# Synthesis of Benzomorphan Scaffolds by Intramolecular Buchwald–Hartwig Arylation and Approach Towards the Total Synthesis of the Macrolide Queenslandon

# Synthese von Benzomorphan Scaffolds durch Intramolekulare Buchwald–Hartwig Arylierung und ein Zugang zur Totalsynthese des Macrolids Queenslandon

DISSERTATION

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# 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 |
| 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 |
| 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 | Di-iso-propyl azodicarboxylate |

| | |
|---|---|
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBALH | Diisobutylaluminium hydride |
| DMAP | 4-Dimethylaminopyridine |
| DME | Dimethoxyethane |
| DMF | N,N-Dimethylformamide |
| DMP | Dess-Martin periodinate |
| 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 |
| h | hour(s) |
| HOMO | Highest occupied molecular orbital |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz |
| $IC_{50}$ | half maximal Inhibitory Concentration |
| IR | Infrared |
| PCC | Pyridinium chlorochromate |
| Piv | Pivaloyl |
| *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 | nanomol |
| NMO | N-Methylmorpholin-N-Oxide |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| Ph | Phenyl |
| 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) |
| TBAF | Tetrabutylammonium fluoride |
| TBDMS | *tert*-Butyldimethylsilyl |
| TBS | *tert*-Butyldimethylsilyl |
| TES | Triethylsilyl |
| THF | Tetrahydrofuran |
| TIPS | Tri-iso-propylsilyl |
| TfO | Trifluoromethanesulfonate |
| TMS | Trimethylsilyl |
| Tos (Ts) | *p*-Toluenesulfonyl |
| Triflate | Trifluoromethane sulfonate |
| UV | Ultraviolet |
| *Z* | cis |

# Chapter I:

# Synthesis of Benzomorphan Scaffolds by Intramolecular Buchwald-Hartwig Arylation

# 1 Introduction

Mankind has always sought to help those who suffer from disease and, of the curative methods used, one of the oldest and most successful has been treatment with drugs. This is especially true of drugs acting on the nervous system. In fact, the earliest historical records indicate that man has long had some useful folk knowledge of drugs to heal, to soothe the spirits and to relieve pain. Thus, the ancient Greeks were aware of the properties of naturally occurring salicylates: for example, Hippocrates recommended juice of the poplar tree for the treatment of eye deseases and extracts of the leaves of the willow for the relief of pain in childbirth; both of these plants contain natural salicylates, the forerunners of aspirin. Also, natural opioids have been in use as medicines since ancient times, when Hippocrates and Galen obtained them from the juice of the poppy. Throughout the Middle Ages from Avicenna to Paracelsus, the number of extraction forms increased, culminating in Sydenham's entry of opium tincture in the pharmacopoeias. So, most of the drugs used by the early civilizations were herbal extracts, very often mixtures of a number of different plants and usually containing large amount of inactive material as well as the active constituents. Some were of animal origin, or were inorganic. Knowledge of the uses to which these 'folk remedies' could be put was the process of 'trial and error', i.e. empirically rather than by any rational process and, of course, it did not include any understanding of the biological actions of drugs, nor of their chemistry.[1]

This kind of folk medicine continued into the nineteenth century, when the scientific revolution and developments in chemistry in particular, brought about remarkable changes. Though the use of chemical analysis it became possible to separate the various constituents of the crude herbal extracts; then each constituent could be tested separately for biological activity, and finally, the chemical nature of the active component or components could be determined.

One of the most famous examples is the isolation of morphine (**1-1**) by Adam Sertürner in 1805. Following the isolation of morphine, further alkaloids were isolated from opium, for example narcotine (**1-2**) in 1817, codeine (**1-3**) in 1832, and thebaine (**1-4**) in 1835.[5]

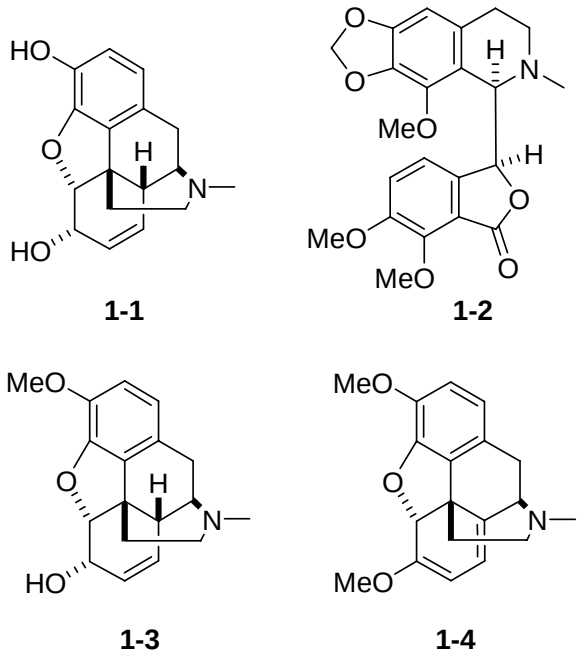



**Figure 1**. Structures of morphine (**1-1**), narcotine (**1-2**), codeine (**1-3**), thebaine (**1-4**).

Since then, morphine was recognized as a main component of opium, responsible for its analgesic activity. It is a very potent analgesic and is used till present days for the treatment of moderate to severe acute and chronic pain of various origins and is regarded as the gold standard for pain treatment.

However, the use of morphine bears some risks of side-effects. With repeated use of morphine, the analgesic effects wane and the dose has to be increased. Furthermore, morphine can cause addiction, an accommodation of the cells of the body to its presence so that its use must be continued or a withdrawal symptome appears. Thus, the problems of opiate addiction has served in part, to intensify efforts directed toward understanding the basic mechanisms of action of these type of drugs and to intensify the search for a better morphine, a substance with morphine's beneficial properties and with attenuated or no harmful side-effects including tolerance and dependence.[2]

From a chemical point of view, determination of the total structure of morphine by Robinson in 1925 was a landmark.[3] Of primary importance in the development of new synthetic

analgesics was the observation that simpler morphine-like compounds could be prepared, which contain only a portion of the parent structure, but which are as or more effective than morphine as analgesics.

The synthesis of hundreds of analogues of varying structure, detailed studies of their pharmacological activity, and the introduction of some of these into clinical medicine are clear indications of the progress being made. Thus, opening rings C and D in morphine (**1-1**) yields compounds containing the benzomorphan ring structure (Figure **2**) which have proven to be particularly interesting in this regard and are an important class of analgesics and other types of drugs.

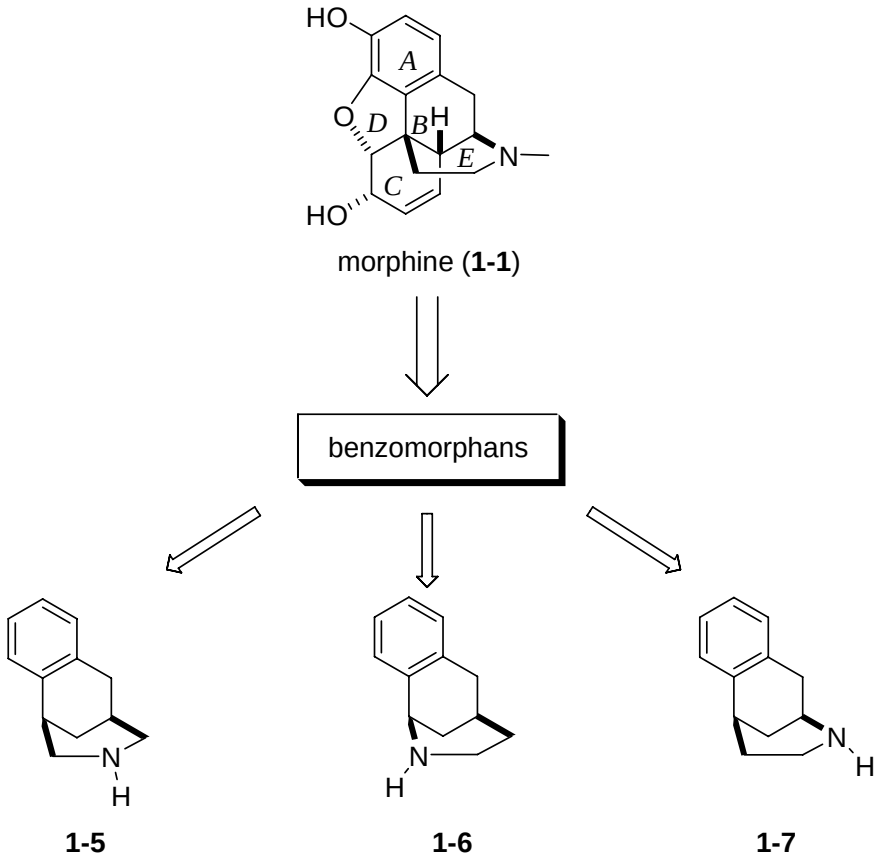
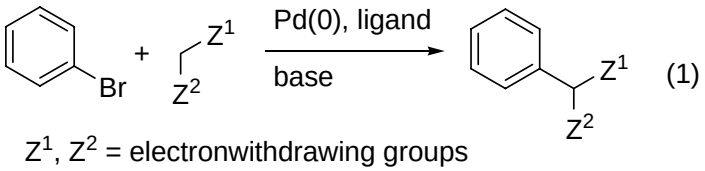



**Figure 2**. Structure of morphine (**1-1**) and benzomorphans (**1-5**, **1-6**, **1-7**).

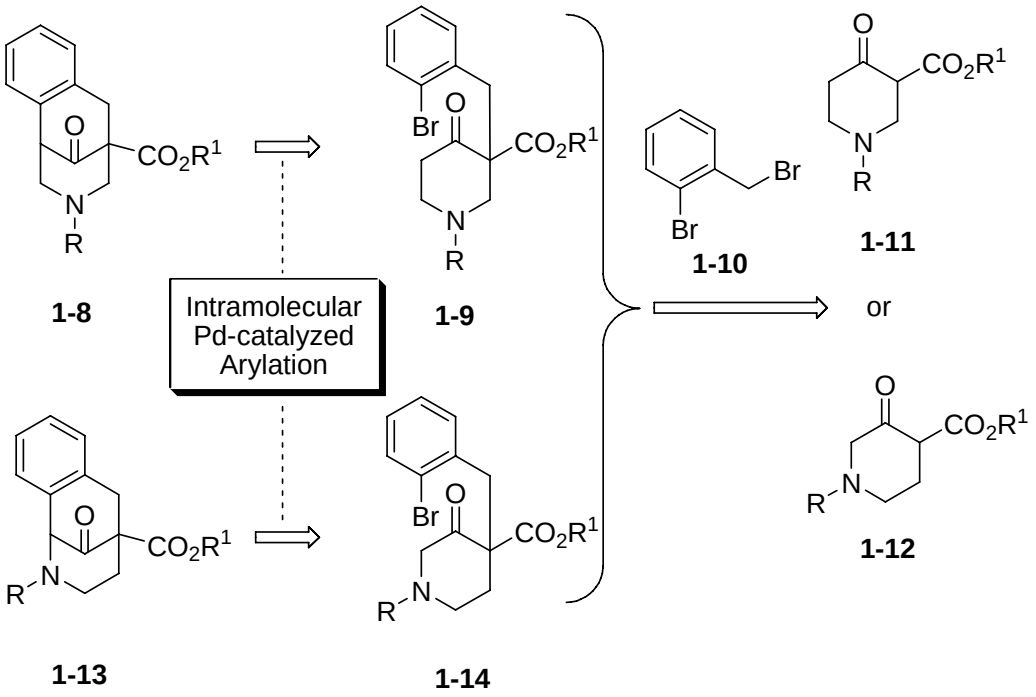
Unfortunately, many compounds which are used today also have dependence-producing and other undesirable side effects of morphine. That is why, the eventual development of effective, strong analgesics, which have no side effects of morphine, represents a reasonable goal for modern synthetic chemistry. Some useful analgesics which approach this ideal may well be benzomorphan derivatives.

In the present investigation, we focused on the design and synthesis of benzomorphan scaffolds, which could be subjected as a starting point in development of novel analgesic drugs. With the advent of new powerful organometallic transformations, such as cross-coupling or C–H insertions, the chemical way to known drugs seem to be substantially broadened. A case in point is the Buchwald–Hartwig arylation of enolates in the presence of a palladium catalyst (Eq. 1).




**Equation 1**.

Our goal was to apply this reaction in an intramolecular setting towards the synthesis of benzomorphan scaffolds (Scheme **1**). Furthermore, it was planned to study the proposed transformation using a variety of substrates and to show the generality of this methodology as a powerful tool in the preparation of various benzomorphan derivatives with potential biological activity.




**Scheme 1**. Approach to benzomorphan synthesis based on intramolecular palladium-catalyzed α-ketone arylation.

# 2 Literature Review

## 2.1 Benzomorphans – a Structural Feature of Analgesic Drugs

Most drugs acting on the nervous system produce their effect by modifying or interfering with synaptic transmission.[4] In the mammalian nervous system, transmission at synapses is mediated by the release of a neurotransmitter. Thus, while the transfer of information from one part of a nerve cell to another is electrical (e.g. by propagated action potentials), the transfer of information from one neurone to another is a chemical event, i.e. via a neurotransmitter which is released from one neurone and acts on the other. Nerve cells all possess the same basic components, i.e. cell body, axon and dendrites (Figure **3**).

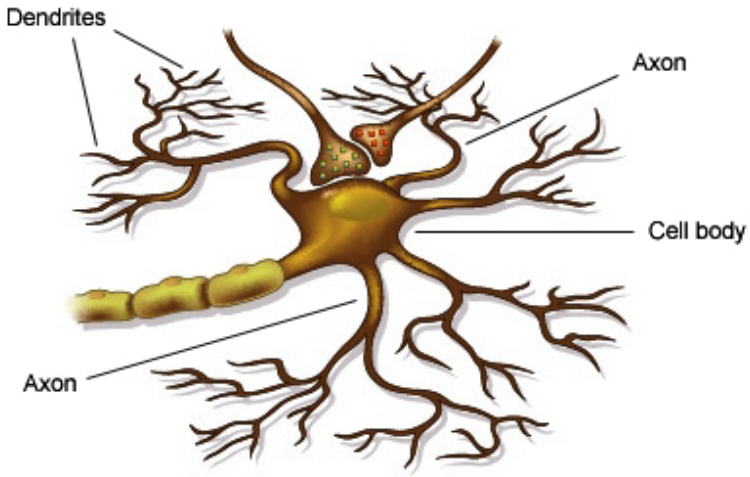



**Figure 3**. Schematic drawing of a nerve cell.

The neurotransmitter is present in the presynaptic nerve terminals where it may be stored in synaptic vesicles ready for release and where, in many cases, it is also synthesized, the enzymes involved in the synthesis being associated with the mitochondria (Figure **4**).

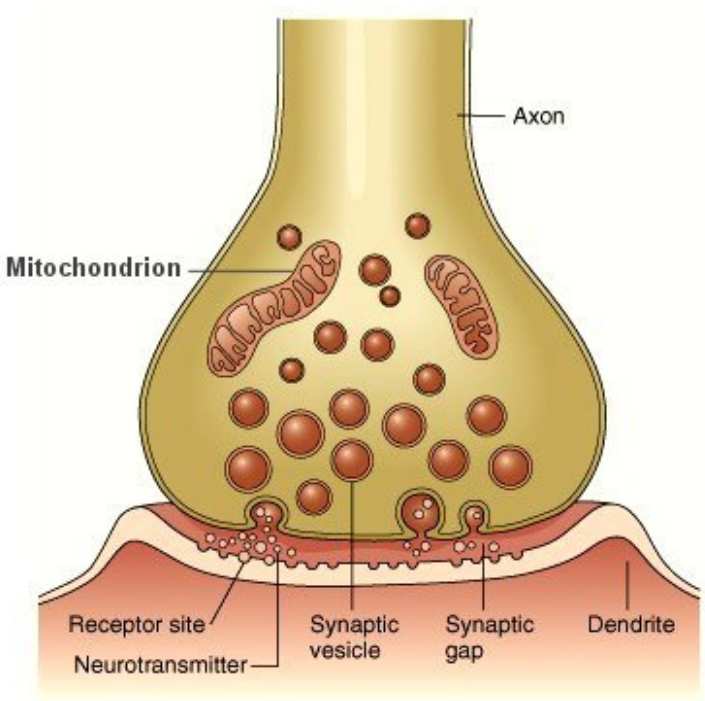



**Figure 4**. Representation of a typical synapse

The transmitter is released from the nerve terminals as the result of the arrival of action potentials, the release being dependent upon the influx of $Ca^{2+}$ ions. The released transmitter diffuses across the synaptic gap to stimulate a receptor on the postsynaptic neurone and this action results in a response in the postsynaptic cell. Many substances have been proposed as synaptic transmitters or neurotransmitters, the best-known being acetylcholine (ACh), noradrenaline, dopamine, 5-hydroxytryptamine (5-HT or serotonine), certain amino acids such as glutamic and aspartic acids, γ-aminobutyric acid and glycine, and also many peptides.

Effects on synaptic transmission by an active drug can be produced at different sites and in different ways: a) presynaptic (uptake of precursor, synthesis, storage or release of transmitter) and b) postsynaptic (agonists mimicking the action of the transmitter, antagonists blocking the action of the transmitter and agonist drugs, or removal of transmitter). Noteworthy, that all paths include the interaction with the transmitter storage or release.

Free nerve endings are identified as pain receptors in pain-sensitive tissues, which spreaded all over a body, e.g. skin, muscles and viscera. The damaged tissue sends out nerve impulses through nerve tracts in the spinal cord to the brain where the stimulus translates to a conscious pain sensation. In addition to nervous pain impulses, injured tissues produce inflammatory pain-producing substances, including bradykinin and other kinins, serotonin, histamine, acetylcholine, excesses of potassium ions, proteolytic enzymes and prostaglandins.

Finally, those substances, which can modify or inhibit the process of pain formation through nerve cells, could in some way cleave or decrease pain and cause analgesic effects.[5] In general, all substances that influence the process of synaptic transmission could be of interest for finding a new pharmaceutical.

It was found that morphine (**1-1**),[6] the natural lead structure confers its activity through an agonistic modulation at the μ-opioid receptors. In the course of structure/activity studies,[7] other opiod receptors, such as the κ-, the δ-, and the ORL-1 receptor were discovered.[8] The desired analgetic properties of opioids result mainly by binding of a ligand to the μ- and the κ-receptor. Of clinical relevance are μ-agonists,[9] partial agonists (compounds that show agonistic as well as antagonistic effects at the μ-receptor) and mixed agonist/antagonists.[10] The latter type of drugs includes compounds that are κ-agonists/μ-agonists or κ-agonists/μ-antagonists, respectively. For example, pentazocine (**2-1**) is classified as κ-agonist/partial μ-agonist (Figure **5**).

Many active drugs contain a cyclic core structure, frequently incorporating heteroatoms. In addition, other positions are decorated with groups that directly interact with matching partners on the receptor. Besides the type, the relative orientation of these groups is a key factor in determining biological activity.

As the essential structural features of such compounds the phenol and the piperidine ring were identified. In order to find analgesics with improved properties and reduced side effects a range of morphine analogs were prepared. These variations include the synthesis of truncated systems. Thus, opening of the cyclohexene ring yields the benzomorphans, such as **1-7**.[11]

Also the nitrogen atoms can be repositioned, as illustrated with structures **1-5** and **1-6**.[12] In addition, variations in the ring size have been performed in the benzomorphan series.[13] The 5-arylmorphan skeleton (**2-2**) represents another important core structure.[14]

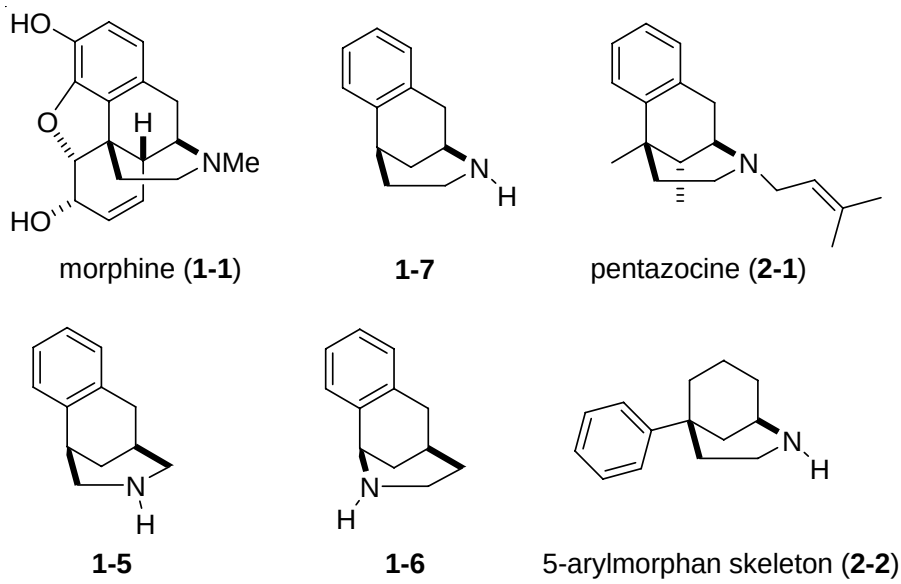



**Figure 5.** Structures of morphine (**1-1**), and prominent analogs derived from it.

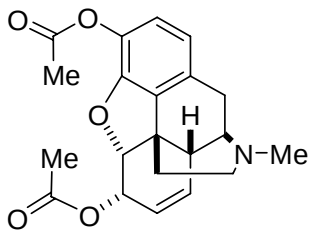
Finally, a range of μ-selective opioids without morphinan structure were discovered over the years.[9] Among the simpler morphine analogs, the benzomorphan and benzazocine tricyclic ring system are one of the most extensively investigated morphine analogues, first prepared and studied in detail by May and Eddy at the National Institutes of Health.[11]

A number of synthetic routes to benzomorphans have been developed, and chemical modifications have provided valuable new benzomorphan derivatives of practical and theoretical importance, very often with biological profiles far different from that of morphine (antitussive, respiratory, gastrointestinal, sedative, and other types of activity).

## 2.2 Clinically Used Benzomorphan Derivatives

Morphine has always been an accepted standard analgesic, the medicament without which, until recently, no one could practice medicine effectively. Its use, however, bears some risks of side-effects (breathing depression to a life-threatening degree, nausea, vomiting, sweating, dizziness, and sluggishness occur frequently). With repeated use of morphine, the analgesic effects wane and the dose has to be increased. Furthermore, morphine can cause addiction.

The earliest attempts to develop a non-dependence-inducing morphine derivative resulted in the preparation of heroin (**2-3**, 3,6-diacetylmorphine) by acetylation of morphine.[15] The potency of heroin was soon recognized. It underwent more investigation than any other product of time, and was introduced into clinical medicine in 1898.[16]



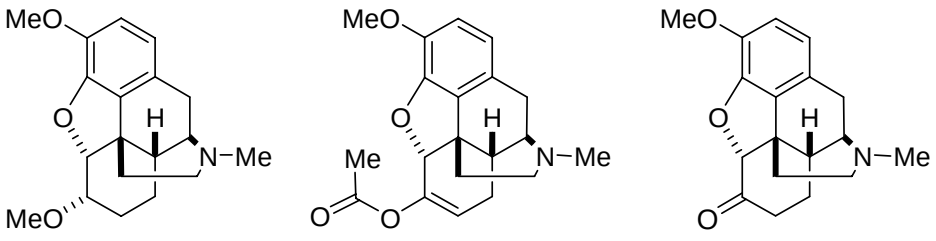

**2-3**

**Figure 6**. Structure of O,O-diacetylmorphine (**2-3**, heroine).

Reports of its reduced respiratory depression and dependence liability were soon shown to be unfounded, but its analgesic effects on animals and man (twice more than morphine) were confirmed. Pharmacological examination of acyl derivatives of morphine showed that heroin and its higher and lower acyl homologues have similar analgesic potencies in rodents and have high physical dependence liability.[17]

The introduction of heroin, although based on inaccurate observations and interpretation, undoubtedly influenced the trend and objectives of morphine research and marked the beginning of the search for an improved analgesic. During the 25 years after the introduction

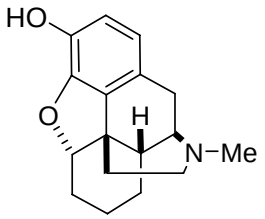
of heroin, other morphine derivatives were incorporated into medical practice some of which are still being used today (Figure **7**). These include dihydrocodeine (**2-4**), thebacon (**2-5**, acetyldihydrocodeinone), hydrocodone (**2-6**, dihydrocodeinone). All of these are analgesics, but mainly used as antitussives.




**2-4** **2-5** **2-6**

**Figure 7**. Structures of dihydrocodeine (**2-4**), thebacon (**2-5**), hydrocodone (**2-6**).

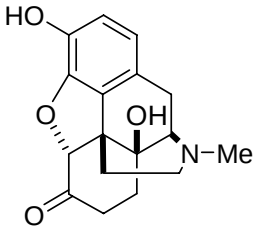
In the 1920s a most significant change in analgesic research came out: the beginning of the first systematic study of structure-activity relationships which endeavored to separate analgesic effectiveness from side-effects and addiction liability. In the USA, this plan was directed from 1929-1939 by the Committee on Drug Addiction of the National Research Council (NRC) with financial support from the Rockefeller Foundation. This program consisted of modification of the morphine molecule at all accessible points and also targeted (modified) partial structures of the morphine molecule, such as phenanthrene, hydrogenated phenanthrene, isoquinoline, dibenzofuran, and carbazole. More than 150 derivatives of morphine and more than 300 synthetic products were tested for analgesic, respiratory, gastrointestinal, sedative, and other central nervous system effects. The significance of the phenolic and alcoholic hydroxyls for intensity of analgesic action was established. Removal of the latter, as in desomorphine (**2-7**, Figure **8**), resulted in the most rapidly acting and potent analgesic known at that time.[18]



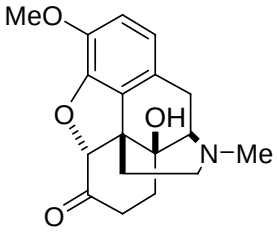

**2-7**

**Figure 8**. Structure of desomorphine (**2-7**).

After 10 years of intensive research, no significant dissociation of potent analgesia and dependence liability was accomplished. As an indirect result of the systematic program the identification of the 17-hydroxy-7,8-dihydro compounds oxycodone (**2-8**, patented in 1925 by E. Merck AG, Germany) and oxymorphone (**2-9**), derived from thebaine, are of particular note (Figure **9**).



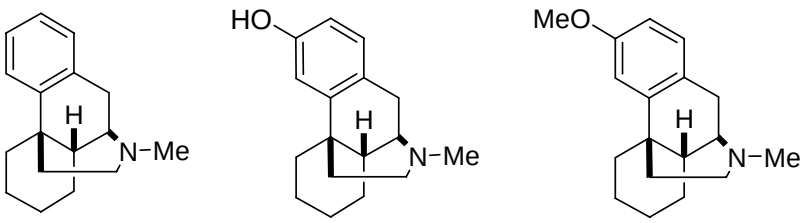

**2-8**




**2-9**

**Figure 9**. Structures of oxycodone (**2-8**), oxymorphone (**2-9**).

The attempts to synthesize morphine led to the synthesis of its basic skeleton by Grewe in 1946.[19] This work, continued by Schnider et al.,[20] yielded the significant discovery that the complete morphine structure is not essential for potent analgesic activity. N-Methylmorphinan (**2-10**) is analgesic, and levorphanol (**2-11**) is an effective therapeutic agent, more potent than morphine (Figure **10**).

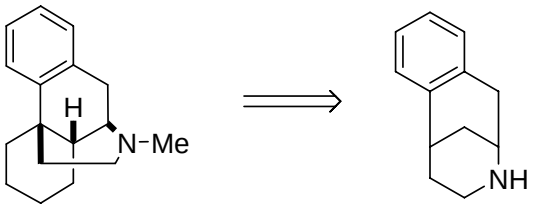



**2-10** **2-11** **2-12**

**Figure 10**. Structures of N-methylmorphinane (**2-10**), levorphanol (**2-11**), dextrometorphan (**2-12**).

Anther example is dextrometorphan (**2-12**), which is a low to medium affinity NMDA channel blocker. The former has been in clinical use as an antitussive* for about 40 years and could therefore be considered as a very safe drug.[21]

The synthesis of N-methylmorphinan (**2-10**) prompted the synthesis of even simpler modifications, benzomorphans (Figure **11**).

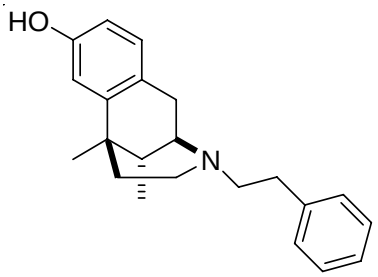



N-Methylmorphinan (**2-10**) **1-7**

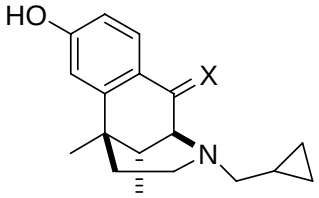
**Figure 11**. From N-methylmorphinan (**2-10**) to benzomorphan (**1-7**).

The first of the benzomorphans family was phenazocine (**2-13**) (analgesic, low dependence capacity). Another analog, ketocyclazocine (**2-14b**), was found to act as κ-agonist.[22] The derivative, bremazocine (**2-15**), is a potent, long lasting κ-agonist with activity at μ-sites as well, however possessing strong psychotomimetic† side effects (Figure **12**).

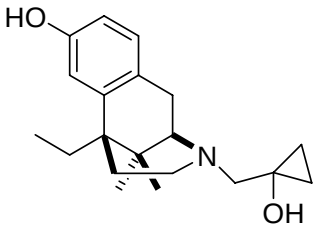
* Antitussive: capable of relieving or suppressing coughing.
† Psychotomimetic: tending to induce hallucinations, delusions, or other symptoms of a psychosis.




**2-13**



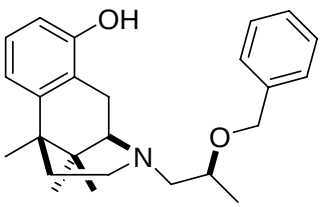

Cyclazocine **2-14a** (X = $H_2$)
Ketocyclazocine **2-14b** (X = O)




**2-15**

**Figure 12**. Structures of phenazocine (**2-13**), cyclazocine (**2-14a**), ketocyclazocine (**2-14b**), bremazocine (**2-15**).

Crobenetine (**2-16**, BIII 890 CL, Figure **13**), is in clinical trials and characterized as a voltage- and frequency-dependent sodium channel blocker.[23] It was demonstrated that BIII 890 CL is a potent, selective, and highly use-dependent $Na^+$ channel blocker that protects brain tissue from the deleterious effects of permanent focal cerebral ischemia in rodents at doses that do not disturb motor coordination. It therefore could be used as a neuroprotective therapy for the treatment of acute thromboembolic stroke.




Crobenetine (**2-16**)
(Boehringer Ingelheim Pharma KG)

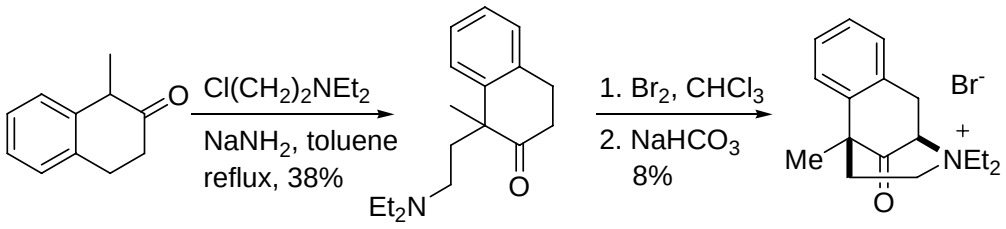
**Figure 13**. Structure of crobenetine (**2-16**).

## 2.3 Overview of Known Methods for the Preparation of Various Benzomorphans

As mentioned before, during the past century the desire of finding simplier morphine analogs resulted in the discovery that the complete morphine structure is not essential for analgesic activity. Besides the biological properties, benzomorphans have been recognized as an interesting scaffold for organic chemists to elaborate innovative approaches and to develop new methodologies. Some of these attempts are presented below.

### 2.3.1 The Tetralone Route

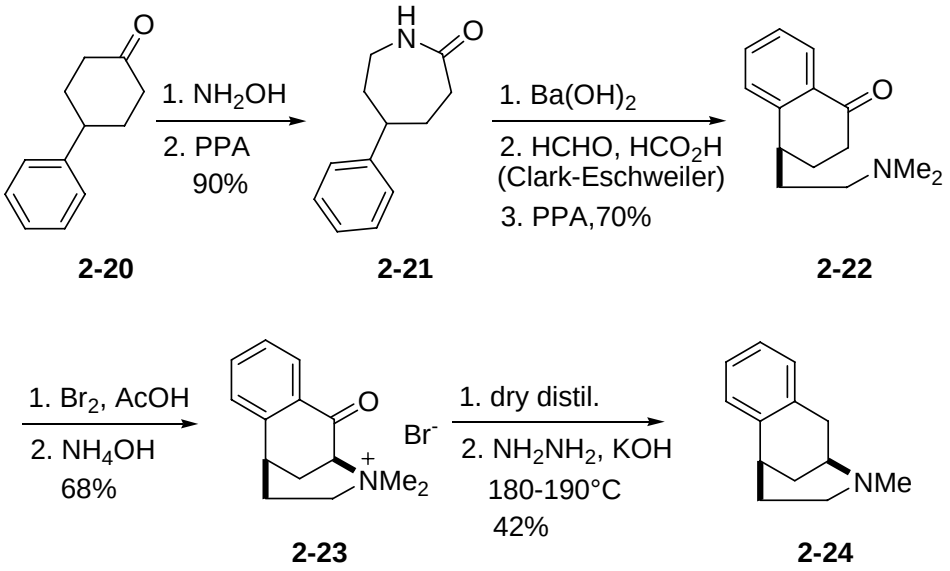
The tetralone route to benzomorphans is referred to the synthetic pathway in which the key intermediate is an appropriately substituted tetralone derivative. The very first result in the construction of the benzomorphan ring skeleton was achieved in 1947 by J. A.Baltrop.[24] The methyl substituted tetralone **2-17** was engaged in the alkylation reaction with 2-chloroethyl-N,N-diethylamine to form the amino ketone **2-18** which was then brominated at the free α-position of the keto group (Scheme **2**). Treatment of the latter under basic conditions ($NaHCO_3$) resulted in the intramolecular alkylation of the tertiary amine and formation of the quaternary salt **2-19**. Although this latter synthesis suffers from low yields, it represents the preparation of the first member of the benzomorphan family.




**2-17** **2-18** **2-19**

**Scheme 2**. Synthesis of benzomorphan **2-19** by J. A. Baltrop.

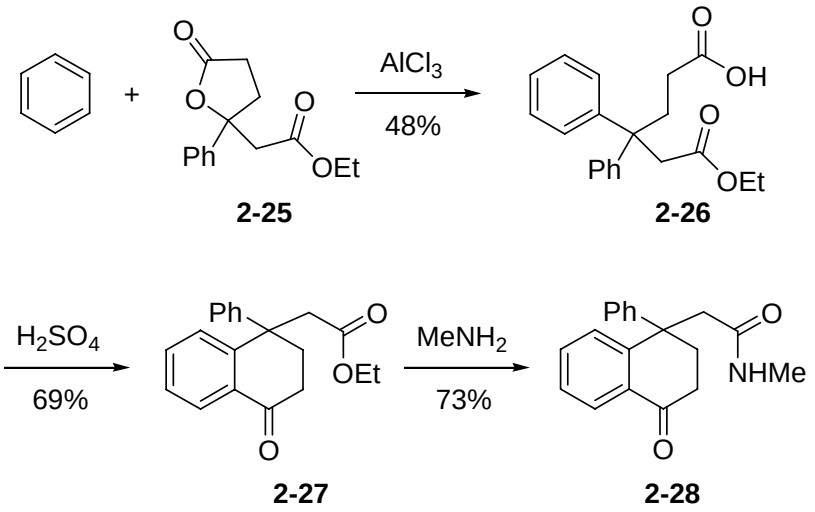
Later this route was applied for the preparation of the "naked" N-methylbenzomorphan **2-24**.[25] The main tetralone precursor for cyclization was synthesized using a very interesting sequence. Thus, 4-phenylcyclohexanone (**2-20**) was converted to the oxime followed by Beckmann-type rearrangement to 5-phenylcaprolactam (**2-21**). Hydrolysis with $Ba(OH)_2$ afforded the amino acid wich was methylated at the free amino function by the Clark-Eschweiler method followed by cyclization with polyphosphoric acid to yield the aminoketone **2-22**. Bromination of the resulting tetralone and treatment with conc. aqueous $NH_4OH$ afforded cyclic quaternized salt **2-23** in unexpectingly high yield of 68%. After dry distillation and reduction under Wolff-Kishner conditions, N-methylbenzomorphan **2-24** was obtained (Scheme **3**).




**Scheme 3**. Synthesis of benzomorphan **2-24** by Mitsuhashi and co-workers.

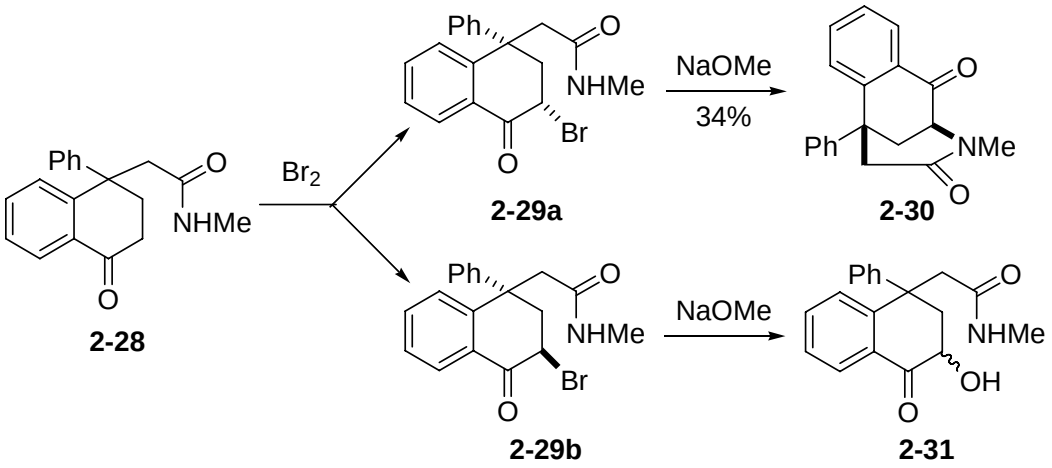
A similar approach was used by G. N. Walker and D. Alkalay,[26] but avoiding quaternary salt formation. Instead, they employed an intramolecular reaction between α-Br-ketone and a mono-substituted amide moiety. The required tetralone derivative was prepared by starting with a Friedel-Crafts condensation of 4-(carbethoxymethyl)-4-phenyl-butyrolactone (**2-25**) with benzene providing a 48% yield of β,β-diphenyladipinic acid (**2-26**) which on cyclization with concentrated sulfuric acid afforded 4-carbethoxymethyl-4-phenyl-1-tetralone (**2-27**),[27]

(Scheme **4**). Reaction of keto ester **2-27** with 40%-aqueos methylamine in ethanol for one week resulted in the formation of 4-carboxamidomethyl-4-phenyl-1-tetralone (**2-28**).



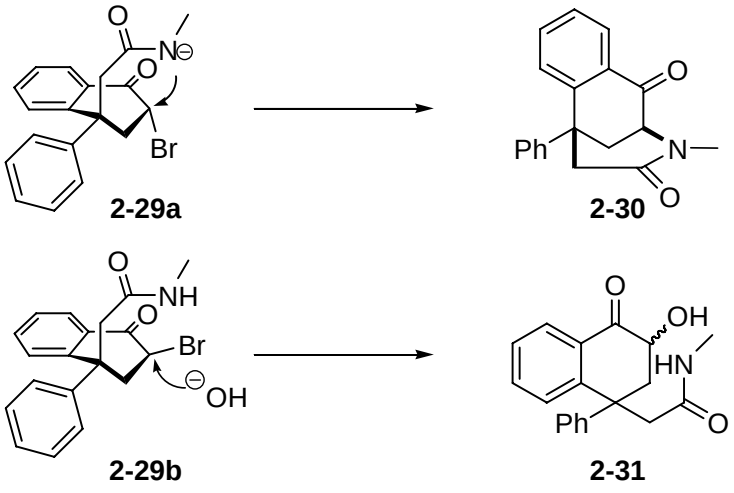

**Scheme 4**. Preparation of 4-carboxamidomethyl-4-phenyl-1-tetralone (**2-28**) by Walker and co-workers.

From this N-methylamide **2-28**, after bromination and treatment with NaOMe the desired benzomorphan derivative **2-30** was obtained in 34% yield (Scheme **5**). Interestingly, the authors note that only one isomer (**2-29a**) from the bromination reaction undergoes the desired cyclization. Another diastereomer **2-29b**, with bromine atom and phenyl substituent are *trans*-, forms only hydroxy ketone **2-31** (Scheme **5**).




**Scheme 5**. Bromination of tetralone **2-28** and treatment of diastereomeric mixture **2-29a,b** with sodium methoxide.

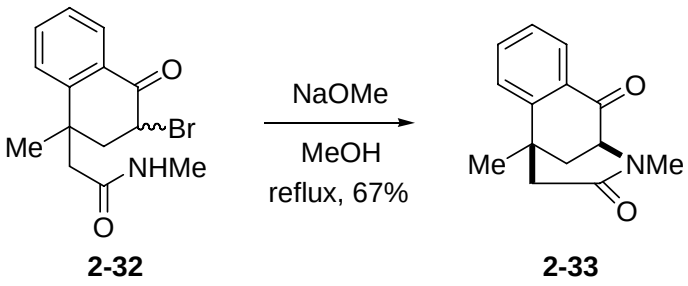
Such selectivity can be satisfyingly explained by the $S_N2$-character of this reaction, which involves backside attack of the α-Br-ketone with the amide as a nucleophile (Scheme **6**).




**Scheme 6**. $S_N2$ reactions of tetralones **2-29a** and **2-29b**.

Extension of the tetralone route through intramolecular reaction between the α-Br-function and a mono-substituted amide moiety was later described by W. L. Nelson and K. F. Nelson.[28] In their investigation the key tetralone **2-32** was prepared by almost the same route

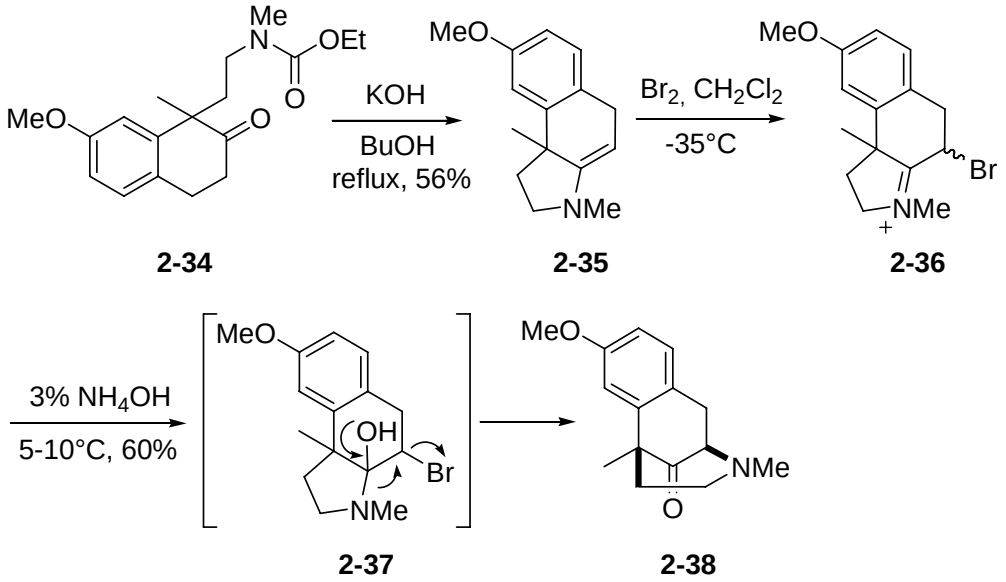
as above, but with methyl instead phenyl substituent in 4-position of the tetralone (Scheme **7**). In contrast to the previously described method, bromination and subsequent cyclization under basic conditions delivered the desired benzomorphan **2-33** with significantly higher yield. Noteworthy, the authors did not observe the formation of hydroxy ketone in this case.




**2-32** **2-33**

**Scheme 7**. Synthesis of benzomorphan **2-33** by W. L. Nelson and K. F. Nelson.

A rather interesting approach was described by Japanese researchers.[29] Analogously to previously highlighted synthetic ways, these authors first prepared the tetralone derivative **2-34**, which after hydrolysis of the urethane residue formed cyclic enamine **2-35**. When this enamine was brominated in $CH_2Cl_2$ and the reaction mixture treated with aqueous ammonium hydroxide at room temperature, the 10-oxobenzomorphan **2-38** was obtained in 81% yield. A possible mechanism for this conversion has been proposed. Thus, attack of hydroxyl anion to the initially formed bromo iminium bromide **2-36** would give intermediate **2-37** which may undergo, presumably in a concerted manner, rearrangement to the desired benzomorphan **2-38** (Scheme **8**).




**Scheme 8**. Synthesis of benzomorphan **2-38** by Takeda and co-workers.

This method had also been successfully used by the same authors to prepare the homobenzomorphan analogue **2-39** as a key intermediate for the synthesis of homobenzomorphan analgetics (Figure **14**).

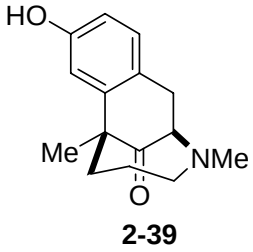
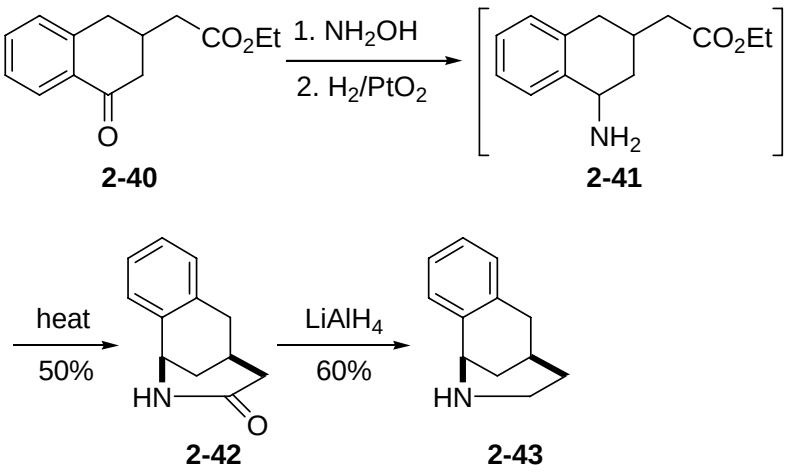



**Figure 14**. Structure of homobenzomorphan derivative **2-39**.

The formation of cyclic lactams has also found its use for the synthesis of benzomorphans (Scheme **9**).[25] Thus, the ethyl ester of 4-tetralone-2-acetic acid (**2-40**) was treated with hydroxylamine in refluxing EtOH to give the oxime, followed by catalytic reduction over Adams catalyst to afford amino ester **2-41**. The crude product was immediately heated to 160–170 °C for 2 hours to form the cyclic lactam **2-42**. Of course, cyclization affects only the *cis*

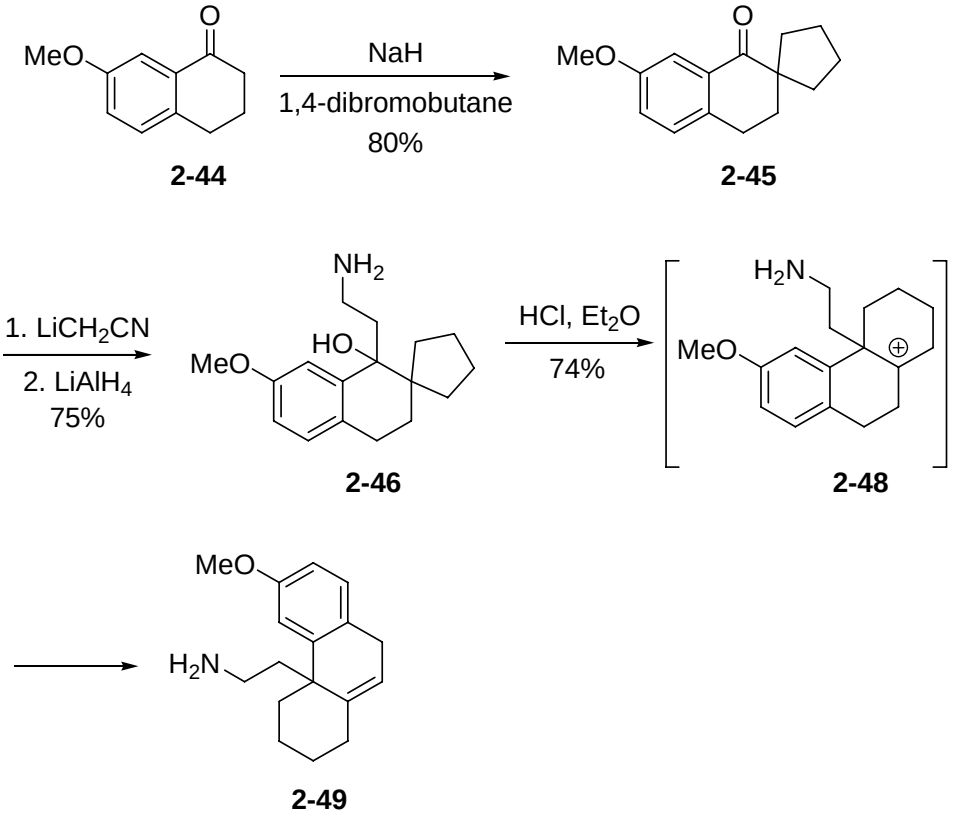
isomer of amino ester **2-41**. The lactam was reduced with lithium aluminium hydride to deliver benzomorphan **2-43**.




**Scheme 9**. Synthesis of benzomorphan **2-43** by intramolecular lactam formation.

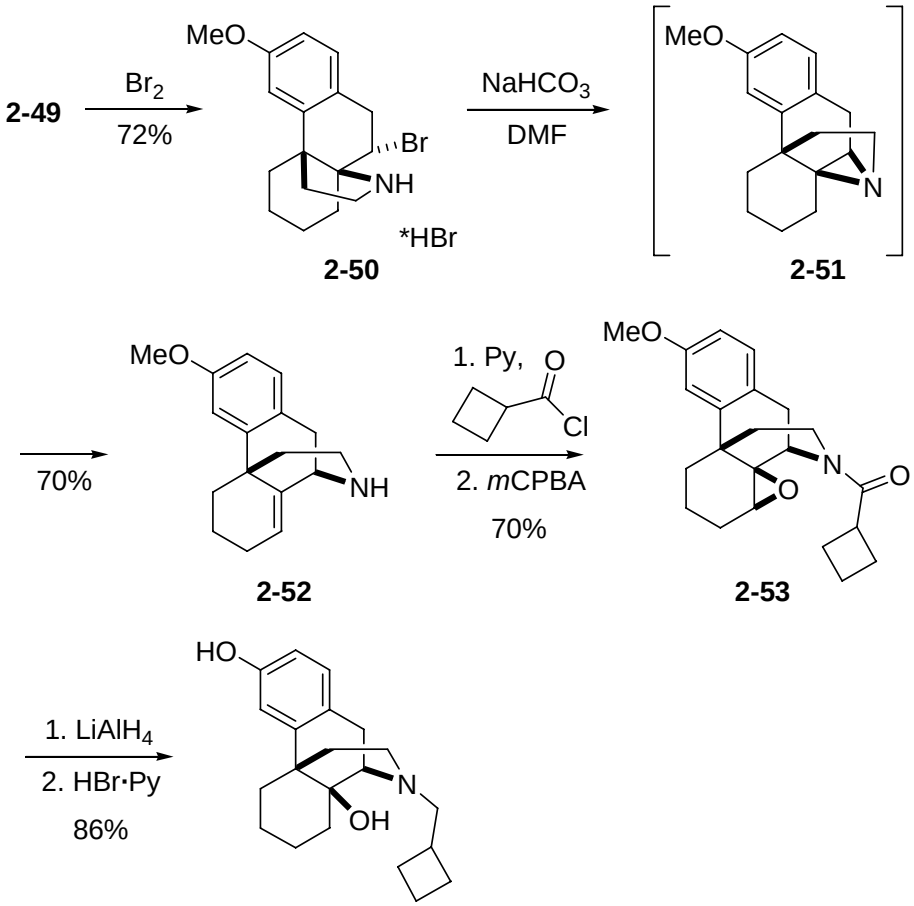
The synthesis of butorphanol **2-54** is a representative example for a succesful application of a multi-step synthesis of a potent pharmaceutical.[30] As an alternative to previously described routes, the authors utilized the synthetic approach to morphinane-related structures, which lend itself to the introduction of the hydroxyl group at the C-14 atom (Scheme **11**).

Alkylation of 7-methoxy-1-tetralone **2-44** with 1,4-dibromobutane using sodium hydride in refluxing benzene gave the spiroketone **2-45** (Scheme **10**). Cyanomethylation of **2-46** led to the hydroxynitrile which was reduced with $LiAlH_4$, without prior isolation, to the amino alcohol **2-47**. Rearrangement of the latter presumably *via* intermediate carbenium ion **2-48**, by refluxing in a mixture of concentrated hydrochloric acid and ether during 24 hours afforded the unsaturated amine **2-49** in 74% yield.




**Scheme 10**. Formation of spiro-aminoketon **2-46** and rearrangement to alkene **2-49**.

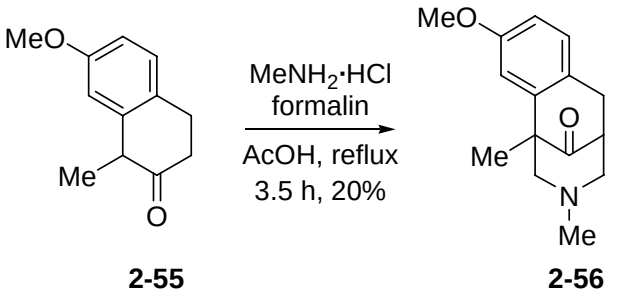
Compound **2-49** was treated with $Br_2$ to give 72% yield the bromohasubanan hydrobromide salt **2-50** (Scheme **11**). Cyclization of **2-50** with sodium bicarbonate in DMF at 130–135 °C led to the isolation of methoxymorphinan **2-52** (70% yield). When the same reaction was carried out at lower temperature, the aziridine hydrobromide **2-51** was isolated and allowed the authors to postulate the fact that this transformation passes through **2-51** as an intermediate in the formation of the alkene **2-52**. Acylation of compound **2-52** by standard procedure readily afforded the corresponding amide. Epoxidation of this unsaturated amide with *m*-chloroperbenzoic acid yielded the expected 8,14-β-epoxide **2-53**. Reduction with $LiAlH_4$ in refluxing THF gave the intermediate amino alkohol which was demethylated with boron tribromide in $CH_2Cl_2$, whereupon 3,14-dihydroxy-N-cyclobutylmethylmorphinan (**2-54**, butorphanol) was obtained in 86% yield. Resolution of the optical isomers was accomplished with *l*-tartaric acid to give the tartrate salt of *l*-butorphanol (*l*-**2-54**).




**Scheme 11**. Synthesis of butorphanol (**2-54**).

Using this synthetic route, several other N-substituted analogues of **2-54** as well as several isomorphinans and hasubanan analogs were readily prepared and proved to be very potent analgetics.[31]

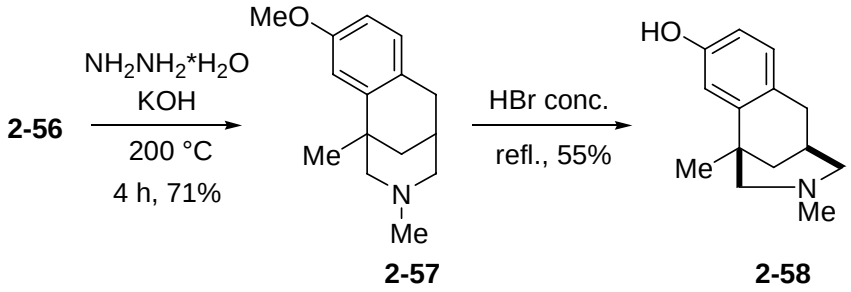
Use of the Mannich reaction extended the tetralone route for the synthesis of benzomorphans. Thus, in 1977 it was reported as a route to benzomorphans such as **2-56**.[32] Utilizing a double Mannich reaction of tetralone **2-55** with $MeNH_2$ and $CH_2O$ under acidic conditions provided the benzomorphan scaffold **2-56** in one step although in rather low yield (Scheme **12**).




**2-55** **2-56**

**Scheme 12**. Preparation of benzomorphan derivative **2-56** using double Mannich reaction.

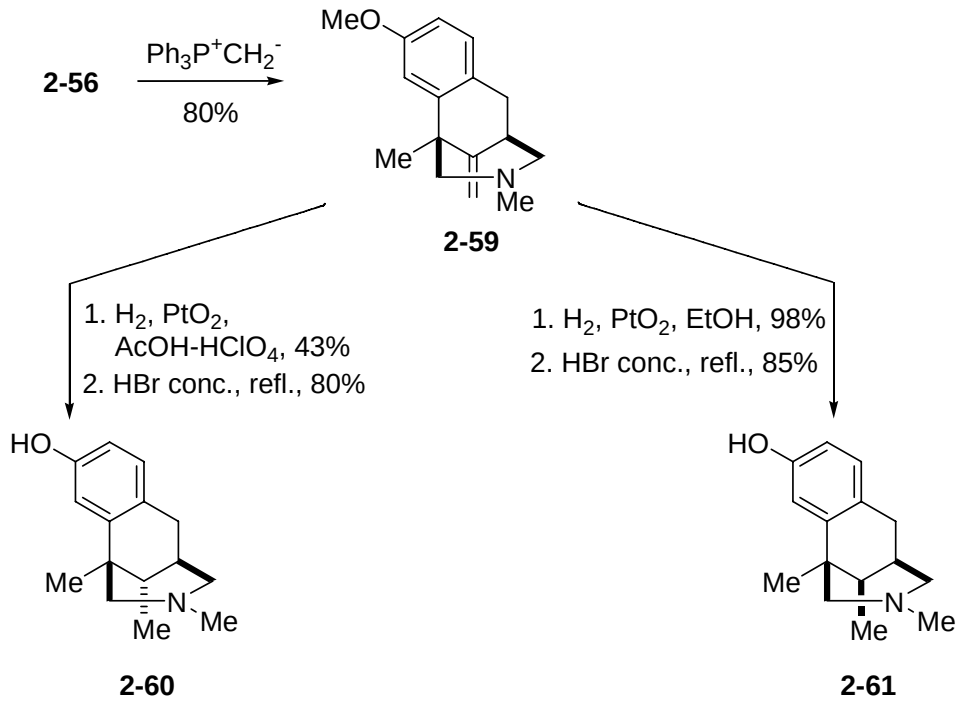
From this ketone were then prepared three benzomorphan derivatives as subjects for biological activity tests (Scheme **13**). Compound **2-57** was available after Wolff-Kishner reaction on scaffold **2-56** in 71% yield. Refluxing of methoxybenzomorphan **2-57** with conc. HBr resulted in O-demethylation and afforded the hydrobromide salt of **2-58**.




**2-57** **2-58**

**Scheme 13**. Preparation of benzomorphan **2-58**.

Wittig reaction of ketone **2-56** with $PPh_3=CH_2$ gave alkene **2-59**, which under different hydrogenation conditions formed two different products (Scheme **14**). At first, under acidic conditions, hydrogenation of **2-59** with $PtO_2$ as catalyst delivered the α-isomer in 48% yield, although under neutral conditions with the same catalyst and EtOH as a solvent only β-isomer was formed. O-Demethylation under the same conditions (refluxing with conc. aqueous HBr) gave 3,6,11-trimethyl-8-hydroxybenzomorphans **2-60** and **2-61**.



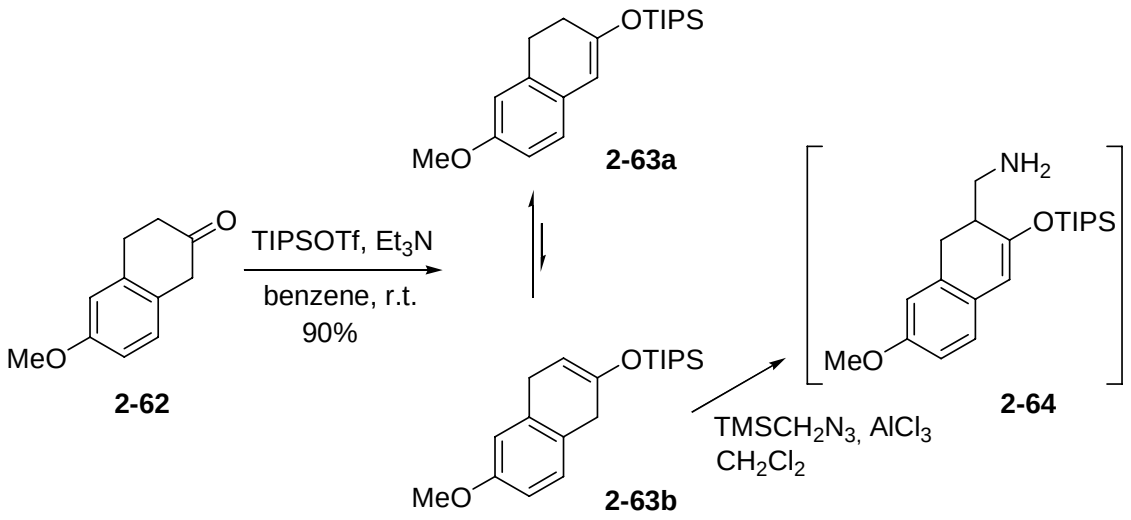

**Scheme 14**. Preparation of benzomorphans **2-60** and **2-61**.

Finally, it was found that compound **2-58** has analgesic potency comparable to that of codeine by the method of stimuli on mouse tail. The other two substances (**2-60** and **2-61**) were also found to be significantly active in the same tests.

The intramolecular Mannich reaction, which leads to benzomorphans from appropriately substituted tetralones, has found its application later for the synthesis of various conformationally constrained *l*-tyrosine analogues as targets for their potential application to SH2 domain ligands.[33]

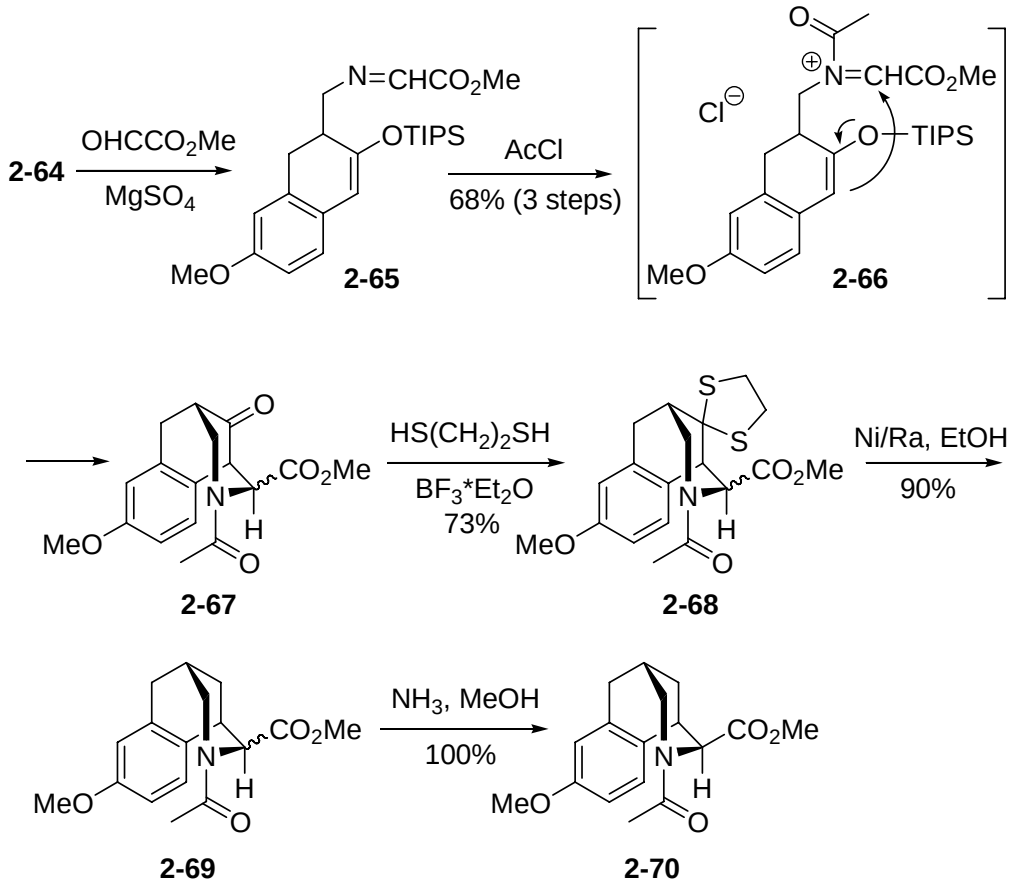
Tetralone **2-62** was subjected to an initial aminomethylation of silyl enol ethers **2-63a,b** which had been obtained as an inseparable mixture (Scheme **15**). Subjecting this mixture to aminomethylation provided the desired primary amine **2-64** as a single regioisomer. The reaction occurred in high yield in spite of the fact that formation of **2-64** proceeded from **2-63b**, which was a minor component in the starting reaction mixture. As the authors note, this implies to the fact that during aminomethylation a reversible equilibrium between **2-63a** and

**2-63b** was maintained with depletion of **2-63b** occurring through transformation to product **2-64**.



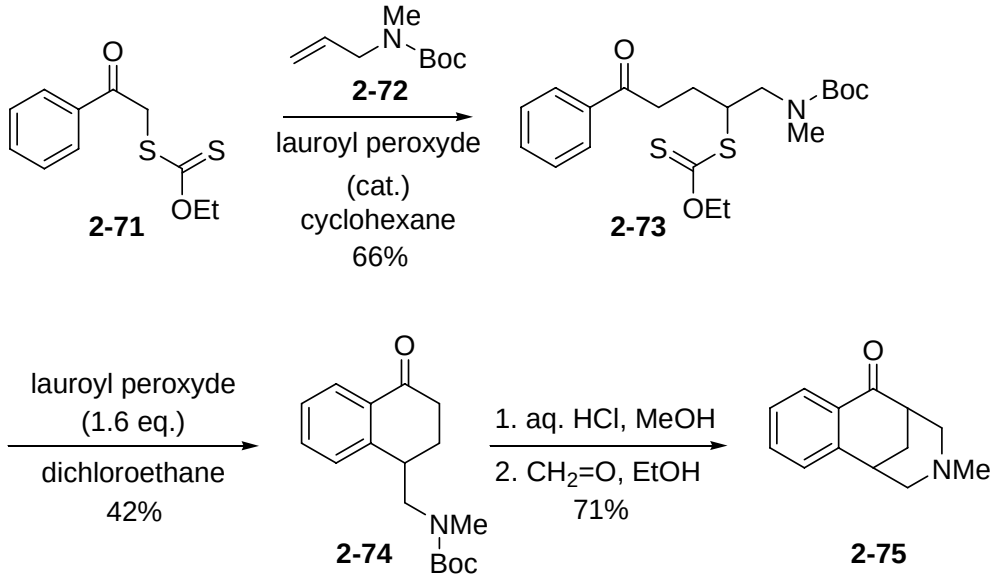

**Scheme 15**. Preparation of precursor **2-64**.

The aminomethylation product **2-64** was reacted with methyl glyoxalate in presence of magnesium sulfate to form imine **2-65** (Scheme **16**). This was acetylated without purification to form an activated acyliminium intermediate (**2-66**) that underwent intramolecular electrophilic cyclization to yield the key tricyclic ketone **2-67** in 68% yield over 3 steps from enol ether **2-63**. The authors note that the 2-carbomethoxy group in ketone **2-67** was obtained as an *endo*-/*exo*-diastereomeric mixture. Reductive deoxygenation of the keto group of ketone **2-67** could be achieved in a two-step manner by initial thioketalization to spiro bisdithiane **2-68**, followed by desulfurization to benzomorphan **2-69** using Raney Nickel in refluxing EtOH. Although undesired *endo* 2-carbomethoxy-containing material could be removed chromatographically at this point, it was found that treatment of ester **2-69** with mild base (2M methanolic ammonia) resulted in epimerization at the 2-position to yield the desired *exo* isomer **2-70** as a single product. Remarkably, formation of the carboxamide side product was not detected under these conditions.



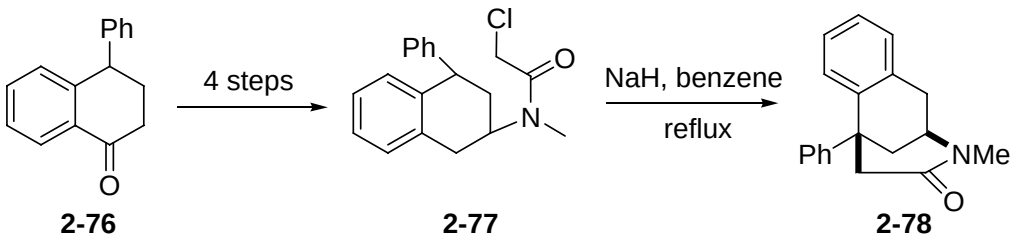

**Scheme 16**. Intramolecular Mannich reaction of imine **2-65** and completion of the synthesis of benzomorphan **2-70**.

In the course of the work on the radical chemistry of xanthates, it was found that radicals with a variety of substituents could be generated and captured in an intermolecular fashion with an unactivated, preferably unhindered olefin.[34] As an example of such a transformation the synthesis of polycyclic structures was peformed as well as one of benzomorphans.[35] Thus, the starting xanthane **2-71** derived from a ketone was treated with olefin **2-72** containing a protected amine in the allylic position in the presence of a radical initiator giving the addition product **2-73** in 66% yield. Finally, the xanthate group in adduct **2-73** was used to obtain tetralone **2-74** *via* a radical cyclization onto the aromatic ring, albeit in moderate yield (42%). Removal of the Boc-protecting group, followed by treatment with hydrochloric acid and formaldehyde allowed the efficient synthesis of the tricyclic derivative **2-75** in 71% yield (Scheme **17**).




**Scheme 17**. Synthesis of benzomorphan **2-75** by Zard and co-workers.

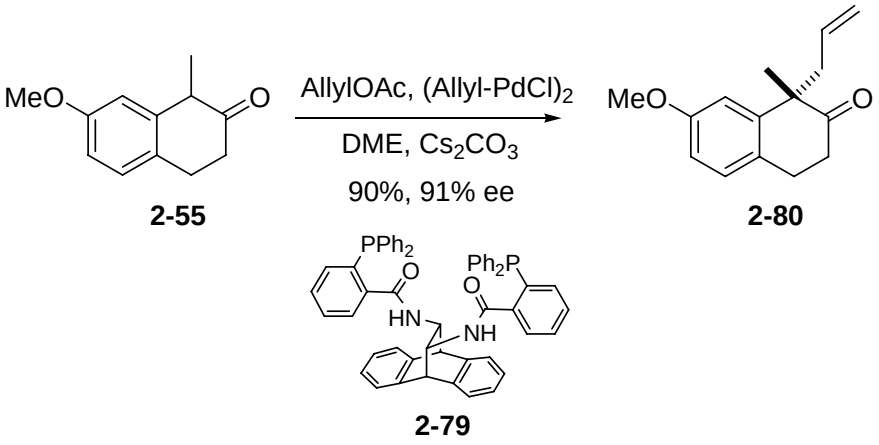
A synthetic sequence, which involves carbon-carbon bond formation rather than carbon-nitrogen bond formation in the cyclization step, has been used for the synthesis of substituted benzomorphan **2-78** in 1967.[36] This route exhibits cyclization induced by formation of tertiary anion from tetraline **2-77** and NaH, followed by its intramolecular nucleophilic attack of chloroacetyl group, leading to benzomorphan **2-78** (yield of product is not given) (Scheme **18**).




**Scheme 18**. Synthesis of benzomorphan **2-78** using carbon-carbon bond forming reaction.

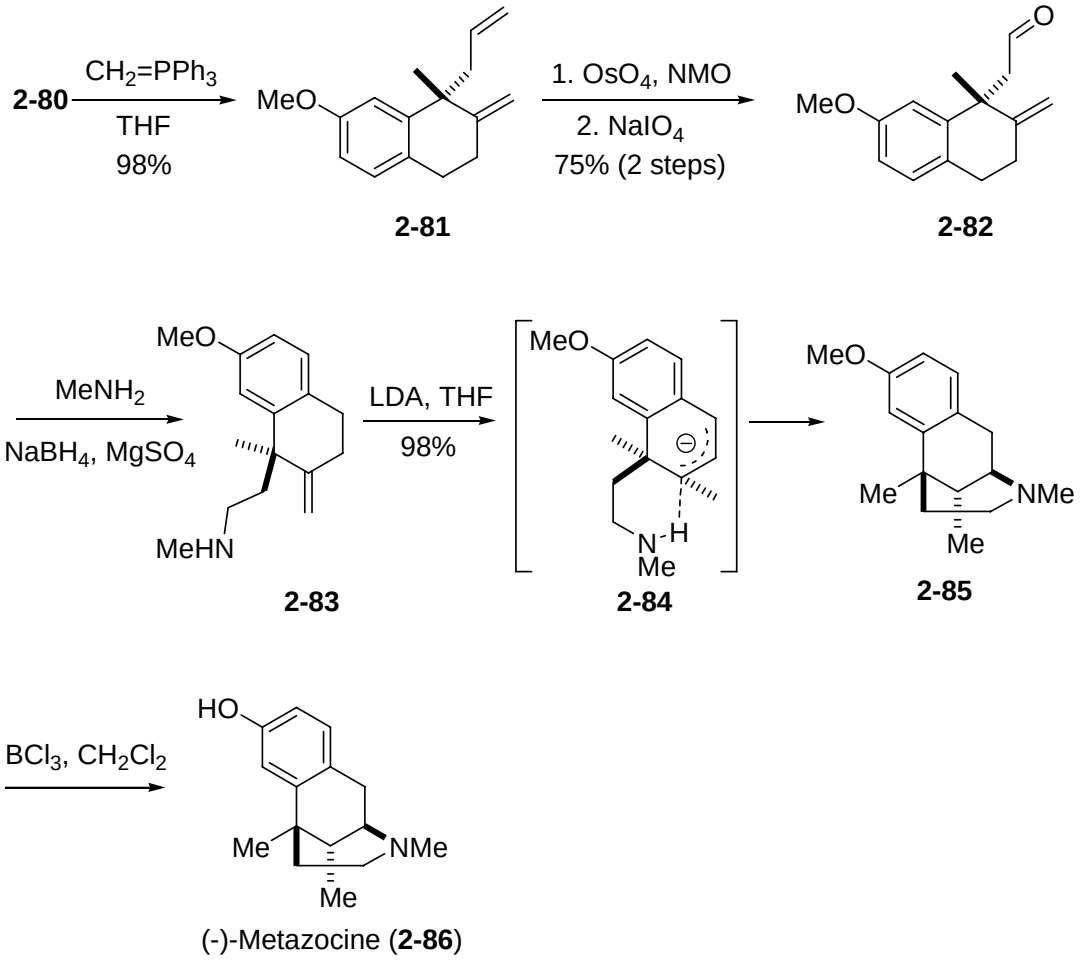
Recently, Barry Trost presented an asymmetric approach to the benzomorphan analgesics metazocine (**2-86**) and pentazocine (**2-1**) as well.[37] Performing the asymmetric allylic

alkylation (AAA)[38] of prochiral tetralone **2-55** and allyl acetate with a catalyst derived from π-allylpalladium chloride dimer (0.5%) and (*R*,*R*)-ligand **2-79** (1.0%) in the presence of cesium carbonate in DME gave tetralone **2-80** in good yield and enantiomeric excess as shown in Scheme **19**.




**Scheme 19**. Asymmetric allylic alkylation of tetralone **2-55**.

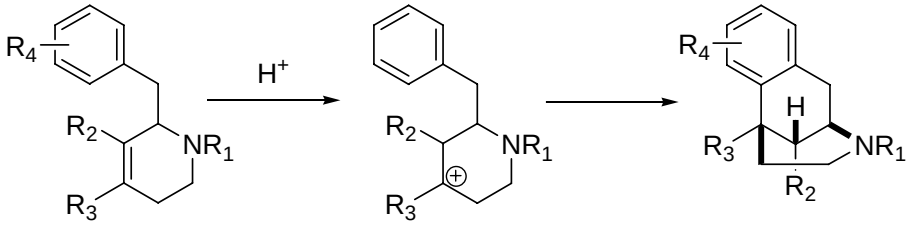
Wittig olefination gave an almost quantitive yield of exocyclic olefin **2-81** (Scheme **20**). Although one-pot cleavage ($OsO_4$, $NaIO_4$) of **2-81** was not succesful, the authors applied stepwise operations wich led to selective cleavage of the less hindered terminal olefin in the presence of the 1,1-disubstituted olefin. Reductive amination provided amine **2-83** in good yield. Completion of the sequence was set through migratory amination, the key speculative step in this synthesis. Treatment of amine **2-83** with catalytic amounts of LDA (20%) in THF led to cycloisomerization to form **2-85** as a single diastereomer in nearly quantitive yield. The authors hypothesize that the high diastereoselective control at C-11 came from intramolecular protonation of the allylic anion **2-84** from the alpha face (i.e. *cis* to the aminoethyl substituent) of an almost flat six-membered ring. Finally, demethylation after treatment of **2-85** with $BCl_3$ in $CH_2Cl_2$ gave (-)-metazocine **2-86** in high yield.




**Scheme 20**. Synthesis of (-)-metazocine (**2-86**) by B. M. Trost and W. Tang.

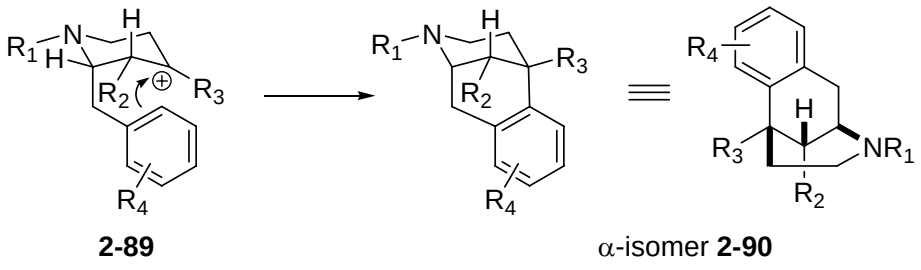
### 2.3.2 Grewe-type Cyclization

This type of reaction first published by R. Grewe in 1946 was found to be the most widely used approach for the construction of the benzomorphan skeleton.[19],[39] Generally, Grewe cyclization is based on the acid-catalyzed intramolecular reaction of appropriately substituted tetrahydropyridines **2-88**. Thus, electrophilic attack of intermediate carbocation **2-89** onto the aromatic ring results in the formation of the bridged cyclic system **2-90** (Scheme **21**).



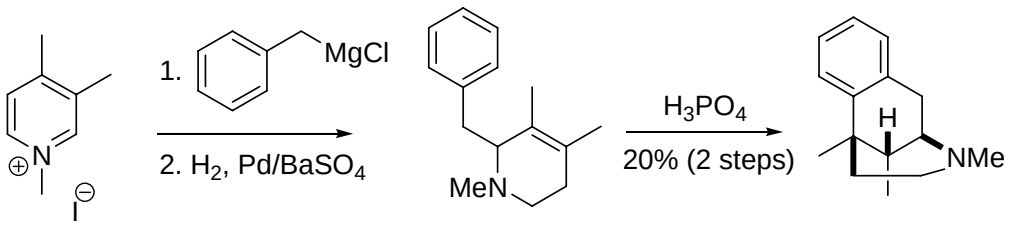

**Scheme 21**. Grewe cyclization.

Interestingly, this mode of reaction is quite general since a variety of tetrahydropyridines are cyclized under acidic conditions, the major product is always that in which the alkyl groups are *cis* with respect to the newly forming ring, and therefore is α-isomer.[40] The *trans* or β-isomer can also be isolated in certain instances, for example when $R_3$ (Scheme **22**) is an aromatic substituent.[41]




**Scheme 22**. Formation of alpha-isomer is predominant in Grewe cyclizations.

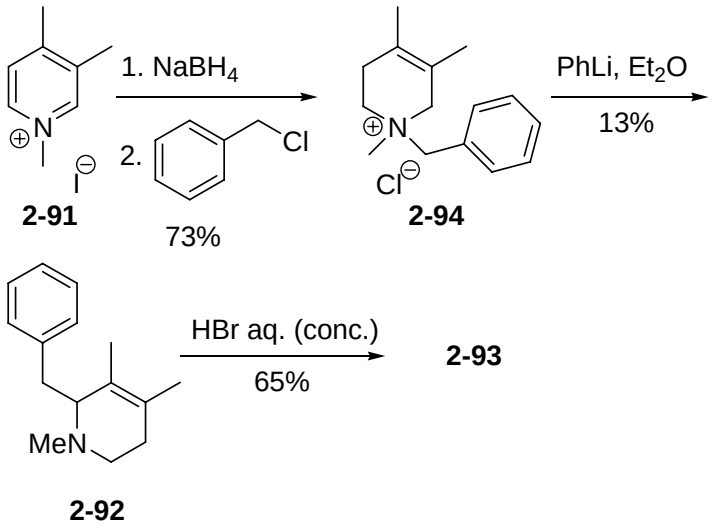
The first benzomorphan prepared using this transformation was the 3,6,11-trimethyl derivative **2-93**.[42] Addition of a benzylic Grignard reagent to 3,4-lutidine methiodide **2-91**, followed immediately by reduction of the unstable intermediate dihydropyridine, afforded **2-92** which was cyclized with 85% $H_3PO_4$ to yield **2-93** in 20% overall yield.




**2-91** **2-92** **2-93**

**Scheme 23**. First synthesis of trimethylbenzomorphan **2-93** by E. May.

Shortly after this work, it was reported that the tetrahydropyridine precursors could be obtained via Stevens rearrangement of the corresponding benzyl alkyl tetrahydropyridinium salts.[43] Thus, sodium borohydride reduction of a 1,3,4-trialkylpyridinium salt **2-91** afforded the tetrahydropyridine, which was quaternized with the appropriate benzyl halide to yield the benzyl alkyl tetrahydropyridinium salt **2-94**. Rearrangement was effected by treating **2-94** with etheral phenyllithium to afford the tetrahydropyridine **2-92** (Scheme **24**). The formation of the shown regioisomer in the Stevens rearrangement over the other possible regioisomer (C-6) is because the ylide intermediate leading to **2-92** is stabilized by conjugation with the double bond. Subsequent cyclization of tetrahydropyridine **2-92** was affected by treatment with 48% aq. HBr.




**Scheme 24**. Synthesis of tetrahydropyridine **2-92** by Stevens rearrangement and cyclization to **2-93**.

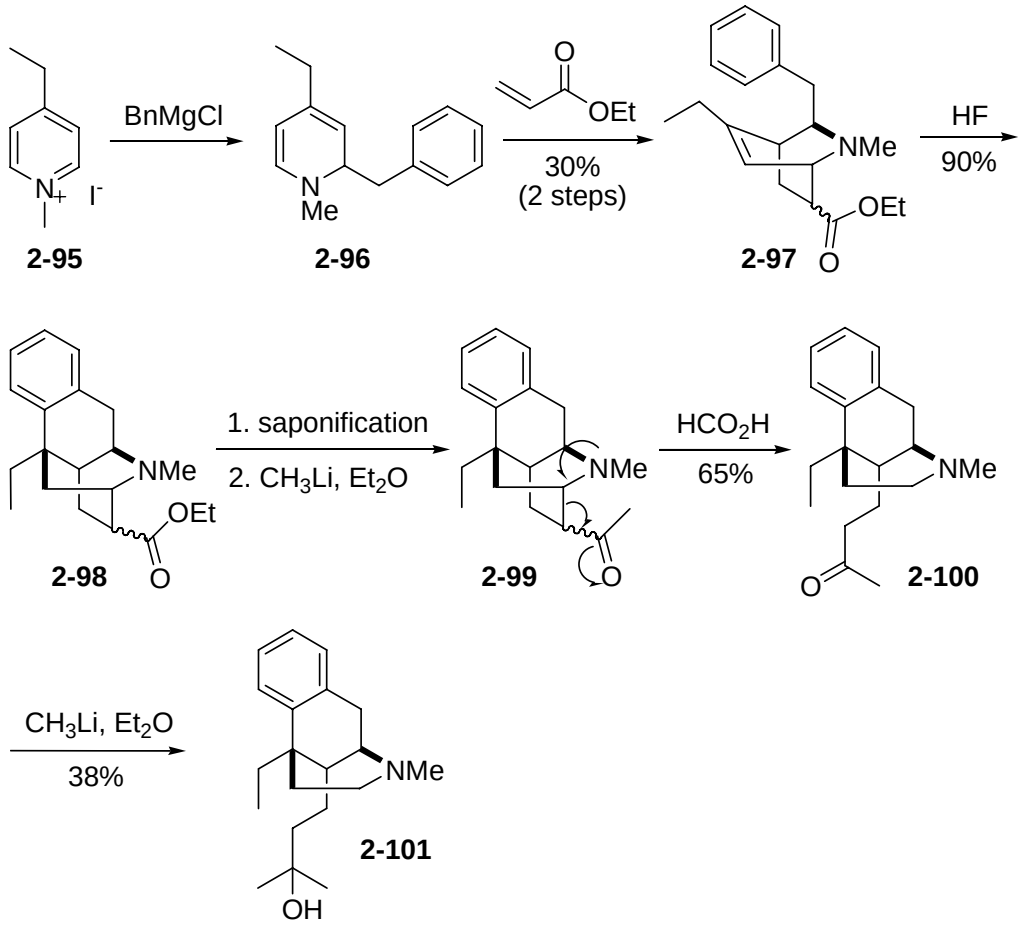
The report of a Grewe-type cyclization of tetrahydropyridines opened a new approach to the synthesis of benzomorphans. As a result, hundreds of compounds have been prepared using this route by variation of $R_1$-$R_4$ in **2-90**.[44]

### 2.3.3 Other Routes to the Benzomophan Ring Skeleton

In this part other synthetic routes are presented which were not applied for a broad scope of benzomorphans but only for the synthesis of separate examples.

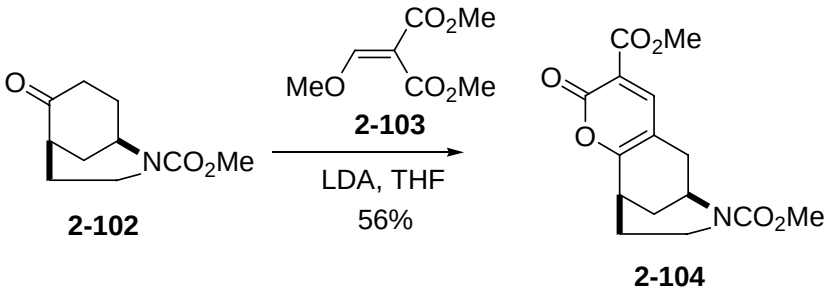
An interesting approach, developed by Michne and co-workers[45] was applied to the preparation of benzomorphan **2-101** (Scheme **25**). The precursor, 1,2-dihydropyridine **2-96**, obtained from the reaction of 4-ethyl-1-methylpyridinium iodide **2-95** and benzylmagnesium chloride was treated with ethyl acrylate in refluxing benzene to give ethyl 3-benzyl-8-ethyl-2-methyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (**2-97**), isolated as its hydrochloride salt in 30% overall yield. Treatment of carboxylate **2-97** with anhydrous HF at room temperature for 24 hours gave the polycycle **2-98**, isolated in 90% yield. Saponification of ester **2-98** to the acid followed by reaction with $CH_3Li/Et_2O$ gave the ketone **2-99**.

Transformation of polycyclic amine **2-99** to benzomorphan **2-100** was accomplished by an acid-catalyzed retro-Mannich reaction of the β-amino ketone system followed by reduction of the intermediate iminium cation. Thus, heating of the ketone **2-99** in mesitylene with excess formic acid for 24 hours at 115–120 °C gave the benzomorphan **2-100** in 65% yield. Finally, treatment with $CH_3Li$ in $Et_2O$ produced the alcohol **2-101**, which was isolated in 38% yield. Compound **2-101** was screened for analgesic activity and found to be 40% as potent as morphine.




**Scheme 25**. Synthesis of benzomorphan **2-101** using a tandem retro-Mannich/reduction reaction.

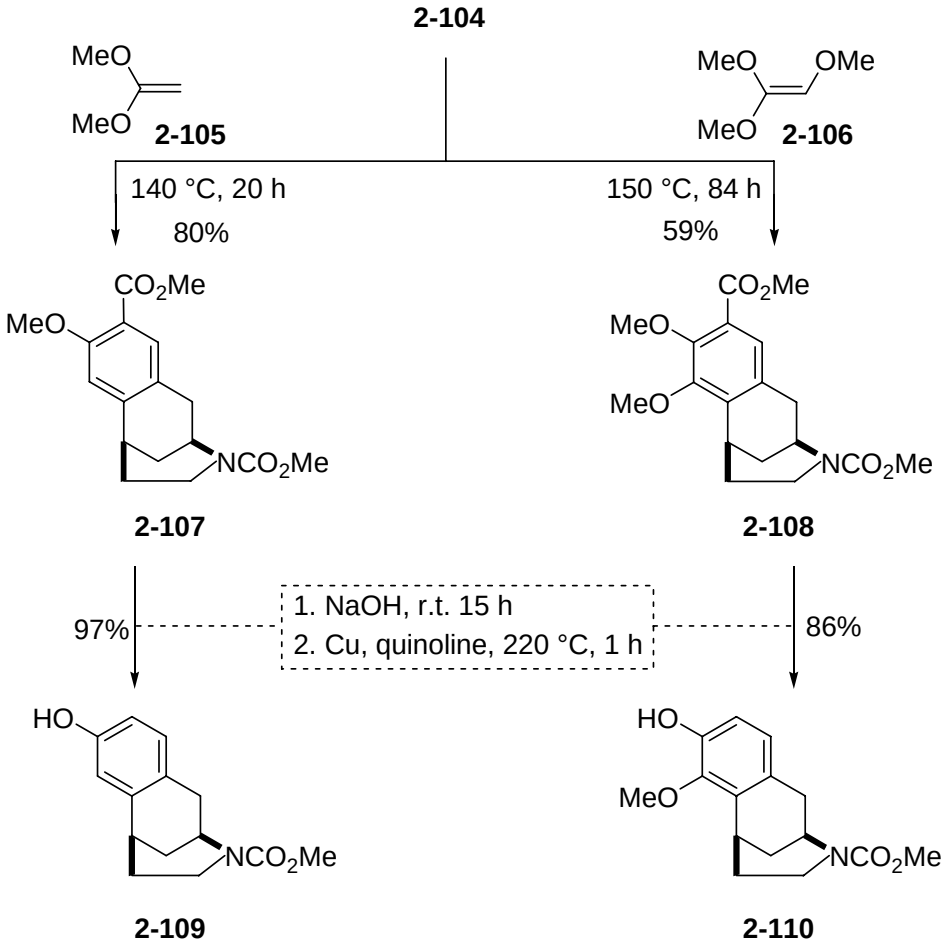
Boger and Mullican[46] developed a direct method for the controlled and selective introduction of oxygenated aromatics for preparation of a representative series of benzomorphans. This route is based on the utilization of inverse electron demand Diels-Alder reaction of 3-carbomethoxy-2-pyrones. The 3-carbomethoxy-2-pyrone **2-104** was readily available from bicyclic amino ketone **2-102** (Scheme **26**) after enolization with LDA in THF followed by addition of dimethyl (methoxymethylene)malonate (**2-103**).




**Scheme 26**. Preparation of the 3-carbomethoxy-2-pyrone **2-104**.

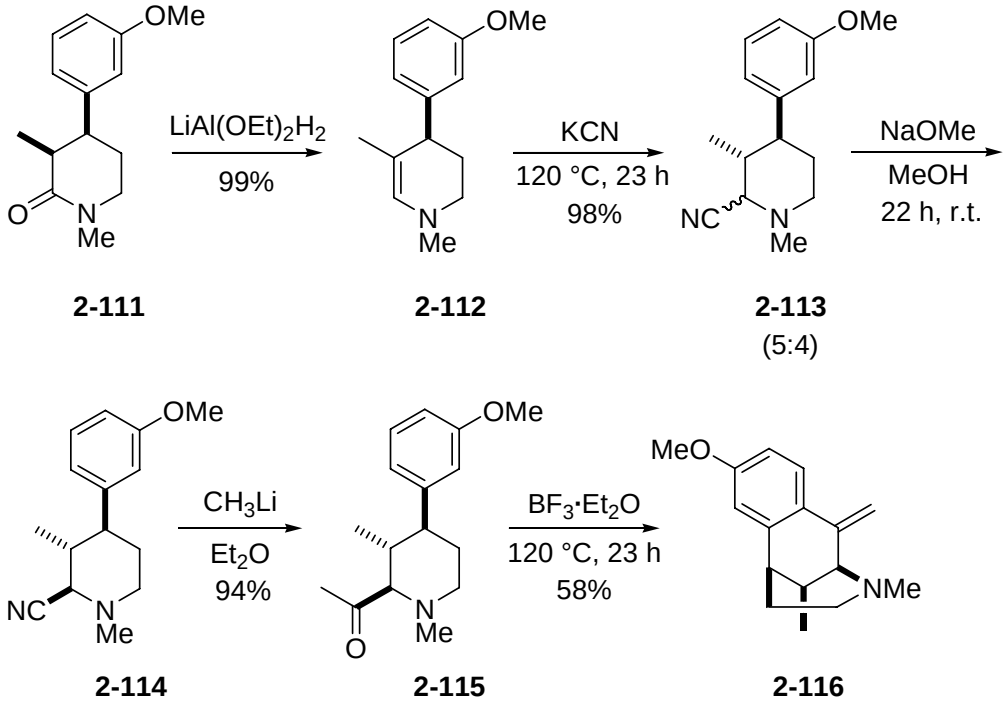
The resulting product, **2-104**, underwent smooth cycloaddition with 1,1-dimethoxyethylene **2-105** to give the amide **2-107** at 140 °C during 20 hours (Scheme **27**). Ester hydrolysis with aqueous NaOH and copper-promoted decarboxylation in quinoline at 220 °C provided the hydroxy-substituted benzomorphan **2-109**. Demethylation of the aryl methyl ether ortho to the carboxylate occurred under the conditions of the reaction.

Similarly, treatment of 3-carbomethoxy-2-pyrone **2-104** with 1,1,2-trimethoxyethylene **2-106** followed by acid treatment of the crude Diels-Alder adduct afforded **2-108**. Ester hydrolysis and copper-promoted decarboxylation provided the selectively protected, unsymmetrical o-catechol benzomorphan **2-110**. Selective demethylation of the aryl methyl ether ortho to the carboxylate occurred prior or concurrent with decarboxylation.



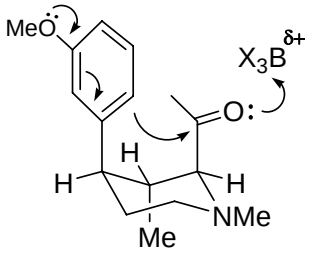

**Scheme 27**. Approach to benzomorphans **2-109** and **2-110** using Diels-Alder reaction of 3-carbomethoxy-2-pyrone **2-104** with dienophiles **2-105** and **2-106**.

Rapoport et al. in 1979 presented a sequence for benzomorphans synthesis starting from 3-methyl-4-(3-methoxyphenyl)-2-piperidone (**2-111**).[47] In their work, substituted racemic piperidine **2-111** was first converted to enamine **2-112** by reduction with $LiAl(OEt_2)H_2$ (Scheme **28**). The crude product was immediately added to solution containing 10 eqiuv. of KCN, affording aminonitrile **2-113** as a 5:4 mixture of diastereomers. Treatment of this isomer mixture with aqueous methanolic NaOH gave total conversion to the more stable aminonitrile isomer **2-114**. Nitrile **2-114** was then elaborated into ketone **2-115** *via* inverse addition to $CH_3Li/Et_2O$ in excellent yield.




**Scheme 28**. Synthesis of β-isomer of benzomorphan **2-116** by Rapoport.

Cyclization of ketone **2-115** was attempted with $BF_3 \cdot Et_2O$ and provided a 58% yield of methylenebenzomorphan **2-116** and significant amounts of epimerized starting material. Extended reaction times, higher temperatures, and varying amounts of $BF_3 \cdot Et_2O$ catalyst had no considerable effect on the product/starting material distribution. A possible transition state for the Lewis acid promoted cyclization is depicted in Figure **15**.

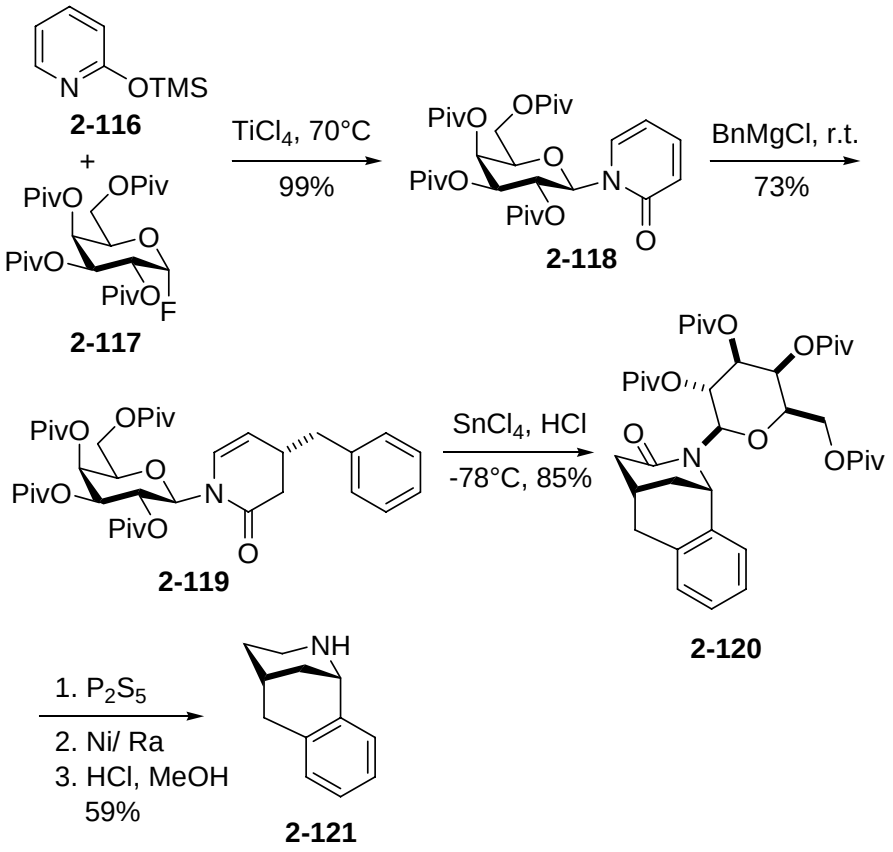



**2-115**

**Figure 15**. Possible transition state for Lewis-acid promoted cyclization of ketone **2-115**.

Later, the intramolecular Friedel-Crafts reaction was applied by several groups for the synthesis of benzomorphans. For example, recently it was demonstrated, that an acid-catalyzed cyclization of 4-benzyl-substituted 5,6-didehydropiperidin-2-ones leads to the formation of the corresponding benzomorphans.[48] β-Selective N-glycosylation of 2-(trimethylsilyloxy)pyridine (**2-116**) with O-pivaloylated galactosyl fluoride (**2-117**) gave the N-galactosyl 2-pyridone **2-118** in good yield (Scheme **29**). This unsaturated heterocyclic structure was transformed regio- and stereoselectively by reaction with benzyl Grignard reagent. After activation by O-silylation using triisopropylsilyltrifluoromethanesulfonate (TIPSOTf), the Grignard addition gave 4-benzylated 5,6-didehydropiperidin-2-one **2-119**. The regioselectivity and the high diastereomeric ratio (99:1) of this process was governed by the facial differentiation of the carbohydrate auxiliary. The authors note, that previously published syntheses using the same benzylpiperidine moiety to form benzomorphans required highly activated aromatic systems and proceeded in a nonregioselective manner. In the case of the 4-benzyldidehydropiperidinone **2-119**, the intramolecular aminoalkylation took place at low temperature in the presence of a mixture of HCl/$SnCl_4$. The intermediate N-acyl iminium ion underwent cyclization to yield the tricyclic benzazocinone **2-120** through electrophilic attack at the phenyl ring exclusively from the *cis* side.

To release the benzomorphan moiety from the carbohydrate auxiliary the benzazocine **2-120** was treated with Lawesson's reagent to give the corresponding thioamide, which was subsequently desulfurated on Raney nickel. Acidic cleavage of the N-glycosidic bond using aqueous HCl in methanol provided the benzomorphan hydrochloride **2-121** with a yield of 59% over the last 3 steps.



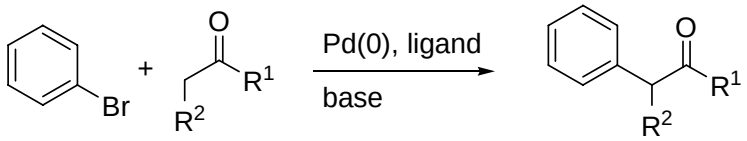

**Scheme 29**. Synthesis of benzomorphan **2-121** by Kunz and co-workers.

Obviously, up to date there is a huge number of syntheses of benzomorphan structures reported in the literature. These cannot be listed within the borders of one dissertation, but what can be noted, is the fact, that all of them either contain minor changes from the above listed routes, or are direct copies of the synthetic sequences.

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

# 3 Goal of Research

As described in the previous part, classical routes to such compounds like benzomorphans include $S_N2$ reactions with a nucleophilic amine, formation of amides, intramolecular Friedel–Crafts alkylation, or iminium ion cyclizations. However, due to the reactions employed, the type of substituents is restricted at certain positions. With the advent of new powerful organometallic transformations, such as cross-coupling or C–H insertions, the chemistry of classical drugs might be substantially broadened. Thus, structures that previously seemed difficult to prepare might be now more easily accessible. The direct introduction of an aryl unit at a nucleophilic carbon is a transformation of central importance to complex molecule synthesis.[49] A synthetic useful subset of this class of reactions is the arylation of ketones at the α-position. A case in point is the Buchwald–Hartwig arylation of enolates in the presence of a palladium catalyst (Equation 2).[50]




**Equation 2**.

Mechanistically, the approach of Buchwald et al., and Hartwig et al. for the synthesis of α-aryl ketones, esters, or other carboxylic acid derivatives, involves the oxidative addition of the Pd(0)$L_n$ to the aryl bromide affording the Pd(II) organometallic intermediate **A** (Figure **16**). Ligand substitution of the bromide by the enolate generated by deprotonation of the corresponding ketone provides the Pd(II) organometallic intermediate **B**. Finally, reductive elimination from intermediate **B** provides the α-aryl ketone and regenerates the Pd(0)$L_n$ catalyst.

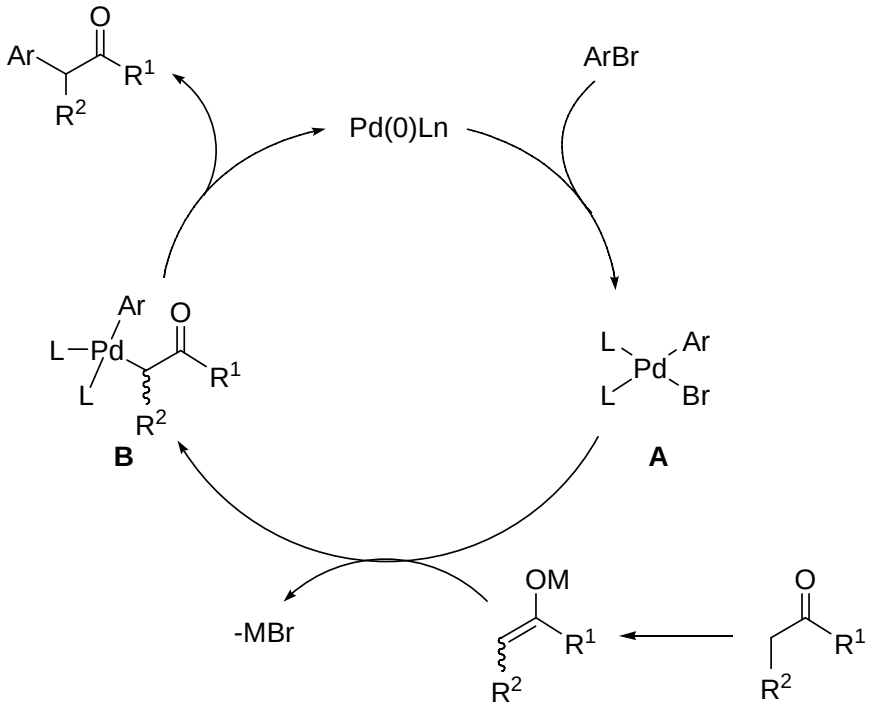
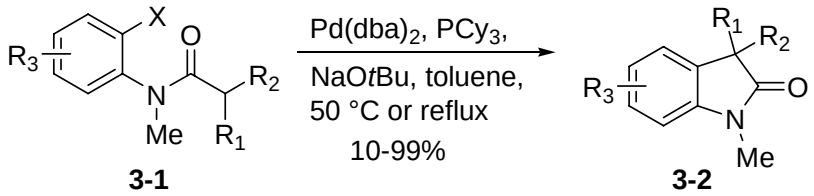



**Figure 16**. Possible catalytic cycle of Pd(0)-catalyzed α-arylation of ketones.

Having successful experience in this type of reactions,[51] we were interested to employ the Buchwald-Hartwig arylation in an intramolecular setting towards the synthesis of new benzomorphan scaffolds.

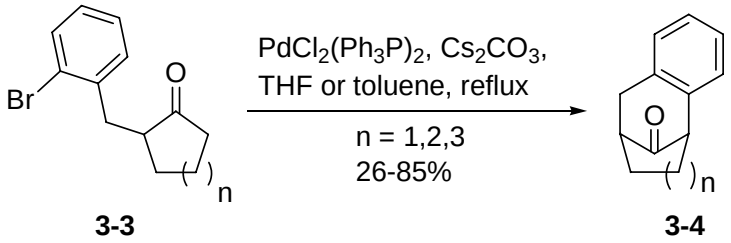
As we have found in the literature, this idea has already proved its potency for the synthesis of various classes of other polycyclic systems.[52] For example, it was demonstrated, that substituted *o*-halo-N-acylanilines **3-1** under palladium catalysis with a sterically hindered phosphine ligand and in presence of a base undergo the desired cyclization to form 2-oxindoles **3-2** in high yield.[53]




X = Cl, Br $R_1$, $R_2$ = Aryl, Hetaryl, Alkyl
$R_3$ = H, CN, MeO

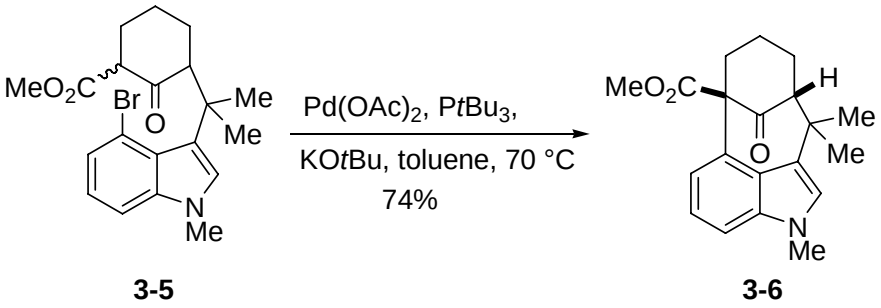
**Scheme 30**. Synthesis of various 2-oxindoles by intramolecular Pd-catalyzed arylation according to Hartwig and co-workers.

Nakai and co-workers utilized the intramolecular arylation of properly designed substrates (**3-3** – **3-4**) by use of a $PdCl_2(Ph_3P)_2$–$Cs_2CO_3$ reaction system to form a variety of carbocyclic compounds (Scheme **31**).[54]




**Scheme 31**. Synthesis of bridged carbocyclic compounds using Pd-catalyzed intramolecular arylation by Nakai and co-workers.

To assemble the tetracyclic ring system towards the synthesis of N-methylwelwitindolinone, Rawal and co-workers successfully engaged the discussed transformation.[55] Thus, indolyl derivative **3-5**, after treatment with $Pd(OAc)_2$, P*t*$Bu_3$ in toluene and KO*t*Bu as base, underwent the desired cyclization in high yield to give the keto ester **3-6** (Scheme **32**).




**3-5** **3-6**

**Scheme 32**. Intramolecular Pd-catalyzed arylation to create the core bicyclo[4.3.1]decane ring system of welwitindolinones by Rawal and co-workers.

The aforementioned examples show, that the selected strategy is a powerful transformation towards the synthesis of complex organic molecules. In the issue of new benzomorphan scaffolds synthesis, compound **3-8** after adding suitable functional groups, appeared as an initial target (Figure **17**). Further disconnection leads to the *o*-bromobenzyl bromides **3-9** and the piperidones **3-10**. Alkylation between the carbonyl and the carboxyl groups (cf. **3-8**) or at the terminus (cf. **3-12**) by Weiler alkylation[56] should provide suitable substrates for the intramolecular ketone arylation.

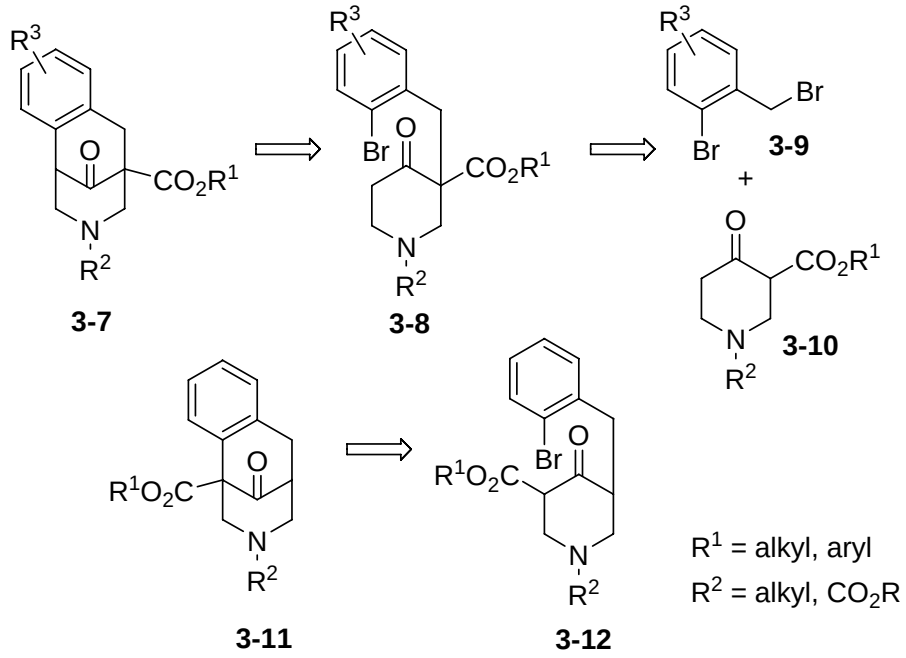
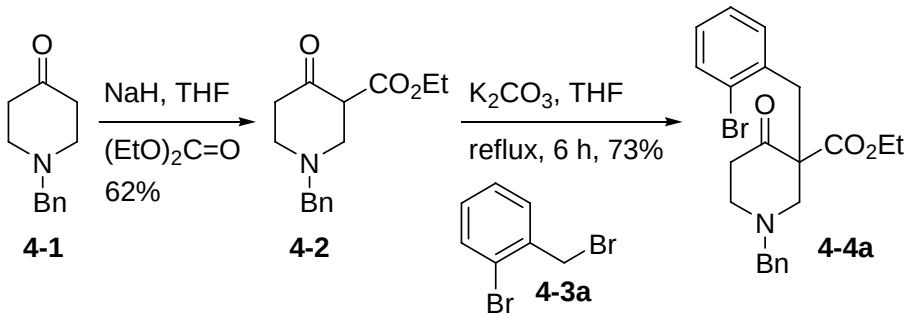



**Figure 17.** Synthetic strategy towards benzomorphans based on an intramolecular Buchwald–Hartwig arylation.

# 4 Results and Discussion

## 4.1 Synthesis of Benzomorphans by Intramolecular Buchwald-Hartwig Arylation of Substituted N-Benzyl-Piperidone Derivatives

The commercially available 1-benzyl-4-oxopiperidine (**4-1**) was first converted into the keto ester **4-2** using diethyl carbonate in the presence of NaH (Scheme **33**). The alkylation of the keto ester **4-2** with *o*-bromobenzyl bromide (**4-3a**) was performed in refluxing THF using potassium carbonate as the base.[57] Under these conditions a reasonable yield for the alkylation product **4-4a** could be obtained.



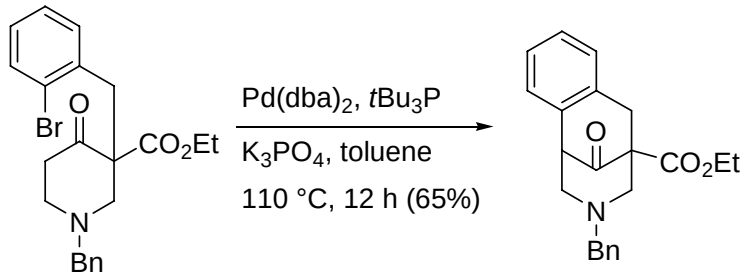

**Scheme 33**. Preparation of substituted piperidine **4-4a**.

Other bases like *t*BuOK in THF or NaH in toluene were tried, but the $K_2CO_3$/THF system gave the best results (Table **1**). Also, after complete reaction, the inorganic materials can be simply filtered out without a special work-up procedure, unlike with other stronger bases. This is an additional advantage in contrast to other conditions tried.

**Table 1**. Alkylation of 3-carbethoxy-1-benzyl-4-oxopiperidine (**4-2**) with *o*-bromobenzyl bromide (**4-3a**) under different conditions.

| Entry | base | solvent | T, °C | yield, % |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | THF | 56 | 73 |
| 2 | *t*BuOK | THF | r.t. | 55 |
| 3 | NaH | toluene | 90 | 55 |

The intramolecular ketone α-arylation was performed using $K_3PO_4$ (3 equiv.), $tBu_3P$ (4 mol-%) and $Pd(dba)_2$ (2 mol-%) in refluxing toluene (Scheme **34**). This way, the tricyclic compound **4-5a** was obtained in 65% yield and other condition were not tried. These conditions ($K_3PO_4$, $tBu_3P$, toluene) proved to be applicable for many substrates and are also very cost efficient if to compare $tBu_3P$ with other ligands used for this type of reaction.[50],[51]




**4-4a** **4-5a**

**Scheme 34**. Palladium-catalyzed intramolecular ketone arylation of **4-4a** to yield the benzomorphan derivative **4-5a**.

The reaction was also run on a multigram scale up to several grams of the product. In this case the product was isolated by precipitation from the reaction mixture after filtration of inorganic material. The structure of the tricyclic ring system **4-5a** was additionally proven by an X-ray analysis (Figure **18**).

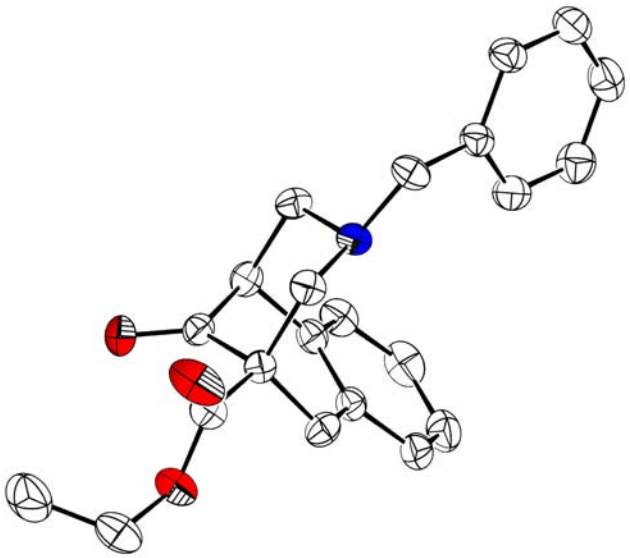


**Figure 18.** X-ray structure of benzomorphan **4-5a**. The crystal sample was obtained by crystallization from hot heptane.

The diversity of the explored synthetic route to benzomorphans was demonstrated by applying a variety of differently substituted benzyl bromides. The compound **4-3b** has the methyl substituent in *ortho*-position to the bromine atom; therefore, it plays the role of a sterically hindered (SH) substrate. The substrate **4-3c** with a methoxy group presents an electron donating (ED) class of substituents. On the other hand, benzyl bromides with fluorine (**4-3d**) and cyano (**4-3e**) groups – are from the electron withdrawing (EW) set (Figure **19**).

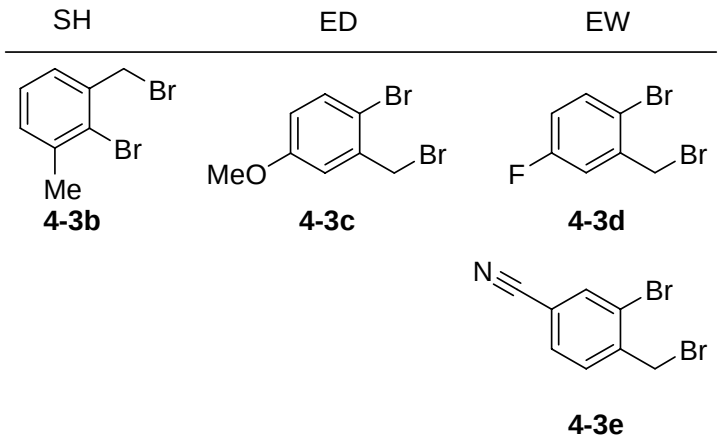
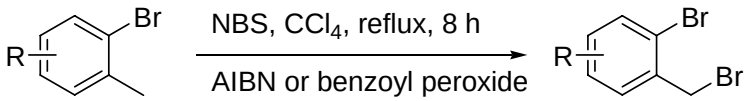
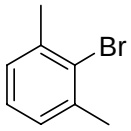
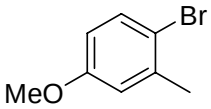
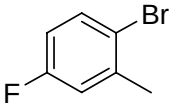
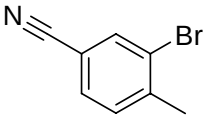



**Figure 19**. Benzyl bromides **4-3b-e** with different types of substituent in the aromatic ring.

All benzyl bromides were prepared from the corresponding toluenes (available from commercial sources) by treatment with N-bromosuccinimide in refluxing $CCl_4$. An exlusion was in the case of 1,3-dimethyl-2-bromobenzene – the attempts to reproduce literature procedure (with NBS in $CCl_4$ and benzoyl peroxide as a radical initiator)[58] did not result in the formation of the desired product. As a result, the bromide **4-3b** was obtained by reaction with elemental bromine and light irradiation (200W) instead of NBS. The yields for the bromination of the toluenes are presented in Table **2**.[59]

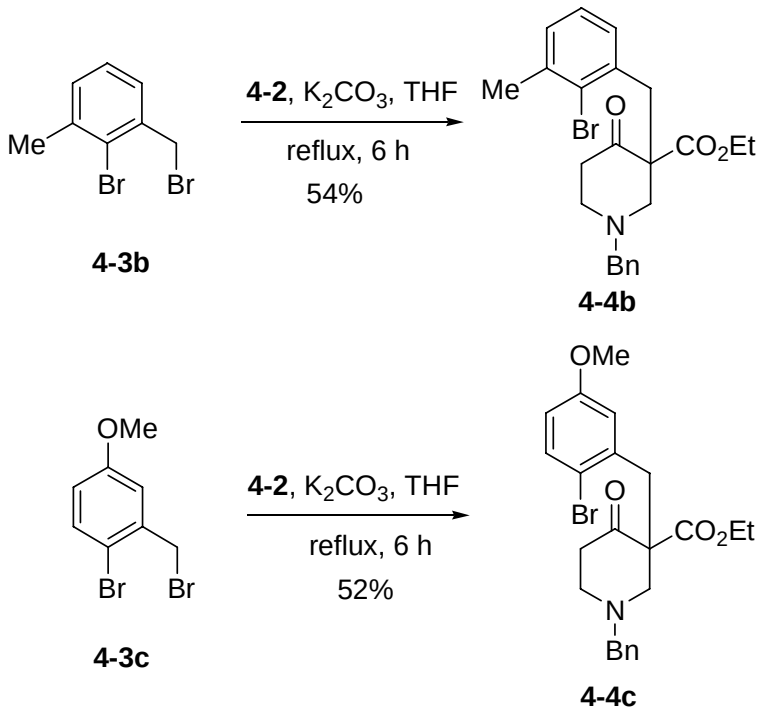
**Table 2**. Preparation of benzyl bromides **4-3b-e**.




| Entry | toluene | product № | yield, % |
|---|---|---|---|
| 1 |  | **4-3b** | 33[a] |
| 2 |  | **4-3c** | 60 |
| 3 |  | **4-3d** | 45 |
| 4 |  | **4-3e** | 63 |

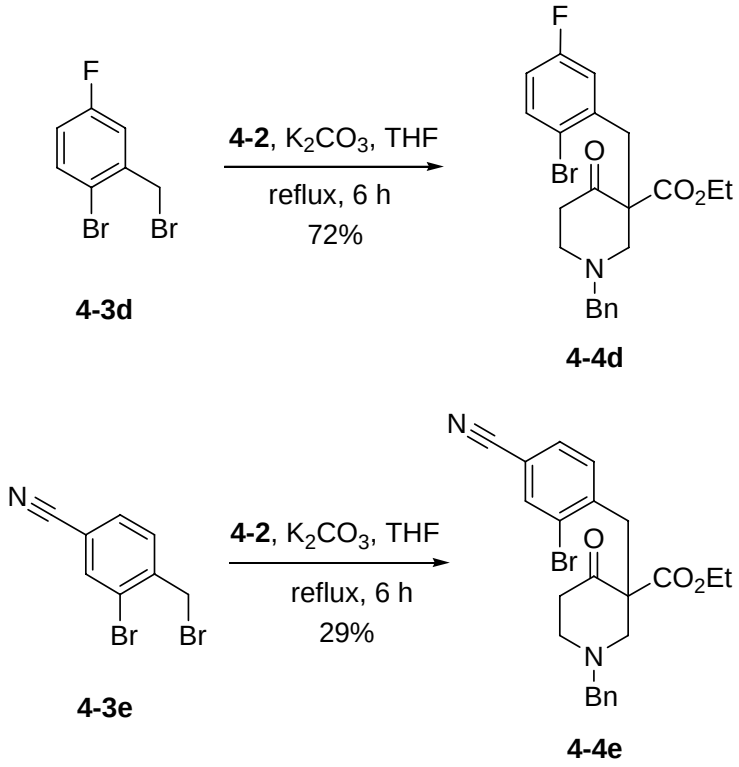
[a] Using elemental bromine and light irradiation

Using benzyl bromides **4-3b** and **4-3c**, substrate **4-4b** which features a sterically demanding methyl group next to the bromo substituent, and substrate **4-4c** with an electron-donating methoxy substituent (Scheme **35**) were prepared.




**Scheme 35**. Alkylation of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**4-2**) with benzyl bromides **4-3b** and **4-3c**.

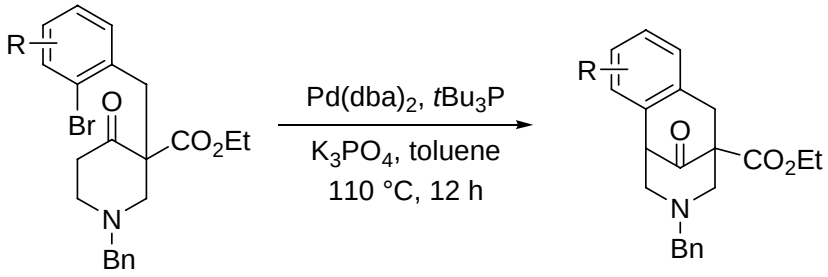
On the other hand, to extend the scope of the studied transformation, two other benzyl bromides were applied for the preparation of compounds **4-4d** and **4-4e** with fluorine and cyano groups, respectively (Scheme **36**). The products were obtained using the same conditions as above in yields of 72% for the product **4-4d** and 29% in the case of the nitrile-substitued compound **4-4e**.

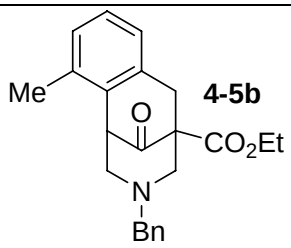
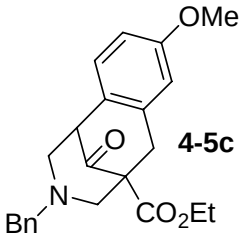
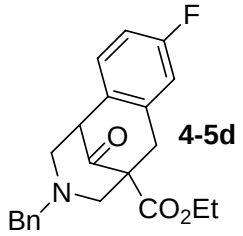
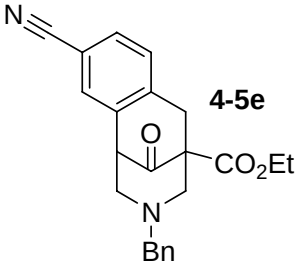



**Scheme 36.** Alkylation of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**4-2**) with benzyl bromides **4-3d** and **4-3e**.

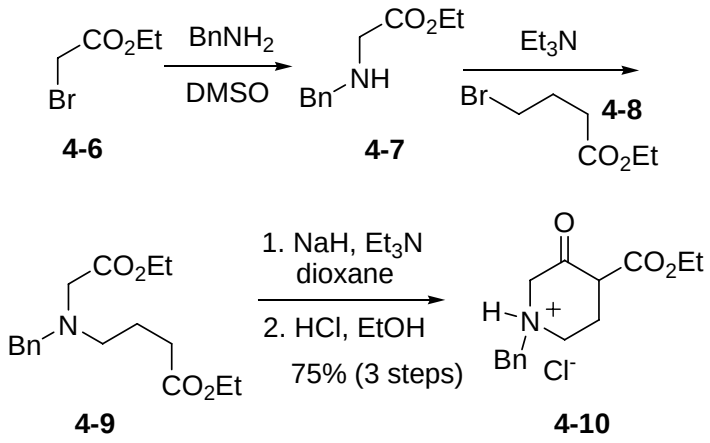
After preparation of the collection of derivatives containing various types of substituents in the aromatic ring we then subjected them to the palladium-catalyzed cyclization under the same conditions as for **4-4a** resulting successfully in benzomorphans **4-5b-e** (Table **3**).

**Table 3**. Palladium-catalyzed intramolecular ketone arylation to yield the benzomorphan derivatives **4-5b-e**.



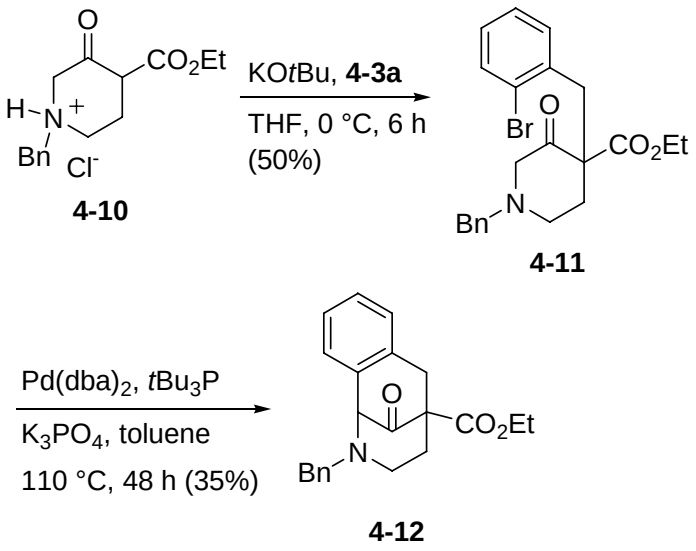

| Entry | R | product | yield, % |
|---|---|---|---|
| 1 | 3-Me |  **4-5b** | 30 |
| 2 | 5-MeO |  **4-5c** | 40 |
| 3 | 5-F |  **4-5d** | 30 |
| 4 | 4-CN |  **4-5e** | 40 |

In another venture, by changing the position of the nitrogen atom in the piperidone ring, the isomeric benzomorphan derivative **4-12** was synthesized. The precursor piperidone **4-10** was prepared in 3 steps as shown in Scheme **37** starting from ethyl 2-bromoacetate (**4-6**) and benzylamine, followed by alkylation of the resulting N-benzylglycine (**4-7**) with ethyl γ-bromobutyrate (**4-8**) to give the diester **4-9**. Treatment of the latter with NaH in dioxane furnished the piperidone **4-10** by Dieckmann condensation.[60]




**Scheme 37**. Synthesis of N-benzyl-4-carbethoxypiperidone-3 hydrochloric salt (**4-10**) from ethyl-2-bromoacetate (**4-6**).

Alkylation of the keto ester **4-10** with the benzyl bromide **4-3a** provided the substrate **4-11**. This piperidone (**4-11**) is somehow unstable at room temperature and therefore should be stored at lower temperatures and under inert atmosphere. Palladium-catalyzed cyclization of **4-11** was performed under similar conditions as for **4-4a** to deliver one more example of benzomorphans synthesized (Scheme **38**).




**Scheme 38.** Alkylation of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (**4-10**) with benzyl bromide **4-3a** and Pd-catalyzed cyclization to **4-12**.

## 4.2 Synthesis of Benzomorphans by Intramolecular Buchwald-Hartwig Arylation of Substituted N-Methyl-Piperidone Derivatives

Because the N-methyl group is rather common in natural products as well as synthetic drugs (Figure **19**), it was of interest to see whether compounds of type **3-7** could be accessed employing the discovered tranformation with N-methyl instead of a N-benzyl group.

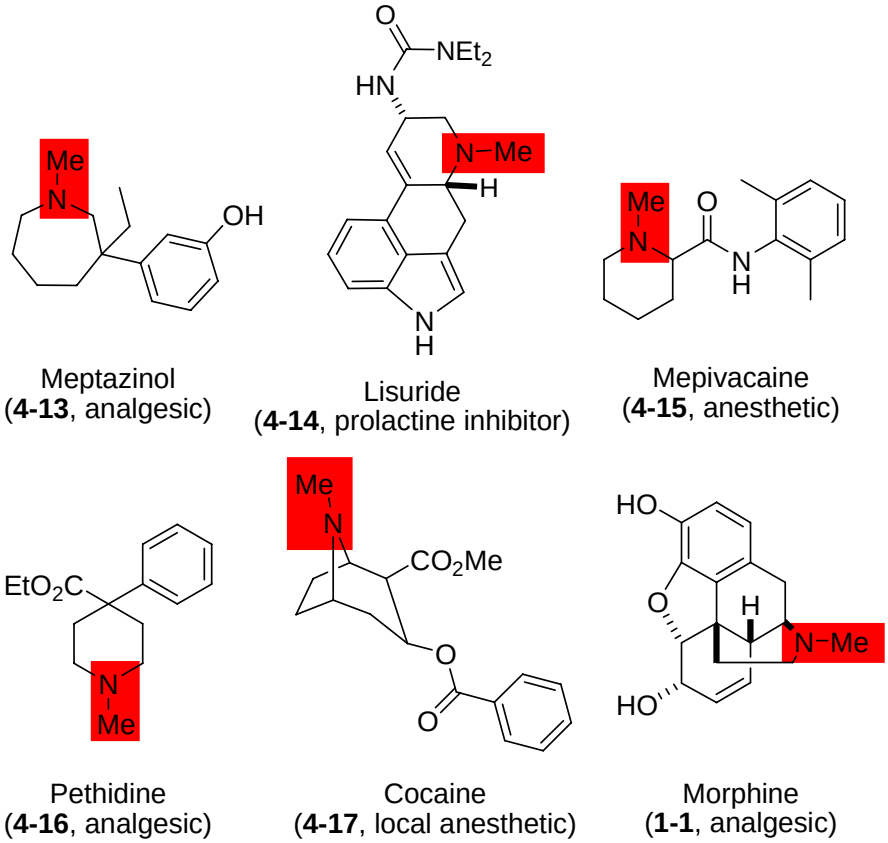
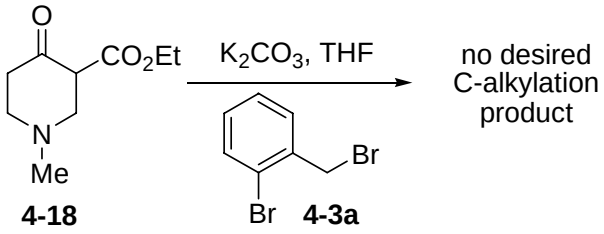


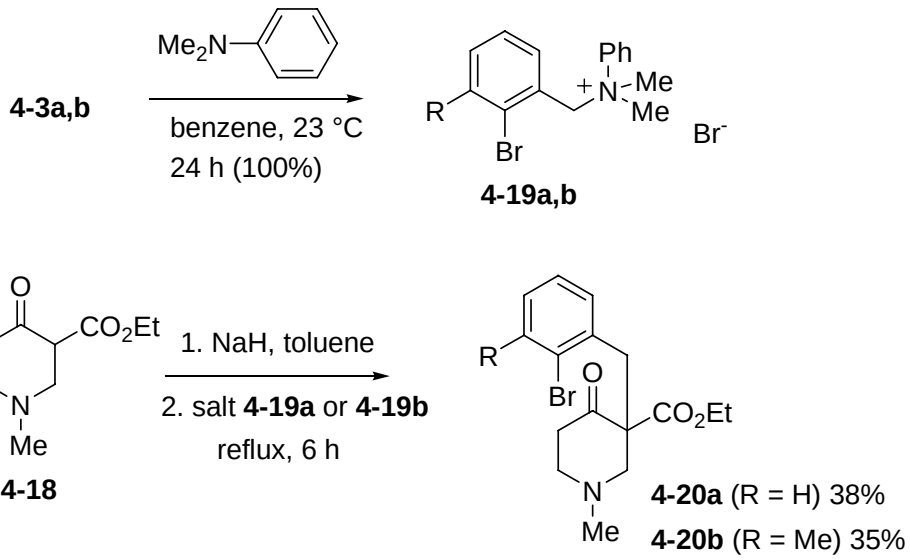

**Figure 19.** Several examples of natural products and synthetic drugs bearing a N-methyl substituent.

In our case, compounds containing a N-Me-substituent might be prepared from the N–H derivative (cf. **4-22**) or directly from N-methyl-4-oxopiperidine-3-carboxylate. The precursor 4-oxopiperidine **4-18** was prepared in an analogous fashion as for the N-benzyl derivative, by carboxylation of N-methyl-4-piperidone (**4-1**) with diethyl carbonate after treatment with NaH (section **4.1**, Scheme **33**). The C-alkylation of the enolate anion of N-methyl-3-carbethoxy-4-piperidone (**4-18**) with *o*-bromobenzyl bromide **4-3a** as it was utilized with N-benzyl-3-carbethoxy-4-piperidone (**4-2**) seemed to be suitable. However, attempts to perform this alkylation with $K_2CO_3$ in refluxing THF did not let us to obtain the desired product, possibly because N- rather than C-alkylation took place (Scheme **39**).



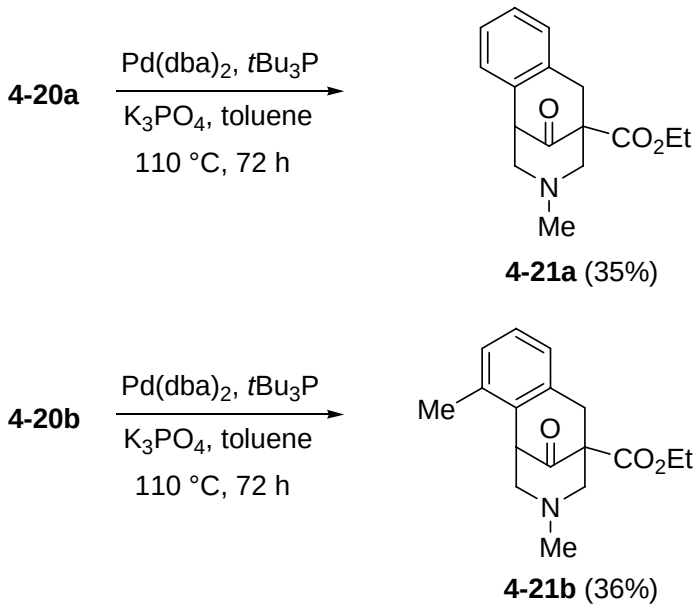

**Scheme 39**. Attempt to alkylate the N-methyl-3-carbethoxy-4-piperidone **4-18** with *o*-bromobenzyl bromide **4-3a**.

To solve this problem it was required to use the ammonium salt **4-19** for the alkylation of **4-18**.[61] The benzylanilinium salts **4-19a,b** were available directly from the previously synthesized *o*-bromobenzyl bromides **4-3a,b** by stirring them with *N*,*N*-dimethylaniline in dry benzene for 24 hours in quantitative yield (Scheme **40**).[62] Thus, treatment of the enolate anion of N-methyl-3-carbethoxy-4-piperidone (**4-18**) with *o*-bromobenzylanilinium salts **4-19a** and **4-19b**, proceeded through the desired C-alkylation providing compounds **4-20a,b**.




**Scheme 40**. Synthesis of ammonium salts **4-19a,b** and alkylation of N-methyl-3-carbethoxy-4-piperidone (**4-18**).

The crucial cyclization was run under the same conditions that had proven useful with the N-benzyl derivatives (from **4-4a** to **4-5a**), but required longer reaction times (Scheme **41**).



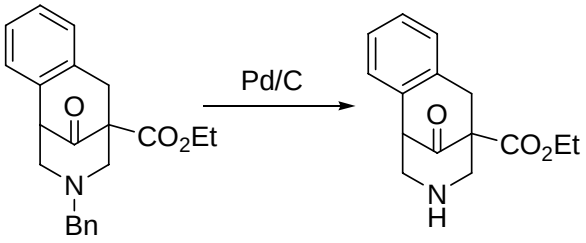

**Scheme 41**. Cyclization to the N-methylsubstituted benzomorphan derivatives **4-21a** and **4-21b**.

While the yield for the tricyclic compound **4-21a** was not very high, this reaction provides the desired compound in a very efficient way. Compound **4-21b** was prepared in an analogous fashion. To improve the yield of N-methylbenzomorphan derivative **4-21a** using other bases than $K_3PO_4$, such as *t*BuOK or *t*BuONa in the cyclization step, did not lead to an improvement – the product was not even observed in the reaction mixture.

## 4.3 Preparation of Benzomorphan Scaffold and Its Derivatization

A further task was recognized in the synthesis of the strategic benzomorphan scaffold **4-22** bearing a secondary amino group, which could be used for further derivatization. It seemed appropriate to remove the N-benzyl protecting group by palladium-catalyzed hydrogenation. However, under various conditions (Table **4**) formation of the desired product was not observed. Most likely, steric hindrance interferes with the hydrogenation step.

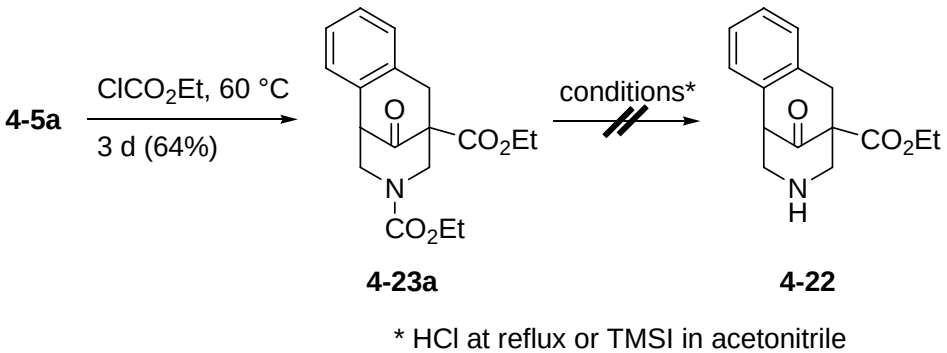
**Table 4**. Attempts to cleave the N-benzyl protecting group by hydrogenation on Pd catalyst.




**4-5a** **4-22**

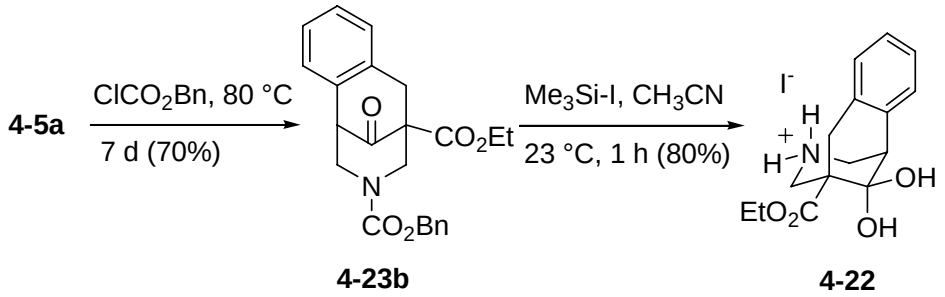
| Time | Solvent | T, °C | Yield, % |
|---|---|---|---|
| 12 | EtOH | r.t. | 0 |
| 24 | EtOH/AcOH | 45 | 0 |
| 72 | EtOH/AcOH | 60 | 0 |

Therefore, we tried to convert the benzyl group into a more reactive urethane protecting group.[63] In the event, stirring of the tricyclic compound **4-5a** with ethoxycarbonyl chloride at elevated temperature for 3 days provided the ethoxycarbonyl compound **4-23a** in good yield (Scheme **42**). Again, attempts to cleave the ethyl carbamate under acidic conditions (concd. HCl, reflux) or with trimethylsilyl iodide (TMSI) were not successful in our hands – the starting material remained unchanged.




**Scheme 42**. Conversion of the N-benzyl compound **4-5a** to the urethane **4-23a**. Attempts to cleave the ethoxycarbonyl group.

A solution was found by using Cbz chloride instead of ethoxycarbonyl chloride. Thus, heating of the tricyclic compound **4-5a** with Cbz chloride for several days led to the Cbz-protected tricyclic piperidone **4-23b** in 70% yield (Scheme **43**). Deprotection was achieved by stirring the Cbz compound **4-23b** with trimethylsilyl iodide (TMS-I) in acetonitrile. This reaction proceeded extremely fast – after 1 hour starting urethane was completely transferred to the secondary amine **4-22**.[64] After the acetonitrile was evaporated in vacuo, the residue was treated with a dichloromethane-water mixture and the product could be then isolated easily by evaporation of the water layer.




**Scheme 43**. Conversion of the N-benzyl compound **4-5a** to the urethane **4-23b**. Cleavage of the Cbz group to yield the ammonium iodide **4-22**.

The deprotected compound **4-22** was isolated as the hydrate and the corresponding ammonium salt. The presence of the hydrate is evident from a characteristic peak in the $^{13}C$ NMR spectrum at $\delta = 91.5$ ppm (Figure **20**).

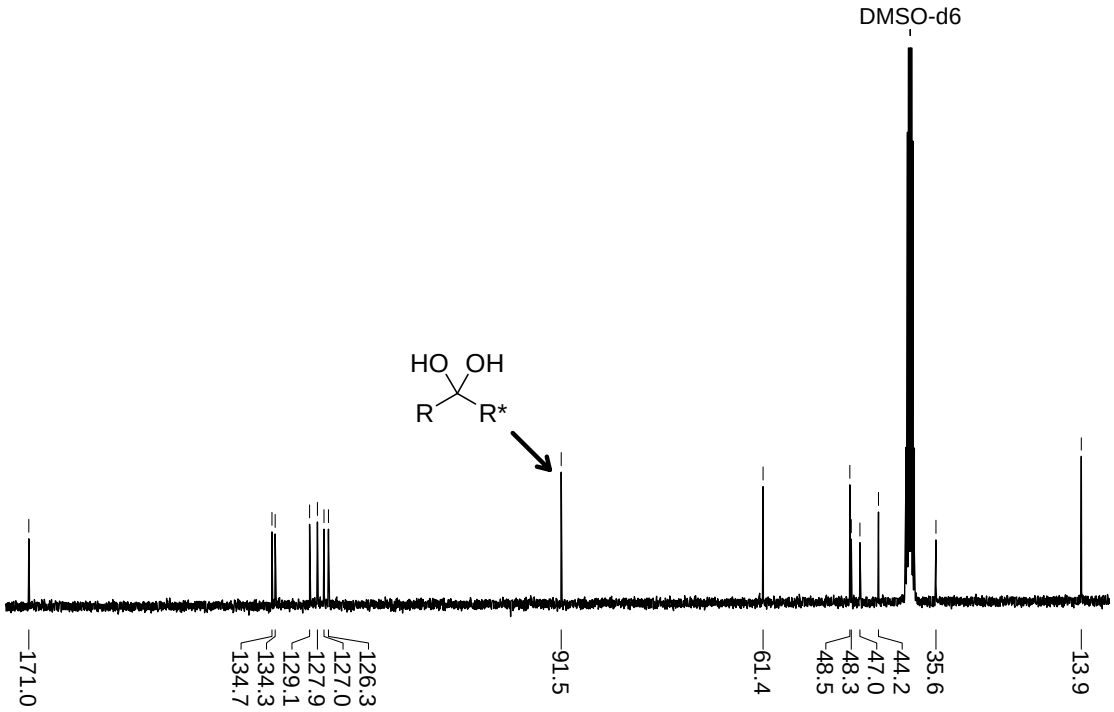
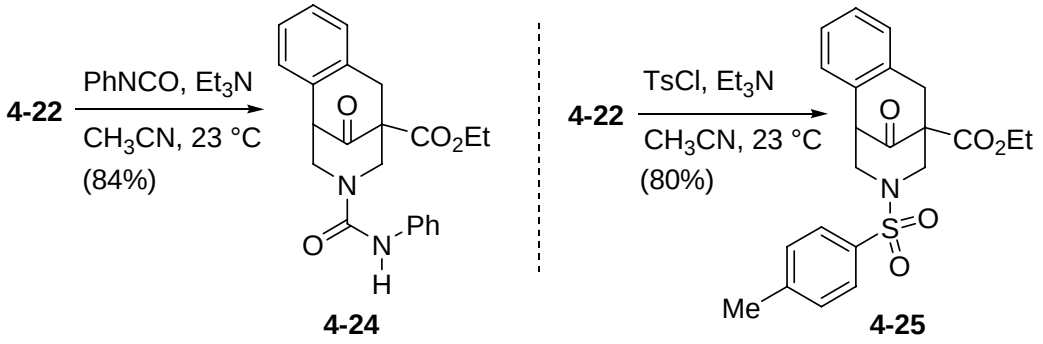



**Figure 20**. $^{13}C$ NMR spectrum of deprotected compound **4-22**.

With the amine **4-22** in hand, two representative N-derivatization reactions were performed in order to show the potential of **4-22** as a useful scaffold (Scheme **44**). Thus, reaction of the amine **4-22** with phenyl isocyanate in the presence of triethylamine gave a high yield of the urea **4-24**. Reaction of **4-22** was also possible with tosyl chloride under comparable conditions yielding the sulfonamide **4-25**.




**Scheme 44**. Derivatization reactions on the tricyclic amino ketone **4-22**.

# 5 Conclusion I

We could show that the tactical sequence of alkylation of a cyclic keto ester with an ortho-bromobenzyl bromide, followed by an intramolecular ketone arylation reaction (Buchwald–Hartwig palladium-catalyzed cyclization) provides an efficient and innovative route to bicyclic benzomorphan scaffolds previously unknown. A number of substrates, which contain electron withdrawing, electron donating, and sterically hindered groups, respectively were subjected to the studied transformation.

Preliminary biological activity results show that compound **4-5a** is active at noradrenaline and serotonine sites. In 5-HT-reuptake inhibition tests, a value of 77% was achieved for a 10µM solution of **4-5a**. Noradrenalin-reuptake inhibition tests showed 80% at the same concentration.[65]

From the N-benzyl compound **4-5a** the amine **4-22** (hydroiodide) could be obtained, which has served as a useful scaffold for further derivatization reactions. The synthesis of an isomeric benzomorphan with different nitrogen atom position (cf. **4-12**) was also shown to be possible by the developed methodology. Other targets that contain an aryl or hetaryl ring in a complex structure should be accessible as well.

Before this method was described there was no methodology known to provide benzomorphans with a broad scope of aromatic ring substituents and nitrogen position variations at once. 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 Queenslandon.

# 6 Introduction

The birth of natural product synthesis as a discipline corresponds with the synthesis of urea by Friedrich Wöhler from ammonium cyanate in 1828, for the reason that this compound is a naturally occurring substance. Besides giving birth to organic synthesis, that sign event served to "discredit" finally the myth that the synthesis of natural products is possible only by nature. These days, the discipline of natural product synthesis is an important field of investigation whose profits broaden from new scientific knowledge to practical applications.[66] Also, natural product synthesis symbolizes the power of chemical synthesis and defines its scope and limitations. It also serves to sharpen the tool of chemical synthesis by expansion into higher molecular complexity, diversity, and efficiency.[67]

Natural product synthesis gives the opportunity for the discovery and invention of new synthetic strategies and methods to be used in a wider range of applications. Another point is that natural products could be produced in larger quantities for further extensive biological investigations and/or medicinal applications. Moreover, to the extent that a natural substance can be synthesized in the laboratory, in a more cost-effective process than the one which requires its extraction from natural source; its use could become economically more sufficient and desirable. Yet another point is that natural products can provide a structural platform which can be elaborated upon, or simplified, to achieve the enhanced potency or improved selectivity or physical and chemical properties.[68] Such events could lead to advanced pharmacological properties than those possessed by the natural products themselves. On the other hand, the chemical synthesis of a natural product still provides the absolute proof of the assigned structure.[69]

Benzolactone represent an important subclass of natural products among the polyketides.[70] The ones that feature acetate as a starter unit normally contain a 14-membered resorcylic acid lactone (RAL) feature.

Resorcylic acid lactones (RALs) are mycotoxins produced by a variety of different fungal strains *via* polyketide biosynthesis (Figure **21**). The fungal polyketide synthases (PKSs)

involved in RAL biosynthesis are large multidomain enzymes that iteratively catalyze the condensation of nine units of acetates or malonates. Different modules can further process the product of each condensation by reduction of the β-ketone or dehydration of the hydroxy ester. Different combinatorial arrangements of the modules involved in processing of the β-ketones in the first five condensations can account for the diversity of functionality present around the RAL macrocycles.[71] Even though their structures are quite similar, each of them displays a characteristic and unique type of biological activity.

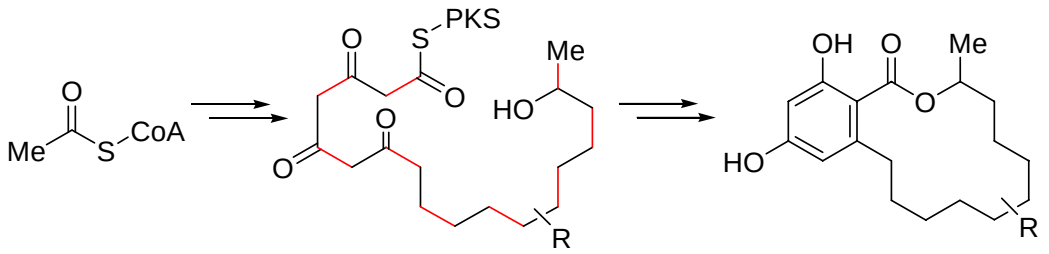
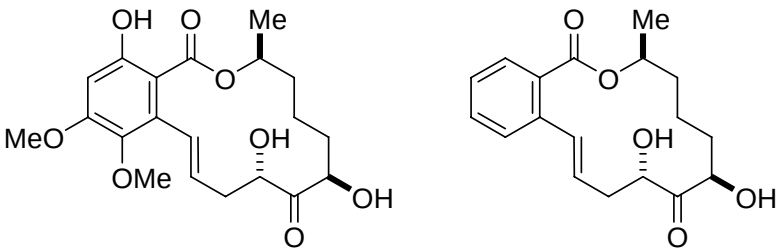



**Figure 21**. Biosynthesis of resorcylic acid lactones.

Queenslandon (**6-1**) was isolated in 2002 from the strain *Chrysosporium queenslandicum* IFM51121 and its relative stereochemistry was illustrated.[72] This macrolactone showed distinct activity against fungi but was devoid of antibacterial activity.




**Queenslandon (6-1)** **6-2**

**Figure 22**. Structure of Queenslandon (**6-1**) and simplified analog **6-2** containing no substituents on the aromatic part.

Queenslandon is an attractive target first of all because of its structural relation to other members of the resorcylic acid lactones, which are known to be effective therapeutic agents and, on the other hand, there is no synthesis of this molecule reported in the literature up to date. Therefore, the total synthesis of queenslandon would prove the absolute configuration of stereogenic centers and possibly will give access to a new promising pharmaceutical.

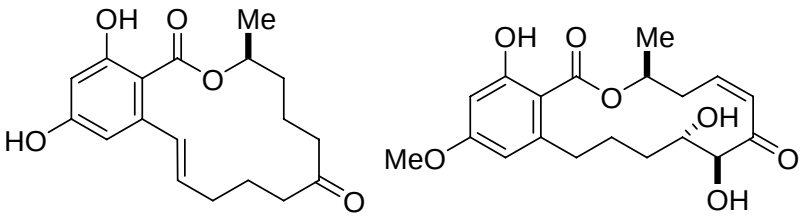
The objective of our research was therefore aimed at the design of an efficient synthetic strategy, which would allow the total synthesis of queenslandon itself, as well as other analogues of this novel natural product.

# 7 Literature review

## 7.1 The Family of 14-Membered Resorcylic Acid Lactones

While 14-membered resorcylic lactones (RALs) have been known for a long time, the more recent discoveries that some members of this class of natural products are potent kinase inhibitors have stimulated a renewed interest in this family of natural products.[73]

The classical benzolactone, the fungal metabolite zearalenone (**7-1**), first isolated in 1962 from the fungus *Gibberella zeae* and reported as exhibiting anabolic, estrogenic and antibacterial properties.[74] This compound was shown to adopt a conformation that mimics the one of 17-estradiol which explained its agonistic estrogenic properties.[75] The resorcylic acid lactone L-783,277 (**7-2**), a fungal metabolite as well, was reported to be a selective inhibitor of MEK,* a threonine/tyrosine specific kinase resulting in antitumor activity (Figure **23**).[76]



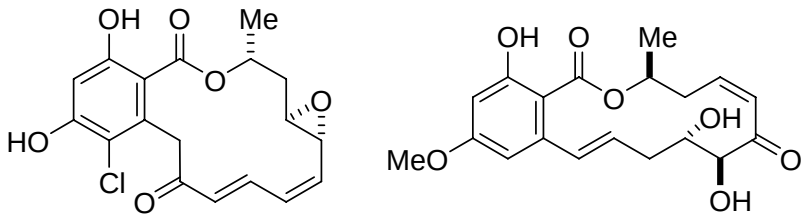

**Zearalenone (7-1)** **L-783,277 (7-2)**

**Figure 23**. Structures of zearalenone (**7-1**) and L-783,277 (**7-2**).

Another prominent member of the benzolactone family, radicicol (**7-3**, Figure **24**), confers its antitumor activity through inhibition of the chaperone HSP90.[77] The related pochonins seem to target HSP90 as well, inducing antiviral and antiparasitic activity.[78] Another *cis*-

* MEK (MAP kinase kinase) is a dual-specificity kinase that phosphorylates the tyrosine and threonine residues and involved in the MAP (Mitogen-activated protein) kinase cascade. The MAP kinases relay, amplify and integrate signals from a variety of extracellular stimuli thereby regulating a cell's response to its environment.

enone RAL, LL-Z1640-2 (**7-4**), was shown[79] to be competitive with ATP and to irreversibly inhibit TAK1.*




**Radicicol (7-3)**
**HSP90 inhibitor**
**20 nM**

**LL-Z1640-2 (7-4)**
**TAK1 inhibitor**
**8.1 nM**

**Figure 24**. Examples of potent kinase or ATPase inhibitors: radicicol (**7-3**) and LL-Z1640-2 (**7-4**).

It follows that the benzolactones are important lead structures for the search of novel antitumor compounds.[80] In particular, structure–activity studies might illuminate key factors that make out the difference in the binding of a certain kinase.[81] All such properties of this subclass of benzolactones make them an attractive target for further biological investigations and structure activity studies.

Protein kinases are recognized as essential components of cellular signal pathways and are directly involved in numerous diseases including cancer, diabetes, and inflammation. In the 50's, it was discovered that phosphorylation can reversibly alter the function of enzymes by protein kinases which catalyze phosphorylation, or by protein phosphatases which are involved in the dephosphorylation step (Figure **25**).[82]

* TAK1 is a MAPKKK involved in the p38 signalling cascade for proinflammation signals

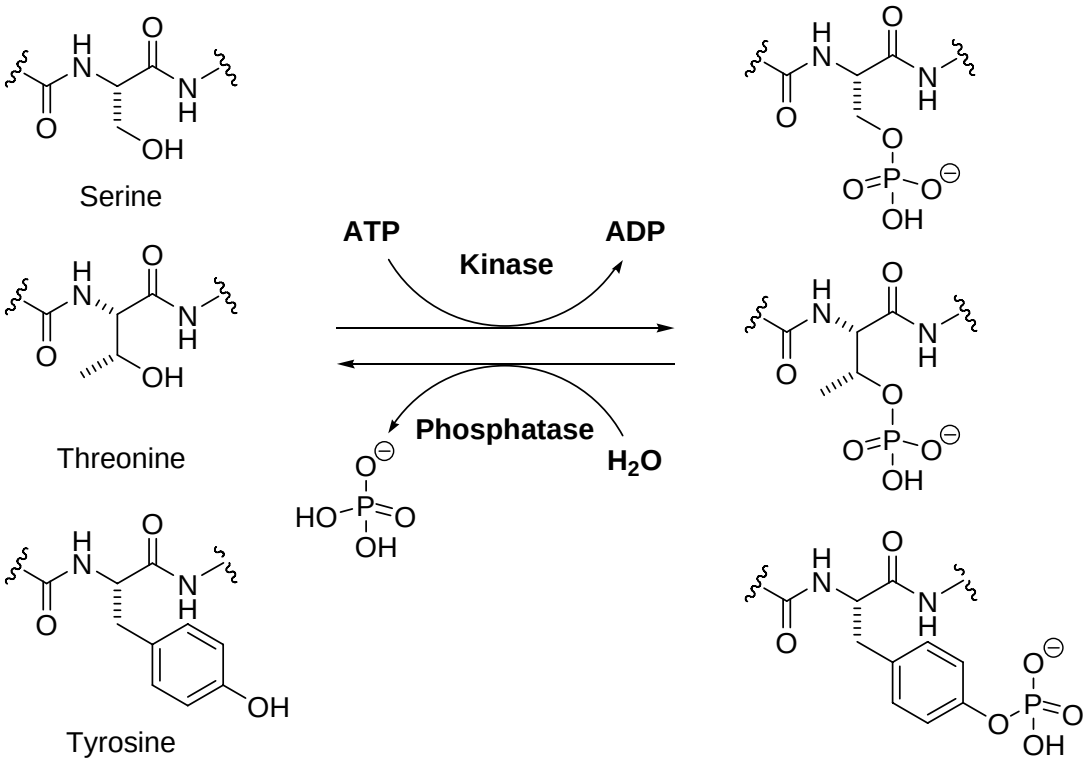
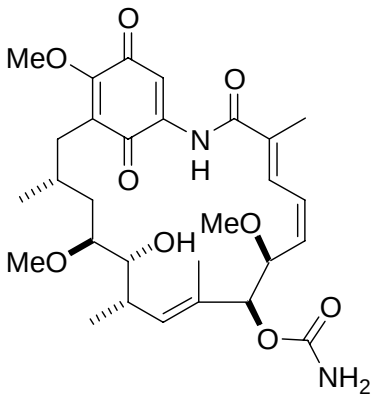



**Figure 25**. Phosphorylation and dephosphorylation mediated by kinases and phosphatases.

These reactions play a crucial role in living organisms for the regulation of a large number of cellular processes (signaling transduction pathways). At the end of 70's, the discovery that the transformation factor of the Rous sarcoma virus (v-Src) is a protein kinase[83] and that tumor-promoting phorbol esters are potent activators of protein kinase C[84] were of relevant significance. These two major observations emphasized the importance of protein phosphorylation at the cellular level, shedding the light on the first connections between abnormal protein phosphorylation and disease. Intensive research over the last thirty years has shown that defects in transduction mechanisms are at the basis of cancer and other human diseases (diabetes, inflammatory disorders, cardiovascular diseases, *etc*.).[85] In addition, the macrolactam geldanamycin is an important lead in the area of HSP90 inhibitors.[86]




**Geldanamycin** (**7-5**)

**Figure 26**. Structure of geldanamycin (**7-5**), the lead HSP90 inhibitor.

Intensive research programs have led to the identification of several specific kinase inhibitors that show encouraging results as a new class of therapeutics. The vast majority of these compounds target the ATP-binding site of the kinase. Similarly, HSP90 (Heat Shock Protein 90) inhibitors target the ATP-binding pocket of the protein and several of them have been identified as potential anticancer agents. Among them, the 14-membered resorcylic acid lactones (RALs) stand out as the most potent ones.

Monorden (**7-3**) was the first resocylic acid lactone isolated in 1953 from *Monosporium nordinii*.[87] After ten years the same molecule was independently isolated from *Nectria radicicola*[88] and called radicicol. With the assignment of its three chiral centers by X-ray crystal structure in 1987 it was shown that the initial structure proposed for monorden was incorrect leading to the common acceptance of radicicol as the name of this molecule.[89] In 1964, mild sedative and moderate antibiotic properties were reported for radicicol.[90] While radicicol was reported to inhibit Src in cellular assays, it was later shown that this observation comes from the fact that radicicol is a potent and selective HSP90 inhibitor. On the other hand, several RALs bearing a *cis*-enone on the 14-membered macrocycle such as LL-Z1640-2 (**7-4**), L-783, 277 (**7-6**), hypothemycin (**7-7**) and radicicol A (**7-8**) have all been reported to be protein kinase inhibitors (Figure **27**).

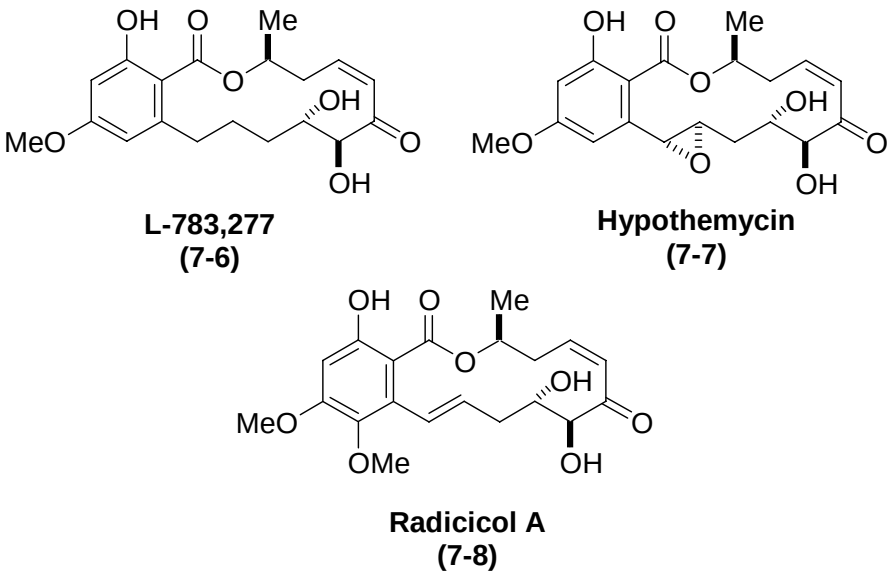
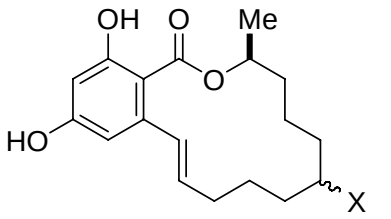



**Figure 27**. Structures of L-783,277 (**7-6**), hypothemycin (**7-7**), and radicicol A (**7-8**).

Radicicol A (**7-8**, Figure **24**) was isolated in 1987 from the fungus strain F/87-2509.04 while looking for interleukin 1 beta (IL1β) inhibitory activity, an important mediator of inflammation.[91] Several years later, Traber and co-workers corroborated this finding along with inhibition of the tumor necrosis factor alpha (TNF-α) secretion, another major factor of inflammation.[92] Its mode of action is related to the degradation of specific mRNA sequences containing AU-rich elements (AREs).[93] Radicicol A was found to inhibit tyrosine phosphorylation of several proteins differentially expressed or modified by a tyrosine kinase. Several other analogs were also found to inhibit IL1β secretion but, without destabilizing mRNA, leading to the speculation that small structural differences are able to change the mode of action and presumably the target of inhibition. This hypothesis was even later corroborated by other members of this family such as LL-Z1640-2 (**7-4**) isolated in 1978,[94] hypothemycin (**7-7**) in 1980[95] from *Hypomiyces tricothecoides* and L-783,277 (**7-6**). In 1999, researchers at Merck isolated L-783,277 (**7-6**) from organic extracts of a *Phoma* sp. (ATCC 74403) and showed it to be a potent, ATP-competitive and irreversible inhibitor of MEK1 with an $IC_{50}$ of 4 nM.[96] At the same time, hypothemycin (**7-7**) was shown to be a slightly less active MEK1 inhibitor with an $IC_{50}$ of 15 nM, providing an explanation to previously reported effects such as inhibition of the *ras*-signaling pathways.[97] In 2003, Matsumoto and co-workers showed that LL-Z1640-2 (**7-4**) inhibited irreversibly the kinase activity of TAK1 ($IC_{50}$ = 8.1 nM) by competing with ATP.[79] The importance of MEK1 and TAK1 in regulating cellular response to stimuli and

translating them into gene expression, cell growth and apoptosis has made these kinases and more generally the kinases involved in the MAP cascade primary targets in drug discovery.

In addition to the aforementioned macrolides, several other RALs have been reported so far in the literature. Representatives of the zearalenone family are zearalenone itself (**7-1**), zearalane (**7-9**), and zeranol (**7-10**) (Figure **28**).




**X = H (Zearalane, 7-9)**
**X = OH (Zeranol, 7-10)**

**Figure 28**. Structures of zearalane (**7-9**) and zeranol (**7-10**).

Extensive research on zearalenone (**7-1**) derivatives allowed the discovery of reduced derivatives such as **7-9** and **7-10** and their biological evaluation showed that they both share the properties of zearalenone. Additionally, zearalane (**7-9**) has shown anthelmintic and immunomodulating properties whereas zearanol (**7-10**, Ralgro® or Ralabol®) has been used to promote growth in cattle and to relieve post-menopausal stress in women.[98]

More recently, new RALs were discovered in a screening for anti-malarial activity.[99] In 2002, along with hypothemycin (**7-7**) as the major secondary metabolite, five new analogs were isolated from the marine mangrove fungus *Aigialus parvus* (Figure **29**).

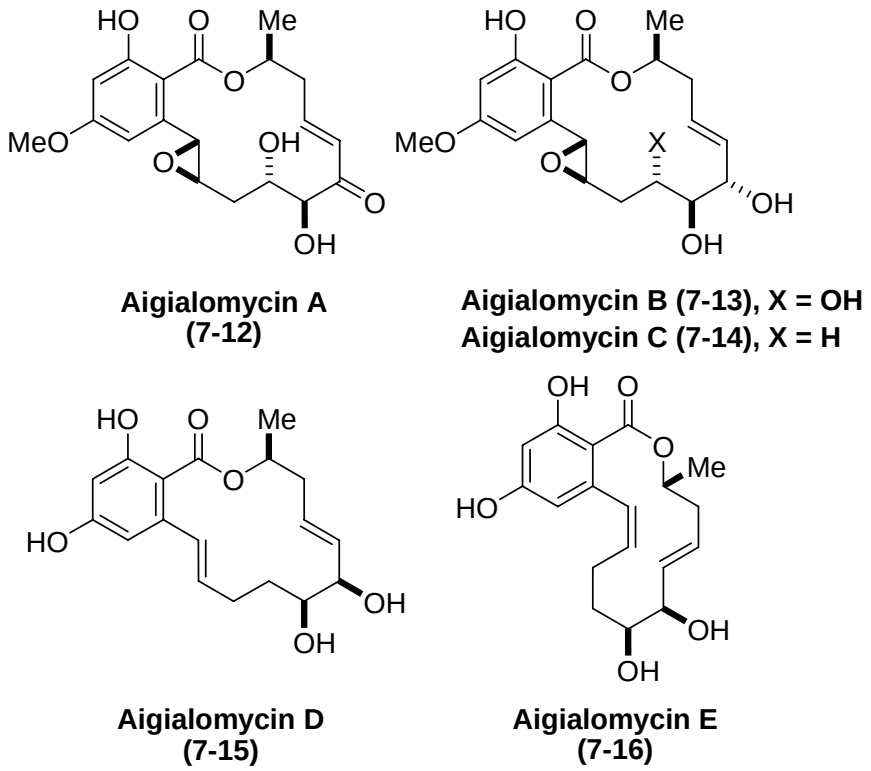



**Figure 29**. Structures of Aigialomycines A-E (**7-12**, **7-13**, **7-14**, **7-15**, **7-16**).

Aigialomycin D (**7-15**) exhibited moderate anti-malarial activity against *Plasmodium falciparum K1* and showed cytotoxicity in two cancer cell lines (KB and BC-1) in the same range as hypothemycin (**7-7**), whereas their analogs were much less active. Further studies have shown that aigialomycin D is able to inhibit some kinases namely CDK1/cyclinB, CDK5/p25 and GSK3 in the micromolar range ($IC_{50}$ from 5 to 14 μM).[100]

In 2003, other new members of the RAL family, pochonins A-F (**7-17** to **7-22**) and radicicol (**7-3**) isolated from *Pochonia chlamydosporia* var. *catenulata* were reported (Figure **30**).[101]

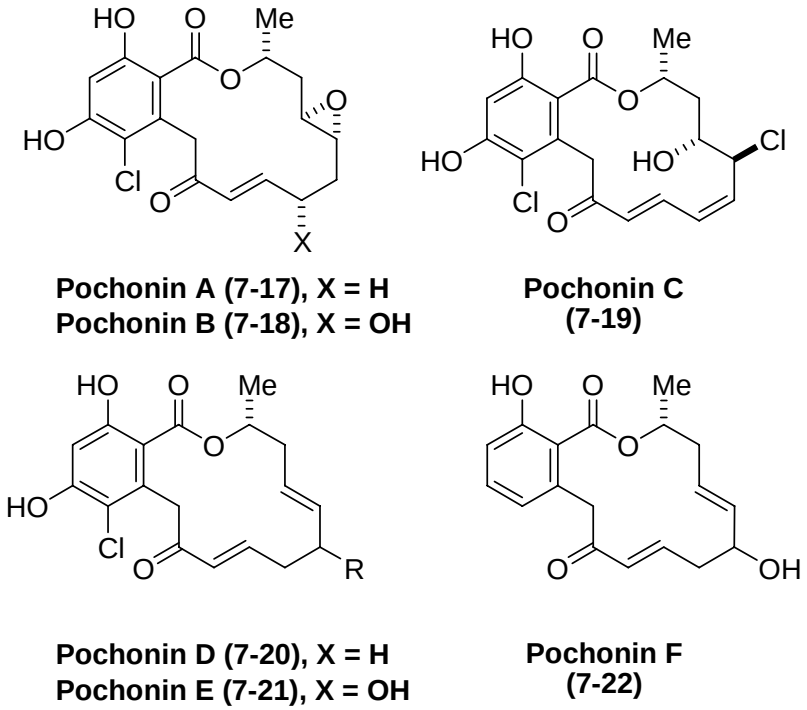



**Figure 30**. Structures of pochonins A-F (**7-17** to **7-22**).

These molecules were identified in a Herpes Simplex Virus 1 (HSV1) replication assay. While radicicol showed activity in the nanomolar range, all the pochonins except pochonin D exhibited bioactivities at the low micromolar range and pochonin D (**7-19**) only showed cytostatic effects. In this assay, HSV inhibition was always accompanied by weak cytostatic effects, therefore providing the low tolerability of these molecules *in vitro*.

## 7.2 Chemical Syntheses of 14-Membered RALs

Besides the biological properties described above, the RALs have been an interesting scaffold for organic chemists to elaborate innovative and convergent total synthesis and to develop new methodologies. The first molecule targeted by synthetic chemists was zearalenone (**7-1**) with its first total synthesis reported in 1968.[102] The retrosynthetic analysis is based on lactone ring closure of the seco acid **7-23**. This key intermediate **7-23** was depicted as a two component system joined by a double bond in which the one component is the aromatic system, 2-formyl-4,6-dimethoxybenzoic acid sodium salt (**7-24**), whereas the second component is the aliphatic moiety **7-25** in which the functionality at C-6 is masked *via* internal ketal formation (Figure **31**).

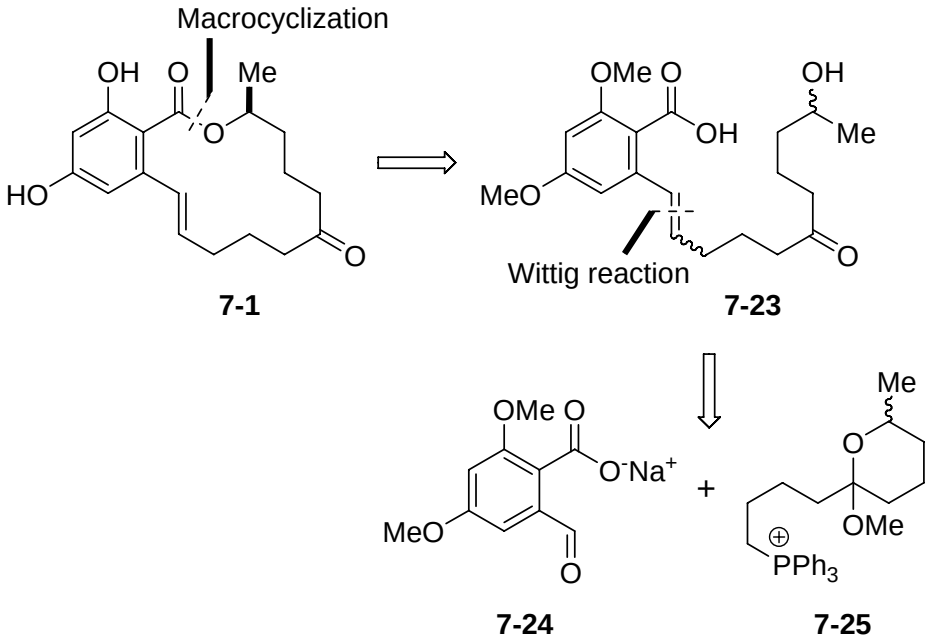
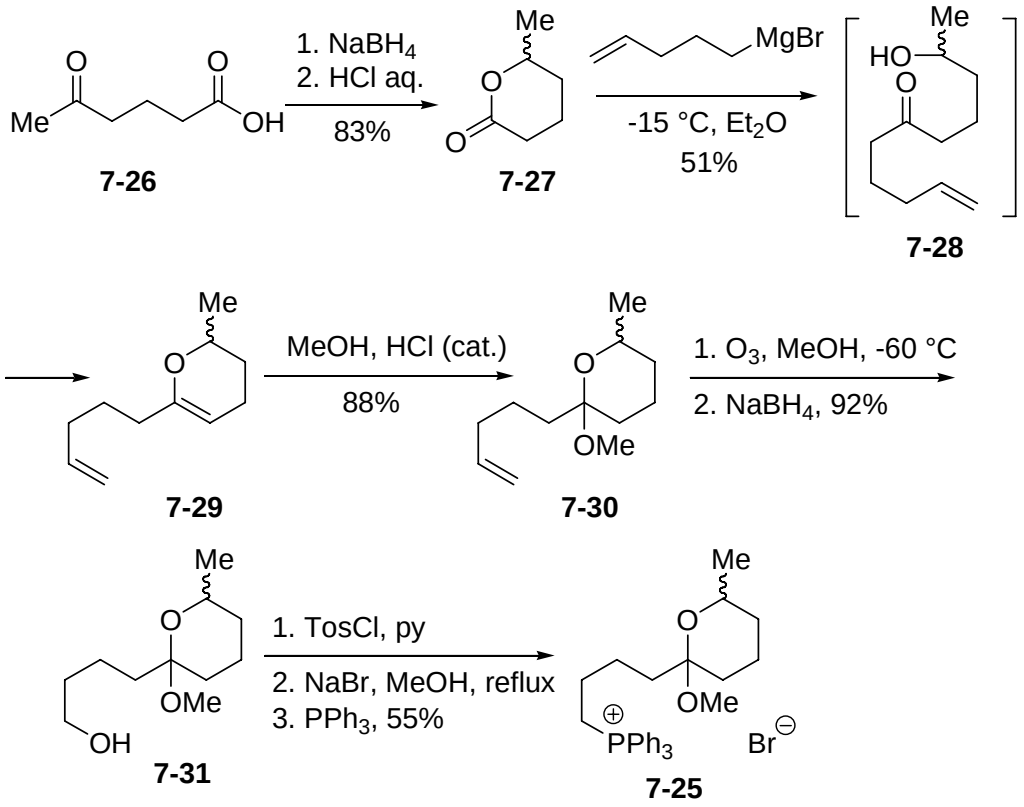


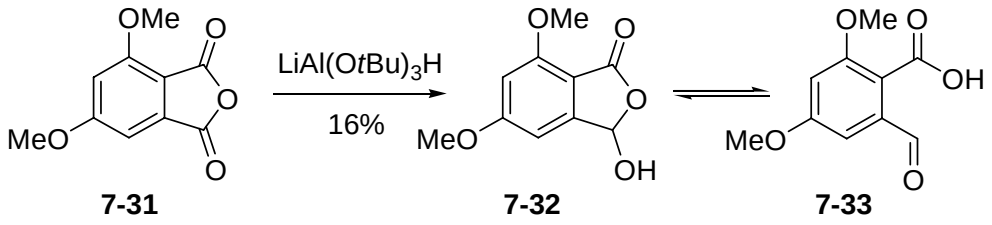

**Figure 31**. Retrosynthetic analysis for zearalenone (**7-1**) by Taub and co-workers.

The cyclic ketal **7-25** was prepared in nine steps starting from 5-ketohexanoic acid **7-26** (Scheme **45**). This acid was converted to 5-hydroxyhexanoic acid lactone **7-27** by reduction followed by acidification and distillation. Treatment of this lactone at –15 °C with 4-pentenylmagnesium bromide permitted the isolation of the 1:1 mixture of isomers **7-28**. Acidification of the latter followed by distillation produced the cyclic enol ether **7-29**. Component **7-29** was then converted in high yield to cyclic ketal **7-30** under acidic conditions. Ozonolysis of **7-30** followed by reduction of the intermediate ozonide provided the carbinol **7-31**, which was transformed to its tosylate derivative with *p*-toluenesulfonyl chloride in pyridine and then to the corresponding bromide with NaBr. The latter was converted in turn with triphenylphosphine to the phosphonium bromide **7-25**.




**Scheme 45**. Synthesis of phosphonium salt **7-25**.

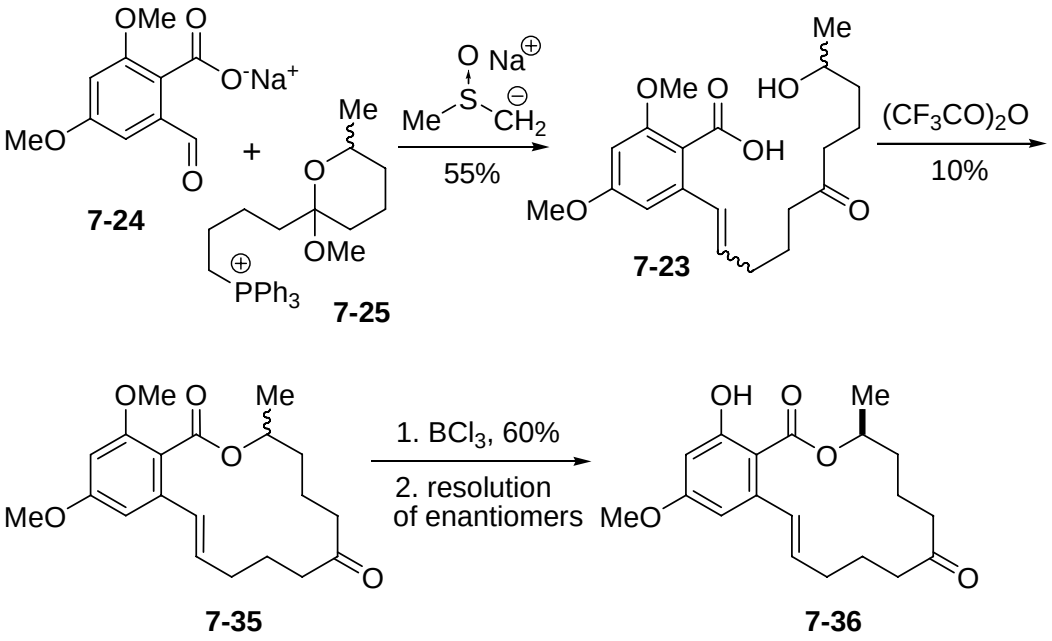
The aromatic component, 2-formyl-4,6-dimethoxybenzoic acid (**7-34**), had been obtained by reduction of the 3,5-dimethoxyphtalic anhydride (**7-32**) with lithium tri-*tert*-butoxyaluminum hydride in THF at 20 °C (Scheme **46**). This phthalaldehydic acid like system exists in solution entirely in the hydroxyphthalide form (**7-33**).




**Scheme 46**. Synthesis of 2-formyl-4,6-dimethoxyphtalide (**7-32**).

The phosphonium salt **7-25** corresponding to the aliphatic component was converted to its ylide with methyl sulfinyl carbanion in DMSO. Treatment of this ylide with the sodium salt **7-24** in DMSO caused formation of a mixture of *cis* and *trans* seco acids **7-23**. Ring closure of the mixture of seco acids **7-23** by treatment with trifluoracetic acid anhydride

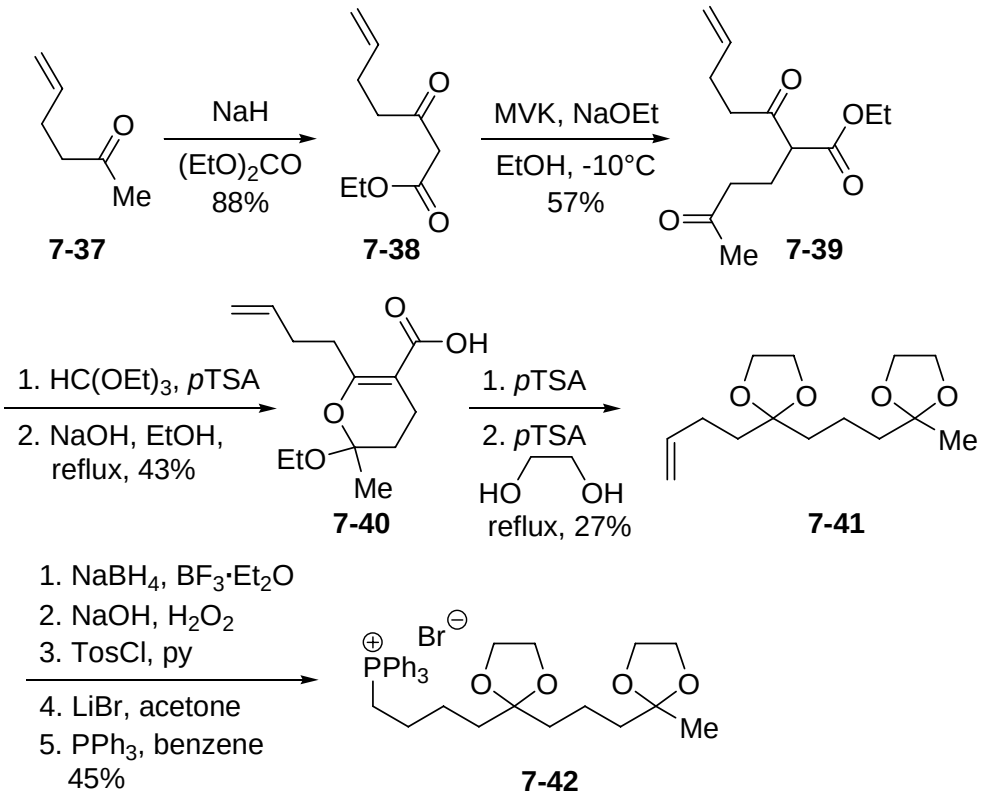
provided (±)-zearalenone dimethyl ether (**7-35**) in extremely low yield of 10%. The latter after selective ether cleavage with boron trichloride yielded the racemic 4-monomethylether which was resolved to give enentiomerically enriched (*S*)-4-methylzearalenone (**7-36**) (Scheme **47**).




**Scheme 47**. Completion of 4-methylzearalenone (**7-36**) synthesis by Taub and co-workers.

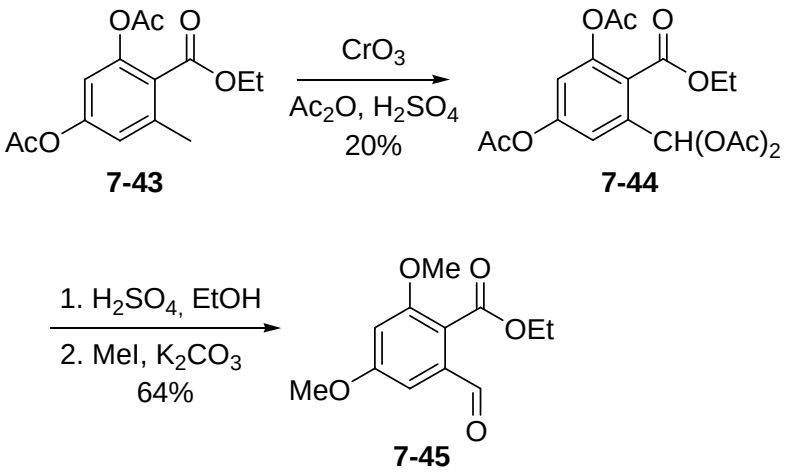
Shortly after that, another group has reported the total synthesis of racemic zearalenone.[103] This approach is very similar to the one presented above, but the aromatic and aliphatic moieties were prepared using different synthetic paths. Thus, carbethoxylation of l-hexen-5-one (**7-37**) gave the β-keto ester **7-38** (Scheme **48**). Michael addition to methyl vinyl ketone then extended the carbon chain to the required length forming the diketo ester **7-39**. Basic hydrolysis of the keto ester **7-39** was achieved by way of the intermediate mixed cyclic ketal **7-40** in which the reactive functions are protected. Decarboxylation and ketal cleavage under acidic conditions then generated 1-decene-5,9-dione, which was then protected with ethylene glycol and double ethylene ketal **7-41** formed. The latter was transferred to phosphonium salt **7-42** in 5 steps with 45% overall yield. Thus, hydroboration of the olefinic bond in **7-41** followed by oxidation with hydrogen peroxide gave the alcohol, which was further converted *via* the *p*-toluenesulfonate ester and the bromide intermediate to the phosphonium salt **7-42**

containing the carbon skeleton and correctly positioned oxygen atoms of the aliphatic portion.



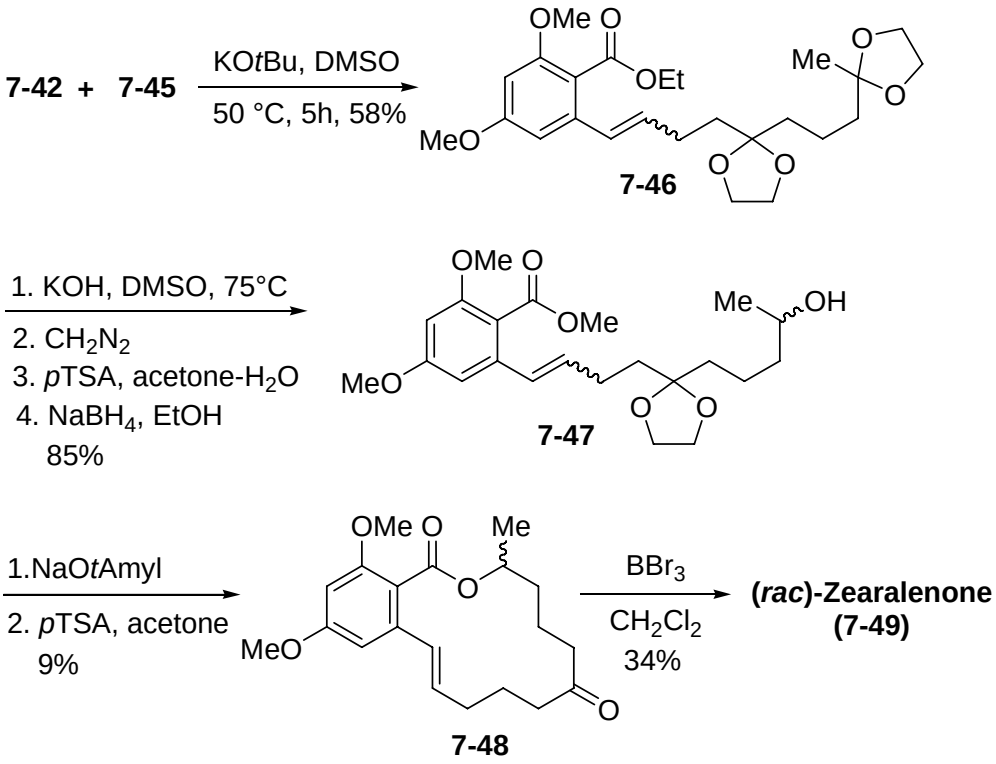

**Scheme 48**. Synthesis of phosphonium salt **7-42**.

The aromatic portion was readily constructed from ethyl orsellinate diacetate (**7-43**) by oxidation with chromium trioxide in sulfuric acid-acetic anhydride mixture to the aldehyde tetraacetate **7-44**, followed by hydrolysis to the phenolic aldehyde and methylation to the required ethyl 4,6-dimethoxy-2-formylbenzoate (**7-45**) (Scheme **49**).




**Scheme 49**. Synthesis of aromatic aldehyde **7-45** from ethyl orsellinate diacetate (**7-43**).

Coupling of the aldehyde **7-45** and phosphonium salt **7-42** proceeded by a Wittig reaction in dimethyl sulfoxide leading to the ester **7-46**, containing the carbon skeleton of zearalenone. Specific cleavage of the ketal at C-10 of the side chain was achieved in aqueous acetone containing *p*-toluenesulfonic acid. (Scheme **50**). The intermediate keto acid was esterified with diazomethane, and then the ketone at C-10 was reduced by sodium borohydride forming the monoketal **7-47**. The lactone ring was formed in 9% yield by base-catalyzed intramolecular ester exchange of the hydroxy ester **7-47** in the presence of *tert*-amyl alcohol as a proton source; the methanol formed being fractionally distilled out of the mixture to displace the ester-lactone equilibrium in favor of the lactone formation. Cleavage of the remaining ketal group gave (*rac*)-zearalenone dimethyl ether (**7-48**). Although the yield at the lactonization stage was low (9%), the authers note, that it was sufficient to allow completion of the synthesis. Reaction of the dimethyl ether **7-48** with boron tribromide gave complete cleavage of methoxy groups in 34% yield to form racemic zearalenone (**7-49**).




**Scheme 50**. Wittig reaction of aromatic aldehyde **7-45** with phosphonium salt **7-42** and completion of (*rac*)-zearalenone (**7-49**) synthesis by Vlattas and co-workers.

Since then, several other research groups have shown interests in developing total syntheses of this natural product[104] and it has also been served as a testing ground for development of new cyclization methodologies such as the Corey-Nicolaou macrolactonization,[105] Masamune's thioester-lactonization,[106] and more recently the ring-closing metathesis (RCM) by Fürstner.[107]

In 1992, Lett and Lampilas reported the first total synthesis of radicicol and confirmation of the absolute configuration of its three stereocenters.[108] Having in mind the sensitivity of the epoxide along with the readily enolisable ketone at the benzylic position, a retrosynthetic analysis with a Stille coupling and a Mitsunobu macrolactonization as key steps was proposed (Figure **32**).

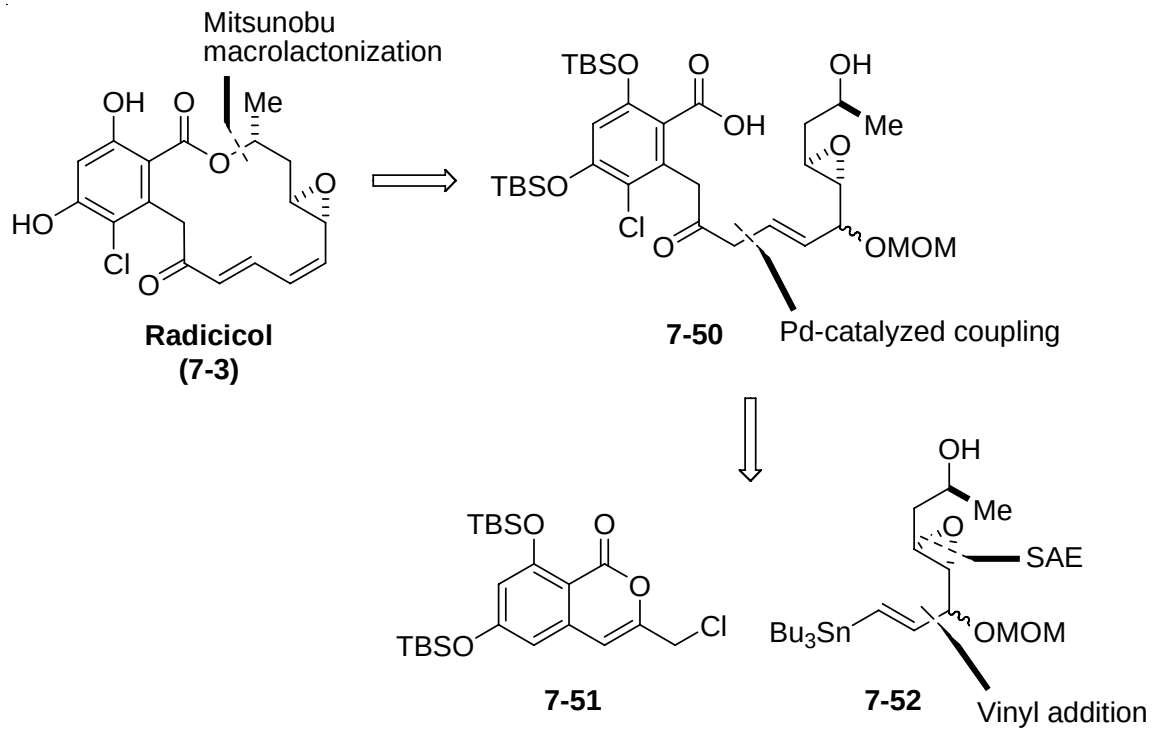
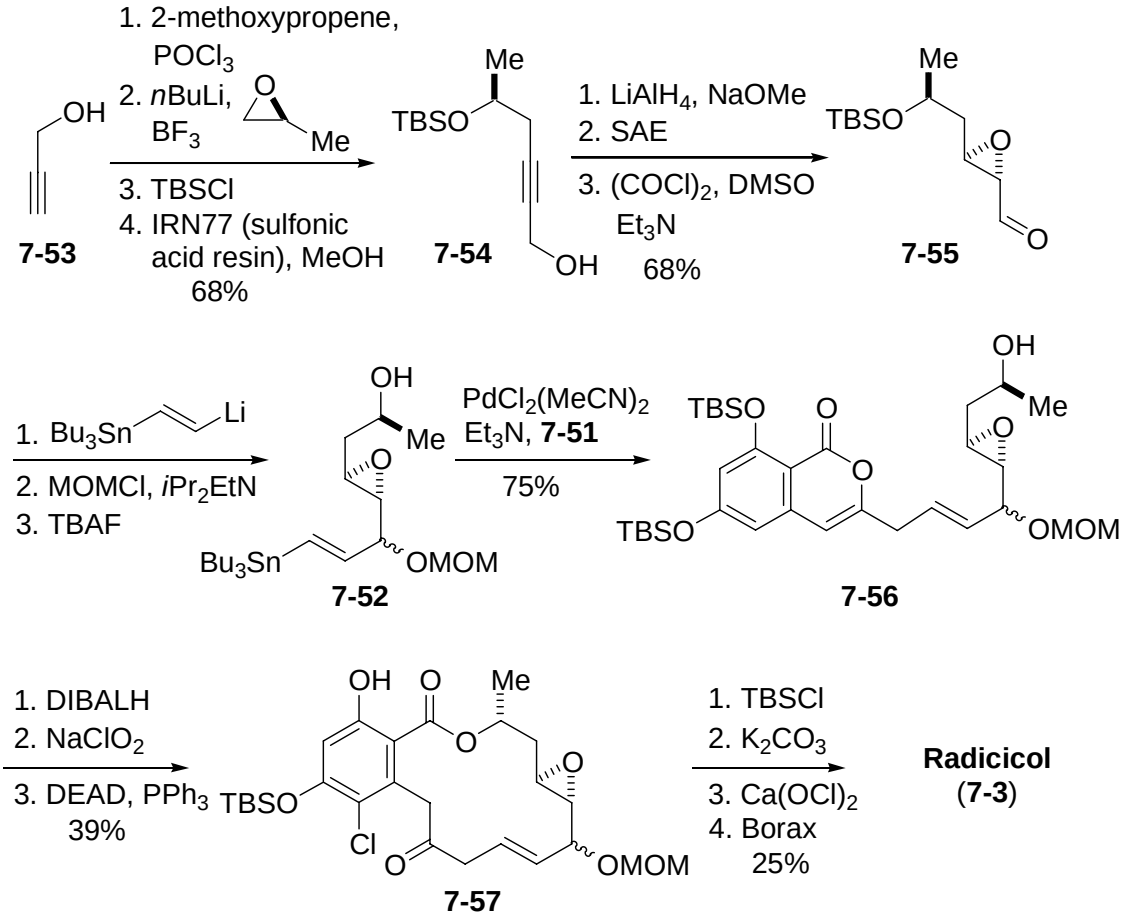


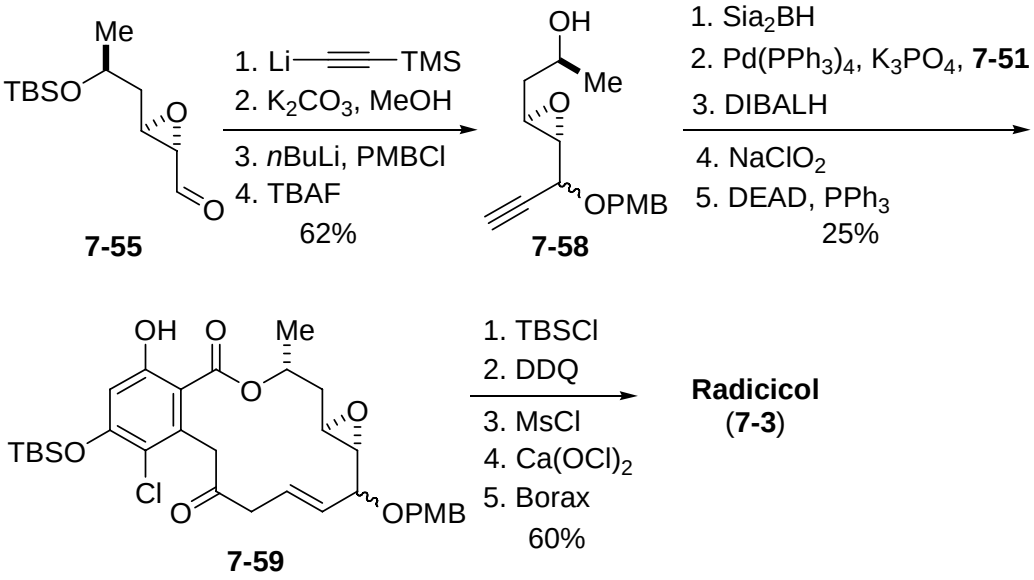

**Figure 32**. Retrosynthetic analysis for radicicol by Lett and co-workers.

The isocoumarin group in **7-51** (obtained in 32% yield from orcinol hydrate) served as a masking moiety for the enolisable ketone in order to expose the conjugated system only at a late stage of the synthesis. Starting with propargyl alcohol (**7-53**), the stannane derivative **7-52** was obtained in 24% yield over 10 steps through a condensation with a lithium salt, reduction of the alkyne and Sharpless asymmetric epoxidation ("SAE") (Scheme **51**). The fragment **7-52** was then used in a Stille coupling with the chlorinated isocoumarin **7-51** to yield the acyclic precursor **7-56** in good yield (75%). Subsequently, isocoumarin opening, oxidation of the resulting aldehyde, Mitsunobu macrolactonization, release of the conjugated dienone by heating with anhydrous $K_2CO_3$ in DME and chlorination as the major steps allowed the isolation of radicicol (**7-3**) in 10% yield over 7 steps.




**Scheme 51**. Synthesis of radicicol (**7-3**) by Lett and co-workers.

Another important feature of this synthesis is the Mitsunobu macrolactonization in which the unprotected *ortho*-phenol was found necessary for high efficiency (71% yield). This way, Lett and co-workers achieved the first total synthesis of radicicol albeit in less than 2% overall yield (18 steps, longest linear sequence) and confirmed the absolute *R* configuration of the three chiral centers of radicicol. A decade later, the same group reported improvements and simplifications of their first synthesis as presented on Scheme **52**.[109]




**Scheme 52**. Improved synthesis of radicicol (**7-3**) by Lett and co-workers.

The main significant improvement involved unmasking the dienone. An orthogonal protecting group on the alcohol in α position to the epoxide turned out to be necessary for the success of the Mitsunobu macrolactonization and a PMB protecting group was found to be better then a MOM group. It was easily removed after the ring formation and replaced by a mesylate that, under basic condition, allowed release of the dienone in 76% yield over two steps.

Shortly before the Lett work, Danishefsky and co-workers published another total synthesis of radicicol.[110] Inspired by their asymmetric synthesis of the radicicol core structure presented a year earlier,[111] the retrosynthetic analysis is based on three main disconnections: a ring-closing metathesis, a dithiane addition and a Mitsunobu esterification (Figure **33**).

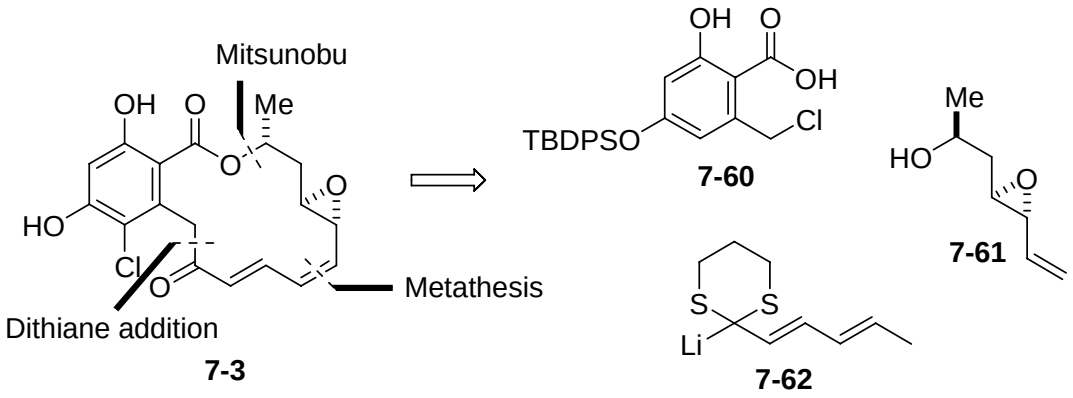
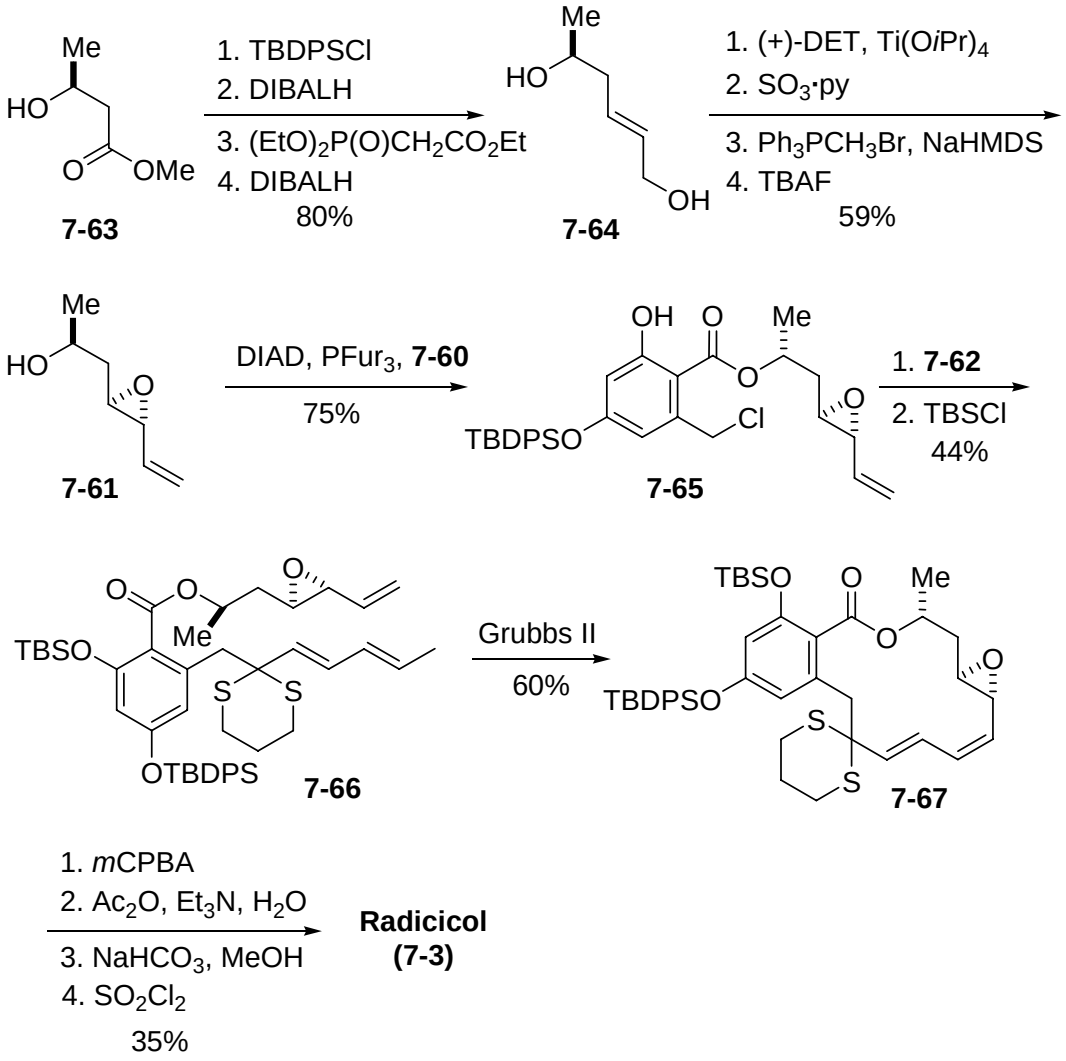


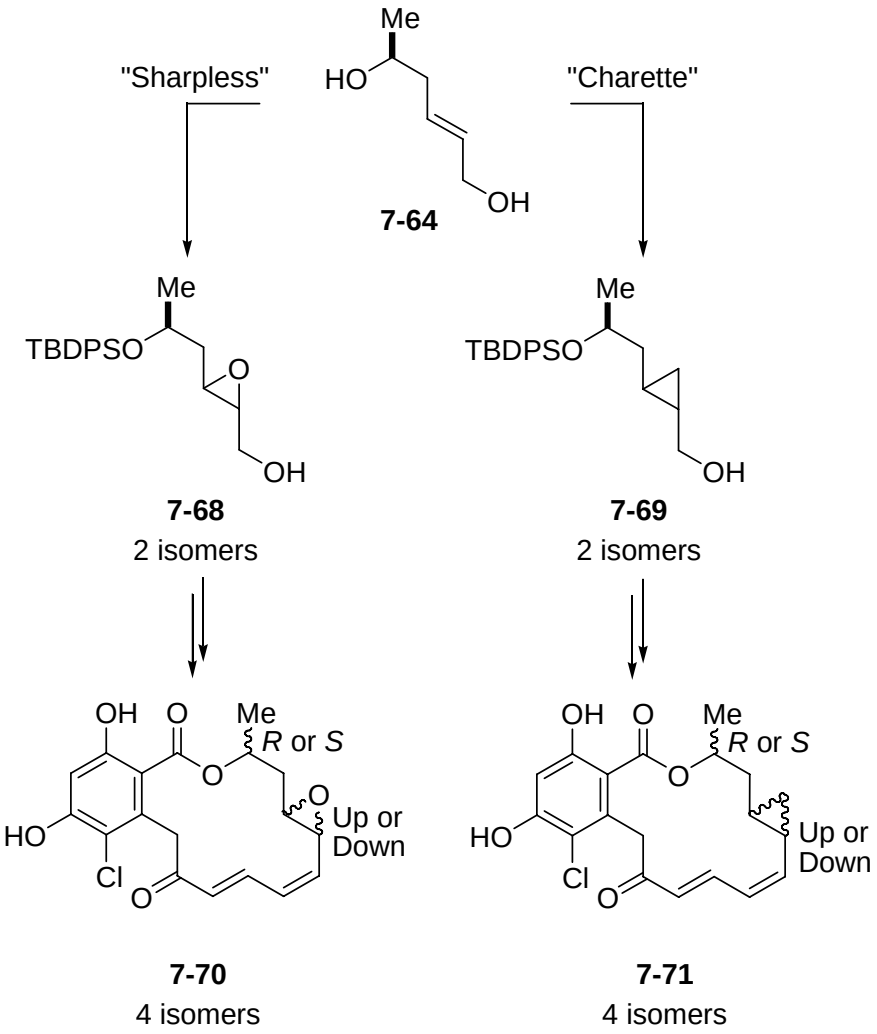

**Figure 33**. Rerosynthetic analysis for radicicol (**7-3**) by Danishefsky and co-workers.

The dithiane moiety **7-62** served as a masked acyl anion equivalent, in order to prevent cyclization to the isocumarin. In the synthesis of the methylated analog, esterification with the benzoic acid bearing methyl protecting groups occurred without any problem *via* the acid chloride. However, when changing to more labile protecting groups, this step proved challenging because of phtalide formation under diverse conditions (Mitsunobu reaction, cabodiimide or acid chloride). Yet again, the presence of the free *ortho*-phenol was essential for the success of this reaction. Starting from the commercially available (*R*)-3-hydroxybutyric acid methyl ester (**7-63**) the alcohol **7-61** bearing the three chiral centers of radicicol was obtained in 47% yield after 8 steps (Scheme **53**). Thereafter, Mitsunobu lactonization with compound **7-60** using a less nucleophilic phosphane ($PFur_3$) and alkylation with the dithiane adduct **7-62** allowed for the formation of the acyclic intermediate **7-66**. Notably, alkylation conditions had to be improved to avoid γ-addition on the diene. Ring-closing metathesis was achieved using Grubbs' second generation catalyst in good yield and excellent selectivity. However, the presence of the TBS-protected *ortho*-phenol was crucial for the success of this reaction otherwise leading to low rate of closure and low yield. Release of the masked conjugated ketone followed by deprotection of silicon ether and chlorination afforded the desired natural product. This synthetic sequence provided radicicol in a 3% overall yield (longest linear sequence).




**Scheme 53**. Synthesis of radicicol (**7-3**) by Danishefsky and co-workers.

Following this methodology, using Sharpless asymmetric epoxydation or the cyclopropanation chemistry developed by Charette and co-workers,[112] four alcohols (**7-68** and **7-69**, Scheme **54**) were synthesized leading to eight different analogs (**7-70**, **7-71**) bearing all possible stereochemistries on the epoxide/cyclopropane moiety and on the methyl group.[113] All these compounds were then evaluated for HSP90 inhibition. A related structure-activity relationship study established that the epoxide was non-essential for HSP90 inhibition whereas the configurations of the methyl substituent at the ester and of the epoxide/cyclpropyl part were important for high activity.[113]




**Scheme 54**. Divergent synthesis of radicicol and cyclopropanradicicol analogs.

However, this methodology developed for radicicol itself was less efficient for the synthesis of the cyclopropane analog **7-72**. In order to keep away from low-yielding steps and to prepare a large amount of cyclopropanradicicol (**7-72**), a second-generation synthesis was developed.[114] The key step of the synthetic sequence was the formation of the aromatic ring through a Diels-Alder cycloaddition of the ynolide **7-74** as the dienophile to the diene **7-73** derived from dimedone (Figure **34**).

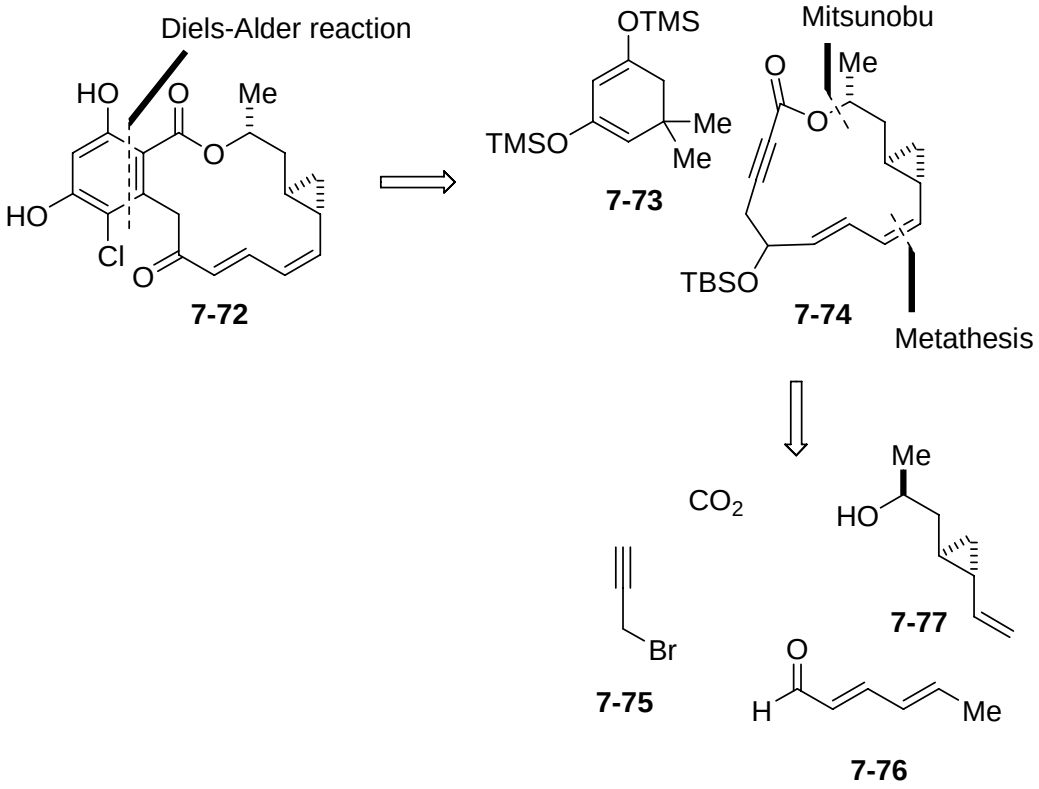
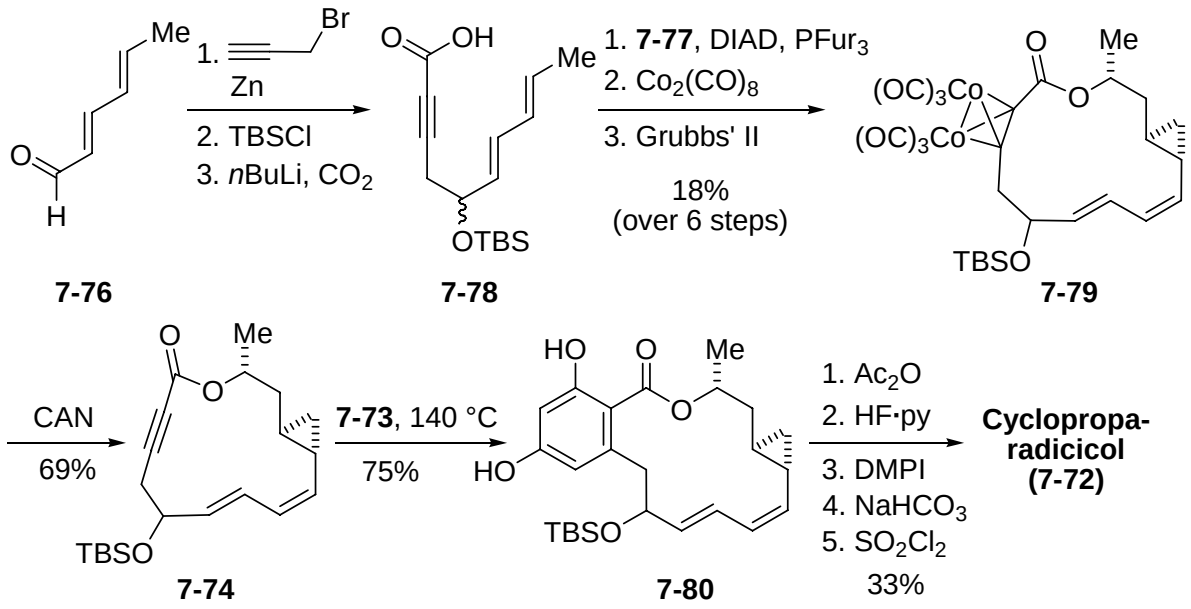



**Figure 34**. Retrosynthetic analysis for cycloproparadicicol (**7-72**) by Danishefsky and co-workers.

The central element of this plan is the construction of the aromatic part at a late stage of the synthesis whereas other protocols start with a modified benzoic acid derivative (Scheme **55**). Thus, Reformatsky-like condensation of propargyl bromide with sorbaldehyde (**7-76**), followed by TBS protection and subsequent reaction of the lithium alkynide with $CO_2$, provided the conjugated carboxylic acid **7-78**. Following reaction of racemic **7-78** and optically pure and defined alcohol **7-77** under Mitsunobu conditions, gave an intermediate ester, which after complexation of alkyne group with cobalt carbonyl complex and RCM using Grubbs' second generation catalyst under mild conditions afforded the macrocyclic precursor **7-79**. Noteworthly, attempts to cyclize the unprotected alkyne under a variety of RCM conditions failed. Authors refer this negative finding to nonproductive coordination of the acetylene to the RCM catalytic machinery. Oxidative removal of the cobalt complex using cerium(IV) ammonium nitrate (CAN), generated the desired cyclic alkynoic ester **7-74** in high yield.



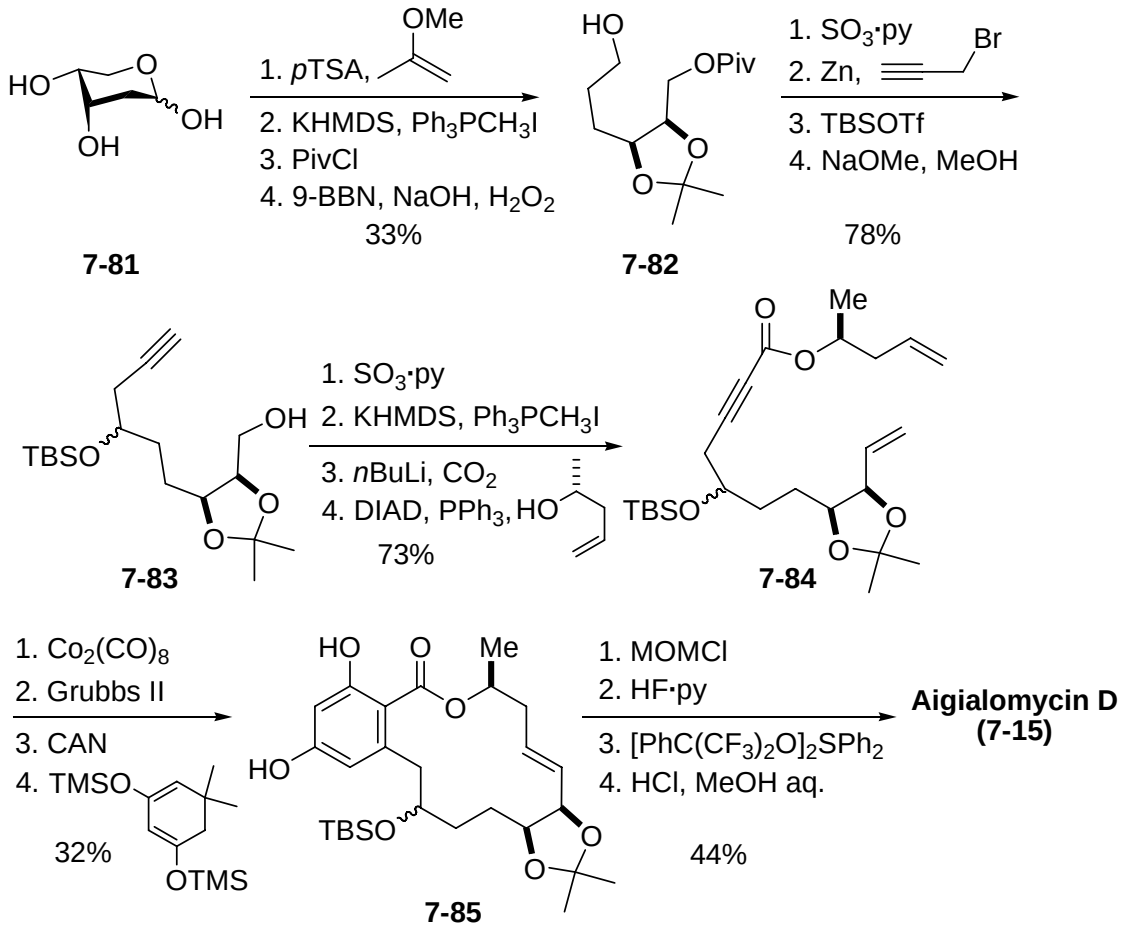

**Scheme 55**. Improved synthesis of cycloproparadicicol by Danishefsky and co-workers.

Construction of the resorcylic skeleton called for a Diels-Alder reaction of **7-74** with dimedone-derived diene, 5,5-dimethyl-1,3-bistrimethylsilyloxycyclohexa-1,3-diene (**7-73**, Scheme **55**) and proceeded smoothly at 140 °C, providing the desired aromatic product **7-80** in 75% yield, after concomitant retro-Diels-Alder loss of isobutene from the initial adduct and hydrolysis of the trimethylsilyl ether groups during chromatography. Transformation of **7-80** to the desired ketone was accomplished following protection of the two phenolic functions and regioselective chlorination using $SO_2Cl_2$ in $CH_2Cl_2$ to afford cycloproparadicicol (**7-72**) in 13 steps and 5% overall yield. Finally, this methodology was suitable to provide the final compound in gram quantities.

Using the same protocol Danishefsky and co-workers published the first total synthesis of aigialomycin D.[115] Starting from D-desoxyribose (**7-81**), the chiral alcohol **7-82** was obtained in a 4 step synthetic sequence (Scheme **56**). Subsequent oxidation followed by propargylation and protecting group manipulation gave alcohol **7-83** as a diastereomeric mixture. Transfer of the alcohol to an alkene, carboxylation and Mitsunobu esterification led to the precursor **7-84**.

Applying the procedure described for cycloproparadicicol (complexation with cobalt carbonyl, ring-closing metathesis, and Diels-Alder cycloaddition reactions as key steps) the intermediate **7-85** was prepared in 60% yield over four steps. Final protection/deprotection

and elimination of water allowed to complete the synthesis of aigialomycin D (**7-15**) in 5% overall yield. With the preparation of this natural product, the Danishefsky group proved the generality of their pathway towards the synthesis of various resorcylic acid lactones.




**Scheme 56**. First total synthesis of aigialomycin D (**7-15**) by Danishefsky and co-workers.

In 2006, the group of Winssinger has reported another synthesis of aigialomycin D.[100] Their approach gave access to the molecule in solution phase, as well as using solid phase, allowing them the synthesis of the natural product as well as several other analogs (Figure **35**). This strategy was successfully applied earlier by the same group for the synthesis of radicicol (**7-3**) and pochonin A (**7-17**).[116]

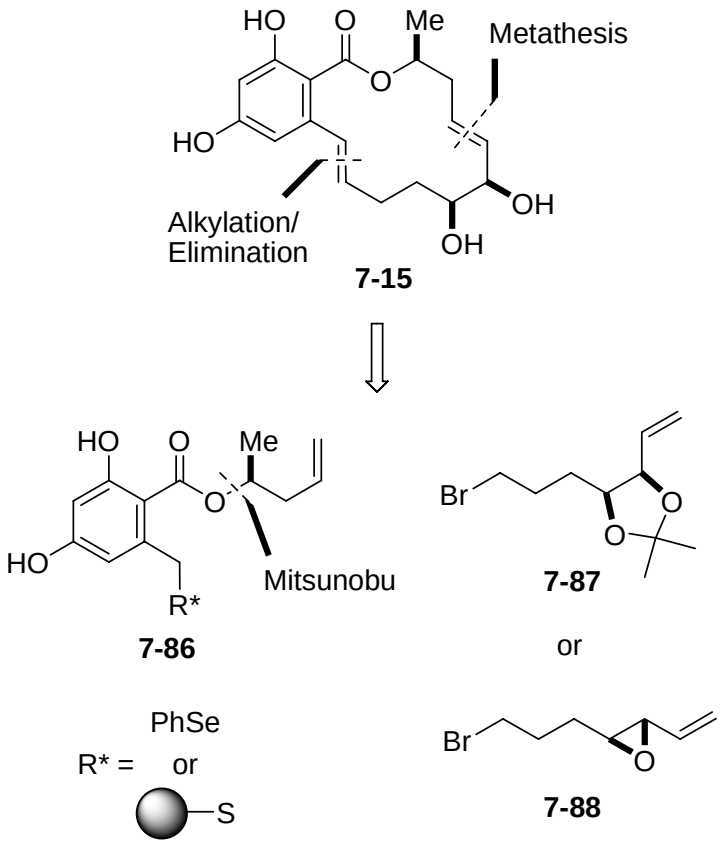
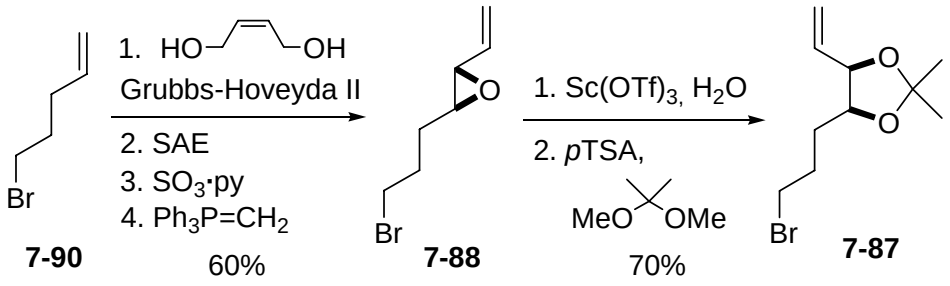



**Figure 35**. Retrosynthetic analysis for Aigialomycin D by Winssinger and co-workers.

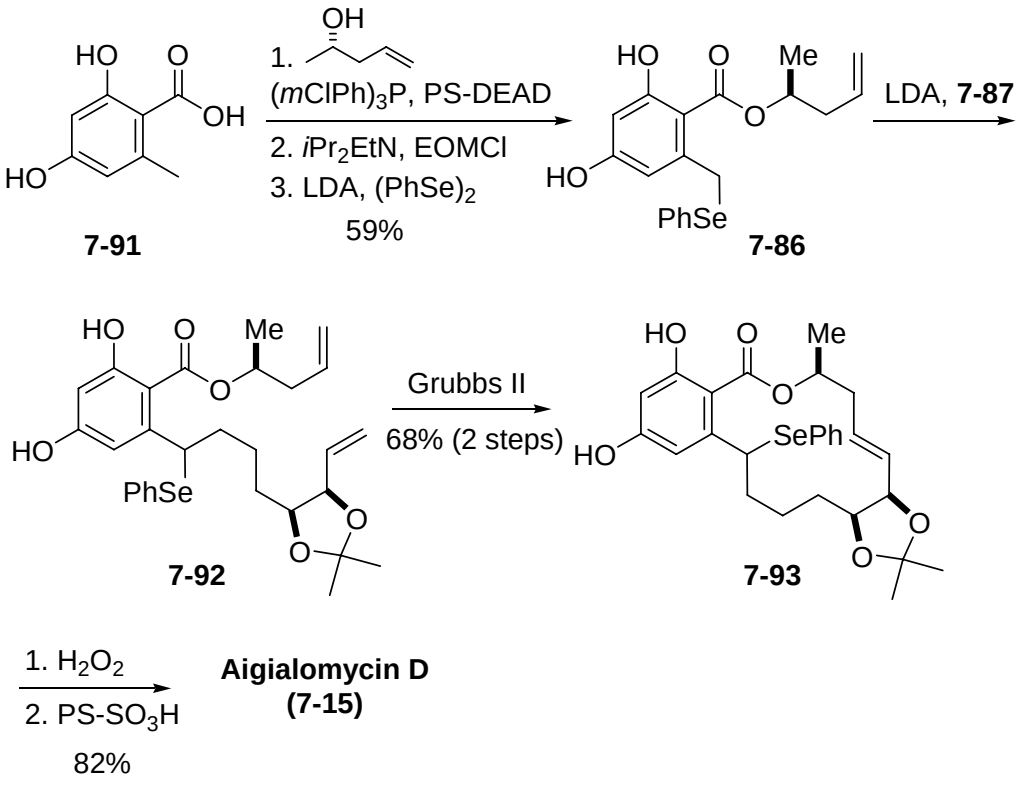
The aliphatic portion **7-87** was prepared in four steps from commercially available substrates (Scheme **57**). Thus, cross-metathesis of 5-bromopentene (**7-90**) with unprotected 1,4-butenediol in the presence of the second-generation Hoveyda–Grubbs catalyst afforded the intermediate allylic alcohol in excellent yield and *E*/*Z* ratio (>25:1). Sharpless epoxidation of the allylic alcohol followed by oxidation with $SO_3$·py and Wittig olefination furnished the epoxide **7-88** in 60% overall yield. The epoxide was converted into the protected diol **7-87** by $Sc(OTf)_3$-catalyzed opening of the epoxide followed by protection with an acetonide group.




**Scheme 57**. Synthesis of epoxyde **7-88** and transformation to acetonide **7-87**.

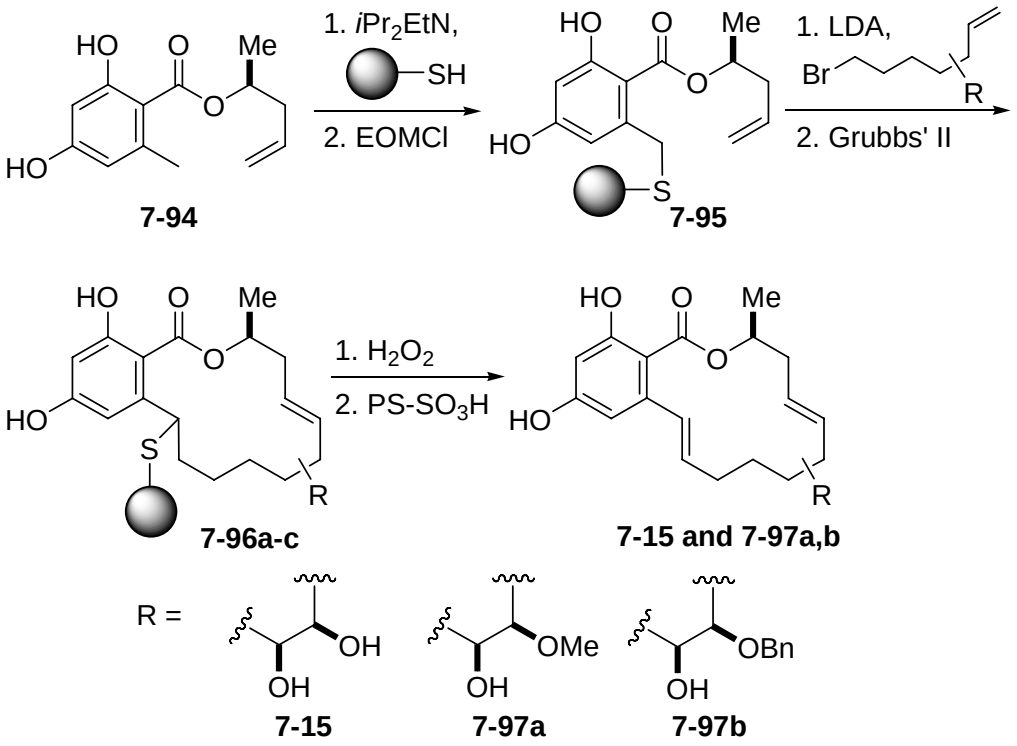
The aromatic portion **7-86** was obtained through a three-step sequence starting with Mitsunobu esterification of the unprotected orsellinic acid (**7-91**) followed by protection of both phenolic groups with the ethoxymethoxy-protecting group. The selenide was introduced at the benzylic position by deprotonation with LDA followed by addition of diphenyldiselenide (59% yield over three steps).

Treatment of **7-92** with second-generation Grubbs catalyst (80 °C for 12 h) provided the macrocycle **7-93** with *E*/*Z* ratio in more than 10:1. This macrocycle was then treated with hydrogen peroxyde to oxidize and eliminate the selenide, thus affording an intermediate which after global deprotection of the acetonide and EOM groups gave access to aigialomycin D (**7-15**) in a total of 10 steps and 16% overall yield (Scheme **58**).




**Scheme 58**. Synthesis of aigialomycin D (**7-15**) by Winssinger and co-workers.

Using the polymer-bounded thioether, the chemistry was carried out on solid phase extending the scope of aigialomycin D analogs (**7-97a,b**). Unprotected ester **7-94** was loaded onto a thiophenol resin, and the phenolic hydroxyls were protected as EOM acetals (Scheme **59**). Alkylation of the polymer-bound thioether with a variety of alkyl bromides yielded the desired metathesis precursors **7-96a**–**c**. Interestingly, the RCM conditions used in solution phase synthesis were not suitable on the solid support leading to the necessity of activation by microwave irradiation in this step. Thus, good yields were attained in $CH_2Cl_2$ solvent at 120 °C under microwave irradiation for 1.5 hours. However, as the catalyst is short-lived at that temperature, additional amounts therefore were required those were added in three portions of 6 mol% each. The compounds were released from the resin by using an oxidation/elimination ($H_2O_2$) procedure followed by global deprotection with sulfonic acid resin to obtain Aigialomycin D (**7-14**) and its analogues **7-97a,b** as well.




**Scheme 59**. Solid phase synthesis of aigialomycin D and analogs by Winssinger and co-workers.

Simultaneously, Pan and co-workers described an enantioselective synthesis of aigialomyin D[117] with another set of key reactions: a Yamaguchi macrolactonization and two Julia-Kociensky couplings to establish the *E* geometry of both double bonds (Figure **36**).

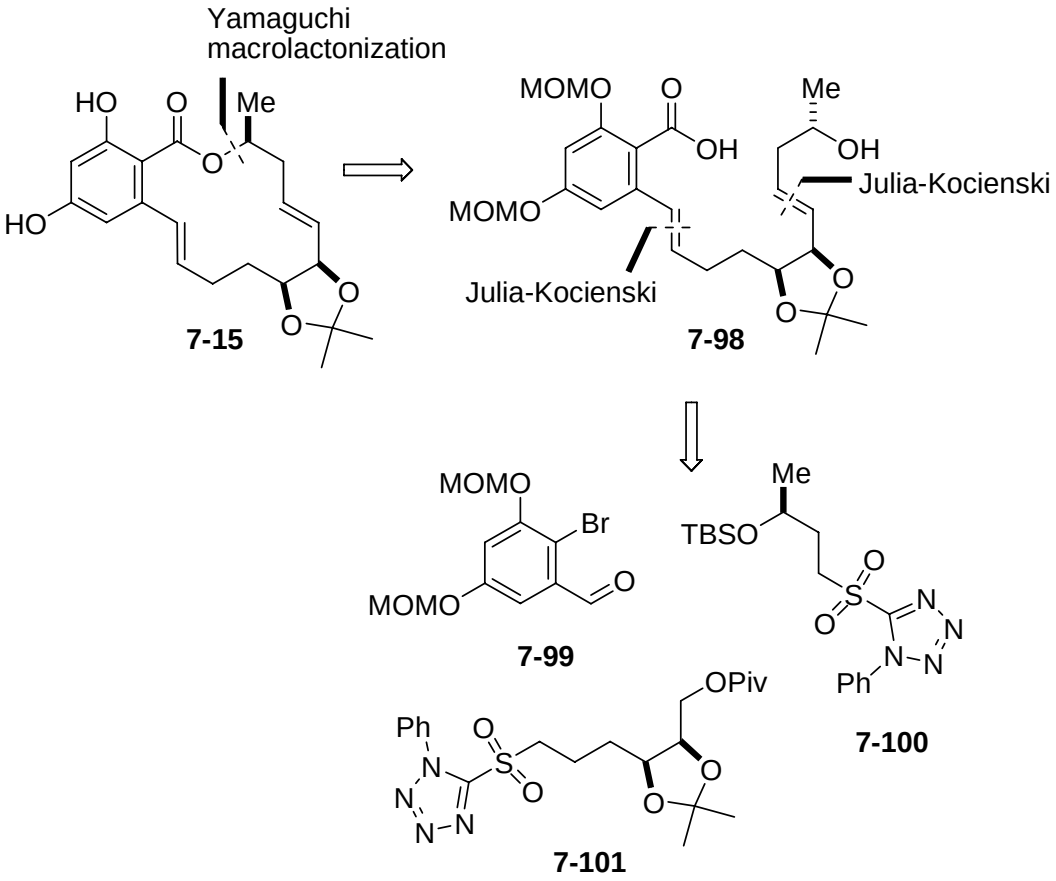
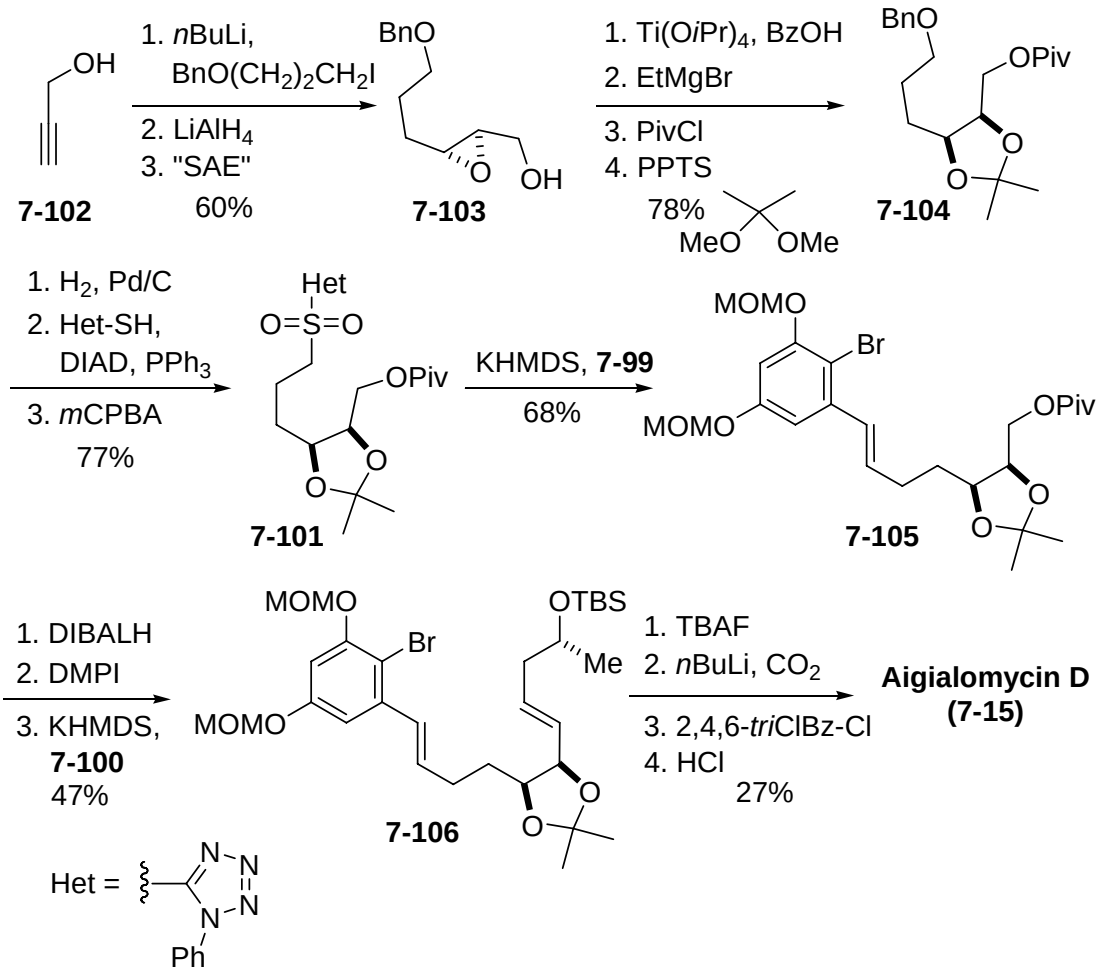



**Figure 36**. Retrosynthetic analysis for aigialomycin D (**7-15**) by Pan and co-workers.

The main intermediate, sulfone **7-101**, bearing the chiral diol masked as an acetonide was obtained in 9 steps from propargylic alcohol (Scheme **60**). Thus, alkylation of **7-102** with 1-((3-iodopropoxy)methyl)benzene, convertion of the alkylation product into an (*E*)-allylic alcohol by $LiAlH_4$ reduction, and Sharpless asymmetric epoxidation led to the epoxy alcohol **7-103** in good yield and selectivity (91% ee). The titanium-assisted regioselective (C-3) opening of 2,3-epoxy alcohol **7-103** with benzoic acid gave an alcohol which was further converted into protected tetraol **7-104** by treatment with EtMgBr followed by protection of the free hydroxy groups (the primary hydroxy group was protected as its pivaloyl derivative and the two secondary hydroxyl groups were engaged in an isopropylidene linkage). Compound **7-104** was easily debenzylated to the corresponding primary alcohol by a standard hydrogenation procedure and Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation of the resultant sulfide furnishing sulfone **7-101** in good yield. A Julia–Kocienski condensation between fragment **7-101** and the functionalized benzaldehyde **7-99** delivered the compound **7-105**. Cleavage of the pivaloate ester followed by oxidation of the resulting alcohol and a second olefination

reaction afforded acyclic precursor **7-106**. Completion of the synthesis was achieved through TBS deprotection, carboxylation to give the benzoic acid derivative, Yamaguchi macrolactonization, acetonide/MOM deprotection steps and allowed the isolation of aigialomycin D (**7-14**) in more than 3% overall yield (18 steps longest linear sequence).




**Scheme 60**. Synthesis of Aigialomycin D (**7-15**) by Pan and co-workers.

The group of Tatsuta in 2001 described the first total synthesis of LL-Z1640-2 (**7-4**) starting from D-ribose.[118] The key elements of their synthesis are a Mukaiyama macrocyclization, a Corey-Fuchs procedure and Sonogashira coupling reaction (Figure **37**).

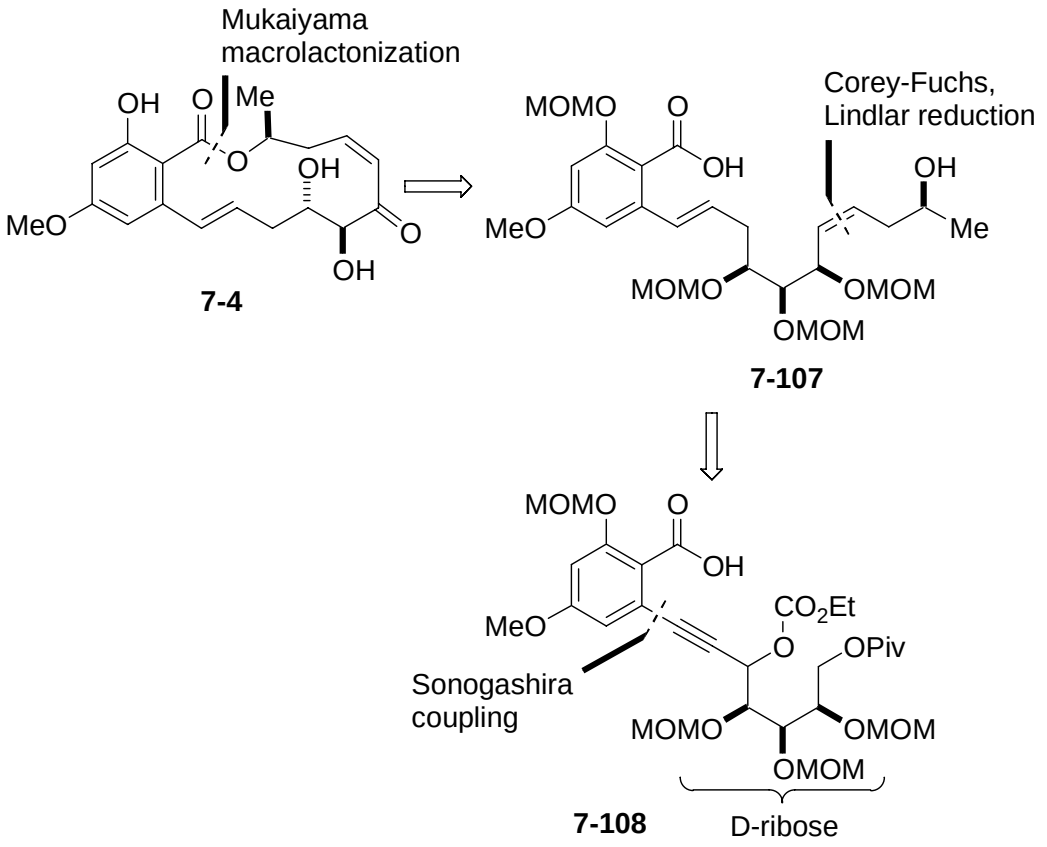
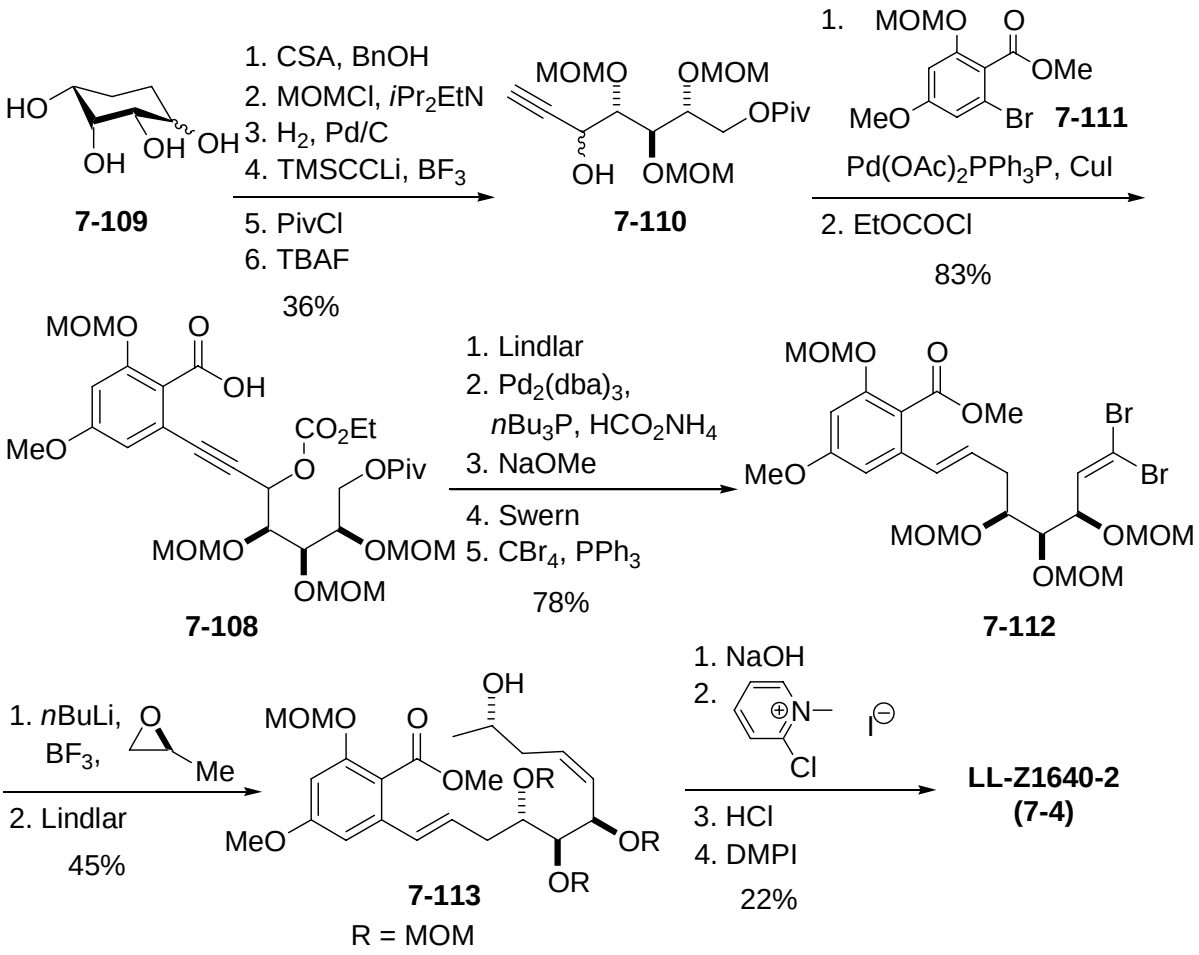



**Figure 37**. Retrosynthetic analysis for LL-Z1640-2 (**7-4**) by Tatsuta and co-workers.

D-ribose (**7-109**) was first transferred to the acetylene **7-110** in a six step sequence. After attachment of the corresponding protecting groups onto the sugar, addition of TMS alkynyl lithium, followed by additional protecting group manipulation, the alkyne intermediate **7-110** was obtained (Scheme **61**). Sonogashira coupling of **7-110** with bromobenzene **7-111** in the presence of $Pd(OAc)_2$, CuI and $PPh_3$ and protection of alcohol with ethoxycarbonyl chloride furnished the acyclic precursor **7-108**. Reduction with Lindlar catalyst ($Pd/BaCO_3$, quinoline/EtOH), hydrogenolysis under Tsuji conditions ($Pd_2(dba)_3$, $n$Bu$_3$P, ammonium formate), deprotection of the pivaloyl group, oxidation of the resulting alcohol and modified Wittig olefination ($CBr_4$, $PPh_3$) gave the dibromo-olefin **7-112**. Exposure of **7-112** to *n*BuLi produced the intermediary lithiated acetylide, which reacted with optically pure (*S*)-propylene oxide followed by a second Lindlar reduction to the *Z*-olefin **7-113**. Finally, saponification, Mukaiyama macrocyclization, MOM deprotection and selective oxidation of the allylic alcohol allowed the completion of the total synthesis of the natural product LL-Z1640-2 (**7-4**).




**Scheme 61**. First total synthesis of LL-Z1640-2 (**7-4**) by Tatsuta and co-workers.

After that, in 2002, based on previous experience from the radicicol and monocillin syntheses, Lett and co-workers reported their own total synthesis of LL-Z1640-2 (**7-4**) along with hypothemycin (**7-7**).[119] This approach to hypotemycin is similar to that of radicicol,[109] and includes Mitsunobu macrolactonization and Suzuki coupling as key steps (Figure **38**).

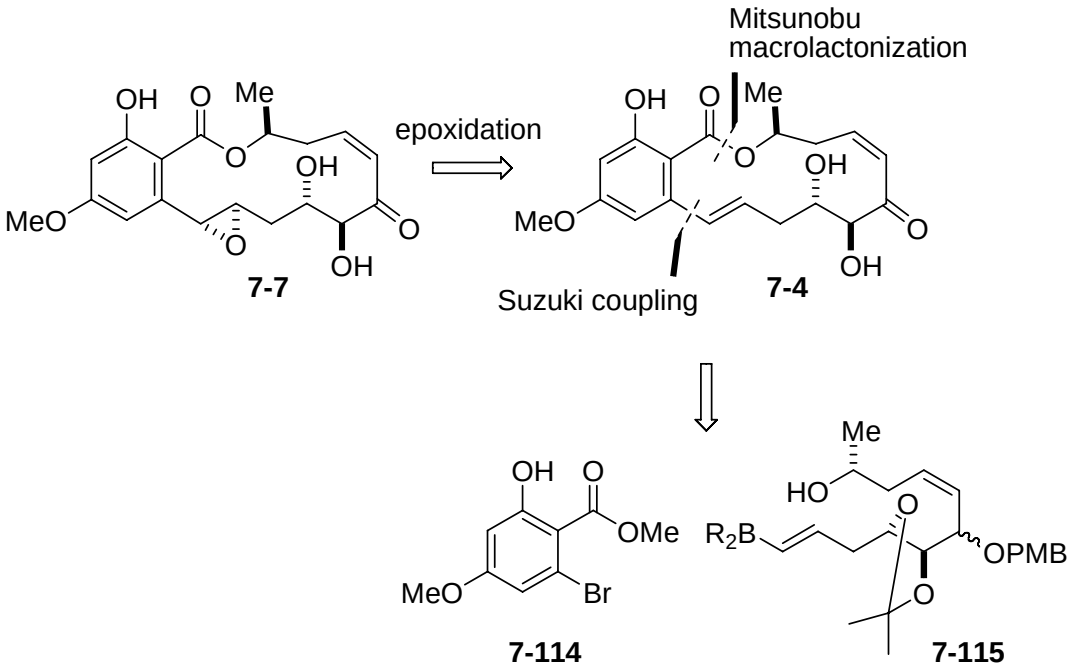
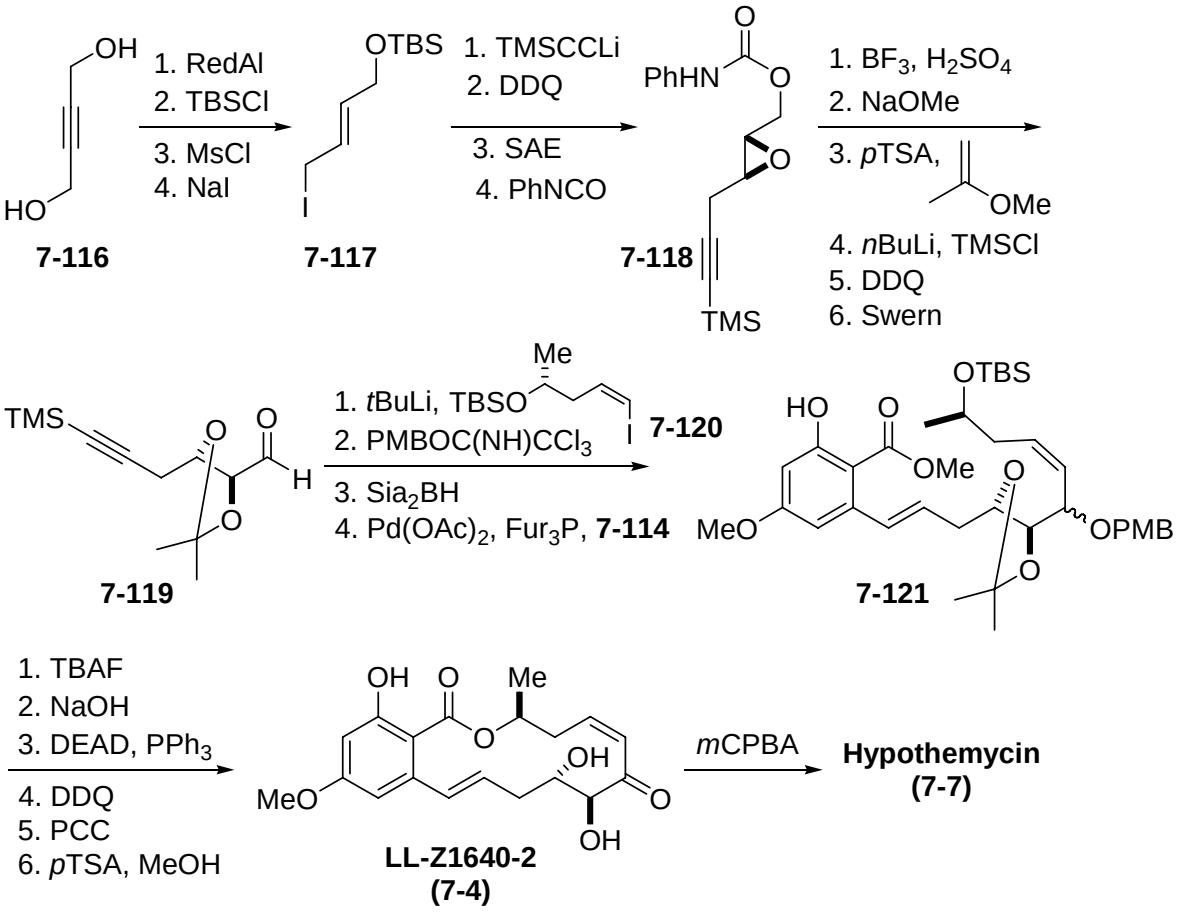



**Figure 38**. Retrosynthetic analysis for hypothemycin (**7-7**) by Lett and co-workers.

The synthesis starts from 1,4-butynediol (**7-116**) which in eight steps was transferred to the epoxide **7-118**. This substance was further converted through a seven step sequence into the aldehyde **7-119** (Scheme **62**). After transmetallation of vinyl iodide **7-120** with *t*BuLi and reaction with the aldehyde **7-119** the obtained alcohol was protected with PMB-trichloroimidate to afford the intermediate, which after hydroboration of the triple bond and subsequent Suzuki coupling with the aromatic bromide **7-114** furnished the desired acyclic precursor **7-121**. The next transformations include TBS deprotection, saponification with NaOH, Mitsunobu macrolactonization, PMB group removal, allylic alcohol oxidation and acetonide deprotection, so, the desired compound LL-Z1640-2 (**7-4**) was obtained. Attempts to invert the sequence (first Mitsunobu reaction and then Suzuki coupling) failed to give the desired products. Final epoxidation of **7-4** using buffered conditions (*m*CPBA/$NaHCO_3$, 3 equiv. $CH_2Cl_2$, −20 to 0 °C, 4 h) formed only one isomer of epoxide, identified as hypothemycin (**7-7**) albeit in poor yield (17%). The authors explain this phenomenon with the unusual low reactivity of the double bond next to the aromatic part and liability of the final product.




**Scheme 62**. Synthesis of L-Z1640-2 (**7-4**) and hypothemycin (**7-7**) by Lett and co-workers.

# 8 Results and Discussion

## 8.1 Retrosynthetic Analysis

The target molecule, queenslandon (**6-1**), consists of four major fragments (Figure **22**).

a) a salicylate-like aromatic part with two additional methoxy groups;
b) ester function as the connection between aromatic and aliphatic moieties;
c) one double bond with *E*-configuration as the second connection between aromatic and aliphatic moieties;
d) α,α'-dihydroxy keton in the aliphatic region.

At first, we have aimed our studies towards the asymmetric synthesis of model compound **6-2** with no substituents in the aromatic part but with the fully functionalized aliphatic segment. The commercial availability and the ease of preparation of basic fragments was an important criterion for the design of the retrosynthesis. Thus, the construction is based on the key bond-forming reactions indicated in Figure **39**. Major challenges that we recognized from a synthetic point of view were the connection of the aliphatic chain to the aryl ring and the creation of the carbohydrate-like sector. For the formation of the macrocycle, we opted for a Mitsunobu macrolactonization strategy. As a further most important key disconnection, a Suzuki coupling at the vinylic position (C9-C10) was envisioned.[120]

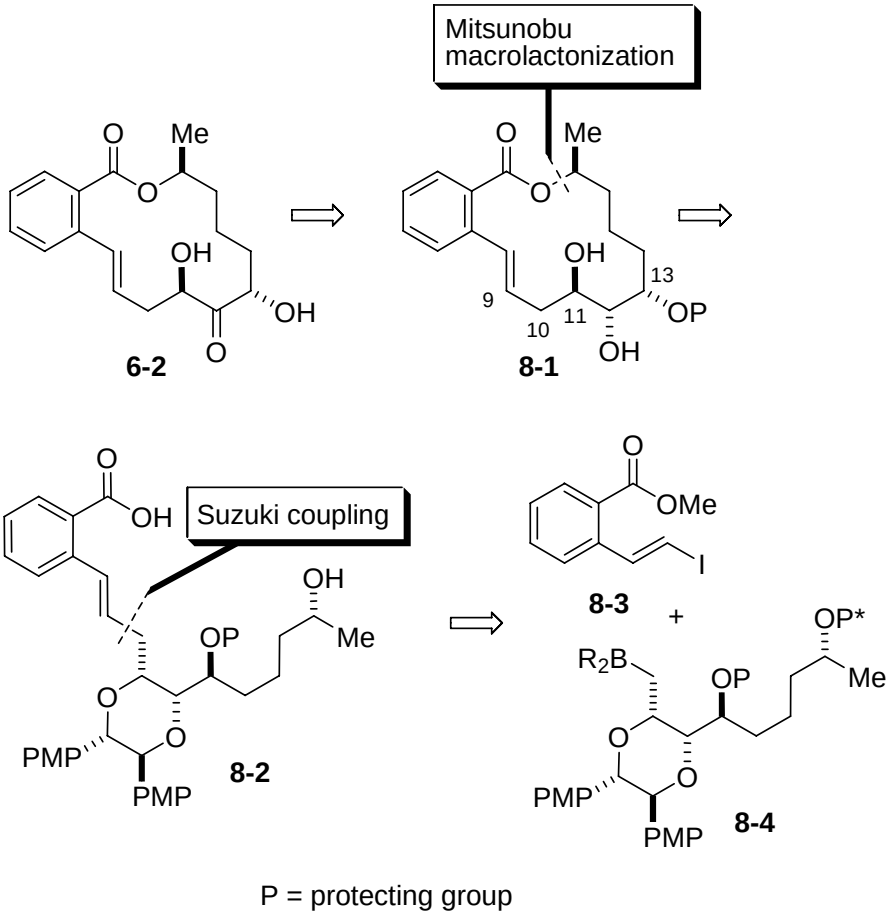



**Figure 39**. Retrosynthetic analysis for the core structure of queenslandon **6-2**.

The necessary alkyl-borane **8-4**, in turn, should result from a diastereoselective hydroboration of an exocyclic enol ether **8-5**. The stereocenter at C13 would be the result of a glycolate aldol reaction of protected δ-hydroxyaldehyde **8-6** and cyclic dioxanone **8-7** (Figure **40**).

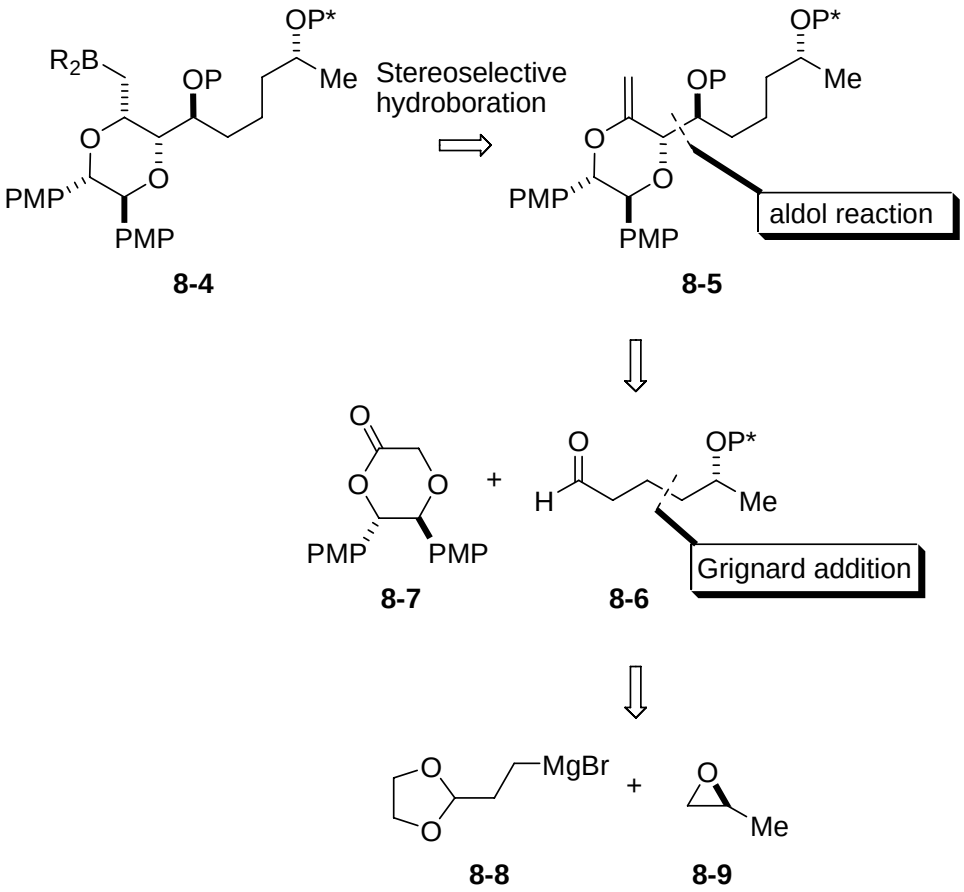



**Figure 40**. Retrosynthetic analysis for alkyl-borane **8-4**.

While the proposed substrate **8-4** is rather complex and the key transformation (selective hydroboration of exocyclic enol ether **8-5**) for this type of substrates was not described in the literature at the time when we started our synthesis, it was decided to address initital attempts for stereoselective construction of the polyol unit in **8-4** to model studies. Using simplier analogs, we sought to distinguish the selectivity in the hydroboration step and to elaborate the efficiency of the chosen transformation.

As an alternative to the presented above retrosynthetic analysis, the aliphatic and the aromatic parts could be connected employing a cross-metathesis reaction between the styrene **8-12** and the olefin **8-13** (Figure **41**).

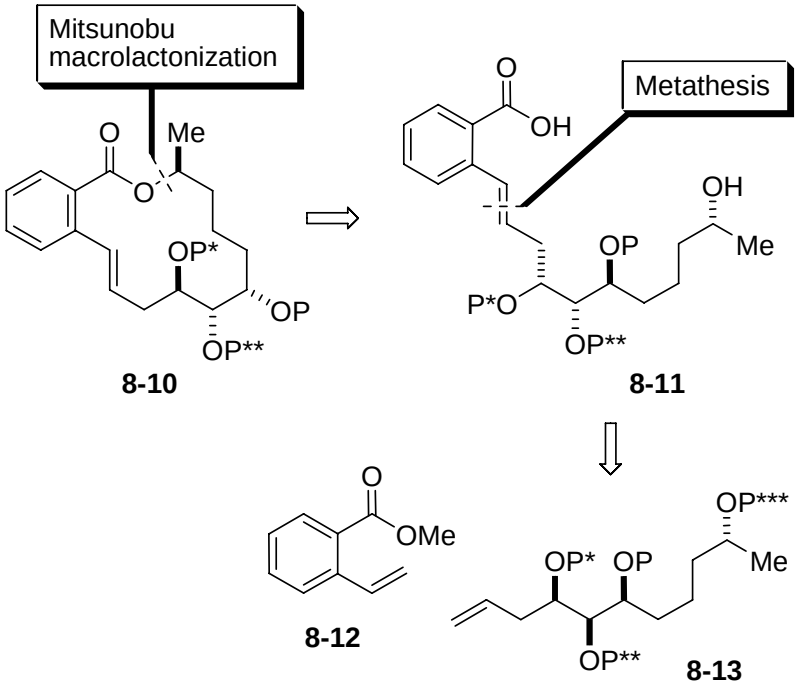



**Figure 41**. An alternative retrosynthetic analysis for the maclolactone **8-10**.

The required olefin **8-13** could be available after selective addition of a chiral allylborane to the aldehyde **8-14**, which, in turn, is the result of an Evans stereoselective aldol reaction between the auxiliary **8-15** and the aldehyde **8-6**, followed by reductive cleavage of the auxiliary.

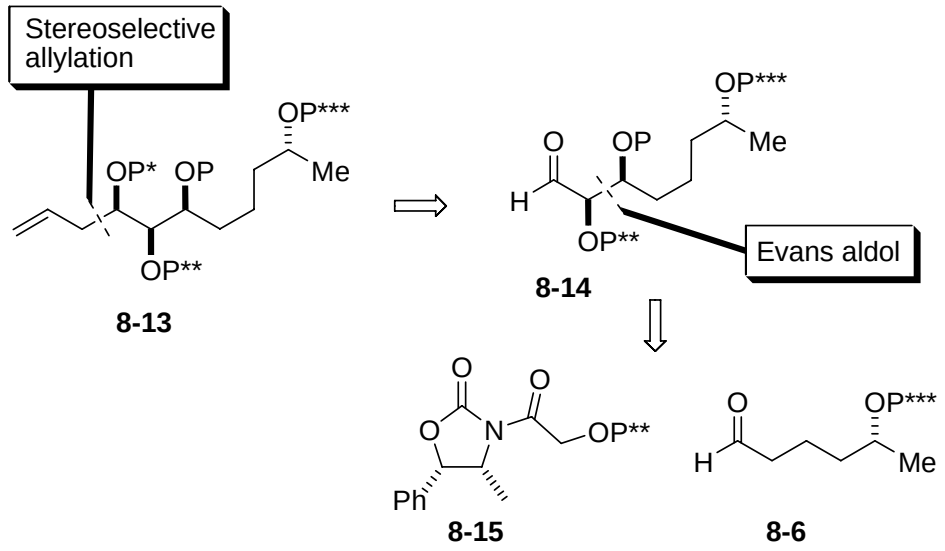
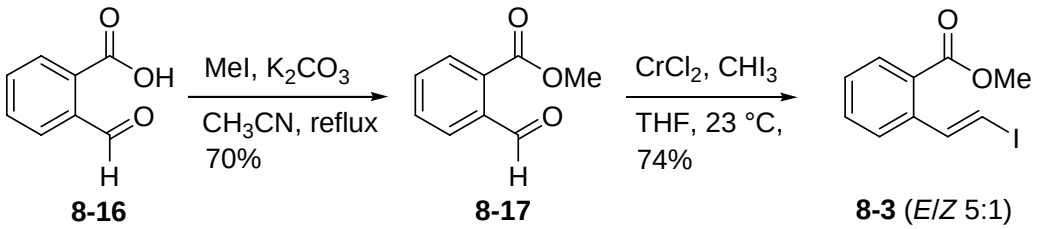



**Figure 42**. Retrosynthetic analysis for the aliphatic part **8-13**.

## 8.2 Syntheses of the Key Precursors

### 8.2.1 Substitued β-iodostyrenes

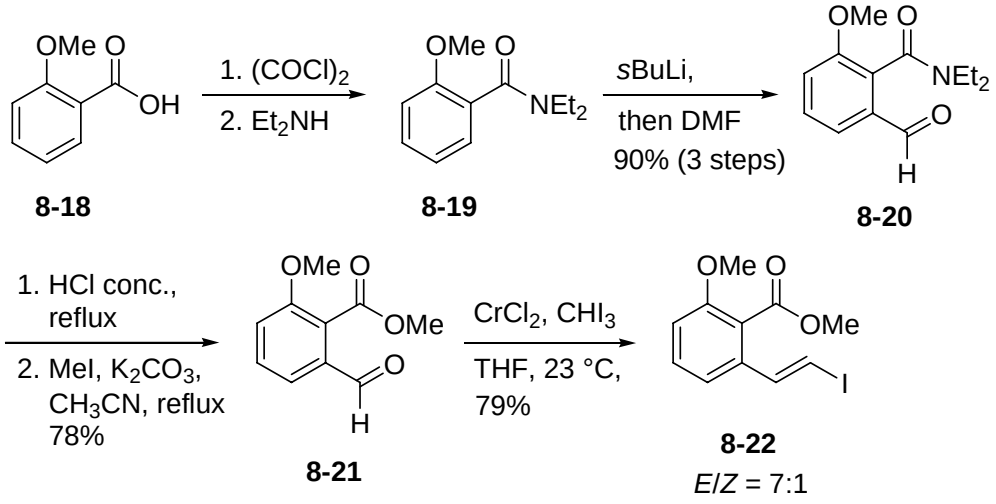
The vinyl iodide **8-3** was prepared starting from the commercially available 2-formylbenzoic acid **8-16**. Thus, esterification with MeI and potassium carbonate in $CH_3CN$ at reflux provided the carbmethoxyester **8-17**. Takai olefination[121] of methyl 2-formylbenzoate (**8-23**) with $CHI_3$ and $CrCl_2$ generated *in situ* (by heating the mixture of anhydrous $CrCl_3$ and Zn powder)[157] provided the desired iodoalkene **8-3** in 74% yield. The *E*/*Z* ratio was found to be around 5:1 (Scheme **62**).




**8-16** **8-17** **8-3** (*E*/*Z* 5:1)

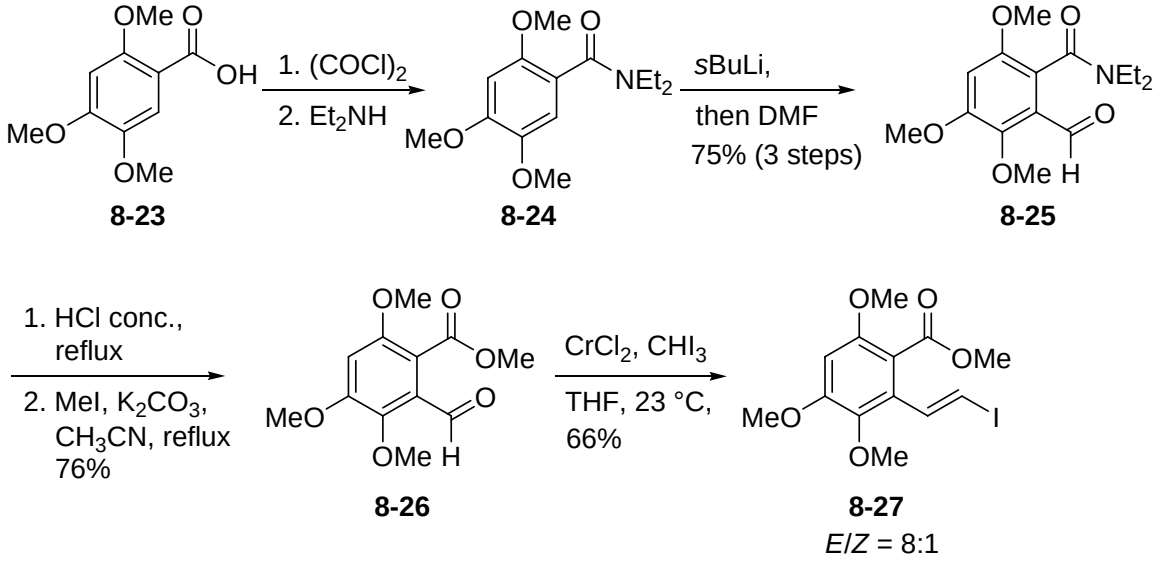
**Scheme 62**. Synthesis of the iodoalkene **8-3** from 2-formylbenzoic acid (**8-16**).

However, substituted 2-formylbenzoic acid derivatives are not commercially available, and therefore we have examined a common strategy for the synthesis of iodoalkenes of type **8-3** with various substituents in the aromatic ring. For example, 2-methoxybenzoic acid (**8-18**) was first converted to the amide **8-19**, which after *ortho*-metalation with *sec*-BuLi[122] and subsequent treatment using excess of DMF, delivered the known aldehyde **8-20** in excellent yield (Scheme **63**).[123] This aldehyde after acidic hydrolysis and esterification under the same conditions as for the discussed above case (**8-16** to **8-17**) gave 2-methoxy-6-formylbenzoic acid methyl ester (**8-21**), which was used for Takai olefination to afford the desired β-iodostyrene **8-22** in high yield.




**Scheme 63**. Synthesis of the iodoalkene **8-22** starting from 2-methoxybenzoic acid (**8-18**).

Meanwhile, the same synthetic sequence was applied to 2,4,5-trimethoxybenzoic acid (**8-23**). In this case, after amide formation, *ortho*-metalation and treatment with DMF the known polysubstituted aromatic aldehyde **8-25** was obtained in 75% yield over three steps.[124] After amide hydrolysis, esterification, and Takai reaction one more example of a β-iodostyrene (**8-27**) was prepared (Scheme **64**).



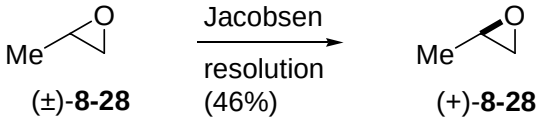

**Scheme 64**. Synthesis of the β-iodostyrene **8-27** from 2,4,5-trimethoxybenzoic acid (**8-23**).

The formylation step should be noted here separately for the reason that, DMF must be added to the lithiated amide derivative **8-19** or **8-24** in one portion at –90 °C. Only so the high yield of the benzaldehyde can be achieved. If to proceed with the addition of dimethylformamide in a dropwise fashion, the product is formed in a very low yield (approx. 15%), but most of the starting material is then recovered.

As a result, we have presented a general and high-yielding approach to the β-iodostyrenes of type **8-3** utilizing the formylation reaction of *ortho*-lithiated N,N-diethylbenzamides, followed by hydrolysis, esterification, and Takai reaction. This pathway opens the possibility to prepare a number of queenslandon analogues with various substituents in the aromatic part of this natural product.

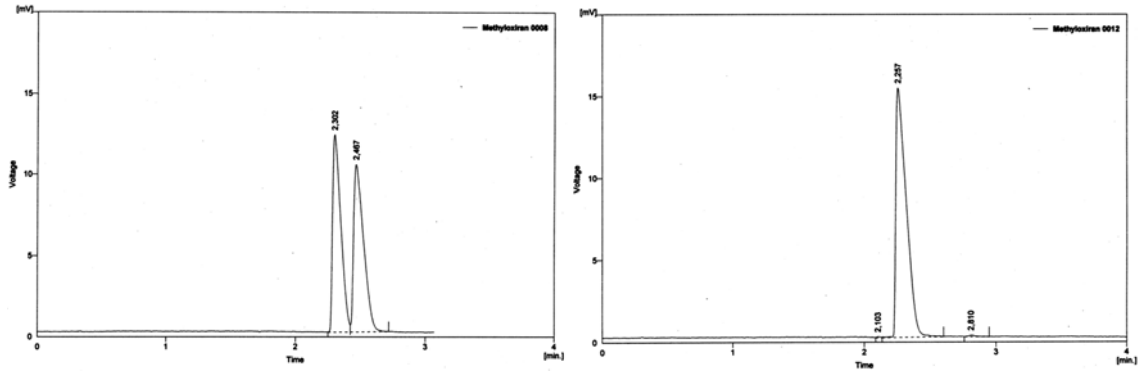
### 8.2.2 Protected (*R*)-δ-hydroxyhexanal (8-6)

In contrast to the known synthesis from chiral lactate ester,[125] the TBDPS-protected aldehyde **8-6** was synthesized starting from racemic propylene oxide [(±)-**8-28**] in four steps. Thus, Jacobsen resolution[126] furnished the pure (*R*)-epoxide (+)-**8-28** (>99% ee, Scheme **65**). The optical purity was determined by chiral GC and after the product was analyzed, we did not observe the second enantiomer on the chromatogramm (Scheme **65**, see right chromatogramm).



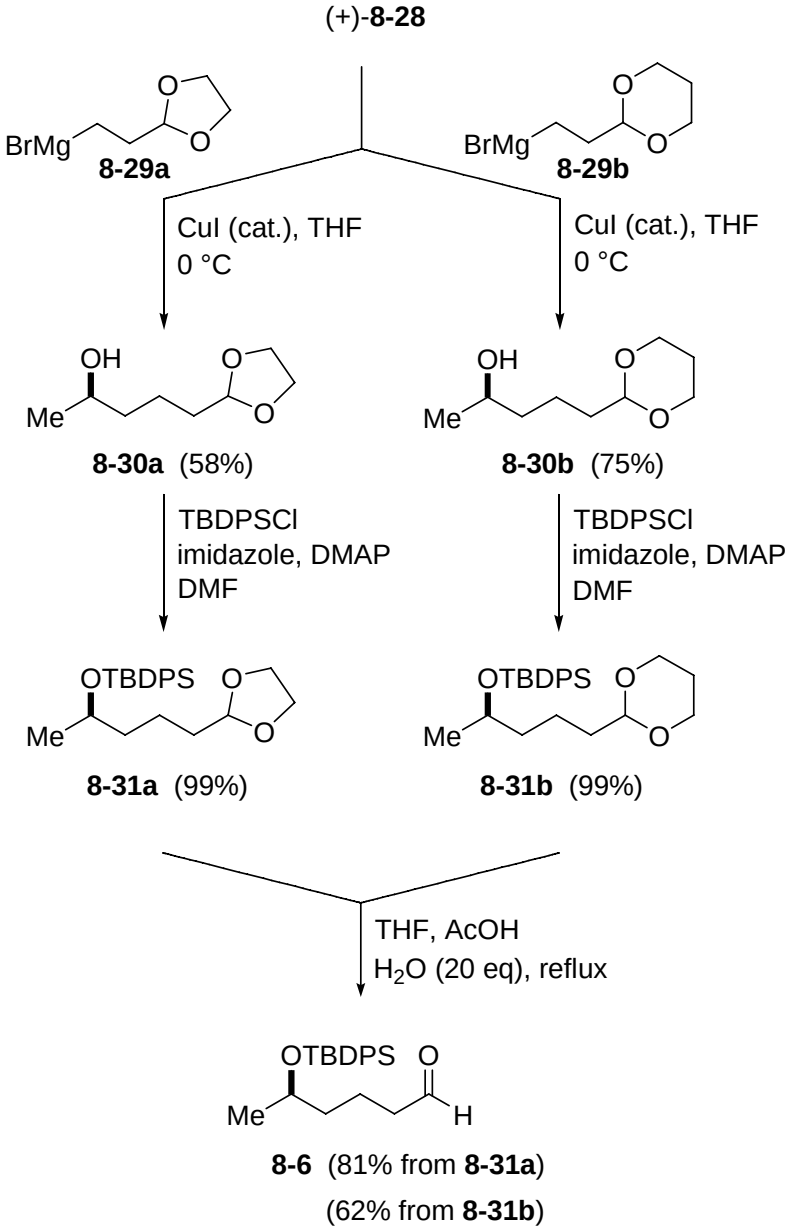

(±)-**8-28** (+)-**8-28**

only one enantiomer
detected by chiral GC




**Scheme 65**. Preparation of (*R*)-epoxide (+)-**8-28** by Jacobsen resolution of racemic propylene oxide and analysis using GC.

Opening of this epoxide with either the Grignard reagent **8-29a** or **8-29b** in the presence of catalytic amounts of CuI led to the corresponding secondary alcohols **8-30a** or **8-30b**, respectively in good yields (Scheme **66**). The hydroxy acetal **8-30a** turned out to be rather sensitive toward internal transacetalization. It was therefore, immediately after isolation, protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl). Hydrolysis of the acetal in compound **8-31a** provided aldehyde **8-6**. The six-membered acetal **8-30b** after Grignard addition could be isolated in higher yield (75% vs 58%) and found to be more stable. However, cleavage of the acetal function on the silyl-protected **8-31b** was less efficient.

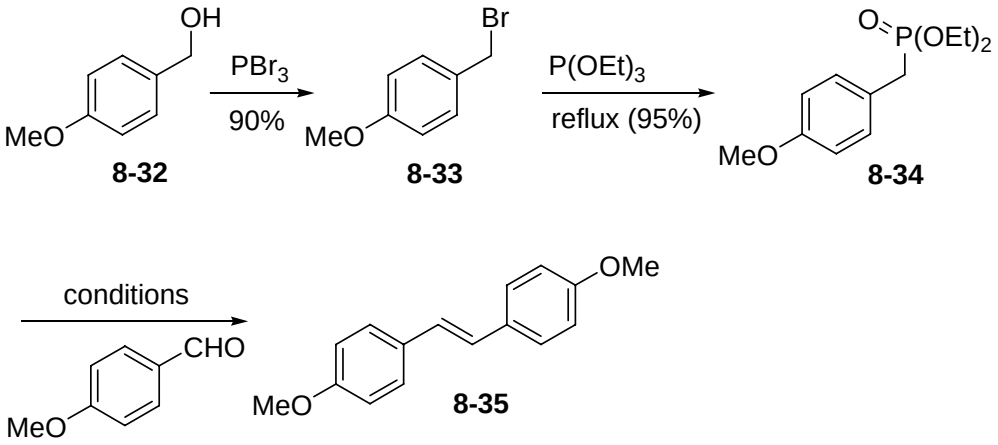



**Scheme 66**. Synthesis of TBDPS-protected δ-hydroxyaldehyde **8-6**.

After all, both paths were found to be equally efficient with the overall 46% yield of the aldehyde **8-6** starting from epoxide (+)-**8-28**.

### 8.2.3 Chiral glycolate auxiliary (8-7)

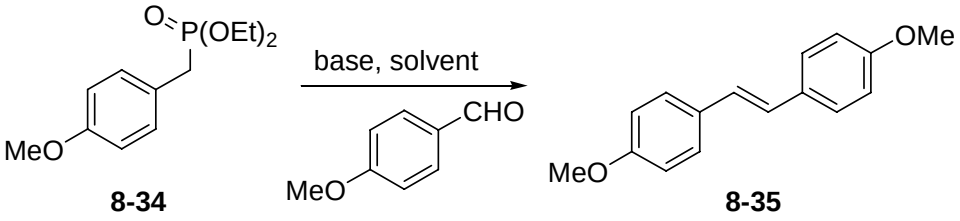
The glycolate **8-7**, developed by Andrus and co-workers,[127] was prepared essentially according to the literature procedure from *p*-methoxybenzylalcohol (**8-32**), but one step was slightly modified. Thus, bromination of alcohol **8-32** with $PBr_3$ afforded the bromide **8-33**, which after distillation was converted to the diethyl *p*-methoxybenzylphosphonate (**8-34**, Scheme **67**). Then it was found that the Wittig-Horner condensation of phosphonate **8-34** with anisaldehyde using NaOMe (Table **7**) as it was proposed by Andrus and co-workers gave only low yields of the stilbene **8-35** irrespective of the solvent (DMF or THF).




**Scheme 67**. Synthesis of the alkene **8-35**.

After trying different conditions, we have found, that a much better yield of alkene **8-35** could be obtained with potassium *tert*-butoxide as base (entry **5**, Table **7**). Probably the basicity of NaOMe was not enough for full deprotonation of the phosphonate **8-34**, which then undergoes the condensation with anisaldehyde.

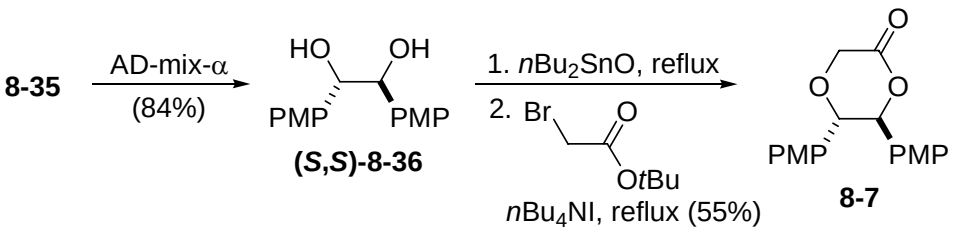
**Table 7**. Conditions optimization for Wittig-Horner reaction of phosphonate **8-34** with *p*-anisaldehyde.




**8-34** **8-35**

| base | solvent | yield, % |
|---|---|---|
| NaOMe | DMF | 48 |
| NaOMe | THF | 38 |
| NaOMe 18-crown-6 | DMF | 36 |
| LiHMDS | THF | 41 |
| *t*BuOK | DMF | 85 (**!**) |

Dihydroxylation[128] of alkene **8-35** using AD-mix-α led to diol **8-36** in high yield and excellent optical purity (>99% ee). Reaction of diol **8-36** with di-*n*-butyltin oxide ($n$Bu$_2$Sn=O) by refluxing in benzene, followed by treatment with *tert*-butyl bromoacetate and subsequent cyclization gave the glycolate **8-7** (Scheme **68**). In the case if cyclization does not proceed to the end, the addition of catalytic amounts of trifluoracetic acid to the reaction mixture accelerates the completion of this reaction and final auxiliary **8-7** could be isolated in 55% yield.




**Scheme 68**. Conversion of alkene **8-35** to cyclic glycolate **8-7**.

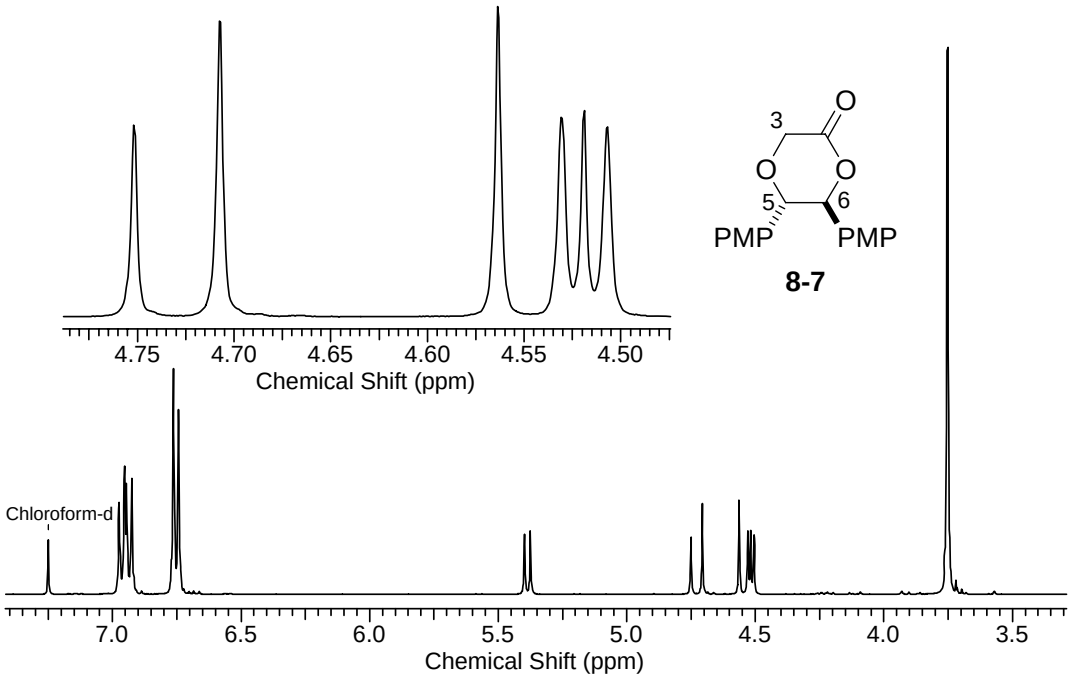
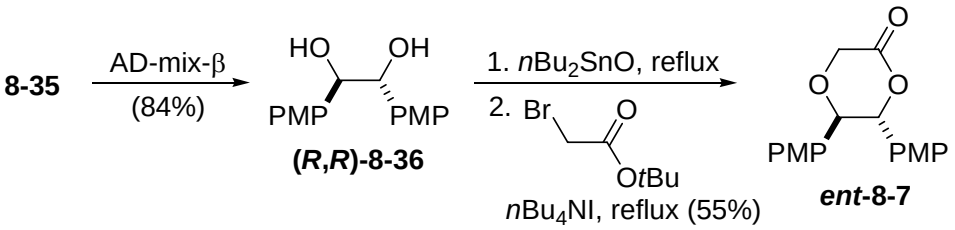



**Figure 43**. $^{1}$H NMR spectrum of the auxiliary **8-7**.

The $^{1}$H NMR spectrum of glycolate **8-7** shows AB system of the methylene protons in the ring. The doublet at $\delta = 4.52$ can be assigned to 5-H.

Using AD-mix-β in dihydroxylation step, the (*R*,*R*)-diol **8-36** was prepared, thus, leading to the other enantiomer of this auxiliary (Scheme **69**), which was also employed in the model studies.




**Scheme 69**. Synthesis of ***ent*-8-7** by using AD-mix-β.

## 8.3 Model Studies on the Tandem Hydroboration/Suzuki Coupling Sequence

In general, clusters of two or more vicinal hydroxyl groups are frequently found in natural products. Because of the importance of 1,2-diols and 1,2,3-triols, a range of methods has been developed for their synthesis. For example, C-C bond-forming reactions on suitable substrates can be used. Thus, aldol reactions,[129] addition reactions to chiral hydroxy aldehydes,[130] Pinacol couplings,[131] or epoxide opening reactions[132] have been employed in this context. In addition, carbon-oxygen bond forming reactions such as epoxidation[133] or dihydroxylation[134] are valuable options. However, the famous Sharpless asymmetric dihydroxylation is less suitable for the synthesis of *anti*- and 1,2-diols. Finally, carbon-hydrogen bond forming reactions (reductions) on carbonyl-containing substrates can be considered. The choice of a certain strategy is largely governed by other functional groups in the near or somewhat remote vicinity of the diol.

Thus, in the framework of the synthesis of a complex benzolactone **6-2**, an *anti*-diol **8-37** flanked by a homoallylic double bond which itself is attached to a functionalized aryl ring is needed (Figure **44**).

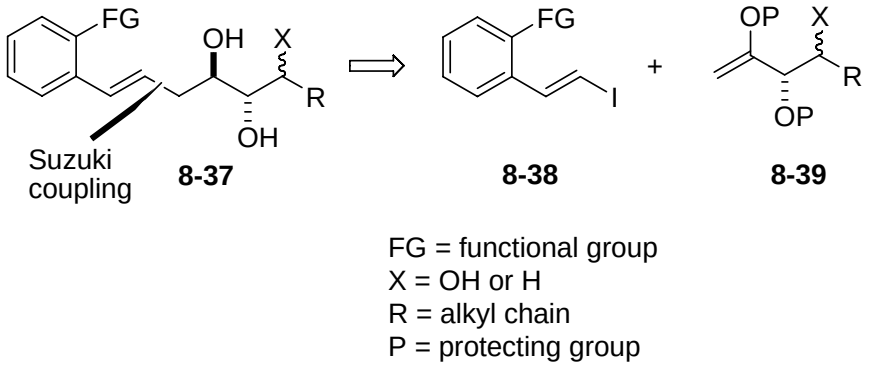
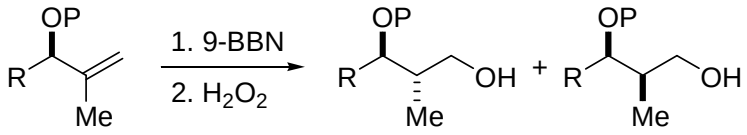



**Figure 44.** Hydroboration/Suzuki cross-coupling strategy for the synthesisof complex diols.

Although homoallylic alcohols can be obtained by the addition of allylmetal compounds to aldehydes, this method is less attractive if a substituent is needed at the alkene terminus of the

product (cf. structure **8-39**). To assemble a system of type **8-37**, we envisioned a tandem diastereoselective hydroboration/Suzuki cross-coupling of (*R*)-alkoxy enol ethers **8-39** with vinyl halides such as **8-38**.

Olefin hydroboration is particularly useful when it can be directed by preexisting chiral centers. Diastereoselective hydroboration of alkenes is an illustrative example for a reaction, which often proceeds with high selectivity to give synthetically useful functionality and for that reason has been employed in the synthesis of many natural products.[135] For acyclic substrates of type **8-40**, the *anti*-product (**8-41**) is favored (Scheme **70**).[136]




**8-40** **8-41** **8-42**

| R | OP | Selectivity |
|---|---|---|
| *n*Bu | OH | 92 : 08 |
| *i*Pr | OH | 96 : 04 |
| *n*Bu | OTMS | 91 : 09 |
| *n*Bu | OAc | 88 : 12 |
| *n*Bu | $OCH_2OBn$ | 84 : 16 |

**Scheme 70**. Hydroboration of allylic alcohols and ethers studied by Still and co-workers.

The overall selectivity of the hydroboration may be rationalized by a simple model, which involves electronic and steric factors.[137] Considering the possible conformations of the starting allylic alcohol, one of the conformers (**a**) would be expected to be the most reactive since the primary interaction between the empty borane p-orbital (LUMO) and the filled π-orbital of the alkene (HOMO) is enhanced by a secondary interaction between a σ-orbital from the asymmetric center and the alkene π-orbital (Figure **45**). This secondary interaction destabilizes the HOMO to promote overlap with the LUMO (i.e. the borane p orbital). This secondary interaction will be maximal when the σ-level is energetically close to the alkene π-

orbital, i.e. when a best electron-donating group occupies the anti position (R is alkyl group). Finally, the attack of the borane to the less hindered side of olefinic π-system would then lead to the less sterically encumbered transition state and thus to the *anti*-product.

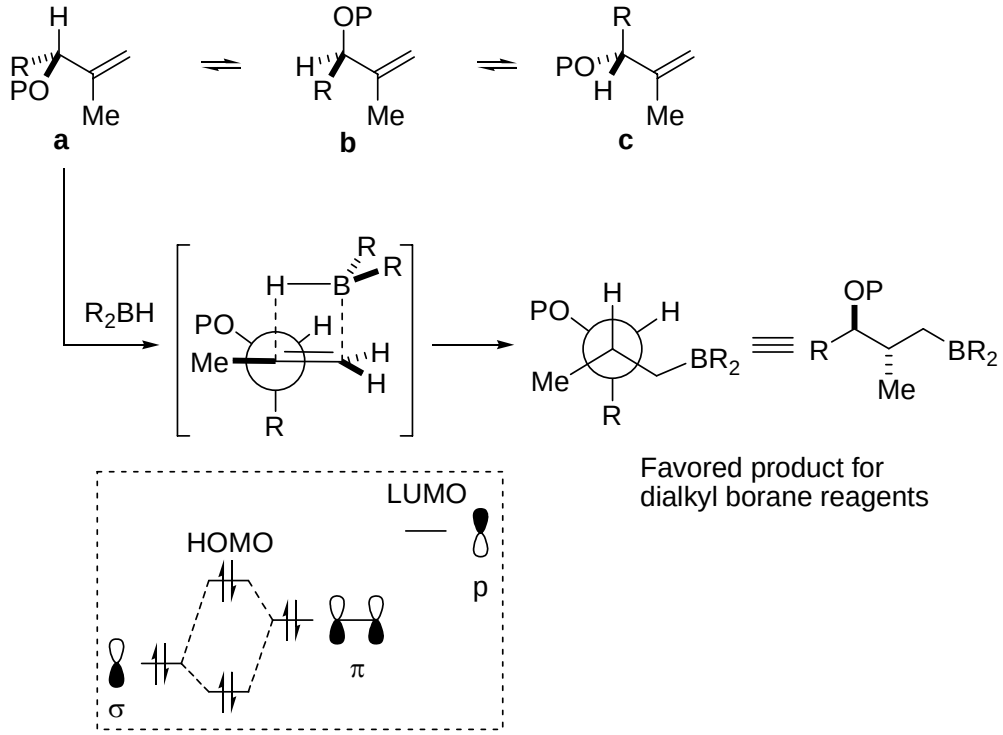
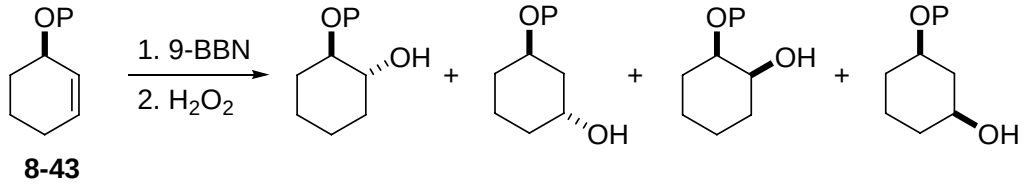



**Figure 45**. A model for diastereoselective hydroboration of substituted olefin **8-13**.

Dialkylborane addition to cyclic allylic alcohol derivatives (**8-43**) takes place from the least hindered face (opposite to alkoxy group) avoiding also the $R_2B/H$ 1,3-diaxial interaction and the 1,2-*anti* product is predominating in the resulting product mixture (Scheme **71**).[138]




**8-43**

| | | | | |
|---|---|---|---|---|
| P = H | 93 | 5 | 2 | 10 |
| P = Bn | 68 | 13 | 0 | 19 |
| P = TBS | 74 | 13 | 0 | 13 |

**Scheme 71**. Hydroboration of cyclic allylic alcohol derivatives (**8-43**) studied by Evans and co-workers.

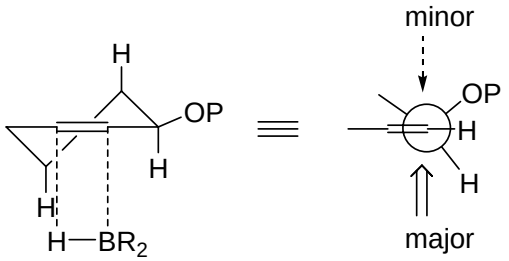
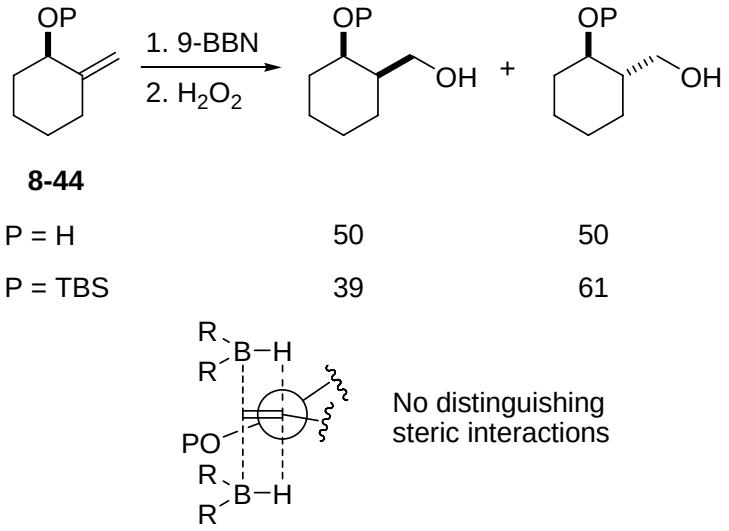


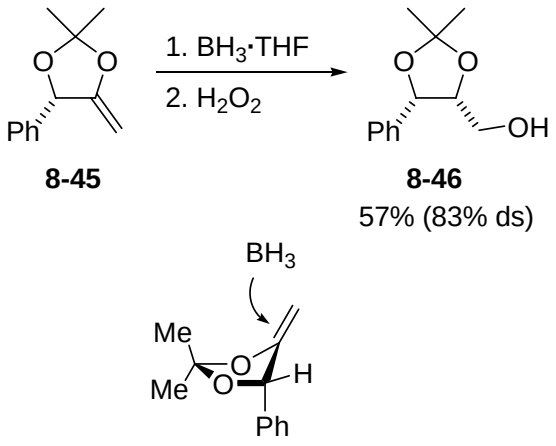

**Figure 46**. Possible transition state for the addition of dialkylborane to the cyclic allylic alcohol derivatives (**8-43**).

In the hydroboration of exocyclic allylic alcohols and ethers (**8-44**) with 9-BBN only marginal levels of stereocontrol is detected (Scheme **72**). The lack of selectivity in this case could result from the absence of distinguishing steric interactions between substrate and hydroborating reagent.[138]




**Scheme 72**. Hydroboration of exocyclic allylic alcohols and ethers (**8-44**) with 9-BBN studied by Evans and co-workers.

Applying more complex substrates containing exocyclic double bonds, Sinaÿ and co-workers reached reasonable selectivities.[139] The hydroboration of five-membered enol ether derivative **8-45**, obtained by Tebbe reaction from acetonide-protected mandelic acid, proceeded regioselectively by virtue of the highly polar nature of the substrate. The high diastereoselection level is expected on the basis of steric grounds (Scheme **73**).



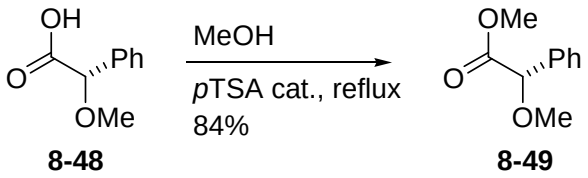

**Scheme 73**. Hydroboration of exocyclic enol ether **8-45** by Sinaÿ and co-workers.

It should be mentioned, that transition metal-catalyzed additions of boranes to a double bond also provide highly distereoselective hydroborations.[140]

We wanted to show that exocyclic enol ethers prepared from 1,3-dioxolan-4-ones and 1,4-dioxan-2-ones are useful substrates for our selected strategy leading to complex diols in high diastereoselectivity. Looking into the literature, there are only a few reports for the tandem hydroboration and Suzuki coupling of glycals derived from carbohydrates.[141] In most of these cases, C-glycosides were the target.[142] Also, an intramolecular diastereoselective hydroboration/Suzuki coupling tactic was successfully employed earlier in our laboratory in a synthesis of the macrolide salicylihalamide A.[143]

### 8.3.1 Preparation of the Required Substrates

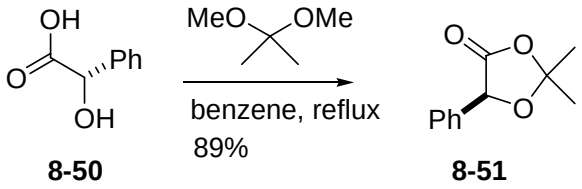
First, we have defined the necessery enol ethers for the proposed transformation. Thus, as the acyclic substrate the mandelic acid derivative **8-49** was choosen. It can be prepared by esterification of commercially available of (*S*)-*O*-methyl mandelic acid (**8-48**) according to a known procedure (Scheme **74**).[144]




**8-48** **8-49**

**Scheme 74**. Methylation of the (*S*)-*O*-methyl mandelic acid (**8-48**).

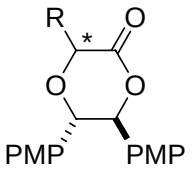
In the other venture, by treating the (*S*)-mandelic acid (**8-50**) with the 2,2-dimethoxypropane in refluxing benzene, the known[145] five-membered glycolate ester **8-51** was obtained and served as an example of a cyclic structure (Scheme **75**).




**8-50** **8-51**

**Scheme 75**. Preparation of cyclic mandelic acid derivative **8-51**.

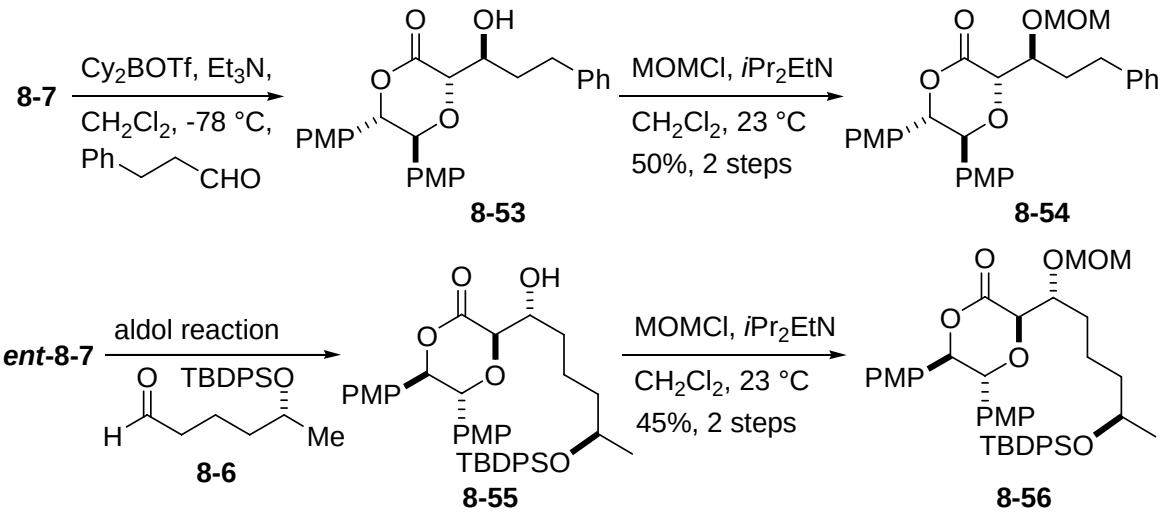
As an advanced version of cyclic substrates, we have opted toward six-membered systems. In this regard, the glycolate derived oxapyrone (**8-52** Figure **45**), developed by Andrus et al.[127] seemed to be the substrate of choice. Not only are both the enantiomers of this auxiliary readily synthesized but also it affords 1,2-*anti* selective aldol addition products, and the *para*-methoxyphenyl (PMP) part can be removed very easily at a later stage to unmask the diol functionality in the product. All these properties make the cyclic substrate **8-52** a very attractive target.




**8-52**

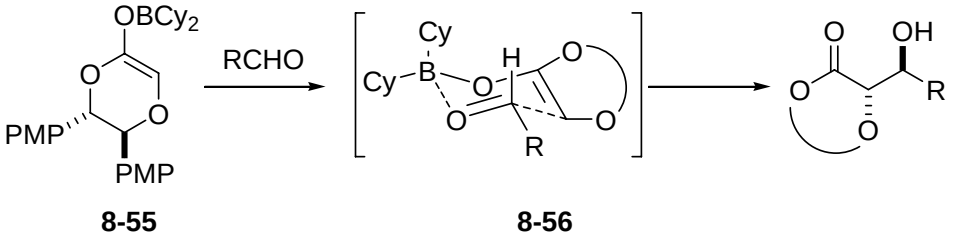
**Figure 45**. Glycolate derived oxapyrone **8-52** developed by Andrus and co-workers.

The synthesis of the six-membered chiral glycolate **8-7** and ***ent*-8-7** (R = H in **8-52**) is discussed in section **8.2.3**. The more complex substrates **8-54** and **8-56** were obtained *via* 1,2-*anti* selective aldol reaction between the auxiliary **8-7** and corresponding aldehydes (Scheme **75**).




**Scheme 75**. *Anti*-selective aldol reactions of the glycolate auxiliaries **8-7** and ***ent*-8-7** with 3-phenylpropanal and aldehyde **8-6**, respectively, followed by MOM-protection.

In this case, aldol reaction leads to the formation of two new chiral centers. The intermediate boronic enolate constrained exclusively to the *E*-conformation, through the chair Zimmerman-Traxler transition arrangement,[130] provides the *anti* adduct (Scheme **76**). Developed by Andrus and co-workers, this type of *anti* selective aldol reaction of enantiopure 5,6-diphenyl-4-oxa-2-pyrone with a broad range of aldehydes proved to be very useful for the synthesis of complex molecules.[127]

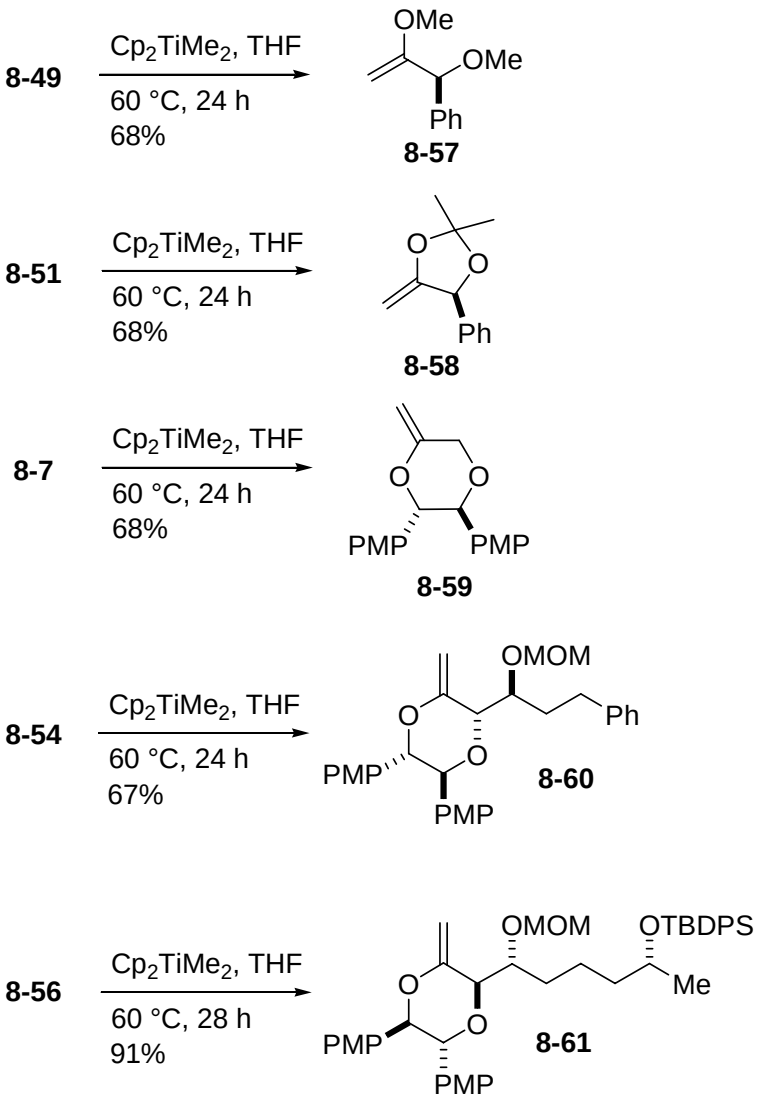



**Scheme 76**. *Anti* selective aldol reaction from *E*-enolate **8-55** through transition state **8-56**.

The aldol products (**8-53** and **8-55**) are somewhat prone to retro aldol reaction. Therefore, their newly formed secondary alcohol function was immediately protected as methoxymethyl (MOM) ether by treatment of crude aldol reaction mixture with *i*$Pr_2$EtN and freshly distilled MOMCl in anhydrous $CH_2Cl_2$ for several days at room temperature (Scheme **75**). Other

attempts at protecting the alcohol (TBSOTf or TIPSOTf and base, BnBr and $Ag_2O$, $BnOC(=NH)CCl_3$ with acidic catalysis) were not successful.

The substrates for the key transformation were readily prepared in high yields by Tebbe olefination using the Petasis reagent ($Cp_2TiMe_2$) in refluxing THF (Scheme **77**).[146] We have turned away from using the traditional Tebbe reagent ($Cp_2ZrMe_2$) since it is much more expensive and more difficult to prepare when compared to $Cp_2TiMe_2$. The reactions were performed under nitrogen atmosphere to avoid decomposition of the Petasis reagent and the products formed. The acyclic enol ether **8-57** and all exocyclic enol ethers (**8-58**, **8-59**, **8-60**, **8-61**) were purified by chromatography on aluminium oxide and used immediately after isolation.

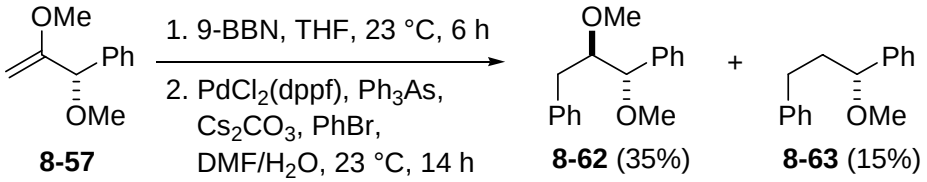



**Scheme 77**. Preparation of acyclic substrate **8-57** and exocyclic enol ethers **8-58**, **8-59**, **8-60** and **8-61** using the Petasis reagent.

### 8.3.2 Studies on the Tandem Hydroboration/Suzuki Coupling Sequence

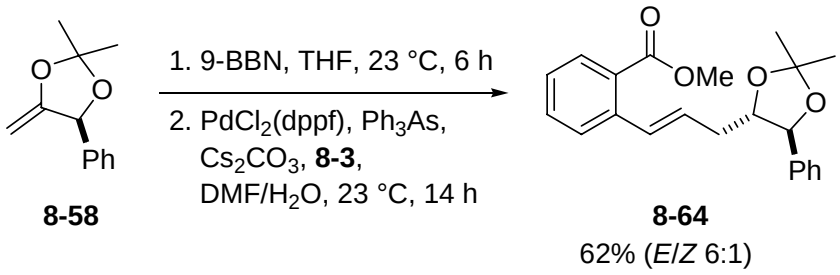
The present study was initiated with an acyclic system **8-57**. Although it has been reported that these substrates are unreactive toward 9-BBN,[147] we found this not to be the case (Scheme **78**). Given the tendency of β-alkoxy boranes to undergo *syn*-elimination (cf. intermediate **8-63**), the formation of some side products for the acyclic substrates was expected.[147] The result of the hydroboration followed by Suzuki cross-coupling with

bromobenzene was a reasonable diastereoselectivity (90:10) but a moderate yield of 35% for the diol derivative **8-62**. The stereochemical outcome (*anti*) was confirmed by the coupling of 5.8 Hz for 1-H/2-H. The spectral data for **8-62** were in complete agreement with the literature data.[148]




**Scheme 78**. Hydroboration followed by Suzuki coupling of chiral enol ether **8-57**.

In contrast, the investigations with the mandelic acid derived cyclic enol ether **8-58** afforded better results (Scheme **79**). Thus, the hydroboration of **8-58** followed by Suzuki coupling with the vinyl iodide **8-3** furnished compound **8-64** in good yield as a mixture of double-bond isomers (*E*/*Z* = 6:1). The diastereomer resulting from the hydroboration step was not detected. Most likely, the *trans*-hydroboration intermediate reacts much faster in the cross-coupling reaction than the corresponding *cis*-diastereomer.




**Scheme 79**. Hydroboration followed by Suzuki coupling of chiral enol ether **8-58** with β-iodostyrene **8-3**.

Surprisingly, the stereochemical outcome (*syn*-diol) for the hydroboration of enol ether **8-58** was opposite to that reported by Sinaÿ when unsubstitued borane was used.[149] An indication for this was the relatively high coupling constant for the vicinal protons in the dioxolane ring (*J* = 8.3 Hz, Figure **46**) for compound **8-64**. This result might be explained by a possible

reversibility of the hydroboration step. On the other hand, much bigger size of 9-BBN in comparison to that of $BH_3$ could be crucial for the selectivity in the presented case. Similar reactions using other five-membered *exo*-methylene compounds with aryl halides (PhBr or **8-3**) gave no results.

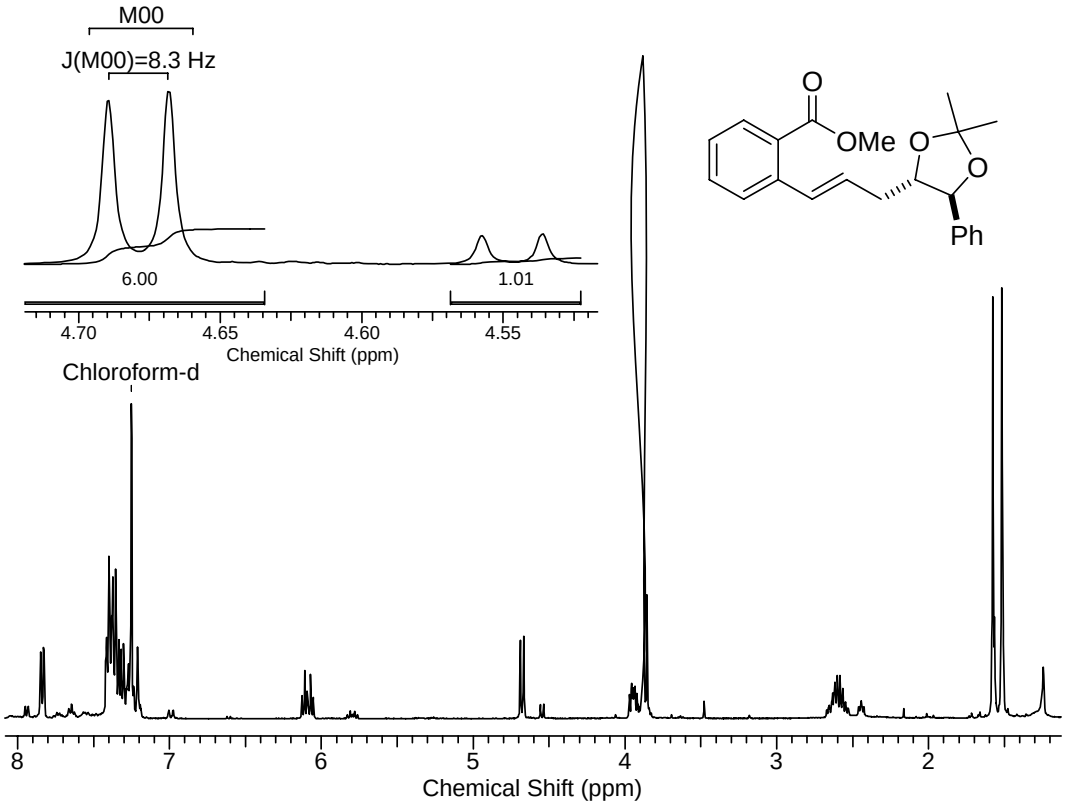
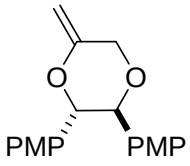
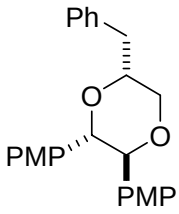
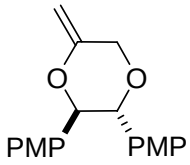
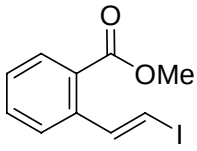
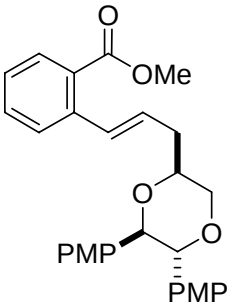
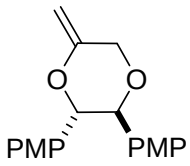
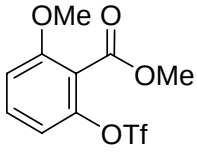
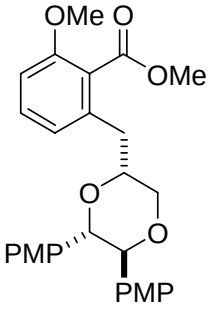



**Figure 46**. $^1$H NMR spectrum of the coupling product **8-64**.

After all, to increase the yields, to make this approach more general, and finally to extend the outcome of the described transformation, we turned our focus towards six-membered systems. Initial studies were carried out on substrates without a side chain (**8-59** and *ent*-**8-59**) (Table **5**). The reactions afforded a single detectable diastereomer in high yield (compounds **8-66**, **8-67**, **8-68**).

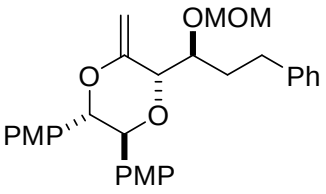
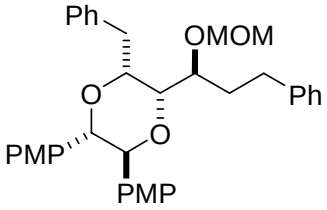
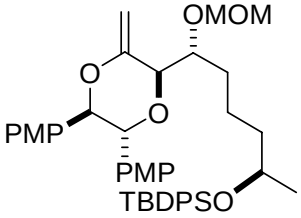
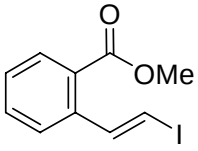
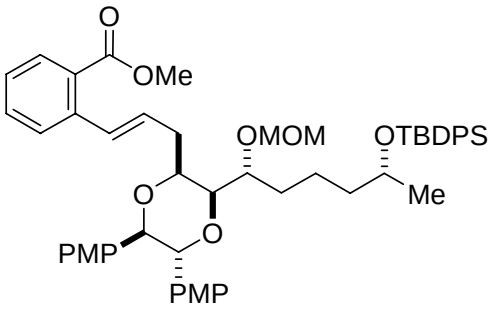
**Table 5**. Suzuki cross-coupling of the exocyclic enol ethers **8-59** and *ent*-**8-59**.

| substrate | $R^2X$ | product[a] | yield, % |
|---|---|---|---|
|  **8-59** | PhBr |  **8-66** | 72 |
|  *ent*-**8-59** |  **8-3** |  **8-67** | 87[b] |
|  **8-59** |  **8-65**[c] |  **8-68** | 53 |

[a] Enol ether (1 equiv, 0.33 M) in THF, 9-BBN (1.2 equiv), 0 °C, stir for 6 h at 23 °C; add this solution to a solution of halide/triflate (1.2 equiv), $Ph_3As$ (0.05 equiv), $Cs_2CO_3$ (2 equiv), $H_2O$ (30 equiv), $PdCl_2(dppf)$ (0.05 equiv), 23 °C, 14–16 h; DMF. [b] *E*/*Z* = 9:1. [c] from S. V. Kühnert[150]

As presented in Table **6**, substrates with a side chain on C3 were also studied. In this case, products **8-69** and **8-70** were obtained in high yield using the same condition as above.

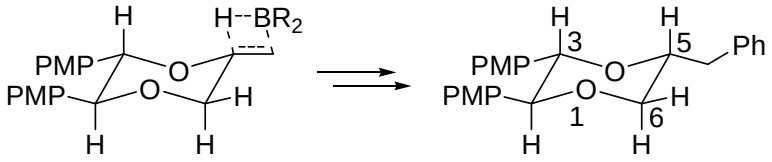
**Table 6**. Suzuki cross-coupling of the exocyclic enol ethers **8-60** and **8-61**.

| substrate | $R^2X$ | product[a] | yield, % |
|---|---|---|---|
|  **8-60** | PhBr |  **8-69** | 76 |
|  **8-61** |  **8-3** |  **8-70** | 74[b] |

[a] Enol ether (1 equiv, 0.33 M) in THF, 9-BBN (1.2 equiv), 0 °C, stir for 6 h at 23 °C; add this solution to a solution of halide/triflate (1.2 equiv), $Ph_3As$ (0.05 equiv), $Cs_2CO_3$ (2 equiv), $H_2O$ (30 equiv), $PdCl_2$(dppf) (0.05 equiv), 23 °C, 14-16 h; DMF. [b] in the presence of KBr (1.2 equiv).

With vinyl iodides as substrates (product **8-67**; Table **5**; compound **8-70**; Table **6**), it was found that in the coupling products the *E*/*Z* ratio is higher than in the starting iodide. This outcome can be explained by much lower reactivity of the corresponding *Z*-vinyl iodides. In fact, if an excess (2 equiv) of the vinyl iodide was used, the recovered vinyl iodide was enriched in the *Z*-isomer.

The stereochemistry of the product in these cases is the result of a pseudoaxial attack of the borane to the double bond (structure **8-71**, Figure **46**). A clear indication of the stereochemical outcome is the coupling constant of 10.6 Hz for the axial-axial coupling for 5-H (structure **8-66**).




**8-71** **8-66**

**Figure 46**. Pseudoaxial attack of borane H-$BR_2$ to double bond of exocyclic enol ether **8-71** and the product of coupling with PhBr (**8-66**).

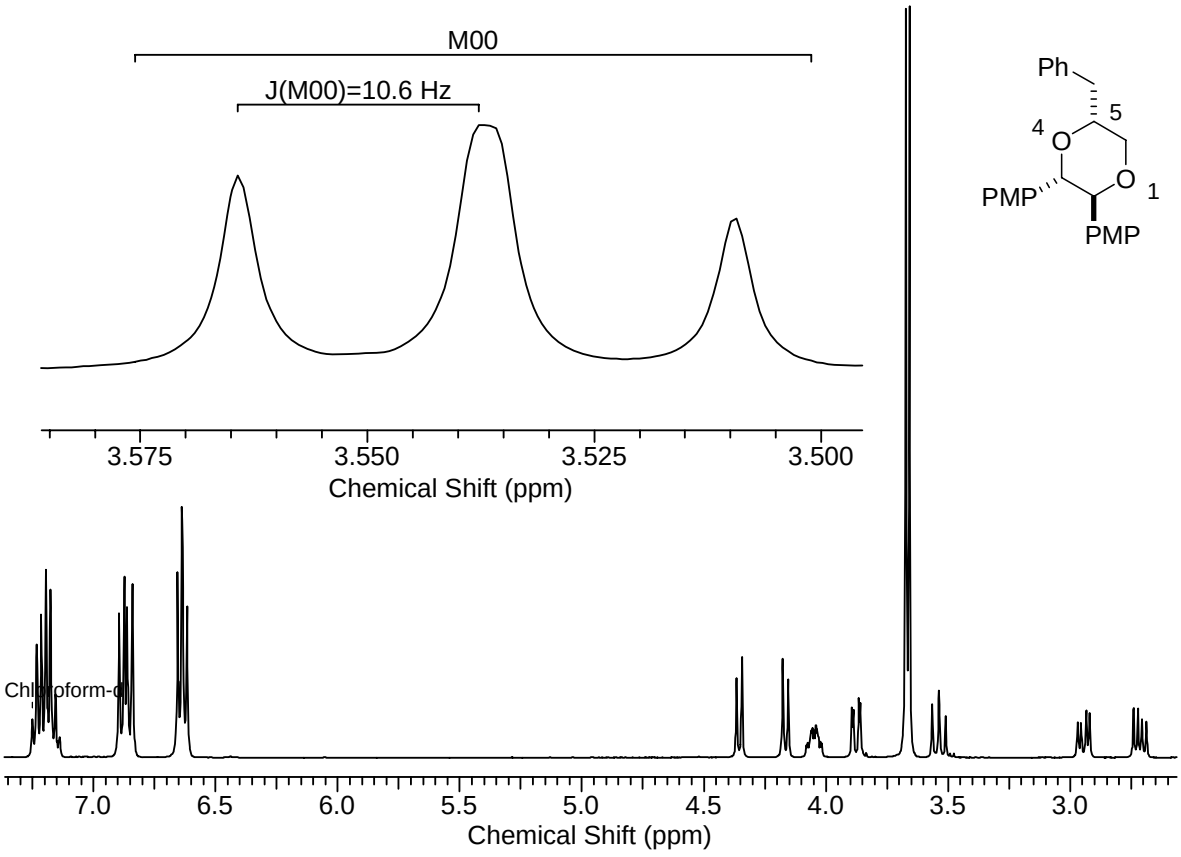
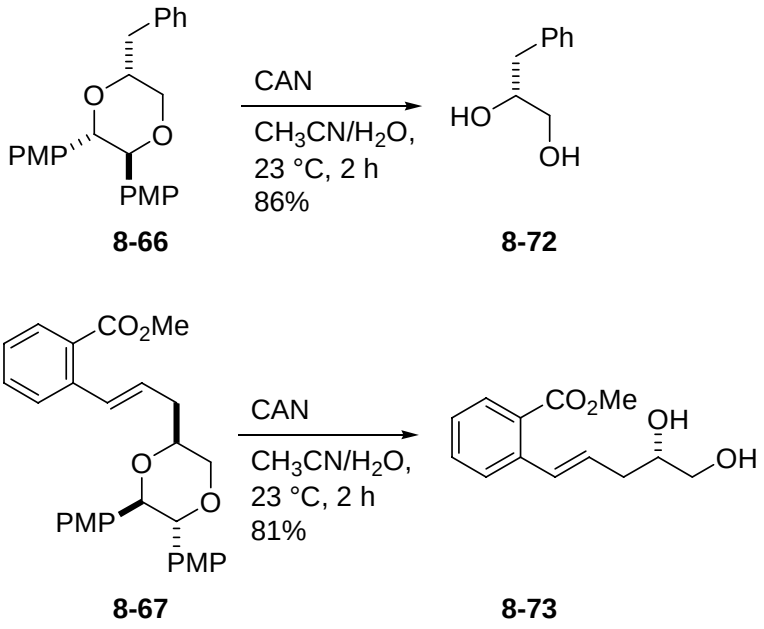



**Figure 47**. $^{1}$H NMR spectrum of the coupling product **8-66**.

An absolute proof for this was obtained by oxidative ether cleavage from **8-66** (Scheme **80**). Thus, stirring a solution of the dioxane **8-66** with CAN in a $CH_3CN/H_2O$ system for 2 h afforded the diol **8-72** in 86% isolated yield. The optical rotation $\{[\alpha]^{20}_D$ = +20.4 (*c* 1.0 in

$CHCl_3$); $[\alpha]^{20}_D$ = +15.0 (*c* 1.0 in $CHCl_3$);[151] $[\alpha]^{20}_D$ = –18.6 (*c* 1.3 in $CHCl_3$)[152] for *ent*-**8-72**} and the spectral characteristics for **8-72** were in complete agreement with that reported in the literature. The sign and value of the optical rotation undoubtedly proved the absolute configuration and enantiomeric purity of **8-72** and thereby that of **8-66**. It also allows a conclusion about the facial selectivity in the hydroboration step. Under similar conditions, the oxidative deprotection of compound **8-67** provided diol **8-73**.

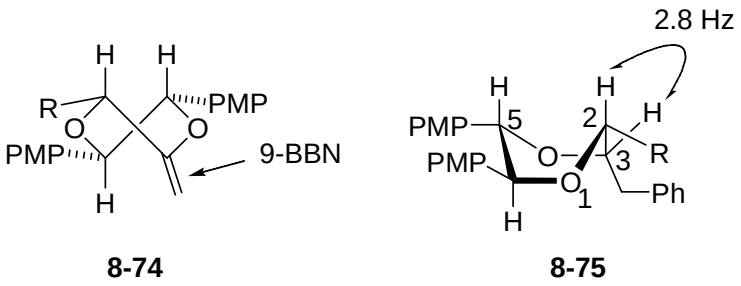



**Scheme 80**. Liberation of the diols from the dioxanes **8-37** and **8-38**.

Given the ease of the liberation of the diol, this method affords synthetically useful enantiomerically pure diols which may be difficult to obtain by traditional methods.

According to Chem3D (8.0) calculations, these substrates with substituents on C3 adopt a twistboat conformation with the *p*-methoxyphenyl groups occupying equatorial positions. Accordingly, the substituent in position 2 points in a pseudoequatorial direction. It is then obvious that the borane approaches from the convex face (cf. structure **8-74**, Figure **48**). In the resulting products such as **8-69** or **8-70**, the 1,4-dioxane ring now shows a more or less distorted boat conformation. A clear indication of the stereochemical outcome is the coupling constant of 2.8 Hz for 2-H/3-H as in **8-75** (Figure **48**). According to calculations, the dihedral

angle between the vicinal hydrogens H-2 and H-3 in **8-75** is approximately 48° and the measured coupling constants in compounds **8-69** and **8-70** is consistent with this angle.




**8-74** **8-75**

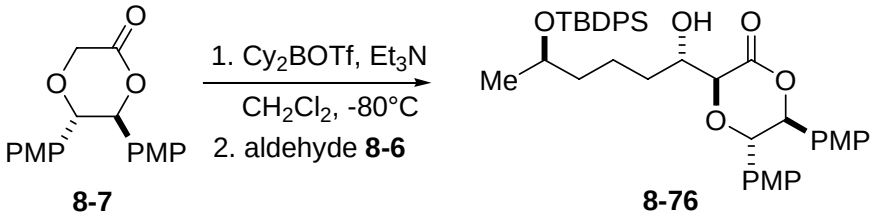
**Figure 48**. Possible twist-boat conformations of 2-substituted-3-methylidene-1,4-dioxanes (**8-74**) and the derived hydroboration/cross-coupling products **8-75**.

In conclusion, we have developed a new and easy alternative for the synthesis of complex *anti*-1,2-diols by a tandem hydroboration/Suzuki coupling sequence of alkoxy enol ethers. An easily available glycolate-based chiral oxapyrone has been employed. The simplicity of the tandem reaction, the easy preparation of both enantiomers of the Andrus' chiral oxapyrone, and a straightforward cleavage procedure complement other methods for the synthesis of highly functionalized diols. This methodology can be then successfully employed in the synthesis of complex natural products, and is used by us for the synthesis of the queenslandon core structure **6-2** as described below.

## 8.4 Synthesis of the Core Structure of the Macrolide Queenslandon

Armed with the powerful methodology for the construction of polyol substructures, we have proceeded with the synthesis of the core structure of the macrolide queenslandon (**6-2**).

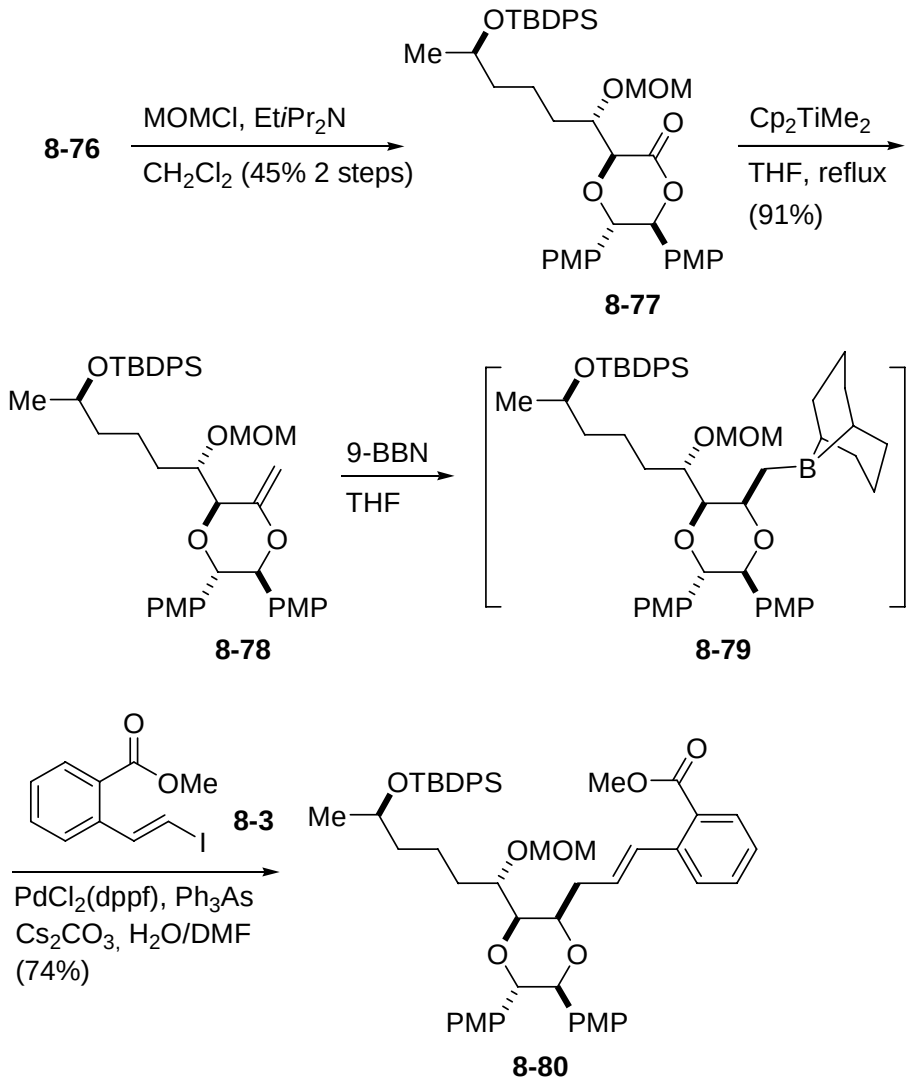
As it is presented in the retrosynthetic analysis (Figure **40**), the aliphatic moiety is constructed from protected δ-hydroxyaldehyde **8-6** and the dioxanone **8-7** *via* an aldol reaction employing the dicyclohexylboron enolate of **8-7** in the presence of $Et_3N$ forming the *anti* adduct **8-76** with high selectivity (9:1 dr, determined by HPLC/MS of crude mixture) (Scheme **81**).[153]




**Scheme 81**. Stereoselective aldol reaction of aldehyde **8-6** with glycolate auxiliary **8-7**.

In this case, aldol reaction leads to the formation of two new chiral centers. As mentioned in section **8.3.1**, the aldol product **8-76** is somewhat prone to retro aldol reaction. Therefore, after the aldol reaction is worked up, the newly formed secondary alcohol function was protected as methoxymethyl (MOM) ether (Scheme **82**). Nevertheless, this route allowed for the convenient preparation of **8-77** in gram amounts.

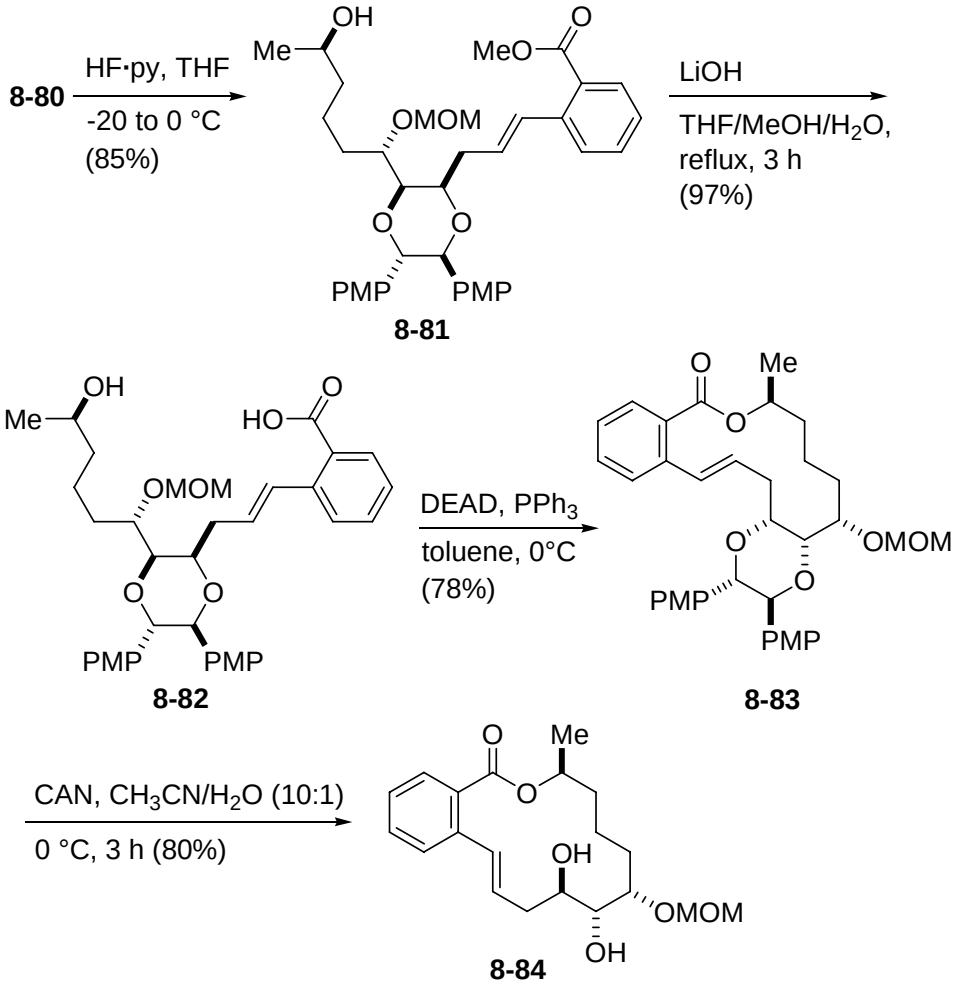
The main substrate for the key Suzuki cross-coupling reaction was prepared in high yield by Tebbe olefination of dioxanone **8-77** using Petasis conditions (Scheme **82**). Following addition of 9-BBN to the enol ether **8-78**, the intermediate borane **8-79** was subjected to a palladium-catalyzed coupling reaction with iodostyrene **8-3**. The latter was obtained by a Takai reaction with an *E*/*Z*-ratio of 5:1. Applying an excess (2.5 equiv) of **8-3** in the Suzuki coupling with **8-79** delivered the alkene **8-80** enriched in the desired *E*-isomer (*E*/*Z* > 20:1).




**Scheme 82.** Protection of aldol product, Tebbe olefination, hydroboration, and Suzuki cross-coupling.

To reach the seco acid **8-82**, the silyl ether of **8-80** was cleaved with an excess of the HF/pyridine complex at -20 °C in THF (Scheme **83**). Using tetra-*n*-butylammonium fluoride (TBAF) in THF, even at reflux, left the starting material unchanged. Saponification of the methyl ester in **8-81** with LiOH after three hours at reflux proceeded essentially in quantitative yield. Macrolactone formation from seco acid **8-82** under standard Mitsunobu conditions (DEAD, $Ph_3P$, toluene, 0 °C) gave rise to lactone **8-83** in unexpectingly high yield (78%). Most likely, conformational constraints on the backbone, imposed by the dioxane ring,

facilitate formation of the macrocycle. Cleavage of the dioxane in macrolactone **8-83** was accomplished with excess ceric ammonium nitrate in a $CH_3CN/H_2O$ mixture at 0 °C resulting in diol **8-84**.




**Scheme 83**. Synthesis of macrolactone **8-84** via Mitsunobu macrolactonization.

Crystallization of lactone **8-84** from methanol provided crystals suitable for X-ray analysis. An ORTEP plot of **8-84** is shown in Figure **49** indicating the configurations at the chiral centers and the conformation of the macrocycle. The X-ray structure additionally proved the facial selectivity of the hydroboration step (**8-78** to **8-79**, and results obtained during model studies), originally inferred from NMR data.

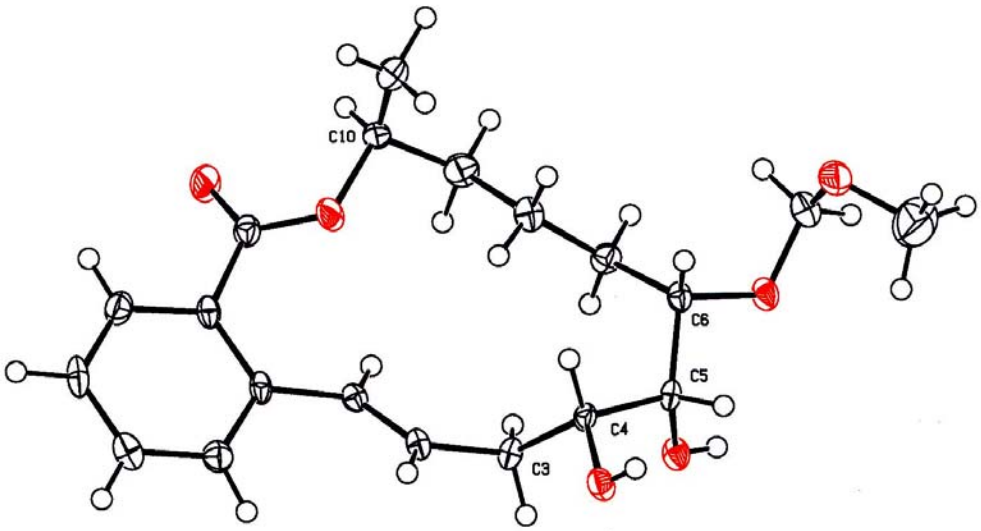
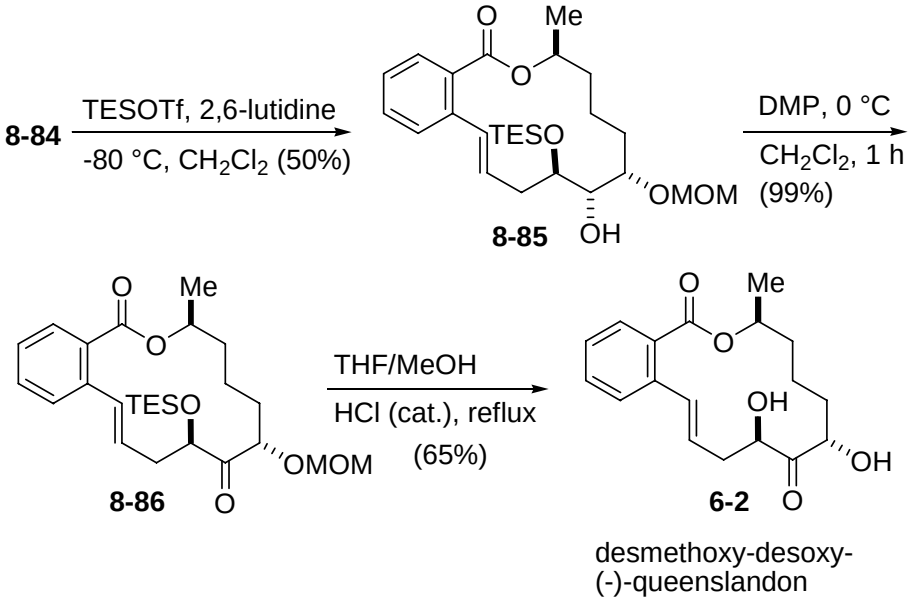



**Figure 49.** X-ray structure of macrolactone **8-84**.

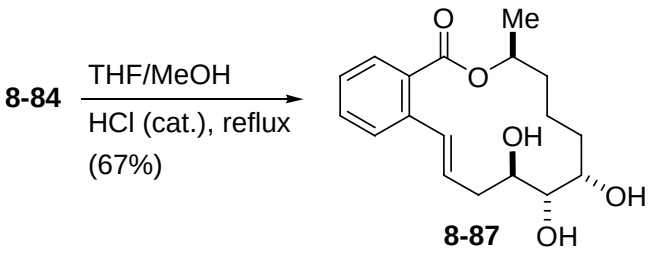
As a final challenge, differentiation of the two secondary hydroxy functions remained. A related transformation was described by Kirschning et al. in their total synthesis of tonantzitlolone where two outside hydroxyl groups of a triol were protected with triethylsilyl chloride (TESCl) and imidazole as base.[154] In the case at hand, the monosilylation of **8-84** with TESCl was indeed possible but the reaction was rather slow, taking up to three weeks. Using the more reactive TESOTf (1.5 equiv), 2,6-lutidine as base, and low temperature (–50 °C), we obtained the desired silyl ether **8-85** in 50% yield within 12 h (Scheme **84**). Besides ether **8-85**, some starting material plus a double protected derivative were present in the reaction mixture.

Subsequent oxidation of alcohol **8-85** with Dess-Martin periodinane in dry $CH_2Cl_2$ followed smoothly and formed the ketone **8-86** in almost quantitative yield. Global deprotection of **8-87** under acidic conditions provided the queenslandon analogue **6-2**.




**Scheme 84.** Selective monoprotection, oxidation, and global deprotection.

Additionally, deprotection of **8-4** led to triol **8-87**: another analogue of queenslandon (**6-1**) (Scheme **85**).




**Scheme 85**. Removal of MOM protecting group in **8-84**.

The regiochemistry in the selective TES-ether formation was inferred from the COSY NMR spectrum of the final compound, dihydroxyketone **6-2**. Most supportive in the assignment was the absence of a cross-peak between 11-H and 13-H (Figure **50**). Rather prominent correlations were seen for the methine H's, 11-H and 13-H, with their neighboring methylene groups (marked as "**c**" and "**f**", respectively). The keto group resonates at $\delta = 212.5$ ppm in the $^{13}C$ NMR spectrum.

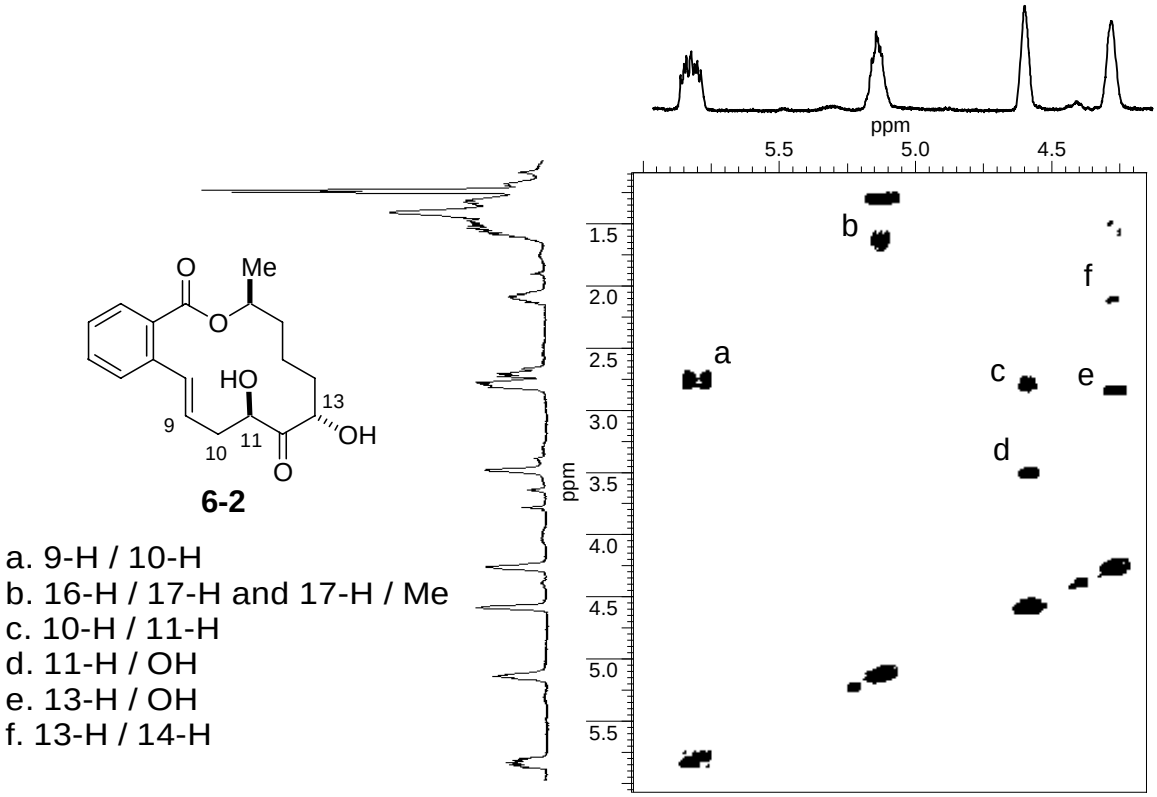
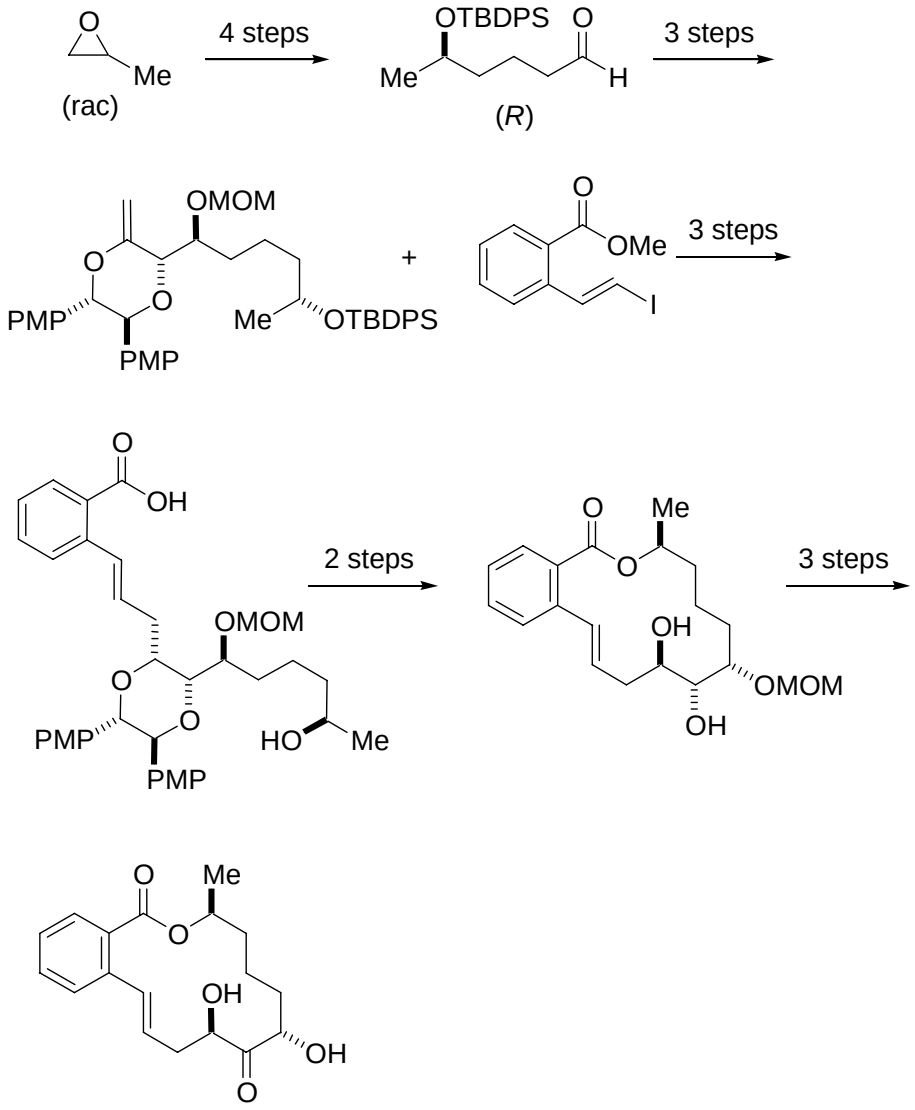



**Figure 50**. Fragment of COSY NMR spectrum of **6-2**.

# 9 Conclusion II

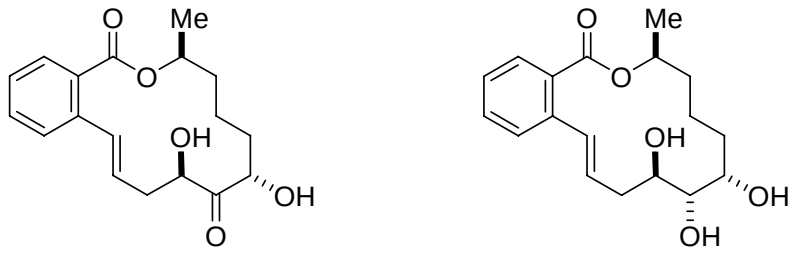
In summary, we developed an efficient asymmetric synthesis of macrolactone **6-2**, featuring the complete aliphatic sector of queenslandon (**6-1**). The key steps in this synthesis were an *anti* selective aldol reaction, a tandem hydroboration/Suzuki cross-coupling, Mitsunobu macrolactonization, and selective mono-protection of diol **8-84**.




**Scheme 86**. Key intermediates in the synthesis of the fully funcionalized core structure of queenslandon **6-2**.

The synthesis of chiral aldehyde **8-6** started from racemic propylene oxide and proved to be more efficient as a known approach. The preparation of the Andrus auxiliary was optimized on the Wittig-Horner step and much higher yields were obtained as using the originally described procedures. All in all, the synthesis was started from cheap and commercially available starting materials. We also note that the chiral dioxane moiety served multiple purposes: (a) as a chiral auxiliary in the aldol reaction; (b) as the directing subunit in the diastereoselective hydroboration step; and (c) as a conformational constraint during the Mitsunobu macrolactonization. All chiral centers were essentially obtained *via* catalytic methods (Jacobsen resolution, ADH).

The synthesis involved 15 steps and proceeded with good overall yield from racemic propylene oxide (**8-9**). Preliminary cytotoxicity assays (L929 mouse fibroblast cells) on macrolactone **6-2** showed an $IC_{50}$ of 40 μg $mL^{-1}$. At the same concentration, **8-87** was less active, reaching an inhibition of 40%.[155]




**6-2** **8-87**

**Figure 51**. The structures of synthesized queenslandon analogues.

The same strategy should allow for the preparation of further queenslandon analogues and the natural product itself.

# 10 Experimental Section

## 10.1 General Remarcs

### 10.1.1 Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and 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 NMR-spectroscopy

All the spectra 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 [$D_6$]DMSO; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ ($\delta H$ = 7.25 ppm, $\delta C$ = 77.0 ppm), [$D_6$]DMSO ($\delta H$ = 2.49 ppm, $\delta C$ = 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).

### 10.1.3 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.

### 10.1.4 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 $cm^{-1}$.

### 10.1.5 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020. 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.

### 10.1.6 Melting Points

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

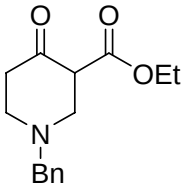
### 10.1.7 Chromatographic Methods

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

**Ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (4-2)**



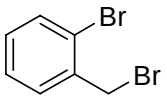

Diethyl carbonate (19.4 mL, 18.9 g, 0.16 mol) was added dropwise under nitrogen atmosphere to a suspension of NaH (9.0 g, ~60% in mineral oil) in anhydrous toluene (125 mL). After the addition of several drops (3–5) of methanol, the mixture was heated at reflux and a solution of N-benzyl-4-piperidone (15.0 g, 0.08 mol) in anhydrous toluene (50 mL) was added dropwise during 35 min. Heating was maintained until the evolution of hydrogen ceased (approx. 2.5 h). The reaction mixture was then cooled to room temperature, stirred for additional 2 h, and acidified by careful addition of glacial AcOH. The resulting mixture was diluted with ice-cold water (~150 mL) and adjusted to pH ~ 8 with aqueous ammonia. The organic layer was separated and the aqueous phase was extracted with toluene (5 × 75 mL). The combined organic fractions were dried over $Na_2SO_4$ and evaporated to afford the crude mixture. Purification *via* column chromatography on silica gel gave the desired carboxylate **4-2**, yield 13.0 g (62%), yellow oil.

**$R_f$** = 0.55–0.6 (petroleum ether/diethyl ether, 2:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.85–1.94 (m, 2H, 5-H), 2.15–2.25 (m, 2H, 6-H), 2.61–2.70 (m, 2H, 2-H), 3.44 (s, 2H, $PhCH_2NR_2$), 4.11 (dd, *J* = 14.1, 7.1 Hz, $CO_2CH_2CH_3$), 4.55–4.64 (m, 1H, 3-H), 7.16–7.28 (m, 5H, aromatic);

NMR spectrum after standing in $CDCl_3$ for some time contains the mixture of two compounds – the carboxylate **4-2** and its enol form.

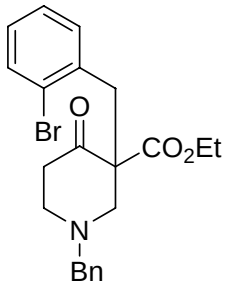
**1-Bromo-2-(bromomethyl)benzene (4-3a)**




A $CCl_4$ (130 mL) solution of *o*-bromotoluene (20.0 g, 117 mmol) and NBS (25.0 g, 140 mmol) was refluxed for 9 h. The solid formed during the reaction was filtered off. After removal of the solvent in vacuo, distillation under reduced pressure gave 1-bromo-2-(bromomethyl)benzene (**4-3a**) as a colorless liquid; yield 22.0 g (75%).

**b.p.** 72–74 °C (0.8 mbar)

**Ethyl N-Benzyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (4-4a)**




To a suspension of anhydrous $K_2CO_3$ (8.01 g, 58 mmol) and ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**4-2**) (3.93 g, 15 mmol) in anhydrous THF (25 mL) was added under nitrogen a solution of 2-bromobenzyl bromide (**4-3a**) (4.5 g, 18.0 mmol) in anhydrous THF (25 mL). The mixture was refluxed for 6 h. Then the inorganic materials were filtered and washed with THF. The combined filtrates were concentrated to give an oily residue. The product was isolated by flash chromatography (petroleum ether/ethyl acetate, 20:1), yield 4.73 g (73 %), slightly yellow oil.

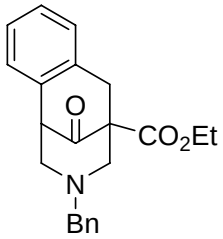
$\mathbf{R_f}$ = 0.05 (petroleum ether/ethyl acetate, 20:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 2.23–2.30 (m, 1H, 6-H), 2.32 (d, *J* = 11.5 Hz, 1H, 2-H), 2.80 (ddd, *J* = 14.4, 3.3, 2.0 Hz, 1H, 6-H), 2.81–2.91 (m, 1H, 5-H), 2.95–3.01 (m, 1H, 5-H), 3.15 (d, *J* = 14.4 Hz, 1H, *o*-$BrC_6H_4CH_2$), 3.45 (d, *J* = 14.4 Hz, 1H, *o*-$BrC_6H_4CH_2$), 3.47 (d, *J* = 13.1 Hz, 1H, $PhCH_2NR_2$), 3.56 (dd, *J* = 11.6, 2.8 Hz, 1H, 2-H), 3.62 (d, *J* = 13.1 Hz, 1H, $PhCH_2NR_2$), 4.00–4.15 (m, 2H, $CO_2CH_2CH_3$), 7.00–7.05 (m, 1H, ar.), 7.02–7.28 (m, 7H, ar.), 7.48 (d, *J* = 8.0 Hz, 1H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 35.8, 40.5, 52.6, 61.0, 61.4, 61.8 (6C, sec.), 62.2 (C-3), 125.9, 127.0, 127.2, 128.1, 128.2, 128.9, 132.1, 132.8, 136.3, 137.7 (ar.), 170.7 ($CO_2Et$), 205.3 (C=O);

**HRMS** (ESI): calcd. for $C_{22}H_{24}BrNO_3$ $[M+H]^+$: 430.1012, found 430.1013.

**Ethyl N-Benzyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)-carboxylate (4-5a)**

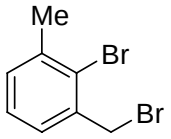



An oven-dried Schlenk tube fitted with a rubber septum was purged with nitrogen and charged with ethyl 1-benzyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (**4-4a**) (4.30 g, 10 mmol), anhydrous toluene (50 mL), $K_3PO_4$ (4.25 g, 20 mmol), and $Pd(dba)_2$ (115 mg, 2 mol%). Then the tube was purged with nitrogen, and *t*$Bu_3P$ (10 mL of 0.04 N in toluene, 4 mol%) was added. The mixture was vigorously stirred in an oil bath at 110 °C for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (100 mL), filtered through Celite and concentrated in vacuo. The crude material was dissolved in diethyl ether and then the solvent was evaporated. This procedure was repeated three times which results in the precipitation of the crude product. The solids were washed with a mixture of pentane/diethyl ether (5:1), filtered and dried in vacuo. Alternatively, the crude material may

be purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 9:1). The precipitation method provided the tricyclic compound **4-5a** (2.3 g, 65%) as a yellow solid.

**$R_f$** = 0.2 (petroleum ether/diethyl ether, 9:1);
**m.p.** 117–119 °C;
**IR** (KBr): $\upsilon_{max}$ = 2985, 2816, 1724, 1450, 1256, 744 $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.75 (dd, *J* = 10.6, 2.5 Hz, 1H, 2-H), 3.00 (ddd, *J* = 10.6, 2.8 Hz, 1H, 2-H), 3.11 (d, *J* = 11.2 Hz, 1H, 4-H), 3.19 (dd, *J* = 11.2, 2.8 Hz, 1H, 4-H), 3.41 (d, *J* = 17.2 Hz, 1H, 6-H), 3.42 (dd, *J* = 2.5 Hz, 1H, 1-H), 3.57 (dd, *J* = 14.5 Hz, 2H, $PhCH_2NR_2$), 4.01 (d, *J* = 17.1 Hz, 1H, 6-H), 4.25 (dd, *J* = 14.1, 7.1 Hz, $CO_2CH_2CH_3$), 6.87–6.95 (m, 3H, ar.), 7.12–7.22 (m, 5H, ar.), 7.25–7.31 (m, 1H, ar.);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 41.0 (C-6), 52.7 (C-1), 59.1 (C-5), 60.2, 61.5, 61.8, 63.5 (4C, sec.), 126.2, 126.2, 127.0, 127.1, 127.5, 128.1 (CH, ar.), 128.2, 136.3, 137.3, 138.2 (3C, quat. ar.), 170.2 ($CO_2Et$), 207.4 (C=O);
**HRMS** (ESI): calcd for $C_{22}H_{23}NO_3$ $[M+H]^+$ 350.1751, found 350.1752; methanol adduct (hemiacetal): calcd for $C_{23}H_{28}NO_4$ $[M+CH_3OH+H]^+$: 382.2013, found 382.2008.

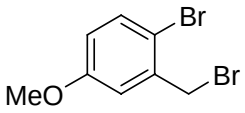
### 2-Bromo-1-(bromomethyl)-3-methylbenzene (4-3b)




2-Bromo-1,3-dimethylbenzene (15.0 g, 0.081 mol) with stirring and irradiation with light (200W lamp) at 80 °C was added $Br_2$ (13.0 g, 0.081 mol) in a dropwise fashion so, that before adding every next drop, the color of bromine in the reaction mixture vanished. After complete addition, the mixture was stirred for additional 30 min and fractionally distilled at reduced pressure to provide benzyl bromide **4-3b**, yield 7.0 g (33%), colorless liquid.

**b. p.** 85–90 °C (1 mbar)

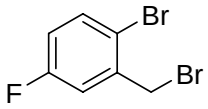
**1-Bromo-2-(bromomethyl)-4-methoxybenzene (4-3c)**[59b]




A mixture of carbon tetrachloride (45 mL), *p*-bromo-*m*-methylanisole (7.5 g, 37.3 mmol), N-bromosuccinimide (7.0 g, 39.3 mmol), and 0.6 g (2.5 mmol) of benzoyl peroxide was heated from room temperature to reflux over a period of 25 min. Soon after the start of the reflux the solution turned orange. After 10 min the spontaneous heating had stopped and almost immediately thereafter the solution became colorless. The mixture was filtered and evaporation of the filtrate yielded crude product. Recrystallization of this material from petroleum ether (b. p. 30–60 °C) yielded 6.3 g (60%) of benzyl bromide **4-3c**.

**m. p.** 88–91 °C.

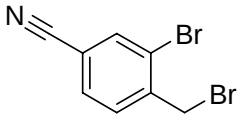
**1-Bromo-2-(bromomethyl)-4-fluorobenzene (4-3d)**




The reaction was performed with 2-bromo-5-fluorotoluene (10.3 g, 54.5 mmol) and with AIBN as radical initiator as described for **4-3a**. Purification of the crude by distillation at reduced pressure gave the benzyl bromide **4-3d** (8.9 g, 63%) as colorless viscous liquid.

**b. p.** 118–124 °C.

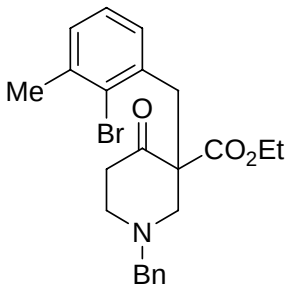
**3-Bromo-4-(bromomethyl)benzonitrile (4-3c)**




The reaction was performed with 3-bromo-4-methylbenzonitrile (2.5 g, 12.8 mmol) and with AIBN as radical initiator as described for **4-3a**. Purification of the crude by column chromatography (petroleum ether/ethyl acetate, 20:1) gave the benzyl bromide **4-3e** (1.5 g, 45%) as colorless solid.

**$R_f$** = 0.23 (petroleum ether/ethyl acetate, 20:1).

**Ethyl N-Benzyl-3-(2-bromo-3-methylbenzyl)-4-oxopiperidine-3-carboxylate (4-4b)**




The reaction was performed with piperidone **4-2** (1.31 g, 5.0 mmol) and the benzyl bromide **4-3b** (1.32 g, 5.0 mmol) as described for **4-4a**. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 20:1) gave the alkylated product **4-4b** (1.2 g, 54%) as colorless crystals.

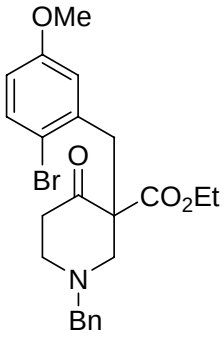
**$R_f$** = 0.05 (petroleum ether/ethyl acetate, 20:1);
**m. p.** 60–61 °C;
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.20–2.27 (m, 1H, 6-H), 2.30 (d, *J* = 11.4 Hz, 1H, 2-H), 2.32–2.38 (m, 4H, $CH_3$Ar and 6-H), 2.78–2.87 (m, 1H, 5-

H), 2.91–2.98 (m, 1H, 5-H), 3.16 (d, *J* = 14.4 Hz, 1H, ArC*H*$_2$), 3.43 (d, *J* = 13.1 Hz, 1H, PhC*H*$_2$NR$_2$), 3.49 (d, *J* = 14.4 Hz, 1H, ArC*H*$_2$), 3.52 (dd, *J* = 11.4, 3.0 Hz, 1H, 2-H), 3.60 (d, *J* = 13.1 Hz, 1H, PhC*H*$_2$NR$_2$), 3.97–4.12 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 6.93–7.05 (m, 3H, ar.), 7.25–7.26 (m, 5H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 24.5 ($CH_3$Ar), 36.5, 40.5, 52.5, 61.1, 61.4, 61.8 (6C, sec.), 62.2 (C-3), 126.3, 127.2, 128.2 (4C, tert. ar.), 128.7 (quat. ar.), 128.9, 129.2, 129.4 (4C, tert. ar.), 136.7, 137.8, 138.4 (3C, quat. ar.), 170.8 ($CO_2$Et), 205.3 (C=O);

**HRMS** (ESI): calcd. for $C_{23}H_{27}BrNO_3$ $[M+H]^+$: 444.1169, found 444.1174.

**Ethyl N-Benzyl-3-(2-bromo-5-methoxybenzyl)-4-oxopiperidine-3-carboxylate (4-4c)**



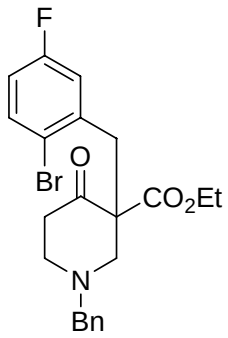

The reaction was performed with piperidone **4-2** (2.61 g, 10.0 mmol) and benzyl bromide **4-3c** (2.95 g, 11.0 mmol) as described for **4-4a**. Purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 9:1) gave the alkylated product **4-4c** (2.4 g, 52 %), yellow oil.

**$R_f$** = 0.1 (petroleum ether/diethyl ether, 9:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.24–2.33 (m, 2H, 2-H and 6-H), 2.40 (ddd, *J* = 14.4, 3.3, 2.0 Hz, 1H, 6-H), 2.97–3.03 (m, 1H, 5-H), 2.83–2.93 (m, 1H, 5-H), 3.13 (d, *J* = 14.4 Hz, 1H, ArC*H*$_2$), 3.41 (d, *J* = 14.4 Hz, 1H, ArC*H*$_2$), 3.50 (d, *J* = 13.3 Hz, 1H, PhC*H*$_2$NR$_2$), 3.58–3.66 (m, 2H, PhC*H*$_2$NR$_2$ and 2-H), 3.72 (s, 3H, $CH_3$OAr), 4.03–4.16 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 6.62 (dd, *J* = 8.8, 3.0 Hz, 1H, 4'-H, ar.), 6.78 (d, *J* = 3.0 Hz, 1H, 6'-H, ar.), 7.21–7.31 (m, 5H, ar.), 7.37 (d, *J* = 8.8 Hz, 1H, 3'-H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2\mathit{C}H_3$), 36.0 (Ar$\mathit{C}H_2$), 40.5 (C-5), 52.6 (Ph$\mathit{C}H_2NR_2$), 55.4 ($\mathit{C}H_3OAr$), 60.9, 61.4, 61.8 (3C, sec.), 62.3 (C-3), 114.3 (tert. ar.), 116.4, 117.5 (quat. ar.), 127.2, 128.2, 128.9, 133.1 (7C, tert. ar.), 137.2, 137.7 (2C, quat. ar.), 158.4 (MeO*C*, quat. ar.), 170.8 ($CO_2Et$), 205.3 (C=O);
**HRMS** (ESI): calcd. for $C_{23}H_{27}BrNO_4$ $[M+H]^+$: 460.1118, found 460.1125.

**Ethyl 3-(2-brom-5-fluorobenzyl)-N-benzyl-4-oxopiperidine-3-carboxylate (4-4d)**



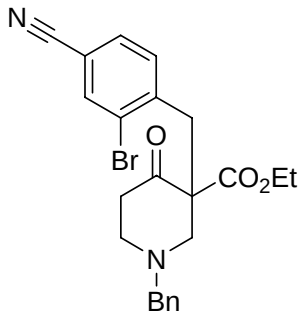

**a)** To a suspension of anhydrous $K_2CO_3$ (13.25 g, 0.096 mol) and ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**4-2**) (6.33 g, 0.024 mol) in anhydrous THF (50 mL) was added under nitrogen atmosphere a solution of 2-bromo-5-fluorobenzyl bromide (**4-3d**, 7.90 g, 0.029 mol) in anhydrous THF (50 mL). The mixture was refluxed for 17 hours. Then inorganic materials were filtered and washed with THF (3 × 25 mL). The combined filtrates were evaporated to give an oily residue. The product was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1), providing **4-4d** as a slightly yellow oil, yield 3.00 g (29%).

**b)** A mixture of potassium *tert*-butoxide (0.130 g, 14 mmol) and anhydrous THF (10 mL) was stirred at room temperature for 0.5 h. The resulting milky solution was cooled to 0 °C, and then 1-benzyl-4-oxopiperidine-3-carboxylate (**4-2**) (0.250 g, 9.5 mmol) in anhydrous THF (10 mL) was added whereby the temperature was kept below 5 °C. The mixture was then warmed to room temperature and further stirred for 1h, resulting in a yellow solution. After cooling to 0 °C a solution of 2-bromo-5-fluorobenzyl bromide (**4-3d**, 0.284 g, 11 mmol) in anhydrous

THF (10 mL) was added dropwise within 0.5 h. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was cooled to 0 °C before saturated $NH_4Cl$ was added. After separation of the layers the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed twice with brine, dried over $Na_2SO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1), providing **4-4d** as a slightly yellow oil, yield 0.230 g (54%).

**$R_f$** = 0.3 (petroleum ether/ethyl acetate, 10:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.20–2.28 (m, 2H, 6-H), 2.35 (ddd, *J* = 14.5, 3.0, 2.0 Hz, 1H, 2-H), 2.79–2.88 (m, 1H, 5-H), 2.92-2.99 (m, 1H, 5-H), 3.07 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 3.36 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 3.45 (d, *J* = 13.2 Hz, 1H, $PhCH_2NR_2$), 3.52 (dd, *J* = 11.6, 2.8 Hz, 1H, 2-H), 3.57 (d, *J* = 13.2 Hz, 1H, $PhCH_2NR_2$), 3.97–4.12 (m, 2H, $CO_2CH_2CH_3$), 6.69–6.76 (m, 1H, ar.), 6.93 (dd, *J* = 9.6, 3.1 Hz, 1H, ar.), 7.15–7.26 (m, 5H, ar.), 7.39 (dd, *J* = 8.6, 5.4 Hz, 1H, ar.);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 36.0, 40.5, 52.7, 61.0, 61.5, 61.7, 62.1, 115.4, 115.6, 118.9, 119.1, 120.0, 127.3, 128.2, 128.9, 133.6, 133.7, 137.6, 138.4, 138.5, 160.2, 162.6, 170.6 ($CO_2Et$), 205.1 (C=O);
**HRMS** (ESI): calcd for $C_{22}H_{24}BrFNO_3$ $[M+H]^+$: 448.09181, found 448.09176.

**Ethyl 3-(2-brom-4-cyanobenzyl)-N-benzyl-4-oxopiperidine-3-carboxylate (4-4e)**

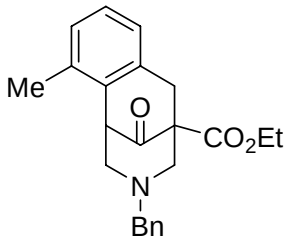



The reaction was performed with piperidone **4-2** (436 mg, 1.65 mmol) and benzyl bromide **4-3e** (500 mg, 1.8 mmol) as described for **4-4a**. Purification of the crude product by flash

chromatography (petroleum ether/diethyl ether, 5:1) gave the alkylated product **4-4e** (563 mg, 72 %), slightly yellow oil.

**$R_f$** = 0.2 (petroleum ether/ethyl acetate, 5:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.20–2.30 (m, 2H, 2-H and 6-H), 2.22–2.26 (m, 1H, 6-H), 2.81–3.01 (m, 2H, 5-H), 3.10 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 3.42 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 3.45–3.50 (m, 2H, $PhCH_2NR_2$), 3.57 (d, *J* = 13.2 Hz, 1H, 2-H), 3.92–4.10 (m, 2H, $CO_2CH_2CH_3$), 7.06–7.12 (m, 2H, ar.), 7.15–7.25 (m, 3H, ar.), 7.28 (d, *J* = 7.9 Hz, 1H, ar.), 7.39 (dd, *J* = 8.1, 1.5 Hz, 1H, ar.), 7.73 (d, *J* = 1.3 Hz, 1H, ar.);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 36.0, 40.4, 52.8, 61.1, 61.7, 61.7, 62.1, 112.0, 117.2, 125.2, 127.4, 128.3, 129.0, 130.4, 132.5, 135.8, 137.8, 142.5, 170.4 ($CO_2Et$), 205.0 (C=O);
**HRMS** (ESI): calcd for $C_{23}H_{24}BrN_2O_3$ $[M+H]^+$: 455.09648, found 455.09658.

**Ethyl N-Benzyl-10-methyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)-carboxylate (4-5b)**




This compound was prepared as described for **4-5a** using 455 mg (1.02 mmol) of the alkylated compound **4-4b**. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1), yield 95 mg (30%), colorless oil.

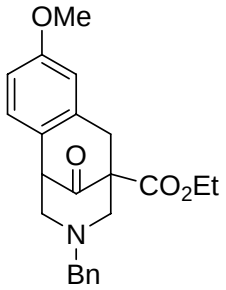
**$R_f$** = 0.1 (petroleum ether/ethyl acetate, 20:1);
**IR** (film): $\upsilon_{max}$ = 2951, 2812, 1728, 1458, 1261, 1107, 744 $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.16 (s, 3H, $CH_3Ar$), 2.71 (dd, *J* = 10.6, 2.5 Hz, 1H, 2-H), 3.02 (ddd, *J* = 10.6, 2.8 Hz, 1H, 2-H), 3.10 (d, *J* = 11.2

Hz, 1H, 4-H), 3.16 (dd, *J* = 11.2, 2.8 Hz, 1H, 4-H), 3.41 (d, *J* = 17.3 Hz, 1H, 6-H), 3.57 (s, 2H, PhC*H*$_2$NR$_2$), 3.65 (dd, *J* = 2.5 Hz, 1H, 1-H), 3.99 (d, *J* = 17.3 Hz, 1H, 6-H), 4.24 (dd, *J* = 14.4, 7.1 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 6.88–6.96 (m, 2H, ar.), 7.01–7.07 (m, 2H, ar.), 7.14–7.20 (m, 4H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2\mathit{C}H_3$), 18.4 ($\mathit{C}H_3$Ar), 41.1 (C-6), 49.0 (C-1), 58.9 (C-5), 59.4, 60.2, 61.5, 63.2 (4C sec.), 124.3, 126.7, 127.0, 127.8 (4C tert. ar.), 128.0, 128.2, 134.6, 136.2, 138.2 (4C quat. ar.), 170.3 ($\mathit{C}O_2$Et), 208.0 (C=O);

**HRMS** (ESI): calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1907, found 364.1917.

## Ethyl N-Benzyl-8-methoxy-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)-carboxylate (4-5c)




This compound was prepared as described for **4-5a** using 577 mg (1.25 mmol) of the alkylated compound **4-4c**. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1), yield 144 mg (40%), yellow oil which crystallizes within several days.

**$R_f$** = 0.1 (petroleum ether/ethyl acetate, 20:1);

**m. p.** 84–85 °C;

**IR** (KBr): $\upsilon_{max}$ = 2943, 2816, 1724, 1608, 1454, 1265, 1088, 741 cm$^{-1}$;

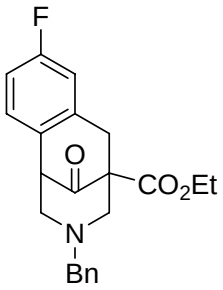
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\mathit{H}_3$), 2.71 (dd, *J* = 10.5, 2.5 Hz, 1H, 2-H), 2.97 (ddd, *J* = 10.6, 2.8, 1H, 2-H), 3.08 (d, *J* = 11.2, 1H, 4-H), 3.15 (dd, *J* = 11.2, 2.8 Hz, 1H, 4-H), 3.38 (d, *J* = 17.4 Hz, 1H, 6-H), 3.39 (dd, *J* = 2.5 Hz, 1H, 1-H), 3.57 (s, 2H, PhC*H*$_2$NR$_2$), 3.84 (s, 3H, C*H*$_3$OAr), 3.97 (d, *J* = 17.4 Hz, 1H, 6-H), 4.20–4.27 (m, 2H,

$CO_2CH_2CH_3$), 6.72–6.75 (m, 2H, ar.), 6.82–6.86 (m, 1H, ar.), 6.93–6.97 (m, 2H, ar.), 7.15–7.19 (m, 3H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 41.1 (C-6), 52.0 (C-1 tert.), 55.3 ($CH_3OAr$), 58.8 (C-5 quat.), 60.3, 61.5, 62.0, 63.4 (4C sec.), 111.4, 112.3, 127.1, 128.1, 128.2, 128.5 (8C tert. ar.), 129.6, 137.4, 138.2 (3C quat. ar.), 158.8 (MeO*C* quat. ar.), 170.3 ($CO_2Et$), 207.5 (C=O);

**HRMS** (ESI): calcd for $C_{23}H_{26}NO_4$ $[M+H]^+$: 380.18563, found 380.18573; methanol adduct (hemiacetal) calcd for $C_{24}H_{30}NO_5$ $[M+CH_3OH+H]^+$: 412.2119, found 412.2111.

## Ethyl N-benzyl-10-fluoro-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (4-5d)




This compound was prepared as described for **4-5a** using 300 mg (0.64 mmol) of the alkylated compound **4-4d**. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1). The fractions containing the product were combined together and concentrated in vacuo. Recrystallization from heptane (2 mL) provides compound **4-5d** as a white crystalline solid, yield 91 mg (37%). Additional amount (21 mg) of product could be separated from the mother filtrate by flash chromatography (overall yield 46%).

**$R_f$** = 0.1 (petroleum ether/ethyl acetate, 20:1);

**m. p.** 104–106 °C;

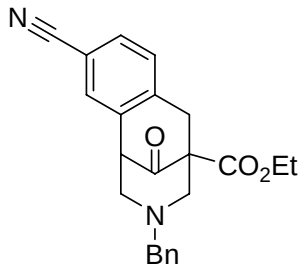
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.76 (dd, *J* = 10.7 2.1, Hz, 1H, 2-H), 2.93–2.99 (m, 1H, 2-H), 3.14 (d, *J* = 11.2 Hz, 1H, 4-H), 3.19 (dd, *J* = 11.2, 2.8 Hz, 1H, 4-H), 3.38 (d, *J* = 17.4 Hz, 1H, $ArCH_2$), 3.41–3.44 (m, 1H, 1-H), 3.56 (dd, *J* =

17.0, 13.5 Hz, 2H, PhC$H_2$NR$_2$), 4.02 (d, $J$ = 17.4 Hz, 1H, ArC$H_2$), 4.20–4.29 (m, 2H, $CO_2CH_2CH_3$), 6.85–6.95 (m, 5H, ar.), 7.15–7.21 (m, 3H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 40.8 (sec.), 52.0 (tert.), 58.6 (quat.), 60.3, 61.7, 61.8 (3C sec.), 63.4, 112.8, 113.1, 113.2, 113.5, 127.2, 128.1, 128.3, 128.9, 128.9, 133.0, 138.0, 138.2, 138.3, 160.8, 163.2, 170.0 ($CO_2$Et), 206.9 (C=O);

**HRMS** (ESI): calcd for $C_{23}H_{27}BrFNO_3$ $[M+MeOH+H]^+$: 400.19179, found 400.19097.

**Ethyl N-benzyl-9-cyano-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (4-5e)**




This compound was prepared as described for **4-5a** using 306 mg (0.64 mmol) of the alkylated compound **4-4e**. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1). The fractions containing the product were combined together and concentrated in vacuo. Crystallization from petroleum ether/ ethyl acetate mixture (8:1, 5 mL) provides compound **4-5** as a white crystalline solid, yield 80 mg (33%). Additional amount (13 mg) of product could be separated from mother filtrate by flash chromatography (overall yield 35%).

**$R_f$** = 0.2 (petroleum ether/ethyl acetate, 5:1);

**m. p.** 158–160 °C;

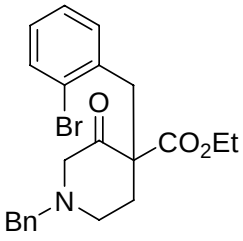
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.25 (t, $J$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.73 (d, $J$ = 10.8 Hz, 1H, 2-H), 2.87–2.95 (m, 1H, 2-H), 3.06–3.15 (m, 2H, 4-H), 3.38 (d, $J$ = 18.3 Hz, 1H, ArC$H_2$), 3.43 (s, 1H, 1-H), 3.50 (dd, $J$ = 21.6, 13.7 Hz, 2H, PhC$H_2$NR$_2$), 3.98 (d, $J$ = 18.3 Hz, 1H,

ArC*H*$_2$), 4.15–4.25 (m, 2H, $CO_2CH_2CH_3$), 6.80 (d, *J* = 5.9 Hz, 2H, ar.), 7.09–7.21 (m, 4H, ar.), 7.26 (d, *J* = 7.9 Hz, ar.), 7.52 (d, *J* = 7.9 Hz, 1H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 41.0, 52.1, 58.9, 60.1, 61.5, 61.8, 63.2 (4C sec.), 110.1, 118.6 (2C quat.), 127.1, 127.4, 128.0, 128.4, 130.7, 131.0, 137.6, 138.9, 142.0, 169.5 ($CO_2$Et), 205.5 (C=O);

**HRMS** (ESI): calcd for $C_{24}H_{29}BrN_2O_3$ $[M+MeOH+H]^+$: 407.19640, found 407.19584.

**Ethyl 1-Benzyl-4-(2-bromobenzyl)-3-oxopiperidine-4-carboxylate (4-11)**



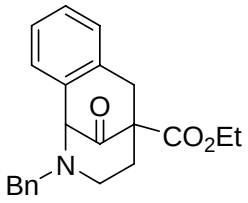

A mixture of potassium *tert*-butoxide (7.5 g, 65.0 mmol) and absolute tetrahydrofuran (150 mL) was stirred at room temperature for 0.5 h. The resulting milky solution was cooled to 0 °C, and then *N*-benzyl-3-oxo-4-piperidine carboxylate hydrochloride[60] (**4-11**) (10.0 g, 33.6 mmol) was added via a powder dropping funnel whereby the temperature was kept below 5 °C. The mixture was then warmed to room temperature and further stirred for 1 h, resulting in a yellow solution. After cooling to 0 °C, a solution of 2-bromobenzyl bromide (8.8 g, 35.2 mmol) in absolute THF (40.0 mL) was added dropwise within 0.5 h. A maximum temperature of 2 °C was observed. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction solution was cooled to 0 °C, before saturated $NH_4Cl$ solution (100 mL) was added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed twice with saturated NaCl solution, dried over $Na_2SO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to yield 7.4 g (50%) of the product **4-11** as a slightly yellow oil. This compound should be used immediately after isolation, or can be kept longer time in inert atmosphere at –20 °C.

**$R_f$** = 0.2 (petroleum ether/ethyl acetate, 10:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.77–1.87 (m, 1H, $CH_2CH_2$), 2.55–2.65 (m, 2H, $CH_2CH_2$), 2.70–2.80 (m, 1H, $CH_2CH_2$), 3.12 (d, *J* = 15.9 Hz, 1H, $ArCH_2$), 3.24 (d, *J* = 15.9 Hz, 1H, $ArCH_2$), 3.31 (d, *J* = 14.1 Hz, 1H, 2-H), 3.51 (d, *J* = 14.1 Hz, 1H, 2-H), 3.57 (s, 2H, $PhCH_2NR_2$), 4.15–4.25 (m, 2H, $CO_2CH_2CH_3$), 7.08–7.15 (m, 1H, ar.), 7.22–7.37 (m, 7H, ar.), 7.57 (d, *J* = 8.1 Hz, 1H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.9 ($CO_2CH_2CH_3$), 30.0, 37.4, 48.7, 58.7, 61.4, 61.5 (6C, sec.), 62.2 (C-4, quat.), 125.9 (quat. ar.), 127.0, 127.3, 128.2, 128.3, 128.8, 132.3, 132.9 (9C tert. ar.), 136.2 (quat. ar.), 137.1 (quat. ar.), 169.8 ($CO_2Et$), 203.9 (C=O);

**Ethyl 2-Benzyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-2-benzazocine-5(2H)-carboxylate (4-12)**




An oven-dried Schlenk tube fitted with a rubber septum was purged with nitrogen and charged with ethyl 1-benzyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (**4-11**) (430 mg, 1 mmol) in 5 mL of anhydrous toluene, $K_3PO_4$ (425 mg, 2 mmol), and $Pd(dba)_2$ (34.5 mg, 6 mol %). Then tube was purged with nitrogen, and *t*$Bu_3P$ (3 mL of 0.04 N in toluene, 12 mol %) was added. The mixture was vigorously stirred in a 110 °C oil bath for 48 h [if starting material is still presented in the reaction mixture, additional amount of $Pd(dba)_2$ (34.5 mg) and *t*$Bu_3P$ (3 mL of 0.04 N in toluene) should be added and heated further, till completion]. The reaction mixture was then cooled to room temperature and filtered through Celite. Then, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 5:1), providing the bicyclic compound **4-12** as a light yellow oil, yield 125 mg (35%).

**$R_f$** = 0.5 (petroleum ether/ethyl acetate, 5:1);

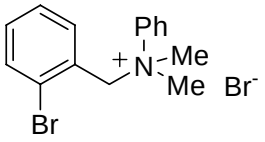
**IR** (film): $\upsilon_{max}$ = 2974, 2831, 1732, 1450, 1227, 737 $cm^{-1}$;

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.98 (ddd, *J* = 13.4, 3.0, 1.8 Hz, 1H, 3-H), 2.49 (ddd, *J* = 12.8, 3.1, 1H, 4-H), 2.61 (ddd, *J* = 12.5, 5.5, 1.8, 1H, 4-H), 2.87 (dddd, *J* = 13.2, 5.5, 1.8 Hz, 1H, 3-H), 3.27 (d, *J* = 17.6 Hz, 1H, 6-H), 3.42 (d, *J* = 13.4 Hz, 1H, $PhCH_2NR_2$), 3.69 (d, *J* = 13.4 Hz, 1H, $PhCH_2NR_2$), 4.07 (d, *J* = 17.6 Hz, 1H, 6-H), 4.08 (s, 1H, 1-H), 4.29 (dd, *J* = 14.4, 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.98 (d, *J* = 7.6 Hz, 1H, ar.), 7.21–7.28 (m, 3H, ar.), 7.30–7.38 (m, 5H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.2 ($CO_2CH_2CH_3$), 37.3 (C-2, sec.), 40.2 (C-6, sec.), 42.8 (C-4, sec.), 57.1 (C-5, quat.), 57.7 ($PhCH_2NR_2$), 61.7 ($CO_2CH_2CH_3$), 67.9 (C-1, tert.), 126.2, 127.1, 127.3, 128.5, 128.6, 128.7 (8C tert. ar.), 129.9 (quat. ar.), 130.4 (tert. ar.), 136.4 (quat. ar.), 137.8 (quat. ar.), 171.2 ($CO_2Et$), 205.0 (C=O);

**HRMS** (ESI): calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1751, found 350.1749.

### *ortho*-Bromobenzyldimethylanilinium bromide (4-19a)

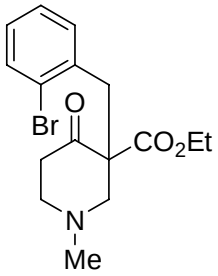



This compound was prepared by a modified literature procedure.[62] N,N-Dimethylaniline (12.2 g, 0.1 mol) and *ortho*-bromobenzyl bromide **4-3a** (25.0 g, 0.1 mol) were mixed and diluted with benzene (100 mL). The resulting solution was stirred at room temperature for 48 h, and then evaporated to dryness. The solids were treated with a 1:1 mixture of petroleum ether/diethyl ether and the slurry was heated before it was filtered. The yield was quantitive. The salt **4-19a** should be kept under nitrogen atmosphere.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.93 (s, 6H), 5.52 (s, 2H), 7.14–7.24 (m, 2H), 7.40–7.54 (m, 5H), 7.86 (d, *J* = 7.7 Hz, 2H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 53.7, 71.7, 121.5, 127.3, 127.7, 127.9, 130.4, 130.7, 132.4, 133.6, 135.4, 144.6;

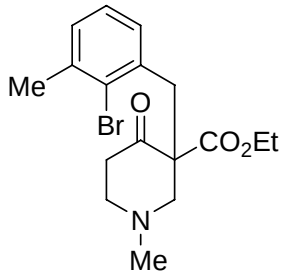
**Ethyl 3-(2-Bromobenzyl)-N-methyl-4-oxopiperidine-3-carboxylate (4-20a)**




To a suspension of NaH (235 mg, 5.85 mmol, 60% in mineral oil) was added ethyl 1-methyl-4-oxopiperidine-3-carboxylate[61] (**4-18**) (1.07 g, 5.8 mmol) in toluene (20 mL). The mixture was then kept at 80 °C for 1 h. Then, powdered *ortho*-bromobenzyldimethylanilinium bromide (**25a**) (2.06 g, 5.55 mmol) was added in one portion to the suspension of the sodium salt at room temperature. This mixture was refluxed for 6 h. After cooling, the mixture was poured carefully into water (30 mL). The organic layer was separated, washed with saturated aqueous NaCl solution (2 × 20 mL), dried with $Na_2SO_4$, filtered, and evaporated to give an oily residue. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give 0.74 g (38%) of **4-20a** as a light yellow oil.

**$R_f$** = 0.25 (petroleum ether/ethyl acetate, 1:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.20 (d, *J* = 11.6 Hz, 1H, 2-H), 2.25–2.32 (m, 4H, N-$CH_3$ and 6-H), 2.42 (ddd, *J* = 14.4, 3.0, 2.0 Hz, 1H, 6-H), 2.84–2.94 (m, 1H, 5-H), 2.97–3.04 (m, 1H, 5-H), 3.17 (d, *J* = 14.4 Hz, 1H, *o*-BrPh$CH_2$), 3.43 (dd, *J* = 11.6, 3.0 Hz, 1H, 2-H), 3.47 (d, *J* = 14.4 Hz, 1H, *o*-BrPh$CH_2$), 4.08–4.17 (m, 2H, $CO_2CH_2CH_3$), 7.03–7.09 (m, 1H, ar.), 7.17–7.20 (m, 2H, ar.), 7.51 (d, *J* = 7.9 Hz, 1H, ar.);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 36.0, 40.5 (2C sec.), 45.6 (N-$CH_3$), 55.8, 61.6 (2C sec.), 62.9 (C-3 quat.), 125.9 (quat. ar.), 127.1 (4C tert. ar.), 128.4, 132.2, 132.9 (4C tert. ar.), 136.1 (quat. ar.), 170.3 ($CO_2$Et), 204.9 (C=O);
**HRMS** (ESI): calcd for $C_{16}H_{21}BrNO_3$ $[M+H]^+$: 354.0699, found 354.0701.

**Ethyl 3-(2-Bromo-3-methylbenzyl)-N-methyl-4-oxopiperidine-3-carboxylate (4-20b)**




The alkylation was performed as described for **4-20a**. For this reaction 1.07 g (5.8 mmol) of **26** and 2.22 g (5.7 mmol) of the anilinium salt **4-19b** were used. The product was isolated by flash chromatography (petroleum ether/diethyl ether, 1:1); yield 0.73 g (35%) as a slightly yellow oil.

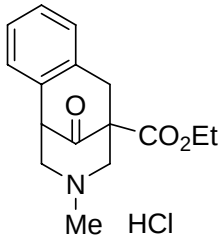
$\mathbf{R_f}$ = 0.2 (petroleum ether/diethyl ether, 1:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.20 (d, *J* = 11.6 Hz, 1H, 2-H), 2.25–2.32 (m, 4H, N-$CH_3$ and 6-H), 2.37–2.45 (m, 4H, $CH_3$Ar and 6-H), 2.84–2.94 (m, 1H, 5-H), 2.96–3.04 (m, 1H, 5-H), 3.22 (d, *J* = 14.4 Hz, 1H, Ar$CH_2$), 3.43 (dd, *J* = 11.6, 2.8 Hz, 1H, 2-H), 3.53 (d, *J* = 14.4 Hz, 1H, Ar$CH_2$), 4.06–4.19 (m, 2H, $CO_2CH_2CH_3$), 6.96–7.00 (m, 1H, ar.), 7.05–7.10 (m, 2H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 13.8 ($CO_2CH_2CH_3$), 24.6 ($CH_3$Ar), 36.7, 40.6 (2C sec.), 45.6 (N-$CH_3$), 55.8, 61.5 (2C sec.), 61.6 (C-3 quat.), 62.9 (sec.), 126.4 (tert. ar.), 128.6 (quat. ar.), 129.3, 129.5 (2C tert. ar.), 136.5, 138.6 (2C quat. ar.), 170.4 ($CO_2$Et), 204.9 (C=O);

**HRMS** (ESI): calcd for $C_{17}H_{23}BrNO_3$ $[M+H]^+$: 368.0856, found 368.0857.

**Ethyl N-Methyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)-carboxylate Hydrochloride (4-21a)**




An oven-dried Schlenk tube fitted with a rubber septum was purged with argon and charged with ethyl 1-methyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (**4-20a**) (745 mg, 2.16 mmol) in 10 mL of anhydrous toluene, $K_3PO_4$ (1.3 g, 6.1 mmol), and $Pd(dba)_2$ (50 mg, 4 mol. %). Then tube was purged with nitrogen, and $t$Bu$_3$P (4 mL of a 0.04 N solution in toluene, 8 mol%) was added. The mixture was vigorously stirred in a 120 °C oil bath for 72 h. The reaction mixture was then cooled to room temperature, diluted with ether (10 mL), and filtered through celite. The filtrate was concentrated under reduced pressure. The crude material was then treated with a concentrated ethanol solution of HCl (1 mL), and subsequently the solvent was evaporated. The residue was dissolved in water (5 mL), and the solution washed with diethyl ether (10 mL) and $CH_2Cl_2$ (10 mL). The aqueous solution was evaporated, and the residue dried in vacuo to give 206 mg (35%) of the salt **4-21a** as a yellow oily solid.

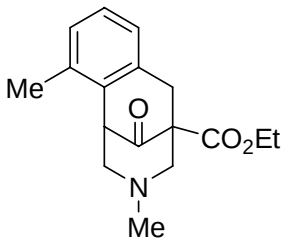
**IR** (film): $\upsilon_{max}$ = 3378 (br), 2819, 2673, 1720, 14589, 1281, 1084, 768 cm$^{-1}$;

**$^1$H NMR** (400 MHz, $CDCl_3$), free base: δ = 1.31 (t, $J$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.25 (s, 3H, N-$CH_3$), 2.67 (dd, $J$ = 10.6, 2.8, 1H, 2-H), 2.99 (ddd, $J$ = 10.6, 2.5 Hz, 1H, 2-H), 3.02 (d, $J$ = 11.2 Hz, 1H, 4-H), 3.15 (dd, $J$ = 11.2, 2.8, 1H, 4-H), 3.39 (dd, $J$ = 2.5 Hz, 1H, 1-H), 3.52 (d, $J$ = 17.45 Hz, 1H, 6-H), 4.02 (d, $J$ = 17.4 Hz, 1H, 6-H), 4.27 (dd, $J$ = 14.4, 7.1 Hz, $CO_2CH_2CH_3$), 6.97 (d, $J$ = 7.6 Hz, 1H, ar.), 7.12–7.25 (m, 3H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 41.0 (sec.), 45.0 (N-$CH_3$), 52.5 (sec.), 58.6 (C-5 quat.), 61.6, 64.7, 66.6 (3C sec.), 126.3, 126.6, 127.2, 127.5 (4C tert. ar.), 135.8, 137.3 (2C quat. ar.), 170.3 ($CO_2$Et), 207.5 (C=O);

**HRMS** (ESI): calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1432; methanol adduct (hemiacetal) calcd for $C_{17}H_{24}NO_4$ $[M+CH_3OH+H]^+$: 306.1700, found 306.1699.

**Ethyl N,10-Dimethyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)-carboxylate (4-21b)**



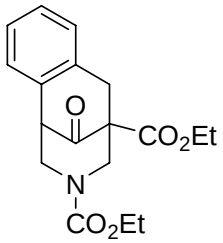

The cyclization was performed as described for **4-21a** using 147 mg (0.4 mmol) of **4-20b**. The cyclized product **4-21b** was isolated by flash chromatography (petroleum ether/ethyl acetate, 20:1), yield 41 mg (36%).

**$R_f$** = 0.15 (petroleum ether/ethyl acetate, 20:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.23 (s, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 2.63 (dd, *J* = 10.6, 2.8 Hz, 1H, 2-H), 2.99 (ddd, *J* = 10.6, 2.5 Hz, 1H, 2-H), 3.02 (d, *J* = 11.2 Hz, 1H, 4-H), 3.14 (dd, *J* = 11.2, 2.8 Hz, 1H, 4-H), 3.49 (d, *J* = 17.3 Hz, 1H. 6-H), 3.60 (dd, *J* = 2.5 Hz, 1H, 1-H), 4.01 (d, *J* = 17.3 Hz, 1H, 6-H), 4.23–4.30 (m, 2H, $CO_2CH_2CH_3$), 6.98–7.03 (m, 2H, ar.), 7.09–7.13 (m, 1H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 18.5 ($CH_3$Ar), 41.0 (sec.), 45.1 (N-$CH_3$), 48.7 (C-1 tert.), 58.5 (C-5 quat.), 61.5, 62.4, 66.3 (3C sec.), 124.6, 126.8, 128.0, 134.7, 135.3, 135.7 (6C ar.), 170.4 ($CO_2$Et), 208.1 (C=O).

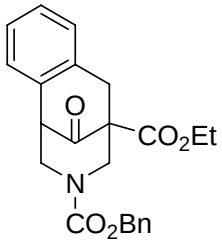
**Diethyl 11-Oxo-1,6-dihydro-1,5-methano-3-benzazocine-3,5(2H)-dicarboxylate (4-23a)**




The N-benzyl-protected substrate **4-5a** (225 mg, 0.64 mmol) was mixed with ethyloxycarbonyl chloride (5 mL) and the mixture was heated at 60 °C for 3 days. Then, the excess of ethylchloroformate was removed by distillation in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 5:1) of the residue gave the product **4-23a** (135 mg, 64%) as an oil. Conversion of starting material was around 75%. According to the NMR data **4-23a** is a mixture of rotamers.

**$R_f$** = 0.1-0.2 (petroleum ether/ethyl acetate, 5:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.1 Hz, 2H); 1.13 (t, *J* = 7.1 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 3.30–3.47 (m, 1.3H), 3.51–3.77 (m, 4H), 3.87–4.05 (m, 1.6H), 4.22-4.32 (m, 2.6H), 4.37–4.60 (m, 0.5H), 4.79 (dd, *J* = 13.6, 3.3 Hz, 0.6H), 7.00–7.13 (m, 2H), 7.14–7.23 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1, 39.0, 52.5, 53.2, 53.9, 59.7, 61.6, 61.8, 126.8, 127.3, 127.7, 128.2, 134.4, 134.8, 155.8, 169.3, 205.3;
**HRMS** (ESI): calcd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1493, found 332.1491.

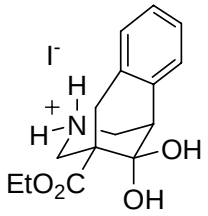
**3-Benzyl 5-Ethyl 11-Oxo-1,6-dihydro-1,5-methano-3-benzazocine-3,5(2H)-dicarboxylate (4-23b)**




The N-benzyl compound **4-5a** (1.0 g, 2.8 mmol) was mixed with benzyloxycarbonyl chloride (5 mL). The resulting mixture was then heated at 80 °C until the reaction was finished (up to 7 days). During this time, every day, additional Cbz chloride (1 mL) was added. The progress of this reaction was followed by LC-MS. After completion, the liquid part was removed by distillation in vacuo at 80 °C. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1), yield 0.78 g (70%) of **4-23b** as a colorless oil. According to the NMR data **4-23b** is a mixture of rotamers.

**$R_f$** = 0.1–0.2 (petroleum ether/ethyl acetate, 5:1);
**IR** (film): $\upsilon_{max}$ = 3440, 2931, 1713, 1443, 1227, 748 $cm^{-1}$;
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.27–1.35 (m, 3H); 3.28–3.46 (m, 1.5H), 3.52–3.59 (m, 1.5H), 3.63–3.77 (m, 1H), 3.90–4.03 (m, 1H), 4.22–4.32 (m, 2.5H), 4.39–4.62 (m, 1.5H), 4.72–4.98 (m, 2H), 6.85–7.02 (m, 2H), 7.03–7.36 (m, 7H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1, 39.0, 39.2, 52.4, 52.4, 53.2, 53.9, 54.1, 59.1, 59.6, 61.9, 67.5, 67.6, 126.8, 126.9, 127.2, 127.4, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 128.4, 128.5, 133.5, 134.3, 134.6, 134.8, 135.8, 136.0, 154.9, 155.6, 169.2, 169.3, 205.2;
**HRMS** (ESI): calcd for $C_{23}H_{24}NO_5$ $[M+H]^+$: 394.1649, found 394.1651.

**Ethyl 11-Oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2H)- carboxylate Hydroiodide Hydrate (4-22)**




A solution of the Cbz-protected compound **4-23b** (350 mg, 0.9 mmol) in $CH_3CN$ (35 mL) was placed in a room temperature water bath and treated with $Me_3SiI$ (1 mL, 7.3 mmol) in a dropwise fashion. The mixture was allowed to stir for 1 h, before the $CH_3CN$ was evaporated in vacuo [longer reaction time (up to 24 h) causes complete decomposition of the product and therefore stirring of the reaction mixture longer than 1 h should be avoided]. The residue was treated with water (35 mL) and this solution was washed with $CH_2Cl_2$. The aqueous phase was then evaporated to dryness resulting in yellow crystals of pure product **4-22**, yield 290 mg (80%).

**m. p.** 170–172 °C;

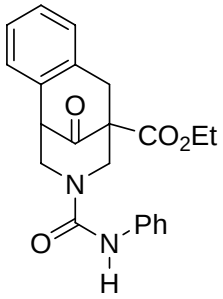
**IR** (KBr): $\upsilon_{max}$ = 3903, 3325, 2924, 2816, 1724, 1458, 1238, 1053, 771 $cm^{-1}$;

**$^1$H NMR** (400 MHz, DMSO-$d_6$): δ = 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.04 (d, *J* = 17.7 Hz, 1H, 6-H), 3.08–3.15 (m, 3H), 3.30–3.53 (m, 3H), 3.64 (d, *J* = 17.7 Hz, 1H, 6-H), 4.13–4.25 (m, 2H, $CO_2CH_2CH_3$), 7.17–7.30 (m, 4H, ar.), 7.30–7.50 (m, 1H), 9.19 (br.s, 1H);

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$): δ = 13.9 ($CO_2CH_2CH_3$), 35.6, 44.2, 47.0, 48.3, 48.5 (5C aliph.), 61.4 ($CO_2CH_2CH_3$), 91.5 ($C(OH)_2$), 126.3, 127.0, 127.9, 129.1 (4C tert. ar.), 134.3, 134.7 (2C quat. ar.), 171.0 ($CO_2Et$);

**HRMS** (ESI): calcd for $C_{15}H_{18}NO_3$ $[M]^+$: 260.1281, found 260.1286; methanol adduct (hemiacetal) calcd for $C_{16}H_{22}NO_4$ $[M+CH_3OH]^+$: 292.1543, found 292.1543.

**Ethyl N-(Anilinocarbonyl)-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3- benzazocine-5(2H)-carboxylate (4-24)**




To a solution of the salt **4-22** (45 mg, 0.11 mmol) in acetonitrile (15 mL) was added $Et_3N$ (25 μL, 0.18 mmol) and the mixture stirred for 1 h. Then, phenylisocyanate (20 μL, 0.18 mmol) was added and stirring was continued for 24 h at room temperature. The solvent was evaporated and the residue treated with hot $CCl_4$. Non-soluble material, which mainly consists of triethylammonium salt, was removed by filtration and the filtrate concentrated in vacuo. The urea derivative **4-24** was obtained as a light yellow powder, yield 35 mg (84%).

**m. p.** 199–203 °C;

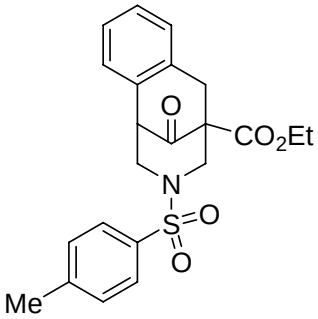
**IR** (KBr): $\upsilon_{max}$ = 3348, 2920, 1743, 1635, 1535, 1446, 1234, 1026, 752 $cm^{-1}$;

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.52 (d, *J* = 17.8 Hz, 1H, 6-H), 3.62–3.69 (m, 3H), 3.93–4.03 (m, 2H, 6-H and 4-H), 4.23–4.33 (m, 2H, $CO_2CH_2CH_3$), 4.88 (dd, *J* = 13.6, 3.0 Hz, 1H, 4-H), 5.47 (br. s, 1H, N*H*Ph), 6.75 (d, *J* = 7.8 Hz, 2H, ar.), 6.91–6.97 (m, 1H, ar.), 7.08–7.17 (m, 4H, ar.), 7.22–7.30 (m, 2H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 39.0 (C-6 sec.), 52.4, 53.5, 54.6, 59.8, 62.0 (5C aliph.), 120.5, 123.4, 127.3, 127.4, 128.1, 128.5, 128.7 (9C tert. ar.), 134.9, 135.1, 138.1 (3C quat. ar.), 155.1 ($R_2NC(=O)NHPh$), 169.2 ($CO_2Et$), 204.6 (C=O);

**HRMS** (ESI): calcd for $C_{22}H_{23}N_2O_4$ $[M+H]^+$: 379.1652, found 379.1656; $[M+Na]^+$: 401.1472, found 401.1475.

**Ethyl 11-Oxo-N-tosyl-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine- 5(2H)-carboxylate (4-25)**




To a solution of the salt **4-22** (48 mg, 0.12 mmol) in acetonitrile (15 mL) was added $Et_3N$ (25 μL, 0.18) and the mixture stirred for 1 h. Then, tosyl chloride (35 mg, 0.18 mmol) was added and stirring was continued for additional 24 h at room temperature. Then, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 3:1), providing the tosylate **4-25** as a light yellow oil, yield 42 mg (80%). This compound contains some hydrate.

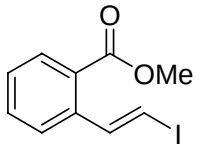
**$R_f$** = 0.1 and 0.3 (petroleum ether/ethyl acetate, 3:1, both spots are the product, compound is in equilibrium with adduct of water addition to the ketone);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.29 (m, 3H, $CO_2CH_2CH_3$), 2.40 (s, 3H, *p*-$CH_3PhSO_2N$), 3.12 (dd, *J* = 11.6, 2.5 Hz, 1H, 4-H), 3.40 (d, *J* = 12.1 Hz, 1H, 4-H), 3.46 (d, *J* = 17.6 Hz, 1H, 6-H), 3.51 (dd, *J* = 2.5 Hz, 1H, 1-H), 3.93 (ddd, *J* = 11.6, 2.8 Hz, 1H, 4-H), 4.03 (d, *J* = 17.6 Hz, 1H, 6-H), 4.13 (dd, *J* = 12.1, 3.3 Hz, 1H, 4-H), 4.26 (dd, *J* = 14.2, 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.95 (d, *J* = 7.6 Hz, 1H, ar.), 7.11 (d, *J* = 7.6 Hz, 1H, ar.), 7.10–7.26 (m, 4H, ar.), 7.46 (d, *J* = 8.3 Hz, 2H, ar.);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 21.5 (*p*-$CH_3PhSO_2N$), 34.0 (C-6 sec.), 51.3, 54.9, 55.9 (3C aliph.), 58.1 (quat.), 62.1 (sec.), 127.1, 127.2, 127.2, 127.9, 128.0, 129.8 (8C tert. ar.), 134.2, 134.7, 134.8, 143.9 (4C quat. ar.), 169.0 ($CO_2Et$), 205.2 (C=O);

**HRMS** (ESI): calcd for $C_{22}H_{24}NO_5S$ $[M+H]^+$: 414.1370, found 414.1366; $C_{22}H_{23}NNaO_5S$ $[M+Na]^+$: 436.1174, found 436.1174.

**Methyl 2-[(*E*)-2-iodovinyl]benzoate (8-3)**




**a) Methyl 2-formylbenzoate (8-17)**:[156] To a stirred solution of 2-formylbenzoic acid (10.0 g, 66.7 mmol) in $CH_3CN$ (100 mL) was added $K_2CO_3$ (55.5 g, 402.2 mmol), followed by MeI (12.5 mL, 28.5 g, 202.1 mmol) and the resulted mixture was refluxed for 24 h. Then solids were filtered and washed twice with $CH_3CN$ (50 mL). Concentration of the filtrate at reduced pressure and vacuum distillation of the residue provided the formyl benzoate (7.6 g, 70%) as a colorless liquid.

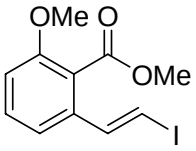
**b. p.** 73–74 °C (0.4 mbar).

**b) Methyl 2-[(*E*)-2-iodovinyl]benzoate (8-3)**: A mixture of anhydrous $CrCl_3$ (23.3 g, 147.0 mmol), freshly activated Zn (8.0 g, 125.0 mmol), and anhydrous NaI (18.4 g, 123.0 mmol) was placed under vacuum and heated to 100 °C for 2-3 min.[157] The solid mixture was stirred for 10 min under vacuum and then the flask was flushed with nitrogen. To the resulted mixture was added abs. THF (300 mL) whereby the color turned immediately to green, which was an indication of the formation of $CrCl_2$. In a separate flask a solution of iodoform (14.4 g, 36.5 mmol) in abs. THF (50 mL) was combined with 2-(carbmethoxy)-benzaldehyde (4.01 g, 24.5 mmol) via a syringe. This solution was transferred via a cannula into the first Schlenk tube. The reaction mixture became brown and was stirred at RT for 4 h. It was then worked up by adding a solution of 1 N HCl (100 mL) and a spatula of EDTA·$Na_2$. The mixture was extracted with $Et_2O$ after being stirred for 30 min at RT. The organic layer was separated, washed with a satd. aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yellow-brown residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) affording 4.3 g (61%) of methyl 2-[(*E*)-2-iodovinyl]benzoate as a 5:1 mixture of *cis* and *trans* isomers.

**$R_f$** = 0.5 (petroleum ether/ethyl acetate, 10:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 6.72 (d, *J* = 14.6 Hz, 1H), 7.33–7.38 (m, 1H), 7.41–7.43 (m, 1H), 7.46–7.51 (m, 1H), 7.90 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.22 (d, *J* = 14.6 Hz, 1H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 52.2, 79.0, 127.5, 128.0, 128.1, 130.6, 132.4, 139.3, 144.1, 167.2.

**Methyl 2-[(*E*)-2-iodovinyl]-6-methoxybenzoate (8-22)**




**a) *N*,*N*-Diethyl-2-methoxybenzamide (8-19)**: To a stirred suspension of the 2-methoxybenzoic acid (3.7 g, 24.2 mmol) in 25 mL of dry benzene was added $(COCl)_2$ (5.3 mL, 60.4 mmol) dropwise over 5 min. The resulting mixture was allowed to stir for 30 min and then the excess of the oxalyl chloride and the solvent were removed at reduced pressure. The solid residue was redissolved in benzene and $Et_2NH$ (3.8 mL, 36.5 mmol) was added dropwise at 0 °C and stirred for additional 3 h. The resulting mixture was diluted with ethyl acetate and washed with 1 N aq. HCl (3 × 20 mL). The organic phase was additionally washed with water, saturated NaCl solution, and dried over anhydrous $MgSO_4$. After that, solvent was remover in vacuo and product was purified via flash chromatography on silica gel affording *N*,*N*-diethyl-2-methoxybenzamide in nearly quantitative yield (5.0 g).

**$R_f$** = 0.22 (petroleum ether/ethyl acetate, 1:1).

**b) *N*,*N*-diethyl-2-formyl-6-methoxybenzamide (8-20)**: To a mixture of the amide from above (**8-19**) (5.0 g, 24.2 mmol) and TMEDA (4.7 mL, 31.2 mmol) in abs. THF and under inert atmosphere at –78 °C, very slowly was added *s*-BuLi (23.0 mL, 30 mmol, 1.3 M in hexane) in a dropwise fashion. The resulting yellow-orange solution was stirred at the same temperature for about 30 min and then at –90 °C DMF (9.3 mL, 120 mmol) was added from a syringe in one portion to this reaction mixture. The resulting reaction mixture was allowed to

stir at –78 °C for about 45 minutes after which it was gradually allowed to come to room temperature and stirred for another one hour. This was followed by the addition of saturated $NH_4Cl$ (50 mL). This mixture was poured into a separating funnel and organic layer was separated. After washing with water (50 mL) and saturated NaCl it was dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure and flash chromatography of the resulting crude product (petroleum ether/ethyl acetate) provided the aldehyde **8-20** as a colorless oil, yield 5.5 g (97%).

**$R_f$** = 0.23 (petroleum ether/ethyl acetate, 1:1).

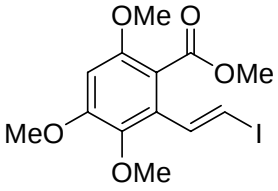
**c) Methyl 2-formyl-6-methoxybenzoate (8-21)**: To a stirred solution of the formilated amide **8-20** (5.6 g, 23.8 mmol) in glacial AcOH (50 mL) was added conc. HCl (50 mL). The resulting solution was warmed to 90 °C and stirred overnight. The solution was concentrated to dryness under reduced pressure and the solid residue was dissolved in $CH_3CN$ (50 mL). To the resulting solution was added anhydrous $K_2CO_3$ (30 g) portionwise, followed by treatment with MeI (7.5 mL, 120 mmol). The reaction mixture was then refluxed for 24 h, after which time solids were filtered and washed twice with $CH_3CN$ (50 mL). Concentration of the filtrate at reduced pressure and flash chromatography of the crude mixture gave the formyl benzoate **8-21** (4.49 g, 93%) as a colorless solid.

**$R_f$** = 0.55 (petroleum ether/ethyl acetate).

**d) Methyl 2-[(*E*)-2-iodovinyl]-6-methoxybenzoate (8-22)**: The reaction was performed with the formyl benzoate **8-21** (2.0 g, 10.3 mmol) as described for **8-3**. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 5:1) gave the iodoalkene **8-22** (2.6 g, 79%, *E*/*Z* = 7:1), yellow solid.

**$R_f$** = 0.4 (petroleum ether/ethyl acetate, 5:1);
**m.p.** 89–92 °C.

**Methyl 2-[(*E*)-2-iodovinyl]-3,4,6-trimethoxybenzoate (8-27)**




**a) *N*,*N*-diethyl-2,4,5-trimethoxybenzamide (8-24)**: To a stirred suspension of the 2,4,5-trimethoxybenzoic acid (2.2 g, 10.5 mmol) in 25 mL of dry benzene was added $(COCl)_2$ (2.3 mL, 26.2 mmol) dropwise over 5 min. The resulting mixture was allowed to stir for 30 min and then the excess of the oxalyl chloride and the solvent were removed at reduced pressure. The solid residue was redissolved in benzene and $Et_2NH$ (1.65 mL, 15.8 mmol) was added dropwise at 0 °C and stirred for additional 3 h. The resulting mixture was diluted with ethyl acetate and washed with 1 N aq. HCl (3 × 10 mL). The organic phase was additionally washed with water, saturated NaCl solution, and dried over anhydrous $MgSO_4$. After that, solvent was removed in vacuo and product was purified via flash chromatography on silica gel affording 2.8 g of *N*,*N*-diethyl-2,4,5-trimethoxybenzamide (**8-24**).

**$R_f$** = 0.12 (petroleum ether/ethyl acetate, 1:1);
**m. p.** 72–75 °C;
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 6.6 Hz, 3H, $CH_2CH_3$), 1.20 (t, *J* = 6.6 Hz, 3H, $CH_2CH_3$), 3.10–3.23 (m, 2H, $CH_2CH_3$), 3.39–3.65 (m, 2H, $CH_2CH_3$), 3.77 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 6.48 (s, 1H, 3-H), 6.72 (s, 1H, 6-H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.8 ($CH_2CH_3$), 14.0 ($CH_2CH_3$), 38.9 ($CH_2CH_3$), 42.8 ($CH_2CH_3$), 56.0 ($OCH_3$), 56.6 ($OCH_3$), 97.6 (C-3), 111.2 (C-6), 118.0 (C-1), 143.2 (C-5), 149.6 (C-4), 150.0 (C-2), 168.5 (C=O);
**HRMS** (ESI): calcd. for $C_{14}H_{22}NO_4$ $[M+H]^+$: 268.15433, found 268.15414.

**b) *N*,*N*-diethyl-2-formyl-3,4,6-trimethoxybenzamide (8-25)**: The reaction was performed with the benzamide **8-24** (2.8 g, 10.5 mmol) as described for **8-20**. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:9) gave the formylated benzamide **8-25** (1.98 g, 64%), colorless solid.

**$R_f$** = 0.33 (petroleum ether/ethyl acetate, 1:9);

**m. p.** 90–94 °C;

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H, $CH_2CH_3$), 1.23 (t, *J* = 7.3 Hz, 3H, $CH_2CH_3$), 3.0 (q, *J* = 7.3 Hz, 2H, $CH_2CH_3$), 3.32–3.45 (m, 1H, $CH_2CH_3$), 3.60–3.72 (m, 1H, $CH_2CH_3$), 3.75 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 6.68 (s, 1H, 5-H), 10.30 (s, 1H, CHO);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 12.1 ($CH_2CH_3$), 13.4 ($CH_2CH_3$), 38.6 ($CH_2CH_3$), 42.5 ($CH_2CH_3$), 56.2 ($OCH_3$), 56.5 ($OCH_3$), 62.5 ($OCH_3$), 102.7 (C-5), 118.1 (C-1), 126.9 (C-2), 146.5 (C-3), 152.0 (C-4), 153.7 (C-6), 166.5 (C=O), 189.6 (CHO);

**HRMS** (ESI): calcd. for $C_{15}H_{21}NO_5$ $[M+Na]^+$: 318.13119, found 318.13125.

**c) Methyl 2-formyl-3,4,6-trimethoxybenzoate (8-26)**: The reaction was performed with the formylated benzamide **8-25** (5.18 g, 17.6 mmol) as described for **8-21**. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:2) gave methyl 2-formyl-3,4,6-trimethoxybenzoate (**8-26**) (3.23 g, 72.5%), colorless solid.

**$R_f$** = 0.55 (petroleum ether/ethyl acetate, 1:2);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.82 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 6.73 (s, 1H, 5-H), 10.33 (s, 1H, CHO);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 52.7 ($OCH_3$), 56.2 ($OCH_3$), 56.7 ($OCH_3$), 62.6 ($OCH_3$), 102.6 (C-5), 113.9 (C-1), 127.4 (C-2), 146.2 (C-3), 153.0 (C-4), 154.6 (C-6), 167.5 ($CO_2Me$), 189.1 (CHO);

**HRMS** (ESI): calcd. for $C_{12}H_{14}NaO_6$ $[M+Na]^+$: 277.06826, found 277.06829

**d) Methyl 2-[(*E*)-2-iodovinyl]-3,4,6-trimethoxybenzoate (8-27)**: The reaction was performed with the formyl benzoate **8-26** (1.7 g, 6.68 mmol) as described for **8-3**. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave the iodoalkene **8-27** (1.66 g, 65.5%, *E*/*Z* = 8:1), yellow solid.

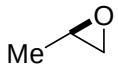
**$R_f$** = 0.57 (petroleum ether/ethyl acetate, 1:1);

**m. p.** 73–76 °C;

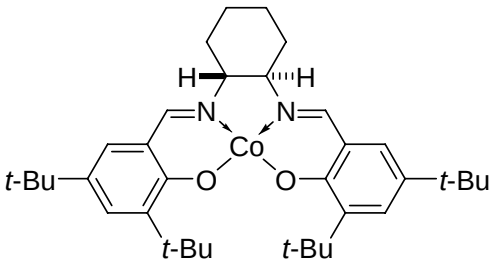
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.70 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 6.46 (s, 1H, 5-H), 6.94 (d, *J* = 14.9 Hz, 1'-H), 7.42 (d, *J* = 14.9 Hz, 2'-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 52.6 ($OCH_3$), 56.1 ($OCH_3$), 56.5 ($OCH_3$), 60.5 ($OCH_3$), 83.2 (C-2'), 96.9 (C-5), 114.6 (C-1), 130.0 (C-2), 138.1 (C-1'), 140.2 (C-6), 153.2 (C-3), 154.3 (C-4), 167.8 (C=O).

**(*2R*)-2-Methyloxirane [(+)-8-28]:**[126]




**a) [(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II)**




A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added dropwise to a solution of ligand [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in $CH_2Cl_2$ (80 mL) via cannula. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at RT and then 30 min at 0 °C. Precipitated solids were then filtrated and rinsed with cold (0 °C) MeOH (2 × 75 mL). The red solid was collected and dried in vacuo to yield [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) (11.6 g, 19.2 mmol, 96%).

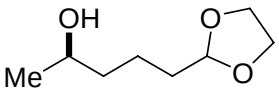
**b) (*2R*)-2-Methyloxirane [(+)-8-28]**:

A flask (100 mL) equipped with a stirring bar was charged with [(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) (242 mg, 400 μmol, 0.002 equiv). The catalyst was dissolved in of toluene (5 mL) and treated with AcOH (240 μL, 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min during which time the color changed from orange-red to dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in racemic propylene oxide (14.0 mL, 11.6 g, 200 mmol) at RT, the reaction flask was cooled to 0 °C, and $H_2O$ (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to RT and stirred 14 h. The desired (*R*)-propylene oxide (5.35 g, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. The ee of the propylene oxide was determined to be >99% by chiral GC analysis.

$[\alpha]^{20}_{D}$ = +11.8 (neat);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 5.3 Hz, 3H, $CH_3$), 2.36 (dd, *J* = 2.8, 5.0 Hz, 1H, $CH_2$), 2.68 (dd, *J* = 4.5, 4.5 Hz, 1H, $CH_2$), 2.89-2.96 (m, 1H, CH).

**(*5R*)-5-Hydroxyhexanal ethandiol acetal (8-30a)**

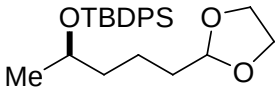



The solution of 2-(2-bromoethyl)-1,3-dioxolane (9.1 g, 6.0 mL, 50 mmol, $d^{20}$ 1.515 g $mL^{-1}$) in anhydrous THF (25 mL) was added dropwise (25-30 min) to a stirred mixture of magnesium turnings (1.5 g, 60 mmol) and anhydrous THF (5 mL) at RT (water bath, inner temperature should not exceed 30 °C). The resulting solution was stirred for further 30 min, and then cooled in an ice bath, followed by the addition of catalytic amounts of CuI (ca. 20 mg, 0.1 mmol). At this temperature, a solution of freshly distilled (*R*)-propylene oxide (5 mL, 4.1 g, 70 mmol) in anhydrous THF (25 mL) was slowly added dropwise within 30-40 min. After complete addition, the reaction mixture was slowly allowed to warm to RT (6 h). Then, the

mixture was treated with saturated $NH_4Cl$ solution (100 mL) and extracted with $Et_2O$ (5 × 50 mL). The combined organic extracts were washed with satd. NaCl solution (100 mL), dried with $MgSO_4$, and filtered. Removal of solvent in vacuum afforded a slightly yellow liquid, which was distilled at low pressure to give the desired (5*R*)-5-hydroxyhexanal ethanediol acetal **8-30a**, yield 4.6 g as a colorless liquid (58%). This acetal was immediately used in the next step.

**b. p.** 72–76 °C at 1 mbar

**(5*R*)-5-(*tert*-Butyldiphenylsilyloxy)hexanal ethandiol acetal (8-31a)**




Freshly distilled (*R*)-5-hydroxyhexanal acetal **8-30a** (4.6 g, 29 mmol) was dissolved in anhydrous DMF (20 mL). To the solution were added at 0 °C imidazole (2.1 g, 30 mmol), DMAP (50 mg), and TBDPS-chloride (8.35 g, 7.9 mL, 34.0 mmol, $d^{20}$ 1.057 g $mL^{-1}$). The resulting mixture was stirred for 12 h and then diluted with ice (ca. 100 g). The product was extracted with $Et_2O$ (3 × 40 mL), the combined organic extracts were washed with satd. NaCl solution (2 × 50 mL), than dried over $MgSO_4$, filtered, and concentrated in vacuo to provide 11.3 g (99%) of acetal **8-31a** as a colorless oil.

**$R_f$** = 0.45 (petroleum ether/EtOAc, 10:1);

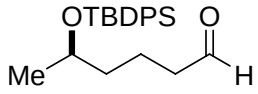
**$[\alpha]^{20}_D$** = +12.0 (*c* 2.0, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (s, 9H, $(CH_3)_3CSi$), 1.06 (d, *J* = 5.1 Hz, 3H, $CH_3CHOSi$), 1.38–1.58 (m, 6H, $(CH_2)_3$), 3.80-3.85 (m, 3H, $OCH_2CH_2O$, $CH_3CHOSi$), 3.90–3.94 (m, 2H, $OCH_2CH_2O$), 4.77 (dd, *J* = 4.8, 4.8 Hz, 1H, $CH_2CHO_2$), 7.32–7.43 (m, 6H, Ph), 7.65–7.70 (m, 4H, Ph);

**$^{13}$C NMR** (100 MHz, $CHCl_3$): δ = 19.2 ($(CH_3)_3CSi$), 19.7 (C-3), 23.1 (C-6), 27.0 ($(CH_3)_3CSi$), 33.9 ($CH_2$), 39.2 (C-4), 64.8 ($CH_2$), 69.4 (C-5), 104.5 ($CHO_2$), 127.4, 127.4, 129.3, 129.4, 134.5, 134.9, 135.8;

**HRMS** (ESI): calcd for $C_{24}H_{35}O_3Si$ $[M+H]^+$: 399.23500, found 399.23498.

### (5*R*)-5-(*tert*-Butyldiphenylsilyloxy)hexanal (8-6)




The acetal **8-31a** (5.0 g, 12.5 mmol) was dissolved in a THF/AcOH mixture (120 mL, 1:2) followed by the addition of water (5 mL). The mixture was refluxed until the starting material was consumed (approximately 30 h). The solvents were evaporated in vacuo and the residue was dissolved in $Et_2O$ (200 mL). The solution was washed with sat. $NaHCO_3$ solution so, that the organic layer is no more acidic. The ether solution was dried over $Na_2SO_4$, filtered, and the solvent evaporated in vacuo. The crude aldehyde was passed through a short pad of silica gel (petroleum ether/EtOAc, 10:1) to give the aldehyde **8-6** (3.6 g, 81%) as a colorless oil.

With PPTS (10% mol) in an acetone/$H_2O$ mixture under reflux the yield after 8 days was ca. 50%; the deprotection was not complete.

**$R_f$** = 0.4 (petroleum ether/EtOAc, 10:1);

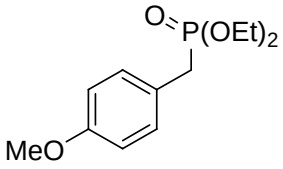
**$[\alpha]^{20}_D$** = +9.5 (*c* 2.3, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (s, 9H, $(CH_3)_3CSi$), 1.07 (d, *J* = 6.1 Hz, 3H, C*H*$_3$CHOSi), 1.36–1.53 (m, 2H, 4-$CH_2$), 1.58-1.67 (m, 2H, C*H*$_2$CH$_2$CHO), 2.27 (ddd, *J* = 1.8, 7.3, 7.3 Hz, 2H, $CH_2$C*H*$_2$CHO), 3.80–3.90 (m, 1H, $CH_3$C*H*OSi), 7.35–7.45 (m, 6H, aromatic TBDPS), 7.65–7.70 (m, 4H, aromatic TBDPS), 9.67 (dd, *J* = 1.8, 1.8 Hz, 1H, C*H*O);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 17.7 (C-3), 19.2 ($(CH_3)_3$*C*Si), 23.1 (C-6), 27.0 ((*C*H$_3$)$_3$CSi), 38.6 (C-4), 43.7 (C-2), 69.0 (C-5), 127.4, 127.5, 129.4, 129.5, 134.3, 134.6, 135.8, 135.9, 202.6 (CHO);

**HRMS** (ESI): calcd for $C_{23}H_{34}NaO_3Si$ $[M+CH_3OH+Na]^+$: 409.21694, found 409.21704.

**Diethyl 4-methoxybenzyl-phosphonate (8-34):**



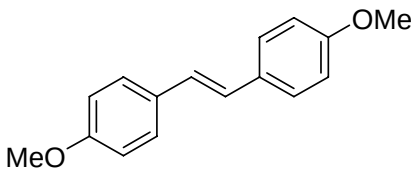

**a) *p*-Methoxybenzyl bromide (8-33)**: Neat *p*-methoxybenzylalcohol (110 mL, 122.4 g, 0.886 mol) was added dropwise to a solution of $PBr_3$ (45 mL, 129.6 g, 0.48 mol) in diethyl ether (500 mL) at RT. After complete addition, stirring was continued for 2 h before the mixture was poured on ice (1 L). The ether layer was separated, washed with satd. $NaHCO_3$ solution, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled under reduced pressure to yield 105 g (89%) of *p*-methoxybenzyl bromide.

**b.p.** 113 °C, 9 mbar [lit.[158] b.p. 77-80 °C (0.8 mm)];
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.81 (s, 3H, $OCH_3$), 4.53 (s, 2H, $CH_2Br$), 6.90 (d, *J* = 8.8 Hz, 2H, aromatic H), 7.35 (d, *J* = 8.8 Hz, 2H, aromatic H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 33.9, 55.0, 113.9, 129.7, 130.2, 159.4.

**b) Diethyl 4-methoxybenzyl-phosphonate (8-34)**: A solution of *p*-methoxybenzylbromide (105.0 g, 0.522 mol) in $P(OEt)_3$ (250 mL) was refluxed for 5 h followed by removal of bromethane and triethylphosphite by distillation at normal pressure.[159] Vacuum distillation of the residue provided 128 g (95%) of product.

**b.p.** 161–165 °C (1 mbar);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.2 Hz, 6H), 3.02 (d, *J* = 21.0 Hz, 2H), 3.71 (s, 3H), 3.90–4.00 (m, 4H), 6.78 (d, *J* = 8.1 Hz, 2H), 7.15 (dd, *J* = 8.1, 2.5 Hz, 2H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 16.2, 32.5 (d, 139.1 Hz), 55.0, 61.9, 113.8, 123.1, 130.6, 158.3.

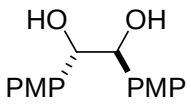
**(*E*)-4,4'-Dimethoxystilbene (8-35)**




To a mechanically stirred solution of diethyl 4-methoxybenzyl-phosphonate (2.59 g, 10 mmol) in DMF (15 mL) was added KO*t*Bu (2.24 g, 20 mmol) portionwise at 0 °C and the solution was stirred for 20 min. Thereafter, freshly distilled *p*-anisaldehyde (2.04 g, 15 mmol), dissolved in DMF (5 mL) was added dropwise to the cooled mixture within 10 min. The solution was allowed to stir for an additional 30 min, then warmed to RT and stirred for 1 h. The reaction was quenched with cold $H_2O$ (50 mL). Crystals were collected by vacuum filtration and washed with cold acetone to give 2.05 g (85%) of the (*E*)-4,4'-dimethoxy-stilbene as a colorless crystalline solid.

**$R_f$** = 0.40 (petroleum ether/EtOAc, 2:1);
**m. p.** 213–215 °C (lit.[127c] **m. p.** 211–214 °C);
**$^1$H NMR** (400 Hz, $CDCl_3$) δ = 3.83 (s, 6 H), 6.87–6.93 (m, 6 H), 7.41–7.44 (m, 4 H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ =: 55.3, 114.1, 126.1, 127.4, 130.4, 159.0.

**(1*S*,2*S*)-1,2-Bis-(4-methoxyphenyl)ethane-1,2-diol (8-36)**

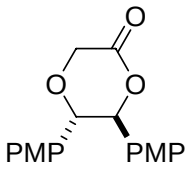



$(DHQ)_2PHAL$ (0.284 g, 0.365 mmol), $K_3Fe(CN)_6$ (36.1 g, 109.4 mmol), $K_2CO_3$ (15.1 g, 109.4 mmol), and $K_2OsO_2(OH)_4$ (0.054 g, 0.146 mmol) were dissolved in a 1:1 mixture of water (182 mL) and *t*-butyl alcohol (182 mL). $MeSO_2NH_2$ (3.47 g, 36.5 mmol) was then added and the vigorously stirred mixture was cooled to 0 °C. At this point stilbene **8-35** (8.75 g, 36.5 mmol) was added in one portion. The resulting mixture was allowed to warm to RT during 3

h, followed by stirring for 30 h. The reaction was quenched with solid $Na_2SO_3$ (55 g) and the solution extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with 2N KOH solution (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by recrystallization from petroleum ether/EtOAc (3:2, 75 mL) provided diol **8-36** (8.4 g, 84%) as a colorless solid.

**$R_f$** = 0.1 (petroleum ether/EtOAc, 2:1);
**$[\alpha]^{20}_D$** = –120 (*c* 1.50, $CH_2Cl_2$); [(*R*,*R*)-isomer using $(DHQD)_2PHAL$: **$[\alpha]^{25}_D$** = +132.4 (*c* 1.50, $CH_2Cl_2$)];
**m. p.** 102–105 °C;
**$^1$H NMR** (400 Hz, $CDCl_3$): δ = 2.90 (br s, 2H, OH), 3.74 (s, 6 H, $OCH_3$), 4.58 (s, 2H, ArC*H*O), 6.71–6.76 (m, 4H), 6.97–7.04 (m, 4 H);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 55.1, 78.7, 113.4, 128.1, 132.0, 159.1.

**(*S*,*S*)-5,6-Bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-7)**




A stirred solution of diol **8-36** (7.09 g, 25.9 mmol), dibutyltin oxide (7.09 g, 28.5 mmol), and benzene (400 mL) was heated to reflux in a flask equipped with a Dean-Stark trap for 24 h. After cooling to RT, tetra *n*-butylammonium iodide (15.3 g, 41.4 mmol) and *tert*-butyl bromoacetate (7.6 mL, 51.8 mmol) were then added and refluxing was continued for 48 h. The mixture was then cooled to RT, diluted with $Et_2O$ (500 mL) and the precipitate was filtered (*n*-$Bu_4NI$ mainly). The filtrate was washed with 10% $Na_2S_2O_3$ solution (500 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (4 × 300 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization of the residue from absolute EtOH (100 mL) provided 4.51 g (55%) of dioxanone **14** as a colorless crystalline solid.

**$R_f$** = 0.14 (petroleum ether/EtOAc, 2:1);

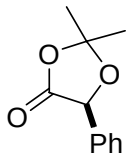
**$[\alpha]^{20}_D$** = –125 (*c* 1.68, $CH_2Cl_2$);

**m.p.** 116–118 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 3.75 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$), 4.52 (d, *J* = 9.4 Hz, 1 H, 5-H), 4.54 (d, *J* = 17.7 Hz, 1H, $CH_2$),4.73 (d, *J* = 17.7 Hz, 1H, $CH_2$), 5.39 (d, *J* = 9.4 Hz, 1 H, 6-H), 6.72–6.78 (m, 4H), 6.92–6.98 (m, 4H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 55.2 ($OCH_3$), 66.2 ($CH_2$), 80.3 (C-5), 86.1 (C-6), 113.7 (2 CH PMP), 113.7 (2 CH PMP), 126.8 (quat C PMP), 127.1 (quat C PMP), 128.5 (2 CH PMP), 128.6 (2 CH PMP), 159.8 (COMe PMP), 159.9 (COMe PMP), 167.2 ($CO_2R$).

**(5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-one (8-51)**




A mixture of (*S*)-mandelic acid (1.0 g, 6.6 mmol) and 2,2-dimethoxypropane (0.97 mL, 0.82 g, 7.9 mmol) was refluxed in benzene (10 mL) with the azeotropic removal of benzene-methanol mixture in a Dean-Stark apparatus for 3 h. The reaction mixture was then cooled down to room temperature and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) on silica gel affording 1.13 g (89%) of the product as a colorless solid.

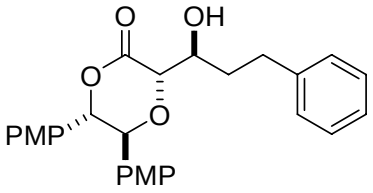
**$R_f$** = 0.7 (hexanes/ethyl acetate, 5:1)

**m. p.** = 71–74 °C

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 1.67 (s, 3H, $CH_3$), 1.73 (s, 3H, $CH_3$) 5.39 (s, 1H, H-5), 7.35–7.50 (m, 5H, aromatic);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 26.2 ($CH_3$), 27.2 ($CH_3$), 75.9 (5-C), 110.9 ($Me_2C$), 126.4 (tert. ar.), 128.7 (tert. ar.), 129.0 (tert. ar.), 134.4 (quat. ar.), 171.4 (C=O).

**(3*S*,5*S*,6*S*)-3-[(1*S*)-3-Phenyl-1-hydroxypropyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-53)**




To a cooled solution (–78 °C) of dioxanone[127] **8-7** (0.233 g, 0.740 mmol) in dry $CH_2Cl_2$ (20 mL) were added in a dropwise fashion $Et_3N$ (0.26 mL, 1.86 mmol) followed by *c*$Hex_2BOTf$[160] (1.85 mL, 1.0 M in abs. hexane) under a nitrogen atmosphere. The resulting solution was stirred at –78 °C for 3 h before freshly distilled 3-phenylpropanal (0.119 g, 0.888 mmol) was added in dry $CH_2Cl_2$ (1 mL) dropwise over 10 min at this temperature. The resulting solution was stirred at –78 °C for 12 h at which time it was quenched by the addition of pH 7 buffer (2.5 mL), MeOH (2 mL) and 30% aqueous $H_2O_2$ (0.5 mL). The solution was vigorously stirred for 1 h and then warmed to room temperature before it was diluted with $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (4 × 50 mL) and the combined organic layers were washed with dilute $NaHCO_3$ solution (30 mL). Drying of the combined organic layers with anhydrous $MgSO_4$ was followed by filtration, and concentration of the filtrate to afford 0.9 g of crude product as a yellow oil, which was used in the next step without further purification. During flash chromatography retro aldol reaction might take place. The selectivity was found to be 10:1 (*anti*/*anti*) via $^1$H NMR and LC-MS of the crude reaction material.

**$R_f$** = 0.27 (petroleum ether/EtOAc, 3:1);

**$[\alpha]^{20}_D$** = –119.5 (*c* 1.0, $CH_2Cl_2$);

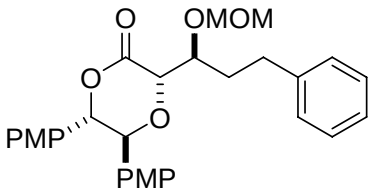
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 1.96–2.06 (m, 1H, $CH_2$), 2.13–2.22 (m, 1H, $CH_2$), 2.74-2.84 (m, 1H, $CH_2$), 2.90–3.00 (m, 1H, $CH_2$), 3.22 (br s, 1H, OH), 3.79 (s, 3H, $CH_3OAr$), 3.80 (s, 3H, $CH_3OAr$), 4.15–4.21 (m, 1H, C*H*OH), 4.5 (d, *J* = 6.0 Hz, 1H, H-3), 4.85 (d, *J* = 9.0 Hz,

1H, H-5), 5.42 (d, *J* = 9.0 Hz, 1H, H-6), 6.77–6.82 (m, 4H, CH, PMP), 6.95–7.02 (m, 4H, CH, PMP), 7.19–7.26 (m, 3H, CH, Ph), 7.29–7.34 (m, 2H, CH, Ph);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 31.4 ($CH_2$), 34.7, 55.2 (2 *C*$H_3$OAr), 71.7 (*C*HOH), 75.7 (C-3), 78.1 (C-5), 84.8 (C-6), 113.7, 125.9, 126.4, 127.7, 128.3, 128.4, 128.5, 128.7 (tert. Ph and PMP), 141.6 (quat. Ph), 159.7, 160.0 (2*C*OMe of PMP), 170.5 (C=O);

**HRMS** (ESI): calcd for $C_{27}H_{28}NaO_6$ $[M+Na]^+$: 503.20402, found 503.20393.

**(3*S*,5*S*,6*S*)-3-[(1*S*)-3-Phenyl-1-(methoxymethoxy)propyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-54)**




To a stirred, cooled (0 °C) solution of crude aldol product (0.9 g) in $CH_2Cl_2$ (90 mL) were added *N*,*N*-diisopropylethylamine (15.4 mL, 11.6 g, 90.0 mmol), chloromethylmethyl ether (3.42 mL, 3.62 g, 45.0 mmol), and tetrabutylammonium iodide (665 mg, 1.80 mmol). The reaction mixture was protected from light and allowed to reach room temperature within 12 h. After stirring for 3 days, saturated aqueous $NaHCO_3$ solution (100 mL) was added followed by $Et_2O$ (150 mL). The organic layer was washed with 1 N HCl (50 mL) and brine (30 ml), and the basic aqueous layer was extracted with $Et_2O$ (2 × 50 ml). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue provided the MOM ether as slightly yellow oil, yield 0.18 g (50%).

**$R_f$** = 0.3 (petroleum ether/EtOAc, 3:1);

**$[\alpha]^{20}_D$** = –68.9 (*c* 0.45, $CH_2Cl_2$);

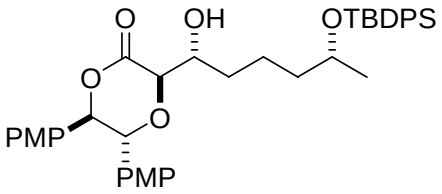
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 2.05–2.21 (m, 2H, $CH_2$), 2.67–2.77 (m, 1H, $CH_2$), 2.78–2.88 (m, 1H, $CH_2$), 3.43 (s, 3H, $OCH_2OCH_3$), 3.74 (s, 3H, C$H_3$OAr), 3.75 (s, 3H, C$H_3$OAr), 4.16–4.23 (m, 1H, 1'-H), 4.79 (dd, *J* = 7.0, 17.0 Hz, 2H, $OCH_2OCH_3$), 4.89 (d, *J* = 3.0 Hz, 1H, 3-

H), 4.95 (d, *J* = 8.5 Hz, 1H, 5-H), 5.40 (d, *J* = 8.5 Hz, 1H, 6-H), 6.72–6.77 (m, 4H, PMP), 6.95–7.02 (m, 4H, PMP), 7.17–7.22 (m, 3H, Ph), 7.25–7.30 (m, 2H, Ph);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 32.1 ($CH_2$), 32.6, 55.1 (2 *C*$H_3$OAr), 56.0 (OCH$_2$O*C*H$_3$), 74.7 (*C*HOMOM), 78.1 (C-3), 80.55 (C-5), 84.6 (C-6), 97.0 (O*C*H$_2$OCH$_3$),113.6, 113.7, 125.9, 127.0, 127.9, 128.3, 128.4, 128.5, 128.6 (tert. Ph and PMP), 141.5 (quat. Ph), 159.7, 159.8 (2 *C*OMe of PMP), 167.9 (C=O);

**HRMS** (ESI): calcd for $C_{30}H_{36}NaO_8$ [M+MeOH+Na]$^+$: 547.23060, found 547.23024.

**(3*R*,5*R*,6*R*)-3-[(1*R*,5R)-5-(*tert*-Butyldiphenylsilyloxy)-1-hydroxyhexyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-55)**




To a cooled (–78 °C) solution of dioxanone *ent*-**8-7** (0.233 g, 0.740 mmol) in dry $CH_2Cl_2$ (20 mL) was added in a dropwise fashion $Et_3N$ (0.26 mL, 1.86 mmol) followed by *c*Hex$_2$BOTf[160] (1.85 mL, 1.0 M in abs. hexane) under a nitrogen atmosphere. The resulting solution was stirred at -78 °C for 3 h at which time (5*R*)-5-(*tert*-butyldiphenylsilyloxy)hexanal (**8-6**) (0.314 g, 0.888 mmol), dissolved in dry $CH_2Cl_2$ (1 mL) was added dropwise over 10 min. The resulting solution was stirred at –78 °C for 12 h before it was quenched at that same temperature by the addition of pH 7 buffer (2.5 mL), MeOH (2 mL) and 30% aqueous $H_2O_2$ (0.5 mL). The mixture was stirred vigorously for 1 h and then warmed to room temperature when it was diluted with $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (4 × 50 mL) and the combined organic layers were washed with dilute $NaHCO_3$ solution (30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 1.0 g of crude product as a yellow oil, which was used for the next step without further purification (approximately half of the product decomposes during flash chromatography on silica gel (petroleum ether/EtOAc, 2:1)). The selectivity was found to be 9:1 (*anti*-1/*anti*-2) according to $^1$H NMR and LC-MS of the crude reaction material.

Data for the purified product:

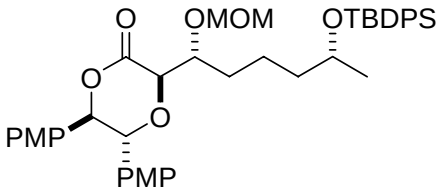
**$R_f$** = 0.48 (petroleum ether/EtOAc, 2:1);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 1.00–1.06 (m, 12H, $(CH_3)_3CSi$, $CH_3CHOSi$), 1.35–1.92 (m, 6H, $(CH_2)_3$), 2.86 (d, *J* = 5.0 Hz, 1H, OH), 3.75 (s, 3H, $CH_3OAr$), 3.76 (s, 3H, $CH_3OAr$), 3.83 (dd, *J* = 6.0, 11.5 Hz, 1H, 5'-H), 4.02–4.08 (m, 1H, CHOH), 4.43 (d, *J* = 5.5 Hz, 1H, 3-H), 4.87 (d, *J* = 9.0 Hz, 1H, 5-H), 5.37 (d, *J* = 9.0 Hz, 1H, 6-H), 6.74 (d, *J* = 8.5 Hz, 2H, CH PMP), 6.76 (d, *J* = 8.5 Hz, 2H, CH PMP), 6.94 (d, *J* = 8.5 Hz, 2H, CH PMP), 6.98 (d, *J* = 8.5 Hz, 2H, CH PMP), 7.30–7.41 (m, 6H, aromatic TBDPS), 7.63–7.68 (m, 4H, aromatic TBDPS);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 19.3 ($(CH_3)_3CSi$), 20.9 (C-3'), 23.1 (C-6'), 27.0 ($(CH_3)_3CSi$), 33.3 (C-2', C-4'), 39.1, 55.2 ($CH_3OAr$), 69.4 (C-5'), 73.0 (CHOH), 76.0 (C-3), 77.9 (C-5), 85.0 (C-6), 113.8, 126.6 (aromatic PMP), 127.4, 127.5 (aromatic TBDPS), 127.9, 128.5, 128.7 (aromatic PMP), 129.4, 129.5 (aromatic TBDPS), 134.6, 134.8 (aromatic TBDPS), 135.8, 135.9 (aromatic TBDPS), 159.7 (COMe), 160.0 (COMe), 170.2 (C=O);

**HRMS** (ESI): calcd for $C_{40}H_{48}NaO_7Si$ $[M+Na]^+$: 723.33236, found 723.33153.

**(3*R*,5*R*,6*R*)-3-[(1*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(methoxymethoxy)hexyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-56)**




To a stirred, cooled (0 °C) solution of crude aldol product **8-55** (1.0 g) in $CH_2Cl_2$ (30 mL) were added *N*,*N*-diisopropylethylamine (5.1 mL, 3.86 g, 30.0 mmol), chloromethylmethyl ether (1.14 mL, 1.20 g, 15.0 mmol), and tetrabutylammonium iodide (222 mg, 0.60 mmol). The reaction mixture was protected from light and allowed to reach room temperature within 12 h. After stirring for 3 days, saturated aqueous $NaHCO_3$ solution (40 mL) was added followed by $Et_2O$ (50 mL). The organic layer was washed with 1 N HCl (150 mL) and brine

(10 mL), and the basic aqueous layer was extracted with $Et_2O$ (2 × 25 mL). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue provided the MOM ether as a slightly yellow oil, yield 0.24 g (45% for two steps from aldehyde).

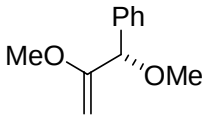
**$R_f$** = 0.18 (petroleum ether/EtOAc, 5:1);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.01–1.06 (m, 12H, $(CH_3)_3CSi$, 6'-H), 1.30–1.40 (m, 1H, $CH_2$), 1.42–1.55 (m, 3H, $CH_2$), 1.65–1.76 (m, 2H, 2'-H), 3.37 (s, 3H, C*H*$_3$OCH$_2$O), 3.75 (s, 3H, $CH_3OAr$), 3.76 (s, 3H, $CH_3OAr$), 3.80–3.88 (m, 1H, 5'-H), 4.04–4.10 (m, 1H, 1-H), 4.73 (dd, *J* = 7.0, 10.0 Hz, 2H, OC*H*$_2$OCH$_3$), 4.77 (d, *J* = 2.5 Hz, 1H, 3-H), 4.98 (d, *J* = 8.5 Hz, 1H, 5-H), 5.39 (d, *J* = 8.5 Hz, 1H, 6-H), 6.74 (d, *J* = 2.0 Hz, 2H, CH PMP), 6.77 (d, *J* = 2.0 Hz, 2H, CH PMP), 6.97 (d, *J* = 3.0 Hz, 2H, CH PMP), 7.00 (d, *J* = 3.0 Hz, 2H, CH PMP), 7.33–7.42 (m, 6H, aromatic TBDPS), 7.65–7.70 (m, 4H, aromatic TBDPS);
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($(CH_3)_3$*C*Si), 21.7 (C-3'), 23.2 (C-6'), 27.0 ((*C*H$_3$)$_3$CSi), 31.0, 39.3 (C-2', C-4'), 55.2 ($CH_3OPh$), 56.0 ($CH_2OCH_3$), 69.4 (C-5'), 74.8 (*C*HOMOM), 78.0 (C-3), 81.1 (C-5), 84.8 (C-6), 96.7 (O*C*H$_2$OCH$_3$), 113.6, 113.7, 127.1 (aromatic of PMP), 127.4, 127.5 (aromatic of TBDPS), 128.0, 128.6, 128.7 (aromatic of PMP), 129.4, 129.5, 134.4 134.8, 135.8 (aromatic of TBDPS), 156.7, 159.8 (2*C*OMe of PMP), 167.8 (C=O);
**HRMS** (ESI): calcd for $C_{42}H_{52}NaO_8Si$ $[M+Na]^+$: 735.33237, found 735.33270.

## General Procedure 1 for Petasis Olefination

To a stirred solution of the substrate (1 equiv, 0.25 M) in dry THF was added the Petasis reagent (3 equiv, solution in toluene (10 % wt)). The resulting orange reaction mixture was warmed to 65 °C and stirred in the dark under an argon atmosphere till more than 90% of the starting material was consumed (as indicated by TLC). The solution was cooled to room temperature and the titanium compounds were precipitated by addition of a large excess of petroleum ether (ca. 50 mL/mmol of substrate). The resulting heterogeneous mixture was poured onto a basic alumina column and eluted quickly. In order to ensure that the entire product was out of the column, the alumina bed was flushed with a petroleum ether/ethyl

acetate (4:1) mixture. The column fractions were pooled together and concentrated. In cases where the stability of the product was good, it was column chromatographed on alumina to obtain the pure compound.

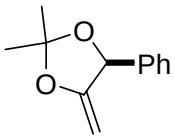
**[(1*S*)-1,2-Dimethoxyprop-2-enyl]benzene (8-57)**




This enol ether was prepared according to general procedure 1, yield 67 mg (56%), colorless oil. This compound was utilized immediately after workup.

**$R_f$** = 0.5 (petroleum ether/ethyl acetate, 9:1);
**$^1$H NMR** ($C_6D_6$, 400 MHz): δ = 3.07 (s, 3H, $OCH_3$), 3.18 (s, 3H, $OCH_3$), 3.97 (d, *J* = 2.0 Hz, 1H, C=C$H_2$), 4.50 (d, *J* = 1.8 Hz, 1H, C=C$H_2$), 4.55 (br s, 1H, PhC*H*), 7.05–7.22 (m, 3H, Ph), 7.53 (d, *J* = 7.3 Hz, 2H, Ph);
**HRMS** (ESI): calcd for $C_{11}H_{14}NaO_2$ $[M+Na]^+$: 201.08860, found 201.08867.

**(5*S*)-2,2-Dimethyl-4-methylene-5-phenyl-1,3-dioxolane (8-58)**

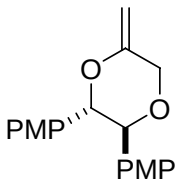



This enol ether was prepared according to general procedure 1. Purification was done by chromatography on $Al_2O_3$ (petroleum ether/ethyl acetate, 18:1), yield 188 mg (92%), slightly yellow oil.

**$R_f$** = 0.5 (petroleum ether/ethyl acetate, 18:1);

**$^1$H NMR** ($C_6D_6$, 400 MHz): δ = 1.32 (s, 3H, $CH_3$), 1.49 (s, 3H, $CH_3$), 3.66 (t, *J* = 1.8 Hz, 1 H, C=$CH_2$), 4.49 (dd like t, *J* = 1.8, 2.3 Hz, 1H, C=$CH_2$), 5.42 (br s, 1H, PhCH), 7.06–7.15 (m, 3H, Ph.), 7.35 (dd, *J* = 8.3, 1.3 Hz, 2H, Ph);
**$^{13}$C NMR** ($C_6D_6$, 100 MHz): δ = 25.0 ($CH_3$ acetonide), 26.7 ($CH_3$ acetonide), 80.0 (*C*HPh), 80.5 (*C*$H_2$=C), 110.9 (*C*($CH_3$)), 128.3, 128.57, 128.64 (tert. ar.), 139.5 (quat. ar.), 160.8 ($CH_2$=*C*).

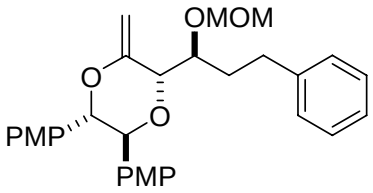
**(2*R*,3*R*)-2,3-Bis(4-methoxyphenyl)-5-methylene-1,4-dioxane (8-59)**




This enol ether was prepared according to general procedure 1, yield 69 mg (68 %), slightly yellow oil. This compound was utilized immediately after workup.

**$R_f$** = 0.3 (petroleum ether/ethyl acetate, 4:1);
**$^1$H NMR** ($C_6D_6$, 400 MHz): δ = 3.17 (s, 3H, C*H*$_3$OAr), 3.18 (s, 3H, C*H*$_3$OAr), 4.19 (s, 1H, C=$CH_2$), 4.24 (d, *J* = 13.1 Hz, 1H, 6-H), 4.28 (d, *J* = 13.1 Hz, 1H, 6-H), 4.48 (d, *J* = 9.3 Hz, 1H, 2-H), 4.69 (s, 1 H, C=$CH_2$), 4.81 (d, *J* = 9.3 Hz, 1H, 3-H), 6.60 (d, *J* = 8.6 Hz, 2H, ar.), 6.62 (d, *J* = 8.6 Hz, 2H, ar.), 6.97 (d, *J* = 8.6 Hz, 2H, ar.), 6.99 (d, *J* = 8.6 Hz, 2H, ar.).

**(3*S*,5*S*,6*S*)-2-Methylidene-3-[(1*S*)-3-phenyl-1-(methoxymethoxy)propyl]-5,6-bis[4-(methyloxy)phenyl]-3-propyl-1,4-dioxane (8-60)**




This enol ether was prepared according to general procedure 1. Purification was done by chromatography on $Al_2O_3$ (petroleum ether/ethyl acetate, 4:1), yield 25 mg (67%), colorless oil.

**$R_f$** = 0.45 (petroleum ether/ethyl acetate, 4:1);

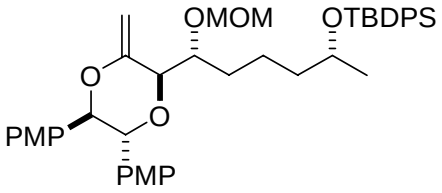
**$[\alpha]^{20}_D$** = –166.3 (*c* 1.12, $CH_2Cl_2$);

**$^1$H NMR** ($C_6D_6$, 400 MHz): δ = 2.00–2.11 (m, 1H, 2'-H), 2.35–2.37 (m, 1H, 2'-H), 2.85–2.99 (m, 2H, 3'-H), 3.18 (s, 6H, C*H*$_3$OAr), 3.33 (s, 3H, OCH$_2$OC*H*$_3$), 4.33 (d, *J* = 9.6 Hz, 1H, 5-H), 4.54 (d, *J* = 9.4 Hz, 1H, 3-H), 4.57 (s, 1H, C=CH$_2$), 4.55–4.62 (m, 1H, 1'-H), 4.64 (d, *J* = 7.1 Hz, 1 H, OC*H*$_2$OCH$_3$), 4.79 (d, *J* = 9.6 Hz, 1H, 6-H), 4.88 (s, 1H, C=CH$_2$), 4.91 (d, *J* = 7.1 Hz, 1H, OC*H*$_2$OCH$_3$), 6.60 (d, *J* = 8.6 Hz, 2H, PMP), 6.62 (d, *J* = 8.6 Hz, 2H, PMP), 6.92 (d, *J* = 8.6 Hz, 2H, PMP), 6.95 (d, *J* = 8.6 Hz, 2H, PMP), 7.02–7.07 (m, 1H, Ph), 7.12–7.16 (m, 2H, Ph), 7.23 (d, *J* = 7.3 Hz, 2H, Ph);

**$^{13}$C NMR** ($C_6D_6$, 100 MHz): δ = 30.9 (C-3'), 33.8 (C-2'), 54.6 (2 ArO*C*H$_3$), 55.6 (OCH$_2$O*C*H$_3$), 74.6 (C-6), 75.5 (C-5), 77.2 (C-1'), 86.0 (C-3), 96.3 (C=*C*H$_2$), 97.6 (O*C*H$_2$OCH$_3$), 113.6 (tert. ar.), 126.0–129.2 (tert. ar.),129.9, 130.0 (quat. PMP), 142.8 (quat. Ph), 156.7 (*C*=CH$_2$), 159.8, 159.9 (2*C*OMe of PMP);

**HRMS** (ESI): calcd for $C_{30}H_{34}NaO_6$ $[M+Na]^+$: 513.22476, found 513.22506.

**(3*R*,5*R*,6*R*)-3-[(1*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(methoxymethoxy)hexyl]-2-methylidene-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-61)**




This enol ether was prepared according to general procedure 1. Purification was done by chromatography on $Al_2O_3$ (petroleum ether/ethyl acetate, 9:1), yield 149 mg (91%), slightly yellow oil.

**$R_f$** = 0.35 (petroleum ether/ethyl acetate, 9:1);

**$[\alpha]^{20}_D$** = +63.8 (*c* 0.8, $CH_2Cl_2$);

**$^1$H NMR** ($C_6D_6$, 400 MHz): δ = 1.06 (d, *J* = 6.1 Hz, 3H, 6'-H), 1.18 (s, 9H, $(CH_3)_3CSi$), 1.43–1.60 (m, 2H, 3'-H, 4'-H), 1.60–1.79 (m, 3H, $CH_2$), 1.84–1.93 (m, 1H, 2'-H), 3.18 (s, 3H, $OCH_3$), 3.19 (s, 3H, $OCH_3$), 3.32 (s, 3H, $CH_2OCH_3$), 3.85–3.95 (m, 1H, 5'-H), 4.36 (d, *J* = 9.3 Hz, 1H, 3-H), 4.59 (m, 1H, 1'-H), 4.60 (s, 1H, C=$CH_2$), 4.68 (d, *J* = 7.0 Hz, 1H, 5-H), 4.84 (dd, *J* = 11.0, 9.5 Hz, 2H, $CH_2OCH_3$), 4.87 (d, *J* = 7.0 Hz, 1H, 6-H), 4.91 (s, 1H, C=$CH_2$), 6.61 (d, *J* = 8.7 Hz, 4H, CH PMP), 6.99 (d, *J* = 8.7 Hz, 2H, CH PMP), 7.02 (d, *J* = 8.7 Hz, 2H, CH PMP), 7.17–7.24 (m, 6H, aromatic), 7.75–7.84 (m, 4H, aromatic);

**$^{13}$C NMR** ($C_6D_6$, 100 MHz): δ = 19.5 ($(CH_3)_3CSi$), 20.3 (C-3'), 23.2 (C-6'), 27.3 ($(CH_3)_3CSi$), 31.9 (C-2'), 40.1 (C-4'), 54.6 (2 $OCH_3$), 55.7 ($CH_2OCH_3$), 70.0 (C-5'), 74.3 (C-6), 75.4 (C-5), 77.7 (C-1'), 86.0 (C-3), 96.3 (C=$CH_2$), 96.9 ($CH_2OCH_3$), 113.7, 127.8, 129.8, 130.0, 130.1, 135.0, 135.2, 136.3, 156.8 (C-2), 159.8, 159.9;

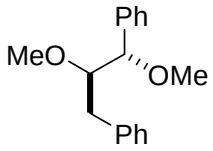
**HRMS** (ESI): calcd for $C_{43}H_{54}NaO_7Si$ $[M+Na]^+$: 733.35310, found 733.35347.

**General procedure 2 for the tandem hydroboration-Suzuki coupling reaction**

A THF solution of the substrate (1 equiv, 0.33 M) in a Schlenk flask was thoroughly degassed by freeze-pump-thaw method. Then 9-BBN (1.2 equiv, 0.5 M solution in THF) was added at 0

°C under an argon atmosphere. The resulting reaction mixture was allowed to stir at room temperature for about 6 hours. Meanwhile, in a separate Schlenk flask, a solution of the halide (or triflate) (1.2 equiv), triphenyl arsine (0.05 equiv), cesium carbonate (2 equiv), water (30 equiv), in DMF (2 mL/ mmol of halide (or triflate)) was degassed by the same method. For the coupling of triflate **21**, KBr (1.2 equiv) was added at this point. This flask was purged with argon and under a continuous flow of argon, $PdCl_2$(dppf) (0.05 equiv) was added. To the resulting red suspension was added the above mixture from the hydroboration reaction. This was then stirred under argon at room temperature for a further 14-16 hours. The reaction was worked up by addition of saturated $NH_4Cl$ solution (15 mL/mmol of substrate). The resulting mixture was poured into a separating funnel and the layers were separated. The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts were washed successively with saturated $Na_2S_2O_3$, water and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and flash column chromatographed on silica, eluting with a petroleum ether/ethyl acetate mixture to afford the pure product.

**[(1*S*,2*R*)-1,2-Dimethoxy-3-phenylpropyl]benzene (8-62)**




The tandem hydroboration/cross coupling reaction to give compound **2** was performed according to general procedure 2, yield 7 mg (35%), colorless oil.

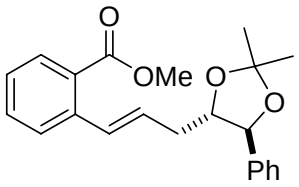
**$R_f$** = 0.5 (petroleum ether/ethyl acetate, 9:1);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.77 (dd, *J* = 14.1, 8.3 Hz, 1H, $CH_2$), 2.94 (dd, *J* = 14.1, 3.3 Hz, 1H, $CH_2$), 2.99 (s, 3H, $OCH_3$), 3.25 (s, 3H, $OCH_3$), 3.45 (ddd, *J* = 8.3, 5.8, 3.3 Hz, 1H, $CH_2CH$(OMe)), 4.08 (d, *J* = 5.8 Hz, 1H, PhC*H*(OMe)), 7.15–7.40 (m, 10H, ar.);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 36.9 ($CH_2$), 56.9 ($OCH_3$), 58.9 ($OCH_3$), 84.8 ($CH_2$*C*H(OMe)), 86.2 (Ph*C*H(OMe)), 125.9, 127.7, 128.1, 129.6 (tert. ar.), 139.3 (quat. ar.);

**HRMS** (ESI): calcd for $C_{17}H_{20}NaO_2$ $[M+Na]^+$: 279.13555, found 279.13550.

**Methyl 2-{(1*E*)-3-[(4*S*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]prop-1-enyl}benzoate (8-64)**




This dioxolane derivative was prepared according to general procedure 2. Compound **6** was obtained as a 6:1 mixture of *E*/*Z* isomers. It is advisable to store it at –20 °C to prevent isomerization of the olefin, yield 22 mg (62%), colorless oil.

**$R_f$** = 0.35 (petroleum ether/ethyl acetate, 9:1);

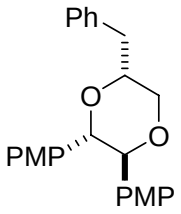
**$[\alpha]^{20}_D$** = –28.6 (*c* 0.8, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 1.52 (s, 3H, $CH_3$), 1.58 (s, 3H, $CH_3$), 2.51–2.68 (m, 2H, $CH_2$), 3.88 (s, 3H, $CO_2CH_3$), 3.90–3.98 (m, 1H, $CH_2CHOR$), 4.68 (d, *J* = 8.3 Hz, 1H, C*H*Ph), 6.09 (td, *J* = 14.2, 7.1 Hz, 1H, CH=C*H*$CH_2$), 7.18–7.43 (m, 9H, ar. and C*H*=$CHCH_2$), 7.84 (d, *J* = 8.6 Hz, 1H, ar.);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 27.1 ($CH_3$), 27.3 ($CH_3$), 34.7 ($CH_2$), 52.0 ($CO_2CH_3$), 82.6 ($CH_2CHOR$), 82.59 (Ph*C*HOR), 108.8 ($CMe_2$), 126.8 (*C*H=$CHCH_2$), 127.0, 127.4 (tert. ar.), 128.2 (CH=*C*H$CH_2$), 128.6, 130.3, 131.2, 132.0 (tert. ar.), 137.6 (quat. ar.), 139.1 (quat. ar.), 167.9 (C=O);

**HRMS** (ESI): calcd for $C_{22}H_{24}NaO_4$ $[M+Na]^+$: 375.15668, found 375.15683.

**(2*S*,3*S*,5*R*)-5-Benzyl-2,3-bis(4-methoxyphenyl)-1,4-dioxane (8-66)**




This dioxane derivative was prepared according to general procedure 2, yield 46 mg (72%), colorless oil.

**$R_f$** = 0.4 (petroleum ether/ethyl acetate, 3:1);

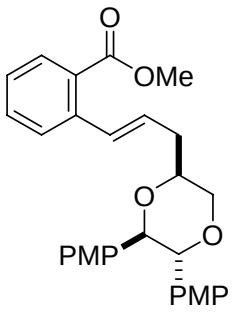
**$[\alpha]^{20}_D$** = –43.4 (*c* 1.0, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.77 (dd, *J* = 14.0, 7.3 Hz, 1H, C*H*$_2$Ph), 3.0 (dd, *J* = 14.0, 5.6 Hz, 1H, C*H*$_2$Ph), 3.59 (dd like t, *J* = 11.4, 10.6 Hz, 1H, 6-H), 3.71 (s, 3H, $CH_3$OAr), 3.73 (s, 3H, $CH_3$OAr), 3.93 (dd, *J* = 11.4, 2.5 Hz, 1H, 6-H), 4.10 (dddd, *J* = 10.6, 7.3, 5.6, 2.5 Hz, 1H, 5-H), 4.22 (d, *J* = 8.8 Hz, 1H, 3-H), 4.41 (d, *J* = 8.8 Hz, 1H, 2-H), 6.68 (d, *J* = 8.6 Hz, 2H, PMP), 6.70 (d, *J* = 8.6 Hz, 2H, PMP), 6.91 (d, *J* = 8.6 Hz, 2H, PMP), 6.94 (d, *J* = 8.6 Hz, 2H, PMP), 7.17–7.32 (m, 5H, aromatic);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 38.6 (*C*$H_2$Ph), 55.1 (2*C*$H_3$OAr), 70.8 (C-6), 76.1 (C-3), 83.3 (C-2), 83.7 (C-5), 113.2 (tert. PMP), 113.3 (tert. PMP), 126.4, 128.4, 128.6, 129.3 (tert. ar.), 130.1 (quat. PMP), 130.4 (quat. PMP), 137.4 (quat Ph), 159.0 (*C*OMe PMP);

**HRMS** (ESI): calcd for $C_{25}H_{26}NaO_4$ $[M+Na]^+$: 413.17233, found 413.17241.

**Methyl 2-{(1*E*)-3-[(2*S*,5*R*,6*R*)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-yl]prop-1-enyl}benzoate (8-67)**




This dioxane derivative was prepared according to general procedure 2, yield 89 mg (87%), colorless foam. This compound was obtained as a 9:1 mixture of *E*/*Z* isomers. It is advisable to store this compound at -20 °C in order to avoid isomerization of the olefin.

**$R_f$** = 0.4 (petroleum ether/ethyl acetate, 9:1);

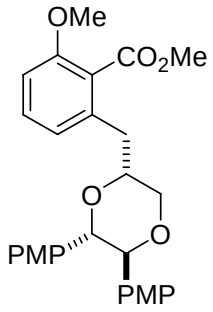
**$[\alpha]^{20}_D$** = +55.7 (*c* 1.4, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.36–2.46 (m, 1H, 3'-H), 2.46–2.56 (m, 1H, 3'-H), 3.59 (dd like t, *J* = 11.3, 10.6 Hz, 1H, 3''-H), 3.64 (s, 6H, $2CH_3OAr$), 3.79 (s, 3H, $CO_2CH_3$), 3.90–3.98 (m, 1H, 2''-H), 4.00 (dd, *J* = 11.3, 2.3 Hz, 3''-H), 4.19 (d, *J* = 9.0 Hz, 1H, 6''-H), 4.36 (d, *J* = 9.0 Hz, 1H, 5''-H), 6.11 (ddd, *J* = 14.2 Hz, 7.3, 7.0 Hz, 1H, 2'-H), 6.62 (d, *J* = 8.6 Hz, 2H, PMP), 6.63 (d, *J* = 8.6 Hz, 2H, PMP), 6.87 (d, *J* = 8.6 Hz, 2H, PMP), 6.89 (d, *J* = 8.6 Hz, 2H, PMP), 7.17 (d, *J* = 14.2 Hz, 1H, 1'-H), 7.19 (t, *J* = 7.8 Hz, 1H, 4-H), 7.35 (t, *J* = 7.8 Hz, 1H, 5-H), 7.45 (d, *J* = 7.8 Hz, 1H, 3-H), 7.78 (d, *J* = 7.8 Hz, 1H, 6-H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 35.7 (C-3'), 52.0 ($CO_2CH_3$), 55.0 ($CH_3OAr$), 71.0 (C-3''), 75.1 (C-2''), 83.3 (C-5''), 83.6 (C-6''), 113.2 (tert. ar.), 113.2 (tert. PMP), 126.8 (C-1'), 128.0 (C-2'), 127.3, 128.6, 128.1, 128.7, 130.1, 130.3, 130.4 (tert. ar.), 131.2 (C-6), 132.0 (C-4), 139.1 (C-2), 159.0 (2 *C*OMe of PMP), 167.8 (C=O);

**HRMS** (ESI): calcd for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.19346, found 497.19317.

**Methyl 2-{[(2*R*,5*S*,6*S*)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-yl]methyl}-6-methoxybenzoate (8-68)**




This dioxane derivative was prepared according to general procedure 2 with added KBr (1.2 equiv), yield 108 mg (53%), colorless foam.

**$R_f$** = 0.2 (petroleum ether/ethyl acetate, 2:1);

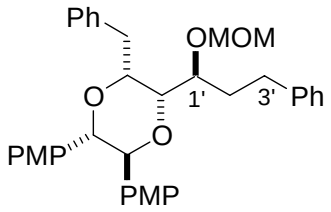
**$[\alpha]^{20}_D$** = –25.1 (*c* 1.1, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.72 (dd, *J* = 14.0, 7.0 Hz, 1'-H), 2.94 (dd, *J* = 14.0, 6.1 Hz, 1H, 1'-H), 3.57 (dd like t, *J* = 11.1, 10.9 Hz, 1H, 3''-H), 3.72 (s, 3H, C*H*$_3$OAr), 3.74 (s, 3H, C*H*$_3$OAr), 3.82 (s, 3H, $CO_2CH_3$), 3.90 (s, 3H, C*H*$_3$OAr), 3.91 (dd, *J* = 11.1, 2.5 Hz, 1H, 3''-H), 4.11 (dddd, *J* = 10.9, 7.0, 6.1, 2.5 Hz, 1H, 2''-H), 4.22 (d, *J* = 8.9 Hz, 1H, 6''-H), 4.39 (d, *J* = 8.9 Hz, 1H, 5''-H), 6.68 (d, *J* = 8.6 Hz, 2H, PMP), 6.70 (d, *J* = 8.6 Hz, 2H, PMP), 6.80 (d, *J* = 8.3 Hz, 1H, 5-H), 6.90 (d, *J* = 8.6 Hz, 2H, PMP), 6.92 (d, *J* = 8.3 Hz, 1H, 3-H), 6.93 (d, *J* = 8.6 Hz, 2H, PMP), 7.27 (t, *J* = 8.3 Hz, 1H, 4-H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 35.7 (C-1'), 52.3 ($CO_2CH_3$), 55.1 (2 *C*H$_3$OAr), 55.9 (*C*H$_3$OAr), 70.8 (C-3''), 75.8 (C-6''), 83.3 (C-5''), 83.7 (C-2''), 109.2 (C-5), 113.2 (2 tert. PMP), 113.3 (2 tert. PMP), 122.6 (C-3), 124.0 (C-1), 128.6 (tert. PMP), 128.7 (tert. PMP), 130.1 (quat. PMP), 130.3 (C-4), 130.4 (quat. PMP), 135.9 (C-2), 156.4 (C-6), 159.0, 159.1 (2 *C*OMe of PMP), 168.6 (C=O);

**HRMS** (ESI): calcd for $C_{28}H_{30}NaO_7$ $[M+Na]^+$: 501.18837, found 501.18819.

**(2S,3*S*,5*R*,6*S*)-2,3-Bis[4-(methyloxy)phenyl]-6-[(1*S*)-3-phenyl-1-(methoxymethoxy) propyl]-5-(phenylmethyl)-1,4-dioxane (8-69)**




This dioxane derivative was prepared according to general procedure 2, yield 18 mg (76%), colorless oil.

**$R_f$** = 0.35 (petroleum ether/ethyl acetate, 3:1);

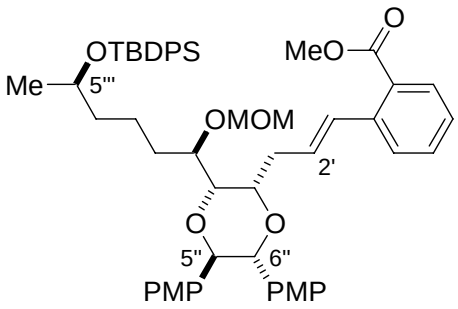
**$[\alpha]^{20}_D$** = +4.1 (*c* 0.81, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 1.97–2.09 (m, 1H, 2'-H); 2.21-2.33 (m, 1H, 2'-H), 2.84 (dd like t, *J* = 8.3, 7.8 Hz, 2H, 3'-H), 2.87 (dd, *J* = 14.2, 8.6 Hz, 1H, C*H*$_2$Ph), 3.03 (dd, *J* = 14.2, 4.6 Hz, 1H, C*H*$_2$Ph), 3.53 (s, 3H, $OCH_2OCH_3$), 3.75 (s, 6H, 2 C*H*$_3$OAr), 3.89 (dd, *J* = 9.1, 2.8 Hz, 1H, 6-H), 4.29 (d, *J* = 9.6 Hz, 1H, 2-H), 4.39-4.33 (m, 1H, 1'-H), 4.40 (d, *J* = 9.6 Hz, 1H, 3-H), 4.61 (ddd, *J* = 8.6, 4.6, 2.8 Hz, 1H, 5-H), 4.86 (d, *J* = 6.8 Hz, 1H, $OCH_2OCH_3$), 4.89 (d, *J* = 6.8 Hz, 1H, $OCH_2OCH_3$), 6.70 (d, *J* = 8.8 Hz, 2H, PMP), 6.71 (d, *J* = 8.8 Hz, 2H, PMP), 6.86 (d, *J* = 8.8 Hz, 2H, PMP), 6.90 (d, *J* = 8.8 Hz, 2H, PMP), 7.13–7.30 (m, 10H, aromatic),

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 29.7 (C-3'), 33.1 (C-2'), 38.0 (*C*$H_2$Ph), 55.1 (2 $CH_3$Ar), 56.4 ($OCH_2OCH_3$), 73.7 (C-2), 74.7 (C-3), 77.8 (C-5), 80.6 (C-1'), 84.5 (C-6), 97.1 ($OCH_2OCH_3$), 113.3 (tert. PMP), 113.2 (tert. PMP), 125.7, 126.1, 128.2, 128.3, 128.6, 128.8, 129.2 (tert. ar.), 130.2 (quat. PMP), 130.4 (quat. PMP), 139.6 (quat. Ph), 142.7 (quat. Ph'), 159.0, 159.1 (2*C*OMe of PMP);

**HRMS** (ESI): calcd for $C_{36}H_{40}NaO_6$ $[M+Na]^+$: 591.27171, found 591.27203.

**Methyl 2-((1*E*)-3-{(2*S*,3*S*,5*R*,6*R*)-3-((1*R*,5*R*)-5-{(*tert*-Butyldiphenylsilyloxy)}-1-{[(methyloxy)methyl]oxy}-hexyl)-5,6-bis[4-(methyloxy)phenyl]-1,4-dioxan-2-yl}-1-propenyl)benzoate (8-70)**




This dioxane derivative was prepared according to general procedure 2. This compound was obtained as a 10:1 mixture of *E*/*Z* isomers. It is advisable to store this compound at -20 °C in order to avoid isomerization of the olefin, yield 180 mg (74%), slightly yellow oil.

$\mathbf{R_f}$ = 0.4 (petroleum ether/ethyl acetate, 4:1);

$\mathbf{[\alpha]^{20}_D}$ = +8.9 (*c* 0.9, $CH_2Cl_2$);

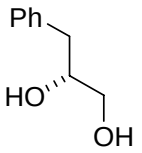
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 0.96 (d, *J* = 6.1 Hz, 3H, 6’’’-H), 1.0 (s, 9H, $(CH_3)_3CSi$), 1.30–1.84 (m, 6H, $CH_2$), 2.48–2.69 (m, 2H, 3’-H), 3.40 (s, 3H, $OCH_2OC\mathit{H}_3$), 3.73 (s, 3H, $CH_3OAr$), 3.74 (s, 3H, $CH_3OAr$), 3.76 (m, 1H, 1’’’-H), 3.78 (dd, *J* = 8.9, 2.5 Hz, 1H, 3’’-H), 3.86 (s, 3H, $CO_2CH_3$), 4.18–4.25 (m, 1H, 5’’’-H), 4.31 (d, *J* = 9.4 Hz, 1H, 5’’-H), 4.43 (d, *J* = 9.4 Hz, 1H, 6’’-H), 4.43–4.51 (m, 1H, 2’’-H), 4.74 (d, *J* = 6.8 Hz, 1H, $OC\mathit{H}_2OCH_3$), 4.77 (d, *J* = 6.8 Hz, 1H, $OC\mathit{H}_2OCH_3$), 6.26 (ddd, *J* = 14.4, 8.1, 7.1 Hz, 1H, 2’-H), 6.68 (d, *J* = 8.6 Hz, 2H, PMP), 6.72 (d, *J* = 8.6 Hz, 2H, PMP), 6.88 (d, *J* = 8.6 Hz, 2H, PMP), 6.94 (d, *J* = 8.6 Hz, 2H, PMP), 7.19–7.44 (m, 9H, aromatic, 1’-H), 7.52 (d, *J* = 7.8 Hz, 1H, 3-H), 7.57–7.66 (m, 4H, aromatic), 7.82 (dd, *J* = 7.8, 1.0 Hz, 1H, 6-H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 18.9 ($(CH_3)_3\mathit{C}Si$); 19.1 (C-3’’C), 22.8 (C-6’’’), 27.0 ($(\mathit{C}H_3)_3CSi$), 30.7 (C-3’), 35.8 (C-2’’’), 39.8 (C-4’’’), 52.0 ($CO_2\mathit{C}H_3$), 55.1 ($\mathit{C}H_3OAr$), 55.2 ($\mathit{C}H_3OAr$), 56.3 ($OCH_2O\mathit{C}H_3$), 69.6 (C-5’’’), 73.4 (C-5’’), 74.7 (C-6’’), 77.9 (C-1’’’), 79.6 (C-3’’), 84.6 (C-2’’), 96.8 ($O\mathit{C}H_2OCH_3$), 113.2 (PMP), 113.3 (PMP), 126.7 (C-9), 127.3, 127.4 (CH, aromatic), 128.2 (C-1), 128.7, 128.8, 129.3, 129.4, 130.2, 130.3 (tert. ar.), 130.5

(C-2'), 131.9 (tert. ar.), 134.6, 134.9 (quat. ar.), 135.80, 135.9 (tert. ar.), 139.3 (C-2), 159.1 (2 *C*OMe of PMP), 168.0 (C=O),

**HRMS** (ESI): calcd for $C_{53}H_{68}NO_9Si$ $[M+NH_4]^+$: 890.46579, found 890.46626.

**(2*R*)-3-Phenylpropane-1,2-diol (8-72)**




To a stirred solution of the dioxane **8-66** (38 mg, 97 μmols) in $CH_3CN/H_2O$ mixture (9:1) (2 mL), was added CAN (117 mg, 0.21 mmol). The resulting yellow solution was stirred at room temperature for 2 h, during which the starting material was completely consumed. The mixture was diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, the crude product loaded onto a silica column and chromatographed using petroleum ether/ethyl acetate (1:1) as eluent to afford pure diol **8-72** as a colorless oil, yield 12.7 mg (86%).

$\mathbf{R_f}$ = 0.3 (petroleum ether/ethyl acetate, 1:1);

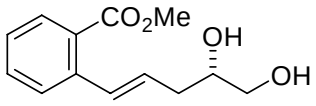
$\mathbf{[\alpha]^{20}_D}$ = +20.4 (*c* 1.0, $CHCl_3$); $\mathbf{[\alpha]^{20}_D}$ = +15.0 (*c* 1.0, $CHCl_3$);[151]

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.13 (br s, 2H, OH), 2.69–2.84 (m, 2H, H-3), 3.50 (dd, *J* = 11.1, 7.1 Hz, 1H, 1-H), 3.68 (dd, *J* = 11.1, 2.8 Hz, 1H, 1-H), 3.87–3.99 (m, 1H, 2-H), 7.17-7.35 (m, 5H, aromatic);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 39.8 (C-3), 66.0 (C-1), 73.0 (C-2), 128.6 (2 tert. ar.), 129.3 (2 tert. ar.), 137.7 (quat. ar.);

**HRMS** (ESI): calcd for $C_9H_{12}NaO_2$ $[M+Na]^+$: 175.07295, found 175.07445.

**(*S*,*E*)-Methyl 2-(4,5-dihydroxypent-1-enyl)benzoate (8-73)**




To a stirred solution of the dioxane **8-67** (40 mg, 84.3 μmol) in $CH_3CN/H_2O$ (9:1) (2 mL), was added CAN (102 mg, 0.186 mmol). The resulting solution was stirred at room temperature for 3 h, during which the starting material was almost completely consumed. The mixture was diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:4) to afford the pure diol **8-73** as a colorless gel, yield 16.2 mg (81%). NMR analysis indicated a ratio of 8:1 of *E*/*Z* isomers.

**$R_f$** = 0.25 (petroleum ether/ethyl acetate, 1:4);

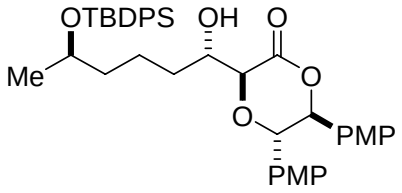
**$[\alpha]^{20}_D$** = +7.9 (*c* 1.1, $CH_2Cl_2$);

**$^1$H NMR** ($CDCl_3$, 400 MHz): δ = 2.25–2.31 (m, 1H, 3'-H), 2.32–2.41 (m, 2H, 3'-H, OH), 2.81 (br s, 1H, OH), 3.46–3.56 (m, 1H, 5'-H), 3.62–3.70 (m, 1H, 5'-H), 3.75–3.81 (m, 1H, 4'-H), 3.82 (s, 3H, $CO_2CH_3$), 5.96 (ddd, *J* = 15.9, 7.9, 7.3 Hz, 1H, 2'-H), 7.09 (d, *J* = 15.9 Hz, 1H, 1'-H), 7.20–7.28 (m, 1H, aromatic), 7.38–7.43 (m, 2H, aromatic), 7.82 (d, *J* = 7.8 Hz, 1H, 3-H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ = 37.0 (C-3'), 52.2 ($CO_2CH_3$), 66.3 (C-5'), 71.3 (C-4'), 127.7 (C-1'), 127.3 (C-2), 128.3 (C-2'), 127.0, 130.3, 132.3, 132.9 (tert. ar.), 139.7 (C-1), 167.8 (C=O);

**HRMS** (ESI): calcd for $C_{13}H_{16}NaO_4$ $[M+Na]^+$: 259.09408, found 259.09413.

**(3*S*,5*S*,6*S*)-3-[(1*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-hydroxyhexyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-76)**




To a cooled (-78 °C) solution of (-)-dioxanone **8-7** (0.233 g, 0.740 mmol) in dry $CH_2Cl_2$ (20 mL) was added in a dropwise fashion $Et_3N$ (0.26 mL, 1.86 mmol) followed by *c*$Hex_2BOTf$[160] (1.85 mL, 1.0 M in abs. hexane). The resulting solution was stirred at -78 °C for 3 h at which time (5*R*)-5-(*tert*-butyldiphenylsilyloxy)hexanal **8-6** (0.314 g, 0.888 mmol), dissolved in dry $CH_2Cl_2$ (1 mL) was added dropwise over 10 min. The resulting solution was stirred at -78 °C for 12 h before it was quenched at the same temperature by the addition of pH 7 buffer (2.5 mL), MeOH (2 mL) and 30% aqueous $H_2O_2$ (0.5 mL). The mixture was stirred vigorously for 1 h and then warmed to RT when it was diluted with $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (4 × 50 mL) and the combined organic layers were washed with satd. $NaHCO_3$ solution (30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford ~1.0 g of crude product as a yellow oil, which was used for the next step without further purification [approximately half of the product can decompose during flash chromatography on silica gel (petroleum ether/EtOAc, 2:1)]. The selectivity was found to be 9:1 (*anti*-1/*anti*-2) according to $^1$H NMR and LC-MS of the crude reaction material.

Data for the purified product:

**$R_f$** = 0.48 (petroleum ether/EtOAc, 2:1);

**$[\alpha]^{20}_D$** = –74.1 (*c* 1.6, $CH_2Cl_2$);

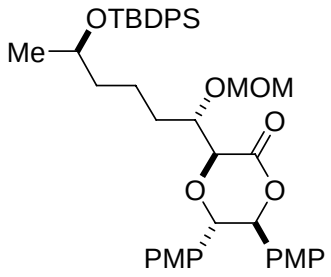
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.03–1.15 (m, 12H, $(CH_3)_3CSi$, C*H*$_3$CHOSi), 1.40–1.79 (m, 6H, $(CH_2)_3$), 3.00 (br s, 1H, OH), 3.75 (s, 6H, $CH_3OAr$), 3.86–3.95 (m, 1H, $CH_3$C*H*OSi), 4.05–4.11 (m, 1H, 1'-H), 4.50 (d, *J* = 5.4 Hz, 1H, 3-H), 4.96 (d, *J* = 9.2 Hz, 1H, 5-H), 5.41 (d, *J* = 9.2 Hz, 1H, 6-H), 6.78 (d, *J* = 8.8 Hz, 2H, CH PMP), 6.79 (d, *J* = 8.8 Hz, 2H, CH PMP),

6.99 (d, *J* = 8.8 Hz, 2H, CH PMP), 7.02 (d, *J* = 8.8 Hz, 2H, CH PMP), 7.34–7.44 (m, 6H, aromatic TBDPS), 7.70–7.75 (m, 4H, aromatic TBDPS);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.1 (($CH_3$)$_3$*C*Si), 20.8 (C-4'), 23.1 (C-6'), 26.9 (($CH_3$)$_3$CSi), 33.3 (C-2'), 39.0 (C-3'), 55.0 (*C*$H_3$OAr), 69.3 (C-5'), 73.1 (C-1'),75.9 (C-3), 77.7 (C-5), 84.8 (C-6), 113.6, 126.5, 127.3, 127.4, 127.8, 128.7, 128.4, 129.3, 134.4, 134.7, 135.7, 159.6, 159.8, 170.0 (C=O);

**HRMS** (ESI): calcd for $C_{40}H_{48}NaO_7Si$ $[M+Na]^+$: 723.33236, found 723.33153.

**(3*S*,5*S*,6*S*)-3-[(1*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(methoxymethoxy)hexyl]-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-77)**




To a stirred, cooled (0 °C) solution of crude aldol product **8-76** (~ 1.0 g) in $CH_2Cl_2$ (30 mL) were added *N*,*N*-diisopropylethylamine (5.1 mL, 3.86 g, 30.0 mmol), chloromethylmethyl ether (MOMCl)[161] (1.14 mL, 1.20 g, 15.0 mmol), and tetrabutylammonium iodide (222 mg, 0.6 mmol). The reaction mixture was protected from light and allowed to reach RT. After stirring for 14 days [daily addition of MOMCl (about 0.1 mL) and *N*,*N*-diisopropylethylamine (about 0.2 mL) can speed up progress of the reaction], satd. aqueous $NaHCO_3$ solution (40 mL) was added followed by $Et_2O$ (50 mL). The organic layer was washed with satd. NaCl solution (100 mL), and the basic aqueous layer was extracted with $Et_2O$ (2 × 25 mL). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc, 3:1) provided MOM ether **8-77** (0.24 g, 45% for two steps from aldehyde **8-6**) as slightly yellow oil.

**$R_f$** = 0.36 (petroleum ether/EtOAc, 3:1);

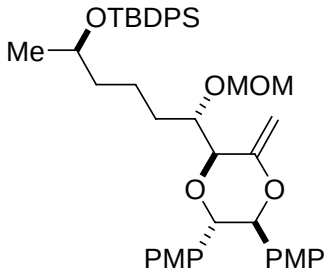
$[\alpha]^{20}_{D}$ = –71.6 (*c* 1.1, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.98–1.06 (m, 12H, $(CH_3)_3CSi$, C*H*$_3$CHOSi), 1.36–1.57 (m, 4H, 2 $CH_2$), 1.63–1.78 (m, 2H, $CH_2$), 3.37 (s, 3H, $OCH_2OCH_3$), 3.75 (s, 3H, $CH_3OAr$), 3.76 (s, 3H, $CH_3OAr$), 3.81–3.87 (m, 1H, 5'-H), 4.03–4.09 (m, 1H, 1'-H), 4.73 (dd, *J* = 8.3, 7.1 Hz, 2H, $OCH_2OCH_3$), 4.77 (d, *J* = 2.6 Hz, 1H, 3-H), 4.98 (d, *J* = 8.6 Hz, 1H, 5-H), 5.37 (d, *J* = 8.6 Hz, 1H, 6-H), 6.73–6.77 (m, 4H, CH PMP), 6.98 (d, *J* = 8.8 Hz, 4H, CH PMP), 7.33–7.42 (m, 6H, aromatic TBDPS), 7.65–7.70 (m, 4H, aromatic TBDPS);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.2 $(CH_3)_3CSi$), 21.5 (C-3'), 23.1 (C-6'), 27.0 ($CH_3)_3CSi$), 30.9, 39.2 (C-2', C-4'), 55.2 ($CH_3OAr$), 56.0 ($OCH_2OCH_3$), 69.4 (C-5'), 74.7 (*C*HOMOM), 77.9 (C-3), 81.1 (C-5), 84.9 (C-6), 96.6 ($OCH_2OCH_3$), 113.6, 113.7, 127.2, 127.4, 127.5, 128.1, 128.6, 128.7, 129.4, 129.5, 134.5, 134.8, 135.8, 135.9, 159.7 (*C*OMe of PMP), 159.8 (*C*OMe of PMP), 167.8 (C=O);

**HRMS** (ESI): calcd for $C_{42}H_{52}NaO_8Si$ $[M+Na]^+$: 735.33237, found 735.33270.

**(3*S*,5*S*,6*S*)-3-[(1*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(methoxymethoxy)hexyl]-2-methylidene-5,6-bis-(4-methoxyphenyl)-[1,4]-dioxan-2-one (8-78)**




To a stirred solution of the lactone **8-77** (924 mg, 1.3 mmol) in dry THF (15 mL) was added the freshly prepared Petasis reagent $Cp_2TiMe_2$ (1.6 g, 7.8 mmol, 6 equiv.) dissolved in toluene (25 mL). The resulting orange reaction mixture was warmed to 65 °C and stirred in the dark under an argon atmosphere until the starting material was consumed (as indicated by TLC, approximately 36 h). The solution was cooled to RT and the titanium compounds were precipitated by addition of petroleum ether (ca. 200 mL). The resulting heterogeneous mixture was poured on a basic alumina column and eluted quickly. In order to ensure that the entire

product was out of the column, the alumina bed was finally flushed with a petroleum ether/EtOAc (4:1) mixture. The fractions were pooled and concentrated in vacuo. Purification was done by chromatography on basic $Al_2O_3$ (petroleum ether/EtOAc, 9:1) yielding 840 mg (91%) of the product as a slightly yellow oil.

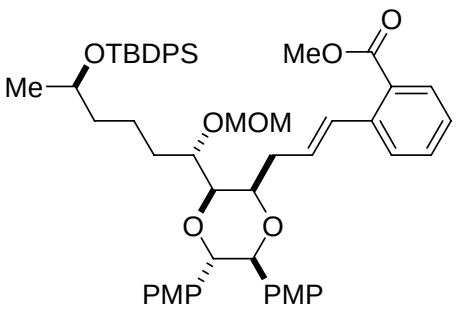
**$R_f$** = 0.35 (petroleum ether/EtOAc, 9:1);

**$^1$H NMR** (400 MHz, $C_6D_6$): δ = 1.06 (d, *J* = 6.1 Hz, 3H, 6'-H), 1.18 (s, 9H, $(CH_3)_3CSi$), 1.43–1.60 (m, 2H, 3'-H, 4'-H), 1.60–1.79 (m, 3H, $CH_2$), 1.84–1.93 (m, 1H, 2'-H), 3.18 (s, 3H, C*H*$_3$OAr), 3.19 (s, 3H, C*H*$_3$OAr), 3.32 (s, 3H, $OCH_2OCH_3$), 3.85–3.95 (m, 1H, 5'-H), 4.36 (d, *J* = 9.3 Hz, 1H, 3-H), 4.59 (m, 1H, 1'-H), 4.60 (s, 1H, C=$CH_2$), 4.68 (d, *J* = 7.0 Hz, 1H, 5-H), 4.84 (dd, *J* = 11.0, 9.5 Hz, 2H, OC*H*$_2$OCH$_3$), 4.87 (d, *J* = 7.0 Hz, 1H, 6-H), 4.91 (s, 1H, C=$CH_2$), 6.61 (d, *J* = 8.7 Hz, 4H, CH PMP), 6.99 (d, *J* = 8.7 Hz, 2H, CH PMP), 7.02 (d, *J* = 8.7 Hz, 2H, CH PMP), 7.17–7.24 (m, 6H, aromatic), 7.75–7.84 (m, 4H, aromatic);

**$^{13}$C NMR** (100 MHz, $C_6D_6$): δ = 19.5 ($(CH_3)_3CSi$), 20.3 (C-3'), 23.2 (C-6'), 27.3 ($(CH_3)_3CSi$), 31.9 (C-2'), 40.1 (C-4'), 54.6 (2 *C*H$_3$OAr), 55.7 ($CH_2OCH_3$), 70.0 (C-5'), 74.3 (C-6), 75.4 (C-5), 77.7 (C-1'), 86.0 (C-3), 96.3 (C=*C*H$_2$), 96.9 (*C*H$_2$OCH$_3$), 113.7, 127.8-129.8, 130.0, 130.1, 135.0, 135.2, 136.3, 156.8 (C-2), 159.9, 159.9;

**HRMS** (ESI): calcd for $C_{43}H_{54}NaO_7Si$ $[M+Na]^+$: 733.35310, found 733.35347.

**Methyl 2-((1*E*)-3-{(2*R*,3*R*,5*S*,6*S*)-3-((1*S*,5*R*)-5-{(*tert*-Butyldiphenylsilyloxy)}-1-{[(methyloxy)methyl]oxy}-hexyl)-5,6-bis[4-(methyloxy)phenyl]-1,4-dioxan-2-yl}-1-propenyl) benzoate (8-80)**




To a solution of the enol ether **8-78** (695 mg, 0.98 mmol) in absolute THF (10 mL) a solution of 9-BBN (2.35 mL, 1.17 mmol, 0.5 M in THF) was added at 0 °C. The resulting reaction mixture was allowed to stir at RT for about 6 h. Meanwhile, in a separate flask, a solution of the methyl 2-[(*E*)-2-iodovinyl]benzoate (**8-3**) (720 mg, 2.5 mmol), triphenyl arsine (15 mg, 0.049 mmol, 5% mol), cesium carbonate (1.3 g, 4.0 mmol), deionized water (0.1 mL), in abs. DMF (24 mL) was prepared. This flask was purged with argon and $PdCl_2$(dppf) (40 mg, 0.049 mmol, 5% mol) was added. To the resulting suspension was added the above mixture from the hydroboration reaction. This was then stirred under argon at RT for a further 14-16 h. The reaction was worked up by addition of satd. $NH_4Cl$ solution (20 mL). The mixture was poured into a separating funnel and extracted twice with EtOAc. The combined organic extracts were washed successively with satd. $Na_2S_2O_3$ solution, water and satd. NaCl solution. The organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (petroleum ether/EtOAc, 4:1) to afford the pure coupling product (630 mg, 74%) as a slightly yellow oil. This compound was obtained as >20:1 mixture of *E*/*Z* isomers. It is advisable to store this compound at -20 °C in order to avoid isomerization of the double bond.

**$R_f$** = 0.4 (petroleum ether/EtOAc, 4:1);

**$[\alpha]^{20}_D$** = +22.0 (*c* 2.0, $CHCl_3$);

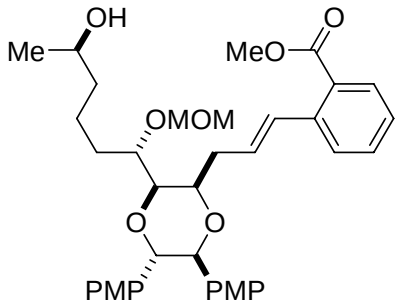
**$^1$H NMR** (400 MHz, $CDCl_3$,): δ = 0.94 (m, 12H, 6’’’-H, $(CH_3)_3CSi$), 1.30–1.84 (m, 6H, $CH_2$), 2.45–2.63 (m, 2H, 3’-H), 3.33 (s, 3H, $OCH_2OCH_3$), 3.64 (s, 3H, $CH_3OAr$), 3.65 (s, 3H,

C*H*$_3$OAr), 3.71–3.79 (m, 2H, 3’’-H, 5’’’-H), 3.79 (s, 3H, $CO_2CH_3$), 4.13–4.19 (m, 1H, 2’’-H), 4.28 (d, *J* = 9.4 Hz, 1H, 5’’-H), 4.37 (d, *J* = 9.4 Hz, 1H, 6’’-H), 4.40–4.44 (m, 1H, 1’’’-H), 4.67 (dd, *J* = 12.9, 6.8 Hz, 2H, OC*H*$_2$OCH$_3$), 6.26 (ddd, *J* = 15.6, 6.8, 6.8 Hz, 1H, 2’-H), 6.62 (d, *J* = 8.6 Hz, 2H, PMP), 6.65 (d, *J* = 8.6 Hz, 2H, PMP), 6.83 (d, *J* = 8.6 Hz, 2H, PMP), 6.87 (d, *J* = 8.6 Hz, 2H, PMP), 7.15–7.33 (m, 9H, aromatic and 1’-H), 7.45 (d, *J* = 7.8 Hz, 1H, 3-H), 7.53–7.58 (m, 4H, aromatic), 7.75 (d, *J* = 7.8 Hz, 1H, 6-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 18.9 ((CH$_3$)$_3$*C*Si), 19.1 (C-3’’’), 23.1 (C-6’’’), 26.9 ((*C*H$_3$)$_3$CSi), 30.7 (C-3’), 35.8 (C-2’’’), 39.9 (C-4’’’), 51.9 ($CO_2CH_3$), 55.0 (2 *C*H$_3$OAr), 56.2 (OCH$_2$O*C*H$_3$), 69.7 (C-5’’’), 73.3 (C-5’’), 74.5 (C-6’’), 77.8 (C-1’’’), 79.6 (C-3’’), 84.7 (C-2’’), 96.7 (O*C*H$_2$OCH$_3$), 113.2 (PMP), 113.3 (PMP), 126.6 (C-9), 127.3, 127.4, 128.1 (C-1), 128.6, 128.7, 129.2, 129.3, 130.2, 130.3, 130.5 (C-2’), 131.8, 134.5 (quat C SiPh), 134.9 (quat C SiPh), 135.8, 139.2 (C-2), 159.1 (2 *C*OCH$_3$ PMP), 167.9 (*C*O$_2$CH$_3$);

**HRMS** (ESI): calcd for $C_{53}H_{68}NO_9Si$ $[M+NH_4]^+$: 890.46579, found 890.46626.

**Methyl 2-((1*E*)-3-{(2*R*,3*R*,5*S*,6*S*)-3-((1*S*,5*R*)-5-hydroxy)-1-(methyloxymethyl)oxy-hexyl-5,6-bis[4-(methyloxy)phenyl]-1,4-dioxan-2-yl}-1-propenyl)benzoate (8-81)**




To a cooled (–20 °C) solution of substrate **8-80** (0.20 g, 0.23 mmol) in dry THF (10 mL) in a plastic vial, pyridine·HF complex (2.0 mL, freshly opened flask) was added slowly in a dropwise fashion (approx. within 15 min.). The resulting solution was stirred at 0 °C for 24 h at which time $K_2CO_3$ was added portionwise until the mixture was basic. The mixture was diluted with THF (20 mL) and stirred for 2 h. Solids were filtered, then washed with $Et_2O$ (50 mL). The filtrate was washed with satd. NaCl solution, dried over $Na_2SO_4$, filtered, and

concentrated in vacuo to afford crude product. Flash chromatography of the residue (petroleum ether/EtOAc, 1:1) furnished hydroxy ester **8-81** (125 mg, 86%) as a colorless oil.

**$R_f$** = 0.32 (petroleum ether/EtOAc, 1:1);

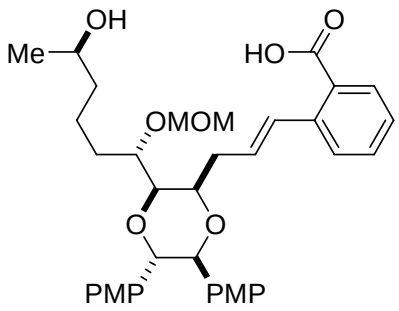
**$[\alpha]^{20}_D$** = –2.7 (*c* 0.9, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 5.8 Hz, 3H, 6’’’-H), 1.25–1.40 (m, 2H, $CH_2$), 1.40–1.60 (m, 2H, $CH_2$), 1.60–1.75 (m, 1H, $CH_2$), 1.75–1.90 (m, 1H, $CH_2$), 2.45–2.65 (m, 2H, 3’-H), 3.37 (s, 3H, $OCH_2OC\mathit{H}_3$), 3.55–3.67 (m, 7H, $C\mathit{H}_3OAr$, 5’’’-H), 3.75–3.84 (m, 4H, $CO_2CH_3$, 3’’-H), 4.15–4.20 (m, 1H, 2’’-H), 4.29 (d, *J* = 9.3 Hz, 1H, 5’’-H), 4.39 (d, *J* = 9.3 Hz, 1H, 6’’-H), 4.45-4.50 (m, 1H, 1’’’-H), 4.73 (dd, *J* = 11.7, 6.8 Hz, 2H, $OC\mathit{H}_2OCH_3$), 6.20 (ddd, *J* = 15.5, 6.5, 6.5 Hz, 1H, β-C*H*=CH), 6.59–6.67 (m, 4H, PMP), 6.81–6.90 (m, 4H, PMP), 7.13–7.23 (m, 2H, 4-H, α-C*H*=CH), 7.33 (dd, *J* = 7.8 Hz, 1H, 5-H), 7.45 (br d, *J* = 7.8 Hz, 1H, 3-H), 7.75 (br d, *J* = 7.8 Hz, 1H, 6-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.1 (C-3’’’), 23.2 (C-6’’’), 30.0 (C-2’’’), 35.7 (C-3’), 39.2 (C-4’’’), 51.9 ($CO_2\mathit{C}H_3$), 55.0 (2 $CH_3OAr$), 56.3 ($OCH_2O\mathit{C}H_3$), 67.2 (C-5’’’), 73.4 (C-3’’), 74.7 (C-1’’’), 78.0 (C-5’’), 79.4 (C-2’’), 84.5 (C-6’’), 96.8 ($O\mathit{C}H_2OCH_3$), 113.2 (2 CH, PMP), 113.3 (2 CH, PMP), 126.6 (C-4), 127.2 (C-3), 128.1 (C-1), 128.5 (2 CH, PMP), 128.7 (2 CH, PMP), 130.0 (C-6, α-*C*H=CH), 130.2 (β-*C*H=CH), 130.3 (quat C PMP), 130.3 (quat C PMP), 131.8 (C-5), 139.1 (C-2), 159.1 (*C*$OCH_3$ PMP), 159.1 (*C*$OCH_3$ PMP), 167.9 (*C*$O_2CH_3$);

**HRMS** (ESI): calcd for $C_{37}H_{49}NaO_9$ $[M+Na]^+$: 657.30340, found 657.30326.

**2-((1*E*)-3-{(2*R*,3*R*,5*S*,6*S*)-3-((1*S*,5*R*)-5-Hydroxy)-1-(methyloxymethyl)oxy-hexyl-5,6-bis[4-(methyloxy)phenyl]-1,4-dioxan-2-yl} -1-propenyl)benzoic acid (8-82)**




A solution of hydroxy ester **8-81** (130 mg, 0.2 mmol) in a mixture of THF (4 mL), MeOH (2 mL), and $H_2O$ (1 mL) was treated with $LiOH{\cdot}H_2O$ (96 mg, 2.3 mmol), followed by stirring the mixture at 60 °C for 20 h. After the mixture cooled to RT, it was diluted with $Et_2O$ (30 mL) and water (20 mL). The organic layer was separated. Through the aqueous layer was bubbled air for 60 min in order to remove the rest of organic solvent. This inorganic solution was then acidified (pH ~ 3) by slow addition of aqueous hydrochloric acid (1 M solution, approx. 2.2 mL) and stirred additionally for 30 min. The white precipitate was filtered, washed with acidified water (20 mL, 0.01 N HCl) and dried in vacuo for several h to give 126 mg (97%) of hydroxy acid **8-82**, which was used in the next step without additional purification.

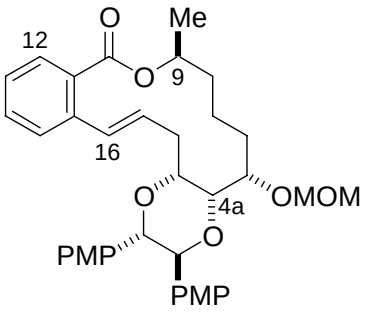
**$R_f$** = 0.2–0.3 (petroleum ether/EtOAc, 1:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.15 (br s, 3H, 6’’’-H), 1.40–1.60 (br m, 3H, $CH_2$), 1.68–2.05 (br m, 3H, $CH_2$), 2.57–2.76 (br m, 2H, 3’-H), 3.47 (br s, 3H, $OCH_2OC\mathit{H}_3$), 3.65–3.83 (br m, 7H, $C\mathit{H}_3OAr$, 5’’’-H), 3.88–3.97 (br m, 1H, 3’’-H), 4.25–4.35 (br m, 1H, 2’’-H), 4.40–4.54 (br m, 3H, 1’’’-H, 5’’-H, 6’’-H), 4.77 (br d, *J* = 8.8 Hz, 2H, $OC\mathit{H}_2OCH_3$), 6.12–6.27 (br m, 1H, β-C*H*=CH), 6.7 (br s, 4H, PMP), 6.93 (br s, 4H, PMP), 7.25–7.32 (br m, 1H, 4-H), 7.36–7.58 (br m, 3H, α-C*H*=CH, 3-H, 5-H), 7.95–8.03 (br m, 1H, 6-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.7 (C-3’’’), 23.6 (C-6’’’), 30.3 (C-2’’’), 35.7 (C-3’), 38.6 (C-4’’’), 55.1 (2 $C\mathit{H}_3OAr$), 56.3 ($OCH_2O\mathit{C}H_3$), 68.0 (C-5’’’), 73.2 (C-3’’), 75.3 (C-1’’’), 78.2 (C-5’’), 78.7 (C-2’’), 84.9 (C-6’’), 96.7 ($O\mathit{C}H_2OCH_3$), 113.3 (2 CH, PMP), 113.3 (2 CH, PMP), 126.9 (C-4), 127.2 (C-3), 127.6 (C-1), 128.6 (2 CH, PMP), 128.8 (2 CH, PMP), 129.3

(β-*C*H=CH), 130.1 (C-6), 130.3 (α-*C*H=CH), 131.2 (quat C PMP), 131.3 (quat C PMP), 132.7 (C-5), 140.0 (C-2), 159.1 (*C*OCH$_3$ PMP), 159.1 (*C*OCH$_3$ PMP), 171.7 ($CO_2H$);
**HRMS** (ESI): calcd for $C_{36}H_{44}NaO_9$ $[M+Na]^+$: 643.28775, found 643.28745.

**(2*S*,3*S*,4a*R*,5*S*,9*S*,18a*R*)-5-(Methoxymethoxy)-2,3-bis(4-methoxyphenyl)-9-methyl-2,3,4a,5,6,7,8,9,18,18adecahydro-11*H*-[1,4]dioxino[2,3-*h*][2]benzoxacyclotetradecin-11-one (8-83)**




To a cooled (0 °C) solution of hydroxy acid **8-82** (120 mg, 0.19 mmol) in abs. toluene (20 mL) was added freshly recrystallized $PPh_3$ (105 mg, 0.4 mmol). After 15 min at the same temperature, the mixture was very slowly treated (approx. 25 min) with DEAD (~40% solution in toluene, 130 μL, 0.4 mmol). Within 15 h of stirring, the reaction mixture was warmed to RT. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give 91 mg (78%) of macrolactone **8-83** as a colorless oil, which was treated with 20 mL of hot heptane followed by evaporation of the solvent to give white solid material.

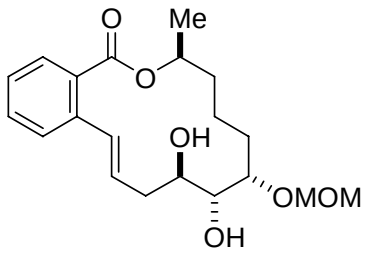
**$R_f$** = 0.55 (petroleum ether/EtOAc, 2:1);
**$[\alpha]^{20}_D$** = +23.5 (*c* 1.8, $CH_2Cl_2$);
**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 5.8 Hz, 3H, C*H*$_3$CHO$_2$CAr), 1.55–1.71 (m, 4H, 2 $CH_2$), 1.85–1.96 (m, 2H, $CH_2$), 2.48–2.55 (m, 1H, 18-H), 3.33–3.43 (m, 1H, 18-H), 3.55 (s, 3H, OCH$_2$OC*H*$_3$), 3.73 (s, 3H, C*H*$_3$OAr), 3.75 (s, 3H, C*H*$_3$OAr), 4.01 (dd, *J* = 6.5, 2.8 Hz, 1H, 4a-H), 4.27 (ddd, *J* = 11.6, 2.8, 2.8 Hz, 1H, 5-H), 4.46 (d, *J* = 9.3 Hz, 1H, 3-H), 4.58–4.54 (m, 1H, 18a-H), 4.70 (d, *J* = 9.3 Hz, 1H, 2-H), 4.87 (d, *J* = 6.6 Hz, 1H, OC*H*$_2$OCH$_3$), 5.00 (d, *J* =

6.6 Hz, 1H, OC*H*$_2$OCH$_3$), 5.22–5.31 (m, 1H, 9-H), 6.17 (ddd, *J* = 15.5, 10.3, 4.8 Hz, 1H, β-C*H*=CH), 6.68-6.75 (m, 4H, PMP), 6.88 (d, *J* = 15.5 Hz, 1H, α-C*H*=CH), 6.91–6.94 (m, 2H, PMP), 6.96–7.00 (m, 2H, PMP), 7.28 (dd, *J* = 7.3, 7.3 Hz, 1H, 13-H), 7.41 (dd, *J* = 7.3, 7.3 Hz, 1H, 14-H), 7.46 (br d, *J* = 7.3, Hz, 1H, 12-H), 7.52 (br d, *J* = 7.3 Hz, 15-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 19.4 (C-6), 19.8 (*C*H$_3$CHO$_2$Ar), 30.7 (C-8), 35.3 (C-18), 35.8 (C-7), 55.1 (2 *C*H$_3$OAr), 56.3 (OCH$_2$O*C*H$_3$), 72.3 (C-9), 72.6 (C-4a), 76.5 (C-5), 76.6 (C-3), 79.8 (C-18a), 86.4 (C-2), 95.7 (O*C*H$_2$OCH$_3$), 113.3 (CH, PMP), 113.4, (CH, PMP), 126.6 (C-15), 126.9 (C-13), 127.7 (C-12), 128.8 (2 CH, PMP), 128.9 (2 CH, PMP), 129.6 (β-C*H*=CH), 130.3 (C-14), 130.4 (2 quat C PMP), 131.1 (α-C*H*=CH), 132.6 (C-11a), 135.8 (C-15a), 159.1 (2 *C*OCH$_3$ of PMP), 169.6 (C=O);

**HRMS** (ESI): calcd for $C_{36}H_{42}NaO_8$ $[M+Na]^+$: 625.27719, found 625.27721.

**(3*S*,7*S*,8*R*,9*R*)-8,9-Dihydroxy-7-(methoxymethoxy)-3-methyl-3,4,5,6,7,8,9,10-octahydro-1*H*-2-benzoxacyclotetradecin-1-one (8-84)**




To a stirred solution of CAN (183 mg, 0.33 mmol, 10 equiv) in a $CH_3CN/H_2O$ mixture (5 mL, 10:1) at 0–5 °C (ice bath) a solution of macrolactone **8-83** (20 mg, 33 μmol) in $CH_3CN$ (1 mL) was added dropwise. The resulting solution was stirred at the same temperature for 8 h, during which time the starting material was completely consumed (if reaction is not finished, additional amount of CAN can be added at 0 °C and stirred further at the same temperature). The mixture was diluted with satd. aqueous $NH_4Cl$ solution (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were washed with satd. aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure; the crude product loaded onto a flash silica gel column and eluted using a $CHCl_3$/MeOH mixture (40:1) to afford pure diol **8-84** (9.6 mg, 80%) as a colorless oil.

**$R_f$** = 0.15 ($CHCl_3$/MeOH, 40:1);

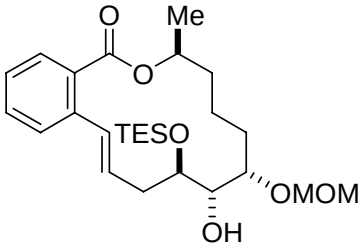
**$[\alpha]^{20}_D$** = +137 (*c* 1.1, $CH_2Cl_2$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CHO$_2$Ar), 1.45–1.60 (m, 3H, $CH_2$), 1.65–1.75 (m, 2H, $CH_2$), 2.03-2.16 (m, 1H, $CH_2$), 2.58–2.77 (m, 2H, C*H*$_2$CH=CH), 3.44 (s, 3H, OCH$_2$OC*H*$_3$), 3.69 (dd, *J* = 3.5, 3.5 Hz, 1H, 8-H), 3.82 (ddd, *J* = 8.8, 3.5, 3.5 Hz, 1H, 7-H), 3.94 (ddd, *J* = 7.3, 4.3, 4.3 Hz, 1H, 9-H), 4.70 (dd, *J* = 18.1, 6.6 Hz, OC*H*$_2$OCH$_3$), 5.24–5.33 (m, 1H, CH$_3$C*H*O$_2$CAr), 6.02 (ddd, *J* = 15.5, 9.8, 5.3 Hz, 1H, β-C*H*=CH), 6.86 (d, *J* = 15.5 Hz, 1H, α-C*H*=CH), 7.26–7.31 (m, 1H, 15-H), 7.38–7.43 (m, 2H, 13-H, 14-H), 7.64 (d, *J* = 7.8 Hz, 1H, 16-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 20.0 (*C*H$_3$CHO$_2$Ar), 20.5 (C-5), 30.8 (C-6), 35.5 (C-4), 37.7 (C-10), 56.1 (OCH$_2$O*C*H$_3$), 71.3 (C-3), 72.0 (C-8), 75.1 (C-9), 83.9 (C-7), 97.0 (O*C*H$_2$OCH$_3$), 127.0 (C-15), 127.5 (C-13), 128.8 (β-*C*H=CH), 129.1 (C-16), 131.2 (C-14), 131.2 (C-16a), 132.5 (α-*C*H=CH), 137.7 (C-12a), 169.0 ($CO_2$R);

**HRMS** (ESI): calcd for $C_{20}H_{28}O_6Na$ $[M+Na]^+$: 387.17781, found 387.17780.

**(3*S*,7*S*,8*S*,9*R*)-8-Hydroxy-7-(methoxymethoxy)-3-methyl-9-[(triethylsilyl)oxy]-3,4,5,6,7,8,9,10-octahydro-1*H*-2-benzoxacyclotetradecin-1-one (8-85)**




To a mixture of MOM-protected triol **8-84** (14 mg, 38 μmol) and 2,6-lutidine (20 μL, 18.5 mg, 0.17 mmol) in abs. $CH_2Cl_2$ (4 mL) at -80 °C was slowly added TESOTf (10 μL). After 3 h at -50 °C additional triflate (5 μL) was added and the resulting mixture stirred further for 12 h at the same temperature. Then the mixture was treated with satd. $NH_4Cl$ solution (3 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were washed with brine,

dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to afford 9.2 mg (50%) of the TES-protected alcohol **8-85** as a colorless oil.

**$R_f$** = 0.45 (petroleum ether/EtOAc, 5:1);

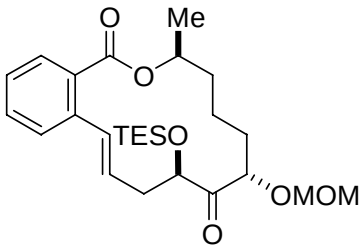
**$[\alpha]^{20}_D$** = –16 (*c* 0.5, $CHCl_3$);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.64 (q, *J* = 15.7, 7.9 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$), 0.97 (t, *J* = 7.9 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$), 1.35 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CHO$_2$Ar), 1.40–1.75 (m, 5H, CH$_2$), 1.95-2.05 (m, 1H, CH$_2$), 2.25 (br s, 1H, OH), 2.46–2.57 (m, 1H, 10-H), 2.66–2.75 (m, 1H, 10-H), 3.40 (s, 3H, C*H*$_3$OCH$_2$O), 3.72–3.78 (m, 2H, 8-H, 9-H), 4.00–4.05 (m, 1H, 7-H), 4.65 (dd, *J* = 10.1, 6.9 Hz, 2H, CH$_3$OC*H*$_2$O), 5.11–5.21 (m, 1H, 3-H), 6.15 (ddd, *J* = 15.7, 7.3, 7.3 Hz, 1H, β-C*H*=CH), 6.97 (d, *J* = 15.7 Hz, 1H, α-C*H*=CH), 7.24–7.31 (m, 1H, 15-H), 7.39–7.44 (m, 2H, 13-H, 14-H), 7.78 (br d, *J* = 7.7 Hz, 16-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 4.9 (OSiCH$_2$*C*H$_3$), 6.9 (OSi*C*H$_2$CH$_3$), 20.2 (*C*H$_3$CHO$_2$Ar), 20.9 (C-5), 29.9 (C-6), 35.1 (C-4), 36.9 (C-10), 55.8 (OCH$_2$O*C*H$_3$), 72.5 (C-3), 73.3 (C-8), 76.7 (C-9), 81.2 (C-7), 95.7 (O*C*H$_2$OCH$_3$), 126.8 (C-15), 127.7 (β-*C*H=CH), 130.0 (C-13), 130.2 (C-16), 130.3 (C-16a), 131.4 (C-14), 131.4 (α-*C*H=CH), 138.1 (C-12a), 168.8 ($CO_2$R);

**HRMS** (ESI): calcd for $C_{26}H_{42}NaO_6Si$ $[M+Na]^+$: 501.26429, found 501.26434.

**(3*S*,7*S*,9*R*)-7-(Methoxymethoxy)-3-methyl-9-[(triethylsilyl)oxy]-4,5,6,7,9,10-hexahydro-1*H*-2-benzoxacyclotetradecine-1,8(3*H*)-dione (8-86)**




To a solution of alcohol **8-85** (5 mg, 10.5 μmol) in abs. $CH_2Cl_2$ (4 mL) at 0 °C (ice bath) was added Dess-Martin periodinane solution in $CH_2Cl_2$ (0.1 mL, 15% wt., 20.5 mg, $d^{20}$ 1.36 g $mL^{-1}$). The resulting mixture was stirred at the same temperature for 1 h. Then the mixture was

treated with satd. $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude ketone **8-86** (5.5 mg) was used in the next step without additional purification.

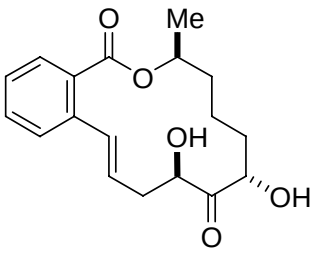
Data for purified product:

**$R_f$** = 0.45 (petroleum ether/EtOAc, 5:1);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 0.63 (q, *J* = 15.6, 7.8 Hz, 6H, OSi(C*H*$_2$CH$_3$)$_3$), 0.97 (t, *J* = 7.8 Hz, 9H, OSi(CH$_2$C*H*$_3$)$_3$), 1.37 (d, *J* = 5.8 Hz, 3H, C*H*$_3$CHO$_2$Ar), 1.45–1.67 (m, 5H, CH$_2$), 1.98–2.10 (m, 1H, CH$_2$), 2.65–2.75 (m, 1H, 10-H), 2.87–2.97 (m, 1H, 10-H), 4.20–4.27 (m, 1H, 7-H), 4.59–4.65 (m, 1H, 9-H), 5.12-5.20 (m, 1H, 3-H), 6.04 (ddd, *J* = 15.6, 7.9, 5.5 Hz, 1H, β-C*H*=CH), 6.96 (d, *J* = 15.6 Hz, α-C*H*=CH), 7.23–7.30 (m, 1H, 15-H), 7.35–7.42 (m, 2H, 13-H, 14-H), 7.78 (d, *J* = 7.3 Hz, 16-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 4.7 (OSi(CH$_2$C*H*$_3$)$_3$), 6.8 (OSi(*C*H$_2$CH$_3$)$_3$), 20.3 (*C*H$_3$CHO$_2$Ar), 20.8 (C-5), 29.3 (C-6), 35.3 (C-4), 38.2 (C-10), 56.1 (*C*H$_3$OCH$_2$O), 72.5 (C-3), 76.3 (C-9), 78.1 (C-7), 96.8 (CH$_3$O*C*H$_2$O), 126.9 (C-15), 127.1 (β-*C*H=CH), 128.1 (C-13), 129.9 (C-16a), 130.1 (C-16), 131.6 (C-14), 132.5 (α-*C*H=CH), 137.7 (C-12a), 168.2 (*C*O$_2$R), 207.3 (R$_2$*C*=O).

### *des*-Oxy-di-*des*-methoxy-(-)-queenslandon (6-2)




A solution of protected ketone **8-86** (5 mg, 10.5 μmol) in a THF/MeOH mixture (4 mL, 1/1) was treated with concentrated HCl (0.1 mL) and refluxed for 36 h. Then the mixture was neutralized with aqueous $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (5 × 10 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated in vacuo.

The residue was purified by flash chromatography ($CHCl_3$/MeOH, 40:1) to give 2.2 mg (65%) of queenslandon analog **6-2**.

**$R_f$** = 0.25 ($CHCl_3$/MeOH, 40:1);

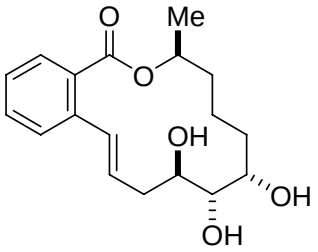
**$[\alpha]^{20}_D$** = –84.5 (*c* 0.15, MeOH);

**$^1$H NMR** (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 3H, C*H*$_3$CHO$_2$Ar), 1.43–1.75 (m, 5H, $CH_2$), 1.98–2.10 (m, 1H, $CH_2$), 2.77–2.95 (m, 3H, 10-H, 13-OH), 3.58 (br s, 1H, 11-OH), 4.30–4.37 (m, 1H, 13-H), 4.61–4.68 (m, 1H, 11-H), 5.14–5.23 (m, 1H, 17-H), 5.87 (ddd, *J* = 15.5, 8.8, 5.1 Hz, 1H, β-C*H*=CH), 7.08 (d, *J* = 15.5 Hz, α-C*H*=CH), 7.28–7.35 (m, 2H, 4-H, 6-H), 7.40–7.47 (m, 1H, 5-H), 7.89 (br d, *J* = 7.8 Hz, 5-H);

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ = 20.4 (*C*H$_3$CHO$_2$Ar), 20.4 (C-15), 33.1 (C-14), 35.3 (C-16), 36.8 (C-10), 72.1 (C-17), 74.8 (C-11), 75.1 (C-13), 126.0 (C-4), 127.3 (β-*C*H=CH), 128.6 (C-6), 129.3 (C-2), 130.9 (C-3), 132.1 (C-5), 133.9 (α-*C*H=CH), 138.6 (C-7), 168.0 ($CO_2$R), 212.5 ($R_2$C=O);

**HRMS** (ESI): calcd for $C_{18}H_{22}O_5Na$ $[M+Na]^+$: 341.13594, found 341.13588.

**(3S,7S,8S,9R)-7,8,9-Trihydroxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-2-benzoxacyclotetra decin-1-one (8-87)**




A solution of MOM-protected diol **8-84** (22 mg, 6 μmol) in a THF/MeOH mixture (4 mL, 1:1) was treated with concentrated HCl (0.1 mL) and refluxed for 36 h. Then the mixture was treated with satd. $NaHCO_3$ solution (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and evaporated to dryness.

Purification by flash chromatography ($CHCl_3$/MeOH, 40:1) afforded the triol **8-87** as a colorless solid (13 mg, 67%).

**$R_f$** = 0.2 ($CHCl_3$/MeOH, 40:1);

**m.p.** 122–126 °C;

**$[\alpha]^{20}_D$** = –34.5 (*c* 0.7, $CH_2Cl_2$);

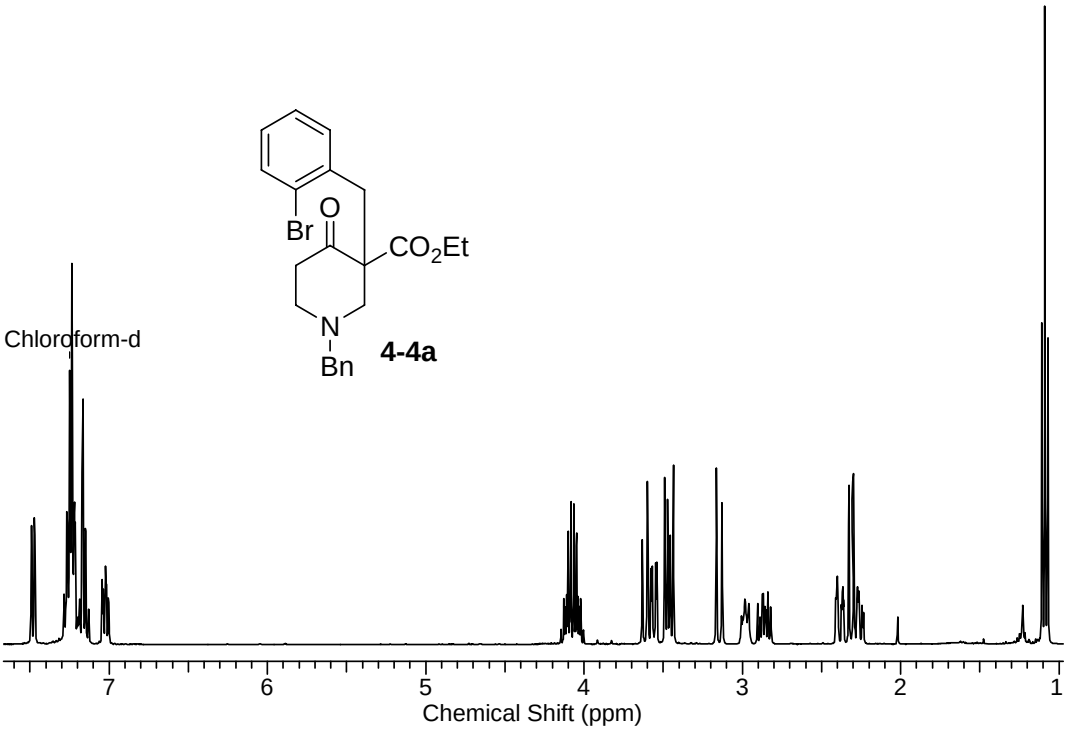
**$^1$H NMR** (400 MHz, $CD_3OD$): δ = 1.24 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CHO$_2$Ar), 1.30–1.85 (m, 6H, $CH_2$), 2.32–2.41 (m, 1H, 10-H), 2.67–2.77 (m, 1H, 10-H), 3.55–3.60 (m, 1H, 8-H), 3.70–3.75 (m, 1H, 7-H), 3.87–3.94 (m, 1H, 9-H), 5.09–5.18 (m, 1H, CH$_3$C*H*O$_2$CAr), 6.05 (ddd, *J* = 15.5, 9.8, 5.3 Hz, 1H, β-C*H*=CH), 6.79 (d, *J* = 15.5 Hz, 1H, α-C*H*=CH), 7.20 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.40 (br d, *J* = 7.5 Hz, 1H), 7.45 (br d, *J* = 7.5 Hz, 1H);

**$^{13}$C NMR** (100 MHz, $CD_3OD$): δ = 19.8 (*C*H$_3$CHO$_2$Ar), 21.0 (C-5), 33.4 (C-6), 36.3 (C-4), 38.8 (C-10), 73.5 (C-3), 74.7 (C-8), 75.2 (C-9), 78.6 (C-7), 127.9 (C-15), 128.2 (C-13), 129.6 (β-*C*H=CH), 131.6 (C-16a), 132.2 (C-14), 132.3 (C-13), 132.8 (α-CH=CH), 138.6 (C-12a), 170.7 ($CO_2$R);

**HRMS** (ESI): calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$: 343.15159, found 343.15203.

# 11 Appendix

## 11.1 NMR-Spectra for important compounds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N
Bn
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Chloroform-d
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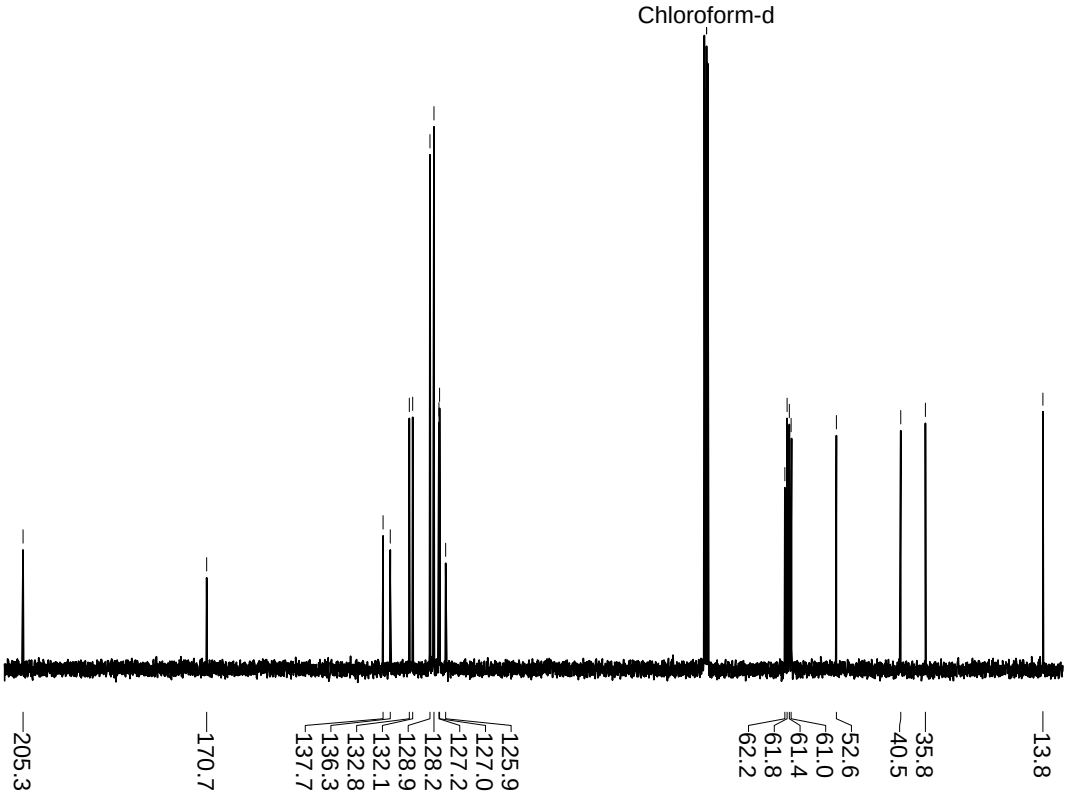
6
5
4
3
2
1
Chemical Shift (ppm)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132.8
132.1
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61.4
61.0
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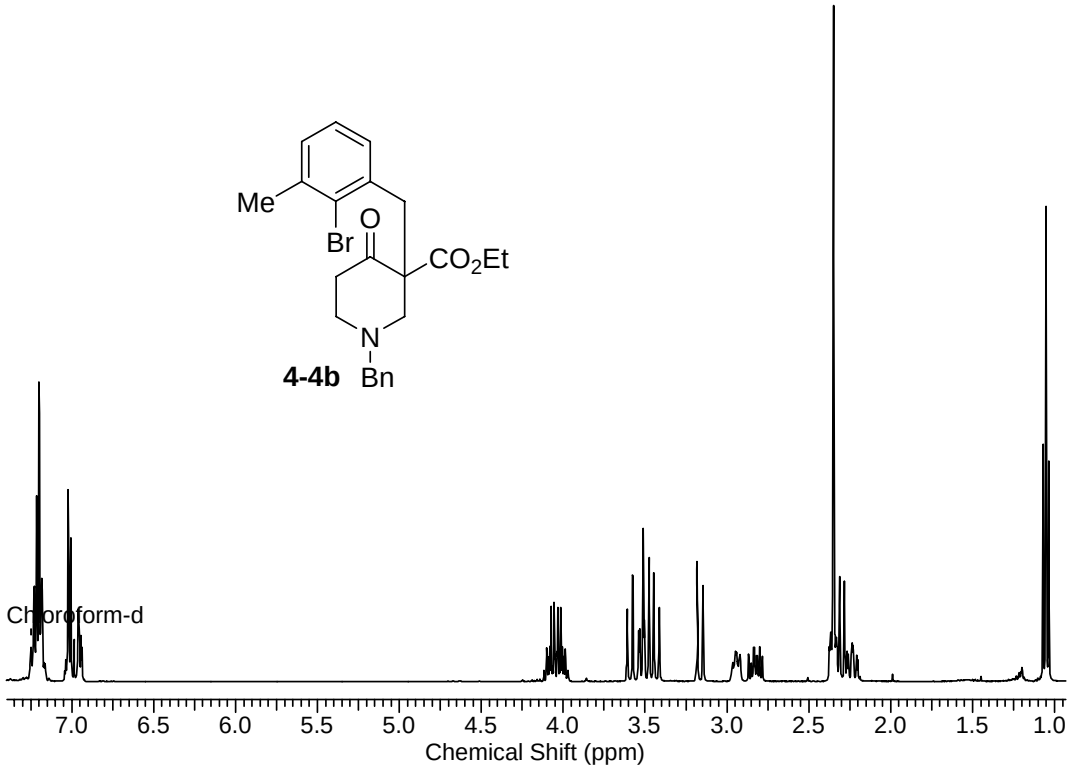
40.5
35.8
13.8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Br
O
CO2Et
N
Bn
4-4b
Chloroform-d
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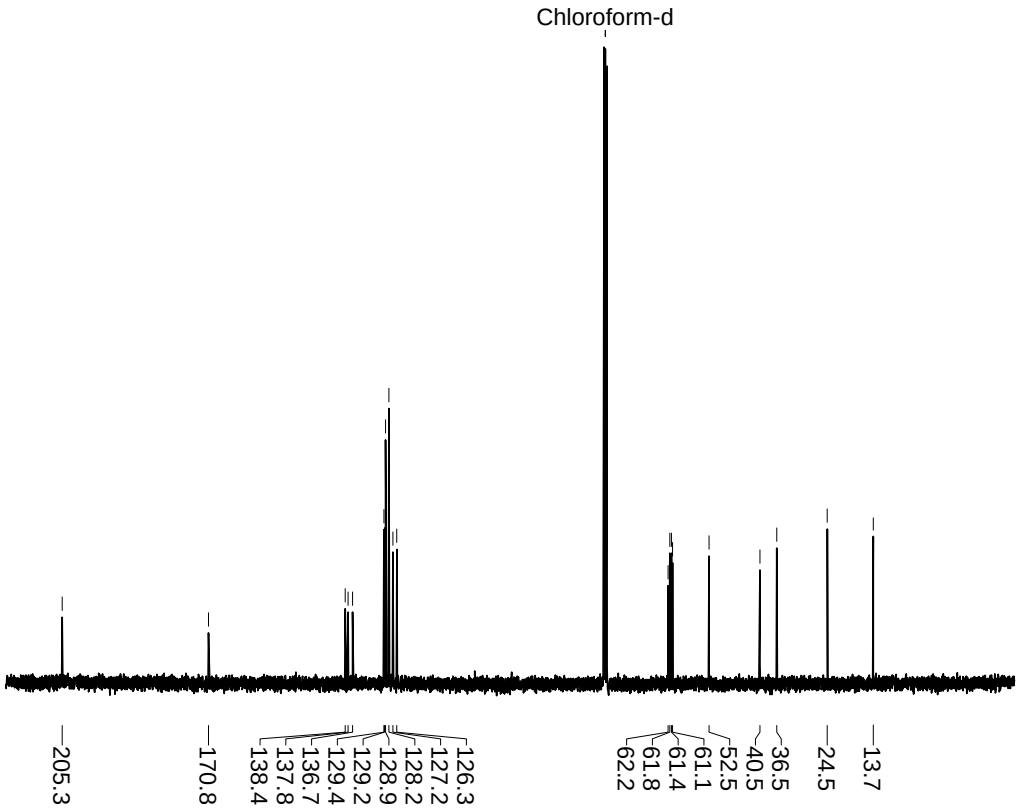
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)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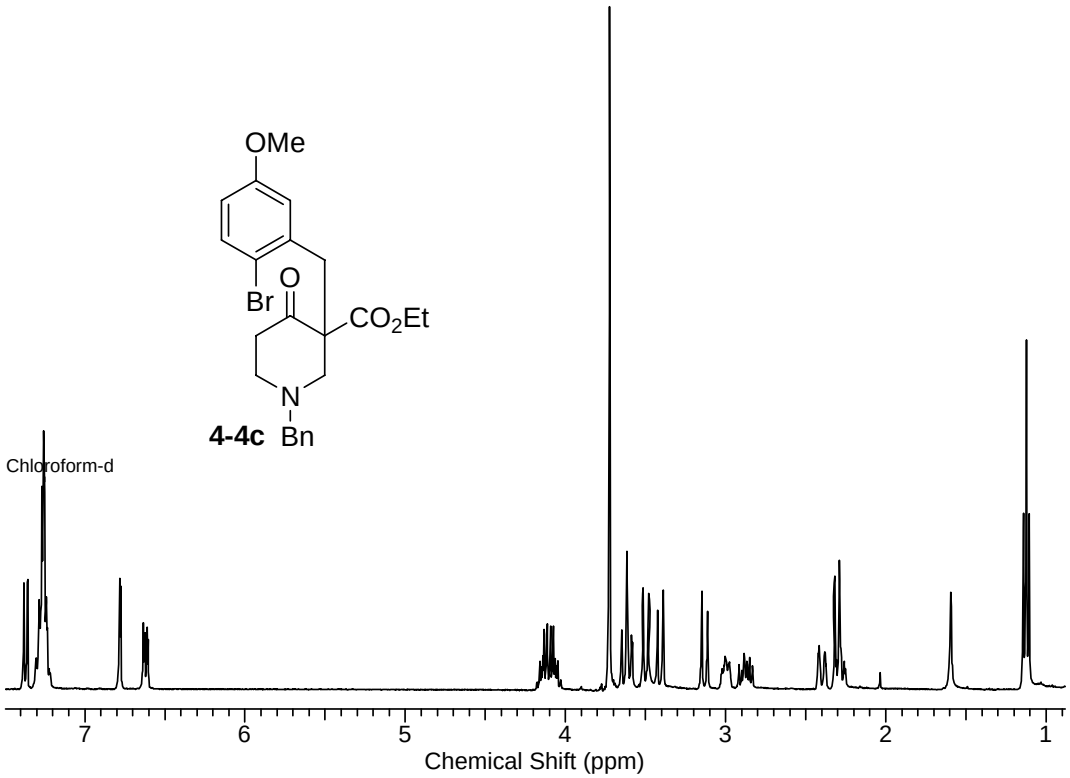
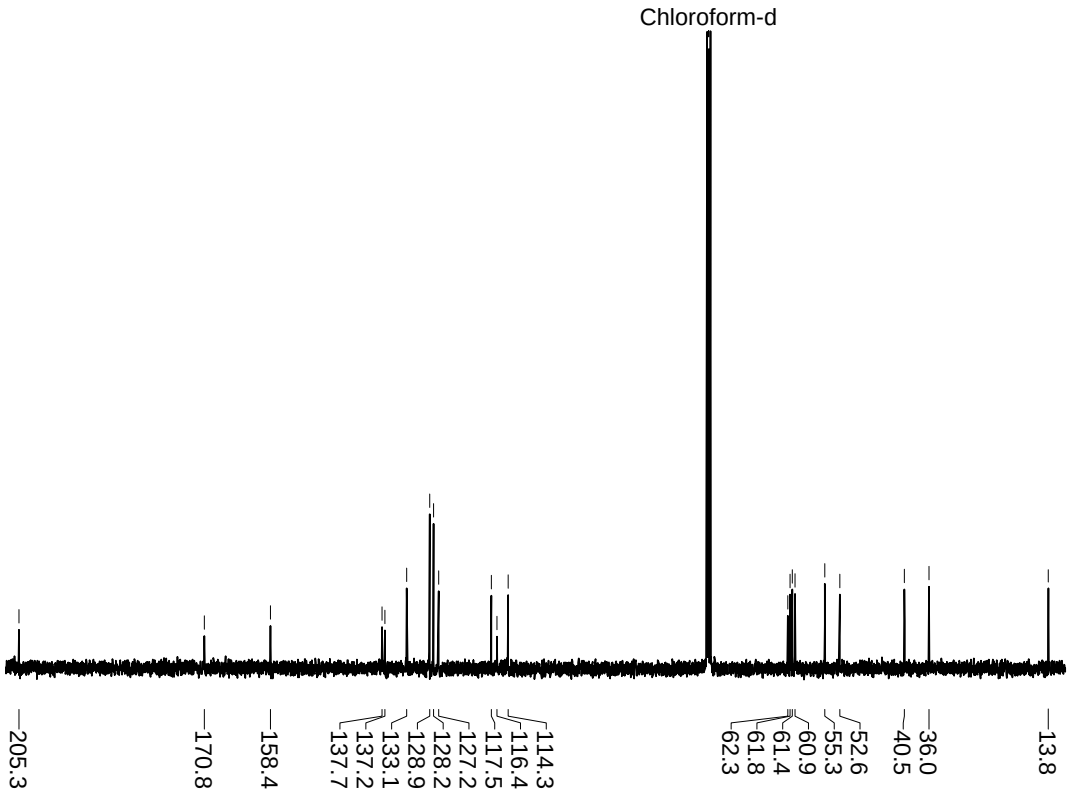
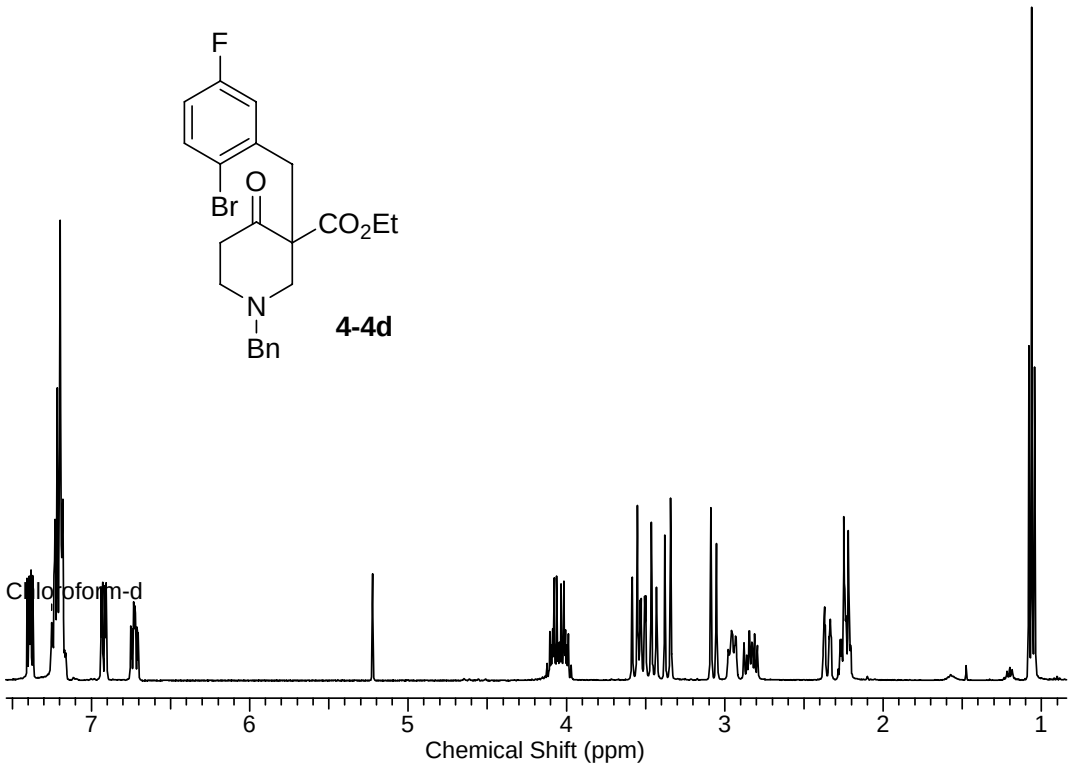
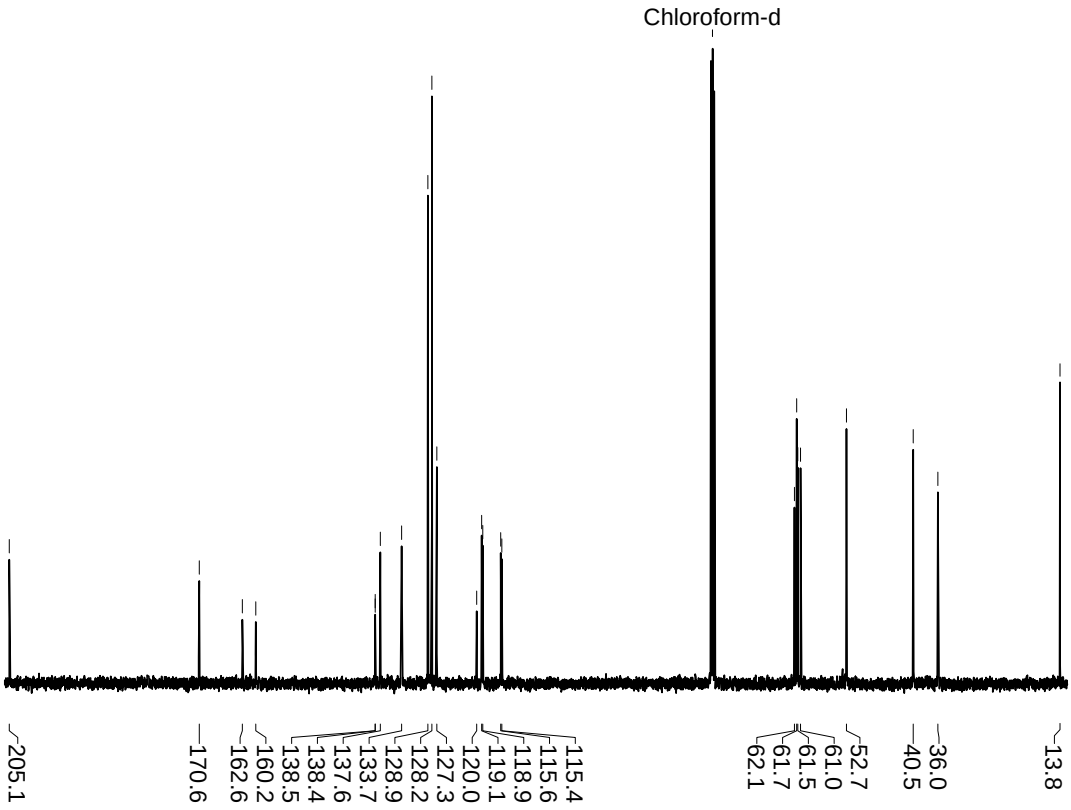
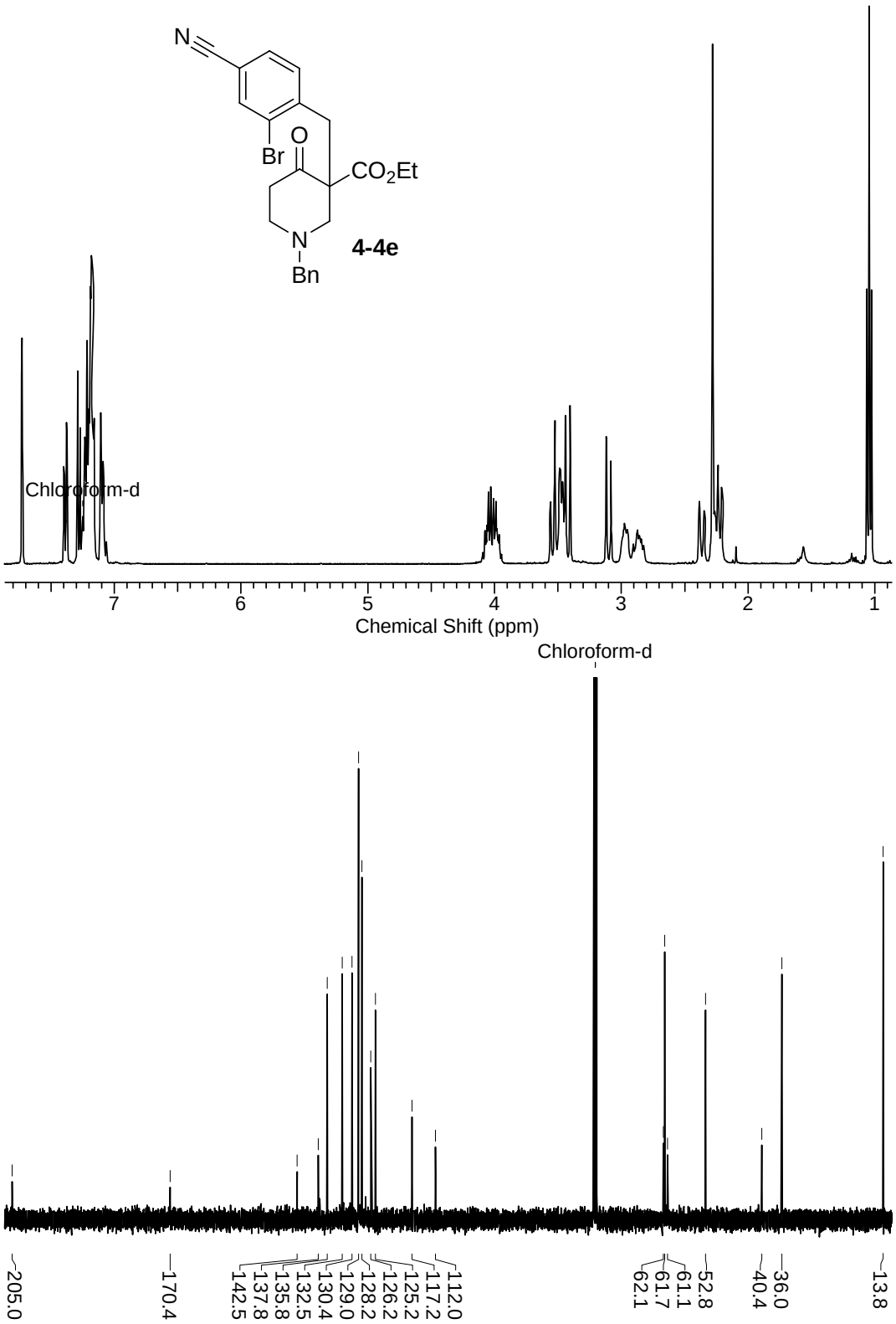
61.1
52.5
40.5
36.5
24.5
13.7

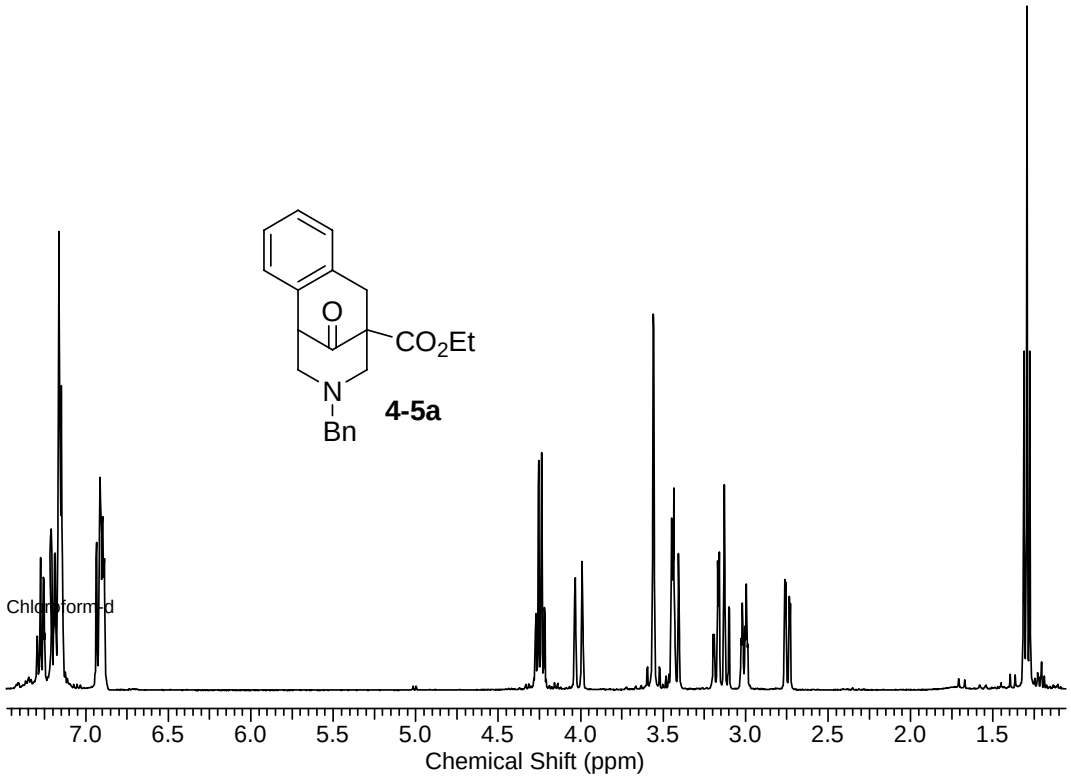

OMe
O
Br
CO2Et
N
Bn
4-4c
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

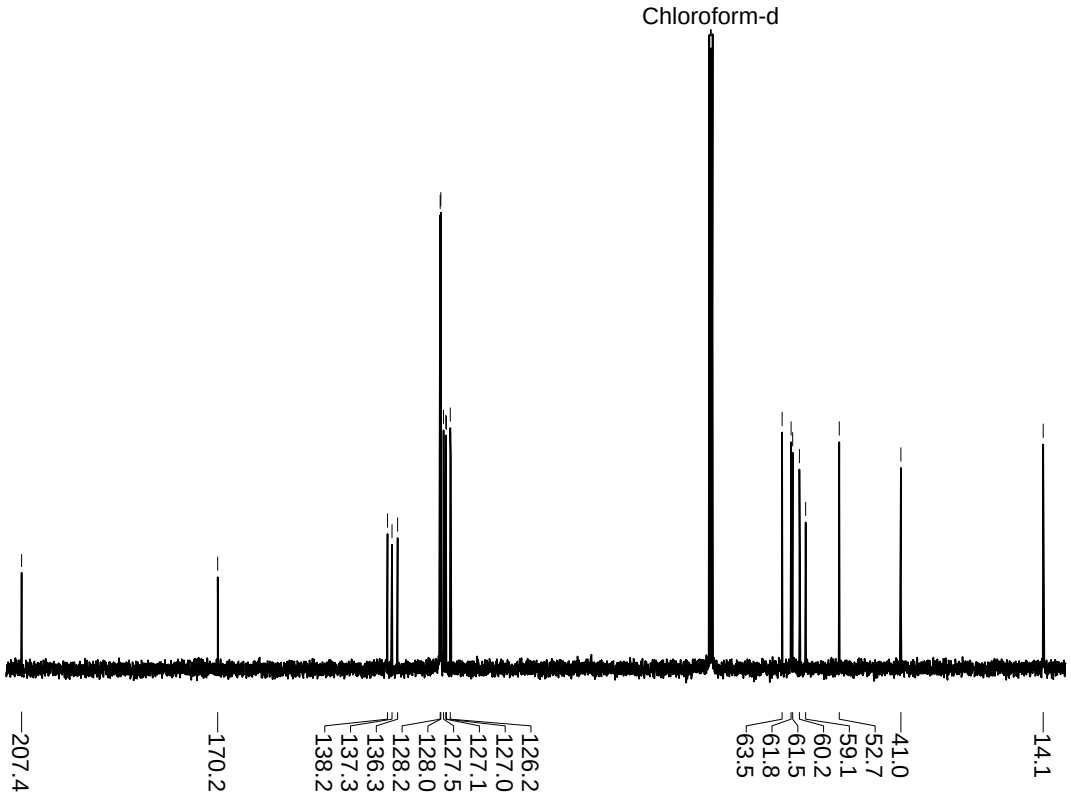

Chloroform-d
205.3
170.8
158.4
137.7
137.2
133.1
128.9
128.2
127.2
117.5
116.4
114.3
62.3
61.8
61.4
60.9
55.3
52.6
40.5
36.0
13.8

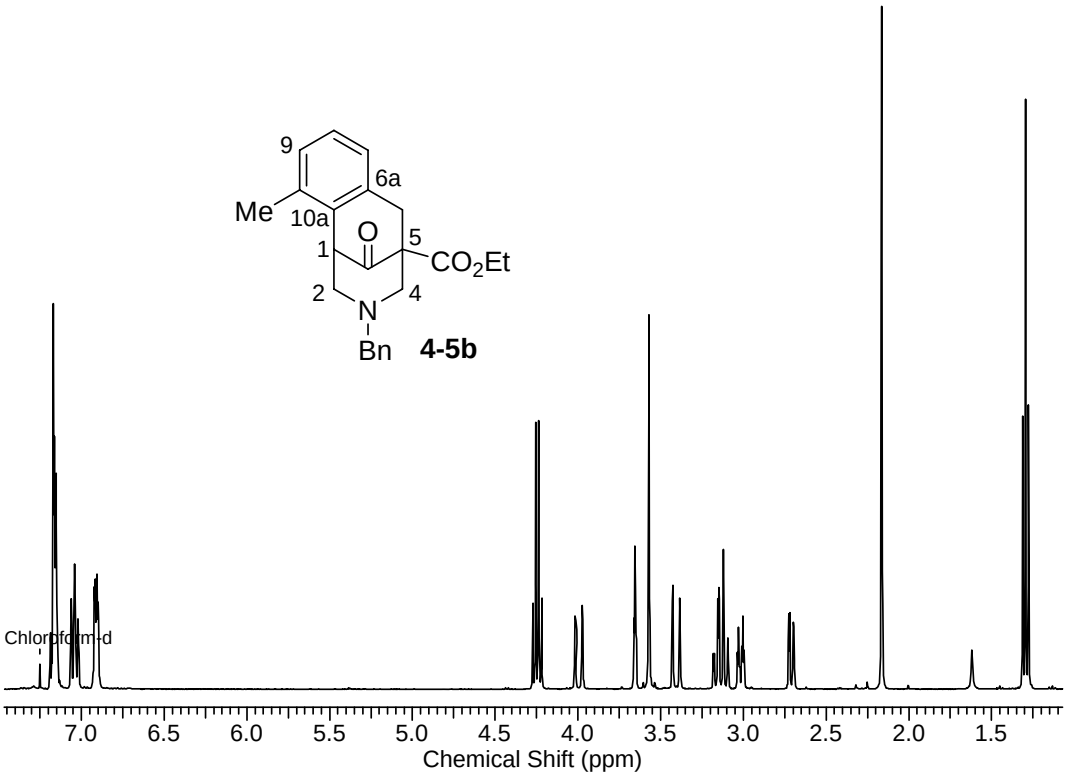

F
O
Br
CO2Et
N
Bn
4-4d
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

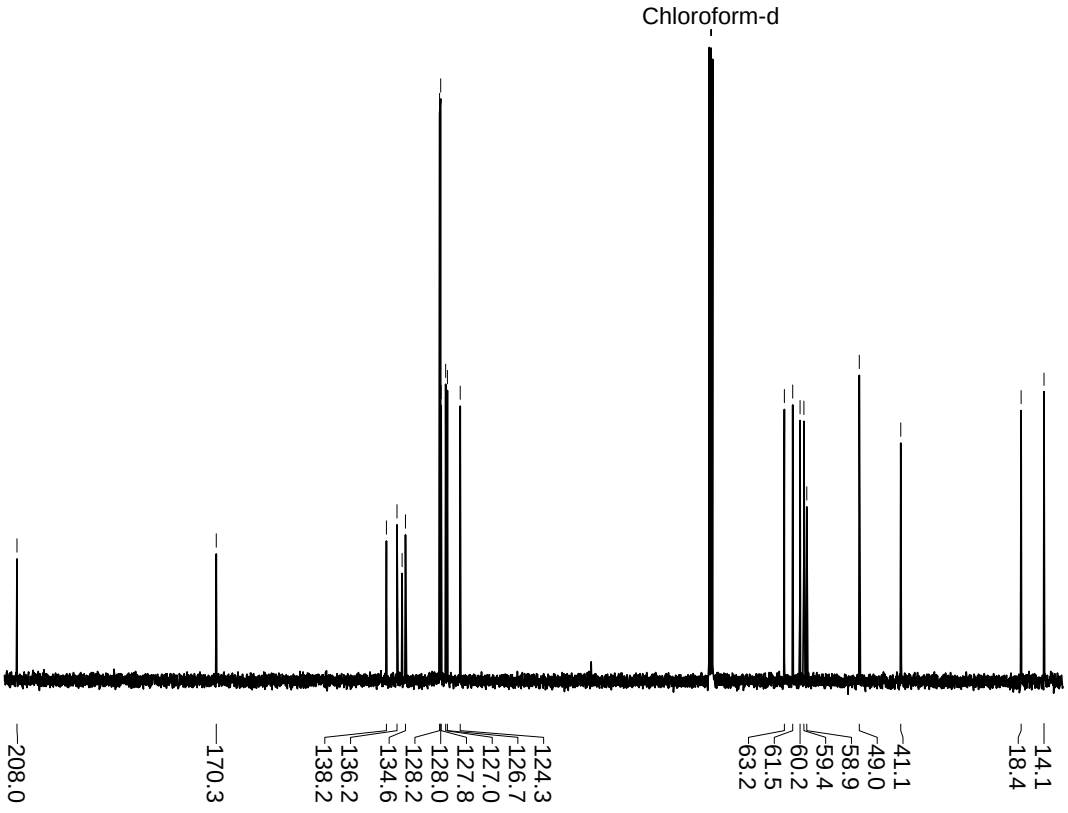

Chloroform-d
205.1
170.6
162.6
160.2
138.5
138.4
137.6
133.7
128.9
128.2
127.3
120.0
119.1
118.9
115.6
115.4
62.1
61.7
61.5
61.0
52.7
40.5
36.0
13.8

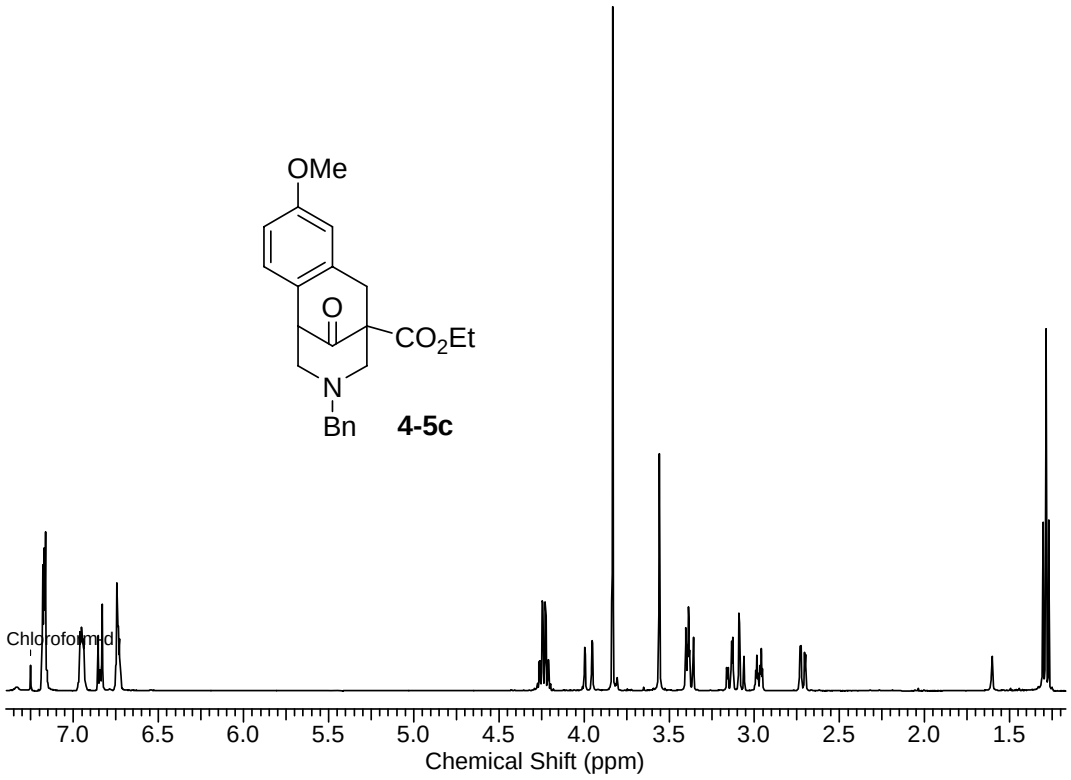

N
O
Br
CO2Et
N
Bn
4-4e
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)
Chloroform-d
205.0
170.4
142.5
137.8
135.8
132.5
130.4
129.0
128.2
126.2
125.2
117.2
112.0
62.1
61.7
61.1
52.8
40.4
36.0
13.8

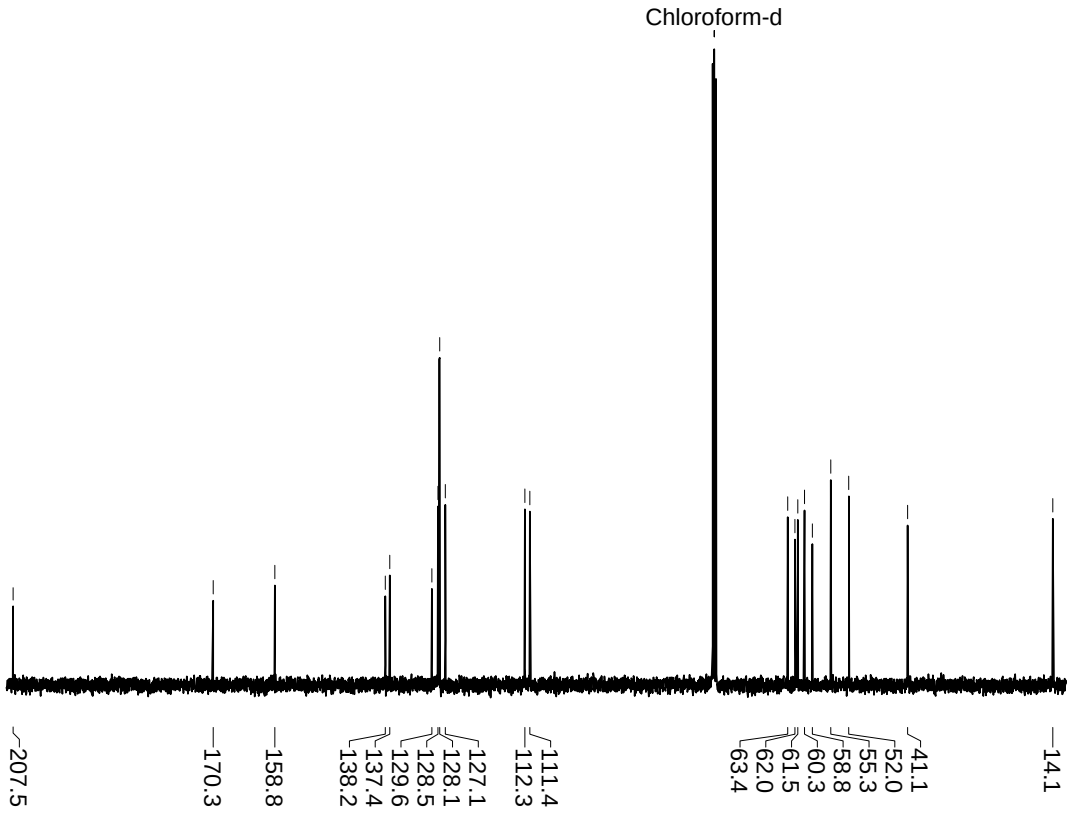

O
CO2Et
N
Bn
4-5a
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

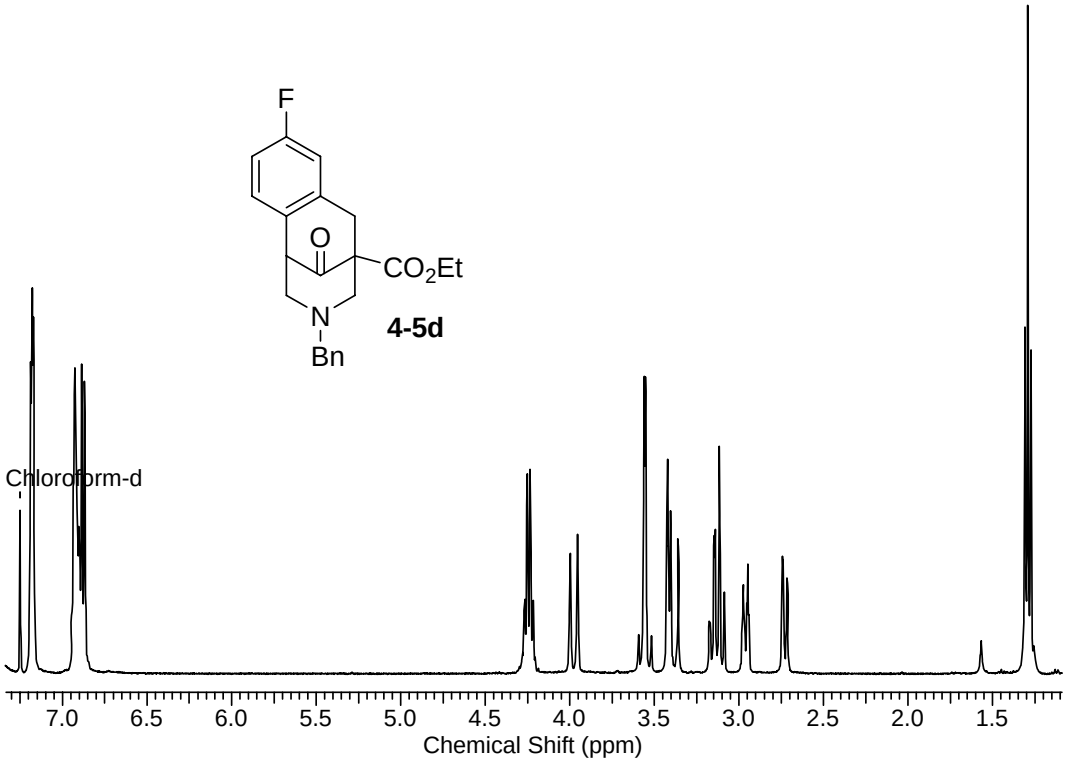

Chloroform-d
207.4
170.2
138.2
137.3
136.3
128.2
128.0
127.5
127.1
127.0
126.2
63.5
61.8
61.5
60.2
59.1
52.7
41.0
14.1

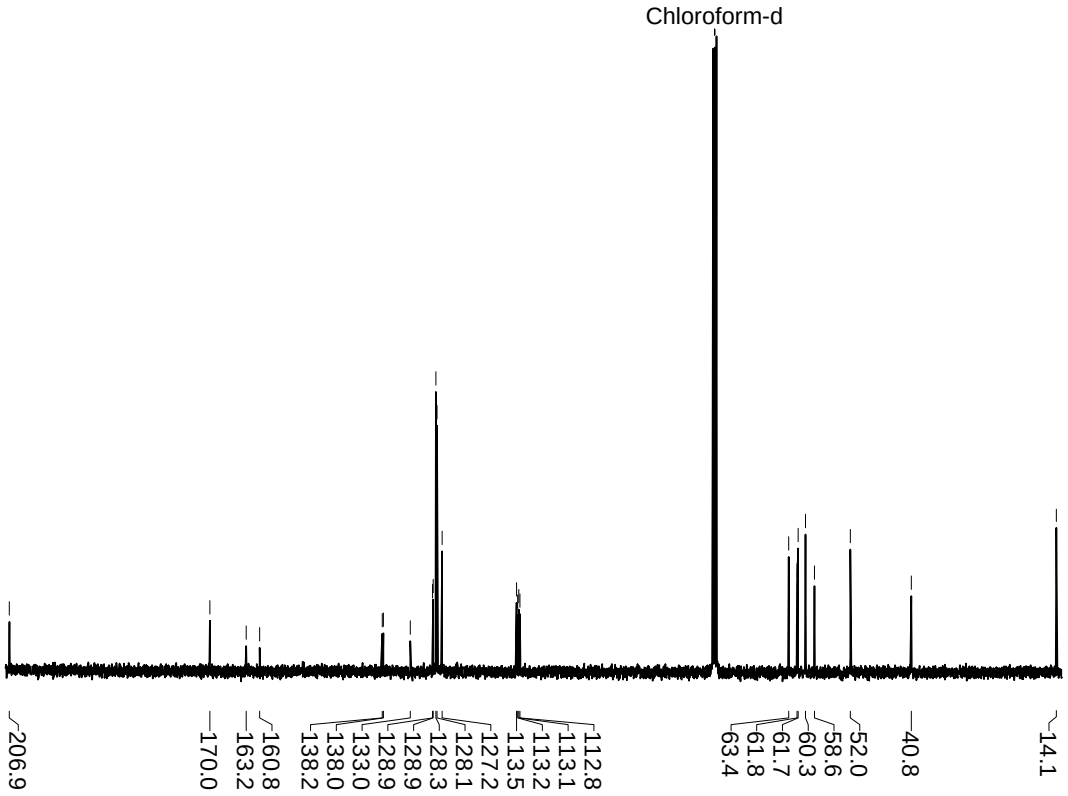

9
6a
Me
10a
O
5
1
CO2Et
2
4
N
Bn
4-5b
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

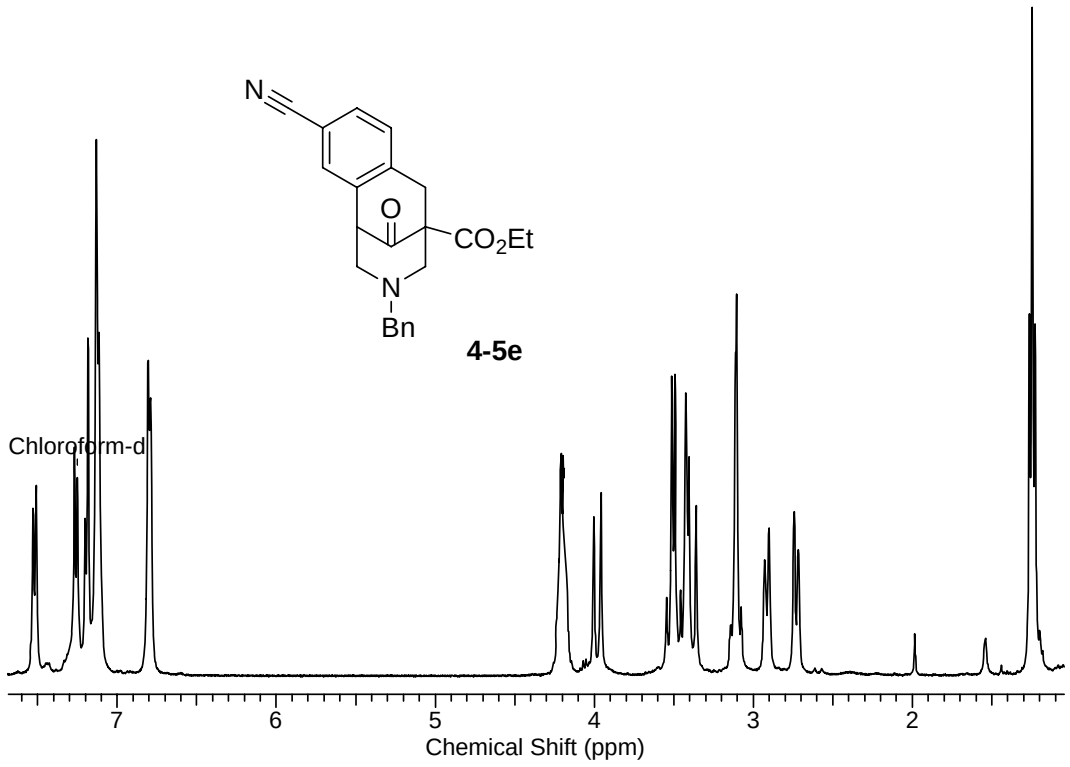

Chloroform-d
208.0
170.3
138.2
136.2
134.6
128.2
128.0
127.8
127.0
126.7
124.3
63.2
61.5
60.2
59.4
58.9
49.0
41.1
18.4
14.1

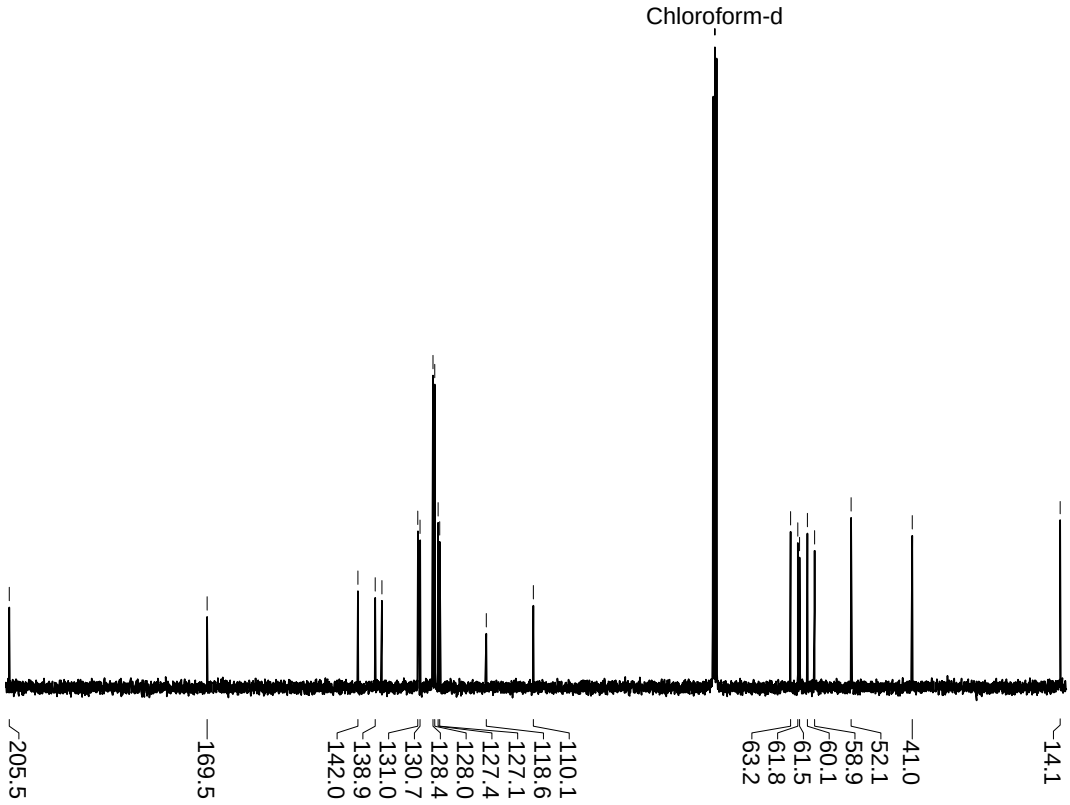

OMe
O
CO2Et
N
Bn
4-5c
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

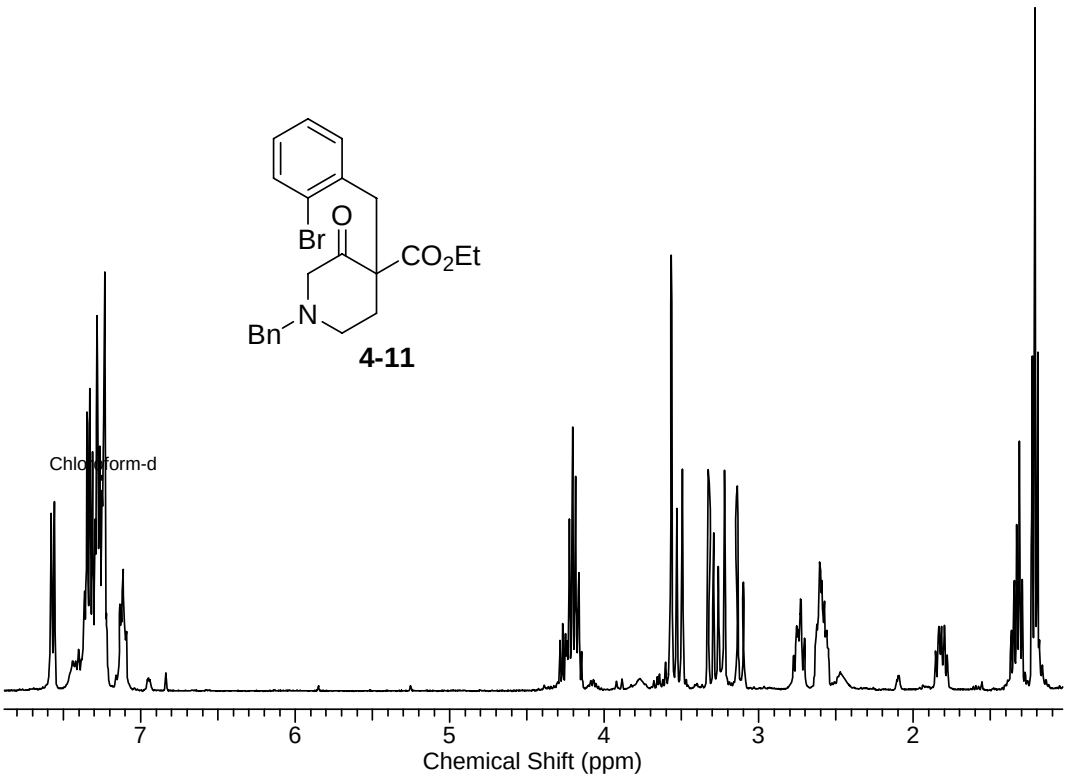

Chloroform-d
207.5
170.3
158.8
138.2
137.4
129.6
128.5
128.1
127.1
112.3
111.4
63.4
62.0
61.5
60.3
58.8
55.3
52.0
41.1
14.1

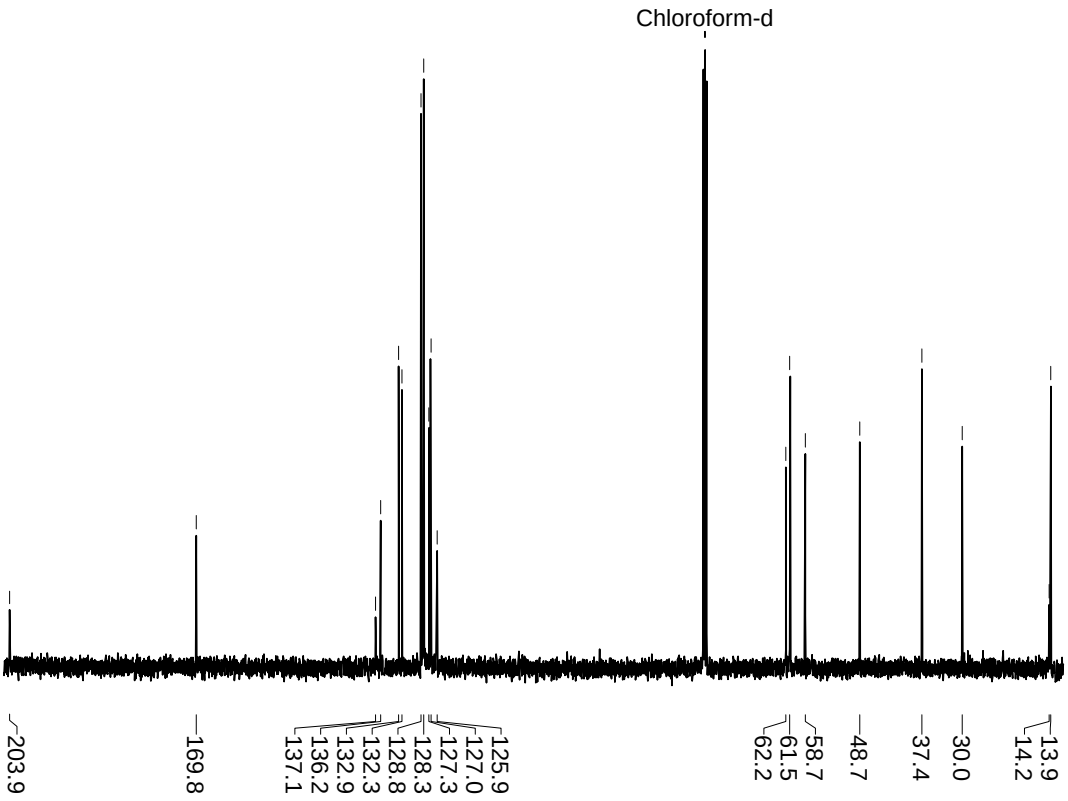

F
O
CO2Et
N
Bn
4-5d
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

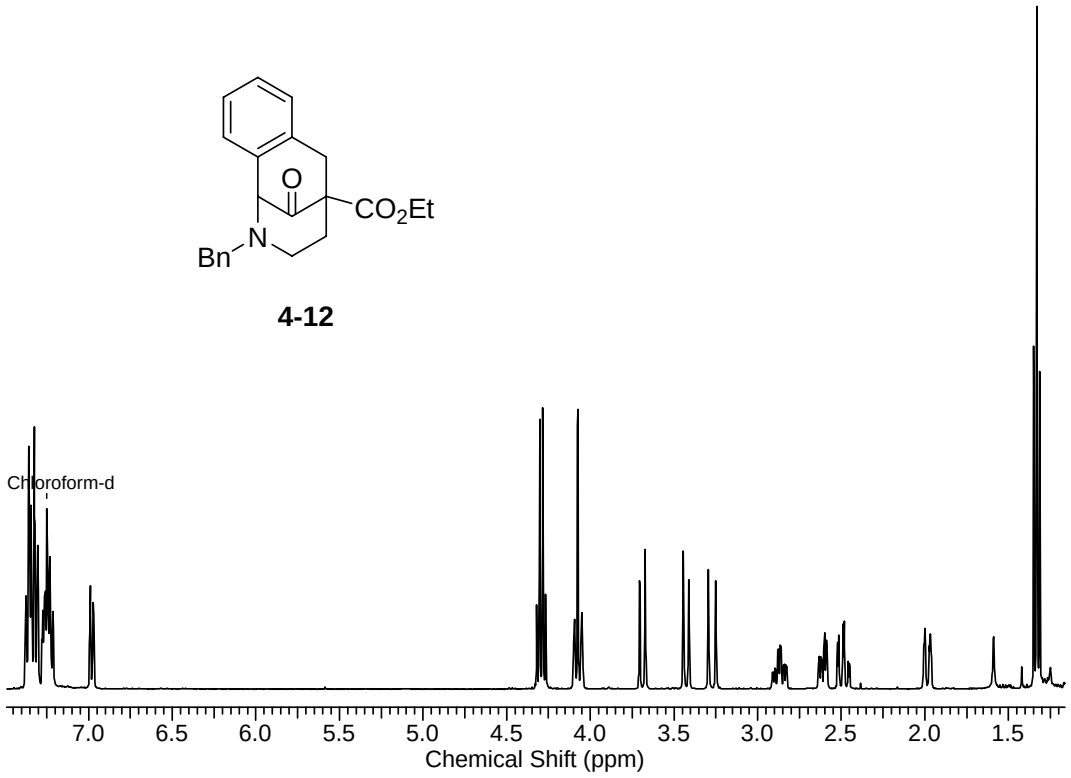

Chloroform-d
206.9
170.0
163.2
160.8
138.2
138.0
133.0
128.9
128.9
128.3
128.1
127.2
113.5
113.2
113.1
112.8
63.4
61.8
61.7
60.3
58.6
52.0
40.8
14.1


N
O
CO2Et
N
Bn
4-5e
Chloroform-d
7
6
5
4
3
2
Chemical Shift (ppm)

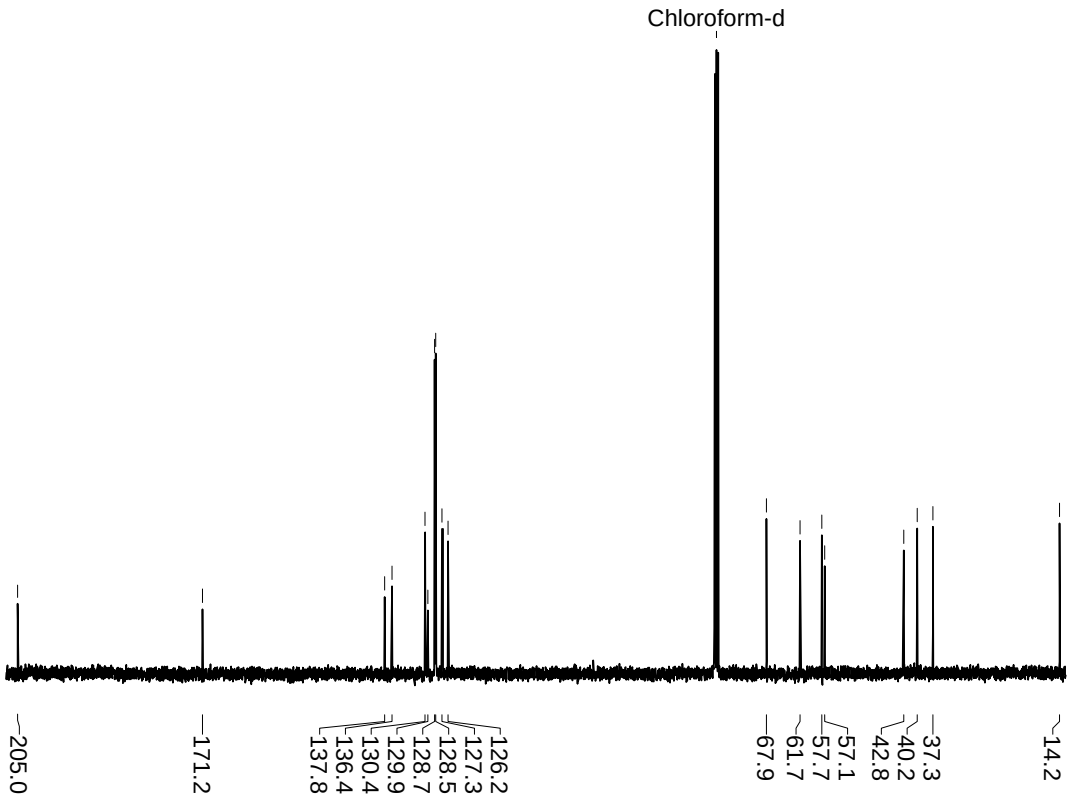

Chloroform-d
205.5
169.5
142.0
138.9
131.0
130.7
128.4
128.0
127.4
127.1
118.6
110.1
63.2
61.8
61.5
60.1
58.9
52.1
41.0
14.1

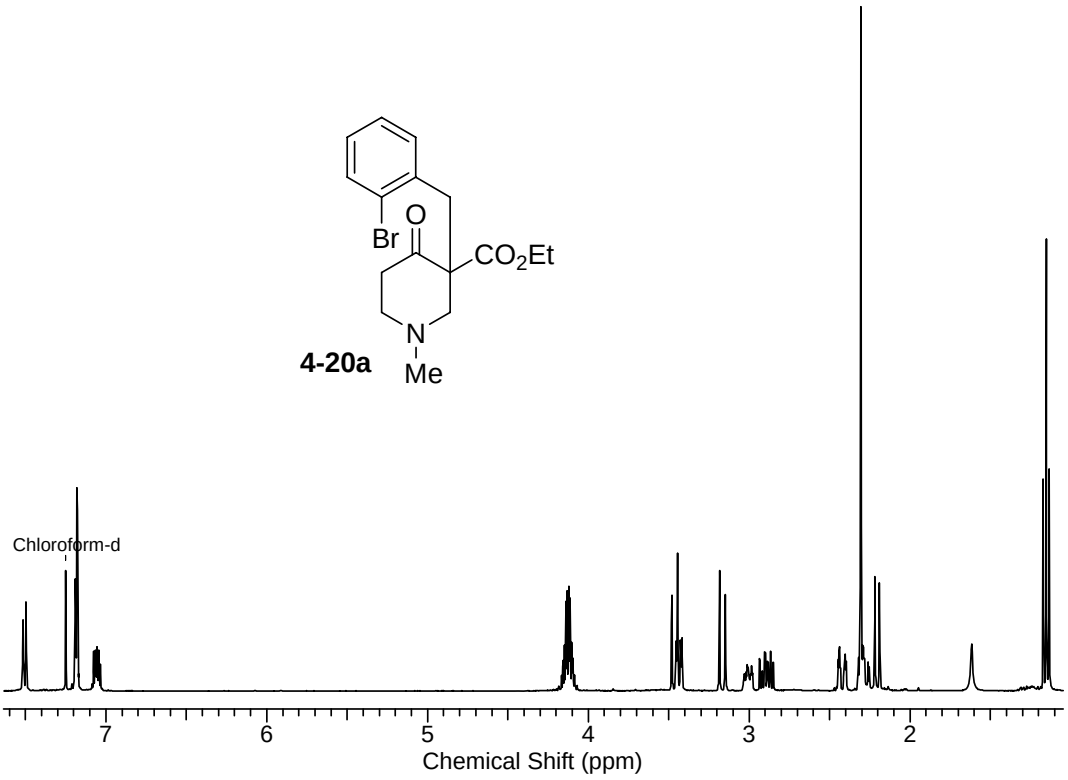

Br
O
CO2Et
N
Bn
4-11
Chloroform-d
7
6
5
4
3
2
Chemical Shift (ppm)

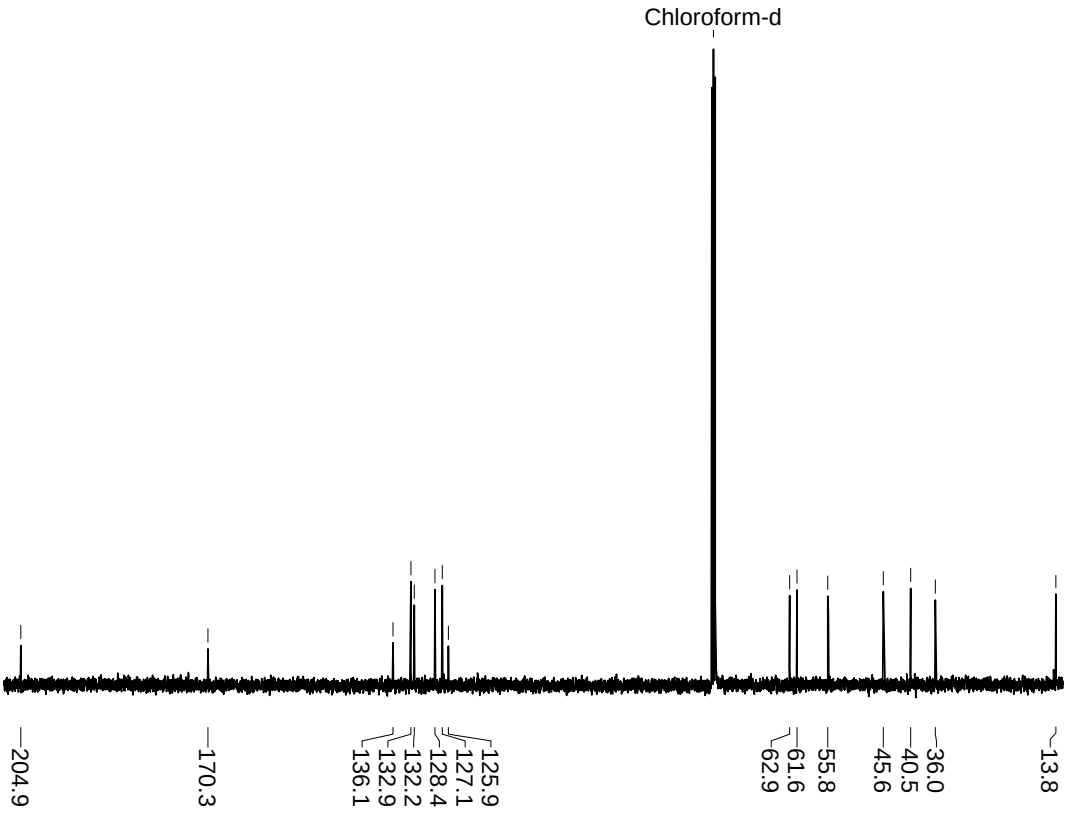

Chloroform-d
203.9
169.8
137.1
136.2
132.9
132.3
128.8
128.3
127.3
127.0
125.9
62.2
61.5
58.7
48.7
37.4
30.0
14.2
13.9

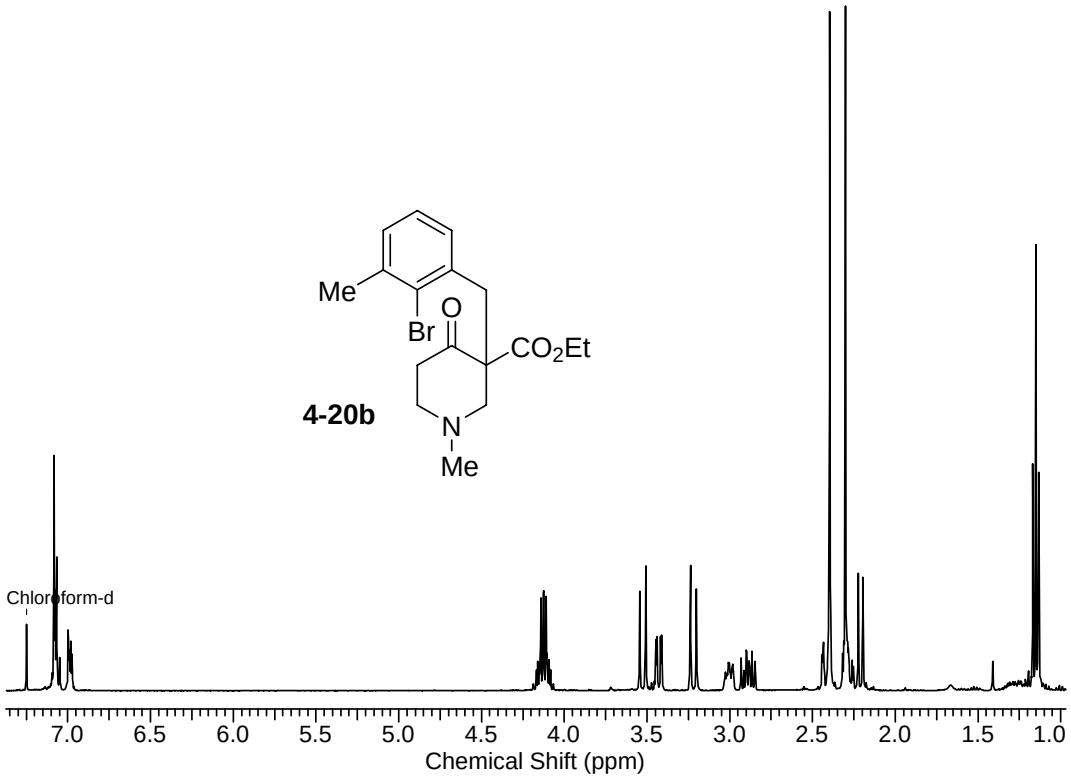

O
CO2Et
N
Bn
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

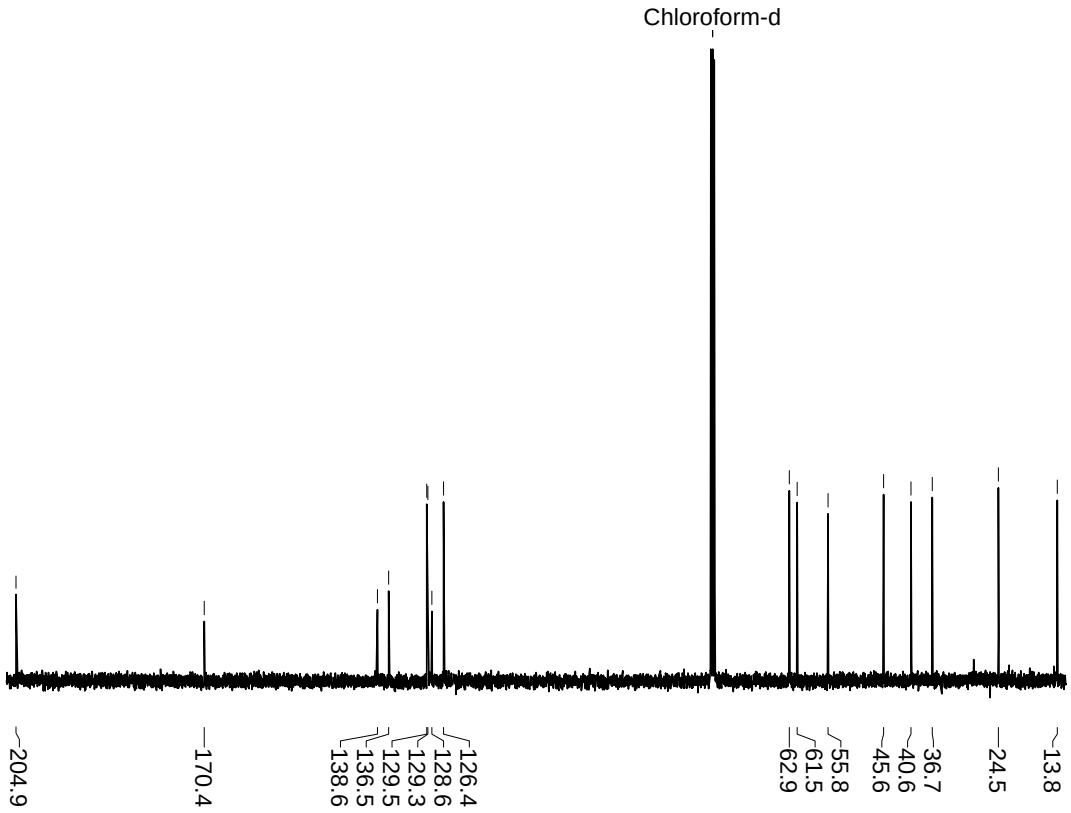
**4-12**

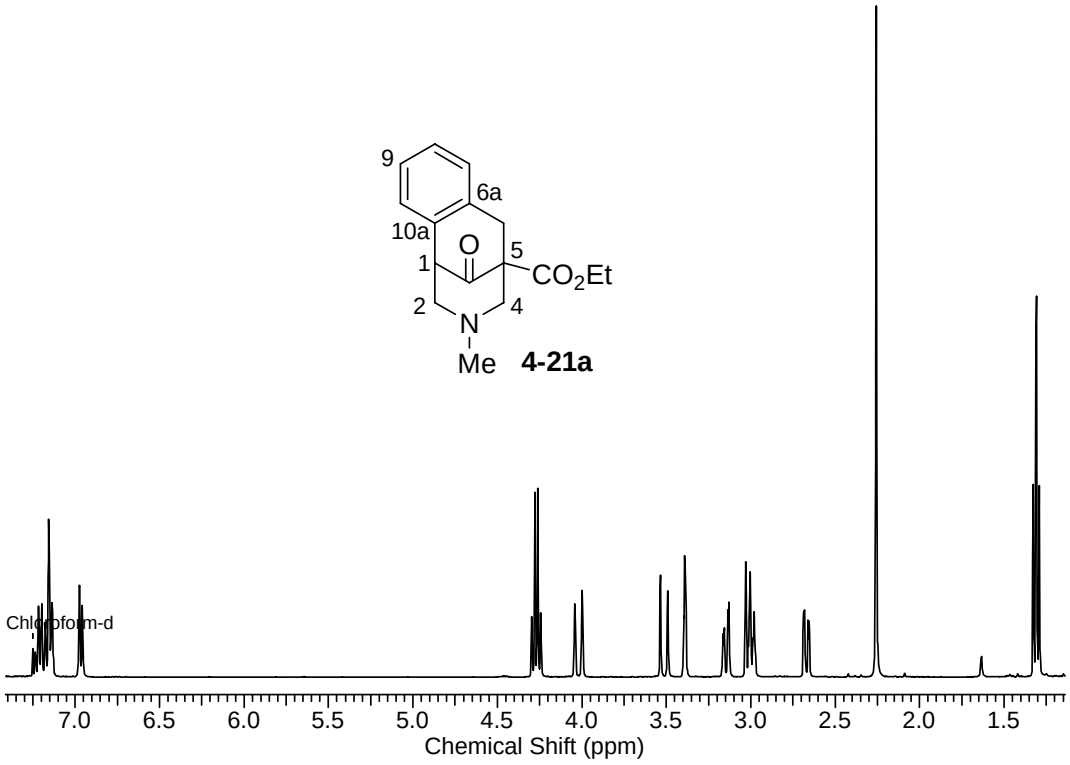

Chloroform-d
205.0
171.2
137.8
136.4
130.4
129.9
128.7
128.5
127.3
126.2
67.9
61.7
57.7
57.1
42.8
40.2
37.3
14.2


Br
O
CO2Et
N
Me
4-20a
Chloroform-d
7
6
5
4
3
2
Chemical Shift (ppm)

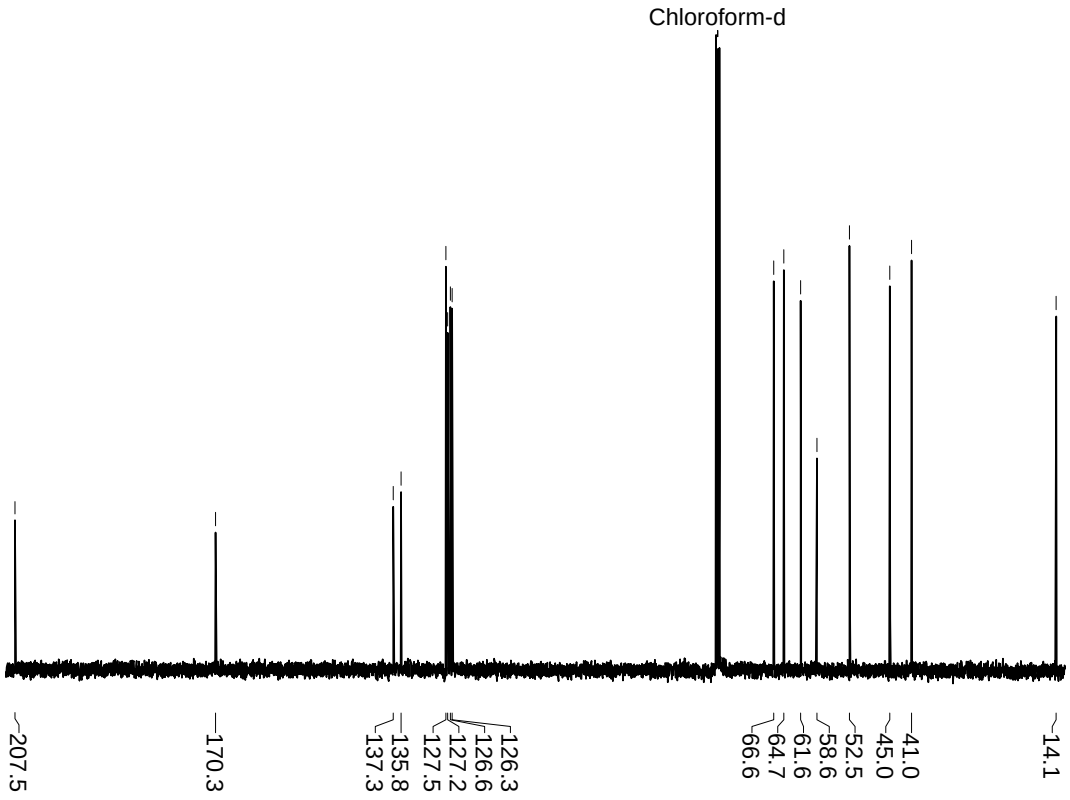

Chloroform-d
204.9
170.3
136.1
132.9
132.2
128.4
127.1
125.9
62.9
61.6
55.8
45.6
40.5
36.0
13.8

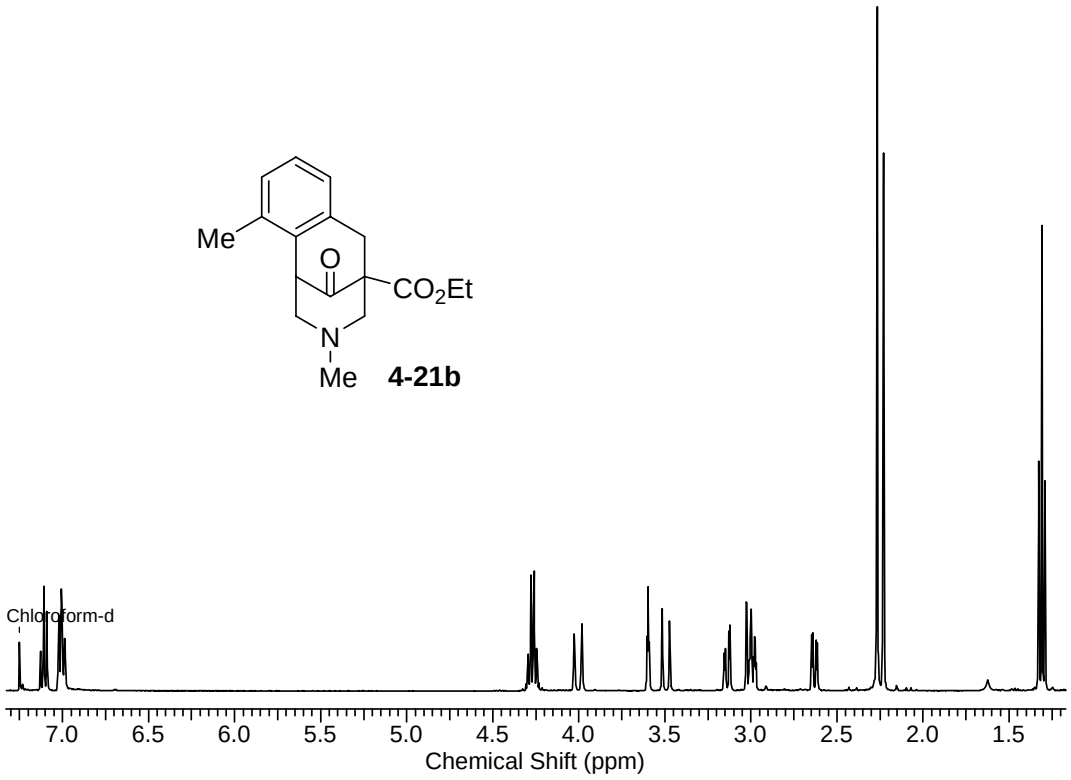

Me
O
Br
CO2Et
4-20b
N
Me
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

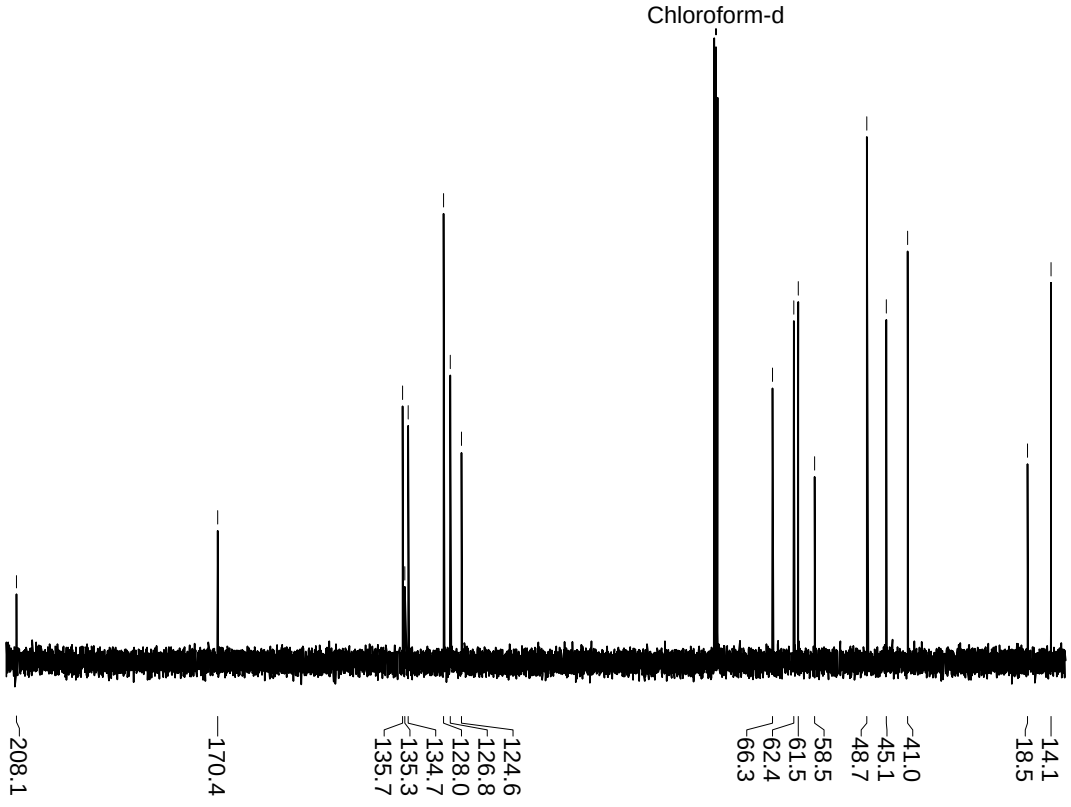

Chloroform-d
204.9
170.4
138.6
136.5
129.5
129.3
128.6
126.4
62.9
61.5
55.8
45.6
40.6
36.7
24.5
13.8

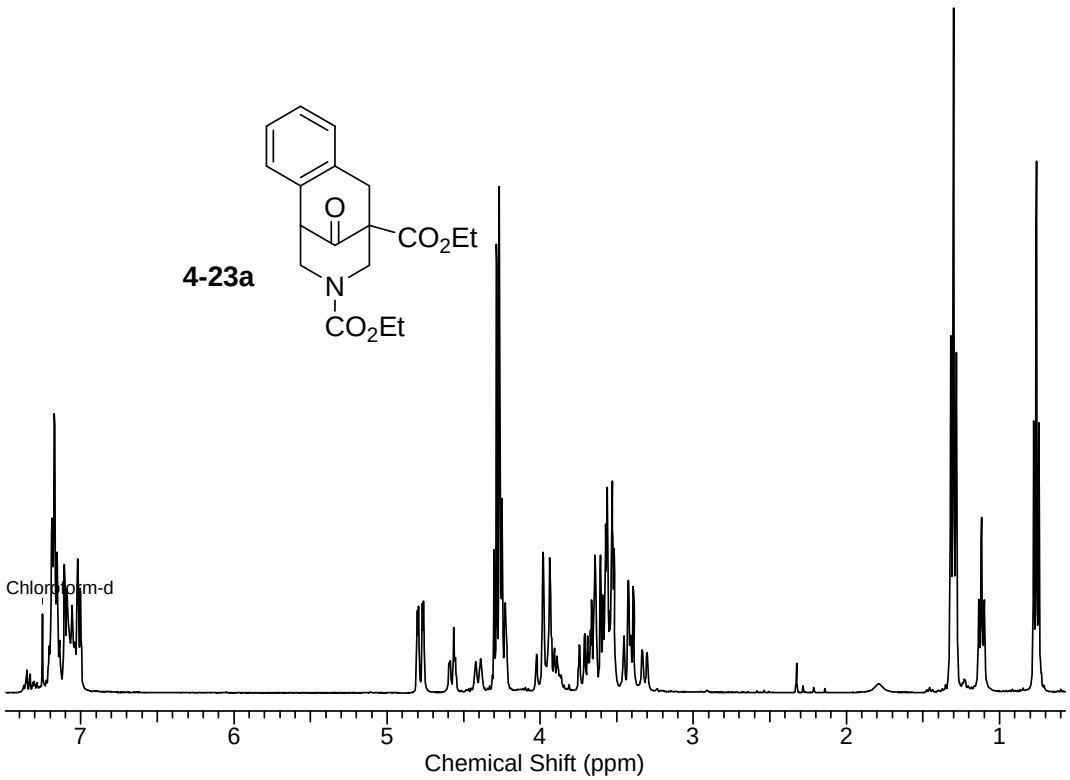

9
6a
10a
O
5
1
$CO_2Et$
2
4
N
Me
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

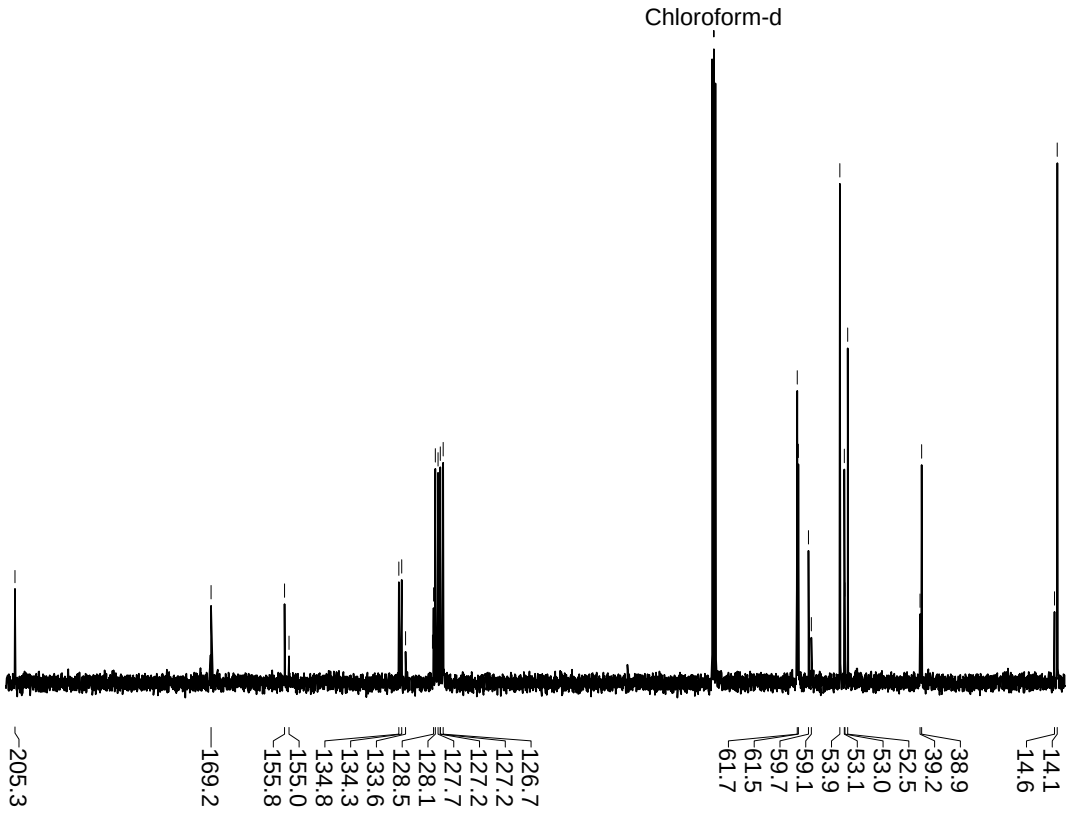
**4-21a**

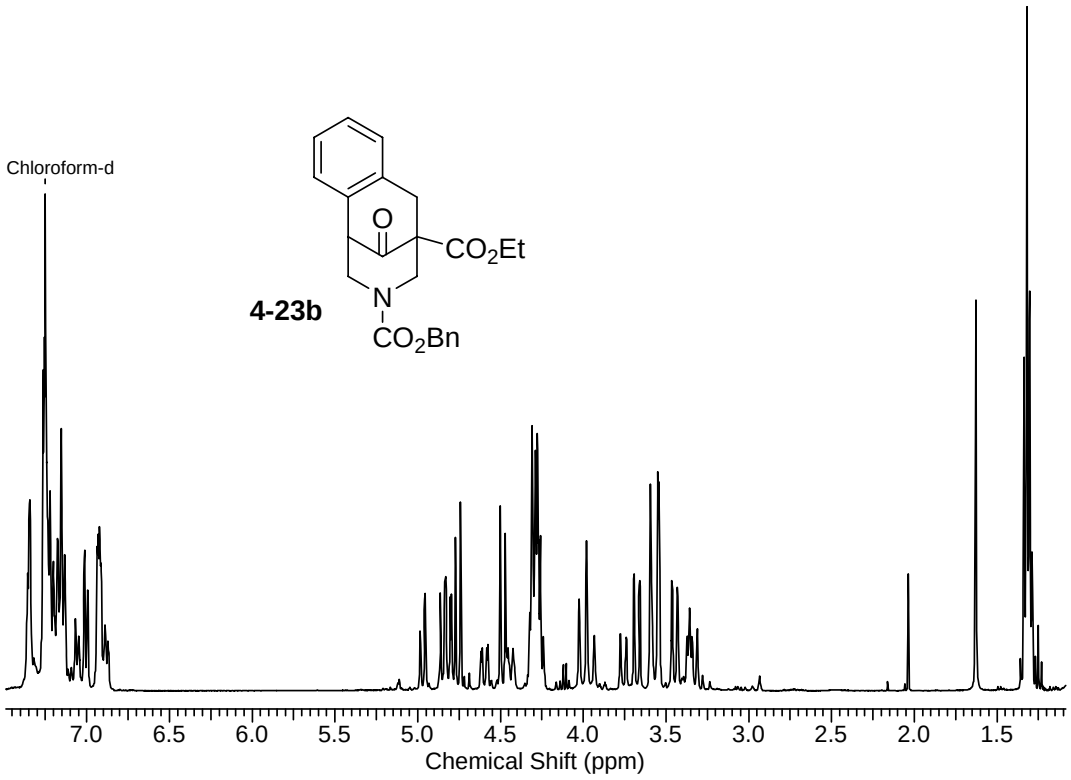

Chloroform-d
207.5
170.3
137.3
135.8
127.5
127.2
126.6
126.3
66.6
64.7
61.6
58.6
52.5
45.0
41.0
14.1

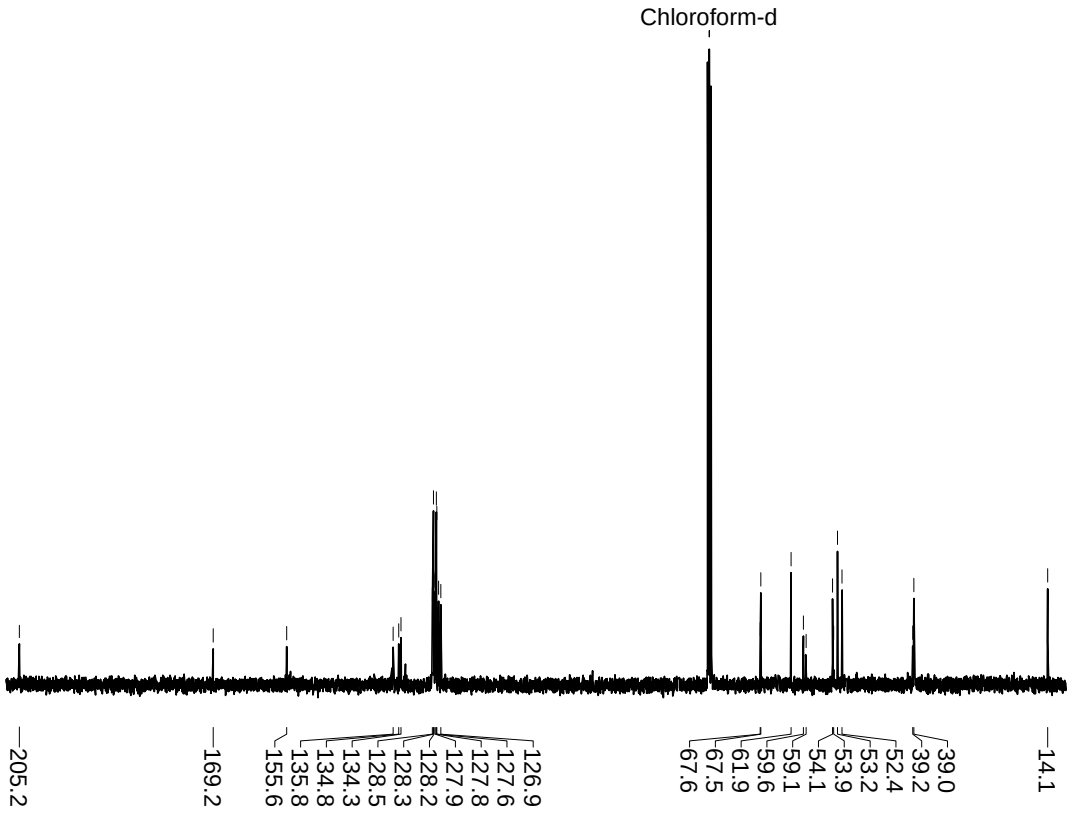

Me
O
CO2Et
N
Me
4-21b
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

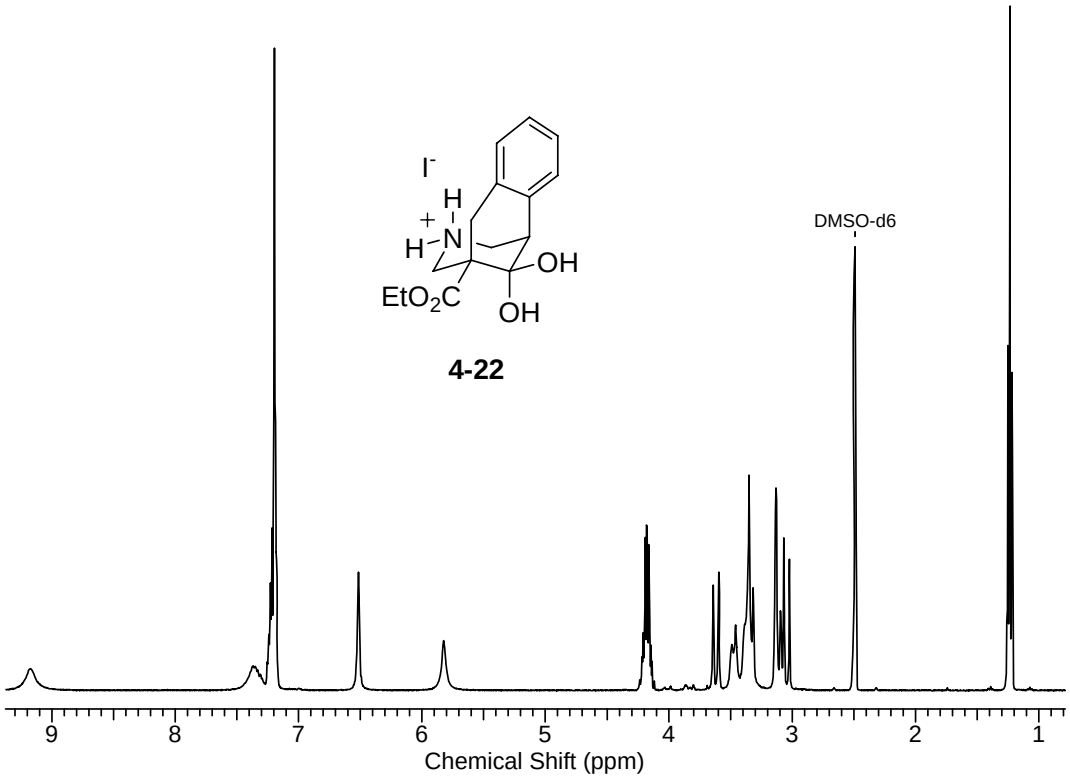

Chloroform-d
208.1
170.4
135.7
135.3
134.7
128.0
126.8
124.6
66.3
62.4
61.5
58.5
48.7
45.1
41.0
18.5
14.1


O
CO2Et
4-23a
N
CO2Et
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

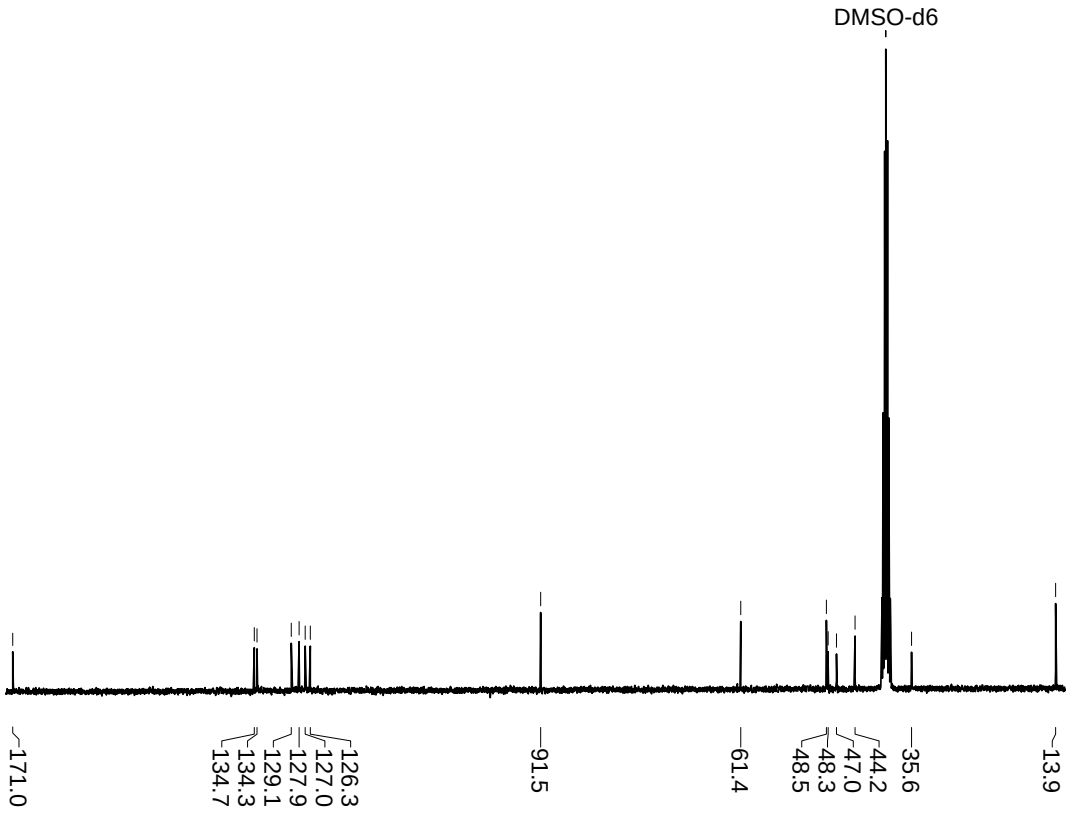

Chloroform-d
205.3
169.2
155.8
155.0
134.8
134.3
133.6
128.5
128.1
127.7
127.2
127.2
126.7
61.7
61.5
59.7
59.1
53.9
53.1
53.0
52.5
39.2
38.9
14.1
14.6

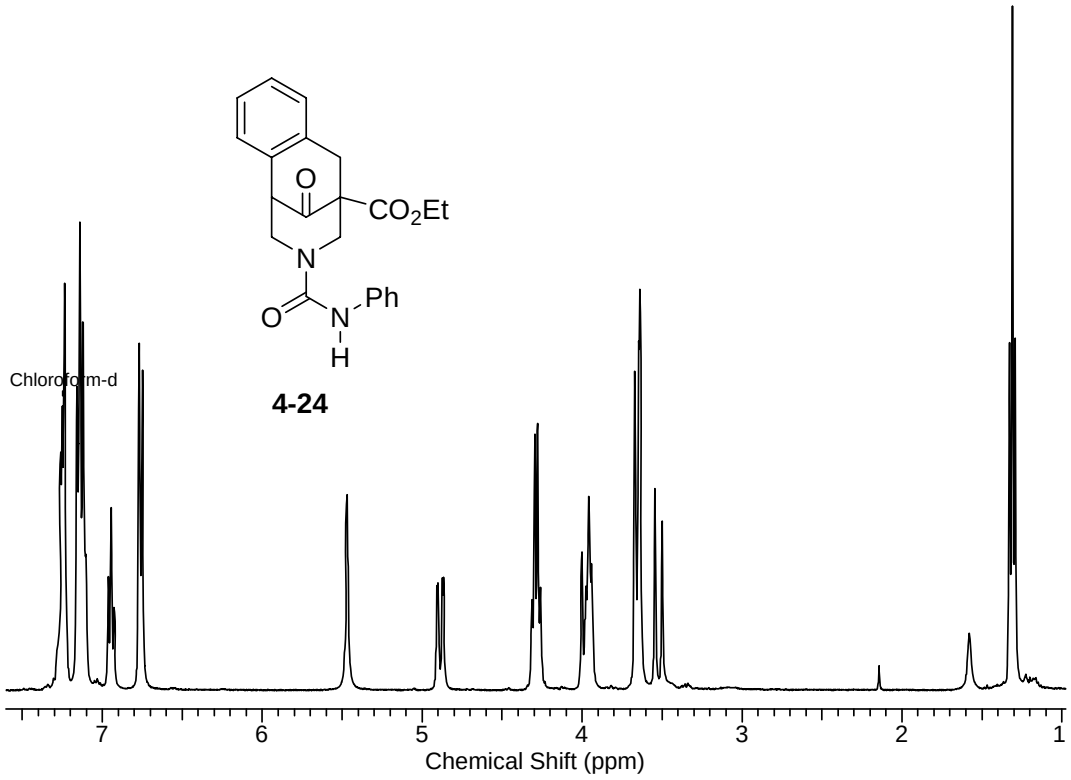

Chloroform-d
O
CO2Et
N
CO2Bn
4-23b
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


Chloroform-d
205.2
169.2
155.6
135.8
134.8
134.3
128.5
128.3
128.2
127.9
127.8
127.6
126.9
67.6
67.5
61.9
59.6
59.1
54.1
53.9
53.2
52.4
39.2
39.0
14.1

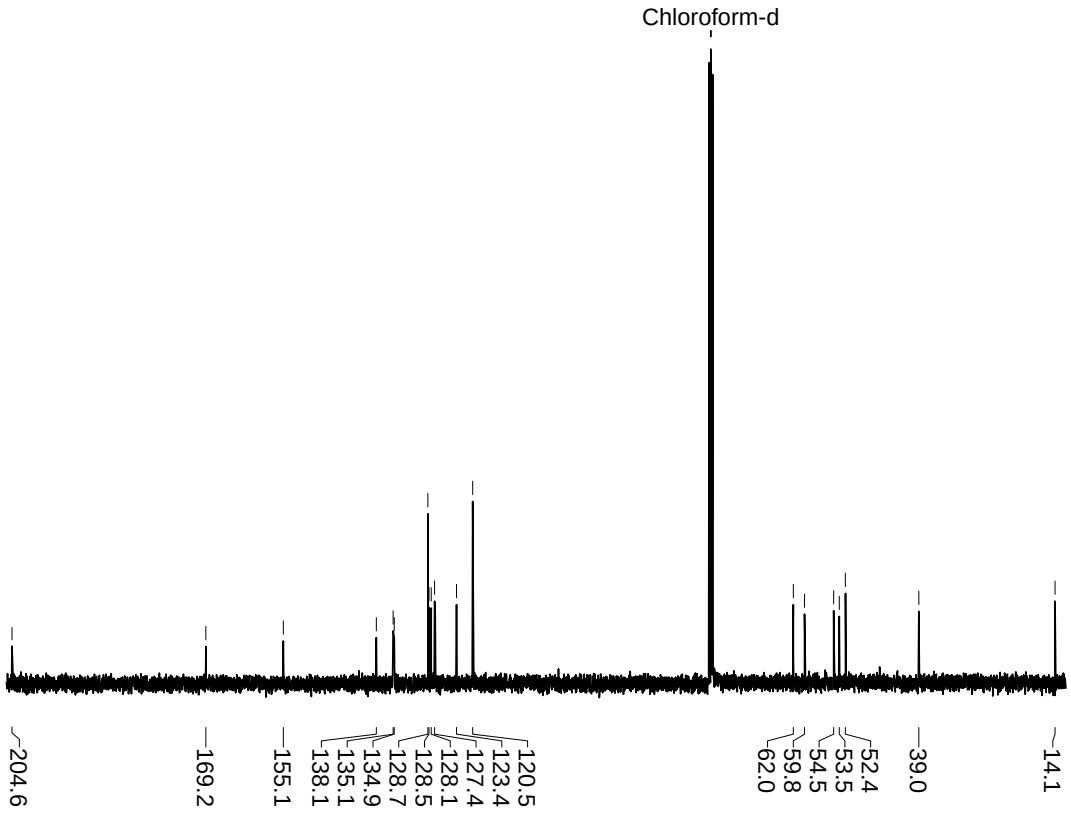

I-
H
+
H–N
OH
EtO2C
OH
DMSO-d6
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

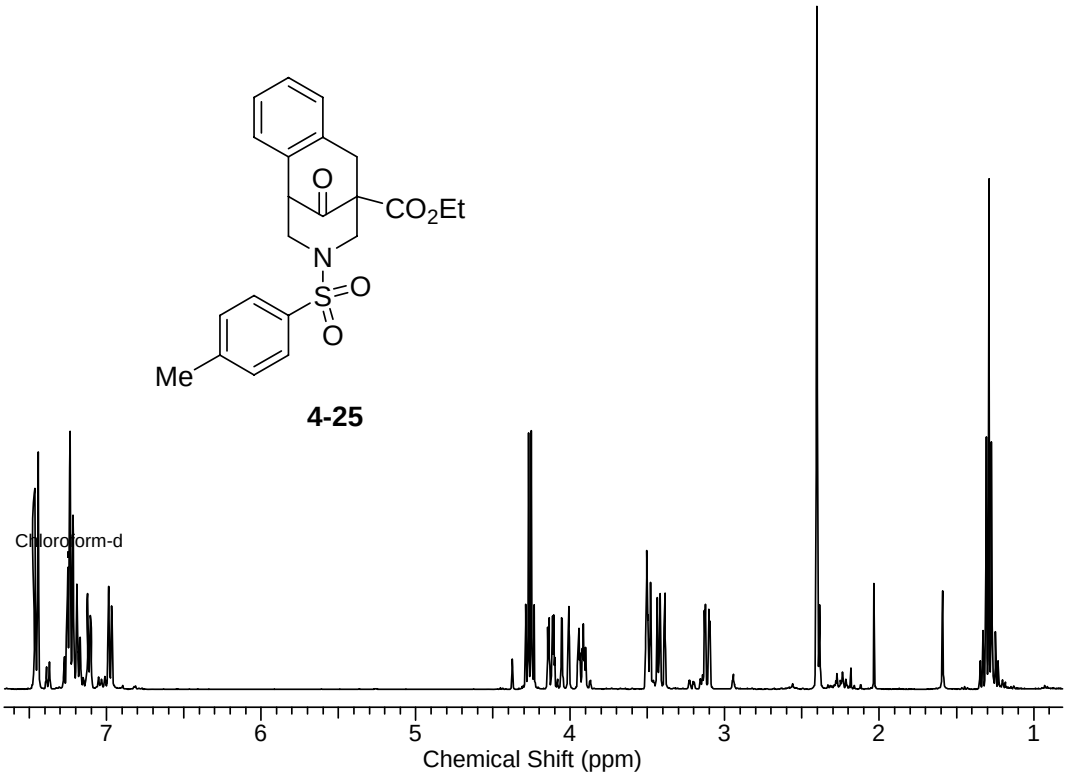
**4-22**


DMSO-d6
171.0
134.7
134.3
129.1
127.9
127.0
126.3
91.5
61.4
48.5
48.3
47.0
44.2
35.6
13.9

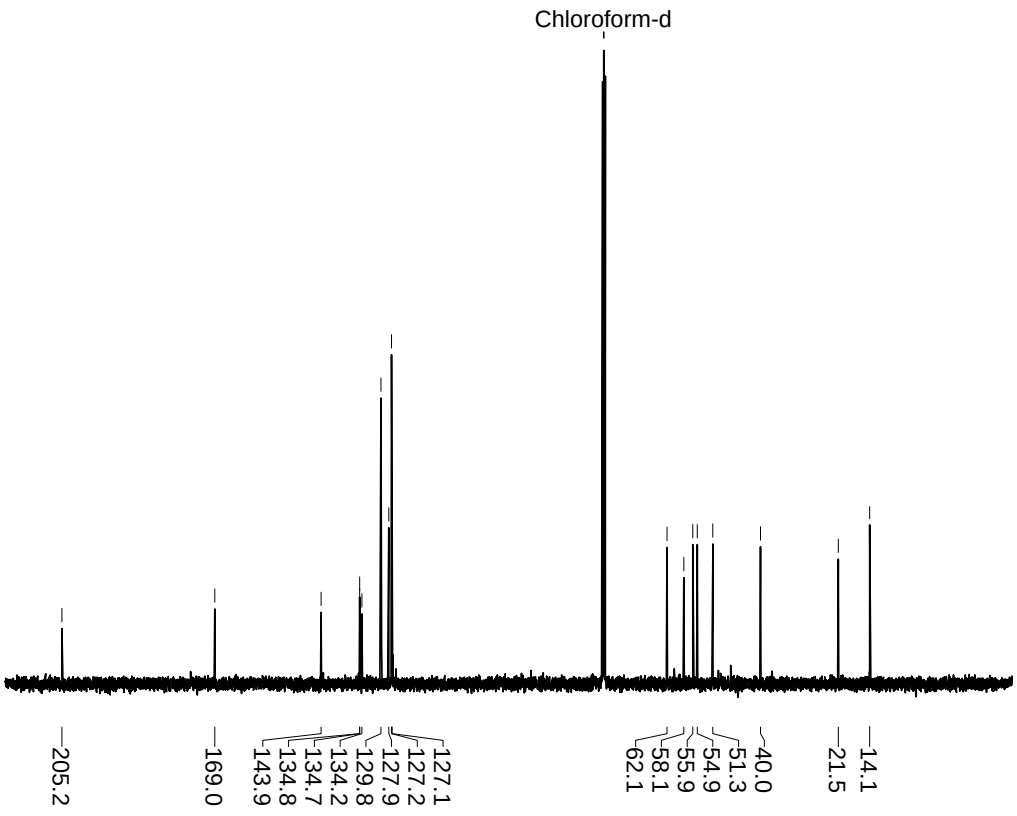

O
CO2Et
N
O
N
Ph
H
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

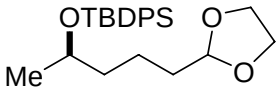
**4-24**


Chloroform-d
204.6
169.2
155.1
138.1
135.1
134.9
128.7
128.5
128.1
127.4
123.4
120.5
62.0
59.8
54.5
53.5
52.4
39.0
14.1


O
CO2Et
N
S
O
O
Me
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

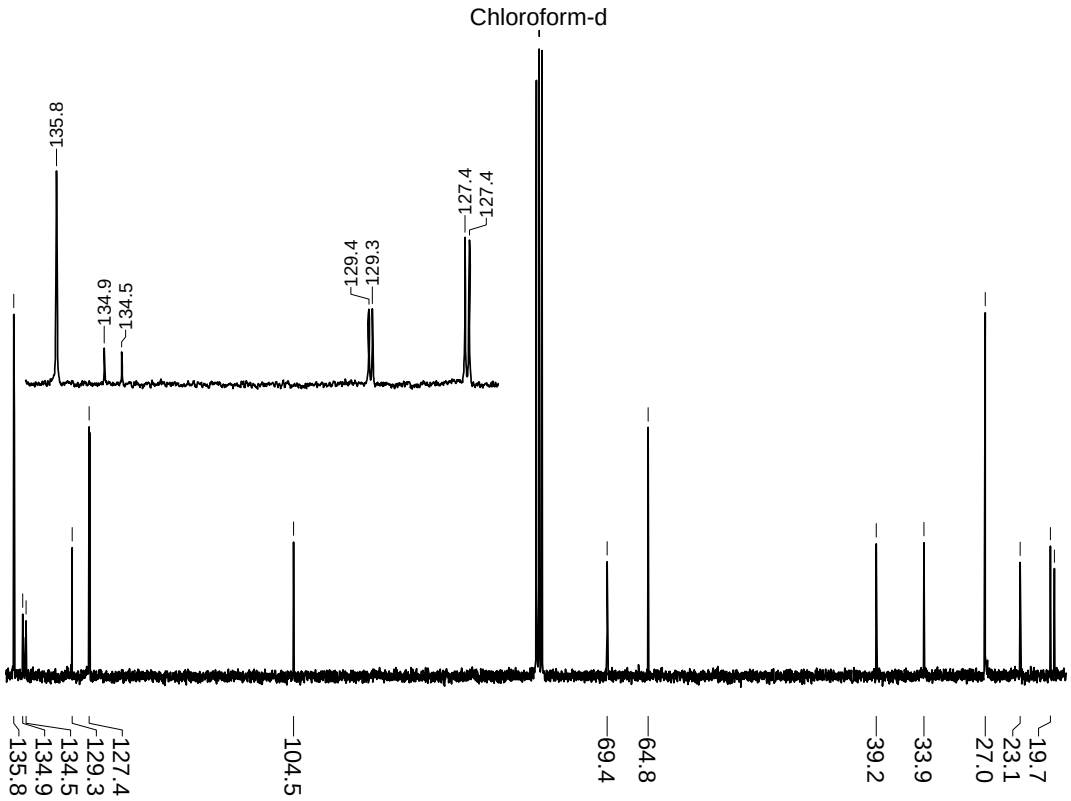
**4-25**

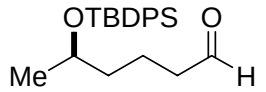

Chloroform-d
205.2
169.0
143.9
134.8
134.7
134.2
129.8
127.9
127.2
127.1
62.1
58.1
55.9
54.9
51.3
40.0
21.5
14.1


OTBDPS
O
Me
O

**8-31a**

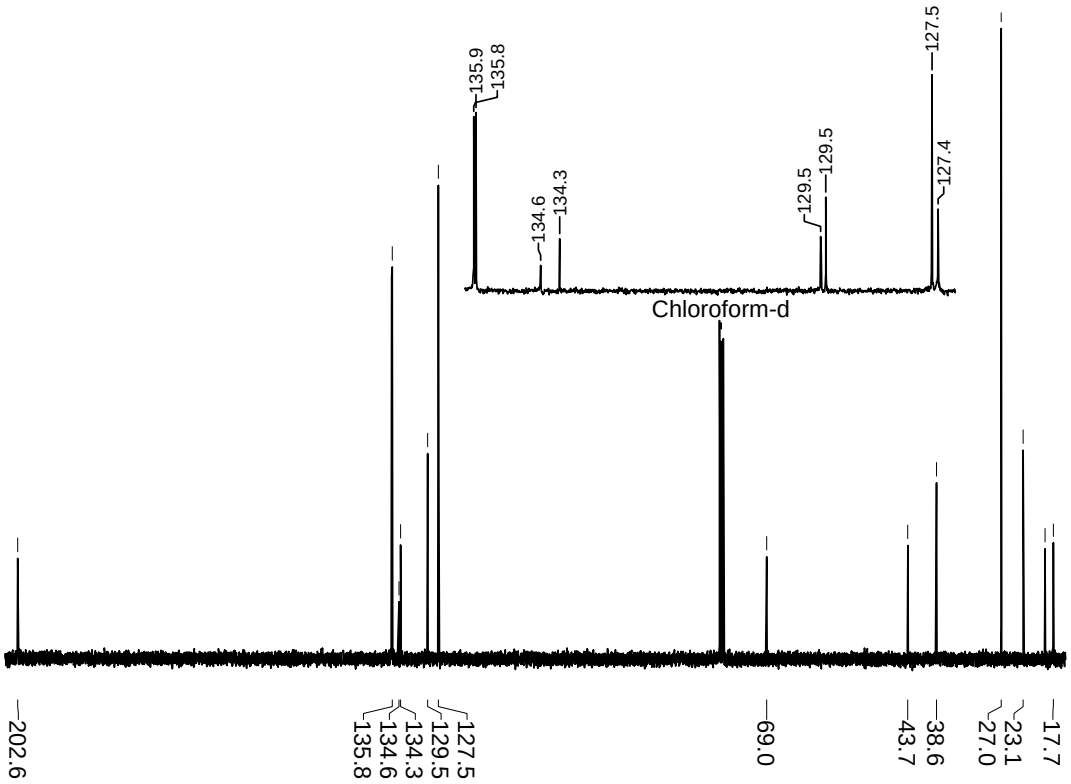

Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

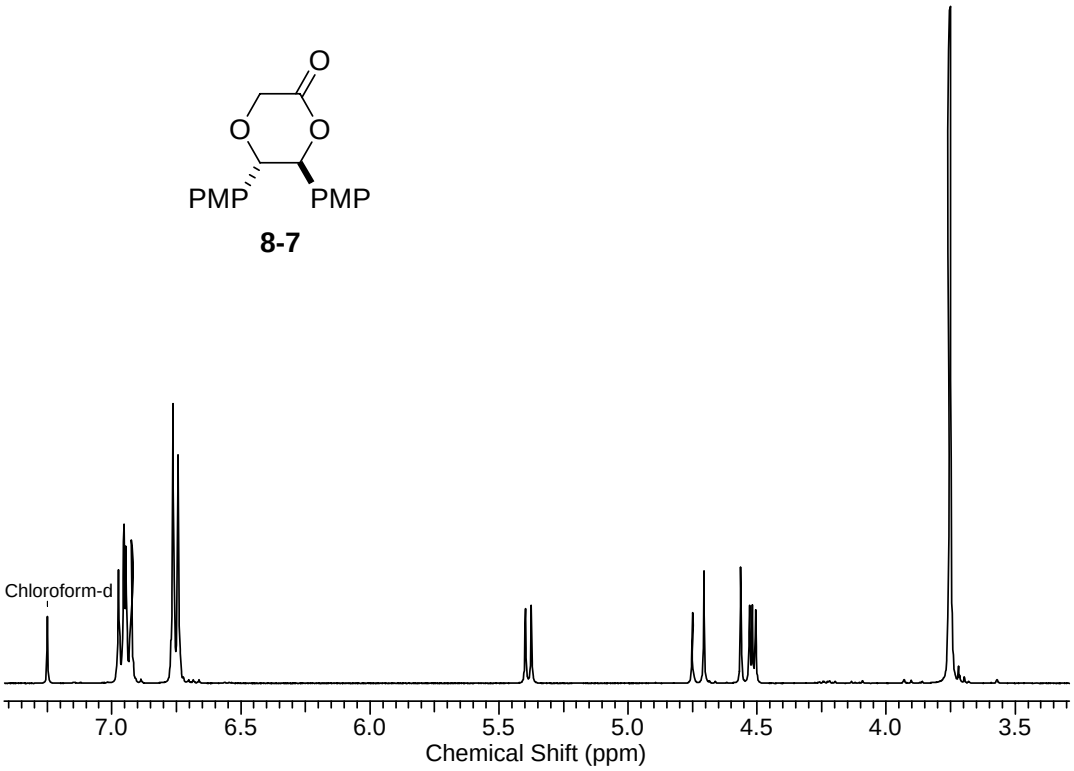

Chloroform-d
135.8
134.9
134.5
129.4
129.3
127.4
127.4
135.8
134.9
134.5
129.3
127.4
104.5
69.4
64.8
39.2
33.9
27.0
23.1
19.7


OTBDPS
O
Me
H

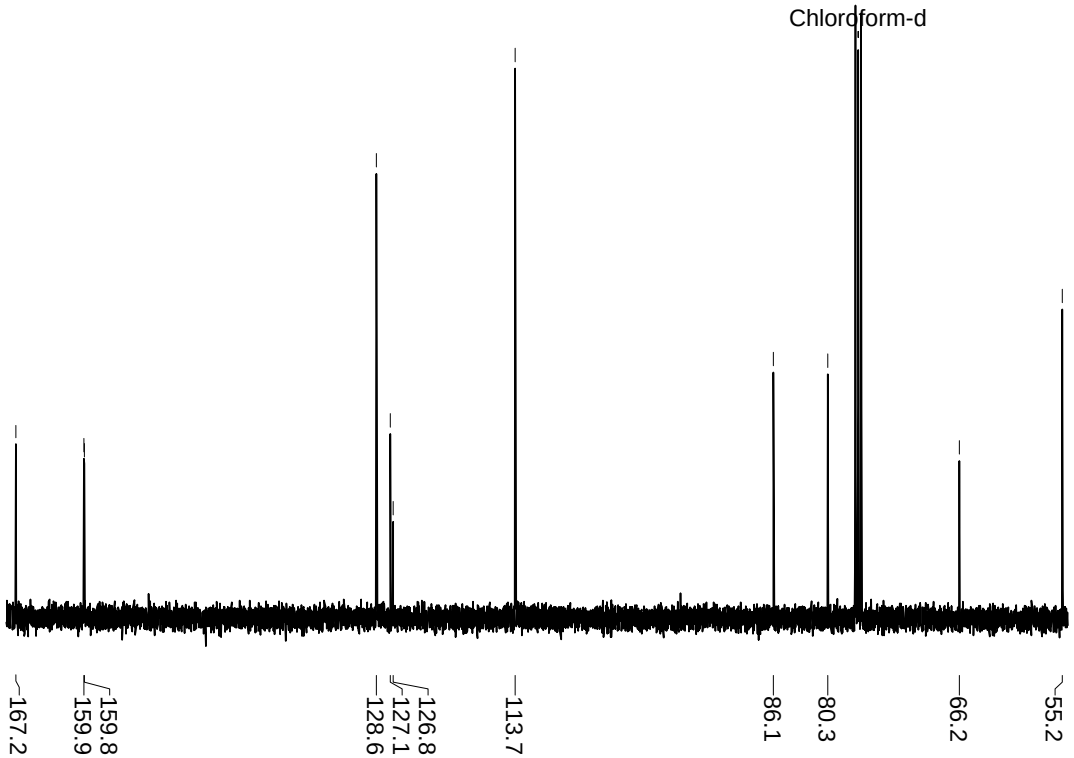
**8-6**

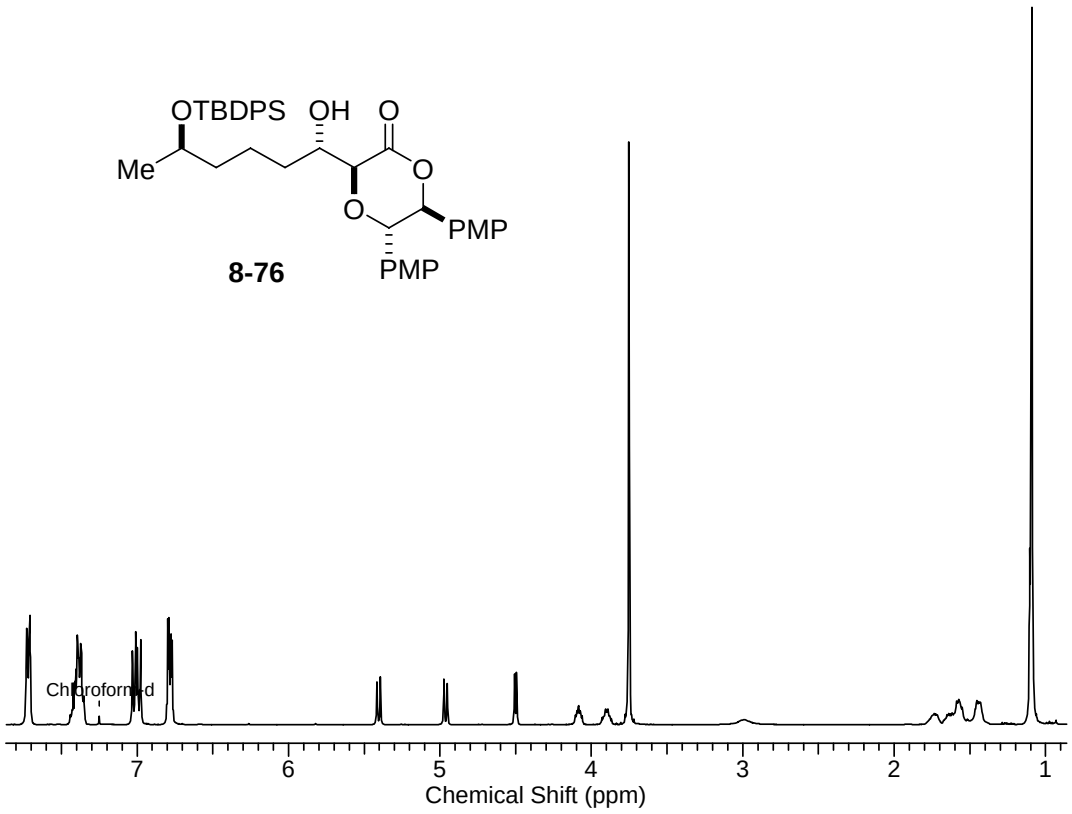

Chloroform-d
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


135.9
135.8
134.6
134.3
129.5
129.5
127.5
127.4
Chloroform-d
202.6
135.8
134.6
134.3
129.5
127.5
69.0
43.7
38.6
27.0
23.1
17.7

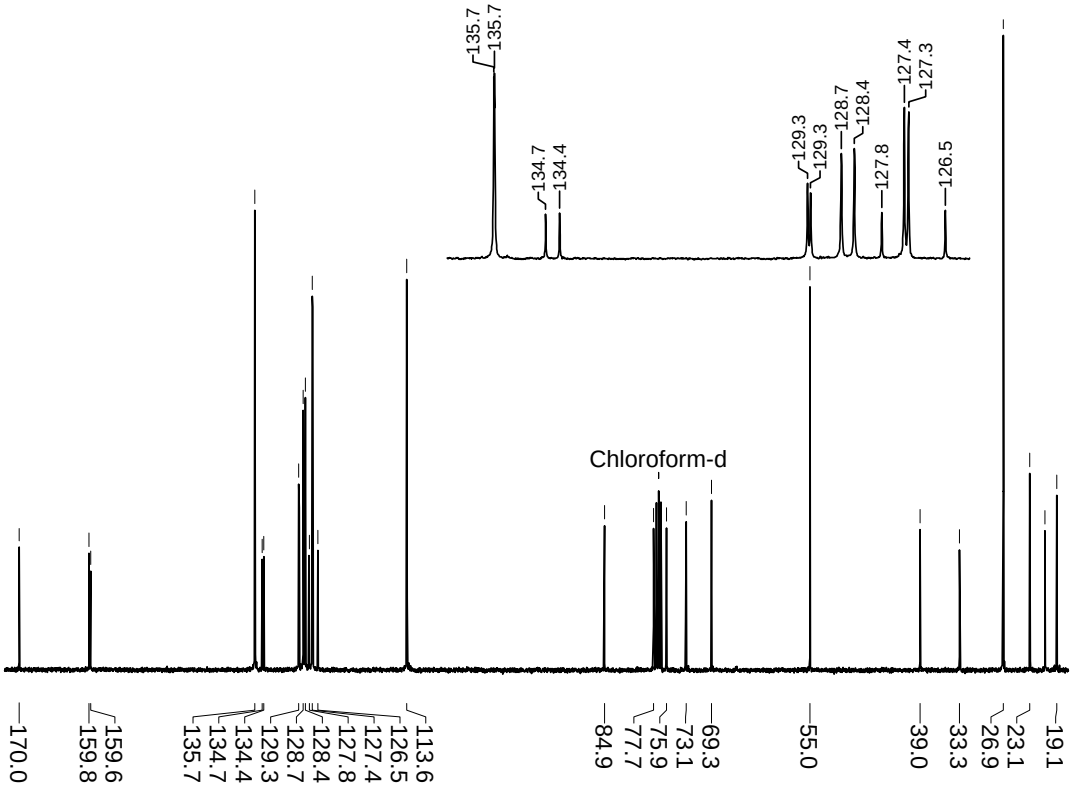

O
O
O
PMP
PMP
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)

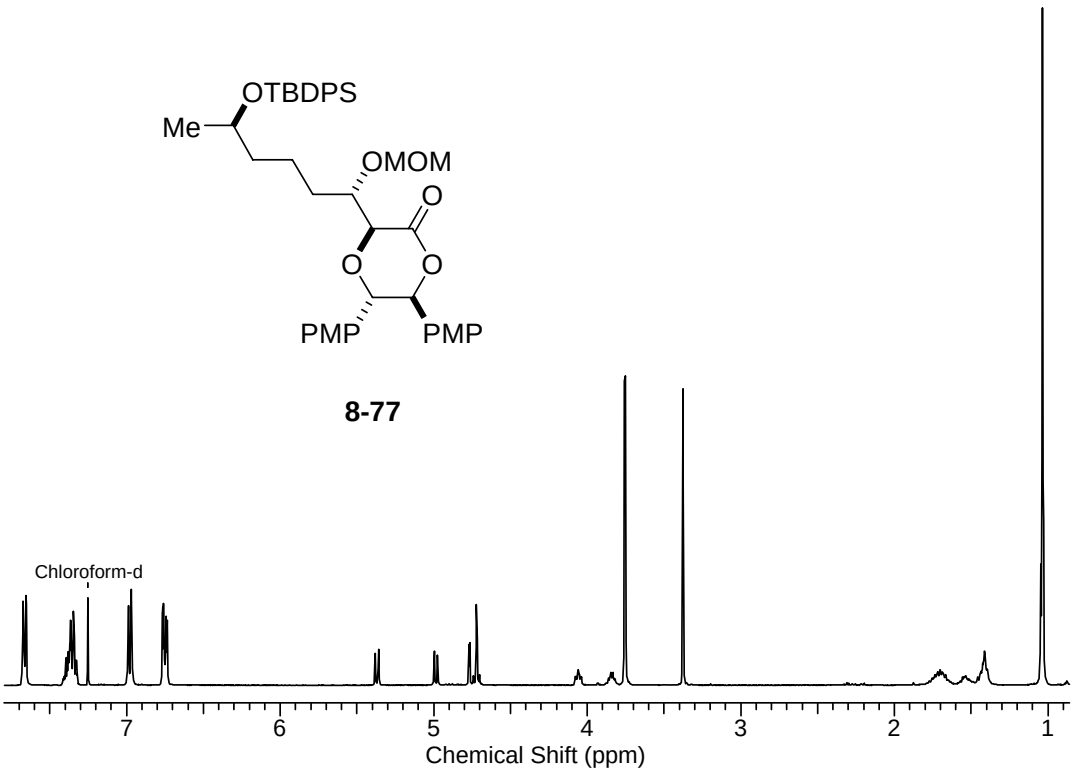
**8-7**


Chloroform-d
167.2
159.9
159.8
128.6
127.1
126.8
113.7
86.1
80.3
66.2
55.2

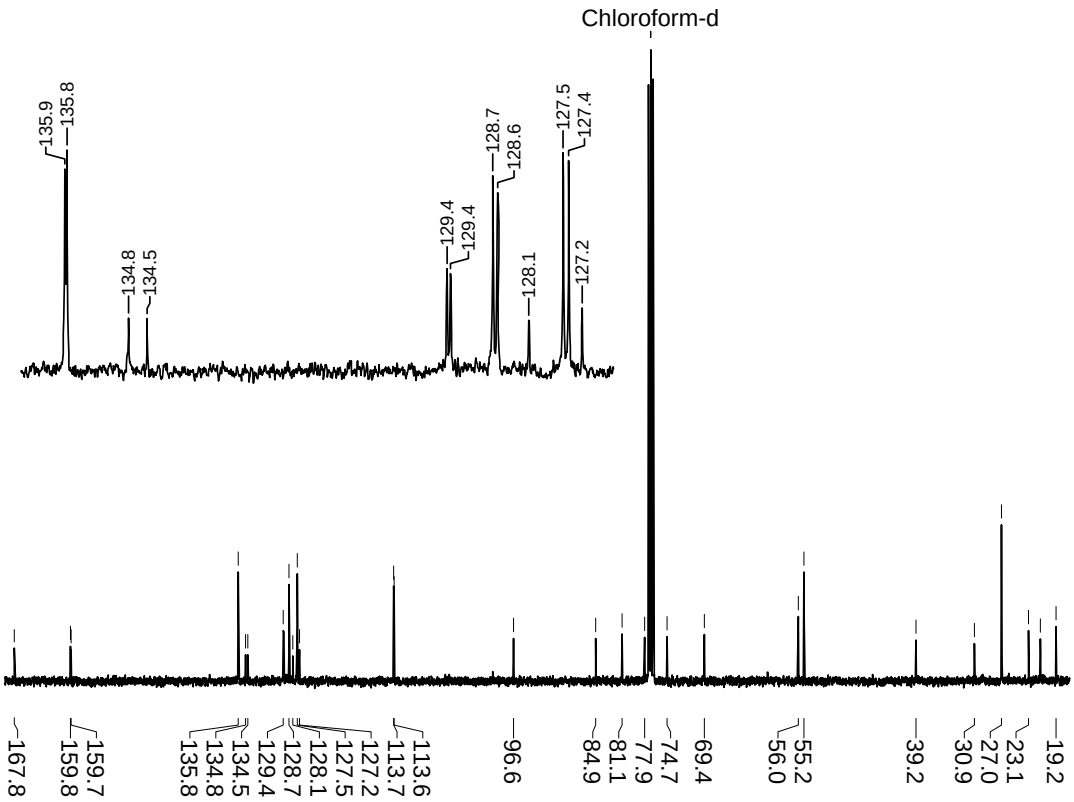

OTBDPS
OH
O
Me
O
O
PMP
PMP
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

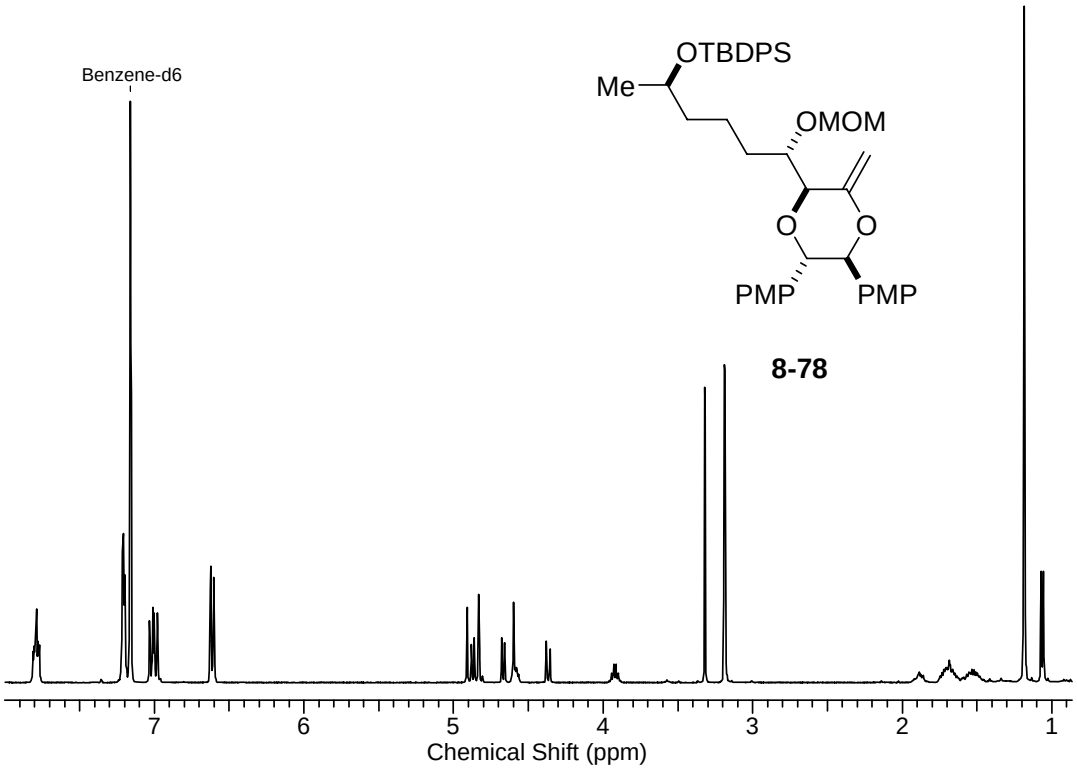
**8-76**

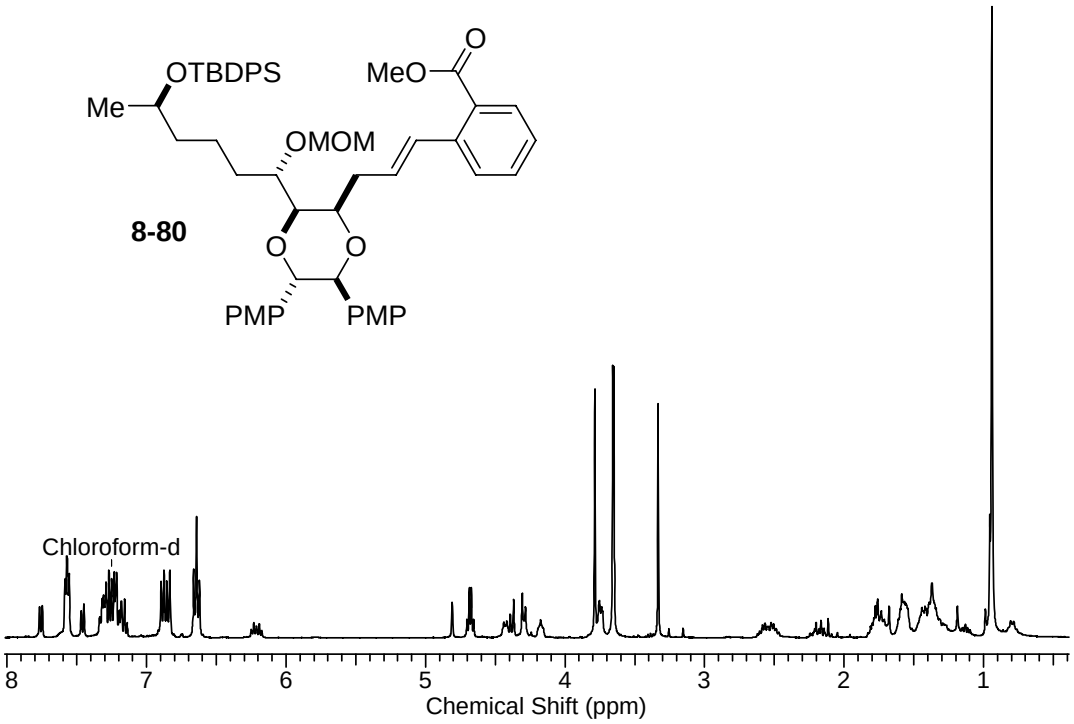

135.7
135.7
134.7
134.4
129.3
129.3
128.7
128.4
127.8
127.4
127.3
126.5
Chloroform-d
170.0
159.8
159.6
135.7
134.7
134.4
129.3
128.7
128.4
127.8
127.4
126.5
113.6
84.9
77.7
75.9
73.1
69.3
55.0
39.0
33.3
26.9
23.1
19.1

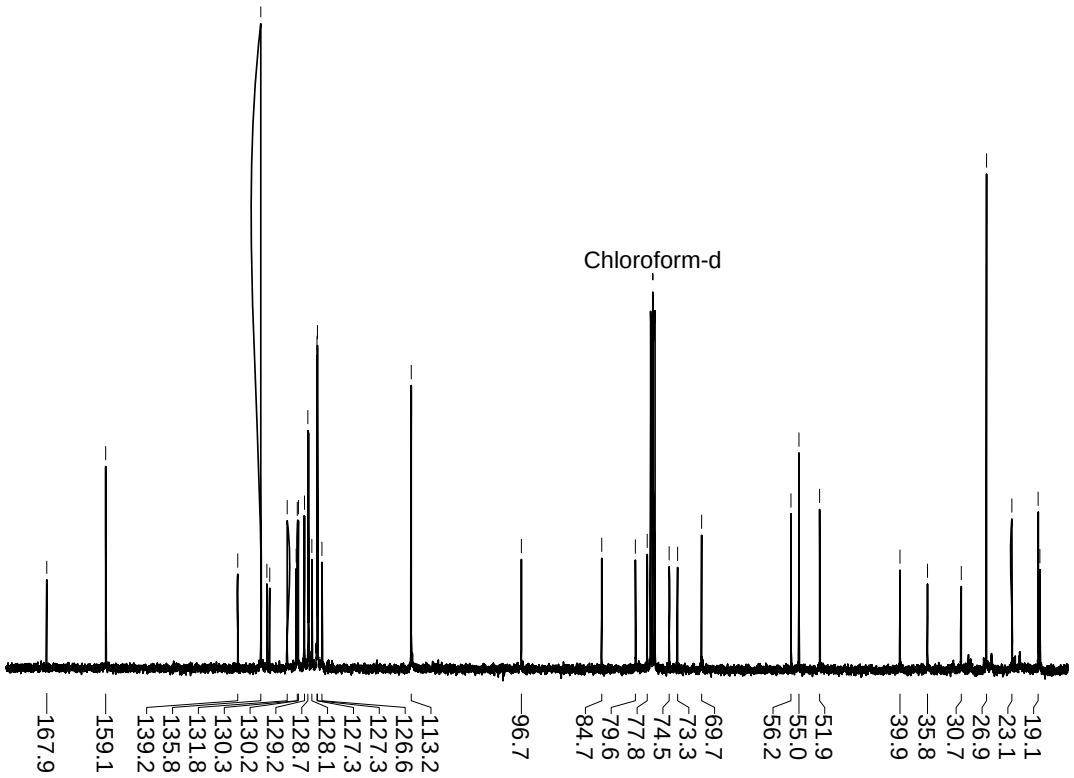

OTBDPS
Me
OMOM
O
O
O
PMP
PMP
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

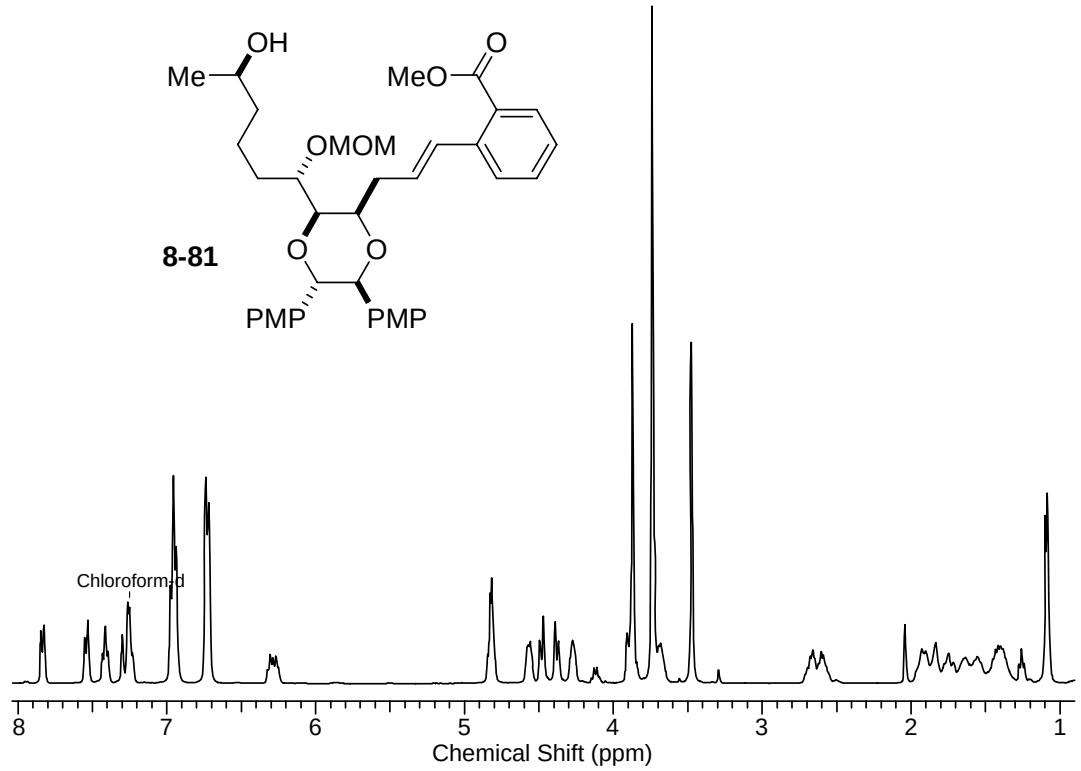
**8-77**

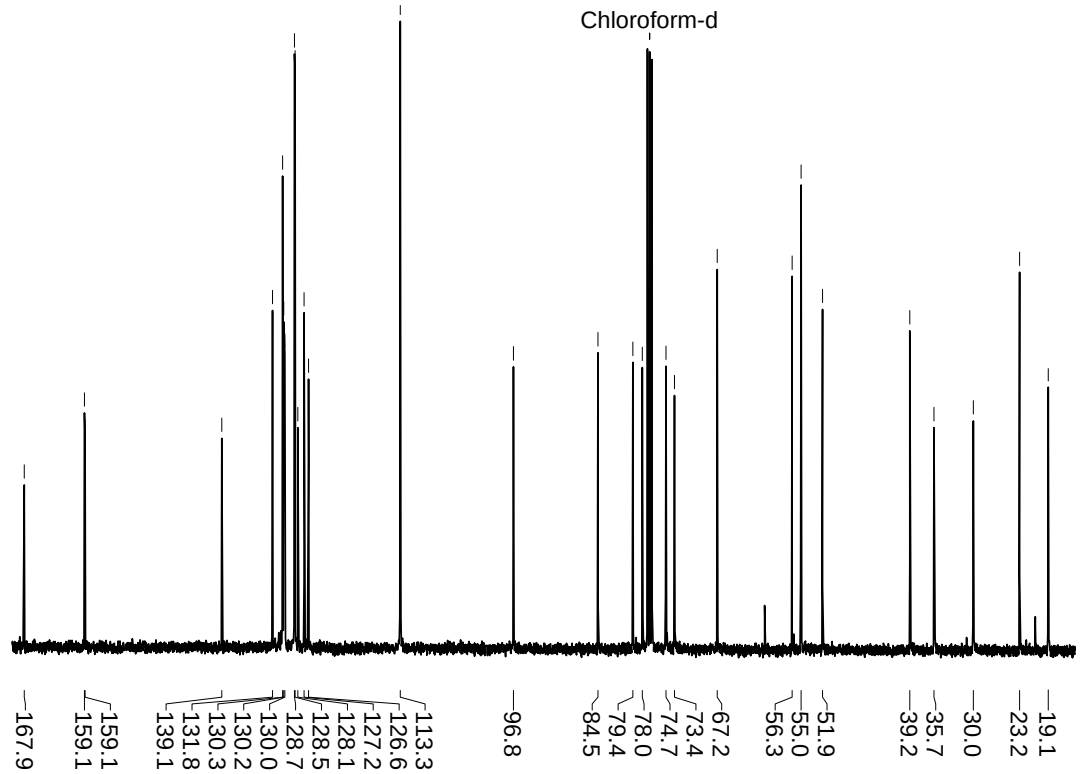

Chloroform-d
135.9
135.8
134.8
134.5
129.4
129.4
128.7
128.6
128.1
127.5
127.4
127.2
167.8
159.8
159.7
135.8
134.8
134.5
129.4
128.7
128.1
127.5
127.2
113.7
113.6
96.6
84.9
81.1
77.9
74.7
69.4
56.0
55.2
39.2
30.9
27.0
23.1
19.2

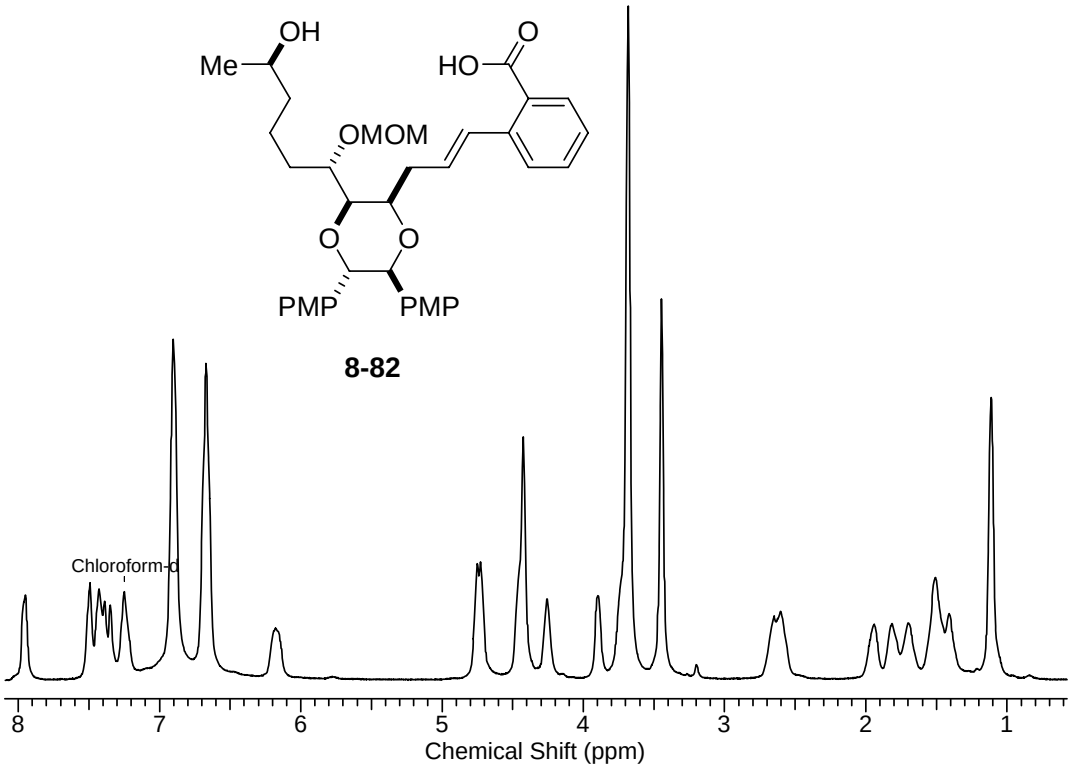

Benzene-d6
OTBDPS
Me
OMOM
O
O
PMP
PMP
8-78
7
6
5
4
3
2
1
Chemical Shift (ppm)


OTBDPS
Me
MeO
O
OMOM
8-80
O
O
PMP
PMP
Chloroform-d
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

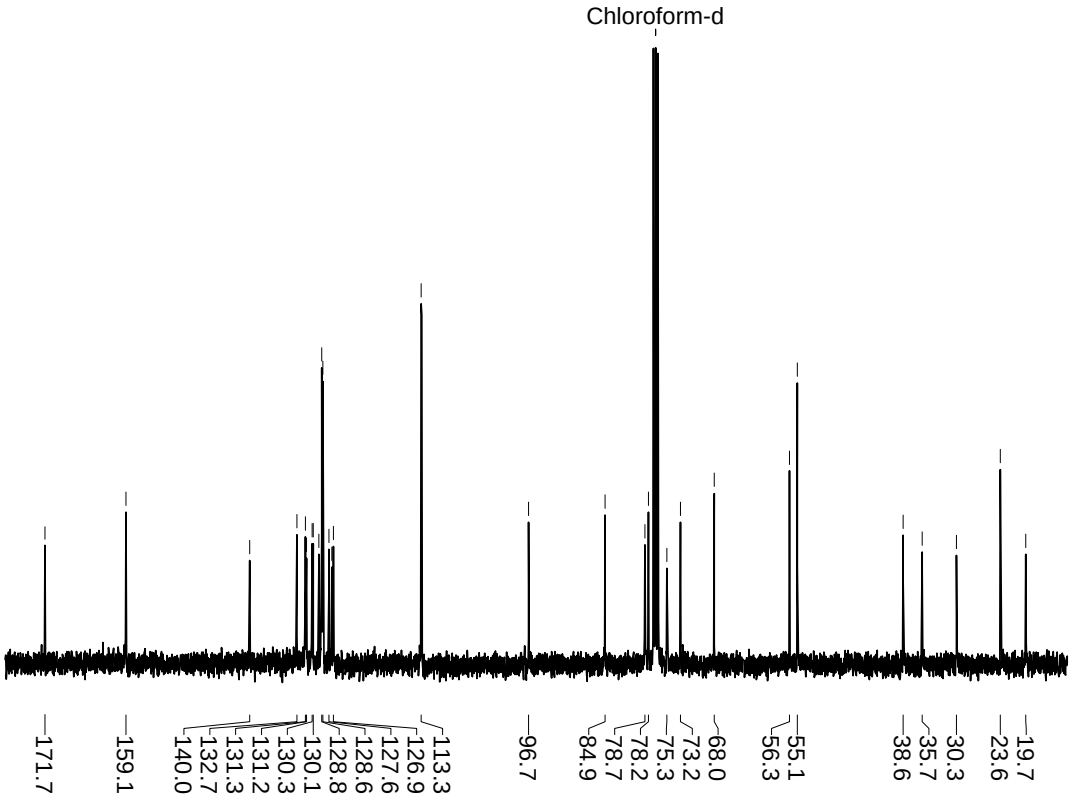

Chloroform-d
167.9
159.1
139.2
135.8
131.8
130.3
130.2
129.2
128.7
128.1
127.3
127.3
126.6
113.2
96.7
84.7
79.6
77.8
74.5
73.3
69.7
56.2
55.0
51.9
39.9
35.8
30.7
26.9
23.1
19.1

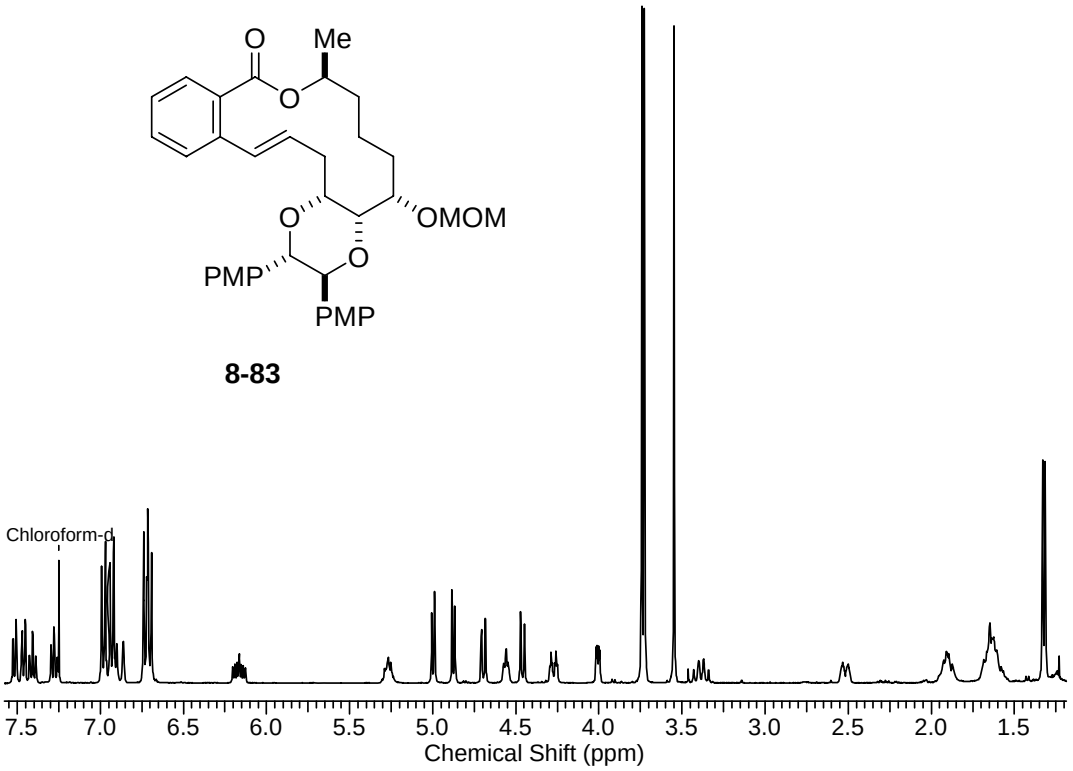

OH
Me
MeO
O
OMOM
8-81
O
O
PMP
PMP
Chloroform-d
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


Chloroform-d
167.9
159.1
159.1
139.1
131.8
130.3
130.2
130.0
128.7
128.5
128.1
127.2
126.6
113.3
96.8
84.5
79.4
78.0
74.7
73.4
67.2
56.3
55.0
51.9
39.2
35.7
30.0
23.2
19.1

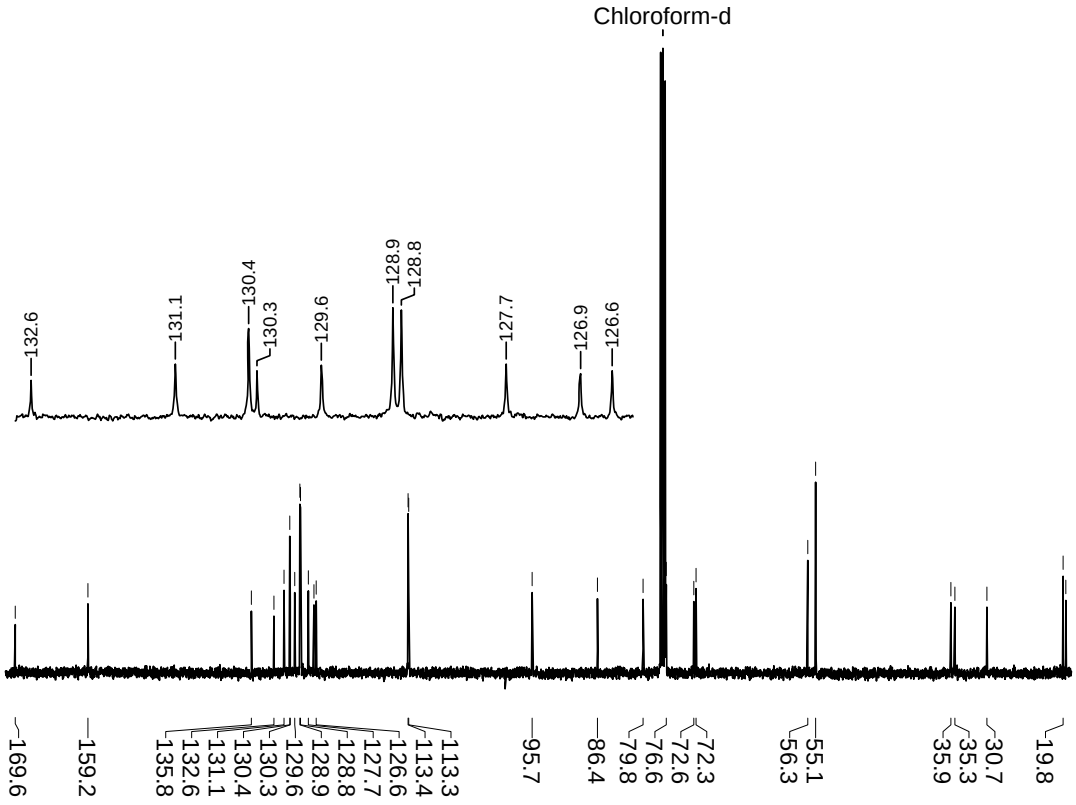

OH
Me
HO
O
OMOM
O
O
PMP
PMP
Chloroform-d
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

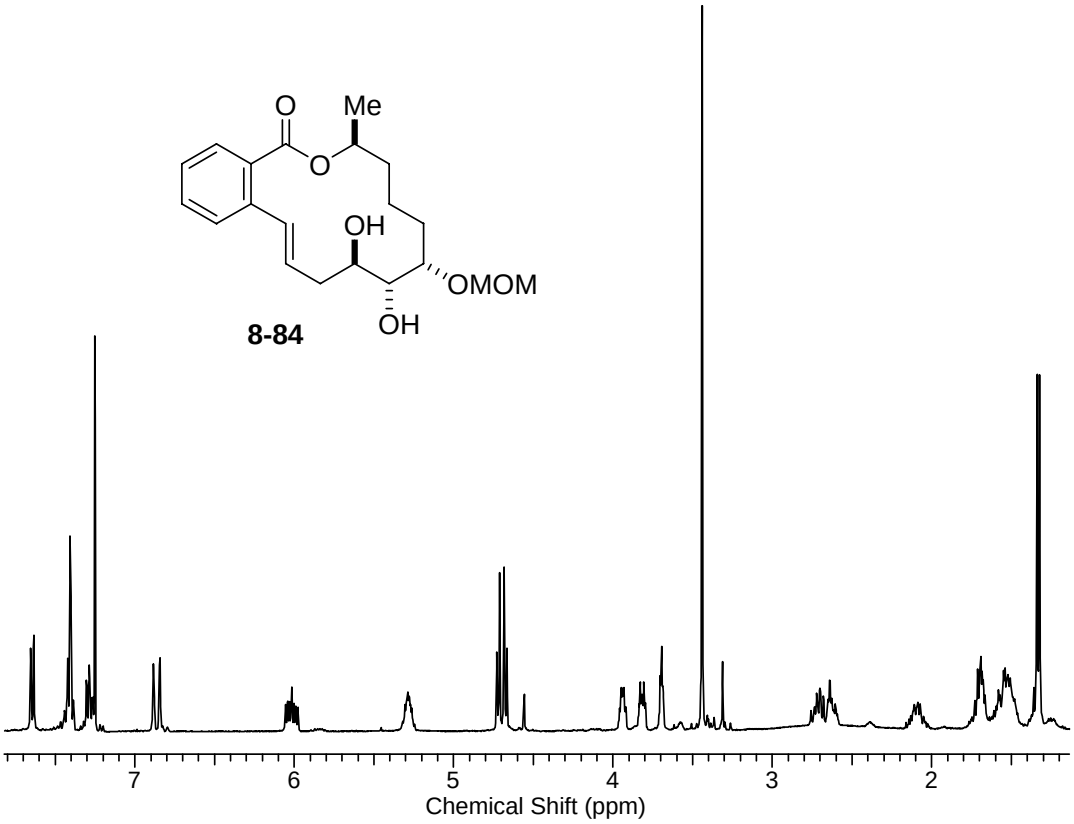
**8-82**


Chloroform-d
171.7
159.1
140.0
132.7
131.3
131.2
130.3
130.1
128.8
128.6
127.6
126.9
113.3
96.7
84.9
78.7
78.2
75.3
73.2
68.0
56.3
55.1
38.6
35.7
30.3
23.6
19.7

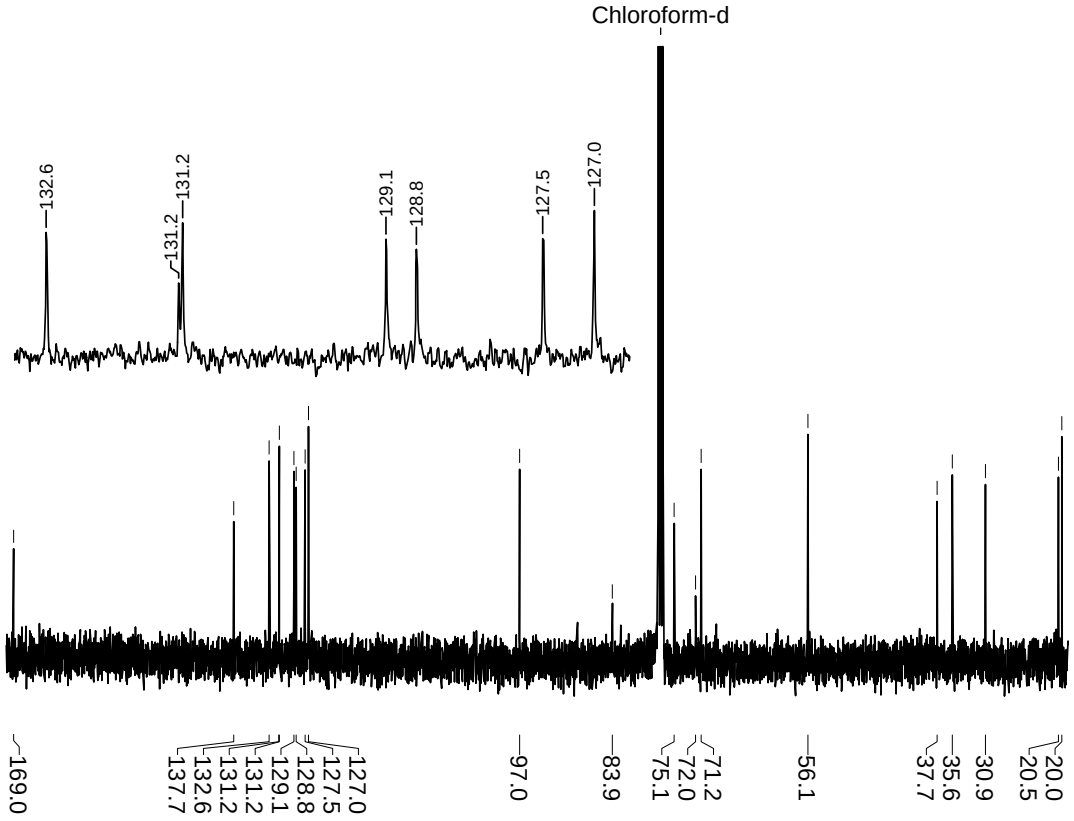

O
Me
O
O
OMOM
O
PMP
PMP
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

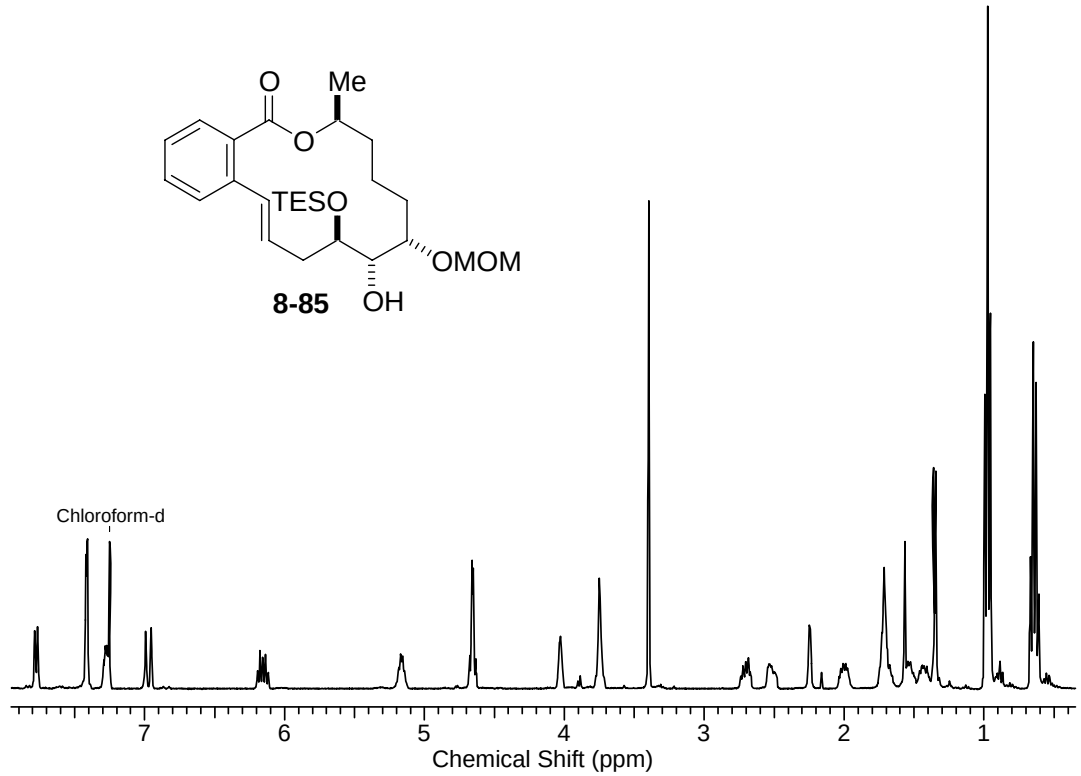
**8-83**


Chloroform-d
132.6
131.1
130.4
130.3
129.6
128.9
128.8
127.7
126.9
126.6
169.6
159.2
135.8
132.6
131.1
130.4
130.3
129.6
128.9
128.8
127.7
126.6
113.4
113.3
95.7
86.4
79.8
76.6
72.6
72.3
56.3
55.1
35.9
35.3
30.7
19.8

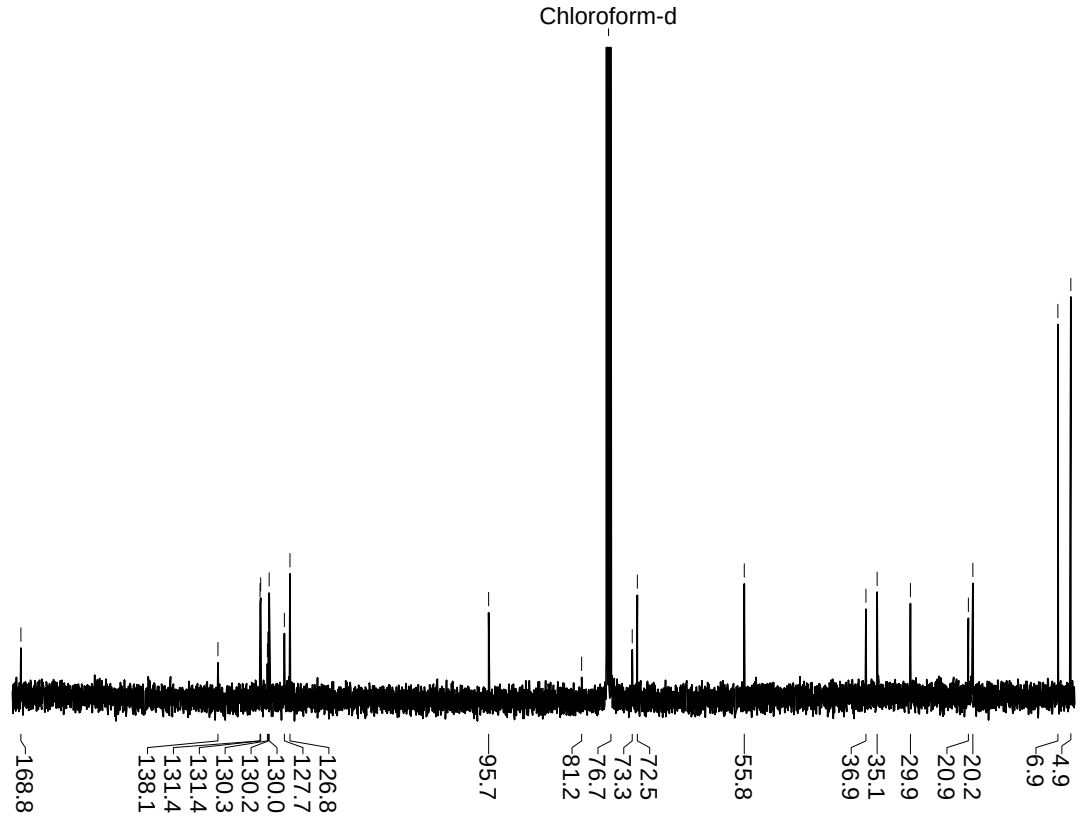

O
Me
O
OH
OMOM
OH
7
6
5
4
3
2
Chemical Shift (ppm)

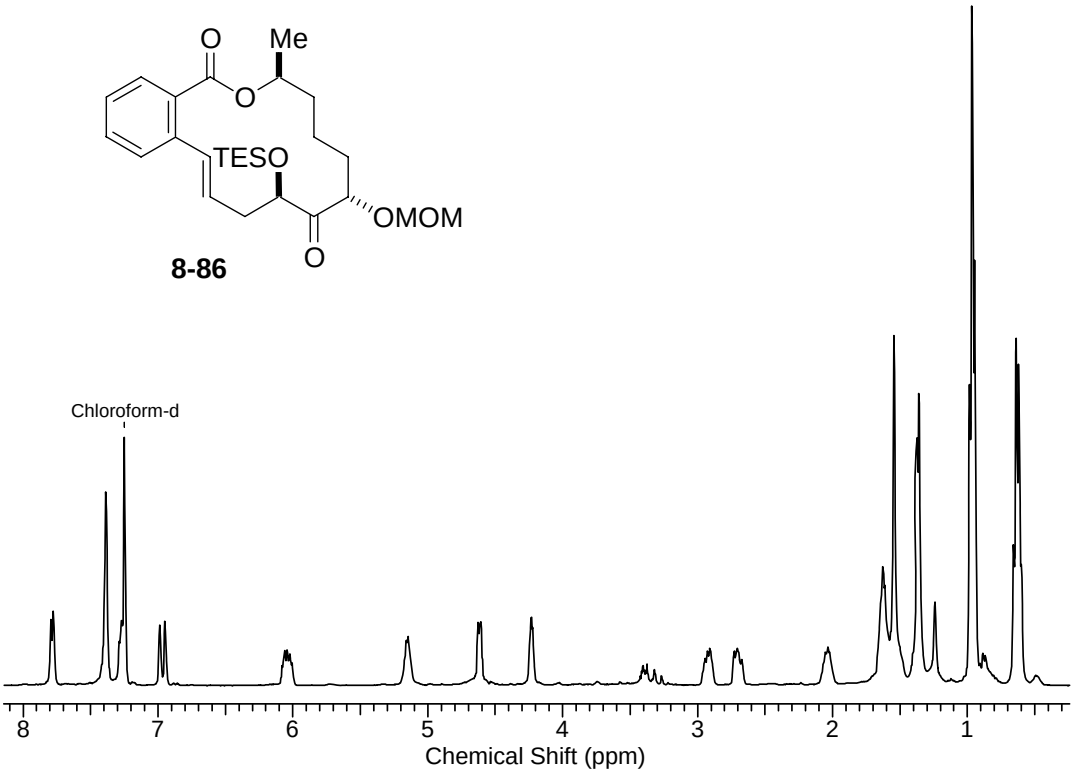
**8-84**


Chloroform-d
132.6
131.2
131.2
129.1
128.8
127.5
127.0
169.0
137.7
132.6
131.2
131.2
129.1
128.8
127.5
127.0
97.0
83.9
75.1
72.0
71.2
56.1
37.7
35.6
30.9
20.5
20.0

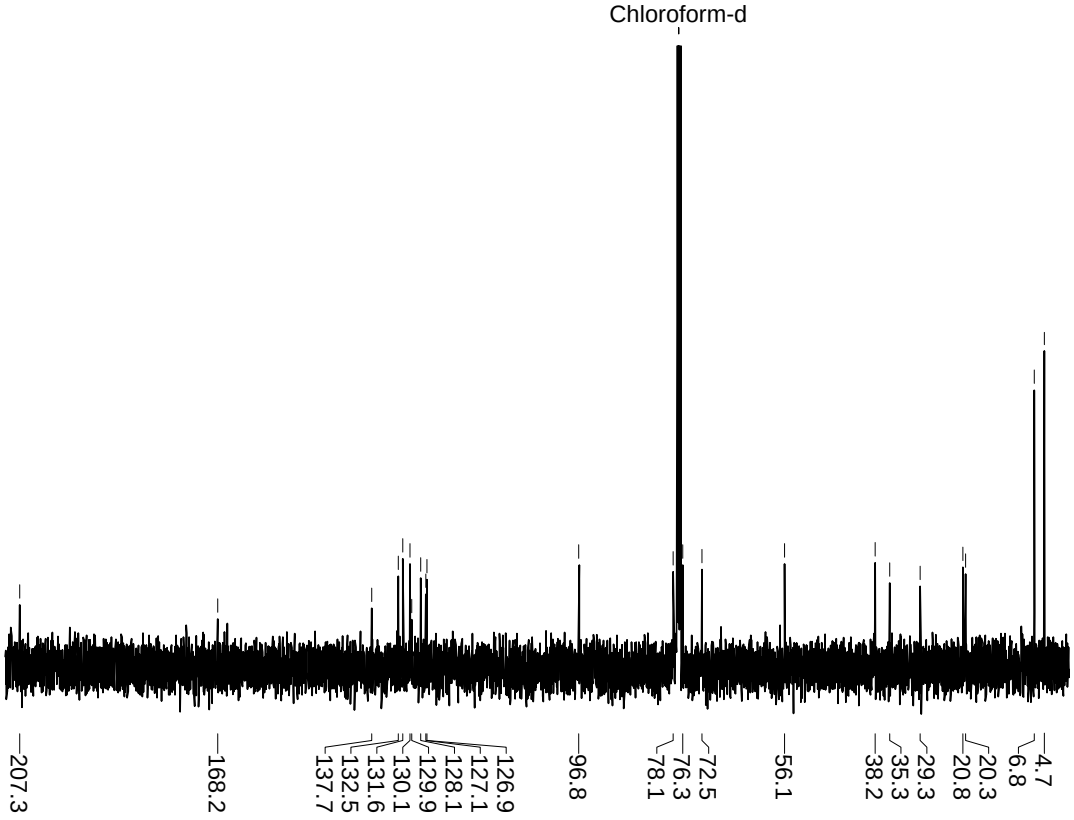

O
Me
O
TESO
OMOM
OH
Chloroform-d
7
6
5
4
3
2
1
Chemical Shift (ppm)

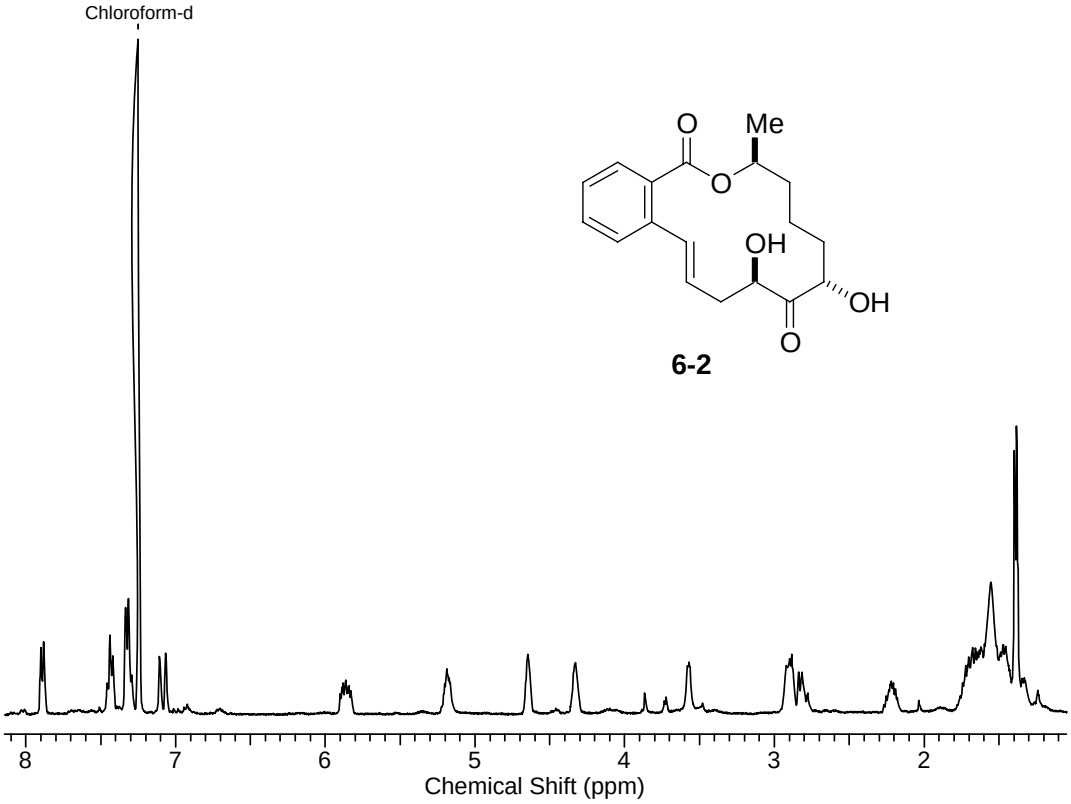
**8-85**


Chloroform-d
168.8
138.1
131.4
131.4
130.3
130.2
130.0
127.7
126.8
95.7
81.2
76.7
73.3
72.5
55.8
36.9
35.1
29.9
20.9
20.2
6.9
4.9

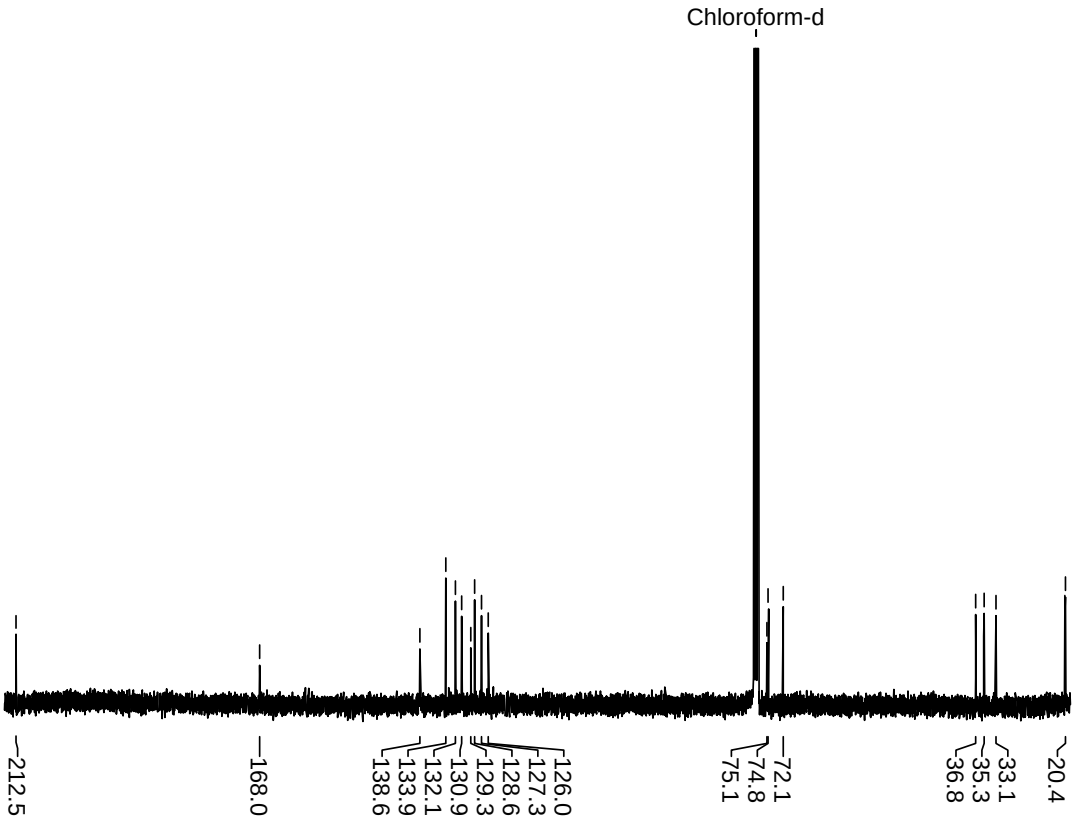

O
Me
O
TESO
OMOM
O
Chloroform-d
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

**8-86**


Chloroform-d
207.3
168.2
137.7
132.5
131.6
130.1
129.9
128.1
127.1
126.9
96.8
78.1
76.3
72.5
56.1
38.2
35.3
29.3
20.8
20.3
6.8
4.7


Chloroform-d
O
Me
O
OH
OH
O
8
7
6
5
4
3
2
Chemical Shift (ppm)

**6-2**


Chloroform-d
212.5
168.0
138.6
133.9
132.1
130.9
129.3
128.6
127.3
126.0
75.1
74.8
72.1
36.8
35.3
33.1
20.4

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