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THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

Volume 11

A Sesquidecade of Sesquiterpenes: Total Synthesis, 1980–1994

Part B: Bicyclic and Tricyclic Sesquiterpenes

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Michael Pirrung

Durham, North Carolina

INTRODUCTION

This book completes the review of sesquiterpenes synthesized in the time period 1979–1994, a sesquidecade. Because of the magnitude of this literature, a smaller portion was published in 1997[1] as Chapters I and II, focusing only on the acyclic and monocyclic sesquiterpenes. This book comprises Chapters III and IV, including the bicyclic and tricyclic sesquiterpenes (counting only carbocyclic rings, not including cyclopropanes).

In keeping with the title of this series, a natural product must be prepared for a synthesis to be included. We are sorry to omit the significant quantity of fine work addressing intricate natural ring systems or compounds whose structures were misassigned (as discovered by the synthesis of the erroneous structure), but the size of the literature in which natural products *were* prepared necessitates limiting our scope. If another sesquiterpene is the starting material, a change of carbon skeleton must occur for a synthesis to be included. We present multiple syntheses of the same compound in chronological order so that the evolution of synthetic strategy can be easily seen. In providing legends for the schemes, syntheses of racemates are not specifically marked. Legends for synthesis schemes producing optically active compounds include either absolute configurations, signs of optical rotation, or both. Each scheme is also identified by the senior author (or the institution at which the work was conducted). This policy is not intended to underemphasize the important and valuable contribution of junior authors to the work. Indeed, many have gone on to achieve significant syntheses of sesquiterpenes in their independent careers.

Since Part A of this book was published in 1997, a new review article on sesquiterpene synthesis has appeared summarizing approaches to triquinanes.[2]

We look forward to seeing the progress synthetic organic chemistry has made when 2004 or 2009 arrives and it is time for another author to undertake the compilation of sesquiterpene total syntheses.

References

1. M. C. Pirrung and A. T. Morehead, Jr., "A Sesquidecade of Sesquiterpenes: Total Synthesis, 1979–1994. Part A: Acyclic and Monocyclic Sesquiterpenes," in *The Total Synthesis of Natural Products,* **10,** D. Goldsmith, Ed., John Wiley & Sons, Inc., New York (1997).
2. G. Mehta and A. Srikrishna, *Chem. Rev.* **97,** 671 (1997).

REAGENT GLOSSARY

(+)-DET	(+)-Diethyltartrate
18-c-6	Eighteen-crown-six
9-BBN	9-Bora[3.3.1]bicyclononane
Ac	Acetyl
acac	Acetylacetone
AIBN	Azobisisobutyronitrile
APA	3-Aminopropylamine
aq.	Aqueous
Ar	Aryl
BHT	Butylated hydroxy toluene
BINAP	Binaphthylphosphine
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
c-hex	Cyclohexyl
CDI	Carbonyl diimidazole
COD	Cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBN	Diazabicyclononene
DBU	Diazabicycloundecene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethylazodicarboxylate
DHP	Dihydropyran
DIBAL-H	Diisobutylaluminum hydride
Dimsyl	Dimethylsulfoxide anion
DIPEA	Diisopropylethyl amine
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMP	3,5-Dimethyl pyrazole
DMPU	N,N′-Dimethylpropyleneurea
DMS	Dimethyl sulfide

DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphorazidate
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppp	Diphenylphosphinopropane
EE	1-Ethoxyethylether
en	Ethylene diamine
Et	Ethyl
EVE	Ethyl vinyl ether
EVK	Ethyl vinyl ketone
fur	Furan or Furyl
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HONSu	*N*-Hydroxysuccinimide
i-Am	Iso-amyl
i-Bu	Iso-butyl
i-Pr	Iso-propyl
Im	Imidazole
im_2CO	Carbonyl diimidazole
imid	Imidazole
K-Selectride®	Potassium tri-*sec*-butylborohydride
KAPA	Potassium 3-aminopropylamide
KHMDS	Potassium hexamethyldisilazane
L-Selectride®	Lithium tri-sec-butylborohydride
LCIA	Lithium *N*-cyclohexylisopropylamide
LDA	Lithium diisopropylamide
LICA	Lithium *N*-isopropylcyclohexylamide
LiHMDS	Lithium hexamethyldisilazane
LiTMP	Lithium tetramethylpiperidide
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MEM	2-Methoxyethoxymethyl
MMPP	Magnesium monoperoxyphthalate
MOM	Methoxy methyl ether
MPM	4-Methoxyphenylmethyl
Ms	Mesyl (methanesulfonyl)
MVK	Methyl vinyl ketone
n-Bu	*n*-Butyl
NaHMDS	Sodium hexamethyldisilazane
nbd	Norbornadiene
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMMO	*N*-Methylmorpholine-*N*-oxide
NMO	*N*-Methylmorpholine-*N*-oxide
NPSP	*N*-Phenylseleno pthalimide

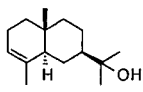
OBO	Trioxabicyclo[2.2.2]octane
oxone®	Potassium peroxymonosulfate
p-TsOH	*para*-Toluenesulfonic acid
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
phe	Phenylalanine
pic	Picrate
Piv	Pivalyl
PPA	Polyphosphoric acid
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
pyr	Pyridine
RaNi	Raney Nickel
Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
rextal	Recrystallize
SEM	2-Trimethylsilylethoxymethyl
t-Amyl	*tert*-Amyl
t-Bu	*tert*-Butyl
TASF	Tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	Tetrabutyl ammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEBA	Triethylbutyl ammonium
TES	Triethylsilyl
Tf	Triflate (trifluoromethanesulfonate)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
Thx	Thexyl
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
TPP	Tetraphenylporphyrin
Tr	Trityl (triphenylmethyl)
trisyl	2,4,6-Triisopropylbenzenesulfonate
Ts	Tosylate
X_c	Chiral Auxilliary
xs	Excess

III. BICYCLIC SESQUITERPENES

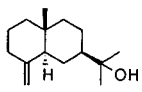
A. Eudesmanes

1. β-Eudesmol, α-Eudesmol, Intermediol, Neointermediol, Amiteol, Cycloeudesmol, Maaliol, α-Selinene, β-Selinene, γ-Selinene, Selinadiene, AE 1, Vetiselinene

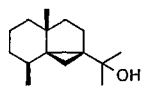
The simplest of the eudesmanes have mostly served as proving grounds for synthetic methodologies; hence a number of new methods in cycloaddition chemistry are seen in the schemes that begin this section.



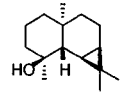
α-eudesmol



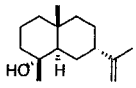
β-eudesmol



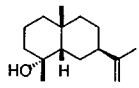
cycloeudesmol



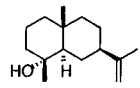
maaliol



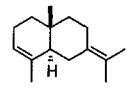
intermedeol



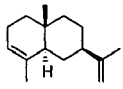
amiteol



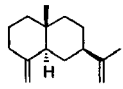
selin-11-en-4α-ol



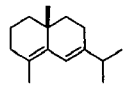
selina-3,7(11)-diene



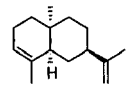
α-selinene



β-selinene



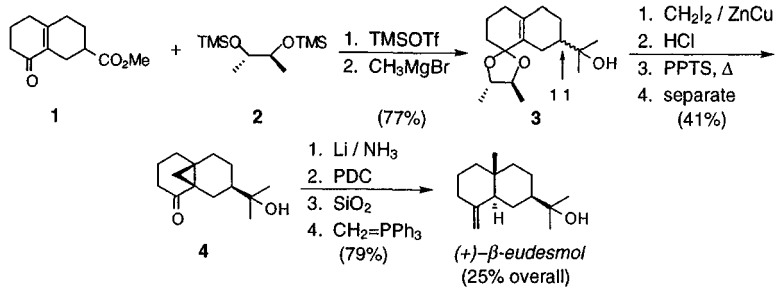
δ-selinene



AE 1

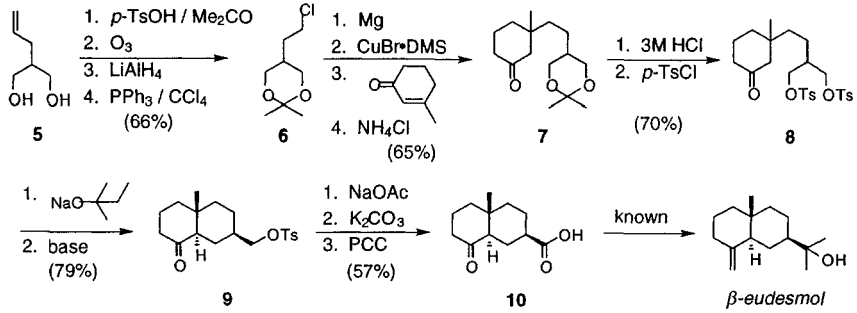
The synthesis of β-eudesmol developed by Mash at the University of Arizona exploits his methodology for creating chiral cyclopropanes.[1] Intermediate **1** was used in an earlier eudesmol synthesis by Carlson. Ketalization with (*2S,3S*)-2,3-butanediol and double Grignard addition provide the expected diastereomeric mixture **3**. This is treated with the Simmons-Smith reagent to give an 8:1:8:1 mixture of four isomers. After deketalization, the undesired diastereomeric series could be selectively destroyed by dehydration. Reductive cyclopropane

opening, ring fusion equilibration, and Wittig methylenation provide the natural product.



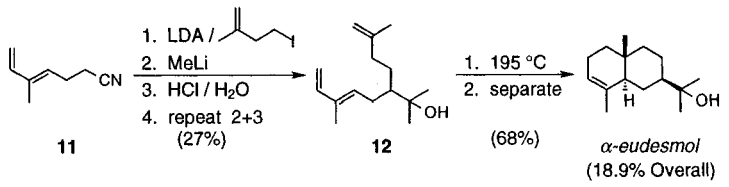
Scheme 1. Mash Synthesis of (+)-β-Eudesmol

Investigation of the intramolecular alkylation of a cyclohexanone resulted in the formal β-eudesmol synthesis described by Spencer.[2] Protection of **5** as an acetonide permits simple chemistry to form **6**. It is converted to its Grignard reagent for conjugate addition to 3-methylcyclohexenone. Base treatment of **8** results in a diastereotopic group selective reaction to form **9** admixed with its *cis*-decalin isomer; equilibration permits full material throughput. Conversion of the remaining tosylate to a carboxylic acid intercepts an earlier Heathcock intermediate. A very similar approach, substituting an aldol ring closure, was later adopted by Kawamata.[3]



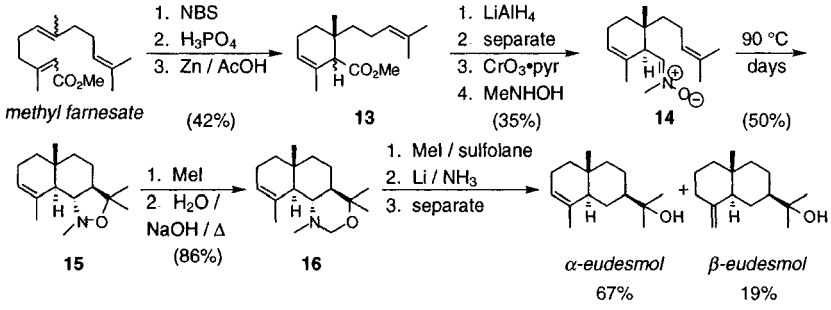
Scheme 2. Spencer Formal Synthesis of β-Eudesmol

The key step in Taber's α-eudesmol synthesis is an internal Diels-Alder reaction.[4] Triene **12** is assembled by a straightforward alkylation sequence. The stereoselectivity in its cycloaddition is only moderate, as might be expected.



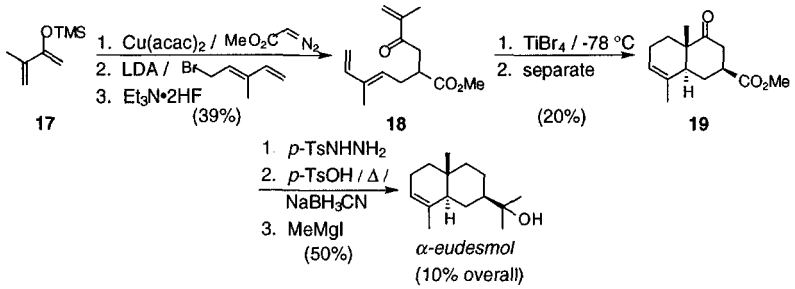
Scheme 3. Taber Synthesis of α-Eudesmol

An intramolecular nitrone cycloaddition is featured in the α-eudesmol synthesis of Schwartz of Florida State.[5] Methyl farnesate is protected for an acid-catalyzed cyclization by bromohydrin formation at the terminal alkene. This permits an improved protocol for the formation of methyl monocyclofarnesate (**13**). Reduction, preparative HPLC, and reoxidation permit formation of the nitrone, which undergoes slow cycloaddition to **15**. Two methylations allow the reductive removal of the nitrogen to yield α-eudesmol. Oddly, if technical sulfolane is used for the methylation, β-eudesmol predominates.



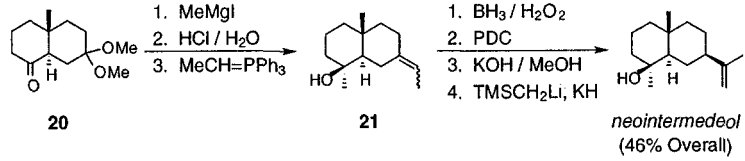
Scheme 4. Schwartz Synthesis of α-Eudesmol

The group of Reissig at Darmstadt completed the α-eudesmol synthesis shown in Scheme 5.[6] It was part of a study of Lewis acid catalysis and stereochemistry of the internal Diels-Alder reaction involving the formation of 7-membered ring chelates. Triene **18** was assembled by (carbomethoxy)cyclopropanation of dienyl ether **17**, alkylation of the resulting cyclopropanecarboxylate, and retro-aldol reaction. Its cycloaddition gives *trans*-decalin **19** as 52% of the product.

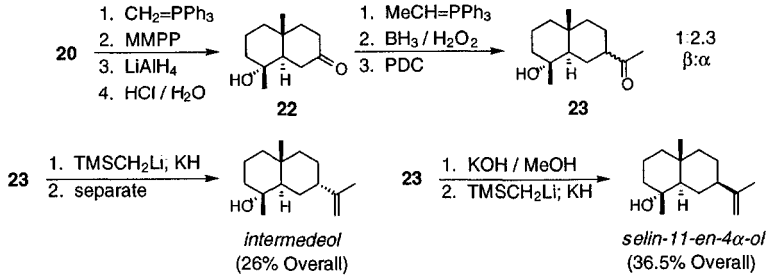


Scheme 5. Reissig Synthesis of α-Eudesmol

The defensive secretions of termites contain a number of fascinating terpenes, including a set of eudesmanes. A group at the Agricultural University at Wageningen, Netherlands, has completed syntheses of several of the compounds to confirm their structures.[7] The 3-carbon appendage is attached by a Wittig-hydroboration-Wittig sequence. Stereochemical control generally derives from equilibration.



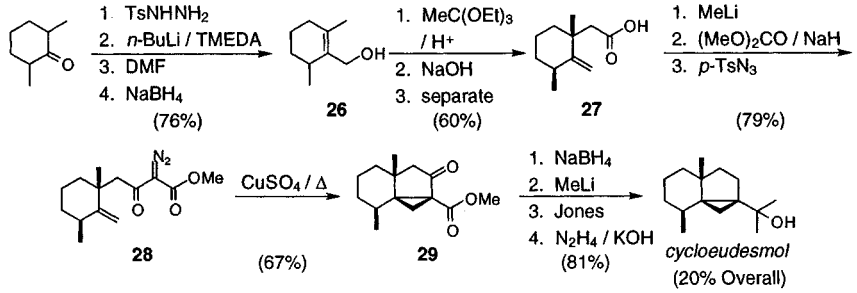
Scheme 6. Wijnberg-de Groot Synthesis of Neointermedeol



Scheme 7. Wijnberg-de Groot Syntheses of Other Termite Terpenes

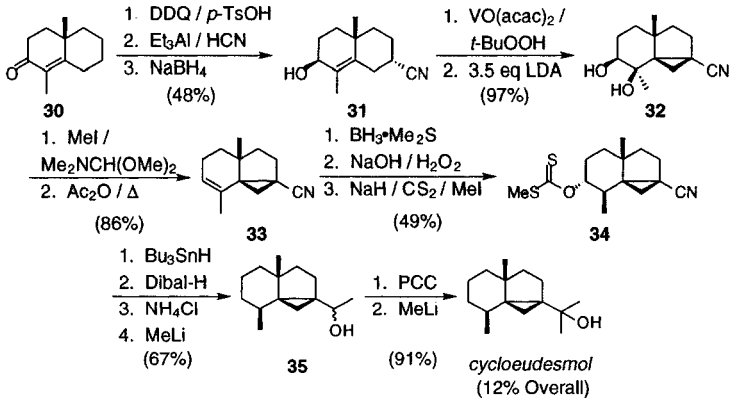
Considerable confusion surrounded the structure of cycloeudesmol, a product of a marine algae; its structure was resolved only around the time of publication of our previous sesquiterpene retrospective. Two syntheses of this compound have appeared, the first from Chen.[8] The 2,6-dimethylcyclohexanone tosylhydrazone

is converted by a Shapiro reaction to the vinyl lithium and then to the allylic alcohol **26**. Orthoester Claisen rearrangement gives a 7:1 mixture of esters that is separated, as the acids, by crystallization. Conversion to diazoketone **28** permits diastereoselective cyclopropanation to **29**. Double Grignard addition is preceded by ketone reduction. Reoxidation and Wolff-Kishner deoxygenation produce the natural product.



Scheme 8. Chen Synthesis of Cycloeudesmol

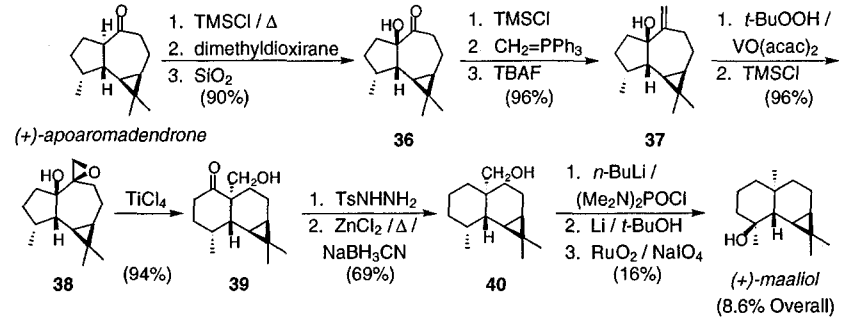
A second synthesis of cycloeudesmol was completed by Ando at Tohoku University.[9] Enone **30** was converted to the dienone for a conjugate addition of cyanide. Stereoselective reduction permits directed epoxidation to introduce the β-epoxide, which is needed to establish the stereochemistry of the cyclopropane in a subsequent Stork ring closure to **32**. Control of the methyl group stereochemistry in the A-ring entails formation of the cyclic orthoformate and



Scheme 9. Ando Synthesis of Cycloeudesmol

elimination to the alkene, followed by hydroboration and a xanthate radical deoxygenation. Elaboration of the nitrile to the isopropylol group is efficient and rational. Ando has also reported in full form his preparation of all of the stereoisomers of the erroneous original structure.[10]

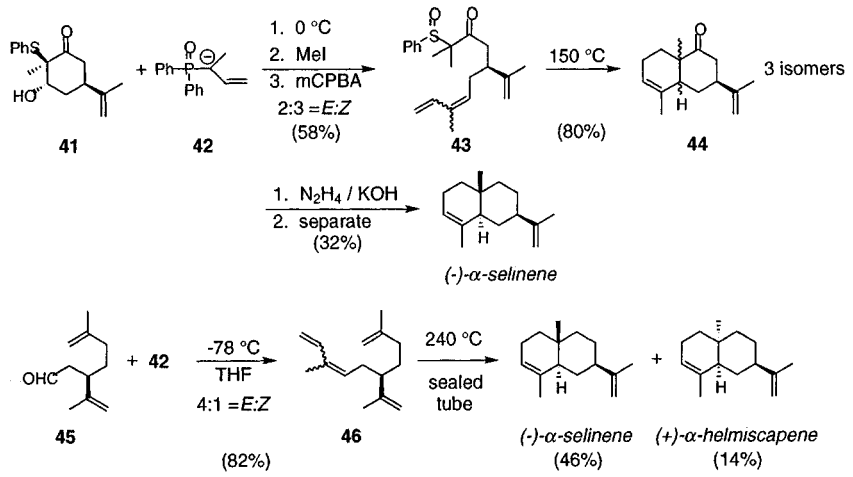
(+)-Aromadendrene is readily available from eucalyptus oil and constitutes a useful terpenic starting material. The Wageningen group has used a product of its ozonolysis, (+)-apoaromadendrone, for the preparation of maaliol.[11] Angular oxidation is accomplished with dimethyldioxirane via the silyl enol ether. Methylenation and selective epoxidation set the stage for a pinacol rearrangement from the 5,7 ring system **38** to the hydronaphthalene. Removal of the resulting ketone and alcohol in **39** yields the 'bare' maaliane skeleton. Introduction of a hydroxyl group at the tertiary position by ruthenium tetroxide is competitive with oxidation adjacent to the cyclopropane, and stereoselective.



Scheme 10. Wijnberg-de Groot Synthesis of (+)-Maaliol

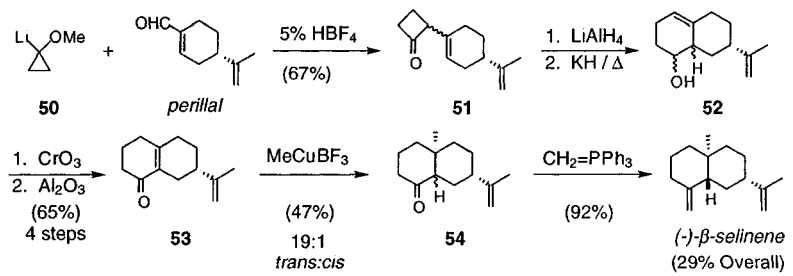
Two preparations of α-selinene have been described by the Caine group at Alabama.[12] The β-hydroxyketone **41**, derived from carvone oxide, undergoes a retroaldol reaction on treatment with excess phosphine oxide anion **42**. In situ, the resulting aldehyde is subject to a Wittig-Horner reaction, and the sulfenyl ketone enolate is methylated. The product is oxidized to sulfoxide **43**. Pyrolysis generates an unsaturated ketone that directly undergoes internal Diels-Alder reaction. The isomer mixture in **43** is irrelevant to the outcome, as either *E* or *Z* dienes give the same product, evidently by pre-equilibration. The resulting mixture **44** is deoxygenated and the natural product isolated by preparative GC. The same Wittig-Horner reagent condenses with limonene-derived aldehyde **45**

to give a tetraene that gives mainly gives selinene on cycloaddition, but also provides a novel *cis*-eudesmane, helmiscapene.



Scheme 11. Caine Syntheses of (-)-α-Selinene

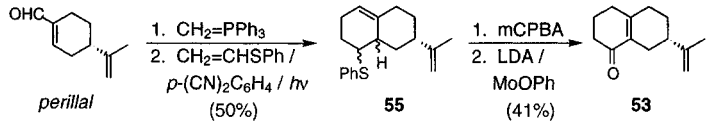
A β-selinene synthesis has been completed by Cohen at Pittsburgh using as the key step an anion-accelerated vinylcyclobutanol rearrangement.[13] A cyclobutanone annulation developed in his lab is applied to perillal. Reduction of **51** and rearrangement in refluxing THF yield **52**. Oxidation and conjugation permit a relatively difficult conjugate addition of the angular methyl group. The resulting ketone **54** is the enantiomer of a substance earlier converted to the natural product, but Cohen devised a more efficient methylenation protocol.



Scheme 12. Cohen Synthesis of (-)-β-Selinene

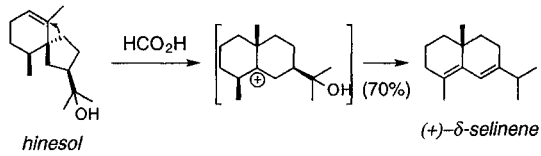
The cation radical Diels-Alder cycloaddition assembles the decalin of selinene in a formal synthesis developed at UT-Austin.[14] Methylenation of perillal gives a

diene that undergoes cycloaddition with phenyl vinyl sulfide promoted by a photochemical electron-transfer sensitizer. The oxidation of sulfide **55** to a ketone proceeds with olefin migration to give the known intermediate **53** from Cohen's work.



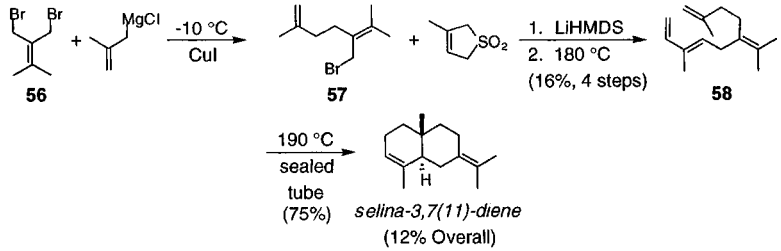
Scheme 13. Bauld Formal Synthesis of (-)-β-Selinene

The interconversions of terpene skeletons are of interest based on their possible mimicry of biosynthetic processes. Itokawa of the Tokyo College of Pharmacy, in reinvestigating the acid-catalyzed rearrangement of hinesol,[15] found that δ-selinene is produced. This process is the reverse of spirovetivane biosynthesis.



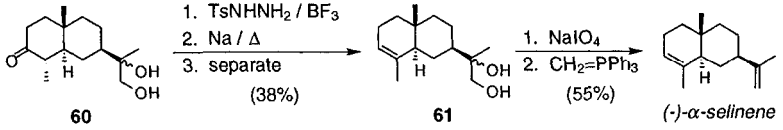
Scheme 14. Itokawa Synthesis of (+)-δ-Selinene

The preparation of a nonconjugated selenadiene has been described by Lee of the Academia Sinica, Taiwan.[16] Alkylation of methallyl Grignard with dibromide **56** provides a bromide that can be alkylated with metalated 3-methyl-3-sulfolene. Pyrolysis in a stream of nitrogen gives a diene that on prolonged pyrolysis gives the Diels-Alder product. α-Selinene and α-eudesmol were also prepared by very similar routes.



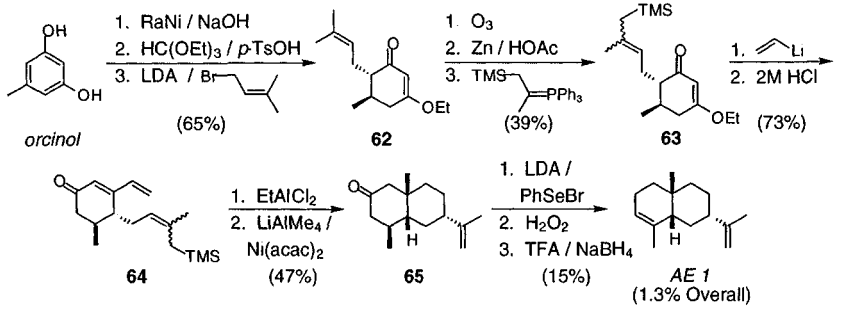
Scheme 15. Lee Synthesis of Selina-3,7(11)-diene

Kutney has used thujone (vide infra) as a chiral starting material for a number of sesquiterpene syntheses via intermediate **60**.[17,18] Here, a Bamford-Stevens reaction introduces an A-ring alkene but also produces the $\Delta^{2,3}$ isomer (70:30) along the way to α-selinene.



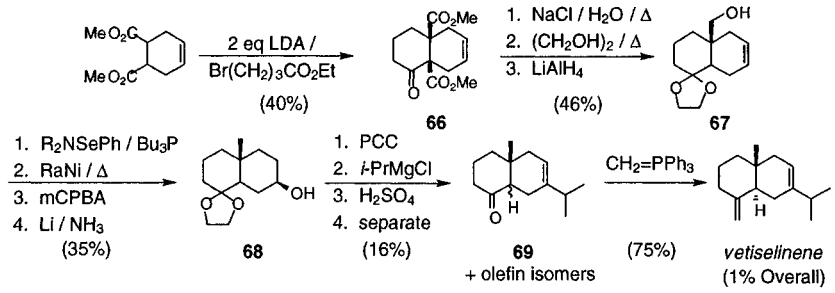
Scheme 16. Kutney Syntheses of (-)-α-Selinene

Schinzer of Braunschweig has used the internal cyclization of an allylic silane-dienone for the synthesis of another termite natural product, AE1, a *cis*-decalin diastereomer of α-selinene.[19] Stork-Danheiser alkylation of a dihydroorcinol-derived enol ether leads to **62**. Conversion to the allylic silane **63** and vinyl lithium addition produce enone **64**, which undergoes π-cyclization under treatment with Lewis acid. This sequence is quite like the Heathcock-Clark synthesis of nootkatone.[20] The angular methyl group is introduced by a nickel-catalyzed conjugate addition. Desaturation and deoxygenation of the ketone give AE1.



Scheme 17. Schinzer Synthesis of AE 1

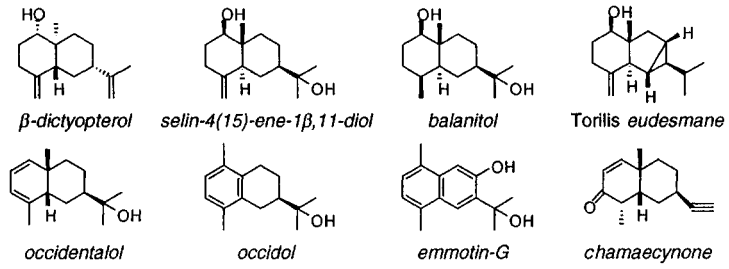
Garratt of University College London has used in a synthesis of vetiselinene[21] a dilithiated cyclohexene-4,5-diester, which is converted by acylation/alkylation to **66**. Krapcho decarboxylation, protection, and reduction yield **67**, which is deoxygenated. Hydration of the alkene yields **68**, permitting oxidation to set up a Grignard addition. After dehydration, **69** is 60% of the mixture.



Scheme 18. Garratt Synthesis of Vetiselinene

2. *β-Dictyopterol, Selin-4(15)-ene-1β,11-diol, Balanitol, Occidentalol, Isochamaecynone, Chamaecynone, Emmotin-G, Occidol*

This group of eudesmanes displays higher oxidation states. Dictyopterol and balanitol are closely related, as are occidol and emmotin, which are rearranged occidentalol relatives. Chamaecynone is a nor-eudesmane.



The oxidized selinene analog dictyopterol has been prepared by de Groot.[22] The conversion of **70** to its dienylacetate permits epoxidation/hydrolysis to provide the γ-hydroxy enone **71**. Strong acid isomerizes the enone to the enol, which ketonizes. The less hindered ketone is selectively ketalized under mild conditions, setting up a Wittig reaction on the remaining carbonyl. Exhaustive hydrolysis gives **73**. Novel reagent **74** is used to convert the ketone into an ester group. After protection, a one step method for conversion of the ester to an isopropenyl group was applied to complete dictyopterol. Beginning with methyl octalone (**70** without the acetoxy group), eudesmol and selinene were also prepared by essentially the same route.