imide **170** (1.14 g, 4.91 mmol, 2.0 equiv) in CH_2Cl_2 (75 mL) at -78 °C. After the reaction mixture was stirred for 10 min at -78 °C, it was warmed to 0-5 °C (ice bath) and stirred for 2 h at this temperature.

The light yellow solution was cooled to -15 °C (ice/salt bath) and the aldehyde **169** (753 mg, 2.38 mmol, 0.97 equiv) was added as a solution in CH_2Cl_2 (25 mL) at -10- -15 °C over 5 min.

[cc]) The product should not be subjected to heating during concentration. Otherwise the crude product becomes dark and the yield will be diminished.

After the reaction mixture was stirred for 3 h at -10- -15 °C it was quenched by addition to 0.5 M pH 7.0 phosphate buffer (100 mL) and MeOH (10 mL) at -5-0 °C. A 2:1 mixture of MeOH and 30% aqueous H_2O_2 (30 mL) was carefully added so as to keep the internal temperature bellow 5 °C (occasional cooling in an ice/salt bath). Volatiles were removed under reduced pressure (50 °C/60 mmHg) and the rest was extracted CH_2Cl_2 (4×25 mL). Combined extract were washed with 5% aqueous $NaHCO_3$ solution (20 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by flash chromatography with hexane/AcOEt 7:3 afforded 935 mg (72% yield) the desired product (R_f = 0.12-0.17) as a pale oil and 868 mg of the Evans auxiliary.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.15 (m, 5H, Ar), 4.80-4.65 (m, 1H), 4.23 (dddd, *J* = 9.14, 7.45, 1.24, 0.61 Hz, 1H), 4.21 (dd, *J* = 9.03, 3.01 Hz, 1H), 3.95-3.85 (m, 1H), 3.79 (dq, *J* = 3.01, 9.03 Hz, 1H), 3.66 (s, 3H), 3.28 (dd, *J* = 13.49, 3.33 Hz, 1H), 2.99 (dd, *J* = 17.44, 3.14 Hz, 1H), 2.81 (dd, *J* = 13.30, 9.54 Hz, 1H), 2.32 (t, *J* = 7.40 Hz, 2H), 1.75-1.40 (m, 8H), 1.29 (dd, *J* = 7.03, 0.75 Hz, 3H), 1.22 (d, *J* = 2.01 Hz, 3H), 0.95 (t, *J* = 7.65 Hz, 9H), 0.59 (q, *J* = 7.95 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ177.21 (C=O), 174.00 (C=O), 152.95 (*O*-C=O), 135.00 (Cq, Ar), 129.35 (2×CH, Ar), 128.87 (2×CH, Ar), 127.32 (CH, Ar), 75.07 & 75.04 (Cq), 72.05 & 71.95 (CH), 66.07 (CH_2), 55.05 (CH), 51.37 (CH_3), 42.20 & 42.17 (CH), 41.73 & 41.43 (CH_2), 38.24 & 38.17 (CH_2), 37.68 (CH_2), 34.35 (CH_2), 28.46 & 28.37 (CH_2), 27.73 & 27.53 (CH_2), 19.78 & 19.76 (CH_2), 10.54 & 10.46 (CH_3), 7.08 (3×CH_3), 6.76 (3×CH_2).

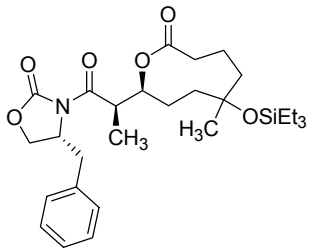
The doubling of some signals is due to the fact that the product is a mixture of two diastereomers.

HRMS ESI: Calcd. for [$C_{29}H_{47}NO_7Si$ + Na]: 572.3020; found: 572.3036.

IR (cm^{-1}, neat): 3527 (br), 2951 (s), 2875 (s), 1779 (s), δ1736 (s), 1696 (s), 1455, 1375 (s), 1289, 1207 (s), 1106, 1045 (s), 1007 (s), 971, 722 (s), 701 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 1.23) = -32.3°.

4-Benzyl-3-[2-(5-methyl-9-oxo-5-triethylsilanyloxy-oxonan-2-yl)-propionyl]-oxazolidin-2-one (187)



$C_{28}H_{43}NO_6Si$
Mol. Wt.: 517,73

"diastereomer I"
and
"diastereomer II"

Method a): The solution of the methyl ester **186** (50 mg, 0.091 mmol) and bis(tri-*n*-butyltin(IV)) oxide (5 µL, 5.85 mg, 9.8 µmol, ca. 0.1 equiv, d = 1.17) in toluene (5 mL) was refluxed over 48 h under argon. The progress of the reaction progress was monitored by TLC. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL), extracted with AcOEt (3×20 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was flashed with hexane/AcOEt 6:4 to give 34.1 mg of a pale oil. This was additionally purified by flash chromatography with hexane/AcOEt 5:1 to afford 10.0 mg (21%) of **187** as a colorless oil. The starting material has an R_f = 0.12-0.17 in hexane/AcOEt 7:3; the product has an R_f = 0.7 in hexane/AcOEt 6:4 and 0.20-0.30 in hexane/AcOEt 5:1, "Vanillin".

Method b): The solution of the methyl ester **186** (50 mg, 0.091 mmol) and bis(tri-*n*-butyltin(IV)) oxide (5 µL, 5.85 mg, 9.8 µmol, ca. 0.1 equiv, d = 1.17) in toluene (3 mL) was heated in the microwave oven over 90 min (300W, 120 °C, stirring ON, cooling ON) followed by reflux over 12 h under conventional heating. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL), extracted with AcOEt (3×20 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was flashed with hexane/AcOEt 10:1 to afford two fractions 5.3 mg (11%, diastereomer I with an R_f = 1.10-1.11) and 3.1 mg (7%, diastereomer II with an R_f = 0.09-0.10).

Diastereomer I:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.30-7.18 (m, 5H, Ar), 5.35-5.25 (m, 1H), 4.63-4.56 (t, *J* = 11.09 Hz, 1H), 4.29-4.23 (ddd, *J* = 10.92, 5.80, 2.05 Hz, 1H), 4.24-4.18 (dd, *J* = 11.44,

4.61 Hz, 1H), 3.22-3.14 (dd, *J* = 13.31, 8.19 Hz, 1H), 3.08-3.01 (dd, *J* = 13.48, 7.68 Hz, 1H), 2.81-2.72 (dq, *J* = 6.06, 7.00 Hz, 1H), 2.38-2.28 (m, 1H), 2.28-2.20 (m, 1H), 1.84-1.72 (m, 2H), 1.70-1.35 (m, 7H), 1.21 (s, 3H), 1.12-1.09 (d, *J* = 6.83 Hz, 3H), 0.94-0.88 (t, *J* = 7.85 Hz, 9H), 0.57-0.50 (q, *J* = 8.02 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ172.90 (Cq), 171.29 (Cq), 149.60 (Cq), 136.87 (Cq), 129.23 (2×CH), 128.52 (2×CH), 126.82 (CH), 78.98 (CH), 74.28 (Cq), 62.72 (CH_2), 52.42 (CH), 41.81 (CH_2), 39.13 (CH), 37.73 (CH_2), 35.82 (CH_2), 34.96 (CH_2), 29.86 (CH_3), 23.01 (CH_2), 20.66 (CH_2), 10.30 (CH_3), 7.09 (3×CH_3), 6.78 (3×CH_2).

HRMS ESI: Calcd. for [$C_{28}H_{43}NO_6Si$ + CH_3CN + Na]: 581.3023; found: 581.3011.

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 1.33) = +5.26°.

Diastereomer II:

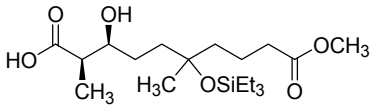
^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.30-7.18 (m, 5H, Ar), 5.33-5.23 (m, 1H), 4.62-4.54 (dd, *J* = 10.24, 11.61 Hz, 1H), 4.35-4.29 (m, 1H), 4.24-4.18 (dd, *J* = 11.61, 4.44 Hz, 1H), 3.26-3.19 (dd, *J* = 13.48, 8.36 Hz, 1H), 3.10-3.03 (dd, *J* = 13.65, 7.85 Hz, 1H), 2.81-2.73 (dq, *J* = 5.89, 7.11 Hz, 1H), 2.42-2.33 (m, 1H), 2.25-2.17 (m, 1H), 1.95-1.86 (m, 1H), 1.72-1.60 (m, 1H), 1.56 (s, 3H), 1.55-1.34 (m, 6H), 1.14 (s, 3H), 1.11 (d, *J* = 7.17 Hz, 3H), 0.96-0.90 (t, J = 8.02 Hz, 9H), 0.59-0.51 (q, *J* = 7.68 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ172.79 (Cq), 171.30 (Cq), 149.53 (Cq), 136.96 (Cq), 129.23 (2×CH), 128.54 (2×CH), 126.82 (CH), 78.28 (CH), 74.41 (Cq), 62.97 (CH_2), 52.65 (CH), 42.14 (CH_2), 39.05 (CH), 36.74 (CH_2), 35.95 (CH_2), 34.81 (CH_2), 27.35 (CH_3), 24.44 (CH_2), 19.74 (CH_2), 10.42 (CH_3), 7.10 (3×CH_3), 6.84 (3×CH_2).

HRMS ESI: Calcd. for [$C_{28}H_{43}NO_6Si$ + CH_3CN + Na]: 581.3023; found: 581.3011.

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 0.53) = -8.3°.

(2R,3S)-3-hydroxy-10-methoxy-2,6-dimethyl-10-oxo-6-(triethylsilyloxy)decanoic acid (188)[137]



$C_{19}H_{38}O_6Si$
Mol. Wt.: 390,59

35% aqueous H_2O_2 solution (41 µL, d = 1.11, 13.82 mg, 0.7276 mmol, 4 equiv) and a solution of $LiOH \cdot H_2O$ (9.2 mg, 0.2183 mmol, 1.2 equiv) in water (1 mL) were added to the solution of the methyl ester **186** (100 mg, 0.1819 mmol, 1 equiv) in THF/water 4:1 mixture (10 mL) at

0 °C. After the reaction mixture was stirred for 1 h at 0 °C, it was quenched by addition of a solution of Na_2SO_3 (92 mg, 0.7276 mmol, 4 equiv) in H_2O (3 mL). The mixture was stirred for 15 min at 0 °C and 2% aqueous HCl solution (3 mL) was added so that the pH was neutral or slightly acidic. The mixture was extracted with AcOEt (3×20 mL). The extract was dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt 1:1 to afford 50 mg (70%) of **188** as a colorless oil. The product has an R_f = 0.20 in hexane/AcOEt 1:1.

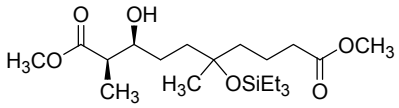
^{1}H-NMR ($CDCl_3$, 200 MHz): δ3.84 (br s, 1H), 3.68 (s, 3H), 2.75-2.55 (m, 1H), 2.31 (t, *J* = 6.71 Hz, 2H), 1.75-1.40 (m, 8H), 1.26 (s, 3H), 1.22 (s, 3H).

HRMS ESI: Calcd. for [$C_{19}H_{38}O_6Si$ + Na]: 413.2335; found: 413.2347.

IR (cm^{-1}, neat): 3600-3000 (br), 2953 (s), 2912 (s), 2875 (s), 1706 (s), 1457, 1414, 1374, 1198, 1170, 1119, 1005 (s), 720 (s).

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 1.05) = +6.10°.

(2R,3S)-Dimethyl 3-hydroxy-2,6-dimethyl-6-(triethylsilyloxy)decanedioate (191)[102]



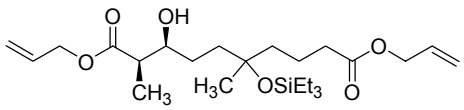
$C_{20}H_{40}O_6Si$
Mol. Wt.: 404,61

The solution of $LiOH·H_2O$ (17 mg, 0.40 mmol, 11 equiv) in H_2O (0.8 mL) was added to the solution of the ester **186** (20.3 mg, 0.036 mmol) in THF/MeOH 1:1 (4 mL) at 0 °C. The progress of the reaction was controlled by TLC. When there was no starting material, AcOEt (10 mL) was added and the organic layer was separated. Aqueous layer was acidified with 1.0 M aqueous $NaHSO_4$ solution to pH 1-2 and extracted with AcOEt (2×10 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt to afford 5.0 mg (34%) of **191** as a colorless oil. It has an R_f = 0.3 in hexane/AcOEt 7:3.

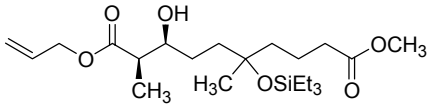
^{1}H-NMR ($CDCl_3$, 200 MHz): δ3.87 (br s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.80-2.50 (m, 2H), 2.34 (t, *J* = 7.14 Hz, 2H), 1.80-1.40 (m, 8H), 1.30 (s, 3H), 1.24 (s, 3H), 0.98 (t, *J* = 7.64 Hz, 9H), 0.63 (q, *J* = 7.78 Hz, 6H).

HRMS ESI: Calcd. for [$C_{20}H_{40}O_6Si$ + Na]: 427.2492; found: 427.2472.

3-Hydroxy-2,6-dimethyl-6-triethylsilanyloxy-decanedioic acid diallyl ester and 3-hydroxy-2,6-dimethyl-6-triethylsilanyloxy-decanedioic acid 1-allyl ester 10-methyl ester[138]



$C_{24}H_{44}O_6Si$
Mol. Wt.: 456,69

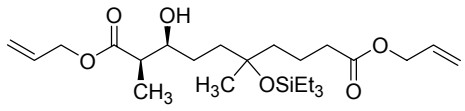


$C_{22}H_{42}O_6Si$
Mol. Wt.: 430,65

LiBr (79 mg, 0.91 mmol, 5 equiv) was premixed with the methyl ester **186** (100 mg, 0.182 mmol) neat, and left for 15-20 min.[dd] Allyl alcohol (2 mL, 29.4 mmol, 162 equiv, d = 0.854) and DBU (13.6 μL, 0.5 equiv, d = 1.018) were added and the reaction mixture was stirred at rt. The progress was monitored by TLC. According the TLC there was no starting material after 15 min. After 2 h at rt the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (5 mL), MTBE (5 mL) and water (5 mL). The mixture was extracted with MTBE (3×20 mL), combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was flushed with hexane/AcOEt 8:1 to afford two fractions: "fraction I": 9.7 mg with R_f = 0.11-0.10 and "fraction II": 6.5 mg with R_f = 0.10-0.09.

[dd]) The methyl ester was added as a solution in THF (1 mL) to the LiBr and the solvent was removed under reduced pressure.

Fraction I, 3-Hydroxy-2,6-dimethyl-6-triethylsilanyloxy-decanedioic acid diallyl ester



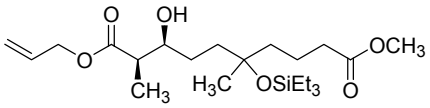
$C_{24}H_{44}O_6Si$
Mol. Wt.: 456,69

^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.95 (ddd, *J* = 10.42, 5.77, 2.26 Hz, 1H), 5.89 (ddd, *J* = 10.45, 5.74, 2.16 Hz, 1H), 5.34 (ddd, *J* = 7.72, 3.07, 1.51 Hz, 1H), 5.30 (ddd, *J* = 7.72, 3.07, 1.51 Hz, 1H), 5.25 (ddd, *J* = 7.81, 2.54, 1.22 Hz, 1H), 5.23 (ddd, *J* = 7.84, 2.57, 1.25 Hz, 1H), 4.61 (ddd, *J* = 5.80, 2.16, 1.10 Hz, 2H), 4.57 (ddd, *J* = 5.77, 1.38, 1.38 Hz, 2H), 3.90-3.80 (m, 1H), 2.68 (dd, *J* = 22.15, 4.58 Hz, 1H), 2.56 (ddd, *J* = 14.40, 7.18, 3.86 Hz, 1H), 2.32 (t, *J* = 7.34 Hz, 2H), 1.71-1.62 (m, 2H), 1.61 (s, 3H), 1.51-1.41 (m, 4H), 1.22 (d, *J* = 1.00 Hz, 1H), 1.20-1.18 (m, 4H), 0.93 (t, *J* = 7.91 Hz, 9H), 0.56 (dq, *J* = 1.63, 7.91 Hz, 6H).

HRMS ESI: Calcd. for [$C_{24}H_{44}O_6Si$ + Na]: 479.2805; found: 479.2796.

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 0.94) = -4.89°.

Fraction II: 3-hydroxy-2,6-dimethyl-6-triethylsilanyloxy-decanedioic acid 1-allyl ester 10-methyl ester



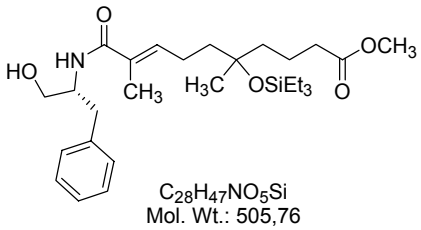
$C_{22}H_{42}O_6Si$
Mol. Wt.: 430,65

^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.92 (ddd, *J* = 22.96, 10.42, 5.77 Hz, 1H), 5.33 (ddd, *J* = 17.19, 3.01, 1.51 Hz, 1H), 5.25 (ddd, *J* = 10.42, 2.45, 1.19 Hz, 1H), 4.62 (dd, *J* = 1.95, 1.07 Hz, 1H), 4.60 (dd, *J* = 2.20, 1.07 Hz, 1H), 3.85 (m, 1H), 3.66 (s, 3H), 2.68 (dd, *J* = 22.52, 4.58 Hz, 1H), 2.56 (ddd, *J* = 14.40, 7.18, 3.86 Hz, 1H), 2.29 (t, *J* = 7.34 Hz, 2H), 1.71-1.61 (m, 2H), 1.60 (s, 3H), 1.51-1.39 (m, 4H), 1.22-1.21 (d, *J* = 1.00 Hz, 1H), 1.20-1.18 (m, 4H), 0.93 (t, *J* = 8.09 Hz, 9H), 0.56 (dq, *J* = 1.63, 7.88 Hz, 6H).

HRMS ESI: Calcd. for [$C_{22}H_{42}O_6Si$ + Na]: 453.2648; found: 453.2657.

$[\alpha]_D^{20}$ ($CHCl_3$, *c* = 0.67) = -5.37°.

(*E*)-Methyl-10-((R)-1-hydroxy-3-phenylpropan-2-ylamino)-5,9-dimethyl-10-oxo-5-(triethylsilyloxy)dec-8-enoate (190)



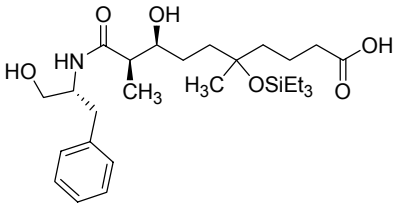
$C_{28}H_{47}NO_5Si$
Mol. Wt.: 505,76

The solution of the methyl ester **186** (51.8 mg, 0.094 mmol, 1 equiv) in Et_2O (5 mL) was added to the slurry of potassium trimethylsilanolate (13.4 mg, 0.104 mmol, 1.11 equiv) in Et_2O (8 mL) at rt. The reaction mixture was stirred for 20 h at rt. The progress was controlled by TLC. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) followed by extraction with AcOEt (3×10 mL). Combined organic extract was dried over $MgSO_4$ and concentrated. Purification by chromatography with hexane/AcOEt 1:1 afforded 12 mg (25%) of **190**. The product has an $R_f = 0.3$ in hexane/AcOEt 1:1 (permanganate).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.15 (5H, Ar), 6.22 (t, $J = 6.82$ Hz, 1H), 5.92 (d, $J = 6.84$ Hz, 1H), 4.30-4.05 (m, 2H), 3.72 (m, 1H), 3.67 (s, 3H), 3.11 (br s, 1H), 3.00-2.80 (m, 2H), 2.30 (t, $J = 7.34$ Hz, 2H), 2.20-2.05 (m, 2H), 1.77 (d, $J = 0.67$ Hz, 3H), 1.70-1.40 (m, 6H), 1.19 (s, 3H), 0.94 (q, $J = 8.02$ Hz, 9H), 0.56 (t, $J = 7.85$ Hz, 6H).

HRMS ESI: Calcd. for [$C_{28}H_{47}NO_5Si$ + Na]: 528.3121; found: 528.3110.

9-(1-Benzyl-2-hydroxy-ethylcarbamoyl)-8-hydroxy-5-methyl-5-triethylsilanyloxy-decanoic acid (189)

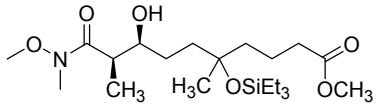


$C_{27}H_{47}NO_6Si$
Mol. Wt.: 509,75

The solution of the methyl ester **186** (50 mg) in MeOH (5 mL) was added to $Ba(OH)_2 \cdot 8H_2O$ (1.60 g) and the resulting suspension was stirred at rt. According to the TLC the reaction was complete in 30 min. Reaction mixture was quenched by the addition of 2% aqueous HCl solution (10 mL) (acidic pH). The mixture was extracted with AcOEt (3×10 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated to afford **189**. The product has an R_f = 0.20-0.30 in hexane/AcOEt 1:1.

HRMS ESI: Calcd. for [$C_{27}H_{47}NO_6Si$ + Na]: 532.3070; found: 532.3058.

8-Hydroxy-9-(methoxy-methyl-carbamoyl)-5-methyl-5-triethylsilanyloxy-decanoic acid methyl ester (194)



$C_{21}H_{43}NO_6Si$
Mol. Wt.: 433,65

The experiment was conducted according to a published procedure.[50b,139] A stirred suspension of *N,O*-dimethyl hydroxylamine hydrochloride[ee] (445 mg, 4.56 mmol, 3.4 equiv) in THF (5 mL) was treated slowly with 2.0 M Me_3Al in heptane (2.3 mL, 4.56 mmol, 3.4 equiv)[ff] at 0 °C and the mixture was allowed to warm to 25 °C. The solution was stirred for 30 min before being cooled to 0 °C and treated slowly with the solution of the hydroxy imide **186** (737 mg, 1.34 mmol) in THF (5 mL). The solution was allowed to warm to 25 °C and stirred for 2.5 h (time is important!). According to the TLC only a small amount of the starting material was left after 1 h and after 2.5 h the reaction was complete.

The reaction mixture was added to saturated aqueous NH_4Cl solution (10 mL) and 2% aqueous HCl solution (10 mL) while stirred at 0 °C. Resulting mixture was extracted with

[ee]) After the *N,O*-dimethyl hydroxylamine was transferred to the Schlenk flask it was stirred over 5 min under reduced pressure. Ca. 1 mL of toluene was added and removed under reduced pressure to dry the substance.
[ff]) Fresh Me_3Al of good quality should be used.

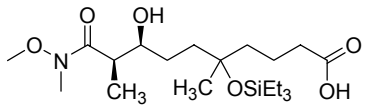
AcOEt (3×15 mL). Combined organic extract was dried over $MgSO_4$ and concentrated to give the crude product. It was purified by flash chromatography on silica gel with hexane/AcOEt 1:1 to afford 437 mg (75%) of **194** as a colorless oil after concentration.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ3.78 (m, 2H), 3.67 (s, 3H), 3.63 (s, 3H), 3.16 (s, 3H), 2.85 (br s, 1H), 2.26 (t, J = 7.3 Hz, 2H), 1.70-1.50 (m, 4H), 1.50-1.35 (m, 4H), 1.17 & 1.16 (2×s, 3H), 1.14 (d, J = 6.8 Hz, 3H), 0.91 (2×t, J = 7.5 Hz, 9H), 0.53 (2×q, J = 7.8 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ178.24, 174.00 & 173.98, 75.08 & 75.07, 72.09 & 72.02, 61.42, 51.35, 41.91, 41.29, 38.54 & 38.43, 38.28, 34.40 & 34.39, 28.47 & 28.39, 27.77 & 27.42, 19.76 & 19.74, 10.17 & 10.12, 7.07, 6.77.

HRMS ESI: Calcd. for [$C_{21}H_{43}NO_6Si$ + Na]: 456.2757; found: 456.2747.

8-Hydroxy-9-(methoxy-methyl-carbamoyl)-5-methyl-5-triethylsilanyloxy-decanoic acid (195)



$C_{20}H_{41}NO_6Si$
Mol. Wt.: 419,63

The experiment was conducted according to a described procedure.[102] The solution of $LiOH·H_2O$ (18.3 mg, 0.43 mmol, 3.6 equiv) in H_2O (1 mL) was added to the solution of the Winereb amide **194** (52 mg, 0.12 mmol) in THF/MeOH 1:1 (3 mL). The mixture was stirred for 3 h at rt while the progress of the reaction was monitored by TLC.

The reaction mixture was diluted with brine (10 mL) and extracted with AcOEt (3×10 mL). Aqueous layer was acidified to pH 1-2 with 0.1 M aqueous $NaHSO_4$ and extracted with AcOEt (2×10 mL). The combined organic extract was washed with brine (10 mL), dried over $MgSO_4$ and concentrated, providing the crude product as a colorless oil. The crude product was purified by flash chromatography on a 18×120 mm silica gel column with CH_2Cl_2 → CH_2Cl_2-MeOH 10:1 to afford 43 mg (85%) of the *seco*-acid as a colorless oil.

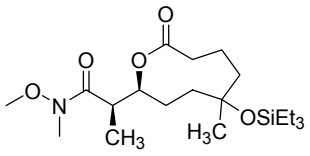
The product has an R_f = 0.31-0.28 in hexane/AcOEt 1:1, 0.52-0.47 in AcOEt, 0.50-0.45 in CH_2Cl_2/MeOH 10:1 and ca. 0 in pure CH_2Cl_2. The starting material has an R_f = 0.11-0.09 in hexane/AcOEt 1:1 and 0.22-0.18 in AcOEt.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ3.79 (m, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 2.88 (br s, 1H), 2.31 (t, J = 7.2 Hz, 2H), 1.70-1.50 (m, 4H), 1.50-1.35 (m, 4H), 1.19 & 1.18 (2×s, 3H), 1.16 (d, J = 7.2 Hz, 3H), 0.92 (2×t, J = 7.5 Hz, 9H), 0.55 (2×q, J = 7.8 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ178.89 (Cq), 178.18 (Cq), 124.23 (CH), 75.11 (Cq), 72.22 & 72.15 (CH), 61.48 (CH_3), 41.82 & 41.19 (CH_2), 38.42 & 38.26 (CH_2), 34.38 (CH_2), 31.87 (CH_3), 28.50 & 2843 (CH_2), 27.82 & 27.47 (CH_3), 19.55 & 19.53 (CH_2), 10.28 & 10.22 (CH_3), 7.11 (CH_3), 6.80 (CH_2).

HRMS ESI: Calcd. for [$C_{20}H_{41}NO_6Si$ + Na]: 442.2601; found: 442.2604.

N-Methoxy-N-methyl-2-(5-methyl-9-oxo-5-triethylsilanyloxy-oxonan-2-yl)-propionamide (196)



$C_{20}H_{39}NO_5Si$
Mol. Wt.: 401,61

The cyclization was conducted according to a reported procedure.[94] The solution of the *seco*-acid **195** (169 mg, 0.403 mmol, 1 equiv) in THF (2 mL) was added at room temperature to a flask containing a solution prepared by dissolving Et_3N (184 µL, 1.32 mmol, d = 0.728 g/mL, 3 equiv) and 2,4,6-trichlorobenzoyl chloride (186 µL, 1.20 mmol, d = 1.561 g/mL, 3 equiv) in THF (10 mL). The resulting cloudy solution[gg] was stirred at room temperature for 5 h and then dissolved in toluene (10 mL). This solution was added over 8.5 h[hh] via syringe pump[ii] to a solution of DMAP (296 mg, 2.42 mmol, 6 equiv) in toluene (400 mL) at reflux. The reaction mixture was stirred for additional 3.5 h[jj], then cooled to room temperature, diluted with ethyl acetate (100 mL), washed with 0.1 M aqueous $NaHSO_4$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Chromatographic purification with hexane/ethyl acetate 3:1 afforded a mixture of diastereomers as a yellow oil (163.8 mg, quant. yield, ca. 1:1 by GC).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.09 (m, 1H), 3.69 & 3.68 (s, 3H), 3.17 (s, 3H), 3.05 (br s, 1H), 2.32-2.15 (m, 2H), 2.0-1.20 (m, 8H), 1.17 & 1.16 (d, *J* = 6.8 Hz, 3H), 1.14 & 1.11 (s, 3H), 0.91 & 0.88 (t, *J* = 8.0 Hz, 9H), 0.53 & 0.50 (q, *J* = 8.0 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ175.58 & 175.51 (Cq), 175.16 & 175.00 (Cq), 77.10 (CH), 76.48, 76.40, 61.53 & 61.44 (CH_3), 46.51 (CH_2), 41.94 (CH_2), 39.28 (CH), 37.37, 37.06,

[gg]) Precipitated $Et_3N{\cdot}HCl$ was noticed in ca. 30 min after the addition of the reagents.
[hh]) Time can be reduced to 5 h.
[ii]) At a speed of 0.045 mL/min.
[jj]) This time can be reduced to 30 min.

36.28 (CH_2) & 36.23 (CH_2), 34.75, 32.08 (CH), 29.59 (CH), 29.15 (CH_3), 27.59, 26.92, 21.38 (CH), 20.32 (CH_2), 14.39 & 14.27 (CH_3), 7.06 & 7.05 (CH_3), 6.81 & 6.80 (CH_2).

HRMS ESI: Calcd. for [$C_{20}H_{39}NO_5Si$ + CH_3CN + Na]: 465.2761; found: 465.2758.

IR (cm^{-1}, neat): 2951 (s), 2875 (m), 2362, 1736 (s), 1661 (s), 1459 (m), 1416, 1376, 1353, 1285, 1246 (m),.1168, 1149, 1130, 1114, 1082, 1055, 1036, 993 (s), 917, 855, 742 (s).

GC, R_t, min (intensity):15.015 (48%), 15.192 (50%).

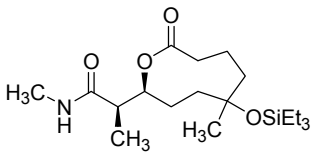
Reaction of the lactone 196 with LDA

Preparation of 0.9 M LDA solution in hexanes/THF:

Diisopropylamine (700 µL, 5 mmol, d = 0.722) was added to a flask containing 2.5 M solution of *n*-BuLi (2 mL, 5 mmol) in hexanes in THF (3 mL) at -78 °C. Clear colorless solution was stirred for 10 min at -78 °C, warmed up to 0 °C and stirred 30 min at 0 °C.

0.9 M LDA solution (550 µL, 0.5 mmol, 2.0 equiv) was added to the solution of the lactone **196** (100 mg, 0.25 mmol) in THF (3 mL) at -78°C. After the reaction mixture was stirred for 1.5 h at -78 °C (reaction control by TLC), it was quenched by the addition of aqueous 0.1 M $NaHSO_4$ solution (15 mL), warmed to rt and extracted with AcOEt (3×10 mL). Combined organic extract was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Chromatographic purification with hexane/AcOEt 1:1 on silica gel afforded four fractions: fraction I with R_f = 0.37-0.32, 13.3 mg (13%); fraction II with R_f = 0.26-0.32, 12.2 mg; (approx. 12%) fraction III with R_f = 0.24-0.28, 12.8 mg (approx. 13%) and fraction IV with R_f = 0.18-0.24, 16.0 mg (17%). The column afterwards flushed with hexane/AcOEt 1:2 to provide two additional fractions: fraction V with R_f = 0.17-0.22, 6.5 mg and fraction VI with R_f = 0.10-0.15, 2.5 mg. Fractions were investigated using spectroscopic methods and HRMS-ESI. Fraction I was characterized a diastereomer of **199**; the structure of the substance constituting fraction II could not be identified, fraction III was identified as a mixture of the unidentified compound with **198** and fraction IV was characterized as a diastereomer of **198.**

***N*-Methyl-2-(5-methyl-9-oxo-5-triethylsilanyloxy-oxonan-2-yl)-propionamide (198)**



$C_{19}H_{37}NO_4Si$
Mol. Wt.: 371,59
(single diastereomer)

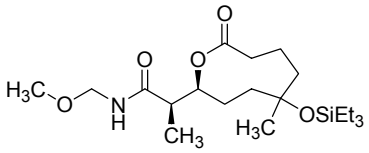
^{1}H-NMR ($CDCl_3$, 400 MHz): δ5.74 (br s, 1H), 5.03 (m, 1H), 2.81 (d, *J* = 4.77 Hz, 3H), 2.37 (dq, *J* = 7.00, 7.09 Hz, 1H), 2.32-2.20 (m, 2H), 1.94-1.81 (m, 1H), 1.79-1.54 (m, 5H), 1.47-1.37 (m, 1H), 1.37-1.26 (m, 1H), 1.19 (d, *J* = 7.03 Hz, 3H), 1.16 (s, 3H), 0.90 (t, *J* = 7.84 Hz, 9H), 0.52 (q, *J* = 7.82 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ175.88 (Cq), 173.74 (Cq), 77.09 (CH), 76.41 (Cq), 45.43 (CH), 37.10 (CH_2), 36.23 (CH_2), 34.88 (CH_2), 29.16 (CH_3), 27.41 (CH_2), 26.31 (CH_3), 20.31 (CH_2), 14.24 (CH_3), 7.09 (3×CH_3), 6.83 (3×CH_2).

HRMS ESI: Calcd. for [$C_{19}H_{37}NO_4Si$ + CH_3CN + Na]: 435.2655; found: 435.2662.

IR (cm^{-1}, neat): 3294 (br), 2951 (s), 2876 (m), 2361 (m), 1737 (s), 1645 (s), 1558 (s), 1457 (m), 1413, 1374, 1349, 1284, 1241 (s), 1149 (s), 1128, 1114, 1055, 1003 (s), 978, 854, 743, 722.

***N*-Methoxymethyl-2-(5-methyl-9-oxo-5-triethylsilanyloxy-oxonan-2-yl)-propionamide (199)**



$C_{20}H_{39}NO_5Si$
Mol. Wt.: 401,61
(single diastereomer)

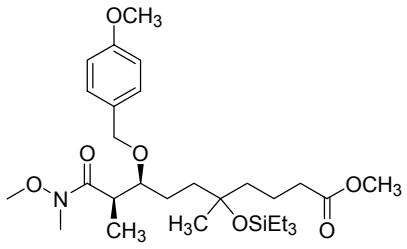
^{1}H-NMR ($CDCl_3$, 400 MHz): δ6.35 (br s, 1H), 5.11 (m, 1H), 4.70 (d, *J* = 6.76 Hz, 2H), 3.33 (s, 3H), 2.46 (dq, *J* = 6.96, 6.96 Hz, 1H), 2.26 (m, 2H), 2.0-1.85 (m, 2H), 1.70-1.40 (m, 4H), 1.30-1.20 (m, 2H), 1.25 (d, *J* = 7.03 Hz, 3H), 1.14 (s, 3H), 0.93 (t, *J* = 7.84 Hz, 9H), 0.55 (q, *J* = 7.82 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ175.80 (Cq), 174.06 (Cq), 77.02 (CH), 76.76 (CH), 76.23 (Cq), 71.30 (CH_2), 56.05 (CH_3), 45.58 (CH), 37.47 (CH_2), 36.27 (CH_2), 29.59 (CH_3), 26.24 (CH_2), 21.69 (CH_2), 13.95 (CH_3), 7.12 (3×CH_3), 6.83 (3×CH_2).

HRMS ESI: Calcd. for [$C_{20}H_{39}NO_5Si$ + Na]: 424.2495, for [$C_{20}H_{39}NO_5Si$ + CH_3CN + Na]: 465.2761; found: 424.2509, 465.2767.

IR (cm^{-1}, neat): 3307 (br), 2950 (s), 2876 (m), 1737 (s), 1661 (s), 1538 (s), 1456 (s), 1374, 1354, 1283, 1227 (s), 1167 (m), 1129 (m), 1056 (s), 1000 (s), 915 (m), 740 (s), 722 (s).

8-(4-Methoxy-benzyloxy)-9-(methoxy-methyl-carbamoyl)-5-methyl-5-triethylsilanyloxy-decanoic acid methyl ester (202)



$C_{29}H_{51}NO_7Si$
Mol. Wt.: 553,80

The experiment was conducted according to a known procedure.[140]

Ph_3CBF_4 (12 mol%, 5 mg) was added to the solution of the alcohol **194** (50 mg, 0.12 mmol, 1 equiv) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (102 mg, 0.36 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 18 h at rt and the progress was monitored by TLC.

When the reaction was complete, the reaction mixture was quenched by the addition of the saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel with hexane/MTBE 2:1 affording 40 mg (63%) of **202** as a colorless oil.

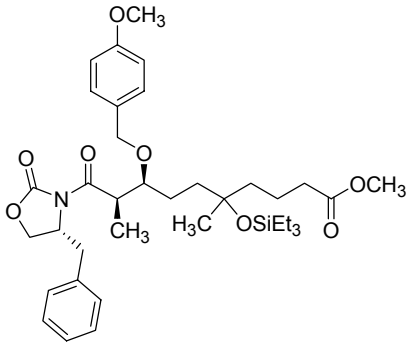
^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.30-7.20 (d, J = 7.40 Hz, 2H), 6.90-6.80 (d, J = 8.68 Hz, 2H), 4.47 (d, J = 10.79 Hz, 1H), 4.43 (d, J = 10.92 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.61-3.55 (br m, 1H), 3.14 (s, 3H), 3.11-3.00 (br m, 1H), 2.25 (t, J = 7.40 Hz, 2H), 1.64-1.52 (m, 4H), 1.50-1.34 (m, 4H), 1.22 (d, J = 6.78 Hz, 3H), 1.14 & 1.12 (2×s, 3H), 0.90 (t, J = 7.84 Hz, 9H), 0.53 (q, J = 7.91 Hz, 6H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ176.23 (Cq, weak), 174.01 (Cq), 159.13 (Cq, Ar), 130.70 (Cq, Ar), 129.55 (CH, Ar), 129.54 (CH, Ar), 113.71 (2×CH, Ar), 80.63 & 80.62 (CH), 75.05 & 75.02 (Cq), 72.28 & 72.22 (CH_2), 61.36 (CH_3), 55.22 (CH_3), 51.37 (CH_3), 41.98 & 41.39 (CH_2), 39.86 & 39.73 (CH, weak), 37.02 (CH_2), 34.50 & 34.48 (CH_2), 32.06 (CH_3, weak), 27.75 & 27.42 (CH_3), 27.09 & 26.89 (CH_2), 19.79 & 19.71 (CH_2), 14.55 & 14.50 (CH_3), 7.15 (3×CH_3), 6.84 (3×CH_2).

HRMS ESI: Calcd. for $[C_{29}H_{51}NO_7Si]$: 553.3435, for $[C_{29}H_{51}NO_7Si + CH_3CN + Na]$: 617.3598; found: 617.3607.

IR (cm^{-1}, neat): 2953 (s), 2910 (s), 2875 (s), 2385 (w), 1738 (s), 1661 (s), 1613 (w), 1514 (s), 1460 (m), 1377 (w), 1248 (s), 1173 (m), 1064 (m), 1037 (m), 1004 (m), 778 (s), 743 (s), 631 (s).

10-(4-Benzyl-2-oxo-oxazolidin-3-yl)-8-(4-methoxy-benzyloxy)-5,9-dimethyl-10-oxo-5-triethylsilanyloxy-decanoic acid methyl ester (203)



$C_{37}H_{55}NO_8Si$
Mol. Wt.: 669,92

The experiment was conducted according to a known procedure.[140]

Ph_3CBF_4 (12 mol%, 5 mg) was added to the solution of the alcohol **186** (73 mg, 0.13 mmol, 1 equiv) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (112 mg, 0.40 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL) at rt. According to the TLC there was no starting material after the reaction mixture was stirred for 15 min at rt.

The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3×10 mL). Combined organic extract was washed with brine (15 mL), dried over $MgSO_4$ and concentrated. Chromatographic purification on silica gel with hexane/AcOEt 6:1 afforded 58 mg (67%) of **203** as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ7.40-7.20 (m, 7H, Ar), 6.85 (d, *J* = 7.51 Hz, 2H), 4.57-4.38 (m, 3H), 4.14-3.96 (m, 3H), 3.77 & 3.76 (s, 3H), 3.65 & 3.66 (s, 3H), 3.64-3.59 (m, 1H), 3.28 (dd, *J* = 13.31, 3.07 Hz, 1H), 2.74 (dd, *J* = 12.80, 10.07 Hz, 1H), 2.29 (t, *J* = 7.34 Hz, 2H), 1.67-1.54 (m, 6H), 1.45-1.39 (m, 2H), 1.27 & 1.26 (d, *J* = 6.83 Hz, 3H), 1.18 (s, 3H), 0.94 (t, *J* = 7.85 Hz, 9H), 0.56 (q, *J* = 7.97 Hz, 6H).

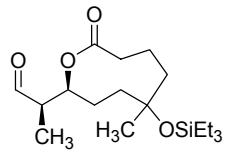
^{13}C-NMR ($CDCl_3$, 100 MHz): δ175.14 & 175.10 (N-C=O), 174.05 & 174.03 (O-C=O), 159.16 & 159.15 (Cq, Ar), 153.08 & 153.06 (N-(O-)C=O), 135.46 & 135.45 (Cq, Ar), 130.67 & 130.65 (Cq, Ar), 129.67 & 129.66 (2×CH, Ar), 129.40 (2×CH, Ar), 128.89 (2×CH, Ar), 127.26 (CH, Ar), 113.65 & 113.63 (2×CH, Ar), 79.91 & 79.69 (CH), 75.07 & 75.06 (Cq),

71.56 & 71.48 (CH_2), 65.95 (CH_2), 55.71 & 55.69 (CH), 55.22 & 55.22 (CH_3), 51.38 (CH_3), 41.82 & 41.51 (CH_2), 41.15 (CH), 37.88 & 37.77 (CH_2), 37.70 (CH_2), 34.48 & 34.46 (CH_2), 27.78 & 27.63 (CH_3), 26.25 (CH_2), 19.85 & 19.80 (CH_2), 12.58 & 12.35 (CH_3), 7.17 (3×CH_3), 6.90 & 6.89 (3×CH_2).

HRMS ESI: Calcd. for [$C_{37}H_{55}NO_8Si$]: 669.3697, for [$C_{37}H_{55}NO_8Si + CH_3CN + Na$]: 733.3860; found: 669.3690, 733.3858.

IR (cm^{-1}, neat): 2952 (s), 2910 (s), 2875 (s), 2359 (w), 1779 (s), 1733 (s), 1699 (s), 1612 (w), 1512 (s), 1456 (m), 1376 (w), 1245 (s), 1209 (s), 1175 (s), 1033 (s), 1004 (m), 823 (s), 742 (m), 720 (m), 703 (m), 655 (m).

2-(5-Methyl-9-oxo-5-triethylsilanyloxy-oxonan-2-yl)-propionaldehyde (201)



$C_{18}H_{34}O_4Si$
Mol. Wt.: 342,55

1.5 M solution of DIBAL in toluene (66 µL, 4 equiv, 0.10 mmol) was added to a stirred solution of the Weinreb amide **196** (10 mg, 0.025 mmol) in THF (1 mL) at -78 °C. After 30 min at -78 °C the excess of DIBAL was quenched by the addition of acetone (3 mL). The mixture was quenched with 1.0 M aqueous solution of tartaric acid (10 mL) and extracted with MTBE (3×10 mL). Combined organic extract was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography with hexane/AcOEt 10:1 to afford 1.1 mg (13%) of **201**. The product has an R_f = 0.2-0.3 in hexane/AcOEt 10:1.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ9.74-9.70 (d, *J* = 1.36 Hz, 1H), 5.40-5.30 (m, 1H), 2.65-2.55 (m, 1H), 2.35-2.20 (m, 2H), 2.10-1.30 (m, 8H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.16 (s, 3H), 0.95-0.85 (t, *J* = 7.84 Hz, 9H), 0.62-0.48 (q, *J* = 7.84 Hz, 6H).

HRMS ESI: Calcd. for [$C_{18}H_{34}O_4Si$]: 342.2226; found: 342.2218.

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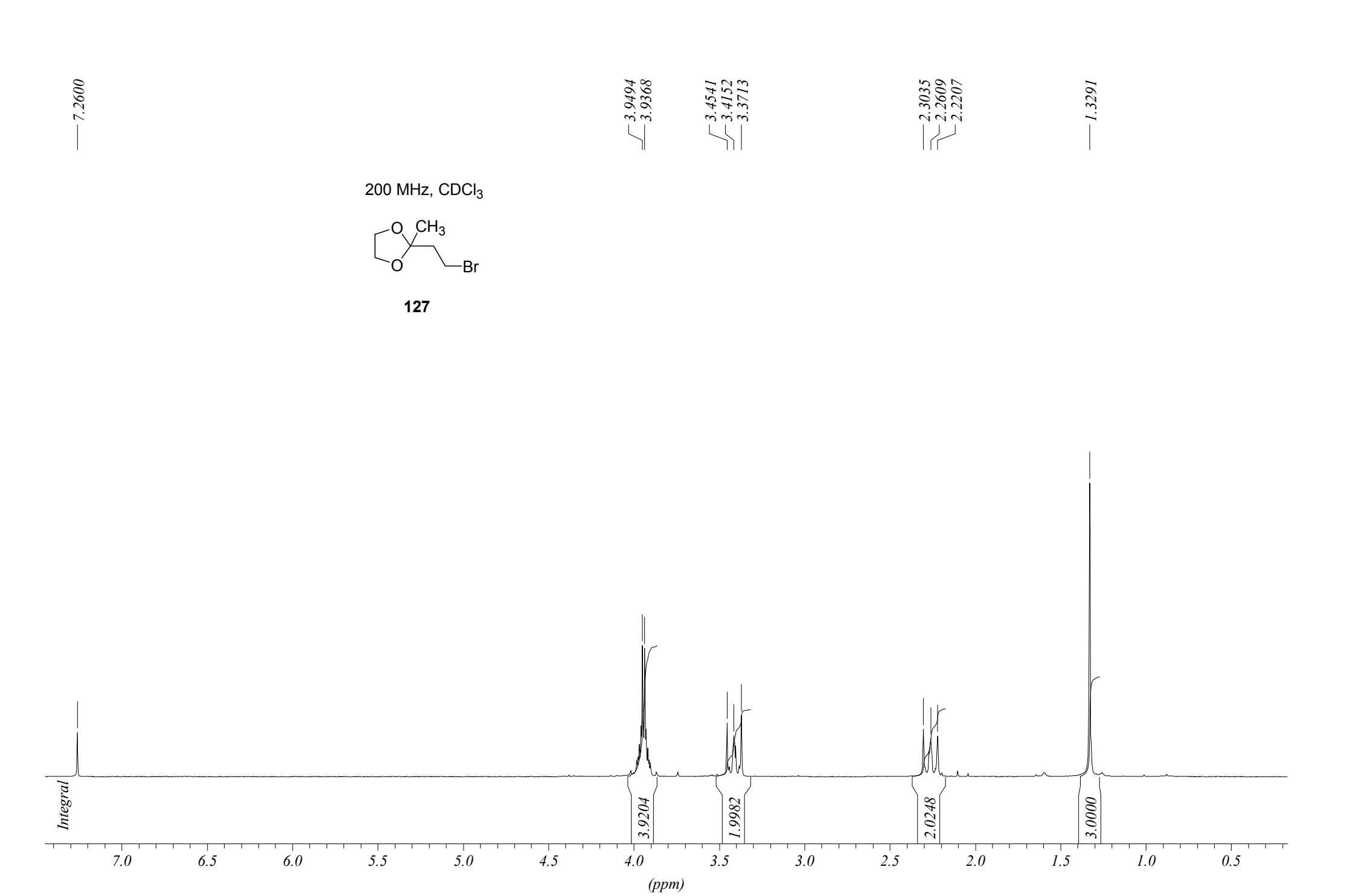
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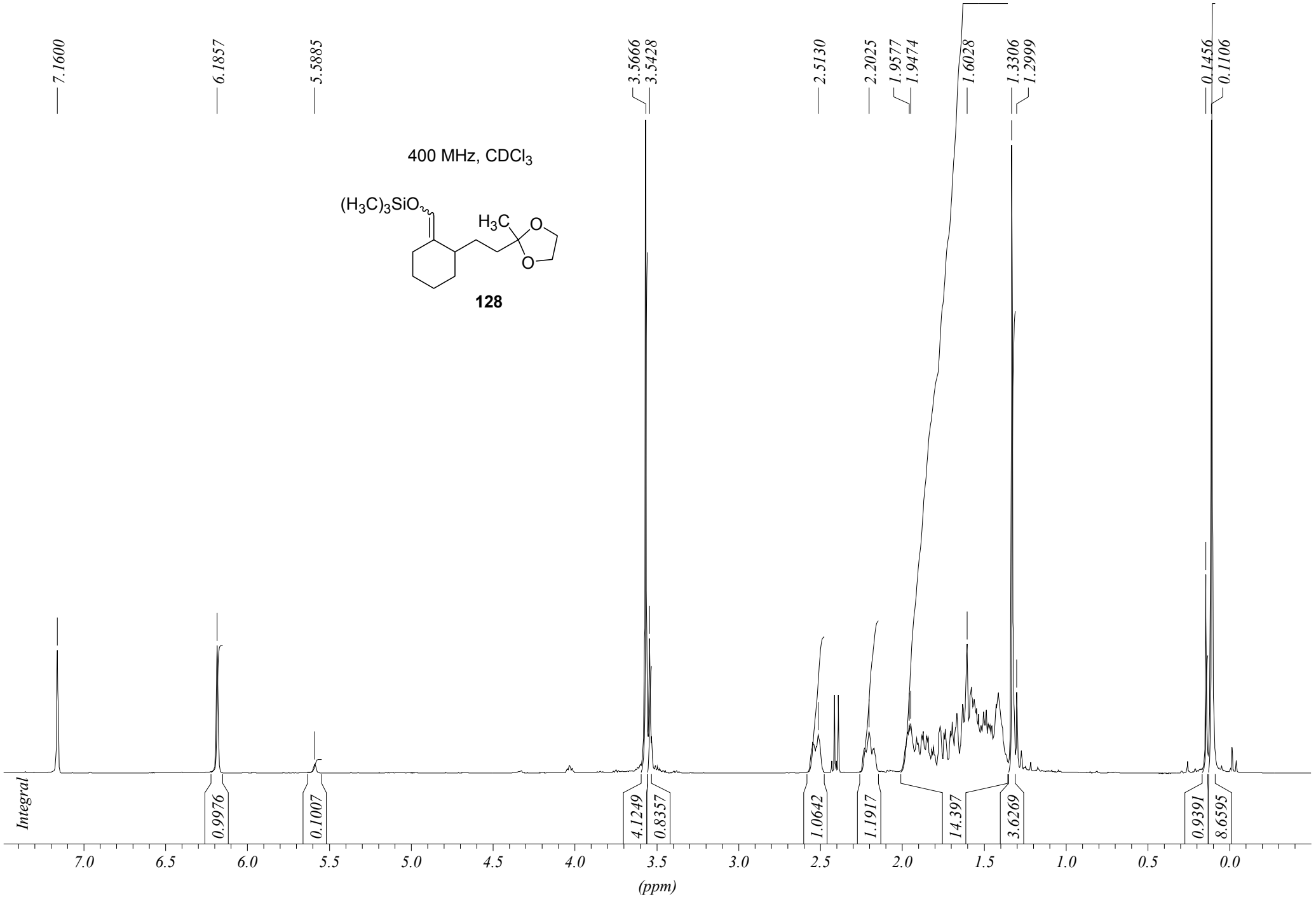
3.4541
3.4152
3.3713
2.3035
2.2609
2.2207
1.3291
200 MHz, CDCl3
O
CH3
O
Br
127
Integral
3.9204
1.9982
2.0248
3.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)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5.5885
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3.5428
2.5130
2.2025
1.9577
1.9474
1.6028
1.3306
1.2999
0.1456
0.1106
400 MHz, CDCl3
(H3C)3SiO
H3C
O
O
128
Integral
0.9976
0.1007
4.1249
0.8357
1.0642
1.1917
14.397
3.6269
0.9391
8.6595
7.0
6.5
6.0
5.5
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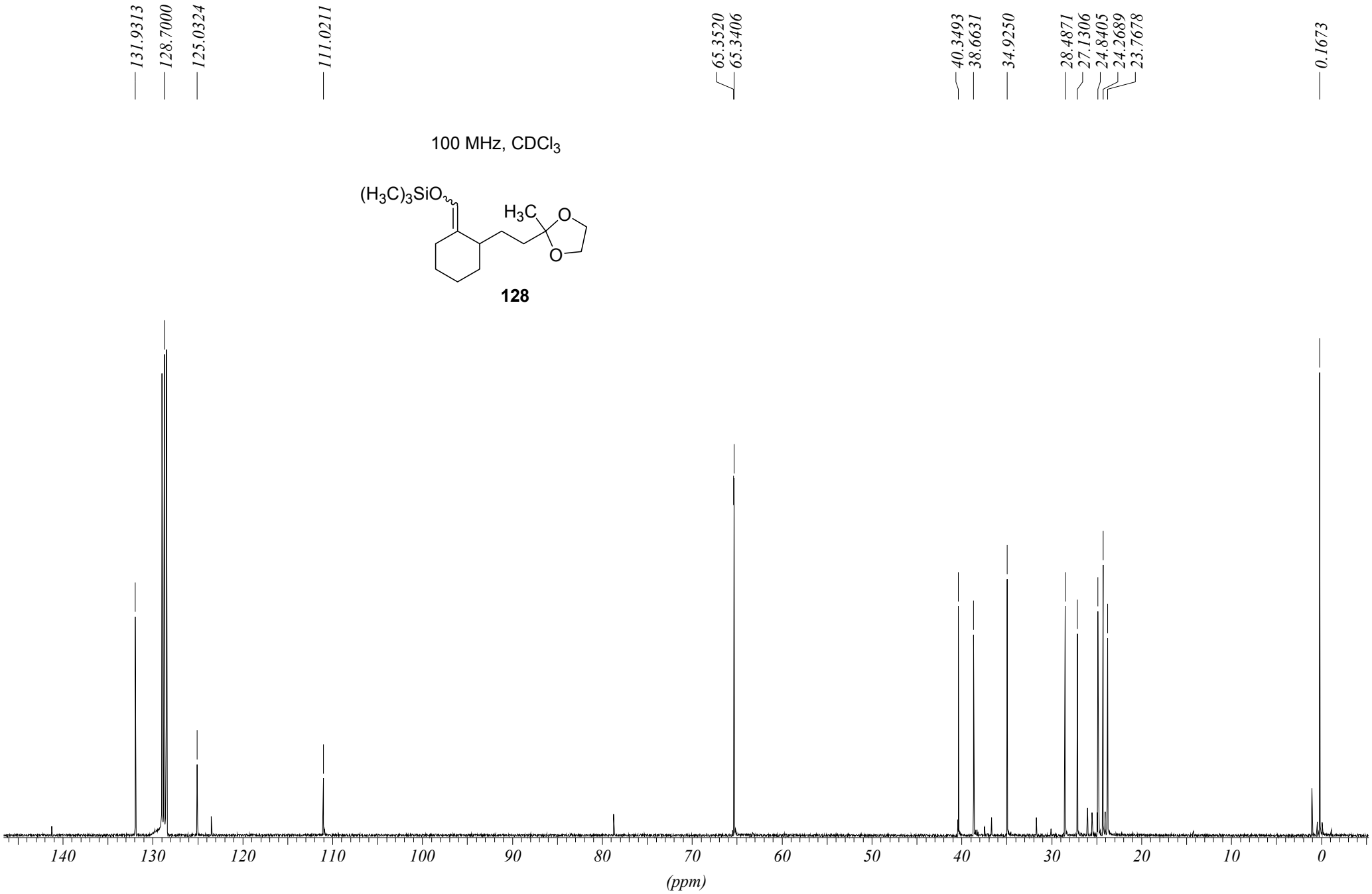
(ppm)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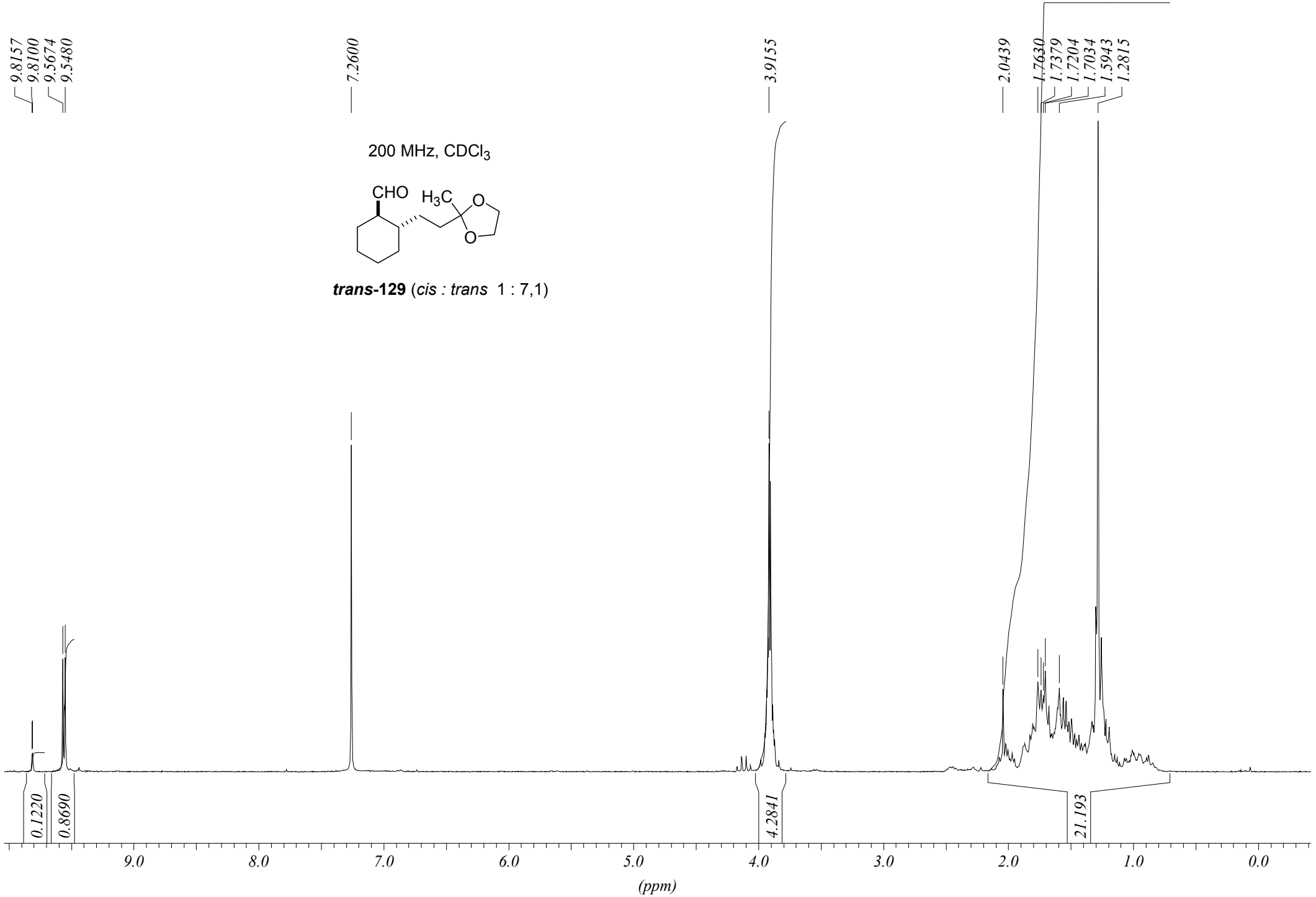
27.1306
24.8405
24.2689
23.7678
0.1673
100 MHz, CDCl3
(H3C)3SiO
H3C
O
O
128
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)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1.7204
1.7034
1.5943
1.2815
200 MHz, CDCl3
CHO
H3C
O
O
trans-129 (cis : trans 1 : 7,1)
0.1220
0.8690
4.2841
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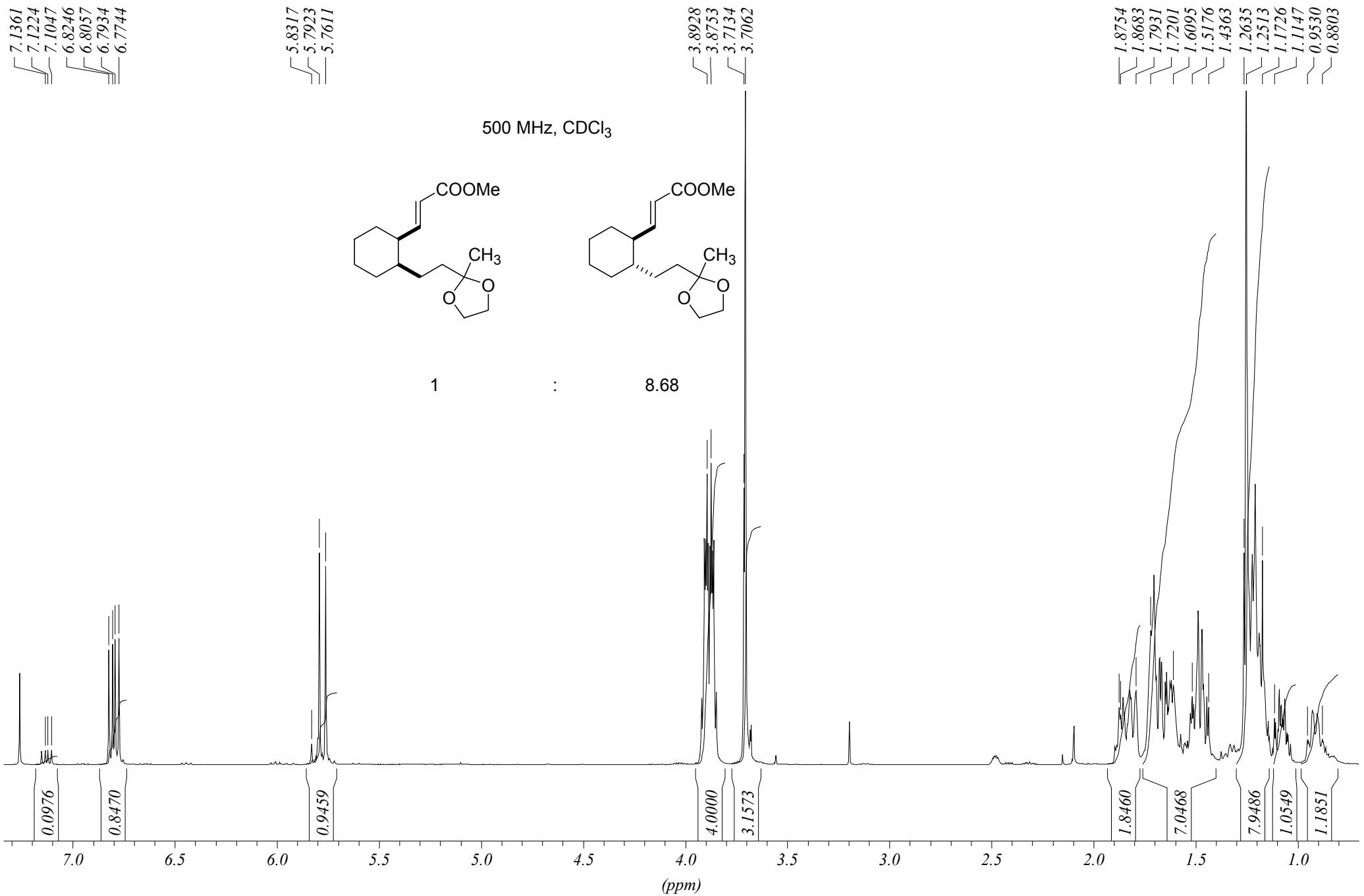
(ppm)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3.8928
3.8753
3.7134
3.7062
1.8754
1.8683
1.7931
1.7201
1.6095
1.5176
1.4363
1.2635
1.2513
1.1726
1.1147
0.9530
0.8803
500 MHz, CDCl3
COOMe
CH3
O
O
COOMe
CH3
O
O
1 : 8.68
0.0976
0.8470
0.9459
4.0000
3.1573
1.8460
7.0468
7.9486
1.0549
1.1851
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

167.1625
153.9401
120.2951
110.1534
64.5568
64.5072
51.3076
46.9312
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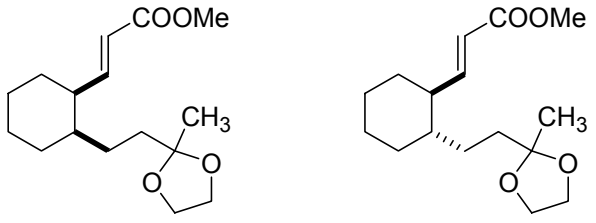
125 MHz, $CDCl_3$



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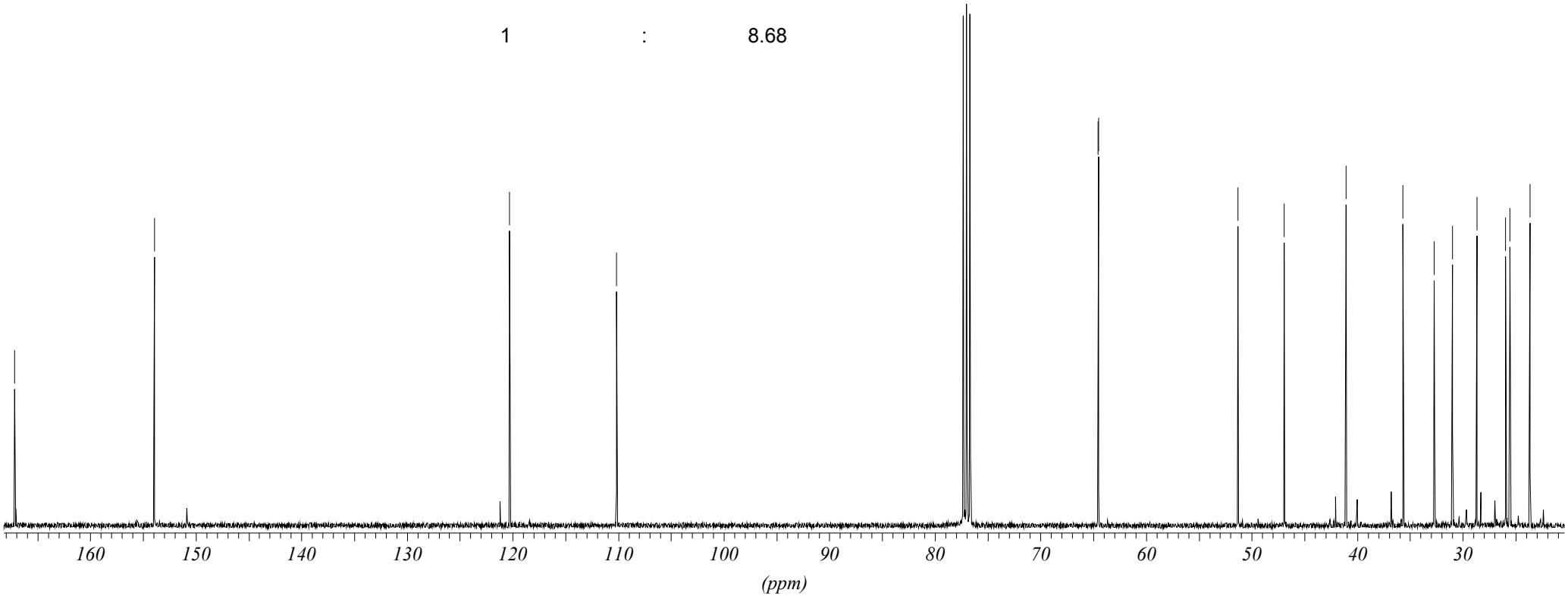

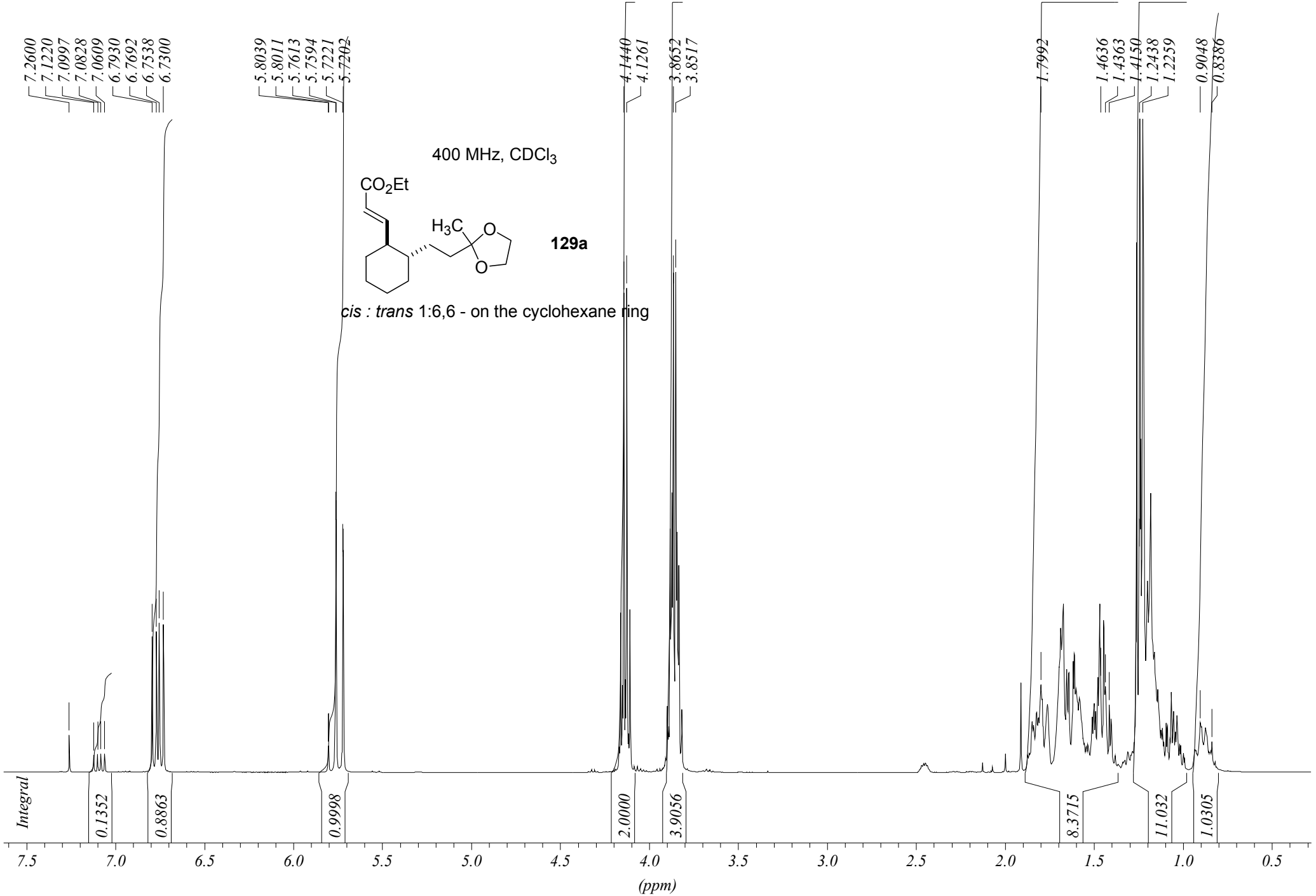
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5.7613
5.7594
5.7221
5.7202
4.1440
4.1261
3.8652
3.8517
1.7992
1.4636
1.4363
1.4150
1.2438
1.2259
0.9048
0.8386
400 MHz, CDCl3
CO2Et
H3C
O
O
129a
cis : trans 1:6,6 - on the cyclohexane ring
Integral
0.1352
0.8863
0.9998
2.0000
3.9056
8.3715
11.032
1.0305
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

166.6786
153.5323
120.6209
110.0715
77.0000
64.4748
64.4234
59.9860
46.8360
40.9697
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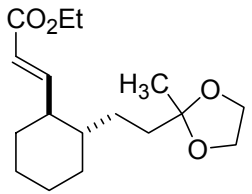
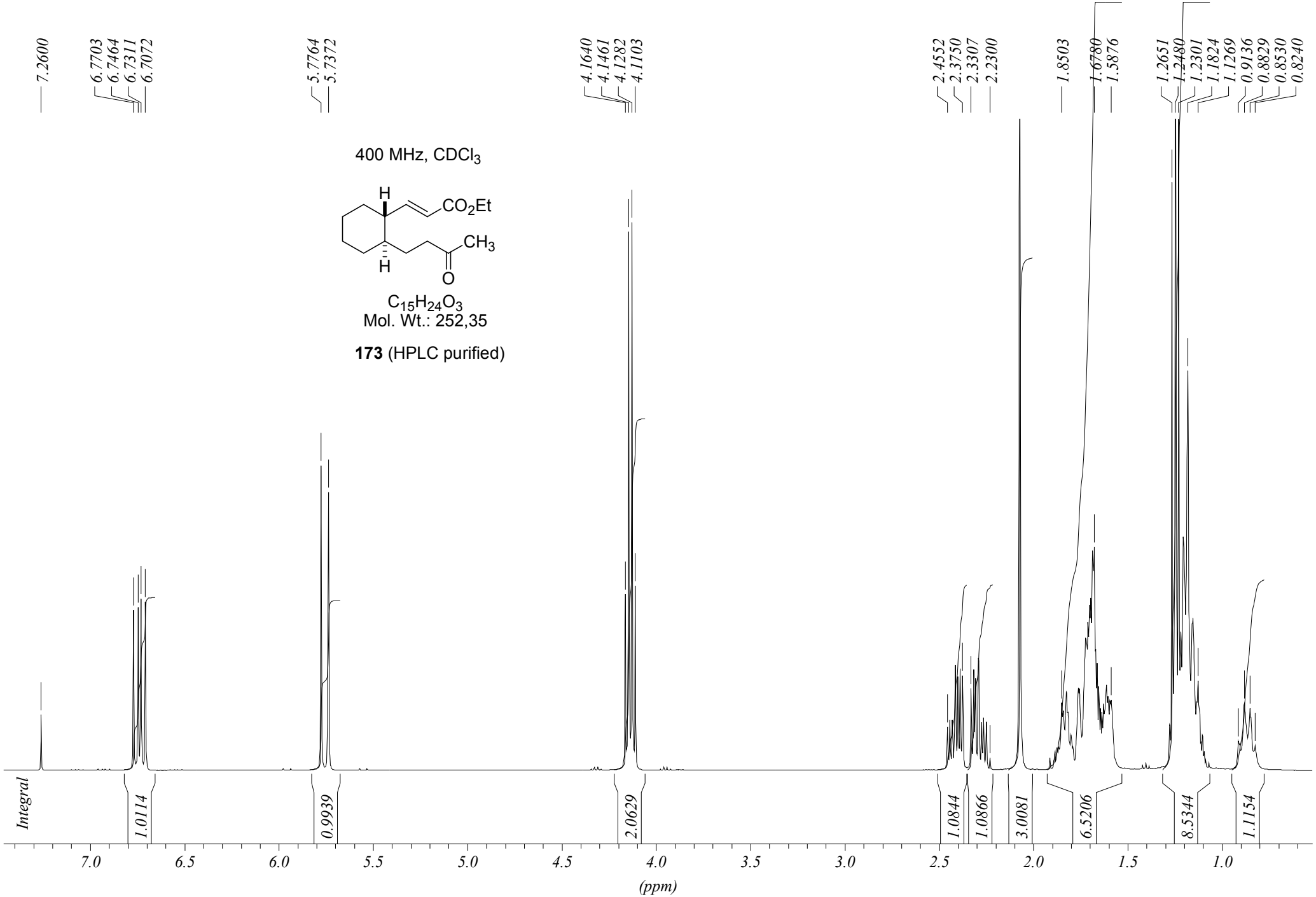
25.4799
23.5670
14.1722

100 MHz, $CDCl_3$



129a

cis : trans 1:6,6 - on the cyclohexane ring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2.3750
2.3307
2.2300
1.8503
1.6780
1.5876
1.2651
1.2480
1.2301
1.1824
1.1269
0.9136
0.8829
0.8530
0.8240
400 MHz, CDCl3
H
CO2Et
CH3
H
O
C15H24O3
Mol. Wt.: 252,35
173 (HPLC purified)
Integral
1.0114
0.9939
2.0629
1.0844
1.0866
3.0081
6.5206
8.5344
1.1154
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

208.8553
166.5757
153.0274
120.9657
77.0000
60.0680
46.8569
40.7658
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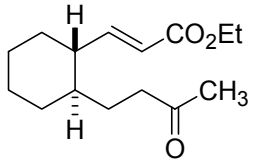
25.7619
25.3618
14.1627

100 MHz, $CDCl_3$



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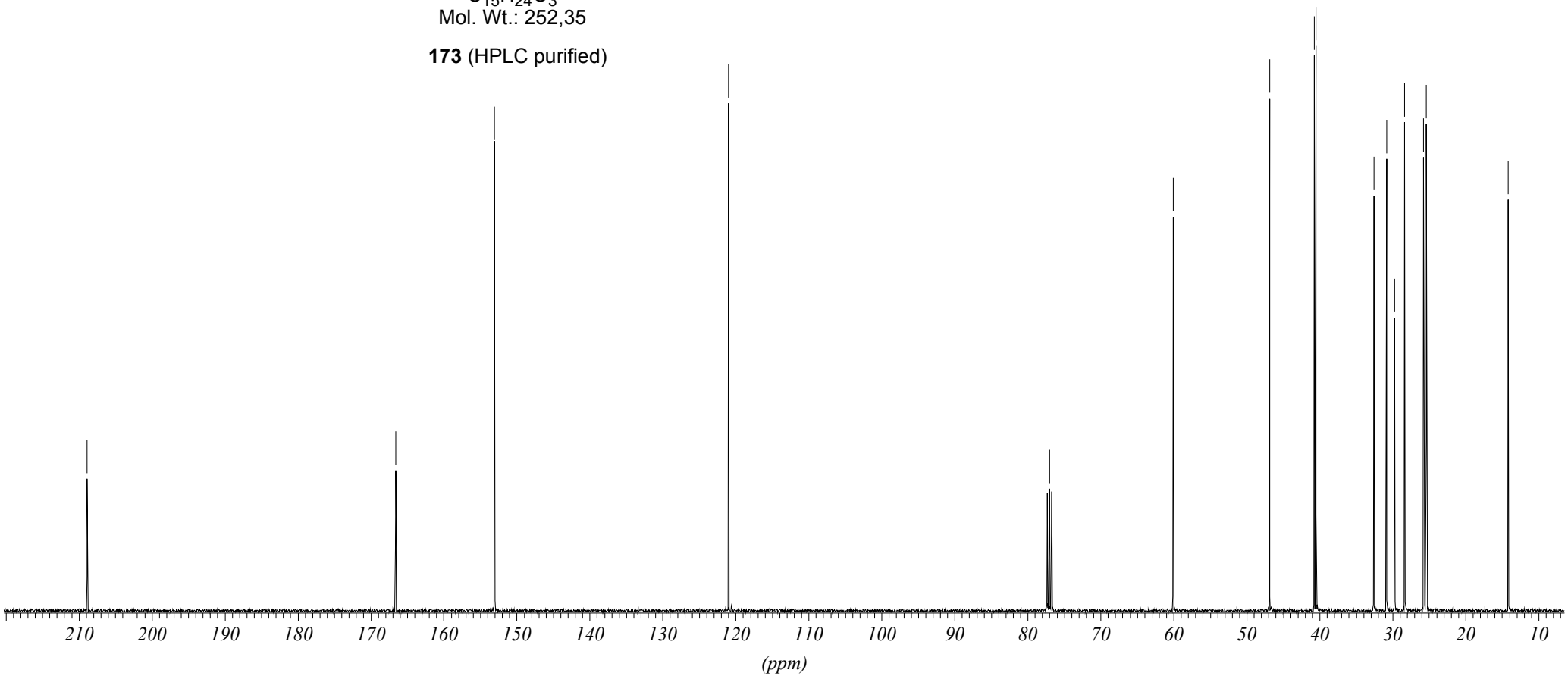
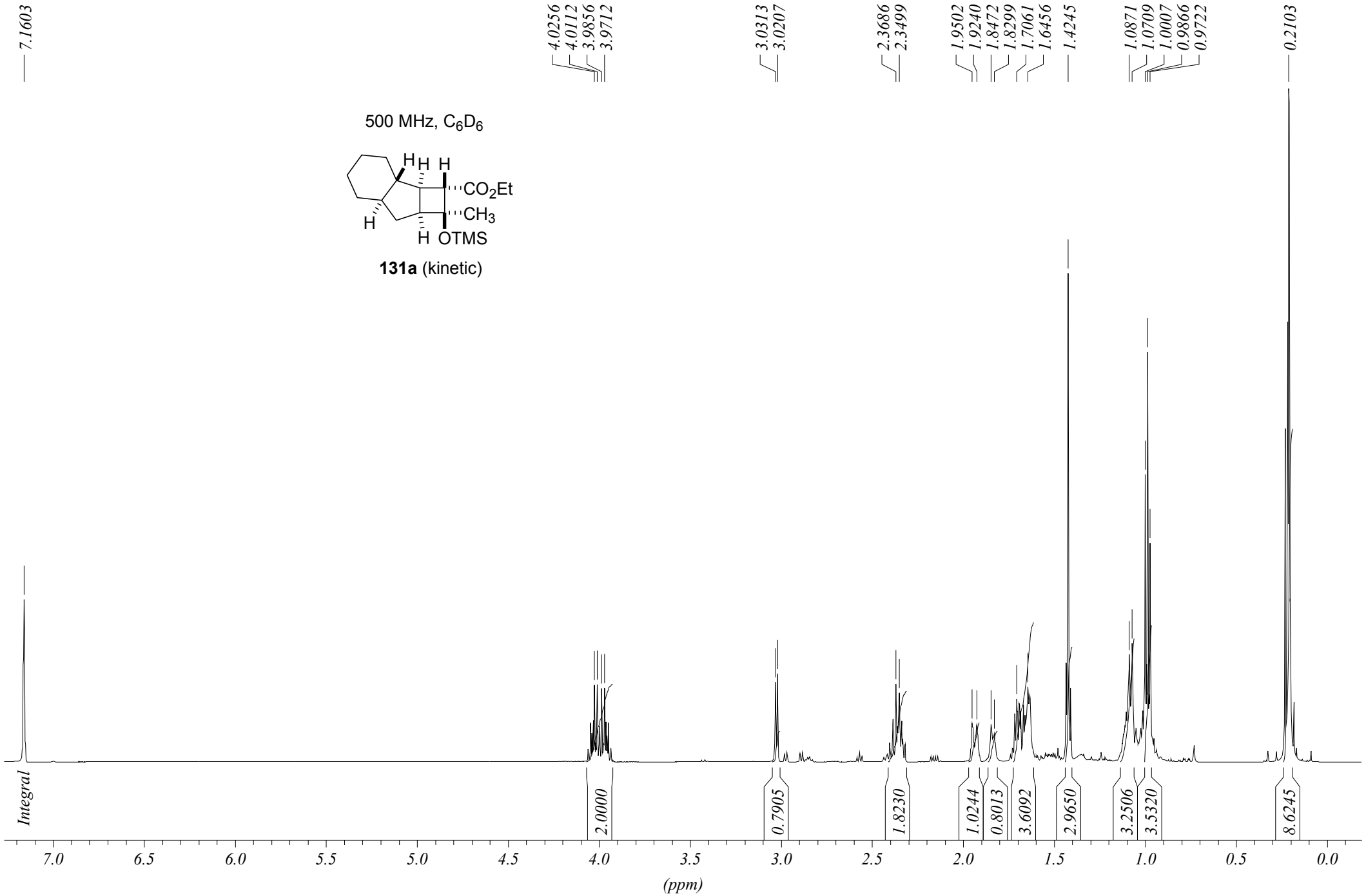
Mol. Wt.: 252,35

173 (HPLC purified)

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1.8472
1.8299
1.7061
1.6456
1.4245
1.0871
1.0709
1.0007
0.9866
0.9722
0.2103
500 MHz, C6D6
H H H
CO2Et
CH3
H
H OTMS
131a (kinetic)
Integral
2.0000
0.7905
1.8230
1.0244
0.8013
3.6092
2.9650
3.2506
3.5320
8.6245
7.0
6.5
6.0
5.5
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4.0
3.5
3.0
2.5
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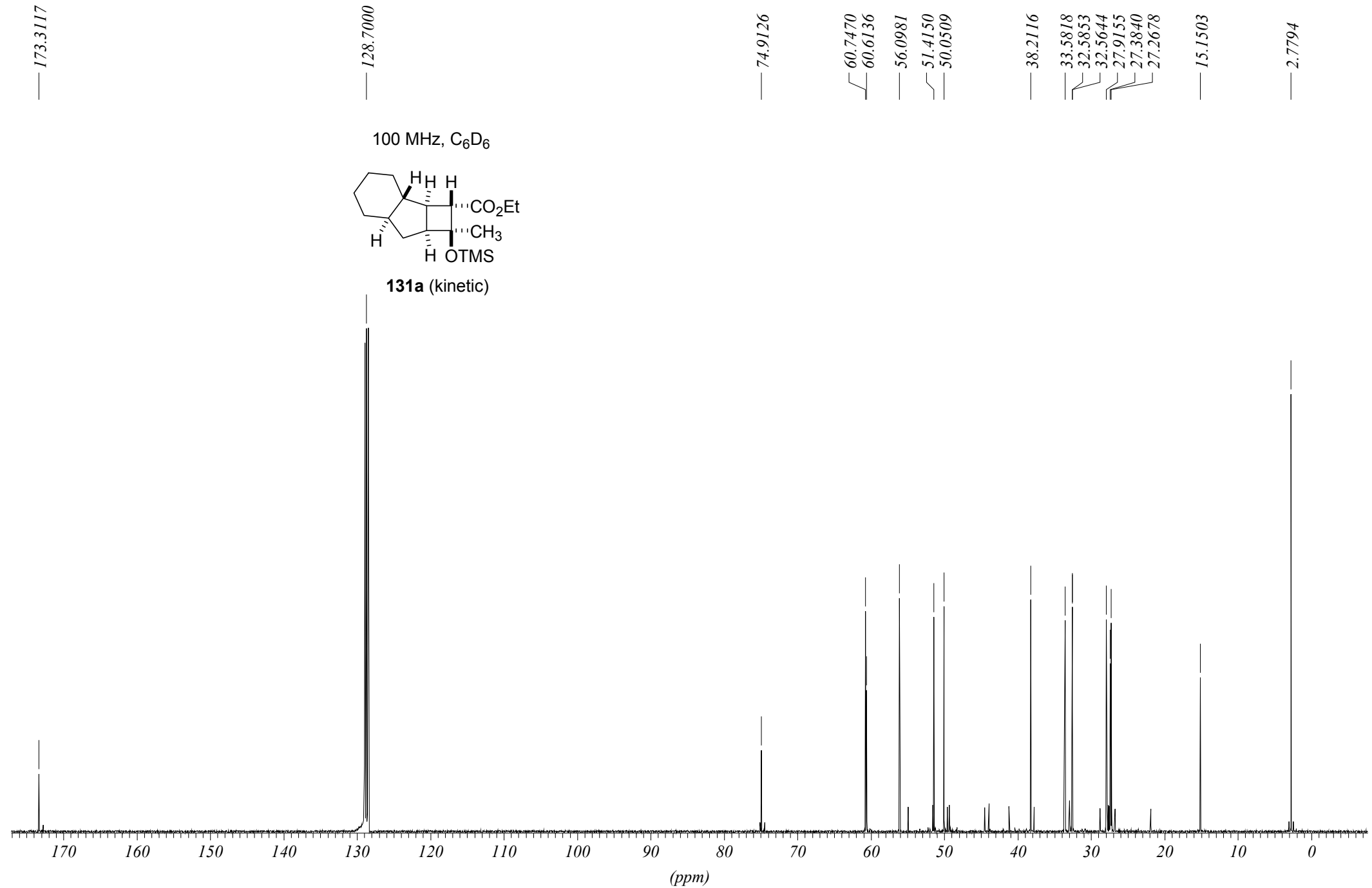
1.5
1.0
0.5
0.0
(ppm)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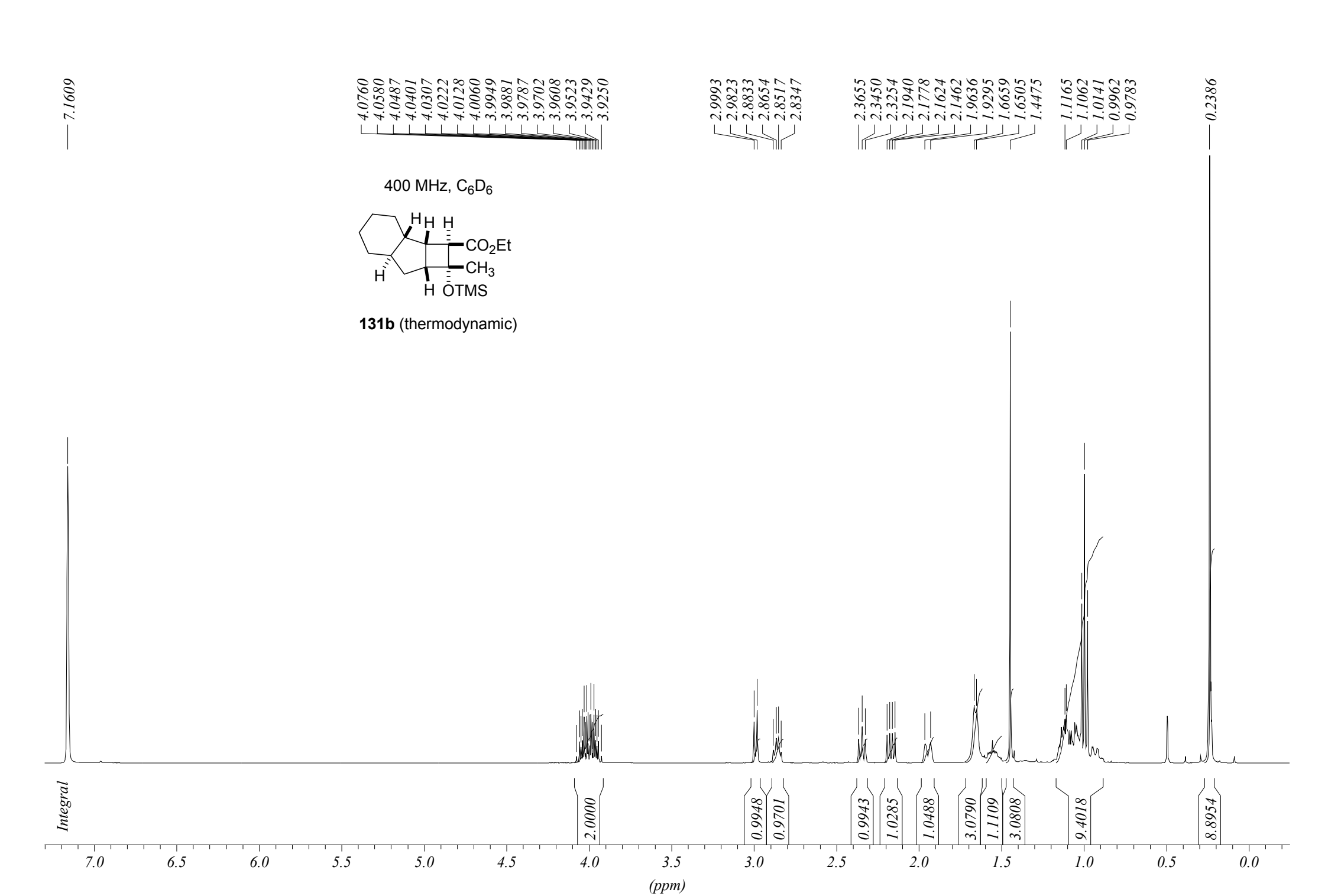
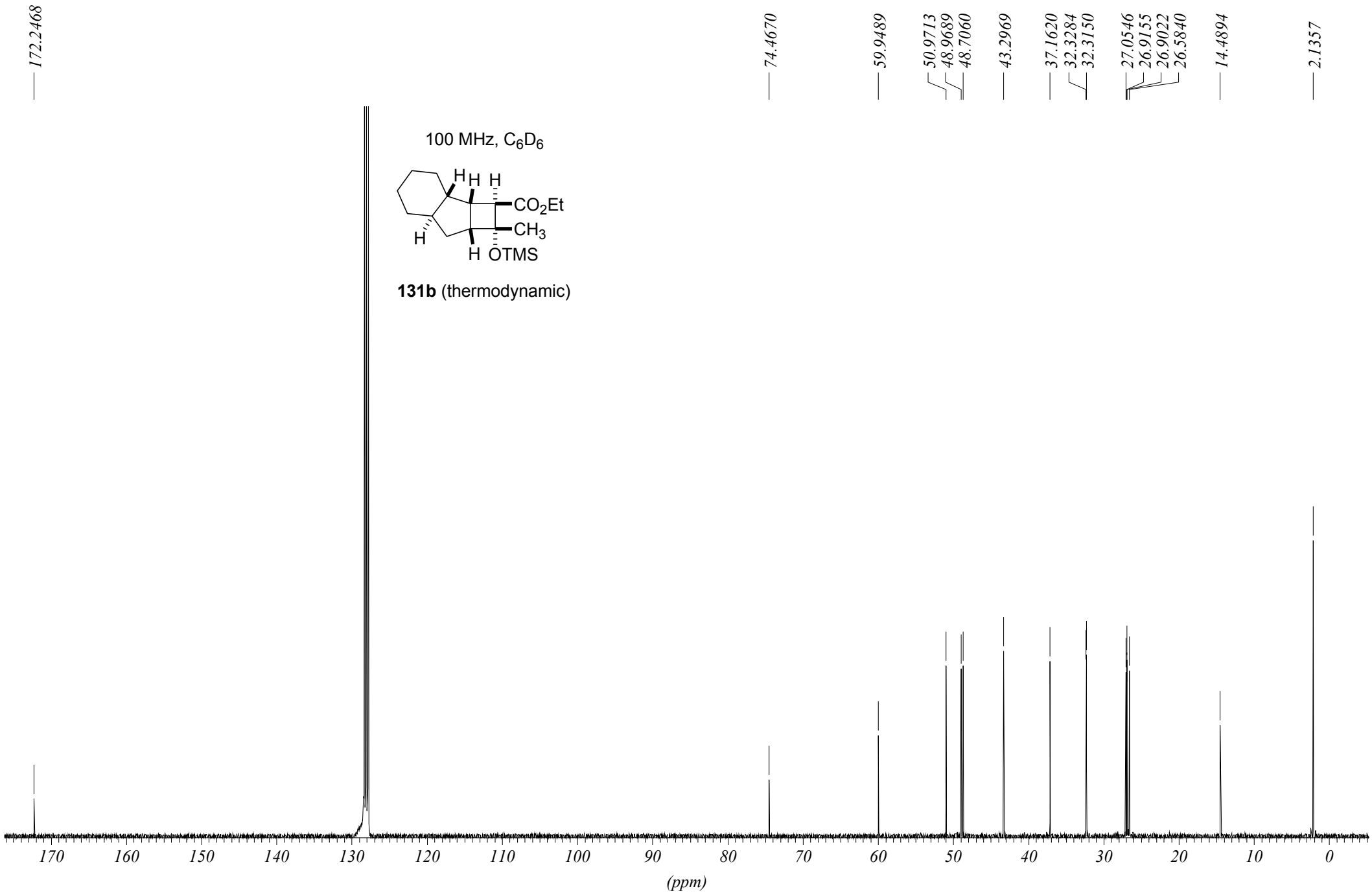
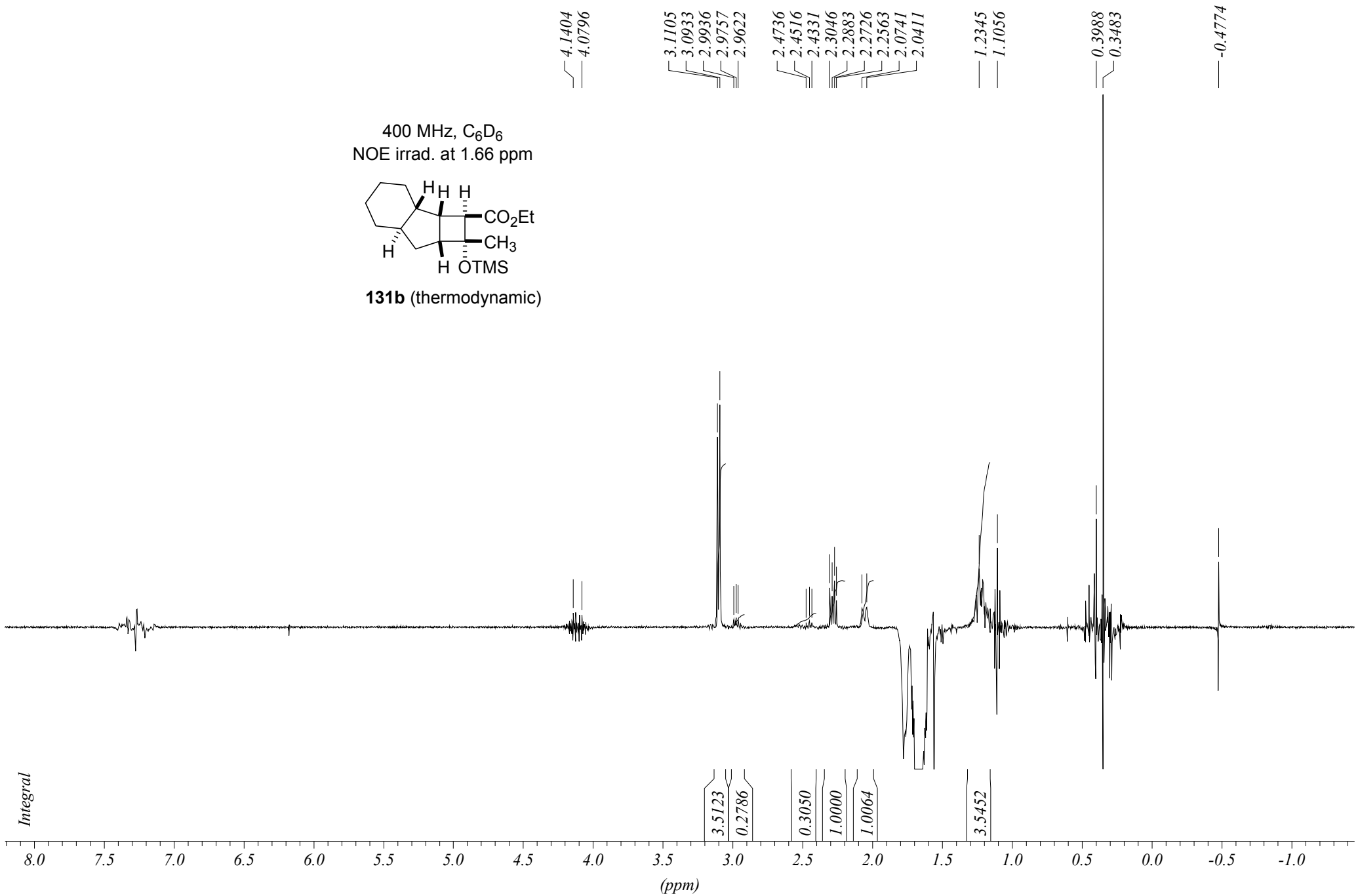
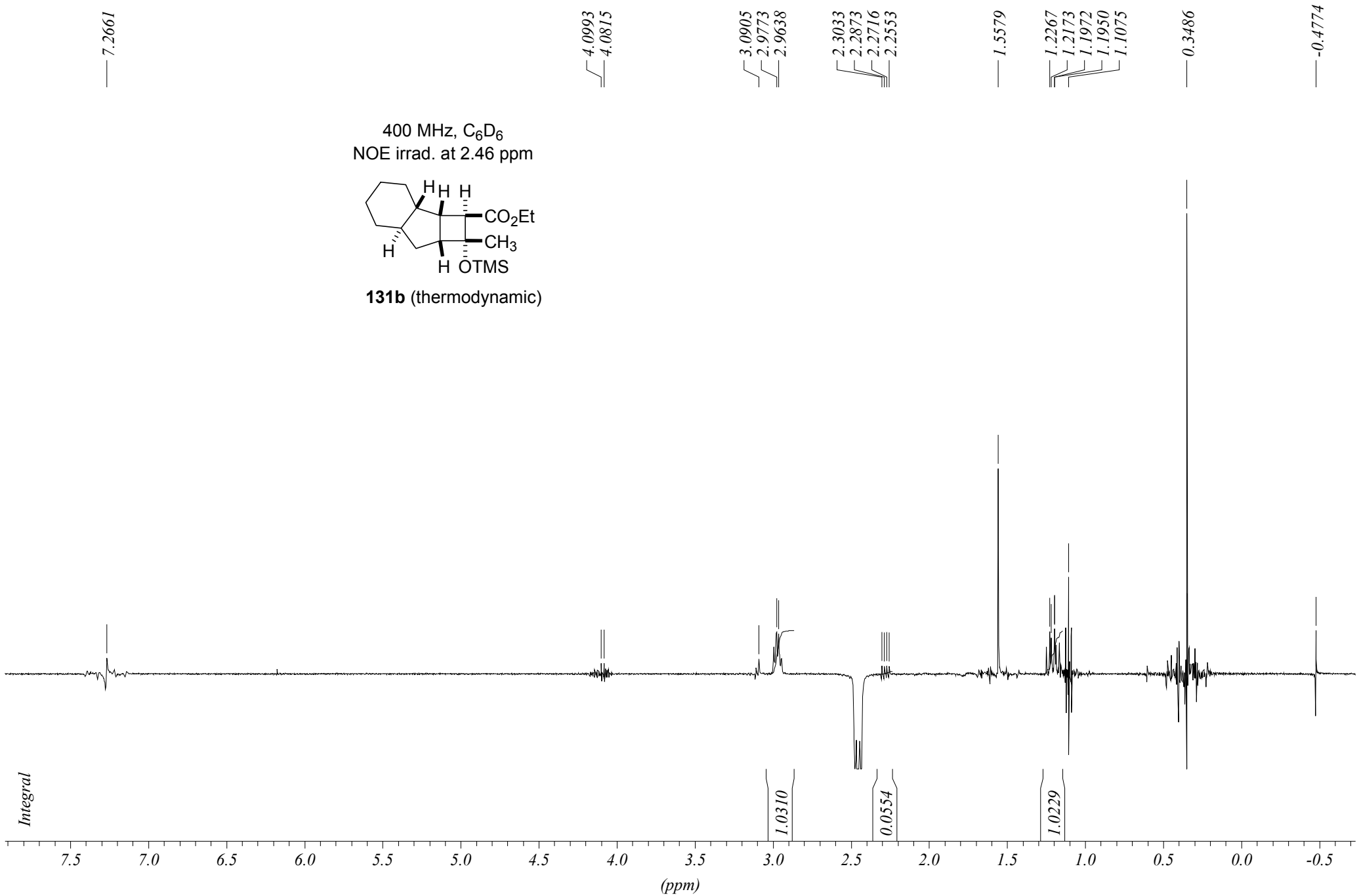
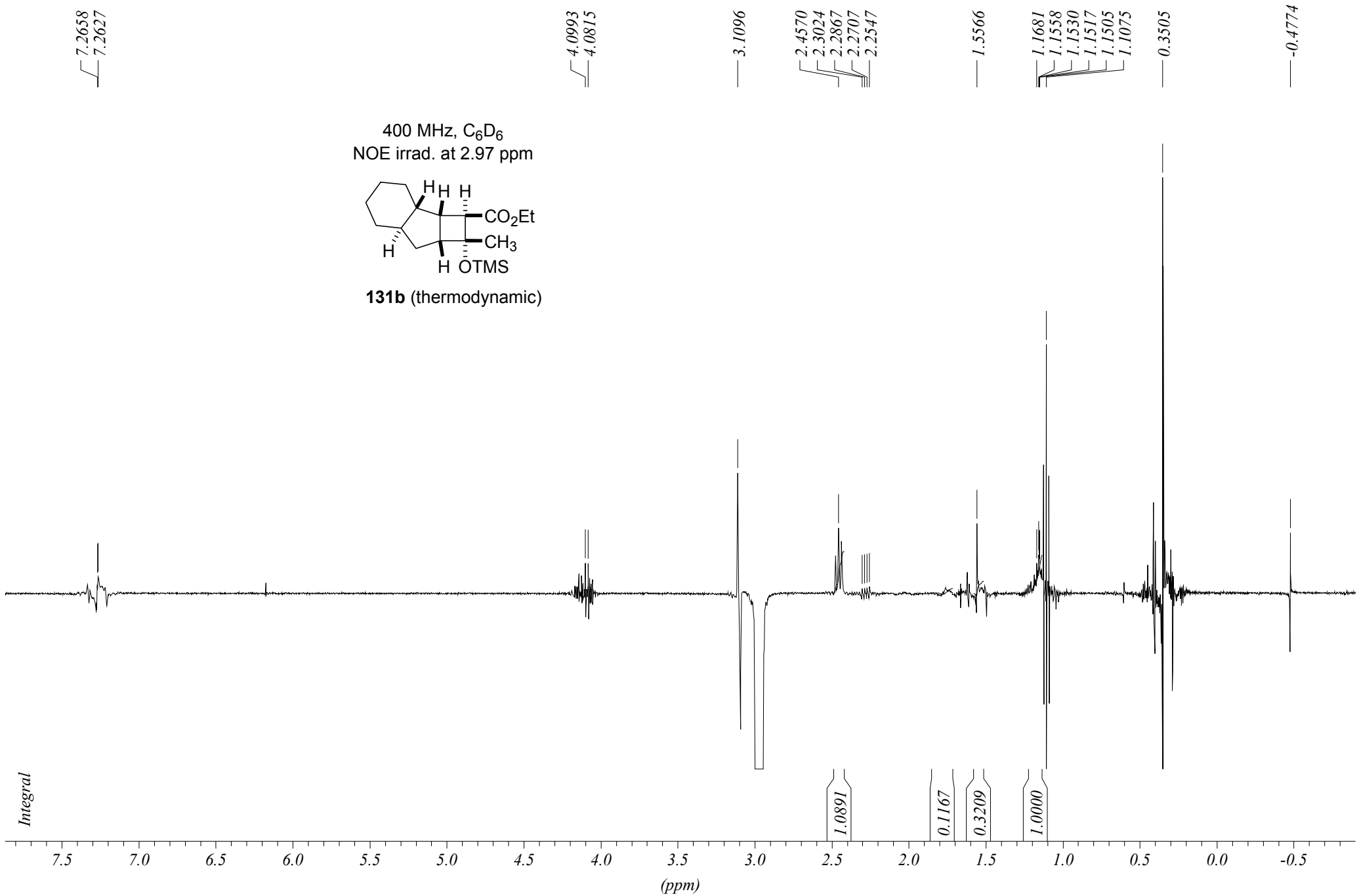
27.3840
27.2678
15.1503
2.7794
100 MHz, C6D6
H H H
CO2Et
CH3
H
H OTMS
131a (kinetic)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

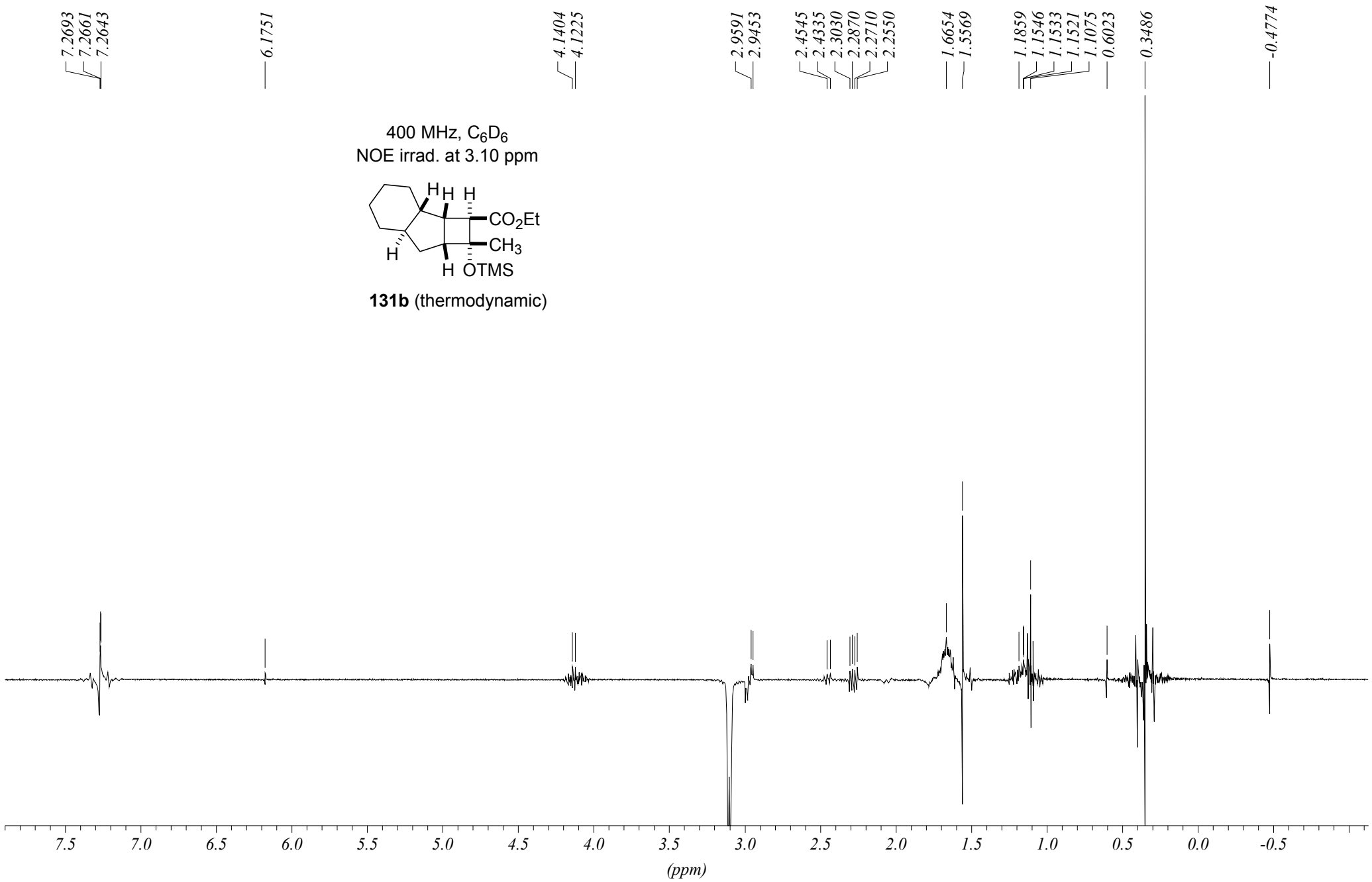

7.1609
4.0760
4.0580
4.0487
4.0401
4.0307
4.0222
4.0128
4.0060
3.9949
3.9881
3.9787
3.9702
3.9608
3.9523
3.9429
3.9250
2.9993
2.9823
2.8833
2.8654
2.8517
2.8347
2.3655
2.3450
2.3254
2.1940
2.1778
2.1624
2.1462
1.9636
1.9295
1.6659
1.6505
1.4475
1.1165
1.1062
1.0141
0.9962
0.9783
0.2386
400 MHz, C6D6
H H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
Integral
2.0000
0.9948
0.9701
0.9943
1.0285
1.0488
3.0790
1.1109
3.0808
9.4018
8.8954
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

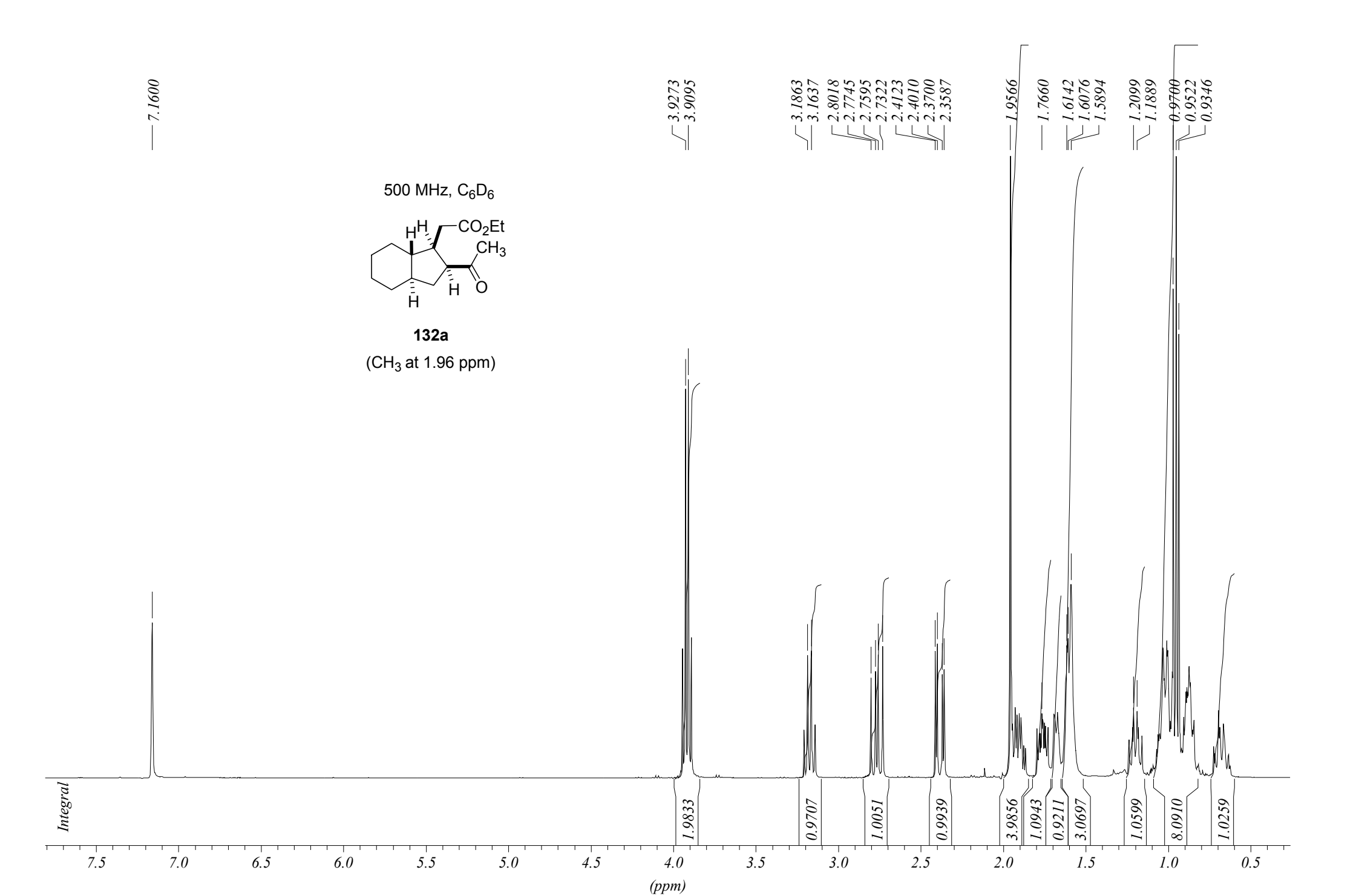

172.2468
74.4670
59.9489
50.9713
48.9689
48.7060
43.2969
37.1620
32.3284
32.3150
27.0546
26.9155
26.9022
26.5840
14.4894
2.1357
100 MHz, C6D6
H H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

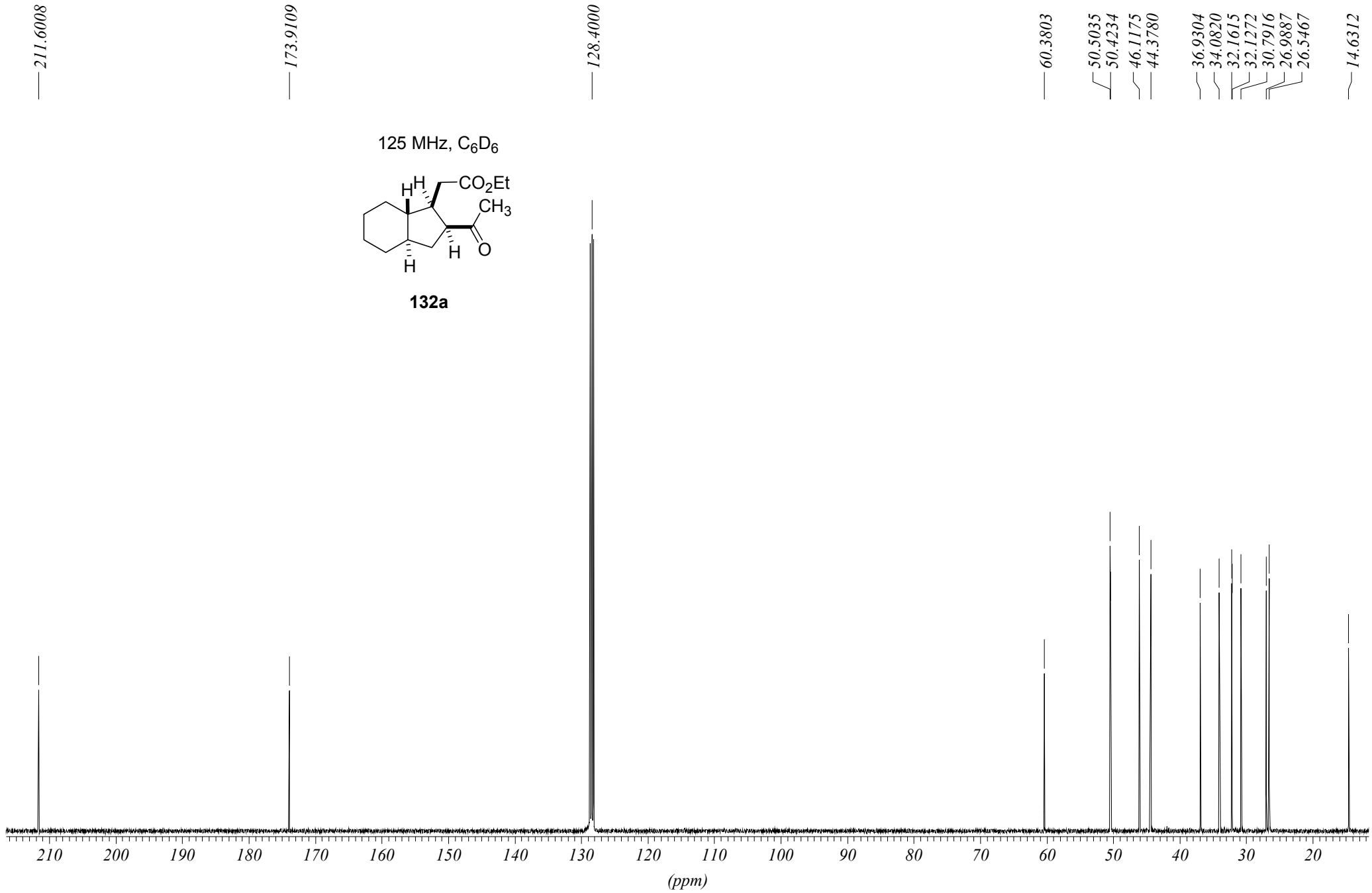

4.1404
4.0796
3.1105
3.0933
2.9936
2.9757
2.9622
2.4736
2.4516
2.4331
2.3046
2.2883
2.2726
2.2563
2.0741
2.0411
1.2345
1.1056
0.3988
0.3483
-0.4774
400 MHz, C6D6
NOE irrad. at 1.66 ppm
H H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
Integral
3.5123
0.2786
0.3050
1.0000
1.0064
3.5452
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
(ppm)

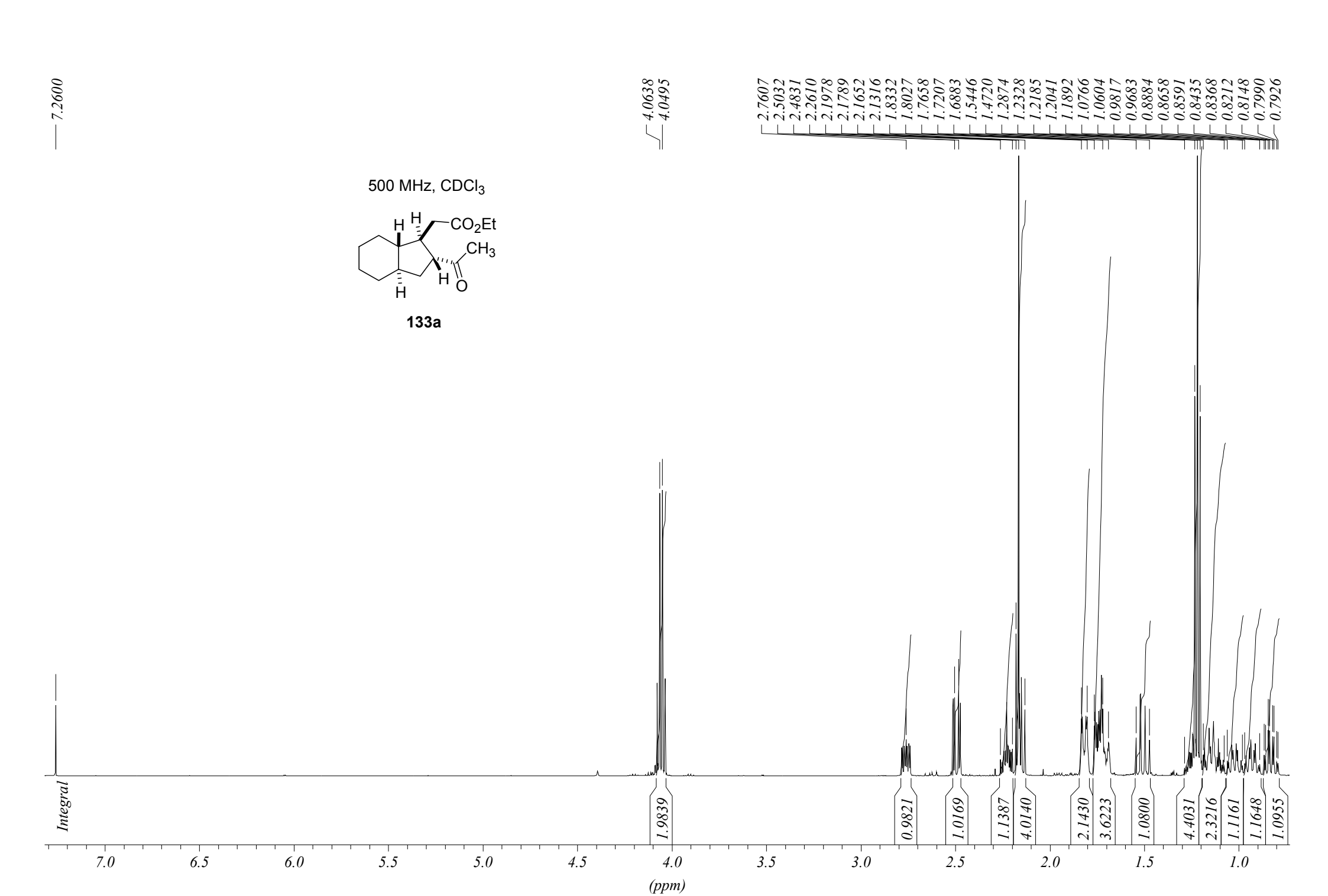

7.2661
4.0993
4.0815
3.0905
2.9773
2.9638
2.3033
2.2873
2.2716
2.2553
1.5579
1.2267
1.2173
1.1972
1.1950
1.1075
0.3486
-0.4774
400 MHz, C6D6
NOE irrad. at 2.46 ppm
H H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
Integral
1.0310
0.0554
1.0229
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

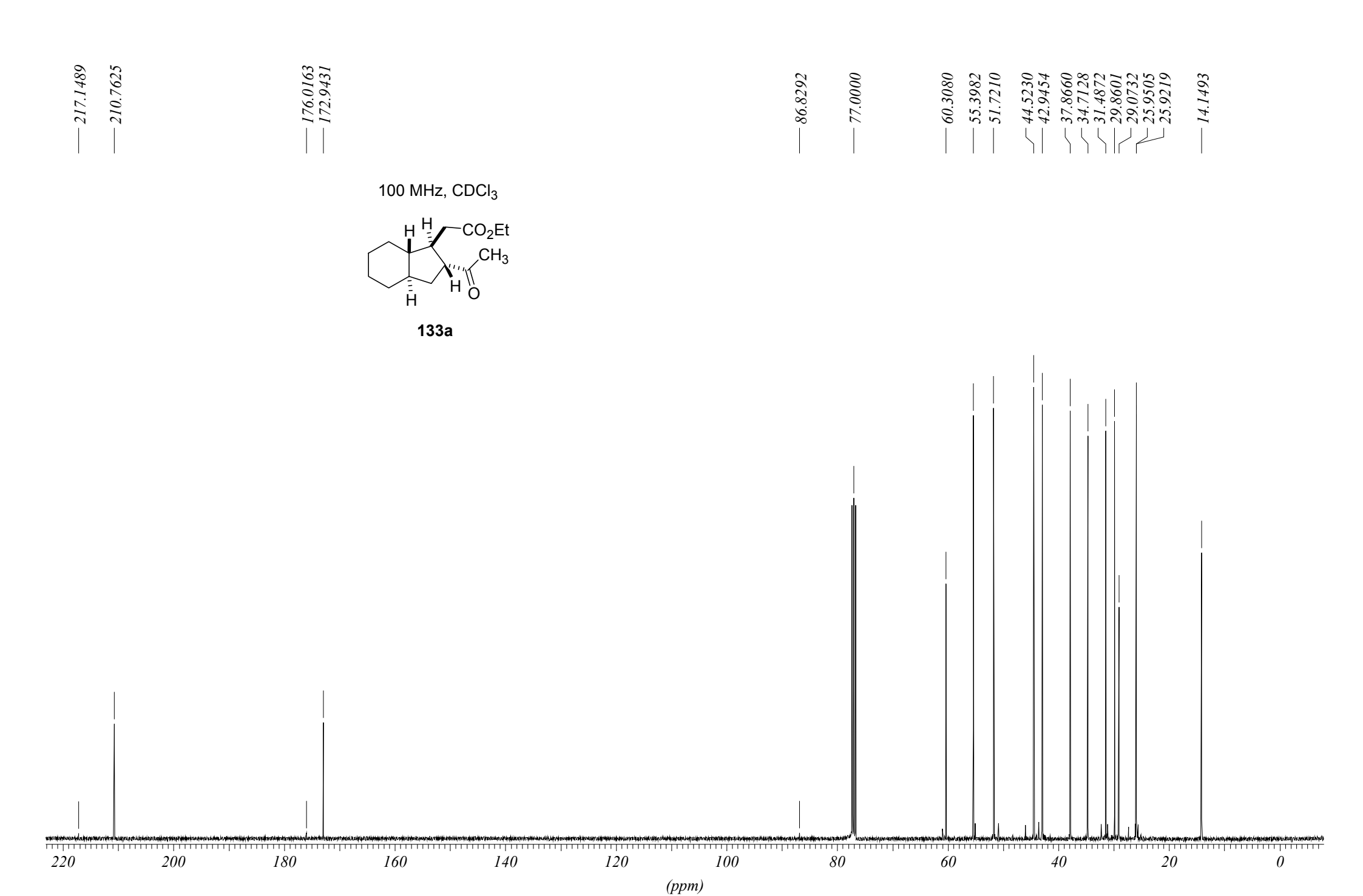

7.2658
7.2627
4.0993
4.0815
3.1096
2.4570
2.3024
2.2867
2.2707
2.2547
1.5566
1.1681
1.1558
1.1530
1.1517
1.1505
1.1075
0.3505
-0.4774
400 MHz, C6D6
NOE irrad. at 2.97 ppm
H H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
Integral
1.0891
0.1167
0.3209
1.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

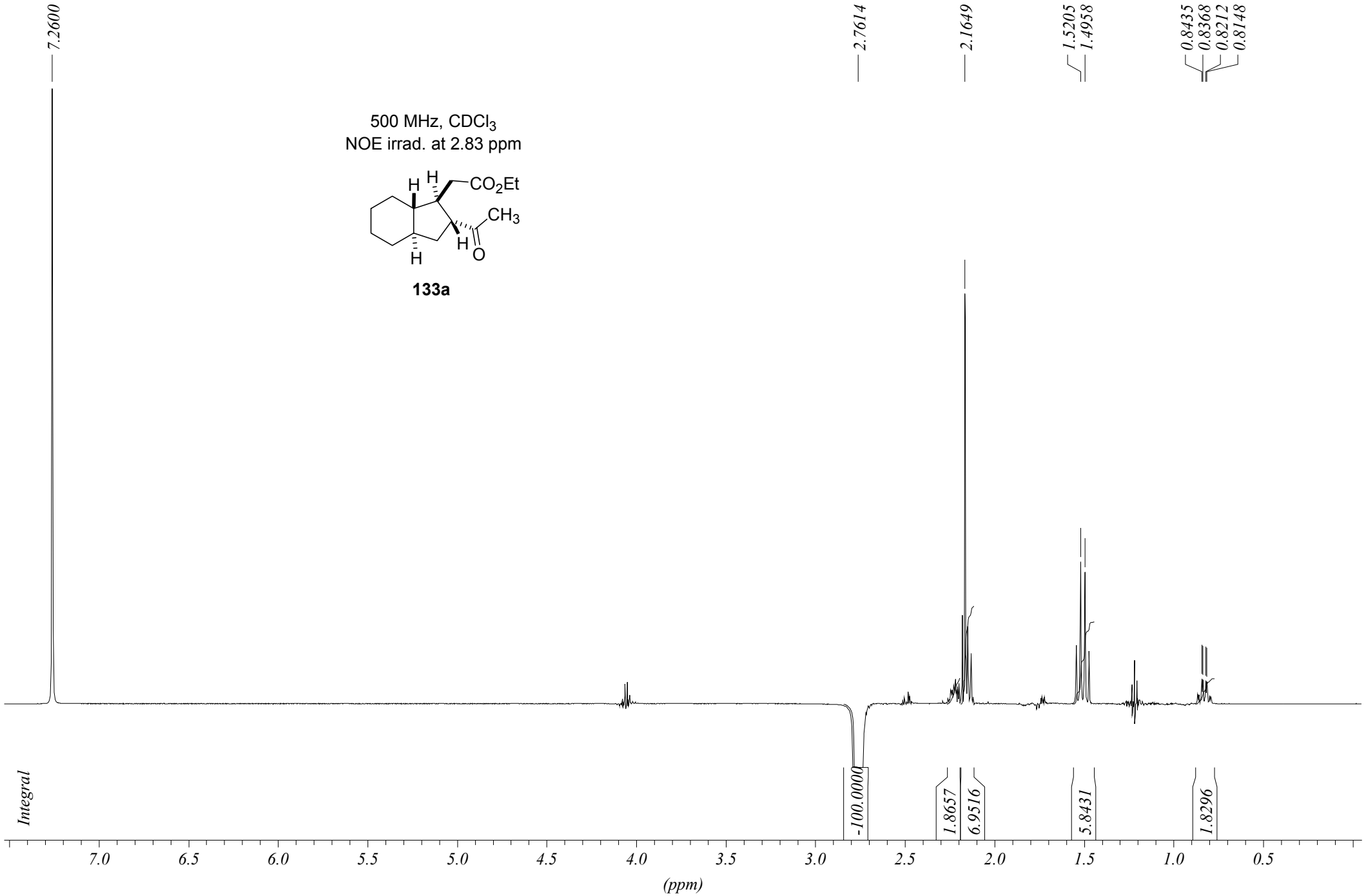

7.2693
7.2661
7.2643
6.1751
4.1404
4.1225
2.9591
2.9453
2.4545
2.4335
2.3030
2.2870
2.2710
2.2550
1.6654
1.5569
1.1859
1.1546
1.1533
1.1521
1.1075
0.6023
0.3486
-0.4774
400 MHz, C6D6
NOE irrad. at 3.10 ppm
H
H H
CO2Et
CH3
H
H OTMS
131b (thermodynamic)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

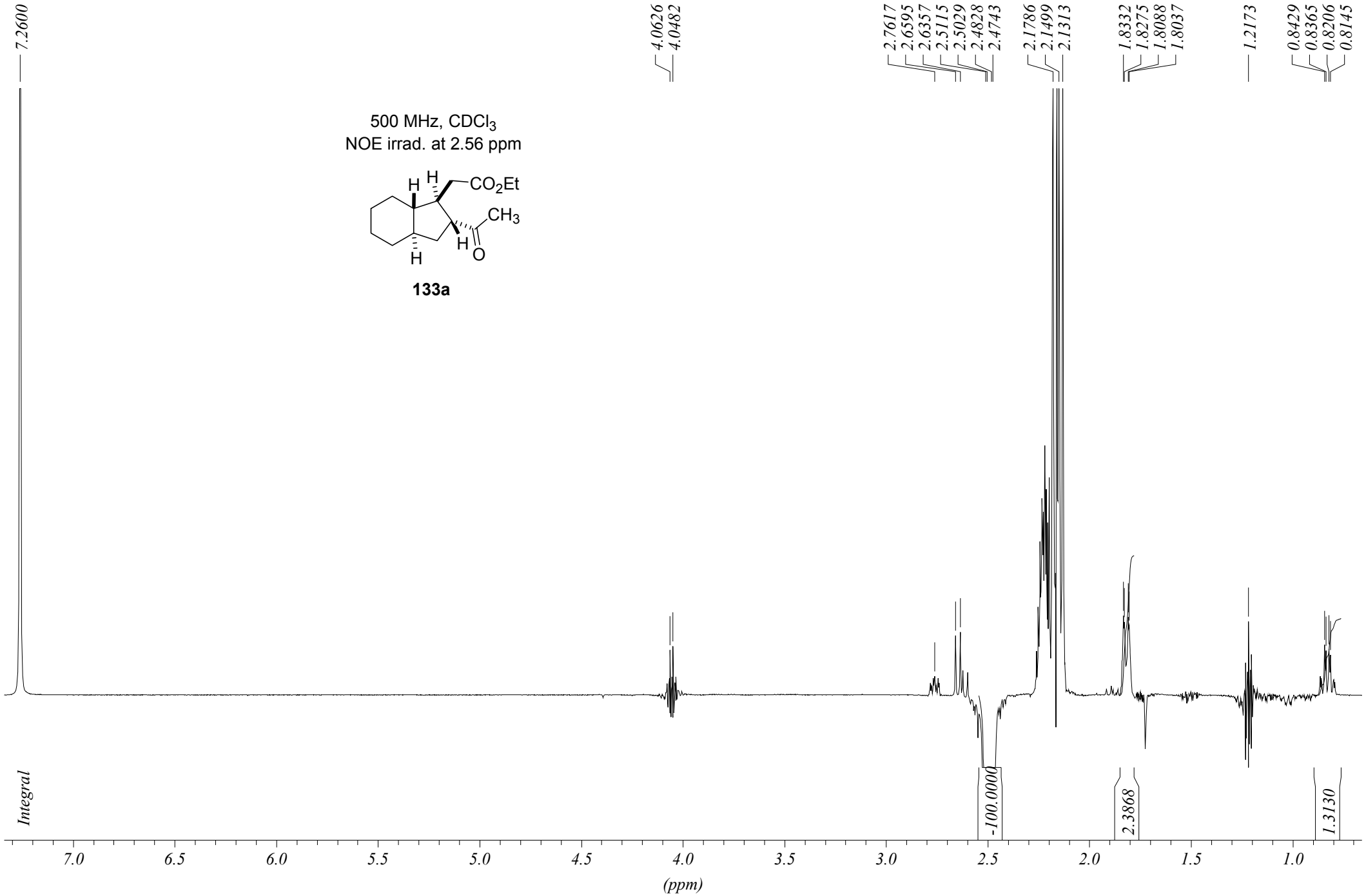

7.1600
3.9273
3.9095
3.1863
3.1637
2.8018
2.7745
2.7595
2.7322
2.4123
2.4010
2.3700
2.3587
1.9566
1.7660
1.6142
1.6076
1.5894
1.2099
1.1889
0.9700
0.9522
0.9346
500 MHz, C6D6
H
H
CO2Et
CH3
H
O
H
132a
(CH3 at 1.96 ppm)
Integral
1.9833
0.9707
1.0051
0.9939
3.9856
1.0943
0.9211
3.0697
1.0599
8.0910
1.0259
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

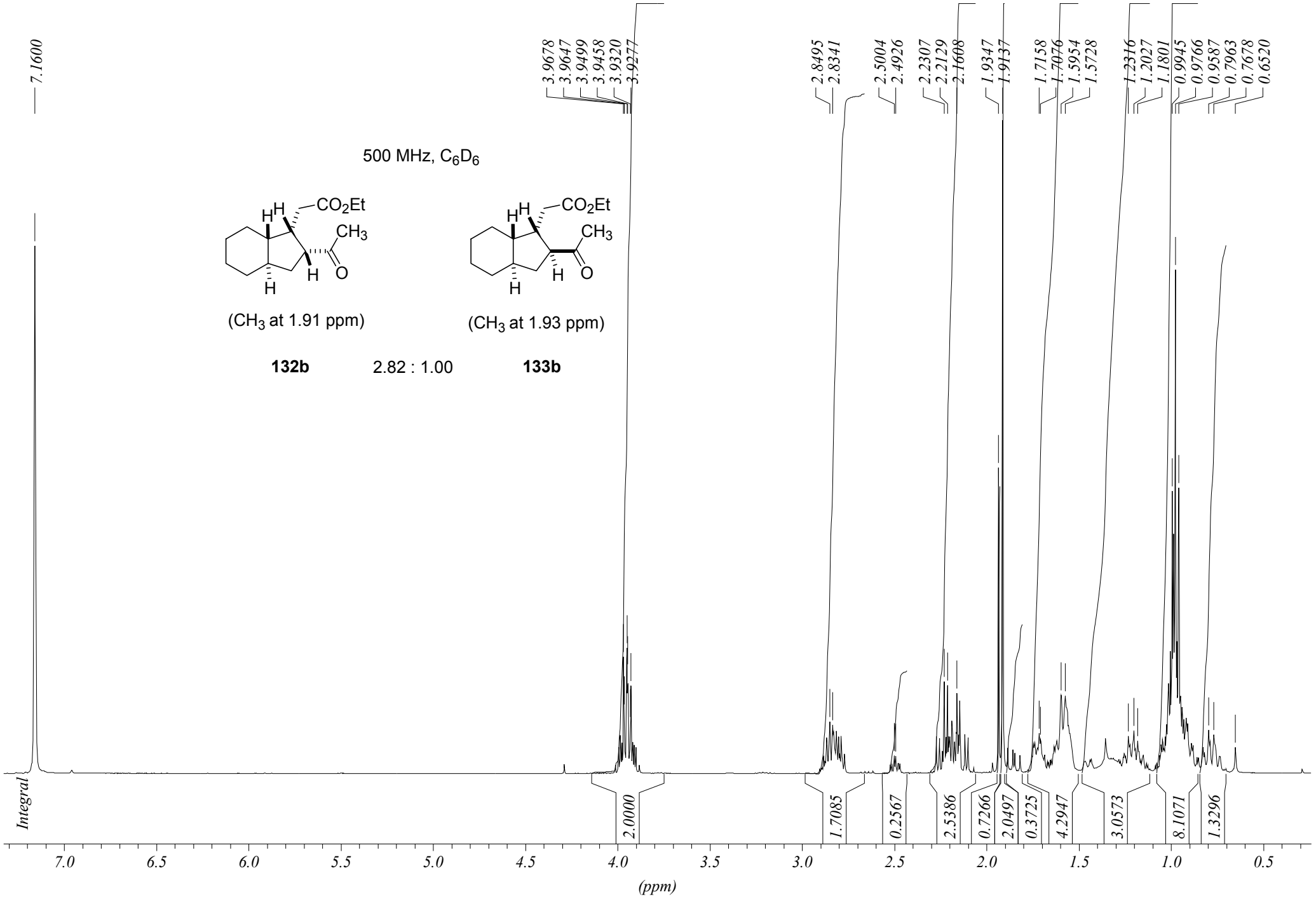

211.6008
173.9109
128.4000
60.3803
50.5035
50.4234
46.1175
44.3780
36.9304
34.0820
32.1615
32.1272
30.7916
26.9887
26.5467
14.6312
125 MHz, C6D6
CO2Et
CH3
O
132a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

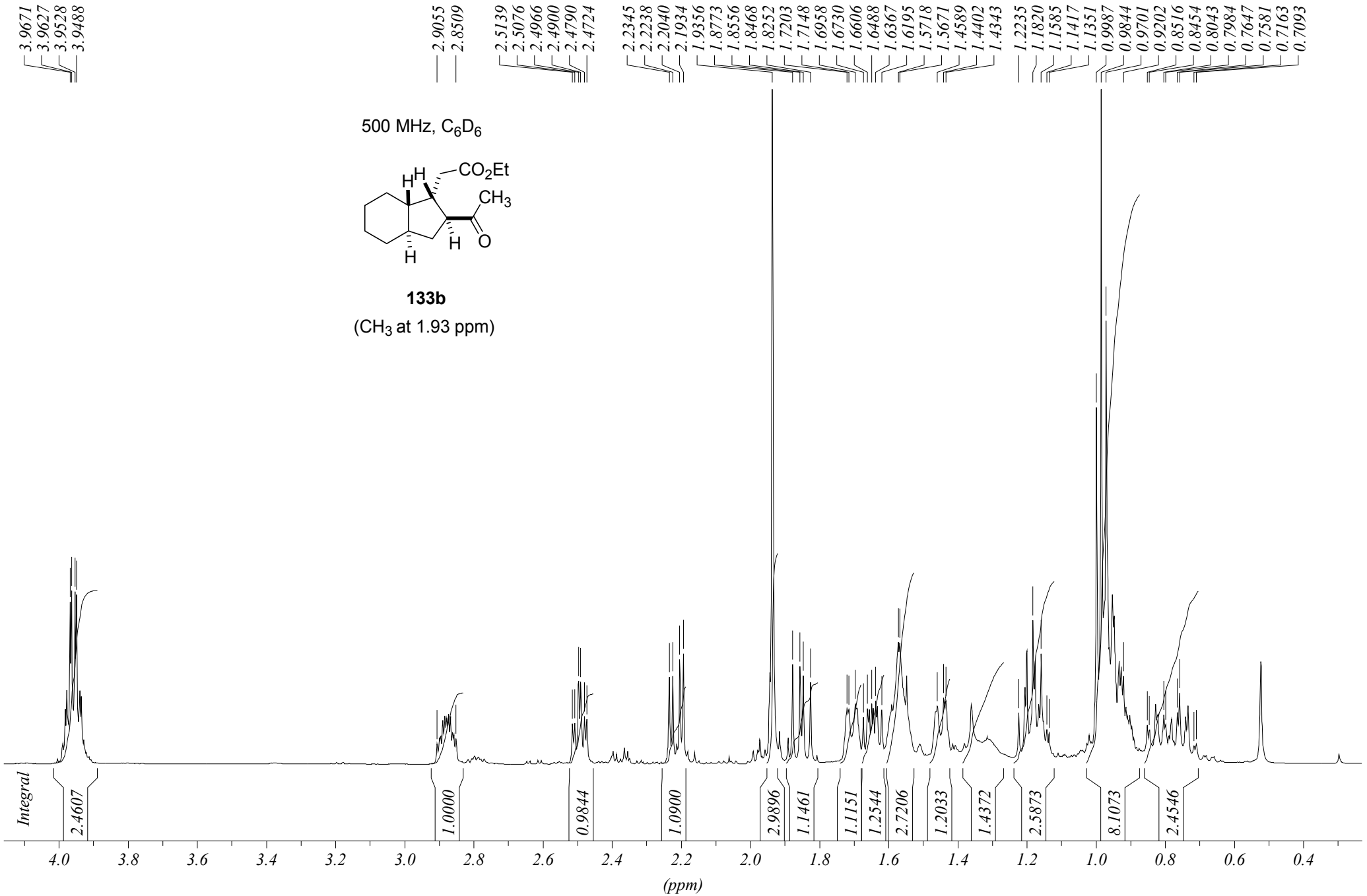

7.2600
4.0638
4.0495
2.7607
2.5032
2.4831
2.2610
2.1978
2.1789
2.1652
2.1316
1.8332
1.8027
1.7658
1.7207
1.6883
1.5446
1.4720
1.2874
1.2328
1.2185
1.2041
1.1892
1.0766
1.0604
0.9817
0.9683
0.8884
0.8658
0.8591
0.8435
0.8368
0.8212
0.8148
0.7990
0.7926
500 MHz, CDCl3
CO2Et
CH3
O
H
133a
Integral
1.9839
0.9821
1.0169
1.1387
4.0140
2.1430
3.6223
1.0800
4.4031
2.3216
1.1161
1.1648
1.0955
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

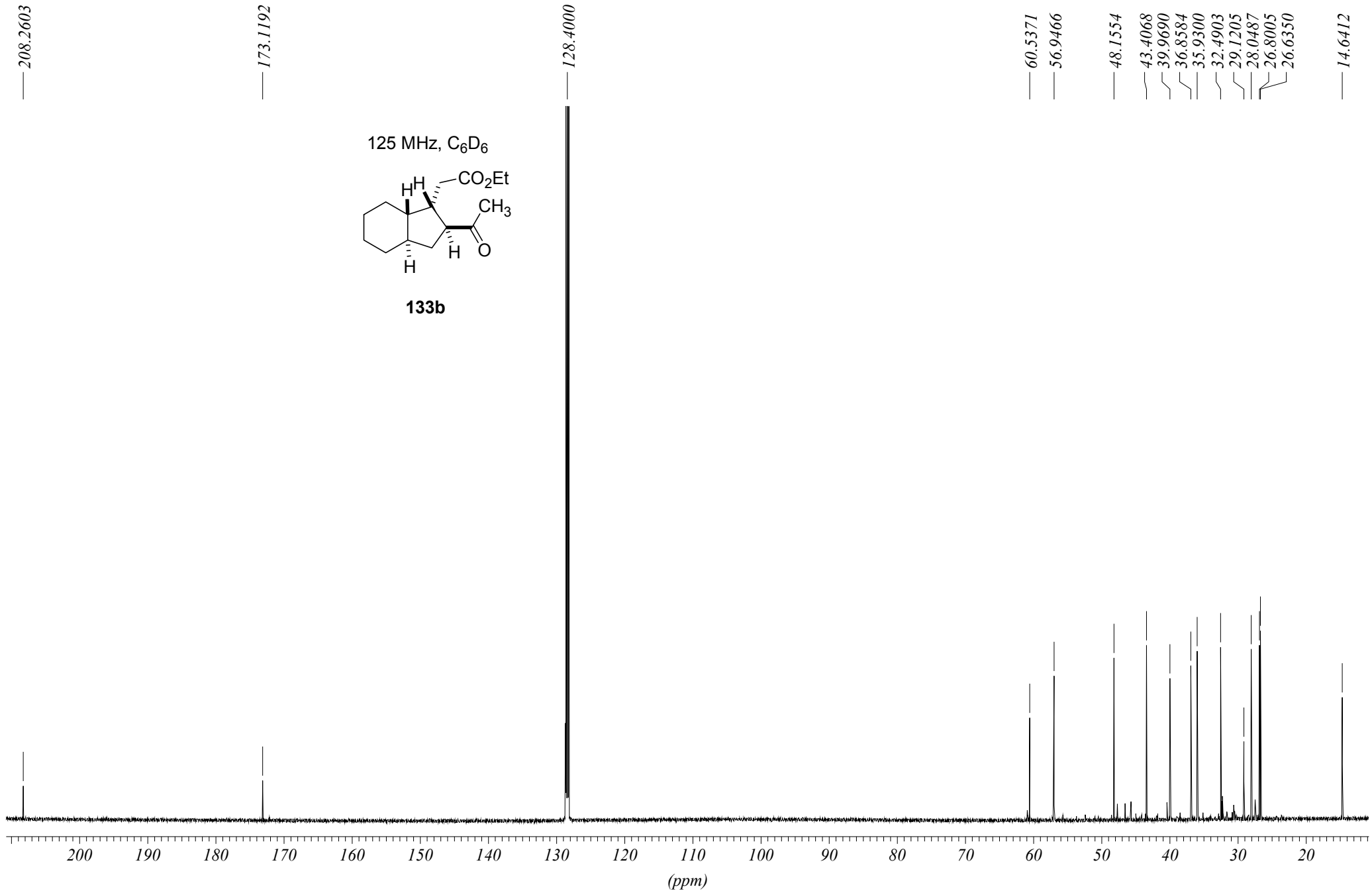

217.1489
210.7625
176.0163
172.9431
86.8292
77.0000
60.3080
55.3982
51.7210
44.5230
42.9454
37.8660
34.7128
31.4872
29.8601
29.0732
25.9505
25.9219
14.1493
100 MHz, CDCl3
H
H
CO2Et
CH3
H
O
H
133a
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

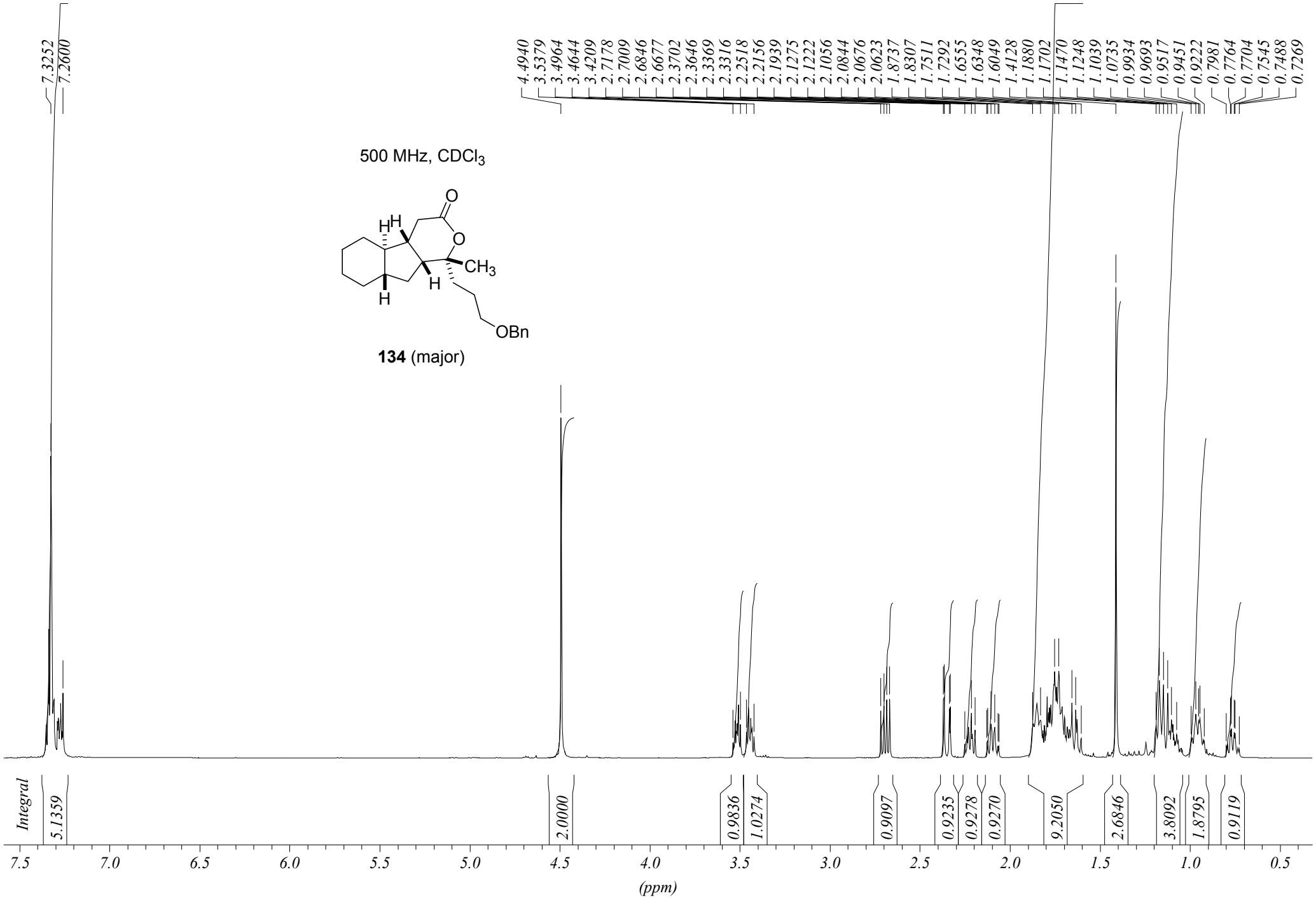

7.2600
2.7614
2.1649
1.5205
1.4958
0.8435
0.8368
0.8212
0.8148
500 MHz, CDCl3
NOE irrad. at 2.83 ppm
H
H
CO2Et
CH3
H
O
H
133a
Integral
-100.0000
1.8657
6.9516
5.8431
1.8296
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

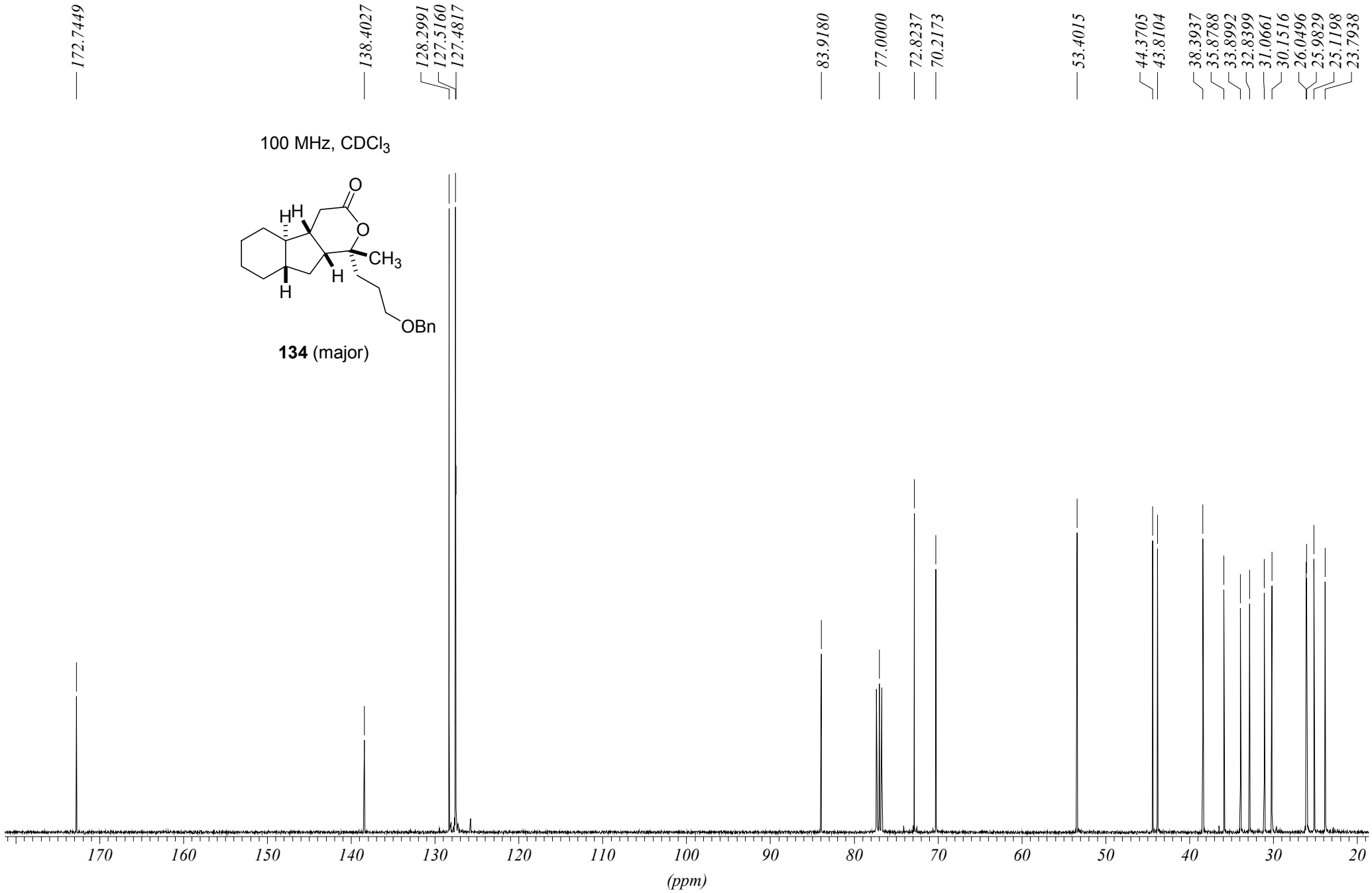

7.2600
4.0626
4.0482
2.7617
2.6595
2.6357
2.5115
2.5029
2.4828
2.4743
2.1786
2.1499
2.1313
1.8332
1.8275
1.8088
1.8037
1.2173
0.8429
0.8365
0.8206
0.8145
500 MHz, CDCl3
NOE irrad. at 2.56 ppm
H
H
CO2Et
CH3
H
O
H
133a
Integral
-100.0000
2.3868
1.3130
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

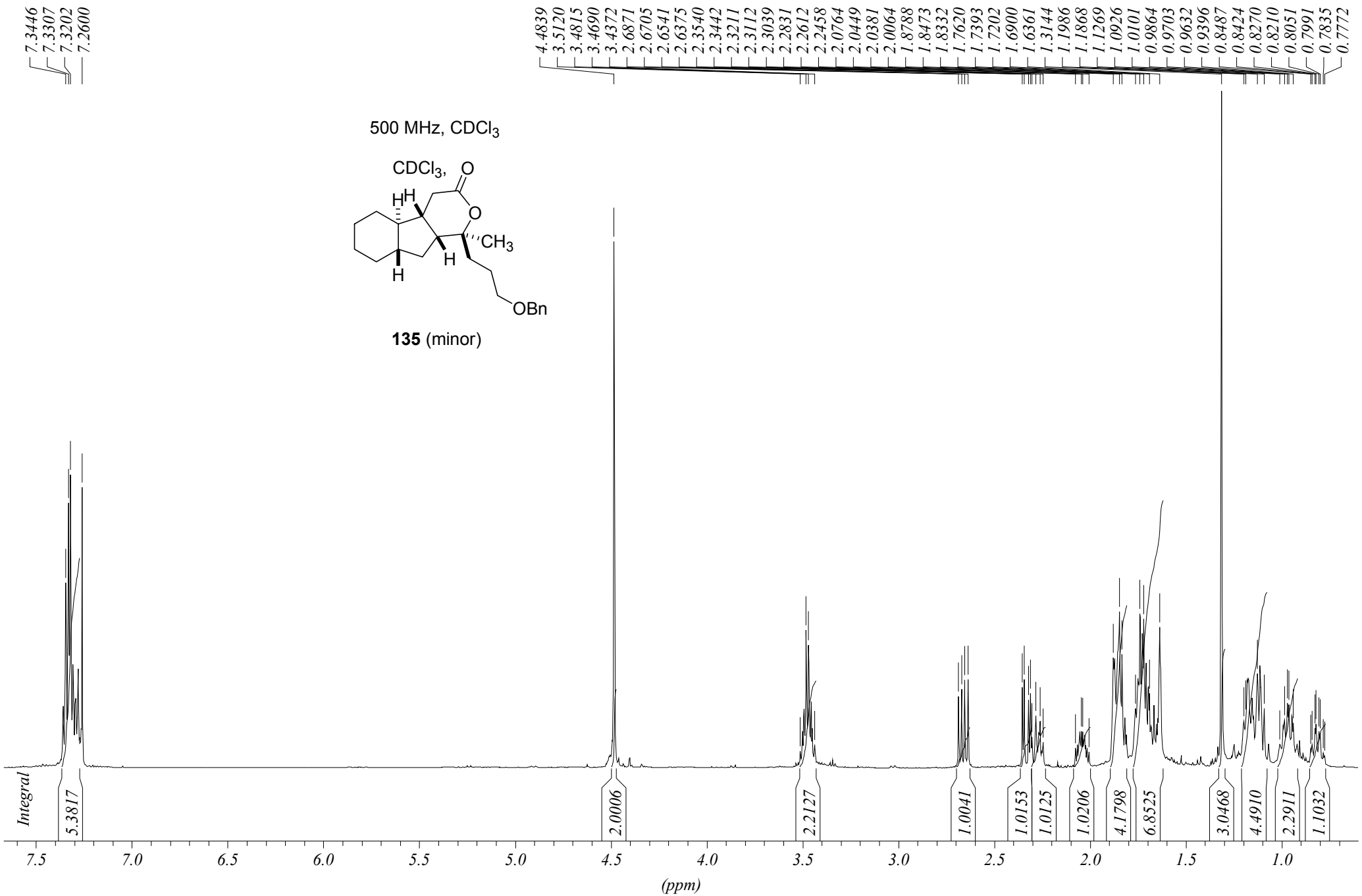

7.1600
3.9678
3.9647
3.9499
3.9458
3.9320
3.9277
2.8495
2.8341
2.5004
2.4926
2.2307
2.2129
2.1608
1.9347
1.9137
1.7158
1.7076
1.5954
1.5728
1.2316
1.2027
1.1801
0.9945
0.9766
0.9587
0.7963
0.7678
0.6520
500 MHz, C6D6
CO2Et
CH3
H
O
(CH3 at 1.91 ppm)
(CH3 at 1.93 ppm)
132b
2.82 : 1.00
133b
Integral
2.0000
1.7085
0.2567
2.5386
0.7266
2.0497
0.3725
4.2947
3.0573
8.1071
1.3296
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

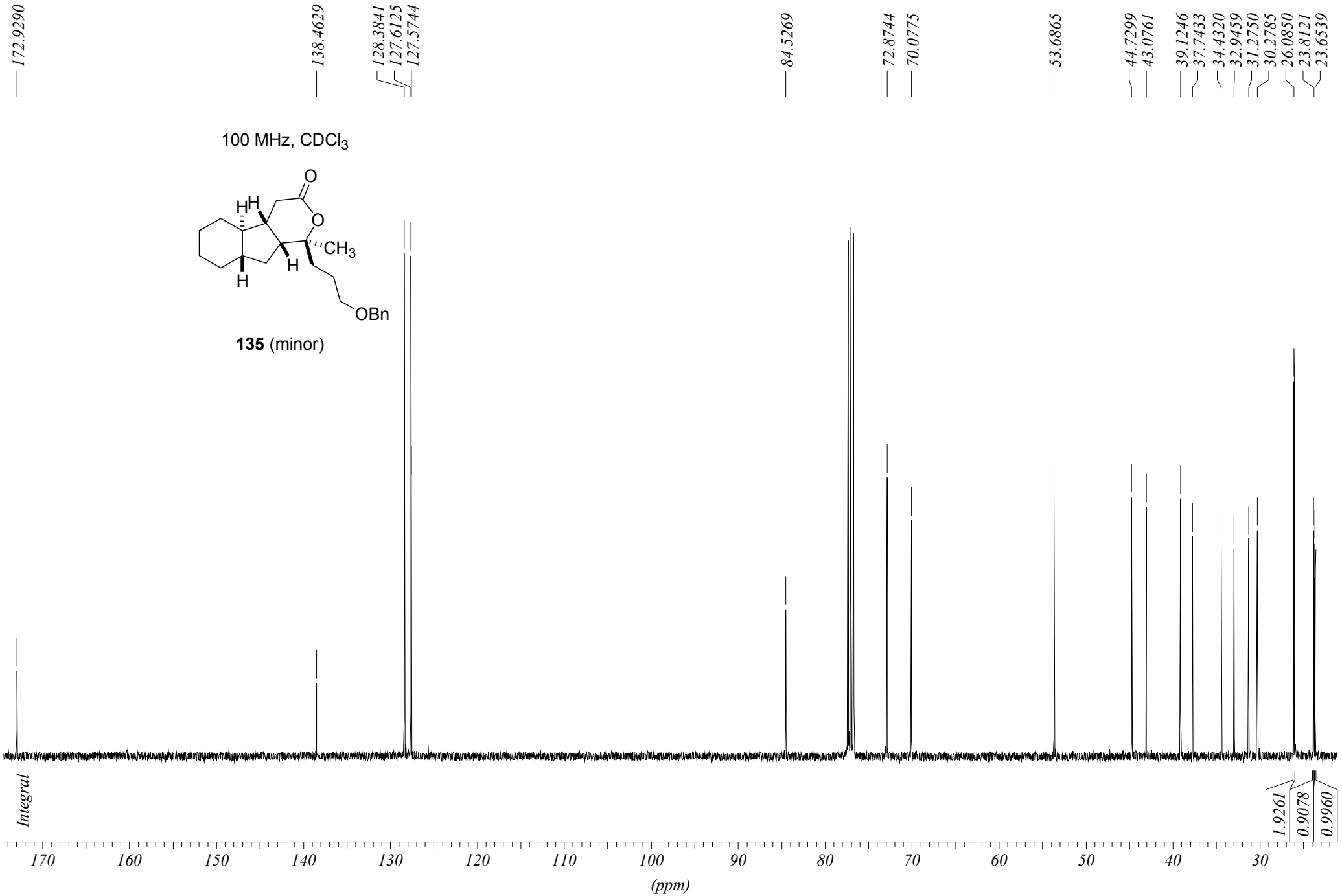

3.9671
3.9627
3.9528
3.9488
2.9055
2.8509
2.5139
2.5076
2.4966
2.4900
2.4790
2.4724
2.2345
2.2238
2.2040
2.1934
1.9356
1.8773
1.8556
1.8468
1.8252
1.7203
1.7148
1.6958
1.6730
1.6606
1.6488
1.6367
1.6195
1.5718
1.5671
1.4589
1.4402
1.4343
1.2235
1.1820
1.1585
1.1417
1.1351
0.9987
0.9844
0.9701
0.9202
0.8516
0.8454
0.8043
0.7984
0.7647
0.7581
0.7163
0.7093
500 MHz, C6D6
CO2Et
CH3
H
H
H
O
133b
(CH3 at 1.93 ppm)
Integral
2.4607
1.0000
0.9844
1.0900
2.9896
1.1461
1.1151
1.2544
2.7206
1.2033
1.4372
2.5873
8.1073
2.4546
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
(ppm)

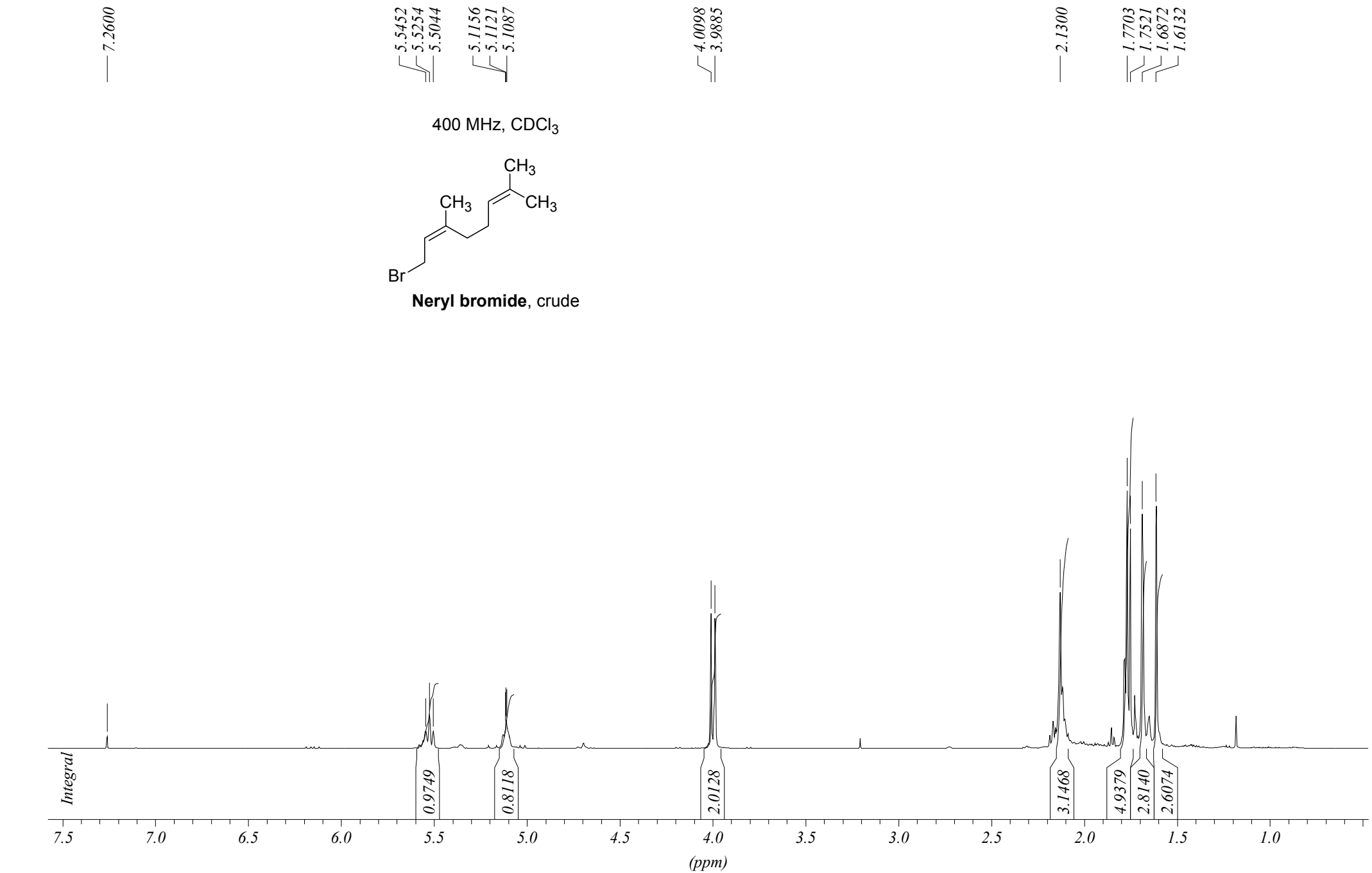

208.2603
173.1192
128.4000
60.5371
56.9466
48.1554
43.4068
39.9690
36.8584
35.9300
32.4903
29.1205
28.0487
26.8005
26.6350
14.6412
125 MHz, C6D6
CO2Et
CH3
H
H
H
O
133b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


7.3252
7.2600
4.4940
3.5379
3.4964
3.4644
3.4209
2.7178
2.7009
2.6846
2.6677
2.3702
2.3646
2.3369
2.3316
2.2518
2.2156
2.1939
2.1275
2.1222
2.1056
2.0844
2.0676
2.0623
1.8737
1.8307
1.7511
1.7292
1.6555
1.6348
1.6049
1.4128
1.1880
1.1702
1.1470
1.1248
1.1039
1.0735
0.9934
0.9693
0.9517
0.9451
0.9222
0.7981
0.7764
0.7704
0.7545
0.7488
0.7269
500 MHz, CDCl3
O
H
H
O
CH3
H
H
OBn
134 (major)
Integral
5.1359
2.0000
0.9836
1.0274
0.9097
0.9235
0.9278
0.9270
9.2050
2.6846
3.8092
1.8795
0.9119
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


172.7449
138.4027
128.2991
127.5160
127.4817
83.9180
77.0000
72.8237
70.2173
53.4015
44.3705
43.8104
38.3937
35.8788
33.8992
32.8399
31.0661
30.1516
26.0496
25.9829
25.1198
23.7938
100 MHz, CDCl3
O
H
H
O
CH3
H
H
OBn
134 (major)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

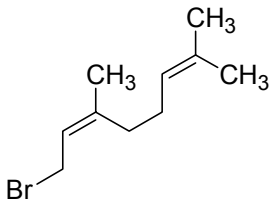

7.3446
7.3307
7.3202
7.2600
4.4839
3.5120
3.4815
3.4690
3.4372
2.6871
2.6705
2.6541
2.6375
2.3540
2.3442
2.3211
2.3112
2.3039
2.2831
2.2612
2.2458
2.0764
2.0449
2.0381
2.0064
1.8788
1.8473
1.8332
1.7620
1.7393
1.7202
1.6900
1.6361
1.3144
1.1986
1.1868
1.1269
1.0926
1.0101
0.9864
0.9703
0.9632
0.9396
0.8487
0.8424
0.8270
0.8210
0.8051
0.7991
0.7835
0.7772
500 MHz, CDCl3
CDCl3,
O
H
H
O
CH3
H
H
OBn
135 (minor)
Integral
5.3817
2.0006
2.2127
1.0041
1.0153
1.0125
1.0206
4.1798
6.8525
3.0468
4.4910
2.2911
1.1032
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


172.9290
138.4629
128.3841
127.6125
127.5744
84.5269
72.8744
70.0775
53.6865
44.7299
43.0761
39.1246
37.7433
34.4320
32.9459
31.2750
30.2785
26.0850
23.8121
23.6539
100 MHz, CDCl3
O
H
H
O
CH3
H
H
OBn
135 (minor)
Integral
1.9261
0.9078
0.9960
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
(ppm)

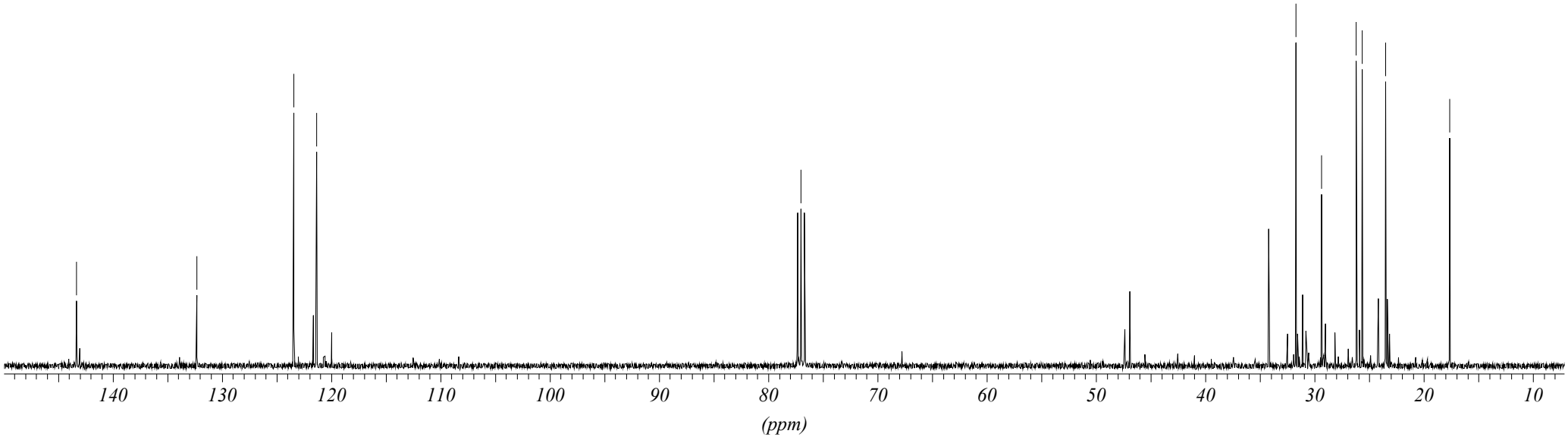

7.2600
5.5452
5.5254
5.5044
5.1156
5.1121
5.1087
4.0098
3.9885
2.1300
1.7703
1.7521
1.6872
1.6132
400 MHz, CDCl3
CH3
CH3
CH3
Br
Neryl bromide, crude
Integral
0.9749
0.8118
2.0128
3.1468
4.9379
2.8140
2.6074
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

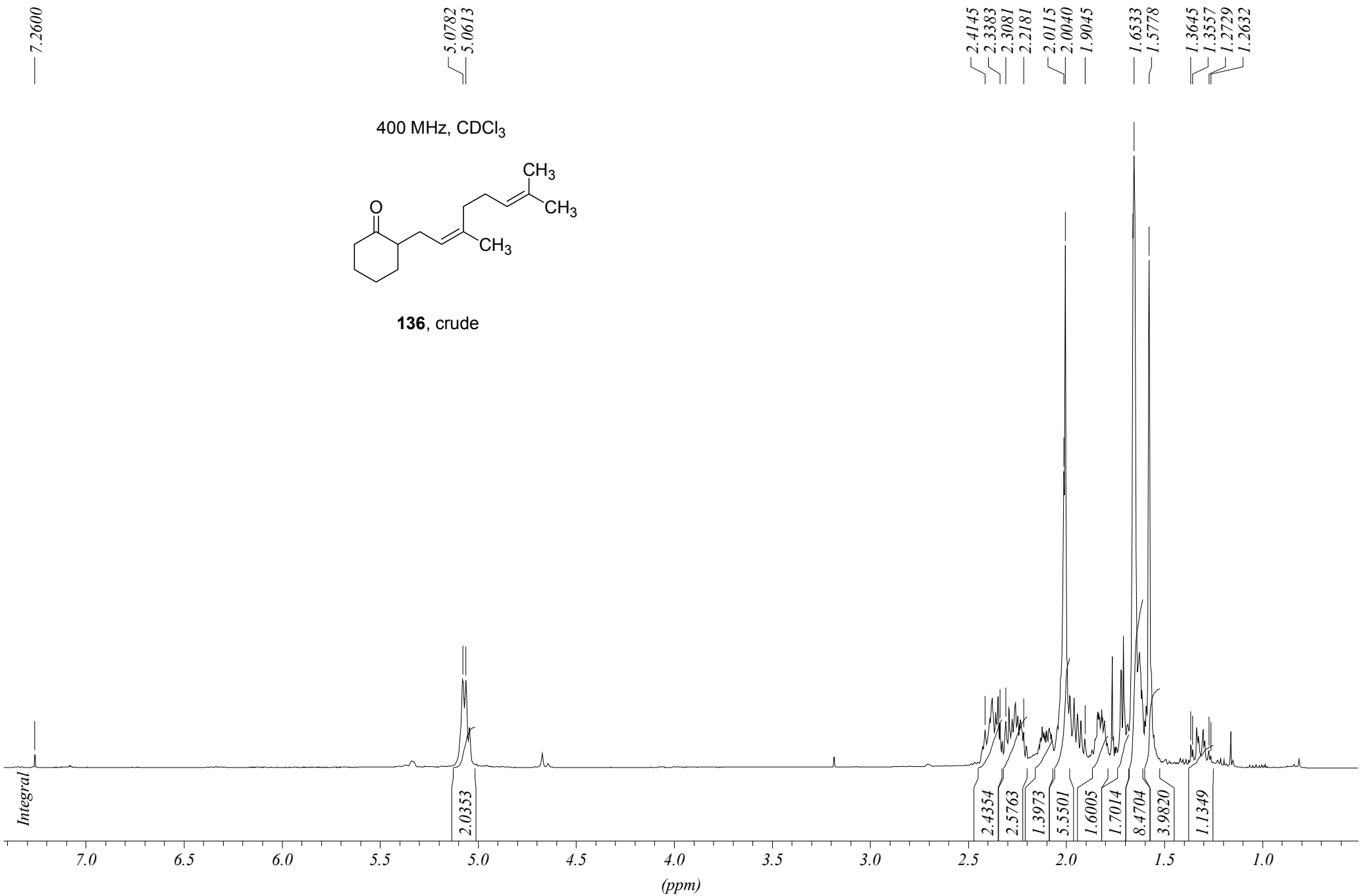
143.3068
132.2982
123.4464
121.3354
77.0000
31.7311
29.3533
26.1849
25.6495
23.5099
17.6493

100 MHz, $CDCl_3$



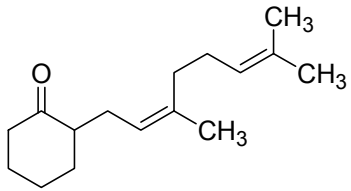
Neryl bromide, crude



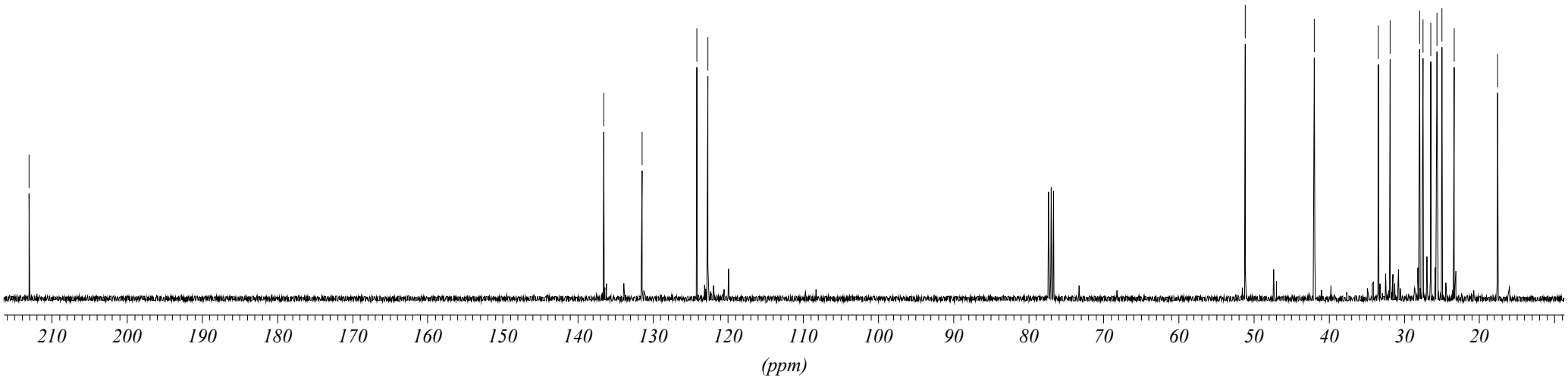

7.2600
5.0782
5.0613
2.4145
2.3383
2.3081
2.2181
2.0115
2.0040
1.9045
1.6533
1.5778
1.3645
1.3557
1.2729
1.2632
400 MHz, CDCl3
CH3
CH3
CH3
O
136, crude
Integral
2.0353
2.4354
2.5763
1.3973
5.5501
1.6005
1.7014
8.4704
3.9820
1.1349
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

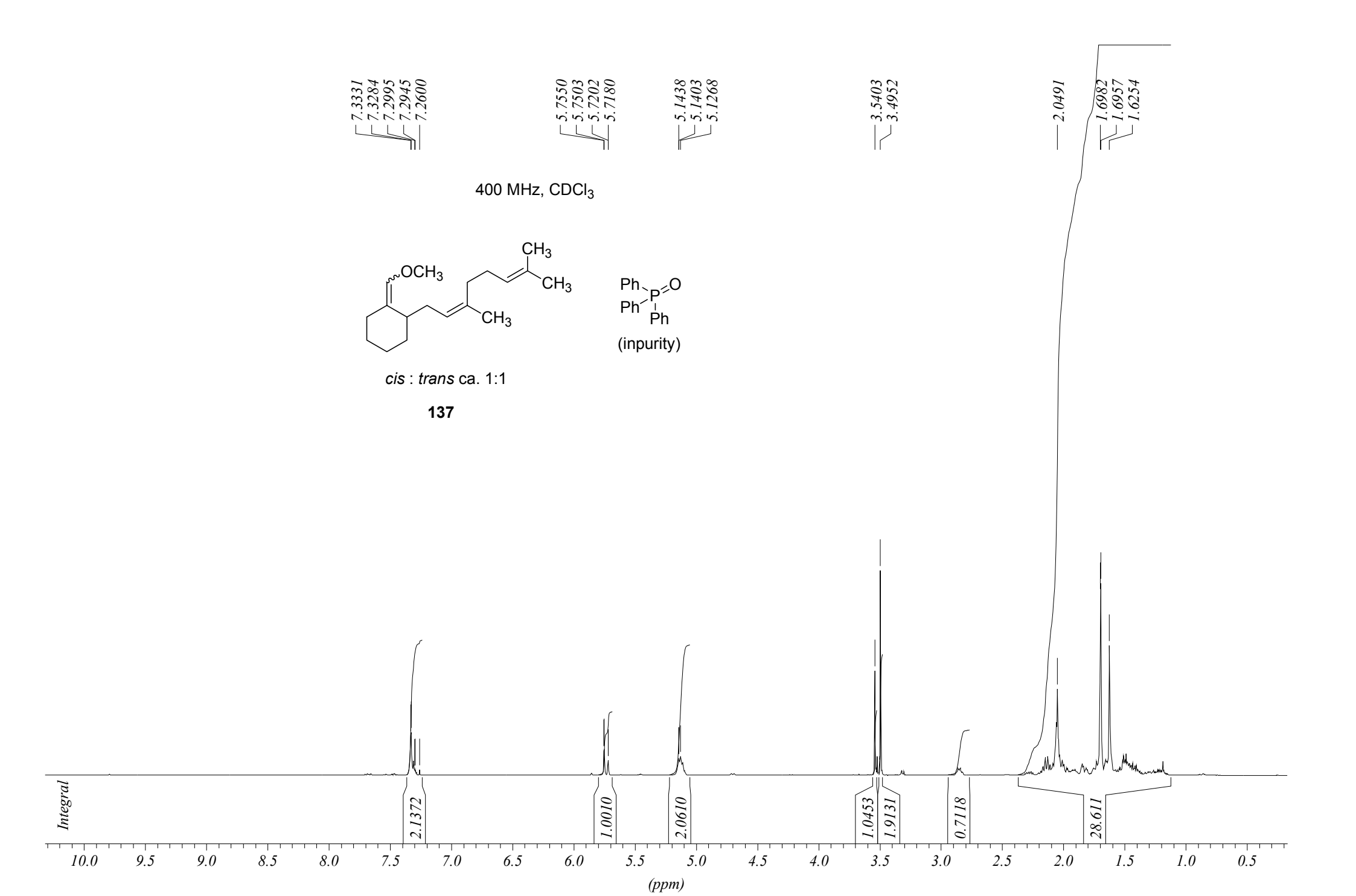
213.0145
136.5717
131.4332
124.1856
122.6500
51.1666
41.9661
33.4229
31.8530
27.9472
27.4747
26.4344
25.6361
24.9636
23.3613
17.5540

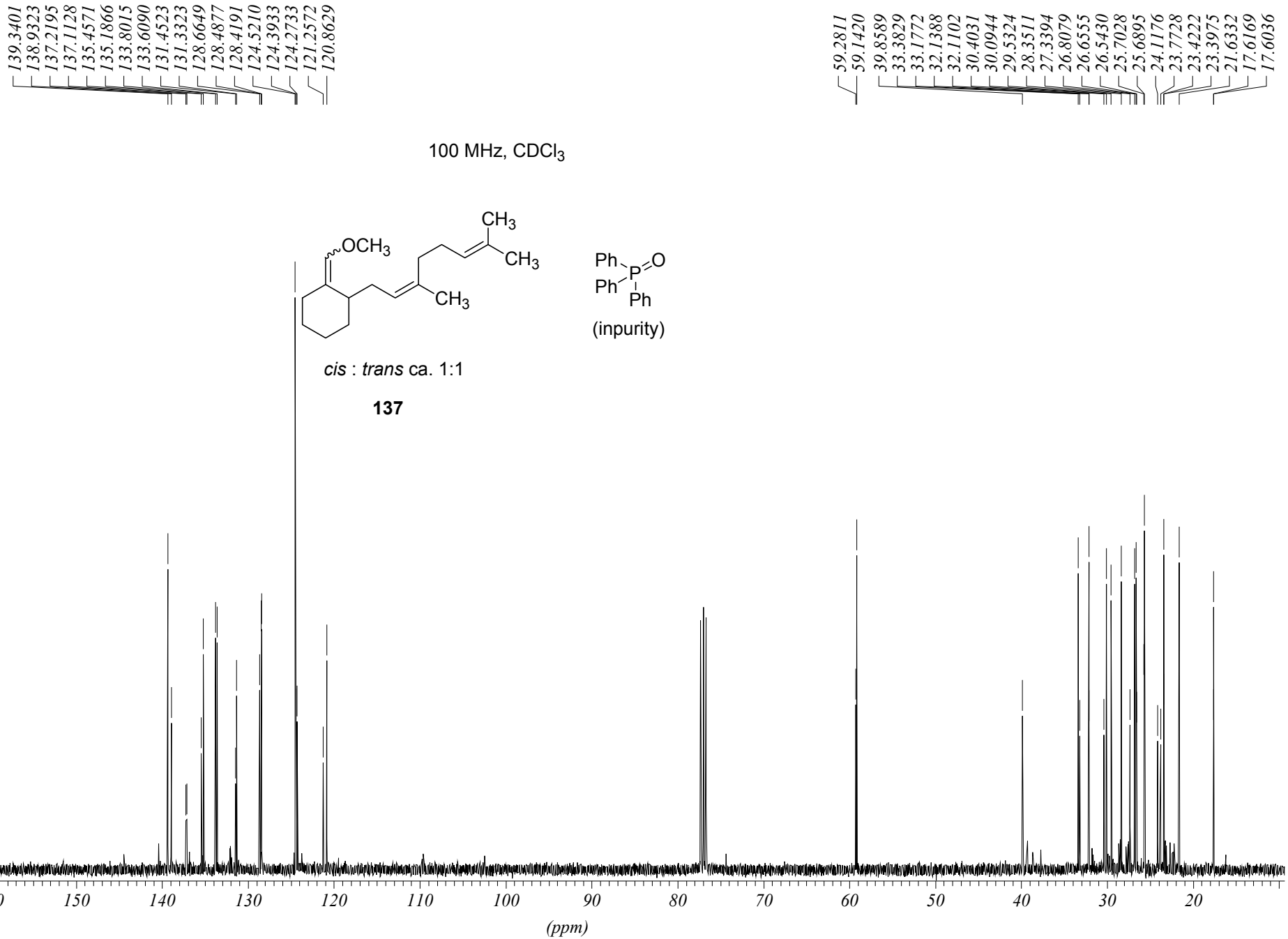
100 MHz, $CDCl_3$

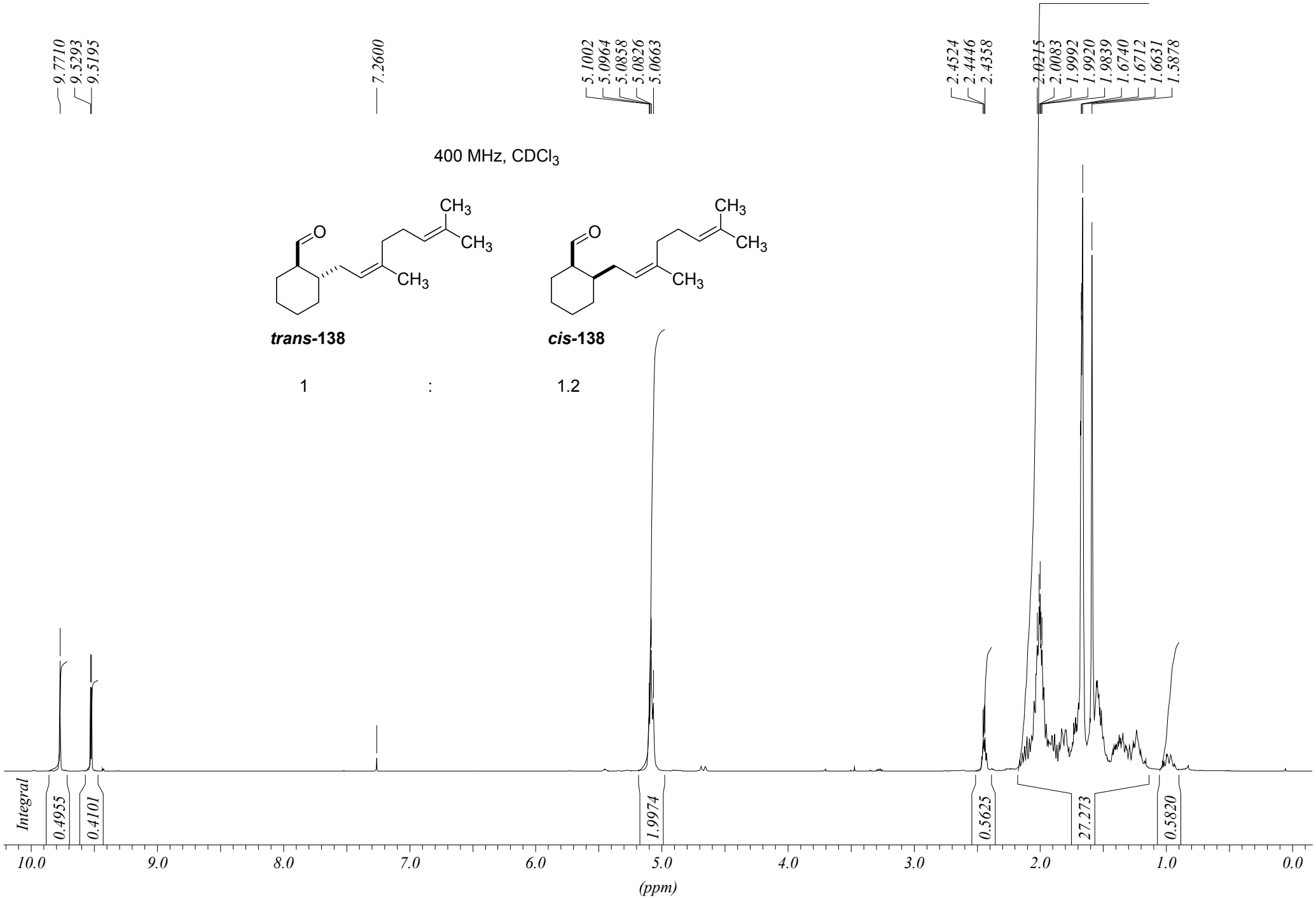


136, crude




7.3331
7.3284
7.2995
7.2945
7.2600
5.7550
5.7503
5.7202
5.7180
5.1438
5.1403
5.1268
3.5403
3.4952
2.0491
1.6982
1.6957
1.6254
400 MHz, CDCl3
OCH3
CH3
CH3
CH3
Ph
Ph
P
O
Ph
(inpurity)
cis : trans ca. 1:1
137
Integral
2.1372
1.0010
2.0610
1.0453
1.9131
0.7118
28.611
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


139.3401
138.9323
137.2195
137.1128
135.4571
135.1866
133.8015
133.6090
131.4523
131.3323
128.6649
128.4877
128.4191
124.5210
124.3933
124.2733
121.2572
120.8629
59.2811
59.1420
39.8589
33.3829
33.1772
32.1388
32.1102
30.4031
30.0944
29.5324
28.3511
27.3394
26.8079
26.6555
26.5430
25.7028
25.6895
24.1176
23.7728
23.4222
23.3975
21.6332
17.6169
17.6036
100 MHz, CDCl3
OCH3
CH3
CH3
CH3
Ph
P
O
Ph
Ph
(inpurity)
cis : trans ca. 1:1
137
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


9.7710
9.5293
9.5195
7.2600
5.1002
5.0964
5.0858
5.0826
5.0663
2.4524
2.4446
2.4358
2.0215
2.0083
1.9992
1.9920
1.9839
1.6740
1.6712
1.6631
1.5878
400 MHz, CDCl3
CH3
CH3
CH3
O
trans-138
CH3
CH3
CH3
O
cis-138
1 : 1.2
Integral
0.4955
0.4101
1.9974
0.5625
27.273
0.5820
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

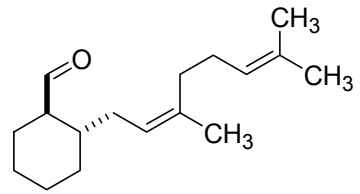
205.5211
205.1686

137.0175
136.6727
131.5609
131.5113
124.2637
124.1742
124.1361
123.4502
122.5547

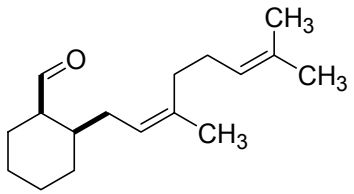
77.3182
77.0000
76.6818

55.3277
51.8372
51.5381
37.8565
37.4964
32.9276
32.0054
31.9521
30.6813
29.2923
26.4325
26.3487
26.0991
25.6571
25.1979
24.7235
23.9957
23.7518
23.6966
23.3670
23.3555
17.5693

100 MHz, $CDCl_3$

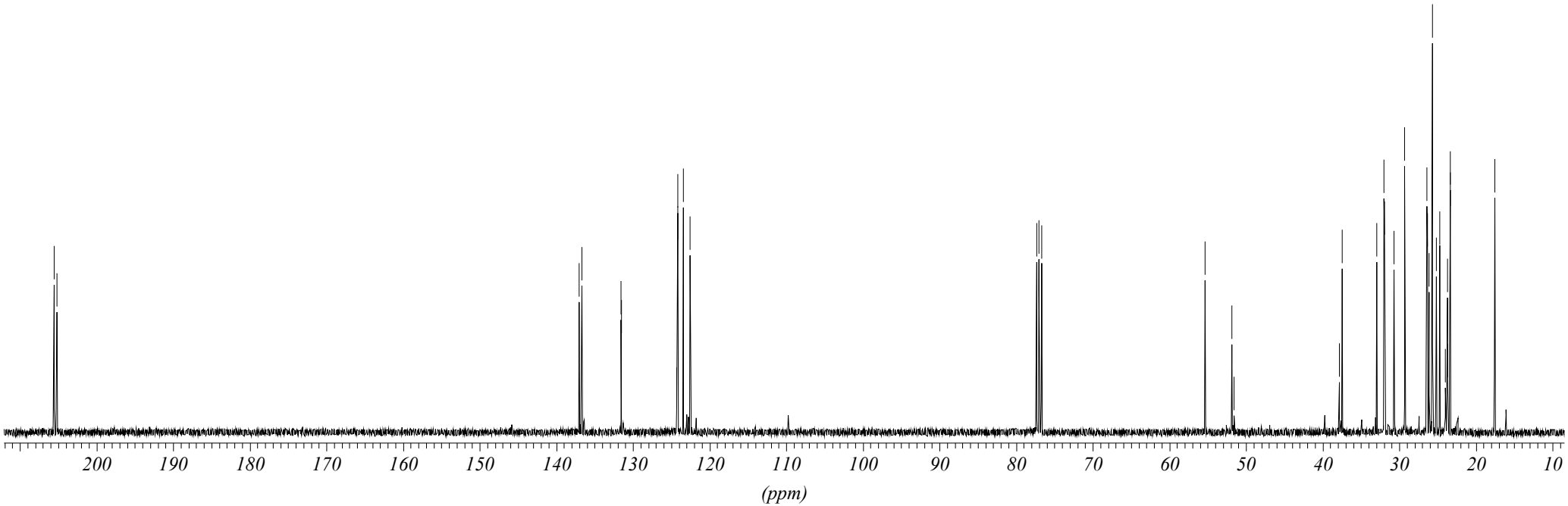


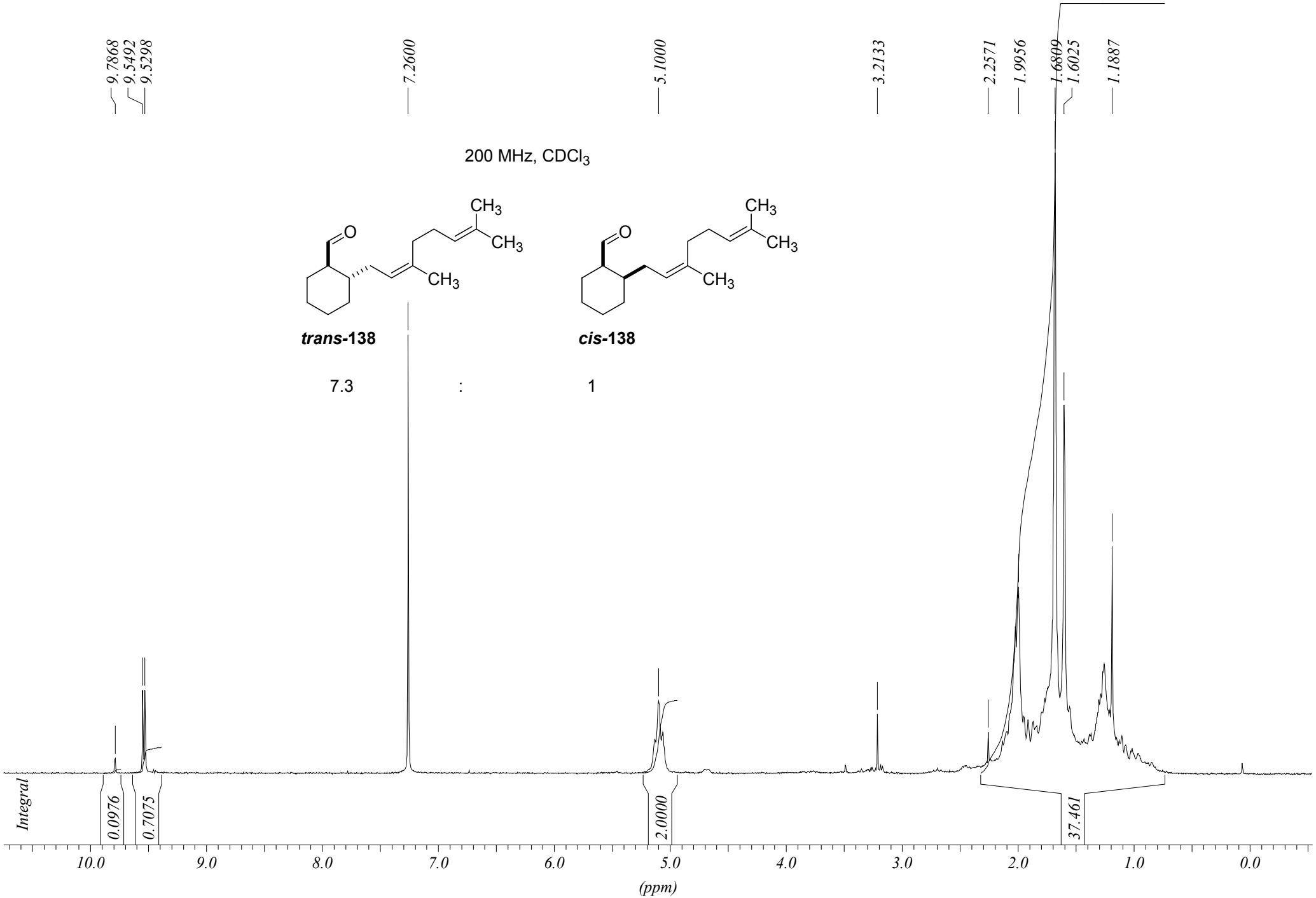
***trans*-138**

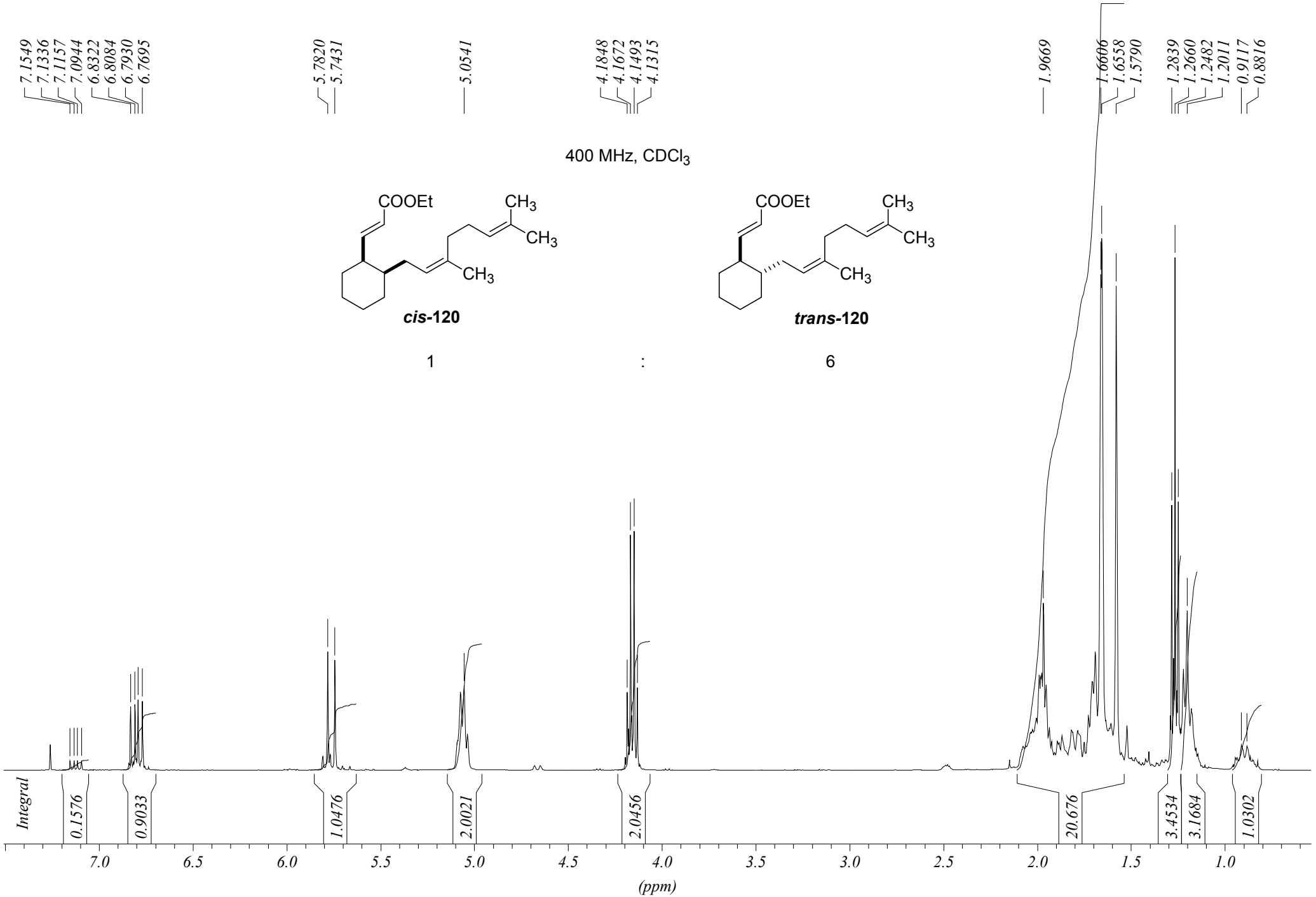


***cis*-138**

1 : 1.2

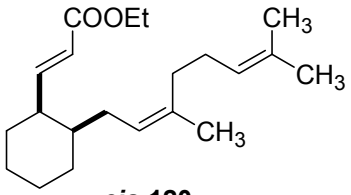



9.7868
9.5492
9.5298
7.2600
5.1000
3.2133
2.2571
1.9956
1.6809
1.6025
1.1887
200 MHz, CDCl3
CH3
CH3
CH3
O
trans-138
CH3
CH3
CH3
O
cis-138
7.3
:
1
Integral
0.0976
0.7075
2.0000
37.461
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

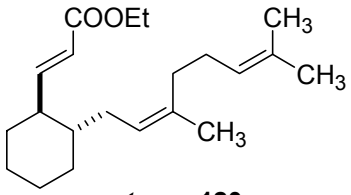

7.1549
7.1336
7.1157
7.0944
6.8322
6.8084
6.7930
6.7695
5.7820
5.7431
5.0541
4.1848
4.1672
4.1493
4.1315
1.9669
1.6606
1.6558
1.5790
1.2839
1.2660
1.2482
1.2011
0.9117
0.8816
400 MHz, CDCl3
COOEt
CH3
CH3
CH3
cis-120
1
:
COOEt
CH3
CH3
CH3
trans-120
6
Integral
0.1576
0.9033
1.0476
2.0021
2.0456
20.676
3.4534
3.1684
1.0302
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

166.7034
153.7095
136.0516
131.3322
124.2904
123.0596
120.5999
77.0000
60.0089
46.6283
42.0328
32.7656
32.6303
31.9654
31.2700
26.4230
25.9886
25.6247
25.5790
23.3975
23.3727
17.5216
14.2103

100 MHz, $CDCl_3$

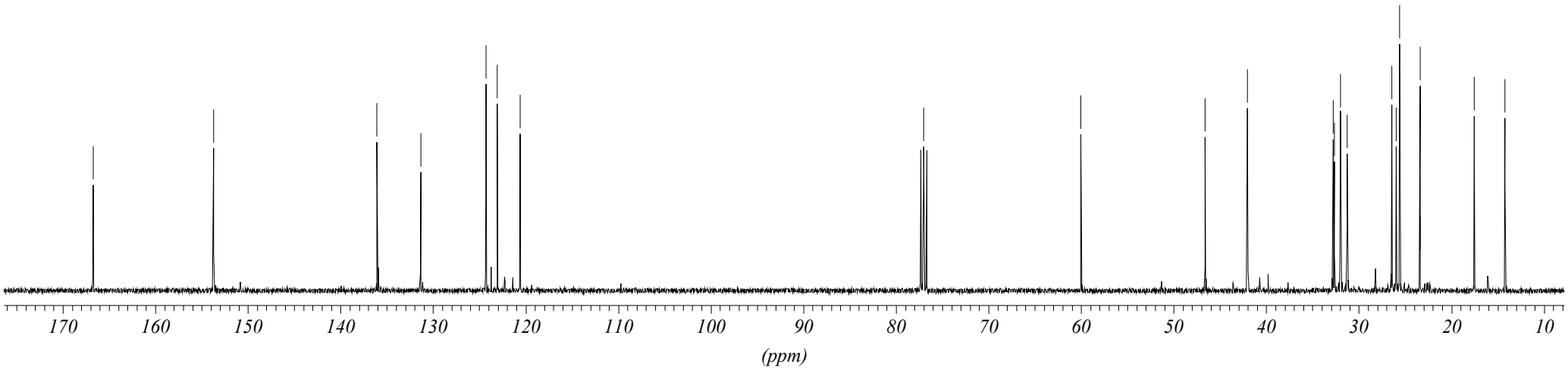


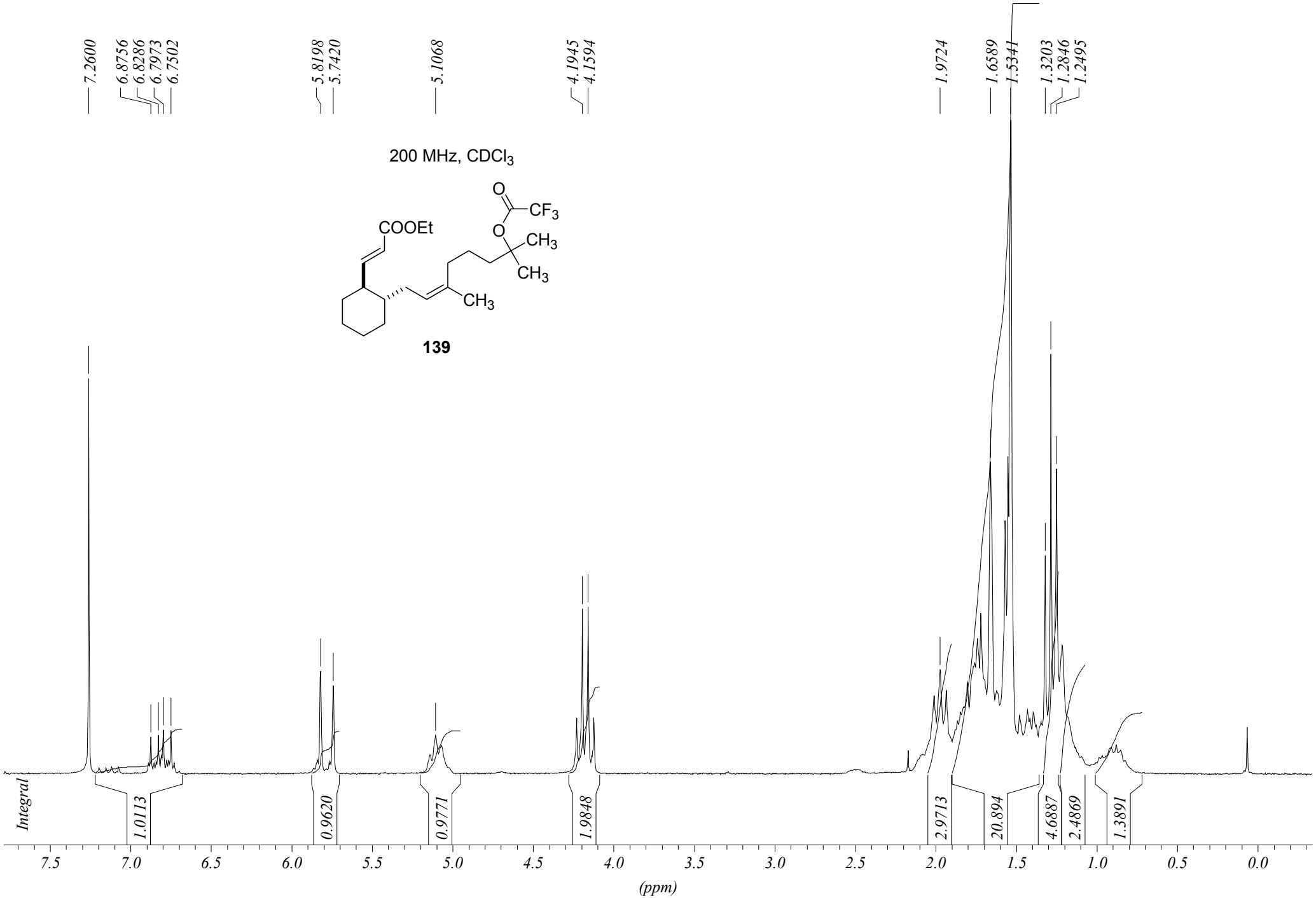
***cis*-120**

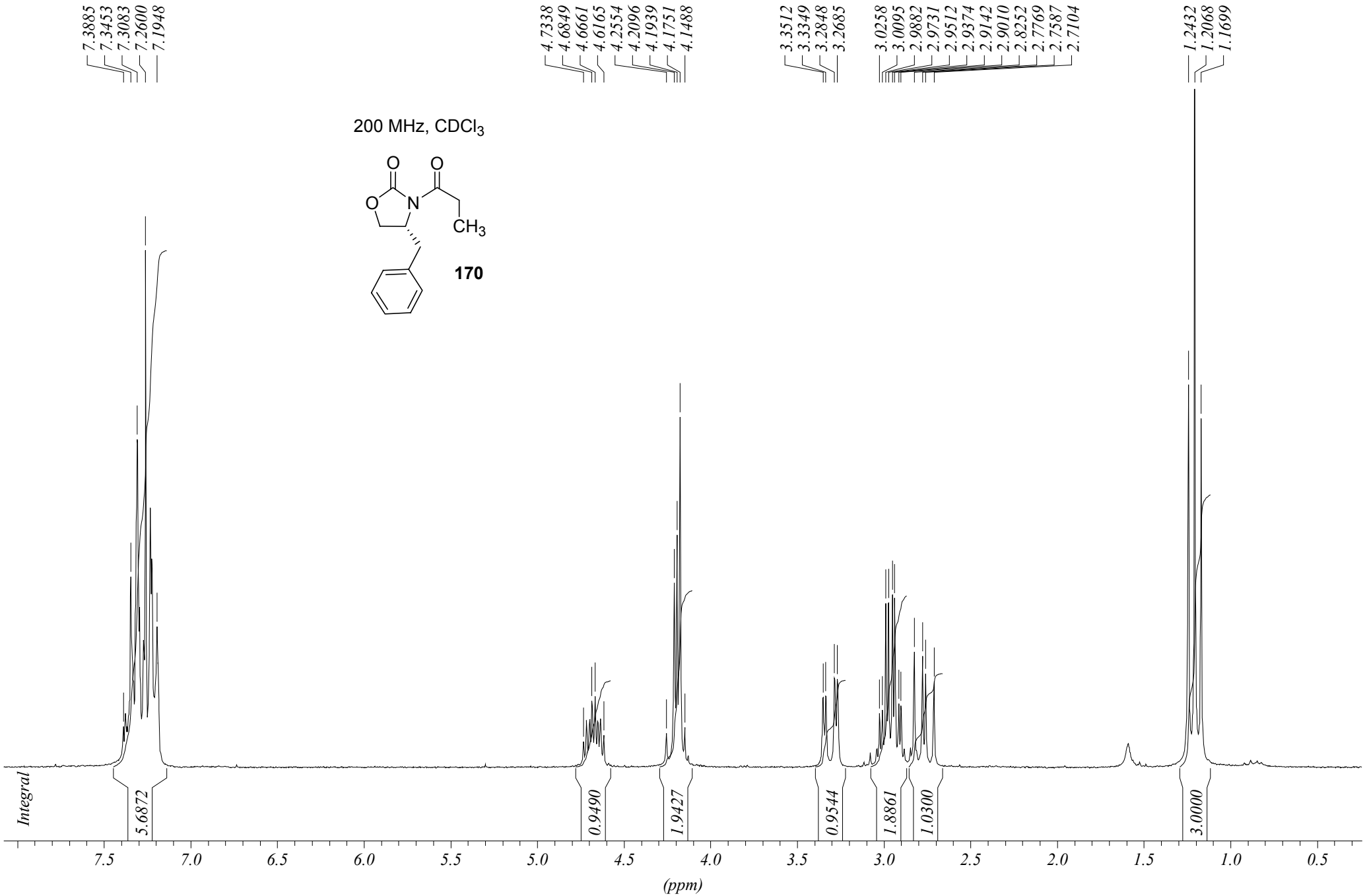


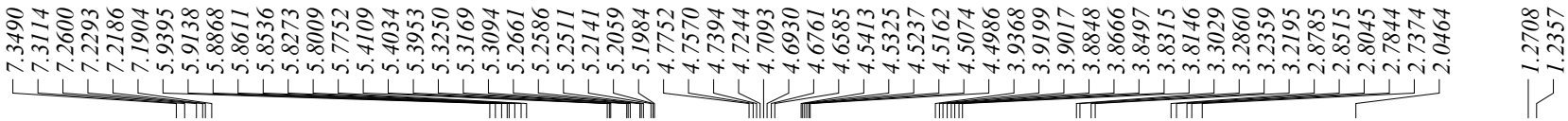
***trans*-120**

1 : 6

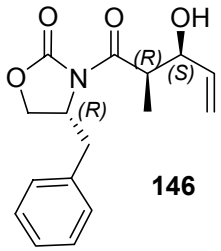



7.2600
6.8756
6.8286
6.7973
6.7502
5.8198
5.7420
5.1068
4.1945
4.1594
1.9724
1.6589
1.5341
1.3203
1.2846
1.2495
200 MHz, CDCl3
COOEt
O
CF3
O
CH3
CH3
CH3
139
Integral
1.0113
0.9620
0.9771
1.9848
2.9713
20.894
4.6887
2.4869
1.3891
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


7.3885
7.3453
7.3083
7.2600
7.1948
4.7338
4.6849
4.6661
4.6165
4.2554
4.2096
4.1939
4.1751
4.1488
3.3512
3.3349
3.2848
3.2685
3.0258
3.0095
2.9882
2.9731
2.9512
2.9374
2.9142
2.9010
2.8252
2.7769
2.7587
2.7104
1.2432
1.2068
1.1699
200 MHz, CDCl3
O
O
O
N
CH3
170
Integral
5.6872
0.9490
1.9427
0.9544
1.8861
1.0300
3.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)



200 MHz, $CDCl_3$



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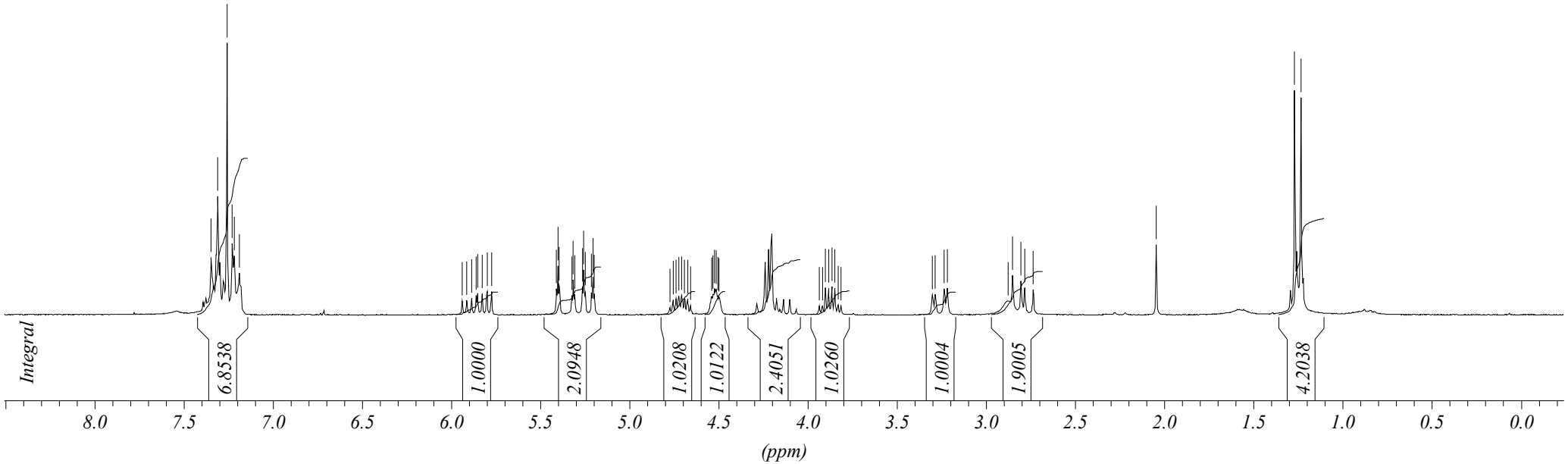
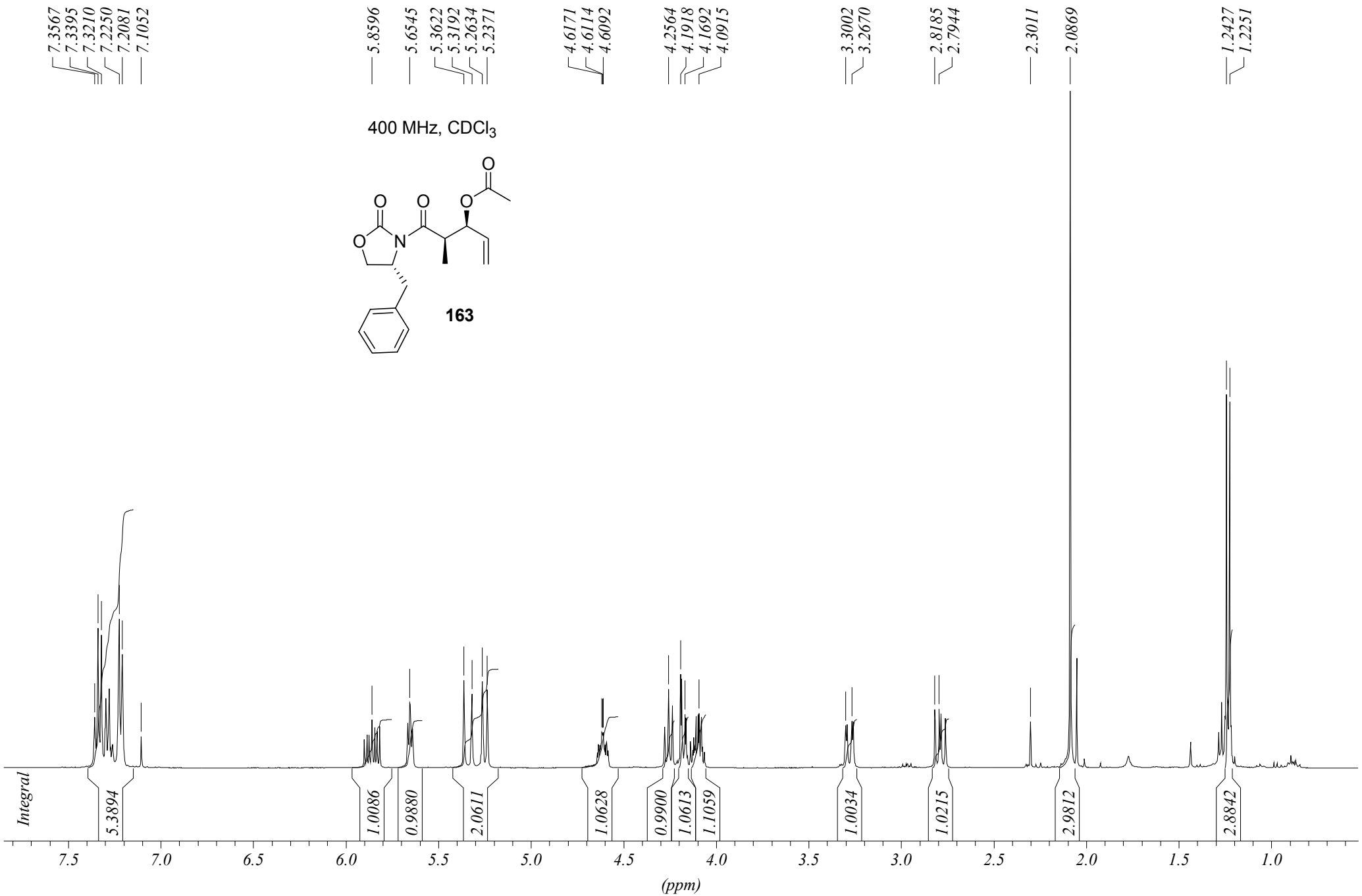
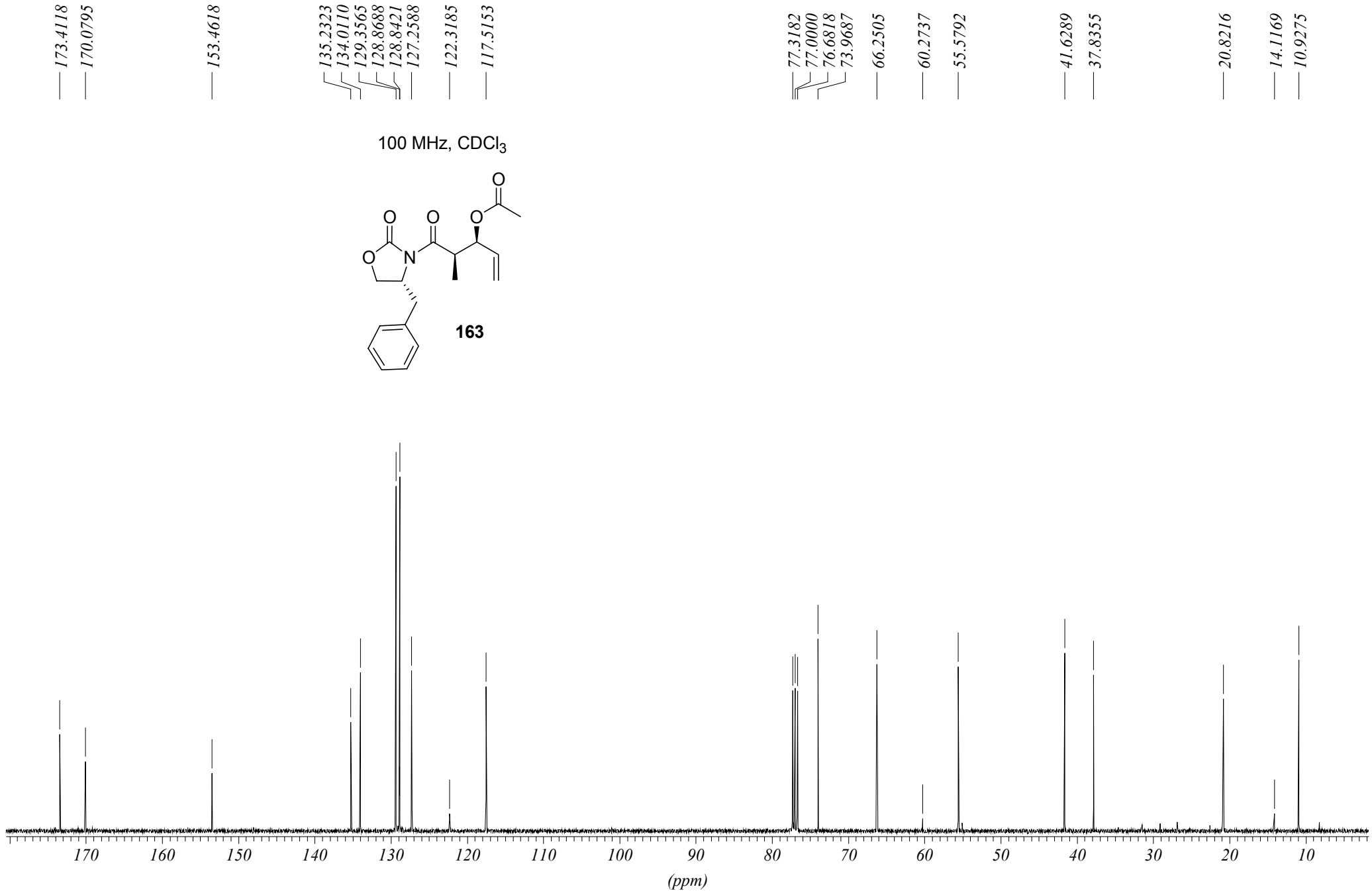
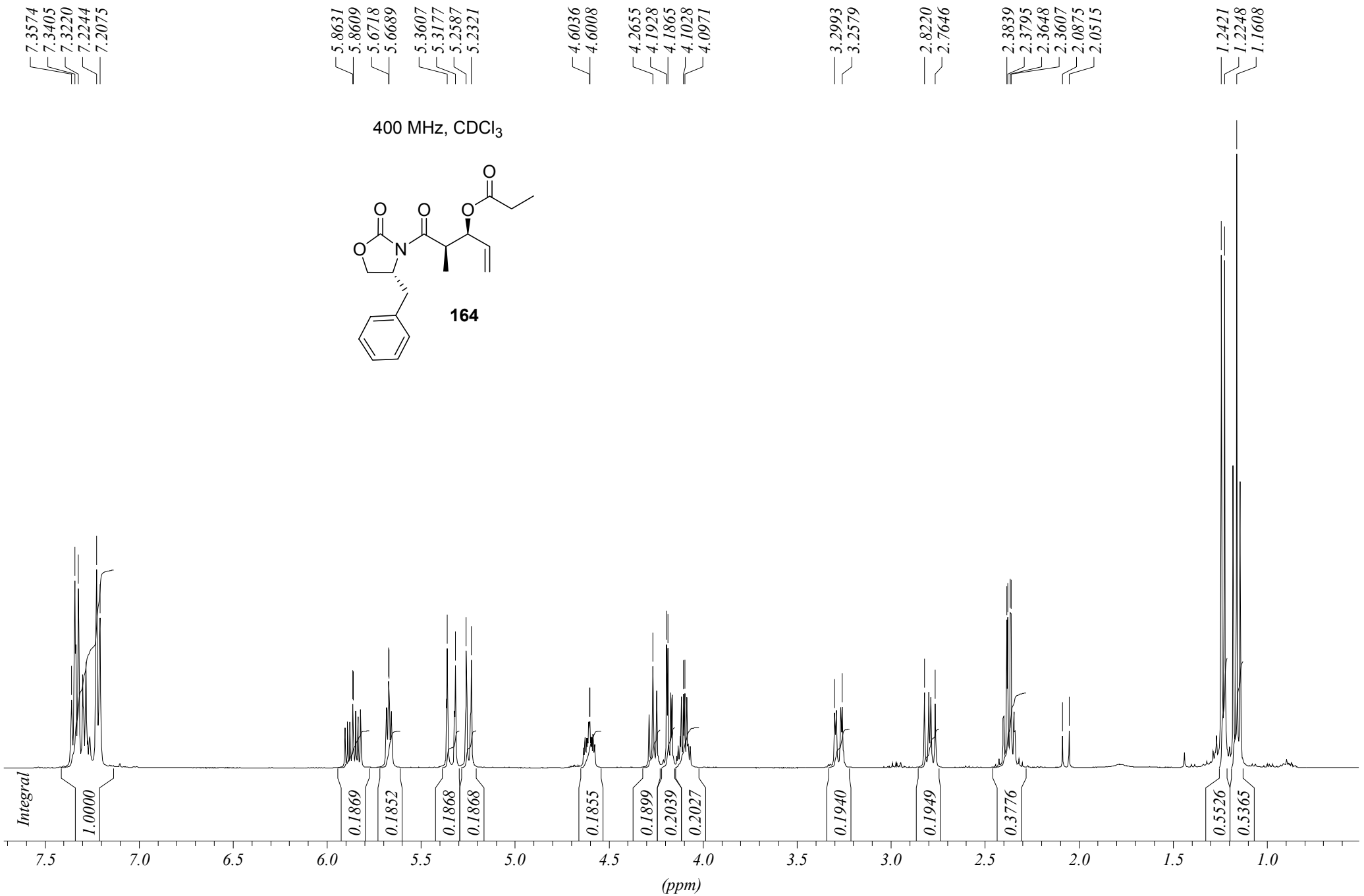


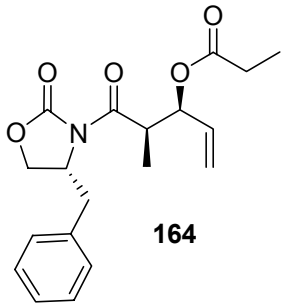

7.3567
7.3395
7.3210
7.2250
7.2081
7.1052
5.8596
5.6545
5.3622
5.3192
5.2634
5.2371
4.6171
4.6114
4.6092
4.2564
4.1918
4.1692
4.0915
3.3002
3.2670
2.8185
2.7944
2.3011
2.0869
1.2427
1.2251
400 MHz, CDCl3
163
Integral
5.3894
1.0086
0.9880
2.0611
1.0628
0.9900
1.0613
1.1059
1.0034
1.0215
2.9812
2.8842
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


173.4118
170.0795
153.4618
135.2323
134.0110
129.3565
128.8688
128.8421
127.2588
122.3185
117.5153
77.3182
77.0000
76.6818
73.9687
66.2505
60.2737
55.5792
41.6289
37.8355
20.8216
14.1169
10.9275
100 MHz, CDCl3
163
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

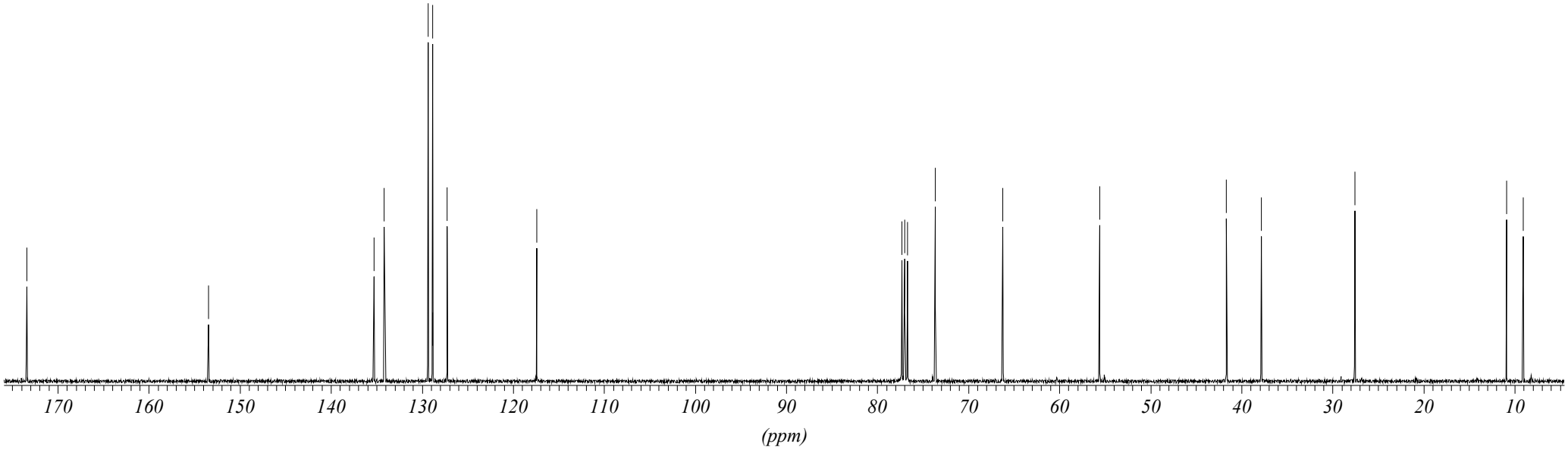

7.3574
7.3405
7.3220
7.2244
7.2075
5.8631
5.8609
5.6718
5.6689
5.3607
5.3177
5.2587
5.2321
4.6036
4.6008
4.2655
4.1928
4.1865
4.1028
4.0971
3.2993
3.2579
2.8220
2.7646
2.3839
2.3795
2.3648
2.3607
2.0875
2.0515
1.2421
1.2248
1.1608
400 MHz, CDCl3
164
Integral
1.0000
0.1869
0.1852
0.1868
0.1868
0.1855
0.1899
0.2039
0.2027
0.1940
0.1949
0.3776
0.5526
0.5365
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

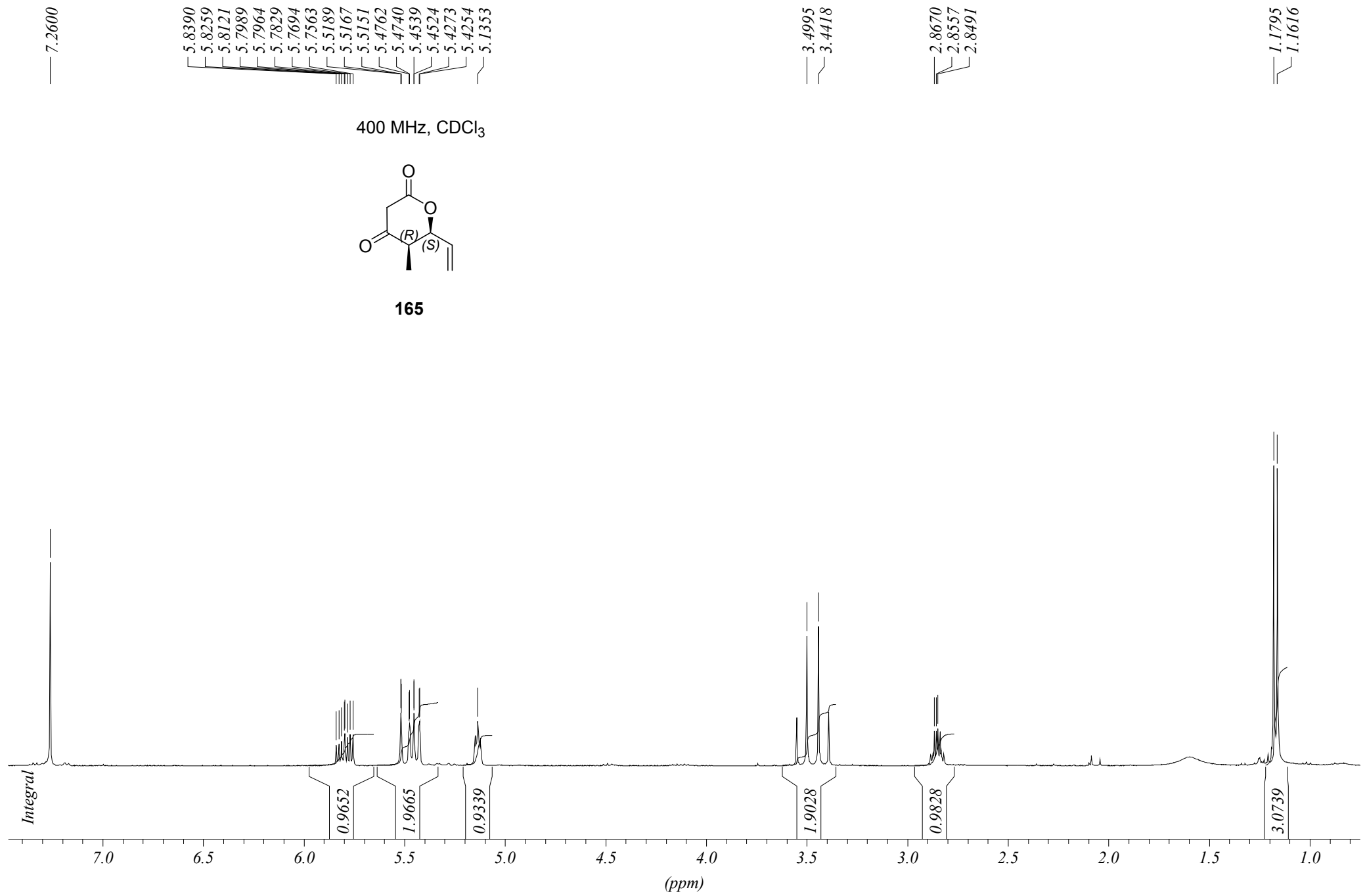
173.4099
153.4676
135.2495
134.1349
129.3527
128.8630
128.8383
127.2474
117.3934
77.3182
77.0000
76.6818
73.6525
66.2467
55.5906
41.6708
37.8279
27.5643
10.8933
9.0547

100 MHz, $CDCl_3$

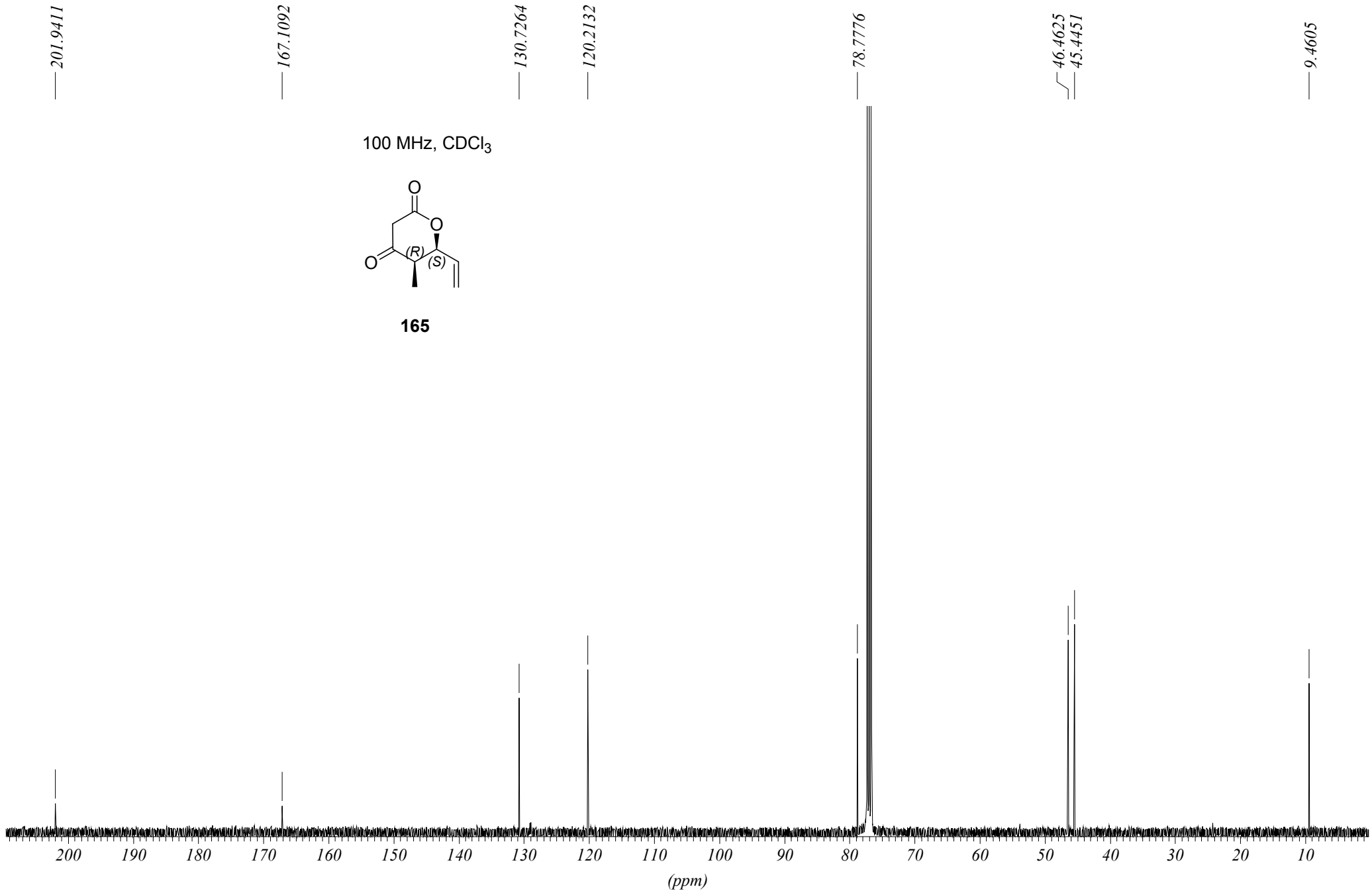


164



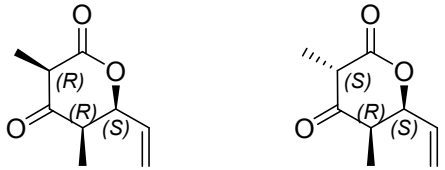

7.2600
5.8390
5.8259
5.8121
5.7989
5.7964
5.7829
5.7694
5.7563
5.5189
5.5167
5.5151
5.4762
5.4740
5.4539
5.4524
5.4273
5.4254
5.1353
3.4995
3.4418
2.8670
2.8557
2.8491
1.1795
1.1616
400 MHz, CDCl3
O
O
O
(R)
(S)
Integral
0.9652
1.9665
0.9339
1.9028
0.9828
3.0739
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

165

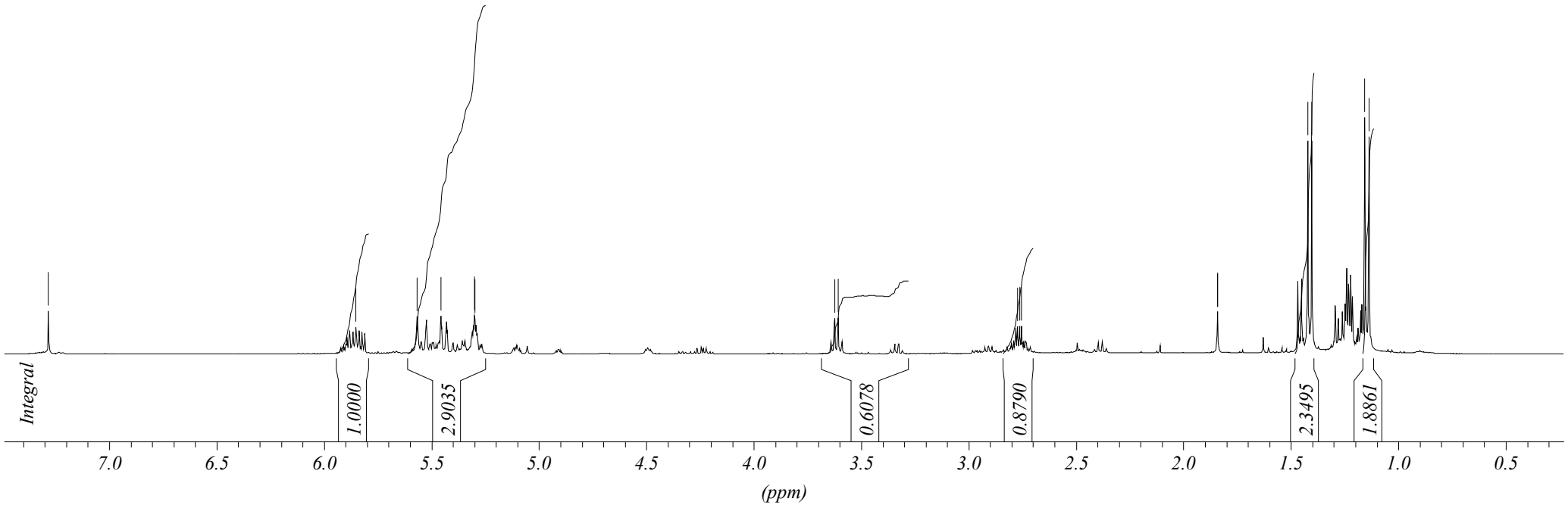

201.9411
167.1092
130.7264
120.2132
78.7776
46.4625
45.4451
9.4605
100 MHz, CDCl3
O
O
O
(R)
(S)
165
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

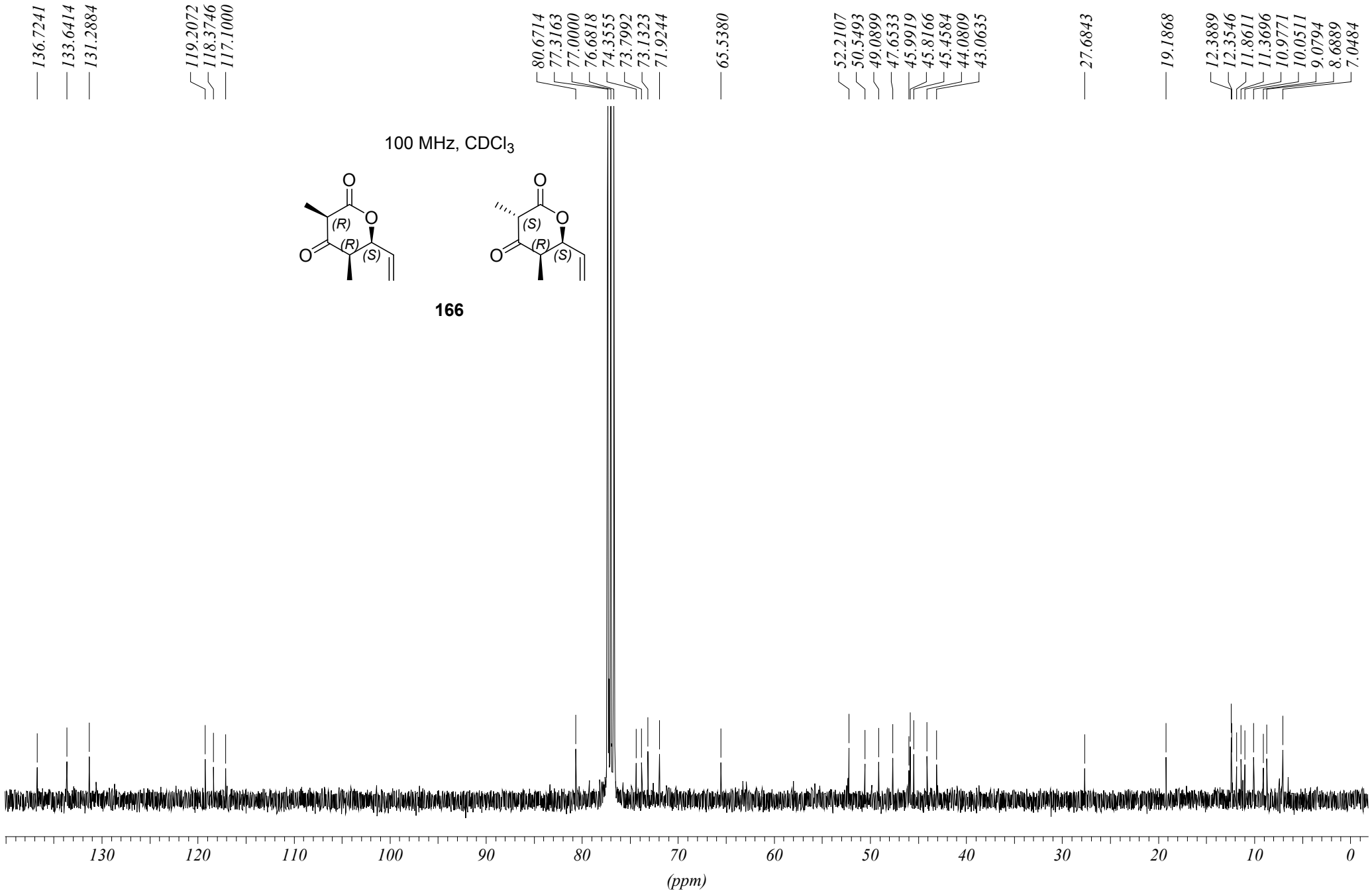
7.2837
5.8530
5.5676
5.4560
5.3011
5.2970
3.6239
3.6070
2.7731
2.7627
2.7543
1.8429
1.8414
1.4211
1.4042
1.1561
1.1373

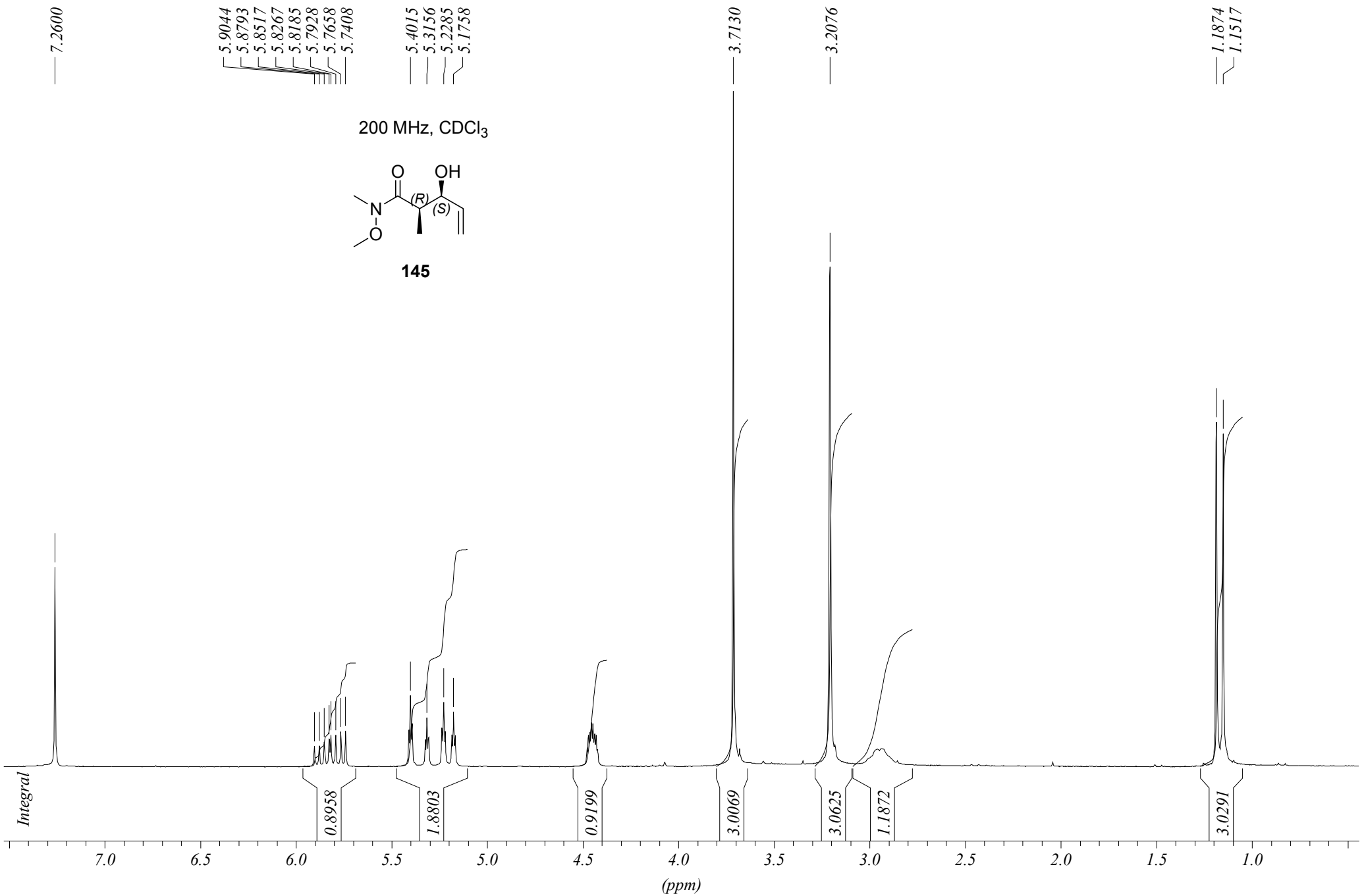
400 MHz, $CDCl_3$

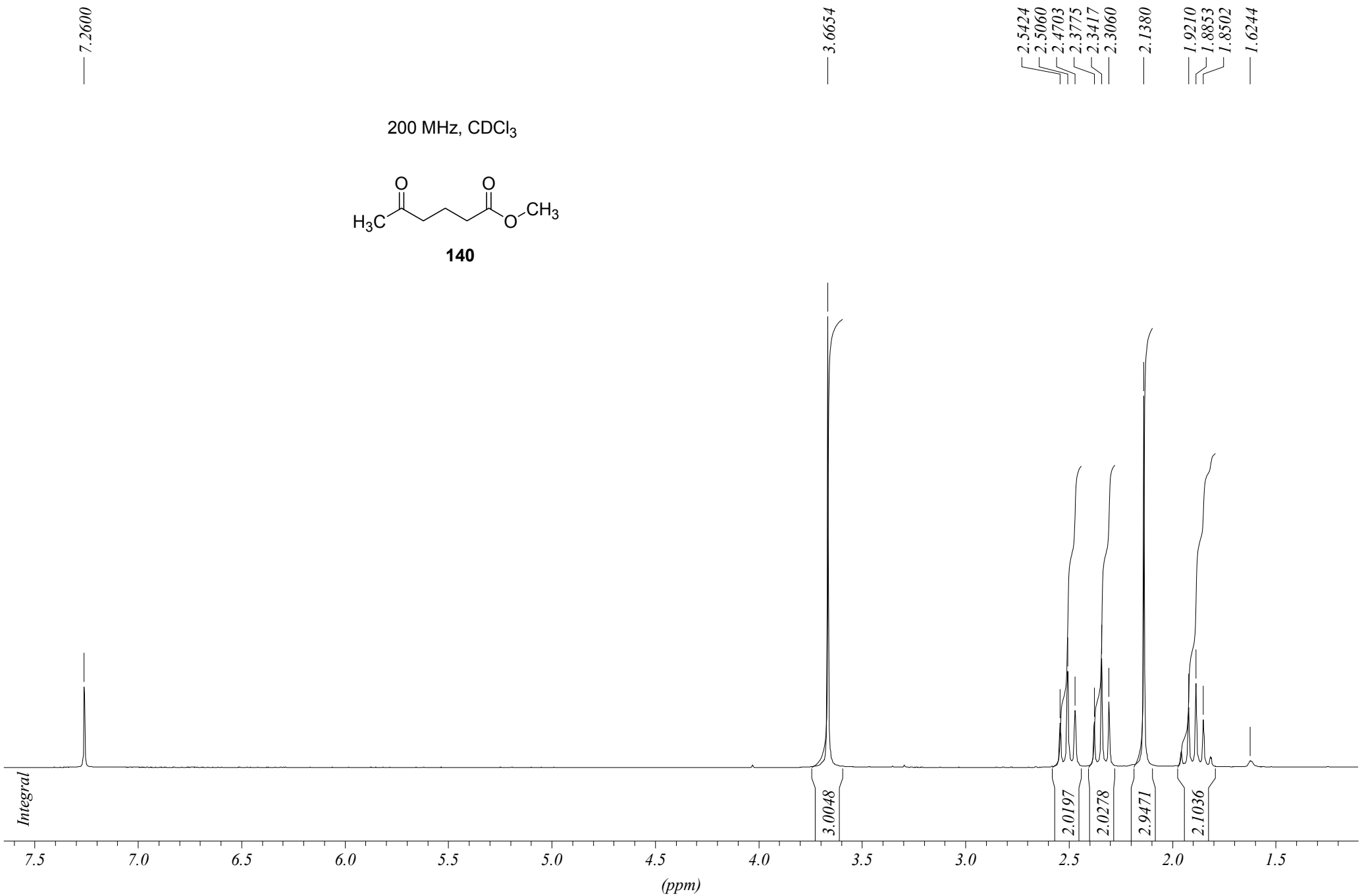


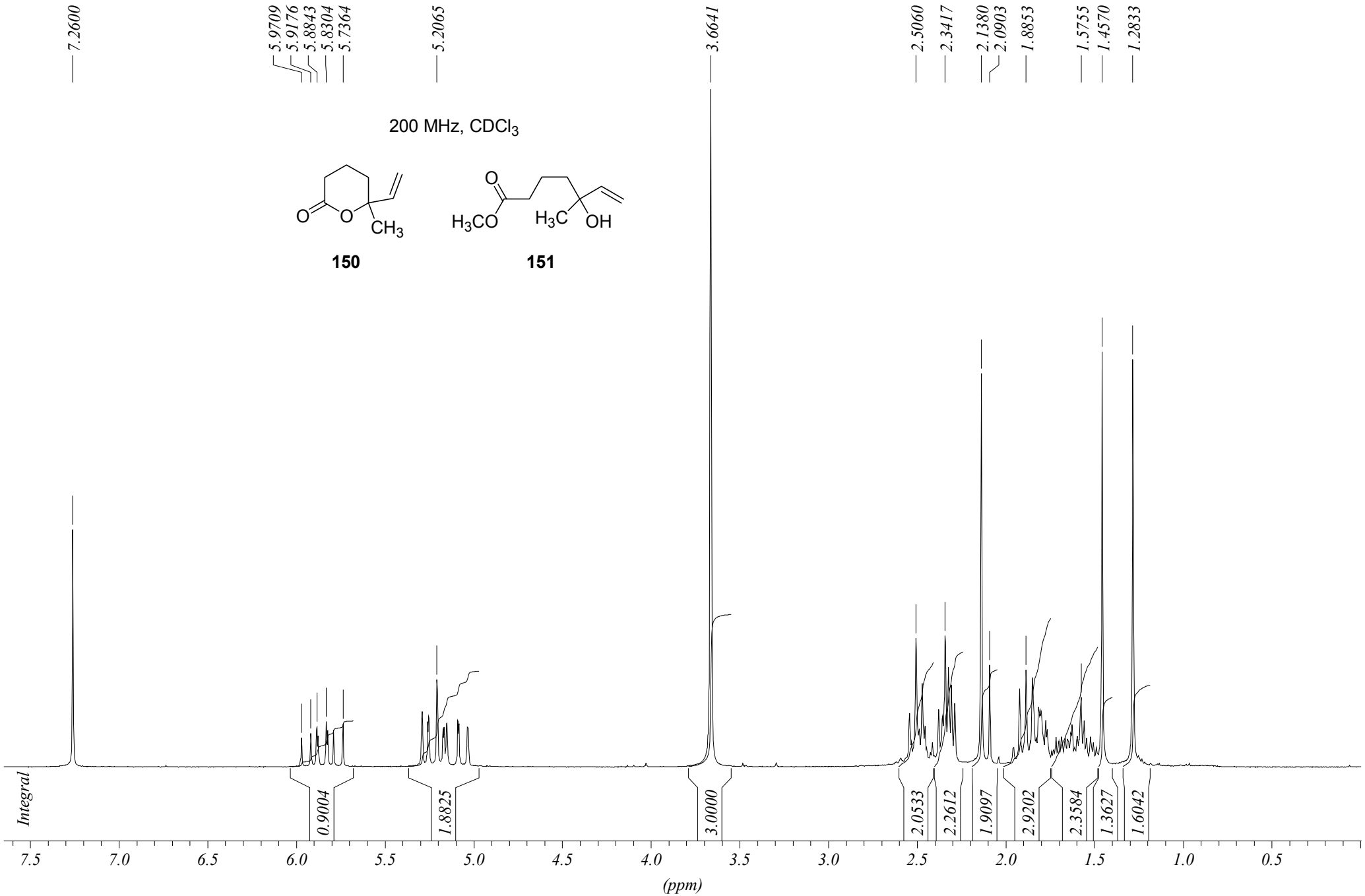
166

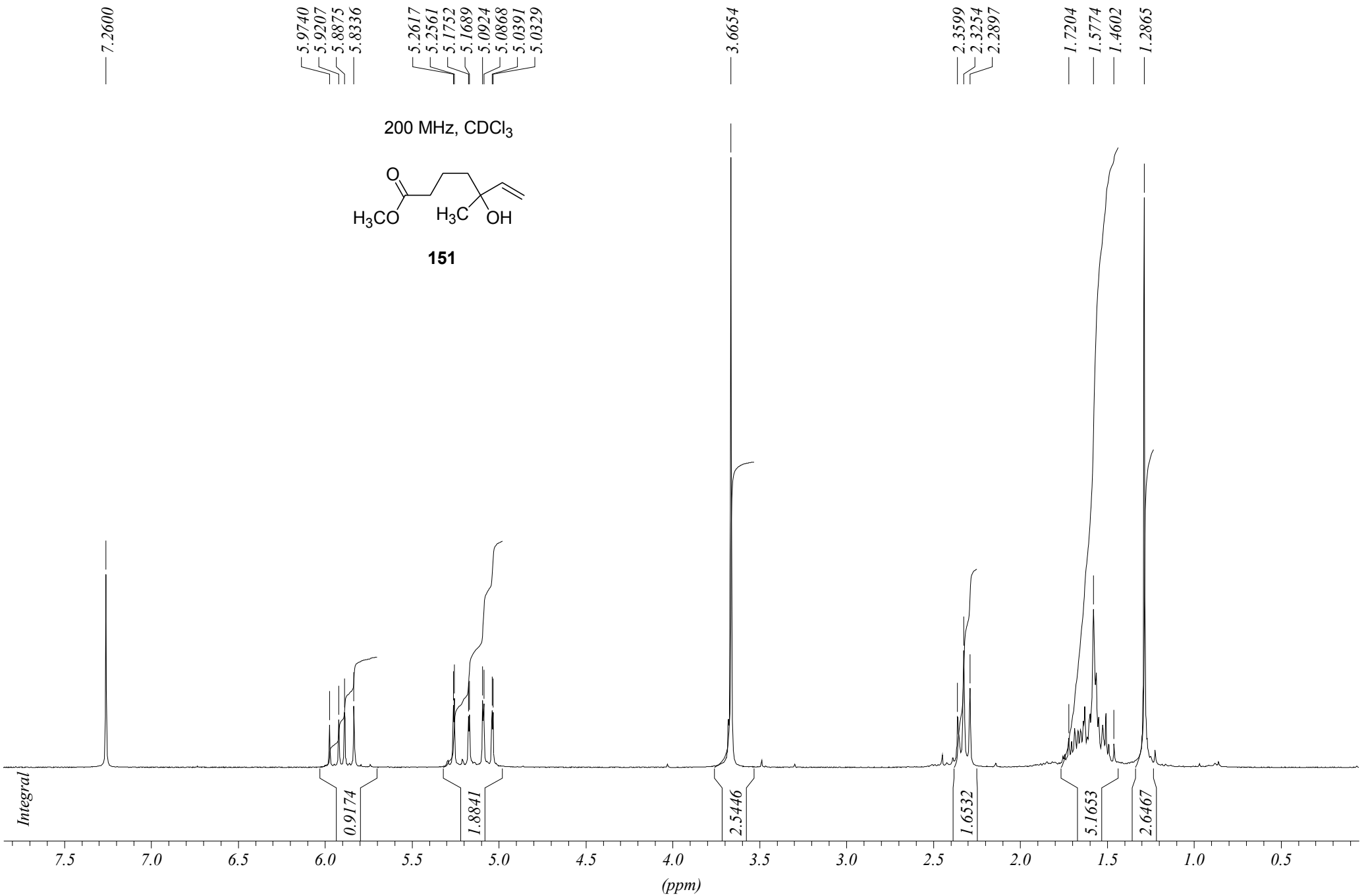


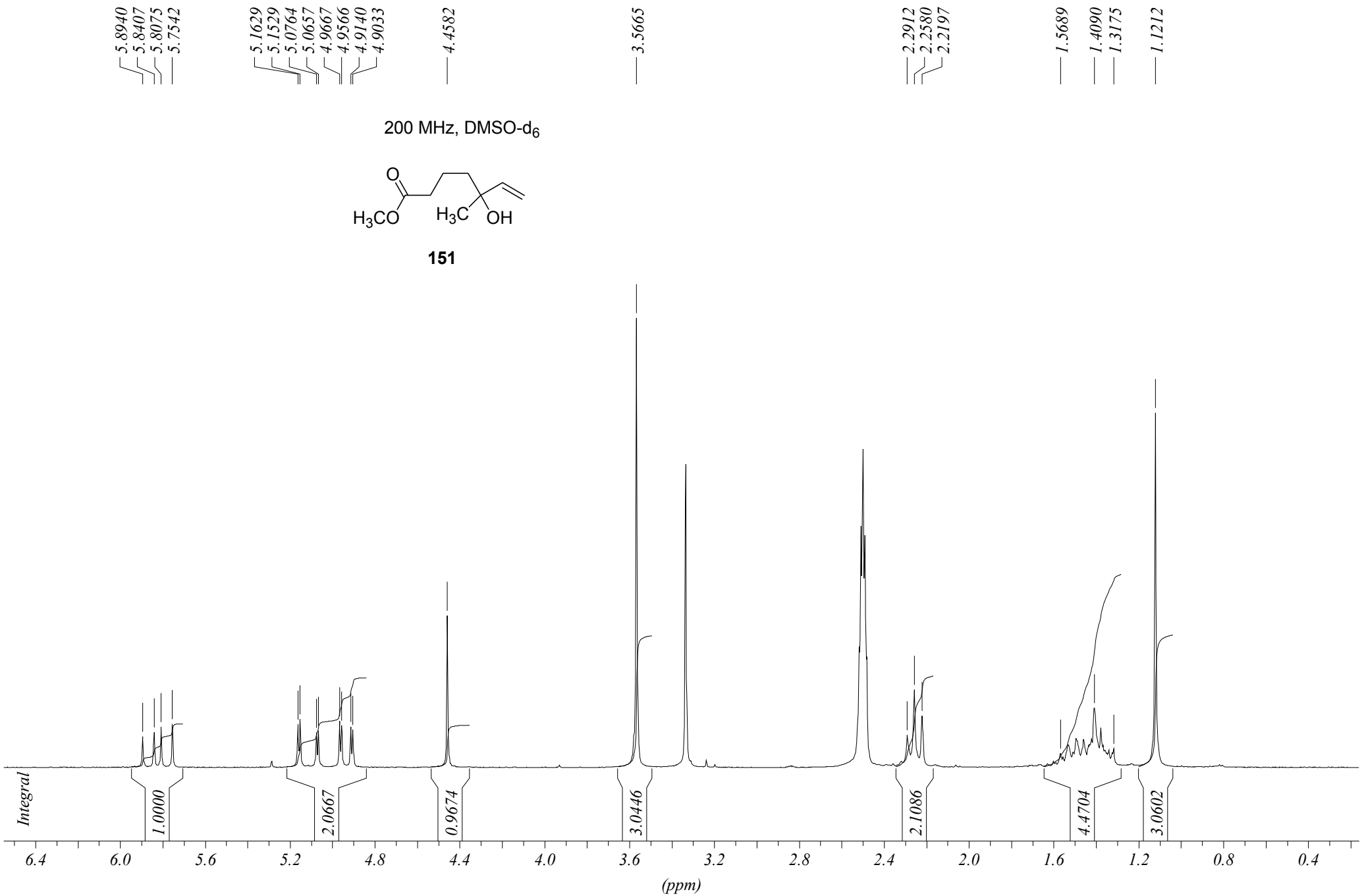

136.7241
133.6414
131.2884
119.2072
118.3746
117.1000
80.6714
77.3163
77.0000
76.6818
74.3555
73.7992
73.1323
71.9244
65.5380
52.2107
50.5493
49.0899
47.6533
45.9919
45.8166
45.4584
44.0809
43.0635
27.6843
19.1868
12.3889
12.3546
11.8611
11.3696
10.9771
10.0511
9.0794
8.6889
7.0484
100 MHz, CDCl3
(R)
(R)
(S)
(S)
(R)
(S)
166
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

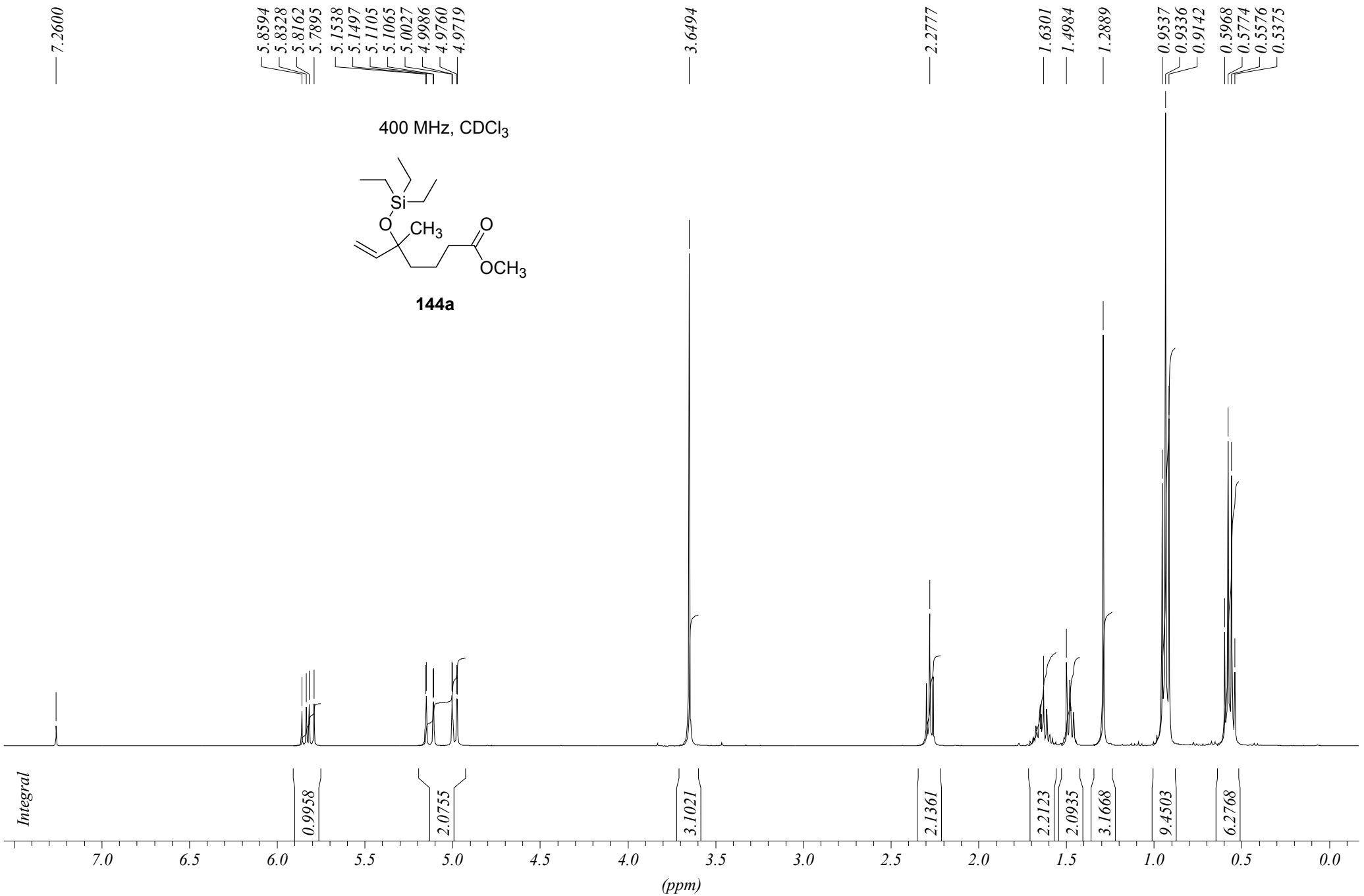

7.2600
5.9044
5.8793
5.8517
5.8267
5.8185
5.7928
5.7658
5.7408
5.4015
5.3156
5.2285
5.1758
3.7130
3.2076
1.1874
1.1517
200 MHz, CDCl3
O
OH
N
O
(R)
(S)
145
Integral
0.8958
1.8803
0.9199
3.0069
3.0625
1.1872
3.0291
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

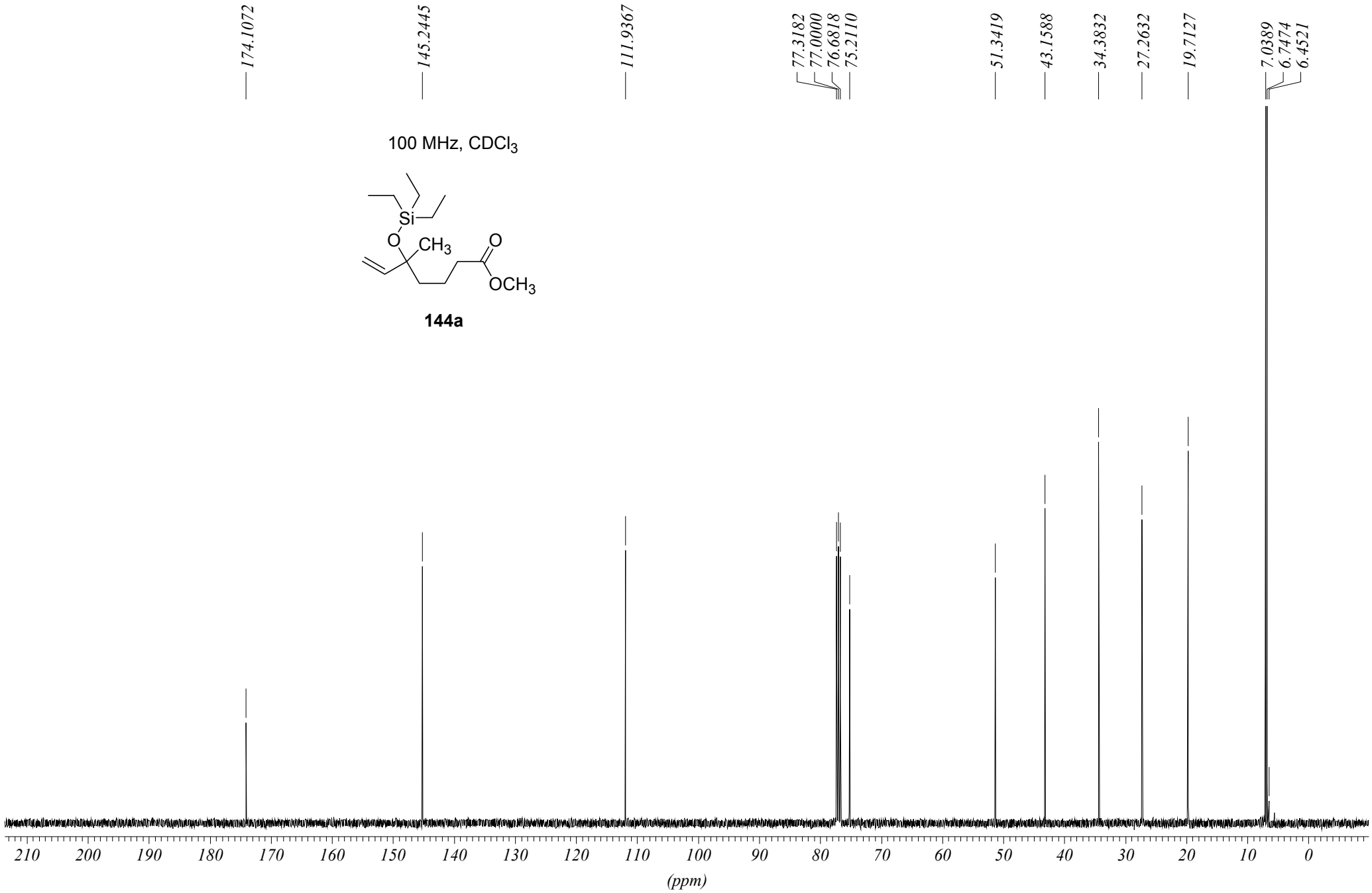

7.2600
3.6654
2.5424
2.5060
2.4703
2.3775
2.3417
2.3060
2.1380
1.9210
1.8853
1.8502
1.6244
200 MHz, CDCl3
O
O
H3C
O
CH3
140
Integral
3.0048
2.0197
2.0278
2.9471
2.1036
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

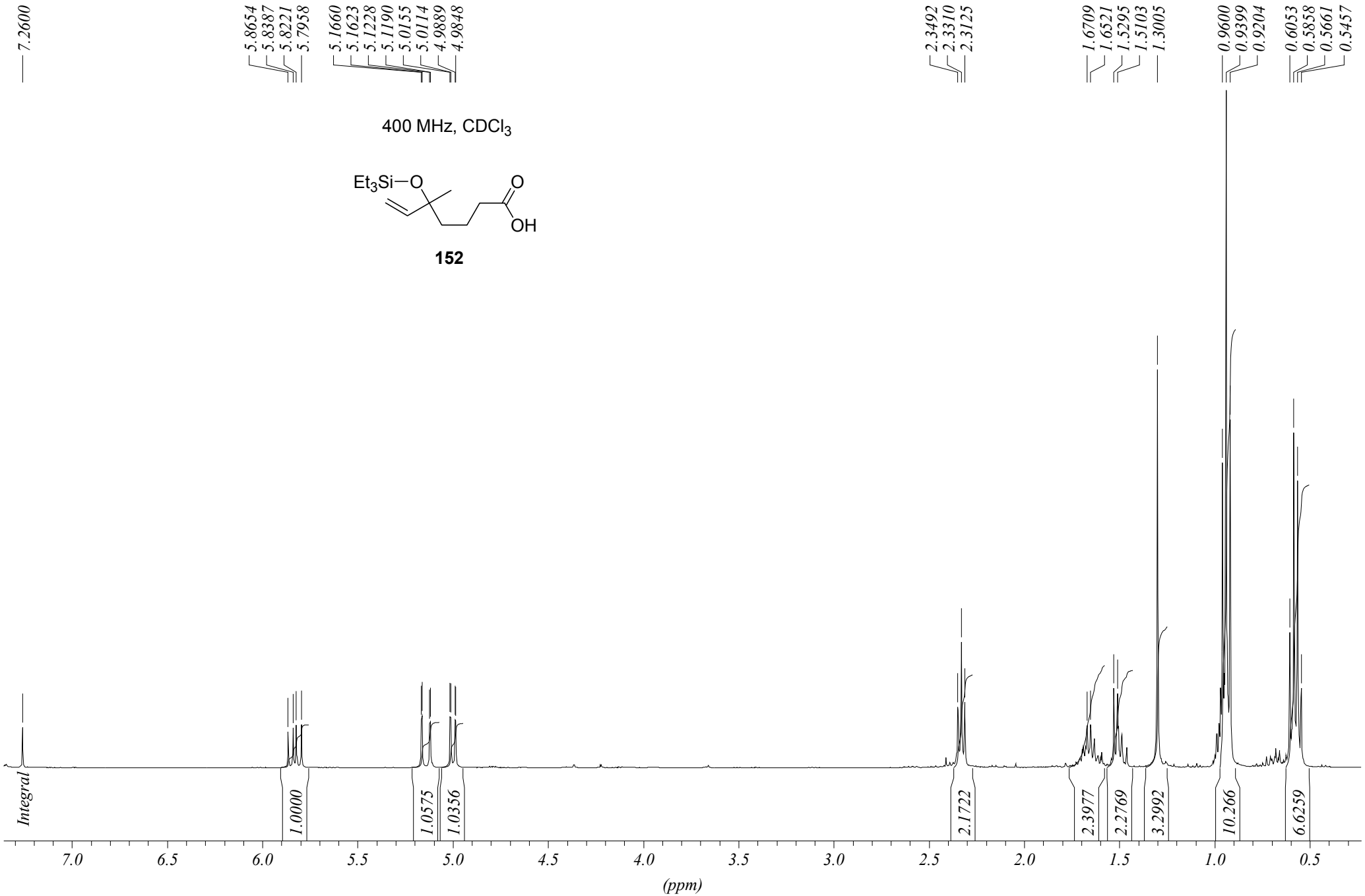

7.2600
5.9709
5.9176
5.8843
5.8304
5.7364
5.2065
3.6641
2.5060
2.3417
2.1380
2.0903
1.8853
1.5755
1.4570
1.2833
200 MHz, CDCl3
O
O
CH3
150
O
H3CO
H3C
OH
151
Integral
0.9004
1.8825
3.0000
2.0533
2.2612
1.9097
2.9202
2.3584
1.3627
1.6042
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


7.2600
5.9740
5.9207
5.8875
5.8336
5.2617
5.2561
5.1752
5.1689
5.0924
5.0868
5.0391
5.0329
3.6654
2.3599
2.3254
2.2897
1.7204
1.5774
1.4602
1.2865
200 MHz, CDCl3
O
H3CO
H3C
OH
151
Integral
0.9174
1.8841
2.5446
1.6532
5.1653
2.6467
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


5.8940
5.8407
5.8075
5.7542
5.1629
5.1529
5.0764
5.0657
4.9667
4.9566
4.9140
4.9033
4.4582
3.5665
2.2912
2.2580
2.2197
1.5689
1.4090
1.3175
1.1212
200 MHz, DMSO-d6
O
H3CO
H3C
OH
151
Integral
1.0000
2.0667
0.9674
3.0446
2.1086
4.4704
3.0602
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
(ppm)

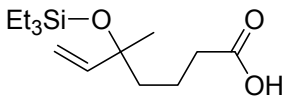

7.2600
5.8594
5.8328
5.8162
5.7895
5.1538
5.1497
5.1105
5.1065
5.0027
4.9986
4.9760
4.9719
3.6494
2.2777
1.6301
1.4984
1.2889
0.9537
0.9336
0.9142
0.5968
0.5774
0.5576
0.5375
400 MHz, CDCl3
Si
O
CH3
O
OCH3
144a
Integral
0.9958
2.0755
3.1021
2.1361
2.2123
2.0935
3.1668
9.4503
6.2768
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


174.1072
145.2445
111.9367
77.3182
77.0000
76.6818
75.2110
51.3419
43.1588
34.3832
27.2632
19.7127
7.0389
6.7474
6.4521
100 MHz, CDCl3
Si
O
CH3
O
OCH3
144a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

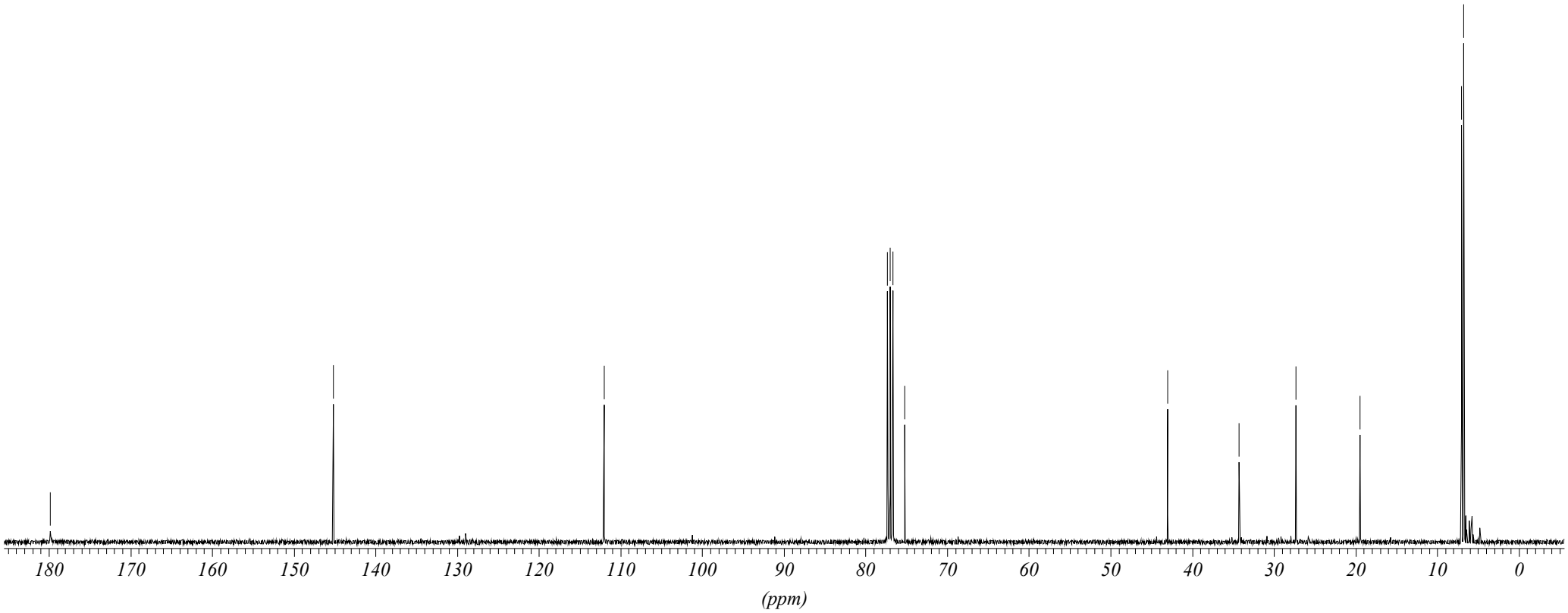

7.2600
5.8654
5.8387
5.8221
5.7958
5.1660
5.1623
5.1228
5.1190
5.0155
5.0114
4.9889
4.9848
2.3492
2.3310
2.3125
1.6709
1.6521
1.5295
1.5103
1.3005
0.9600
0.9399
0.9204
0.6053
0.5858
0.5661
0.5457
400 MHz, CDCl3
Et3Si—O
O
OH
152
Integral
1.0000
1.0575
1.0356
2.1722
2.3977
2.2769
3.2992
10.266
6.6259
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

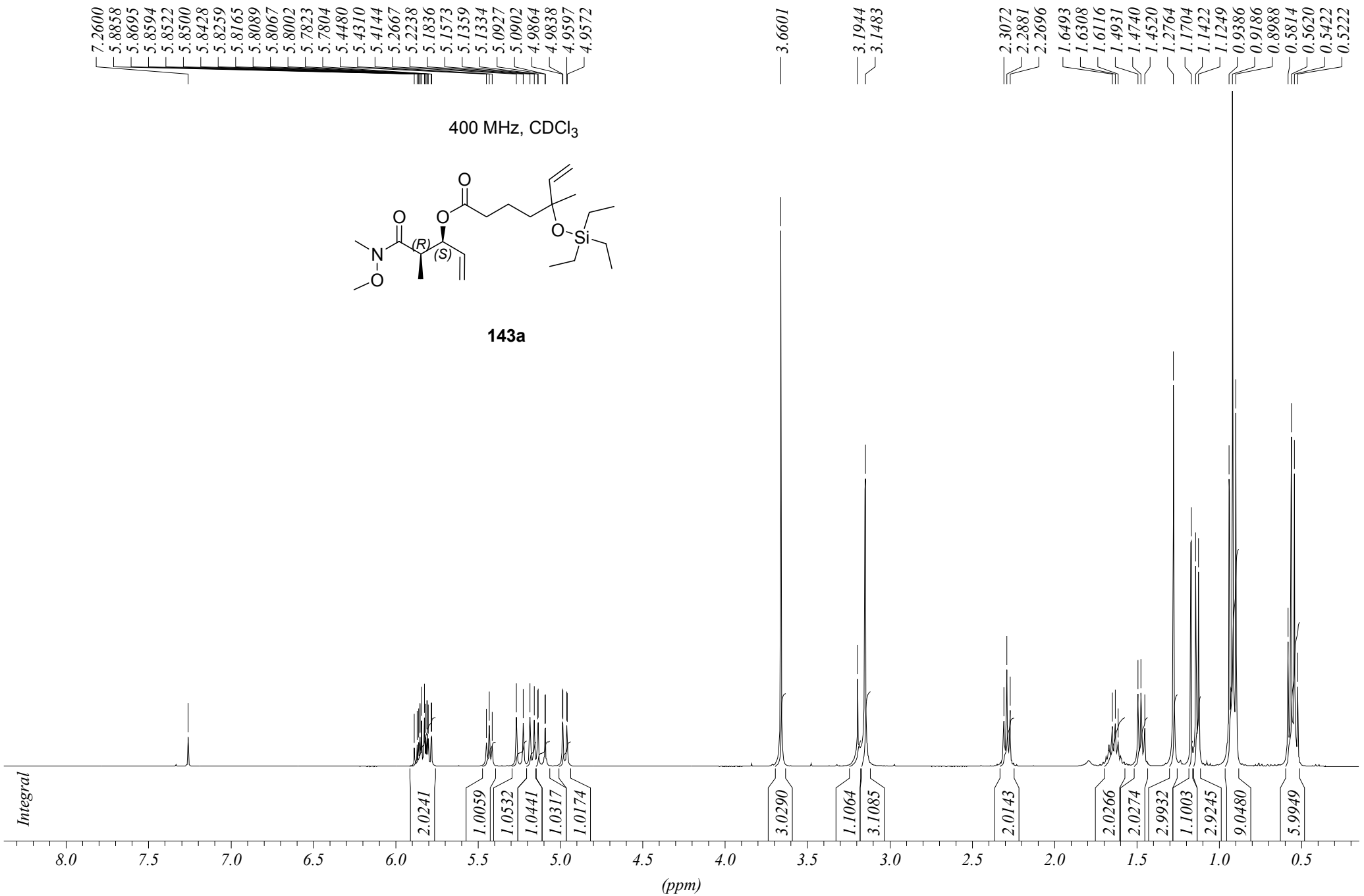
179.8116
145.1740
112.0301
77.3182
77.0000
76.6818
75.1957
43.0140
34.2917
27.2937
19.4498
7.0541
6.7417

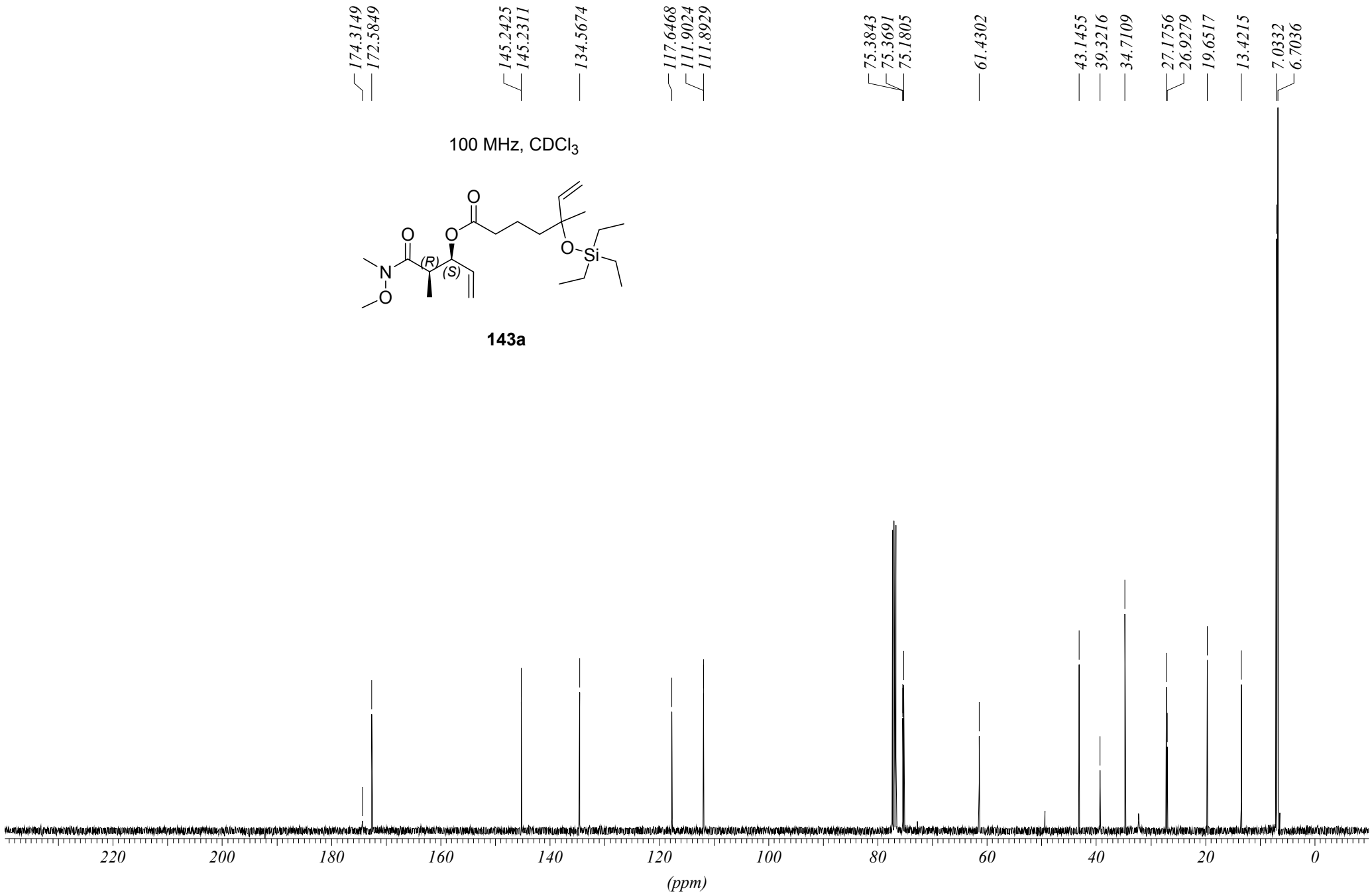
100 MHz, $CDCl_3$



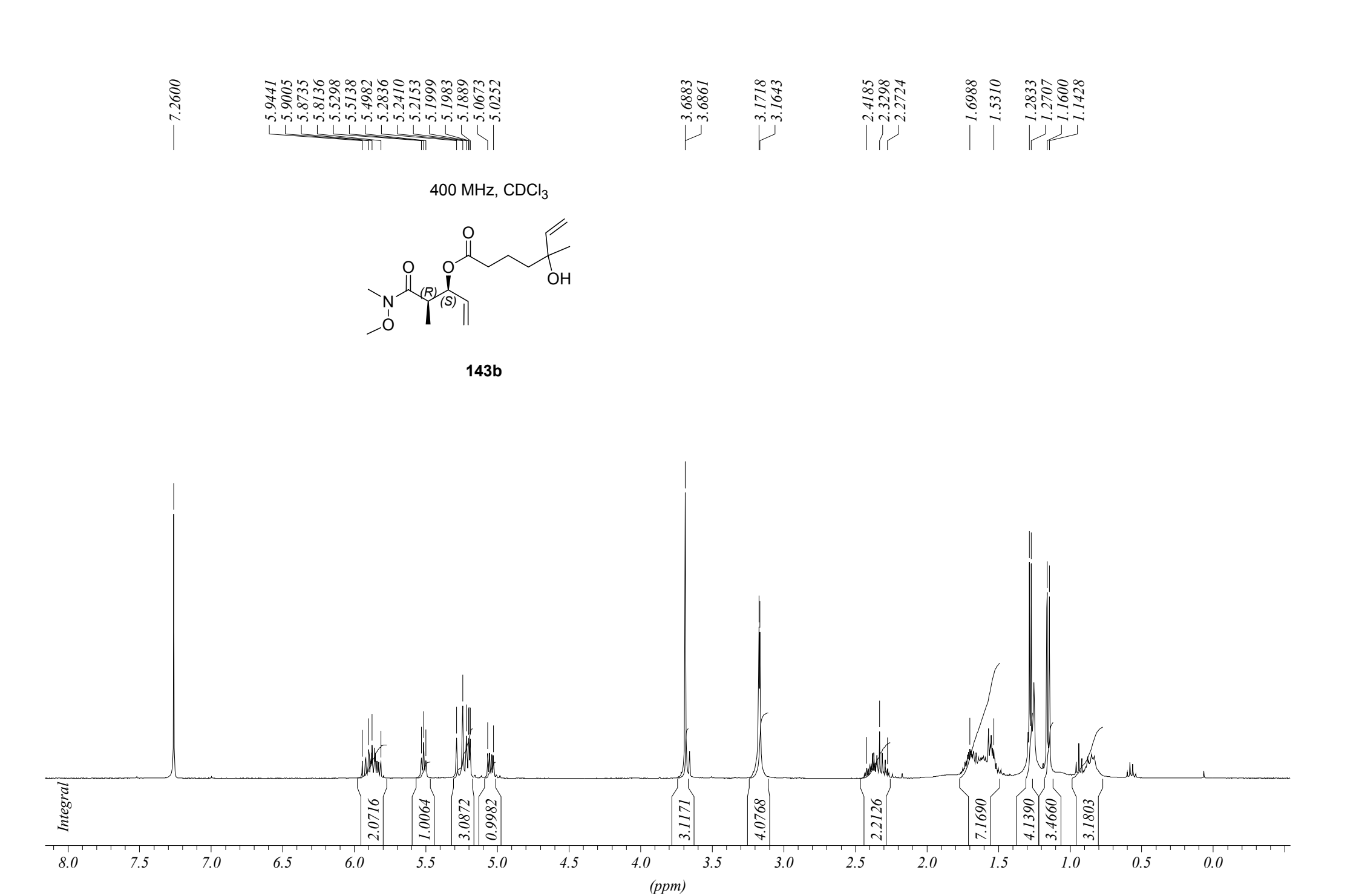
152

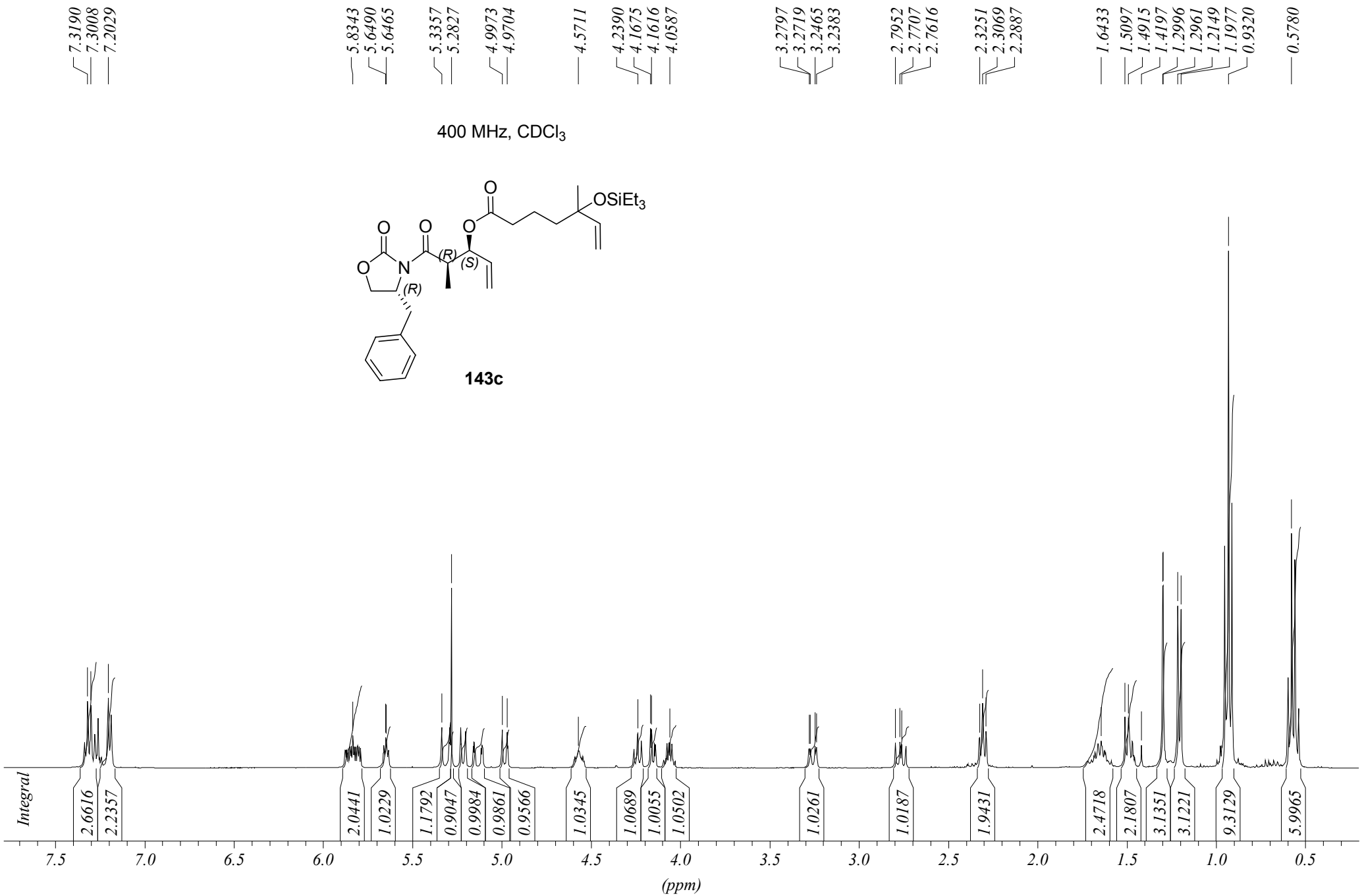


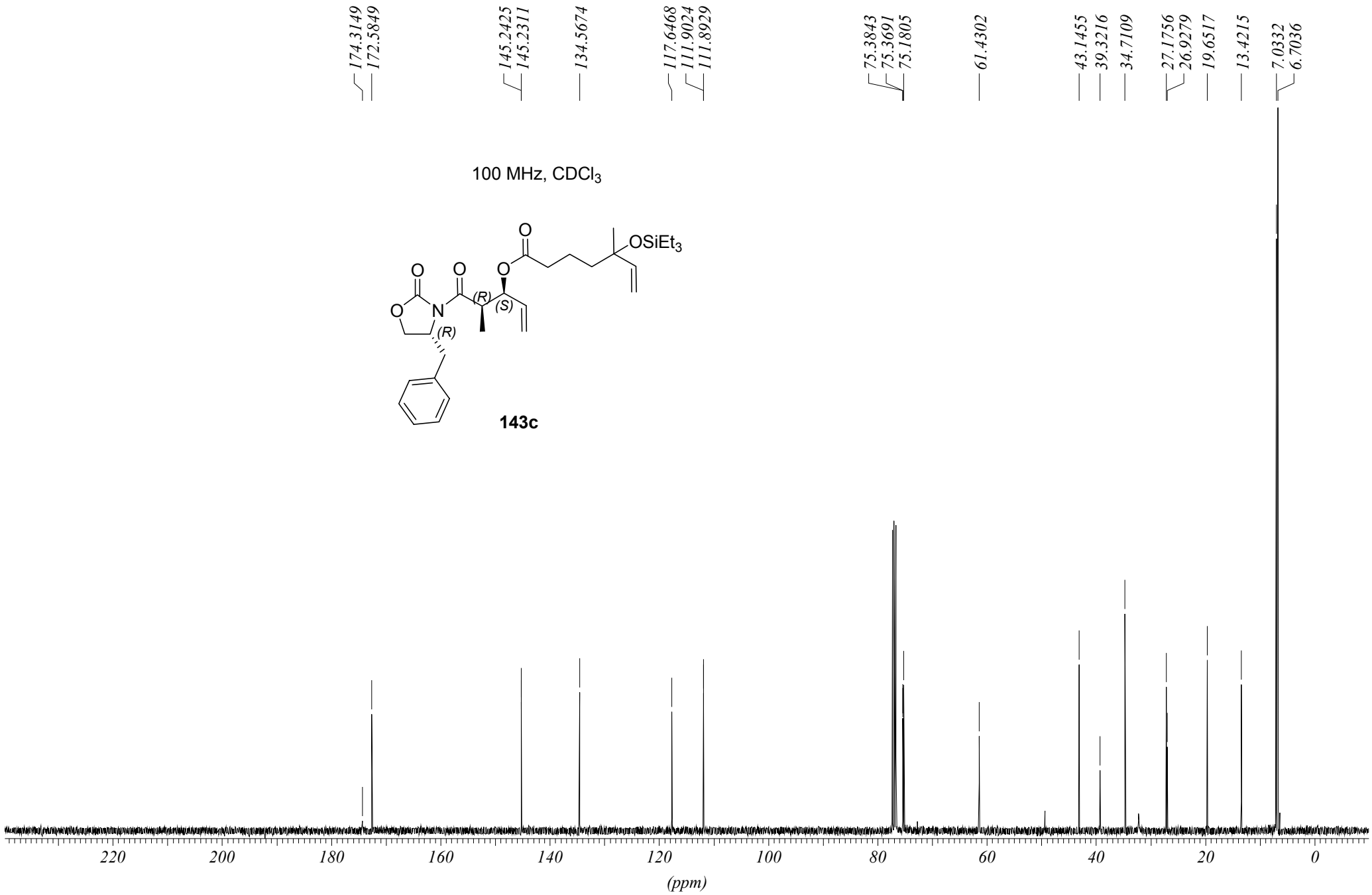

7.2600
5.8858
5.8695
5.8594
5.8522
5.8500
5.8428
5.8259
5.8165
5.8089
5.8067
5.8002
5.7823
5.7804
5.4480
5.4310
5.4144
5.2667
5.2238
5.1836
5.1573
5.1359
5.1334
5.0927
5.0902
4.9864
4.9838
4.9597
4.9572
3.6601
3.1944
3.1483
2.3072
2.2881
2.2696
1.6493
1.6308
1.6116
1.4931
1.4740
1.4520
1.2764
1.1704
1.1422
1.1249
0.9386
0.9186
0.8988
0.5814
0.5620
0.5422
0.5222
400 MHz, CDCl3
O
O
O
O
N
O
(R)
(S)
O
Si
143a
Integral
2.0241
1.0059
1.0532
1.0441
1.0317
1.0174
3.0290
1.1064
3.1085
2.0143
2.0266
2.0274
2.9932
1.1003
2.9245
9.0480
5.9949
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

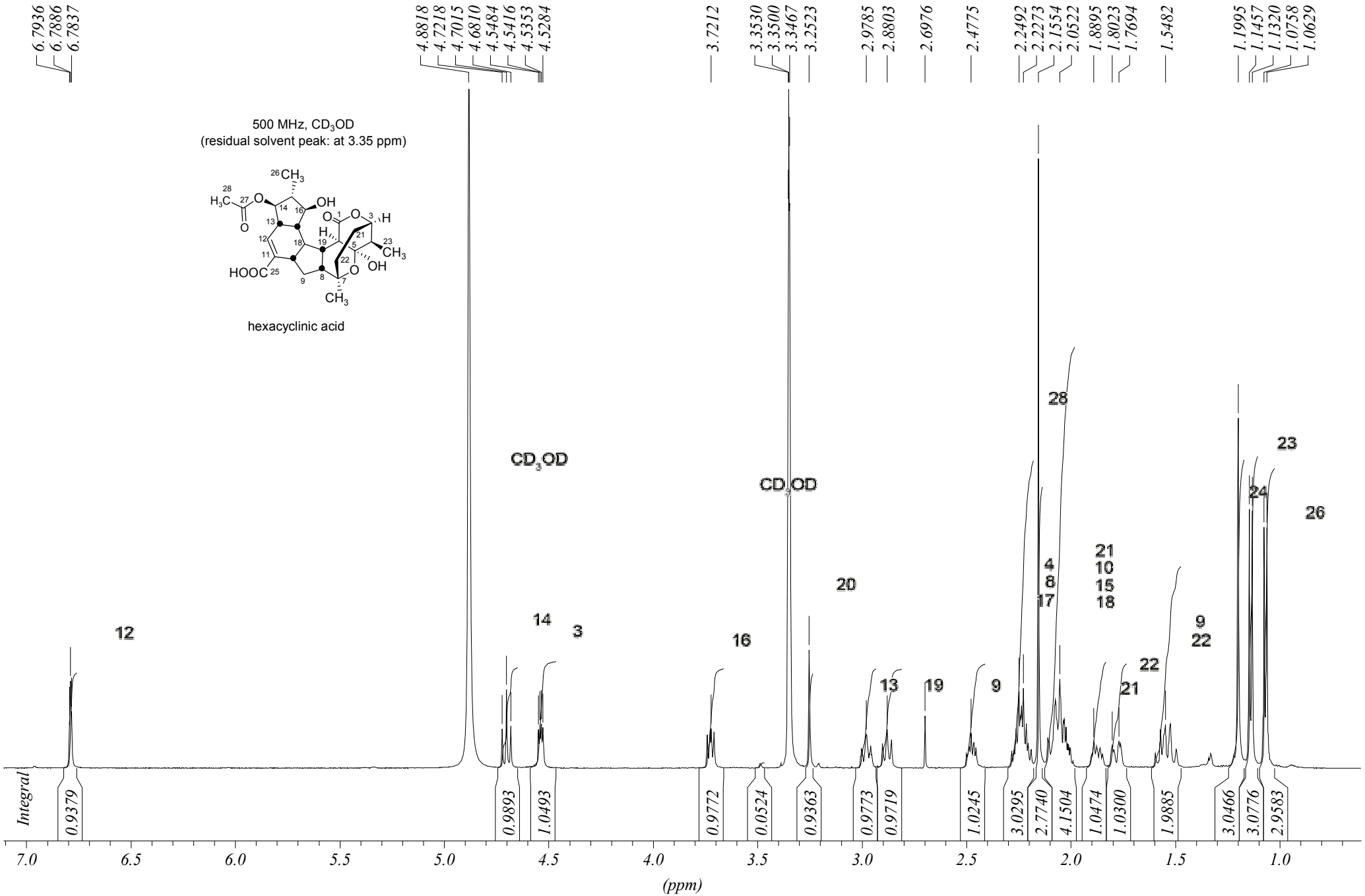

174.3149
172.5849
145.2425
145.2311
134.5674
117.6468
111.9024
111.8929
75.3843
75.3691
75.1805
61.4302
43.1455
39.3216
34.7109
27.1756
26.9279
19.6517
13.4215
7.0332
6.7036
100 MHz, CDCl3
O
O
O
N
O
(R)
(S)
O
Si
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

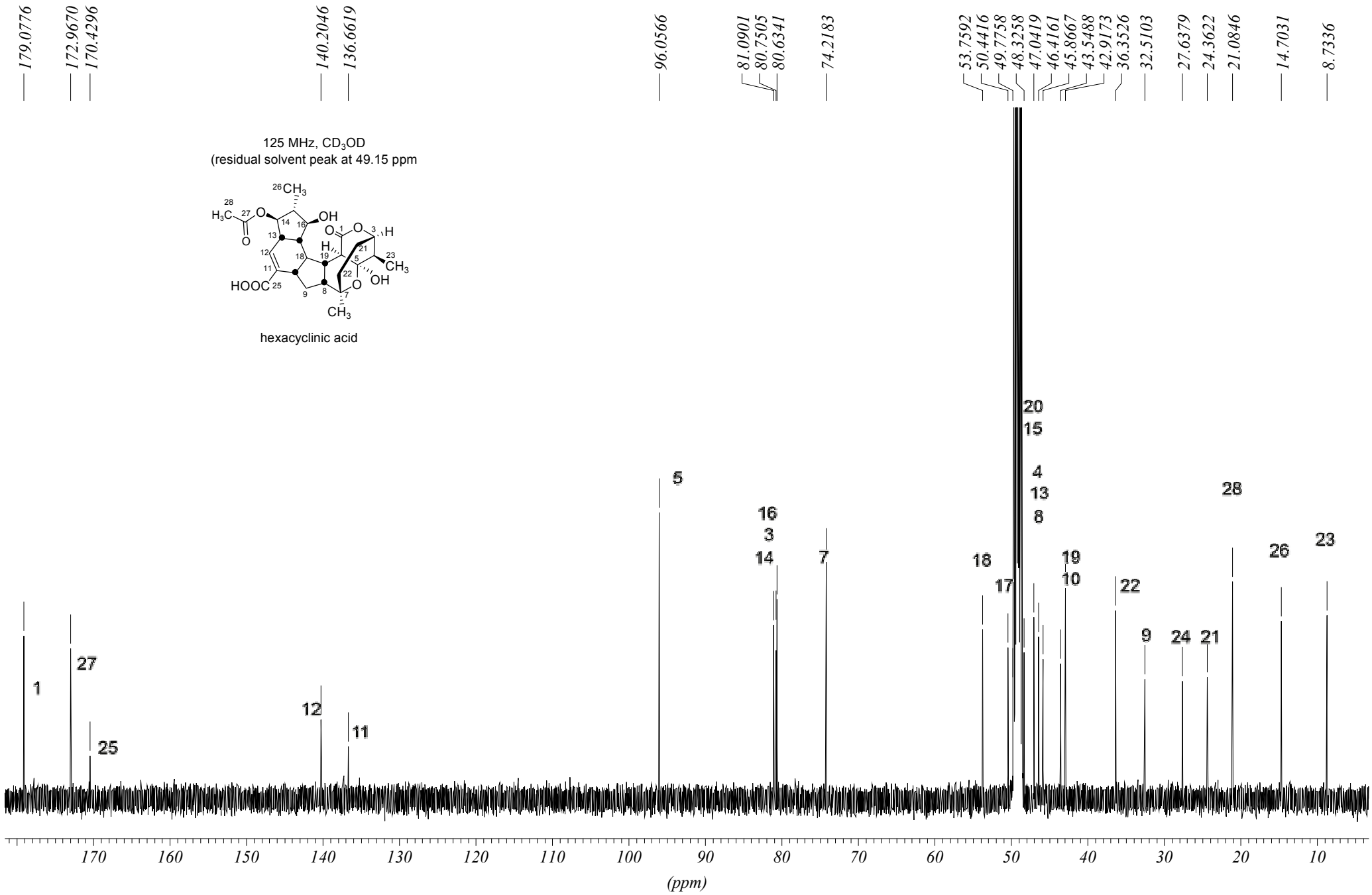
143a

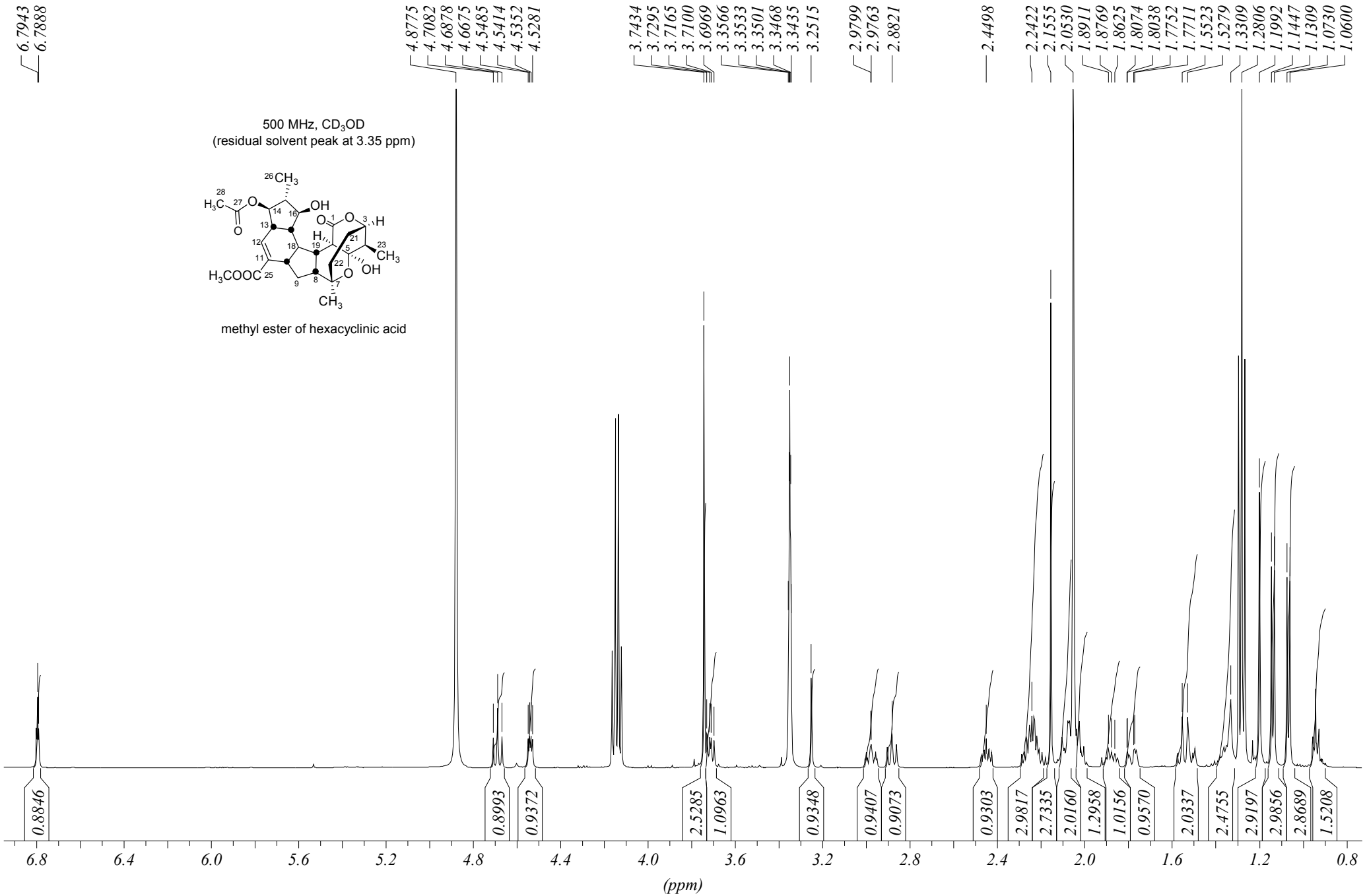

7.2600
5.9441
5.9005
5.8735
5.8136
5.5298
5.5138
5.4982
5.2836
5.2410
5.2153
5.1999
5.1983
5.1889
5.0673
5.0252
3.6883
3.6861
3.1718
3.1643
2.4185
2.3298
2.2724
1.6988
1.5310
1.2833
1.2707
1.1600
1.1428
400 MHz, CDCl3
O
O
O
OH
N
O
(R)
(S)
143b
Integral
2.0716
1.0064
3.0872
0.9982
3.1171
4.0768
2.2126
7.1690
4.1390
3.4660
3.1803
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

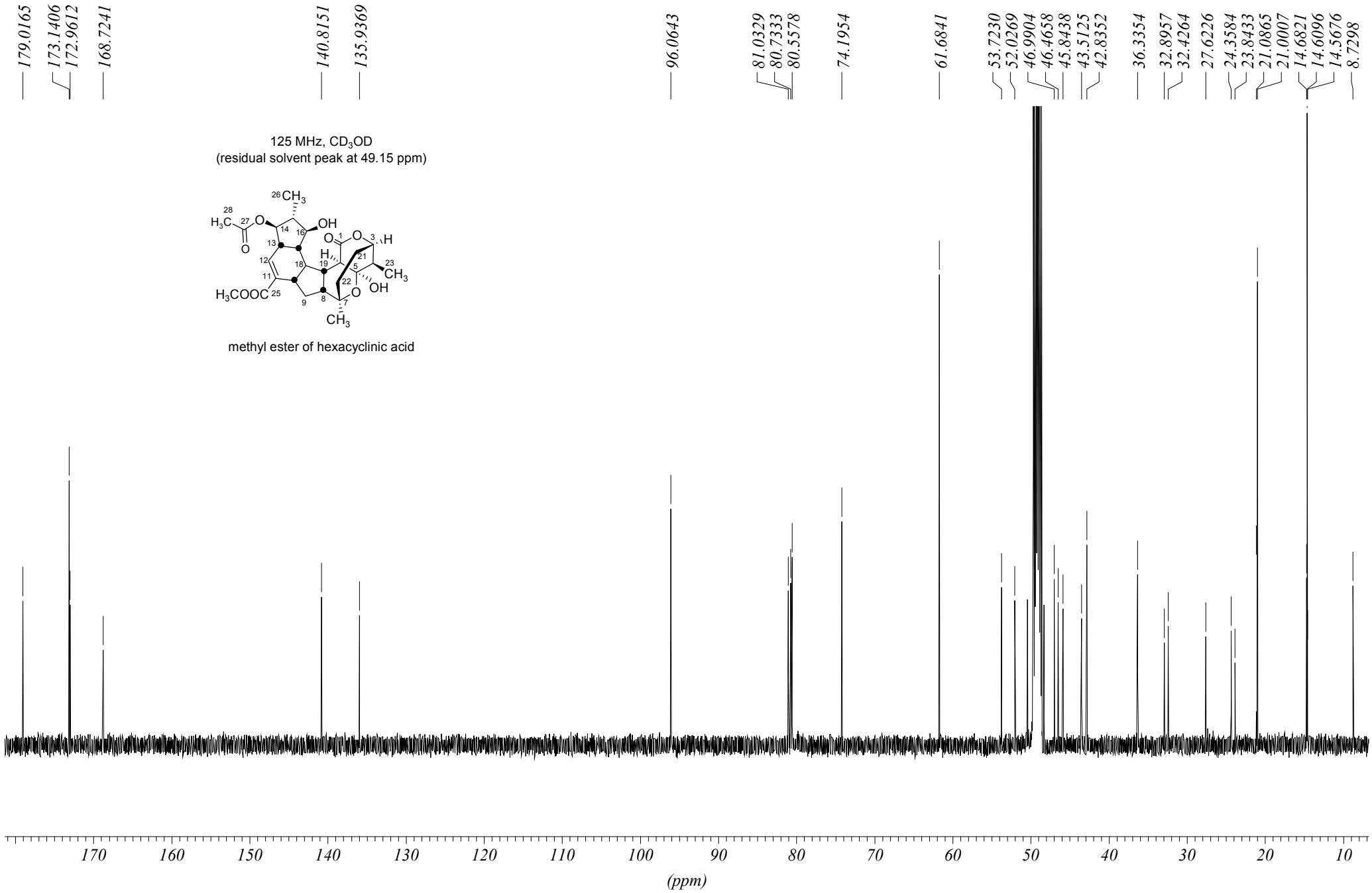

7.3190
7.3008
7.2029
5.8343
5.6490
5.6465
5.3357
5.2827
4.9973
4.9704
4.5711
4.2390
4.1675
4.1616
4.0587
3.2797
3.2719
3.2465
3.2383
2.7952
2.7707
2.7616
2.3251
2.3069
2.2887
1.6433
1.5097
1.4915
1.4197
1.2996
1.2961
1.2149
1.1977
0.9320
0.5780
400 MHz, CDCl3
OSiEt3
(R)
(S)
(R)
143c
Integral
2.6616
2.2357
2.0441
1.0229
1.1792
0.9047
0.9984
0.9861
0.9566
1.0345
1.0689
1.0055
1.0502
1.0261
1.0187
1.9431
2.4718
2.1807
3.1351
3.1221
9.3129
5.9965
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

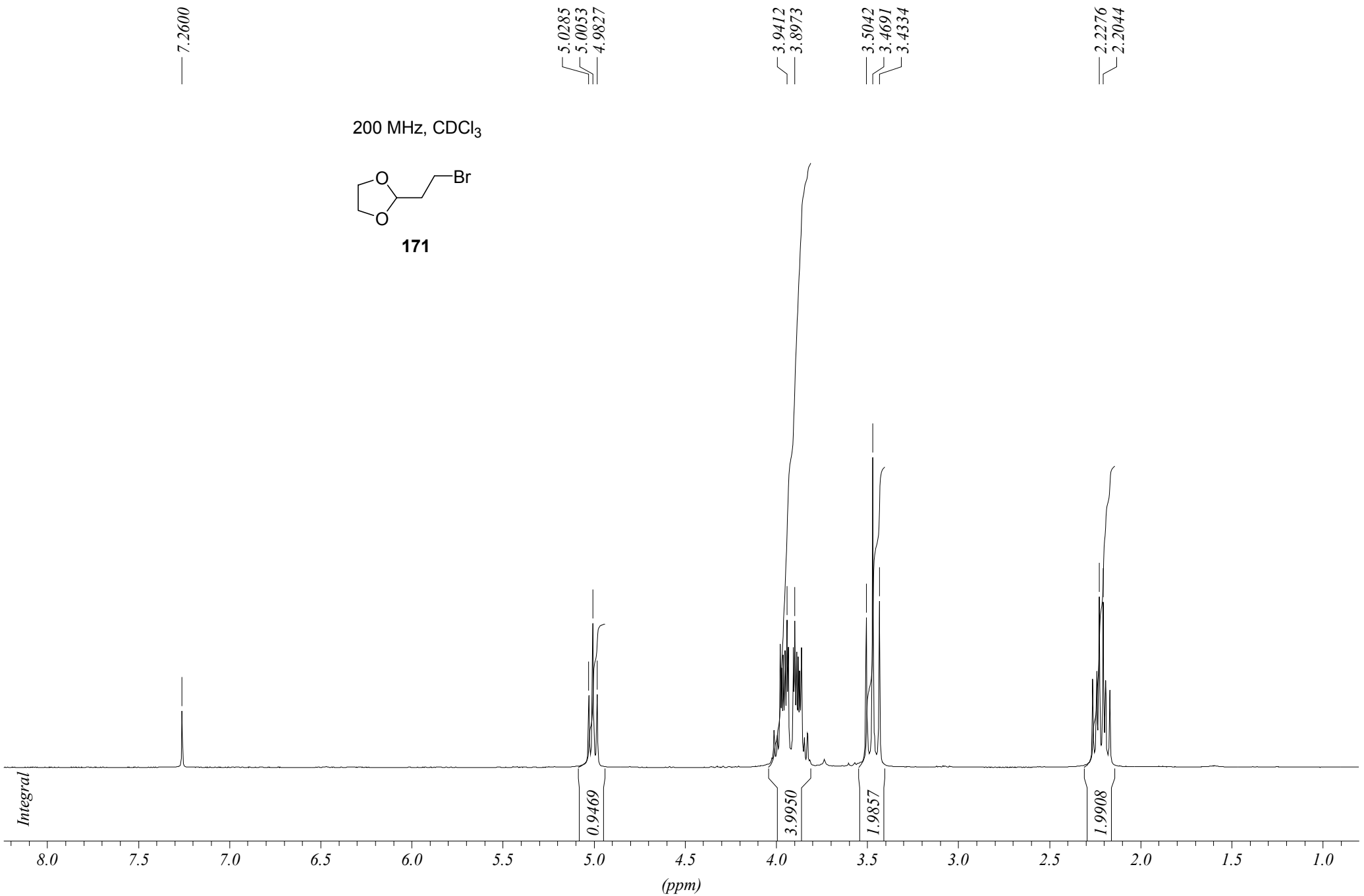

174.3149
172.5849
145.2425
145.2311
134.5674
117.6468
111.9024
111.8929
75.3843
75.3691
75.1805
61.4302
43.1455
39.3216
34.7109
27.1756
26.9279
19.6517
13.4215
7.0332
6.7036
100 MHz, CDCl3
OSiEt3
(R)
(S)
(R)
143c
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

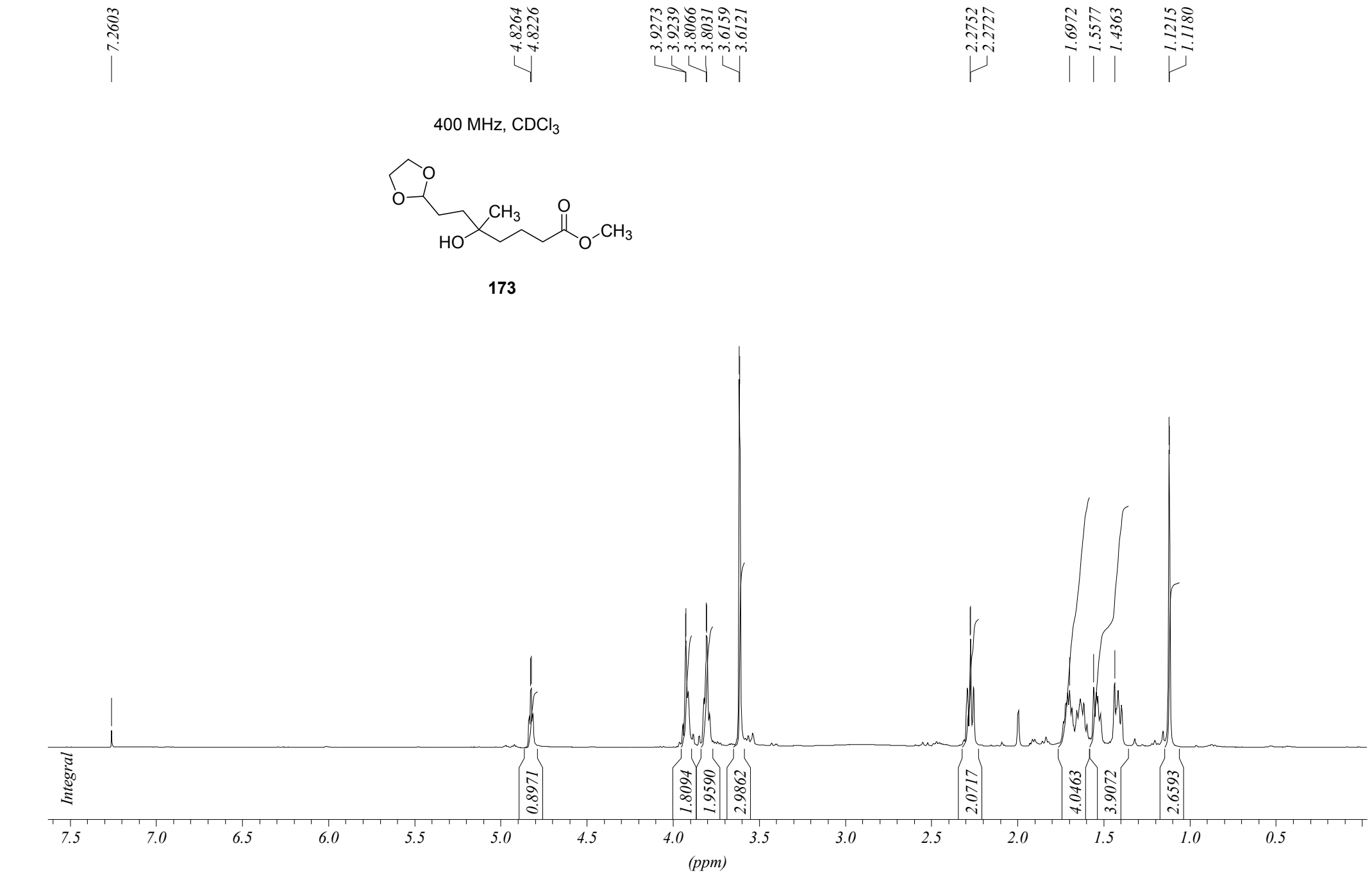

6.7936
6.7886
6.7837
4.8818
4.7218
4.7015
4.6810
4.5484
4.5416
4.5353
4.5284
3.7212
3.3530
3.3500
3.3467
3.2523
2.9785
2.8803
2.6976
2.4775
2.2492
2.2273
2.1554
2.0522
1.8895
1.8023
1.7694
1.5482
1.1995
1.1457
1.1320
1.0758
1.0629
500 MHz, CD3OD
(residual solvent peak: at 3.35 ppm)
hexacyclinic acid
CD3OD
CD3OD
12
14
3
16
20
13
19
9
28
4
8
17
21
10
15
18
22
9
22
21
23
24
26
Integral
0.9379
0.9893
1.0493
0.9772
0.0524
0.9363
0.9773
0.9719
1.0245
3.0295
2.7740
4.1504
1.0474
1.0300
1.9885
3.0466
3.0776
2.9583
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)


179.0776
172.9670
170.4296
140.2046
136.6619
96.0566
81.0901
80.7505
80.6341
74.2183
53.7592
50.4416
49.7758
48.3258
47.0419
46.4161
45.8667
43.5488
42.9173
36.3526
32.5103
27.6379
24.3622
21.0846
14.7031
8.7336
125 MHz, CD3OD
(residual solvent peak at 49.15 ppm
hexacyclinic acid
1
27
25
12
11
5
16
3
14
7
18
17
20
15
4
13
8
19
10
22
9
24
21
28
26
23
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


6.7943
6.7888
4.8775
4.7082
4.6878
4.6675
4.5485
4.5414
4.5352
4.5281
3.7434
3.7295
3.7165
3.7100
3.6969
3.3566
3.3533
3.3501
3.3468
3.3435
3.2515
2.9799
2.9763
2.8821
2.4498
2.2422
2.1555
2.0530
1.8911
1.8769
1.8625
1.8074
1.8038
1.7752
1.7711
1.5523
1.5279
1.3309
1.2806
1.1992
1.1447
1.1309
1.0730
1.0600
500 MHz, CD3OD
(residual solvent peak at 3.35 ppm)
methyl ester of hexacyclinic acid
0.8846
0.8993
0.9372
2.5285
1.0963
0.9348
0.9407
0.9073
0.9303
2.9817
2.7335
2.0160
1.2958
1.0156
0.9570
2.0337
2.4755
2.9197
2.9856
2.8689
1.5208
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
(ppm)

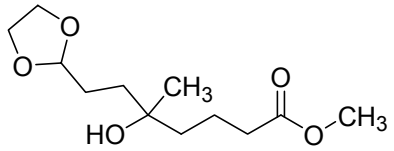

179.0165
173.1406
172.9612
168.7241
140.8151
135.9369
96.0643
81.0329
80.7333
80.5578
74.1954
61.6841
53.7230
52.0269
46.9904
46.4658
45.8438
43.5125
42.8352
36.3354
32.8957
32.4264
27.6226
24.3584
23.8433
21.0865
21.0007
14.6821
14.6096
14.5676
8.7298
125 MHz, CD3OD
(residual solvent peak at 49.15 ppm)
methyl ester of hexacyclinic acid
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


7.2600
5.0285
5.0053
4.9827
3.9412
3.8973
3.5042
3.4691
3.4334
2.2276
2.2044
200 MHz, CDCl3
O
O
Br
171
Integral
0.9469
3.9950
1.9857
1.9908
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

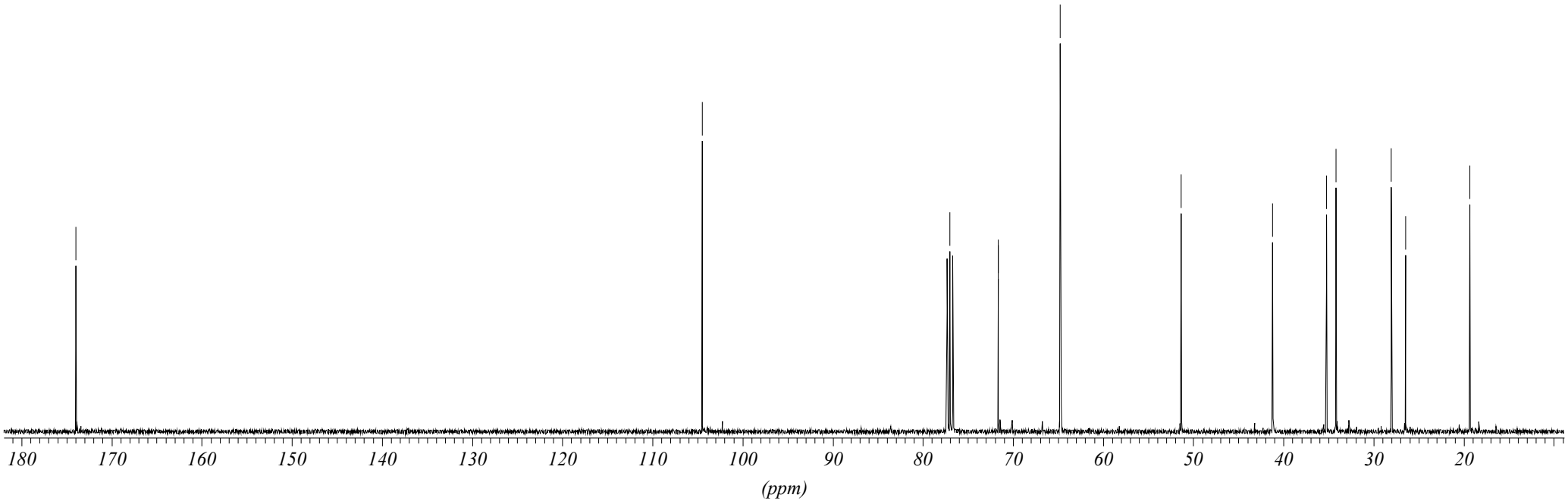

7.2603
4.8264
4.8226
3.9273
3.9239
3.8066
3.8031
3.6159
3.6121
2.2752
2.2727
1.6972
1.5577
1.4363
1.1215
1.1180
400 MHz, CDCl3
O
O
CH3
O
HO
O
CH3
173
Integral
0.8971
1.8094
1.9590
2.9862
2.0717
4.0463
3.9072
2.6593
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

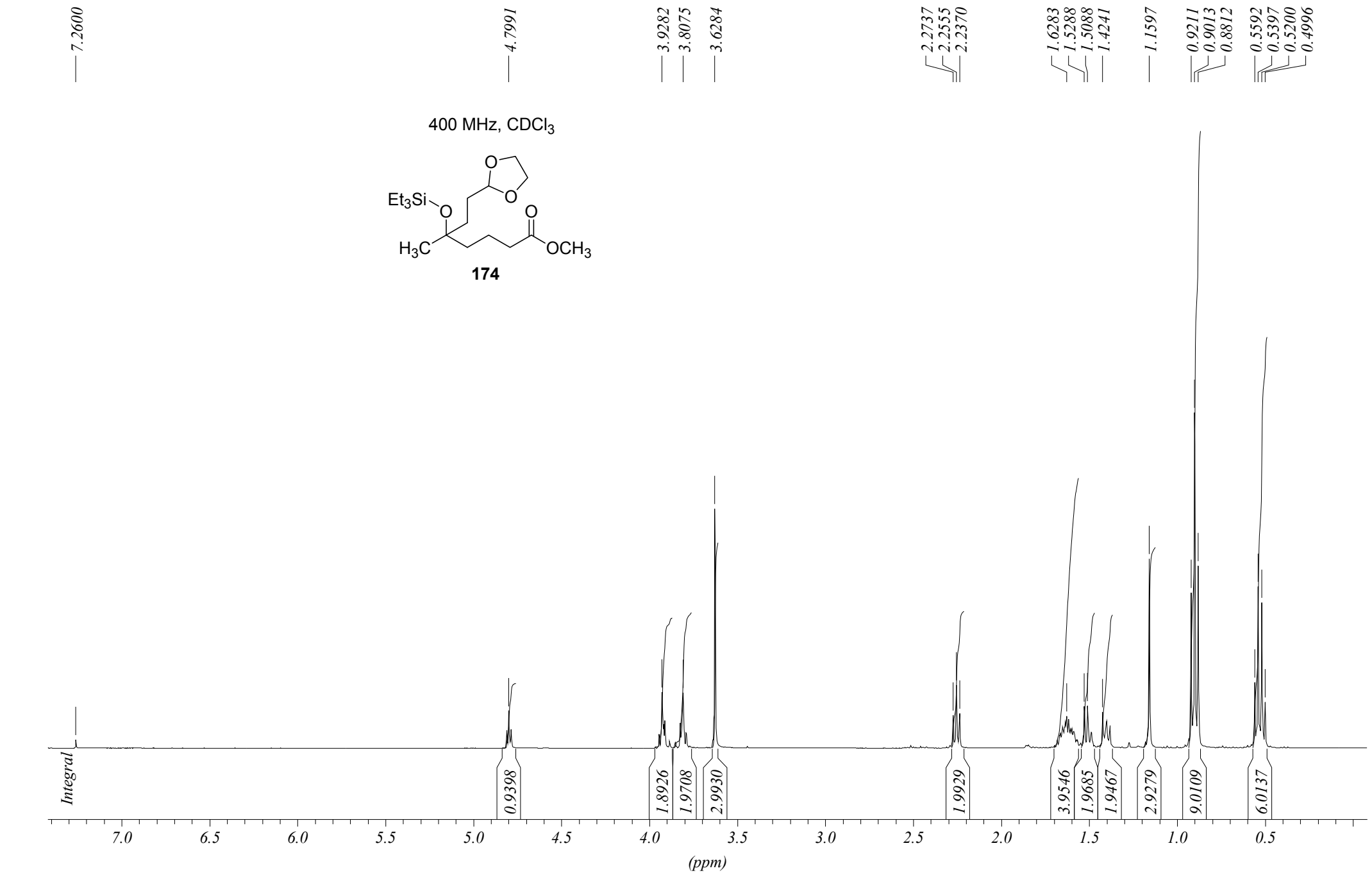
173.9567
104.4872
77.0000
71.6558
71.6500
64.7721
51.3876
41.1888
35.2158
34.2003
28.0272
26.4592
19.3240

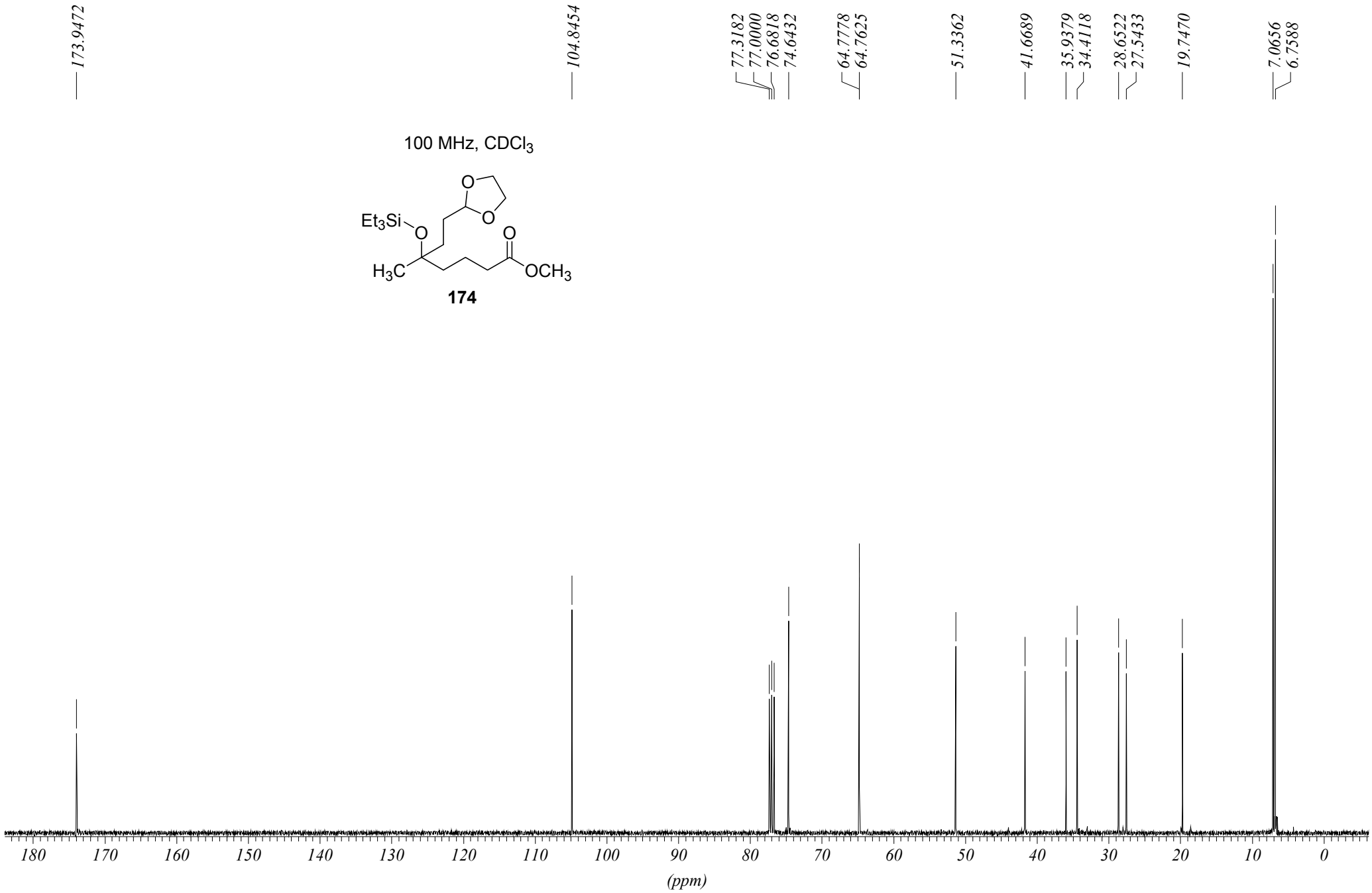
100 MHz, $CDCl_3$



173




7.2600
4.7991
3.9282
3.8075
3.6284
2.2737
2.2555
2.2370
1.6283
1.5288
1.5088
1.4241
1.1597
0.9211
0.9013
0.8812
0.5592
0.5397
0.5200
0.4996
400 MHz, CDCl3
Et3Si
O
O
O
O
H3C
OCH3
174
Integral
0.9398
1.8926
1.9708
2.9930
1.9929
3.9546
1.9685
1.9467
2.9279
9.0109
6.0137
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


173.9472
104.8454
77.3182
77.0000
76.6818
74.6432
64.7778
64.7625
51.3362
41.6689
35.9379
34.4118
28.6522
27.5433
19.7470
7.0656
6.7588
100 MHz, CDCl3
Et3Si
O
O
O
O
H3C
OCH3
174
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

7.2597

4.8233
4.8154
4.8041

3.9188
3.8034
3.6212

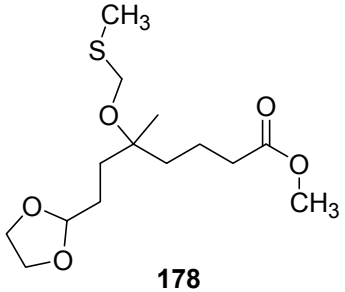
2.2871
2.2693
2.2514
2.1438

1.6621

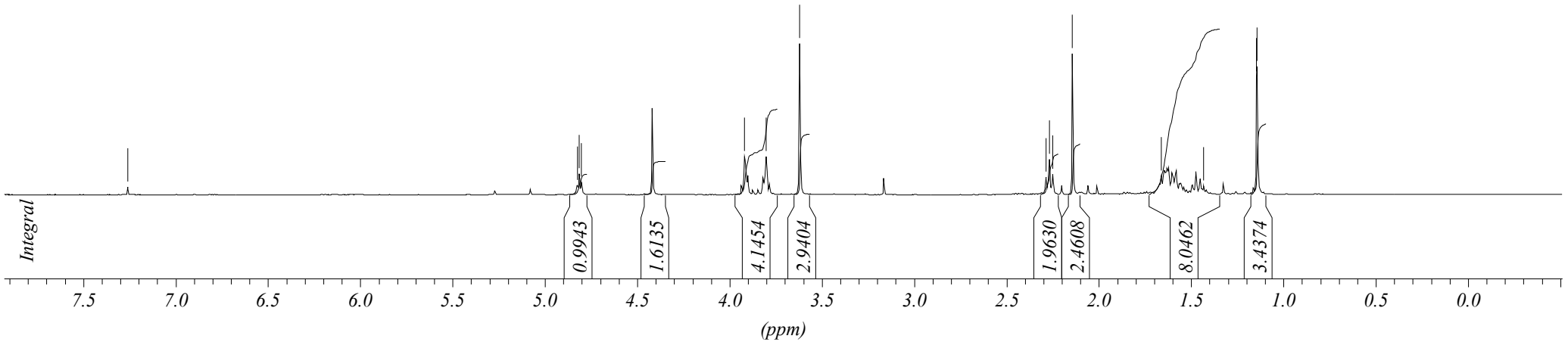
1.4322

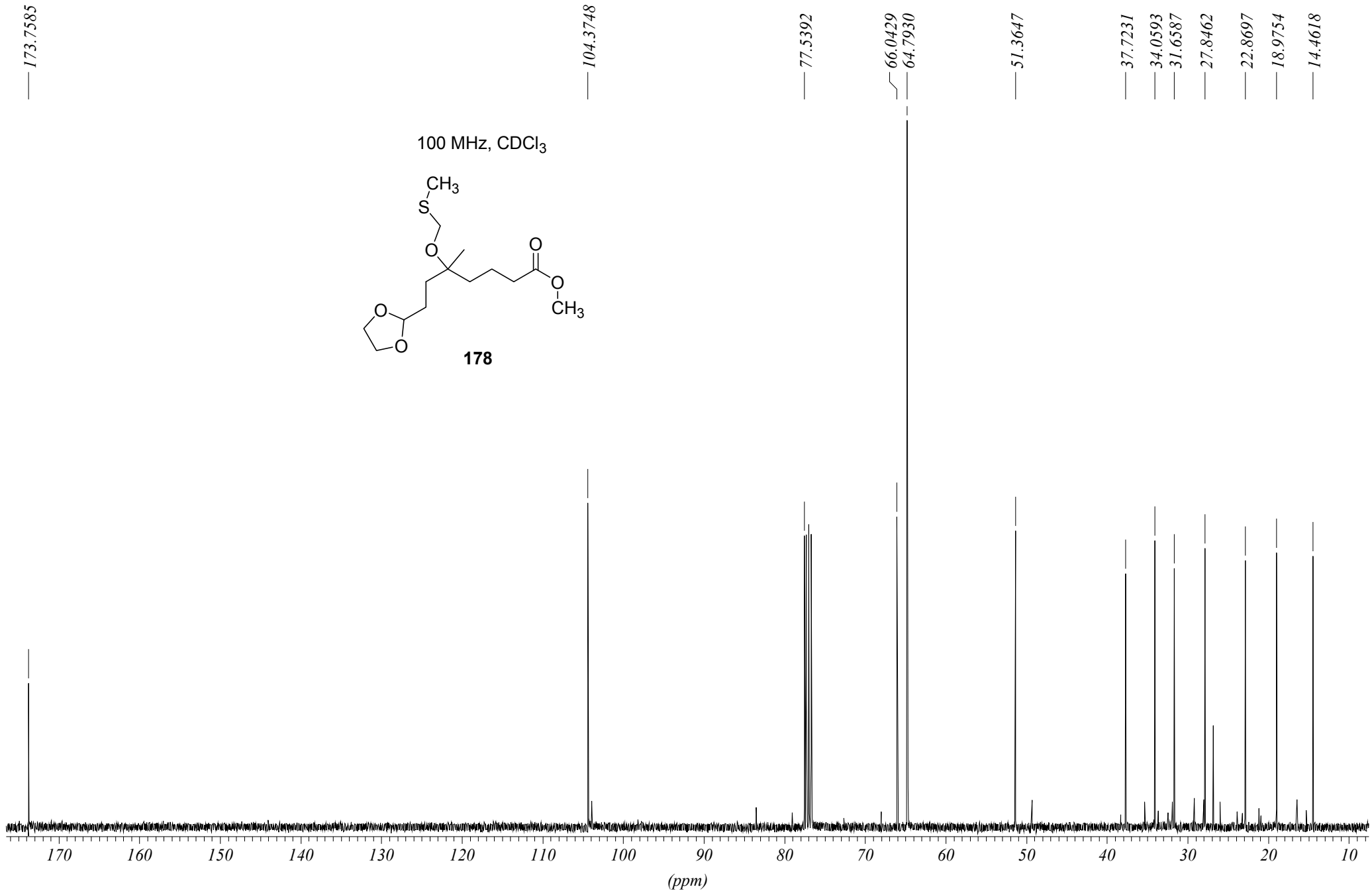
1.1453
1.1428

400 MHz, $CDCl_3$



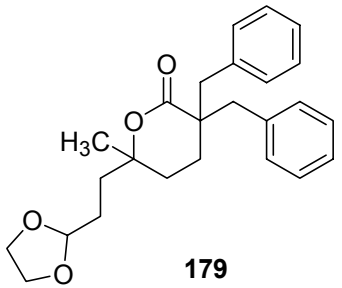
178



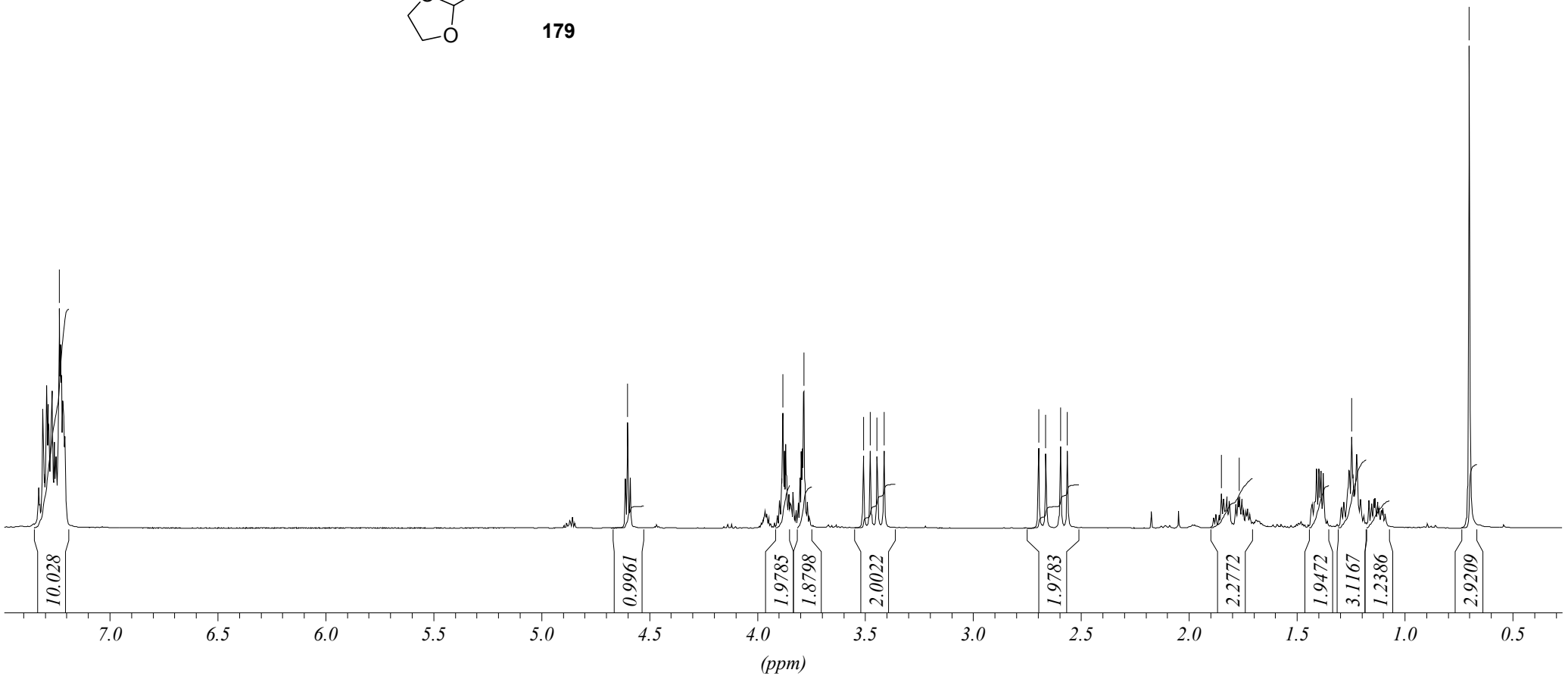

173.7585
104.3748
77.5392
66.0429
64.7930
51.3647
37.7231
34.0593
31.6587
27.8462
22.8697
18.9754
14.4618
100 MHz, CDCl3
CH3
S
O
O
O
O
CH3
O
O
178
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

7.2332
4.5999
3.8823
3.7848
3.5088
3.4762
3.4452
3.4125
2.6959
2.6633
2.5962
2.5636
1.8501
1.7661
1.2471
0.7023

400 MHz, $CDCl_3$

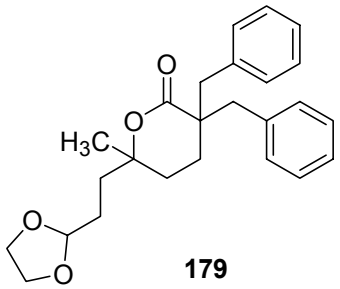


179

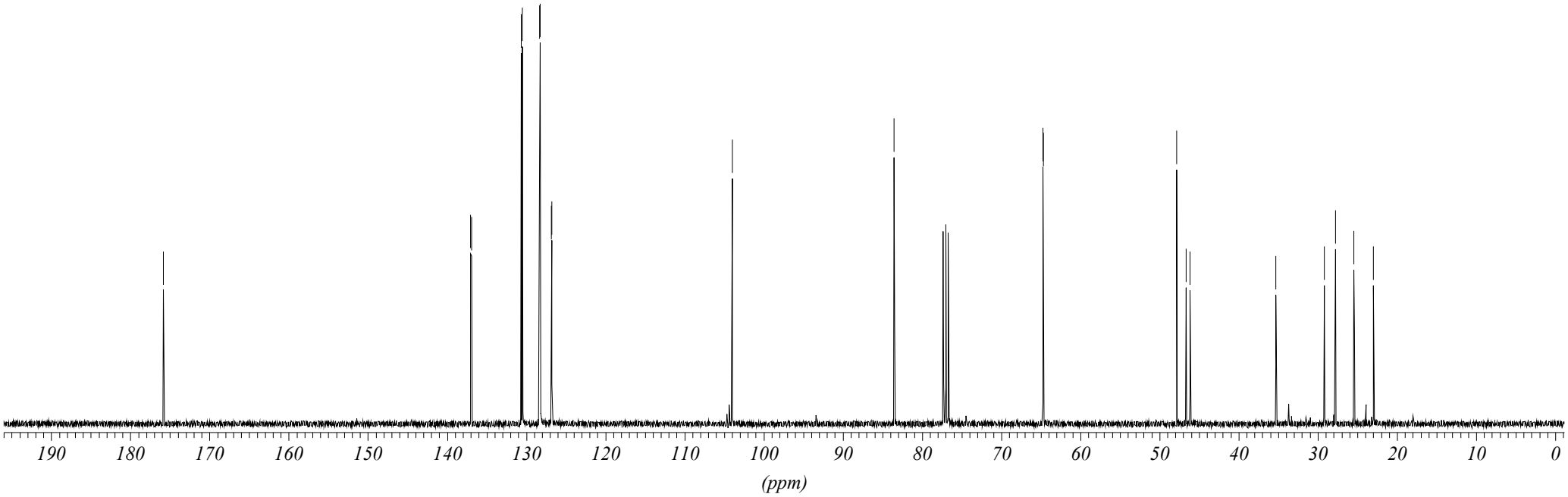


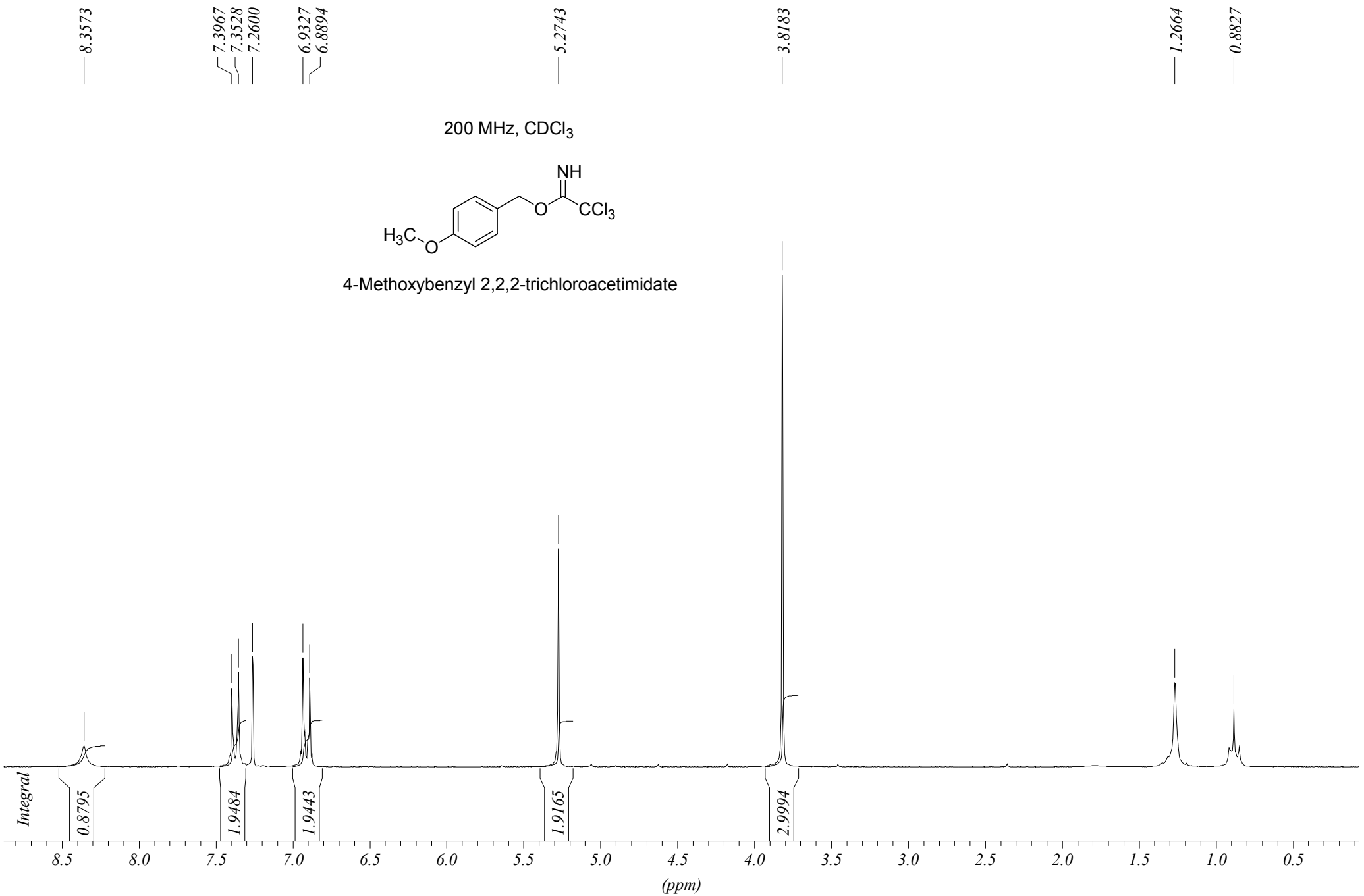
175.8505
137.0233
136.9318
130.6425
130.4901
128.3334
128.2438
126.8473
126.7958
103.9785
83.5045
64.7168
64.6673
47.8229
46.6740
46.1272
35.2748
29.1856
27.7586
25.4189
22.9783

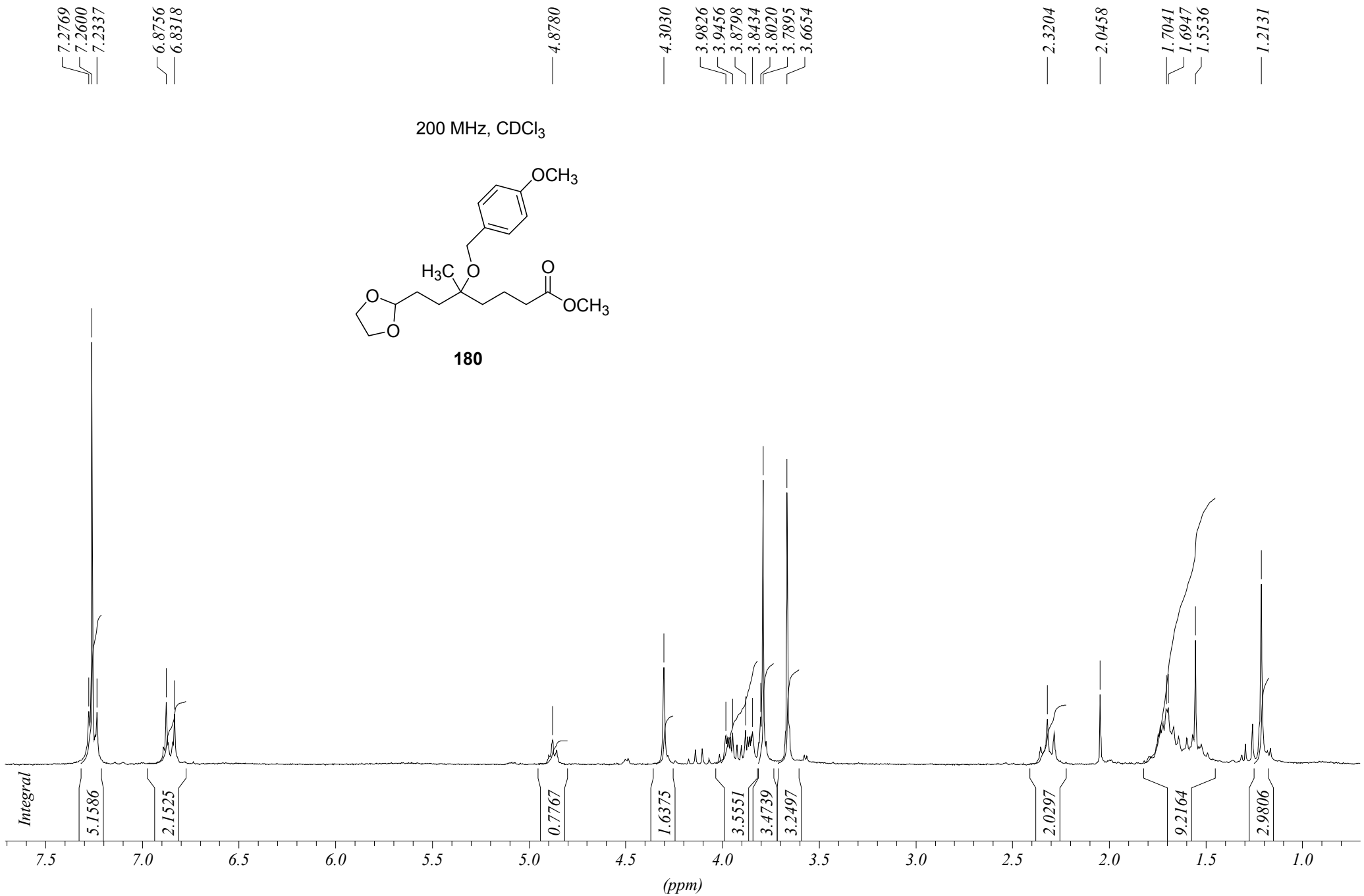
100 MHz, $CDCl_3$

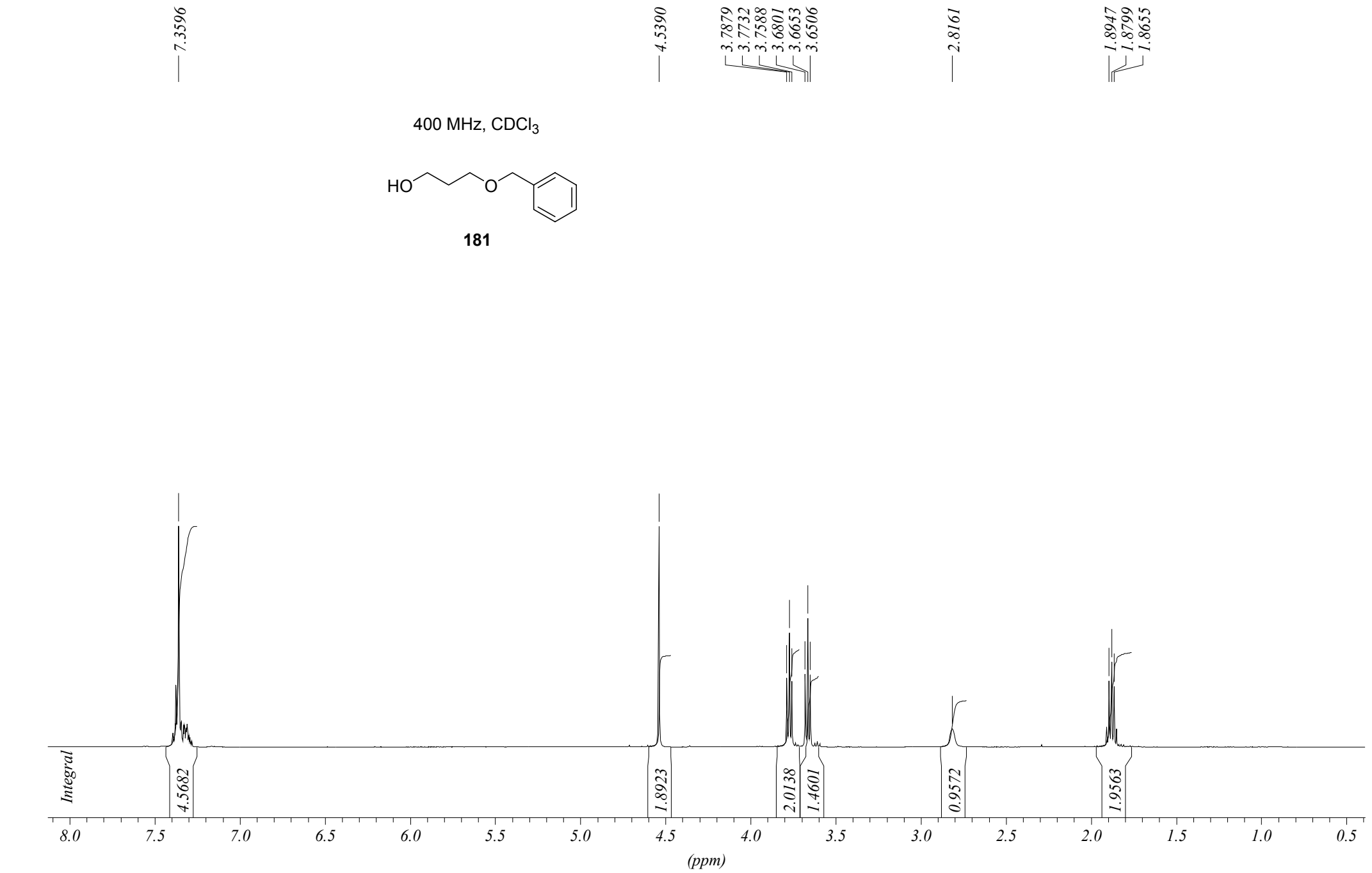


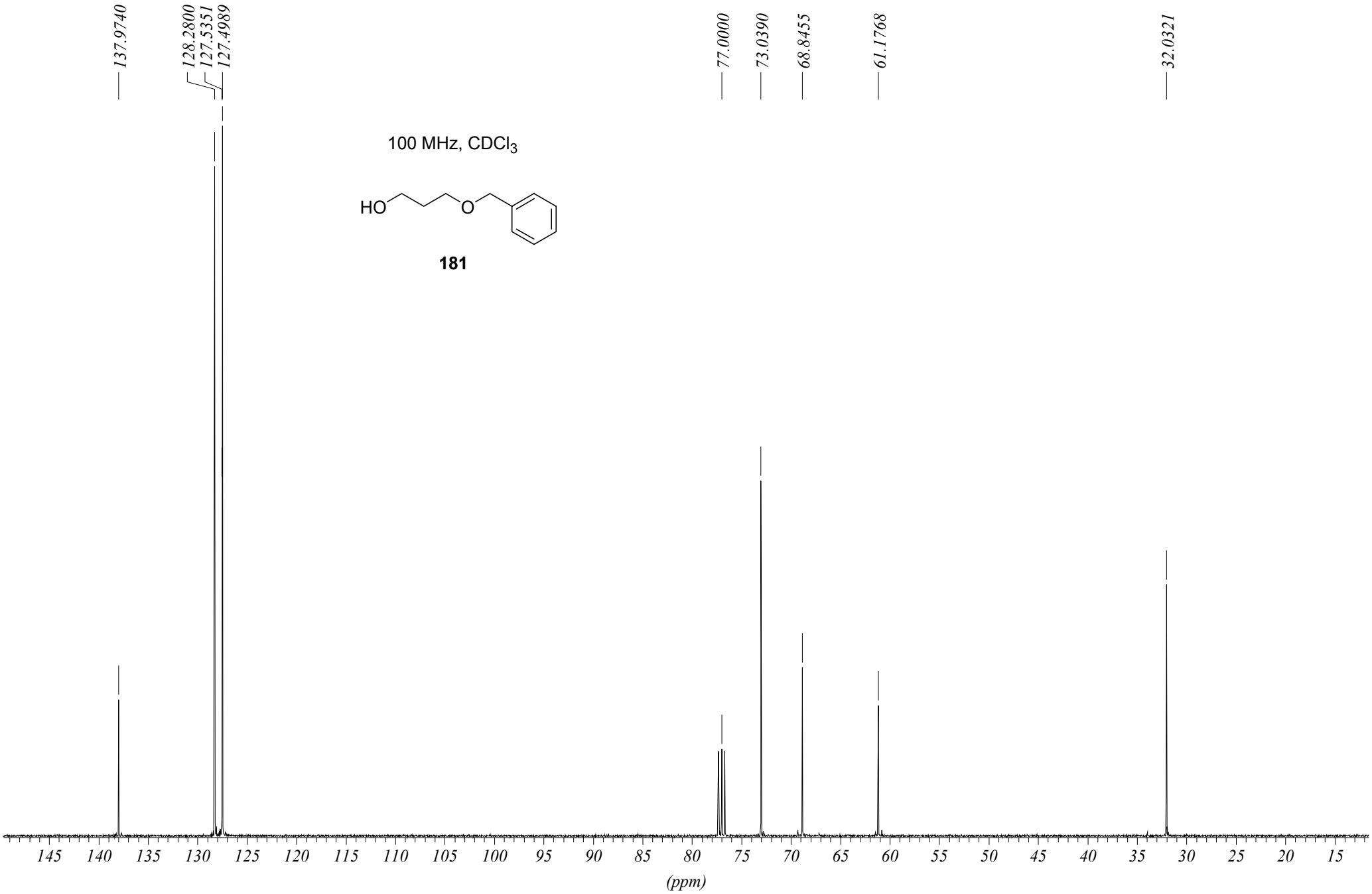
179

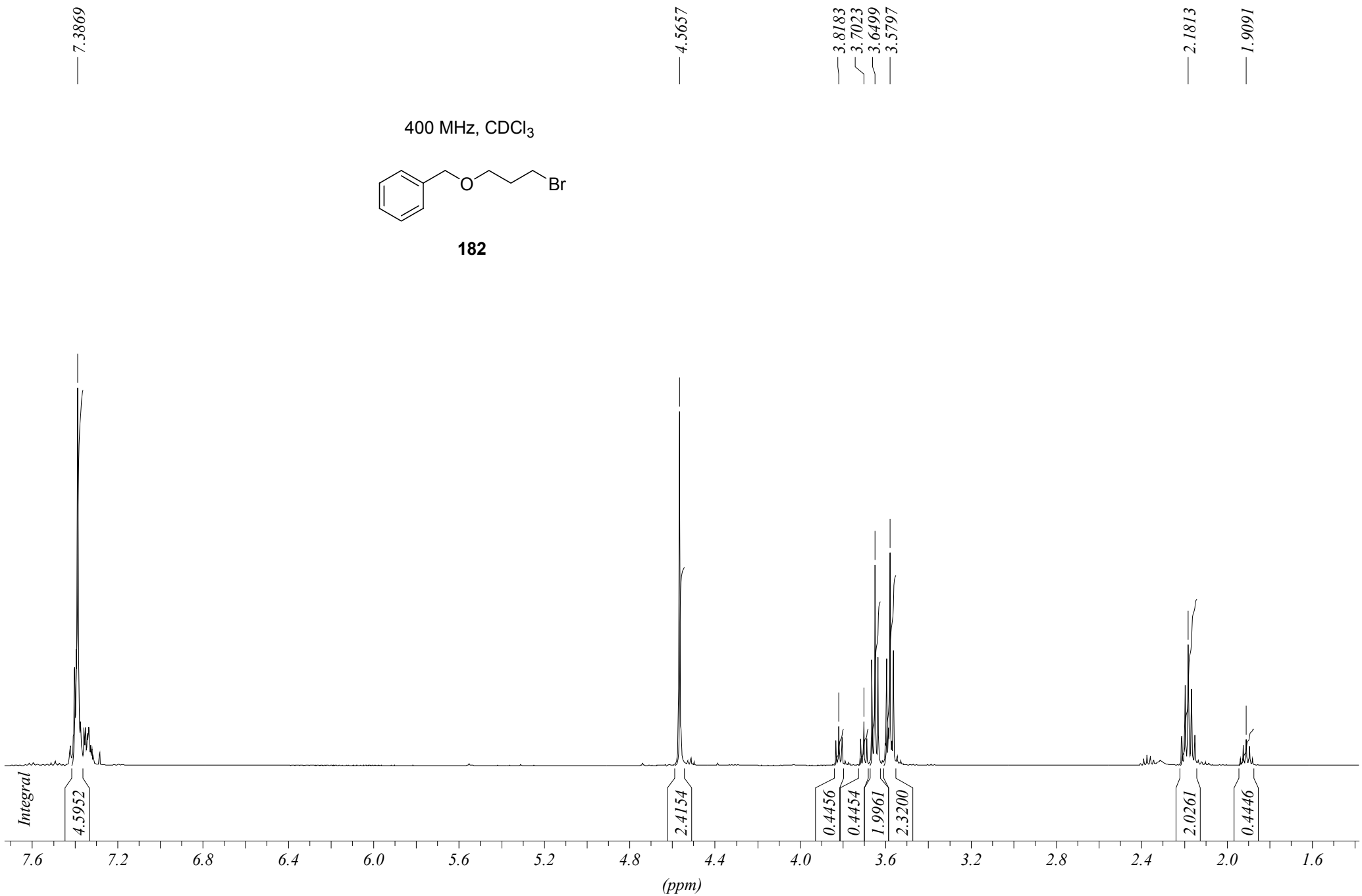


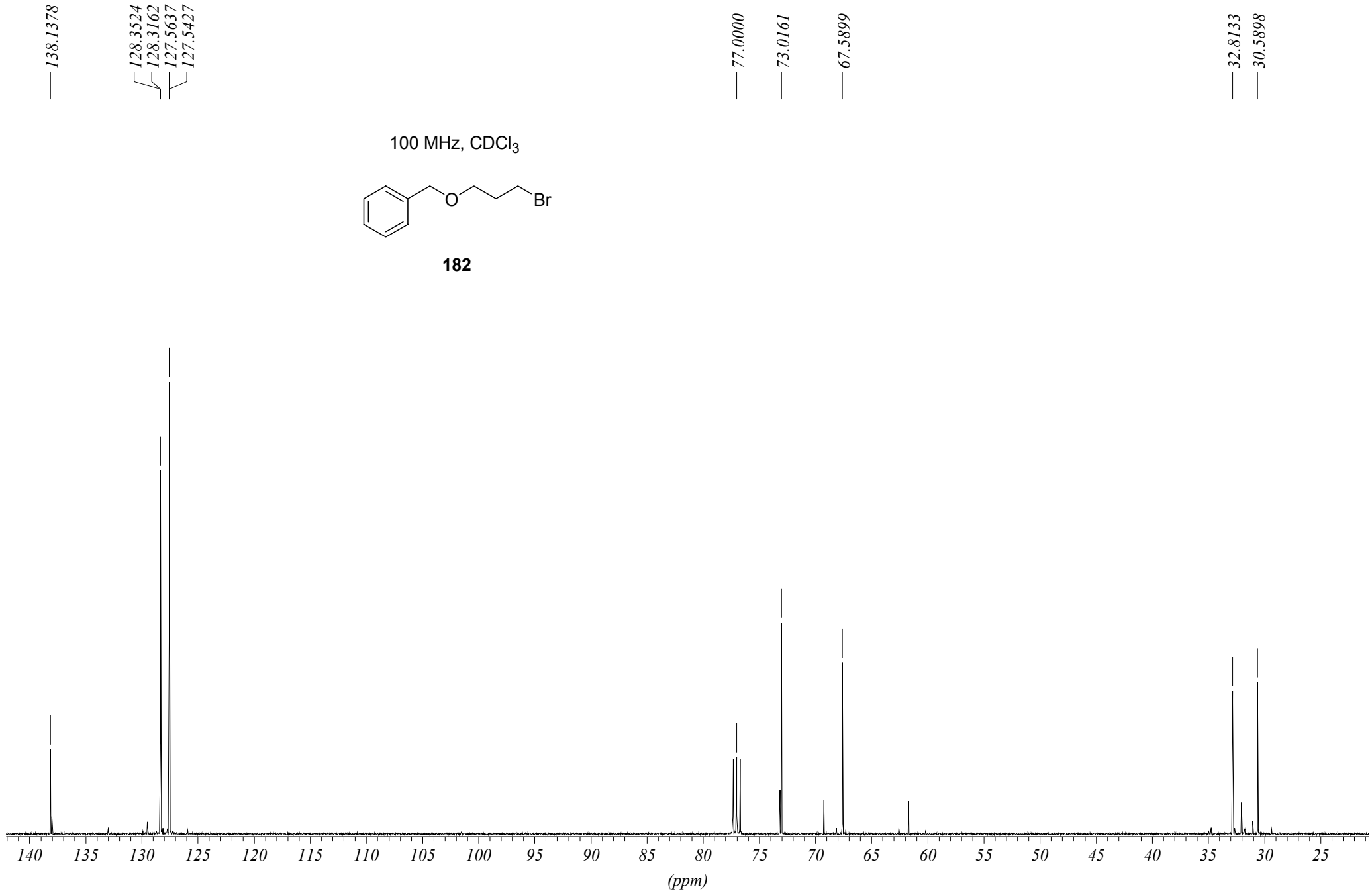

8.3573
7.3967
7.3528
7.2600
6.9327
6.8894
5.2743
3.8183
1.2664
0.8827
200 MHz, CDCl3
NH
O
CCl3
H3C
O
4-Methoxybenzyl 2,2,2-trichloroacetimidate
Integral
0.8795
1.9484
1.9443
1.9165
2.9994
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

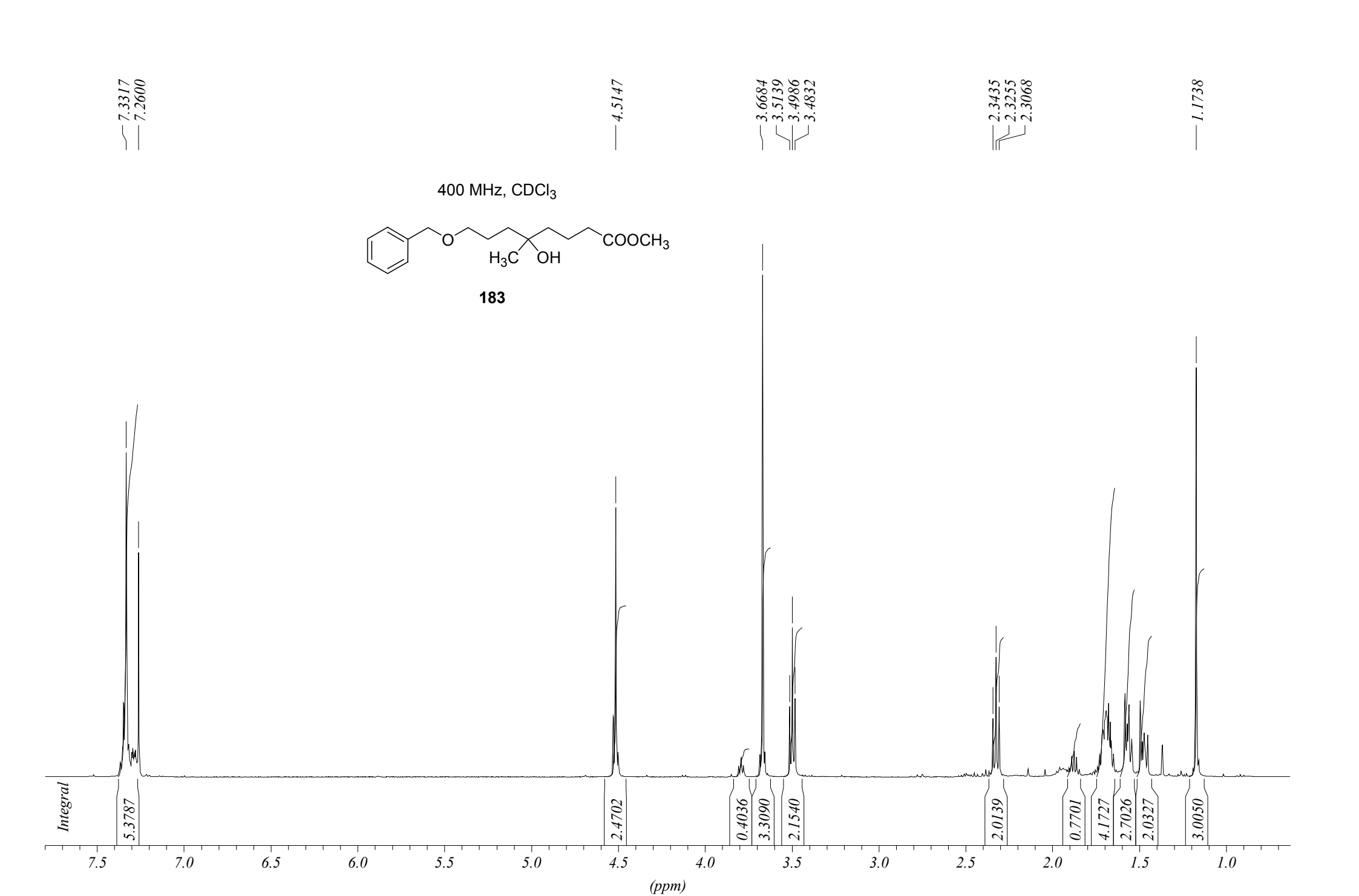

7.2769
7.2600
7.2337
6.8756
6.8318
4.8780
4.3030
3.9826
3.9456
3.8798
3.8434
3.8020
3.7895
3.6654
2.3204
2.0458
1.7041
1.6947
1.5536
1.2131
200 MHz, CDCl3
OCH3
H3C
O
O
O
O
OCH3
180
Integral
5.1586
2.1525
0.7767
1.6375
3.5551
3.4739
3.2497
2.0297
9.2164
2.9806
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

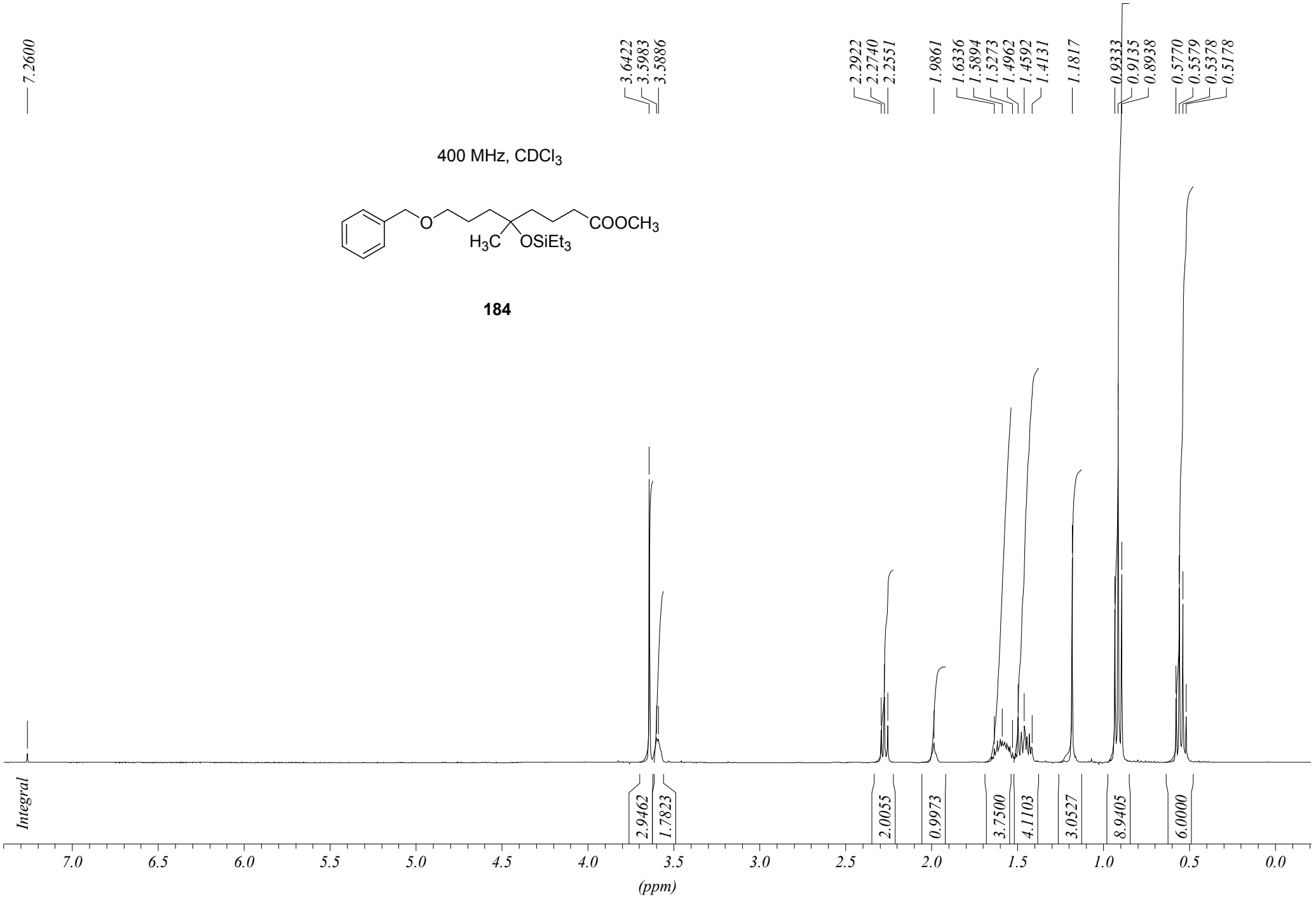

7.3596
4.5390
3.7879
3.7732
3.7588
3.6801
3.6653
3.6506
2.8161
1.8947
1.8799
1.8655
400 MHz, CDCl3
HO
O
181
Integral
4.5682
1.8923
2.0138
1.4601
0.9572
1.9563
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

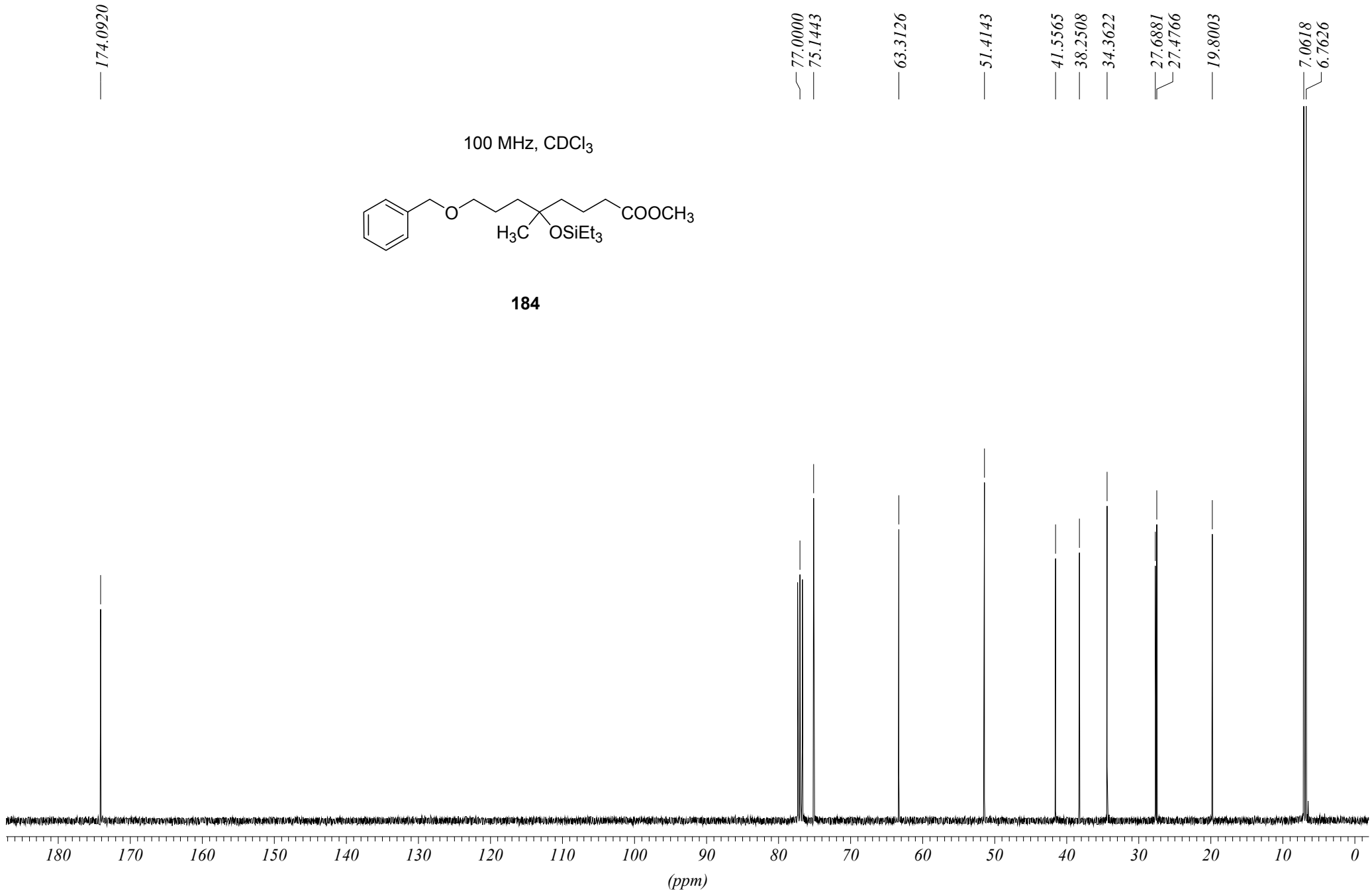

137.9740
128.2800
127.5351
127.4989
77.0000
73.0390
68.8455
61.1768
32.0321
100 MHz, CDCl3
HO
O
181
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
(ppm)

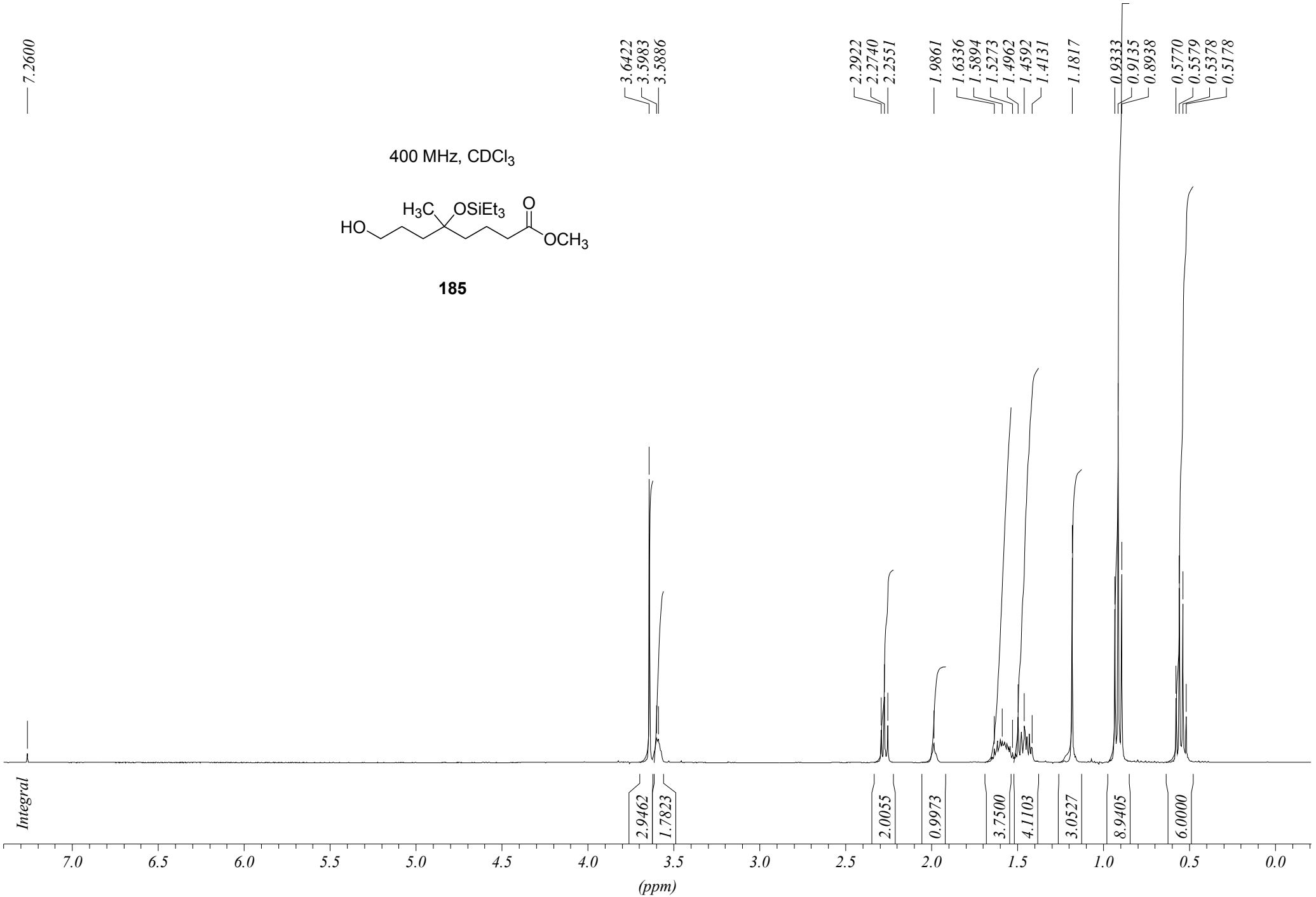

7.3869
4.5657
3.8183
3.7023
3.6499
3.5797
2.1813
1.9091
400 MHz, CDCl3
O
Br
182
Integral
4.5952
2.4154
0.4456
0.4454
1.9961
2.3200
2.0261
0.4446
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
(ppm)

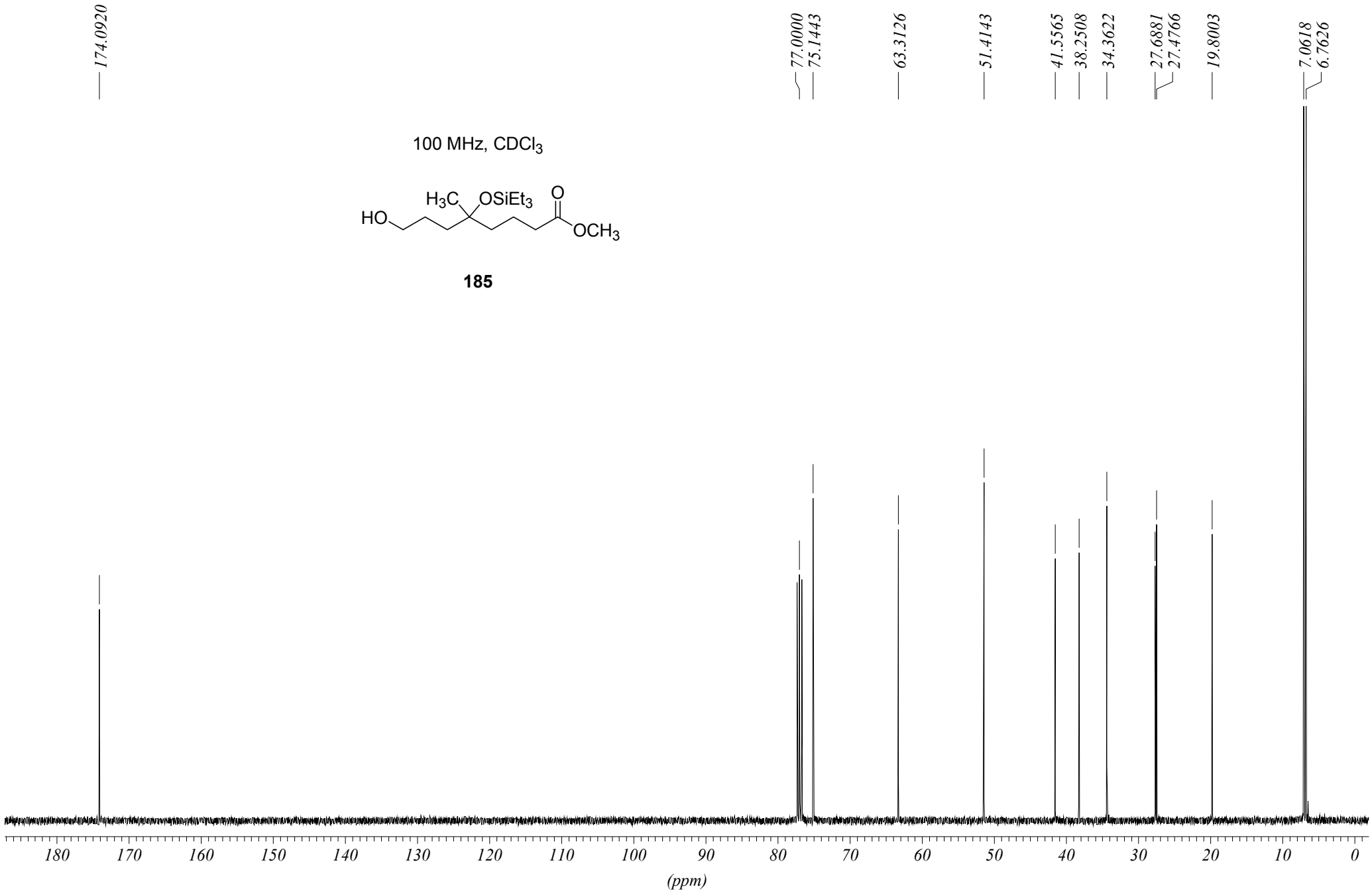

138.1378
128.3524
128.3162
127.5637
127.5427
77.0000
73.0161
67.5899
32.8133
30.5898
100 MHz, CDCl3
O
Br
182
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
(ppm)

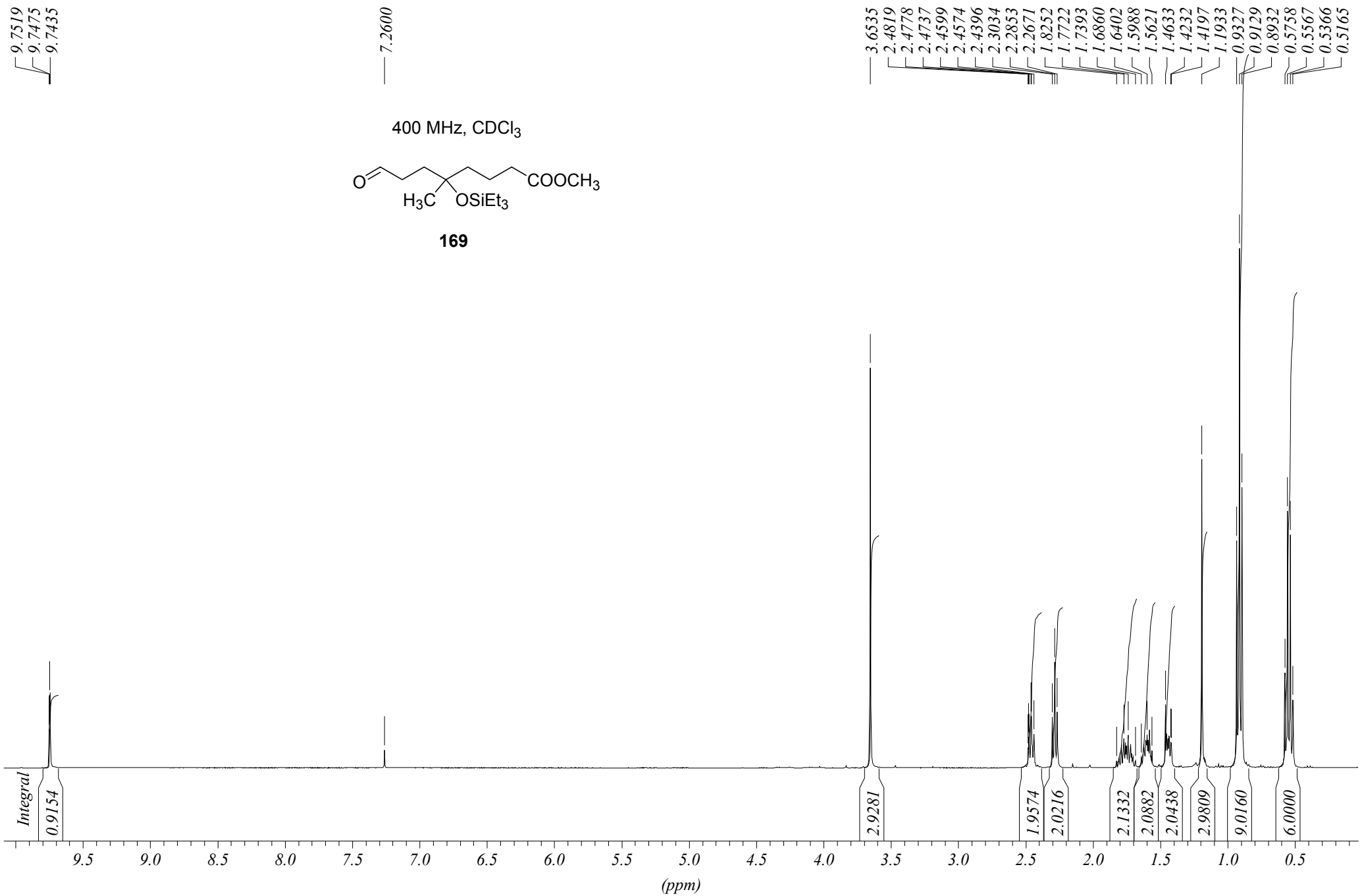

7.3317
7.2600
4.5147
3.6684
3.5139
3.4986
3.4832
2.3435
2.3255
2.3068
1.1738
400 MHz, CDCl3
O
COOCH3
H3C
OH
183
Integral
5.3787
2.4702
0.4036
3.3090
2.1540
2.0139
0.7701
4.1727
2.7026
2.0327
3.0050
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

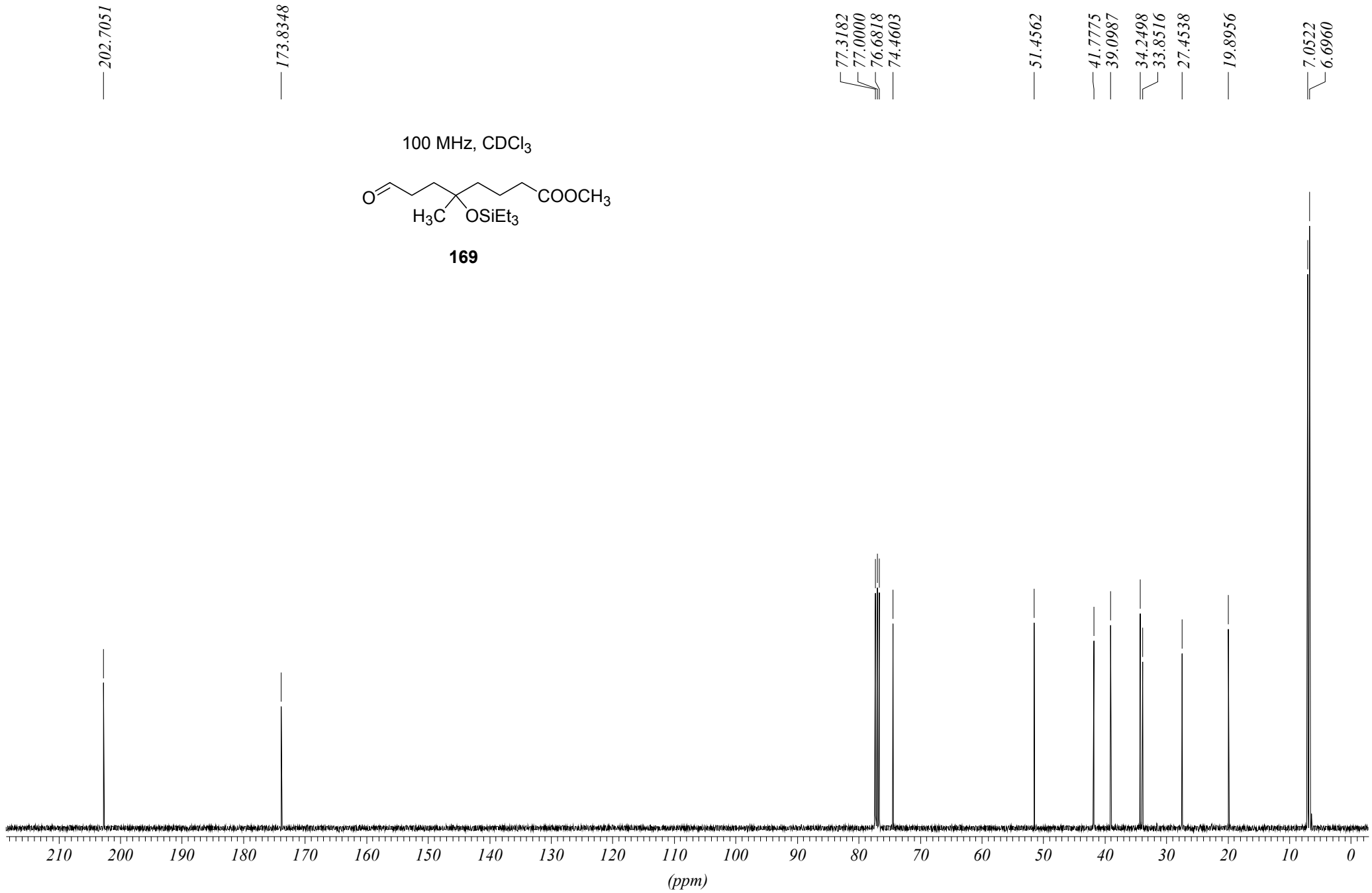

7.2600
3.6422
3.5983
3.5886
2.2922
2.2740
2.2551
1.9861
1.6336
1.5894
1.5273
1.4962
1.4592
1.4131
1.1817
0.9333
0.9135
0.8938
0.5770
0.5579
0.5378
0.5178
400 MHz, CDCl3
O
COOCH3
H3C
OSiEt3
184
Integral
2.9462
1.7823
2.0055
0.9973
3.7500
4.1103
3.0527
8.9405
6.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


174.0920
77.0000
75.1443
63.3126
51.4143
41.5565
38.2508
34.3622
27.6881
27.4766
19.8003
7.0618
6.7626
100 MHz, CDCl3
O
COOCH3
H3C
OSiEt3
184
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


7.2600
3.6422
3.5983
3.5886
2.2922
2.2740
2.2551
1.9861
1.6336
1.5894
1.5273
1.4962
1.4592
1.4131
1.1817
0.9333
0.9135
0.8938
0.5770
0.5579
0.5378
0.5178
400 MHz, CDCl3
H3C
OSiEt3
O
HO
OCH3
185
Integral
2.9462
1.7823
2.0055
0.9973
3.7500
4.1103
3.0527
8.9405
6.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


174.0920
77.0000
75.1443
63.3126
51.4143
41.5565
38.2508
34.3622
27.6881
27.4766
19.8003
7.0618
6.7626
100 MHz, CDCl3
H3C
OSiEt3
O
HO
OCH3
185
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

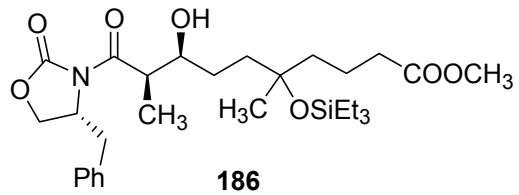

9.7519
9.7475
9.7435
7.2600
3.6535
2.4819
2.4778
2.4737
2.4599
2.4574
2.4396
2.3034
2.2853
2.2671
1.8252
1.7722
1.7393
1.6860
1.6402
1.5988
1.5621
1.4633
1.4232
1.4197
1.1933
0.9327
0.9129
0.8932
0.5758
0.5567
0.5366
0.5165
400 MHz, CDCl3
O
COOCH3
H3C
OSiEt3
169
Integral
0.9154
2.9281
1.9574
2.0216
2.1332
2.0882
2.0438
2.9809
9.0160
6.0000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


202.7051
173.8348
77.3182
77.0000
76.6818
74.4603
51.4562
41.7775
39.0987
34.2498
33.8516
27.4538
19.8956
7.0522
6.6960
100 MHz, CDCl3
O
COOCH3
H3C
OSiEt3
169
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

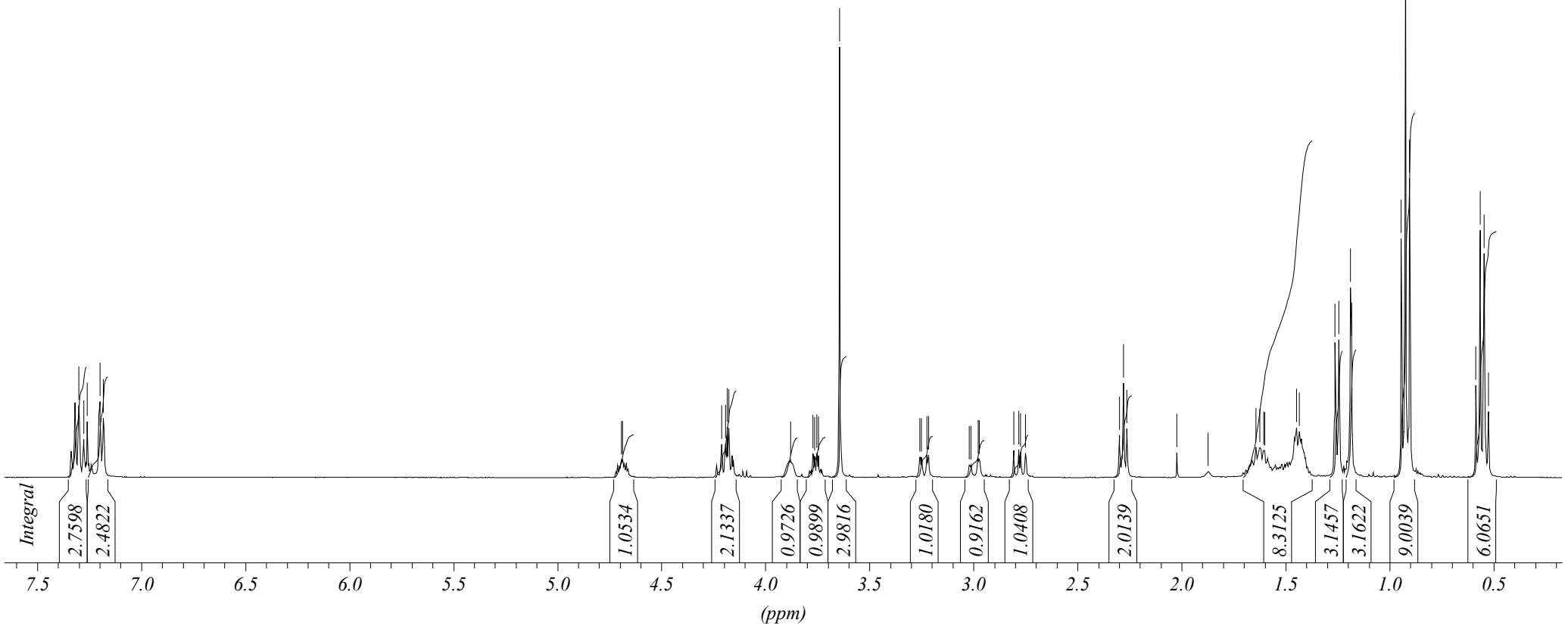
7.3008
7.2776
7.2600
7.1995
7.1825

4.6928
4.6878
4.2114
4.1923
4.1841
4.1766
3.8790
3.7711
3.7633
3.7536
3.7457
3.6447
3.2581
3.2496
3.2242
3.2164
3.0194
3.0125
2.9786
2.9714
2.8071
2.7836
2.7739
2.7503
2.2991
2.2809
2.2624
2.0231
1.8732
1.6430
1.6235
1.6069
1.6016
1.4489
1.4335
1.2623
1.2447
1.1883
1.1836
0.9440
0.9239
0.9044
0.5855
0.5658
0.5460
0.5259

400 MHz, $CDCl_3$

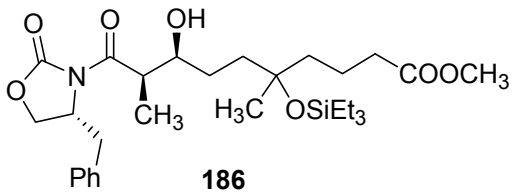


186

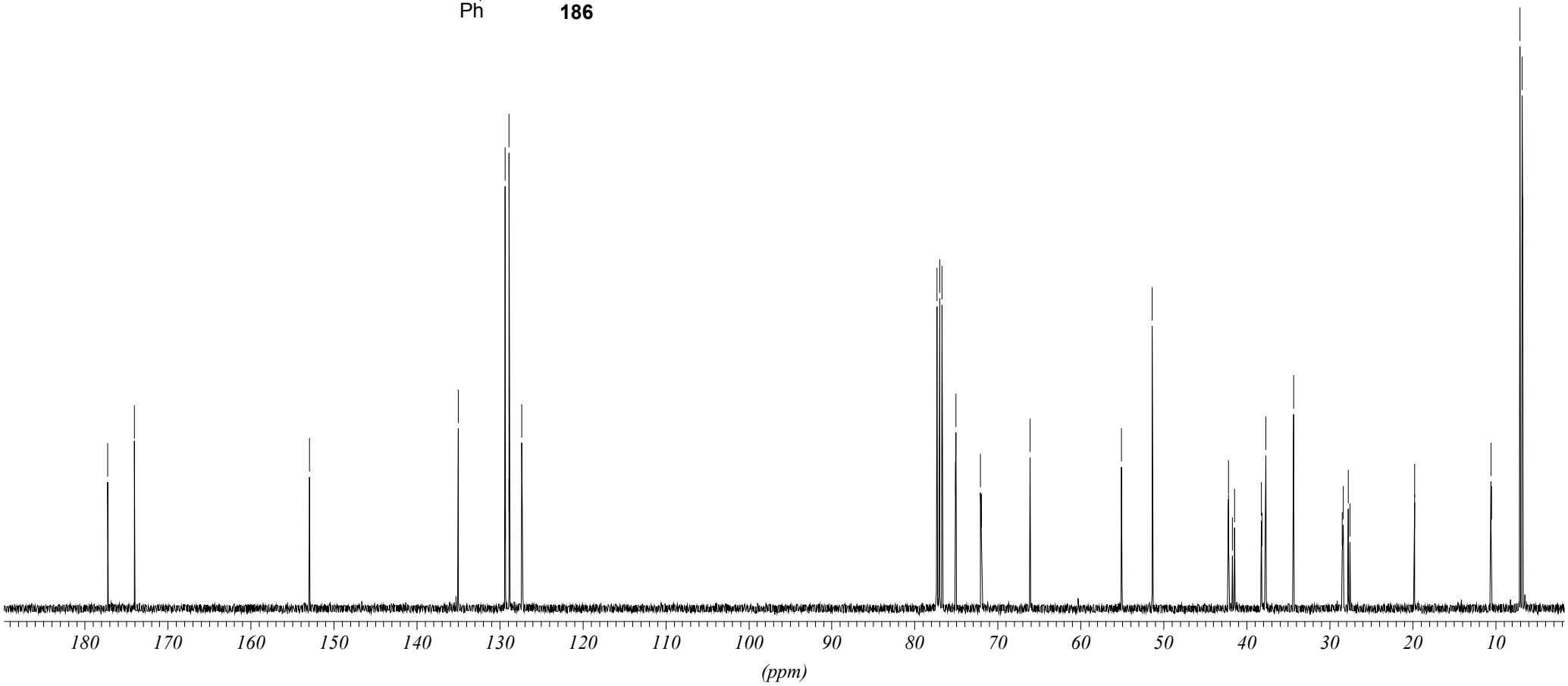


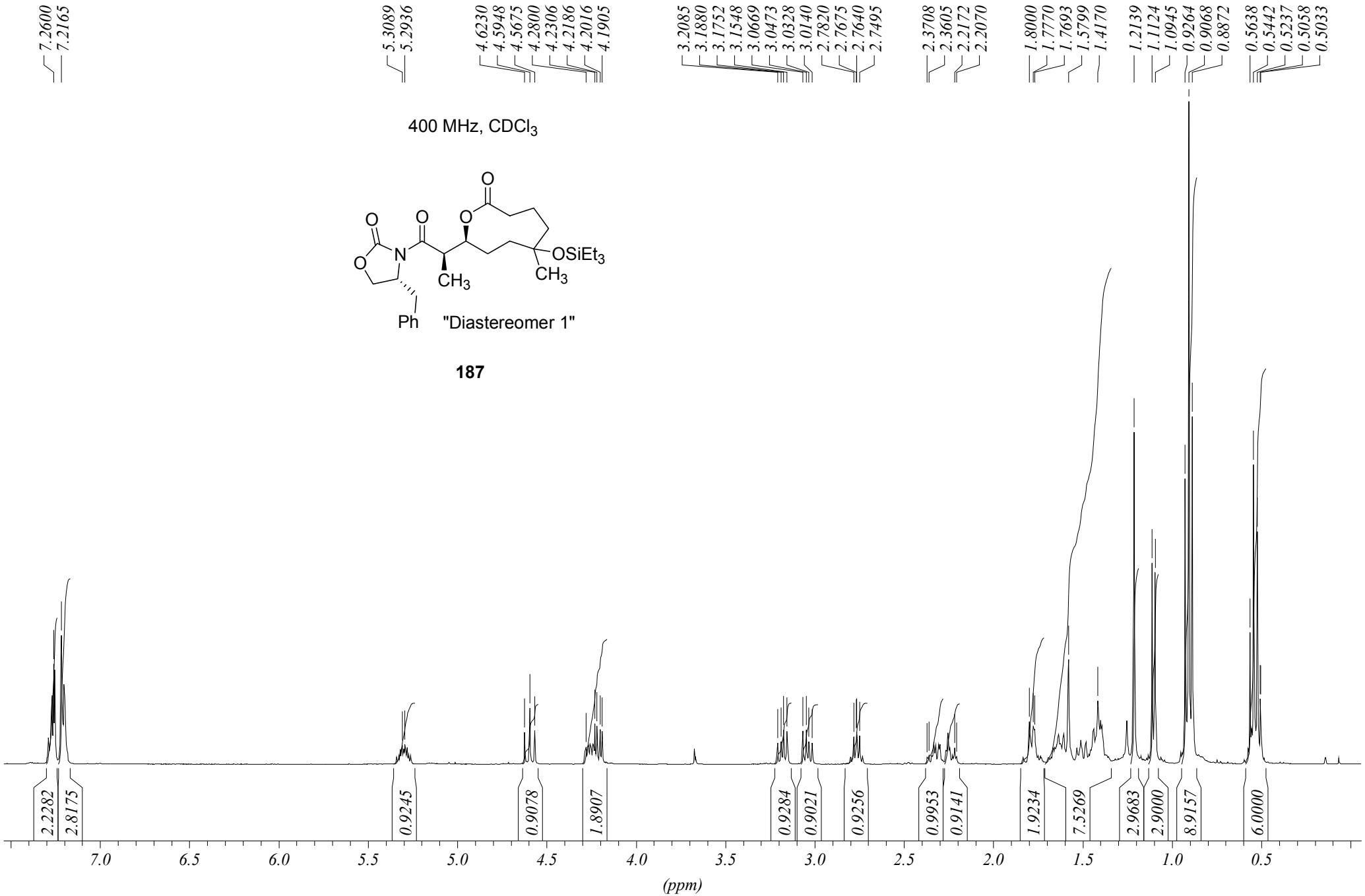
177.2128
173.9986
152.9455
134.9999
129.3451
129.3279
128.8669
128.8535
127.3179
77.3182
77.0000
76.6818
75.0662
75.0376
72.0482
71.9492
66.0657
55.0533
51.3724
42.1986
42.1662
41.7318
41.4250
38.2356
38.1747
37.6755
34.3470
28.4635
28.3721
27.7300
27.5338
19.7775
19.7565
10.5370
10.4646
7.0846
6.7550
6.7455

100 MHz, $CDCl_3$



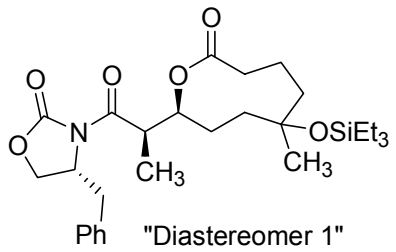
186




7.2600
7.2165
5.3089
5.2936
4.6230
4.5948
4.5675
4.2800
4.2306
4.2186
4.2016
4.1905
3.2085
3.1880
3.1752
3.1548
3.0669
3.0473
3.0328
3.0140
2.7820
2.7675
2.7640
2.7495
2.3708
2.3605
2.2172
2.2070
1.8000
1.7770
1.7693
1.5799
1.4170
1.2139
1.1124
1.0945
0.9264
0.9068
0.8872
0.5638
0.5442
0.5237
0.5058
0.5033
400 MHz, CDCl3
O
O
O
O
N
O
OSiEt3
CH3
CH3
Ph
"Diastereomer 1"
187
2.2282
2.8175
0.9245
0.9078
1.8907
0.9284
0.9021
0.9256
0.9953
0.9141
1.9234
7.5269
2.9683
2.9000
8.9157
6.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

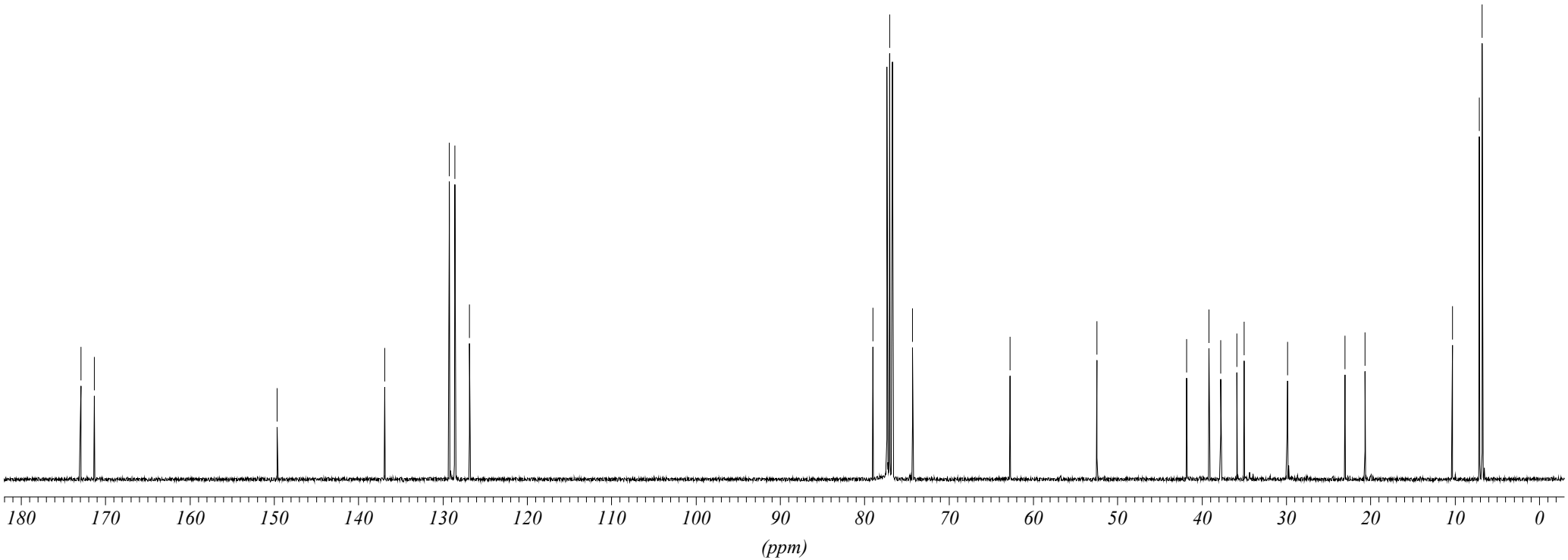
172.8974
171.2855
149.5980
136.8708
129.2270
128.5201
126.8206
78.9796
77.0000
74.2774
62.7239
52.4203
41.8061
39.1292
37.7307
35.8236
34.9605
29.8601
23.0088
20.6558
10.3007
7.0885
6.7798

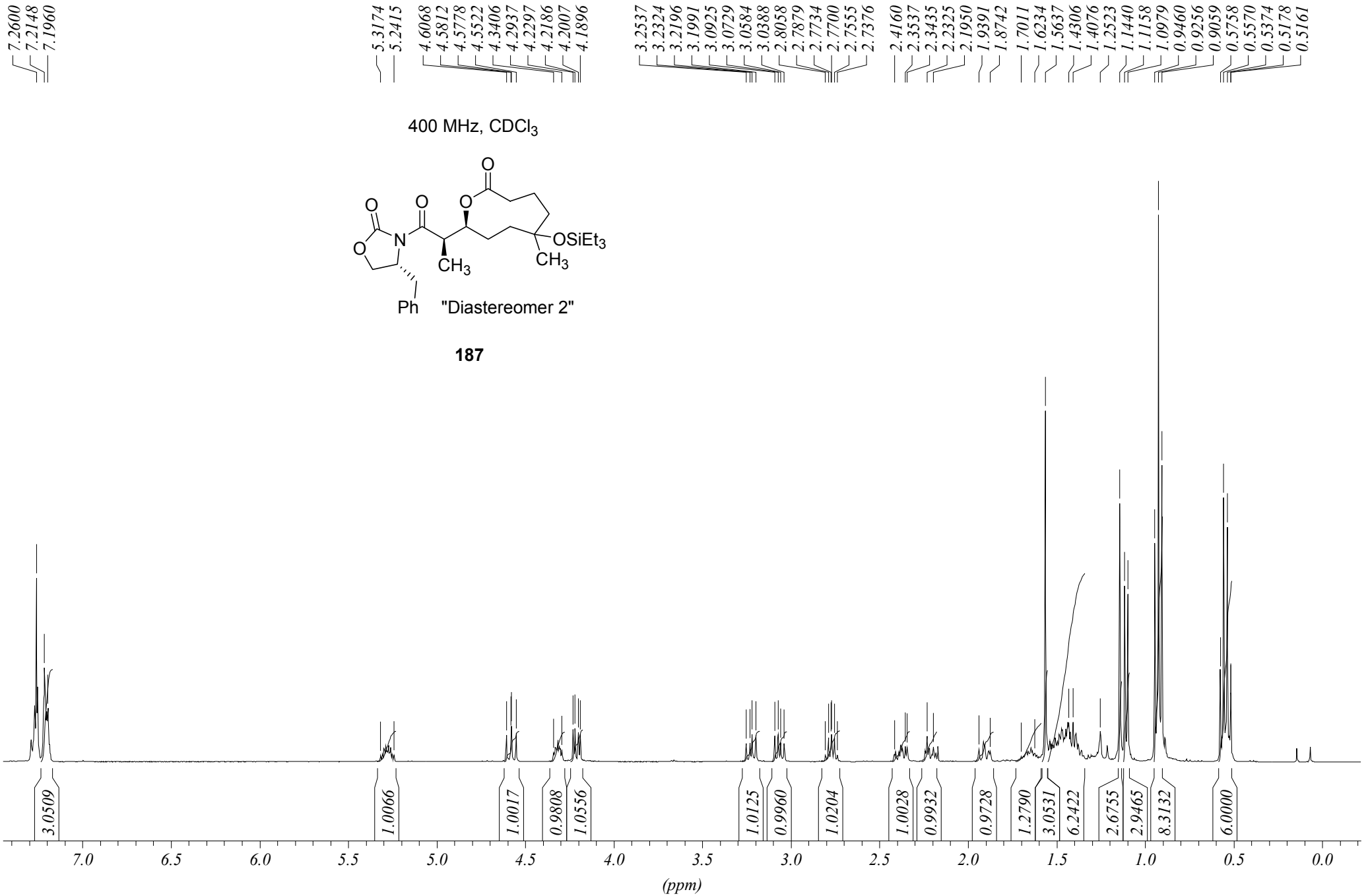
100 MHz, $CDCl_3$

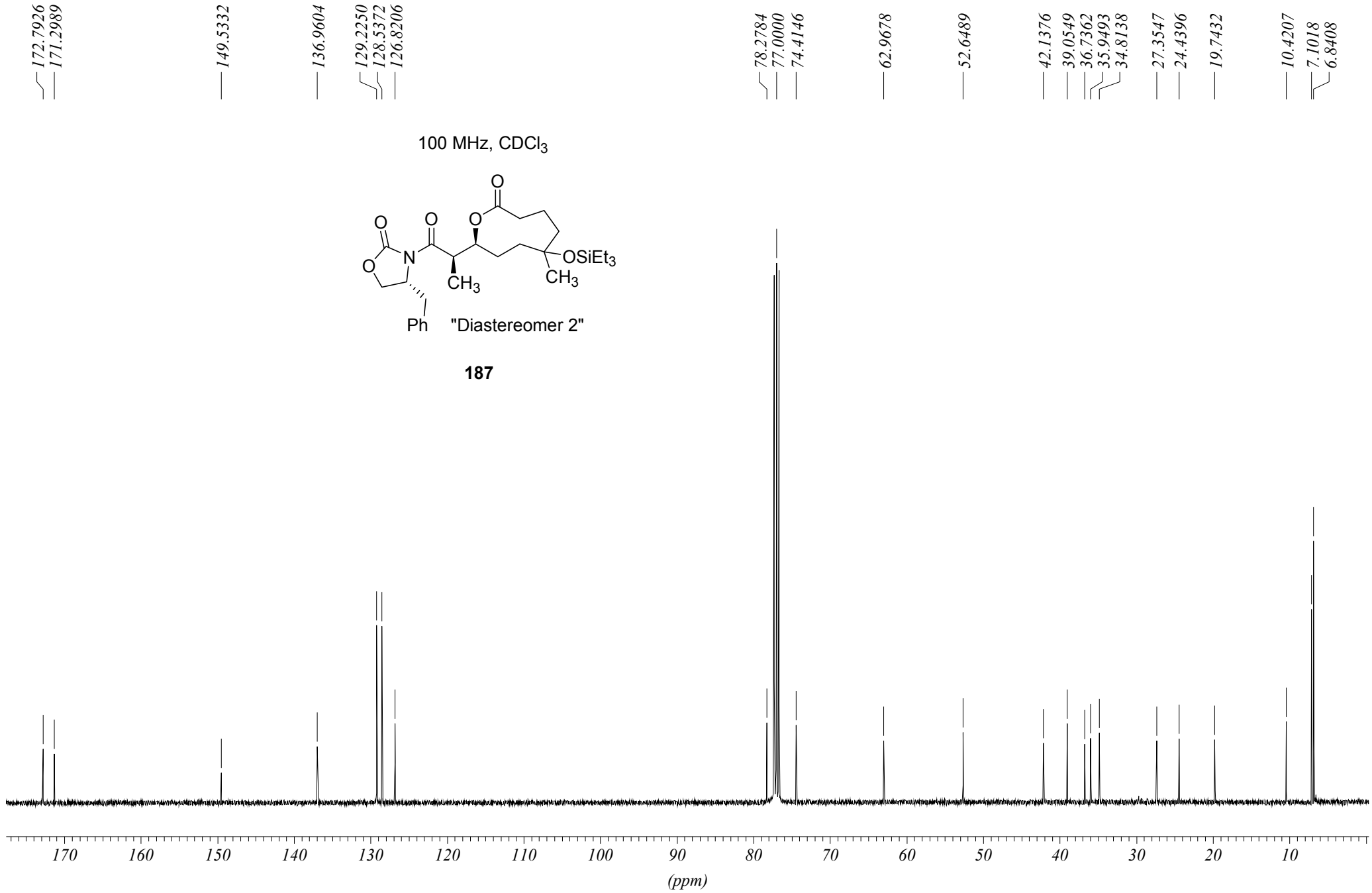


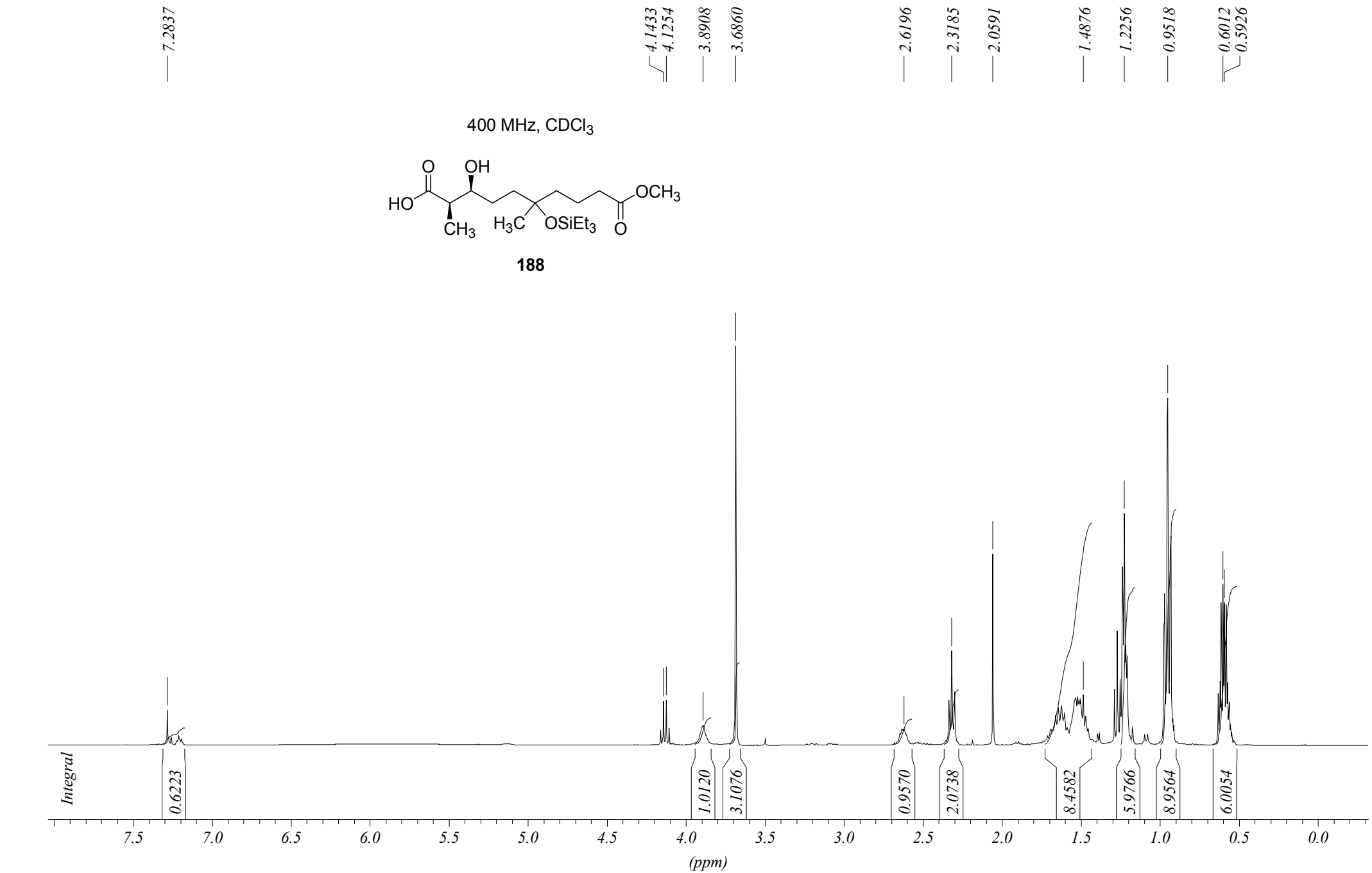
"Diastereomer 1"

187



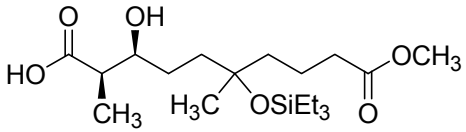

7.2600
7.2148
7.1960
5.3174
5.2415
4.6068
4.5812
4.5778
4.5522
4.3406
4.2937
4.2297
4.2186
4.2007
4.1896
3.2537
3.2324
3.2196
3.1991
3.0925
3.0729
3.0584
3.0388
2.8058
2.7879
2.7734
2.7700
2.7555
2.7376
2.4160
2.3537
2.3435
2.2325
2.1950
1.9391
1.8742
1.7011
1.6234
1.5637
1.4306
1.4076
1.2523
1.1440
1.1158
1.0979
0.9460
0.9256
0.9059
0.5758
0.5570
0.5374
0.5178
0.5161
400 MHz, CDCl3
O
O
O
O
N
O
OSiEt3
CH3
CH3
Ph
"Diastereomer 2"
187
3.0509
1.0066
1.0017
0.9808
1.0556
1.0125
0.9960
1.0204
1.0028
0.9932
0.9728
1.2790
3.0531
6.2422
2.6755
2.9465
8.3132
6.0000
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


172.7926
171.2989
149.5332
136.9604
129.2250
128.5372
126.8206
78.2784
77.0000
74.4146
62.9678
52.6489
42.1376
39.0549
36.7362
35.9493
34.8138
27.3547
24.4396
19.7432
10.4207
7.1018
6.8408
100 MHz, CDCl3
O
O
O
O
N
O
OSiEt3
CH3
CH3
Ph
"Diastereomer 2"
187
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

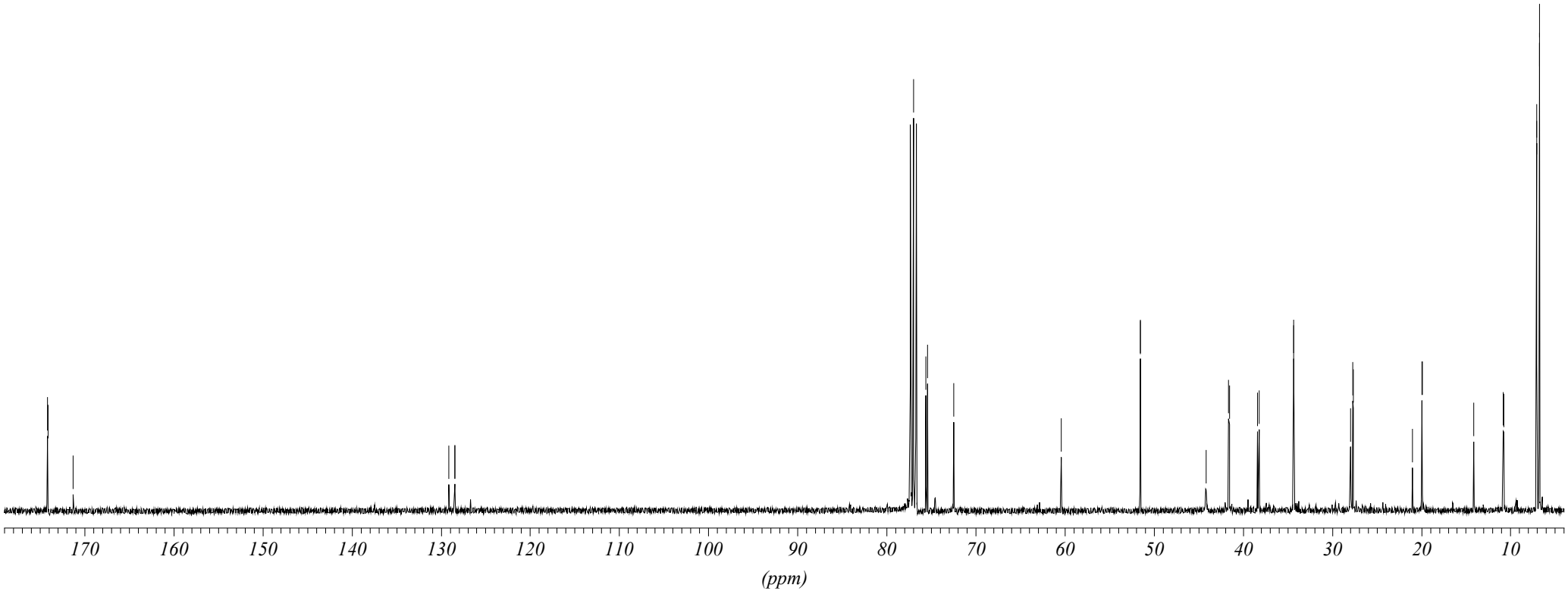

7.2837
4.1433
4.1254
3.8908
3.6860
2.6196
2.3185
2.0591
1.4876
1.2256
0.9518
0.6012
0.5926
400 MHz, CDCl3
O
OH
HO
OCH3
CH3
H3C
OSiEt3
O
188
Integral
0.6223
1.0120
3.1076
0.9570
2.0738
8.4582
5.9766
8.9564
6.0054
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

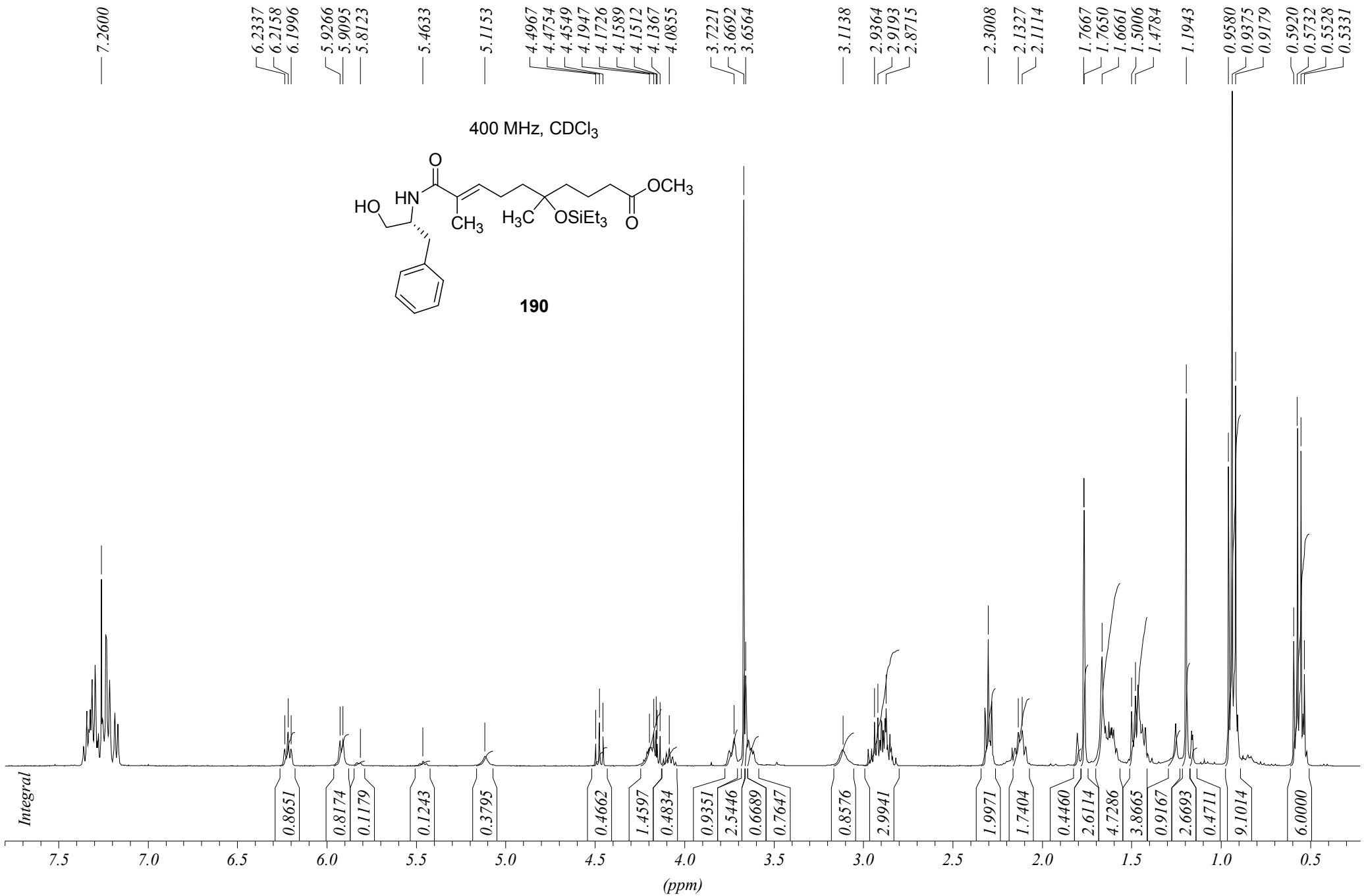
174.1282
174.0882
171.2588
129.1107
128.4610
128.4458
77.0000
75.5787
75.3882
72.4617
60.4166
51.5305
51.5172
44.1438
41.6232
41.5374
38.3957
38.2242
34.3394
34.3013
27.9548
27.6900
27.6500
21.0102
19.9223
19.8842
14.1474
10.8266
10.7713
7.0694
7.0446
6.7474
6.7150

100 MHz, $CDCl_3$



188




7.2600
6.2337
6.2158
6.1996
5.9266
5.9095
5.8123
5.4633
5.1153
4.4967
4.4754
4.4549
4.1947
4.1726
4.1589
4.1512
4.1367
4.0855
3.7221
3.6692
3.6564
3.1138
2.9364
2.9193
2.8715
2.3008
2.1327
2.1114
1.7667
1.7650
1.6661
1.5006
1.4784
1.1943
0.9580
0.9375
0.9179
0.5920
0.5732
0.5528
0.5331
400 MHz, CDCl3
HO
HN
O
CH3
H3C
OSiEt3
OCH3
O
190
Integral
0.8651
0.8174
0.1179
0.1243
0.3795
0.4662
1.4597
0.4834
0.9351
2.5446
0.6689
0.7647
0.8576
2.9941
1.9971
1.7404
0.4460
2.6114
4.7286
3.8665
0.9167
2.6693
0.4711
9.1014
6.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

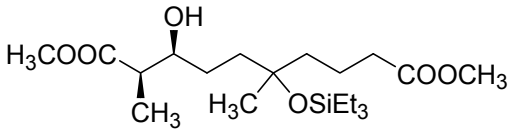
7.2600

4.1732
4.1381
4.1024
4.0666
3.8328
3.7086
3.6685

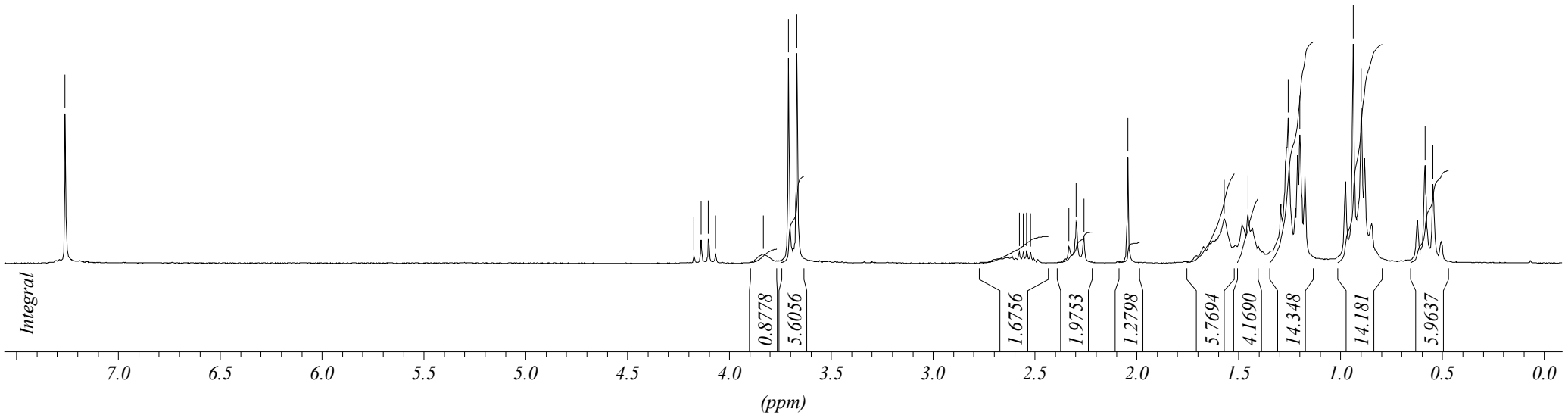
2.5762
2.5568
2.5399
2.5204
2.3317
2.2966
2.2602
2.0439

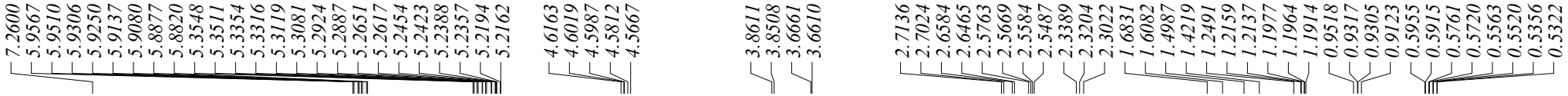
1.5693
1.4539
1.2576
1.1981
0.9360
0.8977
0.5842
0.5454

200 MHz, $CDCl_3$

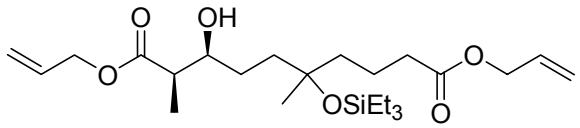


191

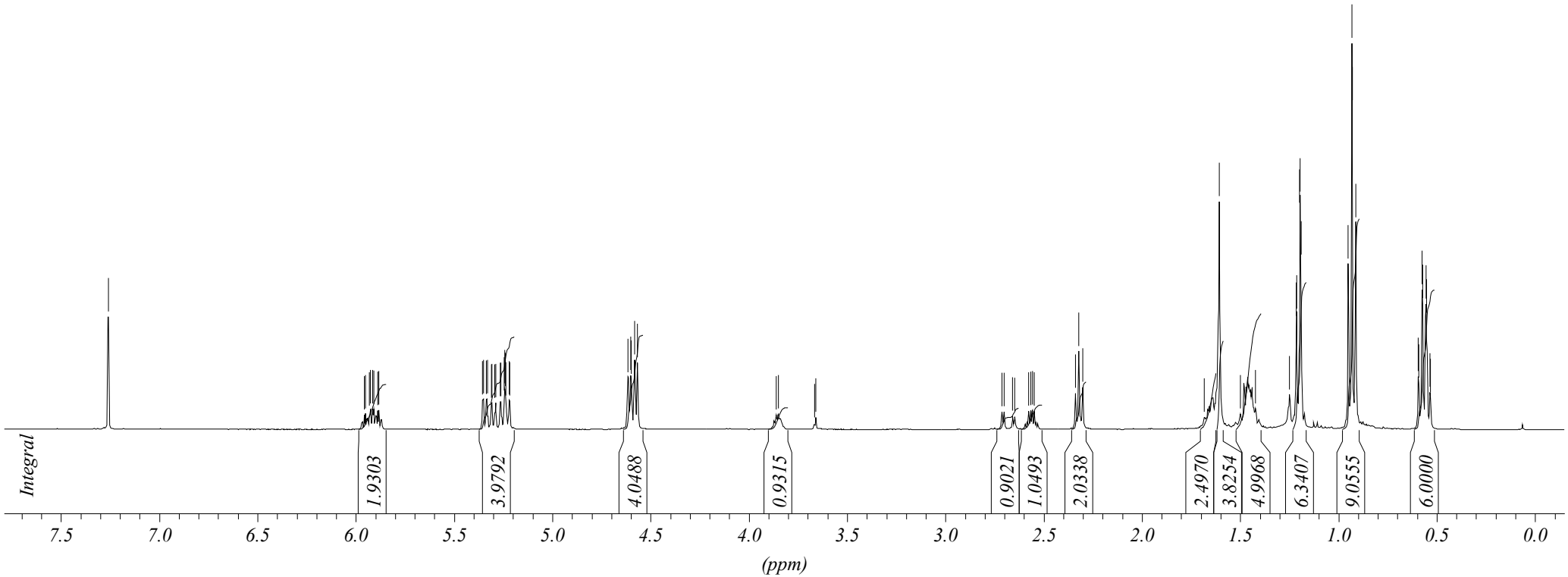


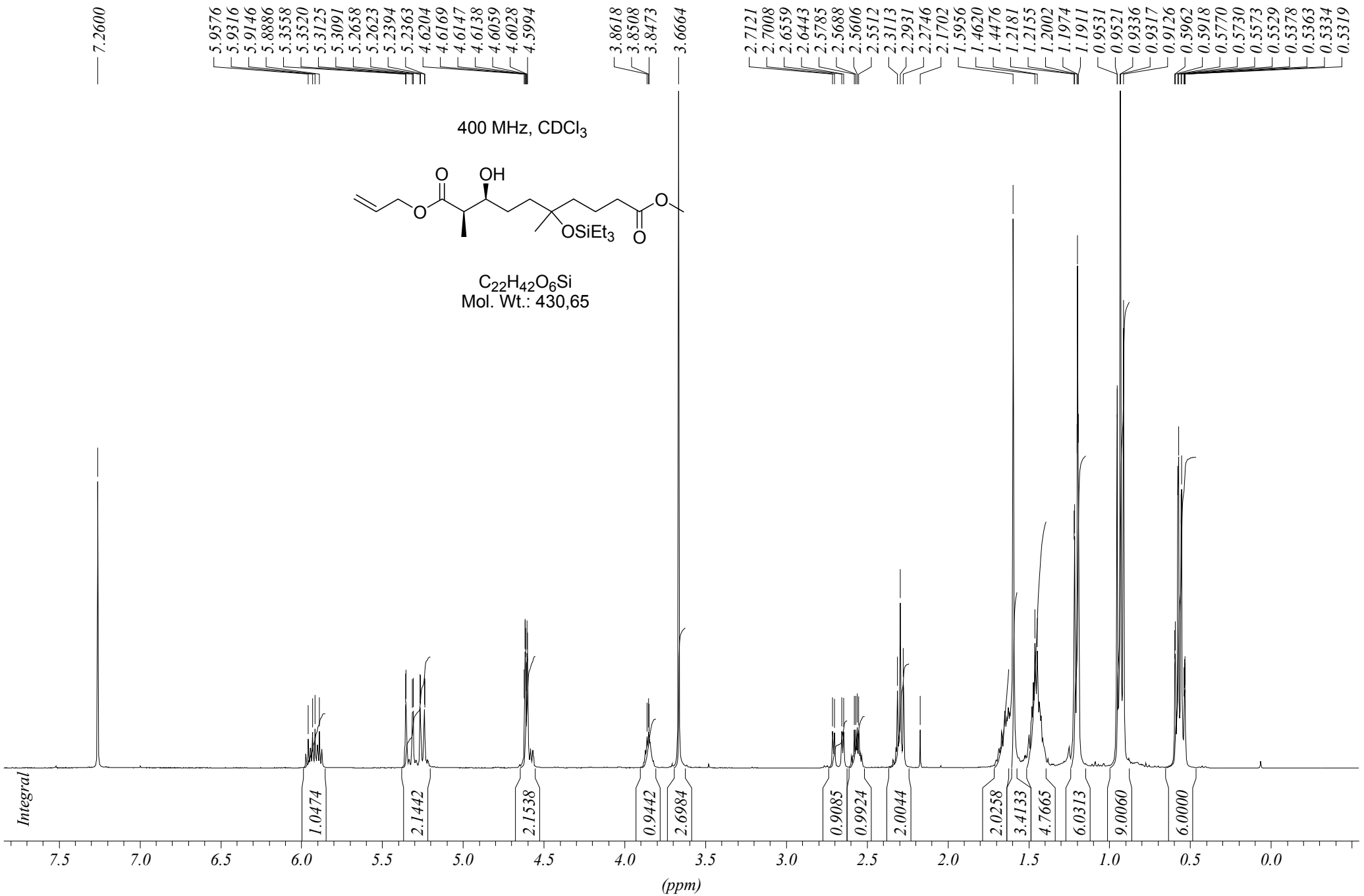


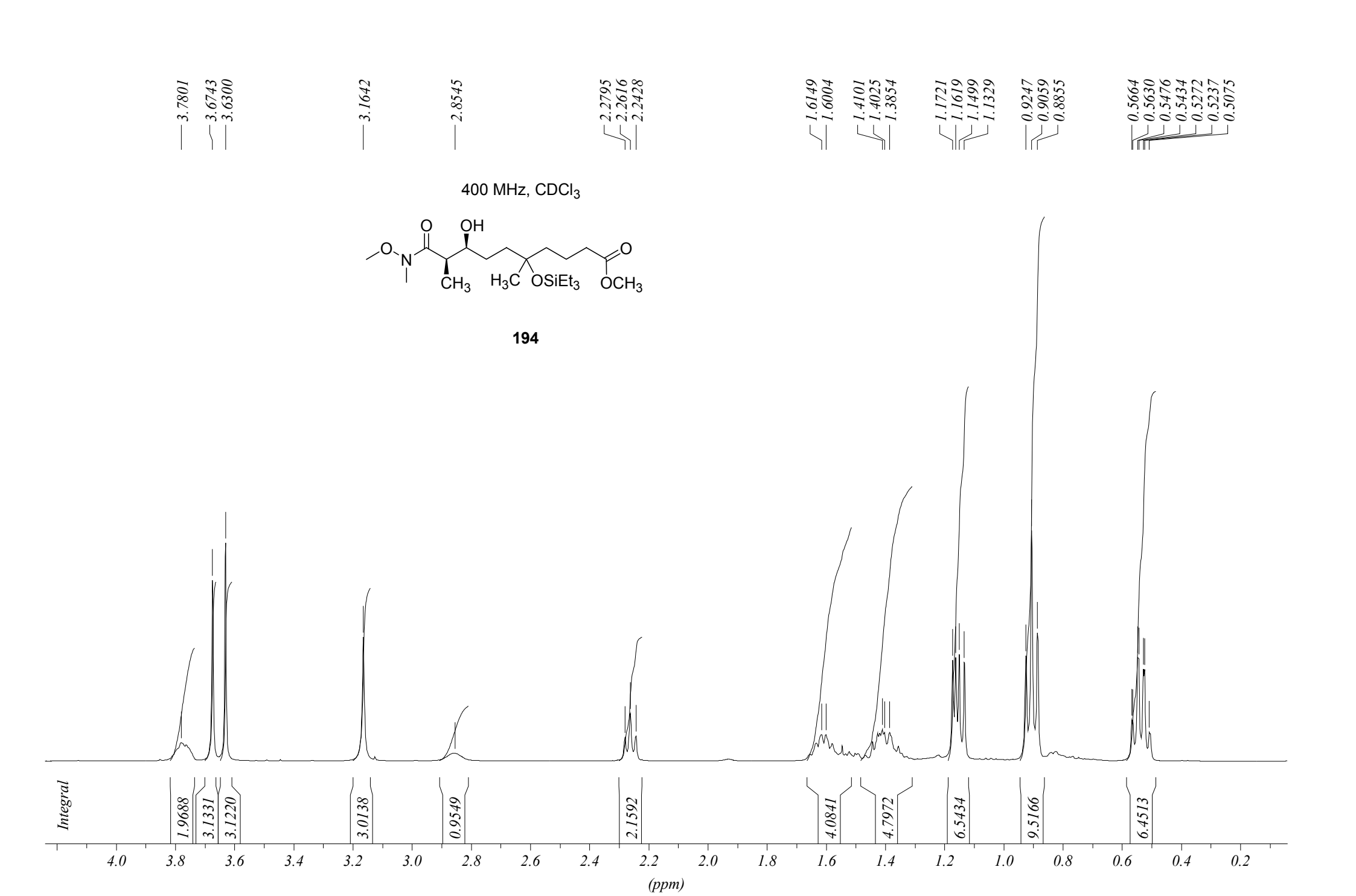
400 MHz, $CDCl_3$

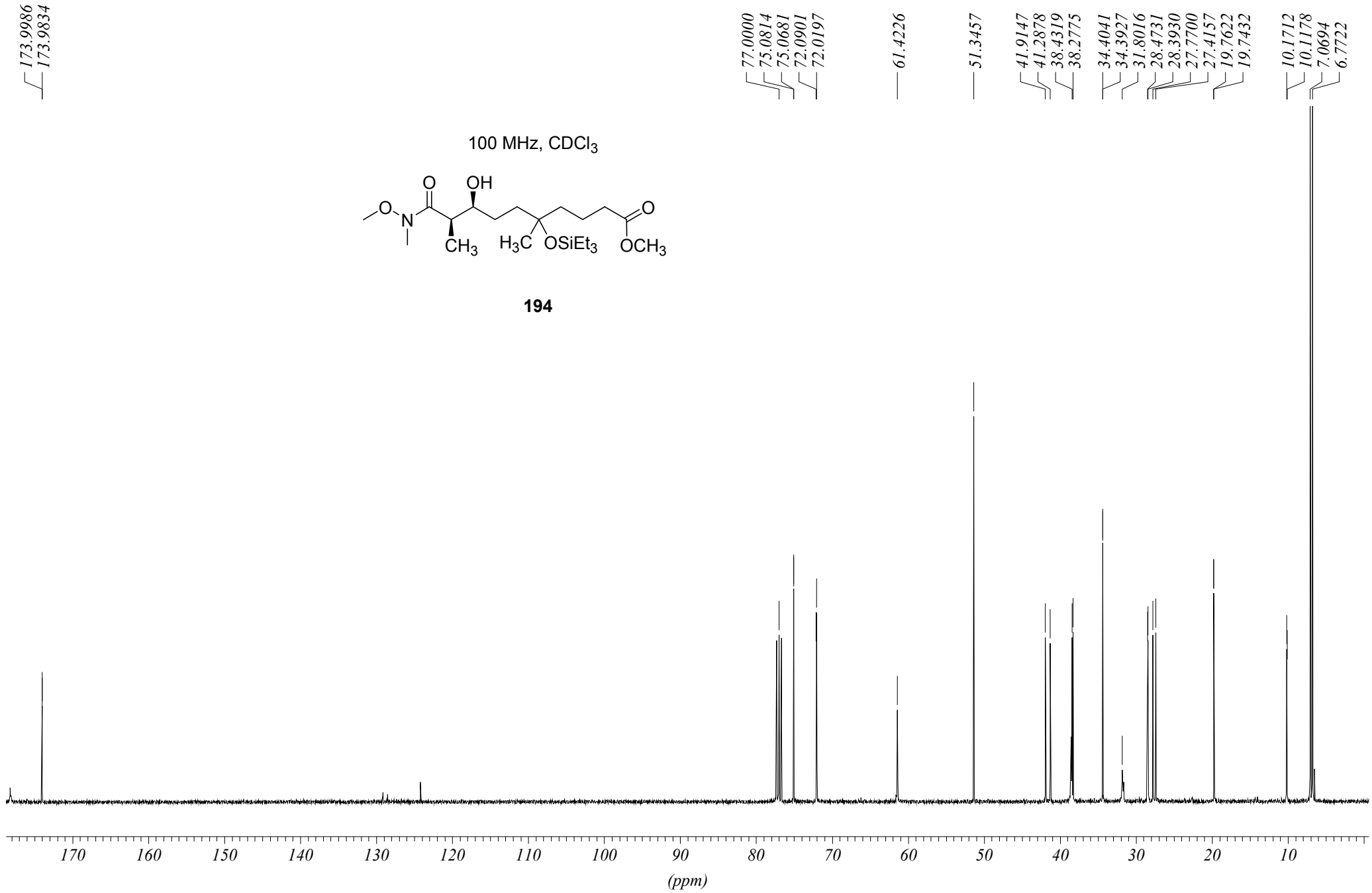


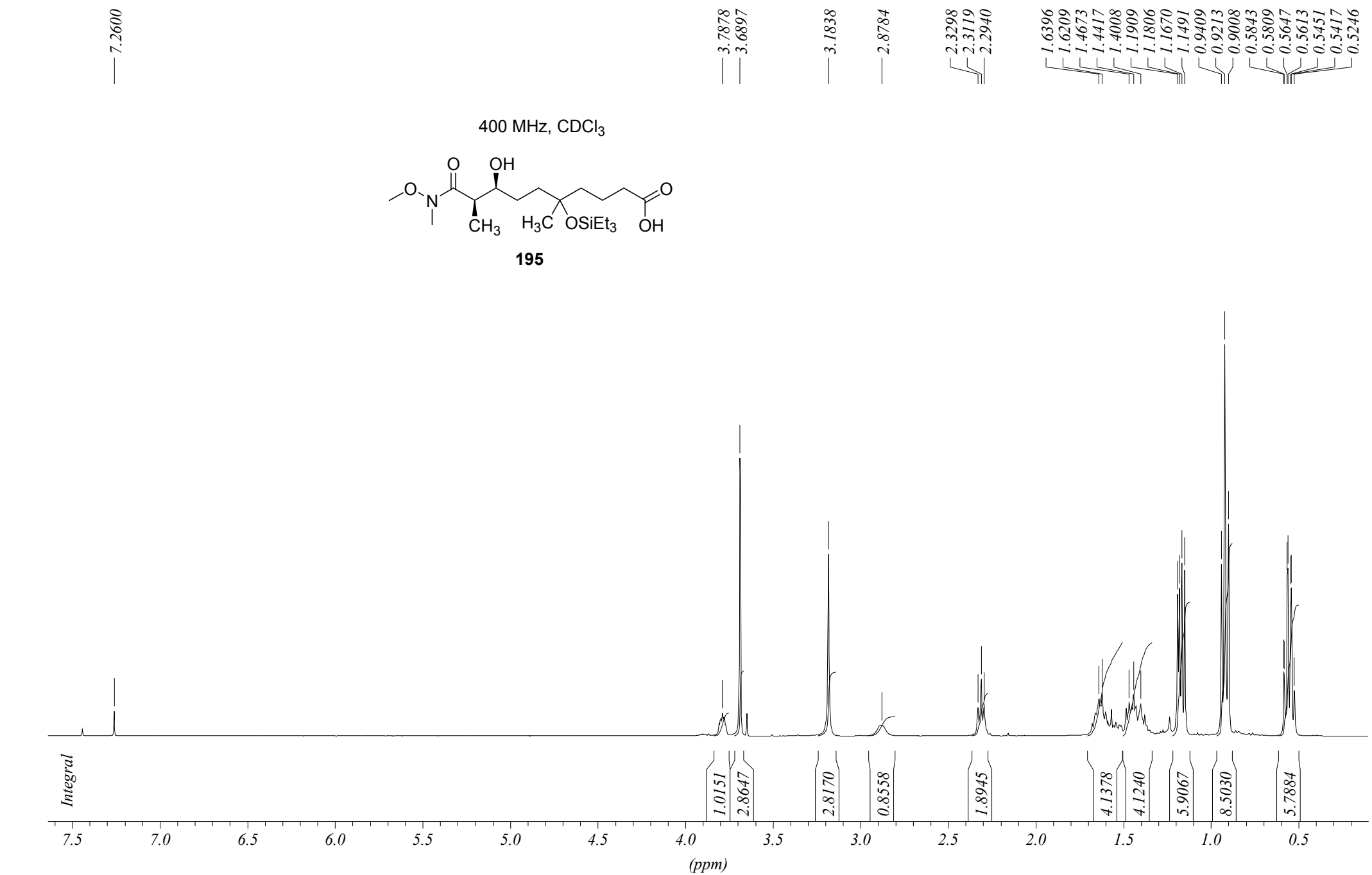
$C_{24}H_{44}O_6Si$
Mol. Wt.: 456,69

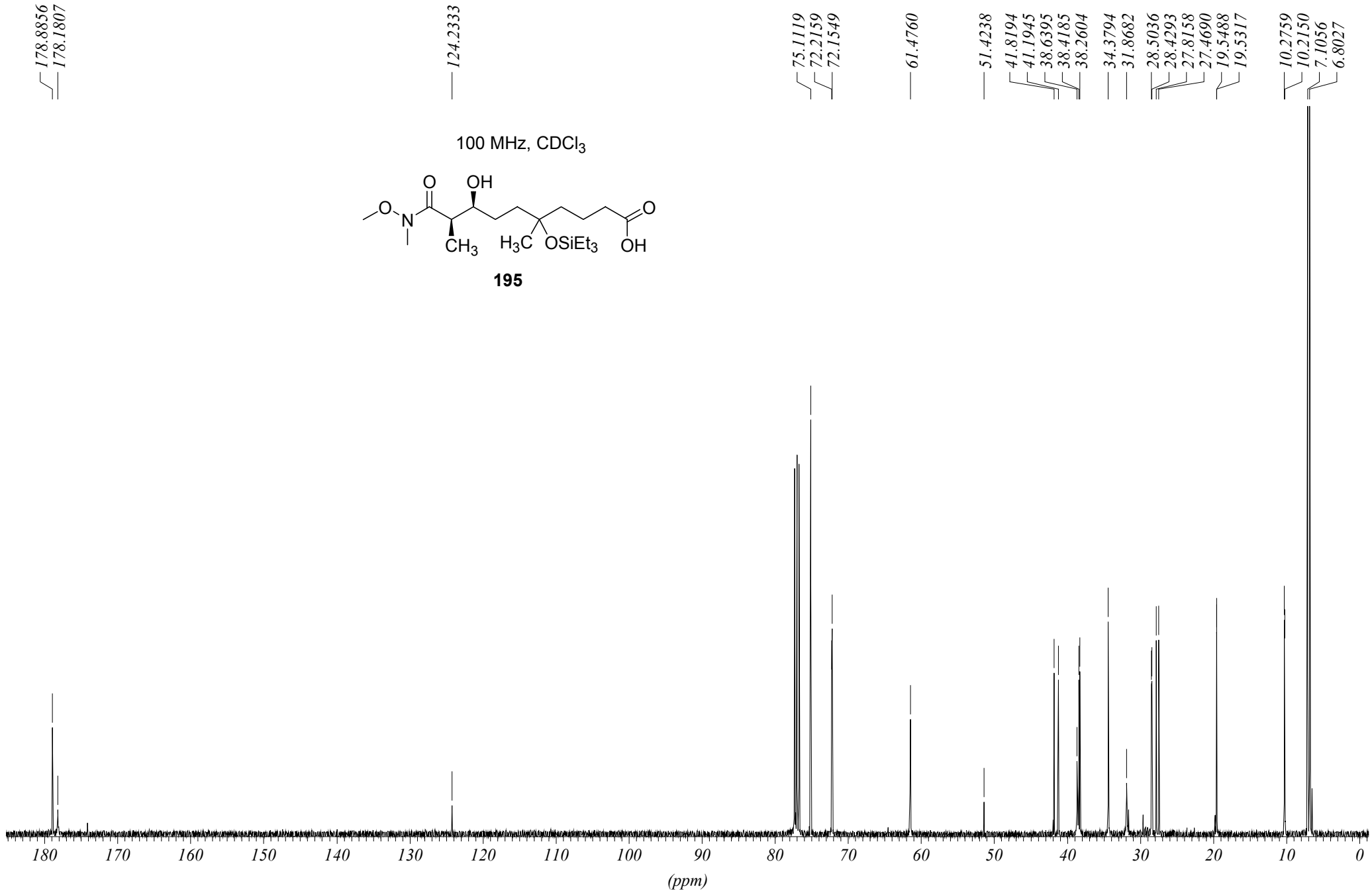


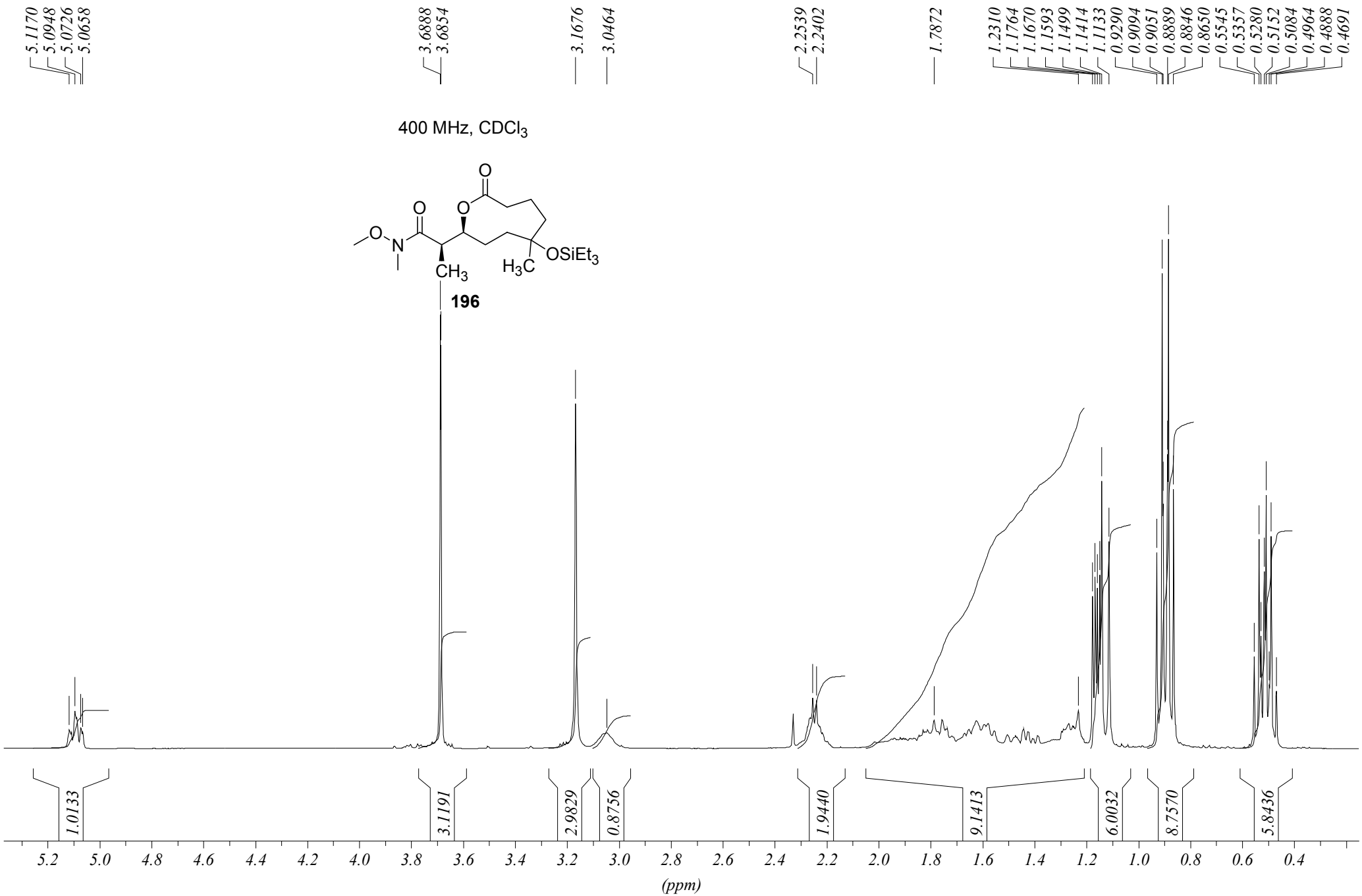

7.2600
5.9576
5.9316
5.9146
5.8886
5.3558
5.3520
5.3125
5.3091
5.2658
5.2623
5.2394
5.2363
4.6204
4.6169
4.6147
4.6138
4.6059
4.6028
4.5994
3.8618
3.8508
3.8473
3.6664
2.7121
2.7008
2.6559
2.6443
2.5785
2.5688
2.5606
2.5512
2.3113
2.2931
2.2746
2.1702
1.5956
1.4620
1.4476
1.2181
1.2155
1.2002
1.1974
1.1911
0.9531
0.9521
0.9336
0.9317
0.9126
0.5962
0.5918
0.5770
0.5730
0.5573
0.5529
0.5378
0.5363
0.5334
0.5319
400 MHz, CDCl3
O
OH
O
O
OSiEt3
O
C22H42O6Si
Mol. Wt.: 430,65
Integral
1.0474
2.1442
2.1538
0.9442
2.6984
0.9085
0.9924
2.0044
2.0258
3.4133
4.7665
6.0313
9.0060
6.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

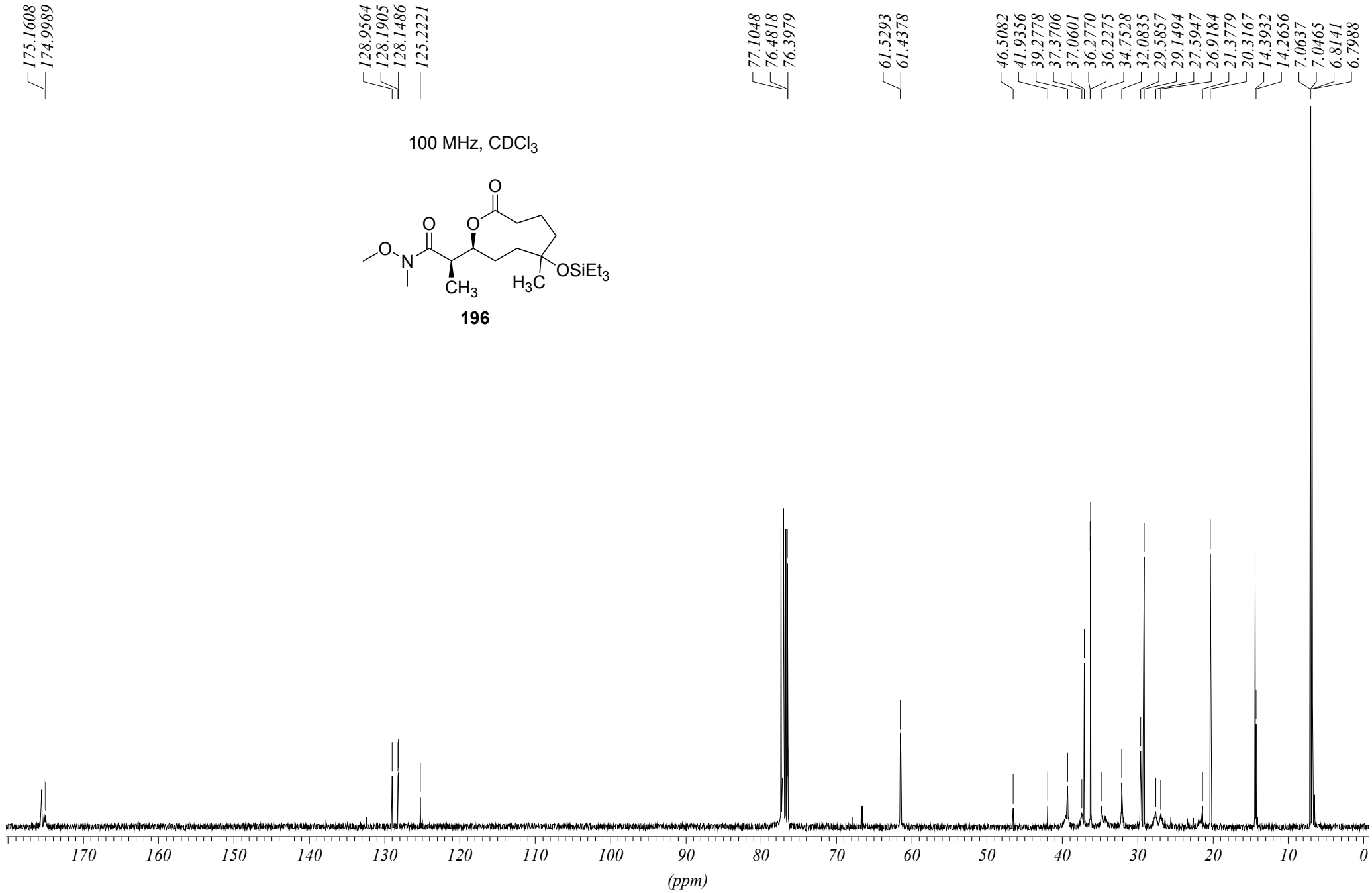

3.7801
3.6743
3.6300
3.1642
2.8545
2.2795
2.2616
2.2428
1.6149
1.6004
1.4101
1.4025
1.3854
1.1721
1.1619
1.1499
1.1329
0.9247
0.9059
0.8855
0.5664
0.5630
0.5476
0.5434
0.5272
0.5237
0.5075
400 MHz, CDCl3
O
OH
O
N
CH3
H3C
OSiEt3
OCH3
194
Integral
1.9688
3.1331
3.1220
3.0138
0.9549
2.1592
4.0841
4.7972
6.5434
9.5166
6.4513
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
(ppm)


173.9986
173.9834
77.0000
75.0814
75.0681
72.0901
72.0197
61.4226
51.3457
41.9147
41.2878
38.4319
38.2775
34.4041
34.3927
31.8016
28.4731
28.3930
27.7700
27.4157
19.7622
19.7432
10.1712
10.1178
7.0694
6.7722
100 MHz, CDCl3
O
OH
O
N
CH3
H3C
OSiEt3
OCH3
194
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

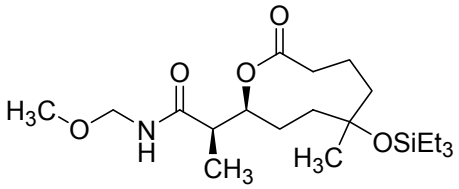

7.2600
3.7878
3.6897
3.1838
2.8784
2.3298
2.3119
2.2940
1.6396
1.6209
1.4673
1.4417
1.4008
1.1909
1.1806
1.1670
1.1491
0.9409
0.9213
0.9008
0.5843
0.5809
0.5647
0.5613
0.5451
0.5417
0.5246
400 MHz, CDCl3
O
OH
O
N
CH3
H3C
OSiEt3
OH
195
Integral
1.0151
2.8647
2.8170
0.8558
1.8945
4.1378
4.1240
5.9067
8.5030
5.7884
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


178.8856
178.1807
124.2333
75.1119
72.2159
72.1549
61.4760
51.4238
41.8194
41.1945
38.6395
38.4185
38.2604
34.3794
31.8682
28.5036
28.4293
27.8158
27.4690
19.5488
19.5317
10.2759
10.2150
7.1056
6.8027
100 MHz, CDCl3
O
OH
O
N
CH3
H3C
OSiEt3
OH
195
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


5.1170
5.0948
5.0726
5.0658
3.6888
3.6854
3.1676
3.0464
2.2539
2.2402
1.7872
1.2310
1.1764
1.1670
1.1593
1.1499
1.1414
1.1133
0.9290
0.9094
0.9051
0.8889
0.8846
0.8650
0.5545
0.5357
0.5280
0.5152
0.5084
0.4964
0.4888
0.4691
400 MHz, CDCl3
O
O
O
O
N
CH3
H3C
OSiEt3
196
1.0133
3.1191
2.9829
0.8756
1.9440
9.1413
6.0032
8.7570
5.8436
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
(ppm)

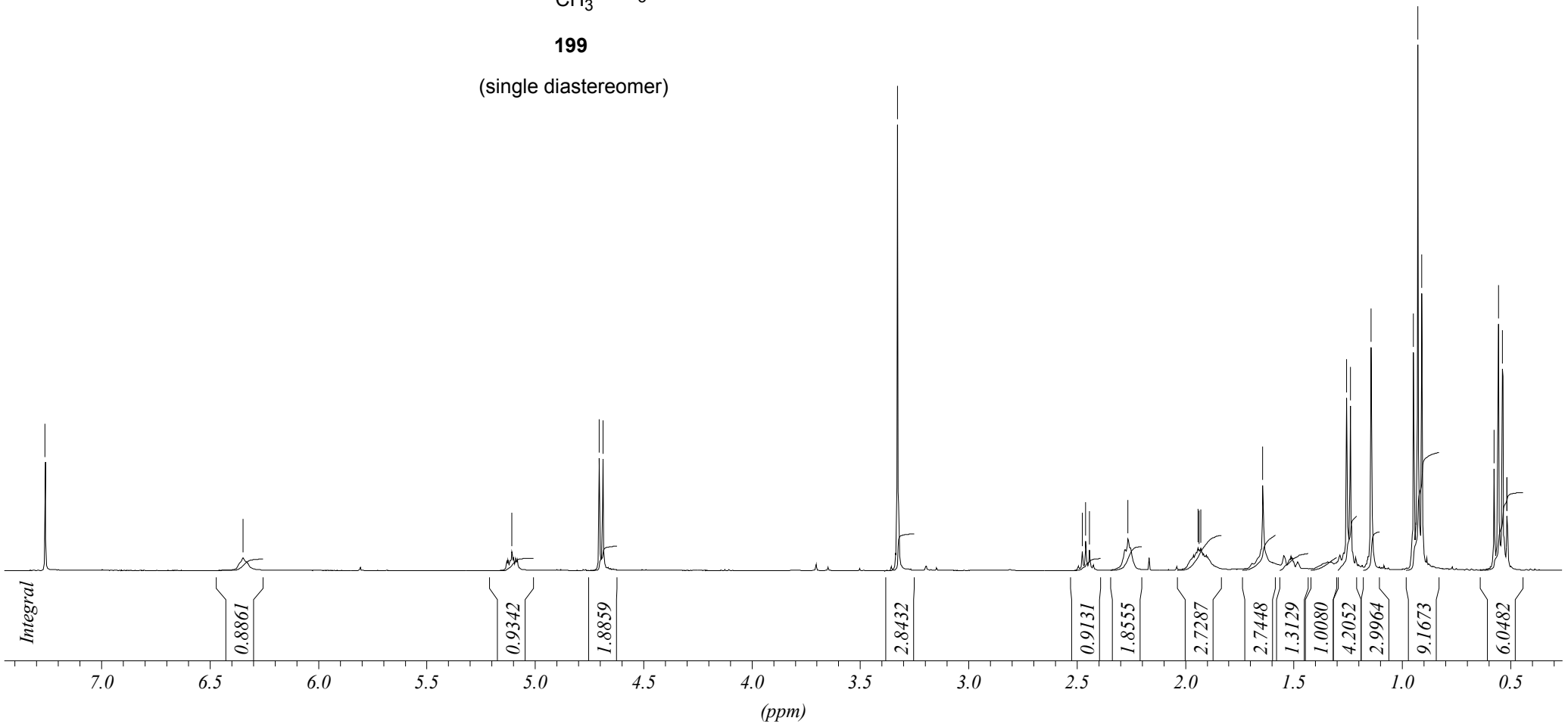

175.1608
174.9989
128.9564
128.1905
128.1486
125.2221
77.1048
76.4818
76.3979
61.5293
61.4378
46.5082
41.9356
39.2778
37.3706
37.0601
36.2770
36.2275
34.7528
32.0835
29.5857
29.1494
27.5947
26.9184
21.3779
20.3167
14.3932
14.2656
7.0637
7.0465
6.8141
6.7988
100 MHz, CDCl3
O
O
O
O
N
CH3
H3C
OSiEt3
196
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

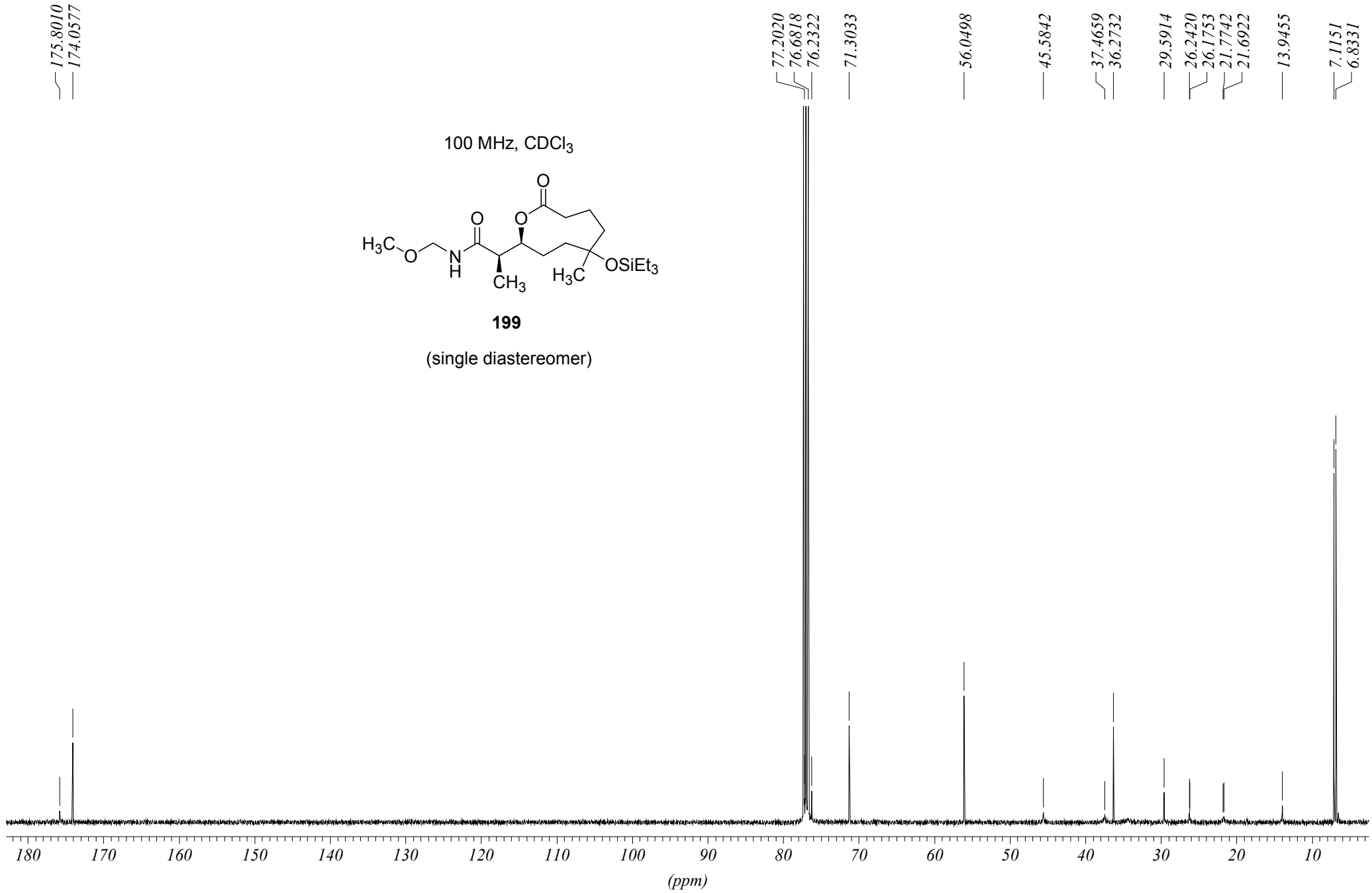
400 MHz, $CDCl_3$

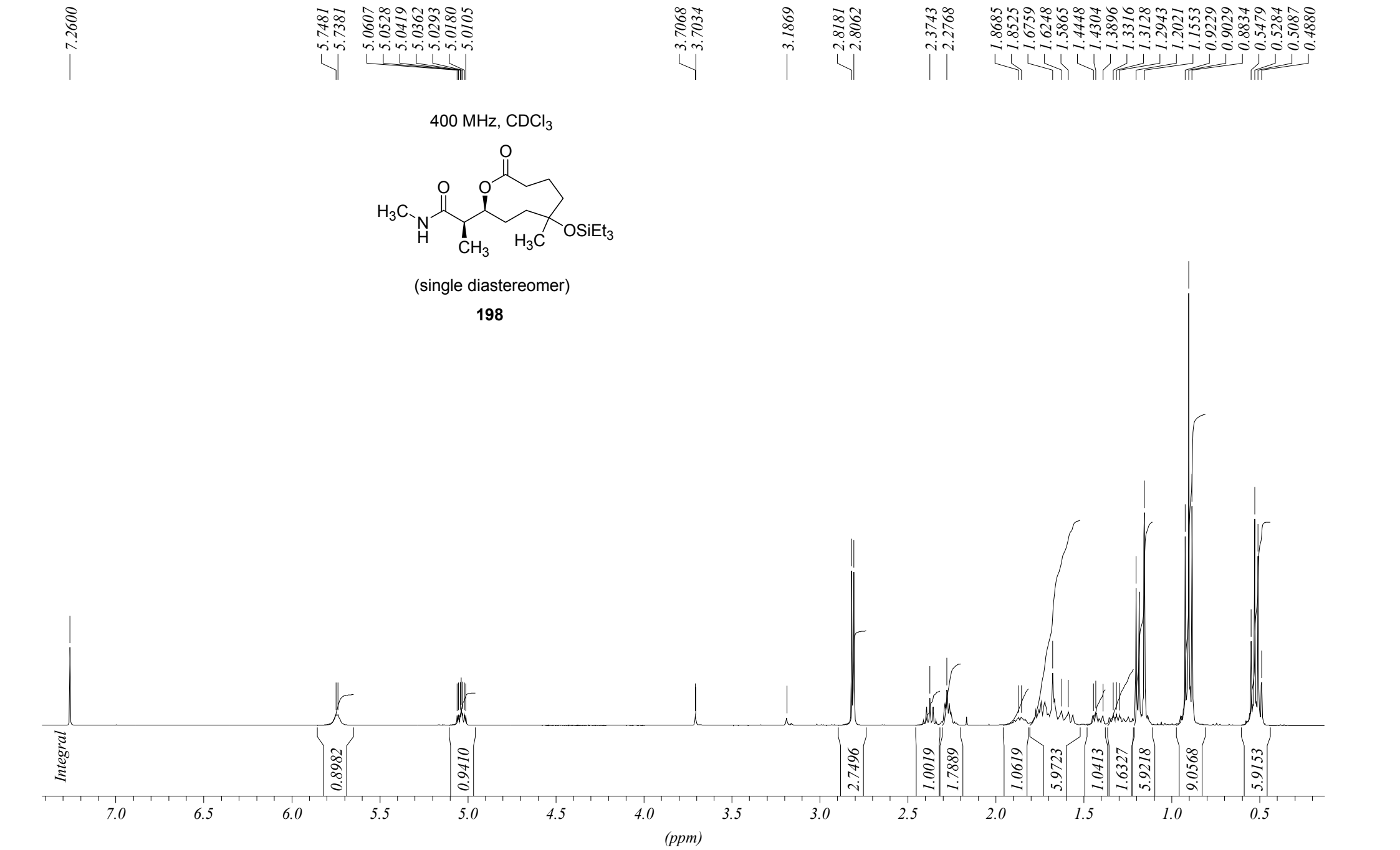


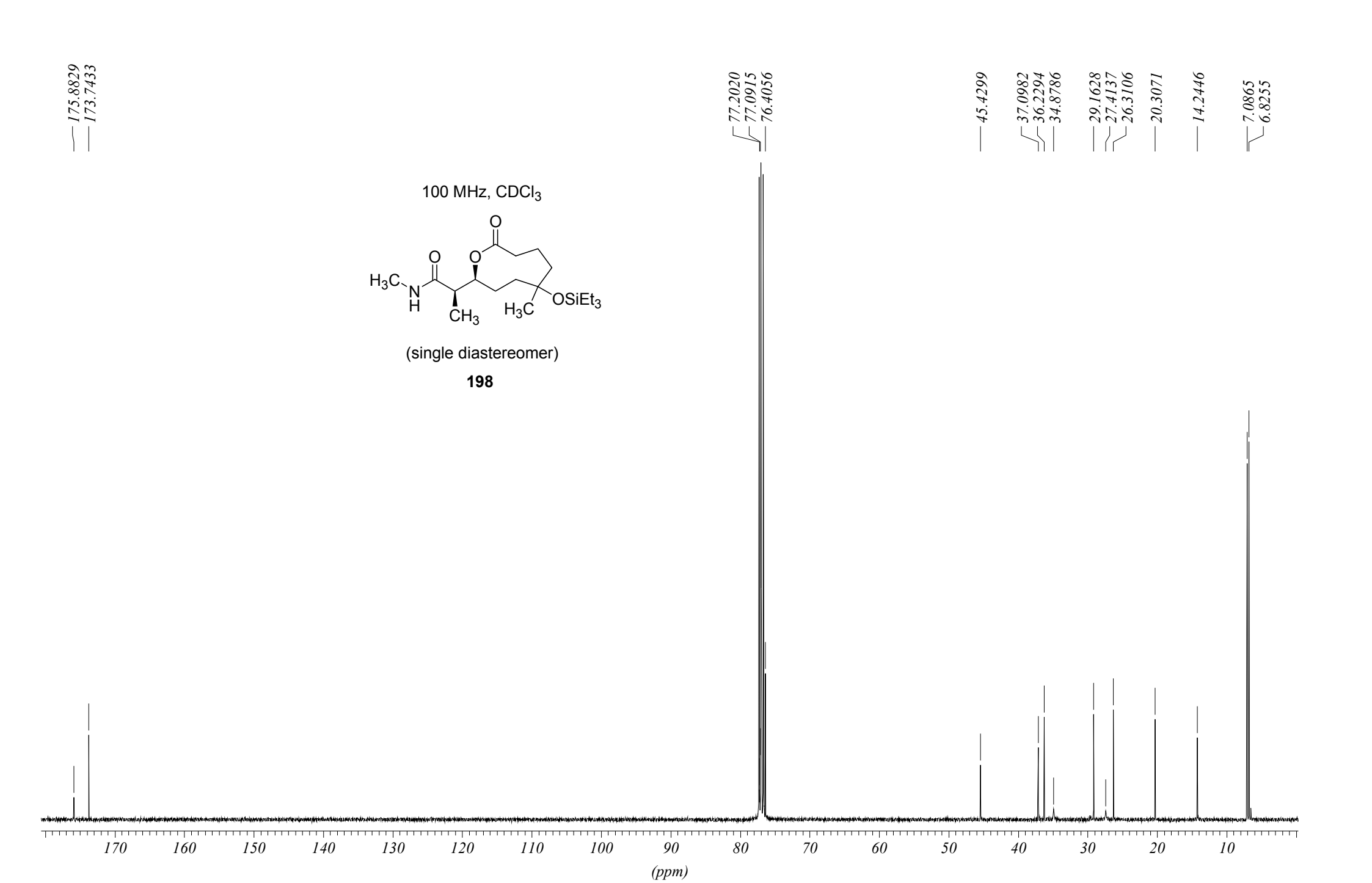
199

(single diastereomer)



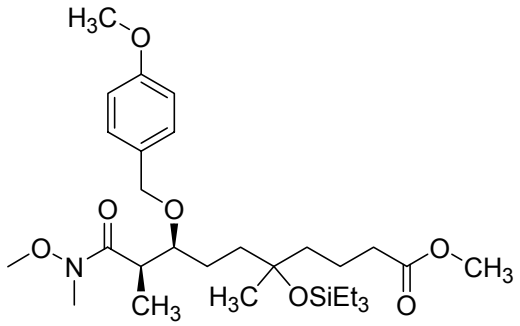

175.8010
174.0577
77.2020
76.6818
76.2322
71.3033
56.0498
45.5842
37.4659
36.2732
29.5914
26.2420
26.1753
21.7742
21.6922
13.9455
7.1151
6.8331
100 MHz, CDCl3
O
O
O
H3C
O
N
H
CH3
H3C
OSiEt3
199
(single diastereomer)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


7.2600
5.7481
5.7381
5.0607
5.0528
5.0419
5.0362
5.0293
5.0180
5.0105
3.7068
3.7034
3.1869
2.8181
2.8062
2.3743
2.2768
1.8685
1.8525
1.6759
1.6248
1.5865
1.4448
1.4304
1.3896
1.3316
1.3128
1.2943
1.2021
1.1553
0.9229
0.9029
0.8834
0.5479
0.5284
0.5087
0.4880
400 MHz, CDCl3
(single diastereomer)
198
Integral
0.8982
0.9410
2.7496
1.0019
1.7889
1.0619
5.9723
1.0413
1.6327
5.9218
9.0568
5.9153
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

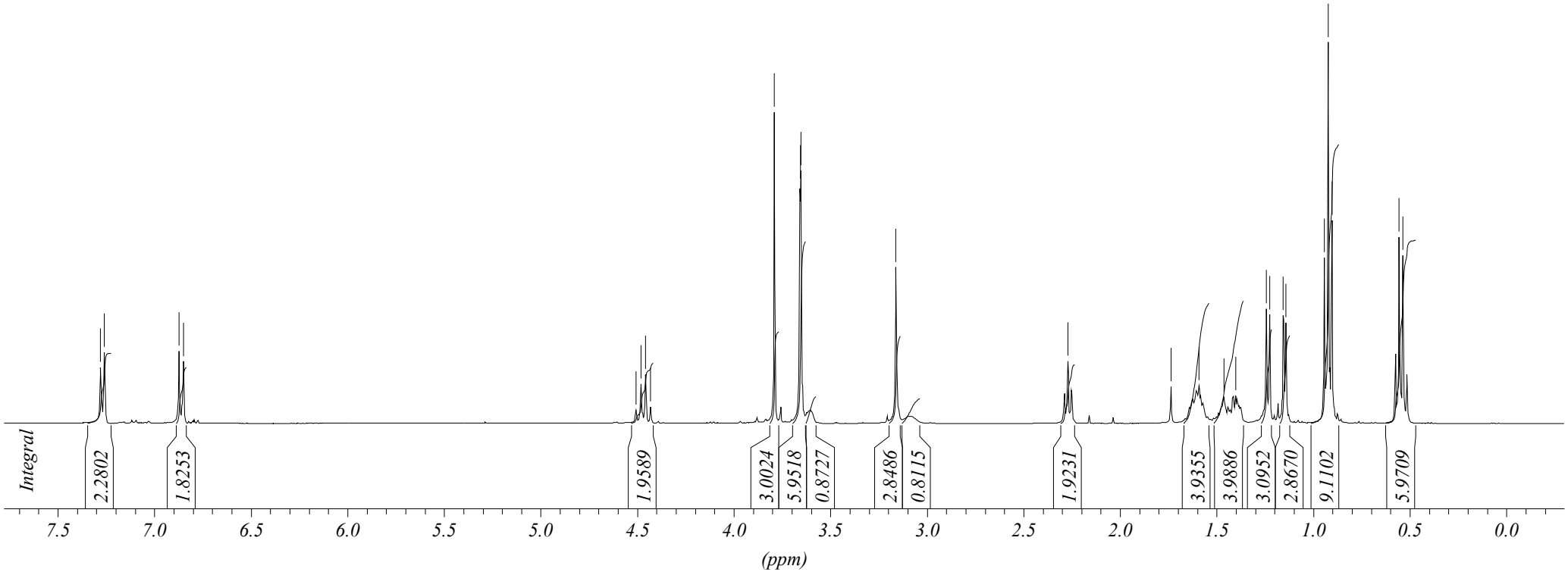

175.8829
173.7433
77.2020
77.0915
76.4056
45.4299
37.0982
36.2294
34.8786
29.1628
27.4137
26.3106
20.3071
14.2446
7.0865
6.8255
100 MHz, CDCl3
O
O
O
H3C
N
H
CH3
H3C
OSiEt3
(single diastereomer)
198
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

7.2785
7.2600
6.8718
6.8501
4.5068
4.4799
4.4579
4.4306
3.7899
3.6560
3.6529
3.1605
2.2702
1.7358
1.5916
1.4620
1.4028
1.2435
1.2262
1.1550
1.1425
0.9427
0.9226
0.9032
0.5554
0.5356

400 MHz, $CDCl_3$

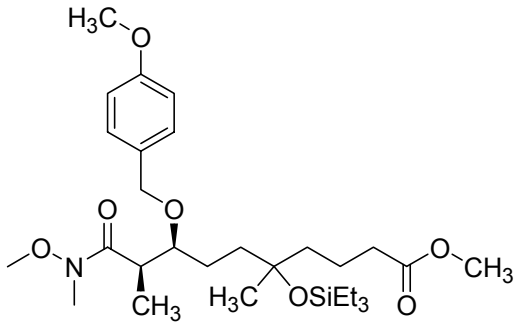


202

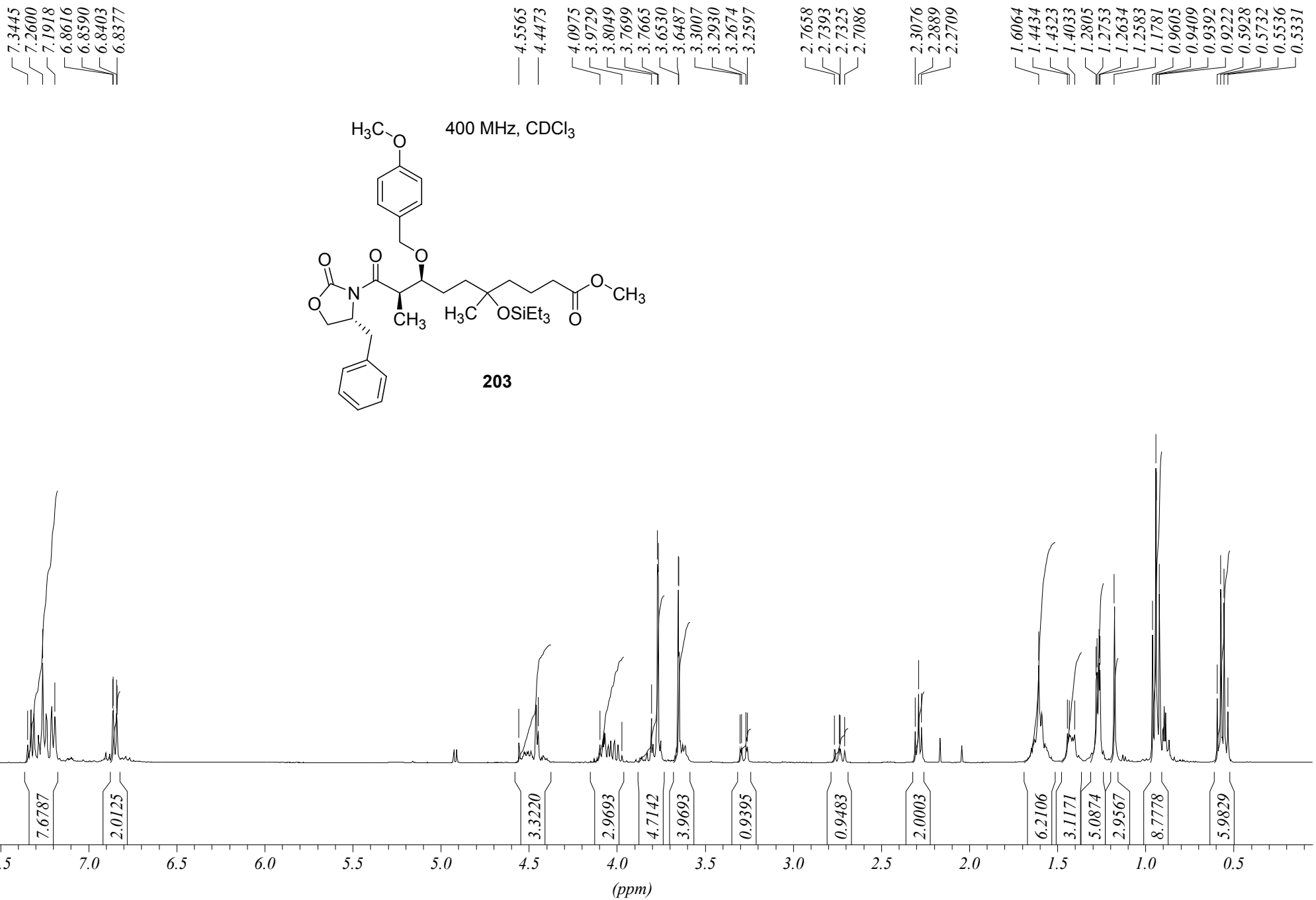


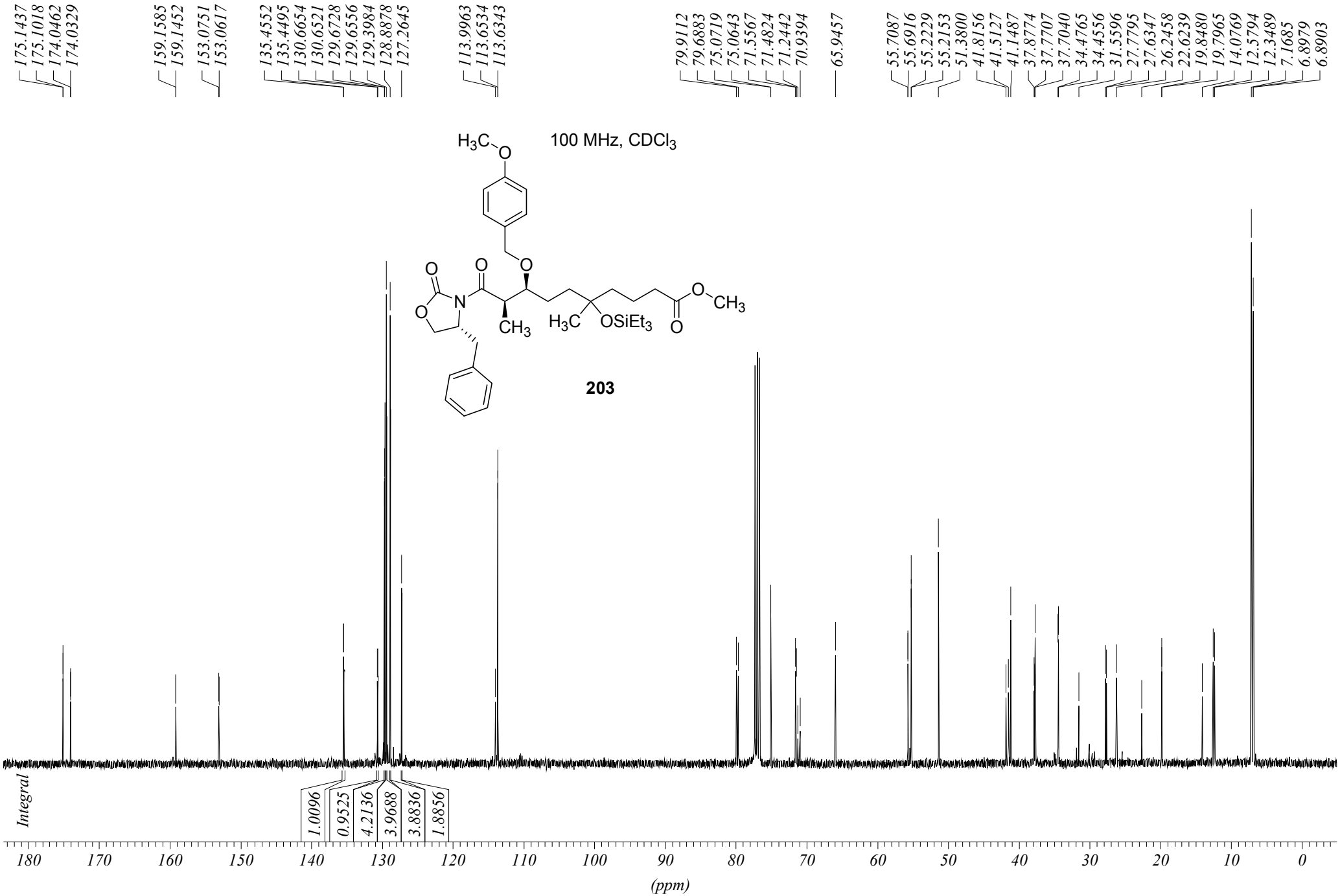
176.2297
174.0119
159.1319
130.7016
129.5489
129.5356
113.7143
80.6333
80.6181
75.0452
75.0242
72.2750
72.2178
61.3597
55.2248
51.3705
41.9756
41.3945
39.8627
39.7274
37.0220
34.4975
34.4765
32.0645
27.7529
27.4233
27.0860
26.8879
19.7889
19.7127
14.5456
14.4961
7.1456
6.8389

100 MHz, $CDCl_3$



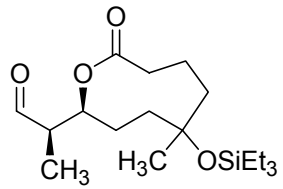
202


7.3445
7.2600
7.1918
6.8616
6.8590
6.8403
6.8377
4.5565
4.4473
4.0975
3.9729
3.8049
3.7699
3.7665
3.6530
3.6487
3.3007
3.2930
3.2674
3.2597
2.7658
2.7393
2.7325
2.7086
2.3076
2.2889
2.2709
1.6064
1.4434
1.4323
1.4033
1.2805
1.2753
1.2634
1.2583
1.1781
0.9605
0.9409
0.9392
0.9222
0.5928
0.5732
0.5536
0.5331
400 MHz, CDCl3
203
Integral
7.6787
2.0125
3.3220
2.9693
4.7142
3.9693
0.9395
0.9483
2.0003
6.2106
3.1171
5.0874
2.9567
8.7778
5.9829
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

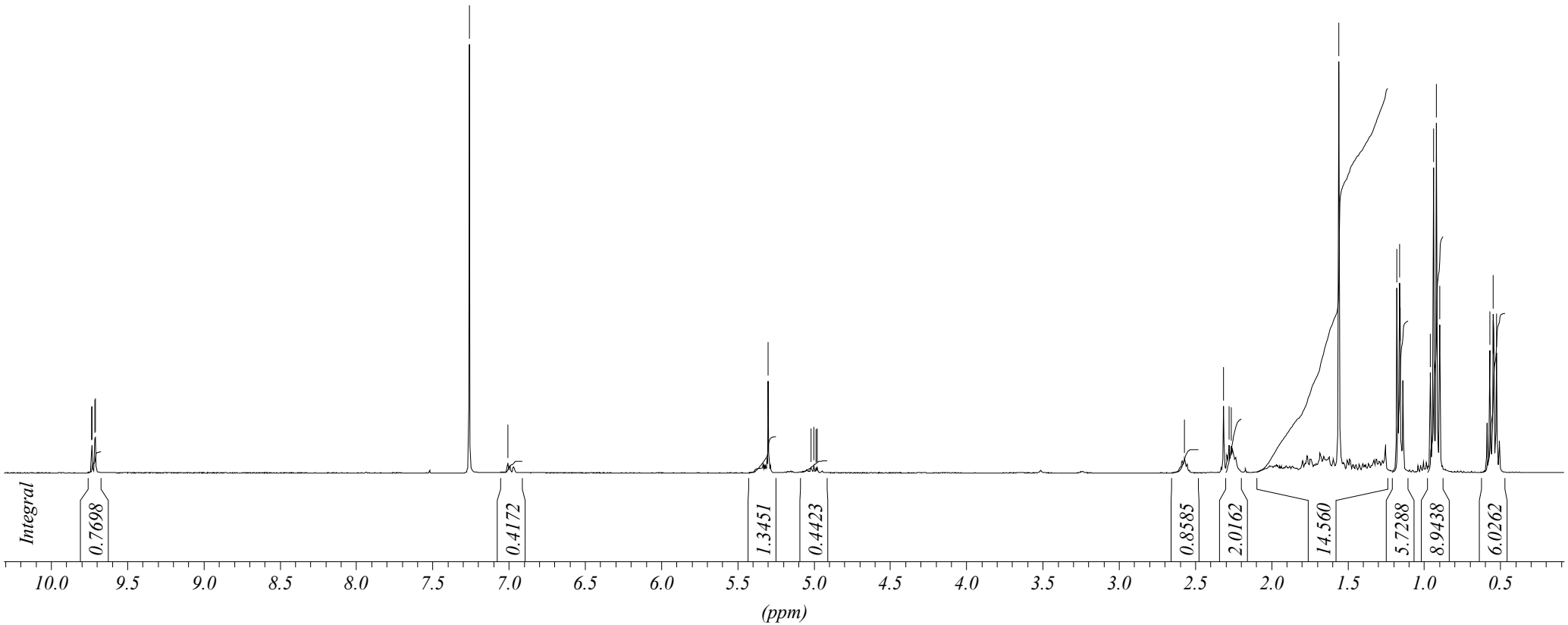

175.1437
175.1018
174.0462
174.0329
159.1585
159.1452
153.0751
153.0617
135.4552
135.4495
130.6654
130.6521
129.6728
129.6556
129.3984
128.8878
127.2645
113.9963
113.6534
113.6343
79.9112
79.6883
75.0719
75.0643
71.5567
71.4824
71.2442
70.9394
65.9457
55.7087
55.6916
55.2229
55.2153
51.3800
41.8156
41.5127
41.1487
37.8774
37.7707
37.7040
34.4765
34.4556
31.5596
27.7795
27.6347
26.2458
22.6239
19.8480
19.7965
14.0769
12.5794
12.3489
7.1685
6.8979
6.8903
100 MHz, CDCl3
203
Integral
1.0096
0.9525
4.2136
3.9688
3.8836
1.8856
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

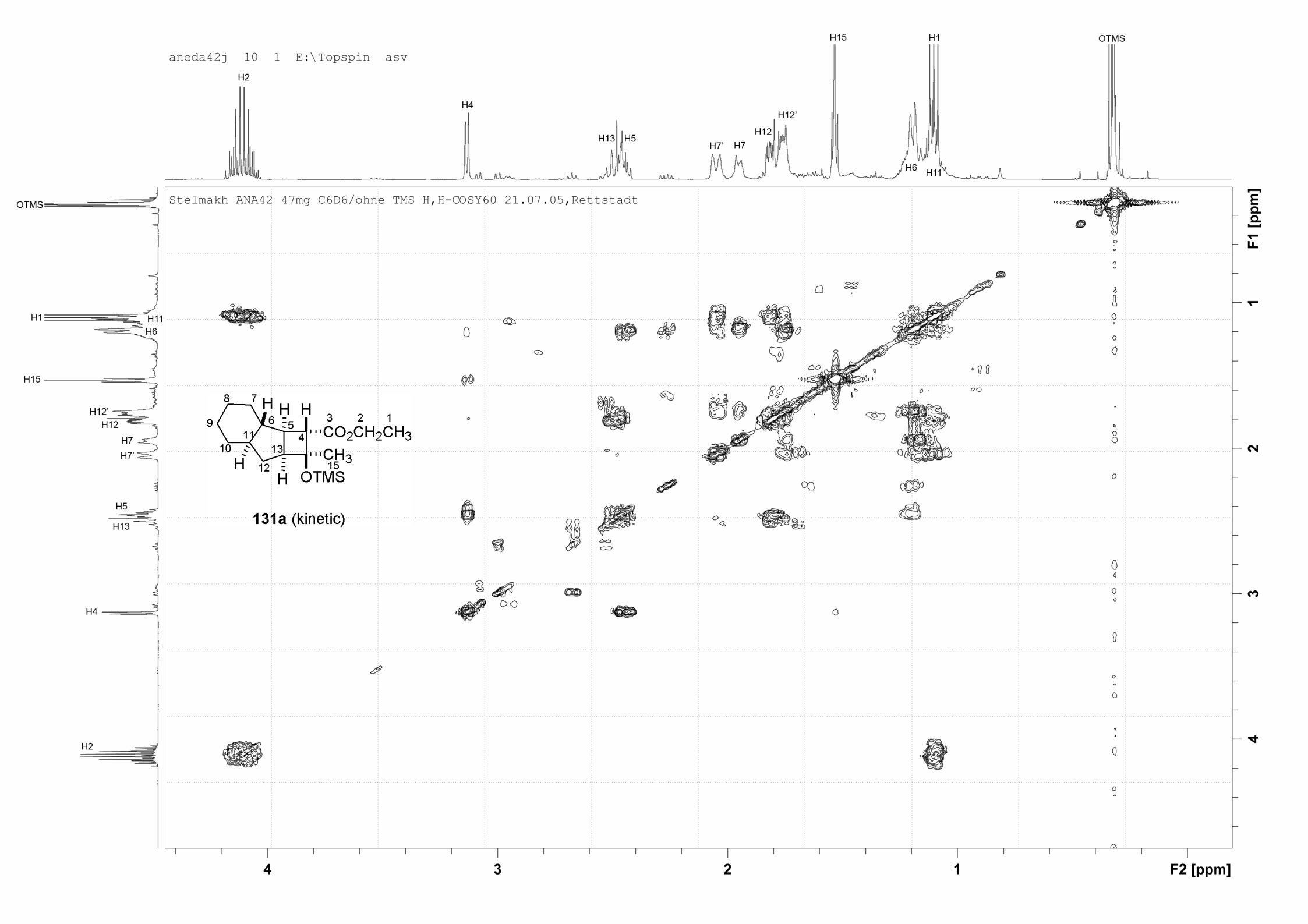
9.7349
9.7315
9.7127
9.7085
7.2600
7.0075
5.2995
5.0171
5.0001
4.9864
4.9788
2.5695
2.3136
2.2795
2.2650
1.5577
1.1772
1.1602
1.1559
0.9588
0.9384
0.9179
0.8983
0.5690
0.5485
0.5451
0.5255

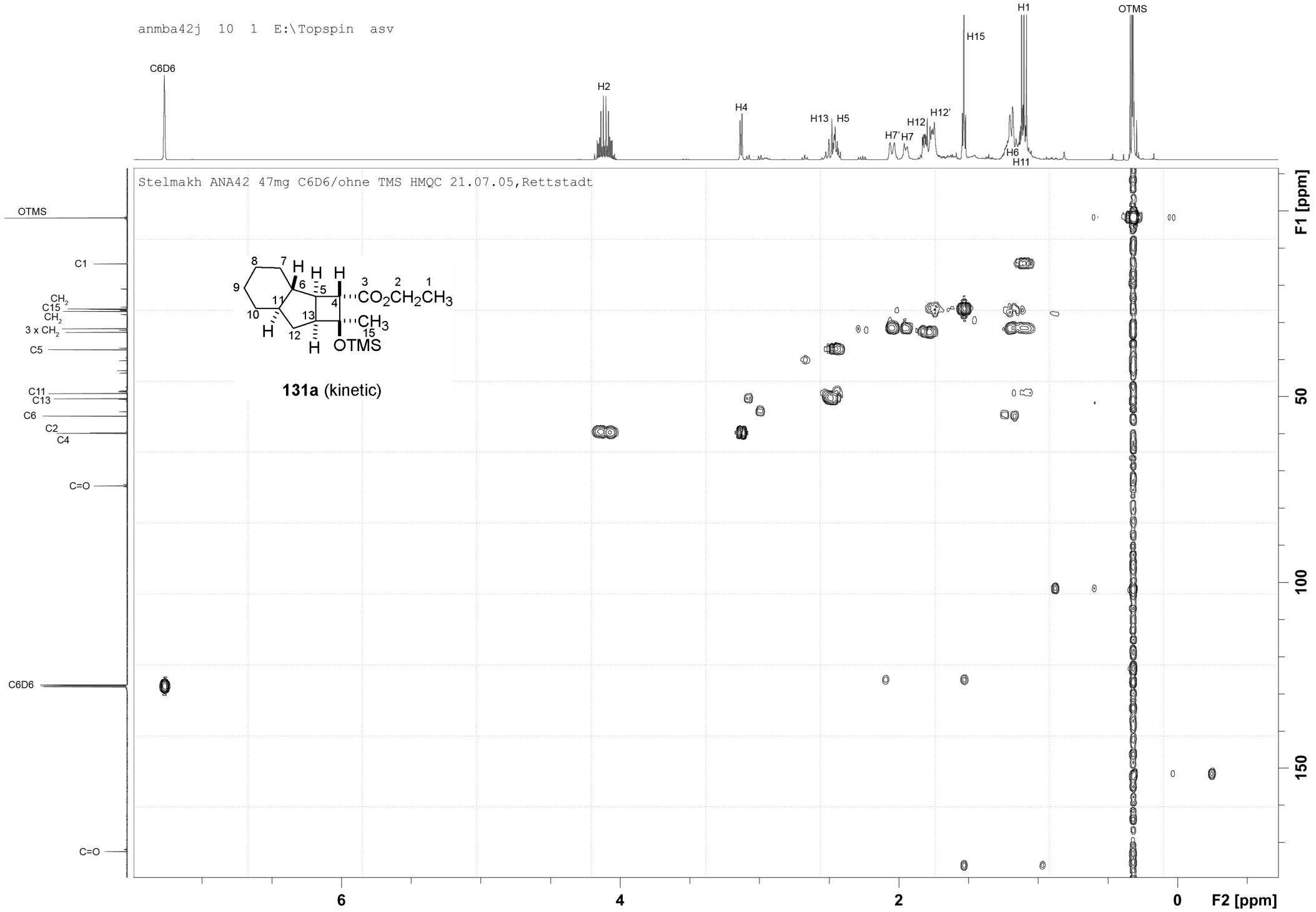
400 MHz, $CDCl_3$

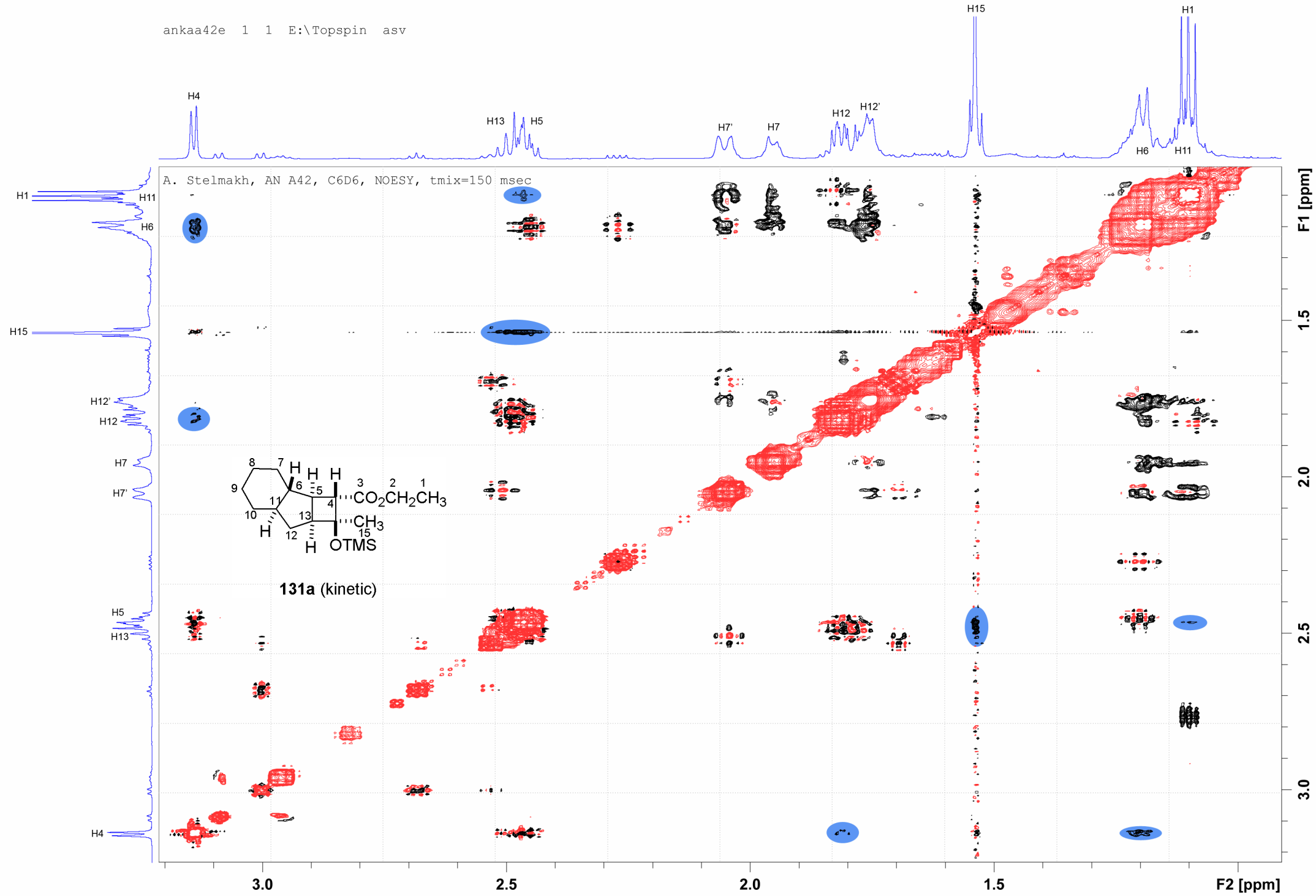


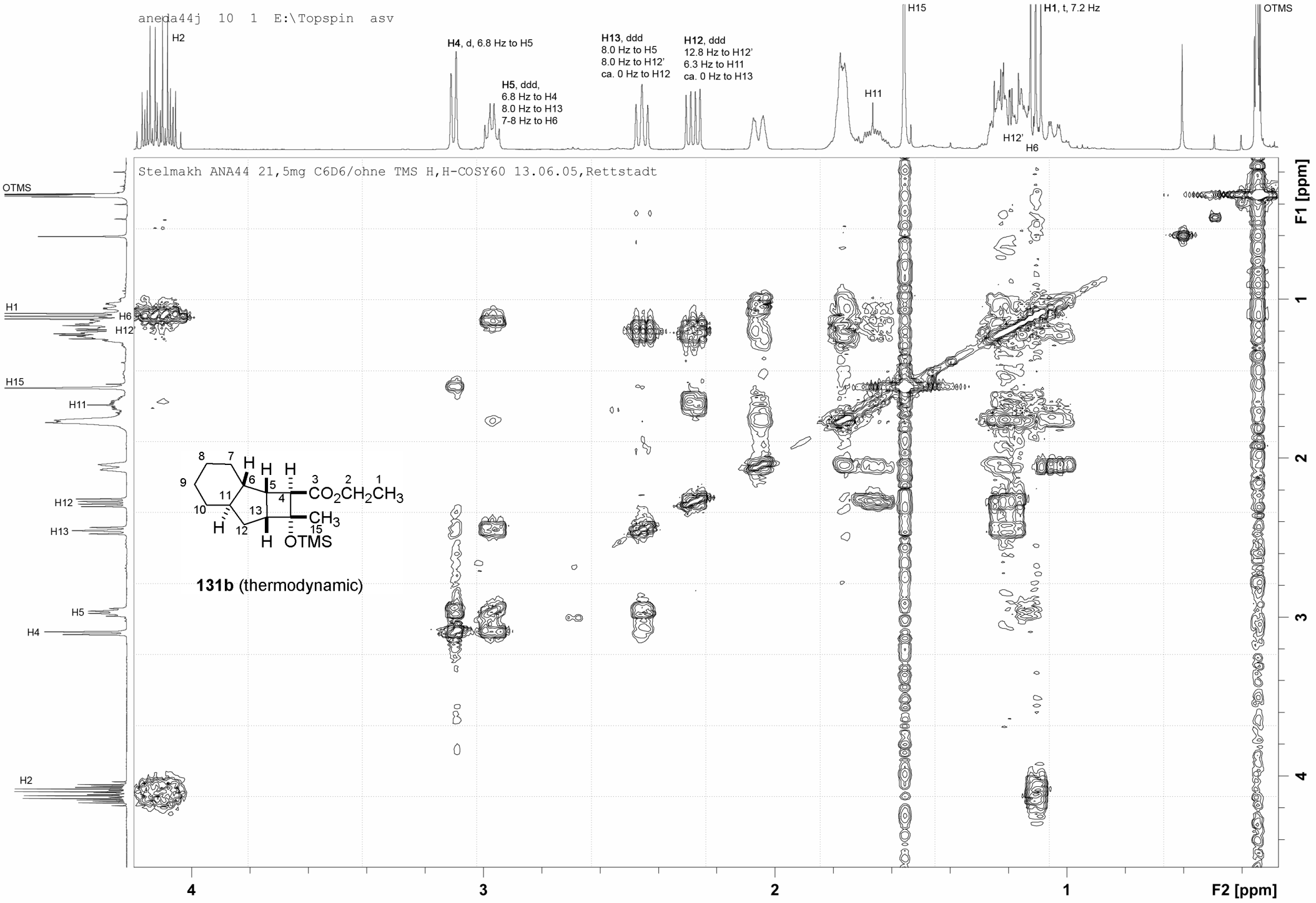
201

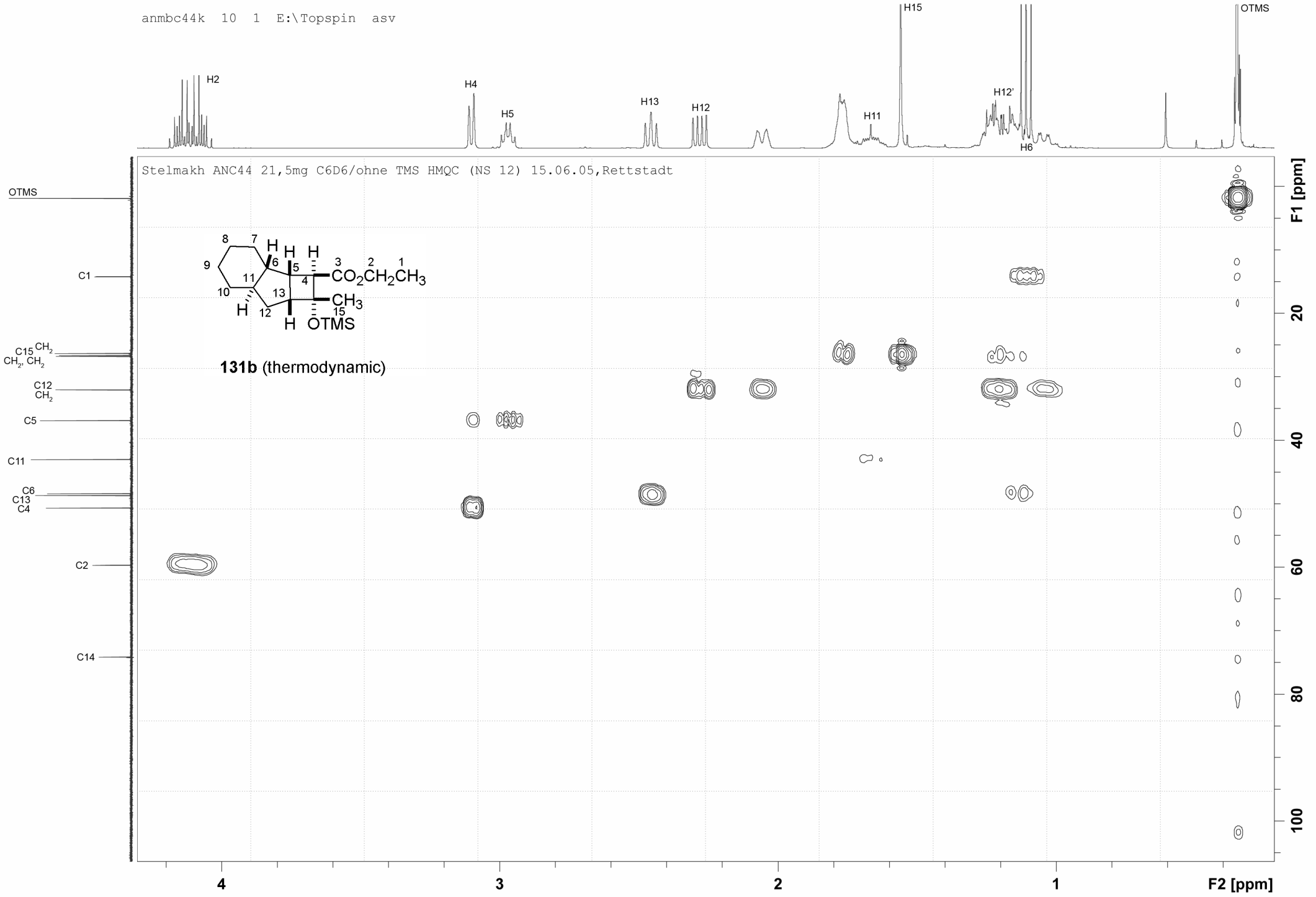


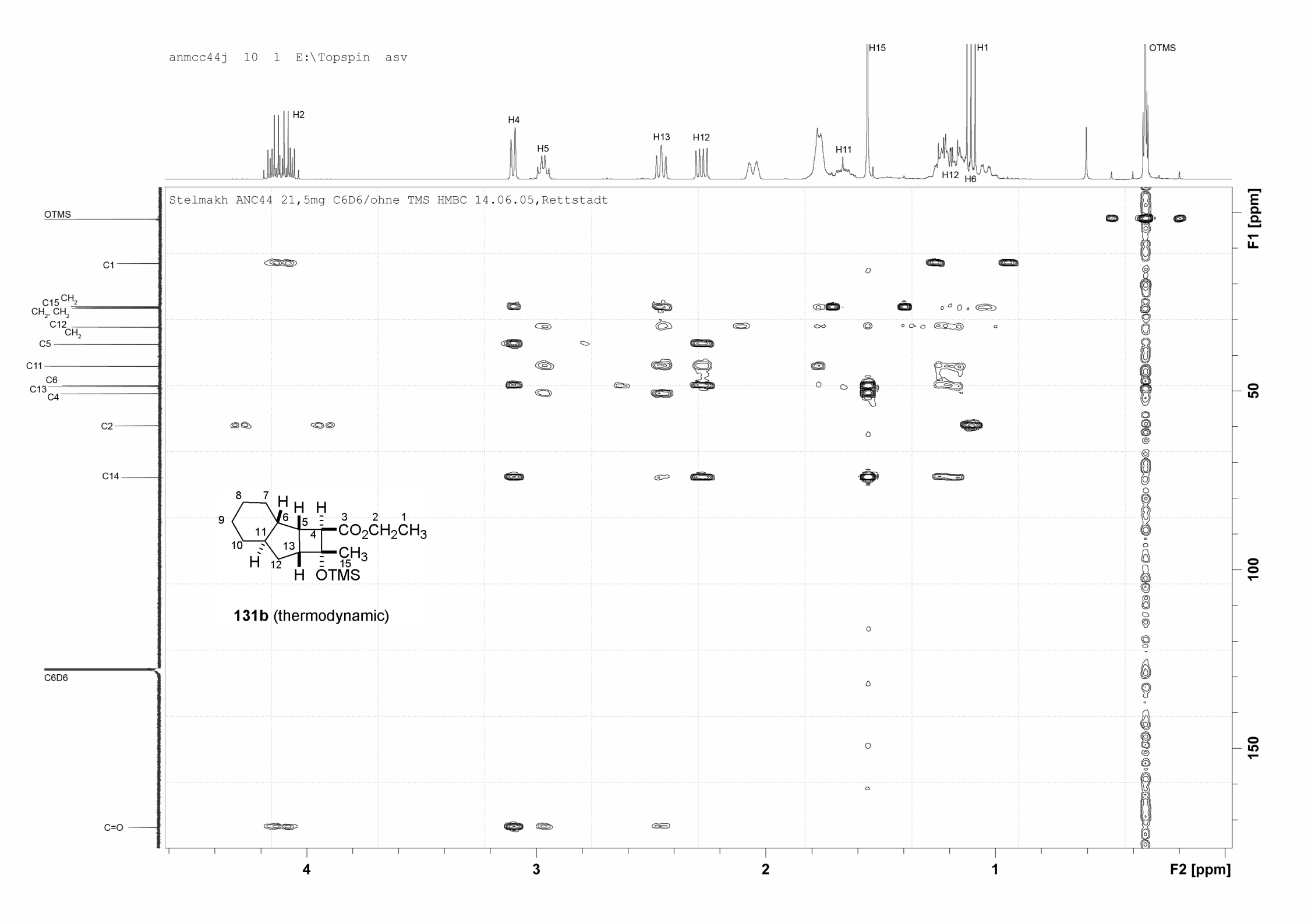

aneda42j 10 1 E:\Topspin asv
Stelmakh ANA42 47mg C6D6/ohne TMS H,H-COSY60 21.07.05,Rettstadt
H2
H4
H13
H5
H7'
H7
H12
H12'
H15
H6
H11
H1
OTMS
F1 [ppm]
F2 [ppm]
131a (kinetic)

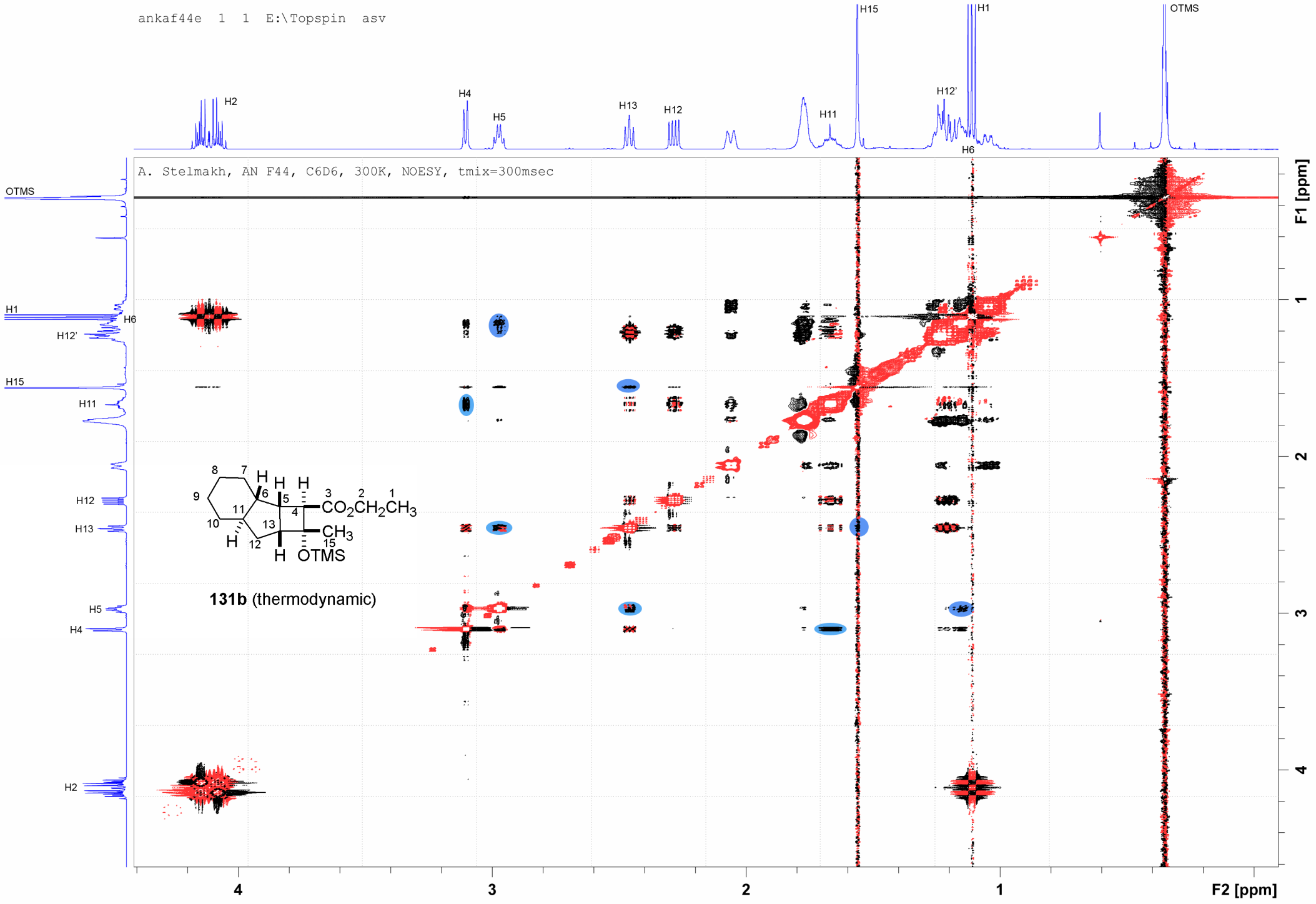

anmba42j 10 1 E:\Topspin asv
C6D6
H2
H4
H13
H5
H7'
H7
H12
H12'
H15
H6
H11
H1
OTMS
Stelmakh ANA42 47mg C6D6/ohne TMS HMQC 21.07.05,Rettstadt
131a (kinetic)
C1
CH2
C15
CH2
3 x CH2
C5
C11
C13
C6
C2
C4
C=O
C6D6
C=O
F1 [ppm]
F2 [ppm]
6
4
2
0
50
100
150

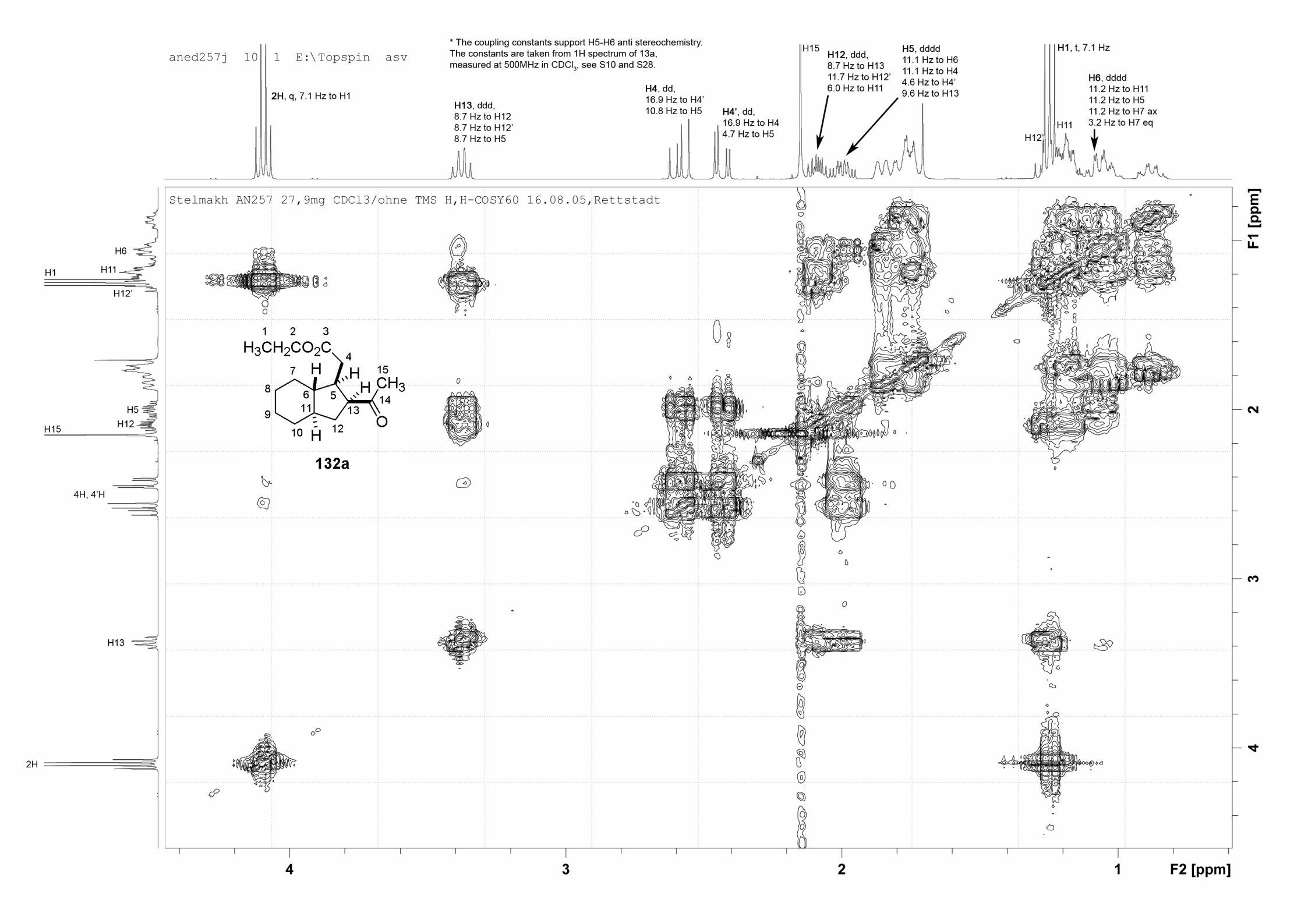

ankaa42e 1 1 E:\Topspin asv
A. Stelmakh, AN A42, C6D6, NOESY, tmix=150 msec
H4
H13
H5
H7'
H7
H12
H12'
H15
H1
H6
H11
H1
H11
H6
H15
H12'
H12
H7
H7'
H5
H13
H4
131a (kinetic)
F1 [ppm]
F2 [ppm]
3.0
2.5
2.0
1.5

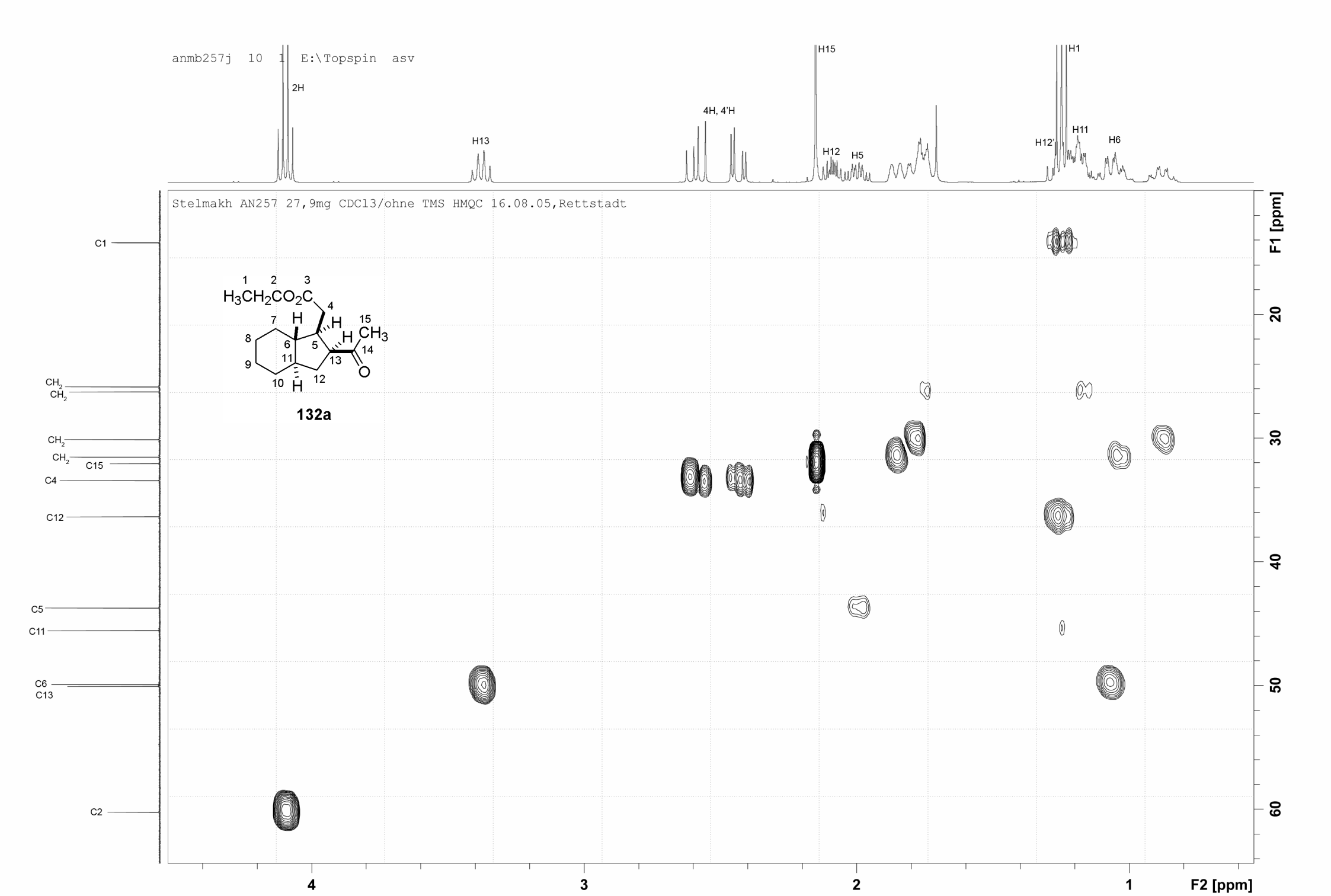

aneda44j 10 1 E:\Topspin asv
H2
H4, d, 6.8 Hz to H5
H5, ddd,
6.8 Hz to H4
8.0 Hz to H13
7-8 Hz to H6
H13, ddd
8.0 Hz to H5
8.0 Hz to H12'
ca. 0 Hz to H12
H12, ddd
12.8 Hz to H12'
6.3 Hz to H11
ca. 0 Hz to H13
H11
H15
H12'
H6
H1, t, 7.2 Hz
OTMS
Stelmakh ANA44 21,5mg C6D6/ohne TMS H,H-COSY60 13.06.05,Rettstadt
OTMS
H1
H6
H12'
H15
H11
H12
H13
H5
H4
H2
131b (thermodynamic)
F1 [ppm]
F2 [ppm]
4
3
2
1


anmbc44k 10 1 E:\Topspin asv
H2
H4
H5
H13
H12
H11
H15
H12'
H6
OTMS
Stelmakh ANC44 21,5mg C6D6/ohne TMS HMQC (NS 12) 15.06.05,Rettstadt
131b (thermodynamic)
OTMS
C1
C15 CH2
CH2, CH2
C12 CH2
C5
C11
C6
C13
C4
C2
C14
F1 [ppm]
F2 [ppm]
4
3
2
1
20
40
60
80
100

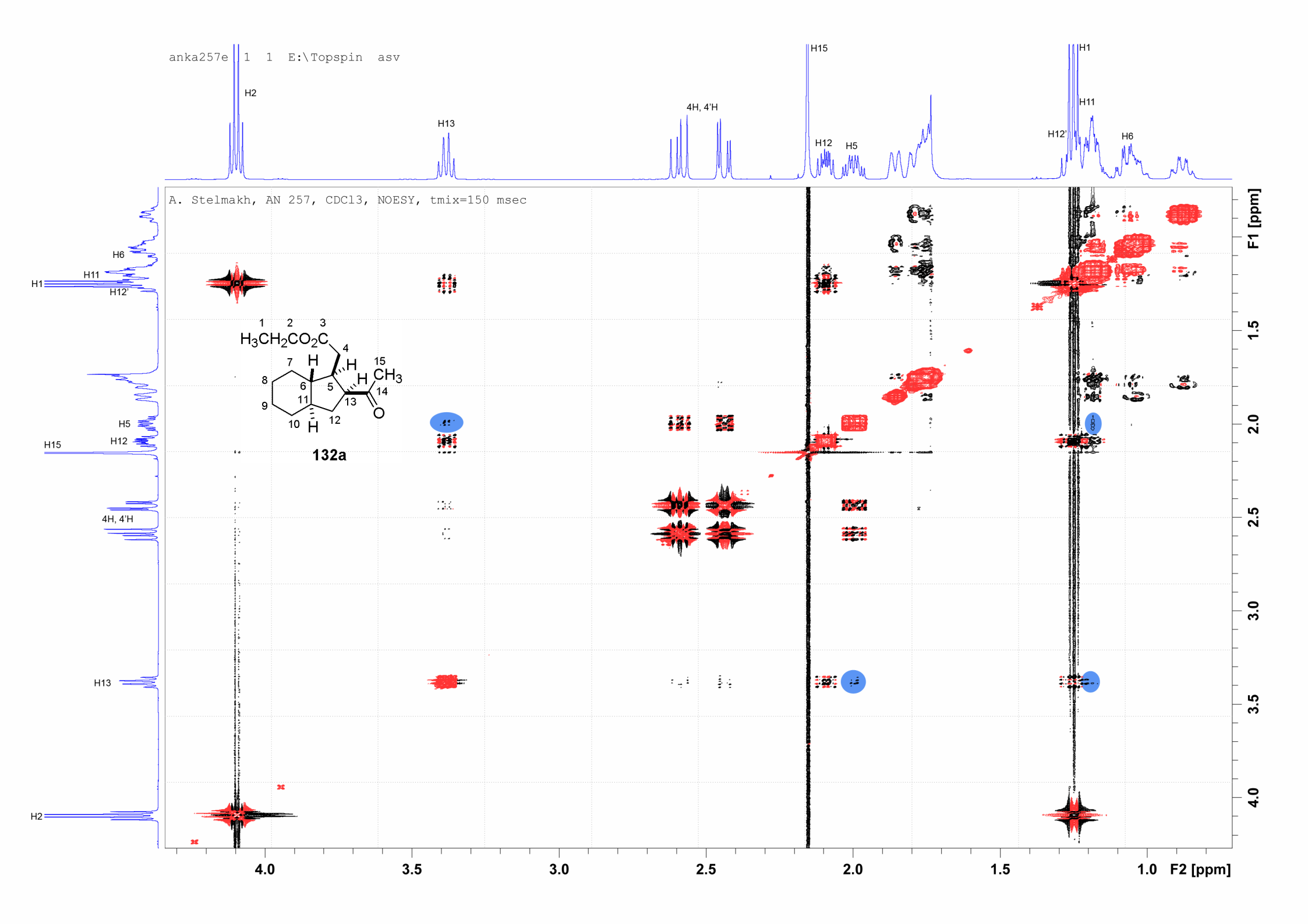

anmcc44j 10 1 E:\Topspin asv
H2
H4
H5
H13
H12
H11
H15
H12
H6
H1
OTMS
Stelmakh ANC44 21,5mg C6D6/ohne TMS HMBC 14.06.05,Rettstadt
OTMS
C1
C15 CH2
CH2, CH2
C12 CH2
C5
C11
C6
C13
C4
C2
C14
C6D6
C=O
131b (thermodynamic)
F1 [ppm]
F2 [ppm]
4
3
2
1
50
100
150

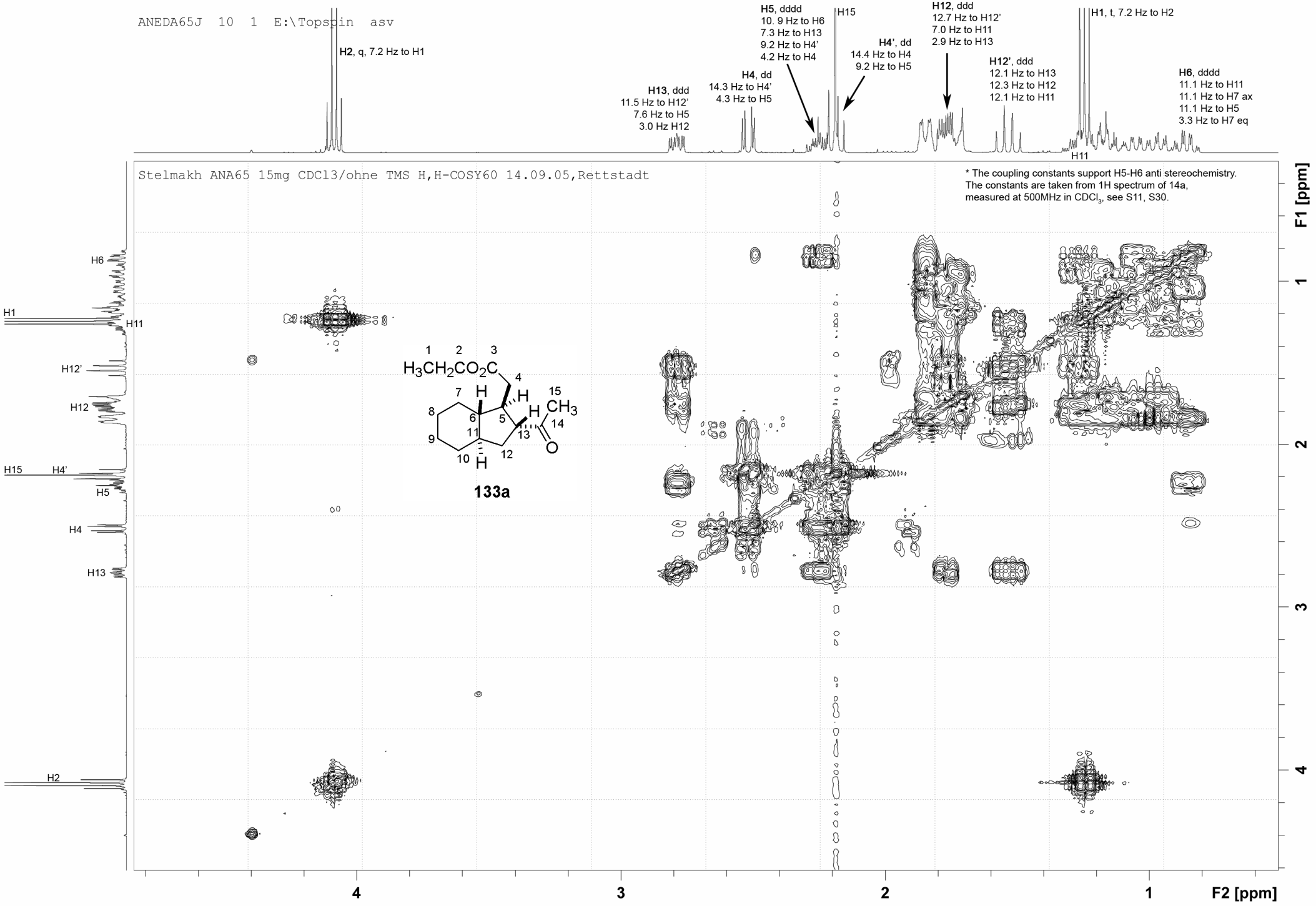

ankaf44e 1 1 E:\Topspin asv
H2
H4
H5
H13
H12
H11
H15
H12'
H1
H6
OTMS
A. Stelmakh, AN F44, C6D6, 300K, NOESY, tmix=300msec
131b (thermodynamic)
F1 [ppm]
F2 [ppm]

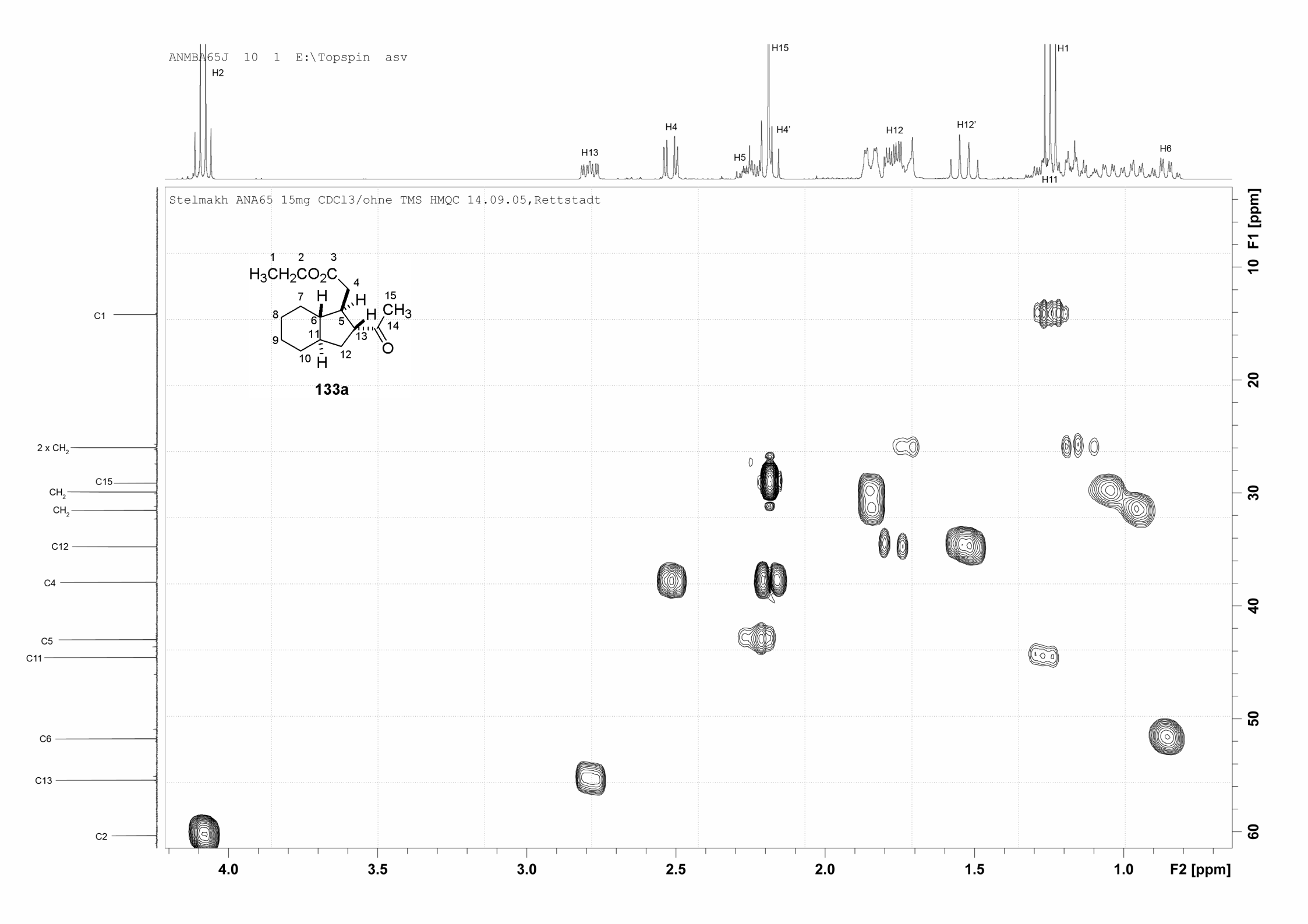

aned257j 10 1 E:\Topspin asv
* The coupling constants support H5-H6 anti stereochemistry.
The constants are taken from 1H spectrum of 13a,
measured at 500MHz in CDCl3, see S10 and S28.
2H, q, 7.1 Hz to H1
H13, ddd,
8.7 Hz to H12
8.7 Hz to H12'
8.7 Hz to H5
H4, dd,
16.9 Hz to H4'
10.8 Hz to H5
H4', dd,
16.9 Hz to H4
4.7 Hz to H5
H15
H12, ddd,
8.7 Hz to H13
11.7 Hz to H12'
6.0 Hz to H11
H5, dddd
11.1 Hz to H6
11.1 Hz to H4
4.6 Hz to H4'
9.6 Hz to H13
H1, t, 7.1 Hz
H6, dddd
11.2 Hz to H11
11.2 Hz to H5
11.2 Hz to H7 ax
3.2 Hz to H7 eq
H12'
H11
Stelmakh AN257 27,9mg CDCl3/ohne TMS H,H-COSY60 16.08.05,Rettstadt
H6
H1
H11
H12'
H5
H15
H12
4H, 4'H
H13
2H
132a
F1 [ppm]
F2 [ppm]
1
2
3
4

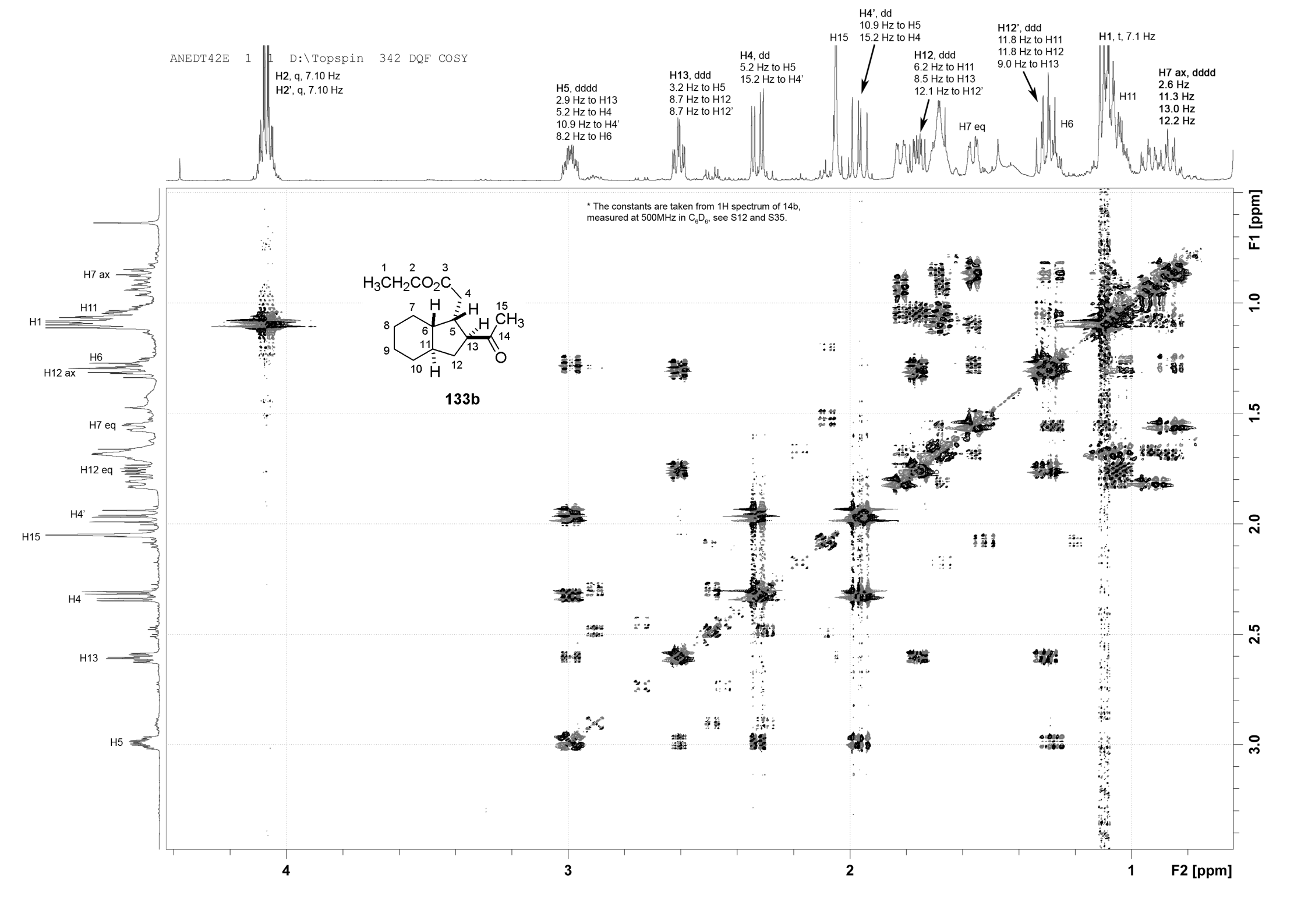

anmb257j 10 1 E:\Topspin asv
2H
H13
4H, 4'H
H15
H12
H5
H1
H12'
H11
H6
Stelmakh AN257 27,9mg CDCl3/ohne TMS HMQC 16.08.05,Rettstadt
C1
CH2
CH2
CH2
CH2
C15
C4
C12
C5
C11
C6
C13
C2
F1 [ppm]
F2 [ppm]
20
30
40
50
60
4
3
2
1

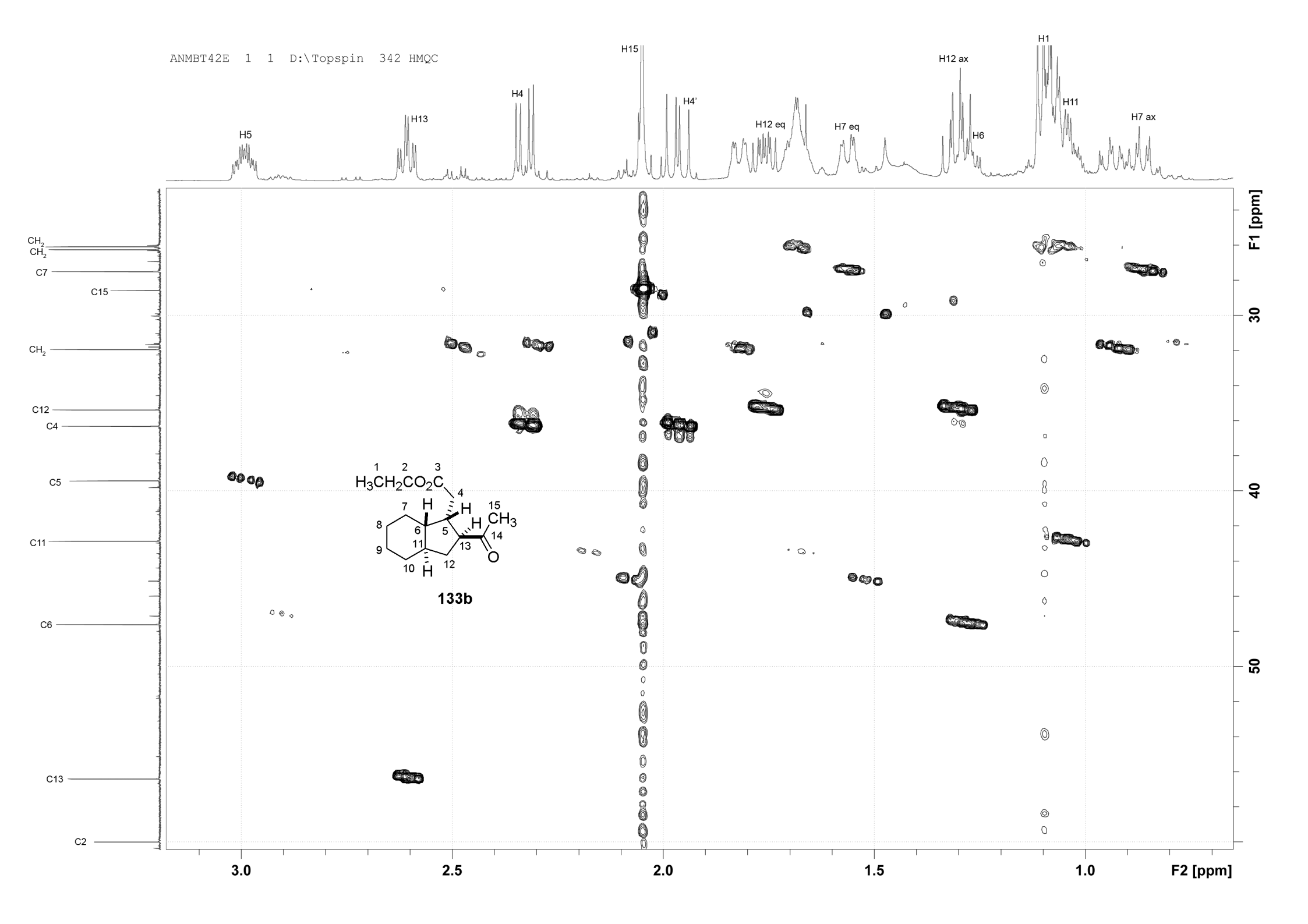
132a

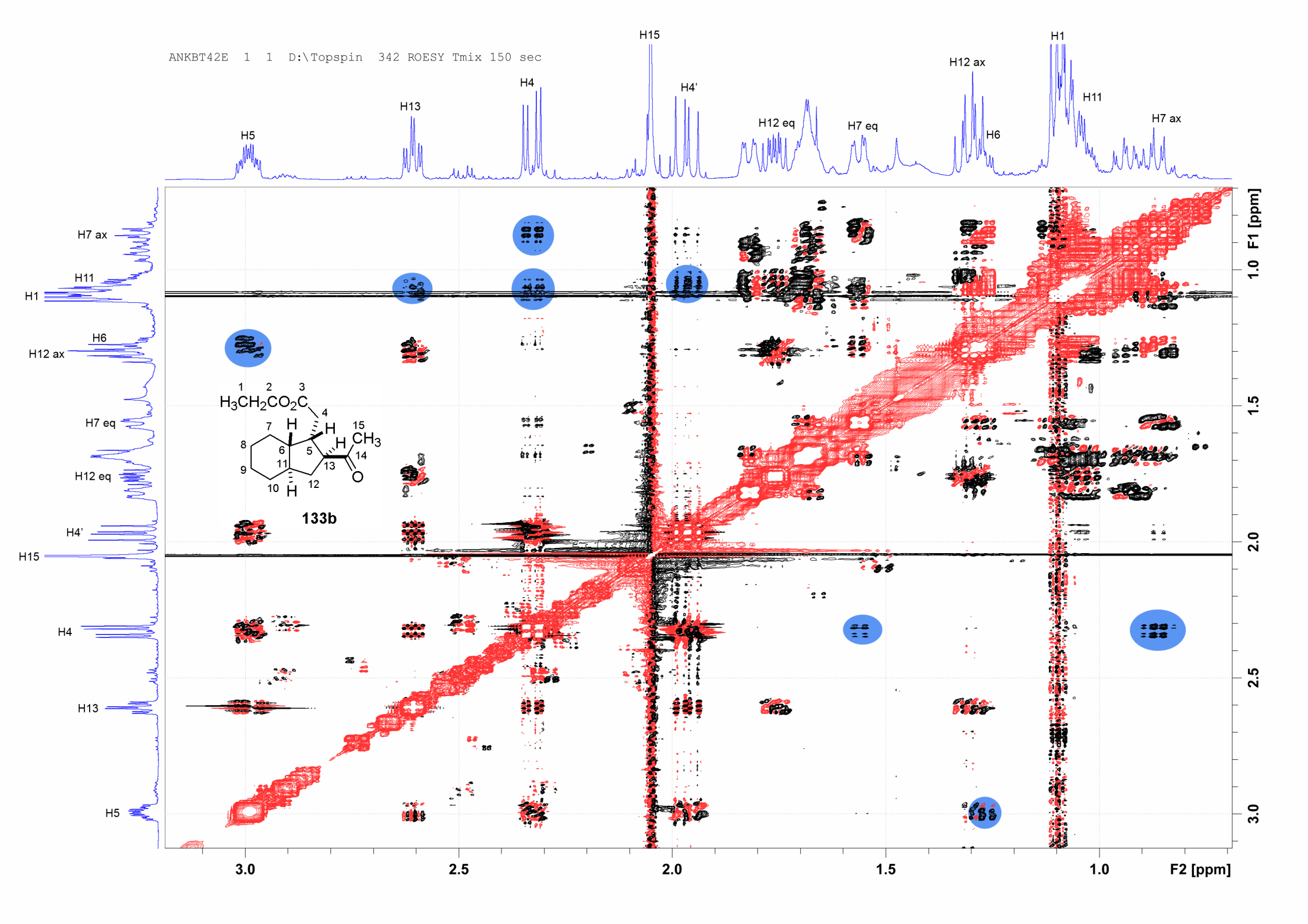

anka257e 1 1 E:\Topspin asv
H2
H13
4H, 4'H
H15
H12
H5
H1
H11
H12'
H6
A. Stelmakh, AN 257, CDCl3, NOESY, tmix=150 msec
132a
F1 [ppm]
F2 [ppm]
4.0
3.5
3.0
2.5
2.0
1.5
1.0


ANEDA65J 10 1 E:\Topspin asv
H2, q, 7.2 Hz to H1
H13, ddd
11.5 Hz to H12'
7.6 Hz to H5
3.0 Hz H12
H4, dd
14.3 Hz to H4'
4.3 Hz to H5
H5, dddd
10. 9 Hz to H6
7.3 Hz to H13
9.2 Hz to H4'
4.2 Hz to H4
H15
H4', dd
14.4 Hz to H4
9.2 Hz to H5
H12, ddd
12.7 Hz to H12'
7.0 Hz to H11
2.9 Hz to H13
H12', ddd
12.1 Hz to H13
12.3 Hz to H12
12.1 Hz to H11
H1, t, 7.2 Hz to H2
H6, dddd
11.1 Hz to H11
11.1 Hz to H7 ax
11.1 Hz to H5
3.3 Hz to H7 eq
H11
Stelmakh ANA65 15mg CDCl3/ohne TMS H,H-COSY60 14.09.05,Rettstadt
* The coupling constants support H5-H6 anti stereochemistry.
The constants are taken from 1H spectrum of 14a,
measured at 500MHz in CDCl3, see S11, S30.
H6
H1
H11
H12'
H12
H15
H4'
H5
H4
H13
H2
133a
F1 [ppm]
F2 [ppm]
1
2
3
4

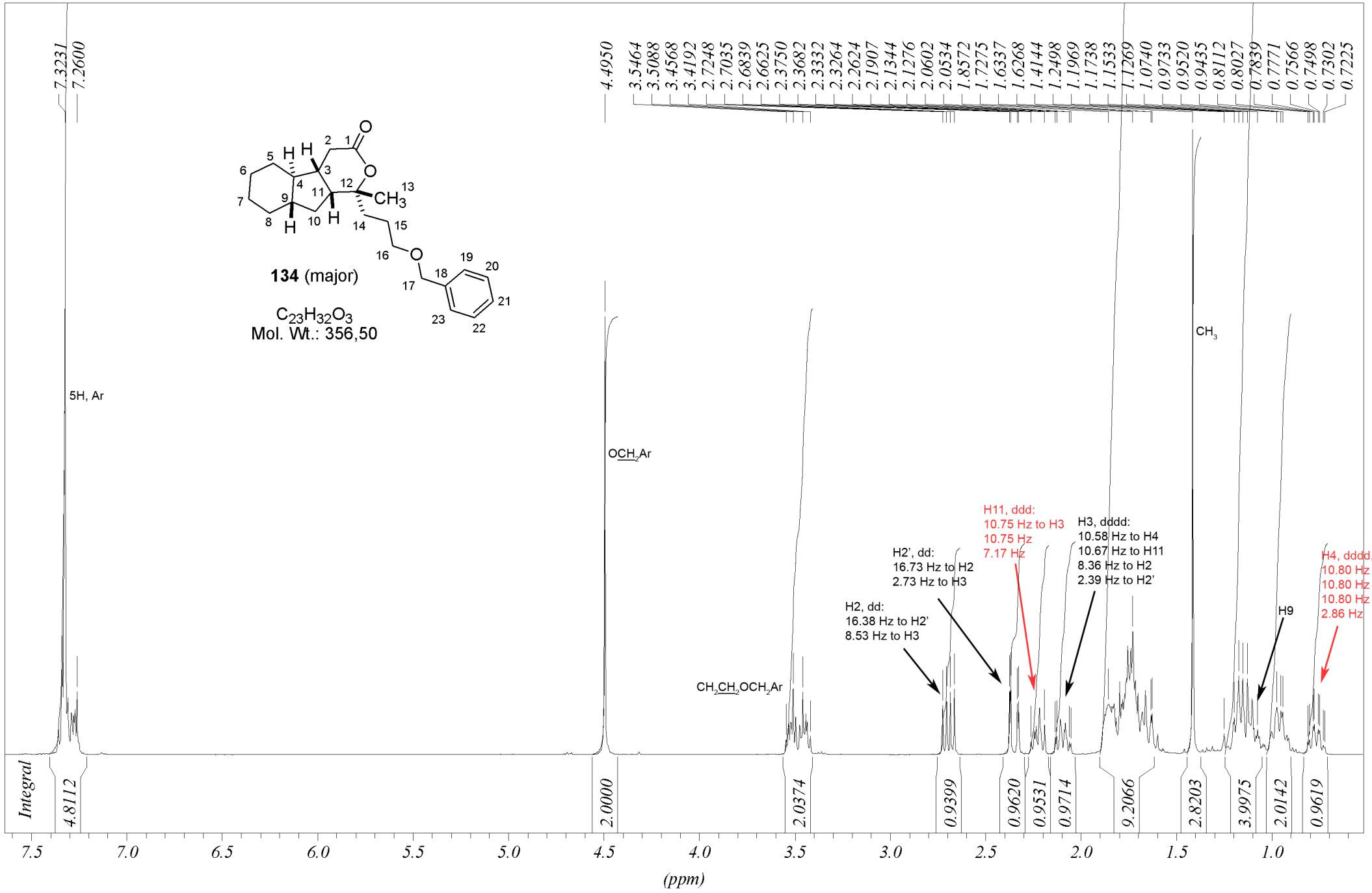

ANMBA65J 10 1 E:\Topspin asv
H2
H13
H4
H5
H15
H4'
H12
H12'
H1
H11
H6
Stelmakh ANA65 15mg CDCl3/ohne TMS HMQC 14.09.05,Rettstadt
133a
C1
2 x CH2
C15
CH2
CH2
C12
C4
C5
C11
C6
C13
C2
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F2 [ppm]
10
20
30
40
50
60
F1 [ppm]

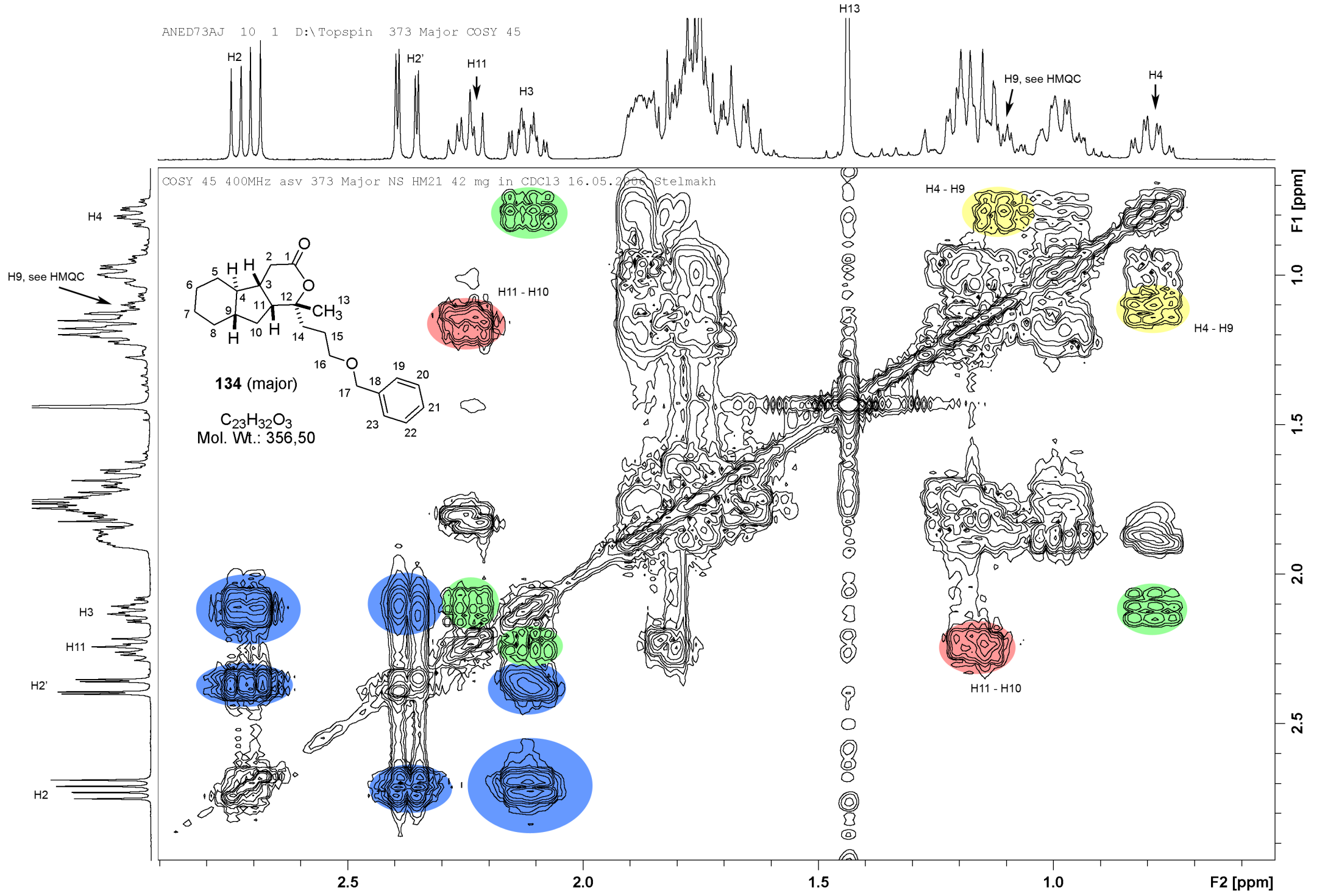

ANEDT42E 1 1 D:\Topspin 342 DQF COSY
H2, q, 7.10 Hz
H2', q, 7.10 Hz
H5, dddd
2.9 Hz to H13
5.2 Hz to H4
10.9 Hz to H4'
8.2 Hz to H6
H13, ddd
3.2 Hz to H5
8.7 Hz to H12
8.7 Hz to H12'
H4, dd
5.2 Hz to H5
15.2 Hz to H4'
H15
H4', dd
10.9 Hz to H5
15.2 Hz to H4
H12, ddd
6.2 Hz to H11
8.5 Hz to H13
12.1 Hz to H12'
H7 eq
H12', ddd
11.8 Hz to H11
11.8 Hz to H12
9.0 Hz to H13
H6
H11
H1, t, 7.1 Hz
H7 ax, dddd
2.6 Hz
11.3 Hz
13.0 Hz
12.2 Hz
* The constants are taken from 1H spectrum of 14b, measured at 500MHz in C6D6, see S12 and S35.
H7 ax
H11
H1
H6
H12 ax
H7 eq
H12 eq
H4'
H15
H4
H13
H5
133b
F1 [ppm]
F2 [ppm]
1.0
1.5
2.0
2.5
3.0
4
3
2
1

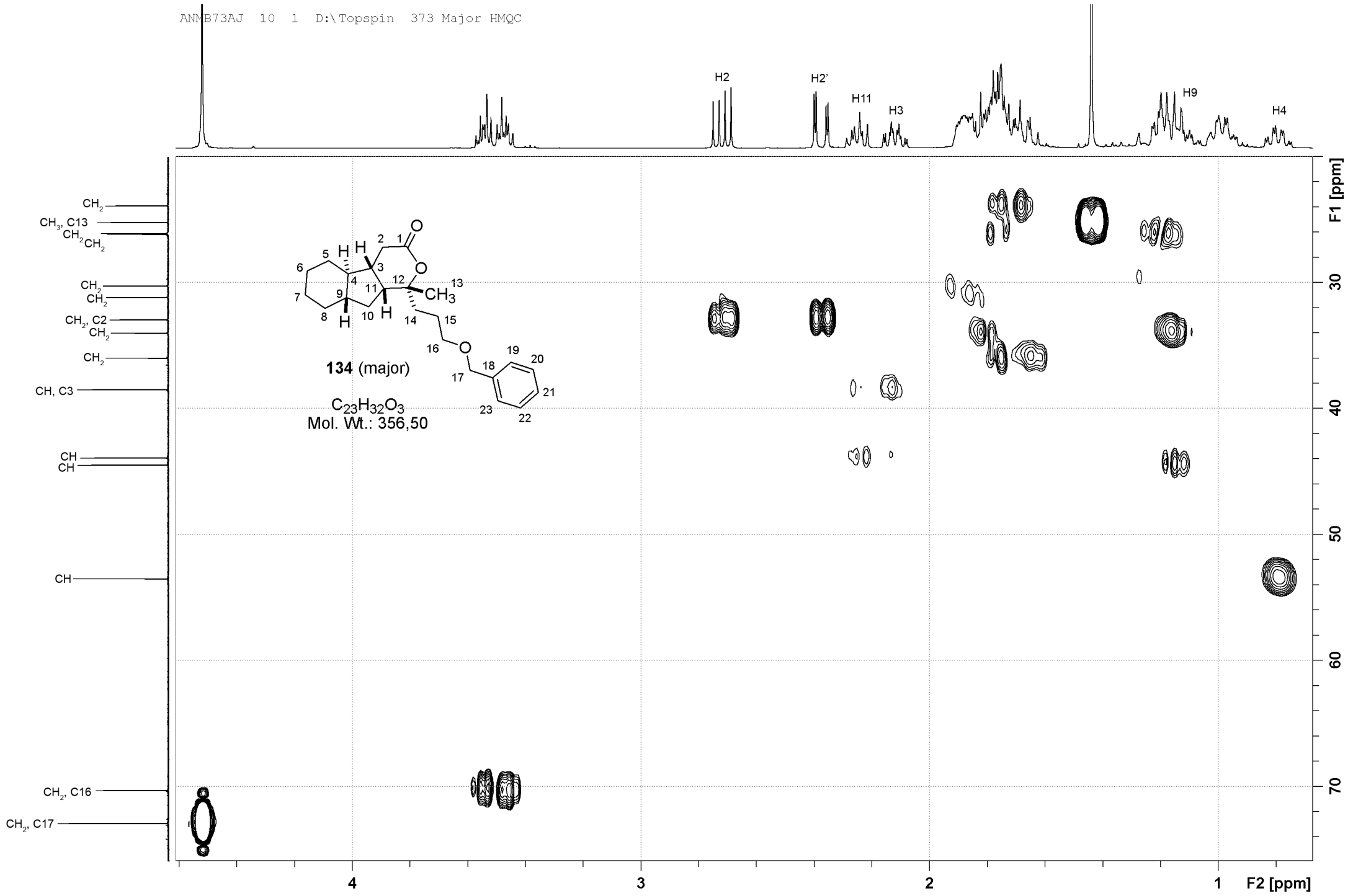

ANMBT42E 1 1 D:\Topspin 342 HMQC
H5
H13
H4
H15
H4'
H12 eq
H7 eq
H12 ax
H6
H1
H11
H7 ax
CH2
CH2
C7
C15
CH2
C12
C4
C5
C11
C6
C13
C2
1 2 3
H3CH2CO2C
4
7
H
H
15
CH3
8
6
5
H
14
9
11
13
O
10
H
12
133b
3.0
2.5
2.0
1.5
1.0
F2 [ppm]
F1 [ppm]
30
40
50

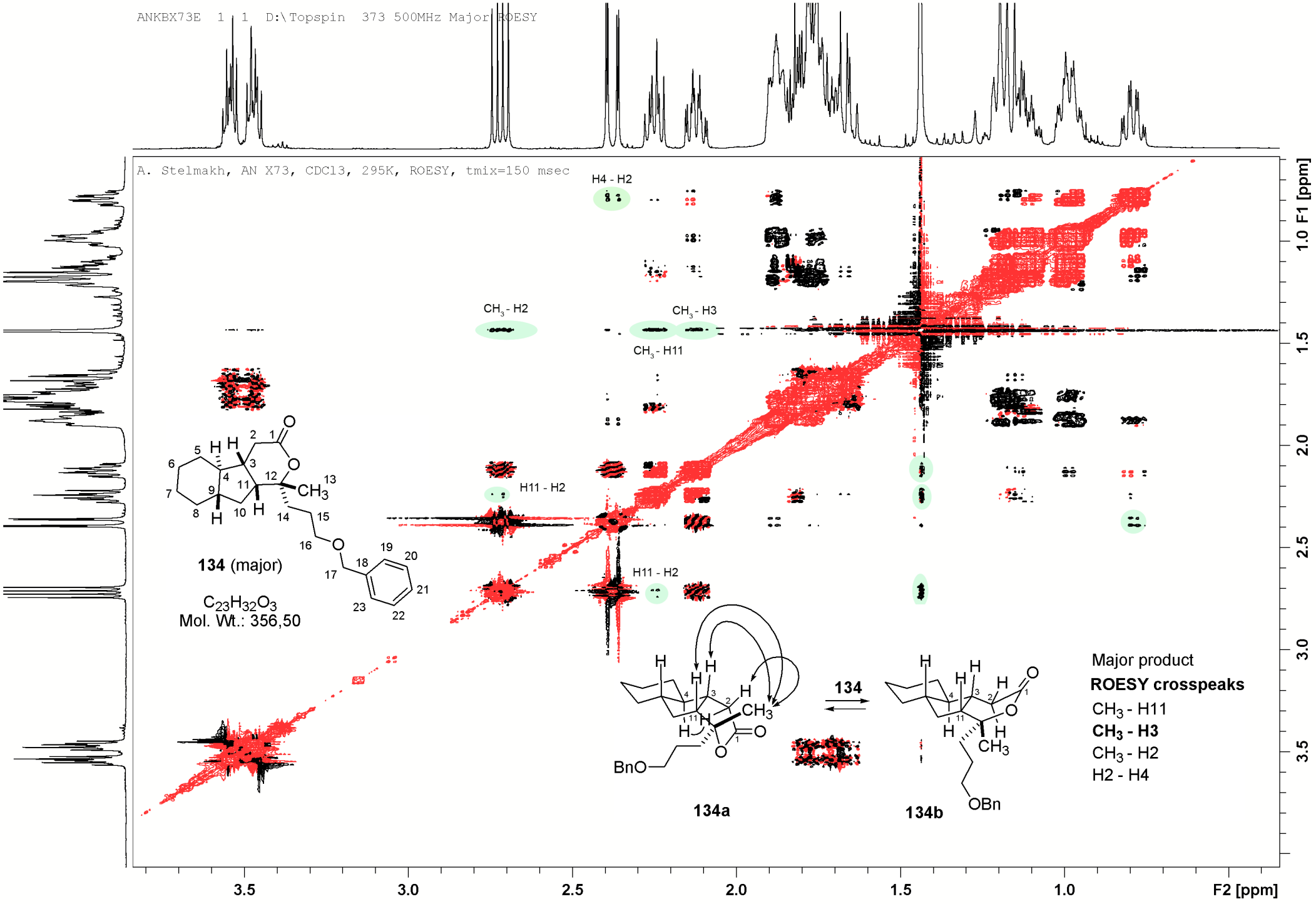

ANKBT42E 1 1 D:\Topspin 342 ROESY Tmix 150 sec
H5
H13
H4
H15
H4'
H12 eq
H7 eq
H12 ax
H6
H1
H11
H7 ax
H7 ax
H11
H1
H6
H12 ax
H7 eq
H12 eq
H4'
H15
H4
H13
H5
1 2 3
H3CH2CO2C
4
7 H
8
6
5
H
15
CH3
14
9
11
13
O
10
12
H
133b
3.0
2.5
2.0
1.5
1.0
F2 [ppm]
1.0
1.5
2.0
2.5
3.0
F1 [ppm]

1H 400MHz asv 373 Major NS HM21 42 mg in CDCl3 16.05.2006 Stelmakh

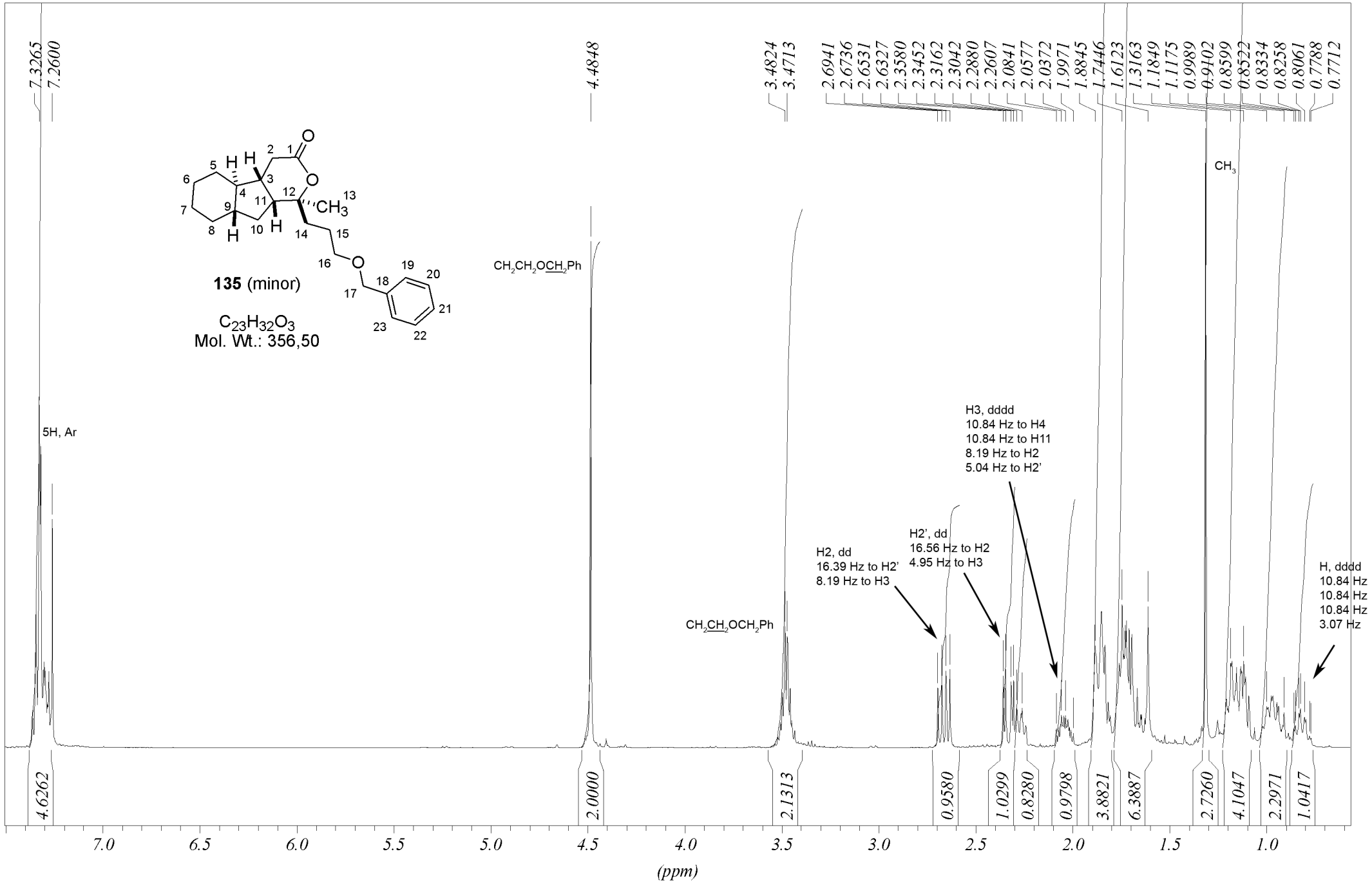


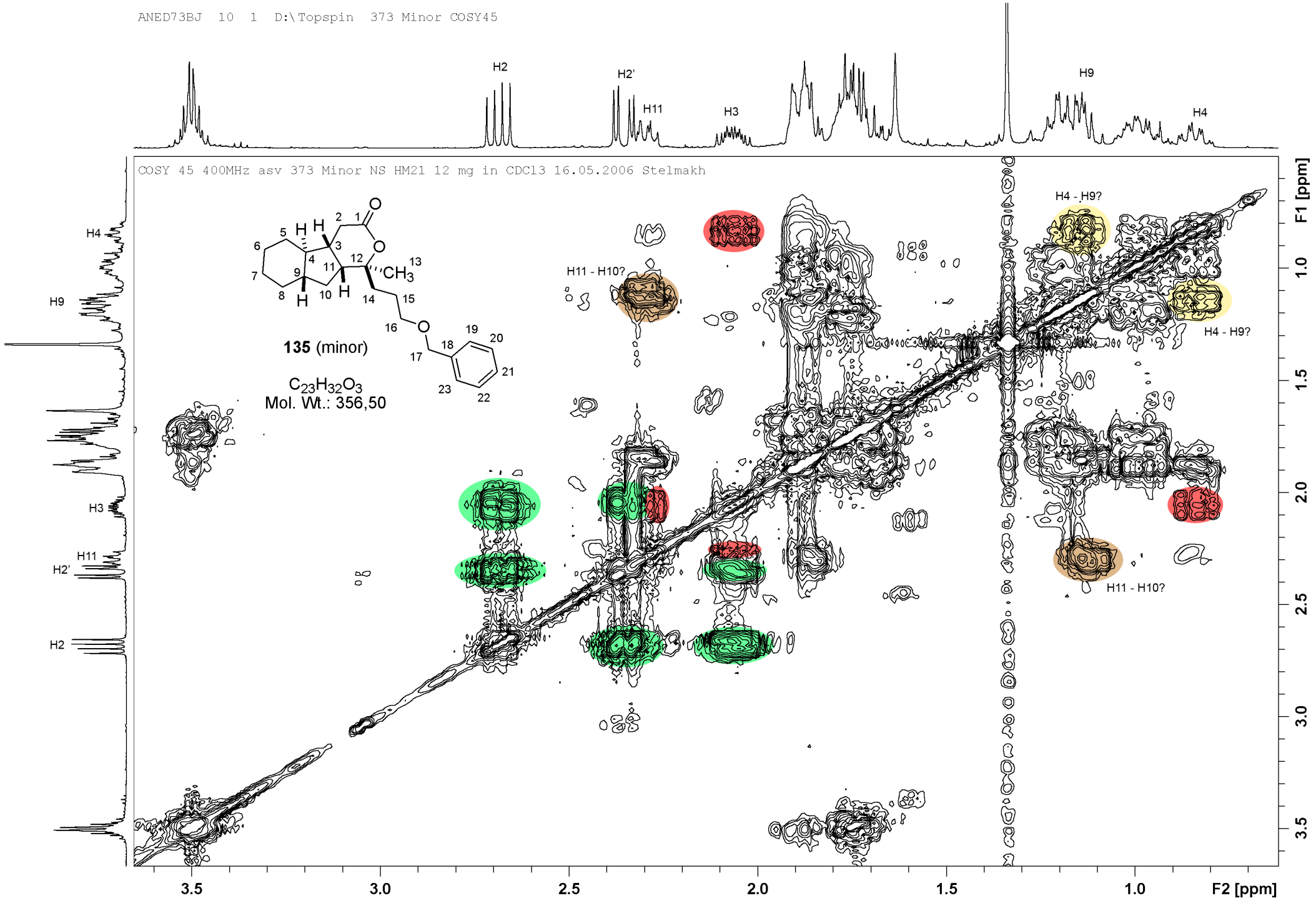

ANED73AJ 10 1 D:\Topspin 373 Major COSY 45
H2
H2'
H11
H3
H13
H9, see HMQC
H4
COSY 45 400MHz asv 373 Major NS HM21 42 mg in CDCl3 16.05.2006 Stelmakh
H4 - H9
H11 - H10
134 (major)
C23H32O3
Mol. Wt.: 356,50
F1 [ppm]
F2 [ppm]
2.5
2.0
1.5
1.0

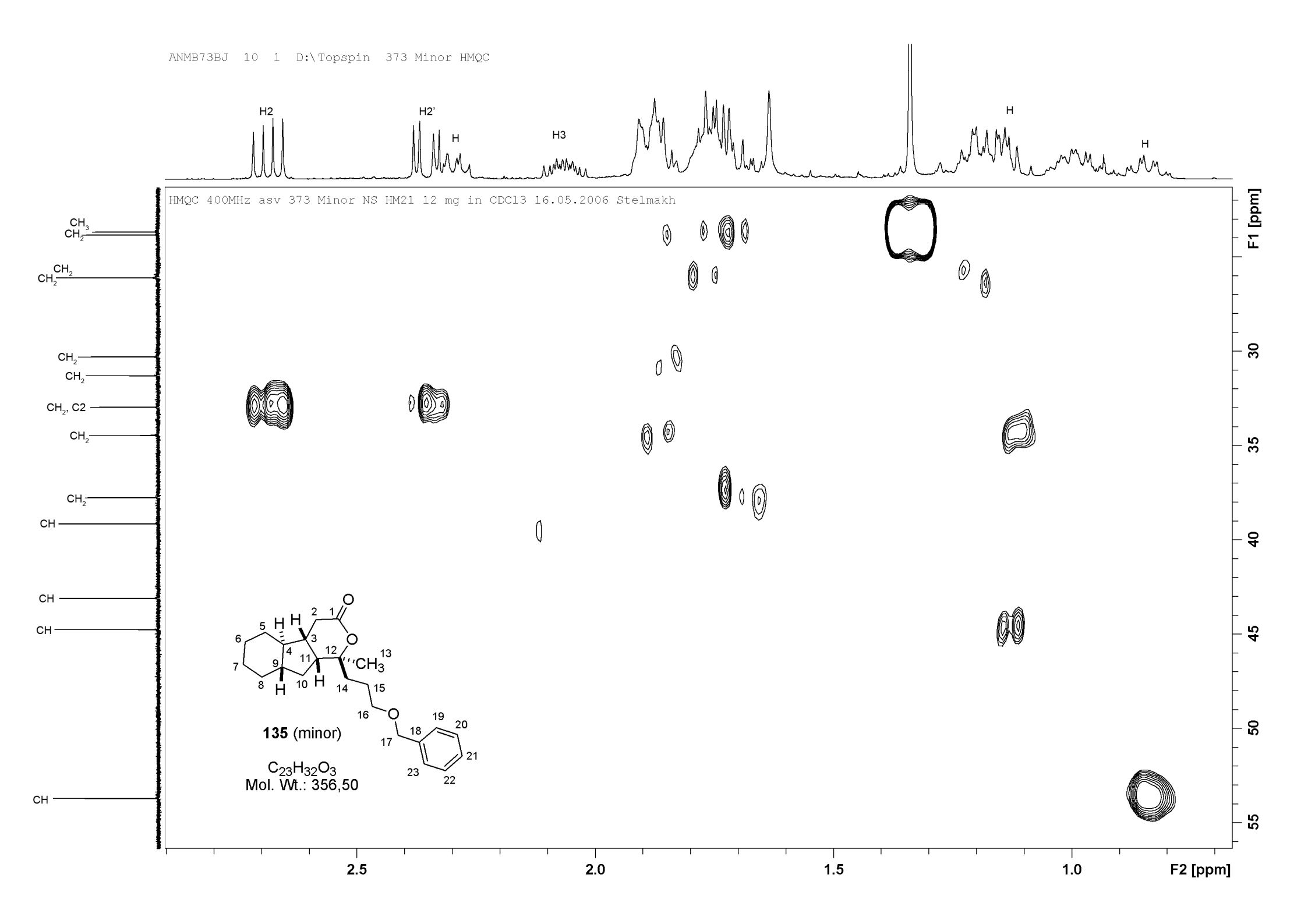

ANMB73AJ 10 1 D:\Topspin 373 Major HMQC
H2
H2'
H11
H3
H9
H4
CH2
CH3, C13
CH2
CH2
CH2
CH2, C2
CH2
CH2
CH, C3
CH
CH
CH
CH2, C16
CH2, C17
134 (major)
C23H32O3
Mol. Wt.: 356,50
F1 [ppm]
F2 [ppm]
4
3
2
1
30
40
50
60
70

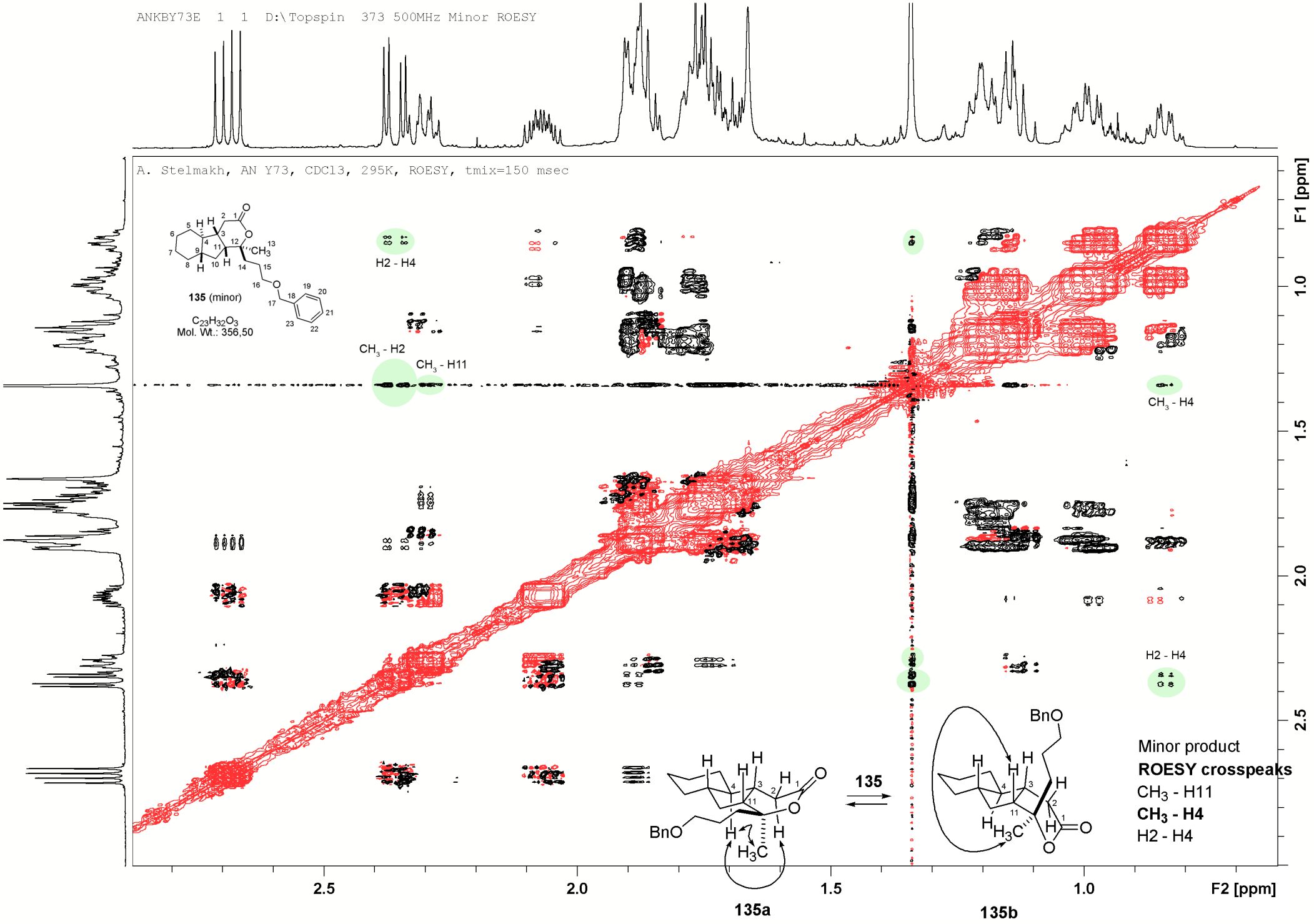

ANKBX73E 1 1 D:\Topspin 373 500MHz Major ROESY
A. Stelmakh, AN X73, CDCl3, 295K, ROESY, tmix=150 msec
H4 - H2
CH3 - H2
CH3 - H3
CH3 - H11
H11 - H2
H11 - H2
134 (major)
C23H32O3
Mol. Wt.: 356,50
134
134a
134b
BnO
OBn
Major product
ROESY crosspeaks
CH3 - H11
CH3 - H3
CH3 - H2
H2 - H4
1.0 F1 [ppm]
1.5
2.0
2.5
3.0
3.5
3.5
3.0
2.5
2.0
1.5
1.0
F2 [ppm]

1H 400MHz asv 373 Minor NS HM21 12 mg in CDCl3 16.05.2006 Stelmakh




ANED73BJ 10 1 D:\Topspin 373 Minor COSY45
H2
H2'
H11
H3
H9
H4
COSY 45 400MHz asv 373 Minor NS HM21 12 mg in CDCl3 16.05.2006 Stelmakh
135 (minor)
C23H32O3
Mol. Wt.: 356,50
H11 - H10?
H4 - H9?
H4 - H9?
H11 - H10?
F1 [ppm]
F2 [ppm]
1.0
1.5
2.0
2.5
3.0
3.5


ANMB73BJ 10 1 D:\Topspin 373 Minor HMQC
H2
H2'
H
H3
H
H
HMQC 400MHz asv 373 Minor NS HM21 12 mg in CDCl3 16.05.2006 Stelmakh
CH3 CH2
CH2 CH2
CH2
CH2
CH2, C2
CH2
CH2
CH
CH
CH
CH
F1 [ppm]
30
35
40
45
50
55
2.5
2.0
1.5
1.0
F2 [ppm]
135 (minor)
C23H32O3
Mol. Wt.: 356,50


ANKBY73E 1 1 D:\Topspin 373 500MHz Minor ROESY
A. Stelmakh, AN Y73, CDCl3, 295K, ROESY, tmix=150 msec
135 (minor)
C23H32O3
Mol. Wt.: 356,50
H2 - H4
CH3 - H2
CH3 - H11
CH3 - H4
H2 - H4
135
135a
135b
Minor product
ROESY crosspeaks
CH3 - H11
CH3 - H4
H2 - H4
F1 [ppm]
F2 [ppm]
1.0
1.5
2.0
2.5

LEBENSLAUF

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	geboren am 08.12.1980 in Tschernihiw, Ukraine Ukrainer, ledig	
Schulische Bildung	05/1998	Schulabschluß mit Auszeichnung (Schwerpunkt Mathematik), Staatliche Schule Nr. 12, Tschernihiw, Ukraine
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Promotion	10/2003 - 03/2007	*"Zur Totalsynthese von Hexacyclinsäure"* Doktorarbeit unter der Leitung von Prof. Dr. Markus Kalesse, Leibniz Universität Hannover Note: *"sehr gut"* (magna cum laude)

wissenschaftliche Publikationen

"Linus Pauling (dedicated to Linus Pauling on occasion of his 100th birthday)" Mikhail Yu. Kornilov, Andriy Stelmakh, *Pulsar* **2001**, *8*, 16-25.

"Tandem Intramolecular Michael-Aldol Reaction as a Tool for the Construction of the C-Ring of Hexacyclinic Acid" Andriy Stelmakh, Timo Stellfeld, Markus Kalesse, *Org. Lett.* **2006**, *8* (16), 3485-3488.

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"Towards the Total Synthesis of Hexacyclinic Acid", ORCHEM 2004, Bad Nauheim, 09.-11. September **2004**.

"Towards the Total Synthesis of Hexacyclinic Acid", "25. Tübinger-Göttinger Gespräche Zur Chemie von Mikroorganismen", Tübingen, 22.-24. September **2004**.

Posterbeiträge

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"Towards the Total Synthesis of Hexacyclinic Acid", "Asymmetric Synthesis with Chemical and Biological Methods", 9th International SFB-Symposium, EUROGRESS Aachen, 10.-11. Oktober **2005**.

"Towards the Total Synthesis of Hexacyclinic Acid", "Recent advances in the Chemistry of Peptides and Natural Products", Leibnizhaus, Holzmarkt 5, D-30159 Hannover, 5. März **2004**.