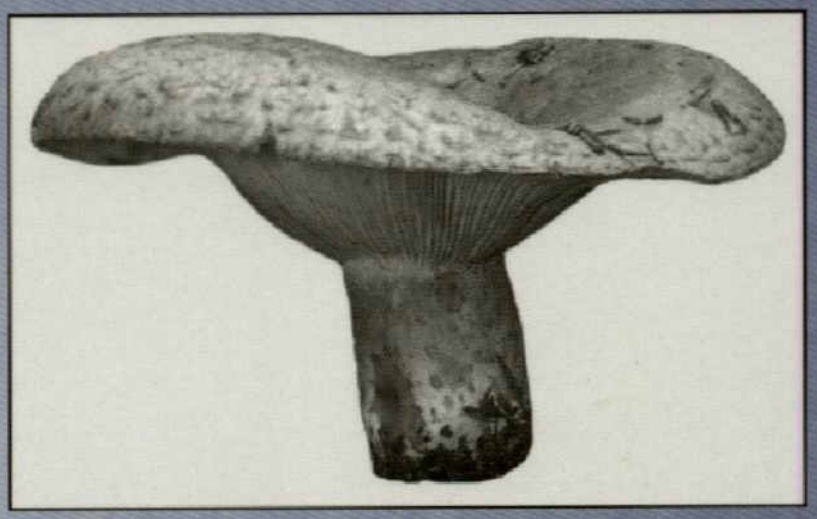
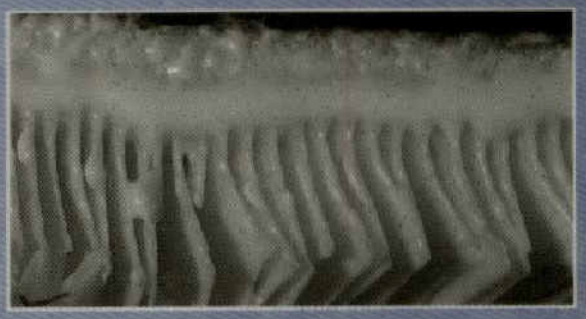
Total Synthesis of Lactarane and Marasmane Sesquiterpenes





Roel P. L. Bell

Total Synthesis of Lactarane and Marasmane Sesquiterpenes

Promotor: dr. Ae. de Groot, hoogleraar in de bio-organische chemie

Co-promotor: dr. J. B. P. A. Wijnberg, universitair hoofddocent, laboratorium voor organische chemie

Roel P. L. Bell

Total Synthesis of Lactarane and Marasmane Sesquiterpenes

Proefschrift
ter verkrijging van de graad van doctor
op gezag van de rector magnificus
van Wageningen Universiteit,
dr. ir. L. Speelman,
in het openbaar te verdedigen
op maandag 30 oktober 2000
des namiddags te vier uur in de Aula.

ISBN 90-5808-306-3

Voorwoord

Hoewel het synthetiseren van de doelmoleculen vaak een solistische bezigheid was wil ik een aantal mensen bedanken voor hun bijdrage aan het in dit boekje beschreven resultaat. Hans, jou enthousiasme, betrokkenheid en overtuiging in de goede afloop heeft mij vele malen geholpen een lichtpunt te zien op de weg van uitgangsmateriaal naar natuurstof. De verhelderende discussies en nauwkeurig gecorrigeerde manuscripten hebben veel bijgedragen aan het behaalde resultaat en mijn visie op de chemische wetenschap. Aede wil ik met name noemen voor de mogelijkheid dit project, dat je altijd enthousiast volgde en begeleidde, te kunnen uitvoeren in een uitstekend uitgerust laboratorium. Hugo en Maurice wil ik bedanken voor hun grote bijdrage aan het in hoofdstuk 4 beschreven onderzoek.

Naast bovengenoemde directe invloeden op het beschreven resultaat zijn er bij elk onderzoek mensen betrokken waarvan hun werk weliswaar minder invloedrijk, maar zeker niet minder belangrijk is. Bep, jou wil ik bedanken voor het opnemen van de vele NMR spectra. Voor de massa bepalingen kon ik altijd een beroep doen op Kees en Hugo. GC analyses werden ondersteund door Elbert en Harm. De dagelijkse bevoorrading van de laboratoriumzaal werd verzorgd door André. Computer berekeningen werden uitgevoerd door Han. Verder wil ik Tommi, Ben, Adri, Edwin, Wiet en Marc bedanken voor hun discussies betreffende het onderzoek waarbij vaak nieuwe suggesties naar voren kwamen.

Behalve de genoemde bijdrage aan meer praktische zaken zijn er nog een aantal mensen geweest die er voor hebben gezorgd dat ik ondanks de soms synthetische tegenslagen graag naar Wageningen kwam. Allereerst wil ik Tommi, Yvonne, Marjon, Wiet, Patrick, André, Edwin, Adri en Marc bedanken voor de prettige samenwerking. Verder noem ik (niet) met name(n) de collega's waarmee het gezellig koffieleuten, lunchen, bierproeven en jeu-de-boulen was.

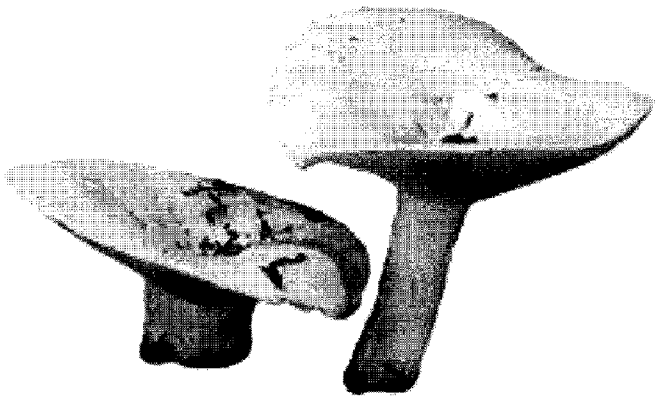
Tot slot wil ik Eveline, mijn vader en moeder en verdere dierbare personen bedanken voor hun steun en interesse gedurende het hele traject dat leidde tot dit boekje.

Roel

Contents

Chapter 1

Introduction

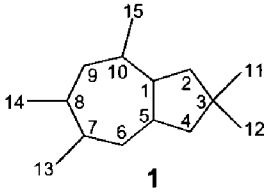


1.1 General Introduction

Since ages men has been intrigued by the colorful and diverse form of organisms referred to as 'mushrooms and toadstools'. Mushrooms, which are the spore-producing fruitbodies of fungi, have not only been stimulating for our fantasy in fairy tails and hallucinations, but also more realistic features have drawn attention. For instance the delicious taste and toxicity of several species are well known. The former has even led to cultivation and economical exploitation. The development of several pharmaceuticals based on structures isolated from mushrooms is a further example of how these organisms are useful for humanity.

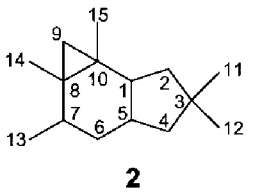
Besides primary metabolites like sugars, amino acids, fatty acids and nucleotides with a well-known and essential function, living organism are known to produce organic compounds with a less distinctive utility, the secondary metabolites. The believe that the secondary metabolites in mushrooms are responsible for the effects mentioned above, initiated a lot of research concerning their isolation, characterization and biological activity.[1] From mushrooms of the genus *Lactarius* a vast number of these compounds have been isolated. The majority belongs to the group of terpenes, also known as terpenoids, isopentenoids, or isoprenoids. Terpenes are compounds with a carbon skeleton built up from multiples of the C_5-unit isopentenyl pyrophosphate.[2] This repeating unit is also the basis for the classification of terpenes: hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterpenes (C_{25}), triterpenes (C_{30}).

Figure 1[3]



1

lactarane



2

marasmane

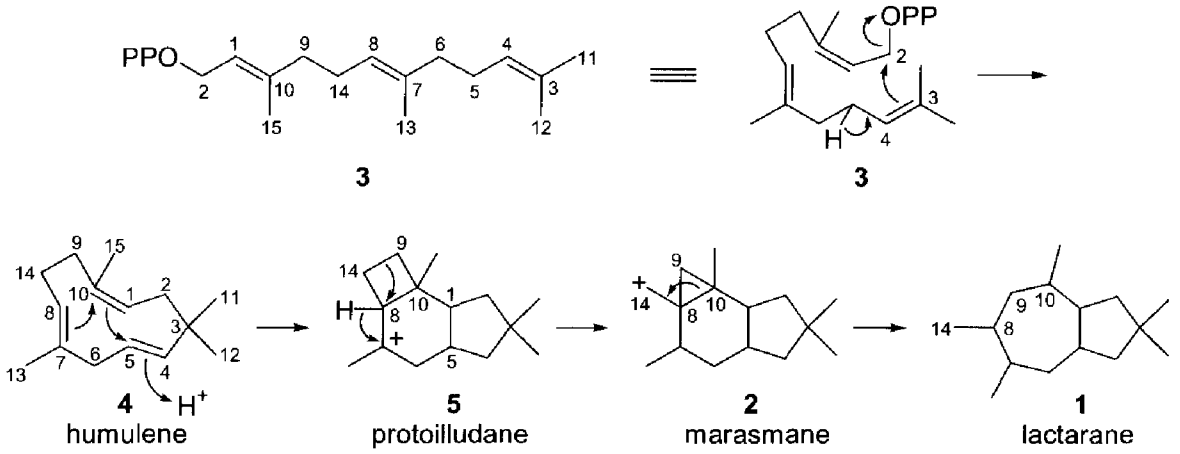
Most of the terpenes from *Lactarius* are sesquiterpenes of which the greater part possess the lactarane (**1**) or, to a lesser extent, the marasmane skeleton (**2**) (Figure 1). In fact, mushrooms of the genus *Lactarius* and the closely related genus of *Russula* are the main source of lactarane and marasmane sesquiterpenes in nature.

1.2 Biosynthesis of Lactarane and Marasmane Sesquiterpenes

The generally accepted biosynthetic route to lactarane and marasmane sesquiterpenes starts with the cyclization of farnesyl pyrophosphate (**3**) to humulene (**4**) by connecting C(2) and C(3) (Scheme 1).[4] Further proton induced ring closure of **4** yields the protoilludane cation **5**, which via

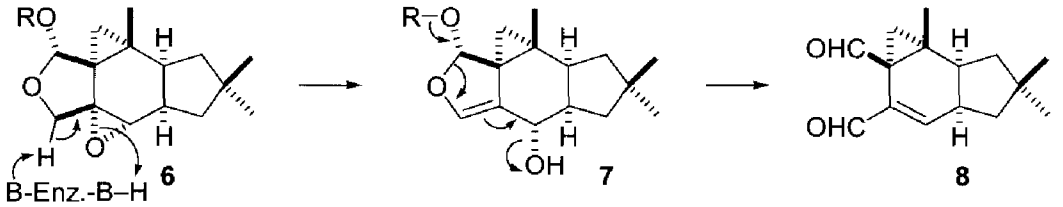
subsequent cyclobutane ring contraction rearranges to the cyclopropylcarbinyl cation **2**. Finally, rearrangement of **2** results in the formation of the lactarane skeleton (**1**).

Scheme 1



This biosynthetic route is supported by the isolation of two protoilludanes from *Lactarius violascens*.[5] Further, it is unambiguously established in several mushrooms of the genus *Lactarius*[6] that marasmanes are the biosynthetic precursors of lactaranes. In these species the only sesquiterpenes present are fatty acid derivatives of the marasmane sesquiterpene velutinal (**6**, R = H) of which the dry weight can amount up to 6% in young fruit bodies. Upon injury to the fruit bodies, the velutinal esters are exposed to enzymes and converted to marasmanes and lactaranes. A suggested enzymatic conversion of stearoylvelutinal (**6**, R = $CO(CH_2)_{16}CH_3$) in *Lactarius vellereus* is shown in Schemes 2 and 3.[6,7] The hydrolysis of the labile ester group in **6** (R = $CO(CH_2)_{16}CH_3$) may take place first since in carefully obtained extracts of *Lactarius vellereus*

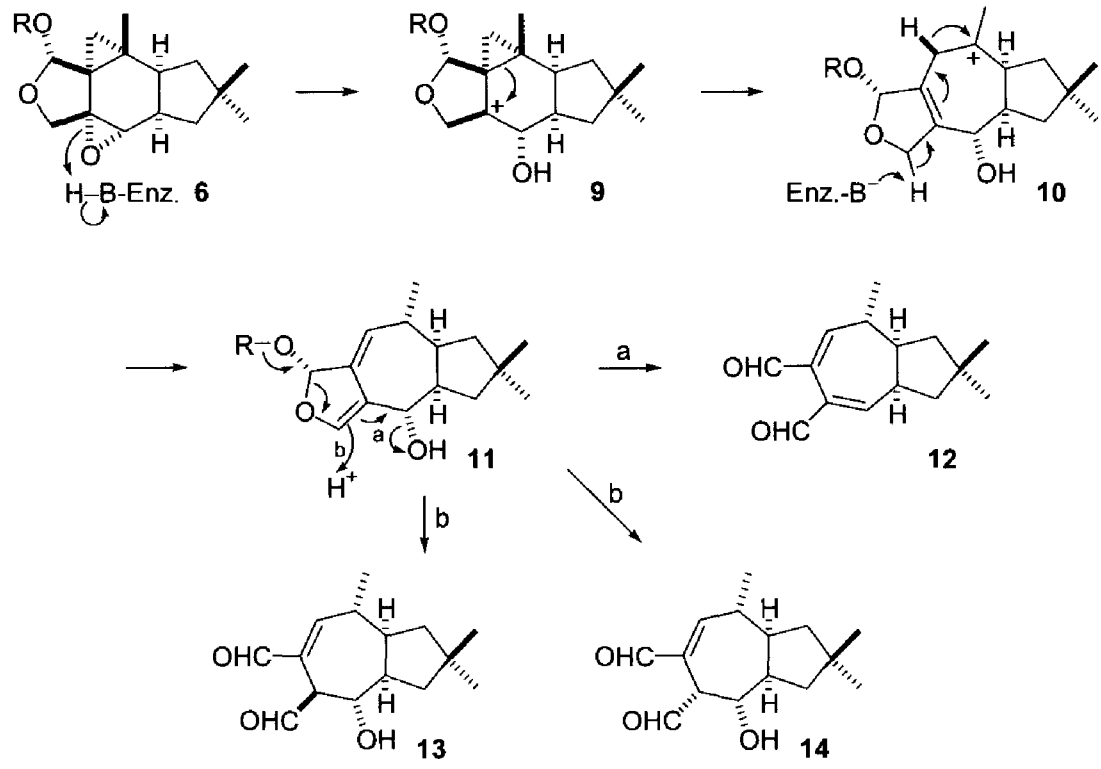
Scheme 2



'free' velutinal (**6**, R = H) is detected. An enzyme-assisted β-elimination of the epoxide in **6** leads to enol **7**, which is further transformed to the marasmane isovelleral (**8**) (Scheme 2). A possible route to lactaranes starts with an enzymatic opening of the epoxide ring, resulting in the cyclopropylcarbinyl cation **9**, which immediately rearranges to the energetically more favorable cation **10** (Scheme 3). Stabilization of this cation via a C(9) to C(10) hydride shift is accompanied

by abstraction of the allylic proton at C(13). The resulting enol **11** is then converted to the lactaranes velleral (**12**), piperdial (**13**), or *epi*-piperdial (**14**).

Scheme 3



1.3 Isolation of Lactarane and Marasmane Sesquiterpenes

Lactaranes are named after *Lactarius vellereus* from which the first lactarane was isolated. Species belonging to the genus *Lactarius* are known to produce a milky substance upon cutting the mushroom's flesh. The marasmanes are named after *Marasmus conigenus*, the source of the first isolated compound with this skeleton.

The isolation and structure elucidation of naturally occurring lactaranes and marasmanes have been reviewed several times in the past.[4,8] The more recent reviews[8] focus on the lactaranes and marasmanes from *Lactarius* origin. Besides the mushrooms of the genus *Lactarius*, which are the main source of the lactaranes and marasmanes, other fungi are known to produce these sesquiterpenes: e.g. the closely related genus *Russula*, *Marasmius*, and *Lentinellus*.[4,7]

All the lactaranes isolated from *Lactarius* possess oxidized C(13) and C(14) positions, frequently connected to each other, thereby forming a furan or lactone ring. Many lactaranes contain unsaturated bonds (up to three) in the 7-membered ring. Hydroxyl groups are often present, mostly at C(6) and C(10). Sometimes C(6) and C(10) are connected to each other by an ether bridge. The junction of the 5,7-membered ring system is always *cis*, except for

furoscrobiculin D.[9] The *cis* ring junction is also present in the 5,6-membered ring system of naturally occurring marasmanes. Also the C(13) and C(14) positions of marasmanes are oxidized and often part of an additional ring system, e.g. lactone or cyclic (hemi)acetal. Frequently an unsaturated bond or sometimes an epoxide or diol moiety is present at the C(6) and C(7) positions of marasmanes. The unfunctionalized C(15) methyl group is characteristic for almost every marasmane and lactarane isolated from *Lactarius*, whereas marasmanes obtained from other genera often possess an oxidized C(15) atom.

Some of the isolated lactaranes and marasmanes are thought to be artifacts formed from the labile velutinal ester **6** during extraction or purification on column.[7,10] Another process known to produce artifacts is oxidation by air.[11] However, no clear dividing line between what can be considered as a natural product or an artifact is available.

1.4 Biological Activities of Lactarane and Marasmane Sesquiterpenes

The biological activities of lactarane and marasmane sesquiterpenes have been thoroughly reviewed in the past.[8] The ability to stop predators from feeding without (directly) killing them, also known as antifeedant activity, has been detected for many of the isolated and synthetically produced compounds. The majority of these antifeedant studies were focussed on several storage pests, but activity against the natural fungivore, the opossum, has also been shown. Generally, compounds with more hydroxyl groups are less active. Isovelleral (**8**) and velleral (**12**) are among the strongest antifeedant substances known. The unsaturated dialdehyde moiety as present in these compounds and piperdial (**13**) and *epi*-piperdial (**14**) is thought to be responsible for their antifeedant activity as well as the pungent taste of some inedible species of *Lactarius*. The unsaturated dialdehyde functionality, which is also found in other biologically active but biogenetically totally different terpenes, is also thought to be responsible for other activities such as mutagenic, cytotoxic, antibacterial, and antifungal activity.

The fact that most marasmanes and lactaranes are formed from the biologically inactive velutinal esters (**6**) upon injury to the mushroom's flesh suggests that these compounds are involved in a chemical defense mechanism. Upon damaging, the velutinal esters are exposed to the cellular content of the mushroom and enzymatically converted, within a few seconds or minutes, to the biologically active isovelleral (**8**), velleral (**12**), or other related unsaturated dialdehydes (e.g. **13**, **14**). After several minutes to hours, these compounds are converted by the mushroom to less toxic substances thereby avoiding prolonged contact to its own antifungals.

1.5 Synthetic Approaches toward Lactarane and Marasmane Sesquiterpenes

1.5.1 Introduction

Recently, a review has appeared discussing the isolation and synthesis of lactarane and marasmane sesquiterpenes from *Lactarius* origin.[8] The reactions with and the interconversions of isolated compounds have been thoroughly described and will not be discussed in this section. In the following paragraphs the total syntheses of lactaranes and marasmanes and attempts to synthesize these molecules, which appeared in literature till July 2000, are discussed. To give a complete overview, the syntheses reviewed by Daniewski and Vidari[8] and some syntheses of molecules strongly resembling the natural compounds are included. In addition to this, a brief discussion of the mechanistical backgrounds of the approaches toward lactarane and marasmane sesquiterpenes described in this thesis is given in paragraph 1.5.4.

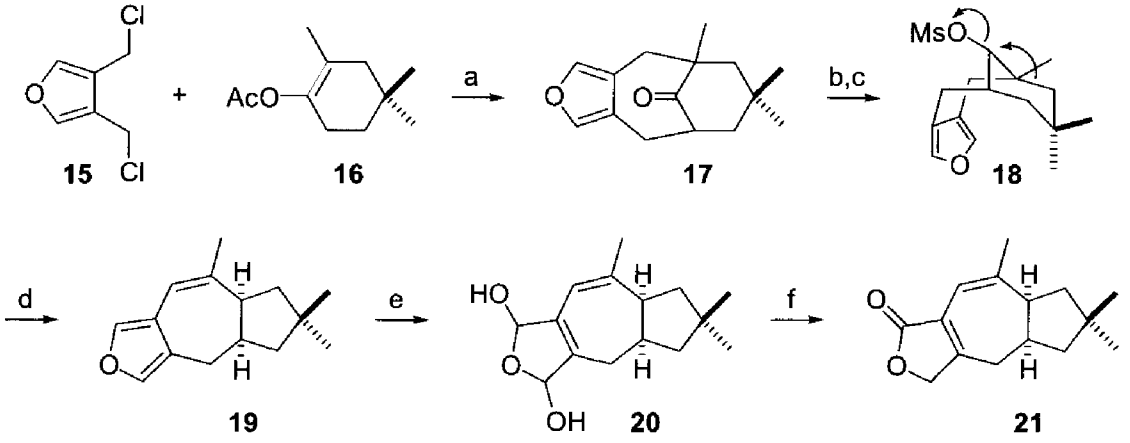
1.5.2 Lactarane Sesquiterpenes

Till today, all the reported papers on the total syntheses of lactarane sesquiterpenes concerned racemic compounds. The strategies used for their construction can roughly be divided into two groups. In the first and largest group ring enlargement methodologies were used to construct the 5,7-membered ring system. In the second group cycloadditions or intermolecular cyclizations were applied as the key step.

1.5.2.1 Ring Enlargements

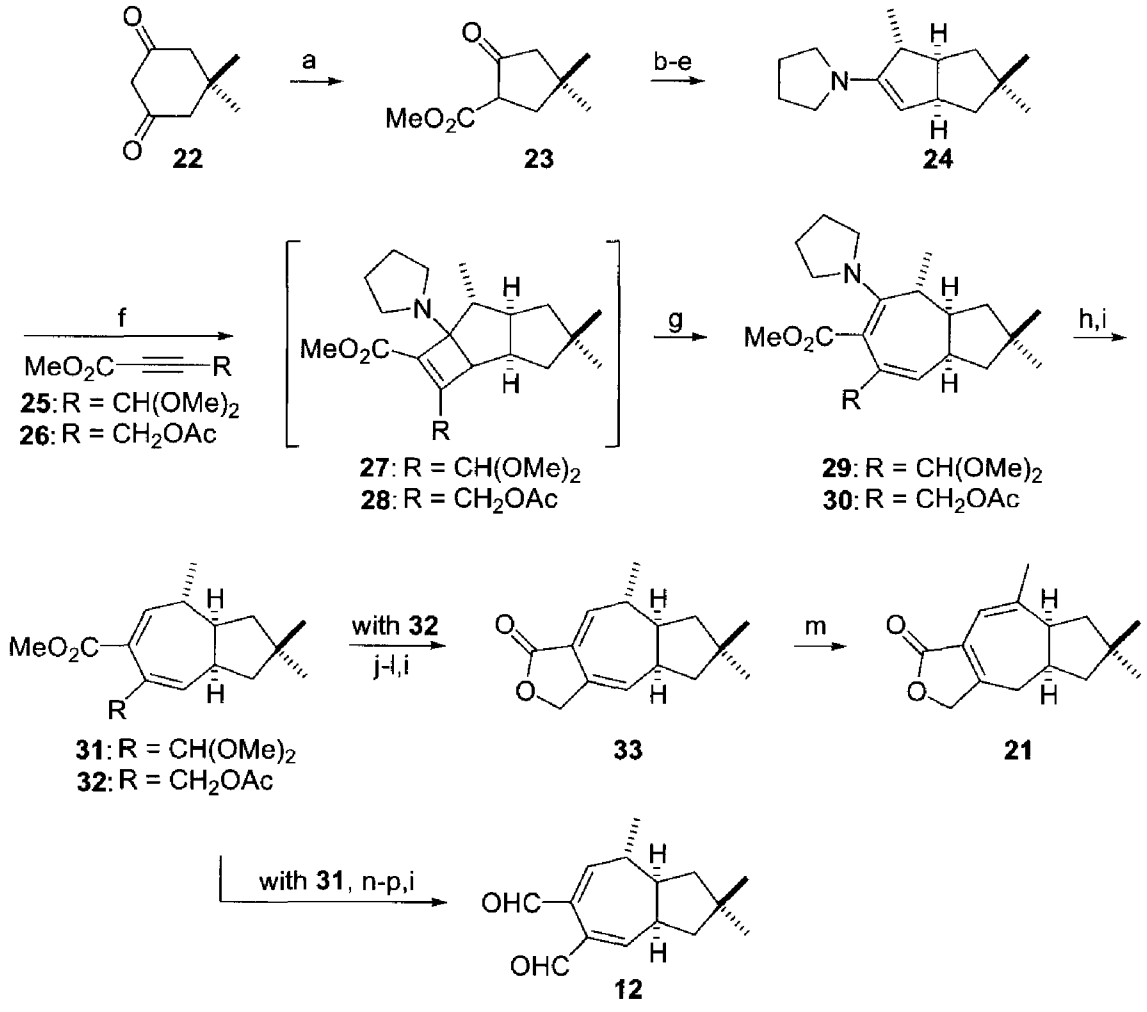
The first total synthesis of a lactarane, reported by Froborg *et al.*, appeared in the literature in 1975.[12] Although the reported stereostructure of the target molecule pyrovellerolactone (**21**) was incorrect,[13] the authors obtained a sample of **21** identical to the natural product. Later, the structure of **21** was revised.[14] For the sake of clarity, the structures depicted in Scheme 4 show the correct stereo- and regiochemistry. The synthesis starts with cycloalkylation of the enol acetate **16** with furan **15** giving tricyclic **17**. Reduction of the carbonyl group in **17** yielded a single product, which was converted into mesylate **18**. In the key step of the synthesis, **18** was treated with sodium pivalate to give **19** in low yield via a solvolytic ring enlargement. Electrochemical oxidation of **19** gave dihydroxy-dihydrofuran **20** along with some overoxidized material. Hydrolysis of **20** yielded pyrovellerolactone (**21**) in low yield.

Scheme 4



a: MeLi, >95%; b: $LiAlH_4$, 90%; c: MsCl, 96%; d: pivalic acid, sodium pivalate, 18%; e: electrochemical oxidation; f: 2 M HCl, 13% from **19**; Total yield 1.9% over 6 steps from **16**

Scheme 5

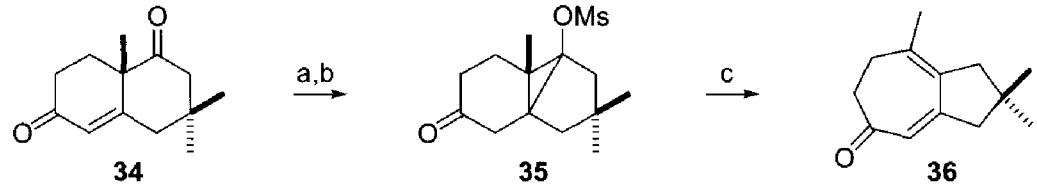


a: hν, 92%; b: *i*) NaH, 2-nitrobut-1-ene, *ii*) HCl, HOAc, 53%; c: *i*) NaOH, *ii*) HCl, 90%; d: Rh/Al_2O_3, H_2, 95%; e: TsOH, pyrrolidine, 76%; f: rt; g: toluene, reflux; h: $(BH_3)_2$; i: column chromatography, 62-70% from **24**; j: NaOH; k: 2 M HCl; l: cat. TsOH, 80% from **32**; m: toluene, reflux, 90%; Total yield 15.1% over 13 steps from **22**; n: DIBALH; o: MnO_2; p: TsOH, 80% from **31**; Total yield 16.7% over 12 steps from **22**

Some years later, a more efficient route to **21** and the total synthesis of velleral (**12**) and vellerolactone (**33**) were published by the same authors.[14] The key step in these syntheses was a [2+2] cycloaddition of enamine **24** with a difunctionalyzed acetylene (**25** or **26**) followed by thermal ring enlargement (Scheme 5). Depending on the substitution pattern of the target molecule, acetylene derivative **25** or **26** was used. Deamination of compound **29** or **30** with diborane yielded **31** or **32**, respectively, without isomerization of the C(10) allylic methyl group. Further functional group transformations gave the target molecules. In the same article the synthesis of several other unnatural lactarane lactones and an unnatural dialdehyde were reported via a similar strategy.

Christensen *et al.* published a synthesis of the basic core of the lactarane skeleton (**36**) in 1984 (Scheme 6).[15] Starting from the known diketone **34**, dissolving metal reduction and subsequent mesylation provided compound **35**, which upon treatment with TfOH rearranged to compound **36**. Some studies concerning functional group transformation on **36** were undertaken, but no natural product was prepared via this method.

Scheme 6

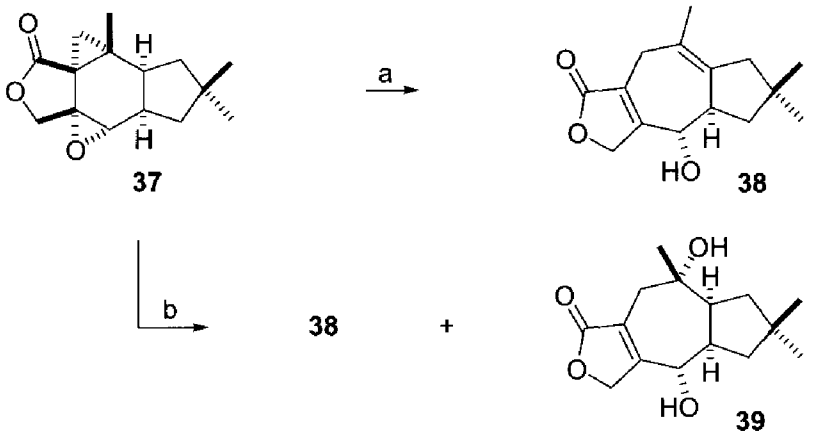


34 **35** **36**

a: Li, NH_3; b: MsCl, pyridine, 65% from **34**; c: TfOH, 91%

In 1992, Thompson and Heathcock published the total synthesis of anhydrolactarorufin A (**38**) and lactarorufin A (**39**).[16] Both compounds were obtained upon acid-catalyzed ring expansion of marasmane derivative **37** (Scheme 7). The synthesis of **37** will be discussed in paragraph 1.5.3.1.

Scheme 7

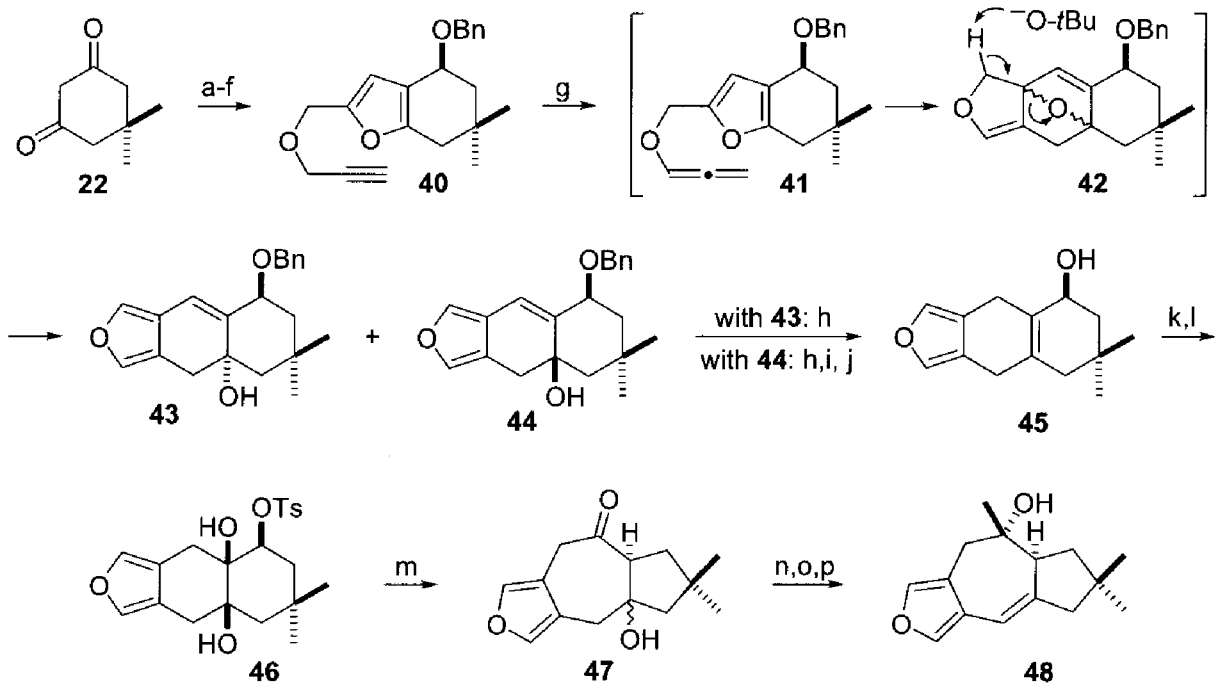


a: H_2SO_4, THF, 82%; Total yield 15.7% over 12 steps from **104**; b: H_2SO_4, THF/H_2O (1:1), 70% **38**, 25% **39**; Total yield 13.4% and 4.7% over 12 steps from **104**

Besides the categorization presented in this paragraph, a further subdivision can be made. This classification is based on the strategy used for the construction of the ring system before enlargement. Several, including the following syntheses used a Diels-Alder approach to build up the initial ring system.

In 1994, Ogino *et al.* published their first synthesis of furoscrobiculin B (**48**),[17] in which a furan ring transfer (FRT) reaction was used for the construction of a furan-annulated decalin system, which in turn was converted to a C(15) norlactarane via a pinacol-type rearrangement (Scheme 8). Starting from dimedone (**22**), compound **40** was prepared in 6 steps. Basic treatment of **40** resulted in the generation of allene **41**, which underwent an intramolecular Diels-Alder reaction to intermediate **42**. Subsequent eliminative opening of the ether-bridge in **42** yielded the compounds **43** and **44** (ratio 1:3). It should be mentioned that no Diels-Alder reaction was observed when alkyne **40** was treated under neutral conditions, which indicated that the formation of allene **41** was essential for the FRT reaction. Compounds **43** and **44** were separately converted to **45**, which via a two-step procedure gave **46** in low yield. Pinacol rearrangement of **46** gave **47** as a 5:2 mixture of diastereoisomers in high yield.[18] After separation, the major diastereoisomer was converted to furoscrobiculin B (**48**) and C(10) *epi*-furoscrobiculin B (ratio 7:2).

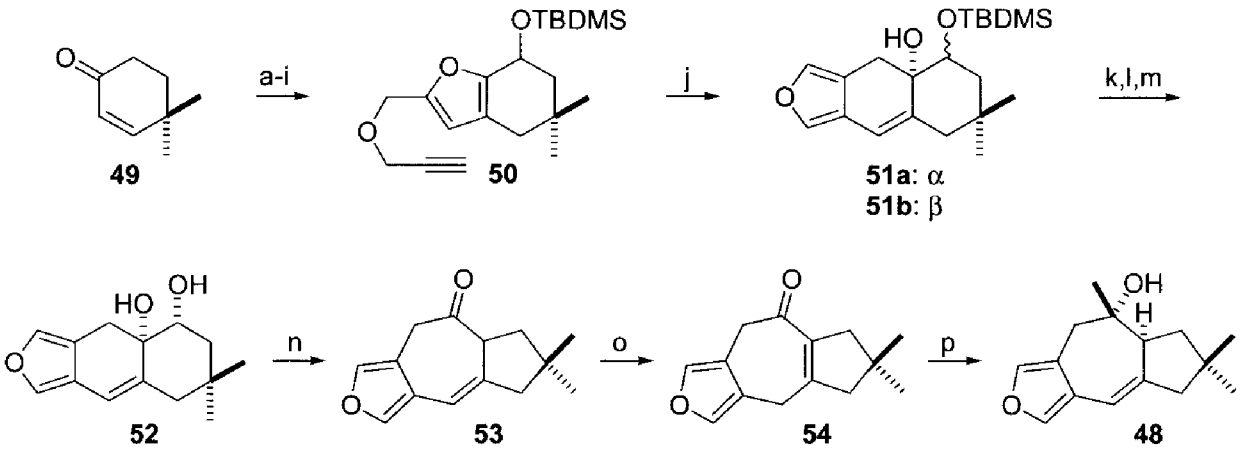
Scheme 8



a: $ClCH_2CHO$, $NaHCO_3$; H_2SO_4, 89%; b: $NaBH_4$, 94%; c: BnBr, NaH, 99%; d: $POCl_3$, DMF, 95%; e: $NaBH_4$, 100%; f: propargyl bromide, NaOH, cat. Bu_4NHSO_4, 98%; g: *t*BuOK, *t*BuOH, 87% (**43**:**44** = 1:3); h: Li, liquid NH_3, 80-90%; i: PDC, 46%; j: DIBALH, 85%; k: OsO_4, 33%; l: TsCl, 80%; m: *t*BuOK, *t*BuOH, 97%; n: Al_2O_3, pyridine, 69% ($\Delta^{1,5}$:$\Delta^{5,6}$ = 4:1); o: MeLi, $CeCl_3$, 79%; p: *t*BuOK, 68% (**48**:C(10) *epi*-**48** = 7:2); Total yield 2.3% over 17 steps from **22**

In 1997, the same group published a slightly modified synthesis of furoscrobiculin B (**48**).[19] The starting material in this approach, enone **49**, was converted in 9 steps to **50**, the substrate for the FRT reaction (Scheme 9). Treatment of **50** with *t*BuOK in *t*BuOH at 80 °C yielded a mixture of **51a** and **51b** (ratio 1:7), the formation of which was believed to be effected by steric hindrance of the geminal methyl group in the intramolecular Diels-Alder reaction. Deprotection of the minor isomer **51a** and deprotection, oxidation, and selective reduction with $Zn(BH_4)_2$ via a chelated intermediate of the major isomer **51b** were used to prepare the desired *cis*-diol **52**. Pinacol rearrangement of **52** gave compound **53**, which after methylation yielded the unnatural *epi*-furoscrobiculin B as major product. To obtain furoscrobiculin B (**48**), **53** was isomerized first to enone **54**, which was then further converted to **48** via a similar procedure as depicted in Scheme 8.

Scheme 9

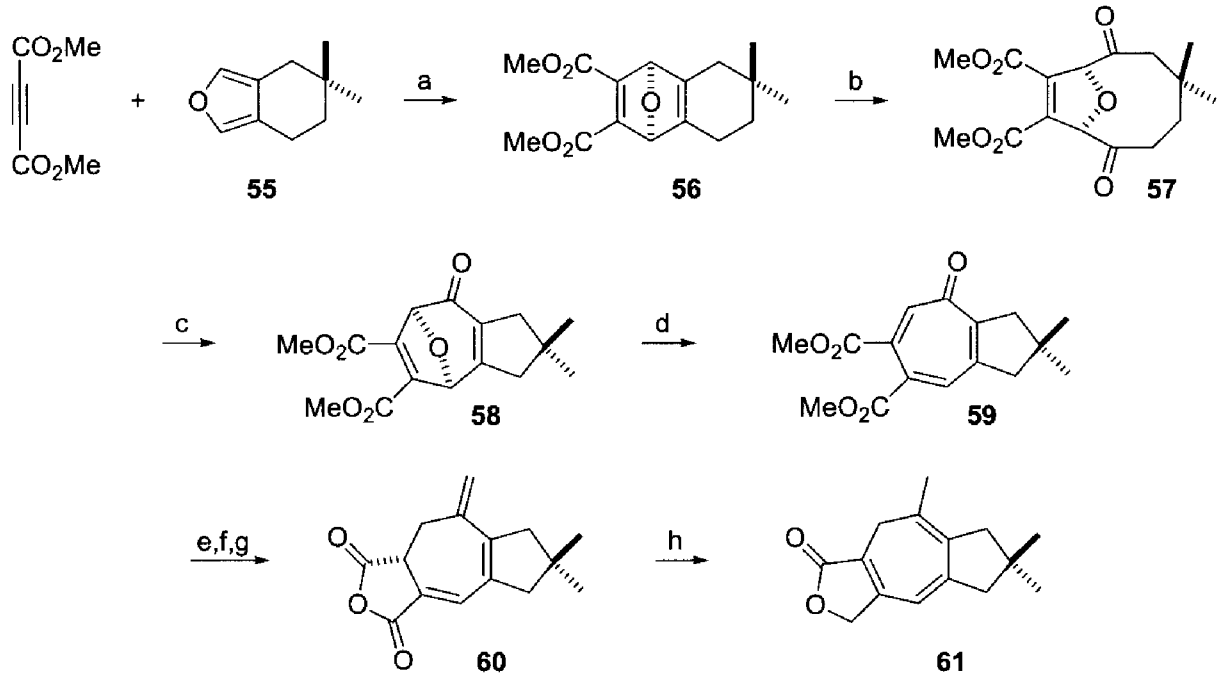


a: H_2O_2, NaOH, 86%; b: NaOH, 74%; c: H_2SO_4 89%; d: $ClCH_2CHO$, $NaHCO_3$; H_2SO_4, 68%; e: $NaBH_4$, 94%; f: TBDMSCl, imidazole, 92%; g: BuLi, DMF; h: $NaBH_4$, 87% over two steps; i: propargyl bromide, NaOH, cat. Bu_4NHSO_4, 92%; j: *t*BuOK, *t*BuOH, 11% **51a**, 77% **51b**; k: TBAF, 76% from **51a**, 100% from **51b**; l: Dess-Martin, 78%; m: 1.5 eq $Zn(BH_4)_2$, 91%; n: TsCl, pyridine 64% (+ 2% **54**); o: Et_3N, pyridine, 55%; p: see Scheme 8, steps o and p; Total yield 3.2% over 18 steps from **49**

Wockenfuß *et al.* published the synthesis of 1(10)-5(6)-bisanhydrolactarorufin A[20] (**61**) in 1997.[21] The strategy for the construction of the lactarane skeleton was based on a Diels-Alder reaction of furan **55** with dimethyl acetylenedicarboxylate followed by oxidative cleavage of the most electronrich double bond in **56** (Scheme 10). The highly regioselective intramolecular aldol condensation of **57** was directed by the steric effect of the geminal dimethyl group. Reductive cleavage of the ether bridge in **58** with $(CH_3)_2BBr$ was followed by a selective hydrogenation of the C(8)-C(9) double bond in **59**. Introduction of C(15) via methylation of the carbonyl group at C(10) with the Nysted reagent was preferred over Wittig olefination to prevent epimerization of the ester group at C(8). Conversion of the diester moiety under standard conditions to anhydride **60** and subsequent reduction with $NaBH_4$ in THF followed by acidic workup yielded 1(10)-5(6)-bisanhydrolactarorufin A (**61**). As the authors indicated, the rather selective reduction of the conjugated carbonyl group in **60** in the presence of an unconjugated carbonyl was somewhat surprising.

Preliminary to this work, Tochtermann *et al.* published the synthesis of a prelactarane.[22] However, further transformation of this compound to a lactarane failed.

Scheme 10

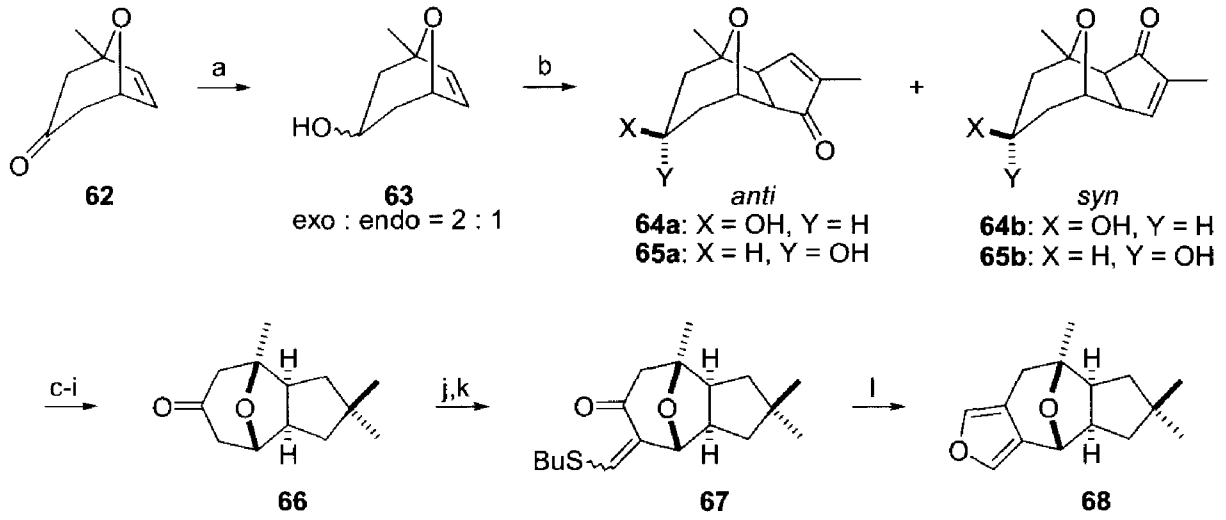


a: toluene, reflux; b: $NaIO_4$, cat. $RuCl_3$; c: cat. MsOH, 31% over three steps; d: Me_2BBr, Et_3N, 41%; e: 10% Pd/C, H_2, 53%; f: $TiCl_4$, Nysted reagent, 59%; g: *i*) NaOH, *ii*) Ac_2O; h: *i*) $NaBH_4$, *ii*) 2 M HCl, 24% over the steps g and h; Total yield 0.9% over 8 steps from **55**

1.5.2.2 Cyclizations

In 1989, Price and Schore published two slightly different syntheses of furanether B (**68**).[23] The first approach started with compound **62** obtained via a known procedure from 2-methylfuran and tetrabromoacetone.[24] Reduction of the ketone in **62** was necessary to prevent discrimination problems with a carbonyl functionality produced in a later stage of the synthesis (Scheme 11). The basic lactarane skeleton was prepared from **63** (a 2:1 exo:endo mixture) via a Pauson-Khand cycloaddition reaction catalyzed by octacarbonyl dicobalt. Although the reaction was completely stereoselective, only exo isomers were formed, the regioselectivity was moderate (*anti*:*syn* = 1.5:1). The reaction mixture, consisting of four isomers, was separated in two pairs, the first one containing the exo alcohols **64a** and **64b**, the second one the endo alcohols **65a** and **65b**. Both pairs were separately converted into the common intermediate **66**. Regioselective formylation of **66** and subsequent treatment with butanethiol gave the thiomethylene derivative **67** as a mixture of geometric isomers. Treatment of **67** with trimethylsulfonium methylsulfate yielded an epoxide, which rearranged on standing at room temperature. Subsequent aromatization of the rearranged product yielded furanether B (**68**).

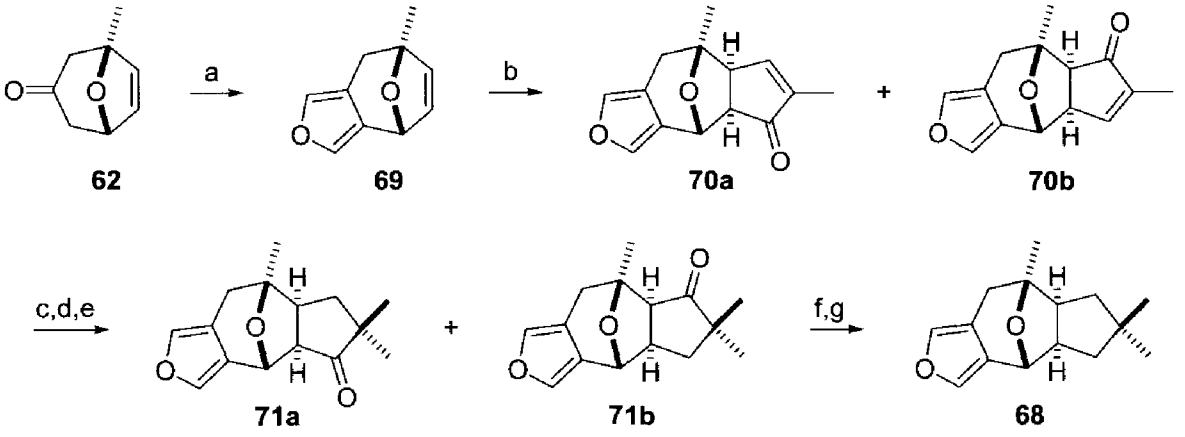
Scheme 11



a: $LiAlH_4$, 94% (exo:endo = 2:1); b: propyne, $Co_2(CO)_8$, CO, 75% (**64a**+**64b**:**65a**+**65b** = 1.5:1); c-i shown for the conversion of **64a**+**64b** (overall yield c-i for **65a**+**65b** is 4.6%) c: TBDMSCl, imidazole, 94%; d: Pd/C, H_2, 100%; e: *t*-BuOK, *t*-BuOH, MeI, 100%; f: $LiAlH_4$, 44%; g: *i*) NaH, *ii*) NaH, CS_2, *iii*) MeI, 100%; h: *i*) Bu_3SnH, *ii*) Bu_3SnH, AIBN, 50%; i: PCC, 60%; j: NaOMe, HCO_2Et, 67%; k: BuSH, TsOH, 100%; l: *i*) trimethylsulfonium methylsulfate, NaOH, *ii*) rt, 24 h, *iii*) HCl, 70%; Total yield 5.6% over 19 steps from **62**

The second publication by Price and Schore presented a more efficient route to furanether B (**68**).[23b] Introduction of the furan moiety earlier in the reaction sequence eliminated the parallel

Scheme 12

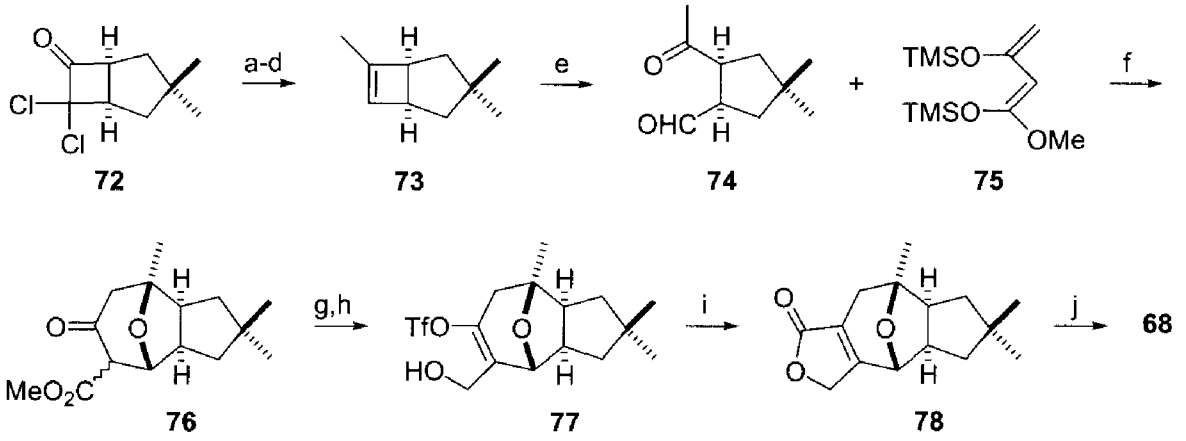


a: see steps j-l of Scheme 11, 45%; b: propyne, $Co_2(CO)_8$, CO, 64% (**70a**:**70b** = 2:1); c: Li(O*t*-Bu)$_3$AlH; d: PCC, 62% over two steps; e: *t*-BuOK, *t*-BuOH, MeI, 45%; f: $LiAlH_4$, 75%; g: *i*) NaH, CS_2, MeI, *ii*) Bu_3SnH, 71%; Total yield 4.3% over 9 steps from **62**

conversion of isomers (see Scheme 11). Starting from compound **62**, the furan ring in compound **69** was introduced via a similar methodology as used in the first approach. Pauson-Khand cycloaddition to **69** exclusively gave a mixture of the exo isomers **70a** and **70b**, which was converted to a mixture of **71a** and **71b**, along with *ca.* 25% of a product in which the ether bridge was opened (Scheme 12). Treatment of the mixture of **71a** and **71b** with $LiAlH_4$ and subsequent deoxygenation yielded furanether B (**68**) as the sole product.

In 1995, another synthesis of furanether B (**68**) was published by Molander *et al.*[25] Their strategy to construct the core of the lactarane skeleton was based on a [3 + 4] annulation reaction of the easily equilibrated compound **74**, which was prepared from **72** according to the sequence shown in Scheme 13. [3 + 4] Annulation of **74** with the bis-trimethylsilyl enol ether **75** gave the lactarane like compound **76** in good yield. The relative stereochemistry of **76** was proven by decarboxylation providing known **66**.[23] Conversion of **76** to its enol triflate and reduction of the ester moiety gave compound **77**, which via a palladium-catalyzed carbonylation afforded butenolide **78**. Reduction of **78** with DIBALH in CH_2Cl_2 to the corresponding lactol and subsequent dehydration yielded furanether B (**68**).

Scheme 13



a: Zn, AcOH, 94%; b: MeMgBr, 87%; c: Ac_2O, Et_3N, DMAP, 85%; d: Na, liquid NH_3; e: *i*) O_3, cat. $NaHCO_3$, *ii*) PPh_3, 46% over 2 steps; f: cat. TMSOTf, 70%; g: NaH, 2-$(Tf)_2$N-5-Cl-pyridine, 78%; h: DIBALH, 85%; i: cat. $Pd(PPh_3)_4$, CO, Bu_3N, LiCl, 90%; j: *i*) DIBALH, CH_2Cl_2, *ii*) 1 M H_2SO_4, 90%; Total yield 12.0% over 10 steps from **72**

1.5.3 Marasmane Sesquiterpenes

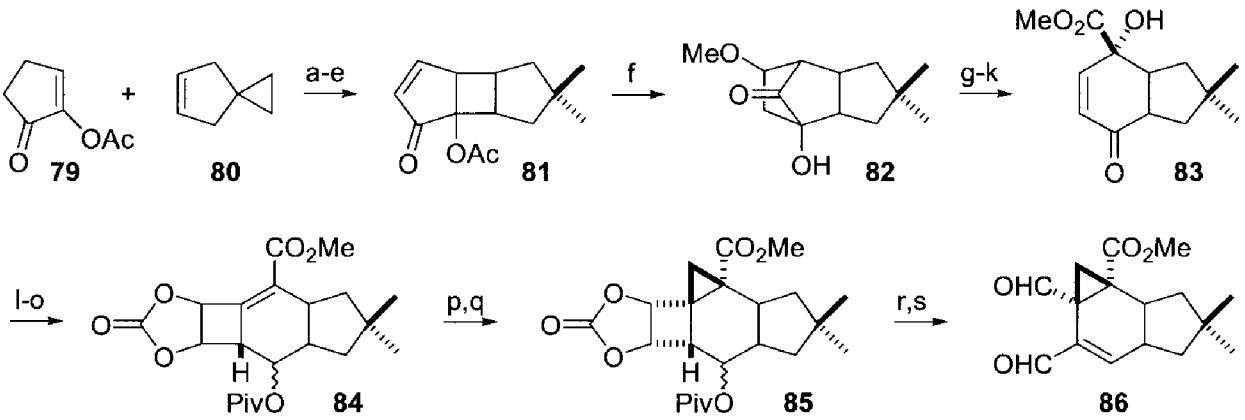
For the construction of marasmane sesquiterpenes three major methodologies can be distinguished. Besides the frequently used Diels-Alder approach, ring enlargements or

intramolecular cyclizations are the other main strategies. However, the categorization used in this paragraph is not based on these strategies, but on the manner of introducing the cyclopropane moiety. Most routes to marasmanes follow a strategy in which the 5,6-membered ring or indene part of the molecule is synthesized prior to introduction of the cyclopropane ring. The remaining synthetic approaches create the indene part as well as the cyclopropane moiety in the key step.

1.5.3.1 Stepwise Approach

In 1970, the first attempt toward the synthesis of a marasmane sesquiterpene was published by Helmlinger *et al.*[26] In one of the last steps, the introduction of the cyclopropane moiety in **84** via a 1,3-dipolar cycloaddition of diazomethane and subsequent irradiation gave compound **85** with the unnatural orientation of the cyclopropane ring (Scheme 14). The strategy for the construction of the basic core of the skeleton was based on a couple of photochemical steps and a base-induced ring enlargement. No yields and comments regarding the stereochemistry of the 5,6-membered ring system were given.

Scheme 14

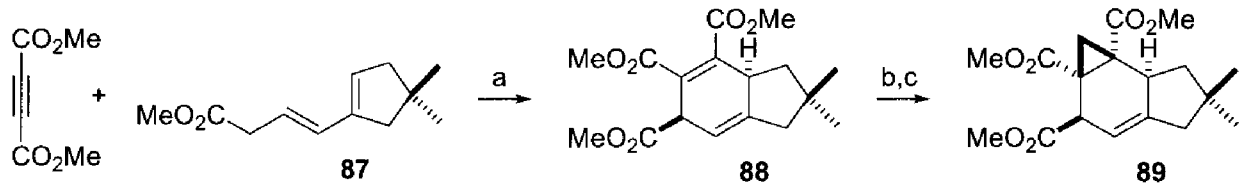


a: hν; b: PtO_2, H_2; c: CrO_3; d: pyridinium bromide perbromide; e: DBN; f: NaOH, MeOH, H_2O; g: $Pb(OAc)_4$; h: CH_2N_2; i: TsOH; j: hν, Rose Bengal, O_2; k: PPh_3; l: hν, (HC=CH)OC(O)O; m; Pt-Rh, H_2; n: conversion to pivalate; o: $POCl_3$; p: CH_2N_2; q: hν; r: hydrolysis; s: Et_3N

In 1973, Wilson *et al.* claimed the first racemic synthesis of a compound possessing the marasmane skeleton.[27] Later, it was shown that the structural assignment was incorrect (*vide infra*)[28] and that instead the isomarasmane **89** was obtained (Scheme 15). The structures depicted in Scheme 15 show the revised stereochemistry. The key step in this synthesis of **89** was a slow Diels-Alder reaction of dimethyl acetylenedicarboxylate with diene **87**. The cyclopropane moiety

was introduced via a 1,3-dipolar cycloaddition of **88** with diazomethane and subsequent irradiation.

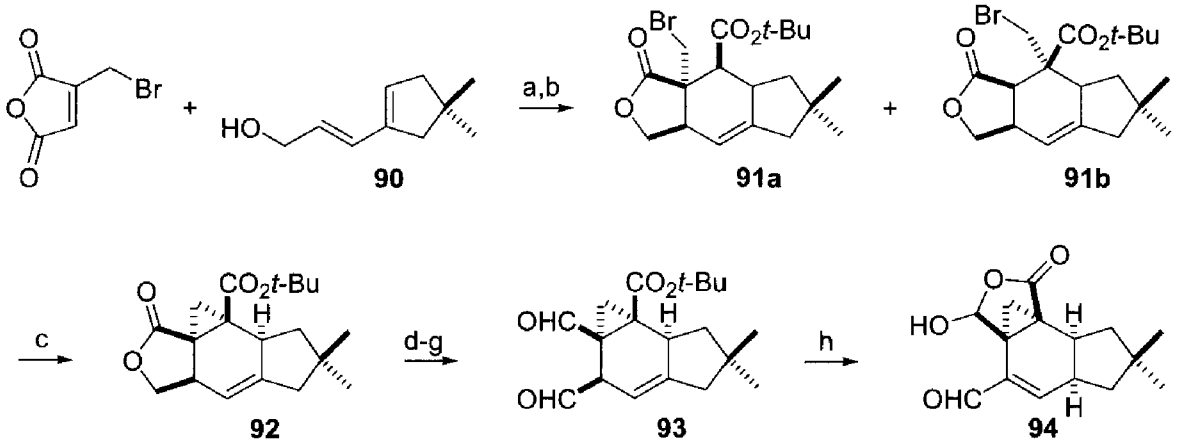
Scheme 15



a: 60 °C; b: CH_2N_2, 70%; c: hν, 76%

Greenlee *et al.* published the first total synthesis of (±)-marasmic acid (**94**) in 1976.[28a] Their initial work was very similar to the approach developed above for compound **89**[27] and resulted in the synthesis of (±)-isomarasmic acid. In a second attempt the core of (±)-marasmic acid (**94**) was synthesized via a Diels-Alder reaction of diene **90** with bromomethylmaleic anhydride resulting in a 1:1 mixture of **91a** and **91b** (Scheme 16). Esterification of this mixture and subsequent treatment with *t*-BuOK yielded cyclopropane **92** as a single compound. Further transformation of **92** gave (±)-marasmic acid (**94**). In 1980, the same synthesis of (±)-isomarasmic acid[28b] and an elaborated discussion on the synthesis of (±)-marasmic acid (**94**)[29] reappeared in the literature by the same authors.

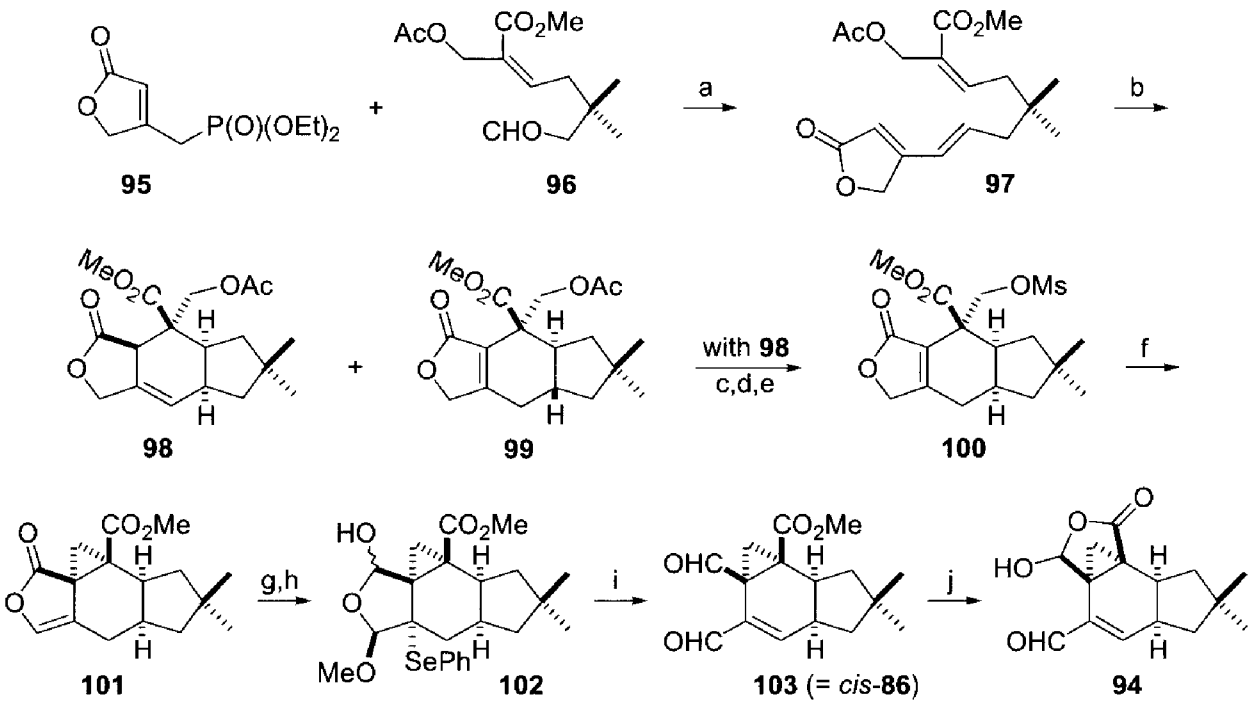
Scheme 16



a: rt; b: isobutylene, TsOH; c: *t*-BuOK, 44% from **90**; d: DIBALH; e: $NaBH_4$, 67% from **92**; f: quinoline, phosgene, 95%; g: DMSO, Et_3N, 25%; h: TfOH, 50%; Total yield 3.5% over 8 steps from **90**

In 1980, another synthesis of (±)-marasmic acid (**94**) and the synthesis of (±)-methyl marasmate (**103** = *cis*-**86**) were published by Boeckman Jr. *et al.*[30] In the key step of the synthesis, triene **97**, obtained via a Wadsworth-Emmons coupling of **95** and **96,** was heated to undergo an intramolecular Diels-Alder reaction yielding a *ca.* 1:1 mixture of *cis*-**98** and *trans*-**99**. The *cis*-product **98** was converted to (±)-marasmic acid (**94**) according to the sequence depicted in Scheme 17. Isomerization of the double bond in **98**, deprotection of the acetate, and subsequent mesylation afforded **100**. Treatment of **100** with DBU gave cyclopropane **101** as the sole product. Further functional group transformations yielded (±)-methyl marasmate (**103**), which was converted to (±)-marasmic acid (**94**) upon treatment with BBr_3. The *trans*-fused adduct **99** was transformed via the same sequence and in comparable yield, as shown for **98**, to *trans*-**94**, which was equilibrized to natural *cis*-**94**.

Scheme 17

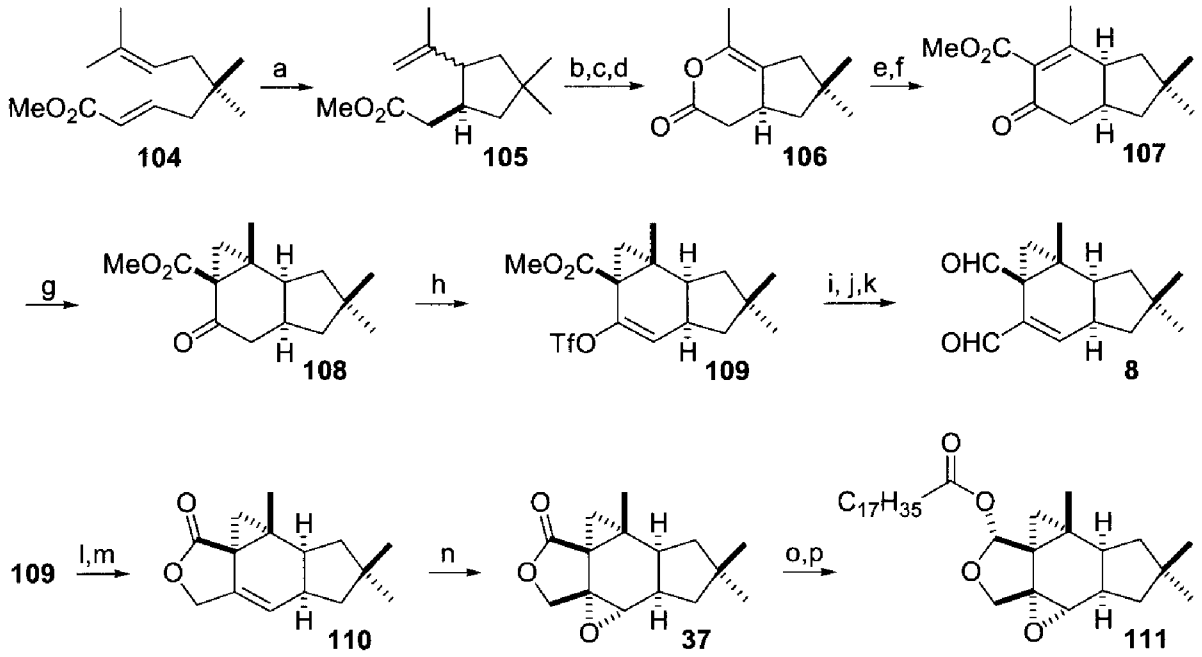


a: NaH, 80%; b: 200 °C, 92% (**98**:**99** ≈ 1:1); c: *t*-BuOK, 100%; d: cat. TsOH, 100%; e: MsCl, Et_3N; f: DBU, >90% over two steps; g: PhSeBr, 92%; h: DIBALH; i: MCPBA, 77% over two steps; j: BBr_3, 50%; Total yield 11.7% over 9 steps from **96**

The synthesis of racemic isovelleral (**8**) appeared in the literature in 1990.[31] This preliminary publication was reported again as a full paper, along with the synthesis of (±)-stearoylvelutinal (**111**), (±)-anhydrolactarorufin A (**38**) (*vide infra*), and lactarorufin A (**39**) (*vide infra*), by Thompson *et al.* in 1992.[16] The synthesis starts with a pyrolytic cyclization of the known 20:1 mixture of *cis*- and *trans*-**104**, yielding a 70:30 mixture of *cis*- and *trans*-**105** (Scheme 18). Further conversion of this mixture followed by intramolecular O-alkylation provided enol lactone

106. Treatment of **106** with α-lithioacetate and subsequent acidic ringclosure gave **107**. The introduction of the cyclopropane moiety was achieved by treatment of **107** with the Corey-Chaykovsky reagent. Conversion of **108** into enol triflate **109** and subsequent palladium-catalyzed methoxycarbonylation yielded a diester, which was converted to (±)-isovelleral (**8**).

Scheme 18



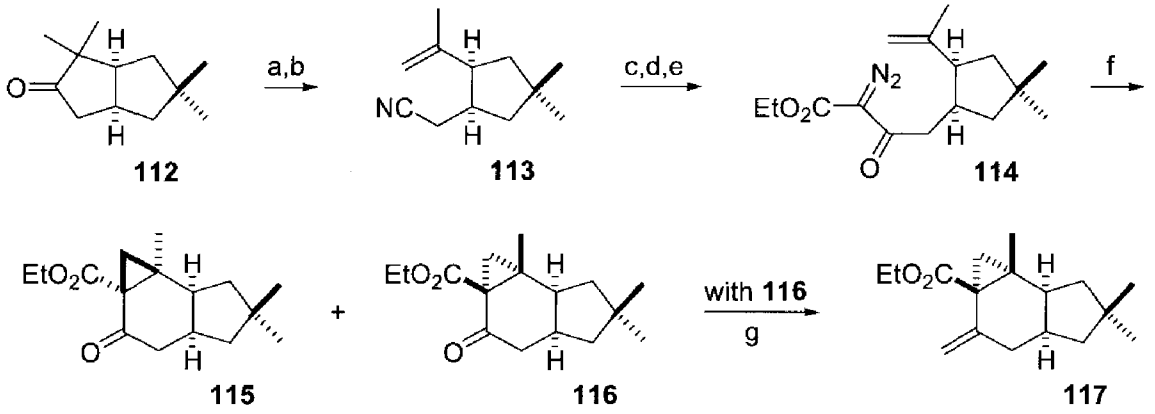
a: 235 °C, 93%; b: KOH, 100%; c: *i*) O_3, *ii*) Me_2S, 100%; d: $(COCl)_2$, 94%; e: $LiCH_2CO_2Me$; f: MsOH, 50% from **106**; g: $Me_2S(O)CH_2$, 65%; h: LDA, Tf_2NPh, 98%; i: $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, CO; 93%; j: DIBALH, 100%; k: $(COCl)_2$, DMSO, Et_3N, 83%; Total yield 21.5% over 11 steps from **104**; l: $Pd(PPh)_3$, Bu_3SnH, LiCl, CO, 88%; m: *i*) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, *ii*) TsOH, 93%; n: dimethyldioxirane, 84%; o: DIBALH, 50%; p: *i*) stearoyl chloride, Et_3N, *ii*) 2-propanol, 63%; Total yield 6.0% over 13 steps from **104**

In the same paper the synthesis of (±)-stearoylvelutinal (**111**) was reported. Starting from enol triflate **109** the lactone ring was introduced first, facilitating a thermodynamic advantage in the epoxidation step (Scheme 18). Epoxidation of **110** proceeded from the α-side of the molecule providing the thermodynamically more favored *cis*-fused lactone **37**. Reduction of **37** with DIBALH gave velutinal and its C(14) epimer as a 5.5:1 mixture. Acylation of this mixture with stearoyl chloride under basic conditions yielded, via equilibration of the anomeric center, (±)-stearoylvelutinal (**111**) as a single diastereoisomer.

1.5.3.2 Direct Approach

The first example of a one step construction of the indene part and cyclopropane moiety of the marasmane skeleton was published by Morisaki *et al.* in 1980.[32] Starting from **112**, an abnormal Beckman rearrangement of its oxime derivative provided **113** in low yield (Scheme 19). Elaboration of the side-chain in **113** yielded azo compound **114**, which in the key step of the synthesis was cyclized via an intramolecular carbene insertion reaction. The crude product mixture of this reaction consisted of **115**, **116**, and an unknown compound in a ratio of 5:1:1, respectively. The major product **115** possessed the unnatural orientation of the cyclopropane moiety. The natural-type product **116** was converted into the marasmane skeleton **117** via a Wittig reaction.

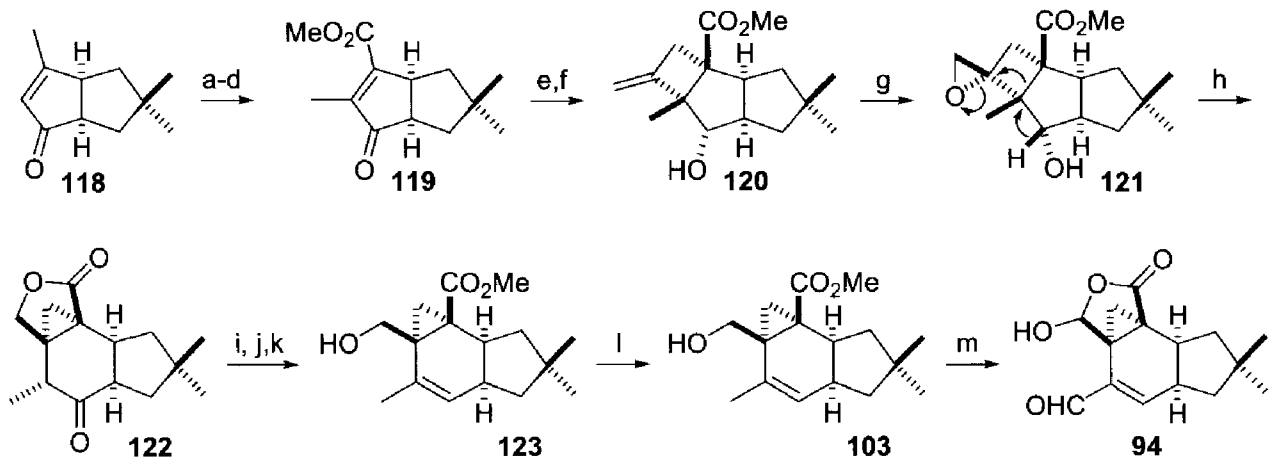
Scheme 19



a: $HONH_2$•HCl, pyridine, 96%; b: TsCl, pyridine, 19%; c: MeLi, 100%; d: NaH, Et_2CO_3, 100%; e: TsN_3, Et_3N, 60%; f: $(MeO)_3P$-CuI, 45% **115** + 9% **116**; g: NaH, DMSO, Ph_3PCH_3Br, 60%; Total yield 0.6% over 7 steps from **112**

In 1990, Tobe *et al.* published a formal total synthesis of (±)-marasmic acid (**94**) via synthesis of (±)-methyl marasmate (**103**).[33] As key step, the acid-catalyzed rearrangement of the 1-oxaspirohexane derivative **121** was used (Scheme 20). The starting material for this synthesis, the known enone **118**, was converted in four steps to compound **119**. [2+2] Cycloaddition of **119** with allene gave, after reduction of the ketone function, photoadduct **120** as major product (91 % selectivity). Stereoselective epoxidation of **120** yielded **121**, which upon treatment with concentrated H_2SO_4 in CH_2Cl_2 at room temperature rearranged smoothly to lactone **122**. The stereochemistry of the methyl group in **122** was assumed to be α on the basis of mechanistic considerations. Further conversion of **122** gave (±)-methyl marasmate (**103**), which was transformed to (±)-marasmic acid (**94**) using the conditions of Boeckman Jr. *et al.*[30]

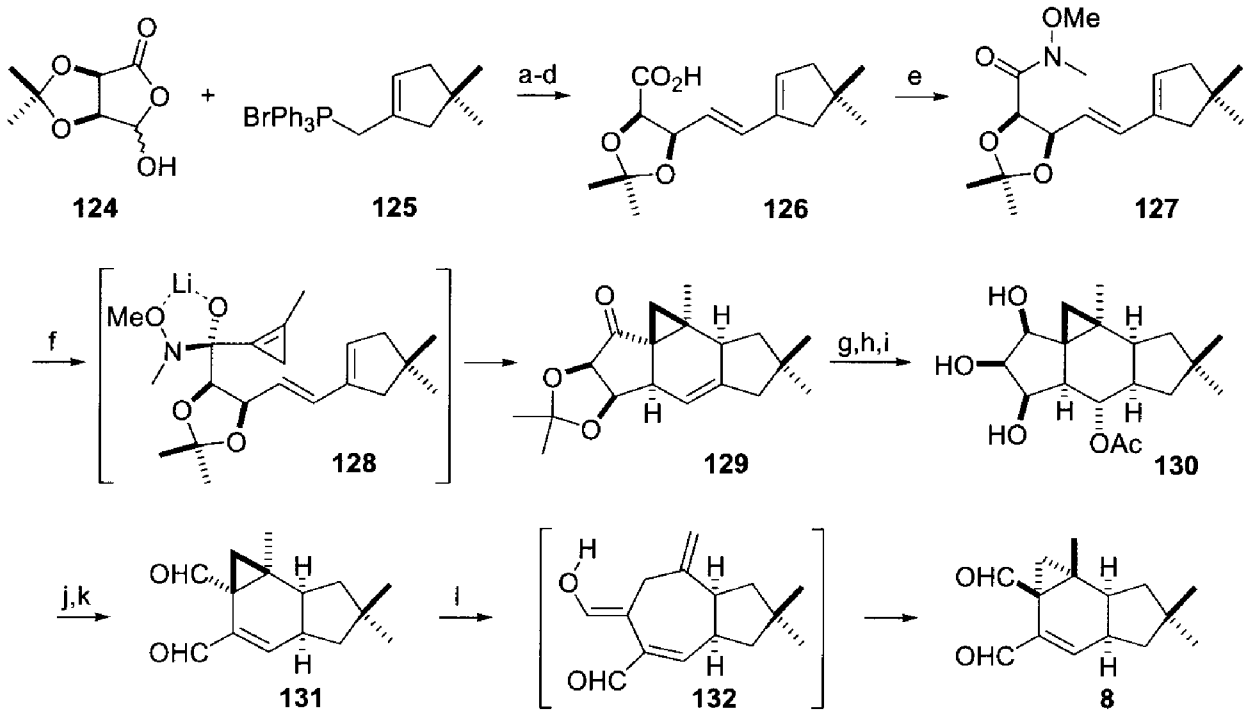
Scheme 20



a: *i*) Br_2, Et_3N, *ii*) $HO(CH_2)_2OH$, TsOH, 91% based on recovered starting material; b: *s*-BuLi, MeI, HMPA, 90%; c: SeO_2, 68%; d: *i*) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot H_2O$, *ii*) MeOH, H_2SO_4, 86%; e: hν, allene, 73%; f: $NaBH_4$, 98%; g: MCPBA, Na_2HPO_4, 89%; h: H_2SO_4, 80%; i: $NaBH_4$; j: MsCl, pyridine, 87% from **122**; k: NaOH, 92%; l: *i*) TBHP, SeO_2, *ii*) DMSO, $(COCl)_2$, Et_3N, 19%; m: ref. 30; Total yield 1.9% over 13 steps from **118**

Bergman *et al.* published the first enantioselective total synthesis of a marasmane sesquiterpene in 1990.[34] They completed the synthesis of (+)-isovelleral (**8**) via a remarkable diastereoselective intramolecular Diels-Alder reaction with a substrate derived from D-ribonic acid γ-lactone (Scheme 21). The synthesis starts with a Wittig reaction of ylide **125** and compound **124** yielding a nonseparable mixture of **126** and its *Z*-isomer in a ratio of 2:3, respectively. This ratio could be improved to 19:1 using a $Hg(OAc)_2$-catalyzed isomerization. Treatment of **126** with 1-chloro-*N*,*N*,2-trimethylprop-1-enylamine yielded compound **127**. Alkylation of **127** with methylcyclopropenyllithium was followed by a spontaneous intramolecular Diels-Alder reaction in which the stereochemical behavior is explained by the intramolecular complexation depicted in structure **128**. The adduct **129** showed the opposite orientation of the cyclopropane moiety for conversion into the natural product. However this problem was overcome in a later stage of the synthesis. Compound **129** was converted to **131**, the diastereoisomer of isovelleral, which could be rearranged thermally via the lactarane intermediate **132** into a mixture of **131** and (+)-isovelleral (**8**) (ratio **131**:**8** ≈ 3:2). Isolation of (+)-isovelleral and subsequent recycling (5 times) of **131** yielded (+)-isovelleral (**8**) in good yield.

Scheme 21



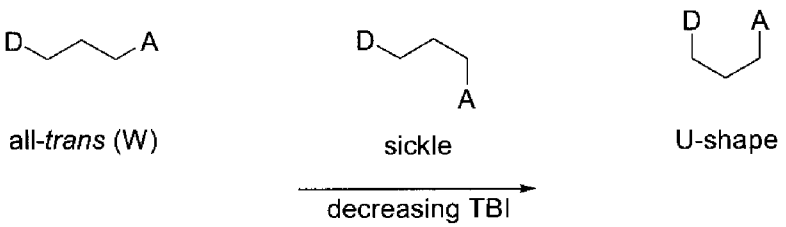
a: BuLi; b: cat. $Hg(OAc)_2$, Zn dust; c: CH_2N_2, column chromatography, 60% from **124**; d: NaOH, 97%; e: MeONHMe•HCl, Et_3N, 85%; f: methylcyclopropenyl-lithium, 68%; g: *i*) BH_3•THF, *ii*) H_2O_2, NaOH, 77%; h: Ac_2O, pyridine; 86%; i: 0.2 M H_2SO_4, 75%; j: $NaIO_4$, k: pyridine, reflux, 55% from **130**; l: mesitylene, reflux (ratio **131**:**8** ≈ 3:2), column chromatography, **131** recycling, 71% after five cycles; Total yield 6.5% over 16 steps from **124**

1.5.4 Perhydronaphthalene-1,4-diol Monosulfonate Esters and Through Bond Interactions (TBI)

The chemical consequences of long-range orbital interactions in stereochemically rigid 1,4-diol monosulfonate esters were extensively investigated by Wijnberg and de Groot in the last decade. Not only studies focussed on the mechanistic part were performed but also the applicability in total synthesis of naturally occurring sesquiterpenes was investigated.[35] It has been shown that under strongly basic conditions elimination, rearrangement, and homofragmentation are the preferred pathways by which these systems react.[36] The synthetic utility of the elimination and rearrangement reaction was demonstrated in the total synthesis of guaiane[37] and alloaromadendrane[38] sesquiterpenes, whereas the homofragmentation was used as key step in the total synthesis of α-santalanes.[39] This thesis focuses on the applicability of the rearrangement of perhydronaphthalene-1,4-diol monosulfonate esters in the total synthesis of lactarane and marasmane sesquiterpenes.

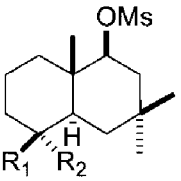
The heterolysis of perhydronaphthalene-1,4-diol monosulfonate esters with strong base in apolar solvents like benzene or toluene is known to be effected by through-bond interactions (TBI).[35a] This phenomenon is best explained by comparison with the delocalization of π-electrons, except that in the case of TBI the σ-bonds of the connecting atoms are involved. TBI between two functionality's can be regarded as delocalization of σ-electrons via σ- and σ*-orbitals of the intervening saturated bridge.[35c,40] Although the energy effect of σ-conjugation[41] is considerably smaller than that observed for the more familiar π-conjugation, several reactions are known to be influenced significantly by TBI.[35] The intensity of TBI is known to depend on the geometry of the backbone as well as the number of bonds separating the connected functionality's. Generally, TBI decrease with increasing number of separating bonds and is optimal for a *trans* (W) orientation between the donor (D) and acceptor (A) group (Figure 2). The latter effect is known as the 'all-*trans* rule'.[40]

Figure 2

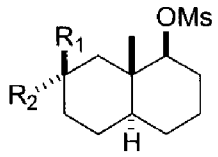


Treatment of the perhydronaphthalene-1,4-diol monosulfonate esters **133-136** with sodium *tert*-amylate in refluxing benzene follows this all-*trans* rule (Scheme 22).[36b] Where compounds **133** and **134**, with an all-*trans* conformation, are fully converted within 10 min, only 50% of the sickle-arranged compounds **135** and **136** have reacted under the same conditions. The diminished

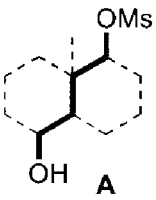
Scheme 22



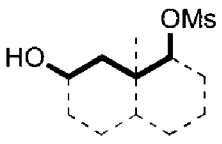
133: R_1 = OH, R_2 = CH_3
134: R_1 = CH_3, R_2 = OH



135: R_1 = OH, R_2 = CH_3
136: R_1 = CH_3, R_2 = OH



A

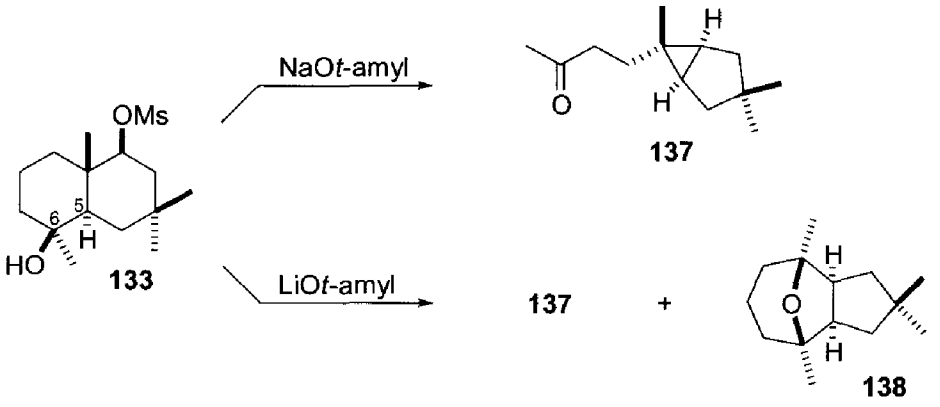


B

TBI in the rate determining heterolysis of mesylates **135** and **136** result in a decreased stabilization of the developing cationic center and therefore a lower reaction rate. The recoveries for the epimeric pairs **133**, **134** and **135**, **136** also show that the relative orientation of the alcoholate does not influence the intensity of TBI.

Besides the influence of TBI on the rate of heterolysis of the sulfonate ester bond, it is known that the electron-donating ability of the alcoholate can influence the product composition of the resulting reaction mixture.[35a,36b,39] This is best demonstrated by the reaction of mesylate **133**. Where the reaction of **133** with sodium *tert*-amylate as base in refluxing benzene produces selectively the homofragmentation product **137**, the corresponding reaction with lithium *tert*-amylate as base results in a *ca.* 2:1 mixture of **137** and the rearranged tricyclic ether **138**, respectively (Scheme 23).[36b]

Scheme 23



The co-occurrence of homofragmentation and rearrangement in the reaction of **133** with lithium *tert*-amylate can be explained by a diminished electron-donating ability of the alcoholate, due to the more covalent character of the Li–O bond[42] resulting in a decreased electron density of the back lobe of the C(6)-C(5) bond and therefore less overlap with the secondary carbocation. The diminished electron-donating ability of the lithium alcoholate also results in a slower reaction.

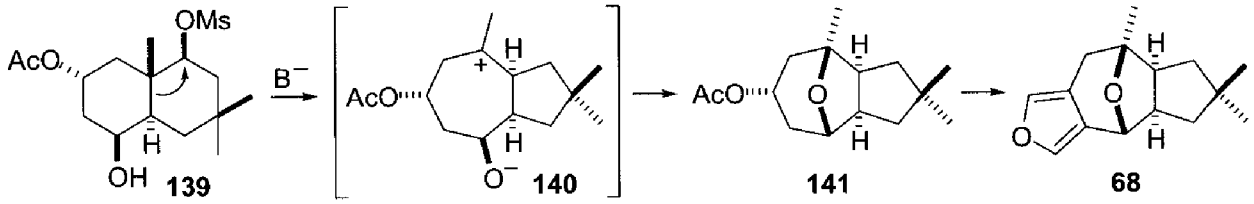
1.6 Scope of this Thesis

This thesis focuses on the applicability of the rearrangement of perhydronaphthalene-1,4-diol monosulfonate esters in the total synthesis of lactarane and marasmane sesquiterpenes.

- In Chapter 1, a brief overview on the mechanistic aspects of this reaction is presented in addition to a review about the total synthesis of lactarane and marasmane sesquiterpenes and a general introduction on these compounds.

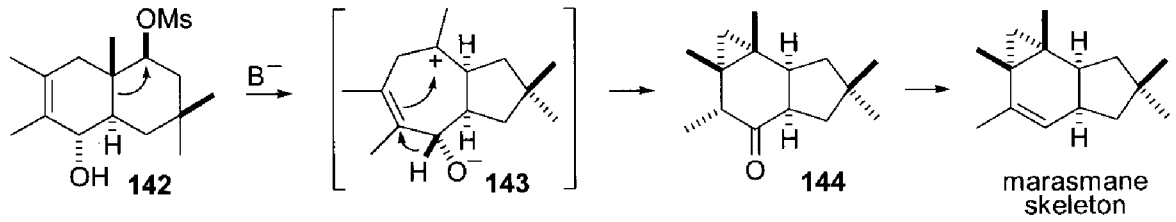
- In Chapter 2, the applicability of the base-induced rearrangement reaction in the synthesis of lactarane sesquiterpenes is described. As a target molecule furanether B (**68**) is chosen (Scheme 24). The construction of the basic core of the skeleton and ether-bridge in one reaction is investigated.

Scheme 24



- In Chapter 3, the one-step construction of the basic core of the marasmane skeleton is investigated (Scheme 25). Besides the skeleton rearrangement an additional cyclopropanation reaction has to be performed which is planned via an electrophilic attack of the carbocation on the double bond in intermediate **143**.

Scheme 25

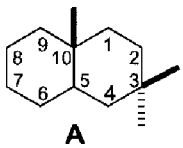


- In Chapter 4, the preparation of a common optically pure synthon for lactarane and marasmane sesquiterpene total synthesis is discussed.
- In Chapter 5, as an application of the methodology developed for the synthesis of the marasmane skeleton, the total synthesis of (+)-isovelleral (**8**) is described.
- In Chapter 6, some concluding remarks and newly obtained insights about the rearrangement of perhydronaphthalene-1,4-diol monosulfonate esters are given.

1.7 References and Notes

1. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, **1991**, Vol. I.
2. Banthorpe, D. V. *Natural Products: Their Chemistry and Biological Significance*; Longman Scientific & Technical: Harlow, **1994**.

3. For reasons of clarity, the numbering of the lactarane and marasmane skeleton is adapted to that of the naphthalene skeleton (**A**) by using the in this thesis described rearrangement reactions.



A

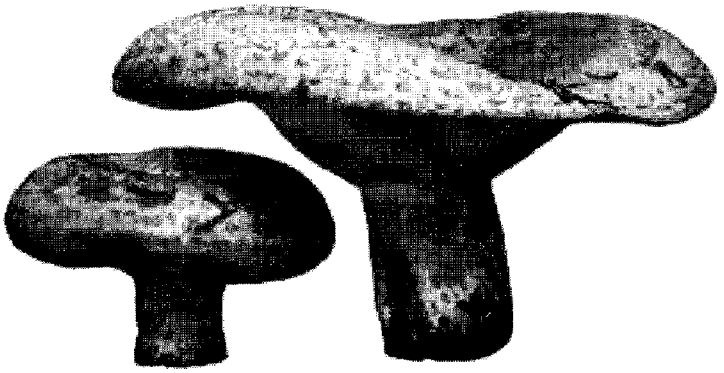
For the in the literature most frequently used numbering of lactaranes and marasmanes see reference 8.

4. Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.
5. Vidari, G.; Garlaschelli, L.; Rossi, A.; Vita Finzi, P. *Tetrahedron Lett.*, **1998**, *39*, 1957.
6. Hansson, T. Ph. D. Thesis, University of Lund, **1992**.
7. Sterner, O. Ph. D. Thesis, University of Lund, **1985**.
8. (a) Vidari, G.; Vita Finzi, P. *Sesquiterpenes and other secondary metabolites of genus Lactarius (Basidiomycetes): chemistry and biological activity*; Elsevier: Amsterdam, **1995**; Vol. 17. (b) Daniewski, W. M.; Vidari, G. *Progress In The Chemistry Of Organic Natural Products* **1999**, *77*, 69.
9. Garlaschelli, L.; Toma, L.; Vidari, G.; Colombo, D. *Tetrahedron* **1994**, *50*, 1211.
10. (a) Sterner, O.; Bergman, R.; Kihlberg, J.; Oluwadiya, J.; Wickberg, B.; Vidari, G.; De Bernardi, M.; De Marchi, F.; Fronza, G.; Vita Finzi, P. *J. Org. Chem.* **1985**, *50*, 950. (b) De Bernardi, M.; Vidari, G.; Vita Finzi, P. *Tetrahedron Lett.* **1982**, *23*, 4623.
11. (a) Sterner, O.; Bergman, R.; Kihlberg, J.; Wickberg, B. *J. Nat. Prod.* **1985**, *48*, 279. (b) De Bernardi, M.; Garlaschelli, L.; Toma, L.; Vidari, G.; Vita Finzi, P. *Tetrahedron* **1993**, *49*, 1489.
12. Froborg, J.; Magnusson, G.; Thorén, S. *J. Org. Chem.* **1975**, *40*, 1595.
13. (a) Magnusson, G.; Thorén, S. *Acta Chem. Scand.* **1973**, *27*, 1573. (b) Magnusson, G.; Thorén, S. *Acta Chem. Scand.* **1973**, *27*, 2396.
14. Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
15. Christensen, J. R.; Reusch, W. *Can. J. Chem.* **1984**, *62*, 1954.
16. Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979.
17. Ogino, T.; Kurihara, C.; Baba, Y.; Kanematsu, K. *J. Chem. Soc., Chem. Comm.* **1994**, 1979.
18. The structural assignment of the diasteriomeric mixture **47** by the authors is probably incorrect. Instead of the bridgehead alcohol, it is more likely that the bridgehead hydrogen is epimerized under the basic conditions.
19. Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1707.
20. This compound was published in the literature under the name of 2(3)-8(9)-bisanhydrolactarorufin A.
21. Wockenfuß, B.; Wolff, C.; Tochtermann, W. *Tetrahedron* **1997**, *53*, 13703.

22. (a) Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C. *Tetrahedron* **1994**, *50*, 9657. (b) Tochtermann, W.; Bruhn, S.; Meints, M.; Wolff, C.; Peters, E.-M.; Peters, K.; Schnering von, H. G. *Tetrahedron* **1995**, *51*, 1623.
23. (a) Price, M. E.; Schore, N. E. *J. Org. Chem.* **1989**, *54*, 5662. (b) Price, M. E.; Schore, N. E. *Tetrahedron Lett.* **1989**, *30*, 5865.
24. Sato, T.; Watanabe, M.; Noyori, R. *Tetrahedron Lett.* **1979**, 2897.
25. Molander, G. A.; Carey, J. S. *J. Org. Chem.* **1995**, *60*, 4845.
26. Helmlinger, D.; Mayo de, P.; Nye, M.; Westfelt, L.; Yeats, R. B. *Tetrahedron Lett.* **1970**, *5*, 349.
27. Wilson, S. R.; Turner, R. B. *J. Org. Chem.* **1973**, *38*, 2870.
28. (a) Greenlee, W. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1976**, *98*, 6075. (b) Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3361.
29. Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367.
30. Boeckman Jr, R. K.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.
31. Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3004.
32. Morisaki, N.; Furukawa, J.; Nozoe, S.; Itai, A.; Iitaka, Y. *Chem. Pharm. Bull.* **1980**, *28*, 500.
33. Tobe, Y.; Yamashita, D.; Takahashi, T.; Inata, M.; Sato, J.-i.; Kakiuchi, K.; Kobiro, K.; Odaira, Y. *J. Am. Chem. Soc.* **1990**, *112*, 775.
34. Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B. *J. Chem. Soc., Chem. Comm.* **1990**, 865.
35. (a) Jenniskens, L. H. D. Ph. D. Thesis, Wageningen University, **1992**. (b) Orru, R. V. A. Ph. D. Thesis, Wageningen University, **1994**. (c) Bastiaansen, P. M. F. M. Ph. D. Thesis, Wageningen University, **1996**.
36. (a) Orru, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (b) Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (c) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240.
37. (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Koike, T.; Yamazaki, K.; Fukumoto, N.; Yashiro, K.; Takeuchi, N.; Tobinaga, S. *Chem. Pharm. Bull.* **1996**, *44*, 646. (c) Piet, D. P.; Orru, R. V. A.; Jenniskens, L. H. D.; van de Haar, C.; van Beek, T. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Chem. Pharm. Bull.* **1996**, *44*, 1400.
38. Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585.
39. Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4955.
40. Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
41. Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669.
42. Paquette, L. A.; Gilday, J. P. *J. Org. Chem.* **1988**, *53*, 4972.

Chapter 2

Total Synthesis of Furanether B*

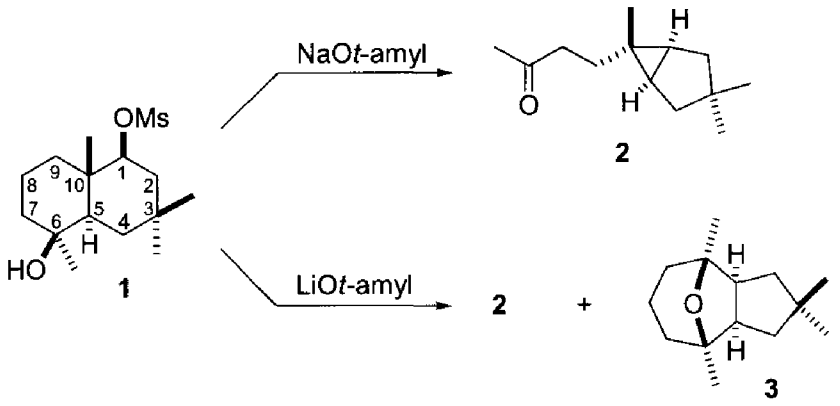


* Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1998**, *63*, 122.

2.1 Introduction

From previous work on the chemical consequences of long-range orbital interactions in stereochemically rigid 1,4-diol monosulfonate esters, it is known that elimination, rearrangement, and homofragmentation are the preferred pathways by which these compounds react upon treatment with a strong base.[1] It has been demonstrated[1a,b] that the reaction outcome not only depends on the specific structural features of the 1,4-diol monosulfonate esters, but also on the nature of the base used as is illustrated in Scheme 1.

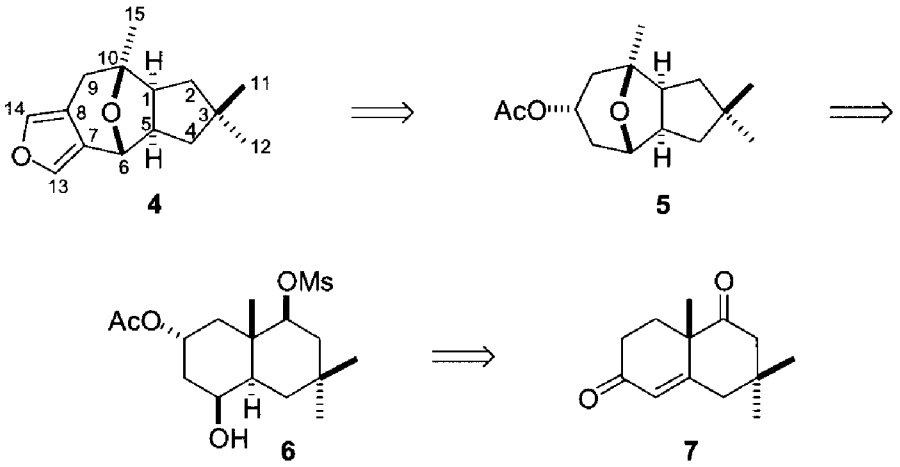
Scheme 1



While the reaction of mesylate **1** with sodium *tert*-amylate in refluxing benzene produces selectively the homofragmentation product **2**, the corresponding reaction with lithium *tert*-amylate as base results in a *ca.* 2:1 mixture of **2** and the rearranged tricyclic ether **3**, respectively.[1b] The co-occurrence of homofragmentation and rearrangement in the reaction of **1** with lithium *tert*-amylate has been explained by a decrease of the electron-donating ability of the alkoxide group with Li^+ as counterion.[2] It is further important to note that the rearranged product **3** formed in this reaction strongly resembles the oxatricyclo[5.3.1.0]undecane ring system present in furanether B (**4**), a lactarane sesquiterpene isolated from the mushroom *Lactarius scrobiculatus*.[3] This strong resemblance and the expectation that a further decrease of the electron-donating ability of the alkoxide function would result in selective formation of the oxatricyclo[5.3.1.0]undecane ring system, have initiated a synthetic study to furanether B itself.

To date, three total syntheses of furanether B have been reported: two complementary syntheses in which the key involves the Pauson-Khand cycloaddition reaction,[4] and one based on a [3 + 4] annulation strategy.[5] The asymmetric synthesis of an intermediate in the Pauson-Khand cycloaddition approach has been reported recently.[6] The synthetic approach toward furanether B in this Chapter starts with the readily available Robinson annulation product **7**,[7] and presents as the key feature the base-induced rearrangement reaction of **6** to establish the bridged ether core of **5** (Scheme 2). Further elaboration of **5** to furanether B (**4**) was planned via the regioselective synthesis of the corresponding butenolides (*vide infra*).

Scheme 2

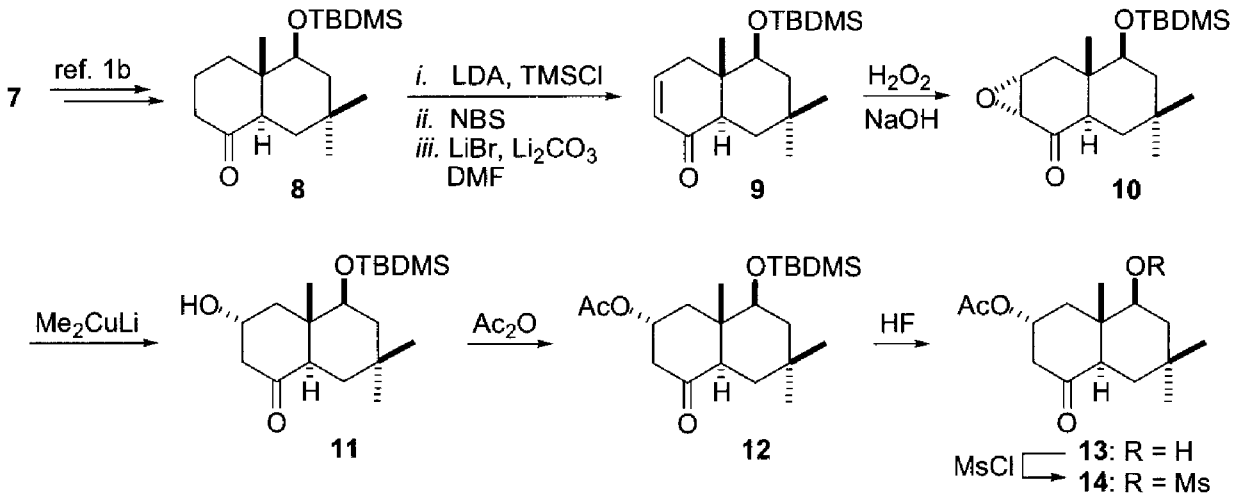


2.2 Results and Discussion

The first series of experiments was directed toward finding reaction conditions that allow selective formation of tricyclic ether **5** from mesylate **6**. For that purpose, the structurally comparable mesylate **1** was used as a model system.[8] After considerable experimentation with a wide range of bases, it was found that treatment of **1** with one equivalent of lithium tri-*tert*-butoxyaluminohydride ($Li(O\textit{t}\text{-}Bu)_3AlH$) in refluxing toluene resulted in a high yield (93%) of the cyclic ether **3** and none of the homofragmentation product **2** was formed. Apparently, the electron-donating ability of the alkoxide group with $Li(O\textit{t}\text{-}Bu)_3Al^+$ as counterion, produced after reaction of **1** with $Li(O\textit{t}\text{-}Bu)_3AlH$, is not strong enough for induction of homofragmentation, and consequently, only rearrangement to tricyclic ether **3** takes place.

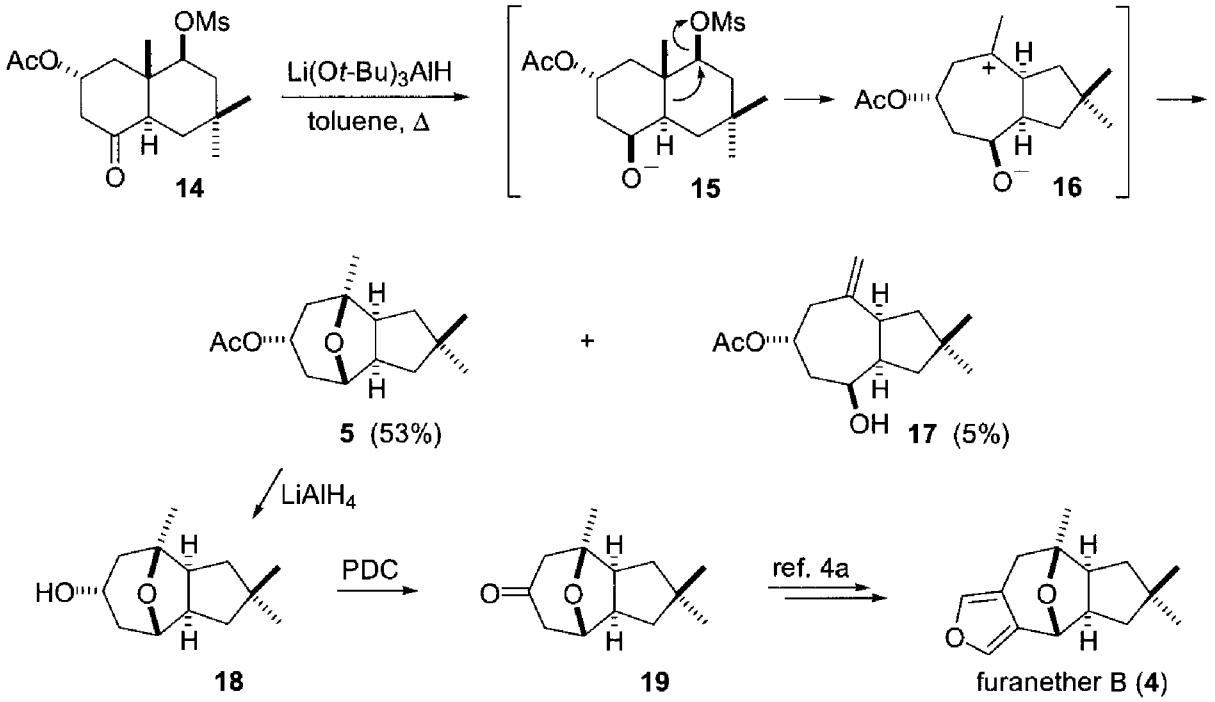
Having thus established that homofragmentation could be suppressed completely, the synthetic route toward furanether B was investigated. A previously described procedure[1b] was used to prepare ketone **8** from the known diketone **7**[7] (Scheme 3). The introduction of a hydroxyl function at the C(8) position of **8** was planned via cleavage of the C(7)–O bond in epoxyketone **10**. This compound was obtained in *ca.* 70% overall yield via bromination of the silyl enol ether of **8**, dehydrobromination, and epoxidation of the resulting enone **9** with H_2O_2 in the presence of NaOH. When the epoxide ring opening in **10** was tried with palladium metal catalysts in the presence of HCO_2H and Et_3N,[9] or ammonium formate,[10] no reaction at all was observed. Also the use of NaI, NaOAc, and AcOH in acetone[11] was not successful. A more promising result was achieved when **10** was treated with lithium in liquid ammonia at –78 °C.[12] The desired product **11** was formed in reasonable yield (44%), but the reaction could not be driven to completion.

Scheme 3



Eventually it was found that reductive cleavage of **10** could be accomplished with 3 equivalents of Me_2CuLi[13] to afford **11** as the sole product in good yield. The broad one-proton signal ($W_{1/2} \approx 22$ Hz) at δ 4.11 in the ^1H NMR spectrum of **11** shows that the hydroxyl group at C(8) possesses the equatorial α orientation. With standard procedures, **11** was then converted to the mesylate **14**.

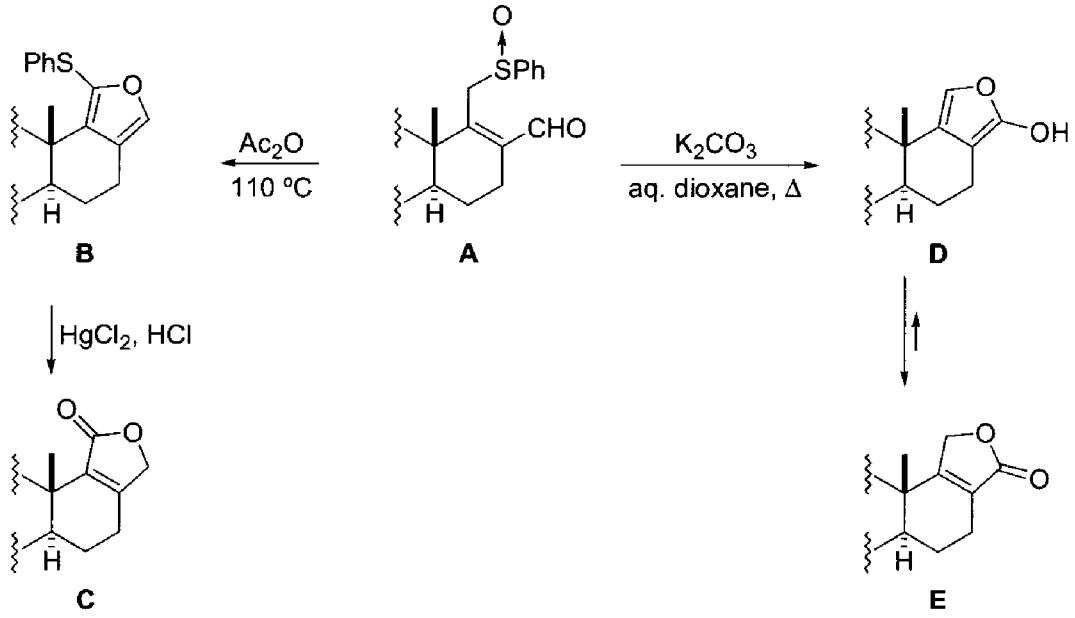
Scheme 4



In the initial synthetic route toward furanether B, the reduction of mesylate **14** and rearrangement of the resulting secondary alcohol **6** to tricyclic ether **5** were planned as two

separate steps. Having demonstrated that selective rearrangement could be achieved with the reducing agent Li(O*t*-Bu)$_3$AlH,[14] it was anticipated that direct conversion of **14** to **5** would be possible via a one-pot reduction/rearrangement process[15] (Scheme 4). A first attempt in which one equivalent of Li(O*t*-Bu)$_3$AlH was employed indeed afforded the desired tricyclic ether **5**, but also starting material **14** was recovered. Further experimentation revealed that the use of 2.5 equivalent of Li(O*t*-Bu)$_3$AlH was required to complete the reaction. In this way, an easily separable 10:1 mixture of **5** and **17**, respectively, was obtained in *ca.* 60% yield.[16] The formation of **5** can easily be explained by intramolecular trapping of the positive charge by the alkoxide substituent in the rearranged intermediate **16**. Because of the presence of a protected hydroxyl group at C(8) in **16**, the possible interference of a Grob fragmentation is blocked.[1b] The formation of a small amount of the exocyclic olefin **17** must proceed via an intramolecular elimination reaction. Remarkably, this latter elimination process is the chief pathway by which other *trans*-fused perhydronaphthalene 1,4-diol monosulfonate esters with a β-hydroxyl group at C(4) react upon treatment with strong base, while cyclic ether formation is only a minor reaction pathway.[17] The stereochemistry of **5** was established by its transformation to the known ketone **19**, thereby completing a formal total synthesis of furanether B. Upon treatment of **5** with $LiAlH_4$ and subsequent oxidation of the resulting alcohol **18**[18] with PDC, ketone **19** was obtained in 75% overall yield. The spectroscopic characteristics for **19** were identical with those reported in the literature.[4a,5]

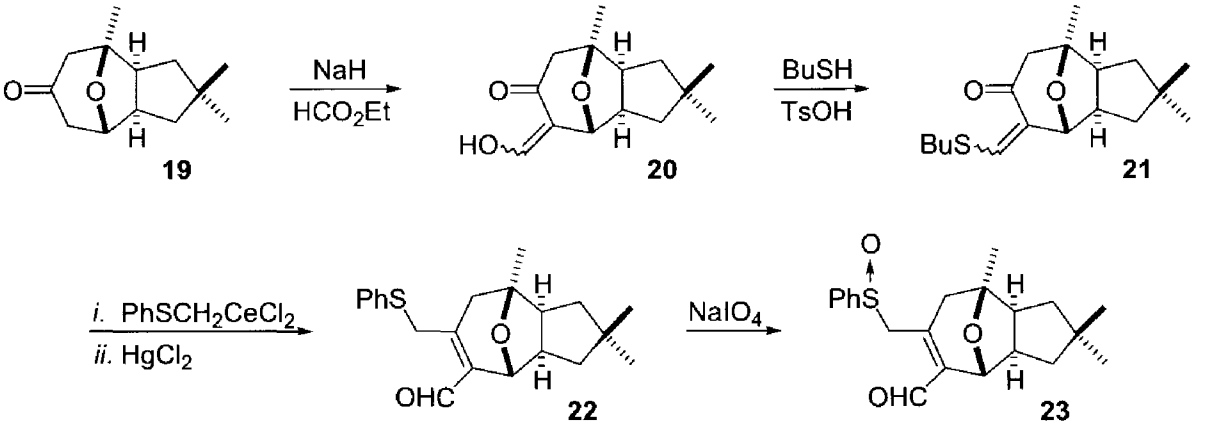
Scheme 5



Earlier research by Jansen and de Groot on the total synthesis of drimane sesquiterpenes has shown that γ-phenylsulfinyl-α,β-unsaturated aldehydes of type **A** could be converted regioselectively either to butenolide **C** or to butenolide **E**, depending on the reaction conditions

used (Scheme 5).[19] In order to test whether these Pummerer-induced cyclization reactions[20] could be employed also, as a common method, for the synthesis of the lactaranolides **31** and **32**, it was needed to prepare sulfoxide **23**. For that purpose, the reaction sequence outlined in Scheme 6 was followed. With a slightly modified formylation procedure,[21] the known thiomethylene derivative **21** was prepared in 84% overall yield.[22] The introduction of the carbon atom that ends up as C(14) in the final product was initially planned via addition of lithiated thioanisole[23] to the C(8) carbonyl group in **21**, immediately followed by $HgCl_2$-assisted hydrolysis of the adduct in dilute HCl.[24] Unfortunately, addition of lithiated thioanisole to **21** refused to give any workable result; mainly conjugate addition was observed. In sharp contrast, its cerium analog reacted very cleanly with **21**, affording the product of 1,2-addition almost exclusively.[25] After $HgCl_2$-assisted hydrolysis of the 1,2-adduct,[26] sulfide **22** was obtained in very good yield (84%). To ensure reproducible high yields in this reaction, sonication of a suspension of anhydrous $CeCl_3$ in dry THF turned out to be essential.[27] After oxidation of sulfide **22** with $NaIO_4$,[28] the desired sulfoxide **23** was obtained in quantitative yield.

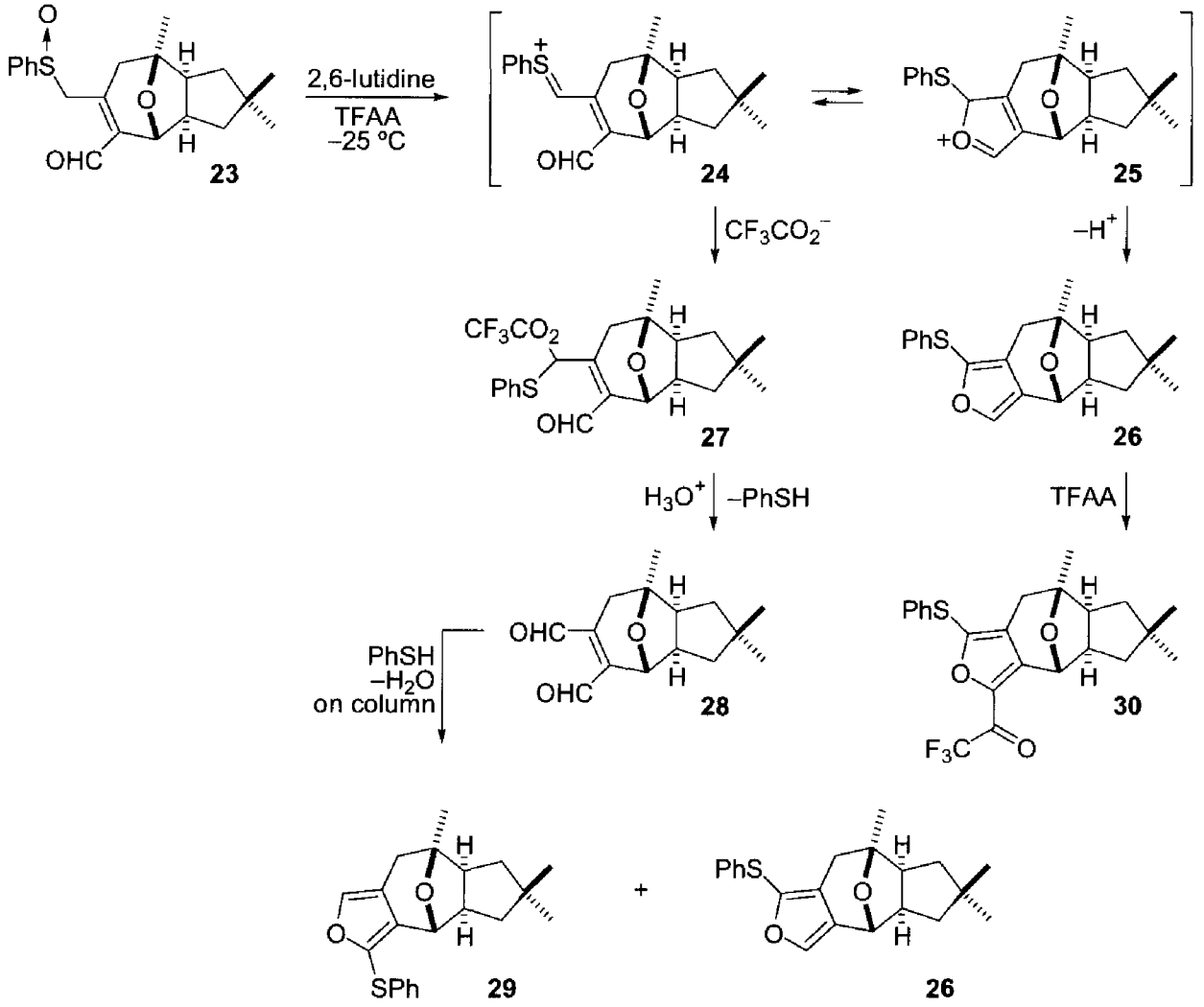
Scheme 6



With **23** in hand, the Pummerer-induced cyclization reactions toward the lactaranolides **31** and **32** could now be investigated. In contrast to the corresponding reactions in the drimane series (see Scheme 5), exposure of **23** to both Ac_2O at 110 °C[19a] and K_2CO_3 in aqueous dioxane at reflux temperature[19b] only led to complex product mixtures in which none of the expected products could be detected. It may be that, at the relatively high temperatures (>100 °C) used in these reactions, cleavage of the bridged ether function is responsible for these poor results. Therefore, trifluoroacetic anhydride (TFAA) at room temperature[29] was tried, but also in that case the outcome was disappointing. A more promising result was obtained by using excess of TFAA in combination with 2,6-lutidine.[30] In this way, an inseparable 5:1:4 mixture of the expected phenylthiofuran **26**, its regioisomer **29**, and the trifluoroacetylated compound **30**, respectively, was produced in *ca.* 70% yield.[31] By using 1 equivalent of both TFAA and 2,6-lutidine, the

formation of **30** could be suppressed and almost pure **26** was produced in 43% yield, together with 35% of the starting material **23**.

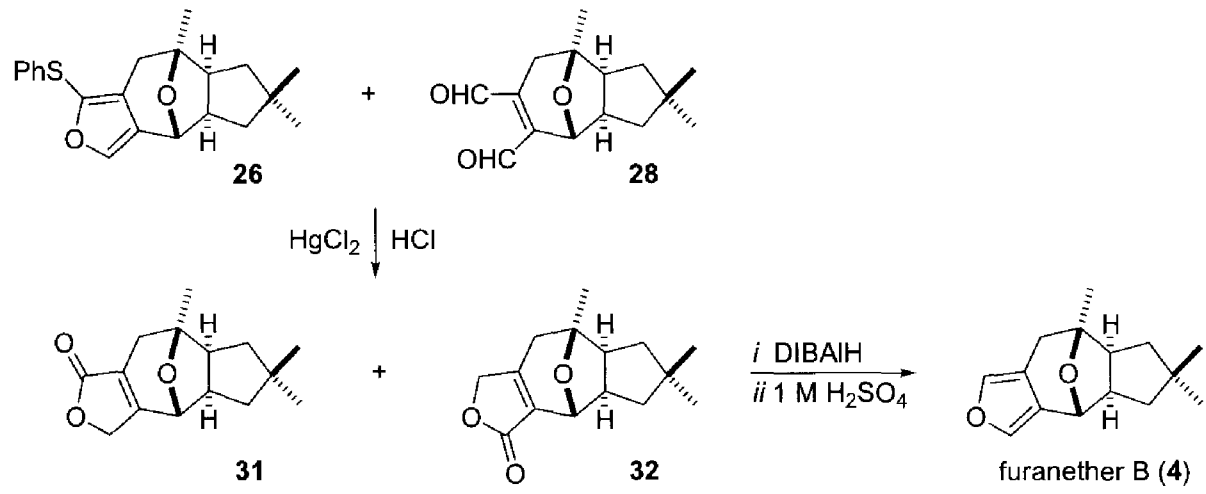
Scheme 7



Eventually, it was found that completion of the reaction without the undesired formation of **30** could be achieved by exposure of **23** to excess of both TFAA and 2,6-lutidine at –25 °C for about 1–2 days. After careful workup,[32] crude **26** was obtained, but ^{1}H NMR and GCMS analysis showed that the product contained considerable amounts of dialdehyde **28**[33] and thiophenol. An attempt to purify this crude **26** by silica gel chromatography led to an inseparable mixture of **26** (major) and **29** (minor) in modest yield, while **28** was not found anymore. These results suggest that, on column, some of **28** reacts with thiophenol to give **29** (and probably also additional **26**) before it decomposes.[34] Because it was expected that acid-catalyzed cyclization of dialdehyde **28** would lead to butenolide formation,[35] the above mixture of **26**, **28**, and thiophenol was directly treated with a $HgCl_2$-aqueous HCl mixture at 35 °C,[36] thereby avoiding the yield-lowering chromatography. In this way, the lactaranolides **31** and **32** were obtained as a 4:1 mixture,[37] respectively, in 80% yield.

These findings are fully compatible with the reaction sequence outlined in Scheme 7. The initially generated thionium ion **24** is either captured by the adjacent aldehyde group to give oxonium ion **25**, which subsequently deprotonates to afford the phenylthiofuran derivative **26**, or it reacts with the trifluoroacetate anion to produce the O,S-ketal **27**. Although **27** could not be detected,[38] its formation is highly probable because of finding both dialdehyde **28** and thiophenol in the crude product mixture after workup. A silica gel-catalyzed reaction of **28** with thiophenol explains the formation of **26** and **29** on column.

Scheme 8



The synthesis of furanether B was completed by reduction of the above 4:1 mixture of **31** and **32** with DIBALH at –78 °C followed by aromatization of the resulting mixture of lactols with 1 M aqueous H_2SO_4.[5] The spectroscopic data for **4** were identical with those reported in the literature.[3a,4a,5] Although **23** refused to react regioselectively to lactaranolide **32**, its regioisomer **31** could be produced as a single product by $HgCl_2$-induced hydrolysis of **26**,[39] albeit in modest overall yield (43% from **23**).

2.3 Conclusion

Summarizing these results, it may stated that the synthetic route toward furanether B (total yield 8.3% over 15 steps from **8**) represents another example of the applicability of the intramolecular base-induced rearrangement of 1,4-diol monosulfonate esters in natural product synthesis. The problems encountered in the regioselective annulation of the lactaranolides studied here contrast sharply with the ease by which the corresponding compounds in the drimane series are formed, and are probably brought on by the presence of the bridged ether function. Nevertheless, the successful completion of the total synthesis of furanether B demonstrates that

the annulation approach based on the Pummerer-induced cyclization reaction is a useful alternative for other furan and butenolide annulation methods.

2.4 Experimental Section

2.4.1 General

All reagents were purchased from Aldrich or Across and used without further purification, unless otherwise stated. All reactions were stirred by use of a magnetic strirring bar. Dry reactions were performed under a steady stream of dry nitrogen or argon with at 140 °C pre-dried glasswork. All ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-E 200 spectrometer. 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra were determined on a DPX 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). MS and HRMS data were obtained with a Finnigan Mat 95 spectrometer. MSD spectra were recorded on a HP 5973 spectrometer. FT-IR spectra were determined on a BIO-RAD FTS-7 infra-red spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with the concentrations denoted in units of g/100 mL. Analytical data were obtained using a Carlo Erba Elemental Analyzer 1106. Melting points are uncorrected. Solvents were freshly distilled by common practice. Product solutions were dried over Mg_2SO_4 prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. For flash chromatography, Merck silica gel 60 (230-400 Mesh) was used with mixtures of distilled ethyl acetate (EA) and petroleum ether bp 40-60 °C (PE) as eluents unless otherwise reported. Reactions were monitored by GC on a Fisons GC 8000 gas chromatograph with a flame ionization detector and a fused silica capillary column (DB-5+ or DB-17+), 30 m x 0.25 mm internal diameter, film thickness 0.25 μm and H_2 as carrier gas or by TLC on Merck silica gel $60F_{254}$ plastic sheets. GC peak areas were integrated electronically with a Fisons integrator DP700 or the Lab Systems X-Chrom integrating system. Compounds on TLC were visualized by UV detection and by spraying with basic $KMnO_4$ and subsequent heating.

2.4.2 Materials

The ketone **8** was prepared from the known Robinson annulation product **7**[7] as previously described.[1b] The compounds **3**,[1b] **4**,[4a,5] **18**,[4a] **19**,[4a,5] **20**,[4a] and **31**[5] were characterized before.

2.4.3 *Procedures and Spectral Data*

All ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$.

(3aα,4β,8β,8aα)-(±)-Decahydro-2,2,4,8-tetramethyl-4,8-epoxyazulene (3).

To a degassed solution of 0.152 g (0.50 mmol) of **1**[1b] in 10 mL of dry toluene was added 0.127 g (0.50 mmol) of Li(O*t*-Bu)$_3$AlH. The reaction mixture was refluxed for 2 h under argon, cooled to 0 °C, and then quenched with 0.5 mL of saturated aqueous Na_2SO_4. After being stirred at 0 °C for 20 min, the reaction mixture was diluted with 25 mL of EA, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to give 0.097 g (93 %) of **3** as a colorless oil. The NMR and mass spectral data for **3** were identical with those reported in the literature.[1b]

(4aα,5α,8aβ)-(±)-4a,5,6,7,8,8a-Hexahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(4*H*)-naphthalenone (9).

To a stirred solution of 56 mL of LDA (2.0 M in THF/heptane) in 100 mL of THF, cooled to –78 °C, was added dropwise a solution of 30.46 g (94.0 mmol) of **8** in 75 mL of THF over 1 h. The reaction mixture was stirred at –78 °C for 1.75 h, after which time 19 mL (0.15 mol) of TMSCl was added dropwise. The reaction mixture was allowed to come to rt, diluted with 100 mL of Et_2O, and filtered through a short pad of basic Al_2O_3. The filter cake was washed with Et_2O, and the filtrate was concentrated under reduced pressure. The remaining residue was taken up in 100 mL of THF, and added dropwise to an ice cold solution of 19.0 g (0.107 mol) of NBS in 150 mL of THF over 40 min. After being stirred at 0 °C for 1 h, the reaction mixture was allowed to come to rt and concentrated under reduced pressure to half its volume. After addition of 200 mL of H_2O, the two-phase mixture was separated, and the aqueous phase was extracted four times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was dissolved in 250 mL of DMF, and 17.4 g (0.235 mol) of Li_2CO_3 and 16.3 g (0.188 mol) of LiBr were added. The reaction mixture was heated at 140 °C for 2.5 h, allowed to come to rt, and filtered through a short pad of Hyflo. The filter cake was washed with 75 mL of DMF, and the filtrate was concentrated under reduced pressure to half its volume. After addition of 300 mL of H_2O, the aqueous layer was extracted four times with PE. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 20:1) to give 28.62 g (94%) of **9** as a yellow oil: ^{1}H NMR δ 0.04 (s, 3H), 0.05 (s, 3H), 0.80 (s, 3H), 0.87 (s, 9H), 0.92 (s, 3H), 0.97 (s, 3H), 1.18–1.41 (m, 3H), 1.61 (dd, J = 3.7, 12.9 Hz, 1H), 2.16 (ddd, J = 2.3, 2.5, 18.9 Hz, 1H), 2.40 (dd, J = 3.7, 12.5 Hz, 1H), 2.50 (dd, J = 5.9, 18.9 Hz, 1H), 3.66 (dd, J = 6.0, 10.2 Hz, 1H), 5.98 (dd, J = 2.5, 10.1 Hz, 1H), 6.81 (ddd, J = 2.3, 5.9, 10.1 Hz, 1H); ^{13}C NMR δ –4.79 (q), –3.96 (q), 10.20 (q), 18.00 (s), 25.76 (3q), 25.84 (q), 30.51 (s), 32.75 (t), 33.09 (q), 39.95 (t), 42.74 (s), 43.30 (t), 49.76 (d), 75.78 (d), 129.07 (d), 146.77 (d), 200.86 (s); MS *m/z* (r.i.) 322 (M^+, 2), 265 (100), 221

(5), 173 (8), 131 (8), 105 (9), 75 (50), 73 (13); HRMS calcd for $C_{19}H_{34}O_2Si$ (M^+) 322.2328, found 322.2327.

(2α,3α,4aβ,5β,8aα)-(±)-3,4,4a,5,6,7,8,8a-Octahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]naphth[2,3]oxiren-1(2*H*)-one (10).

To a stirred solution of 28.62 g (88.7 mmol) of **9** in 400 mL of MeOH were added 31 mL of 35% H_2O_2 and 45 mL of 1 M aqueous NaOH. After being stirred for 16 h, the reaction mixture was diluted with 400 mL of H_2O and 200 mL of brine, and extracted four times with Et_2O. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 20:1) to afford 21.41 g (71%) of **10** as a light yellow solid: mp 83–85 °C (from PE); ^{1}H NMR δ 0.03 (s, 3H), 0.06 (s, 3H), 0.73 (s, 3H), 0.87 (s, 12H), 0.94 (s, 3H), 1.10–1.40 (m, 4H), 1.91 (d, J = 15.4 Hz, 1H), 2.13 (dd, J = 4.9, 15.4 Hz, 1H), 2.82 (dd, J = 3.9, 12.4 Hz, 1H), 3.24 (d, J = 3.7 Hz, 1H), 3.52–3.65 (m, 2H); ^{13}C NMR δ –4.80 (q), –3.94 (q), 12.81 (q), 17.98 (s), 25.60 (q), 25.76 (3q), 30.31 (s), 32.34 (t), 33.03 (q), 37.33 (t), 43.19 (t), 44.55 (d), 46.61 (s), 55.26 (d), 57.29 (d), 75.61 (d), 208.50 (s); MS *m/z* (r.i.) 338 (M^+, 2), 281 (100), 161 (7), 123 (8), 119 (7), 105 (12), 75 (43), 73 (13); HRMS calcd for $C_{19}H_{34}O_3Si$ (M^+) 338.2277, found 338.2279. Anal. calcd for $C_{19}H_{34}O_3Si$: C, 67.42; H, 10.13. Found: C, 67.10; H, 10.19.

(3α,4aβ,5β,8aα)-(±)-3,4,4a,5,6,7,8,8a-Octahydro-3-hydroxy-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(2*H*)-naphthalenone (11).

To a stirred suspension of 19.24 g (101 mmol) of dry CuI in 150 mL of Et_2O, cooled to –25 °C, was added dropwise 105 mL of MeLi (1.6 M in Et_2O) over 12 min. To the resulting bright yellow solution was added dropwise a solution of 11.41 g (33.7 mmol) of **10** in 100 mL of Et_2O over 20 min. After being stirred at –25 °C for 1.5 h, the reaction mixture was quenched with 7.5 mL of saturated aqueous Na_2SO_4. The reaction mixture was allowed to come to rt and filtered through a short pad of Hyflo. The filtrate was dried and concentrated under reduced pressure, and the remaining residue was flash chromatographed (PE:EA = 5:1) to yield 7.37 g (64%) of **11** as a colorless oil: ^{1}H NMR δ 0.03 (s, 3H), 0.05 (s, 3H), 0.65 (s, 3H), 0.86 (s, 9H), 0.89 (s, 3H), 0.95 (s, 3H), 1.25–1.45 (m, 5H), 1.76 (br s, 1H (OH)), 2.20–2.45 (m, 3H), 2.74 (ddd, J = 2.0, 5.5, 13.0 Hz, 1H), 3.60 (dd, J = 6.1, 9.9 Hz, 1H), 4.11 (m, $W_{1/2}$ ≈ 22 Hz, 1H); ^{13}C NMR δ –4.70 (q), –3.95 (q), 11.83 (q), 18.04 (s), 25.85 (3q), 26.12 (q), 30.42 (s), 32.78 (t), 33.03 (q), 41.46 (s), 43.11 (t), 46.27 (t), 50.89 (t), 51.81 (d), 67.34 (d), 75.61 (d), 209.36 (s); MS *m/z* (r.i.) 340 (M^+, 4), 283 (46), 265 (59), 191 (53), 173 (35), 163 (52), 149 (43), 121 (31), 107 (31), 95 (34), 83 (40), 75 (100); HRMS calcd for $C_{19}H_{36}O_3Si$ (M^+) 340.2434, found 340.2431. Anal. calcd for $C_{19}H_{36}O_3Si$: C, 67.02; H, 10.66. Found: C, 66.54; H, 10.78.

(3α,4aβ,5β,8aα)-(±)-3-(Acetyloxy)-3,4,4a,5,6,7,8,8a-octahydro-4a,7,7-trimethyl-5-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(2*H*)-naphthalenone (12).

To a stirred solution of 11.20 g (33.0 mmol) of **11** in 100 mL of pyridine were added 10 mL of Ac_2O and a catalytic amount of DMAP. The reaction mixture was stirred at rt for 16 h, poured into 375 mL of ice cold 4 M aqueous HCl, and extracted four times with EA. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to yield 11.87 g (94%) of **12** as a white solid: mp 66–68 °C (from hexane); ^{1}H NMR δ 0.02 (s, 3H), 0.03 (s, 3H), 0.70 (s, 3H), 0.85 (s, 9H), 0.88 (s, 3H), 0.95 (s, 3H), 1.15–1.50 (m, 5H), 2.03 (s, 3H), 2.20–2.45 (m, 3H), 2.81 (ddd, J = 1.9, 5.8, 13.4 Hz, 1H), 3.59 (dd, J = 6.1, 9.9 Hz, 1H), 5.12 (m, $W_{1/2} \approx$ 23.5 Hz, 1H); ^{13}C NMR δ –4.72 (q), –4.00 (q), 11.64 (q), 18.02 (s), 21.24 (q), 25.81 (3q), 26.05 (q), 30.38 (s), 32.72 (t), 33.00 (q), 41.35 (s), 42.21 (t), 43.09 (t), 46.97 (t), 52.09 (d), 69.16 (d), 75.49 (d), 169.95 (s), 207.88 (s); MS *m/z* (r.i.) 325 (M^+–57, 17), 265 (69), 191 (27), 173 (15), 163 (14), 117 (100), 83 (19), 75 (47), 73 (19); HRMS calcd for $C_{17}H_{29}O_4Si$ (M^+–57) 325.1835, found 325.1828. Anal. calcd for $C_{21}H_{38}O_4Si$: C, 65.93; H, 10.01. Found: C, 65.66; H, 10.08.

(3α,4aβ,5β,8aα)-(±)-3-(Acetyloxy)-3,4,4a,5,6,7,8,8a-octahydro-5-hydroxy-4a,7,7-trimethyl-1(2*H*)-naphthalenone (13).

To a stirred solution of 12.99 g (34.0 mmol) of **12** in 200 mL of MeCN was added 15 mL of 40% aqueous HF. The reaction mixture was stirred at rt for 17 h, poured into 300 mL of saturated aqueous $NaHCO_3$, and extracted four times with EA. The combined organic layers were washed with brine, dried, and evaporated to give 8.73 g (95 %) of **13** as a white solid: mp 164–166 °C (from hexane/EA); ^{1}H NMR δ 0.75 (s, 3H), 0.92 (s, 3H), 0.99 (s, 3H), 1.30–1.62 (m, 5H), 2.03 (s, 3H), 2.28–2.46 (m, 3H), 2.52 (ddd, J = 1.9, 5.0, 12.6 Hz, 1H), 2.81 (ddd, J = 1.9, 5.8, 13.4 Hz, 1H), 3.66 (ddd, J = 5.4, 5.4, 10.8 Hz, 1H), 5.16 (m, $W_{1/2} \approx$ 24.0 Hz, 1H); ^{13}C NMR δ 11.29 (q), 21.15 (q), 26.02 (q), 30.52 (s), 32.74 (t), 32.85 (q), 40.83 (s), 41.76 (t), 42.67 (t), 46.89 (t), 52.01 (d), 68.94 (d), 74.94 (d), 170.00 (s), 207.65 (s); MS *m/z* (r.i.) 226 (M^+–42, 1), 208 (100), 193 (35), 190 (42), 175 (77), 167 (48), 139 (36), 123 (81), 122 (75), 109 (43), 96 (37), 43 (40); HRMS calcd for $C_{13}H_{22}O_3$ (M^+–42) 226.1569, found 226.1565. Anal. calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.68; H, 9.05.

(3α,4aβ,5β,8aα)-(±)-3-(Acetyloxy)-3,4,4a,5,6,7,8,8a-octahydro-4a,7,7-trimethyl-5-[(methylsulfonyl)oxy]-1(2*H*)-naphthalenone (14).

To a stirred solution of 8.73 g (32.5 mmol) of **13** in 100 mL of pyridine was added 3.8 mL (49.1 mmol) of MsCl. After being stirred at rt for 2 h, the reaction mixture was diluted with 450 mL of EA and washed successively with 4 M aqueous HCl (three times), saturated aqueous $NaHCO_3$ (twice), and brine. The organic layer was dried and evaporated, and the remaining residue was crystallized from EA to afford 6.86 g (61%) of **14** as a light yellow solid. The mother liquor was concentrated under reduced pressure and flash chromatographed (PE:EA = 1:1) to

give 4.31 g (38%) of another portion of 14: mp 128–129 °C; ^{1}H NMR δ 0.82 (s, 3H), 0.96 (s, 3H), 1.02 (s, 3H), 1.25–1.45 (m, 2H), 1.55–1.80 (m, 3H), 2.03 (s, 3H), 2.30–2.50 (m, 3H), 2.83 (ddd, J = 1.9, 5.8, 13.6 Hz, 1H), 3.02 (s, 3H), 4.70 (dd, J = 5.5, 11.4 Hz, 1H), 5.14 (m, $W_{1/2}$ ≈ 21.5 Hz, 1H); ^{13}C NMR δ 12.32 (q), 21.19 (q), 25.72 (q), 31.08 (s), 32.46 (t), 32.62 (q), 39.07 (q), 40.12 (s), 40.22 (t), 41.52 (t), 46.80 (t), 51.89 (d), 68.10 (d), 84.75 (d), 169.99 (s), 206.09 (s); MS *m/z* (r.i.) 286 (M^+–60, 9), 245 (19), 190 (100), 175 (43), 163 (45), 147 (18), 121 (30), 107 (19), 95 (21), 43 (53); HRMS calcd for $C_{14}H_{22}O_4S$ (M^+–60) 286.1239, found 286.1239. Anal. calcd for $C_{16}H_{26}O_6S$: C, 55.47; H, 7.57. Found; C, 55.17; H, 7.53.

(3aα,4β,6α,8β,8aα)-(±)-Decahydro-2,2,4-trimethyl-4,8-epoxyazulen-6-ol acetate (5).

The mesylate **14** (0.650 g, 1.88 mmol) was treated with Li(O*t*-Bu)$_3$AlH (2.5 equivalent) for 45 min as described for **1**. Workup and flash chromatography (PE:EA = 5:1) gave 0.248 g (53 %) of **5** as a colorless oil: ^{1}H NMR δ 0.87 (s, 3H), 1.02 (s, 3H), 1.09 (m, 1H), 1.16 (s, 3H), 1.25–1.35 (m, 2H), 1.60-2.00 (m, 5H), 2.03 (s, 3H), 2.76 (q, J = 8.5 Hz, 1H), 2.97 (q, J = 8.6 Hz, 1H), 3.88 (br d, J = 3.6 Hz, 1H), 5.04 (br t, J = 5.0 Hz, 1H); ^{13}C NMR δ 21.55 (q), 22.76 (q), 25.86 (q), 28.16 (q), 34.45 (t), 41.40 (s), 42.24 (t), 42.78 (t), 47.35 (t), 48.51 (d), 50.21 (d), 68.13 (d), 79.01 (d), 79.52 (s), 170.33 (s); MS *m/z* (r.i.) 252 (M^+, 14), 193 (86), 192 (100), 177 (41), 149 (95), 134 (24), 107 (25), 95 (32), 93 (22), 43 (33); HRMS calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1729.

Further elution afforded 0.022 g (5%) of **17**: ^{1}H NMR δ 0.96 (s, 3H), 1.09 (s, 3H), 1.47–1.75 (m, 6H), 2.02 (s, 3H), 2.17 (dd, J = 9.9, 12.3 Hz, 1H), 2.30 (m, 1H), 2.53 (m, 1H), 2.68 (dd, J = 3.4, 12.2 Hz, 1H), 2.94 (br q, J = 9.7 Hz, 1H), 3.85 (br t, J = 6.3 Hz, 1H), 4.89–5.02 (m, 3H); ^{13}C NMR δ 21.36 (q), 27.00 (q), 29.16 (q), 37.58 (s), 40.46 (t), 41.75 (t), 43.81 (t), 45.03 (d), 45.76 (d), 45.83 (t), 70.90 (d), 71.02 (d), 113.68 (t), 147.00 (s), 170.22 (s); MS *m/z* (r.i.) 192 (M^+–60, 78), 177 (57), 174 (37), 159 (68), 149 (29), 123 (42), 107 (39), 95 (44), 43 (100); HRMS calcd for $C_{13}H_{20}O$ (M^+–60) 192.1514, found 192.1510.

(3aα,4β,6α,8β,8aα)-(±)-Decahydro-2,2,4-trimethyl-4,8-epoxyazulen-6-ol (18).

To a stirred suspension of 0.60 g $LiAlH_4$ (15.8 mmol) in 100 mL of Et_2O was added dropwise a solution of 3.62 g (14.4 mmol) of **5** in 50 mL of Et_2O. The reaction mixture was stirred at rt for 1 h, cooled to 0 °C, and then carefully quenched with 2 mL of saturated aqueous Na_2SO_4. After addition of 150 mL of EA, the solution was dried and evaporated. The remaining residue was flash chromatographed (PE:EA = 3:1) to afford 2.43 g (81%) of **18** as a white solid: mp 72–73 °C; ^{13}C NMR δ 22.98 (q), 25.96 (q), 28.31 (q), 37.54 (t), 41.34 (s), 42.86 (t), 45.52 (t), 47.65 (t), 48.59 (d), 50.37 (d), 65.19 (d), 79.49 (d), 79.70 (s). The ^{1}H NMR and mass spectral data for **18** were identical with those reported in the literature.[4a]

(3aα,4β,8β,8aα)-(±)-Octahydro-2,2,4-trimethyl-4,8-epoxyazulen-6(1*H*)-one (19).

To a stirred solution of 2.43 g (11.6 mmol) of **18** in 100 mL of CH_2Cl_2 was added 6.5 g (17.3 mmol) of PDC. After being stirred at rt for 15 h, the reaction mixture was filtered over a short pad of Hyflo. The filtrate was concentrated under reduced pressure and flash chromatographed (PE:EA = 10:1) to give 2.25 g (93 %) of **19** as a colorless oil. The NMR and mass spectral data for **19** were identical with those reported in the literature.[4a,5]

(3aα,4β,8β,8aα)-(±)-Octahydro-7-(hydroxymethylene)-2,2,4-trimethyl-4,8-epoxy-azulen-6(1*H*)-one (20).

To a stirred suspension of 0.78 g (26.0 mmol) of NaH (80% dispersion in mineral oil) in 75 mL of Et_2O was added dropwise 0.5 mL (12.4 mmol) of MeOH at rt. After 5 min, a solution of 8.4 mL (0.10 mol) of ethyl formate and 2.25 g (10.8 mmol) of **19** in 50 mL of Et_2O was added dropwise over 30 min. The reaction mixture was stirred at rt for 1 h, carefully quenched with 1 mL of EtOH, and then mixed with 60 mL of H_2O. The two-phase system was separated, and the aqueous layer was acidified with concentrated aqueous HCl to *ca.* pH 2 and extracted three times with Et_2O. The combined organic layers were then extracted three times with 2 M aqueous KOH. The combined basic aqueous layers were cooled to 0 °C, acidified with concentrated aqueous HCl to *ca.* pH 2, and extracted three times with Et_2O. The combined organic layers were dried and evaporated to afford 2.47 g (95%) of crude **20**,[40] which was used in the next reaction without further purification. The NMR and mass spectral data for **20** corresponded with those reported in the literature.[4a]

(3aα,4β,8β,8aα)-(±)-7-[(Butylthio)methylene]octahydro-2,2,4-trimethyl-4,8-epoxy-azulen-6(1*H*)-one (21).

Compound **21** was prepared from 0.205 g (0.867 mmol) of **20** and 0.11 mL (1.03 mmol) of butanethiol as previously described.[4a] Workup and flash chromatography (PE:EA = 7:1) afforded 0.234 g (88 %) of **21** as a *ca.* 3.5:1 mixture of the *E* and *Z* isomers: ^{1}H NMR (major peaks) δ 4.38, 4.63 (s, s, 1:3.5 ratio, 1H), 6.65, 7.34 (s, s, 1:3.5 ratio, 1H); HRMS calcd for $C_{18}H_{28}O_2S$ (M^+) 308.1810, found 308.1809.

(3aα,4β,8β,8aα)-(±)-1,2,3,3a,4,7,8,8a-Octahydro-2,2,8-trimethyl-6-[(phenylthio)-methyl]-4,8-epoxyazulene-5-carboxaldehyde (22).

To a stirred fine dispersion of anhydrous $CeCl_3$ in 5 mL of THF (prepared from 0.714 g (1.92 mmol) of $CeCl_3 \cdot 7H_2O$ by heating at 140 °C under reduced pressure (0.1 mmHg) and sonication[27]), cooled to –78 °C, was added 3.7 mL of lithiated thioanisole (0.49 M in Et_2O)[41] over 10 min under argon. The mixture was stirred at –78 °C for 1.5 h, and then a solution of 0.286 g (0.930 mmol) of **21** in 3 mL of THF was added dropwise over 8 min. Stirring was continued at the same temperature for another 45 min, after which time 2 mL of saturated aqueous NH_4Cl was added. The reaction mixture was allowed to come to rt, diluted with 10 mL of THF, and filtered

through a short pad of Hyflo. The filter cake was washed three times with THF, and the filtrate was concentrated under reduced pressure. The remaining residue was dissolved in 5 mL of EtOH containing 4% H_2O, and then 0.301 g (1.11 mmol) of $HgCl_2$ was added. The mixture was stirred at rt for 5 min, diluted with 75 mL of Et_2O, and filtered through a short pad of Hyflo. The filtrate was washed three times with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 7:1) to give 0.267 g (84%) of **22** as a colorless oil: ^{1}H NMR δ 0.84 (s, 3H), 1.03 (s, 3H), 1.10–1.50 (m, 3H), 1.32 (s, 3H), 1.59 (m, 1H), 2.19–2.43 (m, 2H), 2.49, 2.55 (AB q, J_{AB} = 19.4 Hz, 2H), 3.33 (d, J = 13.2 Hz, 1H), 4.14 (d, J =13.2 Hz, 1H), 4.49 (s, 1H), 7.20–7.45 (m, 5H), 9.32 (s, 1H); ^{13}C NMR δ 22.75 (q), 25.87 (q), 28.20 (q), 34.93 (t), 41.09 (s), 42.96 (t), 44.07 (t), 45.79 (t), 51.91 (d), 55.53 (d), 74.66 (d), 79.99 (s), 128.76 (d), 129.13 (2d), 132.88 (s), 134.18 (2d), 141.49 (s), 148.87 (s), 185.94 (d); MS *m/z* (r.i.) 342 (M^+, 32), 250 (11), 248 (21), 233 (100), 215 (7), 206 (8), 191 (25), 161 (7), 125 (7), 95 (15); HRMS calcd for $C_{21}H_{26}O_2S$ (M^+) 342.1654, found 342.1654.

(3aα,4β,8β,8aα)-(±)-1,2,3,3a,4,7,8,8a-Octahydro-2,2,8-trimethyl-6-[(phenylsulfinyl)-methyl]-4,8-epoxyazulene-5-carboxaldehyde (23).

To a stirred solution of 0.171 g (0.50 mmol) of **22** in 10 mL of MeOH was added a solution of 0.167 g (0.78 mmol) of $NaIO_4$ in 1 mL of H_2O. After being stirred at rt for 3 d, the reaction mixture was diluted with 50 mL of MeOH and filtered through a short pad of Hyflo. The filtrate was concentrated under reduced pressure, and the remaining residue was taken up in 50 mL of Et_2O. The solution was washed with H_2O (twice) and brine, dried, and evaporated to give 0.177 g (99%) of **23** as a *ca.* 2:1 mixture of two diastereomers: ^{1}H NMR (major peaks) δ 0.86 (s, 3H), 1.04 (s, 3H), 1.17, 1.20 (s, s, 2:1 ratio, 3H), 3.60, 3.79 (B parts of AB q, J = 13.0 Hz, 2:1 ratio, 1H), 3.98, 4.19 (A parts of AB q, J = 13.0 Hz, ratio 1:2, 1H), 4.56, 4.59 (s, s, 1:2 ratio, 1H), 7.48–7.64 (m, 5H), 9.38, 9.56 (s, s, 1:2 ratio, 1H); ^{13}C NMR δ 22.38, 22.47 (q), 25.88 (q), 28.16, 28.21 (q), 41.05, 41.09 (s), 43.04 (t), 45.99, 46.08 (t), 47.35, 47.45 (t), 52.26, 52.32 (d), 55.45, 55.69 (d), 56.36, 56.78 (t), 74.99, 75.10 (d), 79.64, 79.76 (s), 124.28 (2d), 129.36 (2d), 131.78, 131.82 (s), 140.37 (s), 141.44, 141.68 (s), 144.93, 145.35 (s), 186.42, 187.11 (d); MS *m/z* (r.i.) 358 (M^+, 3), 343 (1), 342 (1), 341 (1), 233 (100), 205 (61), 191 (26), 81 (21), 69 (38), 43 (33); HRMS calcd for $C_{21}H_{26}O_3S$ (M^+) 358.1603, found 358.1600. Anal. calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31. Found: C, 70.20; H, 7.12.

(4α,4aβ,7aβ,8α)-(±)-4,4a,5,6,7,7a,8,9-Octahydro-6,6,8-trimethyl-1-(phenylthio)-4,8-epoxyazuleno[5,6-*c*]furan (26).

To a stirred solution of 37.2 mg (0.11 mmol) of **23** in 1 mL of CH_2Cl_2 were added 12.5 μL (0.11 mmol) of 2,6-lutidine and 15.5 μL (0.11 mmol) of TFAA under argon. The reaction mixture was stirred at rt for 25 min, quenched with 5 mL of saturated aqueous $NaHCO_3$, and diluted with 10 mL of Et_2O. The two-phase mixture was separated, and the organic layer was washed twice with 1 M aqueous HCl and four times with brine. The organic layer was dried and

evaporated, and the remaining residue was flash chromatographed (PE:EA = 10:1) to give 16.0 mg (43%) of **26** (GC purity >90%):[42] ^{1}H NMR δ 0.89 (s, 3H), 1.10 (s, 3H), 1.27–1.50 (m, 3H), 1.40 (s, 3H), 1.70 (m, 1H), 2.44–2.83 (m, 4H), 4.80 (s, 1H), 7.08–7.36 (m. 5H), 7.38 (s, 1H); ^{13}C NMR δ 23.51 (q), 26.03 (q), 28.31 (q), 36.00 (t), 41.47 (s), 42,87 (t), 45.95 (t), 51.02 (d), 55.88 (d), 75.18 (d), 80.12 (s), 126.02 (d), 126.51 (s), 126.94 (2 d), 128.68 (s), 129.04 (2 d), 136.17 (s), 136.69 (d), 137.50 (s); MS *m/z* (r.i.) 340 (M^+, 100), 325 (11), 297 (9), 269 (22), 231 (31), 187 (44), 145 (29), 91 (52), 77 (37), 43 (75); HRMS calcd for $C_{21}H_{24}O_2S$ (M^+) 340.1497, found 340.1500.

Further elution (PE:EA = 1:1) afforded 12.9 mg (35%) of starting material **23**.

(4α,4aβ,7aβ,8α)-(±)-4,4a,5,6,7,7a,8,9-Octahydro-6,6,8-trimethyl-4,8-epoxyazuleno-[5,6-*c*]furan-1(3*H*)-one (31) and its regioisomer 32.

To a stirred solution of 19.6 mg (0.055 mmol) of **23** in 1 mL of CH_2Cl_2, cooled to –35 °C, were added 30 μL (0.3 mmol) of 2,6-lutidine and 40 μL (0.3 mmol) of TFAA under argon. The reaction mixture was kept at –25 °C for 22 h, after which time another 20 μL (0.2 mmol) of 2,6-lutidine and 25 μL (0.2 mmol) of TFAA were added. After standing at –25 °C for an additional 22 h, the reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$ and diluted with 25 mL of Et_2O. The two-phase mixture was separated, and the organic layer was washed successively with 1 M aqueous HCl (twice), 1 M aqueous NaOH (twice), and brine (four times). The organic layer was dried and evaporated, and the remaining residue was dissolved in 3 mL of MeOH. After addition of 150 mg (0.55 mmol) of $HgCl_2$ and 1 mL of 4 M aqueous HCl, the solution was heated at 35 °C for 2.5 d. The reaction mixture was then diluted with 50 mL of Et_2O, washed four times with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1 to 1:1) to give 10.9 mg (80%) of a white solid which, according to GC and NMR analysis, appeared to be a *ca.* 4:1 mixture of **31** and **32**, respectively.[43] This mixture was used in the next reaction without separation. The NMR and mass spectral data for **31** (major component) corresponded with those reported in the literature;[5] those for **32** (minor component) are shown below.

32: ^{1}H NMR (major peaks) δ 0.85 (s, 3H), 1.05 (s, 3H), 1.39 (s, 3H), 4.50 (br s, 1H), 4.66 (br s, 2H); MS *m/z* (r.i.) 248 (M^+, 32), 233 (29), 215 (19), 206 (29), 191 (100), 145 (37), 105 (54), 95 (64), 77 (39), 43 (90); HRMS calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1402.

Furanether B (4).

Furanether B (**4**) was prepared from 8.3 mg (0.033 mmol) of the above 4:1 mixture of **31** and **32** in a fashion identical to that described for the conversion of **31** to **4**.[5] Workup and flash chromatography (PE:EA = 5:1) afforded pure **4** as a white solid in 99% yield: mp 58 °C (lit.[5] mp 62–63 °C). The NMR and mass spectral data for **4** were identical with those reported in the literature.[3a,4a,5]

2.5 References and Notes

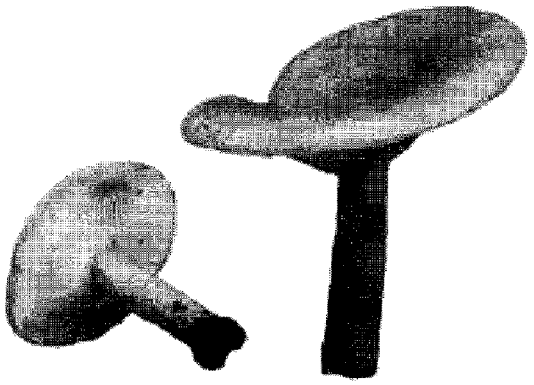
1. (a) Orru, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (b) Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (c) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240.
2. See paragraph 1.5.4.
3. (a) Battaglia, R.; De Bernardi, M.; Fronza, G.; Mellerio, G.; Vidari, G.; Vita-Finzi, P. *J. Nat. Prod.* **1980**, *43*, 319. (b) Vidari, G.; Vita Finzi, P. *Sesquiterpenes and other secondary metabolites of genus Lactarius (Basidiomycetes): chemistry and biological activity*; Elsevier: Amsterdam, **1995**; Vol. 17. (c) Daniewski, W. M.; Vidari, G. *Progress In The Chemistry Of Organic Natural Products* **1999**, *77*, 69.
4. (a) Price, M. E.; Schore, N. E. *J. Org. Chem.* **1989**, *54*, 5662. (b) Price, M. E.; Schore, N. E. *Tetrahedron Lett.* **1989**, *30*, 5865.
5. Molander, G. A.; Carey, J. S. *J. Org. Chem.* **1995**, *60*, 4845.
6. Davies, H. M. L.; Ahmed, G.; Rowen Churchill, M. *J. Am. Chem. Soc.* **1996**, *118*, 10774.
7. Heathcock, C. H.; Gray, D. *Tetrahedron* **1971**, *27*, 1239.
8. From a previous study,[1b] a relatively large quantity of **1** was available.
9. Torii, S.; Okumoto, H.; Nakayasu, S.; Kotani, T. *Chem. Lett.* **1989**, 1975.
10. Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922.
11. (a) Paulsen, H.; Eberstein, K.; Koebernick, W. *Tetrahedron Lett.* **1974**, 4377. (b) Rennecke, R.-W.; Eberstein, K.; Köll, P. *Chem. Ber.* **1975**, *108*, 3652.
12. McChesney, J. D.; Wycpalek, A. F. *J. Chem. Soc., Chem. Commun.* **1971**, 542.
13. (a) Bull, J. R.; Lachmann, H. H. *Tetrahedron Lett.* **1973**, 3055. (b) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819.
14. Li(O*t*-Bu)$_3$AlH is known to reduce ketones selectively in the presence of ester functions, see: Levine, S. G.; Eudy, N. H. *J. Org. Chem.* **1970**, *35*, 549.
15. It was assumed that reduction of the ketone function in **14** with Li(O*t*-Bu)$_3$AlH would proceed from the less sterically hindered α side.
16. As a minor side reaction, some elimination of the acetate group had taken place.
17. (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585.
18. The alcohol **18** was also produced by treatment of **14** with $LiAlH_4$ in refluxing toluene, but the yield of this reaction only amounted to 30%.
19. (a) de Groot, A.; Jansen, B. J. M. *J. Org. Chem.* **1984**, *49*, 2034. (b) Jansen, B. J. M.; Bouwman, C. T.; de Groot, A. *Tetrahedron Lett.* **1994**, *35*, 2977.
20. For a review of the Pummerer reaction, see: DeLucchi, O; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157.

21. The formylation procedure described in reference 4a gave **20** in only 42% yield.
22. It should be noted that the reported conversion[4a] of **21** to furanether B could not be achieved in acceptable yield.
23. (a) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097. (b) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1131.
24. A similar protocol has proven to be successful in the synthesis of annulated drimane sesquiterpenes.[19]
25. For a relevant report on organocerium reagents, see: Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
26. In contrast to corresponding reactions described in reference 19, the $HgCl_2$-assisted hydrolysis to **22** proceeded smoothly without using acid.
27. Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759.
28. Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.
29. Sharma, A. K.; Swern, D. *Tetrahedron Lett.* **1974**, 1503.
30. Jommi, G.; Pagliarin, R.; Sisti, M.; Tavecchia, P. *Synth. Commun.* **1989**, *19*, 2467.
31. By ^1H NMR and GCMS analysis of the 5:1:4 mixture, the following data for **29** were obtained: ^1H NMR ($CDCl_3$, main peaks) δ 0.82 (s, 3H), 1.05 (s, 3H), 1.39 (s, 3H), 4.77 (s, 1H); MS *m/z* (r.i.) 340 (M^+, 100), 325 (1), 297 (36), 269 (5), 231 (70), 203 (33), 115 (34), 91 (39), 77 (37), 43 (81); HRMS calcd for $C_{21}H_{24}O_2S$ (M^+) 340.1497, found 340.1503. For **30** these data were: ^1H NMR ($CDCl_3$, main peaks) δ 1.11 (s, 3H), 1.37 (s, 3H), 1.54 (s, 3H), 5.18 (s, 1H); MS *m/z* (r.i.) 436 (M^+, 68), 421 (6), 393 (11), 367 (14), 325 (20), 285 (9), 187 (13), 109 (36), 91 (31), 77 (32), 43 (100); HRMS calcd for $C_{23}H_{23}F_3O_3S$ (M^+) 436.1320, found 436.1321.
32. After being dried, the solution was concentrated under reduced pressure at –15 °C. If the solution was concentrated at room temperature, considerable amounts of **29** were detected in the remaining product mixture.
33. By ^1H NMR and GCMS analysis of the crude product mixture, the following data for **28** were obtained: ^1H NMR ($CDCl_3$, main peaks) δ 0.84 (s, 3H), 1.06 (s, 3H), 1.37 (s, 3H), 4.75 (s, 1H), 10.64 (s, 1H), 10.68 (s, 1H); MS *m/z* (r.i.) 248 (M^+, 9), 219 (23), 205 (35), 187 (22), 152 (43), 123 (39), 107 (40), 95 (51), 77 (50), 43 (100).
34. Lactarane dialdehydes are supposed to be highly reactive compounds, see: Sterner, O. Ph. D. Thesis, University of Lund, **1985**.
35. Jansen, B. J. M. Ph. D. Thesis, Wageningen Agricultural University, **1993**.
36. At room temperature, the reaction took more than two weeks to achieve completion.
37. The chromatographic separation of **31** and **32** appeared to be problematic.
38. Stable O,S-ketals formed in Pummerer rearrangements have been reported. For example, see: (a) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. (b) Padwa, A.; Kappe, C. O.; Cochran, J. E.; Snyder, J. P. *J. Org. Chem.* **1997**, *62*, 2786.

39. The reaction was performed with **26** obtained from the incomplete reaction of **23** with 1 equivalent of TFAA and 2,6-lutidine.
40. According to the ^{1}H NMR spectrum, **20** most likely consisted of a *ca.* 9:1 mixture of the intramolecularly hydrogen-bonded *Z*-isomer (one-proton singlet at δ 7.52) and the ketoaldehyde form (one-proton singlet at δ 9.58), respectively. Also, see reference 4a.
41. A solution of lithiated thioanisole (0.49 M in ether) was prepared by the following procedure. To a stirred solution of 0.9 mL (7.67 mmol) of thioanisole in 10 mL of ether was added 4.8 mL (7.68 mmol) of *n*-BuLi (1.6 M in hexane). The solution was heated at reflux temperature for 15 h and then cooled to rt.
42. GC analysis revealed the presence of small amounts (<5%) of **29** and **30**.
43. Pure **31** could be obtained upon treatment of **26**[39] with $HgCl_2$ and 4 M aqueous HCl at 35 °C.

Chapter 3

A Novel Route to Marasmane Sesquiterpenes via a Tandem Rearrangement-Cyclopropanation Reaction*

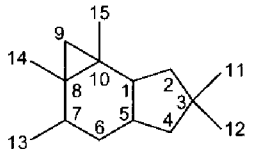


* Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* submitted.

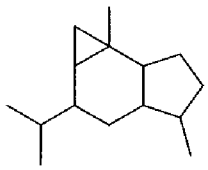
3.1 Introduction

The majority of marasmane sesquiterpenes[1] found in nature are secondary metabolites of fungi belonging to the genus of *Lactarius*.[2] Many of these compounds exhibit interesting physiological activities such as antifeedant, antifungal, and antibacterial.[2] The formation of marasmanes from a common precursor upon injury to the mushroom, together with the mentioned activities, provides evidence for the believe that these sesquiterpenes are involved in the chemical defense system against predators.[2] In contrast to the vast number of isolated marasmanes, only a few total syntheses of these compounds have been described.[2b]

Figure 1



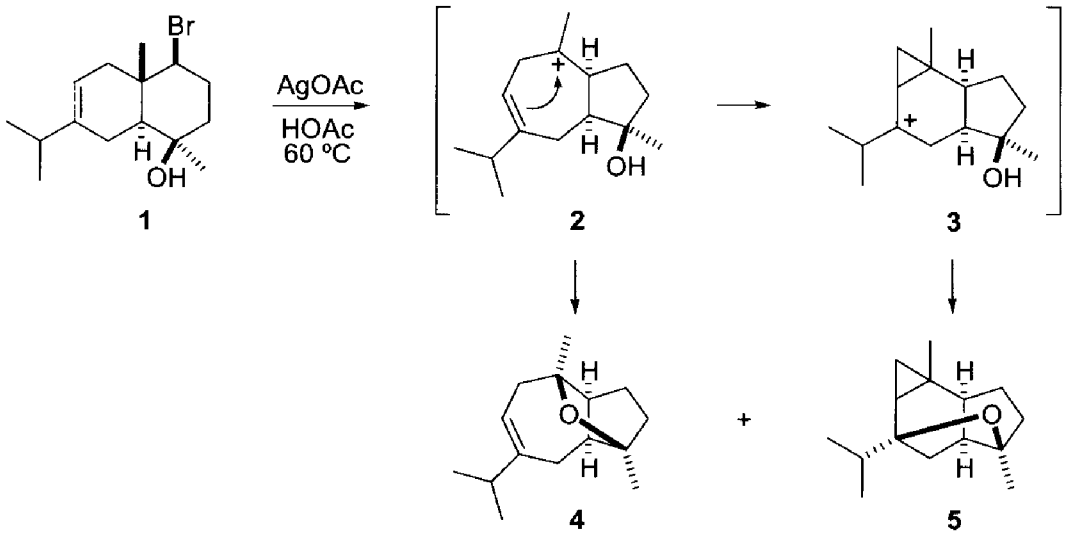
marasmane



ivaxillarane

The tricyclic core of marasmanes is also present in sesquiterpenes belonging to the very small group of ivaxillaranes (Figure 1).[3] Although not aiming at the synthesis of a particular ivaxillarane, Howard *et al.*[4] found that solvolytic rearrangement of the naturally occurring eudesmane **1** resulted in a *ca.* 70% yield of a 3:2 mixture of guaiane **4** and the ivaxillarane derivative **5**, the latter with unknown orientation of the cyclopropane ring (Scheme 1). The formation of compound **5** was explained by rearrangement of the initially formed homoallylic carbocation **2** to the cyclopropylcarbinyl cation **3**, and subsequent trapping of the newly formed

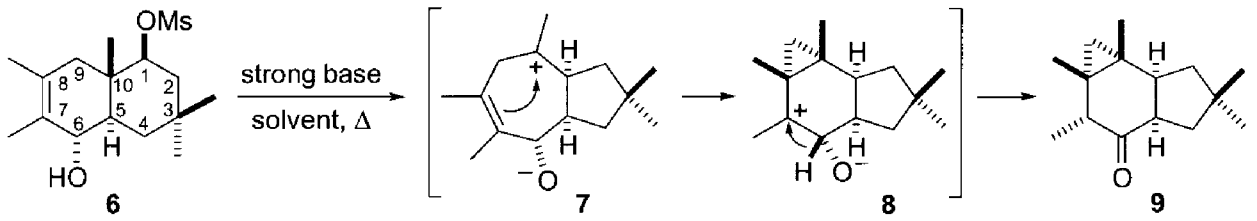
Scheme 1



1 2 3 4 5

positive center by the hydroxyl group. The outcome of this reaction suggests that it might be possible to convert an appropriately functionalized *trans*-fused octahydro-naphthalene system to the tricyclic cyclopropa[*e*]indene system present in marasmanes in one single step. In the next part of this Chapter a new synthetic approach toward the marasmane skeleton using the tandem rearrangement-cyclopropanation sequence as the key step is described.

Scheme 2

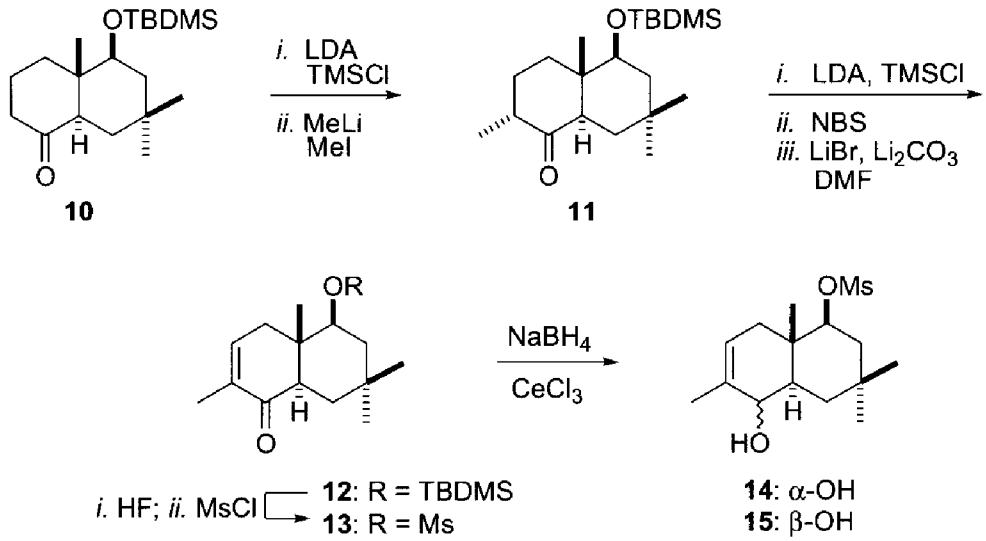


Mesylate **6** possessing an α-positioned hydroxyl group at C(6) was estimated to be a suitable substrate for studying this novel route to the marasmane skeleton (Scheme 2). The equatorial position of the hydroxyl group is essential because the presence of a β-hydroxyl group probably gives rise to formation of an ether bridge.[5] On the basis of our previous work on the chemical consequences of through-bond interactions (TBI) in *trans*-fused perhydronaphthalene-1,4-diol monosulfonate esters,[6] it was expected that in refluxing benzene or toluene a deprotonated hydroxyl group in **6** would induce ionization and rearrangement to carbocation **7** (Scheme 2). Successive rearrangement of **7** to the cyclopropylcarbinyl cation **8** followed by a stabilizing 1,2-H shift[7] was thought to give the marasmane ketone **9**. Because exploratory *ab initio* calculations[8] indicated that the cyclopropylcarbinyl cation **8** is much more stable (ΔE = 31.1 kcal mol^{-1}) than the corresponding cation with the opposite orientation of the cyclopropane ring, it was expected that **9** would have the same stereochemistry as found in naturally occurring marasmanes.

3.2 Results and Discussion

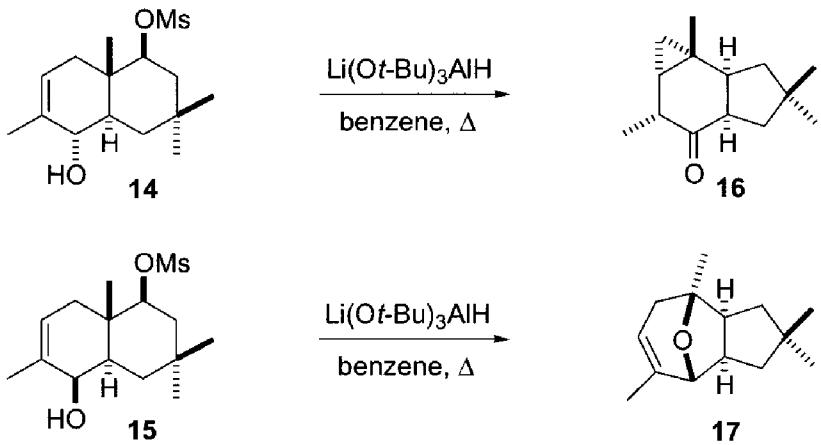
The first experiments were directed toward finding reaction conditions that allow selective formation of the tricyclic cyclopropa[*e*]indene skeleton present in marasmanes. For that purpose, the mesylate **14**, structurally identical to **6** but lacking the methyl group at C(8), was used as a model compound (Scheme 3). The synthesis of **14** started with the known compound **10**.[6d] Methylation of the silyl enol ether of **10** with MeLi and MeI[9] afforded ketone **11**. After introduction of the double bond via bromination of the silyl enol ether of **11** and subsequent dehydrobromination, the resulting enone **12** was treated successively with HF and MsCl to produce mesylate **13** in good overall yield. Reduction of enone **13** with $NaBH_4$ in the presence of $CeCl_3$[10] gave a separable mixture of **14** and **15** in a ratio of *ca.* 2:3. Attempts for the selective formation of **14** or the conversion of **15** in **14** under Mitsunobu conditions[11] were unsuccessful.

Scheme 3



With mesylate **14** available its conversion via the rearrangement-cyclopropanation mechanism could be investigated. It was found that treatment of **14** with 2.5 eq Li(O*t*-Bu)$_3$AlH in refluxing benzene for 22 h gave ketone **16** as the only identifiable compound in 36% yield (Scheme 4). The formation of **16** probably proceeded via a mechanism similar to that depicted in Scheme 2. Reduction of **16** by the bulky Li(O*t*-Bu)$_3$AlH was not expected to occur because of strong steric hindrance at both sides of the carbonyl group. The high-field signals at δ 0.12, 0.37, and 1.04 in the ^{1}H NMR spectrum of **16** and the presence of a doublet (δ 27.21, J = 158.6 Hz) and triplet (δ 15.24, J = 158.9 Hz) with large coupling constants in the ^{1}H-coupled ^{13}C NMR spectrum were diagnostic for the trisubstituted cyclopropane moiety. The relative stereochemistry of **16** was assigned on the basis of a 2D NOE NMR experiment.

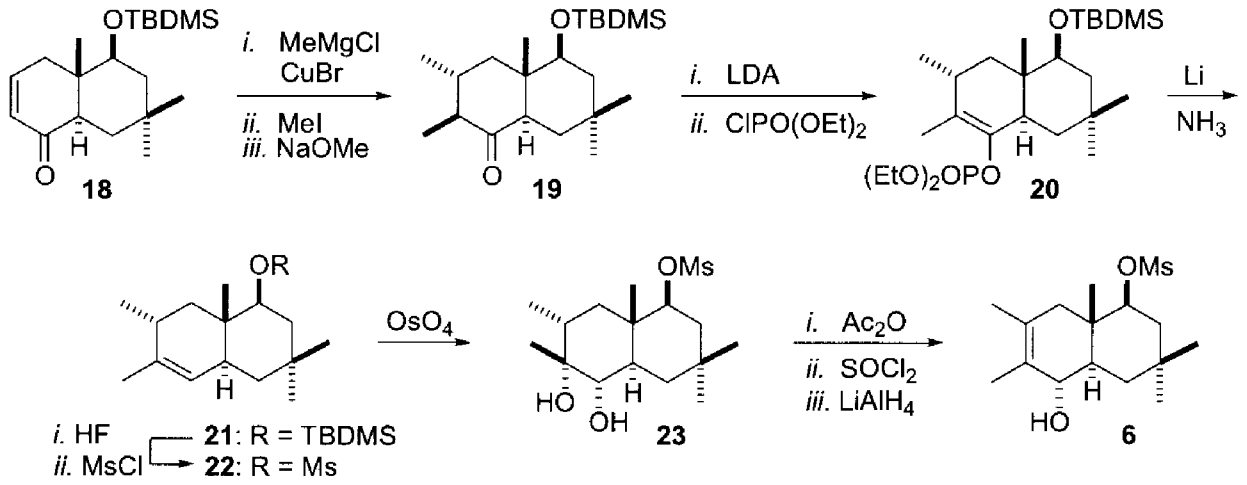
Scheme 4



Upon treatment of **15** with Li(O*t*-Bu)$_3$AlH under similar conditions as used for alcohol **14**, a fast reaction (1.75 h) yielded the bridged ether **17** in 68% (Scheme 4), thus confirming the expectation that a β-positioned hydroxyl group would lead to ether bridge formation.

Having demonstrated the feasibility of the approach, further studies toward the synthesis of the marasmane skeleton were focused on the rearrangement of compound **6**. To prevent the problems encountered for the synthesis of the α-hydroxyl moiety present in **14**, the introduction of this group in **6** was planned via selective osmylation of olefin **22**. Starting from the known enone **18**,[6f] the equatorial methyl groups in compound **19** were introduced through cuprate-catalyzed 1,4-addition of MeMgI, methylation of the resulting enolate, and epimerization (Scheme 5). Generation of the enolate of ketone **19** with LDA and trapping by diethyl chlorophosphate[12] gave compound **20**,[13] which upon treatment with lithium in liquid ammonia yielded alkene **21** as the sole product in good overall yield. Further transformation of **21** in **22** using standard procedures and dihydroxylation of **22** with a stoïchiometric amount of OsO_4[14] afforded selectively diol **23** in good yield. The large coupling constant (d, J = 10.7 Hz) observed for the H-6 signal at δ 3.10 in the ^{1}H NMR spectrum of **23**, is indicative for the α-orientation of the hydroxyl group at C(6). After protection of the secondary hydroxyl group in **23** as its acetate, the tertiary hydroxyl group was eliminated through addition of $SOCl_2$. Reductive cleavage of the protecting acetate group with $LiAlH_4$ yielded the desired α-alcohol **6**.

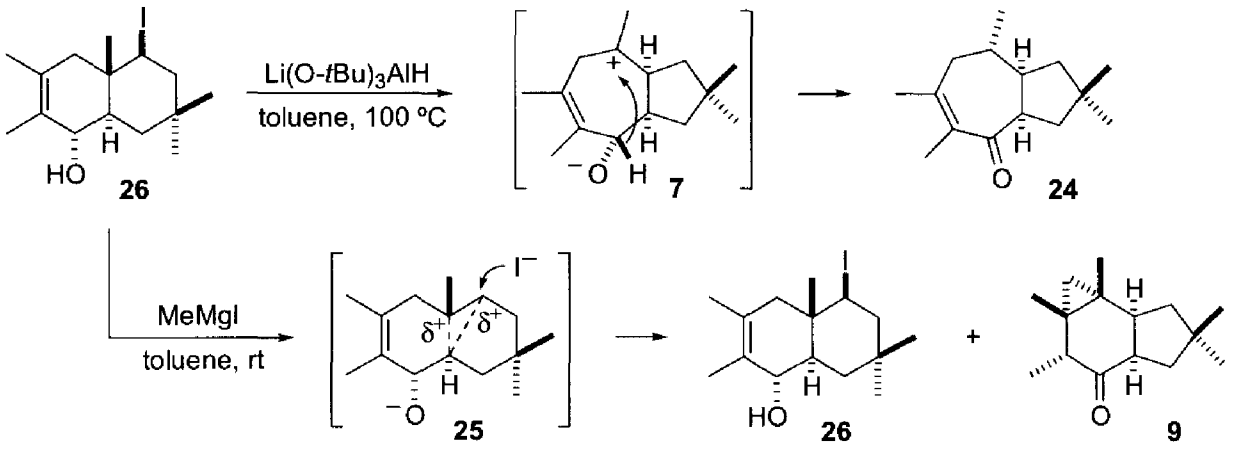
Scheme 5



When mesylate **6** was treated with Li(O*t*-Bu)$_3$AlH in toluene at 100 °C, the lactarane enone **24** was isolated as the main product (Scheme 6).[15] Apparently, a transannular hydride shift trapping the intermediate tertiary cation **7** was energetically more favorable than rearrangement to **9**. Upon treatment of mesylate **6** with MeMgI[16] in toluene at room temperature a smooth reaction was observed yielding a small amount of the desired marasmane ketone **9**[17] (6%) and, as major product (56%), the iodide **26** (Scheme 6). The splitting pattern of the H-1 signal (J = 13.0 and 4.3 Hz) at δ 4.40 in the ^{1}H NMR spectrum of **26** indicates that iodide **26** is formed with retention of

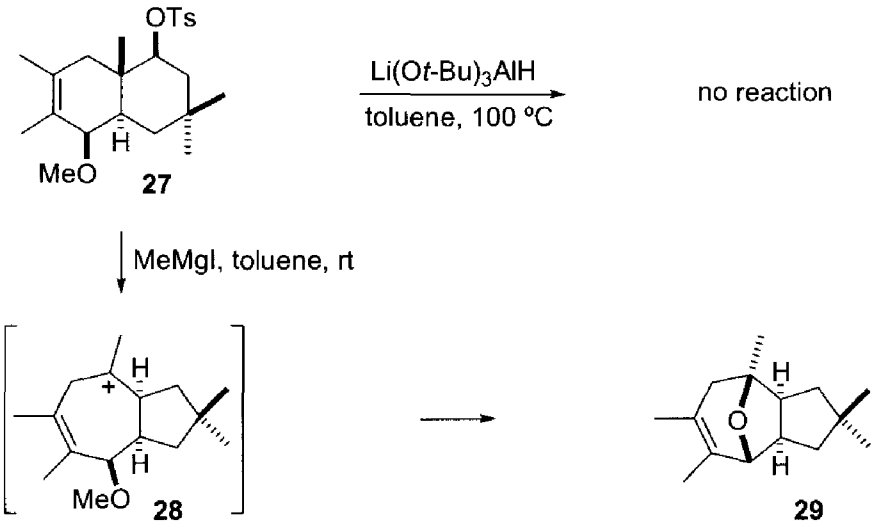
configuration suggesting the intermediacy of the bridged structure **25**.[18] Iodide formation was also observed on reaction of alcohol **14** with MeMgI, but to a lesser extent (31%) than in the reaction of **6** (56%). On the other hand, **14** gave more rearrangement-cyclopropanation product than **6** (22% of **16** versus 6% of **9**). This indicates that the pathway leading to **9** is energetically less favorable than the one leading to **16** probably[19] due to the increased steric interaction in the formation of intermediate **8** (Pitzer strain, Me versus H).

Scheme 6



The striking difference in reactivity of the mesylates **6** and **14** upon treatment with Li(O*t*-Bu)$_3$AlH in comparison with treatment with MeMgI can be explained by a faster heterolysis of the sulfonate ester bond through Lewis acid interaction with MeMgI or MgI_2 present via the Schlenk equilibrium.[20] Support for this hypothesis is found in the reactions of the protected alcohol **27**. Where exposure of **27** to MeMgI in toluene at room temperature resulted in the selective formation of the rearranged cyclic ether **29**, treatment of **27** with Li(O*t*-Bu)$_3$AlH in

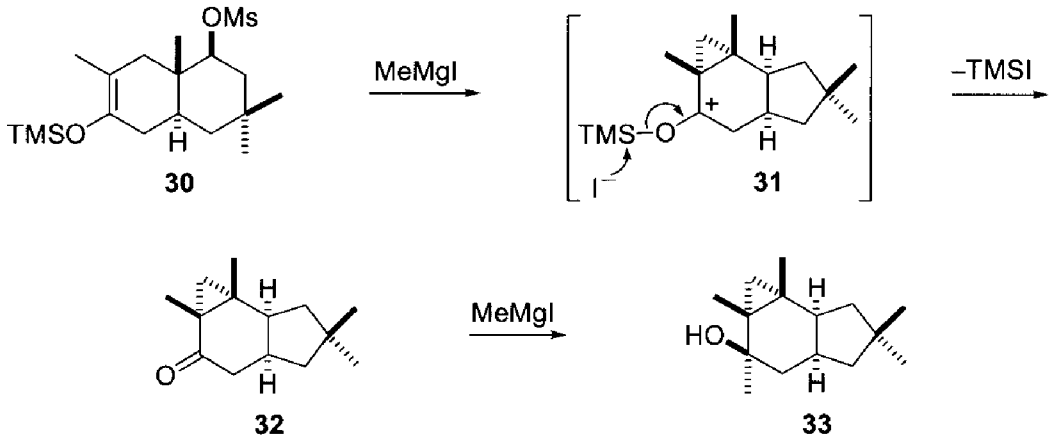
Scheme 7



refluxing toluene only gave recovered starting material (Scheme 7). This experiment clearly shows that the heterolysis of the sulfonate ester bond can exclusively be achieved by chelation with MeMgI or MgI_2 without involvement of TBI.[6] Further, the selective formation of cyclic ether **29** indicates that intramolecular stabilization of the homoallylic carbocation **28** through trapping by the proximate β-positioned methoxy group is preferred over nucleophilic attack by iodide.

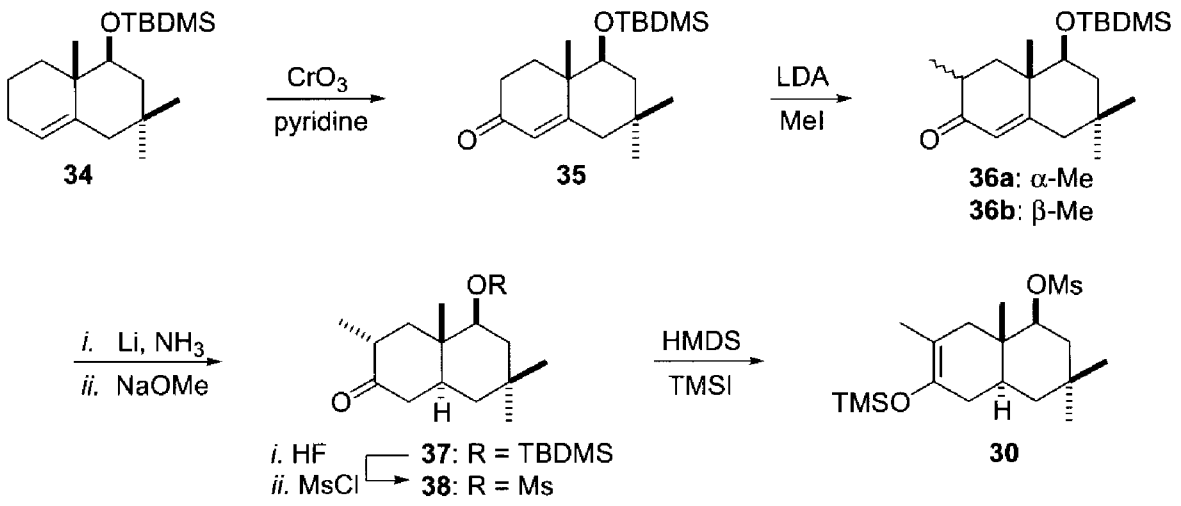
To overcome the high transition state energy leading to an intermediate like **8** and suppress iodide formation the cyclopropylcarbinyl cation must be much more stable than the homoallylic cation. On the basis of these considerations it was decided to investigate the reaction of silyl enol ether **30** with MeMgI (Scheme 8). Since the silyloxy group at C(7) would both increase the electron density of the double bond in **30** and effectively stabilize the cyclopropylcarbinyl cation **31**, a fast rearrangement of **30** to normarasmane ketone **32** was expected without appreciable iodide formation. Addition of MeMgI to ketone **32** would lead to the final product in this one-pot operation, the marasmane alcohol **33**.

Scheme 8



The synthesis of **30** started with allylic oxidation of the known olefin **34**[6d] with CrO_3-pyridine complex[21] yielding enone **35** in 83% yield (Scheme 9). Methylation of **35** gave **36** as a *ca.* 1:1 mixture of epimers (67% yield). Reduction of this mixture with Li in liquid NH_3 and subsequent epimerization afforded the *trans*-fused ketone **37**[22] as the sole product. Conversion of **37** to mesylate **38** without in between purification and treatment of **38** with HMDS and TMSI[23] completed the synthesis of the thermodynamically favored silyl enol ether **30**.

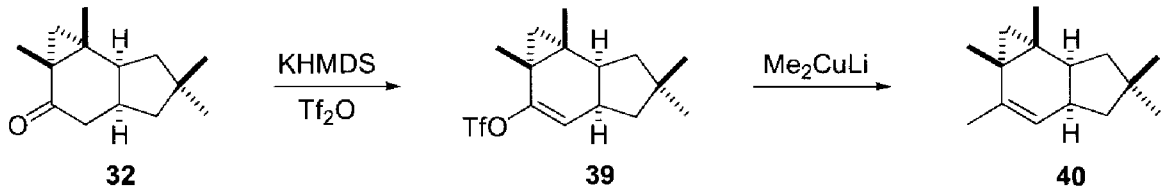
Scheme 9



When compound **30** was treated with excess MeMgI at room temperature, a fast reaction took place yielding a mixture of ketone **32**, the expected alcohol **33**, and most likely the trimethylsilyl ether of **33**. This reaction outcome clearly indicated that the enhanced electron density of the double bond and the intermediacy of the very stable oxonium ion **31** indeed resulted in an almost selective formation of rearrangement-cyclopropanation products. Column chromatography provided pure **32** and **33** in 25% and 17% yield, respectively, along with an impure sample of the trimethylsilyl ether of **33** (39%; GC purity *ca.* 85%). The structure of **32** was established by NMR spectroscopy. The presence of the cyclopropane ring was confirmed by the C(9) signal (t, $J_{CH} \approx$ 160 Hz) at δ 28.40 in the ^{1}H-coupled ^{13}C NMR spectrum. A NOE difference experiment in which selective irradiation of H-9α at δ 1.11 resulted in positive enhancements of the H-5 (δ 1.91), H-1 (δ 2.09), and H-6 (δ 2.21) signals was consistent with the assigned stereochemistry. The orientation of the methyl group at C(7) in **33** could not be estimated by NMR analysis, but was assumed to be α for steric reasons.[24] The isolation of ketone **32** could be explained by the action of MeMgI as a base resulting in enolization instead of alkylation. The formation of the silyl ether of **33** probably proceeded via silylation of alcohol **33** with TMSI generated during the reaction or by the addition of MeMgI to the oxonium ion **31**.

A selective formation of ketone **32** could be achieved in 73% yield when mesylate **30** was treated with MgI_2[25] under basic conditions.[26] Conversion of **32** with MeMgCl yielded the desired marasmane **33** as a single compound in 61% yield.

Scheme 10



Having developed an efficient route toward ketone **32**, the synthesis of marasmane **40**, with a characteristic C(6)-C(7) double bond frequently present in naturally occurring marasmanes,[2] was also investigated. Treatment of **32** with KHMDS[27] and Tf_2NPh afforded enol triflate **39** in 67% yield, which via a modified Stille coupling with Me_2CuLi[28] was converted to the $\Delta^{6,7}$-marasmene **40** in 60% yield (Scheme 10).

3.3 Conclusion

It can be concluded that this new synthetic route toward the marasmane skeleton is efficient and short. In eight or nine steps starting from the known alkene **34**, alcohol **33** and olefin **40** could be obtained in 17.0% and 11.2% overall yield, respectively. The key step in this approach, the tandem rearrangement-cyclopropanation reaction of appropriately functionalized decalins to marasmane-like products under the influence of magnesium salts, is new and proceeds selectively under very mild conditions.

3.4 Experimental Section

3.4.1 General Comments[29] and Materials

All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise.

Ketone **10** and olefin **34** were prepared as previously described.[6d] Enone **18** was obtained from ketone **10**.[6f]

3.4.2 Procedures and Spectral Data

(2α,4aβ,5β,8aα)-(±)-Octahydro-2,4a,7,7-tetramethyl-5-[[(1,1-dimethylethyl)dimethyl-silyl]oxy]-1(2*H*)-naphthalenone (11).

To a stirring solution of 2.025 g (6.25 mmol) of **10** in 50 mL THF, cooled to –78 °C, was added dropwise 3.75 mL LDA (2.0 M in THF/heptane) over 10 min. The solution was stirred at –78 °C for 1 h, and then 1.20 mL (9.38 mmol) of TMSCl was added. The reaction mixture was allowed to warm to rt, stirred for an additional 2 h, and filtered through a short pad of silica gel. The filter cake was washed with EA, and the filtrates were concentrated. The remaining residue was flash chromatographed (PE:EA 40:1) to give 2.215 g (89%) of a white solid. To a stirring solution containing 1.987 g (5.02 mmol) of this solid in 50 mL THF was added 3.8 mL MeLi (1.6 M in Et_2O). The solution was stirred at rt for 2.5 h, after which 0.95 mL (15.1 mmol) of MeI was added. After being stirred for another 1h, the reaction mixture was quenched with 25 mL of water

and extracted with PE. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 40:1) to give 1.489 g (88%) of **11** as a colorless oil: ^{1}H NMR δ 0.02 (s, 3H), 0.04 (s, 3H), 0.67 (s, 3H), 0.85 (s, 9H), 0.89 (s, 3H), 0.94 (s, 3H), 1.19 (d, *J* = 7.4 Hz, 3H), 1.19-1.33 (m, 4H), 1.45-1.70 (m, 2H), 1.75-1.86 (m, 1H), 2.00 (dt, *J* = 14.8, 5.9 Hz, 1H), 2.42-2.53 (m, 2H), 3.60 (dd, *J* = 10.2, 5.8 Hz, 1H); ^{13}C NMR δ –4.19 (q), –4.03 (q), 10.75 (q), 17.75 (s), 18.36 (q), 25.77 (3q), 26.09 (q), 28.39 (t), 30.40 (s), 32.09 (t), 32.79 (t), 33.15 (q), 43.32 (t), 43.68 (d), 44.95 (s), 47.71 (d) 75.85 (d), 216.36 (s); MS *m/z* (r.i.) 338 (M^+ 5), 281 (100), 189 (22), 133 (7), 119 (12), 95 (7), 75 (35), 73 (11); HRMS calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.2641, found 338.2644.

(4aα,5α,8aβ)-(±)-4a,5,6,7,8,8a-Hexahydro-2,4a,7,7-tetramethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(4*H*)-naphthalenone (12).

A solution of 3.712 g (10.98 mmol) of **11** in 30 mL of THF was added dropwise over 1 h to a stirring solution of 6.6 mL of LDA (2.0 M in THF/heptane) in 50 mL of THF at –78 °C. The reaction mixture was stirred at –78 °C for 5 h and, after addition of 2.1 mL (16.55 mmol) of TMSCl, allowed to come to rt. Most of the solvent was evaporated, and the concentrate was diluted with Et_2O and filtered through a short pad of basic Al_2O_3. The filter cake was washed with Et_2O, and the combined filtrates were concentrated. The remaining residue (4.93 g) was taken up in 25 mL of THF and added dropwise over 20 min to a stirring solution of 2.35 g (13.20 mmol) of NBS in 50 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 45 min, diluted with water, and extracted with PE. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was dissolved in 50 mL of DMF, and 2.03 g (27.5 mmol) of Li_2CO_3 and 1.91 g (22.0 mmol) of LiBr were added. The reaction mixture was heated at 120 °C for 1.5 h, allowed to come to rt, diluted with brine and water, and extracted with PE. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 40:1) to give 3.166 g (86%) of **12** as a colorless oil: ^{1}H NMR δ 0.02 (s, 3H), 0.03 (s, 3H), 0.75 (s, 3H), 0.85 (s, 9H), 0.89 (s, 3H), 0.95 (s, 3H), 1.15-1.37 (m, 3H), 1.60 (dd, *J* = 14.2, 3.1 Hz, 1H), 1.72 (br s, 3H), 2.15 (br d, *J* = 18.6 Hz, 1H), 2.34 (dd, *J* =13.0, 3.6 Hz, 1H), 2.44 (dd, *J* = 18.6, 6.1 Hz, 1H), 3.63 (dd, *J* = 10.2, 6.0 Hz, 1H), 6.52 (br d, *J* = 6.1 Hz, 1H); ^{13}C NMR δ –4.75 (q), –3.94 (q), 10.28 (q), 15.84 (q), 18.03 (s), 25.81 (3q), 25.89 (q), 30.60 (s), 33.10 (t), 33.17 (q), 39.90 (t), 42.93 (s), 43.30 (t), 49.62 (d), 75.94 (d), 134.70 (s), 141.36 (d), 201.02 (s); MS *m/z* (r.i.) 336 (M^+, 5), 295 (6), 279 (100), 203 (15), 187 (9), 177 (7), 135 (6), 119 (7), 75 (27), 73 (11); HRMS calcd for $C_{20}H_{36}O_2Si$ (M^+) 336.2486, found 336.2484.

(4aα,5α,8aβ)-(±)-4a,5,6,7,8,8a-Hexahydro-2,4a,7,7-tetramethyl-5-[(methylsulfonyl)oxy]-1(4*H*)-naphthalenone (13).

(12a). To a stirring solution of 1.021 g (3.04 mmol) of **12** in 25 mL of MeCN was added 1.75 mL of 50% aqueous HF. After being stirred at rt for 21 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed

with brine, dried, and evaporated to give 0.705 g of **12a** as a yellow oil: ^{1}H NMR δ 0.78 (s, 3H), 0.92 (s, 3H), 0.98 (s, 3H), 1.16-1.71 (m, 4H), 1.74 (br s, 3H), 1.98 (s, 1H (OH)), 2.18-2.50 (m, 3H), 3.68 (dd, *J* = 11.5, 4.9 Hz, 1H), 6.55 (m, 1H); ^{13}C NMR δ 10.05 (q), 15.85 (q), 25.91 (q), 30.78 (s), 33.07 (q), 33.14 (t), 42.54 (s), 43.01 (t), 49.53 (d), 75.51 (d), 134.79 (s), 141.19 (d), 200.90 (s); MS *m/z* (r.i.) 222 (M^+, 100), 207 (19), 189 (49), 139 (14), 137 (19), 123 (47), 110 (54), 82 (22), 41 (12), 40 (23); HRMS calcd for $C_{14}H_{22}O_2$ (M^+) 222.1629, found 222.1622.

(13). To a solution containing 0.660 g of **12a** in 10 mL of pyridine was added 0.35 mL (4.46 mmol) of MsCl. After being stirred at rt for 1 h, the reaction mixture was diluted with EA and washed successively with 4 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and evaporated, and the remaining residue was flash chromatographed (PE:EA = 2:1) to give 0.827 g (97%) of **13** as a white solid: ^{1}H NMR δ 0.86 (s, 3H), 0.97 (s, 3H), 1.02 (s, 3H), 1.26 (dd, *J* = 14.5, 12.7 Hz, 1H), 1.53-1.70 (m, 3H), 1.74 (br s, 3H), 2.40-2.48 (m, 3H), 3.00 (s, 3H), 4.74 (dd, *J* = 11.0, 6.1 Hz, 1H), 6.53 (m, 1H); ^{13}C NMR δ 11.07 (q), 15.77 (q), 25.53 (q), 31.30 (s), 32.78 (q), 32.82 (t), 38.96 (q), 39.08 (t), 40.39 (t), 41.60 (s), 49.35 (d), 86.04 (d), 134.97 (s), 140.43 (d), 199.19 (s); MS *m/z* (r.i.) 285 (M^+–15, 2), 204 (100), 189 (78), 176 (51), 161 (35), 123 (18), 109 (17), 82 (20), 79 (17), 55 (18), 41 (31); HRMS calcd for $C_{14}H_{21}O_4S$ (M^+–15) 285.1161, found 285.1154.

(1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-Octahydro-2,4a,7,7-tetramethyl-5-[(methylsulfonyl)oxy]-1-naphthalenol (14) and (1α,4aα,5α,8aβ)-(±)-1,4,4a,5,6,7,8,8a-octahydro-2,4a,7,7-tetramethyl-5-[(methylsulfonyl)oxy]-1-naphthalenol (15).

To a stirring solution of 0.200 g (0.667 mmol) of **13** in 7.5 mL of MeOH were added 0.255 g (0.684 mmol) of $CeCl_3$•$7H_2O$ and 0.259 g (6.84 mmol) of $NaBH_4$. After being stirred at rt for 30 min, the reaction mixture was quenched with 1M aqueous HCl, diluted with Et_2O, washed with brine. The organic layer was dried and evaporated, and the remaining residue was flash chromatographed (PE:EA = 7:1 to 2:1) to give in order of elution, 98.0 mg (49%) of **15** and 68.4 mg (34%) of **14**, both as colorless oils.

14: ^{1}H NMR δ 0.80 (s, 3H), 0.97 (s, 3H), 0.99 (s, 3H), 1.12 (d, *J* = 12.7 Hz, 1H), 1.45-1.77 (m, 5H), 1.71 (br s, 3H), 1.90-2.11 (m, 2H), 2.96 (s, 3H), 3.59 (br d, *J* = 8.6 Hz, 1H), 4.53 (dd, *J* = 10.1, 6.7 Hz, 1H), 5.39 (m, 1H); ^{13}C NMR δ 10.56 (q), 19.16 (q), 25.79 (q), 31.88 (s), 32.93 (q), 37.18 (t), 38.11 (t), 38.70 (s), 38.91 (q), 40.98 (t), 44.26 (d), 72.59 (d), 87.50 (d), 121.93 (d), 134.69 (s); MS *m/z* (r.i.) 302 (M^+, 39), 206 (100), 191 (47), 189 (21), 163 (31), 123 (21), 121 (27), 110 (33), 107 (20), 95 (21); HRMS calcd for $C_{15}H_{26}O_4S$ (M^+) 302.1552, found 302.1545.

15: ^{1}H NMR δ 0.94 (s, 3H), 0.98 (s, 3H), 1.01 (s, 3H), 1.12 (d, *J* = 9.7 Hz, 1H), 1.47 (br s, 1H (OH)), 1.57-1.68 (m, 4H), 1.76 (br s, 3H), 1.88 (br d, *J* = 17.4 Hz, 1H), 2.14 (dd, *J* = 17.4, 5.6 Hz, 1H), 2.96 (s, 3H), 3.72 (br s, 1H), 4.49 (dd, *J* = 8.6, 8.6 Hz, 1H), 5.44 (br d, *J* = 5.6 Hz, 1H); ^{13}C NMR δ 12.27 (q), 20.79 (q), 25.87 (q), 31.77 (s), 33.04 (q), 36.39 (s), 36.53 (t), 38.82 (t), 39.94 (q), 40.66 (d), 41.23 (t), 71.25 (d), 88.01 (d), 122.42 (d), 134.36 (s); MS *m/z* (r.i.) 302 (M^+, 60),

206 (100), 191 (40), 188 (35), 173 (40), 163 (35), 121 (24), 110 (25), 107 (24), 95 (25); HRMS calcd for $C_{15}H_{26}O_4S$ (M^+) 302.1552, found 302.1541.

(1aα,2β,3aβ,6aβ,6bα)-(±)-1,1a,3a,4,5,6,6a,6b-Octahydro-2,5,5,6b-tetramethylcyclopropa-[*e*]inden-3(2*H*)-one (16).

To a stirring solution of 68.4 mg (0.227 mmol) of **14** in 10 mL of degassed benzene was added 0.144 g (0.566 mmol) of Li(O*t*-Bu)$_3$AlH. The reaction mixture was refluxed for 22 h under Ar, cooled to rt, and then quenched with 1 mL of saturated aqueous Na_2SO_4. After being stirred for 5 min, the reaction mixture was diluted with Et_2O, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give 16.8 mg (36%) of **16** as a colorless oil: ^{1}H NMR (400 MHz) δ 0.12 (dd, *J* = 5.5, 4.8 Hz, H-9α), 0.37 (ddd, *J* = 8.3, 5.5, 1.3 Hz, H-9β), 0.98 (s, 3H), 1.04 (dddd, *J* = 8.3, 4.8, 3.0, 1.3 Hz, H-8) 1.09 (s, 3H), 1.10 (s, 3H), 1.10 (d, *J* = 6.5 Hz, 3H) 1.40 (dd, *J* = 13.1, 8.5 Hz, H-4β), 1.57 (t, *J* = 12.3 Hz, H-2β), 1.79 (ddd, *J* = 13.1, 9.4, 2.3 Hz, H-4α), 1.85 (ddd, *J* = 12.3, 6.8, 2.3 Hz, H-2α), 2.68 (ddd, *J* = 9.8, 9.4, 8.5 Hz, H-5), 2.82 (dddd, *J* = 12.3, 9.8, 6.8, 1.3 Hz, H-1), 3.07 (qdd, *J* = 6.5, 3.0, 1.3 Hz, H-7); ^{13}C NMR δ 15.21 (q), 15.24 (t), 18.64 (s), 24.28 (q), 27.21 (d), 27.32 (q), 29.79 (q), 38.76 (d), 40.37 (s), 45.43 (d), 46.04 (t), 48.33 (t), 49.84 (d), 216.23 (s); MS *m/z* (r.i.) 206 (M^+, 50), 123 (100), 110 (27), 107 (15), 95 (23), 82 (34), 81 (23), 67 (16), 55 (17), 41 (17); HRMS calcd for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1670.

(3aα,4β,8β,8aα)-(±)-1,2,3,3a,4,7,8,8a-Octahydro-2,2,5,8-tetramethyl-4,8-epoxyazulene (17).

The β-alcohol **15** (0.113 g, 0.374 mmol) was treated with 0.237 g of Li(O*t*-Bu)$_3$AlH (0.93 mmol) for 1.75 h as described for **14**. Workup and flash chromatography (PE:EA = 5:1) gave 51.9 mg (67%) of **17** as a colorless oil: ^{1}H NMR δ 0.85 (s, 3H), 1.01 (s, 3H), 1.10-1.60 (m, 4H), 1.23 (s, 3H), 1.63 (br s, 3H), 1.81 (dm, *J* = 17.6 Hz, 1H), 2.29 (dm, *J* = 17.6 Hz, 1H), 2.41 (q, *J* = 8.8 Hz, 1H), 2.71 (ddd, J = 9.8, 8.8, 8.3 Hz, 1H), 3.74 (s, 1H), 5.13 (br s, 1H); ^{13}C NMR δ 19.32 (q), 22.97 (q), 26.00 (q), 28.30 (q), 40.77 (t), 41.36 (s), 42.94 (t), 46.25 (t), 52.16 (d), 54.83 (d), 79.42 (s), 81.12 (d), 116.27 (d), 139.79 (s); MS *m/z* (r.i.) 206 (M^+, 56), 191 (26), 163 (27), 121 (19), 109 (40), 107 (38), 95 (18), 93 (18), 43 (30), 32 (100); HRMS calcd for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1673.

(2α,3β,4aα,5α,8aβ)-(±)-Octahydro-2,3,4a,7,7-pentamethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1(2*H*)-naphthalenone (19).

To a stirring mixture of 0.130 g (0.632 mmol) of CuBr•DMS and 1.1 mL (6.32 mmol) of HMPA in 15 mL of THF, cooled to –40 °C, was added dropwise 4.0 mL of MeMgI (1 M in Et_2O) over 5 min. After 15 min, a solution of 1.01 g (3.14 mmol) of **18** in 15 mL THF was added dropwise over 15 min, and stirring was continued at –40 °C for 1.25 h. After addition of 1.0 mL (16.1 mmol) of MeI, the reaction mixture was allowed to come to rt, stirred for 21 h, quenched

with saturated aqueous NH_4Cl, and diluted with water. After stirring for 30 min, PE was added, and the two-phase mixture was separated. The organic layer was washed twice with saturated aqueous NH_4Cl, dried, and evaporated. The remaining residue was taken up into 20 mL of NaOMe (1 M in MeOH) and heated at 60 °C for 20 h. The reaction mixture was allowed to come to rt, concentrated, and diluted with PE. The organic phase was washed with brine, dried, and evaporated to give 1.08 g of crude **19** as a yellow oil, which was used in the next reaction without further purification. Flash chromatography (PE:EA = 5:1) provided a pure sample: ^{1}H NMR (400 MHz, benzene-d_6) δ 0.17 (s, 3H), 0.18 (s, 3H), 0.84 (s, 3H), 0.92 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.99 (s, 3H), 1.08 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H), 1.40-1.75 (m, 7H), 2.06 (dd, J = 13.0, 4.0 Hz, 1H), 2.18 (ddd, J = 13.0, 3.0, 1.0 Hz, 1H), 3.61 (dd, J = 11.0, 5.0 Hz, 1H); ^{13}C NMR NMR (100 MHz, benzene-d_6) δ –4.33 (q), –3.74 (q), 11.92 (q), 12.39 (q), 18.46 (s), 21.39 (q), 26.24 (3q), 26.48 (q), 30.81 (s), 33.45 (q), 34.02 (t), 37.05 (d), 44.00 (t), 44.30 (s), 47.15 (t), 51.43 (d), 52.10 (d), 76.71 (d), 210.74 (s); MS *m/z* (r.i.) 352 (M^+, 3), 295 (100), 203 (24), 119 (10), 75 (24), 73 (8); HRMS calcd for $C_{21}H_{40}O_2Si$ (M^+) 352.2798, found 352.2798.

(3α,4aβ,5β,8aα)-(±)-3,4,4a,5,6,7,8,8a-Octahydro-2,3,4a,7,7-pentamethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-naphthalenyl diethyl phosphate (20).

To a stirring solution of 1.08 g (3.07 mmol) of crude **19** in 17.5 mL of THF was added 2.4 mL of LDA (2.0 M in THF/heptane). The solution was stirred at rt for 24 h, and then 1.3 mL (9.35 mmol) of Et_3N and 0.48 mL (3.32 mmol) of diethyl chlorophosphate were added. After 30 min, the reaction mixture was diluted with Et_2O and washed twice with 1 M aqueous HCl. The combined aqueous layer were back-extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. After drying and evaporation, the remaining residue was flash chromatographed (PE:EA = 3:1) to afford 1.07 g (70% from **18**) of **20** as a light yellow oil: ^{1}H NMR δ 0.02 (s, 6H), 0.70 (s, 3H), 0.85 (s, 9H), 0.93 (s, 3H), 0.94 (br s, 3H), 1.00 (d, J = 6.4 Hz, 3H), 1.09-1.61 (m, 5H), 1.31 (br t, J = 7.2 Hz, 6H), 1.63 (dd, J = 2.5, 2.5 Hz, 3H), 1.87 (dd, J = 12.7, 6.0 Hz, 1H), 2.13 (m, 1H), 2.35 (m, 1H), 3.38 (dd, J = 11.0, 5.0 Hz, 1H), 4.12 (dq, $^3J_{H,P}$ = 7.2 Hz, $^3J_{H,H}$ = 7.2 Hz, 4H); ^{13}C NMR δ –4.75 (q), –4.08 (q), 10.19 (q), 14.32 (q), 16.28 (2q; d, $^3J_{C,P}$ = 6 Hz), 18.08 (s), 20.17 (q), 25.89 (3q), 26.77 (q), 31.21 (s), 31.78 (d), 33.37 (q), 34.59 (t), 40.07 (d), 41.01 (s), 43.37 (t), 43.59 (t), 63.94 (2t; d, $^2J_{C,P}$ = 6 Hz), 75.31 (d), 122.94 (s; d, $^3J_{C,P}$ = 7 Hz), 141.88 (s; d, $^2J_{C,P}$ = 11 Hz); MS *m/z* (r.i.) 488 (M^+, 7), 334 (70), 277 (41), 269 (41), 211 (34), 203 (45), 202 (94), 199 (100), 187 (48), 155 (42), 75 (31); HRMS calcd for $C_{25}H_{49}O_5PSi$ (M^+) 488.3087, found 488.3083.

(1α,4aβ,7β,8aα)-(±)-1,2,3,4,4a,7,8,8a-Octahydro-3,3,6,7,8a-pentamethyl-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]naphthalene (21).

A solution of 1.07 g (2.19 mmol) of **20** and 0.82 mL (8.70 mmol) of *t*-BuOH in 15 mL of THF was added dropwise over 10 min to a stirring solution of 0.15 g (21.6 mmol) of Li in 25 mL of liquid NH_3 at –78 °C. After being stirred at –78 °C for 2.5 h, the reaction mixture was quenched

with 10 mL of MeOH and NH_3 was allowed to evaporate by standing at rt. The remaining layer was diluted with Et_2O and washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying and evaporation, the remaining residue was flash chromatographed (PE) to give 0.528 g (72%) of **21** as a colorless oil: ^{1}H NMR δ 0.00 (s, 3H), 0.01 (s, 3H), 0.66 (s, 3H), 0.73-1.57 (m, 5H), 0.87 (s, 9H), 0.91 (s, 3H), 0.92 (s, 3H), 0.98 (d, J = 6.7 Hz, 3H), 1.60 (br s, 3H), 1.89-2.16 (m, 2H), 1.94 (dd, J = 12.3, 6.3 Hz, 1H), 3.36 (dd, J = 11.2, 4.9 Hz, 1H), 4.92 (br s, 1H); ^{13}C NMR δ –4.69 (q), –4.07 (q), 9.54 (q), 18.12 (s), 19.96 (q), 20.94 (q), 25.93 (3q), 26.91 (q), 31.63 (s), 32.38 (d), 33.27 (q), 38.55 (d), 39.51 (s), 40.12 (t), 44.05 (t), 44.70 (t), 75.71 (d), 125.18 (d), 137.03 (s); MS *m/z* (relative intensity) 336 (M^+, 5), 279 (100), 203 (57), 199 (12), 119 (6), 75 (49), 73 (11); HRMS calcd for $C_{21}H_{40}OSi$ (M^+) 336.2848, found 336.2843.

(1α,4aβ,7β,8aα)-(±)-1,2,3,4,4a,7,8,8a-Octahydro-3,3,6,7,8a-pentamethyl-1-[(methyl-sulfonyl)oxy]naphthalene (22).

(21a). To a solution of 0.303 g (0.902 mmol) of **21** in a mixture of 5 mL of MeCN and 4 mL of Et_2O was added 0.5 mL of 50% aqueous HF. After being stirred for 3 h, the reaction mixture was diluted with Et_2O, washed with brine, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried and evaporated to give 0.205 g of **21a** as a pale yellow oil: ^{1}H NMR δ 0.68 (s, 3H), 0.91 (s, 6H), 0.99 (d, J = 6.7 Hz, 3H), 0.86-1.21 (m, 3H), 1.55 (br s, 1H (O<u>H</u>)), 1.60 (br s, 3H), 1.38-1.42 (m, 2H), 1.93-2.18 (m, 3H), 3.39 (dd, J = 9.1, 7.3 Hz, 1H), 4.92 (br s, 1H); ^{13}C NMR δ 9.23 (q), 19.75 (q), 20.87 (q), 26.83 (q), 31.67 (s), 32.18 (d), 33.12 (q), 38.47 (d), 38.97 (s), 39.99 (t), 43.34 (t), 44.01 (t), 75.30 (d), 124.85 (d), 136.89 (s); MS *m/z* (r.i.) 222 (M^+, 39), 207 (49), 204 (100), 189 (98), 175 (43), 161 (51), 137 (36), 119 (38), 109 (39), 85 (36); HRMS calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1986.

(22). To a solution of 0.205 g (0.901 mmol) of **21a** in 5 mL of pyridine was added 0.105 mL (1.36 mmol) of MsCl. The reaction mixture was stirred at rt for 2h, diluted with Et_2O, washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. Drying and evaporation gave an oily residue which was flash chromatographed (PE:EA = 20:1) to afford 0.263 g (97%) of **22** as a light yellow oil: ^{1}H NMR (benzene-d_6) δ 0.77 (s, 3H), 0.78 (s, 3H), 0.79 (s, 3H), 0.85 (dd, J =3.4, 1.5 Hz, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.97-1.11 (m, 2H), 1.55 (br s, 3H), 1,67 (d, J = 11.6 Hz, 1H), 1.76 (ddd, J = 6.5, 2.7, 0.9 Hz, 1H), 1.91-2.06 (m, 3H), 2.26 (s, 3H), 4.51 (dd, J = 11.5, 5.3 Hz, 1H), 4.85 (br s, 1H); ^{13}C NMR (benzene-d_6) δ 9.96 (q), 19.41 (q), 20.61 (q), 26.02 (q), 31.83 (s), 32.14 (q), 32.50 (d), 37.87 (d), 38.56 (s), 38.68 (q), 39.55 (t), 41.04 (t), 43.75 (t), 86.11 (d), 124.16 (d), 136.93 (s); MS *m/z* (r.i.) 300 (M^+, 18), 204 (100), 189 (94), 175 (35), 162 (28), 161 (33), 135 (22), 133 (24), 121 (21), 119 (39); HRMS calcd for $C_{16}H_{28}O_3S$ (M^+) 300.1759, found 300.1759.

(1α,2α,3α,4aβ,5β,8aα)-(±)-Decahydro-2,3,4a,7,7-pentamethyl-5-[(methylsulfonyl)oxy]-1,2-naphthalenediol (23).

To a stirring solution of 0.325 g (1.08 mmol) of **22** in 2.5 mL of pyridine, cooled at 0 °C, was added dropwise a solution of 0.275 g (1.08 mmol) of OsO_4 in 2.5 mL of pyridine. After being stirred at 0 °C for 15 min, the reaction mixture was diluted with 50 mL of EA and then, under vigorous stirring, mixed with 25 mL of saturated aqueous Na_2SO_3 and 10 mL of water. The two-phase mixture was stirred for 15 min and separated. The aqueous layer was extracted with EA, and the combined organic layers were washed successively with 1 M aqueous HCl, saturated aqueous Na_2SO_3, and brine. Drying and evaporation produced an oily residue which was flash chromatographed (PE:EA = 1:1) to give 0.271 g (75%) of **23** as a white solid: ^{1}H NMR δ 0.85 (s, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.98 (s, 6H), 1.07 (apparently t, J = 13.5 Hz, 1H), 1.22-1.70 (m, 8H), 1.25 (s, 3H), 1.95 (br s, 1H), 2.96 (s, 3H), 3.10 (br d, J = 10.7 Hz, 1H), 4.45 (dd, J = 9.2, 7.7 Hz, 1H); ^{13}C NMR δ 11.04 (q), 14.88 (q), 24.22 (q), 26.50 (q), 31.88 (s), 33.01 (q), 34.53 (d), 35.68 (t), 38.71 (s), 38.79 (q), 40.46 (d), 40.61 (t), 40.87 (t), 73.56 (s), 74.77 (d), 88.08 (d); MS *m/z* (r.i.) 334 (M^+, 5), 238 (40), 167 (33), 166 (36), 153 (65), 149 (34), 136 (27), 123 (25), 109 (32), 72 (100), 43 (29); HRMS calcd for $C_{16}H_{30}O_5S$ (M^+) 334.1814, found 334.1817.

(1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-Octahydro-2,3,4a,7,7-pentamethyl-5-[(methyl-sulfonyl)oxy]-1-naphthalenol (6).

(23a). To a stirring solution of 0.166 g (0.497 mmol) of **23** in 1 mL of pyridine and 5 mL of CH_2Cl_2, cooled to 0 °C, were added 8.5 mg (69.6 μmol) of DMAP and 60 μL (0.639 mmol) of Ac_2O. The reaction mixture was stirred at 0 °C for 40 min and then 0.145 mL (1.99 mmol) of $SOCl_2$ was added. After being stirred for another 20 min, the reaction mixture was diluted with Et_2O and washed successively with 1 M aqueous HCl and brine. The organic phase was dried and evaporated. The remaining residue was flash chromatographed (PE:EA = 3:1) to give 0.174 g (98%) of **23a** as a light yellow oil: ^{1}H NMR δ 0.85 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.04-1.22 (m, 4H), 1.50 (br s, 3H), 1.64 (br s, 3H), 1.62-1.74 (m, 2H), 2.00-2.13 (m, 1H), 2.08 (s, 3H), 2.99 (s, 3H), 4.56 (dd, J = 10.3, 6.6 Hz, 1H), 5.22 (br d, J = 9.4 Hz, 1H); ^{13}C NMR δ 10.63 (q), 14.00 (q), 19.65 (q), 21.07 (q), 25.73 (q), 31.74 (s), 32.82 (q), 36.90 (s), 38.19 (t), 39.00 (q), 40.76 (t), 41.40 (d), 44.19 (t), 75.64 (d), 86.82 (d), 123.68 (s), 129.36 (s), 171.42 (s); MS *m/z* (r.i.) 358 (M^+, 4), 301 (18), 205 (17), 202 (81), 187 (100), 146 (45), 133 (26), 124 (15), 119 (15), 42 (21); HRMS calcd for $C_{18}H_{30}O_5S$ (M^+) 358.1814, found 358.1820.

(6). To a stirred solution of 81 mg (0.226 mmol) of **23a** in 5 mL of Et_2O was added 12.7 mg (0.335 mmol) of $LiAlH_4$. After 20 min, the reaction mixture was quenched with brine, extracted with EA, and washed with brine. The organic phase was dried and evaporated to give 69.6 mg (97%) of a colorless oil which according to NMR analysis, was almost pure **6**: ^{1}H NMR δ 0.79 (s, 3H), 0.98 (s, 3H), 1.00 (s, 3H), 1.04-1.27 (m, 3H), 1.47 (ddd, J = 12.5, 8.5, 3.4 Hz, 1H), 1.58-1.72 (m, 2H), 1.62 (br s, 3H), 1.69 (br s, 3H), 1.88-2.08 (m, 2H), 2.99 (s, 3H), 3.58 (br d, J = 7.2 Hz, 1H), 4.55 (dd, J = 10.4, 6.5 Hz, 1H); ^{13}C NMR δ 10.50 (q), 14.29 (q), 19.69 (q), 25.76 (q),

31.88 (s), 32.91 (q), 37.26 (t), 37.97 (s), 38.94 (q), 40.93 (t), 44.34 (t), 44.45 (d), 73.85 (d), 87.41 (d), 126.70 (s), 127.54 (s); MS *m/z* (r.i.) 316 (M^+, 62), 301 (100), 220 (45), 205 (80), 177 (44), 124 (55), 123 (40), 121 (40), 95 (21), 55 (32); HRMS calcd for $C_{16}H_{28}O_4S$ (M^+) 316.1708, found 316.1709.

(3aα,8α,8aα)-(±)-1,2,3,3a,8,8a-Hexahydro-2,2,5,6,8-pentamethyl-4(7*H*)-azulenone (24).

To a stirring solution of 15.0 mg (47.5 μmol) of **6** in 3 mL of degassed toluene was added 38.5 mg (0.151 mmol) of Li(O*t*-Bu)$_3$AlH. The reaction mixture was heated at 100 °C for 3h and then cooled to rt. After dilution with Et_2O, the organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give 2.7 mg (26%) of **24** as a colorless oil: ^{1}H NMR (benzene-d_6) δ 0.72 (d, J = 6.5 Hz, 3H), 0.93 (s, 3H), 1.07 (apparently t, J = 12.6 Hz, 1H), 1.21-1.45 (m, 4H), 1.26 (s, 3H), 1.46 (br s, 3H), 1.72-2.06 (m, 2H), 1.84 (br s, 3H), 2.56 (dd, J = 13.7, 4.9 Hz, 1H), 2.98 (ddd, J = 9.8, 8.3, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 16.27 (q), 22.36 (2q), 30.00 (q), 30.32 (q), 37.70 (d), 38.34 (s), 41.07 (t), 46.85 (t), 47.03 (t), 50.86 (d), 55.64 (d), 139.92 (s), 144.32 (s), 205.21 (s); MS *m/z* (r.i.) 220 (M^+, 74), 205 (38), 177 (30), 124 (50), 123 (100), 121 (24), 96 (47), 95 (22), 81 (21), 41 (21); HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1824.

Further elution afforded 3.4 g (23%) of recovered starting material.

(1aα,2β,3aβ,6aβ,6bα)-(±)-1,1a,3a,4,5,6,6a,6b-Octahydro-1a,2,5,5,6b-pentamethylcyclopropa[*e*]inden-3(2*H*)-one (9) and (1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-octahydro-5-iodo-2,3,4a,7,7-pentamethyl-1-naphthalenol (26).

To a stirring solution of 20.6 mg (65.2 μmol) of **6** in 5 mL of degassed toluene was added 0.1 mL of MeMgI (0.8 M in Et_2O). After stirring at rt for 40 min, another 0.1 mL of MeMgI (0.8 M in Et_2O) was added, and stirring was continued for 45 min. The reaction mixture was quenched with brine and diluted with Et_2O. The organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to afford, in order of elution, 0.8 mg (6%) of **9** (GC purity ≈ 87%) and 12.7 mg (56%) of **26**, both as colorless oils.

9: IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR δ 0.01 (br d, J = 5.6 Hz, 1H), 0.28 (d, J = 5.6 Hz, 1H), 0.85-1.45 (m, 3H), 0.93 (s, 3H), 1.05 (s, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.11 (s, 3H), 1.13 (s, 3H), 1.60-1.90 (m, 2H), 2.60-2.85 (m, 2H); MSD *m/z* (r.i.) 220 (M^+, 12), 205 (7), 191 (6), 177 (10), 163 (7), 150 (12), 135 (9), 123 (100), 109 (27), 96 (36), 81 (39), 69 (17), 55 (20), 41 (29).

26: ^{1}H NMR δ 0.86 (s, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 1.03-1.25 (m, 3H), 1.51-1.84 (m, 3H), 1.62 (br s, 3H), 1.68 (br s, 3H), 1.98 (ddd, J = 13.4, 4.3, 2.1 Hz, 1H), 2.14 (apparently t, J = 13.2 Hz, 1H), 3.51 (br s, 1H), 4.40 (dd, J = 13.0, 4.3 Hz, 1H); ^{13}C NMR δ 14.34 (q), 14.40 (q), 19.59 (q), 25.22 (q), 32.60 (q), 35.21 (s), 37.82 (t), 38.52 (s), 44.93 (d), 49.22 (t), 49.40 (t), 49.60 (d), 75.66 (d), 126.85 (s), 128.20 (s); MS *m/z* (r.i.) 348 (M^+, 37), 221 (55), 205 (26), 203 (100), 149 (65), 133 (24), 123 (30), 119 (22), 83 (20), 73 (32), 43 (21), 41 (23); HRMS calcd for $C_{15}H_{25}OI$ (M^+) 348.0950, found 348.0948.

(1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-Octahydro-5-iodo-2,4a,7,7-tetramethyl-1-naphthalenol.

A stirred solution of 39.1 mg (0.129 mmol) of **14** in 10 mL of benzene was treated with 0.5 mL of MeMgI (1 M in Et_2O) for 35 min as described above for **6**. Workup and flash chromatography (PE:EA = 10:1) gave, in order of elution, 6.0 mg (23%) of **16** and 13.3 mg (31%) of (1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-octahydro-5-iodo-2,4a,7,7-tetramethyl-1-naphthalenol, both as colorless oils.

(1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-Octahydro-5-iodo-2,4a,7,7-tetramethyl-1-naphthalenol: ^{1}H NMR δ 0.91 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.21-1.27 (m, 1H), 1.43 (br s, 1H), 1.57-2.23 (m, 6H), 1.74 (s, 3H), 3.56 (br d, J = 9.0 Hz, 1H), 4.43 (dd, J = 13.1, 4.3 Hz, 1H), 5.40 (br d, J = 4.2 Hz, 1H); ^{13}C NMR δ 14.36 (q), 19.08 (q), 25.16 (q), 32.53 (q), 35.09 (s), 37.64 (t), 39.19 (s), 43.04 (t), 44.68 (d), 49.14 (t), 49.44 (d), 74.27 (d), 122.66 (d), 134.80 (s); MS *m/z* (r.i.) 334 (M^+, 2), 207 (61), 189 (100), 133 (12), 123 (32), 119 (13), 109 (8), 107 (10), 105 (8), 95 (17), 81 (10); HRMS calcd for $C_{14}H_{23}IO$ (M^+) 334.0786, found 334.0770.

(1α,4aβ,5β,8aα)-(±)-1,4,4a,5,6,7,8,8a-Octahydro-1-methoxy-2,3,4a,7,7-pentamethyl-5-naphthalenyl 4-methylbenzenesulfonate (27).

(19a). To a stirring solution of 0.773 g (2.20 mmol) of **19** in 10 mL of THF were added successively 0.56 mL (4.41 mmol) of TMSCl and 1.4 mL of LDA (2.0 M in THF/heptane). After stirring at rt for 1.5 h, additional amounts of 0.15 mL (1.18 mmol) of TMSCl and 0.3 mL of LDA (2.0 M in THF/heptane) were added. The reaction mixture was stirred at rt for another 40 min, then diluted with PE, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was back-extracted with PE, and the combined organic layers were dried and evaporated. To a solution of the remaining residue in 10 mL of THF, cooled to 0 °C, was added 0.471 g (2.65 mmol) of NBS. After being stirred at 0 °C for 20 min, the reaction mixture was come to rt, diluted with PE, and washed with water. The water layer was back-extracted with PE, and the combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried, and evaporated. The remaining residue was dissolved in 15 mL of DMF and treated with 0.438 g (5.93 mmol) of Li_2CO_3 and 0.411 g (4.73 mmol) of LiBr as described for the synthesis of **12**. Workup and flash chromatography (PE:EA = 20:1) gave 0.706 g (92%) of **19a** a light yellow oil: ^{1}H NMR δ 0.03 (s, 3H), 0.05 (s, 3H), 0.72 (s, 3H), 0.87 (s, 9H), 0.90 (s, 3H), 0.96 (s, 3H), 1.12-1.36 (m, 3H), 1.59 (dd, J = 15.6, 5.6 Hz, 1H), 1.72 (br s, 3H), 1.86 (br s, 3H), 2.13-2.40 (m, 3H), 3.61 (dd, J = 10.2, 5.9 Hz, 1H); ^{13}C NMR δ –4.69 (q), –3.95 (q), 10.36 (q), 10.89 (q), 18.08 (s), 21.59 (q), 25.83 (3q), 25.94 (q), 30.67 (s), 33.22 (q), 33.41 (t), 41.49 (s), 43.37 (t), 46.68 (t), 48.67 (d), 75.99 (d), 129.79 (s), 150.30 (s), 200.27 (s); MS *m/z* (r.i.) 350 (M^+, 6), 293 (100), 217 (10), 201 (12), 199 (6), 159 (6), 119 (7), 75 (24), 73 (9); HRMS calcd for $C_{21}H_{38}O_2Si$ (M^+) 350.2641, found 350.2643.

(19b). To a stirring solution of 0.706 g (2.02 mmol) of **19a** in 10 mL of MeCN was added 1 mL of 50% aqueous HF. After being stirred at rt for 21 h, the reaction mixture was diluted with EA and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried and

evaporated to give 0.473 g (99%) of **19b** as a white solid: ^{1}H NMR δ 0.75 (s, 3H), 0.92 (s, 3H), 0.99 (s, 3H), 1.15-1.47 (m, 4H), 1.63 (br d, J = 14.3 Hz, 1H), 1.73 (br s, 3H), 1.88 (br s, 3H), 2.28-2.52 (m, 2H), 2.30 (dd, J = 12.5, 3.7 Hz, 1H), 3.67 (dd, J = 11.5, 4.9 Hz, 1H); ^{13}C NMR δ 10.13 (q), 10.90 (q), 21.51 (q), 25.95 (q), 30.88 (s), 33.10 (q), 33.45 (t), 41.12 (s), 43.15 (t), 45.97 (t), 48.59 (d), 75.63 (d), 129.91 (s), 150.17 (s), 199.95 (s); MS *m/z* (r.i.) 236 (M^+, 90), 203 (66), 151 (21), 139 (64), 137 (39), 124 (100), 123 (25), 96 (42), 41 (15); HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1773.

(19c). To a solution of 0.102 g (0.432 mmol) of **19b** in 2 mL of pyridine was added 0.413 g (2.17 mmol) of TsCl. After being stirred at rt for 3 d, the reaction mixture was diluted with Et_2O and washed successively with 1 M aqueous HCl, 1 M aqueous NaOH, and brine. After drying and evaporation, the remaining residue was flash chromatographed (PE:EA = 5:1) to give 0.161 g (96%) of **19c** as a colorless oil: ^{1}H NMR δ 0.78 (s, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.12-1.65 (m, 4H), 1.70 (br s, 3H), 1.80 (br s, 3H), 2.19 (br s, 2H), 2.28 (dd, J = 12.5, 3.7 Hz, 1H), 2.44 (s, 3H), 4.54 (dd, J = 12.1, 4.8 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 10.87 (q), 11.11 (q), 21.41 (q), 21.69 (q), 25.40 (q), 31.18 (s), 32.74 (q), 33.05 (t), 39.79 (t), 40.38 (s), 45.19 (t), 48.46 (d), 86.77 (d), 127.81 (2d), 129.82 (2d), 129.92 (s), 134.44 (s), 144.80 (s), 149.89 (s), 198.48 (s); MS *m/z* (r.i.) 390 (M^+, 0.2), 375 (2), 218 (100), 203 (54), 190 (28), 189 (8), 175 (24), 124 (12), 123 (9), 91 (18); HRMS calcd for $C_{22}H_{30}O_4S$ (M^+) 390.1865, found 390.1858, HRMS calcd for $C_{21}H_{27}SO_4$ (M^+–15) 375.1630, found 375.1629.

Reduction of 19c. To a stirring solution of 0.161 g (0.413 mmol) of **19c** in 10 ml of Et_2O was added 23.8 mg (0.627 mmol) of $LiAlH_4$. After being stirred at rt for 30 min, the reaction mixture was quenched with brine and diluted with EA. The organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give, in order of elution, 82.8 mg (51%) of β-alcohol **19d** and 55.1 mg (34%) of α-alcohol **19e**, both as colorless oils.

19d: ^{1}H NMR δ 0.89 (s, 3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.06 (br d, J = 12.0 Hz, 1H), 1.33-1.83 (m, 7H), 1.50 (br s, 3H), 1.69 (br s, 3H), 2.42 (s, 3H), 3.65 (br s, 1H), 4.32 (dd, J = 12.0, 4.8 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, benzene-d_6) δ 12.91 (q), 16.73 (q), 19.57 (q), 21.29 (q), 26.02 (q), 31.78 (s), 33.24 (q), 37.09 (t), 37.60 (s), 41.02 (d), 41.21 (t), 45.61 (t), 72.64 (d), 88.42 (d), 127.27 (s), 127.61 (s), 128.34 (2d), 129.87 (2d), 136.03 (s), 144.22 (s).

19e: ^{1}H NMR (benzene-d_6) δ 0.72 (s, 3H), 0.76 (s, 3H), 0.85 (s, 3H), 0.95 (m, 1H), 1.21 (ddd, J = 12.4, 9.1, 3.4 Hz, 1H), 1.40 (br s, 3H), 1.44-1.88 (m, 6H), 1.62 (br s, 3H), 1.85 (s, 3H), 3.32 (br d, J = 9.0 Hz, 1H), 4.54 (dd, J = 11.8, 5.0 Hz, 1H), 6.74 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (benzene-d_6) δ 10.66 (q), 14.42 (q), 19.45 (q), 21.09 (q) 25.73 (q), 31.73 (s), 32.91 (q), 37.46 (t), 38.22 (s), 40.88 (t), 44.55 (t), 44.62 (d), 73.37 (d), 87.58 (d), 126.73 (s), 128.17 (2d), 128.29 (s), 129.70 (2d), 135.70 (s), 144.10 (s).

(27). To a stirring solution of 21.0 mg (53.6 μmol) of **19d** in 1 mL of DMF were added 8.4 mg (0.263 mmol) of NaH (75% dispersion in mineral oil) and 33 μL (0.530 mmol) of MeI. After

being stirred at rt for 19 h, the reaction mixture was quenched with brine and diluted with PE. The organic phase was washed with brine, dried, and evaporated to give 11.7 mg (54%) of **27** as a colorless oil. The aqueous layers were diluted with water and extracted with EA and Et_2O. The combined organic layers were dried and evaporated to yield 12.8 mg of impure **27**: ^{1}H NMR (benzene-d_6) δ 0.80 (s, 3H), 0.87 (s, 3H), 0.92 (m, 1H), 1.15 (s, 3H), 1.30-1.75 (m, 5H), 1.40 (br s, 3H), 1.69 (br s, 3H), 1.81 (s, 3H), 1.98 (br d, J = 16.1 Hz, 1H), 2.82 (d, J = 4.4 Hz, 1H), 3.19 (s, 3H), 4.57 (dd, J = 11.1, 5.6 Hz, 1H), 6.69 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H); ^{13}C NMR (benzene-d_6) δ 12.66 (q), 16.81 (q), 19.27 (q), 21.06 (q), 25.94 (q), 31.70 (s), 33.12 (q), 36.82 (t), 37.55 (s), 41.00 (t), 41.77 (d), 45.62 (t), 62.04 (q), 83.37 (d), 88.25 (d), 126.70 (s), 126.91 (s), 127.52 (2d), 129.61 (2d), 136.00 (s), 143.83 (s).

(3aα,4β,8β,8aα)-(±)-1,2,3,3a,4,7,8,8a-Octahydro-2,2,5,6,8-pentamethyl-4,8-epoxyazulene (29).

Under an argon atmosphere, a stirring solution of 11.7 mg (28.8 μmol) of **27** in 5 mL of degassed toluene was treated with 0.2 mL MeMgI (0.8 M in Et_2O) for 40 min as described for **6**. Workup and flash chromatography (PE:EA = 20:1) gave 5.4 mg (85%) of almost pure **29** as a light yellow oil: ^{1}H NMR δ 0.85 (s, 3H), 1.02 (s, 3H), 1.10-1.56 (m, 4H), 1.25 (s, 3H), 1.51 (br s, 3H), 1.60 (br s, 3H), 1.70 (br d, J = 17.5 Hz, 1H), 2.25 (br d, J = 17.5 Hz, 1H), 2.38 (apparently q, J = 8.9 Hz, 1H), 2.66 (apparently dt, J = 10.2, 8.4 Hz, 1H), 3.74 (s, 1H); ^{13}C NMR δ 15.06 (q), 17.50 (q), 23.00 (q), 26.07 (q), 28.34 (q), 41.44 (s), 43.00 (t), 46.33 (t), 46.43 (t), 52.15 (d), 54.44 (d), 80.24 (s), 81.91 (d), 121.63 (s), 131.66 (s); MS *m/z* (r.i.) 220 (M^+, 57), 205 (34), 177 (52), 135 (17), 123 (100), 121 (40), 109 (23), 107 (23), 43 (22), 32 (86); HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1829.

(4aα,5α)-(±)-4,4a,5,6,7,8-Hexahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-2(3*H*)-naphthalenone (35).

To a stirring solution of 1.514 g (4.92 mmol) of **34** in 90 mL CH_2Cl_2 was added 6.0 g (23.24 mmol) of CrO_3•(pyridine)$_2$.[21] The reaction was stirred at rt and, after 15.5 and 7 h, two other portions (6.0 g (23.24 mmol) and 1.7 g (6.58 mmol), respectively) of CrO_3•(pyridine)$_2$ were added. After being stirred at rt for a total time of 40 h, the reaction mixture was filtered through a short path of silica, which was washed with CH_2Cl_2. Evaporation of the combined filtrates and flash chromatography (PE:EA = 2:1) of the remaining residue gave 1.307 g (83%) of **35** as a light yellow oil: ^{1}H NMR δ 0.02 (s, 3H), 0.03 (s, 3H), 0.83 (s, 3H), 0.87 (s, 9H), 1.00 (s, 3H), 1.12 (s, 3H), 1.41 (ddd, J = 13.2, 4.9, 2.3 Hz, 1H), 1.57 (dd, J = 13.2, 11.5 Hz, 1H), 1.71 (m, 1H), 1.86 (dd, J = 14.3, 2.3 Hz, 1H), 2.08 (m, 1H), 2.25 (br d, J = 14.3 Hz, 1H), 2.33-2.42 (m, 2H), 3.53 (dd, J = 11.5, 4.9 Hz, 1H), 5.74 (br s, 1H); ^{13}C NMR δ –4.81 (q), –3.98 (q), 15.46 (q), 18.04 (s), 25.82 (3q), 25.88 (q), 32.07 (s), 32.21 (q), 33.97 (t), 34.97 (t), 41.53 (s), 43.56 (t), 45.56 (t), 75.78 (d), 126.84 (d), 167.95 (s), 199.65 (s); MS *m/z* (r.i.) 307 (M^+–15, 1), 265 (100), 209 (3), 199 (3),

129 (4), 105 (3), 75 (13), 73 (7); HRMS calcd for $C_{18}H_{31}O_2Si$ (M^+–15) 307.2093, found 307.2090.

(3α,4aβ,5β)-(±)-4,4a,5,6,7,8-Hexahydro-3,4a,7,7-tetramethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2(3*H*)-naphthalenone (36a) and (3α,4aα,5α)-(±)-4,4a,5,6,7,8-hexahydro-3,4a,7,7-tetramethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2(3*H*)-naphthalenone (36b).

To a stirring solution of 0.544 g (1.69 mmol) of **35** in 18 mL of THF were added 1.25 mL of LDA (2.0 M in THF/heptane) and, after 10 min, 0.210 mL (2.33 mmol) of MeI. The reaction mixture was stirred at rt for 30 min, quenched with brine, and diluted with Et_2O. The organic phase was washed with 1 M aqueous HCl and brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to afford 0.383 g (67%) of a 1:1 mixture of stereoisomers **36a** and **36b** as a colorless oil. A pure sample of **36a** was obtained from another reaction, after equilibration with NaOMe (1.0 M in MeOH) and flash chromatography (PE:EA = 7:1).

36a: ^{1}H NMR δ 0.01 (s, 3H), 0.03 (s, 3H), 0.82 (s, 3H), 0.88 (s, 9H), 0.99 (s, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.14 (s, 3H), 1.29-1.66 (m, 3H), 1.85 (dd, J = 14.6, 2.4 Hz, 1H), 2.08 (dd, J = 13.3, 4.7 Hz, 1H), 2.19-2.49 (m, 2H), 3.49 (dd, J = 11.5, 4.9 Hz, 1H), 5.72 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ –4.74 (q), –4.02 (q), 14.80 (q), 15.52 (q), 18.07 (s), 25.84 (4q), 31.97 (s), 32.23 (q), 36.99 (d), 42.18 (s), 43.85 (t), 44.45 (t), 45.19 (t), 76.30 (d), 126.49 (d), 166.67 (s), 201.91 (s); MS *m/z* (r.i.) 321 (M^+–15, 1), 293 (4), 279 (100), 199 (4), 187 (6), 143 (4), 119 (6), 75 (8), 73 (5); HRMS calcd for $C_{19}H_{33}O_2Si$ (M^+–15) 321.2250, found 321.2247.

36b: ^{1}H NMR (major peaks) δ 0.79 (s, 3H), 1.02 (s, 3H), 1.74 (dd, J = 12.2, 2.0 Hz, 1H), 3.84 (dd, J = 11.0, 5.1 Hz, 1H).

(3α,4aβ,5β,8aα)-(±)-3,4,4a,5,6,7,8,8a-Octahydro-3,4a,7,7-tetramethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2(1*H*)-naphthalenone (37).

A solution of 0.383 g (1.140 mmol) of a 1:1 mixture of **36a** and **36b** and 0.175 mL (1.83 mmol) of *t*-BuOH in 7.5 mL of THF was added dropwise over 10 min to a stirring solution of 45 mg (6.48 mmol) of Li in 25 mL of liquid NH_3, at –78 °C. After being stirred at –78 °C for 15 min, the reaction mixture was quenched with 3.51 g (65.6 mmol) of NH_4Cl and NH_3 was allowed to evaporate by standing at rt. The remaining layer was diluted with water and extracted with Et_2O. The combined organic layers were washed successively with 1 M aqueous HCl and brine, dried, and evaporated. The remaining residue was dissolved in 10 mL of Et_2O to which 5 mL of NaOMe (1.0 M in MeOH) was added. The reaction mixture was stirred at rt for 1.25 h, diluted with Et_2O, and washed successively with 1 M aqueous HCl and brine. Drying and evaporation gave 0.377 g of **37** as a colorless oil, which was used in the next reaction without further purification. A pure sample was obtained after flash chromatography (PE:EA = 10:1): ^{1}H NMR δ –0.01 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 0.89 (s, 3H), 0.91 (s, 3H), 0.99 (s, 3H), 0.99 (d, J = 6.4 Hz, 3H), 1.09-1.49 (m, 5H), 1.67 (tt, J = 13.0, 3.6 Hz, 1H), 2.02 (dd, J = 13.8, 3.7, 1H), 2.13 (t, J

= 6.6 Hz, 1H), 2.23 (d, J = 13.2 Hz, 1H), 2.40-2.57 (m, 1H), 3.35 (d, J = 11.3, 4.8 Hz, 1H); ^{13}C NMR δ –4.75 (q), –4.04 (q), 9.45 (q), 14.63 (q), 18.06 (s), 25.86 (3q), 26.64 (q), 31.81 (s), 33.01 (q), 39.83 (s), 40.89 (d), 41.13 (d), 41.36 (t), 43.82 (t), 44.10 (t), 47.72 (t), 76.08 (d), 213.22 (s); MS *m/z* (r.i.) 338 (M^+, 3), 281 (100), 189 (14), 145 (3), 133 (6), 119 (11), 95 (3), 75 (22), 73 (7); HRMS calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.2641, found 338.2639.

(3α,4aβ,5β,8aα)-(±)-3,4,4a,5,6,7,8,8a-Octahydro-3,4a,7,7-tetramethyl-5-[(methylsulfonyl)-oxy]-2(1*H*)-naphthalenone (38).

The 0.377 g of **37** was treated with 50% aqueous HF and MsCl as described for the synthesis of **22**. Workup and flash chromatography (PE:EA = 2:1) gave 0.295 g (86% from **36a** and **36b**) of **38** as a white solid: ^{1}H NMR δ 0.97 (s, 6H), 1.01 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.26 (dt, J = 13.1, 4.0 Hz, 2H), 1.70-1.86 (m, 4H), 2.04-2.16 (m, 2H), 2.23 (d, J = 14.6 Hz, 1H), 2.40-2.53 (m, 1H), 2.99 (s, 3H), 4.47 (t, J = 8.4 Hz, 1H); ^{13}C NMR δ 9.99 (q), 14.40 (q), 26.21 (q), 32.30 (s), 32.56 (q), 38.85 (s), 38.94 (q), 40.61 (2d), 40.79 (2t), 43.42 (t), 46.18 (t), 86.73 (d), 211.34 (s); MS *m/z* (r.i.) 302 (M^+, 20), 224 (15), 207 (21), 206 (39), 191 (23), 163 (16), 110 (100), 109 (17), 43 (17); HRMS calcd for $C_{15}H_{26}O_4S$ (M^+) 302.1552, found 302.1548.

(1α,4aβ,8aα)-(±)-1,2,3,4,4a,5,8,8a-Octahydro-3,3,7,8a-tetramethyl-6-[(trimethylsilyl)oxy]-1-[(methylsulfonyl)oxy]naphthalene (30).

To a solution of 0.283 g (0.937 mmol) of **38** in 40 mL of Et_2O were added 0.234 mL (1.11 mmol) of HMDS and 0.145 mL (1.02 mmol) of TMSI. The reaction mixture was stirred at rt for 2 h and, after addition of 0.215 mL (1.55 mmol) of Et_3N, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with Et_2O. The two-phase system was separated and the organic layer was washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying and evaporation the remaining residue was flash chromatographed on basic Al_2O_3 (PE:EA = 5:1) to afford 0.282 g (80%) of **30** as a colorless oil: ^{1}H NMR (benzene-d_6) δ 0.19 (s, 9H), 0.77 (s, 3H), 0.80 (s, 6H), 0.91-1.18 (m, 3H), 1.41-1.83 (m, 6H), 1.64 (s, 3H), 2.33 (s, 3H), 4.52 (dd, J = 12.2, 4.4 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 0.53 (3q), 9.59 (q), 16.37 (q), 25.41 (q), 31.67 (s), 32.48 (q), 34.02 (t), 36.04 (d), 37.43 (s), 37.97 (q), 40.49 (t), 41.19 (t), 43.06 (t), 86.66 (d), 109.17 (s), 141.31 (s); MS *m/z* (r.i.) 374 (M^+, 100), 279 (45), 278 (85), 263 (83), 207 (27), 173 (28), 141 (25), 110 (74), 43 (25); HRMS calcd for $C_{18}H_{34}O_4SSi$ (M^+) 374.1947, found 374.1939.

(1aα,3aβ,6aβ,6bα)-(±)-1,3,3a,4,5,6,6a,6b-Octahydro-1a,5,5,6b-tetramethylcyclopropa-[*e*]-inden-2(1a*H*)-one (32) and (1aα,2α,3aβ,6aβ,6bα)-(±)-decahydro-1a,2,5,5,6b-pentamethyl-cyclopropa[*e*]inden-2-ol (33).

A solution of 28.5 mg (76.2 μmol) of **30** in 5 mL of degassed toluene was treated with 0.5 mL of MeMgI (0.8 M in Et_2O) for 30 min as described above for **6**. Workup and flash chromatography (PE:EA = 5:1) gave in order of elution, 8.8 mg of an oil which mainly consisted

(*ca.* 60%) of the trimethylsilyl ether of **33**, 3.9 mg (25%) of **32**, and 2.9 mg (17%) of **33**, all as colorless oils.

32: ^{1}H NMR (400 MHz, benzene-d_6) δ 0.30 (d, J = 4.9 Hz, 1H), 0.82 (s, 3H), 0.91 (s, 6H), 1.00 (dd, J = 13.3, 3.4 Hz, 1H), 1.02 (t, J = 12.6 Hz, 1H), 1.11 (d, J = 4.9 Hz, 1H), 1.32 (s, 3H), 1.39 (dd, J = 13.3, 6.9 Hz, 1H), 1.44 (dd, J = 12.6, 6.6 Hz, 1H), 1.88 (dd, J = 19.1, 6.4 Hz, 1H), 1.91 (m, 1H), 2.09 (ddd, J = 12.6, 6.9, 6.6 Hz, 1H), 2.21 (dd, J = 19.1, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 14.49 (q), 20.63 (q), 28.40 (t), 30.81 (q), 31.40 (q), 32.77 (s), 34.87 (s), 36.09 (d), 37.44 (s), 40.75 (t), 43.71 (d), 45.84 (t), 49.57 (t), 208.50 (s); MS *m/z* (r.i.) 206 (M^+, 80), 191 (44), 178 (100), 164 (52), 163 (96), 136 (53), 123 (56), 121 (59), 107 (63), 95 (38); HRMS calcd for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1673.

33: ^{1}H NMR (400 MHz, benzene-d_6) δ –0.10 (d, J = 4.6 Hz, 1H), 0.46 (d, J = 4.6 Hz, 1H), 0.76 (br s, 1H), 0.92 (s, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.12 (s, 6H), 1.20 (dd, J = 14.8, 2.1 Hz, 1H), 1.40 (dd, J = 14.8, 8.6 Hz, 1H), 1.54-1.61 (m, 3H), 1.73 (dd, J = 12.3, 9.4 Hz, 1H), 2.04 (m, 1H), 2.43 (apparently dt, J = 10.9, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 14.88 (q), 22.21 (q), 23.82 (t), 25.21 (s), 27.22 (q), 29.26 (q), 29.46 (s), 29.90 (q), 32.01 (d), 37.96 (s), 39.50 (t), 42.00 (d), 48.39 (t), 50.95 (t), 73.54 (s); MS *m/z* (r.i.) 222 (M^+, 12), 204 (100), 189 (76), 175 (44), 162 (38), 139 (37), 133 (32), 123 (41), 119 (38), 109 (35), 95 (37); HRMS calcd for $C_{15}H_{26}O$ (M^+) 222.1984, found 222.1982.

Trimethylsilyl ether of 33: ^{1}H NMR (benzene-d_6, main peaks) δ –0.08 (d, J = 4.6 Hz, 1H), 0.20 (s, 9H), 0.43 (d, J = 4.6 Hz, 1H), 1.10 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.25 (s, 3H), 1.37 (s, 3H); MSD *m/z* 294 (M^+).

Treatment of 30 with MgI_2.

To a stirring solution of 63.6 mg (0.170 mmol) of **30** and 0.180 mL (0.853 mmol) of HMDS in 5 mL of degassed toluene was added 70.0 mg (0.252 mmol) of MgI_2. After being stirred at rt for 2 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with Et_2O. The organic phase was washed successively with water, 1 M aqueous HCl, and brine After drying and evaporation the remaining residue was flash chromatographed on basic Al_2O_3 (PE:EA = 20:1) to give 25.6 g (73%) of **32** as a colorless oil.

Treatment of 32 with MeMgCl.

To a stirring solution of 24.3 mg (0.118 mmol) of **32** in 5 mL of THF was added 0.1 mL of MeMgCl (3 M in THF). After stirring at rt for 1.25 h and 4.25 h, two other 0.1 mL-portions of MeMgCl (3 M in THF) were added. The reaction mixture was stirred at rt for an additional 4 h, quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic phase was washed with saturated aqueous NH_4Cl, dried, and evaporated. The remaining residue was flash chromatographed on basic Al_2O_3 (PE:EA = 10:1) to afford 16.1 mg (61%) of **33** as a colorless oil.

(1aα,3aβ,6aβ,6bα)-(±)-2-[(Trifluoromethylsulfonyl)oxy]-1,1a,3a,4,5,6,6a,6b-Octahydro-1a,5,5,6b-tetramethylcyclopropa[*e*]indene (39).

To a stirring solution of 10.0 mg (48.5 μmol) of **32** and 87.0 mg (0.244 mmol) of Tf_2NPh in 1.5 mL of a 2:1 mixture of THF and toluene, cooled to –78 °C, was added 0.5 mL of KHMDS (0.5 M in toluene). After being stirred at –78 °C for 2 h, the reaction mixture was quenched with brine and diluted with Et_2O. The organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 7:1) to give 11.0 mg (67%) of **39** as a colorless oil: ^{1}H NMR (benzene-d_6) δ 0.23 (d, J = 4.7 Hz, 1H), 0.85 (s, 6H), 0.94 (s, 3H), 1.05 (d, J = 13.3, 1.6 Hz, 1H), 1.15 (s, 3H), 1.18-1.50 (m, 4H), 1.92-2.07 (m, 2H), 5.05 (br s, 1H); ^{13}C NMR (benzene-d_6) δ 14.32 (q), 20.36 (q), 20.72 (s), 27.53 (s), 29.00 (t), 31.48 (q), 31.68 (q), 37.32 (s), 37.63 (d), 41.98 (d), 45.19 (t), 47.66 (t), 116.70 (d), 118.98 (s; q $J_{C,F}$ = 320 Hz), 151.63 (s); MS *m/z* (r.i.) 338 (M^+, 57), 205 (100), 187 (30), 177 (28), 121 (52), 109 (35), 107 (38), 91 (33), 69 (76), 41 (30); HRMS calcd for $C_{15}H_{21}O_3SF_3$ (M^+) 338.1164, found 338.1161.

(1aα,3aβ,6aβ,6bα)-(±)-1,1a,3a,4,5,6,6a,6b-Octahydro-1a,2,5,5,6b-pentamethylcyclopropa[*e*]indene (40).

To a stirring suspension of 0.1065 g (0.559 mmol) of CuI in 2 mL of THF, cooled to –10 °C, was added 0.55 mL of MeLi (1.6 M in Et_2O). After being stirred at –10 °C for 45 min, a solution of 18.9 mg (55.9 μmol) of **39** in 1 mL of THF was added via cannula. The reaction mixture was allowed to warm to 0 °C, stirred at that temperature for an additional 1.25 h, and then quenched with saturated aqueous NH_4Cl. After dilution with Et_2O, the organic phase was washed with saturated aqueous NH_4Cl and brine, dried, and evaporated. The remaining residue was flash chromatographed (pentane) to give 6.8 mg (60%) of **40** as a colorless oil: ^{1}H NMR (400 MHz, benzene-d_6) δ 0.31 (d, J = 3.6 Hz, 1H), 0.95 (d, J = 3.6 Hz, 1H), 1.05 (s, 3H), 1.13 (s, 3H), 1.18 (s, 6H), 1.37 (dd, J = 13.0, 1.4 Hz, 1H), 1.45 (dd, J = 12.1, 11.7 Hz, 1H), 1.73 (dd, J = 12.1, 7.6 Hz, 1H), 1.86 (dd, J = 13.0, 7.7 Hz, 1H), 1.86 (br s, 3H), 2.35-2.42 (m, 2H), 4.91 (br s, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 17.37 (q), 21.33 (q), 21.86 (s), 22.29 (q), 25.91 (s), 29.35 (t), 32.19 (q), 32.41 (q), 37.87 (s), 39.14 (d), 43.88 (d), 45.78 (t), 49.02 (t), 123.40 (d), 137.90 (s); MS *m/z* (r.i.) 204 (M^+, 80), 189 (68), 175 (40), 162 (30), 133 (64), 119 (80), 108 (100), 106 (27), 105 (34), 93 (28); HRMS calcd for $C_{15}H_{24}$ (M^+) 204.1878, found 204.1876.

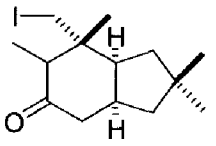
3.5 References and Notes

1. For the sake of clarity the numbering of the marasmane skeleton was derived from the corresponding numbering in the naphthalene skeleton (see compound **6**). For the numbering of the marasmane skeleton most frequently used in literature, see: reference 2.

2. (a) Vidari, G.; Vita-Finzi, P. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1995**; Vol. 17, pp 153-206. (b) Daniewski, W. M.; Vidari, G. *Progress In The Chemistry Of Organic Natural Products* **1999**, *77*, 69.
3. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, **1991**, Vol. I, pp 553-554.
4. Howard, B. M.; Fenical, W. *J. Org. Chem.* **1977**, *42*, 2518.
5. See Scheme 1 and reference 6f.
6. (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (c) Orru, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (d) Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (e) Piet, D. P.; Orru, R. V. A.; Jenniskens, L. H. D.; van de Haar, C.; van Beek, T. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Chem. Pharm. Bull.* **1996**, *44*, 1400. (f) Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1998**, *63*, 122.
7. A similar carbocation, generated via acid-catalyzed rearrangement, was terminated by a 1,2-H shift. Tobe, Y.; Yamashita, D.; Takahashi, T.; Inata, M.; Sato, J.-i.; Kakiuchi, K.; Kobiro, K.; Odaira, Y. *J. Am. Chem. Soc.* **1990**, *112*, 775.
8. The energy difference was calculated with B3LYP/6-31G(d,p) using the computer program: Gaussian 98 (Revision A.7), Gaussian, Inc., Pittsburgh PA, 1998.
9. Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.
10. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
11. Mitsunobu, O. *Synthesis* **1981**, 1.
12. Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, *26*, 2145.
13. Without epimerization of the methyl group at C(7), **19** refused to give **20**.
14. Attempts to perform the dihydroxylation reaction with a catalytic amount of the toxic OsO_4 were less successful. With trimethylamine-*N*-oxide as co-oxidant a considerable amount of over oxidized product was obtained in addition to 53% of **23**.
15. According to ^{1}H NMR spectroscopy, the crude reaction mixture contained a trace amount of the marasmane ketone **9**.
16. Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4955.
17. The key spectral data observed for **9** strongly resembled those measured for compound **16** and lactaropallidine. For a detailed spectral analysis of lactaropallidine see: De Bernardi, M.; Fronza, G.; Mellerio, G.; Valla, V.; Vidari, G.; Vita-Finzi, P. *Gazz. Chim. Ital.* **1984**, *114*, 163.
18. Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426.
19. It was expected that the tetrasubstituted double bond in **6** was only slightly less reactive than the trisubstituted one in mesylate **14**. For a relative rate study on electrophilic

additions of carbocations to 'simple' alkenes, see: Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473.

20. (a) Place, P.; Roumestant, M.-L.; Gore, J. *Bull. Soc. Chem. Fr.* **1976**, 169. (b) Kraus, W.; Gräf, H.-D. *Synthesis* **1977**, 461. (c) Kraus, W.; Gräf, H.-D. *Angew. Chem.* **1975**, *87*, 878. (d) Madaeva, O. S. *Zh. Obshch. Khim. Engl. Ed.* **1957**, *27*, 2630.
21. Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.
22. The *trans* ring junction in **37** was concluded from the splitting pattern of H(5), which appeared as a triple triplet (J = 13.0, 3.6 Hz) at δ 1.67 in the ^{1}H NMR spectrum. This signal could only originate from H(5) when both neighboring methylenes were more or less symmetrically positioned around H(5).
23. Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.
24. Inspection of a molecular model of ketone **32** indicates that the β direction of attack is strongly shielded.
25. MgI_2 should be added quickly to avoid air contact as much as possible. Prolonged air contact will lead to inactivity of the reagent.
26. Without HMDS opening of the cyclopropane ring was observed to give iodide **A**.



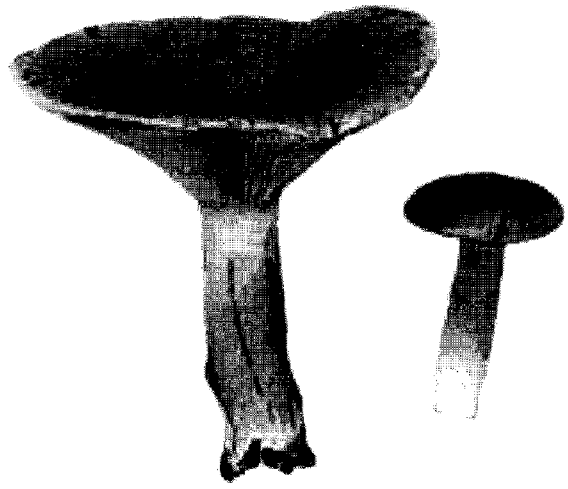
A

^{1}H NMR (benzene-d_6) δ 0.74 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.14-1.46 (m, 4H), 1.75 (app q, J = 12.0 Hz, 1H), 1.87-2.11 (m, 2H), 2.21 (q, J = 6.9 Hz, 1H), 2.31 (m, 1H), 2.78 (d, J = 10.3 Hz, 1H), 3.01 (d, J = 10.3 Hz, 1H); ^{13}C NMR (benzene-d_6) δ 7.88 (q), 20.53 (t), 25.77 (q), 32.45 (q), 32.90 (q), 37.06 (s), 38.26 (d), 40.58 (t), 42.02 (s), 44.31 (t), 46.28 (d), 47.41 (t), 48.09 (d), 209.49 (s); MS *m/z* (r.i.) 334 (M^+, 8), 207 (100), 189 (36), 165 (11), 135 (22), 123 (14), 109 (30), 95 (18), 69 (18), 55 (9); HRMS calcd for $C_{14}H_{23}OI$ (M^+) 334.0794, found 334.0802.

27. The use of LDA gave in this case poor results. For a successful use of LDA, see: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979.
28. (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.
29. See also paragraph 2.4.1.

Chapter 4

Optically Pure Building Block for the Syntheses of Lactarane and Marasmane Sesquiterpenes*



* Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Bell, R. P. L.; Wijnberg, J. P. B. A.; de Groot, A. *Tetrahedron: Asymm.* **1999**, *10*, 2729.

4.1 Introduction

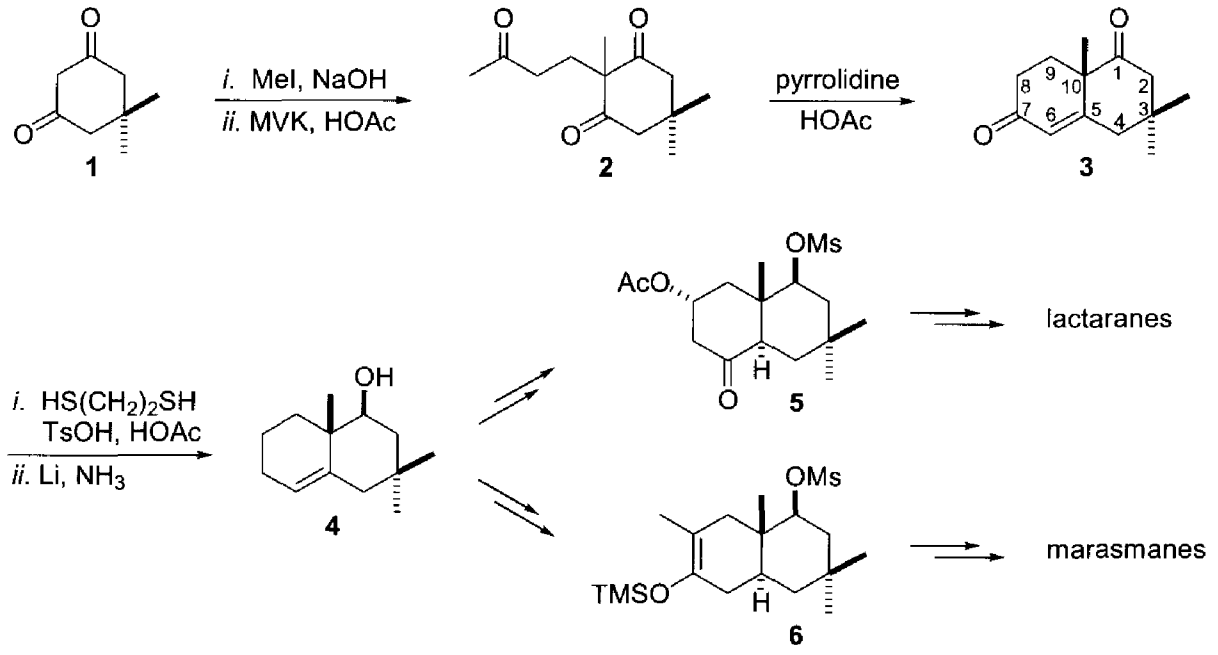
In contrast to the vast number of isolated lactaranes and marasmanes, only a few total syntheses of these compounds have been described.[1] All of these syntheses lead to racemic products, except for the total synthesis of the marasmane (+)-isovelleral.[1] The only known syntheses of optically active lactaranes have been achieved starting from natural congeners.[2b] Since the absolute configuration of naturally occurring lactaranes is correlated with that of the marasmanes,[2] the syntheses of these two types of sesquiterpenes can, in principle, start from the same chiral building block. Having demonstrated the syntheses of lactarane and marasmane sesquiterpenes starting from the same racemic synthon **4** (Scheme 1),[3] a method enabling the introduction of optical activity in the preparation of this synthon was searched for.

4.2 Results and Discussion

4.2.1 Asymmetric Synthesis

The above mentioned racemic syntheses of synthon **4** started from commercially available dimedone (**1**) (Scheme 1). Methylation and annulation of methylvinylketone (MVK) provides dione **3**, which via selective ketalization followed by dissolving metal reduction yields alcohol **4**.

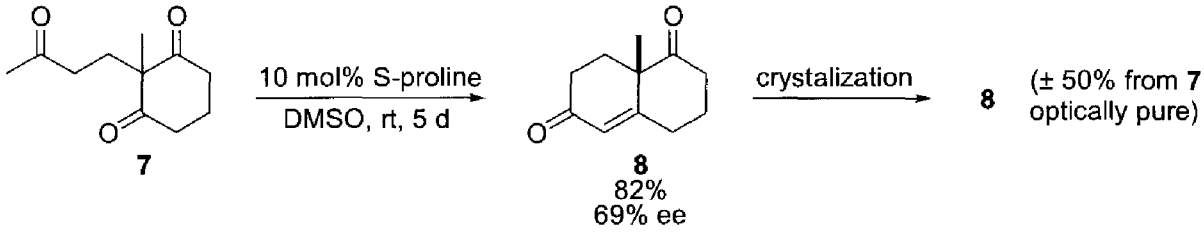
Scheme 1



Dione **3** strongly resembles the known Wieland-Miescher ketone **8**, of which both enantiomers can be prepared in optically pure form via an amino acid-catalyzed asymmetric cyclization

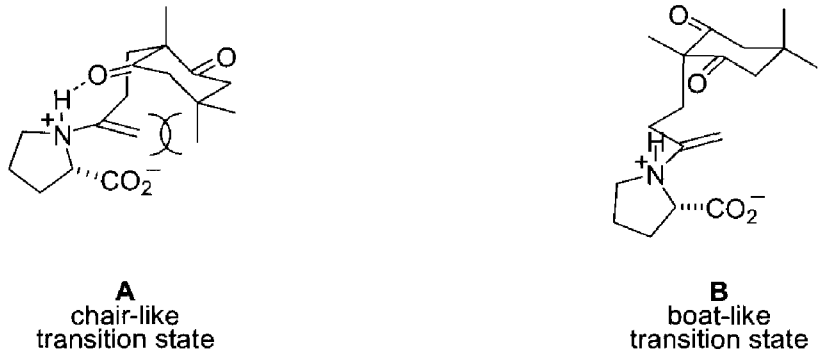
followed by selective crystallization (Scheme 2).[4] The synthesis of (*S*)-**3**, required for the preparation of naturally occurring lactarane and marasmane sesquiterpenes, was first investigated via this method.

Scheme 2



Several conditions for the cyclization of **2** were tested but in all cases dione **3** was obtained as a racemate. This lack of asymmetric induction can be explained by the steric hindrance of the axial methyl group at C(3) in the transition state (Figure 1).[5] In the proposed mechanism for the asymmetric cyclization, a preferential complexation of the initially formed enamine with one of the ketones is suggested (structure **A**, Figure 1).[5] A substituent at C(3) disfavors this conformation, leading to a boat shaped transition state in which the interatomic distances for complexation are to large (structure **B**, Figure 1).

Figure 1

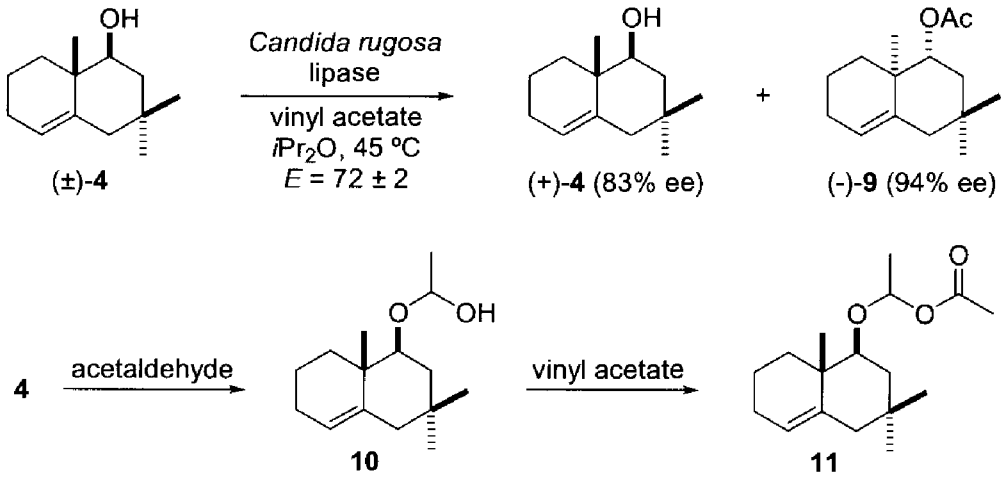


4.2.2 Enzyme Screening

Optically pure alcohol **4** can, in principle, be obtained by an enzymatic kinetic resolution. Hydrolytic enzymes such as proteases, esterases and lipases are very well suited for the kinetic resolution of racemic alcohols and esters in water or organic solvents.[6] However, hydrolase-mediated regio- or stereoselective conversions of perhydronaphthalenol derivatives are relatively rare.[6f-h,7] Nevertheless, the enzyme mediated resolution of alcohol **4** was investigated.

For initial screening, **4** was incubated with 19 different esterases, lipases and proteases in the presence of a five-fold excess of vinyl acetate, in octane. Very little or no reaction was observed after 6 days of incubation with 14 enzymes. The lipase B from *Candida antarctica* and lipase PS (*Pseudomonas cepacia*) gave, instead of the expected acetate **9**, a slow conversion into acetal **11** (Scheme 3). The formation of the latter compound can be explained by the reaction of **4** with

Scheme 3



acetaldehyde, formed during the reaction from vinylacetate, to produce hemi-acetal **10**, which is acetylated by the enzyme. Three enzymes displayed a clean conversion of the substrate: *Candida rugosa* lipase (CRL), cholesterol esterase (CE) and *Chromobacterium viscosum* lipase (CVL) (Table 1).

Table 1.

Enzymatic esterification of (±)-**4**

Enzyme	Solvent	Acyl donor[a]	Conversion (%)					
			2 h	6 h	22 h	46 h	70 h	6 d
CRL	octane	VA	14.7	20.4	23.2	23.5	23.5	23.5
CRL	octane	IPA	4.3	7.0	10.1	14.9[b]	-[c]	-
CRL	toluene	VA	25.0	31.1	-	-	35.4	35.4
CRL	*i*Pr$_2$O	VA	32.3	38.8	50.0	-	-	-
CE	octane	VA	-	-	-	-	-	6.0
CVL	octane	VA	-	-	-	-	-	4.0

[a] VA = vinyl acetate, IPA = *iso*propenyl acetate

[b] Byproducts start to appear

[c] Not determined

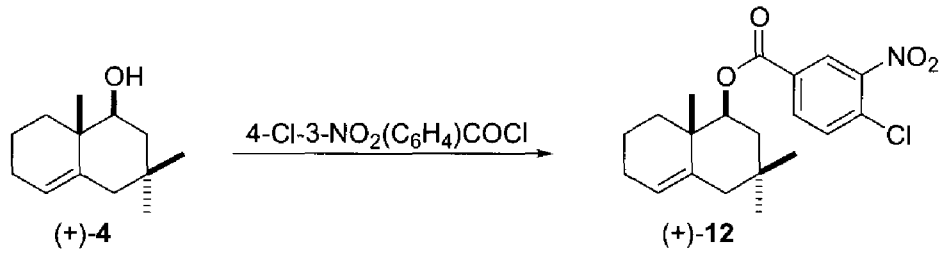
Since CRL gave by far the fastest reaction, all further experiments were conducted with this enzyme. Remarkably, the enzymatic reaction in octane stopped after 22 h at only 23% conversion. Changing the acyl donor to *iso*propenyl acetate led to an even lower conversion. Performing the reaction in toluene improved the velocity slightly, but a much faster reaction was observed in iPr$_2$O. Incubation of **4** at 45 °C for 22 h gave a 50% conversion, with an enantiomeric excess (ee) of the resulting acetate (–)-**9** of 94% (Scheme 3). The background of this solvent effect is unknown; usually, CRL works better in apolar solvents such as octane (log P = 4.5) than in more polar solvents like iPr$_2$O (log P = 1.9).[6a,8] Possibly, some product inhibition is taking place in the more hydrophobic solvents. Unfortunately, working in iPr$_2$O led to a decreased stability of the enzyme, since performing the esterification of **4** with reused enzyme gave a 50% reduced reaction rate. CRL-mediated hydrolysis of racemic **9** in water was relatively fast, but hardly stereoselective ($E = \approx 5$).

Careful examination of the ee$_p$ during various stages of the CRL-mediated esterification of **4** with vinyl acetate in iPr$_2$O allowed an accurate determination of the E-value,[9] which proved to be 72 ± 2 %. The remaining alcohol (+)-**4** was obtained in 83% ee, the acetate (–)-**9** in 94% ee. The ee of (–)-**4**, required[10] for the synthesis of naturally occurring lactarane and marasmane sesquiterpenes, could be enhanced to >98% by performing the kinetic resolution a second time. Via this methodology optically pure (+)-**4** (ee >98 %) was prepared on a 5 g scale. Reduction of (–)-**9** with LiAlH$_4$ gave alcohol (–)-**4**. In this way, the kinetic resolution of **4** was easily accomplished, yielding both enantiomers with high ee.

4.2.3 Determination of the Absolute Configuration of (+)-4

Since no optically pure reference material of **4** or any derivative was available, the only way to determine the absolute configuration of the enzymatic product was by X-ray analysis of a crystalline derivative. Several attempts to prepare suitable crystalline derivatives were unsuccessful. Esterification of (+)-**4** with 3,4,5-triiodobenzoyl chloride[6a] gave a couple of unidentified compounds. The racemic 4-bromobenzoyl derivative of **4** was easily obtained as a high-melting solid, but the corresponding optically active material was not crystalline. Treatment of (+)-**4** with 4-chloro-3,5-dinitrobenzoyl chloride gave decomposition products. Finally, suitable crystals of ester (+)-**12** were obtained from the reaction of (+)-**4** with 4-chloro-3-nitrobenzoyl chloride in pyridine (Scheme 4). The crystal structure of (+)-**12** was determined and the absolute configuration was established based on anomalous dispersion.[11] The molecule displays the *S* configuration at C(1) and C(10). A second crystal from the same batch displayed the same absolute configuration.

Scheme 4



(+)-**4** (+)-**12**

4.3 Conclusion

It has been show that octahydro-3,3,8a-trimethyl-1-naphthalenol (**4**) can be resolved on a synthetic useful scale using *Candida rugosa* lipase, giving (+)-**4** in an ee >98%. This enantiomer is a useful optically pure building block for the synthesis of naturally occurring lactaranes and marasmanes. The absolute configuration of (+)-**4** was established by X-ray analysis of its 4-chloro-3-nitrobenzoate **12**.

4.4 Experimental Section

4.4.1 General Comments[12] and Materials

All ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$.

Candida rugosa lipase (type VII), porcine pancreas lipase, thermolysin and subtilisin Carlsberg were from Sigma; α-chymotrypsin, *Rhizomucor miehei* lipase (Chirazyme L-9, lyo.) and *Candida antarctica* lipase (Chirazyme L-2 lyo.) were from Boehringer; cholesterol esterase, lipase PS (*Pseudomonas cepacia*), lipase AP6 (*Aspergillus* sp.), lipase N (*Rhizopus* sp.), lipase R-10 (*Penicillium roqueforti*), protease P6 (*Aspergillus melleus*) and acylase 30,000 (*Aspergillus* sp.) were from Amano; *Chromobacterium viscosum* lipase, *Aspergillus niger* lipase and *Geotrichum candidum* lipase were from Biocatalysts Ltd; *Humicola lanuginosa* lipase (SP 523) was from Novo Nordisk.

Alcohol **4** was synthesized according to Orru *et al.*[13]

4.4.2 Apparatus and Analytical Techniques

Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) was used as shift reagent for CLIS-NMR. The enzymatic reactions were carried out at 45 °C in a New Brunswick Scientific G24 Environmental Incubator Shaker at 350 rpm. GC analysis and measurements to

determine the ee were carried out with a Varian 3600 gas chromatograph provided with flame ionization detector and a Lab Systems X-Chrom integrating system and a 50 m capillary WCOT fused silica column filled with CP-Cyclodextrine B-236-M-19, film thickness 0.25 μm, using a temperature programme of 80-170 °C, rate 2°C/min and H_2 as carrier gas. Tetradecane was used as an internal standard. The acetates (–)-**9** and (+)-**9** were baseline separated by this method, but the peaks of the enantiomers of alcohol **4** showed considerable overlap. In order to separate the alcohols, samples of the enzymatic reaction mixture were silylated using TMSCl and HMDS.[14] A GC oven temperature of 90 °C was used for this purpose. The *E*-value could be determined most accurately from the ee and the conversion, at an oven temperature of 90 °C, using the computer program SIMFIT.[15]

4.4.3 Procedures and Spectral Data

Enzyme screening.

In a 4 mL screw cap vial (Chrompack) was placed 1 mL of a solution containing 100 mM of (±)-**4** and 500 mM of vinyl acetate (freshly distilled) in octane. A suitable amount of enzyme (5-100 mg, depending on the purity) was added to the prewarmed solution and the mixture was incubated at 45 °C. At regular time intervals, samples were analyzed by GC in order to monitor conversion and ee. Very slow or no reaction was observed with porcine pancreas lipase, *Rhizomucor miehei* lipase, lipase AP6 (*Aspergillus* sp.), lipase N (*Rhizopus* sp.), lipase R-10 (*Penicllium roqueforti*), *Aspergillus niger* lipase, *Geotrichum candidum* lipase, lipoprotein lipase from two microbial sources, α-chymotrypsin, thermolysin, subtilisin Carlsberg, protease P6 (*Aspergillus melleus*) and acylase 30,000 (*Aspergillus* sp.). Blank reactions containing (±)-**4** and vinyl acetate in octane without enzyme showed no conversion.

(1*R*,8a*R*)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenyl acetate [(–)-9] and (1*S*,8a*S*)-1,2,3,4,6,7,8,8a-octahydro-3,3,8a-trimethyl-1-naphthalenol [(+)-4].

To a solution of 1.94 g (10 mmol) of (±)-**4** and 4.30 g (50 mmol) of freshly distilled vinyl acetate in 45 mL of iPr_2O, 7.5 g of *Candida rugosa* lipase was added. The mixture was shaken at 45 °C for 22 h after which the enzyme was filtered off. The filtrate was dried and evaporated. The remaining residue was flash chromatographed (EA:PE = 9:1) yielding 0.81 g of (–)-**9** (34%, 94% ee) and 1.04 g of (+)-**4** (54%, 83% ee).

(–)-**9**: ^{1}H NMR δ 0.82 (s, 3H); 0.89 (s, 3H); 0.99 (s, 3H); 1.20-2.20 (m, 10H); 1.96 (s, 3H); 4.69 (m, 1H); 5.34 (m, 1H); HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1778; $[\alpha]_D^{20}$ = –48° ($CHCl_3$, c = 2.2).

(+)-**4**: ^{1}H NMR δ 0.82 (s, 3H); 0.95 (s, 3H); 0.98 (s, 3H); 1.34-2.20 (m, 10H); 3.48 (m, 1H); 5.38 (m, 1H). This remaining alcohol was once more incubated with CRL under the conditions described above, yielding (+)-**4** with >98% ee: $[\alpha]_D^{20}$ = +69° ($CHCl_3$, c = 2.9).

Large scale resolution of (±)-4.

A suspension of 10.0 g (51.5 mmol) of (±)-**4**, 100 mL (1.08 mol) of vinyl acetate, and 40 g of *Candida rugosa* lipase in 500 mL of iPr_2O was shaken at 45 °C for 2 d. Another 50 mL (0.54 mol) of vinyl acetate and 20 g of *Candida rugosa* lipase were added and shaken was continued for another 2 d after which the reaction mixture was filtered over hyflo, washed with Et_2O, evaporated, and flash chromatographed (EA:PE = 5:1) yielding 5.06 g of (+)-**4**. This 5.06 g of (+)-**4** was dissolved in 250 mL iPr_2O and again treated via the above procedure with 50 mL (0.54 mol) of vinyl acetate and 20 g of *Candida rugosa* lipase yielding 4.60 g (46%, >98% ee) of (+)-**4**.

Reduction of (–)-9 to (–)-4.

To a stirring suspension of 0.102 g (2.7 mmol) of $LiAlH_4$ in 25 mL of Et_2O, a solution of 0.524 g (2.2 mmol) of (–)-**9** in 25 mL of dry Et_2O was added dropwise over a 20 min period. After stirring at rt for 20 min, the reaction mixture was quenched with 1 M aqueous HCl. The two phase system was separated and the water layer was extracted with Et_2O. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (EA:PE = 9:1) yielding 0.421 g (98%) of (–)-**4** (95% ee): $[\alpha]_D^{20} = -67°$ ($CHCl_3$, c = 12.2).

(1*S*,8a*S*)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenyl 4-chloro-3-nitrobenzoate (12).

To a stirring solution of 0.194 g (1.0 mmol) of (+)-**4** (83% ee) and 0.122 g (1.0 mmol) of DMAP in 5 mL of pyridine was added 0.438 g (2.0 mmol) of 4-chloro-3-nitrobenzoyl chloride. The reaction mixture was refluxed for 3 hours. After cooling to rt, the reaction mixture was poured into 20 mL of water, brought to pH 4 with concentrated H_2SO_4 and extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (EA:PE = 4:1) giving 220 mg of an oil which partly crystallized after addition of 2 mL of hexane yielding 70 mg of crystals of a racemic mixture of **12** and *ent*-**12**, mp 92-94 °C. The mother liquor was decanted and evaporated. The remaining residue (110 mg) was recrystallized from MeOH yielding 90 mg of (+)-**12** (>95% ee, determined by CLIS-NMR, mp 61-64 °C, $[\alpha]_D^{20} = +92$ ($CHCl_3$, c = 2,2)) which was used for X-ray diffraction analysis: ^{1}H NMR δ 0.93 (s, 3H); 0.98 (s, 3H); 1.18 (s, 3H); 1.40-2.20 (m, 10H); 5.00 (m, 1H); 5.45 (m, 1H); 7.62 (d, J = 8.4 Hz, 1H); 8.11 (dd, J = 8.4, 2.0 Hz, 1H); 8.43 (d, J = 2.0 Hz, 1H); HRMS calcd for $C_{20}H_{24}ClNO_4$ (M^+) 377.1394, found 377.1402; Anal. calcd for $C_{20}H_{24}ClNO_4$: C, 63.57%, H, 6.40%, N, 3.71%. Found: C, 63.28%, H, 6.45%, N, 3.28%.

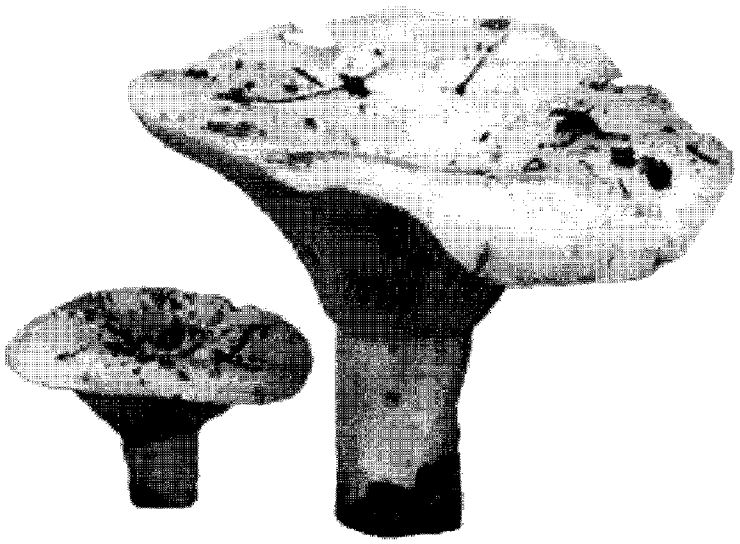
4.5 References and Notes

1. See Chapter 1.

2. (a) Vidari, G.; Vita-Finzi, P. *Sesquiterpenes and other secondary metabolites of genus Lactarius (Basidiomycetes): chemistry and biological activity*; Elsevier: Amsterdam, **1995**; Vol. 17. (b) Daniewski, W. M.; Vidari, G. *Progress In The Chemistry Of Organic Natural Products* **1999**, *77*, 69.
3. See Chapters 2 and 3.
4. For example see: Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53 and references therein.
5. Agami, C.; Meynier, F.; Puchot, C. *Tetrahedron* **1984**, *40*, 1031.
6. (a) Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Camacho Mondril, N. L. F. L.; Boavida dos Santos, P. M. A. C.; de Groot, A. *Tetrahedron: Asymm.* **1996**, *7*, 497. (b) Heinsman, N. W. J. T.; Orrenius, S. C.; Marcelis, C. L. M.; de Sousa Teixeira, A.; Franssen, M. C. R.; van der Padt, A.; Jongejan, J. A.; de Groot, A. *Biocatal. Biotransform.* **1998**, *16*, 145. (c) Franssen, M. C. R.; Goetheer, E. L. V.; Jongejan, H.; de Groot, A. *Tetrahedron Lett.* **1998**, *39*, 8345. (d) Kloosterman, M.; Elferink, V. H. M.; van Iersel, J.; Roskam, J.-H.; Meijer, E. M.; Hulshof, L. A.; Sheldon, R. A. *TIBTECH* **1988**, *6*, 251. (e) Klibanov. A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (f) Theil, F. *Chem. Rev.* **1995**, *95*, 2203. (g) Koskinen, A. M. P.; Klibanov, A. M., Eds. *Enzymatic reactions in organic media*; Blackie Academic & Professional: Glasgow, **1996**; 314. (h) Anderson, E. M.; Larsson, K. M.; Kirk, O. *Biocatal. Biotransform.* **1998**, *16*, 181.
7. (a) Huber, U.; Boland, W.; König, W. A.; Gehrke, B. *Helv. Chim. Acta* **1993**, *76*, 1949. (b) Nair, M. S.; Anilkumar, A. T. *Tetrahedron: Asymm.* **1996**, *7*, 511. (c) Tanimoto, H.; Oritani, T. *Tetrahedron: Asymm.* **1996**, *7*, 1695. (d) Toyooka, N.; Nishino, A.; Momose, T. *Tetrahedron* **1997**, *53*, 6313. (e) Fujiwara, Y.; Yamamoto, T.; Bando, T.; Shishido, K. *Tetrahedron: Asymm.* **1997**, *8*, 2793. (f) Garcia-Granados, A.; Parra, A.; Simeó, Y.; Extremera, A. L. *Tetrahedron* **1998**, *54*, 14421. (g) Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymm.* **1998**, *9*, 1789.
8. Laane, C.; Boeren, S.; Vos, K.; Veeger, C. *Biotechnol. Bioeng.* **1987**, *30*, 81.
9. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
10. For the determination of the absolute configuration, see next paragraph.
11. For details see: Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron: Asymm.* **1999**, *10*, 2729.
12. See also paragraph 2.4.1.
13. Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374.
14. Müller, B.; Göke, G. *Deutsche Lebensmittel-Rundschau* **1972**, *68*, 222.
15. Jongejan, J. A.; van Tol, J. B. A.; Geerlof, A.; Duine, J. A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 247.

Chapter 5

Total Synthesis of (+)-Isovelleral*



* Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* submitted.

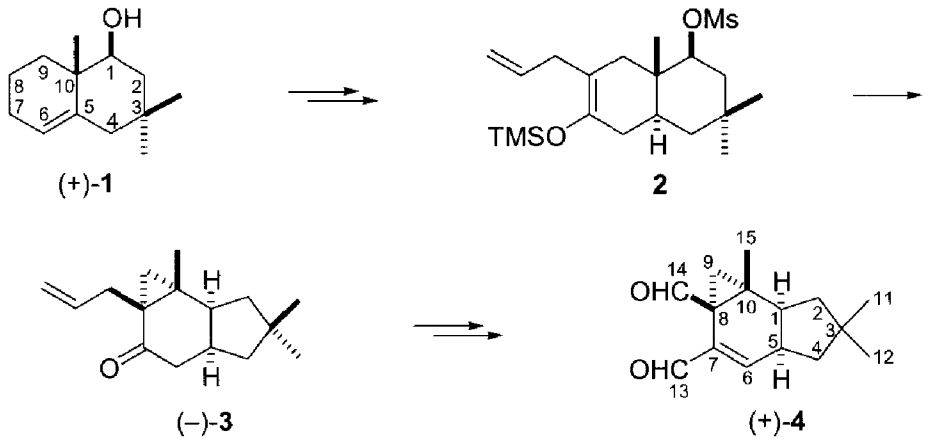
5.1 Introduction

The successful synthesis of the marasmane skeleton via a tandem rearrangement-cyclopropanation reaction and the availability of enantiomerically pure starting material tempted us to investigate this new strategy for the synthesis of (+)-isovelleral (**4**). This hot tasting compound has been found in many mushroom species belonging to the genus *Lactarius*.[1] Its formation within a few seconds after injury of the mushroom by a predator and its biological activities indicate that (+)-isovelleral is one of the active compounds in the mushroom's chemical defense system.[1]

5.2 Results and Discussion

In the literature two syntheses of isovelleral have been reported. The first one published by Bergman *et al.* describes the synthesis of (+)-isovelleral via thermal rearrangement of its diastereoisomer possessing the unnatural orientation of the cyclopropyl moiety (see Chapter 1, Scheme 21).[2] The second synthesis published by Thompson *et al.* reports on the synthesis of racemic isovelleral (see Chapter 1, Scheme 18).[3] The approach toward (+)-isovelleral (**4**), as is described in this Chapter starts with the easily obtainable optically pure alcohol (+)-**1** (Scheme 1).[4] Conversion of (+)-**1** to silyl enol ether **2** is followed by the key step of this synthesis, a MgI_2-induced rearrangement-cyclopropanation reaction (**2** → **3**). With **3** in hand, the preparation of (+)-isovelleral (**4**) is planned through conversion of the allyl moiety to an aldehyde group[5] and introduction of the second aldehyde group following a known procedure.[3]

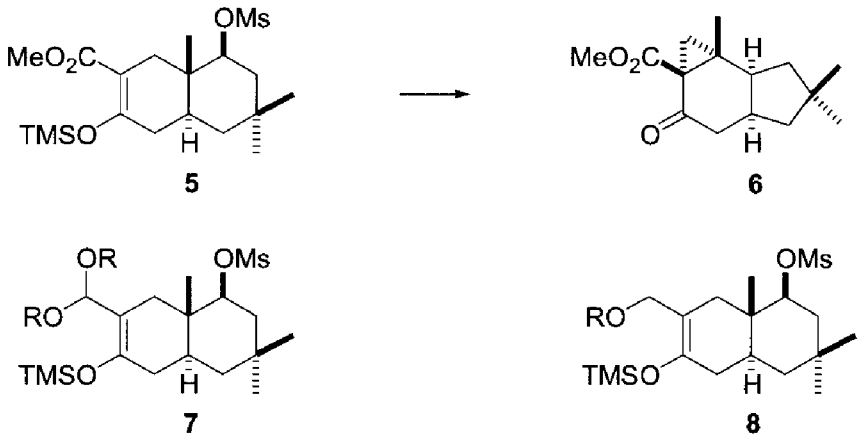
Scheme 1



The synthesis of a compound similar to **2** with, instead of the allyl moiety, an oxidized functionality at C(8) was also considered. Although **6** is a known compound which has been converted to isovelleral,[3] its formation from **5**[6] via the rearrangement-cyclopropanation sequence

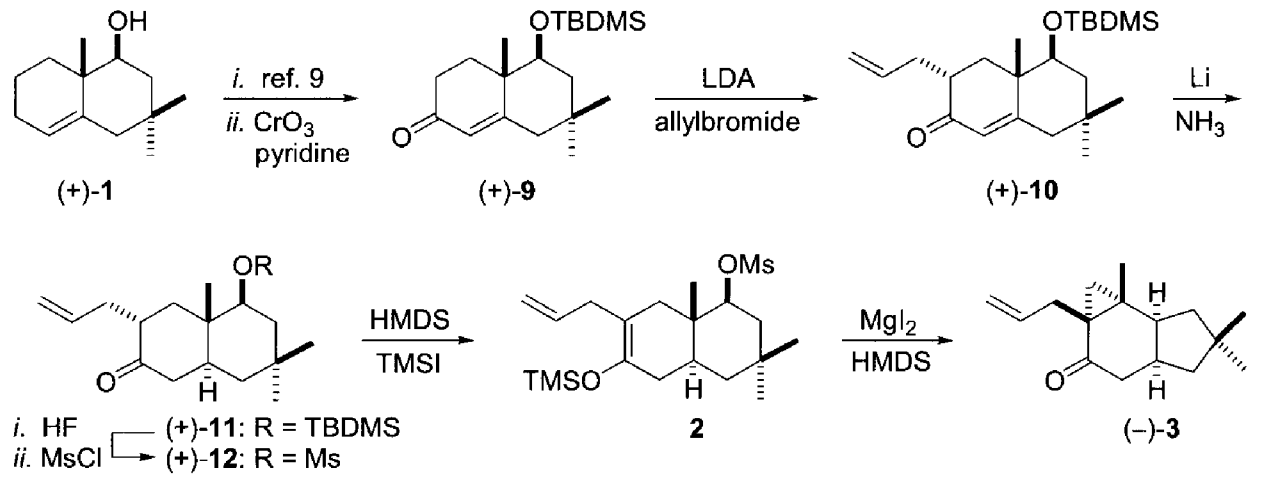
was assumed to be doubtful (Scheme 2), since it is shown[7] that the cyclopropanation step is influenced by the steric bulk of C(8) substituent (Pitzer strain) and the electron density of the C(7)-C(8) double bond. An acetal protected aldehyde group as C(8) substituent like in **7** was not considered as a good choice because of its steric bulk and its instability toward TMSI.[8] The synthesis of **8** with a protected hydroxymethyl group as C(8) substituent was briefly investigated, but the introduction of such a moiety turned out to be troublesome and did not lead to the desired silyl enol ether **8**.

Scheme 2



The optically pure alcohol (+)-**1** (ee >98%)[4] was used as the starting material for the synthesis of silyl enol ether **2**. The alcohol (+)-**1**, easily prepared on a multigram scale,[4a] was converted via a known procedure[9] to enone (+)-**9** (Scheme 3). Alkylation of (+)-**9** with LDA and allyl bromide had to be carried out at –20 °C and in the presence of HMPA. Lithium in liquid ammonia[10] reduction of (+)-**10** yielded ketone (+)-**11**, which by standard reactions was converted to compound (+)-**12** (71% yield from (+)-**9**). Treatment of (+)-**12** with HMDS and TMSI afforded

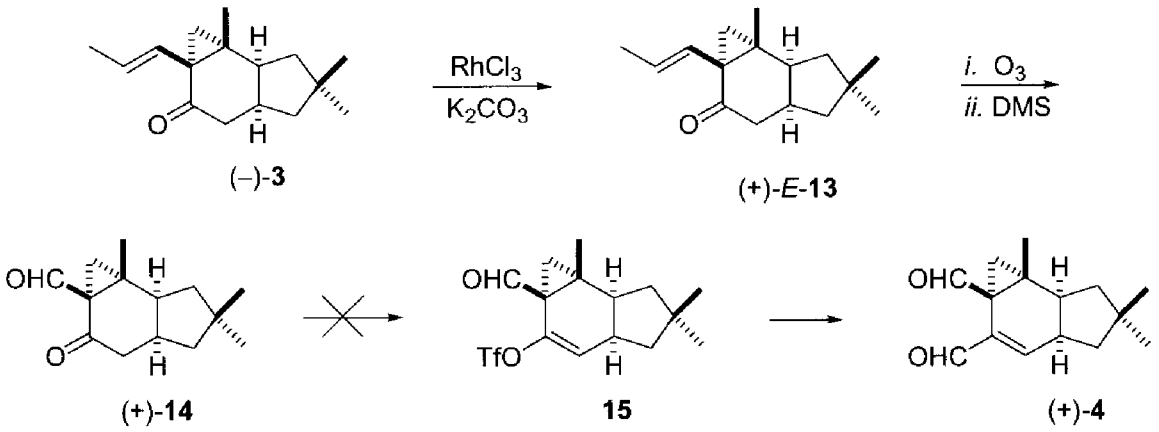
Scheme 3



the desired silyl enol ether **2**. The key MgI_2-induced rearrangement-cyclopropanation of **2**, in the presence of HMDS, proceeded smoothly to give, after acidic workup,[11] the rearranged ketone (–)-**3** in excellent yield (89% yield).

Having accomplished the successful rearrangement to the tricyclic ketone (–)-**3**, its conversion to (+)-isovelleral was investigated initially as is outlined in Scheme 4. Isomerization of the double bond in (–)-**3** with $RhCl_3$[5,12] and K_2CO_3[12b] in ethanol at 60 °C yielded (+)-*E*-**13** along with a small amount of the *Z*-isomer. Ozonolysis of (+)-*E*-**13** in a mixture of MeOH and CH_2Cl_2 at –78 °C followed by reductive workup with DMS afforded the desired aldehyde (+)-**14**.[13] Unfortunately, the one-carbon homologation of (+)-**14** via a palladium-catalyzed carbonylation could not be accomplished because the preparation of the required enol triflate **15** failed probably due to internal chelation of the enolate function with the proximate aldehyde group.[14]

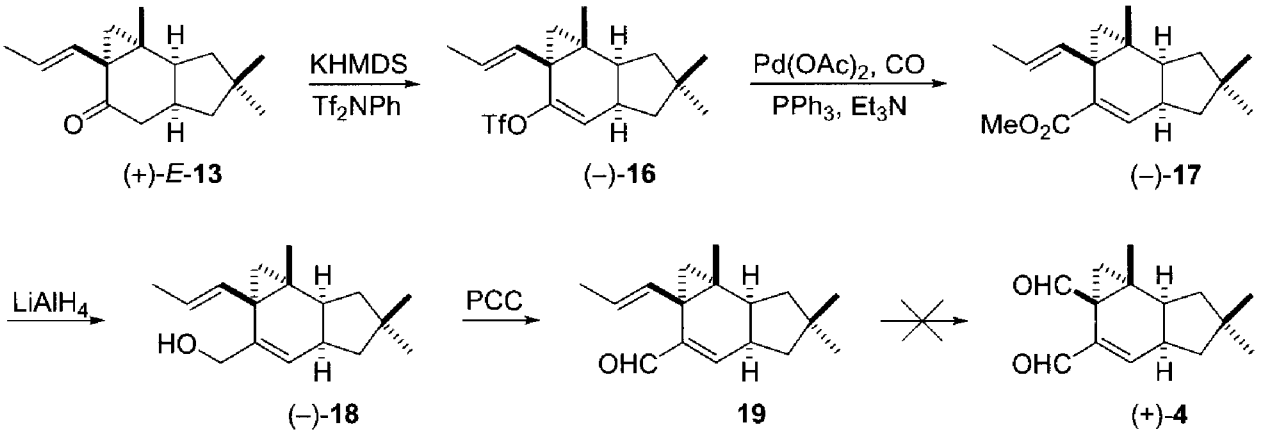
Scheme 4



To circumvent this problem, the carbonyl function in (+)-*E*-**13** was first converted to the α,β-unsaturated aldehyde moiety prior to selective ozonolysis of the electron richer double bond in **19** (Scheme 5).[5,15] Treatment of (+)-*E*-**13** with KHMDS and Tf_2NPh gave without any problems the enol triflate (–)-**16** in 94 % yield. Palladium-catalyzed methoxycarbonylation resulted in a *ca.* 4:1 mixture of α,β-unsaturated ester (–)-**17** and the corresponding carboxylic acid.[16] Reduction of this mixture with $LiAlH_4$[17] yielded alcohol (–)-**18** as a single compound, which was oxidized with PCC[18] to give **19**. Disappointingly, treatment of both **19** and (–)-**17** with ozone in CH_2Cl_2 at –78 °C resulted in a complex reaction mixture.[19] Since it is known that the cyclopropane moiety is stable under the applied conditions,[20] the degradation of (–)-**17** and **19** is most probably initiated by an interaction of the proximate carbonyl moiety at C(13) with the intermediate carbonyl oxide.[21] When triflate (–)-**16**, without a proximate carbonyl group, was treated with ozone followed by reductive workup with $NaBH_4$, alcohol (–)-**20** was formed in an acceptable yield along with a diastereomeric mixture of two unreduced cross-ozonides (Scheme 6).[22] The identity of the latter compounds was deduced from the ^1H NMR spectrum showing two doublets at δ 1.26 (J = 5.0 Hz, 3H) and δ 1.31 (J = 5.0 Hz, 3H), a quartet at δ 5.11 (J = 5.0 Hz, 2H), and two

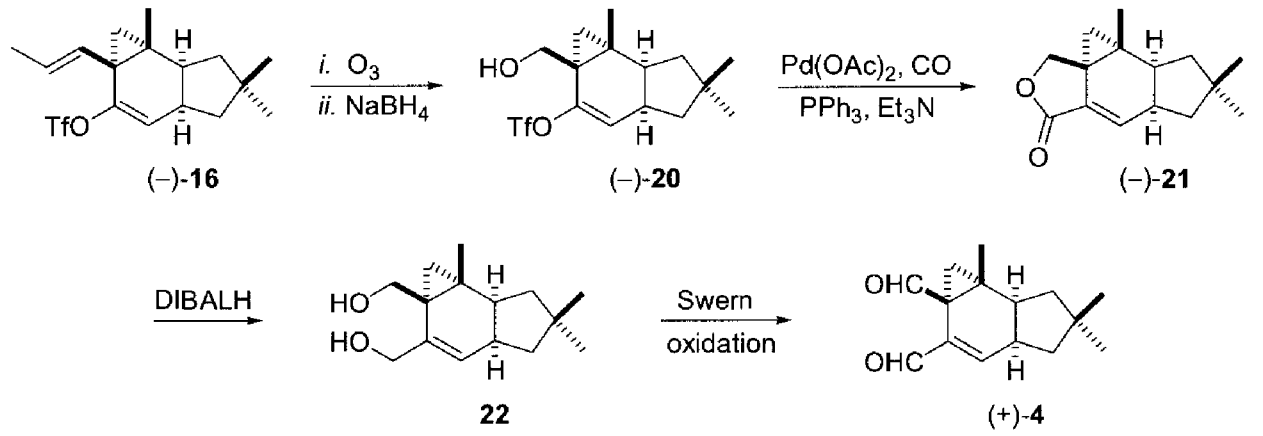
singlets at δ 5.06 (1H) and δ 5.19 (1H). Further evidence was obtained from the ^{13}C NMR spectrum in which typical ozonide signals were found at δ 102.4 (d), δ 103.0 (d) and δ 104.0 (2d). The isolation of the cross-ozonide mixture indicated that the reducing ability of $NaBH_4$[23] was too weak to reduce all of the four possible diastereoisomers. Due to lack of starting material (–)-**16**, the formation of alcohol (–)-**20** was not further optimized,[24] but the results clearly show that an alkyl-substituted double bond can selectively be ozonolized in the present of an enol triflate.

Scheme 5



With (–)-**20** available, completion of the synthesis of (+)-isovelleral (**4**) could easily be achieved (Scheme 6). Pd-catalyzed carbonylation of enol triflate (–)-**20** gave lactone (–)-**21**, which after reduction with DIBALH, affording the known diol **22**,[3] and subsequent Swern oxidation[3] completed the synthesis of (+)-isovelleral (**4**). The spectroscopic data for (+)-isovelleral ($[\alpha]_D^{20}$ = +234° ($CHCl_3$, c = 0.16)[2,25]) were identical to those reported in literature.[3]

Scheme 6



5.3 Conclusion

In conclusion it can be stated that the tandem rearrangement-cyclopropanation strategy developed for the synthesis of simple marasmanes, is also very useful for the synthesis of more complex marasmanes, as shown here for (+)-isovelleral. Starting from the known optically pure alcohol (+)-**1**, (+)-isovelleral is synthesized in 14 steps in an overall yield of 6.5%.

5.4 Experimental Section

5.4.1 General Comments[26] and Materials

All ^{1}H and ^{13}C NMR spectra were recorded in benzene-d_6.

Compound (+)-**1** was obtained as described (see Chapter 4, compound (+)-**4**). Compound (+)-**9** (see Chapter 3, compound **35**), **22**,[3] and (+)-isovelleral (**4**)[2,3,25] were characterized before.

5.4.2 Procedures and Spectral Data

(4a*S*,5*S*)-4,4a,5,6,7,8-Hexahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-2(3*H*)-naphthalenone [(+)-9].

(1a). Starting from 5.37 g (27.7 mmol) of (+)-**1**, optically pure TBDMS-protected alcohol **1a** was prepared according to a known procedure[9] without purification. The crude protected alcohol **1a** was treated with a 60.0 g, 17.5 g, and 15.0 g portion of CrO_3•(pyridine)$_2$[27] as described for racemic **9** (see Chapter 3, compound **35**). Workup and flash chromatography (PE:EA = 5:1) gave 6.98 g (78% from (+)-**1**) of (+)-**9** as a yellow oil: $[\alpha]_D^{20} = +82°$ ($CHCl_3$, c = 1.21).

(3*R*,4a*S*,5*S*)-4,4a,5,6,7,8-Hexahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethyl-silyl]-oxy]-3-(2-propenyl)-2(3*H*)-naphthalenone [(+)-10].

To a stirring solution of 5.75 mL of BuLi (1.6 M in hexane) in 15 mL of THF, cooled to 0 °C, was added 1.42 mL (10.10 mmol) of *i*Pr$_2$NH. After being stirred at that temperature for 20 min, the reaction mixture was cooled to –20 °C and a solution of 1.475 g (4.58 mmol) of (+)-**9** in 15 mL of THF was added via cannula. After 15 min and an additional period of 20 min, 1.6 mL (9.20 mmol) of HMPA and 1.6 mL (18.5 mmol) of allyl bromide were added, respectively. Stirring was continued for 1.3 h, after which the reaction mixture was quenched with 1 M aqueous HCl, diluted with Et_2O, washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to give 1.396 g (83%) of (+)-**10** as a yellow oil: ^{1}H NMR δ –0.02 (s, 3H), 0.00 (s, 3H), 0.63 (s, 3H), 0.75 (s, 3H), 0.95 (s, 9H), 0.96 (s, 3H), 1.21 (br d, *J* = 14.2 Hz, 1H), 1.26-1.53 (m, 3H), 1.87 (br d, *J* = 14.2 Hz, 1H), 2.09-2.31 (m, 3H), 2.90 (m,

1H), 3.39 (dd, J = 11.4, 4.9 Hz, 1H), 4.99 (br s, 1H), 5.06 (br d, J = 6.0 Hz, 1H), 5.80 (m, 1H), 5.83 (br d, J = 1.8 Hz, 1H); ^{13}C NMR δ –4.90 (q), –4.31 (q), 15.14 (q), 17.99 (s), 25.44 (q), 25.76 (3q), 31.50 (s), 31.82 (q), 33.88 (t), 41.25 (t), 41.39 (d), 41.86 (s), 43.89 (t), 44.58 (t), 76.43 (d), 116.33 (t), 127.03 (d), 136.81 (d), 164.47 (s), 198.05 (s); MS *m/z* (r.i.) 362 (M^+, 1), 305 (100), 263 (28), 219 (11), 75 (21), 73 (16); HRMS calcd for $C_{22}H_{38}O_2Si$ (M^+) 362.2641, found 362.2643; $[\alpha]_D^{20}$ +79° ($CHCl_3$, c = 2.39).

(3*R*,4a*S*,5*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-4a,7,7-trimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-(2-propenyl)-2(1*H*)-naphthalenone [(+)-11].

To a stirring solution of 56 mg (8.07 mmol) of Li in 10 mL of liquid NH_3, cooled to –78 °C, was added dropwise a solution of 0.591 g (1.61 mmol) of (+)-**10** and 0.30 mL (3.14 mmol) of *t*-BuOH in 10 mL of THF. After being stirred at –78 °C for 30 min, the reaction mixture was quenched with 4.3 g (80.4 mmol) of NH_4Cl and NH_3 was allowed to evaporate by standing at rt. The remaining layer was diluted with water and extracted with Et_2O. The combined organic layers were washed successively with 1 M aqueous HCl and brine, dried, and evaporated yielding 0.599 g of (+)-**11** as a white solid which was used in the next reaction without further purification: ^{1}H NMR δ 0.01 (s, 3H), 0.03 (s, 3H), 0.62 (m, 1H), 0.73 (s, 3H), 0.79 (s, 3H), 0.81 (s, 3H), 0.91-1.10 (m, 2H), 0.97 (s, 9H), 1.26 (ddd, J = 13.2, 4.9, 2.0 Hz, 1H), 1.42 (tt, J = 12.6, 4.2 Hz, 2H), 1.84-2.23 (m, 5H), 2.77 (m, 1H), 3.22 (dd, J = 11.3, 4.8 Hz, 1H), 5.01 (br s, 1H), 5.08 (br d, J = 3.8 Hz, 1H), 5.83 (m, 1H); ^{13}C NMR δ –4.91 (q), –4.33 (q), 9.16 (q), 17.96 (s), 25.77 (3q), 26.36 (q), 31.39 (s), 32.74 (q), 34.04 (t), 39.48 (s), 40.31 (d), 41.03 (t), 43.90 (t), 44.47 (2t), 45.43 (d), 76.15 (d), 116.08 (t), 136.92 (d), 208.81 (s); MS *m/z* (r.i.) 364 (M^+, 2), 307 (100), 173 (4), 145 (6), 75 (29), 73 (10), 28 (15); HRMS calcd for $C_{22}H_{40}O_2Si$ (M^+) 364.2798, found 364.2805; $[\alpha]_D^{20}$ = +29° ($CHCl_3$, c = 1.43).

(3*R*,4a*S*,5*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-4a,7,7-trimethyl-5-[(methylsulfonyl)oxy]-3-(2-propenyl)-2(1*H*)-naphthalenone [(+)-12].

(11a). To a stirring solution of 0.555 g of (+)-**11** in 10 mL of MeCN was added 7 drops of 50% aqueous HF. After being stirred at rt for 2 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and brine. Drying and evaporation gave 0.393 g of **11a** as a yellow oil which was used in the next reaction without further purification. A pure sample was obtained after flash chromatography (PE:EA = 3:1): ^{1}H NMR δ 0.60 (ddd, J = 13.4, 3.4, 1.5 Hz, 1H), 0.68 (s, 3H), 0.73 (s, 3H), 0.77 (s, 3H), 0.79-1.22 (m, 3H), 1.38 (tt, J = 12.7, 3.9 Hz, 1H), 1.81-2.23 (m, 5H), 2.70 (m, 1H), 3.03 (dd, J = 10.5, 5.8 Hz, 1H), 4.98-5.11 (m, 2H), 5.87 (m, 1H); ^{13}C NMR δ 8.79 (q), 26.39 (q), 31.39 (s), 32.74 (q), 33.96 (t), 39.07 (s), 40.40 (d), 41.13 (t), 43.33 (t), 43.83 (t), 43.91 (t), 45.71 (d), 74.88 (d), 116.08 (t), 136.99 (d), 209.19 (s).

[(+)-12]. To a solution containing 0.393 g of **11a** in 1 mL of pyridine and 2 mL of CH_2Cl_2 was added 0.175 mL (2.25 mmol) of MsCl. After being stirred at rt for 2.75 h, the reaction mixture was diluted with Et_2O, washed with 1 M aqueous HCl and brine, dried, and evaporated. The

remaining residue was flash chromatographed (PE:EA = 5:1 to 3:1) to give 0.416 g (85% from (+)-**10**) of (+)-**12** as a colorless oil: ^{1}H NMR δ 0.51 (ddd, *J* = 13.6, 3.4, 1.8 Hz, 1H), 0.66 (s, 3H), 0.67 (s, 3H), 0.68 (s, 3H), 0.69-1.02 (m, 2H), 1.38 (apparently tt, *J* = 12.9, 3.9 Hz, 1H), 1.45 (apparently t, *J* = 12.6 Hz, 1H), 1.67 (ddd, *J* = 13.0, 4.7, 1.8 Hz, 1H), 1.78 (apparently t, *J* = 13.4 Hz, 1H), 1.88-2.09 (m, 4H), 2.25 (s, 3H), 2.64 (m, 1H), 4.27 (dd, *J* = 11.9, 4.8 Hz, 1H), 4.96 (br s, 1H), 5.03 (br d, *J* = 5.1 Hz, 1H), 5.81 (m, 1H); ^{13}C NMR δ 9.54 (q), 25.78 (q), 31.72 (s), 32.22 (q), 33.72 (t), 37.86 (q), 38.51 (s), 40.11 (d), 40.49 (t), 40.93 (t), 43.28 (t), 43.34 (t), 45.26 (d), 86.07 (d), 116.37 (t), 136.66 (d), 207.72 (s); MS *m/z* (r.i.) 328 (M^+, 4), 232 (13), 217 (6), 122 (6), 95 (7), 73 (10), 81 (10), 79 (100), 32 (54), 31 (65); HRMS calcd for $C_{17}H_{28}O_4S$ (M^+) 328.1708, found 328.1703; $[\alpha]_D^{20}$ = +10° ($CHCl_3$, c = 1.32).

(1*S*,4a*S*,8a*R*)-1,2,3,4,4a,5,8,8a-Octahydro-3,3,8a-trimethyl-6-[(trimethylsilyl)oxy]-1-[(methylsulfonyl)oxy]-7-(2-propenyl)-naphthalene (2).

To a solution of 0.392 g (1.20 mmol) of (+)-**12** in 10 mL of CH_2Cl_2 were added 0.685 mL (3.25 mmol) of HMDS and 0.37 mL (2.60 mmol) of TMSI. The reaction mixture was stirred at rt for 35 min, after which the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and Et_2O. The organic phase was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried, and evaporated yielding 0.537 g of **2** as a yellow oil which was used in the next reaction without purification. A pure sample was obtained after flash chromatography (PE:EA = 5:1): ^{1}H NMR δ 0.14 (s, 9H), 0.74 (s, 3H), 0.74-0.88 (m, 2H), 0.75 (s, 3H), 0.78 (s, 3H), 1.43-1.86 (m, 5H), 1.97 (br d, *J* = 16.5 Hz, 1H), 2.11 (br d, *J* = 16.5 Hz, 1H), 2.30 (s, 3H), 2.80 (dd, *J* = 6.8, 14.6 Hz, 1H), 2.94 (dd, *J* = 6.8, 14.6 Hz, 1H), 4.52 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.99 (br d, *J* = 9.9 Hz, 1H), 5.06 (br d, *J* = 17.0 Hz, 1H), 5.79 (apparently ddt, *J* = 6.8, 9.9, 17.0 Hz, 1H); ^{13}C NMR δ 0.56 (3q), 9.56 (q), 25.40 (q), 31.66 (s), 32.46 (q), 34.06 (t), 34.69 (t), 35.94 (d), 37.37 (s), 37.88 (q), 40.47 (t), 40.59 (t), 41.26 (t), 86.70 (d), 111.15 (s), 115.08 (t), 136.45 (d), 142.07 (s).

(1a*R*,3a*S*,6a*S*,6b*R*)-1,3,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethyl-1a-(2-propenyl)cyclopropa[*e*]inden-2(1a*H*)-one [(–)-3].

To a stirring solution of 0.537 g of **2** and 0.545 mL (2.58 mmol) of HMDS in 10 mL of degassed toluene was added 0.662 g (2.38 mmol) of MgI_2. After being stirred at rt for 1.3 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with Et_2O. The organic phase was washed successively with brine, 1 M aqueous HCl, brine, and saturated aqueous $Na_2S_2O_3$. After drying and evaporation the remaining residue was flash chromatographed (PE:EA = 10:1) to give 0.247 g (89%) of (–)-**3** as a yellow oil: ^{1}H NMR δ 0.37 (d, *J* = 5.0 Hz, 1H), 0.82 (s, 3H), 0.91 (s, 3H), 0.94 (m, 1H), 0.96 (s, 3H), 1.01 (d, *J* = 5.0 Hz, 1H), 1.12 (apparently t, *J* = 12.5 Hz, 1H), 1.37 (dd, *J* =13.3, 6.7 Hz, 1H), 1.47 (dd, *J* =12.5, 6.5 Hz, 1H), 1.75-2.26 (m, 5H), 2.84 (dd, *J* = 14.9, 6.7 Hz, 1H), 5.02 (br d, *J* =10.2 Hz, 1H), 5.07 (br d, *J* = 17.0 Hz, 1H), 6.07 (apparently ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H); ^{13}C NMR δ 20.60 (q), 26.30 (t), 30.91 (q), 31.42 (q), 32.40 (s), 33.31 (t), 35.56 (d), 37.20 (s), 38.80 (s), 40.85 (t), 43.44

(d), 45.32 (t), 48.98 (t), 115.63 (t), 137.45 (d), 207.50 (s); MS *m/z* (r.i.) 232 (M^+, 59), 163 (100), 136 (29), 123 (43), 121 (34), 107 (47), 95 (69), 93 (27), 67 (32), 41 (30); HRMS calcd for $C_{16}H_{24}O$ (M^+) 232.1827, found 232.1824; $[\alpha]_D^{20} = -29°$ ($CHCl_3$, c = 1.85).

Trimethylsilyl enol ether of (–)-3: ^1H NMR (major peaks) δ 0.21 (s, 9H), 1.01 (s, 3H), 1.14 (s, 3H), 1.16 (s, 3H), 3.05 (dd, *J* = 15.2, 6.3 Hz, 1H), 4.30 (d, *J* = 4.4 Hz, 1H), 5.01-5.20 (m, 2H), 6.07 (m, 1H).

(1a*S*,3a*S*,6a*S*,6b*R*)-1,3,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethyl-1a-[(1*E*)-1-propenyl]-cyclopropa[*e*]inden-2(1a*H*)-one [(+)-*E*-13] and (1a*S*,3a*S*,6a*S*,6b*R*)-1,3,3a,4,5,6,6a,6b-octahydro-5,5,6b-trimethyl-1a-[(1*Z*)-1-propenyl)]cyclopropa[*e*]inden-2(1a*H*)-one (*Z*-13).

To a stirring solution of 36.8 mg (0.159 mmol) of (–)-**3** in 2 mL of abs EtOH were added 22 mg (0.159 mmol) of K_2CO_3 and 4.7 mg (17.9 μmol) of $RhCl_3 \cdot 3H_2O$. The reaction mixture was heated at 60 °C for 2 h, allowed to come rt, and diluted with Et_2O. The organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give 28.3 mg (77%) of a 10:1 mixture of (+)-*E*-**13** and *Z*-**13** as a colorless oil.

(+)-*E*-**13** was obtained after careful flash chromatography: ^1H NMR (400 MHz) δ 0.82 (s, 3H), 0.90 (s, 3H), 0.90 (d, *J* = 5.2 Hz, 1H), 0.93 (s, 3H), 1.05 (dd, *J* = 13.2, 3.8 Hz, 1H), 1.11 (apparently t, *J* = 12.5 Hz, 1H), 1.14 (d, *J* = 5.2 Hz, 1H), 1.41 (ddd, *J* = 13.2, 7.3, 0.8 Hz, 1H), 1.48 (dd, *J* = 12.5, 6.6 Hz, 1H), 1.65 (dd, *J* = 6.5, 1.7 Hz, 3H), 1.89-1.99 (m, 2H), 2.16 (apparently dt, *J* = 12.4, 7.0 Hz, 1H), 2.23 (m, 1H), 5.31 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.09 (dd, *J* = 15.5, 1.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 18.20 (q), 20.54 (q), 24.79 (t), 30.60 (q), 31.22 (q), 35.79 (s), 36.45 (d), 37.42 (s), 41.37 (t), 42.12 (s), 43.30 (d), 45.90 (t), 49.73 (t), 127.40 (d), 127.62 (d), 206.98 (s); MS *m/z* (r.i.) 232 (M^+, 20), 190 (100), 175 (22), 136 (26), 135 (20), 121 (33), 107 (22), 95 (29), 67 (28), 41 (23); HRMS calcd for $C_{16}H_{24}O$ (M^+) 232.1827, found 232.1825; $[\alpha]_D^{20} = +20°$ ($CHCl_3$, c = 1.16).

Z-**13** was obtained after careful flash chromatography: ^1H NMR δ 0.58 (d, *J* = 4.8 Hz, 1H), 0.83 (s, 3H), 0.93 (s, 3H), 0.96 (s, 3H), 0.99-1.53 (m, 4H), 1.28 (d, *J* = 4.8 Hz, 1H), 1.63 (br d, *J* = 6.8 Hz, 3H), 1.69-2.03 (m, 2H), 2.05-2.41 (m, 2H), 5.40 (br d, *J* = 10.6 Hz, 1H), 5.80 (dq, *J* = 10.6, 6.8 Hz, 1H); ^{13}C NMR δ 14.78 (q), 21.25 (q), 28.68 (t), 30.68 (q), 31.42 (q), 33.16 (s), 35.87 (d), 37.25 (s), 38.33 (s), 40.87 (t), 42.91 (d), 45.27 (t), 48.97 (t), 126.97 (d), 131.26 (d), 204.74 (s).

(1a*R*,3a*S*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethyl-2-oxo-1*H*-cyclopropa-[*e*]indene-1a-carbaldehyde [(+)-14].

A solution of 38.5 mg (0.166 mmol) of (+)-*E*-**13** in 3 mL of MeOH and 1 mL of CH_2Cl_2 was cooled to –78 °C and O_3 was bubbled through the solution until the solution turned faintly blue. Then the reaction mixture was purged with nitrogen and a few drops of DMS were added. The reaction mixture was allowed to come to rt, stirred for 1.5 h, and concentrated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give 9.6 mg (26%) of (+)-**14** as a colorless

oil: ^{1}H NMR δ 0.76 (s, 3H), 0.84-0.96 (m, 2H), 0.87 (s, 3H), 0.94 (s, 3H), 1.03 (d, *J* = 4.9 Hz, 1H), 1.29 (apparenty dd, *J* = 13.4, 7.1 Hz, 2H), 1.62 (m, 1H), 1.67 (d, *J* = 4.9 Hz, 1H), 1.79 (dd, *J* = 17.6, 7.8 Hz, 1H), 1.85 (m, 1H), 2.01 (dd, *J* = 17.6, 8.8 Hz, 1H), 10.50 (s, 1H); ^{13}C NMR δ 17.46 (q), 27.69 (t), 30.95 (q), 31.30 (q), 34.90 (d), 36.66 (s), 40.40 (t), 42.44 (s), 42.98 (d), 44.29 (t), 47.83 (s), 48.21 (t), 196.71 (d), 205.37 (s); MS *m/z* (r.i.) 220 (M^+, 100), 205 (64), 177 (46), 135 (48), 121 (60), 109 (47), 107 (49), 83 (74), 55 (43), 41 (46); HRMS calcd for $C_{14}H_{20}O_2$ (M^+) 220.1463, found 220.1458; $[\alpha]_D^{20}$ = +137° (*t*BuOMe, c = 0.12).

(1a*S*,3a*R*,6a*S*,6b*R*)-2-[(Trifluoromethylsulfonyl)oxy]-1,1a,3a,4,5,6,6a,6b-octahydro-5,5,6b-trimethyl-1a-[(1*E*)-1-propenyl]cyclopropa[*e*]indene [(–)-16].

To a stirring solution of 66.6 mg (0.287 mmol) of (+)-*E*-**13** and 0.205 g (0.573 mmol) of Tf_2NPh in 5 mL of THF, cooled to –78 °C, was added 1.15 mL of KHMDS (0.5 M in toluene). The reaction mixture was stirred at this temperature for 1 h, quenched with brine, allowed to come to rt, and diluted with Et_2O. The organic phase was washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to give 98.4 mg (94%) of (–)-**16** as a colorless oil: ^{1}H NMR δ 0.82 (d, *J* = 4.8 Hz, 1H), 0.84 (s, 3H), 0.86 (s, 3H), 0.93 (d, *J* = 4.8 Hz, 1H), 0.95 (s, 3H), 1.07 (dd, *J* = 13.3, 1.4 Hz, 1H), 1.22 (m, 1H), 1.39-1.52 (m, 2H), 1.60 (dd, *J* = 3.5, 1.2 Hz, 3H), 1.95-2.10 (m, 2H), 5.08 (br s, 1H), 5.40-5.51 (m, 2H); ^{13}C NMR δ 17.68 (q), 20.59 (q), 26.65 (t), 28.89 (s), 29.46 (s), 31.50 (q), 31.75 (q), 37.34 (s), 37.78 (d), 41.12 (d), 45.15 (t), 47.65 (t), 116.96 (d), 119.20 (s; q $J_{C,F}$ = 320 Hz), 125.99 (d), 131.75 (d), 150.47 (s); MS *m/z* (r.i.) 364 (M^+, 80), 231 (59), 203 (100), 135 (39), 119 (27), 105 (36), 95 (48), 91 (25), 69 (54), 28 (32); HRMS calcd for $C_{17}H_{23}O_3SF_3$ (M^+) 364.1320, found 364.1321; $[\alpha]_D^{20}$ = –37° ($CHCl_3$, c = 0.51).

Methyl (1a*S*,3a*R*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-octahydro-5,5,6b-trimethyl-1a-[(1*E*)-1-propenyl]cyclopropa[*e*]indene-2-carboxylate [(–)-17].

Under a CO atmosphere, 1.0 mL of a solution of 23.1 mg (88.1 μmol) of Ph_3P, and 10.0 mg (44.5 μmol) of $Pd(OAc)_2$ in 5.0 mL DMF was added to 53.1 mg (0.146 mmol) of (–)-**16**, 0.236 mL (5.84 mmol) of MeOH, and 41 μL (0.295 mmol) of Et_3N. After being stirred at rt for 17 h, the reaction mixture was diluted with Et_2O, washed with water, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 10:1) to give in order of elution 21.7 mg (54%) of a 2:1 mixture of (–)-**17** and probably the carboxylic acid derivative of (–)-**17** and 12.7 mg (32%) of (–)-**17**, both as colorless oils.

(–)-**17**: ^{1}H NMR δ 0.87 (d, *J* = 4.4 Hz, 1H), 0.91 (s, 3H), 0.92 (d, *J* = 4.4 Hz, 1H), 1.00 (s, 3H), 1.01 (s, 3H), 1.24-1.36 (m, 2H), 1.49-1.60 (m, 2H), 1.65 (dd, *J* = 6.3, 1.5 Hz, 3H), 2.12-2.29 (m, 2H), 3.45 (s, 3H), 5.48 (dq, *J* = 15.5, 6.3 Hz, 1H), 5.68 (dd, *J* =15.5, 1.5 Hz, 1H), 6.12 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR δ 17.97 (q), 22.38 (q), 26.48 (s), 27.08 (s), 28.43 (t), 31.29 (q), 31.76 (q), 37.54 (s), 38.78 (d), 41.41 (d), 45.72 (t), 47.52 (t), 50.93 (q), 126.16 (d), 132.28 (d), 136.66 (d), 136.76 (s), 168.06 (s); MS *m/z* (r.i.) 274 (M^+, 100), 259 (29), 215 (46), 178 (91), 173 (34), 159

(34), 145 (28), 119 (34), 91 (24); HRMS calcd for $C_{18}H_{26}O_2$ (M^+) 274.1933, found 274.1933; $[\alpha]_D^{20} = -28°$ ($CHCl_3$, c = 0.59).

Carboxylic acid derivative of (–)-**17**: ^1H NMR (major peaks) δ 1.70 (dd, *J* = 6.2, 1.3 Hz, 3H), 6.34 (d, *J* = 2.3 Hz, 1H).

((1a*S*,3a*R*,6a*S*,6b*R*)-(1,1a,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethyl-1a-[(1*E*)-1-propenyl]cyclopropa[*e*]inden-2-yl)methanol [(–)-18].

The 2:1 mixture (21.7 mg) obtained in the previous step was dissolved in 2 mL of Et_2O, and to this 5.8 mg (0.153 mmol) of $LiAlH_4$ was added. After being stirred at rt for 15 min, the reaction mixture was quenched with 1 M aqueous HCl and diluted with Et_2O. The organic layer was washed with brine, dried, and evaporated to give 18.6 mg (94%) of (–)-**18** as a colorless oil: ^1H NMR δ 0.78 (d, *J* = 3.8 Hz, 1H), 0.85 (d, *J* = 3.8 Hz, 1H), 0.99 (s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.25-1.43 (m, 3H), 1.54 (br d, *J* = 6.3 Hz, 3H), 1.57-1.75 (m, 2H), 2.28-2.43 (m, 2H), 4.01 (br AB_d, *J* = 13.3 Hz, 1H), 4.15 (br AB_d, *J* = 13.3 Hz, 1H), 5.13 (br s, 1H), 5.35 (dq, *J* = 15.2, 6.3 Hz, 1H), 5.69 (br d, *J* = 15.2 Hz, 1H); ^{13}C NMR δ 17.54 (q), 20.83 (q), 26.27 (t), 26.37 (s), 28.20 (s), 31.74 (q), 32.02 (q), 37.52 (s), 38.52 (d), 42.14 (d), 45.23 (t), 48.30 (t), 65.78 (t), 123.18 (d), 128.41 (d), 130.66 (d), 140.54 (s); MS *m/z* (r.i.) 264 (M^+, 69), 215 (50), 173 (52), 161 (39), 159 (45), 150 (80), 145 (35), 107 (35), 105 (100), 91 (43); HRMS calcd for $C_{17}H_{26}O$ (M^+) 264.1984, found 264.1989; $[\alpha]_D^{20} = -16°$ ($CHCl_3$, c = 0.86).

Similarly, reduction of pure (–)-**17** afforded (–)-**18** in quantitative yield.

(1a*S*,3a*R*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethyl-1a-[(1*E*)-1-propenyl]-cyclopropa[*e*]indene-2-carbaldehyde (19).

To a stirring solution of 17.9 mg (72.8 μmol) of (–)-**18** in 2 mL of CH_2Cl_2 was added 39.8 mg (0.143 mmol) of PCC. After being stirred at rt for 1.5 h, the reaction mixture was flash chromatographed (PE:EA = 10:1) to give 4.4 mg (25%) of **19** as a colorless oil: ^1H NMR δ 0.60 (d, *J* = 4.4 Hz, 1H), 0.81 (d, *J* = 4.4 Hz, 1H), 0.89 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 1.11 (apparently t, *J* = 12.2 Hz, 1H), 1.19 (dd, *J* = 13.3, 2.5 Hz, 1H), 1.48 (br dd, *J* = 12.2, 6.3 Hz, 1H), 1.57 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.67 (br d, *J* = 6.4 Hz, 3H), 2.01-2.30 (m, 2H), 5.31 (dq, *J* = 15.4, 6.4 Hz, 1H), 5.72 (br d, *J* = 15.4 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR[28] δ 17.64 (q), 20.91 (q), 25.91 (s), 26.52 (t), 26.90 (s), 31.00 (q), 31.50 (q), 37.27 (s), 39.13 (d), 41.46 (d), 45.33 (t), 47.01 (t), 126.32 (d), 130.19 (d), 146.62 (d), 191.44 (d); MS *m/z* (r.i.) 244 (M^+, 19), 229 (100), 159 (24), 148 (31), 145 (25), 133 (40), 131 (23), 105 (24), 91 (29), 41 (22); HRMS calcd for $C_{17}H_{24}O$ (M^+) 244.1827, found 244.1826.

(1a*R*,3a*R*,6a*S*,6b*R*)-2-[(Trifluoromethylsulfonyl)oxy]-1,1a,3a,4,5,6,6a,6b-octahydro-1a-(hydroxymethyl)-5,5,6b-trimethylcyclopropa[*e*]indene [(–)-20].

Through a solution of 34.1 mg (93.7 μmol) of (–)-**16** in 5 mL of freshly distilled CH_2Cl_2, cooled to –78 °C, O_3 was bubbled until the solution turned faintly blue. Then the reaction mixture

was immediately purged with nitrogen and 15 drops of DMS were added. After 10 min, 18.5 mg (0.489 mmol) of $NaBH_4$, followed by 5 mL of MeOH were added, and the reaction mixture was allowed to come to rt and stirred for another 40 min. Then the reaction mixture was quenched with 1 M aqueous HCl, diluted with Et_2O, washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 3:1) to afford, in order of elution, 4.7 mg (12%) of probably a diastereomeric mixture of two cross ozonides and 12.9 mg (39%) of (–)-**20**, both as colorless oils.

(–)-**20**: ^{1}H NMR δ 0.34 (d, J = 4.8 Hz, 1H), 0.46 (br s, O<u>H</u>), 0.79 (d, J = 4.8 Hz, 1H), 0.84 (s, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 1.05 (dd, J = 13.3, 1.5 Hz, 1H), 1.36-1.49 (m, 3H), 1.90-2.02 (m, 2H), 2.90 (br AB_d, J = 12.1 Hz, 1H), 4.11 (br AB_d, J = 12.1 Hz, 1H), 5.15 (br s, 1H); ^{13}C NMR δ 20.24 (q), 26.65 (t), 28.03 (s), 28.13 (s), 31.60 (2q), 37.24 (s), 37.52 (d), 41.49 (d), 45.01 (t), 47.62 (t), 61.15 (t), 118.29 (d), 119.18 (s; q $J_{C,F}$ = 320 Hz), 150.01 (s); MS *m/z* (r.i.) 354 (M^+, 42), 221 (100), 203 (57), 161 (40), 107 (40), 105 (39), 95 (42), 91 (47), 69 (54), 41 (38); HRMS calcd for $C_{15}H_{21}O_4SF_3$ (M^+) 354.1113, found 354.1112; $[\alpha]_D^{20}$ = –31° ($CHCl_3$, c = 0.25).

cross ozonides: ^{1}H NMR (major peaks) δ 1.26 (d, J = 5.0 Hz, 3H), 1.31 (d, J = 5.0 Hz, 3H), 5.06 (s, 1H), 5.11 (q, J = 5.0 Hz, 2H), 5.19 (s, 1H); ^{13}C NMR (major peaks) δ 102.4 (d), 103.0 (d), 104.0 (2d).

Ozonolysis of *Z*-12 to (–)-20 and (1a*S*,3a*R*,6a*S*,6b*R*)-2-[(Trifluoromethylsulfonyl)oxy]-1,1a,3a,4,5,6,6a,6b-octahydro-5,5,6b-trimethyl-cyclopropa[*e*]indene-1a-carbaldehyde (15).

Through a solution of 14.8 mg (40.7 μmol) of *Z*-**16** in 5 mL of freshly distilled CH_2Cl_2, cooled to –78 °C, O_3 was bubbled until the solution turned faintly blue. Then the reaction mixture was immediately purged for 10 min with nitrogen followed by the addition of 0.5 mL of DIBALH (1 M in hexane). After 30 min, the reaction mixture was quenched with 1 M aqueous HCl, diluted with Et_2O, brought to rt, washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 5:1) to give 5.0 mg (35%) of (–)-**20** as a colorless oil and 3.6 mg of impure **15** as a colorless oil.

15: ^{1}H NMR (major peaks) δ 0.76 (s, 3H), 0.84 (s, 3H), 0.85 (s, 3H), 5.10 (d, J = 2.2 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR[29] δ 18.32 (q), 29.82 (t), 30.17 (s), 31.34 (q), 31.56 (q), 36.98 (s), 37.48 (d), 39.22 (s), 41.00 (d), 44.92 (t), 47.10 (t), 119.14 (d), 145.56 (s), 194.36 (d).

Reduction of 15 to (–)-20.

To a stirring solution of 3.6 mg (10.2 μmol) of **15** in 1 mL of MeOH and 1 mL of CH_2Cl_2 was added 7.1 mg (0.188 mmol) of $NaBH_4$. After being stirred at rt for 1.3 h, the reaction mixture was diluted with Et_2O, quenched with 1 M aqueous HCl, washed with brine, dried, and evaporated to afford 2.2 mg (61%) of (–)-**20**.

(1a*S*,5a*S*,8a*S*,8b*R*)-5a,6,7,8,8a,8b-Hexahydro-7,7,8b-trimethyl-cyclopropa[4,5]indeno-[5,6-*c*]furan-4(1*H*)-one [(–)-21].

Under a CO atmosphere, 1.0 mL of a DMF solution containing 47.5 μL (1.17 mmol) of MeOH, 8.2 μL (59 μmol) of Et_3N, 0.93 mg (3.5 μmol) of Ph_3P, and 0.40 mg (1.8 μmol) of $Pd(OAc)_2$ was added to 10.4 mg (29.4 μmol) of (–)-**20**. After being stirred at rt for 3.25 h, the reaction mixture was diluted with PE, washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (PE:EA = 3:1) to give 5.8 mg (85%) of (–)-**21** as a white solid: ^{1}H NMR (400 MHz) δ 0.66 (s, 3H), 0.68 (d, J = 4.5 Hz, 1H), 0.80-0.86 (m, 2H), 0.82 (s, 3H), 0.83 (s, 3H), 1.14 (dd, J = 13.4, 1.7 Hz, 1H), 1.21 (m, 1H), 1.48 (dd, J = 13.4, 8.4 Hz, 1H), 1.95-2.06 (m, 2H), 3.64 (AB_d, J = 8.8 Hz, 1H), 3.82 (AB_d, J = 8.8 Hz, 1H), 6.18 (d, J = 2.1 Hz, 1H); ^{13}C NMR δ (100 MHz) 19.07 (q), 24.97 (s), 26.76 (s), 26.95 (t), 31.70 (q), 31.84 (q), 37.56 (s), 40.12 (d), 42.28 (d), 44.57 (t), 47.30 (t), 69.89 (t), 130.20 (s), 133.50 (d), 168.82 (s); MS *m/z* (r.i.) 232 (M^+, 91), 217 (100), 187 (53), 176 (27), 147 (31), 122 (57), 121 (54), 107 (29), 91 (33), 84 (32); HRMS calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1463; $[\alpha]_D^{20}$ = –16° ($CHCl_3$, c = 0.29).

(1a*S*,3a*R*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-Octahydro-5,5,6b-trimethylcycloprop[*e*]indene-1a,2-dimethanol (22).

To a stirring solution of 5.8 mg (25.0 μmol) of (–)-**21** in 2 mL of Et_2O, cooled to –78 °C, was added 0.125 mL of DIBALH (1 M in hexane). After stirring at –78 °C for 15 min, the reaction mixture was allowed to come to rt. Then another 50 μL of DIBALH (1 M in hexane) was added, and stirring was continued for 25 min. After dilution with Et_2O, the reaction mixture was quenched with 1 M aqueous HCl, washed with brine, dried, and evaporated to give 5.6 mg of **22** as a white solid, which was used in the next reaction without purification.

(+)-Isovelleral (4).

To a stirring solution of 17 μL (0.192 mmol) of oxalyl chloride in 1.2 mL of CH_2Cl_2, cooled to –78 °C, were added successively 27 μL (0.377 mmol) of DMSO and a solution of 5.6 mg of **22** in 0.3 mL of CH_2Cl_2 and 0.1 mL of DMSO. After stirring at –78 °C for 25 min, another 20 μL (0.225 mmol) of oxalyl chloride was added, and stirring was continued for 10 min. Then the reaction mixture was quenched with 0.10 mL (0.719 mmol) of Et_3N and, after stirring for 5 min, allowed to come to rt and filtered through a short pad of silica gel. The filter cake was washed with PE:EA = 3:1, and the combined filtrates were concentrated. The remaining residue was flash chromatographed (PE:EA = 5:1) to afford 3.2 mg (55% from (–)-**21**) of (+)-**4** as a white solid: $[\alpha]_D^{20}$ = +234° ($CHCl_3$, c = 0.16).[2,25]

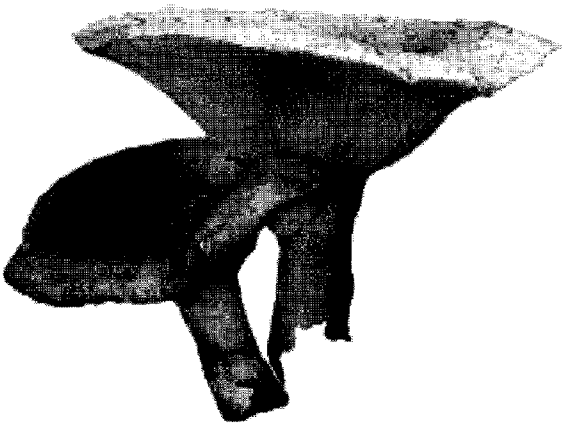
5.5 References and Notes

1. (a) Vidari, G.; Vita-Finzi, P. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, **1995**; Vol. 17, pp 153-206. (b) Daniewski, W. M.; Vidari, G. *Progress In The Chemistry Of Organic Natural Products* **1999**, *77*, 69.
2. Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B. *J. Chem. Soc., Chem. Comm.* **1990**, 865.
3. (a) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3004. (b) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5979.
4. (a) See Chapter 4. (b) Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron: Asymm.* **1999**, *10*, 2729.
5. Hanselmann, R.; Benn, M. *Synth. Commun.* **1996**, *26*, 945.
6. An attempt to synthesize **5** was made, but failed in the last step due to resisted formation of the silyl enol ether.
7. See Chapter 3.
8. TMSI formed in the MgI_2-induced rearrangement-cyclopropanation reaction is known to cleave acetals. See: Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *48*, 4175.
9. Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374.
10. In case of overreduction, oxidation of the crude mixture with PDC was applied.
11. Acidic workup was required to remove HMDS and to hydrolyze the silyl enol ether of (–)-**3** also present in the reaction mixture.
12. (a) Takemoto, Y.; Ohra, T.; Sugiyama, K.; Imanishi, T.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 571. (b) Nakamura, H.; Arata, K.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, 2435.
13. Although crude ^{1}H NMR spectroscopy revealed the presence of aldehyde (+)-**14** as major product, its low yield after purification by chromatography can be explained by the opening of the highly activated cyclopropane ring on column.
14. According to reference 3, the synthesis of the enol triflate derived from **6** proceeds without problems.
15. (a) Staroske, T.; Hennig, L.; Welzel, P.; Hofmann, H.-J.; Müller, D.; Häusler, T.; Sheldrick, W. S.; Zillikens, S.; Gretzer, B.; Pusch, H.; Glitsch, H. G. *Tetrahedron* **1996**, *52*, 12723. (b) Odinokov, V. N.; Ishmuratov, G. Y.; Sokol'skaya, O. V.; Galeeva, R. I.; Muslukhov, R. R.; Tolstikov, G. A. *Russ. J. Org. Chem.* **1993**, *29*, 19.
16. The formation of carboxylic acid can be explained by traces of water present in DMF or MeOH used.
17. Reduction of (–)-**17** with DIBALH afforded also alcohol (–)-**18**.

18. Probably the Swern-oxidation used for a similar transformation would be a better method (*vide infra*, reference 3).
19. Oxidative cleavage of the propenyl moiety with OsO_4 in the presence of $NaIO_4$[12a] was unsuccessful probably due to steric hindrance.
20. Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Suzuki, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 31.
21. Wu, H.-J.; Lin, C.-C. *J. Org. Chem.* **1996**, *61*, 3820.
22. For NMR data of cross-ozonides see: Griesbaum, K.; Bandyopadhyay, A. R.; Meister, M. *Can. J. Chem.* **1986**, 1553.
23. Longer reaction time and the use of more $NaBH_4$ gave the same ozonide mixture.
24. Ozonolysis of *Z*-**16**, obtained after careful column chromatography, in CH_2Cl_2 at –78 °C gave after quenching with excess of DIBALH a separable mixture of (–)-**20** and aldehyde **15**. Aldehyde **15** could be converted to alcohol (–)-**20** by treatment with $NaBH_4$, through which the total yield of (–)-**20** in this reaction amounted to 50%.
25. Magnusson, G.; Thorén, S.; Wickberg, B. *Tetrahedron Lett.* **1972**, 1105.
26. See also paragraph 2.4.1.
27. Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.
28. The signal of C(7) was most probaly covered by the signal of benzene-d_6.
29. Due to the low concentration of the sample the $\underline{C}F_3$ signal could not be assigned.

Chapter 6

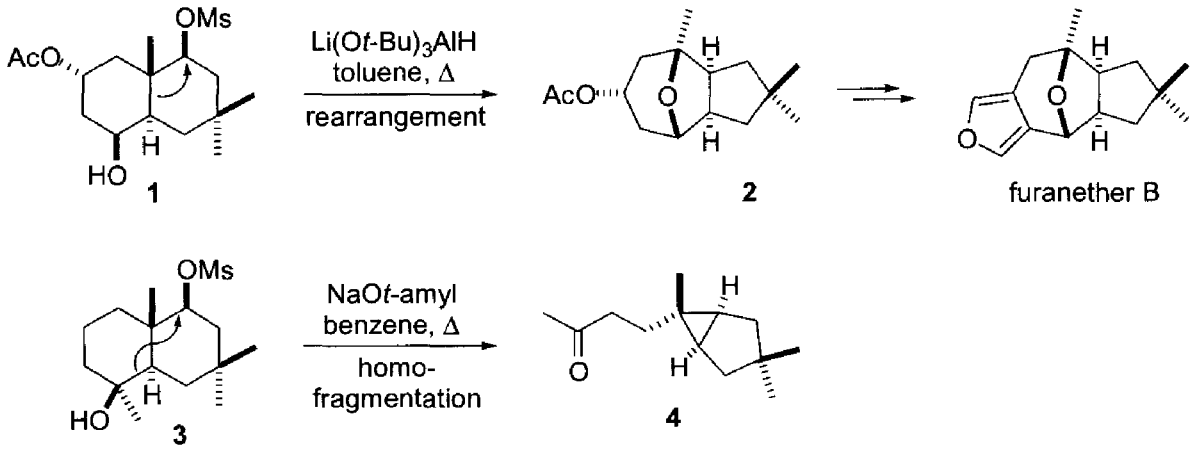
Concluding Remarks and Outlook



6.1 General Discussion

The chemical consequences of long range orbital interactions in perhydronaphthalene-1,4-diol monosulfonate esters have been studied extensively by Wijnberg and de Groot in the last decade. In addition to studies focussed on the mechanistic aspects of through-bond interactions (TBI),[1] their applications to total syntheses have been demonstrated with the typical reactions of carbocations, like rearrangement, (homo)fragmentation, and elimination, as the key step.[2] In this thesis other examples of how TBI-mediated transformations of perhydronaphthalene-1,4-diol monosulfonate esters can be used in sesquiterpene synthesis are presented.

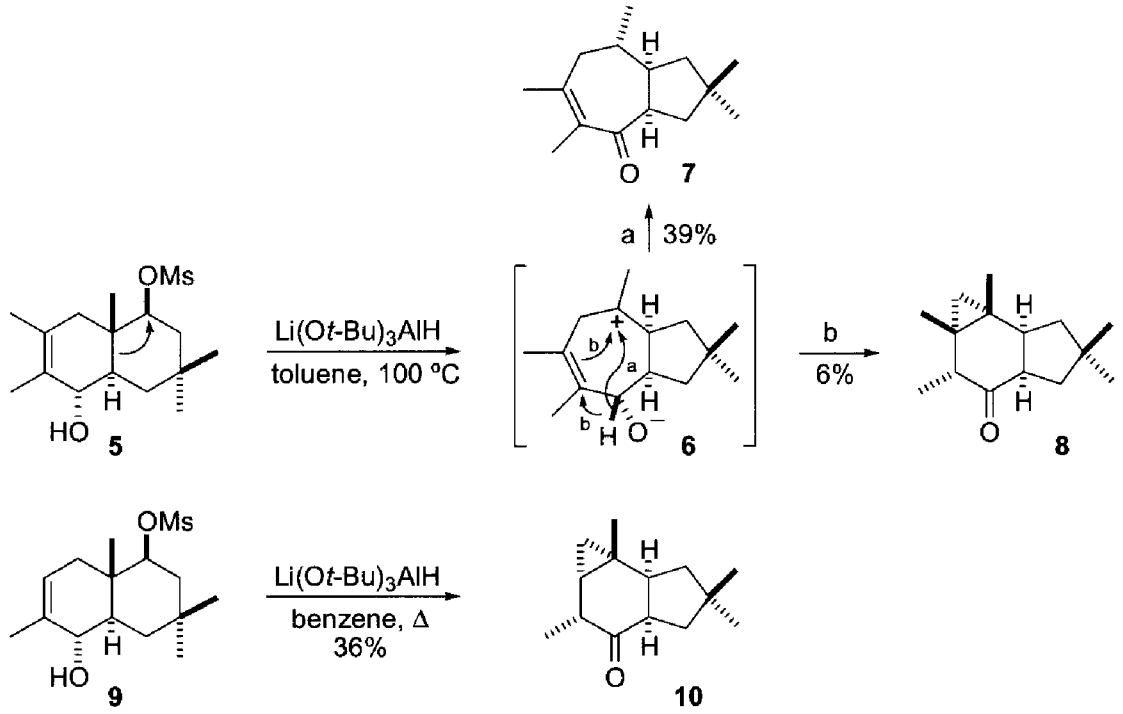
Scheme 1



The successful synthesis of furanether B, described in Chapter 2, demonstrates that decreasing the electron-donating ability of an alkoxide derived from an all-*trans* perhydronaphthalene-1,4-diol monosulfonate ester results in rearrangement (**1** → **2**) instead of homofragmentation (**3** → **4**) (Scheme 1).[3]

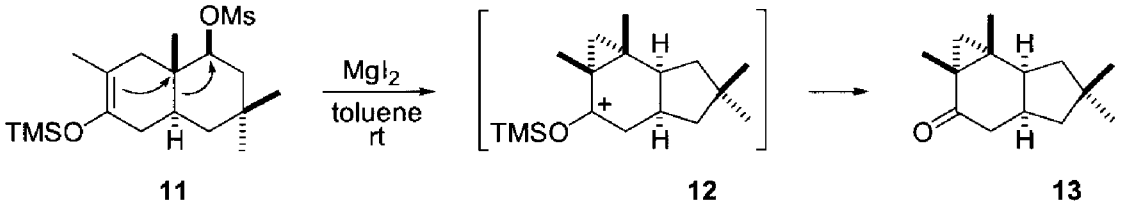
The concept of base-induced rearrangement of perhydronaphthalene-1,4-diol monosulfonate esters developed for the synthesis of furanether B, in combination with an intramolecular cyclopropanation proved to be less successful for the synthesis of the marasmane skeleton **8** (Scheme 2). Although rearrangement of mesylate **5** took place, the resulting cation **6** reacted preferentially to the lactarane ketone **7** (39%) via a transannular hydrogen shift. The formation of marasmane **8**, only in trace amounts (6%), is explained by the highly energetic transition state leading to **8** due to unfavorable Pitzer strain. Support for this explanation was found when mesylate **9** was treated under similar conditions, affording the normarasmane **10** with less Pitzer strain (H instead of Me) in moderate yield (36%).

Scheme 2



Therefore, to overcome the energetically unfavorable Pitzer strain, the stability of the cyclopropylcarbinyl cation formed after the cyclopropanation step was strongly enhanced by introducing an oxygen atom, adjacent to the cationic center. The intermediacy of this very stable oxonium ion **12** generated upon treatment of mesylate **11** with MgI_2 at room temperature proved to be very effective and the desired normarasmane ketone **13** could be isolated in good yield (73%) (Scheme 3).

Scheme 3

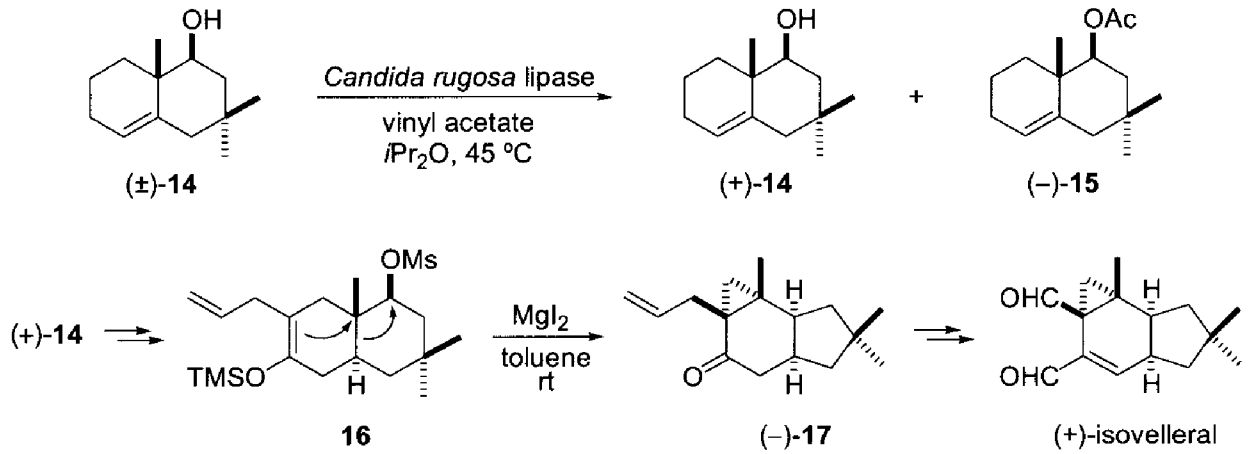


The use of MgI_2 in the reaction of mesylate **11** turned out to be a valuable alternative for the TBI-initiated sulfonate heterolysis. A synthetic advantage of this new methodology is that the synthesis of starting material for these rearrangement reactions is simplified since the laborious introduction of the α-alcohol at C(6) can be omitted. A further advantage of this system turned out to be the mild reaction conditions (room temperature) facilitating rearrangement.

Optically pure (+)-**14**, needed as starting material for the preparation of (+)-isovelleral by following the methodology described for the synthesis of the marasmane skeleton, was obtained

via an enzymatic resolution of racemic **14** by using *Candida rugosa* lipase (Scheme 4). An alternative preparation of (+)-**14** analogous to a method reported in the literature[4] was unsuccessful, probably for steric reasons.

Scheme 4



The synthesis of (+)-isovelleral via the MgI_2-induced tandem rearrangement-cyclopropanation reaction of substrate **16**, prepared from (+)-**14**, was successful. Although the oxidative degradation of the C(8) substituent was not optimized (Scheme 4) it was shown that a selective ozonolysis of a disubstituted double bond in the presence of an enol triflate is possible.

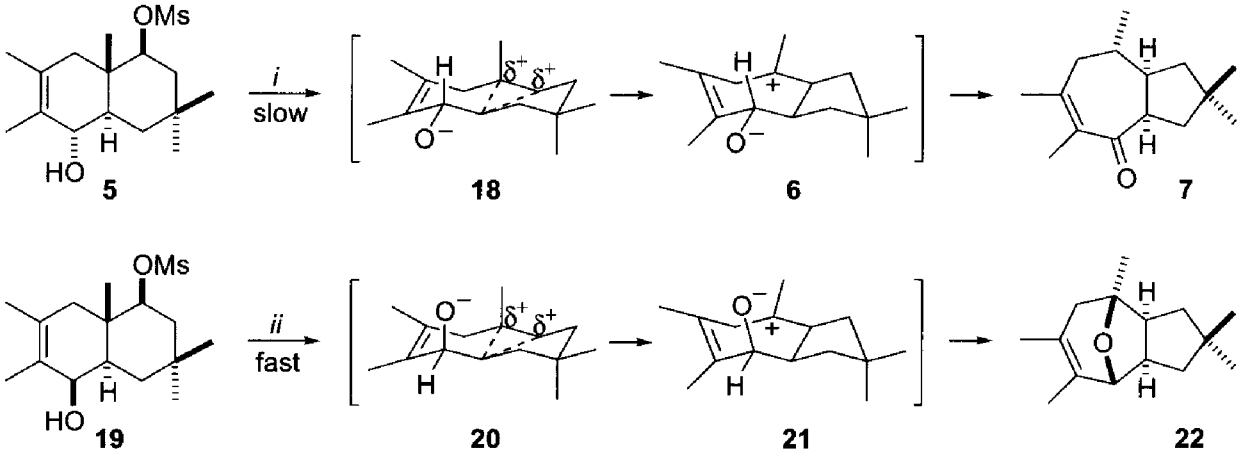
More straightforward syntheses of (+)-isovelleral via the rearrangement-cyclopropanation of C(8) oxygenated compounds similar to **16** were attempted, but failed due to difficulties in the preparation of these substrates.

6.2 Stability of Cationic Intermediates

The concept of TBI explains very well most of the differences in reactivity and product formation observed for perhydronaphthalene-1,4-diol monosulfonate esters upon treatment with strong base.[1] However, one aspect of these cation-mediated reactions, which proved to be very significant during the investigations described in this thesis, was not considered in detail. The studies conducted toward the synthesis of the marasmane skeleton clearly revealed that in addition to stabilization by TBI, the stability of the intermediate and final cationic species is also important. This is very well illustrated by the reactions of the α- and β-alcohols **5** and **19** with $Li(Ot\text{-}Bu)_3AlH$ (Scheme 5).

Whereas exposure of α-alcohol **5** to $Li(Ot\text{-}Bu)_3AlH$ in refluxing toluene resulted in a slow formation of the rearranged enone **7**, treatment of β-alcohol **19** under similar conditions gave a relatively fast conversion to the rearranged cyclic ether **22**. Since it has been shown that TBI for

Scheme 5



i 3.2 eq. Li(O*t*-Bu)$_3$AlH, toluene, 100 °C, 3 h, 39% **7**, 12% **5**

ii 2.2 eq. Li(O*t*-Bu)$_3$AlH, toluene, 100 °C, 2 h, 55% **22**

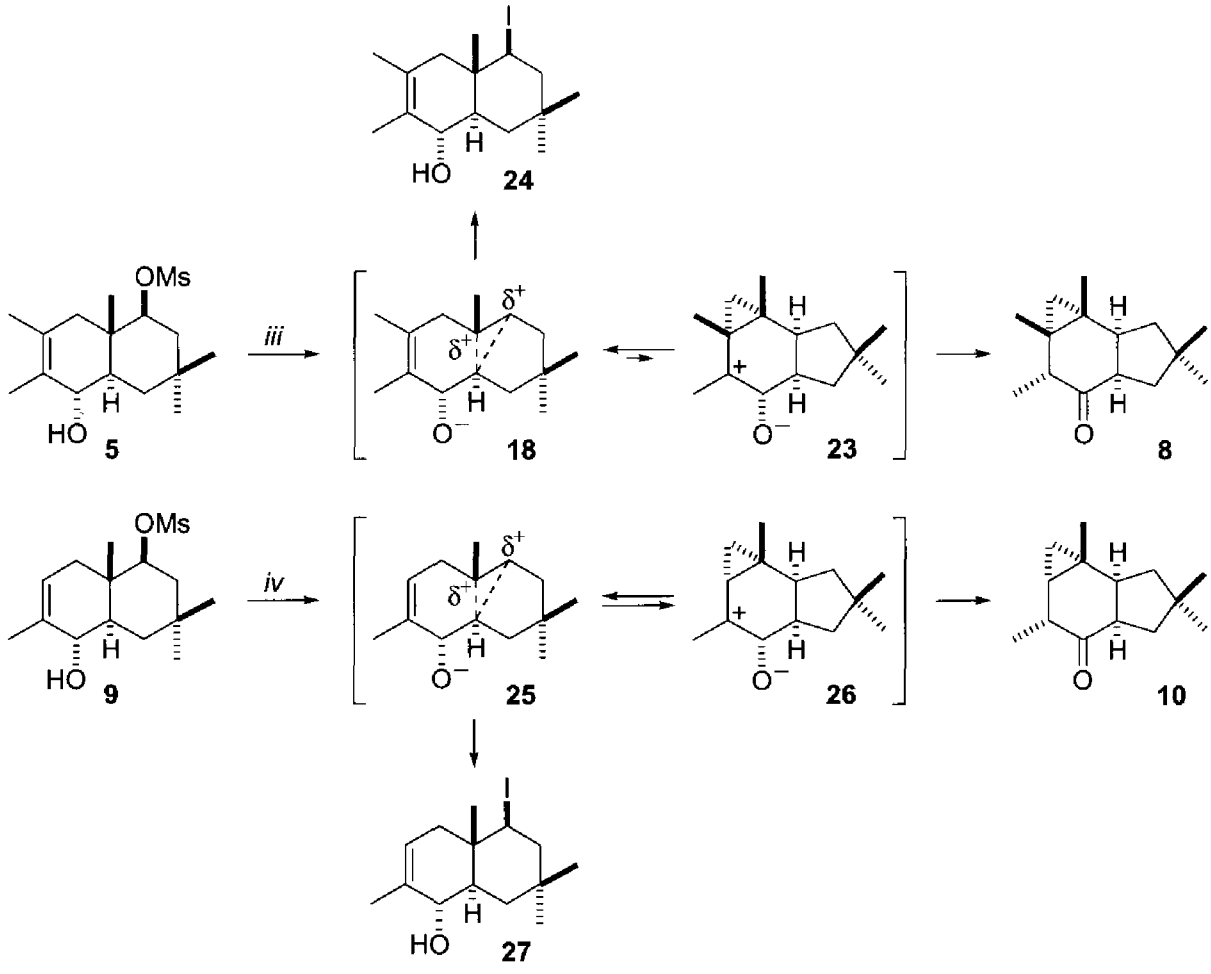
epimeric alcohols are equal,[3,5] the difference in reaction rate between **5** and **19** can be explained by the ease of stabilizing the tertiary cations **6** and **21**. The lone pair of the β-positioned alcoholate in intermediate **21** is closer to the tertiary cation then the more distant σ-bond of H(6) in intermediate **6**. Therefore, the positive charge in the former is trapped more easily as a result of which **19** will react faster.

The rate determining step of these reactions is most probably the generation of the initial bridged cations **18** and **20** and therefore any stabilizing factor in another part of the reaction sequence has normally no influence on the reaction rate. Nevertheless the above described explanation is still valuable. Since the initially formed bridged cations **18** and **20** are generated in apolar solvents like benzene or toluene, it is most likely that they exist as contact ion pairs with the mesylate as counterion. As a consequence, rearrangement of these species has to compete with recombination of the mesylate (internal return) and therefore, any stabilizing factor in the process of rearrangement will result in a faster reaction.

A similar influence of the stability of intermediate cations on the reaction outcome was observed for rearrangements initiated by magnesium salts. For instance, treatment of mesylate **5** with MeMgI gave iodide **24** (56%) as the major product (Scheme 6). Treatment of mesylate **9** under similar conditions resulted in the formation of a mixture of iodide **27** (31%) and the rearranged ketone **10** (23%). In these transformations there are two different pathways by which the bridged intermediates **18** and **25** can react: attack of iodide and rearrangement. The rate of the first, S_N1 like process, is more or less the same for both intermediates **18** and **25**. Therefore, the composition of the reaction mixture is determined by the rate of rearrangement. Since the less Pitzer-strained cation **26** is more stable then cation **23**, its formation will be easier resulting in a higher yield of the cyclopropane product **10** in comparison to compound **8**. Another consequence

of the better stabilized cation **26** is that iodide formation in the reaction of mesylate **9** will be less than found for the reaction of **5**.

Scheme 6



iii 2.5 eq. MeMgI, toluene, rt, 1.2 h, 6% **8**, 56% **24**

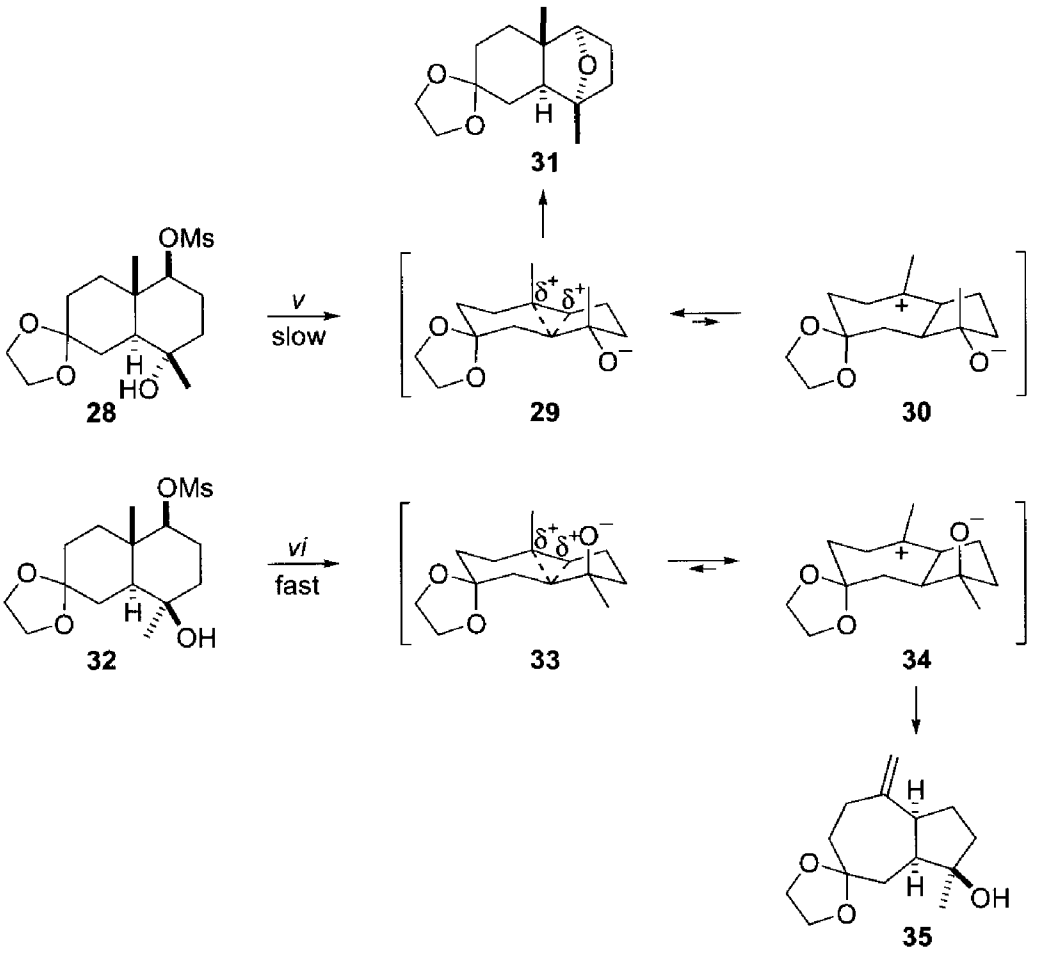
iv 3.9 eq. MeMgI, benzene, rt, 35 min, 23% **10**, 31% **27**

Increasing the stability of the cyclopropylcarbinyl cation by introduction of an oxygen atom adjacent to the positive charge can even result in selective formation of a rearranged cyclopropane adduct. This was demonstrated with mesylate **11**, which on exposure to MgI_2 selectively gave ketone **13** with the stable oxonium ion **12** as intermediate (Scheme 3).

A similar difference in reaction rate, as observed for the epimeric alcohols **5** and **19** was reported by Orru *et al.* for the epimeric alcohols **28** and **32** (Scheme 7).[5b] Orru explained this difference as a result of 1,3-diaxial steric hindrance between the angular methyl group at C(10) and the axial methyl group at C(4) in **28**. Therefore the C(5)-C(10) central bond is no longer exactly antiperiplanar to the mesylate group and hence the tendency to rearrange will be diminished. Although this steric hindrance might account for some difference in reaction rate,

stabilization of the positive charge in cation **34** by the proximate β-alcoholate gives a better explanation. Since this additional stabilization is not possible in cation **30**, compound **28** will react slower with the unrearranged bridged ether **31** as the sole product.

Scheme 7

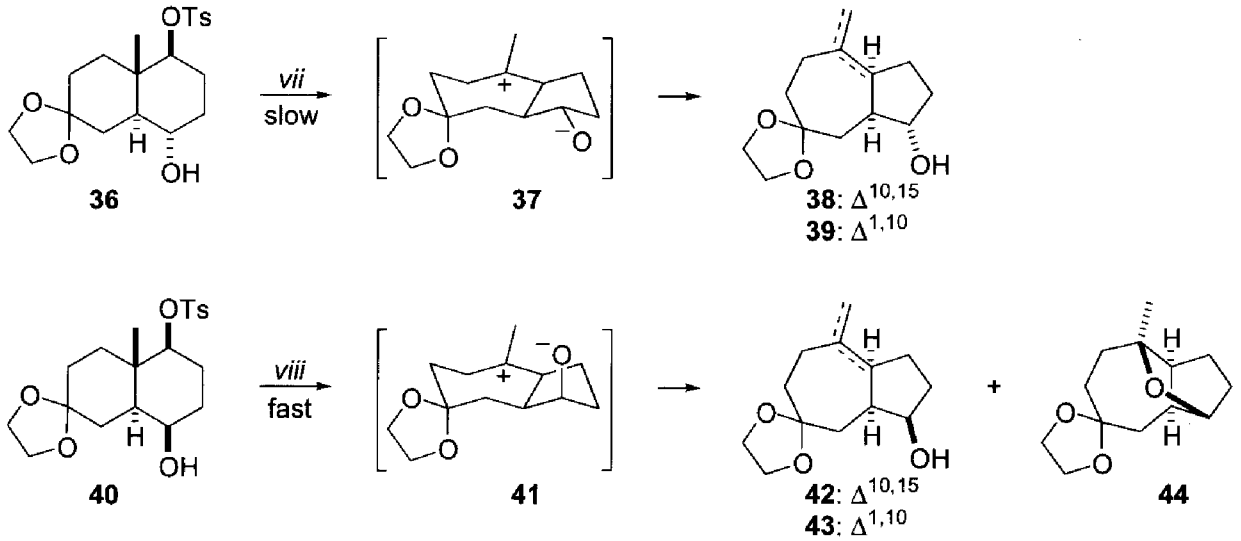


v 5 eq. NaO*t*-amyl, benzene, Δ, 10 min, 66% **28**, 34% **31**

vi 5 eq. NaO*t*-amyl, benzene, Δ, 10 min, 21% **32**, 76% **35**

The explanation given here to explain the results of Orru *et al.* is consistent with the findings of Jenniskens.[1a] Upon treatment with sodium *tert*-amylate in refluxing benzene, the β-alcohol **40** showed a faster reaction than the corresponding α-alcohol **36** (Scheme 8). This phenomenon was explained by Jenniskens as a result of a 'through-space' interaction between the axial β-alcoholate group with the positive charge in intermediate **41**. The observed rates for the reactions of **36** and **40** clearly indicate that the 1,3-diaxial repulsion between the substituents at C(4) and C(10) only marginally contribute to the difference in reaction rates. Since the largest deviation from the optimal antiperiplanar alignment of the C(5)-C(10) central bond was expected for the faster reacting axial alcohol **40**.

Scheme 8



vii 2.2 eq. NaO*t*-amyl, benzene, Δ, 21 h, 59% **36**, 4% **38**, 9% **39**

viii 2.2 eq. NaO*t*-amyl, benzene, Δ, 20 h, 57% **42**, 15% **43**, 7% **44**, 11% other

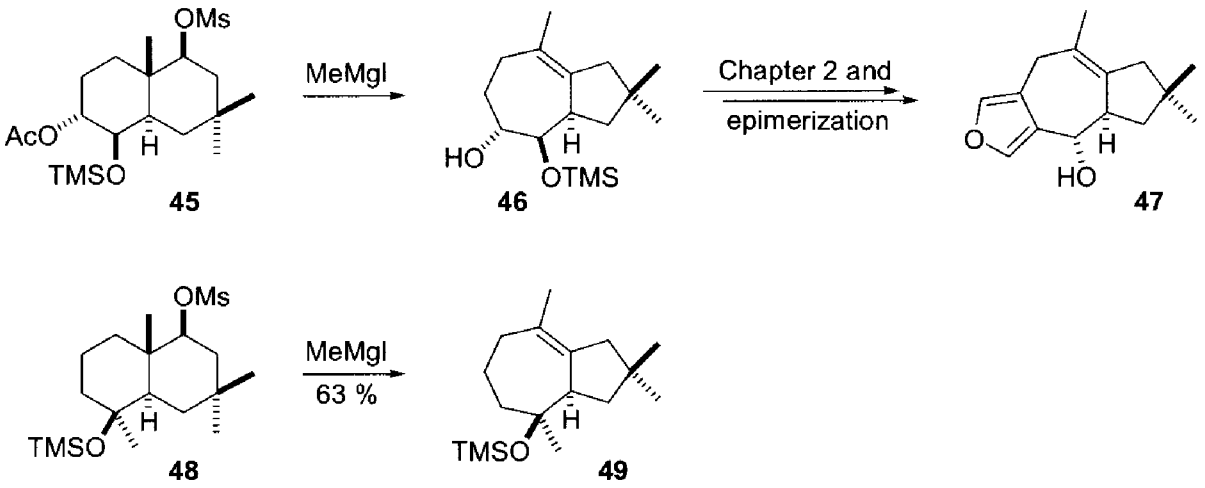
6.3 Outlook

In this paragraph the synthetic applicability of the methods described in this thesis is discussed for other lactaranes, marasmanes and sesquiterpenes with an ivaxillarane or protoilludane skeleton.

6.3.1 Lactarane Sesquiterpenes

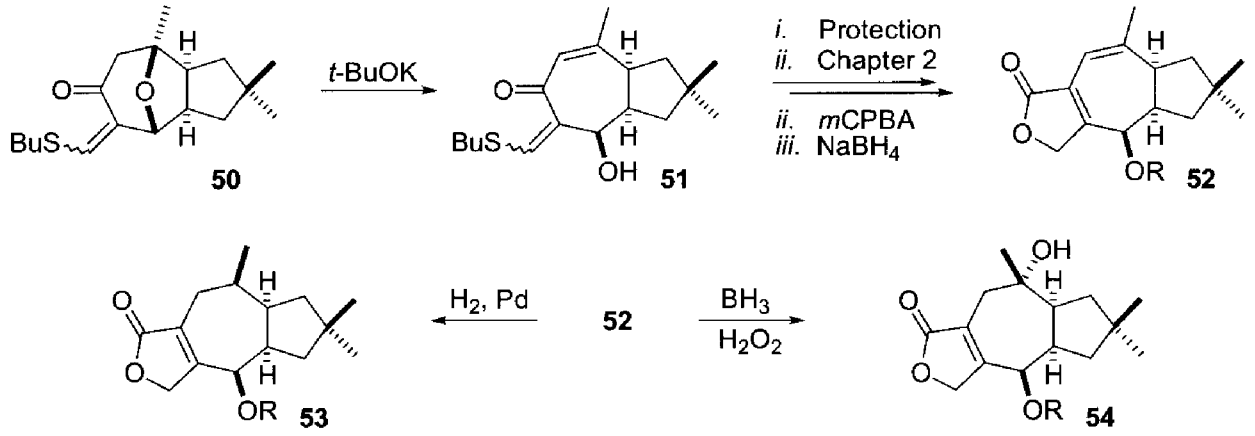
Starting from the enantiopure building block (+)-**4** (mentioned in Chapter 4), optically pure furanether B may be prepared via the route outlined in Chapter 2. Other optically pure lactaranes may also be available via an extension on this approach. For instance, the C(1)-C(10) double bond characteristic for several naturally occurring lactaranes can possibly be synthesized as shown in Scheme 9 for compound **47**. Since it has been shown that compound **48** rearranges almost selectively to olefin **49** upon treatment with MeMgI,[6] it is expected that **45** will react similarly to **46**.

Scheme 9



The β-C(15) methyl group present in a number of lactaranes may be available starting from the known compound **50** (Scheme 10).[7] Selective opening of the ether bridge in **50** via a β-elimination is expected to give compound **51**.[8] Further conversion of **51** probably gives **52**. Catalytic reduction[9] or oxidative hydroboration[10] of the C(9)-C(10) double bond in **52** will predominantly occur from the bottom side providing for the β-C(15) methyl group.

Scheme 10

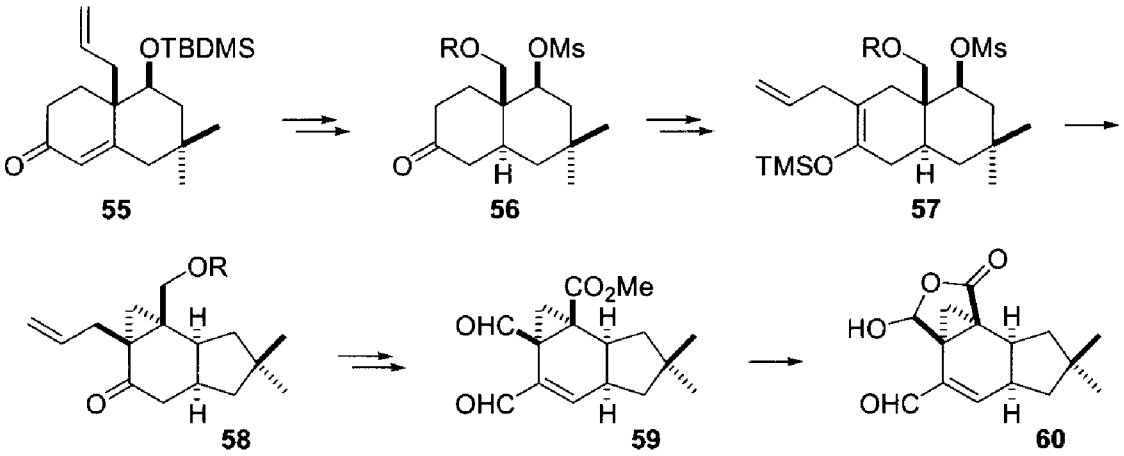


6.3.2 Marasmane Sesquiterpenes

C(15)-oxidized marasmanes, like (+)-marasmic acid, are believed to be available via the reaction sequence outlined in Scheme 11. An early introduction of an allyl moiety at C(10), conform the procedures described in Chapter 4 and 3 will provide compound **55** which in turn can be transformed to the C(15)-oxidized compound **56**.[11] Further transformations[12] are expected

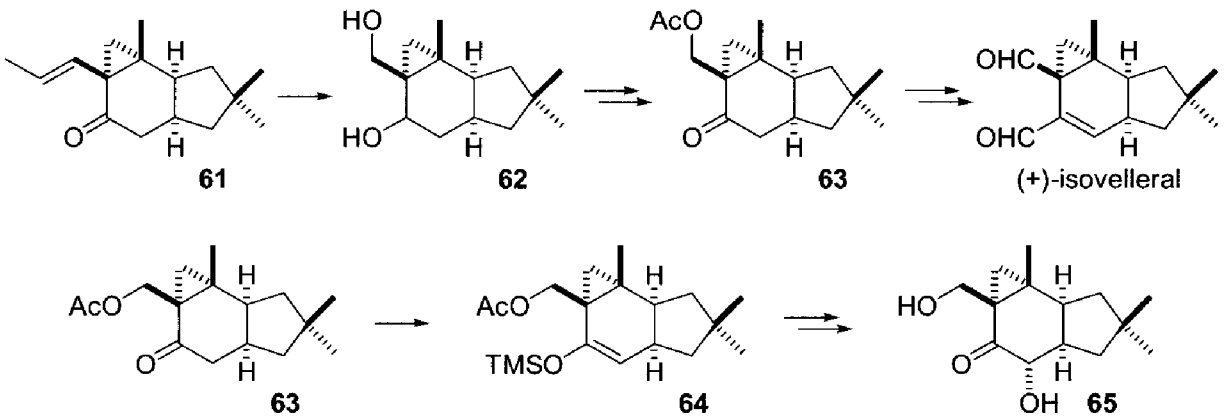
to give the known methyl marasmate (**59**), which upon treatment with BBr_3 will give (+)-marasmic acid (**60**).[13]

Scheme 11



A more efficient approach toward (+)-isovelleral can possibly be achieved when ozonolysis of compound **61**[12] is followed by reduction (Scheme 12). Selective protection of the resulting diol **62** and subsequent oxidation may provide compound **63** which, in turn, can be transformed to (+)-isovelleral conform the route presented in Chapter 5. The normarasmane **65**[14] can be obtained via oxidation of the silyl enol ether **64** derived from compound **63**.

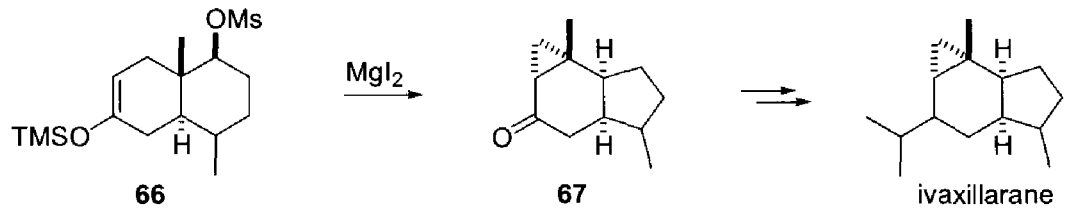
Scheme 12



6.3.3 Miscellaneous

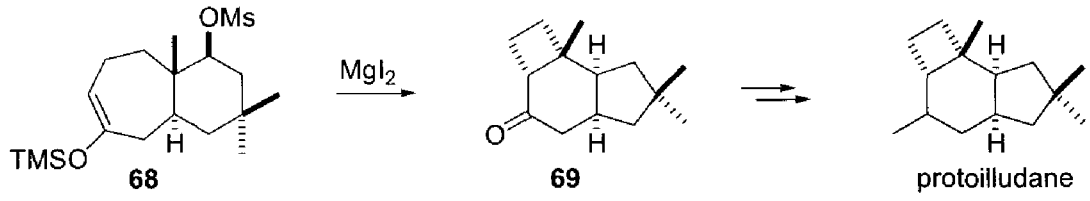
The MgI_2-induced rearrangement-cyclopropanation reaction may also be a useful tool for the synthesis of ivaxillarane[15] sesquiterpenes (Scheme 13).

Scheme 13



A similar rearrangement strategy can possibly be used for the synthesis of the cyclobutane moiety in protoilludanes, the biosynthetic precursors of marasmanes and lactaranes (Scheme 14).

Scheme 14

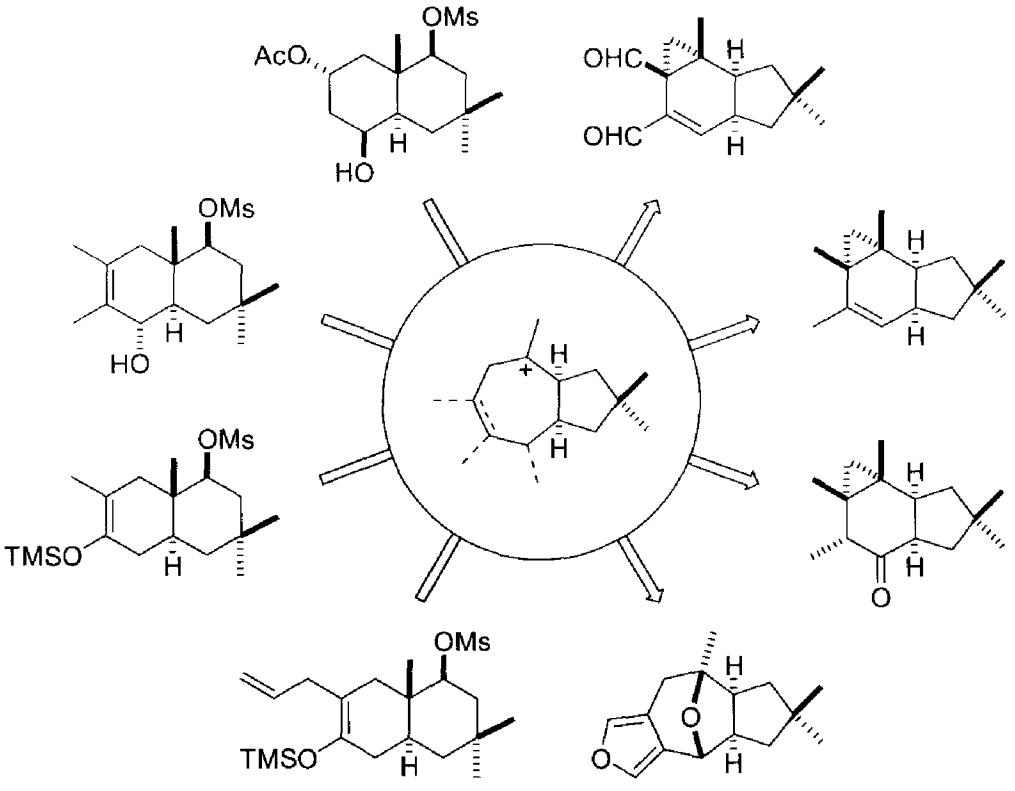


6.4 References and Notes

1. (a) L. H. D. Jenniskens PhD thesis, Wageningen Agricultural University, **1992**. (b) R. V. A. Orru PhD thesis, Wageningen Agricultural University, **1994**. (c) P. M. F. M. Bastiaansen PhD thesis, Wageningen Agricultural University, **1996**.
2. (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (c) Piet, D. P.; Orru , R. V. A.; Jenniskens, L. H. D.; van de Haar, C.; van Beek, T. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Chem. Pharm. Bull.* **1996**, *44*, 1400. (d) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4955.
3. Orru , R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374.
4. For example see: Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53 and references therein.
5. (a) See paragraph 1.6. (b) Orru , R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199.
6. Unpublished results.
7. See Chapter 2.

8. (a) Price, M. E.; Schore, N. E. *Tetrahedron Lett.* **1989**, *30*, 5865. (b) Chikamatsu, H.; Maeda, M.; Nakazaki, M. *Tetrahedron* **1969**, *25*, 4751.
9. Daniewski, W. M.; Gumulka, M.; Ptaszynska, K.; Skibicki, P.; Jacobsson, U.; Norin, T. *Phytochemistry* **1992**, *31*, 3933.
10. Daniewski, W. M.; Gumulka, M.; Ptaszynska, K.; Kamienski, B.; Skibicki, P.; Jacobsson, U.; Norin, T. *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **1989**, *37*, 289.
11. Hanselmann, R.; Benn, M. *Synth. Commun.* **1996**, *26*, 945.
12. See Chapter 5.
13. Boeckman Jr, R. K.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.
14. Daniewski, W. M.; Kroszczynski, W.; Skibicki, P.; De Bernardi, M.; Fronza, G.; Vidari, G.; Vita Finzi, P. *Phytochemistry* **1988**, *27*, 187.
15. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, **1991**, Vol. I.

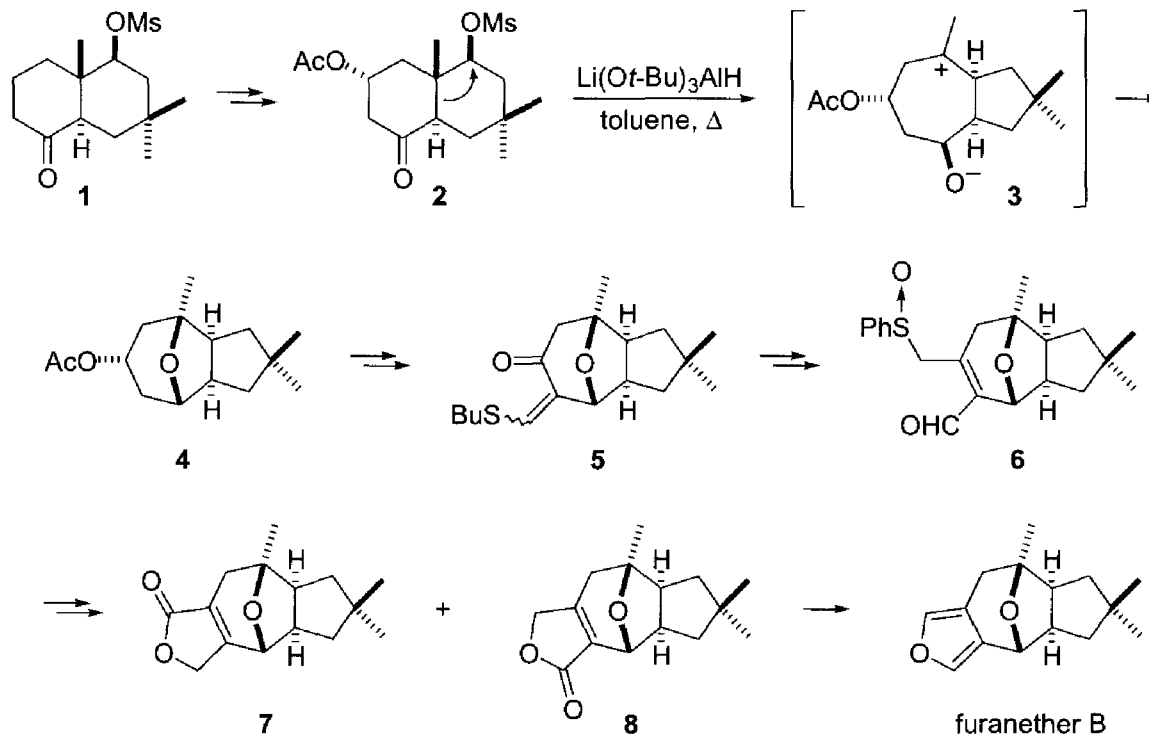
Summary



Lactarane and marasmane sesquiterpenes are mostly found in nature as metabolites from mushrooms of the genera *Lactarius* and *Russula*. Because a considerable number of these compounds possesses a variety of interesting biological activities, they are assumed to take part in the mushroom's chemical defense mechanism. The total synthesis of these natural products via extension of the base-induced rearrangement of perhydronaphthalene 1,4-diol monosulfonate esters, initially designed for the synthesis of *cis*-hydroazulenes, is the key subject of this thesis.

The first synthetic challenge was the total synthesis of the lactarane furanether B (Scheme 1). Upon exposure to Li(O*t*-Bu)$_3$AlH in refluxing toluene mesylate **2**, prepared from the readily available ketone **1**, underwent rearrangement to the *cis*-fused cation intermediate **3**. Intramolecular trapping of the positive charge in **3** by the proximate alcoholate provided tricyclic ether **4**. Completion of the synthesis of the natural product was accomplished by an annulation method based on a Pummerer-induced cyclization reaction of compound **6**.

Scheme 1

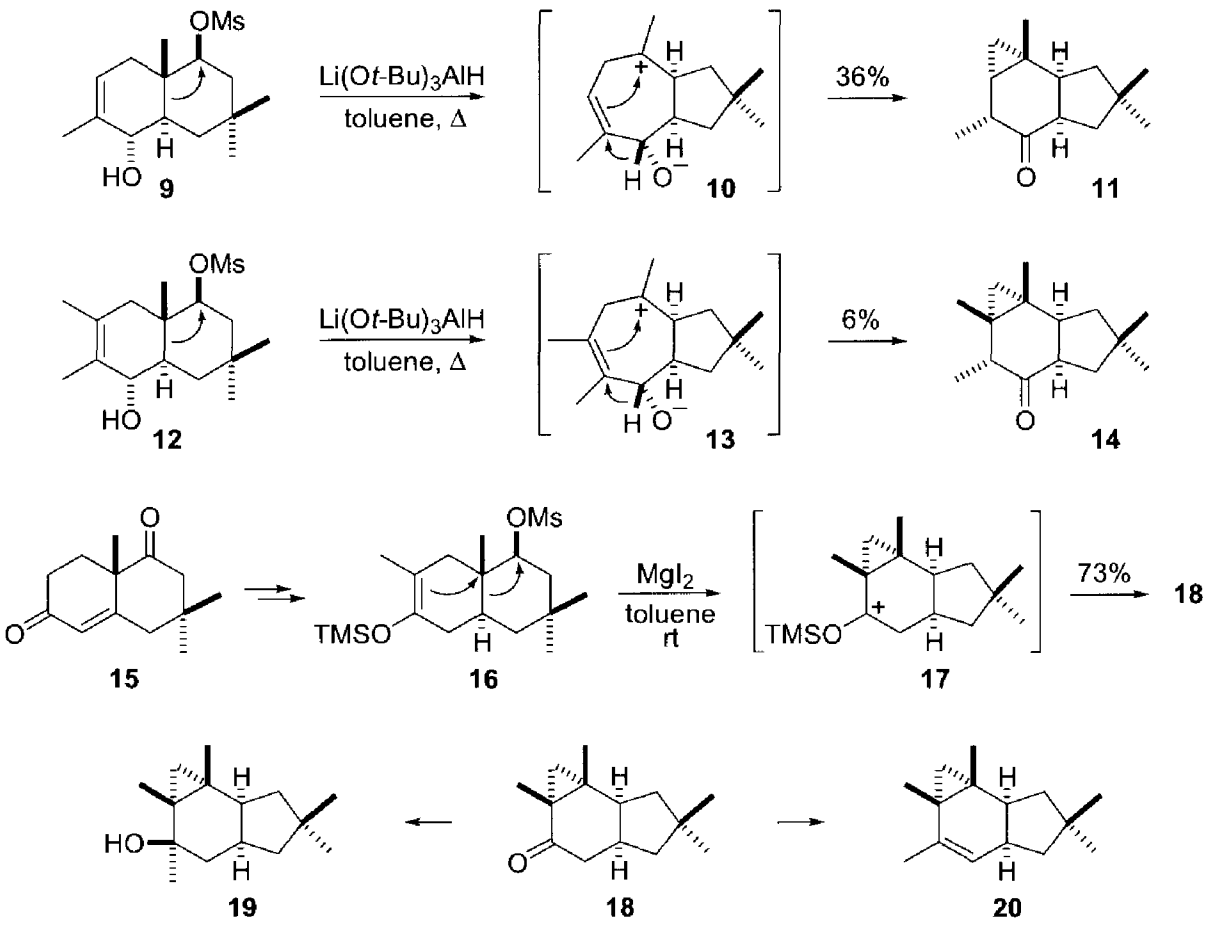


As a second objective the synthesis of the marasmane skeleton via a tandem rearrangement-cyclopropanation reaction was investigated. Initial studies on model system **9** lacking the methyl group at C(8) demonstrated that this tandem reaction could be applied successfully for the synthesis of the tricylic core of marasmanes as followed from the formation of ketone **11** (Scheme 2). However, poor results were obtained with the fully substituted system **12** probably due to severe steric hindrance (Pitzer strain) in the cyclopropanation step (**13** → **14**).

In contrast the silyl enol ether **16**, prepared form the easily available dione **15**, rearranged readily to the normarasmane compound **18** upon treatment with the Lewis-acid MgI_2. In this case,

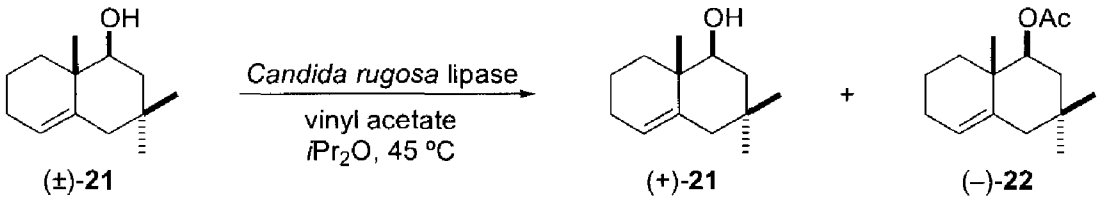
the better stabilized cyclopropylcarbinyl cation **17** compensated for the increased steric hindrance caused by Pitzer strain. Compound **18** was then further converted to the two 'simple' marasmanes **19** and **20**.

Scheme 2



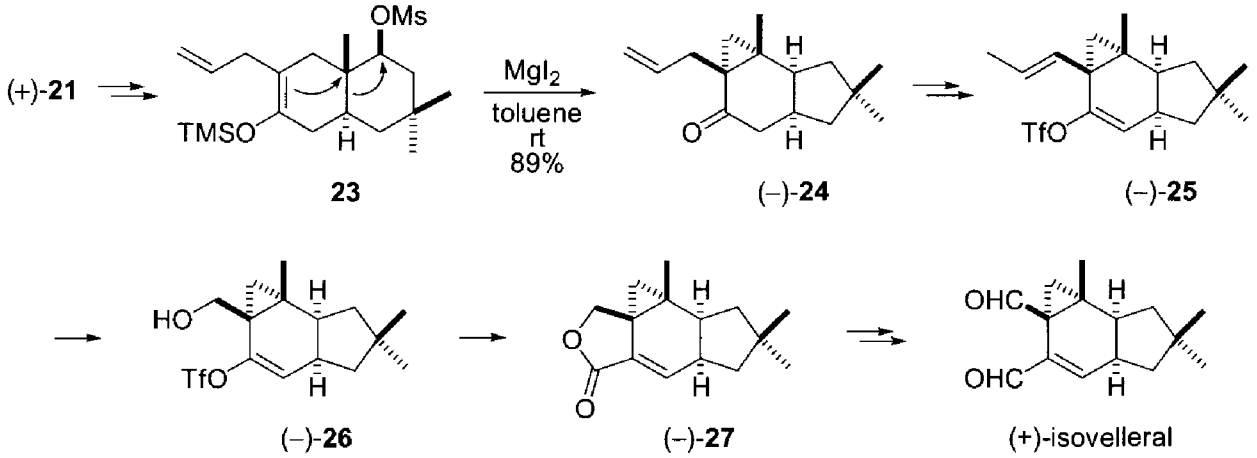
Optically pure (+)-**21**, needed for the preparation of (+)-isovelleral via the tandem rearrangement-cyclopropanation reaction, was obtained via an enzymatic resolution of racemic **21** with *Candida rugosa* lipase (Scheme 3). The enantiomericaly pure building block (+)-**21** might also be used for the synthesis of optically pure lactaranes via the sequence developed for furanether B.

Scheme 3

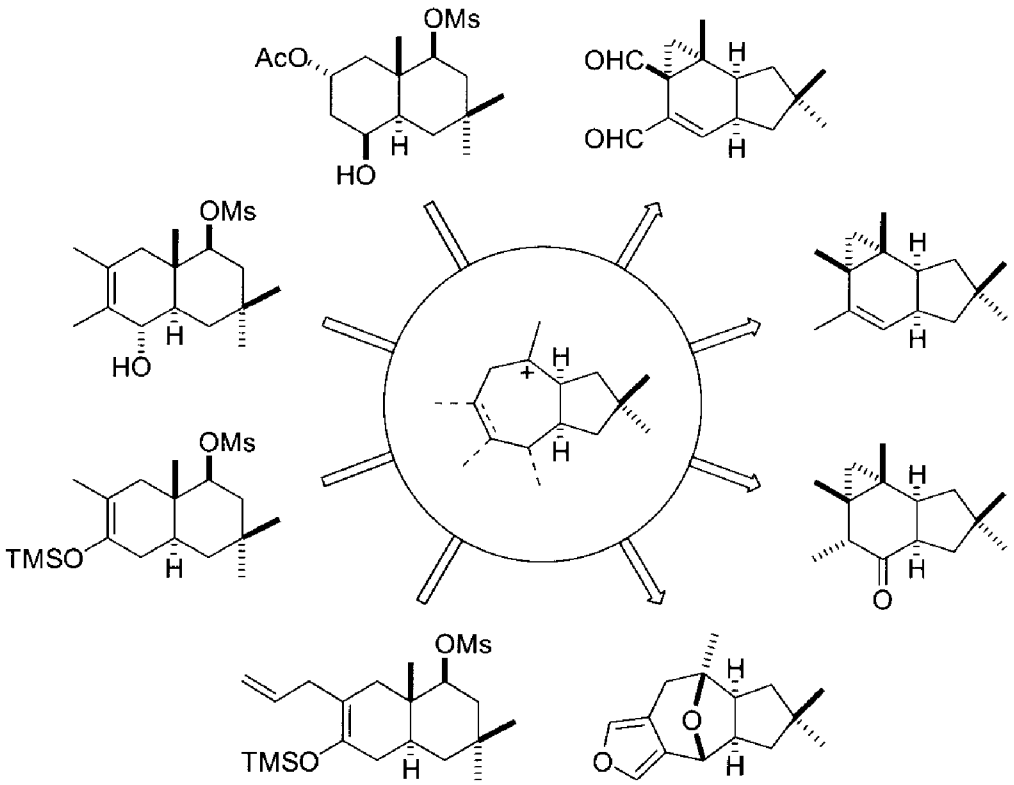


The methodology developed for the synthesis of the marasmane skeleton was successfully applied in the synthesis of (+)-isovelleral. When mesylate **23** possessing an allyl group was treated with MgI_2, ketone (–)-**24** was obtained in high yield (Scheme 4). The best route to synthesize both aldehydes groups, present in (+)-isovelleral, proved to be the following. Isomerization of the double bond present in (–)-**24** and enolization of the ketone followed by treatment with Tf_2NPh gave (–)-**25**. Selective ozonolysis of the allyl moiety in (–)-**25** and subsequent treatment with $NaBH_4$ afforded enol triflate (–)-**26**, which via palladium-catalyzed methoxycarbonylation, reduction and Swern oxidation gave (+)-isovelleral. When a different sequence was applied, the ozonolysis of the allyl group or the synthesis of the enol triflate moiety turned out to be troublesome.

Scheme 4



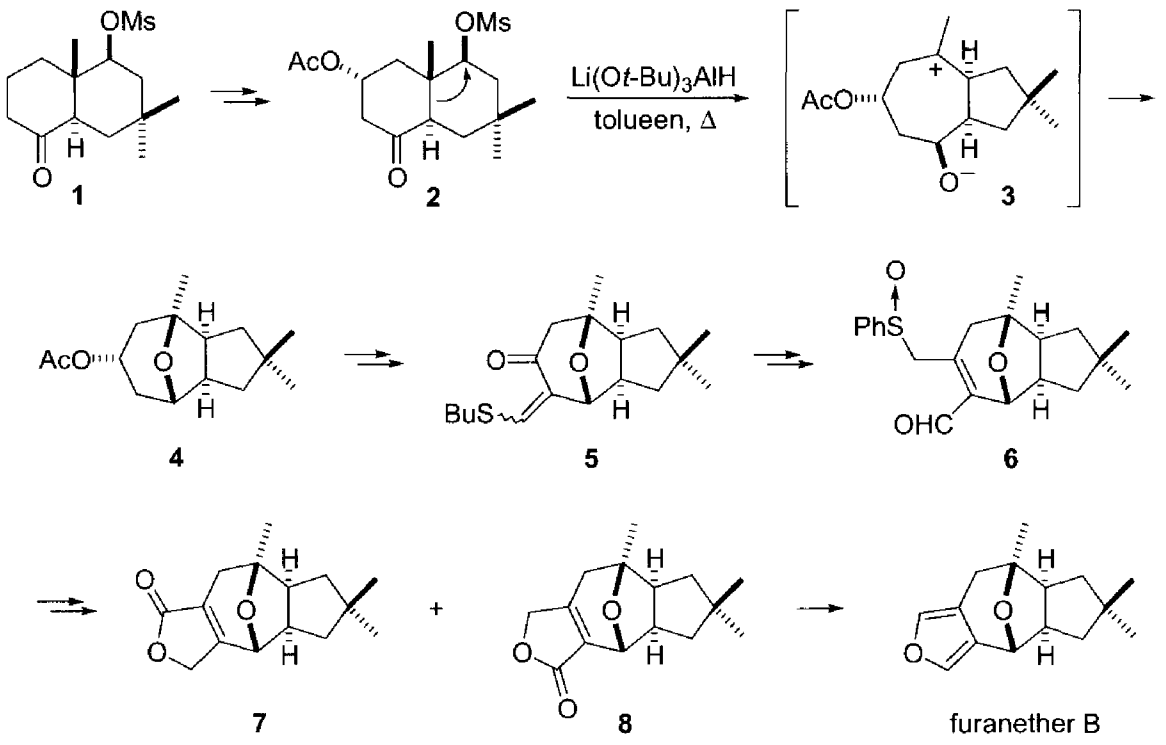
Samenvatting



Lactaraan en marasmaan sesquiterpenen worden in de natuur voornamelijk gevonden in paddestoelen van de genera *Lactarius* en *Russula*. Deze verbindingen, die vaak interessante biologische activiteiten blijken te bezitten, worden verondersteld deel uit te maken van het chemische afweermechanisme van de paddestoel. In dit proefschrift wordt de totaalsynthese van deze sesquiterpenen via een base-geïnduceerde omlegging van 1,4-diol monosulfonaat esters onderzocht.

Als eerste onderwerp werd de synthese van het lactaraan furanether B bekeken (schema 1). Het mesylaat **2**, dat uitgaande van keton **1** gemakkelijk te verkrijgen is, werd behandeld met Li(O*t*-Bu)$_3$AlH in refluxende tolueen. Onder deze condities legde het mesylaat **2** om naar het *cis*-verknoopte intermediair cation **3** dat vervolgens werd afgevangen door het alcoholaat. De zo verkregen tricyclische verbinding **4** werd vervolgens omgezet in het doelmolecuul furanether B via een route met als belangrijkste stap de Pummerer-geïnduceerde ringsluiting van verbinding **6**.

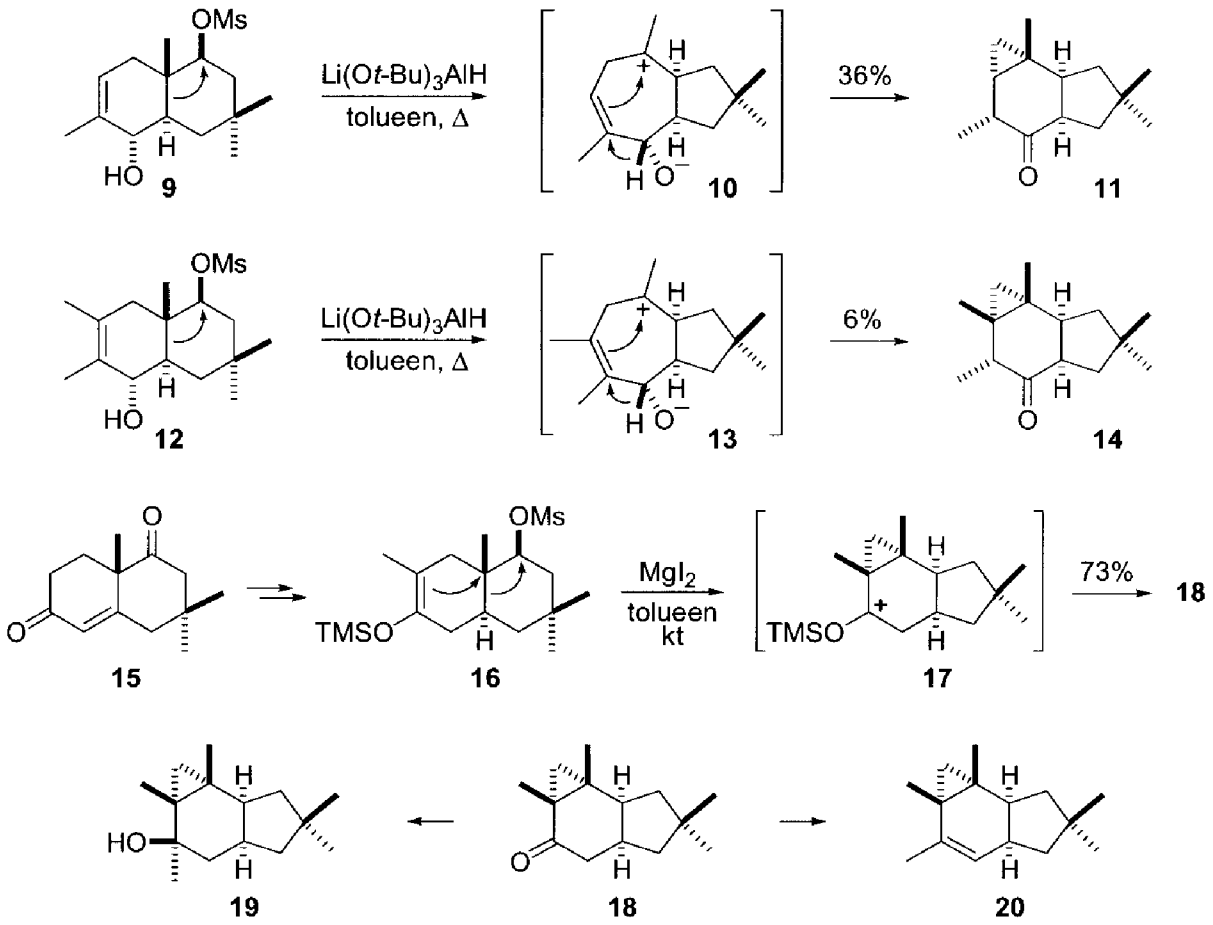
schema 1



Als tweede onderwerp werd de synthese van het marasmaan skelet via een tandem omlegging-cyclopropanerings reactie bestudeerd. Model studies naar de omzetting van mesylaat **9** met Li(O*t*-Bu)$_3$AlH toonde aan dat het tricylische basis skelet van marasmanen, zoals aanwezig in verbinding **11**, in een redelijke opbrengst te verkrijgen is (schema 2). Het bleek echter dat het volledig gesubstitueerde marasmaan skelet **14** via deze reactie slechts in lage opbrengst werd gevormd. Waarschijnlijk is de grote sterische hinder (Pitzer strain) in de cyclopropanerings (**13** → **14**) stap hiervan de oorzaak.

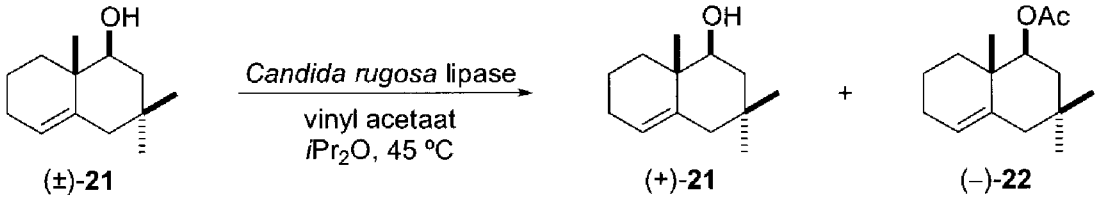
De silyl enol ether **16**, bereid uit het gemakkelijk te synthetiseren diketon **15**, geeft echter na behandeling met het Lewis-zuur MgI_2, in hoge opbrengst de omgelegde verbinding **18**. Een betere stabilisatie van het cyclopropylcarbinyl cation in intermediair **17**, als compensatie voor de nadelige sterische hinder in de cyclopropanerings reactie, ligt hieraan ten grondslag. Het normarasmaan product **18** werd vervolgens omgezet in de twee 'eenvoudige' marasmanen **19** en **20**.

schema 2



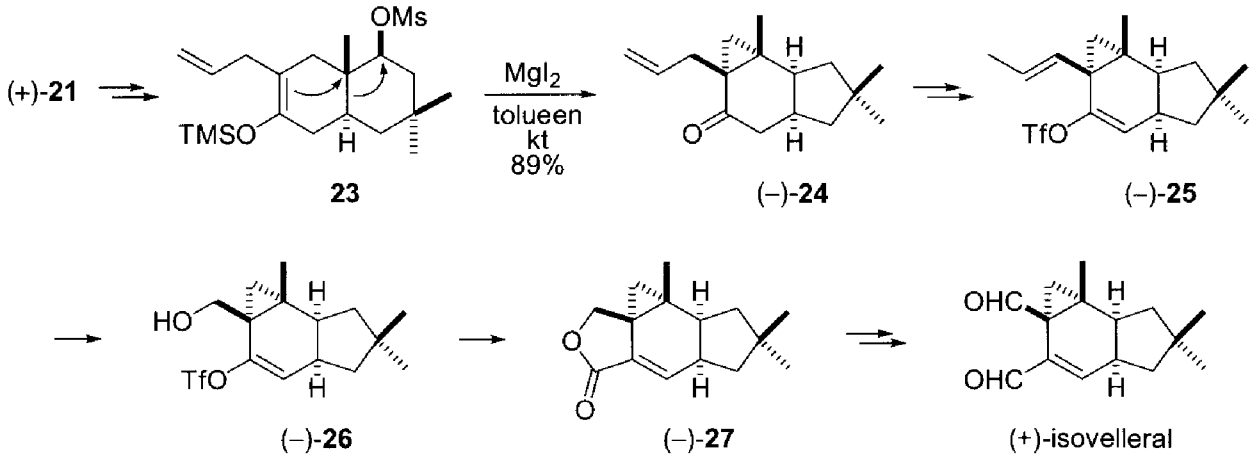
Voor de synthese van enantiomeer zuiver (+)-isovelleral werd de bereiding van de optisch zuivere bouwsteen (+)-**21** onderzocht. Dit synthon, dat verkregen kan worden via een enzymatische resolutie van racemisch **21** (schema 3), kan ook gebruikt worden voor de synthese van enantiomeer zuivere lactaranen via de route ontwikkeld voor furanether B.

schema 3



De methode die ontwikkeld was voor de synthese van het marasmaan skelet kon goed toegepast worden in de synthese van (+)-isovelleral. De behandeling van mesylaat **23** met MgI_2 gaf in hoge opbrengst keton (–)-**24** (schema 4). Omzetting van deze verbinding in (+)-isovelleral bleek het beste te gaan via de volgende route. Allereerst werd de dubbele binding in (–)-**24** geïsomeriseerd en het keton omgezet in een enol triflaat. Vervolgens werd de allyl groep in verbinding (–)-**25** selectief geozonolyseerd waarbij enol triflaat (–)-**26** werd verkregen. Palladium gekatalyseerde methoxycarbonylering van (–)-**26** gevolgd door reductie en Swern oxidatie gaf (+)-isovelleral. Een andere volgorde van de hierboven genoemde reactiestappen gaf problemen bij de selectieve ozonolyse van de allyl groep of de synthese van het enol triflaat.

schema 4



Curriculum Vitae

Roel Peter Liesbeth Bell werd geboren op 21 juni 1970 te Roggel alwaar hij verder opgroeide. Het stellig uitroepen van: "Deze school maak ik nog af en daarna stop ik met leren" tijdens zijn verblijf op de kleuterschool bleek zijn verdere levensloop niet te hebben bepaald. In 1986 behaalde hij het diploma aan de toenmalige MAVO de Kreppel te Heythuysen waarna hij het voortgezet onderwijs vervolgde aan de scholengemeenschap St. Ursula te Horn alwaar hij in 1988 het HAVO diploma behaalde. In datzelfde jaar begon hij zijn HLO studie aan de Hogeschool Heerlen waar hij koos voor de chemische studierichting en zich verder specialiseerde in de preperatieve organische chemie. Zijn stage- en afstudeerperiode van deze studie bracht hij door bij DSM Research te Geleen, alwaar hij werd begeleid door dr. D. Callant en prof. dr. J. G. de Vries. In 1992 ontving hij het getuigschrift van deze opleiding waarna hij zijn studie vervolgde met een doorstroomprogramma scheikunde aan de Katholieke Universiteit Nijmegen. Na een hoofdvakstage organische chemie bij dr. I. Funaki, L. Thijs en prof. dr. B. Zwanenburg werd het doctoraalexamen afgelegd in 1995. Van 1995 tot en met 1999 was hij werkzaam als assistent in opleiding (AIO) bij de vakgroep organische chemie van Wageningen Universiteit. Het tijdens deze periode uitgevoerde onderzoek, begeleid door dr. J. B. P. A. Wijnberg en prof. dr. A. de Groot, staat beschreven in dit proefschrift.

Stellingen

1. Het door Ogino *et al.* gestelde pinacol type mechanisme verklaart slechts gedeeltelijk de productvorming in de omzetting van tosylaat **9**.

   Bron: Ogino, T.; Kurihara, C.; Baba, Y.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1979.

2. De door Arnone *et al.* gegeven structuren voor de verbindingen isolactarorufin (**18**) en lactarorufin (**19**) zijn onjuist.

   Bron: Arnone, A.; De Gregorio, C.; Mele, A.; Nasini, G.; Pava de, O. V. *J. Chem. Soc., Perkin Trans. 1* **2000**, 745.

3. In de door Juntunen *et al.* gegeven verklaring voor de vorming van 1-(5'-*O*-trifenylmethyl-3'-deoxy-β-D-glycero-pentofuraan-2-ulosyl)uracil (**4**) wordt ten onrechte een E1 type mechanisme buiten beschouwing gelaten.

   Bron: - Juntunen, S.; Chattopadhyaya, J. *Acta Chem. Scand. B* **1985**, 149.
   - Dit proefschrift.

4. De uitspraak van Daniewski *et al.* dat alle geïsoleerde lactaranolide en furanolactaraan sesquiterpenen een *cis* verknoopt azuleen skelet bevatten is onjuist.

   Bron: Daniewski, W. M.; Vidari, G. *Progress in the Chemistry of Organic Natural Products* **1999**, p. 100.

5. Het is niet met zekerheid te zeggen dat de door Mansour *et al.* geponeerde onverzadigde carbonzuren ook de daadwerkelijke uit de dinoflagallaten geïsoleerde verbindingen zijn.

   Bron: Mansour, M. P.; Volkman, J. K.; Holdsworth, D. G.; Jackson, A. E.; Blackburn, S. I. *Phytochemistry* **1999**, *50*, 541.

6. De structuur toekenning van 3,15-dihydroxy-18-norabieta-3,8,11,13-tetraene (**7**) door Ankli *et al.* is dubieus te noemen.

   Bron: Ankli, A.; Heilmann, J.; Heinrich, M.; Sticher, O. *Phytochemistry* **2000**, *54*, 531.

7. Het is hoogst onwaarschijnlijk dat de door Gil *et al.* voorgestelde cationen **B** en **C** gevormd worden via basische hydrolyse van oleuropein aglycone.

   Bron: Gil, M.; Haïdour, A.; Ramos, J. L. *Phytochemistry* **1998**, *49*, 1311.

8. Het nummeren van het koolstofskelet in een publicatie vergemakkelijkt het lezen en voorkomt vergissingen.

9. Door het uitbesteden van fundamenteel gericht onderzoek zal binnen de grote chemische industrie het aantal spin-off projecten afnemen.

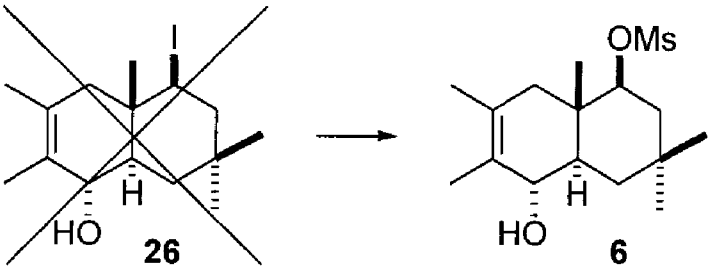
10. De tekst die volgens het promotiereglement verplicht opgenomen moet worden in een proefschrift gaat voorbij aan de mogelijkheid om te promoveren om 13.30 h.

    Bron: Promotiereglement Wageningen Universiteit (geldende per september 1999), p. 6.

11. De uitdrukking: de puntjes op de i zetten is niet juist.

Erratum

The upper left structure (**26**)
depicted in Scheme 6, page 52
must be replaced by compound (**6**)
as shown in Scheme 5, page 51.



Stellingen behorende bij het proefschrift: **Total Synthesis of Lactarane and Maramane Sesquiterpenes**.

Wageningen, 30 oktober 2000. Roel P. L. Bell