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# DISSERTATION

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„Syntheses of highly functionalized cyclopentane segments: Toward the total synthesis of PI-3.“

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-Arthur Schnitzler '*Liebelei*'

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# List of abbreviations

| | |
|---|---|
| (*R*)-HYTRA | (*R*)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate |
| 2,2-DMP | 2,2-dimethoxypropane |
| 9-BBN | 9-Borabicyclo[3.3.1]nonane |
| AACT | Acetyl-CoA transferase |
| ABC | ATP binding cassette |
| Ac | Acetyl |
| acac | Acetylacetonato |
| acac-CoA | Acetoacetyl-coenzyme A |
| acetyl-CoA | Acetyl-coenzyme A |
| AD | *Anno Domini* |
| ATP | Adenosine triphosphate |
| BC | Before Christ |
| brsm | Based on recovered starting material |
| BSA | Bis(trimethylsilyl)acetamide |
| cat | Catalytic |
| CDP-ME | 4-Diphosphocytidyl-2-*C*-methylerythritol |
| CDP-MEP | 4-Diphosphocytidyl-2-*C*-methyl-D-erythritol 2-phosphate |
| chxn | Cyclohexane |
| CMK | 4-Diphosphocytidyl-2-*C*-methyl-D-erythritol kinase |
| CMS | 2-*C*-Methyl-D-erythritol 2,4-cyclodiphosphate synthase |
| CNS | Central nervous system |
| CSA | Camphorsulfonic acid |
| CTP | Cytidine triphosphate |
| DACH-phenyl | 1,2-Diaminocyclohexane-*N*,*N*'-bis(2-diphenylphosphinobenzoyl) |
| DBU | Diazabicyloundecane |
| DCA | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichlor-5,6-dicyano-1,4-benzochinon |
| DIAD | Diisopropyl azodicarboxylate |
| DIBALH | Diisobutylaluminum hydride |
| DIPA | Diisopropylamine |
| DMAP | 4-Dimethylaminopyridine |
| DMAPP | Dimethylallyl pyrophosphate |
| DMDO | Dimethyldioxirane |
| DMF | Dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | Dimethyl sulfide |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| dppf | 1,1'-Bis(diphenylphosphino)ferrocene |
| dr | Diastereomeric ratio |
| DXP | 1-Deoxy-D-xylulose 5-phosphat |
| DXR | DXP reductoisomerase |
| e.g. | for example (abbreviation of Latin "*exempli gratia*") |
| EC | Enzyme Commission (number) |
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| eq | Equivalents |
| et al | *et alia* |
| etc | *et cetera* |
| FDA | Food and Drug Administration |

| | |
|---|---|
| FGI | Functional group interconversions |
| GGPP | geranylgeranyl pyrophosphate |
| GRAS | Generally recognized as safe |
| HAART | Highly active antiretroviral therapy |
| HIV | Human immunodeficiency virus |
| HMB-PP | (*E*)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate |
| HMG-CoA | (*S*)-3-hydroxy-3-methylglutaryl-Coenzyme A |
| HMGR | HMG-CoA reductase |
| HMGS | HMG-CoA synthase |
| HMPA | Hexamethylphosphoramide |
| HWE | Horner-Wadsworth-Emmons |
| IBX | 2-Iodoxybenzoic acid |
| IPI | Isopentenyl pyrophosphate isomerase |
| IPP | Isopentenyl pyrophosphate |
| IPPS | Isoprenyl pyrophosphate synthases |
| KHMDS | Potassium bis(trimethylsilyl)amide |
| LAB | Lithium amidotrihydroborate |
| LAH | Lithium aluminum hydride |
| LDA | Lithium diisopropylamide |
| liq. | Liquid |
| MCF-7 | Michigan Cancer Foundation-7 |
| MCS | 2-C-Methyl-D-erythritol 2,4-cyclodiphosphate synthase |
| MDC | Mevalonate-5-pyrophosphate decarboxylase |
| MDR | Multidrug resistance |
| MEcPP | 2-*C*-Methyl-D-erythritol 2,4-cyclopyrophosphate |
| MEP | 2-*C*-Methyl-D-erythritol 4-phosphate |
| MK | Mevalonate kinase |
| MOMCl | Methoxymethyl chloride |
| MVA | Mevalonic acid |
| *n*-$Bu_2BOTf$ | Dibutylborontriflate |
| *n*-BuLi | *n*-Butyllithium |
| $NADP^+$ | Nicotinamide adenine dinucleotide phosphate |
| NaHMDS | Sodium bis(trimethylsilyl)amide |
| NBD | Nucleotide binding domain |
| NCI | National Cancer Institute |
| NCS | *N*-Chlorosuccinimide |
| NHK | Nozaki–Hiyama–Kishi |
| nm | Nanometer |
| NMO | *N*-Methylmorpholine *N*-oxide |
| NMR | Nuclear magnetic resonance |
| PDC | Pyridinium dichromate |
| Pgp | P-glycoprotein |
| PhMe | Toluene |
| $PhNTf_2$ | *N*-Phenyl-bis(trifluoromethanesulfonimide) |
| PMB | *para*-Methoxybenzyl |
| PMK | Phosphomevalonate kinase |
| POP | Prolyl endopeptidase; prolyl oligopeptidase (EC 3.4.21.26) |
| PP | Pyrophosphate |
| PPTS | Pyridinium *p*-toluenesulfonate |
| *p*-TsOH | *p*-Toluenesulfonic |
| py | Pyridine |
| quant | Quantitatively |

| | |
|---|---|
| RCM | Ring closing metathesis |
| rfx | Reflux |
| rt | Room temperature |
| SAR | Structureactivity relationships |
| TASF | Tris(dimethylamino)sulfur (trimethylsilyl)difluoride |
| TBAF | Tetra-*n*-butylammonium fluoride |
| TBAI | Tetra-*n*-butylammonium iodide |
| TBME | Methyl tert-butyl ether |
| TBS | *tert*-Butyldimethylsilyl |
| TES | Triethylsilyl |
| Tf | Triflate (trifluoromethanesulfonate group) |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TMS | Trimethylsilyl |
| TPA | 12-*O*-Tetradodecanylphorbol-13-acetate |
| xs | Excess |

# Abstract

Consisting of more than 2000 known species the genus *Euphorbia* is considered to be one of the largest genera in the plant kingdom. Many species of the widely distributed spurges, have been extensively used in traditional herbal folk medicine to cure various health conditions, such as skin diseases, gonorrhea, migraine, intestinal parasites and warts.

Since the isolation of jathrophone in 1970 by Kupchan, the interest in active ingredients of members of the Euphorbiaceae family is steadily increasing. The milky latices of *Euphorbia* species contain a vast number of structurally diverse diterpenes, which show a wide range of biological properties, among those, antiproliferative and multidrug resistance modulating activities are most remarkable.

Despite the large number of Euphorbiaceae constituents isolated so far, only few have been synthesized up to now. Prompted by the pharmacological properties of jatrophane diterpenes as well as the challenging structural features of the terpene-based natural products, the work discussed within this thesis is devoted to the development of a synthetic approach toward the jatrophane diterpene Pl-3. The natural product consists of a highly oxygenated trans-fused bicyclo[10.3.0]pentadecane skeleton and was isolated in 2003 by Hohmann and co-workers from *Euphorbia platyphyllos*, a glabrous or pubescent annual plant, which occurs mainly in southern Europe.

*En route*, three approaches toward five-membered ring synthons, useful in the synthesis of various jatrophane diterpenes were developed. The first approach features a diastereoselective C-2 elongation, an RCM reaction and a hydroboration reaction as key transformations. Due to the orthogonal protecting group strategy the two achieved diastereomeric cyclopentane fragments are useful building blocks for the synthesis of jatrophane diterpenes in general. The improvements in our second approach are strongly based on metal catalyzed reactions and include an enyne metathesis and a palladium-catalyzed, reductive epoxide opening reaction. The novel application of the DACH-phenyl Trost ligand in the diastereoselective, reductive epoxide opening is an extension of Shimizu's protocol and demonstrates a new, valuable method, which can be utilized in the synthesis of complex natural products. The conceptually different, third approach starts from (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one and features an enzymatic kinetic chiral resolution, a Baeyer–Villiger oxidation and an iodolactonization reaction as key steps. Additionally, a substrate controlled alkylation protocol was elaborated, which grants access to the (C4, C15)-*trans*-substituted five-membered ring fragment, present in the majority of jatrophane

diterpenes. The established protocols are important synthetic achievements and constitute the foundation for the total synthesis of the jatrophane diterpene Pl-3.

## Zusammenfassung

Die Gattung Euphorbia gehört zur Pflanzenfamilie der Wolfsmilchgewächse und gilt mit ihren mehr als 2000 bekannten Arten als eine der größten Gattungen im Pflanzenreich. Viele Wolfsmilchgewächse wurden in der traditionellen Pflanzenheilkunde verwendet um verschiedene Krankheiten, wie beispielsweise Gonorrhö, Migräne, Darmparasiten, Hautkrankheiten und Warzen zu heilen.

Seit der Isolation von Jathrophon durch Kupchan im Jahr 1970, ist das Interesse an den bioaktiven Wirkstoffen der Mitglieder der Euphorbiaceae Pflanzenfamilie stetig angewachsen. Die milchigen Latizes verschiedener *Euphorbia*-Arten enthalten eine Vielzahl von strukturell unterschiedlichen Diterpenen, welche ein breites Spektrum an biologischen Eigenschaften zeigen, darunter besonders hervorzuheben sind die Wirksamkeit als Multidrug-Resistance Modulatoren und antiproliferative Eigenschaften.

Trotz der großen Zahl isolierter Naturstoffe aus der Familie der Euphorbiaceae, wurden bis heute nur sehr wenige davon synthetisiert. Durch die pharmakologischen Eigenschaften der Jatrophan Diterpene, sowie den faszinierenden Strukturmerkmalen dieser terpenbasierenden Naturstoffe, wird im Rahmen dieser Arbeit die Entwicklung eines neuen Syntheseansatzes des Jatrophan Diterpens Pl-3 vorgestellt. Pl-3 besteht aus einem hoch oxygenierten, *trans*-verknüpften Bicyclo[10.3.0]pentadecan Grundgerüst und wurde 2003 von Hohmann und Mitarbeitern aus *Euphorbia platyphyllos*, einer vor allem in Südeuropa auftretenden, einjährigen, krautigen Pflanze isoliert.

Auf dem Weg zu einer möglichen Totalsynthese von Pl-3 wurden drei neue Wege zu fünfgliedrigen Ringsynthonen entwickelt, welche bei der Synthese von verschiedenen Jatrophan Diterpenen nützlich sein können. In der ersten Synthesestrategie werden eine diastereoselektive C-2 Kettenverlängerung, eine RCM-Reaktion und eine Hydroborierungsreaktion als Schlüsselreaktionen verwendet. Aufgrund der verwendeten, orthogonalen Schutzgruppenstrategie sind die dabei hergestellten Fünfringfragmente nützliche Bausteine für die Synthese von verschiedenen Jatrophan Diterpenen. Unser zweiter, verbesserter Zugang basiert vorwiegend auf metallkatalysierten Reaktionen und beinhaltet eine Eninmetathese und eine Palladium katalysierte, reduktive Epoxidöffnungsreaktion. Die neuartige Anwendung der DACH-Phenyl Trost-Liganden in der diastereoselektiven, reduktive Epoxidöffnung stellt eine

Erweiterung von Shimizus Protokoll dar, die bei der Synthese komplexer Naturstoffe genutzt werden kann. Der konzeptionell unterschiedliche, dritte Zugang geht von (±)-*cis*-Bicyclo[3.2.0]hept-2-en-6-on aus und als Schlüsselschritte werden eine enzymatische kinetische Racematspaltung, eine Baeyer–Villiger Oxidation und eine Iodolaktonisierung verwendet. Zusätzlich wurde ein substratgesteuertes Alkylierungsprotokoll ausgearbeitet, welches den Zugang zu (C4, C15)-*trans*-substituierte Fünfringsynthons liefert, welche in der überwiegenden Mehrzahl der Jatrophan Diterpene vorhanden ist. Die etablierten Protokolle und Methoden sind wichtige Syntheseleistungen und bilden die Grundlage für eine spätere Totalsynthese des Jatrophan Diterpens Pl-3.

# 1 Introduction

The *Euphorbiaceae* plant family is estimated to cover over 260 genera and more than 6490 species,[1] which occur mainly in the tropics, whereby the majority of the members of this huge family of flowering plants is found in the Indo-Malayan and tropical American region. Nonetheless, many species are found in non-tropical areas such as the Mediterranean Basin, the Middle East, South Africa, Madagascar and the southern USA. In the European flora seven genera with over 100 species are endemic.

Various plants of this diverse plant family are of considerable economic importance. One example, cassava (*Manihot esculenta*), is an important agricultural product, as cassava-based dishes are widely consumed especially in Africa, Asia and Latin America.[2] For the usage as biodiesel fuels *Jatropha curcas* and the castor oil plant (*Ricinus communis*) are of significant interest.[3, 4] Probably the best known example for an economically important member of the family *Euphorbiaceae* is the para rubber tree (*Hevea brasiliensis*), which is still the primary source of natural rubber.

Comprising more than 2000 known species, which are commonly referred to as spurges, the genus *Euphorbia* is one of the largest genera within the Euphorbiaceae family and even in the plant kingdom. It is the largest occurring genus in Europe, including perennial and annual herbs and small shrubs. When cut, many *Euphorbia* species exude a milky sap, termed as latex. This sap is suggested to have a protective role in healing processes after mechanical injury of the plant and in deterring herbivores. For this reason, it is hardly surprising that the sap of various species of the genus *Euphorbia* has extremely caustic and irritant properties. One further main characteristic feature present in all species of the genus is the reduction and aggregation of the flowers into a cluster called cyathium.[2]

The name *Euphorbia* derives from Euphorbus, the personal physician of king Juba II of Mauretania (50 BC – 23 AD), who treated the king with a plant exhibiting powerful medicinal properties and after successful therapy, the plant was named after him.[5] Hence, the official botanical name was assigned by the taxonomist Carl von Linné who described *Euphorbia antiquorum* as type species for the genus *Euphorbia* in the first edition of his book *Species Plantarum*[6] in 1753. In traditional medicine some species of the genus *Euphorbia* have been used for the treatment of skin diseases, gonorrhea, migraine, against intestinal parasites and for curing warts.[7] There are even species used for the treatment of cancerous condition.[8] Taking advantage of the toxic plant ingredients some spurges were utilized for poison fishing, especially in tropical Africa.[9] Furthermore,

Candelilla wax, obtained from *Euphorbia antisyphilitica,* is classified by the Food and Drug Administration (FDA) as a substance *Generally Recognized As Safe* (GRAS) for application in the foods industry and is nowadays found as a food additive or glazing agent.[10] In earlier times *Euphorbia antisyphilitica* was employed for the treatment of sexually transmitted diseases. The use of the same plant as a purgative or laxative may have led to the common name "spurges", which is used for the herbaceous, leafy species of the whole *Euphorbiaceae* family. The word "spurge" is taking account of this important attribute as it derives from the Middle English/Old French word *espurgier* which means "to purge".

Despite the economic importance of other genera of the Euphorbiaceae plant family, as already mentioned before, the main uses of members of the genus *Euphorbia* are horticultural. For the Christmas holiday season, different cultivars of poinsettia (*Euphorbia pulcherrima*) are widely grown pot plants in Europe, the United States and other countries. Some herbaceous species are cultivated as ornamental plants as for instance the cypress spurge (*Euphorbia cyparissias*) or the Mediterranean spurge (*Euphorbia characias*) and among the cactiform euphorbia the succulent *Euphorbia trigona* is a quite popular indoor plant.

## 2 Genus Euphorbia and medicine

As mentioned above, species of the Euphorbiaceae family have been used in traditional folk medicine over centuries. Pliny the Elder already documented the use of the latex of certain species for the removal of warts, as a fish poison or as a cathartic.[11] In traditional Chinese medicine several species play a major role for the treatment of various diseases such as ascites, cancer, edema and warts.[12] Due to their broad application as plant remedies the interest in the biologically active compounds was steadily growing. Especially diterpenes have been revealed as metabolites with significant biological activities within phytochemical and biological investigations. Phorbol (**2**) was the first compound isolated in pure form from an Euphorbiaceae species (Figure 1). The substance was isolated in 1935 from the plant purging croton (*Croton tiglium*) one of the "50 fundamental herbs" of the traditional Chinese medicine.[13] Its relative structure as well as its absolute configuration was elucidated by Hecker *et al* in 1967 by X-ray analysis of a derivative.[14] After Van Duuren and coworkers reported the tumor-promoting properties of seeds from *Croton tiglium,* many different bioactive phorbol esters were isolated from this species and biologically evaluated. 12-*O*-Tetradodecanylphorbol-13-acetate (TPA; **1**) is used nowadays as a standard tumor-promoting agent in biochemical experiments.[15, including references cited herein]

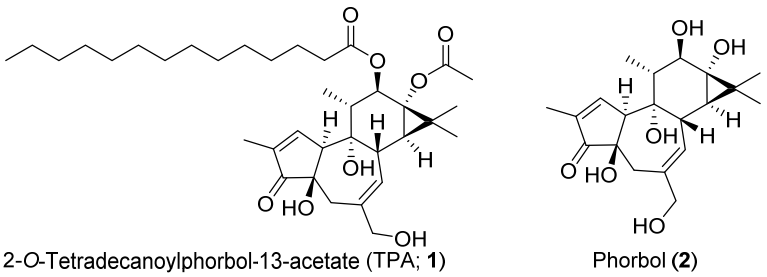



**Figure 1: TPA (1) and Phorbol (2).**

Ever since the isolation of phorbol (**2**), hundreds of mainly terpene-based natural products were isolated from members of the Euphorbiaceae family.[7, 16-19] The chemical diversity of the isoprenoid constituents is remarkable and hundreds of compounds comprising many different core frameworks such as the jatrophane, lathyrane, tigliane, ingenane, myrsinol, daphnane *etc* were found (Figure 2).

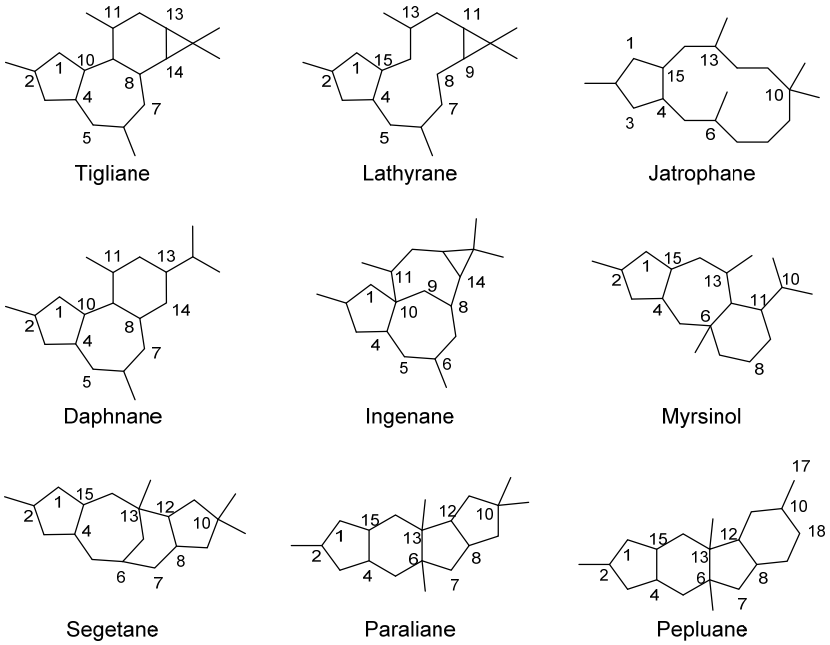


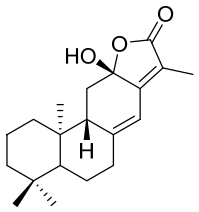

**Figure 2: Different diterpene frameworks.**

The structurally diverse diterpenes exhibit various oxygenation stages and stereoisomers and these compounds are usually substituted with different acyl groups (propanoyl, butanoyl, isobutyryl, benzoyl, nicotinoyl, angeloyl, acetyl, *etc*). *Exo*-cyclic as well as *endo*-cyclic double bonds are common structural motifs which can be found at all possible positions. In most of the frameworks elucidated to date, a five-membered ring is present, which is, despite all variety, nearly always trans-fused to the rest of the molecule. Other positions with more or less consistent configuration are C3, C4 and C15, whereby C4 and C15 represent the ring junctions of the above-mentioned five-membered ring. Due to their broad structural diversity and their wide range of potentially valuable biological activities diterpenes occurring in plants of the Euphorbiaceae family are of considerable interest in the context of natural product drug discovery programs. To show

this often cited wide range of biological activities, a few representative examples are highlighted in the following section.

## 2.1 Biological activity of depicted examples

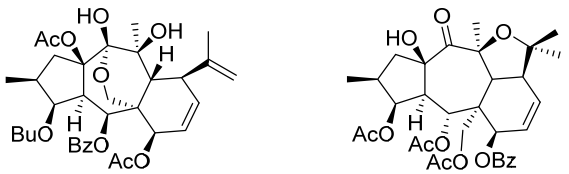
The *ent*-abietane diterpene *ent*-12-hydroxy-12[*R*]-abieta-8(14),13(15)-dien-16,12-olide (**3**) was isolated from the tubers of *Euphorbia sessili* and showed moderate to strong growth inhibition against *Bacillus cereus*, *Bacillus subtilis*, *Micrococcus flavas*, *Moraxella catarrhalis*, *Neisseria sicca*, and *Candida albicans* CBS 5763 at 12.5 $\mu$g/mL concentration.[20]




*ent*-12-Hydroxy-12[*R*]-abieta-8(14),13(15)-dien-16,12-olide (**3**)

**Figure 3: *ent*-12-hydroxy-12[*R*]-abieta-8(14),13(15)-dien-16,12-olide (3).**

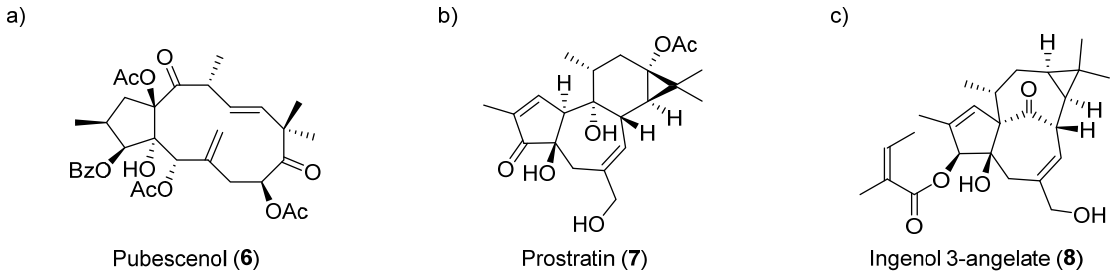
During their investigations of biologically active plant metabolites from *Euphorbia decipiens*, a species endemic in Iran, Ahmad and coworkers isolated different diterpenes. Among those, two myrsinol-type diterpenoids **4** and **5** were identified, which were found to be active against prolyl oligopeptidase (POP, EC 3.4.21.26)[21]. Compound **4** showed an $IC_{50}$ value of 3.2 $\mu$M, with the positive control of bacitracin ($IC_{50}$ of 129 $\mu$M) and compound **5** exhibited an $IC_{50}$ of 16.9 ±1.3 $\mu$M, which was compared with the positive control of *Z*-pro-prolinal ($IC_{50}$ of 1.27 ±0.01 nM).[22, 23]




**4** **5**

**Figure 4: Myrsinol-type diterpenes.**

POP is a strongly conserved enzyme with the ability to cleave peptides at internal proline residues. Although cytoplasmic POP is able to digest a large number of biologically active peptides *in vitro*, there is only limited evidence that POP is responsible for the metabolic degradation of peptides. Nevertheless, it is beyond dispute that POP has influence on several functions of the central nervous system, including learning and memory and plays a crucial role in hypertension, bipolar disorders as well as in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, which identifies POP as a potential drug target.[24-29]




Pubescenol (**6**) Prostratin (**7**) Ingenol 3-angelate (**8**)

**Figure 5: Bioactive diterpenes from *Euphorbia pubescens.***

In the search for new anticancer agents Ferreira and coworkers isolated and characterized different diterpenes from *Euphorbia pubescens.* They reported the moderate *in vitro* effect of the jatrophane diterpene pubescenol (**6**; Figure 5a) on the human tumor cell lines MCF-7 (breast adenocarcinoma), NCI-H460 (nonsmall cell lung cancer) and SF-268 (CNS cancer).[30]

In the last years considerable efforts in the treatment of HIV-positive patients were made. Today, it is possible to decrease plasma viremia below the limits of detection in the majority of HIV-infected individuals. However, the required highly active antiretroviral therapy (HAART) suffers from a few drawbacks. As HAART targets are only actively replicating HIV affected cells of the immune system, the elimination of latently infected, resting $CD4^+$T cells is not possible by the application of this therapy. The complete elimination of the virus would require long-term treatment of HIV-patients and exposing them to side effects such as the emergence of resistance through viral mutations as well as general weakening of the patient due to general side effects. Another important factor is the financial burden, which is often associated with long-time therapy.

To circumvent these problems new forms of therapies have to be developed. One possible novel access is the induction of viral gene expression in latently infected $CD4^+$T cells, which potentially leads to the elimination of the same through host anti-HIV immunity.[31, 32] A possible drug candidate, which stimulates viral gene expression in latently infected cells is prostratin (**7**; Figure 5b), first isolated from *Pimelea prostrata* and characterized by Hecker and coworkers in 1976.[33] In the following, **7** was isolated from *Euphorbia cornigera* by Evans and coworkers,[34] and from *Euphorbia fischerania* by Liu and coworkers[35].

The ingenane-type diterpene ingenol 3-angelate (**8**; Figure 5c) was isolated of different species from the Euphorbiaceae family, for example from *Euphorbia peplus* by Hohmann and coworkers in 1999.[36] In January 2012, the FDA granted approval for the use of ingenol 3-angelate (Picato®, LEO Pharma) in the treatment of actinic keratosis, a pre-cancerous skin condition that appears as a dry, scaly, sometimes hyperkeratotic lesion as a result of prolonged and repeated sun exposure.

The topically applied gel formulation contains the natural product (**8**) without structural modification, a quite remarkable fact.[37]

### 2.1.1 MDR – reversal effect[38-41]

With approximately 575 000 cancer-related deaths in 2011 in the USA, malignant neoplasms are the second most common cause of death after cardiovascular diseases.[42] Therefore, the development of new and more effective therapies for the treatment of cancerous condition is extremely important. The failure of chemotherapy due to the development of tumor cell resistance to multiple drugs is called multidrug resistance (MDR). The cellular mechanisms of MDR have been thoroughly investigated in the past few years. Different processes leading to drug resistance have been identified and they can be divided in two general classes: Those that influence the delivery (increasing efflux, reduced drug influx) and those originating in the cancer cell such as activation of detoxifying proteins (e.g. Cytochrome P450 oxidases) or mechanisms that repair drug-induced DNA damage (see Figure 6).

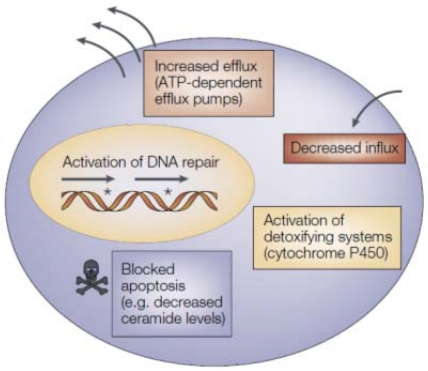



**Figure 6: Cellular mechanisms of MDR.[38]**

The overexpression of active drug efflux pumps in the membranes of cancer cells is mainly responsible for the resistance to hydrophobic drugs.[43] Thus, the ATP binding cassette (ABC) transporters P-glycoprotein (Pgp), MRP1 and ABCG2 were identified to be implicated as major contributors to MDR in cancer. Among those Pgp is the best-studied membrane protein. Pgp is expressed in the brain, the testis and the placenta preventing the penetration of cytotoxins. Moreover, it has a quite similar role in the kidneys, the pancreas, the intestine and the adrenal gland in restricting drug entry through the gastrointestinal tract and excreting toxic substances into the urine.[44, 45] Much effort has been devoted to the elucidation of the precise functioning of the ABC transporters, but it is not fully understood to date. High-resolution X-ray crystal structures of Pgp revealed that this *trans*-membrane protein consists of two homologous halves, each comprising six *trans*-membrane helices and a cytoplasmic nucleotide-binding domain (NBD).

The crystal structure appears to confirm a region containing different subsites where various drugs can bind, rather than one distinct drug-binding site.[46]

Although the mode of action of Pgp has been thoroughly investigated, some uncertainties remain. The accepted catalytic cycle is outlined in Figure 7 and starts with binding of two ATP molecules with low affinity ($ATP_L$) to Pgp. In catalytically active Pgp one of the ATP molecules is bound tightly and very fast ($ATP_T$). This induces a conformational change in one half of the NBD dimer, thus offering the possibility of binding a drug (illustrated as red sphere) within the cytoplasmic membrane. Hydrolysis of the $ATP_T$ to ADP and $P_i$ triggers the drug transport through a switch from an inward facing to an outward facing conformation. Up to now it has not been sufficiently elucidated if the drug is transported first to the outer leaflet of the membrane or directly to the extracellular aqueous phase. The newly gained ADP and $P_i$ induce the opening of the closed dimeric ATP binding site and a simultaneous ATP site affinity switch, which results in a tight binding conformation of the second molecule of ATP (former $ATP_L$). Another ATP molecule substitutes the loosely bound ADP to finish the catalytic cycle.[38, 47-49]

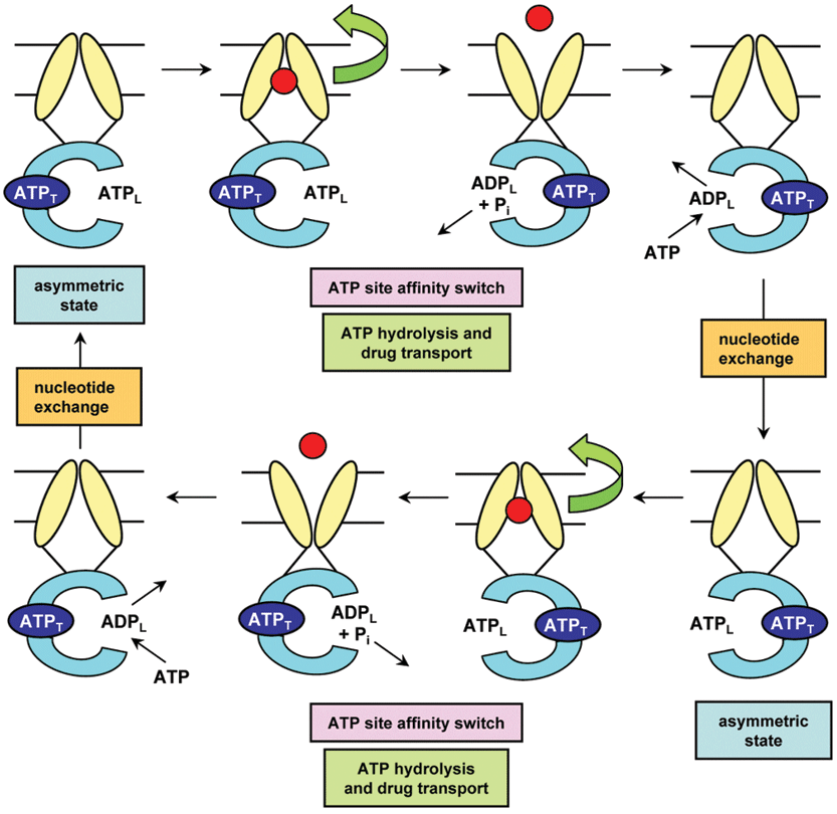



**Figure 7: Pgp catalytic cycle.**[50]

In the last 30 years literally hundreds of substrates of Pgp have been identified. [51-53] The large diversity within the substrate pool makes it impossible to make generalizations or predictions about Pgp´s preferred substrate type. Furthermore, a restriction of favoured substrate structures

is additionally hampered, as many Pgp substrates are lipid-soluble, large (200-1900 Da) organic molecules, which possess the ability to cross the lipid bilayers readily by passive diffusion.

The identification of novel compounds that can reverse MDR mediated by ABC transporters had a large impact on the development of new strategies to combat cancer. These modulators have the ability to lower the pump efflux activity leading to cell death caused by restoring the cytotoxicity of the applied drug during *in vitro* experiments. Pgp modulators are structurally as diverse as the Pgp substrates and include calcium channel blockers such as verapamil, cyclic peptides, steroids and others.[38]

Although a promising method, the treatment with MDR reversal agents clearly suffers from several drawbacks. For instance, if the inhibition of the transporters succeeds, it leaves sensitive tissue, susceptible to be harmed by cytotoxic compounds.[54] In addition, MDR reversal agents may be not specific enough to interfere solely with the desired target. First clinical trials with substances such as verapamil showed low effectiveness at non-toxic doses.[55] Another problem concerns pharmacokinetic interactions. The serum level of anticancer drugs is increased when Pgp inhibitors were applied.

Simultaneously, parallel studies revealed that the reduction of anticancer drug doses leads to an undertreatment of cancer cells and the desired tumor-inhibiting effect could not be achieved for a significant amount of patients.[56] A few MDR modulators are in clinical trials showing promising results in cancer therapy, however it remains unknown whether Pgp transporters are the appropriate targets for the development of successful future cancer treatment.

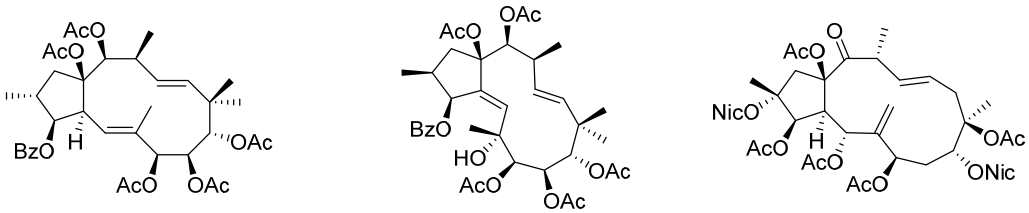



**Figure 8: Bioactive jatrophane diterpenes.**

Various jatrophane diterpenes were found to be very active in reversing multidrug resistance. As an example, euphosalicin (**11**; Figure 8) showed to be a more active *in vitro* MDR-reversal agent in mouse lymphoma cells than the control substance verapamil.[57] In contrary to other jatrophane diterpenes euphosalicin comprises a 9(10→18) *abeo*jatrophane skeleton leading to a thirteen-membered ring annulated to the five-membered ring fragment.

Due to the diverse oxygenation as well as acylation and varied stereochemical substitution pattern found among jatrophane diterpenes structure-activity-relationships (SAR) studies are hard to conduct. Nevertheless, Hohmann and coworkers recognized lipophilicity as an important factor for the activity, though they stated that the tested compounds do not comprise a uniform series as regards their substitution and stereochemistry.[58] In their SAR studies, Lanzotti *et al* investigated the Pgp binding properties of ten closely related jatrophane diterpenes. They validated not only the general MDR reversing potential of jatrophane polyesters within their studies but also suggested the involvement of the "southwestern" part of the molecules in binding to Pgp.[59]

The compelling biological activity of jatrophane diterpenes makes this class of natural products a target of interest. In the course of contributing to this field, our research group developed different approaches toward the total syntheses of Pl-3 (**9**), Pl-4 (**10**) and euphosalicin (**11**), depicted in Figure 8.

# 3 Biogenesis

This chapter aims to give a brief summary of the biogenesis of cyclic diterpenes and to specifically present an overview of the scarce knowledge of the biogenesis of jatrophane diterpenes.[60] Despite the immense diversity of terpenes encompassing physiological important hormones, membrane lipids, insect attractants or anti-feedants, fragrances, anticancer drugs *etc*, all terpenes are derived from a sequential assembly of the same building blocks. Sequential condensation of the interconvertible isomers isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) leads to isoprenoid oligomers such as geranyl (**48**), farnesyl (**51**), geranylgeranyl pyrophosphate (**52**), squalene and phytoene.[61] Modification of these oligomers by different types of cyclization reactions as well as further oxidations and skeletal rearrangements lead to the structural diversity found among terpenes.

## 3.1 Biosynthesis of IPP and DMAPP

Although IPP and DMAPP are the universal precursors for isoprenoid biosynthesis, in green plants, isoprenoid biosynthesis occurs *via* two separate pathways: On one hand the mevalonate (MVA) pathway[62, 63] and on the other hand the more recently discovered 1-deoxy-D-xylulose 5-phosphate/2-C-methyl-D-erythritol 4-phosphate (DXP/MEP) pathway[64-66]. The two pathways are active in different subcellular compartments and are responsible for the production of the diverse diterpenes (see Figure 9)[67]. A deeper understanding of this segregation and how the individual biosynthetic intermediates inter-relate has still to be gained.[68, 69]

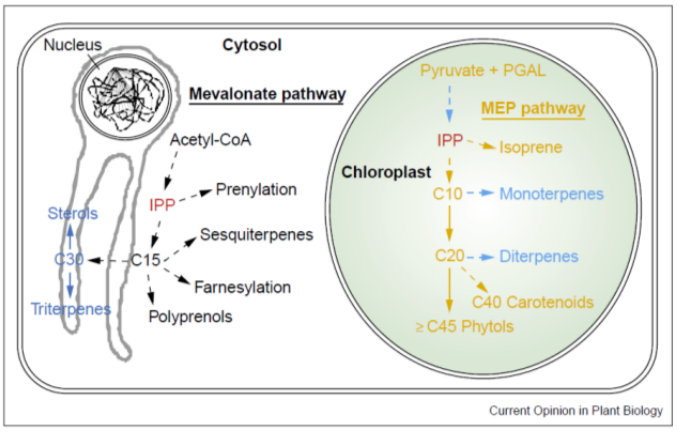
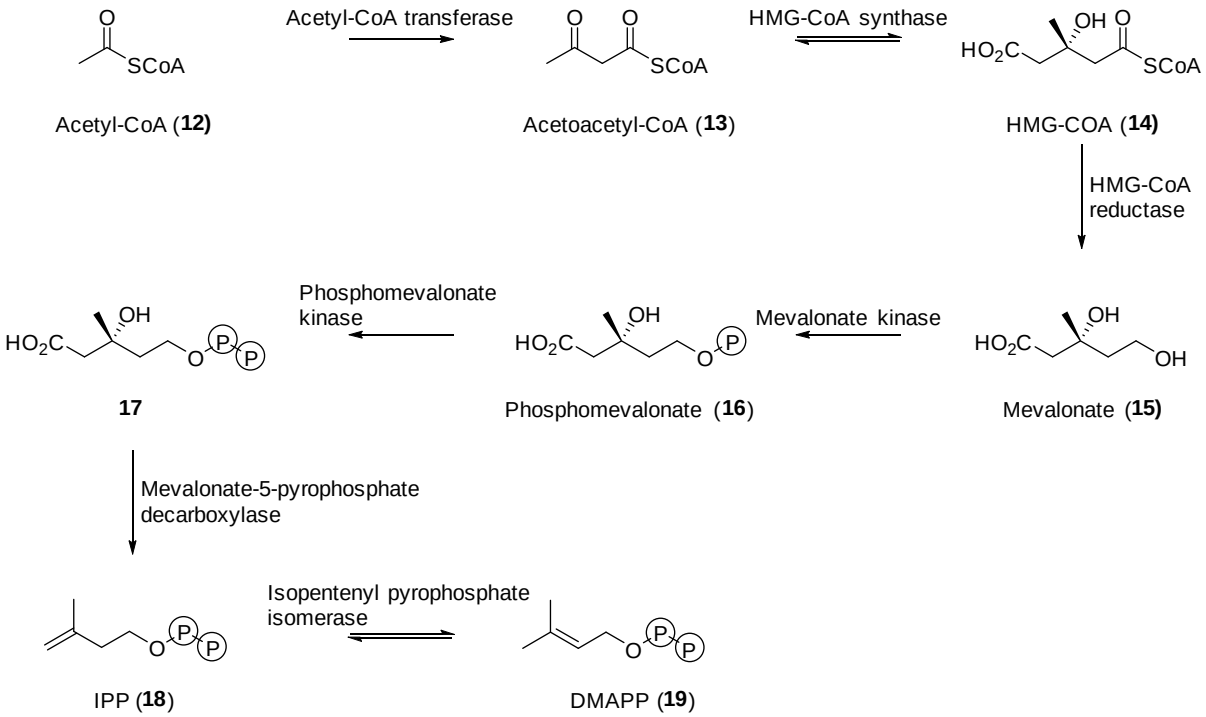



**Figure 9: The MVA pathway and MEP pathway are active in different subcellular compartments.**[67]

### 3.1.1 The mevalonic acid pathway

This pathway is one of the best investigated biosynthetic pathways and its elucidation was recognized with two separate Nobel Prizes in Physiology and Medicine for Konrad Bloch and Feodor Lynen in 1964. The accepted biosynthesis of IPP and DMAPP as described in many text books[60, 62, 63] is outlined in Scheme 1.



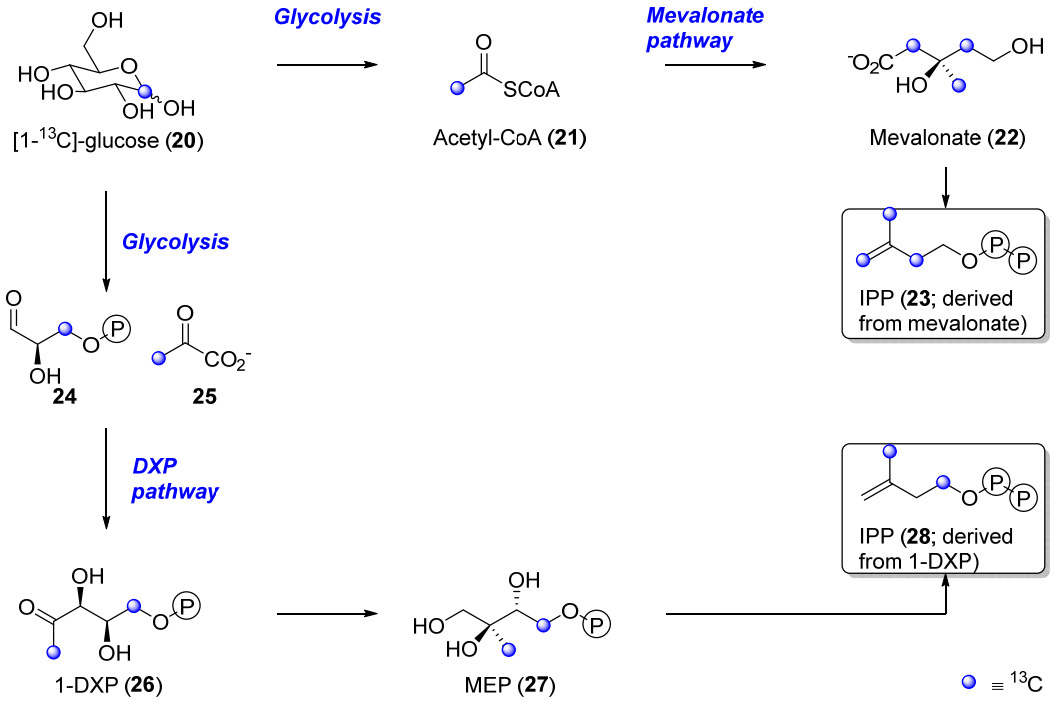

**Scheme 1: The MVA pathway.**[70]

Starting from acetyl-coenzyme A (acetyl-CoA; **12**) the first step is a Claisen-type condensation with another molecule of acetyl-CoA to give acetoacetyl-CoA (acac-CoA; **13**) mediated by acetyl-CoA transferase (AACT; EC 2.3.1.9). In an aldol-type process another molecule of acetyl-CoA is added to produce (*S*)-3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA; **14**) catalyzed by HMG-CoA

synthase (HMGS; EC 4.1.3.5). The next step is of special importance as it is the rate determining step in the cholesterol synthesis. Herein, HMG-CoA (**14**) is irreversibly reduced to mevalonate (**15**) under the control of HMG-CoA reductase (HMGR; EC 1.1.1.34), the target of statins used in cholesterol-lowering therapy.[71, 72] Three consecutive phosphorylations, the first mediated by mevalonate kinase (MK; EC 2.7.1.36) leading to 5-phosphomevalonate (**16**), the second by phosphomevalonate kinase (PMK; EC 2.7.4.2) maintaining 5-pyrophosphomevalonate (**17**) and the third mediated by mevalonate-5-pyrophosphate decarboxylase (MDC; EC 4.1.1.33) lead to 3-isopentenyl pyrophosphate (IPP; **18**) under the loss of carbon dioxide. The isomerization to dimethylallyl pyrophosphate (DMAPP; **19**) is accomplished by isopentenyl pyrophosphate isomerase (IPI; EC 5.3.3.2).

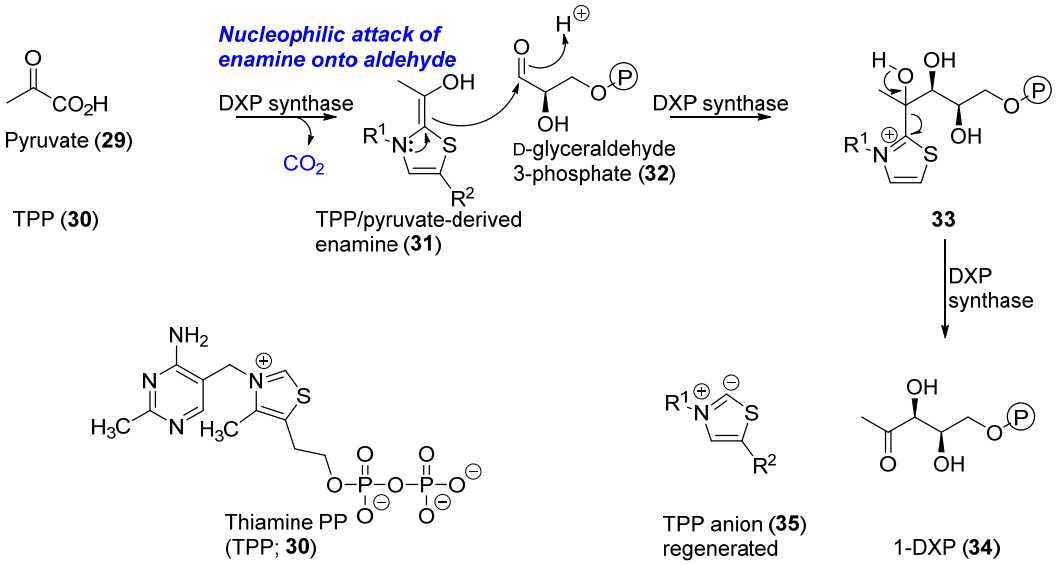
### 3.1.2 The methylerythritol 4-phosphate (MEP) pathway[64, 65, 69, 73]

In the 90´s Rohmer, Arigoni and coworkers published their results on a second, independent pathway for the terpene biosynthesis.[64-66] With the newly established MEP pathway it was possible to explain the various experimental inconsistencies, concerning the mevalonate pathway, which occurred over the previous years. The MEP pathway is active in the plastids of green tissues and oil gland cells in plants as well as in most bacteria. The crucial experiment, which finally led to the elucidation of the above mentioned pathway, is outlined in Scheme 2. If 1-$^{13}$C labeled glucose (**20**) is degraded through glycolysis and the metabolic product, acetyl-CoA (**21**), is directly introduced into the mevalonic pathway the resulting IPP (**23**) has to be $^{13}$C-labeled at the positions 2, 4 and 5. These expectations were not fulfilled but $^{13}$C incorporation at the positions 1 and 5 (**28**), confirmed by NMR spectroscopy, was reported by Rohmer and Lichtenthaler *et al*.[66, 74] These facts could be explained by the description of the newly found MEP pathway.




**Scheme 2: Labeling experiment.**[75]

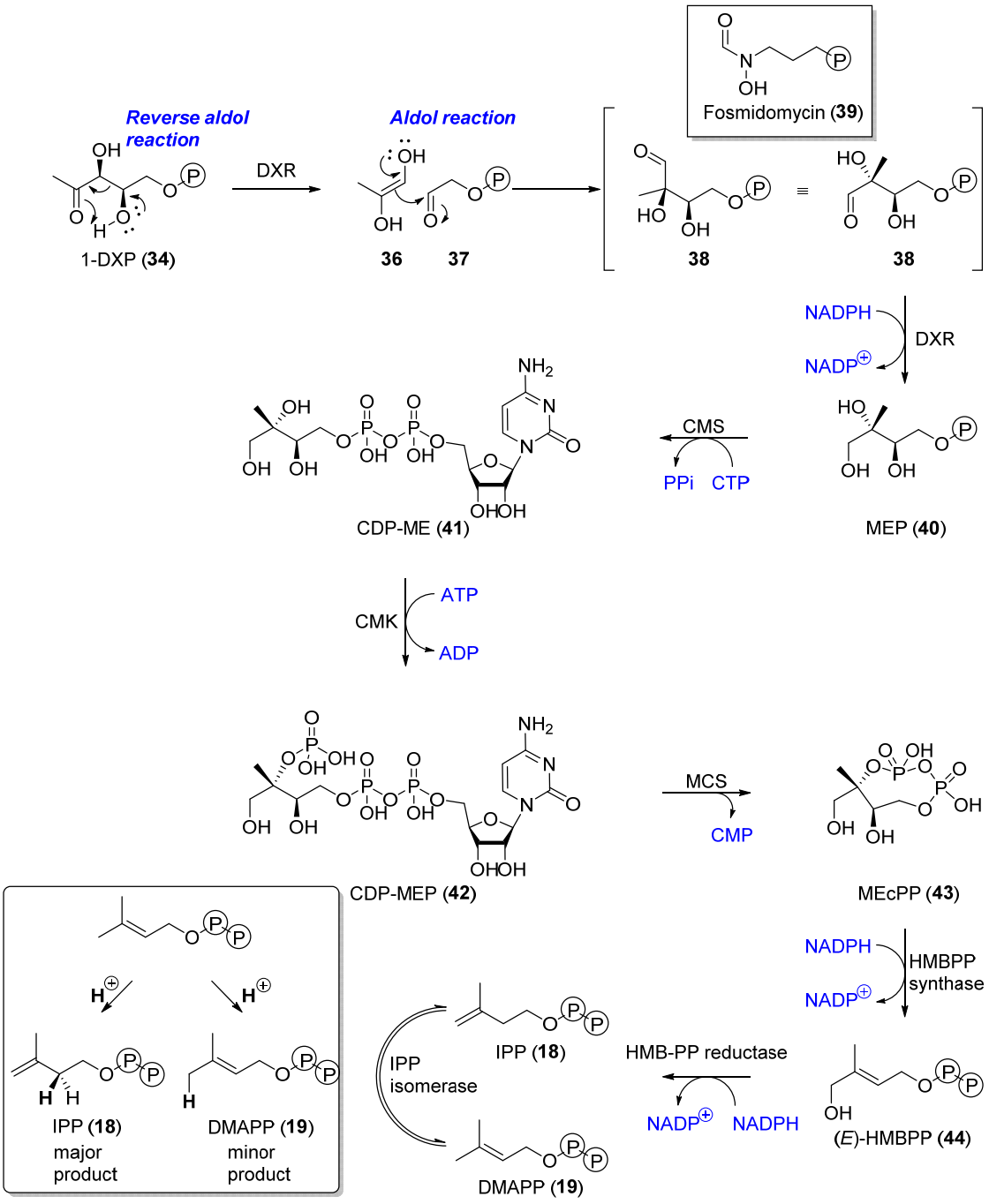
The Rohmer pathway as depicted in Scheme 3 and Scheme 4 starts from pyruvate (**29**) and glyceraldehyde 3-phosphate (**32**), which are available from the anaerobic degradation of glucose.[62, 63] Mediated by 1-deoxy-D-xylulose 5-phosphate synthase (DXP-synthase; EC 2.2.1.7) 1-deoxy-D-xylulose 5-phosphate (1-DXP; **34**) is generated under the loss of one molecule of carbon dioxide.




**Scheme 3: MEP pathway-part one.**[75]

The next step can be considered as key step in this pathway. DXP reductoisomerase (DXR; EC 1.1.1.267) catalyzes the skeletal rearrangement and the reduction[76] of 1-DXP to form 2-C-

methylerythritol 4-phosphate (MEP; **40**) (see Scheme 4). This early step is of significant pharmacological interest. As the MEP pathway is used by pathogens such as malaria or tuberculosis, but is not present in humans, its enzymes are attractive drug targets.[77] The antibiotic fosmidomycin (**39**) originally isolated from *Streptomyces lavendulae*[78] acts as an analog of the intermediate **38** inhibiting further terpenoid production by the MEP pathway without affecting the mevalonate pathway.[79]

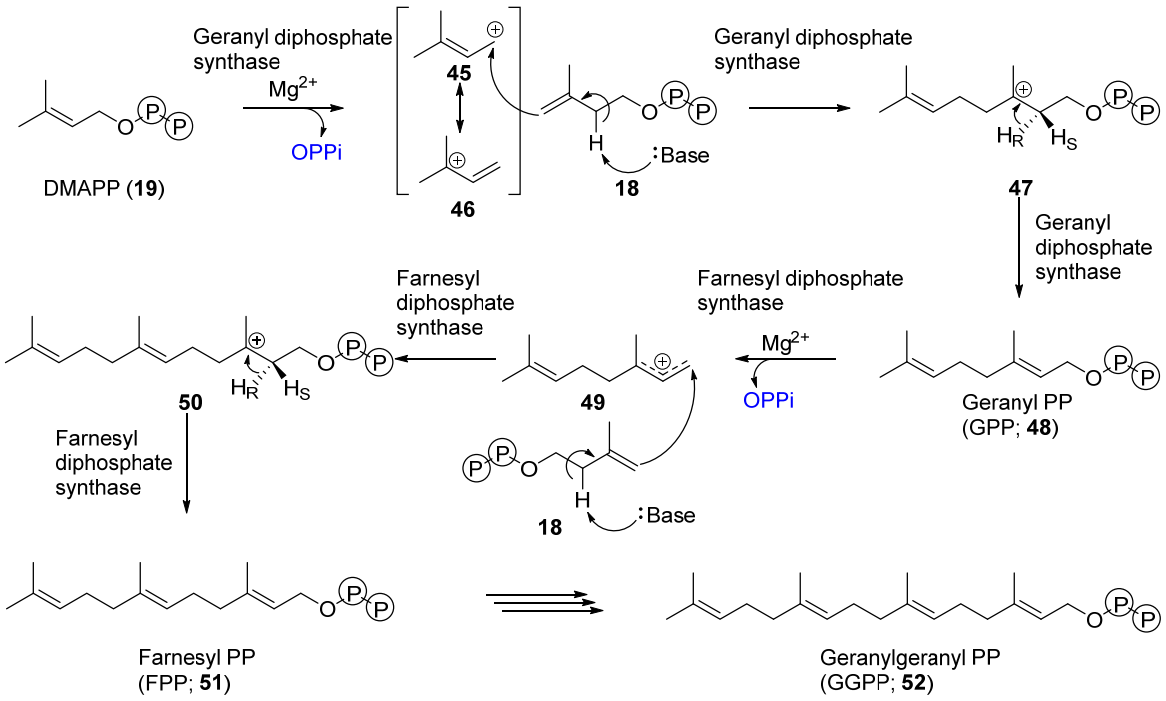



**Scheme 4: MEP pathway-part two.**[60,76]

However, to obtain IPP from MEP the hydroxyl groups have to be reductively removed. In a first step toward this achievement the phosphorus-oxygen lyase, 2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (CMS; EC 4.6.1.12), catalyzes the reaction of MEP with cytidine triphosphate (CTP) to produce 4-diphosphocytidyl-2-C-methylerythritol (CDP-ME; **41**), which is then phosphorylated with consumption of ATP by 4-diphosphocytidyl-2-C-methyl-D-erythritol kinase (CMK; EC 2.7.1.148). The resultant 4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate (CDP-MEP; **42**) is then converted into the cyclic phosphoanhydride 2-C-methyl-D-erythritol 2,4-cyclopyrophosphate (MEcPP; **43**), losing cytidine phosphate by the phosphorous-oxygen lyase (2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase; MCS; EC 4.6.1.12). Until this stage, various enzymes were used to further functionalize MEP but the oxidation state is still the same. In the next step MEcPP is converted to (*E*)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP; **44**) by mediation of the oxidoreductase HMB-PP synthase (EC 1.17.7.1). Thereby, the required reduction equivalent is delivered by a dithiol which is oxidized to a disulfide group. In the last step, water is eliminated by HMB-PP reductase (EC 1.17.1.2), whereby NADPH is used as cofactor, producing predominantly IPP but also DMAPP. The ratio of the two intermediates is also possible to be balanced by IPP isomerase.

### 3.1.3 Biosynthesis of diterpenes - Geranylgeranyl pyrophosphate

Isoprenyl pyrophosphate synthases (IPPS) represent one class of prenyltransferases[80] and catalyze the formation of long-chain prenyl pyrophosphates. In Scheme 5 the enzymatic reactions are outlined. After elimination of the phosphate moiety in DMAPP affording the corresponding allylic cation, nucleophilic attack of IPP (**18**) leads to an intermediate tertiary cation **47**. Loss of a proton gives geranyl pyrophosphate (**48**) and the same reaction sequence starts again. Generation of the allylic cation, nucleophilic attack of IPP and loss of a proton leads to the C15 molecule farnesyl pyrophosphate (**51**). As diterpenes are formed from four C5 units a further addition of IPP is required to gain access to geranylgeranyl pyrophosphate (GGPP; **52**).

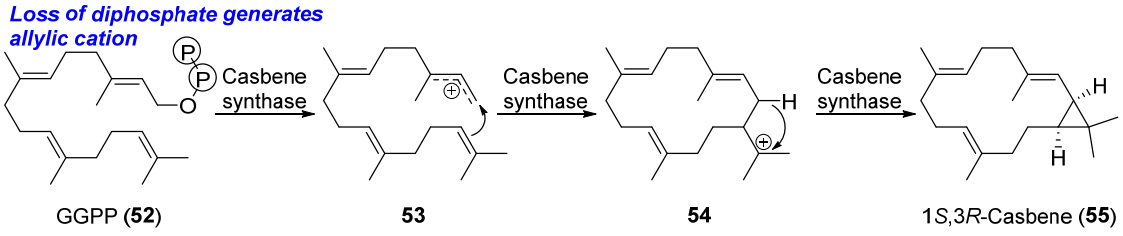



**Scheme 5: Biosynthesis of GGPP.**[60]

### 3.1.4 Diterpene cyclases

So far, four different GGPP cyclases, namely the casbene synthase, the *ent*-kaurene synthase A, the abietadiene synthase and the taxadiene synthase, have been identified and were found to be responsible for the cyclization of geranylgeranyl pyrophosphate leading to different cyclic diterpenes.[81, 82]

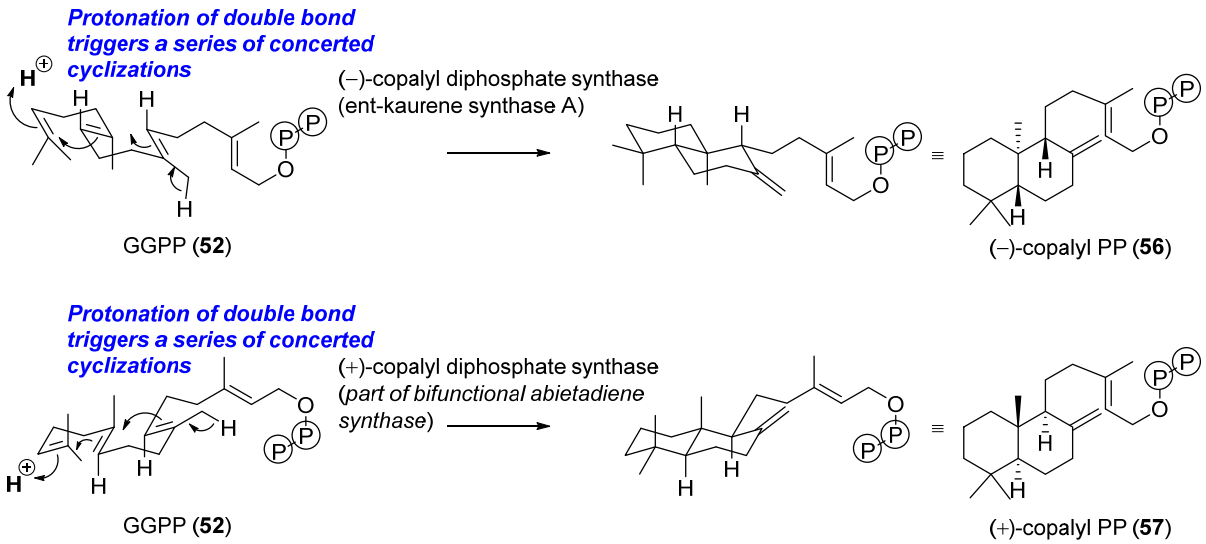
The casbene synthase was already characterized in 1978 by Dueber, Adolf and West from seedlings of *Ricinis communis*.[83] It catalyzes the formation of (1*S*,3*R*)-casbene (**55**), an antifungal metabolite, from GGPP (**52**). During the process the diphosphate group is eliminated, followed by nucleophilic attack on the resulting allylic cation **53** by the terminal double bond which delivers a 14-membered ring system. Loss of a proton leads to the formation of a cyclopropane ring and the desired product **55** (Scheme 6).




**Scheme 6: Casbene synthase.**[81]

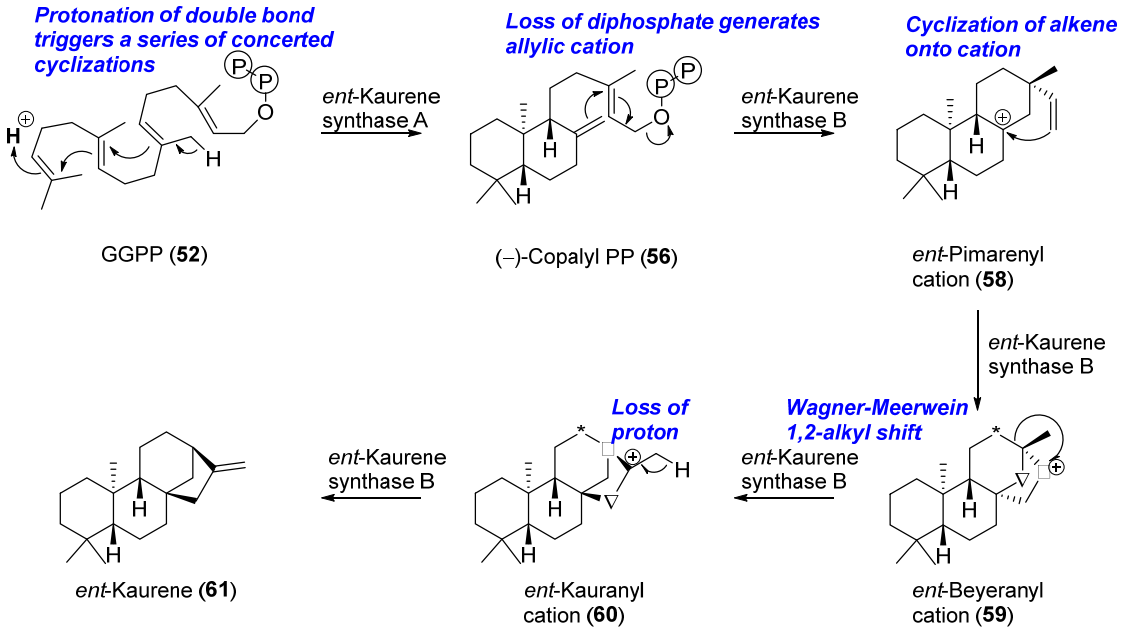
Formation of the initial carbocation need not necessarily be triggered by the loss of the diphosphate group of GGPP. Another common mechanism, described in Scheme 7, is the

initiation of the cyclization sequence by protonation of the double bond at the head of the chain. *ent*-Kaurene synthase A uses this mechanism and catalyzes the reaction of GGPP (**52**) to (−)-copalyl PP (**56**). This important intermediate still bears the diphosphate group, which can be lost later on within the biogenetic pathway to produce a further carbocation and facilitate a further cyclization. The surface of the enzyme has an important role in controlling the folding mode during the transition state of the reaction. As outlined in Scheme 7 (+)-copalyl diphosphate synthase (part of bifunctional abietadiene synthase) delivers (+)-copalyl PP (**57**) as product, because of the alternative folding of GGPP in the transition state.



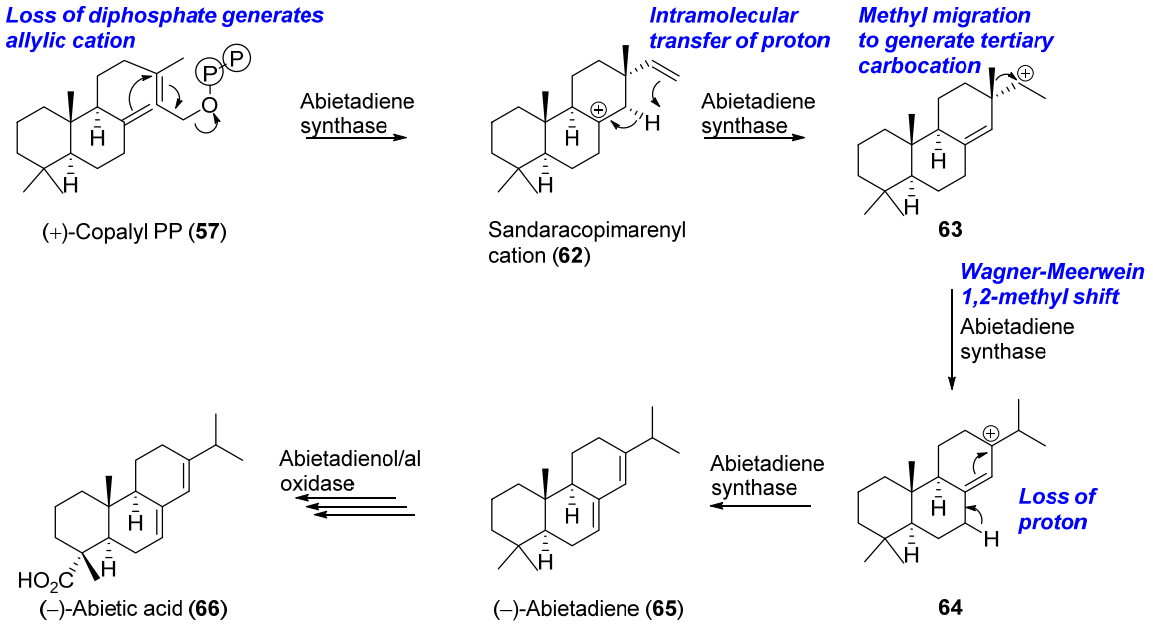

**Scheme 7: Copalyl diphosphate synthases.**[60, 81]

*ent*-Kaurene (**61**) is elaborated from (−)-copalyl PP (**56**) by a sequence of cyclizations and a rearrangement induced by the loss of the diphosphate moiety. Each step is catalyzed by *ent*-kaurene synthase B (see Scheme 8),[84] which is not classified as a GGPP cyclase because its cyclization substrate is (−)-copalyl PP (**56**) rather than GGPP (**52**).[85, 86]



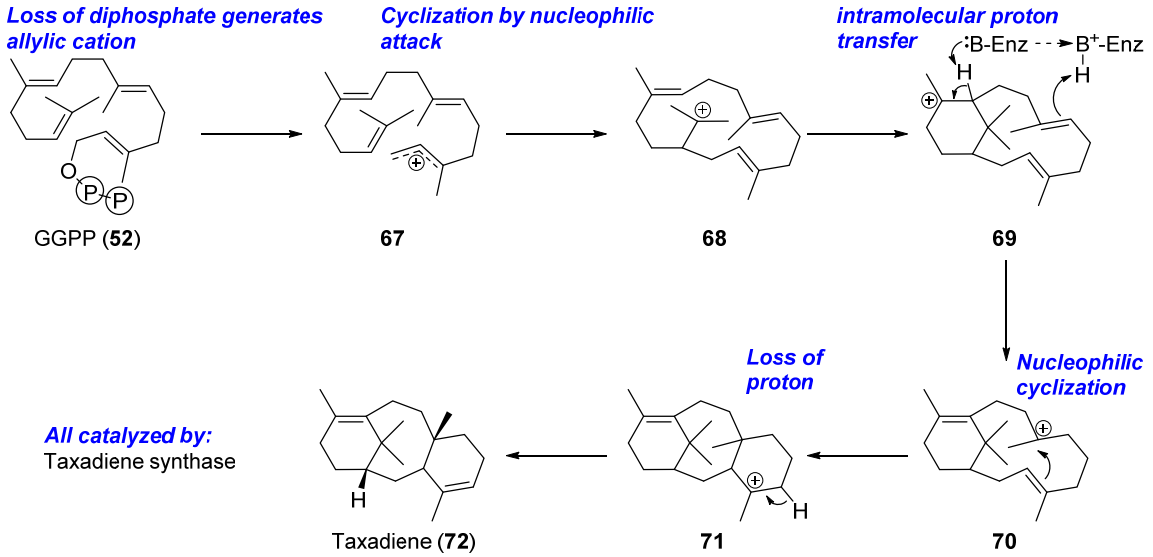

**Scheme 8 *ent*-Kaurene synthase B.**[60]

In contrast to *ent*-kaurene synthase B, the bifunctional abietadiene synthase, which involves the above mentioned (+)-copalyl diphosphate synthase, is a GGPP cyclase and catalyzes the whole biogenetic pathway to abieta-7,13-diene (**65**) from GGPP (**52**) (Scheme 9). (+)-Copalyl diphosphate (**57**) is assembled as outlined above (see Scheme 7), then, the loss of the diphosphate group generates an intermediate allylic cation enabling the formation of the third ring. In contrast to the biosynthesis of *ent*-kaurene (**61**) the next step is an internal proton transfer, which relocates the carbocation to the side-chain (**63**). Wagner-Meerwein 1,2-methyl shift generates a tertiary carbocation (**64**) and loss of a proton gives the product (−)-abietadiene (**65**).




**Scheme 9: Abietadiene synthase.**[60]

The taxadiene synthase[87, 88] is the fourth known GGPP cyclase. Again, loss of the diphosphate group initiates the cyclization sequence (see Scheme 10).[89, 90] Nucleophilic attack results in the macrocyclization and enables a carbocation mediated formation of the six-membered ring in **69**. Similar to the abietadiene synthase, the taxadiene synthase can utilize the proton released in the following cyclohexene formation step to protonate another double bond, which causes effective relocation of the cationic center in **69**. A last cyclization reaction followed by the loss of a proton gives taxadiene (**72**).



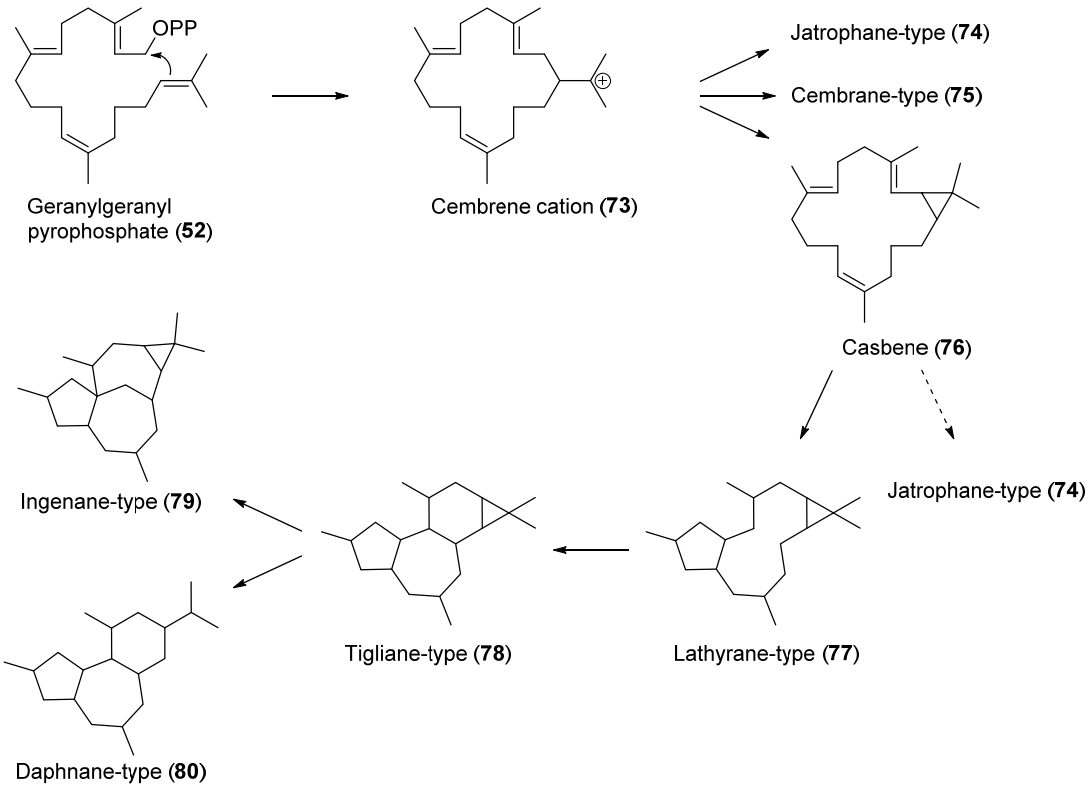

**Scheme 10: Taxadiene synthase.**[60, 81]

For the description of the general properties of the GGPP cyclases, MacMillan and Beale introduced the terminology of type A and type B cyclization. If initiation occurs by ionization of the diphosphate moiety it is referred to as type A and if initiation occurs by protonation at the C14-C15-double bond it is referred to as type B cyclization. This terminology includes the possibility of successive initiations, meaning a type A may be followed by a type B or *vice versa*, catalyzed by the same or a separate enzyme.[81] This system allows a fast description of the biogenesis of the different diterpenes.

Despite all the knowledge gained in the last century concerning the biosynthesis of terpenes in general and diterpenes in particuar, many biosynthetic pathways and associated enzymes still have to be elucidated. While it is well established that most macrocyclic diterpenoids are biosynthesized from an isomer of geranylgeranyldiphosphate,[91] the exact process leading to the core framework of jatrophane diterpenes remains unknown.

### 3.1.5 Biosynthesis of jatrophane diterpenes

The only proposal found for a biogenetic formation of the framework of jatrophane diterpenes was published by Adolf and Hecker in the late 1970´s and is outlined in Scheme 11.[92]




**Scheme 11: Biogenetic formation of the framework of jatrophane diterpenes.[92]**

# 4 Syntheses of jatrophane diterpenes

So far five total syntheses of jatrophane diterpenes have been published.

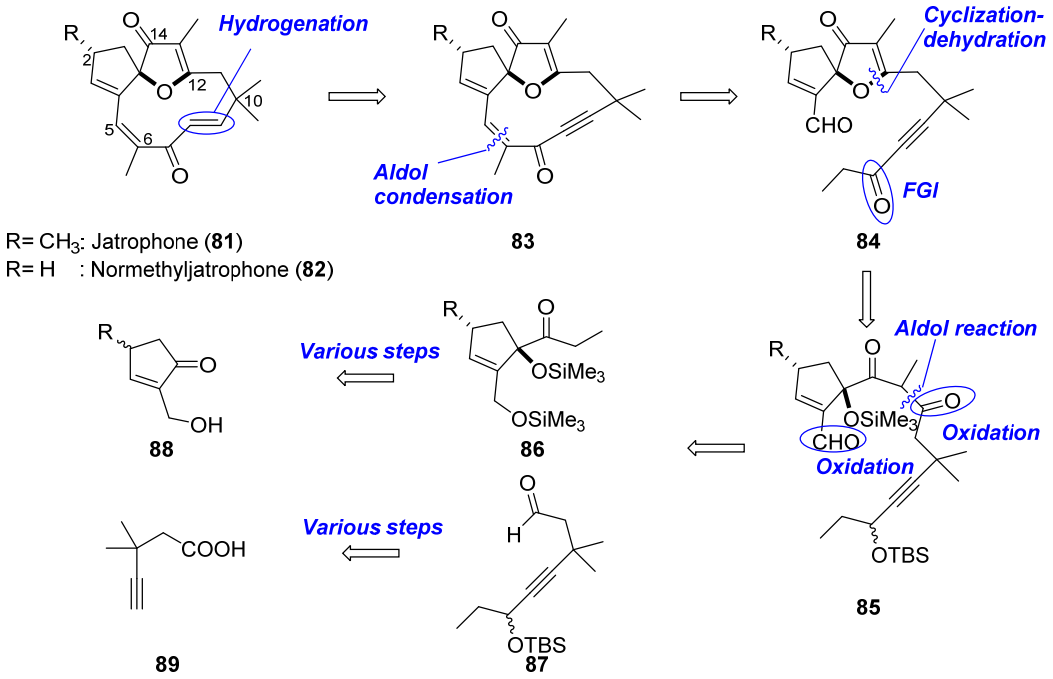
- Synthesis of (±)-jatrophone (**81**) by Smith *et al* in 1981[93]
- Synthesis of (+)-hydroxyjatrophone A (**103**) and (+)-hydroxyjatrophone B (**104**) by Smith *et al* in 1989[94]
- Synthesis of (±)-*epi*-jatrophone (**127**) and (±)-jatrophone (**81**) by Hegedus *et al* in 1990[95]
- Synthesis of (+)-jatrophone (**145**) by Wiemer *et al* in 1992[96]
- Synthesis of (-)-15-acetyl-3-propionyl-characiol (**164**) by Hiersemann *et al* in 2009[97]

The following section provides a short overview of theses synthetic achievements. In this section the jatrophane numbering will be used for established building blocks.

## 4.1 (±)-Jatrophone (81) by Smith *et al*

Kupchan and coworkers isolated jatrophone from extracts of *Jatropha gossypiifolia*[98] in 1970 as part of their investigations concerning the identification of tumor inhibitors of plant origin. *Jatropha gossypiifolia* was used ethnomedically for the treatment of cancer.[99] The primarily proposed structure was unambiguously confirmed by the same group in 1976, presenting NMR and X-ray studies.[100] Jatrophone shows significant inhibitory activity against a variety of cancer cell lines.[98, 99]

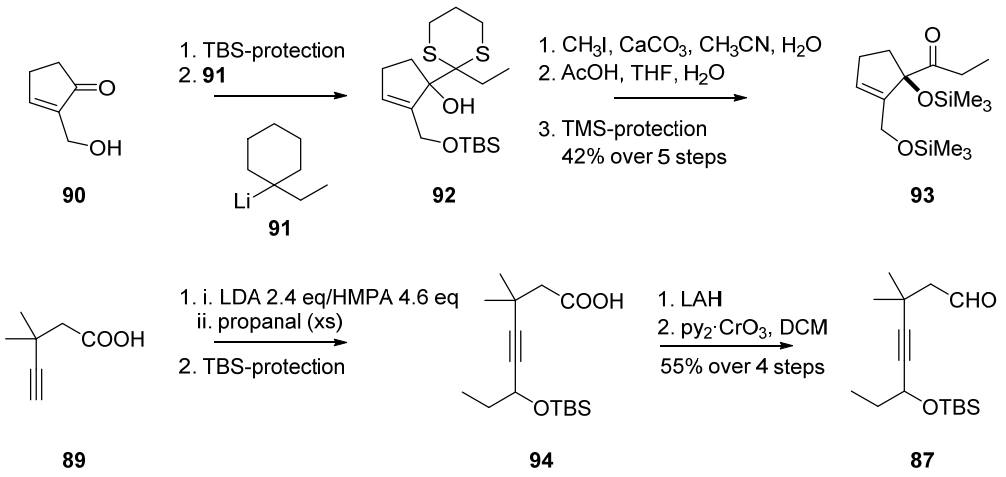
In 1981 this macrocyclic diterpene was synthesized by Smith *et al* using different aldol reactions as key steps. As outlined in Scheme 12, Smith *et al* introduced an acetylene moiety, which should be selectively reduced to the *trans*-olefin in the last step. The main consideration for using the acetylene was to control the configuration required at the C5-C6 double bond. After the examination of molecular models of **83**, Smith anticipated that the C5-C6 double bond *Z*-configuration should be considerably more stable, and be favorably generated in an aldol condensation providing the macrocycle **83**. The 3-(*2H*)-furanone ring system in **84** was expected to be available in a short sequence involving an acid-catalyzed cyclization-dehydration reaction. The required precursor **85** should be established by an aldol reaction of **86** and **87** followed by an oxidation reaction. This leads back to two building blocks (**86** and **87**), which are available in rather short sequences from readily available starting materials **88** and **89**.




**Scheme 12: Retrosynthetic analysis of jatrophone (81) by Smith *et al*.**

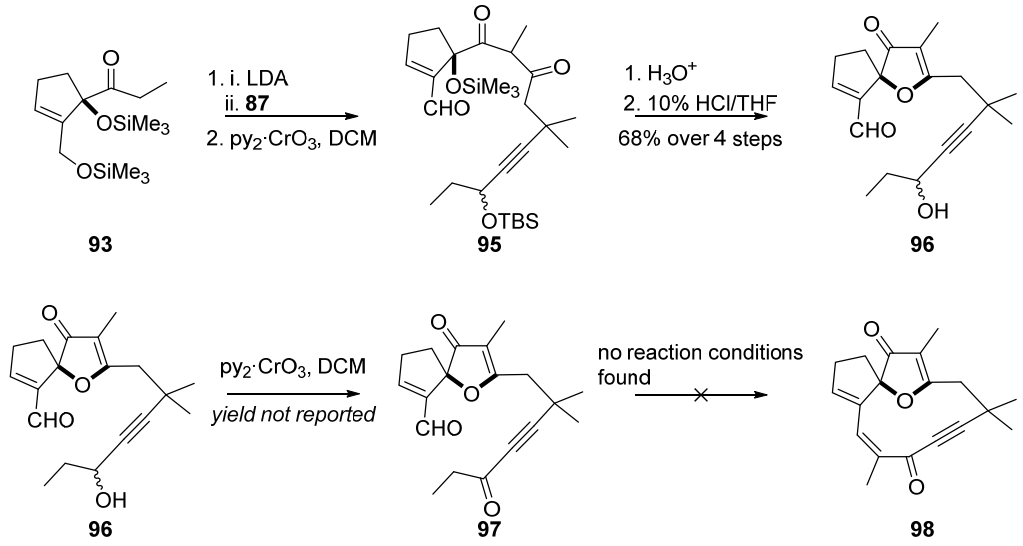
The synthesis of intermediate **93** started with TBS-protection of readily available 2-(hydroxymethyl)cyclopent-2-en-1-one **90**[101] followed by a Corey-Seebach Umpolung-reaction[102, 103] to give intermediate **92**. Subsequent treatment with methyl iodide under basic conditions delivered the corresponding ketone. Removal of the silyl ether by using aqueous acetic acid in tetrahydrofuran afforded a keto diol, which was silylated again to yield the desired intermediate **93**.

The second building block **87** was prepared from acid **89**. The dianion generated by the treatment of **89** with an excess of LDA and HMPA was quenched by the addition of propanal. After protection of the resultant hydroxy acid, the derived silyl ether **94** was reduced to the corresponding alcohol and subsequently oxidized (Collins oxidation)[104] to aldehyde **87**, which represents the second building block (see Scheme 13).




**Scheme 13: Syntheses of intermediates** 93 **and** 87**.**

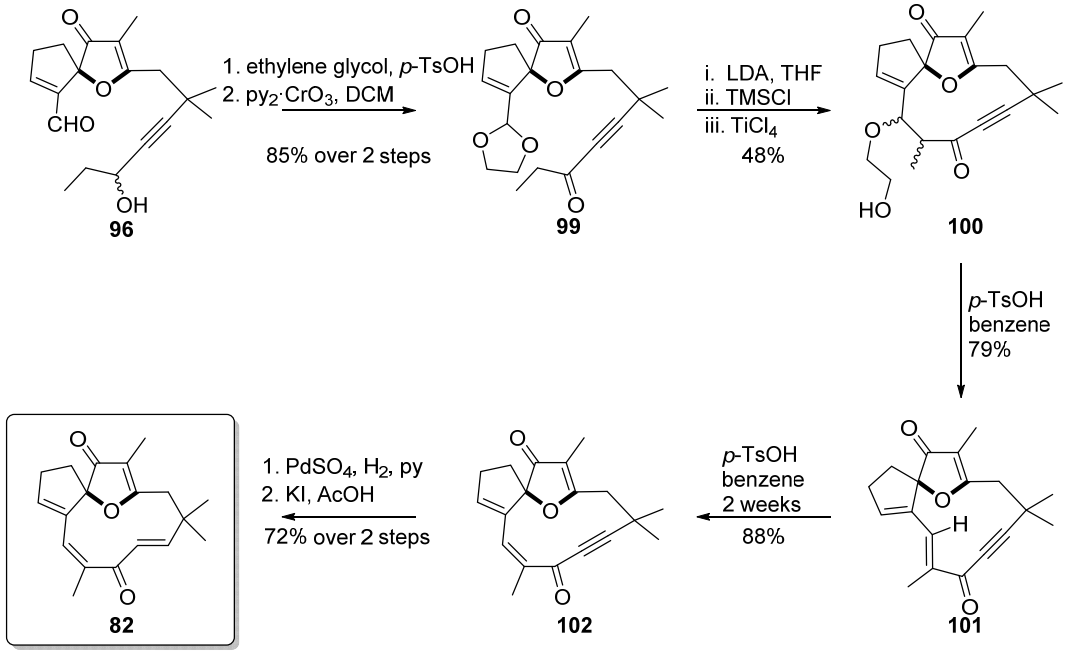
With the two building blocks in hand, Smith and coworkers employed their newly established synthetic protocol for the elaboration of furanones. The aldol reaction of ketone **93** with aldehyde **87** and subsequent oxidation gave the desired diketone **95** and additionally the allylic silyl ether was oxidized to the requisite aldehyde within the same step. Acid-catalyzed deprotection and a cyclization-dehydration sequence delivered the desired spirofuranone **96** in great overall yield (68%) over 4 steps.




**Scheme 14: Synthesis of intermediate** 97**.**

Oxidation using the Collins reagent delivered the precursor **97** of the key macrocyclization reaction. Unfortunately, the key cyclization failed to afford the desired intermediate **98** under both basic and acidic conditions. As this direct access failed, a slightly modified approach was established featuring a Mukaiyama aldol reaction[105-107], Scheme 15. For this purpose aldehyde **96** was initially allowed to react with ethylene glycol under acidic conditions and further oxidation

gave the desired intermediate **99**. The silyl enol ether was prepared by reaction of **99** with LDA in THF at −78 °C and subsequent addition of TMSCl. Without isolation, the cyclization was achieved under the influence of Lewis acid $TiCl_4$ at −78 °C leading to two diastereomeric products in 48% yield. X-ray analysis of the major diastereomer delivered an unambiguous proof for the successful macrocyclization.




**Scheme 15: Completion of the synthesis of normethyljatrophone (**82**).**

Elimination of ethylene glycol was carried out in benzene under acidic catalysis. Surprisingly, NMR spectroscopy showed the generation of the less stable *trans*-double bond (see Scheme 15; **101**). Under the same reaction conditions, but significantly slower, isomerization to the desired double bond occurred. To complete the synthetic goal the acetylene moiety in **102** was selectively *cis*-hydrogenated followed by the isomerization to normethyljatrophone **82**. Smith and coworkers accomplished the racemic synthesis of *rac*-jatrophone (**81**) by applying the newly developed strategy and the utilization of slightly altered starting materials.

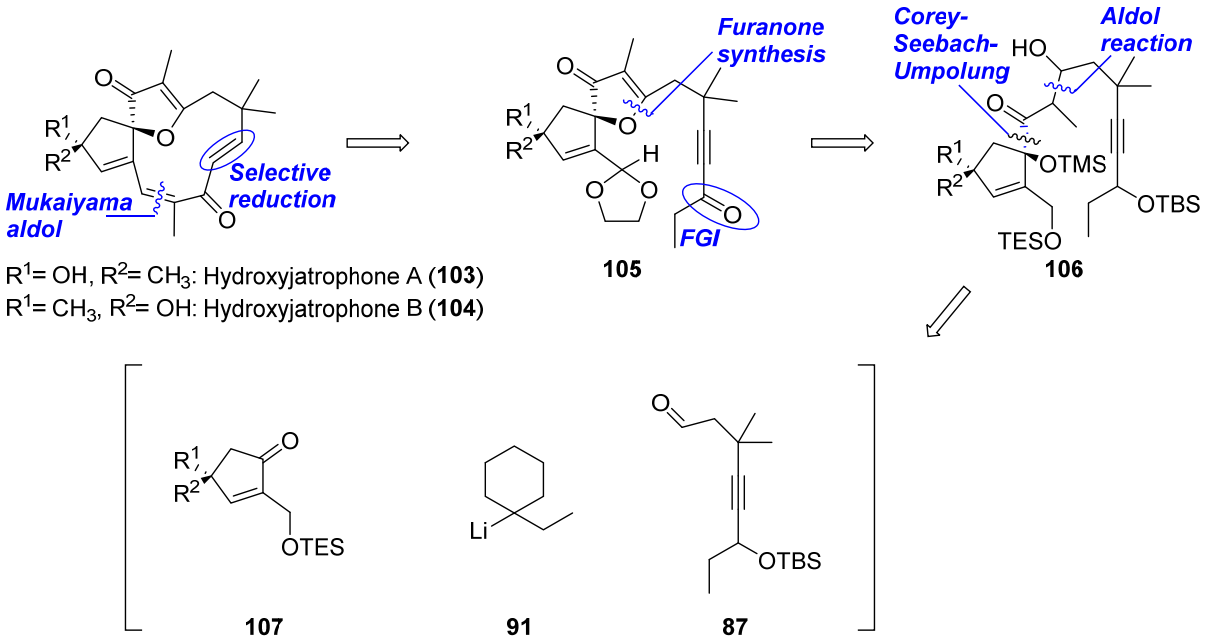
## 4.2 (+)-hydroxyjatrophone A (103) and (+)-hydroxyjatrophone B (104)

The antileukemic diterpenes hydroxyjatrophones A (**103**) and B (**104**) were, as jatrophone (**81**) earlier, isolated from *Jatropha gossypifolia*, and characterized by Smith, Cordell and coworkers in 1983.[108] As the newly found jatrophane diterpenes structurally resemble the already synthesized jatrophone (**81**) Smith and coworkers tried to extend their initially developed strategy.

The retrosynthetic analysis is shown in Scheme 16 for both hydroxyjatrophones. In analogy to the synthesis of jatrophone (**81**), in the last step, a selective reduction of the triple bond should

deliver the desired alkene present in the hydroxyjatrophones and the macrocyclization should be accomplished by an intramolecular Mukaiyama acetal-aldol reaction, leading back to intermediate **105**.[105-107] This advanced 3(2*H*)-furanone intermediate should be obtained by applying the well-established acid-promoted cyclization dehydration protocol and a functional group interconversion from **106**. The required, advanced intermediate **106** was envisioned to be accessible by the same strategy as employed in the jatrophone synthesis discussed above. A Corey-Seebach Umpolung-reaction and an aldol reaction should be accomplished leading back to the advanced cyclopentane fragment **107** and already known building blocks **91** and **87**.

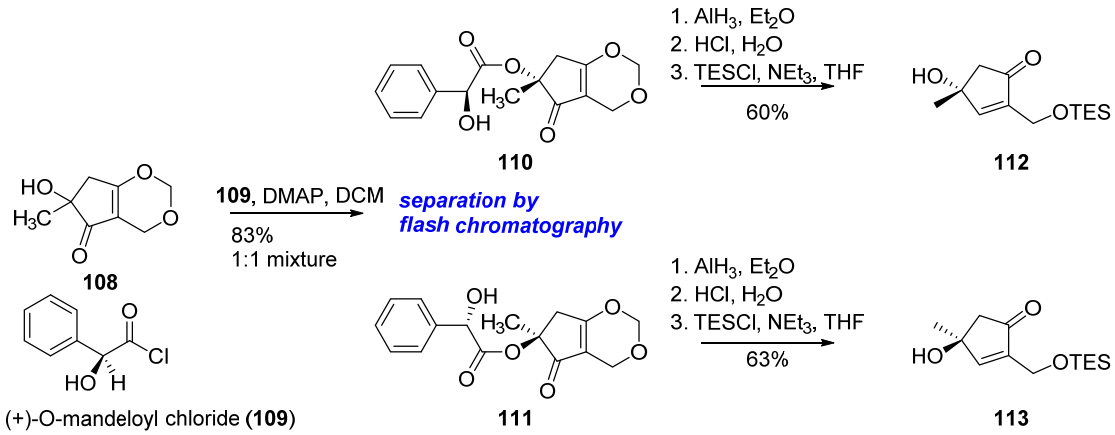
Overall, the retrosynthetic analysis is essentially identical for both hydroxyjatrophone A and B, except for the choice of the enantiomeric cyclopentenone (**107**) as starting material.




$R^1$= OH, $R^2$= $CH_3$: Hydroxyjatrophone A (**103**)
$R^1$= $CH_3$, $R^2$= OH: Hydroxyjatrophone B (**104**)

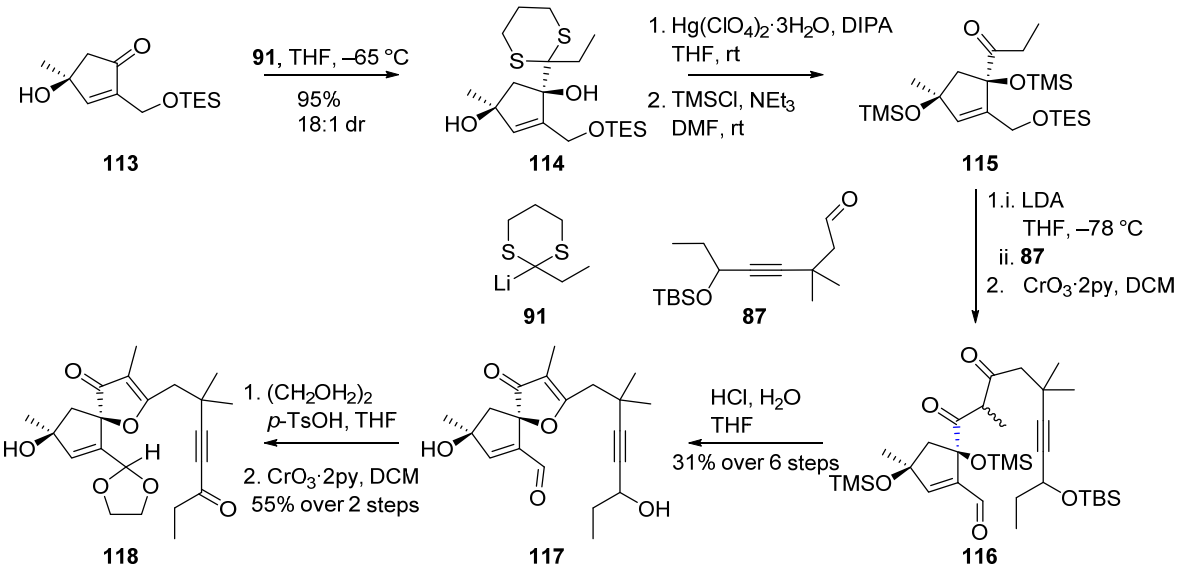
**Scheme 16: Retrosynthetic analysis of the hydroxyjatrophones A (**103**) and B (**104**) by Smith *et al*.**

Due to the fact that both enantiomers of the cyclopentenone **107** were required in equal amounts, chiral resolution of the racemic starting material seemed to be an appropriate strategy. For this purpose, racemic tertiary alcohol **108**, available in a three step sequence from 1,3-cyclopentanedione,[109] was converted to diastereomeric esters **110** and **111** by treatment with (*S*)-(+)-*O*-mandeloyl chloride (**109**) under standard esterification conditions. As indicated in Scheme 17 the diastereomers were separable by simple flash chromatography. Reduction of **110** with alane, prepared from lithium aluminum hydride and sulfuric acid,[110, 111] was followed by an acid mediated hydrolysis of the acetal and elimination of water. Selective protection of the primary hydroxyl group as silyl ether resulted in enantiomerically pure **112**. In the same way (+)-**113** could be obtained starting from **111**.



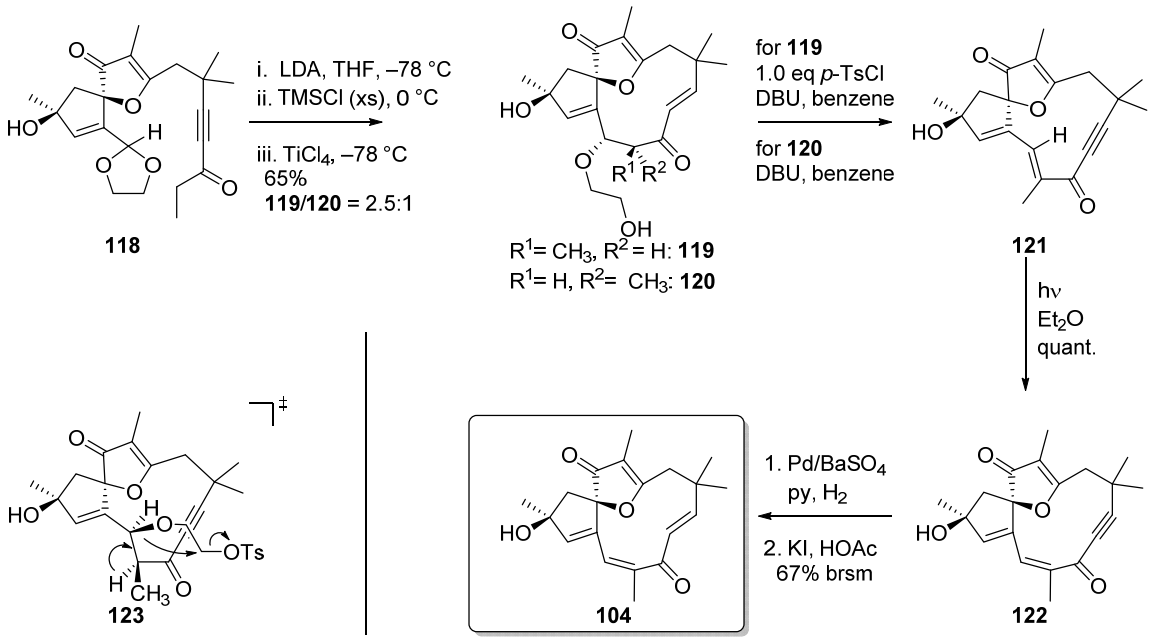

**Scheme 17: Chiral resolution of** 108**.**

Continuing the synthesis of hydroxyjatrophone B (**104**), the next step was a Corey-Seebach Umpolung-reaction[112](see Scheme 18). Reaction of cyclopentenone **113** with 2-lithio-2-ethyl dithiane (**91**) delivered a mixture of diastereomers strongly favoring the desired diol **114**. Preventing the decomposition of the starting material within the next step proved to be a tedious task but upon addition of a mercury(II) salt, the dithiane moiety could be hydrolyzed in the presence of diisopropylamine to afford the corresponding ketone. After silylation of both tertiary hydroxyl groups, **115** was treated with LDA, followed by addition of aldehyde **87**. The diastereomeric aldol products were oxidized using the Sarett reagent ($CrO_3$·2py)[113, 114] affording intermediate **116**. As anticipated, the allylic TES-protected hydroxyl group was converted to the corresponding aldehyde in course of the oxidation of the secondary alcohol, delivering the required precursor for the upcoming 3(2*H*)-furanone synthesis. This was achieved by treatment with aqueous hydrochloric acid, which led to the desired acid-promoted cyclization, and concomitant desilyation afforded advanced intermediate **117** in excellent overall yield. Acetalization of the aldehyde under mild conditions followed by another Collins´ oxidation provided keto-acetal **118**.



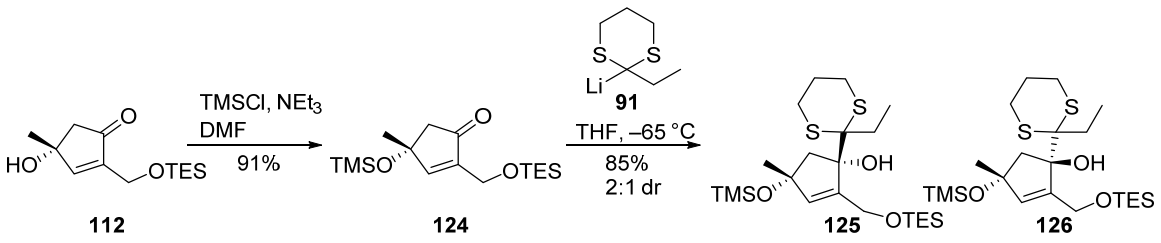

**Scheme 18: Snythesis of intermediate** 118**.**

The required TMS enol ether was prepared *via* reaction of ketone **118** with LDA and subsequent treatment with TMS chloride. The envisioned Mukaiyama-acetal aldol reaction was mediated by the addition of titanium tetrachloride providing two diastereomeric β-alkoxy ketones **119** and **120** (see Scheme 19). Due to the tertiary hydroxyl group present in **119** and **120** prolonged treatment with *p*-toluene sulfonic acid to eliminate ethylene glycol, as used in the jatrophone synthesis described above, additionally led to an undesired C2-hydroxyl elimination. To prevent this side reaction, elimination was mediated by treatment with *p*-toluenesulfonyl chloride and diazabicyloundecane (DBU) in case of the major diastereomer **119**. Thin layer chromatography suggested the formation of an intermediate (presumably **123**), which decomposed during flash chromatography to yield the *trans*-olefin **121**. However, elimination of ethylene glycol from minor diastereomer **120** did not require conversion to the corresponding tosylate prior to the elimination reaction but delivered *trans*-olefin **121** upon treatment solely with DBU. The desired *cis*-double bond could be obtained by photoisomerization at 254 nm in ether to yield **122** nearly quantitatively. Finally, hydroxyjatrophone B (**104**) was isolated after semihydrogenation of the alkyne and isomerization of the double bond.




**Scheme 19: Completion of the synthesis of hydroxyjatrophone B (**104**).**

Hydroxyjatrophone A (**103**) is accessible by the same approach starting from cyclopentenone (−)-**112**. In this case, the tertiary hydroxyl group was additionally protected as silyl ether to yield intermediate **124** (Scheme 20). The following Corey-Seebach Umpolung-reaction using 2-lithio-2-ethyl dithiane (**91**) gave a 2:1 mixture of diastereomers favoring the undesired one (**125**). Although the result is not fully satisfying, the TMS protection of the tertiary alcohol prior to the crucial dithiane addition significantly contributed to increase the yield of the desired isomer. In the following, the synthesis could be completed to provide (+)-hydroxyjatrophone A (**103**).



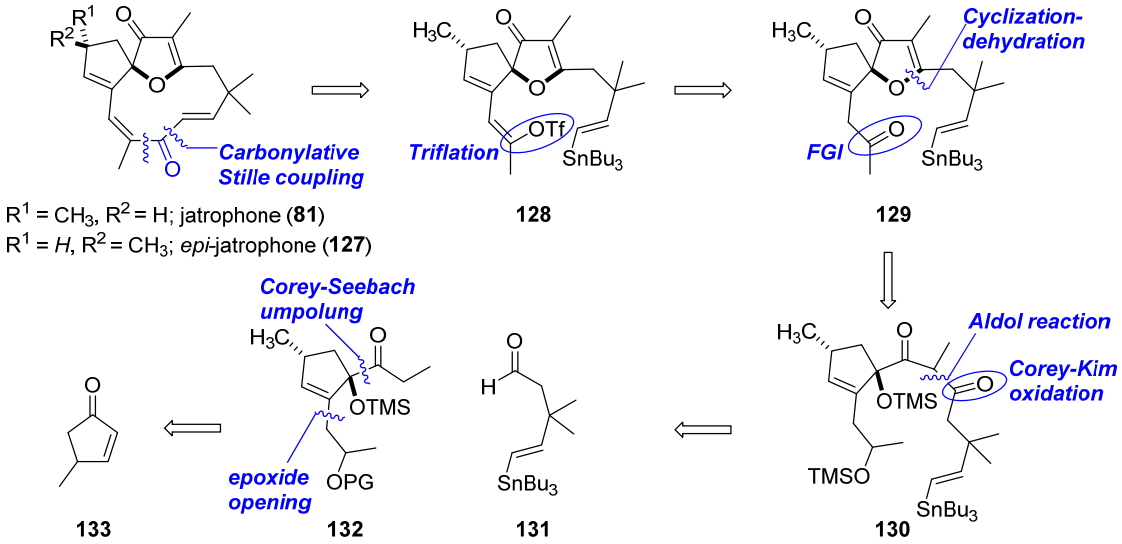

**Scheme 20: Synthesis of intermediate** 126**.**

## 4.3 (±)-*epi*-jatrophone (127) and (±)-jatrophone (81) by Hegedus *et al*

A method driven synthesis of racemic jatrophone (**81**) was presented by Stille, Hegedus and coworkers in 1990.

Their retrosynthetic analysis of (±)-jatrophone (**81**) is outlined in Scheme 21. The last step should be a carbonylative Stille coupling[115, 116] to form the macrocyclic dienone, with **128** as precursor. The vinyl triflate moiety should be available by applying standard protocols from ketone **129**,[117]

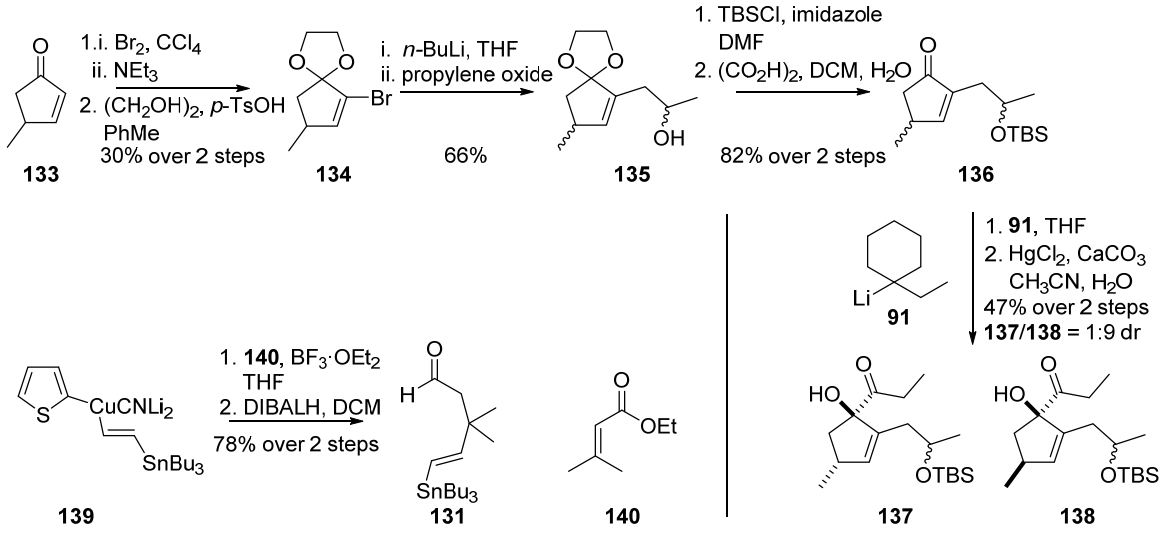
which may be obtained by an acid-catalyzed cyclization-dehydration sequence from diketone **130**, as introduced by Smith *et al.*[93] Diketone **130** might be accessible by an aldol condensation of **132** and aldehyde **131** followed by a Corey-Kim oxidation[118]. Similar to the approaches of Smith and coworkers, Hegedus *et al* envisioned cyclopentene **132** to arise from cyclopentenone **133** *via* reaction with an acyl anion equivalent and an epoxide opening reaction.




**Scheme 21 Retrosynthetic analysis of *rac*-jatrophone (81) by Hegedus *et al.***

The synthesis, as outlined in Scheme 22, started from readily available cyclopentenone **133**[119], which was first brominated, followed by a dehydrobromination reaction[120]. Reaction with ethylene glycol under acidic catalysis delivered acetal **134**. The introduced bromine was used in a halogen-metal exchange reaction with *n*-butyllithium to deliver a selectively lithiated species. Reaction of the lithiated intermediate with propylene oxide yielded alcohol **135**, which was protected as silyl ether under standard conditions. Treatment with oxalic acid resulted in α,β-unsaturated ketone **136**, which was employed in the Corey-Seebach Umpolung-reaction. 1,2-addition of 2-lithio-2-ethyl-1,3-dithiane (**91**), was followed by hydrolysis of the dithiane moiety using a mercury(II) salt, generating two diastereomeric hydroxyl ketones **137** and **138**. Initially, the major diastereomer **138** was used for the synthetic approach toward *epi*-jatrophone (**127**) and afterwards the established methodology was applied in the synthesis of jatrophone (**81**), which is described below.

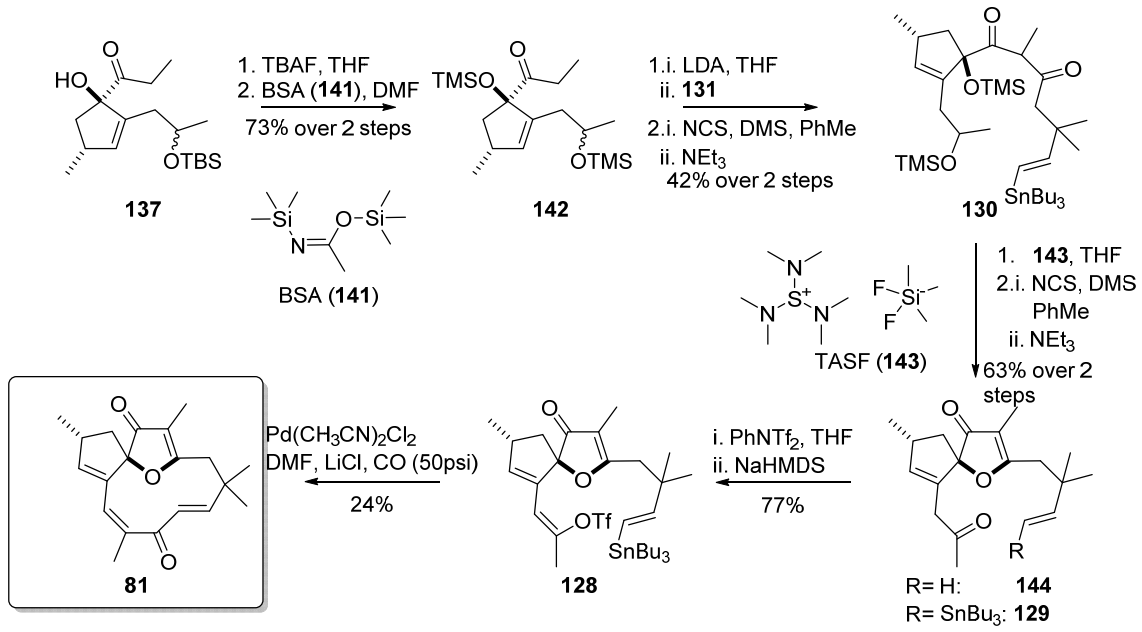
The second building block **131** was accessible in a very short sequence starting from ester **140**. Lewis acid catalyzed 1,4-addition of Lipshutz-cuprate **139**[121] was followed by diisobutylaluminum reduction providing aldehyde **131** in good overall yield.




**Scheme 22: Syntheses of building blocks** 131**,** 137 **and** 138**.**

With the building blocks in hand, Hegedus and coworkers proceeded with TBS-deprotection of cyclopentenone **137**, followed by bis-silyl protection with bis(trimethylsilyl)acetamide (**141**) to obtain **142** in good overall yield. Aldol condensation of ketone **142** with aldehyde **131** gave a complex mixture of diastereomers. Subsequent Corey-Kim oxidation provided the desired diketone **130**. The following formation of the 3(2*H*)-furanone proved to be more troublesome as anticipated, and initial treatment with hydrochloric acid[93, 94] afforded the corresponding protiodestannylated spirofuranone **144**. With **144** in hand the authors tried to conduct an intramolecular carbonylative Heck coupling,[122, 123] which was not successful. Finally, the synthesis of 3(2*H*)-furanone was achieved under aprotic conditions. Treatment of diketone **130** with the anhydrous fluoride ion source tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF; **143**)[124], followed by another Corey-Kim oxidation provided furanone **129** in good yield. At this point all remaining steps were dedicated to prepare the carbonylative Stille coupling. Ketone **129** was converted to *Z*-vinylic triflate **128**, which was subjected to carbonylative Stille coupling conditions (see Scheme 23) to afford (±)-jatrophone (**81**) as a white crystalline solid.

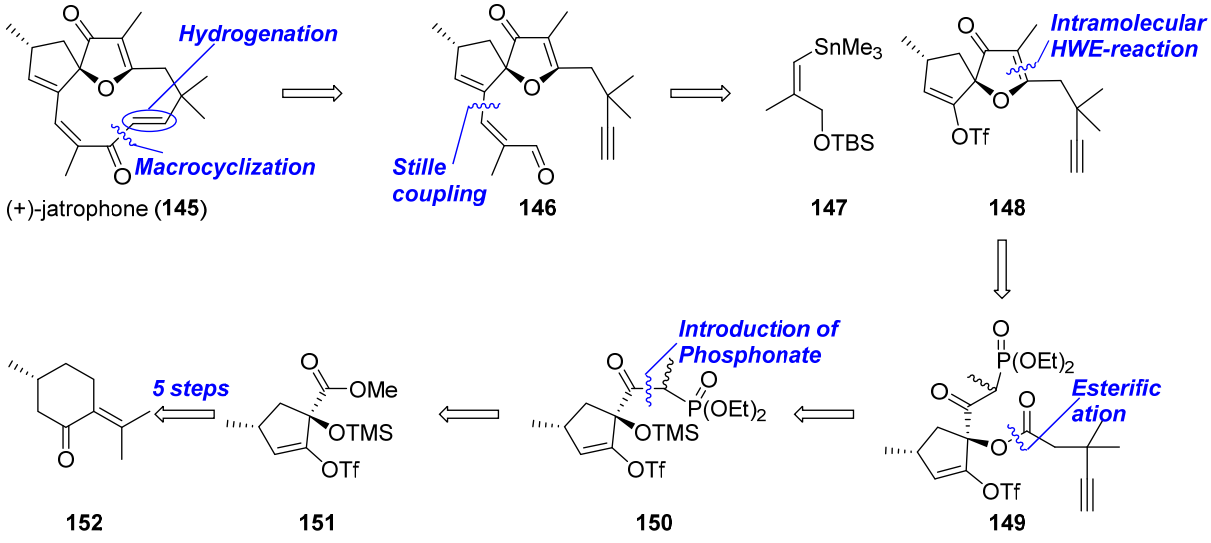
As mentioned above, (±)-*epi*-jatrophone (**127**) was prepared from cyclopentenone **137** following the same procedures.




**Scheme 23: Completion of the synthesis of *rac*-jatrophone (81).**

## 4.4 (+)-Jatrophone (145) by Wiemer *et al*

Intrigued by the combination of an interesting skeleton and significant biological activity Wiemer and Han tried to find a more efficient route to (+)-jatrophone (**145**).

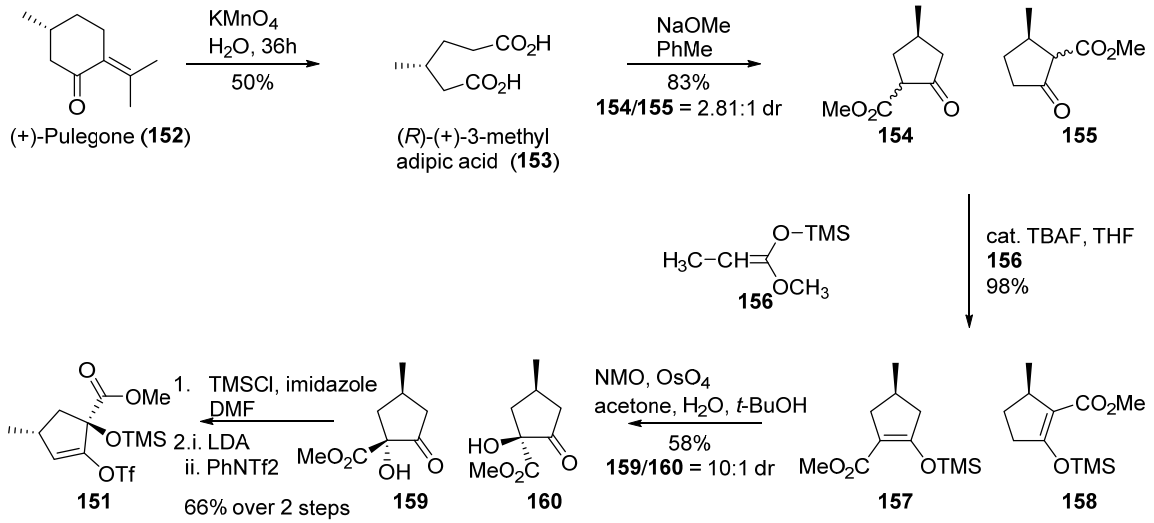



**Scheme 24: Retrosynthetic analysis of (+)-jatrophone (145) by Wiemer *et al*.**

Despite the identical endgame published by Smith,[93, 94] Wiemer´s strategy to (+)-jatrophone (**145**) for the elaboration of the natural product differs significantly. The precedent macrocyclization was planned to be performed by treatment of acetylenic aldehyde **146** with base. **146** should be obtained by Stille coupling of stannane **147** and triflate **148**. In contradiction to the other syntheses the 3(2*H*)-furanone moiety was envisioned to be obtained from ester **149** *via* an

intramolecular Horner-Wadsworth-Emmons (HWE) reaction.[125, 126] The ester should be readily available from **150** using a protocol recently developed by the same group, featuring direct acylation of TMS-protected alcohol **150** using iron(III)chloride as catalyst.[125, 126] This leads back to intermediate **150** which should be derived from triflate **151** *via* reaction with the anion of diethyl ethylphosphonate. The required cyclopentene **151** is known to be accessible from (+)-pulegone (**152**) in a 5 step sequence.[127, 128]

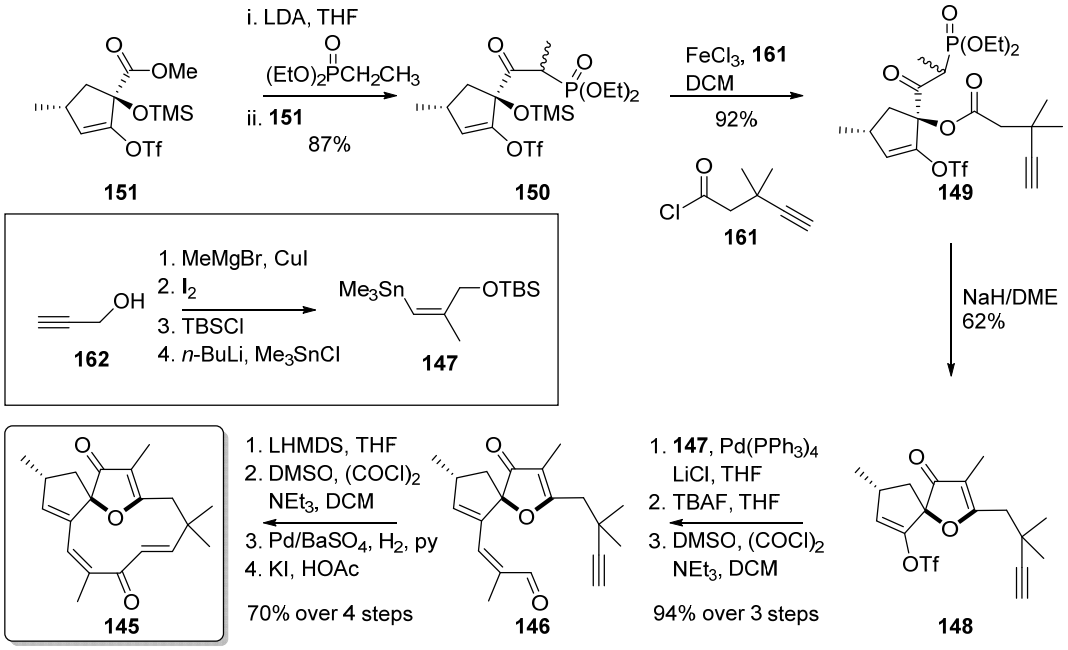
(+)-Pulegone (**152**), which is commercially available in high enantiomeric purity, was treated with potassium permanganate in water to yield dicarboxylic acid **153** (Scheme 25). Subsequent Dieckmann condensation delivered a mixture of regioisomeres **154** and **155**, which were used without separation in the next steps. Subsequent silyl enol ether formation afforded the corresponding regioisomeres **157** and **158**. Fortunately, Rubottom-oxidation[129] did only affect isomer **157** to yield another mixture of diastereomeres, strongly favoring the desired α-hydroxy ketone **159**. The diastereomeres were separated, **159** was protected as silyl ether, and the ketone was converted to the corresponding vinyl triflate **151**. Both stereogenic centers of (+)-jatrophone (**145**) were set in their desired absolute stereochemistry in this important five-membered ring intermediate **151**.




**Scheme 25: Synthesis of intermediate** 151**.**

Treatment of ester **151** with the anion of diethyl ethylphosphonate gave β-keto phosphonate **150**, which was converted to intermediate **149** using a previously developed esterification protocol, utilizing $FeCl_3$ as catalyst.[125, 126] The preparation of the 3(2*H*)-furanone was achieved by an intramolecular HWE reaction in acceptable yield. This set the stage for the following Stille coupling to incorporate a four-carbon unit possessing the C5-C6 double bond with the crucial *Z*-stereochemistry. The required vinylstannane **147** was synthesized in a straightforward sequence,

which started with the CuI-catalzyed addition of MeMgBr to the triple bond of propargylic alcohol (**162**) (see Scheme 26). Treatment with iodine and subsequent TBS-protection resulted in the isolation of stannane **147**.[130] Stille coupling of triflate **148** and stannane **147** delivered the desired product in nearly quantitative yield. Treatment of the coupling product with tetra-*n*-butylammonium fluoride resulted in deprotection of the hydroxyl group and was followed by Swern oxidation to afford acetylenic aldehyde **146**. As envisioned, reaction with base under strictly anhydrous conditions led to the intended macrocyclization. Finally, the synthesis of (+)-jatrophone (**145**) was accomplished *via* Swern oxidation, hydrogenation of the triple bond to the *cis*-double bond followed by double bond isomerization, using the conditions introduced by Smith *et al*.



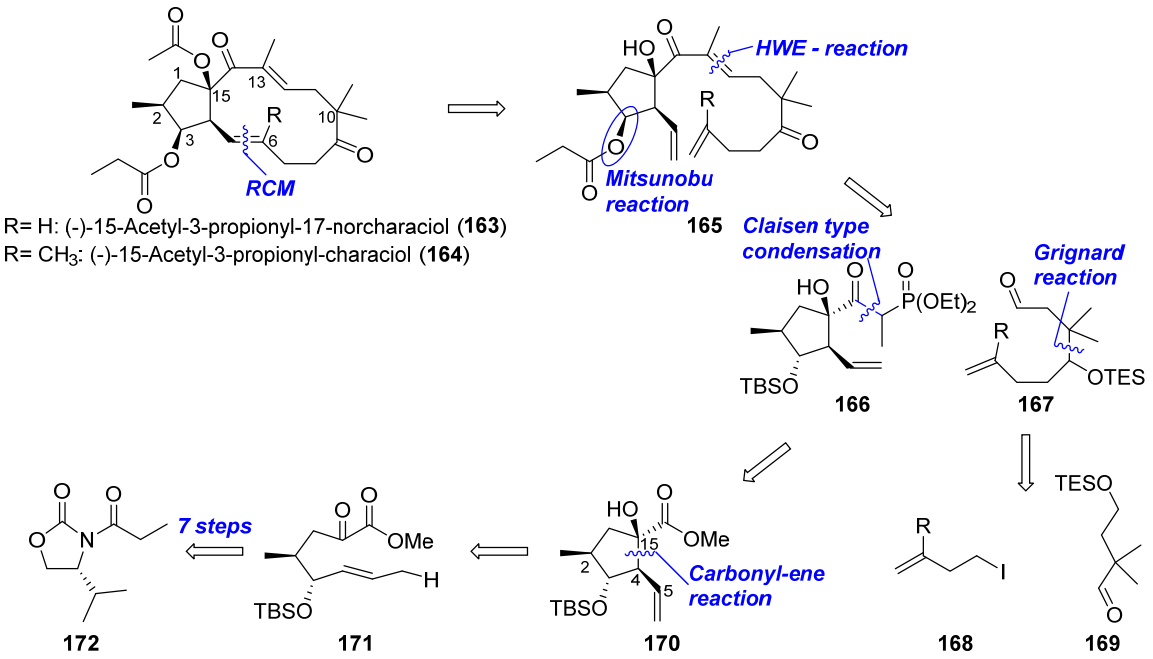

**Scheme 26: Completion of the synthesis of (+)-jatrophone (**145**).**

## 4.5 (–)-15-acetyl-3-propionyl-characiol (164) by Hiersemann *et al*

Along with seven other diterpenoid esters of the jatrophane type, (-)-15-acetyl-3-propionyl-characiol (**164**) was isolated from *Euphorbia characias* by Seip and Hecker in the year 1984.[131] During the course of their work to establish a reliable synthetic strategy toward the jatrophane framework, Hiersemann and coworkers presented the synthesis of the non-natural diterpene (-)-15-acetyl-3-propionyl-17-norcharaciol (**163**),[132] prior to the synthesis of the natural product. As this synthesis is of significant importance for the subsequent synthetic work in this field, it will be described in the following section.

### 4.5.1 (–)-15-Acetyl-3-propionyl-17-norcharaciol (157)

After a preliminary study toward the five-membered ring segment of diverse jatrophane diterpenes in 2004,[133] the synthesis of this non-natural diterpene was the second contribution of Hiersemann and coworkers in this field.

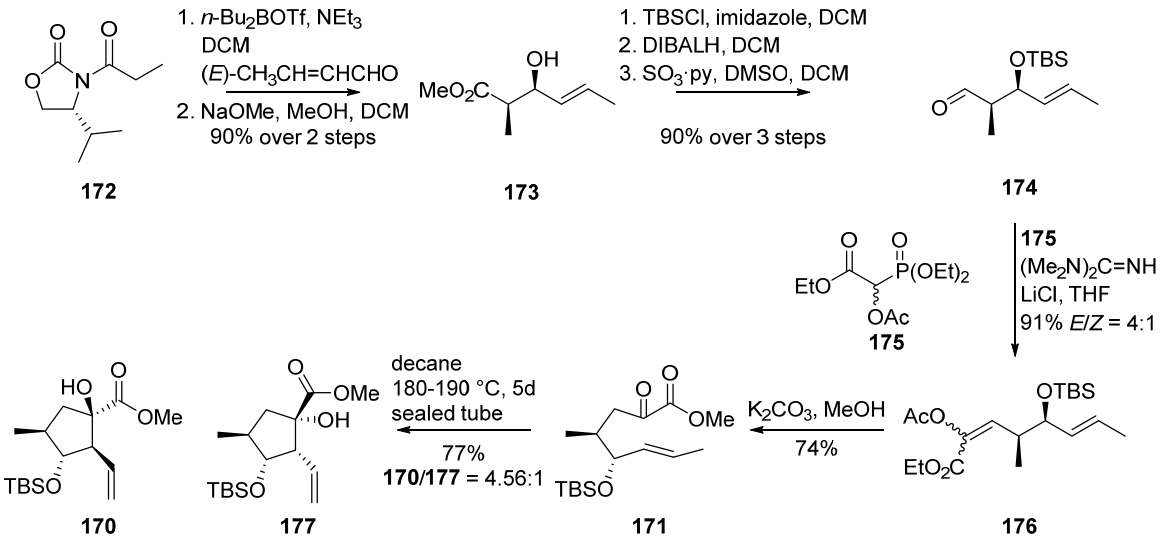



**Scheme 27: Retrosynthetic analysis by Hiersemann *et al*.**

As outlined in the retrosynthetic analysis (Scheme 27) the macrocycle should be closed by a ring closing metathesis (RCM) reaction[134-137] providing intermediate **165**. The stereogenic center at C3 should be established by a Mitsunobu-type reaction.[138, 139] This advanced intermediate should be available by an HWE reaction of β-keto phosphonate **166** and aldehyde **167**, which may be obtained from iodide **168** and aldehyde **169** by a Grignard reaction. Cyclopentane building block **166** was envisioned to arise from ester **170** *via* a Claisen type reaction utilizing the anion of diethyl ethylphosphonate. α-Hydroxy ester **170** may be established by a diastereoselective intramolecular carbonyl ene reaction from α-keto ester **171**, which should be provided in a seven-step sequence from readily available oxazolidinone **172**[140].

Preparation of enantiomerically pure ester **170** started with an asymmetric Evans-aldol reaction[140, 141] from oxazolidinone **172** (Scheme 28). Subsequent removal of the auxiliary led to the desired ester **173** and recovery of the auxiliary in 97% yield. After protection of the secondary alcohol as silyl ether, the ester moiety was reduced to the corresponding alcohol, followed by Parikh-Doering protocol,[142] to afford aldehyde **174**. Conversion of aldehyde **174** to the desired α-keto ester **171** was conducted following a modified procedure previously introduced by Schmidt

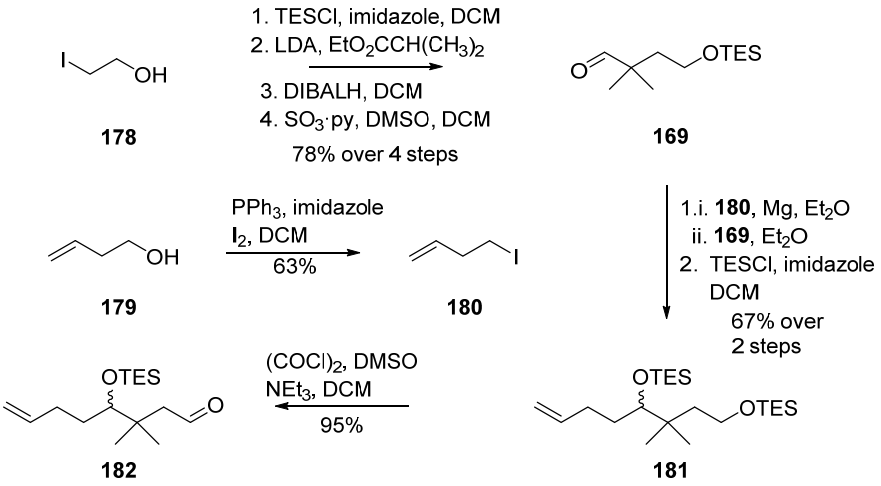
*et al*.[143] Thus, aldehyde **174** was allowed to react with phosphonate **175** in an HWE reaction affording intermediate **176**, which was further converted to α-keto ester **171** under basic conditions. The important five-membered ring intermediate **170** was now elaborated by means of a carbonyl ene reaction under relatively harsh reaction conditions. Over five days at elevated temperatures in a sealed tube, α-keto ester **171** was converted to a mixture of diastereomeric cyclopentanes **170** and **177** in good yield. (The carbonyl ene reaction leading to **170** will be discussed later on in section 5.3 in more detail.)




**Scheme 28: Synthesis of advanced five-membered ring synthon** 170**.**

The second building block (**182**) used in the synthesis of (−)-15-acetyl-3-propionyl-17-norcharaciol (**163**) was prepared in a short sequence starting from alcohol **178** (Scheme 29). Triethylsilane ether protection of **178** was followed by chain-elongation *via* an $S_N2$-reaction. The intermediary ester was reduced with diisobutylaluminum hydride under standard conditions and Parikh-Doering oxidation afforded aldehyde **169**. Subsequent reaction with the Grignard reagent derived from iodide **180** and further silyl ether protection of the newly formed hydroxyl group resulted in bis-protected diol **181**. As anticipated the primary silyl ether group could be selectively oxidized in a Swern oxidation[144-146] and aldehyde **183** was obtained.

After the elaboration of a highly stereocontrolled access to **170** and an efficient route to **182** further efforts where focused toward the synthesis of the macrocycle.

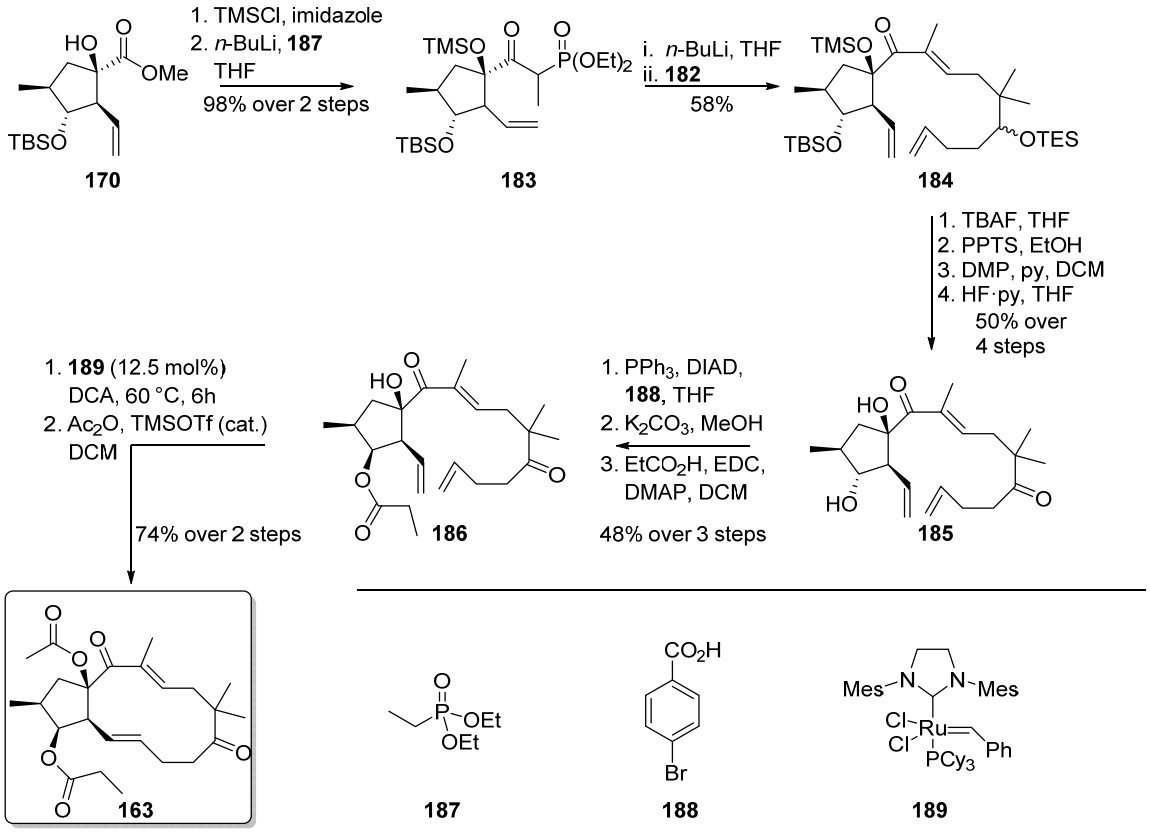



**Scheme 29: Synthesis of intermediate** 182**.**

In analogy to Wiemer's strategy[96], the tertiary hydroxyl group of **170** was protected as trimethylsilyl ether and subsequent addition of the anion of diethyl ethylphosphonate gave β-keto phosphonate **183** (Scheme 30). The phosphonate-stabilized carbanion generated by treatment of **183** with *n*-butyllithium underwent a HWE reaction with aldehyde **182**, selectively afforded the product with the desired double bond conformation in moderate yield. The synthesis was continued by selective deprotection of the triethylsilyl and trimethylsilyl protecting groups and subsequent Dess-Martin-periodinane oxidation[147] of the secondary alcohol. Finally, the last remaining protecting group was cleaved to afford diol **185**.

At this point the two remaining major tasks were the inversion of the undesired stereochemistry at C3 and the late stage macrocyclization. At first the stereochemistry at C3 in **185** was inverted by a Mitsunobu reaction to provide the corresponding benzoate, which was cleaved under standard basic conditions in methanol. The resulting diol was selectively esterified to afford RCM precursor **186**. The required cyclization was achieved utilizing the 2$^{nd}$ generation Grubbs catalyst (**189**), and subsequent acetylation delivered **163** in excellent yield.

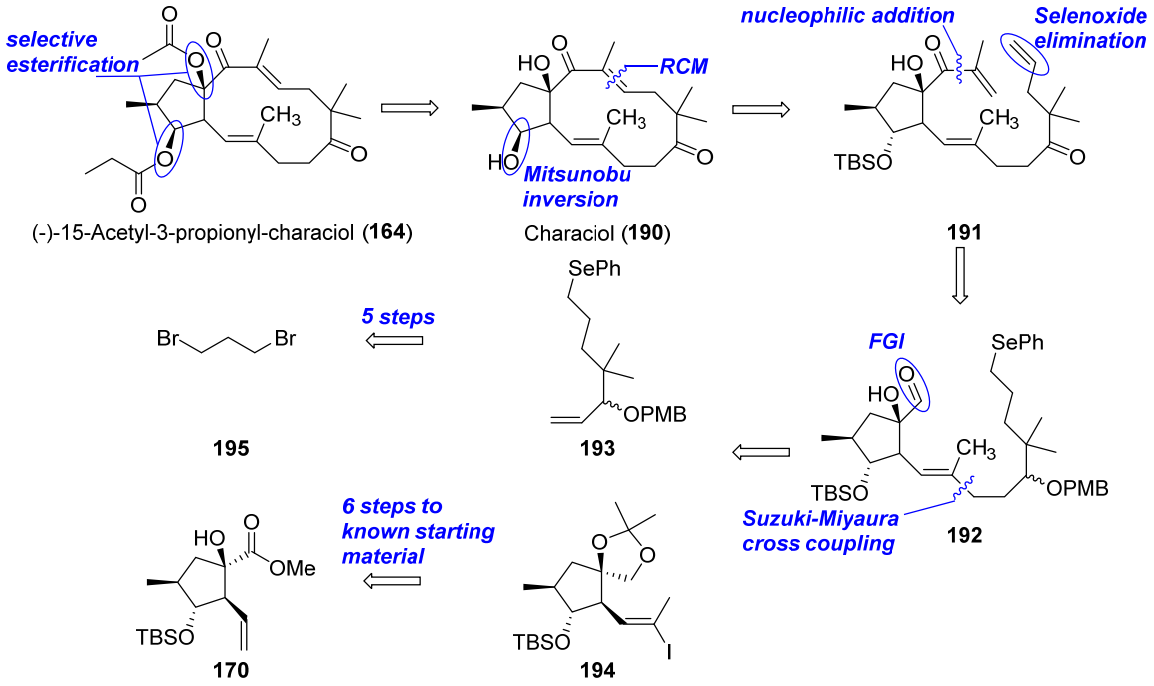
As medium-sized rings can successfully be prepared *via* the RCM reaction,[148-150] Hiersemann and coworkers tried different catalysts and conditions[151-153] to achieve the synthesis of **164** by the same strategy, but all their attempts failed. Thus, Hiersemann and coworkers developed a new approach based on a different strategy to close the macrocycle, as discussed in the following section.




**Scheme 30: Completion of the synthesis of (−)-15-Acetyl-3-propionyl-17-norcharaciol (**163**).**

### 4.5.2 (−)-15-acetyl-3-propionyl-characiol (164)

The last steps in the proposed retrosynthesis (Scheme 31) should be two selective esterification reactions ultimately delivering the target molecule **164**. This leads back to diol **190**, which has been named characiol by Seip and Hecker.[131] The macrocycle should be obtained *via* an RCM reaction, which results in the formation of a trisubstituted double bond. Considering the previous synthesis, success of such a demanding RCM reaction was not guaranteed. Again, a late stage Mitsunobu reaction should be utilized to adjust the stereogenic center at C3. These transformations lead back to intermediate **191**, with double bonds in place for the key RCM reaction. One of these double bonds should be installed by nucleophilic addition, whereas the second double bond was envisioned to be elaborated by elimination of the corresponding selenoxide. This intermediate **192** should be obtained *via* a Suzuki-Miyaura coupling[154] by reaction of alkene **193** and iodide **194**. Both of the coupling partners may be accessible either from commercially available **195** or from already known building block **170**.



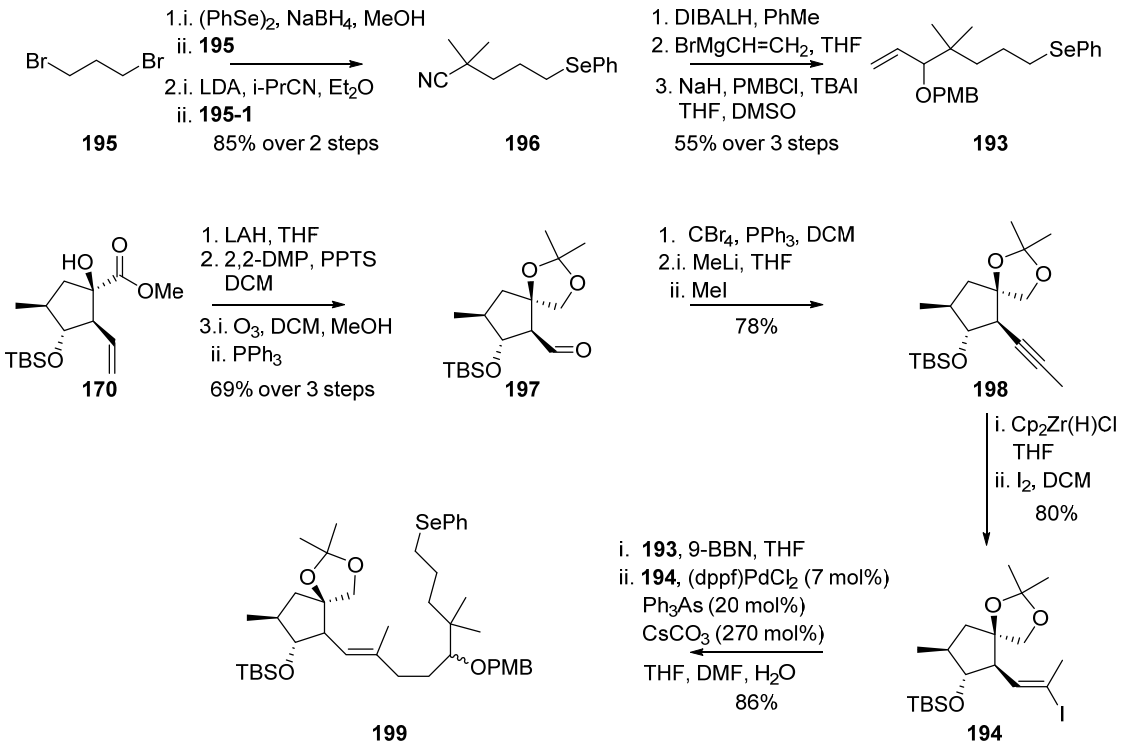

**Scheme 31: Retrosynthetic analysis of (–)-15-acetyl-3-propionyl-characiol** 164 **by Hiersemann *et al*.**

Cross coupling partners **193** and **194** were obtained as outlined in Scheme 32. The preparation of alkene **193** started from commercially available dibromide **195** which was converted to (3-bromopropyl)(phenyl)selane using a phenyl selenyl borane complex.[155] Subsequent treatment with the enolate of isobutyronitrile afforded nitrile **196** and was followed by reduction to the corresponding aldehyde. Grignard reaction with vinylmagnesium bromide delivered an allylic alcohol, which was protected as its *p*-methoxybenzyl ether[156], affording the desired compound **193**.

Building block **170** was already introduced in the previous synthesis of (-)-15-acetyl-3-propionyl-17-norcharaciol (**163**) and with a highly stereocontrolled route to this cyclopentane segment in hand,[132, 133, 157] Hiersemann and coworkers planned to proceed with this key intermediate. Of significant importance was the protection of the hydroxyl ester, as this moiety is very sensitive to different reaction conditions.

Reduction to the corresponding 1,2-diol and acetal protection using 2,2-DMP afforded the corresponding acetonide, which is stable under reaction conditions applied in the subsequent steps. Next, ozonolysis furnished aldehyde **197** and set the stage for the following Corey-Fuchs protocol.[158] The synthesis was continued by olefination[159] of aldehyde **197** affording a dibromoolefin which was allowed to react with an excess of methyllithium affording an intermediary lithium acetylide, which was quenched by the addition of methyliodide providing alkyne **198**. Reaction with the Schwartz reagent[160, 161] afforded a vinyl zirconium species, which

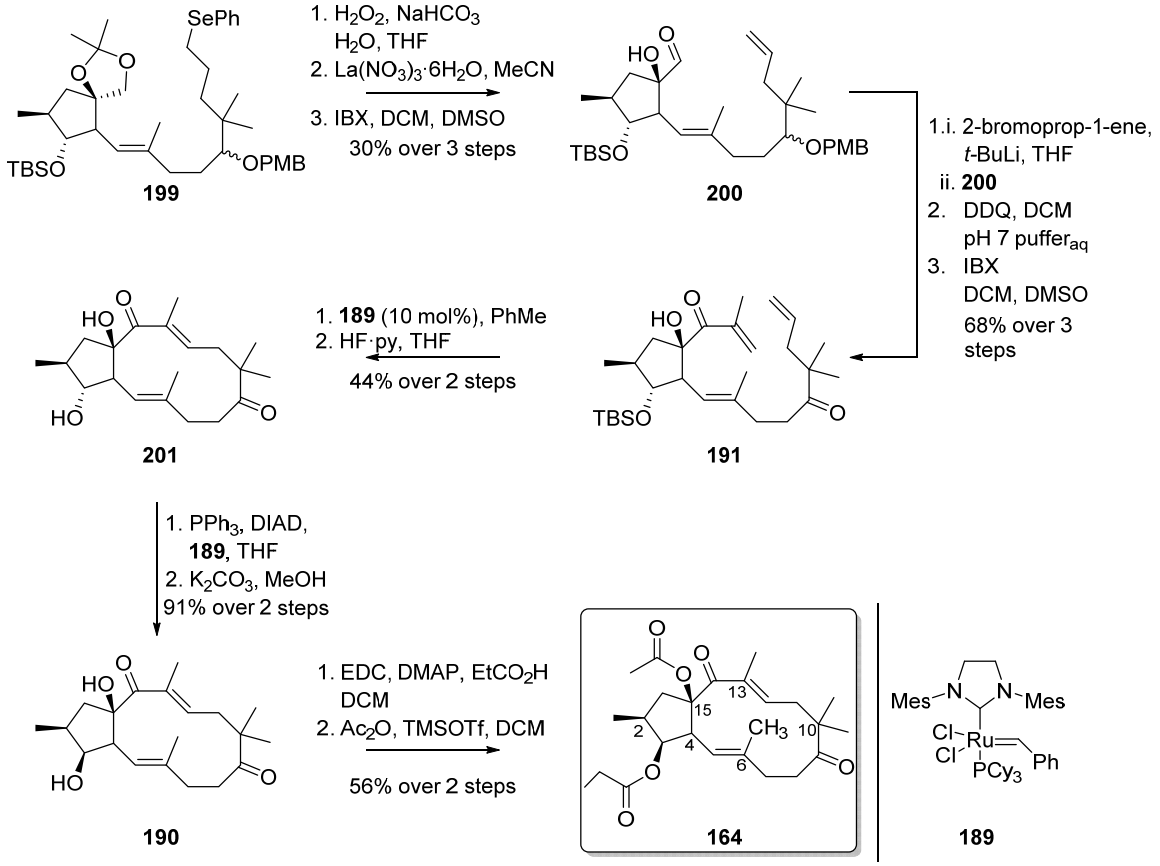
was in turn allowed to react *in situ* with iodine yielding the desired vinyl iodide **194** as a single double bond isomer. Conditions described by Johnson and Brown[162] were applied to perform the Suzuki-Miyaura coupling between alkene **193** and vinyl iodide **194**. This crucial step installed the trisubstituted C5-C6 double bond and afforded **199** in 86% yield. It is noteworthy that many authors switch to a Suzuki-type coupling in order to circumvent a Stille coupling, due to the toxicity of alkylstannanes. However, very often toxic additives, as in the present case triphenylarsine, have to be added to enhance the yield.




**Scheme 32: Synthesis of intermediate** 199**.**

Conversion of the selenide to the selenoxide led to immediate *syn*-elimination affording the C12-C12´ double bond.[163, 164] The isopropylidene acetal was cleaved without affecting the other protecting groups utilizing a Lewis acidic lanthanum(III) salt,[165] and subsequent IBX-oxidation[166] afforded α-hydroxy aldehyde **200** in moderate overall yield. The newly formed aldehyde was exposed to *in situ* generated isopropenyl lithium[167] to afford another diol. Subsequent oxidative cleavage of the *p*-methoxy benzyl group with DDQ in a biphasic mixture of solvents,[168] and IBX oxidation of the secondary alcohols to the corresponding ketones granted access to the desired RCM precursor **191**. The required macrocyclization could be conducted utilizing 2nd generation Grubbs´ catalyst **189**[152] in refluxing toluene. From this point the remaining steps were similar to the previous synthesis. Thus, deprotection of the *tert*-butylsilyl ether was followed by Mitsunobu reaction to establish the correct stereochemistry at C3. Finally, cleavage of the intermediate

benzoate, derived from the Mitsunobu reaction, afforded characiol (**190**) and regioselective esterification[169, 170] provided the target molecule **164**.

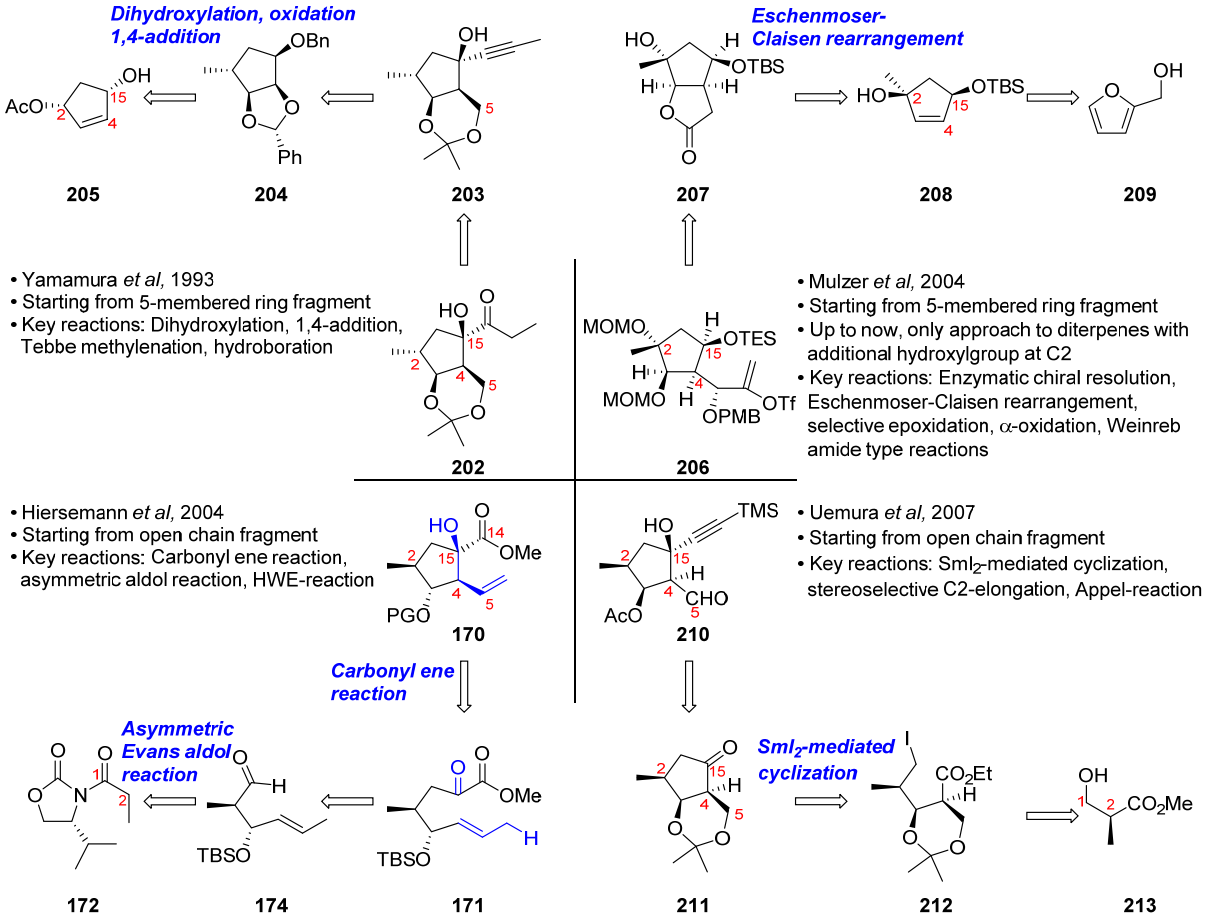



**Scheme 33: Completion of the synthesis of (−)-15-acetyl-3-propionyl-characiol (**164**).**

# 5 Partial syntheses - Synthetic efforts toward five-membered ring fragments

To the best of my knowledge, only the approaches toward jatrophane diterpenes depicted below were presented in recent years. All retrosynthetic analyses, lead back to a cyclopentane segment as the crucial building block, for which a scalable access is desirable. As outlined in Scheme 34, the approaches toward the envisioned five-membered ring building blocks clearly differ. In this section the following approaches will be presented:

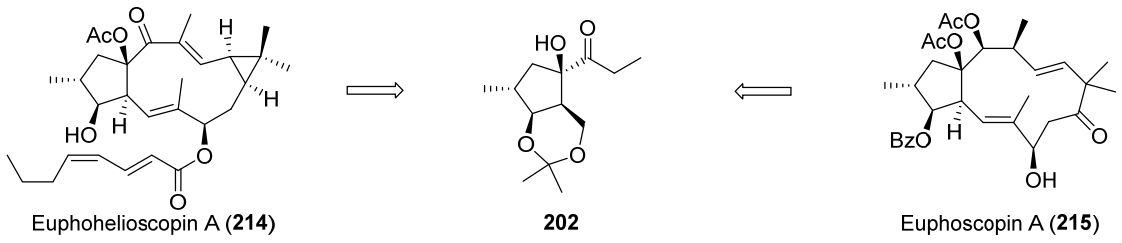
- Yamamura´s intermediate (**202**)[171]
- En route to pepluanine A (**224**) and euphosalicin (**11**) by Mulzer *et al*[172, 173]
- Hiersemann´s cyclopentane fragment **170**[133]
- Cyclopentane segment **210** for the synthesis of kansuinine A (**246**) by Uemura *et al*[174]




**Scheme 34: Different approaches to five-membered ring fragments useful in the syntheses of jatrophane diterpenes.**

## 5.1 Synthesis of an optically active cyclopentane derivative by Yamamura *et al*

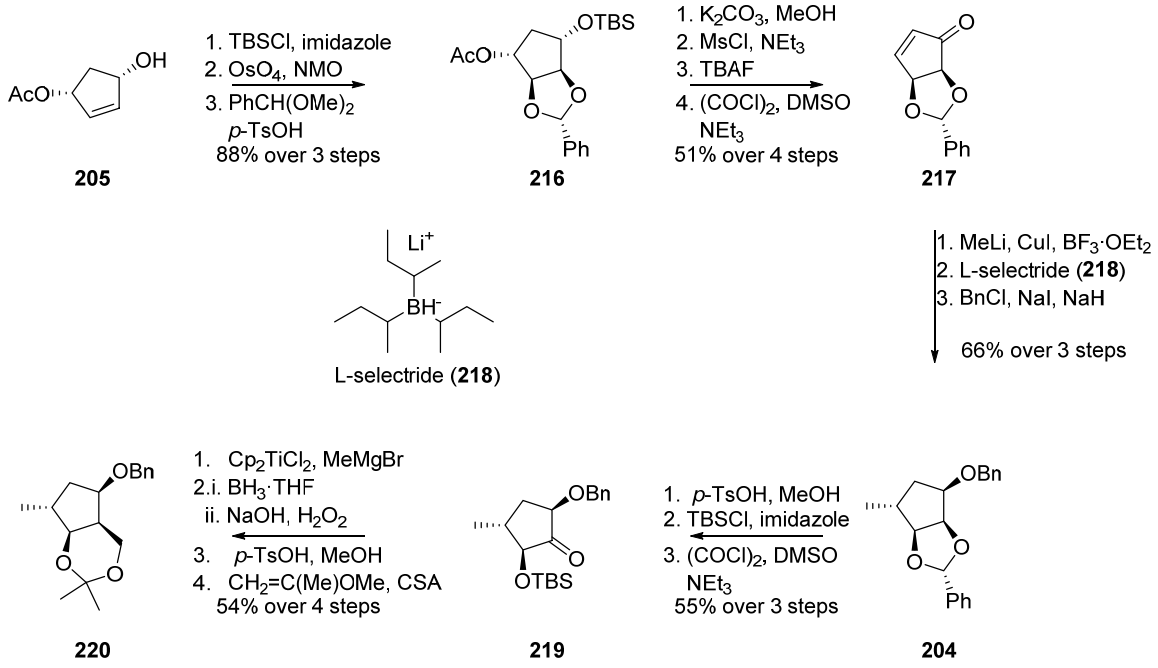
In 1993, Yamamura and coworkers presented their synthesis of an optically active cyclopentane derivative, which is shared by the majority of the diterpenes isolated from *Euphorbia heliscopia* (Scheme 35). Their goal was to establish a practical route to the selected five-membered ring **202** for further synthetic studies.




**Scheme 35: Retrosynthetic analyses leading back to five-membered ring intermediate** 202**.**

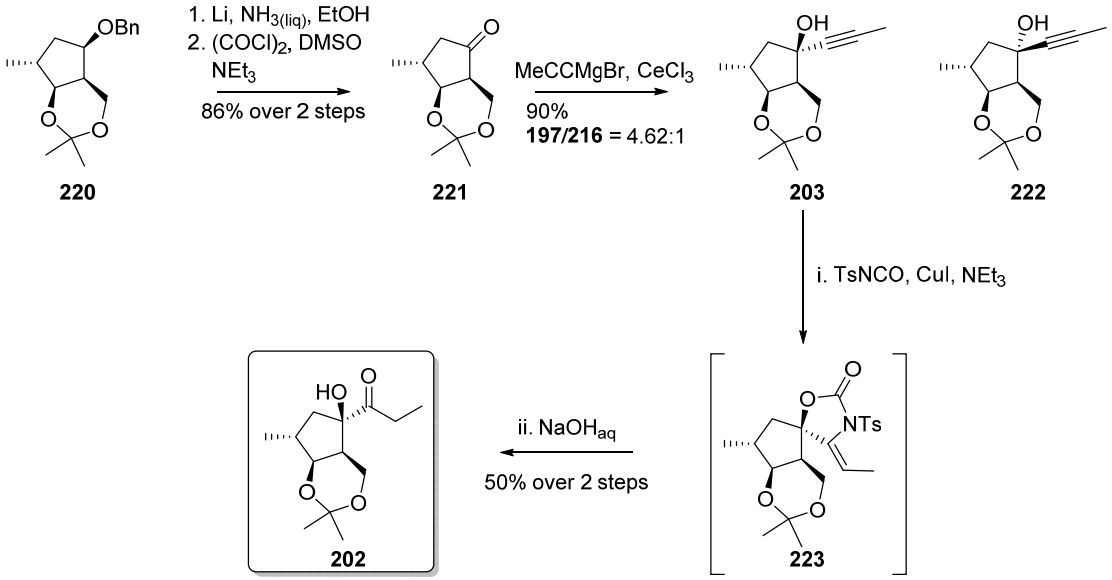
The preparation of the cyclopentane **202** started from alcohol **205**, which is accessible *via* a sequence previously published by Mori *et al*.[175] After protection of the allylic alcohol as *tert*-

butylsilyl ether the double bond was dihydroxylated utilizing osmium tetroxide. Subsequent protection of the diol as the benzylidene acetal gave intermediate **216** in good overall yield. Next, transformation of the acetyl group into a mesyl group was conducted *via* basic deprotection followed by mesylation under standard reaction conditions and fluoride mediated silyl ether cleavage and oxidation of the resulting free hydroxyl group afforded α,β-unsaturated ketone **217**. Treatment with methyllithium and catalytic amounts of copper iodide and borontrifluoride etherate delivered the desired 1,4-adduct,[176] which was further reduced and the resulting hydroxyl group was benzylated to afford **204**. Further deprotection of the diol and selective silyl protection was followed by Swern oxidation of the remaining free hydroxyl group to provide ketone **219**. Petasis methylenation[177] then granted access to the olefination product, which was submitted to an hydroboration-oxidation sequence and subsequent conversion of the 1,3-diol gave **220** in moderate yield.




**Scheme 36: Synthesis of intermediate** 220**.**

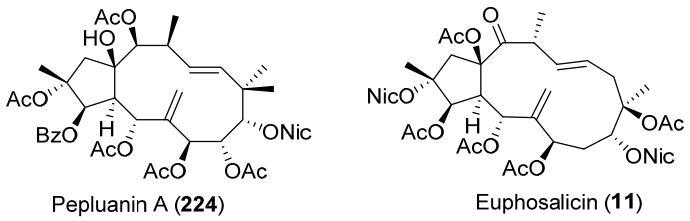
Birch reduction[178] resulted in cleavage of the benzyl ether and was followed by Swern oxidation to afford ketone **221**. Treatment of the latter with 1-propynyl magnesium bromide resulted in the isolation of the separable diastereomeric adducts **203** and **222**. Finally, reaction of **203** with TsNCO resulted in the introduction of an ethyl ketone group *via* cyclic carbamate **223** leading to the desired building block **202**.




**Scheme 37: Completion of the synthesis of cyclopentane** 202**.**

## 5.2 Concise route to a highly oxygentated cyclopentane by Mulzer *et al*

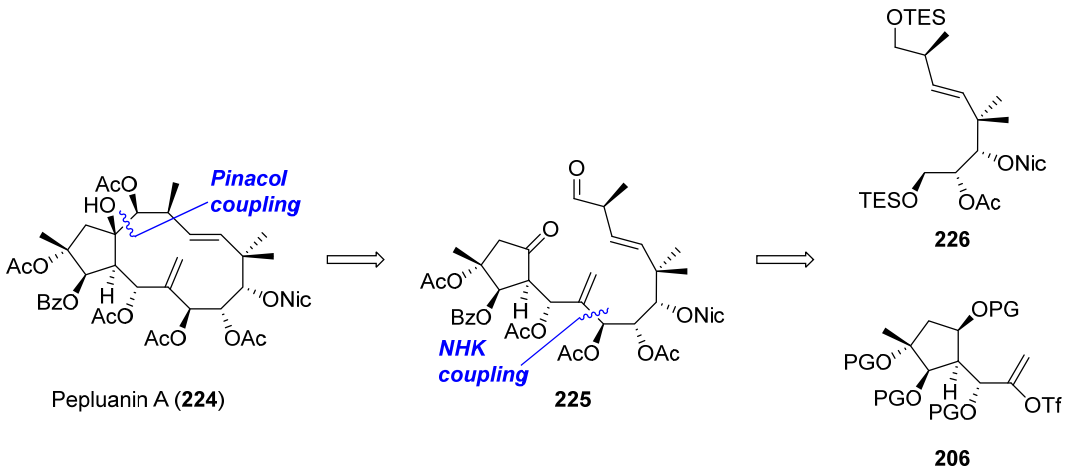
An asymmetric synthesis of a highly oxygenated cyclopentane fragment (**206**), which should act as an advanced intermediate in the total synthesis of the macrocyclic diterpenes pepluanin A (**224**)[179] and euphosalicin (**11**)[57] was elaborated by Mulzer and coworkers in 2004.




**Scheme 38: Pepluanin A (**218**) and euphosalicin (**11**) – synthetic targets of interest.**

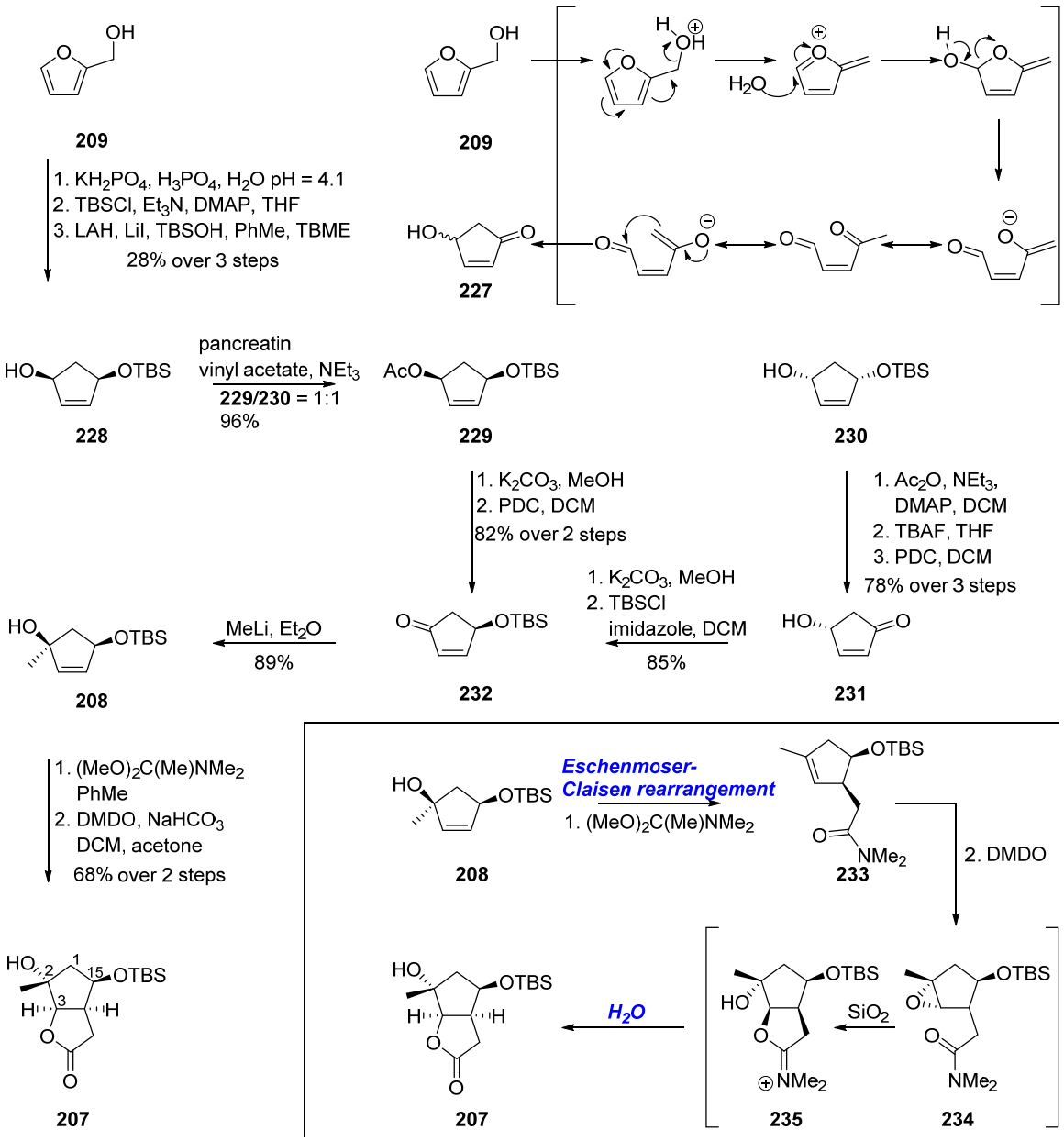
Since both diterpenoid targets show significant Pgp inhibitory activity, larger quantities of these natural products are desirable to allow more detailed studies to investigate their MDR reversal activities.

As outlined in Scheme 39 the retrosynthetic analysis of pepluanin A (**224**) intended a late stage pinacol coupling[180] to close the macrocycle as well as a Nozaki–Hiyama–Kishi (NHK) coupling[181-183] to attach the side chain fragment **226**. This leads back to advanced triflate **206**, which is elaborated in a creative synthesis featuring a Claisen-Eschenmoser rearrangement[184], an intramolecular *trans*-lactonization, Davis hydroxylation and regioselective enoltriflate formation as key steps.




**Scheme 39: Retrosynthetic analysis of pepluanin A (**218**) leading back to advanced building block** 206**.**

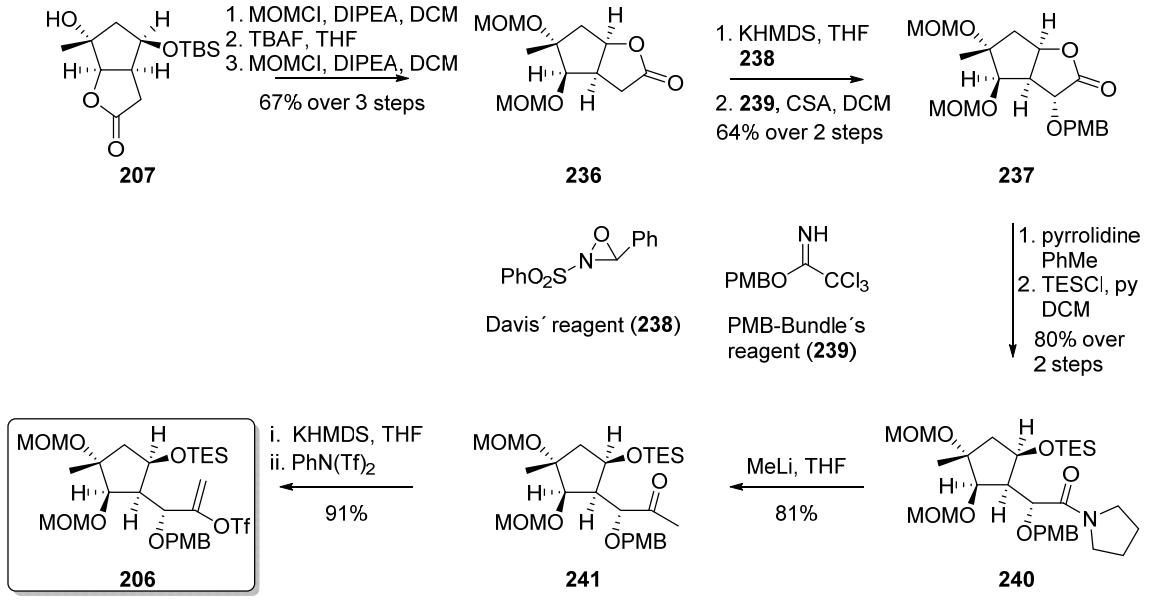
The first steps in the synthesis followed a protocol introduced by Curran and coworkers.[185, 186] Starting from commercially available furfuryl alcohol, carbocycle **227** was obtained *via* an acid catalyzed rearrangement (see Scheme 40). Subsequent protection of the hydroxyl group was followed by lithium aluminum hydride reduction under rather uncommon conditions, using lithium iodide and *tert*-butylsilyl alcohol as additives. Enzymatic chiral resolution was used to gain access to optically pure **229** and **230**. **229** was converted to known intermediate **232**[187] in two steps. **230** could be converted to the same intermediate **232** by a slightly longer sequence.[188] Therein, alcohol **230** was acetylated, followed by silyl ether cleavage to yield ketone **231** after oxidation. A deprotection, protection sequence afforded ketone **232**,[189] which was allowed to react with methyllithium to afford the desired 1,2-adduct **208**. Next, Eschenmoser-Claisen rearrangement afforded the envisioned amide in good yield. Generation of the epoxide using dimethyldioxirane delivered epoxide **234** and the following flash column chromatography of the crude product triggered an intramolecular epoxide-opening lactonization reaction affording lactone **207** in good overall yield.




**Scheme 40: Synthesis of lactone** 207**.**

The next steps were dedicated to prepare the crucial α-oxidation regarding the lactone functionality in **237**. As the newly introduced hydroxyl group should exclusively possess (*R*)-configuration, the authors planned to utilize the convex/concave handle inherent to *cis*-fused bicycles. Hence it was necessary to alter the lactone functionality in **207** from the C3 oxygen to the C15 oxygen. This task was achieved by the protection of the free tertiary hydroxyl group as methoxymethyl ether, followed by treatment with tetra-butylammonium fluoride, which affected the conversion to the desired lactone. Protection of the remaining hydroxyl group as methoxy methyl ether resulted in the isolation of the desired lactone **236** (Scheme 41). Generation of the ester enolate was achieved by treatment with potassium bis(trimethylsilyl)amide and hydroxylation from the sterically less hindered convex side utilizing the Davis reagent (**238**)[190]

delivered only one isomer of the α-hydroxy ester. Subsequent reaction with PMB-Bundle´s reagent (**239**)[191] under acidic catalysis provided the desired orthogonally protected lactone **237**. After opening of the lactone moiety in **237** with pyrrolidine, the resulting alcohol was protected as silyl ether to accomplish the synthesis of intermediate **240**. Methylketone **241** was established by reaction of amide **240** with an excess of methyllithium, whereupon amide **240** imitates the properties of a Weinreb amide[192]. The remaining regioselective vinyl triflate formation, was achieved by kinetically controlled deprotonation followed by treatment with *N*-phenyl-bis(trifluoromethanesulfonimide). To the best of my knowledge the synthesis is the sole synthetic approach toward an advanced five-membered ring fragment featuring an additional alcohol functionality at C2.



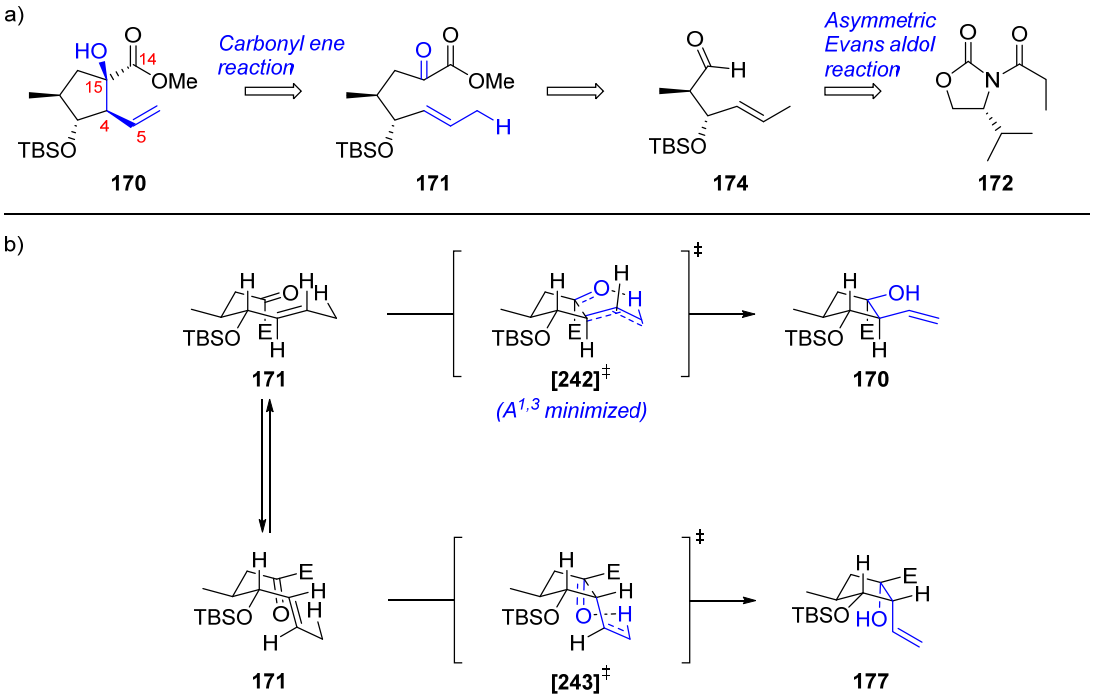

**Scheme 41: Completion of the synthesis of five-membered ring** 206**.**

## 5.3 Enantioselective synthesis of a highly functionalized cyclopentane segment by Hiersemann *et al*

Over the last decade the Hiersemann group has contributed immensely to the development of synthetic strategies toward jatrophane diterpenes. Within their first report in this field, they presented the synthesis of the C14 to C5 (jatrophane numbering) cyclopentane fragment **170**,[133] a building block of central importance for their later synthesis of the diterpenes **163** and **164**,[97, 193] discussed earlier.

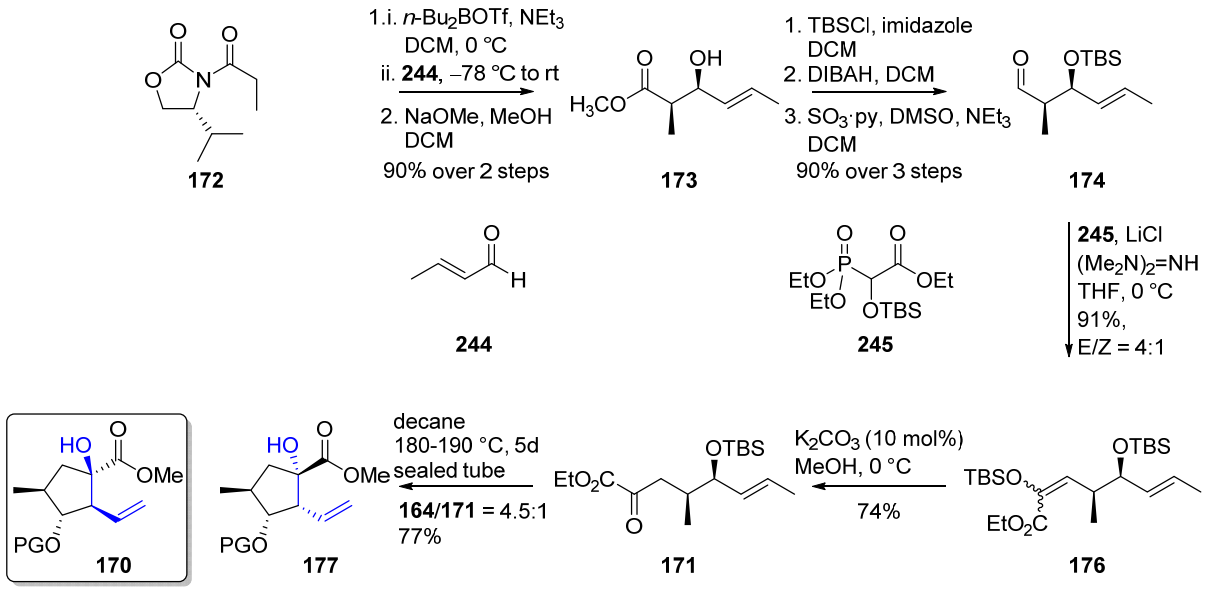
In their retrosynthetic considerations, Hiersemann and coworkers envisioned that a thermal intramolecular carbonyl ene reaction could be used as a key step to assemble the crucial five-membered ring **170** from an acyclic α-keto ester **171** (see Scheme 42a). They expected that the

absolute configuration at C3 (jatrophane numbering) of the α-keto ester **171** together with the pericyclic nature of the transition state would lead to the desired five-membered ring fragment. This assumption was based on the qualitative analysis depicted in Scheme 42b. The minimization of the 1,3-allylic strain in transition state **242** compared to the competing transition state **243** should be energetically preferred and result in the predominant formation of the desired stereoisomer **170**. As the required absolute configuration at C3 is the opposite to the absolute configuration at C3 in characiol (**190**), Hiersemann´s later target, he was confident that an inversion of the configuration would be possible at a later stage of the synthesis. The acyclic α-keto ester **171** should be accessible *via* a HWE reaction and a functional group interconversion from aldehyde **174**, which should in turn be obtained through an asymmetric Evans´ aldol reaction finally leading back to oxazolidinone **172**.




**Scheme 42: Retrosynthetic and mechanistic considerations toward a five-membered building block by Hiersemann *et al*.**

Starting from oxazolidinone **172**, Evans´ aldol methodology was followed by a transesterification reaction to cleave the auxiliary and afford ester **173** in excellent yield. Subsequent protection of the secondary hydroxyl group was followed by reduction of the methyl ester. The corresponding alcohol was oxidized under Parikh-Doering conditions to yield aldehyde **174**. Lithiated **245** reacted in a HWE olefination with **174** to provide predominantly *E*-configured silyl enol ether **176**. Under basic conditions the silyl enol ether was cleaved to furnish the cyclization precursor α-keto ester **171**, which was heated at 180 to 190 °C in decane in a sealed tube for five days to obtain a mixture of diastereomeric cyclopentanes **170** and **177**.



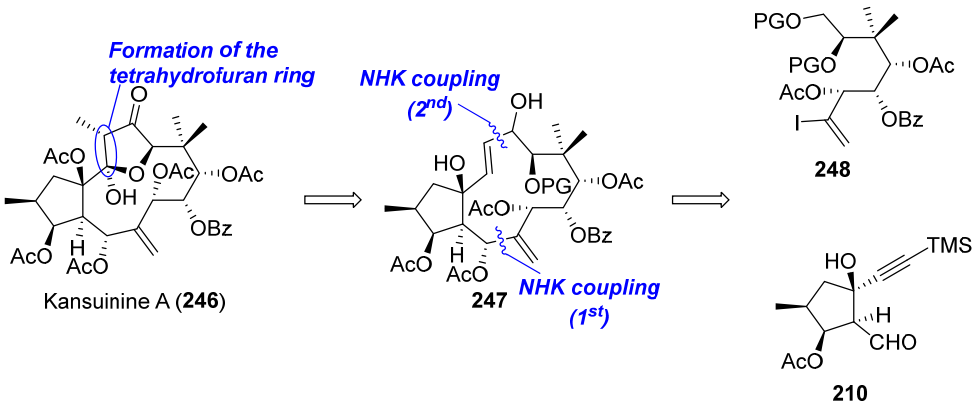

**Scheme 43: Synthesis of cyclopentane 170.**

In an overall short sequence Hiersemann and coworkers developed a practicable synthesis of cyclopentane fragment **170**. After the publication of the synthesis of **170** in 2004[133] they provided an optimization of the reaction conditions in 2006[133] in course of the synthesis of (−)-15-acetyl-3-propionyl-17-norcharaciol (**163**)[132].

## 5.4 Concise synthesis of a highly functionalized cyclopentane segment by Uemura *et al*

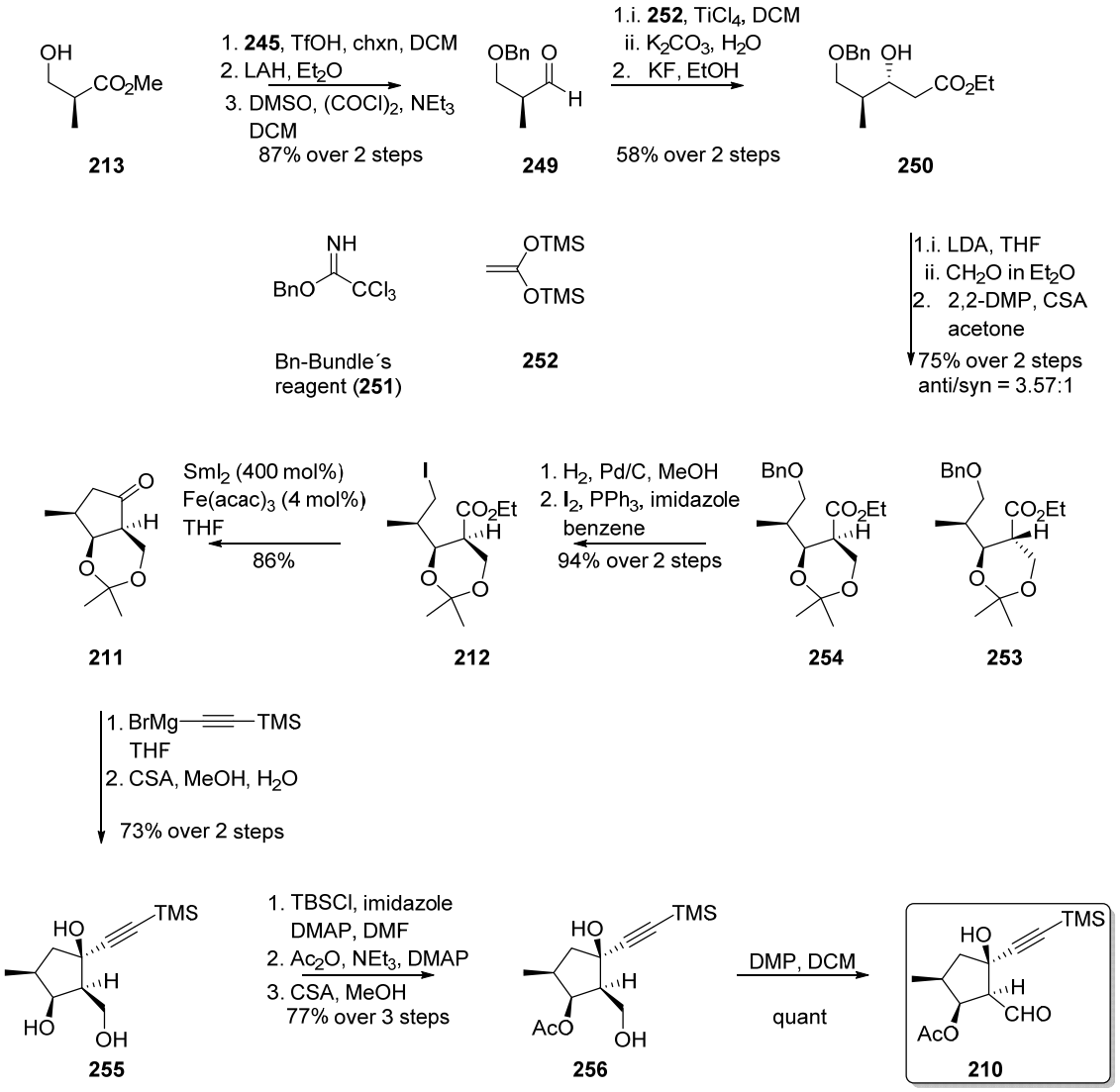
Another highly oxygenated jatrophane diterpene is the target molecule of the Japanese research group around Uemura. Kansuinine A (**246**) was isolated from *Euphorbia kansui* in 1975,[194, 195] and shows analgesic activity and induction of the neuron growth factor production.[196, 197]

Retrosynthetic considerations are illustrated in Scheme 44. The macrocycle is envisioned to be elaborated by two NHK coupling reactions based on iodide **248** and the cyclopentane segment **210**. The synthesis should be concluded by installation of the tetrahydrofuran ring in kansuinine A (**246**).




**Scheme 44: Retrosynthetic analysis of kansuinine A by Uemura *et al*.**

Preparation of aldehyde **210** started from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **213**[198, 199] Protection of the primary alcohol using the benzyl-Bundle´s reagent (**251**)[191], was followed by reduction of the ester to the corresponding alcohol and subsequent oxidation delivered aldehyde **249** in good overall yield. Mukaiyama-aldol reaction of *C*,*O*-bis(trimethylsilyl)ketene acetal (**252**) and aldehyde **249**, was followed by desilylation to yield ethyl ester **250** with high enantioselectivity.[200, 201] The synthesis was continued by the the addition of lithium diisopropylamide and subsequent reaction with anhydrous formaldehyde solution in ether[202] to afford two diastereomeric aldol products. Furthermore, isopropylidene protection of the 1,3-diols afforded the chromatographically separable acetals **253** and **254**. Reductive cleavage of the benzyl ether in **254** was followed by an Appel reaction[203] to obtain the corresponding iodide **212**. Now the stage was set for the samarium(II) iodide mediated cyclization[204, 205] which was envisioned to establish the carbocycle **211**. After extensive experimentation Uemura and coworkers found reaction conditions leading to the desired cyclopentane segment **211** in 86% yield (Scheme 45). At this point only few transformations remained to complete the synthesis of the desired cyclopentane segment. Nucleophilic addition of trimethylsilylethynylmagnesium bromide selectively proceeded from the less hindered side and subsequent acidic deprotection of the isopropylidene group granted access to triol **255**. After transformation of the primary hydroxyl group in **255** into the silyl ether, the secondary alcohol was acetylated, followed by the cleavage of the previously installed silyl group tetrabutylammonium fluoride, and the product **256** was exposed to Dess-Martin periodinane[147] to finally afford cyclopentane **210**.




**Scheme 45: Synthesis of five-membered ring** 210**.**

# 6 Aim of the synthetic work

The work discussed within this thesis is focusing on the development of a synthetic approach toward the jatrophane diterpene Pl-3 (**9**). Special attention is given to the elaboration of different routes dealing with the syntheses of five-membered ring fragments. These fragments are useful in the intended synthesis of Pl-3 but could also serve as key fragments in prospective approaches to other jatrophane diterpenes. As discussed earlier (section 2) the jatrophane skeleton consists of a five-membered ring, which is *trans*-annulated to a twelve-membered macrocycle. Euphosalicin (**11**) represents an exception as in this case one methyl group of the germinal dimethyl moiety at C10 is incorporated into the macrocycle, leading to a 13-membered ring.

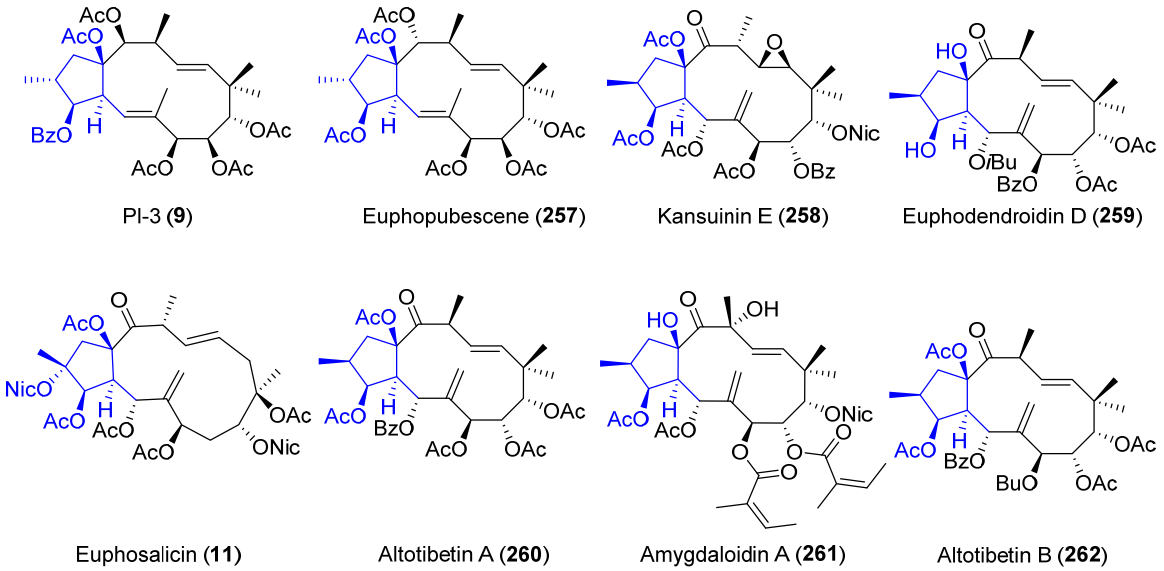
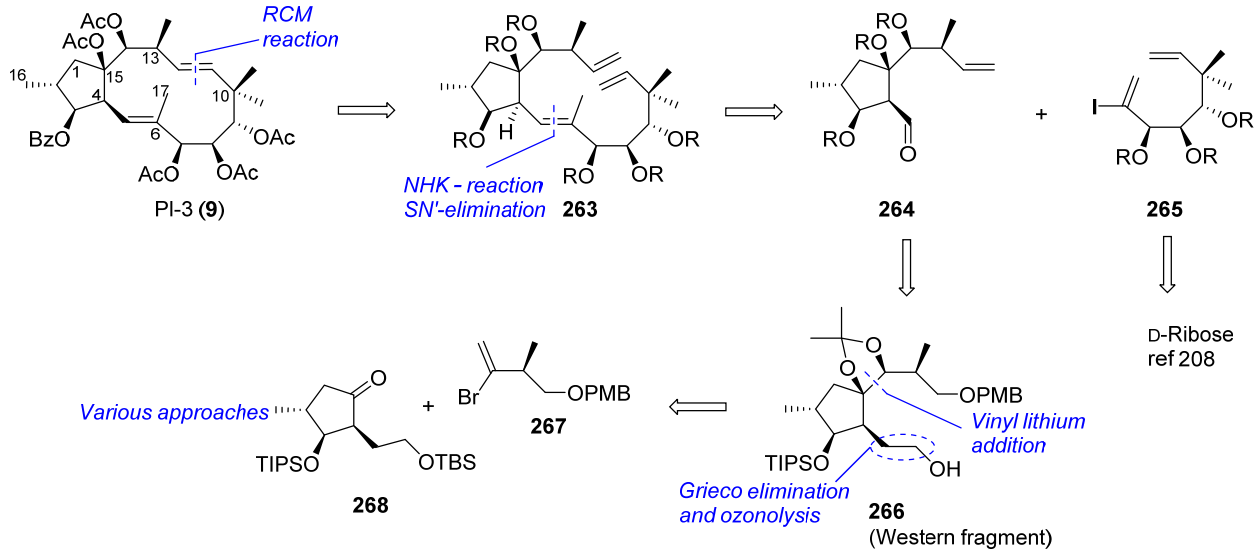



**Figure 10: Different jatrophane diterpenes.**

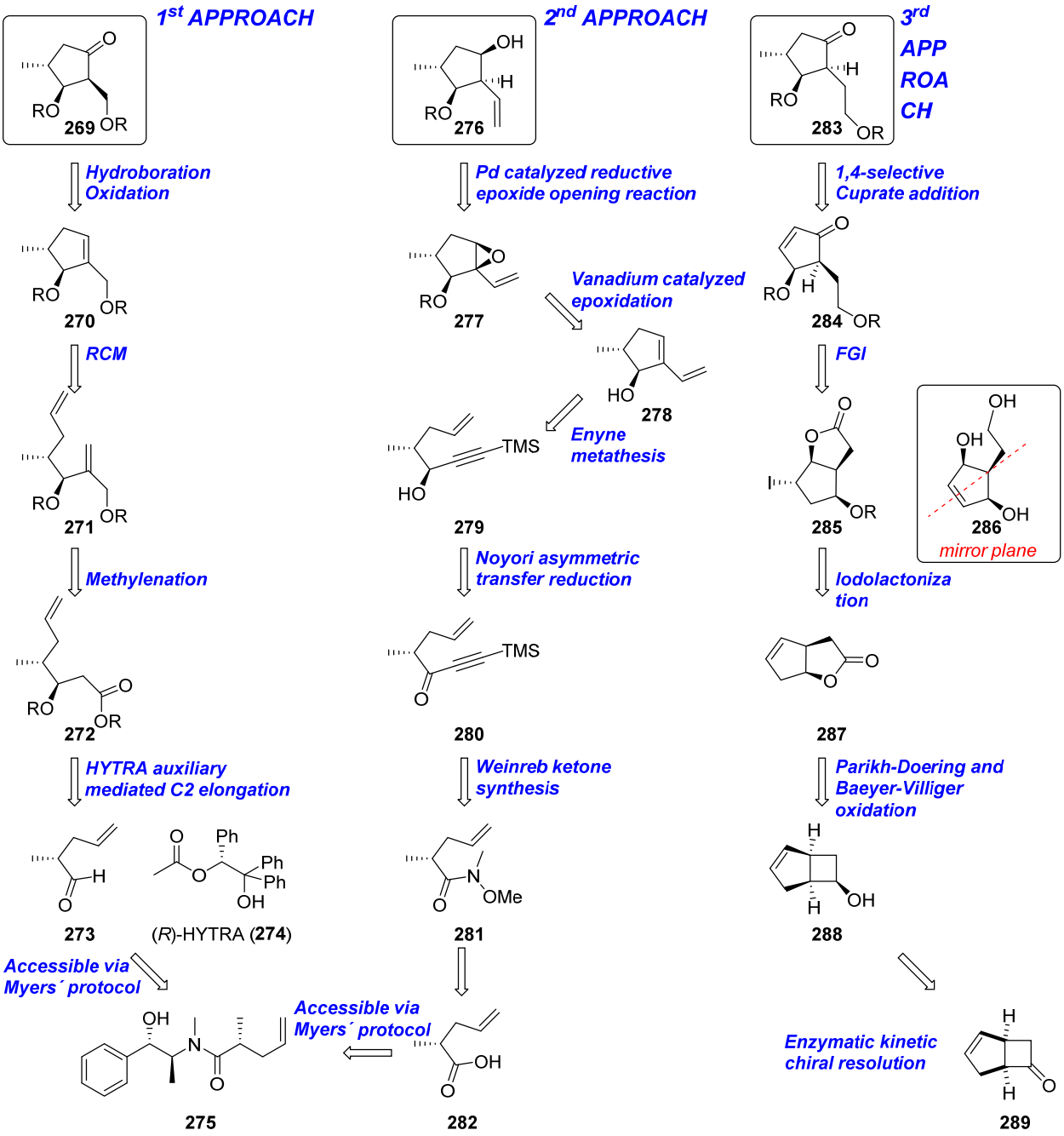
A few representative examples, shown in Figure 10, should give an insight into the diversity of structures found among jatrophane diterpenes. The framework is highly oxygenated and most of the hydroxyl functionalities are part of an ester. Benzoates and acetates are the most common ester groups present, but nicotinates, propionates or others can be found as well. Beside the different ester groups, also ketones, *exo*-methylene groups and internal alkene moieties are common structural motifs. Despite all these structural differences within the macrocycle the five-membered ring fragment seems rather consistent in most of the isolated diterpenes. As already mentioned, in the majority of jatrophane diterpenes the macrocycle is *trans*-annulated to the five-membered ring, determining the configuration of two stereogenic centers. Furthermore, an unsubstituted $CH_2$-group at C1 as well as the configuration of the free hydroxyl group or, alternatively, an ester-functionality at C3 of the jatrophane skeleton remains unaltered throughout the whole family of diterpenes. The only commonly found variation is at C2, whereby both methyl-substituted stereoisomers as well as an additional ester group can be found (see Figure 10).




**Scheme 46: Retrosynthetic considerations toward Pl-3 (9).**

As outlined in the retrosynthetic analysis (Scheme 46), an RCM reaction is intended to be the final key-step to close the twelve-membered macrocycle of Pl-3. The RCM-precursor is envisaged to be prepared by an NHK coupling reaction of aldehyde **264** and vinyl iodide **265** with subsequent reductive alkene shift (C6-C17 to C5-C6 double bond, jatrophane numbering).[206, 207] This strategy takes advantage of the comprehensive work carried out by Hiersemann and coworkers on their way to (−)-15-*O*-acetyl-3-*O*-propionylcharaciol (**164**). The Hiersemann group was able to demonstrate that, although the C12-C13 ring closure can be accomplished by an RCM reaction, this reaction is not feasible for the elaboration of the sterically congested trisubstituted C5-C6 double bond.[97, 157] The vinyliodide **265** is available from D-ribose following a protocol developed in our group.[208] Aldehyde **264** leads back to the western fragment **266**, which should be available from cyclopentane intermediate **268** *via* a vinyl lithium addition, to establish the needed *trans*-annulation, followed by a subsequent ozonolysis reduction sequence.

In accordance with the approaches discussed in the previous section, we share the understanding of other research groups and also identified a five-membered ring fragment as intermediate of central importance. To gain access to various jatrophane diterpenes we envisaged to design a short and general approach toward the five-membered ring segment **268**. In course of this PhD thesis three different strategies, could be reported. The major disconnections are outlined in Scheme 47 from a retrosynthetic point of view.




**Scheme 47: Retrosynthetic analysis of different five-membered ring fragments elaborated in course of this PhD thesis.**

In the first approach a Brown hydroboration oxidation sequence in the last step should be used to install the ketone and define the stereochemistry at C4.[209] This sequence leads back to cyclopentene **270**, which should be established *via* an RCM reaction from the linear precursor **271**. This intermediate was envisioned to be available by a stereoselective C2 elongation, employing (*R*)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate (HYTRA; **274**),[210, 211] of aldehyde **273** followed by an Eschenmoser methylenation reaction[212]. The enantiomeric aldehyde **273** should be readily available in a short sequence starting with Myers´ alkylation protocol[213, 214] of the

corresponding pseudoephedrine propionamide and allyl iodide. Subsequent lithium amidotrihydroborate (LAB) reduction of the amide followed by oxidation with IBX should selectively furnish the desired enantiomerically pure aldehyde **273**.

This strategy allows the concise and diastereoselective preparation of the two isomers with opposite configuration at C2 by the utilization of enantiomeric starting materials, in comparable, good yield. Due to the easily available starting materials and the overall short sequence this route opens access to a highly functionalized five-membered ring segment useful in the synthesis of diverse jatrophane diterpenes.

In order to improve the first approach described above, the route targeting **276** within our second approach was changed considerably. Instead of the challenging Brown hydroboration oxidation sequence a new protocol aspiring a palladium catalyzed reductive epoxide opening reaction was developed, which should serve as final key step for the preparation of the desired five-membered ring fragment **276**. A selective vanadium catalyzed epoxidation reaction using the allylic alcohol functionality as a directing group suggested diene **278** as possible precursor. An enyne metathesis reaction, followed by TMS-cleavage, seemed to be perfectly suitable to deliver the desired diene **278** leading back to acyclic enyne **279**. The asymmetric center at C3 should be introduced by a Noyori asymmetric transfer reduction.[215] As an appropriate starting material for the sequence we decided to utilize chiral carboxylic acid **282**, available again *via* the Myers' asymmetric alkylation protocol, which should be employed in a Weinreb ketone synthesis to deliver ketone **280**.

Although the first approach offers a concise route toward different jatrophane diterpenes the C2 elongation step using HYTRA is not atom efficient. This drawback and the relative low yielding hydroboration oxidation sequence are circumvented in the second approach. Therein, basically the same starting material was chosen, as the Myers´ protocol proofed to be very reliable in terms of yield and optical purity of the products. The majority of reactions accomplished in the second approach were metal catalyzed leading to an overall excellent atom economy. Especially the diastereoselective Noyori reduction of ketone **280** determining the configuration at C3, which was set by the HYTRA mediated chain elongation reaction in the first approach, requires a catalyst loading of only 0.65 mol%. Furthermore, the novel application of the DACH-phenyl Trost ligand in the stereoselective palladium catalyzed reductive epoxide opening is a valuable extension of Shimizu's protocol and should be of interest for the preparation of complex natural products.[216-220]

The third approach developed in course of this PhD thesis is a conceptually different route toward the western fragment of Pl-3. As outlined in Scheme 47 substrate-controlled, diastereoselective

1,4-cuprate addition should serve to install the methyl group at C2. Functional group adjustments suggested lactone **285** as precursor for the desired enone **284**, while **285** itself was envisioned to be accessible from enantiomerically pure bicyclo[3.2.0]hept-2-en-6-ol **288** by a short sequence featuring a Baeyer-Villiger reaction as key transformation.[221] The starting material became accessible on a multi-gram scale from commercially available racemic ketone *rac*-(**289**) *via* a protocol developed earlier in our group.[222, 223]

The overall efficiency of this route could be greatly improved by taking advantage of the latent symmetry present in lactone **285** (shown in unprotected intermediate **286**, Scheme 47). As the iodolactonization reaction is strongly pH-dependent both enantiomers of alcohol **288** can be efficiently converted into lactone **285**. Each step in this reaction is easily scalable without diminishing the yield of the reaction.

Concerning the installation of side chain, the development of an applicable method for the alkylation of ketone **265** with an appropriate lithiated vinyl bromide **267** (see Scheme 46) proved to be a tedious task. While the addition of vinyl magnesium bromide as test substrate afforded the corresponding tertiary alcohol in nearly quantitative yield, extensive screening of reaction conditions was required to install vinyl bromide **267**. The best result was obtained when the reaction was carried out in a solvent mixture of pentane and diethyl ether in a ratio of 3:2. Vinyl bromide **267** was lithiated with *t*-BuLi at −78 °C and ketone **268** was added slowly to the lithiated species.

Summarizing, we developed three approaches toward five-membered ring synthons, which rely on different methodologies and are useful in the syntheses of various jatrophane diterpenes. Additionally, an alkylation protocol was developed to establish the *trans*-annulation existent in the majority of jatrophane diterpenes. The established protocols are important synthetic achievements and constitute the foundation for the total synthesis of the jatrophane diterpene Pl-3.

In the following, three manuscripts, published in course of this PhD thesis, are presented covering detailed discussion of our retrosynthetic analyses and synthetic achievements.

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# 8 LIST OF PUBLICATIONS

## Peer reviewed publications

- *Jatrophane Diterpenes - Preparation of the Western Fragment of Pl-3.*
  Lentsch, C.; Fürst, R.; Mulzer, J.; Rinner, U. *Eur J Org Chem*. Manuscript accepted (Nov-26 2013).
- *Synthetic Studies Towards an Advanced Precursor of the Jatrophane Diterpene Pl-4.*
  Fürst, R.; Lentsch, C.; Rinner, U. *Synthesis*, **2013**, DOI: 10.1055/s-0033-1338565.
- *Enyne Metathesis Approach towards the Cyclopentane Motif of Jatrophane Diterpenes.*
  Lentsch, C.; Fürst, R.; Rinner, U., *Synlett* **2013**, *24* (EFirst), 2665-2670.
- *Towards the Total Synthesis of Pl-3: Preparation of the Eastern Fragment through a Diastereoselective $SmI_2$-Mediated Reformatsky Reaction.*
  Fürst, R.; Lentsch, C.; Rinner, U. *Eur J Org Chem* **2013**, (12), 2293-2297.
- *Syntheses of Galbulimima Alkaloids*.
  Rinner, U.; Lentsch, C.; Aichinger, C. *Synthesis* **2010**, *2010* (22), 3763-3784.
- *General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes.*
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- *Synthetic Tools for Addressing Biological and Medicinal Chemical Questions.*
  M. Braitsch, M. Fischer, R. Hollaus, C. Lentsch, R. Lichtenecker, M. Nagl, C. Nowikow, C. Schmölzer, W. Schmid, MEDIMOND International Proceedings*, Joint Meeting of Medicinal Chemistry* **2009**, 21-26.

## Poster presentations

- *Jatrophane Diterpenes – Evaluation of strategies Towards the Preparation of Highly Functionalized Cyclopentanes*.
  Lentsch, C.; Fürst, R.; Rinner, U. Presented at the 15th Latest Trends in Organic Synthesis Meeting, St. Catharines (LTOS), Ontario, Canada, August 8-11, 2012.
- *Preparation of Highly Functionalized Five-Membered Ring Synthons – Different Strategies to Key Intermediates in the Synthesis of Diterpenes.*
  Lentsch, C.; Rinner, U. Presented at the 14. Österreichische Chemietage, Linz, Austria, September 26-29, 2011.
- *Towards the Total synthesis of Euphosalicin: Preparation of the Five-Membered Ring Fragment*.
  Dank, C.; Lentsch, C.; Rinner, U. Presented at the 14. Österreichische Chemietage, Linz, Austria, September 26-29, 2011.
- *Efficient Preparation of Highly Functionalized Five-Membered Ring Synthons used in the Synthesis of Jatrophane Diterpenes.*
  Lentsch, C.; Fürst, R.; Rinner, U. Presented at the 14th Latest Trends in Organic Synthesis Meeting (LTOS), St. Catharines, Ontario, Canada, August 11-14, 2010.
- *Progress in the Total Synthesis of Euphosalicin*.
  Aichinger, C.; Lentsch, C.; Rinner, U. Presented at the 14th Latest Trends in Organic Synthesis Meeting (LTOS), St. Catharines, Ontario, Canada, August 11-14, 2010.

- *Multi-drug resistance reversal agents: Update on the synthesis of euphosalicin.*
  Aichinger, C.; Lentsch, C.; Rinner, U. Presented at the 240th National Meeting of the American Chemical Society, Boston, MA, USA, August 22-26, 2010.
- *Highlights on the way to the first total synthesis of Pl-3*.
  Lentsch, C.; Fürst, R.; Rinner, U. Rinner, U. Presented at the 240th National Meeting of the American Chemical Society, Boston, MA, USA, August 22-26, 2010.
- *Preparation of Highly Functionalized Five-Membered Ring Synthons used in the Synthesis of Diterpenes*.
  Aichiniger, C.; Lentsch, C.; Rinner, U. Presented at the 13. Österreichische Chemietage, Vienna, Austria, August 24-27, 2009.
- *Towards the Total Synthesis of Euphosalicin: Preparation of the C6-C14 Fragment.*
  Aichinger, C.; Lentsch, C.; Rinner, U. Presented at the 13. Österreichische Chemietage, Vienna, Austria, August 24-27, 2009.
- *Synthesis of a Highly Functionalized Cyclopentane Segment: Toward the Total Synthesis of Jatrophane Diterpenes*.
  Rinner, U.; Lentsch, C.; Aichinger, C.; Mulzer, J. Presented at the Synthesefest, Munich, Germany, March 17-18, 2009.
- *Progress in the First Total Synthesis of Pl-3, a Potent Multidrug Resistance Reversal Agent*.
  Aichinger, C.; Lentsch, C.; Rinner, U. Presented at the Tenth Tetrahedron Symposium, Paris, France, June 23-26, 2009.
- *Towards the First Total Synthesis of Euphosalicin. A Structurally Unique Euphorbiaceae Diterpene*.
  Aichinger, C.; Lentsch, C.; Rinner, U. Presented at the Tenth Tetrahedron Symposium, Paris, France, June 23-26, 2009.
- *Towards the first total synthesis of the Euphorbiaceae diterpene Pl-3, a potent multidrug resistance (mdr) reversal agent.*
  Lentsch, C.; Siengalewicz, P.; Rinner, U. Presented at the 236th National Meeting of the American Chemical Society, Philadelphia, PA, USA, August 17-21, 2008.
- *Towards the first total synthesis of euphosalicn, a structurally unique jatrophane diterpene.*
  Rinner, U.; Lentsch, C.; Mulzer, J. Presented at the 236th National Meeting of the American Chemical Society, Philadelphia, PA, USA, August 17-21, 2008.
- *Towards the first total synthesis of the Euphorbiaceae diterpene Pl-3, a potent multidrug resistance (mdr) reversal agent*.
  Lentsch, C.; Siengalewicz, P.; Rinner, U. Presented at the 13th Latest Trends in Organic Synthesis Meeting (LTOS), St. Catharines, Ontario, Canada, August 13-16, 2008.
- *Towards the first total synthesis of euphosalicin, a structurally unique jatrophane diterpene.*
  Rinner, U.; Lentsch, C.; Mulzer, J. Presented at the 13th Latest Trends in Organic Synthesis Meeting (LTOS), St. Catharines, Ontario, Canada, August 13-16, 2008.

## Oral presentations

- *Towards the total synthesis of Pl-3 - general syntheses of highly functionalized five membered ring synthons*.
  VISOC 2011, Vienna, Austria; Mai 21, 2011.

- *Highlights on the way to the first total synthesis of Pl-3 - general syntheses of highly functionalized five membered ring synthons*.
  Fall 2010 ACS National Meeting, Boston, USA, August 22-26, 2010.
- *Diterpenes with remarkable biological properties – general syntheses of highly functionalized five membered ring synthons*.
  18. Nachwuchswissenschaftler Symposium Bioorganische Chemie 2009, Hannover, Germany; September 28-30, 2009.

# 9 APPENDIX I

Lentsch, C.; Rinner, U., General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes. *Org. Lett*. **2009**, 5326-5328. DOI: 10.1021/ol902221y.

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# General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes†

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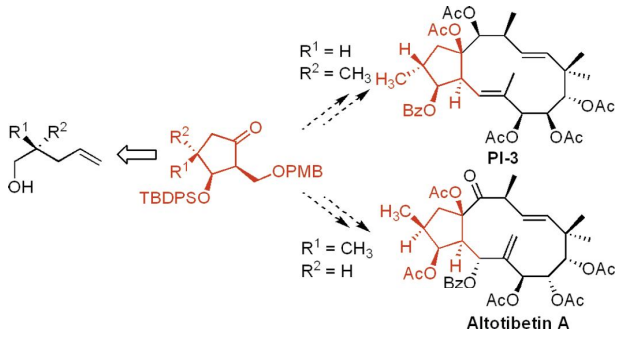
## ABSTRACT




**Short and efficient syntheses of two diastereomeric cyclopentane segments present in most jatrophane diterpenes were achieved. Key steps are a stereoselective C-2 elongation, an RCM, and a hydroboration reaction. An orthogonal protecting group methodology makes these segments useful building blocks for diterpene synthesis.**

Since the isolation of jathrophone in 1970 by Kupchan,[1] the interest in active ingredients in members of the Euphorbiaceae family is steadily increasing. The milky latices of *Euphorbia* species contain a vast number of structurally diverse diterpenes, and a considerable amount of terpenes from the tigliane, ingenane, daphnane, and jatrophane families were isolated.[2] Among the protruding biological activities of many of these natural products, antiproliferative activity[3] and multidrug resistance modulating properties[4,5] are most remarkable.

The general structure of the jatrophane skeleton, a highly functionalized *trans*-bicyclo[10.3.0]pentadecane framework, and selected examples of biologically interesting members of this class of natural products are shown in Figure 1. Despite the large number of jatrophane diterpenes isolated, the interesting synthetic challenge, and the promising biological properties, preparative work on this class of natural products can be regarded as a new field as only a few research groups are actively pursuing the synthesis of Euphorbiaceae constitutents.[6−8]

A common strucutral motif of the cyclopentane moiety of jatrophane diterpenes is the methyl group at C2 (jatrophane numbering) which can be present in either an *R* or *S* configuration as well as an oxygen functionality at C3 (Figure 1). The stereochemical pattern of this oxygen at C3 is identical in all jatrophane diterpenes with a small number

† Dedicated to Prof. Tomas Hudlicky on the occasion of his 60th birthday in recognition of his contributions to synthetic organic chemistry.

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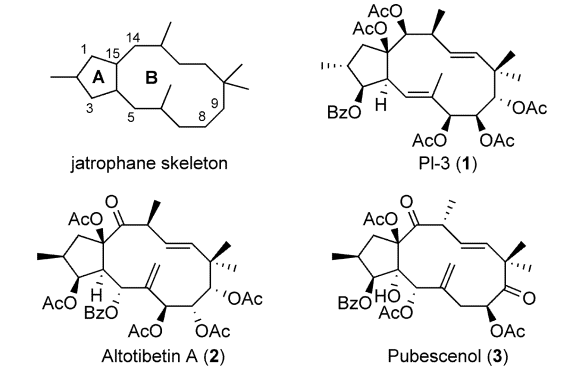



**Figure 1.** Jatrophane skeleton and selected diterpenes.

of exceptions. Although cylopentanes are common structural motifs in natural products, the syntheses of such segments are often lengthy and tedious, especially when highly functionalized.

While designing a synthesis of Pl-3 (**1**), a biologically highly active member of the jatrophane family which was first isolated by Hohmann in 2003 from *Euphorbia platyphyllos*,[9] we envisaged to devise a short and more general approach toward the five-membered ring segment to get access to various diterpenes of this family of natural products such as altotibetin A (**2**)[10] with reversed stereochemistry of the methyl group at C2. Synthetic equivalents required for preparing the corresponding natural products are shown in Figure 2.

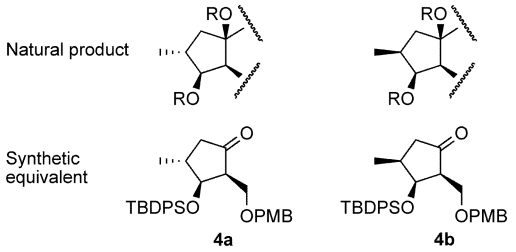
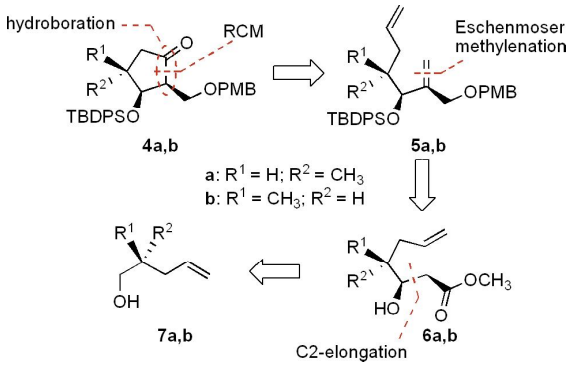



**Figure 2.** Natural product motif and synthetic equivalent.

The retrosynthetic analysis for the preparation of ketones **4a** and **4b** is outlined in Scheme 1. The key step in this sequence is a RCM reaction to establish the five-membered ring from linear precursors.

The double bond generated in this reaction can be used in a directed hydroboration/oxidation protocol to install the ketone functionality and to define the stereochemistry of the latter ring junction at C4. The precursor for the key RCM reaction was envisaged to be prepared by oxidation of alcohols **7a** and **7b**, both readily available, and stereoselective C2 elongation of the corresponding aldehydes, followed by Eschenmoser methylenation.[11]

**Scheme 1.** Retrosynthetic Analysis




Alcohols **7a** and **7b** were prepared by Myers' alkylation of the corresponding pseudoephedrine propionamide with allyl iodide and LAB reduction following a literature procedure.[12] Oxidation of alcohol **7** with IBX under standard conditions cleanly afforded aldehyde **8**. The high volatility of this material complicated the workup; however, direct distillation of the aldehyde from the reaction mixture afforded the product in good yield. The stereochemical stability of this α-chiral aldehyde, even after prolonged storage at room temperature, was demonstrated by reduction of the carbonyl group and subsequent conversion to the corresponding Mosher ester. Stereoselective C2-elongation was achieved in excellent yield using (*R*)-HYTRA (**9**) as chiral auxiliary.[13] As the determination of the diastereomeric ratio was not possible at this point, compound **10** was further transesterified to the corresponding methyl ester in quantitative yield using sodium methoxide. Interpretation of NMR spectra revealed a diastereomeric ratio of at least 10:1 for both esters **6a** and **6b**.

A crucial step in the reaction sequence was the incorporation of the exomethylene functionality. Originally, we intended to apply Eschenmoser's salt,[11] but all attempts resulted in either reisolation of the starting material when alcohol **6** was used or elimination if the

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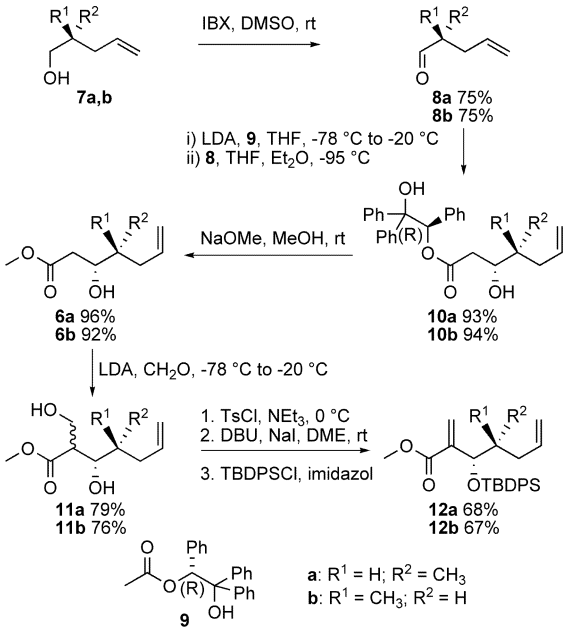
hydroxyl group was protected as the silyl ether prior to the reaction. The problem could be solved by treatment of double-deprotonated ester **6** with freshly prepared formaldehyde solution, conversion of the primary hydroxy functionality into the corresponding tosylate, and elimination effected by exposure of this material to DBU.[14] Protection of the secondary alcohol as silyl ether afforded **12** in good yield (Scheme 2). The ester functionality in

**Scheme 2.** Preparation of Ester **12**




**12** was further reduced using DIBAL-H at 0 °C and converted to PMB-ether **13** using Bundle's reagent.[15] This material served as precursor for the key RCM reaction. Exposure of this material to Grubbs' second-generation catalyst[16] cleanly afforded cyclopentene derivative **14** which was used in the hydroboration reaction with thexylborane.[17] The bulkiness of the silyl ether prevented attack of the borane reagent from the top face of the molecule and selectively affords the desired stereoisomer (**15**). Oxidation of the hydroxyl functionality concludes the synthetic route and delivers ketones **4a** and **4b** in excellent yield (Scheme 3).

The stereochemical relationship of the substituents on the cyclopentyl ring was unambiguously elucidated and proven by NOE correlation experiments. The crucial cross-couplings are illustrated in Figure 3.

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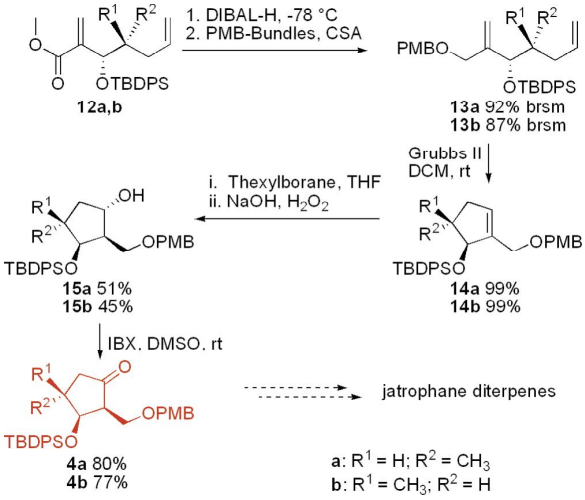
**Scheme 3.** Synthesis of Cyclopentanes **4a** and **4b**




The synthesis of highly versatile cyclopentane fragments **4a** and **4b** present in most jatrophane diterpenes has been

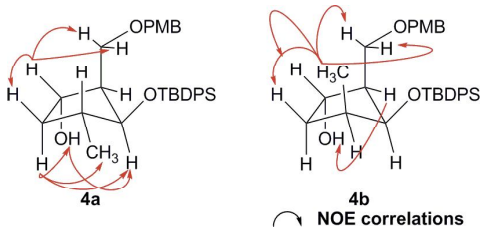



**Figure 3.** NOE correlations in cyclopentanes **15a** and **15b**.

achieved in only 12 steps and good overall yield. Further application of these highly functional five membered ring segments in the preparation of jatrophane diterpenes is currently under investigation and will be reported in due course.

**Acknowledgment.** We thank Dr. Hanspeter Kählig (University of Vienna) for assistance with NMR spectra. The Fonds zur Förderung der wissenschaftlichen Forschung (FWF) is gratefully acknowledged for financial support of this work (Project Nos. FWF-R45-N19 and FWF-P20697-N19).

**Supporting Information Available:** Experimental procedures for all new compounds and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902221Y

## Supporting Information:

# General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes

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# 1. General Methods

**Synthetic methods:** All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum) unless otherwise noted.

**Solvents and chemical purification:** Tetrahydrofuran was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, benzene and toluene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. Dimethyl sulfoxide and *N,N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. Dichloromethane was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral, activity I. Dry solvents were stored under an argon atmosphere over molecular sieves (4 Å).

Triethylamine, diethylisopropylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use.

All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using Merck silica gel 60-$F_{254}$ glass plates. The plates were developed with a mixture of hexane/ethyl acetate or toluene/ethyl acetate. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [$H_2SO_4$ (conc., 22 mL), phosphormolybdic acid (20 g), $Ce(SO_4)_2$ (0.5 g), 378 mL $H_2O$)] or silica gel impregnated with iodine.

**Chromatography:** Preparative column chromatography and flash chromatography was performed with silica gel 60 from Merck (0.040-0.063 µm, 240-400 mesh).

For HPLC separations on analytical scale module systems from Jasco (PU-980, UV-975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was Superphere Si 60 (40 µm, Merck) or Nucleosil 50 (4 µm, Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

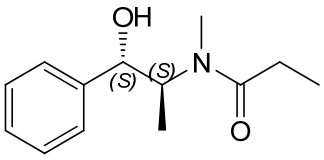
Solvents were removed by rotary evaporation at 30 °C at the appropriate pressure, unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

**Optical rotations:** Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^{T}_{D}$, concentration (g/100 mL), and solvent.

**NMR spectra:** NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CDCl_3$ signal ($^{1}H$, $\delta$ = 7.26, $^{13}C$, $\delta$ = 77.16). All $^{1}H$ and $^{13}C$ shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broadened signal). Coupling constants *J* are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY).

**IR spectra:** IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR spectrometer and are reported in wave numbers ($cm^{-1}$). All compounds were measured as a thin film on silicon single crystal plate.

## 2. Experimental part

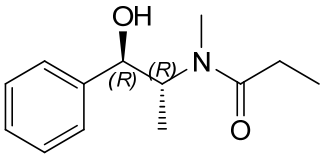



**(*S*,*S*)-Pseudoephedrine propionamide (**S1**).** A flask charged with (+)-pseudoephedrine (2.00 g, 12.10 mmol, 1.0 eq), DCM (25 mL) and triethylamine (1,47 g, 2.02 mL, 14.5 mmol, 1.2 eq) was placed in a water bath at 20 °C and propionic chloride (1.23 g, 1.16 mL, 13.3 mmol, 1.1 eq) was slowly added to the solution. The white slurry was stirred at 20 °C for 30 min before the excess of propionic chloride was quenched by the addition of water. The organic layer was separated and washed with half saturated sodium bicarbonate twice and 1 N hydrochloric acid. The organic extract was dried with magnesium sulfate and concentrated *in vacuo* to furnish a white solid. Recrystallisation from toluene afforded the desired product **S1** (2.45 g, 92%) as white crystals.

**$^{1}$H-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz) δ 7.37-7.25 (m, 5H), 4.60-4.55 (m, 1H), 4.44 (t, 1H, *J* = 7.0 Hz), 4.31(brs, 1H), 4.00* (m, 1H), 2.91* (s, 1H), 2.80 (s, 1H), 2.57-2.47* (m, 2H), 2.43-2.23 (m, 2H), 1.17-0.96 (m, 6H).

**$^{13}$C-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz) δ 176.34 (C=O), 142.62 (C), 128.84 (CH), 128.49 (CH), 127.77 (CH), 127.05 (CH), 126.53 (CH), 77.16 (C), 76.78 (CH), 75.63* (CH), 58.72* (CH), 58.40 (CH), 27.71 ($CH_2$), 26.97* ($CH_2$), 26.83 (CH), 15.39* (CH), 14.59 (CH), 9.73* (CH), 9.32 (CH).

These spectral characteristics were identical to those previously reported.[1]

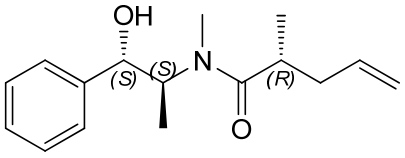



**(*R*,*R*)-Pseudoephedrine propionamide (**S2**).** Amide **S2** was prepared following the same procedure as described for amide **S1**. (-)-pseudoephedrine (5.25 g, 31.75 mmol, 1.0 eq) and propionic chloride (3.05 mL, 34.93 mmol, 1.1 eq) gave amide **S2** (6.11 g, 87%).

**$^{1}$H-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz) δ 7.37-7.25 (m, 5H), 4.60-4.55 (m, 1H), 4.44 (t, 1H, *J* = 7.0 Hz), 4.31(brs, 1H), 4.00* (m, 1H), 2.91* (s, 1H), 2.80 (s, 1H), 2.57-2.47* (m, 2H), 2.43-2.23 (m, 2H), 1.17-0.96 (m, 6H).

**$^{13}$C-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz) δ 176.34 (C=O), 142.62 (C), 128.84 (CH), 128.49 (CH), 127.77 (CH), 127.05 (CH), 126.53 (CH), 77.16 (C), 76.78 (CH), 75.63* (CH), 58.72* (CH), 58.40 (CH), 27.71 ($CH_2$), 26.97* ($CH_2$), 26.83 (CH), 15.39* (CH), 14.59 (CH), 9.73* (CH), 9.32 (CH).

These spectral characteristics were identical to those previously reported.[1]




**(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide (**S3**).** To a suspension of flame-dried lithium chloride (1.14 g, 26.8 mmol, 5.93 eq) in THF (5.5 mL) was added diisoproylamine (1.42 mL, 10.15 mmol, 2.24 eq) at -78 °C followed by *n*-butyllithium (2.5 M in hexanes, 3.90 mL, 9.68 mmol, 2.14 eq). The suspension was stirred for 15 min at 0 °C then cooled to -78 °C. A solution of amide **S1** (1.00 g, 4.52 mmol, 1.00 eq) in tetrahydrofurane (13.4 mL) was added via cannula over 10 min and the solution was vigorously stirred for 60 min. After 15 min at 0 °C, 10 min at room temperature, and recooling to -78 °C, allyl iodide (1.14 g, 6.78 mmol, 1.5 eq) was added neat and the reaction mixture was stirred for 1 h at -78 °C and an additional 60 min at 0 °C. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (10 mL) and saturated sodium dithiosulfate solution (1 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate twice. The combined organic solution was washed with brine, and dried over magnesium sulfate. Concentration under reduced pressure provided known amide **S3** (1.30 g, quant.) as a viscous yellow oil, which was used without further purification.

**$R_f$**= 0.22 (hexane/ethyl acetate = 2/1)

**Optical Rotation:** $[\alpha]^{20}_{D}$ (c 1.50, $CHCl_3$) = +76.1.

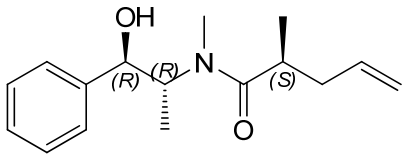
**$^1$H-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz) δ 7.38-7.24 (m, 5H), 5.84-5.64 (m, 1H), 5.13-4.98 (m, 2H), 4.63-4.57 (m, 1H), 4.44 (brs, 1H), 2.91* (s, 3H), 2.86 (s, 3H), 2.68* (1H, m), 2.51* (1H, m), 2.35 (1H, m), 2.17* (m, 1H), 2.09 (m, 1H), 1.13-1.08 (m, 6H).

**$^{13}$C-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz) δ 178.49 (C=O), 142.64 (C), 136.82 (CH), 136.15 (CH), 128.88 (CH), 128.58 (CH), 128.47 (CH), 127.74 (CH), 127.04 (CH), 126.51 (CH), 116.64 (C), 77.16 (C), 76.64 (CH), 75.66* (CH), 38.18 ($CH_2$), 36.71 (CH), 35.94* (CH), 17.72* (CH), 17.13 (CH), 14.62 (CH).

**IR** (thin film) ν 3390, 3133, 2975, 2360, 1617, 1537, 1452, 1427, 1408, 1171, 1050, 960, 914, 871, 702, 672 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{16}H_{24}O_2N$ $[M+H]^+$, 262.1807; found, 262.1808 +/- 5ppm.

These spectral characteristics were identical to those previously reported.[1]




**(*S*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide (**S4**).** Amide **S4** was prepared as described for amide **S3**. Pseudoephedrine propionamide **S2** (10.00 g, 45.20 mmol, 1.0 eq) gave amide **S4** (11.95 g, quant.) as a viscous yellow oil, which was used without further purification.

**$R_f$**= 0.22 (hexane/ethyl acetate = 2/1)

**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = -74.9.

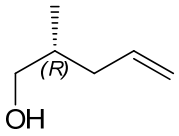
**$^1$H-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz) δ 7.38-7.24 (m, 5H), 5.84-5.64 (m, 1H), 5.13-4.98 (m, 2H), 4.63-4.57 (m, 1H), 4.44 (brs, 1H), 2.91* (s, 3H), 2.86 (s, 3H), 2.68* (1H, m), 2.51* (1H, m), 2.35 (1H, m), 2.17* (m, 1H), 2.09 (m, 1H), 1.13-1.08 (m, 6H).

**$^{13}$C-NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz) δ 178.49 (C=O), 142.64 (C), 136.82 (CH), 136.15 (CH), 128.88 (CH), 128.58 (CH), 128.47 (CH), 127.74 (CH), 127.04 (CH), 126.51 (CH), 116.64 (C), 77.16 (C), 76.64 (CH), 75.66* (CH), 38.18 ($CH_2$), 36.71 (CH), 35.94* (CH), 17.72* (CH), 17.13 (CH), 14.62 (CH).

**IR** (thin film) ν 3386, 3064, 2974, 2934, 1617, 1452, 1408, 1374, 1303, 1111, 1083, 1050, 1027, 995, 914, 837, 757, 702, 641, 422, 405 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{16}H_{24}O_2N$ $[M+H]^+$, 262.1807; found, 262.1809 +/- 5ppm.

These spectral characteristics were identical to those previously reported.[1]




**(*R*)-2-Methylpent-4-en-1-ol (**7a**).** A solution of *n*–butyllithium in hexanes (2.5 M, 1.84 mL, 4.2 mmol, 4.0 eq) was added to a solution of freshly distilled diisopropylamine in tetrahydrofurane at -78 °C. The resulting solution was stirred for 10 min at -78 °C then warmed to 0 °C and kept at this temperature for 20 min. The borane-ammonia complex (0.166 g, 4.66 mmol, 4.2 eq) was added in one portion and the suspension was stirred for 25 min at 0 °C before it was warmed to ambient temperature. After 15 min the suspension was cooled to 0 °C again. A solution of amide **S3** (0.30 g, 1.15 mmol, 1.0 eq) in tetrahydrofurane (0.5 mL) was added with a syringe. The reaction mixture was warmed to 20 °C and kept for 4 h at this temperature. Excess hydride was quenched by careful addition of 3 N hydrochloric acid (14 mL) at 0 °C. The mixture was stirred for 90 min at 0 °C and then extracted with four portions of diethyl ether (4 x 10 mL). The combined organic extract was sequentially washed with 3 N hydrochloric acid (10 mL), 2 N potassium hydroxide (10 mL), brine and was dried over magnesium sulfate. Concentration in *vacuo* (40 °C; 180 mbar) afforded alcohol **7a** (92 mg, 86% yield) as a clear liquid.

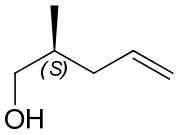
$\mathbf{R_f}$= 0.51 (hexane/ethyl acetate = 2/1)

**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +2.5.

**δ $^1$H-NMR** ($CDCl_3$, 400 MHz) δ 5.87-5.76 (m, 1H), 5.07-5.01 (m, 2H), 3.55-3.44 (m, 2H), 2.21-2.14 (m, 1H), 1.99-1.92 (m, 1H), 1.80-1.68 (m, 1H), 1.31 (d, 1H, *J* = 4.9 Hz), 0.93 (d, 3H, *J* = 6.8 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) 137.12 (CH), 116.23 ($CH_2$), 77.16 (C), 68.09 ($CH_2$), 38.01 ($CH_2$), 35.78 (CH), 16.52 (CH).

**IR** (thin film) ν 3210, 2554, 2381, 1836, 1458, 1253, 1195, 870, 701, 671, 419, 414, 407 $cm^{-1}$.




**(*S*)-2-Methylpent-4-en-1-ol (**7b**).** Alcohol **7b** was prepared following the same procedure as described for alcohol **7a**. Amide **S4** (11.36 g, 43.46 mmol, 1 eq) gave alcohol **7b** (4.00 g, 92%).

**$R_f$**= 0.51 (hexane/ethyl acetate = 2/1)

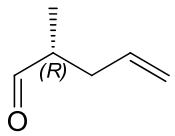
**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = -2.5.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 5.87-5.76 (m, 1H), 5.07-5.01 (m, 2H), 3.55-3.44 (m, 2H), 2.21-2.14 (m, 1H), 1.99-1.92 (m, 1H), 1.80-1.68 (m, 1H), 1.31 (d, 1H, *J* = 4.9 Hz), 0.93 (d, 3H, *J* = 6.8 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) 137.12 (CH), 116.23 ($CH_2$), 77.16 (C), 68.09 ($CH_2$), 38.01 ($CH_2$), 35.78 (CH), 16.52 (CH).

**IR** (thin film) ν 3212, 2556, 2370, 1843, 1457, 1253, 1195, 870, 701, 671, 423, 419, 407 $cm^{-1}$.

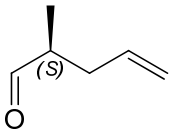
These spectral characteristics were identical to those previously reported.[2]




**(*R*)-2-Methylpent-4-enal (**8a**).** Alcohol **7a** (2.00 g, 20 mmol, 1.0 eq) was added neat to a solution of IBX (8.4 g, 30 mmol, 1.5 eq) in dimethyl sulfoxide (34 mL) at ambient temperature. The reaction was monitored by thin layer chromatography (hexane/ethyl acetate = 2/1; detection by UV and $KMnO_4$). After consumption of the starting material the aldehyde was distilled (70-85 °C oil bath temperature; 50 mbar) over a simple distillation bridge into a cooled (-78 °C) Schlenk-flask. Aldehyde **8a** (1.47 g, 75%) was used directly after distillation.

**$R_f$**= 0.36 (hexane/ethyl acetate = 2/1)

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 9.66 (d, 1H, *J* = 1.4 Hz), 5.81-5.71 (m, 1H), 5.12-5.06 (m, 2H), 2.51-2.40 (m, 1H), 1.11 (d, 3H, *J* = 7.0 Hz).

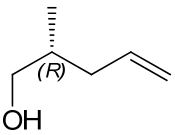



**(*S*)-2-Methylpent-4-enal (**8b**).** Aldehyde **8b** was prepared following the same procedure as described for aldehyde **8a**. Alcohol **7b** (4.00 g, 39.93 mmol, 1 eq) gave aldehyde **8b** (2.97 g, 75%).

**$R_f$**= 0.36 (hexane/ethyl acetate = 2/1)

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 9.66 (d, 1H, *J* = 1.4 Hz), 5.81-5.71 (m, 1H), 5.12-5.06 (m, 2H), 2.51-2.40 (m, 1H), 1.11 (d, 3H, *J* = 7.0 Hz).

These spectral characteristics were identical to those reported.[3]

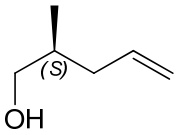



**(*R*)-2-Methylpent-4-en-1-ol (**7a-B**).** Aldehyde **8a** (0.1 g, 1mmol, 1 eq) was dissolved in dichloromethane (0.4 mL) and cooled to -78 °C. DIBALH (1.5 M in toluene; 1.0 mL, 1.5 mmol, 1.5 eq) was added slowly and the solution was allowed to warm to rt over 2 h. After stirring at rt for another hour the solution was cooled to 0 °C and excess hydride was quenched by slow addition of a saturated aqueous solution of ammonium chloride (0.5 mL). The resulting mixture was stirred with Na/K – tartrate for 12 h and extracted with dichloromethane three times. The combined organic layer was dried over magnesium sulfate, filtered and reduced in *vacuo* (40 °C; 180 mbar). Purification by flash chromatography (pentane/diethyl ether = 10/1) afforded alcohol **7a-B** (0.080 g, 80%).

**$R_f$**= 0.51 (hexane/ethyl acetate = 2/1)

**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +2.5.

**δ $^1$H-NMR** ($CDCl_3$, 400 MHz) δ 5.87-5.76 (m, 1H), 5.07-5.01 (m, 2H), 3.55-3.44 (m, 2H), 2.21-2.14 (m, 1H), 1.99-1.92 (m, 1H), 1.80-1.68 (m, 1H), 1.31 (d, 1H, *J* = 4.9 Hz), 0.93 (d, 3H, *J* = 6.8 Hz).

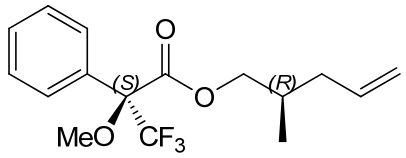



**(*S*)-2-Methylpent-4-en-1-ol (**7b-B**).** Alcohol **7b-B** was prepared following the same procedure as described for alcohol **7a-B**. Aldehyde **8b-B** (0.1 g, 1mmol, 1 eq) gave alcohol **7b-B** (0.083 g, 83%).

**$R_f$**= 0.51 (hexane/ethyl acetate = 2/1)

**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = -2.5.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 5.87-5.76 (m, 1H), 5.07-5.01 (m, 2H), 3.55-3.44 (m, 2H), 2.21-2.14 (m, 1H), 1.99-1.92 (m, 1H), 1.80-1.68 (m, 1H), 1.31 (d, 1H, *J* = 4.9 Hz), 0.93 (d, 3H, *J* = 6.8 Hz).




**(*S*)-((*R*)-2-Methylpent-4-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**S5**).** Alcohol **7a** (6.4 mg, 0.06 mmol, 1.0 eq) was dissolved in DIPEA (34 µL, 0.19 mmol, 3.0 eq) and (*R*)-(−)-MTPA-Cl[4] (14 µL, 0.076 mmol, 1.2 eq) was added. The reaction mixture was stirred for 6 hours. TLC did not show total consumption of starting material, so an additional amount of DIPEA (17 µL, 0.095 mmol, 1.5 eq) and (*R*)-(−)-MTPA-Cl (7 µL, 0.038 mmol, 0.6 eq) was added. After stirring for another 12 h TLC showed total consumption of the starting material. The cloudy solution was diluted with DCM (5 mL), washed with water twice and the organic layer was dried over magnesium sulfate. After filtration over a small plug of silica the solvent was removed in *vacuo*. The yield was not determined. The residue was used directly for NMR studies.

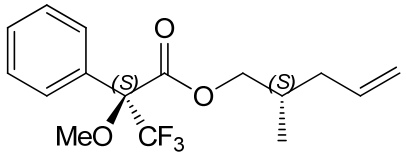
The same procedure was carried out on alcohol **7a-B**.

**$R_f$**= 0.80 (hexane/ethyl acetate = 5/1)

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.53-7.51 (m, 2H), 7.41-7.40 (m, 3H), 5.78-5.67 (m, 1H), 5.03-4.97 (m, 2H), 4.21-4.13 (m, 2H), 3.55 (d, 3H, *J* = 1.1 Hz), 2.14-2.06 (m, 1H), 1.99-1.91 (m, 2H), 0.94 (d, 3H, *J* = 6.3 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 135.74 (CH), 132.52 (C), 129.75 (CH), 128.56 (CH), 127.53 (CH), 127.52 (CH), 117.12 ($CH_2$), 77.16 (C), 70.60 ($CH_2$), 55.56 (CH), 37.56 ($CH_2$), 32.46 (CH), 16.64 (CH).

**$^{19}$F-NMR** ($CDCl_3$, 565 MHz) δ -72.8.




**(*S*)-((*S*)-2-Methylpent-4-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**S6**).** Mosher ester **S6** was prepared following the same procedure as described for Mosher ester **S5**.

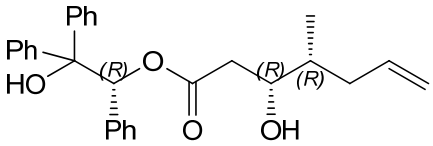
The same procedure was carried out on alcohol **7b-B**.

**$R_f$**= 0.80 (hexane/ethyl acetate = 5/1)

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.58-7.49 (m, 2H), 7.46-7.36 (m, 3H), 5.79-5.69 (m, 1H), 5.05-4.97 (m, 2H), 4.26 (dd, 1H, *J* = 10.7, 4.9 Hz), 4.10 (dd, 1H, *J* = 10.7, 5.5 Hz), 3.56 (s, 3H), 2.14-2.08 (m, 1H), 2.00-1.92 (m, 2H), 0.94 (d, 3H, *J* = 6.4 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 166.75 (C=O), 135.72 (CH), 132.51 (C), 129.74 (CH), 128.54 (CH), 127.52 (CH), 123.47 (q, $CF_3$), 117.09 ($CH_2$), 77.16 (C), 70.58 ($CH_2$), 55.53 (CH), 37.57 ($CH_2$), 32.42 (CH), 16.58 (CH).

**$^{19}$F-NMR** ($CDCl_3$, 565 MHz) δ -71.97.




**(3*R*,4*R*)-((*R*)-2-Hydroxy-1,2,2-triphenylethyl) 3-hydroxy-4-methylhept-6-enoate (**10a**).** A two necked, round bottomed flask was charged with dry tetrahydrofuran (19 mL), cooled to -78 °C and diisopropylamine (3.45 mL, 24.64 mmol, 2.69 eq) was injected via syringe. The mixture was stirred and treated with *n*-butyllithium in hexanes (2.5 M, 9.67 mL, 24.18 mmol, 2.64 eq). After removal of the dry ice/aceton bath stirring was continued for 20 min at 0 °C. The solution was recooled to -78 °C and added to a suspension of (*R*)–HYTRA (3.04g, 9.16 mmol, 1.0 eq) in tetrahydrofuran (15 mL). The yellow suspension was

warmed to -20 °C and kept at this temperature for 30 min to facilitate double deprotonation before the clear red solution was cooled to -95 °C (methanol/liquid nitrogen). Aldehyde **8a** (900 mg, 9.16 mmol, 1.0 eq) in diethylether (4 mL) was added very slowly (30 min) with a syringe pump and was stirred for 90 min at -95 °C. Saturated ammonium chloride solution (20 mL) was added and the suspension was allowed to warm to room temperature. The organic layer was separated and washed with water twice. The aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water, dried with magnesium sulfate and evaporated to dryness. Purification by flash chromatography (toluene/ethyl acetate = 19/1) gave ester **10a** (3.67 g, 93%). The *de* was determined at a later stage of the synthesis and the stereochemistry was confirmed using NOE experiments at cyclic compound **15a**.

**$R_f$**= 0.24 (hexane/ethyl acetate = 5/1)

**$R_f$**= 0.28 (toluene/ethyl acetate = 19/1)

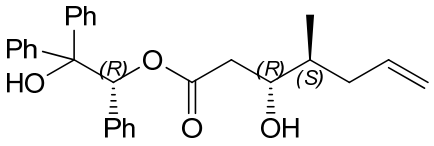
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +154.5.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.60-7.57 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.28 (m, 1H), 7.21-7.07 (m, 10H), 6.74 (s, 1H), 5.77-5.66 (m, 1H), 5.02-4.98 (m, 2H), 3.81-3.76 (m, 1H), 2.83 (s, 1H), 2.46-2.28 (m, 2H), 2.20-2.13 (m, 2H), 1.91-1.83 (m, 1H), 1.51-1.44 (m, 1H), 0.82 (d, 3H, *J* = 6.9 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 171.81 (C=O), 144.71 (C), 142.65 (C), 136.95 (CH), 135.62 (C), 128.53 (CH), 128.21 (CH), 128.00 (CH), 127.72 (CH), 127.64 (CH), 127.59 (CH), 127.29 (CH), 126.38 (CH), 126.33 (CH), 116.44 ($CH_2$), 80.42 (C), 79.09 (CH), 77.16 (C), 70.66 (CH), 39.55 ($CH_2$), 37.76 (CH), 37.70 ($CH_2$), 13.77 (CH).

**IR** (thin film) v 3503, 2964, 1718, 1495, 1448, 1155, 1065, 1033, 989, 890, 751, 695, 668, 644, 620, 405 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{28}H_{30}NaO_4$ $[M+Na]^+$, 453.2042; found, 453.2043 +/- 5ppm.



**(3*R*,4*S*)-((*R*)-2-Hydroxy-1,2,2-triphenylethyl) 3-hydroxy-4-methylhept-6-enoate (**10b**).** Ester **10b** was prepared following the same procedure as described for ester **10a**. (*R*) – HYTRA (8.67 g, 26.09 mmol, 1.0 eq) and aldehyde **8b** (2.87 g, 28.7 mmol, 1.1 eq) gave ester **10b** (10.56 g, 94%). The *de* was determined at a later stage of the synthesis and the stereochemistry was confirmed using NOE experiments at cyclic compound **15b**.

**$R_f$**= 0.24 (hexane/ethyl acetate = 5/1)

**$R_f$**= 0.28 (toluene/ethyl acetate = 19/1)

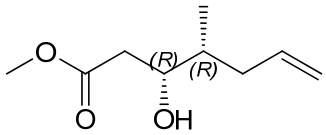
**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +157.6.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.60-7.57 (m, 2H), 7.40-7.36 (m, 2H), 7.31-7.27 (m, 1H), 7.21-7.12 (m, 8H), 7.08-7.06 (m, 2H), 6.74 (s, 1H), 5.76-5.66 (m, 1H), 5.02-4.95 (m, 2H), 3.81-3.63 (m, 1H), 2.83 (s, 1H), 2.40-2.36 (m, 2H), 2.20-2.14 (m, 1H), 1.91-1.83 (m, 1H), 1.58-1.50 (m, 1H), 0.81 (3H, d, *J* = 6.9 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 171.99 (C=O), 144.71 (C), 142.64 (C), 136.89 (CH), 135.62 (C), 128.54 (CH), 128.53 (CH), 128.23 (CH), 128.01 (CH), 127.73 (CH), 127.61 (CH), 127.30 (CH), 126.39 (CH), 126.34 (CH), 116.43 ($CH_2$), 80.42 (C), 79.06 (CH), 77.16 (C), 71.59 (CH), 38.79 ($CH_2$), 37.98 (CH), 36.96 ($CH_2$), 15.17 (CH).

**IR** (thin film) ν 3523, 2965, 1718, 1496, 1448, 1340, 1156, 1066, 1033, 989, 914, 752, 672, 668, 620 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{28}H_{30}NaO_4$ $[M+Na]^+$, 453.2042; found, 453.2047 +/- 5ppm.




**(3*R*,4*R*)-Methyl 3-hydroxy-4-methylhept-6-enoate (**6a**).** To a solution of ester **10a** (3.10 g, 7.48 mmol, 1.0 eq) in methanol (20 mL) was added sodium methoxide (0.24 g, 4.48 mmol, 0.6 eq) at 0 °C and the solution was stirred at ambient temperature for 2 h before the mixture was heated to 45 °C until total consumption of starting material (8 h). The resulting mixture was treated with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered and concentrated in *vacuo*. The crude product was suspended in hexane and stirred for 3

h. The white solid was filtered off and the residue was purified by flash chromatography (toluene/ethyl acetate = 19/1) to afford the desired product **10a** (1.24 g, 96%) containing small amounts of impurities. Further purification was performed by HPLC. At this step the *de* for the stereoselective C-2 elongation could be determined being 10 to 1.

**$R_f$**= 0.16 (toluene/ethyl acetate = 19/1)

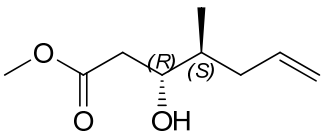
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +24.6.

**$^1$H-NMR** (10:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 5.84-5.73 (m, 1H), 5.08-5.00 (m, 2H), 4.01-3.96 (m, 1H), 3.88-3.82* (m, 1H), 3.71 (s, 3H), 2.91* (d, 1H, *J* = 4.1 Hz), 2.71 (d, 1H, *J* = 3.9 Hz), 2.55-2.41 (m, 2H), 2.33-2.23 (m, 1H), 1.99-1.90 (m, 1H), 1.72-1.59 (m, 1H), 0.92 (3H, d, *J* = 6.9 Hz), 0.89* (1H, d, *J* = 6.8 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$) δ 173.88 (C=O), 137.09 (CH), 116.45 ($CH_2$), 77.16 (C), 71.61* (CH), 70.71 (CH), 51.93 (CH), 38.80 ($CH_2$), 38.16* (CH), 38.11* ($CH_2$), 38.00 (CH), 37.64 ($CH_2$), 37.04* ($CH_2$), 15.18* (CH), 14.01 (CH).

**IR** (thin film) ν 3502, 3177, 2964, 2359, 1734, 1653, 1640, 1559, 1437, 1392, 1174, 1077, 992, 947, 913, 671, 422, 418, 415 $cm^{-1}$.

**HRMS** (EI) calcd for $C_9H_{14}O_2$ $[M-H_2O]^+$, 154.0994; found, 154.0990 +/- 5ppm.




**(3*R*,4*S*)-Methyl 3-hydroxy-4-methylhept-6-enoate (**10b**).** Methyl ester **6b** was prepared following the same procedure as described for methyl ester **6a**. Ester **10b** (11.97 g, 28.89 mmol, 1 eq) gave methyl ester **6b** (4.6 g, 92%). At this step the de for the stereoselective C-2 elongation could be determined being 10 to 1.

**$R_f$**= 0.16 (toluene/ethyl acetate = 19/1)

**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +35.7.

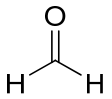
**$^1$H-NMR** (10:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 5.84-5.74 (m, 1H), 5.07-5.00 (m, 2H), 4.00-3.95* (m, 1H), 3.89-3.82 (m, 1H), 3.71 (s, 3H), 2.92 (d, 1H, *J* = 4.1 Hz), 2.90* (d, 1H, *J* = 4.3 Hz), 2.53 (dd, 1H, *J* = 16.3, 2.8 Hz), 2.42 (dd, 1H, *J* = 16.3,

9.6 Hz), 2.32-2.26 (m, 1H), 1.99-1.92 (m, 1H), 1.72-1.64 (m, 1H), 0.92* (1H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.8 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$) δ 173.96 (C=O), 137.09* (CH), 137.00 (CH), 116.45 ($CH_2$), 77.16 (C), 71.61 (CH), 70.71* (CH), 51.93 (CH), 38.81* (C), 38.16 (CH), 38.11 ($CH_2$), 38.00* (CH), 37.64* ($CH_2$), 37.03 (C), 15.17 (CH), 14.00* (CH).

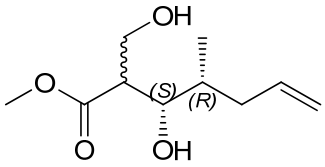
**IR** (thin film) ν 3468, 3076, 2959, 1738, 1732, 1640, 1439, 1289, 1173, 1056, 993, 913, 643, 483, 421, 406 $cm^{-1}$.

**HRMS** (EI) calcd for $C_9H_{14}O_2$ $[M-H_2O]^+$, 154.0994; found, 154.0991 +/- 5ppm.



**Formaldehyde (monomeric anhydrous solution).** Paraformaldehyde was cracked at 140 °C. The gaseous formaldehyde was passed through a thick cannula into diethyl ether or THF at -78 °C by a strong argon stream. The molarity of the solution was determined by NMR.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 9.73 (s, 2H).




**(3*S*,4*R*)-Methyl 3-hydroxy-2-(hydroxymethyl)-4-methylhept-6-enoate (**11a**).** LDA was prepared by adding *n*-BuLi (2.5M in hexanes; 9.71 mL, 24.3 mmol, 2.2 eq) to a solution of DIPA (3.5 mL, 24.73 mmol, 2.24 eq) in THF (25 mL) at -78 °C. A solution of methyl ester **6a** (1.9 g, 11.04 mmol, 1 eq) was cooled to -78 ° before the previously prepared LDA was added at -78 °C and the mixture was stirred at -20 °C for 1.5 h to accomplish double deprotonation of methyl ester **6a**. The solution was cooled to -40 °C and formaldehyde (0.5 M in THF; 88 mL, 44 mmol, 4.0 eq) was added. After stirring for one hour at -40 °C the solution was kept at -30 °C for another hour before the reaction was quenched by addition of a saturated solution of aqueous ammonium hydrogencarbonate. The reaction mixture was extracted four times with ethyl acetate, washed with brine, dried over magnesium sulfate and the solvent was removed *in vacuo*. The yellow viscous oil was purified by flash chromatography to yield diol **11a** (1.76 g, 79%).

$\mathbf{R_f}$= 0.24 (hexane/ethyl acetate = 1/1)

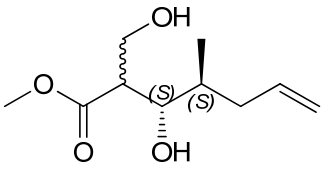
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +0.8.

**$^1$H-NMR** (~4:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 5.83-5.72 (m, 1H), 5.08-5.02 (m, 2H), 4.06-3.86 (m, 2H), 3.82-3.72 (m, 4H), 2.83-2.73 (m, 1H), 2.70 (1H, d, *J* = 7.3 Hz), 2.52* (1H, d, *J* = 5.7 Hz), 2.38 (1H, t, *J* = 6.1 Hz), 2.25-2.13 (m, 1H), 2.03-1.96 (m, 1H), 1.80-1.65 (m, 1H), 1.00* (1H, d, *J* = 6.8 Hz), 0.96 (2H, d, *J* = 6.8 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$, 100MHz) δ 174.80 (C=O), 136.50 (CH), 116.86* ($CH_2$), 116.78 ($CH_2$), 77.16 (C), 74.61* (CH), 74.32 (CH), 62.89 ($CH_2$), 61.90* ($CH_2$), 52.18 (CH), 49.96 (CH), 49.73* (CH), 38.35* ($CH_2$), 38.29 ($CH_2$), 36.44 (CH), 36.25* (CH), 14.10 (CH), 13.90* (CH).

**IR** (thin film) ν 3434, 3103, 2957, 2359, 1718, 1652, 1639, 1557, 1437, 1403, 1172, 1142,1040, 937, 913, 671, 419, 404 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{10}H_{16}O_3$ $[M-H_2O]^+$, 184.1099; found, 184.1093 +/- 5ppm.




**(3*S*,4*S*)-Methyl 3-hydroxy-2-(hydroxymethyl)-4-methylhept-6-enoate (**11b**).** Diol **11b** was prepared following the same procedure as described for diol **11a**. Methyl ester **6b** (1.47 g, 8.57 mmol, 1 eq) gave diol **11b** (1.31 g, 76%).

$\mathbf{R_f}$= 0.24 (hexane/ethyl acetate = 1/1)

**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +6.1.

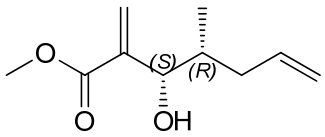
**$^1$H-NMR** (~3:2 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 5.85-5.73 (m, 1H), 5.12-4.99 (m, 2H), 4.03-3.93 (m,2H), 3.90-3.85* (m,1H), 3.76* (s, 3H), 3.75 (s, 3H), 3.57 (td, 1H, *J* = 8.3, 3.0 Hz), 3.06 (d, 1H, *J* = 8.4 Hz), 2.84 (ddd, 1H, *J* = 10.6, 5.3, 3.0 Hz), 2.72* (dt, 1H, *J* = 4.1, 4.1 Hz), 2.53-2.42 (m, 1H), 2.00-1.91 (m, 1H), 1.78-1.67 (m, 1H), 0.88 (3H, d, *J* = 6.8 Hz), 0.87* (3H, d, *J* = 6.8 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$, 100 MHz) δ 174.80* (C=O), 174.38 (C=O), 136.88* (CH), 136.78 (CH), 116.70 ($CH_2$), 77.16 (C), 76.16 (CH), 76.03* (CH), 63.66 ($CH_2$),

60.77* ($CH_2$), 52.25* (CH), 52.08 (CH), 48.92 (CH), 48.58* (CH), 37.41 (CH), 37.04 ($CH_2$), 36.88* ($CH_2$), 36.49* (CH), 15.96 (CH), 15.82* (CH).

**IR** (thin film) ν 3435, 3075, 2957, 1734, 1718, 1639, 1437, 1379, 1198, 1170, 1042, 912, 586, 422, 416, 405 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{10}H_{16}O_3$ $[M-H_2O]^+$, 184.1099; found, 184.1094 +/- 5ppm.




**(3*S*,4*R*)-Methyl 3-hydroxy-4-methyl-2-methylenehept-6-enoate (**S7**).** To a solution of **11a** (0.74 g, 3.63 mmol, 1.0 eq) in DCM (15 mL) was added triethylamine (0.61 mL, 4.36 mmol, 1.2 eq) and *p*-toluene sulfonic acid chloride (0.721 g, 3.78 mmol, 1.04 eq) at 0 °C. After stirring for 15 min a spatula of DMAP was added and the resulting mixture was stirred at 0 °C over night. The reaction was quenched at 0 °C by addition of a saturated ammonium chloride solution. The layers were separated and the aqueous phase was extracted five times with ethyl acetate. The combined organic layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting tosylate was provided as yellow oil (1.21 g, 94%) and used without further purification. The tosylate (1.21 g, 3.39 mmol, 1.0 eq) was dissolved in DME (18 mL) and sodium iodide (1.52 g, 10.18 mmol, 3.0 eq) was added. By addition of DBU (1.01 mL, 6.78 mmol, 2.0 eq) a white precipitate formed immediately. The suspension was stirred for another 30 min at rt to turn the reaction to completion. After dilution with diethyl ether (10 mL) water was added and the mixture was stirred for another 10 min. The layers were separated and the aqueous phase was extracted with diethyl ether three times. The combined organic layer was washed with brine, dried over magnesium sulfate and reduced *in vacuo*. The resulting oil was purified by flash chromatography (hexane/ethyl acetate = 3/1) to yield α,β-unsaturated ester **S7** (0.568 g, 91%; 86% over two steps).

**$R_f$**= 0.51 (hexane/ethyl acetate = 3/1)

**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = -7.2.

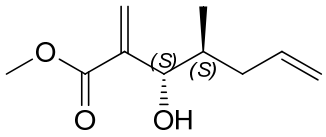
**$^1$H-NMR** (10:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 6.29 (dd, 1H, *J* = 1.1, 0.6 Hz), 6.26* (d, 1H, *J* = 1.2 Hz), 5.86-5.76 (m, 2H), 5.08-5.01 (m, 2H), 4.36 (t, 1H, *J* = 5.8 Hz), 4.09* (t, 1H, *J* = 7.9 Hz), 3.78* (s, 3H), 3.77 (s, 3H), 2.63* (d, 1H, *J* = 8.1 Hz), 2.23

(d, 1H, *J* = 6.8 Hz) 2.21-2.16 (m, 1H), 2.00-1.83 (m, 2H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.82* (d, 3H, *J* = 6.6 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$, 100 MHz) δ 167.09 (C=O), 141.65 (C), 137.02 (CH), 126.73* ($CH_2$), 126.00 ($CH_2$), 116.46 ($CH_2$), 77.16 (C), 74.63 (CH), 51.99 (CH), 38.53 ($CH_2$), 37.72* (CH), 36.95 (CH), 36.55* ($CH_2$), 16.42* (CH), 13.55 (CH).

**IR** (thin film) ν 3503, 3173, 2970, 2360, 1718, 1660, 1639, 1573, 1437, 1422, 1288, 1231, 1195, 1182, 1161, 1134, 1111, 1067, 994, 934, 912, 866, 821, 789 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{10}H_{14}O_2$ $[M-H_2O]^+$, 166.0994; found, 166.0987 +/- 5ppm.




**(3*S*,4*S*)-Methyl 3-hydroxy-4-methyl-2-methylenehept-6-enoate (**S8**).** α,β-Unsaturated ester **S8** was prepared following the same procedure as described for α,β-unsaturated ester **S7**. Diol **11b** (1.8 g, 8.90 mmol, 1.0 eq) gave α,β-unsaturated ester **S8** (0.57 g, 76% over two steps).

**$R_f$**= 0.48 (hexane/ethyl acetate = 3/1)

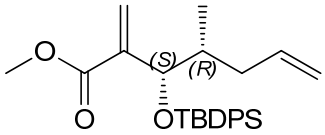
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = -6.9.

**$^1$H-NMR** (10:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, $CDCl_3$, 400 MHz) δ 6.29* (brs, 1H), 6.26 (d, 1H, *J* = 1.2 Hz), 5.85-5.75 (m, 2H), 5.07-5.01 (m, 2H), 4.36* (t, 1H, *J* = 5.8 Hz), 4.09 (t, 1H, *J* = 7.6 Hz), 3.78 (s, 3H), 3.77 (s, 3H), 2.63 ( d, 1H, *J* = 8.4 Hz), 2.47-2.40 (m, 1H), 2.24* (d, 1H, *J* = 6.8 Hz), 2.00-1.83 (m, 2H), 0.88* (d, 3H, *J* = 6.6 Hz), 0.82 (d, 3H, *J* = 6.6 Hz).

**$^{13}$C-NMR** (asterisk denotes minor diastereomer peaks, $CDCl_3$, 100 MHz) δ 167.28 (C=O), 141.08 (C), 137.13 (CH), 126.72 (C), 125.99* ($CH_2$), 116.46 ($CH_2$), 77.25 (CH), 77.16 (C), 52.05 (CH), 38.53* ($CH_2$), 37.72 (CH), 36.94* (CH), 36.54 ($CH_2$), 16.41 (CH), 13.54* (CH).

**IR** (thin film) ν 3502, 3143, 2963, 2360, 1718, 1653, 1639, 1559, 1440, 1423, 1285, 1232, 1161, 1134, 1116, 1065, 1040, 937, 912, 795 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{10}H_{14}O_2$ $[M-H_2O]^+$, 166.0994; found, 166.0986 +/- 5ppm.




**(3*S*,4*R*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-4-methyl-2-methylenehept-6-enoate (**12a**).** A solution of **S7** (0.834 g, 4.56 mmol, 1.0 eq) in DMF (4.5 mL), imidazole (0.931 g, 13.67 mmol, 3 eq) and TBDPSCl (1.77 mL, 6.83 mmol, 1.2 eq) was stirred at room temperature. After 24 h TLC did not show complete consumption of the starting material, so an additional amount of imidazole (0.931 g, 13.67 mmol, 3 eq) and TBDPSCl (1.77 mL, 6.83 mmol, 1.2 eq) was added. The solution was stirred for another 48 h before it was poured into saturated ammonium chloride solution. The aqueous phase was extracted with DCM three times, the organic layer was washed with water, dried over magnesium sulfate, filtered and reduced *in vacuo*. The crude product was purified by flash chromatography (hexane/ethyl acetate = 9/1) to yield silyl ether **12a** (1.52 g, 79%) as a colorless oil.

**$R_f$**= 0.87 (hexane/ethyl acetate = 5/1)

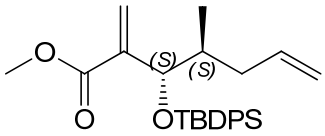
**Optical Rotation:** $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +12.4.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.68-7.59 (m, 4H), 7.44-7.31 (m, 6H), 6.22 (d, 1H, *J* = 1.6 Hz), 5.90 (t, 1H, *J* = 1.4 Hz), 5.67-5.57 (m, 1H), 4.92-4.83 (m, 2H), 4.77 (d, 1H, *J* = 2.5 Hz), 3.62 (s, 3H), 2.13-2.06 (m, 1H), 1.75-1.62 (m, 2H), 1.08 (s, 9H), 0.77 (d, 3H, *J* = 6.6 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100MHz) δ 166.74 (C=O), 142.07 (C), 137.79 (CH), 136.23 (CH), 136.20 (CH), 134.10 (C), 134.04 (C), 129.76 (CH), 129.71 (CH), 127.61 (CH), 127.57 (CH), 126.64 ($CH_2$), 115.68 ($CH_2$), 77.16 (C), 74.25 (CH), 51.70 (CH), 38.83 (CH), 37.30 ($CH_2$), 27.31 (CH), 19.70 (C), 13.61 (CH).

**IR** (thin film) ν 2931, 2876, 2858, 1798, 1719, 1557, 1472, 1454, 1427, 1409, 1390, 1347, 1282, 1235, 1112, 891, 822, 791, 740, 727, 701, 653, 612, 595, 507, 450, 421 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{22}H_{25}O_3Si$ $[M\text{-}t\text{Bu}]^+$, 365.1573; found, 365.1570 +/- 5ppm.




**(3*S*,4*S*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-4-methyl-2-methylenehept-6-enoate (**12b**).** Silyl ether **12b** was prepared following the same procedure as described for silyl ether **12a**. α,β-Unsaturated ester **S8** (0.50 g, 2.69 mmol, 1eq) gave silyl ether **12b** (0.99 g, 87%).

**$R_f$**= 0.86 (hexane/ethyl acetate = 5/1)

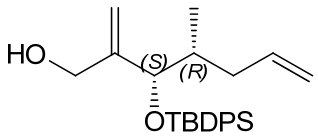
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.50, $CHCl_3$) = +15.2.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.68-7.59 (m, 4H), 7.44-7.30 (m, 6H), 6.22 (d, 1H, *J* = 1.6 Hz), 5.87 (t, 1H, *J* = 1.4 Hz), 5.67-5.57 (m, 1H), 4.92-4.88 (m, 2H), 4.69 (dd, 1H, *J* = 4.5, 0.7 Hz), 3.62 (s, 3H), 2.25-2.20 (m, 1H), 1.78-1.58 (m, 2H), 1.08 (s, 9H), 0.75 (d, 3H, *J* = 6.7 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 166.78 (C=O), 141.86 (C), 137.76 (CH), 136.22 (CH), 136.20 (CH), 134.04 (C), 129.74 (CH), 129.69 (CH), 127.60 (CH), 127.55 (CH), 127.08 ($CH_2$), 115.74 ($CH_2$), 77.16 (C), 74.80 (CH), 51.71 (CH), 39.38 (CH), 36.08 ($CH_2$), 27.28 (CH), 19.68 (C), 15.02 (CH).

**IR** (thin film) ν 2931, 2877, 2858, 25471721, 1537, 1427, 1346, 1278, 1232, 1112, 877, 821, 767, 740, 726, 701, 648, 611, 551, 506 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{22}H_{25}O_3Si$ [M-*t*Bu]$^+$, 365.1573; found, 365.1559 +/- 5ppm.




**(3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methyl-2-methylenehept-6-en-1-ol (**S9**).** To a solution of silyl ether **12a** (0.05 g, 0.12 mmol, 1.0 eq) in THF (0.3 mL) was added DIBALH (1.5 M in toluene; 0.17 mL, 0.26 mmol, 2.2 eq) dropwise at -78 °C. After the addition was complete, the solution was allowed to warm to -10 °C and was stirred for 3 h. Excess of reducing agent was quenched by addition of MeOH and an aqueous saturated solution of Na/K – tartrate was added and the biphasic system was stirred vigorously over night. The layers were separated and the aqueous layer was extracted with diethyl ether three times. The combined organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography gave educt **12a** (0.023 g, 0.05 mmol, 45%) and the desired alcohol **S9** (0.024 g, 0.06 mmol, 95% brsm).

**$R_f$**= 0.42 (hexane/ethyl acetate = 5/1)

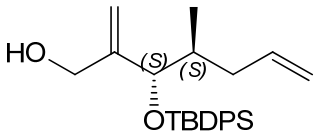
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.00, $CHCl_3$) = +7.5.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.73-7.65 (m, 4H), 7.46-7.33 (m, 6H), 5.69-5.56 (m, 1H), 5.03 (dd, 1H, *J* = 3.1, 1.6 Hz), 4.94-4.87 (m, 3H), 4.13-4.11 (m, 2H), 3.95-3.89 (m, 1H), 2.16-2.12 (m, 1H), 1.70-1.62 (m, 2H), 1.08 (m, 9H), 0.84 (d, 3H, *J* = 6.3 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 148.70 (C), 137.43 (CH), 136.41 (CH), 136.34 (CH), 134.95 (CH), 134.03 (C), 134.01 (C), 129.83 (CH), 127.87 (CH), 127.77 (CH), 127.61 (CH), 127.53 (CH), 115.97 ($CH_2$), 113.39 ($CH_2$), 79.94 (CH), 77.16 (C), 63.50 ($CH_2$), 38.19 (CH), 37.40 ($CH_2$), 27.34 (CH), 19.72 (C), 15.27 (CH).

**IR** (thin film) ν 3362, 3113, 3072, 3024, 2931, 2363, 1639, 1542, 1472, 1435, 1427, 1278, 1112, 955, 911, 879, 821, 781, 740, 728, 701, 655, 611, 579, 507 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{21}H_{25}O_2Si$ $[M\text{-}t\text{Bu}]^+$, 337.1624; found, 337.1614 +/- 5ppm.




**(3*S*,4*S*)-3-(*tert*-Butyldiphenylsilyloxy)-4-methyl-2-methylenehept-6-en-1-ol (**S10**).** Allylic alcohol **S10** was prepared following the same procedure as described for allylic alcohol **S9**. Silyl ether **12b** (0.022 g, 0.052 mmol, 1eq) gave educt **12b** (0.011 g, 0.026 mmol, 50%) and the desired allylic alcohol **S10** (0.010 g, 0.025 mmol, 96% brsm).

**$R_f$**= 0.40 (hexane/ethyl acetate = 5/1)

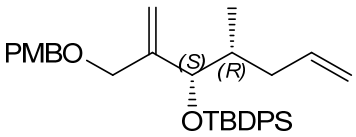
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.00, $CHCl_3$) = +8.5.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.69-7.65 (m, 4H), 7.46-7.33 (m, 6H), 5.65-5.54 (m, 1H), 5.02 (d, 1H, *J* = 1.5 Hz), 4.93-4.88 (m, 3H), 4.15 (dd, 1H, *J* = 14.4, 4.5 Hz), 4.08 (d, 1H, *J* = 6.6 Hz), 3.95 (dd, 1H, *J* = 14.4, 7.9 Hz), 2.38-2.32 (m, 1H), 1.72-1.58 (m, 2H), 1.17 (dd, 1H, *J* = 7.9, 4.6 Hz), 1.08 (s, 9H), 0.74 (d, 3H, *J* = 6.6 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 148.45 (C), 137.56 (CH), 136.40 (CH), 136.31 (CH), 134.95 (CH), 133.96 (C), 129.85 (CH), 129.74 (CH), 127.87 (CH), 127.78 (CH), 127.63 (CH), 127.55 (CH), 116.00 ($CH_2$), 113.35 ($CH_2$), 80.41 (CH), 77.16 (C), 63.27 ($CH_2$), 38.33 (CH), 37.30 ($CH_2$), 27.34 (CH), 19.67 (C), 15.46 (CH).

**IR** (thin film) ν 3354, 3113, 3072, 3024, 2930, 2361, 1639, 1540, 1472, 1437, 1427, 1280, 1111, 957, 910, 880, 821, 787, 740, 728, 701, 671, 611, 573, 508 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{21}H_{25}O_2Si$ $[M\text{-}t\text{Bu}]^+$, 337.1624; found, 337.1627 +/- 5ppm.




***tert*-Butyl((3*S*,4*R*)-2-((4-methoxybenzyloxy)methyl)-4-methylhepta-1,6-dien-3-yloxy)diphenylsilane (**13a**).** To a solution of allylic alcohol **S9** (0.46 g, 1.17 mmol, 1.0 eq) in DCM (2.91) was added PMB-Bundle's reagent[5] (0.7 M in heptane; 4.75 mL, 3.32 mmol, 2.0 eq) and a small spatula of CSA. The solution turned cloudy after stirring for 3 h. After stirring for 12 h an additional amount of PMB-Bundles's reagent (0.7 M in heptane; 2.38 mL, 1.66 mmol, 1.0 eq) and a small spatula of CSA were added. After stirring for 7 h TLC showed total consumption of the starting material. The mixture was diluted with DCM and poured into a solution of aqueous saturated ammonium chloride. The layers were separated and the aqueous phase was extracted with DCM four times. The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting dark yellow oil was purified by flash chromatography (hexane/ethyl acetate = 19/1) to afford PMB ether **13a** (0.58 g, 97%).

**$R_f$**= 0.85 (toluene/ethyl acetate = 5/1)

**$R_f$**= 0.58 (hexane/ethyl acetate = 9/1)

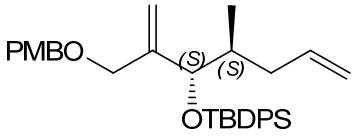
**Optical Rotation**: $[\alpha]^{20}_{D}$ (c 1.00, $CHCl_3$) = -5.4.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.68-7.62 (m, 4H), 7.43-7.30 (m, 6H), 7.21-7.16 (m, 2H), 6.87-6.83 (m, 2H), 5.62-5.51 (m, 1H), 5.17 (d, 1H, *J* = 1.7 Hz), 5.08 (d, 1H, *J* = 1.5 Hz), 4.88-4.81 (m, 2H), 4.34-4.31 (m, 2H), 4.11 (d, 1H, *J* = 4.5 Hz), 3.88 (s, 2H), 3.80 (s, 3H), 2.08-2.02 (m, 1H), 1.68-1.58 (m, 2H), 1.06 (s, 9H), 0.79 (d, 2H, *J* = 6.4 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 146.22 (C), 137.79 (CH), 136.42 (CH), 136.30 (CH), 134.41 (C), 134.05 (C), 130.68 (C), 129.87 (CH), 129.65 (CH), 129.29 (CH), 127.53 (CH), 127.46 (CH), 115.65 ($CH_2$), 114.00 (CH), 113.86 (CH), 113.74 ($CH_2$), 79.03 (CH), 77.16 (C), 72.00 ($CH_2$), 70.03 ($CH_2$), 55.43 (CH), 38.04 (CH), 37.68 ($CH_2$), 27.33 (CH), 19.78 (C), 14.64 (CH).

**IR** (thin film) ν 2930, 1558, 1513, 1495, 1427, 1336, 1248, 1199, 1111, 878, 822, 782, 740, 730, 702, 595, 511 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{33}H_{42}O_3SiNa$ $[M+Na]^+$, 537.2801; found, 537.2809 +/- 5ppm.



***tert*-Butyl((3*S*,4*S*)-2-((4-methoxybenzyloxy)methyl)-4-methylhepta-1,6-dien-3-yloxy)diphenylsilane (**13b**).** PMB ether **13b** was prepared following the same procedure as described for PMB ether **13a**. Allylic alcohol **S10** (0.365 g, 0.925 mmol, 1.0 eq) gave PMB ether **13b** (0.43 g, 91%).

**$R_f$**= 0.60 (hexane/ethyl acetate = 9/1)

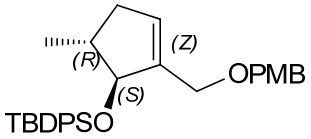
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.00, $CHCl_3$) = -6.0.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.68-7.61 (m, 4H), 7.43-7.23 (m, 6H), 7.21-7.18 (m, 2H), 6.87-6.84 (m, 2H), 5.61-5.51 (m, 1H), 5.17 (d, 1H, *J* = 1.7 Hz), 5.00 (d, 1H, *J* = 0.9 Hz), 4.89-4.83 (m, 2H), 4.34 (s, 2H), 4.05 (d, 1H, *J* = 5.5 Hz), 3.94 (s, 1H), 3.94 (s, 1H), 3.80 (s, 3H), 2.30-2.26 (m, 1H), 1.67-1.56 (m, 2H), 1.05 (s, 9H), 0.71 (d, 3H, *J* = 6.5 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 159.24 (C), 145.95 (C), 137.87 (CH), 136.39 (CH), 136.26 (CH), 134.37 (C), 130.72 (C), 129.86 (CH), 129.68 (CH), 129.65 (CH), 129.27 (CH), 127.54 (CH), 127.47 (CH), 115.70 ($CH_2$), 114.00 (CH), 113.87 (CH), 113.57 ($CH_2$), 79.67 (CH), 77.16 (C), 72.11 ($CH_2$), 69.67 ($CH_2$), 55.42 (CH), 38.26 (CH), 36.90 ($CH_2$), 27.30 (CH), 19.72 ($CH_2$), 15.70 (CH).

**IR** (thin film) ν 2931, 1700, 1612, 1541, 1513, 1492, 1427, 1333, 1247, 1199, 1111, 882, 821, 777, 702, 671, 508 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{33}H_{42}O_3SiNa$ $[M+Na]^+$, 537.2801; found, 537.2815 +/- 5ppm.




***tert*-Butyl((1*S*,5*R*)-2-((4-methoxybenzyloxy)methyl)-5-methylcyclopent-2-enyloxy)diphenylsilane (**14a**).** To a solution of PMB ether **13a** (0.15 g, 0.29 mmol, 1.0 eq) in DCM Grubbs' 2$^{nd}$ generation catalyst[6] (0.012 g, 0.014 mmol, 0.05 eq) was added in one portion. After stirring for 6 h at 30 °C another portion of Grubbs' 2$^{nd}$ generation catalyst (0.012 g, 0.014 mmol, 0.05 eq) was added in one portion and the resulting solution was stirred until TLC showed total consumption of the starting material. The solvent was removed *in vacuo* and the crude brownish residue was purified by flash chromatography (hexane/ethyl acetate = 9/1) to yield cyclopentene **14a** (0.14 g, 99%).

**$R_f$**= 0.54 (hexane/ethyl acetate = 9/1)

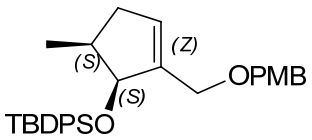
**Optical Rotation**: $[\alpha]^{20}_D$ (c 0.625, $CHCl_3$) = -25.6.

**$^{1}$H-NMR** ($CDCl_3$, 400 MHz) δ 7.70-7.67 (m,4H), 7.43-7.32 (m, 6H), 7.21-7.18 (m, 2H), 6.87-6.84 (m, 2H), 5.74 (brs, 1H), 4.39-4.38 (m, 1H), 4.35 (s, 1H), 4.34 (s, 1H), 4.02 (s, 2H), 3.81 (s, 3H), 2.66-2.58 (m, 1H), 2.18-2.10 (m, 1H), 1.71 (d, 1H, *J* = 16.77 Hz), 1.04 (s, 9H), 0.60 (d, 1H, *J* = 7.20 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 142.41 (C), 136.23 (CH), 136.11 (CH), 134.86 (C), 134.22 (C), 130.77 (C), 129.74 (CH), 129.69 (CH), 129.60 (CH), 129.51 (CH), 127.66 (CH), 127.56 (CH), 113.84 (CH), 85.58 (CH), 77.16 (C), 72.14 ($CH_2$), 66.94 ($CH_2$), 55.44 (CH), 41.55 (CH), 38.63 ($CH_2$), 27.20 (CH), 19.56 (C), 19.37 (CH).

**IR** (thin film) ν 3069, 2956, 2930, 2855, 1612, 1587, 1513, 1472, 1427, 1361, 1301, 1248, 1172, 1111, 1080, 911, 850, 821, 740, 702, 611, 507, 419 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{31}H_{38}O_3SiNa$ $[M+Na]^+$, 509.2488; found, 504.2498 +/- 5ppm.




***tert*-Butyl((1*S*,5*S*)-2-((4-methoxybenzyloxy)methyl)-5-methylcyclopent-2-enyloxy)diphenylsilane (**14b**).** Cyclopentene **14b** was prepared following the same procedure as for cyclopentene **14a**. PMB ether **13b** (0.433 g, 0.84 mmol, 1.0 eq) yielded cyclopentene **14b** (0.405 g, 99%).

**$R_f$**= 0. 54 (hexane/ethyl acetate = 9/1)

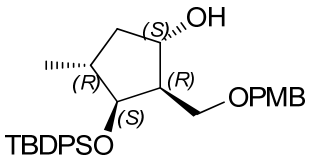
**Optical Rotation**: $[\alpha]^{20}_{D}$ (c 0.99, $CHCl_3$) = -17.8.

**$^{1}$H-NMR** ($CDCl_3$, 400 MHz) δ 7.73-7.65 (m, 4H), 7.43-7.31 (m, 6H), 7.14-7.10 (m, 2H), 6.87-6.81 (m, 2H), 5.73 (brs, 1H), 4.85 (d, 1H, *J* = 6.4 Hz), 4.20 (d, 1H, *J* = 14.16), 4.16 (d, 1H, *J* = 14.16), 3.87-3.82 (m, 1H), 3.80 (s, 3H), 3.63-3.60 (m, 1H), 2.33-2.27 (m, 1H), 2.22-2.14 (m, 1H), 2.02-1.92 (m, 1H), 1.07 (s, 9H), 0.97 (d, 3H, *J* = 7.0 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 142.85 (C), 136.39 (CH), 136.21 (CH), 136.18 (CH), 134.96 (CH), 130.75 (C), 129.88 (CH), 129.82 (CH), 129.72 (CH), 129.61 (CH), 129.45 (CH), 129.27 (CH), 128.69 (CH), 127.88 (CH), 127.67 (CH), 127.56 (CH), 113.78 (CH), 79.39 (CH), 77.16 (C), 72.17 ($CH_2$), 67.30 ($CH_2$), 55.43 (CH), 38.55 (CH), 37.97 ($CH_2$), 27.25 (CH), 19.85 (C), 15.58 (CH).

**IR** (thin film) ν 3070, 2930, 2856, 1612, 1587, 1512, 1462, 1427, 1361, 1301, 1247, 1172, 1111, 1037, 821, 741, 702, 610, 507, 419 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{31}H_{38}O_3SiNa$ $[M+Na]^+$, 509.2488; found, 504.2493 +/- 5ppm.




**(1*S*,2*R*,3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-((4-methoxybenzyloxy)methyl)-4-methylcyclopentanol (**15a**).** To a solution of $BH_3$·THF (1 M in THF; 0.185 mL, 0.185 mmol, 3 eq) was added 2,3-dimethyl-2-butene (0.022 mL, 0.185 mmol, 3 eq) dropwise at 0 °C. After stirring at 0 °C for 1.5 h the resulting thexylborane solution was added dropwise to a solution of cyclopentene **4a** (0.030 g, 0.062 mmol, 1 eq) in THF (0.3 mL) at -20 °C.[7] The solution was stirred at -20 °C for one hour, at -10 °C for another hour, and at 0 °C for one additional hour before being allowed to warm to rt. After 3 h at rt TLC showed total consumption of the starting material. The solution was cooled to 0 °C and quenched by careful addition of MeOH (1 mL). NaOH (3.6 M) was added, followed by hydrogen peroxide. The solution was allowed to come to rt over 12 h. The reaction mixture was poured into a saturated ammonium chloride solution and extracted with DCM three times. The combined organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (toluene/ethyl acetate = 20/1) afforded cyclopentanol **15a** (0.016 g, 51%).

**$R_f$**= 0.22 (hexane/ethyl acetate = 5/1)

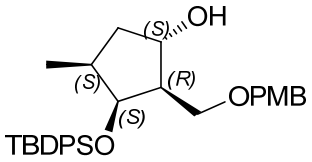
**Optical Rotation**: $[\alpha]^{20}_D$ (c 0.357, $CHCl_3$) = -17.1.

**$^1$H-NMR** ($CDCl_3$, 600 MHz) δ 7.66-7.63 (m, 4H), 7.44-7.40 (m, 2H), 7.37-7.34 (m, 4H), 7.11-7.09 (m, 2H), 6.84-6.82 (m, 2H), 4.23 (1H, d, *J* = 11.6 Hz), 4.19 (1H, d, *J* = 11.6 Hz),3.94 (brs, 1H), 3.81 (s, 3H), 3.36 (dd, 1H, *J* = 6.4, 6.4 Hz), 3.34 (dd, 1H, *J* = 9.0, 4.4 Hz), 2.96 (dd, 1H, *J* = 9.0, 9.0 Hz), 2.30 (d, 1H, *J* = 3.4 Hz), 2.27-2.18 (m, 3H), 1.89 (ddd, 1H, *J* = 13.6, 8.7, 5.0 Hz), 1.41 (ddd, 1H, *J* = 13.5, 7.7, 7.1 Hz), 1.02 (s, 9H), 0.72 (d, 3H, *J* = 6.8 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 125 MHz) δ 159.25 (C), 136.11 (CH), 134.10 (C), 134.04 (C), 130.42 (C), 129.78 (CH), 129.30 (CH), 127.68 (CH), 127.67 (CH), 127.66 (CH), 113.85 (CH), 81.90 (CH), 77.16 (C), 74.86 (CH), 72.85 ($CH_2$), 71.11 ($CH_2$), 57.07 (CH), 55.43 (CH), 40.21 (CH), 39.73 ($CH_2$), 27.11 (CH), 19.44 (C), 18.79 (CH).

**IR** (thin film) ν 3068, 2929, 2856, 2358, 1612, 1513, 1472, 1427, 1361, 1248, 1172, 1111, 822, 740, 703, 671, 610, 506, 436, 419, 408 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{31}H_{40}O_4SiNa$ $[M+Na]^+$, 527.2594; found, 527.2605 +/- 5ppm.




**(1*S*,2*R*,3*S*,4*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-((4-methoxybenzyloxy)methyl)-4-methylcyclopentanol (**15b**).** Cyclopentanol **15b** was prepared following the same procedure[7] as described for cyclopentanol **15a**. Cyclopentene **4b** (0.030g, 0.062 mmol, 1 eq) yielded cyclopentanol **15b** (0.014 g, 45%).

$R_f$= 0.24 (hexane/ethyl acetate = 5/1)

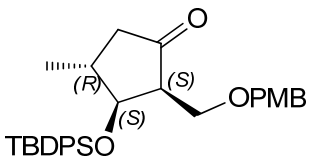
**Optical Rotation**: $[\alpha]^{20}_D$ (c 1.30, $CHCl_3$) = -28.8.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.64-7.62 (m, 4H), 7.45-7.33 (m, 6H), 7.15-7.12 (m, 2H), 6.86-6.83 (m, 2H), 4.42 (t, 1H, *J* = 5.4 Hz), 4.37 (dd, 1H, *J* = 13.7, 6.4 Hz), 4.27 (s, 2H), 3.81 (s, 3H), 3.42-3.33 (m, 2H), 2.26 (brs, 1H), 2.20-2.11 (m, 1H), 2.04-1.96 (m, 1H), 1.92-1.85 (m, 1H), 1.68-1.61 (m, 2H), 1.04 (s, 9H), 0.86 (d, 3H, *J* = 7.1 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 159.32 (C), 136.11 (CH), 136.07 (CH), 134.24 (C), 134.14 (C), 130.47 (C), 129.77 (CH), 129.45 (CH), 127.70 (CH), 127.65 (CH), 113.91 (CH), 77.43 (CH), 77.16 (C), 76.63 (CH), 73.10 ($CH_2$), 71.38 ($CH_2$), 55.42 (CH), 53.90 (CH), 39.07 ($CH_2$), 38.27 (CH), 27.25 (CH), 19.92 (C), 15.94 (CH).

**IR** (thin film) ν 3435, 3070, 2930, 2857, 1612, 1587, 1513, 1462, 1427, 1361, 1302, 1248, 1173, 1111, 1037, 821, 741, 702, 610, 509, 426, 419 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{31}H_{40}O_4SiNa$ $[M+Na]^+$, 527.2594; found, 527.2603 +/- 5ppm.




**(2*S*,3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-((4-methoxybenzyloxy)methyl)-4-methylcyclopentanone (**4a**).** IBX (0.017 g, 0.060 mmol, 1.5 eq) was dissolved in DMSO (0.12) and a solution of cyclopentanol **15a** (0.020 g, 0.040 mmol, 1.0 eq) in DMSO (0.05 mL) was added

followed by a DMSO (0.05 mL) rinse. The solution was stirred at rt until TLC showed total consumption of the starting material. Water was added and the precipitate was filtered off and washed with diethyl ether. The filtrate was extracted with diethyl ether three times, the combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and reduced *in vacuo*. Purification by flash chromatography yielded cyclopentanone **4a** (0.016 g, 80%).

**$R_f$**= 0.49 (hexane/ethyl acetate = 5/1)

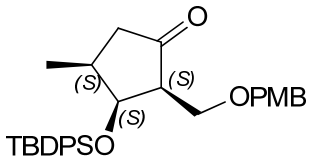
**Optical Rotation**: $[\alpha]^{20}_D$ (c 0.700, $CHCl_3$) = -65.7.

**$^1$H-NMR** ($CDCl_3$, 400 MHz) δ 7.27-7.64 (m, 4H), 7.45-7.40 (m, 2H), 7.38-7.32 (m, 4H), 7.01-6.99 (m, 2H), 6.81-6.79 (m, 2H), 4.15 (t, 1H, *J* = 8.1 Hz), 4.10 (d, 1H, *J* = 9.7 Hz), 4.06 (d, 1H, *J* = 11.6 Hz), 3.79 (s, 3H), 3.64 (dd, 1H, *J* = 9.3, 2.8 Hz), 3.25 (dd, 1H, *J* = 9.2, 3.4 Hz), 2.50 (ddd, 1H, *J* = 18.1, 7.8, 1.8 Hz), 2.39-2.35 (m, 1H), 2.26-2.14 (m, 1H), 1.71 (dd, 1H, *J* = 18.2, 11.6 Hz), 1.05 (s, 9H), 0.90 (3H, d, *J* = 6.6 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 215.06 (C), 159.12 (C), 136.11 (CH), 133.94 (C), 133.82 (C), 130.47 (C), 129.91 (CH), 129.88 (CH), 129.13 (CH), 127.74 (CH), 127.71 (CH), 113.70 (CH), 78.35 (CH), 77.16 (C), 72.82 ($CH_2$), 65.72 ($CH_2$), 58.96 (CH), 55.41 (CH), 46.12 ($CH_2$), 38.46 (CH), 27.09 (CH), 19.58 (C), 17.68 (CH).

**IR** (thin film) ν 2930, 2858, 1750, 1612, 1514, 1472, 1427, 1248, 1111, 821, 741, 704, 671, 613, 506, 423, 418 $cm^{-1}$.

**HRMS** (EI) calcd for $C_{31}H_{38}O_4SiNa$ $[M+Na]^+$, 525.2437; found, 525.2445 +/- 5ppm.




**(2*S*,3*S*,4*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-((4-methoxybenzyloxy)methyl)-4-methylcyclopentanone (**4b**).** Cyclopentanon **4b** was prepared following the same procedure as described for cyclopentanone **4a**. Cyclopentanol **15b** (0.017 g, 0.035 mmol, 1eq) yielded cyclopentanone **4b** (0.014 g, 77%).

**$R_f$**= 0.35 (hexane/ethyl acetate = 9/1)

**Optical Rotation**: $[\alpha]^{20}_D$ (c 0.525, $CHCl_3$) = +22.8.

**$^{1}$H-NMR** ($CDCl_3$, 400 MHz) δ 7.71-7.67 (m, 4H), 7.44-7.41 (m, 2H), 7.37-7.33 (m, 2H), 7.14 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 4.68 (brs, 1H), 4.18 (s, 1H), 3.81 (s, 3H), 3.71 (d, 2H, *J* = 6.2 Hz), 2.61-2.57 (m, 1H), 2.36-2.27 (m, 1H), 2.15-2.04 (m, 2H), 1.05 (s, 9H), 0.80 (d, 3H, *J* = 6.4 Hz).

**$^{13}$C-NMR** ($CDCl_3$, 100 MHz) δ 216.06 (C), 159.28 (C), 136.33 (CH), 136.26 (CH), 133.77 (C), 133.65 (C), 130.49 (C), 129.89 (CH), 129.80 (CH), 129.56 (CH), 127.71 (CH), 127.69 (CH), 113.86 (CH), 77.16 (C), 76.07 (CH), 72.70 ($CH_2$), 65.03 ($CH_2$), 59.29 (CH), 55.45 (CH), 42.61 ($CH_2$), 36.44 (CH), 27.34 (CH), 20.23 (C), 15.67 (CH).

**IR** (thin film) ν 2932, 2858, 1745, 1613, 1514, 1473, 1428, 1362, 1249, 1148, 1111, 1087, 1037, 821, 743, 704, 667, 648, 604, 509, 418 $cm^{-1}$.

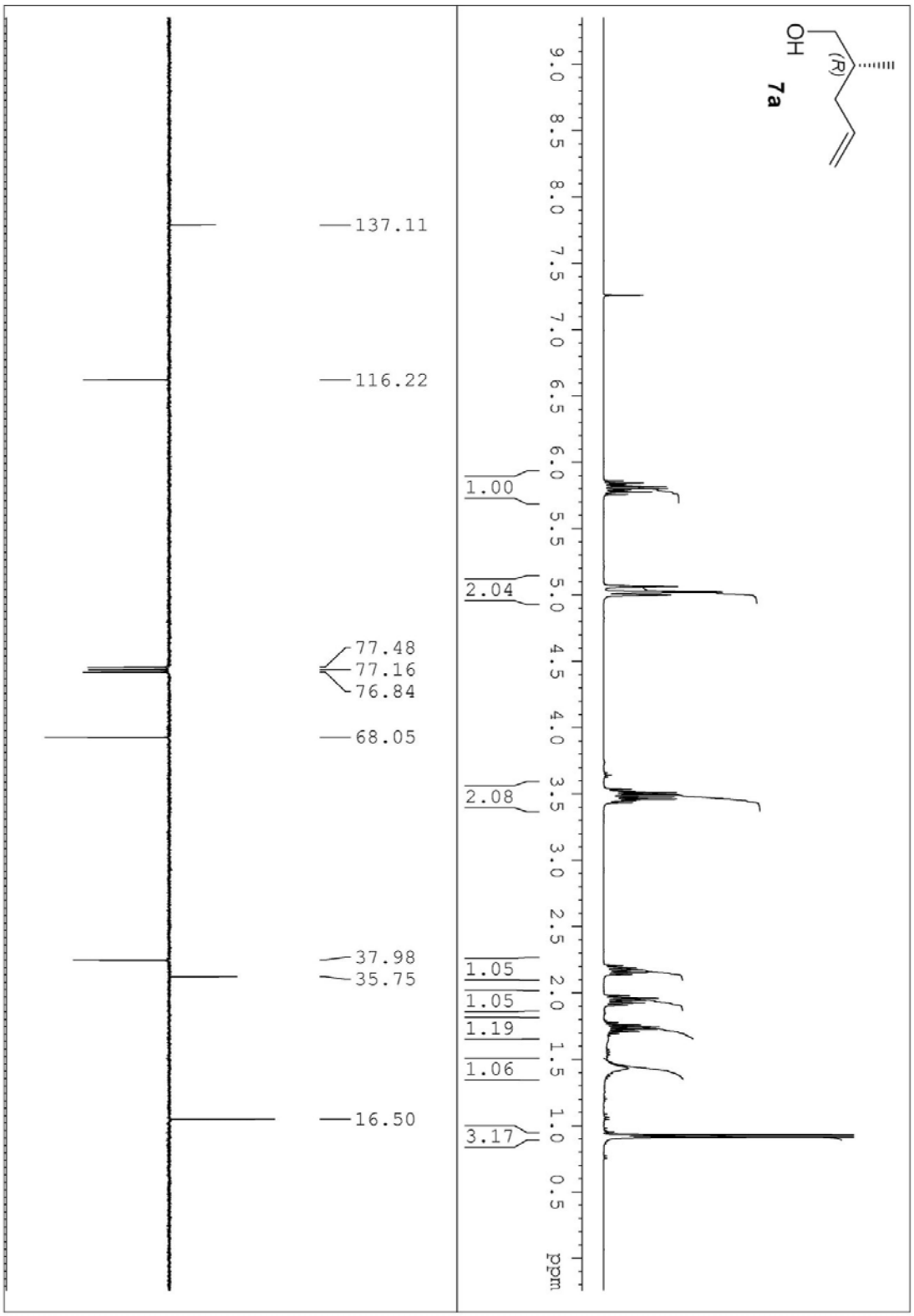
**HRMS** (EI) calcd for $C_{31}H_{38}O_4SiNa$ $[M+Na]^+$, 525.2437; found, 525.2437 +/- 5ppm.

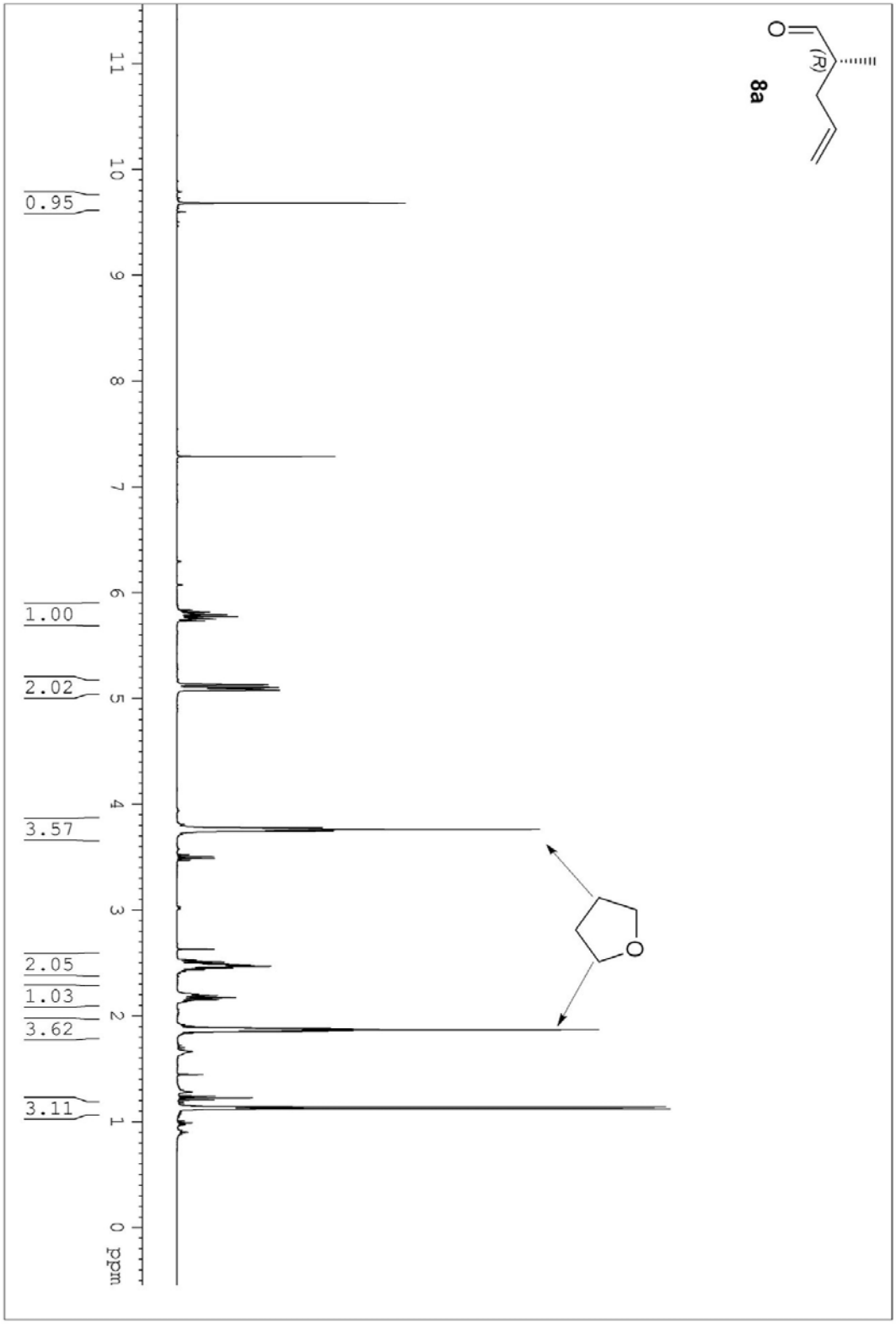
# 3. References


(1) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.
(2) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.
(3) Lin, N. H.; Overman, L. E.; Rabinovitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062-9072.
(4) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
(5) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240-1241.
(6) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org Lett* **1999**, *1*, 953-956.
(7) Castagner, B.; Leighton, J. L. *Tetrahedron* **2007**, *63*, 5895-5902.

## 4. Selected NMR Spectra

Solvent: $CDCl_3$
Instrument frequency: $^{1}H$: 400 MHz
$^{13}C$: 100 MHz


OH
(R)
7a
137.11
116.22
77.48
77.16
76.84
68.05
37.98
35.75
16.50
1.00
2.04
2.08
1.05
1.05
1.19
1.06
3.17
ppm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(R)
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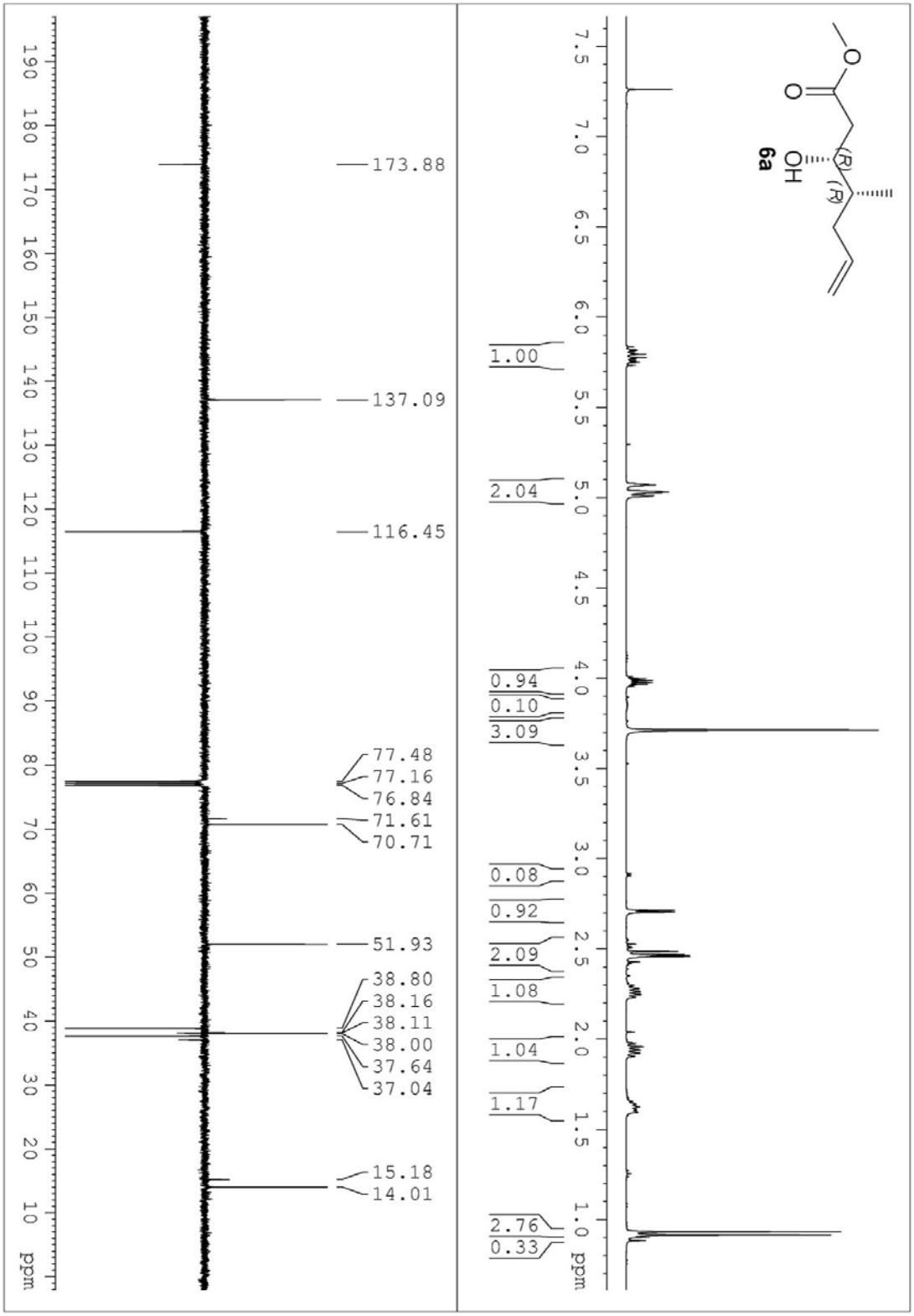
1.00
2.02
3.57
2.05
1.03
3.62
3.11
11
10
9
8
7
6
5
4
3
2
1
0 ppm


6a
1.00
2.04
0.94
0.10
3.09
0.08
0.92
2.09
1.08
1.04
1.17
2.76
0.33
ppm
173.88
137.09
116.45
77.48
77.16
76.84
71.61
70.71
51.93
38.80
38.16
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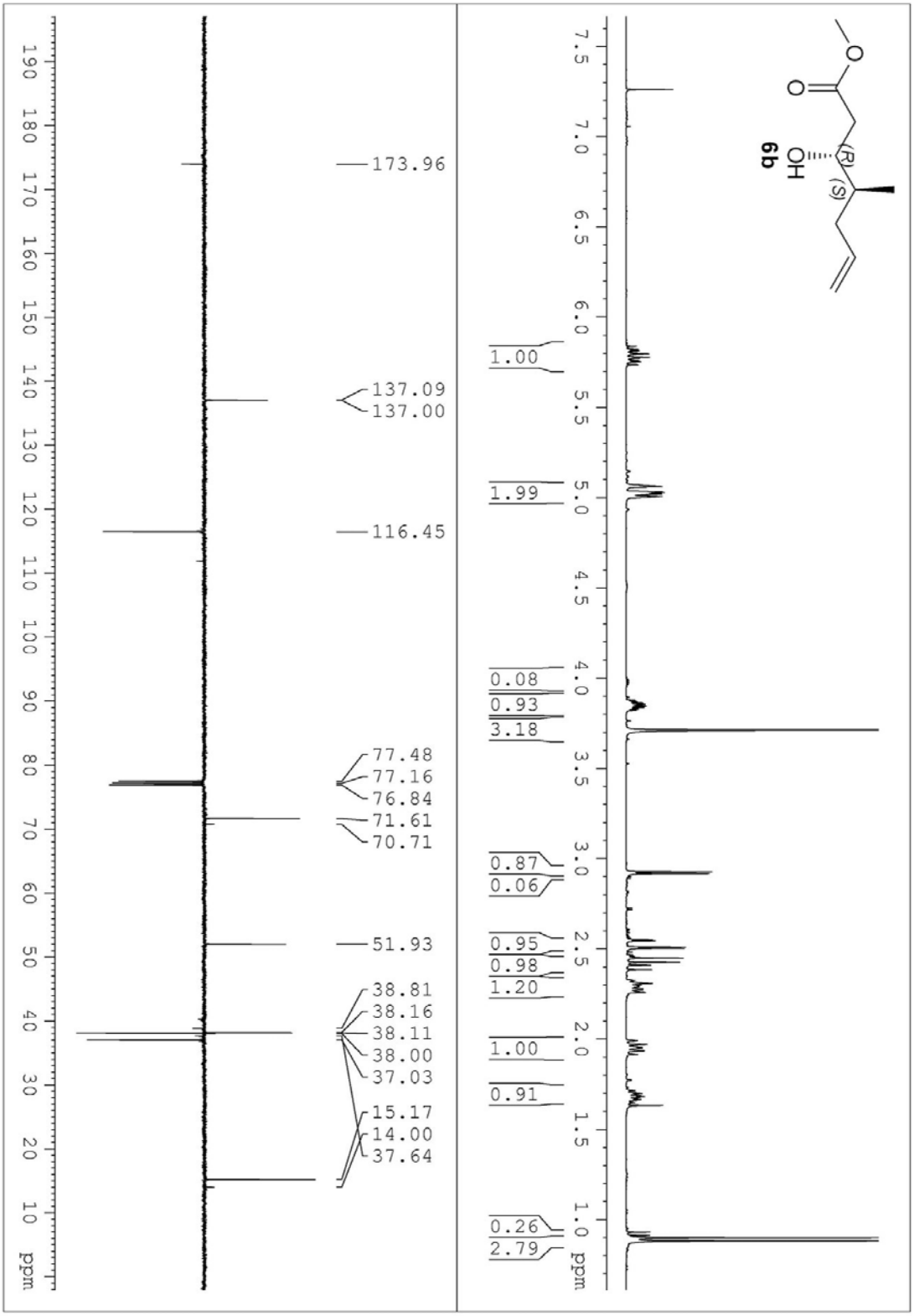
37.64
37.04
15.18
14.01
ppm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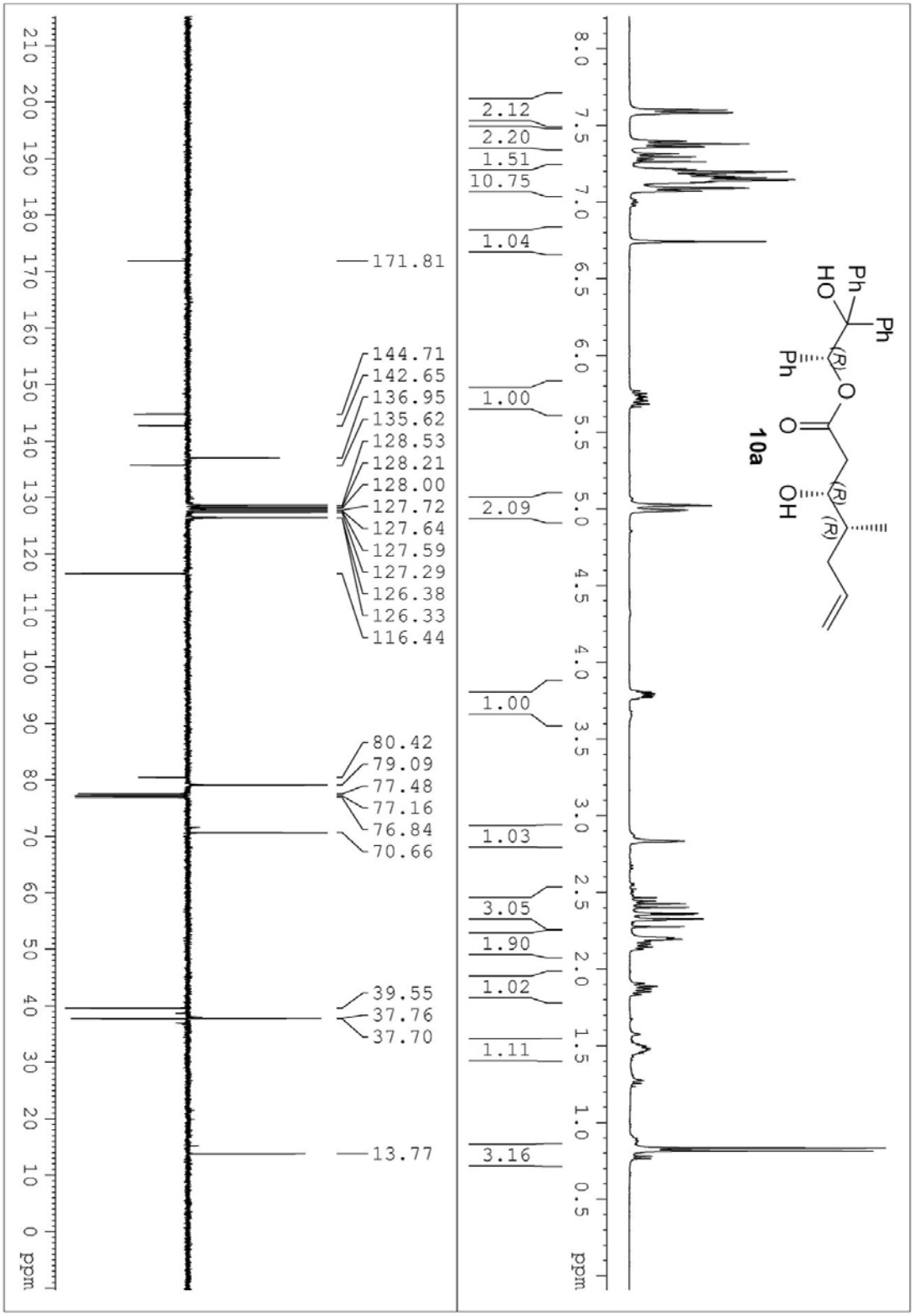
137.09
137.00
116.45
77.48
77.16
76.84
71.61
70.71
51.93
38.81
38.16
38.11
38.00
37.03
15.17
14.00
37.64
1.00
1.99
0.08
0.93
3.18
0.87
0.06
0.95
0.98
1.20
1.00
0.91
0.26
2.79
ppm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Ph
HO
Ph
Ph
O
O
OH
(R)
(R)
(R)
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2.20
1.51
10.75
1.04
1.00
2.09
1.00
1.03
3.05
1.90
1.02
1.11
3.16
ppm
171.81
144.71
142.65
136.95
135.62
128.53
128.21
128.00
127.72
127.64
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127.29
126.38
126.33
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77.48
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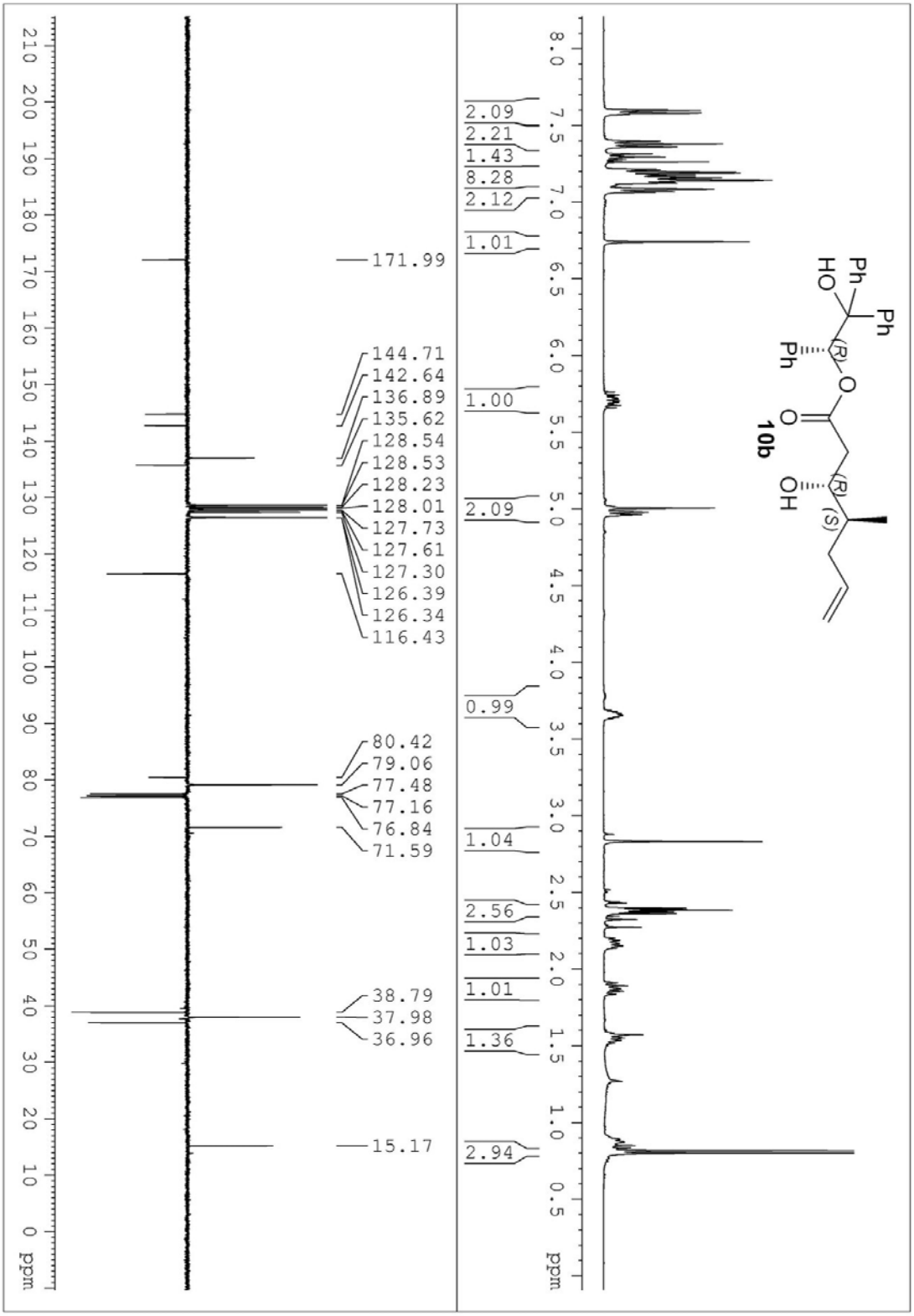
39.55
37.76
37.70
13.77
ppm


10b
Ph
HO
Ph
Ph
O
O
OH
(R)
(R)
(S)
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2.21
1.43
8.28
2.12
1.01
1.00
2.09
0.99
1.04
2.56
1.03
1.01
1.36
2.94
171.99
144.71
142.64
136.89
135.62
128.54
128.53
128.23
128.01
127.73
127.61
127.30
126.39
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38.79
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36.96
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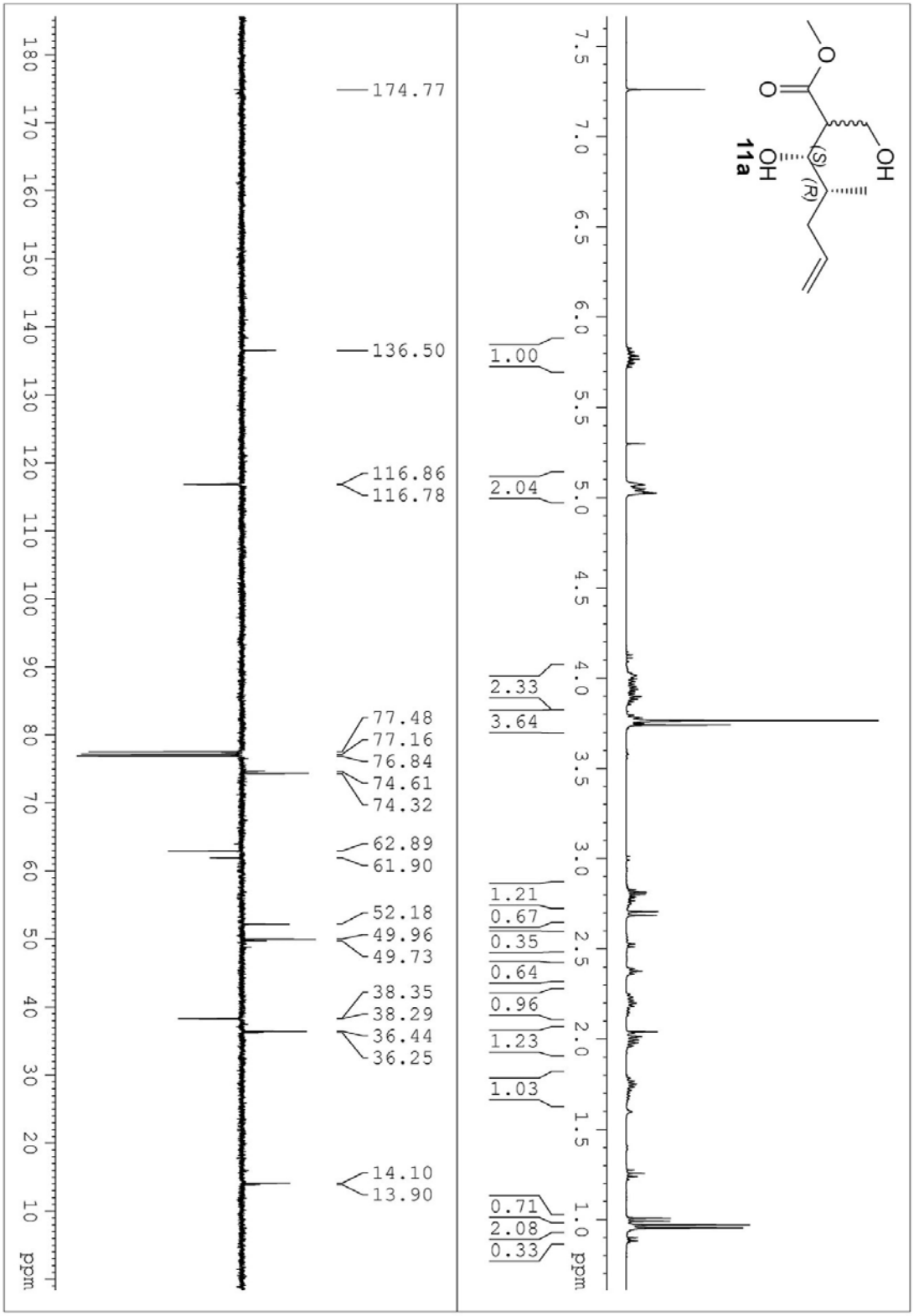
ppm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OH
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(R)
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2.33
3.64
1.21
0.67
0.35
0.64
0.96
1.23
1.03
0.71
2.08
0.33
174.77
136.50
116.86
116.78
77.48
77.16
76.84
74.61
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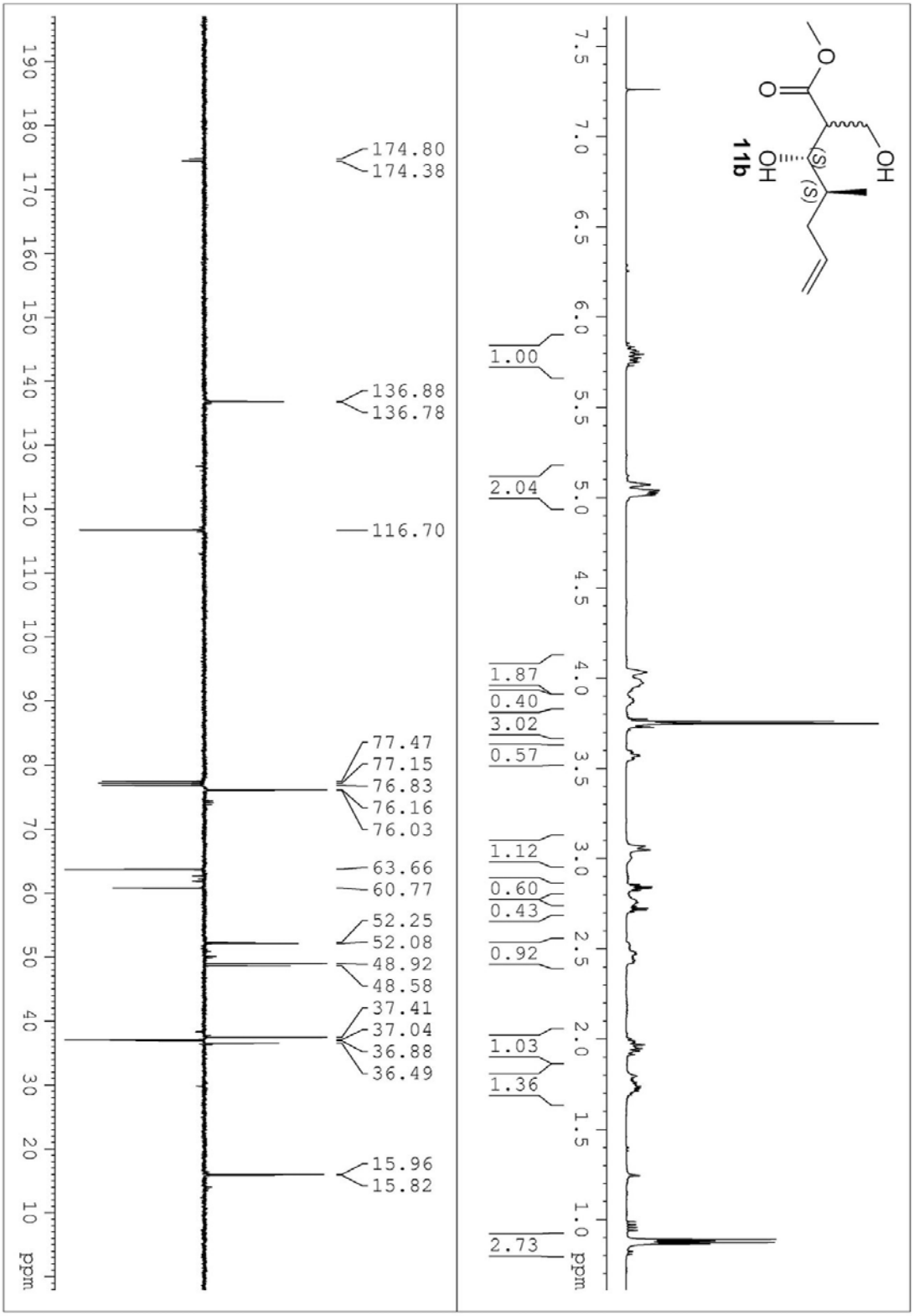
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(S)
OH
O
O
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0.43
0.92
1.03
1.36
2.73
ppm
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136.78
116.70
77.47
77.15
76.83
76.16
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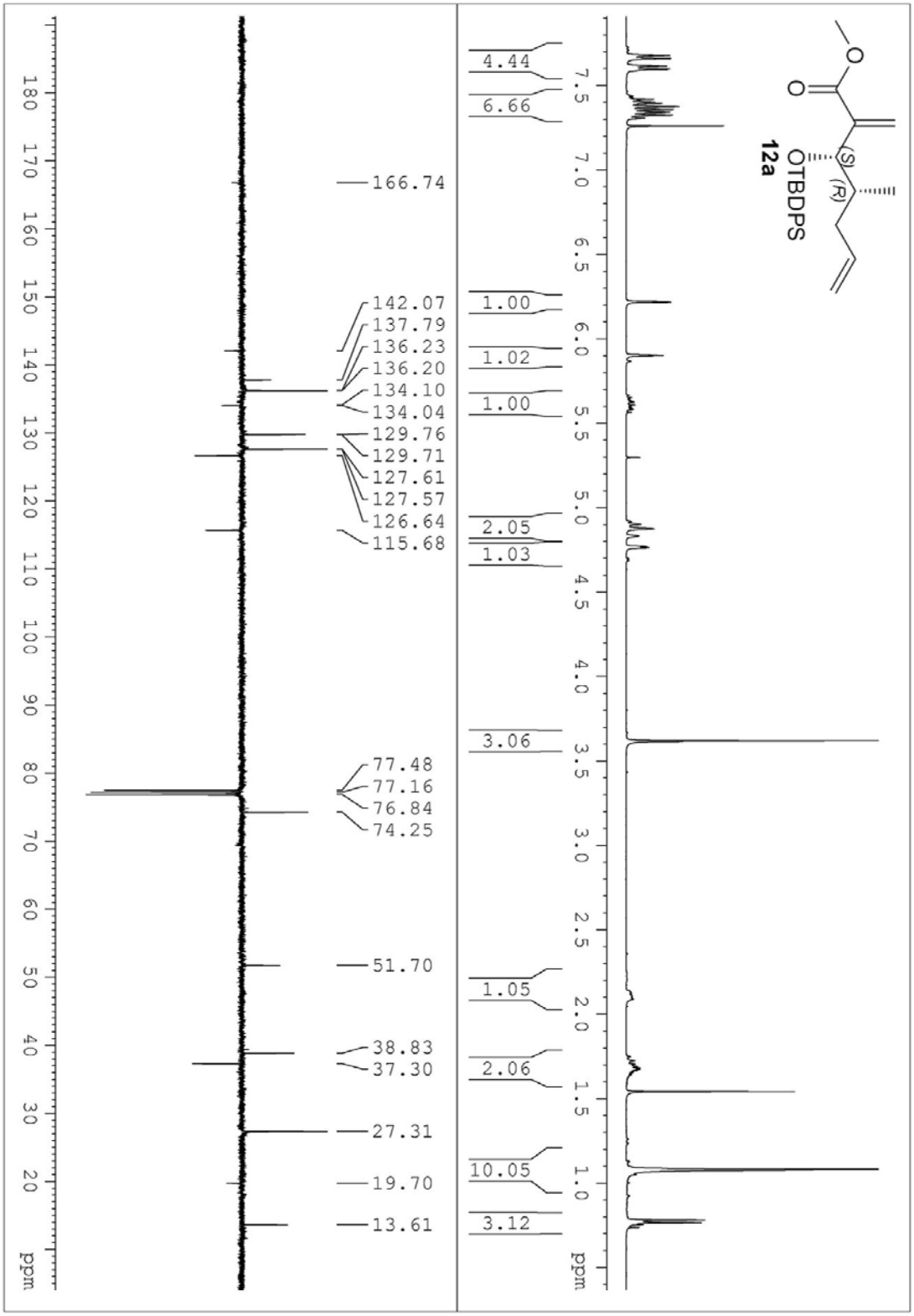
15.82
ppm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1.00
2.05
1.03
3.06
1.05
2.06
10.05
3.12
ppm
166.74
142.07
137.79
136.23
136.20
134.10
134.04
129.76
129.71
127.61
127.57
126.64
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77.16
76.84
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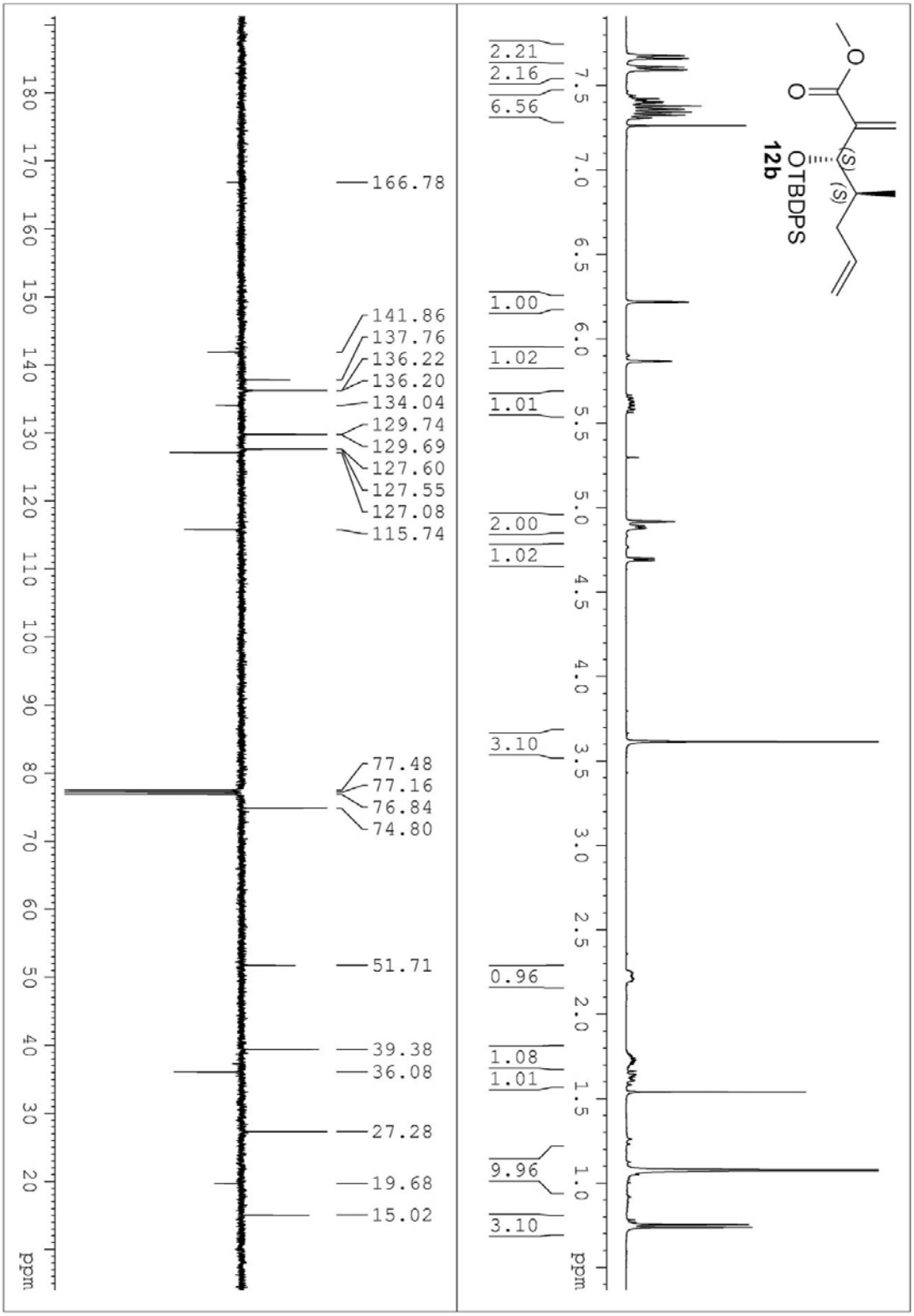
37.30
27.31
19.70
13.61
ppm


12b
OTBDPS
(S)
(S)
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2.16
6.56
1.00
1.02
1.01
2.00
1.02
3.10
0.96
1.08
1.01
9.96
3.10
166.78
141.86
137.76
136.22
136.20
134.04
129.74
129.69
127.60
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36.08
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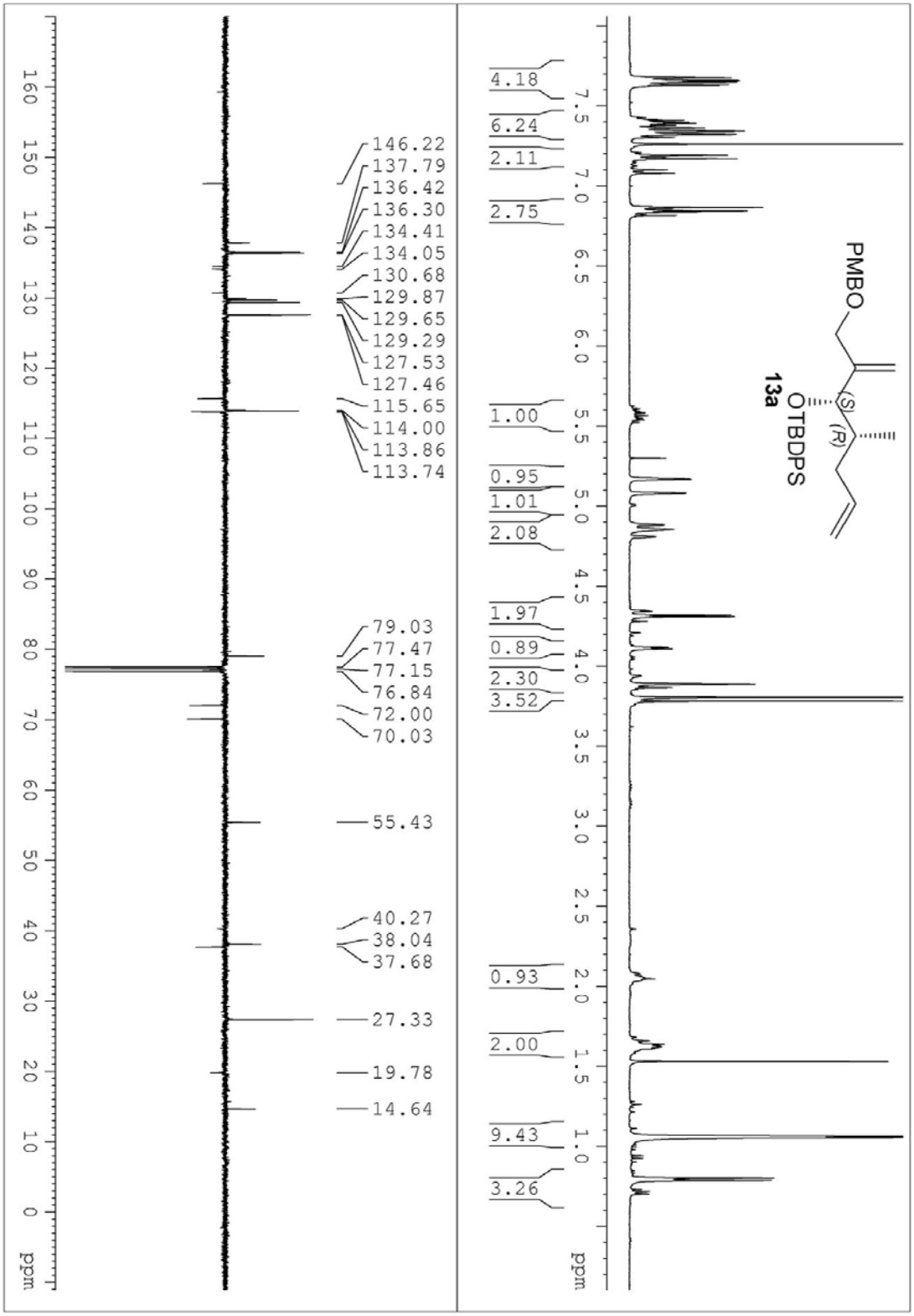
19.68
15.02
ppm


PMBO
(S)
(R)
OTBDPS
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1.97
0.89
2.30
3.52
0.93
2.00
9.43
3.26
ppm
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137.79
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136.30
134.41
134.05
130.68
129.87
129.65
129.29
127.53
127.46
115.65
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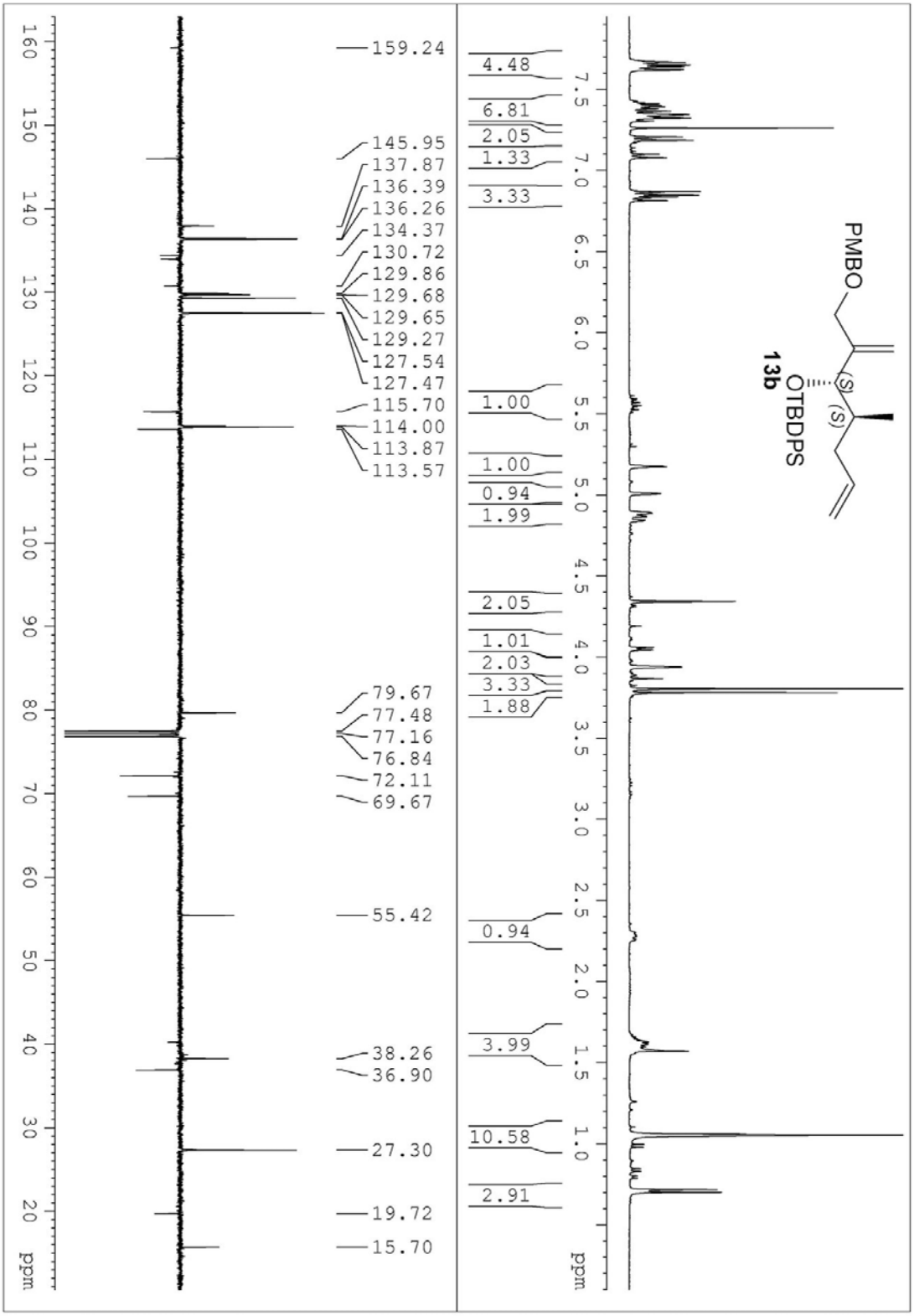
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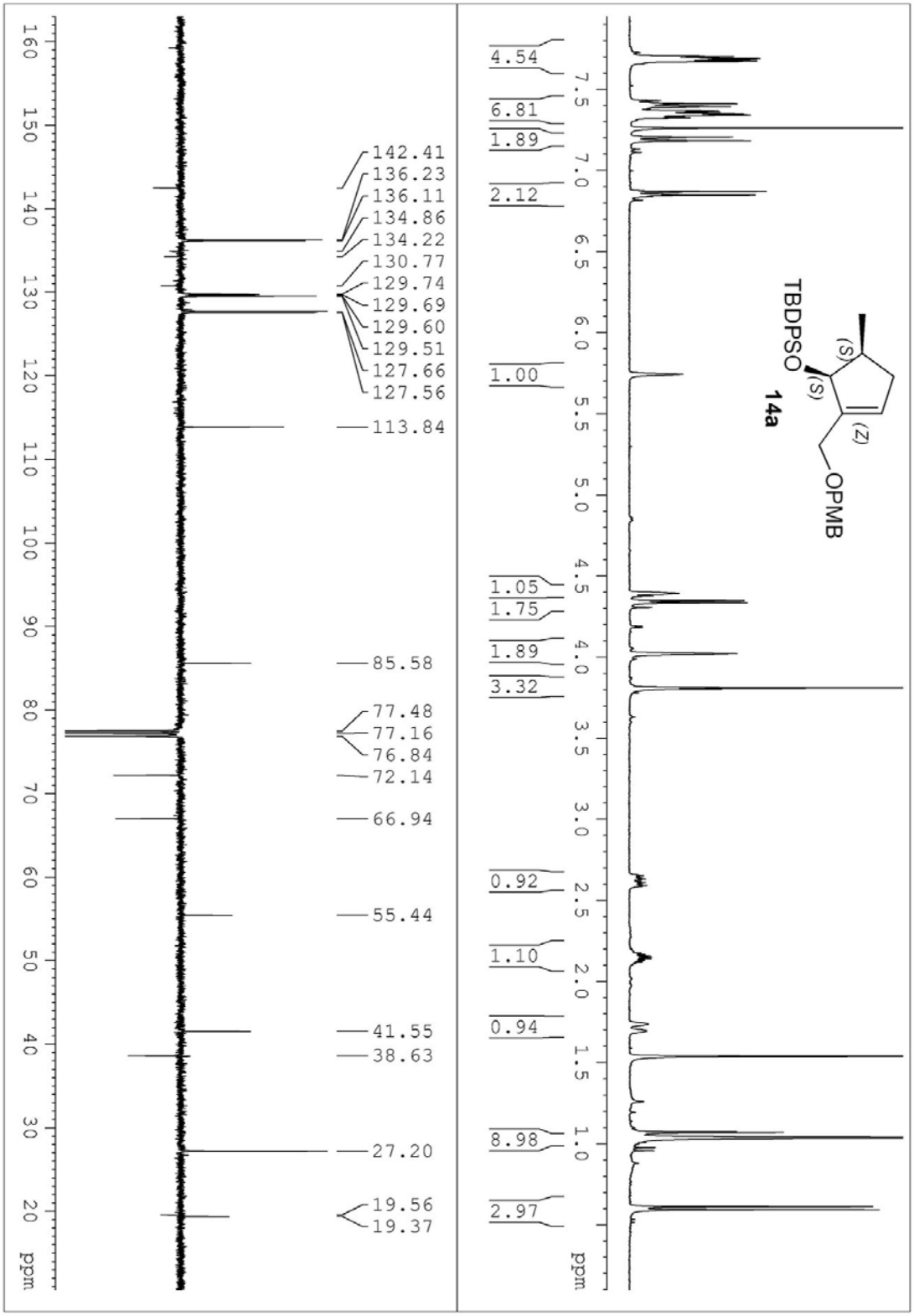
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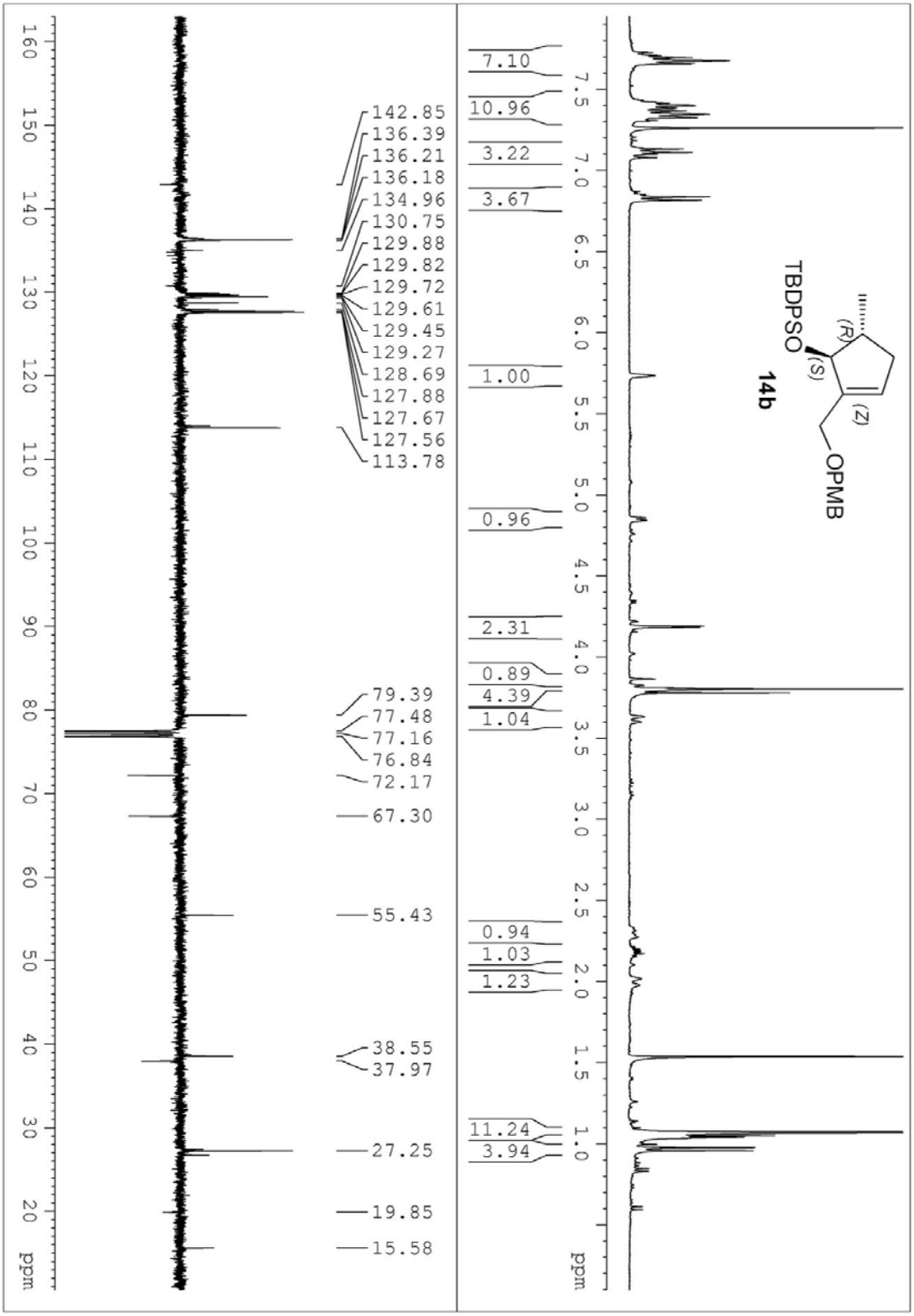
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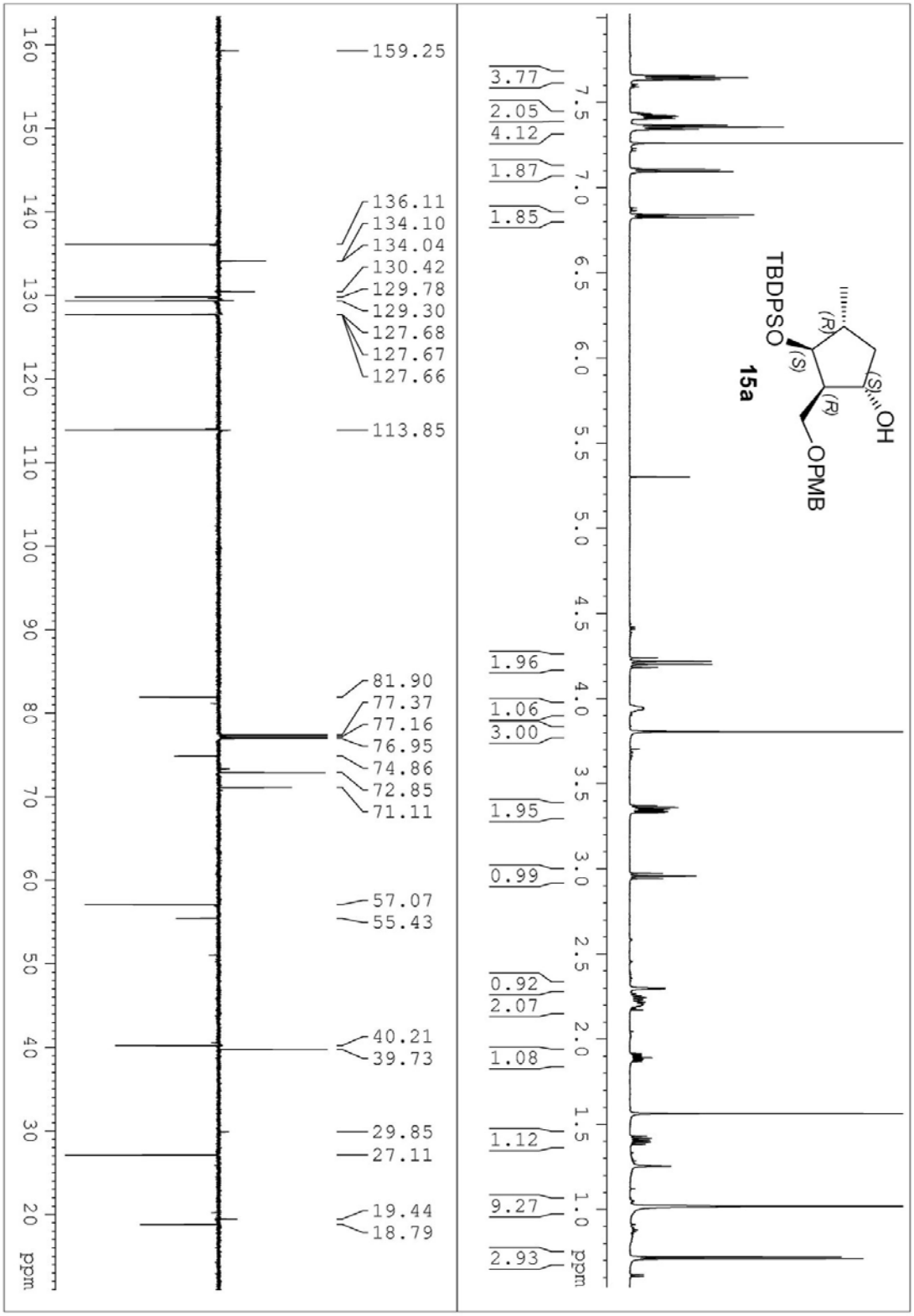
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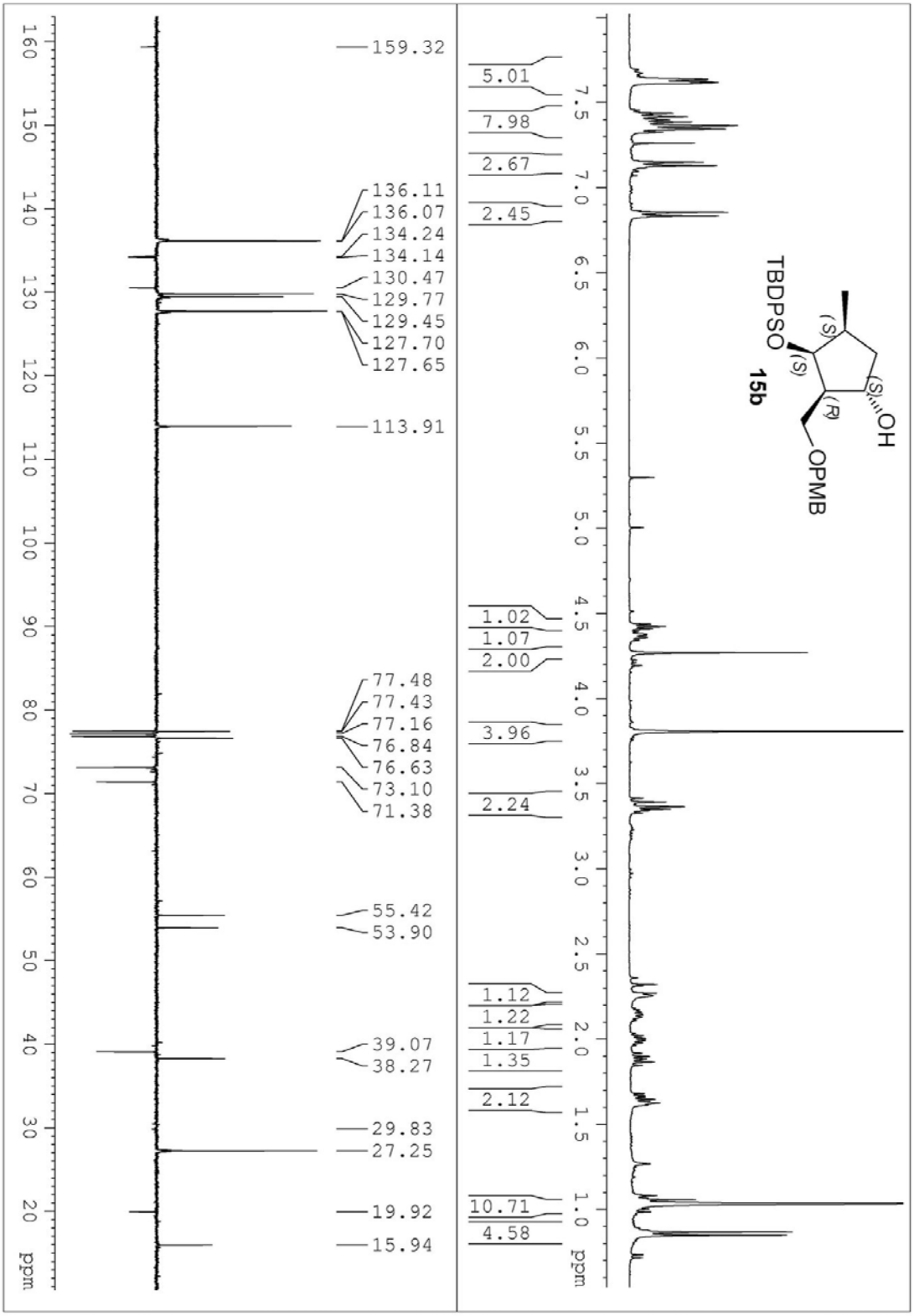
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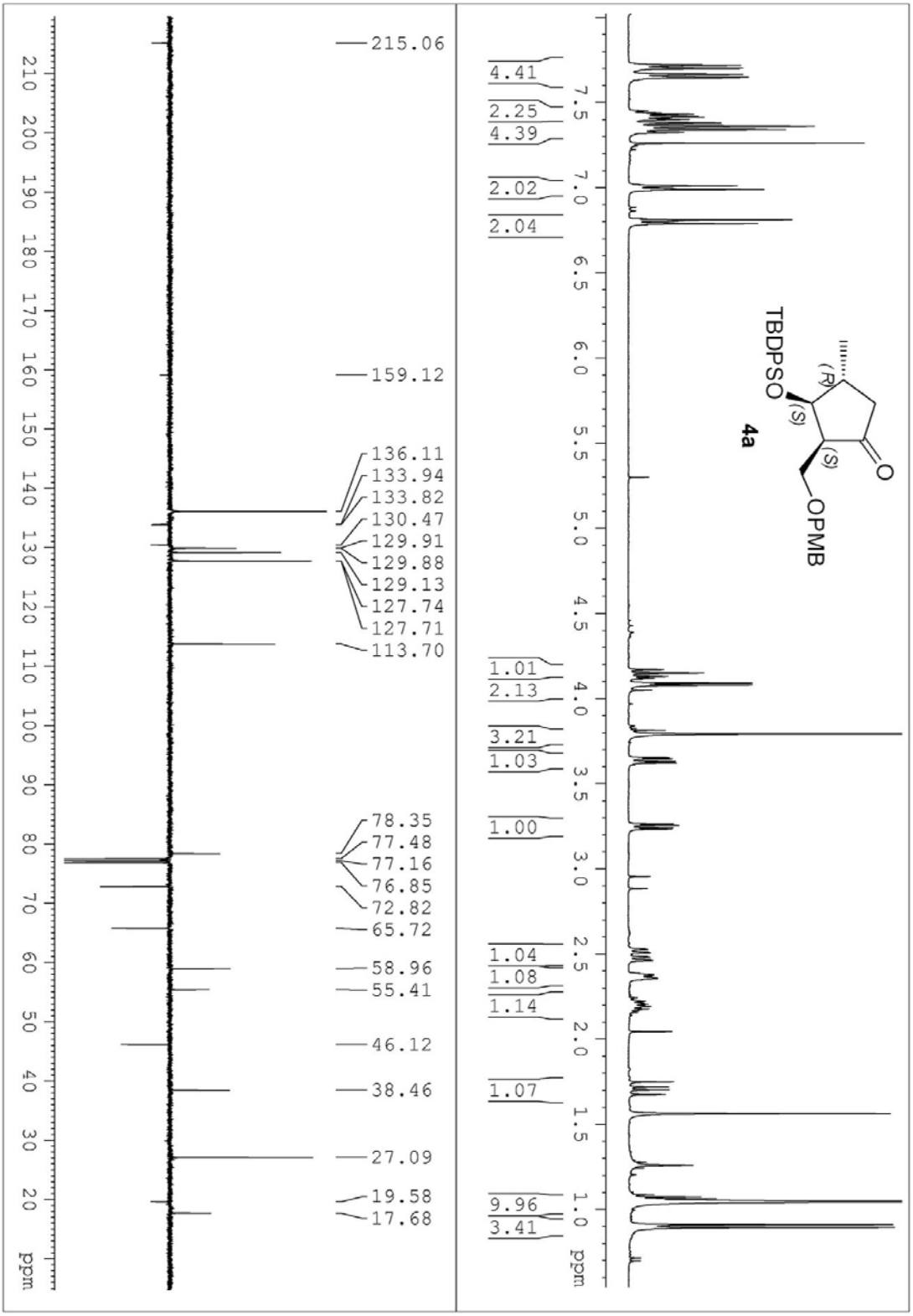
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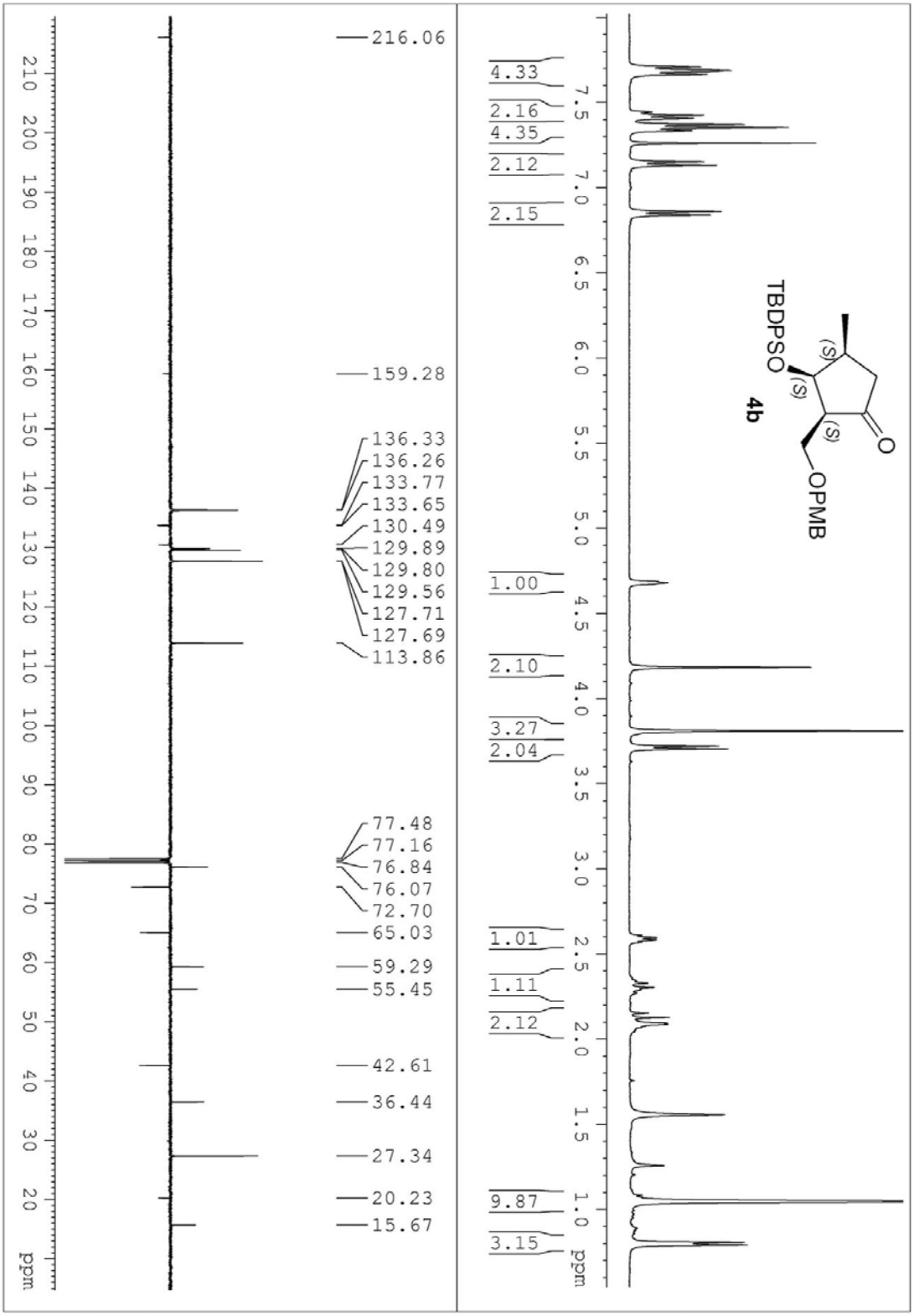
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# 10 APPENDIX II

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# Enyne Metathesis Approach towards the Cyclopentane Motif of Jatrophane Diterpenes

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**Abstract:** A short and efficient synthesis of the cyclopentane moiety of the jatrophane diterpene PI-3 has been developed. The route features an enyne metathesis reaction, and a stereoselective palladium-catalyzed reductive epoxide opening as key steps.

**Key words:** metathesis, palladium, natural products, stereoselective synthesis, terpenoids

With more than 2000 known species, the Euphorbiaceae family is one of the largest and most diverse of all genera. Many species of the widely distributed spurges, as members of this family are commonly referred to, have been extensively used in traditional herbal folk medicine to cure various health conditions, such as skin diseases, gonorrhea, migraine, intestinal parasites, and warts.[1]

Since the isolation of jatrophone in 1970 by Kupchan and co-workers,[2] considerable effort has been devoted to the isolation and structure elucidation of bioactive constituents of spurges. As a result of this intensive study, a vast number of structurally complex isoprenoid constituents have been obtained, some of which revealed highly interesting biological properties ranging from antiproliferative to pronounced multi-drug-resistance (MDR) reversal activity.[3,4]

While it is well established that most macrocyclic diterpenoids are biosynthesized from an isomer of geranylgeranyl diphosphate,[5] the exact process leading to the different core frameworks of jatrophane diterpenes and related natural products remains unknown. Despite the differences in the twelve-membered macrocycle of jatrophane diterpenes (oxygenation pattern, double bond geometry, stereochemistry of substituents), structural features in the cyclopentane moiety are essentially identical in many of these fascinating natural products. Some examples of recently isolated biologically interesting jatrophane diterpenes are shown in Figure 1.[6–8]

We have been interested in the active ingredients of the Euphorbiaceae family for some time, partly due to their intriguing biological properties but also because of the fascinating synthetic challenge presented by this class of natural products. Additionally, only a few routes to jatrophane diterpenes have been reported so far.[9–23]

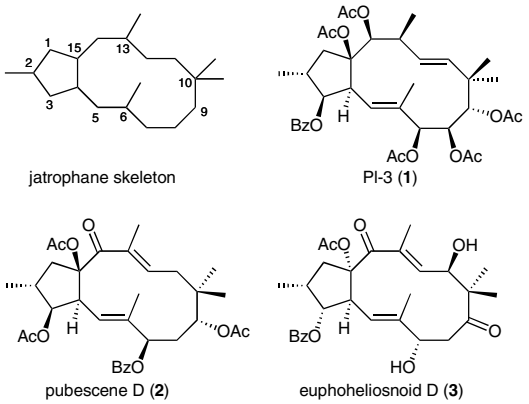


**Figure 1** Jatrophane diterpenes

As a result of our ongoing efforts towards Euphorbiaceae diterpenes, we have devised a route towards PI-3 (**1**).[19] This bicyclic natural product was isolated from an Hungarian sample of the annual herbaceous plant *Euphorbia platyphyllos* by Hohmann and co-workers in 2003 and has been shown to possess remarkable MDR reversal activity.[6]

The synthetic strategy, outlined in Scheme 1, is based on the late stage connection of three building blocks (**5**–**7**). The final operation in the preparation of the jatrophane diterpene is a metathesis reaction to close the macrocycle. Building block **5** becomes available from D-ribose via a samarium diiodide mediated diastereoselective Reformatsky reaction as key step as recently reported.[19] Advanced intermediate **6** should be accessible via selective reductive opening of epoxide **8**, followed by oxidation of the secondary alcohol and addition of the corresponding lithiated vinyl halide. Epoxide **8** was envisaged to be prepared from the corresponding diene, the product of the key enyne metathesis reaction of alkyne **9**. As suitable starting material for the sequence we decided to utilize chiral carboxylic acid **10**,[24] available on multigram scale via the Myers asymmetric alkylation protocol.[25] Vinyl halide **7** will be prepared from commercially available Roche ester. The route to both synthetic intermediates **5** and **6** is highly flexible and allows the preparation of structurally related intermediates for the synthesis of other jatrophane diterpenes.

As outlined in Scheme 2, the sequence started with the preparation of chiral carboxylic acid **10**.[24] Thus, reaction of pseudoephedrine (**11**) with propionyl chloride afforded

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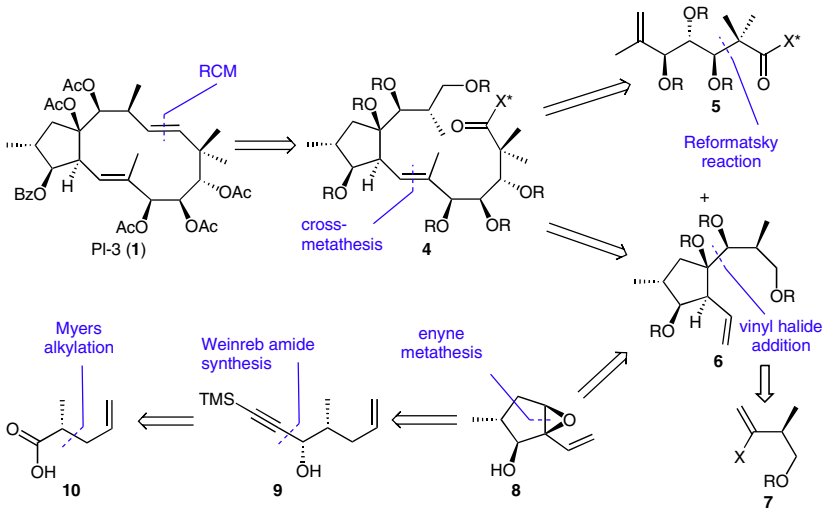
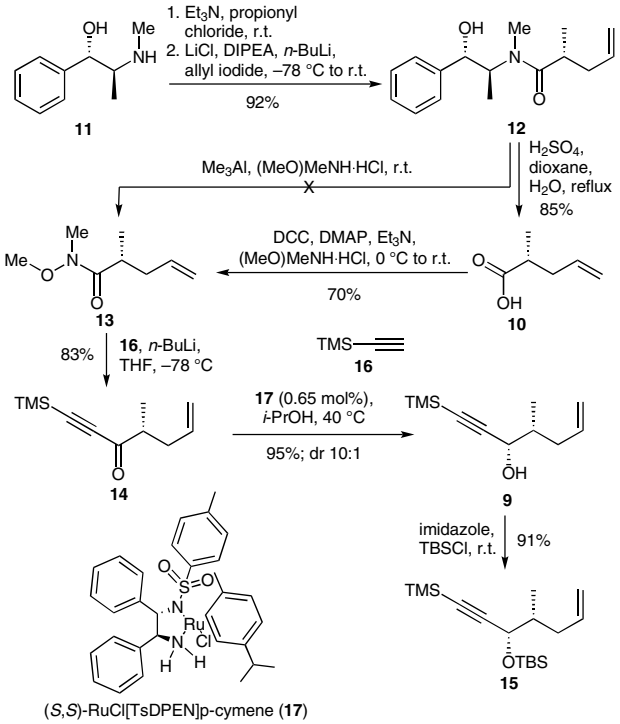



**Scheme 1** Retrosynthetic analysis of PI-3.

the precursor for the diastereoselective Myers alkylation with allyl iodide and amide **12** was obtained in excellent yield as single diastereomer.[25]

Next, amide **12** had to be converted to the corresponding Weinreb amide to facilitate the nucleophilic attack of deprotonated ethynyl trimethylsilane (**16**). Unfortunately, the trimethyl aluminum catalyzed reaction of amide **12** with *N*-methylhydroxylamine hydrochloride did not afford the desired product[26] and Weinreb amide **13** had to be accessed in a two-step procedure via initial acid hydrolysis of **12** and subsequent exposure of the carboxylic acid (**10**) to *N*-methlyhydroxylamine hydrochloride, DCC, $Et_3N$, and a catalytic amount of DMAP. Reaction of Weinreb amide **13** with deprotonated ethynyltrimethylsilane then afforded enynone **14** in high yield.

With **14** in hand, the stereoselective reduction of the carbonyl moiety could be attempted. Initial experiments with the CBS reagent[27] or Alpine borane[28] delivered the de-

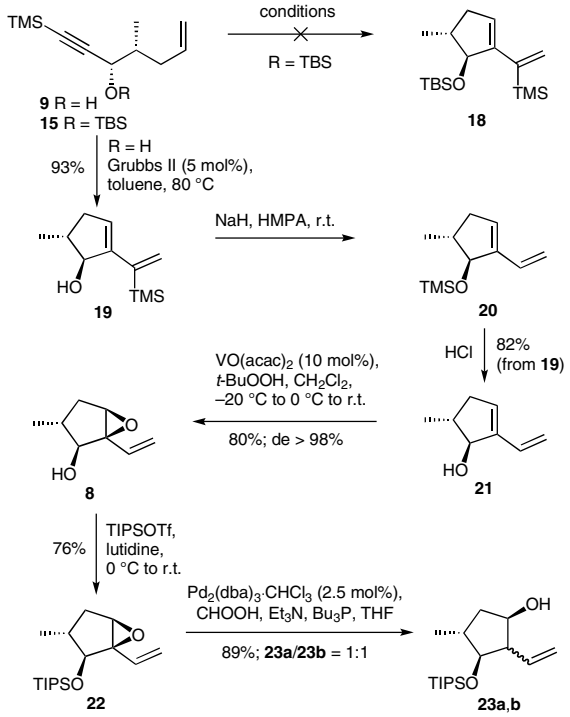



**Scheme 2** Preparation of metathesis precursors **15**

sired secondary alcohol in disappointingly low yield as a nearly racemic mixture. Finally, reduction of the ketone in **14** was achieved in highly diastereoselective manner following the Noyori asymmetric hydrogenation protocol. When allowed to react with significantly dried isopropyl alcohol as transfer reducing agent at elevated temperatures (40 °C) in the presence of ruthenium catalyst **17**, ynol **9** was obtained in excellent yield and stereoselectivity.[29,30] The synthesis of the enyne metathesis precursor was completed after silylation of the newly installed hydroxyl moiety (**15**).

The key enyne metathesis reaction proved to be more challenging than anticipated (Scheme 3). Extensive experimentation with silyl ether **15** with either the 1st or 2nd generation Grubbs metathesis catalyst in $CH_2Cl_2$ or toluene at different concentrations only led to isolation of the starting material. Only when alcohol **9** was allowed to react with Grubbs 2nd generation catalyst in carefully degassed and ethene-purged toluene, small amounts of **19** could be isolated. Careful optimization of the reaction conditions and slow addition of the metathesis catalyst over six hours via a syringe pump increased the yield of the desired material to 90%.[31]




**Scheme 3** Synthesis of cyclopentane **23a**,**b**

Next, we intended to functionalize the endocyclic double bond in cyclopentene **19**. All attempts to directly access the desired oxirane resulted in a homoallylic epoxidation of the exocyclic double bond because of the electron-donating properties of the TMS moiety. Thus, the silyl group had to be cleaved prior to the epoxidation in order to exclusively address the endocyclic double bond. As shown in Table 1, several methods were investigated to achieve the cleavage of the TMS group. Reaction of **19** with TBAF (1.0 M in THF) resulted in low and irreproducible yields of the desired product, along with decomposition of the starting material. The use of DMSO instead of THF did not improve the outcome of the reaction. When TBAF trihydrate was employed, **21** was isolated in 12% yield along with unreacted starting material.

**Table 1** Conditions for the Cleavage of the TMS Group in **19**

| Entry | Reagents and conditions | Yield |
|---|---|---|
| 1 | TBAF (1.0 M, THF), THF, r.t. | no reaction |
| 2 | TBAF (1.0 M, THF), DMSO, 50 °C | no reaction |
| 3 | TBAF (1.0 M, THF), DMSO, 80 °C | 10%; decomposition |
| 4 | TBAF (1.0 M, THF), DMSO, 100 °C | 10%; decomposition |
| 5 | TBAF trihydrate, THF | 12% |
| 6 | KHMDS, THF | unidentified products |
| 7 | LHMDS, THD | unidentified products |
| 8 | NaH, THF | 15% |
| 9 | NaH–HMPA, THF | 82% |

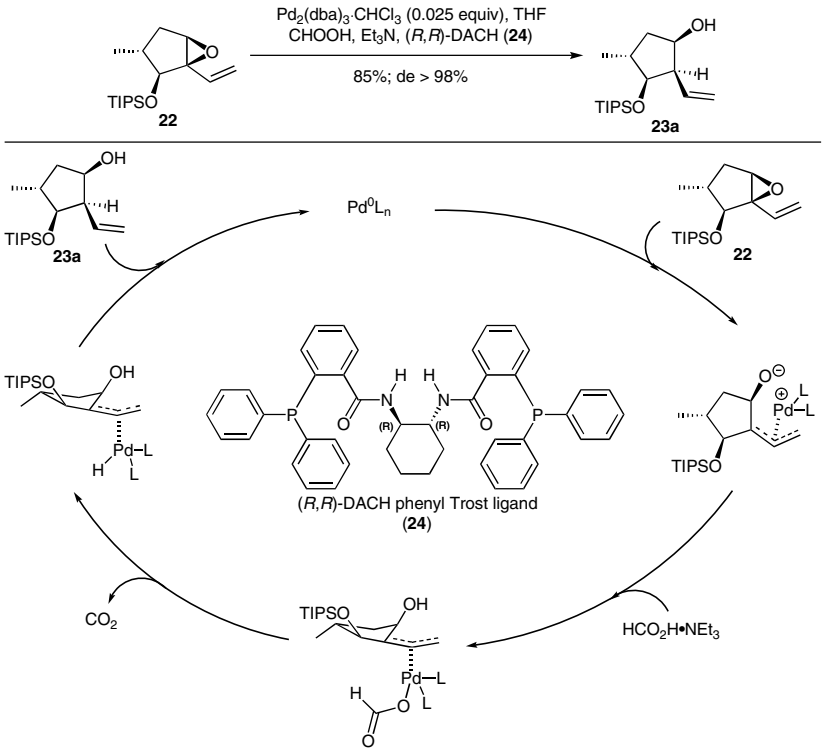
We then turned our attention to the cleavage of the silyl group via a Brook rearrangement,[32,33] taking advantage of the adjacent hydroxyl moiety. Initial experiments with NaH, LHMDS, or KHMDS proved unsuccessful, but when HMPA was added to the reaction mixture, **21** could be isolated in an excellent yield of 84% after subsequent cleavage of the silyl ether during acidic workup.[34]

With desilylated alkene **21** in hand, the vanadium-catalyzed directed epoxidation with *tert*-butyl hydroperoxide as oxidant delivered the desired oxirane **8** as the sole isolable product. Next, the secondary hydroxyl moiety was protected as TIPS ether and oxirane **22** was obtained as substrate for the key reductive epoxide opening reaction.

Palladium-catalyzed reductive epoxide openings were described by Tsuji and Shimizu in 1986.[35] A few years later, Shimizu reported the influence of the double bond geometry on the stereochemical outcome of this highly useful protocol. Shimizu further demonstrated that in the case of terminal alkenes 1:1 mixtures of stereoisomers were obtained because of the π-σ-π interconversion of the π-allylpalladium complex.[36]

Taking these observations into consideration, we were not surprised to also isolate a 1:1 mixture of stereoisomers (**23a** and **23b**) in 89% yield when epoxy alkene **22** was allowed to react with $Pd(dba)_3{\cdot}CHCl_3$ with $Bu_3P$ as ligand, $Et_3N$, and formic acid as reductant.

The mechanistic similarity of the palladium-catalyzed reductive epoxide opening and the Tsuji–Trost allylation motivated us to further investigate this interesting reaction. The asymmetric version of the Tsuji–Trost allylation




**Scheme 4** Mechanistic rationale for the selective epoxide opening and formation of alcohol **23a**

has many beautiful applications in natural product synthesis.[37,38] Trost also described the palladium-catalyzed reaction of vinylic epoxides and reported the asymmetric alkylation of vinylglycidols.[39,40] This protocol has been successfully employed in the asymmetric synthesis of (–)-malyngolide.[41] Although the palladium-catalyzed reaction has only been applied to carbon or oxygen nucleophiles, we reasoned that the DACH phenyl Trost ligand (**24**) might also be suitable for the intended reductive epoxide opening. The reaction, along with the mechanistic rationale, which shows the attack of the hydride from the bottom face, is outlined in Scheme 4. Trost developed a working model which allows the prediction of the stereochemical outcome of the palladium-catalyzed allylation reaction.[42] Among others, Lloyd-Jones contributed to this area with some interesting studies indicating that depending on concentration, temperature, and solvents, the catalytically active species might exist as monomer or oligomer.[43,44] Thus, a general prediction of the exact nature of the intermediary palladium species seems extremely challenging.

We were delighted to see that the palladium-catalyzed reaction of epoxy alkene **22** in the presence of the chiral Trost ligand **24** afforded the desired stereoisomer of the cyclopentane building block as the only isolable product in excellent 85% yield.[45] Reaction of **22** in the presence of the enantiomer of ligand **24** resulted in low yield of the desired product, along with mainly decomposed material. The absolute configuration of **23a** has been unambiguously confirmed by correlation NMR experiments (see Supporting Information).

To our knowledge, this is the first application of the DACH-phenyl Trost ligand in a reductive allylic epoxide opening reaction and constitutes an extension to the protocol described by Shimizu and co-workers for the stereoselective conversion of terminal epoxy alkenes.[36]

Summarizing, we were able to design a short and concise synthesis of the cyclopentane motif present in PI-3 (**1**). The route can also be utilized for the preparation of other structurally related jatrophanes as the five-membered rings show very similar or identical substitution patterns in many jatrophane diterpenes. Furthermore, the novel application of the DACH-phenyl Trost ligand in the stereoselective palladium-catalyzed reductive epoxide opening is a valuable extension of Shimizu's protocol and should be of interest for the preparation of complex natural products.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

 

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(30) **Preparation of Alcohol 9**: Acetylene **14** (1.0 g, 5.15 mmol, 1.0 equiv) was dissolved in freshly distilled 2-propanol (45 mL; degassed by three pump-freeze-thaw cycles prior to use). The solution was stirred at 40 °C and catalyst **17** (20 mg, 0.003 mmol, 0.0065 equiv; for preparation see Supporting Information), dissolved in 2-propanol (1 mL), was added via a syringe pump over 6 h. After consumption of the starting material the reaction was reduced in vacuo (30 °C, 40 mbar) and the residue (ca. 3 mL) was purified by flash column chromatography (hexane–EtOAc, 9:1) to afford **9** (950 mg, 95%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.77–5.87 (m, 1 H), 5.02–5.10 (m, 2 H), 4.28 (dd, *J* = 5.44, 5.44 Hz, 1 H), 2.33–2.40 (m, 1 H), 1.97–2.04 (m, 1 H), 1.78–1.86 (m, 2 H), 1.00 (s, 3 H), 0.18 (br s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 137.17 (CH), 116.65 ($CH_2$), 105.76 (C), 90.65 (C), 66.98 (CH), 39.40 (CH), 36.86 ($CH_2$), 15.08 (Me), 0.03 (Me). HRMS (ESI): *m/z* [M – Me]$^+$ calcd for $C_{10}H_{17}OSi$: 181.1049; found: 181.1044 ±5 ppm. $[\alpha]_D^{20}$ +3.8° (*c* = 1.630, $CHCl_3$). IR (ATR): 3351, 2960, 2352, 2171, 1640, 1376, 1249, 983, 947, 911, 838, 759, 698, 638 cm$^{-1}$.
(31) **Preparation of Cyclopentene 19**: Toluene (1.5 L) was degassed by an argon purge of approximately 1 h. Enyne **9** (3.00 g, 15.28 mmol, 1 equiv) was added and the solution was purged with argon for 10 min and with ethene for 10 min. Grubbs 2nd generation catalyst (0.649 g, 0.764 mmol, 0.005 equiv) was added in one portion and the solution was purged with ethene for 15 min. The mixture was heated to 80 °C for 16 h at positive pressure of ethene. After total consumption of the starting material, the mixture was reduced in vacuo (40 °C, 60 mbar) to a volume of approximately 70 mL. This volume was applied on a column and eluted with hexane (300 mL). After purification by flash column chromatography (hexane–EtOAc, 19:1), **19** (2.80 g, 93%) was isolated as a slightly brownish fluid. $^1$H NMR (400 MHz, $CDCl_3$): δ = 5.92 (d, *J* = 2.80 Hz, 1 H), 5.79 (dd, *J* = 2.69, 2.69 Hz, 1 H), 5.52 (d, *J* = 2.69 Hz, 1 H), 4.54 (br s, 1 H), 2.72–2.79 (m, 1 H), 2.11–2.20 (m, 1 H), 1.90–1.96 (m, 1 H), 1.51 (br s, 1 H), 1.09 (d, *J* = 7.12 Hz, 3 H), 0.17 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 146.23 (C), 145.72 (C), 130.73 (CH), 125.82 ($CH_2$), 84.31 (CH), 41.47 (CH), 38.97 ($CH_2$), 19.71 (Me), –0.59 (Me). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{20}NaOSi$: 219.1181; found: 219.1183 ±5 ppm. $[\alpha]_D^{20}$ –89.1° (*c* = 1.030, $CHCl_3$).
(32) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886.
(33) **Preparation of 21**: NaH (60% dispersion in mineral oil, 0.224 g, 5.60 mmol, 2.2 equiv) was added to HMPA (1.66 mL, 9.57 mmol, 3.75 equiv) in one portion. After 5 min, a solution of **19** (0.500 g, 2.55 mmol, 1 equiv) in THF (1.66 mL) was added. After consumption of the starting material as indicated by TLC analysis (60 min) the reaction was quenched via addition of a sat. aqueous solution of $NH_4Cl$. The solution was acidified to pH 2 by addition of HCl (1 M) and stirred for approximately 20 min. The aqueous solution was extracted with $CH_2Cl_2$ (3 × 20 mL) and dried over $MgSO_4$. Silica was added and the solvent was reduced in vacuo. The crude product was purified by flash column chromatography (dry loading; pentane–$Et_2O$, 10:1). The solvent was carefully reduced under reduced pressure (700 mbar, 35 °C) to yield **21** (260 mg, 82%) as a colorless liquid. Note: The product is highly volatile; thus, yields vary between 40% and 82%. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.45 (dd, *J* = 17.73, 11.00 Hz, 1 H), 5.82 (dd, *J* = 2.63, 2.63 Hz, 1 H), 5.41–5.46 (m, 1 H), 5.14 (dd, *J* = 10.89, 0.84 Hz, 1 H), 4.52 (br s, 1 H), 2.71–2.78 (m, 1 H), 2.14–2.23 (m, 1 H), 1.87–1.94 (m, 1 H), 1.51 (br s, 1 H), 1.10 (d, *J* = 7.16 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 143.58 (C), 133.11 (CH), 131.87 (CH), 115.01 ($CH_2$), 83.20 (CH), 42.56 (CH), 38.60 ($CH_2$), 19.67 (Me). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_8H_{12}NaO$: 147.0786; found: 147.0788 ±5 ppm. $[\alpha]_D^{20}$ –70° (*c* = 0.2250, $CHCl_3$). IR (ATR): 3316, 2954, 2924, 2868, 1641, 1454, 1374, 1260, 1021, 988, 905, 813 cm$^{-1}$.
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(40) Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649.
(41) Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013.
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(45) **Preparation of 23a**: The reaction was carried out in Schlenk flasks using degassed solvents. A Schlenk flask containing $Pd_2(dba)_3 \cdot CHCl_3$ (4.4 mg, 2.5 mol%) and (*R*,*R*)-DACH ([138517-61-0], 8.7 mg, 7.5 mol%) was purged with argon five times before $CH_2Cl_2$ (0.6 mL) was added. After 5 min a mixture of $Et_3N$ (117 μL, 0.844 mmol, 5.0 equiv) and formic acid (32 μL, 0.844 mmol, 5.0 equiv) in $CH_2Cl_2$ (0.6 mL) was added and stirring was continued for additional 5 min before epoxide **22** (50 mg, 0.169 mmol, 1.0 equiv) was added neat followed by $CH_2Cl_2$ (0.1 mL). The reaction was stirred until TLC analysis showed total consumption of the starting material (3 h). A sat. aqueous solution of $NH_4Cl$ was added and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), the organic extracts were dried over $MgSO_4$, filtered and reduced in vacuo. The crude product was purified by flash column chromatography (hexane–EtOAc, 40:1) delivering the desired product **23a** (43 mg, 86%) as a colorless oil as sole isolable product. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.20–6.26 (m, 1 H), 5.22–5.24 (m, 1 H), 5.20 (d, *J* = 0.78 Hz, 1 H), 4.07–4.11 (m, 1 H), 3.98 (br d, *J* = 3.90 Hz, 1 H), 3.25 (d, *J* = 11.16 Hz, 1 H), 2.36–2.40 (m, 1 H), 2.32–2.36 (m, 1 H), 2.25 (ddd, *J* = 14.42, 8.99, 0.95 Hz, 1 H), 1.51 (ddd, *J* = 14.37, 5.37, 5.37 Hz, 1 H), 1.05–1.13 (m, 21 H), 0.97 (d, *J* = 7.32 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 135.16 (CH), 117.43 ($CH_2$), 85.48 (CH), 78.18 (CH), 52.81 (CH), 43.47 ($CH_2$), 41.40 (CH), 20.87 (Me), 18.21 (Me), 18.16 (Me), 12.37 (CH). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{34}NaO_2Si$: 321.2226; found: 321.2223 ±5 ppm. $[\alpha]_D^{20}$ –5° (*c* = 1.0900, $CHCl_3$). IR (ATR): 3531, 2943, 2866, 2359, 2342, 1636, 1463, 1419, 1383, 1119, 1060, 1014, 997, 912, 881, 847, 823, 729, 678 $cm^{-1}$.

 

# Supporting Information

## Enyne Metathesis Approach Towards the Cyclopentane Motif of Jatrophane Diterpenes

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## General Methods

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum) unless otherwise noted.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, toluene and benzene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral, activity I. DMSO and *N*,*N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. Dry solvents were stored under an argon atmosphere over molecular sieves (4Å). Triethylamine, diethylisopropylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use. If noted, chemicals were purified according to "*Purification of laboratory chemicals (4th ed.)*" or therein cited references.[1] All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using ALUGRAM®Xtra SIL G aluminum sheets (Silica 60) purchased from Macherey-Nagel. The plates were developed with a mixture of hexane/ethyl acetate or toluene/ethyl acetate. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [$H_2SO_4$ (conc., 22 mL), phosphomolybdic acid (20.0 g), $Ce(SO_4)_2$ (0.5 g), 378 mL $H_2O$)] or silica gel impregnated with iodine.

Preparative column chromatography and flash chromatography was performed with silica gel 60 from Merck (0.040-0.063 µm, 240-400 mesh). For HPLC separations on analytical scale module systems from Jasco (PU-980, UV-975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was Superphere Si 60 (40 µm, Merck) or Nucleosil 50 (4 µm, Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

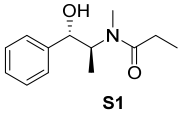
Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^T_D$, concentration (g/100 mL), and solvent.

NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in CDCl3 solutions and referenced to the residual $CDCl_3$ signal ($^1H$, $\delta$ = 7.26, $^{13}C$, $\delta$ = 77.16).[2] All $^1H$ and $^{13}C$ shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton

resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY)

IR spectra were recorded using a Bruker vertex 70 FT-IR spectrometer and are reported in wave numbers ($cm^{-1}$). All compounds were measured using the attenuated total reflection accessory Standard Golden Gate ATR, a single reflection monolithic diamond ATR module.

# Experimental Part



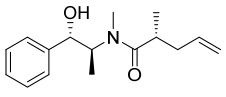

**S1**

**(*S*,*S*)-Pseudoephedrine propionamide (**S1**)**. To a solution of (+)-pseudoephedrine (2.00 g, 12.1 mmol), and $NEt_3$ (1.47 g, 2.02 mL, 14.5 mmol) in DCM (25 mL) at r.t. (water bath) was slowly added propionyl chloride (1.23 g, 1.16 mL, 13.3 mmol) over 10 min. The white slurry was stirred at 20 °C for 30 min before the excess of propionic chloride was quenched by the addition of $H_2O$ (25 mL). The organic layer was separated and washed with half saturated $NaHCO_3$ (2 x 25 mL) and HCl (25 mL; 1 M). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo* to furnish a white solid. Recrystallisation from toluene afforded the desired product **S1** (2.45 g, 92 %) as white crystals.

$^1$H-NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz): δ = 7.37-7.25 (m, 5H), 4.60-4.55 (m, 1H), 4.44 (t, 1H, *J* = 7.0 Hz), 4.31(brs, 1H), 4.00* (m, 1H), 2.91* (s, 1H), 2.80 (s, 1H), 2.57-2.47* (m, 2H), 2.43-2.23 (m, 2H), 1.17-0.96 (m, 6H).

$^{13}$C-NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz): δ = 176.34 (C), 142.62 (C), 128.84 (CH), 128.49 (CH), 127.77 (CH), 127.05 (CH), 126.53 (CH), 77.16 (C), 76.78 (CH), 75.63* (CH), 58.72* (CH), 58.40 (CH), 27.71 ($CH_2$), 26.97* ($CH_2$), 26.83 (CH), 15.39* (CH), 14.59 (CH), 9.73* (CH), 9.32 (CH).

These spectral characteristics were identical to those previously reported.[3]




**12**

**(*R*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide (**12**).** To a suspension of extensively flame-dried lithium chloride (1.14 g, 26.8 mmol) in THF (5.5 mL) was added diisoproylamine (1.42 mL, 10.15 mmol) at −78 °C followed by *n*-BuLi (2.5 M in hexanes, 3.90 mL, 9.68 mmol). The suspension was stirred for 15 min at 0 °C before it was cooled to −78 °C. A solution of amide **S1** (1.00 g, 4.52 mmol) in THF (13.4 mL) was added *via* cannula over 10 min and the solution was vigorously stirred for 60 min. After 15 min at 0 °C, and 10 min at r.t., the reaction was cooled to −78 °C, and allyl iodide (1.14 g, 6.78 mmol) was added neat. The

reaction mixture was stirred for 1 h at −78 °C and 60 min at 0 °C. The reaction mixture was then quenched by the addition of saturated aqueous $NH_4Cl$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (25 mL), and dried over $MgSO_4$. Concentration under reduced pressure provided known amide **12** (1.30 g, quant.) as a viscous yellow oil, which was used without further purification.

$^1$H-NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz): δ = 7.38-7.24 (m, 5H), 5.84-5.64 (m, 1H), 5.13-4.98 (m, 2H), 4.63-4.57 (m, 1H), 4.44 (brs, 1H), 2.91* (s, 3H), 2.86 (s, 3H), 2.68* (1H, m), 2.51* (1H, m), 2.35 (1H, m), 2.17* (m, 1H), 2.09 (m, 1H), 1.13-1.08 (m, 6H).

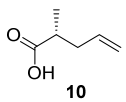
$^{13}$C-NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 100 MHz): δ = 178.49 (C), 142.64 (C), 136.82 (CH), 136.15 (CH), 128.88 (CH), 128.58 (CH), 128.47 (CH), 127.74 (CH), 127.04 (CH), 126.51 (CH), 116.64 (C), 77.16 (C), 76.64 (CH), 75.66* (CH), 38.18 (CH2), 36.71 (CH), 35.94* (CH), 17.72* (CH), 17.13 (CH), 14.62 (CH).

HRMS (ESI) (m/z): $[M+H]^+$ calcd. for $C_{16}H_{24}O_2N$: 262.1807; found: 262.1808 ±5 ppm

$[\alpha]^{20}_D$: +76.1° (c=1.5; $CHCl_3$).

IR (thin film): ν 3390, 3133, 2975, 2360, 1617, 1537, 1452, 1427, 1408, 1171, 1050, 960, 914, 871, 702, 672 $cm^{-1}$.

These spectral characteristics were identical to those previously reported.[3]



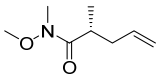

**10**

**(*R*)-2-Methylpent-4-enoic acid (**10**).** A 250 mL round bottomed flask was charged with amide **12** (8.4 g, 32.1mmol), dioxane (50 mL) and $H_2SO_4$ (9 M, 50 mL). The biphasic mixture was heated to reflux for 6 h. After cooling to 0 °C aqueous NaOH ($H_2O$ / NaOH = 1 / 1 w %) was added until pH > 10. The solution was diluted with water (100 mL) and DCM (200 mL) was added. The aqueous layer was acidified to pH ≤ 2 by slow addition of sulfuric acid (6M). The acidified aqueous solution was extracted with DCM (3 x 200 mL) and the combined organic extracts were reduced to a volume of approximately 50 mL and washed with HCl (2 x 40 mL; 1M) to remove the dioxane. The resulting organic layer was dried over $MgSO_4$, filtered and reduced *in vacuo* yielding acid **10** (3.04 g, 83 %) as colorless oil which was used without further purification.

$^1$H-NMR (250MHz, $CDCl_3$): δ = 5.82-5.72 (m, 1H); 5.12-5.04 (m, 2H); 2.60-2.52 (m, 1H); 2.49-2.41 (m, 1H); 2.25-2.17 (m, 1H); 1.19 (d, *J* = 7.00, 3H).

$[\alpha]^{20}_D$: −10.9° (c=1.11; $CHCl_3$).

These spectral characteristics were identical to those previously reported.[4]



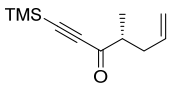
13

**(*R*)-*N*-Methoxy-*N*,2-dimethylpent-4-enamide (**13**).** A solution of acid **10** (9.106 g, 80 mmol) in DCM (200 ml) was cooled to 0 °C before *N*,*N'*-dicyclohexylcarbodiimide (18.11 g, 88 mmol) followed by 4-dimethylaminopyridine (0.975 g, 7.98 mmol) was added. The mixture was stirred for 15 min and *N*,*O*-dimethylhydroxylamine hydrochloride (9.34 g, 96 mmol) followed by $NEt_3$ (13,45 ml, 96 mmol) was added within 5 min. The reaction was allowed to warm to r.t. and was stirred for 16 h. $H_2O$ (200 mL) was added and the suspension was filtered. The filter cake was washed with DCM (3 x 50 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and reduced *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 19:1) afforded the desired amide **13** (10.04 g, 80 %) as colorless oil.

$^1$H-NMR (400MHz, $CDCl_3$): δ = 5.76 (ddd, *J* = 17.18, 10.16, 7.03 Hz, 1H); 5.09-4.99 (m, 2H); 3.69 (s, 3H); 3.18 (s, 3H); 3.00-2.89 (m, 1H); 2.46-2.39 (m, 1H); 2.17-2.09 (m, 1H); 1.13 (d, *J* = 6.88 Hz, 1H).

$[\alpha]^{20}_D$: −26.1° (c=1.175; $CHCl_3$).

These NMR characteristics were identical to those previously reported for the enantiomeric Weinreb amide.[5]



14

**(*R*)-4-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-one (**14**).** A solution of ethynyltrimethylsilane (6.20 ml, 43.9 mmol) in THF (142 mL) was cooled to −40 °C and *n*-BuLi (2.5 M in cyclohexane; 17.54 ml, 43.9 mmol) was added dropwise over 10 min. The solution was stirred at −40 °C for 5min before it was allowed to warm to 0 °C over 15 min. After one h at 0 °C the solution was re-

cooled to −20 °C before a solution of Weinreb amide **13** (4.6 g, 29.3 mmol) in THF (28 mL) was added over 15 min. The reaction mixture was stirred at −20 °C for 1.5 h, and quenched by pouring in a separation funnel containing a saturated aqueous solution of $NH_4Cl$ (250 mL). The phases were separated and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $Na_2SO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) to yield the desired product (**14**) (5.18 g, 91%) as colorless oil.

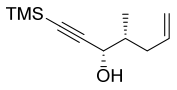
$^1$H-NMR (250MHz, $CDCl_3$): δ = 5.74 (dddd, *J* = 17.00, 10.21, 7.34, 6.72Hz, 1H); 5.11-5.03 (m, 2H); 2.64 (qdd, *J* = 6.98, 6.94, 6.78 Hz, 1H); 2.54 (ddddd, *J* = 14.13, 6.41, 6.41, 1.29, 1.29 Hz, 1H); 2.20 (ddddd, *J* = 14.25, 7.20, 7.00, 1.18, 1.18 Hz, 1H); 1.18 (d, *J* = 6.92 Hz, 3H), 0.25 (s, 9H).

$^{13}$C-NMR (63MHz, $CDCl_3$): δ = 191.07 (C); 135.19 (CH); 117.36 ($CH_2$); 101.31 (C); 99.13 (C); 48.05 (CH); 36.86 ($CH_2$); 15.55 ($CH_3$); -0.59 ($CH_3$).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{11}H_{18}NaOSi$: 217.1025; found: 217.1019 ±5 ppm.

$[\alpha]^{20}_D$: −4.1° (c=1.200; $CHCl_3$).

IR (ATR): 2946, 2934, 1673, 1641, 1457, 1415, 137, 1345, 1251, 1158, 1125, 1057, 990, 915, 841, 760, 703, 628 $cm^{-1}$.




**9**

**(3*S*,4*R*)-4-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-ol (9).** The catalyst was prepared in analogy to a procedure developed by Noyori and co-workers:[6] RuCl[(*S*,*S*)-Tsdpen](p-cymene) ([192139-90-5], 150 mg, 0.236 mmol, 1.0 eq) and KOH (13.23 mg, 0.236 mmol, 1.0 eq) were dissolved in DCM (3.3 mL). After addition of water (3.3 mL) the orange solution turned violet instantly. The biphasic mixture was stirred for 5 min, the phases were separated and the organic layer was washed with water (2 x 2 mL). The organic layer was dried over $CaH_2$, filtered and reduced *in vacuo* to afford the active catalyst (115 mg, 82 %) as violet solid.

Acetylene **14** (1.0 g, 5.15 mmol, 1 eq) was dissolved in 2-propanol (45 mL) which was freshly distilled and degassed by 3 pump-freeze-thaw cycles prior to use. The solution was stirred at 40 °C and the previously prepared catalyst (20 mg, 0.003 mmol, 0.0065 eq), dissolved in 2-propanol (1 mL), was added *via* a syringe pump over 6 h. After consumption of the starting material the reaction was reduced *in vacuo* (30 °C, 40 mbar) and the residue (~3 mL) was purified by flash

column chromatography (hexane/EtOAc 9:1) to afford the desired product (950 mg, 95 %) as colorless.

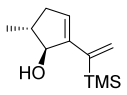
$^{1}$H-NMR (400MHz, $CDCl_3$): δ = 5.87-5.77 (m, 1H); 5.10-5.02 (m, 2H); 4.28 (dd, *J* = 5.44, 5.44 Hz, 1H); 2.40-2.33 (m, 1H); 2.04-1.97 (m, 1H); 1.86-1.78 (m, 2H); 0.18 (bs, 9H).

$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 137.17 (CH); 116.65 ($CH_2$); 105.76 (C); 90.65 (C); 66.98 (CH); 39.40 (CH); 36.86 ($CH_2$); 15.08 ($CH_3$); 0.03 ($CH_3$).

HRMS (ESI) (m/z): $[M\text{-}CH_3]^+$ calcd. for $C_{10}H_{17}OSi$: 181.1049; found: 181.1044 ±5 ppm.

$[\alpha]^{20}_D$: +3.8° (c=1.630; $CHCl_3$).

IR (ATR): 3351, 2960, 2352, 2171, 1640, 1376, 1249,983, 947, 911, 838, 759, 698, 638 $cm^{-1}$.




**19**

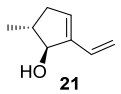
**(1*S*,5*R*)-5-Methyl-2-(1-(trimethylsilyl)vinyl)cyclopent-2-en-1-ol (**19**).** Toluene (1.5 L) was degassed by an argon purge of approximately 1 hour. Enyne **9** (3.00 g, 15.28 mmol, 1 eq) was added and the solution was purged with argon for 10 min and with ethene for 10 min. Grubbs catalyst 2nd generation (0.649 g, 0.764 mmol, 0.005 eq) was added in one portion and the solution was purged with ethene for 15 min. The mixture was heated to 80 °C for 16 h at positive pressure of ethene. After total consumption of the starting material, the mixture was reduced *in vacuo* (40 °C; 60 mbar) to a volume of approximately 70 mL. This volume was applied on a column and eluted with 300 mL of hexane. After purification by flash column chromatography (hexane/EtOAc 19:1), **19** (2.80 g, 14.26 mmol, 93 %) was isolated as a slightly brownish fluid.

$^{1}$H-NMR (400MHz, $CDCl_3$): δ = 5.92 (d, *J* = 2.80 Hz, 1H); 5.79 (dd, *J* = 2.69, 2.69 Hz, 1H); 5.52 (d, *J* = 2.69 Hz, 1H); 4.54 (bs, 1H); 2.79-2.72 (m, 1H); 2.20-2.11 (m, 1H); 1.96-1.90 (m, 1H); 1.51 (bs, 1H); 1.09 (d, *J* = 7.12 Hz); 0.17 (s, 9H).
$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 146.23 (C); 145.72 (C); 130.73 (CH); 125.82 ($CH_2$); 84.31 (CH); 41.47 (CH); 38.97 ($CH_2$); 19.71 ($CH_3$); -0.59 ($CH_3$).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{11}H_{20}NaOSi$: 219.1181; found: 219.1183 ±5 ppm.

$[\alpha]^{20}_D$: −89.1° (c=1.030; $CHCl_3$).

IR (ATR): 3324, 2955, 2926, 2844, 2362, 2341, 1456, 1403, 1373, 1248, 1020, 925, 836, 759, 690, 668, 618 $cm^{-1}$.




21

**(1*S*,5*R*)-5-Methyl-2-vinylcyclopent-2-en-1-ol (**21**).** NaH (60 % dispersion in mineral oil, 0.224 g, 5.60 mmol) was added to HMPA (1.66 ml, 9.57 mmol) in one portion. After 5 min, a solution of **19** (0.500 g, 2.55 mmol) in THF (1.66 ml) was added. After consumption of the starting material as indicated by TLC analysis (60 min) the reaction was quenched *via* addition of a saturated aqueous solution of $NH_4Cl$. The solution was acidified to pH 2 by addition of HCl (1 M) and stirred for approximately 20 min. The aqueous solution was extracted with DCM (3 x 20 mL) and dried over $MgSO_4$. Silica was added and the solvent was reduced *in vacuo*. The crude product was purified by flash column chromatography (dry loading; pentane/$Et_2O$ = 10:1). The solvent was carefully reduced under reduced pressure (700 mbar, 35 °C) to yield **21** (260 mg; 82 %) as colorless liquid.

Note: This reaction is very difficult to carry out, because of the volatility of the product. The yields vary between 40% and 82%.

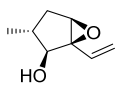
$^1$H-NMR (400MHz, $CDCl_3$): δ = 6.45 (dd, *J* = 17.73, 11.00 Hz, 1H); 5.82 (dd, *J* = 2.63, 2.63 Hz, 1H); 5.46-5.41 (m, 1H); 5.14 (dd, *J* = 10.89, 0.84 Hz, 1H); 4.52 (bs, 1H); 2.78-2.71 (m, 1H); 2.23-2.14 (m, 1H); 1.94-1.87 (m, 1H); 1.51 (bs, 1H); 1.10 (d, *J* = 7.16 Hz, 3H).

$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 143.58 (C); 133.11 (CH); 131.87 (CH); 115.01 ($CH_2$); 83.20 (CH); 42.56 (CH); 38.60 ($CH_2$); 19.67 ($CH_3$).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_8H_{12}NaO$: 147.0786; found: 147.0788 ±5 ppm.

$[\alpha]^{20}_D$: −70° (c=0.2250; $CHCl_3$).

IR (ATR): 3316, 2954, 2924, 2868, 1641, 1454, 1374, 1260, 1021, 988, 905, 813 $cm^{-1}$.




8

**(1*S*,2*S*,3*R*,5*R*)-3-Methyl-1-vinyl-6-oxabicyclo[3.1.0]hexan-2-ol (**8**).** To a solution of **21** (80 mg, 0.644 mmol) in DCM (7.5 mL) at −20 °C was added $VO(acac)_2$ (17.1 mg, 0.064 mmol) in one portion, followed by the dropwise addition of *tert*-butylhydroperoxide (in decane 5.5M; 0.129 ml, 0.709 mmol). The reaction was kept at −20 °C for one h and one h at 0 °C before the mixture was allowed to warm to r.t. As the reaction was not finished, *tert*-butylhydroperoxide (in decane 5.5M;

0.064 mL, 0.354 mmol) was added and stirring was continued at r.t. for one hour. The reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (5 mL; 10 w%) and a saturated aqueous solution of $NH_4Cl$ (5 mL). The aqueous solution was extracted with DCM (5 x 6 mL), dried over $MgSO_4$, filtered and reduced *in vacuo* over a short Vigreux column (530 mbar, 40 °C). The residue was purified by distillation in a Kugelrohr apparatus to yield **8** (72 mg, 80 %) as colorless oil.

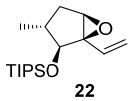
$^1$H-NMR (400MHz, $CDCl_3$): δ = 5.68 (dd, *J* = 17.61, 10.88 Hz, 1H); 5.45 (dd, *J* = 17.48, 1.46 Hz, 1H); 5.24 (dd, *J* = 10.88, 1.46 Hz, 1H); 3.72 (dd, *J* = 9.54, 7.58 Hz, 1H); 3.23 (bs, 1H); 2.06 (dd, *J* = 14.72, 7.40 Hz, 1H); 1.59-1.47 (m, 1H); 1.33 (d, *J* = 9.54 Hz, 1H); 1.19 (ddd, *J* = 14.18, 9.90, 1.34 Hz, 1H); 0.96 (d, *J* = 6.85 Hz, 3H).

$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 132.66 (CH); 119.35 ($CH_2$); 80.06 (CH); 67.13 (C); 63.43 (CH); 36.47 (CH); 33.55 ($CH_2$); 17.20 ($CH_3$).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_8H_{12}NaO_2$: 163.0735; found: 163.0729 ±5 ppm.

$[\alpha]^{20}_D$: −48.3° (c=1.885; $CHCl_3$).

IR (ATR): 3427, 2958, 2930, 2872, 1733, 1456, 1390, 1251, 1189, 1066, 989, 927, 903, 848, 739, 641 $cm^{-1}$.




**22**

**Triisopropyl(((1*R*,2*S*,3*R*,5*R*)-3-methyl-1-vinyl-6-oxabicyclo[3.1.0]hexan-2-yl)oxy)silane (22).** To a solution of epoxide **8** (60 mg, 0.428 mmol) in DCM (0.3 mL) was added lutidine (0.15 mL, 1.28 mmol at 0 °C, followed by triisopropylsilyl trifluoromethanesulfonate (0.128 mL, 0.472 mmol). The reaction was allowed to warm to r.t. As the reaction was not complete after 2 h (TLC control), additional lutidine (0.075 mL, 0.64 mmol) was added, followed by triisopropylsilyl trifluoromethanesulfonate (0.060 mL, 0.221 mmol) at r.t. After 30 min, TLC analysis showed total consumption of the starting material. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 40:1) to yield the desired product (**22**) (96 mg, 76 %) as colorless oil.

$^1$H-NMR (400MHz, $CDCl_3$): δ = 6.06(dd, *J* = 17.18, 10.86 Hz, 1H); 5.42 (dd, *J* =17.18, 1.77 Hz, 1H); 5.21 (dd, *J* = 10.86, 1.77 Hz, 1H); 4.04 (d, *J* = 7.33 Hz, 1H); 3.17 (bs, 1H); 2.17 (dd, *J* =

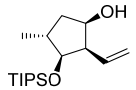
14.15, 7.58 Hz, 1H); 1.83 (qddd, 7.16, 9.97, 7.58, 7.14 Hz, 1H); 1.31 (ddd, *J* = 14.15, 10.11, 1.26 Hz, 1H); 1.11-1.02 (m, 24H).

$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 133.07 (CH); 117.12 ($CH_2$); 82.31 (CH); 67.56 (C); 63.51 (CH); 35.99 (CH); 33.99 ($CH_2$); 18.46 ($CH_3$); 17.74 ($CH_3$); 13.20 (CH).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{32}NaO_2Si$: 319.2069; found: 319.2071 ±5 ppm.

$[\alpha]^{20}_D$: −42.7° (c=0.8700; $CHCl_3$).

IR (ATR): 2943, 2866, 2353, 1714, 1462, 1383, 1144, 1117, 1067, 919, 882, 814, 677 $cm^{-1}$.




**23a**

**(1*R*,2*R*,3*S*,4*R*)-4-Methyl-3-((triisopropylsilyl)oxy)-2-vinylcyclopentan-1-ol (**23a**).** The reaction was carried out in Schlenk flasks using degassed solvents. A Schlenk flask containing $Pd_2(dba)_3{\cdot}CHCl_3$ (4.4 mg, 2.5 mol%) and (*R*,*R*)-DACH ([138517-61-0], 8.7 mg, 7.5 mol%) was purged with argon 5 times before DCM (0.6 mL) was added. After 5 min a mixture of $NEt_3$ (117µL, 0.844 mmol, 5.0 eq) and formic acid (32 µL, 0.844 mmol, 5.0 eq) in DCM (0.6 mL) was added and stirring was continued for additional 5 min before epoxide **22** (50 mg, 0.169 mmol, 1.0 eq) was added neat followed by DCM (0.1 mL). The reaction was stirred until TLC analysis showed total consumption of the starting material (3 h). A saturated aqueous solution of $NH_4Cl$ was added and the mixture was extracted with DCM (3 x 20 mL), the organic extracts were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 40:1) delivering the desired product **23a** (43 mg, 86%) as colorless oil as sole isolable product.

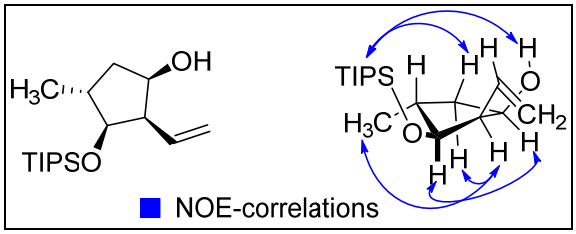
$^1$H-NMR (400MHz, $CDCl_3$): δ = 6.26-6.20 (m, 1H); 5.24-5.22 (m, 1H); 5.20 (d, *J* = 0.78 Hz, 1H); 4.11-4.07 (m, 1H); 3.98 (bd, 3.90 Hz, 1H); 3.25 (d, *J* = 11.16 Hz, 1H); 2.40-2.36 (m, 1H); 2.36-2.32 (m, 1H); 2.25 (ddd, *J* = 14.42, 8.99, 0.95 Hz, 1H); 1.51 (ddd, *J* = 14.37, 5.37, 5.37 Hz, 1H); 1.13-1.05 (m, 21H); 0.97 (d, *J* = 7.32 Hz, 3H).

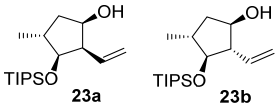
$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 135.16 (CH); 117.43 ($CH_2$); 85.48 (CH); 78.18 (CH); 52.81 (CH); 43.47 ($CH_2$); 41.40 (CH); 20.87 ($CH_3$); 18.21 ($CH_3$); 18.16 ($CH_3$); 12.37 (CH).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{34}NaO_2Si$: 321.2226; found: 321.2223 ±5 ppm.

$[\alpha]^{20}_{D}$: −5° (c=1.0900; $CHCl_3$).

IR (ATR): 3531, 2943, 2866, 2359, 2342, 1636, 1463, 1419, 1383, 1119, 1060, 1014, 997, 912, 881, 847, 823, 729, 678 $cm^{-1}$.




**(1*R*,2*S*,3*S*,4*R*)-4-Methyl-3-((triisopropylsilyl)oxy)-2-vinylcyclopentan-1-ol (**23a/b**).** The following reaction was carried out in Schlenk flasks using degassed solvents. To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.7 mg, 0.0026 mmol, 2.6 mol%) and $Bu_3P$ (~1 µL,0.0026, 2.6 mol%) in THF (0.1 mL) was added $NEt_3$ (28 µL, 0.20 mmol, 2 eq) and formic acid (19 µL, 0.51 mmol, 5 eq). After 5 min, a solution of epoxide **22** (30 mg, 0.10 mmol, 1 eq) in THF (0.2 mL + 0.1 mL rinse) was added. After 3 h TLC analysis showed total consumption of the starting material and two new spots (hexane/EtOAc = 9:1 $R_f$ = 0.80 for **23a** and 0.43 for **23b**, respectively) were identified. The reaction mixture was filtered over a short plug of silica (rinsed with DCM) and reduced *in vacuo*. The mixture was purified by flash column chromatography (hexane/ethyl acetate 19:1) to yield **23a** (14 mg, 46%) and **23b** (13 mg, 43%) as colorless oil.

Data for **23a** see above.

**Isomer 23b:**

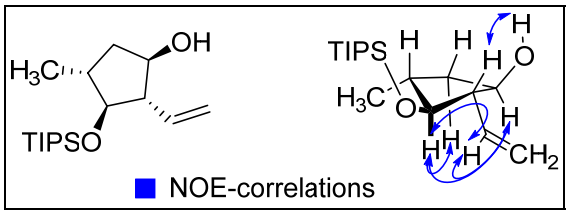
$^1$H-NMR (400MHz, $CDCl_3$): δ = 5.66 (ddd, *J* = 17.33, 10.36, 8.21 Hz, 1H); 5.13 (ddd, 17.18, 1.52, 1.52 Hz, 1H); 5.08 (ddd, *J* = 10.36, 1.52, 1.26 Hz, 1H); 4.01 (dddd, *J* = 7.58, 6.06, 3.85, 3.79 Hz, 1H); 3.78 (dd, *J* = 3.79, 3.79 Hz, 1H); 2.61-2.57 (m, 1H); 2.53 (d, *J* = 7.58 Hz, 1H); 2.29-2.19 (m ,1H); 2.10 (dddd, *J* = 13.64, 8.84, 3.54, 1.01 Hz, 1H); 1.57 (ddd, *J* = 13.39, 7.33, 6.06 Hz, 1H); 1.08-1.03 (m, 24H).

$^{13}$C-NMR (100MHz, $CDCl_3$): δ = 137.93 (CH); 116.72 ($CH_2$); 85.41 (CH); 77.50 (CH); 61.94 (CH); 41.57 (CH); 41.24 ($CH_2$); 20.06 ($CH_3$); 18.23 ($CH_3$); 18.22 ($CH_3$); 12.47 (CH).

HRMS (ESI) (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{34}NaO_2Si$: 321.2226; found: 321.2224 ±5 ppm.

$[\alpha]^{20}_{D}$: −6° (c=0,8650; $CHCl_3$).

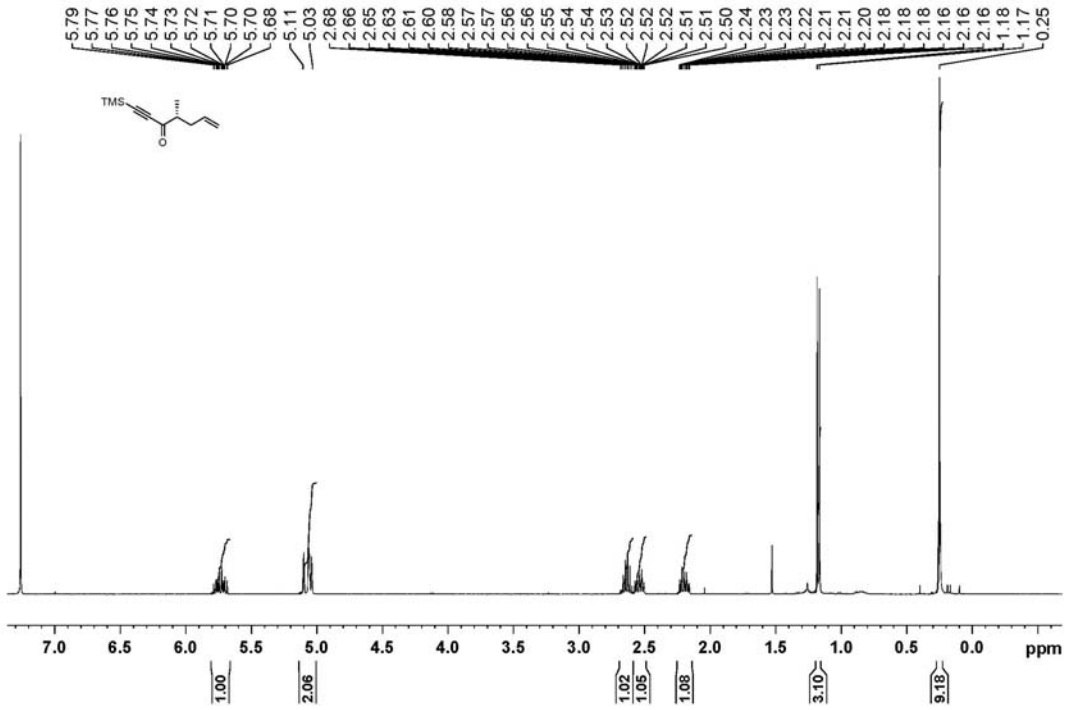
IR (ATR): 3352, 2925, 2866, 2360, 2341, 1636, 1463, 1374, 1258, 1051, 914, 882, 851, 801, 772 668 $cm^{-1}$.

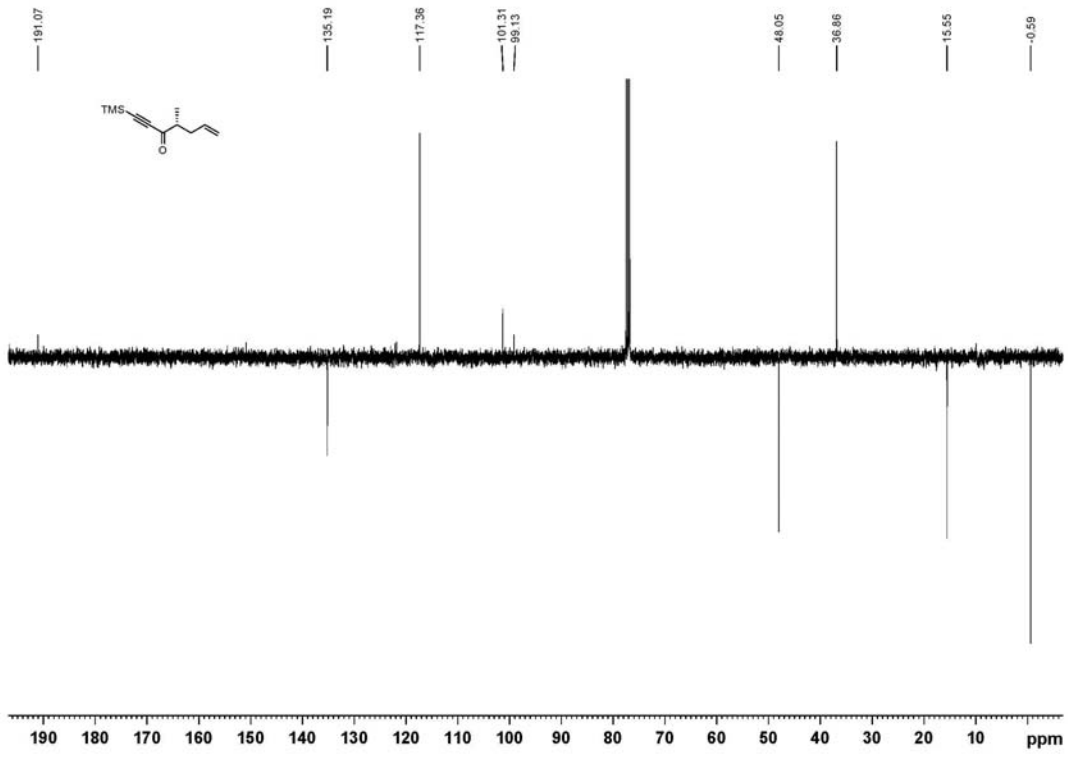


## Selected Spectra

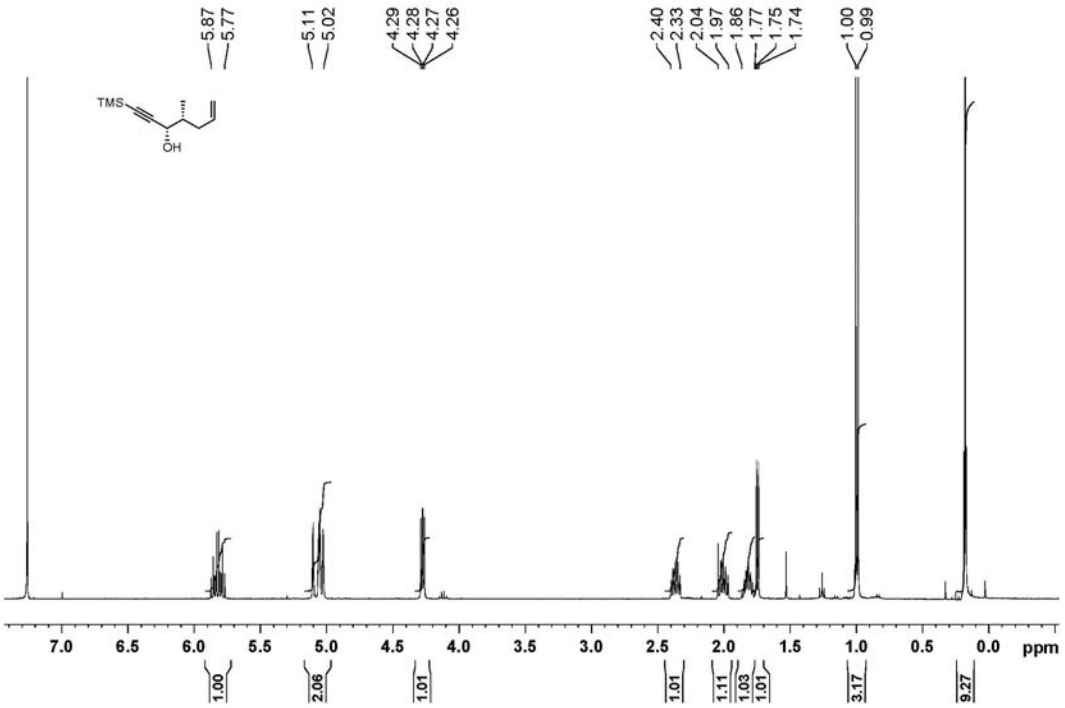
Solvent: $CDCl_3$
Instrument frequency: $^{1}H$: 400 MHz
$^{13}C$: 100 MHz

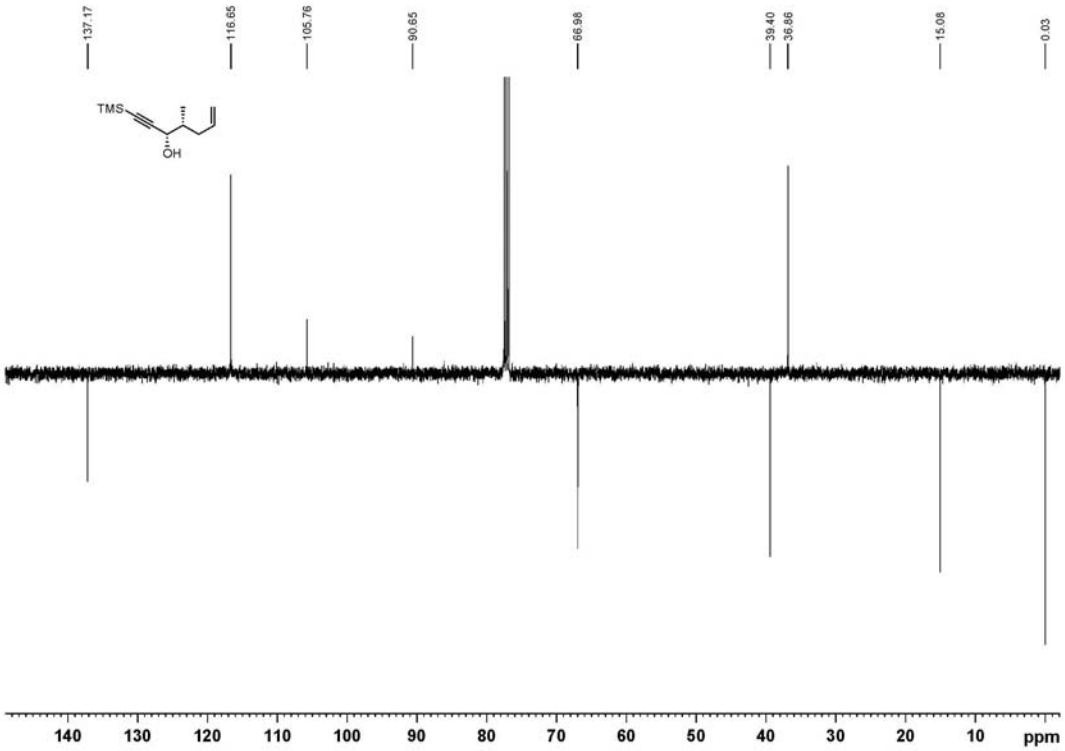
**(*R*)-4-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-one (**14**)**



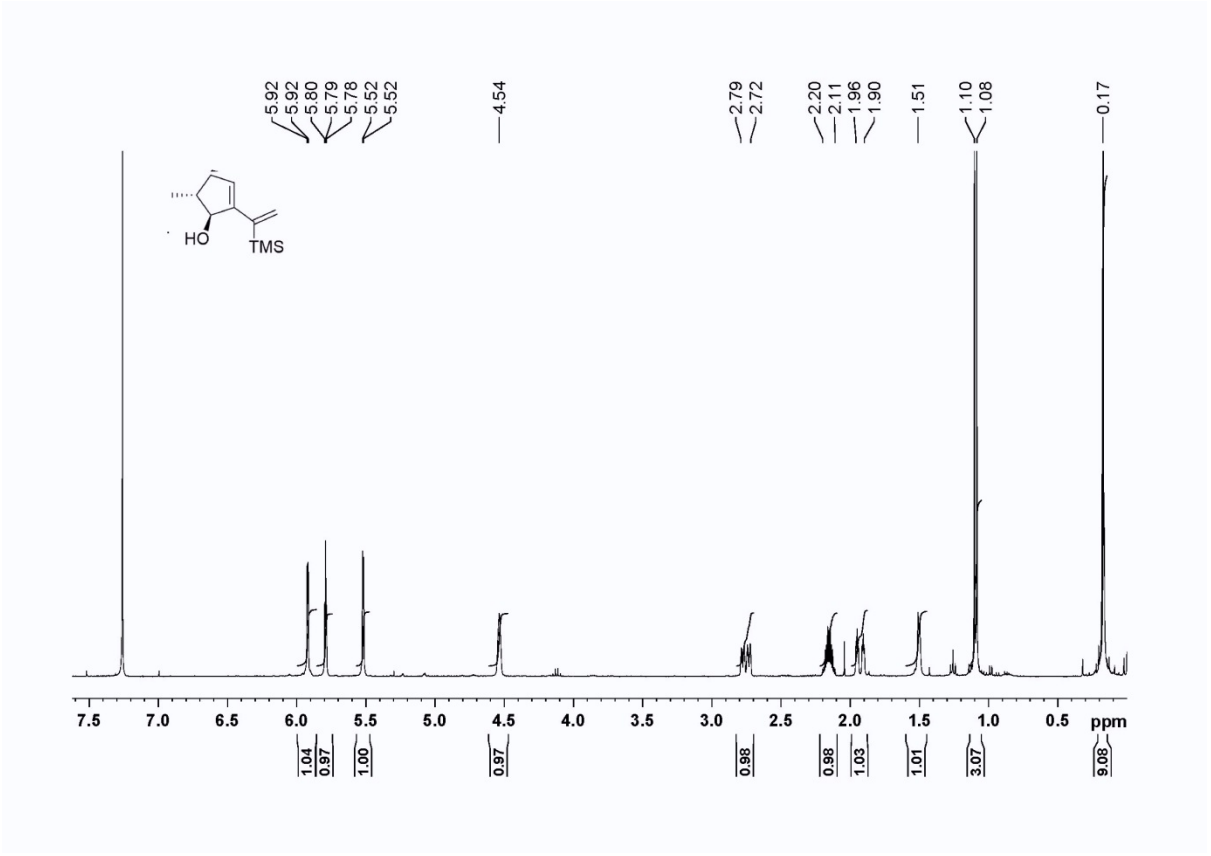



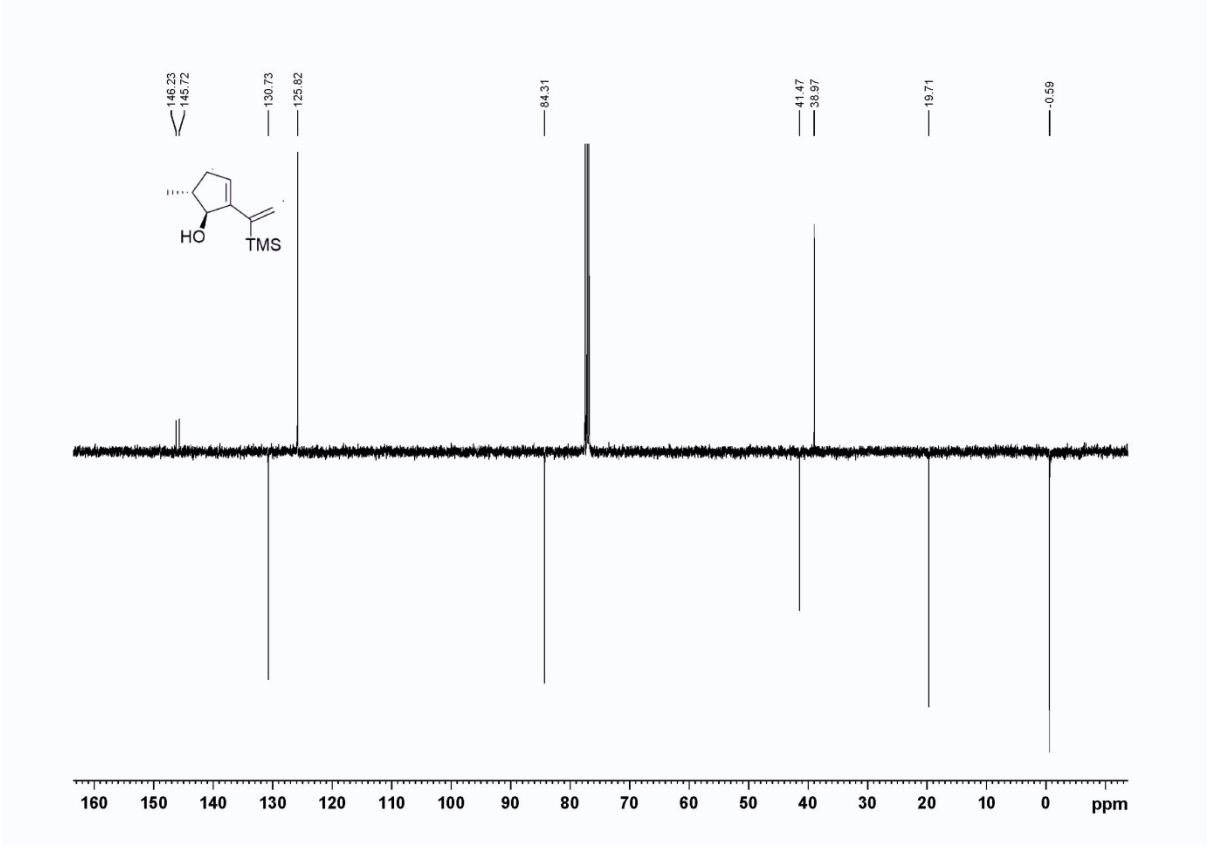
**(3*S*,4*R*)-4-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-ol (9)**



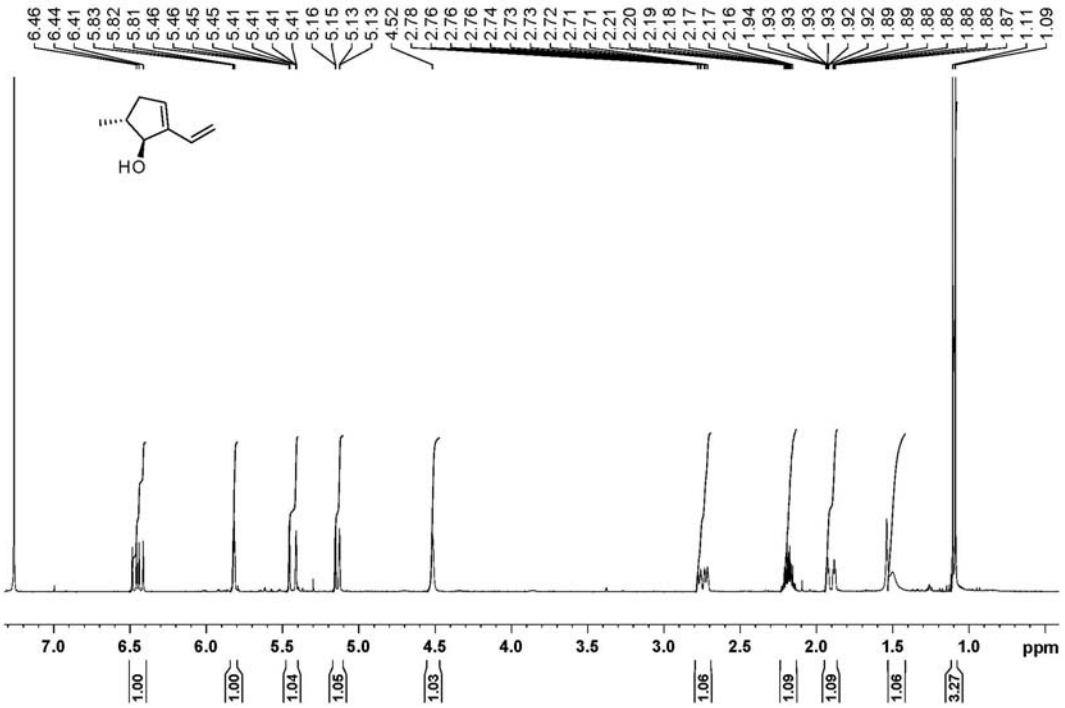



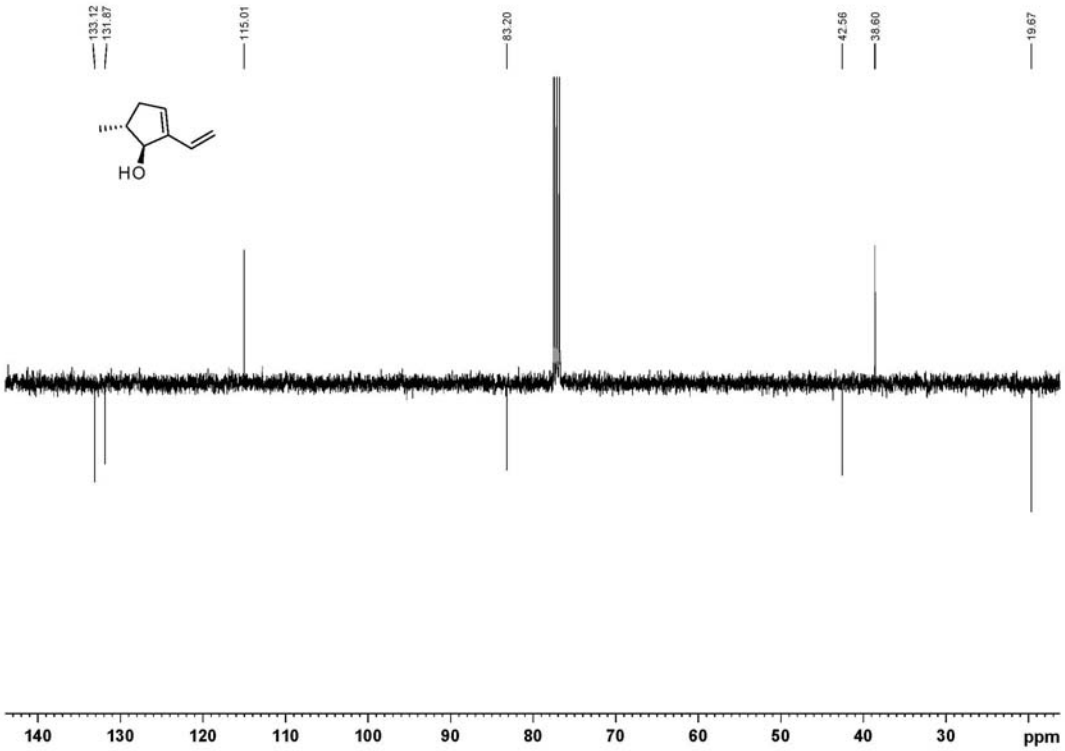
**(1*S*,5*R*)-5-Methyl-2-(1-(trimethylsilyl)vinyl)cyclopent-2-en-1-ol (**19**)**



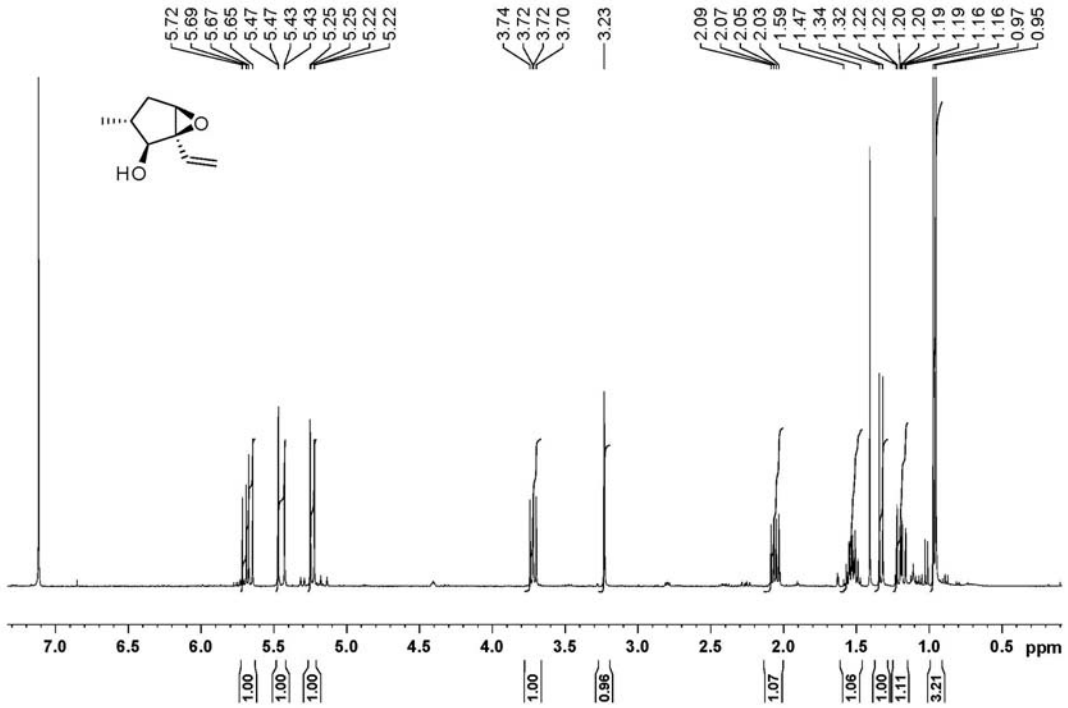



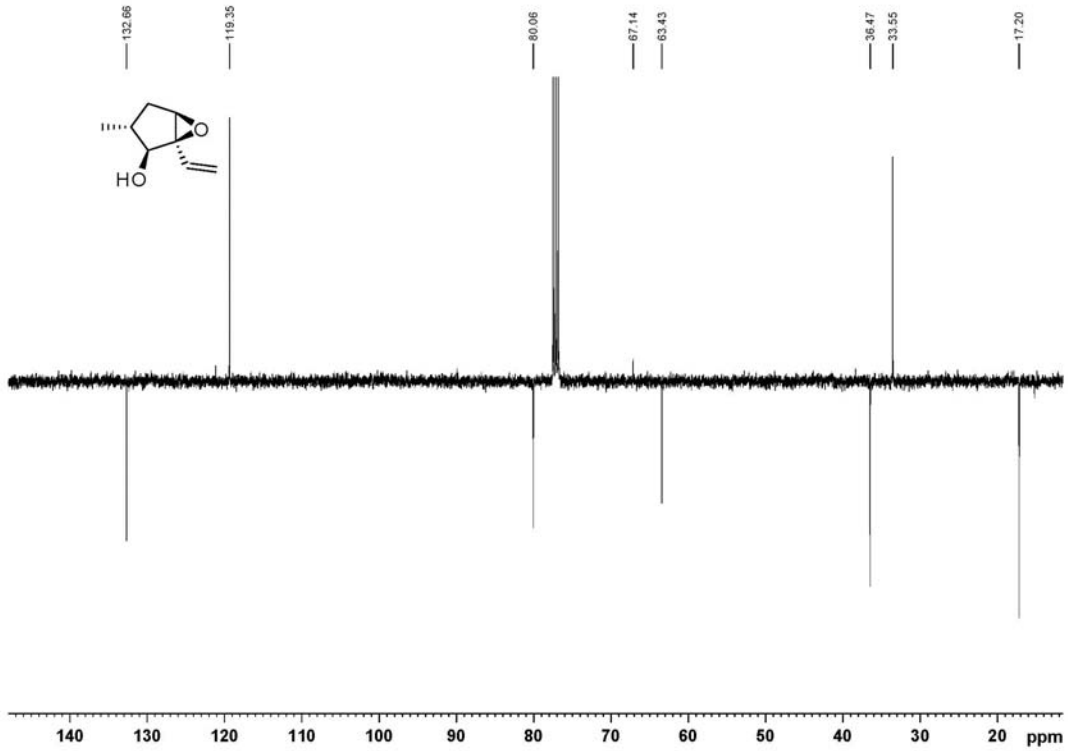
**(1*S*,5*R*)-5-Methyl-2-vinylcyclopent-2-en-1-ol (**21**)**



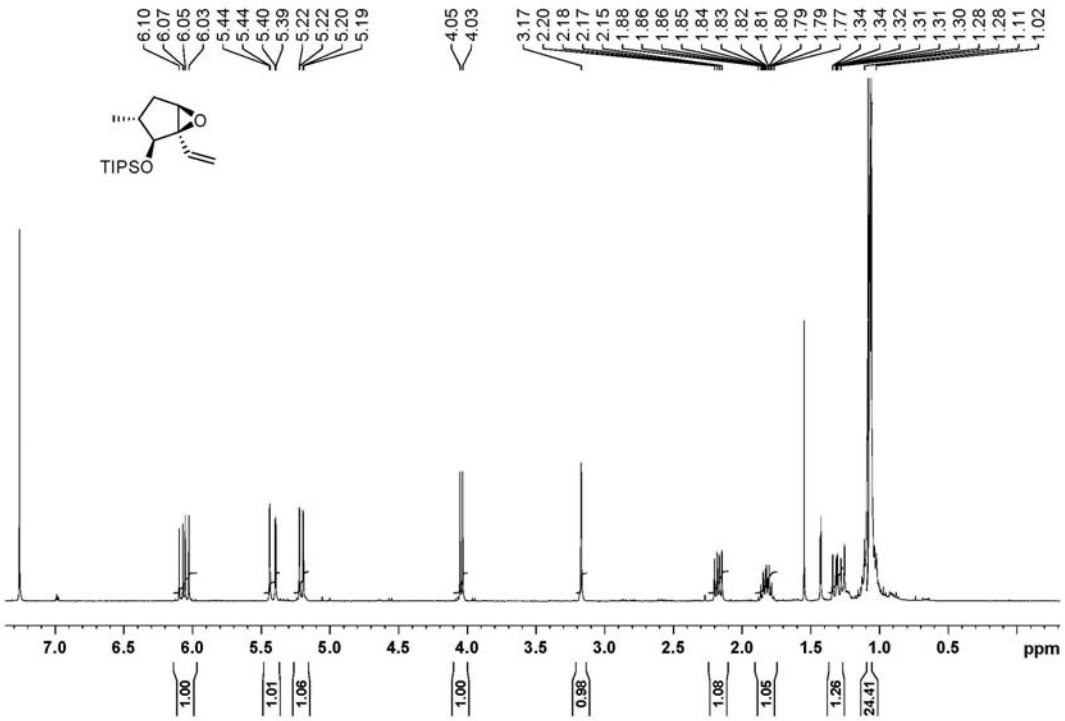



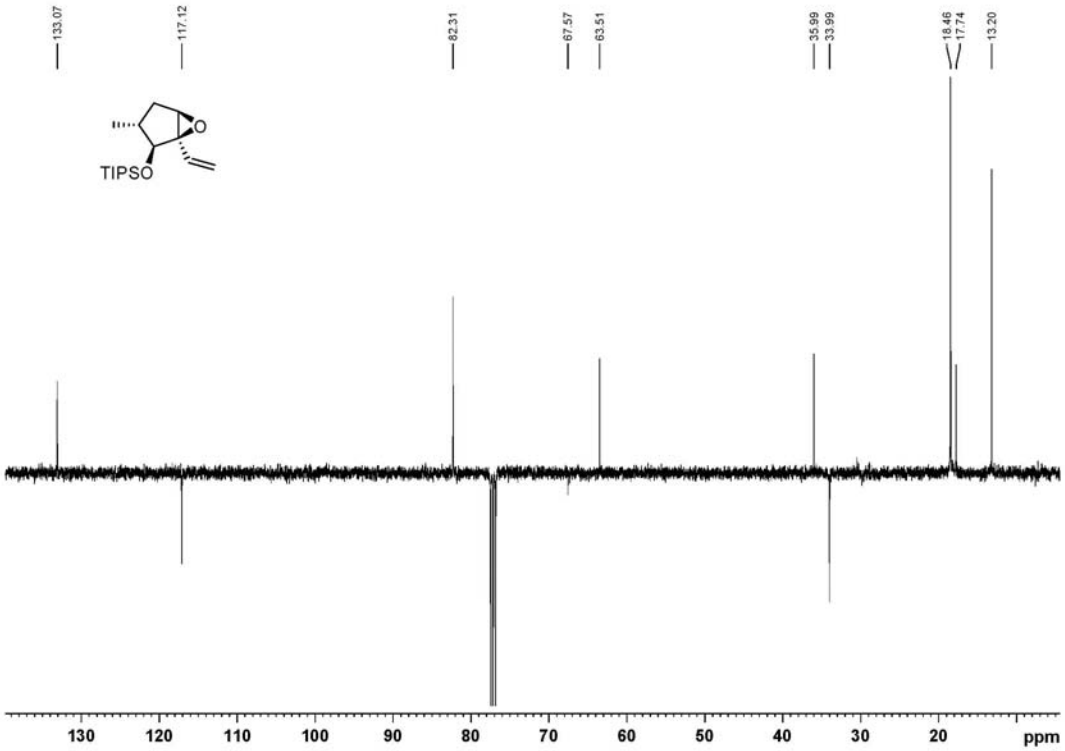
**(1*S*,2*S*,3*R*,5*R*)-3-Methyl-1-vinyl-6-oxabicyclo[3.1.0]hexan-2-ol (**8**)**



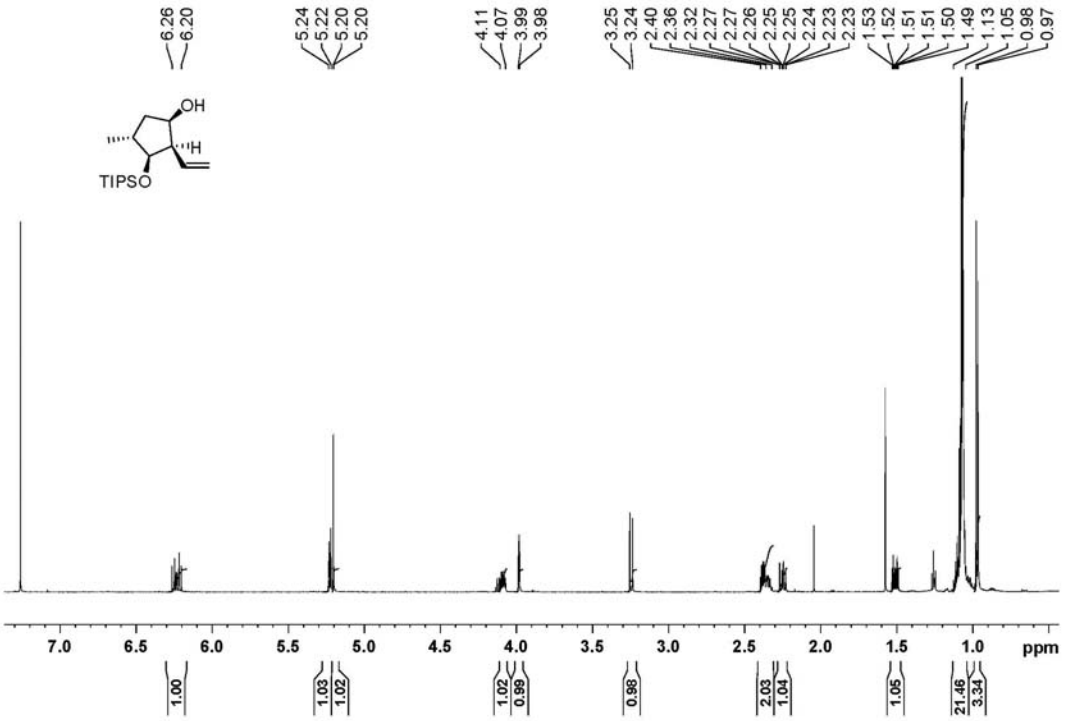



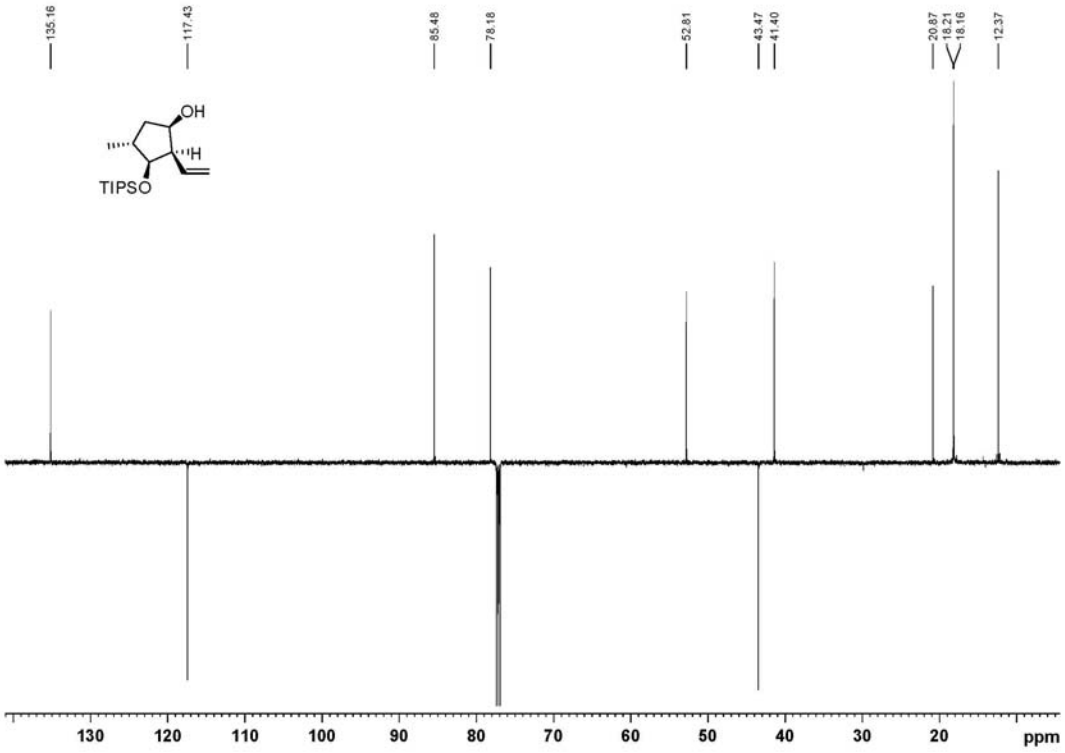
**Triisopropyl(((1*R*,2*S*,3*R*,5*R*)-3-methyl-1-vinyl-6-oxabicyclo[3.1.0]hexan-2-yl)oxy)silane (**22**)**



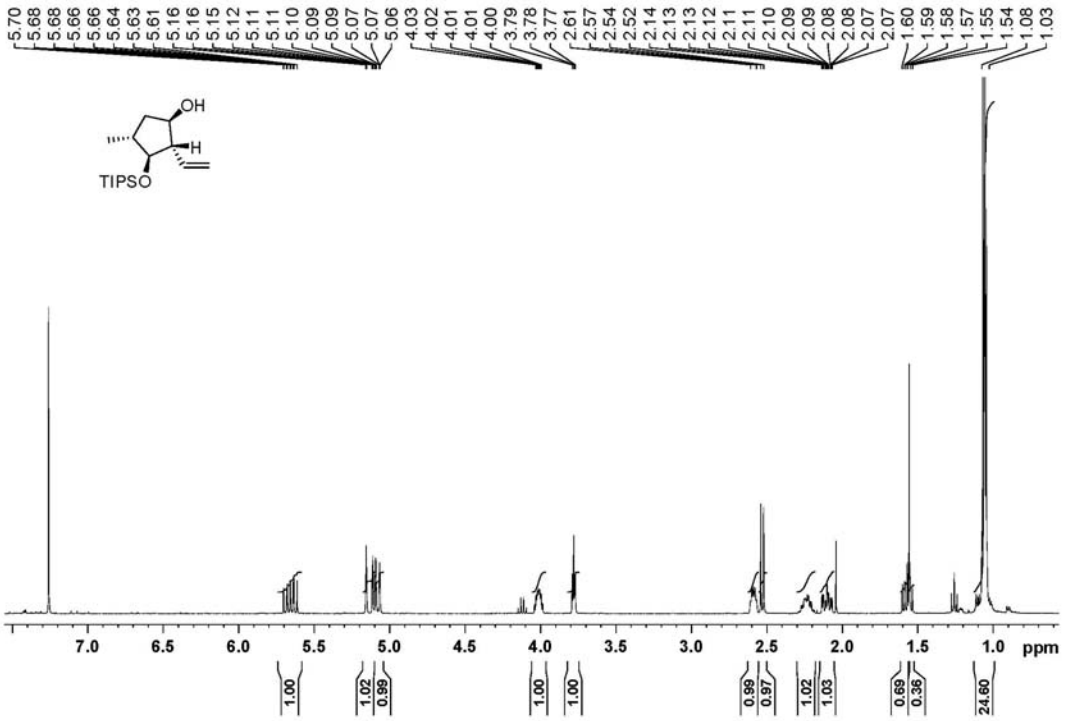



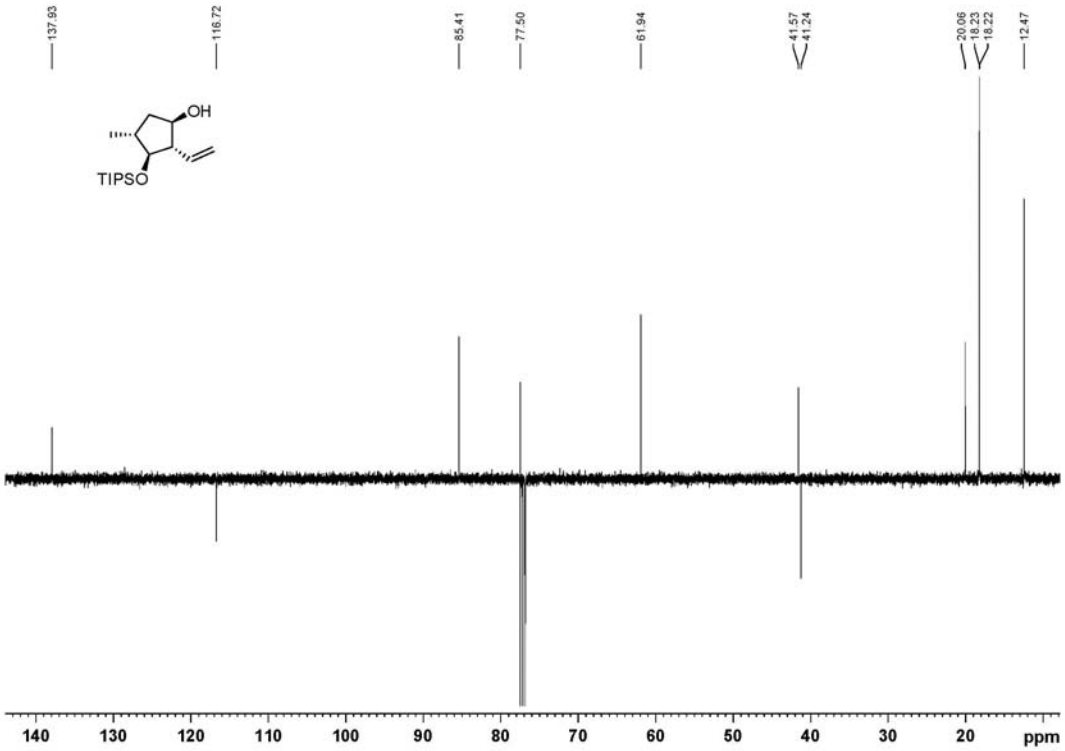
**(1*R*,2*R*,3*S*,4*R*)-4-Methyl-3-((triisopropylsilyl)oxy)-2-vinylcyclopentan-1-ol (**23a**)**



**(1*R*,2*S*,3*S*,4*R*)-4-Methyl-3-((triisopropylsilyl)oxy)-2-vinylcyclopentan-1-ol (**23b**)**



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# 11 APPENDIX III

Lentsch, C.; Fürst, R.; Mulzer, J.; Rinner, U., Jatrophane Diterpenes - Preparation of the Western Fragment of Pl-3. *Eur. J. Org. Chem*. **2013**. Early View: DOI: 10.1002/ejoc.201301616.

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SHORT COMMUNICATION

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# Jatrophane Diterpenes: Preparation of the Western Fragment of Pl-3

Christoph Lentsch,[a] Rita Fürst,[a] Johann Mulzer,[a] and Uwe Rinner*[a]

**Keywords:** Natural products / Total synthesis / Medicinal chemistry / Terpenoids / Oxidation / Lithium

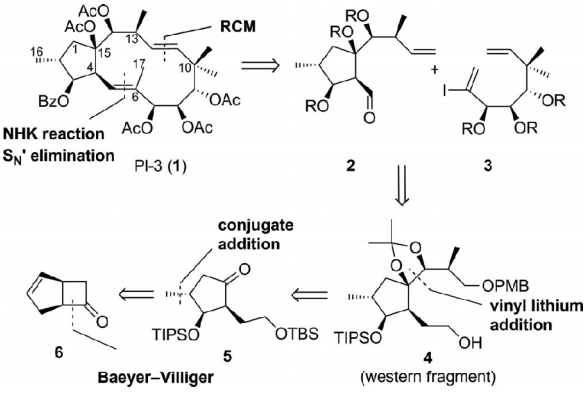
Jatrophane diterpenes are structurally intriguing natural products with promising biological properties. Herein, the synthesis of the western fragment of the Euphorbiaceae constituent Pl-3 starting from (1*R*,5*S*)-bicyclo[3.2.0]hept-2-en-6-one is described. Key steps in the sequence include a Baeyer–Villiger oxidation, an iodolactonization reaction, and the installation of the northern side chain through the addition of a lithiated vinyl bromide. The overall efficiency of the route is increased by taking advantage of latent symmetry.

## Introduction

The genus *Euphorbia* belongs to the Euphorbiaceae family and is considered to be one of the largest genera in the plant kingdom, consisting of more than 2000 known species.[1] Members of this plant family, also commonly referred to as spurges, are endemic in tropical and subtropical regions but can also be found in temperate climate zones. The milky latex of *Euphorbia* plants is a rich source of structurally complex and compelling terpene-based natural products. Since the isolation of jatrophone in 1970,[2] more than 300 different compounds have been isolated. The chemical constituents, mostly diterpenes from the tigliane, ingenane, daphnane, and jatrophane families, show a wide range of biological activities. Among those, multidrug resistance modulating properties, as well as antiproliferative activity, particularly found in jatrophane diterpenes, are most important.[3]

Despite the fascinating structural features and diverse biological properties of the large number of Euphorbiaceae constituents isolated so far, only a few have been synthesized up to now.[4] In recent years, various synthetic strategies toward different jatrophane diterpenes have been presented.[5] Prompted by the pharmacological properties of jatrophane diterpenes as well as the challenging structural features of the terpene-based natural products, we concentrate on the synthesis of Pl-3 (**1**). The jatrophane diterpene Pl-3 consists of a highly oxygenated *trans*-fused bicyclo[10.3.0]pentadecane skeleton and was isolated in 2003 by Hohmann and co-workers from *Euphorbia platyphyllos*, a glabrous or pubescent annual plant that occurs mainly in the southern parts of Europe.[6] Recently, we presented a short and general approach toward five-membered ring synthons suitable for the preparation of various jatrophane diterpenes.[5h] Herein, we report a conceptually different and improved route toward the western fragment of Pl-3.

As outlined in the retrosynthetic analysis (Scheme 1), a ring-closing metathesis (RCM) reaction is intended to be the final key step to close the 12-membered macrocycle. The RCM precursor is envisaged to be prepared by a Nozaki–Hiyama–Kishi (NHK) coupling reaction of aldehyde **2** and vinyl iodide **3** with subsequent reductive alkene shift (C6–C17 to C5–C6 double bond, jatrophane numbering).[7] This strategy takes advantage of the comprehensive work performed by Hiersemann and co-workers on their way to (–)-15-*O*-acetyl-3-*O*-propionylcharaciol. The Hiersemann group was able to demonstrate that, although the C12–C13 ring closure can be accomplished by a RCM reaction, this reaction is not feasible for the elaboration of the sterically congested trisubstituted C5–C6 double bond.[4e,5d] The




Scheme 1. Retrosynthetic analysis (TIPS = triisopropylsilyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl).

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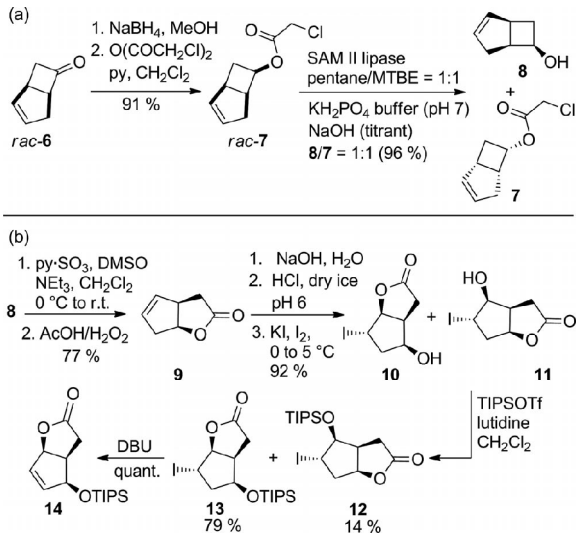
elaboration of aldehyde **2** from intermediate **4** requires the removal of carbon C6, which will be accomplished through elimination and subsequent ozonolytic cleavage, as previously demonstrated by the Hiersemann group.[4e] Cyclopentyl fragment **4** should become accessible from bicyclic ketone **6** by Baeyer–Villiger oxidation, an iodolactonization, and a vinyllithium coupling reaction as key steps.

## Results and Discussion

The synthesis of **14** commenced with enantiomerically pure bicyclo[3.2.0]hept-2-en-6-ol (**8**), as outlined in Scheme 2. This building block became available on a multigram scale from racemic ketone *rac*-(**6**) through diastereoselective reduction with sodium borohydride, followed by esterification with chloracetic anhydride and subsequent enzymatic resolution of chloroacetate *rac*-**7** (Scheme 2, a).[8] Oxidation of the alcohol functionality in **8** (Scheme 2, b) delivered enantiomerically pure bicyclic ketone **6**, which was converted into lactone **9** by treatment of the alkene with aqueous hydrogen peroxide in acetic acid. Lactone **9** was obtained as the sole product of the Baeyer–Villiger oxidation in excellent yield.[9]

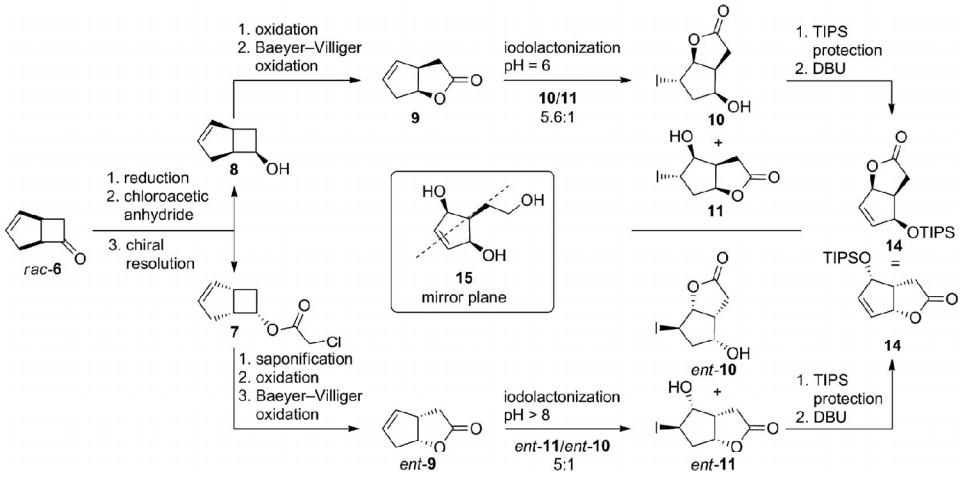



Scheme 2. Preparation of lactone **14** (py = pyridine, MTBE = methyl *tert*-butyl ether, Tf = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).

Next, we turned our attention to the functionalization of the double bond. As iodolactonization was identified as the most feasible procedure to elaborate the stereochemical pattern present in the natural product, lactone **9** was allowed to react with iodine under different reaction conditions. The iodolactonization showed a distinct pH-dependent product formation. Whereas desired iodolactone **10** was favored at pH 6, **11** was isolated as major product if the pH was higher than 8. The inseparable mixture of iodolactones could be easily separated by flash column chromatography after formation of corresponding silyl ethers **12** and **13**.[10]

As the originally envisioned direct methylation of the iodide could not be achieved, we decided to follow a slightly modified approach and targeted the installation of the methyl functionality by conjugate addition. Thus, cyclopentene **14** was prepared in quantitative yield through DBU-mediated elimination of the iodide in **13**. At that point, the great advantage of the latent symmetry in cyclopentene **14** became evident, as the mirror plane present in the substrate (shown in unprotected intermediate **15**, Scheme 3) allowed the conversion of antipodal alcohol *ent*-**8** into enantiomerically pure lactone **14** (Scheme 3). The "enantiomeric switch" was accomplished simply by adjusting the pH during the iodolactonization reaction. As a consequence of the symmetry, both enantiomers of alcohol **8** were efficiently converted into lactone **14**.

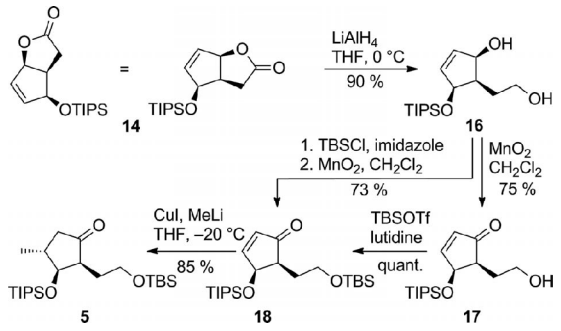
Reduction of the lactone functionality in **14** with lithium aluminum hydride afforded diol **16** in excellent yield (Scheme 4). Next, silylation of the primary hydroxy functionality, followed by allylic oxidation delivered enone **18**,




Scheme 3. Advantage of latent symmetry in the synthesis of **14**.

which served as the substrate for the conjugate addition reaction. Although enone **18** was also accessible in comparable yield by performing the reaction sequence in reverse order, that is, allylic oxidation followed by silylation with TBS-triflate (via **17**), the initial route was favored because of the lower cost of the reagents. Selective 1,4-addition of a methyl cuprate afforded five-membered ring synthon **5** in excellent yield as a single isomer. The preparation of **5** is easily scalable and the short reaction sequence allowed perfect control of all stereogenic centers.

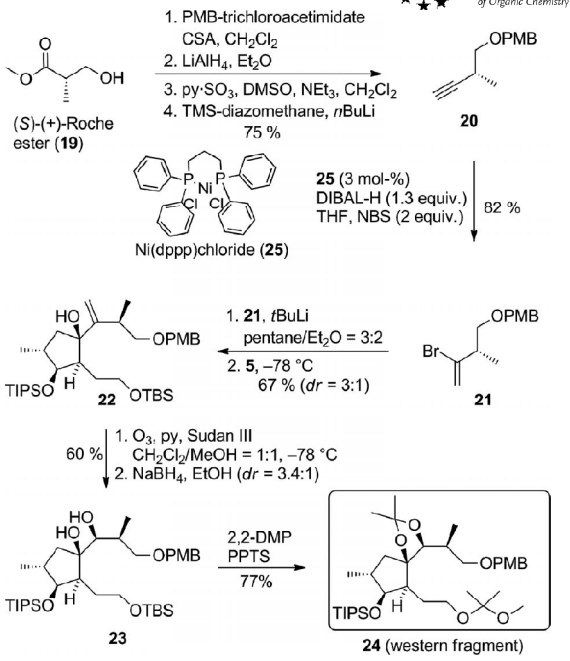



Scheme 4. Preparation of ketone **5**.

Vinyl bromide **21** was prepared in five steps from commercially available (*S*)-(+)-Roche ester (**19**), as shown in Scheme 5. Protection of the hydroxy functionality as a PMB ether was followed by a reduction/oxidation sequence to access the corresponding aldehyde. Next, C1 elongation with TMS-diazomethane afforded alkyne **20** in good overall yield. Vinyl bromide **21** was isolated after regioselective hydroalumination catalyzed by nickel catalyst **25** and subsequent addition of *N*-bromosuccinimide (NBS), following Hoveyda's protocol.[11]

Alkylation of ketone **5** with lithiated vinyl bromide **21** proved to be a tedious task. Whereas the addition of vinylmagnesium bromide as test substrate afforded the corresponding tertiary alcohol in nearly quantitative yield, desired product **22** was not obtained by employing the Grignard reagent derived from vinyl bromide **21**. Reaction of **21** with sodium naphthalide and coupling under Barbier-type conditions also did not solve the problem. Next, bromide **21** was converted into the corresponding boronate and employed in transition-metal-catalyzed coupling reactions, also without success. Finally, the problem was solved upon lithiation of bromide **21** with *t*BuLi in a solvent mixture of pentane/diethyl ether in a ratio of 3:2, followed by slow addition of ketone **5** to the lithiated species. Desired adduct **22** was obtained in 67% yield as a 3:1 diastereomeric mixture, favoring the desired isomer. A detailed discussion of all coupling attempts is provided in the Supporting Information.

Next, ozonolytic cleavage of the exomethylene functionality in the presence of Sudan III as indicator to prevent benzylic oxidation of the PMB protecting group was followed by selective reduction with sodium borohydride in ethanol, and advanced diol **23** was isolated in a 3.4:1 dia-




Scheme 5. Synthesis of the western fragment of Pl-3 (CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, 2,2-DMP = 2,2-dimethoxypropane, PPTS = pyridinium *para*-toluenesulfonate).

stereomeric ratio. The synthesis of the western fragment of Pl-3 was concluded after protection of **23** as an acetonide with concomitant cleavage of the primary silyl ether and protection of the resulting primary alcohol as a ketal. Finally, intermediates **24** and **26** (prepared through acetonide protection of the undesired diastereomeric diol, which was afforded after reduction of ozonolysis product of **22**; see the Supporting Information) served to unambiguously define the relative relationship of all stereogenic centers through NOE correlation studies, as outlined in Figure 1.

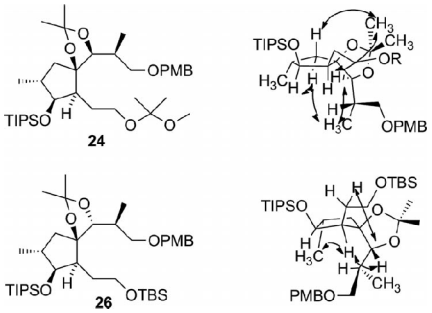



Figure 1. NOE correlations in cyclopentanes **24** and **26**.

## Conclusions

Summarizing, the synthesis of the western fragment of Pl-3 was achieved in a short and stereoselective manner.

Importantly, the overall efficiency of the route was greatly improved by taking advantage of the latent symmetry present in lactone **14**, which allowed the use of both enantiomeric forms of bicyclic alcohol **8** as a starting material for the preparation of **24**. The utilization of **24** in the preparation of Pl-3 is currently under investigation, and further results will be reported in due course.

## Experimental Section

**(3a*R*,6a*S*)-3,3a,6,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (9):**[9,12] To a solution of **6** (9.76 mL, 92 mmol, 1.0 equiv.) in acetic acid (237 mL) and water (26 mL) was added a solution of $H_2O_2$ (30% in water, 22.7 mL, 222 mmol, 2.4 equiv.) in acetic acid (195 mL) and water (22 mL) at 0 °C. The mixture was stirred for 24 h at 0 °C before water (200 mL) was added. The crude product was extracted with $CH_2Cl_2$ (6× 200 mL), and the combined organic extract was washed with aqueous $Na_2SO_3$ (10%, 200 mL) and saturated $NaHCO_3$ (600 mL). ***Note:*** Vigorous formation of $CO_2$ was observed. The workup must be performed with great care! The organic layer was dried with $MgSO_4$ and reduced in vacuo. The product was purified by kugelrohr (bulb-to-bulb) distillation to afford **9** (10.2 g, 88%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.80–5.78 (m, 1 H), 5.59–5.57 (m, 1 H), 5.15–5.11 (m, 1 H), 3.53–3.49 (m, 1 H), 2.80–2.71 (m, 3 H), 2.47–2.42 (m, 1 H) ppm. $[\alpha]_D^{20}$ = –102.3 (*c* = 1.03, $CHCl_3$), m.p. 42–43 °C.

**(3a*S*,4*S*,6*S*,6a*S*)-4-Hydroxy-6-iodohexahydro-2*H*-cyclopenta[*b*]-furan-2-one (10):**[10] Lactone **9** (1.0 g, 8.06 mmol, 1.0 equiv.) was added to a solution of NaOH (0.80 g, 20 mmol, 2.48 equiv.) in water (41 mL). After stirring for 30 min at room temperature, the resulting homogeneous solution was cooled to 0 °C and HCl (32 wt.-% in water, 1.9 mL, 19.7 mmol, 2.44 equiv.) was added. After stirring for approximately 30 s, pH 6 was obtained by the addition of dry ice. A solution of KI (12.04 g, 72.5 mmol, 9.0 equiv.) and $I_2$ (6.13 g, 24.17 mmol, 3.0 equiv.) in water (21 mL) was added in one portion. The mixture was allowed to stir for 24 h between 0 and 5 °C before the reaction mixture was diluted with $CH_2Cl_2$ (150 mL) and quenched by the addition of solid $Na_2SO_3$ (addition until a clear yellow solution over a white precipitate was observed). The resulting colorless solution was saturated with Rochelle's salt and extracted exhaustively with $CH_2Cl_2$. To quantitatively transfer the reaction product into the organic phase, the mixture was extracted at least 10 times (80 mL $CH_2Cl_2$ each time, progress was monitored by TLC analysis). The combined organic layer was washed with brine (200 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash column chromatography (pure toluene to toluene/EtOAc, 5:1) afforded an inseparable mixture of **10** and **11** (2.0 g, 92%) as a slightly yellow oil. The mixture was used for the next step without further purification.

**(1*R*,2*S*,3*S*,4*R*)-2-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-1-{(*R*)-4-[(4-methoxybenzyl)oxy]-3-methylbut-1-en-2-yl}-4-methyl-3-[(triisopropylsilyl)oxy]cyclopentan-1-ol (22):** To a solution of bromide **21** (0.255 g, 0.896 mmol, 1.2 equiv.) in $Et_2O$/pentane (3:2, 4.0 mL) was added a solution of *tert*-butyllithium (1.7 M in pentane, 0.92 mL, 1.57 mmol, 2.1 equiv.) at –78 °C. After 30 min at that temperature, the reaction mixture was allowed to stir at room temperature for 5 min. After recooling of the slightly yellow mixture to –78 °C, a solution of **5** (0.320 g, 0.746 mmol, 1.0 equiv.) in $Et_2O$/pentane (3:2; 3.5 mL) was added slowly (over a period of 10 min). Stirring at that temperature was continued for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3× 20 mL). The combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc, 40:1) to afford **22** (0.237 g, 50%) as a colorless oil with the corresponding C1 epimer (**S10**, see Supporting Information) as a side product (80 mg, 17%). ***Note:*** The exact ratio of the solvents is essential for the success of this reaction. $Et_2O$ and pentane, freshly distilled from sodium, were mixed in a 3:2 ratio, and this solvent mixture was stored over molecular sieves (3 Å) prior to use. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27–7.24 (m, 2 H), 6.89–6.85 (m, 2 H), 5.28 (s, 1 H), 4.91 (s, 1 H), 4.48 (d, *J* = 11.6 Hz, 1 H), 4.38 (d, *J* = 11.6 Hz, 1 H), 4.11 (d, *J* = 3.8 Hz, 1 H), 4.00 (s, 1 H), 3.80 (s, 3 H), 3.69 (ddd, *J* = 9.8, 6.9, 4.7 Hz, 1 H), 3.63–3.57 (m, 1 H), 3.46 (dd, *J* = 9.1, 4.9 Hz, 1 H), 3.28 (dd, *J* = 9.1, 9.1 Hz, 1 H), 2.44–2.23 (m, 2 H), 2.08 (ddd, *J* = 10.0, 3.3, 3.3 Hz, 1 H), 1.85 (dddd, *J* = 14.4, 9.8, 5.0, 4.9 Hz, 1 H), 1.63–1.57 (m, 1 H), 1.61 (dd, *J* = 13.9, 3.3 Hz, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.13–1.09 (m, 21 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 159.24 (C), 153.93 (C), 131.05 (C), 129.25 (CH), 113.85 (CH), 109.31 ($CH_2$), 86.17 (C), 83.27 (CH), 75.91 ($CH_2$), 72.72 ($CH_2$), 62.15 ($CH_2$), 55.41 ($CH_3$), 47.86 ($CH_2$), 45.35 (CH), 40.17 (CH), 34.81 (CH), 26.12 ($CH_3$), 25.41 (C), 20.80 (CH), 20.42 (CH), 18.30 ($CH_3$), 12.72 (CH), –5.16 ($CH_3$) ppm. HRMS (ESI): calcd. for $C_{36}H_{66}NaO_5Si_2$ $[M + Na]^+$ 657.4346; found 657.4332 ± 5 ppm. $[\alpha]_D^{20}$ = +3.7 (*c* = 0.81, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3494, 2954, 2866, 2360, 2341, 1716, 1613, 1586, 1540, 1513, 1462, 1386, 1360, 1248, 1220, 1097, 1031, 882, 834, 774, 669, 657 $cm^{-1}$.

**Supporting Information** (see footnote on the first page of this article): Experimental details and copies of the $^1$H NMR and $^{13}$C NMR spectra of all compounds.

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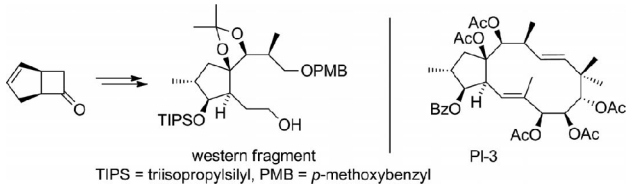
Total Synthesis




The synthesis of the western fragment of Pl-3 is developed by taking advantage of the latent symmetry in an intermediate; both enantiomers are thus converted into the desired substrate. Key steps of the synthesis include a Baeyer–Villiger oxidation, an iodolactonization reaction, and the addition of a vinyllithium species to the completed cyclopentane moiety of the natural product.

**C. Lentsch, R. Fürst, J. Mulzer, U. Rinner*** ..... **1–6**

Jatrophane Diterpenes: Preparation of the Western Fragment of Pl-3

**Keywords:** Natural products / Total synthesis / Medicinal chemistry / Terpenoids / Oxidation / Lithium

# Supporting Information

## Jatrophane Diterpenes – Preparation of the Western Fragment of Pl-3

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## General Methods

All non-aqueous reactions were carried out under a positive pressure of argon using oven-dried (100 °C) or flame-dried glassware (under vacuum) unless otherwise noted.

THF was dried by distillation from potassium under argon. Diethyl ether, dimethoxyethane, toluene and benzene were purified by distillation and dried by distillation from sodium/benzophenone ketyl under argon. DCM was purified by distillation and dried by distillation from phosphor pentoxide and passage over aluminum oxide, neutral, activity I. DMSO and *N*,*N*-dimethylformamide were dried by distillation from calcium hydride under reduced pressure. Dry solvents were stored under an argon atmosphere over molecular sieves (4Å). Triethylamine, diethylisopropylamine and diisopropylamine were distilled from calcium hydride under an atmosphere of argon prior to use. If noted, chemicals were purified according to "*Purification of laboratory chemicals (4$^{th}$ ed.)*" or therein cited references.[1] All other commercially available reagents were used without further purification. Except if indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography using ALUGRAM®Xtra SIL G aluminum sheets (Silica 60) purchased from Macherey-Nagel. The plates were developed with a mixture of hexane/ethyl acetate or toluene/ethyl acetate. Unless the compound was colored, UV-active spots were detected at longwave UV (254 nm) or shortwave (180 nm). Most plates were additionally treated with one of the following visualization reagents: CAM [$H_2SO_4$ (conc., 22 mL), phosphomolybdic acid (20 g), $Ce(SO_4)_2$ (0.5 g), 378 mL water)] or silica gel impregnated with iodine.

Preparative column chromatography and flash chromatography were performed with silica gel 60 from Merck (0.040-0.063 µm, 240-400 mesh). For HPLC separations on analytical scale module systems from Jasco (PU-980, UV-975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was Superphere Si 60 (40 µm, Merck) or Nucleosil 50 (4 µm, Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^T_D$, concentration (g/100 mL), and solvent.

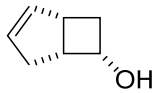
NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and

referenced to the residual $CDCl_3$ signal ($^1H$, δ = 7.26, $^{13}C$, δ = 77.16).[2] All $^1H$ and $^{13}C$ shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broadened signal). Coupling constants J are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY)

IR spectra were recorded using a Bruker vertex 70 FT-IR spectrometer and are reported in wave numbers ($cm^{-1}$). All compounds were measured using the attenuated total reflection accessory Standard Golden Gate ATR, a single reflection monolithic diamond ATR module.

High resolution mass spectra were performed on a mass spectrometer using ESI-mode and a UHR-TOF (Qq-TOF) mass analyzer (acetonitrile/MeOH 1:1, +1% $H_2O$).

## Experimental part



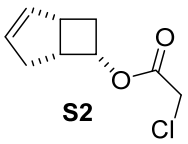

**S1**

**(±)-*cis*-Bicyclo[3.2.0]hept-2-en-6-ol (**S1**).**[3] Sodium borohydride (4.37 g, 116 mmol, 0.5 eq) was suspended in methanol (125 ml) and the solution was cooled to −78 °C. After the evolution of hydrogen gas has ceased, a solution of (*rac*)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (25.0 g, 231 mmol, 1.0 eq) in methanol (62 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred at −78 °C for one hour, before it was allowed to warm to rt. $Et_2O$ (60 mL) and aqueous HCl (58 mL, 2M) were carefully added. The layers were separated and the organic phase was extracted with water (3 x 80 mL). The combined aqueous phase was back-extracted with $Et_2O$/hexane (1:1; 3 x 100 mL). The combined organic phase was washed with brine (150 mL) and dried over $MgSO_4$. The solvents were removed at 35 °C and 250 mbar to yield **S1** (24.16 g, 95 %) as a slightly yellow oil. The product was used for the next step without any further purification.

**$^1$H-NMR (250MHz, $CDCl_3$):** δ = 5.85 (bs, 2H); 4.42 (m, 1H); 3.16 (m, 1H); 3.02 (m, 1H); 2.76 (m, 1H); 2.69 (m, 1H); 2.40 (m, 1H); 1.68 (bs, 1H); 1.59 (ddd, *J* = 12.9, 4.5, 1.1Hz, 1H).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_7H_{10}ONa$: 133.0629; found: 133.0628 ±5 ppm.

These spectral characteristics are identical to those reported by Fairlamb *et al*.[4]




**S2**

**(±)-*cis*-Bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate (**S2**).** To a solution of **S1** (25.4 g, 231 mmol, 1.0 eq) and pyridine (18.7 mL, 231 mmol, 1.0 eq) in DCM (116 mL) was added a solution of chloroacetic anhydride (43.9 g, 231 mmol, 1.0 eq) in DCM (116 ml) dropwise over a period of 30 min at 0 °C. After stirring for one hour at 0 °C, methanol (100 mL) was added and the solution was allowed to warm to rt. DCM (100 mL) was added and the mixture was washed with aqueous HCl (1M; 3 x 100 mL). The organic phase was washed with water (2 x 150 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash column chromatography (hexane/EtOAc 7:1) to afford **S2** (41.30 g, 96 %) as a colorless oil.

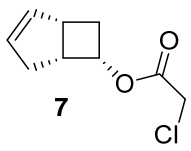
**$^1$H-NMR (250MHz, $CDCl_3$):** δ = 5.82 (bs, 2H); 5.28 (dt, *J* = 8.1, 5.9Hz, 1H); 4.05 (s, 2H); 3.32 (m, 1H); 3.06 (m, 1H); 2.77 (m, 1H); 2.50 (m, 2H); 1.82 (m, 1H).

**$^{13}$C-NMR (63MHz, $CDCl_3$):** δ = 167.1 (C); 134.6 (CH); 132.8 (CH); 70.1 (CH); 41.6 (CH); 41.4 ($CH_2$); 41.1 (CH); 37.0 ($CH_2$); 33.0 ($CH_2$).

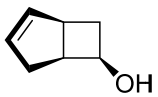
**HRMS (ESI) (m/z):** $[M]^+$ calcd. for $C_9H_{11}ClO_2$: 186.0448; found: 186.0444 ±5 ppm.

**IR (film):** 2941; 1758; 1414; 1349; 1311; 1286; 1186; 1047; 1001 $cm^{-1}$.

These spectral characteristics are identical to those reported by Mulzer *et al*.[3b]




**7**




**8**

**(1*S*,5*R*,6*S*)-Bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate (**S3**) and (1*R*,5*S*,6*R*)-bicyclo[3.2.0]hept-2-en-6-ol (**7**).** To a solution of racemic **S2** (22.0 g, 118 mmol, 1.0 eq) in a mixture of pentane (92 mL) and MTBE (92 mL) was added a potassium dihydrogenphosphate buffer solution (50 mM, pH 7.0; 283 mL) and the biphasic system was vigorously stirred at rt. After the addition of SAM II lipase (100 mg) the pH of the reaction mixture was monitored and continuously adjusted to 7.0 using a Merck Titrino 702SM and 0.5M NaOH. After consumption of 0.5 eq NaOH (0.5M; 118 mL, 58.9 mmol, 0.5 eq) the reaction was terminated by the addition of HCl (2M). The pH was adjusted to 4 and the layers were separated. The aqueous phase was extracted with $Et_2O$ (2 x 250 mL) and the combined organic layer was dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude material was purified by flash column chromatography (hexane/EtOAc 7:1) to afford **7** (10.68 g, 57.2 mmol, 48 %) as well as **8** (6.30 g, 57.2 mmol, 48 %) both in optically pure form, as colorless oils.

**(1*S*,5*R*,6*S*)-Bicyclo[3.2.0]hept-2-en-6-yl 2-chloroacetate (**7**)**

**$^1$H-NMR (250MHz, $CDCl_3$):** δ = 5.82 (bs, 2H); 5.28 (dt, *J* = 8.1, 5.9Hz, 1H); 4.05 (s, 2H); 3.32 (m, 1H); 3.06 (m, 1H); 2.77 (m, 1H); 2.50 (m, 2H); 1.82 (m, 1H).

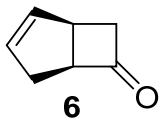
**$[\alpha]^{20}_D$:** −19.9° (c = 1.00; $CHCl_3$).

**(1R,5S,6R)-bicyclo[3.2.0]hept-2-en-6-ol (**8**)**

**$^1$H-NMR (250MHz, $CDCl_3$):** δ = 5.85 (bs, 2H); 4.42 (m, 1H); 3.16 (m, 1H); 3.02 (m, 1H); 2.76 (m, 1H); 2.69 (m, 1H); 2.40 (m, 1H); 1.68 (bs, 1H); 1.59 (ddd, *J* = 12.9, 4.5, 1.1Hz, 1H).

**$[\alpha]^{20}_D$:** −80.7° (c = 1.15; $CHCl_3$).

The NMR spectral characteristics are identical to the racemic products **S2** and **S1**. Faber *et al* reported $[\alpha]_D$: −75.8° (c=2.46; $CHCl_3$; ee = 98.4%).[5] The optical rotation of ***ent*-7** was first determined by Newton et al[6] to be $[\alpha]_D$: 61.5° (c = 1.0; $CHCl_3$) and later published (without information regarding the temperature) by Medici *et al*. to be $[\alpha]_D$: 68° (c = 1.1; $CHCl_3$).[7]




**6**

**(1*R*,5*S*)-Bicyclo[3.2.0]hept-2-en-6-one (6).**

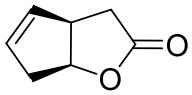
**Method A: Oxidation with IBX:** To a solution of **7** (0.50 g, 4.54 mmol, 1.0 eq) in EtOAc (45 mL) was added IBX (1.9 g, 6.8 mmol, 1.5 eq). The suspension was heated to reflux until TLC analysis showed total consumption of the starting material (3 h). The mixture was cooled to 0 °C, filtered and reduced by careful destillation under reduced pressure (~220 mbar) to a volume of approximately 3-5 mL using a Vigreux column. The residue was applied on a silica gel column (2 cm diameter, 25cm length) packed with pentane. The product was eluted with pentane (50 mL), followed by a mixture of pentane and $Et_2O$ (10:1) to afford ketone **6** (0.39 g, 80 %) as a colorless oil.

**Method B: Oxidation under Parikh-Doering conditions**: To a solution of alcohol **7** (2.00 g, 18.2 mmol, 1.0 eq) in DMSO (15.5 mL) and DCM (90 mL) was added triethylamine (10.2 ml, 72.6 mmol, 4.0 eq) and $SO_3$·pyridine (5.78 g, 36.3 mmol, 2.0 eq) at 0 °C. The reaction mixture was stirred for 2 h when TLC analysis indicated complete consumption of the starting material. The reaction was quenched by the addition of aqueous HCl (1M, 90 mL) and the mixture was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with water (100 mL), dried over $MgSO_4$ and the solvent was carefully removed under reduced pressure (550mbar, 40 °C). The crude product was purified *via* Kugelrohr distillation (bulb-to-bulb distillation) and **6** (1.65 g, 84 %) was obtained as a colorless oil.

**$^1$H-NMR (250MHz, $CDCl_3$):** δ = 5.86-5.83 (m, 1H); 5.80-5.78 (m, 1H); 3.90-3.84 (m, 1H); 3.51-3.44 (m, 1H); 3.32 (ddd, *J*=17.40, 8.62, 3.00Hz, 1H); 2.74-2.66 (m, 2H); 2.48 (ddddd, *J*= 17.31, 9.88, 2.10, 2.00, 1.71Hz, 1H).

**$[\alpha]^{20}_D$:** +90.3 ° (c = 1.13; $CHCl_3$).

These spectral characteristics are identical to those reported by Abraham[8] for (±)-bicyclo[3.2.0]hept-2-en-6-one.



**9**

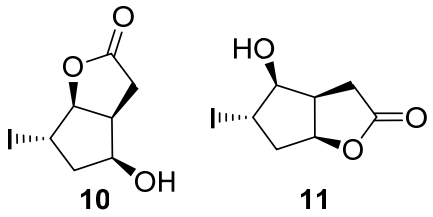
**(3a*R*,6a*S*)-3,3a,6,6a-Tetrahydro-2H-cyclopenta[b]furan-2-one (**9**).**[9,10] To a solution of **7** (9.76 mL, 92 mmol, 1.0 eq) in acetic acid (237 mL) and water (26 mL) was added a solution of $H_2O_2$ (30 % in water, 22.7 mL, 222 mmol, 2.4 eq) in acetic acid (195 mL) and water (22 mL) at 0 °C. The mixture was stirred for 24 h at 0 °C before water (200 mL) was added. The crude product was extracted with DCM (6 x 200 mL) and the combined organic extracts were washed with aqueous $Na_2SO_3$ (10 %, 200 mL) and saturated $NaHCO_3$ (600 mL). Note: Vigorous formation of $CO_2$ is observed. The work-up must be carried out with great care! The organic layer was dried over $MgSO_4$ and reduced *in vacuo*. The product was purified *via* Kugelrohr distillation (bulb-to-bulb distillation) affording **9** (10.2 g, 88 %) as a white solid.

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 5.80-5.78 (m, 1H); 5.59-5.57 (m, 1H); 5.15-5.11 (m, 1H); 3.53-3.49 (m, 1H); 2.80-2.71 (m, 3H); 2.47-2.42 (m, 1H).

**$[\alpha]^{20}_D$:** −102.3° (c = 1.03; $CHCl_3$).

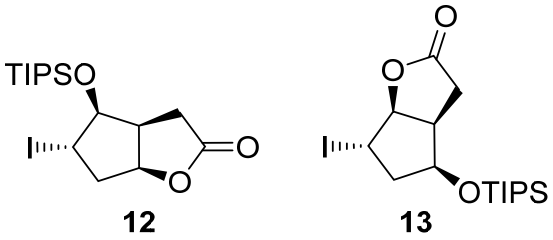
**mp:** 42-43 °C.

These spectral characteristics are identical to those reported by Grieco.[10]




10 11

**(3a*S*,4*S*,6*S*,6a*S*)-4-Hydroxy-6-iodohexahydro-2H-cyclopenta[b]furan-2-one (**10**).**[11] Lactone **9** (1.0 g, 8.06 mmol, 1.0 eq) was added to a solution of NaOH (0.80 g, 20 mmol, 2.48 eq) in water (41 mL). After stirring for 30 min at rt the resulting homogenous solution was cooled to 0 °C and HCl (32 w% in water, 1.9 mL, 19.7 mmol, 2.44 eq) was added. After stirring for approximately 30 seconds, pH 6 was adjusted by the addition of dry ice. A solution of KI (12.04 g, 72.5 mmol, 9.0 eq) and $I_2$ (6.13 g, 24.17 mmol, 3.0 eq) in water (21 mL) was added in one portion. The mixture was allowed to stir for 24 h between 0 and 5 °C before the reaction was diluted with DCM (150 mL) and quenched by the addition of solid $Na_2SO_3$ (addition until a clear yellow solution over white a precipitate was observed). The resulting colorless solution was saturated with Rochelle's salt and extracted exhaustively with DCM. In order to quantitatively transfer the reaction product into the organic phase, the mixture had to be extracted at least 10 times (80 mL of DCM each, progress was monitored by TLC analysis). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by flash column chromatography (pure toluene to toluene/EtOAc 5:1) afforded an inseparable mixture of **10** and **11** (2.0 g, 92 %) as a slightly yellow oil. The mixture was used for the next step without further purification.




12 13

**(3a*R*,4*S*,6*S*,6a*S*)-6-Iodo-4-((triisopropylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one (**13**).** To the inseparable mixture of **10** and **11** (6.79 g, 25.3 mmol, 1.0 eq) in DCM (25 mL) was added lutidine (8.8 mL, 76 mmol, 3.0 eq) and the resulting slightly yellow solution was cooled to 0 °C before triisopropylsilyl trifluormethansulfonate (11.64 g, 38.0 mmol, 1.5 eq) was added slowly over a period of 20 min. After 14 h the reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (25 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column

chromatography (hexane/EtOAc 9:1) affording **13** (8.48 g, 79 %) and **12** (1.54 g, 14 %) as colorless oils.

**(3a*R*,4*S*,6*S*,6a*S*)-6-Iodo-4-((triisopropylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one (**13**).**

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 5.15 (d, *J* = 6.82Hz, 1H); 4.83 (ddd, *J* = 8.40, 8.40, 5.68Hz, 1H); 4.34 (d, *J* = 4.55Hz, 1H); 3.19-3.13 (m, 1H); 3.08 (dd, *J* = 18.71, 2.98Hz, 1H); 2.53 (dd, *J* = 18.72, 10.88Hz, 1H); 2.34-2.28 (m, 1H); 2.06 (ddd, *J* = 14.54, 8.96, 5.56Hz, 1H); 1.29-1.04 (m, 21H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 176.74 (C); 91.19 (CH); 72.83 (CH); 42.75 ($CH_2$); 40.90 (CH); 27.87 ($CH_2$); 23.23 (CH); 18.09 ($CH_3$); 18.05 ($CH_3$); 12.20 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{16}H_{29}INaO_3Si$: 447.0828; found: 447.0825 ±5 ppm.

**$[\alpha]^{20}_D$:** +6.0 ° (c = 1.24; $CHCl_3$).

**IR (ATR):** 2942, 2891, 2865, 2349, 1785, 1462, 1411, 1383, 1352, 1317, 1295, 1248, 1156, 1126, 1055, 1031, 997, 962, 936, 919, 881, 854, 835, 772, 681, 660 $cm^{-1}$.

**(3a*S*,4*S*,5*S*,6a*S*)-5-Iodo-4-((triisopropylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one (**12**).**

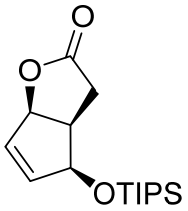
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 5.07 (ddd, *J* = 7.32, 7.30, 4.04Hz, 1H); 4.53 (dd, *J* = 5.68, 3.43Hz, 1H); 4.16 (ddd, *J* = 5.75, 4.03, 4.03Hz, 1H); 3.39-3.32 (m, 1H); 2.79 (dd, *J* = 18.35, 3.10Hz, 1H); 2.72 (ddd 15.49, 5.93, 4.13Hz, 1H); 2.63 (ddd, *J* = 15.53, 6.71, 4.55Hz, 1H); 2.57 (dd, *J* = 18.31, 10.70Hz, 1H); 1.15-1.02 (m, 21H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 176.97 (C); 83.62 (CH); 81.38 (CH); 42.59 ($CH_2$); 41.45 (CH); 28.88 ($CH_2$); 28.85 (CH); 18.17 ($CH_3$); 18.15 ($CH_3$); 12.60 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{16}H_{29}INaO_3Si$: 447.0828; found: 447.0826 ±5 ppm.

**$[\alpha]^{20}_D$:** +108.7 ° (c = 1.05; $CHCl_3$).

**IR (ATR):** 2943, 2891, 2866, 2349, 1777, 1463, 1384, 1355, 1287, 1256, 1220, 1186, 1160, 1133, 1095, 1049, 1018, 997, 974, 954, 913, 881, 847, 824, 797, 772, 742, 682, 663 $cm^{-1}$.




**14**

**(3a*R*,4*S*,6a*R*)-4-((Triisopropylsilyl)oxy)-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**14**).** To a solution of **13** (2.00 g, 4.71 mmol, 1.0 eq) in THF (47 mL) was added DBU (0.85 mL, 5.66 mmol, 1.2 eq). The mixture was stirred at reflux for one hour (completion of the reaction was indicated by TLC analysis). During that period the solution turned into a turbid suspension. The reaction mixture was cooled to rt and filtered. The filtrate was washed with brine once (50 mL) and was dried over $MgSO_4$. The solvent was reduced *in vacuo* delivering **13** (1.4 g, >99 %) in quantitative yield as a colorless oil which was used without further purification in the next step.

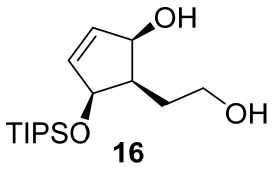
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 6.03 (ddd, *J* = 5.69, 1.59, 0.99Hz, 1H); 5.96 (ddd, *J* = 5.70, 1.62, 1.62Hz, 1H); 5.26-5.24 (m, 1H); 4.98-4.96 (m, 1H); 3.34 (dddd, *J* = 10.95, 7.26, 7.26, 7.26Hz, 1H), 2.99 (dd, *J* = 18.73, 7.20Hz, 1H); 2.44 (dd, 18.71, 10.87Hz, 1H); 1.17-1.04 (m, 21H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 177.42 (C); 139.62 (CH); 130.05 (CH); 85.90 (CH); 75.32 (CH); 42.27 (CH); 28.54 ($CH_2$); 18.11 ($CH_3$); 18.08 ($CH_3$); 12.26 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{16}H_{28}NaO_3Si$: 319.1705; found: 319.1712 ±5 ppm.

**$[\alpha]^{20}_D$:** −35.1 ° (c = 1.19; $CHCl_3$).

**IR (ATR):** 2943, 2866, 2348, 1775, 1463, 1417, 1365, 1329, 1259, 1166, 1126, 1081, 1049, 1024, 1006, 951, 901, 881, 842, 779, 681, 660 $cm^{-1}$.




**16**

**(1*R*,4*S*,5*R*)-5-(2-Hydroxyethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (**16**).** A solution of **14** (1.4 g, 4.72 mmol, 1.0 eq) in dry THF (20 mL) was added dropwise to a vigorously stirred suspension of LAH (0.181 g, 4.77 mmol, 1.01 eq) in dry THF (17 mL) at 0 °C. The mixture was stirred at 0 °C for 3.5 h before the reaction was terminated by the careful addition of EtOAc. A saturated aqueous solution of Rochelle´s salt (20 mL) was added and the mixture was stirred for 3 h until the layers became clear and easily separable. The layers were separated and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phase was dried over $MgSO_4$ and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford **16** (1.20 g, 85 %) as a colorless oil.

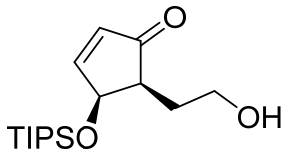
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 6.20 (dd, *J* = 5.74, 2.50Hz, 1H); 6.14 (dd, *J* = 5.76, 2.28Hz, 1H); 4.67 (dd, *J* = 5.44, 2.28Hz, 1H); 4.47 (bs, 1H); 3.90-3.78 (m, 2H); 2.17 (dddd, *J* = 9.24, 5.42, 5.41, 5.40Hz, 1H); 2.03-1.85 (m, 4H); 1.08-1.07 (m, 21H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 137.56 (CH); 137.17 (CH); 76.68 (CH); 76.02 (CH); 62.02 ($CH_2$); 46.64 (CH); 27.67 ($CH_2$); 18.30 ($CH_3$); 18.25 ($CH_3$); 12.58 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{16}H_{32}NaO_3Si$: 323.2018; found: 323.2008 ±5 ppm.

**$[\alpha]^{20}_D$:** +40.7 ° (c = 1.17; $CHCl_3$).

**IR (ATR):** 3328; 2942; 2866; 2349; 2328; 1463; 1122; 1088; 1055; 1013; 996; 882; 771; 677; 660 $cm^{-1}$.




**17**

**(4*S*,5*S*)-5-(2-Hydroxyethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (**17**).** To a solution of **16** (1.1 g, 3.66 mmol, 1.0 eq) in DCM (73 mL) was added $MnO_2$ (4.77 g, 54.9 mmol, 15 eq) at rt. The mixture was stirred until complete consumption of the starting material was indicated by TLC analysis (16 h). Celite was added and the mixture was stirred for further 10 min. The solution was filtered through a plug of celite and the residue was carefully washed with DCM. The filtrate was concentrated *in vacuo* and the crude enone was purified by flash column chromatography (hexane/EtOAc 2:1 to 1:1) to afford **17** (815 mg, 75 %) as a colorless oil.

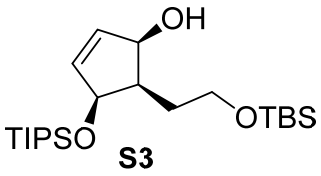
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.55 (dd, *J* = 5.76, 2.24Hz, 1H); 6.23 (dd, *J* = 5.78, 1.26Hz, 1H); 5.12 (ddd, *J* =6.01, 2.25, 1.25Hz, 1H); 3.86-3.73 (m, 2H); 2.69 (ddd, *J* = 8.53, 5.76, 5.76Hz, 1H); 2.65 (dd, *J* = 6.78, 5.02Hz, 1H), 2.06 (dddd, *J* = 14.59, 6.49, 5.24, 5.24Hz, 1H); 1.74 (dddd, *J* = 14.59, 8.44, 7.37, 5.12Hz, 1H), 1.14-1.08 (m, 21H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 210.46 (C); 163.77 (CH); 133.79 (CH); 72.73 (CH); 61.28 ($CH_2$); 49.29 (CH); 29.58 ($CH_2$); 18.18 ($CH_3$); 18.13 ($CH_3$); 12.50 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{16}H_{30}NaO_3Si$: 321.1862; found: 321.1854 ±5 ppm.

**$[\alpha]^{20}_D$:** +66.7 ° (c = 1.09; $CHCl_3$).

**IR (ATR):** 3406; 2942; 2891; 2865; 2347; 1702; 1462; 1354; 1128; 1039; 1014; 880; 767; 677; 657 $cm^{-1}$.




**S3**

**(1*R*,4*S*,5*R*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (**S3**).** To a solution of **16** (0.50 g, 1.66 mmol, 1.0 eq) in DCM (2 mL) was added imidazole (0.283 g, 4.16 mmol, 2.5 eq), followed by *tert*-butyldimethylsilyl chloride (0.27 g, 1.83 mmol, 1.1 eq) at rt. The reaction was stirred until TLC-analysis indicated total consumption of the starting material (3 h). The reaction mixture was diluted with DCM (20 mL) and quenched by the addition of an aqueous saturated solution of $NH_4Cl$ (10 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extract was washed with water (15 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) delivering **S3** (0.61 g, 89 %) as a colorless oil.

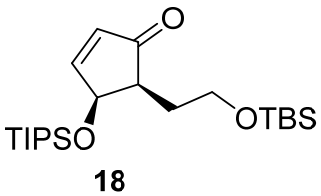
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 6.11 (dd, *J* = 5.76, 2.24Hz, 1H); 6.03 (ddd, *J* = 5.76, 2.24, 0.76Hz, 1H); 4.69 (dd, *J* = 5.78, 2.26Hz, 1H); 4.47 (ddd, *J* = 8.66, 6.15, 2.25Hz, 1H); 3.85 (ddd, *J* = 10.05, 6.76, 4.28Hz, 1H); 3.72 (ddd, *J* = 9.98, 7.33, 4.33Hz, 1H); 2.83 (d, *J* =8.77Hz, 1H); 2.30 (dddd, *J* = 8.78, 6.02, 6.02, 4.51Hz, 1H); 1.94 (dddd, *J* = 14.59, 8.75, 7.31, 4.30Hz, 1H); 1.83 (dddd, *J* = 14.68, 6.65, 4.39, 4.25Hz, 1H); 1.09-1.06 (m, 21H); 0.91 (s, 9H); 0.08-0.07 (m, 6H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 133.89 (CH); 136.66 (CH); 76.74 (CH); 75.77 (CH), 62.47 ($CH_2$); 46.79 (CH); 27.32 ($CH_2$); 26.09 ($CH_3$); 18.43 (C); 18.29 ($CH_3$); 18.24 ($CH_3$); 12.55 (CH); -5.26 ($CH_3$); -5.31 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{22}H_{46}NaO_3Si_2$: 437.2883; found: 437.2884 ±5 ppm.

**$[\alpha]^{20}_D$:** +29.9 ° (c = 1.00; $CHCl_3$).

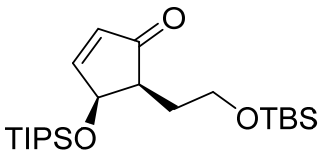
**IR (ATR):** 3393; 2928; 2892; 2865; 2350; 1640; 1462; 1386; 1361; 1254; 1219; 1091; 1062; 1007; 834; 810; 774; 750; 677; 660 $cm^{-1}$.




**18**

**(4*S*,5*S*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (**18**).** To a solution of **S3** (0.50 g, 1.21 mmol, 1.0 eq) in DCM (24 mL) was added $MnO_2$ (1.57 g, 18.1 mmol, 1.5 eq) and the solution was stirred for 12 h at rt. As TLC-analysis indicated remaining starting material, additional $MnO_2$ (1.05 g, 12.05 mmol, 10 eq) was added and the reaction was completed after stirring for additional 1.5 h at rt. Celite was added and the mixture was stirred for 10 min. The solution was filtered through a plug of celite and the residue was washed with DCM. The filtrate was concentrated *in vacuo* and the crude enone was purified by flash column chromatography (hexane/EtOAc 19:1) to afford **18** (408 mg, 82%) as a colorless oil.

Spectral data are given below.




**18**

**(4*S*,5*S*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (**18**).** To a solution of **17** (0.105 g, 0.352 mmol, 1.0 eq) in DCM (0.35 mL) was added lutidine (0.123 mL, 1.06 mmol, 3.0 eq). The solution was cooled to 0 °C, *tert*-butyldimethylsilyl trifluormethansulfonate (0.121 ml, 0.528 mmol, 1.5 eq) was added and the reaction mixture was allowed to warm to rt. After 30 min at rt, TLC-analysis indicated complete consumption of the starting material and the mixture was diluted with DCM (10 mL). The reaction was terminated by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (hexane/EtOAc 40:1) afforded **18** (130 mg, 90 %) as a colorless oil.

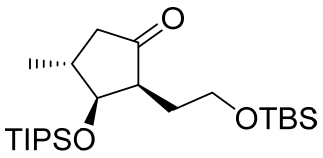
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.48 (dd, *J* = 6.02, 2.26Hz, 1H); 6.17 (dd, *J* = 5.76, 1.24Hz, 1H); 5.08 (ddd, *J* = 6.02, 2.00, 1.50Hz, 1H); 3.84-3.74 (m, 2H); 2.64 (ddd, *J* = 7.90, 5.89, 6.03Hz, 1H); 1.99 (dddd, *J* = 13.43, 6.75, 6.71, 6.65Hz, 1H); 1.67 (dddd, *J* = 13.99, 7.85, 6.10, 6.02Hz, 1H); 1.26-1.06 (m, 21H); 0.88 (s, 9H); 0.05 (s, 3H); 0.04 (s, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 209.54 (C); 162.77 (CH), 133.82 (CH); 72.65 (CH); 60.68 ($CH_2$); 47,34 (CH); 30.04 ($CH_2$); 26.06 (CH); 18.40 (C); 18.21 ($CH_3$); 18.17 ($CH_3$); 12.56 ($CH_3$); -5.17 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{22}H_{44}NaO_3Si_2$: 435.2727; found: 435.2746 ±5 ppm.

**$[\alpha]^{20}_D$:** +46.3 ° (c = 1.50; $CHCl_3$).

**IR (ATR):** 2946; 2928; 2866; 2351; 1718; 1463; 1386; 1359; 1254; 1132; 1098; 1061; 882; 835; 774; 680; 660 $cm^{-1}$.




**5**

**(2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentanone (**5**).** A suspension of copper iodide (purified as described by Dieter;[12] 0.203 g, 1.07 mmol, 1.1 eq,) in $Et_2O$ (2.4 mL) was stirred for one hour at 0 °C before a solution of methyllithium (1.6M in $Et_2O$; 1.33 mL, 2.13 mmol, 2.2 eq) was added. After the addition the suspension turned into a clear yellow solution. The mixture was cooled to −78 °C and a solution of **18** (0.40 g, 0.97 mmol, 1.0 eq) in $Et_2O$ (2.4 mL) was added. The mixture was stirred at −78 °C for one hour when TLC-analysis showed total consumption of the starting material. The reaction was quenched by the addition of an aqueous saturated solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 40:1) delivering **5** (0.371 g, 89 %) as a colorless oil.

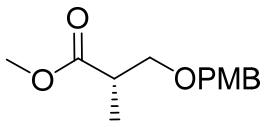
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 4.26 (d, *J* = 4.24Hz, 1H); 3.77 (ddd, *J* = 10.05, 6.02, 6.02Hz, 1H); 3.70 (ddd, *J* = 9.93, 7.28, 5.64Hz, 1H); 2.59-2.49 (m, 2H); 2.43-2.35 (m, 1H); 1.93-1.82 (m, 2H); 1.79-1.70 (m, 1H); 1.15-1.04 (m, 24H); 0.87 (s, 9H); 0.04 (s, 6H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 219.15 (C); 78.68 (CH); 61.10 ($CH_2$); 49.10 (CH); 42.44 ($CH_2$); 37.06 (CH); 26.87 ($CH_2$); 26.06 ($CH_3$); 19.06 (CH); 18.40 (C); 18.26 ($CH_3$); 12.88 (CH); -5.16 ($CH_3$); -5.18 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{23}H_{48}NaO_3Si_2$: 451.3040; found: 451.3039 ±5 ppm.

**$[\alpha]^{20}_D$:** +47.4 ° (c = 1.31; $CHCl_3$).

**IR (ATR):** 2945; 2892; 2866; 2360; 2341; 1718; 1463; 1387; 1359; 1253; 1181; 1132; 1099; 1061; 882; 853; 774; 679; 669; 658 $cm^{-1}$.



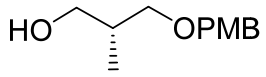

**S4**

**(*S*)-Methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (**S4**).** Camphorsulfonic acid (1.97 g, 8.47 mmol, 0.01 eq) was added to a solution of (*S*)-(+)-Roche ester (10.0 g, 85 mmol, 1.0 eq) and PMB-trichloroacetimidate[13] (35.9 g, 127 mmol, 1.5 eq) in DCM (56 mL). The mixture was stirred until TLC-analysis indicated complete consumption of the starting material (16 h). The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ (80 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 70 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$, filtered and reduced *in vacuo.* The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) to afford **S4** (20.0 g, 99 %) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ = 7.21-7.25 (m, 2H), 6.84-6.90 (m, 2H), 4.47 (d, *J* = 11.8Hz, 1H), 4.44 (d, *J* = 11.8Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 3.63 (dd, *J* = 9.0, 7.3Hz, 1H), 3.46 (dd, *J* = 9.0, 6.0Hz, 1H), 2.72-2.81 (m, 1H), 1.17 (d, *J* = 7.0Hz, 3H) ppm.

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ = 175.5 (C); 159.4 (C); 130.4 (C); 129.4 (CH); 113.9 (CH); 72.9 ($CH_2$); 71.8 ($CH_2$); 55.4 ($CH_3$); 51.9 ($CH_3$); 40.4 (CH); 14.2 ($CH_3$) ppm.

These spectral characteristics are identical to those previously reported for the enantiomeric (*R*)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate.[14]



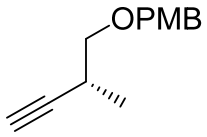

**S5**

**(*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol (**S5**).** To a suspension of LAH (1.59 g, 42.0 mmol, 1.0 eq) in $Et_2O$ (40 mL) was added a solution of **S4** (10.0 g, 42.0 mmol, 1.0 eq) in $Et_2O$ (30 mL). After one hour at 0 °C and 1.5 h at rt, TLC- analysis indicated complete consumption of the starting material. The reaction was quenched by the addition of water (8 mL) followed by NaOH (aqeous 15 w%; 4 mL). Solid $MgSO_4$ (two spoons) was added and the mixture was stirred for 30 min before it was filtered over a plug of celite. The residue was washed with DCM, the filtrate was reduced *in vacuo* and the crude product was purified by flash column chromatography (hexane/EtOAc 3:1) to afford **S5** (7.98 g, 90 %) as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ = 7.22-7.27 (m, 2H), 6.85-6.90 (m, 2H), 4.47 (d, *J* = 12.0Hz, 1H), 4.43 (d, *J* = 12.0Hz, 1H), 3.81 (s, 3H), 3.56-3.67 (m, 2H), 3.53 (dd, *J* = 9.0, 4.5Hz, 1H), 3.39 (dd, *J* = 9.0, 8.3Hz, 1H), 2.51 (dd, *J* = 6.8, 4.5Hz, 1H), 1.99-2.12 (m, 1H), 0.87 (d, *J* = 7.0Hz, 3H) ppm.

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ = 159.4 (C); 130.3 (C); 129.4 (CH); 114.0 (CH); 75.4 ($CH_2$); 73.2 ($CH_2$); 68.2 ($CH_2$); 55.4 ($CH_3$); 35.7 (CH); 13.6 ($CH_3$) ppm.

These spectral characteristics are identical to those previously reported for the enantiomeric (*S*)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-ol.[14]




**20**

**(*R*)-1-Methoxy-4-(((2-methylbut-3-yn-1-yl)oxy)methyl)benzene (**20**).** To a solution of **S5** (5.22 g, 24.8 mmol, 1.0 eq) in DCM (140 mL) was added DMSO (17.6 mL, 249 mmol, 10.0 eq) followed by $NEt_3$ (20.9 mL, 149 mmol, 6.0 eq) and $SO_3$·pyridine (11.86 g, 74.4 mmol, 3.0 eq) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred until total consumption of the starting material (2 h). The reaction was terminated by the addition of a saturated aqueous solution of $NH_4Cl$ (280 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with HCl (1M; 2 x 100 mL) and brine (150 mL). After drying over $Na_2SO_4$ and filtration the solvent was reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 9:1) to yield the corresponding aldehyde (5.01 g, 97 %) as a colorless oil. The product was immediately used in the next step without any further purification.

A solution of TMS-Diazomethane (2M in $Et_2O$; 14.65 ml, 29.3 mmol, 1.22 eq) in THF (34 mL) was cooled to −78 °C. *n*-Butyllithium (2.5M in hexanes; 11.1 mL, 27.9 mmol, 1.16 eq) was added and the mixture was stirred for 30 min. A solution of the freshly prepared aldehyde from above (5.01 g, 24.0 mmol, 1.0 eq) in THF (12 mL) was added slowly (15 min). After one hour at −78 °C the mixture was allowed to warm to rt and stirred until total consumption of the starting material (4 h). The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (100 mL), the layers were separated and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) delivering **20** (4.29 g, 87 %) as a colorless oil.

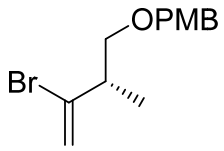
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.28-7.26 (m, 2H); 6.90-6.86 (m, 2H); 4.52 (d, *J* = 11.85Hz, 1H); 4.48 (d, *J* = 11.81Hz, 1H); 3.81 (s, 3H); 3.50 (dd, *J* = 9.08, 6.24Hz, 1H); 3.35 (dd, *J* = 9.11, 7.26Hz, 1H); 2.73 (qddd, *J* = 6.80, 6.97, 6.28, 2.32Hz, 1H); 2.07 (d, *J* = 2.44Hz, 1H); 1.21 (d, *J* = 6.96Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.39 (C); 130.46 (C); 129.40 (CH); 113.96 (CH); 86.63 (CH); 73.71 ($CH_2$); 72.89 ($CH_2$) 69.07 (C); 55.44 ($CH_3$); 26.70 (CH); 17.80 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{13}H_{16}NaO_2$: 227.1048; found: 227.1051 ±5 ppm.

**$[\alpha]^{20}_D$:** +1.4 ° (c = 1.02; $CHCl_3$).

**IR (ATR):** 3292, 2936, 2905, 2859, 2349, 1612, 1586, 1512, 1462, 1357, 1302, 1246, 1209, 1173, 1087, 1034, 817, 672, 637 $cm^{-1}$.




**21**

**(*S*)-1-(((3-Bromo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (**21**).**[15] To a solution of [1,3-bis(diphenylphosphino)propane]nickel(II)chloride (0.024 g, 0.044 mmol, 0.03 eq) in THF (1.5 mL) was added a solution of DIBAL-H (1M in cyclohexane, 1.90 mL, 1.90 mmol, 1.3 eq) at rt. The resulting black solution was cooled to 0 °C before **20** (0.300 g, 1.469 mmol, 1.0 eq) was added neat (followed by a THF rinse; approximately 0.1 mL) slowly over a period over 3 to 5 min. The resulting black solution was allowed to warm to room temperature and was stirred for 2 h. A solution of *N*-bromosuccinimide (0.523 g, 2.94 mmol, 2.0 eq) in THF (4.40 mL) was added *via* a syringe at 0 °C. The mixture was stirred for one hour at 0 °C before the reaction was quenched by pouring the mixture into a separatory funnel, containing a mixture of a saturated solution of Rochelle's salt (20 mL) and $Et_2O$ (20 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 9:1) yielding **21** (0.343 g, 82 %) as a slightly yellow oil.

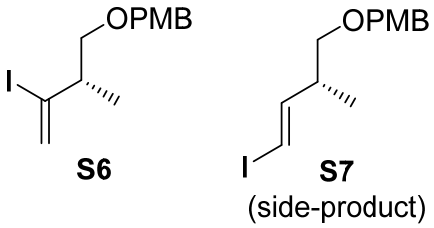
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.27-7.25 (m, 2H); 6.89-6.87 (m, 2H); 5.68 (dd, *J* = 1.72, 0.64, 1H); 5.48 (d, *J* = 1.76Hz, 1H); 4.48 (d, *J* = 11.66Hz, 1H); 4.45 (d, *J* = 11.69Hz, 1H); 3.80 (s, 3H), 3.50 (dd, *J* = 9.48, 7.15Hz, 1H); 3.33 (dd, *J* = 9.47, 6.10Hz, 1H); 2.70 (qdd, *J* = 6.85, 6.80, 6.40Hz, 1H), 1.10 (d, *J* = 6.74Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.35 (C); 138.18 (C); 130.56 (C); 129.37 (CH); 117.08 ($CH_2$); 113.93 (CH); 72.95 ($CH_2$); 72.84 ($CH_2$); 55.43 ($CH_3$); 44.54 (CH); 16.86 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{13}H_{17}{}^{79}BrNaO_2$: 307.0310; found: 307.0313 ±5 ppm.

**$[\alpha]^{20}_D$:** −0.8 ° (c = 1.29; $CHCl_3$).

**IR (ATR):** 2934, 2906, 2856, 1612, 1586, 1512, 1463, 1357, 1302, 1246, 1208, 1172, 1093, 1035, 890, 819 $cm^{-1}$.




**S6** **S7**
(side-product)

**(*S*)-1-(((3-Iodo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (**S6**).**[15] To a solution of [1,3-bis(diphenylphosphino)propane]nickel(II)chloride (0.127 g, 0.235 mmol, 0.03 eq) in THF (7.8 mL) was added a solution of DIBAL-H (1M in cyclohexane, 10.18 mL, 10.18 mmol, 1.3 eq) at rt. The resulting black solution was cooled to 0 °C before **20** (1.600 g, 7.83 mmol, 1.0 eq) was added slowly over a period of 3 to 5 min. The resulting black solution was allowed to warm to rt and was stirred for 2 h before a solution of *N*-iodosuccinimide (3.52 g, 15.67 mmol, 2.0 eq) in THF (23.5 mL) was added *via* a syringe at 0 °C. The mixture was stirred for one hour at 0 °C before the reaction was quenched by pouring the mixture into a separatory funnel, containing a mixture of a saturated solution of Rochelle's salt (80 mL) and $Et_2O$ (80 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3 x 80 mL). The combined organic extract was washed with brine (150 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography (hexane/EtOAc 9:1) yielding **S6** (1.88 g, 72 %) as a slightly yellow oil. (In some batches minor amounts (up to 10%) of the side-product, the terminal vinyl iodide **S7,** were formed.)

**(*S*)-1-(((3-Iodo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (**S6**).**

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.28-7.24 (m, 2H); 6.90-6.87 (m, 2H); 6.21 (bs, 1H); 5.82 (d, *J* = 1.52Hz, 1H); 4.49 (d, *J* = 11.65Hz, 1H); 4.45 (d, *J* = 11.45Hz, 1H); 3.81 (s, 3H); 3.38 (dd, *J* = 9.51, 7.39Hz, 1H); 3.26 (dd, *J* = 9.55, 5.94Hz, 1H); 2.29-2.21 (m, 1H); 1.01 (d, *J* = 6.72Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.32 (C); 130.51 (C); 129.39 (CH); 125.80 ($CH_2$); 118.46 (C); 113.90 (CH); 73.86 ($CH_2$); 72.94 ($CH_2$); 55.40 ($CH_3$); 46.61 (CH), 18.04 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{13}H_{17}INaO_2$: 355.0171; found: 355.0161 ±5ppm.

**$[\alpha]^{20}_D$:** −1.0 (c = 0.80; $CHCl_3$).

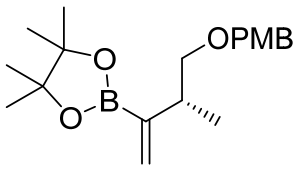
**IR (ATR):** 2962, 2932, 2854, 2349, 1611, 1585, 1512, 1462, 1357, 1302, 1246, 1172, 1091, 1035, 897, 818, 772, 617 $cm^{-1}$.

**(*R*,*E*)-1-(((4-Iodo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (**S7**).**

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.26-7.23 (m, 2H); 6.90-6.87 (m, 2H); 6.51 (dd, *J* = 14.51, 7.39Hz, 1H); 6.08 (dd, *J* = 14.49, 1.16Hz, 1H); 4.43 (s, 2H); 3.81 (s, 3H); 3.34-3.26 (m, 2H); 2.56-2.45 (m, 1H); 1.02 (d, *J* = 6.80Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.37 (C); 149.08 (CH); 130.54 (C); 129.35 (CH); 113.97 (CH); 75.32 (CH); 73.80 ($CH_2$); 72.87 ($CH_2$); 55.44 ($CH_3$); 40.85 (CH); 16.28 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{13}H_{17}INaO_2$: 355.0171; found: 355.0168 ±5 ppm.




**S8**

**(*R*)-2-(4-((4-Methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S8**).** To a solution of [1,3-bis(diphenylphosphino)propane]nickel(II)chloride (0.032 g, 0.059 mmol, 0.03 eq) in THF (5.9 mL) was added a solution of DIBAL-H (1M in cyclohexane, 2.55 ml, 2.55 mmol, 1.3 eq) at rt. The resulting black solution was cooled to 0 °C before **20** (0.400 g, 1.958 mmol, 1.0 eq) was added slowly over a period of 3 to 5 min. The mixture was allowed to warm to rt and was stirred for 2 h before the reaction was cooled to 0 °C and MeOBpin (0.963 ml, 5.87 mmol, 3.0 eq) was added *via* a syringe. The solution was heated to 80 °C for 24 h before the reaction was terminated by pouring into an Erlenmeyer flask containing water (20 mL). The mixture was filtered through a pad of celite. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 40:1 to 19:1) and **S8** (0.692 g, 75 %) was obtained as a colorless oil.

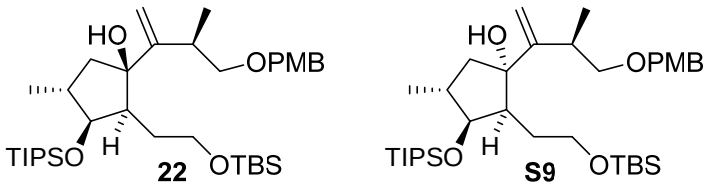
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.27-7.24 (m, 2H); 6.88-6.84 (m, 2H); 5.81 (d, *J* = 3.08Hz, 1H); 5.64 (d, *J* = 2.36Hz, 1H); 4.45 (d, *J* = 12.47Hz, 1H); 4.42 (d, *J* = 12.59Hz, 1H); 3.80 (s, 3H); 3.48 (dd, *J* = 9.16, 6.52Hz, 1H); 3.32 (dd, *J* = 9.16, 7.32Hz, 1H); 2.68 (qdd, *J* = 6.89, 6.85, 6.70Hz, 1H); 1.24 (s, 6H); 1.23 (s, 6H); 1.07 (d, *J* = 6.88Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.17 (C); 131.21 (C); 129.29 (CH); 128.54 ($CH_2$); 113.82 (CH); 83.37 (C); 74.81 ($CH_2$); 72.54 ($CH_2$); 55.43 ($CH_3$); 39.27 (CH); 24.94 ($CH_3$); 24.82 ($CH_3$); 17.01 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{19}H_{29}BNaO_4$: 355.2057; found: 355.2063 ±5 ppm.

**$[\alpha]^{20}_D$:** +0.2 (c = 0.80; $CHCl_3$).

**IR (ATR):** 2976, 2933, 2852, 1612, 1513, 1464, 1415, 1389, 1371, 1304, 1247, 1214, 1171, 1144, 1089, 1037, 968, 947, 852, 820, 695 $cm^{-1}$.




**22** **S9** (side product)

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((*R*)-4-((4-methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (22).** To a solution of bromide **21** (0.255 g, 0.896 mmol, 1.2 eq) in $Et_2O$/pentane (3:2; 4.0 mL) was added a solution of *tert*-butyllithium (1.7M in pentane, 0.92 mL, 1.57 mmol, 2.1 eq) at −78 °C. After 30 min at that temperature the reaction mixture was allowed to stir at rt for 5 min. After re-cooling of the slightly yellow mixture to −78 °C a solution of **5** (0.320 g, 0.746 mmol, 1.0 eq) in $Et_2O$/pentane (3:2; 3.5 mL) was added slowly (over a period of 10 min). Stirring at that temperature was continued for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc 40:1) to afford **22** (0.237 g, 50 %) as a colorless oil and the corresponding C-1 epimer (**S10**) as side product (80 mg, 17 %).

Note: The exact ratio of the solvents is essential for the success of this reaction. $Et_2O$ and pentane, freshly distilled from sodium, were mixed in a 3:2 ratio and this solvent mixture was stored over molecular sieves (3 Å) prior to use.

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((*R*)-4-((4-methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**22**).**

**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.27-7.24 (m, 2H); 6.89-6.85 (m, 2H); 5.28 (s, 1H); 4.91 (s, 1H); 4.48 (d, *J* = 11.64Hz, 1H); 4.38 (d, *J* = 11.64Hz, 1H); 4.11 (d, *J* = 3.79Hz, 1H); 4.00 (s, 1H); 3.80 (s, 3H); 3.69 (ddd, *J* = 9.79, 6.87, 4.72Hz, 1H); 3.63-3.57 (m, 1H); 3.46 (dd, *J* = 9.08, 4.88Hz, 1H); 3.28 (dd, *J* = 9.09, 9.09Hz, 1H); 2.44-2.23 (m, 2H); 2.08 (ddd, *J* = 10.00, 3.32, 3.30Hz, 1H); 1.85 (dddd, *J* = 14.43, 9.82, 4.95, 4.89Hz, 1H); 1.63-1.57 (m, 1H); 1.61 (dd, *J* = 13.90, 3.28Hz, 1H); 1.15 (d, *J* = 6.76, 3H); 1.13-1.09 (m, 21H); 0.98 (d, *J* = 7.08Hz, 3H); 0.88 (s, 9H); 0.03 (s, 6H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.24 (C); 153.93 (C); 131.05 (C); 129.25 (CH); 113.85 (CH); 109.31 ($CH_2$); 86.17 (C); 83.27 (CH); 75.91 ($CH_2$); 72.72 ($CH_2$); 62.15 ($CH_2$); 55.41 ($CH_3$); 47.86 ($CH_2$); 45.35 (CH); 40.17 (CH); 34.81 (CH); 26.12 ($CH_3$); 25.41 (C); 20.80 (CH); 20.42 (CH); 18.30 ($CH_3$); 12.72 (CH); -5.16 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{36}H_{66}NaO_5Si_2$: 657.4346; found: 657.4332 ± 5ppm.

**$[\alpha]^{20}_D$:** +3.7 ° (c = 0.81; $CHCl_3$).

**IR (ATR):** 3494; 2954; 2866; 2360; 2341; 1716; 1613; 1586; 1540; 1513; 1462; 1386; 1360; 1248; 1220; 1097; 1031; 882; 834; 774; 669; 657 $cm^{-1}$.

**C1 – epimer (**S9**).**

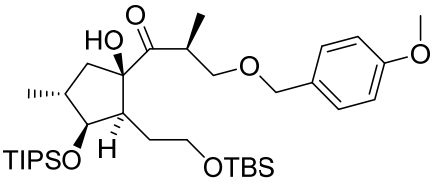
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.26-7.24 (m, 2H); 6.87-6.85 (m, 2H); 5.34 (bs, 1H); 4.93 (d, *J* = 1.00Hz, 1H); 4.46 (d, *J* = 11.64Hz, 1H); 4.41 (d, *J* = 11.60Hz, 1H); 4.11 (d, *J* = 3.80Hz, 1H); 4.01 (s, 1H); 3.80 (s, 3H); 3.71 (ddd, *J* = 9.99, 5.81, 4.17Hz, 1H); 3.61 (ddd, *J* = 9.60, 9.60, 4.80Hz, 1H); 3.46 (dd, *J* = 9.34, 4.78Hz, 1H); 3.25 (dd, 9.36, 9.08Hz, 1H); 237-2.28 (m, 2H); 2.20 (dd, *J* = 14.40, 9.12Hz, 1H); 2.10 (ddd, *J* = 10.36, 3.28, 3.28Hz, 1H); 1.82 (dddd, *J* = 14.34, 9.91, 4.55, 4.48Hz, 1H); 1.62-1.54 (m, 1H); 1.28-1.05 (m, 21H); 1.16 (d, *J* = 6.84Hz, 3H); 0.98 (d, *J* = 7.32Hz, 3H); 0.88-0.87 (m, 9H); 0.02 (s, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 158.90 (C); 153.45 (C); 130.6 (C); 129.21 (CH); 113.86 (CH); 109.57 ($CH_2$); 86.28 (C); 83.11 (C); 76.50 ($CH_2$); 72.66 ($CH_2$); 61.80 ($CH_2$); 55.43 ($CH_3$); 47.15 ($CH_2$); 44.82 (CH); 40.20 (CH); 34.70 (CH); 26.08 ($CH_3$); 25.23 ($CH_2$); 20.78 ($CH_3$); 19.84 ($CH_3$); 18.30 ($CH_3$); 18.20 (C); 12.72 (CH); -5.16 ($CH_3$).

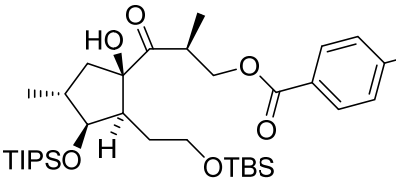
**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{36}H_{66}NaO_5Si_2$: 657.4346; found: 657.4312 ±5ppm.

**$[\alpha]^{20}_D$:** +22.4 ° (c = 1.01; $CHCl_3$).

**IR (ATR):** 3505; 2954; 2930; 2866; 2360; 2341; 1613; 1513; 1461; 1381; 1360; 1248; 1220; 1172; 1097; 1033; 882; 834; 774; 669; 657 $cm^{-1}$.




**S10**




**S11**

**(*S*)-1-((1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-hydroxy-4-methyl-3-((triisopropylsilyl)oxy)cyclopentyl)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-one (**S10**).** Ozone was bubbled through a solution of **22** (0.04 g, 0.063 mmol, 1.0 eq), pyridine (0.63 mmol, 0.05 mL, 10 eq) and a spatula tip of Sudan III as indicator in a mixture of DCM and methanol (1:1; 1.3 mL) at −78 °C until the red solution turned colorless. The primary ozonide was reduced by the addition of triphenylphosphane (20 mg, 0.076 mmol, 1.2 eq). The reaction mixture was allowed to warm to rt over 12 h. DCM (5 mL) was added and the reaction mixture was washed with a saturated aqueous solution of $NH_4Cl$ (5 mL), dried over $MgSO_4$, filtered and the solvent was reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) to afford **S10** (34 mg, 84 %) as a colorless oil.

Note: If the reaction was carried out without pyridine, cleavage of the TBS–ether and decomposition of the starting material was observed. When the reaction was carried out without Sudan III as indicator, benzoate **S11** was observed as major constituent. The characteristic blue color of ozone in a mixture of DCM and methanol (1:1) is not useful as indicator in this case.

**(*S*)-1-((1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-hydroxy-4-methyl-3-((triisopropylsilyl)oxy)cyclopentyl)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-one (**S10**).**

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.22-7.20 (m, 2H); 6.86-6.84 (m, 2H); 4.43 (d, *J* = 12.42Hz, 1H); 4.40 (d, *J* = 12.27Hz, 1H); 4.04 (dd, *J* = 3.72, 1.24Hz, 1H); 3.92 (s, 1H);3.79 (s, 3H); 3.67-3.57 (m, 3H); 3.51 (ddd, *J* = 9.86, 7.20, 7.20Hz, 1H); 3.46 (dd, *J* = 8.32, 4.80Hz, 1H); 2.51 (ddd, *J* = 7.04, 6.24, 3.80Hz, 1H); 2.29-2.20 (m, 1H); 2.16 (dd, *J* = 14.14, 8.58Hz, 1H); 1.87 (dddd, *J* = 14.03, 7.07, 7.07, 5.56Hz, 1H); 1.67-1.57 (m, 2H); 1.12-1.05 (m, 21H); 1.06 (d, *J* = 6.56Hz, 3H); 0.93 (d, *J* = 7.32Hz, 3H); 0.89-0.88 (m, 9H); 0.03 (s, 3H); 0.02 (s, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 215.94 (C); 159.21 (C); 130.70 (C); 129.31 (CH); 113.79 (CH); 89.45 (C); 83.93 (CH); 72.78 (CH2); 72.17 ($CH_2$); 62.51 ($CH_2$); 55.39 ($CH_3$); 47.31 ($CH_2$); 46.76 (CH); 41.06

(CH); 40.42 (CH); 26.92 ($CH_2$); 26.06 ($CH_3$); 19.87 ($CH_3$); 18.40 (C); 18.29 ($CH_3$); 13.74 ($CH_3$); 12.68 (CH); −5.18 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{35}H_{64}NaO_6Si_2$: 659.4139; found: 659.4138 ±5 ppm.

**$[\alpha]^{20}_D$:** +26.1 ° (c = 0.70; $CHCl_3$).

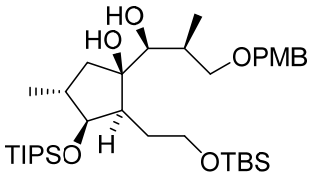
**IR (ATR):** 3497; 2928; 2864; 2360; 1713; 1613; 2586; 1513; 1461; 1386; 1360; 1301; 1247; 1171; 1085; 1039; 1012; 937; 881; 832; 775; 678 $cm^{-1}$.

**Side product (**S11**) – benzylic oxidation.**

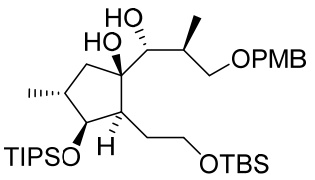
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.96-7.92 (m, 2H); 6.91-6.90 (m, 2H); 4.45 (d, *J* = 6.04Hz, 2H); 4.06 (d, *J* = 3.54Hz, 1H); 4.00 (s, 1H); 3.85 (s, 3H); 3.72(dt, *J* = 6.84, 6.10Hz, 1H); 3.61 (ddd, *J* = 9.85, 7.58, 5.31Hz, 1H); 3.53 (ddd, *J* = 9.85, 7.07, 7.07Hz, 1H); 2.53 (ddd, *J* = 7.58, 5.81, 3.79Hz, 1H); 2.29-2.15 (m, 2H); 1.92-1.84 (m, 1H); 1.67-1.54 (m, 2H); 1.17 (d, *J* = 6.84Hz, 1H); 1.09-1.08 (m, 21H); 0.93 (d, *J* = 6.96Hz, 3H); 0.89-0.88 (m, 9H); 0.04 (s, 3H); 0.03 (s, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 215.06 (C); 166.20 (C); 163.48 (C); 131.76 (CH); 122.79 (C); 113.71 (CH); 89.82 (C); 84.00 (CH); 66.15 ($CH_2$); 62.32 ($CH_2$); 55.56 ($CH_3$); 47.94 ($CH_2$); 46.97 (CH); 40.53 (CH); 40.52 (CH); 26.94 ($CH_2$); 26.06 ($CH_3$); 20.03 ($CH_3$); 18.41 (C); 18.28 ($CH_3$); 13.53 ($CH_3$); 12.66 (CH); -5.16 ($CH_3$); −5.18 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{35}H_{62}NaO_7Si_2$: 673.3932; found: 673.3929 ±5 ppm.



**23**



**S12**

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((1S,2S)-1-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**23**).** To a solution of **S10** (35 mg, 0.055 mmol, 1.0 eq) in EtOH (0.4 mL) and a few drops of DCM (approximately 0.1 mL) was added $NaBH_4$ (4.2 mg, 0.11 mmol, 2 eq). After 24 h at rt, the solution was diluted with DCM (5 mL) and quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (5 mL). The mixture was extracted with DCM (3 x 5 mL). The combined organic extract was dried over $MgSO_4$, filtered and the solvent was reduced in *vacuo.* The crude product was filtered through a short plug of silica and purified by HPLC to afford **23** (25 mg, 71 %) and diasteromer **S12** (21 %, 7.5 mg) as colorless oils.

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((1S,2S)-1-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**23**).**

**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.25-7.23 (m, 2H); 6.89-.685(m, 2H); 4.42 (s, 2H); 3.99 (d, *J* = 3.56Hz, 1H); 3.80 (s, 3H); 3.78-3.62 (m, 5H); 3.51 (dd, *J* = 9.16, 4.88Hz, 1H); 3.45 (dd, *J* = 5.50, 5.50Hz, 1H); 2.28-2.19 (m, 1H); 2.14-2.02 (m, 2H); 2.05 (dd, *J* = 13.92, 8.88Hz, 1H); 1.91-1.83 (m, 1H); 1.77-1.69 (m, 1H); 1.66 (dd, *J* = 13.88, 4.28Hz, 1H); 1.14 (d, *J* = 7.12Hz, 3H); 1.09-1.08 (m, 21H); 0.91 (d, *J* = 7.32Hz, 3H); 0.89 (s, 9H); 0.05 (s, 6H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.39 (C); 130.26 (C); 129.51 (CH); 113.94 (CH); 86.04 (C); 83.98 (CH); 76.23 (CH); 74.92 ($CH_2$); 73.25 ($CH_2$); 62.99 ($CH_2$); 55.42 ($CH_3$); 44.37 (CH); 41.22 ($CH_2$); 39.72 (CH); 34.43 (CH); 26.10 ($CH_3$); 25.55 ($CH_2$); 20.27 ($CH_3$); 18.45 (C); 18.32 ($CH_3$); 16.97 ($CH_3$); 12.69 (CH); -5.17 ($CH_3$); −5.21 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{35}H_{66}NaO_6Si_2$: 661.4296; found: 661.4287 ±5 ppm.

**$[\alpha]^{20}_D$:** +3.1° (c = 0.45; $CHCl_3$).

**IR (ATR):** 3509, 2928, 2866, 1612, 1513, 1463, 1388, 1302, 1249, 1173, 1082, 1036, 1005, 938, 882, 835, 775, 677 $cm^{-1}$.

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((1*R*,2*S*)-1-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**S12**).**

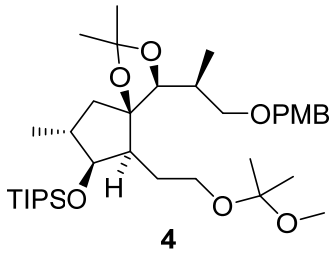
**$^{1}$H-NMR (400MHz, $CDCl_3$):** δ = 7.27-7.25 (m, 2H); 6.88-6.85 (m, 2H); 4.49 (d, *J* = 11.60Hz, 1H); 4.42 (d, *J* = 11.56Hz, 1H); 3.95 (dd, *J* = 4.18, 1.58Hz, 1H); 3.94 (s, 1H); 3.80-3.76 (m, 1H); 3.80 (s, 3H); 3.66 (dd, *J* = 9.42, 4.88Hz, 1H); 3.62 (d, *J* = 7.08Hz, 1H); 3.46 (dd, *J* = 8.75, 8.09Hz, 1H); 3.29 (dd, *J* = 8.90, 5.58Hz, 1H); 2.80 (d, 7.60Hz, 1H); 2.24-2.07 (m, 3H); 2.05-2.00 (m, 1H); 1.96-1.92 (m, 1H); 1.91-1.83 (m, 1H); 1.33 (dd, *J* = 13.40, 5.20Hz, 1H); 1.15-1.08 (m, 21H); 0.97 (d, *J* = 7.16Hz, 3H); 0.95 (d, *J* = 7.48Hz, 3H); 0.89 (m, 9H); 0.56-0.49 (m, 6H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.66 (C); 131.08 (C); 129.29 (CH); 113.87 (CH); 84.86 (C); 83.94 (CH); 76.30 (CH); 74.70 ($CH_2$); 72.96 ($CH_2$); 62.78 ($CH_2$); 55.42 ($CH_3$); 48.94 (CH); 44.70 ($CH_2$); 36.24 (CH); 26.28 ($CH_2$); 26.08 ($CH_3$); 20.60 ($CH_3$); 18.60 (C); 18.32 ($CH_3$); 12.73 (CH); 11.28 ($CH_3$); -5.24 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{35}H_{66}NaO_6Si_2$: 661.4296; found: 661.4283 ±5ppm.

**$[\alpha]^{20}_D$:** +5.8 ° (c = 0.38; $CHCl_3$).

**IR (ATR):** 3462, 2948, 2928, 2866, 2362, 2341, 1613, 1513, 1463, 1386, 1361, 1301, 1247, 1172, 1093, 1034, 1013, 938, 882, 834, 775, 720, 679, 668, 653, 630, 618 $cm^{-1}$.




**4**

**Triisopropyl(((4*S*,5*R*,6*S*,7*S*,8*R*)-4-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6-(2-((2-methoxypropan-2-yl)oxy)ethyl)-2,2,8-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)oxy)silane (**4**).** To a mixture of 2,2-dimethoxypropane (0.2 mL, 1.6 mmol, 100 eq) and pyridinium *p*-toluenesulfonate (0.4 mg, 1.6 µmol, 0.1 eq) was added **23** (10 mg, 0.016 mmol, 1.0 eq) at rt. After 24 h, when TLC-analysis indicated total consumption of the starting material, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and was extracted with EtOAc (3 x 5 mL). The combined organic extract was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) to afford **4** (8 mg, 77 %) as a colorless oil.

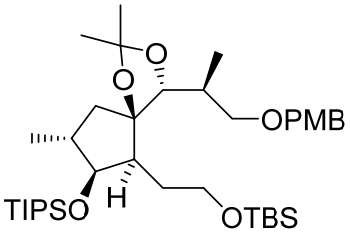
**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.27-7.25 (m, 2H); 6.88-6.85 (m, 2H); 4.49 (d, *J* = 11.70Hz, 1H); 4.41 (d, *J* = 11.70Hz, 1H); 3.98 (dd, *J* = 5.36, 2.54Hz, 1H); 3.80 (s, 3H); 3.77 (d, *J* = 10.16Hz, 1H); 3.63 (dd, *J* = 9.03, 3.20Hz, 1H); 3.48-3.43 (m, 1H); 3.44 (dd, *J* = 9.00, 7.14Hz, 1H); 3.36 (ddd, *J* = 8.99, 8.99, 4.94Hz, 1H); 3.17 (s, 3H); 2.29-2.25 (m, 1H); 2.21 (dd, *J* = 13.55, 8.85Hz, 1H); 2.18-2.13 (m, 1H); 2.10-2.03 (m, 2H); 1.66-1.62 (m, 1H); 1.35-1.32 (m, 1H); 1.35 (s, 3H); 1.31 (s, 3H); 1.30 (s, 3H); 1.28 (s, 3H); 1.08-1.06 (m, 21H); 1.03 (d, *J* = 6.59Hz, 3H); 0.98 (d, *J* = 6.96Hz, 3H).

**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.10 (C); 131.34 (C); 129.09 (CH); 113.77 (CH); 106.29 (C); 99.78 (C); 90.94 (C); 82.31 (CH); 81.53 (CH); 73.37 ($CH_2$); 72.70 ($CH_2$); 59.65 ($CH_2$); 55.42 ($CH_2$); 48.49 ($CH_3$); 47.54 ($CH_2$); 43.94 (CH); 40.37 (CH); 33.57 (CH); 29.85 (C); 26.87 ($CH_3$); 25.68 ($CH_3$); 25.08 ($CH_2$); 24.63 ($CH_3$); 24.61 ($CH_3$); 20.66 ($CH_3$); 18.38 ($CH_3$); 18.34 ($CH_3$); 14.82 ($CH_3$); 13.25 (CH).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{36}H_{64}NaO_7Si$: 659.4319; found: 659.4317 ±5 ppm.

**$[\alpha]^{20}_D$:** +8 ° (c = 0.23; $CHCl_3$).

**IR (ATR):** 2927, 2866, 2361, 2341, 1717, 1610, 1513, 1464, 1378, 1249, 1209, 1170, 1094, 1038, 997, 882, 774, 668 $cm^{-1}$.




**26**

***tert*-Butyl(2-((4*R*,5*R*,6*S*,7*S*,8*R*)-4-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,8-trimethyl-7-((triisopropylsilyl)oxy)-1,3-dioxaspiro[4.4]nonan-6-yl)ethoxy)dimethylsilane (**26**).** To a mixture of 2,2-dimethoxypropane (0.19 ml, 1.6 mmol, 100 eq) and pyridinium *p*-toluenesulfonate (0.4 mg, 1.6 µmol, 0.1 eq) was added **S13** (10 mg, 0.016 mmol, 1.0 eq) at rt. After 3 h, when TLC-analysis indicated complete consumption of the starting material, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and was extracted with EtOAc (3 x 5 mL). The combined organic extract was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude product was purified by flash column chromatography (hexane/EtOAc 19:1) to afford **26** (10 mg, 92%) as a colorless oil.

**$^1$H-NMR (400MHz, $CDCl_3$):** δ = 7.25-7.23 (m, 2H); 6.88-6.85 (m, 2H); 4.43 (d, *J* = 11.73Hz, 1H); 4.39 (d, *J* = 11.77Hz, 1H); 3.85 (dd, *J* = 6.24, 3.88Hz, 1H); 3.80 (s, 3H); 3.71-3.60 (m, 3H); 3.39 (dd, *J* = 9.07, 5.78Hz, 1H); 3.25 (dd, *J* = 9.01, 7.24Hz, 1H); 2.13-2.07 (m, 1H); 2.04-1.85 (m, 4H); 1.54 (m, 1H); 1.37-1.31 (m, 4H); 1.27 (s, 3H); 1.09-1.06 (m, 24H); 0.94 (d, *J* = 7.04Hz, 3H); 0.88 (s, 9H); 0.02 (s, 6H).

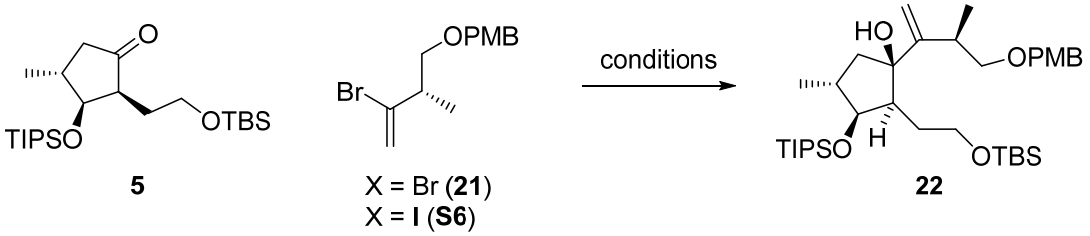
**$^{13}$C-NMR (100MHz, $CDCl_3$):** δ = 159.30 (C); 130.72 (C); 129.27 (CH); 113.94 (CH); 106.64 (C); 91.13 (C); 80.95 (CH); 80.19 (CH); 73.34 ($CH_2$); 72.74 ($CH_2$); 62.37 ($CH_2$); 55.41 ($CH_3$); 44.91 (CH); 41.22 ($CH_2$); 40.14 (CH); 34.51 (CH); 29.85 (C); 28.64 ($CH_3$); 27.35 ($CH_3$); 26.94 ($CH_2$); 26.16 ($CH_3$); 19.73 ($CH_3$); 18.41 ($CH_3$); 18.38 ($CH_3$); 14.44 ($CH_3$); 13.35 (CH); -5.07 ($CH_3$); -5.10 ($CH_3$).

**HRMS (ESI) (m/z):** $[M+Na]^+$ calcd. for $C_{38}H_{70}NaO_6Si_2$: 701.4609; found: 701.4612 ±5 ppm.

**$[\alpha]^{20}_D$:** +6 ° (c = 0.30; $CHCl_3$).

**IR (ATR):** 2927, 2864, 2360, 1613, 1513, 1463, 1376, 1366, 1248, 1216, 1172, 1096, 1055, 918, 882, 835, 775, 680 $cm^{-1}$.

**Screening of the reaction conditions for the preparation of** 22




**5** X = Br (**21**) X = **I** (**S6**) **22**

**Table 1**

| **Generation of the Grignard reagent (**GR**)** | | | | **Reaction with** 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | Br | 2.0 eq Mg, 0.05 eq 1,2-dibromoethane | THF, 3 h, reflux | 1.1 eq GR THF, 4 h, 0 °C to rt | No reaction |
| **2** | Br | 2.0 eq Mg, 0.05 eq 1,2-dibromoethane | THF, 3h, reflux | 2.0 eq GR 3.0 eq $CeCl_3$ THF, 4 h, 0 °C to rt | No reaction |
| **3** | Br | 2.0 eq Mg, 0.05 eq 1,2-dibromoethane | THF, 3h, reflux | 2.0 eq GR THF, 8 h, rt to reflux | No reaction but slow decomposition |
| **4** | Br, I | 2.0 eq Mg, 0.05 eq 1,2-dibromoethane | THF, 3h, reflux | 2.0 eq GR 3.0 eq $CeCl_3$ THF, 8 h, rt to reflux | No reaction but slow decomposition |
| **5** | Br, I | 2.0 eq, Mg, $I_2$ | THF, 3h, 60°C | 1.3 eq GR THF, 8 h, rt to reflux | No reaction but slow decomposition |

**Preparation of the Grignard reagent:**

To a suspension of magnesium (0.034 g, 1.4 mmol, 2.0 eq) in THF (0.1 mL) was added a 0.1 mL aliquot of a solution of **21** (0.20 g, 0.70 mmol, 1.0 eq) (or **S6**; see Table 1) in THF (0.90 mL). 1,2-Dibromoethane (6 µl, 0.07 mmol, 0.05 eq) or a crystal of iodine (see Table 1) was added to initiate the Grignard reaction.

The remaining solution of **21** (or **S7**; see table) in THF was added and the reaction mixture was heated to reflux (or to 60 °C; see Table 1) for 3 h.

**Reaction without Lewis acidic additive (Table 1; entries 1, 3, 5)**

**Representative procedure:**

To a solution of **5** (0.100 g, 0.233 mmol, 1.0 eq) in $Et_2O$ (1.5 mL) was added the previously prepared solution of the Grignard reagent (1.0 to 2.0 eq; see Table 1) and the reaction mixture was stirred as described in Table 1.

The reaction was quenched by the addition of an aqueous saturated solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

→Outcome see Table 1.

**Reaction with Lewis acidic additive (Table 1; entries 2, 4)**

**Representative procedure:**

$CeCl_3$ was dried according to Dimitrov and coworkers.[16]

A suspension of cerium(III)chloride (0.172 g, 0.70 mmol, 3.0 eq) in THF (1.6 mL) was stirred for 10 min at rt before a solution of **5** (0.100 g, 0.23 mmol, 1.0 eq) in dry THF (2.25 mL) was added at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. A solution of the previously prepared Grignard reagent (1.0 to 2.0 eq; see Table 1) was added to the reaction mixture and stirred as described in Table 1.

The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 1.

**Table 2**

| **Generation of the Grignard reagent (**GR**)** | | | | **Reaction with** 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | Br | 2.0 eq *t*-BuLi<br>2.2 eq $MgBr_2$ in $Et_2O$ | THF, 1 h −78 °C<br>1h 0 °C | 1.1 eq GR<br>THF, 1 h 0 °C, 1 h rt | No reaction |
| **2** | Br | 2.0 eq *t*-BuLi<br>2.2 eq $MgBr_2$ in $Et_2O$ | THF, 1 h −78 °C<br>1 h 0 °C | 2 eq GR<br>THF, 1 h 0 °C, 1 h rt | No reaction |
| **3** | Br | 2.0 eq *t*-BuLi<br>2.2 eq $MgBr_2$ in $Et_2O$ | THF, 1 h −78 °C<br>1 h 0 °C | 3.0 eq GR<br>THF, 1 h 0 °C, 5 h rt | No reaction |
| **4** | Br | 2.0 eq *t*-BuLi<br>2.2 eq $MgBr_2$ in $Et_2O$ | $Et_2O$, 1 h −78 °C<br>1 h 0 °C | 2.0 eq GR<br>$Et_2O$, 1 h 0 °C, 5 h rt | No reaction |
| **5** | Br | 2.0 eq *t*-BuLi<br>2.2 eq $MgBr_2$ in $Et_2O$ | THF, 1 h −78 °C<br>1 h 0 °C | 3.0 eq GR<br>3.0 eq $CeCl_3$<br>THF, 1 h 0 °C, 1 h rt | No reaction |

**Preparation of a 1M $MgBr_2$ solution in $Et_2O$**[17]:

To a slurry of powdered magnesium (0.52 g, 21.4 mmol, 1.07 eq) in $Et_2O$ (15 mL) was added 1,2-dibromoethane (1.72 mL, 20 mmol, 1.0 eq) in toluene (5 mL) dropwise over a period of approximately 45 min (the rate of addition was adjusted to maintain gentle reflux). The resulting solution was stirred for additinal 30 min at rt and afterwards it kept under an argon atmosphere for approximately one hour before being used (while standing at room temperature finely dispersed, not converted magnesium deposited on the wall of the flask). For further use the concentration of the magnesium bromide solution was assumed to be 1.0 M.

**Reaction without Lewis acidic additive (Table 2; entries 1, 2, 3, 4)**

**Representative procedure:**

To a solution of halide **21** (0.130 g, 0.46 mmol, 2.0 eq) in $Et_2O$ (3.7 mL) was added *tert*-butyllithium (1.9M in pentane; 0.493 mL, 0.938 mmol, 4.08 eq) at −78 °C. The reaction mixture was stirred for 10 min before a freshly prepared solution of $MgBr_2$ (1M in $Et_2O$; 0.522 mL, 0.522 mmol, 2.27 eq) was added and the reaction mixture was stirred for 10 min. A solution of **5** (0.100 g, 0.23 mmol, 1.0 eq) in $Et_2O$ (1.5 mL) was added at −78 °C. The reaction mixture was warmed to 0 °C and was stirred at that temperature for one hour before it was warmed to rt. Stirring was continued for an additional hour.

The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 2.

**Reaction with Lewis acidic additive (Table 2; entry 5):**

To a solution of halide **21** (0.20 g, 0.70 mmol, 3.0 eq) in THF (0.25 mL) was added *tert*-butyllithium (1.9M in pentane; 0.76 mL, 1.45 mmol, 6.3 eq) at −78 °C. The reaction mixture was stirred for 15 min before a freshly prepared solution of $MgBr_2$ (1M in $Et_2O$; 0.807 mL, 0.807 mmol, 3.5 eq) was added. After 10 min at −78 °C the reaction mixture was allowed to warm to 0 °C.

A suspension of cerium(III)chloride (0.172 g, 0.70 mmol, 3.0 eq) in THF (1.6 mL) was stirred for 10 min at rt before a solution of **5** (0.100 g, 0.23 mmol, 1.0 eq) in dry THF (2.25 mL) was added to the reaction mixture at 0 °C. The resulting mixture was stirred for 30 min at 0 °C.

The previously prepared solution of the Grignard reagent (1.85 mL, 0.70 mmol, 3.0 eq) was added and the reaction mixture was stirred for one hour at 0 °C and 5 h at rt. The reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous layer was

extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 2.

**Table 3**

| **Generation of the metal organyl (**MO**)** | | | | **Reaction with** 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | Br | 3.0 eq sodium naphthalenide | THF, −78 °C | 1.5 eq MO, −78 °C to rt, THF | No reaction |
| **2** | Br | 3.0 eq sodium naphthalenide, Barbier conditions | THF, −78 °C | 1.5 eq MO, −78 °C to rt, THF | No reaction |
| **3** | Br | 6.0 eq, sodium naphthalenide, Barbier conditions, 3 additions (until persistent color) | THF, −78 °C | 1.5 eq MO, −78 °C to rt, THF | Reisolated educt (70 %) and unidentified side-products |

**Preparation of Sodium naphthalenide[18] solution:**

Naphthalene (0.63 g, 3.3 mmol) and sodium (0.114 g, 3.3 mmol) were placed in a Schlenk flask and THF (6.6 mL) was added. The dark blue-green colored mixture was stirred for 50 min at −20 °C and 30 min at room temperature.

**Representative procedure[19] (Table 3; entries 1, 2, 3):**

To a solution of bromide **21** (0.050 g, 0.175 mmol, 1.5 eq) and **5** (0.05 g, 0.117 mmol, 1.0 eq) in THF (0.58 mL) was added the freshly prepared sodium naphthalenide solution (0.5M in THF; 0.93 mL, 0.47 mmol, 4.0 eq) at −78 °C. (Table 3, entry 3: After one hour at that temperature sodium naphthalenide was added until the characteristic dark blue-green color persisted (2.0 additional equivalents were added)). The reaction was allowed to stir at rt over night.

The reaction was quenched by the addition of water (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 3.

**Table 4**

| Generation of the metal organyl (MO) | | | | Reaction with 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | -Br, -I | 2.0 eq *t*-BuLi | $Et_2O$, −78 °C | 1.2 eq MO, −78 °C to 10 °C (5h), toluene | Educt (70 %) and decomposition |
| **2** | -Br | 2.0eq *t*-BuLi 1.0eq $CeCl_3$ | THF, −78 °C | 1.3 eq MO, −78 °C to −20 °C, THF | Educt (25 %) and decomposition |

**Representative procedure (Table 4; entries 1, 2):**

To a solution of bromide **21** (0.043 g, 0.152 mmol, 1.3 eq) (and cerium(III)chloride; see Table 4, entry 2) in $Et_2O$ (0.64 mL) was added *tert*-butyllithium (1.9M in pentane; 0.160 mL, 0.303 mmol, 2.6 eq) at −78 °C. After 40 min at that temperature the reaction mixture was warmed to rt and stirred for 5 min before it was re-cooled to −78 °C. A solution of **5** (0.050 g, 0.117 mmol, 1.0 eq) in toluene (0.53 mL) was added slowly (5 min) to the slightly yellow solution. The reaction mixture was stirred for one hour before it was warmed to −20 °C and was allowed to warm to 10 °C over a period of 4 h. The reaction was quenched by addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 4.

**Table 5**

| **Generation of the metal organyl (**MO**)** | | | | **Reaction with** 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | Br | 2.0 eq *t*-BuLi | THF, −78 °C | 1.3 eq MO,<br>−78 °C to −20 °C to rt, THF | No reaction |
| **2** | Br | 2.0 eq *t*-BuLi | THF, −78 °C | 1.3 eq MO,<br>2eq $CeCl_3$<br>−78 °C to −20 °C to rt, THF | Educt (30 %) and decomposition |
| **3** | Br | 2.0 eq *t*-BuLi | THF, −78 °C | 1.3 eq MO,<br>2 eq LiCl,<br>−78 °C to −20 °C to rt, THF | No reaction |
| **4** | Br | 2.0 eq *t*-BuLi | THF, −78 °C | 1.3 eq MO,<br>2 eq $Sc(OTf)_3$<br>−78 °C to −20 °C to rt, THF | No reaction |
| **5** | Br | 2.0 eq *t*-BuLi | THF, −78 °C | 1.3 eq MO,<br>2 eq $Yb(OTf)_3$<br>−78 °C to −20 °C to rt, THF | No reaction |

**Representative procedure (Table 5; entries 1, 2, 3, 4, 5)**

To a solution of bromide **21** (0.035 g, 0.121 mmol, 1.3 eq) in THF (0.19 mL) was added *tert*-butyllithium (1.9M in pentane; 0.127 mL, 0.242 mmol, 2.6 eq) at −78 °C. After stirring for 20 min at that temperature cerium(III)chloride (0.046 g, 0.186 mmol, 2 eq) (or another additive; see Table 5) was added and the reaction mixture was stirred for 20 min.

A solution of **5** (0.04 g, 0.093 mmol, 1 eq) in THF (0.12 mL) was added slowly (3 min) to the slightly yellow solution at −78 °C. After 3 h the reaction was warmed to −20 °C over one hour and was allowed to warm to rt over one hour. After stirring for 2 h at rt the reaction was quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1).

Outcome see Table 5.

**Table 6**

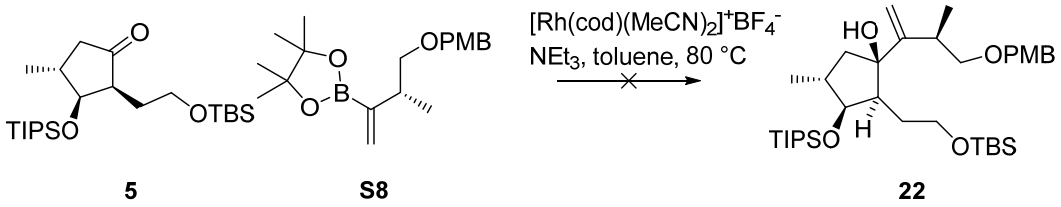
| **Generation of the metal organyl (**MO**)** | | | | **Reaction with** 5 | |
|---|---|---|---|---|---|
| **Entry** | **-X** | **Halide exchange** | **conditions** | **conditions** | **yield** |
| **1** | Br,<br>I | 2 eq *t*-BuLi,<br>2.5 eq HMPA | −78 °C,<br>Pentane/$Et_2O$ 3/2 | 2.5 eq MO,<br>−78 °C to −20 °C<br>Pentane/$Et_2O$ = 3/2 | Educt (53%) and unidentified side products |
| **2** | Br,<br>I | 2 eq *t*-BuLi<br>1 eq $CeCl_3$·LiCl solution | −78 °C, THF | 2.7 eq MO,<br>−78 °C to −20 °C<br>THF | Decomposition |

**Preparation of a solution of $CeCl_3 \cdot 2$ LiCl in THF (according to Knochel and coworkers[20]):**

Commercially available $CeCl_3 \cdot 7H_2O$ (0.10 mol, 37.1 g, 1.0 eq) was mixed with LiCl (0.20 mol, 8.40 g, 2.0 eq) in a 500-mL Schlenk flask and water (100 mL) was added slowly under vigorous stirring. The resulting slurry was stirred under high vacuum (0.01 mbar) at rt for 4 h (a second cooling trap is necessary). Stirring was continued for 4 h at 40 °C, 12 h at 60 °C, 4 h at 80 °C, 4 h at 100 °C, 12 h at 120 °C, 4 h at 140 °C and finally 5 h at 160 °C. The slow increase of temperature and highly efficient stirring proved to be essential according to the cited literature.[20] The resulting solid was cooled to rt and THF was added until a total volume of 300 mL was reached. Then, molecular sieves (3 Å, 50 g) were added and the resulting mixture was stirred vigorously for 48 h at rt. Finally, the insoluble material (mostly crushed molecular sieves) was removed by inert filtration under an argon atmosphere. A clear and colorless solution of $CeCl_3 \cdot 2LiCl$ (0.3M in THF) was obtained which was stored at room temperature under argon until used.

**Representative procedure (Table 6; 1, 2):**

A solution of *tert*-butyllithium (1.7M in pentane; 0.370 mL, 0.630 mmol, 5.38 eq) in THF (0.34 mL) was cooled to −78 °C before iodide **S7** (0.105 g, 0.315 mmol, 2.7 eq) in THF (0.45 mL) was added slowly over a period of 30 min. After the addition was completed, the slurry suspension was stirred for 5 min, before the previously prepared $CeCl_3 \cdot 2LiCl$ (0.3M in THF; 1.1 mL, 0.33 mmol, 2.8 eq) solution (or HMPA; see table 6, entry 1) was slowly added (5 min). During the addition the color of the reaction mixture turned deep orange. After stirring for one hour at −78 °C ketone **5** (0.05 g, 0.117 mmol, 1.0 eq) dissolved in THF (0.86 mL) was added dropwise. The solution was warmed to −20 °C and stirred at that temperature for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1). Outcome see Table 6.




**5** **S8** **22**

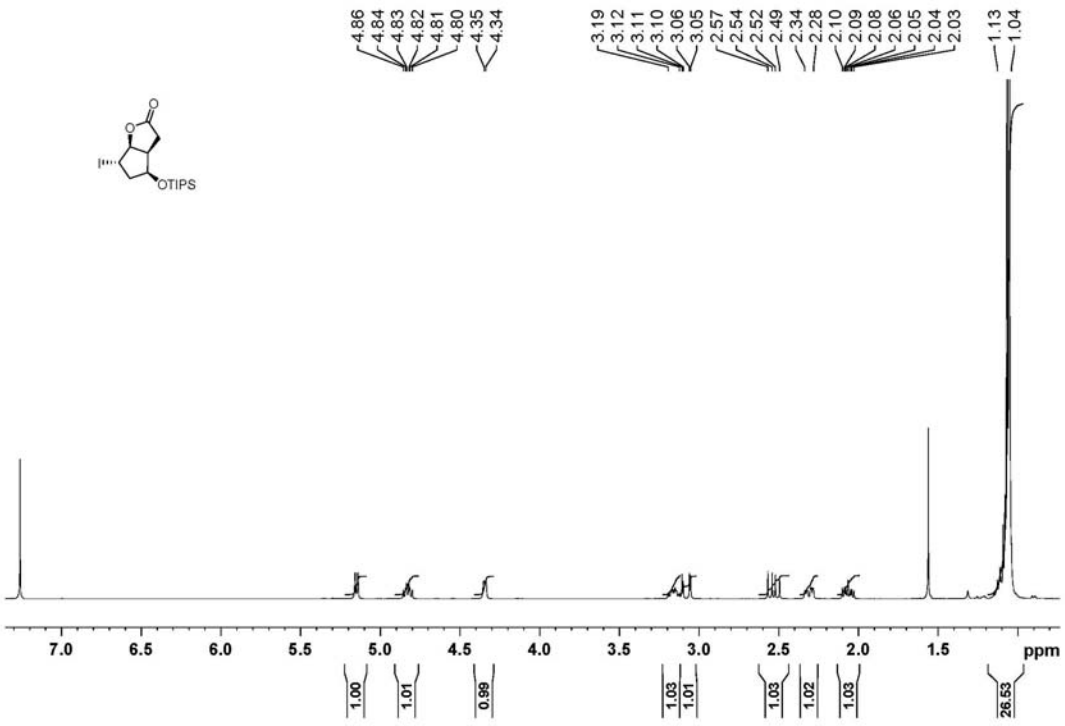
A solution of ketone **5** (0.100 g, 0.233 mmol, 1 eq) and **S8** (0.093 g, 0.280 mmol, 1.2 eq) in degassed, dry toluene (2.59 mL) was transferred to a Schlenk flask containing

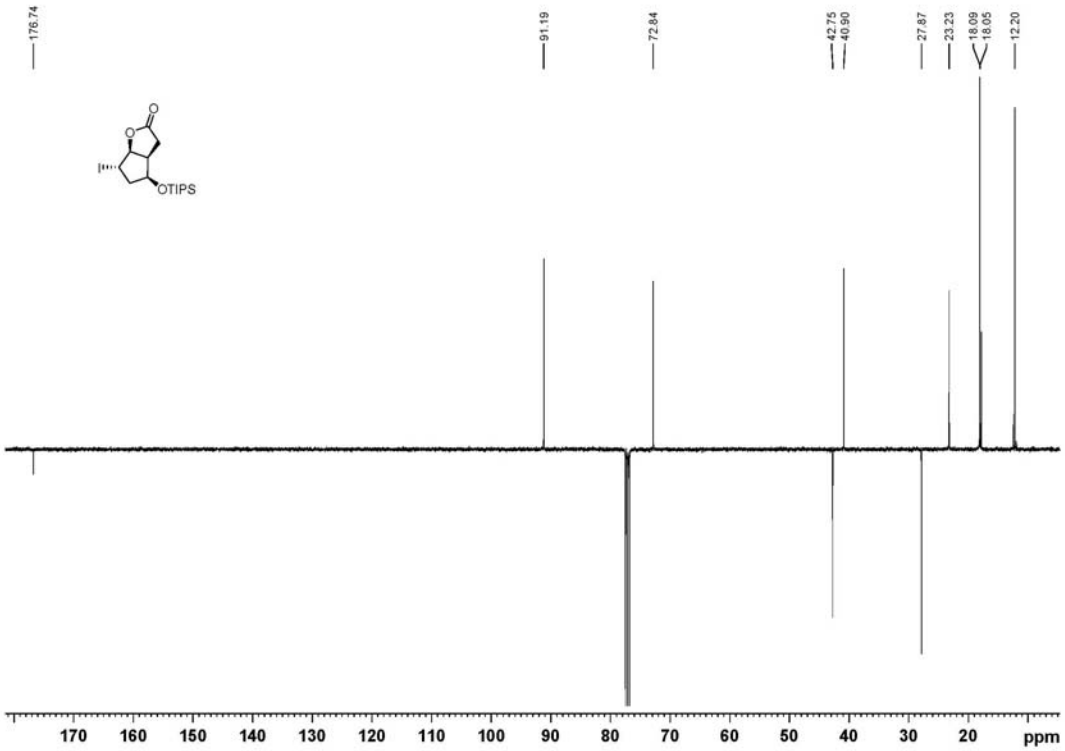
$[Rh(cod)(MeCN)^2]^+BF^{4-}$ (0.022 g, 0.058 mmol, 25 mol%). Next, triethylamine (0.066 mL, 0.466 mmol, 2 eq) was added to the flask at rt. The reaction mixture was heated to 80 °C for 20 h.[21] The reaction was quenched by the addition of water (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo*. The crude material was purified by flash column chromatography (hexane/EtOAc 40:1). No reaction was observed and educt **5** (50 mg, 50 %) was reisolated.

## NMR spectra

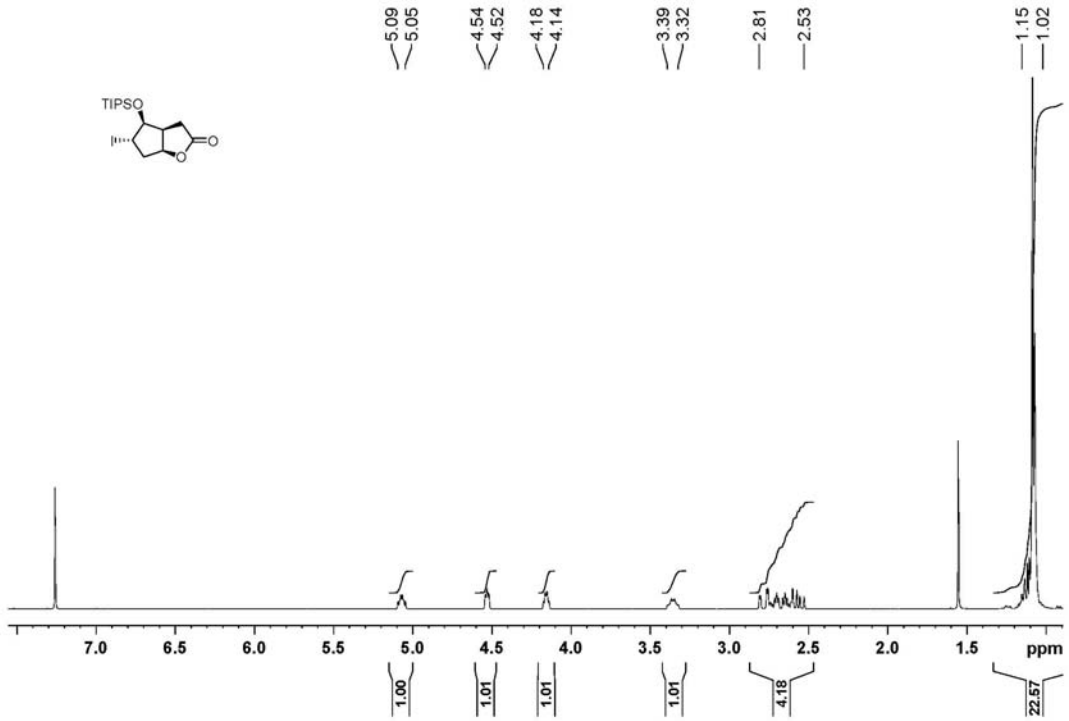
Solvent: $CDCl_3$
Instrument frequency: $^{1}H$: 400 MHz
$^{13}C$: 100 MHz

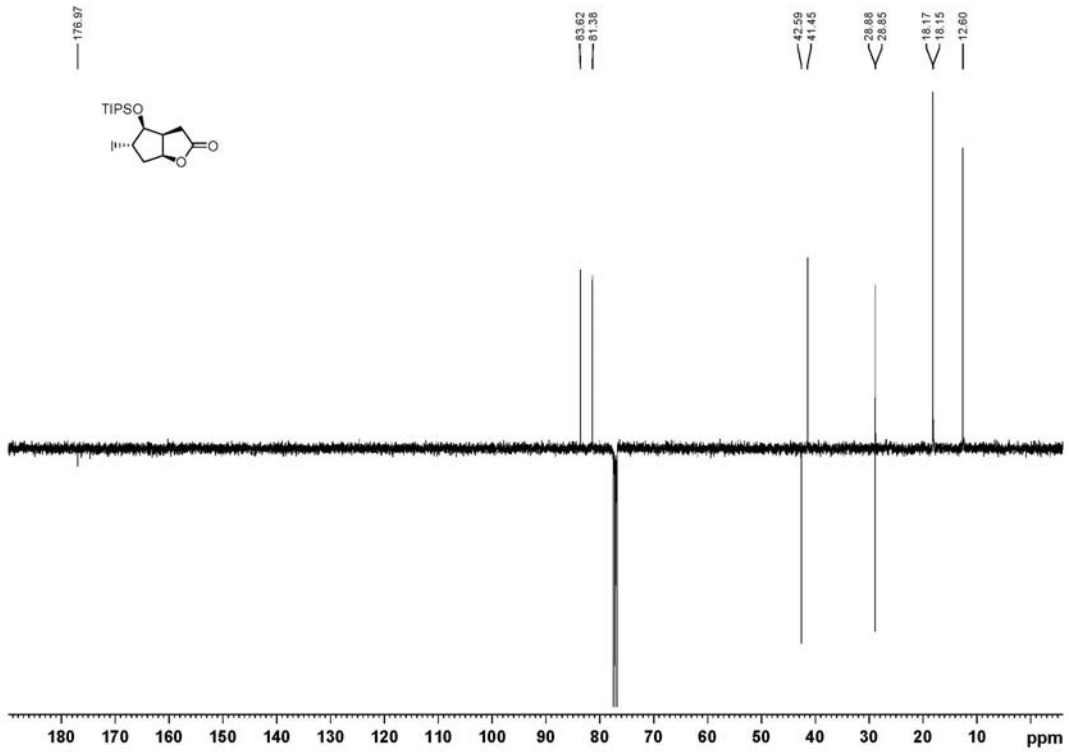
**(3a*R*,4*S*,6*S*,6a*S*)-6-Iodo-4-((triisopropylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one (13).**



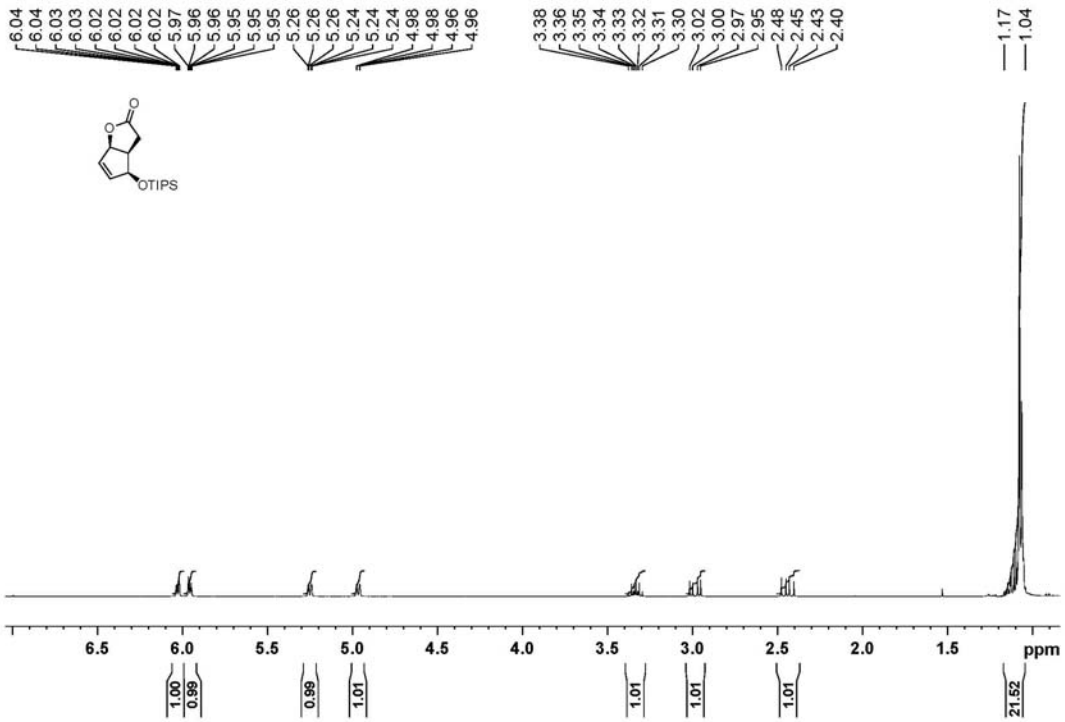



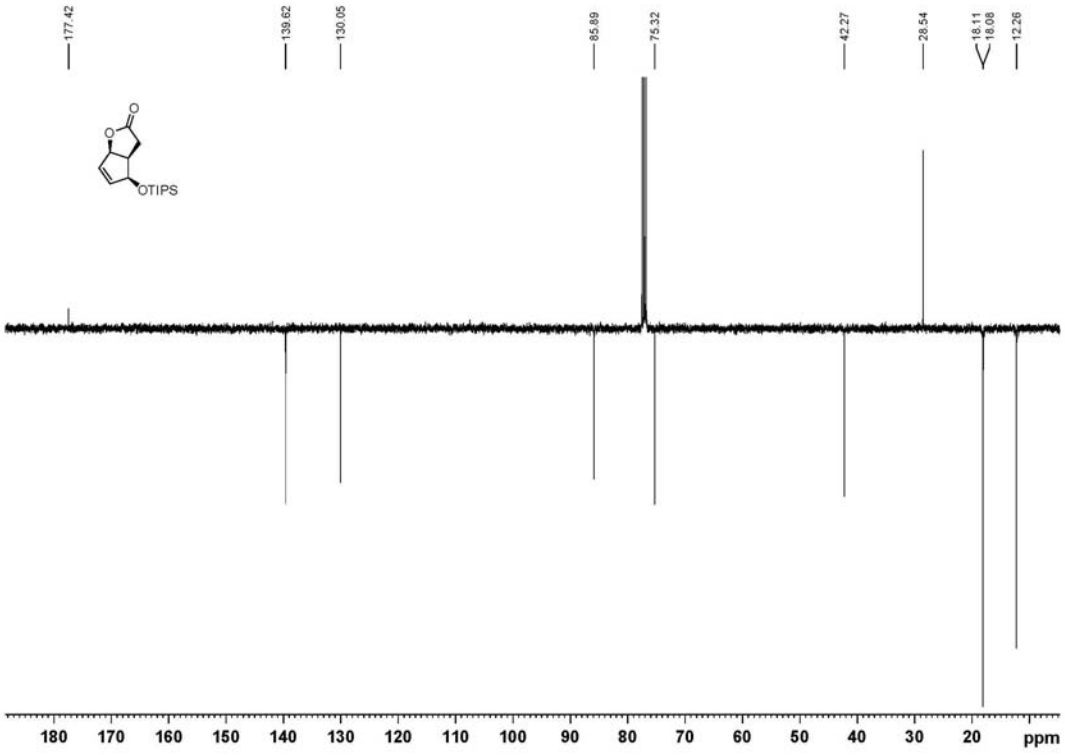
**(3a*S*,4*S*,5*S*,6a*S*)-5-Iodo-4-((triisopropylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one (**12**).**



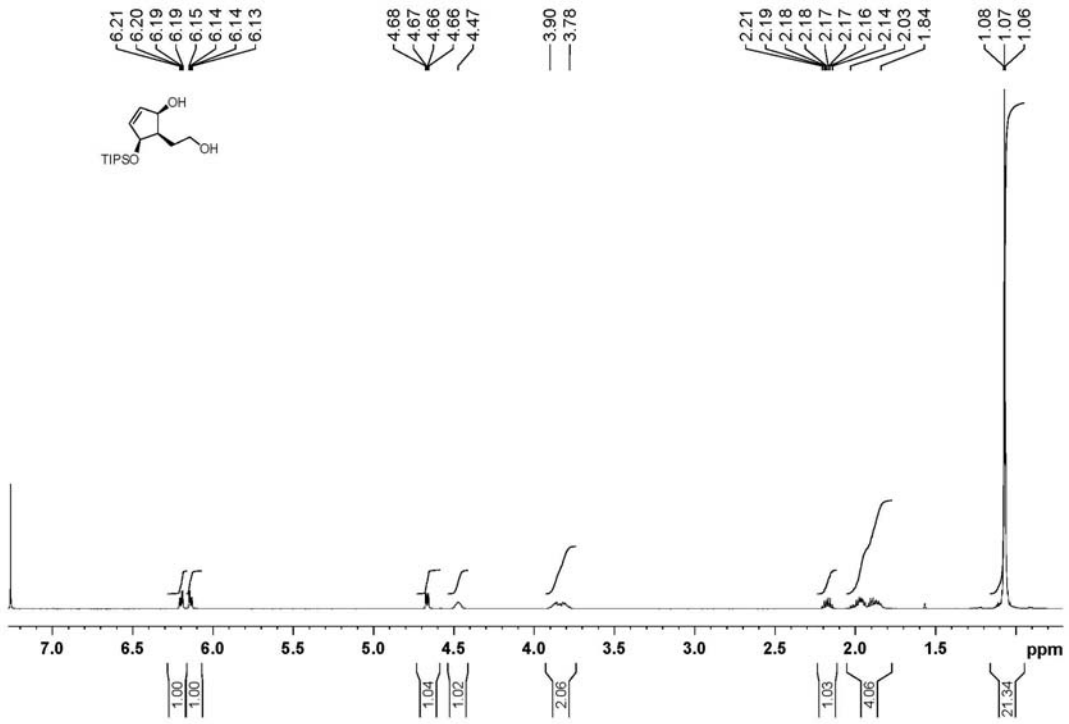



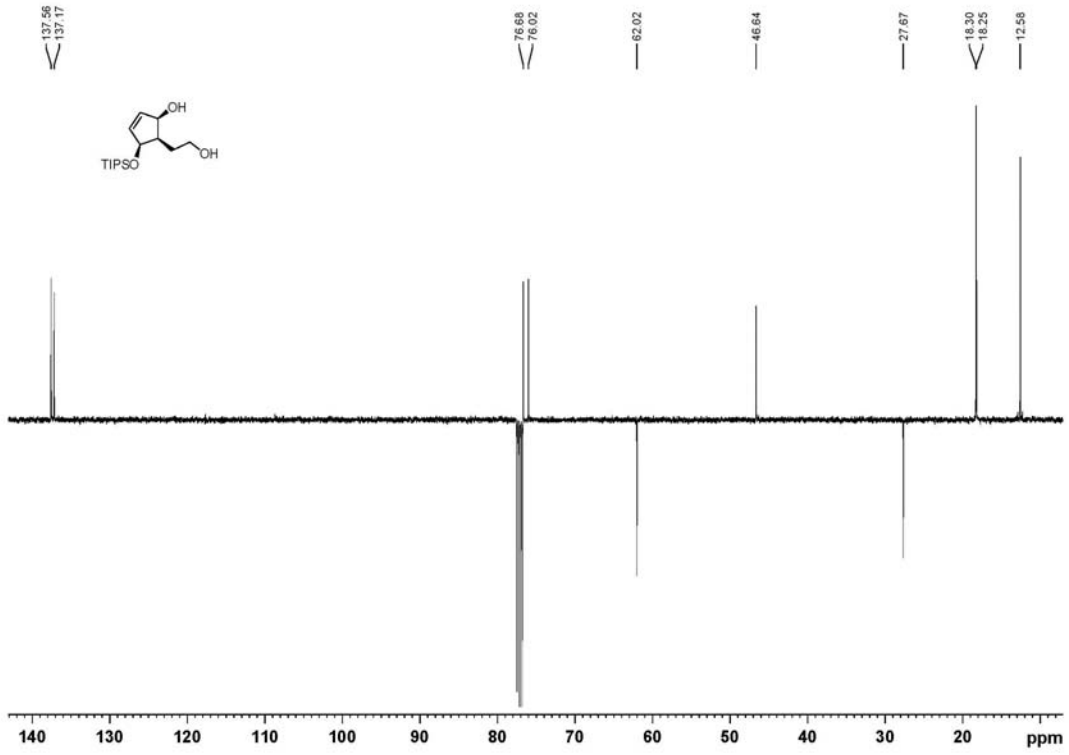
**(3a*R*,4*S*,6a*R*)-4-((Triisopropylsilyl)oxy)-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**14**).**



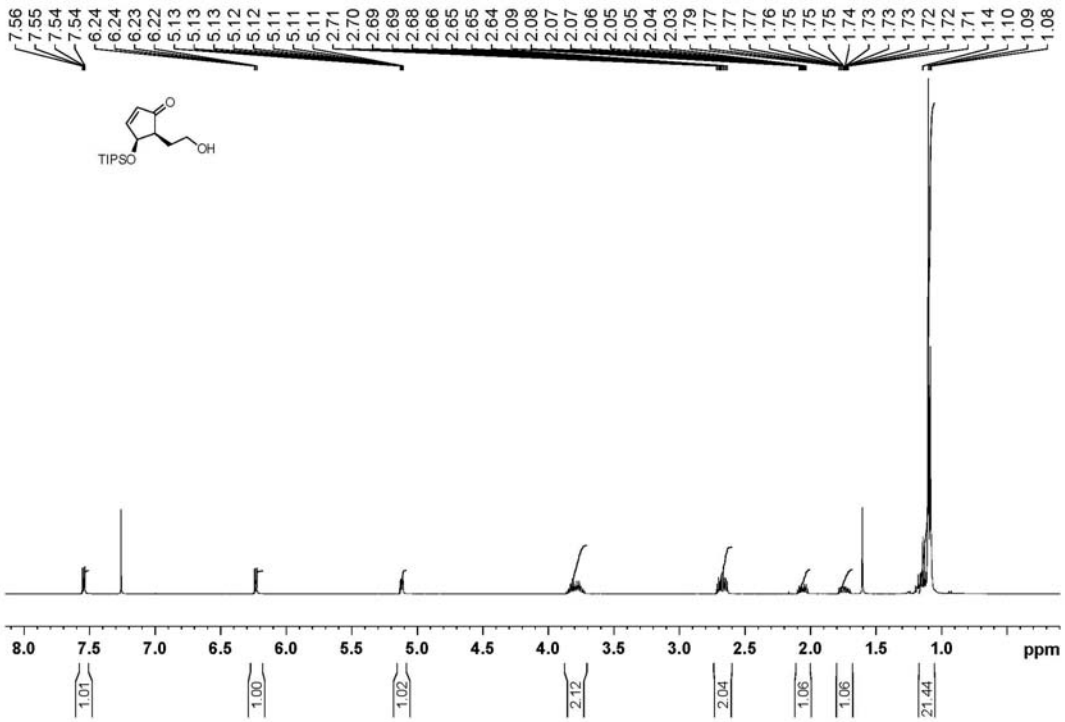



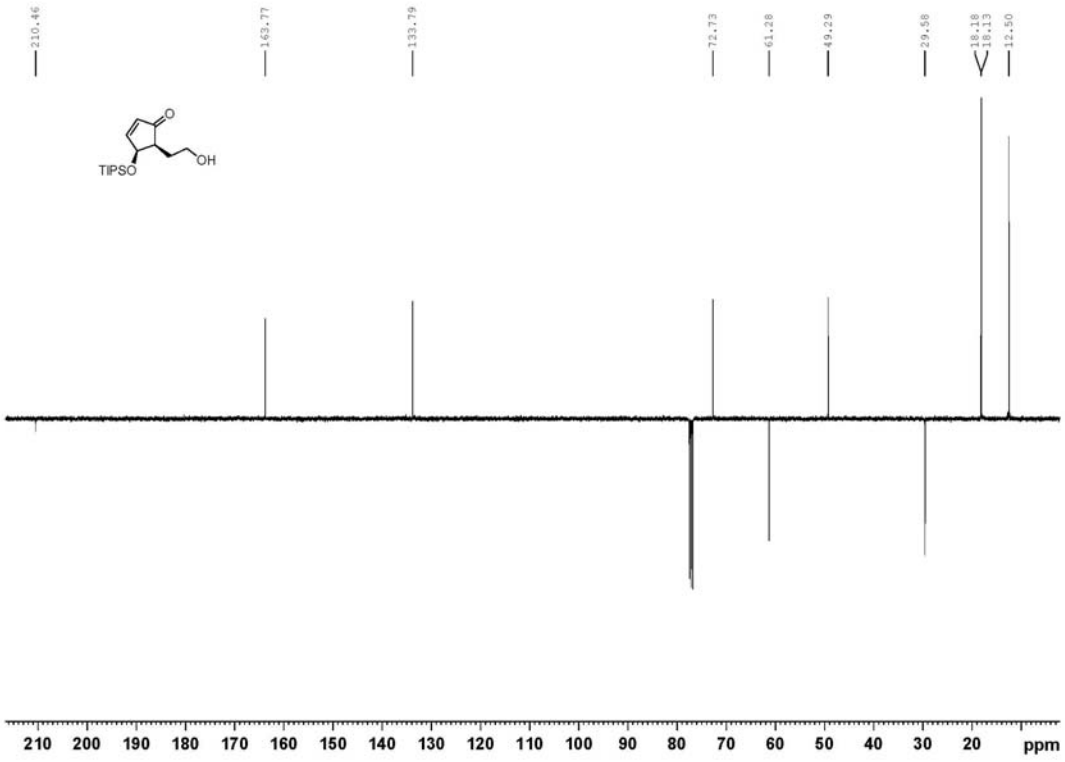
**(1*R*,4*S*,5*R*)-5-(2-Hydroxyethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (16).**



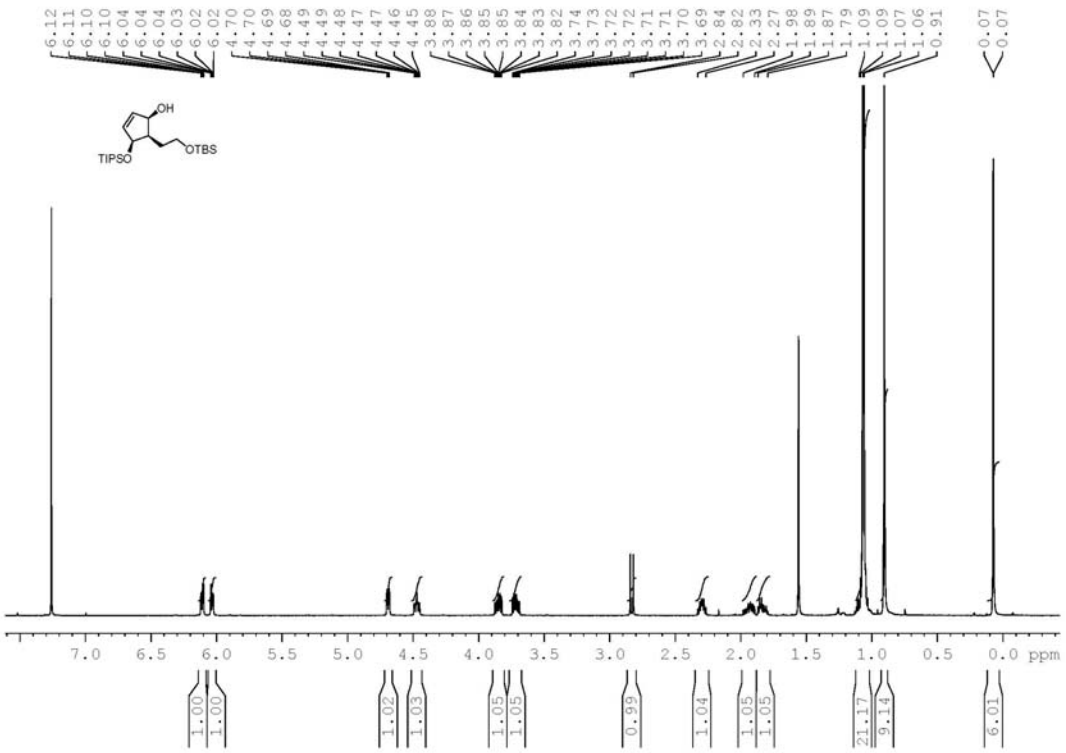



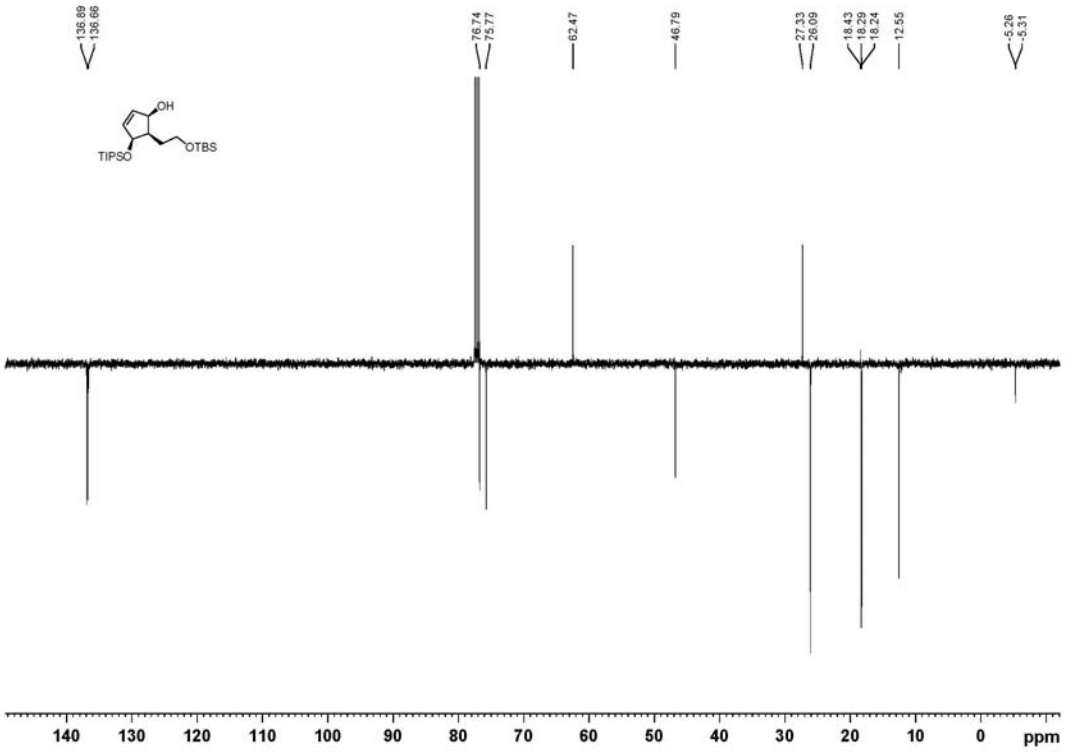
**(4*S*,5*S*)-5-(2-Hydroxyethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (17).**



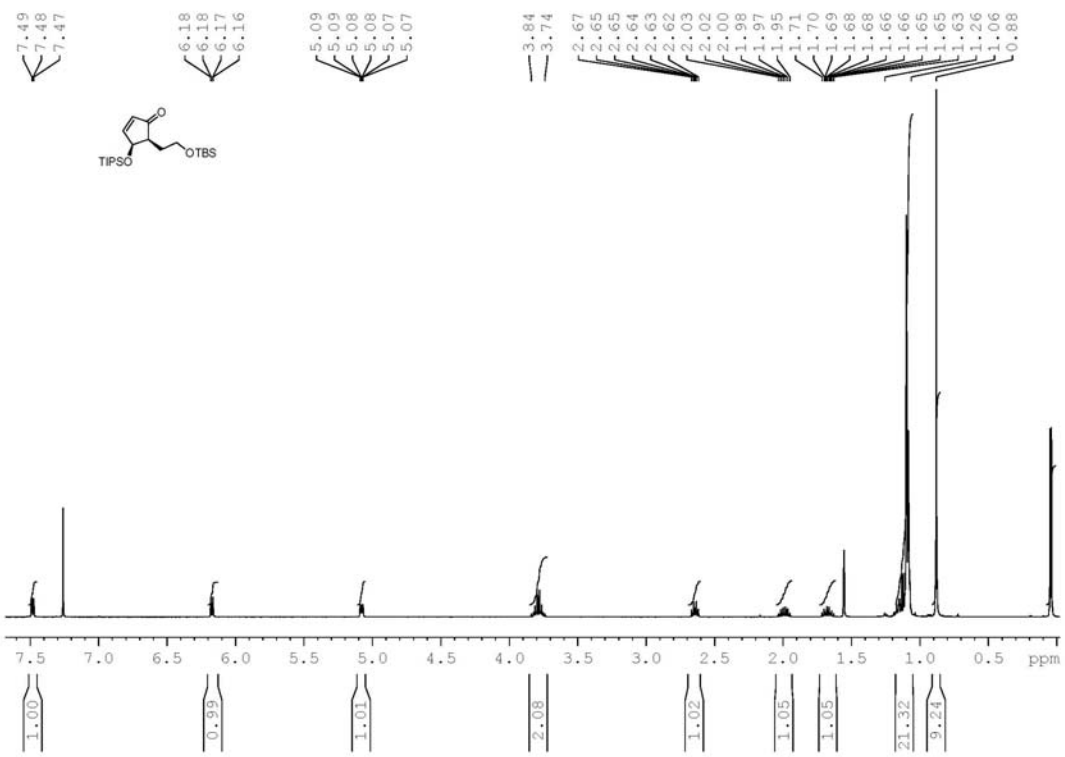



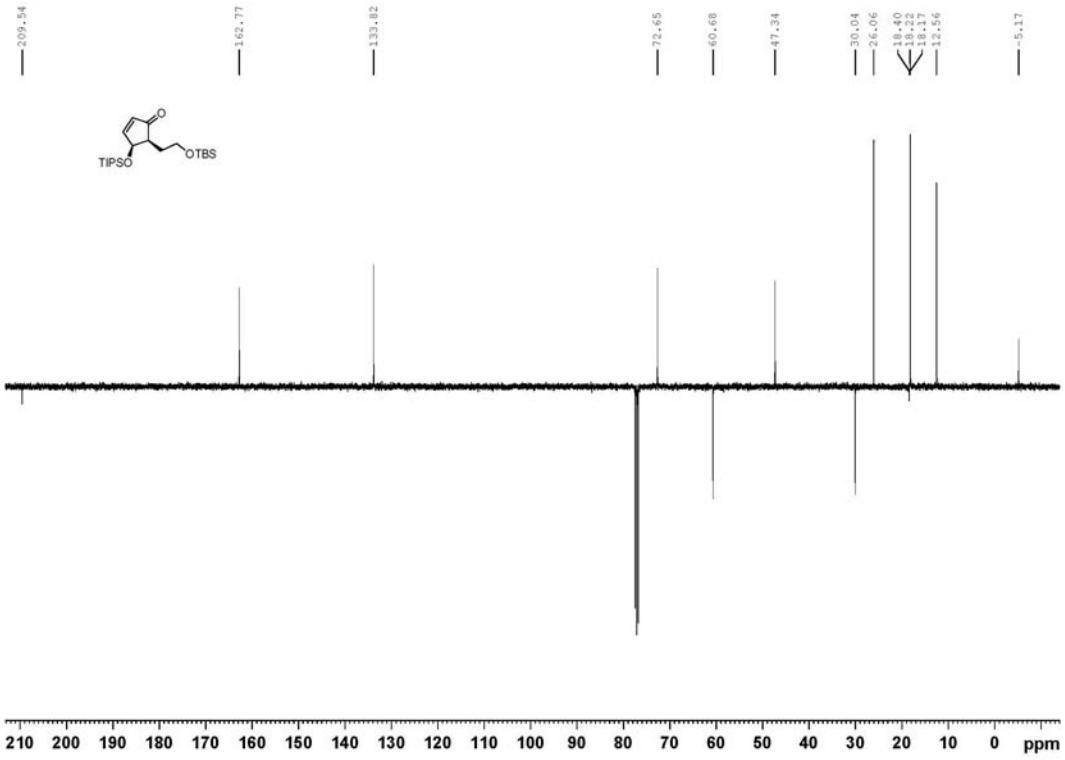
**(1*R*,4*S*,5*R*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (**S3**).**



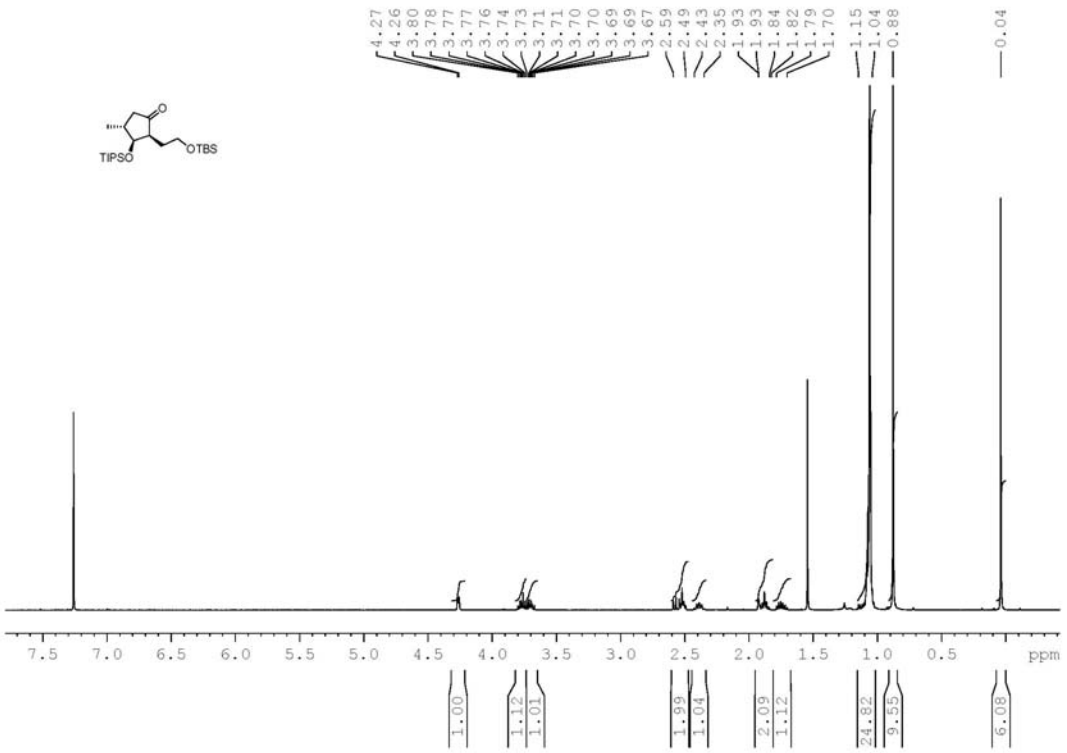



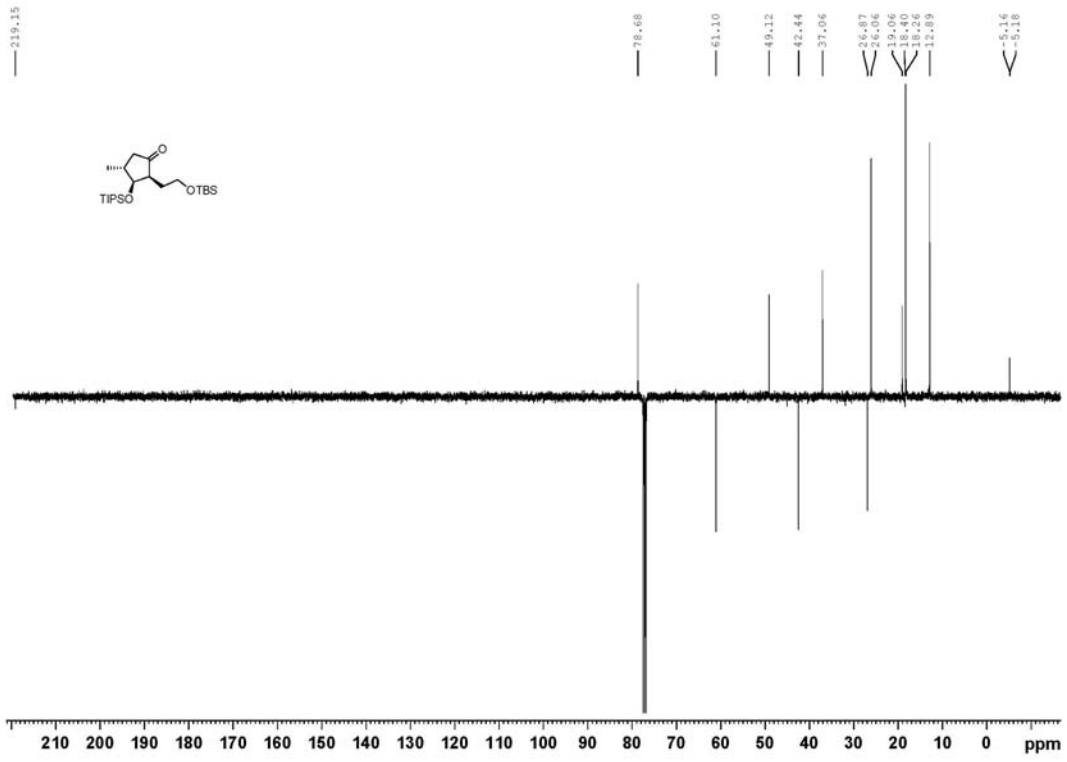
**(4*S*,5*S*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-((triisopropylsilyl)oxy)cyclopent-2-enone (**18**).**



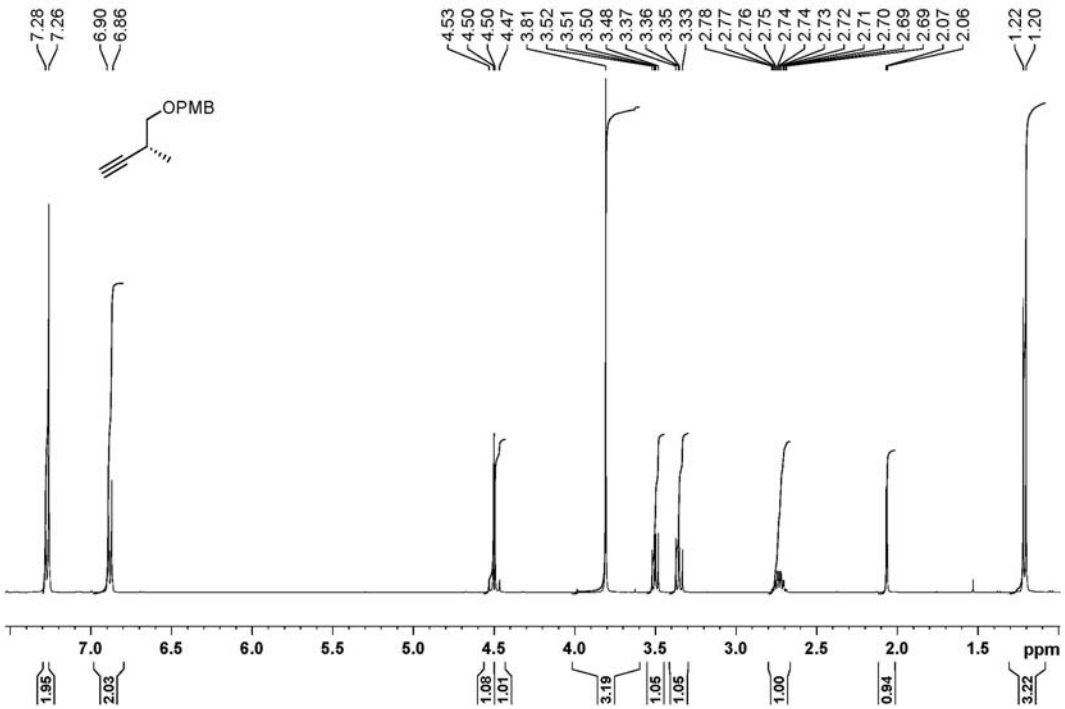



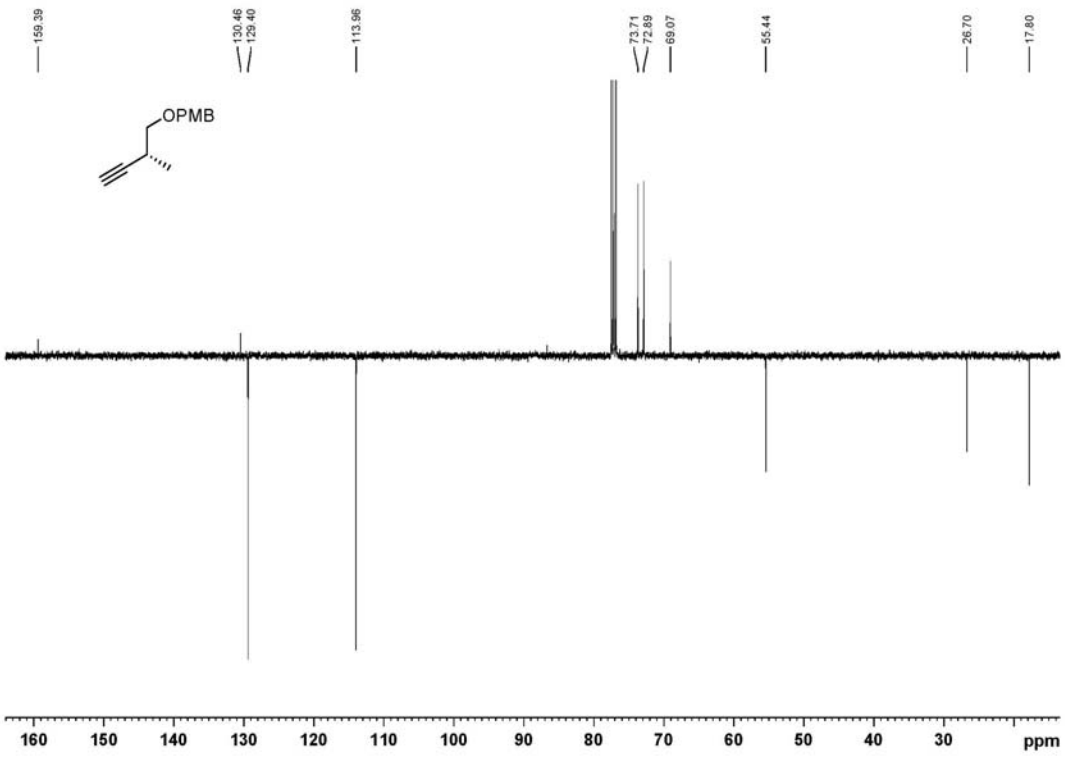
**(2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentanone (5).**



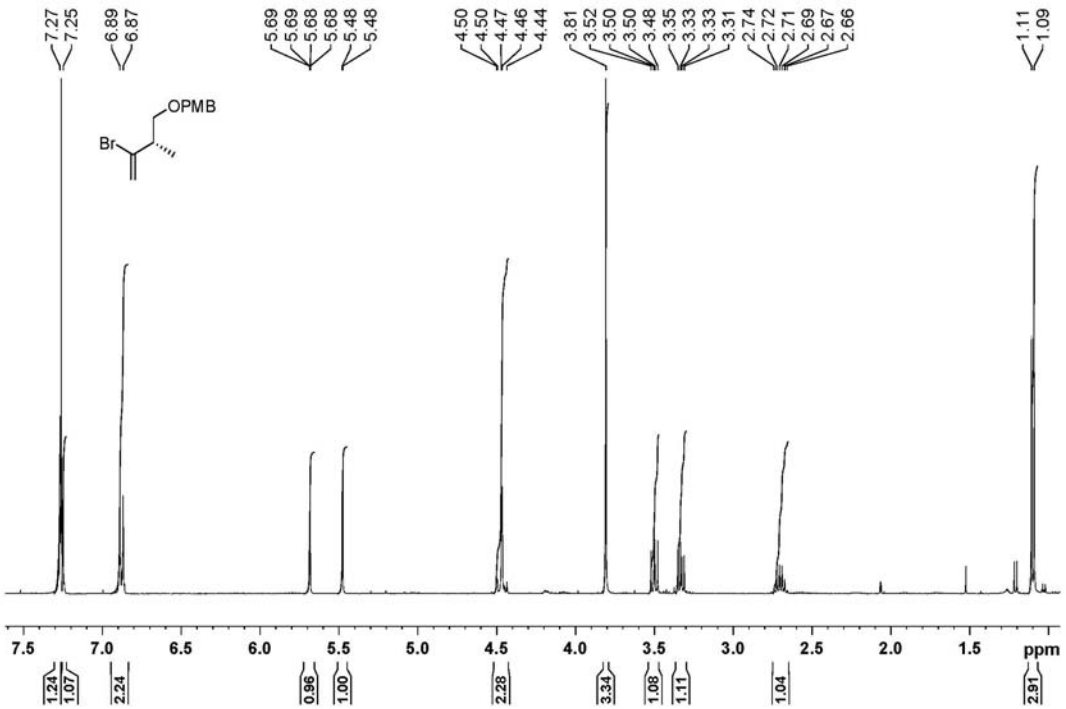



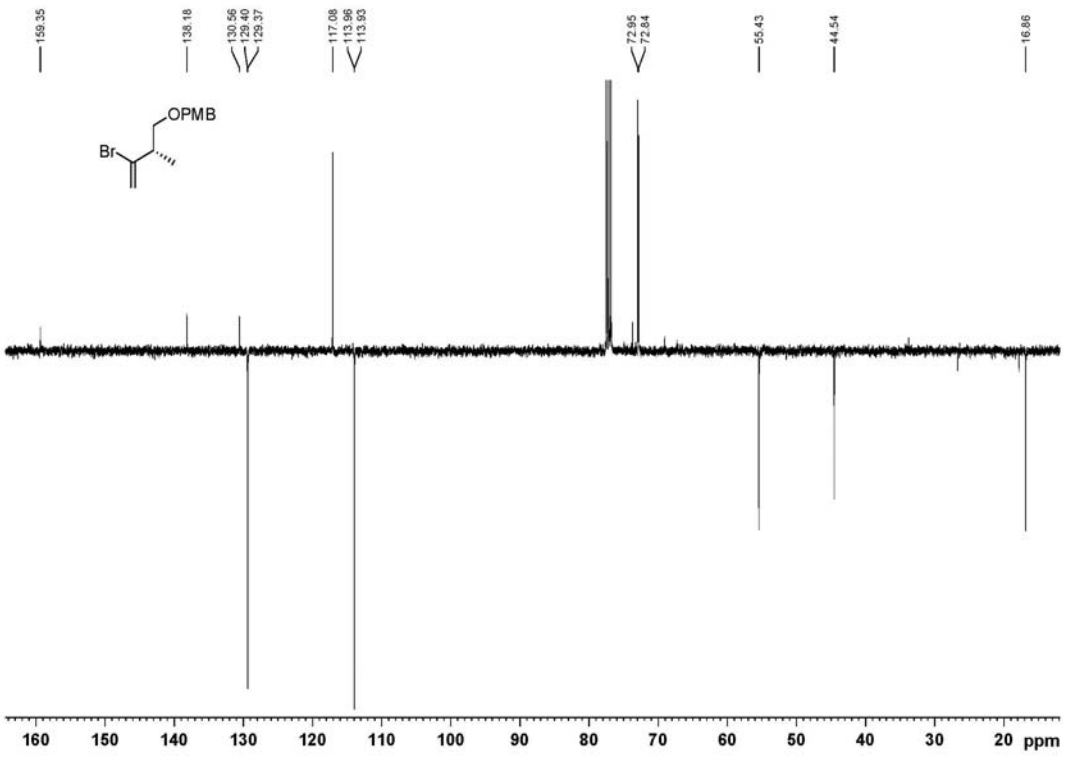
**(*R*)-1-Methoxy-4-(((2-methylbut-3-yn-1-yl)oxy)methyl)benzene (20).**



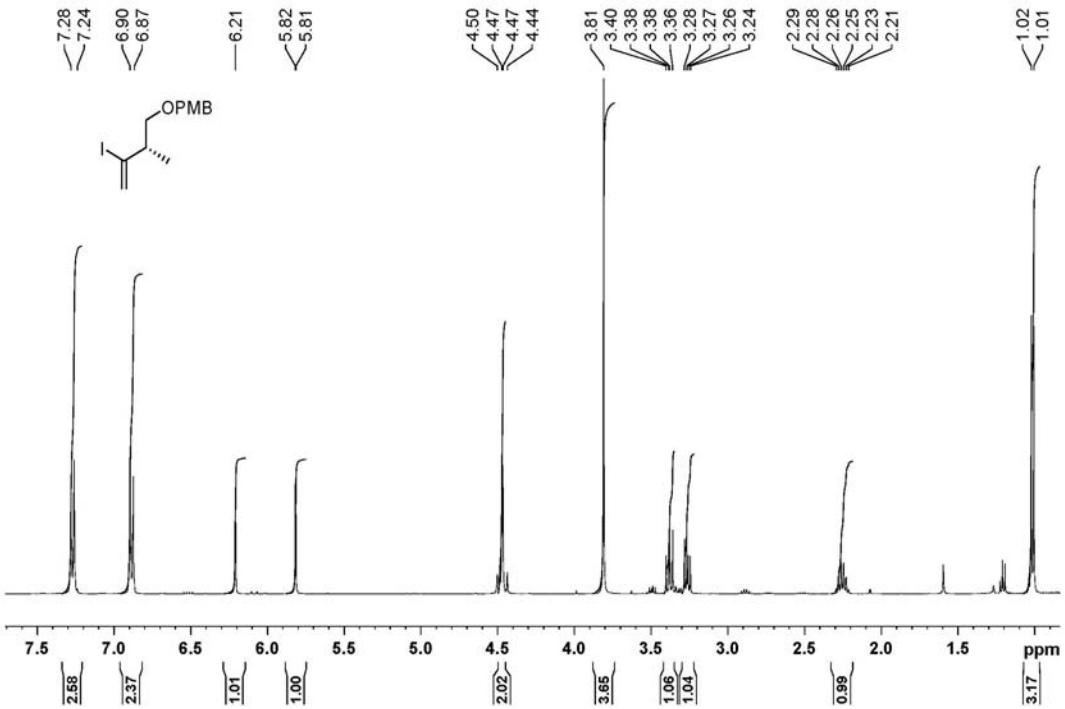



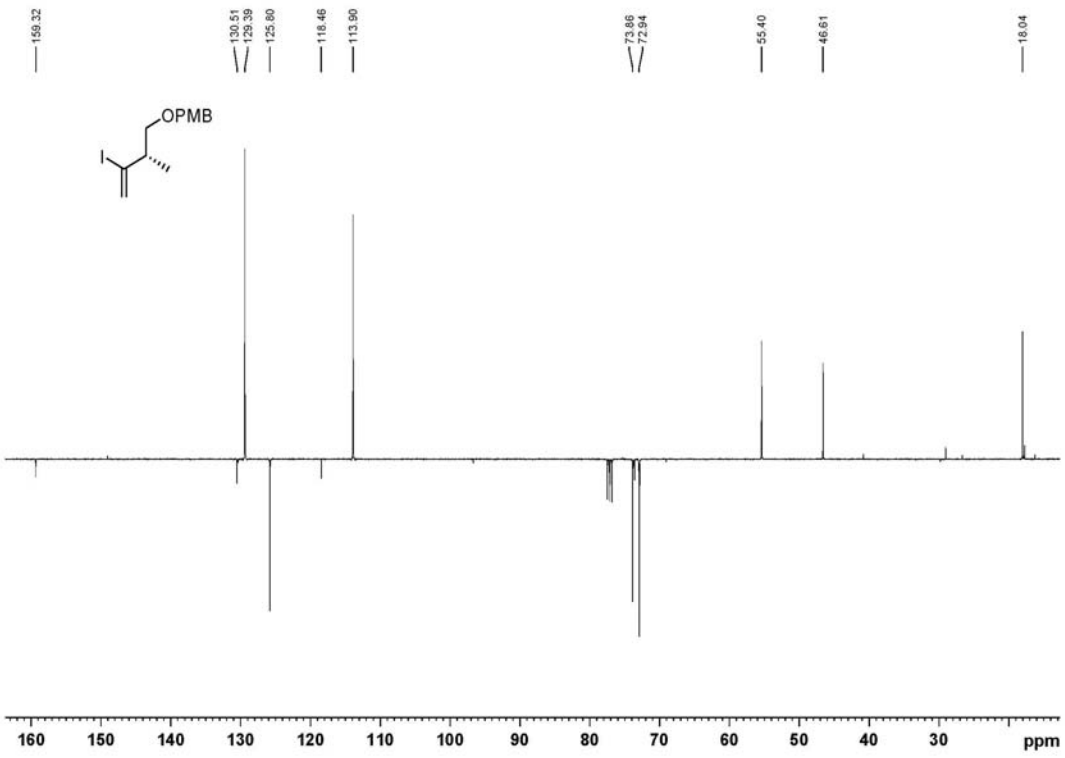
**(*S*)-1-(((3-Bromo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (21).**



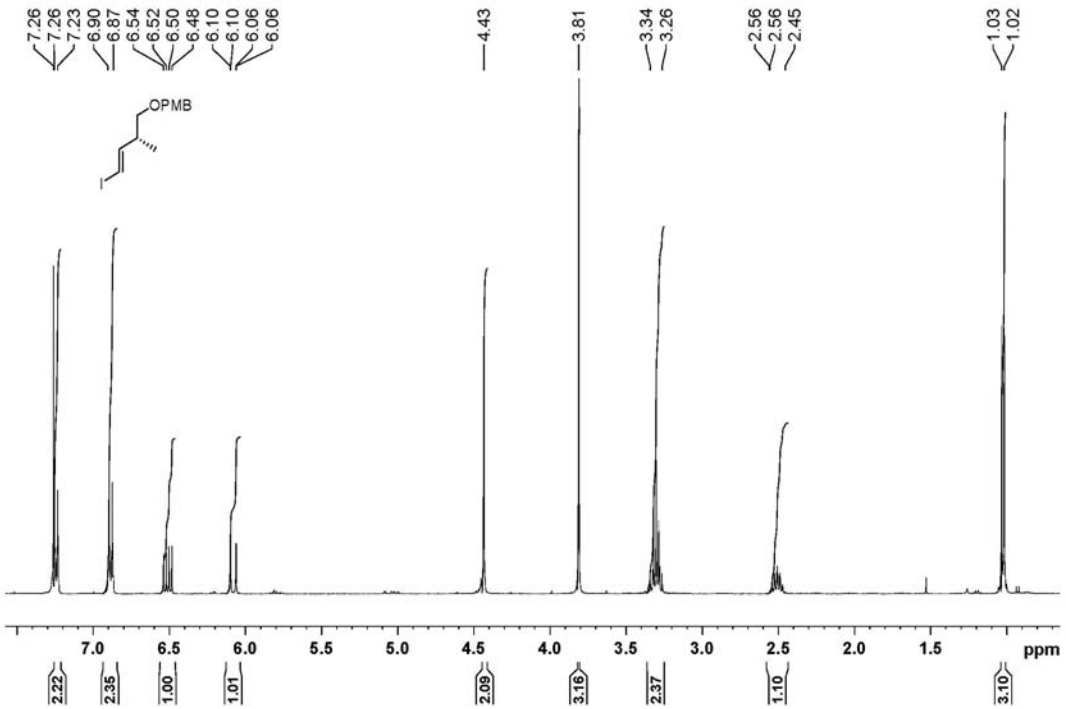



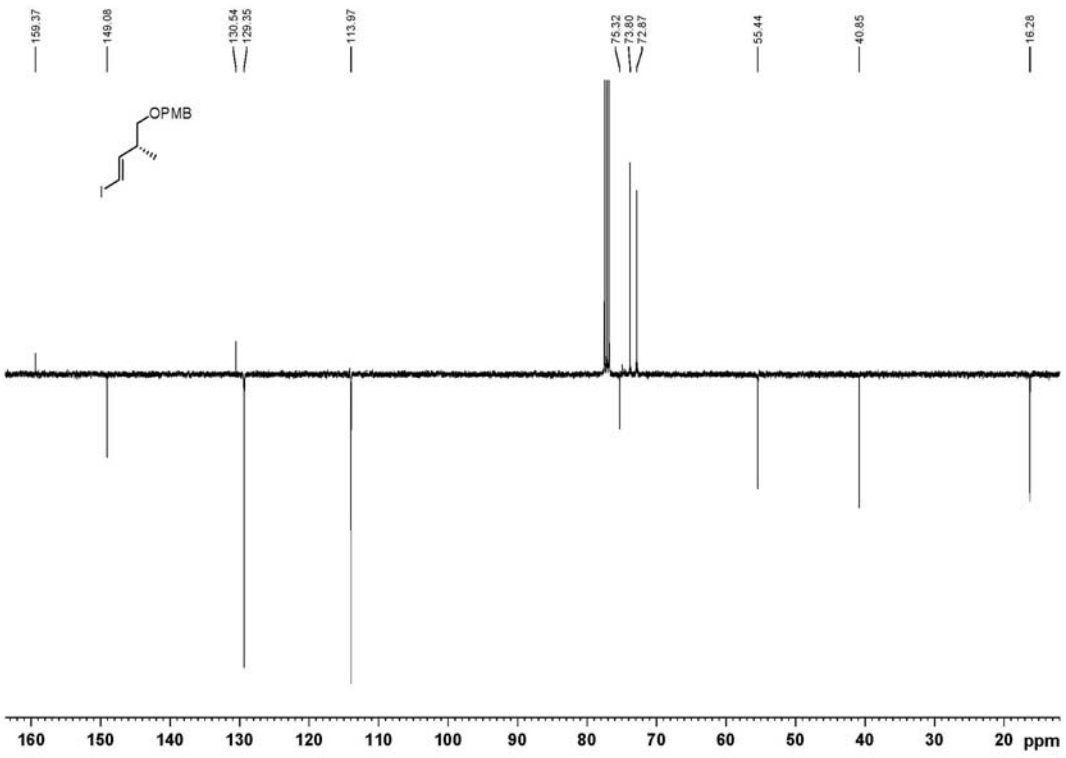
**(*S*)-1-(((3-Iodo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (S6).**



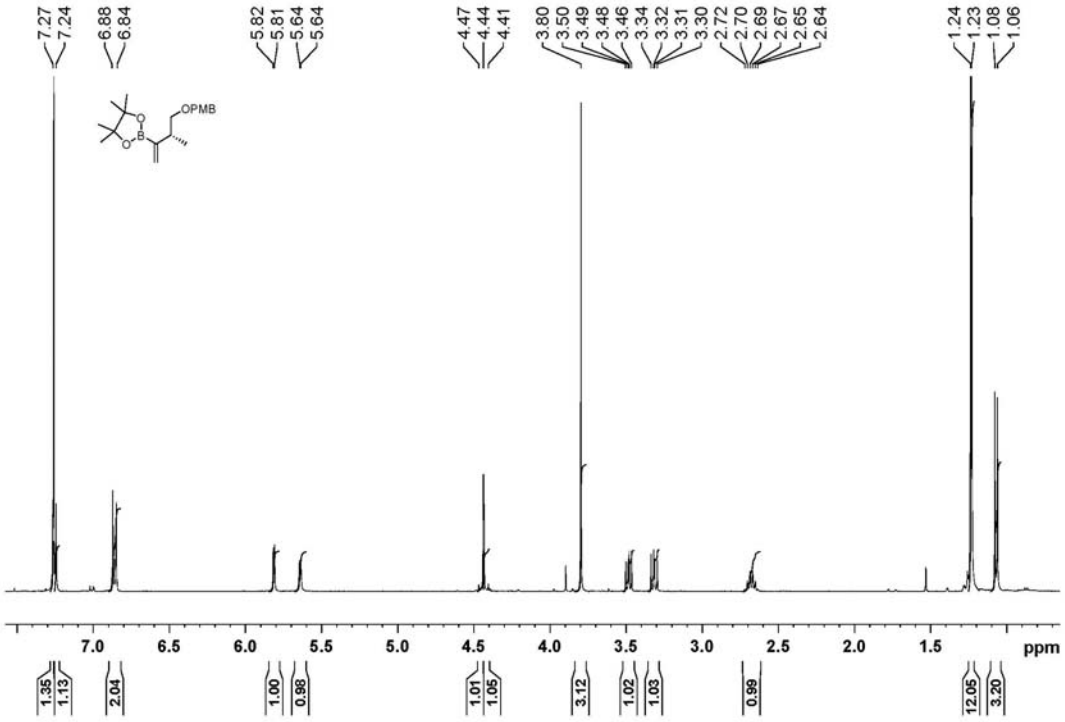



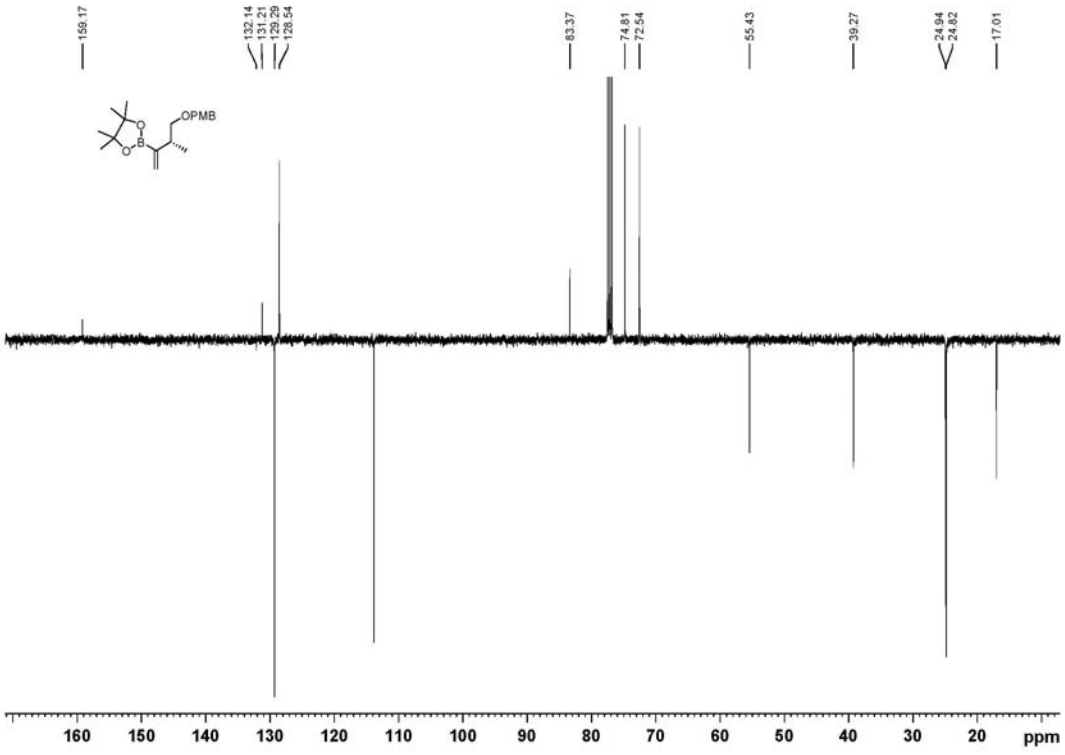
**(*R*,*E*)-1-(((4-Iodo-2-methylbut-3-en-1-yl)oxy)methyl)-4-methoxybenzene (S7).**



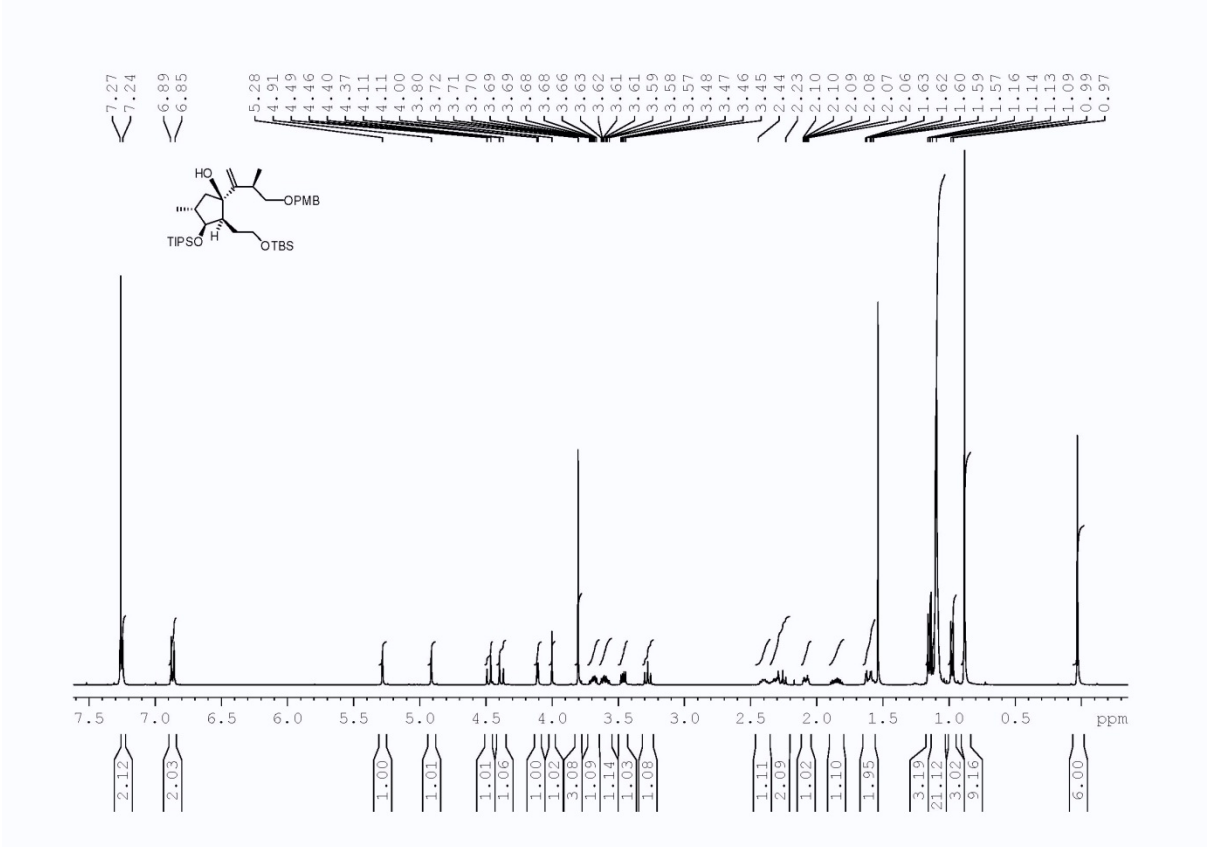



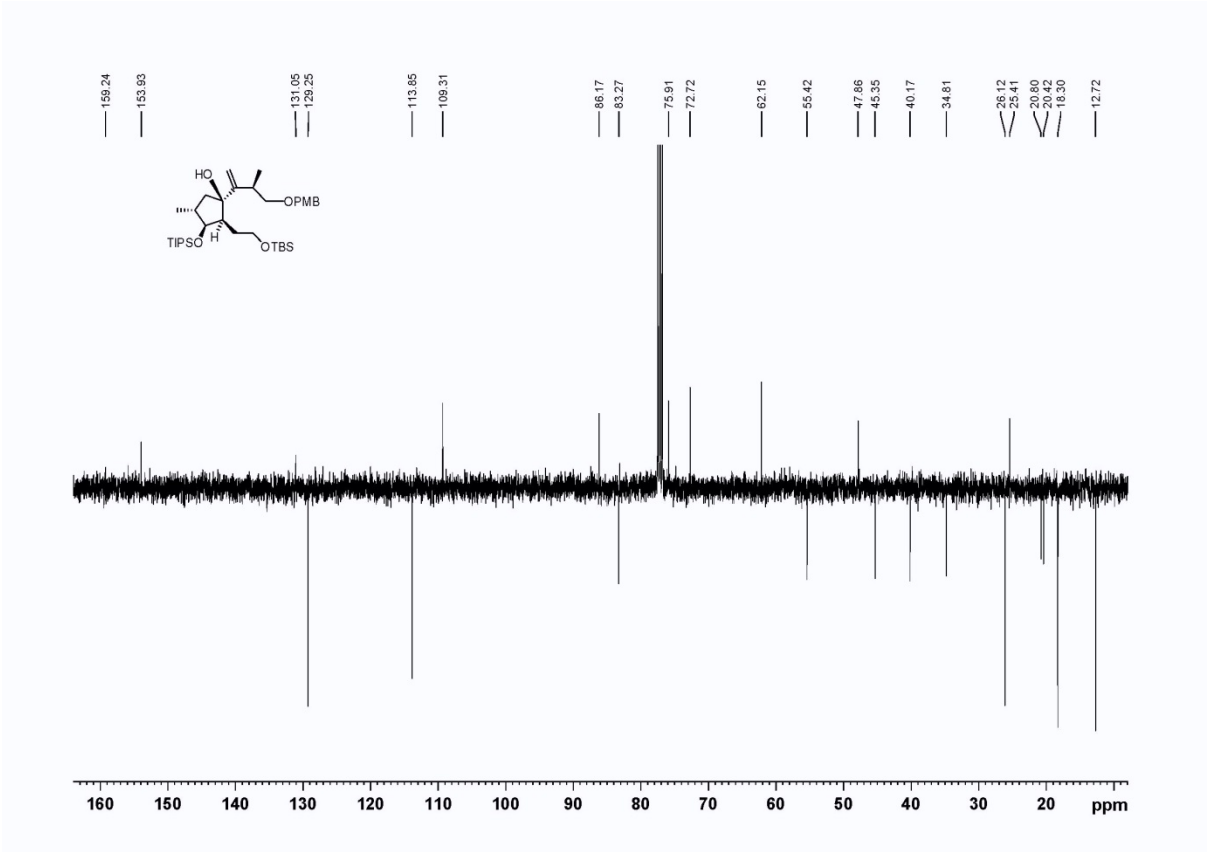
**(*R*)-2-(4-((4-Methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S8).**



**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((*R*)-4-((4-methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**22**).**






**(1S,2S,3S,4R)-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((R)-4-((4-methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**S9**)**

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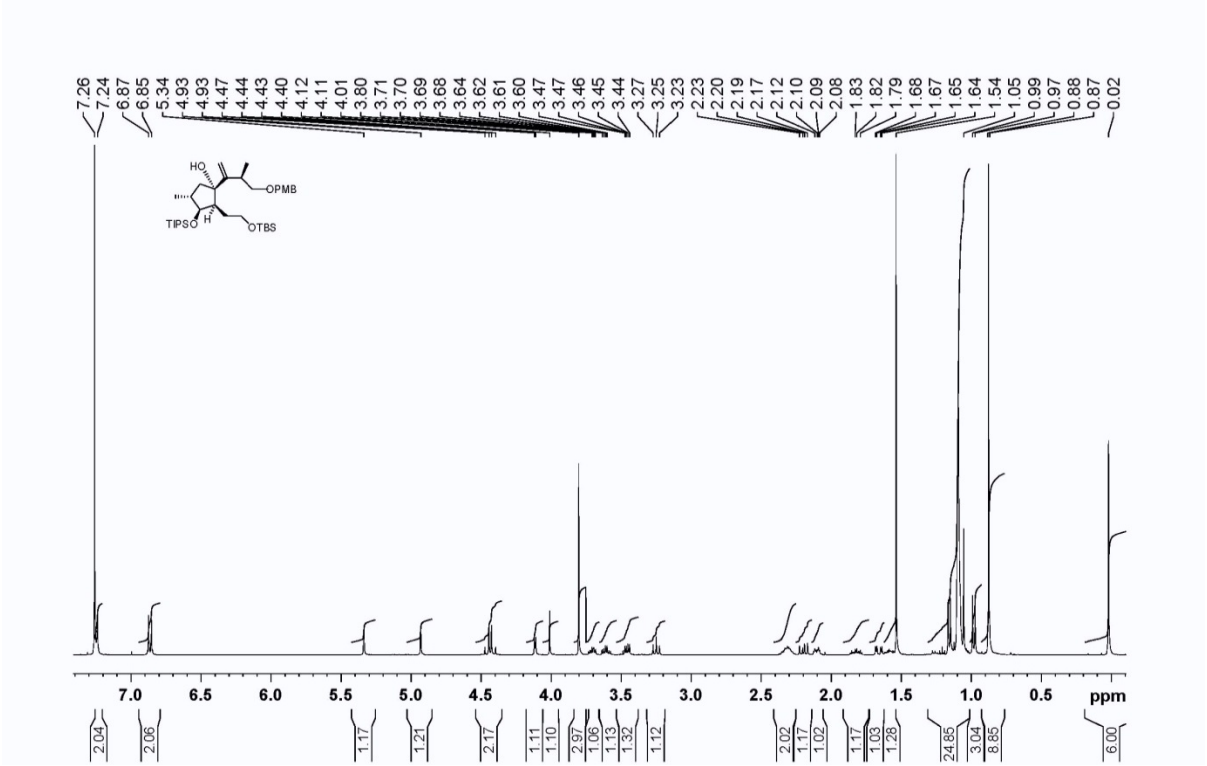
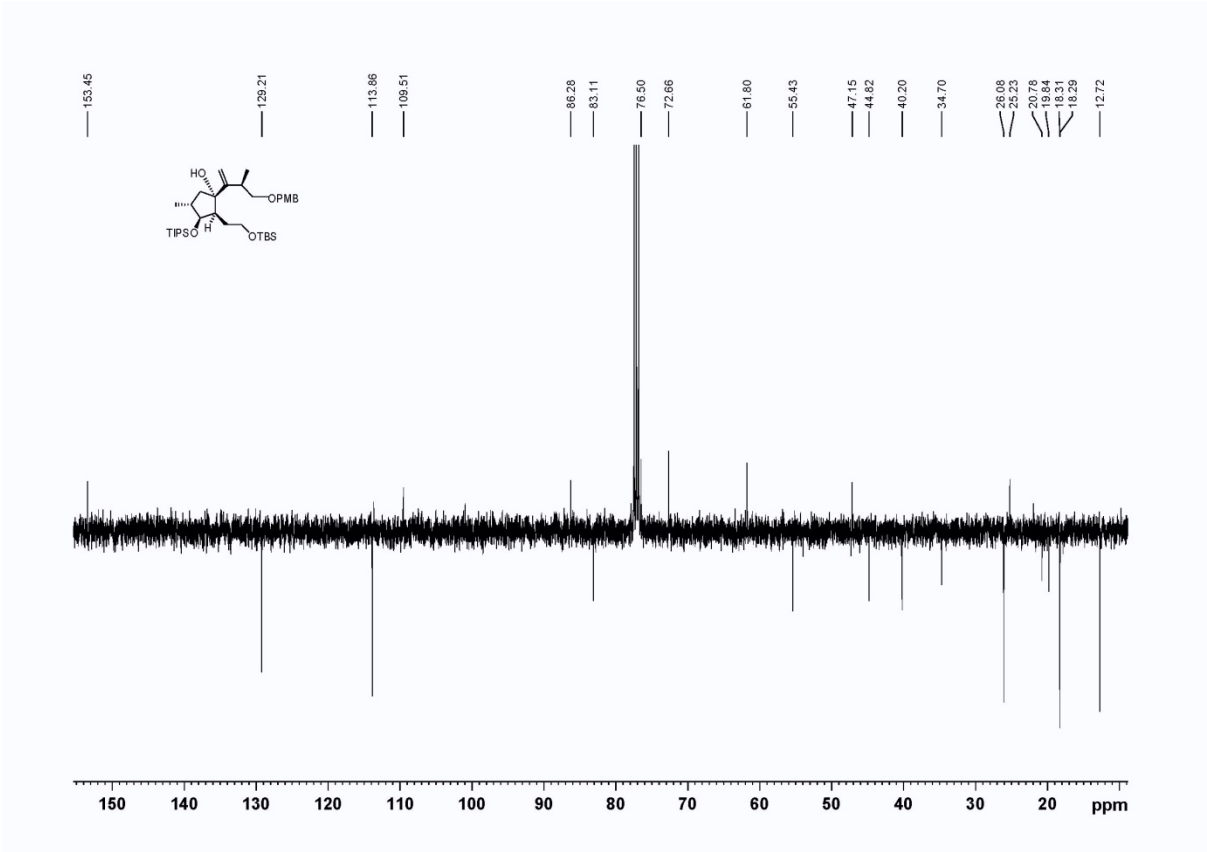
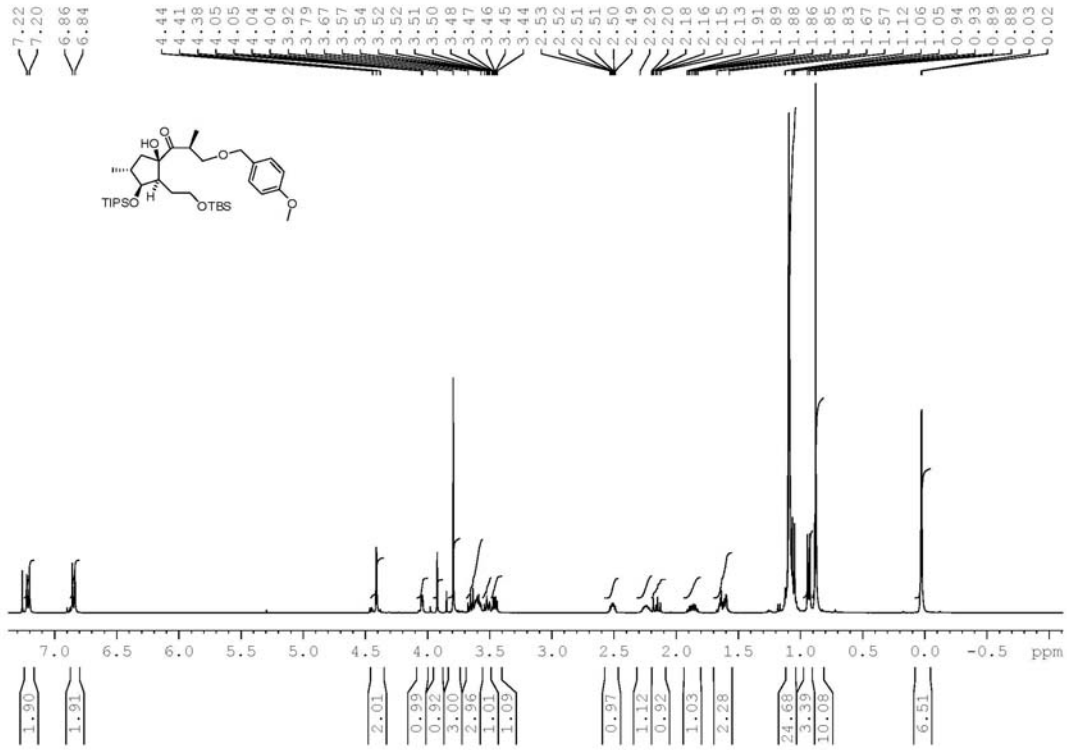
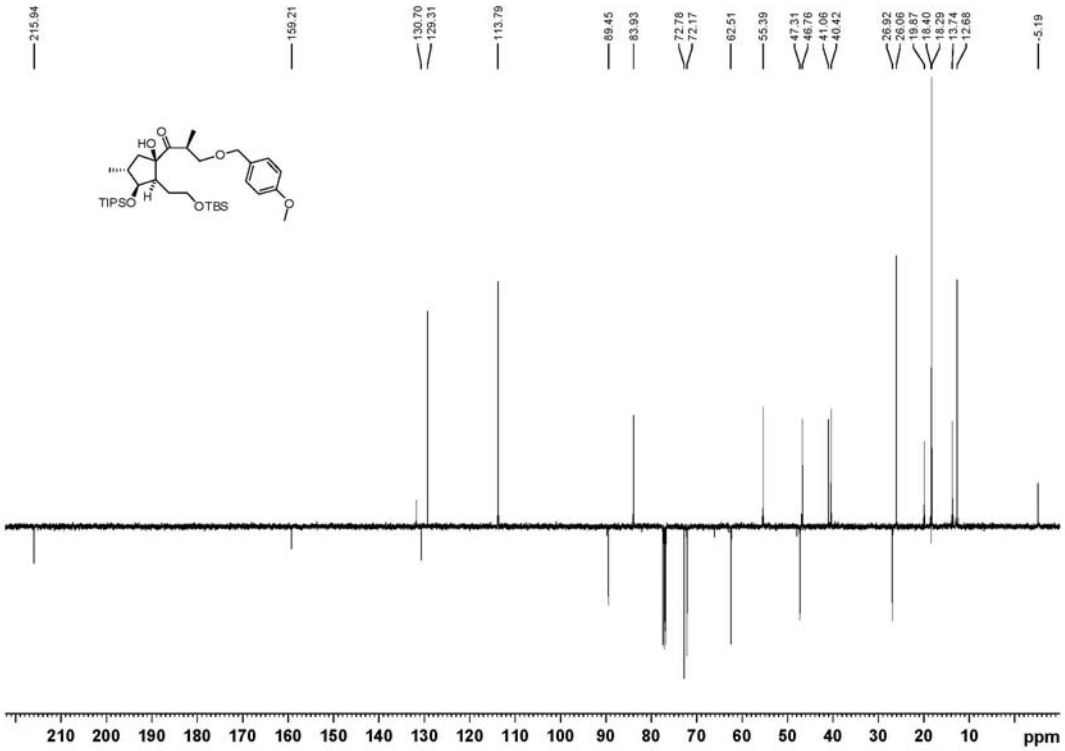


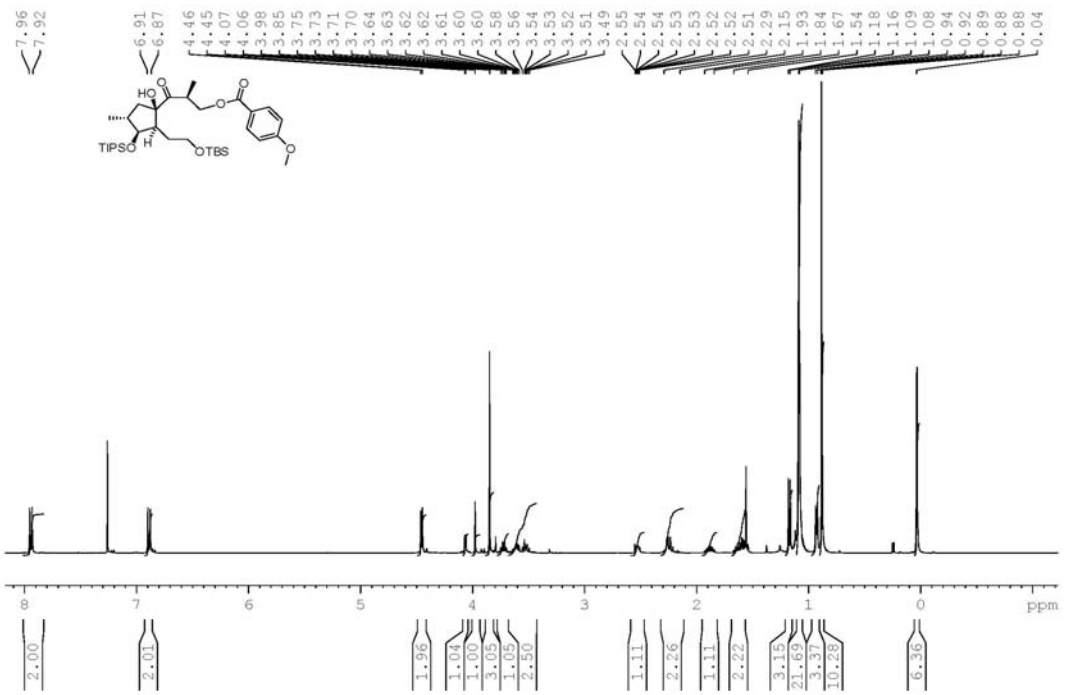


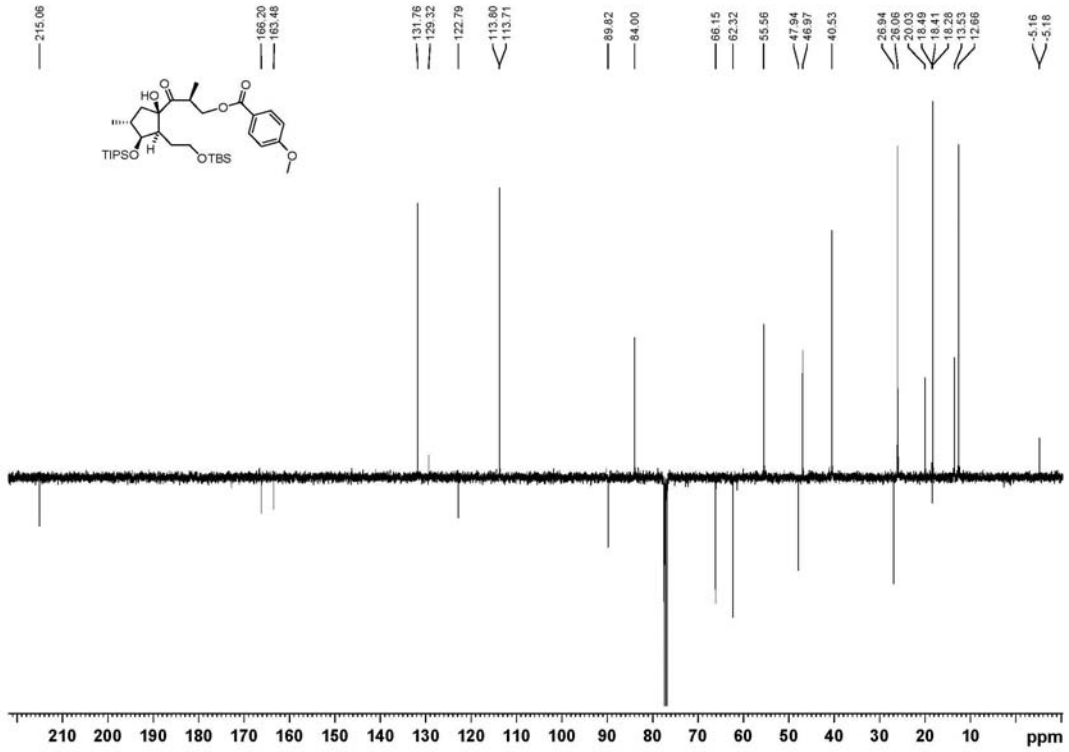

**(*S*)-1-((1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-hydroxy-4-methyl-3-((triisopropylsilyl)oxy)cyclopentyl)-3-((4-methoxybenzyl)oxy)-2-methylpropan-1-one (**S10**).**



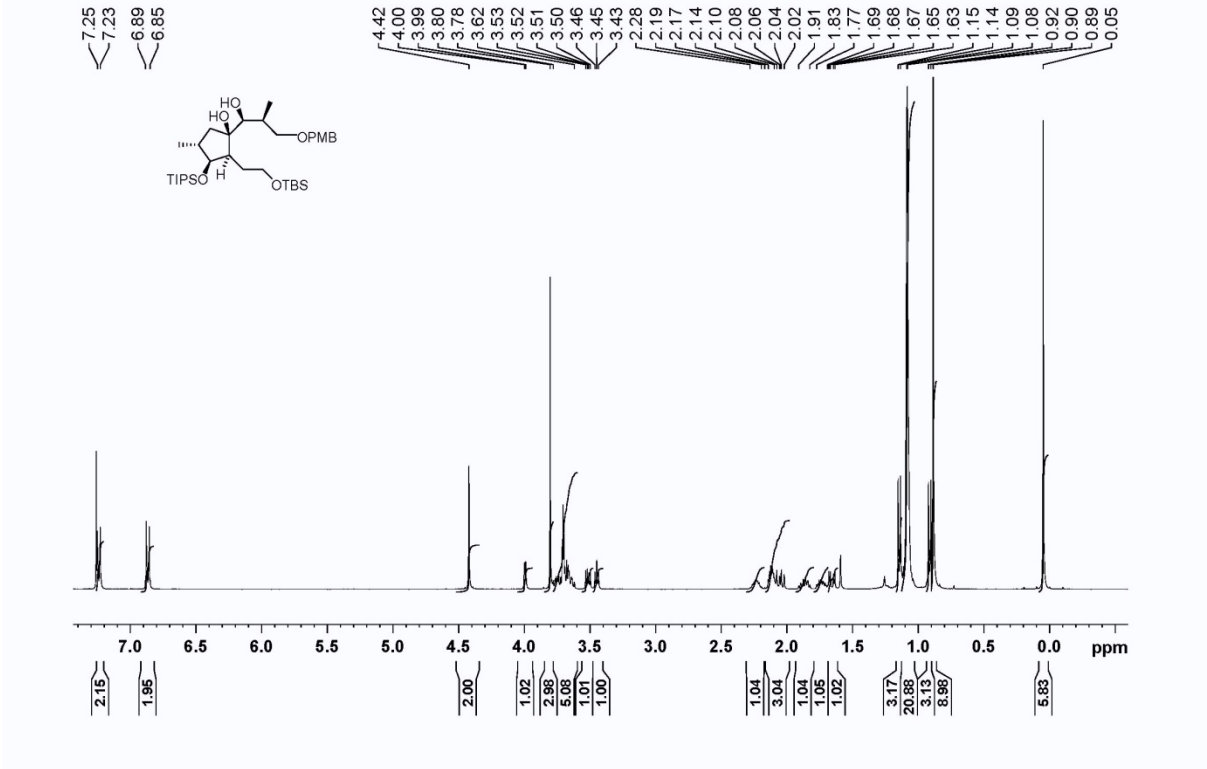


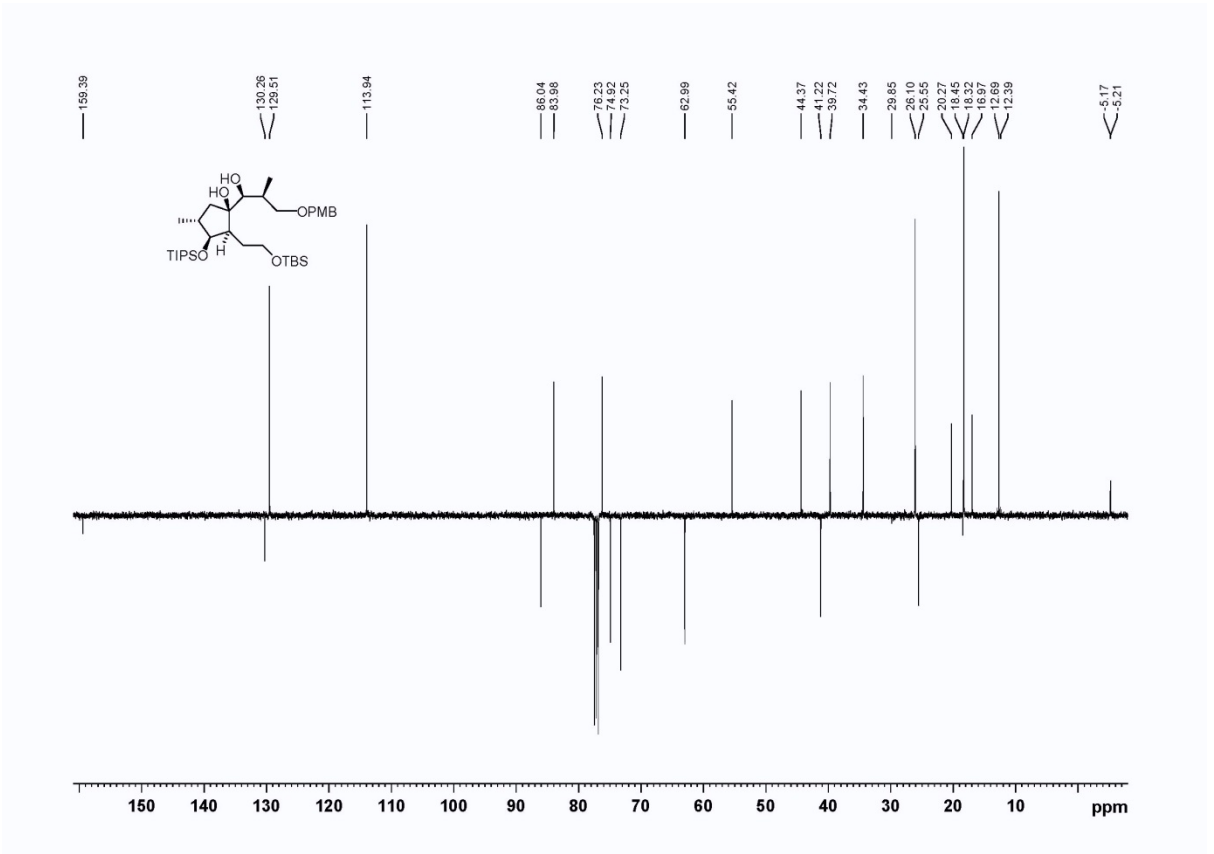

**(S)-3-((1R,2S,3S,4R)-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-hydroxy-4-methyl-3-((triisopropylsilyl)oxy)cyclopentyl)-2-methyl-3-oxopropyl 4-methoxybenzoate (**S11**)**



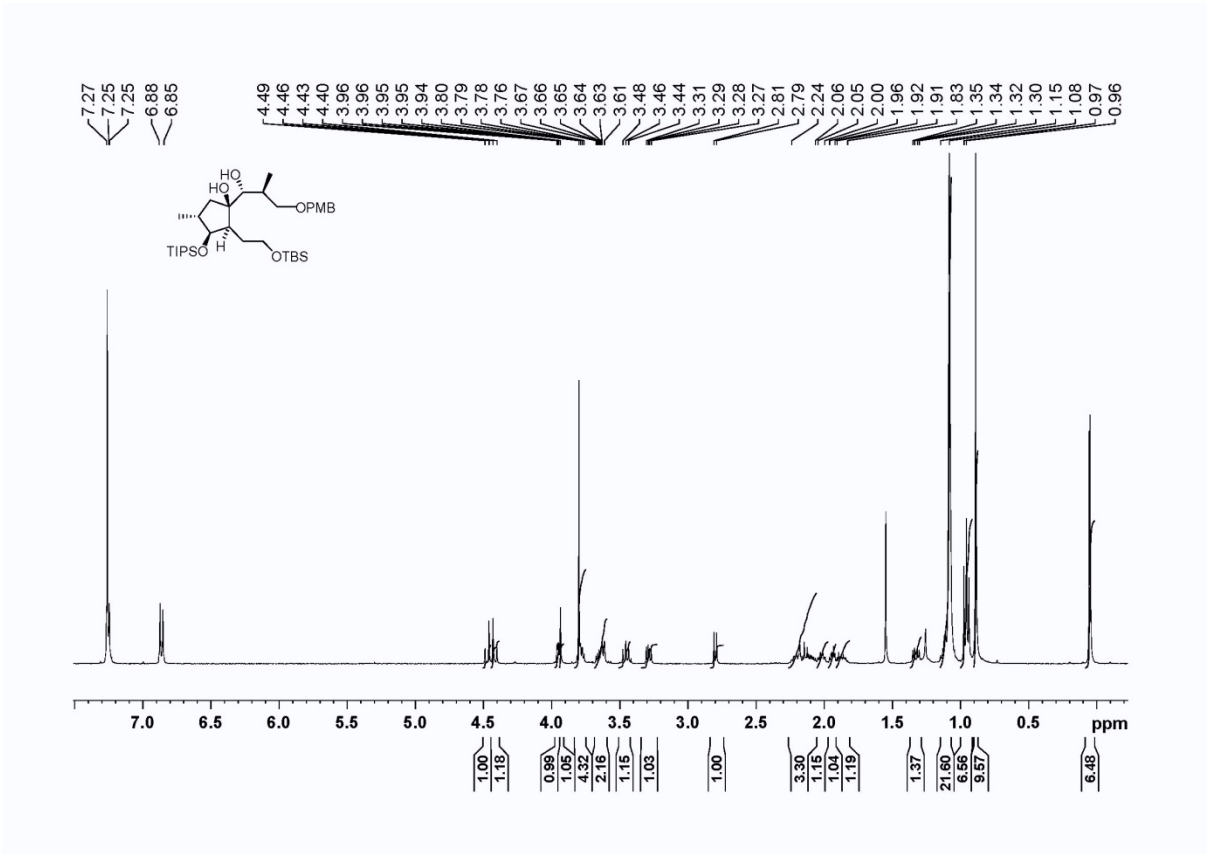


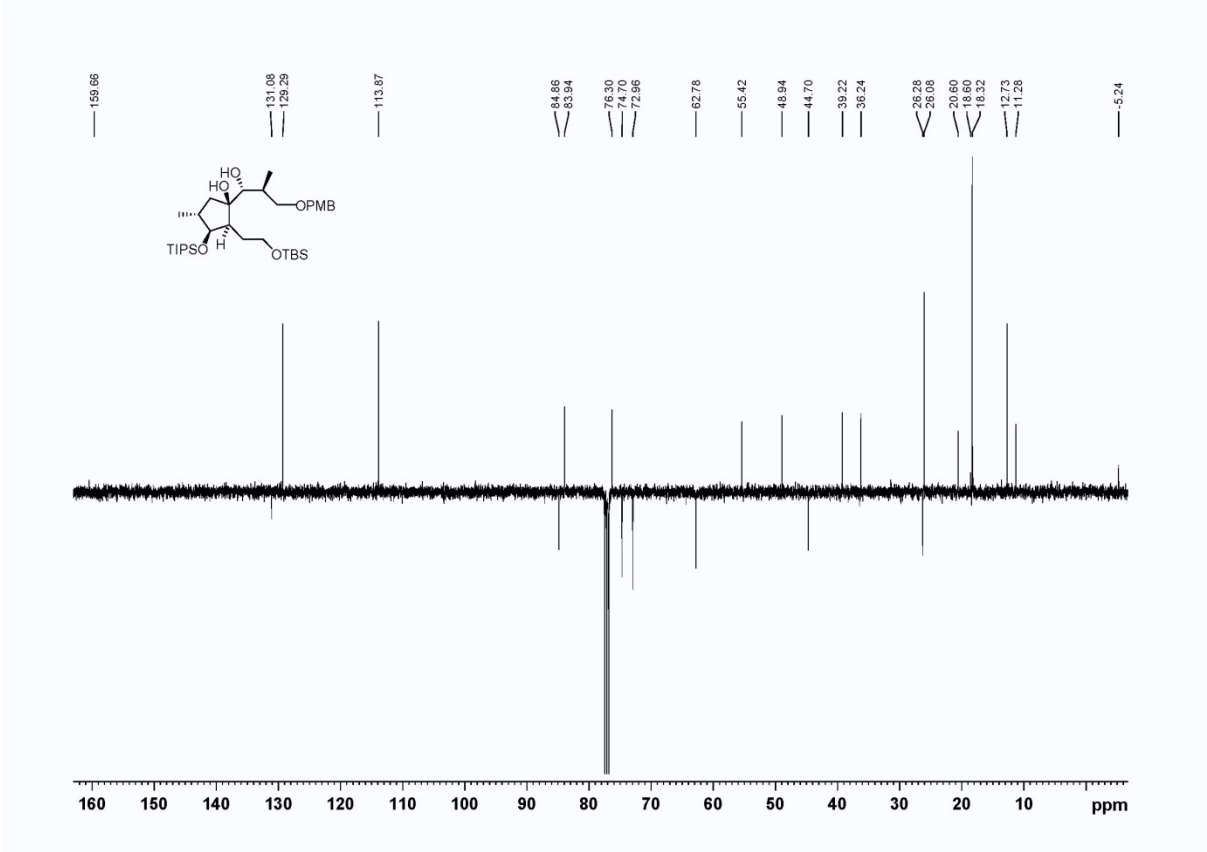

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((1S,2S)-1-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (23).**



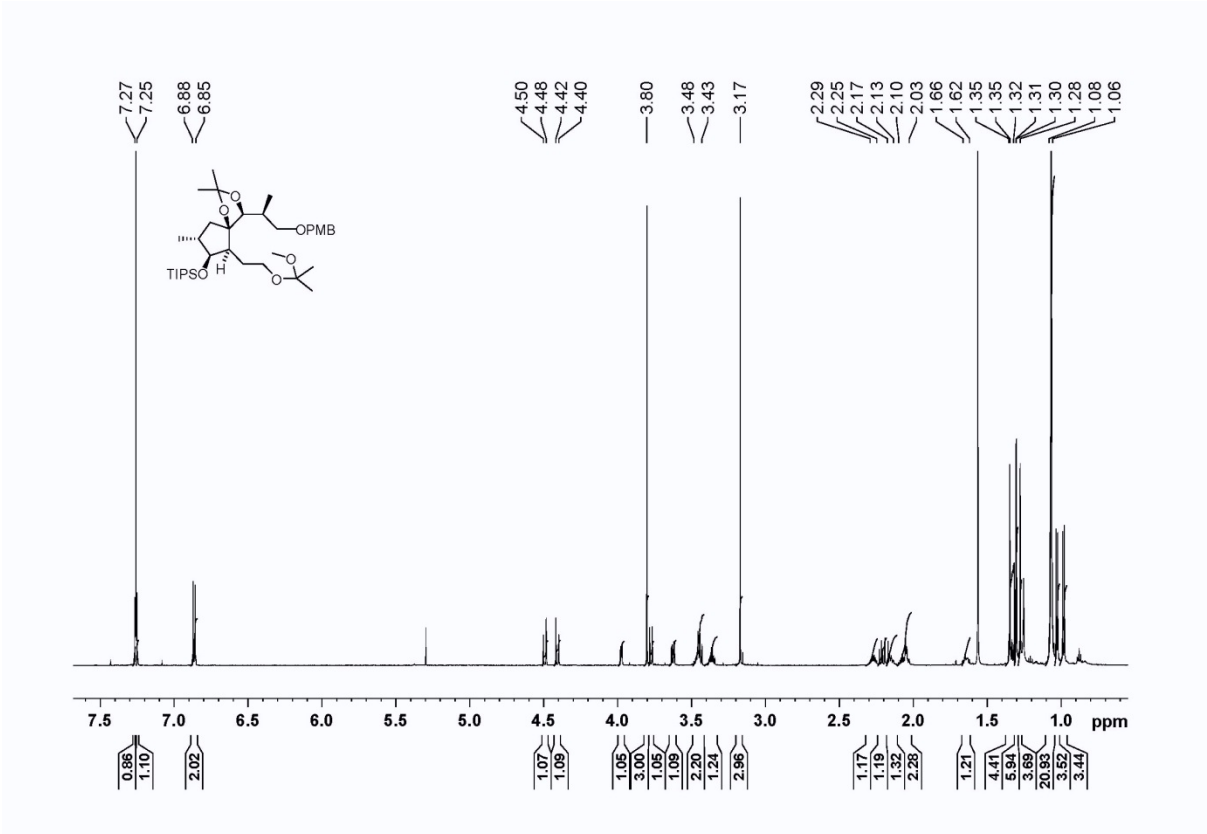


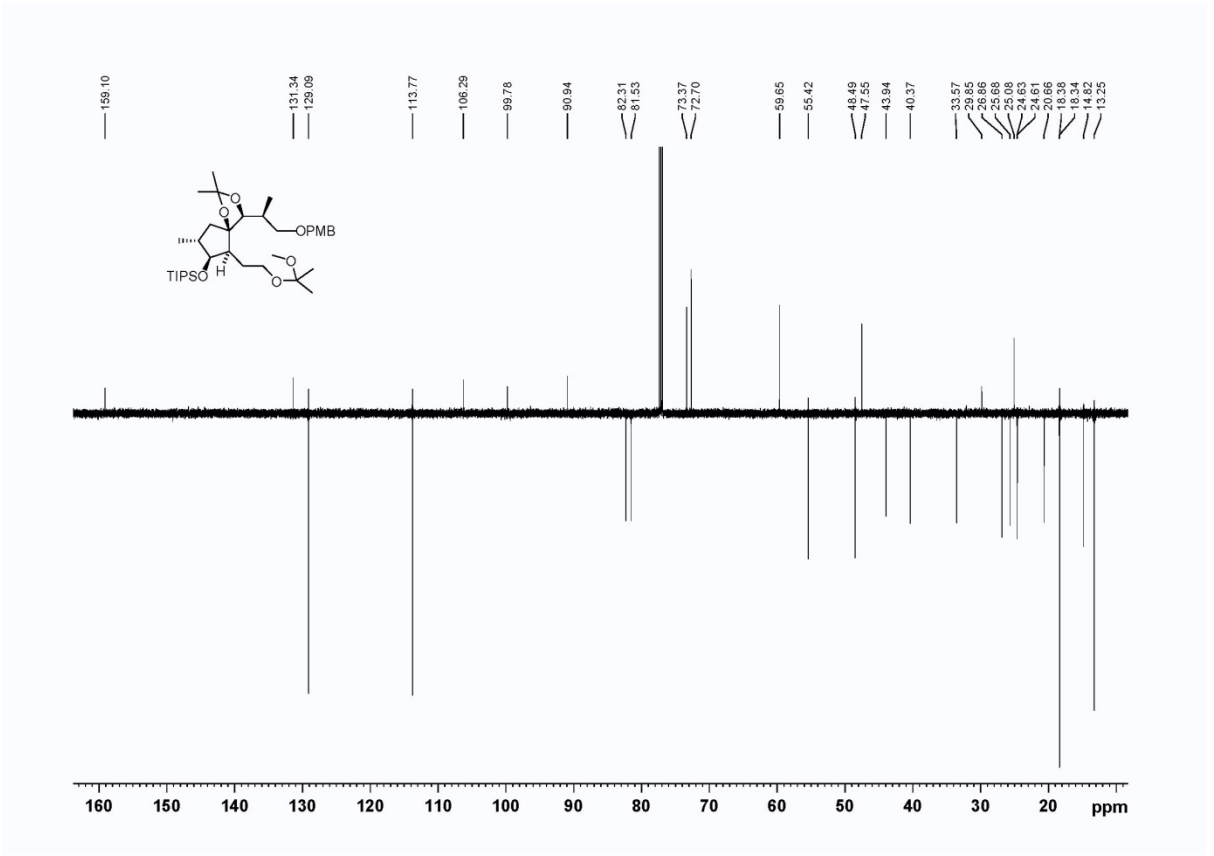

**(1*R*,2*S*,3*S*,4*R*)-2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1-((1*R*,2*S*)-1-hydroxy-3-((4-methoxybenzyl)oxy)-2-methylpropyl)-4-methyl-3-((triisopropylsilyl)oxy)cyclopentan-1-ol (**S12**).**



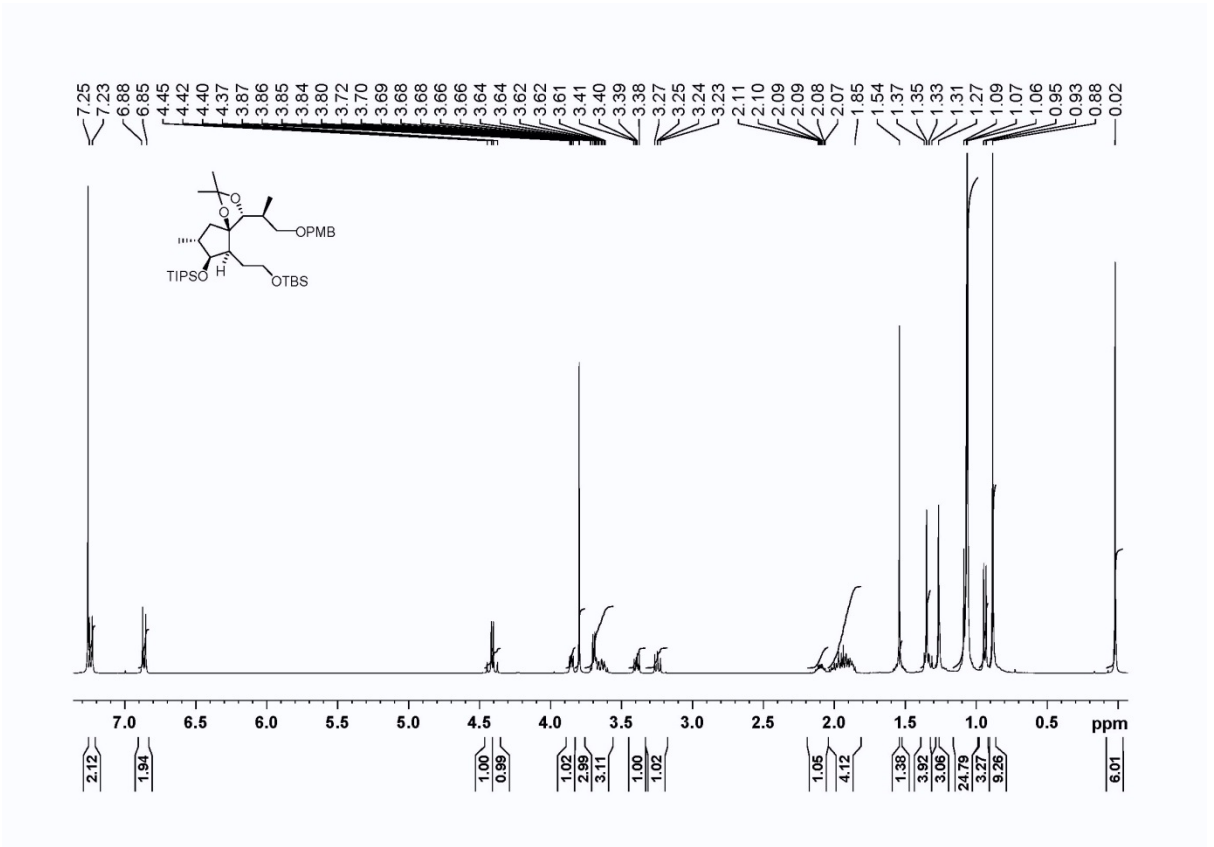


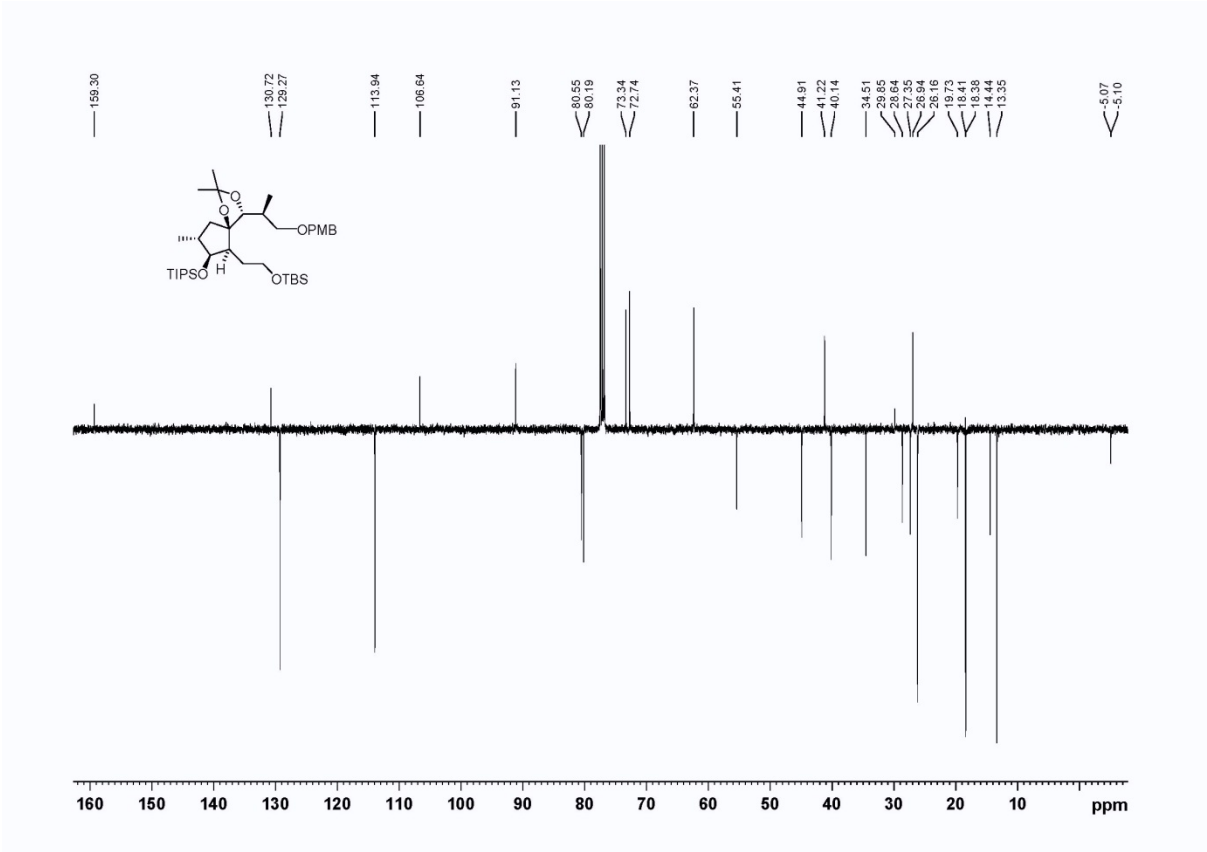

**Triisopropyl(((4*S*,5*R*,6*S*,7*S*,8*R*)-4-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6-(2-((2-methoxypropan-2-yl)oxy)ethyl)-2,2,8-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)oxy)silane (4).**






***tert*-Butyl(2-((4*R*,5*R*,6*S*,7*S*,8*R*)-4-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,8-trimethyl-7-((triisopropylsilyl)oxy)-1,3-dioxaspiro[4.4]nonan-6-yl)ethoxy)dimethylsilane (26).**



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# 12 CURRICULUM VITAE


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## Personal details

Citizenship: Austria

## Education and Qualifications

| | |
|---|---|
| ***Spring 2008 - present*** | Ph.D. studies under the supervision of Univ.-Prof Dr. Johann Mulzer in the area of synthesis of biologically important diterpenes; "**Jatrophane Diterpenes with Remarkable Multidrug-Resistant-Reversal (MDR) Effect – Towards the First Total Synthesis of Pl-3**". |
| ***Spring 2008*** | Graduation with honors. |
| ***Spring 2007*** | Start of the Master thesis "Indium assisted allylation-transformations on the highly functionalized carbohydrate framework" under the supervision of Univ.-Prof Dr. Walther Schmid. |
| ***Fall 2002*** | **University of Vienna**: Studies towards the Master´s degree in Chemistry. |
| ***Fall 2001*** | **University of Vienna**: Studies towards the Master´s degree in Biology. |
| ***Sept. 2000 - May `01*** | Military service. |
| ***June 2000*** | Matura (Graduation) with honors. |
| ***1996 - 2000*** | **Gymnasium mit technischem Schwerpunkt**, Austria (secondary school with emphasis on metal processing). |
| ***1992 - 1996*** | **Realgymnasium Reutte**, Austria (Secondary school, lower grade). |
| ***1988 - 1992*** | Elementary school in Innsbruck then Reutte. |

## Scholarships

Förderstipendium UNI Wien, (1 year Ph.D. grant, financed by the university of Vienna)
Leistungsstipendium (excellence scholarship) UNI Wien Antragsnummer (2008-01058)

## Employment history

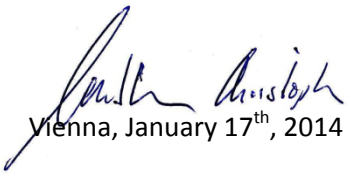
| | | |
|---|---|---|
| ***2008 – present*** | University of Vienna; tutor and lecturer in different chemistry courses of graduate and undergraduate students. | |
| ***Jun. 2007 – Aug. 2007*** | Project collaborator | OeSD (Österreichische Staatsdruckerei) |
| ***Summer 2003, 2004, 2005*** | Chemical surface engineering | Plansee AG |
| ***Summer 1999, 2000, 2001, 2002*** | Testing, quality control | Ceratizit |
| ***Summer 1998*** | Recycling | Plansee AG |

## Language, Special Skills

| | |
|---|---|
| ***Languages*** | English: spoken – excellent; comprehension – excellent; written – excellent.<br>German: Native language.<br>French: Basic knowledge. |
| ***Technical*** | Proficient in the different Microsoft operating systems, and most common office tools (Excel, Word, Power Point). Advanced Visual Basic for Applications programming skills. Profound experience with a variety of chemistry software, such as Topspin, Beilstein, Scifinder and ChemOffice. Experience with advanced NMR techniques, IR, and other analysis methods (HPLC, mass-spectrometry). |

## Interests

Various sports (track and field athletics, mountain biking, snowboarding, bouldering). Enthusiastic amateur photographer.



Vienna, January 17th, 2014