Synthesis of Spirocyclic Scaffolds by Aminoallylation/RCM Sequence
and
Approach Toward the Total Synthesis of the Macrolide Dictyostatin

Synthese Spiroverknüpfter Scaffolds durch eine Aminoallylierung/Ringschluss Metathese Sequenze
und
ein Zugang zur Totalsynthese des Macrolids Dictyostatin

DISSERTATION

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my Grandmother

Publications:

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E. V. Prusov, H. Röhm, M. E. Maier, Chemoenzymatic Synthesis of the C10-C23 Segment of Dictyostatin. *Org. Lett.* **2006**, *8*, 1025–1028.

V. G. Nenajdenko, E. P. Zakurdaev, E. V. Prusov, E. S. Balenkova, A novel convenient approach to the synthesis of 2-substituted analogs of ornithine and homolysine. *Russian Chemical Bulletin* **2005**, *53*, 2866–2870.

V. G. Nenajdenko, E. P. Zakurdaev, E. V. Prusov, E. S. Balenkova, Convenient synthesis of melatonin analogues: 2- and 3-substituted -N-acetylindolylalkylamines. *Tetrahedron* **2004**, *60*, 11719–11724.

Table of Contents

Abbreviations

abs.	absolute
Ac	Acetyl
ACh	Acetylcholine
ADP	Adenosine diphosphate
AIBN	Azobisisobutyronitrile
aq.	aqueous
ar. (arom.)	aromatic
ATP	Adenosine 5'-triphosphate
BBN (9-)	9-Borabicyclo[3.3.1]nonane
BAIB	Bis-acetoxyiodosobenzene
Bn	Benzyl
br	broad (NMR)
Boc	*tert*-Butoxy carbonyl
b.p.	Boiling point
Bu	Butyl
Bz	Benzoyl
c	Concentration
CAN	Cerium(IV) ammonium nitrate
Cbz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
CSA	Camphor sulfonic acid
Cy	cyclohexyl
δ	Chemical shift in ppm (NMR)
d	Doublet (NMR)
dba	*trans*,*trans*-dibenzylideneacetone
DCM	Dichloromethane
de	Diastereomeric excess

DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Diisopropyl azodicarboxylate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E	trans
ee	Enantiomeric excess
EI	Electron impact
EOM	Ethoxymethoxymethyl
Eq.	equation
ESI	Electronspray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fig.	Figure
Fur	Furyl
g	gram(s)
GC	Gas chromatography
Grubbs 1st	bis(tricyclohexylphosphine)benzylidene ruthenium dichloride
Grubbs 2nd	[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene](tricyclohexylphosphine) benzylidene ruthenium dichloride
h	hour(s)
HEH	Hantzsch ester, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
HOMO	Highest occupied molecular orbital

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
HTX	Histrionicotoxin
Hz	Hertz
IC_{50}	half maximal Inhibitory Concentration
IR	Infrared
*i*Pr	isopropyl
J	coupling constant
L	liter(s)
LA	Lewis acid
LC	Liquid chromatography
LDA	Lithium diisopropylamide
HMDS	Hexamethyldisilazane
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (NMR)
*m*CPBA	*meta*-perbenzoic acid
Me	Methyl
MeOH	Methanol
mg	milligram
µg	microgram
MOM	Methoxymethyl
Ms	Methanesulfonyl
MVK	Methylvinylketone
m/z	Mass to charge ratio (MS)
NBS	N-bromosuccinimide
nM	nanomolar
NMO	N-Methylmorpholine-N-Oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PCC	Pyridinium chlorochromate
PFL	Pseudomonas fluorescens lipase

Ph	Phenyl
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPA	Polyphosphoric acid
PPTS	Pyridinium *para*-toluene sulfonate
*p*TSA	*para*-Toluene sulfonic acid
Py	Pyridine
q	Quartet (NMR)
RCM	Ring-closing metathesis
R_f	Retention factor (TLC)
RT	Room temperature (ca. 23 °C)
s	Singlet (NMR)
Sia	Siamyl (1,2-dimethylpropyl)
t	Triplet (NMR)
TCBC	2,4,6-trichloro-benzoyl chloride
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TfO	Trifluoromethane sulfonate
TMS	Trimethylsilyl
Tos (Ts)	*p*-Toluenesulfonyl
Triflate	Trifluoromethane sulfonate
UV	Ultraviolet
Z	cis

Chapter I

Synthesis of Spirocyclic Scaffolds by Aminoallylation/RCM sequence

1 Introduction

In our current society medicines play an extremely important role in the management of health care problems and are considered to become even more important in the coming years. The world pharmaceutical market value in 2006 was estimated to be 600 billions $ and it's rising at approx 7-10% annually. To sustain this growth major pharmaceutical companies need to introduce to market 2-4 novel chemical entities (NCE) per year, while the actual average number is only 0.75[1]. This gap was called "innovation deficit" and attributed to increased demand on safety of new drugs. The average number of clinical trials per new drug application steadily increased from the 30 in 1970s, about 40 in 1980s to 70 in the 1990s[2]. The more strict safety regulations are also reflected on prolonged duration of the drug development process, from about 8 years in 1960s to 15 years by now.

Since drug safety cannot be compromised, there is constant demand for strategies that can enhance R&D productivity, namely accelerate drug discovery and reduce failure rates during the later drug development. Throughout the most of the history of pharmacy and medicinal chemistry, drug discovery was limited to isolation of active substances from plants and organisms. With growing potential of synthetic organic chemistry preparation of derivatives and analogs aiming for better medicines became the common practice.

But in recent two decades the pharmaceutical industry sustained a "paradigm shift" in the area of drug discovery. With the advent of combinatorial chemistry (CC) and high throughput screening (HTS) nature lost its status as a sole drugs source. Compound libraries synthesized from simple building blocks are now the most frequent starting point for lead identification and optimization. Due to the huge number of compounds needed to successfully identify a lead, fully automated systems were developed. The whole process, starting from chemical synthesis and ending with biological testing and data storage is computerized. Compound libraries are used not only to discover lead structures, but for improving already existing ones.

Due to constant isolation or identification of new drug targets, medicinal chemistry must respond adequately providing novel interesting combinatorial libraries. The inspiration still frequently comes from nature, when isolated compounds exhibiting biological activities serve

as starting point for development of new drugs. The usual tactic here is to identify crucial regions within the molecule that are important for biological activity by simplification or preparation of synthetic analogs.

Although the number of compounds which undergoes biological testing has exploded, reaching at some companies 200000 data-points per day and 2-5 millions sample stock collections are common place in industry today, the number of new chemical entities didn't increase proportionally. Thus, not only the number of tested compounds, but a proper design of combinatorial libraries plays a crucial role for successful drug discovery.

To address this issue many important concepts were introduced. Among them, quantitative structure-activity relationship (QSAR) and adsorption, delivery, metabolism and excretion (ADME) are the two most important ones. Soon it was realized, that compounds in combinatorial libraries must fulfill somewhat contradicting demands, they should cover a broad chemical space yet their physical properties must stay within "drug-likeness" limits. At the beginning of the HTS era many "hits" that showed good *in vitro* activity failed to reach the market due to pharmacokinetic reasons, namely poor bioavailability and high toxicity.

A usual practice today is to make compound collections by derivatization of so called scaffolds, a rigid structure which defines specific activity. Such scaffold structures for automated preparation of combinatorial libraries must be itself produced and, what's important, in gram scale quantities. Thus, methods which allow short and efficient preparation of such structures are required. With the discovery of new powerful chemical reactions, structures which earlier were regarded as difficult to make can be reviewed. Because most of the scaffolds represent cyclic and heterocyclic structures, methods for the synthesis of medium sized rings are of particular interest here.

Recently, the ring closing metathesis reaction became a valuable tool in organic chemistry. It was applied to the synthesis of complex structures with various ring size, most frequently in total synthesis of natural products. At the same time, there are only a handful examples of scaffold preparation via RCM reaction. Our goal in this project was to fill this gap and develop a novel method for the synthesis heterocyclic scaffolds based on simple reactions and RCM as

a key step. As target objects we chose nitrogen containing spirocyclic compounds because of their interesting structure and biological properties.

2 Literature Review

2.1 Privileged structures and scaffolds in modern drug discovery

The term "privileged structure" was first introduced in 1988[3]. A privileged structure was defined as substructural feature which confers desirable (often drug-like) properties on compounds containing that feature or "a single molecular framework able to provide ligands for diverse receptors." It often consists of a semi-rigid scaffold which is able to present multiple hydrophobic residues without undergoing hydrophobic collapse. It was envisaged, that the privileged structures could be a valuable alternative in the search for new receptor ligands by suitably decorating these substructures. Since then, an increasing number of substructural frameworks have been described as privileged structures, including indoles, tryptamines, benzodiazepines, aryl piperazines, spiro phenylpiperidines, benzopyranes and 1,4-dihydropyridines (**Figure 1**). These privileged structures have since then, deliberate or not, been used extensively in medicinal chemistry programs to identify new hits.

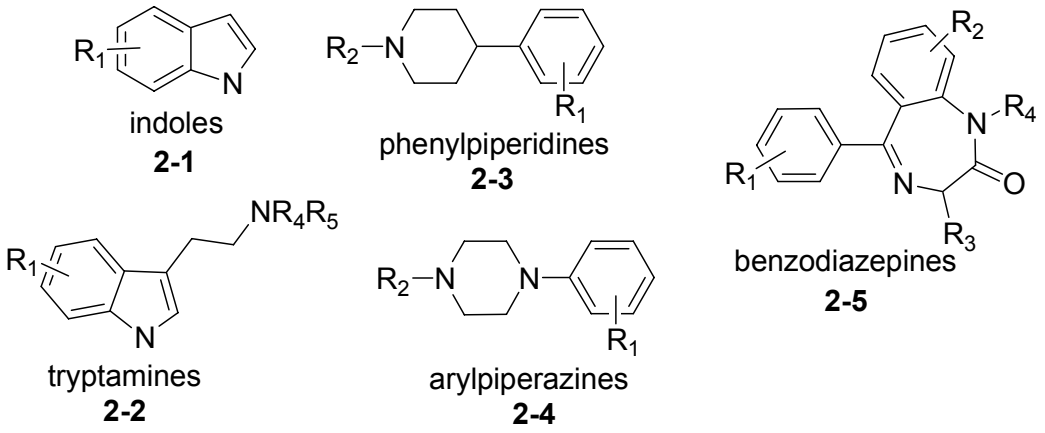


Figure 1. Examples of "privileged structures".

The concept of privileged structures in drug design is highly attractive, because the rational design of new leads has been limited by the lack of detailed structural information for many receptors. Privileged structures might provide the medicinal chemist with common, non-peptide, orally available substructures that would be suitable starting points in parallel synthesis. The idea is that the incorporation of privileged structures into combinatorial libraries, combined with information from homology modeling of a specific receptor or from known ligands, will increase the probability of finding valuable hits. The privileged structure

will thus provide affinity while selectivity is introduced by the variation in the rest of the molecule. Ultimately, a single, large combinatorial library of privileged structures might provide ligands for a whole series of receptors.

As a logical extension, the concept of scaffold emerges from privileged structures. A scaffold is defined as core portion of a molecule common to all members of a combinatorial library[4]. It's usually a rigid, cyclic (often bicyclic or even polycyclic) structure which is capable of binding to a broad spectrum of targets. It also holds necessarily pharmacophores and lipophilic groups. They can be divided into two types: *in situ* scaffolds, formed during library production which contain residues of at least two building blocks or preformed scaffolds, which are incorporated into the library as a unit. The preformed scaffold must contain some functional groups suitable for further derivatization to provide access to the large number of compounds. It also should maintain ability to bind to different receptor targets. Thus, invention of a new good scaffold is a very complicated task. Alternatively, scaffolds can be selected from already existing different combinatorial libraries by analyzing activities and finding similarities via computational methods – scaffold hopping. A hierarchial classification of scaffolds based on the iterative removal of the rings accordind to certain rules was introduced recently[5]. In another paper the analysis of the scaffold composition of several types of commercially available screening collections is provided[6].

Interesting types of rigid structures which could be promising scaffolds are spiro compounds. By adding heteroatoms and/or functional groups in one or two rings a broad diversity of structures can be achieved (**Figure 2**). Spirocyclic structures are also characterized by a unique spacial arrangement of rings, thus making binding possible to previously unknown sites.

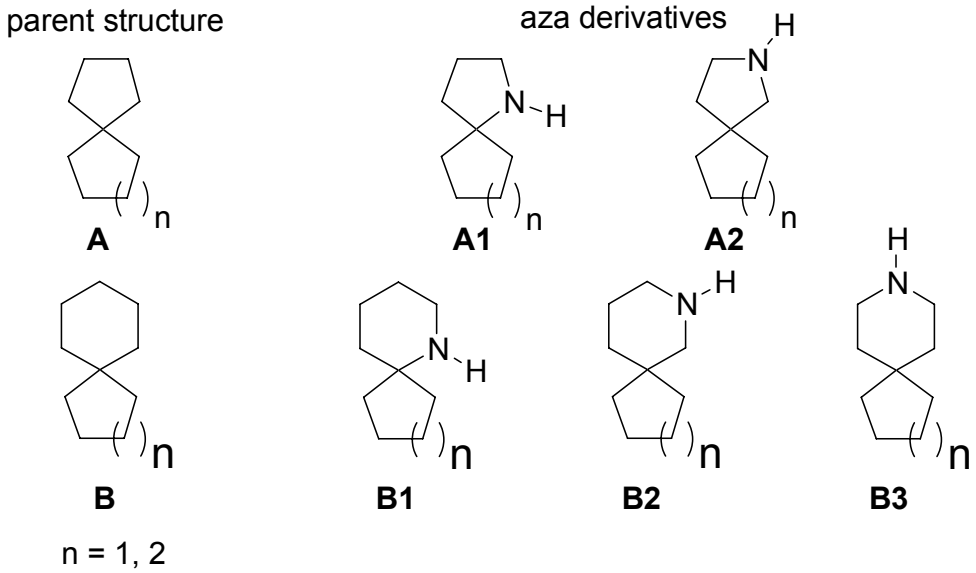


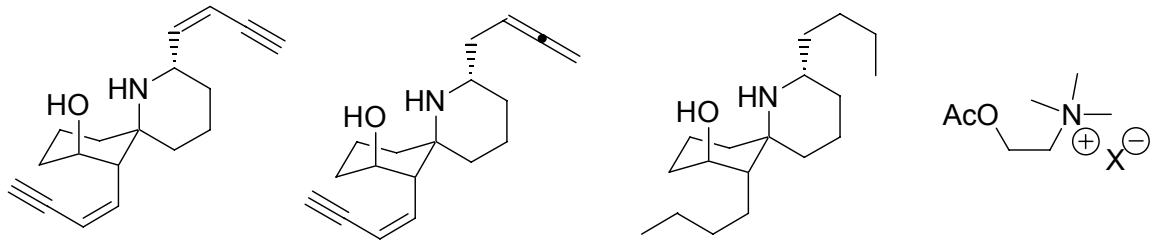
Figure 2. Genealogy of spiro scaffolds.

A good scaffold must possess functional groups suitable for further derivatization. The most commonly used is the amino group, which can be modified by a vast number of reactions, including alkylation, acylation, sulfonylation, urea formation, and others. The second one is the carbonyl function with which Grignard addition, reductive amination and multicomponent reactions are usually done. Other important groups are carboxyl, alcohol and multiple bonds.

2.2 Natural compounds and drugs containing a spiroheterocyclic skeleton

The spiro skeleton is not uncommon in natural products and appears in a number of alkaloids. The most representative families of such compounds are described below.

In 1823, a western traveler by the name of Captain Charles Stuart Cochrane reported on his expeditions around the lowland tropical rain forests of Colombia. He encountered tribes of native Indians who used poison arrows and blowgun darts for hunting. Eventually, he discovered that the poison had been extracted from small brightly colored frogs. In 1971 out of this poison a number of potent neurotoxins was isolated by J. W. Daly[7,8] and named histrionicotoxins (**Figure 3**), after the subspecies from which it is extracted, *Dendrobates histrionicus*.



histrionicotoxin (2-6) **dihydroisohistrionicotoxin (2-7)** **perhydrohistrionicotoxin (2-8)** **acetyl choline**

Figure 3. Alkaloids of histrionicotoxin family.

Histrionicotoxin (**2-6**), is a spirocyclic piperidine, and is one of a family of eleven compounds, which differ in their side-chains. Some exhibit acetylenic functionality (as in histrionicotoxin-HTX- itself), and others have allenic side-chains or saturated side-chains. The spirocyclic core of the HTX family is unique in the world of natural products and has therefore been the subject of much study in the chemical community. The cis-enyne moiety is also a very unusual feature in the natural product kingdom. The closest that nature comes to producing this type of unsaturation is in the bacterium-derived compounds known as enediynes, including such antibiotics as calicheamicin, and also the neocarzinostatins, esperamicins and the dynemicins.

The toxins that have been isolated originate from small glands on the back of the frogs, which were originally thought to produce, and then store the poison. Interestingly, when the frogs are kept in captivity, the level of the toxins that they produce is severely diminished, and in most species is not produced at all. This has led to the assertion nowadays that the toxins are somehow introduced into the frog via diet or by some other outside influence.

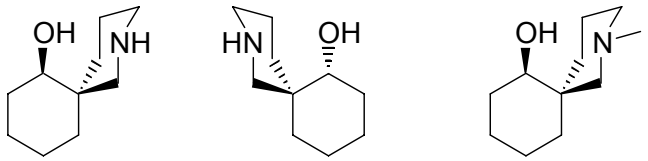
HTX has a very similar spatial arrangement of important functional groups as the neurotransmitter acetylcholine. The distance between the nitrogen and the hydroxyl groups in both acetylcholine and HTX is approximately 2.7 angstroms. It is due to this similarity that the toxin can affect the nervous system.

The histrionicotoxins have been shown to be potent nicotinic non-competitive antagonists. This means that HTX acts as a ligand that antagonizes the response to acetylcholine without actually blocking the binding sites of acetylcholine. The toxin has the ability to block the channel associated with the protein-bound acetylcholine receptor known as the IMRC (ionic conductance modulator receptor complex). This causes a reduction in the conductance across the channel and also a reduction in the time which the channel is open.

Unlike the highly toxic batrachotoxins (also derived from frogs) HTX shows a fairly low toxicity level in mammals. An administered dose of 5-10 mg/kg in mice only induces slight

locomotive difficulties and prostration. Although the molecule has a low toxicity level, it does draw particular biological interest due to its excellent selectivity for the nicotinic acetylcholine receptor.

Another interesting group of natural products containing a spirocyclic moiety are *Nitraria* alkaloids, namely nitramine, isonitramine and sibirin (**Figure 4**). They were isolated in the mid-80s by russsian chemists from plants of different *Nitraria* species, e.g. *Nitraria sibirica*, *Nitraria komarovii* and *Nitraria schoberi*.



(+)-nitramine **2-9** **(+)-isonitramine** **2-10** **(-)-sibirine** **2-11**

Figure 4. Alkaloids isolated from *Nitraria* plants.

The notable difference from the previously described histrionicotoxin family is that *Nitraria* alkaloids possess a 2-azaspiro[5,5]undecane skeleton. Their structure was determined by X-ray analysis of the corresponding picrate salts. Although, no apparent biological activity was reported for these compounds, they became attractive targets for total synthesis and methodological studies.

In 1997, the tricyclic alkaloid fasicularin (**2-21**) was isolated by a SmithKline Beecham group from the ascidian *Neptheis fasicularis* collected in Pohnpei, Micronesia (**Figure 5**)[9]. NMR and NOE experiments led to the assignment of the structure, relative stereochemistry, and conformation of fasicularin as depicted in **2-21**. Unfortunately, upon isolation the optical rotation of natural fasicularin was not measured, and thus, it has not been possible to compare enantiomerically pure synthetic material with the natural alkaloid to establish its absolute configuration.

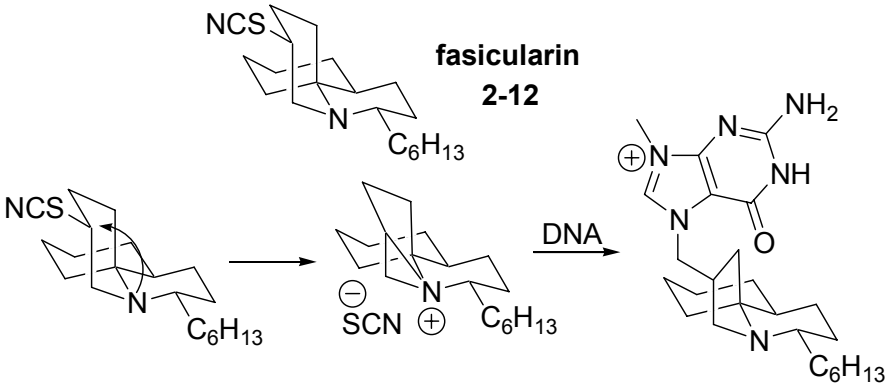


Figure 5. Structure and cytotoxity mechanism of fasicularin.

Fasicularin (**2-21**) was found to have biological activity against a DNA repair-deficient strain of yeast, as well as cytotoxicity against kidney epithelial cells extracted from African green monkey. Recently, Gates et al. investigated the ability of fasicularin to damage DNA by acting as an alkylating agent[10]. In this experiment, mixed-sequence duplex DNA was treated with racemic synthetic fasicularin, and after thermal treatment the guanine alkylation product could be detected (**Figure 5**). The assumption was that fasicularin is first converted to the aziridinium ion which is subsequently attacked by N(7) of the guanine base leading to the observed alkylation product. Although the regiochemistry of the opening of aziridinium ion was not actually proven, it was assumed that nucleophilic attack occurred at the methylene carbon. It was also found in control experiments that the thiocyanate anion formed in the process does not cause DNA strand cleavage.

Until very recently, spirocyclic structures were not frequently found in combinatorial libraries, mainly due to limited number of general approaches toward such compounds. To be interesting for medicinal chemistry, such a route must not only provide the spiro core itself, but should also allow useful functional groups to be placed at predefined positions.

Nevertheless, some biologically active spirocyclic compounds were found by screening. Potent substance P antagonist possessing a 1,8-diaza[5.5]undecane skeleton has been invented at Pfizer Inc by rational drug design as a conformationally rigid analog of CP-99,994[11]. Examination by X-ray crystallography and ^{1}H NMR revealed differences in relative orientation of the phenyl rings in crystal and solution.

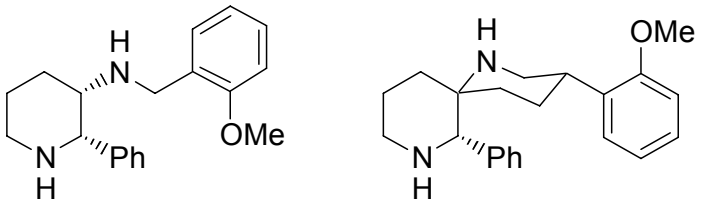


Figure 6. Structures of potent substance P antagonist and its rigid analog.

As another example, the 3,9-diazaspiro[5.5]undecane ring system was investigated as a suitable scaffold for preparing potent and selective GPIIb–IIIa antagonists, from which the most potent one **2-15** is shown in **Figure 7**[12]. A very similar hit structure **2-16** has been identified in the series where pharmacophore groups were attached through the carboxyl function to the 9-azaspiro[5.5]undecane-3-carboxylate template[13].

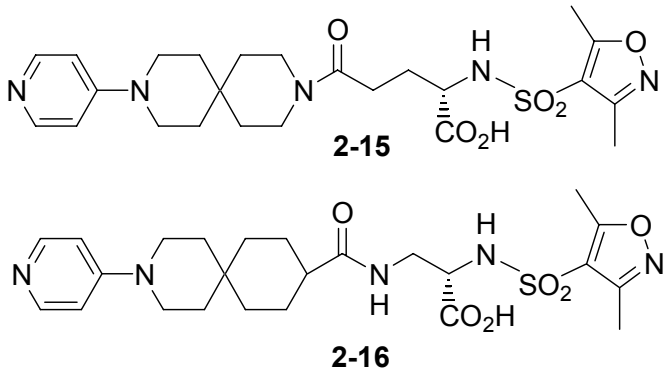


Figure 7. Structures of selective GPIIb–IIIa antagonists.

Recently, Jansen Pharmaceutica filed a patent in which the synthesis and biological evaluation of 236 spirocyclic compounds has been claimed[14]. The substances were found to be potent NK_1 receptors antagonists and some of them exhibit selectivity over NK_2 and NK_3.

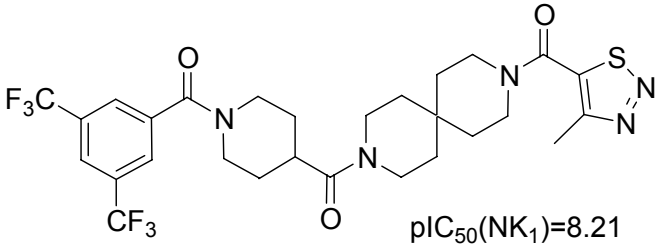


Figure 8. Example of a potent NK_1 receptor antagonist.

2.3 Overview of Known Methods for the Preparation of Various Spirocyclic Structures.

To give a general picture of existing methods for the synthesis of spirocyclic compounds relevant references from the literature were collected. This review is focused on, but not limited to, approaches to different aza- and diazaspiro[5.5]undecanes.

2.3.1 1-Azaspiro[5.5]undecane

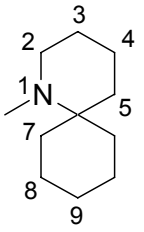
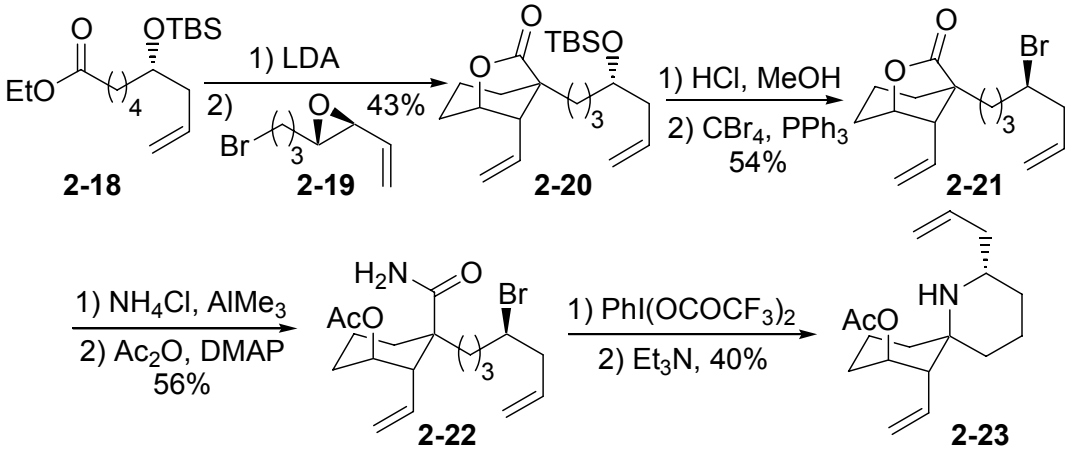


Figure 9. 1-azaspiro[5,5]undecane skeleton.

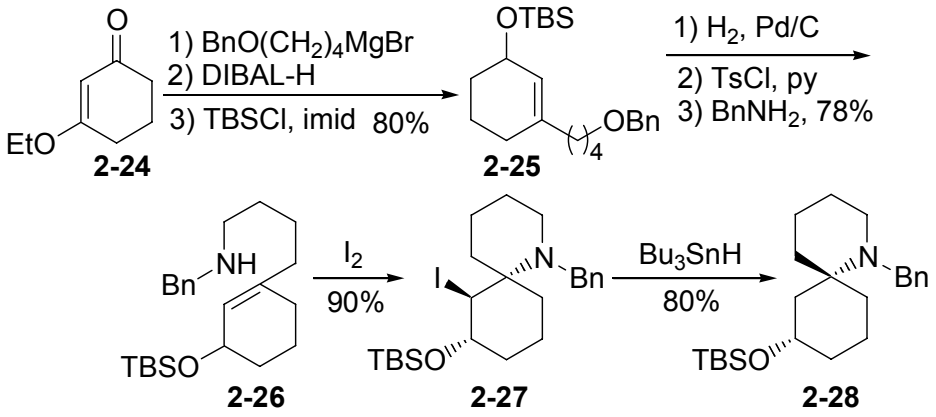
As was described in the previous section, the 1-azaspiro[5,5]undecane skeleton appears most frequently in histrionicotoxin alkaloid family. Thus, a number of approaches toward histrionicotoxin itself and its analogs inevitably include construction of the spirocyclic core. Obviously, retrosynthetic disconnections of the two carbon-nitrogen bonds are the first to consider. For instance, intramolecular nucleophilic substitution was used in the first Stork-Zhao total synthesis of (-)-HTX (**Scheme 1**)[15].



Scheme 1. Total synthesis of (-)-HTX by Stork-Zhao.

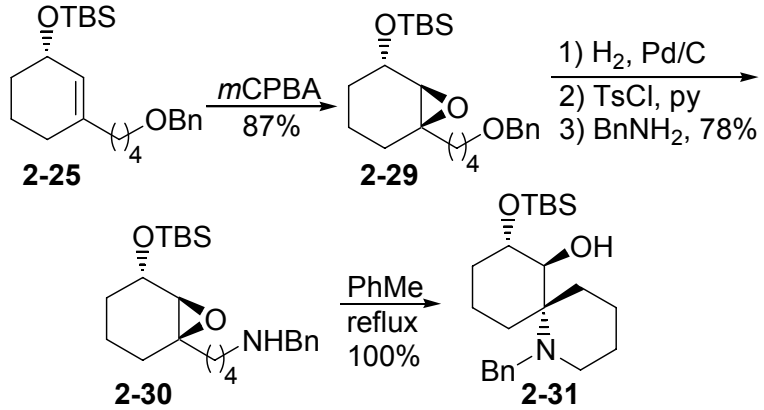
In a series of publications the Tanner group extensively researched another pathway, where substitution occurs at the tertiary carbon (**Scheme 2**)[16,17]. Starting from the well known Stork β-alkoxycyclohexenone **2-24**, a ω-benzyloxyalkyl side-chain was introduced by Grignard reaction and acidic hydrolysis. The resulting enone was reduced and converted to amine **2-26**

by simple manipulations. Treatment of **2-26** with excess of iodine resulted in clear formation of spiro iodide **2-27** with excellent yield. Subsequent radical de-iodination afforded the core structure of HTX.



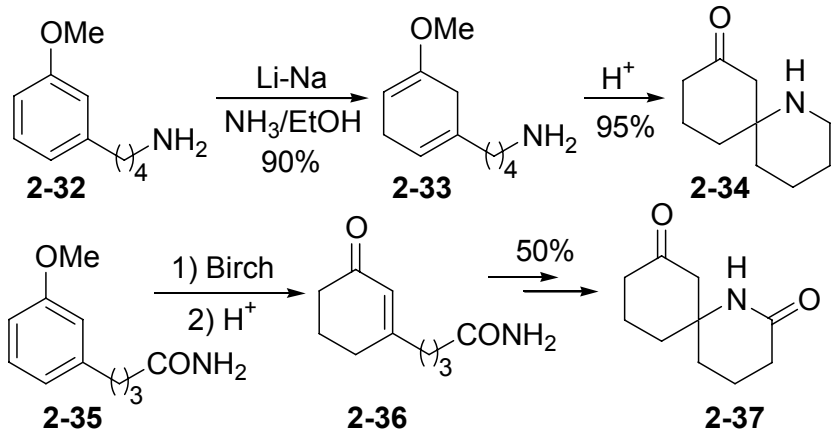
Scheme 2. Synthesis of the (-)-HTX skeleton by Tanner via electrophile induced cyclization.

As an alternative, intramolecular epoxide opening can be used equally well[18]. The newly formed hydroxyl function can later be substituted with an alkyl chain or reduced (**Scheme 3**).



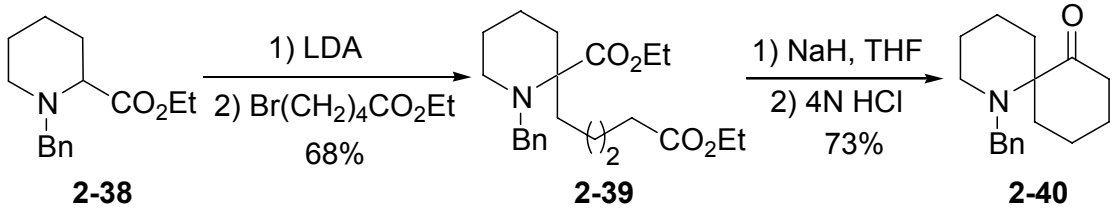
Scheme 3. Approach to HTX core by intramolecular epoxide opening.

Magnus reported the preparation of spirolactams by intramolecular Michael addition of amines or amides to an enone[19]. Birch reduction of 3-butylaminoanisole afforded enol ether **2-33**, which under acidic conditions spontaneously cyclizes to spiroketone **2-34**. Similarly, spirolactam **2-37** can be obtained from 3-butyramidoanisol (**Scheme 4**).



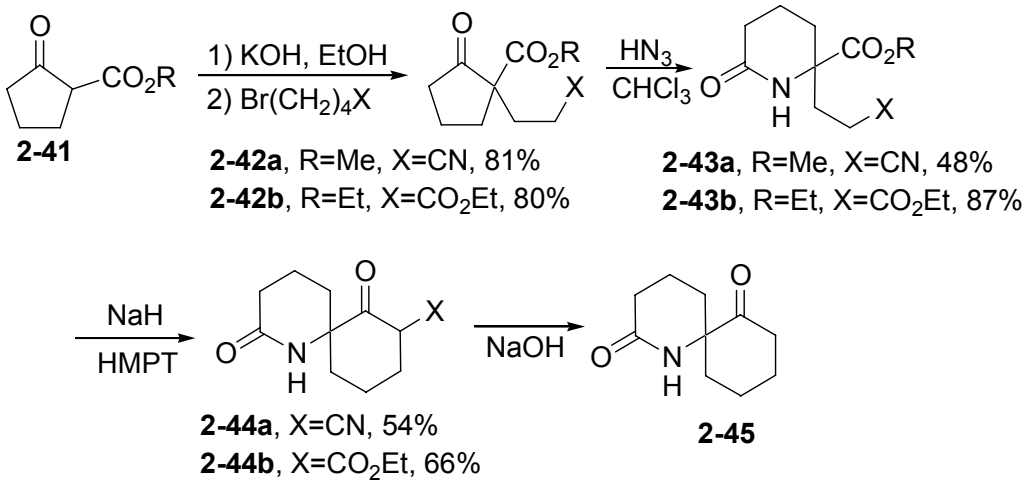
Scheme 4. Synthesis of spiroketones from anisolalkylamines.

Another general approach to cyclic structures is based on carbon–carbon bond formation by intramolecular condensation (**Scheme 5**). For instance, Dieckmann condensation of diester **2-39**, prepared by alkylation of protected pipecolinic acid, leads directly to spiroketone **2-40**[20].



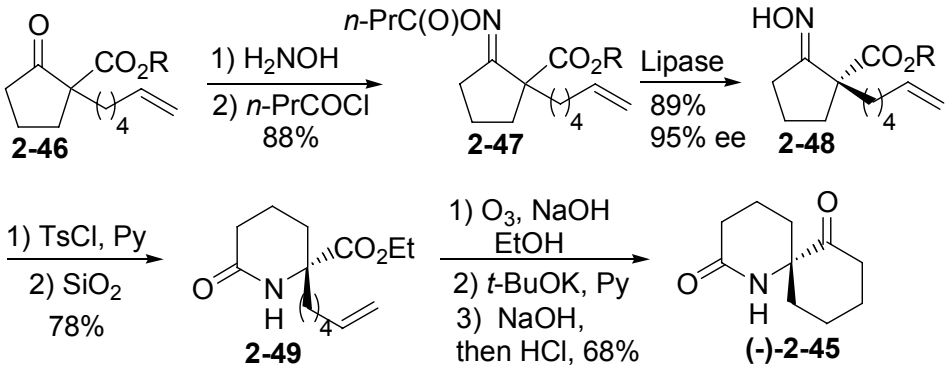
Scheme 5. Construction of spiropiperidone core by alkylation/Dieckmann condensation.

In another example[21], cyclopentanone-2-ethylcarboxylate was used for alkylation and converted to valerolactam by Schmidt rearrangement at the next step. However, somewhat lower yields were obtained for the cyclization reaction (**Scheme 6**).



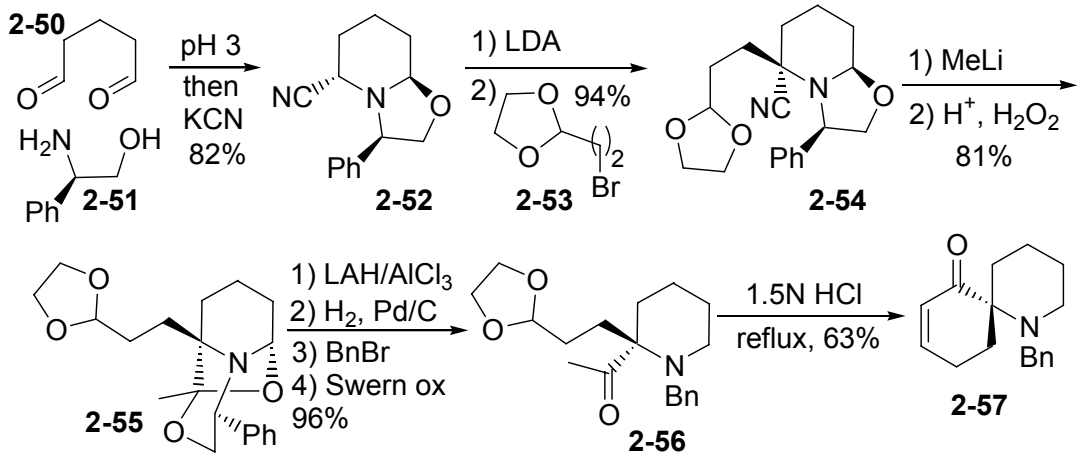
Scheme 6. Application of Schmidt rearrangement for synthesis of spiroketones.

Enzymatic kinetic resolution of racemic oxime ester **2-47** enables preparation of chiral spirolactam by tosyl chloride mediated Beckmann rearrangement[22]. Ozonolysis of the double bond in basic ethanol resulted in direct formation of diester, which then cyclized accordingly.



Scheme 7. Enantioselective approach to spirolactam **2-45** by enzymatic resolution of oxime ester **2-47**.

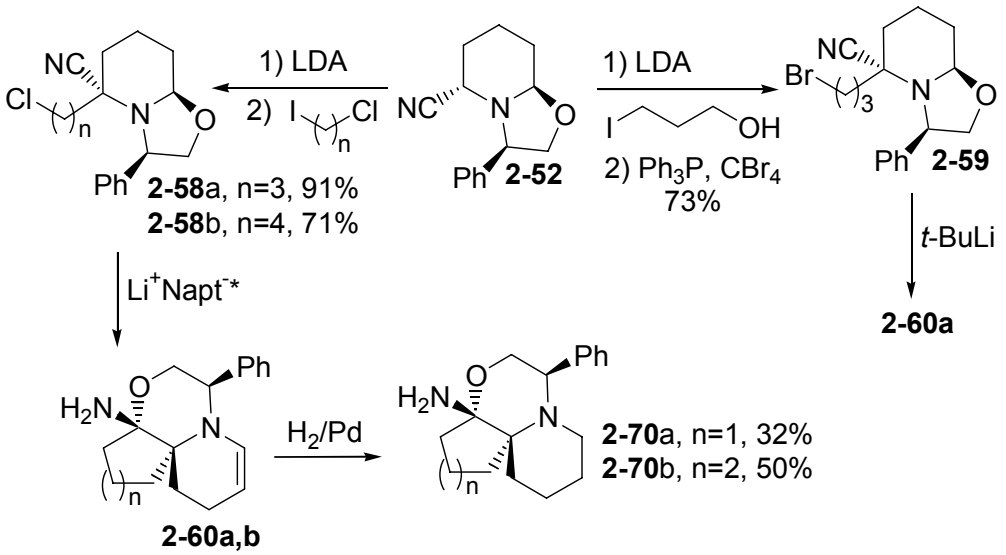
A powerful approach to enantiomerically pure spiro structures was developed by Husson[23]. It is based on a chiral 2-cyanopiperidine building block **2-52** prepared by condensation of glutaraldehyde with phenylglycinol and potassium cyanide (**Scheme 8**). Alkylation of this compound with 3-brompropanal acetal **2-53** proceeds with retention of stereochemistry and excellent yield. Subsequent addition of methyl lithium to the cyano group and imine hydrolysis resulted in formation of an unexpected cyclic ketal **2-55**. After several chemical manipulations including Lewis acid assisted reduction of ketal, removal of the phenylglycinol auxiliary by hydrogenation, protection of the nitrogen atom, and oxidation, ketoacetal **2-56** was obtained. Upon treatment with hydrochloric acid it underwent intramolecular aldol condensation leading to the desired spiro enone **2-57**.



Scheme 8. Preparation of chiral spiroketone from cynopiperidine.

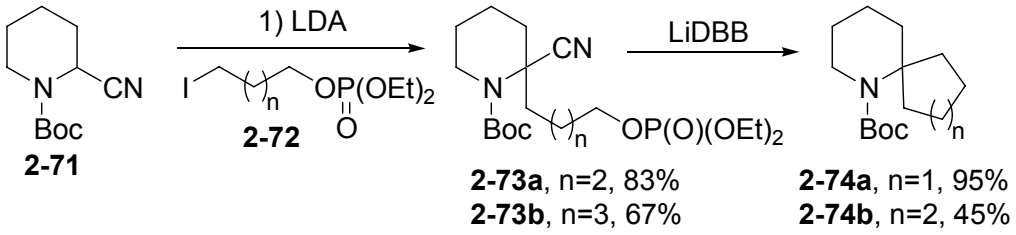
Intramolecular addition of alkyllithium function to the cyano group can be employed as well (**Scheme 9**). An appropriate unsymmetrical 1,ω-dihaloalkane **2-58** or 3-iodopropanol is then used for alkylation, in the latter case followed by Appel reaction to furnish cyclization precursor **2-59**. Treatment with a strong electron donor or a halogen-metal exchange reagent

resulted in formation of unstable hemiaminal **2-60a,b**, which can be hydrogenated to spiropiperidines[24].



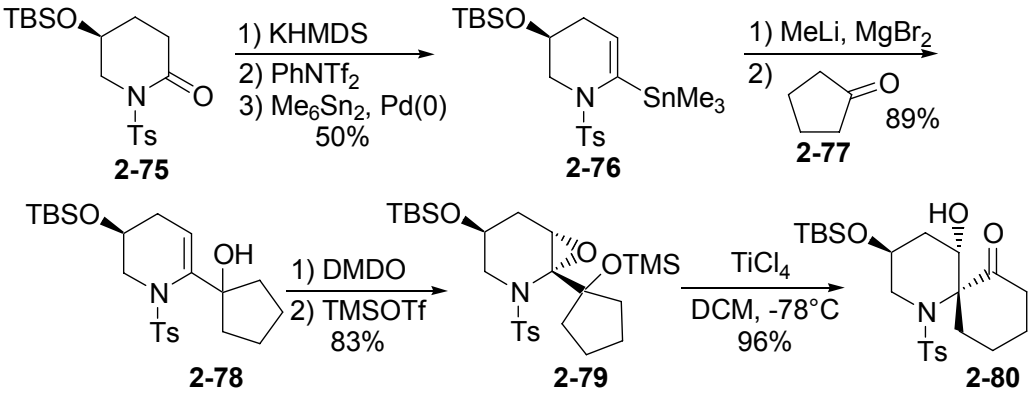
Scheme 9. Preparation of chiral spiropiperideines from cynopiperidine.

It is also known, that the cyano group itself is a pseudo-halogen and can undergo bond cleavage by treatment with strong electron donors. Thus, protected 2-cyanopiperidine is synthetically equivalent to pyridine-2,2-bis-nucleophile. Applying an appropriately designed 1,ω-bis-electrophile with two leaving groups of different type allowed for a straightforward preparation of simple spirocycles (**Scheme 10**)[25].



Scheme 10. Synthesis of simple spiropiperidines by intramolecular alkylation.

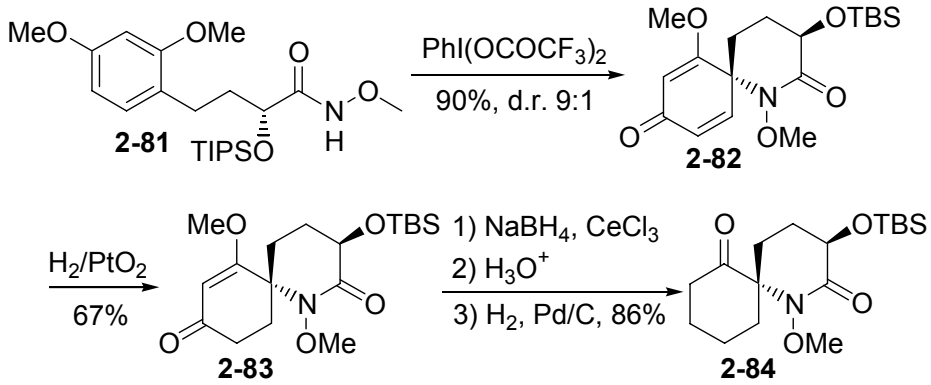
Another general approach to spiro ketones was invented by Dake[26]. It's based on Lewis acid promoted 1,2-semipinacol rearrangement of α-siloxy-epoxides. They can be prepared by addition of the corresponding vinyl Grignard reagents to ketones followed by stereoselective epoxidation and silylation (**Scheme 11**). Finally, treatment of epoxide **2-79** with titanium tetrachloride in DCM at -78°C afforded a single diastereomer of spirocyclic ketone **2-80** in excellent yield.



Scheme 11. Semipinacol rearrangement of siloxy epoxides.

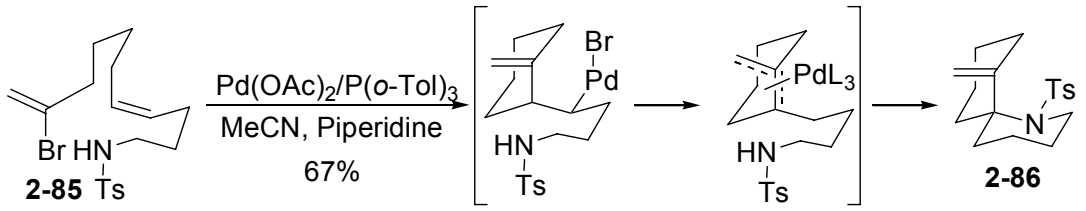
The reaction was thoroughly investigated with regard to ring size and conditions[27,28] and was successfully employed for a formal asymmetric synthesis of fasicularin[29,30].

Wardrop reported on the stereoselective intramolecular cyclization of a nitrenium ion generated by oxidation of methoxyamide **2-81** (**Scheme 12**) with hypervalent iodine compounds[31]. A highly electron-rich aromatic ring is essential for the reaction to proceed since the anisole analog fails to deliver the desired product.



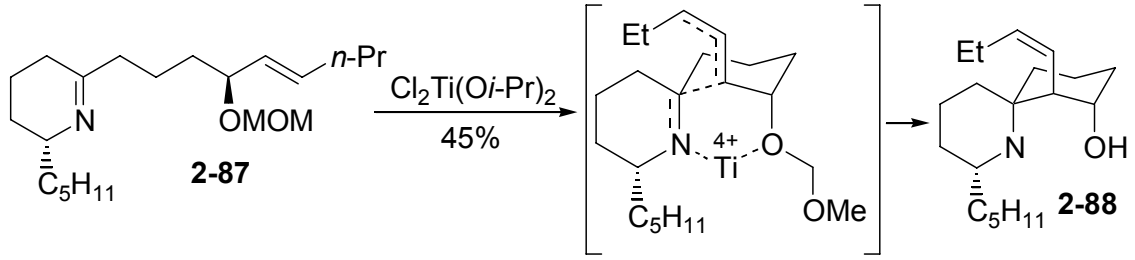
Scheme 12. Intramolecular cyclization of nitrenium ion.

A comprehensive research article devoted to the synthesis of bridged, fused bicyclic and spiro compounds via domino intramolecular Heck reaction/allylic substitution reactions was published by Weinreb[32]. For example, heating of diene **2-85** (**Scheme 13**) in presence of a palladium catalyst and base resulted in formation of exo-methylene 1-azaspiro[5.5]undecene **2-86**. Similarly, the diene with the one carbon shorter chain gave 1-azaspiro[5.4]decene in 55% yield.



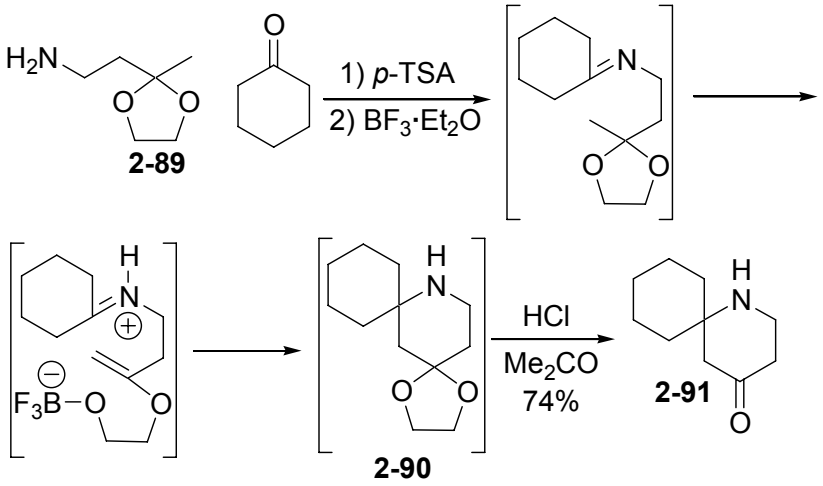
Scheme 13. Domino Heck reaction-allylic substitution route to spiro structures.

A Lewis acid promoted intramolecular imino ene-reaction was used by Tanner in his other enantioselective synthesis of (-)-12H-HTX[33]. In order to explain the diastereoselectivity in this spiro cyclization, a chelation controlled chair-like transition state was proposed (**Scheme 14**).



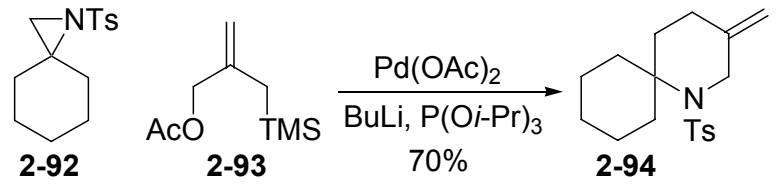
Scheme 14. Approach to (-)-12H-HTX based on an intramolecular ene-reaction.

A very short approach to simple spirocyclic ketones by intramolecular Mannich reaction has been described[34] (**Scheme 15**). The notable advantage here is that the product **2-91** contains an unprotected nitrogen atom and can be directly used for further derivatization.



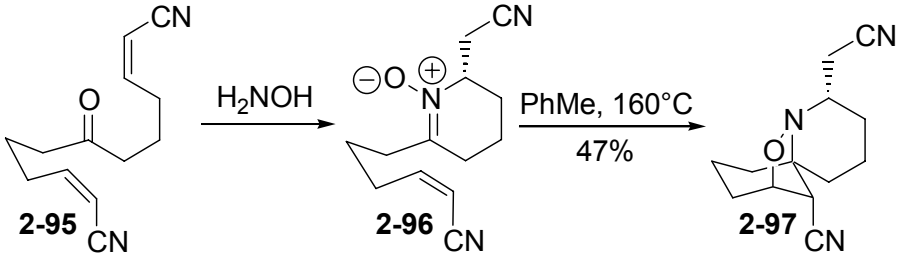
Scheme 15. Synthesis of spiroketones by intramolecular Mannich reaction.

Few cycloaddition reactions were found to be useful for construction of spirocycles. For example, a [3+3] dipolar cycloaddition of N-tosyl aziridines (**Scheme 16**) has been developed by Harrity[35,36] and used for their formal total synthesis[37] of 12H-HTX.



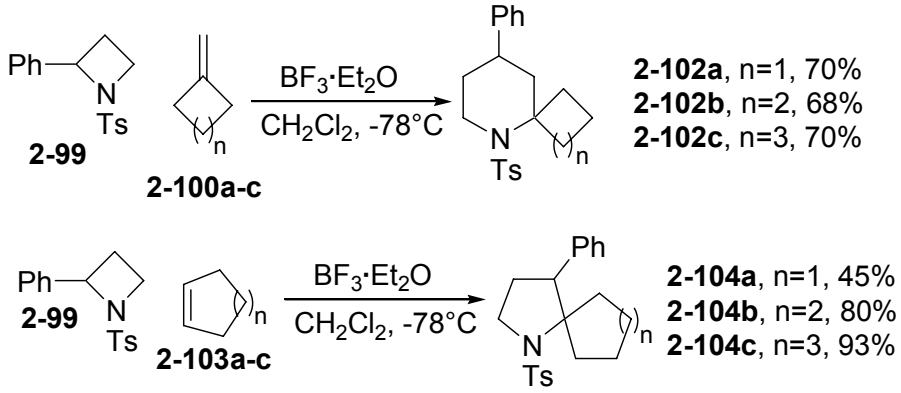
Scheme 16. Synthesis of spiro compounds by dipolar cycloaddition.

A domino Michael addition/nitrone [2+3] dipolar cycloaddition was invented by Stockmann[38] and used in the synthesis of HTX[39]. A notable feature of this reaction is formation of both rings in a single chemical step from a highly symmetrical ketone, albeit in moderate yield. The required ketone can be easily prepared from the corresponding dialdehyde by condensation with acetonitrile or by cross-metathesis of the alkene with acrylonitrile.



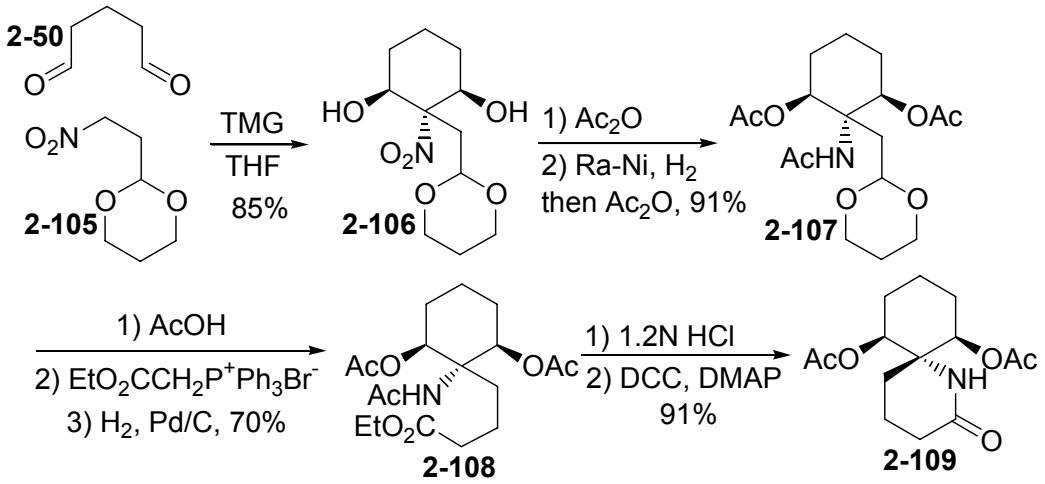
Scheme 17. Domino Michael addition/nitrone cycloaddition approach to the HTX core.

Mann reported that 2-phenyl-N-tosylazetidine **2-99** undergoes ring opening and [4+2] dipolar cycloaddition to exocyclic non-activated alkenes **2-100a-c** in presence of borontrifluoride etherate[40](**Scheme 18**). Interestingly, reaction with endocyclic alkenes **2-103a-c** leads not to the expected fused bicyclic products, but rather to 1-aza[4.x]spiroalkanes **2-104a-c** as well. Formation of a more stable tertiary cation by 1,2-proton shift was proposed to explain this phenomena.



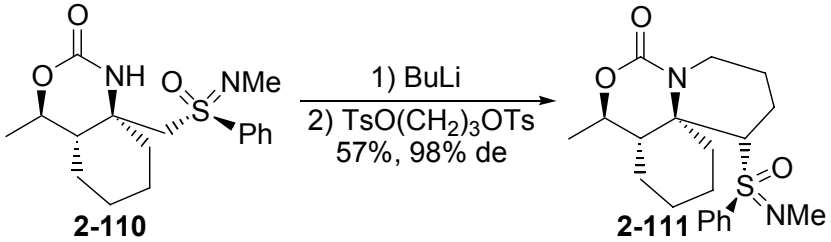
Scheme 18. A domino azetidine opening/dipolar cycloaddition approach to spiro compounds.

The sequence of double Henry reaction, catalytic reduction, and intramolecular acylation (**Scheme 19**) has been used to provide access to compound **2-108**, which was then subjected to enzymatic desymmetrization[41].



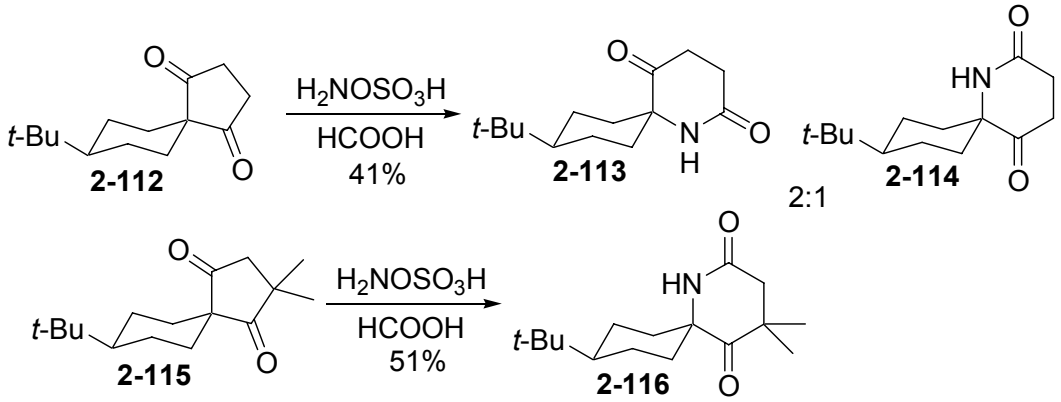
Scheme 19. Synthesis of *meso*-diacetate (TMG = 1,1,3,3-tetramethylguanidine).

Recently, a modular asymmetric synthesis of spiropiperidines by one-pot double alkylation has been achieved by Gais[42]. Deprotonation of sulfoximine **2-110** with excess of base followed by addition of 1,3-propanediol ditosylate resulted in formation of tricyclic compound **2-111** with 98% diastereoselectivity (**Scheme 20**). The sulfoximine group can then be replaced with a chlorine atom.



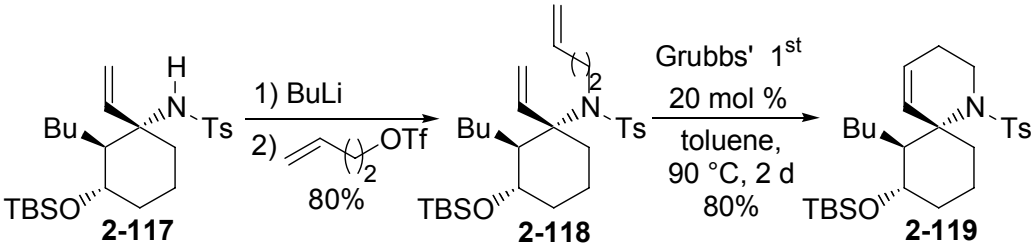
Scheme 20. Modular asymmetric synthesis of spiropiperidines.

As was shown by Burnell, carbocyclic spiroketones undergo Beckmann rearrangement to oxolactams by treatment with hydroxylamine-O-sulfonic acid in acidic conditions[43]. However, this reaction has little practical meaning due to the low yield and poor diastereoselectivity.



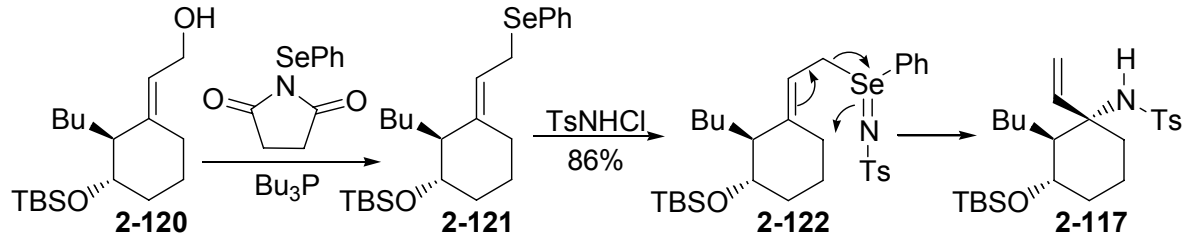
Scheme 21. Beckmann rearrangement approach to spirolactams.

The ring closing metathesis approach to spiro compounds was also pioneered by the Tanner group en route to 12H-HTX[44]. According to their retrosynthetic plan, the formation of a double bond next to the spiro center should lead to the spiro core. Alkylation of **2-117** with 4-bromo-1-butene proved to be unexpectedly problematic. Success was eventually achieved by generation of the lithium salt of the tosylamide in THF-HMPT mixture followed by addition of homoallyl triflate (**Scheme 22**). Difficulties have been encountered also in the metathesis step where multiple loads of catalyst and prolonged exposure to high temperatures were required to drive reaction to the completion.



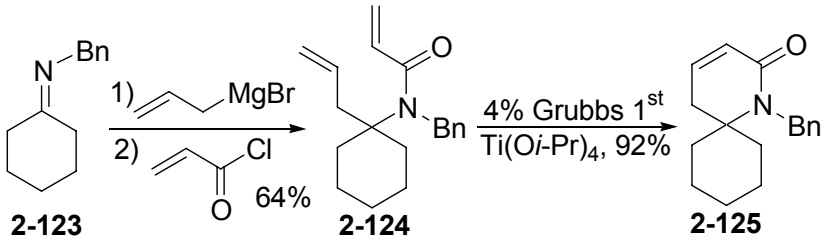
Scheme 22. RCM approach to synthesis of 12H-HTX core

To prepare the required allylsulfonamide, a [2,3]-sigmatropic rearrangement of N-tosylimineselenate **2-122** was used (**Scheme 23**).



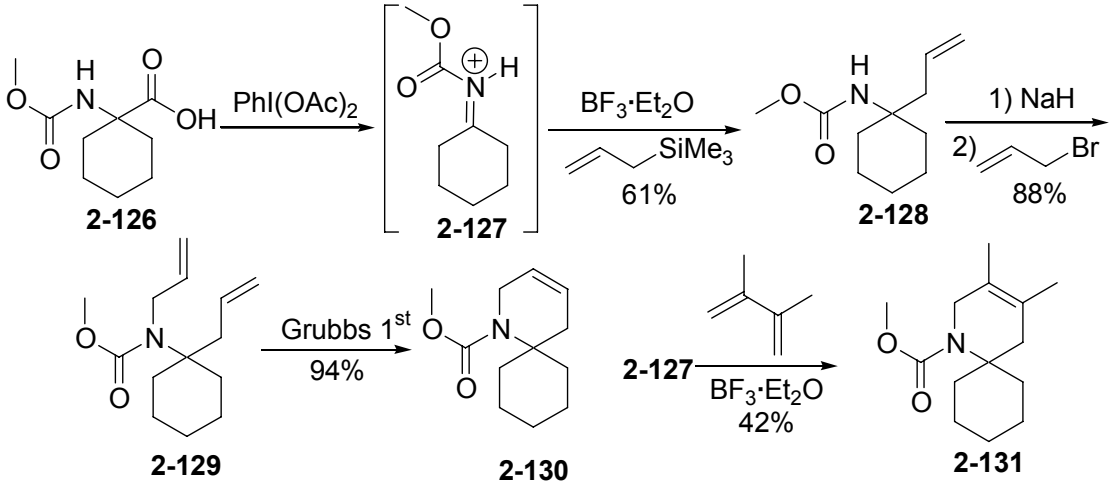
Scheme 23. Synthesis of 1-vinyl-cyclohexylamine tosylate **2-117**.

Contrary to the vinyl derivative described above, 1-allyl-1-benzylamino cyclohexane can easily be made by addition of the Grignard reagent to the corresponding imine[45]. Acylation of the product with acryloyl chloride gave rise to RCM precursor **2-124** in only two steps. Upon exposure to Grubbs 1st generation catalyst in presence of titanium tetraisopropoxide the α,β-unsaturated spirolactam **2-125** can be secured with a very good yield (**Scheme 24**).



Scheme 24. Synthesis and RCM of allylacrylamides.

An interesting way to generate reactive iminium species from N-carbamate protected amino acids has been recently reported[46]. Bisacetoxyiodobenzene mediated decarboxylation of **2-126** followed by nucleophilic addition of allyltrimethylsilane results in formation of homoallylamine **2-128**. After alkylation of the acidic carbamate with allyl bromide a RCM reaction leads to spiropiperidine 2-130 in excellent yield (**Scheme 25**). Iminum ion **2-127** can also undergo Diels-Alder cycloaddition with simple dienes.



Scheme 25. Synthesis of spiropiperidines from iminium salts by RCM or cycloaddition.

2.3.2 2-Azaspiro[5.5]undecane

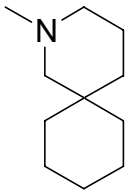
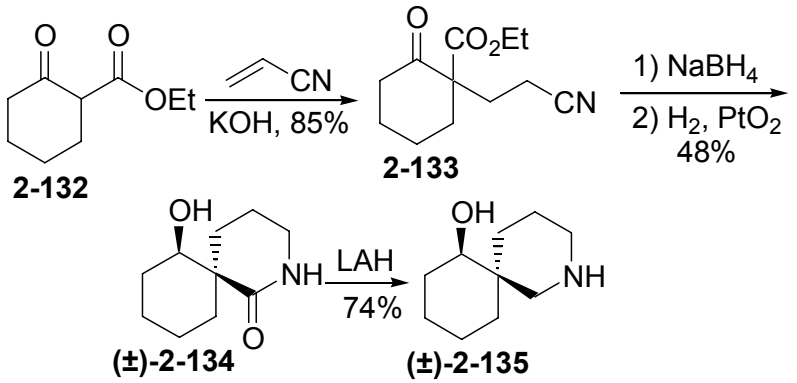


Figure 10. The 2-azaspiro[5.5]undecane skeleton.

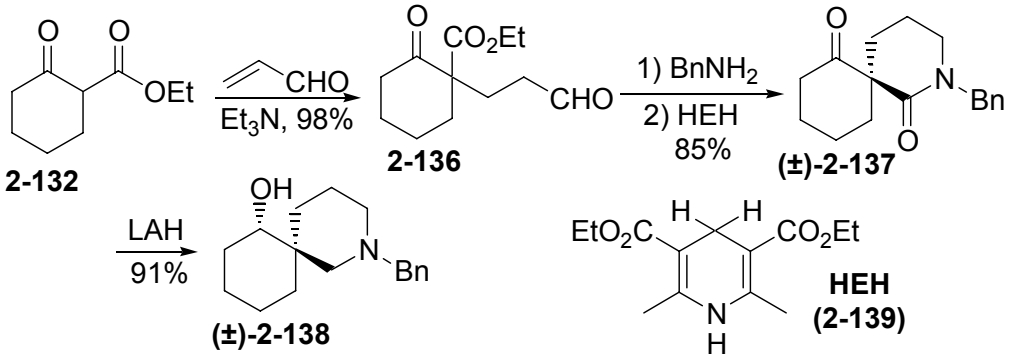
Similar to 1-azaspiro compounds retrosynthetic disconnection of the two nitrogen-carbon bonds in 2-azaspiro[5.5]undecanes is the most obvious. The ring formation can be achieved by nucleophilic attack to a sp^3 or acyl carbon.

For example, conjugate addition of ethyl 2-cyclohexanone carboxylate to acrylonitrile followed by reduction of the ketone and hydrogenation of the cyano group resulted in spontaneous ring closure to spirolactam **2-135** (**Scheme 26**)[47]. Reduction of the amide function with LAH gave racemic nitramine.



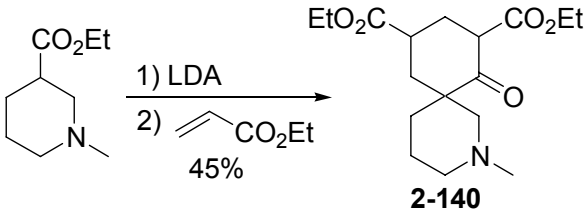
Scheme 26. Synthesis of nitramine from β-dicarbonyl compounds.

In essentially the same way, acrolein can be used as Michael acceptor[48]. The obtained aldehyde **2-136** (**Scheme 27**) is then subjected to imine formation and chemoselective biomimetic reduction with Hantzsch 1,4-dihydropyridine **2-139** to provide the amine, which undergoes in situ cyclization to oxolactam **2-137**. By simultaneous reduction of the amide and keto functions with LAH isomeric isonitramine could be prepared.



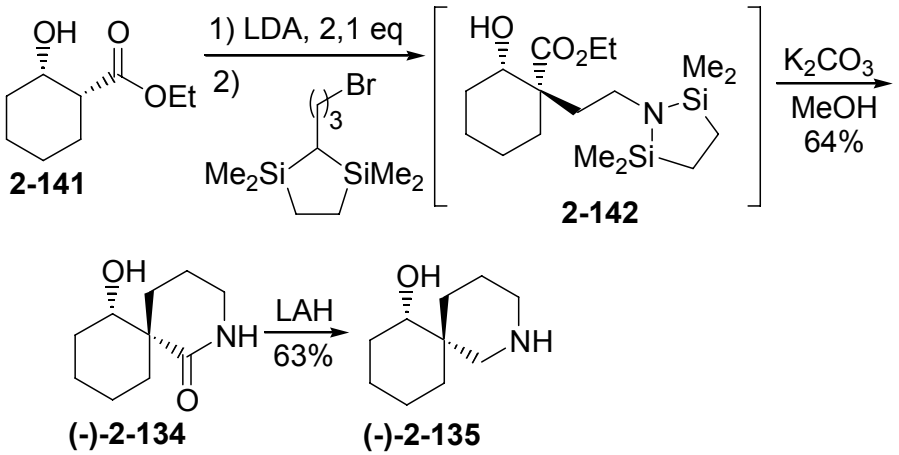
Scheme 27. Synthesis of nitramine from β-dicarbonyl compounds.

An interesting example of spontaneous formation of a spirocyclic core is interrupted base-induced acrylate polymerization[49]. Deprotonation of N-methyl-nipecotic acid ethyl ester (**Scheme 28**) followed by addition of 2.3 equivalents of ethyl acrylate produces spirocyclic ketone **2-140**. The reaction proceeds via a sequence of two Michael additions and Dieckmann condensation. Despite a moderate yield, the route is very short and requires only simple reagents making it suitable for scaffold synthesis.



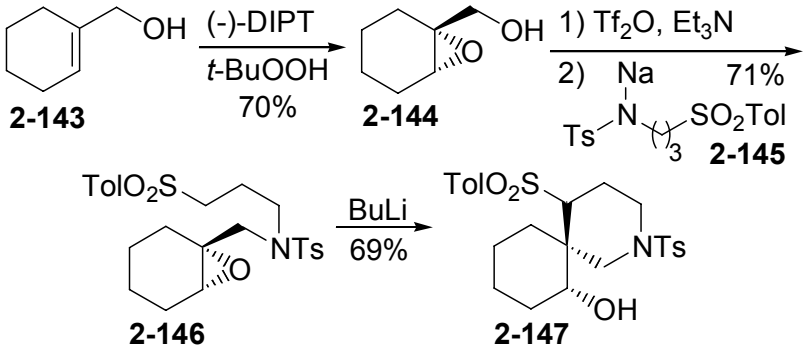
Scheme 28. Synthesis of spiroketones by interrupted polymerization of acrylate.

The enantioselective synthesis of *Nitraria* alkaloids was achieved by Kimpe[50]. Alkylation of chiral β-hydroxycyclohexane carboxylate **2-141** with a protected alkylamine fragment was followed by cyclization under basic conditions to lactam **(-)-2-134** (**Scheme 29**). As usual, next step consisting of reduction of amide using $LiAlH_4$ provided nitramine.



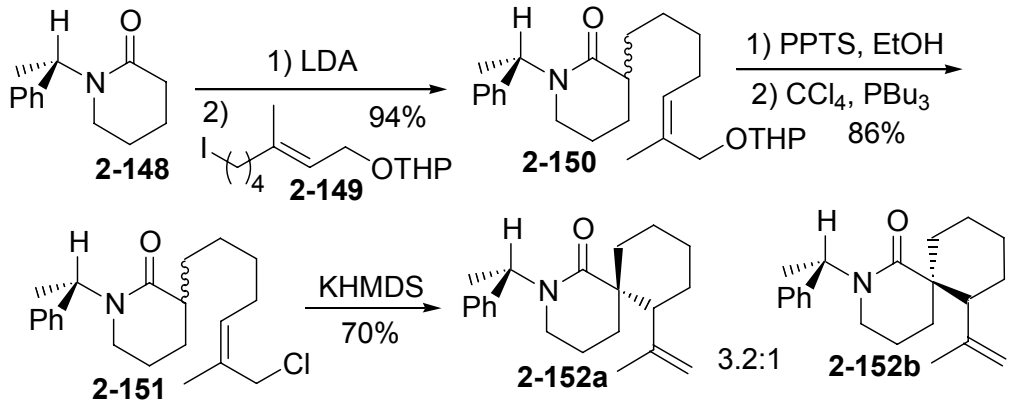
Scheme 29. Asymmetric synthesis of siberine by Kimpe.

Similar to his histrionicotoxin synthesis Tanner used intramolecular epoxide opening for preparation of racemic[51] and enantiomeric[52] siberine (**Scheme 30**). A C-nucleophile was generated by deprotonation of acidic sulfone **2-146**.



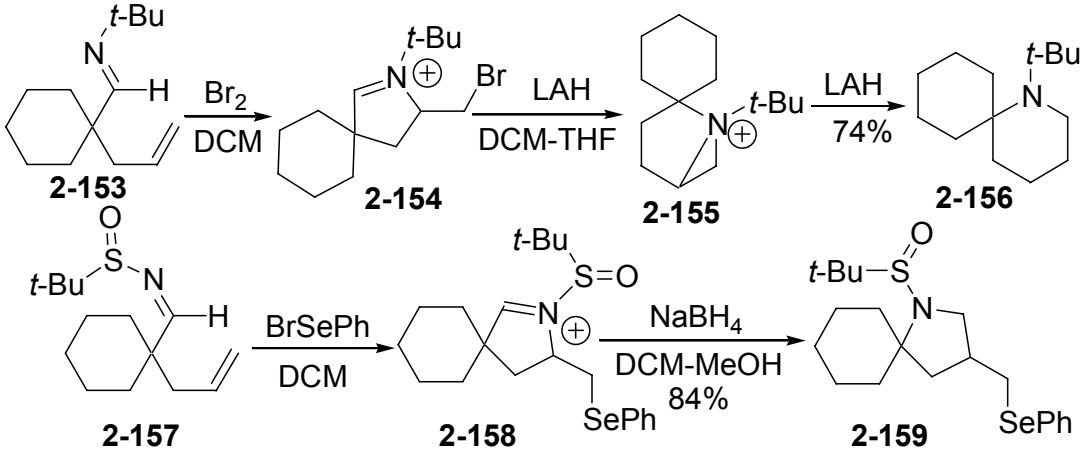
Scheme 30. Asymmetric synthesis of siberine by Tanner.

Kim developed another approach to racemic[53] and chiral[54] *Nitraria* alkaloids based on an intramolecular S_N2' reaction (**Scheme 31**). Valerolactam **2-150** bearing a chiral residue at the nitrogen atom can be alkylated twice, first nonselective, and then with moderate degree of asymmetric induction. In the latter case, triple allylic strain controls preferential formation of the desired diastereomer.



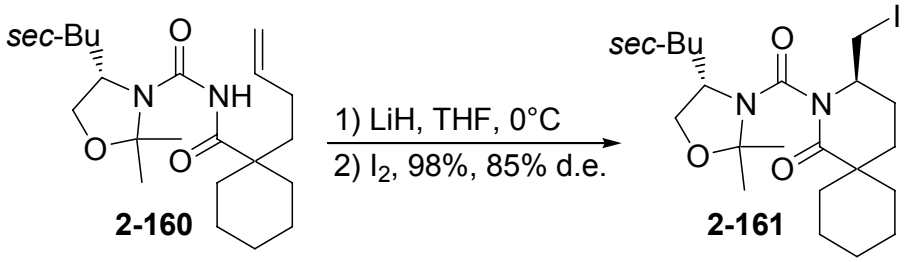
Scheme 31. Syntheis of *Nitraria* alkaloids by Kim.

An example of aziridine rearrangement leading to spirocycles was reported by De Kimpe[55]. Treatment of N-*t*-butyl imine **2-153** with bromine followed by reduction with LAH results in formation of an aziridinium ion **2-154**, which then was opened with a second equivalent of hydride (**Scheme 32**). Contrary, when an electron withdrawing sulfinamide protecting group was used, rearrangement did not take place due to low nucleophilicity of the nitrogen atom and 1-aza[4.5]decene derivative **2-159** was the only product[56].



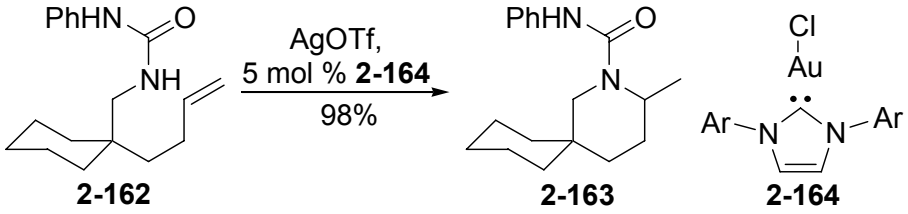
Scheme 32. Synthesis of simple spirocycles by electrophile induced cyclization/reduction.

Asymmetric electrophile induced cyclization of urea **2-160** bearing a chiral auxiliary was recently described[57]. The use of lithium hydride turned out to be essential to obtain good yield and diastereoselectivity.



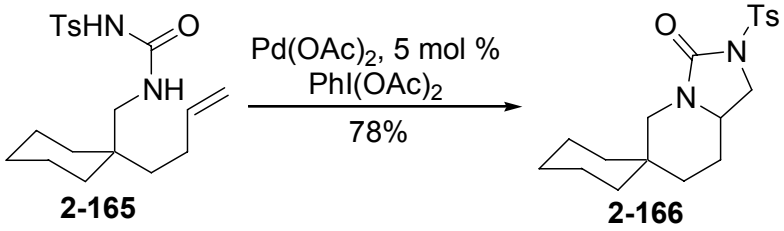
Scheme 33. Enantioselective cyclization of chiral urea.

A number of isolated examples of spirocycle formation can be found in studies related to Lewis acid catalyzed intramolecular hydroamination of terminal alkenes. Widenhoefer reported cyclization of amines and carbamates in presence of platinum[58] and gold[59,60] complexes (**Scheme 34**). Toste achieved enantioselective hydroamination of trisubstituted allenes[61].



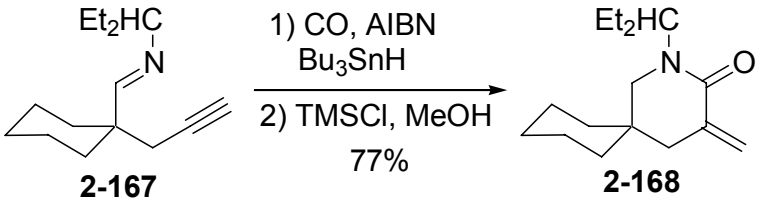
Scheme 34. Gold (I) carbenoid complexes catalyzed intramolecular hydroamination.

Tosylated ureas undergo palladium catalyzed oxidative diamination as described by Muniz[62]. The product features orthogonally protected nitrogen atoms, hence selective derivatization can be done afterwards.



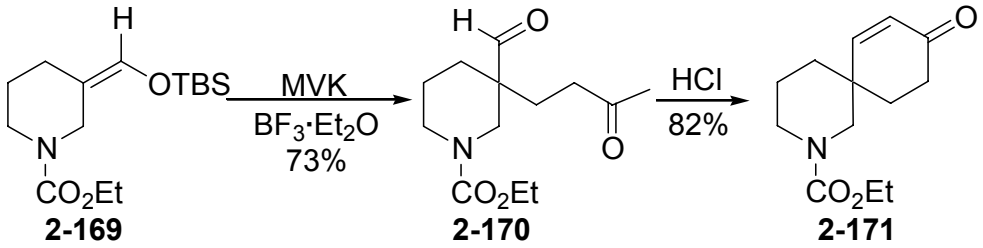
Scheme 35. Intramolecular oxidative diamination of terminal alkenes

Radical domino carbonylation/cyclization reaction of imines mediated by tributyltin hydride has been found by Ryu[63]. The reaction proceeds exclusively by a 6-endo pathway due to "polarity-matched" combination of an acyl radical and an imine N=C bond.



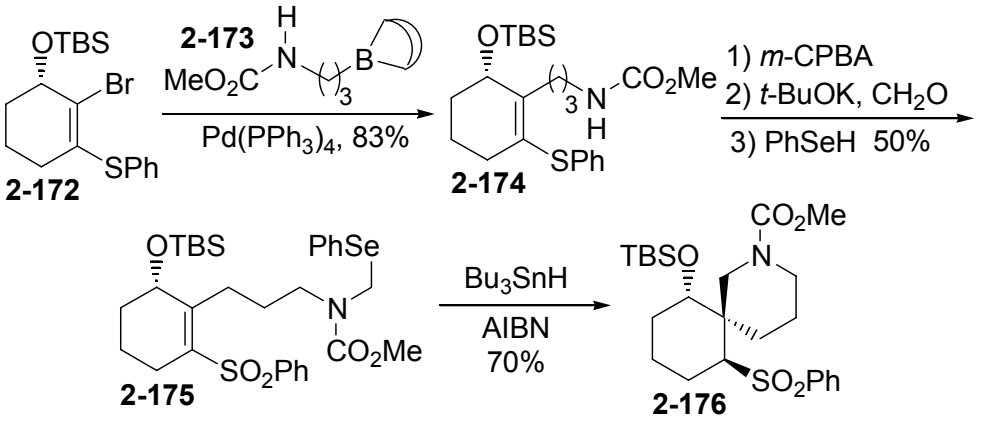
Scheme 36. Synthesis of spirolactam by radical carbonylation/cyclization.

A very short and efficient approach to spiroenone **2-171** by intramolecular aldol condensation was recently reported (**Scheme 37**)[64]. The required ketoaldehyde **2-170** was prepared by Michael addition of enol ether **2-169** to methyl vinyl ketone in presence of Lewis acid.



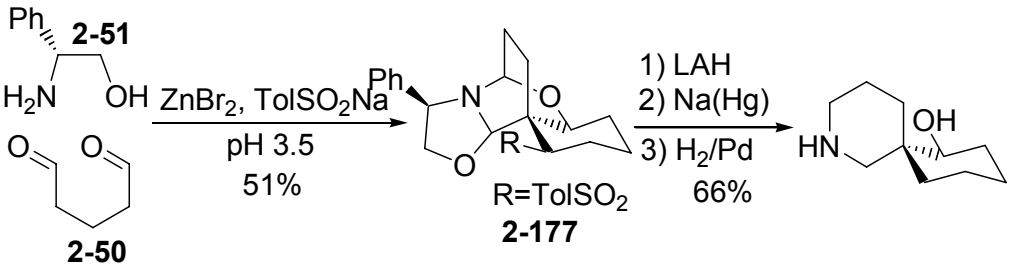
Scheme 37. Synthesis of spiroenone by intramolecular croton condensation.

Radical spirocyclization of (alkoxycarbonylamino)methylene phenylselenide **2-175** proceeds with high degree of diastereoselectivity[65] (**Scheme 38**). The required intermediate **2-174** has been obtained by Suzuki cross-coupling between vinyl bromide **2-172** and hydroboration product of carbamate protected allylamine. In the absence of a bulky phenylsulfonyl group the reaction gave significant quantity of the fused bicyclic compound as a byproduct.



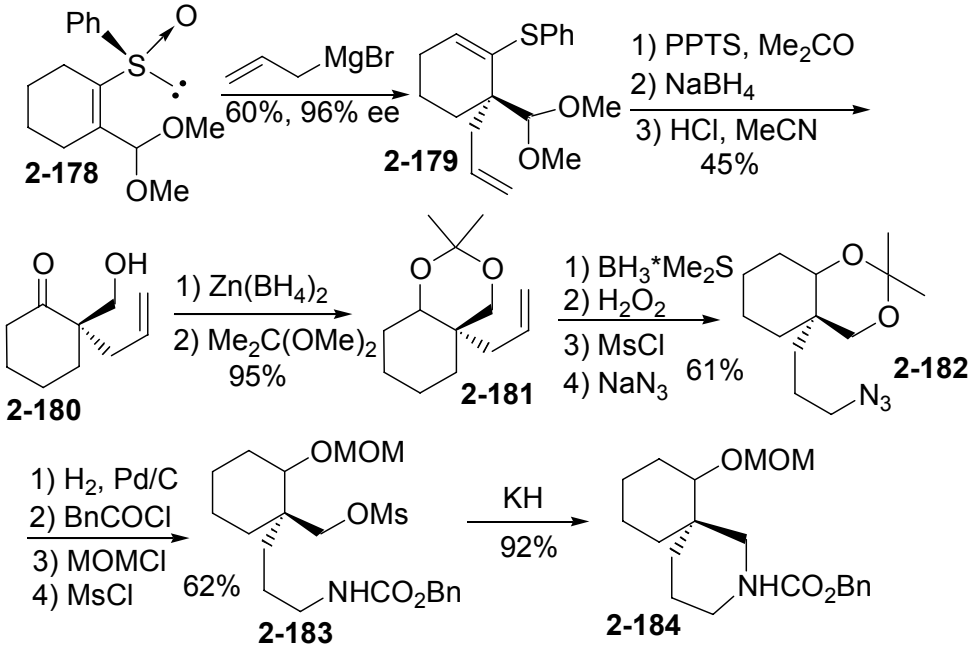
Scheme 38. Approach to the nitramine core by cyclization of a methylene radical.

Futhermore, biomimetic approaches to racemic[66] and enantiopure[67] *Nitraria* alkaloids were developed. According to Husson, condensation of phenylglycinol with glutaraldehyde in presence of toluensulfinate anion (**Scheme 39**) resulted in formation of spirocompound **2-177** as major diastereomer, which can be isolated in pure form by crystallization. The outcome of this highly efficient reaction suggests that **2-177** is the most thermodynamically stable compound resulting from a series of equilibration reactions. After reductive opening of the two hemiaminals with $LiAlH_4$ and hydrogenolysis of chiral N substituent (-)-isonitramine could be secured in a good yield.



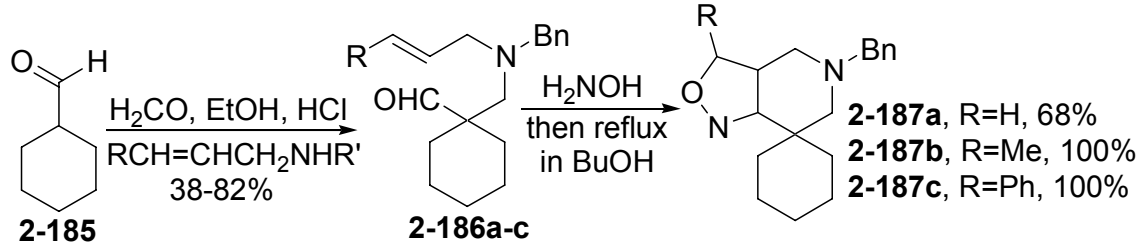
Scheme 39. Biomimetic synthesis of (-)-isonitramine.

Pummerer type rearrangement leads to a highly enantioselective construction of the quaternary centre of spirocyclic system **2-184** (**Scheme 40**)[68]. However, removal of thiol group and construction of the second ring takes a significant number of steps, thus making this method not really suitable for scaffold synthesis.



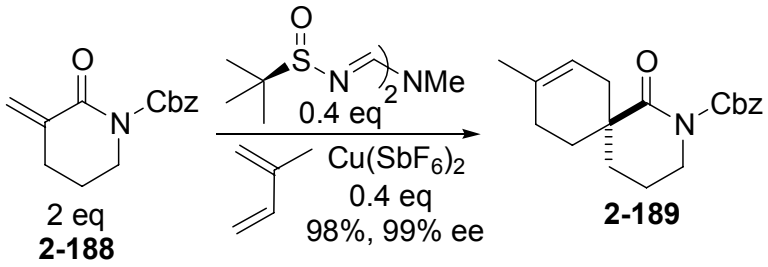
Scheme 40. Enantioselective synthesis of nitramine core by Pymmerer type rearrangement.

A series of isoxazoline fused 2-azaspiropiperidines were prepared by intramolecular [2+3] dipolar cycloaddition[69] (**Scheme 41**). The reaction provides carbon-carbon bond formation and ring closure. The required allylamines were synthesized by Mannich reaction from cyclohexanecarbaldehyde.



Scheme 41. Synthesis of fused spiropiperidines by intramolecular cycloaddition.

Asymmetric Lewis acid catalyzed Diels-Alder cycloaddition of 3-methylenevalerolactam gave enantiopure lactam **2-189** with exceptionally high yield and enantiomeric excess[70].



Scheme 42. Synthesis of spirolactam **2-189** by Diels-Alder cycloaddition.

2.3.3 3-Azaspiro[5.5]undecane, 3,9-Diazaspiro[5.5]undecane, and 2,9-Azaspiro[5.5]undecane

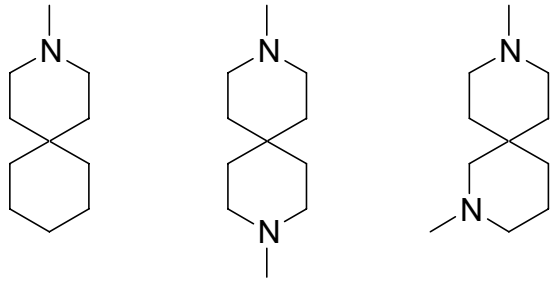
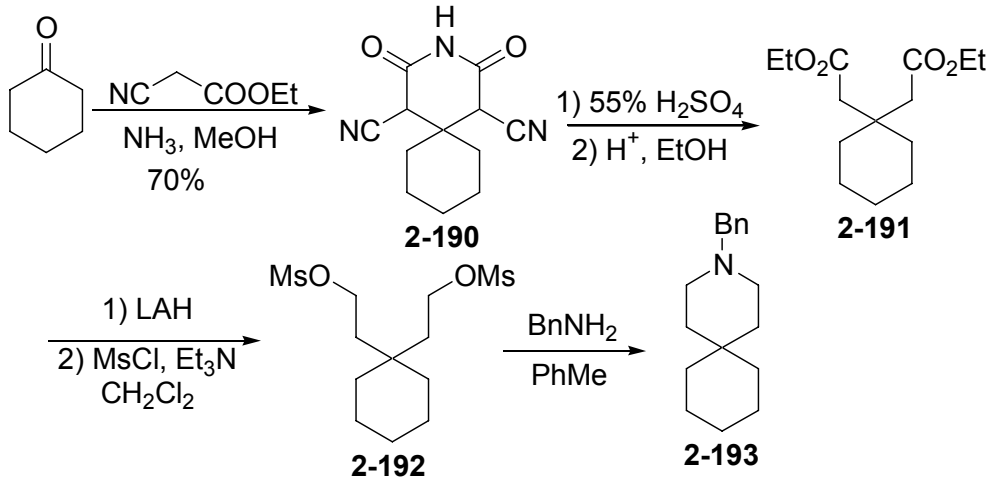


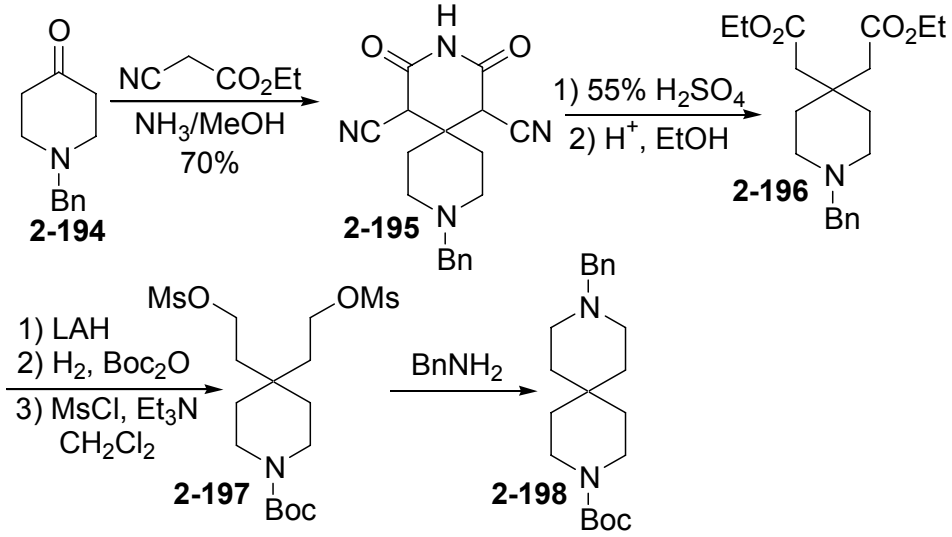
Figure 11. 3-azaspiro[5.5]undecane and related structures.

Spirocyclic compounds of this type are among the earliest described in the literature. They were first explored by Icilio Guareschi[71] whose name was later given to the reaction itself and its product. It has been found, that treatment of cyclohexanone with two equivalents of ethyl cyanoacetate in presence of ammonia results in formation of spiroimide **2-190** (**Scheme 43**). First, Knoevenagel condensation between ethyl cyanoacetate and cyclohexanone leads to a highly activated alkene, which undergoes Michael addition of a second molecule of ethyl cyanoacetate. The resulting diester reacts with ammonia to produce spiroimide **2-190**.



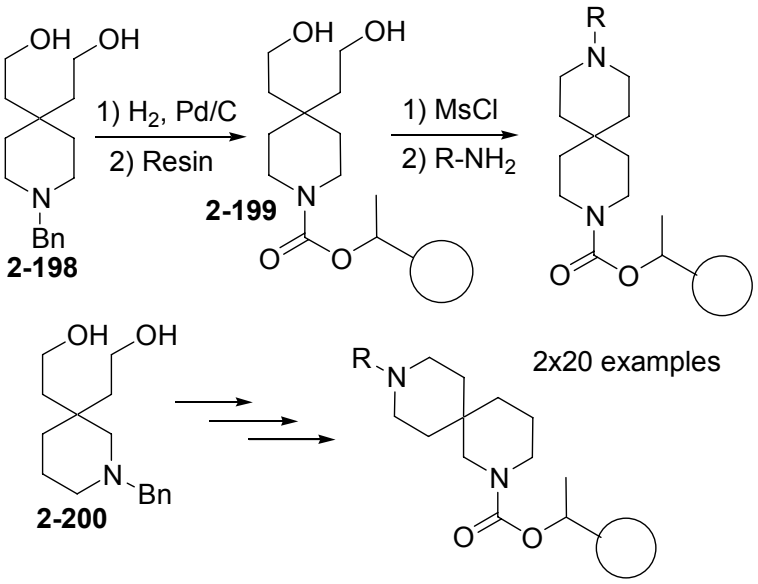
Scheme 43. Formation of Guareschi imide and its further transformation to azaspiroundecane.

Acidic hydrolyses of imide and nitrile with concomitant decarboxylation followed by esterification furnished compound **2-191**. Reduction to diol and subsequent mesylation afforded useful intermediate **2-192**, in which double nucleophilic substitution with benzylamine leads to spiropiperidone **2-193**. If N-protected 4-piperidone is used as starting material, the corresponding 3,9-diazaspiro[5,5]undecene core is readily accessible by essentially the same route[72].



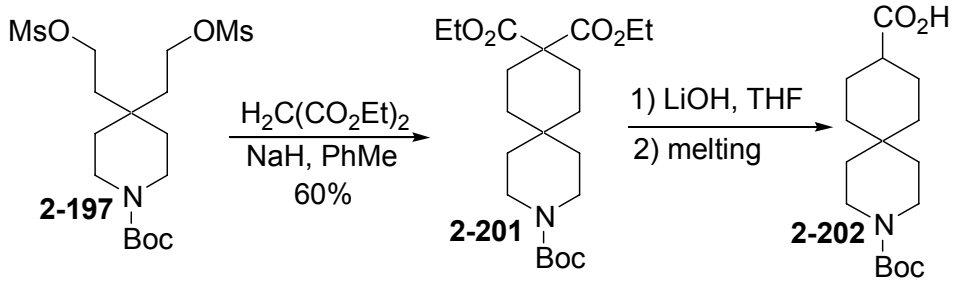
Scheme 44. Synthesis of diazaspiroundecane from N-benzyl 4-piperidone.

Described route is robust enough to be used for combinatorial synthesis on solid phase[73]. The debenzylated diol **2-198** was loaded on the activated resin and then mesylated. Further treatment with a set of primary amines resulted in a medium size spirocyclic compound library (**Scheme 45**). Diol building block **2-200**, which was prepared[74] from N-benzyl 3-piperidone, works equally well.



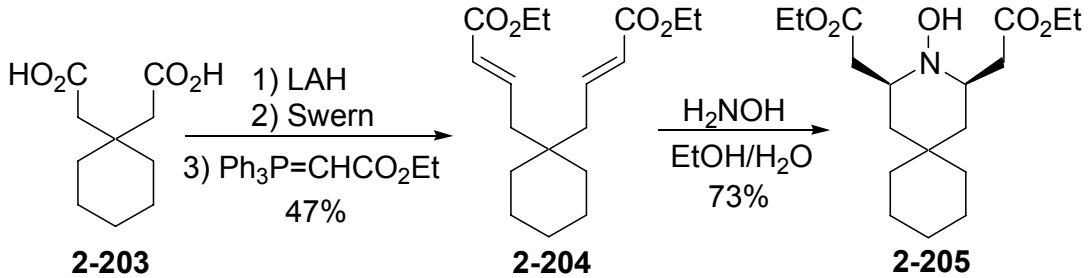
Scheme 45. Combinatorial synthesis of spiro compounds library.

If diethylmalonate is used as a bis-nucleophile, formation of a carbocyclic ring bearing a carboxylic function is possible (**Scheme 46**). Further modification of spiro-acid **2-202** can be done via peptide coupling or by formation of Weinreb amide followed the addition of alkyllithium reagents.



Scheme 46. Synthesis of carbocyclic spiropiperidine **2-202** using diethylmalonate.

Instead of double nucleophilic substitution, double Michael addition of very nucleophilic hydroxylamine can be done[75]. The required symmetrical Michael acceptor was easily prepared from the corresponding dicarboxylic acid **2-203** by a sequence of reduction to alcohol, oxidation to aldehyde and Wittig reaction (**Scheme 47**).



Scheme 47. Synthesis of spiropiperidine **2-205** by double Michael addition.

2.3.4 1,8-Diazaspiro[5.5]undecane and 1,9-Diazaspiro[5.5]undecane

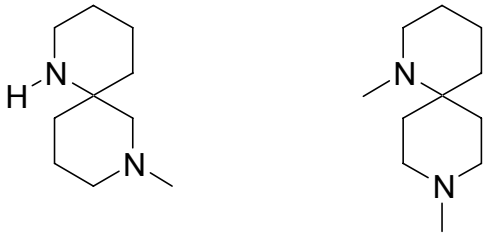
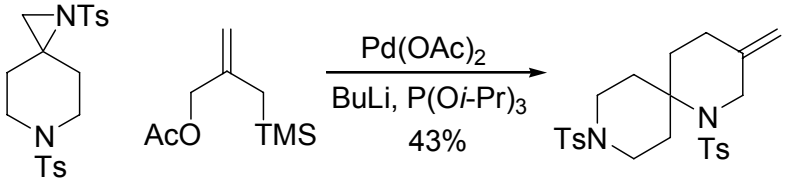


Figure 12. 1,8- and 1,9-diazaspiro[5.5]undecane skeleton.

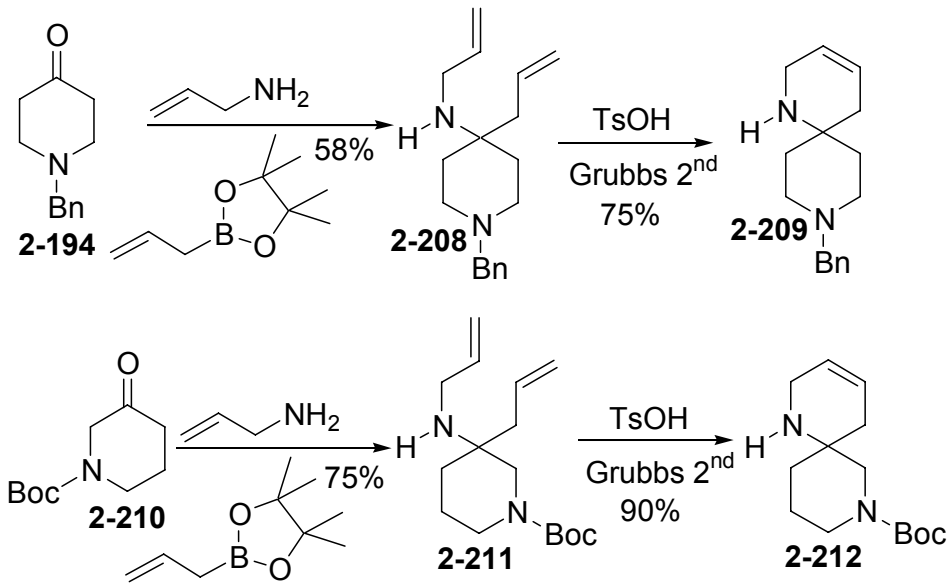
Generally speaking, methods for preparation of 1,8-diazaspiro and 1,9-diazaspiro compounds are similar to those for 1-azaspiroundecanes, with the difference that the starting material already possess one piperidine ring. For example, described as earlier by Harrity [3.3] cycloaddition between aziridine **2-206** and alkene **2-93** gives exomethylene diazaspiro piperidine, albeit in low yield.



2-206 **2-93** **2-207**

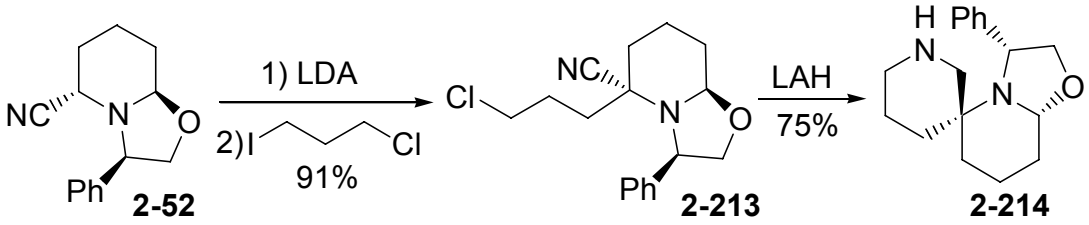
Scheme 48. Sythesis of diazaspiro piperidine by [3.3] cycloaddition.

A multicomponent reaction (**Scheme 49**) between N-protected piperidone, allylamine, and allylborpinacolate leads directly to RCM precursor **2-208**[76]. Due to the presence of a nucleophilic amino group in these substrates, ligand substitution in the catalyst complex can occur. Hence, equimolar amounts of Brönsted or Lewis acid are required to suppress catalyst poisoning. It has been found that addition of p-toluenesulphonic acid allows the RCM reaction to proceed with good yield.



Scheme 49. Aminoallyllation/RCM approach to spirocylic scaffolds.

Husson's 2-cyanopiperidine building block can be used for the synthesis of 2-azaspiroundecanes with even greater success as for 1-diazaspiro[77,78]. Stereoselective alkylation of the lithium anion of **2-52** with a 1,ω-dihaloalkane (**Scheme 50**), proceeds with retention of configuration at the tertiary carbon. Reduction of cyano group with LAH generates an imine anion which immediately cyclizes by intramolecular nucleophilic substitution. Addition of second hydride anion resulted in formation of enantioenriched spirocycles.



Scheme 50. Synthesis of chiral spirocycles from a cyynopiperidine building block.

2.3.5 2,8-Azaspiro[5.5]undecane

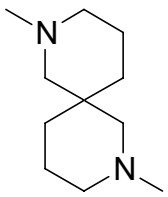
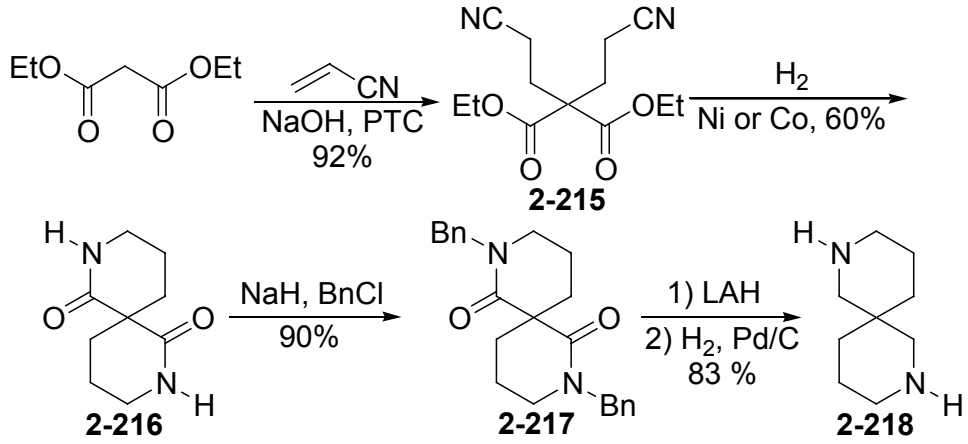


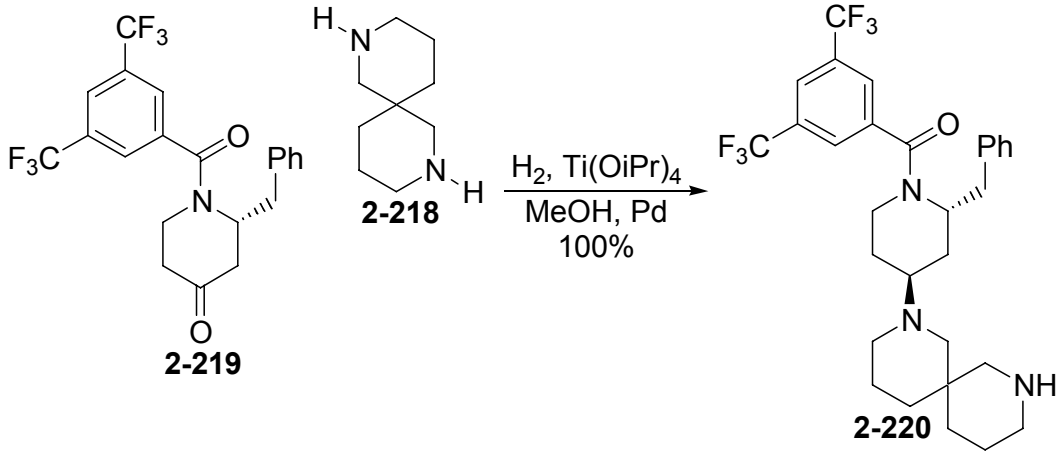
Figure 13. 2,8-diaspiro[5.5]undecane

Due to the inherent molecular symmetry in spiro compounds of this type an extremely short approach could be developed. Namely, double conjugate addition of diethyl malonate to acrylonitrile followed by hydrogenation of two cyano groups ultimately leads to in situ formation of diamide **2-216**[79]. The diamide then could be N-benzylated and reduced to corresponding benzyl protected diamine. Another hydrogenation gave rise to the free amine.



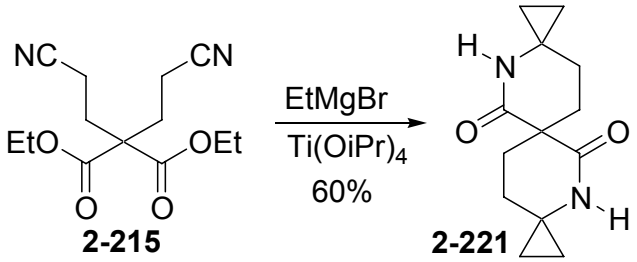
Scheme 51. Synthesis of diazaspiroundecane **2-218**

This spirodiamine was used for the preparation of neurokinin antagonists[14].



Scheme 52. Synthesis of neurokinin antagonist by reductive amination.

An interesting reaction was recently reported by Bertus[80]. Treatment of dinitrile **2-215** with ethylmagnesium bromide in presence of titanium isopropoxide resulted in Kulinkovich-type cyclopropanation followed by in situ cyclization to diamide **2-221** (**Scheme 52**).



2-215 **2-221**

Scheme 52. Domino aza-Kulinkovich/cyclisation reaction.

In conclusion, this literature review of different approaches to nitrogen containing spirocyclic structures and their derivatives, illustrates that they represent not only a core structure of many biologically active substances, but are also an interesting target for the development of novel and convergent methodologies in organic chemistry.

3 Goal of Research

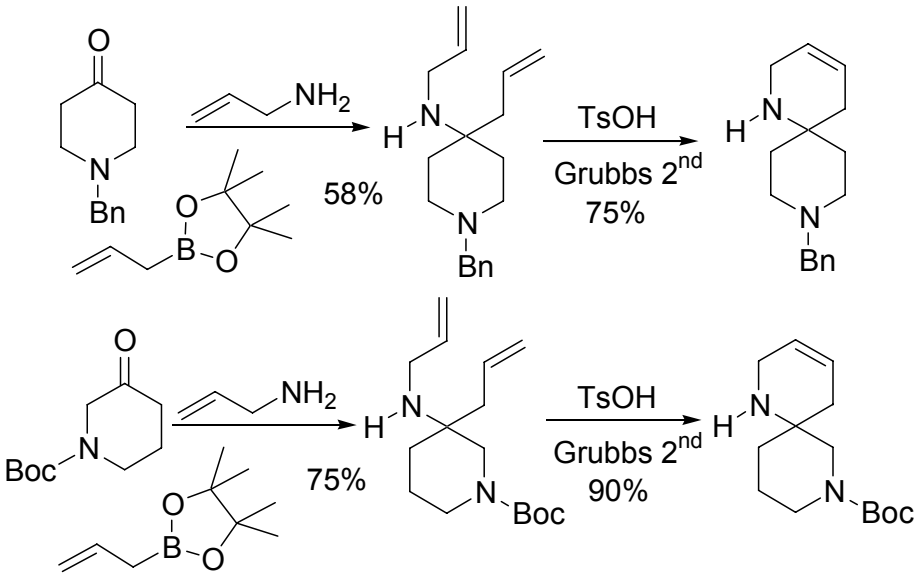
As one can see from the literature review, spirocyclic skeletons represent interesting scaffolds for preparation of combinatorial libraries of compounds. The classical routes to 1-azaspirocyclic compounds include intramolecular nucleophilic substitution, intramolecular amide formation, Dieckmann condensation, intramolecular conjugate addition, Diels-Alder and nitrone cycloadditions, and ring closing metathesis. The last reaction is particularly interesting for the following reasons:

a) It's catalytic.

b) It requires rather simple molecular setup, namely two terminal double bonds.

c) The reaction proceeds under very mild conditions and it tolerates various functional groups.

In fact, the RCM reaction has already been used for the synthesis of aza- and diazaspirocyclic systems. However, in all these examples the double bond was lacking any functionality. This is a significant drawback for potential scaffolds, because a very limited number of further reactions can be done with such compounds (e.g. hydrogenation) and certain functionalization reactions would lead to region isomers.



Scheme 53. Examples for the synthesis of spiroheterocyclic compounds based on RCM.

Our goal was to develop a RCM based approach to spirocyclic compounds with the double bond bearing some kind of functional group. As such functional group we selected methyl carboxylate, due to the ability of the unsaturated ester to participate in a number of reactions,

for example Michael addition, reduction, amide formation, and others. Another apparent advantage is that starting materials for RCM reaction can be readily obtained by alkylation of the corresponding nitrogen compounds with methyl α-(bromomethyl) acrylate.

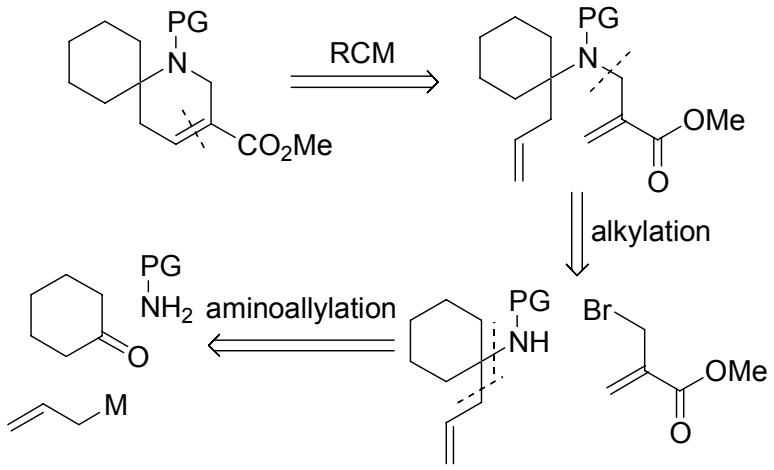


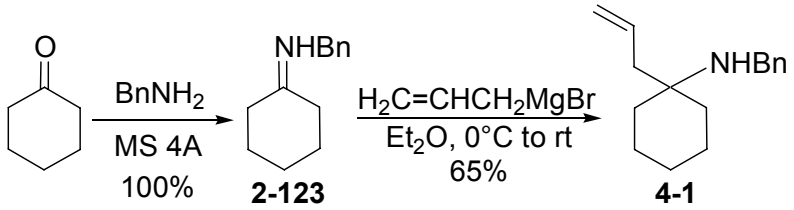
Figure 14. Synthetic strategy towards spiro scaffolds based on aminoallylation/RCM.

The required N-protected 1-allyl-cyclohexylamines can be traced back to simple cyclic ketones, a protected amine and an allyl anion synthon. Some examples of such compounds were presented in the literature review, but so far no general and efficient procedure was published. Therefore, the development of a novel approach toward spirocyclic scaffolds with a substituted double bond appeared as an interesting task. The following section describes how we achieved our goals.

4 Results and Discussion

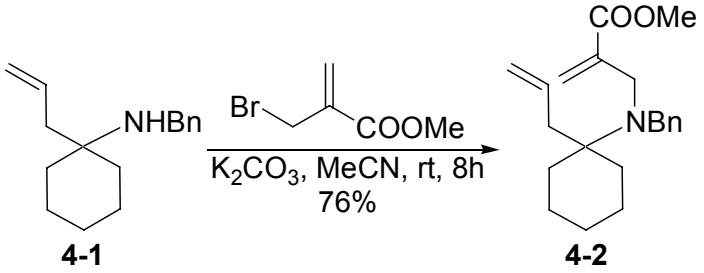
4.1 Initial investigation of RCM strategy on N-alkyl protected spirocycles

As one can see from our retrosynthetic analysis, we planed to construct the spirocyclic skeleton starting from a molecule with an already existing ring and to establish the second via metathesis of terminal double bonds. Thus, to make a six-membered ring one would need a chain of eight atoms, for example two allyl groups and one carbon-heteroatom unit. We prepared the required diallylamines from cyclohexanone in three simple steps. A quantitative formation of the imine with benzylamine, followed by Grignard reagent addition led to 1-allyl-1-N-benzylaminocyclohexane (**4-1**) with good yield.



Scheme 54. Preparation 1-allyl-1-(N-benzylamino)-cyclohexane **4-1**

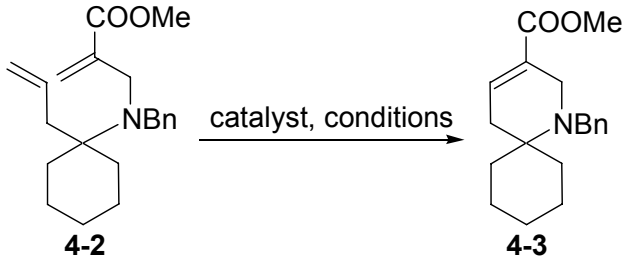
The resulting homoallylamine was treated with methyl (bromomethyl)acrylate[81], which is an excellent electrophile due to the presence of allylic and α,β-unsaturated systems.



Scheme 55. Synthesis of RCM precursor **4-2**.

The reaction proceeds smoothly in acetonitrile in presence of two equivalents of finely powdered potassium carbonate as a base. Having now our model substrate in hand we attempted to achieve the RCM under known conditions. It's known that for substances with basic amines one has to block the Lewis base centre with Lewis or Brønsted acid, otherwise the electron rich nitrogen will substitute weakly bound ligands in the catalyst complex and shut down the metathesis reaction. In a related literature example titanium (IV) isopropoxide and p-toluenesulfonic acid were used for this purpose. Our investigation revealed, that the

RCM reaction of N-benzyl protected diallylamines bearing the acrylate moiety proceeds only in presence of second generation Grubbs catalyst and p-toluenesulfonic acid (**Scheme 56**).

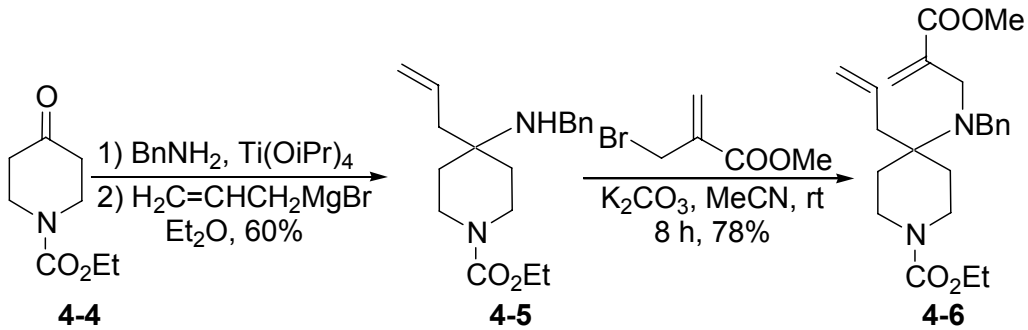


4-2 **4-3**

Scheme 56. Conditions screening for RCM reaction of **4-2**.

Catalyst	Condition	Yield, %
10% 1st Generation Grubbs'	CH_2Cl_2, room temperature or reflux	-
10% 1st Generation Grubbs'	CH_2Cl_2, room temperature or reflux, 1 esq. $Ti(OiPr)_4$	-
5% 2nd Generation Grubbs'	CH_2Cl_2, room temperature or reflux, 1 eq TsOH	trace
5% 2nd Generation Grubbs'	Toluene, 1 eq pTsOH, 55°C, 4h	80

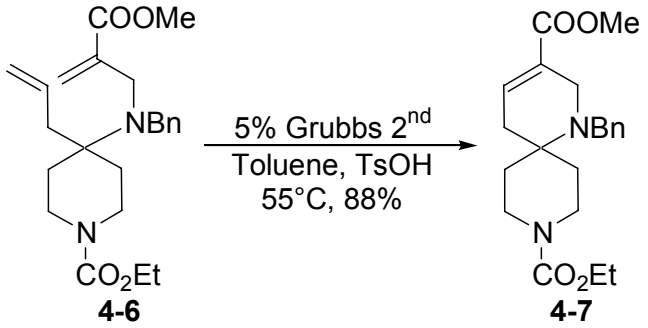
The best conditions were found to be heating the substrate with 5% 2nd Grubbs and 1.1 equivalents of toluenesulfonic acid monohydrate at 55°C in absolute and degassed toluene. Formation of the spiro structure was confirmed by appearance of a single acrylate proton resonance at 6.9 ppm in the ^{1}H NMR spectrum of **4-3**. The whole sequence was repeated with a more elaborated object, namely N-carbethoxy-4-piperidone (**4-4**) (**Scheme 57**). Here, in situ prepared benzylimine reacted with the Grignard reagent to form the desired 4-allyl-4-benzylaminopipridine **4-5**. The alkylation reaction also proceeded cleanly and afforded the RCM precursor **4-6** in good yield.



4-4 **4-5** **4-6**

Scheme 57. Synthesis of a more elaborated substrate for RCM reaction.

Subjecting **4-6** to the above described RCM conditions provided the highly substituted spirocyclic compound **4-7** (**Scheme 58**). One should note that there are two orthogonally protected nitrogen atoms in this molecule, thus making it possible to selectively deprotect and functionalize them.



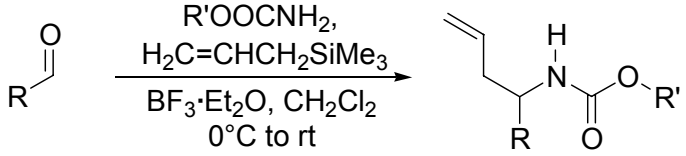
Scheme 58. Synthesis of spirocyclic scaffold **4-7** with orthogonally protected nitrogen atoms.

Having successfully achieved the synthesis of N-benzyl protected spirocyclic esters we proved that RCM reaction could be effectively used for the construction of spirocyclic structures with trisubstituted double bond and looked toward improvement and simplification of this method.

4.2 Preparation of Spirocyclic Scaffolds and their Derivatization

4.2.1 Extension of the Veenstra methodology to ketones

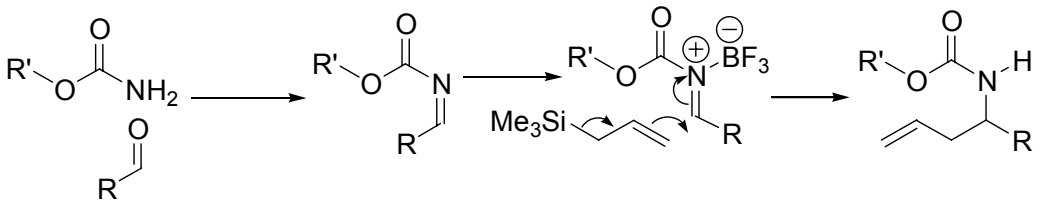
It was reported[82] that aldehydes undergo a domino imine formation/allylation reaction in presence of a carbamate ester, allyltrimethylsilane and a Lewis acid (**Scheme 59**).



Scheme 59. Synthesis of N-carbamate protected homoallylamines by Veenstra.

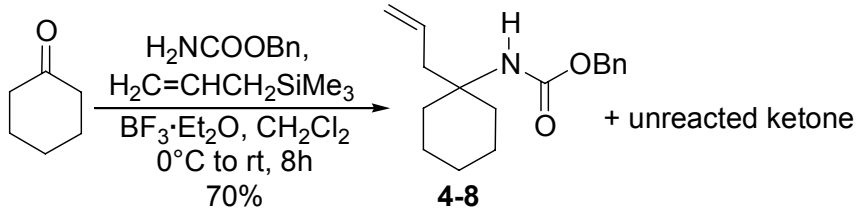
This reaction drew our attention because it introduces a protected amino group and alkyl chain with terminal double bond in one chemical step. This is a considerable advantage compared to the addition of Grignard reagents to imines, where isolation of the intermediate N-benzyl-homoallylamine is required. The carbamate protecting group also makes the N-H bond relatively acidic, thus further functionalization (e.g. alkylation) should be easily possible.

The reaction involves formation of an electrophilic iminium ion from the aldehyde and carbamate, followed by addition of allyltrimethylsilane (**Scheme 60**).



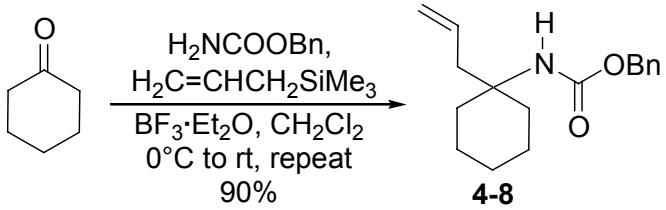
Scheme 60. Mechanism of the Veenstra reaction.

We decided to extend this methodology to cyclic ketones, and found that the described reaction does proceed with cyclohexanone, but stops at approximately 70% conversion, even when a large excess of other reagents was used (**Scheme 61**).



Scheme 61. Carbaminoallylation reaction of cyclohexanone in unoptimized conditions.

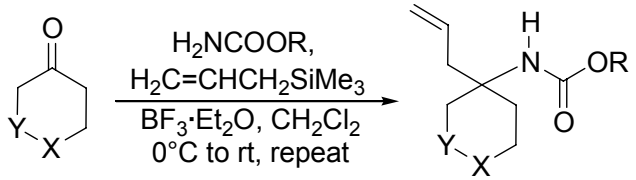
Careful analysis of the reaction mixture after quenching revealed that only product and starting material were present, so we tried to resubject it to the initial conditions with a 30% load of reagents.



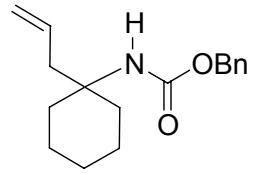
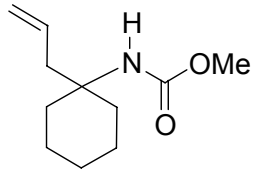
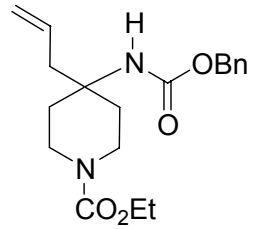
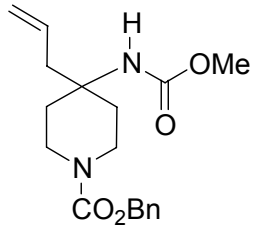
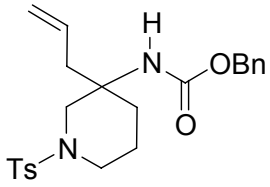
Scheme 62. Synthesis of carbamate protected 1-allyl-cyclohexylamine

Gratifyingly, almost complete conversion was observed with no need for further purification of the N-carbalkoxy homoallylamines. We then applied this modified procedure to some other cyclic ketones and carbamic esters and found it to be quite general.

Table 1. Yields of carbamate protected homoallylamines



n	X	Y	R	Structure	Yield, %

4-8	CH_2	CH_2	Bn		88
4-9	CH_2	CH_2	Me		90
4-10	NCOOEt	CH_2	Bn		85
4-11	NCOOBn	CH_2	Me		78
4-12	CH_2	NTs	Bn		25

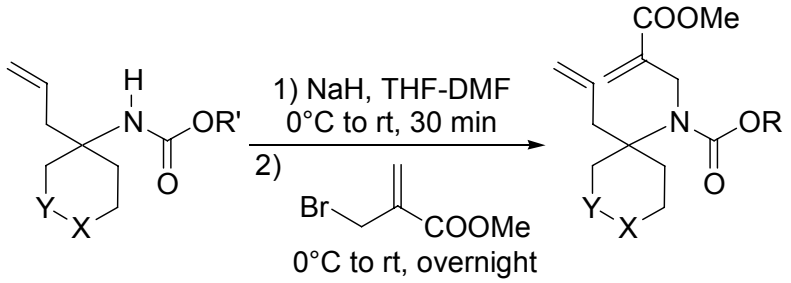
The one notable exception was the reaction with N-tosyl-3-piperidone, where we obtained the desired homoallylamine in only 25% yield. This can be explained by formation of a stabilized enamide with significantly lowered electrophilicity.

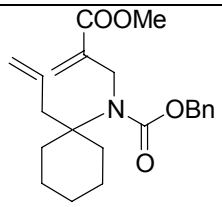
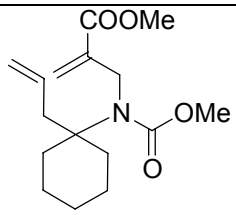
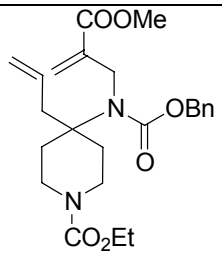
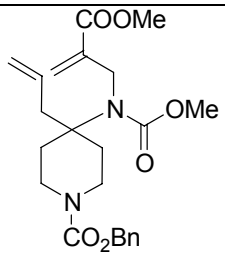
4.2.2 Allylation of carbamates

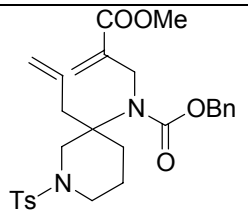
Similarly to the series with benzyl protected amines our next goal was to introduce a methacrylate subunit in our substrates. The classical conditions for an amide or carbamate alkylation are deprotonation with sodium hydride in DMF or THF, followed by addition of an alkylation agent. We tried both solvents for this reaction but obtained only moderate yields of

product. However, the mixture of DMF and THF in ratio 3:2 was found to be the solvent system of choice for this reaction, giving reproducibly high yields of the product. Treatment of the homoallylamines with two equivalents of mineral oil free sodium hydride at 0°C results in clean deprotonation within half an hour. After addition of methyl 2-bromomethylacrylate, the reaction was allowed to come to room temperature overnight. In this way we successfully achieved alkylation of all our substrates with the yields presented in Table 2.

Table 2. Yields of alkylation products.



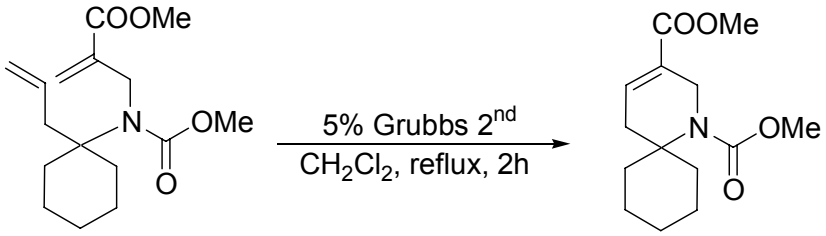
n	X	Y	R	Structure	Yield, %
4-13	CH_2	CH_2	Bn		80
4-14	CH_2	CH_2	Me		80
4-15	NCOOEt	CH_2	Bn		80
4-16	NCOOBn	CH_2	Me		65

4-17	CH_2	NTs	Bn		65

One should note that due to the high polarity of the carbamate protecting group, the obtained alkylation products were not soluble in the classical eluent mixture of petroleum ether and ethyl acetate. Thus, column chromatography was performed with an appropriate combination of toluene and diethyl ether as mobile phase. The RCM precursors did not exhibit tendency toward polymerization and they appeared mostly as slightly yellow oils.

4.2.3 RCM of carbamate protected diallylamines

As soon as the first model substrate was synthesized, studies of RCM reaction on this kind of object were undertaken. It was found, that the desired cyclization goes well in conditions very similar to the ones described for N-alkylamines, although the acid was not needed any more and a slightly lower temperature in refluxing DCM was sufficient for the reaction to proceed (**Scheme 65**).

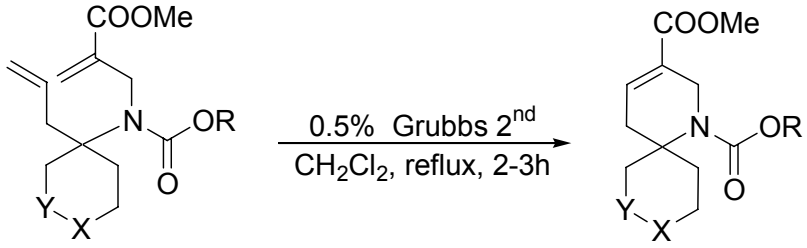


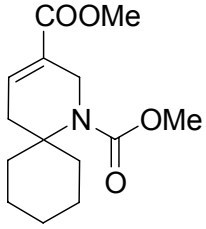
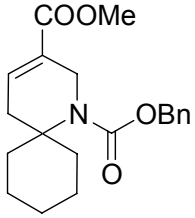
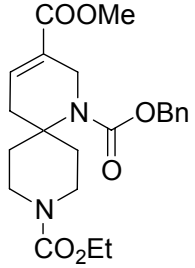
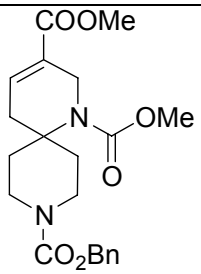
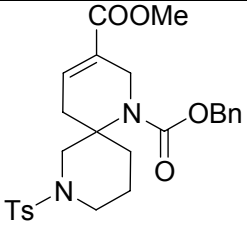
4-14 **4-18**

Scheme 65. Metathesis reaction of carbamate protected diallylamines.

Our following investigation with higher substrate loads showed that even 0.5% mol of the 2nd generation Grubbs catalyst is enough to accomplish the RCM reaction within 2-3 h and with good to excellent yields. Having now the best conditions in hand we applied them to the previously synthesized carbamate protected diallylamines and obtained the corresponding spirocyclic compounds.

Table3. Synthesis of N-carbamate protected spirocyclic scaffolds by RCM reaction.

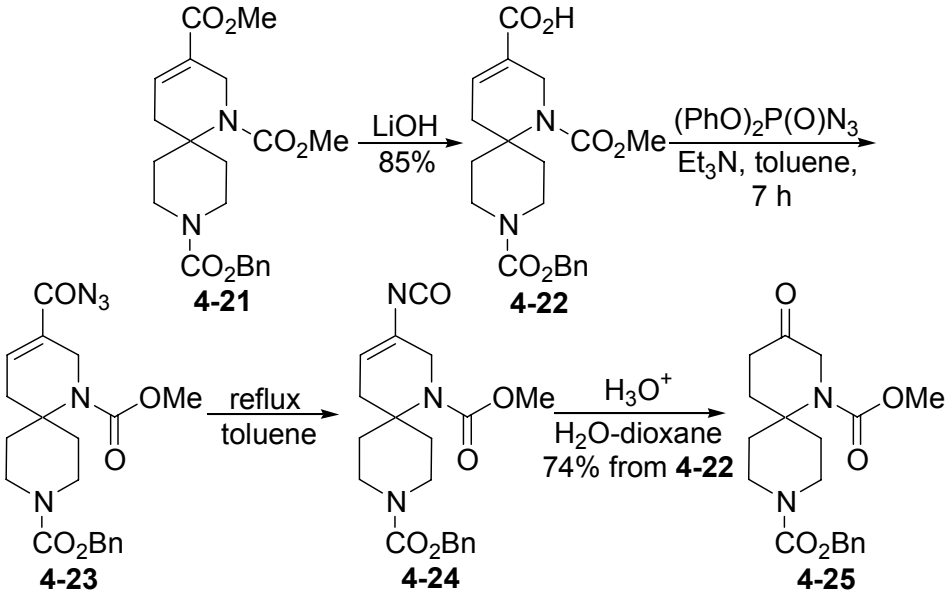


n	X	Y	R	Structure	Yield, %
4-18	CH_2	CH_2	Me		94
4-19	CH_2	CH_2	Bn		90
4-20	NCOOEt	CH_2	Bn		85
4-21	NCOOBn	CH_2	Me		90
4-22	CH_2	NTs	Bn		65

As one can see, preparation of spirocyclic scaffolds possessing orthogonally protected nitrogen atoms by the developed route is easily possible. We then looked towards further modifications of the spirocyclic unsaturated compounds.

4.2.4 Conversion to spirocyclic ketones

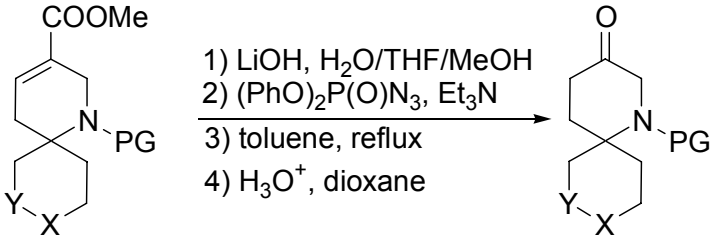
To illustrate the synthetic potential of the prepared spirocyclic scaffolds we decided to achieve conversion of the α,β-usaturated esters to corresponding ketones using a degradation sequence consisting of Curtius rearrangement and hydrolysis of the resulting en-isocyanates. As a model object we chose compound **4-21** to evaluate the stability of the benzyloxycarbonyl group during the Curtius rearrangement. First, the ester was smoothly saponified to the acid by treatment with a lithium hydroxide solution in a THF-ethanol-water mixture. The crude acid was subjected to reaction with the Yamada reagent providing in one step the corresponding acylazide, which undergoes Curtius rearrangement by refluxing it in toluene (**Scheme 66**).

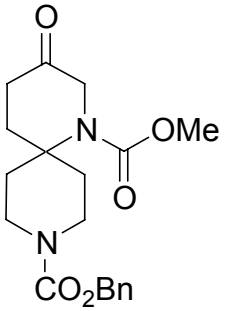
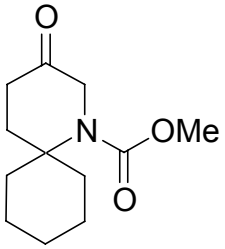
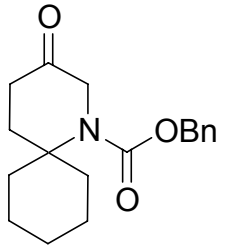
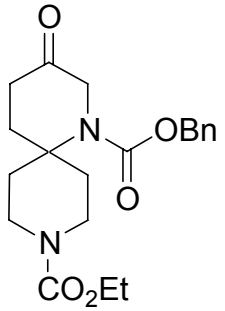


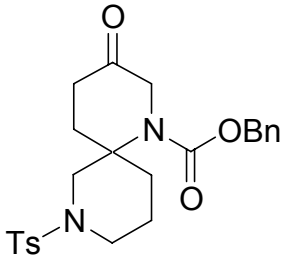
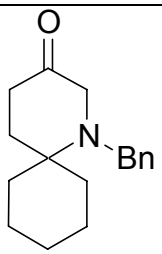
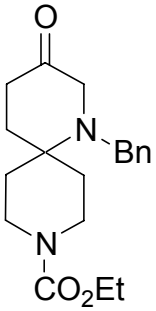
Scheme 66. Synthesis of spirocyclic ketone **4-25** by Curtius rearrangement.

The resulting unsaturated isocyanate **4-24** was then easily hydrolysed to ketone **4-25** under acidic conditions. Although this sequence includes four chemical steps, no isolation or purification of intermediates is required, thus all operations can be done in one day. The yields for the final products are generally good and do not vary much with substituent or protection groups.

Table 4. Conversion of unsaturated esters to spirocyclic ketones.

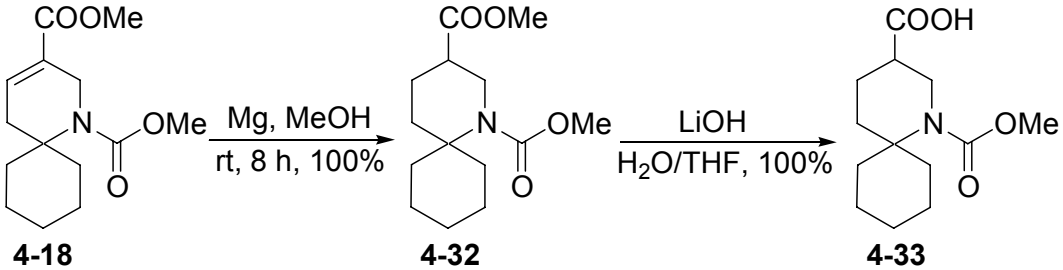


n	X	Y	PG	Structure	Yield
4-25	NCO_2Bn	CH_2	COOMe		63%
4-26	CH_2	CH_2	COOMe		60
4-27	CH_2	CH_2	COOBn		66
4-28	NCO_2Et	CH_2	COOBn		65

4-29	CH_2	NTs	COOBn		50
4-30	CH_2	CH_2	Bn		70
4-31	NCOOEt	CH_2	Bn		65

4.2.5 Further reactions on carboxyl and carbonyl groups

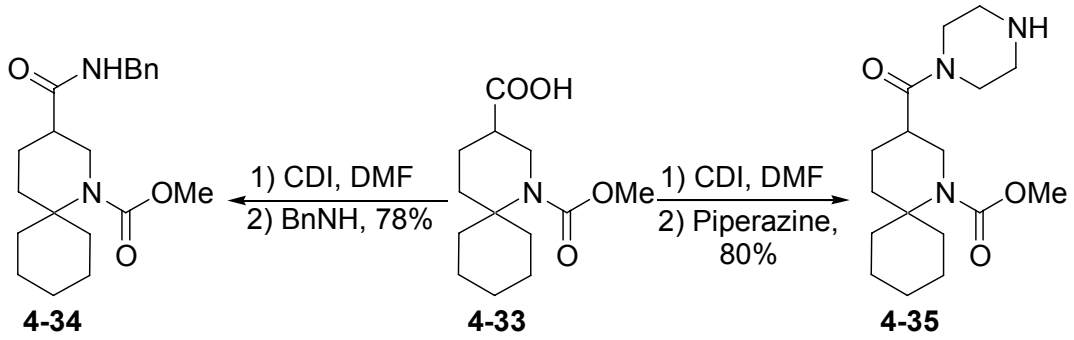
Another synthetic opportunity was conjugate reduction of the unsaturated ester. This transformation proceeds with quantitative yield using magnesium metal in methanol at room temperature[83]. The resulting saturated ester was saponified to the corresponding acid as was previously described (**Scheme 67**).



4-18 **4-32** **4-33**

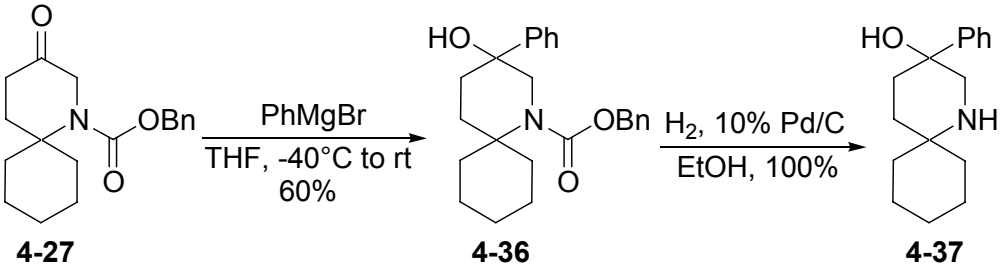
Scheme 67. Synthesis of saturated acid **4-33**

A classical amide synthesis via the 1,1'-carbonyldiimidazole (CDI) derivative was then used to obtain compounds **4-34** and **4-35** (**Scheme 68**). The latter amide contains a free NH function and could be further modified by various reactions, such as alkylation, acylation or sulfonylation.



Scheme 68. Synthesis of amide derivatives of saturated acid **4-33**

One of the most frequently used reactions for derivatization of a carbonyl group is the addition of organometallic species, and particularly Grignard reagents. To prove the utility of the synthesized ketones as possible scaffolds in this regard we introduced compound **4-27** in a reaction with phenyl magnesium bromide and obtained the corresponding alcohol **4-36** (**Scheme 69**). The moderate yield of product can be attributed to competitive enolization of the keto function.



Scheme 69. Addition of a Grignard reagent to spirocyclic ketone.

After deprotection of the CBZ group via catalytic hydrogenation at ambident pressure aminoalcohol **4-37** was obtained. This substance contains a β-phenethylamine motif and thus could be interesting for biological evaluation or further transformations.

5 Conclusion I

We were able to show that the tactical sequence of aminoallylation of a cyclic ketone with an ester of carbaminic acid and allyltrimethylsilane, followed by alkylation with methyl α-bromomethylacrylate and ring closing metathesis reaction provides an efficient and innovative route to nitrogen containing spirocyclic scaffolds. In contrast to substances prepared earlier by similar methods, our scaffolds possess a functionalized double bond suitable for further derivatization. A number of substrates, containing protected nitrogen atoms in different positions of the ring, were synthesized in gram scale quantities.

The synthesis of the different classes of compounds (unsaturated ester, saturated ester and ketones) was shown to be possible by the developed methodology. Examples of derivatization of the prepared scaffolds via amide formation and Grignard reagent addition were made. From the corresponding adduct **4-34** the aminoalcohol **4-35** was obtained by deprotection of benzyloxycarbonyl group, which contains a β-phenethylamine motif and could serve as a useful scaffold for further derivatization reactions.

Before this method was described there was no methodology known to provide spirocyclic compounds with a selectively functionalizable double bond and variations in the position of the nitrogen as well. Therefore, the obtained results represent a valuable contribution to the field of modern organic chemistry.

Chapter II

Approach towards the Total Synthesis of the Macrolide Dictyostatin

6 Introduction

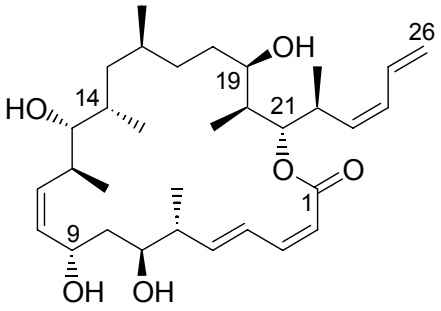
Water is the cradle of live and marine species are the most ancient creation on the Earth. Throughout half billion years of evolution, they accumulate a unique collection of methods to defend themselves against aggression. The simplest sea animals like corals, sponges and plankton produce the most complex and toxic non-peptide substances ever known, such as palytoxin, brevetoxin and maitotoxin. Only 5 micrograms of these cytotoxic compounds can kill the human being within a few minutes. But it's the dose what makes a difference between cure and gift. Such toxins, applied accordingly can be used for treatment of anticipated cell growth. Therefore, the vast amount of natural products isolated from plants, animals, fungi and bacteria was tested as potential drug candidates. It's a big challenge to find a substance with a balance of toxicity, complexity, stability and availability, and only few from thousand can later enter the market as drugs.

Although many complex natural products are very interesting from a biological point of view, they are usually present in organisms in ultra low quantities. This sometimes significantly hampers extensive clinical research of such compounds. Thus, alternative sources and in the first place, chemical synthesis must provide access to required amounts. Another important role of total synthesis is to prove the assigned structure and determine absolute stereochemistry of complicated molecules[84]. At the same time, many useful reactions and techniques were discovered in the course of total synthesis. Some methodologies, e.g. the asymmetric aldol reaction and peptide coupling reagents, have been specially developed for the purpose of total synthesis of natural products and then found wide use in other fields of chemistry. To add more, one can gain fundamental knowledge about applicability of already existing reactions to new and elaborated objects.

An especially interesting class of natural products is represented by polyketides. From a biological point of view, polyketides are secondary metabolites of bacteria, fungi, sponges, and small animals. They appear to be unnecessary for an organism internal functioning but can be used for the purpose of defense and intercellular communication. Polyketide fragments are derived from the oligomerization of propionyl and acetyl subunits in a similar process to fatty acid synthesis. Such fragments then can be linked by double bonds, saturated chains or even heterocycles. When these molecules posses a macrolactone ring one would call it macrolide.

Polyketide macrolides exhibit a number of biological activities but the most important ones are cytotoxic and antibiotic.

One peculiar member of the polyketide macrolide family (-)-dictyostatin (**6-1)** attracted our attention as a possible target for total synthesis (**Figure 15**). Its structure is extremely complex and features a 22-membered macrolactone ring with a *Z*,*E*-dienoate system, three oligopropionate fragments, and a terminal diene unit. Dictyostatin was isolated in 1993 by Pettit[85] from a marine sponge of the genus *Spongia sp* and, ten years later, re-isolated by Wright[86] and co-workers from a *lithistida* sponge of the family *Corallistidae*, harvested at great depths off the Jamaican coast. The latter group also discovered the strong cytotoxic properties of this compound against various murine (rats and mice) and human cancer cell lines.



(-)-Dictyostatin
(6-1)

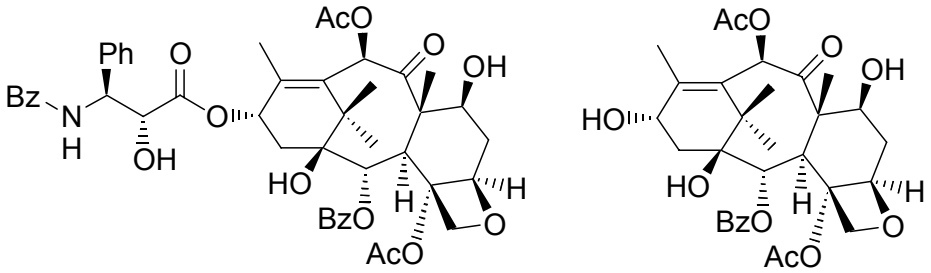
Figure 15. Structure of dictyostatin.

Despite the fact that two finished total syntheses of dictyostatin were published even before we started this project, our intention was not only to achieve a strategically different synthesis of this beautiful molecule itself, but also to investigate the utility of recently developed reactions and methodologies. For instance, we were trying to put an accent on the use of enzyme catalyzed enantioselective reactions throughout the synthesis. The knowledge obtained en route to dictyostatin can be used in the future for planning the synthesis of other targets.

7 Literature review

7.1 Cancer treatment with microtubule stabilizing agents

Cancer is a class of diseases related to discrepancies in cell growth, differentiation or death. Cancer statistic is astonishing. Every third man and every fifth women in developed countries will acquire some sort of cancer at or close to 50. It is known that earlier diagnostic and timely executed therapy can greatly improve the survivability rate of cancer patients. There are several different strategies to cancer treatment, e.g. surgery, radiotherapy, immunotherapy, etc. Most of them have a goal to kill selectively tumor cells, to stop cell growth or to cause apoptosis - programmed cell self death. Chemotherapy is the strategy which relies on the use of pharmaceutical substances. It was found, that some natural products exhibit very high cytotoxicity toward cancer cell lines. The most prominent of them is the polyhydroxylated sesquiterpene Taxol® (**Figure 16**) isolated from the bark of the Pacific yew tree, *Taxus brevifolia.*



Taxol

Figure 16. Taxanes family.

To explain the Taxol® mode of action, one should take a closer look at cell biology. One important cancer hallmark is uncontrolled cell division which leads to tumor growth. The cell division cycle consists of several stages, in some of them internal structure and organelle positions undergo significant change. These translocations, e.g. physical segregation of sister chromatids, are provided by so called microtubules. Microtubules not only constitute cell's internal framework, providing structural strength, they also serve as "railroad" for special motoric proteins, which move along them. Microtubules are superpolymers of tubulin, a protein with approximately 53 kDa mass which exists in α and β form. These can form a heterodimer, which in presence of magnesium salts and GTP aggregate into tube-type

structure (**Figure 17**). Normally, microtubules exist in a dynamic equilibrium, which means their length can be modulated by conditions inside the cell. The same heterodimer can form a stable complex with taxol, which then undergoes irreversible polymerization. Detailed X-ray crystallography studies showed that stabilized microtubules have a different structure from the normal ones, they consist of 12 protofilaments instead of 13 and thus are 2 nm thinner.

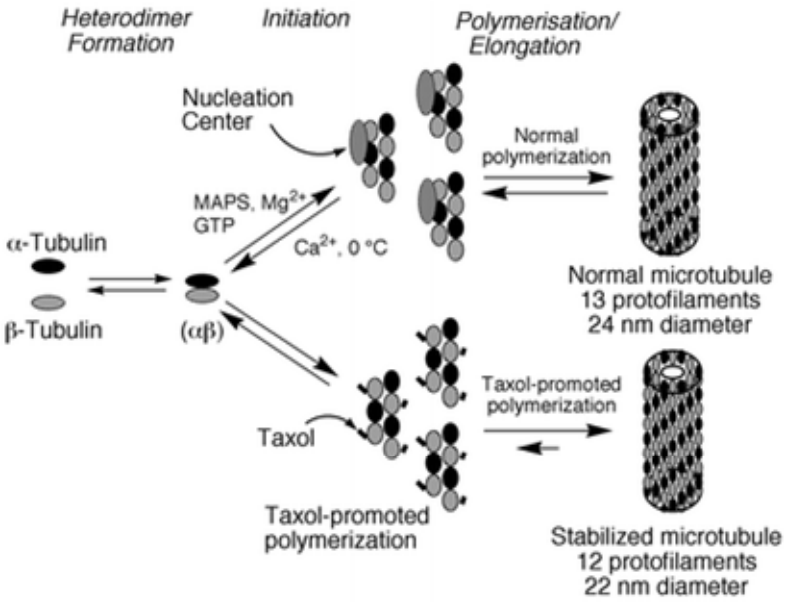
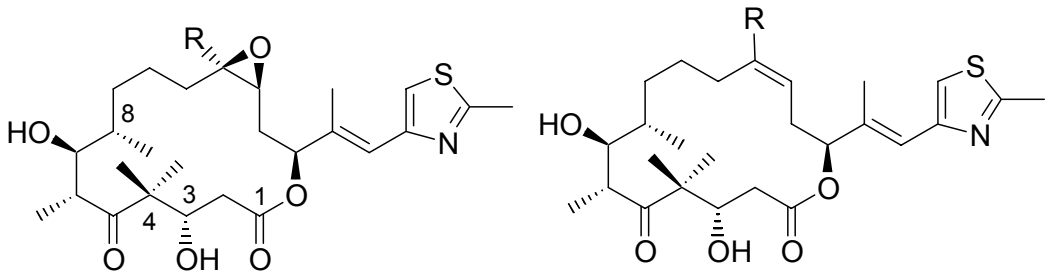


Figure 17. Normal and Taxol® promoted tubulin polymerization and dynamic instability. Picture is taken from the reference 86.

Taxol® is currently marketed as a drug for treatment of various epithelial type cancer, e.g. breast, ovarian and lung. Although two total synthesis of Taxol were independently accomplished by Nicolaou and Holton, they are quite lengthy and have low overall yields and thus aren't practical for drug production. The supply problem in case of Taxol® was solved by semi-synthesis from 10-deacetylbaccatin III which is isolated from renewable sources of *Taxus baccata*. There are several reviews on chemistry and biology of taxol related compounds available[87].

Another group of highly promising compounds was isolated from Myxobacterium and called epothilones, reflecting their common structural elements, epoxide, thiazole, and ketone (**Figure 18**). The microtubulin stabilizing properties of the epothilones was discovered in 1995 by Merck pharmaceutical company during a high-throughput screening program.



R=H, Epothilone A
R=Me, Epothilone B

R=H, Epothilone C
R=Me, Epothilone D

Figure 18. Structures of natural epothilones.

Due to its relatively simple structure, about two dozen total syntheses of epothilone were made. The most important ones were achieved by Nicolaou[88], Danishefsky[89], Mulzer[90], Schinzer[91], and White[92]. A review devoted to the chemistry of epothilones has been composed by Mulzer[93]. As soon as the best synthetic pathways were found, preparation of simplified or modified analogs took place, followed by extensive QSAR studies. The crucial regions for activity were identified at C4-C8, C3, and the epoxide fragment. The nitrogen atom of the heterocyclic moiety must be placed in *ortho*-position. Currently, along with natural epothilone B and D at least five analog compounds are in clinical trial (**Figure 19**).

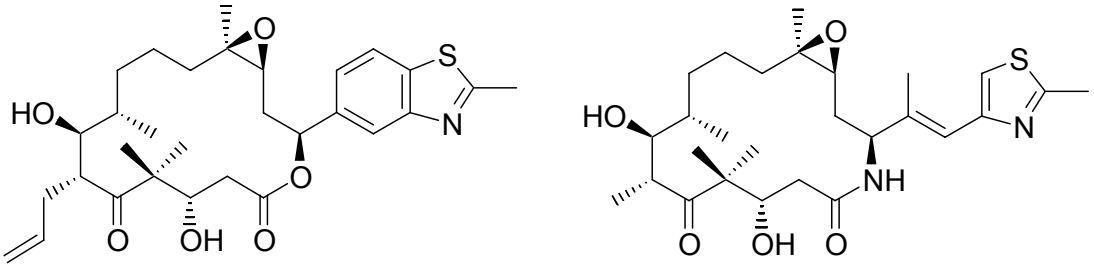


Figure 19. Epothilone analogs which are currently in clinical trials.

Another potent tubulin stabilizing compound discodermolide (**Figure 20**) was isolated from the marine sponge *Discodermia dissoluta* by Gunasekera and co-workers at the Harbor Branch Oceanographic Institute in 1990[94]. Biological screening of this compound revealed startling cytotoxicity, causing cell cycle arrest in the G2/M phase in a variety of human and murine cell lines[95].

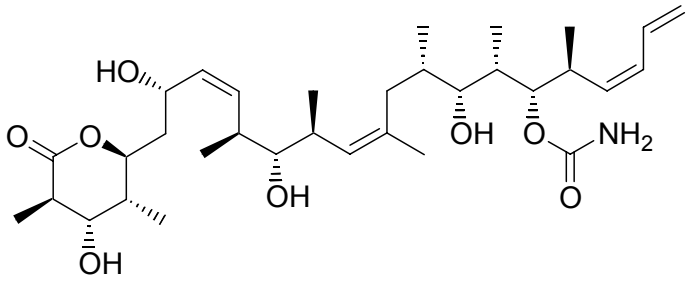


Figure 20. Structure of marine polyketide discodermolide.

Discodermolide has been recognized as one of the most potent tubulin polymerizing agents presently known. Despite having no apparent structural similarities, discodermolide has been found to stabilize microtubules more potently than Taxol® and competitively inhibits its binding to tubulin polymers. The growth of Taxol-resistant ovarian and colon cancer cells is inhibited by discodermolide with an IC_{50} of <2.5 nM[96], while the timing and type of DNA fragmentation induced is consistent with the induction of apoptosis[97].

Figure 21. Cells treated with discodermolide, microtubule-green, nucleus-red.
Picture is taken from the NOAA official web site, Division of Biomedical Marine Research Harbor Branch Oceanographic Inst.

Due to the unique biological profile of discodermolide, it has been considered as a promising candidate for clinical development as a chemotherapeutic agent for cancer treatment. The extremely scarce supply of discodermolide from the natural source (0.002% w/w frozen sponge) promoted 10 years of extensive research[98] toward the total synthesis of

discodermolide by Schreiber, Myles, Marshall, and Panek. Finally, after an one gram-scale synthesis was performed by Amos B. Smith and development of a practical route was achieved by Paterson, all these efforts culminated in an outstanding work done at Novartis Pharma where 61 g of discodermolide were produced by total synthesis[99]. This quantity was required to supply phase I clinical trials, thus making this compound very short from entering the market. Unfortunately, as a result of this study further development of discodermolide was canceled due to high in vivo toxicity and low stability. Nevertheless, the search for similar compounds continued, and eventually resulted in recognition of the marine macrolide dictyostatin (**Figure 22**) as a possible "follow-up" candidate because of its structural resemblance to discodermolide.

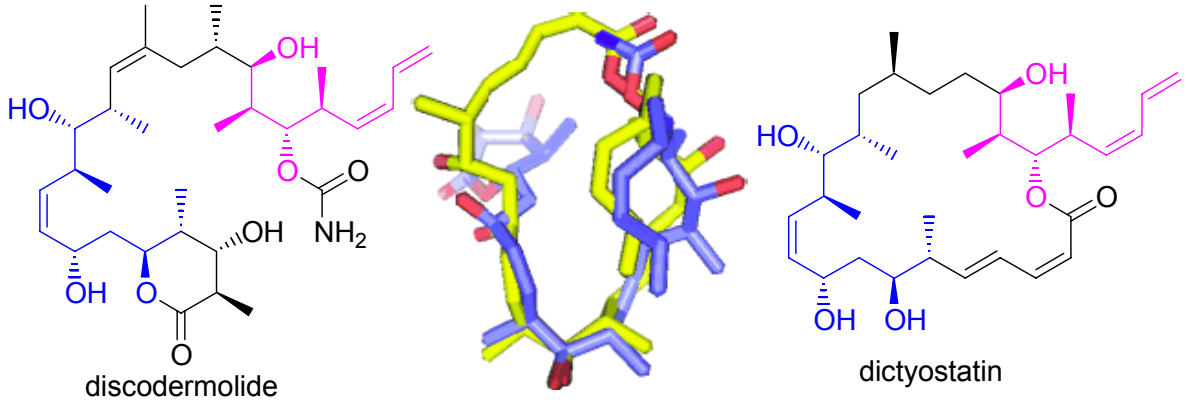


Figure 22. Comparison of discodermolide and dictyostatin structures and overlay of the lowest energy conformations obtained from molecular mechanics calculation and NMR-data.

Indeed, almost ten years after isolation, Isbrucker found dictyostatin to be cytotoxic for various cancer assays, including lines resistant to paclitaxel due to mutations in β-tubulin. Dictyostatin is also active against multidrug resistant (MDR) cell lines with overexpressed P-glycoprotein efflux pump.

The natural abundance of dictyostatin is even less then that of discodermolide and was estimated to be 3.4×10^{-7}% of sponge dry weight. Such a small value makes it impossible to meet the demand required for biological studies by isolation of material from organisms, thus leaving chemical synthesis the only reasonable supply source. However, the molecular architecture of dictyostatin is somewhat more complex when compared to discodermolide due to presence of the 22-membered macrolactone ring and *Z*,*E*-dienoate fragment, making a total synthesis of this compound an encouraging challenge.

7.2 Previous Dictyostatin syntheses

So far four total syntheses of dictyostatin were achieved. The first two were almost simultaneously completed by the Paterson and Curran groups and published in the same issue of Angewandte Chemie. Till the beginning of 2004 the exact stereochemistry of dictyostatin at C14 and C16 was still under question and has been established by Wright and Paterson on the basis of high resolution ^{1}H NMR data, modeling studies, and comparison to discodermolide[100].

7.2.1 Synthesis of Dictyostatin by Paterson and Curran

The Paterson synthesis of dictyostatin is possibly the most elegant one[101]. Retrosynthetic disconnections were done at the lactone bond and the C10-C11 *Z*-double bond, thus splitting the molecule into two big subunits (**Figure 23**). The upper part was then traced back to two smaller fragment, each containing a *syn,anti*-stereotriad, for preparation of which the intermediate from the discodermolide synthesis was used.

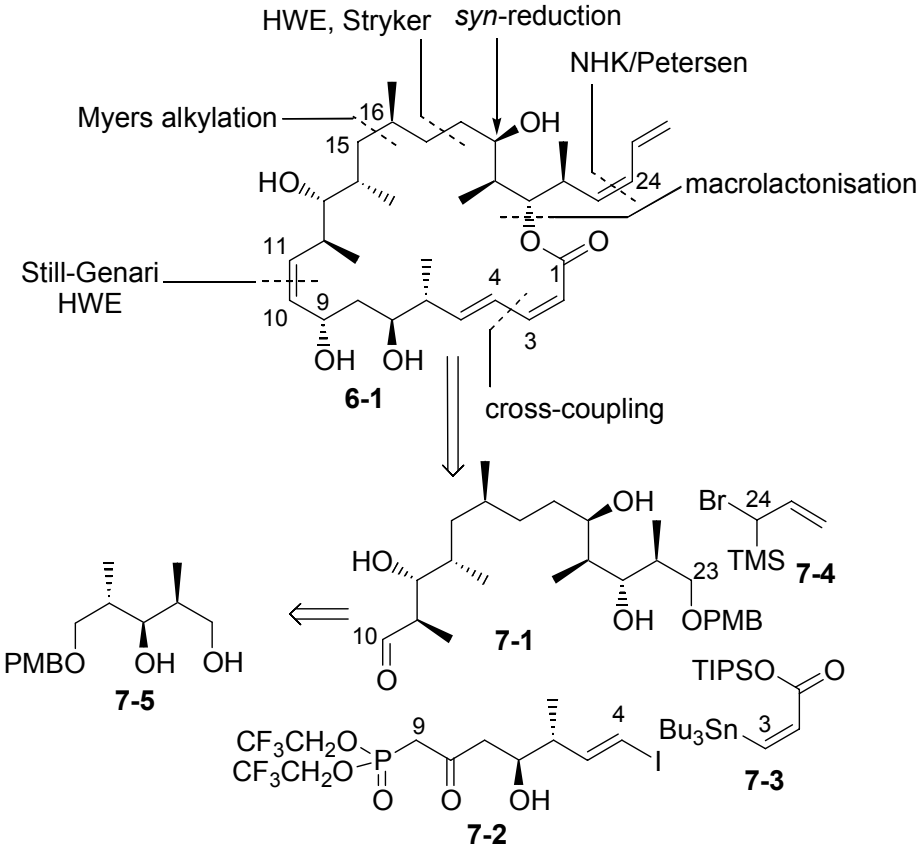
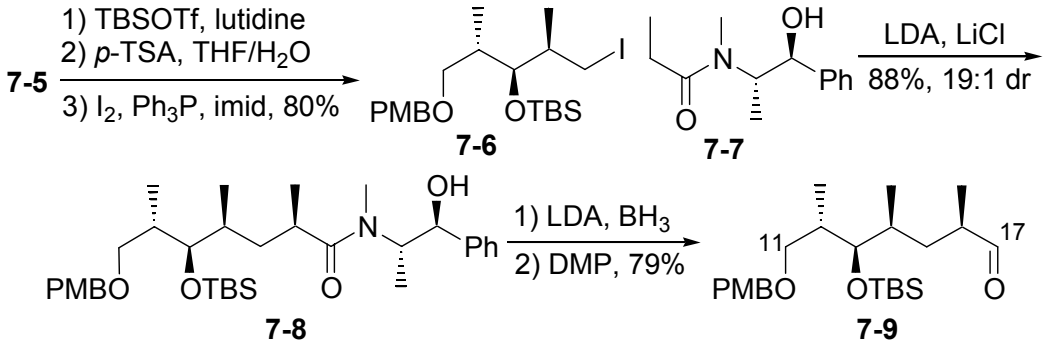


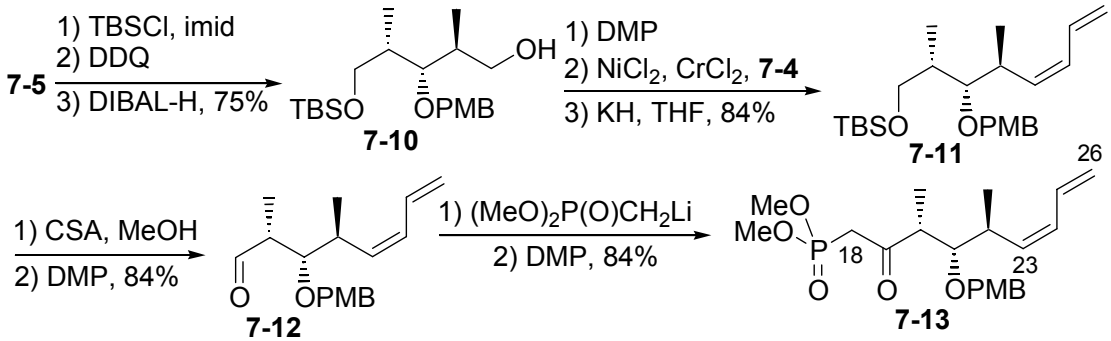
Figure 23. Retrosynthetic analysis of dictyostatin by Paterson.

The common precursor **7-5** has been converted to alkyl iodide **7-6** in three simple steps, which then was used for Myers alkylation[102] (**Scheme 70**). Reductive auxiliary cleavage and oxidation afforded aldehyde **7-9**.



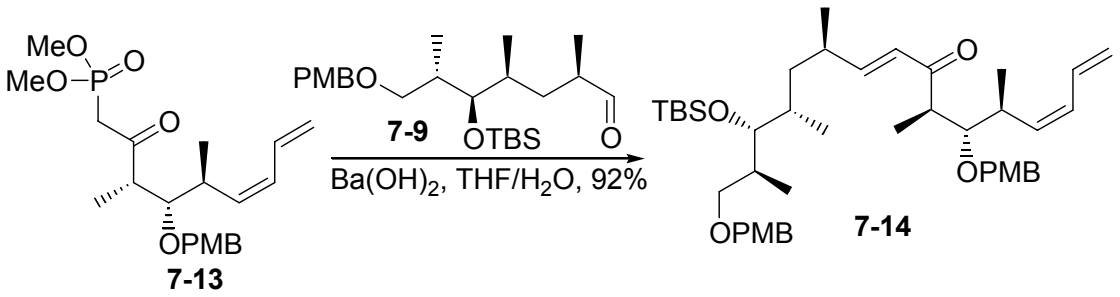
Scheme 70. Synthesis of the left-hand (C11-C17) fragment **7-9**.

The right-hand building block **7-13** was prepared from the same starting material **7-5**, in which the reactivity site was "turned around" by selective protection of the primary alcohol as TBS ether, oxidative PMP acetal formation followed by selective acetal opening with DIBAL-H (**Scheme 71**). Oxidation to the aldehyde followed by Nozaki-Hiyama-Kishi reaction with bromallyltrimethyl silane resulted in stereoselective formation of *anti*-hydroxy silane, which upon treatment with potassium hydride underwent *Z*-selective Peterson elimination leading to installation of terminal *Z*-diene unit C24-C26.



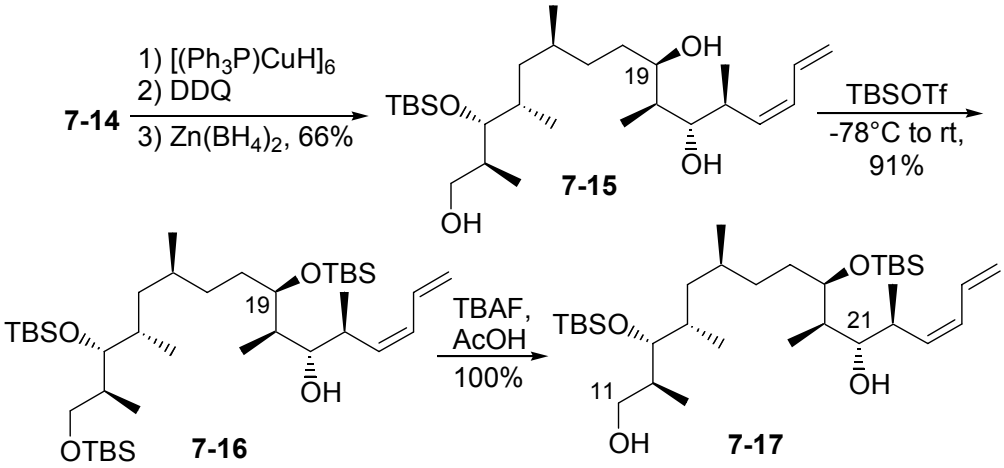
Scheme 71. Synthesis of the right-hand (C18-C26) part **7-13**.

From aldehyde **7-12** by addition of metallated dimethyl methylphosphonate and oxidation of the secondary alcohol the ketophosphonate **7-13** was made. The two fragments were then joined by HWE reaction using barium hydroxide as a base (**Scheme 72**).



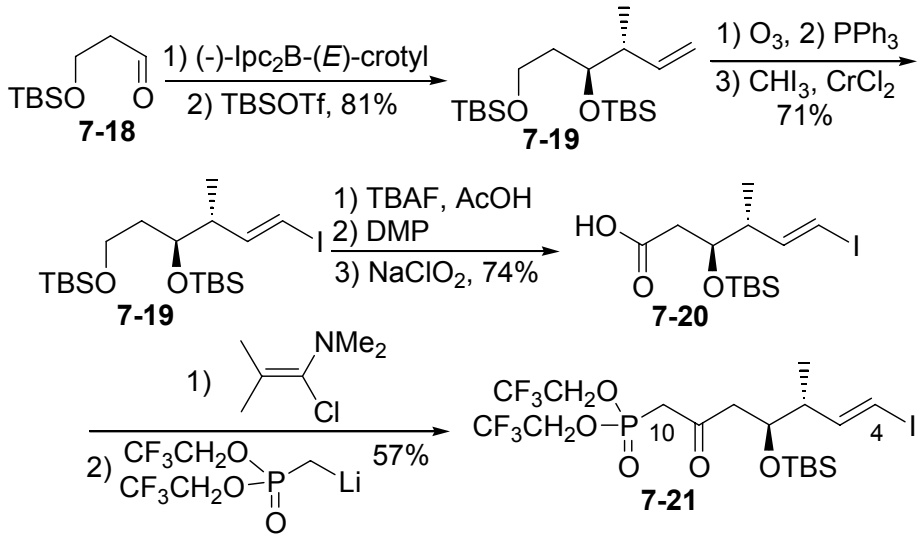
Scheme 72. Synthesis of top (C11-C26) fragment **7-14**.

Conjugate reduction of the α,β-unsaturated ketone **7-14** with the Stryker hydride[103] and nonselective deprotection of the two PMB groups led to a ketodiol, on which a *syn*-selective reduction was executed with zinc borohydride (**Scheme 73**). The following protection group manipulations include selective silylation of the primary and C19 hydroxyl functions, whereas due to sterical hindrance the alcohol at C21 remained free. Selective deprotection of the primary alcohol was then accomplished with a TBAF-acetic acid mixture leading to intermediate **7-17**.



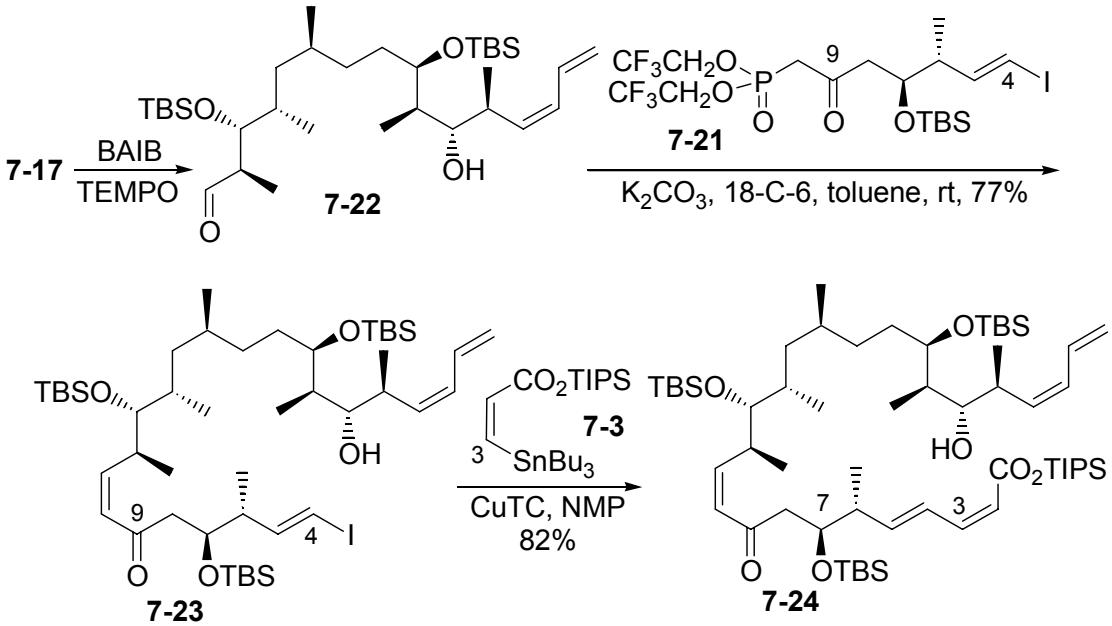
Scheme 73. Selective *syn*-reduction and protection at C19.

The synthesis of the bottom fragment was started from monoprotected 1,3-propanediol. Brown crotylboration with (-)-Ipc_2B-(*E*)-crotyl served to establish the *anti*-stereochemistry at C6,C7 (**Scheme 74**). Oxidative cleavage of the double bond followed by a Takai reaction[104] gave rise to *E*-vinyl iodide **7-19**. Selective deprotection of primary alcohol allowed oxidation to acid **7-20**. Via the corresponding acid chloride, **7-20** was converted to the Still-Gennari type phosphonate **7-21**.



Scheme 74. Synthesis of bottom (C4-C10) fragment.

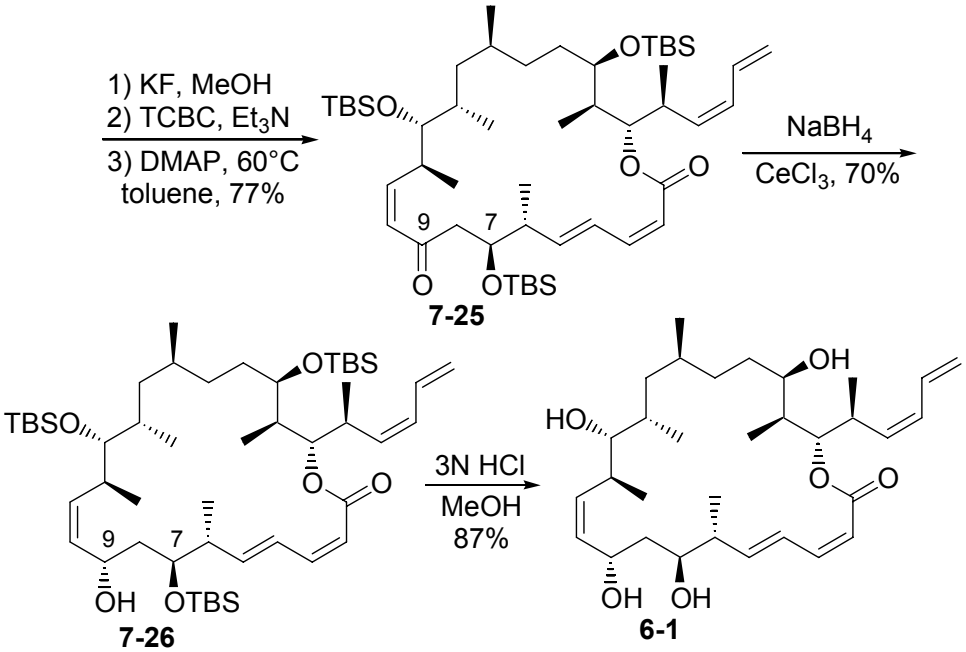
The top and bottom parts were then coupled by a Still-Gennari[105] modified HWE reaction in presence of dibenzo-18-crown-6 which gave a 7:1 *E*/*Z* ratio of enone **7-23** (**Scheme 75**). A subsequent Liebeskind-type cross-coupling with Z-tributyltinacrylate provided the complete carbon backbone of dictyostatin.



Scheme 75. Bottom fragment attachment and completing of carbon backbone of dictyostatin (CuTC = copper(I)-thiophene-2-carboxylate).

Deprotection of the carboxylic acid with KF in methanol followed by Yamaguchi macrolactonization afforded cyclic enone **7-25**, on which reduction under Luche[106] conditions proceeded preferentially from the exocyclic side and delivered the desired 7,9-*anti*-diol **7-26**

(**Scheme 76**). Global deprotection with HF-pyridine complex led to completion of the dictyostatin synthesis.



Scheme 76. End-play of the Paterson synthesis.

The Curran approach has some similarity to the one described above regarding strategy and tactics (**Figure 24**)[107]. One can note the identical use of a Myers alkylation for elongation and installation of the stereochemistry at C16. Furthermore a HWE to couple fragments of the upper part and the use of a common starting building block are similar.

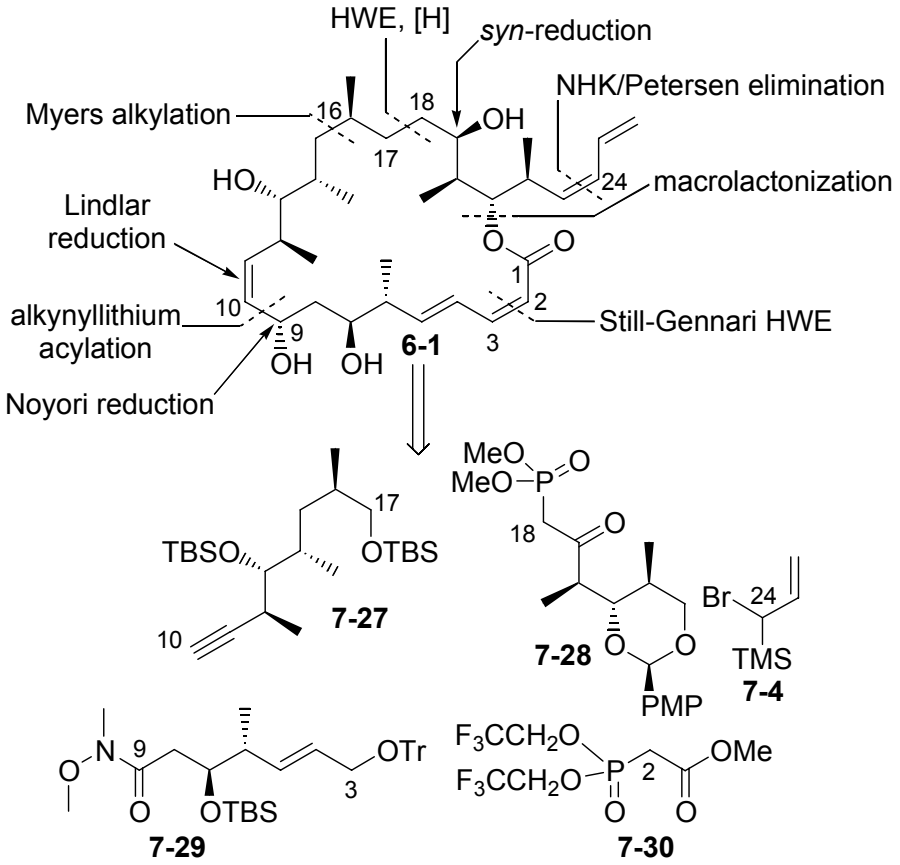
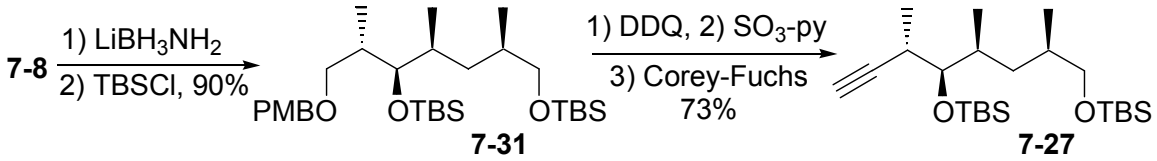


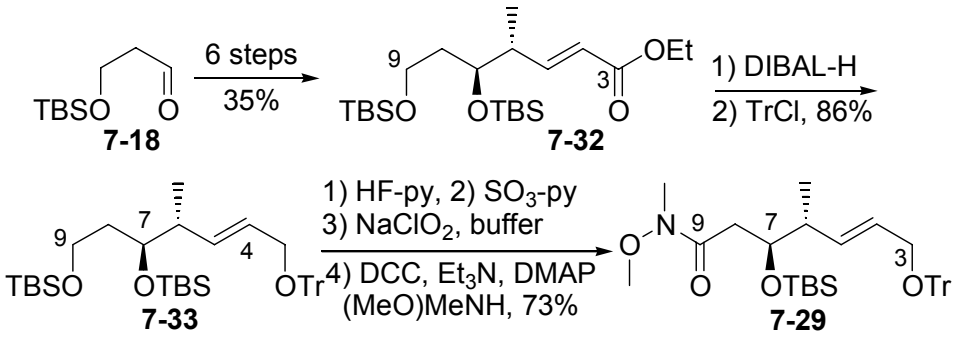
Figure 24. Retrosynthetic analysis of dictyostatin by Curran.

Here again, starting from discodermolide common precursor **7-5**, phosphonate **7-28** was prepared by the following steps: formation of PMP acetal, oxidation to carboxylic acid, Weinreb amide synthesis and reaction with metallated dimethyl methyl phosphonate. The C10-C17 segment was composed via Myers alkylation, reductive auxiliary cleavage, protecting group manipulation and Corey-Fuchs alkyne synthesis.



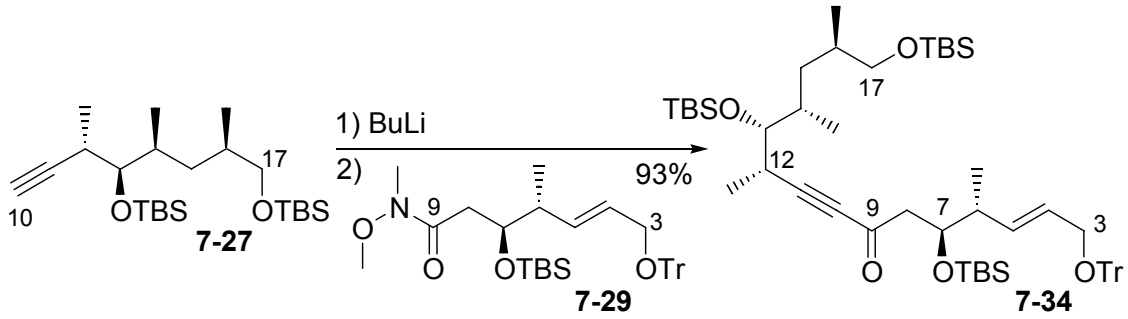
Scheme 77. Synthesis of C10-C17 segment.

The preparation of α,β-unsaturated ester **7-32** was done according to an earlier reported procedure[108]. Reduction to the allylic alcohol and orthogonal protection of this site as trityl ether, followed by oxidation on the other side to carboxylic acid and Weinreb amide formation gave rise to C9-C3 fragment **7-29** (**Scheme 78**).



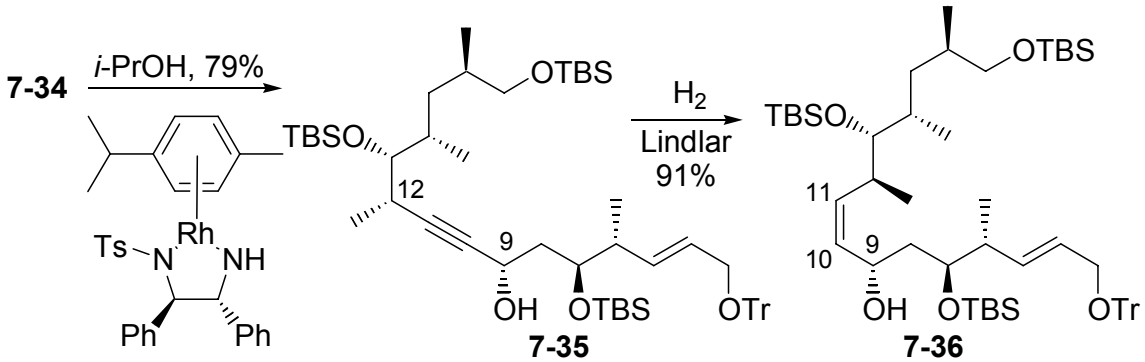
Scheme 78. Synthesis of C9-C3 segment.

Acylation of alkynyl lithium derivative of **7-27** with Weinreb amide **7-29** went with exceptionally high yield, thus allowing efficient combination of the right and bottom fragments (**Scheme 79**).



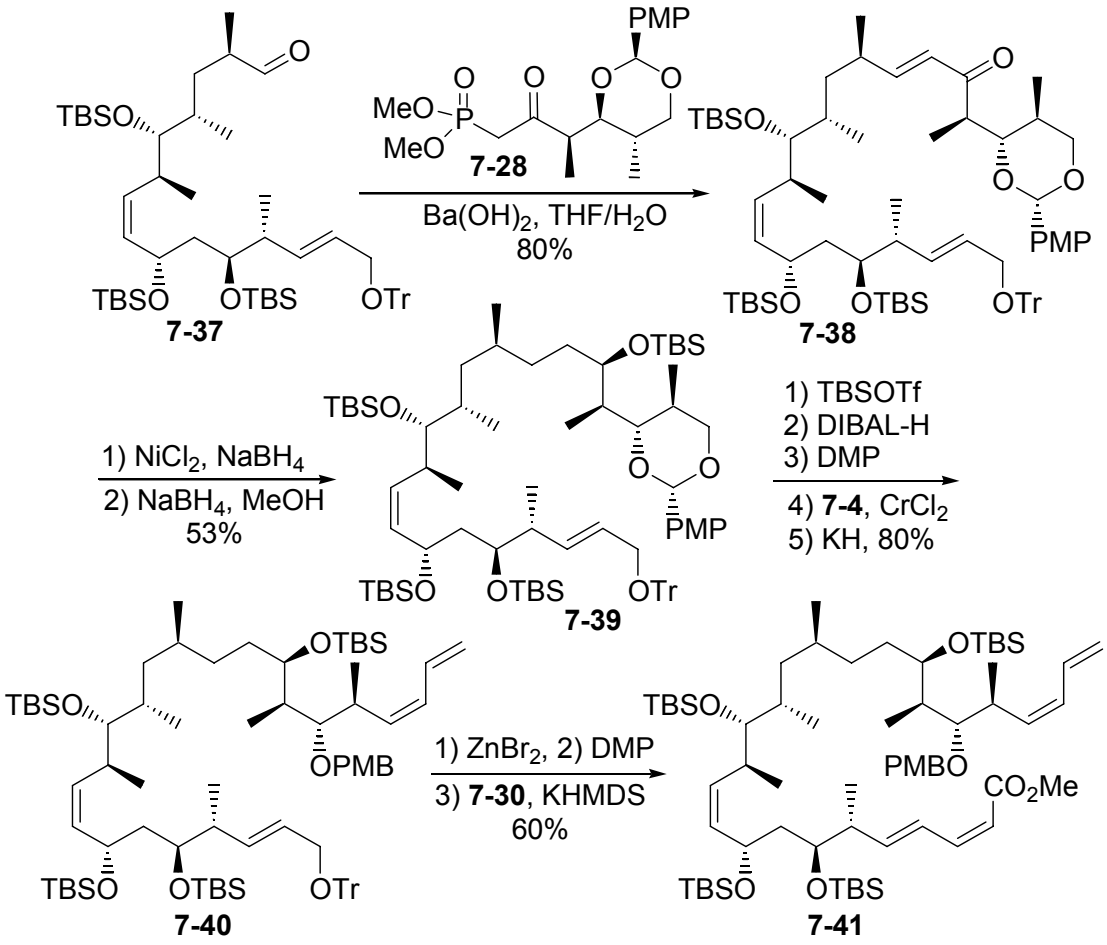
Scheme 79. Fragment assembly by addition of alkynyl lithium to Weinreb amide **7-29**.

Noyori transfer hydrogenation[109] of alkynyl ketone **7-34** provided the correct stereochemistry at C9 and hydrogenation of the triple bond on Lindlar catalyst served to establish the C10-C11 Z-double bond in the intermediate **7-36** (**Scheme 80**).



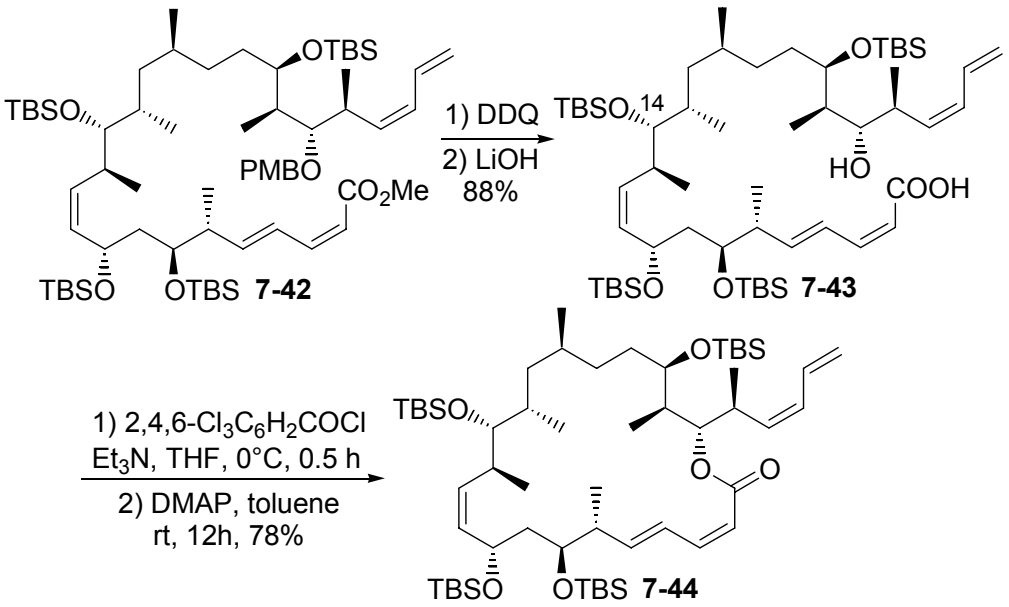
Scheme 80. Noyori and Lindlar hydrogenations.

After deprotection of the primary TBS ether and oxidation, the resulting aldehyde **7-37** was coupled to the right-hand fragment **7-28** by HWE reaction (**Scheme 81**). Sequential reduction of the resulting enone **7-38** to ketone in presence of nickel boride and non-selective reduction of the keto function to a *syn*-diol was followed by installation of the terminal diene unit as previously described.



Scheme 81. Attachment of the third fragment and installation of dienoate fragment.

Removal of the trityl group, oxidation and Still-Gennary olefination completed the carbon backbone of the molecule. Oxidative removal of the PMB group was followed by ester saponification to produce seco acid **7-43**, which was subjected to Yamaguchi macrolactonization giving fully protected dictyostatin (**Scheme 82**).



Scheme 82. Seco-acid synthesis and macrolactonization.

Notably, Curran observed isomerization of C1-C2 dienoate double bond under Yamaguchi conditions for 14-epi-dictyostatin but not for dictyostatin itself[110].

7.2.2 Synthesis by Phillips

Somewhat different tactics were used in the total synthesis of dictyostatin developed by the Phillips group[111], showcasing their invented silyloxy-enyne cyclization[112] for installation of two stereocenters at C12 and C22 (**Figure 25**). Although the strategic bond disconnection is somewhat similar to previous syntheses, one should note application of the RCM reaction and intramolecular Still-Gennari olefination for the establishing of C10,C11 and C1,C2 *Z*-double bonds respectively.

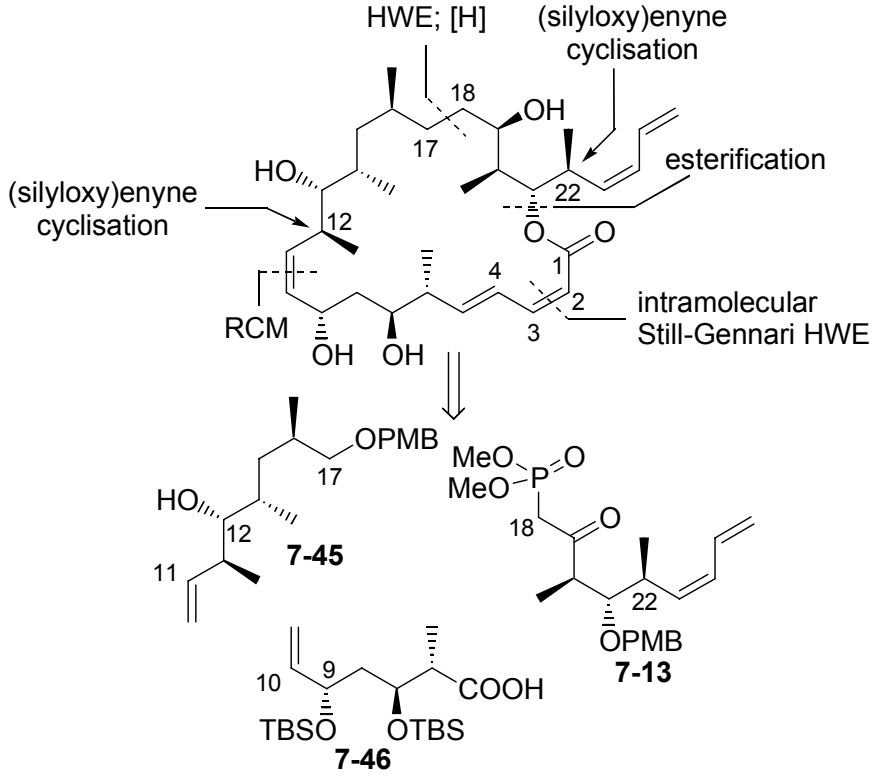
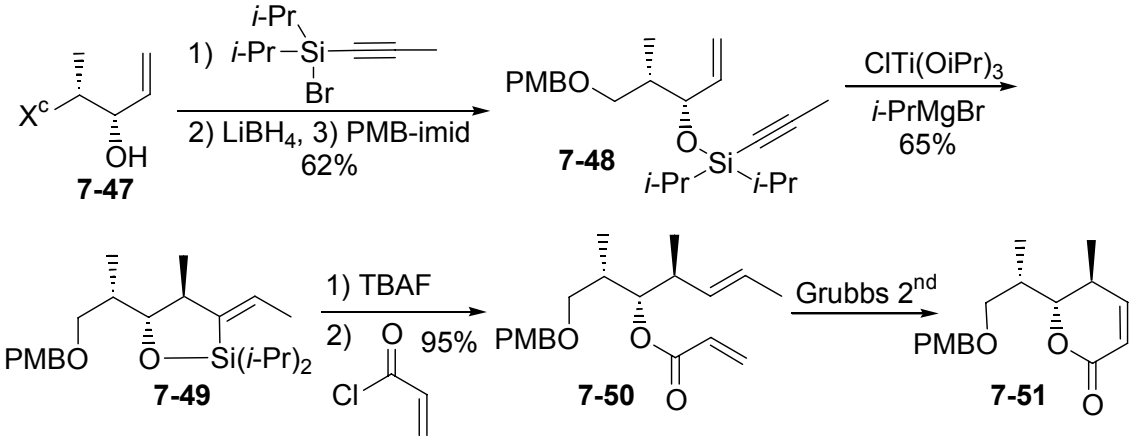


Figure 25. Retrosynthetic analysis of dictyostatin by Phillips.

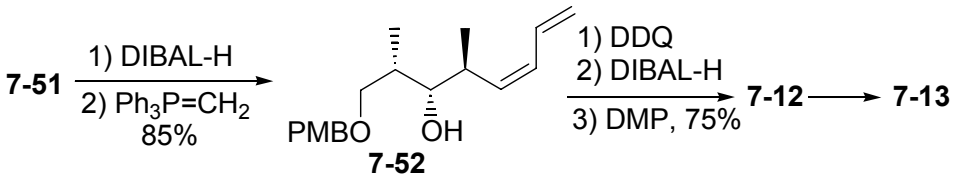
The Evans aldol adduct with acrolein was treated with (ethynyl)diisopropylbromosilane, leading to the corresponding silyl ether (**Scheme 83**). This transformation serves not only to control the stereochemistry during the following steps, but also as protection group. The subsequent auxiliary cleavage and protection of the primary alcohol gave intermediate **7-48**, which upon treatment with low-valent titanium species underwent stereoselective cyclization, giving after hydrolysis compound **7-49**.



Scheme 83. Synthesis of the C18-C23 stereotriad by silyloxyenyne cyclization.

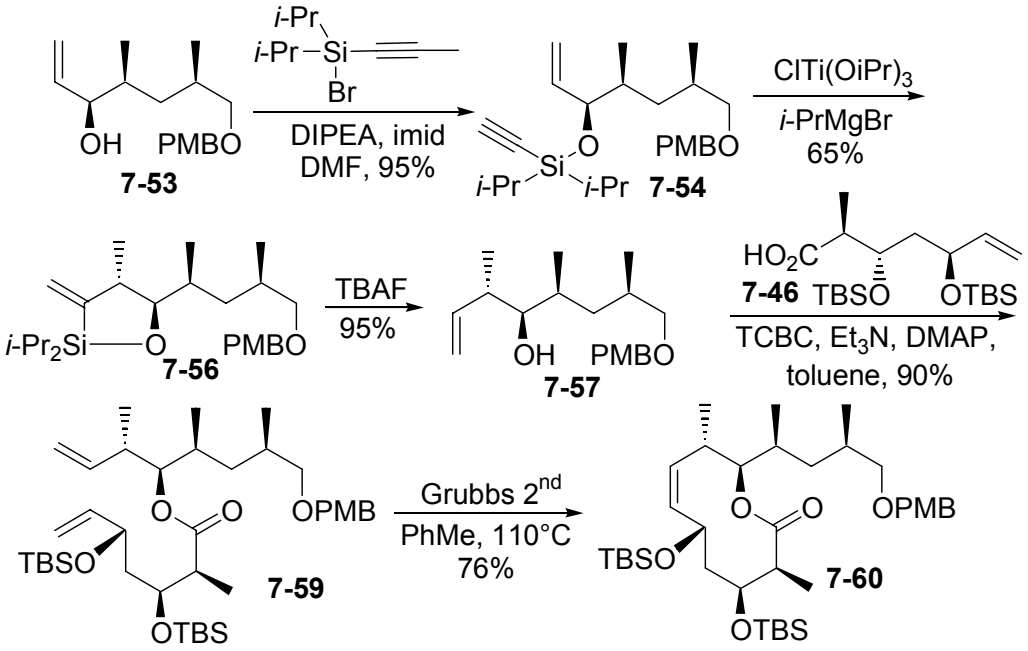
After removal of the silicon residue the resulting alcohol was acylated with acryloyl chloride and subjected to a RCM reaction. Without isolation, the unsaturated lactone was opened with

DIBAL-H to an aldehyde which was immediately trapped with triphenyl methylenephosphorane. By this way the terminal *Z*-diene fragment was secured in excellent yield.



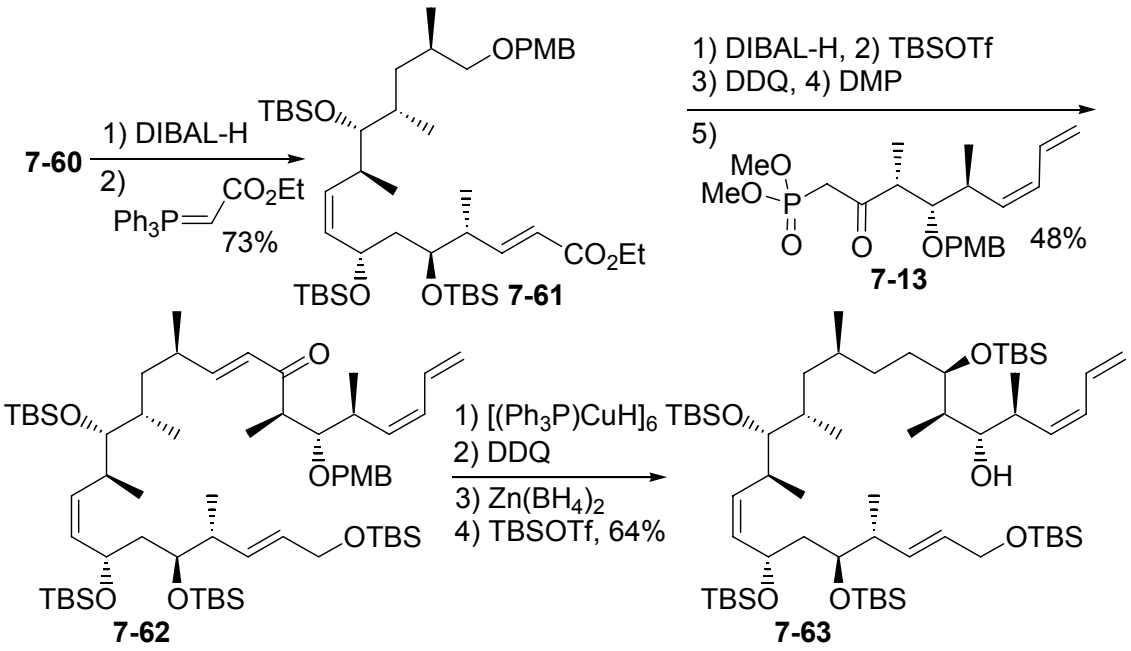
Scheme 84. Synthesis of C18-C26 fragment.

By classical protecting group manipulation the PMB ether was transposed to the internal hydroxyl group and methyl phosphonate has been installed like in the Paterson synthesis. The intermediate **7-53** was prepared in 8 steps from the Roche ester via reduction, Myers alkylation, Wittig reaction, Sharpless asymmetric epoxidation, and epoxide opening. After esterification with acid **7-46** (**Scheme 85**) containing a terminal double bond a RCM reaction was executed leading to formation of the *Z*-macrolactone **7-60** exclusively.



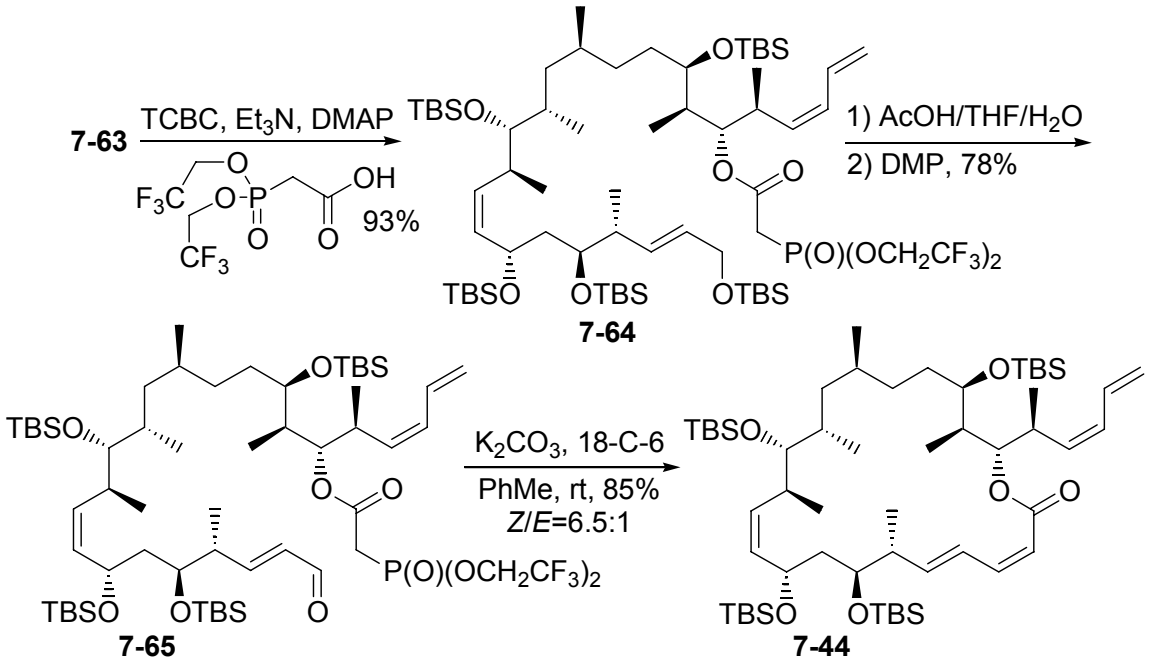
Scheme 85. Synthesis of C5-C17 fragment via silyloxyenyn cyclization and RCM.

The next steps from **7-60** are very similar to those of the Curran synthesis (**Scheme 86**). The earlier described HWE reaction, Stryker hydride and zinc borohydride reductions served to convert enone to the *syn*-diol **7-63**.



Scheme 86. Fragment combination and *syn*-reduction.

Formation of the macrocyclic ring was done by intramolecular Still-Gennari HWE reaction, affording the desired Z-alkene with 6.5:1 selectivity (**Scheme 87**).



Scheme 87. Synthesis of macrolactone **7-44** by intramolecular Still-Gennari HWE reaction.

7.2.3 Synthesis by Ramachandran

The most recent published total synthesis of dictyostatin has been done by the Ramachandran group[113]. Known for their extensive research in the area of asymmetric reactions with boron

compounds, this approach relies heavily on the enantioselective crotylboration for stereotriad synthesis. Retrosynthetic bond disconnections were done similarly to previous cases, namely at the macrolactone ring, and between carbons C9,C10 and C17,C18 (**Figure 26**).

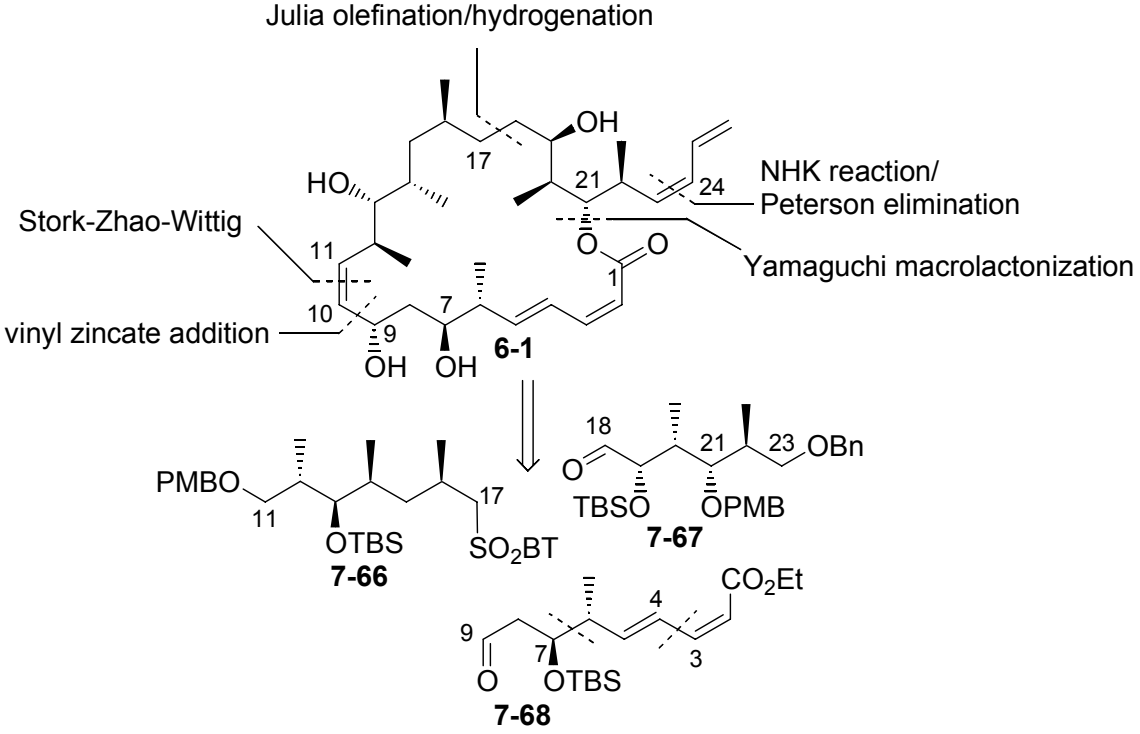
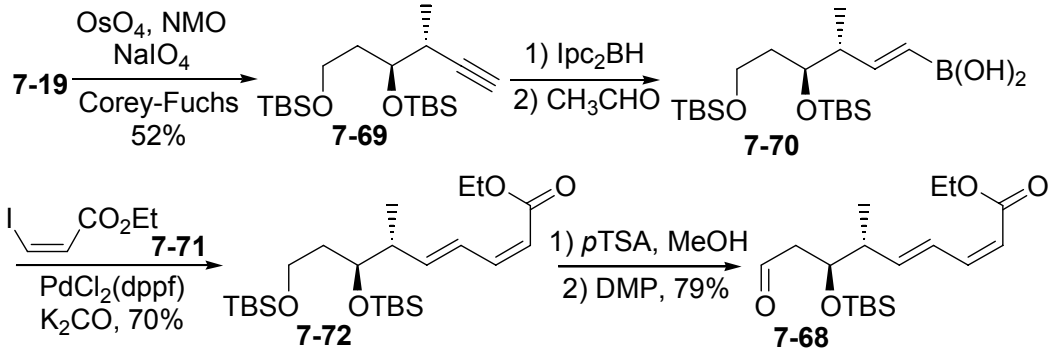


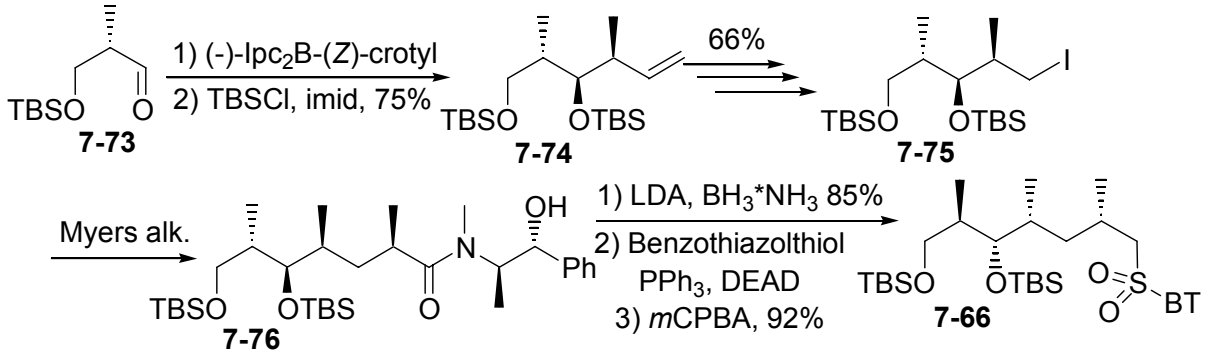
Figure 26. Retrosynthetic analysis of dictyostatin by Ramachandran.

The synthesis of the lower part starts almost exactly as the Paterson one, where asymmetric crotylboration of protected β-hydroxypropanal delivers the *anti* stereochemistry at C6,C7 (**Scheme 88**). Then, instead of a Takai reaction, a sequence of Corey-Fuchs[114] alkyne formation and hydroboration was executed to generate a reactive synthon for installation of the dienoate moiety. A subsequent Suzuki crosscoupling with ethyl 3-*Z*-iodoacrylate furnished the desired fragment **7-68**.



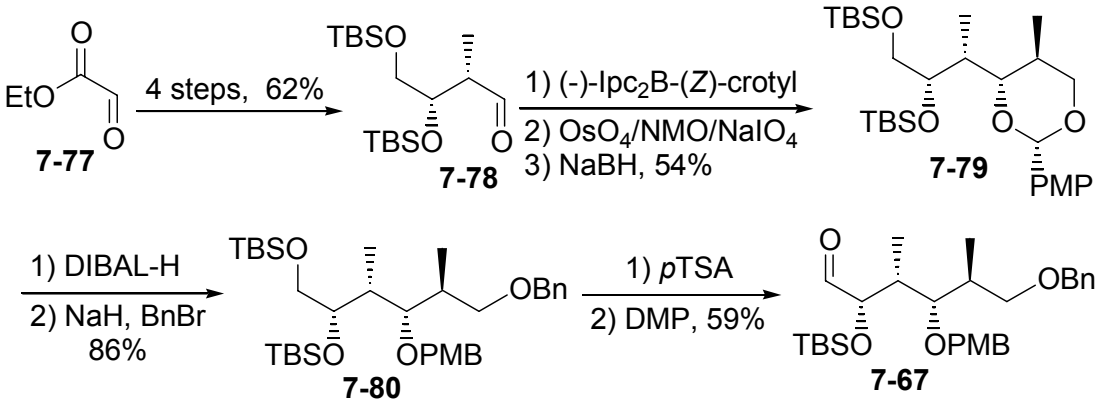
Scheme 88. Synthesis of bottom fragment **7-68** by Brown crotylboration/crosscoupling reaction.

The upper left-hand part of the molecule was prepared from a derivative of the Roshe ester via crotyl boration (**Scheme 89**). After a standard sequence of dihydroxylation/periodate cleavage, the resulting aldehyde was reduced and converted to alkyl iodide **7-75**. Here again, the Myers alkylation was employed to create the stereocenter at C16.



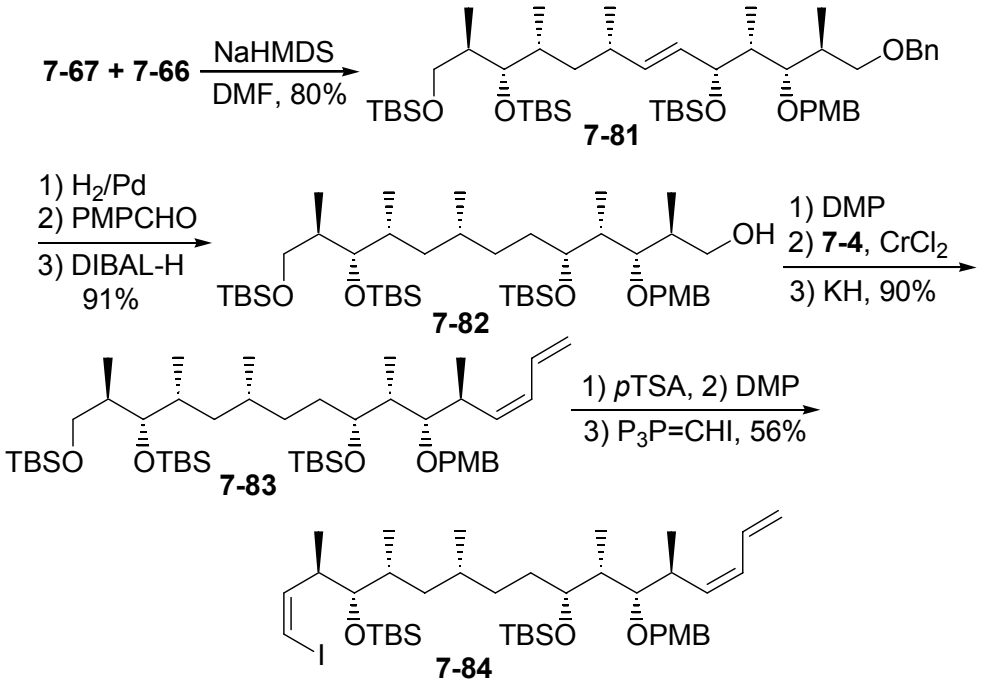
Scheme 89. Synthesis of the left–hand part (C11-C17) of the top fragment.

After reductive auxiliary cleavage, the primary alcohol was subjected to a Mitsunobu reaction with benzothiazol-2-thiol to give after oxidation the required sulfone (**Scheme 90**).



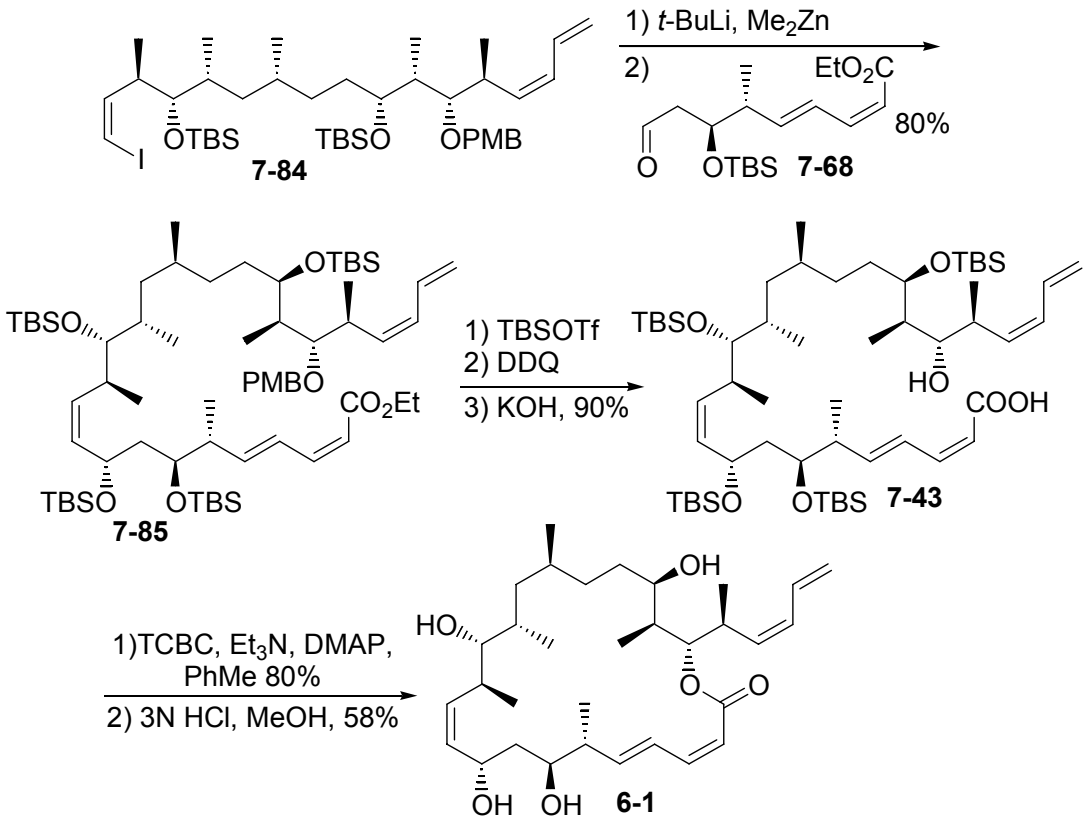
Scheme 90. Synthesis of right–hand part (C18-C23) of top fragment.

The left-hand and right-hand parts of the top fragment were coupled by the Kocienski variant of the Julia olefination[115] (**Scheme 91**). One should note the "inverted" polarity of reagents for this reaction in comparison to the HWE used in the Paterson and Curran syntheses. The hydrogenation of the double bond went simultaneously with deprotection of the both benzyl ethers. The resulting diol was converted to the PMP acetal, which was then opened at the terminal position. The installation of the diene unit was done as described earlier. Deprotection of the TBS ether on the other side followed by oxidation and Stork-Zhao[116] olefination provided *Z*-vinyl iodide **7-84**.



Scheme 91. Installation of terminal diene unit and of *Z*-vinyl iodide on the top fragment.

The assembly of the two fragments C1-C9 and C10-C26 was done by addition of vinyl zincate derived from **7-84** to aldehyde **7-68** (**Scheme 92**). Completion of the synthesis was trivial and consists of oxidative deprotection of PMB ether, ester saponification, Yamaguchi macrolactonization under Curran's conditions and global deprotection.



Scheme 92. Fragment assembly and completion of the synthesis.

7.3 Overview of the key reactions used

Due to the complexity of the target molecule one would need a broad spectrum of synthetic tools to successfully accomplish the synthesis. Therefore, an overview of the most important reactions used for our dictyostatin synthesis is provided below. Because of limited space of this work for each reaction only the general information and relevant references are given.

7.3.1 Evans aldol reaction

One of the most frequently appearing fragment in many natural products, especially in polyketides, is the sequence of alternating methyl and hydroxyl groups along the carbon backbone[117]. Depending on the length these blocks are usually called stereotriad, stereotetrad, or stereopentad. According to thr relative configuration of vicinal methyl and hydroxyl groups they can be classified as *syn* or *anti*. The most straightforward approach for construction of stereotriads is the aldol reaction. In general, *E*-enolates of ketones or ester derivatives produce *anti* aldol products and *Z*-enolates produce *syn* aldol reactions according to a chair-like transition state (**Figure 27**) proposed by Zimmerman, well known as Zimmerman-Traxler model[118].

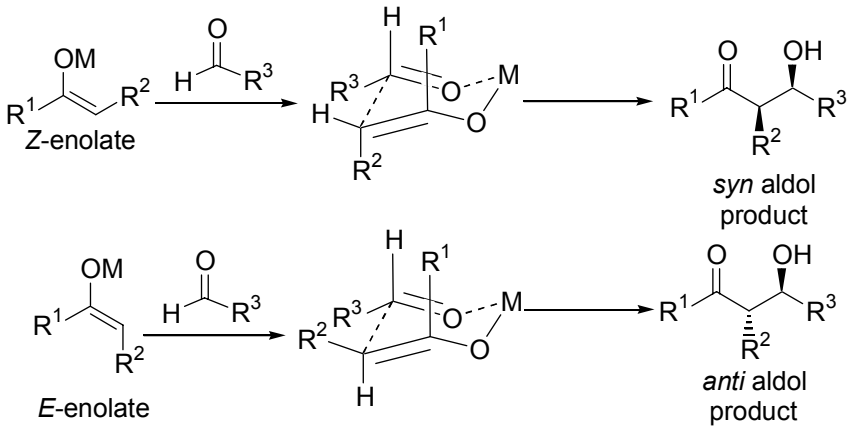


Figure 27. Zimmerman-Traxler transition states for *E*- and *Z*-enolates.

To perform this reaction in enantioselective fashion one should introduce a source of chirality either in the enolate or aldehyde. In 1981 Evans published a seminal paper[119] devoted to the application of N-acylated oxazolidinones as chiral auxiliaries for diastereoselective *syn* aldol reactions (**Figure 28**). As an imide, the acylated oxazolidinone can produce only the *Z*-enolate upon treatment with dibutylboron triflate and a tertiary amine. Due to the relatively short bond between oxygen and boron a rather tight six-membered chair like transition state leads to preferential formation of one *syn* adduct.

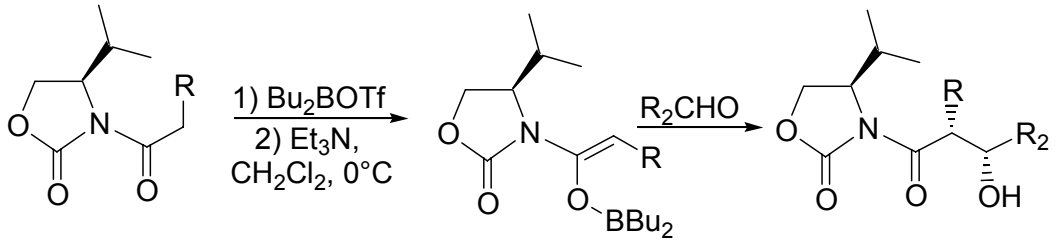


Figure 28. Evans aldol reaction.

The observed diastereoselectivity arises from blockage of one side of the enolate by the bulky group in the oxazolidinone ring (**Figure 29**). In the reaction transition state, the carbonyl group of the oxazolidinone and the C-O bond of enolate arrange in an *anti* fashion to each other in order to minimize dipole-dipole repulsions. Such an arrangement allows approach of the aldehyde to the enolate only from the less hindered side of the chiral auxiliary.

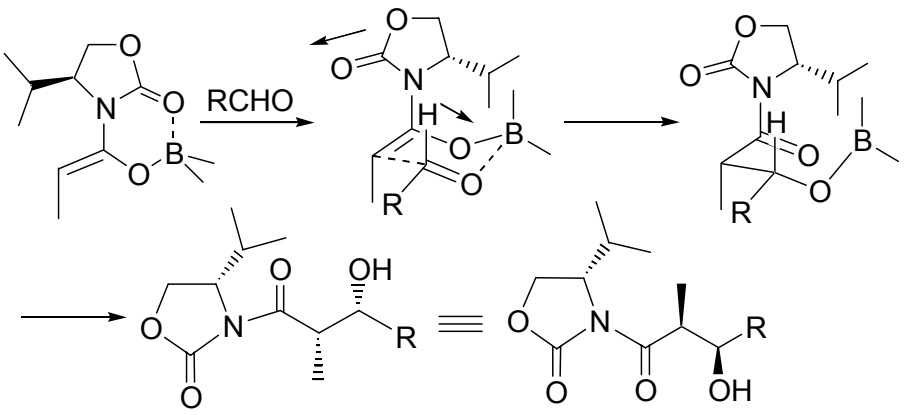


Figure 29. Transition state for Evans aldol reaction.

The reaction turned out to be exceptionally reagent controlled, providing diastereomeric ratios up to 1:600 for matched cases and no less then 1:20 in mismatched cases with aldehydes bearing a stereogenic center at the α-position. This methodology was used in uncountable number of natural product syntheses, firstly by Evans himself and later by other groups working in the same field. One can mention total syntheses of the macrolide antibiotics cytovaricin,[120] ionomycin,[121] and macbecin[122] as showcase examples. Due to its fundamental meaning the reaction became a topic in some general organic chemistry textbooks.

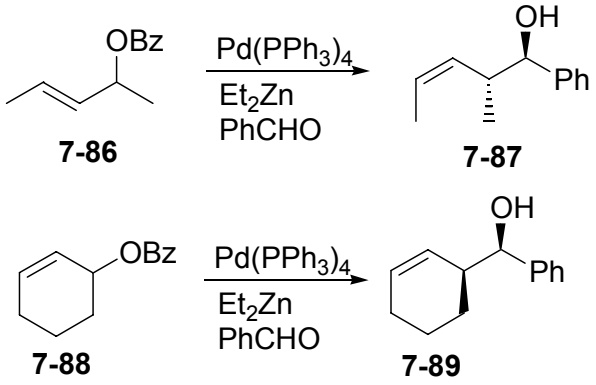
Since the original publications, some other similar reactions were developed. Recently, Crimmins and coworkers published a detailed account of their work in asymmetric aldol additions employing titanium(IV) enolates of *N*-acyloxazolidinones, *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones[123]. The work of Nagao showed that not only propionate, but also enantioselective acetate aldol reactions could be successfully achieved with relaed auxiliaries[124].

7.3.2 Addition of chiral allenylzincates to aldehydes

Contrary to the *syn*-aldol reaction described in the previous paragraph, creation of the *anti* orientated methyl and hydroxyl group represents some difficulties. One reason for this is that esters which can be converted to *E*-enolates generally induce low facial selectivity with most chiral auxiliaries. Therefore, other options like Frater alkylation, opening of Sharples epoxides, or Brown asymmetric crotylboration are frequently used.

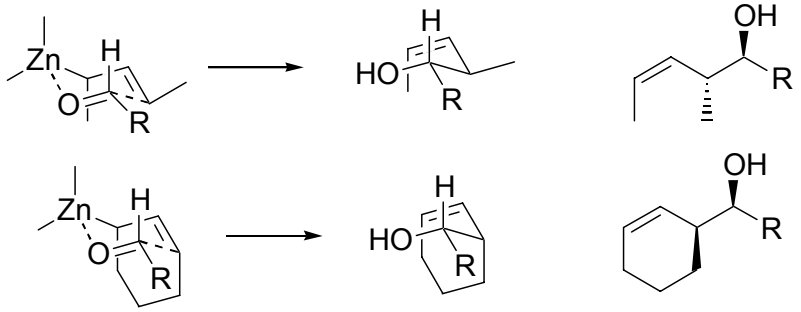
The recently developed Abiko aldol reaction partially solves this problem, but requires preparation of special reagents such as dicyclohexylboronyl triflate and an ephedrine based chiral auxiliary with a molecular weight of 548. Thus, the development of other methods for

installation of the *anti*-stereochemistry was undertaken by various groups. One particularly interesting example is the reaction of allenylzinc compounds with aldehydes. As originally was discovered by Tamaru[125] and coworkers, palladium(0) catalyzed metallation of allylic benzoates with diethyl zinc followed by reaction with an aldehyde proceeds in a highly stereoselective manner providing *anti*-addition products (**Scheme 93**).



Scheme 93. Addition of allylzincates to aldehydes.

The stereochemical outcome of this reaction could be easily rationalized by comparing the corresponding transition states (**Scheme 94**). In case of 1,3-disubstituted allylic zincates the most favorable conformation features an equatorial orientation of the substituent at the double bond terminus and an axial orientation at the zinc side. Because the aldehyde residue also occupies an equatorial position in the six-membered transition state, the reaction gives the *Z-anti*-product. Contrary to that, cyclohexenyl zincates are locked in a double-axial conformation, thus leading to *Z-syn*-adducts exclusively.



Scheme 94. Transition state for allylzincates addition.

This method however drew little attention and found limited use in organic synthesis. Some time later the Marshall group reported a highly stereo- and enantioselective addition of allenylzinc species to aldehydes[126] (**Figure 30**). After thorough investigation of this reaction they identified as best leaving group a mesylate, and found optimal reaction conditions, such as temperature, concentration, amount of diethyl zinc, and catalyst.

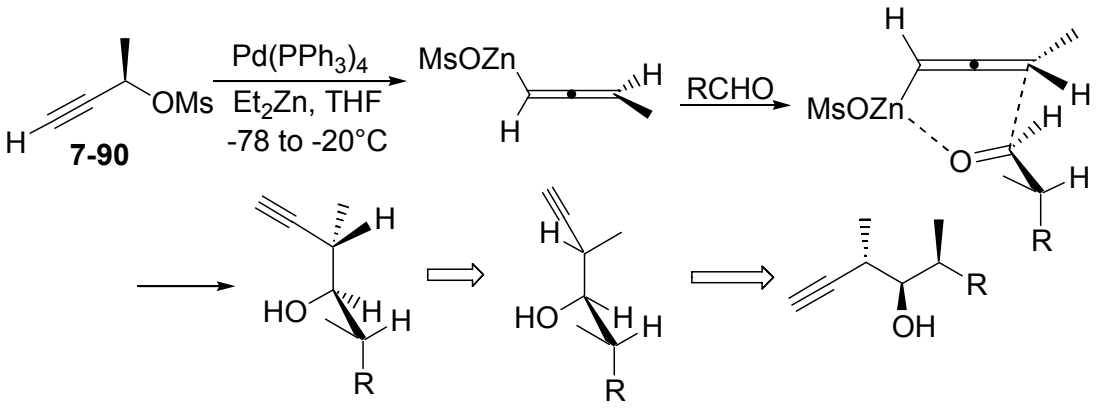


Figure 30. Transition state for Marshall allenyl zincate addition.

The reaction proceeds via a distorted six-membered transition state, thus minimizing sterical interaction between equatorial substituents. For the formation of the reactive species, namely chiral allenylzincates, the following catalytic cycle was proposed (**Figure 31**). The S_N2' reaction of the mesylate with the palladium catalyst leads to the allenylpalladium intermediate **A** which undergoes a transmetallation reaction with diethylzinc to give the allenylzincate **B**.

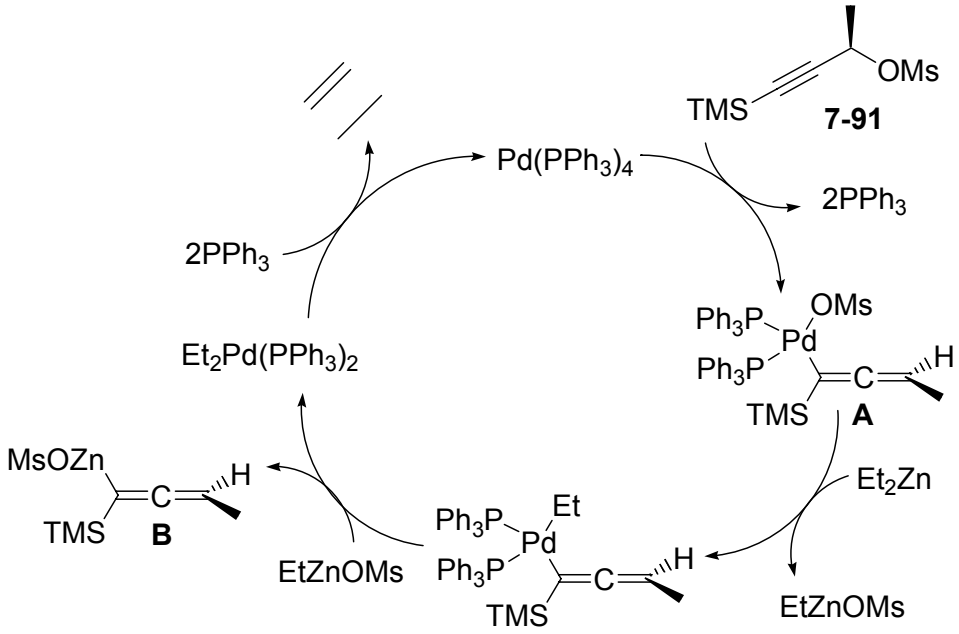
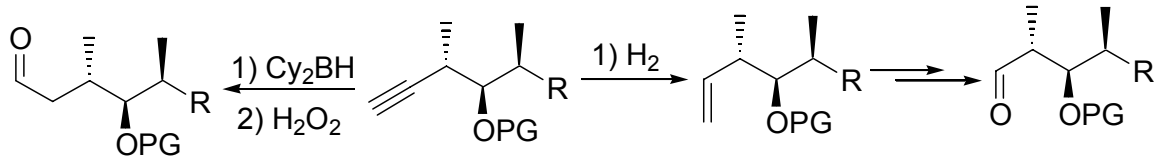


Figure 31. Catalytic cycle for Marshall reaction.

Instead of diethylzinc other electron donors, such as indium metal or indium (I) iodide could be successfully employed[127]. The reaction is highly reagent controlled, though some decrease in the diastereomeric ratio is observed for mismatched cases. The addition of allenyl zincates was extensively used by the Marshall group in the total synthesis of natural products such as zincosporin[128], (-)-callistatin A[129], leptofuranin D[130], discodermolide[131] and others.

Although the described reaction delivers products with a triple bond instead of a carboxylic function as in aldol reaction, this can be easily changed by simple chemical transformation (**Scheme 94**). Catalytic hydrogenation followed by either ozonolysis or dihydroxylation/periodate cleavage affords the corresponding aldehyde, whereas hydroboration with dicyclohexylborane and treatment with basic hydrogen peroxide solution leads to the homoaldehyde[132].



Scheme 94. Possible further transformations of triple bond.

At the same time, the triple bond itself is a valuable nucleophilic synthon and can be used for further transformations, e.g. addition to aldehydes, alkylation[133], epoxide opening, cross-coupling, etc.

7.3.3 *Syn*-reduction of β-hydroxyketones

As was shown in previous paragraphs reagent controlled addition to aldehydes is the most common approach to stereotriad fragments. These methods are usually quite reliable. However, equimolar amounts of chiral auxiliaries and Lewis acid are required. Thus, studies were undertaken for shortening and simplification of stereotriad synthesis. One possible way is to use a stereocenter already existing in the molecule as a chirality source and to create another one via internal asymmetric induction. For example, reactions of boron enolates of ketones bearing a chirality center can proceed in a highly diastereselective manner and create two new stereocenters. Another option is the asymmetric reduction of β-hydroxyketones, which can be done both *syn*- and *anti*-selective. If a hydroxyl function is located at the β-position to the carbonyl group, then so called 1,3-asymmetric induction can occur. The exact stereochemical outcome depends strongly whether intra- or intermolecular hydride delivery takes place.

Most of the *syn*-reduction methods rely on chelating coordination of the hydroxyl and carbonyl functions by means of a hard Lewis acid, e.g. metal cation (**Figure 32**). For this purpose Al, Zn, and B are the metals of choice, due to their small ionic radius and high affinity to oxygen.

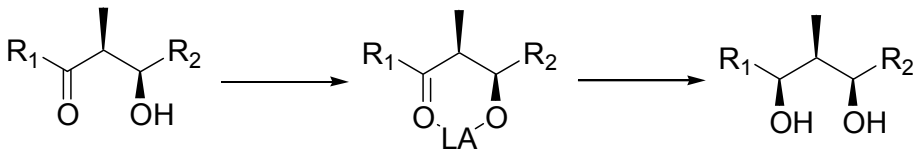


Figure 32. General principle of *syn*-selective reductions of the β-hydroxyketones.

At the beginning, the Lewis acid forms a covalent bond with the oxygen atom of the hydroxyl group, and then the six-membered chelate is attacked by an external hydride according to Fürst-Plattner rule (**Figure 33**). In the depicted chelate this occurs from the top. In this case, the carbon atom of the carbonyl moves upwards towards the nucleophile, leading to a chair-like transition state and product. Conversely, attack from the bottom leads to a highly strained "twist boat"-like conformation.

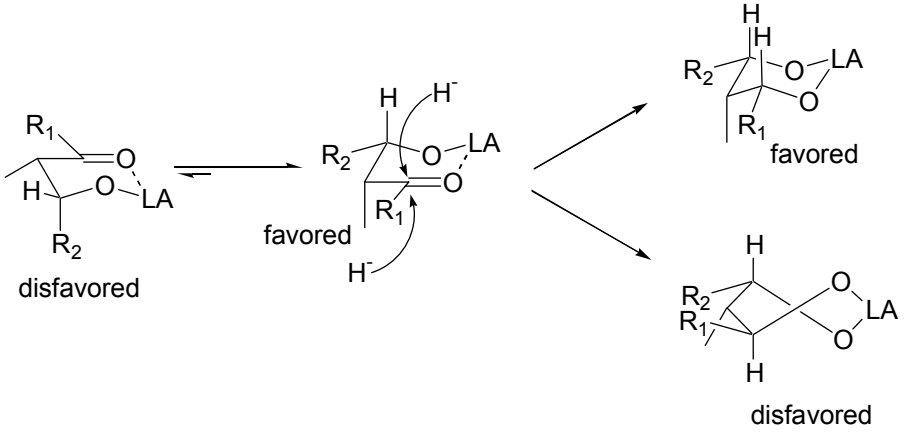


Figure 33. Transition state and mode of attack for *syn*-selective reduction.

Among all possible combinations, three methods were found to be synthetically useful. The first one, the so called Narasaka[134]-Prasad[135] reduction is based on treatment of the hydroxyketone with methoxydiethylborane to form the chelate, followed by addition of sodium borohydride as reducing agent (**Figure 34**).

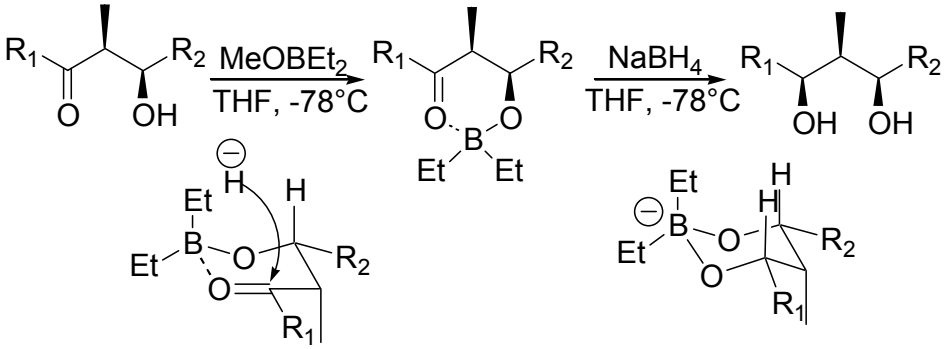
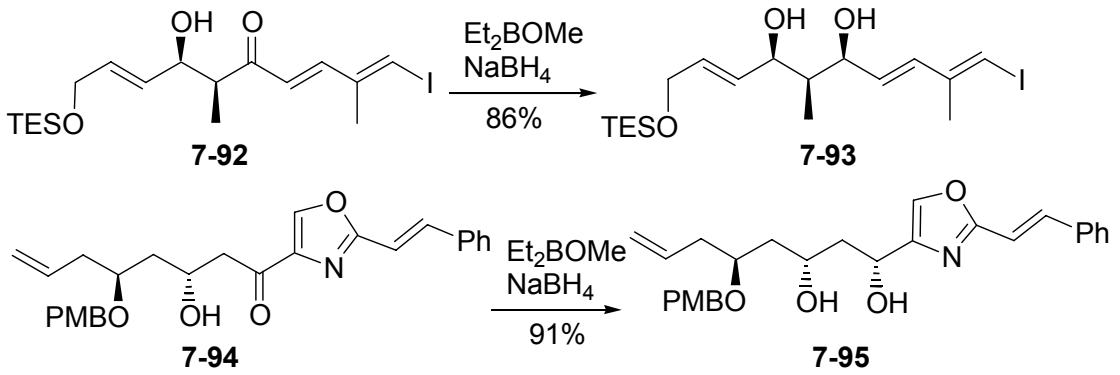


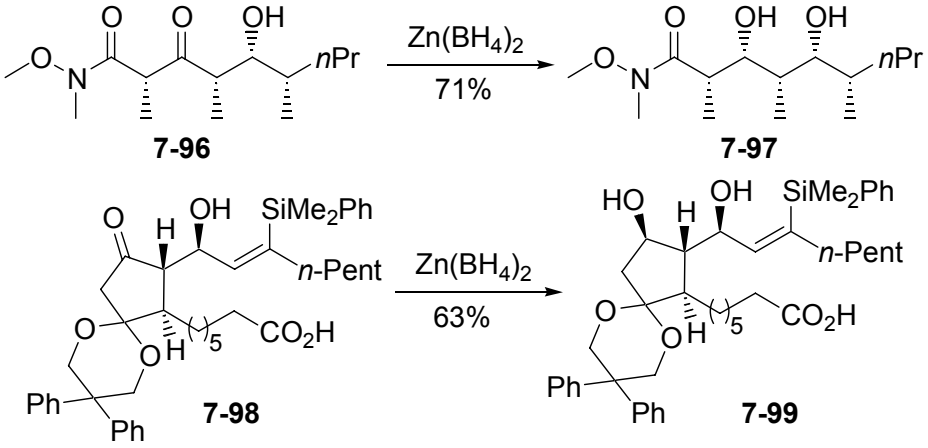
Figure 34. Mechanism of the Narasaka-Prasad reduction.

This method was used in a number of natural product syntheses such as roxaticin[136], (-)-FR182877[137], hennoxazole A[138] (**Scheme 95**), and apicularen[139].



Scheme 95. Applications of the Narasaka-Prasad method.

The second method employs zinc borohydride for both coordination and reduction. This particular procedure was already used in published dictyostatin syntheses. Although it is advantageous to use only one reagent, the preparation of commercially not available zinc borohydride is complicated and requires several filtrations under argon. The maximum attained concentration of the reagent is only 0.16 M in ether so a large volume of solution should be stored. This method was used in a number of natural products syntheses, e.g. oasomycin A[140], oleandolide[141], siphonarienal[142], and (-)-prostaglandin E_1[143] (**Scheme 96**).



Scheme 96. Applications of zinc borohydride reduction.

Similarly, the third method developed by Kiyooka[144] and coworkers, employs as Lewis acid diisobutylaluminium hydride, which also works as hydride source (**Figure 35**). This protocol is experimentally much simpler but requires a solution of DIBAL-H in THF, otherwise insufficient coordination occurs thus decreasing the diastereomeric ratio.

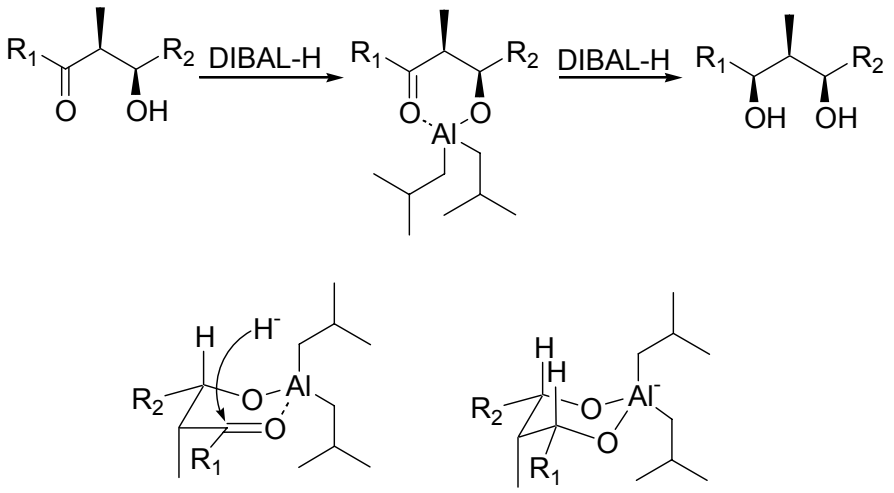
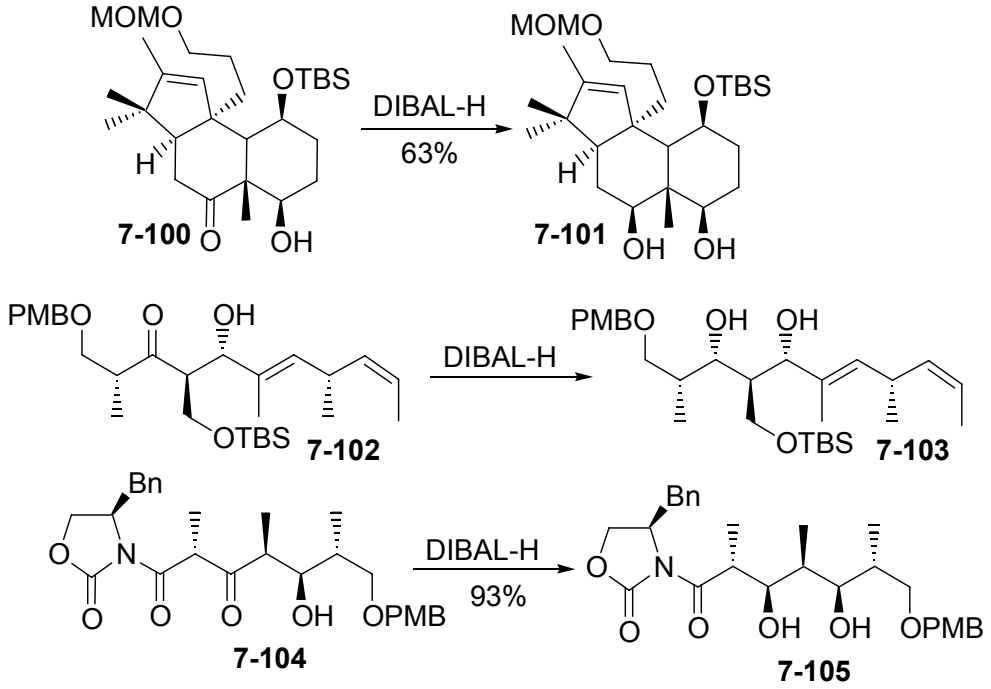


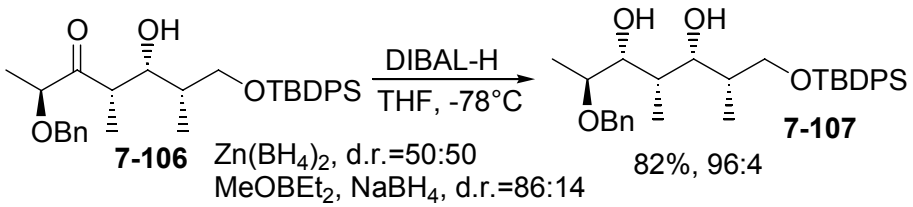
Figure 35. Mechanism of Kiyooka reduction.

Examples of stereoselective reduction with DIBAL-H can be found in the total syntheses of dumsin A[145], and (+)-tedanolide[146]. It was used to establish the stereochemistry after Evans dipropionate aldol reaction[147,148].



Scheme 97. Applications of the Kiyooka protocol.

As reported by Urpi[149] et al., *syn*-reduction with DIBAL-H can deliver the desired *syn*-diol with high diastereoselectivity where the two other methods gave unsatisfactory results.



Scheme 98. A particular example of DIBAL-H *syn*-reduction.

7.3.4 Enzyme catalyzed kinetic resolution and desymmetrization

The world is chiral and so is the vast number of biologically active compounds. Thus it's always raising demand for efficient methods for preparation of enantiomerically pure compounds. In recent years the use of enzymes as catalysts for chemical transformations became more and more widespread due to the following reasons:

a) Highly chemo-, regio-, and stereoselective processes can be developed.
b) Enzymes are environmentally friendly and produce minimal amount of waste.
c) Reactions usually proceed under very mild conditions, thus minimizing formation of possible side-products.
d) Enzymes are catalysts and can be used multiple times, especially when immobilized on a solid support.

Despite this, organic chemists have been somewhat reluctant to employ biocatalysts in their syntheses. This could be explained by the fact that in their natural form, most of the enzymes are very sensitive catalysts that exert their activity mainly in aqueous solution. Moreover, their handling requires some biochemistry knowledge. However, some recent advances carried out in the biocatalysis field have "approached" enzymes to organic synthesis:

a) They can operate in nonaqueous media accepting a broad range of substrates[150].
b) Immobilization techniques increase their stability and simplify their handling[151].

Thus, many enzymes can now be acquired and used as any other chemical.

There are two main groups of chemical transformations which can be done using enzymes, namely asymmetric synthesis and kinetic resolution of racemic mixtures. They differ conceptually in the fact that by asymmetric synthesis formation of one or more chirality elements happens within a substrate molecule, whereas by kinetic resolution one of the enantiomers is converted to a separable derivative. Obviously, in the latter case theoretical yield can not exceed 50% and practically even lower. This can be a significant drawback when only one enantiomer is needed. The desymmetrization of symmetric compounds (usually *meso*-compounds) consists of elimination of symmetry elements in the substrate molecule.

When these symmetry elements (e.g. mirror plane) preclude chirality, enantioselectivity can be achieved. Because desymmetrization belongs to asymmetric synthesis, the maximum yield of theoretically 100% can be reached.

Formation or hydrolysis of an ester function is the most frequently used enzyme catalyzed chemical transformation. It's catalyzed by the corresponding enzymes – lipases (or more generally hydrolases). Because an ester must contain an alcohol and a carboxylic acid as well, a broad spectrum of substrates and reactions can be used to obtain the desired product. For example, for kinetic resolution (or desymmetrization) of an alcohol one can choose from esterification, hydrolysis, and transesterification depending on yield and enantiomeric excess (**Figure 36**).

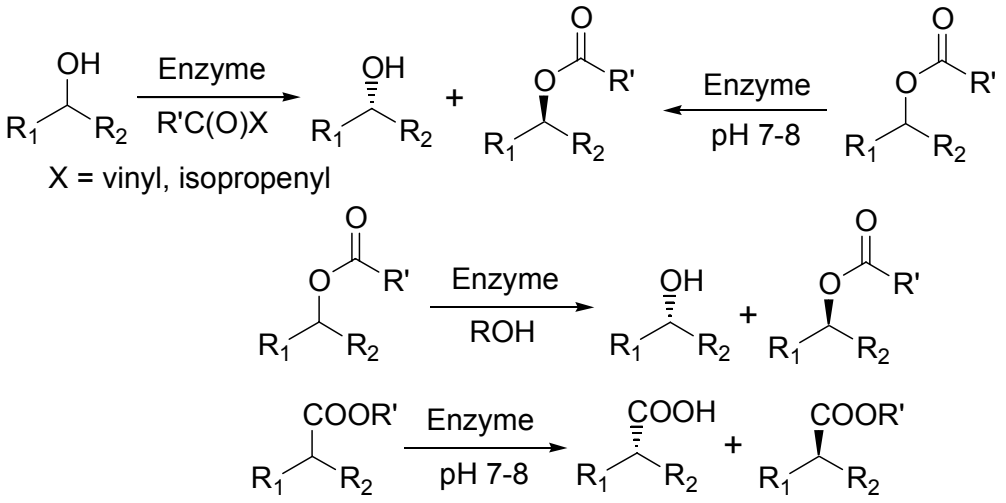
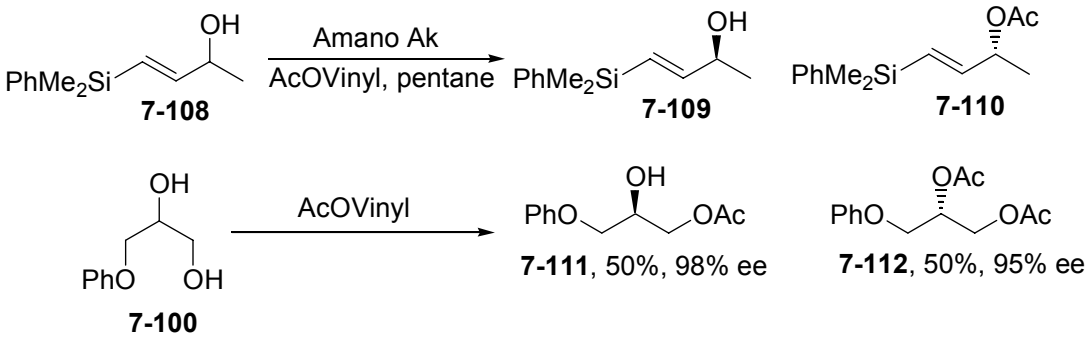


Figure 36. Scope of reactions catalyzed by hydrolases.

Enzymes are catalysts, since they only increase the rate with which an equilibrium between the reacting species will be reached. To drive a reaction as far as possible to completion, special acylation agents (so called "irreversible acyl transfer agents") were developed[152]. The simplest and most commonly employed one is vinyl acetate, produced on industrial scale quantities for polymer synthesis. After transesterification with an alcohol, vinyl acetate gives ethenol which ultimately tautomerizes to acetaldehyde, thus making the reverse reaction almost non-existent. The 2-propenyl acetate or vinyl butyrate work equally well. However, it was found that active carbonyl compounds such as acetaldehyde or acetone can deactivate enzymes, possibly by formation of imines with free -NH_2 residues of lysine amino acids located at the surface. The use of O-acylated oximes was proposed to overcome these difficulties[153].

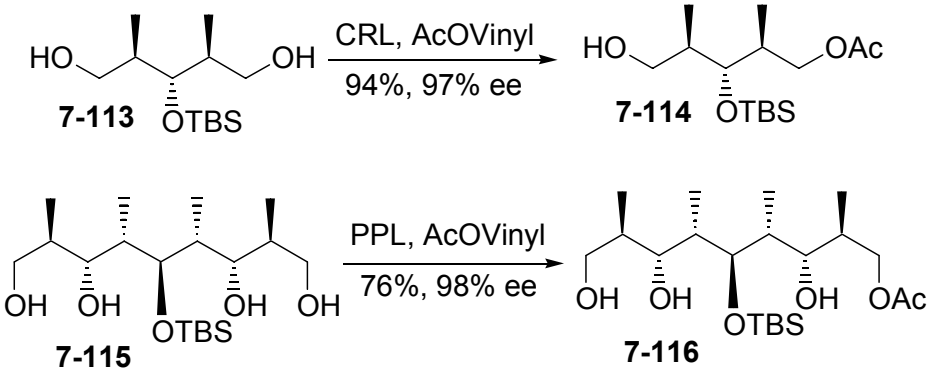
As was pointed out earlier, classical kinetic resolution can provide a maximum of 50% yield of each enantiomer. This property usually is considered as drawback, but can be useful where

both enantiomers are required. Some times, the undesired enanthiomer can be equilibrated to the racemate or converted in a separate step to the required compound. For instance, preparation of enantioenriched crotylsilanes by resolution of allylic alcohol **7-108** has been developed by Panek[154] (**Scheme 99**). After separation and acetate cleavage in **7-110** each alcohol can be converted to a useful building block for total synthesis of natural products. An interesting example for a resolution of a diol was reported by Theil[155].



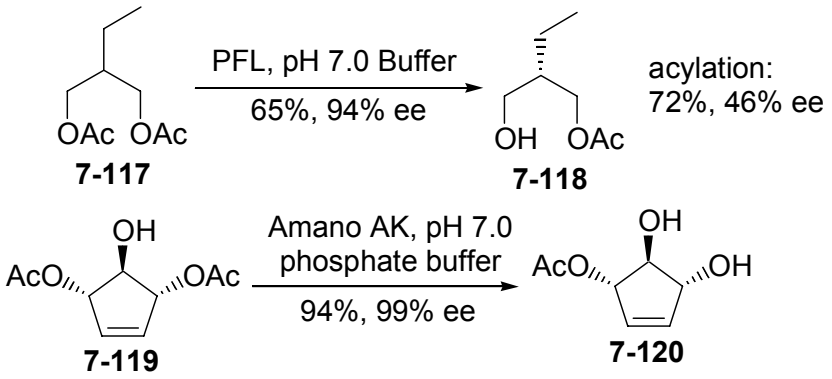
Scheme 99. Kinetic resolution of alcohols and diols.

For the reason stated above, desymmetrization of *meso*-compounds is more preferred. For instance, a secondary metabolite isolated from the skin of the anaspidean mollusk Dolabrifera was synthesized in five steps (58% overall yield) via the enzymatic desymmetrization catalyzed by *Candida rugosa* lipase (**Scheme 100**)[156]. The monoester **7-114** was obtained in excellent yield and *ee* when intact molecular sieves was added to the medium to trap the byproduct acetaldehyde, which is essential to achieve high enantioselectivity. Additionally, the C(19)-C(27) fragment of rifamycin S has been successfully prepared by stereoselective acylation of the *meso* polyol **7-115** by vinyl acetate (solvent and acyl donor) in the presence of porcine pancreas lipase[157]. This reaction afforded monoacetate **7-116** in good yield and enantiomeric purity, and the enzyme was highly regioselective for a primary alcohol end group, the two unproctected secondary alcohols being left untouched.



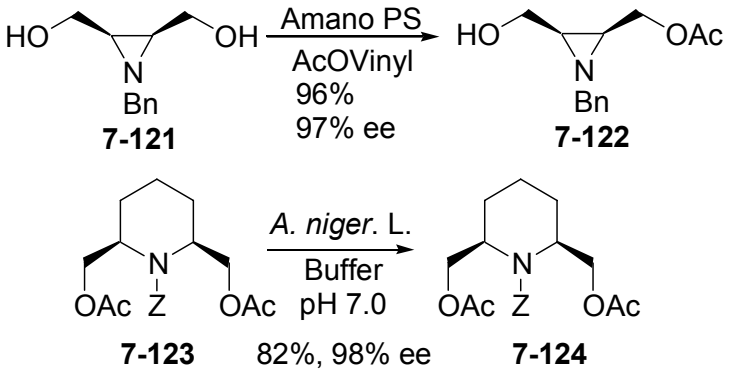
Scheme 100. Preperation of polyketide building blocks by desymmetrization.

In some cases, hydrolysis of the diacetates was found to give better yield and enantiomeric excess than acylation of the corresponding diol. Indeed, PFL catalyzed hydrolysis of 2-ethylpropan-1,3-diol diacetate proceeds with 94% ee, whereas acylation of 2-ethylpropan-1,3-diol only gave 46% ee (**Scheme 101**)[158]. For most objects (but not for all) hydrolysis of the diacetates can provide access to enantiomeric products[159].



Scheme 101. Desymmetrization of prochiral acetates.

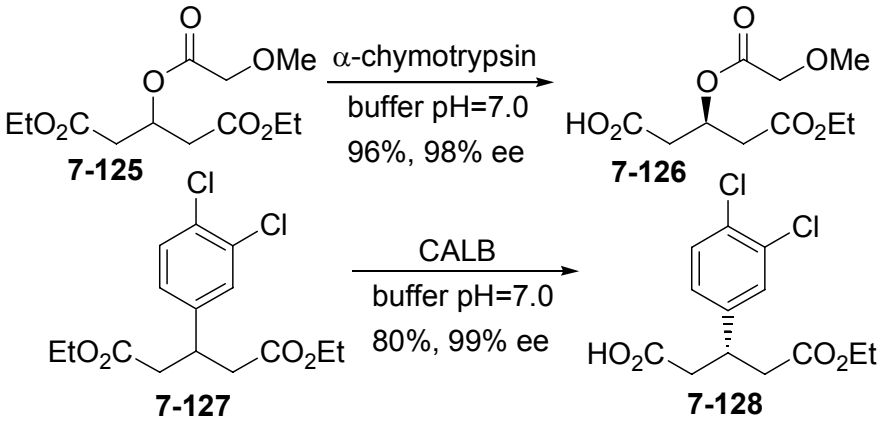
Optically active alcohols containing heterocycles constitute an important class of intermediates in the synthesis of different pharmaceutical substances. Prati[160] and co-workers have carried out the Amano PS lipase-catalyzed desymmetrization of aziridine **7-121**, whose monoacetylated derivative, obtained in high yield and *ee* (**Scheme 102**), is related to a key compound used in the total synthesis of the antibiotic FR-900482. The piperidine ring is another widespread structural fragment of biologically active compounds. In this sense, both enantiomers of different *cis*-2,6- and *cis*,*cis*-2,4,6-substituted piperidines have been obtained through desymmetrization strategies developed by Chenevert[161] and co-workers.



Scheme 102. Desymmetrization of heterocyclic *meso*-diols.

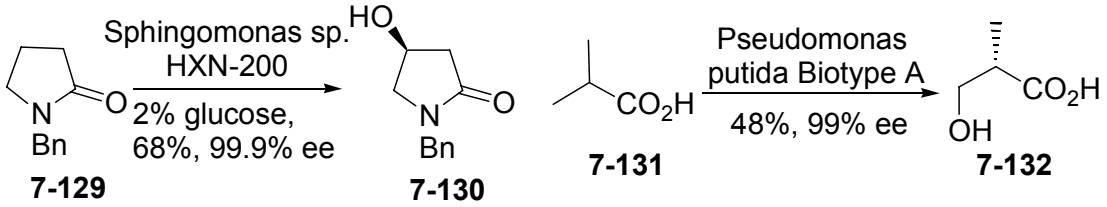
Finally, one should mention desymmetrization of different *meso* and prochiral esters possessing the prochirality element in the alkyl chain. These compounds can be easily prepared from inexpensive sources. For instance, a versatile building block for the synthesis of statins was prepared by Öhrlein and co-workers by desymmetrization of diethyl 3-

hydroxyglutarate derivative **7-125**[162]. Similarly, the enzymatic desymmetrization of the prochiral diethyl 3-[3',4'-dichlorophenyl]-glutarate, an intermediate in the synthesis of a series of neurokinin receptor antagonists, has been successfully developed and scaled up (**Scheme 103**)[163].



Scheme 103. Desymmetrization of prochiral diesters

Other useful stereoselective reactions catalyzed by enzymes are hydrolysis of amides, nitriles, and anhydrides. To a lesser extent enzymes were used for the stereoselective reduction of carbonyl compounds, because such reaction requires stochiometric amounts of sensitive cofactors. Stereoselective methyl[164] and methylene[165] group hydroxylation was also reported (**Scheme 104**).



Scheme 104. Enzyme catalyzed enantioselective hydroxylation.

A comprehensive review devoted to enantioselective enzymatic desymmetrization in organic synthesis was recently published[166].

The mechanism of enzyme catalysis was a subject of thorough investigation. It was found that the active site of lipases consists of a so called catalytic triad, the sequence of three amino acids, aspartic acid, histidine and serine[167]. The OH residue in serine works as “nucleophile”, the imidazole ring in histidine as a “base” and the carboxyl group of aspartic acid as “acid” (**Figure 37**).

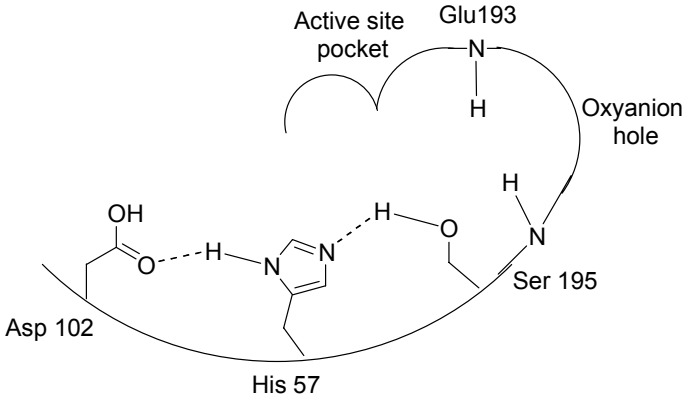


Figure 37. Approximate representation of the active cente of a lipase.

To show the principle of enzymatic catalysis during enantioselective hydrolysis an ester will be used as example. At the beginning, formation of a covalent bound complex between substrate and enzyme occurs by attack of the serine hydroxyl at the carboxyl function (**Figure 38**). The negatively charged oxygen atom of the tetrahedral intermediate forms two hydrogen bonds in the so called "anion hole" with protons of amide groups of serine and glutamine. At the same time the chiral residue of the alcohol must fit in the "active site pocket" of the enzyme. If one enantiomer fits better then the other, optically enriched products will be observed.

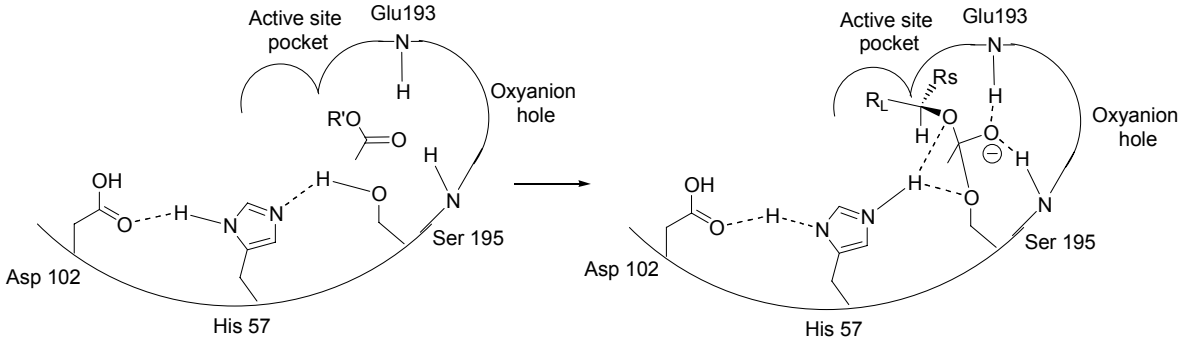


Figure 38. Formation of a covalent bound complex between substrate and enzyme.

Then tetrahedral intermediate collapses with expelling of the alcohol. The acylated enzyme then reacts with water in a similar manner, but with release of an acetic acid molecule and recovering of the serine OH group.

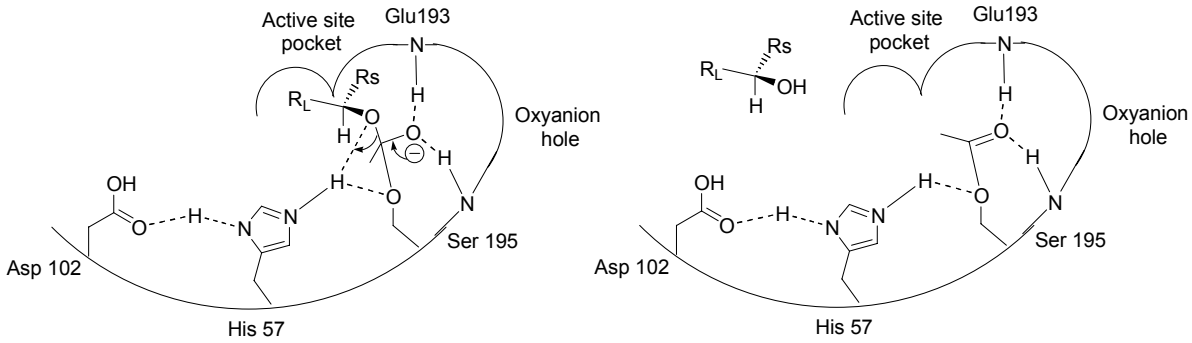


Figure 39. Collapse of the tetrahedral intermediate and release of the alcohol.

In conclusion, one can expect ever growing application of enzymes in organic chemistry.

7.3.5 Yamaguchi macrolactonization

Natural polyhydroxylated macrocyclic lactones (or macrolides) exhibit a wide spectrum of interesting properties including such important medicinal activities as antibiotic, cytotoxic, antiangiogenic. Macrolactones vary in size from 8-membered ones such as octalactins to the 60-membered quinolidomicins (**Figure 40**). From their first isolation in the 50s, macrolide antibiotics, such as erythromycin, were widely used to treat bacterial infections, and because of their safety and efficacy, they are still the preferred therapeutic agents for treatment of respiratory infections. The 20-membered apoptolidin selectively induces apoptosis in rat glia cells transformed with adenovirus E1A oncogen in the presence of normal cells and inhibits the mithochondrial F_0F_1-ATPase[168]. Actin-binding marine macrocyclic lactones are also a large class of natural products possessing potent antitumor activity and benzolactone enamides with antibiotic and cytotoxic activity are also worthy of note.

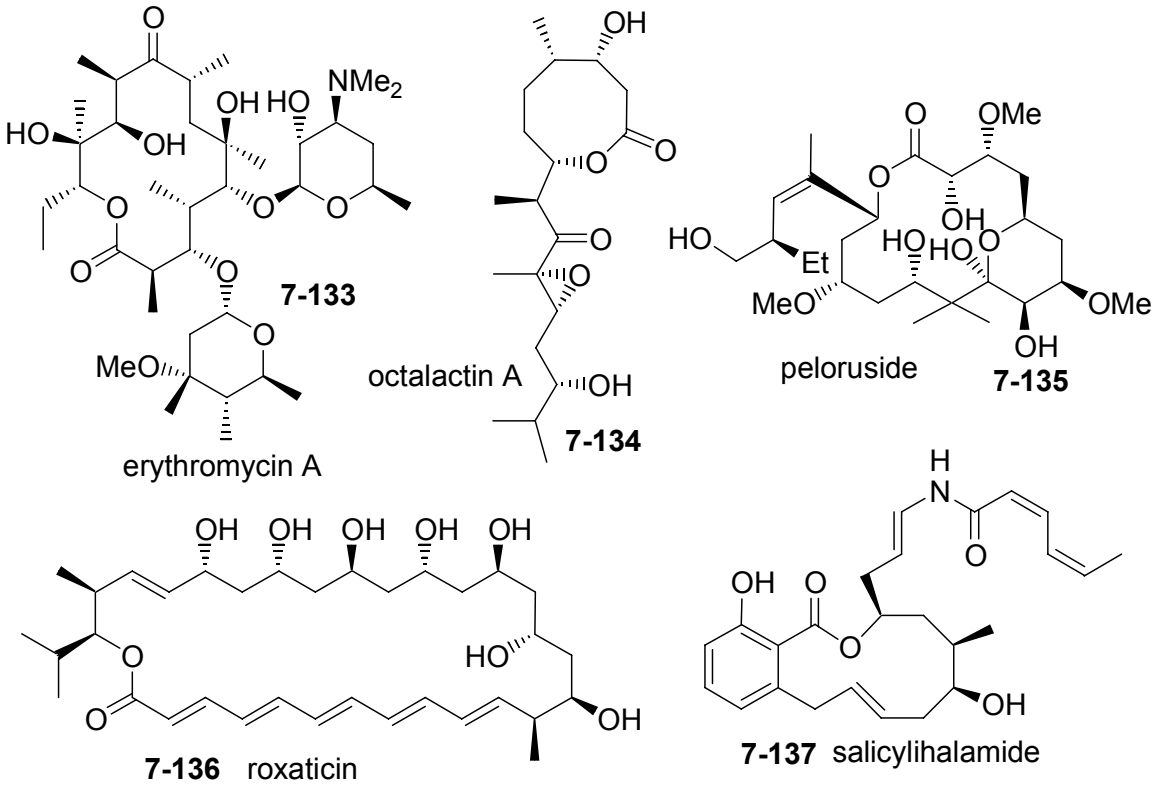


Figure 40. Examples of naturally occurring macrolactones.

Even though many other efficient macrocyclization methods such as the RCM, intramolecular cross-coupling, Nozaki-Hiyama-Kishi, and HWE reactions have been developed over the years, the lactonization of seco-acids is still the most frequently used approach to obtain macrocyclic lactones. Due to entropic and enthalpic factors direct cyclization is generally not possible without activation of either the alcohol or the carboxylic acid side. With more than 200 papers using this methodology, the Yamaguchi reagent, 2,4,6-trichlorobenzoyl chloride (TCBC) (**7-138**), is probably the most popular reagent for performing macrolactonizations[169]. In the classical procedure (**Figure 41**), the mixed anhydride is prepared in THF in the presence of triethylamine or Hünig's base. After filtration of the NEt_3-HCl salt and evaporation, the mixed anhydride is dissolved in toluene and slowly added by syringe pump to a highly diluted solution of DMAP (2-5 equiv) at high temperature (80 °C or reflux).

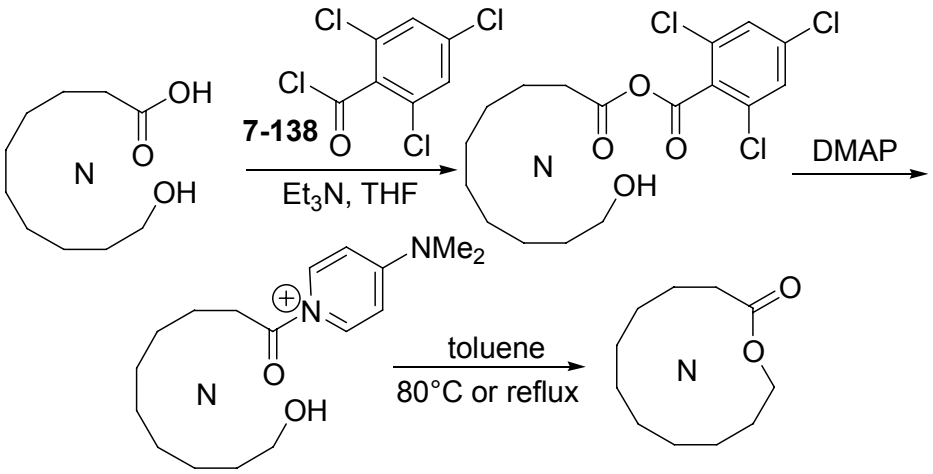
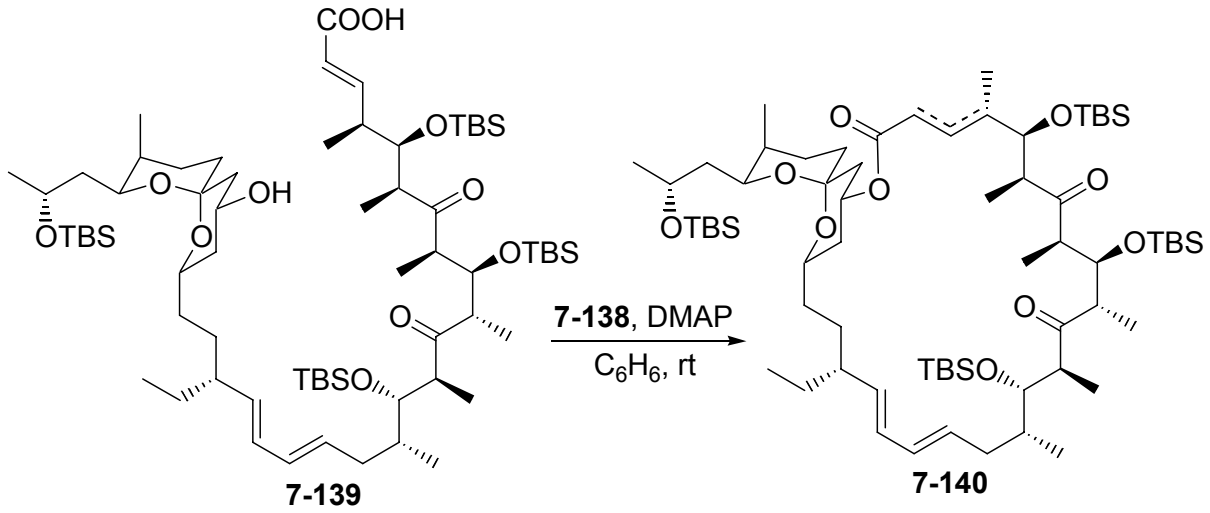


Figure 41. Mechanism of Yamaguchi macrolactonizations.

Competitive formation of a symmetrical anhydride of the seco-acid in these reactions has been observed only in the total synthesis of hygrolidin[170]. Generally, filtration of the NEt_3-HCl salt is not crucial, but Evans has shown in the synthesis of roxaticin that it was essential to prevent the acid-promoted decomposition of the polyene unit of roxaticin[171]. The use of the 2,6-dichloro derivative with no alteration in the reactivity was also described before the Yamaguchi reagent was commercially available. The use of pyrrolidinopyridine as supernucleophilic catalyst has also been described[172] along with an excellent article[173] about these additives. More recently, a polymer-supported DMAP reagent has been reported[174] in the total synthesis of epothilone C using a multistep application of immobilized reagents and scavengers.

There have been many variations and modifications of the original Yamaguchi procedure. Two major modifications have been developed by Yonemitsu in several papers [175,176,177] dedicated to the total synthesis of erythronolide derivatives. In the first of these two modifications, known as the "modified Yamaguchi conditions", Yonemitsu identified the beneficial effect of the direct addition of a large amount of DMAP to the preformed mixed anhydride, generally at room temperature and without the need for slow dilution. See, for example, the syntheses of oleandolide[178,179] and bryostatin 2[180]. In the second of Yonemitsu's two modifications, known as the "Yonemitsu conditions", the mixed anhydride is not preformed and DMAP is directly introduced at room temperature from the beginning. These less basic conditions turned out to be highly efficient in, for example, the total synthesis of rutamycin B[181], where the Keck, Mukaiyama, and Corey procedures gave mainly the

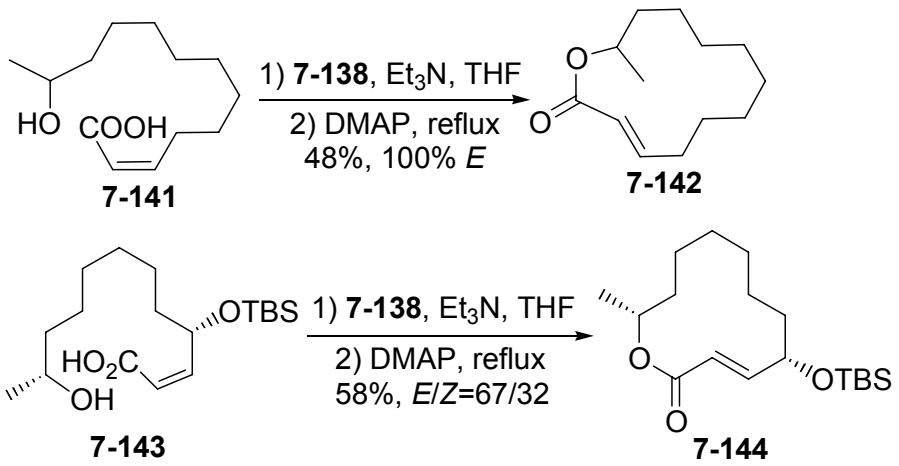
deconjugated β/γ lactone as the major product and the classical Yamaguchi procedure gave a 1:1 mixture of the β/γ and α/β lactones (**Scheme 106**).



Scheme 106. Isomerization of the α,β to the β,γ double bond.

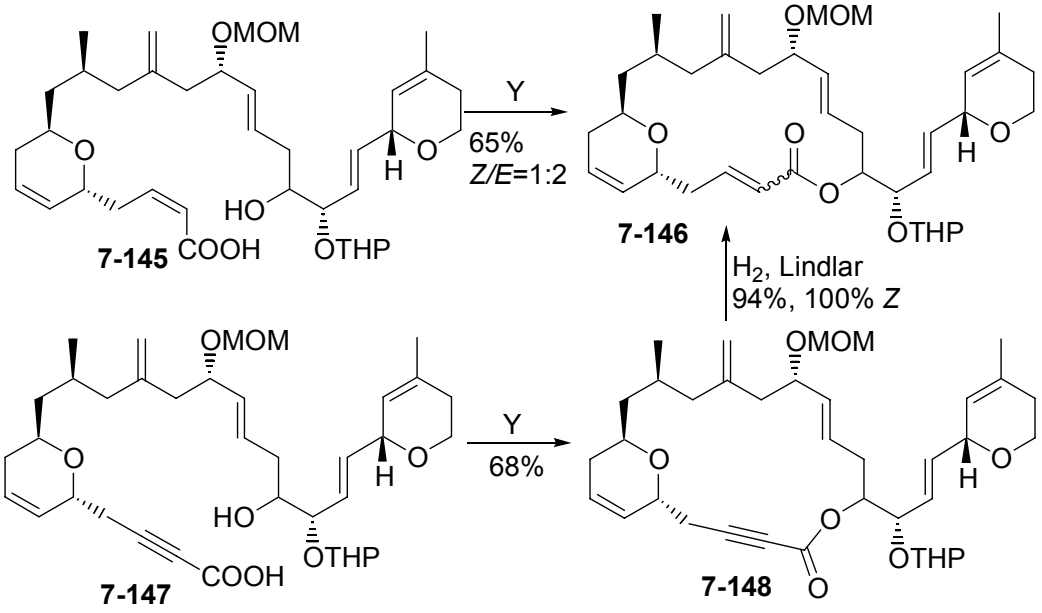
Since macrolactonizations are usually carried out on very advanced substrates and consequently methodological studies are rather difficult and rare, there is still no rule about the best conditions to realize a Yamaguchi macrolactonization on a particular substrate. The general trend, however, seems to be use of the Yonemitsu conditions on rather large macrocycles (for example, the Yonemitsu conditions failed in the synthesis of the callipeltoside aglycon[182]) and classical conditions on medium ring lactones (to prevent the formation of diolides and oligomers). Evans has shown the influence of temperature and rate of addition in reducing diolide formation and destannylation in the macrolactonization of a sensitive lepicidin precursor[183].

The main drawback of the Yamaguchi procedure is the use of the highly basic DMAP and high temperature. These factors sometimes lead to undesirable side reactions such as α,β to β,γ isomerization of conjugated double bonds *(vide supra)*, epimerization of sensitive chiral centers[184], and *Z*/*E* isomerization of conjugated double bonds (Scheme 25)[185,186].



Scheme 107. Isomerization of a conjugated double bond under Yamaguchi conditions.

In some cases the latter problem can be solved by performing the macrolactonization on the ynoic seco-acid followed by hydrogenation of the triple bond (**Scheme 108**) [187].



Y = 1) **7-138**, Et_3N, THF, 2) DMAP, reflux

Scheme 108. One possible solution to the problem of isomerization.

A review partially devoted to the Yamaguchi macrolactonization protocol was recently composed by Campagne[188].

7.3.6 Intramolecular Nozaki-Hiyama-Kishi reaction

The intramolecular Nozaki-Hiyama-Kishi reaction is another powerful approach toward the synthesis of medium and large rings. A wide range of active halides, including vinyl, allyl,

aryl, alkyl and alkynyl iodides and bromides can be used as substrates. Mechanistically, the reaction proceeds via insertion of fine metal nickel species generated by reduction of Ni^{2+} with $CrCl_2$ followed by transmetallation to Cr^{3+} compounds, which undergo addition to the carbonyl group (**Figure 40**).

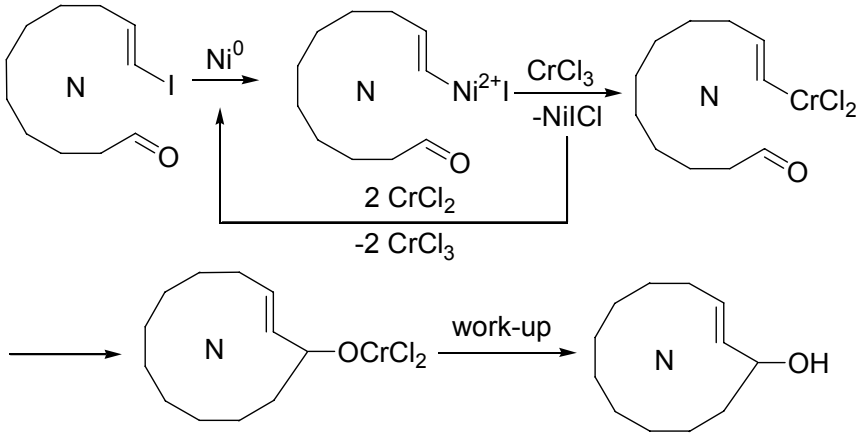
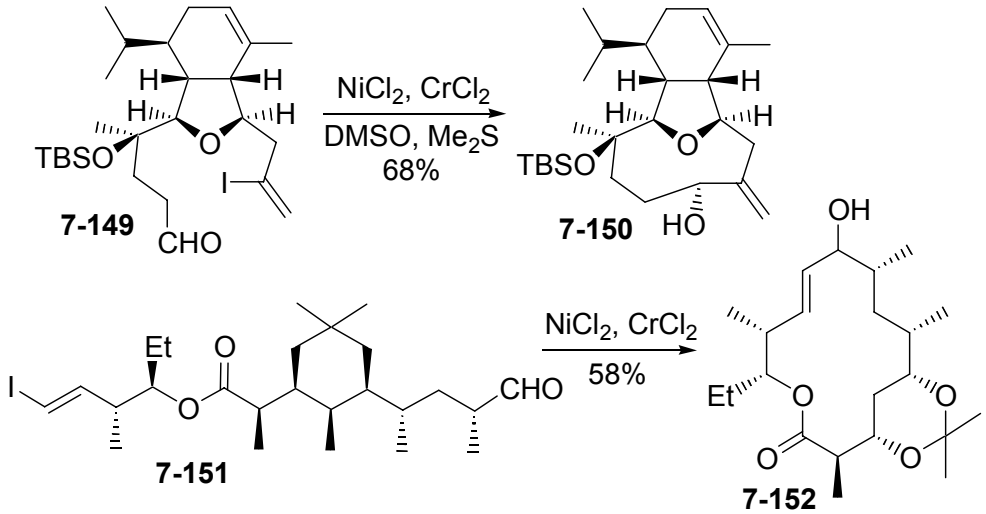


Figure 40. Reaction mechanism for stoichiometric intramolecular NHK reaction.

The reaction is usually performed in highly polar aprotic solvents such as DMSO, DMF, acetonitrile, THF or their combination. Depending on the molecular architecture some degree of diastereoselectivity can be achieved. Examples for application can be found in synthesis of eleutherobine[189], deacetoxyalcyonin acetate[190], narbonolide[191], and others.



Scheme 109. Application of Nozaki-Hiyama-Kishi macrocyclization in total synthesis.

Recently, catalytic variants of this transformation were discovered by Fürstner[192] and Kishi[193]. For this purpose ligand screening was undertaken and bipyridyl (**7-153**) and phenanthroline (**7-154**) complexes of nickel and chromium respectively were found to be the best catalysts (**Figure 41**).

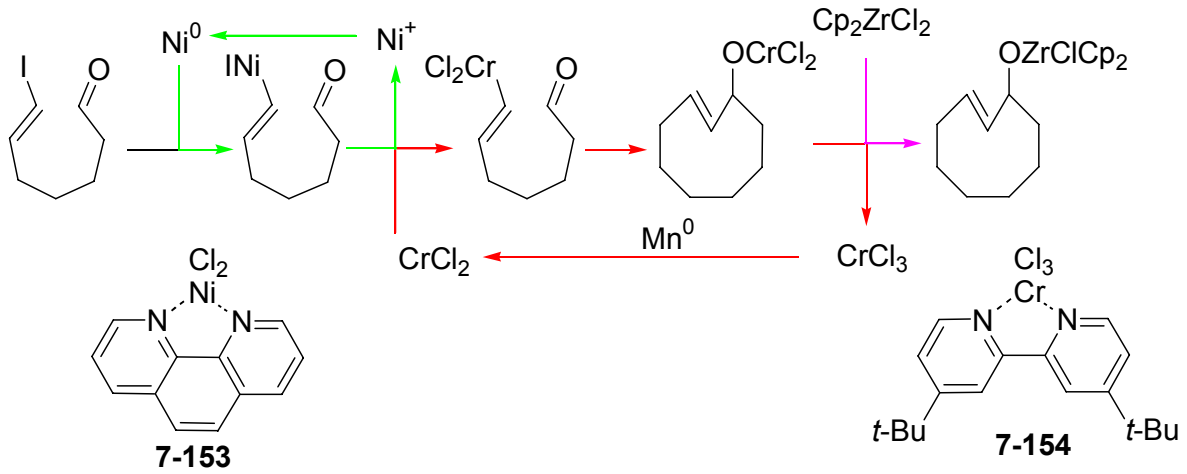
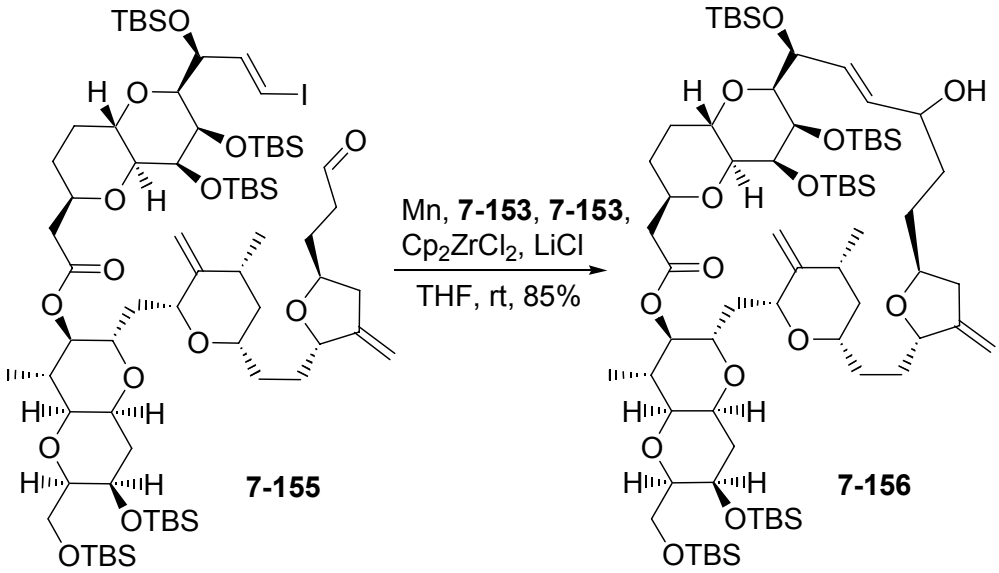


Figure 41. Catalytic cycles for Mn mediated NHK reaction.

As was shown by Kishi himself, in case of halichondrin related compound **7-155** catalytic conditions delivered the desired product while the stoichiometric variant failed to do so[194].



Scheme 110. Example of NHK-macrocyclization on a very complex object.

A significant advantage of this reaction in comparison to the Yamaguchi macrocyclization is that very mild conditions are used, thus making side-reactions less probable.

8 Results and Discussion

8.1 Retrosynthetic analysis of dictyostatin

The target molecule, dictyostatin (**6-1**), features the following distinct fragments (**Figure 41**).

a) a terminal *Z*-diene unit
b) C19-C22 *syn,syn,anti*-stereotetrad
c) C12-C14 *anti,syn*-stereotriad
d) C10-C11-*Z*-double bond
e) C1-C5 *E,Z*-dienoate

In our retrosynthetic analysis we followed the general trend of previous dictyostatin syntheses and divided the target molecule into two main subunits, namely top (**8-1**) and bottom (**8-2**) fragments (**Figure 42**).

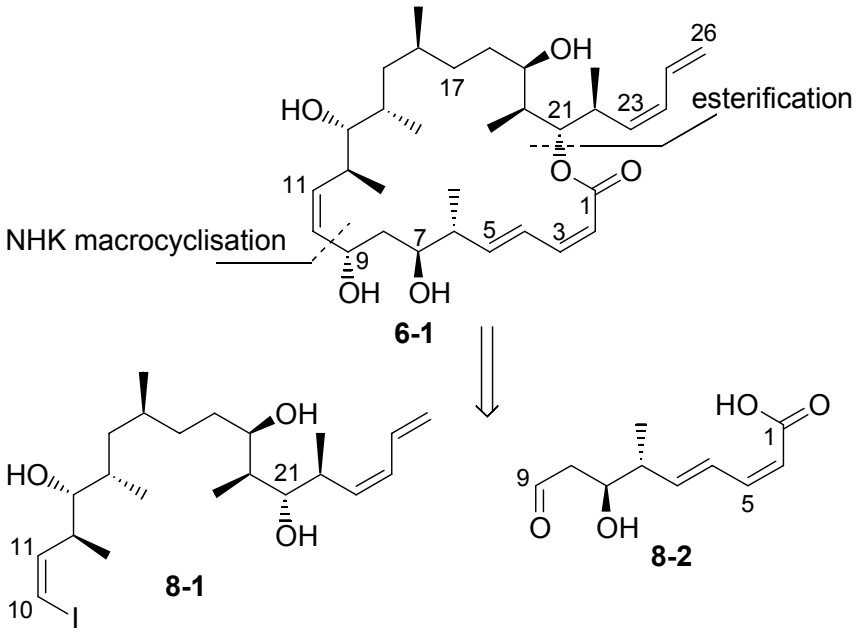


Figure 42. Retrosynthetic analysis for dictyostatin (protecting groups are omitted).

The upper part can be obtained from the intermediate **8-3**, which in turn was traced back to two fragments, vinyl alkyl di-iodide **8-3** and ketone **8-6** (**Figure 43**). These intermediates were supposed to be coupled by alkylation. *Syn*-reduction of ketone would deliver the desired stereochemistry at C19.

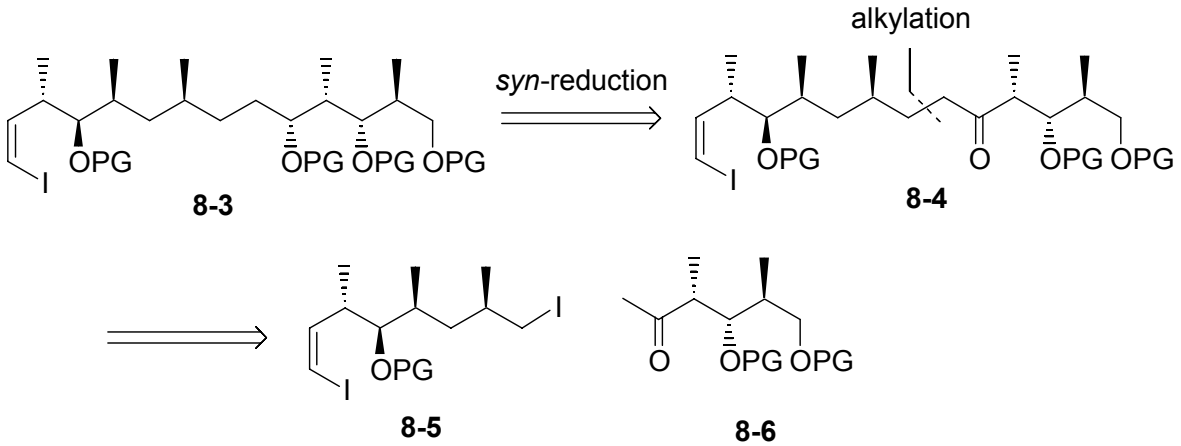


Figure 43. Retrosynthetic analysis for the C10-C23 fragment of dictyostatin.

The required alkyl di-iodide **8-5** can be synthesized by Stork-Zhao olefination of the corresponding aldehyde **8-8**, which logically originates from an Abiko aldol reaction and aldehyde **8-9**. The latter compound we planed to prepare by enzymatic desymmetrization of 2,4-dimethylpentane-1,5-diol (**Figure 44**).

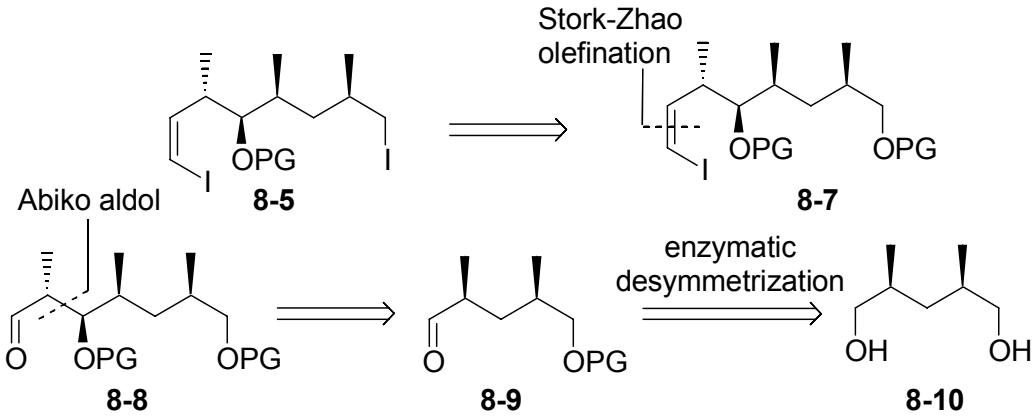


Figure 44. Retrosynthetic analysis for the C10-C17 fragment of dictyostatin.

Another option is to establish the Z-vinyl iodide by sequential iodination/reduction of a triple bond (**Figure 45**). However, due to its relative high acidity, the triple bond must be protected with a trimethylsilyl group for the alkylation step. Such an alkyne could be obtained via allenyl zincate addition to the already mentioned aldehyde **8-9**.

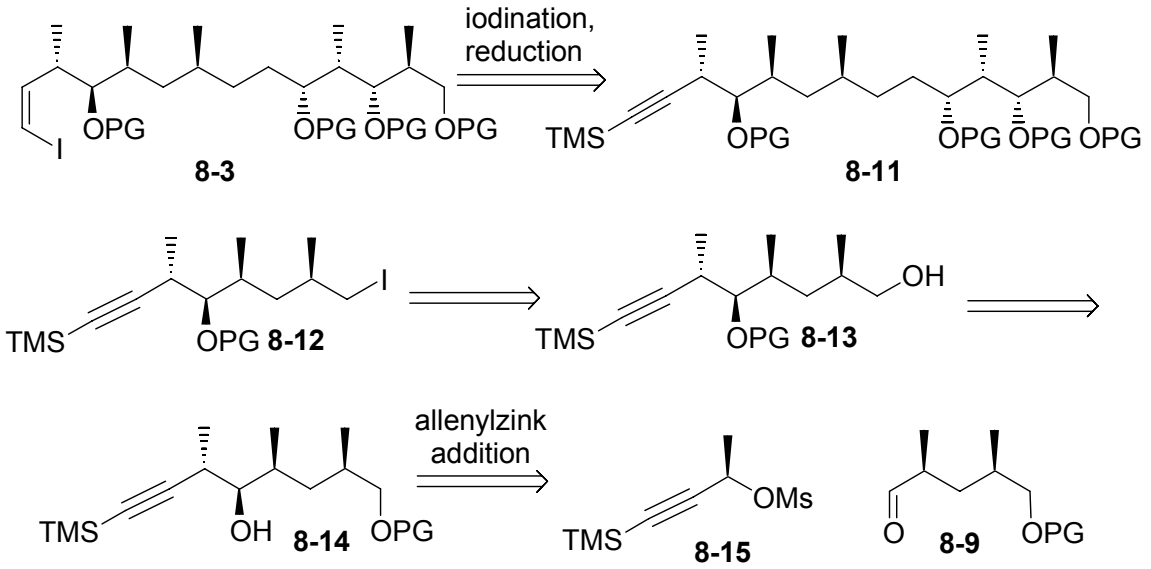


Figure 45. Retrosynthetic analysis for alkyl iodide **8-3**.

Alternatively, the C10-C23 segment of dictyostatin can be secured by acylation of the corresponding alkyllithium compound with a Weinreb amide (**Figure 46**). This disconnection does not allow the presence of a vinyl iodide in the left-hand fragment, thus an appropriate synthetic equivalent must be used, e.g. the one carbon extended iodide **8-18**.

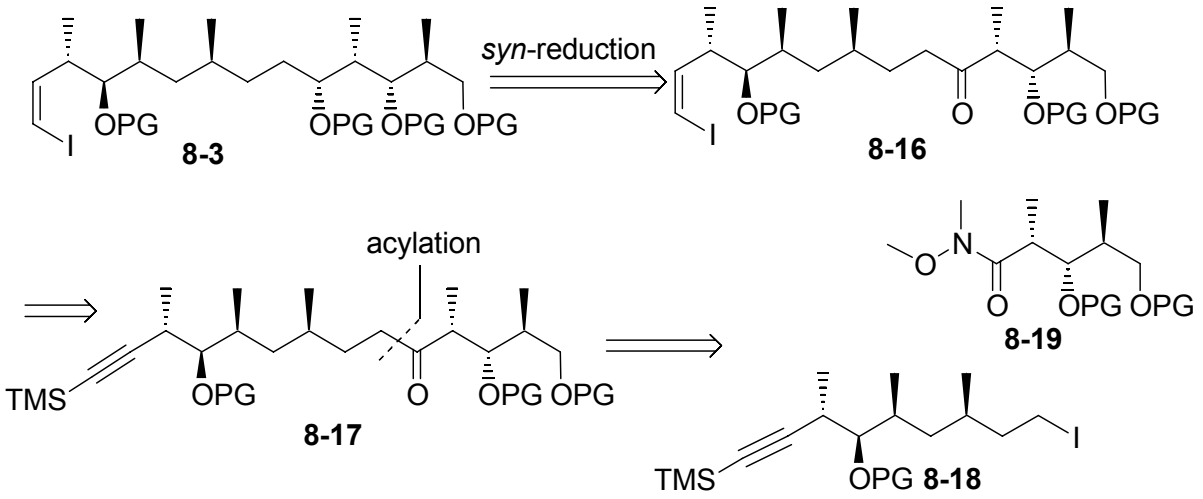


Figure 46. Alternative retrosynthetic analysis for the C10-C23 segment of dictyostatin.

The one carbon elongation of alcohol **8-22** could be achieved by a classical sequence of Wittig reaction with methoxymethyl phosphorane, hydrolysis of the enol ether and reduction.

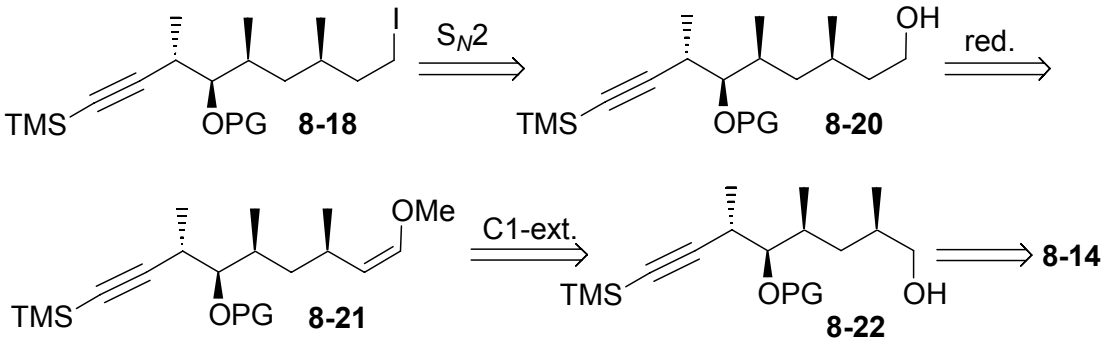


Figure 47. Retrosynthetic analysis for the aliphatic part **8-13**.

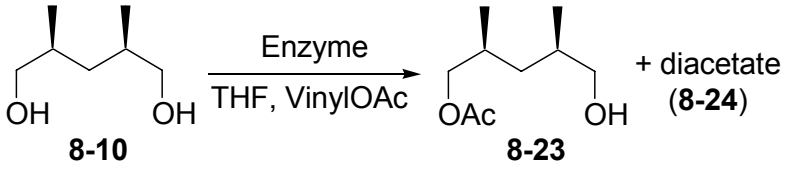
As one can see, our retrosynthetic analysis for dictyostatin is quite different from the existing ones in both strategy and tactics. Many of the proposed reactions and transformations were never used for the synthesis of this target molecule.

8.2 Syntheses of the Key Precursors

8.2.1 Desymmetrysation of meso-2,4-dimetyl-1,5-pentanediol

Our first goal en route to dictyostatin was to develop a simple and reliable method for the preparation of a chiral building block based on 2,4-dimethyl-1,5-pentanediol. Similar fragments were already described earlier in the literature, however no detailed procedure, suitable for multigram scale synthesis experimental was found[195, 196]. We decided to perform our own screening for suitable enzymes and conditions in order to have first hand information about this reaction. Thus, diol **8-10** was allowed to react with vinyl acetate in presence of three enzymes, namely Amano AK lipase, Amano PS lipase, and Novozyme 435. The obtained mixture of acetate and diacetate was purified by column chromatography and analyzed with regard to the enantiomeric excess and ratio (**Table 1**).

Table 5. Desymmetrization of 2,4-dimethyl-1,5-pentanediol.



Enzyme	Mono-/Diacetate	ee of **8-23**
Amano AK	6:1	98%
Amano PS	4:1	30%
Novozyme 435	2:1	n.d.

It was found, that the best results can be obtained when Amano AK lipase from Aldrich (Cat. № 53,473-10) was used as catalyst. The enantiomeric excess of the isolated monoacetate was determined by chiral GC (**Figure 48**) and cross-checked with the classical Mosher ester technique[197]. For this purpose racemic 2,4-dimethyl-1,5-pentanediol monoacetate was synthesized and converted to the Mosher derivative. Comparison of exhibited data is shown in **Figure 49**.

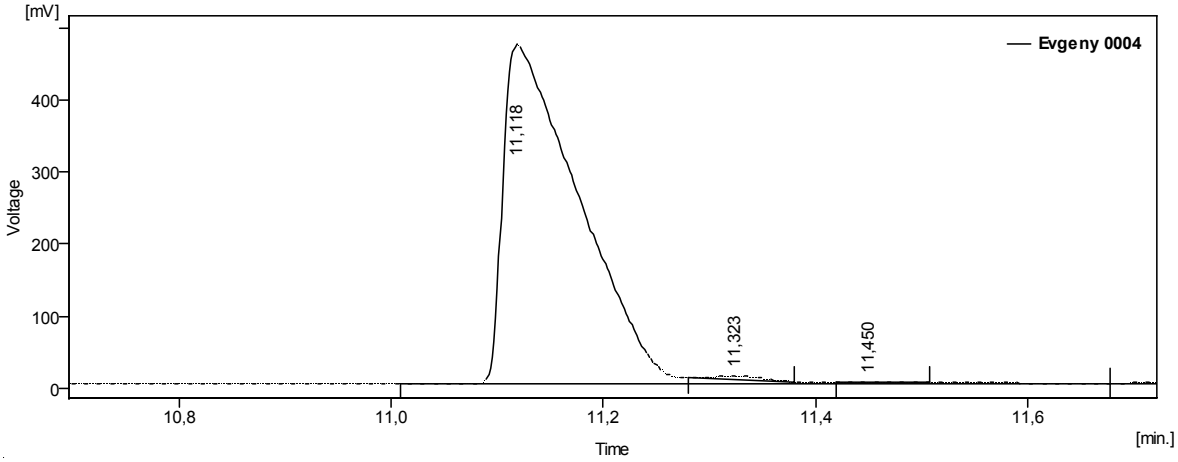


Figure 48. Chiral GC of (2*R*,4*S*)-2,4-dimethylpentane-1,5-diol-acetate (**8-23**), major isomer t_R = 11.118, minor isomer t_R = 11.323.

One should note the difference in shift not only for protons near the Mosher ester, but also the protons of the acetate group, which is situated at the other end of molecule. From this observation one can suggest that the molecule may exist in an arc–conformation.

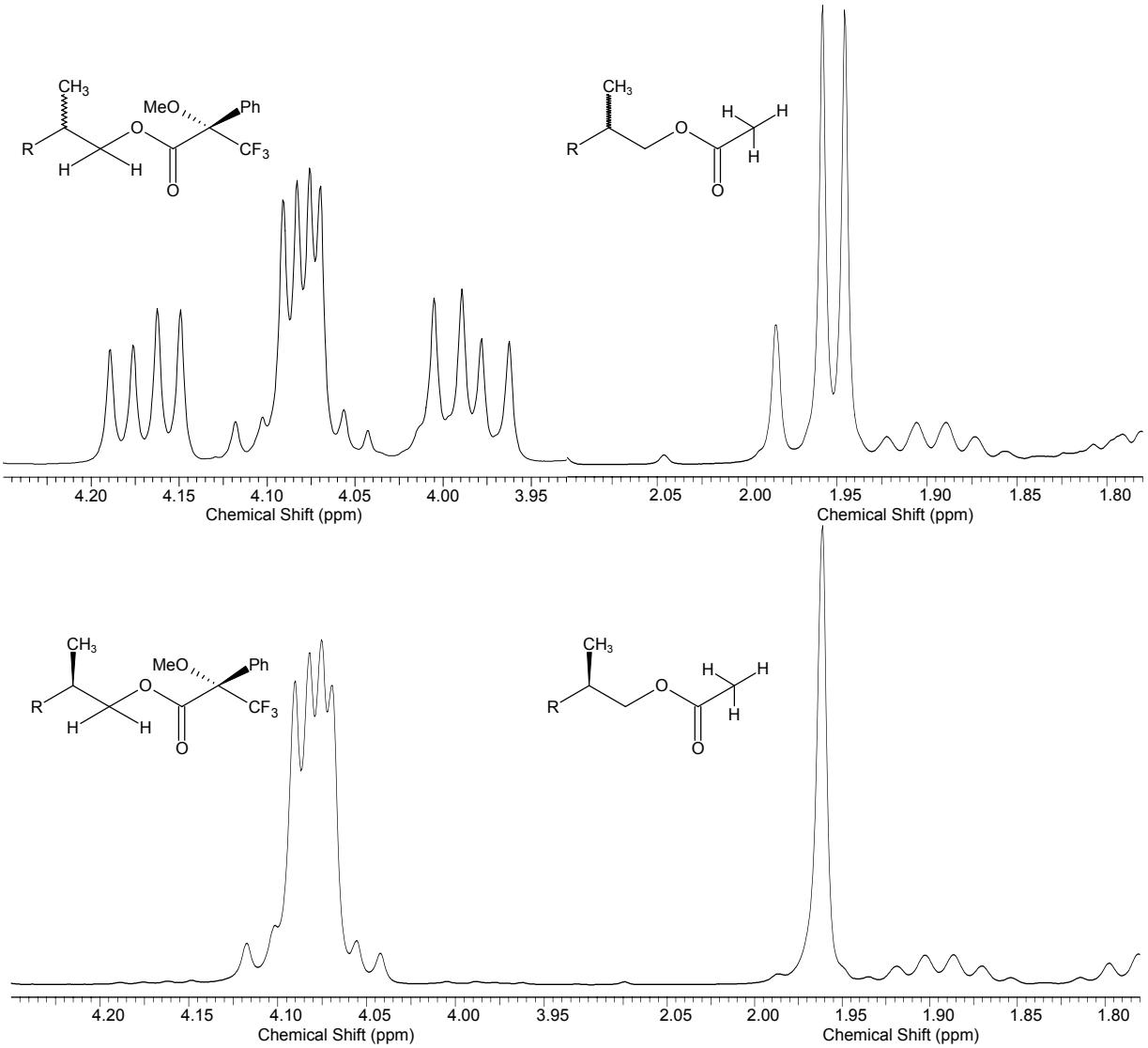
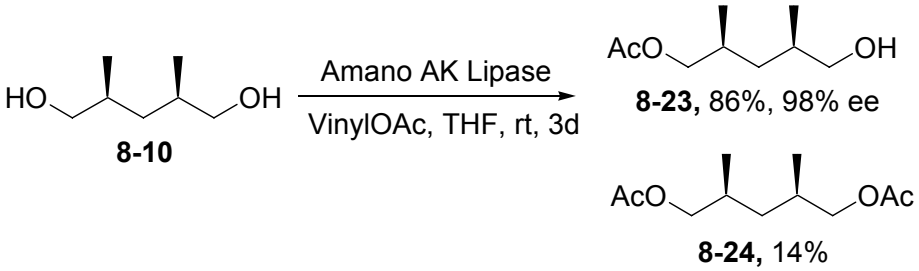


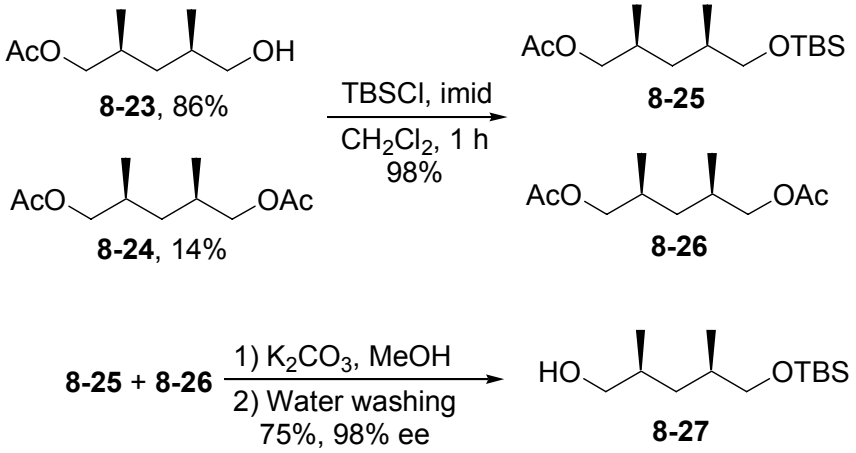
Figure 49. Comparison of NMR spectra of Mosher esters of **8-23** and **rac-8-23**.

After optimization of the conditions we were able to adjust the substrate/enzyme ratio so, that the reaction took 72 h for completion. These conditions gave us a reliably high ee of the product (**Scheme 112**).



Scheme 112. Enzymatic desymmetrization of 2,4-dimethy-1,5-lpentanediol under optimized conditions.

Some difficulties that we encountered were the competitive formation of the 2,4-dimethylpentane-1,5-diol diacetate **8-24**. Because column chromatography should possibly be avoided at the beginning of the synthesis, we came up with an alternative separation and purification technique based on the high solubility of 2,4-dimethylpentane-1,5-diol in water (**Scheme 113**). Accordingly, the mixture of mono- and diacetate was directly treated with TBSCl, where only the monoacetate can form a silyl ether **8-25**.

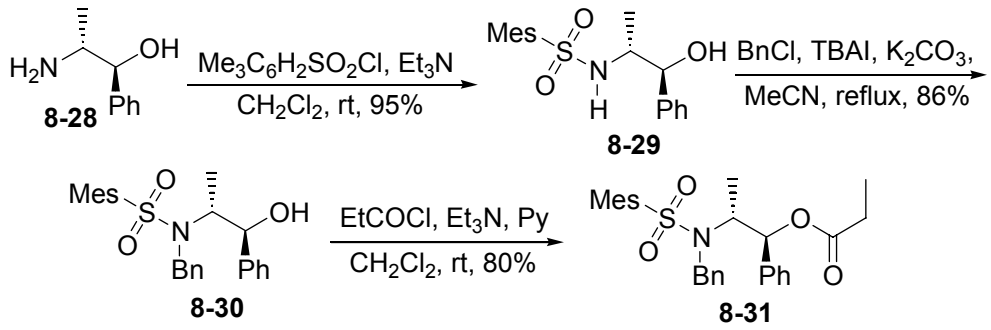


Scheme 113. Purification of intermediate **8-27**.

After cleavage of the acetate groups under basic conditions in methanol, the released 2,4-dimethylpentane-1,5-diol could be washed out with water. It was proven by Mosher ester ^{1}H NMR analysis, that there was no difference in the ee value of monoacetate **8-23** and TBS ether **8-27**. We repeatedly used this procedure to obtain up to 27 g of the intermediate **8-27**.

8.2.2 Abiko auxiliary

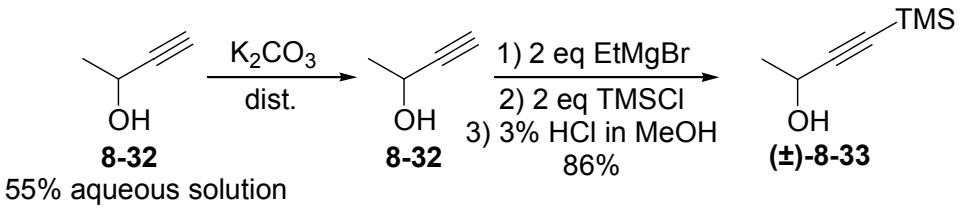
The Abiko aldol reaction is a newly developed methodology for introduction of vicinal *anti*-orientated methyl and hydroxyl groups. It's an ester of nor-ephedrine derivative **8-30**. Compound was **8-31** obtained in three steps, namely sulfonylation, benzylation and acylation according to literature procedure. It is worth to mention, that all intermediates here are highly crystalline solids.



Scheme 114. Synthesis of Abiko auxiliary **8-30** and Abiko reagent **8-31**.

8.2.3 Preparation of chiral propargyl mesylate

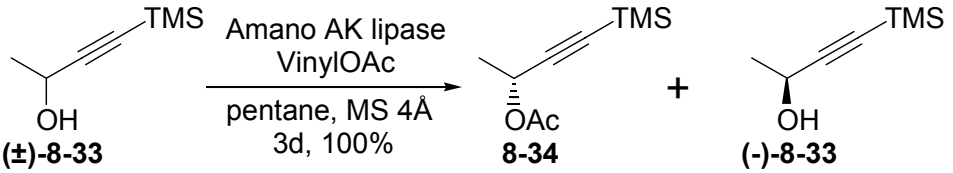
Starting from the commercially available 55% solution of butyn-2-ol in water we prepared neat alcohol **8-32** by means of saturation with potassium carbonate followed by extraction and distillation (**Scheme 115**). Then, deprotonation with ethylmagnesium bromide resulted in formation of *C,O*-dianion, which reacts preferentially on the *C*-side.



Scheme 115. Synthesis of TMS-buty-2-nol.

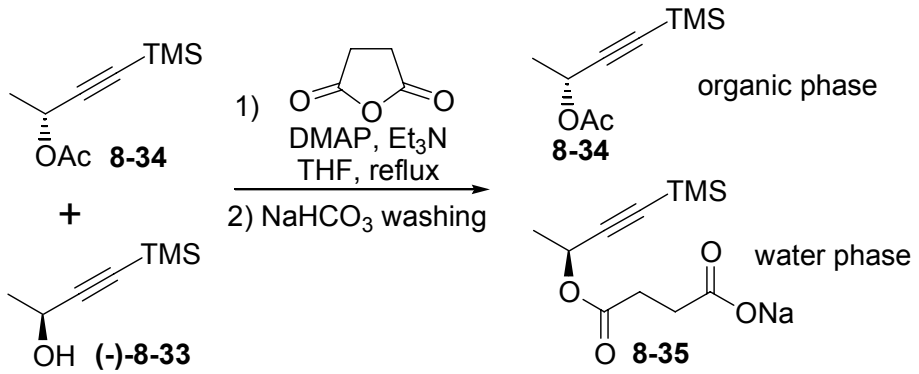
However, we found that some residual amounts (approximately 15%) of double *C*,*O*-silylated compound was present in **8-33** even after distillation, and therefore this mixture was treated with 3% HCl in methanol to complete the ether cleavage.

Enzymatic kinetic resolution of 4-TMS-butin-2-ol was performed in accordance to a published procedure (**Scheme 116**). After 3 days NMR analysis of the crude reaction mixture revealed that the amounts of alcohol and acetate were equal.



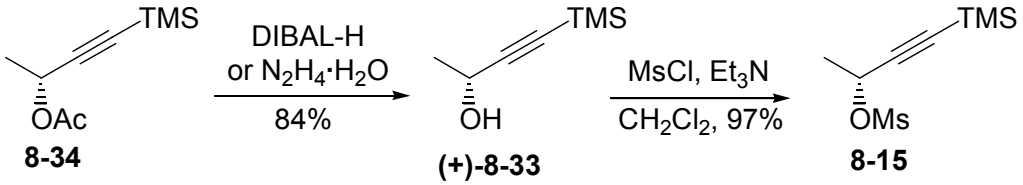
Scheme 116. Enzymatic kinetic resolution of racemic butyn-2-ol.

To separate unacylated alcohol **(-)-8-33** from the acetate **8-34** the so called "succinate trick" was used (**Scheme 117**)[198]. The foregoing mixture was treated with succinic acid anhydride to form the monoester of alcohol which could then be extracted into aqueous sodium carbonate solution, while the acetate remained in the organic phase.



Scheme 117. Separation of alcohol **(-)-8-33** from acetate **8-34** by succinate trick.

In the original procedure the free alcohol **(+)-8-33** was released from the acetate **8-34** by reduction with DIBAL-H, giving ethanol as the only byproduct (**Scheme 118**). This is a reasonable drawback, because for large scale preparation significant amounts of costly DIBAL-H solution is required. We found that acetate cleavage could be easily achieved by treatment with hydrazine hydrate in ethanol. The acyl hydrazide formed in this reaction is water soluble and washed out by extraction.

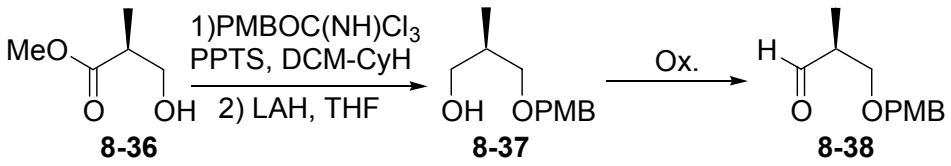


Scheme 118. Synthesis of chiral propargylic mesylate **8-15**.

On the last step the alcohol function was converted to the mesylate ester thus turning it into a good leaving group, which is required for further reaction. Although, this preparation is somewhat lengthy, all steps are high yielding and experimentally simple, thus making chiral alkynylmesylates valuable four carbon building blocks for organic synthesis. Recently, even a much more efficient and shorter procedure for preparation of chiral propargylic alcohols was published. It's based on catalytic Noyori transfer hydrogenation of alkynyl ketones, which are available by manganese oxide oxidation of corresponding racemic alcohols[199].

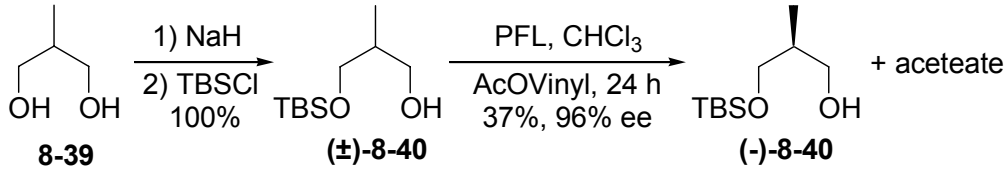
8.2.4 Synthesis of right-hand fragment

We decided to prepare the C19-C23 fragment of dictyostatin from known intermediate **8-43**. The common route to this compound (**Scheme 119**) starts from commercially available 2-methy-3-hydroxy (2S)-3-hydroxy-2-methylpropionic acid methyl ester **8-36** (Roche ester) which is quite costly (6 €/g).



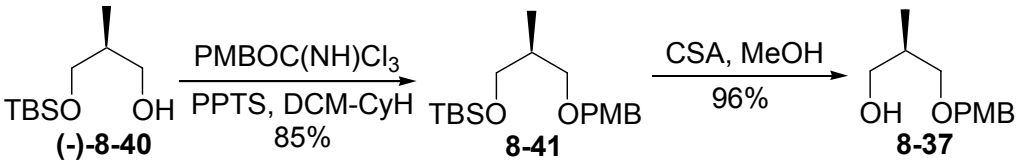
Scheme 119. General route to aldehyde **8-38**.

As an alternative, desymmetrization of 2-methyl-1,3-propanediol was investigated. Unfortunately, this reaction doesn't proceed well, probably due to close proximity of the hydroxyl groups. Therefore, the required chiral three carbon building block was prepared by enzyme catalyzed kinetic resolution of racemic TBS protected 2-methyl-1,3-propanediol[200]. When the acylation reaction was allowed to reach 63% of conversion, the enantiomeric excess of the remaining 37% of alcohol **(-)-8-40** was determined to be 96% (**Scheme 120**).



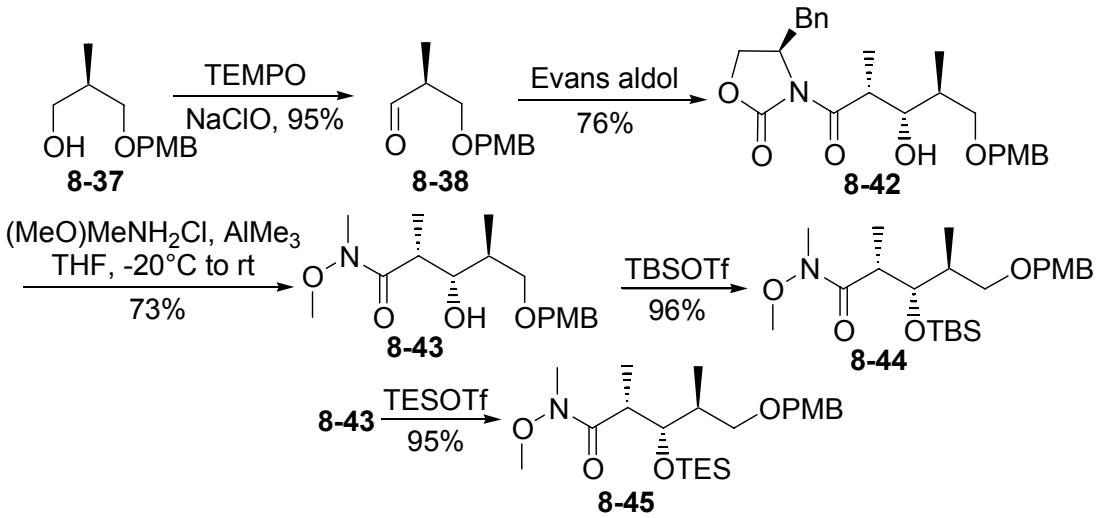
Scheme 120. Kinetic resolution of TBS protected 2-methyl-1,3-propanediol.

Since the product of this reaction has opposite configuration, inversion was done by etherification with PMB-imidate[201],[202] followed by deprotection of the silyl ether leading to desired alcohol **8-37** (**Scheme 121**).



Scheme 121. Synthesis of alcohol **8-37**.

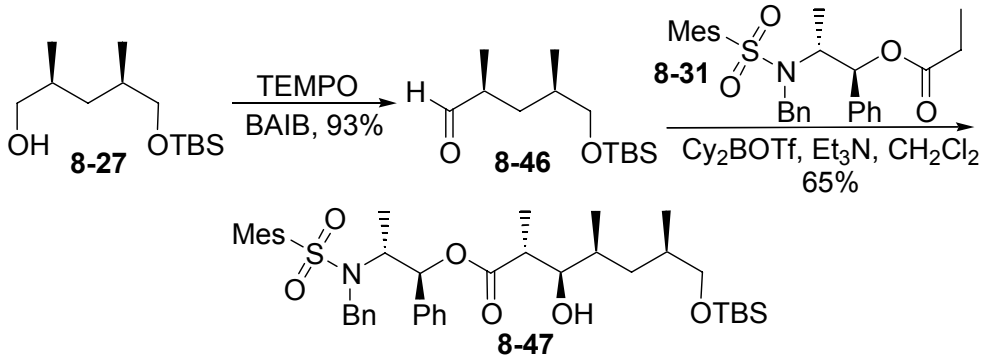
Further chemical transformations were done in full accordance with published procedures. Alcohol was oxidized to aldehyde **8-38** and introduced in an Evans aldol reaction (**Scheme 123**). After isolation the aldol adduct **8-42** was converted to Weinreb amide **8-43** by the classical trimethylaluminum-mediated method. Protection of hydroxyl function as silyl ether afforded intermediates **8-44** or **8-45**.



Scheme 123. Synthesis of differently protected Weinreb amides by Evans aldol reaction.

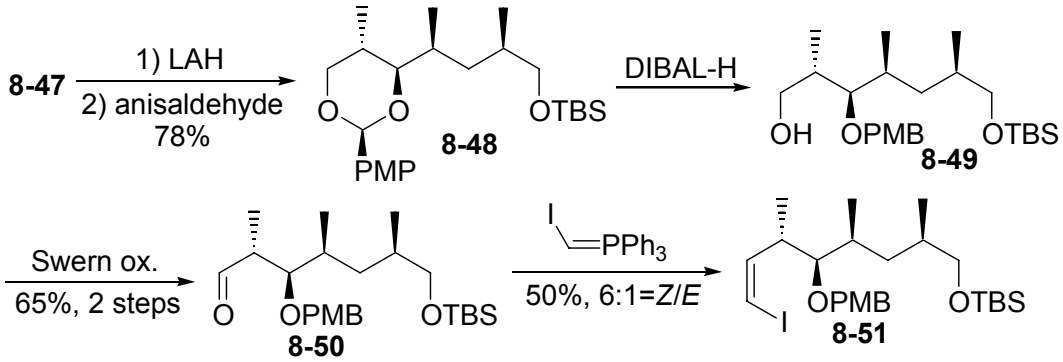
8.3 Attempted extension via Abiko aldol and Stork-Zhao reactions

After all intermediates required for construction of the top fragment were prepared, we proceeded further according to our synthetic plan. Our initial tactic was to use an Abiko *anti*-aldol reaction followed by Stork-Zhao reaction to create the stereocenter at C11 and to establish the *Z*-vinyl iodide functionality at C9. It was found that the aforementioned aldol reaction does proceed between auxiliary **8-31** and aldehyde **8-27** with excellent diastereomeric ratio but the yield of desired product **8-47** was rarely more than 65% (**Scheme 124**). Variations in ratio of dicyclohexylboronyl triflate, aldehyde and triethylamine failed to improve it.



Scheme 124. Abiko aldol reaction with aldehyde **8-46**.

After standard auxiliary cleavage with LAH, the resulting diol was converted into PMP acetal **8-48** with anisaldehyde, followed by selective deprotection of the terminal alcohol (**Scheme 125**).

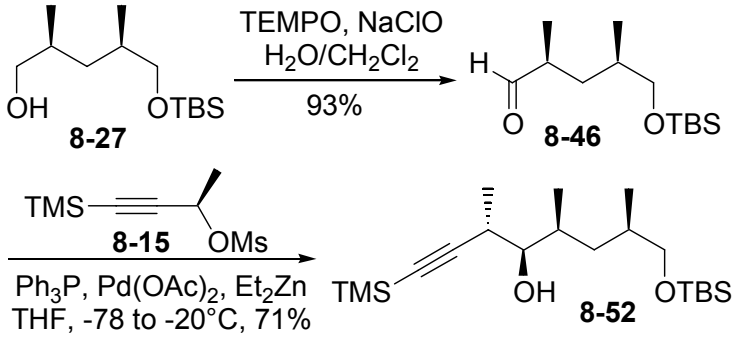


Scheme 125. Auxiliary cleavage and synthesis of vinyl iodide **8-51** by Stork-Zhao olefination.

The derived aldehyde **8-50** was subjected to Stork-Zhao reaction to give the desired vinyl iodide in 50% yield and 6:1 *Z*/*E* ratio. We judged this sequence to be too elaborated and low yielding and thus turned to the more promising Marshall reaction.

8.4 Extension via Marshall allenylzincate methodology

We decided to employ the Marshal allenylzincate methodology and found that aldehyde **8-27** reacted smoothly with mesylate **8-15** (**Scheme 126**) to give the desired product in 71% yield and 93:7 diastereomeric ratio (**Figure 50**). By this way, introduction of a four carbon fragment, the *anti* stereochemistry at C12-C13 and the protected triple bond was achieved in one chemical step. The only drawback of this reaction is the relatively long time required for complete consumption of aldehyde.



Scheme 126. Synthesis of **8-52** by Marshall allenylzincate addition.

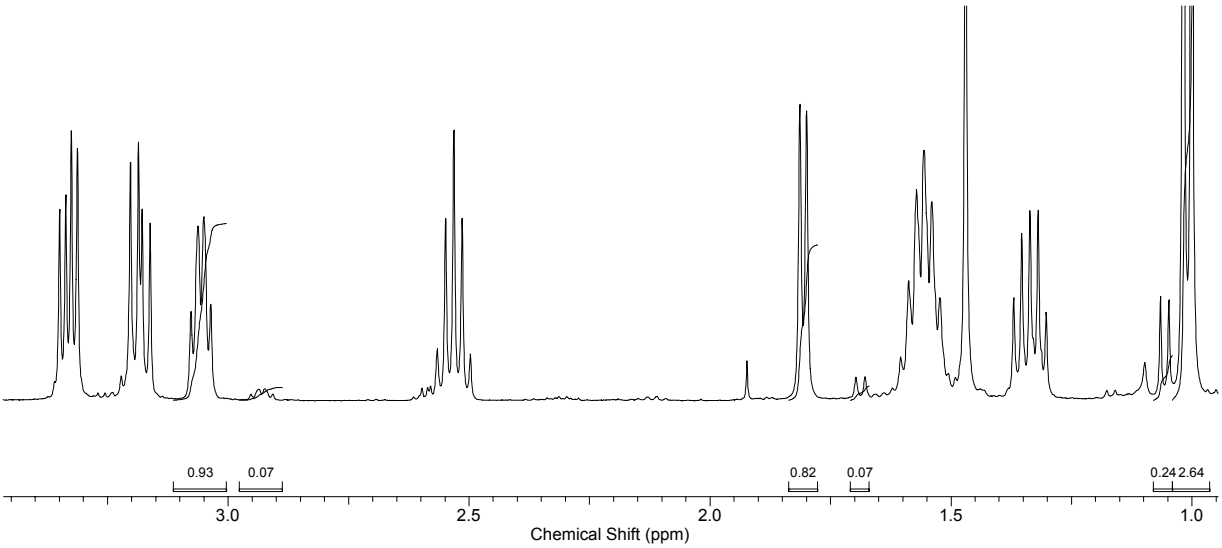
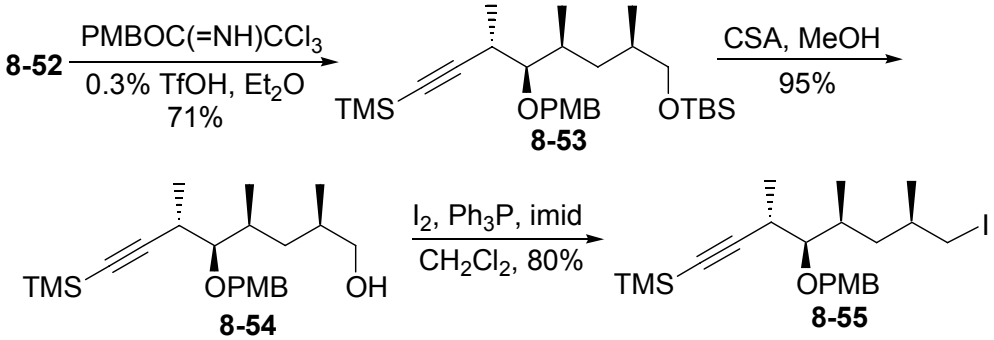


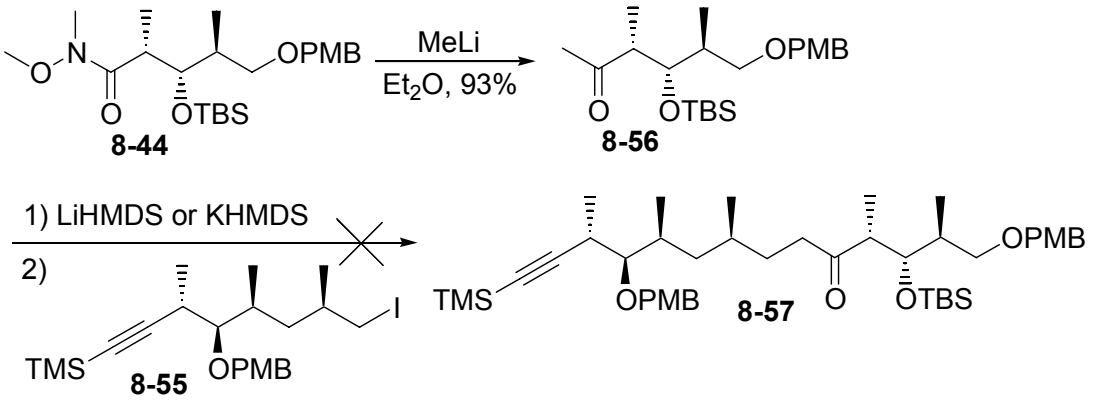
Figure 50. A fragment of the ^{1}H NMR spectrum of compound **8-52**.

Protection of the secondary alcohol function in the obtained stereotriad as PMB ether was somewhat troubling, probably due to sterical hindrance of the hydroxyl group. The only conditions which give satisfactory yield of product were treatment with 1.5 equivalents of PMB-imidate in diethyl ether with 0.3 mol % trifluoromethanesulfonic acid as catalyst. After cleavage of the primary TBS ether, the hydroxyl function was converted to alkyl iodide **8-55** by S_N2 reaction with iodine, triphenylphosphine and imidazole.



Scheme 127. Preparation of alkyliodide **8-55**.

Having one part of the molecule in hand we then prepared the required right-hand building block by simple addition of methyllithium to Weinreb amide **8-44** (**Scheme 128**). This reaction gave an excellent yield of methyl ketone **8-56** which was then deprotonated with KHMDS or LiHMDS followed by addition of alkyl iodide **8-55**.

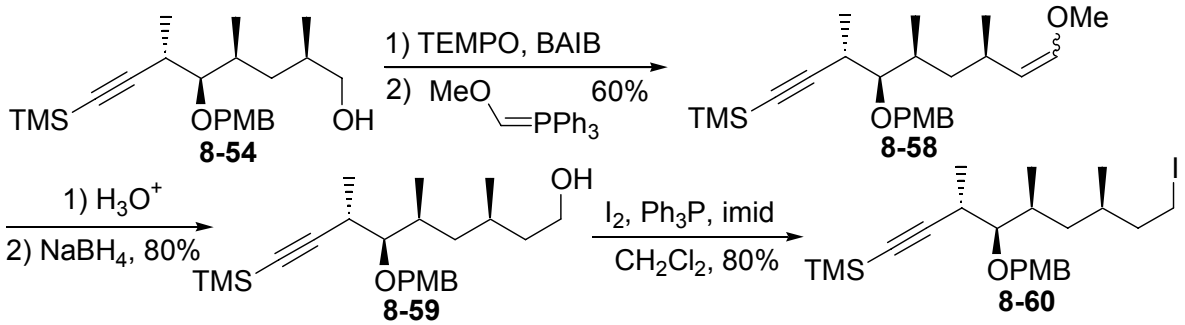


Scheme 128. Attempted synthesis of C10-C23 segment of by alkylation.

Unfortunately, the desired alkylation product was not isolated from these test reactions. One possible explanation for this is the sterical hindrance of the methyl group in the molecule of alkyl iodide, similar to the neopentyl effect in the S_N2 reaction. Keeping in mind that Weinreb amide **8-44** reacts nicely with methyllithium we decided to employ this reaction for fragment assembly.

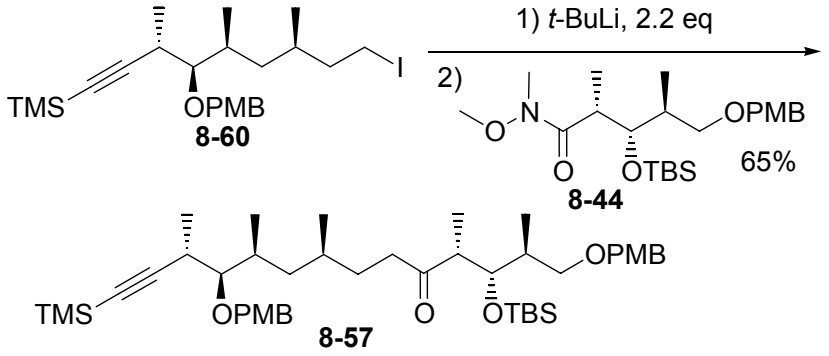
8.5 Coupling of the right and left fragments via alkyllithium addition to Weinreb amide

After unsuccessful attempts to combine fragments **8-55** and **8-56** by alkylation we reverted to another option, namely direct acylation of the alkyllithium compound derived from the one carbon elongated alkyl iodide. This elongation was achieved by classical sequence[203] of oxidation, Wittig reaction with (methoxymethylene)(triphenyl)phosphorane, hydrolysis of the enol ether and reduction (**Scheme 129**). Treatment of the resulting alcohol with iodine and triphenylphosphine in presence of imidazole resulted in formation of desired alkyl iodide **8-60** with a very good yield.



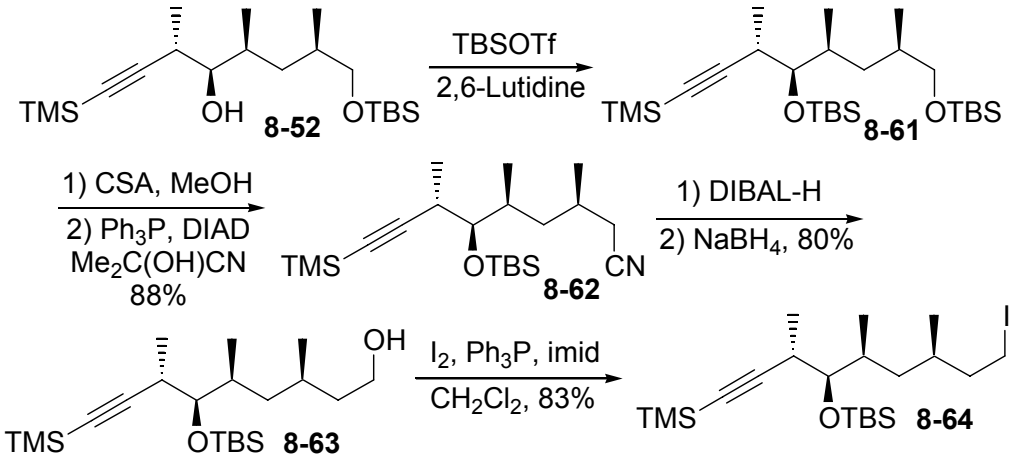
Scheme 129. Synthesis of alkyl iodide **8-60** via one carbon elongation.

We found, that halogen-metal exchange on iodide **8-60** proceeds smoothly and after acylation with Weinreb amide **8-44** furnished the desired ketone **8-57** in 65% yield.



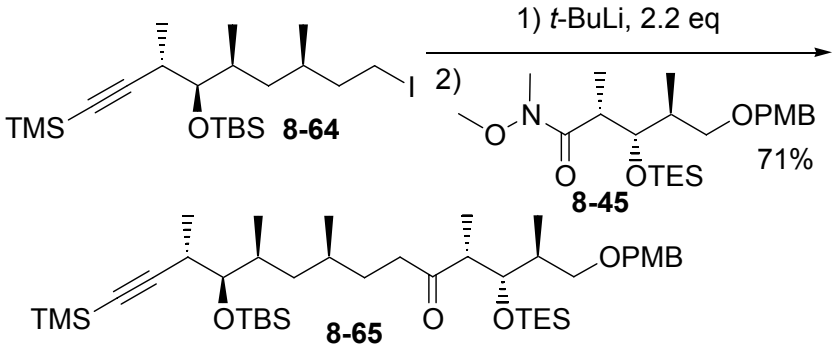
Scheme 130. Coupling of fragments by alkyllithium acylation.

Due to difficulties in gram scale preparation of vinyl ether **8-58** we decided to improve the one carbon extension sequence by using a Mitsunobu reaction. We also wanted to implement a different protecting group pattern in this series in order to achieve selective deprotection of the terminal PMB ether at the later steps. Thus, the secondary TBS protecting group was introduced in the alcohol **8-52**, followed by selective deprotection of the primary alcohol (**Scheme 131**). The resulting intermediate was converted to nitrile **8-62** with a very good yield by treatment with DIAD, Ph_3P, and acetone cyanohydrin as cyanide ion source. The following sequential reduction to aldehyde and to alcohol provided the desired elongated compound **8-63**. Transformation to alkyl iodide **8-64** from alcohol **8-63** was done as previously described.



Scheme 131. Synthesis of alkyl iodide **8-64**.

Due to the presence of the secondary TBS ether in the alkyl iodide **8-64** we coupled it with another Weinreb amide **8-45**, which has the orthogonally protected C21 hydroxyl group (**Scheme 132**).

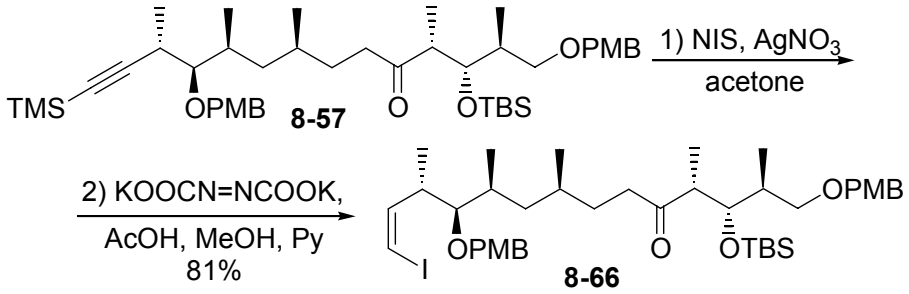


Scheme 132. Synthesis of advanced intermediate **8-65**.

We noticed a slight increase of product yield for this fragment combination. The main by-product isolated from this reaction was the alkane corresponding to alkyl iodide, which is normal occurrence for such methal halogen exchange reaction.

8.6 *Z*-vinyl iodide synthesis and *syn*-selective reduction

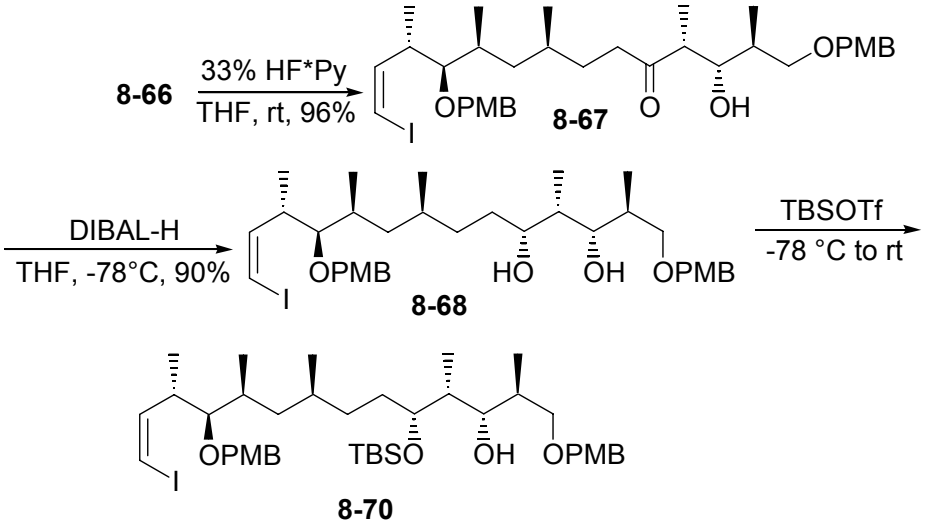
After construction of the carbon chain was finished, we continued with the creation of the remaining stereocenters and a suitable functional group at C10,C11. Thus, treatment of trimethylsilyl alkyne **8-57** with N-iodosuccinimide in presence of silver nitrate resulted in quantitative conversion to iodoalkyne, which was without purification subjected to a *Z*-specific diimide reduction[204] (**Scheme 133**). Although, at least 10 equivalents of potassium azadicarboxylate were required to achieve complete conversion, this method provided vinyl iodide **8-66** in excellent yield. One should note that any other than iodide substituted triple bond will be reduced to the alkane under these conditions.



Scheme 133. Convertion of triple bond to vinyl iodide.

Our next task was to achieve a *syn*-selective reduction of the carbonyl function in compound **8-66**. Deprotection of the TBS group proceeded cleanly by treatment with a 33% solution of HF-pyridine complex (Olah reagent) in THF (**Scheme 134**). We tried all three methods presented in a literature review, namely reduction with $NaBH_4$ in presence of diethylmethoxyborane, reduction with zinc borohydride and reduction with 2.2 eq of DIBAL-H at low temperature. The first method gave us a 1:2 diastereomeric mixture of diols, while

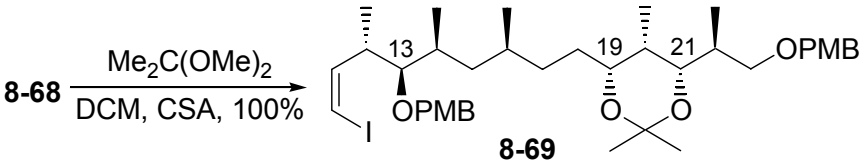
the second one was ruled out because of the tedious preparation of the zinc borohydride. The DIBAL-H reduction was found to be the method of choice due to combination of high selectivity, good chemical yield, experimental simplicity and commercial availability of the reagent.



Scheme 134. *Syn*-selective reduction of the hydroxyketone.

However, we found that certain conditions must be obeyed in order to obtain reproducible results. Concentration of the substrate should be 40 mM or less, addition of the first equivalent of DIBAL-H must be slow, and 3-3.5 equivalents of DIBAL-H solution in THF are usually required for complete reduction.

The relative stereochemistry of the hydroxyl groups at C19, C21 was confirmed by the Rychnovsky method[205]. Acetonide of diol **8-69** has been prepared (**Scheme 135**) and its ^{13}C spectra exhibits two very different signals for the acetal methyl groups at 19.7 and 30.0 ppm, together with 98.6 ppm shift of the ketal carbon, clearly indicating a *syn* relationship (**Figure 51**).



Scheme 135. Synthesis of acetonide derivative **8-69** for stereochemical analysis.

Different sterical demand of the two hydroxyl groups allowed selective silylation of the less hindered one with a bulky silyl protecting group, providing our first model substrate **8-70** for NHK reaction.

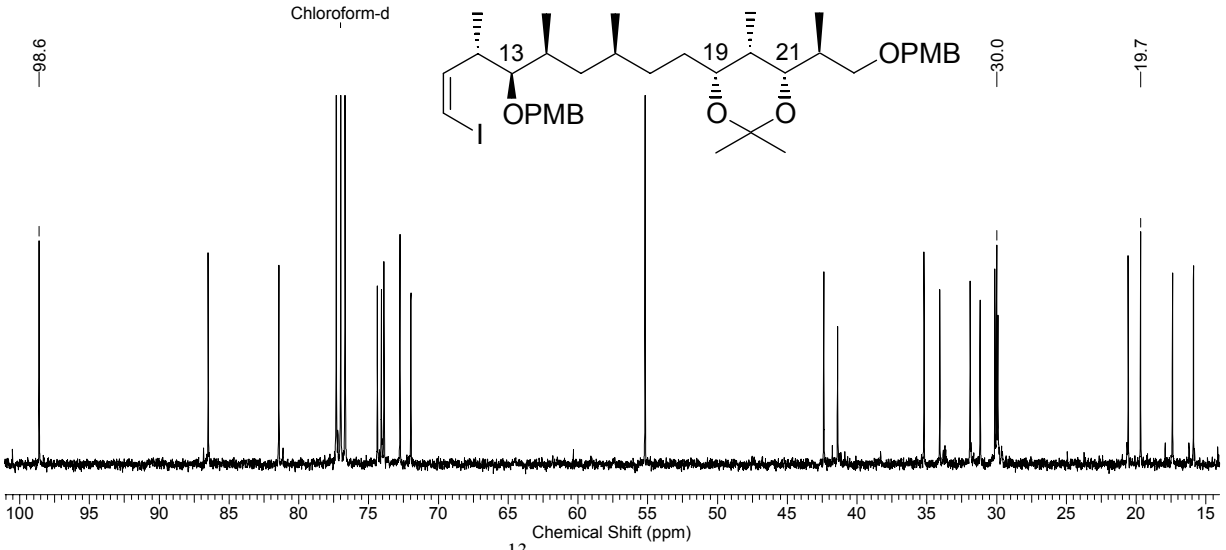
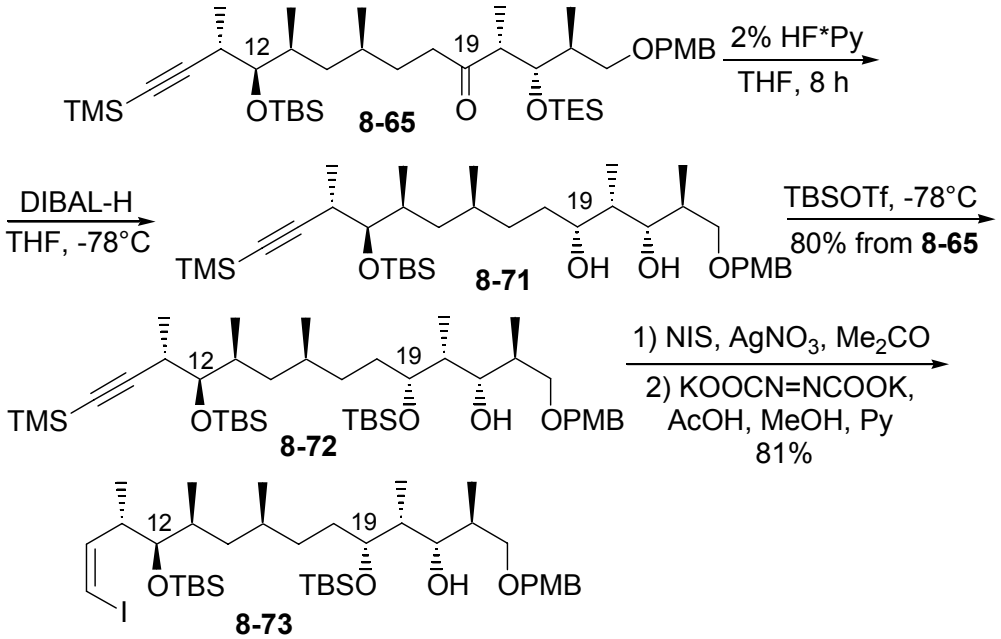


Figure 51. A fragment of the ^{13}C NMR spectrum of the diol acetonide **8-69**.

In the C13-OTBS series we decided to change the sequence of steps to avoid difficulties associated with handling compounds with an acid sensitive triethylsilyl protecting group. Thus, selective deprotection of the TES group was done using classical Masamune conditions with 2% solution of HF-pyridine complex in THF (**Scheme 136**). The resulting hydroxyketone was reduced to *syn*-diol **8-71** as previously described. Selective protection of the C19 hydroxyl function and conversion of the triple to Z-vinyl iodide give rise to another upper fragment (**8-73**) of dictyostatin.

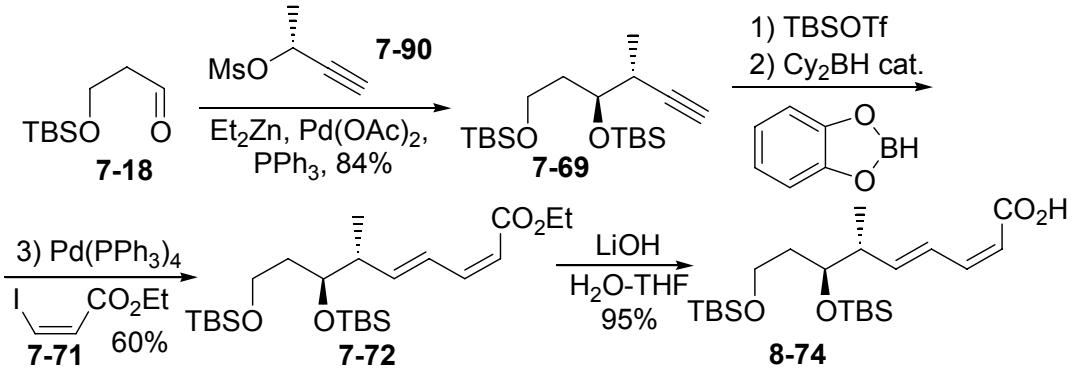


Scheme 136. Synthesis of a modified C10-C23 fragment.

As one can see, we achieved a very straightforward synthesis of the C10-C23 segment of dictyostatin in 16 linear steps from which only 10 require column chromatography.

8.7 Synthesis of C1-C9 fragment

The synthesis of the bottom fragment of dictyostatin was performed by Julia Jägel while working on her diploma thesis[206]. A very straightforward approach was developed using the previously described Marshall allenyl zincate addition. Enantiomeric propargyl mesylate **7-90** reacts smoothly with aldehyde **7-18** and afforded the desired product with *anti*-oriented methyl and hydroxyl groups. Diastereo- and enantioselectivity determined by ^{1}H NMR spectra and chiral GC were found to be 93:7. Hydroboration of the triple bond with catecholborane in presence of catalytic amounts of dicyclohexylborane followed by Suzuki cross-coupling resulted in an one-pot preparation of the entire fragment.



Scheme 137. Synthesis of C1-C9 fragment **7-72**

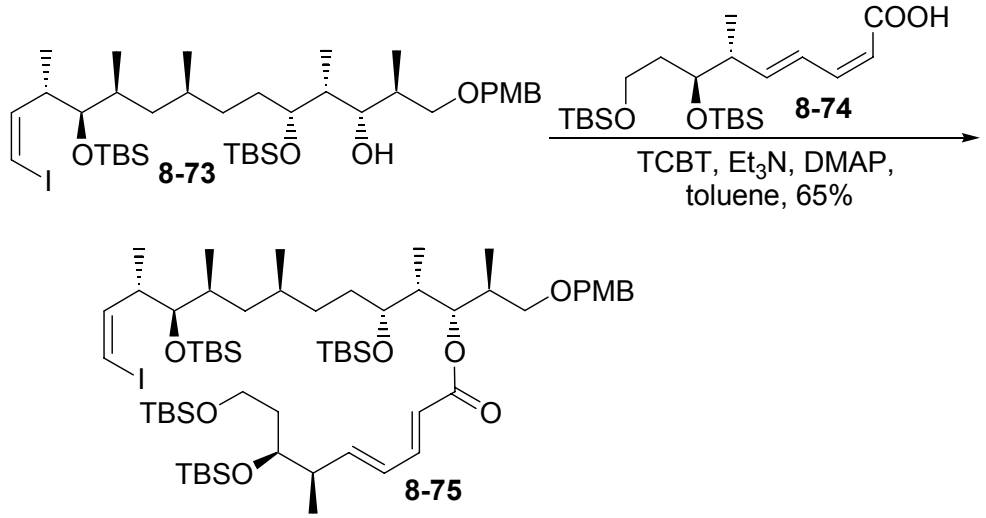
Depending on the fragment combination strategy, suitable derivative can be obtained from compound **7-72** by either hydrolysis to carboxylic acid or by deprotection of the primary hydroxyl function and oxidation to aldehyde.

8.8 Attempted Nozaki-Hiyama-Kishi macrocyclization

Having all fragments of the molecule in hand we were looking for an appropriate "end play" of the synthesis. In our retrosynthetic analysis we proposed to employ an intramolecular Nozaki-Hiuyama-Kishi reaction to close the macrocyclic ring. This reaction proceeds under very mild conditions, and can deliver the macrocyclic ring even in some very complicated cases.

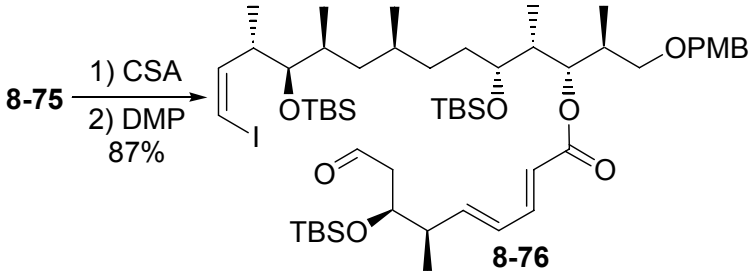
We supposed to prepare the required substrate for intramolecular NHK in three steps, namely esterification, deprotection of primary silyl ether and oxidation. However, when alcohol **8-73** and acid **8-74** were subjected to Yamaguchi type esterification conditions the product with completely isomerized C2-C3 double bond was isolated (**Scheme 138**). The fact of the

isomerization was confirmed by the extremely big coupling constant (15.4 Hz) of the 2-H and 3-H protons, clearly indicating an *E*-relationship. Attempted esterification by the Shiina protocol[207] gave no product at all.



Scheme 138. Esterefication of **8-73** with **8-74** accompanied by isomerization.

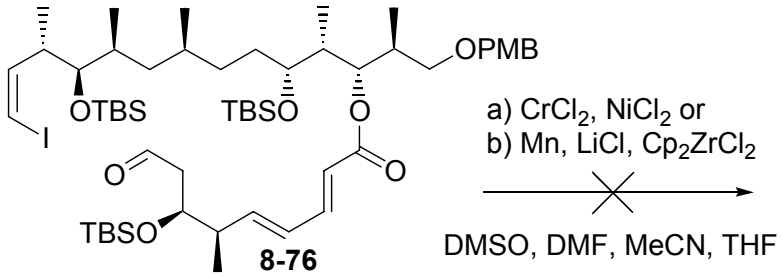
Despite these rather disappointing findings, we decided to go further and investigate the NHK macrocyclization reaction. On the resulting *E*,*E*-ester the terminal TBS group was removed followed by mild oxidation to aldehyde (**Scheme 139**).



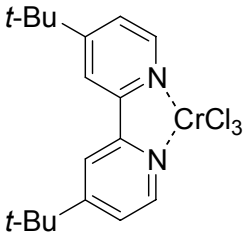
Scheme 139. Synthesis of aldehyde **8-76** for NHK macrocyclization.

We executed numerous attempts to achieve ring closing in substrate **8-76** but were unable to do so. Stochiometrical and catalytic variants of NHK reaction conditions were tried in different solvents and solvent combinations (**Table 6**). Although, in some cases we did observe complete consumption of starting material, the desired product was never isolated from the reaction mixture.

Table 6. Scope of conditions tried for NHK macrocyclization.



8-76



7-154

7-153

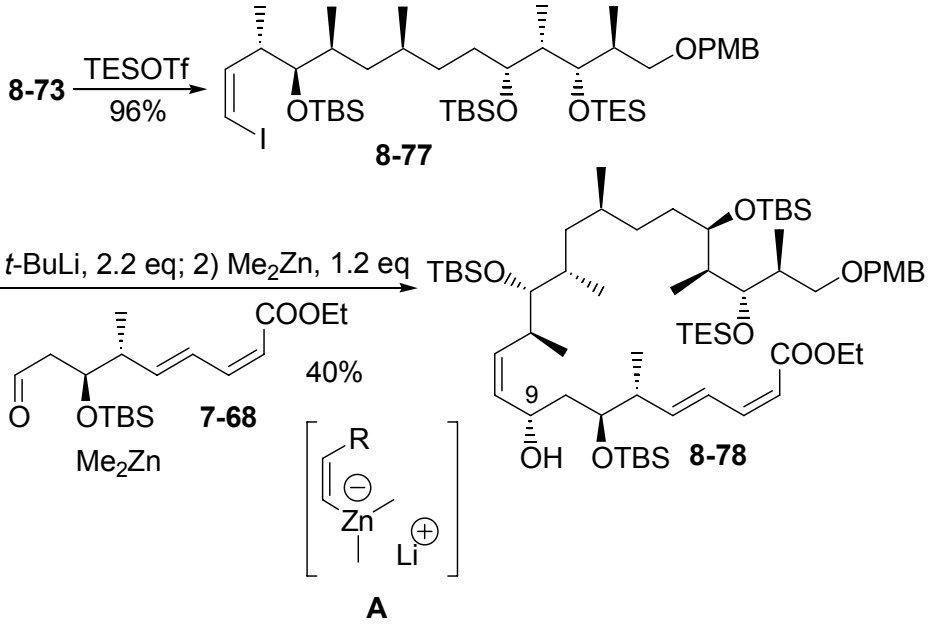
Solvent	Conditions	Outcome
THF	$CrCl_2$ (10 eq), $NiCl_2$ (0.1 eq)	No reaction
DMF-THF=3:1	$CrCl_2$ (20 eq), $NiCl_2$ (0.1 eq)	No reaction
THF-DMSO=3:1	$CrCl_2$ (20 eq), $NiCl_2$ (0.1 eq)	No reaction
THF	Mn, LiCl, **7-153**, **7-154**, Cp_2ZrCl_2	Decomposition
MeCN	Mn, LiCl, **7-153**, **7-154**, Cp_2ZrCl_2	Decomposition

This could be explained by competitive reduction of the aldehyde due to an unfavorable geometry of the substrate with regard to the cyclization mode.

8.9 Study of alternative coupling strategy

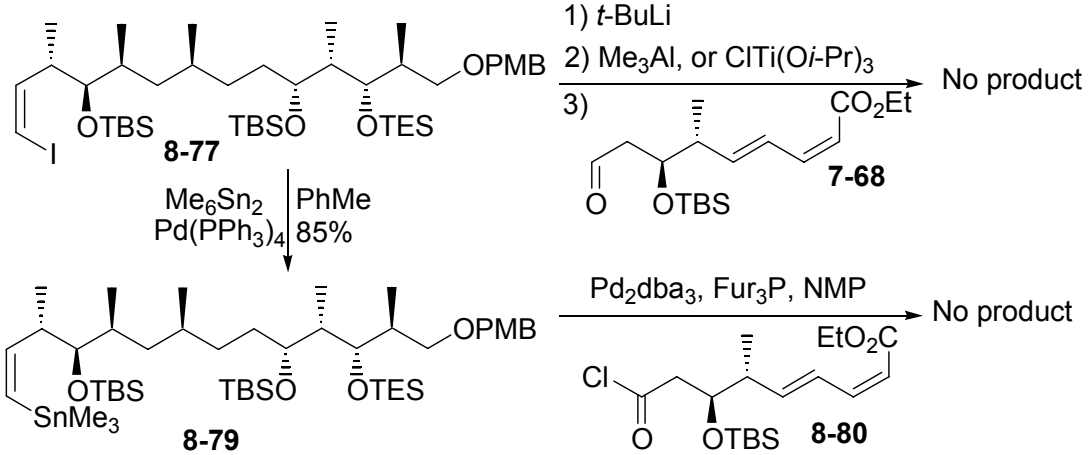
After unsuccessful attempts to join the fragments of the molecule by esterification/NHK reactions we revised our strategy and decided to form the bond between C9 and C10 carbons prior to macrolactonization. A literature search revealed that alkenyl zincate addition to an aldehyde was previously reported by Williams[208]. We prepared the fully protected top **8-77** fragment and subjected it to metal-halogen exchange with *tert*-butyllithium (**Scheme 140**). To the vinyllithium compound were added 1.2 equivalents of the dimethyl zinc. The mixture was stirred for 15 minutes and the *ate*-complex **A** was transferred by canula to the mixture of aldehyde **7-68** and dimethyl zinc. It seems that the vinylzincate is configurationally stable and

less basic. Nevertheless, the reaction is not very clean and generates a number of products. But the desired alcohol could be isolated in 40% yield.



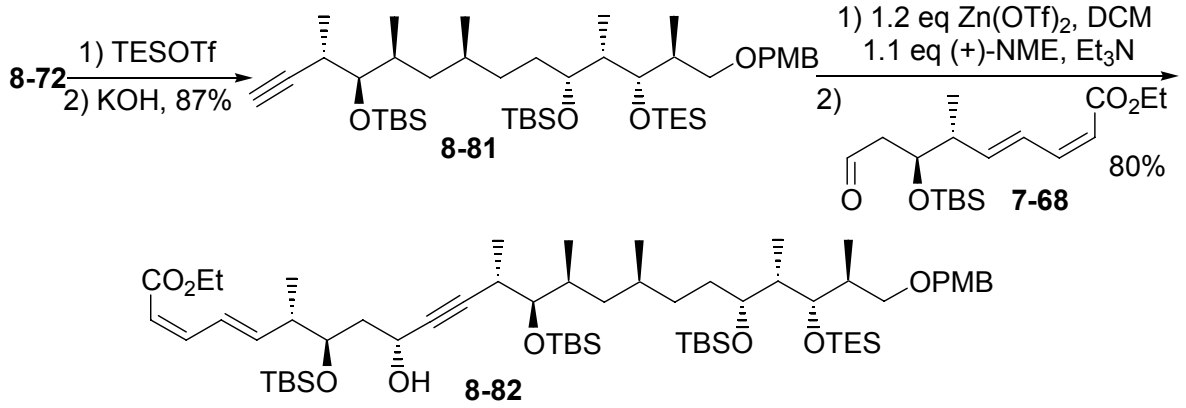
Scheme 140. Fragment coupling by zincate addition.

In order to improve the yield of the desired product some other *ate*-type metallorganic species were investigated (**Scheme 141**). Thus, the vinyllithium obtained by exchange as described earlier was transmetallated with trimethylaluminium or ClTi(O*i*-Pr)$_3$ and then aldehyde **7-68** was adedd. The alcohol **8-78** was not isolated from these reactions. Attempted acylation of the mixed cuprate prepared from the vinyllithium and butyl-(2-thienyl)-cyanocuprate was not successful either. The vinyl stannane **8-79** was obtained by insertion of Me_6Sn_2 under palladium catalyzed conditions but failed to react with the acyl chloride **8-80**.



Scheme 141. Attemted couplings via ate-complexes and stannane acylation.

We suspected that the bulky OTBS protection group located in the near proximity of the *Z*-double bond reactive terminus creates significant sterical hindrance for the attack of an electrophile. To ascertain this assumption, alkynyl addition to aldehydes were investigated. Deprotonation of **8-81** with BuLi or EtMgBr followed by addition of aldehyde gave a messy reaction with a number of products. Alkynyl titanium reagent generated from alkynyl lithium and $ClTi(O\textit{i}\text{-}Pr)_3$ failed to react with the aldehyde. Eventually, the Carreira[209] methodology for asymmetric addition of alkynes to aldehydes was employed (**Scheme 142**). Under slightly modified conditions, namely DCM was used as a solvent together with excess of zinc triflate, the reaction proceeds cleanly and the desired propargylic alcohol has been isolated in 80% yield based on recovered alkyne (1.25 equivalent was used to drive the reaction to complete consumption of aldehyde because it was not separable from the product by column chromatography).

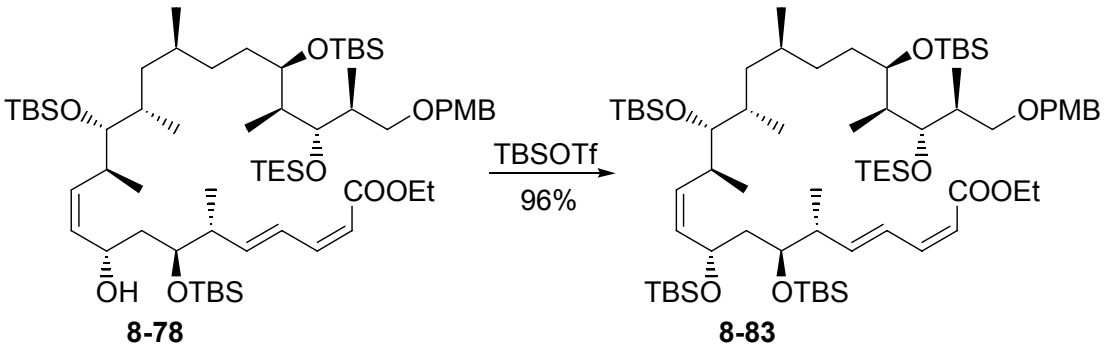


Scheme 142. Coupling of fragments by Carreira alkynylation.

On the next step hydrogenation of the triple bond to a Z-double was attempted. However, all conditions tried and catalysts including Lindlar, Rosemund, and nickel boride[203], resulted in preferential reduction of the α,β-unsaturated ester. This can also be explained by sterical hindrance near the triple bond.

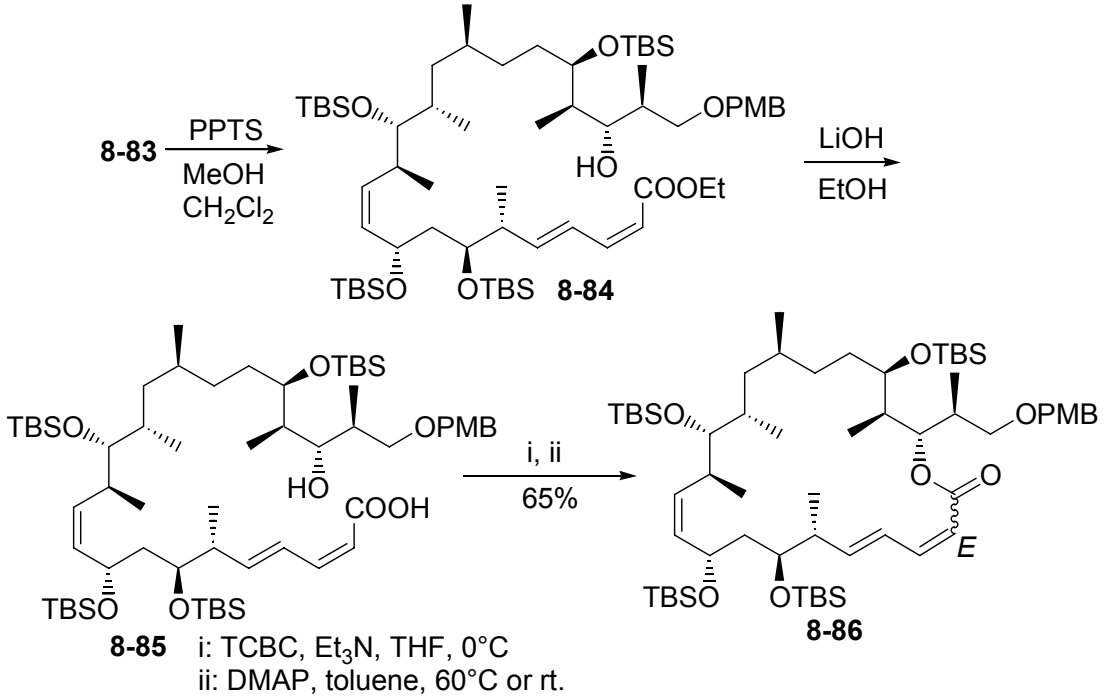
8.10 Completion of the synthesis

With no real success in improving condition for the crucial coupling, we were forced to accept the moderate yield of coupling product **8-78** in the reaction via the vinyl zincate and to proceed further (**Scheme 143**).



Scheme 143. Protection of zincate adduct **8-78**.

Deprotection of the triethylsilyl group in **8-83** was achieved by treatment with PPTS in a mixture of methanol and CH_2Cl_2, while reaction with 2% HF-Py complex generates significant amounts of by-products, mainly deprotected TBS ether in β-position (**Scheme 144**). The following alkali hydrolysis of the ethyl ester was trivial. The resulting seco-acid **8-85** was subjected to the Yamagichi macrolactonization protocol. To our great disappointment, we have found that again almost complete isomerization of the double bond next to the carboxyl group occurred when conditions reported by Paterson were used (**Figure 52**). Attempted macrolactonization by Curran's procedure gave a somewhat better result with a 1:1 *E*/*Z* isomeric mixture. It was about this time when a full paper describing the same isomerization phenomena in the dictyostatin C14-epimer was published by the Curran group[110].



Scheme 144. Synthesis of seco-acid **8-85** and attempted macrolactonization.

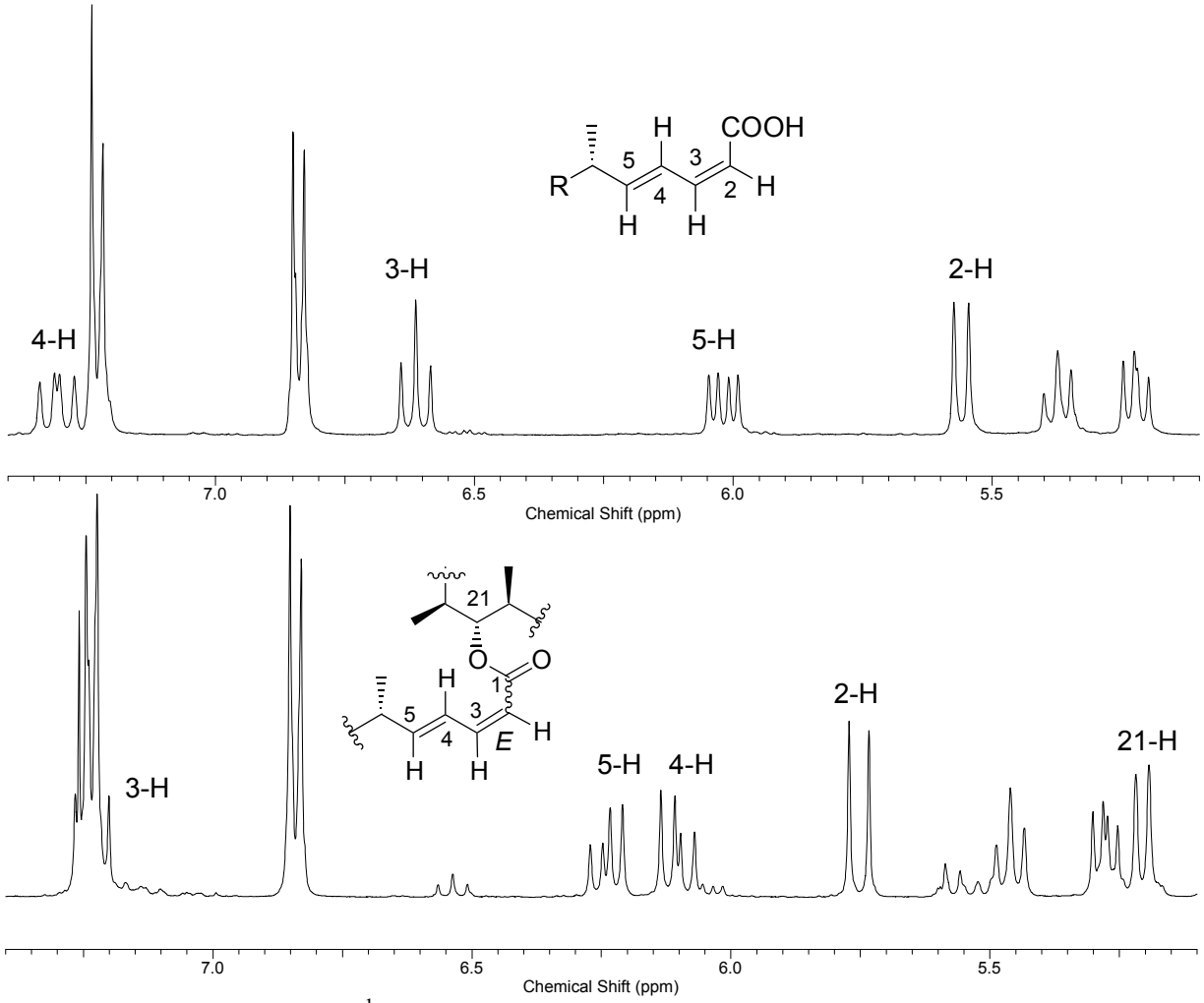
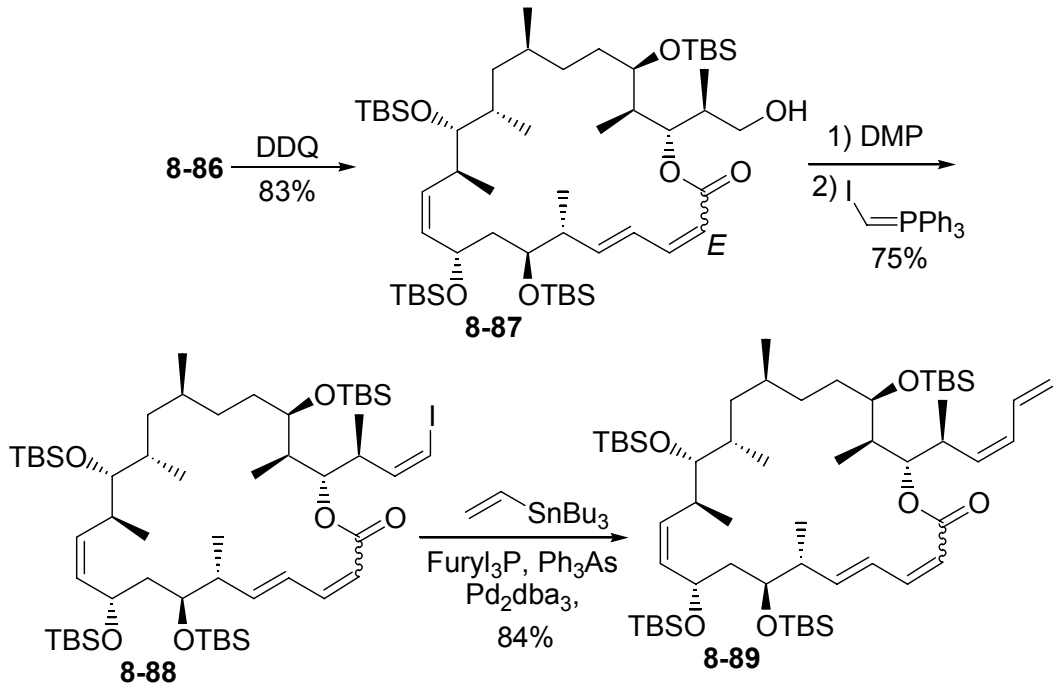


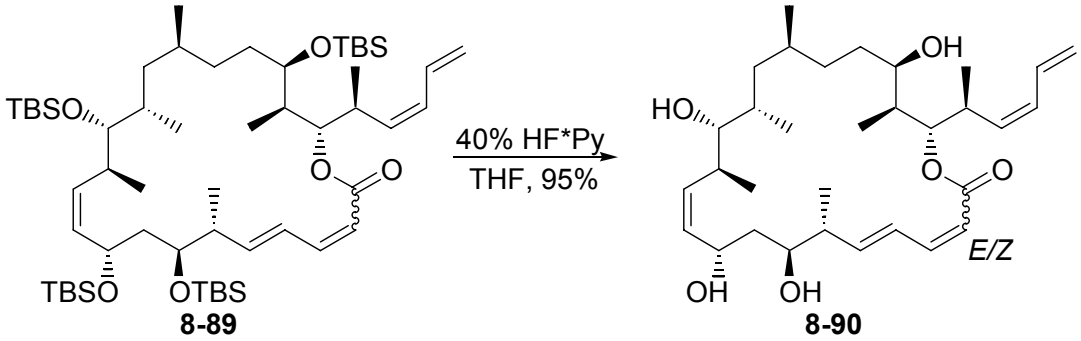
Figure 52. Fragments of ^{1}H NMR spectra of seco-acid (top) and macrolactone (bottom).

Nevertheless, we decided to continue our synthesis to obtain the previously unknown dictyostatin analogue. The classical deprotection of PMB ether with DDQ furnished the terminal alcohol which was later oxidized to aldehyde **8-87** (**Scheme 145**). After some unsuccessful attempts to install the terminal Z-diene unit by the Nozaki-Hiyama-Kishi reaction/Peterson elimination sequence we searched for an alternative route. As we discovered, the already mentioned Stork-Zhao olefination followed by Stille cross-coupling with vinyltributylstannane afforded the desired diene system in acceptable yield. In case of the correct macrolactone this protocol should allow preparation of different dictyostatin analogues by variation of ylide or/and organometallic reagent.



Scheme 145. Installation of diene unit by olefination/cross-coupling sequence.

Global deprotection of all alcohol functions proceeded cleanly by treatment with a 40% solution of HF-pyridine complex in THF to give 2-*E*-dictyostatin isomer **8-90** in 95% yield. To avoid substance loss on silica gel the final chromatography was performed using LiChroprep® DIOL (40-63 μm) stationary phase (Merck Nr 113973) with 1.5 % MeOH in CH_2Cl_2 eluent.

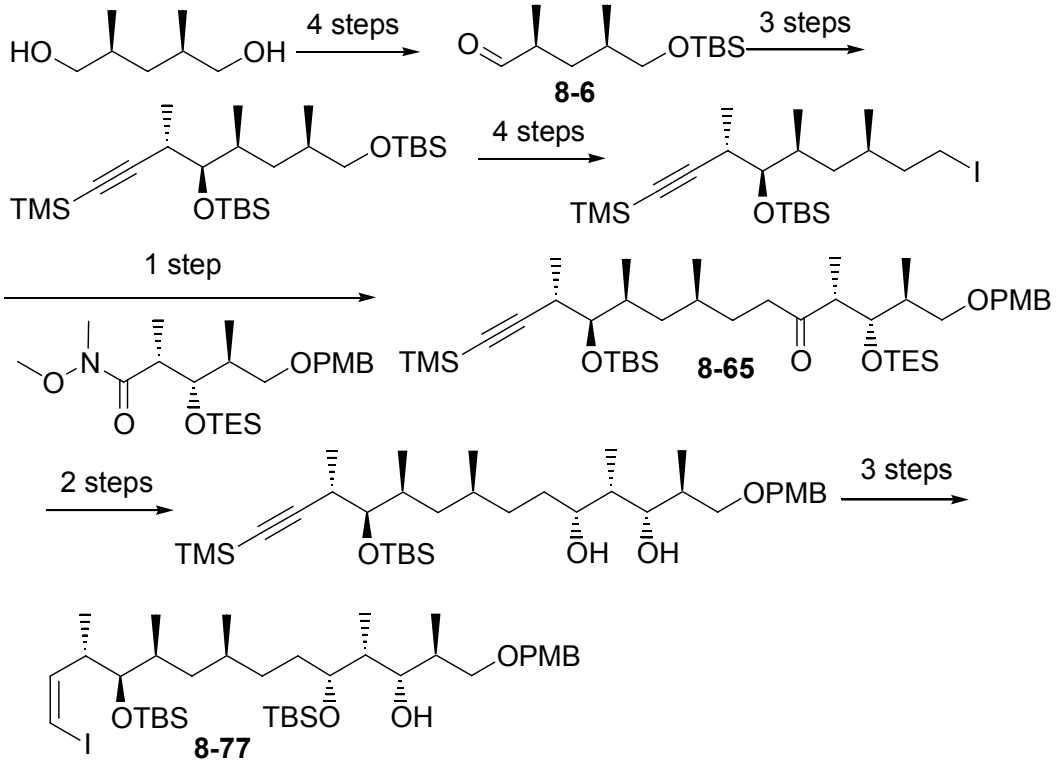


Scheme 146. Global deprotection of dictyostatin analog.

All described above transformations were repeated with *E*/*Z* isomers mixture obtained at the macrolactonization step. At the end, separation of two dictyostatin isomers was attempted by means of HPLC coupled to NMR.

9 Conclusion II

In summary, we developed an efficient synthesis of the top fragment of dictyostatin, which constitutes approximately 2/3 of the carbon backbone of the molecule. The key steps in this synthesis were an enzymatic desymmetrization, *anti*-selective allenylzincate addition, acylation of an alkyllithium compound with a Weinreb amide, *syn*-selective reduction of β-hydroxyketone, and stereospecific reduction of alkynyl iodide to *Z*-vinyl iodide.

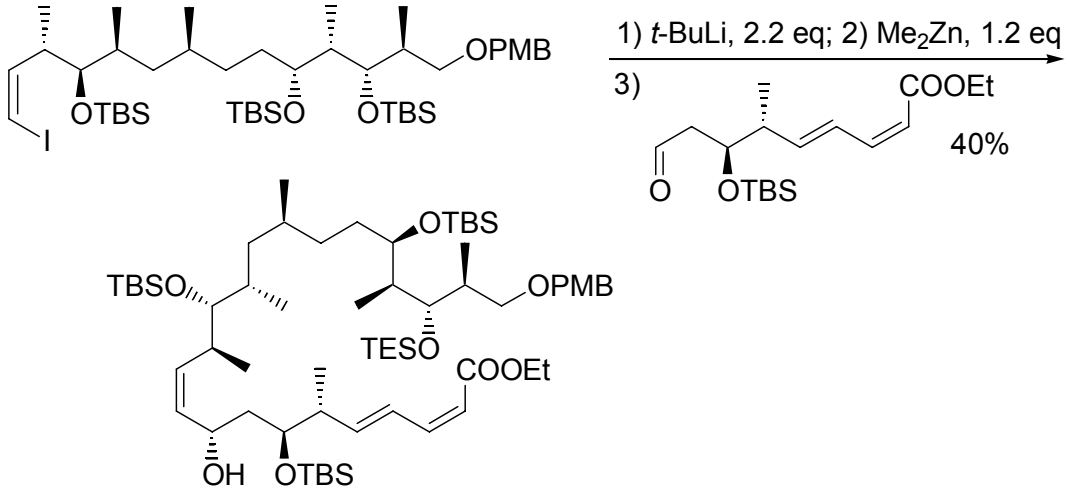


Scheme 147. Key intermediates in the synthesis of the top fragment of dictyostatin.

The synthesis of chiral aldehyde **8-6** started from racemic 2,4-dimethy-1,5-pentanediol and was performed without using column chromatography. Application of the Marshall reaction allowed us to introduce a four carbon building fragment in one chemical step. All in all, five of eight chiral centers in **8-77** were essentially obtained *via* enzyme catalyzed reactions (kinetic resolution of acetate, desymmetrization of *meso*-alcohol). *Syn*-reduction on **8-65** was performed by a very simple protocol using commercially available DIBAL-H.

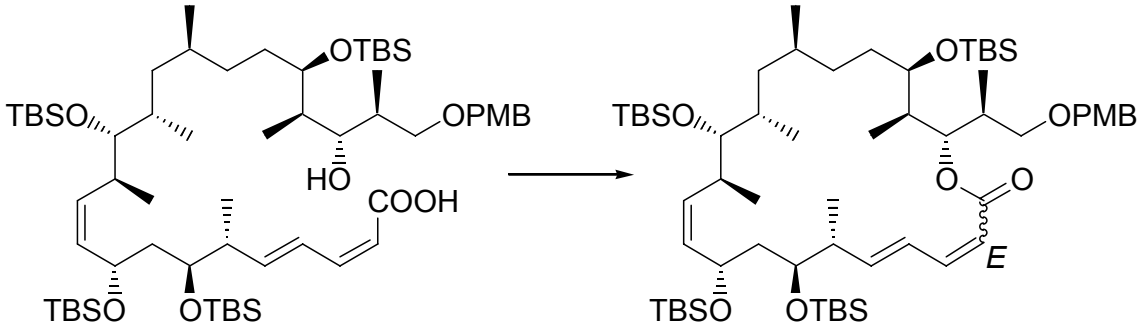
We also conducted a detailed study of fragment assembly and found that only addition of the vinyl zincate derived from vinyl iodide **8-77** to aldehyde **7-68** provided the desired coupling product with moderate but reproducible yield. Failure of other reagent combinations can be

explained by sterical hindrance from the bulky TBS protection group near the C10-C11 double bond.



Scheme 148. Fragment assembly via vinyl zincate addition.

Unexpected difficulties, associated with isomerization of the sensitive Z-dienoate double bond, were identified when esterification and macrolactonization reactions under Yamaguchi conditions were attempted on hydroxy acid **8-85**. This problem can be possibly solved in the future by performing esterification with ethyl *Z*-3-iodoacrylate followed by formation of the macrocycle ring via intramolecular cross-coupling reaction.



Scheme 148. Macrolactonization accompanied by isomerization.

Futhermore, an alternative pathway for installation of the terminal Z-diene unit was developed. Combination of a Stork-Zhao olefination followed by Stille cross-coupling reaction with tributylvinylstannane provided the desired compound reliably with good yield. These findings should provide ground for the successful dictyostatin synthesis in our laboratory.

10 Experimental Section

10.1 General Remarks

10.1.1 Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents which were obtained from commercial suppliers were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

10.1.2 Special note about working with Grubbs 2nd generation catalyst

It was found that second generation Grubbs' catalyst, namely (tricyclohexylphosphine)(1,3-dimesityl-4,5-dihydoimidazol-2-ylidene)methylideneruthenium dichloride, is extremely moisture, oxygen and light sensitive. Thus, to obtain satisfactory results some precautions should be taken. We used the following technique: a freshly bought batch of the catalyst (500 mg from Aldrich) was transferred into a glowbox and then weighted into 20-25 portions. Each portion was secured in a tightly closed brown glass vial with rubber septum cap and used when necessarily as a whole. The catalyst was introduced into the reaction simply by pouring the powder through the second neck with moderate counter flow of inert gas.

10.1.3 NMR-spectroscopy

All the spectra, exept compound **8-90**, were measured on a Bruker Advance 400 spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$ or $[D_4]MeOH$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH = 7.25 ppm, δC = 77.0 ppm), $[D_4]MeOH$ (δH = 2.49 ppm, δC = 39.5 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, *J* = coupling constant (Hz), integration, peak assignment in italic form).

10.1.4 Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

10.1.5 Infrared Spectroscopy

The FT-IR spectra were recorded on a Fourier Transform Infrared Spectrometer model Jasco FT/IR-430. Solid samples were pulverized with potassium bromide and percent reflection (R%) was measured. The percent transmittance (T%) of liquid substances were measured in film between potassium bromide plates. Absorption band frequencies are reported in cm^{-1}.

10.1.6 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020 or on a PerkinElmer Instruments Polarimetr Model 341. They are reported as follows: $[\alpha]^{temperature}_{D}$ (concentration, solvent). The unit of *c* is g/100 mL. Anhydrous CH_2Cl_2, $CHCl_3$ or EtOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

10.1.7 Melting Points

Melting points were determined with a Büchi Melting point B-540 apparatus and were not corrected.

10.1.8 Chromatographic Methods

Flash column chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel or Merck KGaA.

Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H_2. Chiral gas chromatographic analyses were carried out on 13.5 m × 0.25 mm column filled with deactivated fused silica with 30% 6-TBDMS-2,3-diacetyl-β-cyclodextrin in PS 086 (d_f = 0.13 μm) and carrier gas H_2 at 50 kPa and 30 °C.

For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.

Analytical thin layer chromatography (TLC) was performed on precoated with silica gel 60 F_{254} plates (Merck) or Polygram Sil G/UV_{254} (Macherey Nagel). The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$] and 0.4 g $Ce(SO_4)_2{\cdot}4H_2O$ were dissolved in 400 mL of 10%

H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

10.2 Experimental procedures

All the experimental procedures are arranged in the ascending order of number of the compound.

General procedure 4 for the preparation of imines from cyclic ketones and benzylamine. A mixture of benzylamine (12 mmol), the cyclic ketone (10 mmol), and molecular sieves 4Å in toluene (25 mL) was slowly stirred for 24 h. Thereafter, the molecular sieves was filtered off, and washed with toluene. The combined filtrates were concentrated in vacuo. The crude benzylimines were used without further purification.

General procedure 5 for the addition of allylmagnesium bromide to the benzylimines. To a solution of N-benzylimine (10 mmol) in abs. Et_2O (20 mL, 2 mL/mmol of imine) was added dropwise a solution of allylmagnesium bromide (10 mL, 2M in Et_2O, 20 mmol) at 0 °C with vigorous stirring. Stirring was continued for 1 h at 0 °C, and 3 h at room temperature. The reaction was quenched with saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was purified by flash chromatography.

To a mixture of N-carbethoxy-4-piperidone (**4-4**) (1.14 g, 6.7 mmol) and benzylamine (0.8 g, 0.8 mL, 7.3 mmol, 1.1 eq) was added titanium tetraisopropide (4 mL, 13.4 mmol, 2 eq) with vigorous stirring. After 4 h at room temperature, vaccum was applied to the flask and kept for 15 min at 1 mbar. The resulting viscous oil was dissolved with Et_2O (35 mL). Then, allylmagnesium bromide (7 mL, 1M in Et_2O) was added dropwise over 15-30 min followed by stirring the mixture overnight at room temperature. The mixture was diluted with additional Et_2O (30 mL) and poured into saturated aqueous NH_4Cl solution (30 mL) and stirred for 30 min. Then two-phase mixture was filtered through a pad of Celite. After separation of the layers, the aqueous layer was extracted with Et_2O (2×30 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography.

Ethyl 4-[(benzyl)amino]-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-5). yield 1.2 g (60%);

$\mathbf{R_f}$ = 0.64 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 1.32–1.58 (m, 4H, 3,5-H), 2.19 (d, *J* = 7.3 Hz, 2H, H_2C=CHCH_2), 3.21–3.34 (m, 2H, 2,6-H), 3.53–3.80 (m, 2H, 2,6-

H), 3.57 (s, 2H, $PhCH_2$), 4.04 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 5.02–5.11 (m, 2H, $H_2C=CHCH_2$), 5.73 (ddt, *J* = 17.0, 10.0 7.6 Hz, 1H, $H_2C=CHCH_2$), 7.12–7.32 (m, 5H, CH_{ar});
^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3CH_2O), 34.6 (C-3,5), 39.4 (C-2,6), 42.2 ($H_2C=CHCH_2$), 45.3 ($PhCH_2$), 52.5 (C-4), 61.0 (CH_3CH_2O), 118.5 ($H_2C=CHCH_2$), 126.8 (CH_{ar}, *para*), 128.1 (CH_{ar}, *ortho*), 128.3 (CH_{ar}, *meta*), 133.0 ($H_2C=CHCH_2$), 140.9 (C_{ar}), 155.6 (CO_2Et).

General procedure 6 for alkylation of N-benzylamines. To a solution of the N-benzylamine (6 mmol) in acetonitrile (20 mL, 3 mL/mmol) was added finely powdered potassium carbonate (1.78 g, 12.0 mmol, 2 equiv), and then bromomethylmethacrylate (7.2 mmol, 1.2 g, 0.7 ml, 1.2 equiv.) in acetonitrile (2 mL). This mixture was stirred overnight, filtered, and the filter cake washed with acetonitrile. The combined filtrates were evaporated and the residue purified by flash chromatography.

Methyl 2-{[(benzyl)(1-prop-2-en-1-ylcyclohexyl)amino]methyl}prop-2-enoate (4-2). yield 3.0 g (76%);
R_f = 0.67 (Et_2O/toluene, 1:3);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.75 (m, 10H, CH_2), 2.31 (d, *J* = 7.3 Hz, 2H, $H_2C=CHCH_2$), 3.42 (s, 2H, NCH_2), 3.51 (s, 3H, CO_2CH_3), 3.70 (s, 2H, $PhCH_2$), 4.89–5.02 (m, 2H, $H_2C=$), 5.67 (s, 1H, $H_2C=C(CO_2Me)$, *E*), 5.84 (s, 1H, ($H_2C=C(CO_2Me)$, *Z*)), 5.95 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, $H_2C=CHCH_2$), 7.12 (t, *J* = 7.3 Hz, 2H, CH_{ar}, *para*), 7. 21 (t, *J* = 7.3 Hz, 2H, CH_{ar}, *meta*), 7.28 (d, *J* = 7.3 Hz, 2H, CH_{ar}, *ortho*);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (CH_2), 26.4 (CH_2), 33.4 (CH_2), 38.3 ($H_2C=C(CO_2Me)CH_2$), 49.8 ($H_2C=CHCH_2$), 51.8 (CO_2CH_3), 54.0 ($PhCH_2$), 60.4 (C_{quat}), 117.2 ($H_2C=CH$), 126.7 ($H_2C=C(CO_2Me)$), 126.8 (CH_{ar}, *ortho*, *para*), 128.9 (CH_{ar}, *ortho*), 129.2 (CH_{ar}, *meta*), 136.1 ($H_2C=CHCH_2$), 139.3 ($H_2C=C(CO_2Me)$), 142.2 (C_{ar}), 167.8 (CO_2Me).
HRMS (EI): calcd for $C_{21}H_{30}NO_2$ $[M+H]^+$: 328.22711, found 328.22710.

Ethyl 4-[{2-[(methyloxy)carbonyl]prop-2-en-1-yl}(benzyl)amino]-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-6). yield 1.1 g (78%);
R_f = 0.56 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.44–1.74 (m, 4H, $C_{quat}CH_2$), 2.32 (d, *J* = 7.3 Hz, 2H, H_2C=CHC*H*$_2$), 3.14–3.25 (m, 2H, NCH_2), 3.41–3.45 (m, 2H, H_2C=C(CO_2Me)C*H*$_2$), 3.48–3.58 (m, 2H, NCH_2), 3.56 (s, 3H, CO_2CH_3), 3.70 (s, 2H, $PhCH_2$), 4.01 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 4.97–5.06 (m, 2H, *H*$_2$C=CHCH$_2$), 5.56–5.58 (m, 1H, H_2C=C(CO_2Me), *E*), 5.80–5.93 (m, 2H, H_2C=C*H*CH_2, (H_2C=C(CO_2Me), *Z*)), 7.02–7.14 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (C*H*$_3$CH$_2$O), 32.5 (C_{quat}*C*H$_2$), 37.7 (H_2C=C(CO_2Me)*C*H$_2$), 39.8 (NCH_2), 50.0 (H_2C=CH*C*H$_2$), 51.5 (CO_2*C*H$_3$), 53.5 ($PhCH_2$), 58.6 (C_{quat}), 61.0 (CH_3*C*H$_2$O), 119.2 (H_2*C*=CHCH$_2$), 126.5 (CH_{ar}, *para*), 126.7 (H_2*C*=C(CO_2Me)), 127.9 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 134.5 (H_2C=*C*HCH$_2$), 139.3 (H_2C=*C*(CO_2Me)), 141.0 (C_{ar}),155.4 (NCO_2Et), 167.2 (H_2C=C(*C*O_2Me)).

HRMS (EI): calcd for $C_{23}H_{33}N_2O_4$ $[M+H]^+$: 401.24348, found 401.24341.

General procedure 7 for the RCM of the N-benzyl protected dienes. To a degassed solution of the diene in toluene (10 mL/mmol) was added TsOH monohydrate (1.1 equiv.) followed by heating of the mixture to 50 °C for 30 min. Then, the 2nd generation Grubbs catalyst was added (5 mol %) and the mixture stirred for 4 h at 55 °C. Then, saturated Na_2CO_3 solution was added (2 mL/mmol) and the resulting mixture filtered through a pad of Celite. The layers of the filtrate were separated. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (toluene/Et_2O).

Methyl 1-(benzyl)-1-azaspiro[5.5]undec-3-ene-3-carboxylate (4-3). yield 160 mg (80%) white crystals;

M.p. 117-119°C;

R_f = 0.53 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.37 (m, 5H, CH_2), 1.45–1.56 (m, 1H, CH), 1.63–1.77 (m, 4H, CH_2), 1.98–2.05 (m, 2H, 5-H), 3.21 (s, 2H, 2-H), 3.49 (s, 2H, $PhCH_2$), 3.56 (s, 3H, CO_2CH_3), 6.93–6.98 (m, 1H, C*H*=C(CO_2Me)), 7.12 (t, *J* = 7.3 Hz, 2H, CH_{ar}, *para*), 7. 21 (t, *J* = 7.3 Hz, 2H, CH_{ar}, *meta*), 7.28 (d, *J* = 7.3 Hz, 2H, CH_{ar}, *ortho*);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (C-8), 26.5 (C-9), 32.6 (C-5), 34.6 (C-7), 44.0 (C-2), 50.3 ($PhCH_2$), 51.3 (CO_2CH_3), 53.1 (C_{quat}), 126.4 (CH_{ar}, *para*), 127.4 (HC=*C*(CO_2Me)), 128.1 (CH_{ar}, *ortho*, *meta*), 137.7 (C*H*=C(CO_2Me)), 140.9 (C_{ar}), 166.9 (CO_2Me).

HRMS (EI): calcd for $C_{19}H_{26}NO_2$ $[M+H]^+$: 300.19581, found 300.19563.

9-Ethyl 3-methyl 1-(benzyl)-1,9-diazaspiro[5.5]undec-3-ene-3,9-dicarboxylate (4-7). yield 240 mg (88%);

$\mathbf{R_f}$ = 0.61 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.31–1.43 (m, 2H, 7,11-H), 1.78–1.91 (m, 2H, 7,11-H), 2.04–2.11 (m, 2H, 5-H), 3.25 (s, 2H, 2-H), 3.37–3.47 (m, 2H, 8,10-H), 3.51 (s, 2H, PhCH$_2$), 3.54–3.70 (m, 2H, 8,10-H), 3.61 (s, 3H, CO_2CH_3), 4.07 (q, *J* = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 6.97–7.02 (m, 1H, C*H*=C(CO$_2$Me)), 7.13–7.30 (m, 5H, CH$_{ar}$);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (*C*H$_3$CH$_2$O), 31.9 (C-5), 33.9 (C-7,11), 39.1 (C-8,10), 44.2 (C-2), 50.4 (PhCH$_2$), 51.5 (CO_2CH_3), 51.9 (C-6), 61.2 (CH$_3$*C*H$_2$O), 126.8 (CH$_{ar}$, *para*), 127.4 (C-3), 128.0 (CH$_{ar}$, *meta*), 128.4 (CH$_{ar}$, *ortho*), 137.0 (C-4), 140.0 (C$_{ar}$), 155.7 (NCO$_2$Et), 166.7 (CO_2Me).

HRMS (EI): calcd for $C_{21}H_{29}N_2O_4$ $[M+H]^+$: 373.21218, found 373.21192.

General procedure 1 for carbamino allylation of cyclic ketones. To a cooled (0 °C) solution of the ketone (10 mmol), the carbaminic acid ester (12 mmol), and allyltrimethylsilane (14 mmol, 2 mL) in CH_2Cl_2 (10 mL), freshly distilled BF_3·Et_2O (1.70 g, 12.0 mmol, 1.52 mL) was slowly added dropwise over 3 min with vigorous stirring. Then the reaction mixture was stirred for 1 h at 0 °C and 8 h at room temperature. At this point approximately 80% conversion was usually achieved. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL) followed by separation of the layers. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was resubmitted for the same reaction, but this time with a 30% load of carbamate, allylsilane, and BF_3·Et_2O (namely 3.6 mmol of ester, 4.2 mmol of silane, 3.6 mmol of BF_3·Et_2O), to produce almost complete conversion. The crude material was used without further purification.

Benzyl (1-prop-2-en-1-ylcyclohexyl)carbamate (4-8). yield 2.4 g (88%), slightly green oil;

$\mathbf{R_f}$ =0.78 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.55 (m, 8H, 4 CH$_2$), 1.70–2.00 (m, 2H, CH$_2$), 2.40 (d, *J* = 7.3 Hz, 2H, H$_2$C=CHC*H*$_2$), 4.46 (s, 1H, NH), 4.89–5.02 (m, 4H, PhCH$_2$, H$_2$C=), 5.68 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H$_2$C=C*H*CH$_2$), 7.20–7.32 (m, 5H, CH$_{ar}$);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (CH), 26.0 (CH_2), 34.7 (CH_2), 42.9 (H_2C=CH*C*H_2), 55.1 (C_{quat}), 66.4 ($PhCH_2$), 118.5 (H_2*C*=CH), 128.4 (CH_{ar}, *ortho*, *para*), 128.9 (CH_{ar}, *meta*), 134.1 (H_2C=*C*HCH$_2$), 137.3 (C_{ar}), 154.9 (C=O).

HRMS (EI): calcd for $C_{20}H_{42}O_2Si_2Na$ $[M+Na]^+$: 393.26155, found 393.26159.

Methyl (1-prop-2-en-1-ylcyclohexyl)carbamate (4-9). yield 1.77 g (90%), slightly green oil;

R_f =0.75, (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.60 (m, 8H, 4 CH_2), 1.80–2.00 (m, 2H, CH_2), 2.43 (d, *J* = 7.1 Hz, 2H, H_2C=CHC*H*$_2$), 3.59 (s, 3H, OCH_3), 4.45 (s, 1H, NH), 4.97–5.08 (m, 2H, H_2C=), 5.73 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H_2C=C*H*CH$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_2), 25.6 (CH_2), 34.7 (CH_2), 42.5 (H_2C=CH*C*H_2), 51.4 (OCH_3), 54.5 (C_{quat}), 66.4 ($PhCH_2$), 117.9 (H_2*C*=CH), 133.7 (H_2C=*C*HCH$_2$), 155.2 (C=O).

Ethyl 4-({[(benzyl)oxy]carbonyl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-10). yield 2.15 g (85%), slightly yellow oil;

R_f = 0.64 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.43–1.55 (m, 2H, CH_2), 1.90–2.10 (m, 2H, CH_2), 2.36–2.56 (m, 2H, H_2C=CHC*H*$_2$), 2.96–3.19 (m, 2H, CH_2N), 3.68–3.97 (m, 2H, CH_2N), 4.10 (q, *J* = 7.1 Hz, 2H, CH_3C*H*$_2$O), 4.64 (s, 1H, NH), 4.97–5.17 (m, 4H, $PhCH_2$, H_2C=CH), 5.70 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H_2C=C*H*CH$_2$), 7.27–7.37 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 34.0 (CH_2), 39.4 (CH_2N), 42.3 (H_2C=CH*C*H_2), 53.2 (C_{quat}), 61.2 (CH_3*C*H_2O), 66.2 ($PhCH_2$), 119.0 (H_2*C*=CH), 128.0 (CH_{ar}, *ortho*), 128.1 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 132.5 (H_2C=*C*HCH$_2$), 136.4 (C_{ar}), 154.6 (CO_2Bn), 155.4 (CO_2Et).

Benzyl 4-{[(methyloxy)carbonyl]amino}-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-11). yield 2.6 g (78%), slightly yellow oil;

R_f = 0.52 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41–1.55 (m, 2H, CH_2), 1.90–2.10 (m, 2H, CH_2), 2.37–2.48 (m, 2H, H_2C=CHC*H*$_2$), 2.96–3.19 (m, 2H, CH_2), 3.60 (s, 3H, OCH_3), 3.71–3.97 (m, 2H, CH_2),

4.50 (s, 1H, NH), 4.97–5.17 (m, 4H, $PhCH_2$, H_2C=), 5.68 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H_2C=C*H*CH_2), 7.22–7.37 (m, 5H, CH);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.5 (CH_2), 40.0 (CH_2N), 42.8 (H_2C=CHC*H*$_2$), 55.1 (C_{quat}), 53.5 (CH_3O), 67.5 ($PhCH_2$), 119.5 (H_2C=CH), 128.3 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *para*), 128.9 (CH_{ar}, *meta*), 133.0 (H_2C=*C*HCH_2), 137.2 (C_{quat}), 155.6 (CO_2Bn), 155.8 (CO_2Me).

Benzyl {1-[(4-methylphenyl)sulfonyl]-3-prop-2-en-1-ylpiperidin-3-yl}carbamate (4-12). Yield 1.07 g (25%), colorless oil;

R_f = 0.75 (Et_2O/toluene, 2:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.20 (m, 1H, CH_2), 1.55–1.67 (m, 1H, CH_2), 1.71–1.86 (m, 1H, CH_2), 2.17–2.53 (m, 7H, CH_2, H_2C=CHC*H*$_2$, CH_3), 4.93–5.17 (m, 5H, $PhCH_2$, H_2C=, NH), 5.64–5.76 (m, 1H, H_2C=C*H*CH_2), 7.27–7.39 (m, 7H, CH_{ar}), 7.57–7.64 (m, 2H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (*C*H_2CH_2N), 21.5 (CH_3), 31.0 (C-4), 39.4 (*C*H_2N*C*H_2), 40.2 (H_2C=CH*C*H_2), 46.4 (CH_2*C*H_2N), 53.2 (C_{quat}), 53.8 (C_{quat}*C*H_2N), 66.3 ($PhCH_2$), 119.2 (H_2*C*=CH), 127.5 (CH_{ar}, *ortho*, Ts), 128.0 (CH_{ar}, *ortho*, Bn), 128.1 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.8 (CH_{ar}, *meta*, Ts), 132.2 (H_2C=*C*HCH_2), 133.0 (O_2S*C*, Ts), 136.5 (C_{ar}, Bn), 143.7 (CH_3-C_{ar}, Ts), 154.5 (CO_2Bn).

General procedure 2 for alkylation of the carbamates with bromomethylmethacrylate. A suspension of NaH (60% in mineral oil, 800 mg, 20 mmol, 2 equiv.) was washed twice with abs. THF, and then re-suspended in a mixture of THF/DMF (2mL/3mL, respectively). To this suspension at 0 °C was added the corresponding carbamate (10 mmol) in THF (2 mL) with vigorous stirring over 5 min. Then, the reaction mixture was stirred at 0 °C for 30 min, before bromomethylmethacrylate (3.6 g, 2.0 mL, 2 equiv.) was added over 5 min. The reaction mixture was stirred for 1 h at 0 °C, and then allowed to stir overnight with concomitant warming to room temperature. Thereafter, the mixture was poured into a stirred mixture of saturated NH_4Cl solution/Et_2O (20/20 mL). After separation of the layers, the water phase was extracted with Et_2O (10 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O mixtures).

Methyl 2-{[{[(benzyl)oxy]carbonyl}(1-prop-2-en-1-ylcyclohexyl)amino]methyl}prop-2-enoate (4-13). yield 2.5 g (80%), colorless oil;

R_f = 0.88 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.04–1.57 (m, 8H, CH_2), 2.17–2.29 (m, 2H, CH_2), 2.65 (d, *J* = 7.3 Hz, 2H, H_2C=CHC*H_2*), 3.69 (s, 3H, CO_2CH_3), 4.01 (s, 2H, H_2C=C(CO_2Me)C*H_2*), 4.87–5.04 (m, 4H, PhCH_2, H_2C=), 5.54–5.72 (m, 2H, H_2C=C*H*CH_2, (*H_2*C=C(CO_2Me), *E*)), 7.17–7.35 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (CH_2), 25.4 (CH_2), 34.1 ($C_{quat}CH_2$), 36.7 (H_2C=C(CO_2Me)*C*H_2), 45.2 (H_2C=CH*C*H_2), 51.9 (CO_2CH_3), 62.1 (C_{quat}), 66.6 (PhCH_2), 118.1 (H_2*C*=CH), 124.5 (H_2*C*=C(CO_2Me)CH_2), 127.7 (CH_{ar}, *ortho*, *para*), 128.3 (CH_{ar}, *meta*), 134.0 (H_2C=*C*HCH_2), 136.9 (C_{ar}), 138.6 (H_2C=*C*(CO_2Me)CH_2), 155.9 (CO_2Bn), 166.6 (CO_2Me).

HRMS (EI): calcd for $C_{22}H_{29}NO_4Na$ $[M+Na]^+$: 394.19888, found 394.19881

Methyl 2-{[[(methyloxy)carbonyl](1-prop-2-en-1-ylcyclohexyl)amino]methyl}prop-2-enoate (4-14). yield 2.4 g (80%), colorless oil;

R_f = 0.71 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.60 (m, 8H, CH_2), 2.17–2.28 (m, 2H, CH_2), 2.65 (d, *J* = 7.3 Hz, 2H, H_2C=CHC*H_2*), 3.55 (s, 3H, NCO_2C*H_3*), 3.70 (s, 3H, CO_2CH_3), 4.06 (s, 2H, H_2C=C(CO_2Me)CH_2), 4.93–5.03 (m, 2H, H_2C=CH), 5.60 (s, 1H, *H_2*C=C(CO_2Me), *E*), 5.66 (ddt, *J* = 17.0, 10.0, 7.3 Hz, 1H, H_2C=C*H*CH_2), 6.22 (s, 1H, *H_2*C=C(CO_2Me), *Z*);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_2), 22.6 (CH_2), 34.1 ($C_{quat}CH_2$), 36.7 (H_2C=C(CO_2Me)*C*H_2), 42.5 (H_2C=CH*C*H_2), 51.8 (H_2C=C(CO_2*C*H_3)), 52.0 (NCO_2CH_3), 61.8 (C_{quat}), 118.0 (H_2C=CH), 124.2 (H_2*C*=C(CO_2Me)CH_2), 134.1 (H_2C=*C*HCH_2), 138.6 (H_2C=*C*(CO_2Me)CH_2), 156.7 ($HNCO_2CH_3$), 166.6 (CO_2Me).

HRMS (EI): calcd for $C_{16}H_{25}NO_4Na$ $[M+Na]^+$: 318.16758, found 318.16757

Ethyl 4-({2-[(benzyloxy)carbonyl]prop-2-en-1-yl}{[(benzyl)oxy]carbonyl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-15). yield 2.5 g (80%), colorless oil;

R_f = 0.57 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 3H, C*H_3*CH_2O), 1.62–1.73 (m, 2H, $C_{quat}CH_2$), 2.21–2.30 (m, 2H, $C_{quat}CH_2$), 2.67 (d, *J* = 7.3 Hz, 2H, H_2C=CHC*H_2*), 2.92–3.05 (m, 2H, NCH_2), 3.69 (s, 3H, CO_2CH_3), 3.72–3.85 (m, 2H, NCH_2), 4.04 (q, *J* = 7.1 Hz, CH_3CH_2O),

4.06–4.09 (m, 2H, H_2C=C(CO_2Me)CH_2), 4.91–5.05 (m, 2H, H_2C=CHCH_2), 5.01 (s, 2H, PhCH_2), 5.54 (s, 1H, H_2C=C(CO_2Me), *E*), 5.63 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H_2C=C*H*CH_2), 6.21 (s, 1H, H_2C=C(CO_2Me), *Z*), 7.18–7.30 (m, 5H, CH);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (*C*H_3CH_2O), 33.5 (C_{quat}CH_2), 36.0 (H_2C=C(CO_2Me)*C*H_2), 40.2 (NCH_2), 45.4 (H_2C=CH*C*H_2), 51.9 (CO_2CH_3), 60.3 (C_{quat}), 61.3 (CH_3*C*H_2O), 66.8 (PhCH_2), 119.2 (H_2*C*=CHCH_2), 124.7 (H_2*C*=C(CO_2Me)), 127.8 (CH_{ar}, *ortho*), 127.9 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 132.8 (H_2C=*C*HCH_2), 136.5 (C_{ar}), 138.1 (H_2C=*C*(CO_2Me)CH_2), 155.3 (CO_2Et), 158.8 (CO_2Bn), 166.3 (H_2C=C(*C*O_2Me)).

HRMS (EI): calcd for $C_{24}H_{32}N_2O_6Na$ $[M+Na]^+$: 467.21526, found 467.21537

Benzyl 4-([(methyloxy)carbonyl]{2-[(methyloxy)carbonyl]prop-2-en-1-yl}amino)-4-prop-2-en-1-ylpiperidine-1-carboxylate (4-16). yield 2.1 g (65%), colorless oil;

R_f = 0.52 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.80 (m, 2H, C_{quat}CH_2), 1.26–2.36 (m, 2H, C_{quat}CH_2), 2.73 (d, *J* = 7.6 Hz, 2H, H_2C=CHCH_2), 2.99–3.15 (m, 2H, NCH_2), 3.61 (s, 3H, H_2C=C(CO_2*C*H_3)), 3.75 (NCO_2*C*H_3), 3.81–3.95 (m, 2H, NCH_2), 4.06–4.10 (m, 2H, H_2C=C(CO_2Me)CH_2), 5.03–5.15 (m, 2H, H_2C=CHCH_2), 5.09 (s, 2H, PhCH_2), 5.59 (s, 1H, H_2C=C(CO_2Me), *E*), 5.70 (ddt, *J* = 17.0, 10.0, 7.6 Hz, 1H, H_2C=C*H*CH_2), 6.27 (s, 1H, H_2C=C(CO_2Me), *Z*), 7.27–7.37 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.5 (C_{quat}CH_2), 36.0 (H_2C=C(CO_2Me)*C*H_2), 40.3 (NCH_2), 45.5 (H_2C=CH*C*H_2), 51.9 (H_2C=C(CO_2*C*H_3)), 52.3 (NCO_2*C*H3), 60.0 (C_{quat}), 67.1 (PhCH_2), 119.1 (H_2*C*=CHCH_2), 124.5 (H_2*C*=C(CO_2Me)CH_2), 127.8 (CHar, *ortho*), 128.0 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 132.9 (H_2C=*C*HCH_2), 136.6 (C_{quat}), 138.1 (H_2C=*C*(CO_2Me)), 155.1 (CO_2Bn), 155.6 (NCO_2Me), 166.3 (H_2C=C(*C*O_2Me)).

HRMS (EI): calcd for $C_{23}H_{31}N_2O_6$ $[M+H]^+$: 431.21766, found 431.21785

Methyl 2-[([(benzyloxy)carbonyl]{1-[(4-methylphenyl)sulfonyl]-3-prop-2-en-1-ylpiperidin-3-yl}amino)methyl]prop-2-enoate (4-17). yield 600 mg (50%), colorless oil;

R_f = 0.71 (Et_2O/toluene, 2:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.87 (m, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.45–2.58 (m, 2H, CH_2), 2.73–2.92 (m, 2H, CH_2), 3.27–3.45 (m, 1H, CH_2), 3.70 (d, *J* = 11.1 Hz, 1H, CH_2), 3.67 (s, 3H, CO_2CH_3), 3.73–3.84 (m, 1H, CH_2), 3.99–4.08 (m, 2H, CH_2), 4.16–4.24 (m, 2H,

CH_2), 4.90–5.13 (m, 4H, H_2C=$CHCH_2$, $PhCH_2$), 5.53 (s, 1H, H_2C=C(COOMe), *E*), 5.61 (m, 1H, H_2C=C*H*CH_2), 6.17 (s, 1H, H_2C=C(COOMe), *Z*), 7.18–7.33 (m, 7H, CH_{ar}), 7.48–7.54 (m, 2H, CH_{ar}, *ortho*, Ts,);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (CH_2), 21.5 (CH_3), 31.3 ($C_{quat}CH_2$), 37.0 (H_2C=C(CO_2Me)*C*H_2), 45.3 (H_2C=CH*C*H_2), 46.0 (CH_2NTs), 49.7 (CO_2CH_3), 52.8 (ZN*C*H_2C(CO_2Me), 60.5 (C_{quat}), 67.1 ($PhCH_2$), 68.8 (C_{quat}*C*H_2NTs), 119.3 (H_2*C*=$CHCH_2$), 124.9 (H_2*C*=C(CO_2Me)), 127.5 (CH_{ar}, *ortho*, Ts, CH_{ar}, *para*, Bn), 128.0 (CH_{ar}, *ortho*, Bn), 128.4 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 129.8 (CH_2CH=*C*(CO_2Me)), 132.6 (H_2C=*C*HCH_2), 133.4 (O_2SC_{ar}, Ts), 136.4 (C_{ar}, Bn), 138.0 (H_2C=*C*(CO_2Me)), 143.4 (CH_3*C*$_{ar}$, Ts), 155.9 (CO_2Bn), 166.4 (CO_2CH_3).

General procedure 3 for the ring closing metathesis (RCM) of N-carbamate protected amines. A solution of diene in abs. CH_2Cl_2 (3 mL/mmol) was degassed by bubbling of N_2 or Ar through it, and then transferred into a two neck flask (25 mL), equipped with reflux condenser and attached to a vacuum inert gas line. The flask was carefully purged with inert gas three times, then 2nd generation Grubbs catalyst (0.5 mol%, 4.4 mg/mmol) was added, and the reaction mixture refluxed for 4 h. The reaction progress can be monitored by TLC. After comple reaction, the solvent was evaporated and the residue subjected to flash chromatography (toluene/Et_2O).

Dimethyl 1-azaspiro[5.5]undec-3-ene-1,3-dicarboxylate (4-18). yield 514 mg (94%), colorless oil;

R_f = 0.51 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.56 (m, 8H, CH_2), 2.20–2.25 (m, 2H, CH_2), 2.43 (d, *J* = 13.1 Hz, 2H, C_{quat}C*H*$_2$HC=C(CO_2Me)), 3.57 (s, 3H, CH=C(CO_2C*H*$_3$)), 3.68 (s, 3H, NCO_2CH_3), 4.17–4.21 (m, 2H, CH_2N), 6.87–6.92 (m, 1H, C*H*=C(CO_2Me));

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (CH_2), 25.9 (CH_2), 35.2 (C_{quat}*C*H_2), 36.3 (*C*H_2HC=), 42.3 (CH_2N), 51.6 (CH=C(CO_2*C*H_3)), 52.2 (NCO_2*C*H_3), 56.5 (C_{quat}), 128.9 (HC=*C*(CO_2Me)), 138.0 (*C*H=C(CO_2Me)), 156.4 ($HNCO_2CH_3$), 165.7 (H_2C=C(*C*O_2Me)).

HRMS (EI): calcd for $C_{14}H_{21}NO_4Na$ $[M+Na]^+$: 290.13628, found 290.13655

3-Methyl 1-(benzyl) 1-azaspiro[5.5]undec-3-ene-1,3-dicarboxylate (4-19). yield 460 mg (90%);

R_f = 0.79, (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.64 (m, 8H, CH_2), 2.28–2.33 (m, 2H, CH_2), 2.35–2.43 (m, 2H, C*H*$_2$HC=C(CO_2Me)), 3.73 (s, 3H, CO_2CH_3), 4.30 (s, 2H, CH_2N), 5.08 (s, 2H, $PhCH_2$), 6.93–6.98 (m, 1H, C*H*=C(CO_2Me)), 7.27–7.37 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (CH_2), 25.9 (CH_2), 35.2 ($C_{quat}CH_2$), 36.3 (*C*H_2HC=C(CO_2Me)), 42.4 (CH_2N), 51.7 (CO_2CH_3), 56.7 (C_{quat}), 66.8 ($PhCH_2$), 127.7 (CH_{ar}, *ortho*), 127.8 (CH_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 128.9 (HC=*C*(CO_2Me)), 136.8 (C_{ar}), 138.0 (*C*H=C(CO_2Me)), 155.8 (NCO_2Bn), 165.7 (*C*O_2Me).

HRMS (EI): calcd for $C_{20}H_{25}NO_4Na$ $[M+Na]^+$: 366.16758, found 417.16805.

9-Ethyl 3-methyl 1-(benzyl) 1,9-diazaspiro[5.5]undec-3-ene-1,3,9-tricarboxylate (4-20). yield 680 mg (85%);

R_f = 0.36 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3H, C*H*$_3$$CH_2O$), 1.38–1.48 (m, 2H, 7-H, 11-H), 2.28–2.35 (m, 2H, 5-H), 2.46–2.65 (m, 2H, 7-H, 11-H), 3.05–3.20 (m, 2H, 8-H, 10-H), 3.70–3.90 (m, 2H, 8-H, 10-H), 3.73 (s, 3H, CO_2CH_3), 4.10 (q, *J* = 7.1 Hz, 2H, CH_3C*H*$_2$O), 4.21–4.39 (m, 2H, 5-H), 5.07 (s, 2H, $PhCH_2$), 6.94–6.99 (m, 1H, C*H*=C(CO_2Me)), 7.27–7.40 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$), δ = 14.7 (*C*$H_3$$CH_2O$), 34.4 (C-7, C-11), 35.7 (C-5), 40.0 (C-8, C-10), 42.6 (C-2), 51.8 (CO_2CH_3), 54.8 (C-6), 61.2 (CH_3CH_2O), 67.1 ($PhCH_2$), 127.8 (CH_{ar}, *ortho*), 128.0 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 128.6 (C-3), 136.3 (C_{ar}), 137.2 (C-4), 155.6 (NCO_2Et), 155.9 (NCO_2Bn), 165.4 (CO_2Me).

HRMS (EI): calcd for $C_{22}H_{29}N_2O_6$ $[M+H]^+$: 417.20201, found 417.20184.

1,3-Dimethyl 9-(benzyl) 1,9-diazaspiro[5.5]undec-3-ene-1,3,9-tricarboxylate (4-21). yield 1.533 g (90%);

R_f = 0.50 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.48 (m, 2H, 7-H, 11-H), 2.25–2.36 (m, 2H, 5-H), 2.45–2.70 (m, 2H, 7-H, 11-H), 3.05–3.25 (m, 2H, 8-H, 10-H), 3.62 (s, 3H, CO_2CH_3), 3.74

(NCO_2CH_3), 3.81–3.95 (m, 2H, 8-H, 10-H), 4.08–4.40 (m, 2H, 2-H), 5.11 (s, 2H, $PhCH_2$), 6.92–6.99 (m, 1H, 4-H), 7.27–7.40 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.4 (C-7, C-11), 35.7 (C-5), 40.1 (C-8, C-10), 42.4 (C-2), 51.7 (CO_2CH_3)), 52.4 (NCO_2CH_3), 54.5 (C-6), 66.9 ($PhCH_2$), 128.9 (C-3), 127.7 (CH_{ar}, *ortho*), 127.9 (Ch_{ar}, *para*), 128.4 (CH_{ar}, *meta*), 136.7 (C_{ar}), 137.1 (C-4), 155.2 (NCO_2Bn), 156.5 (NCO_2Me), 165.4 (CO_2Me).

HRMS (EI): calcd for $C_{21}H_{26}N_2O_6Na$ $[M+Na]^+$: 425.16831, found 425.16836

1-Benzyl 3-methyl 8-[(4-methylphenyl)sulfonyl]-1,8-diazaspiro[5.5]undec-3-ene-1,3-dicarboxylate (4-22). yield 370 mg (65%), white crystals;

M.p. 133-135°C;

R_f = 0.55 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.80 (m, 3H, CH_2), 2.25–2.75 (m, 4H, CH_2), 2.35 (s, 3H, $ArCH_3$), 2.96–3.06 (m, 1H, CH_2), 3.12–3.24 (m, 1H, CH_2), 3.27–3.45 (m, 1H, CH_2), 3.70 (d, *J* = 11.1 Hz, 1H, CH_2), 3.70 (s, 3H, CO_2CH_3), 4.20–4.43 (m, 2H, 7-H), 5.00 (s, 2H, $PhCH_2$), 6.93–7.02 (m, 1H, 3-H), 7.15–7.35 (m, 7H, CH_{ar}), 7.45–7.60 (m, 2H, CH_{ar}, *ortho*, Ts,);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH_3), 21.9 (C-10), 31.9 (C-11), 32.8 (C-5), 41.9 (C-2), 46.8 (C-9), 51.9 (CO_2CH_3), 52.2 (C-7), 56.1 (C-6), 67.0 ($PhCH_2$), 127.5 (CH_{ar}, *ortho*, Ts), 127.7 (CH_{ar}, *ortho*, Bn), 128.0 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 129.8 (C-3), 133.4 (O_2SC_{ar}, Ts), 136.4 (C_{ar}, Bn), 137.2 (C-4), 143.5 (CH_3C_{ar}, Ts), 155.1 (NCO_2Bn) 165.2 (CO_2CH_3).

HRMS (EI): calcd for $C_{26}H_{31}N_2O_6S$ $[M+H]^+$: 499.18973, found 499.18978.

General procedure 8 for the degradation of the unsaturated esters to ketones. To a solution of the unsaturated ester in a mixture of THF/MeOH/H_2O (3:2:1, v/v, 6 mL/mmol) was added LiOH (5 equiv.) and the mixture stirred at room temperature for 3 h. Then, saturated NH_4Cl solution (1mL/mmol) was added, and most of the organic solvents removed in vacuo. The partly solid residue was extracted with CH_2Cl_2 (3 × 10 mL per mmol), dried with Na_2SO_4, filtered, and concentrated in vacuo. The obtained residue was dissolved in toluene (5 mL/mmol), followed by addition of triethylamin (3 equiv.) and diphenylphosphorylazide (1.2

equiv.). After stirring of the mixture for 5 h at room temperature, it was filtered through a pad of SiO_2 (flash silica gel, 2 cm). The silica gel was additionally washed with toluene (10 mL). The filtrate was then refluxed for 1 h. The solution, containing the rearranged isocyanate was evaporated and the residue taken up in dioxane (5 mL/mmol). To this solution 1N HCl was added (1 mL/mmol) and the mixture stirred for 2 h at room temperature. Thereafter, the mixture was concentrated in vacuo and the obtained residue purified by flash chromatography.

Methyl 3-oxo-1-azaspiro[5.5]undecane-1-carboxylate (4-26). yield 184 mg (60%), colorless oil;

R_f = 0.47 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.67 (m, 8H, CH_2), 1.96–2.03 (m, 2H, CH_2), 2.31–2.39 (m, 2H, 5-H), 2.59–2.69 (m, 2H, 4-H), 3.57 (s, 3H, $COOCH_3$), 4.04 (s, 2H, 2-H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 (C-8,10), 24.9 (C-9), 28.5 (C-5), 31.2 (C-7,11), 34.2 (C-4), 51.9 (C-2), 52.1 ($COOCH_3$), 58.6 (C-6), 155.3 (NCO_2Me), 208.3 (C=O).

HRMS (EI): calcd for $C_{12}H_{20}NO_3$ $[M+H]^+$: 226.14377, found 226.14600.

Benzyl 3-oxo-1-azaspiro[5.5]undecane-1-carboxylate (4-27). yield 240 mg (66%), white crystals;

M.p. 85-87°C;

R_f = 0.78 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.67 (m, 8H, CH_2), 1.96–2.04 (m, 2H, CH_2), 2.31–2.39 (m, 2H, 5-H), 2.61–2.74 (m, 2H, 4-H), 4.08 (s, 2H, 2-H), 5.02 (s, 2H, $PhCH_2$), 7.27–7.37 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3 (C-8,10), 24.9 (C-9), 28.6 (C-5), 31.3 (C-7,11), 34.3 (C-4), 52.0 (C-2), 58.8 (C-6), 67.0 ($PhCH_2$), 127.9 (CH_{ar}, *ortho*), 128.0 (CH_{ar}, *para*), 128.5 (CH_{ar}, *meta*), 136.3 (C_{ar}), 154.7 (NCO_2Bn), 208.3 (C=O).

HRMS (EI): calcd for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$: 324.15701, found 324.15695.

9-Ethyl 1-(benzyl) 3-oxo-1,9-diazaspiro[5.5]undecane-1,9-dicarboxylate (4-25). yield 340 mg (70%), colorless oil;

R_f = 0.24 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.26 (m, 3H, C*H*$_3$CH$_2$O), 1.40–1.56 (m, 2H, 7,11-H), 2.00–2.11 (m, 2H, 7,11-H), 2.34–2.47 (m, 2H, 5-H), 2.77–3.05 (m, 4H, 4-H, 8,10-H), 3.85–4.20 (m, 6H, 8,10-H, 2-H, CH$_3$C*H*$_2$O), 5.02 (s, 2H, PhCH$_2$), 7.15–7.40 (m, 5H, CH$_{ar}$);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (*C*H$_3$CH$_2$O), 28.6 (C-5), 31.1 (C-7,11), 34.0 (C-4), 40.5 (C-8,10), 52.0 (C-2), 56.9 (C-6), 61.4 (CH$_3$*C*H$_2$O), 67.3 (PhCH$_2$), 128.0 (CH$_{ar}$, *ortho*), 128.2 (CH$_{ar}$, *para*), 128.5 (CH$_{ar}$, *meta*), 135.9 (C$_{ar}$), 154.6 (NCO$_2$Bn), 155.3 (NCO$_2$Et), 207.1 (C=O).

1-Methyl 9-(benzyl) 3-oxo-1,9-diazaspiro[5.5]undecane-1,9-dicarboxylate (4-25). yield 800 mg (63%), white crystals;
M.p. 108-111°C;
R$_f$ = 0.36 (Et$_2$O/toluene, 1:1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.56 (m, 2H, 7,11-H), 2.01–2.07 (m, 2H, 7,11-H), 2.36–2.42 (m, 2H, 5-H), 2.78–2.90 (m, 2H, 4-H), 2.92–3.07 (m, 2H, 8,10-H), 3.59 (CO$_2$CH$_3$), 3.90–4.10 (m, 2H, 8,10-H), 4.06 (s, 2H, 2-H), 5.02–5.12 (m, 2H, PhCH$_2$), 7.21–7.31 (m, 5H, CH);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (C-5), 31.1 (C-7,11), 33.9 (C-4), 40.7 (C-8,10), 51.9 (C-2), 52.5 (CO$_2$*C*H$_3$), 56.6 (C-6), 67.1 (PhCH$_2$), 127.8 (CH$_{ar}$, *ortho*), 127.9 (CH$_{ar}$, *para*), 128.4 (CH$_{ar}$, *meta*), 136.7 (C$_{ar}$), 155.1 (NCO$_2$Bn), 155.3 (NCO$_2$Me), 207.1 (C=O).
HRMS (EI): calcd for $C_{19}H_{24}N_2O_5Na$ $[M+Na]^+$: 383.15774, found 383.15760.

Methyl 8-[(4-methylphenyl)sulfonyl]-3-oxo-1,8-diazaspiro[5.5]undecane-1-carboxylate (4-29). yield 170 mg (50%), white crystals;
M.p. 89-91°C;
R$_f$ = 0.33 (Et$_2$O/toluene, 1:1);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.90 (m, 4H, H-10,11), 2.15–2.26 (m, 1H, CH$_2$), 2.31–2.41 (m, 4H, CH$_3$, CH$_2$), 2.42–2.66 (m, 3H, CH$_2$), 3.49 (dd, *J* = 11.5, 16.8 Hz, 2H, 2-H), 3.70 (d, *J* = 11.1 Hz, 1H, CH$_2$), 3.89 (d, *J* = 18.4 Hz, 1H, 7-H), 4.24 (d, *J* = 18.4 Hz, 1H, 7-H), 4.94 (dd, *J* = 12.3, 19.6 Hz, 2H, PhCH$_2$), 7.14–7.29 (m, 7H, CH$_{ar}$), 7.53 (m, 2H, CH$_{ar}$, *ortho*, Ts);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (CH$_3$), 22.2 (C-10), 27.2 (C-5), 29.5 (C-11), 33.8 (C-4), 45.8 (C-9), 48.5 (C-7), 52.0 (C-2), 57.3 (C-6), 66.4 (PhCH$_2$), 127.2 (CH$_{ar}$, *ortho*, Ts), 127.9

(CH_{ar}, ortho, Bn), 128.2 (CH_{ar}, *para*, Bn), 128.5 (CH_{ar}, *meta*, Bn), 129.7 (CH_{ar}, *meta*, Ts), 133.7 (O_2SC_{ar}), 135.6 (C_{ar}, Bn), 143.5 (CH_3C_{ar}, Ts), 154.5 (NCO_2Bn), 206.4 (C=O).

HRMS (EI): calcd for $C_{24}H_{28}N_2O_5SNa$ $[M+Na]^+$: 479.16111, found 479.16142.

1-(Benzyl)-1-azaspiro[5.5]undecan-3-one (4-30). yield 79 mg (70%), red crystals;

M.p. 65-67°C;

R_f = 0.76 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.44 (m, 3H, CH_2), 1.46–1.58 (m, 3H, CH_2), 1.63–1.78 (m, 4H, CH_2), 1.88 (t, *J* = 6.7 Hz, 2H, 5-H), 2.36 (t, *J* = 6.7 Hz, 2H, 4-H), 3.02 (s, 2H, 2-H), 3.60 (s, 2H, $PhCH_2$), 7.10–7.30 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (C-8,10), 26.1 (C-9), 30.8 (C-5), 32.3 (C-7,11), 35.6 (C-4), 51.5 ($PhCH_2$), 54.6 (C-6), 55.5 (C-2), 126.8 (CH_{ar}, *para*), 128.3 (CH_{ar}, *ortho*, *meta*), 140.0 (C_{ar}), 212.0 (C=O).

HRMS (EI): calcd for $C_{17}H_{24}NO$ $[M+H]^+$: 258.18524, found 258.18503.

Ethyl 3-oxo-1-(benzyl)-1,9-diazaspiro[5.5]undecane-9-carboxylate (4-31). yield 80 mg (65%), red crystals;

M.p. 95-97°C;

R_f = 0.43 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H, CH_3CH_2O), 1.47–1.66 (m, 2H, 7,11-H), 1.88–2.05 (m, 4H, 7,11-H, 5-H), 2.37–2.48 (m, 2H, 4-H), 3.06 (s, 2H, 2-H), 3.24–3.40 (m, 2H, 8,10-H), 3.61 (s, 2H, $PhCH_2$), 3.67–3.82 (m, 2H, 8,10-H), 4.08 (q, *J* = 7.1 Hz, 2H, CH_3CH_2O), 7.10–7.30 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3CH_2O), 30.5 (C-5), 32.1 (C-7,11), 35.5 (C-4), 39.8 (C-8,10), 51.5 (C-2), 53.4 (C-6), 55.3 ($PhCH_2$), 61.4 (CH_3CH_2O), 127.1 (CH_{ar}, *para*), 128.2 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 139.0 (C_{ar}), 155.6 (NCO_2Et), 211.0 (C=O).

HRMS (EI): calcd for $C_{19}H_{27}N_2O_3$ $[M+H]^+$: 331.20162, found 331.20159.

Dimethyl 1-azaspiro[5.5]undecane-1,3-dicarboxylate (4-32). To a solution of the unsaturated ester **18b** (180 mg, 0.67 mmol) in dry MeOH (10 mL), Mg turnings (65 mg, 2.7 mmol, 4 equiv.) were added, and reaction mixture was vigorously stirred for 7 h. Thereafter, the resulting gel was partitioned between saturated NH_4Cl solution (25 mL) and Et_2O (25 mL).

The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to give 180 mg (100%) of ester **4-32** as colorless oil, pure enough for the next transformation.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.58 (m, 8H, CH_2), 1.64–1.69 (m, 2H, CH_2), 1.72–1.89 (m, 2H, CH_2), 2.30-2.40 (m, 1H, CHCOOMe), 2.51-2.69 (m, 2H, CH_2), 3.35 (dd, *J* = 14.0 Hz, *J* = 9.7 Hz, 1H, H-2), 3.56 (s, 3H, $CH(CO_2C\mathit{H}_3)$), 3.61 (s, 3H, NCO_2CH_3), 3.93 (dd, *J* = 14.0 Hz, *J* = 5.1 Hz, 1H, H-2);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (C-4), 22.2 (C-9), 22.7, 25.2 (C-8,10), 30.0 (C-5), 31.9, 33.1 (C-7,11), 39.6 ($HC(CO_2CH_3)$), 41.5 (CH_2N), 51.5 ($HC(CO_2\mathit{C}H_3)$), 51.7 ($NCO_2\mathit{C}H_3$), 58.5 (C_{quat}), 155.8 (NCO_2Me), 174.2 ($HC(\mathit{C}O_2Me)$).

HRMS (EI): calcd for $C_{14}H_{23}NO_4Na$ $[M+Na]^+$: 292.15193, found 292.15197.

1-[(Methyloxy)carbonyl]-1-azaspiro[5.5]undecane-3-carboxylic acid (4-33). A solution of ester **4-18** (160 mg, 0.6 mmol) in a mixture of THF (3 mL), MeOH (2 mL), and H_2O (1 mL) was treated with LiOH (200 mg, 5.0 mmol, 8 equiv.) and stirred for 3 h at room temperature. The compleation of reaction was confirmed by TLC. The reaction mixture was then concentrated under reduced pressure to remove the bulk of the solvents. The residue was partitioned between saturated NH_4Cl solution (10 mL) and Et_2O (10 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, yielding acid **4-33** (150 mg, 100%), which was pure enough for the next transformation.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.59 (m, 8H, CH_2), 1.63–1.72 (m, 2H, CH_2), 1.75–1.90 (m, 2H, CH_2), 2.30-2.40 (m, 1H, CH), 2.51-2.69 (m, 2H, CH_2), 3.34-3-46 (m, 1H, H-2), 3.57 (s, 3H, NCO_2CH_3), 3.86-4.00 (m, 1H, H-2), 8.10-8.80 (bs, 1H, COOH);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (C-4), 22.4 (C-9), 22.9, 25.2 (C-8,10), 30.0 (C-5), 32.1, 33.2 (C-7,11), 39.9 ($H\mathit{C}(CO_2CH_3)$), 41.6 (CH_2N), 52.0 ($NCO_2\mathit{C}H_3$), 58.8 (C_{quat}), 156.3 (NCO_2Me).

Methyl 3-{[(benzyl)amino]carbonyl}-1-azaspiro[5.5]undecane-1-carboxylate (4-34). To a solution of acid **4-33** (75 mg, 0.3 mmol) in DMF (5 mL) was added CDI (64 mg, 0.4 mmol, 1.3 equiv.) followed by stirring of the mixture at 50 °C for 2 h. Then, benzylamine (65 mg, 65 µL, 0.6 mmol, 2 equiv.) was added and stirring continued for 8 h at 60 °C. After cooling, the

mixture was partitioned between 1N HCl (25 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O, 2:1) to give amide **4-34** (80 mg, 78%) as a colorless oil.

R_f = 0.40 (Et_2O/toluene, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.87 (m, 13H, CH, CH_2), 2.29-2.56 (m, 3H, CH, CH_2), 3.42-3.51 (m, 1H, CH_2), 3.47 (s, 3H, CH(CO_2CH_3)), 3.61 (s, 3H, NCO_2CH_3), 3.75 (dd, *J* = 14.3 Hz, *J* = 4.9 Hz, 1H, H-2), 4.31 (d, *J* = 5.1 Hz, 2H, $PhCH_2N$), 6.49 (s, 1H, C(O)NH), 7.13–7.27 (m, 5H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (C-4), 22.4 (C-9), 22.8, 25.3 (C-8,10), 29.9 (C-5), 31.7, 33.2 (C-7,11), 41.4 (H*C*CO_2Me)), 42.1 ($PhCH_2N$), 43.3 (CH_2N), 51.8 (NCO_2CH_3), 58.9 (C_{quat}), 127.3 (CH_{ar}, *para*), 127.6 (CH_{ar}, *ortho*), 128.5 (CH_{ar}, *meta*), 138.2 (C_{ar}), 156.3 (NCO_2CH_3), 173.9 (*C*(O)NHBn)).

HRMS (EI): calcd for $C_{20}H_{29}N_2O_3$ $[M+H]^+$: 345.21727, found 345.21701.

Methyl 3-(1-piperazinylcarbonyl)-1-azaspiro[5.5]undecane-1-carboxylate (4-35). To a solution of acid **4-33** (75 mg, 0.3 mmol) in DMF (5 mL) was added CDI (64 mg, 0.4 mmol, 1.3 equiv.) followed by stirring of the mixture at 65 °C for 2 h. Then, piperazine (120 mg, 1.5 mmol, 5 equiv.) was added and stirring continued for 5 h at 65 °C. After cooling, the mixture was partitioned between 1N HCl (25 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo resulting in amide **32** (82 mg, 80%) as an yellow oil.

R_f = 0.13 (Et_2O/CH_2Cl_2, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.93 (m, 12H, CH_2), 2.20-2.49 (m, 2H, CH_2), 2.61-2.92 (m, 6H, CH_2), 3.22-3.32 (m, 1H, CH), 3.35-3.62 (m, 4H, CH_2), 3.57 (s, 3H, CH(CO_2CH_3)), 3.86-3.96 (dd, *J* = 14.0 Hz, *J* = 3.8 Hz, 1H, H-2);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0 (C-4), 22.0 (C-9), 22.9, 25.3 (C-8,10), 30.4 (C-5), 32.8, 33.1 (C-7,11), 36.9 (H*C*(CO_2CH_3)), 42.1, 42.4 ($CH_2N(CO)CH_2$), 45.6 (CH_2N), 46.3 (CH_2NHCH_2), 51.7 (NCO_2CH_3), 58.7 (C_{quat}), 156.0 (NCO_2Me), 172.0 (HC(*C*(O)N)).

HRMS (EI): calcd for $C_{17}H_{30}N_3O_3$ $[M+H]^+$: 324.22817, found 324.22812.

Benzyl 3-hydroxy-3-phenyl-1-azaspiro[5.5]undecane-1-carboxylate (4-36). To a vigourosly stirred solution of ketone **4-27** (90 mg, 0.3 mmol) in THF (2 mL) was added a solution of PhMgBr (200 μL, 3M in Et_2O, 0.6 mmol, 2 equiv) at –40°C in a dropwise fashion. The reaction mixture was then allowed to reach room temperature within an 1 h. The reaction was quenched by addition of saturated NH_4Cl solution (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (toluene/Et_2O, 2:1) to give alcohol **34** (70 mg, 60%) as white crystals, m.p. 125-127°C;

R_f = 0.58 (Et_2O/toluene, 1:3);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.62 (m, 10H, 5xCH_2), 1.68–1.77 (m, 1H, CH*H*), 1.95–2.14 (m, 2H, CH_2), 2.31–2.41 (m, 1H, CH*H*), 2.69–2.79 (m, 1H, CH*H*), 3.51 (d, *J* = 14.5 Hz, 1H, 2-H), 3.87 (d, *J* = 14.5 Hz, 1H, 2-H), 5.02 (s, 2H, PhCH_2), 7.13–7.28 (m, 8H, CH_{ar}), 7.39 (d, *J* = 7.3 Hz, 2H, CH_{ar});

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.9 (C-8,10), 25.6 (C-9), 29.9 (C-5), 32.1, 33,6 (C-7,11), 34.2 (C-4), 52.2 (C-2), 58.9 (C-6), 66.8 (PhCH_2), 72.9 (C-3), 124.5 (CH_{ar}, *ortho*), 127.1 (CH_{ar}, *para*), 127.8 (CH_{ar}, *meta, para*), 128.3 (CH_{ar}, *ortho*), 128.4 (CH_{ar}, *meta*), 136.7 (C_{ar}), 146.3 (C_{ar}), 156.6 (NCO_2Bn).

HRMS (EI): calcd for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.22202, found 380.22193.

3-Phenyl-1-azaspiro[5.5]undecan-3-ol (4-37). A flask containing a solution of benzyl carbamate **4-36** (7.2 mg, 0.02 mmol) and 10% Pd/C (1 mg) in EtOH (1 mL) was connected to a ballon filled with hydrogen. The suspension was stirred at room temperature for 4 h, then filtered through a pad of celite. The filtrate was concentrated in vacuo to give amino alcohol **34** (5 mg, 100%) as white crystals.

M.p. 110-112°C;

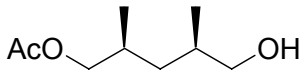
R_f = 0.2 (Et_2O/toluene, 3:1);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.78 (m, 13H, CH*H*, 6xCH_2), 1.92–2.04 (m, 1H, C*H*H), 2.63 (d, *J* = 12.5 Hz, 1H, 2-H), 3.10 (d, *J* = 12.5 Hz, 1H, 2-H), 2.70–3.90 (bs, 2H, OH, NH), 7.19 (t, 1H, *J* = 7.3 Hz, $CH_{ar,\ para}$), 7.28 (t, 2H, *J* = 7.3 Hz, $CH_{ar,\ meta}$), 7.44 (d, 2H, *J* = 7.3 Hz, $CH_{ar,\ orto}$);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 21.9 (C-8,10), 26.2 (C-9), 29.3 (C-4), 31.3 (C-5), 32.7 (C-7), 40.6 (C-11) 50.7 (C-6), 51.2 (C-2), 70.6 (C-3), 124.7 (CH_{ar}, *ortho*), 126.9 (CH_{ar}, *para*), 128.2 (CH_{ar}, *meta*), 145.9 (C_{ar}).

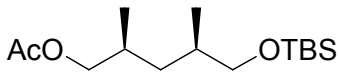
HRMS (EI): calcd for $C_{16}H_{24}NO$ $[M+H]^+$: 246.18524, found 258.18518.

(2*S*,4*R*)-5-hydroxy-2,4-dimethylpentyl acetate (8-23)



To a solution of *meso*-diol **8-10** (14.0 g, 0.107 mol) and vinyl acetate (9.5 g, 10 mL, 0.11 mol) in THF (300 mL) was added Amano Lipase AK from Pseudomonas fluorescence, 100 mg, (Aldrich Cat. Nr. 53,473-0), and the resulting suspension was stirred at room temperature using a mechanical stirrer. After 24 h additional vinyl acetate (2 mL) was added, and stirring continued for a total of 80 h. Then the reaction mixture was filtered through a Celite pad (2 cm), and the filtrate concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (150 mL), and the solution washed with 15% NaCl water solution (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a mixture of mono- and diacetate (17.2 g, 85/15 ratio) as a slightly yellow oil, 80% yield of monoacetate. An analytical sample was prepared by flash chromatography (Et_2O/toluene, 1:4). The analysis by chiral GC [(column: heptakis(2,3-diacetyl-6-TBDMS)-β-cyclodextrin (30%) PS 86 (70%), d_f = 0.13 μ, size: 25 m × 0.25 mm), mobile phase: H_2, 90/2/4/140, pressure: 80 kPa, retention time (main): 11.1 min, (minor): 11.3 min] showed 98% ee, which was confirmed by NMR of Mosher ester, R_f = 0.7 (Et_2O).

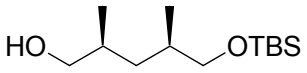
(2*S*,4*R*)-5-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-2,4-dimethylpentyl acetate (8-25)



To a solution of 2.0 g of the acetate mixture from the previous step (corresponding to 9.4 mmol of monoacetate **8-23**) and imidazole (1.4 g, 20 mmol, 2 equiv) in CH_2Cl_2 (6 mL) was added *tert*-butyldimethylchlorsilane (1.5 g, 10 mmol, 1.05 equiv) in small portions over 15 min, and the reaction mixture was stirred for additional 40 min. The imidazole hydrochloride was filteret off, and the filtrate washed with water (2 × 20 mL), 3% HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and

concentrated in vacuo to give 3.0 g (98%) of the crude product **8-25** as colorless oil, which used for the next step without further purification.

(2*S*,4*R*)-5-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-2,4-dimethylpentan-1-ol (**8-27**)



To a solution of the crude silyl ether **8-25** from the previous step (3.0 g) in MeOH (12 mL) was added powdered K_2CO_3 (1.68 g, 12 mmol) and the mixture stirred for 2 h. Thereafter the solids were removed by filtration and the filtrate concentrated in vacuo. The residue was redissolved in petroleum ether (15 mL), washed with water (3 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo affording the alcohol **8-27** as a colorless oil (2.1 g, 75% from 2,4-dimethylpentane-1,5-diol).

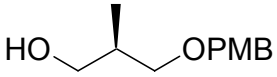
R_f = 0.2 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -3 (c 1 in CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.87–0.90 (m, CH*CH*HCH, CH_3), 0.92 (d, 3H, *J* = 6.8 Hz, CH_3), 1.37–1.46 (m, 1H, CH*CH*HCH), 1.63–1.75 (m, 2H, 2×(CH)), 3.32–3.52 (m, 4H, CH_2OH, CH_2OSi);

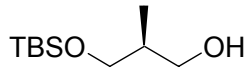
^{13}C NMR (100 MHz, $CDCl_3$) δ =-5.4 ($(CH_3)_2Si$), 17.7, 17.8(2×CH_3), 18.3 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 33.2, 33.3 (2×CH), 37.3 (CHCH_2CH), 68.2, 68.3 (CH_2OH, CH_2OSi).

(2*R*)-2-methyl-3-({[4-(methyloxy)phenyl]methyl}oxy)propan-1-ol 8-37



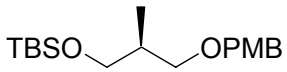
A solution of silyl ether **8-41** (2.0 g, 6.0 mmol) in MeOH (10 mL) was treated with CSA (70 mg, 0.3 mmol, 0.05 equiv) and the mixture stirred for 2 h at room temperature. The reaction was quenched by addition of Et_3N (1 mL) and all volatiles were evaporated. The residual oil was dissolved in CH_2Cl_2 (10 mL), and the solution filtered through a pad of silica gel (2 cm) followed by washing the pad with CH_2Cl_2 (2 × 10 mL). Evaporation of the CH_2Cl_2 afforded alcohol **8-37** (1.2 g, 96%) as a colorless oil which was pure enough for the next step, oxidation to the known aldehyde **8-38**.

(2*S*)-3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-2-methylpropan-1-ol (*S*)-**(-)-8-40**



A mixture of rac-**8-40** (6.12 g, 30 mmol), vinylacetate (12 mL, 120 mmol, 4 equiv) and Amano Lipase AK from Pseudomonas fluorescence, 330 mg, (Aldrich Cat. Nr. 53,473-0) in $CHCl_3$ (60 mL) was stirred at 30 °C for 23 h. Thereafter, the lipase was filtered off and the filtrate concentrated in vacuo. Separation of alcohol and acetate by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave (S)-**8-40** (2.3 g, 37.5%) as a colorless oil. R_f = 0.46 (EtOAc/petroleum ether, 1:4).

(1,1-dimethylethyl)(dimethyl){[(2*S*)-2-methyl-3-({[4-(methyloxy)phenyl]methyl}oxy)propyl]oxy}silane 8-41



To a stirred solution of alcohol (*S*)-**8-40** (2.24 g, 11 mmol) and PMBOC(=NH)CCl_3 (4.1 g, 14.5 mmol) in cyclohexane (10 mL) was added PPTS (125 mg, 0.55 mmol, 0.05 equiv) at 0 °C (ice bath). After 2 h, the cooling bath was removed and stirring continued for 12 h at room temperature. The formed precipitate was removed by filtration, the filtrate washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was triturated with 10 mL petroleum ether and the precipitate was filtered again, followed by evaporation of the filtrate. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1) to afford di-ether **8-41** (3.0 g, 85%) as a colorless oil.

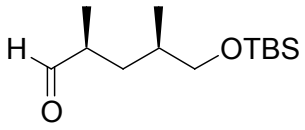
R_f = 0.8 (EtOAc/petroleum ether = 1:9);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $(CH_3)_2SiO$), 0.87 (s, 9H, $(CH_3)_3CSiO$), 0.91 (d, 3H, *J* = 6.8 Hz, *CH_3*CH), 1.85–1.98 (m, 1H, CH_3*CH*), 3.28 (dd, 1H, *J* = 9.1 Hz, *J* = 6.1 Hz, *CH*HOTBS), 3.41 (dd, 1H, *J* = 9.1 Hz, *J* = 6.4 Hz, *C*H*H*OTBS), 3.50 (dd, 1H, *J* = 9.7 Hz, *J* = 5.7 Hz, *CH*HOPMB), 3.55 (dd, 1H, *J* = 9.7 Hz, *J* = 5.7 Hz, *C*H*H*OPMB), 3.80 (s, 3H, OCH_3), 4.42 (s, 2H, O*CH_2*PMP), 6.86 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 7.25 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.4 ($(CH_3)_2SiO$), 14.0 (*CH_3*CH), 18.3 ($(CH_3)_3$*C*Si), 25.9 ((*CH_3*)$_3$CSi), 36.3 (CH_3*CH*), 55.2 (OCH_3), 65.1 (CH_2OTBS), 72.2 (O*CH_2*PMP), 72.7

(*CH*$_2$OPMB), 113.7 (m-CH$_{arom}$), 129.1 (o-CH$_{arom}$), 130.9 (CH$_2$C$_{quat\ arom}$), 159.0, 159.0 (CH$_3$OC$_{quat\ arom}$).

(2*S*,4*R*)-5-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-2,4-dimethylpentanal (8-46)



To a stirred solution of alcohol **8-27** (2.46 g, 10.0 mmol) in CH_2Cl_2 (35 mL) a mixture of iodobenzene diacetate (4.83g, 15 mmol, 1.5 equiv) and TEMPO (78 mg, 0.5 mmol, 0.05 equiv) was added in five portions over a period of 30 min. The orange reaction mixture was stirred for an additional 60 min at 23 °C before a 25% solution of sodium thiosulphate (10 mL) was added. The mixture was stirred for 15 min and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL), and brine. The organic phase was dried over Na_2SO_4, and filtered through a short pad of silica gel (2 cm), followed by washing the pad with CH_2Cl_2 (2 × 10 mL). After removal of the solvent in vacuo, the residue was subjected to a high-vacuum (0.03 mm Hg) distillation at room temperature with the receiver flask immersed in liquid nitrogen, in order to remove PhI. The oily aldehyde **8-46** (2.4 g, 98%) was immediately used for the next step.

R$_f$ = 0.64 (EtOAc/petroleum ether = 1:9);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.87–0.90 (m, CH*CH*HCH, (*CH$_3$*)CHCH$_2$O), 1.08 (d, 3H, *J* = 6.8 Hz, (*CH$_3$*)CHCHO), 1.60–1.72 (m, 1H, CH*C*H*H*CH), 1.80–1.90 (m, 1H, *CH*CH$_2$O), 2.40–2.51 (m, 1H, *CH*CHO), 3.41 (d, 2H, *J* = 5.6 Hz, CH$_2$OSi), 9.56 (d, 1H, *J* = 2.3 Hz, CHO);

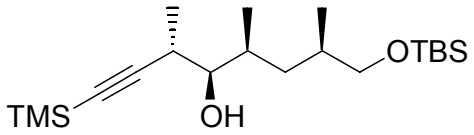
^{13}C NMR (100 MHz, $CDCl_3$) δ =-5.5 ($(CH_3)_2Si$), 14.3 ((*CH$_3$*)CHCHO), 17.1((*CH$_3$*)CHCH$_2$OSi), 18.3 ($(CH_3)_3CSi$), 25.9 ((*CH$_3$*)$_3$CSi), 33.4 (*CH*CH$_2$O), 34.6 (CH*CH$_2$*CH), 44.2 (*CH*CHO), 67.8 (CH$_2$OSi), 205.4 (CHO).

(*R*)-3-Butyn-2-ol (8-33)

To a 100-mL round-bottomed flask, equipped with a magnetic stir bar, is added a solution of (*R*)-4-trimethylsilyl-3-butyn-2-ol acetate (5.1 g, 28 mmol) in ethanol (20 mL, not absolute) followed by addition of hydrazine hydrate (2.75 g, 2.8 mL, 55.0 mmol). After 6 h, TLC

analysis (EtOAc/hexanes = 1:1) of the mixture indicated complete cleavage of the acetate group. The solution was concentrated in *vacuo*, diluted with Et_2O (40 mL). This solution was washed with 1N HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (2 × 10 mL), to yield 3.0 g (75%) of (*R*)-3-butyn-2-ol as a clear oil that can be used without further purification or distilled, b.p. 85 °C at 9 mm Hg.

(3*S*,4*R*,5*S*,7*R*)-8-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-3,5,7-trimethyl-1-(trimethylsilyl)oct-1-yn-4-ol (8-52)



To a stirred solution of $Pd(OAc)_2$ (88 mg, 0.4 mmol, 0.040 equiv) in THF (100 mL) at -78 °C was added PPh_3 (105 mg, 0.4 mmol, 0.040 equiv), aldehyde **8-46** (2.44 g, 10 mmol), and mesylate (*R*)-**8-15** (2.6 g, 13 mmol, 1.30 equiv). Diethylzinc (28 mL, 1 M in hexane) was added over 10 min, and after stirring for 5 min the mixture was warmed to -20 °C and stirred for 3 days at this temperature. The reaction was quenched with NH_4Cl/Et_2O (1:1), and the layers were separated. The Et_2O layer was washed with brine and stirred with $MgSO_4$ and finely powdered active charcoal. The solution was filtered and concentrated, followed by purification of the residue by flash chromatography (Et_2O/petroleum ether, 1:25) to give 2.68 g (71%) of alkyne **8-52** as an inseparable 92.5:7.5 mixture of diastereomeric alcohols as a slightly green-yellow oil.

R_f = 0.57 (Et_2O/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -10.5 (c 1 in CH_2Cl_2);

IR (film): υ_{max} = 3471, 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 6H, $(CH_3)_2SiO$), 0.14 (s, 9H, $(CH_3)_3SiC$), 0.88 (s, 9H, $(CH_3)_3CSiO$), 0.87–1.03 (m, 7H, CH*CH*HCH, (*CH*$_3$)CHCH$_2$O, (*CH*$_3$)CHCHOH), 1.15 (d, 3H, *J* = 7.1 Hz, *CH*$_3$CHC≡C), 1.43–1.52 (m, 1H, CH*C*H*H*CH), 1.64–1.76 (m, 2H, *CH*CH$_2$OSi, CH$_2$*CH*CHOH), 1.95 (d, 1H, *J* = 5.6 Hz, OH), 2.63–2.72 (m, 1H, *CH*C≡C), 3. 32 (dd, 1H, *J* = 9.7 Hz, *J* = 6.7 Hz, *C*H*H*OSi), 3.47 (dd, 1H, *J* = 9.7 Hz, *J* = 5.2 Hz, *CH*HOSi);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-5.4 ($(CH_3)_2Si$), -0.1 ($(CH_3)_3SiC$), 14.1 (HOCHCH(*CH*$_3$)CH$_2$), 17.6 (*CH*$_3$CHC≡C), 17.8 ((*CH*$_3$)CHCH$_2$OSi), 18.3 ($(CH_3)_3$*C*Si), 25.9

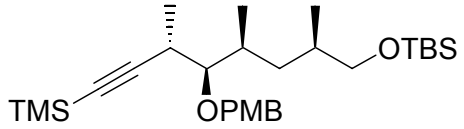
((CH_3)$_3$CSi), 32.0 (*CH*C≡C), 32.9, 33.1 (*CH*CH_2OSi, CH_2*CH*CHOH), 37.8 (CH*CH_2*CH), 68.0 (CH_2OSi), 77.0 (*CH*OH), 87.4 (C≡*C*Si), 108.4 (*C*≡CSi);

HRMS (EI) : calcd. for $C_{20}H_{42}O_2Si_2Na$ $[M+Na]^+$: 393.26155, found 393.26159.

4-Methoxybenzyl 2,2,2-trichloroethanimidoate

This compound (also referred as PMB-imidate) was obtained from 4-methoxybenzyl alcohol and trichloroacetonitrile via the procedure described by Bundell[201] and distilled, b.p. 100 °C at 0.1 mmHg, lit. 135-137 °C at 0.7 mmHg[202].

(1,1-dimethylethyl)(dimethyl){[(2*R*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-5-({[4-(methyloxy)phenyl]methyl}oxy)-8-(trimethylsilyl)oct-7-yn-1-yl]oxy}silane (**8-53**)



To a vigorously stirred solution of Marshall adduct **8-52** (1.50 g, 4.0 mmol) and PMBOC(=NH)CCl_3 (1.7 g, 6.0 mmol, 1.5 equiv) in Et_2O (10 mL) at 0 °C was added dropwise a solution of TfOH (0.2 M in Et_2O, 30 µL, 6 µmol). After 3 h the same amount of TfOH was added. Stirring was continued for further 4 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with petroleum ether and the formed precipitate removed by filtration, followed by concentration of the filtrate. The crude product was purified by flash chromatography (Et_2O/petroleum ether, 1:25) to afford **8-53** (1.32 g, 70%) as slightly green-yellow oil.

R_f = 0.63 (Et_2O/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -9.6 (c 1 in CH_2Cl_2);

IR (film): υ_{max} = 2956, 2931, 2858, 2166, 1614, 1514, 1464, 1250, 1173, 1091, 1039 cm^{-1};

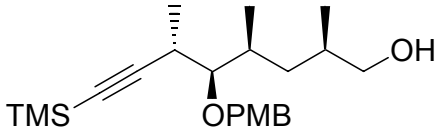
^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, (CH_3)$_2$SiO), 0.13 (s, 9H, (CH_3)$_3$SiC), 0.88 (s, 9H, (CH_3)$_3$CSiO), 0.87–1.03 (m, 7H, CH*CH*HCH, (*CH_3*)CHCH$_2$O, (*CH_3*)CHCHOPMB), 1.15 (d, 3H, *J* = 6.8 Hz, *CH_3*CHC≡C), 1.49–1.59 (m, 1H, CH*C*H*H*CH), 1.65–1.88 (m, 2H, *CH*CH_2OSi, CH_2*CH*CHOPMB), 2.74–2.83 (m, 1H, *CH*C≡C), 3.25 (dd, 1H, *J* = 7.7 Hz, *J* = 3.2 Hz, *CH*OPMB), 3.31 (dd, 1H, *J* = 9.7 Hz, *J* = 6.6 Hz, *C*H*H*OSi), 3.43 (dd, 1H, *J* = 9.7 Hz, *J* = 5.2 Hz, *CH*HOSi), 3.79 (s, 3H, OCH_3), 4.50 (d, 1H, *J* = 10.6 Hz, OC*H*H*P*MP), 4.83 (d, 1H, *J*

= 10.6 Hz, O*CH*HPMP), 6.85 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 7.31 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ =-5.4 ($(CH_3)_2SiO$), 0.1 ($(CH_3)_3SiC$), 14.5 (PMBOCHCH(*CH*$_3$)CH_2), 17.6 (*CH*$_3$CHC≡C), 17.7 ((*CH*$_3$)$CHCH_2OSi$), 18.4 ($(CH_3)_3$*C*Si), 26.0 ((*CH*$_3$)$_3$CSi), 30.5 (*CH*C≡C), 32.2, 33.1 (*CH*CH_2OSi, CH_2*CH*CHOPMB), 38.2 (CH*CH*$_2$CH), 55.3 (OCH_3), 68.2 (CH_2OSi), 74.2 (O*CH*$_2$PMP), 84.5 (*CH*OPMB), 85.0 (C≡*C*Si), 110.8 (*C*≡CSi), 113.6 (m-CH_{arom}), 129.1 (o-CH_{arom}), 131.4 ($CH_2C_{quat\ arom}$), 159.0 ($CH_3OC_{quat\ arom}$);

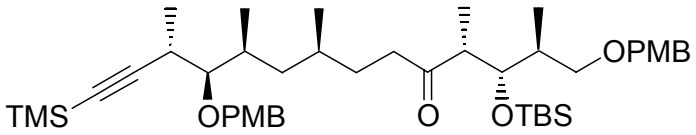
HRMS (EI) : calcd. for $C_{28}H_{50}O_3Si_2Na$ $[M+Na]^+$: 513.31907, found 513.31915.

(2*R*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-5-({[4-(methyloxy)phenyl]methyl}oxy)-8-(trimethylsilyl)oct-7-yn-1-ol (8-54)



A solution of silyl ether **8-53** (1.32 g, 2.7 mmol) in MeOH (5 mL) was treated with CSA (23 mg, 0.1 mmol) and the mixture stirred for 2 h at room temperature. The reaction was quenched by addition of Et_3N (1 mL) and the volatiles evaporated. The resulting oil was dissolved in CH_2Cl_2 (10 mL), filtered through a pad of silica gel (2 cm) followed by washing the pad with CH_2Cl_2 (2 × 20 mL). Evaporation of CH_2Cl_2 afforded alcohol **8-54** (966 mg, 95%) as a colorless oil, which was pure enough for the next step.

(2*S*,3*S*,4*R*,8*S*,10*S*,11*R*,12*S*)-3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-2,4,8,10,12-pentamethyl-1,11-bis({[4-(methyloxy)phenyl]methyl}oxy)-14-(trimethylsilyl)tetradec-13-yn-5-one 8-57



To a vigorously stirred solution of iodide **8-60** (450 mg, 0.9 mmol) in Et_2O (5 mL) at -78 °C was added dropwise 1.5 M solution of tert-butyllitium in pentane (1.2 mL, 1.8 mmol). After 30 min solution of Weinreb amide **8-44** (470 mg, 1.0 mmol) in Et_2O (1 mL) was introduced dropwise via syringe keeping internal temperature below -75 °C, and stirred for another 30 min. Cooling bath was removed and reaction allowed to warm to room temperature over 10

min. After dilution with 10 mL Et_2O, reaction was quenched with aqueous NH_4Cl. Organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (EtOAc/petroleum ether = 1:10) to obtain keton **23** (438 mg, 65%) as a colorless oil.

R_f = 0.5 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -17 (c 0.92 in CH_2Cl_2);

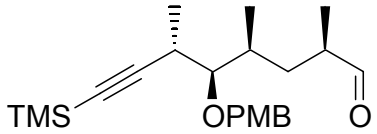
IR (film): υ_{max} = 2956, 2931, 2164, 1711, 1614, 1514, 1462, 1375, 1302, 1250, 1173, 1085, 1039 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 3H, $(CH_3)SiO$), 0.04 (s, 3H, $(CH_3)SiO$), 0.13 (s, 9H, $(CH_3)_3SiC$), 0.81 (d, 3H, *J* = 6.1 Hz, $(CH_3)CHCH_2CH_2$), 0.85 (d, 3H, *J* = 6.6 Hz, $(CH_3)CH$), 0.87 (s, 9H, $(CH_3)_3CSiO$), 0.88 (d, 3H, *J* = 6.8 Hz, $(CH_3)CH$), 0.93 (d, 3H, *J* = 7.1 Hz, $(CH_3)CH$), 1.00–1.10 (m, 1H, $CHCHHCH$), 1.05 (d, 3H, *J* = 7.1 Hz, CH_3CHCO), 1.15 (d, 3H, *J* = 7.1 Hz, $CH_3CHC{\equiv}C$), 1.14–1.24 (m, 1H, $CHHCH_2CO$), 1.37–1.46 (m, 2H, $CHCHHCH$, $CH_2CH(CH_3)CH_2CH_2$), 1.53–1.64 (m, 1H, $CHHCH_2CO$), 1.77–1.91 (m, 2H, $CHCH_2OPMB$, $PMBOCHCH(CH_3)CH_2$), 2.29–2.50 (m, 2H, CH_2CO), 2.73–2.83 (m, 2H, $CHC{\equiv}C$, $CHCO$), 3.18 (dd, 1H, *J* = 9.2 Hz, *J* = 6.3 Hz, $CHHOPMB$), 3.22 (dd, 1H, *J* = 7.7 Hz, *J* = 2.9 Hz, $CHOPMB$), 3.49 (dd, 1H, *J* = 9.2 Hz, *J* = 5.9 Hz, $CHHOPMB$), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.96 (dd, 1H, *J* = 5.9 Hz, *J* = 4.4 Hz, $CHOTBS$), 4.37 (s, 2H, OCH_2PMP), 4.50 (d, 1H, *J* = 10.9 Hz, $OCHHPMP$), 4.84 (d, 1H, *J* = 10.9 Hz, $OCHHPMP$), 6.85 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 6.86 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 7.23 (d, 2H, *J* = 8.6 Hz, o-CH_{arom}), 7.30 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.2 ($(CH_3)SiO$), -3.9 ($(CH_3)SiO$), 0.1 ($(CH_3)_3SiC$), 13.4 (CH_3CHCO), 14.4 ($PMBOCHCH(CH_3)CH_2$), 17.7 ($CH_3CHC{\equiv}C$), 18.3 ($(CH_3)_3CSi$), 19.8 ($(CH_3)CHCH_2CH_2$), 26.0 ($(CH_3)_3CSi$), 26.8 ($(CH_3)CHCH_2CH_2$), 30.0 (CH_2CH_2CO), 30.4 ($CHC{\equiv}C$), 32.0 ($CH_2CHCHOPMB$), 38.7 ($CHCH_2OPMB$), 39.6 (CH_2CO), 41.8 ($CHCH_2CH$), 49.8 ($CHCO$), 55.2 (OCH_3x2), 71.7 (CH_2OPMB), 72.6 (OCH_2PMP), 74.0 (OCH_2PMP), 74.6 (CHOTBS), 84.3 ($CHOPMB$), 85.1 ($C{\equiv}CSi$), 110.8 ($C{\equiv}CSi$), 113.5, 113.6 (m-CH_{arom}x2), 129.0, 129.1 (o-CH_{arom}x2), 130.6, 131.3 ($CH_2C_{quat\ arom}$x2), 158.9, 159.0 ($CH_3OC_{quat\ arom}$x2), 213.7 (CO).

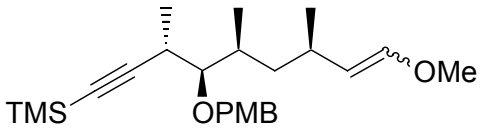
HRMS (EI) : calcd. for $C_{44}H_{72}O_6Si_2Na$ $[M+Na]^+$: 775.47596, found 775.47528

(2*R*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-5-({[4-(methyloxy)phenyl]methyl}oxy)-8-(trimethylsilyl)oct-7-ynal



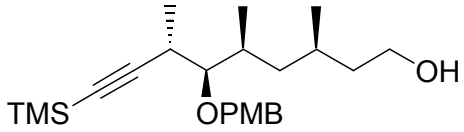
To a solution of alcohol **8-54** (966 mg, 2.57 mmol) in dichloromethane (10 mL) was added a mixture of iodobenzene diacetate (1.3 g, 4.0 mmol) and TEMPO (30 mg, 0.2 mmol) in five portions over a period of 30 min with vigorous stirring. The orange reaction mixture was stirred for an additional 60 min at 25 °C before a 25% solution of sodium thiosulphate (7 mL) was added. The mixture was stirred for 15 min, and the organic phase separated. The aqueous phase was re-extracted with CH_2Cl_2 (10 mL), and the combined organic layers were washed with water (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo at 20 °C. After removing PhI as described for compound **8-46**, the crude aldehyde was used directly in the next step.

trimethyl[(3*S*,4*R*,5*S*,7*R*)-3,5,7-trimethyl-9-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl}oxy)non-8-en-1-yn-1-yl]silane (8-58)



A suspension of (methoxymethyl)-triphenylphosphonium chloride (1.37 g, 4.0 mmol) in THF (10 mL) was cooled to -78 °C and then NaHMDS (2 M in THF, 2.1 mL, 4.2 mmol) was added dropwise. The resulting orange solution was stirred for 1 h, and then the above aldehyde (893 mg, 2.4 mmol) in THF (2 mL) was added via syringe. After stirring for an additional 2 h at -78 °C, the mixture was allowed to warm to room temperature within 30 min, and then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. This crude material was then passed through a plug of silica gel in order to separate nonpolar impurities, and the resulting mixture of two enol ethers ((*E*)- and (*Z*)-olefin isomers) **8-58** was then carried on directly into the following hydrolysis reaction.

(3*R*,5*S*,6*R*,7*S*)-3,5,7-Trimethyl-6-({[4-(methyloxy)phenyl]methyl}oxy)-9-(trimethylsilyl)non-8-yn-1-ol (8-59)



To a stirred solution of enol ether **8-58** (634 mg, 1.6 mmol) in a mixture of MeCN (5 mL) and water (1 mL) at room temperature was added dropwise conc. (36%) hydrochloric acid (0.1 mL). After 2 h $NaBH_4$ (100 mg, 3 mmol) was added in small portions directly into the reaction mixture, and stirring was continued for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and the mixture extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/petroleum ether = 1:4), to give alcohol **8-59** (500 mg, 80%) as a colorless oil.

R_f = 0.2 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -5.27 (c = 0.85 in CH_2Cl_2);

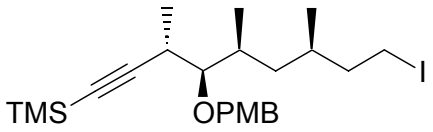
IR (film): υ_{max} = 3425, 2958, 2933, 2164, 1614, 1514, 1460, 1376, 1302, 1250, 1174, 1064, 1037 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.13 (s, 9H, $(CH_3)_3SiC$), 0.87 (d, 3H, *J* = 6.6 Hz, (*CH*$_3$)CH), 0.88 (d, 3H, *J* = 6.6 Hz, (*CH*$_3$)CH), 0.95–10.7 (m, 1H, CH*CH*HCH), 1.15 (d, 3H, *J* = 7.1 Hz, *CH*$_3$CHC≡C), 1.49–1.59 (m, 1H, CH*C*H*H*CH), 1.65–1.75 (m, 2H, *C*H*H*CH_2OH, OH), 1.78–1.88 (m, 2H, *CH*HCH_2OH, CH_2*CH*CHOPMB), 2.74–2.83 (m, 1H, *CH*C≡C), 3.25 (dd, 1H, *J* = 7.5 Hz, *J* = 3.2 Hz, *CH*OPMB), 3.56–3.71 (m, 2H, CH_2OH), 3.79 (s, 3H, OCH_3), 4.50 (d, 1H, *J* = 10.9 Hz, OC*H*HPMP), 4.84 (d, 1H, *J* = 10.9 Hz, O*CH*HPMP), 6.86 (d, 2H, *J* = 8.6 Hz, *m*-CH_{arom}), 7.30 (d, 2H, *J* = 8.6 Hz, *o*-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = 0.1 ($(CH_3)_3SiC$), 14.4 (PMBOCHCH(*CH*$_3$)CH_2), 17.7 (*CH*$_3$CHC≡C), 20.1 ((*CH*$_3$)$CHCH_2CH_2OH$), 26.8 ((CH_3)*CH*CH_2CH_2OH), 30.4 (*CH*C≡C), 32.0 (CH_2*CH*CHOPMB), 39.7 (*CH*$_2CH_2OH$), 41.9 (CH*CH*$_2$CH), 55.3 (OCH_3), 61.0 (*CH*$_2$OH), 73.9 (O*CH*$_2$PMP), 84.1 (*CH*OPMB), 85.2 (C≡*C*Si), 110.7 (*C*≡CSi), 113.6 (*m*-CH_{arom}), 129.2 (*o*-CH_{arom}), 131.3 ($CH_2C_{quat\ arom}$), 159.0 ($CH_3OC_{quat\ arom}$);

HRMS (EI): calcd. for $C_{23}H_{38}O_3SiNa$ $[M+Na]^+$: 413.24824, found 413.24800.

[(3*S*,4*R*,5*S*,7*R*)-9-Iodo-3,5,7-trimethyl-4-({[4-(methyloxy)phenyl]methyl}oxy)non-1-yn-1-yl](trimethyl)silane 8-60



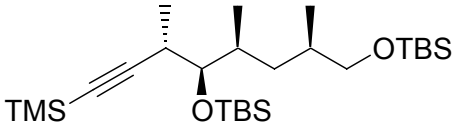
To a stirred solution of PPh_3 (570 mg, 2.2 mmol) and imidazole (170 mg, 2.5 mmol) in dry CH_2Cl_2 (5 mL) was added I_2 (508 mg, 2.0 mmol). The mixture was stirred at room temperature for 20 min, and then alcohol (**8-59**) (460 mg, 1.2 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After being stirred at room temperature for additional 2 h, the reaction was quenched by addition saturated aqueous $NaHCO_3$ solution and CH_2Cl_2 (10 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (EtOAc/petroleum ether = 1:10), to give iodide **8-60** (500 mg, 80%) as a colorless oil.

R_f = 0.8 (EtOAc/petroleum ether = 1:9);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.13 (s, 9H, $(CH_3)_3SiC$), 0.86 (d, 3H, *J* = 6.6 Hz, (*CH*$_3$)CH), 0.88 (d, 3H, *J* = 6.8 Hz, (*CH*$_3$)CH), 0.96–1.06 (m, 1H, CH*CH*HCH), 1.16 (d, 3H, *J* = 7.1 Hz, *CH*$_3$CHC≡C), 1.38–1.47 (m, 1H, CH*C*H*H*CH), 1.49–1.68 (m, 2H, *CH*HCH$_2$I, (CH$_3$)*CH*CH$_2$CH$_2$I), 1.77–1.88 (m, 2H, *C*H*H*CH$_2$I, CH$_2$*CH*CHOPMB), 2.74–2.83 (m, 1H, *CH*C≡C), 3.25 (dd, 1H, *J* = 7.5 Hz, *J* = 3.2 Hz, *CH*OPMB), 3.56–3.71 (m, 2H, CH$_2$I), 3.79 (s, 3H, OCH$_3$), 4.50 (d, 1H, *J* = 10.9 Hz, OC*H*HPMP), 4.84 (d, 1H, *J* = 10.9 Hz, OC*H*HPMP), 6.86 (d, 2H, *J* = 8.6 Hz, *m*-CH$_{arom}$), 7.30 (d, 2H, *J* = 8.6 Hz, *o*-CH$_{arom}$);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 0.1 ($(CH_3)_3SiC$), 5.1 (CH_2I), 14.4 (PMBOCHCH(*CH*$_3$)CH$_2$), 17.7 (*CH*$_3$CHC≡C), 20.1 ((*CH*$_3$)CHCH$_2$CH$_2$I), 26.8 ((CH$_3$)*CH*CH$_2$CH$_2$I), 30.4 (*CH*C≡C), 32.0 (CH$_2$*CH*CHOPMB), 39.7 (*CH*$_2$CH$_2$I), 41.2 (CH*CH*$_2$CH), 55.3 (OCH_3), 73.9 (O*CH*$_2$PMP), 84.0 (*CH*OPMB), 85.4 (C≡*C*Si), 110.5 (*C*≡CSi), 113.6 (*m*-CH$_{arom}$), 129.2 (*o*-CH$_{arom}$), 131.2 (CH$_2$C$_{quat\ arom}$), 159.0 (CH$_3$OC$_{quat\ arom}$).

(2*R*,4*S*,5*R*,6*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4,6-trimethyl-8-(trimethylsilyl)-7-octyn-1-ol *tert*-butyl(dimethyl)silyl ether 8-61



To a stirred solution of alcohol **8-52** (3.7 g, 10 mmol) and 2,6-lutidine (2.8 g, 2.8 mL, 26 mmol) in CH_2Cl_2 (30 mL) at 0°C was added TBSOTf (3 mL, 3.45 g, 13 mmol). The reaction mixture was allowed to warm to room temperature over 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL), and diluted with CH_2Cl_2 (10 mL). The organic phase was separated, and the water layer extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with 1N HCl (5 mL), saturated aqueous $NaHCO_3$ soltuion, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product (4.84 g) was used further without any purification. An analytical sample was prepared by flash chromatography (EtOAc/petroleum ether = 1:40).

R_f = 0.87 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -7.1 (c = 1.5 in CH_2Cl_2);

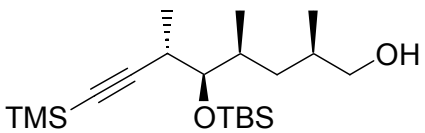
IR (film): υ_{max} = 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 6H, $(CH_3)_2SiO$), 0.14 (s, 9H, $(CH_3)_3SiC$), 0.88 (s, 9H, $(CH_3)_3CSiO$), 0.87–1.03 (m, 7H, CH*CH*HCH, (*CH*$_3$)CHCH$_2$OTBS, (*CH*$_3$)CHCHOTBS), 1.15 (d, 3H, *J* = 7.1 Hz, *CH*$_3$CHC≡C), 1.43–1.52 (m, 1H, CH*C*H*H*CH), 1.64–1.76 (m, 2H, *CH*CH$_2$OSi, CH$_2$*CH*CHOH), 1.95 (d, 1H, *J* = 5.6 Hz, OH), 2.63–2.72 (m, 1H, *CH*C≡C), 3. 32 (dd, 1H, *J* = 9.7 Hz, *J* = 6.7 Hz, *C*H*H*OTBS), 3.47 (dd, 1H, *J* = 9.7 Hz, *J* = 5.2 Hz, *CH*HOSi);

^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.4 ($(CH_3)_2Si$), -0.1 ($(CH_3)_3SiC$), 14.1 (HOCHCH(*CH*$_3$)CH$_2$), 17.6 (*CH*$_3$CHC≡C), 17.8 ((*CH*$_3$)CHCH$_2$OTBS), 18.3 ($(CH_3)_3$*C*Si), 25.9 ((*CH*$_3$)$_3$CSi), 32.0 (*CH*C≡C), 32.9, 33.1 (*CH*CH$_2$OTBS, TBSOCH*CH*(CH$_3$)CH$_2$), 37.8 (CH*CH*$_2$CH), 68.0 (CH$_2$OTBS), 77.0 (CHOTBS), 87.4 (C≡*C*Si), 108.4 (*C*≡CSi);

HRMS (EI): calcd. for $C_{26}H_{56}O_2Si_3Na$ $[M+Na]^+$: 507.34803, found 507.34825.

(2*R*,4*S*,5*R*,6*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4,6-trimethyl-8-(trimethylsilyl)-7-octyn-1-ol



To a solution of disilyl ether **8-61** in a mixture of MeOH (15 mL) and DCM (15 mL) at rt were added few crystals of CSA (approx. 10 mg). The reaction mixture was stirred until no starting material was detected by TLC analysis (4-6 h). The reaction was quenched by addition of Et_3N (100 μLI, before all volatiles were removed by evaporation. The crude product was purified by

flash chromatography (EtOAc/petroleum ether = 1:9) to give 3.3 g (90%) of the primary alcohol.

R_f = 0.27 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -9.8 (c = 7.3 in CH_2Cl_2);

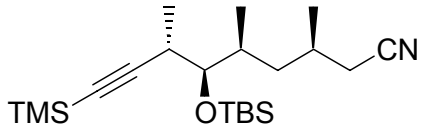
IR (film): υ_{max} = 3471, 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 3H, $(CH_3)_2SiO$), 0.07 (s, 3H, $(CH_3)_2SiO$), 0.11 (s, 9H, $(CH_3)_3SiC$), 0.89 (s, 9H, $(CH_3)_3CSiO$), 0.85–1.01 (m, 7H, CH*CH*HCH, (*CH₃*)CHCH$_2$OH, CH$_2$(*CH₃*)CHCHOTBS), 1.15 (d, 3H, *J* = 7.1 Hz, *CH₃*CHC≡C), 1.46 (s, 1H, OH), 1.47–1.56 (m, 1H, CH*C*H*H*CH), 1.63–1.75 (m, 1H, TBSOCH*CH*(CH$_3$)CH$_2$), 1.78–1.89 (m, 1H, (CH$_3$)*CH*CH$_2$OH), 2.58–2.66 (m, 1H, *CH*C≡C), 3.34 (dd, 1H, *J* = 10.6 Hz, *J* = 6.7 Hz, *C*H*H*OH), 3.48 (t, 1H, *J* = 3.5 Hz, *CH*OTBS), 3.53 (dd, 1H, *J* = 10.6 Hz, *J* = 4.7 Hz, *CH*HOH);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.1 ($(CH_3)_2Si$), -0.1 ($(CH_3)_3SiC$), 15.9 (TBSOCHCH(*CH₃*)CH$_2$), 17.5 (*CH₃*CHC≡C), 17.7 ((*CH₃*)CHCH$_2$OH), 18.3 ($(CH_3)_3$*C*Si), 26.0 ((*CH₃*)$_3$CSi), 32.7 (*CH*C≡C), 33.1, 33.8, (*CH*CH$_2$OH, CH$_2$*CH*CHOTBS), 38.2 (CH*CH$_2$*CH), 67.7 (CH$_2$OH), 77.2 (*CH*OTBS), 85.9 (C≡*C*Si), 110.2 (*C*≡CSi);

HRMS (EI): calcd. for $C_{20}H_{42}O_2Si_2Na$ $[M+Na]^+$: 393.26155, found 393.26149.

(3*R*,5*S*,6*R*,7*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3,5,7-trimethyl-9-(trimethylsilyl)-8-nonynenitrile 8-62



A solution of the alcohol from the previous step (3.3 g, 9 mmol) in diethyl ether (30 mL, 0.3 M) was cooled to 0°C. Recrystallized PPh_3 (7.8 g, 30 mmol) was added portionwise and the solution was stirred at this temperature for 10 minutes. Then DIAD (5.4 g, 5.4 mL, 27 mmol) was added dropwise (a precipitate was formed) and the reaction was stirred for 20 minutes before the acetone cyanohydrin (2.3 g, 2.5 mL, 27 mmol) was added dropwise. The reaction mixture was warmed to room temperature overnight, and stirred for another 10 h. The mixture was diluted with Et_2O/hexane (1:1, 20 mL) (hydrazo ester and $OPPh_3$ precipitated), and filtered. The filtrate was concentrated under reduced pressure. The residue was triturated with petroleum ether and filtered from the precipitate one more time. After concentration of the

filtrate, the crude product was purified by flash chromatography (Et_2O/petroleum ether = 1:12) to yield 3.1 g (91%) of the desired nitrile **8-62**.

R_f = 0.5 (Et_2O/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -11.5 (c = 1.5 in CH_2Cl_2);

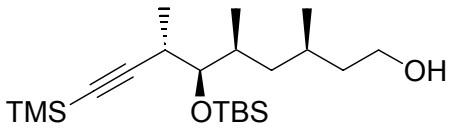
IR (film): υ_{max} = 3471, 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H, $(CH_3)_2SiO$), 0.08 (s, 3H, $(CH_3)_2SiO$), 0.12 (s, 9H, $(CH_3)_3SiC$), 0.88 (d, 2H, *J* = 6.8 Hz, $CH_2(CH_3)CHCHOSi$), 0.90 (s, 9H, $(CH_3)_3CSiO$), 1.10 (d, 3H, *J* = 6.6 Hz, $CH_3CHC{\equiv}C$), 1.15 (d, 3H, *J* = 7.1 Hz, $(CH_3)CHCH_2CN$), 1.17–1.25 (m, 1H, CH*CH*HCH), 1.50–1.59 (m, 1H, CH*C*H*H*CH), 1.83–1.85 (m, 1H, SiOCH*CH*$(CH_3)CH_2$), 1.88–2.01 (m, 1H, (CH_3)*CH*CH_2OH), 2.14 (dd, 1H, *J* = 16.7 Hz, *J* = 7.6 Hz, *C*H*H*CN), 2.34 (dd, 1H, *J* = 16.7 Hz, *J* = 4.7 Hz, *CH*HOH), 2.58–2.66 (m, 1H, *CH*C≡C), 3.48 (t, 1H, *J* = 3.3 Hz, *CH*OSi);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.6 ($(CH_3)_2Si$), -0.1 ($(CH_3)_3SiC$), 15.9 (SiOCHCH$(CH_3)CH_2$), 17.5 ($CH_3CHC{\equiv}C$), 18.3 ($(CH_3)_3CSi$), 20.3 ($(CH_3)CHCH_2CN$), 24.0 (CH_2CN), 26.0 ($(CH_3)_3CSi$), 28.1 ($CHCH_2CN$), 32.5 (*CH*C≡C), 34.0, (SiOCH*CH*$(CH_3)CH_2$), 40.9 (CHCH_2CH), 77.2 (*CH*OSi), 86.3 (C≡*C*Si), 109.8 (*C*≡CSi), 118.8 (CH_2CN);

HRMS (EI): calcd. for $C_{21}H_{41}NOSi_2Na$ $[M+Na]^+$: 402.26189, found 402.26183.

(3*R*,5*S*,6*R*,7*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3,5,7-trimethyl-9-(trimethylsilyl)-8-nonyn-1-ol 8-63



A solution of nitrile **8-62** (3.1 g, 8.1 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 °C. DIBAL-H (10 mL, 1 M in hexane, 10 mmol) was added dropwise, and the mixture stirred for 2 h at -78 °C. The reaction mixture was then warmed to room temperature and poured into a mixture of ice (20 g), 1N HCl (60 mL), and Et_2O (60 mL). The organic phase was separated and the water phase was extracted with diethyl ether (50 mL). The combined organic layers were washed with brine (50 mL, 25 mL), dried with Na_2SO_4, and the solvents were removed under reduced pressure. The residue was dissolved in a mixture of THF (20 mL) and MeOH (5 mL), and cooled to 0 °C. $NaBH_4$ (2.25 g, 8.0 mmol) was added in small portions over 30 min. The reaction was allowed to warm to room temperature overnight, before all volatiles were

removed by evaporation in vacuo. The residue was partioned between saturated aqueous $NaHCO_3$ (30 mL) and Et_2O (60 mL). The organic phase was separated and the water phase extracted with diethyl ether (20 mL). The combined organic layers were washed with brine (50 mL, 25 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether = 1:9) to yield 2.53 g (81%) of the alcohol **8-63**.

R_f = 0.28 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -14.8 (c = 10.2 in CH_2Cl_2);

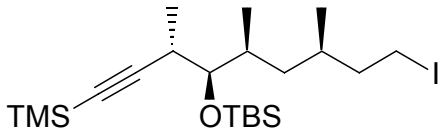
IR (film): υ_{max} = 3471, 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 3H, $(CH_3)_2SiO$), 0.07 (s, 3H, $(CH_3)_2SiO$), 0.12 (s, 9H, $(CH_3)_3SiC$), 0.90 (s, 9H, $(CH_3)_3CSiO$), 0.85–1.08 (m, 8H, *C*H*H*OH, CH*CH*HCH, (*CH*$_3$)CHCH$_2$CH$_2$OH, CH$_2$(*CH*$_3$)CHCHOSi), 1.15 (d, 3H, *J* = 7.3 Hz, *CH*$_3$CHC≡C), 1.21–1.72 (m, 5H, CH$_2$*OH*, *CH*$_2$CH$_2$OH, (CH$_3$)*CH*CH$_2$CH$_2$OH, CH*C*H*H*CH), 1.77–1.89 (m, 1H, SiOCH*CH*(CH$_3$)CH$_2$), 2.55–2.67 (m, 1H, *CH*C≡C), 3.49 (t, 1H, *J* = 3.5 Hz, *CH*OSi), 3.59–3.71 (m, 1H, *CH*HOH);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.1 ($(CH_3)_2Si$), -4.0 ($(CH_3)_2Si$), 0.1 ($(CH_3)_3SiC$), 15.5 (SiOCHCH(*CH*$_3$)CH$_2$), 17.4 (*CH*$_3$CHC≡C), 18.4 ($(CH_3)_3$*C*Si), 20.3 ((*CH*$_3$)CHCH$_2$CH$_2$OH), 26.0 ((*CH*$_3$)$_3$CSi), 27.1 ((CH$_3$)*CH*CH$_2$CH$_2$OH), 32.8 (*CH*C≡C), 33.6 (CH$_2$*CH*CHOSi), 39.3 (CH*CH*$_2$CH), 42.6 (*CH*$_2$CH$_2$OH), 61.2 (CH$_2$OH), 77.2 (*CH*OSi), 85.9 (C≡*C*Si), 110.4 (*C*≡CSi);

HRMS (EI): calcd. for $C_{21}H_{44}O_2Si_2Na$ $[M+Na]^+$: 407.27720, found 407.27707.

tert-butyl{[(1*R*,2*S*)-1-[(1*S*,3*R*)-5-Iodo-1,3-dimethylpentyl]-2-methyl-4-(trimethylsilyl)-3-butyn-1-yl]oxy}dimethylsilane 8-64



This iodide was prepared from 2.53 g (6.5 mmol) of the alcohol **8-63** by the procedure described for the PMB analogue **8-59** to give 2.0 g (80% yield) of iodide **8-64** as colorless oil.

R_f = 0.88 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -22.3 (c = 2.3 in CH_2Cl_2);

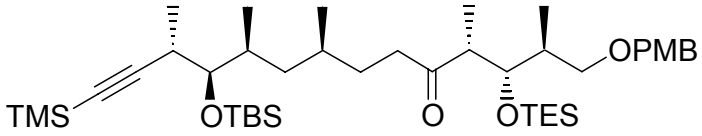
IR (film): υ_{max} = 3471, 2956, 2931, 2858, 2164, 1649, 1462, 1388, 1251, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H, $(CH_3)_2SiO$), 0.08 (s, 3H, $(CH_3)_2SiO$), 0.12 (s, 9H, $(CH_3)_3SiC$), 0.90 (s, 9H, $(CH_3)_3CSiO$), 0.85–0.91 (m, 6H, $(CH_3)CHCH_2CH_2I$, $CH_2(CH_3)CHCHOSi$), 1.00–1.09 (m, 1H, CHCHHCH), 1.15 (d, 3H, *J* = 7.1 Hz, $CH_3CHC{\equiv}C$), 1.41–1.68 (m, 3H, CH_2CH_2OH, CHCHHCH), 1.77–1.87 (m, 1H, $(CH_3)CHCH_2CH_2I$), 1.88–1.99 (m, 1H, $SiOCHCH(CH_3)CH_2$), 2.56–2.66 (m, 1H, $CHC{\equiv}C$), 3.09–3.18 (m, 1H, CHHI), 3.25–3.33 (m, 1H, CHHI), 3.49 (t, 1H, *J* = 3.7 Hz, CHOSi);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.0 ($(CH_3)_2Si$), -3.9 ($(CH_3)_2Si$), 0.1 ($(CH_3)_3SiC$), 5.2 (CH_2I), 15.6 ($SiOCHCH(CH_3)CH_2$), 17.5 ($CH_3CHC{\equiv}C$), 18.4 ($(CH_3)_3CSi$), 19.4 ($(CH_3)CHCH_2CH_2OH$), 26.0 ($(CH_3)_3CSi$), 31.3 ($(CH_3)CHCH_2CH_2I$), 32.7 ($CHC{\equiv}C$), 33.7 ($CH_2CHCHOSi$), 40.4 ($CHCH_2CH$), 41.8 (CH_2CH_2I), 77.3 (CHOSi), 86.0 ($C{\equiv}CSi$), 110.2 ($C{\equiv}CSi$);

HRMS (EI): calcd. for $C_{21}H_{43}OISi_2Na$ $[M+Na]^+$: 517.17893, found 517.17914.

(5*S*,6*R*,10*S*,12*S*,13*R*)-3,3-Diethyl-5-{(1*S*)-2-[(4-methoxybenzyl)oxy]-1-methylethyl}-6,10,12,15,15,16,16-heptamethyl-13-[(1*S*)-1-methyl-3-(trimethylsilyl)-2-propyn-1-yl]-4,14-dioxa-3,15-disilaheptadecan-7-one 8-65



Obtained as described for **8-57** from iodide **8-64** (0.7 g, 1.4 mmol) and Weinreb amide **8-45** (0.62 g, 1.4 mmol) to give 746 mg (71%) of product as colorless oil.

R_f = 0.75 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -23.3 (c = 2 in CH_2Cl_2);

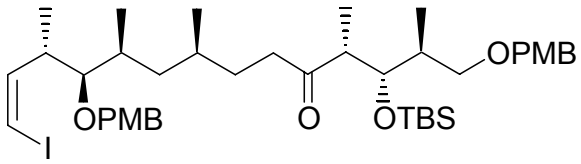
IR (film): υ_{max} = 3457, 2957, 2931, 2164, 1709, 1587, 1514, 1462, 1410, 1376, 1302, 1249, 1172, 1087, 1040 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 3H, $(CH_3)SiO$), 0.08 (s, 3H, $(CH_3)SiO$), 0.11 (s, 9H, $(CH_3)_3SiC$), 0.57 (q, 6H, *J* = 7.8 Hz, $OSi(CH_2CH_3)_3$), 0.80–0.96 (m, 27H, $OSi(CH_2CH_3)_3$, $(CH_3)_3CSiO$, 3×$(CH_3)CH$), 0.97–1.03 (m, 1H, CHCHHCH), 1.06 (d, 3H, *J* = 7.1 Hz, CH_3CHCO), 1.15 (d, 3H, *J* = 7.1 Hz, $CH_3CHC{\equiv}C$), 1.14–1.24 (m, 1H, $CHHCH_2CO$), 1.32–1.46 (m, 2H, CHCHHCH, $CH_2CH(CH_3)CH_2CH_2$), 1.57–1.70 (m, 1H, $CHHCH_2CO$), 1.77–1.91 (m, 2H, $CHCH_2OPMB$, $TBSOCHCH(CH_3)CH_2$), 2.29–2.52 (m, 2H, CH_2CO), 2.55–2.64 (m, 1H, $CHC{\equiv}CSi$), 2.72–2.81 (m, 1H, CHCO), 3.15–3.22 (m, 1H, CHHOPMB), 3.46–3.53

(m, 2H, CHOTBS, *CH*HOPMB), 3.79 (s, 3H, OCH_3), 3.97 (t, 1H, *J* = 5.3 Hz, *CH*OTES), 4.38 (s, 2H, OCH_2PMP), 6.86 (d, 2H, *J* = 8.34 Hz, m-CH_{arom}), 7.23 (d, 2H, *J* = 8.34 Hz, o-CH_{arom});
^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.0 ($(CH_3)SiO$), -3.9 ($(CH_3)SiO$), 0.1 ($(CH_3)_3SiC$), 5.3 ($OSi(CH_2CH_3)_3$), 7.0 ($OSi(CH_2CH_3)_3$), 13.0 (CH_3CHCO), 15.2 (CH_3), 15.4 (CH_3), 17.7 ($CH_3CHC{\equiv}C$), 18.4 ($(CH_3)_3CSi$), 19.8 ($(CH_3)CHCH_2CH_2CO$), 26.0 ($(CH_3)_3CSi$), 29.7 ($CHCH_2CH_2CO$), 29.9 (CH_2CH_2CO), 32.9 ($CHC{\equiv}C$), 33.6 (CH), 38.3 (CH), 39.8 (CH_2CO), 42.4 ($CHCH_2CH$), 49.9 (*CH*CO), 55.2 (OCH_3), 73.3 (CH_2OPMB), 74.1 (OCH_2PMP), 75.2 (CHOTES), 77.3 (CHOTBS), 85.8 ($C{\equiv}CSi$), 110.5 ($C{\equiv}CSi$), 113.7 (m-CH_{arom}), 129.2 (o-CH_{arom}), 130.7 ($CH_2C_{quat\ arom}$), 159.0 ($CH_3OC_{quat\ arom}$), 213.8 (CO).
HRMS (EI): calcd. for $C_{42}H_{78}O_5Si_3Na$ $[M+Na]^+$: 769.50493, found 769.50488

(2*S*,3*S*,4*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-3-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-14-iodo-2,4,8,10,12-pentamethyl-1,11-bis({[4-(methyloxy)phenyl]methyl}oxy)tetradec-13-en-5-one

8-66



To a solution of alkyne **8-57** (420 mg, 0.56 mmol, protected from light by covering the flask with aluminium foil) in DMF (1 mL) were added NIS (150 mg, 0.67 mmol, 1.2 equiv) and $AgNO_3$ (12 mg, 0.12 equiv) sequentially followed by stirring of the mixture for 2 h. Then the reaction mixture was diluted with EtOAc (10 mL), washed with water (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and filtered through SiO_2 (2 cm) followed by washing the column with CH_2Cl_2 (2 × 10 mL). Evaporation of the solvent gave crude product which was used without further purification. R_f = 0.4 (EtOAc/petroleum ether = 1:9). The iodoalkyne from the previous reaction was dissolved in MeOH (12 mL) and then dipotassiumazadicarboxylate (1.0 g, 5.0 mmol, 10 equiv) and pyridine (0.5 mL) were added. After stirring was started, 50 µL AcOH was added dropwise every 2 h, until no starting material could be detected by TLC, (overall 150 µL, 6h). The mixture was diluted with EtOAc (20 mL), washed with water (2 × 30 mL), saturated aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash

chromatography (EtOAc/petroleum ether = 1:10) to give vinyliodide **8-66** (360 mg, 80%) as a light yellow oil.

R_f = 0.46 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = 10.8 (c = 0.71 in CH_2Cl_2);

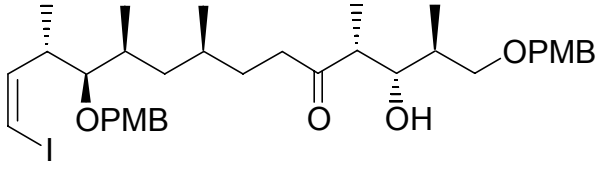
IR (film): υ_{max} = 2956, 2931, 1708, 1612, 1514, 1462, 1375, 1302, 1250, 1174, 1085, 1039 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.04 (s, 3H, $(CH_3)SiO$), 0.00 (s, 3H, $(CH_3)SiO$), 0.78 (d, 3H, *J* = 6.6 Hz, $(CH_3)CH$), 0.83 (s, 9H, $(CH_3)_3CSiO$), 0.89 (d, 3H, *J* = 6.6 Hz, $(CH_3)CH$), 0.91 (d, 3H, *J* = 6.6 Hz, $(CH_3)CH$), 0.93 (d, 3H, *J* = 7.1 Hz, $(CH_3)CH$), 1.00–1.10 (m, 1H, CH*CH*HCH), 1.00 (d, 3H, *J* = 6.6 Hz, CH_3CHCO), 1.01 (d, 3H, *J* = 6.8 Hz, $CH_3CHC{=}C$), 1.04–1.34 (m, 3H, CH_2, CH), 1.35–1.47 (m, 1H, CH), 1.53–1.65 (m, 1H, C*H*H), 1.65–1.75 (m, 1H, CH), 1.76–1.87 (m, 1H, CH), 2.21–2.46 (m, 2H, CH_2CO), 2.68–2.82 (m, 2H, *CH*C=C, *CH*CO), 3.08 (dd, 1H, *J* = 5.3 Hz, *J* = 4.3 Hz, *CH*OPMB), 3.14 (dd, 1H, *J* = 9.1 Hz, *J* = 6.6 Hz, C*H*HOPMB), 3.44 (dd, 1H, *J* = 9.2 Hz, *J* = 5.7 Hz, *CH*HOPMB), 3.74 (s, 6H, OCH_3x2), 3.94 (dd, 1H, *J* = 5.9 Hz, *J* = 4.4 Hz, *CH*OTBS), 4.33 (s, 2H, OCH_2PMP), 4.46 (s, 2H, OCH_2PMP), 6.09 (d, 1H, *J* = 7.5 Hz, I*CH*=CH), 6.24 (dd, 1H, *J* = 9.0 Hz, *J* = 7.5 Hz, ICH=*CH*CH), 6.81 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 6.82 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 7.19 (d, 2H, *J* = 8.6 Hz, o-CH_{arom}), 7.22 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.2 ($(CH_3)SiO$), -3.9 ($(CH_3)SiO$), 13.3 (CH_3), 14.4 (CH_3), 17.7 (CH_3), 18.3 ($(CH_3)_3CSi$), 19.8 (CH_3), 26.0 ($(CH_3)_3CSi$), 26.8 (CH_3), 29.1 (CH_2CH_2CO), 29.6. (CH), 33.8 (CH_2CHCHOPMB), 38.7 (*CH*CH_2OPMB), 39.4 (CH_2CO), 41.8 (CHCH_2CH), 49.8 (*CH*CO), 55.2 (OCH_3x2), 71.8 (CH_2OPMB), 72.6 (OCH_2PMP), 74.2 (OCH_2PMP), 74.6 (CHOTBS), 81.6 (I*CH*=CH), 86.4 (*CH*OPMB), 113.6, 113.6 (m-CH_{arom}x2), 129.0, 129.1 (o-CH_{arom}x2), 130.6, 131.1 ($CH_2C_{quat\ arom}$x2), 143.8 (ICH=*CH*CH), 159.0, 159.0 ($CH_3OC_{quat\ arom}$x2), 213.8 (CO);

HRMS (EI): calcd. for $C_{41}H_{65}IO_6SiNa$ $[M+Na]^+$: 831.34873, found 831.34936.

(2*S*,3*S*,4*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-3-Hydroxy-14-iodo-2,4,8,10,12-pentamethyl-1,11-bis({[4-(methyloxy)phenyl]methyl}oxy)tetradec-13-en-5-one 8-67



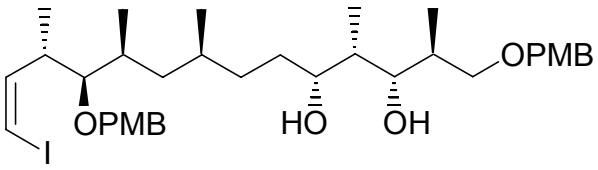
To a stirred solution of ketone **8-66** (160 mg, 0.2 mmol) in THF (2 mL, in a plastic test tube) at 0°C (ice bath) was added dropwise HF-pyridine complex (1 mL, 70% HF). The reaction mixture was allowed to warm to room temperature. After 2 h the mixture was partioned between an ice-cooled mixture of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) by slow addition via plastic pipette. After separation of the layers, the water later was extracted with Et_2O (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, affording ketol **8-67** (140 mg, 95%), as a colorless oil which was used for the next step without further purification.

R_f = 0.5 (EtOAc/petroleum ether = 1:2);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (d, 3H, *J* = 7.1 Hz, CH_3), 0.83-0.91 (m, 1H, CH*CH*HCH), 0.87 (d, 3H, *J* = 7.3 Hz, CH_3), 0.93–1.01 (m, 1H, CH), 0.95 (d, 3H, *J* = 6.6 Hz, CH_3), 1.04 (d, 3H, *J* = 6.8 Hz, CH_3), 1.10 (d, 3H, *J* = 7.1 Hz, CH_3), 1.16–1.79 (m, 8H, CH_2, 2×*CH*H, 3×CH, OH), 1.80–1.92 (m, 1H, CH), 2.37–2.53 (m, 2H, *CH_2*CO), 2.53–2.63 (m, 1H, *CH*CO), 2.75–2.86 (m, 1H, *CH*CCH=C), 3.11 (dd, 1H, *J* = 5.4 Hz, *J* = 4.0 Hz, *CH*OPMB), 3.49–3.59 (m, 3H, *CH*HOPMB, CH), 3.74 (s, 6H, 2×OCH_3), 3.84 (d, 1H, *J* = 8.1 Hz, *CH*OH), 4.40 (d, 1H, *J* = 11.62 Hz, O*CH*HPMP), 4.45 (d, 1H, *J* = 11.62 Hz, O*CH*HPMP), 4.50 (s, 2H, O*CH_2*PMP), 6.12 (d, 1H, *J* = 7.5 Hz, I*CH*=CH), 6.28 (dd, 1H, *J* = 9.0 Hz, *J* = 7.5 Hz, ICH=*CH*CH), 6.85 (d, 4H, *J* = 8.6 Hz, 2×m-CH_{arom}),7.22 (d, 2H, *J* = 8.6 Hz, o-CH_{arom}), 7.26 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.1 (CH_3), 13.9 (CH_3), 15.8 (CH_3), 17.4 (CH_3), 20.4 (CH_3), 29.1 (CH_2), 29.5 (CH), 33.9 (CH), 35.9 (CH), 38.2 (CH_2), 40.6 (CH_2), 42.4 (CH), 48.5 (*CH*CO), 55.2 (OCH_3x2), 73.1 (*CH_2*OPMB), 74.1 (O*CH_2*PMP), 74.3 (O*CH_2*PMP), 74.9 (CHOH), 81.6 (I*CH*=CH), 86.5 (*CH*OPMB), 113.6, 113.8 (2×m-CH_{arom}), 129.1, 129.3 (o-2×CH_{arom}), 129.9, 131.1 (2×$C_{quat\ arom}CH_2$), 143.8 (ICH=*CH*CH), 159.0, 159.2 ($CH_3OC_{quat\ arom}$×2), 214.9 (CO).

(2*S*,3*S*,4*S*,5*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-14-Iodo-2,4,8,10,12-pentamethyl-1,11-bis({[4-(methyloxy)phenyl]methyl}oxy)tetradec-13-ene-3,5-diol 8-68

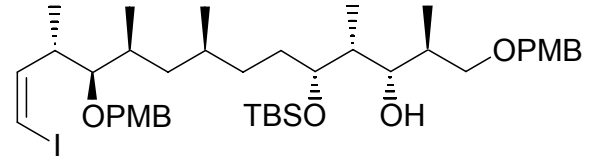


To a stirred solution of ketol **8-67** (100 mg, 0.14 mmol) in THF (1.5 mL) at -78°C was added dropwise DIBAL-H (1M in THF, 0.7 mL, 0.7 mmol, 5 equiv), and the reaction mixture was stirred for 4 h. The reaction was quenched by addition of NH_4Cl (2 mL), and the mixture diluted with Et_2O (10 mL). The organic phase was separated, washed with 1N HCl (3 mL), saturated aqueous $NaHCO_3$ solution (2 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo, giving diol **8-68** (80 mg, 80%) as a colorless oil. The next step was carried out without any purification. The *syn*-orientation of the OH-groups was confirmed by NMR analysis of the corresponding acetone ketal. (See **Figure 51** on page 114)

R_f =0.34 (EtOAc/petroleum ether = 1:2)

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-5-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-14-iodo-2,4,8,10,12-pentamethyl-1,11-bis({[4-(methyloxy)phenyl]methyl}oxy)tetradec-13-en-3-ol

8-70



To a stirred solution of diol **8-68** (80 mg, 0.11 mmol) and 2,6-lutidine (26 mg, 28 µL, 0.24 mmol) in CH_2Cl_2 (1 mL) at -78°C was added dropwise TBSOTf (30 µL, 34.5 mg, 0.13 mmol). The reaction was allowed to warm to room temperature over 30 min, and then quenched by addition of water (5 mL), and diluted with CH_2Cl_2 (10 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/petroleum ether = 1:11) to produce final compound **8-70** (79 mg, 88%) as a colorless oil.

R_f = 0.76 (EtOAc/petroleum ether = 1:2);

$[\alpha]^{20}_D$ = 15.6 (c = 1 in CH_2Cl_2);

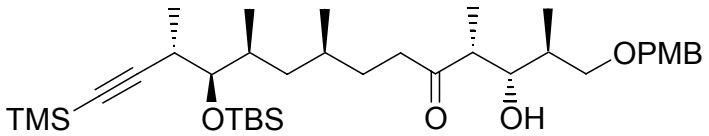
IR (film): υ_{max} = 3500, 2956, 2929, 2856, 1612, 1514, 1462, 1360, 1302, 1250, 1174, 1079, 1037 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3H, $(CH_3)SiO$), 0.07 (s, 3H, $(CH_3)SiO$), 0.85 (d, 3H, *J* = 7.1 Hz, *CH*$_3$CHCH$_2$OPMB) 0.87 (d, 3H, *J* = 6.6 Hz, (*CH*$_3$)CHCH$_2$CH$_2$), 0.88 (s, 9H, $(CH_3)_3CSiO$), 0.90 (d, 3H, *J* = 6.6 Hz, (*CH*$_3$)CH), 0.94 (d, 3H, *J* = 7.1 Hz, (*CH*$_3$)CH), 0.97–1.10 (m, 2H, *CH*Hx2), 1.04 (d, 3H, *J* = 6.8 Hz, *CH*$_3$CHCH=HC), 1.20–1.75 (m, 7H, *CH*Hx2, CH_2, CHx3), 1.84–1.96 (m, 1H, *CH*CH$_2$OPMB), 2.75–2.87 (m, 1H, *CH*CC=C), 3.11 (dd, 1H, *J* = 5.8 Hz, *J* = 3.8 Hz, *CH*OPMB), 3.45–3.58 (m, 3H, *CH*$_2$OPMB, CH), 3.72–3.78 (m, 1H, CH), 3.79 (s, 6H, OCH_3x2), 4.41 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.46 (d, 1H, *J* = 11.4 Hz, O*CH**H*PMP), 4.50 (s, 2H, O*CH*$_2$PMP), 6.11 (d, 1H, *J* = 7.5 Hz, I*CH*=CH), 6.27 (dd, 1H, *J* = 8.8 Hz, *J* = 7.5 Hz, ICH=*CH*CH), 6.85 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 6.86 (d, 2H, *J* = 8.6 Hz, m-CH_{arom}), 7.25 (d, 2H, *J* = 8.6 Hz, o-CH_{arom}), 7.26 (d, 2H, *J* = 8.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 ($(CH_3)SiO$), -3.7 ($(CH_3)SiO$), 6.7 (SiOCHCH(*CH*$_3$)), 14.1 (*CH*$_3$CHCH$_2$OPMB), 15.8 (PMBOCHCH(*CH*$_3$)CH$_2$), 17.4 (*CH*$_3$CHCH=C), 18.3 ($(CH_3)_3$*C*Si), 20.7 ((*CH*$_3$)CHCH$_2$CH$_2$), 25.9 ((*CH*$_3$)$_3$CSi), 30.4 ((CH$_3$)*CH*CH$_2$CH$_2$), 30.0 (CH), 30.4 (CH_2), 31.7(CH_2), 34.1 (CH$_2$*CH*CHOPMB), 36.5 (*CH*CH$_2$OPMB), 41.4 (CH*CH*$_2$CH), 42.5 (CH$_3$*CH*CH=C), 55.3 (OCH_3×2), 72.9 (O*CH*$_2$PMP), 74.4 (*CH*$_2$OPMB), 74.4 (O*CH*$_2$PMP), 74.6 (CHOTBS), 77.1, 77.2 (*CH*x2), 81.5 (I*CH*=CH), 86.7 (*CH*OPMB), 113.6, 113.7 (m-CH_{arom}×2), 129.1, 129.2 (o-CH_{arom}×2), 130.4, 131.1 ($CH_2C_{quat\ arom}$×2), 143.7 (ICH=*CH*CH), 159.0, 159.1 ($CH_3OC_{quat\ arom}$×2);

HRMS (EI): calcd. for $C_{41}H_{67}IO_6SiNa$ $[M+Na]^+$: 833.36438, found 833.36455.

(2*S*,3*S*,4*R*,8*S*,10*S*,11*R*,12*S*)-11-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxy-1-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyl-14-(trimethylsilyl)-13-tetradecyn-5-one



To a stirred solution of ketone **8-65** (746 mg, 1 mmol) in THF (6 mL, in plastic test tube) at 0°C (ice bath) was added dropwise HF-pyridine complex (120 µL, 70% HF). The reaction mixture was allowed to warm to room temperature. After 2 h it was partioned between an ice-cooled mixture of Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (40 mL) by slow addition via plastic pipette. After separation of the layers, the aqueous layer was extracted with Et_2O (25

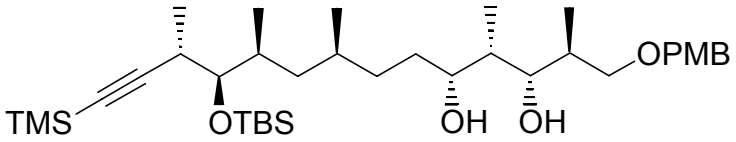
mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, affording ketol **25** (650 mg, 95%), as a colorless oil, used for the next step without purification.

R_f = 0.33 (EtOAc/petroleum ether = 1:9);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 3H, $(CH_3)SiO$), 0.07 (s, 3H, $(CH_3)SiO$), 0.11 (s, 9H, $(CH_3)_3SiC$), 0.82-0.93 (m, 18H, $(CH_3)_3CSiO$, 3×(CH_3)CH), 0.99-1.06 (m, 1H, CH*CH*HCH), 1.11 (d, 3H, *J* = 6.8 Hz, CH_3CHCO), 1.14 (d, 3H, *J* = 7.1 Hz, CH_3CHC≡C), 1.18–1.29 (m, 1H, *CH*HCH$_2$CO), 1.35–1.51 (m, 2H, CH*C*H*H*CH, CH$_2$*CH*(CH$_3$)CH$_2$CH$_2$), 1.60–1.70 (m, 1H, *C*H*H*CH$_2$CO), 1.76–1.91 (m, 3H, OH, *CH*CH$_2$OPMB, TBSOCH*CH*(CH$_3$)CH$_2$), 2.41–2.53 (m, 2H, CH_2CO), 2.55–2.64 (m, 2H, *CH*C≡CSi, *CH*CO), 3.48 (t, 1H, *J* = 3.3 Hz, CHOTBS), 3.53 (d, 2H, *J* = 5.6 Hz, CH$_2$OPMB), 3.78 (s, 3H, OCH$_3$), 3.83 (dd, 1H, *J* = 8.3 Hz, *J* = 3.0 Hz, *CH*OH), 4.41 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.45 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 6.85 (d, 2H, *J* = 8.6 Hz, m-CH$_{arom}$), 7.22 (d, 2H, *J* = 8.6 Hz, o-CH$_{arom}$);

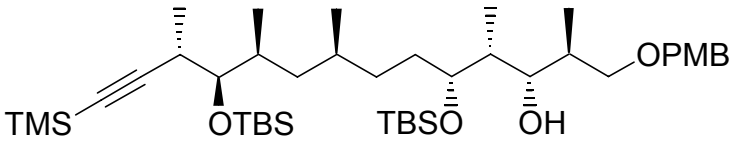
^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.0 ($(CH_3)SiO$), -3.9 ($(CH_3)SiO$), 0.1 ($(CH_3)_3SiC$), 9.2 (CH_3), 13.9 (CH_3), 15.4 (CH_3), 17.5 (CH_3CHC≡C), 18.4 ($(CH_3)_3CSi$), 20.0 ((CH_3)CHCH$_2$CH$_2$CO), 26.0 ((CH_3)$_3$CSi), 29.8 (*CH*CH$_2$CH$_2$CO), 29.9 (CH_2CH$_2$CO), 32.6 (*CH*C≡C), 33.6 (CH), 35.9 (CH), 38.7 (CH_2CO), 42.3 (CHCH_2CH), 48.5 (*CH*CO), 55.2 (OCH$_3$), 73.1 (CH_2OPMB), 74.1 (OCH_2PMP), 75.0 (CHOH), 77.3 (CHOTBS), 85.8 (C≡*C*Si), 110.4 (*C*≡CSi), 113.8 (m-CH$_{arom}$), 129.3 (o-CH$_{arom}$), 130.0 (CH$_2$C$_{quat\ arom}$), 159.2 (CH$_3$OC$_{quat\ arom}$), 214.8 (CO).

(2*S*,3*S*,4*S*,5*R*,8*S*,10*S*,11*R*,12*S*)-11-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyl-14-(trimethylsilyl)-13-tetradecyne-3,5-diol 8-71



Obtained as described for **8-68** to give 630 mg, 97%. The crude compound was used without further purification.

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*)-5,11-bis{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyl-14-(trimethylsilyl)-13-tetradecyn-3-ol 8-72



Obtained as described for **8-70** to give 525 mg (88% yield) of **8-72** as colorless oil.

R_f = 0.75 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -16 (c = 1 in CH_2Cl_2);

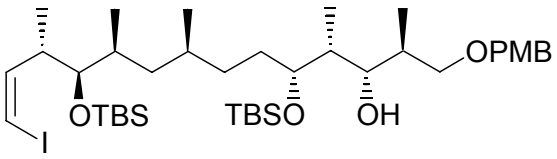
IR (film): υ_{max} = 3507, 2957, 2856, 2164, 1613, 1587, 1514, 1472, 1463, 1407, 1376, 1360, 1302, 1250, 1173, 1086, 1039 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.01-0.17 (m, 21H, 2×$(CH_3)_2SiO$, $(CH_3)_3SiC$), 0.78–1.06 (m, 33H, 2×$(CH_3)_3CSiO$, 4×(*CH_3*)CH, CH*CH*HCH, *CH_2*CH_2CHOH), 1.14 (d, 3H, *J* = 7.1 Hz, *CH_3*CH), 1.21–1.54 (m, 4H, CH_2*CH_2*CHOH, OH, CH*C*H*H*CH), 1.56–1.72 (m, 2H, 2×CH), 1.76–1.86 (m, 1H, CH), 1.87–1.98 (m, 1H, (CH_3)*CH*CH_2CH_2), 2.53–2.66 (m, 1H, *CH*C≡CSi), 3.45–3.61 (m, 4H, CH_2OPMB, 2×CHOTBS), 3.53 (d, 2H, *J* = 5.6 Hz,), 3.73–3.83 (m, 1H, *CH*OH), 3.79 (s, 3H, OCH_3), 4.41 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.47 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 6.85 (d, 2H, *J* = 7.6 Hz, m-CH_{arom}), 7.24 (d, 2H, *J* = 7.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 ($(CH_3)SiO$), -4.0 ($(CH_3)SiO$), -3.9 ($(CH_3)SiO$), -3.8 ($(CH_3)SiO$), 0.1 ($(CH_3)_3SiC$), 6.8 (CH_3), 14.0 (CH_3), 15.4 (CH_3), 17.4 (*CH_3*CHC≡C), 18.0 ($(CH_3)_3$*C*Si), 18.4 ($(CH_3)_3$*C*Si), 20.0 (CH_2(*CH_3*)$CHCH_2CH_2$), 25.9 ((*CH_3*)$_3$CSi), 26.0 ((*CH_3*)$_3$CSi), 30.4 (*CH*CH_2CH_2CHOTBS), 31.4 (CH_2*CH_2*CHOTBS), 31.9 (*CH_2*CH_2CHOTBS), 33.0 (*CH*C≡C), 33.5 (CH), 36.5 (CH), 37.4 (CH), 42.7 (CH*CH_2*CH), 55.2 (OCH_3), 73.0 (*CH_2*OPMB), 74.5 (O*CH_2*PMP), 76.9 (CHOH), 77.2 (2xCHOTBS), 85.8 (C≡*C*Si), 110.5 (*C*≡CSi), 113.7 (m-CH_{arom}), 129.2 (o-CH_{arom}), 130.4 ($CH_2C_{quat\ arom}$), 159.1 ($CH_3OC_{quat\ arom}$).

HRMS (EI): calcd. for $C_{42}H_{80}O_5Si_3Na$ $[M+Na]^+$: 771.52058, found 771.52076.

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-5,11-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-14-iodo-1-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyl-13-tetradecen-3-ol 8-73



Obtained from 525 mg of **8-72** as described for **8-66** to give 530 mg (93% yield) of **8-73** as colorless oil.

R_f = 0.61 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = 5.2 (c = 2.5 in CH_2Cl_2);

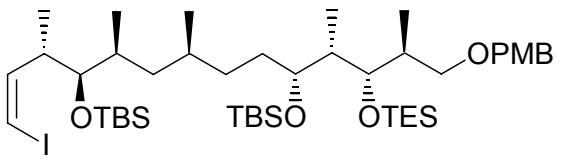
IR (film): υ_{max} = 3505, 2956, 2856, 1722, 1612, 1587, 1513, 1472, 1462, 1406, 1377, 1360, 1302, 1251, 1172, 1078, 1037 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.01–0.10 (m, 12H, 2×$(CH_3)_2SiO$,), 0.78–1.06 (m, 32H, 2×$(CH_3)_3CSiO$, 4×(*CH_3*)CH, CH*CH*HCH, *CH_2*CH_2CHOH), 0.96 (d, 3H, *J* = 6.8 Hz, *CH_3*CH)), 1.20–1.48 (m, 4H, CH*CH*HCH, 2×CH), 1.55–1.71 (m, 3H, CH_2*CH_2*CHOH, CH), 1.84–1.96 (m, 1H, (CH_3)*CH*CH_2CH_2), 2.61–2.74 (m, 1H, *CH*CH=CHI), 3.43–3.59 (m, 4H, CH_2OPMB, 2×CHOTBS), 3.73–3.83 (m, 1H, *CH*OH), 3.78 (s, 3H, OCH_3), 4.41 (d, 1H, *J* = 11.6 Hz, O*CH*HPMP), 4.47 (d, 1H, *J* = 11.6 Hz, O*CH*HPMP), 6.09 (d, 1H, *J* = 7.3 Hz, CH=C*H*I), 6.26 (t, 1H, *J* = 8.1 Hz, C*H*=CHI), 6.85 (d, 2H, *J* = 7.6 Hz, m-CH_{arom}), 7.24 (d, 2H, *J* = 7.6 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 ((CH_3)SiO), -3.8 ((CH_3)SiO), -3.7 ((CH_3)SiO), -3.6 ((CH_3)SiO), 6.6 (TBSOCHCH(*CH_3*)CHOH), 14.0 ((*CH_3*)$CHCH_2$OPMB), 16.0 (TBSOCHCH(*CH_3*)CH_2), 17.9 (*CH_3*CHC=CCHI), 18.0 ($(CH_3)_3$*C*Si), 18.4 ($(CH_3)_3$*C*Si), 20.5 (CH_2CH(*CH_3*)CH_2CH_2), 25.9 ((*CH_3*)$_3$CSi), 26.1 ((*CH_3*)$_3$CSi), 30.6 ((CH_3)*CH*CH_2CH_2CHOTBS), 30.9 (CH_2*CH_2*CHOTBS), 32.0 (*CH_2*CH_2CHOTBS), 35.6 (TBSOCHCH(*CH_3*)CH_2CH), 36.6 (TBSOCH*CH*(CH_3)CHOH), 37.3 ((CH_3)*CH*CH_2OPMB), 41.3 (CH*CH_2*CH), 43.1 (*CH*CH=CHI), 55.2 (OCH_3), 72.9 (*CH_2*OPMB), 74.2 (O*CH_2*PMP), 77.2, 77.3 (2xCHOTBS), 79.1 (CHOH), 81.2 (CH=C*H*I), 113.7 (m-CH_{arom}), 129.2 (o-CH_{arom}), 130.4 ($CH_2C_{quat\ arom}$), 144.1 (C*H*=CHI), 159.1 ($CH_3OC_{quat\ arom}$).

HRMS (EI): calcd. for $C_{42}H_{80}O_5Si_3Na$ $[M+Na]^+$: 827.39334, found 827.39461.

(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,13*Z*)-5,11-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[triethylsilyl]oxy}-14-iodo-1-[(4-methoxybenzyl)oxy]-2,4,8,10,12-pentamethyl-13-tetradecen-3-ol 8-77



Obtained from **8-73** as described for **8-44** as colorless oil.

R_f = 0.87 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -2.3 (c = 2.5 in CH_2Cl_2);

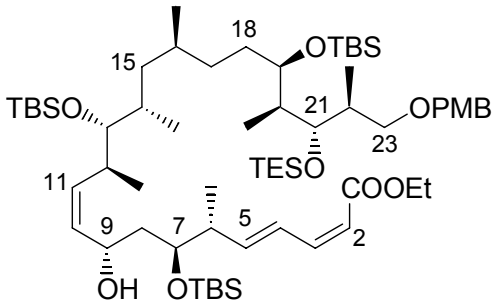
IR (film): υ_{max} = 2951, 1717, 1612, 1587, 1513, 1462, 1413, 1378, 1361, 1302, 1249, 1171, 1077, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00–0.07 (m, 12H, 2×$(CH_3)_2SiO$), 0.58 (q, 6H, *J* = 7.8 Hz, OSi(CH_2CH_3)$_3$), 0.81–1.00 (m, 44H, 2x$(CH_3)_3CSiO$, OSi(CH_2CH_3)$_3$, 5×(CH_3)CH, $CHCH_2CH$,), 1.20–1.41 (m, 4H, $CH_2CH_2CHOTES$, 2×CH), 1.55–1.71 (m, 3H, CH, CH_2), 1.95–2.06 (m, 1H, $(CH_3)CHCH_2CH_2$), 2.63–2.73 (m, 1H, *CH*CH=CHI), 3.21 (t, 1H, *J* = 8.7 Hz, CHOTES), 3.46 (t, 1H, *J* = 3.5 Hz, CHOTBS), 3.54 (dd, 1H, *J* = 9.0 Hz, *J* = 3.9 Hz, C*H*HOPMB), 3.57–3.67 (m, 2H, CHOTBS, C*H*HOPMB), 3.79 (s, 3H, OCH_3), 4.38 (d, 1H, *J* = 11.6 Hz, O*CH*HPMP), 4.42 (d, 1H, *J* = 11.6 Hz, O*CH*HPMP), 6.10 (d, 1H, *J* = 7.3 Hz, CH=C*H*I), 6.25 (t, 1H, *J* = 8.1 Hz, C*H*=CHI), 6.86 (d, 2H, *J* = 8.1 Hz, m-CH_{arom}), 7.24 (d, 2H, *J* = 8.1 Hz, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.4 ($(CH_3)SiO$), -3.8 ($(CH_3)SiO$), -3.7 ($(CH_3)SiO$), -3.6 ($(CH_3)SiO$), 5.7 (OSi(CH_2CH_3)$_3$), 7.2 (OSi(CH_2CH_3)$_3$), 10.1 (TBSOCHCH(CH_3)CHOTES), 15.8 ((CH_3)$CHCH_2$OPMB), 15.9 (TBSOCHCH(CH_3)CH_2), 17.7 (CH_3CHC=CCHI), 18.1 ($(CH_3)_3CSi$), 18.4 ($(CH_3)_3CSi$), 20.5 ($CH_2CH(CH_3)CH_2CH_2$), 25.9 ((CH_3)$_3$CSi), 26.2 ((CH_3)$_3$CSi), 30.7 ($(CH_3)CHCH_2CH_2$CHOTBS), 30.8 (CH_2CH_2CHOTBS), 32.2 (CH_2CH_2CHOTBS), 35.3 (TBSOCH*CH*(CH_3)CH_2CH), 37.0 (TBSOCH*CH*(CH_3)CHOTES), 39.8 ($(CH_3)CHCH_2$OPMB), 41.4 (CHCH_2CH), 43.4 (*CH*CH=CHI), 55.2 (OCH_3), 72.0 (CH_2OPMB), 72.7 (OCH_2PMP), 73.3 (CHOTBS), 76.1 (CHOTBS), 79.0 (CHOTES), 81.3 (CH=C*H*I), 113.7 (m-CH_{arom}), 129.1 (o-CH_{arom}), 130.9 ($CH_2C_{quat\ arom}$), 144.1 (C*H*=CHI), 159.0 ($CH_3OC_{quat\ arom}$).

HRMS (EI): calcd. for $C_{45}H_{87}IO_5Si_3Na$ $[M+Na]^+$: 941.47982, found 941.48056.

ethyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*S*,21*S*,22*S*)-7,13,19-tris{[*tert*-Butyl(dimethyl)silyl]oxy}-9-hydroxy-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-21-[(triethylsilyl)oxy]-2,4,10-tricosatrienoate 8-78



To a -78°C cooled solution of *t*-BuLi (1.5M in pentane, 0.6 mL, 0.9 mmol) in Et_2O (1 mL), was added a solution of vinyl iodide **8-77** (450 mg, 0.45 mmol) in Et_2O (0.7 mL). After stirring at -78°C for 15 min, dimethylzinc (2.0M in toluene, 0.145 mL, 0.29 mmol) was added dropwise and the reaction mixture was further stirred at -78°C for 15 min. In a separate flask to a solution of aldehyde **7-68** (220 mg, 0.5 mmol) in Et_2O (0.8 mL) was added dimethylzinc (2.0M in toluene, 0.145 mL, 0.29 mmol) in a dropwise fashion. After stirring for 30 min at –78°C, the liquid from the first flask was transferred via cannula to the second. The mixture was stirred at -78°C for 1 h and the reaction was quenched with saturated NH_4Cl solution (3.0 mL) at -30°C, warmed to rt and diluted with Et_2O (5.0 mL). Layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude product was purified by flash column chromatography (1:15 to 1:10 = EtOAc/Hexanes) to furnish the alcohol **8-77** (180 mg, 0.063 mmol, 40%) as a light yellow oil.

R_f = 0.4 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = 17.1 (c = 2 in CH_2Cl_2);

IR (film): υ_{max} = 3507, 2956, 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

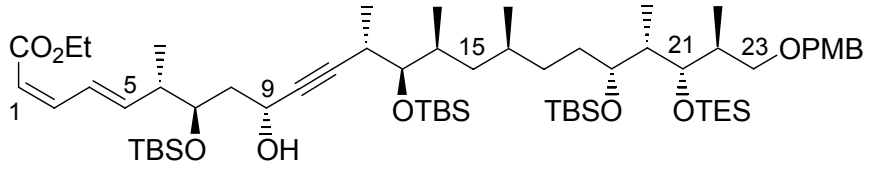
^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.02–0.13 (m, 18H, 3×$(CH_3)_2SiO$), 0.57 (q, 6H, *J* = 8.0 Hz, OSi(CH_2CH_3)$_3$), 0.76–1.12 (m, 58H, 3×$(CH_3)_3CSiO$, OSi(CH_2CH_3)$_3$, 6×(CH_3)CH, 15-H', 17'), 1.20–1.45 (m, 7H, 17-H'', 2×CH, $CO_2CH_2CH_3$), 1.45–1.61 (m, 3H, CH, CH_2), 1.62–1.73 (m, 2H, 2×CH), 1.95–2.06 (m, 1H, 16-H), 2.54–2.64 (m, 1H, 6-H), 2.64–2.74 (m, 1H, 12-H), 3.19 (t, 1H, *J* = 8.7 Hz, CHOTES), 3.35 (dd, 1H, *J* = 5.4 Hz, *J* = 2.2 Hz, 19-H), 3.53 (dd, 1H, *J* = 9.0 Hz, *J* = 4.0 Hz, C*H*HOPMB), 3.57–3.67 (m, 2H, CHOTBS, C*H*HOPMB), 3.77 (s, 3H,

OCH_3), 3.90–3.96 (m, 1H, 7-H), 4.16 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.37 (d, 1H, *J* = 11.8 Hz, O*CH*HPMP), 4.41 (d, 1H, *J* = 11.8 Hz, O*CH*HPMP), 4.60 (m, 1H, 9-H), 5.31 (dd, 1H, *J* = 10.5 Hz, *J* = 8.3 Hz, 11-H), 5.46 (t, 1H, *J* = 10.5 Hz, 10-H), 5.57 (d, 1H, *J* = 11.4 Hz, 2-H), 5.99 (dd, 1H, *J* = 15.4 Hz, *J* = 7.3 Hz, 5-H), 6.51 (t, 1H, *J* = 11.4 Hz, 3-H), 6.84 (d, 2H, *J* = 8.7 Hz, m-CH_{arom}), 7.22 (d, 2H, *J* = 8.7 Hz, o-CH_{arom}) 7.38 (dd, 1H, *J* = 15.3 Hz, *J* = 11.2 Hz, 4-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 (2×(CH_3)SiO), -4.4 ((CH_3)SiO), -3.8 ((CH_3)SiO), -3.7 ((CH_3)SiO), -3.3 ((CH_3)SiO), 5.6 (OSi(CH_2CH_3)$_3$), 7.1 (OSi(CH_2CH_3)$_3$), 10.1 (*CH*$_3$-C-20), 14.2 ($CO_2CH_2CH_3$), 14.4 (*CH*$_3$-C-22), 14.7 (*CH*$_3$-C-6), 15.8 (*CH*$_3$-C-14), 18.0 (2x$(CH_3)_3C$Si), 18.4 ($(CH_3)_3C$Si), 19.7 (*CH*$_3$-C-12), 20.5 (*CH*$_3$-C-16), 25.8 ($(CH_3)_3$CSi), 25.9 ($(CH_3)_3$CSi), 26.2 ($(CH_3)_3$CSi), 30.5 (C-16), 31.1 (C-18), 32.2 (C-17), 34.2 (C-14), 36.4 (C-12), 37.1 (C-20), 39.9 (C-22), 40.1 (C-8), 41.8 (C-15), 42.8 (C-6), 55.2 (OCH_3), 59.8 ($CO_2CH_2CH_3$), 64.6 (C-9), 71.9 (*CH*$_2$OPMB), 72.6 (C-7), 72.7 (O*CH*$_2$PMP), 73.3 (CHOTBS), 76.0 (CHOTBS), 79.0 (CHOTES), 113.7 (m-CH_{arom}), 118.8 (C-2), 126.8 (C-4), 129.2 (o-CH_{arom}), 130.8 ($CH_2C_{quat\ arom}$), 131.5 (C-10), 135.5 (C-11), 145.1 (C-3), 146.9 (C-5), 159.0 ($CH_3OC_{quat\ arom}$) 166.4 (C-1).

HRMS (EI): calcd. for $C_{63}H_{121}O_9Si_4$ $[M+H]^+$: 1133.80822, found 1133.80725.

Ethyl (2*Z*,4*E*,6*R*,7*S*,9*S*,12*S*,13*R*,14*S*,16*S*,19*R*,20*S*,21*S*,22*S*)-7,13,19-tris{[*tert*-butyl(dimethyl)silyl]oxy}-9-hydroxy-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-21-[(triethylsilyl)oxy]-2,4-tricosadien-10-ynoate 8-82



The zinc triflate powder (190 mg, 0.52 mmol) was dried in *vacuo* (0.1 mbar) at 150°C for 3 h and the flask then purged with inert gas. In a separate flask N-methylephedrine (86 mg, 0.48 mmol), was put under vacuum/purged with the inert gas (3 times) and then dissolved in CH_2Cl_2 (1 mL). To this solution Et_3N (74 µL, 0.52 mmol) was added and mixture was transfered to the zinc triflate via syringe. The resulting suspension was vigorously stirred at room temperature for 2 hours. The solution of alkyne **8-81** (330 mg, 0.42 mmol) in CH_2Cl_2 (0.7 mL) was added and stirring was continued for another 45 min before aldehyde (127 mg, 0.38 mmol) in CH_2Cl_2 (0.3 mL) was finally added. The reaction mixture was stirred overnight,

diluted with CH_2Cl_2 (5 mL), washed with 1N HCl (2 × 3 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product which was purified by flash chromatography (EtOAc/PE = 1:15) to give 350 mg of the alcohol (82%, based on recovered alkyne) as colorless oil.

R_f = 0.78 (EtOAc/petroleum ether = 1:4);

$[\alpha]^{20}_D$ = –25.4 (c = 2 in CH_2Cl_2);

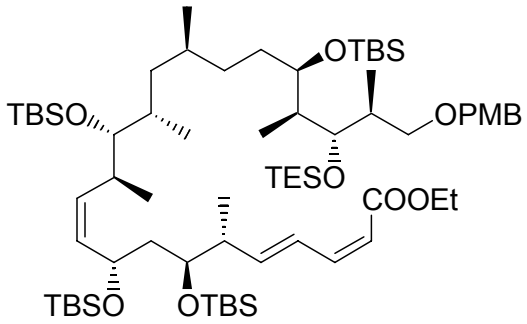
IR (film): υ_{max} = 3507, 2957, 2856, 2164, 1613, 1587, 1514, 1472, 1463, 1407, 1376, 1360, 1302, 1250, 1173, 1086, 1039 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.02–0.12 (m, 18H, 3×$(CH_3)_2SiO$), 0.57 (q, 6H, *J* = 8.0 Hz, OSi(CH_2CH_3)$_3$), 0.78–1.00 (m, 51H, 3×$(CH_3)_3CSiO$, OSi(CH_2CH_3)$_3$, 4×$(CH_3)CH$, 15-H', 17-H), 1.06 (d, 3H, *J* = 6.8 Hz, CH_3CH), 1.13 (d, 3H, *J* = 7.1 Hz, CH_3CH), 1.19–1.55 (m, 6H, $CO_2CH_2CH_3$, 18-H, 15-H'', CH), 1.61–1.84 (m, 4H, 4×CH), 1.95–2.06 (m, 1H, 16-H), 2.17–2.37 (s, 1H, OH), 2.47–2.66 (m, 2H, 2xCH), 3.45–3.61 (m, 4H, CH_2OPMB, 2×CHOTBS), 3.73–3.83 (m, 1H, 9-H), 3.77 (s, 3H, OCH_3), 3.98 (ddd, 1H, *J* = 8.1 Hz, *J* = 3.9 Hz, *J* = 3.7 Hz, CH), 4.16 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.37 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.41 (d, 1H, *J* = 11.9 Hz, O*CH*HPMP), 4.45 (dd, 1H, *J* = 8.7 Hz, *J* = 2.2 Hz, CH), 5.57 (d, 1H, *J* = 11.4 Hz, 2-H), 5.97 (dd, 1H, *J* = 15.4 Hz, *J* = 7.6 Hz, 5-H), 6.51 (t, 1H, *J* = 11.4 Hz, 3-H), 6.84 (d, 2H, *J* = 8.6 Hz, m–CH_{arom}), 7.23 (d, 2H, *J* = 8.6 Hz, o–CH_{arom}), 7.38 (dd, 1H, *J* = 15.3 Hz, *J* = 11.2 Hz, 4-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.6 ($(CH_3)SiO$), -4.5 (2×$(CH_3)SiO$), -4.0 (2×$(CH_3)SiO$), -3.9 ($(CH_3)SiO$), 5.6 (OSi(CH_2CH_3)$_3$), 7.1 (OSi(CH_2CH_3)$_3$), 10.0 (CH_3), 14.1 (CH_3), 14.2 ($CO_2CH_2CH_3$), 15.8 (CH_3), 17.3 (CH_3-C-12), 18.0 (2x$(CH_3)_3CSi$), 18.4 ($(CH_3)_3CSi$), 19.9 (CH_3-C-16), 25.8 ($(CH_3)_3CSi$), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 30.3 (C-16), 31.4 (C-18), 32.2 (C-17, CH), 33.1 (C-12), 36.9 (CH), 39.8 (CH), 39.8 (C-15), 42.6 (C-8), 42.7 (CH), 55.1 (OCH_3), 59.2 (C-11). 59.8 ($CO_2CH_2CH_3$), 71.9 (CH_2OPMB), 72.0 (C-13), 72.6 (OCH_2PMP), 73.2 (C-21), 76.1 (C-7), 76.9 (C-19), 82.9 (C-11), 88.3 (C-10), 113.6 (m-CH_{arom}), 116.2 (C-2), 126.9 (C-4), 129.0 (o-CH_{arom}), 130.8 ($CH_2C_{quat\ arom}$), 145.0 (C-3), 146.3 (C-5), 159.0 ($CH_3OC_{quat\ arom}$), 166.4 (C-1).

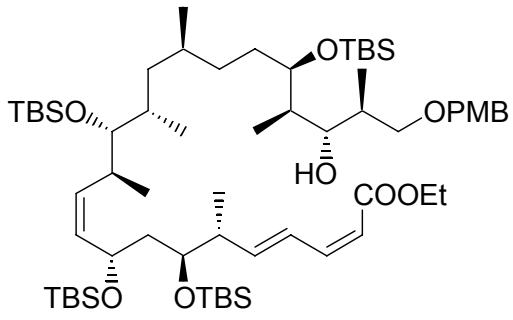
HRMS (EI): calcd. for $C_{63}H_{118}O_9Si_4Na$ $[M+Na]^+$: 1155.79016, found 1155.79028.

Ethyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*S*,21*S*,22*S*)-7,9,13,19-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-21-[(triethylsilyl)oxy]-2,4,10-tricosatrienoate 8-83



To a stirred solution of the alcohol **8-77** (180 mg, 0.18 mmol) and 2,6-lutidine (45 mg, 45 µL, 0.45 mmol) in CH_2Cl_2 (1 mL) at 0°C was added TBSOTf (62 µL, 72 mg, 0.27 mmol). The reaction mixture was allowed to warm to room temperature over 30 min. At this point reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL), and diluted with CH_2Cl_2 (5 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with 1N HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product (200 mg, 100%) was used further without purification. R_f = 0.88 (EtOAc/petroleum ether = 1:9);

Ethyl (2*Z*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*)-7,9,13,19-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-21-hydroxy-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-2,4,10-tricosatrienoate 8-84



To a solution of silyl ether **8-83** (95 mg, 0.076 mmol), in a mixture of MeOH (0.5 mL) and CH_2Cl_2 (2.5 mL) at rt were added few crystals of PPTS (approx. 3 mg). The reaction mixture was stirred until no starting material was detected by TLC analysis (4-6 h). Reaction was quenched by addition of Et_3N (100 µL), before all volatiles were removed by evaporation. The resulting oil (85 mg) was directly used for the next step.

R_f = 0.63 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = –26 (c = 2 in CH_2Cl_2);

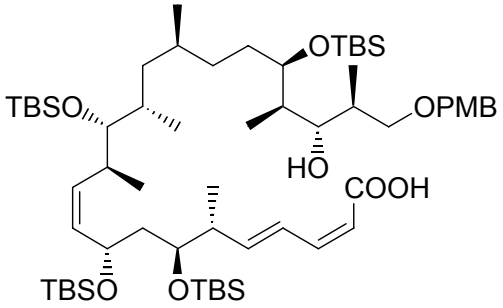
IR (film): υ_{max} = 3507, 2956, 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.02–0.13 (m, 18H, 4×$(CH_3)_2SiO$), 0.76–1.12 (m, 58H, 4×$(CH_3)_3CSiO$, 6×(*CH_3*)CH, 15-H', 17'), 1.20–1.45 (m, 7H, 17-H'', 2×CH, CO_2CH_2*CH_3*), 1.45–1.61 (m, 3H, CH, CH_2), 1.62–1.73 (m, 2H, 2×CH), 1.95–2.06 (m, 1H, 16-H), 2.54–2.64 (m, 1H, 6-H), 2.64–2.74 (m, 1H, 12-H), 3.19 (t, 1H, *J* = 8.7 Hz, CHOH), 3.35 (dd, 1H, *J* = 5.4 Hz, *J* = 2.2 Hz, 19-H), 3.53 (dd, 1H, *J* = 9.0 Hz, *J* = 4.0 Hz, C*H*HOPMB), 3.57–3.67 (m, 2H, CHOTBS, C*H*HOPMB), 3.77 (s, 3H, OCH_3), 3.90–3.96 (m, 1H, 7-H), 4.16 (q, 2H, *J* = 7.2 Hz, CO_2*CH_2*CH_3), 4.37 (d, 1H, *J* = 11.8 Hz, O*CH*HPMP), 4.41 (d, 1H, *J* = 11.8 Hz, O*CH*HPMP), 4.60 (m, 1H, 9-H), 5.31 (dd, 1H, *J* = 10.5 Hz, *J* = 8.3 Hz, 11-H), 5.46 (t, 1H, *J* = 10.5 Hz, 10-H), 5.57 (d, 1H, *J* = 11.4 Hz, 2-H), 5.99 (dd, 1H, *J* = 15.4 Hz, *J* = 7.3 Hz, 5-H), 6.51 (t, 1H, *J* = 11.4 Hz, 3-H), 6.84 (d, 2H, *J* = 8.7 Hz, m-CH_{arom}), 7.22 (d, 2H, *J* = 8.7 Hz, o-CH_{arom}) 7.38 (dd, 1H, *J* = 15.3 Hz, *J* = 11.2 Hz, 4-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 ((CH_3)SiO), -4.4 ((CH_3)SiO), -4.2 (2×(CH_3)SiO), -3.7 ((CH_3)SiO), -3.4 ((CH_3)SiO), -3.0 ((CH_3)SiO), 6.7 (*CH_3*-C-20), 13.2 (CO_2CH_2*CH_3*), 14.0 (*CH_3*-C-22), 14.3 (*CH_3*-C-6), 15.2 (*CH_3*-C-14), 18.0 ((CH_3)$_3$*C*Si), 18.1 (2x(CH_3)$_3$*C*Si), 18.4 ((CH_3)$_3$*C*Si), 19.4 (*CH_3*-C-12), 20.4 (*CH_3*-C-16), 25.8 ((*CH_3*)$_3$CSi), 25.9 (2×(*CH_3*)$_3$CSi), 26.2 ((*CH_3*)$_3$CSi), 30.5 (C-16), 31.2 (C-18), 31.9 (C-17), 34.9 (C-14), 35.6 (C-12), 36.6 (C-20), 37.4 (C-22), 41.51 (C-8), 42.3 (C-15), 43.5 (C-6), 55.2 (OCH_3), 59.8 (CO_2*CH_2*CH_3), 66.4 (C-9), 72.0 (*CH_2*OPMB), 73.0 (C-7), 74.4 (O*CH_2*PMP), 77.0 (CHOTBS), 77.2 (CHOTBS), 79.8 (CHOH), 113.7 (m-CH_{arom}), 116.0 (C-2), 126.8 (C-4), 129.2 (o-CH_{arom}), 130.4 ($CH_2C_{quat\ arom}$), 132.7 (C-10, C-11), 145.2 (C-3), 147.1 (C-5), 159.1 ($CH_3OC_{quat\ arom}$) 166.5 (C-1).

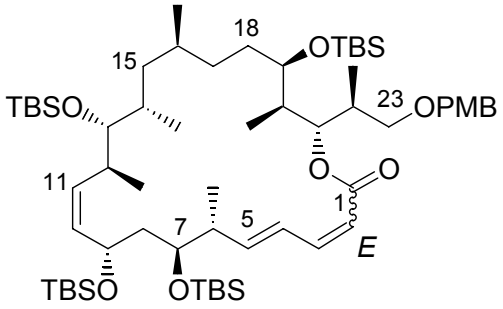
HRMS (EI): calcd. for $C_{63}H_{118}O_9Si_4Na$ $[M+Na]^+$: 1153.77451, found 1153.77166.

(2*E*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*)-7,9,13,19-tetrakis{[*tert*-Butyl(dimethyl)silyl]oxy}-21-hydroxy-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-2,4,10-tricosatrienoic acid 8-85



To a solution of the above alcohol in of EtOH (2.5 mL) was added 3N LiOH (0.25 mL) and the reaction mixture was stirred at 30°C for 72 h. Then Et_2O (10 mL) was added and the resulting solution was shaken with 1N HCl (5 mL). The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated to give the desired seco-acid **8-85** (80 mg).

(2*E*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*)-7,9,13,19-tetrakis{[*tert*-Butyl(dimethyl)silyl]oxy}-21-oxy-23-[(4-methoxybenzyl)oxy]-6,12,14,16,20,22-hexamethyl-2,4,10-tricosatrienoic acid lactone 8-86



A solution of seco-acid **8-85** (73 mg, 0.073 mmol) in THF (2 mL) was treated at 0 °C with Et_3N (0.060 mL, 0.44 μmol) and 2,4,6-trichlorobenzoyl chloride (0.055 mL, 0.36 μmol). The reaction mixture was stirred at 0°C for 30 min and then added to 4-DMAP (24 mL, 0.02 M solution in toluene) at 75°C. After stirring for 12 h, the reaction mixture was concentrated, Et_2O (10 mL) was added and this solution was washed with 1N HCl (2 × 5 mL) and dried over Na_2SO_4. Purification by flash column chromatography (EtOAc/hexane 2:98) furnished macrolactone **8-86** (48 mg, 65%) as a colorless oil (13% of inseparable 2-*Z* isomer was detected in NMR spectra).

R_f = 0.83 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -55 (c = 0.9 in CH_2Cl_2);

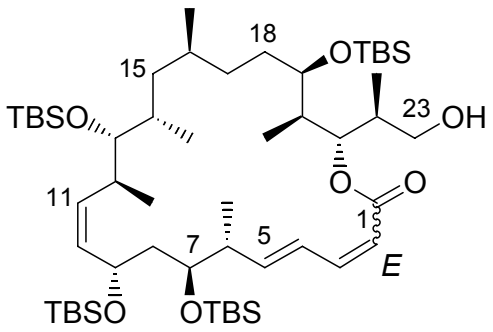
IR (film): υ_{max} = 2956, 1730, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.03–0.15 (m, 24H, 4×$(CH_3)_2SiO$), 0.35–0.45 (m, 1H, 15-H'), 0.69 (d, 3H, *J* = 5.8 Hz, CH_3), 0.75 (d, 3H, *J* = 5.8 Hz, CH_3), 0.76–1.15 (m, 50H, 4×$(CH_3)_3CSiO$, 4×(*CH_3*)CH, 2×CH), 1.22–1.40 (m, 2H, 2×CH), 1.45–1.57 (m, 3H, 3×CH), 1.70–1.80 (m, 1H, 14-H), 1.95–2.06 (m, 1H, 16-H), 2.11–2.23 (m, 1H, 6-H), 2.45–2.55 (m, 1H, 12-H), 2.54–2.64 (m, 1H, CH), 3.21 (t, 1H, *J* = 8.7 Hz, 23-H''), 3.37–3.51 (m, 3H, 7-H, 19-H, 23-H'), 3.78 (s, 3H, OCH_3), 3.98 (d, 1H, *J* = 9.9 Hz, *CH*OTBS), 4.22 (ddd, 1H, *J* = 16.9 Hz, *J* = 10.9 Hz, *J* = 5.8 Hz, 9-H), 4.35 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.39 (d, 1H, *J* = 11.4 Hz, O*CH*HPMP), 4.60 (t, 1H, *J* = 9.1 Hz, 19-H), 5.20 (d, 1H, *J* = 10.1 Hz, 21-H), 5.27 (dd, 1H, *J* = 11.4 Hz, *J* = 7.8 Hz, 11-H), 5.46 (t, 1H, *J* = 10.5 Hz, 10-H), 5.75 (d, 1H, *J* = 15.4 Hz, 2-H), 6.10 (dd, 1H, *J* = 10.9 Hz, *J* = 15.4 Hz, 4-H), 6.24 (dd, 1H, *J* = 9.6 Hz, *J* = 15.4 Hz, 5-H), 6.84 (d, 2H, *J* = 8.7 Hz, m-CH_{arom}), 7.19-7.27 (m, 3H, 3-H, o-CH_{arom});

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.5 (2×$(CH_3)SiO$), -4.3 ($(CH_3)SiO$), -4.2 ($(CH_3)SiO$), -4.1 ($(CH_3)SiO$), -3.6 ($(CH_3)SiO$), -3.0 ($(CH_3)SiO$), -2.3 ($(CH_3)SiO$), 10.5 (*CH_3*-C-20), 14.8 (*CH_3*-C-14), 16.1 (*CH_3*-C-22), 18.0 (2×$(CH_3)_3CSi$), 18.4 ($(CH_3)_3CSi$), 18.7 ($(CH_3)_3CSi$, *CH_3*-C-16), 19.6 (*CH_3*-C-6), 19.8 (*CH_3*-C-12), 25.8 ((*CH_3*)$_3$CSi), 25.9 ((*CH_3*)$_3$CSi), 26.2 ((*CH_3*)$_3$CSi), 26.4 ((*CH_3*)$_3$CSi), 30.4 (C-16), 31.0 (C-18), 32.8 (C-17), 34.4 (C-14), 35.1 (C-12), 36.5 (C-20), 39.1 (C-15), 40.2 (C-22), 45.2 (CH), 47.0 (C-8), 55.2 (OCH_3), 66.6 (C-9), 72.4 (CHOTBS), 72.8 (O*CH_2*PMP), 73.1 (*CH_2*OPMB), 73.3 (C-21), 76.0 (CHOTBS), 77.5 (CHOTBS), 113.6 (m-CH_{arom}), 119.6 (C-2), 128.0 (C-4), 129.3 (o-CH_{arom}), 130.9 ($CH_2C_{quat\ arom}$), 131.6 (C-10), 132.5 (C-11), 145.7 (C-3), 146.4 (C-5), 159.0 ($CH_3OC_{quat\ arom}$) 167.6 (C-1).

HRMS (EI): calcd. for $C_{61}H_{118}O_8Si_4N$ $[M+NH_4]^+$: 1104.79290, found 1104.79356.

(2*E*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*)-7,9,13,19-tetrakis{[*tert*-Butyl(dimethyl)silyl]oxy}-21-oxy-23-hydroxy-6,12,14,16,20,22-hexamethyl-2,4,10-tricosatrienoic acid lactone 8-87



To a cooled to 0°C solution of compound **8-86** (44 mg, 0.04 mmol) in a mixture of CH_2Cl_2/H_2O (1 mL, 20:1) was added DDQ (7.4 mg, 0.052 mmol, 1.3 equiv) and the mixture was allowed to warm to rt and stirred for 2 h. Then it was quenched with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 4:1) afforded **8-87** (33 mg, 83% yield) as colorless oil.

R_f = 0.4 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = -50 (c=0.76 in CH_2Cl_2);

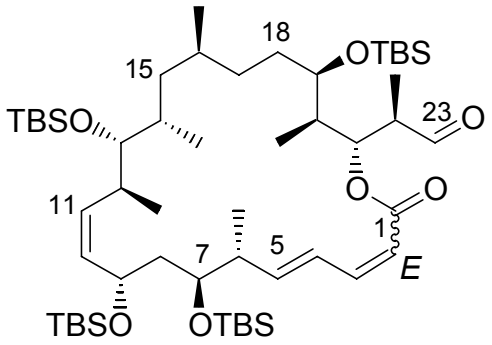
IR (film): υ_{max} = 3514, 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.05–0.15 (m, 24H, 4×$(CH_3)_2SiO$), 0.29–0.43 (m, 1H, 15-H), 0.67–0.75 (m, 6H, 2×CH_3), 0.76–1.15 (m, 51H, 4×$(CH_3)_3CSiO$, 4x(*CH_3*)CH, 3×CH), 1.22–1.40 (m, 2H, 2×CH), 1.45–1.57 (m, 4H, 3×CH, OH), 1.68–1.71 (m, 2H, 2×CH), 1.85–1.95 (m, 1H, 16-H), 2.11–2.23 (m, 1H, 6–H), 2.43–2.55 (m, 1H, 12-H), 3.35 (dd, 1H, *J* = 12.0 Hz, *J* = 1.4 Hz, 23-H'), 3.39–3.46 (m, 2H, 7-H, 19-H), 3.57 (dd, 1H, *J* = 12.0 Hz, *J* = 1.4 Hz, 23-H''), 3.98 (d, 1H, *J* = 9.6 Hz, *CH*OTBS), 4.56 (t, 1H, *J* = 8.9 Hz, 19-H), 5.22 (d, 1H, *J* = 10.1 Hz, 21-H), 5.23 (dd, 1H, *J* = 11.4 Hz, *J* = 7.8 Hz, 11-H), 5.45 (t, 1H, *J* = 10.7 Hz, 10-H), 5.75 (d, 1H, *J* = 15.4 Hz, 2-H), 6.08 (dd, 1H, *J* = 10.9 Hz, *J* = 15.4 Hz, 4-H), 6.23 (dd, 1H, *J* = 9.6 Hz, *J* = 15.4 Hz, 5-H), 7.25 (dd, 1H, *J* = 10.9 Hz, *J* = 15.4 Hz, 3-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.6 ($(CH_3)SiO$), -4.5 ($(CH_3)SiO$), -4.3 (2x$(CH_3)SiO$), -4.1 ($(CH_3)SiO$), -3.6 ($(CH_3)SiO$), -3.1 ($(CH_3)SiO$), -2.4 ($(CH_3)SiO$), 10.2 (*CH_3*-C-20), 14.4 (*CH_3*-C-22), 16.0 (*CH_3*-C-14), 17.9 ($(CH_3)_3$*C*Si), 18.2 ($(CH_3)_3$*C*Si), 18.3 ($(CH_3)_3$*C*Si), 18.6 ($(CH_3)_3$*C*Si), 18.9 (*CH_3*-C-16), 19.9 (*CH_3*-C-6), 22.6 (*CH_3*-C-12), 25.8 ((*CH_3*)$_3$CSi), 26.0 ((*CH_3*)$_3$CSi), 26.1 ((*CH_3*)$_3$CSi), 26.3 ((*CH_3*)$_3$CSi), 30.6 (C-16), 31.3 (C-18), 32.2 (C-17), 34.7 (C-12), 37.0 (C-20), 39.1 (C-15), 39.8 (C-22), 45.3 (CH), 47.0 (C-8), 63.6 (C-23), 66.6 (C-9), 72.5 (CHOTBS), 73.3 (C-21), 75.8 (CHOTBS), 77.2 (CHOTBS), 118.8 (C-2), 127.8 (C-4), 131.6 (C-10), 132.0 (C-11), 146.8 (C-3), 147.6 (C-5), 169.8 (C-1).

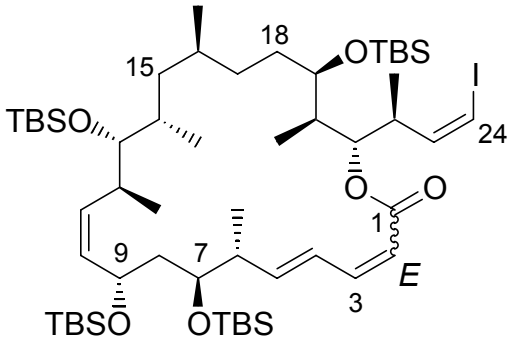
HRMS (EI): calcd. for $C_{53}H_{106}O_7Si_4Na$ $[M+Na]^+$: 967.70884, found 967.70903.

Aldehyde



To a cooled (0° C) solution of the alcohol **8-87** (33 mg, 0.038 mmol) in CH_2Cl_2 (7 mL) was added a solution of Dess-Martin periodinane in CH_2Cl_2 (15% wt, 0.15 mL, 0.05 mmol). After stirring for 0.5 h at 0 °C and for 2 h at room temperature, the reaction mixture was filtered through a short silica gel column (2 cm), and eluted with CH_2Cl_2/EtOAc, 4:1 to give 33 mg of the aldehyde which was used directly in the next reaction.

(2*E*,4*E*,6*R*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-7,9,13,19-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-21-oxy-24-iodo-6,12,14,16,20,22-hexamethyl-2,4,10-tetracosatetraenoic acid lactone 8-88



To a suspension of $(Ph_3P^+CH_2I)I^-$ (90 mg, 0.17 mmol) in THF (1.5 mL) at 0 °C, was added dropwise NaHMDS (2M in THF, 0.08 mL, 0.16 mmol) and the dark red solution was stirred at rt for 25 min before it was cooled to -78 °C. HMPA (0.1 mL, 0.57 mmol) was added followed by dropwise addition of a THF (1.0 mL) solution of the above aldehyde (33 mg, 0.038 mmol). After stirring at -78 °C for 10 min, the reaction mixture was warmed to rt and stirred there for 1 h before it was quenched with satd. NH_4Cl (5.0 mL) solution. The solid was filtered off, and the filtrate diluted with Et_2O (10.0 mL) and then the layers were separated. The aqueous layer was extracted with Et2O (3×10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude product was purified

by flash column chromatography (EtOAc/petroleum ether = 1:35) to provide the vinyl iodide **8-88** (22 mg, 0.022 mmol, 75%) as a light yellow oil.

R_f = 0.81 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = 95 (c = 2.3 in CH_2Cl_2);

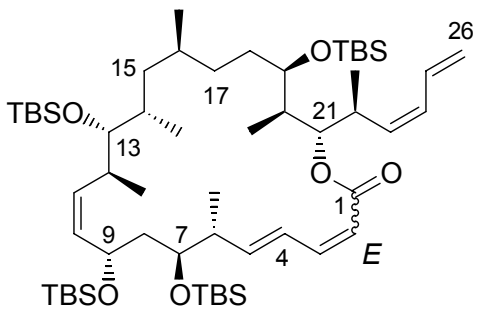
IR (film): υ_{max} = 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.04–0.15 (m, 24H, 4×$(CH_3)_2$SiO), 0.37–0.49 (m, 1H, CH-15), 0.67 (d, 3H, *J* = 6.1 Hz, CH_3), 0.75 (d, 3H, *J* = 6.8 Hz, CH_3), 0.76–1.15 (m, 51H, 4x$(CH_3)_3$CSiO, 4×(*CH_3*)CH, 3×CH), 1.22–1.40 (m, 2H, 2×CH), 1.45–1.57 (m, 3H, 3×CH), 1.65–1.80 (m, 2H, 2×CH), 1.87–1.97 (m, 1H, 16-H), 2.10-2.21 (m, 1H, 22-H), 2.45–2.55 (m, 1H, 12-H), 2.76–2.89 (m, 1H, CH), 3.37–3.46 (m, 2H, 7-H, *CH*OTBS), 3.97 (d, 1H, *J* = 9.4 Hz, *CH*OTBS), 4.56 (t, 1H, *J* = 8.7 Hz, 19-H), 5.27 (dd, 1H, *J* = 11.4 Hz, *J* = 7.8 Hz, C11-H), 5.31 (d, 1H, *J* = 10.1 Hz, 21-H), 5.42 (t, 1H, *J* = 10.9 Hz, 10-H), 5.75 (d, 1H, *J* = 15.4 Hz, 2-H), 6.03–6.14 (m, 3H, 23-H, 24-H, 4-H), 6.21 (dd, 1H, *J* = 9.6 Hz, *J* = 15.4 Hz, 5-H), 7.19 (dd, 1H, *J* = 10.9 Hz, *J* = 15.4 Hz, 3-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.6 (2×(CH_3)SiO), -4.3 ((CH_3)SiO), -4.1 (2x (CH_3)SiO), -3.6 ((CH_3)SiO), -3.0 ((CH_3)SiO), -2.3 ((CH_3)SiO), 10.9 (*CH_3*-C-20), 16.2 (*CH_3*-C-14), 16.5 (*CH_3*-C-22), 18.0 ($(CH_3)_3$*C*Si), 18.2 ($(CH_3)_3$*C*Si), 18.3 (2x$(CH_3)_3$*C*Si), 18.7 (*CH_3*-C-12), 19.4 (*CH_3*-C-6), 19.7 (*CH_3*C-16), 25.9 ((*CH_3*)$_3$CSi), 26.0 ((*CH_3*)$_3$CSi), 26.2 ((*CH_3*)$_3$CSi), 26.4 ((*CH_3*)$_3$CSi), 29.7 (*CH_2*CH_2CHOTBS, CH_2*CH_2*CHOTBS) 30.4 ((CH_3)*CH*CH_2CH_2CHOTBS), 34.1 (C-12), 35.6 (C-20), 39.6 (C-15), 42.9 (C-22), 45.1 (CH), 47.0 (C-8), 66.5 (C-9), 72.4 (CHOTBS), 73.6 (C-21), 75.9 (CHOTBS), 77.2 (CHOTBS), 82.0 (C-24), 119.5 (C-2), 128.1 (C-4), 131.5 (C-10), 132.5 (C-11), 143.8 (C-23), 145.7 (C-3), 146.4 (C-5), 167.4 (C-1).

HRMS (EI): calcd. for $C_{54}H_{106}IO_6Si_4$ $[M+H]^+$: 1089.61057, found 1089.61198.

2-*E*-7,9,13,19-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-dictyostatin 8-89



To a stirred solution of vinyl iodide **8-88** (17 mg, 0.016 mmol), in a mixture of THF (0.25 mL) and DMF (0.35 mL), vinyl tributylstannane (20 μL, 20 mg, 0.060 mmol) was added. In a separate flask $Furyl_3P$ (2.3 mg, 0.01 mmol), $Pd_2(dba)_3$ (2.5 mg, 0.0025 mmol), and Ph_3As (3 mg, 0.01 mmol) were dissolved in THF (0.1 mL) and DMF (0.1 mL), and then transferred to the first flask via syringe. The reaction mixture was stirred for 12 h, diluted with Et_2O (10.0 mL), washed with satd. NH_4Cl (5.0 mL) solution, then with brine, and dried with Na_2SO_4. The filtrate was then concentrated in *vacuo*. The crude product was purified by flash chromatography (gradient, petroleum ether to EtOAc/petroleum ether = 1:40) to provide diene **8-89** (13 mg, 84% yield) as a colorless oil.

R_f = 0.81 (EtOAc/petroleum ether = 1:9);

$[\alpha]^{20}_D$ = 8.1 (c = 1.25 in CH_2Cl_2);

IR (film): υ_{max} = 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

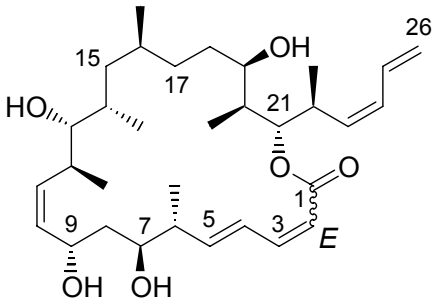
^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.04-0.15 (m, 24H, 4×$(CH_3)_2SiO$), 0.36–0.47 (m, 1H, 15-H'), 0.67 (d, 3H, *J* = 6.1 Hz, CH_3), 0.75 (d, 3H, *J* = 6.8 Hz, CH_3), 0.76–1.15 (m, 49H, 4×$(CH_3)_3CSiO$, 4×(*CH_3*)CH, CH), 1.22–1.40 (m, 2H, 2×CH), 1.45–1.57 (m, 3H, 3×CH), 1.67–1.76 (m, 2H, 2×CH), 1.87–1.97 (m, 1H, 16-H), 2.07–2.17 (m, 1H, 22-H), 2.43–2.55 (m, 1H, 12-H), 2.86–2.99 (m, 1H, CH), 3.34–3.46 (m, 2H, 7-H, *CH*OTBS), 3.96 (d, 1H, *J* = 9.6 Hz, *CH*OTBS), 4.56 (t, 1H, *J* = 8.7 Hz, 19-H), 5.05 (d, 1H, *J* = 10.1 Hz, 26-H(*Z*)), 5.13 (d, 1H, *J* = 16.7 Hz, 26-H(*E*)), 5.21 (d, 1H, *J* = 8.6 Hz, 21-H), 5.27 (dd, 1H, *J* = 11.4 Hz, *J* = 7.8 Hz, 12-H), 5.35 (t, 1H, *J* = 10.4 Hz, 23-H), 5.42 (t, 1H, *J* = 10.6 Hz, 10-H), 5.69 (d, 1H, *J* = 15.4 Hz, H-2), 5.92 (t, 1H, *J* = 11.0 Hz, 24-H) 6.06 (dd, 1H, *J* = 10.4 Hz, *J* = 15.4 Hz, 4-H), 6.19 (dd, 1H, *J* = 9.6 Hz, *J* = 15.4 Hz, H-5), 6.59 (ddd, 1H, *J* = 10.5 Hz, *J* = 10.6 Hz, *J* = 16.8 Hz, 25-H), 7.18 (dd, 1H, *J* = 10.7 Hz, *J* = 15.3 Hz, 3-H);

^{13}C NMR (100 MHz, $CDCl_3$) δ =-4.6 (2×$(CH_3)SiO$), -4.3 ($(CH_3)SiO$), -4.1 (2x $(CH_3)SiO$), -3.6 ($(CH_3)SiO$), -3.0 ($(CH_3)SiO$), -2.3 ($(CH_3)SiO$), 10.9 (*CH_3*-C-20), 16.2 (*CH_3*-C-14), 16.5 (*CH_3*-C-6), 18.0 ($(CH_3)_3CSi$), 18.2 ($(CH_3)_3CSi$), 18.3 (2x$(CH_3)_3CSi$), 18.7 (*CH_3*-C-16), 19.4 (*CH3*-C-22), 19.7 (*CH_3*-C-12), 25.9 ((*CH_3*)$_3$CSi), 26.0 ((*CH_3*)$_3$CSi), 26.2 ((*CH_3*)$_3$CSi), 26.4 ((*CH_3*)$_3$CSi), 30.4 (CH), 30.7 (C-17) 33.1 (C-18) 34.2 (C-16), 35.4 (C-12), 35.6 (C-20), 39.6 (C-15), 40.5 (C-22), 45.1 (CH), 47.0 (C-8), 66.5 (C-9), 72.4 (CHOTBS), 74.0 (C-21), 76.1

(CHOTBS), 77.2 (CHOTBS), 117.2 (C-26), 119.7 (C-2), 128.1 (C-24), 129.1 (C-4), 131.5 (C-10), 132.2 (C-11, C-25), 135.2 (C-24), 145.4 (C-3), 146.0 (C-5), 167.2 (C-1).

HRMS (EI): calcd. for $C_{56}H_{108}O_6Si_4$ $[M+H]^+$: 989.72957, found 989.72760.

2-*E*-dictyostatin 8-90



To a stirred solution of **8-89** (13 mg, 0.013 mmol) in THF (0.35 mL, in a plastic test tube) at -50 °C was added dropwise HF-pyridine complex (0.25 mL, 70% HF). The reaction mixture was allowed to warm to room temperature. After 1 h reaction it was partitioned between a stirred mixture of EtOAc (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) by slow addition via plastic pipette. After separation of the layers, the aqueous layer was extracted with EtOAc (2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on Diol® phase with 1.5% MeOH in CH_2Cl_2 affording tetraol **8-90** (6.5 mg, 95%), R_f = 0.5 (EtOAc/petroleum ether = 1:2);

R_f = 0.76 ($MeOH/CH_2Cl_2$ = 1:9);

$[\alpha]^{20}_D$ = 4.0 (c = 0.65 in CH_2Cl_2);

IR (film): υ_{max} = 3500, 1715, 1636, 1612, 1587, 1513, 1463, 1420, 1378, 1302, 1250, 1182, 1031, cm^{-1};

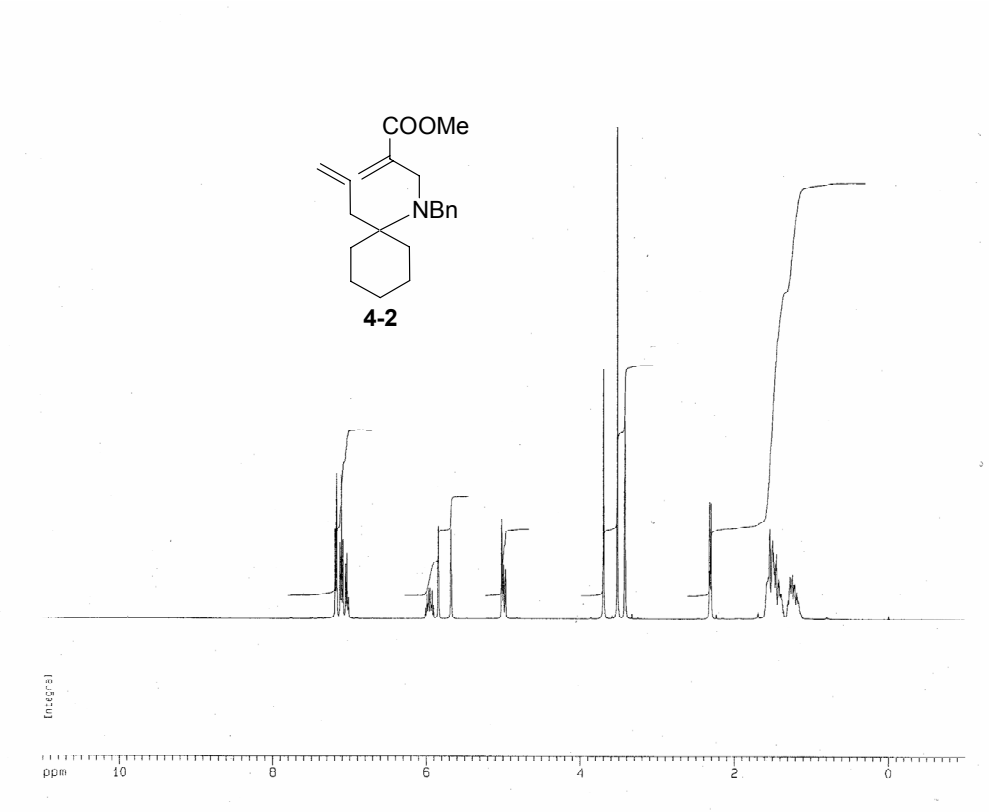
^{1}H NMR (600 MHz, CD_3OD) δ = 0.66–0.73 (m, 1H, 15-H'), 0.81 (d, 3H, *J* = 6.1 Hz, *CH*$_3$-C-16), 0.82 (d, 3H, *J* = 6.8 Hz, *CH*$_3$-C-14), 0.90 (d, 3H, *J* = 6.8 Hz, *CH*$_3$-C-12), 0.97–1.04 (m, 1H, 17-H'), 0.98 (d, 3H, *J* = 6.8 Hz, *CH*$_3$-C-22), 1.06–1.13 (m, 1H, 18-H') 1.07 (d, 3H, *J* = 6.8 Hz, *CH*$_3$-C-20), 1.15 (d, 3H, *J* = 6.8 Hz, *CH*$_3$-C-6), 1.28–1.33 (m, 1H, 18-H'), 1.29–1.36 (m, 1H, 8-H'), 1.41–1.48, (m, 1H, 15-H'), 1.44–1.51 (m, 1H, 17-H''), 1.48–1.54 (m, 1H, 16H), 1.67-1.74 (m, 1H, 8-H''), 1.71–1.77 ((m, 1H, 14-H), 1.87-1.93 (m, 1H, 20-H), 2.14-2.23 (m, 1H, 6-H), 2.51–2.58 (m, 1H, 12-H), 2.96-3.04 (m, 1H, 22-H), 3.08 (dd, 1H, *J* = 7.0 Hz, *J* = 4.1 Hz, 13-H), 3.25 (dd, 1H, *J* = 10.1 Hz, *J* = 6.5 Hz, 19-H), 3.85 (d, 1H, *J* = 11.5 Hz, 7-H), 4.61 (t, 1H, *J* = 9.0 Hz, 9-H), 5.03–5.09 (m, 2H, 21-H, 26-H(*Z*)), 5.13 (d, 1H, *J* = 16.7 Hz, 26-

H(*E*)), 5.21 (t, 1H, *J* = 10.6 Hz, 11-H), 5.25 (t, 1H, *J* = 10.4 Hz, C*H*=CHCH=CH_2), 5.42 (dd, 1H, *J* = 11.0 Hz, *J* = 8.1 Hz, 10-H), 5.73 (d, 1H, *J* = 15.1 Hz, 2-H), 5.93 (t, 1H, *J* = 11.0 Hz, *CH*CH=CH_2) 6.04 (dd, 1H, *J* = 9.5 Hz, *J* = 15.3 Hz, CH=*CH*-CH=CHCO$_2$CH), 6.14 (dd, 1H, *J* = 11.0 Hz, *J* = 15.3 Hz, 5-H), 6.63 (ddd, 1H, *J* = 10.5 Hz, *J* = 10.6 Hz, *J* = 16.9 Hz, 25-H), 7.17 (dd, 1H, *J* = 10.7 Hz, *J* = 15.1 Hz, 3-H);

^{13}C NMR (150 MHz, CD_3OD) δ = 11.0 (*CH_3*-C-20), 14.9 (*CH_3*-C-14), 17.6 (*CH_3*-C-22), 17.7 (*CH_3*-C-6), 18.1 (*CH_3*-C-12), 21.1 (*CH_3*-C-16), 30.1 (C-16), 30.7 (C-18) 32.5 (C-14) 36.4 (C-17), 36.7 (C-22), 37.1 (C-12), 40.8 (C-15), 42.3 (C-20), 44.5 (C-8), 45.3 (C-6), 65.9 (C-C9), 72.0 (C-7), 76.0 (C-13, C-19), 76.2 (C-21), 117.9 (C-26), 120.5 (C-2), 130.6 (C-24), 130.8 (C-4), 133.0 (C-11), 133.5 (C-25), 135.6 (C-10), 135.7 (C-23), 147.0 (C-3, C-5), 169.0 (C-1).
HRMS (EI): calcd. for $C_{32}H_{53}O_6Na$ $[M+Na]^+$: 555.36561, found 555.36575.

11 Appendix

11.1 NMR-Spectra for important compounds

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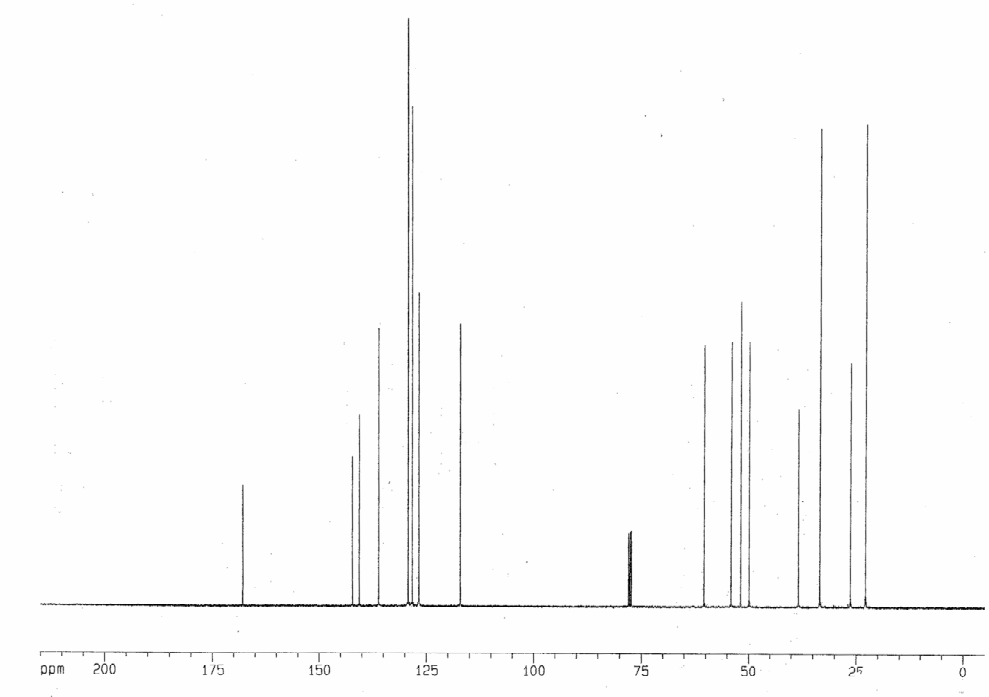


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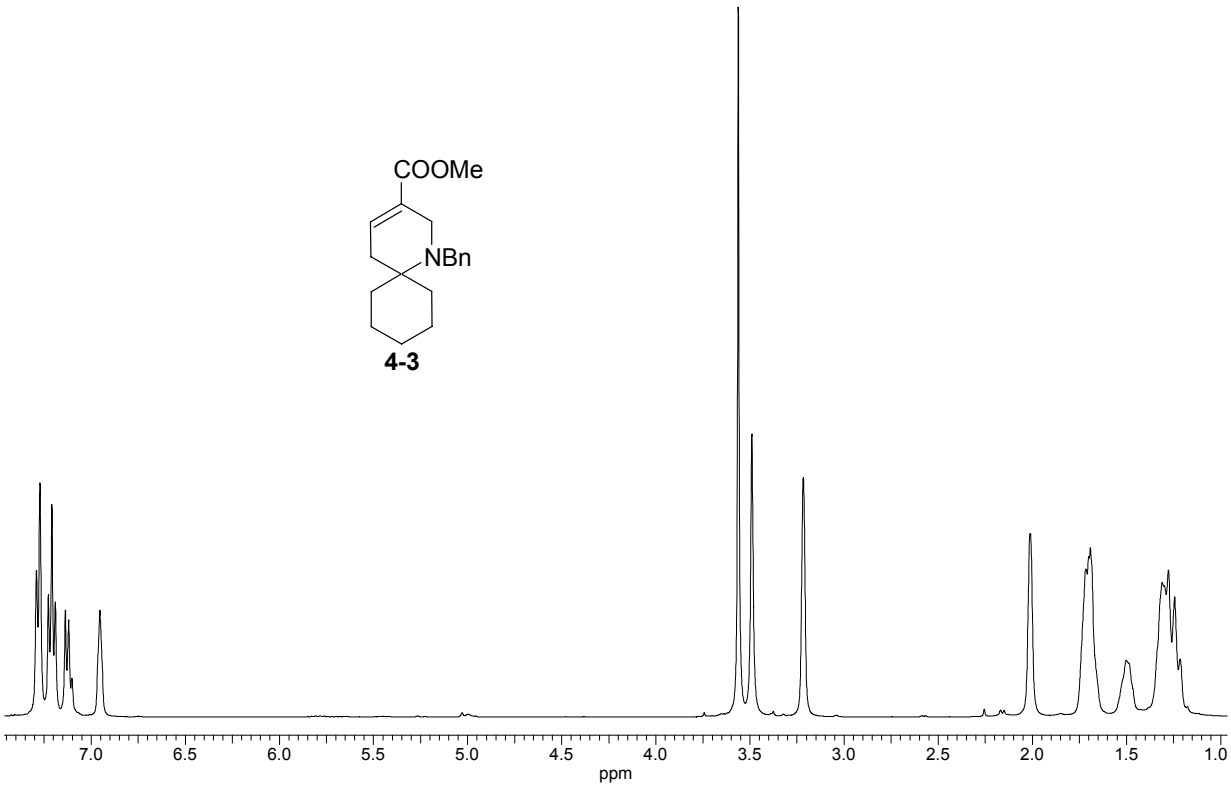
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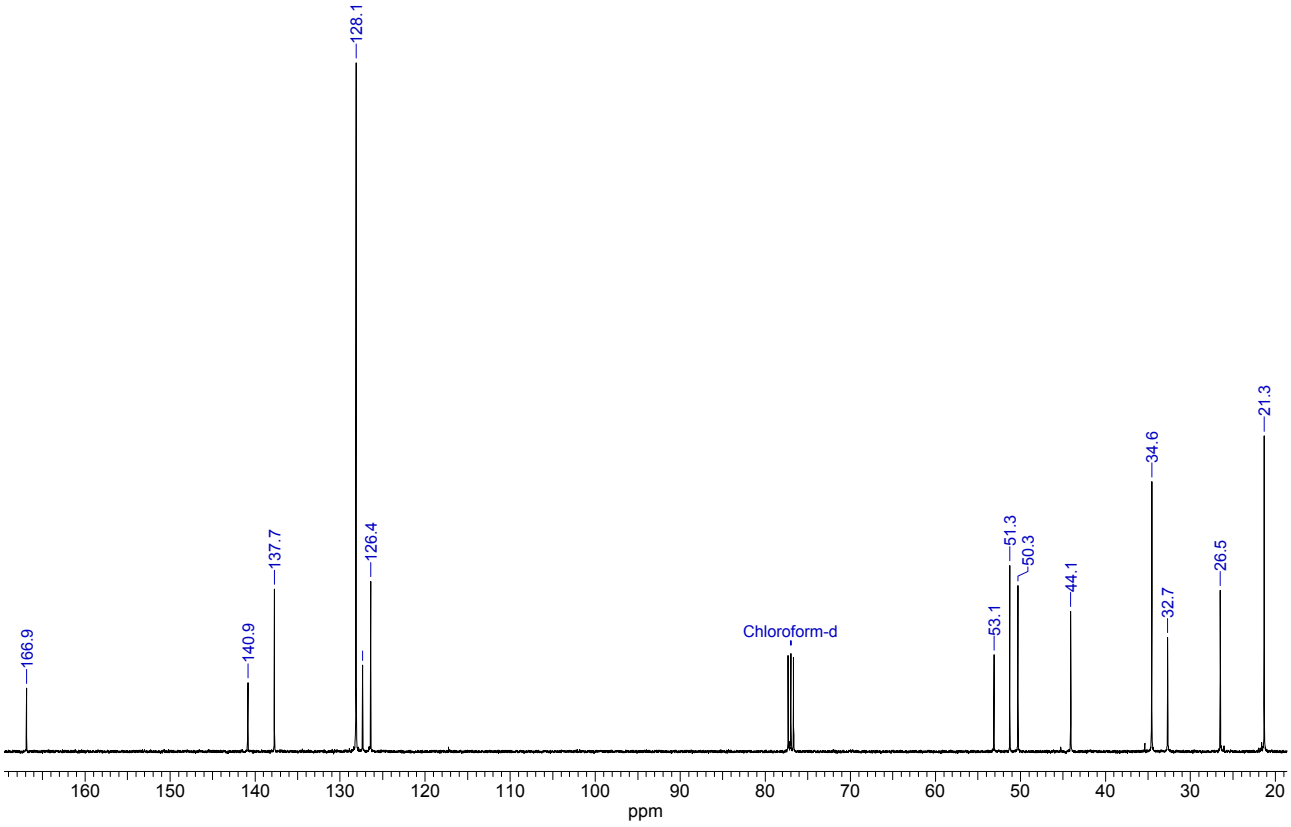
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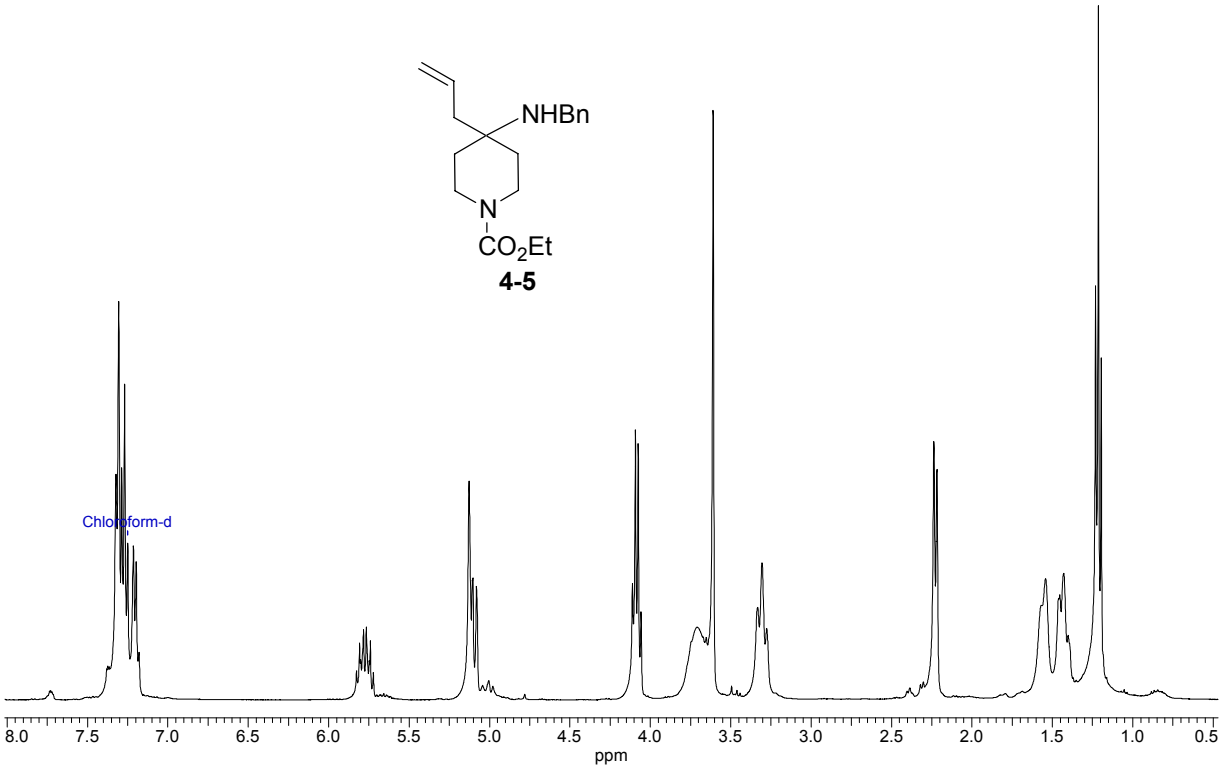
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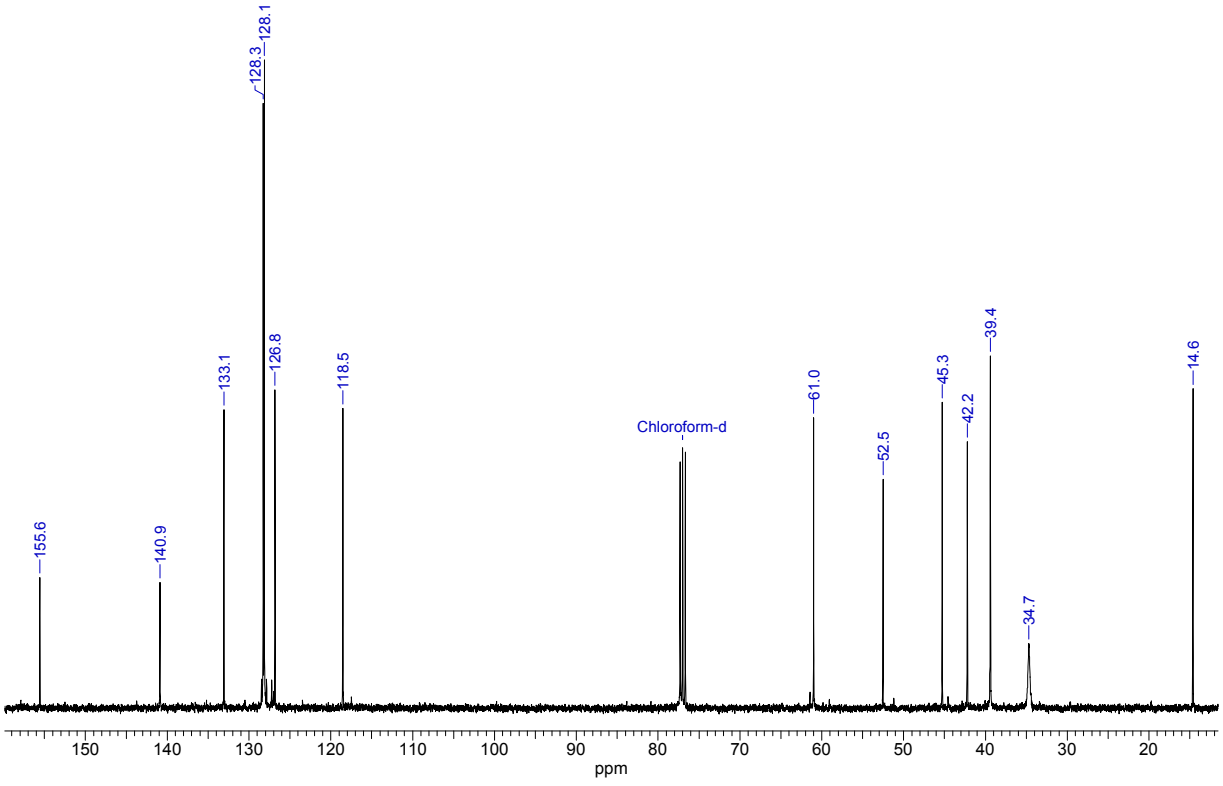
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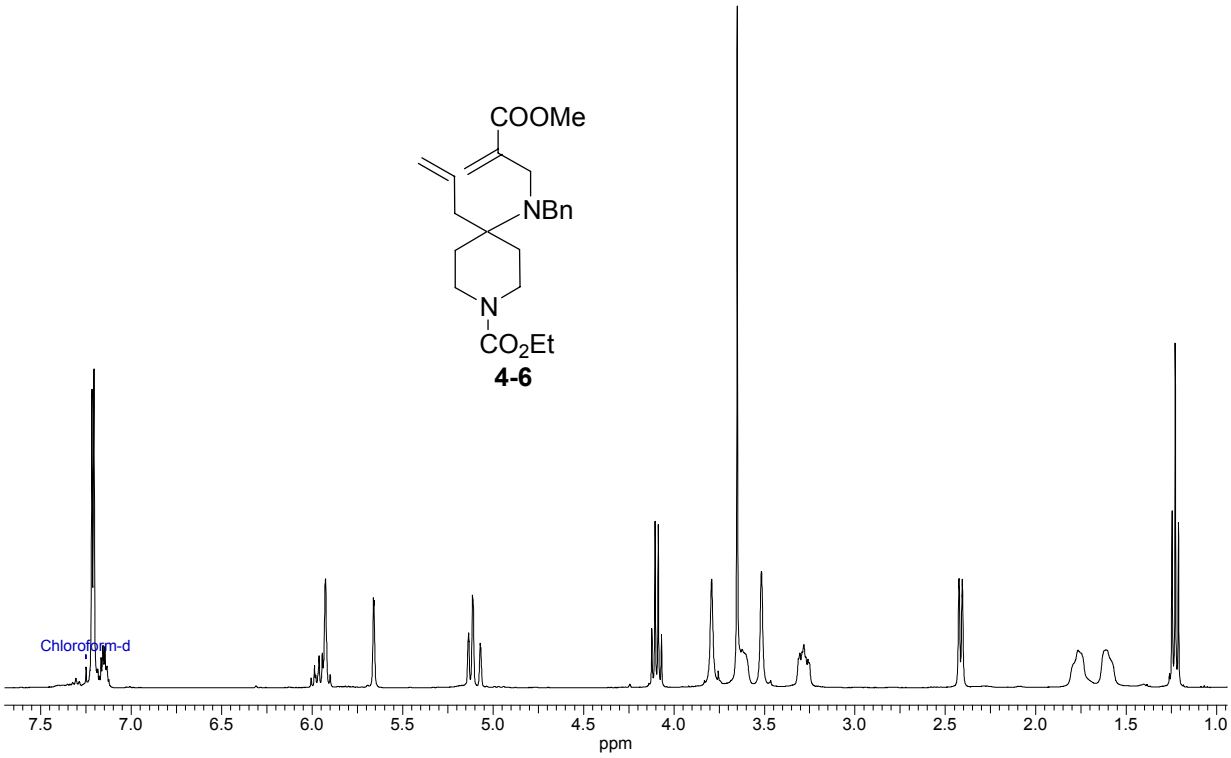
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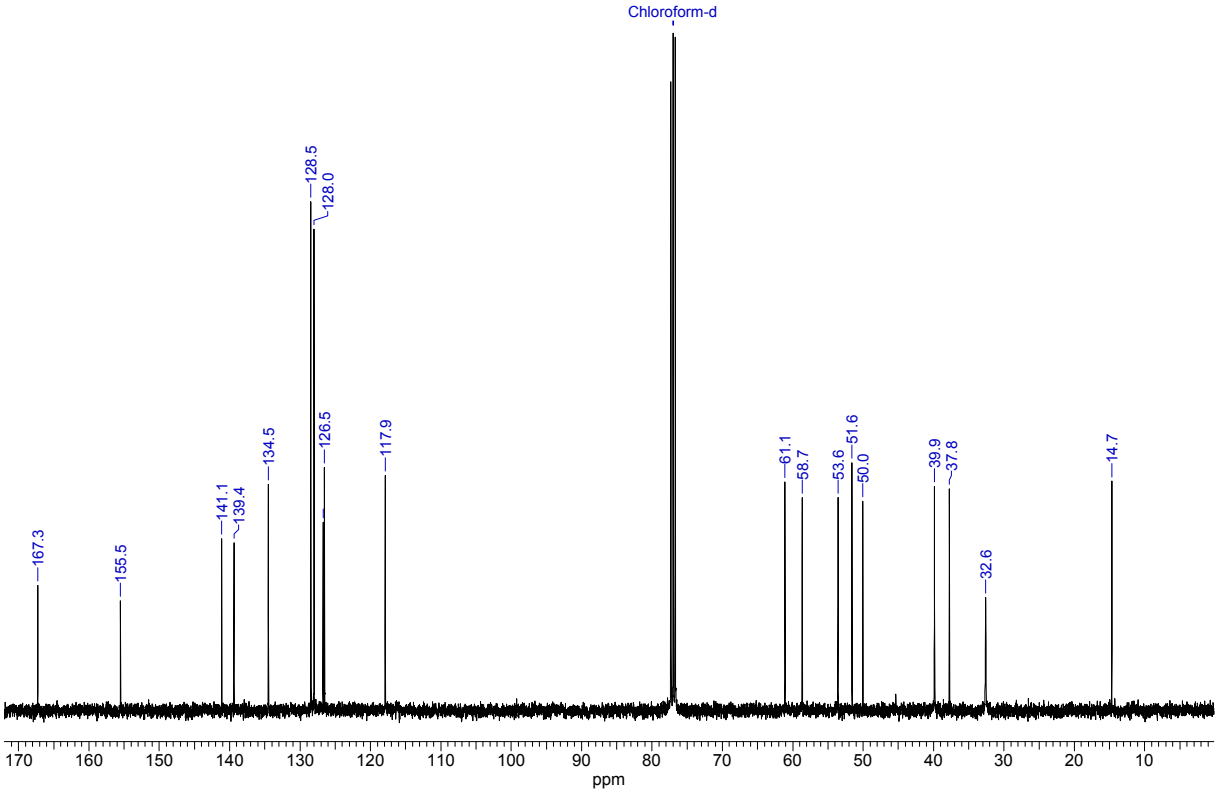
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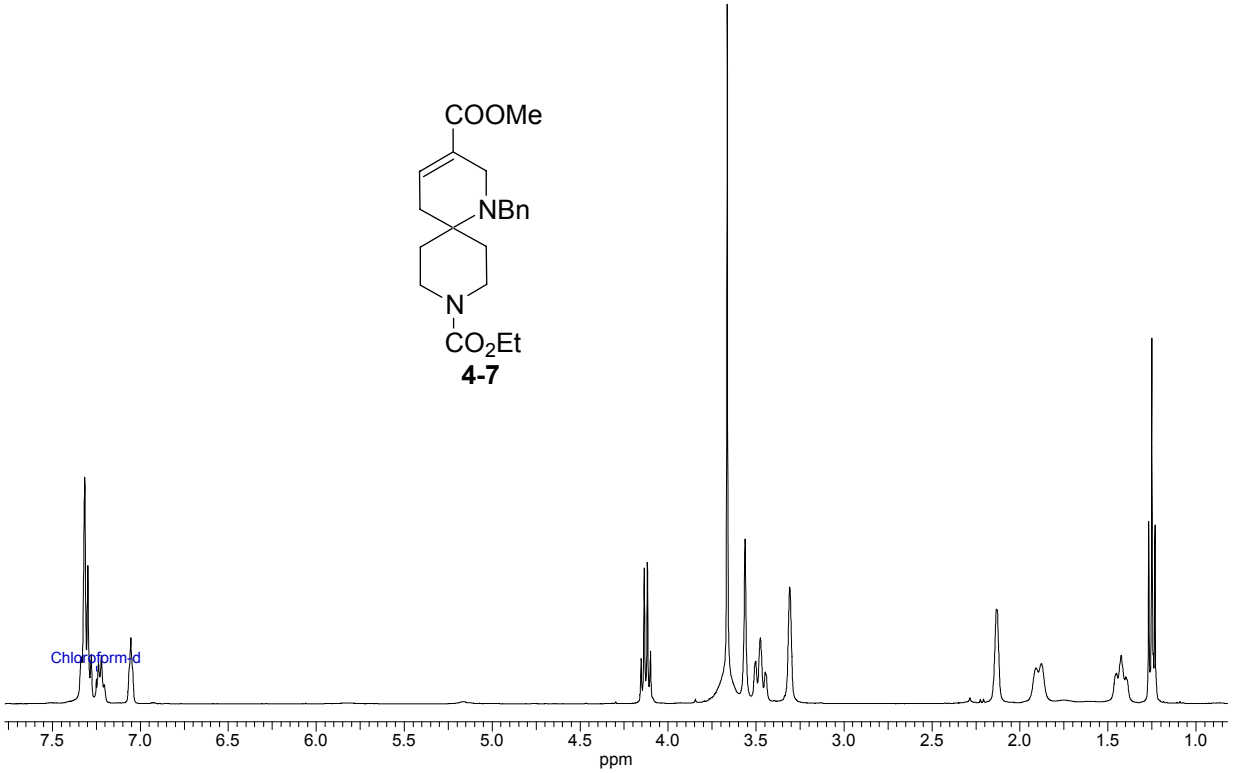
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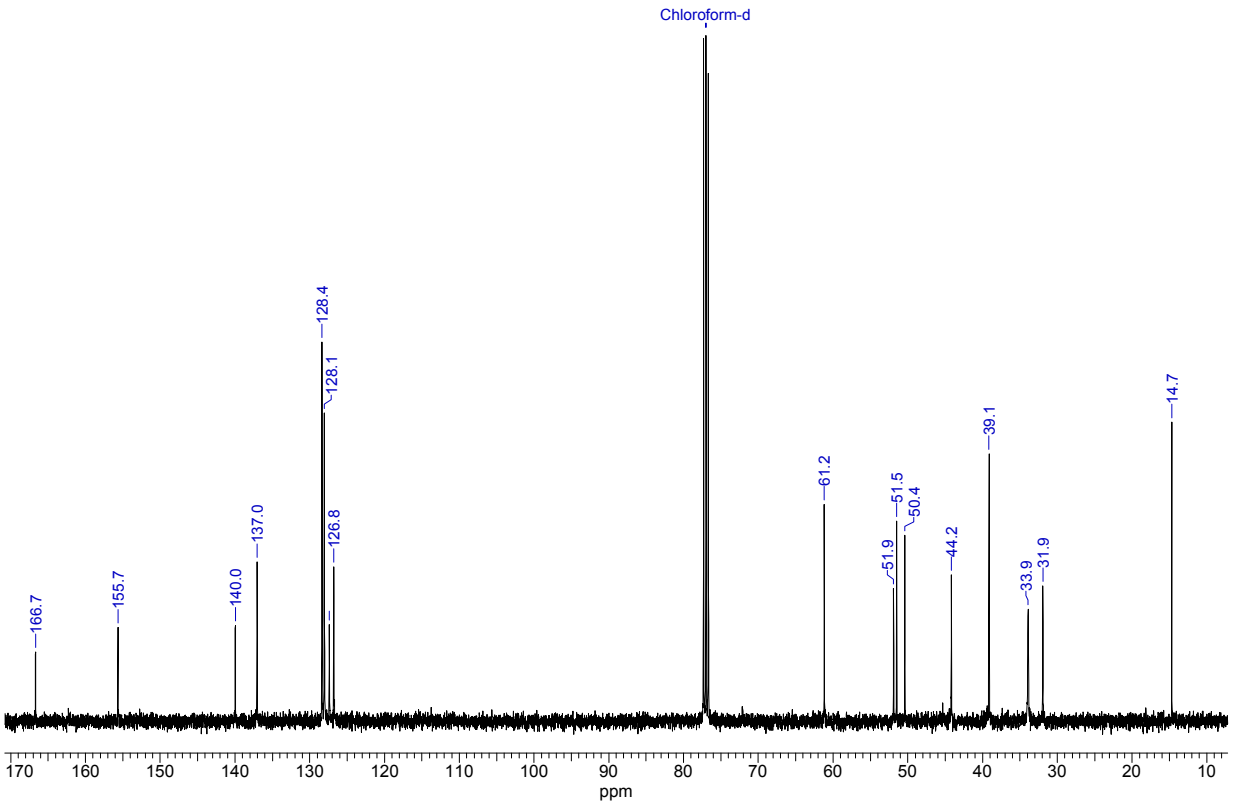
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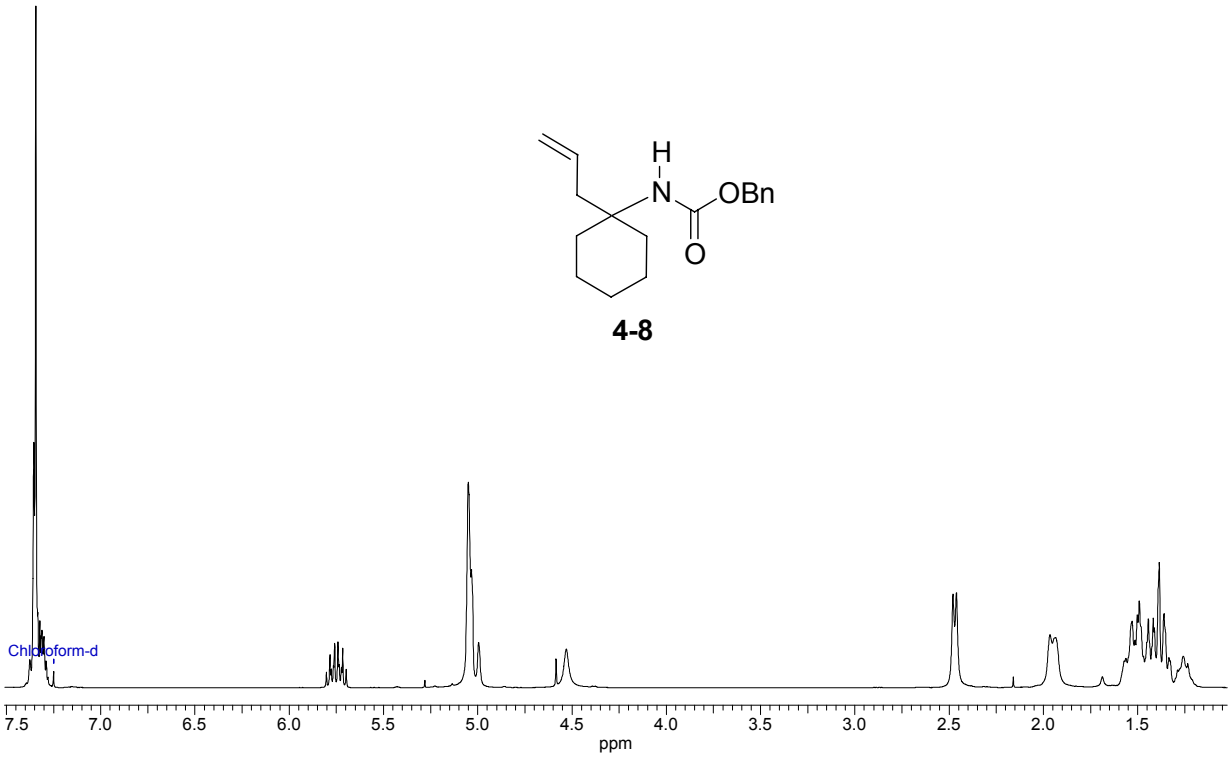
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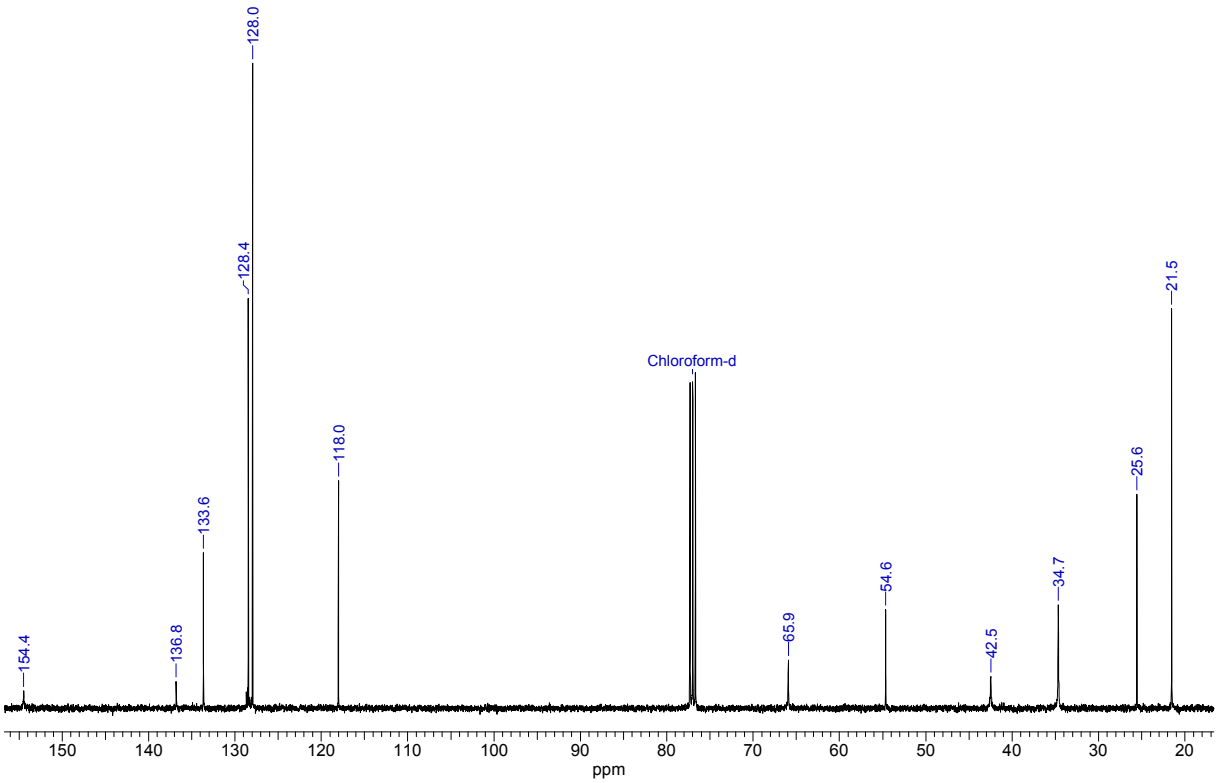
4-8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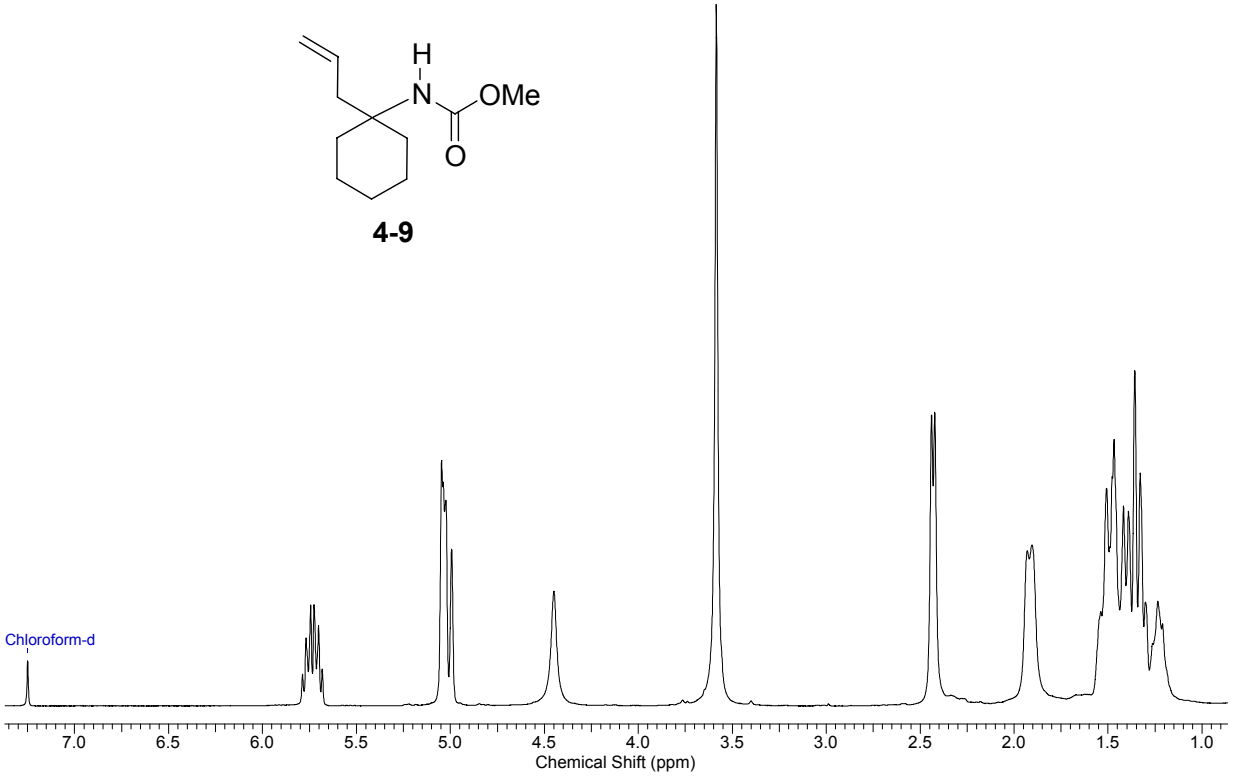
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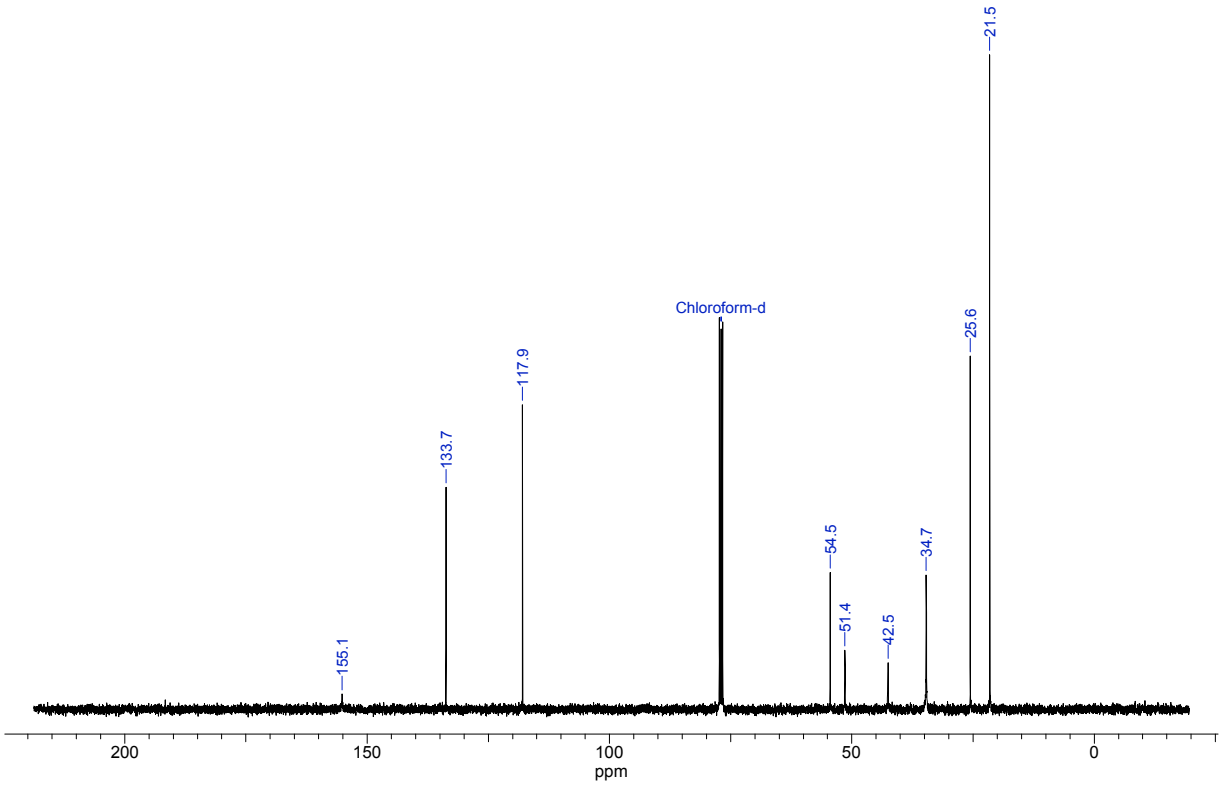
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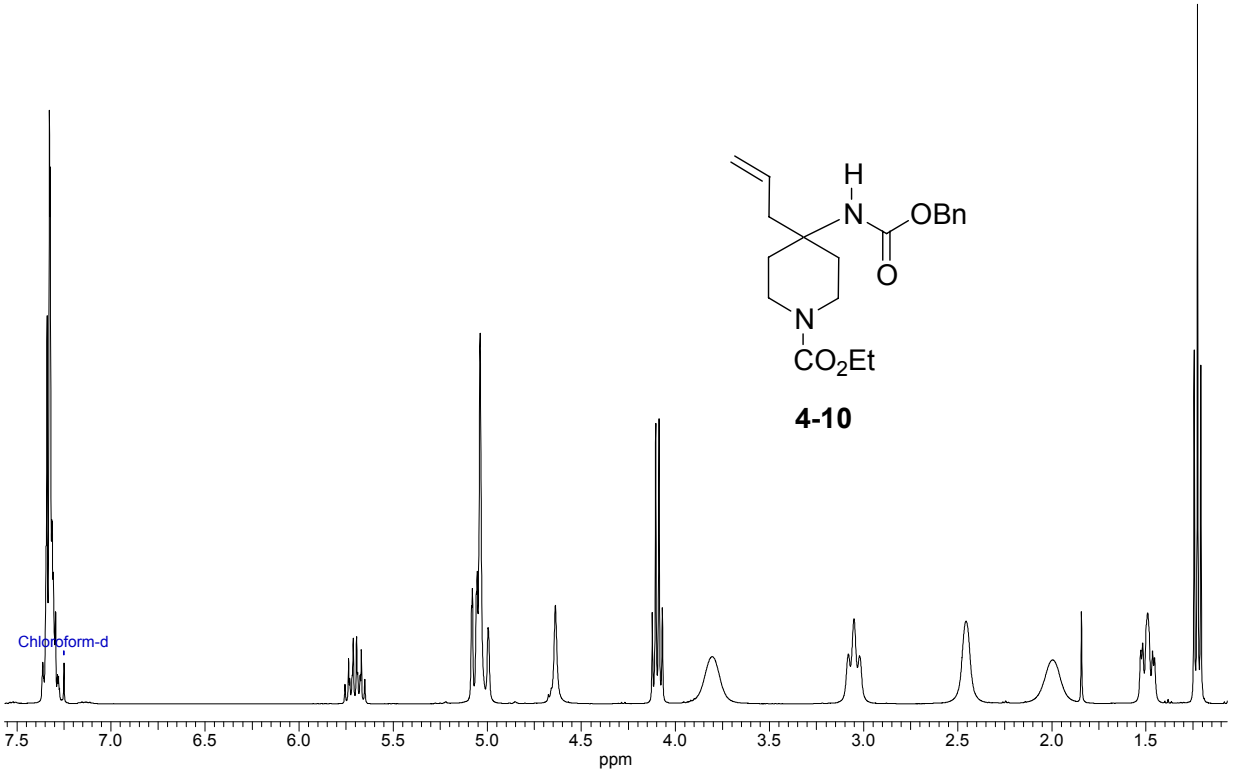
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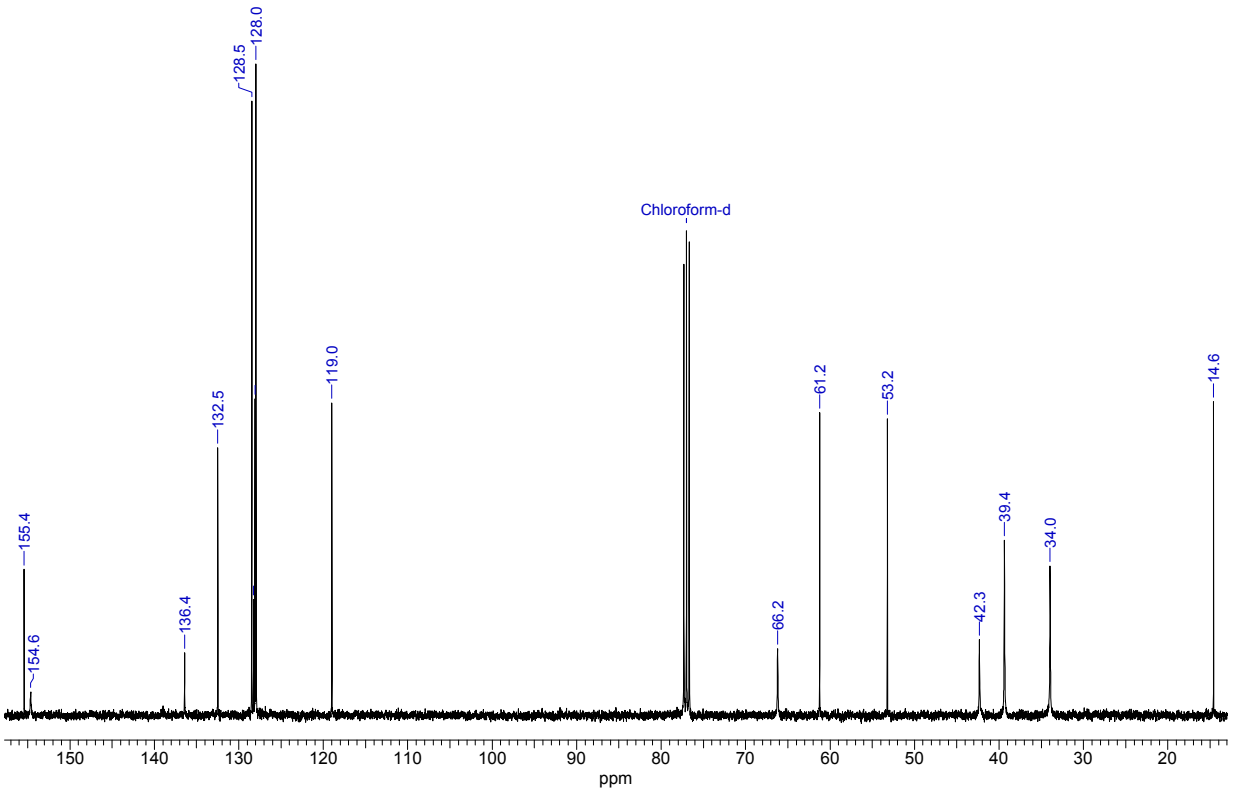
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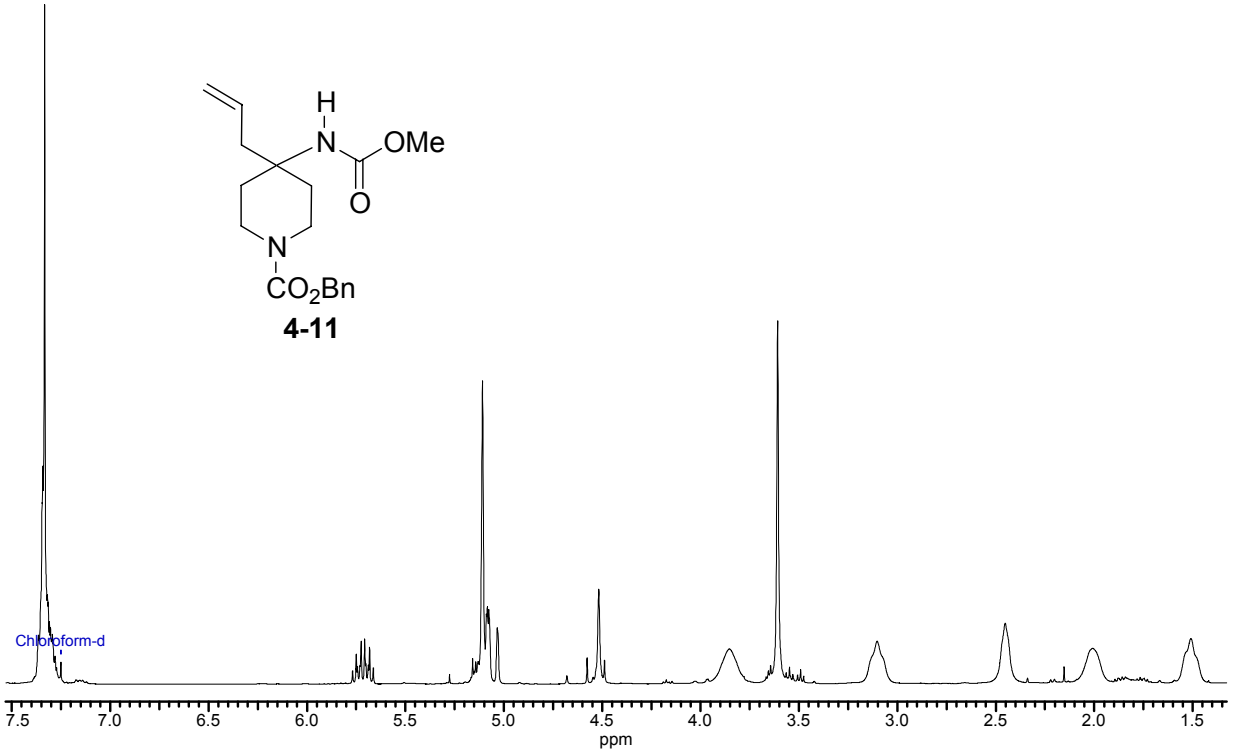
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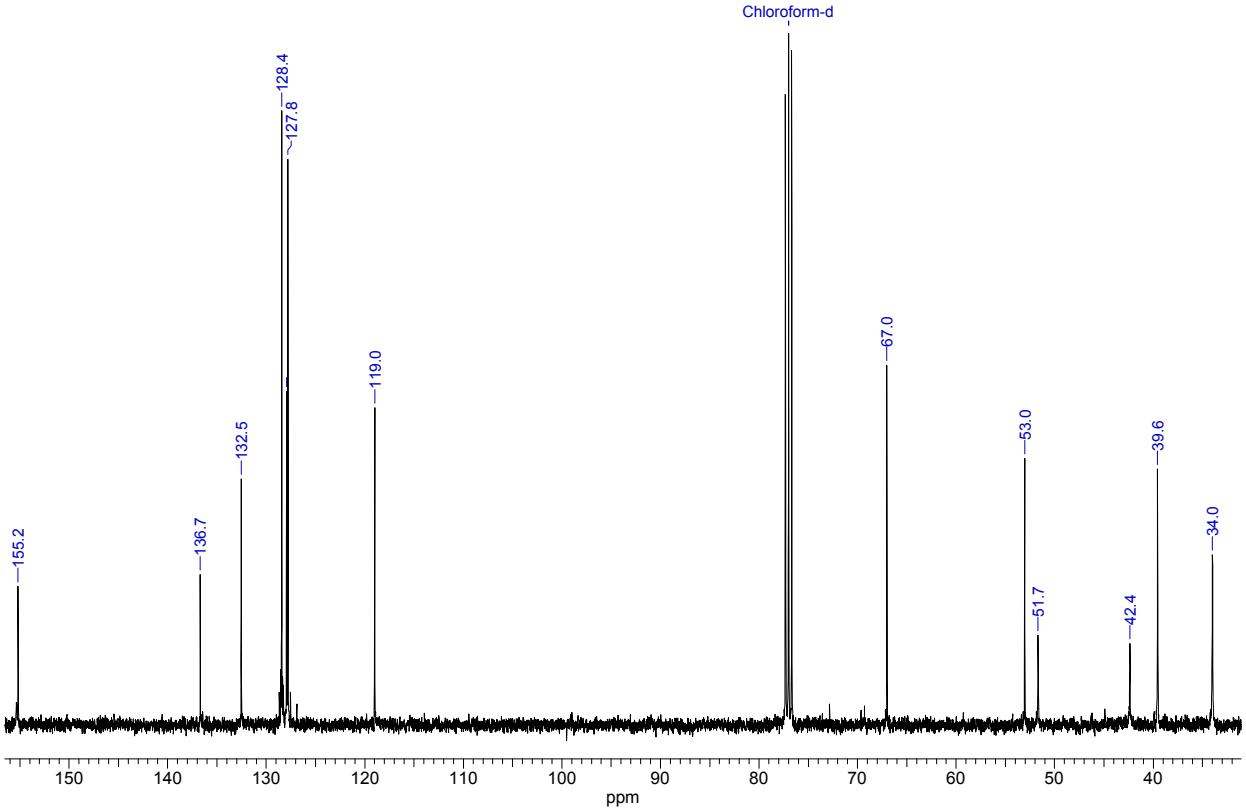
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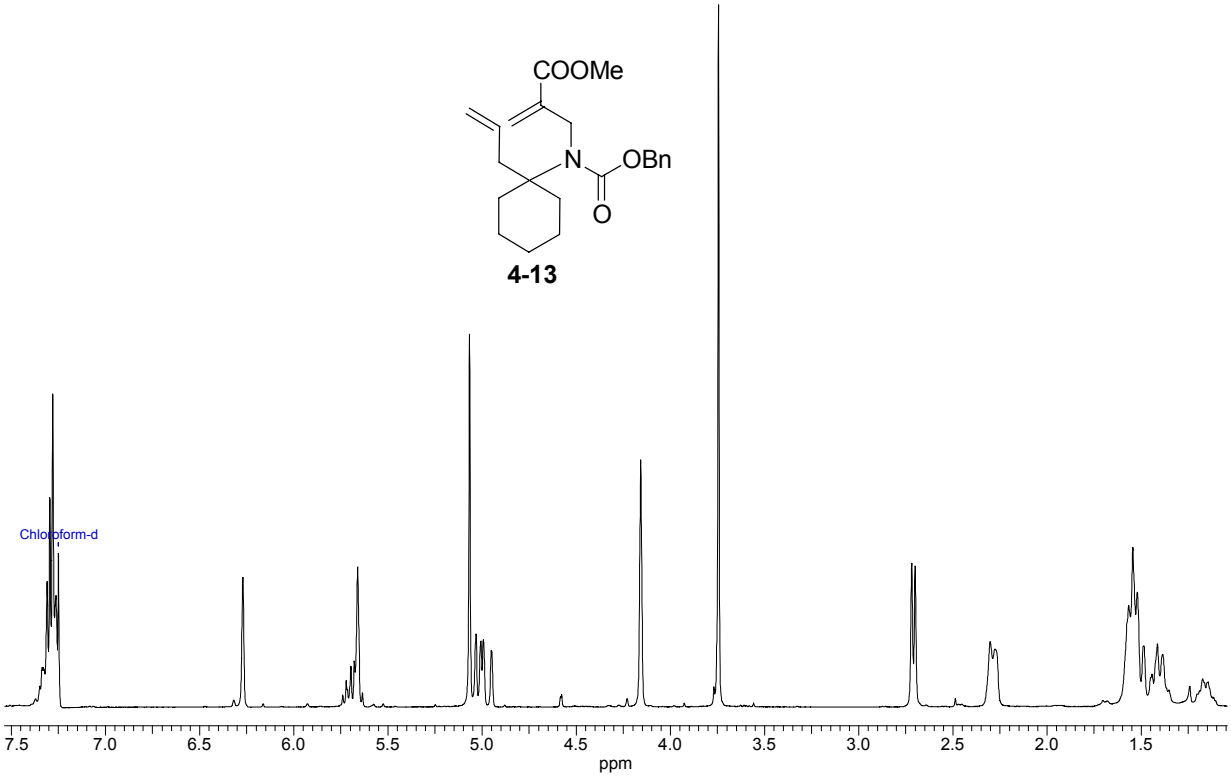
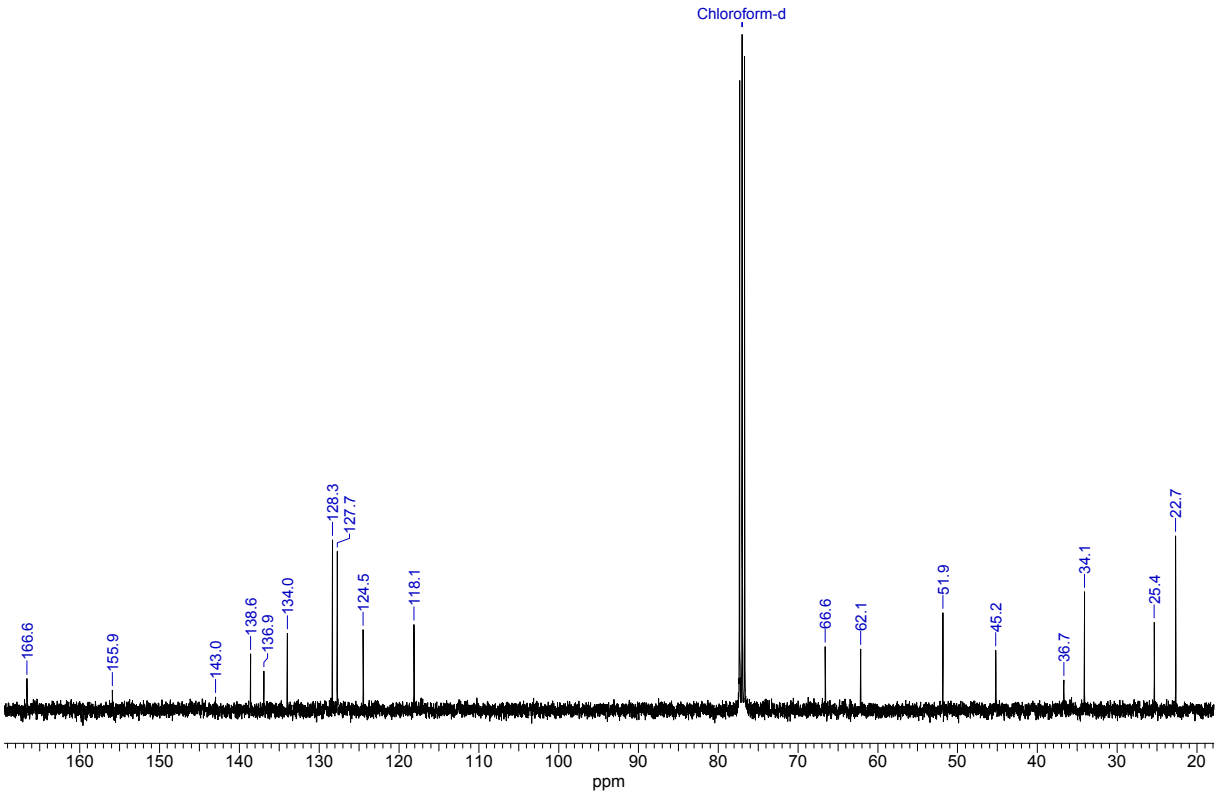
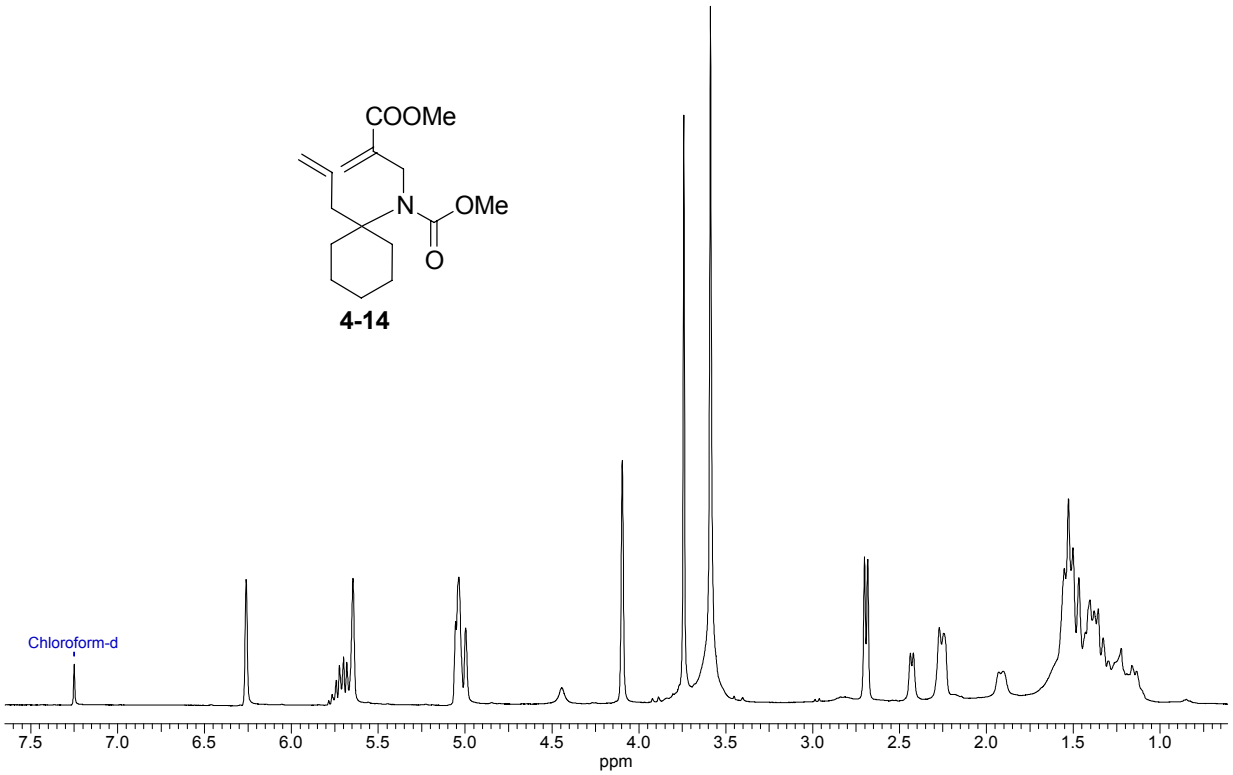
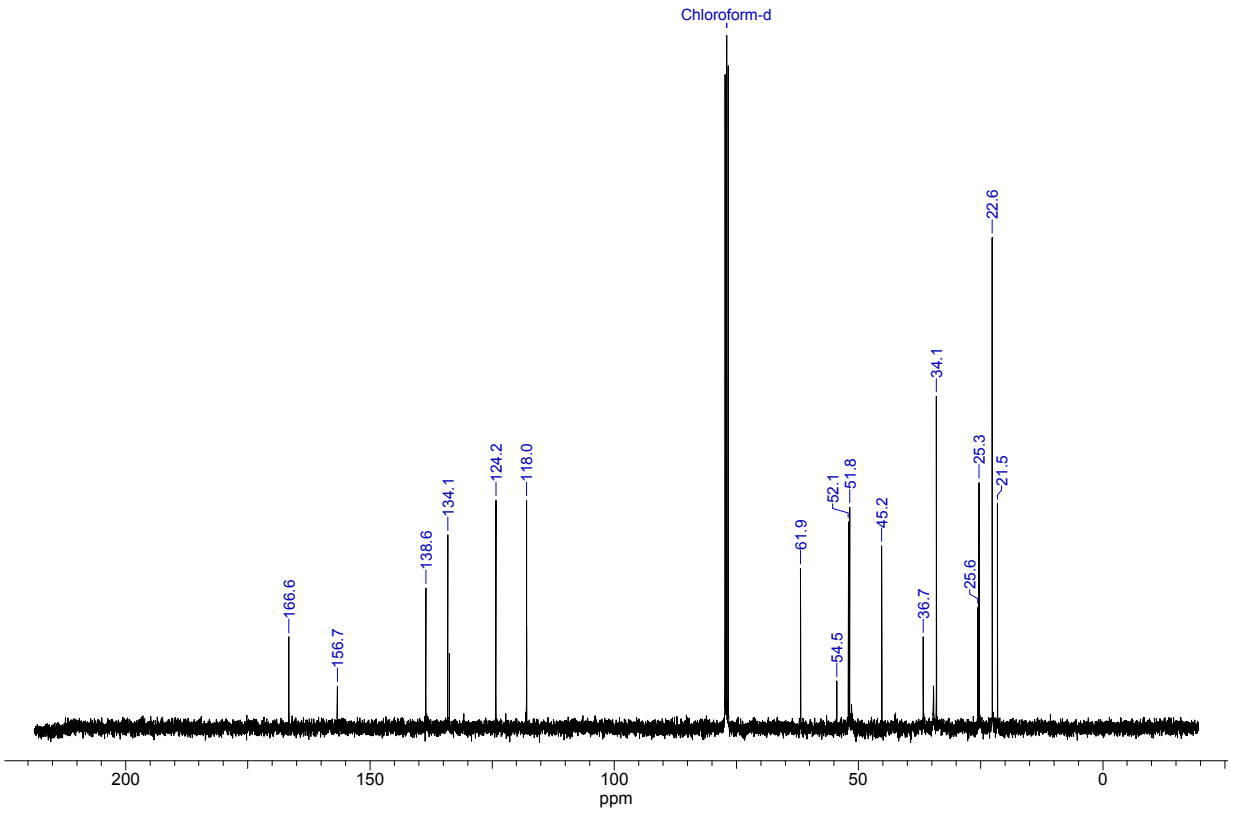

COOMe
N
OBn
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

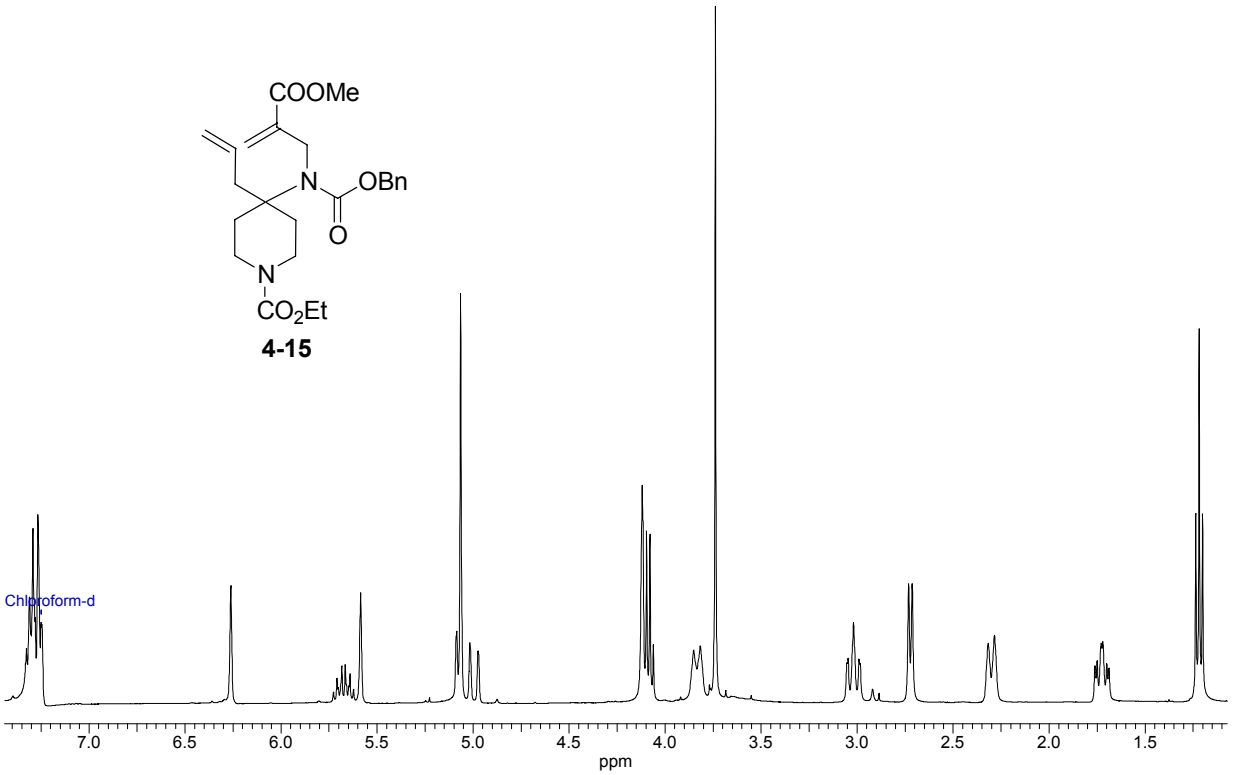
4-13

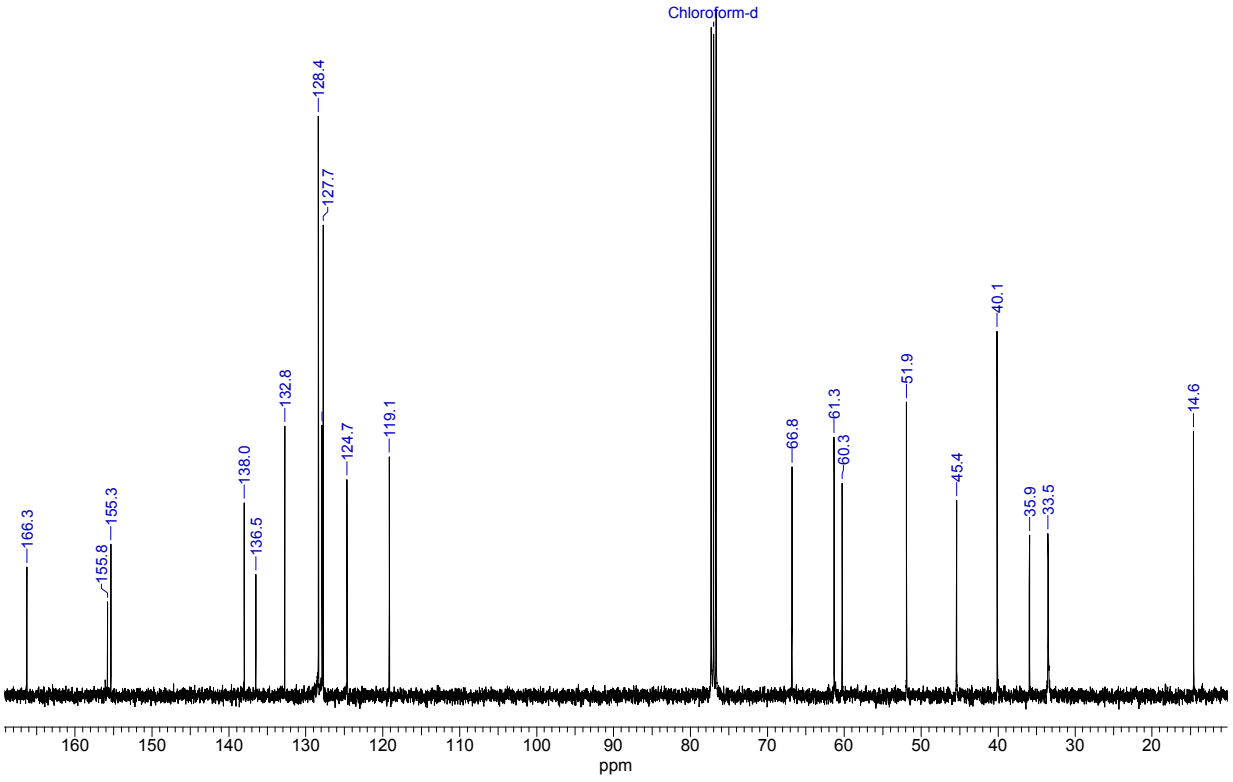

Chloroform-d
166.6
155.9
143.0
138.6
136.9
134.0
128.3
127.7
124.5
118.1
66.6
62.1
51.9
45.2
36.7
34.1
25.4
22.7
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

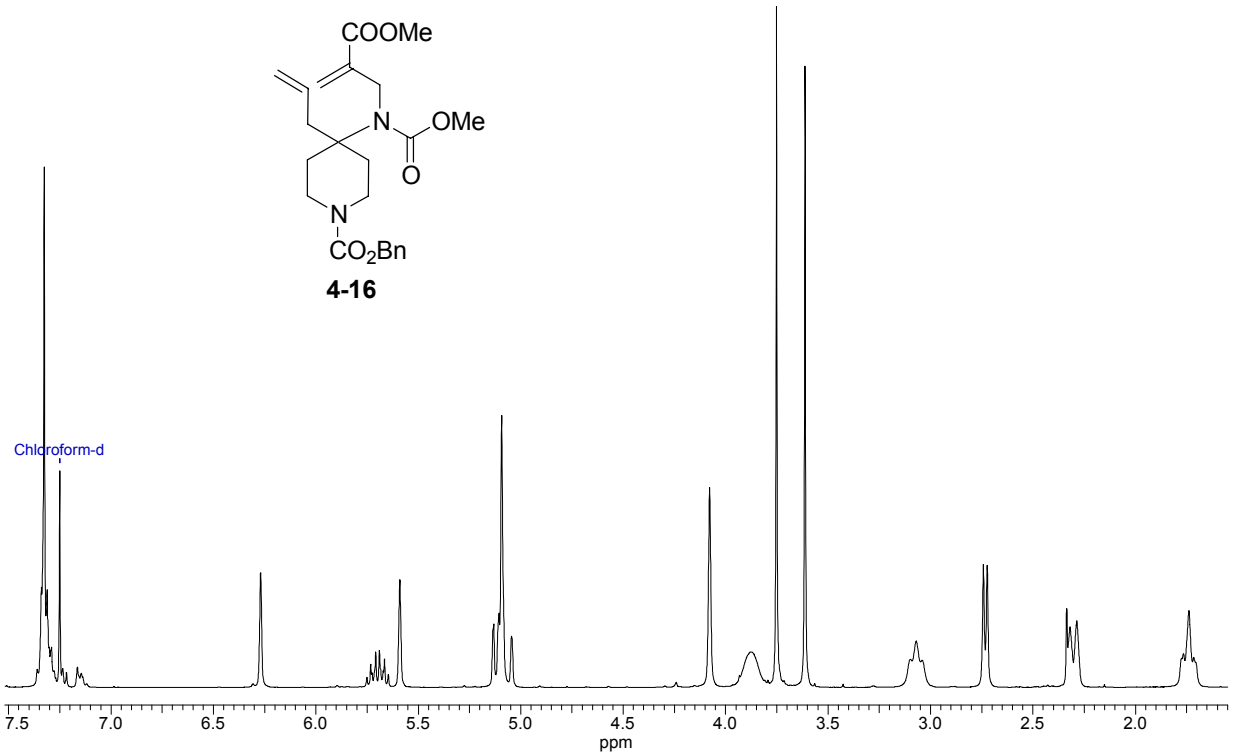

COOMe
N
OMe
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

4-14

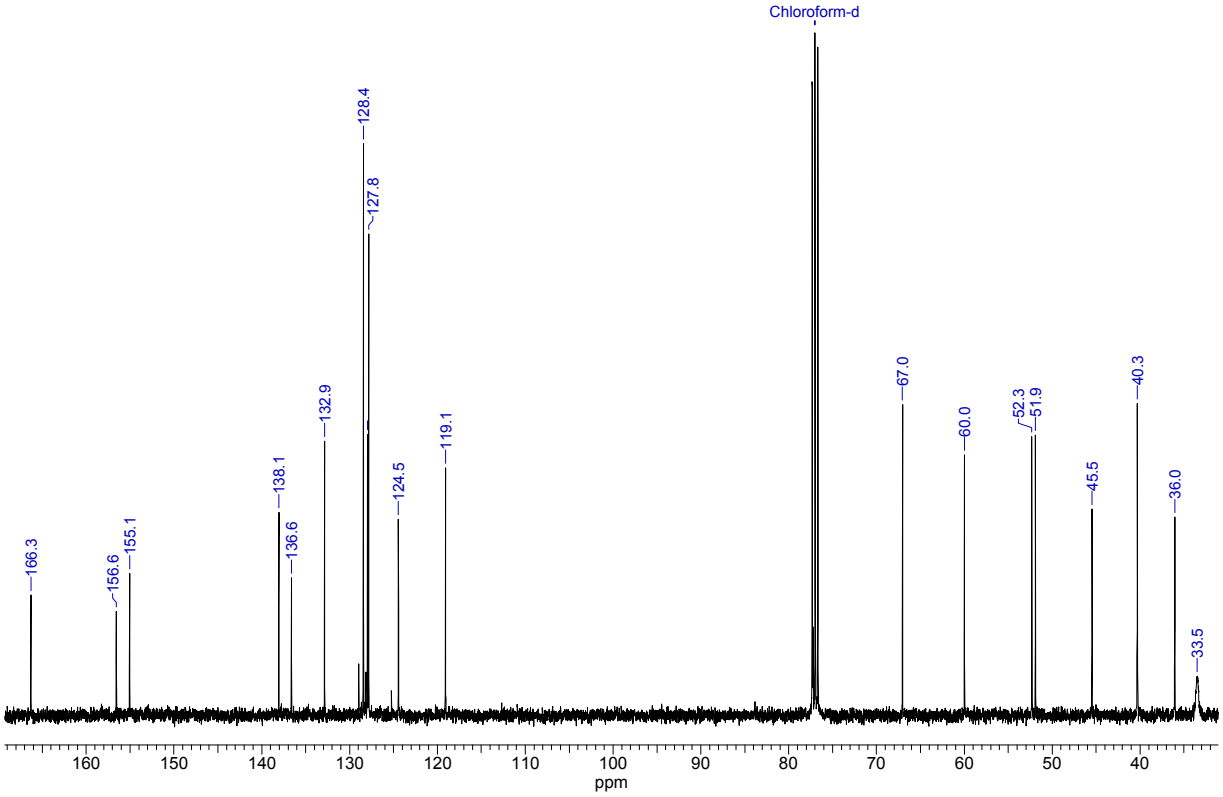

Chloroform-d
166.6
156.7
138.6
134.1
124.2
118.0
61.9
54.5
52.1
51.8
45.2
36.7
34.1
25.6
25.3
22.6
21.5
200
150
100
50
0
ppm

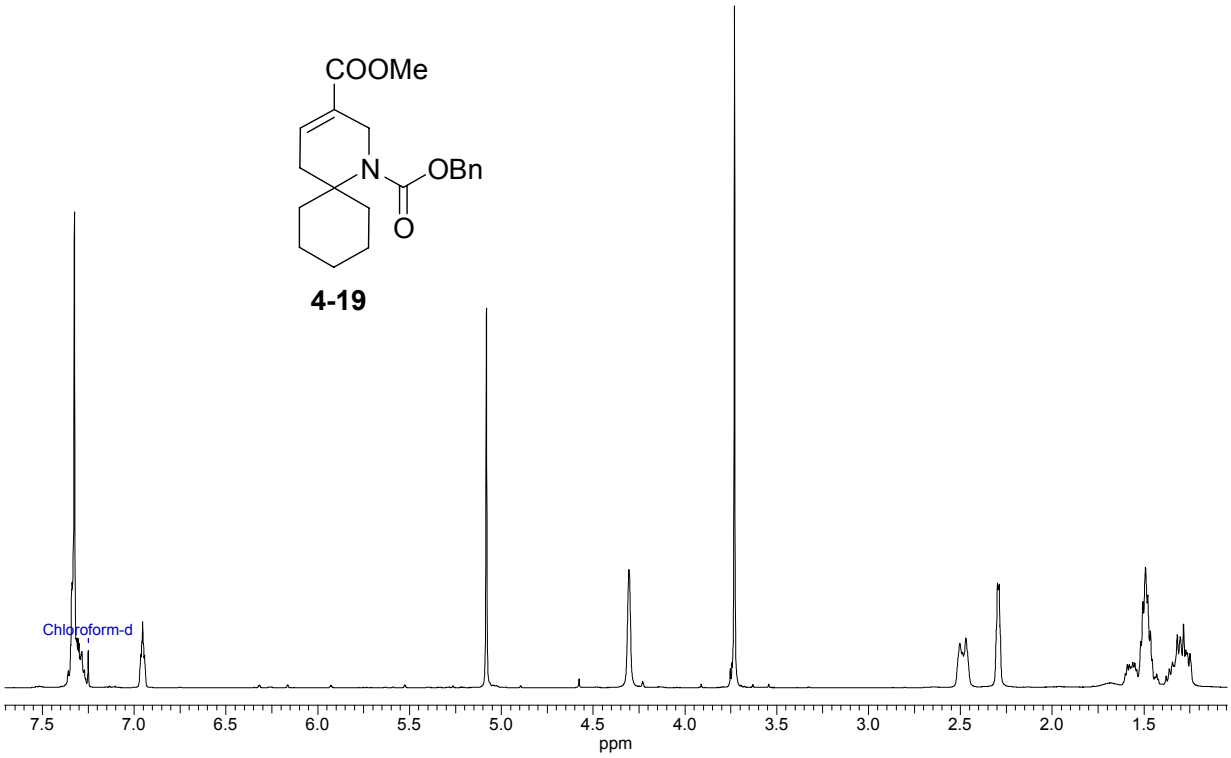

COOMe
N
OBn
O
N
CO2Et
4-15
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

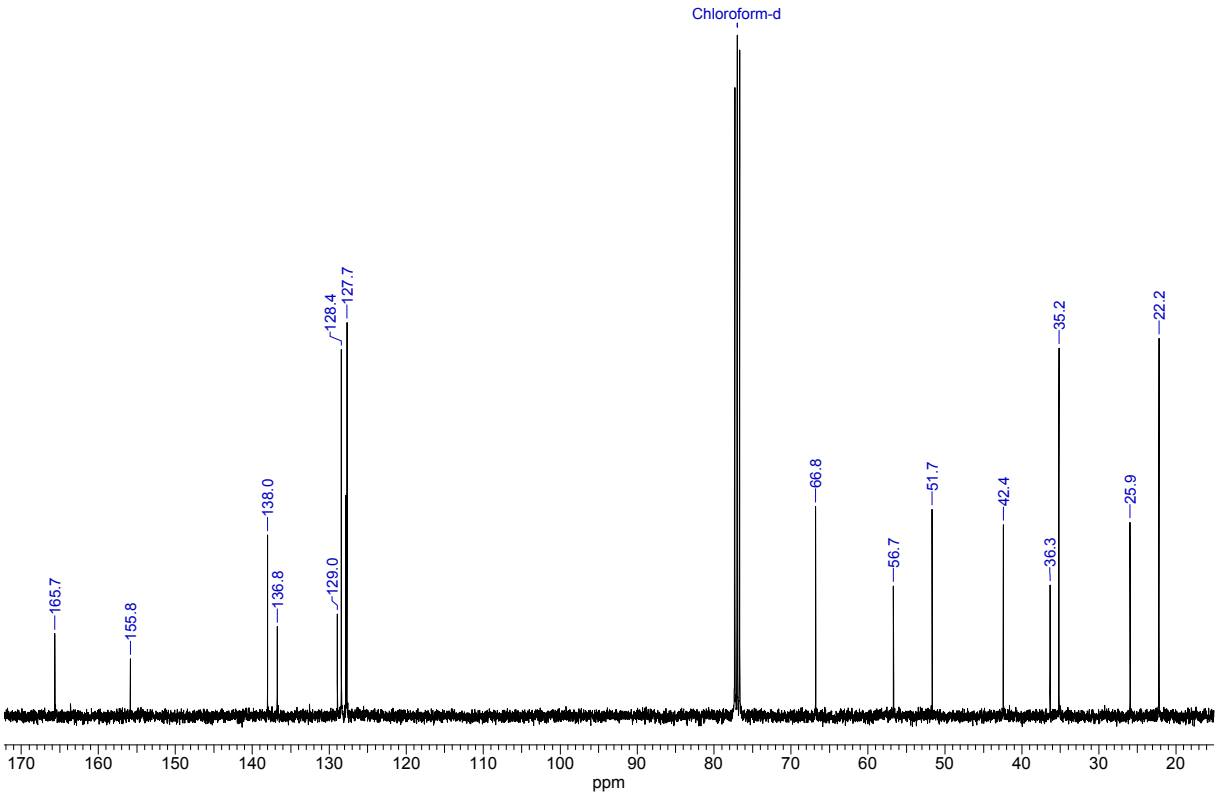

Chloroform-d
166.3
155.8
155.3
138.0
136.5
132.8
128.4
127.7
124.7
119.1
66.8
61.3
60.3
51.9
45.4
40.1
35.9
33.5
14.6
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

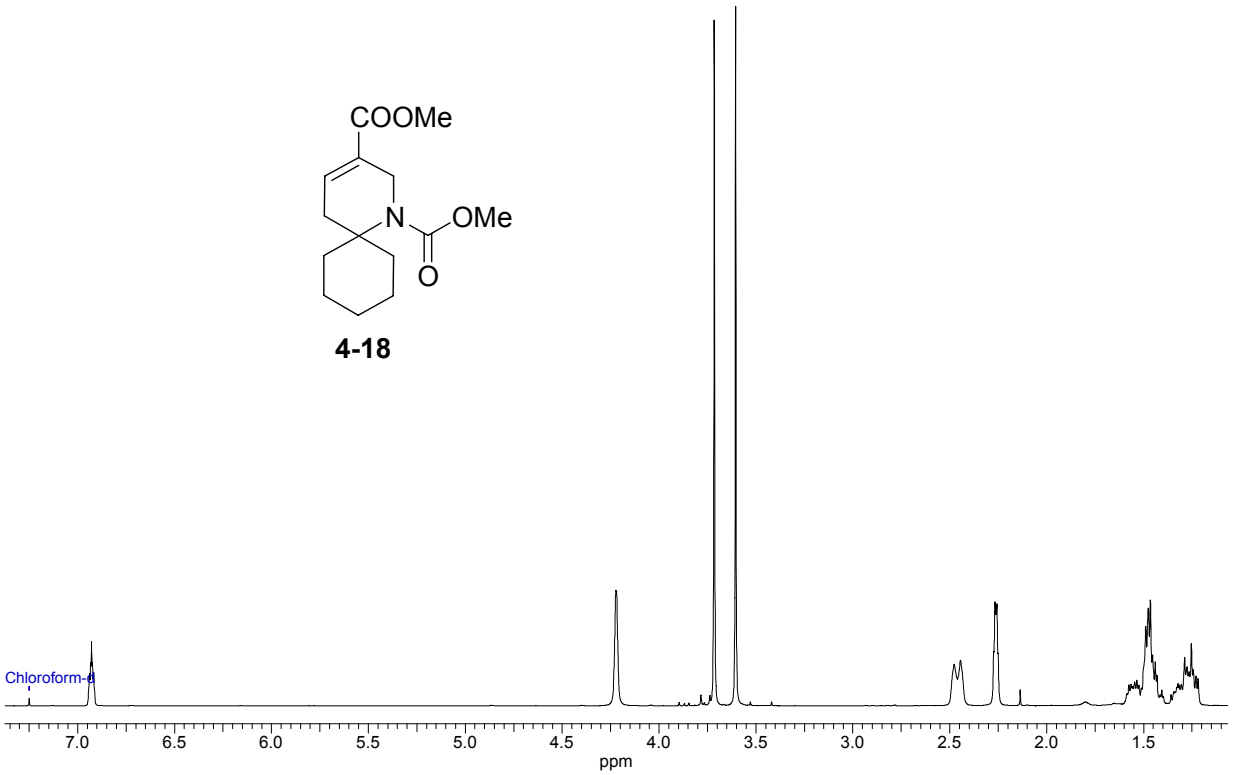

COOMe
N
OMe
O
N
CO2Bn
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

4-16

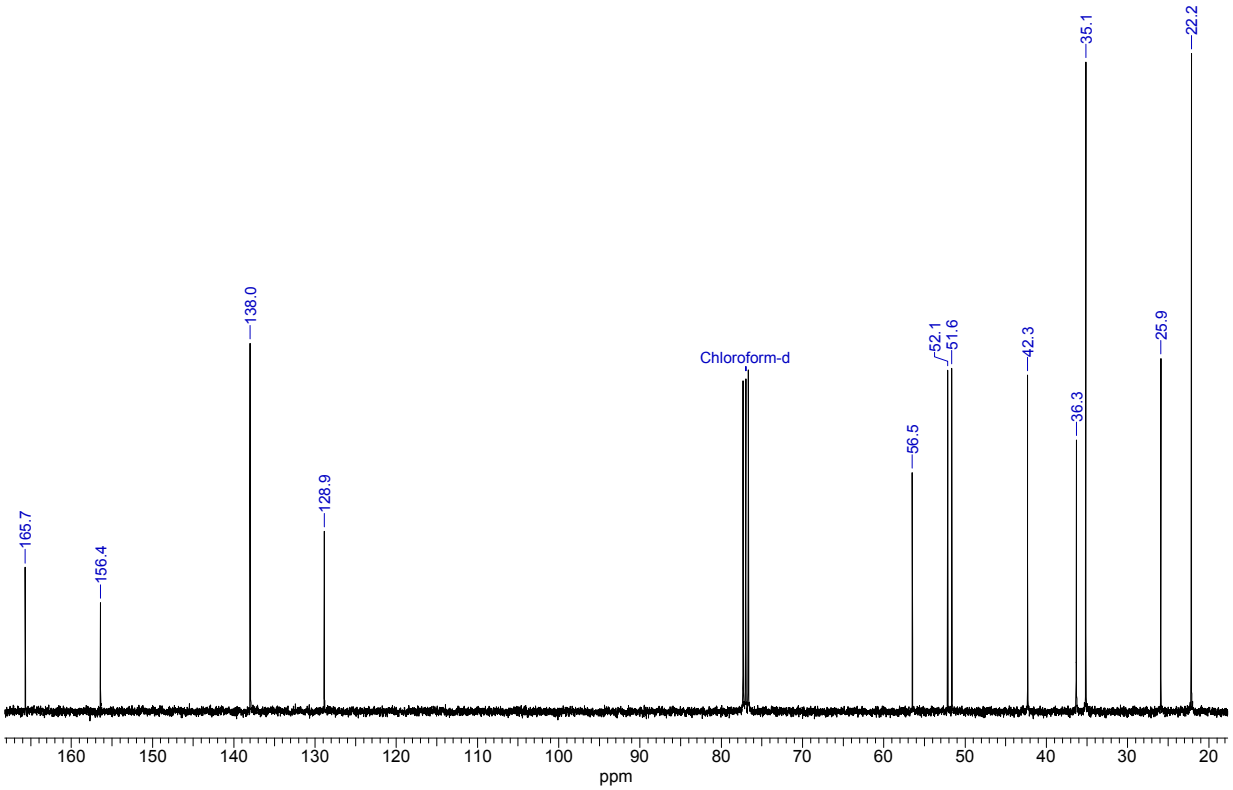

Chloroform-d
166.3
156.6
155.1
138.1
136.6
132.9
128.4
127.8
124.5
119.1
67.0
60.0
52.3
51.9
45.5
40.3
36.0
33.5
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

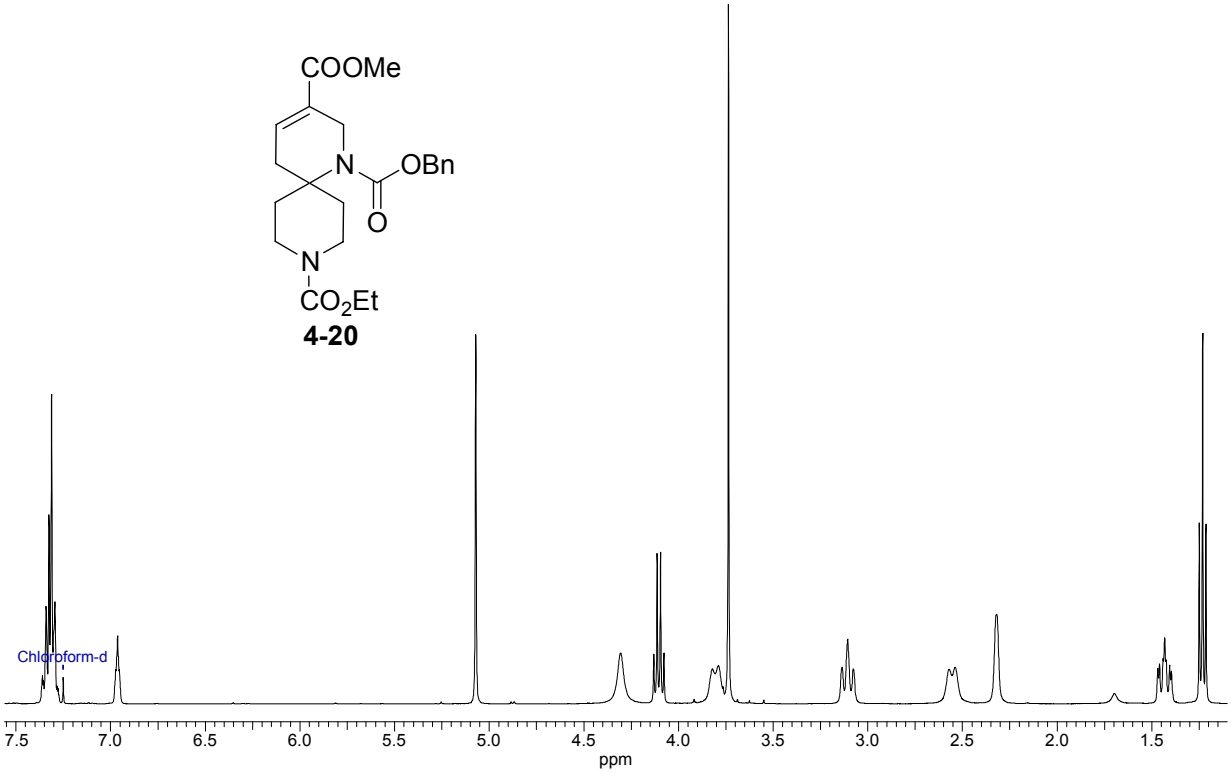

COOMe
N
OBn
O
4-19
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

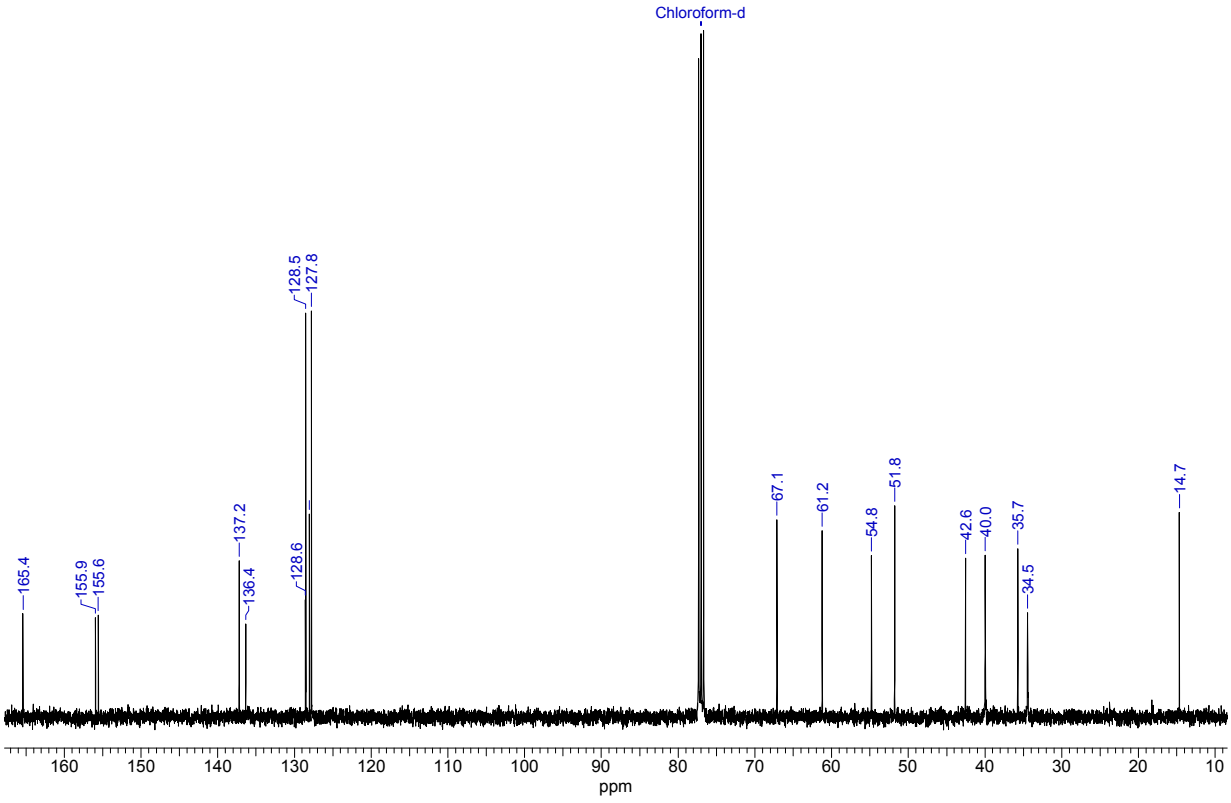

Chloroform-d
165.7
155.8
138.0
136.8
129.0
128.4
127.7
66.8
56.7
51.7
42.4
36.3
35.2
25.9
22.2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

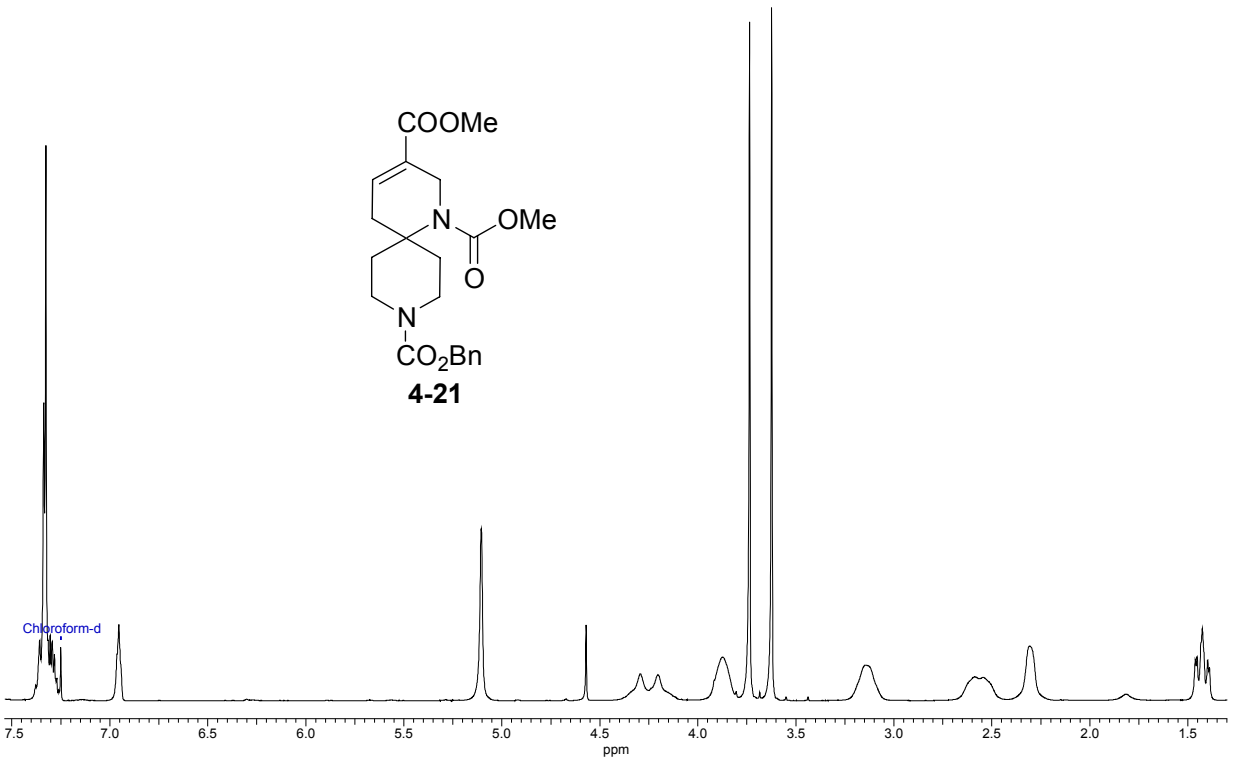

COOMe
N
OMe
O
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

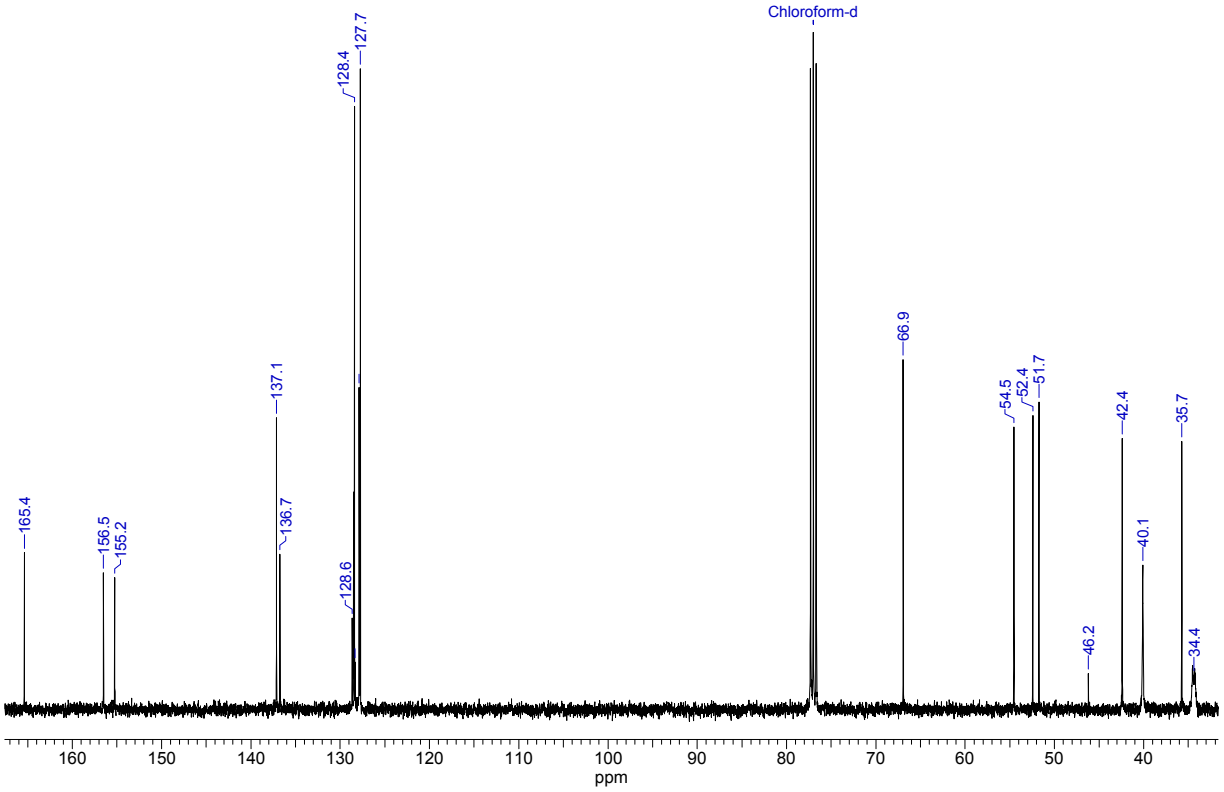
4-18

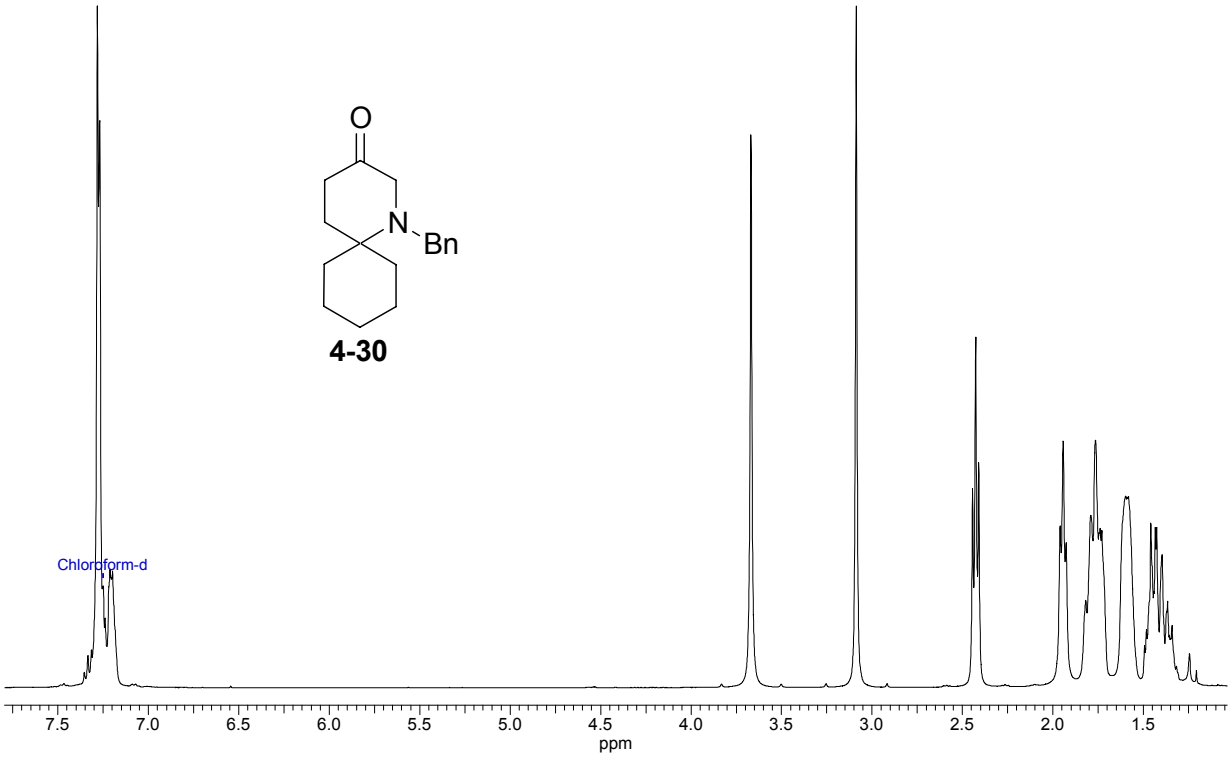

165.7
156.4
138.0
128.9
Chloroform-d
56.5
52.1
51.6
42.3
36.3
35.1
25.9
22.2
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

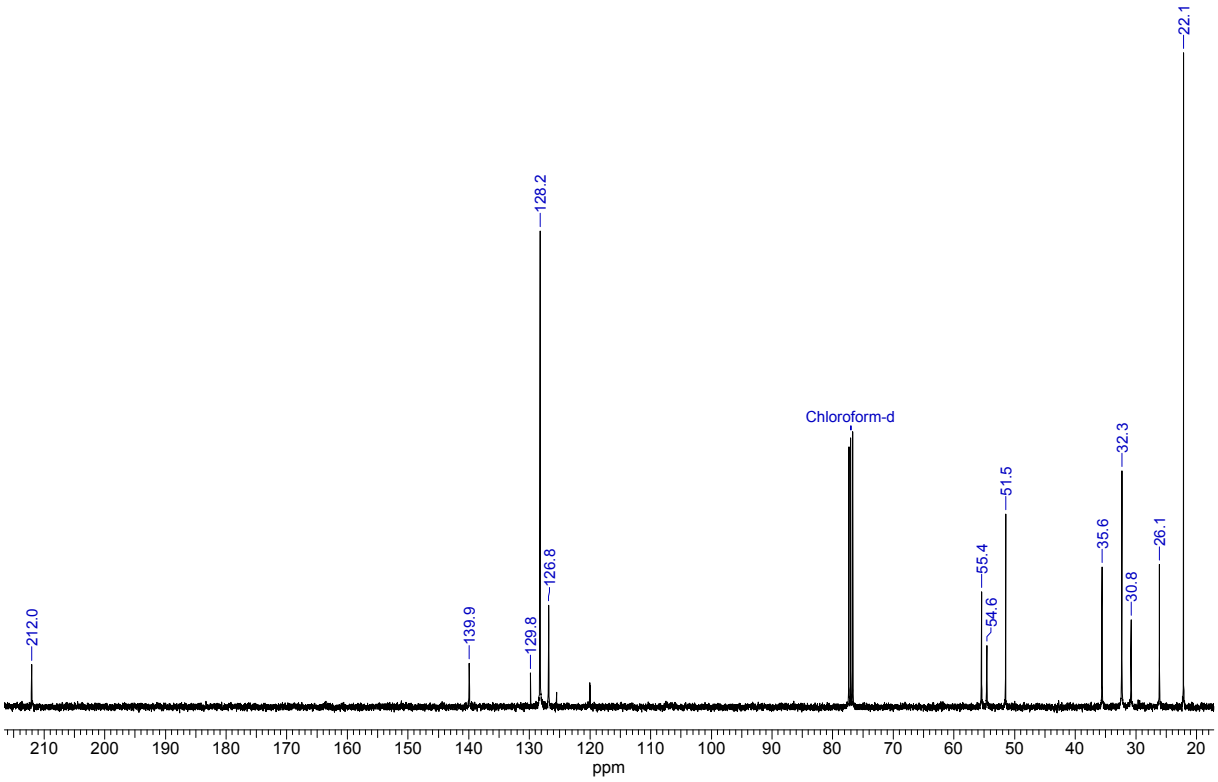

COOMe
N
OBn
O
N
CO2Et
4-20
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

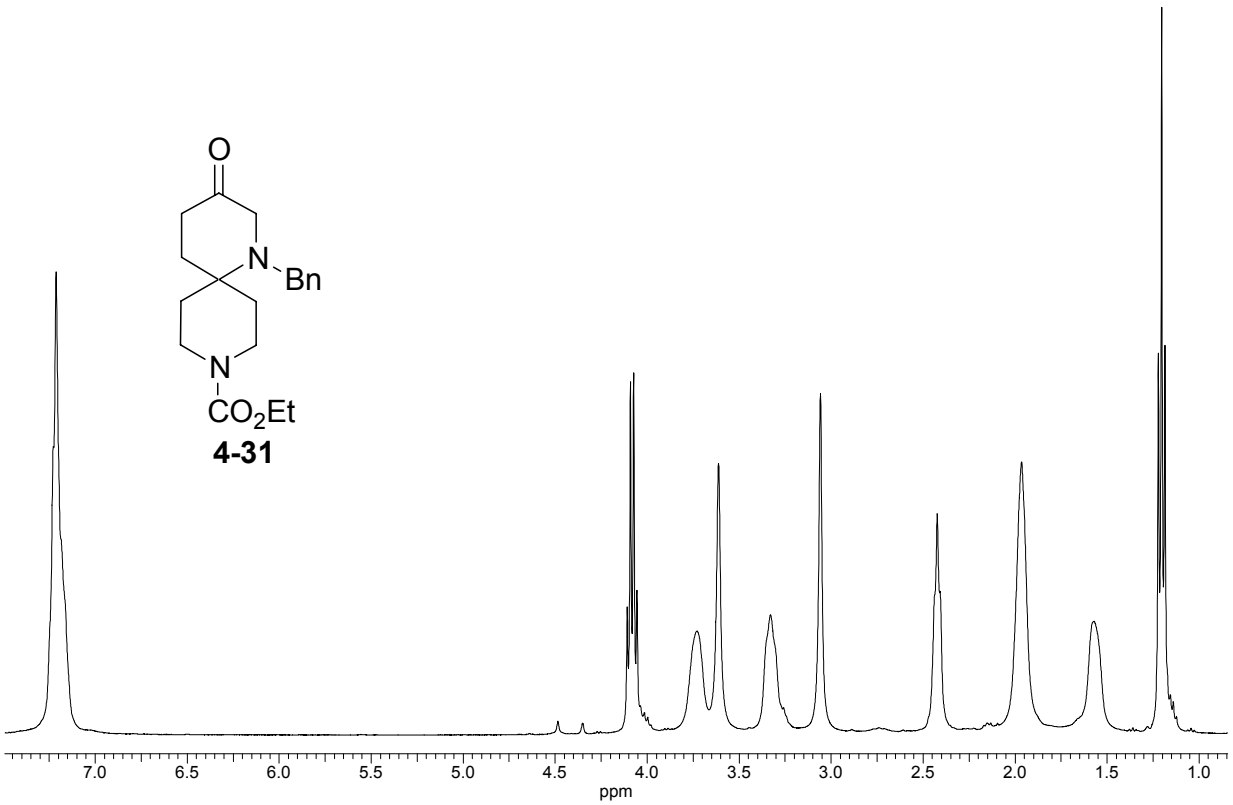

Chloroform-d
165.4
155.9
155.6
137.2
136.4
128.6
128.5
127.8
67.1
61.2
54.8
51.8
42.6
40.0
35.7
34.5
14.7
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

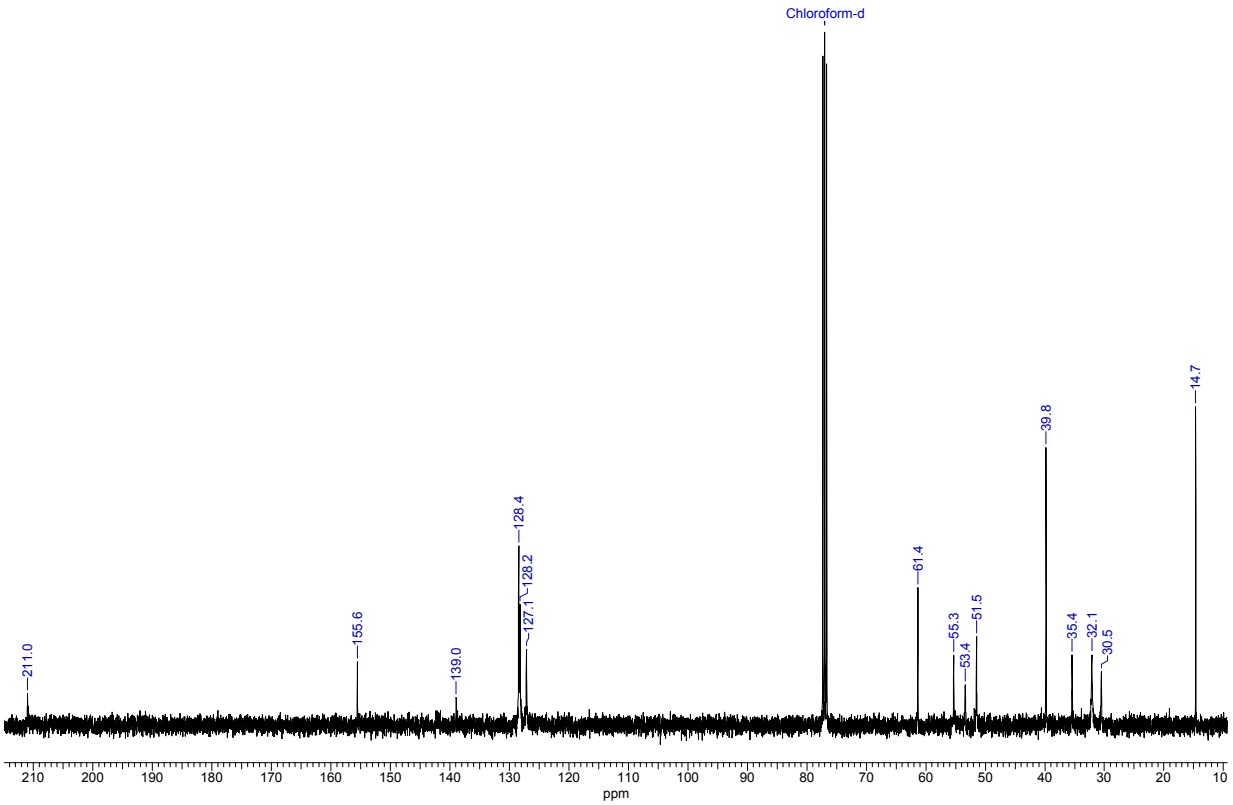

COOMe
N
OMe
O
N
CO2Bn
4-21
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

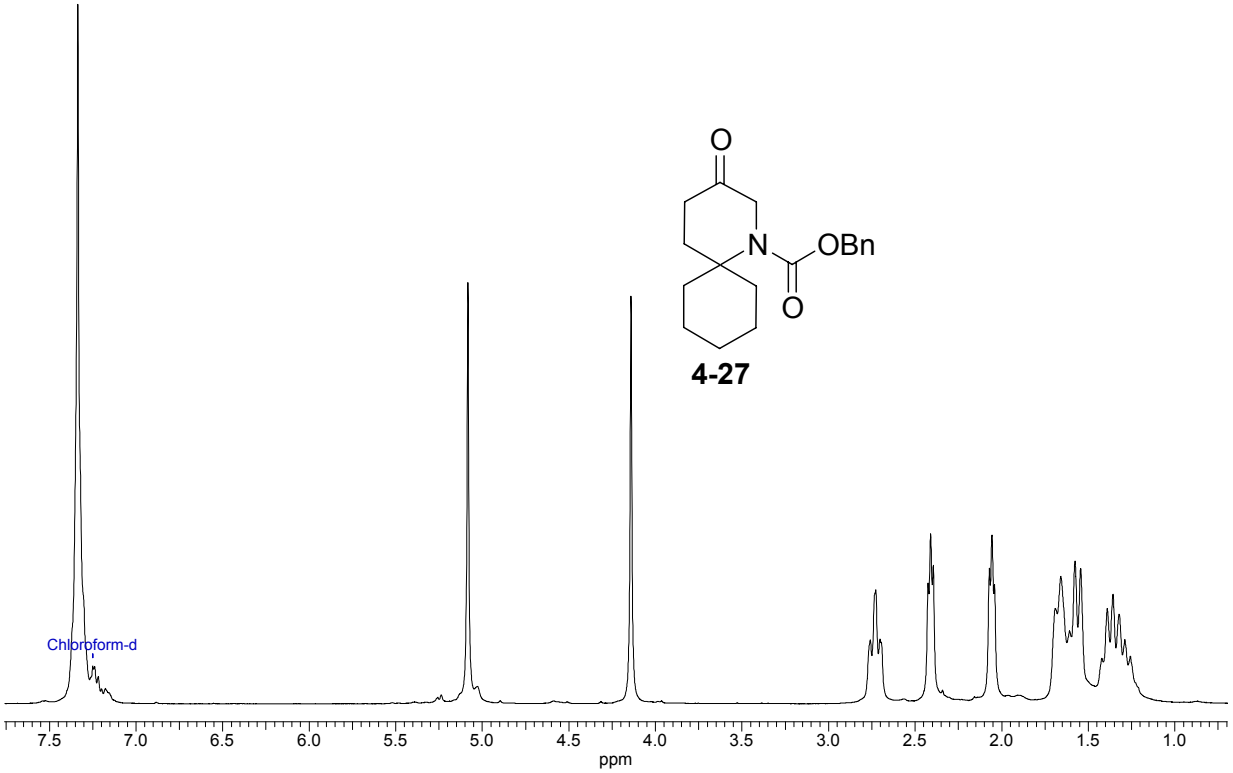

Chloroform-d
165.4
156.5
155.2
137.1
136.7
128.6
128.4
127.7
66.9
54.5
52.4
51.7
46.2
42.4
40.1
35.7
34.4
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

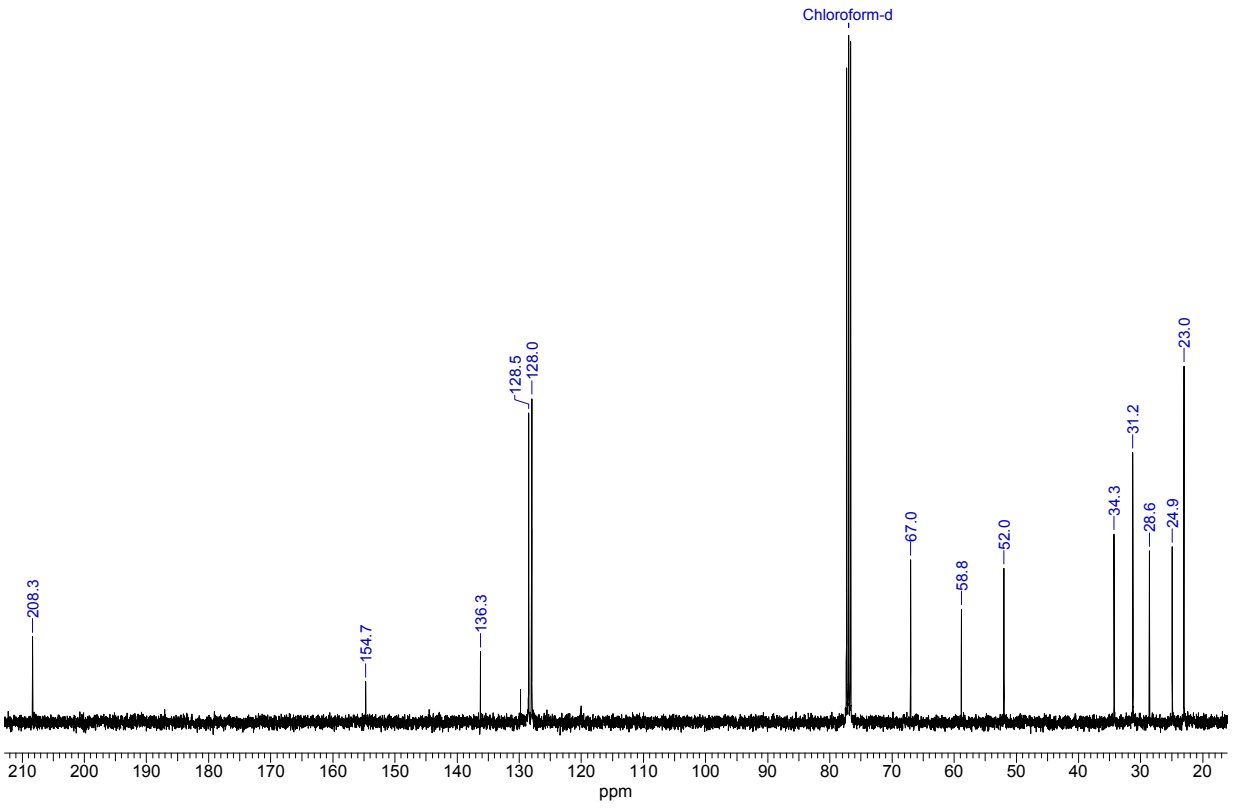

O
N
Bn
4-30
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

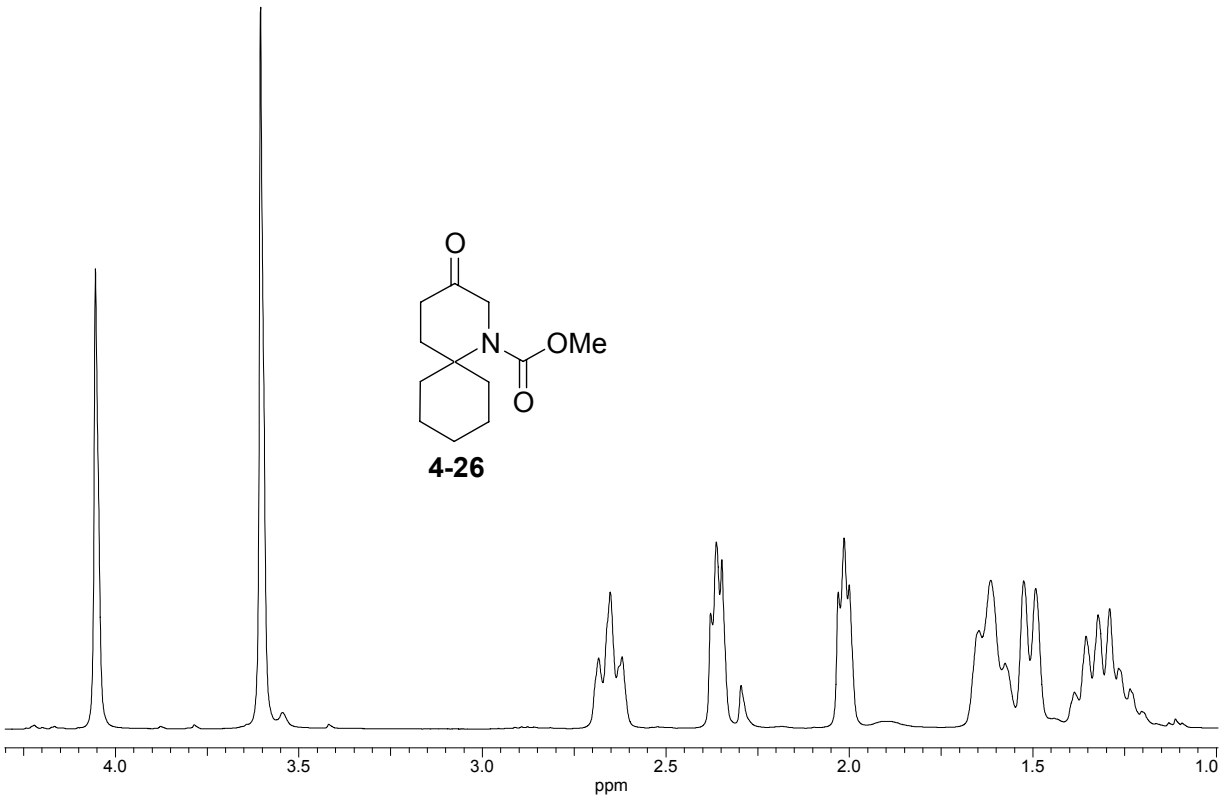

212.0
139.9
129.8
128.2
126.8
Chloroform-d
55.4
54.6
51.5
35.6
32.3
30.8
26.1
22.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

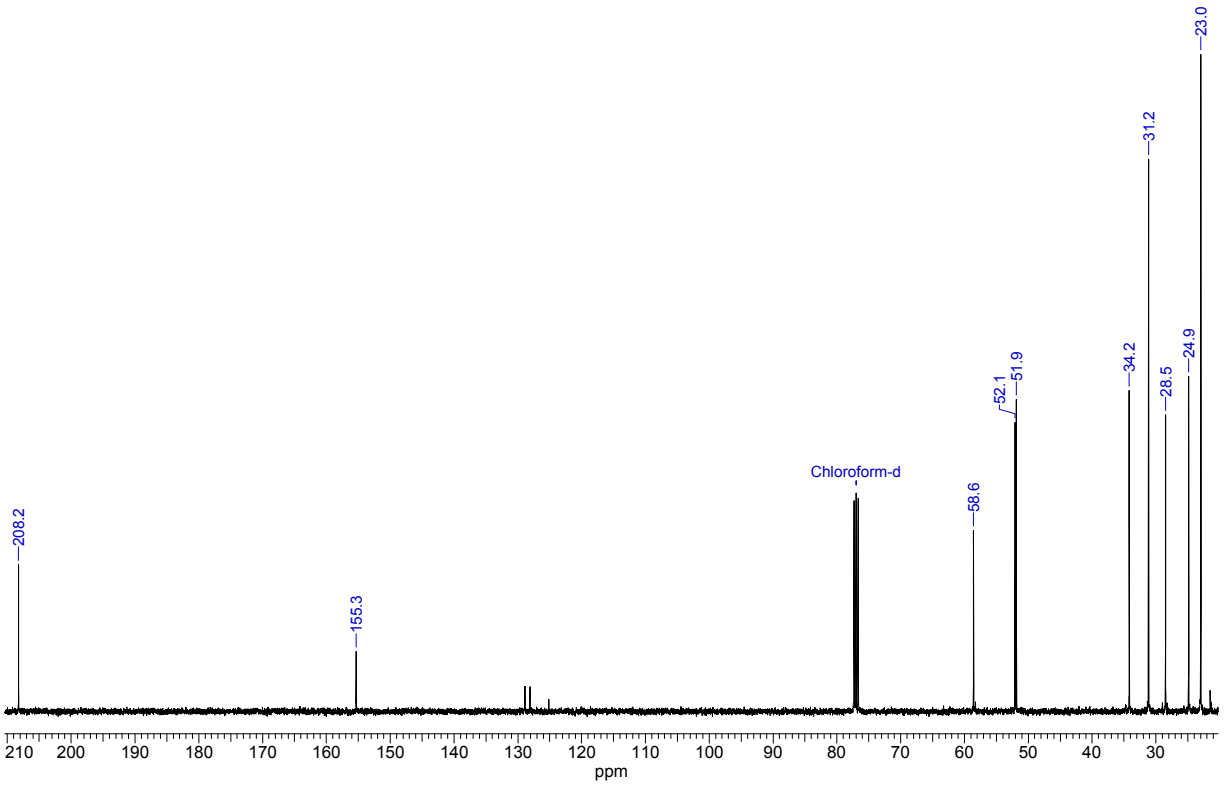

O
N
Bn
N
CO2Et
4-31
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

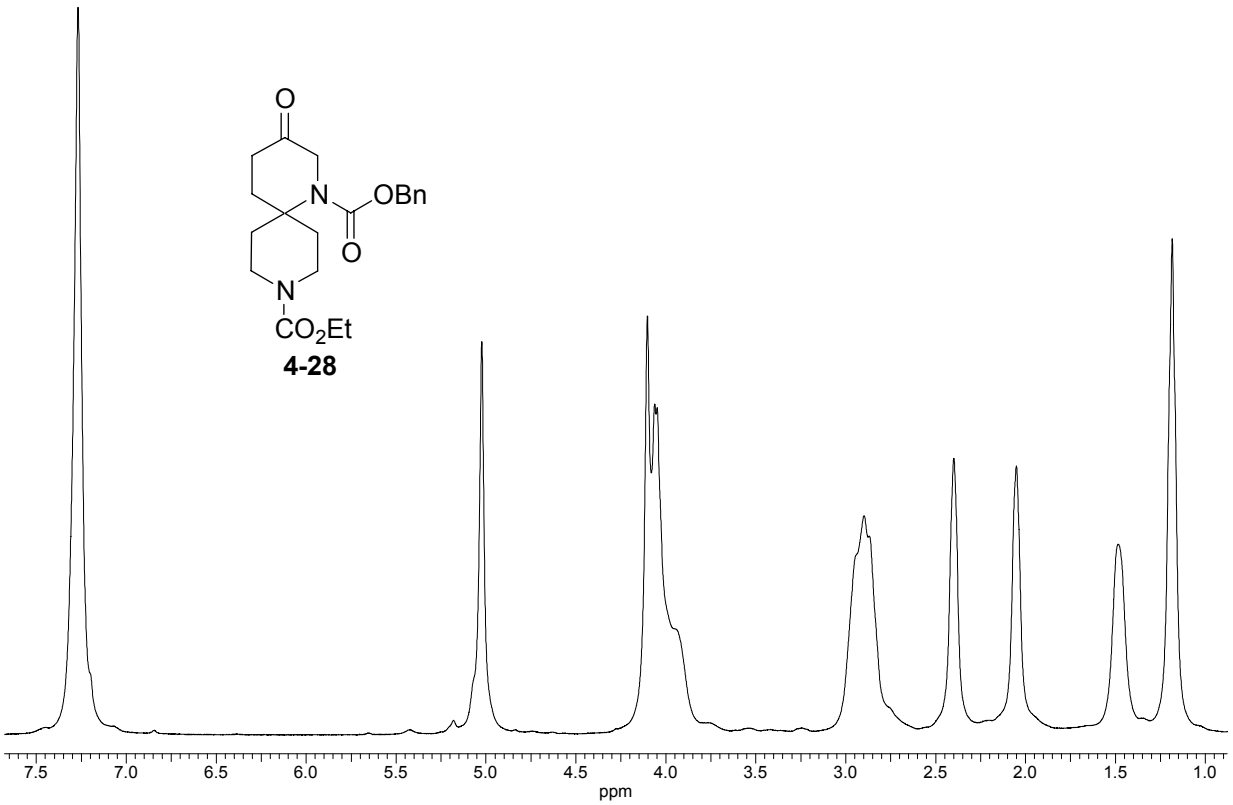

Chloroform-d
211.0
155.6
139.0
128.4
128.2
127.1
61.4
55.3
53.4
51.5
39.8
35.4
32.1
30.5
14.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

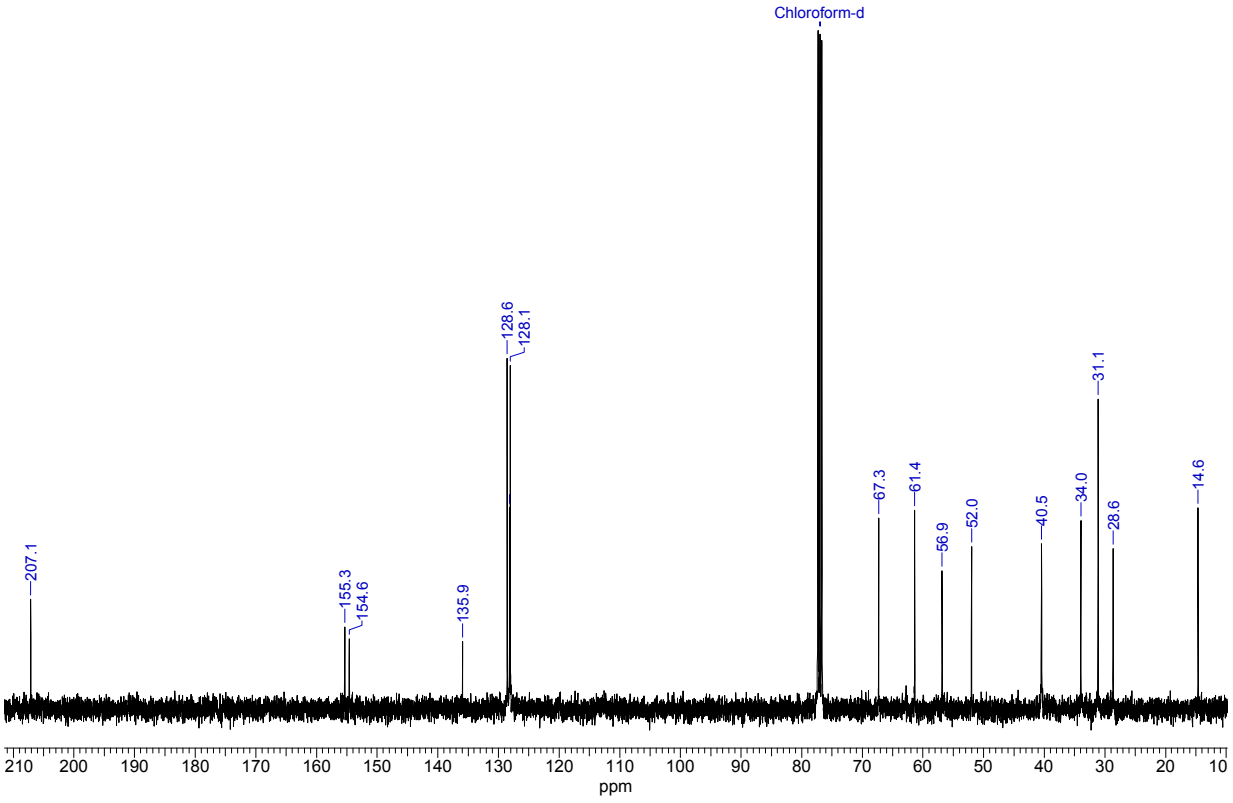

O
N
OBn
O
4-27
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

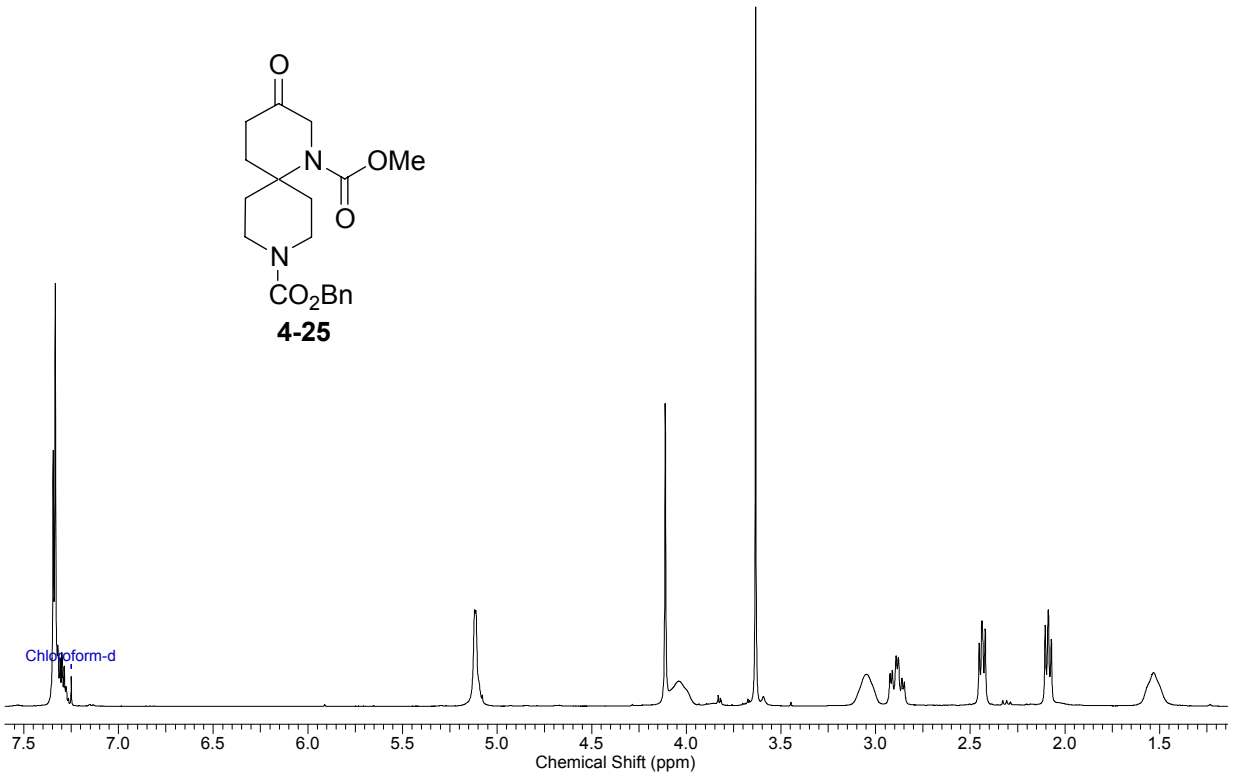

Chloroform-d
208.3
154.7
136.3
128.5
128.0
67.0
58.8
52.0
34.3
31.2
28.6
24.9
23.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

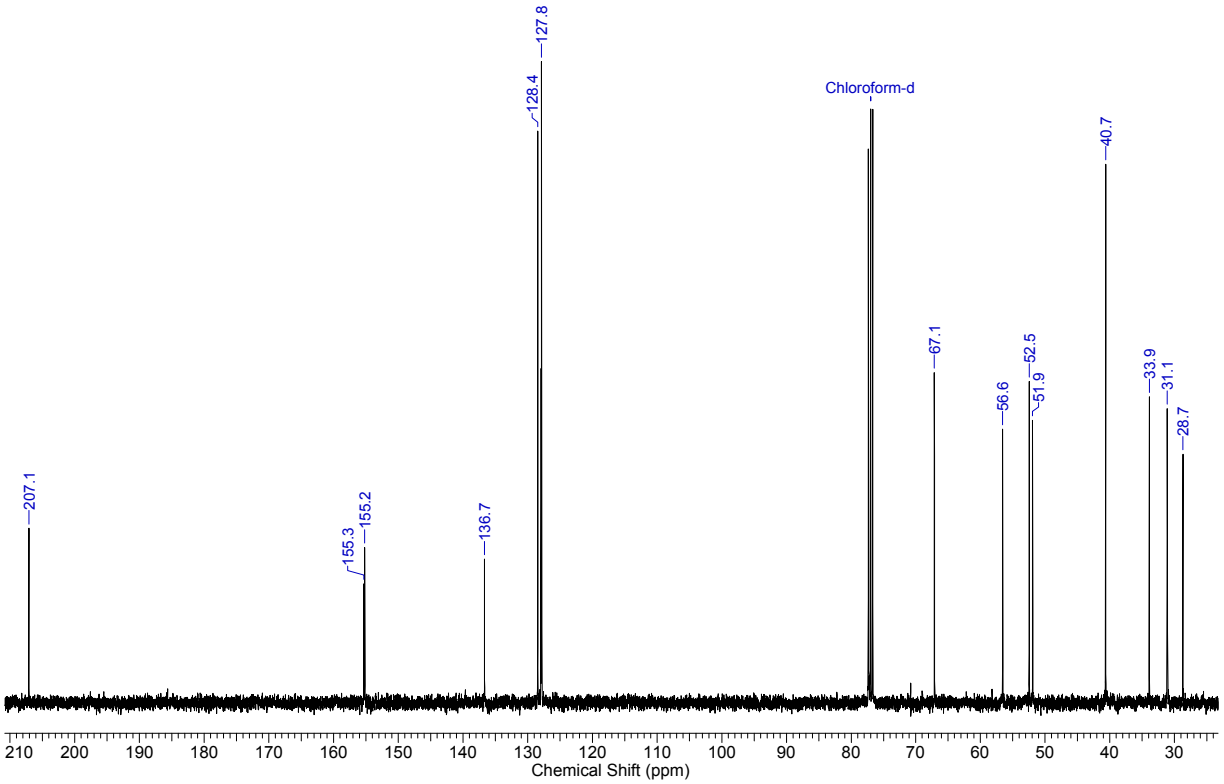

O
N
OMe
O
4-26
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

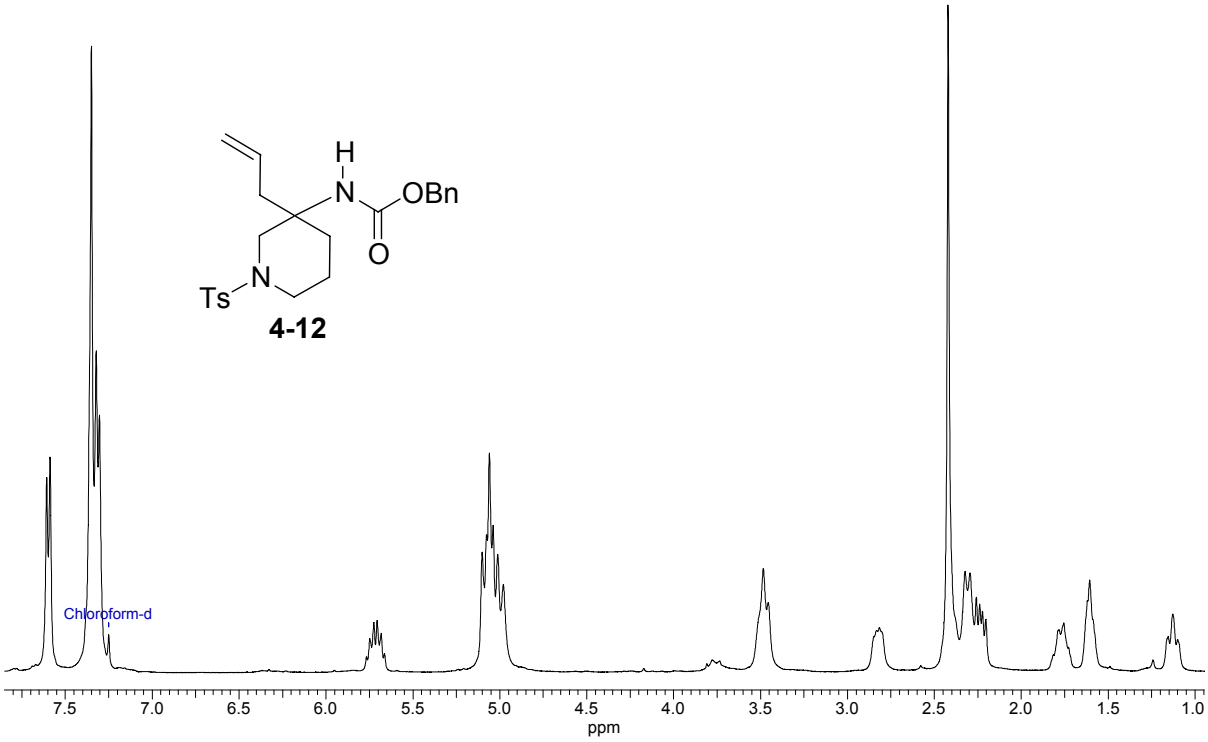

208.2
155.3
Chloroform-d
58.6
52.1
51.9
34.2
31.2
28.5
24.9
23.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

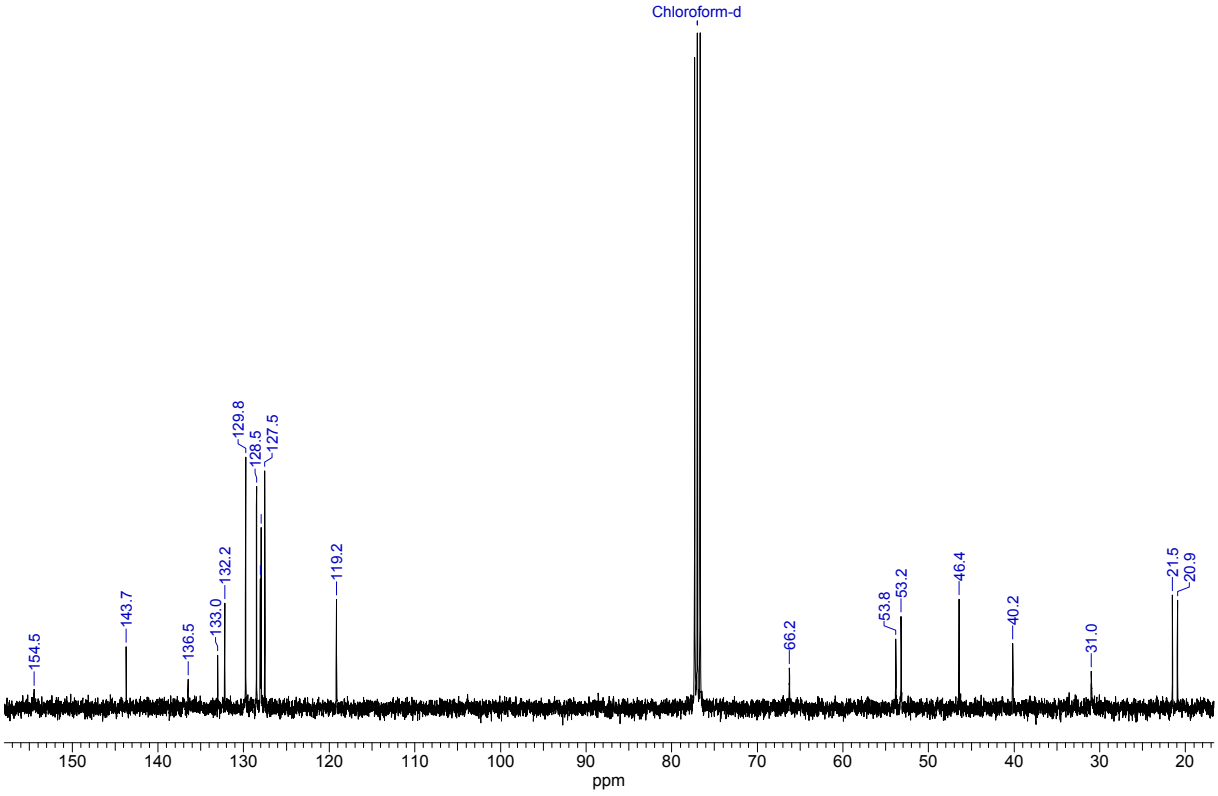

O
N
OBn
O
N
CO2Et
4-28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

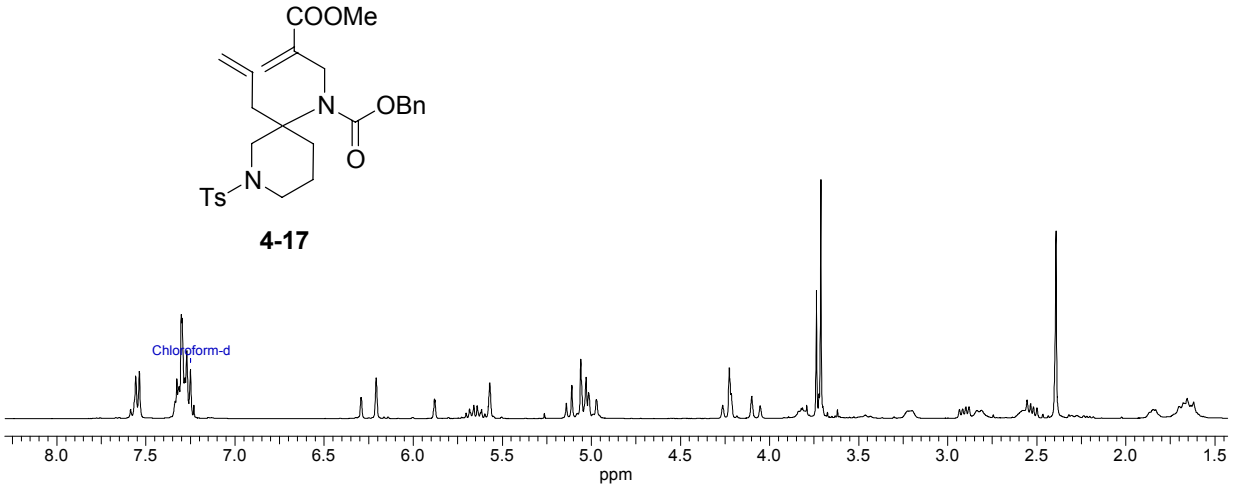

Chloroform-d
207.1
155.3
154.6
135.9
128.6
128.1
67.3
61.4
56.9
52.0
40.5
34.0
31.1
28.6
14.6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
N
OMe
O
N
CO2Bn
4-25
Chloroform-d
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
Chemical Shift (ppm)

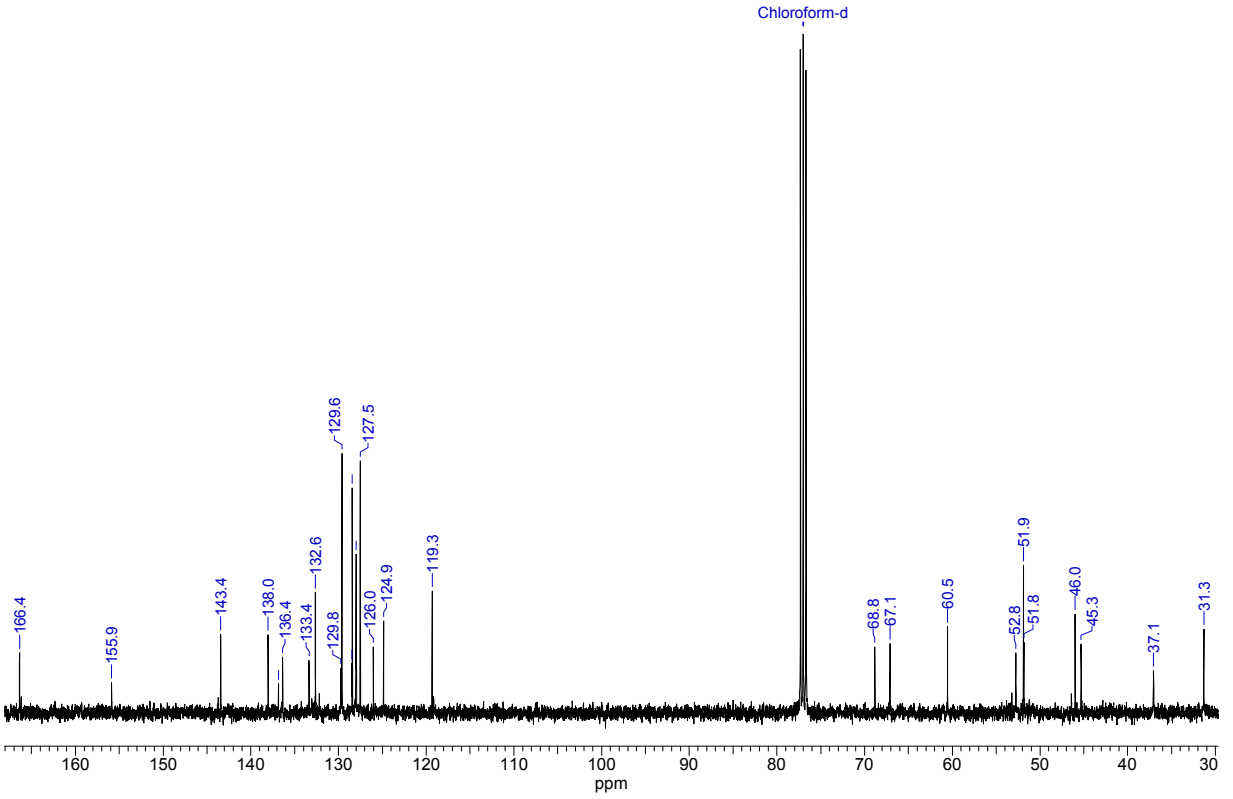

207.1
155.3
155.2
136.7
128.4
127.8
Chloroform-d
67.1
56.6
52.5
51.9
40.7
33.9
31.1
28.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

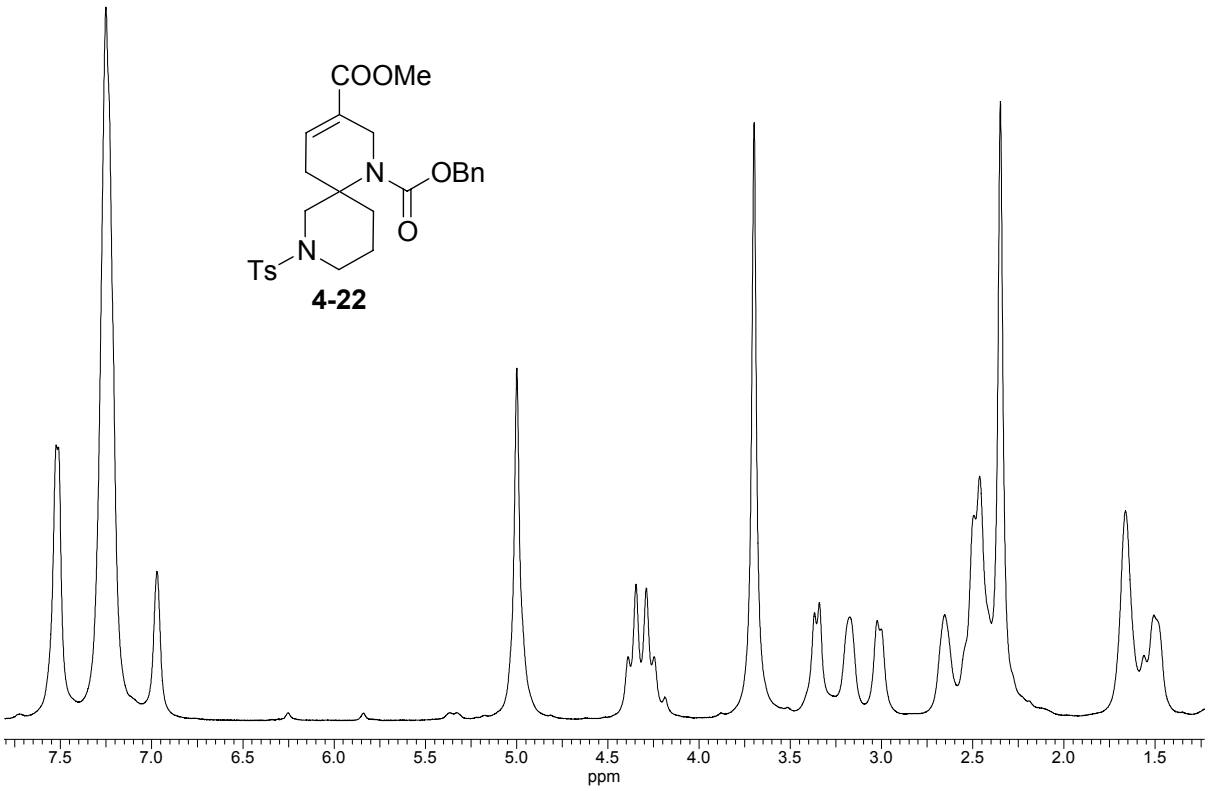

H
N
OBn
O
N
Ts
4-12
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

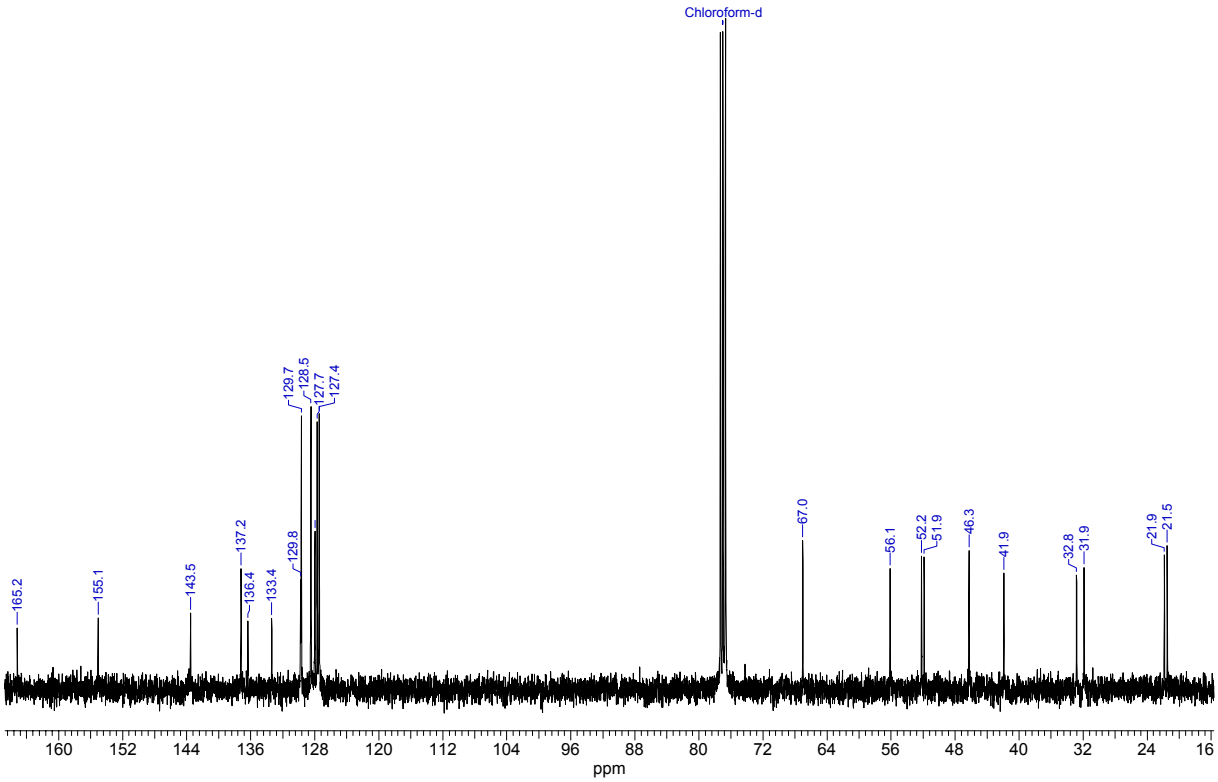

Chloroform-d
154.5
143.7
136.5
133.0
132.2
129.8
128.5
127.5
119.2
66.2
53.8
53.2
46.4
40.2
31.0
21.5
20.9
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

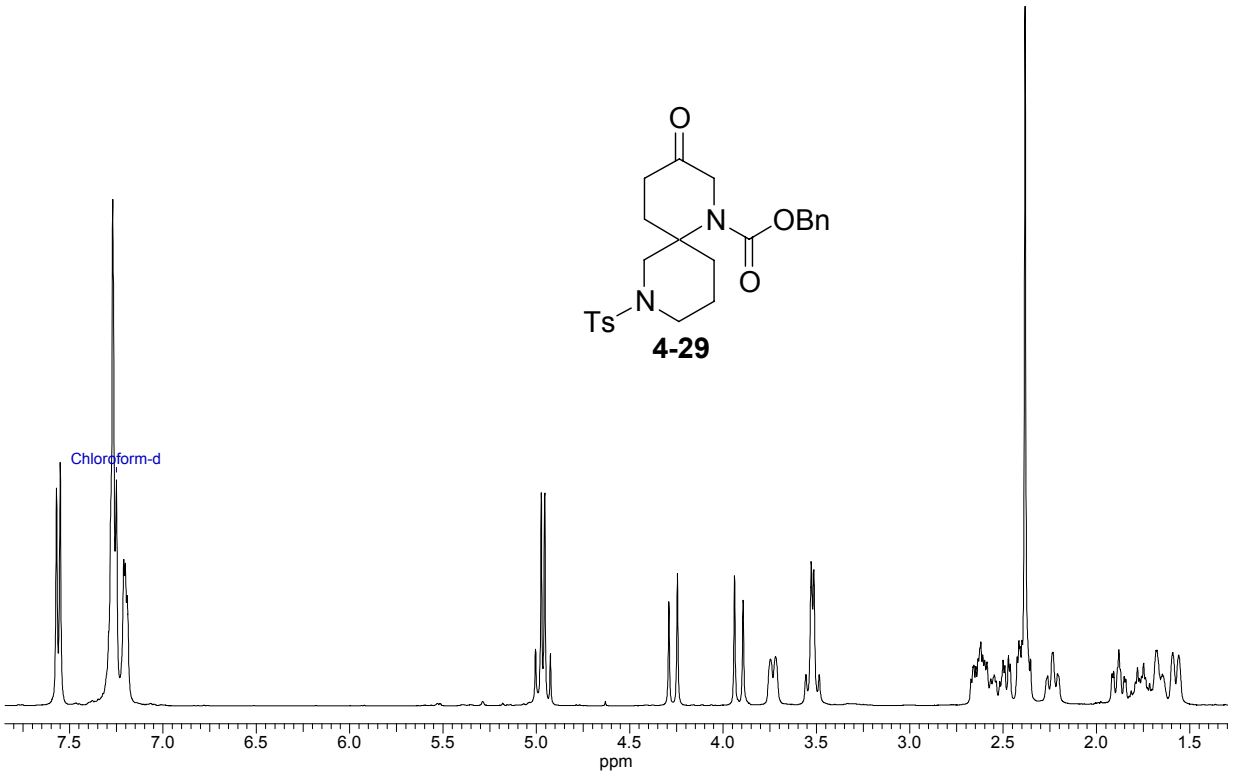

COOMe
N
OBn
O
N
Ts
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

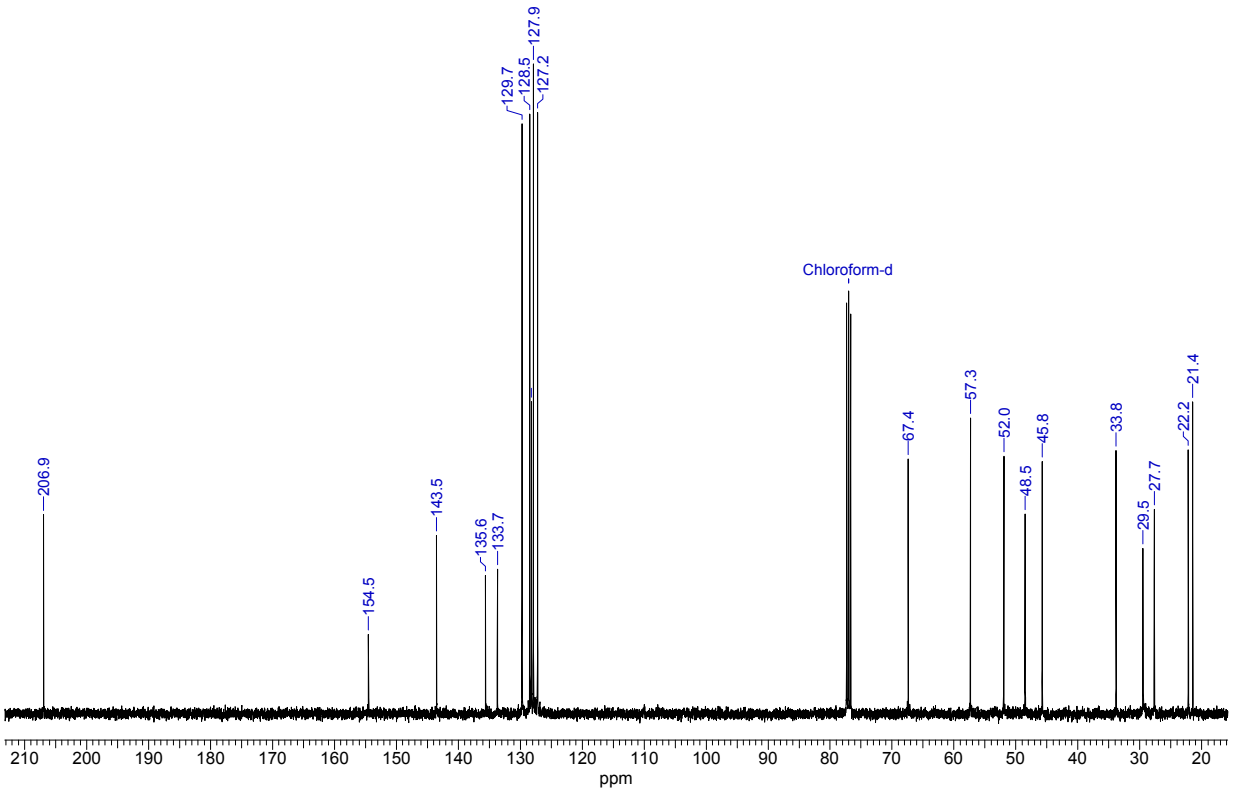
4-17

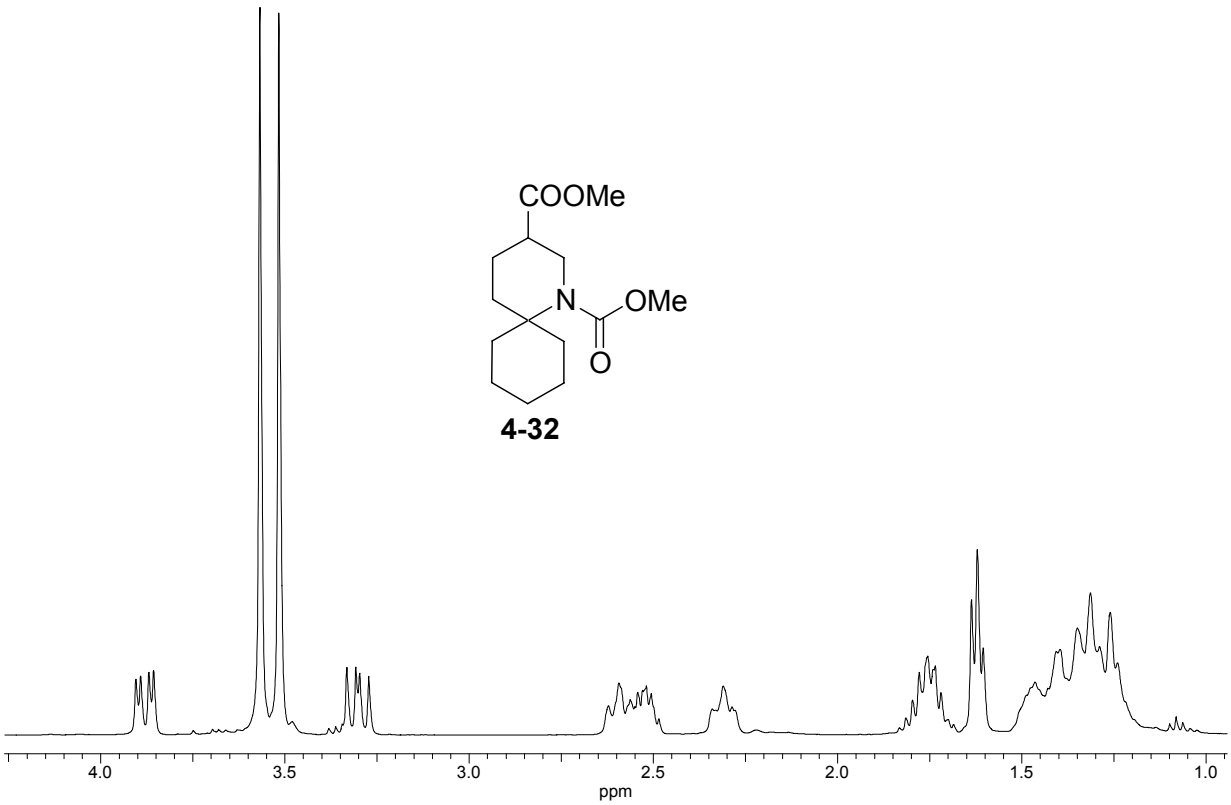

Chloroform-d
166.4
155.9
143.4
138.0
136.4
133.4
132.6
129.8
129.6
127.5
126.0
124.9
119.3
68.8
67.1
60.5
52.8
51.9
51.8
46.0
45.3
37.1
31.3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

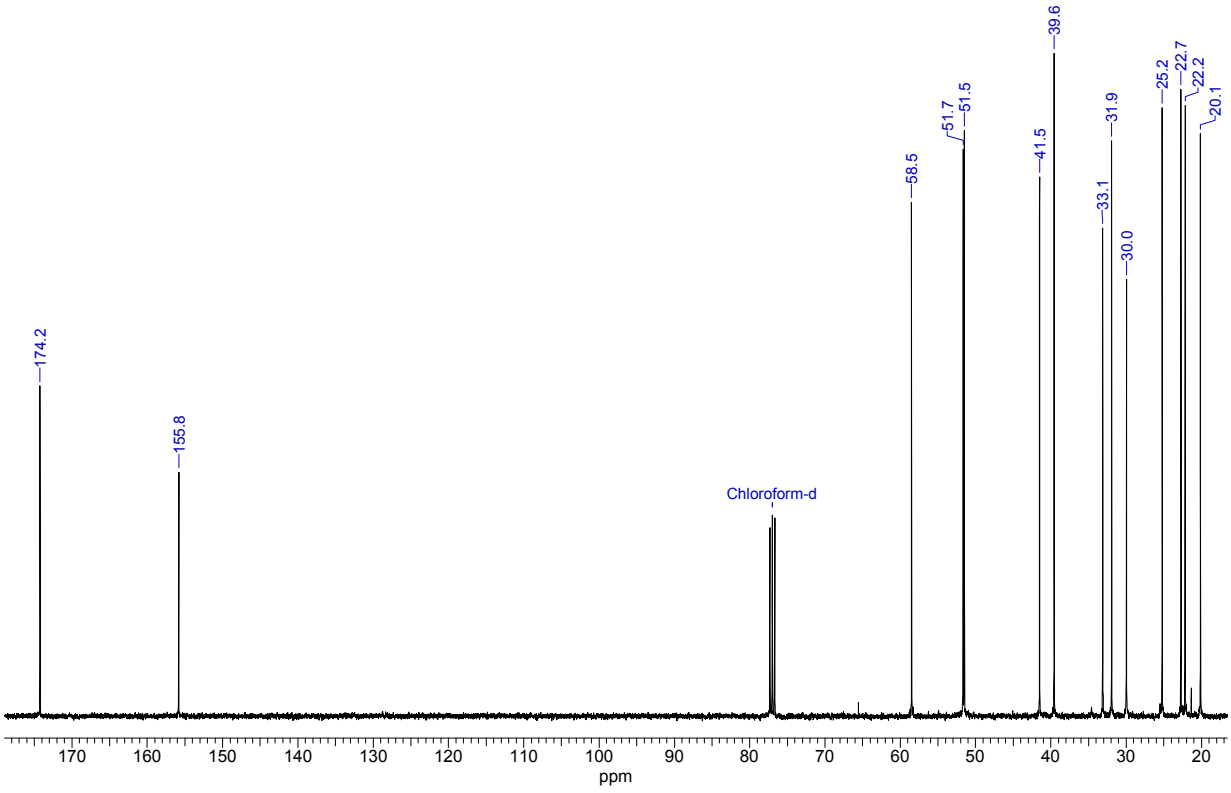

COOMe
N
OBn
O
N
Ts
4-22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

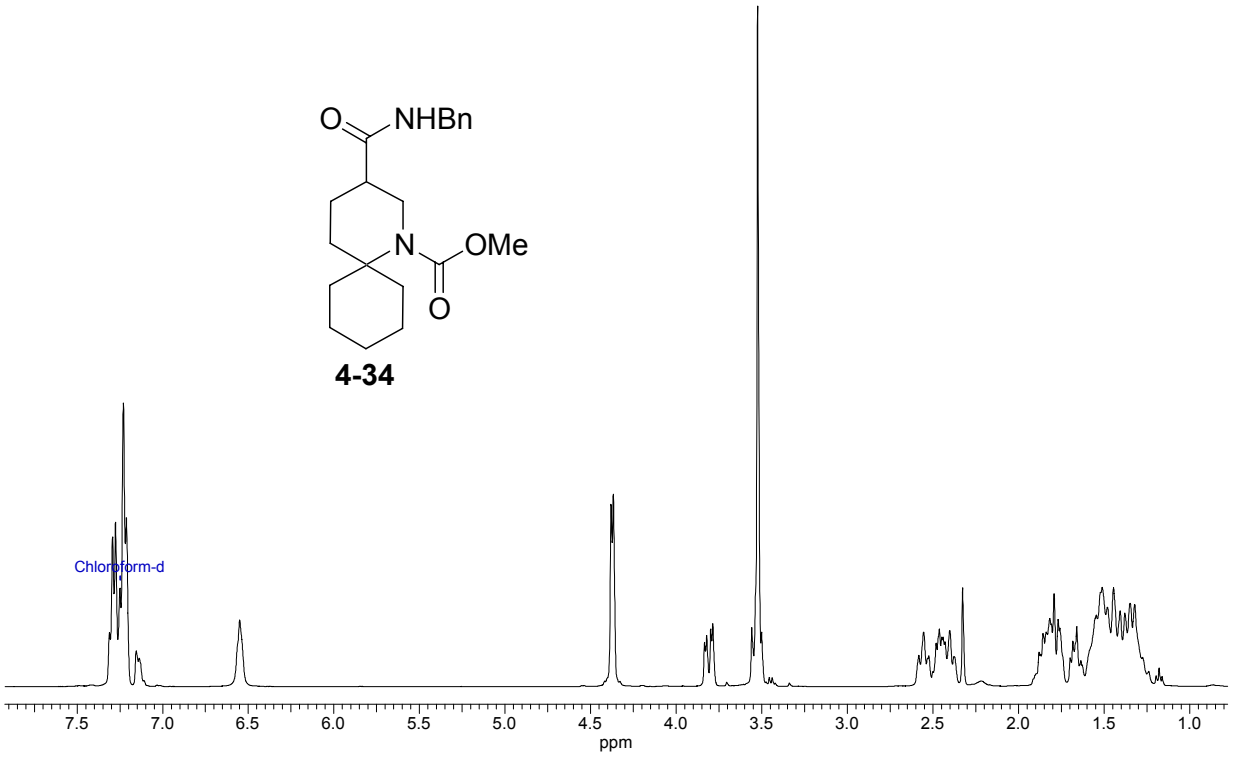

Chloroform-d
165.2
155.1
143.5
137.2
136.4
133.4
129.8
129.7
128.5
127.7
127.4
67.0
56.1
52.2
51.9
46.3
41.9
32.8
31.9
21.9
21.5
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm


O
N
OBn
O
Ts
N
4-29
Chloroform-d
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

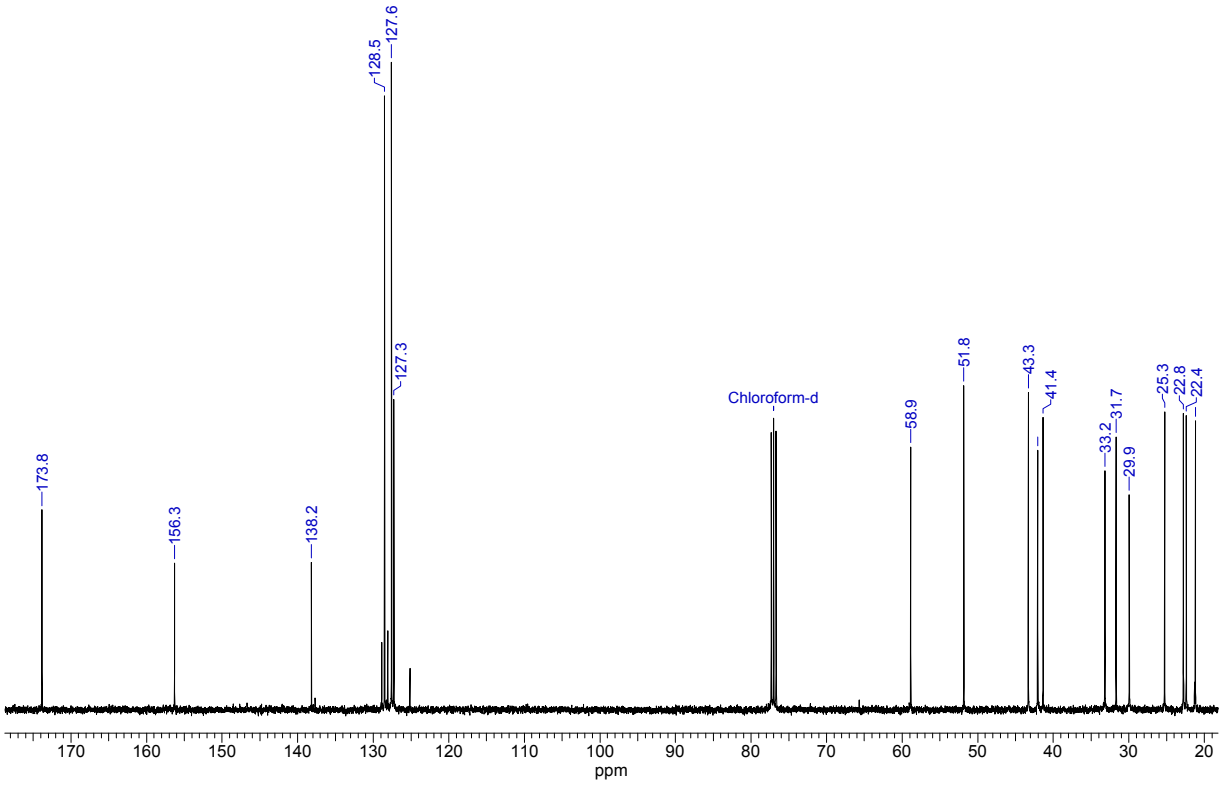

206.9
154.5
143.5
135.6
133.7
129.7
128.5
127.9
127.2
Chloroform-d
67.4
57.3
52.0
48.5
45.8
33.8
29.5
27.7
22.2
21.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

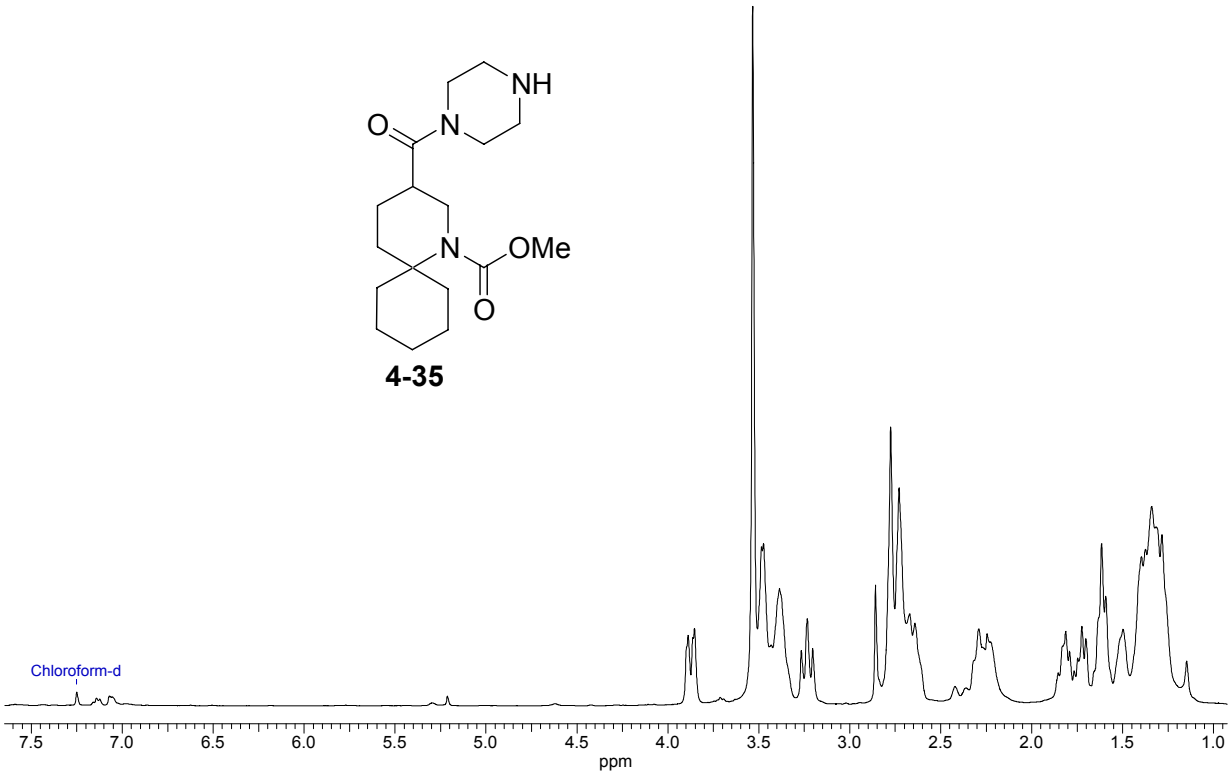

COOMe
N
OMe
O
4-32
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


174.2
155.8
Chloroform-d
58.5
51.7
51.5
41.5
39.6
33.1
31.9
30.0
25.2
22.7
22.2
20.1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

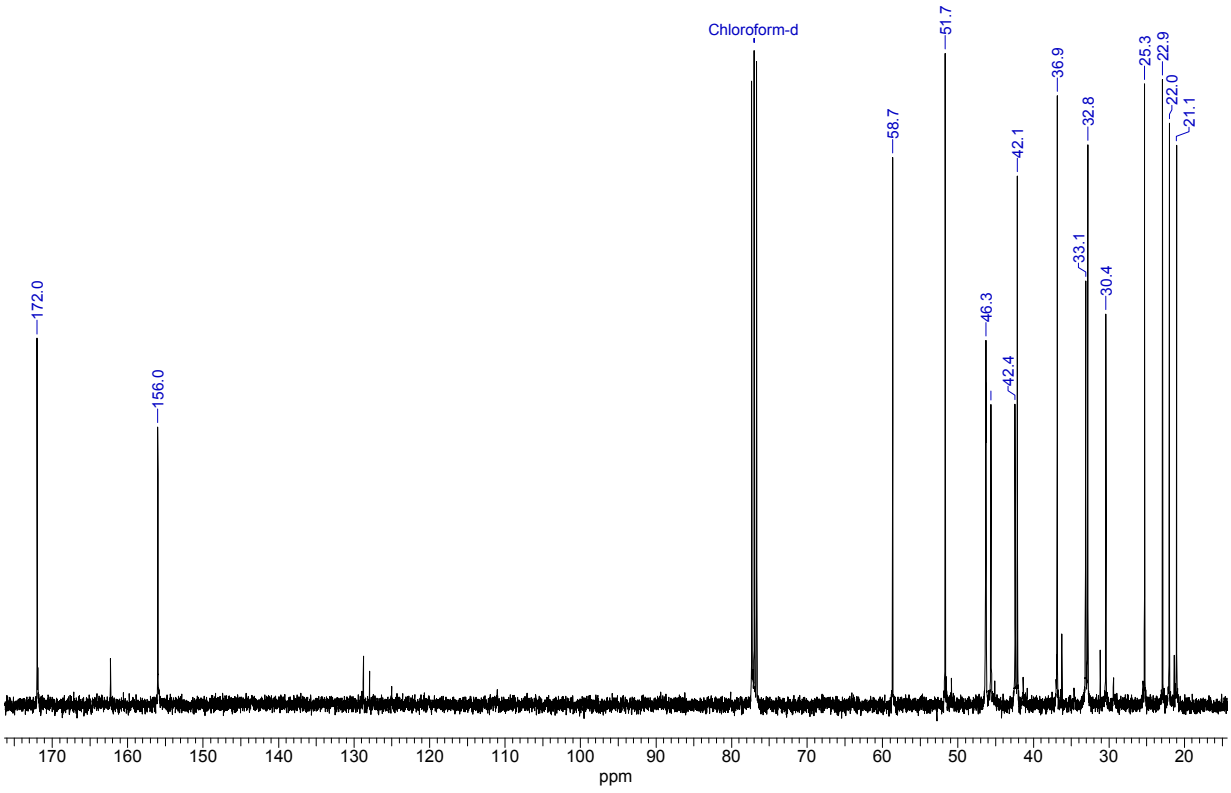

O
NHBn
N
OMe
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

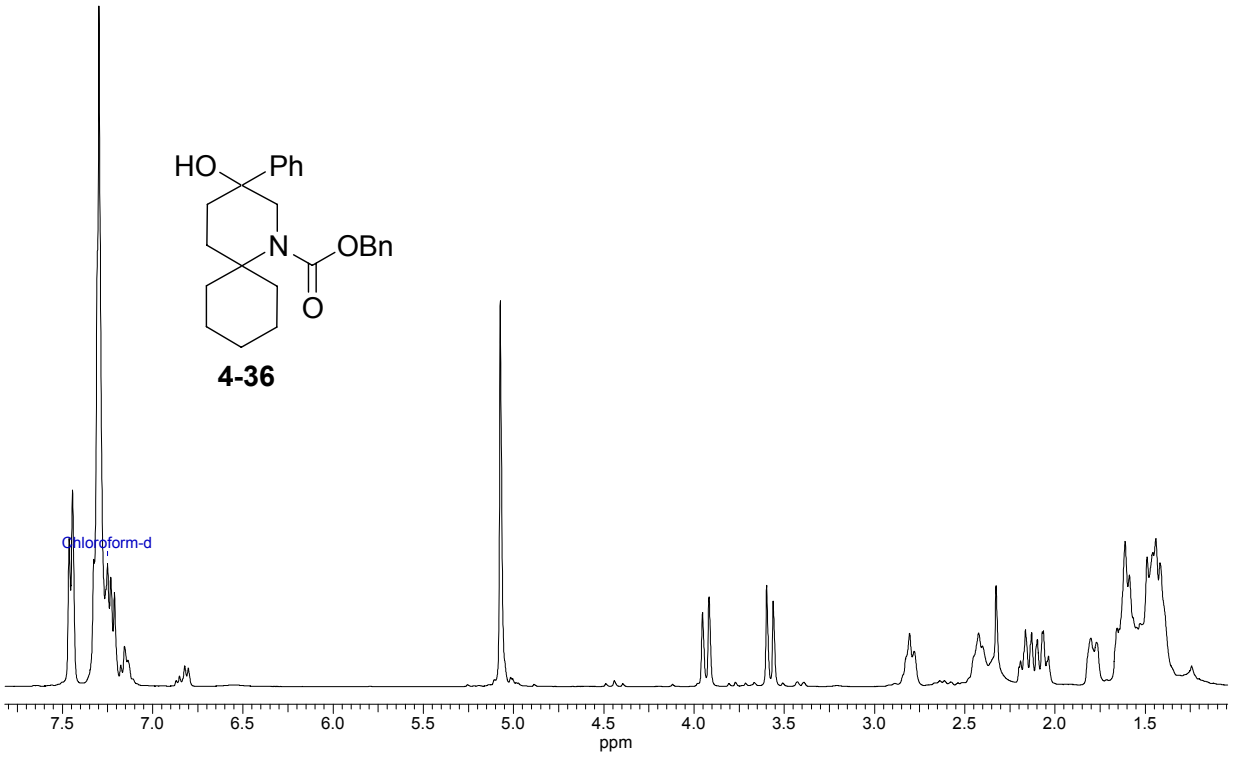
4-34


173.8
156.3
138.2
128.5
127.6
127.3
Chloroform-d
58.9
51.8
43.3
41.4
33.2
31.7
29.9
25.3
22.8
22.4
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

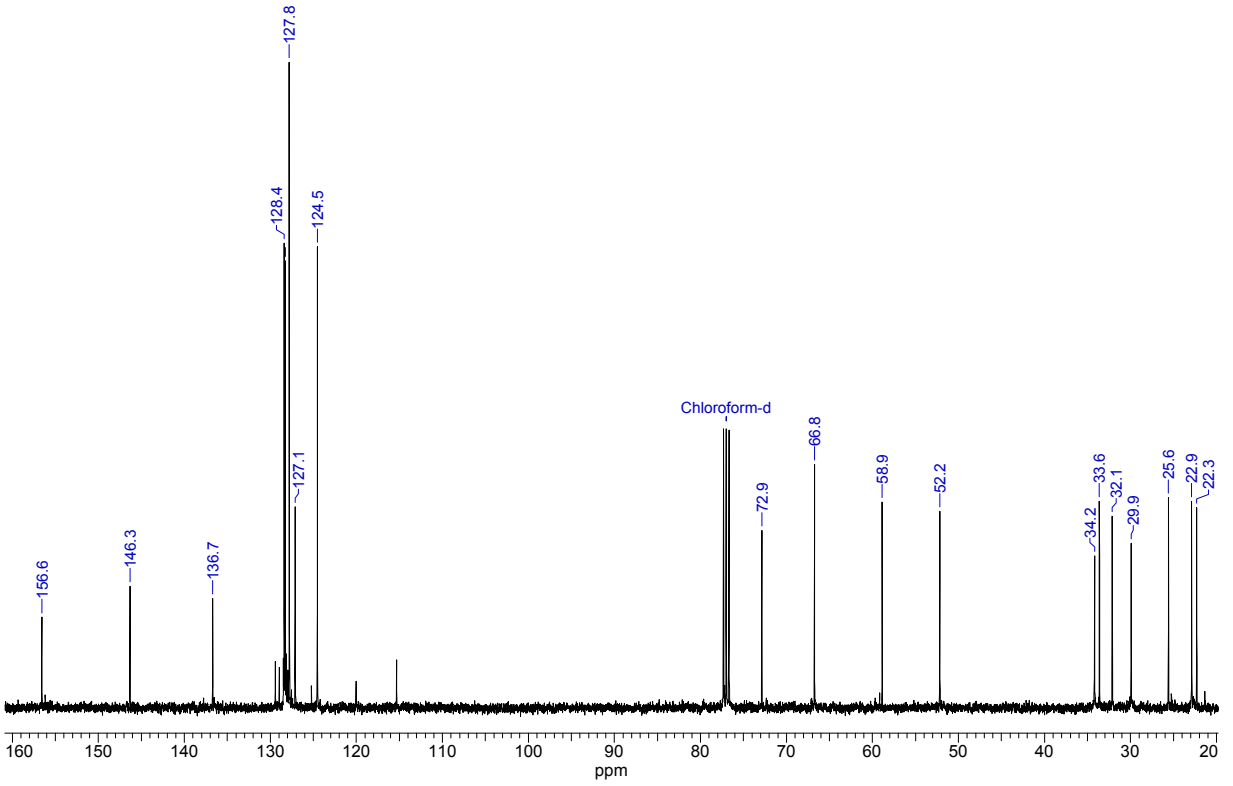

NH
O
N
N
OMe
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

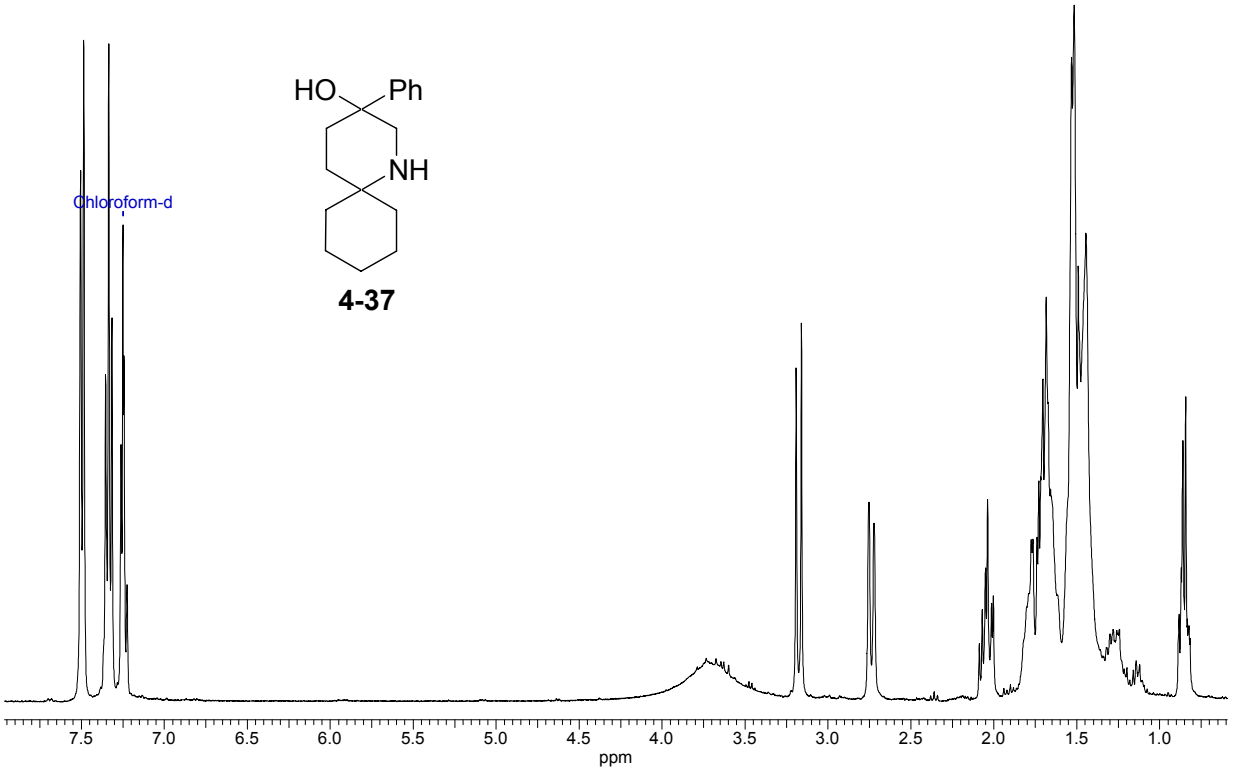
4-35


Chloroform-d
172.0
156.0
58.7
51.7
46.3
42.4
42.1
36.9
33.1
32.8
30.4
25.3
22.9
22.0
21.1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

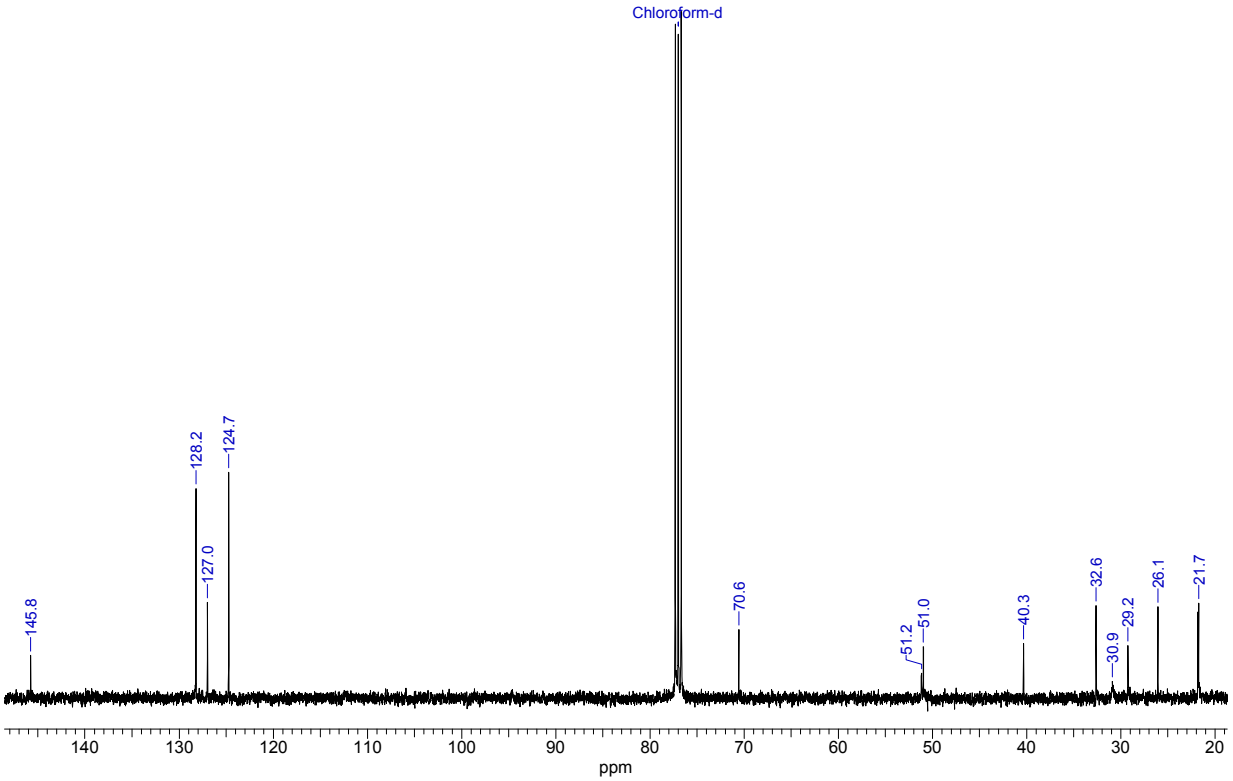

HO
Ph
N
OBn
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

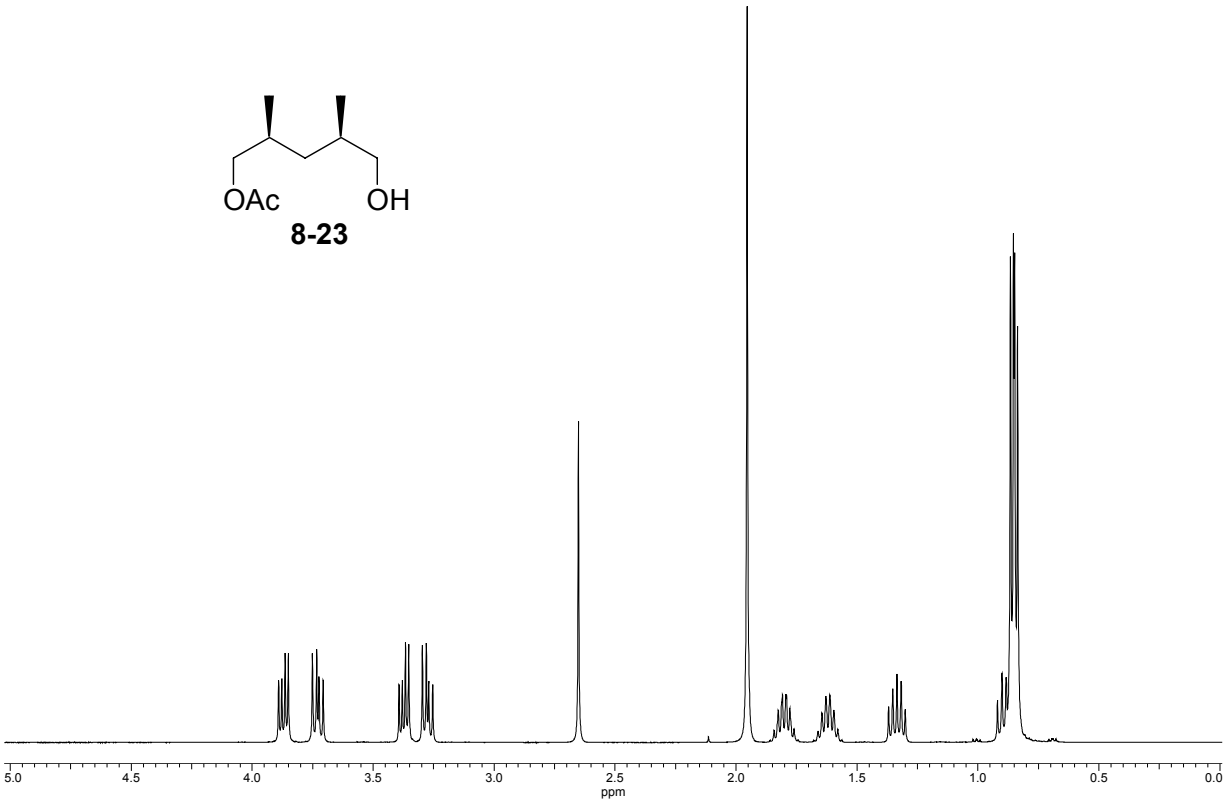
4-36

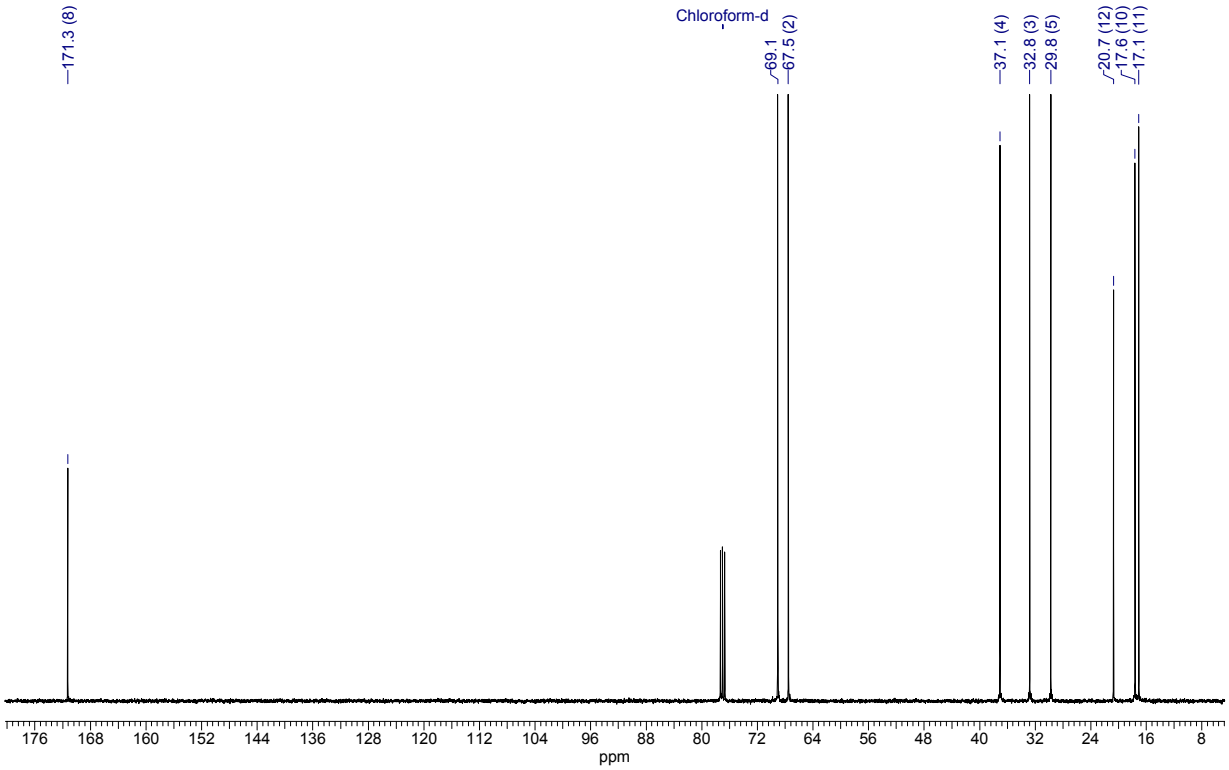

156.6
146.3
136.7
128.4
127.8
127.1
124.5
Chloroform-d
72.9
66.8
58.9
52.2
34.2
33.6
32.1
29.9
25.6
22.9
22.3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

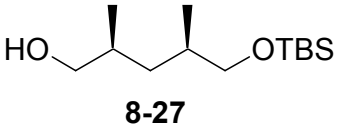

HO
Ph
NH
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

4-37


Chloroform-d
145.8
128.2
127.0
124.7
70.6
51.2
51.0
40.3
32.6
30.9
29.2
26.1
21.7
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

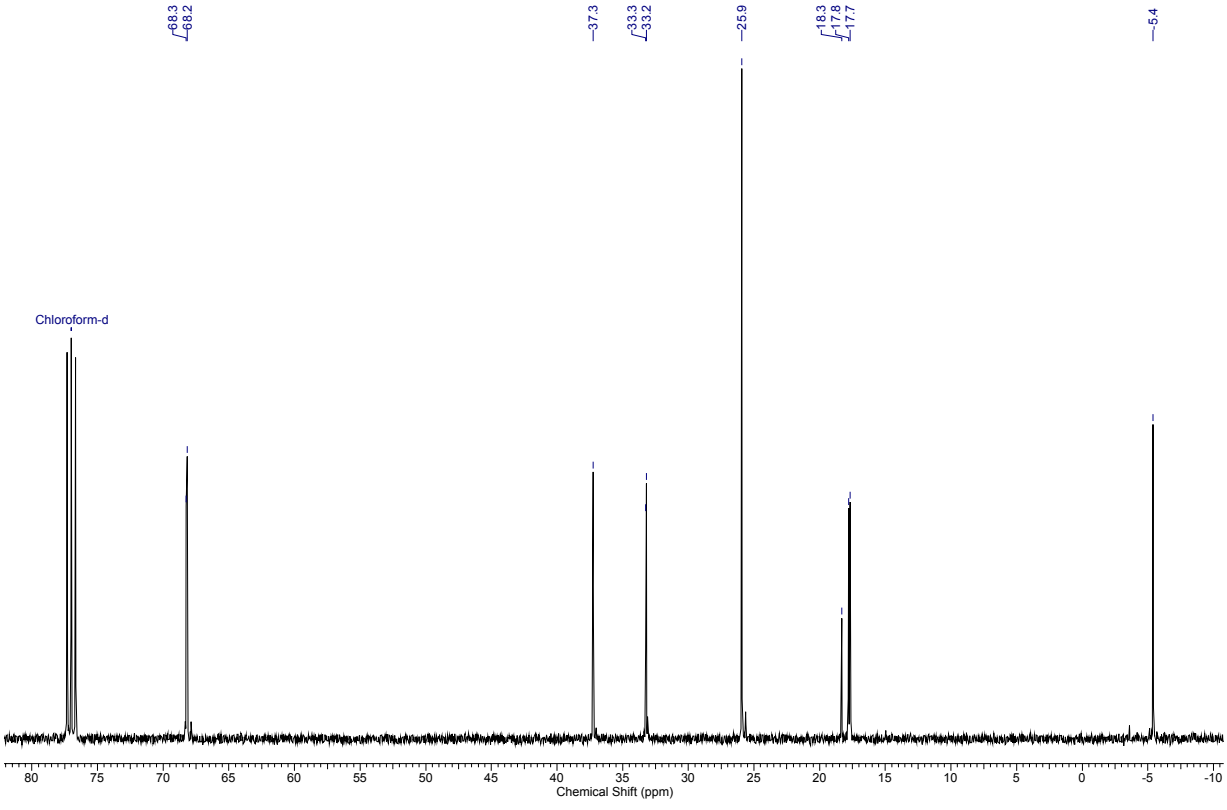

OAc
OH
8-23
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

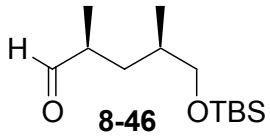

171.3 (8)
Chloroform-d
69.1
67.5 (2)
37.1 (4)
32.8 (3)
29.8 (5)
20.7 (12)
17.6 (10)
17.1 (11)
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
ppm


HO
OTBS

8-27

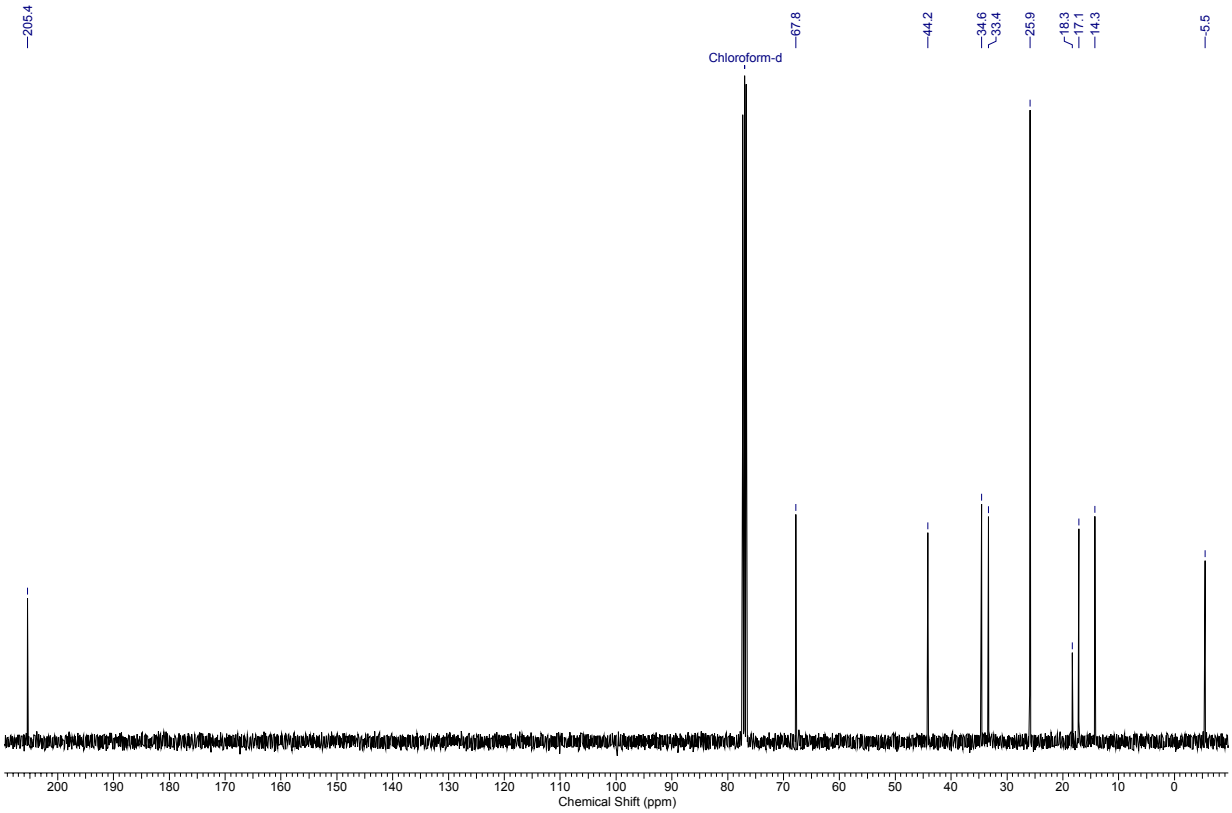
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

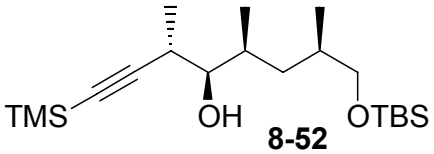

68.3
68.2
37.3
33.3
33.2
25.9
18.3
17.8
17.7
5.4
Chloroform-d
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
Chemical Shift (ppm)


H
O
OTBS

8-46

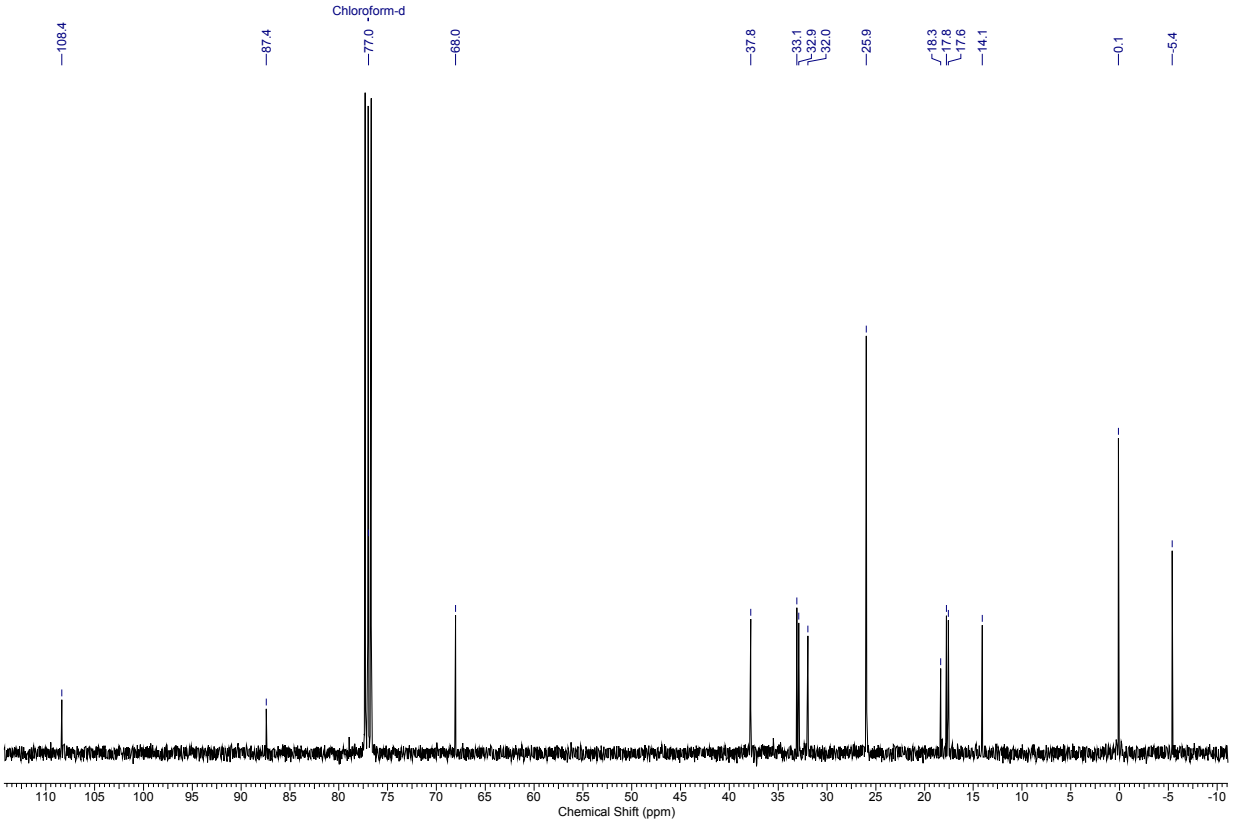
Chloroform-d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

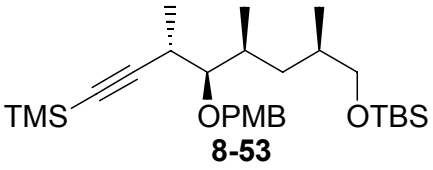

205.4
67.8
44.2
34.6
33.4
25.9
18.3
17.1
14.3
5.5
Chloroform-d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


TMS
OH
OTBS

8-52

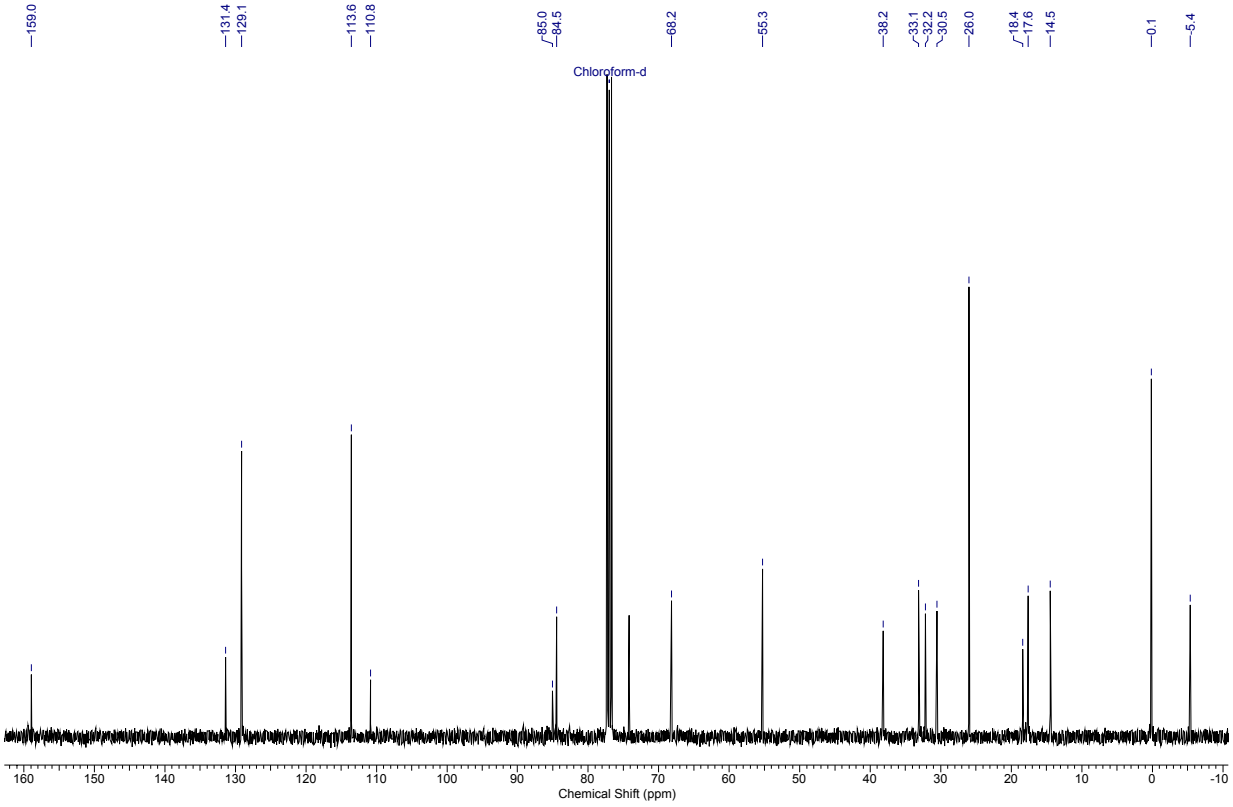
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

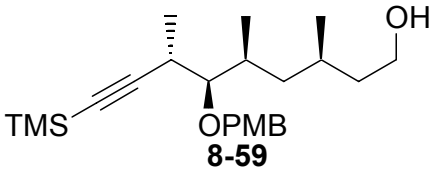

Chloroform-d
108.4
87.4
77.0
68.0
37.8
33.1
32.9
32.0
25.9
18.3
17.8
17.6
14.1
0.1
-5.4
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
Chemical Shift (ppm)


TMS
OPMB
OTBS

8-53

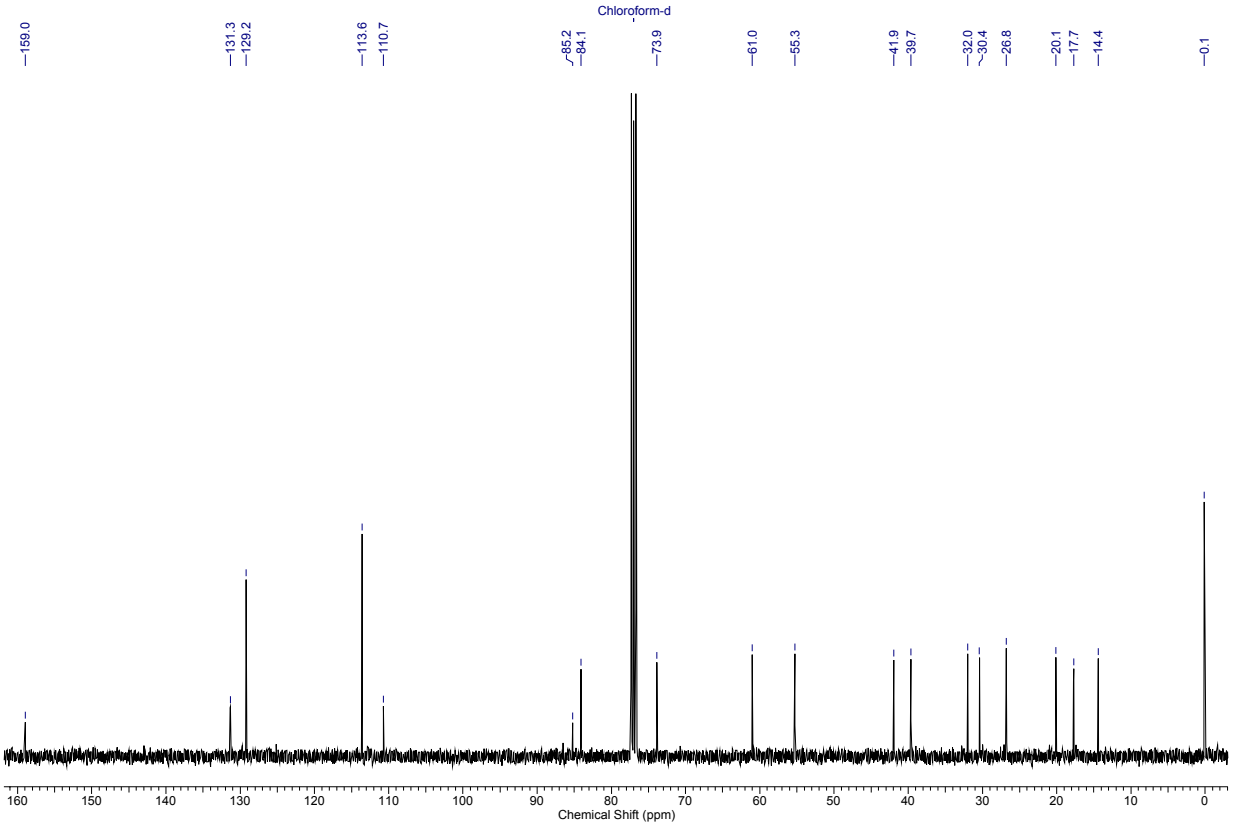
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

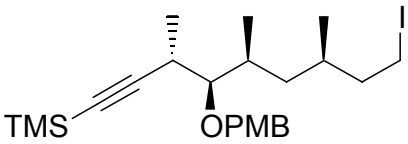

159.0
131.4
129.1
113.6
110.8
85.0
84.5
68.2
55.3
38.2
33.1
32.2
30.5
26.0
18.4
17.6
14.5
0.1
-5.4
Chloroform-d
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OH
TMS
OPMB

8-59

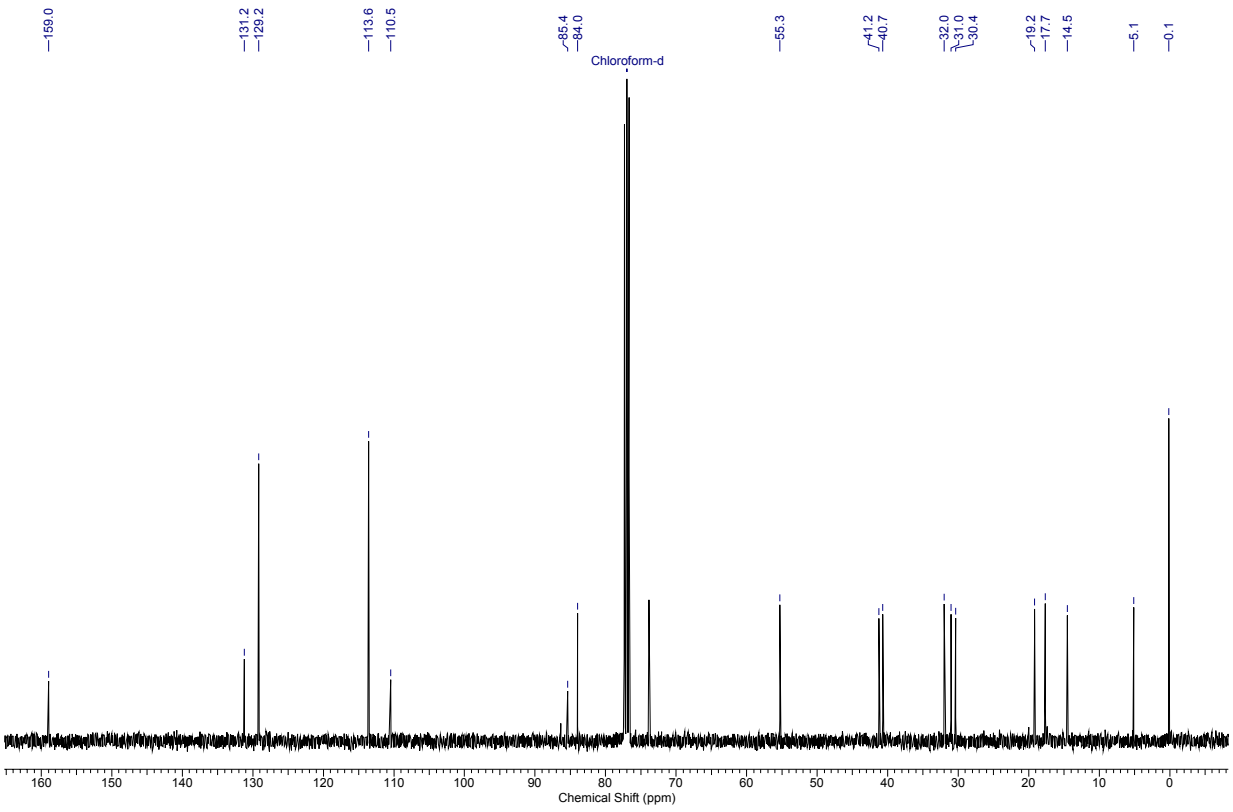
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

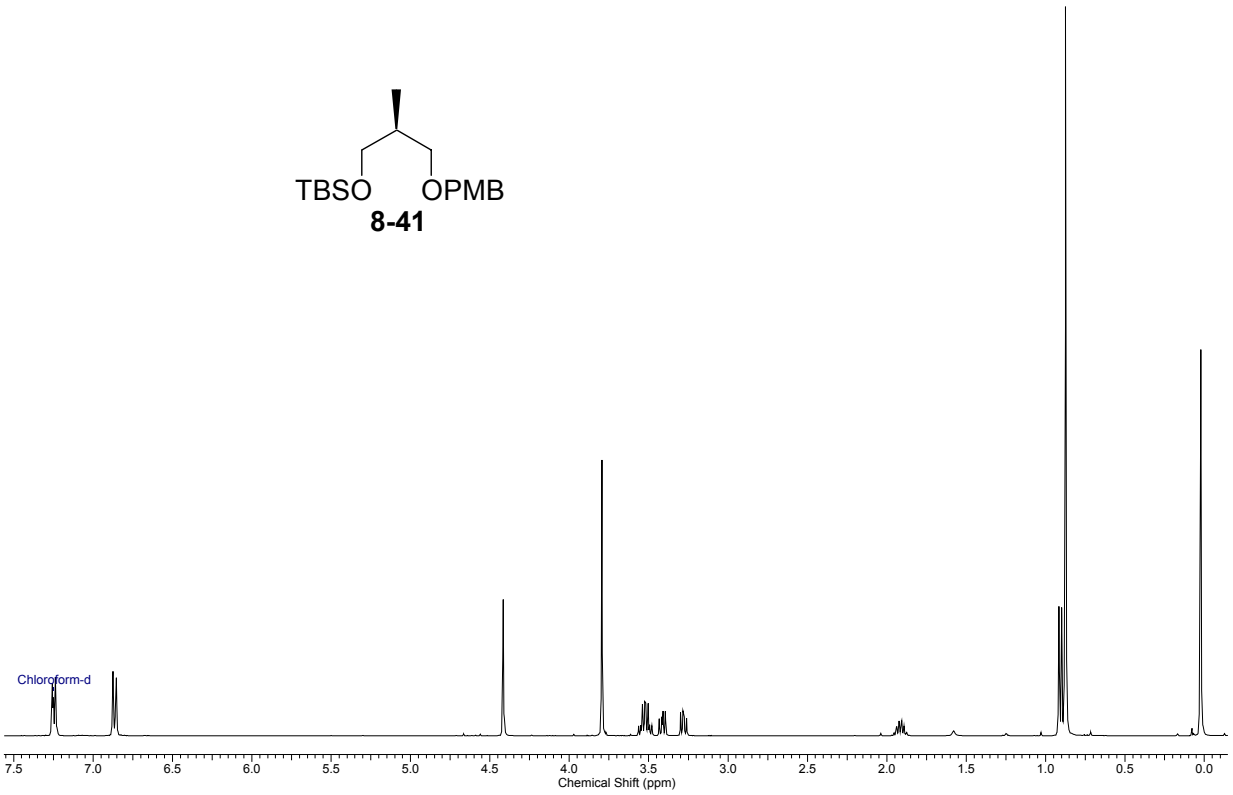

159.0
131.3
129.2
113.6
110.7
85.2
84.1
Chloroform-d
73.9
61.0
55.3
41.9
39.7
32.0
30.4
26.8
20.1
17.7
14.4
0.1
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

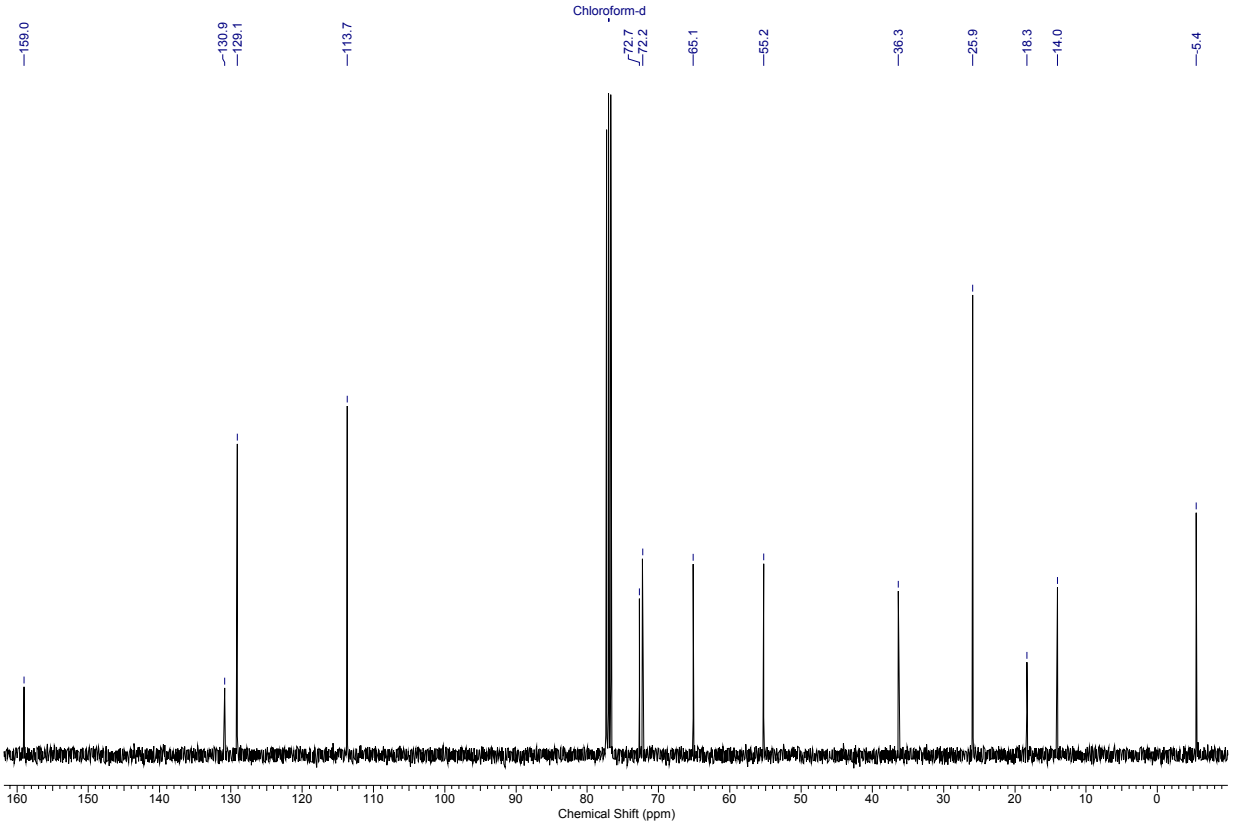

TMS
OPMB

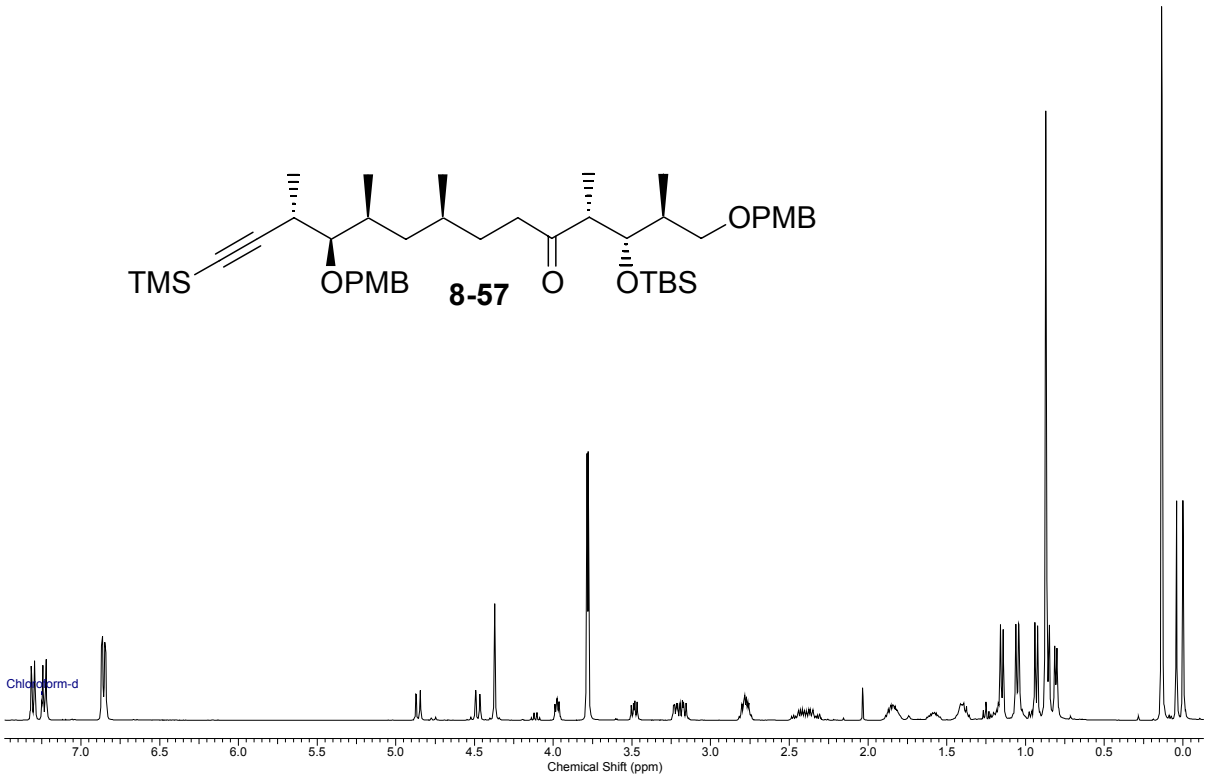
8-60

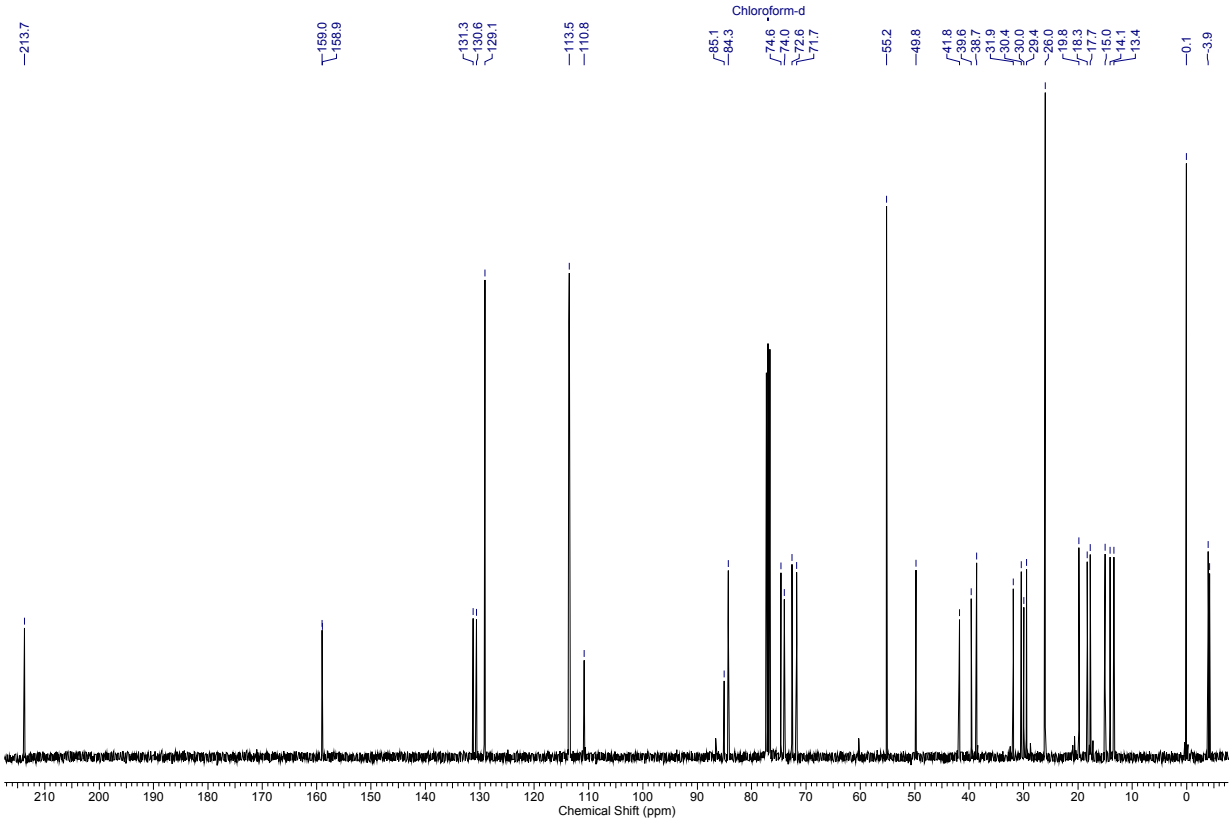
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

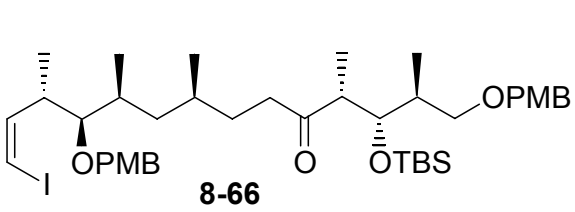

159.0
131.2
129.2
113.6
110.5
85.4
84.0
55.3
41.2
40.7
32.0
31.0
30.4
19.2
17.7
14.5
5.1
0.1
Chloroform-d
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


TBSO
OPMB
8-41
Chloroform-d
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
Chemical Shift (ppm)


159.0
130.9
129.1
113.7
Chloroform-d
72.7
72.2
65.1
55.2
36.3
25.9
18.3
14.0
5.4
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

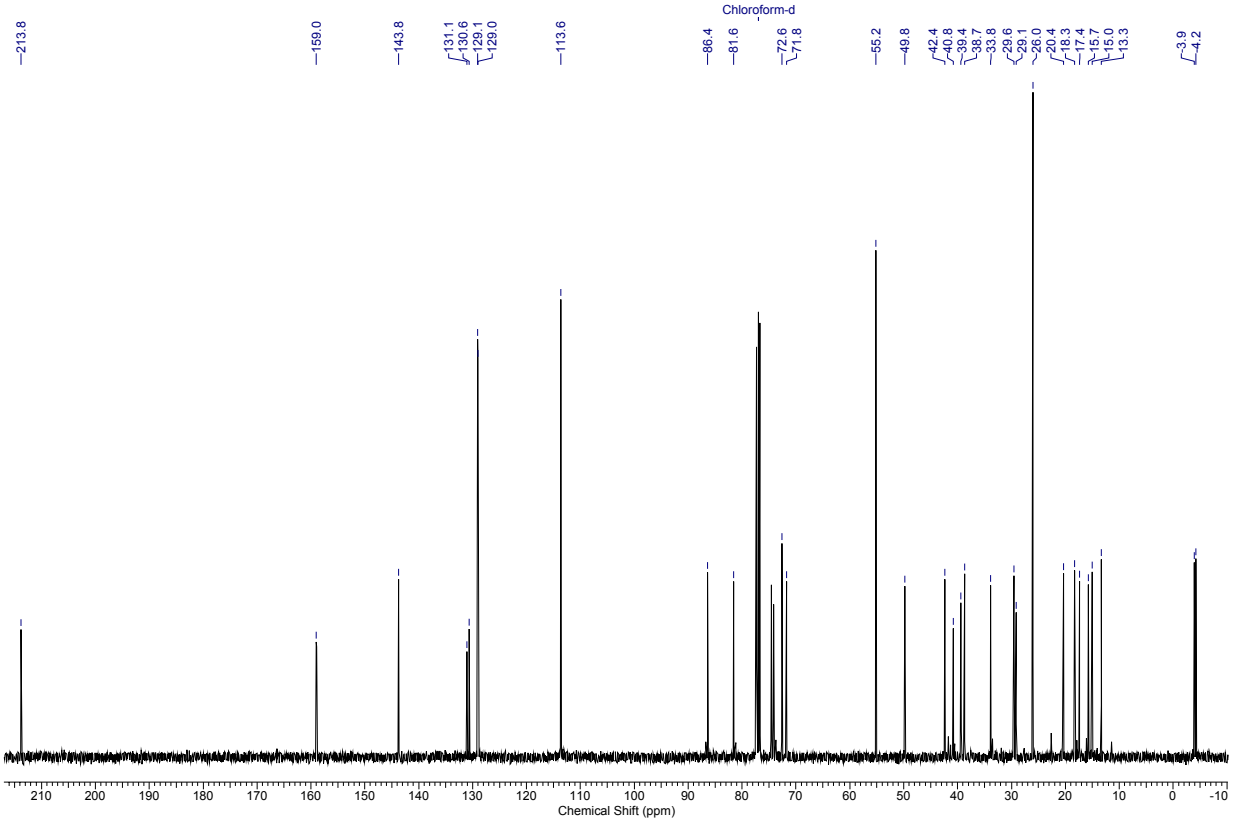

TMS
OPMB
8-57
O
OTBS
OPMB
Chloroform-d
Chemical Shift (ppm)

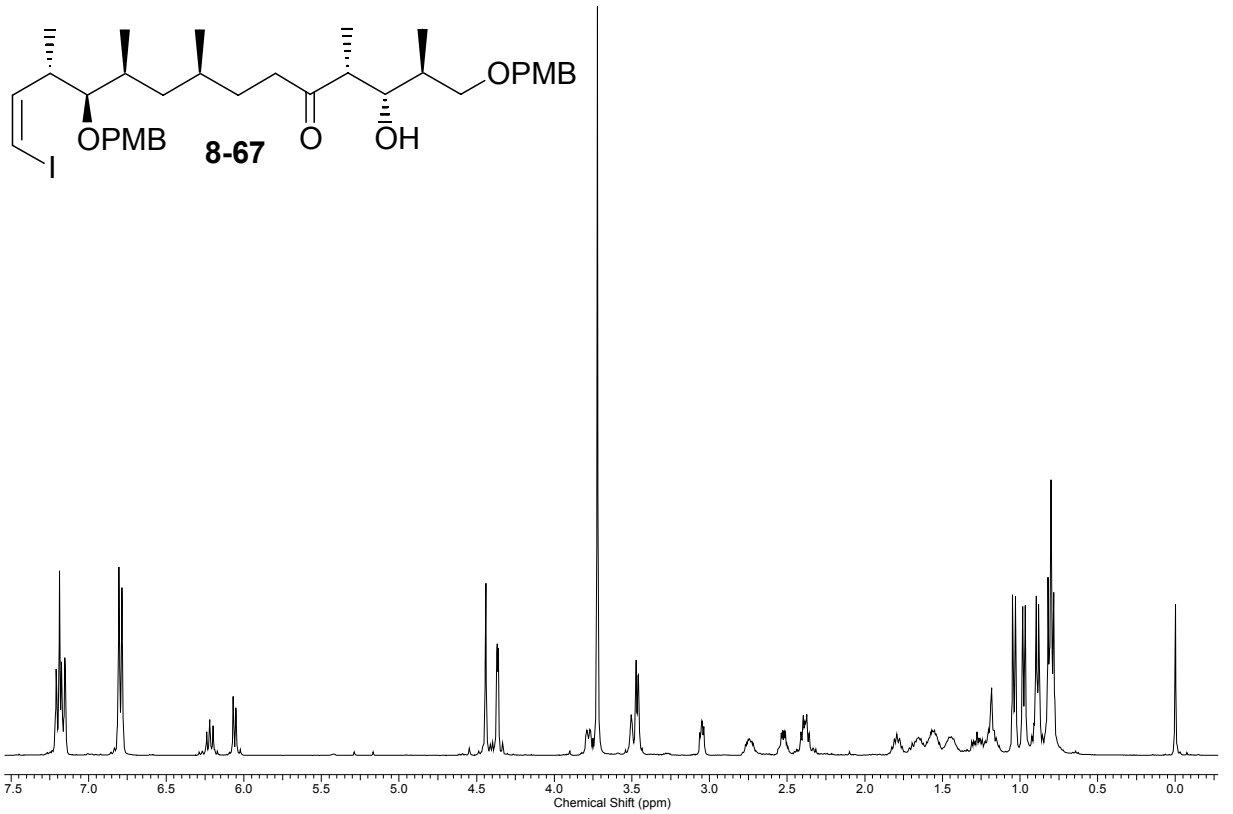

213.7
159.0
158.9
131.3
130.6
129.1
113.5
110.8
85.1
84.3
Chloroform-d
74.6
74.0
72.6
71.7
55.2
49.8
41.8
39.6
38.7
31.9
30.4
30.0
29.4
26.0
19.8
18.3
17.7
15.0
14.1
13.4
0.1
-3.9
Chemical Shift (ppm)

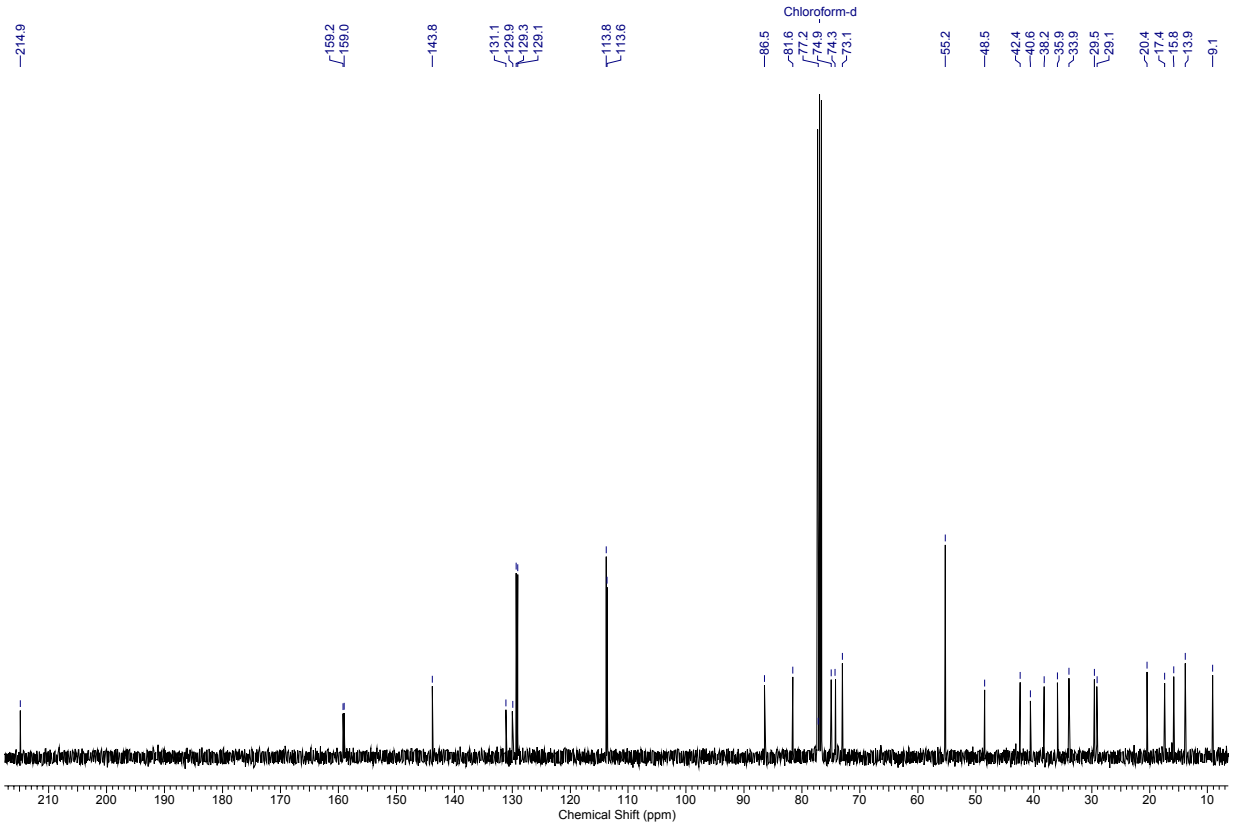

OPMB
OPMB
O
OTBS
I

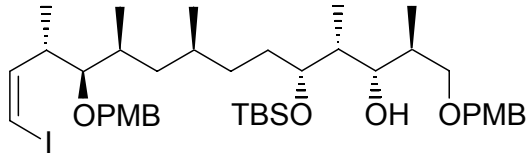
8-66

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
Chemical Shift (ppm)


213.8
159.0
143.8
131.1
130.6
129.1
129.0
113.6
Chloroform-d
86.4
81.6
72.6
71.8
55.2
49.8
42.4
40.8
39.4
38.7
33.8
29.6
29.1
26.0
20.4
18.3
17.4
15.7
15.0
13.3
3.9
4.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

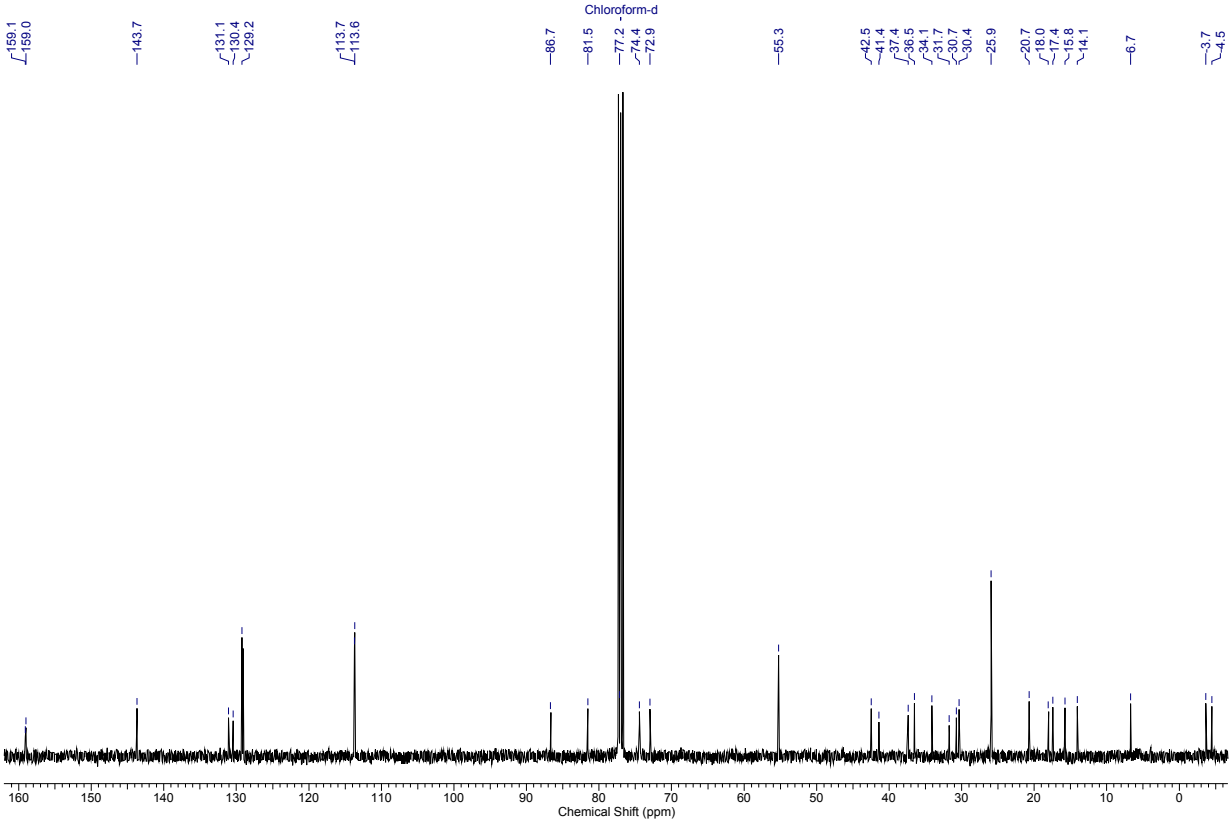

OPMB
OPMB
8-67
O
OH
I
Chemical Shift (ppm)

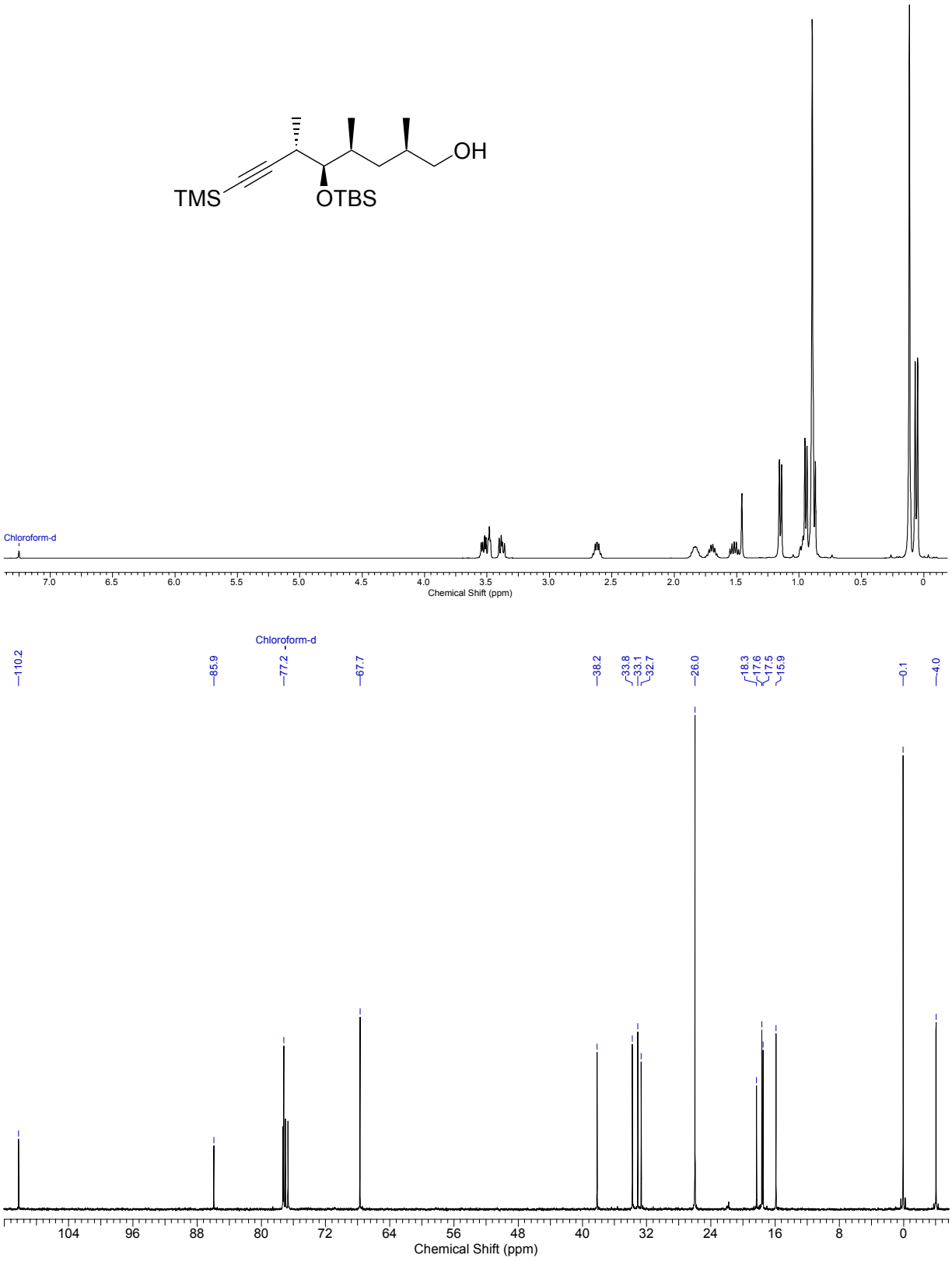

214.9
159.2
159.0
143.8
131.1
129.9
129.3
129.1
113.8
113.6
86.5
81.6
77.2
74.9
74.3
73.1
Chloroform-d
55.2
48.5
42.4
40.6
38.2
35.9
33.9
29.5
29.1
20.4
17.4
15.8
13.9
9.1
Chemical Shift (ppm)

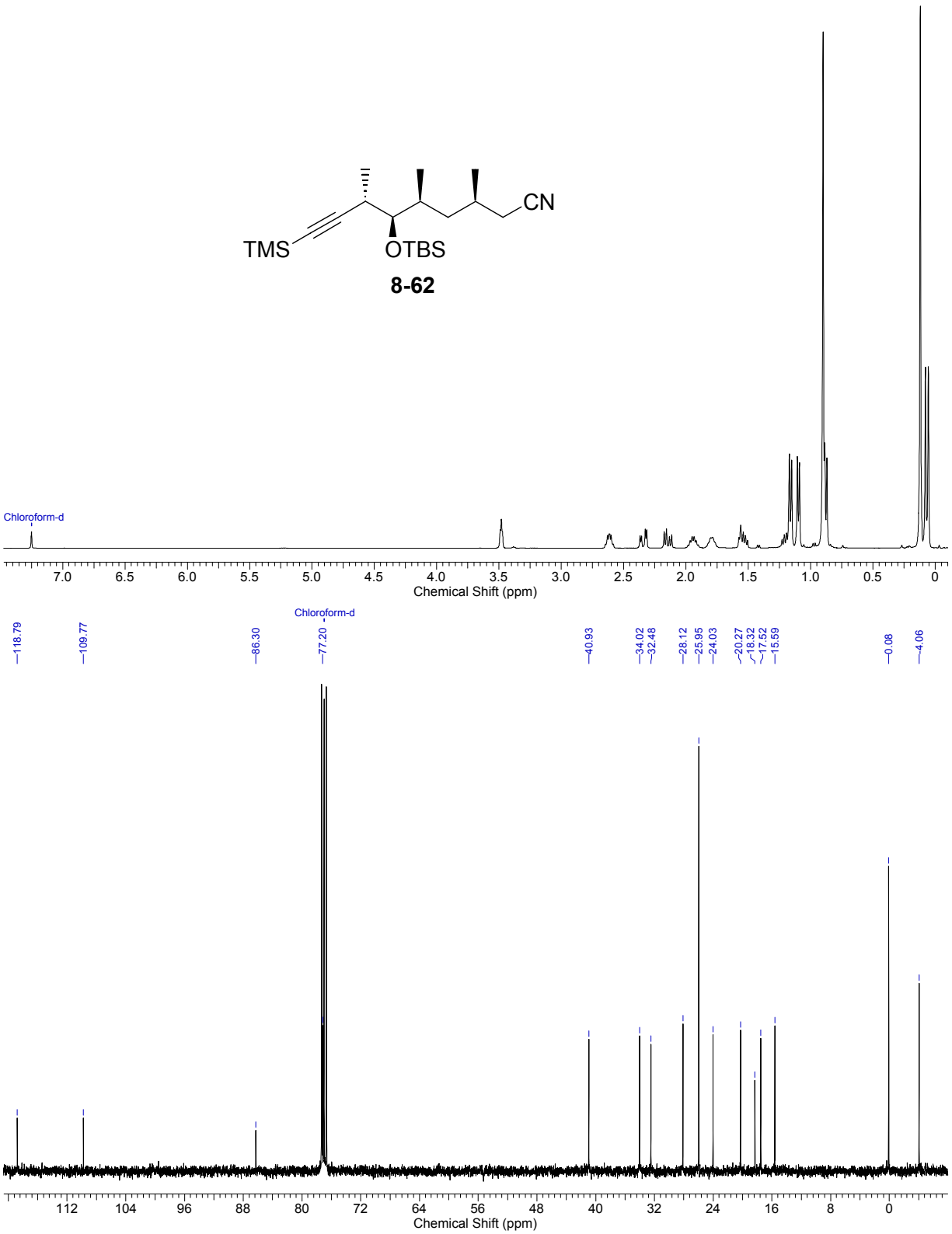

OPMB
TBSO
OH
OPMB
I

8-70

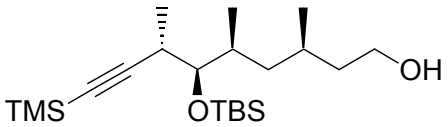
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)


Chloroform-d
159.1
159.0
143.7
131.1
130.4
129.2
113.7
113.6
86.7
81.5
77.2
74.4
72.9
55.3
42.5
41.4
37.4
36.5
34.1
31.7
30.7
30.4
25.9
20.7
18.0
17.4
15.8
14.1
6.7
3.7
-4.5
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


OH
TMS
OTBS
Chloroform-d
Chemical Shift (ppm)
Chloroform-d
110.2
85.9
77.2
67.7
38.2
33.8
33.1
32.7
26.0
18.3
17.6
17.5
15.9
0.1
-4.0
Chemical Shift (ppm)

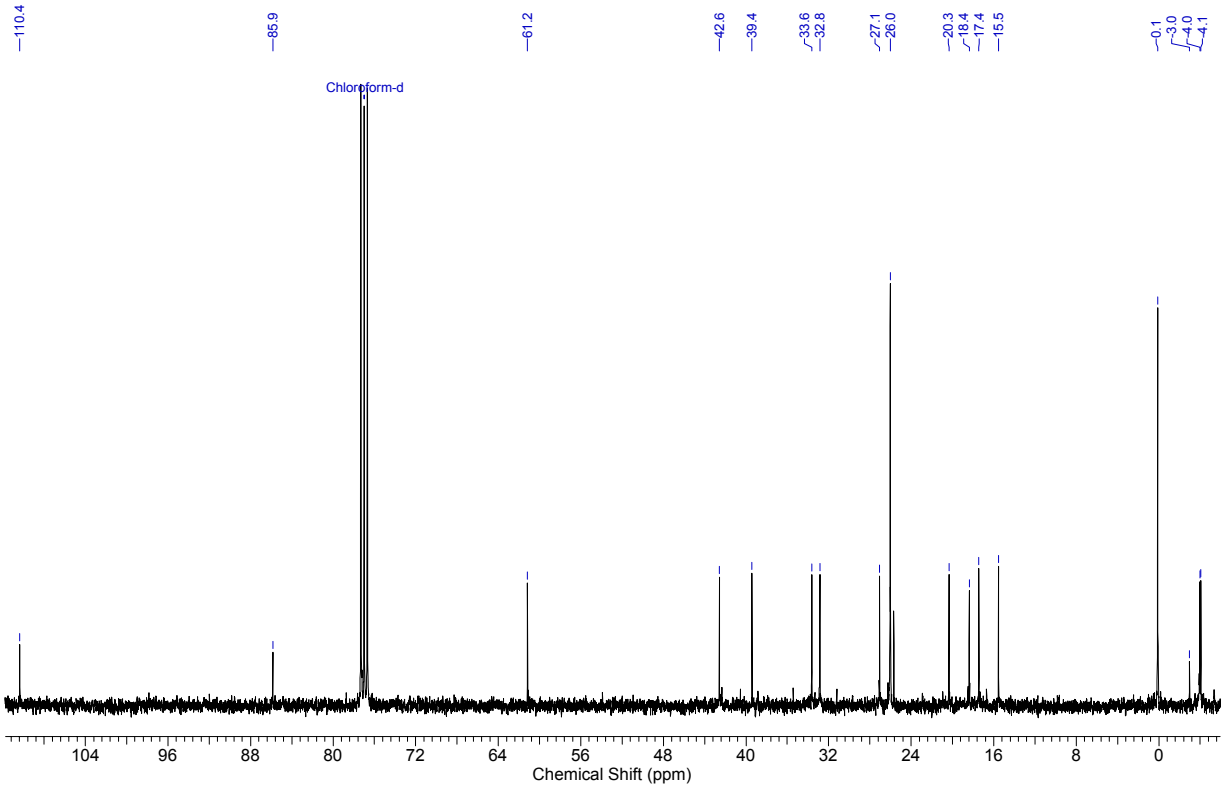

TMS
OTBS
CN
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)
118.79
109.77
86.30
Chloroform-d
77.20
40.93
34.02
32.48
28.12
25.95
24.03
20.27
18.32
17.52
15.59
0.08
-4.06
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

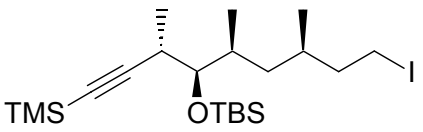
8-62


TMS
OTBS
OH

8-63

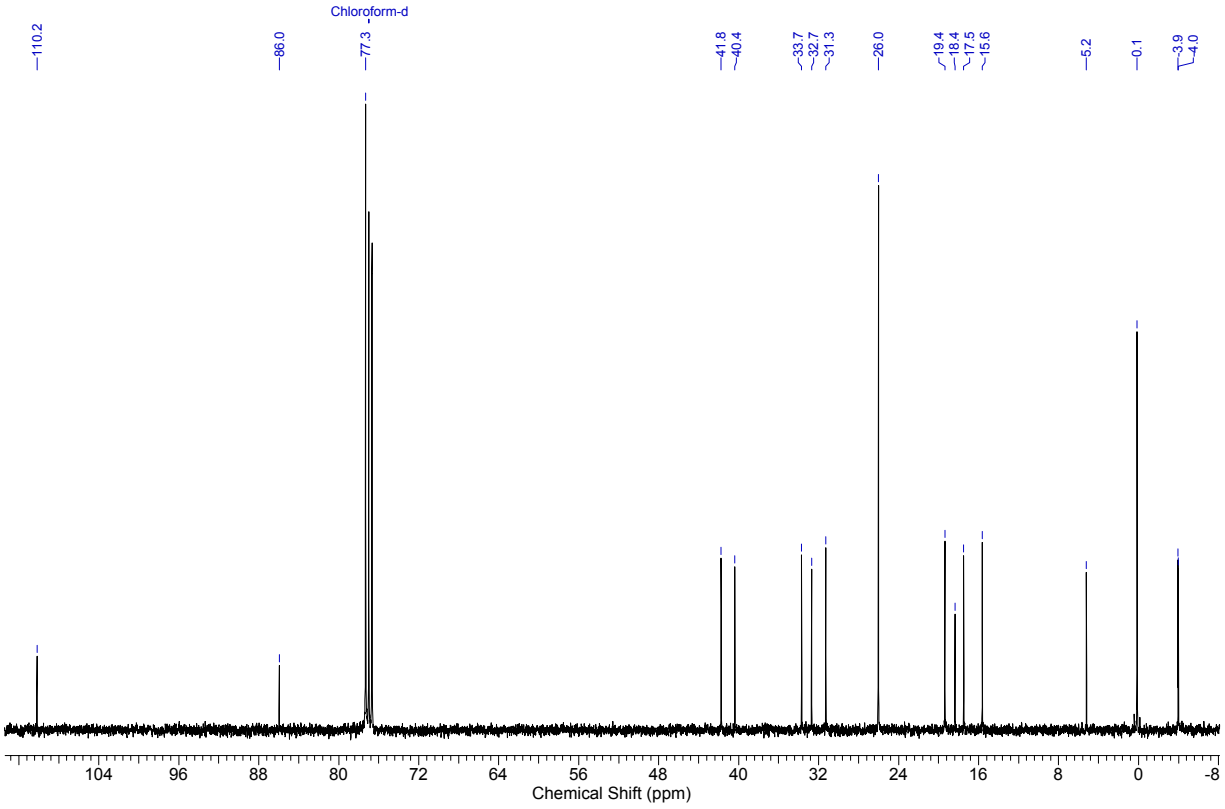
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

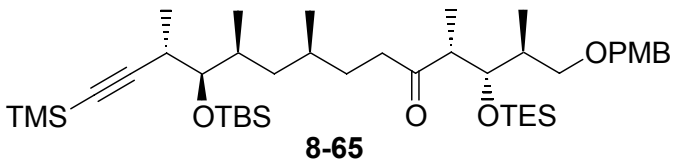

110.4
85.9
61.2
42.6
39.4
33.6
32.8
27.1
26.0
20.3
18.4
17.4
15.5
0.1
3.0
4.0
4.1
Chloroform-d
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


TMS
OTBS
I

8-64

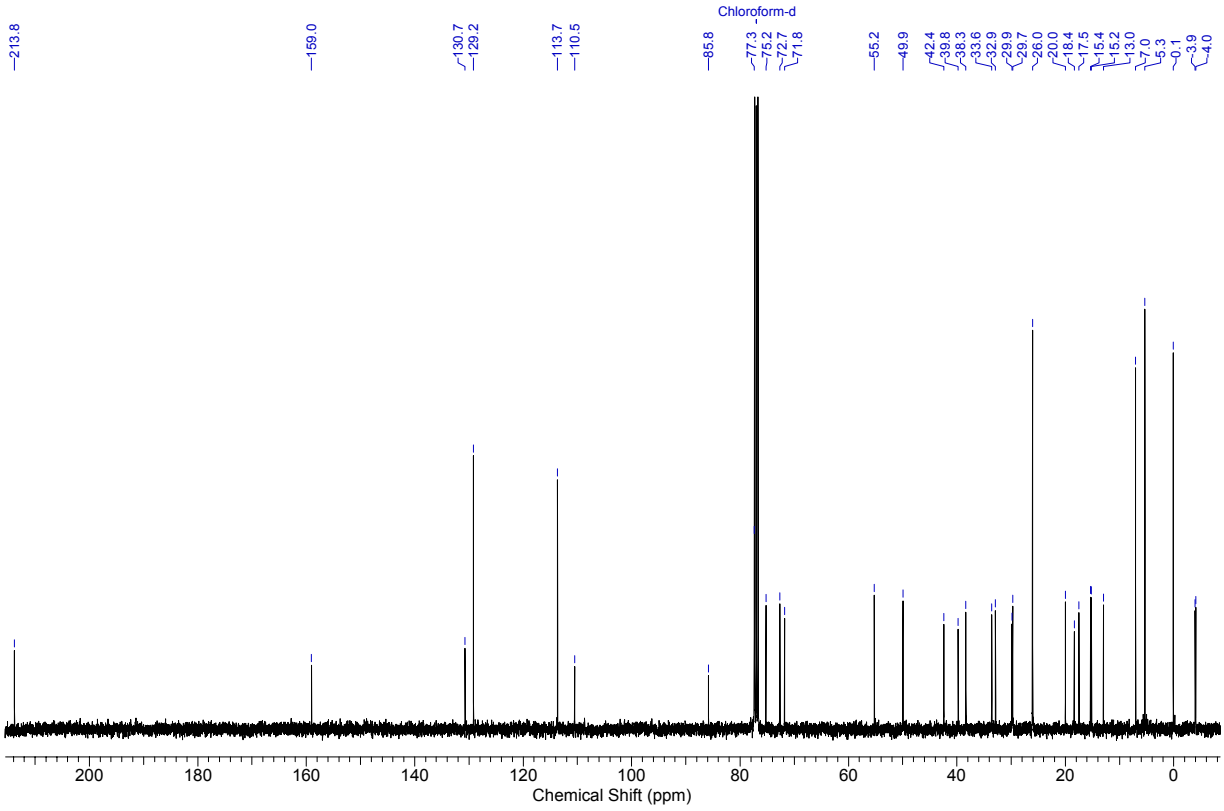
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

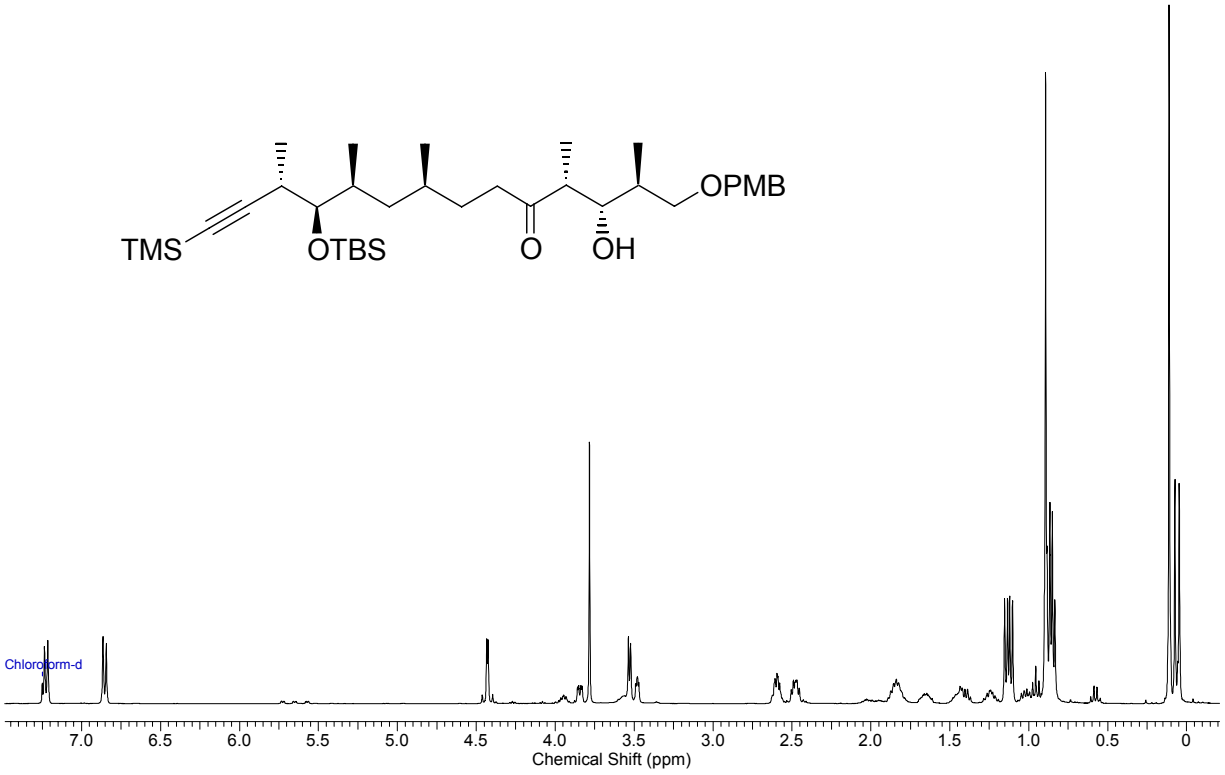

Chloroform-d
110.2
86.0
77.3
41.8
40.4
33.7
32.7
31.3
26.0
19.4
18.4
17.5
15.6
5.2
0.1
-3.9
-4.0
104
96
88
80
72
64
56
48
40
32
24
16
8
0
-8
Chemical Shift (ppm)

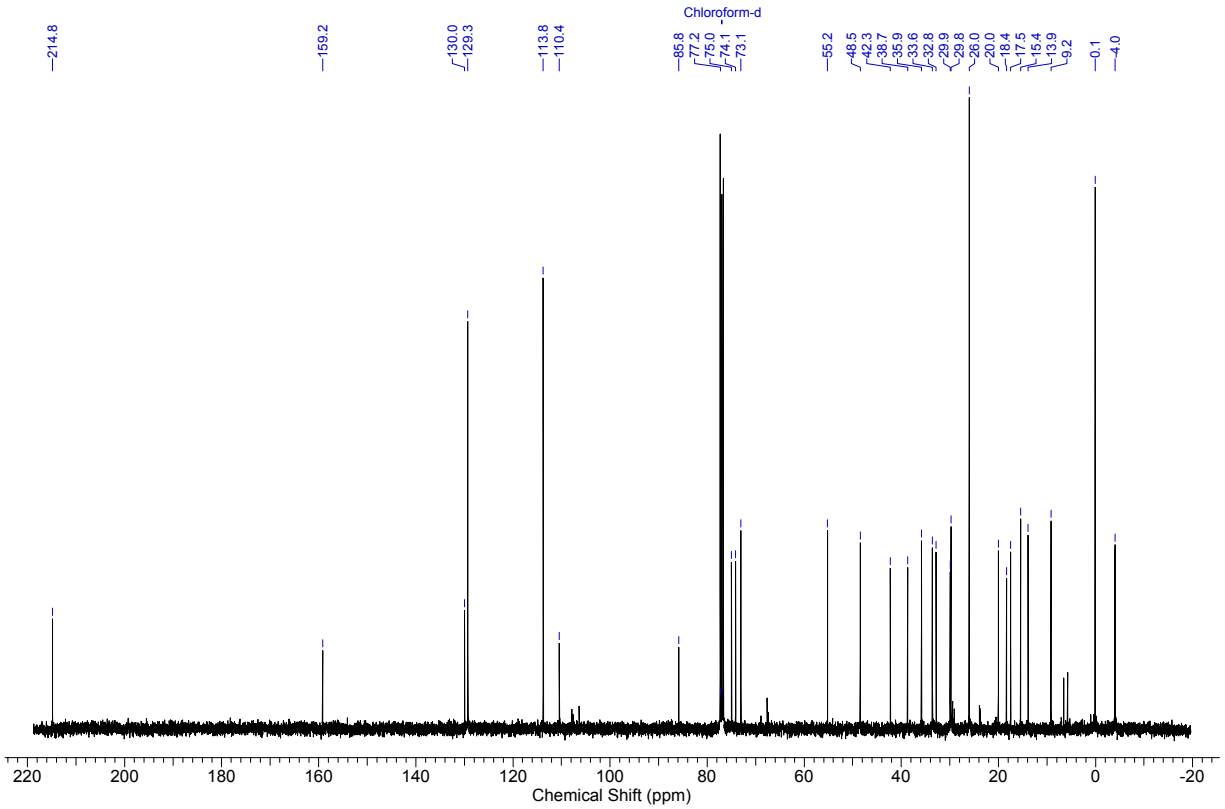

TMS
OTBS
O
OTES
OPMB

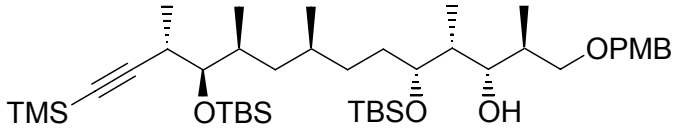
8-65

Chloroform-d
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
Chemical Shift (ppm)


213.8
159.0
130.7
129.2
113.7
110.5
Chloroform-d
85.8
77.3
75.2
72.7
71.8
55.2
49.9
42.4
39.8
38.3
33.6
32.9
29.9
29.7
26.0
20.0
18.4
17.5
15.4
15.2
13.0
7.0
5.3
0.1
3.9
4.0
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

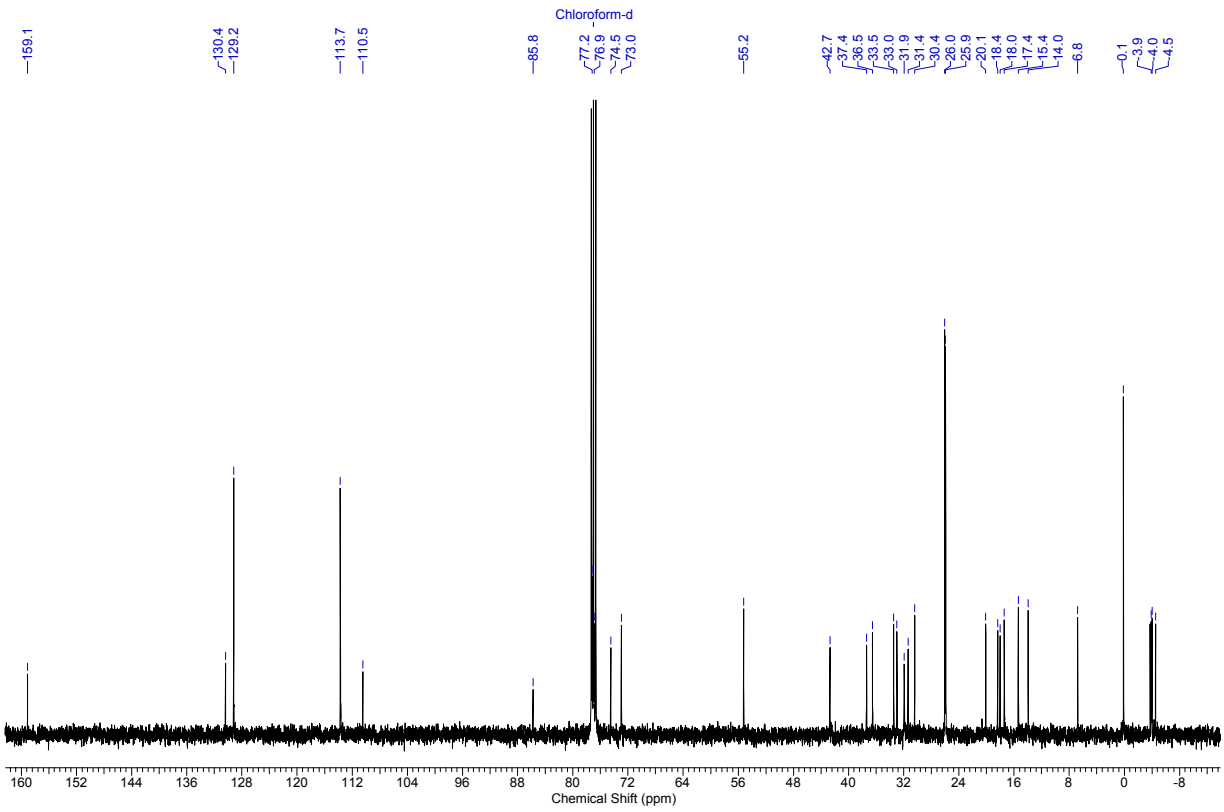

TMS
OTBS
O
OH
OPMB
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

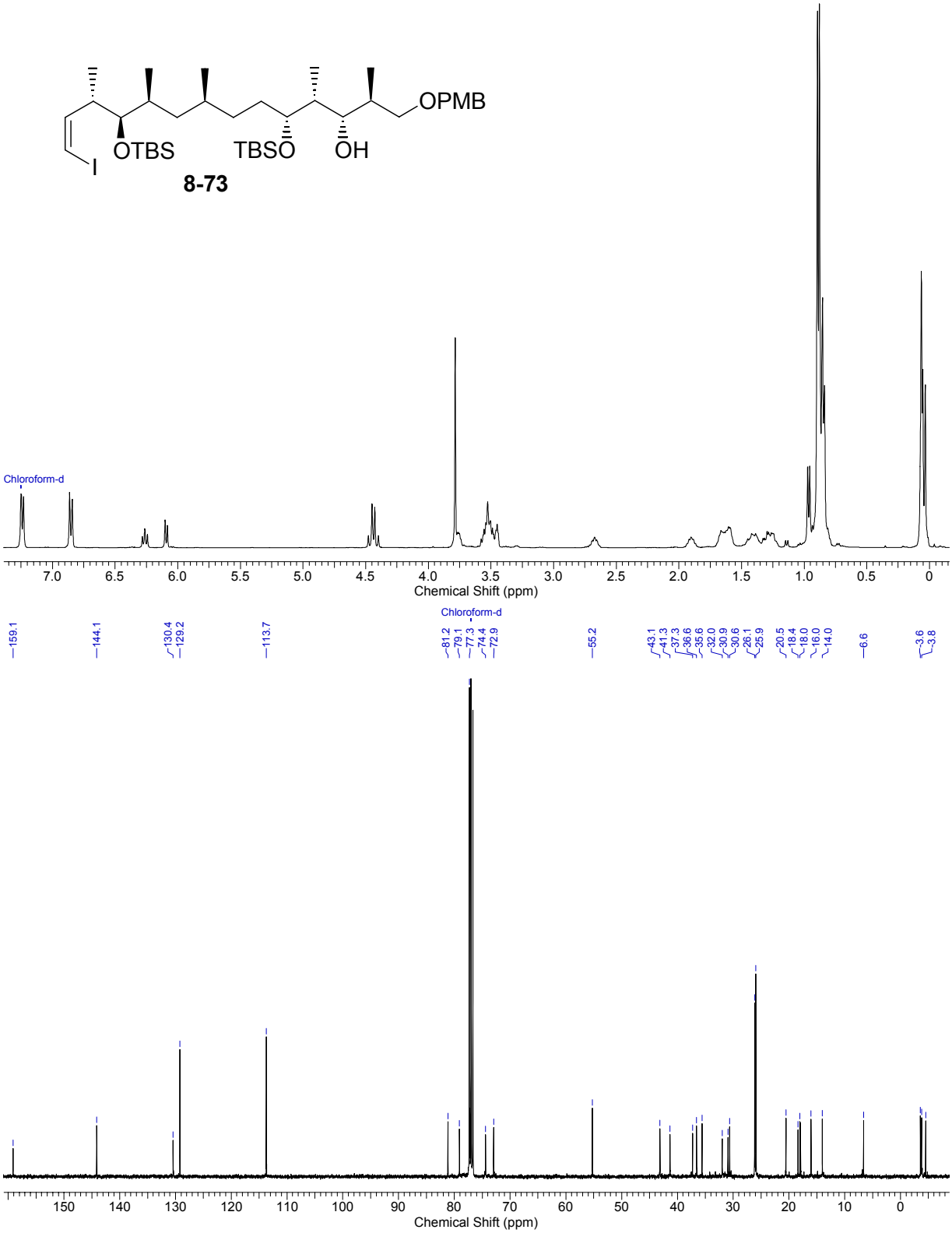

214.8
159.2
130.0
129.3
113.8
110.4
Chloroform-d
85.8
77.2
75.0
74.1
73.1
55.2
48.5
42.3
38.7
35.9
33.6
32.8
29.9
29.8
26.0
20.0
18.4
17.5
15.4
13.9
9.2
0.1
4.0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

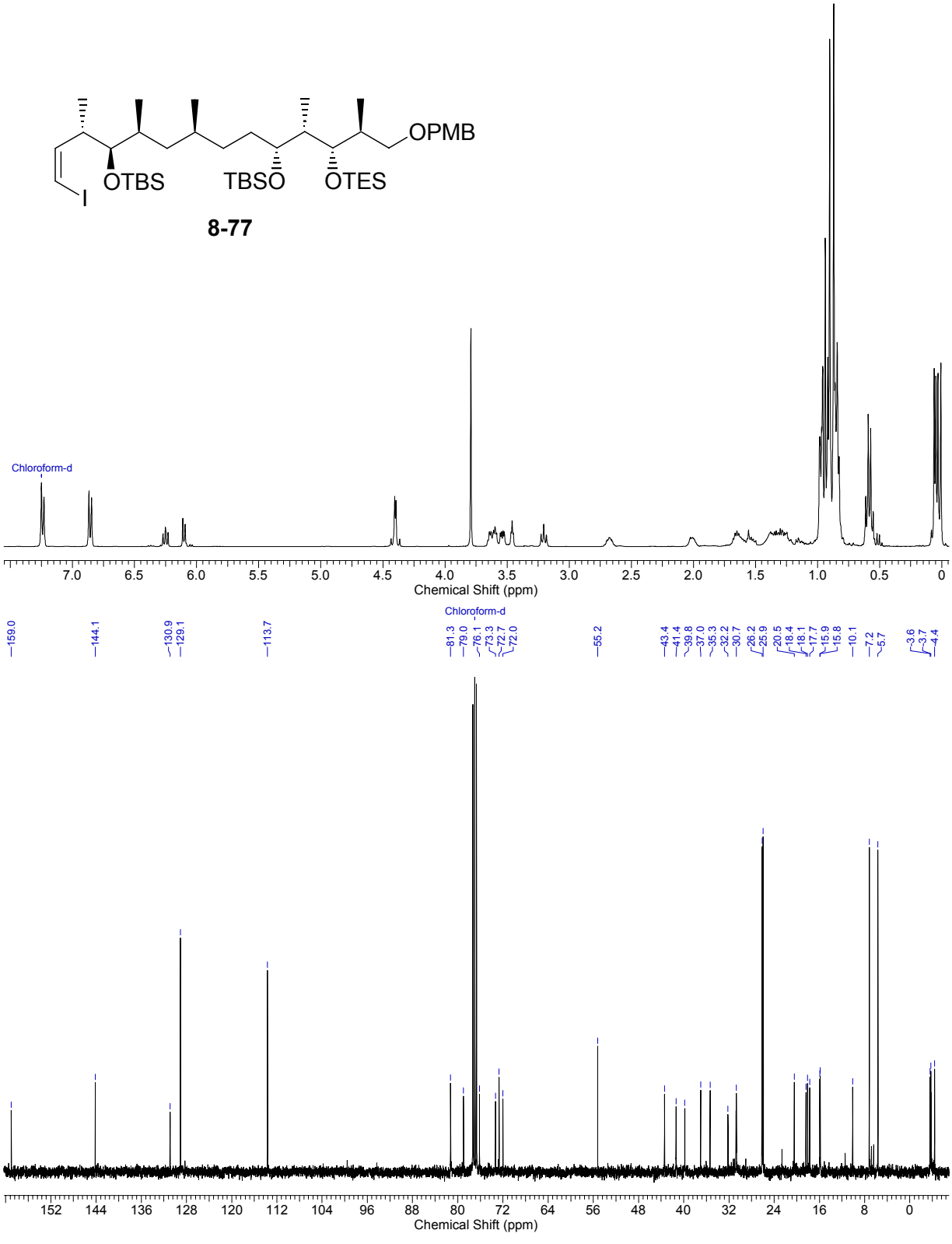

TMS
OTBS
TBSO
OH
OPMB

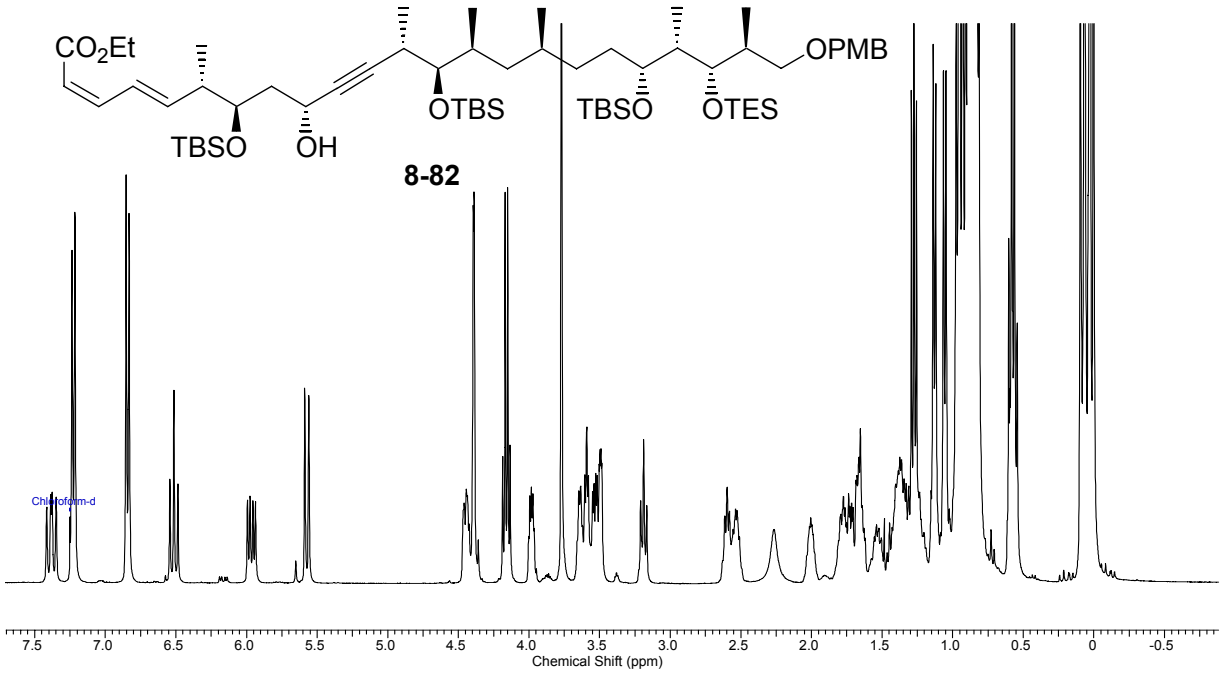
8-72

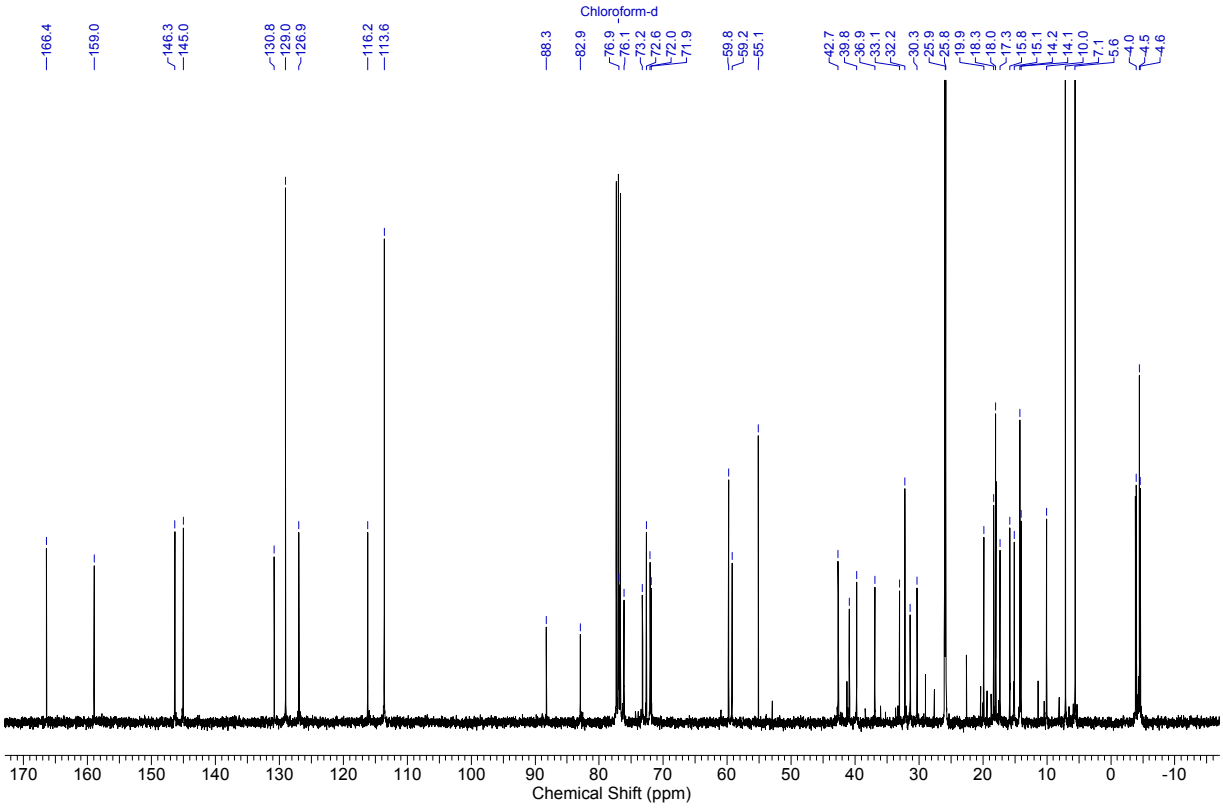
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

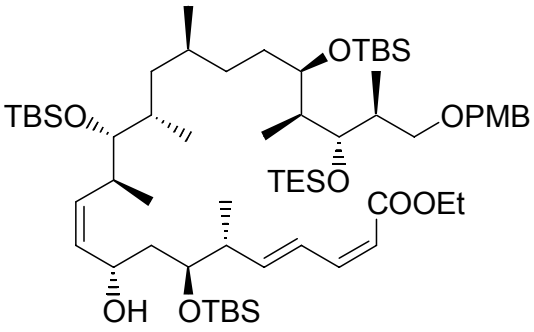

159.1
130.4
129.2
113.7
110.5
85.8
Chloroform-d
77.2
76.9
74.5
73.0
55.2
42.7
37.4
36.5
33.5
33.0
31.9
31.4
30.4
26.0
25.9
20.1
18.4
18.0
17.4
15.4
14.0
6.8
0.1
-3.9
-4.0
-4.5
160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)


OPMB
OTBS
TBSO
OH
I
8-73
Chloroform-d
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
Chemical Shift (ppm)
Chloroform-d
159.1
144.1
130.4
129.2
113.7
81.2
79.1
77.3
74.4
72.9
55.2
43.1
41.3
37.3
36.6
35.6
32.0
30.9
30.6
26.1
25.9
20.5
18.4
18.0
16.0
14.0
6.6
-3.6
-3.8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


OPMB
OTBS
TBSO
OTES
I
8-77
Chloroform-d
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
Chemical Shift (ppm)
Chloroform-d
159.0
144.1
130.9
129.1
113.7
81.3
79.0
76.1
73.3
72.7
72.0
55.2
43.4
41.4
39.8
37.0
35.3
32.2
30.7
26.2
25.9
20.5
18.4
18.1
17.7
15.9
15.8
10.1
7.2
5.7
-3.6
-3.7
-4.4
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

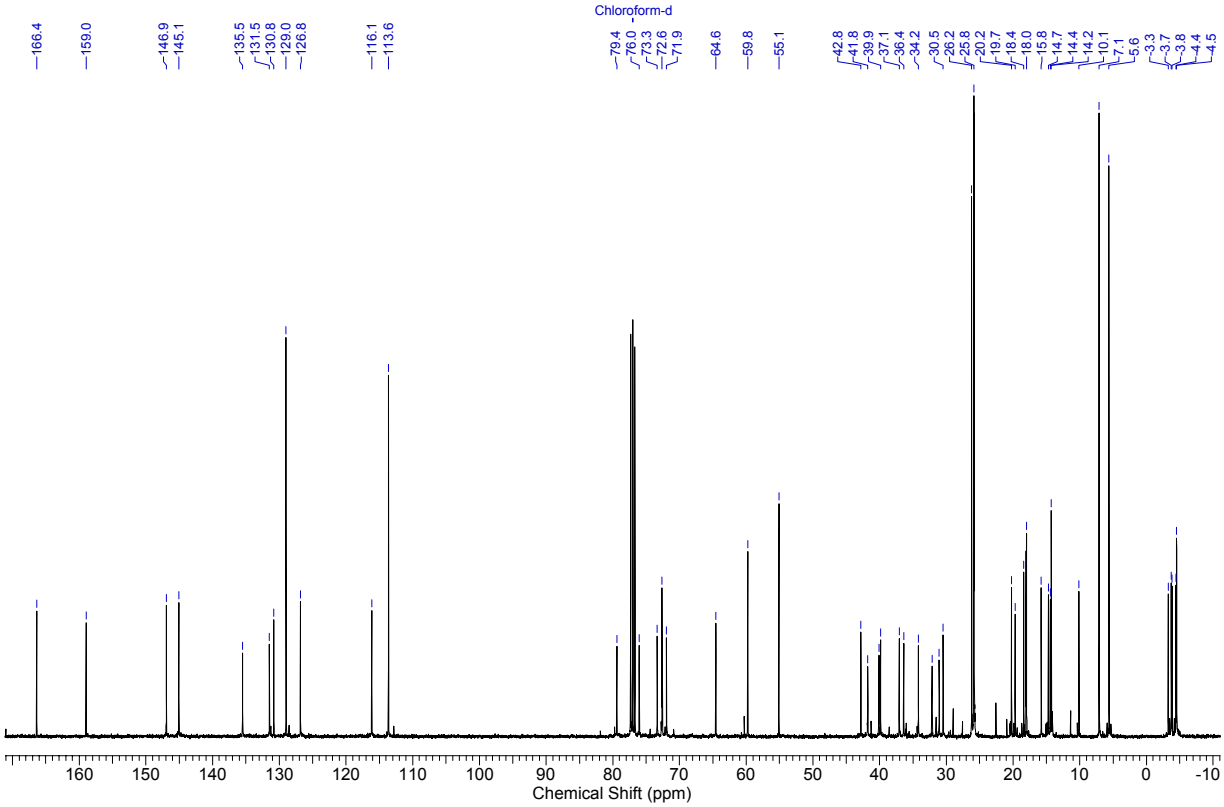

CO2Et
TBSO
OH
OTBS
TBSO
OTES
OPMB
8-82
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

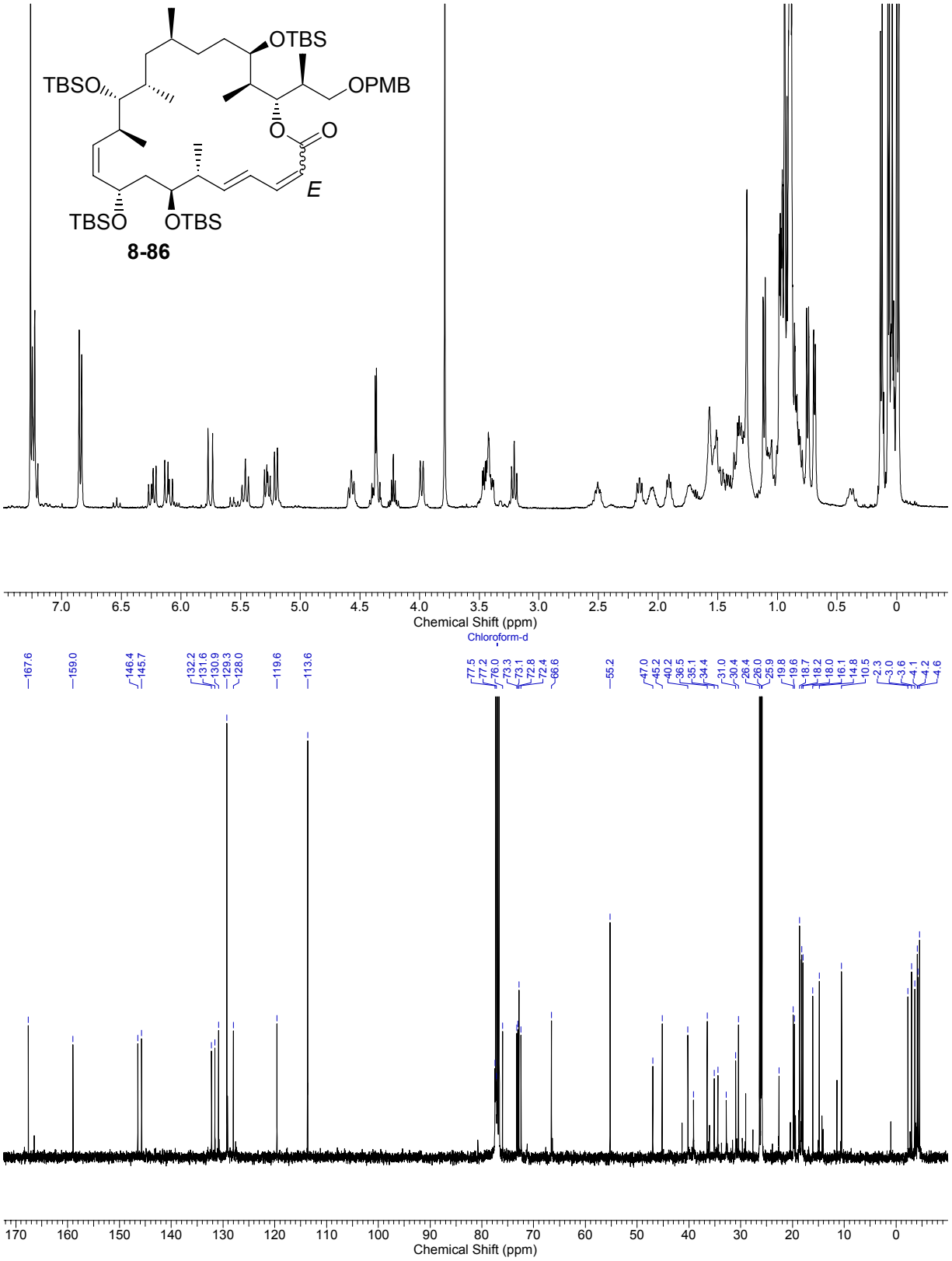

Chloroform-d
166.4 159.0 146.3 145.0 130.8 129.0 126.9 116.2 113.6
88.3 82.9 76.9 76.1 73.2 72.6 72.0 71.9 59.8 59.2 55.1
42.7 39.8 36.9 33.1 32.2 30.3 25.9 25.8 19.9 18.3 18.0 17.3 15.8 15.1 14.2 14.1 10.0 7.1 5.6 4.0 4.5 4.6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

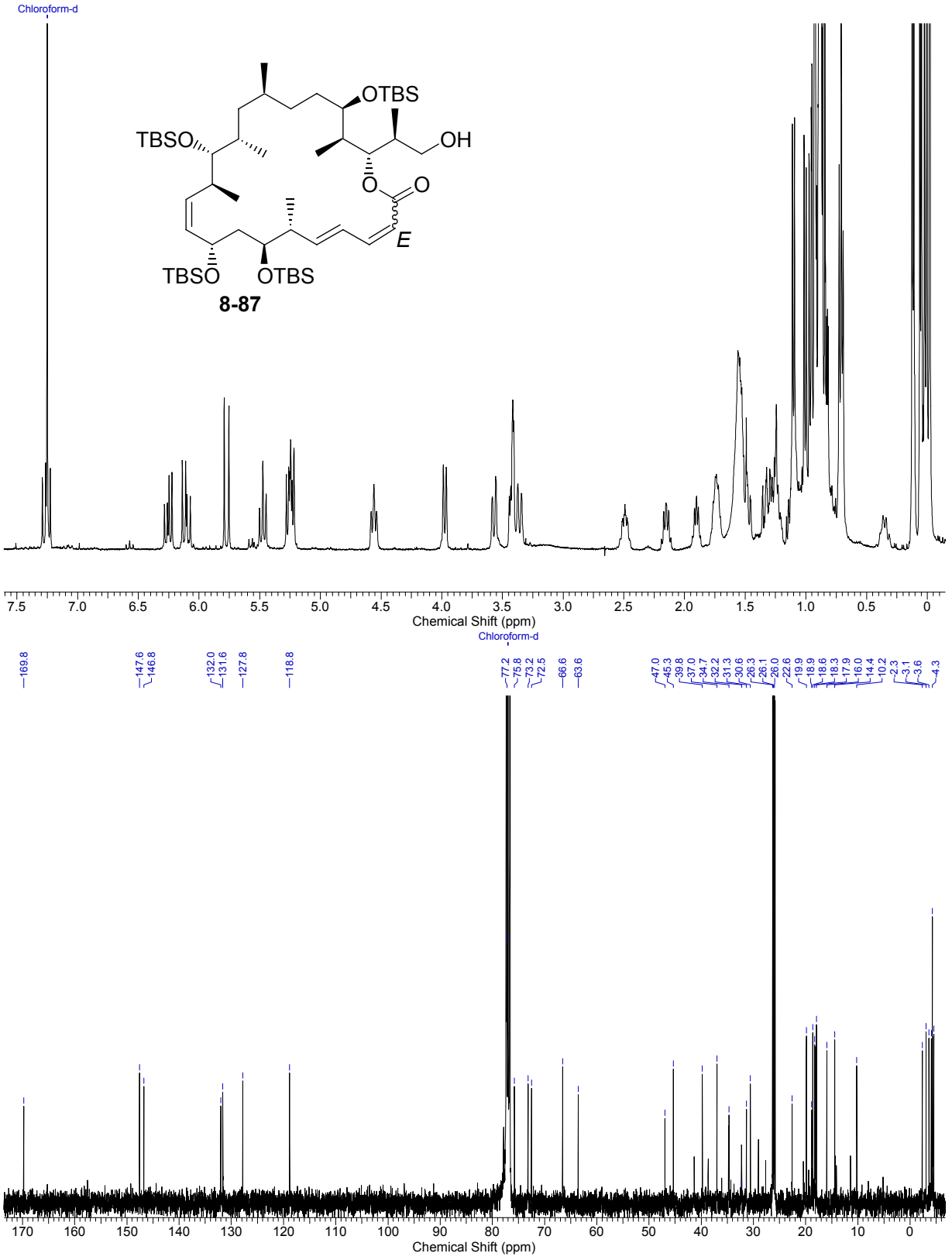

OTBS
TBSO
OPMB
TESO
COOEt
OH
OTBS

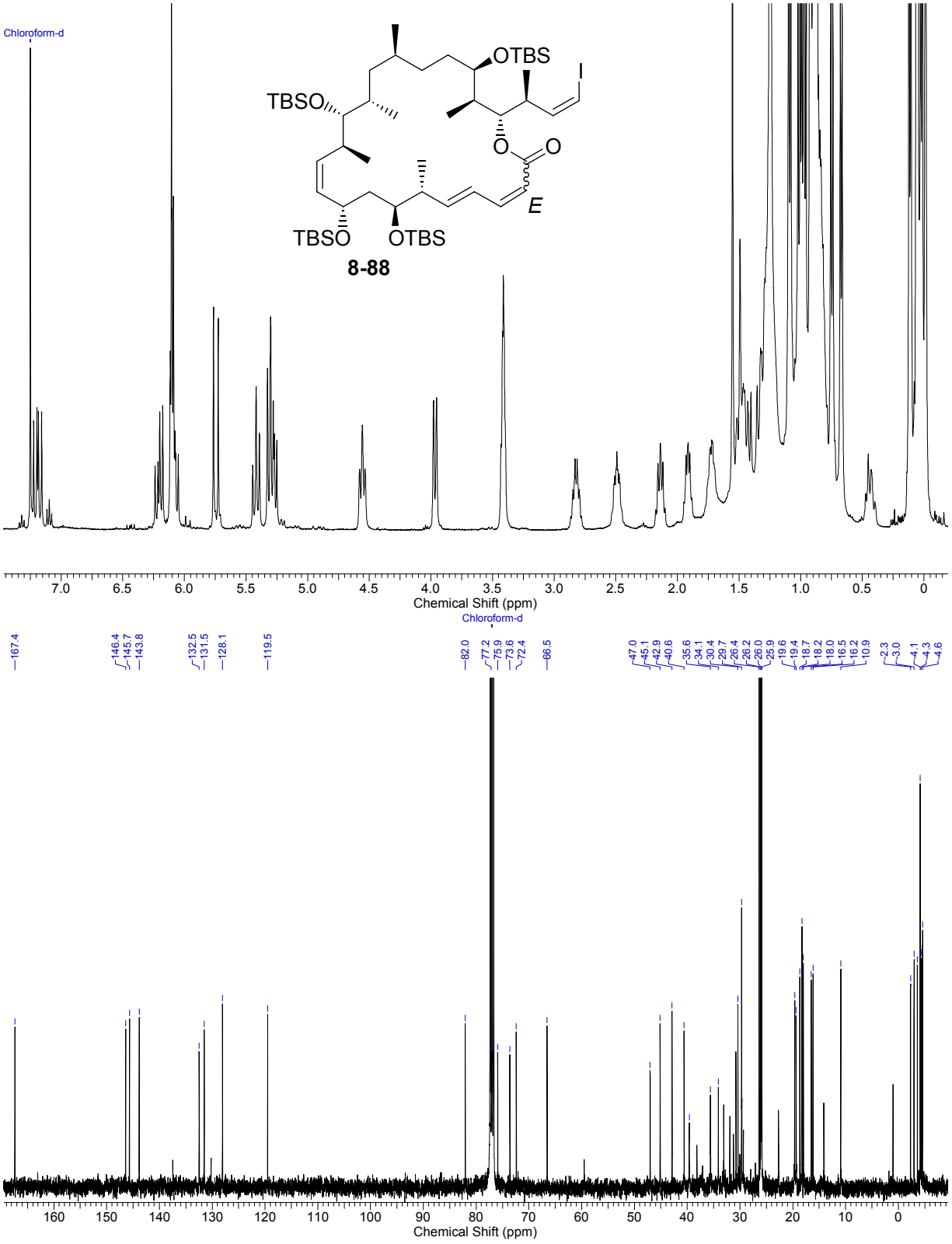
8-78

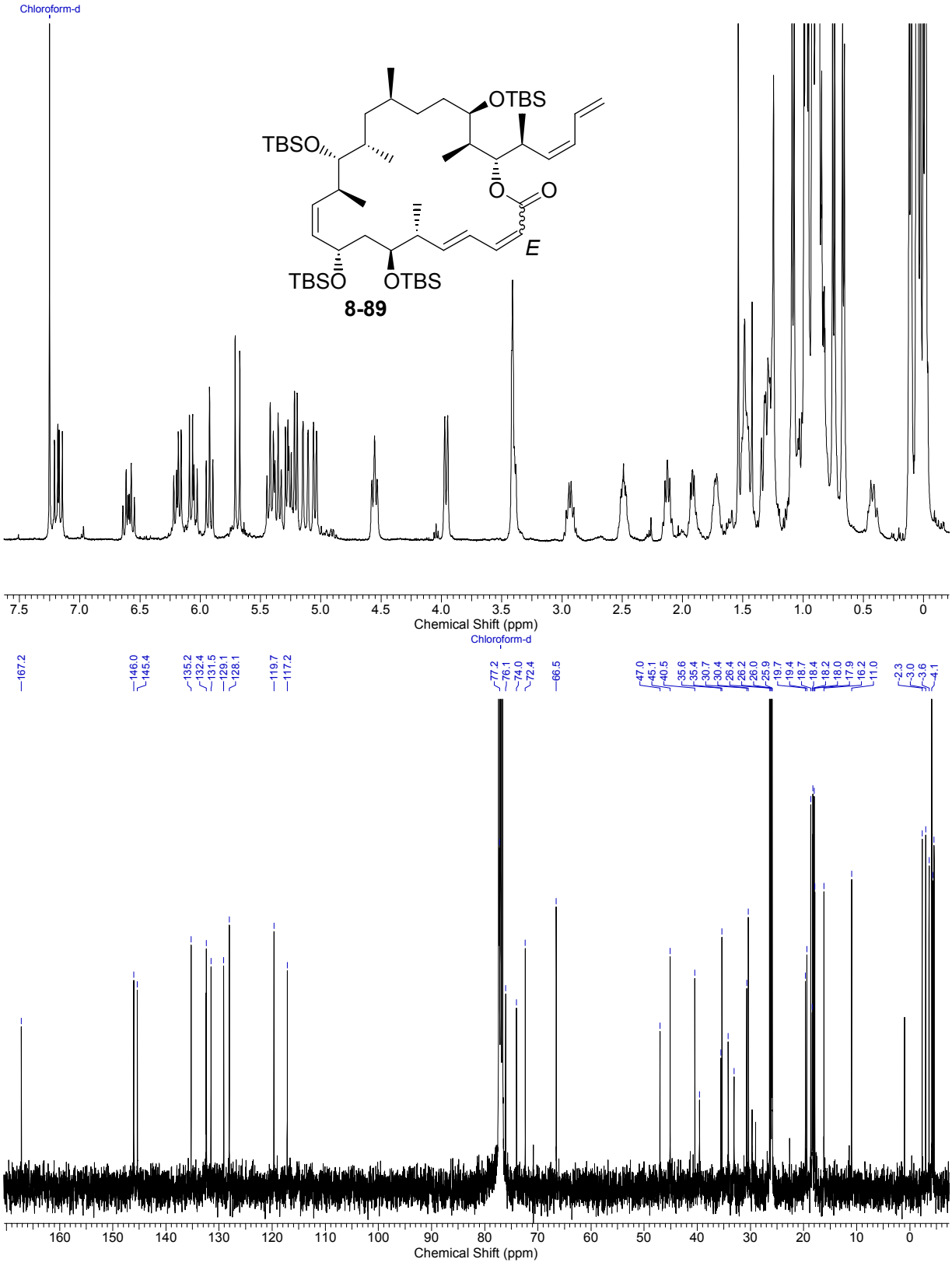
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

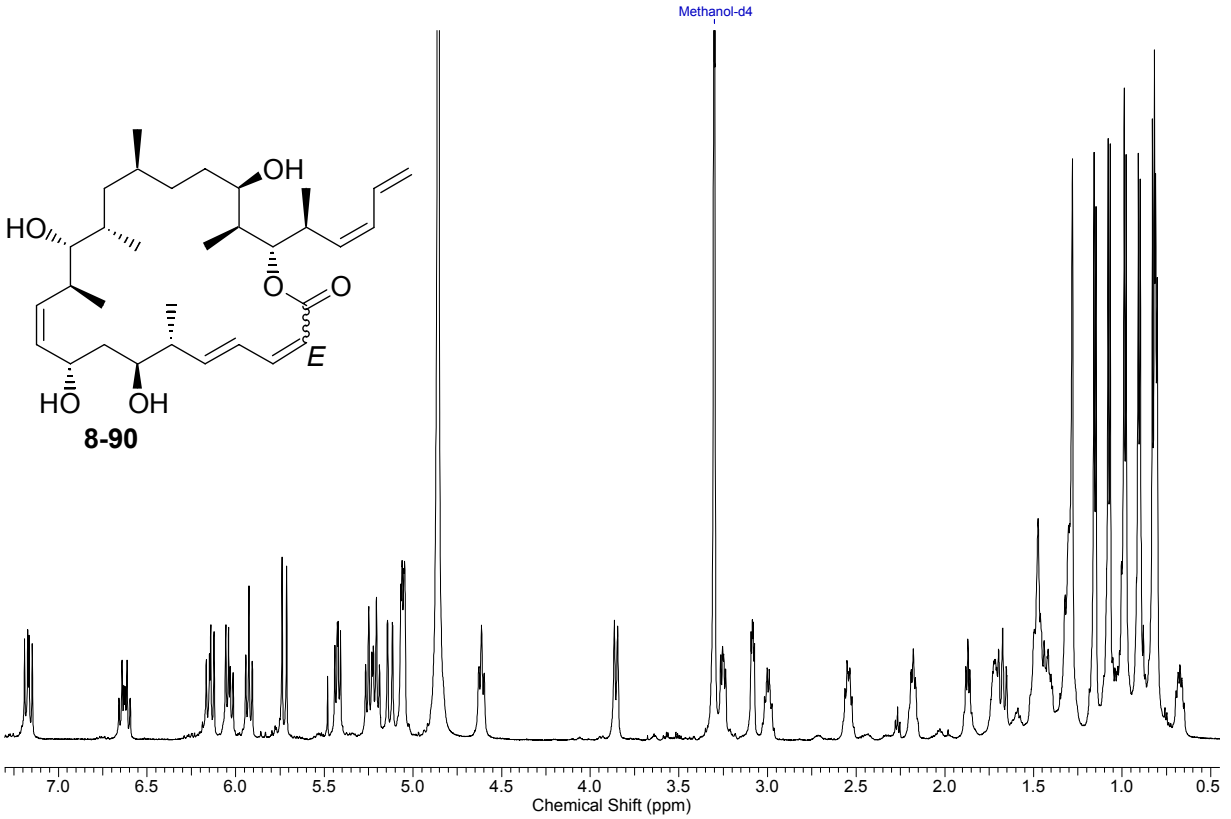

166.4
159.0
146.9
145.1
135.5
131.5
130.8
129.0
126.8
116.1
113.6
Chloroform-d
79.4
76.0
73.3
72.6
71.9
64.6
59.8
55.1
42.8
41.8
39.9
37.1
36.4
34.2
30.5
26.2
25.8
20.2
19.7
18.4
18.0
15.8
14.7
14.4
14.2
10.1
7.1
5.6
-3.3
-3.7
-3.8
-4.4
-4.5
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

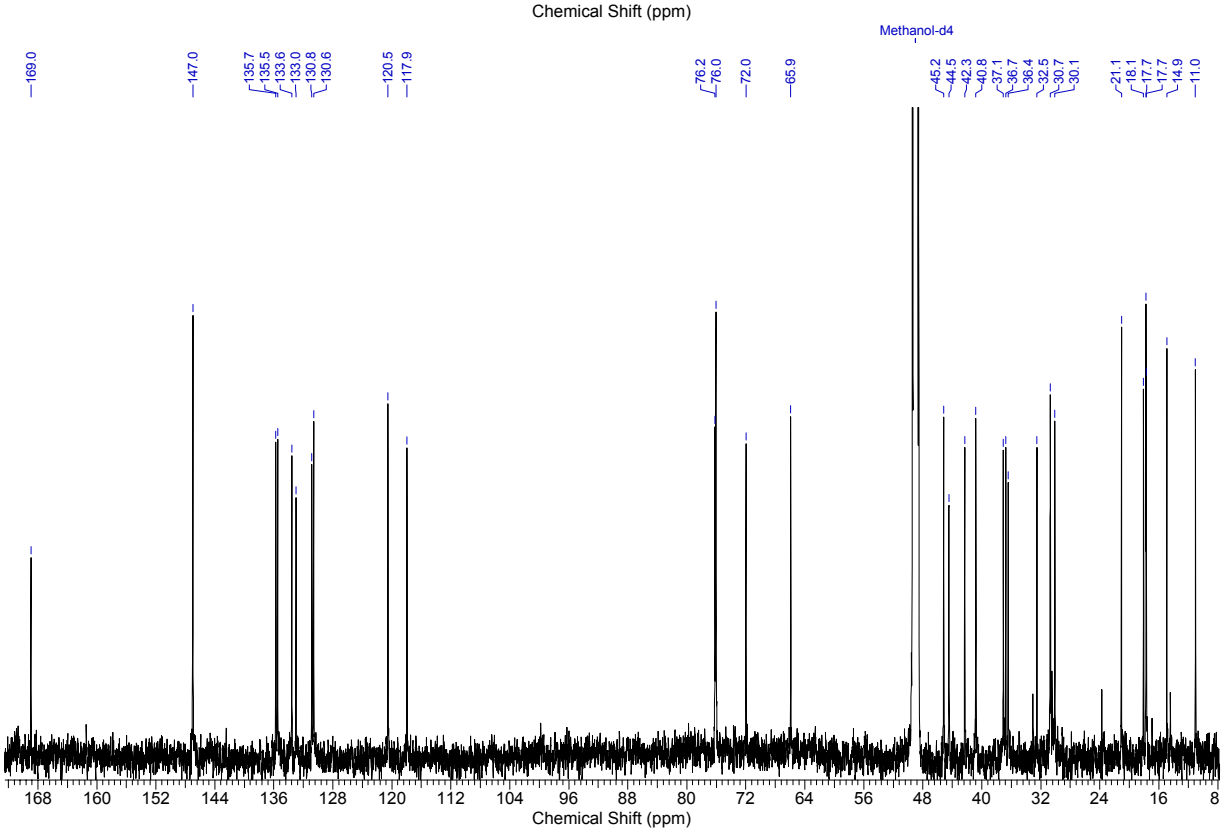

OTBS
TBSO
OPMB
O
O
E
TBSO
OTBS
8-86
Chemical Shift (ppm)
Chloroform-d
Chemical Shift (ppm)

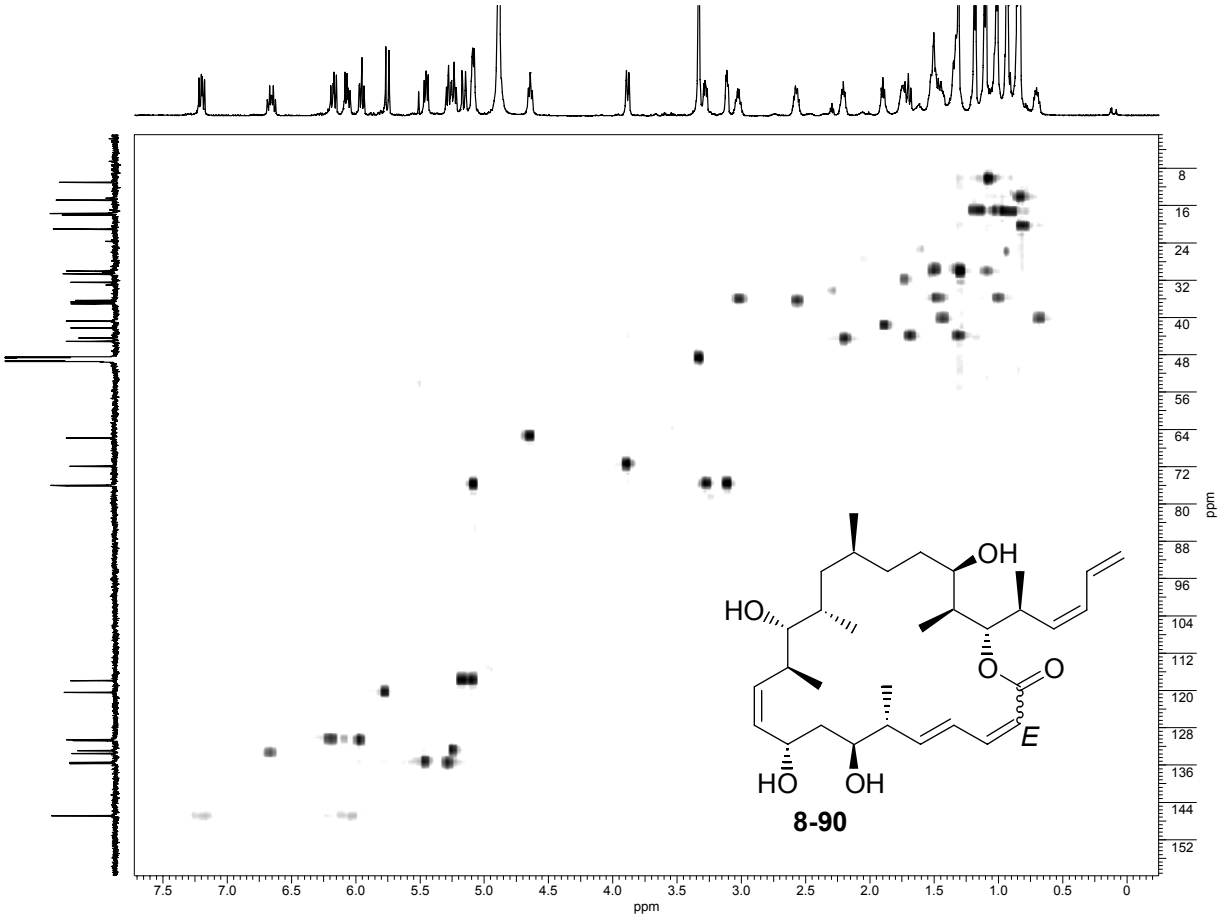

Chloroform-d
OTBS
TBSO
OH
O
O
E
TBSO
OTBS
8-87
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)
Chloroform-d
169.8
147.6
146.8
132.0
131.6
127.8
118.8
77.2
75.8
73.2
72.5
66.6
63.6
47.0
45.3
39.8
37.0
34.7
32.2
31.3
30.6
28.3
26.1
26.0
22.6
19.9
18.9
18.6
18.3
17.9
16.0
14.4
10.2
-2.3
-3.1
-3.6
-4.3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


Chloroform-d
OTBS
I
TBSO
O
O
E
TBSO
OTBS
8-88
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
Chemical Shift (ppm)
Chloroform-d
167.4
146.4
145.7
143.8
132.5
131.5
128.1
119.5
82.0
77.2
75.9
73.6
72.4
66.5
47.0
45.1
42.9
40.6
35.6
34.1
30.4
29.7
28.4
26.2
26.0
25.9
19.6
19.4
18.7
18.2
18.0
16.5
16.2
10.9
-2.3
-3.0
-4.1
-4.3
-4.6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


Chloroform-d
OTBS
TBSO
O
O
E
TBSO
OTBS
8-89
Chemical Shift (ppm)
Chloroform-d
167.2
146.0
145.4
135.2
132.4
131.5
129.1
128.1
119.7
117.2
77.2
76.1
74.0
72.4
66.5
47.0
45.1
40.5
35.6
35.4
30.7
30.4
28.4
26.2
26.0
25.9
19.7
19.4
18.7
18.4
18.2
18.0
17.9
16.2
11.0
-2.3
-3.0
-3.6
-4.1
Chemical Shift (ppm)


Methanol-d4
OH
HO
O
O
E
HO
OH
8-90
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
Chemical Shift (ppm)


Methanol-d4
169.0
147.0
135.7
135.5
133.6
133.0
130.8
130.6
120.5
117.9
76.2
76.0
72.0
65.9
45.2
44.5
42.3
40.8
37.1
36.7
36.4
32.5
30.7
30.1
21.1
18.1
17.7
17.7
14.9
11.0
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)


OH
HO
O
O
E
HO
OH
8-90
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
ppm
8
16
24
32
40
48
56
64
72
80
88
96
104
112
120
128
136
144
152
ppm

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