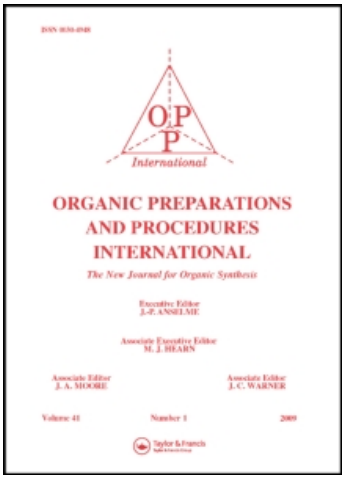


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT PROGRESS IN THE SYNTHESIS OF LABDANE DITERPENOIDS. A REVIEW

Bahlul Z. S. Awen[a]; Masato Nozawa[b]; Hisahiro Hagiwara[b]
[a] Department of Medicinal and Pharmaceutical Chemistry Faculty of Pharmacy, Al-Fateh University, Tripoli, LIBYA [b] Graduate School of Science and Technology, Niigata University, Niigata, JAPAN

To cite this Article Awen, Bahlul Z. S. , Nozawa, Masato and Hagiwara, Hisahiro(2008) 'RECENT PROGRESS IN THE SYNTHESIS OF LABDANE DITERPENOIDS. A REVIEW', Organic Preparations and Procedures International, 40: 4, 317 — 363
To link to this Article: DOI: 10.1080/00304940809458095
URL: http://dx.doi.org/10.1080/00304940809458095

ORGANIC PREPARATIONS AND PROCEDURES INT., 40 (4), 317-363 (2008)

RECENT PROGRESS IN THE SYNTHESIS OF LABDANE DITERPENOIDS. A REVIEW

Bahlul Z. S. Awen,[†] Masato Nozawa,[††] and Hisahiro Hagiwara*[††]

[†]*Department of Medicinal and Pharmaceutical Chemistry*
Faculty of Pharmacy, Al-Fateh University
Seedi Elmasry, P. O. Box 13610, Tripoli, LIBYA

[††]*Graduate School of Science and Technology, Niigata University*
8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata, 950-2181, JAPAN
e-mail:hagiwara@gs.niigata-u.ac.jp

RECENT PROGRESS IN THE SYNTHESIS OF LABDANE DITERPENOIDS. A REVIEW

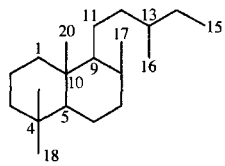
Bahlul Z. S. Awen,[†] Masato Nozawa,[††] and Hisahiro Hagiwara*[††]

[†]*Department of Medicinal and Pharmaceutical Chemistry*
Faculty of Pharmacy, Al-Fateh University
Seedi Elmasry, P. O. Box 13610, Tripoli, LIBYA

[††]*Graduate School of Science and Technology, Niigata University*
8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata, 950-2181, JAPAN
e-mail:hagiwara@gs.niigata-u.ac.jp

INTRODUCTION

Labdane diterpenoids have a bicyclic framework illustrated in the basic skeleton below and are the most common diterpenoids, which are widely distributed in terrestrial as well as marine organisms. Recent progress on the isolation of labdane diterpenoids are compiled in the review by Hanson.[1] Biogenetically, cyclization of geranylgeranylpyrophosphate provides the bicyclic framework of labdane diterpenoids. In contrast to other diterpenoids, there is less structural diversity in labdane diterpenoids. In most of these compounds, the relative stereochemistry of the ring junctures is *trans*. With regard to the absolute stereochemistry, there are two enantio-series. Some of these compounds exhibit a wide range of biological properties[2] such as anti-mutagenic,[2c] anti-bacterial and anti-fungal,[2d] cytotoxic,[2e] anti-inflammatory and analgesic activities,[2g] etc.

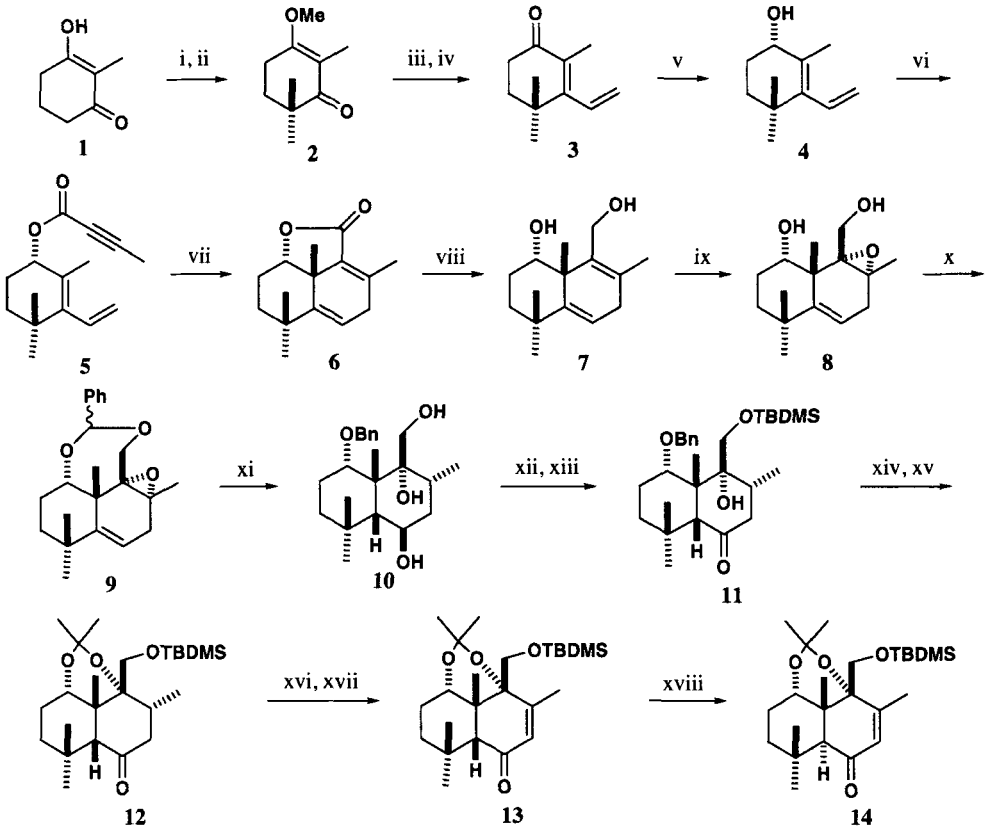


In view of such interesting biological activities of labdane diterpenoids, many synthetic studies have been reported so far and still much efforts are being devoted to develop more efficient, stereo-controlled and general synthetic approaches. This article covers recent progress in the synthetic studies of labdane diterpenoids from 1996 to present.

I. SYNTHESIS

1. From Synthetic Monocyclic Precursors

The total synthesis of forskolin (**24**) was elaborated starting from cyclohexa-1,3-dione (**1**) as shown in *Schemes 1* and *2*, which was transformed into tetrolic acid ester (**5**) in 6 steps in 53% overall yield. Intramolecular Diels-Alder reaction of the diene ester **5** was carried out



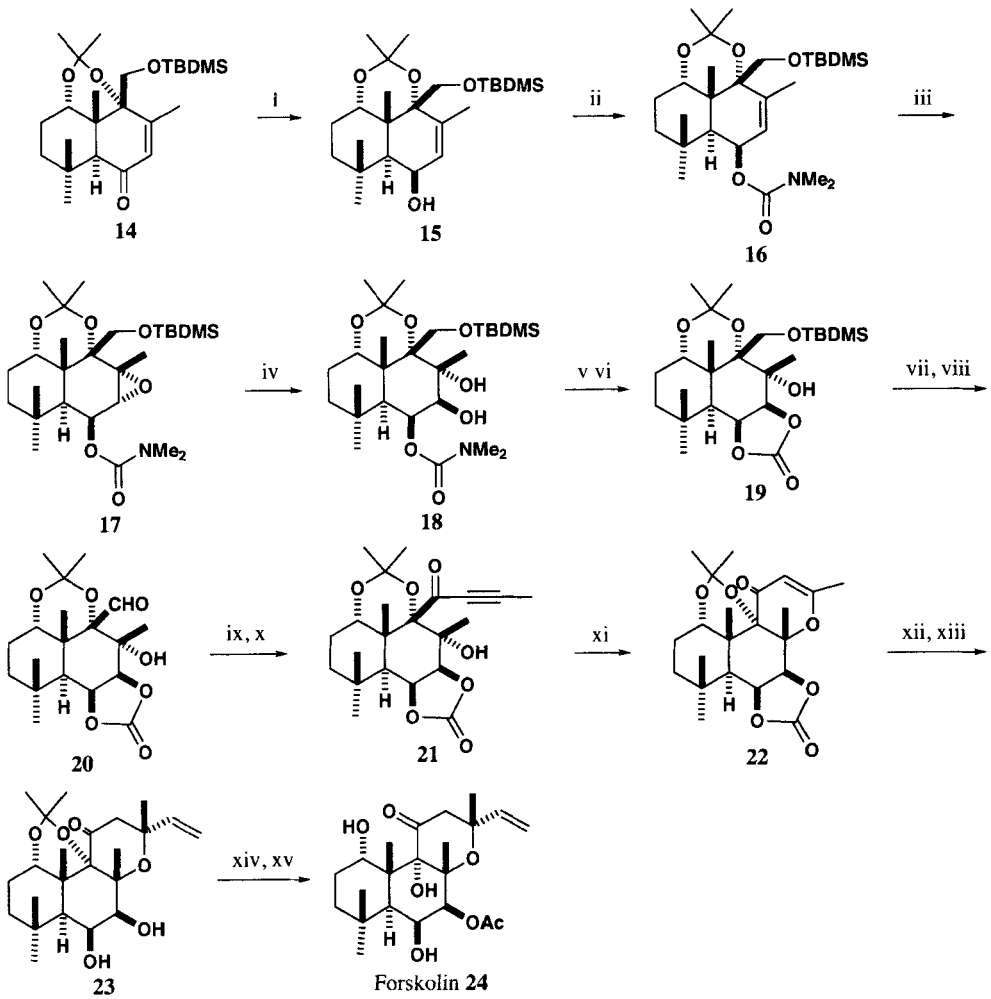
i) K_2CO_3, Me_2SO_4; ii) LDA, MeI; iii) vinylMgBr; iv) H^+; v) LAH; vi) DCC, 2-butynoic acid; vii) Δ; viii) LAH; ix) TBHP, $VO(acac)_2$; x) $PhCH(OMe)_3$, CCl_4; xi) $LiBF_4$, BH_3•THF; xii) TBDMSCl; xiii) CrO_3•2pyr; xiv) H_2, Pd/C; xv) $Me_2CH(OMe)_2$; xvi) LDA, PhSeCl; xvii) H_2O_2; xviii) basic Al_2O_3, 100°C.

Scheme 1

under carefully controlled conditions to furnish the lactone **6**. $VO(acac)_2$ mediated epoxidation with *t*-butyl hydroperoxide (TBHP) gave the α-epoxide **8** regioselectively, at C-8 and C-9. Hydroboration of the epoxide **9** resulted in hydroxylation at C-6 along with epoxide opening from β-face of the epoxide **9**. Thus, two α-hydroxyls at C-1 and C-9 were successfully installed. After several protection sequences, the enone moiety **14** was introduced by selenylation and oxidative elimination.[3]

Enone **14** was subsequently transformed into epoxy carbamate **17** after reduction with diisobutylaluminum hydride (DIBAL-H), followed by carbamation and *m*-chloroperbenzoic acid (MCPBA) epoxidation (*Scheme 2*).

The stereospecific formation of the 6β, 7β, 8α-triols was successfully accomplished *via* the BF_3•Et_2O assisted opening of epoxy carbamate **17**. Protection, deprotection and Swern oxidation gave the aldehyde **20**, which was reacted with propynyllithium. After Collins oxidation, treatment of the acetylenic ketone **21** with cesium carbonate resulted in ring closure to



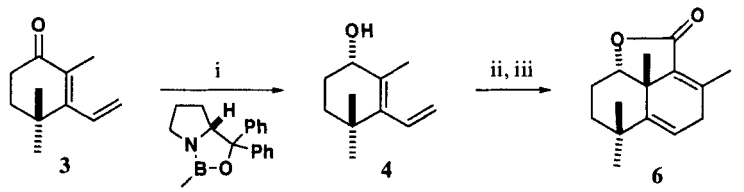
i) DIBAL; ii) *n*-BuLi, $Me_2N(C=O)Cl$; iii) MCPBA; iv) BF_3•OEt_2; v) LAH; vi) carbonyldiimidazole; vii) TBAF; viii) Swern; ix) MeCCLi; x) CrO_3•2pyr; xi) Cs_2CO_3, MeOH; xii) $(vinyl)_2CuLi$; xiii) NaOH; xiv) PTSA; xv) Ac_2O, pyr.

Scheme 2

afford the dihydropyran ring. Addition of divinylcopperlithium proceeded from the desired α-face of the molecule, albeit in lower yield. Deprotection and acetylation furnished racemic forskolin (**24**).

In order to improve the yield of vinylcuprate addition product, the hydroxy groups at C-6 and C-7 were protected as the acetonide. A slightly modified synthetic sequence increased the yield significantly. In spite of some difficulty in the hydrolysis of acetonide, forskolin (**24**) was obtained in a moderate yield.[4]

As shown in *Scheme 3*, asymmetric reduction of dienone **3** with catecholborane according to a modified Corey oxazaborolidine (CBS) methodology[5] furnished allylic alcohol **4** in 98% ee. Esterification of chiral alcohol **4** with tetrolic acid followed by intramolecular Diels-

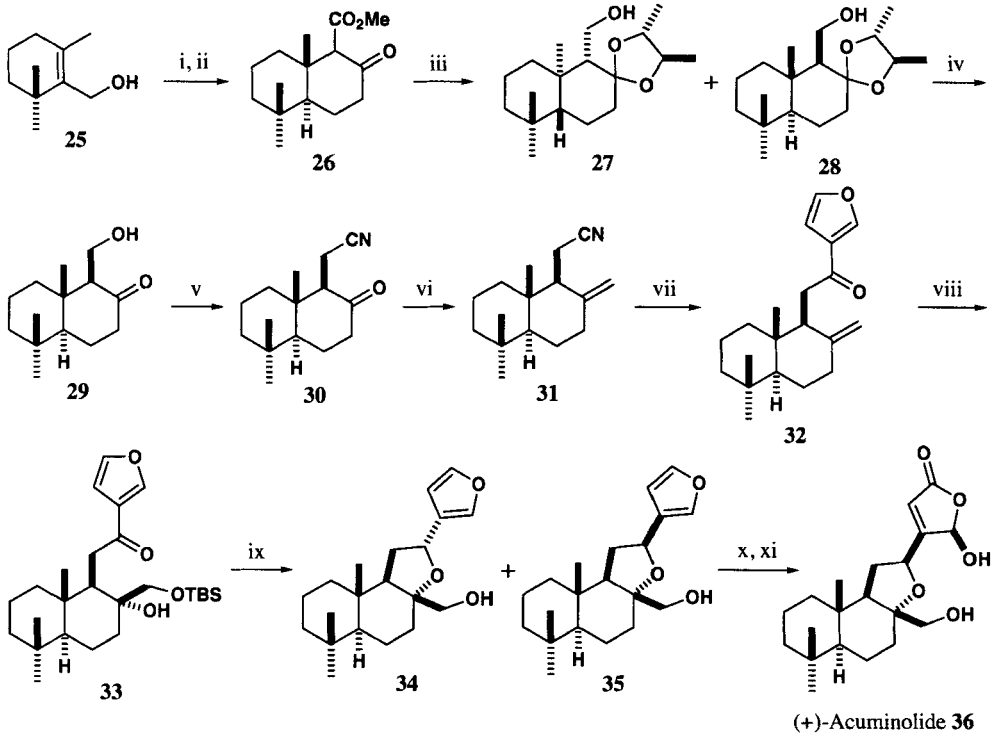


i) catecholborane, 98% *ee*; ii) tetrolic acid, dicyclohexylcarbodiimide, DMAP; iii) 185°C.

Scheme 3

Alder reaction provided the key tricyclic lactone **6** in 98% *ee*, demonstrating the feasibility of optically active forskolin synthesis.

(+)-Acuminolide (**36**) was isolated from *Neouvaria acuminatissima*, was found to possess cytotoxic activity in human cell lines. The total synthesis of (+)-acuminolide (**36**) (*Scheme 4*) was achieved along with other bi-, tri-, or tetracyclic terpenoids.[6a]



i) PBr_3, pyr, then dianion of methyl acetoacetate; ii) $SnCl_4$; iii) (2*R*, 3*R*)-2,3-butanediol, then LAH; iv) PTSA, acetone, H_2O; v) PTSCl, pyr then NaCN; vi) $Ph_3P{=}CH_2$; vii) DIBAL-H, 3-bromofuran, *sec*-BuLi, Dess-Martin periodinane; viii) OsO_4, pyr, $NaHSO_3$, then TBSCl; ix) L-Selectride; x) PTSCl, CH_2Cl_2; xi) O_2, $^iPr_2NEt$.

Scheme 4

Bromination of cyclogeraniol followed by alkylation with the dianion of methyl acetoacetate and cyclization with $SnCl_4$ provided the bicyclic keto ester, which was transformed into acetal alcohols **27** and **28** with (2*R*, 3*R*)-2,3-butanediol and subsequent $LiAlH_4$ reduction.

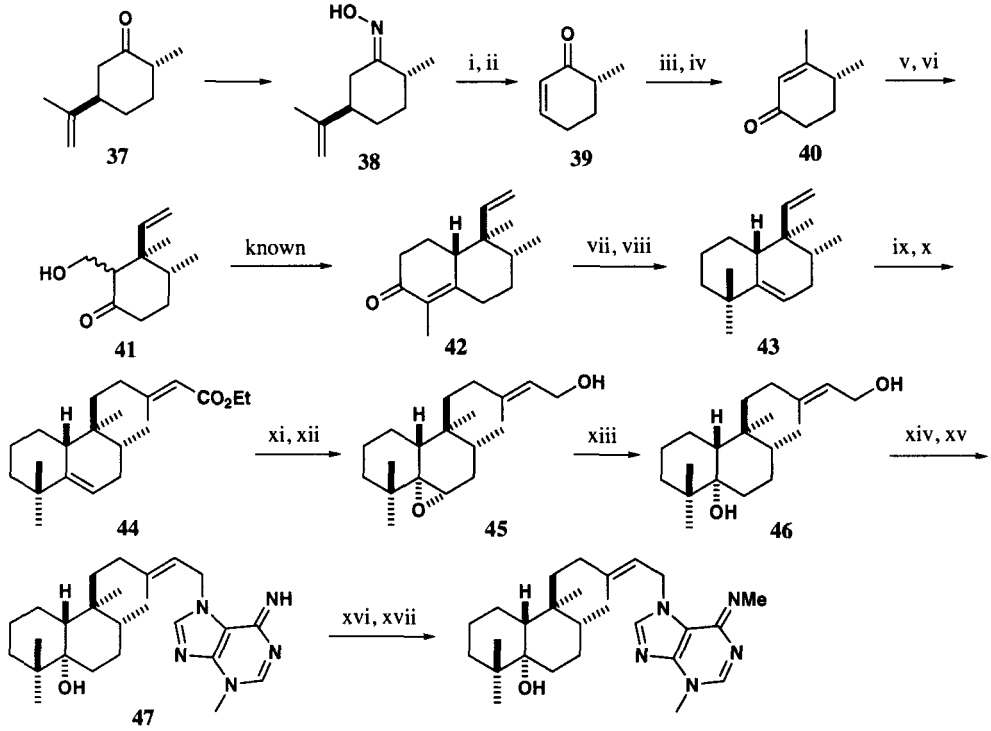
Optical resolution was carried out easily by column chromatography. Hydrolysis of the acetal gave enantiomerically pure (+)- or (–)-β-hydroxyketone **29**, whose absolute stereostructures were confirmed by comparison with the reported data.[6b] The (+)-β-hydroxyketone **29** was transformed into *exo*-methylenenitrile **31** by a sequence of tosylation, substitution by cyanide and Wittig methylenation. Reduction of nitrile **31** by DIBAL-H and subsequent addition of 3-lithiofuran to the resulting aldehyde afforded the furyl alcohol as a mixture of diastereomers, which was oxidized by Dess-Martin periodinane. Oxidation by OsO_4 proceeded selectively from the less hindered α-face of the molecule to give the diol, which was mono-protected as a *t*-butyldimethylsilyl (TBDMS)ether. Final conversion to (+)-acuminolide (**36**) was accomplished by reduction of the carbonyl group of furylketone **33** at C-12 by L-selectride, tetrahydrofuran formation after tosylation, and finally oxygenation with singlet oxygen in the presence of tetraphenylporphine and diisopropylethylamine. Abstraction of the less congested proton of the 1,4-*endo*-peroxide by a bulky base furnished the desired γ-hydroxybutenolide moiety. Thus, the absolute stereostructure of the natural product **36** was determined.

2. From Cyclic Monoterpenoids

Cyclic monoterpenoids with several asymmetric centers have been good starting materials, since they are available in large quantities. Among them, carvone (**49**) is a useful starting material due to the easy availability of both of its enantiomers.

(+)-Agelasimine A (**48**), isolated from the orange sponge *Agelas mauritiana*, displays various interesting biological activities such as cytotoxicity, inhibition of adenosine transfer and so on. Optically active (+)-*trans*-tetrahydrocarvone (**37**) was purified as its oxime **38**, which was transformed into methylcyclohexenone **39** by ozonolysis and subsequent treatment with $FeSO_4$-$Cu(OAc)_2$. Addition of MeLi followed by pyridinium chlorochromate (PCC) oxidation gave the 3,4-dimethylenone **40**. Conjugate addition of vinylmagnesium bromide and aldol reaction provided vinylketone **41**, which was transformed into the decalone **42** according to a known procedure.[7a] Methylation followed by a modified Wolff-Kishner reduction afforded the olefinic compound **43**. Suzuki cross-coupling reaction of the 9-borabicyclo[3.3.1]nonane (9-BBN) derivative led to α,β-unsaturated ester **44**. The α-hydroxy group at C-9 of **46** was introduced by epoxidation and hydride reduction. The allylic alcohol was brominated at the side-chain and substituted with 3-methyladenine. Further methylation furnished agelasimine A (**48**). The absolute stereostructure was established by this synthesis (*Scheme 5*).[7b]

Metasequoic acid (**60**) is an antifungal diterpene isolated from *Metasequoia glyptostroboides*, has a rare cyclopropane ring moiety. The β-keto ester of *R*-(–)-carvone (**49**) (*Scheme 6*) was alkylated with 6-bromo-3-methylhexa-1,3-diene to give triene **52**. Alternatively, triene **52** was obtained by alkylation of 3-iodopropionaldehyde diethylacetal followed by two successive Wittig condensations. Intramolecular Diels-Alder reaction was carried out in the presence of propylene oxide to give the tricyclic product **53** as a single isomer. Decarboxylation took



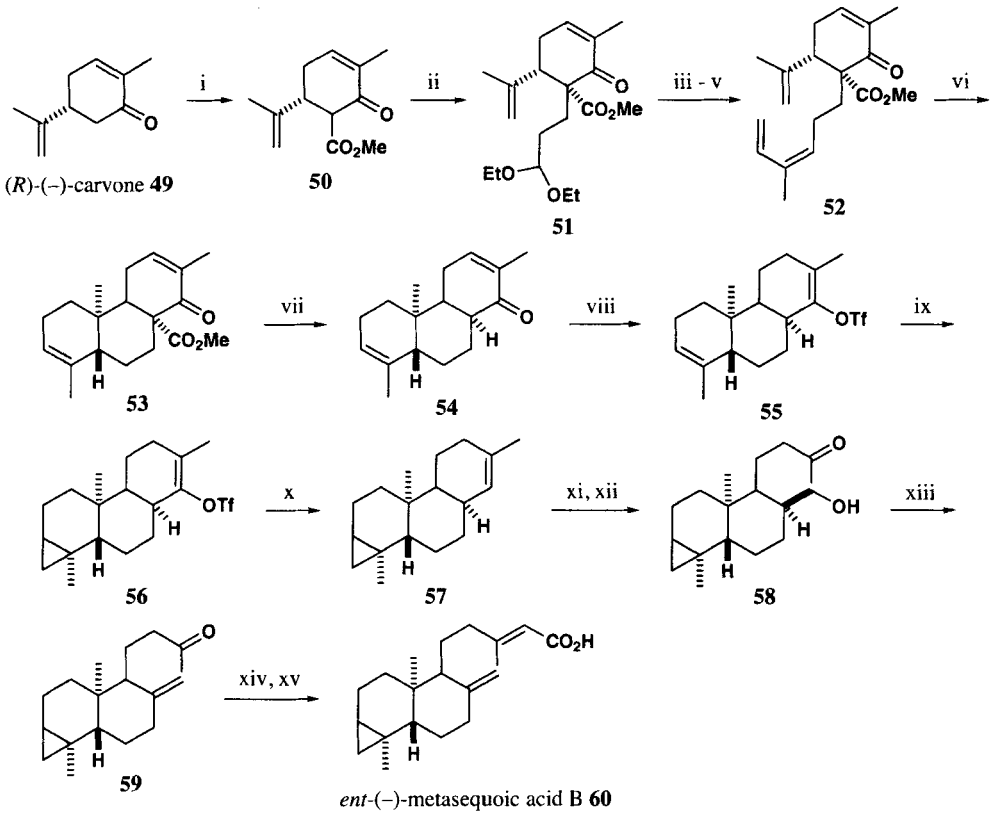
(+)-Agelasimine A **48**

i) O_3; ii) $FeSO_4$, $Cu(OAc)_2$; iii) MeLi; iv) PCC; v) vinyl-MgBr, CuBr, Me_2S; vi) HCHO, $Yb(OTf)_3$; vii) MeI, *t*-BuOK; viii) H_2NNH_2, KOH; ix) 9-BBN; x) $PdCl_2$, $Me(I)CH_2{=}CHCO_2Et$; xi) MCPBA; xii) DIBAL-H; xiii) LAH; xiv) BBr_3; xv) 3-methyladenine; xvi) MeI; xvii) NaOH.

Scheme 5

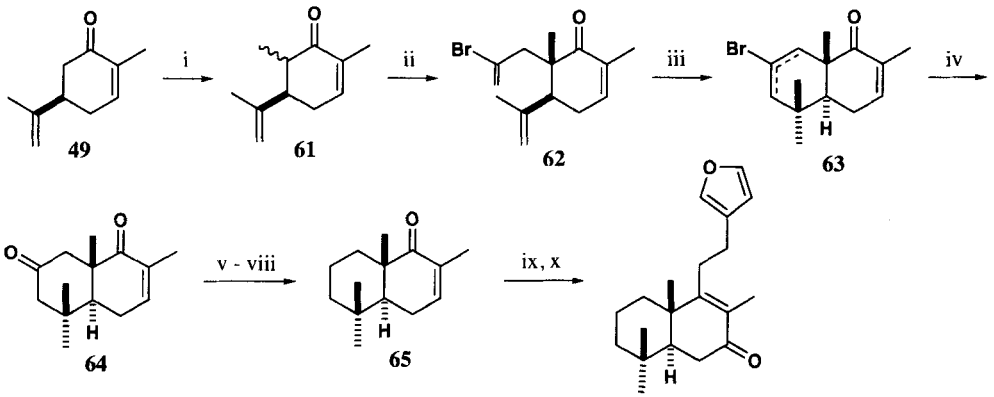
place smoothly. Conjugate reduction of the enone **54** by L-selectride and subsequent trapping of the enolate with Comin's reagent[8a] afforded the enol triflate **55**. Cyclopropane ring was introduced chemoselectively and stereoselectively by a modified Simmons-Smith condition. Reduction of the enol triflate **56** was effected by $Pd(OAc)_2$ and *n*-butylammonium formate to give the olefin **57**. Ozonolysis of the olefin **57** followed by chemoselective reduction provided the alcohol **58**. The *exo*-methylene was introduced by Grieco's method.[8b] Horner-Wadsworth-Emmons condensation of the ketone and subsequent hydrolysis completed the synthesis of *ent*-metasequoic acid B (**60**), thereby establishing the absolute stereochemistry of the natural product.[8c]

Hispanone (**66**) is a fungicidal and bacteriocidal furolabdane, which was isolated from mediterranean medicinal plants *Ballota saxitilis* and *Galeopsis angustifolia*. Alkylation of (*R*)-carvone (**49**) with MeI and lithium diisopropylamide (LDA) provided a diastereomeric mixture of 6-methylcarvone (**61**) (*Scheme 7*). Subsequent alkylation with 2,3-dibromopropene stereoselectively gave a single isomer, which was treated with trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) to result in acid catalyzed cyclization leading to decalin framework as a mixture of double bond isomers. The vinyl bromide **63** was hydrolyzed with H_2SO_4 and



i) LDA, NC-CO_2Me; ii) NaH, $(EtO)_2CHCH_2CH_2I$; iii) PPTS; iv) $Ph_3P{=}C(CHO)Me$; v) $Ph_3P{=}CH_2$; vi) propylene oxide, 190°C; vii) pyr, H_2O, 230°C; viii) L-selectride, Comins' reagent; ix) Et_2Zn, CH_2I_2; x) $Pd(OAc)_2$, *n*-Bu_3N, HCO_2H, DMF; xi) O_3, Me_2S; xii) $NaBH_4$, –78°C; xiii) Grieco protocol; xiv) Wadsworth-Emmons reaction; xv) KOH, EtOH.

Scheme 6



i) LDA, MeI; ii) LDA, 2,3-dibromopropene; iii) TFA, TFAA; iv) H_2SO_4, CF_3SO_3Ag; v) $NaBH_4$; vi) MsCl; vii) Δ; viii) H_2, Wilkinson cat.; ix) Li, 3-(bromoethyl)furan; x) PCC.

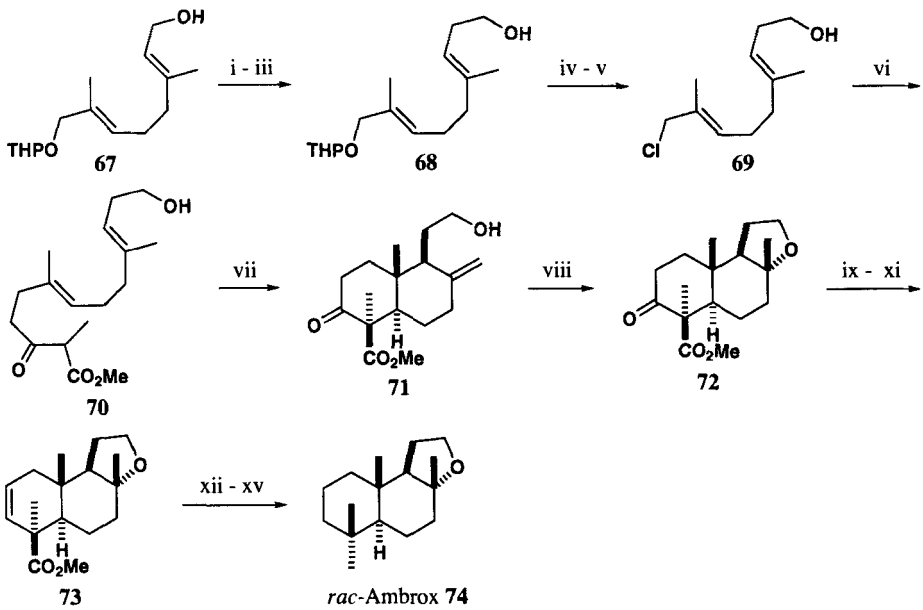
Scheme 7

silver trifluoromethanesulfonate. Reduction of the carbonyl group at C-2 by $NaBH_4$ and mesylation followed by thermal elimination gave a mixture of double bond isomers **63**. Acid catalyzed hydrolysis of the vinyl ether **63**, selective reduction of the carbonyl group at C-2 and subsequent mesylation followed by thermal elimination provided the $\Delta^{2,3}$-olefinic compound, whose regioselective catalytic hydrogenation was carried out employing Wilkinson catalyst. The resulting decalone **65** would be a useful precursor as a starting material for the syntheses of various natural products. Addition of (3-furyl)ethyllithium followed by oxidation by PCC completed the total synthesis of hispanone (**66**).[9]

3. From Biogenetic Cyclization

To construct cyclic framework of labdane diterpenoids, cyclization of polyene is a useful tool. Radical or cationic cyclization provides bicyclic compounds stereoselectively in one operation.

Racemic ambrox (**74**) was synthesized as shown in *Scheme 8* by radical polyene cyclization as a key step. The radical precursor **70** was prepared by the alkylation of dianion of methyl 2-methylacetoacetate with the allylic chloride **69**. Oxidative free-radical cyclization with



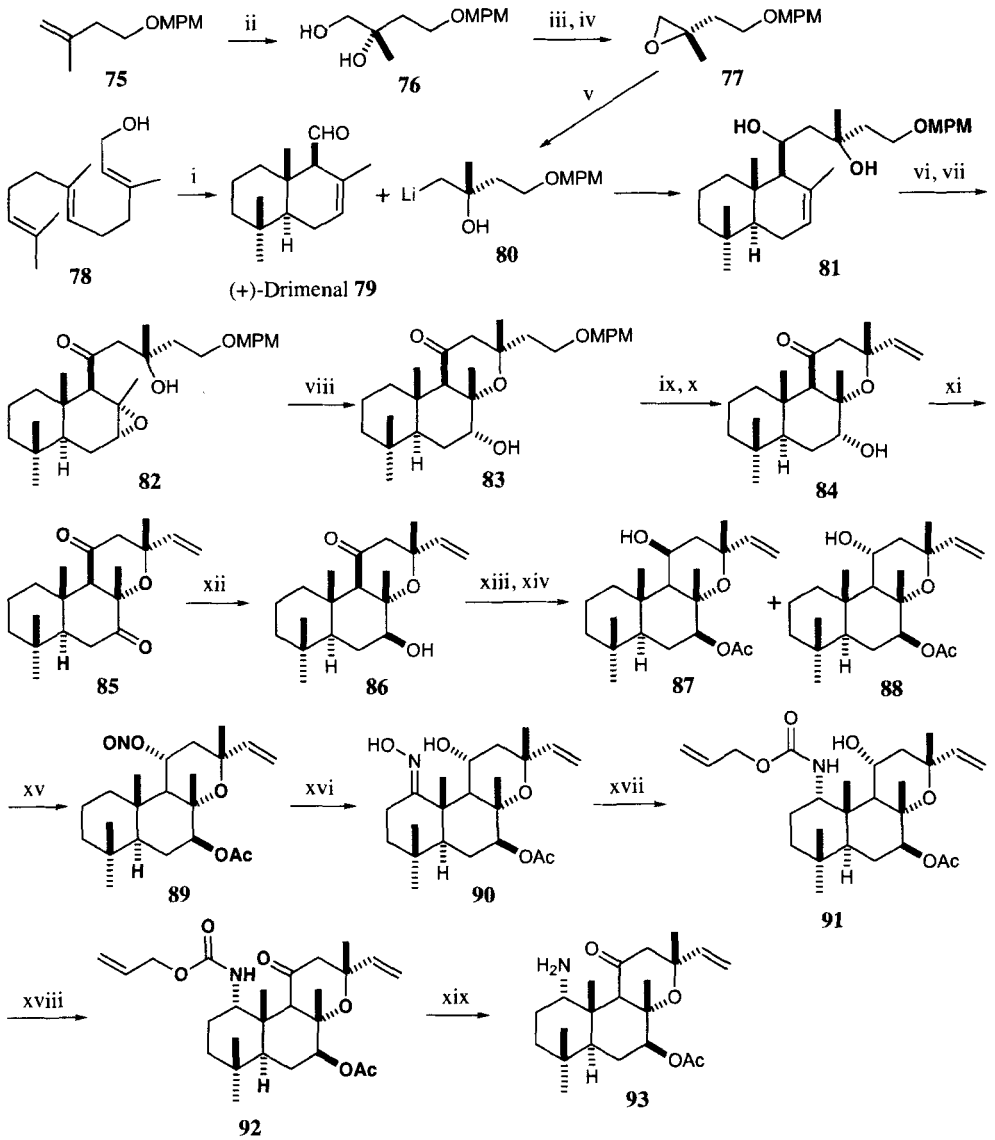
i) Swern; ii) $Ph_3P{=}CH_2$; iii) disiamylborane; iv) H^+; v) NCS; vi) NaH, *n*-BuLi, methyl 2-methylacetoacetate; vii) $Mn(OAc)_3$, $Cu(OAc)_2$; viii) CF_3CO_2H; ix) $NaBH_4$; x) CF_3SO_2Cl; xi) DMAP; xii) LAH; xiii) CS_2, DBU, MeI; xiv) Bu_3SnH; xv) H_2, Pd/C.

Scheme 8

$Mn(OAc)_3$ and $Cu(OAc)_2$ provided selectively the single bicyclic product **71**. Intramolecular cyclization in trifluoroacetic acid led to the tetrahydrofuran **72** along with the trifluoroacetate of the starting alcohol **71**. Carbonyl group at C-3 of **72** was reduced and dehydrated *via* trifluoromethanesulfonate to give the olefin **73**. The ester group was transformed into methyl group by

reduction and subsequent deoxygenation by Barton's radical protocol. Catalytic hydrogenation of the product finally furnished *rac*-ambrox (**74**).[10]

The 1α-amino-1,6,9-trideoxy analogue of forskolin (**93**) was synthesized from (–)-drimenol, which was prepared by cationic cyclization of farnesol (**78**) and resolution as camphanic ester (*Scheme 9*).[11a] The optically active epoxide **77**, a side-chain fragment, was



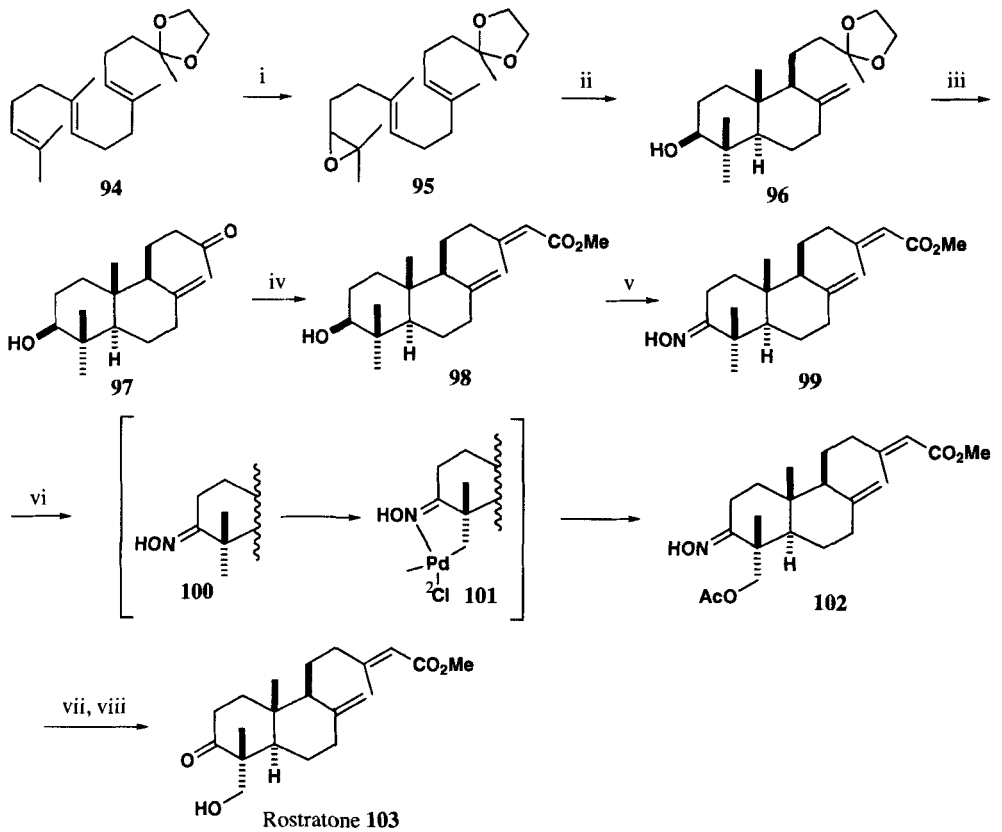
i) known; ii) Sharpless dihydroxylation; iii) TsCl, pyr; iv) NaH, THF; v) 4,4'-di-*t*-butylbiphenyl, Li, THF; vi) IBX, DMSO; vii) MCPBA, $CHCl_3$; viii) CF_3SO_3H, toluene; ix) CAN, $CHCl_3$; x) *o*-NO_2PheSeCN, *n*-Bu_3P then H_2O_2; xi) IBX, DMSO; xii) $NaBH_4$, EtOH; xiii) Ac_2O, pyr; xiv) SmI_2, diethyleneglycol; xv) NOCl, pyr; xvi) hν, benzene; xvii) $NaBH_3CN$, NH_4OAc, MeOH then allyl chloroformate, dioxane; xviii) IBX, DMSO; xix) $Pd(PPh_3)_4$, THF.

Scheme 9

prepared *via* the Sharpless asymmetric dihydroxylation of olefin **75**.

Reductive opening of epoxide **77** with the radical anion of 4,4'-di-*t*-butylbiphenyl (Freeman's salt)[11b] furnished lithioalkoxide **80**, which was reacted with drimenal (**79**) to afford alcohol **81** as a single diastereomer having requisite carbons and functionalities for further transformation. Treatment of epoxide **82** with trifluoromethanesulfonic acid resulted in ring closure from the α-face of the molecule to give tetrahydropyran ring. The terminal olefin was introduced by Grieco's method.[11c] Configuration at C-7 was inverted by oxidation and regio- and stereoselective reductions. After acetylation, reduction with SmI_2 in diethyleneglycol furnished 11-α-alcohol **88** as the major product. The amino group at C-1 was introduced by Barton's remote nitrite photolysis to afford hydrazone **90**, which was stereoselectively reduced with $NaBH_3CN$ and $TiCl_3$ to give the α-amino compound. Protection of the amino group as an allylcarbamate, oxidation of the hydroxyl at C-11 and deprotection provided the target compound **93**.

The present synthesis of rostratone (**103**) found in the plant *Nolana rostrata*. (*Scheme 10*)



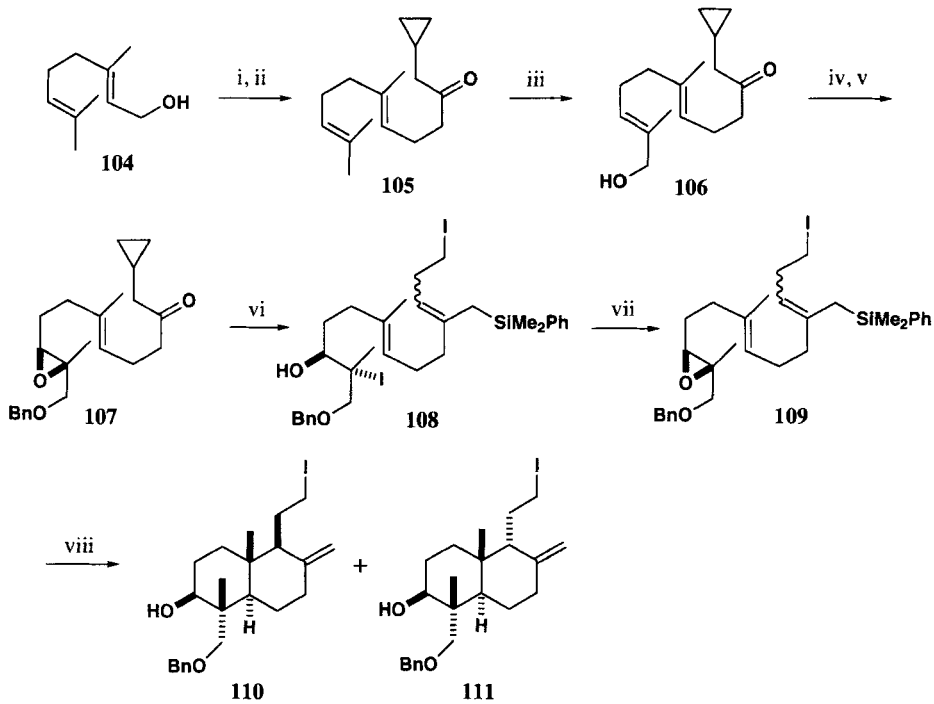
Rostratone **103**

i) NBS, H_2O then K_2CO_3; ii) cat. Cp_2TiCl_2, Mn, TMSCl, collidine; iii) $CeCl_3$, NaI, H_2O;
iv) $(EtO)_2POCH_2CO_2Me$, NaH; v) Dess-Martin periodinane then NH_2OH;
vi) Na_2PdCl_4 then pyr, $Pb(OAc)_4$; vii) $TiCl_3$, H_2O; viii) known.

Scheme 10

comprised two key reactions, Ti(III) mediated polyene cyclization and Pd catalyzed remote C-H oxidation of C-4 methyl group. The acetal of geranylacetone **94** was transformed into the terminal epoxide **95** by conventional procedure. Radical cyclization of the polyene **95** was effected by employing Cp_2TiCl_2 and Mn to give the bicyclic alcohol **96** stereoselectively. Deprotection of the acetal and Horner-Wadsworth-Emmons reaction furnished the unsaturated ester **98**. Dess-Martin oxidation followed by treatment with hydroxylamine led to the oxime **99**, which was converted into the target compound **103** by remote hydroxylation.[12] The reaction proceeded by the treatment with $NaPdCl_4$ leading to palladacycle dimer and subsequent oxidation by $Pb(OAc)_4$.

Optically active labdane intermediates **110** and **111** were synthesized by cationic polyene cyclization as shown in *Scheme 11*. Allylic oxidation of the terminal methyl of the cyclopropylketone **105** and subsequent Sharpless diethyltartrate (DET)[13a] epoxidation gave the



i) PPh_3, I_2, imidazole; ii) LDA, cyclopropylmethylketone; iii) SeO_2, TBHP; iv) Sharpless epoxidation; v) NaH, BnBr, Bu_4NI; vi) $ClMgCH_2SiMe_2Ph$ then MgI_2; vii) K_2CO_3; viii) $BF_3{\bullet}OEt_2$.

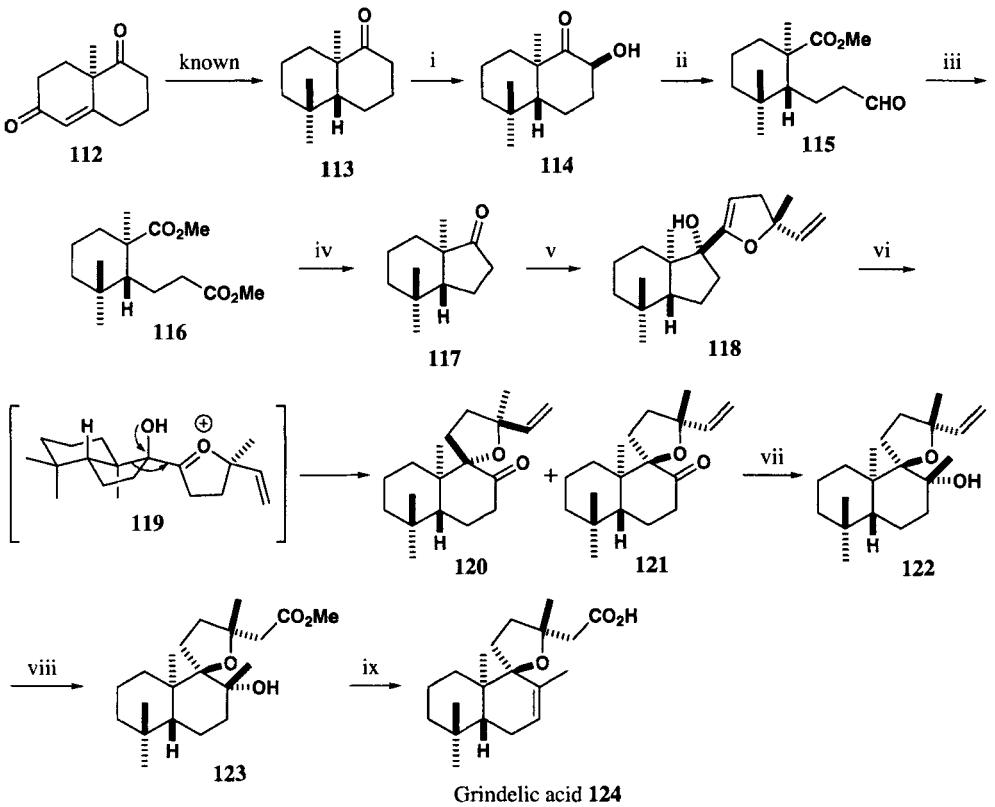
Scheme 11

O-benzylated chiral epoxy alcohol **107**. Requisite allylsilane moiety for termination of polyene cyclization was introduced by the reaction of silylmethyl Grignard reagent. Treatment of the polyene **109** with $BF_3{\bullet}OEt_2$ furnished diastereomeric bicyclic compounds **110** and **111** in an equal ratio.[13b]

4. Syntheses from Wieland-Miescher Ketone

Wieland-Miescher ketone (**112**) and its analogues are useful precursors for the syntheses of terpenoids having various decalin frameworks as core structures. Easy availability of both the enriched enantiomers facilitates their use for enantiocontrolled syntheses. Rigid bicyclic core enables stereoselective introduction of various requisite functional groups.

Grindelic acid (**124**), isolated from *Grindelia* species, has a characteristic *spiro*-tetrahydrofuran ring, though its absolute configuration is yet to be determined. Paquette and Wang elaborated total synthesis of (+)-grindelic acid (**124**), an antipode of the natural product, through a stereocontrolled oxonium ion activated pinacol ring expansion as a key step. Since the *trans*-indanone **117** is difficult to prepare from Hajos-Wiechert ketone, a route by ring contraction from (–)-Wieland-Miescher ketone (**112**) was employed (*Scheme 12*).



i) $Pyr{\bullet}HBr_3$, HOAc, NaOH, DMF; ii) $Pb(OAc)_2$, MeOH; iii) $NaClO_2$, H_2SO_4, MeOH; iv) $NaN(TMS)_2$, LiCl, DMSO, 120°C; v) 2,3-dihydro-2-methyl-2-vinylfuran, *t*-BuLi, $CeCl_3$; vi) CSA; vii) MeLi, $CeCl_3$; viii) BH_3, H_2O_2, PCC, I_2, KOH, MeOH; ix) $SOCl_2$, DMAP, pyr, KOH, MeOH, H_2O.

Scheme 12

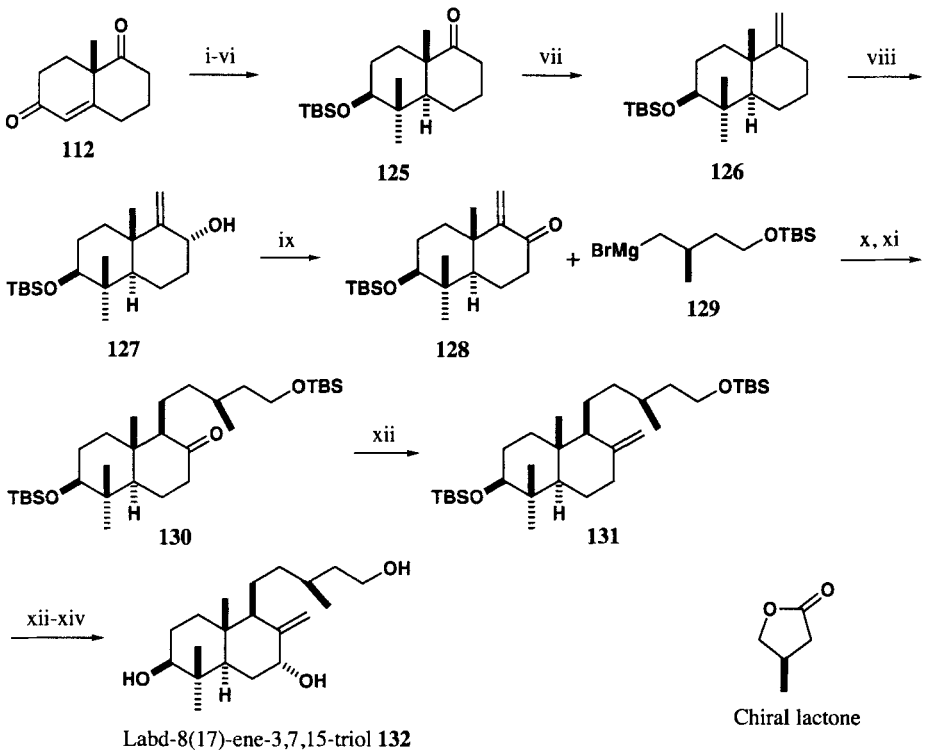
Bromination of the *trans*-decalone **113** obtained in 5 steps from Wieland-Miescher ketone (**112**) and subsequent substitution provided the hydroxyketone **114**, which was cleaved by

$Pb(OAc)_4$ to give the formyl ester. Oxidation by sodium chlorite followed by esterification gave the diester **116**. Dieckman cyclization and Krapcho decarboxylation furnished the requisite *trans*-indanone **117**. The optically active dihydrofuran fragment was prepared from linalool. Since five-membered ketones are amenable to enolization, cerium chloride was added for the 1,2-addition of the vinyllithium reagent derived from the dihydrofuran. The addition proceeded from the less hindered β-face of the molecule to give the single stereoisomer **118**. Treatment of alcohol **118** with camphorsulfonic acid (CSA) initiated and promoted pinacol ring expansion *via* the oxonium ion to give the *spiro*-tetrahydrofurans **120** and **121** in a ratio of 1:10.4, in which the relative stereochemistry of the major product **121** was assigned by NOE experiment. Addition of methyllithium, hydroboration of terminal olefin, PCC oxidation and esterification provided the hydroxyester **123**. Dehydration and hydrolysis completed the total synthesis of natural grindelic acid (**124**), which demonstrates unequivocally that natural (–)-grindelic acid (**124**) is a true labdane diterpenoid (*Scheme 12*).[14]

Labd-8(17)-ene-3β,7,15-triol (**132**) was isolated from *Araucaria imbricata*. The optically active protected ketone **125** was obtained from (*S*)-(+)-Wieland-Miescher ketone (**112**). The enone **128** was synthesized by Wittig reaction, allylic oxidation by SeO_2 and subsequent Moffat oxidation. The side-chain fragment was obtained from the chiral lactone shown, which was converted to the Grignard reagent **129**. Conjugate addition of the Grignard reagent to enone **128** installed the side-chain moiety. Olefination at C-8 with $Zn/TiCl_4/CH_2Br_2$, deprotection followed by allylic oxidation at C-7 furnished the target compound **132**, which established that the natural compound **132** possessed the (13*S*) absolute configuration as shown in *Scheme 13*.[15]

Hispanolone (**137**) was isolated from *Ballota hispanica* and *Leonurus heterophyllus* and employed in the synthesis of the specific platelet activating factor antagonist prehispanolone. The decalone **113** was synthesized from racemic Wieland-Miescher ketone (**112**). Mono-methylation was carried out according to the method of Sondheimer by silyl enol ether formation followed by desilylation-methylation with tetrabutylamonium fluoride (TBAF) and MeI. Bromination with pyridinium bromide perbromide and subsequent dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the enone **65**. Addition of lithium acetylide and PCC oxidation provided enone **136**. The furan ring was introduced by Sonogashira coupling with 3-bromofuran. Hydrogenation gave the enone **66**. Though epoxidation of the enone was unsuccessful, MCPBA epoxidation gave α-epoxide after $NaBH_4$ reduction and protection as TBDMS ether. MCPBA oxidation, desilylation, $LiAlH_4$ reduction and oxidation completed the synthesis of the target molecule **137** (*Scheme 14*).[16]

Chapecoderins (**143**) ~ (**145**) were isolated from the Brazilian medicinal plant, *Echinodorus macrophyllus*. They are structurally rare seco- or rearranged labdanes. The total syntheses of these compounds were accomplished for the first time in 2001.[17] The decalone **134** prepared from (S)-(+)-Wieland-Miescher ketone analogue **138** was reacted with the anion of *tert*-butyl acetate. Dehydration of the product **139** followed by reduction and acetylation provided acetate **141**.



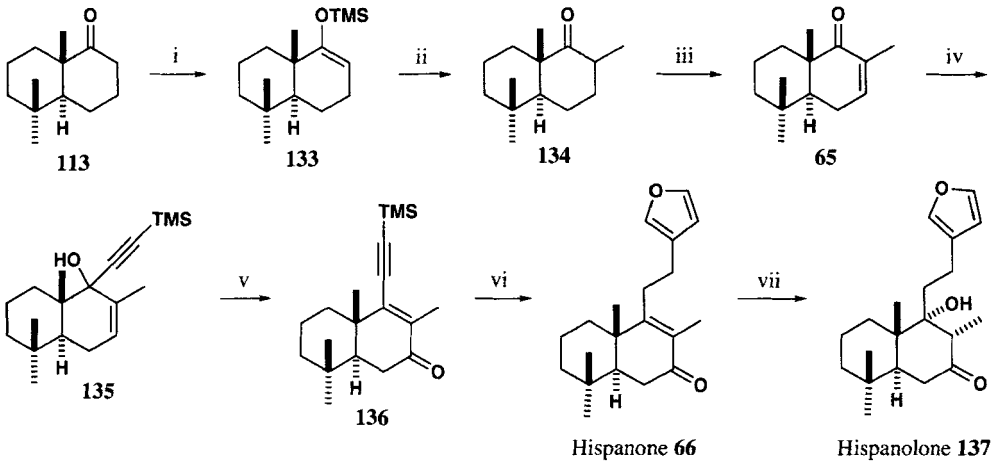
i) 2-ethyl-2-methyl-1,3-dioxolane, PTSA, ethylene glycol; ii) *n*-propanol, Et_3N, PhSH, formaldehyde; iii) Li/NH_3, MeI; iv) $NaBH_4$, EtOH; v) aq. hydrochloric acid; vi) TBDMS triflate, Et_3N; vii) $Ph_3P{=}CH_2$, NaH, DMSO; viii) cat. SeO_2, TBHP; ix) DMSO, $(CF_3CO)_2O$, Et_3N; x) cat. CuI, ether, then acetic anhydride; xi) 10% KOH in MeOH; xii) Zn, $TiCl_4$, CH_2Br_2; xiii) HF, MeCN; xiv) cat. SeO_2, TBHP.

Scheme 13

Ozonolysis in methanol gave diketone **142**, which was treated with α-phenylsulfinyl-γ-butyrolactone and DBU under gradual heating to furnish chapecoderin A (**143**) *via* β-elimination of acetic acid from the β-acetoxyketone moiety, conjugate addition of the lactone and thermal elimination of sulfinic acid to give chapecoderin A (**143**) and chapecoderin B (**144**) as a minor product. Cyclization of chapecoderin A (**143**) with pyrollidine and benzoic acid yielded chapecoderin C (**145**). Thus, the absolute stereochemistries of these compounds were established (*Scheme 15*).

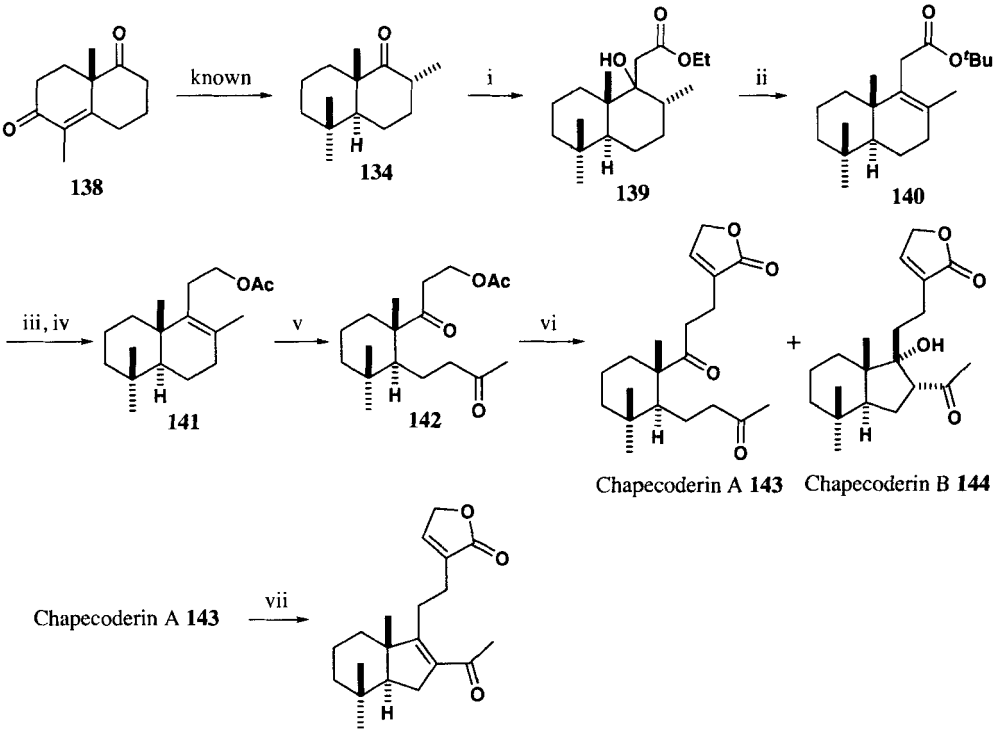
5. *From Sesquiterpenoids and Related Compounds*

Synthetic efforts from sesquiterpenoids as a starting material for labdane synthesis are rare. (–)-Marginatone (**151**) is a marine labdane furanoditerpene, isolated from the marine sponge *Aplysilla glacialis*. Its synthesis was accomplished *via* (+)-coronarin E (**149**).[18a] Synthetic (–)-albicanol (**146**) was oxidized by chromium oxide/pyridine complex to give albicanal (**146**), which was condensed with 3-furylmethyl triphenylphosphorane to afford coronarin E (**149**) in



i) TMSCl, THF; ii) MeI, TBAF, molecular sieves, THF; iii) DBU, toluene, reflux; iv) lithium trimethylsilylacetylide, Et_2O; v) PCC, florisil, CH_2Cl_2; vi) K_2CO_3, MeOH, 3-bromofuran, $Pd(PPh_3)_4$, CuI, H_2, Pd/C; vii) $NaBH_4$, $CeCl_3$, imidazole, TBDMSCl, MCPBA, TBAF, LAH, PDC, molecular sieves.

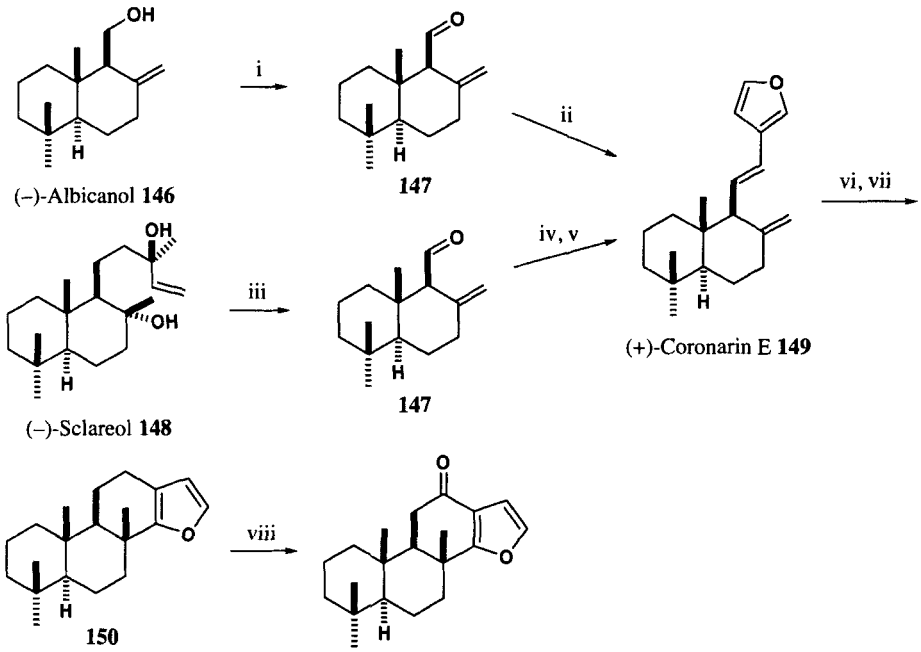
Scheme 14



i) LDA, HMPA, CH_3CO_2t-Bu; ii) $SOCl_2$, DMAP, pyr, r.t.; iii) LAH, Et_2O, r.t.; iv) acetic anhydride, DMAP, pyr, r.t.; v) O_3/O_2, CH_3OH, –20°C, Me_2S; vi) α-phenylsufinyl-γ-butyrolactone, DBU, benzene; vii) pyrrolidine, benzoic acid.

Scheme 15

moderate yield. Alternatively, based on the procedure of Jung and Seifert,[18b] (–)-sclareol (**148**) was transformed into coronarin E (**149**) in a much better yield. Dehydration in refluxing HMPA of the furyl alcohol improved the yield. Selective reduction of the side-chain double bond of (+)-coronarin E (**149**) was carried out by Pd/C and ammonium formate. Subsequent electrophilic cyclization of dihydrocoronarin by BF_3•OEt_2 led to the tetracyclic skeleton **150** stereoselectively which upon allylic oxidation by *t*-butylhydroperoxide (TBHP) and NaOCl, gave (–)-marginatone (**151**). Thus, the absolute stereochemistry of the natural product was confirmed (*Scheme 16*).

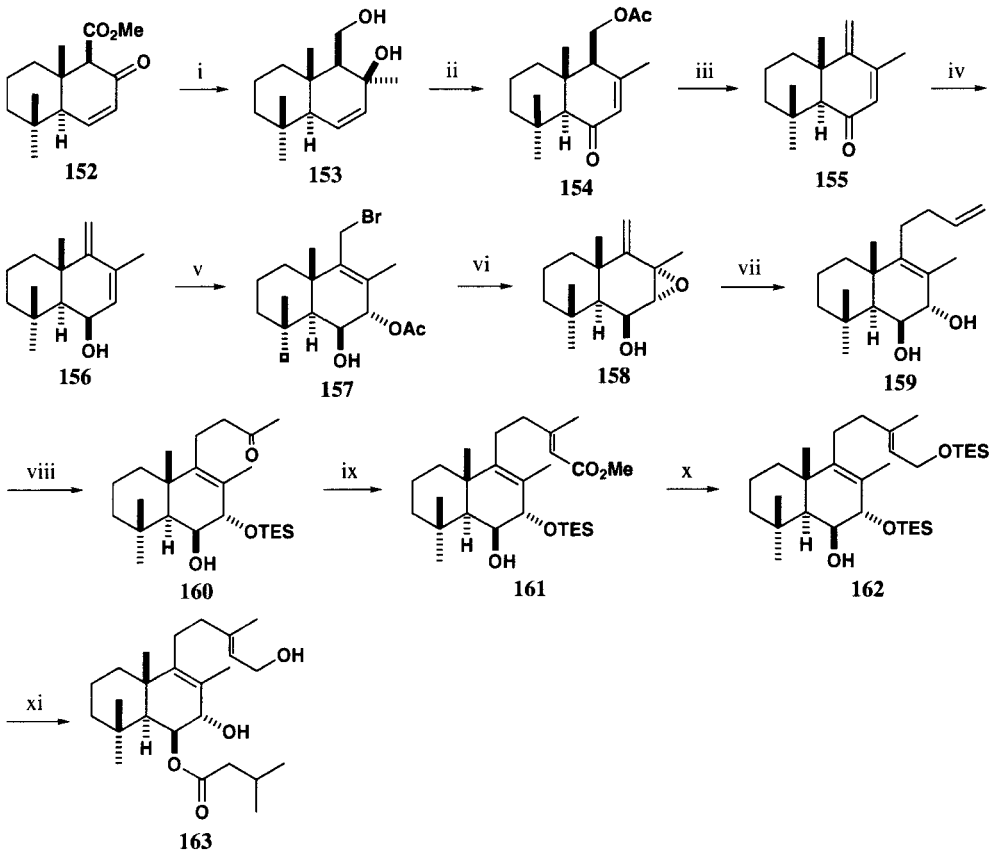


i) CrO_3-Pyr; ii) *n*-BuLi, 3-furylmethyl triphenylphosphorane; iii) known, 7 steps; iv) 3-furyllithium; v) HMPA, heat; vi) $HCOONH_4$, 10% Pd/C, MeOH, reflux; vii) BF_3•Et_2O, CH_2Cl_2, r.t.; viii) TBHP, 70% aq. NaOCl, AcOEt.

Scheme 16

6β-Isovaleroxylabda-8,13-diene-7α,15-diol (**163**) isolated from *Trimusculus reticulatus* exhibits repellent activity against starfish. The key to the success of the introduction of substituents was S_N2' substitution. The synthesis has started from the decalone **152**, obtained easily from β-ionone. Reduction, oxidation of the allylic alcohol and addition of methyllithium provided diol **153**. Acetylation followed by PCC allylic oxidation led to enone **154**, which was treated with alkali and acid to give the dienone **155**. Reduction by DIBAL-H proceeded selectively from the α-face of the molecule to give the β-axial-alcohol **156**. Treatment with NBS effected regio- and stereoselective attack of acetoxy group the 7α-acetate; treatment of **157** with K_2CO_3 afforded the α-epoxide **158** by S_N2' displacement. Addition of allylcuprate also proceeded in an S_N2' fashion to install a homoallylic moiety at C-9. After selective protection of

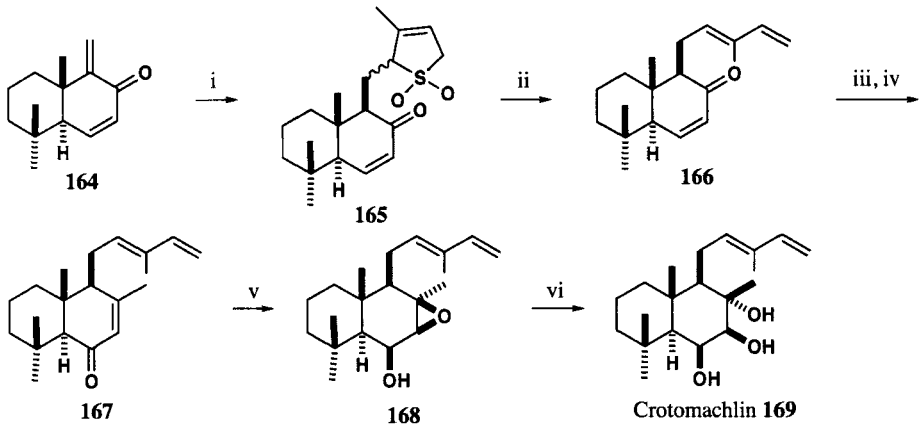
C-7 hydroxy group, Wacker oxidation provided methyl ketone **160**. Horner-Wadsworth-Emmons condensation, reduction and esterification at C-6 hydroxyl finally completed the total synthesis of the target compound **163**, as a racemate (*Scheme 17*).[19] Later on, compound **163** in its natural enantiomeric form was synthesized from (+)-larixol (**239**).[39]



i) LAH then $BaMnO_4$ then MeLi; ii) Ac_2O then PCC; iii) K_2CO_3; iv) DIBAL-H; v) NBS, AcOH; vi) K_2CO_3, MeOH; vii) allylmagnesium bromide, CuBr, SMe_2, LiBr; viii) $PdCl_2$, CuCl, DMF, H_2O, O_2, TESCl, pyr; ix) $(EtO)_2P(O)CH_2CO_2Et$, NaH; x) DIBAL-H, TESCl, py; xi) isovaleric acid, DCC, DMAP, TBAF.

Scheme 17

Crotomachlin (**169**) isolated from *Croton macrostachys* exhibits potent antilipoxygenase activity. As illustrated in *Scheme 18*, dienone **164** available from β-ionone, was treated with the carbanion of 3-methylsulfolane, generated from LHMDS and tetramethylethylenediamine (TMEDA). Thermolysis of the resulting sulfolane furnished the *trans*-diene **166**. Addition of MeLi followed by allylic oxidation with PCC led to enone **167**, which was reduced with DIBAL-H to give the β-axial alcohol. Epoxidation of the alcohol with TBHP and $VO(acac)_2$ gave β-epoxide **168**. Among various acidic reaction conditions, treatment of the epoxide **168** with *p*-toluenesulfonic acid in THF-H_2O provided racemic crotomachlin (**169**) (*Scheme 18*).[20]



i) 3-methylsulfolane, LHMDS, TMEDA; ii) pyr, toluene, 120°C; iii) MeLi; iv) PCC, AcONa; v) DIBAL-H; vi) $VO(acac)_2$, TBHP; vii) PTSA, THF, H_2O.

Scheme 18

6. Interconversions of Labdane Diterpenoids

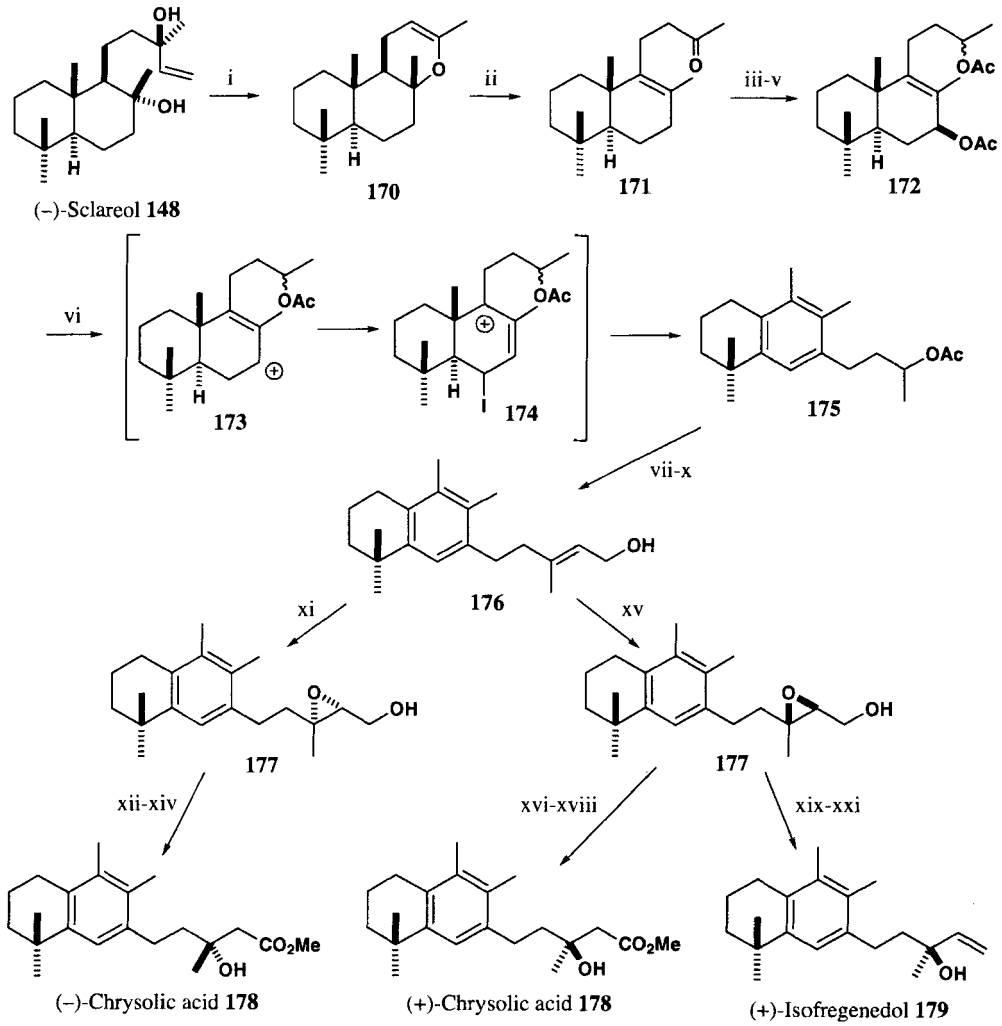
Several labdane diterpenoids are abundant in nature and commercially available. Thus they are useful starting materials for chemical transformations. Since they already have the labdane framework, modification of functional groups by manipulation of existing functional groups leads to other labdane natural products. Among these are sclareol (**148**), sclareolide (**207**), larixol (**239**), manool (**280**) and communic acid (**299**). Most of the methods involved side-chain degradations of labdanes.

(–)-Sclareol (**148**) is a commercially available labdane diterpenoid from *Salvia sclarea* (claysage). It has been utilized as a starting material for various terpenoid syntheses, especially for terpenoids which do not have functional groups in the left ring of decalin portion. Synthetic transformations of the side-chain and the right ring led to the desired synthetic targets.

(–)-Chrysolic acid (**178**) and (+)-isofregenedol (**179**) were isolated from *Chrysothamnus paniculatus* and *Haplopappus parvifolius*, respectively. These compounds belong to the structurally rare B ring aromatic diterpenes, and their absolute stereostructures were deduced on biogenetic basis.

$KMnO_4$ oxidation of sclareol **148** led to the dihydropyran derivative **170**, which was treated with HI in benzene to give the olefinic ketone **171**. Allylic oxidation, $LiAlH_4$ reduction and subsequent acetylation provided the allylic acetate **172**. Treatment of **172** with HI in benzene induced cationic successive rearrangement of the side-chain and the methyl group at ring juncture to yield B aromatic ring compound **175**; **175** could also be derived from zamoranic acid **288** (*vide infra*). Horner-Wadsworth-Emmons condensation of the methylketone derived from reduction and PCC oxidation of acetate **175**, provided the unsaturated ester, which was reduced with DIBAL-H to give the allylic alcohol **176**. Sharpless asymmetric epoxidation using (+)- and (–)-

DET afforded both enantiomers of the epoxides **177**. Reduction with $LiAlH_4$, pyridinium dichromate (PDC) oxidation and esterification furnished both enantiomer of chrysolic acid (**178**). Tosylation of the hydroxyepoxide, substitution by iodine and reductive opening by zinc in acetic acid provided (+)-isofregenedol (**179**). Thus, the absolute configuration of the natural products was established based on Sharpless asymmetric epoxidation (*Scheme 19*).[21]

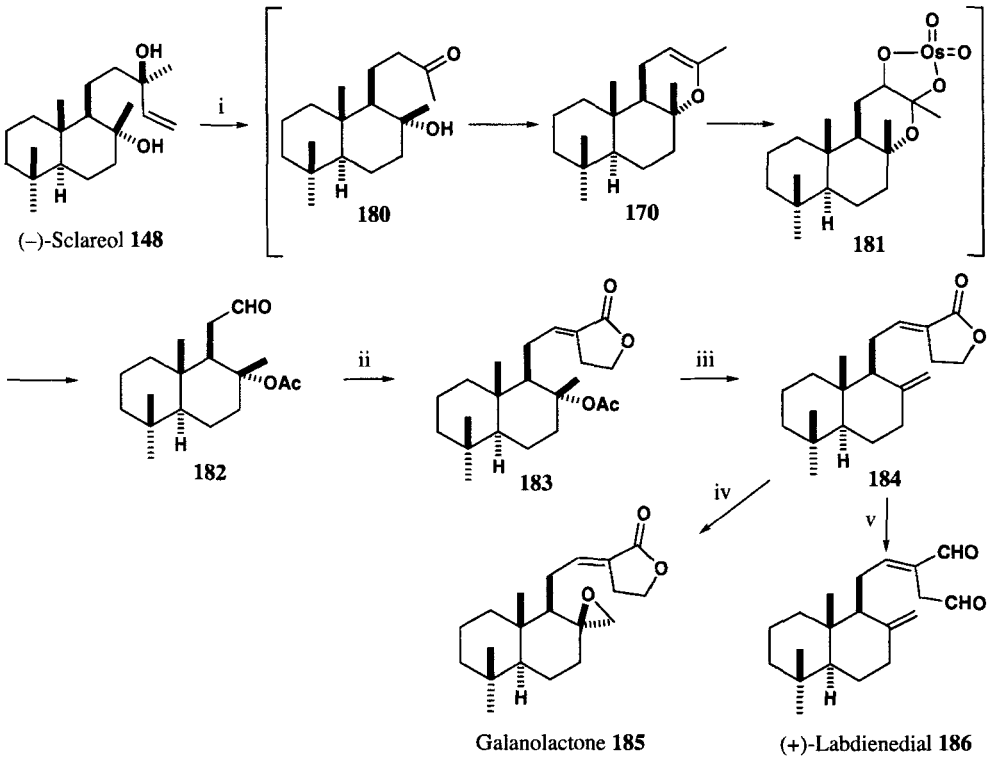


i) $KMnO_4$, $MgSO_4$, SiO_2; ii) HI, benzene; iii) Na_2CrO_4, Ac_2O, AcONa, AcOH; iv) LAH, THF; v) Ac_2O, pyr; vi) HI, benzene, reflux; vii) LAH; viii) PCC, DCM; ix) $(EtO)_2P(O)CH_2CO_2Me$, NaH; x) DIBAL; xi) D-(-)-DET, TBHP,Ti(*i*-PrO)$_4$; xii) LAH, THF; xiii) PDC, DMF; xiv) CH_2N_2; xv) L-(+)-DET, TBHP, Ti(*i*-PrO)$_4$; xvi) LAH, THF; xvii) PDC, DMF; xviii) CH_2N_2; xix) TsCl, pyr; xx) Zn-Cu, CuI; xxi) Zn, AcOH.

Scheme 19

Galanolactone (**185**) and labdienedial (**186**) isolated from *Alpinia galanga* show cytotoxic and antifungal activities. A short, regiospecific synthesis of these compounds was first

achieved from sclareol (**148**). Unlike $KMnO_4$ oxidation, OsO_4 oxidation of sclareol (**148**) afforded the acetoxyaldehyde **182**. This interesting transformation was proposed to proceed *via* a four-step sequence as shown in *Scheme 20*. The acetoxy group at C-8 of aldehyde **182** rearranged from the side-chain at C-13. Horner-Wadsworth-Emmons reaction provided *E*-α-methylene-γ-butyrolactone **183**. Regioselective deacetoxylation followed by epoxidation with MCPBA afforded (+)-galanolactone (**185**) as a minor diastereomer along with 8-*epi*-isomer. Reduction of the α-methylene-γ-butyrolactone and subsequent PCC oxidation gave (+)-labdienedial (**186**) (*Scheme 20*).[22]



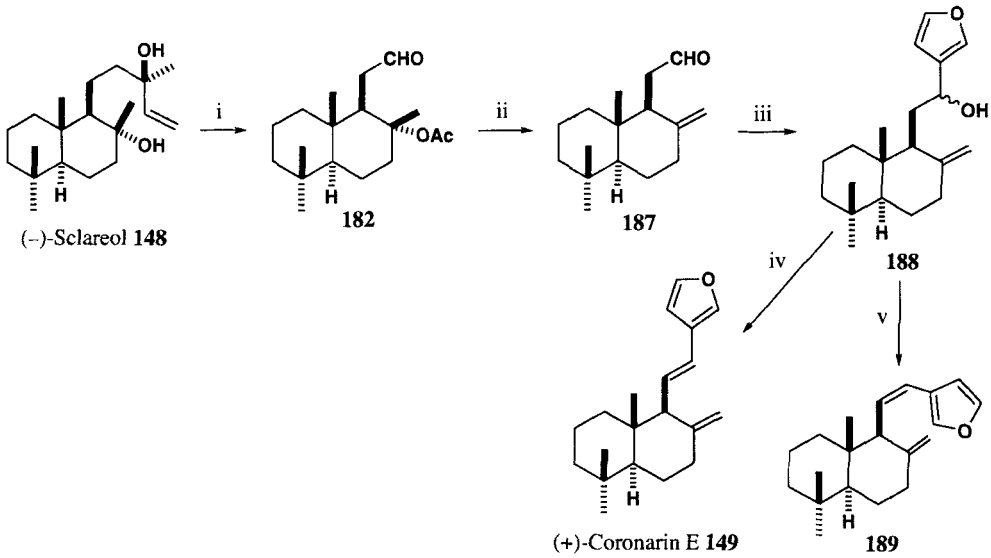
Galanolactone **185** (+)-Labdienedial **186**

i) OsO_4, $NaIO_4$, *t*-BuOH, THF; ii) diethylphosphono-2-butyrolactone, NaH; iii) quinoline, reflux; iv) MCPBA; v) LAH then PCC.

Scheme 20

(+)-Coronarin E (**149**) was isolated from Brazilian medicinal plant, *Hedychium coronarium*. Jung *et al.* demonstrated the pilot synthesis of coronarin E (**149**) from (–)-sclareol (**148**) in 4 steps in an overall yield of 22%. The side-chain of sclareol (**148**) was cleaved by OsO_4 to give the acetoxyaldehyde **182**. Regioselective deacetylation by collidine, addition of 3-furyllithium and subsequent dehydration with methanesulfonyl chloride furnished (+)-coronarin E (**149**) (*Scheme 21*).[23]

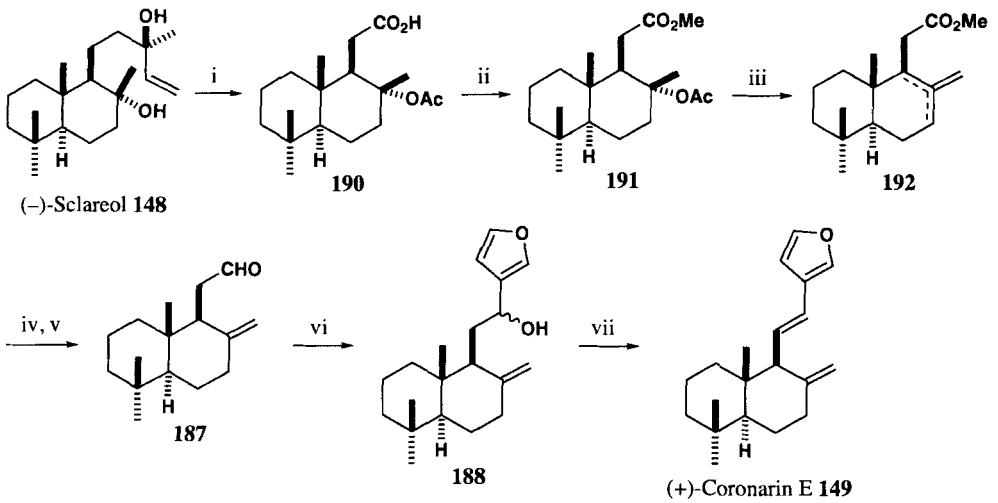
Seifert *et al.* also achieved the synthesis of coronarin E (**149**) from (–)-sclareol (**148**) *via* a similar synthetic sequence in seven steps. Four carbon atoms of the side-chain of sclareol (**148**)



i) OsO_4, $NaIO_4$; ii) collidine, reflux; iii) 3-bromofuran, *n*-BuLi; iv) MsCl, 2,6-lutidine; v) SeO_2, TBHP.

Scheme 21

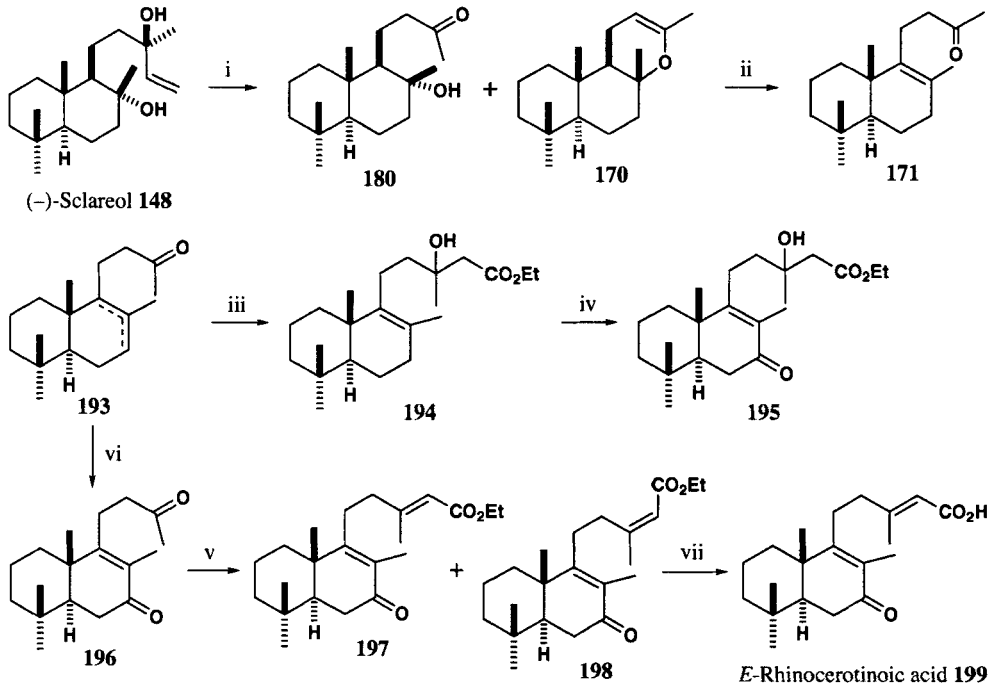
were oxidatively cleaved by $RuCl_3$ and $NaIO_4$ to give the acetoxy acid **190**. Esterification with Me_2SO_4 followed by pyrolysis afforded a mixture of double bond isomers **192**, which were transformed into aldehyde **187** by $LiAlH_4$ reduction and Swern or PCC oxidation. Reaction of the major $\Delta^{8,17}$-isomer with 3-furyllithium and dehydration with hexachloroacetone and pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene furnished (+)-coronarin E (**149**). No *Z*-double bond isomer was detected (*Scheme 22*).[24]



i) $RuCl_3$, $NaIO_4$, H_2O, MeCN, CCl_4; ii) Me_2SO_4, $LiOH{\bullet}H_2O$, DMF; iii) $KHCO_3$, DMSO, 150°C; iv) LAH, THF; v) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; vi) 3-furyllithium, THF; vii) $Cl_3CCOCCl_3$, PPTS, benzene.

Scheme 22

E-Rhinocerotinoic acid (**199**) obtained from the South African medicinal plant *Elytropappus rhinocerotis* exhibits anti-inflammatory activity. Based on the previous synthesis from sclareol (**148**) by Rivett *et al.*, an improved synthetic sequence was achieved in five steps in a 32% overall yield starting from (–)-sclareol (**148**). The side-chain was cleaved by $KMnO_4$. Dehydration with iodine followed by allylic oxidation by Collins reagent and Horner-Wadsworth-Emmons condensation led to *E*-ethyl rhinocerotinoate (**197**), which was hydrolyzed to give the target compound **199** (*Scheme 23*).[25]



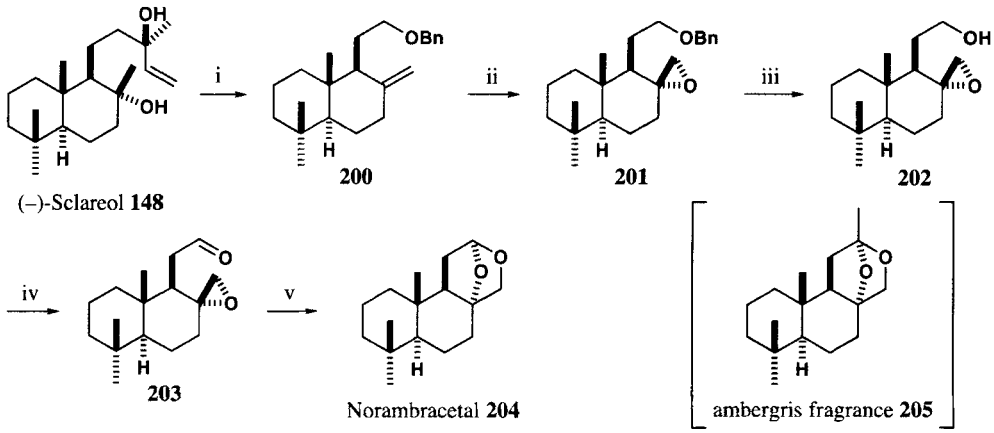
i) $KMnO_4$, acetone; ii) I_2, benzene; iii) Zn, $BrCH_2CO_2Me$; iv) CrO_3; v) Horner–Emmons reaction; vi) Collins reagent; vii) KOH.

Scheme 23

Ambergris is one of the most important fragrance components, in which ambrox (**74**) is the major constituent. It has a tetranor-labdane framework. Because of its importance in aroma field, various synthetic efforts have been reported.

Norambracetal (**204**), an ambergris fragrance, was synthesized from (–)-sclareol (**148**). The benzyl ether of γ-homofarnesylic alcohol (**200**) was prepared from sclareol (**148**). Epoxidation, deprotection of the benzyl ether by hydrogenation and subsequent PDC oxidation provided epoxyaldehyde **203**. Acid-catalyzed cycloacetalization gave norambracetal (**204**) (*Scheme 24*).[26]

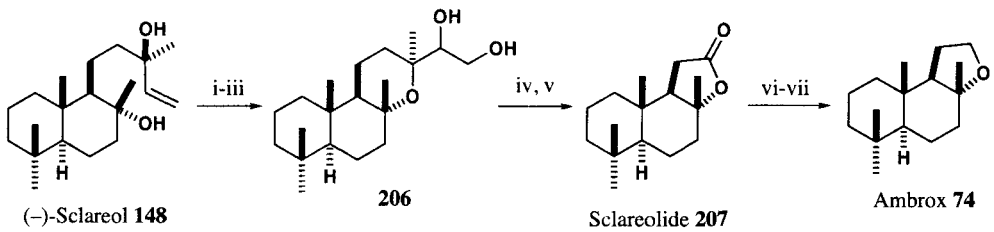
A practical preparative method of ambrox (**74**) from (–)-sclareol (**148**) has been reported by Moulines *et al.*,[27] in which no metallic oxidants such as Mn, Os or Ru were employed for transformation of the side-chain. Epoxidation of the terminal olefin by peracetic acid followed by Payne rearrangement and subsequent intramolecular cyclization furnished diol-



i) known, 5 steps; ii) MCPBA, $NaHCO_3$; iii) Pd/C, H_2; iv) PDC, molecular seives 4Å, HOAc; v) PPTS.

Scheme 24

oxide **206**, which was cleaved by sodium periodate. Baeyer-Villiger reaction of the resulting aldehyde gave sclareolide (**207**). All intermediates were used for the subsequent reactions without further purification. After hydride reduction of **207**, intramolecular cyclization was carried out with *n*-BuLi and *p*-toluenesulfonyl chloride to avoid the use of pyridine and gave ambrox (**74**). This method greatly alleviates the waste disposal problem and raises the overall yield of ambrox (**74**) to 75% (*Scheme 25*).

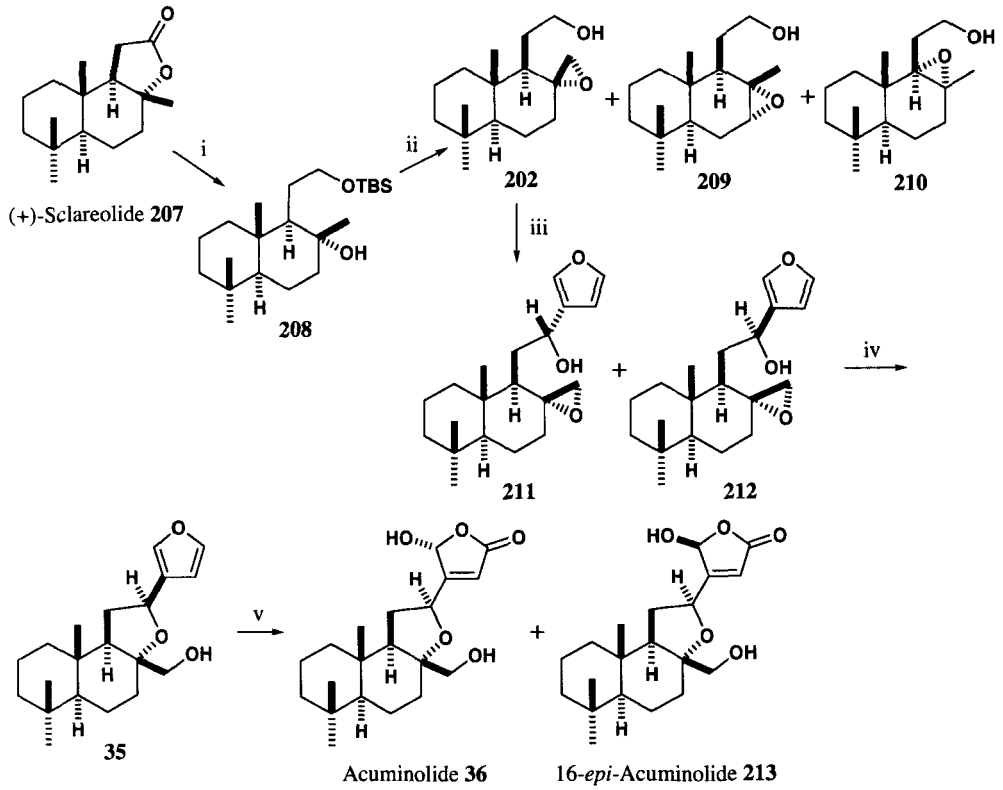


i) AcO_2H, AcONa; ii) aq. NaOH, *t*-BuOH; iii) H_2SO_4, AcOEt; iv) $NaIO_4$, THF; v) AcO_2H; vi) LAH, THF; vii) *n*-BuLi, TsCl.

Scheme 25

Acuminolide (**36**) is a cytotoxic diterpenoid isolated from the stem bark of *Neouvaria acuminatissima*. Reduction of (+)-sclareolide (**207**) followed by selective protection of primary alcohol provided tertiary alcohol **208**, which upon dehydration with trifluoromethanesulfonyl chloride gave a mixture of double bond isomers. After epoxidation of the major $\Delta^{8,17}$-isomer, oxidation of alcohol **202** to the aldehyde with Collins reagent followed by addition of 3-furyl-lithium gave a separable mixture of 12*R*- and 12*S*-furylalcohol **211** and **212**. Treatment of 12*S*-alcohol **212** with *p*-toluenesulfonic acid in nitromethane resulted in opening of the epoxide ring followed by α-face attack of the hydroxy group to sp^2 carbocation due to steric compression between the methyl group at C-10 and the side-chain. Photooxygenation with singlet oxygen in

the presence of Hunig's base furnished an inseparable mixture of acuminolide **36** and its C-16 epimer **213**. An analogous reaction sequence was used in the synthesis of 17-*O*-acetylacuminolide and 16-*epi*-17-*O*-acetylacuminolide (*Scheme 26*).[28]

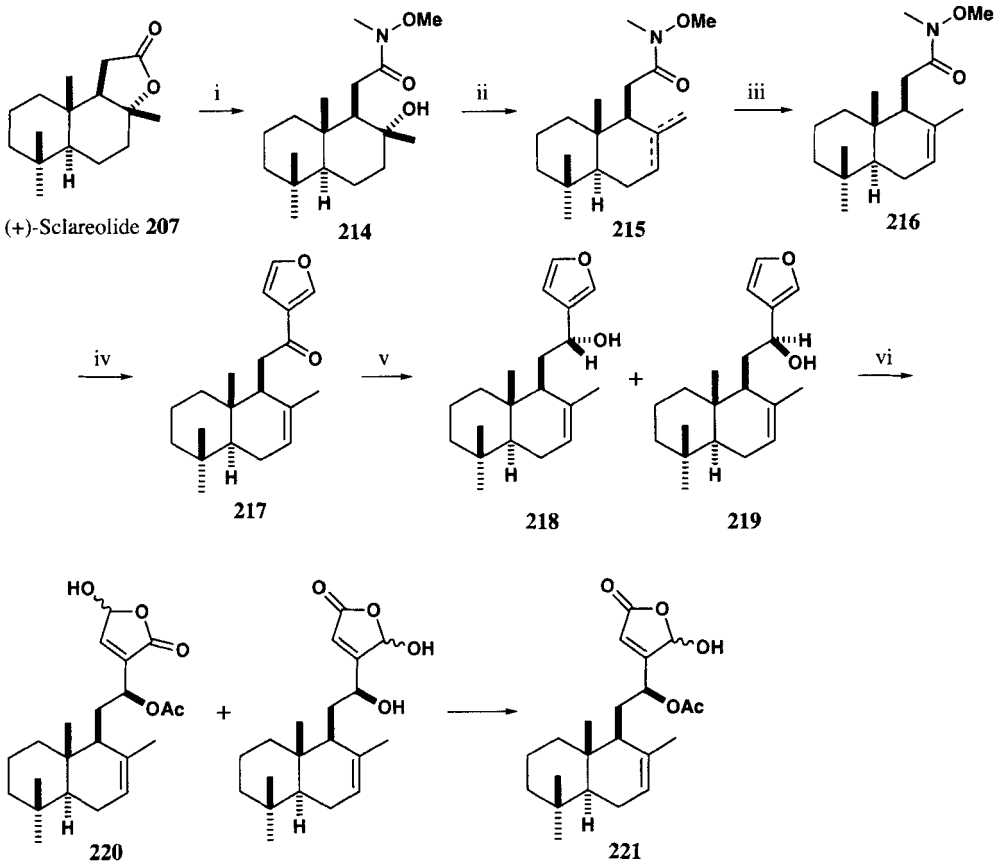


i) LAH, THF, TBDMSCl, Et_3N, 4-DMAP, CH_2Cl_2; ii) 12-crown-4, *n*-BuLi, CF_3SO_2Cl, 4-DMAP, *n*-Bu_4NF, MCPBA; iii) CrO_3•2pyr, 3-furyllithium; iv) PTSA, $MeNO_2$; v) O_2, rose bengal, Hunig base.

Scheme 26

(12*S*,16ξ)-12,16-Dihydroxy-*ent*-labda-7,13-dien-15,16-olide (**222**) isolated from *Alomira myriadenia* shows significant cytotoxic activity against human oral epidermoid carcinoma and against colon cancer. Aminolysis of (+)-sclareolide (**207**) by *N*-methoxy-*N*-methylamine gave Weinreb's amide **214**, which was treated with thionyl chloride to provide *exo*- and *endo*-olefinic compounds **215**. The *exo*-double bond rearranged to the *endo*-isomer **216**. Reaction with 3-furyllithium yielded the furylketone **217**. Reduction with sodium borohydride in the presence of $CeCl_3$ gave two epimeric alcohols **218** and **219** in an equal ratio. Their absolute stereochemistries were established by Mosher's method. Photooxidation of the furan moiety of (12*S*)-alcohol **219** by singlet oxygen in the presence of rose bengal provided γ-hydroxybutenolides **220** and **221**. Comparison of the spectral data of the acetate of compound **221** with those of the peracetate of natural **222** established the relative stereochemistry at C-12. The absolute stere-

ochemistry of the natural product **222** was determined to belong to the *normal*-series by comparison of specific rotations (*Scheme 27*).[29]

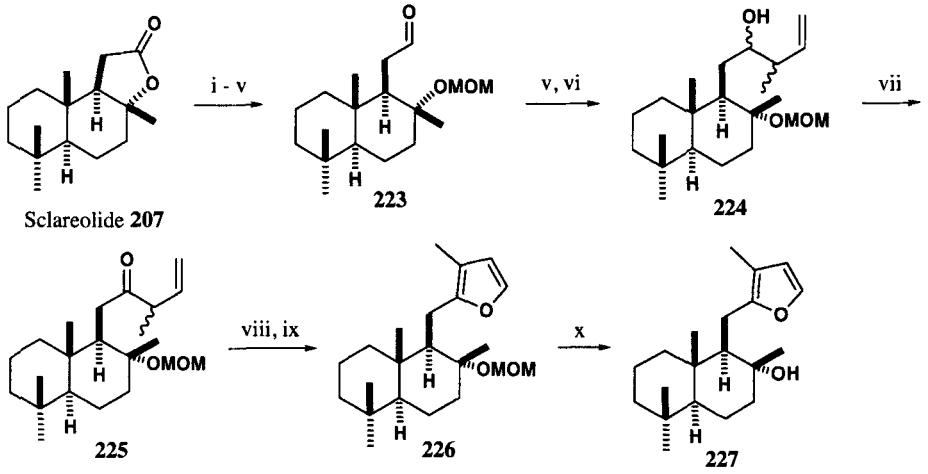


i) Me_3Al, MeONHMe, HCl; ii) $SOCl_2$, pyr; iii) H^+; iv) 3-bromofuran, *n*-BuLi; v) $CeCl_3$, $NaBH_4$, MeOH; vi) Ac_2O, pyr.

Scheme 27

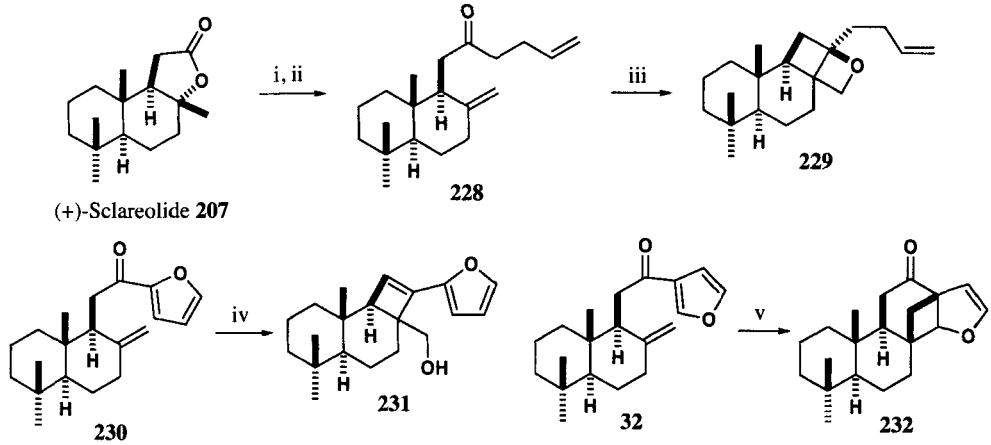
Methylfurolabdane **227** was isolated from the cuticular wax of the leaves of *Nicotiana tabacum* and is believed to be responsible for tobacco flavor from aerobic oxidation with other labdane constituents. Reduction of (+)-sclareolide (**207**), subsequent protection, deprotection and oxidation gave the aldehyde **223**. Addition of *trans*-crotylmagnesium chloride followed by chromium oxidation provided the ketoolefin **225**. The furan ring was installed by OsO_4 oxidation and subsequent acid-catalyzed cyclization (*Scheme 28*).[30]

(+)-Sclareolide (**207**) was transformed into the Weinreb amide, which was reacted with Grignard reagents to give various olefinic side-chain derivatives. Intramolecular [2+2] photocycloaddition of these derivatives led to terpene-like oxetane **229** and cyclobutane derivatives **231** and **232** (*Scheme 29*).[31]



i) LAH; ii) TBDMSCl; iii) MOMCl; iv) TBAF; v) PDC; vi) $CH_3CH{=}CHCH_2MgCl$; vii) CrO_3-pyr; viii) OsO_4, NMO; ix) PTSA; x) H^+.

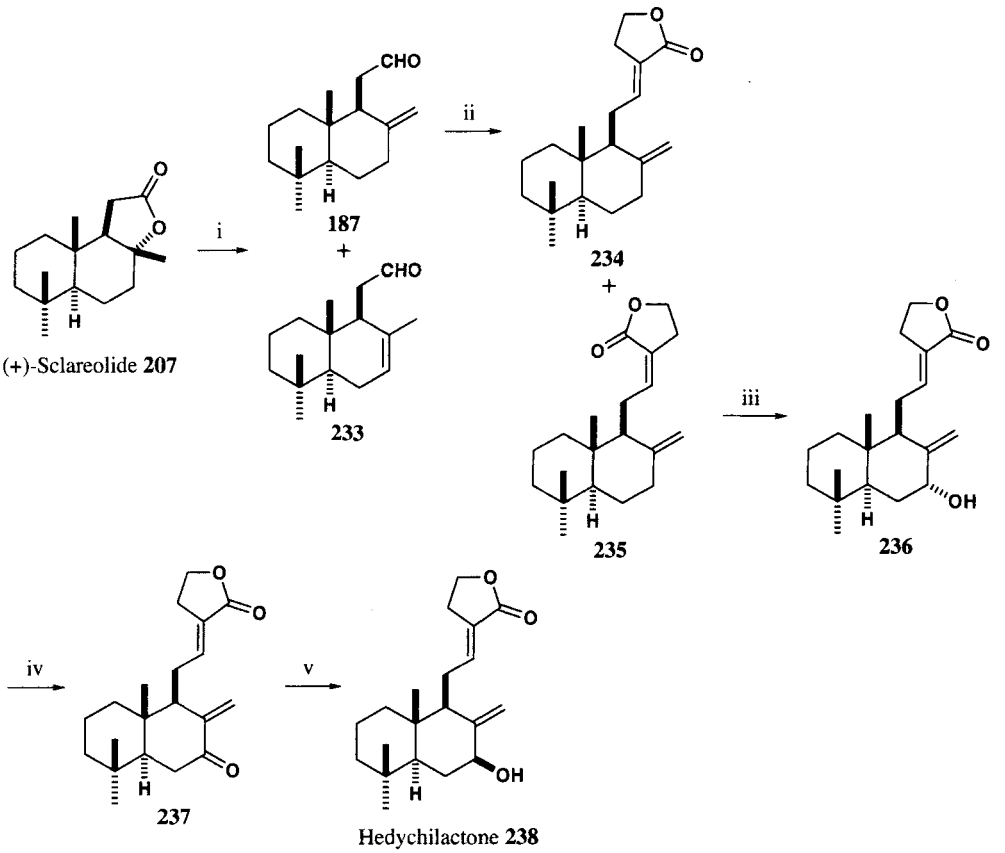
Scheme 28



i) dimethylaluminium amide; ii) $LiCH_2CH_2CH{=}CH_2$, THF; iii) hν, MeCN; iv) hν, MeCN; v) hν, MeCN.

Scheme 29

Hedychilactone (**238**) a traditional medicinal plant in India, China, and Brazil used for the treatment of inflammation and rheumatism was isolated from *Hedychium coronarium*. The *exo*-methylene decalone **187**, derived in 4 steps from (+)-sclareolide (**207**), was treated with diethylphosphino-2-γ-butyrolactone to provide a mixture of *E*- and *Z*-butyrolactones **234** and **235**. SeO_2-allylic oxidation of the major *E*-butyrolactone **234** led to the 7α-hydroxy isomer **236**. The hydroxy group was epimerized by a Swern oxidation followed by $NaBH_4$ reduction to furnish hedychilactone (**238**) (*Scheme 30*).[32] The growth inhibitory activity of some intermediates was screened against five cancer cell lines.



i) known, 4 steps; ii) diethylphosphono-2-butyrolactone; iii) SeO_2, TBHP; iv) Swern oxidation; v) $NaBH_4$, MeOH.

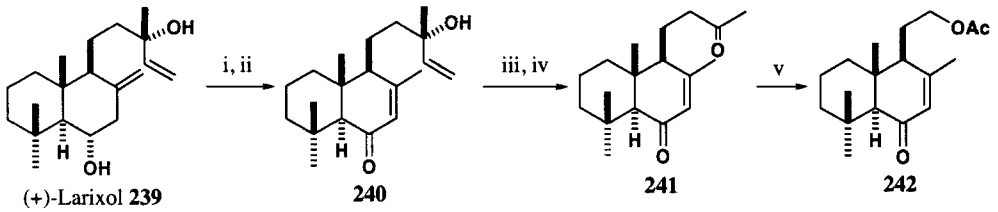
Scheme 30

In view of its structure, larixol (**239**) appears to be an excellent candidate as an abundant, cheap and readily available starting material for the semi-synthesis of polyoxygenated diterpenes which often present interesting biological activities, however, its availability from natural sources is often very scarce. Larixol (**239**), and in particular its 6-acetate (larixyl acetate) (**243**), are major constituents (> 10 %) of the oleoresins of several *Larix* species, such as *L. decidua, L. gmelini, L. eurolepsis* and *L. pendula*.

Toward this goal, (+)-larixol (**239**) was selected as a suitable starting material because of its attractively functionalized *trans*-decalin ring system. In addition, larixol (**239**) is easily extracted from the oleoresin of larch tree in which it is abundant. The potential of larixol (**239**) in synthesis has been demonstrated by the preparation of terpenoids such as borjatriol (**260**), 6-oxo-ambrox, hedychenone (**270**), and yunnancoronarins A (**271**) and D.

Oxidation by Dess-Martin periodinane of (+)-larixol (**239**) followed by base-catalyzed isomerization provided enone **240**. After regioselective epoxidation of the side-chain of **240**, the epoxy alcohol was cleaved by periodic acid to give the methyl ketone **241**. Baeyer-Villiger

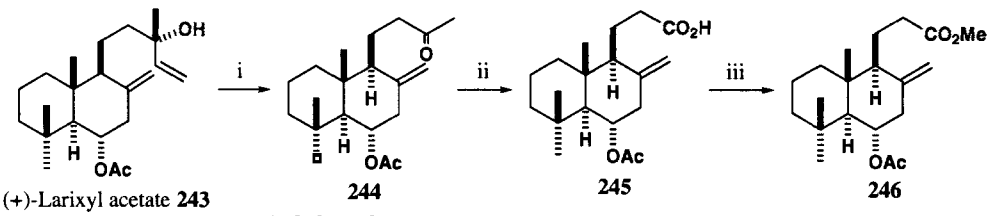
oxidation of the resulting methyl ketone **241** provided acetate **242** in moderate yield, which would be a potent intermediate for the synthesis of polyhydroxylated labdane diterpenes such as forskolin (**24**) (*Scheme 31*).[33]



i) Dess-Martin periodinane, CH_2Cl_2; ii) 1*N* methanolic NaOMe; iii) TBHP, $VO(acac)_2$, lutidine; iv) HIO_5, THF; v) MCPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2.

Scheme 31

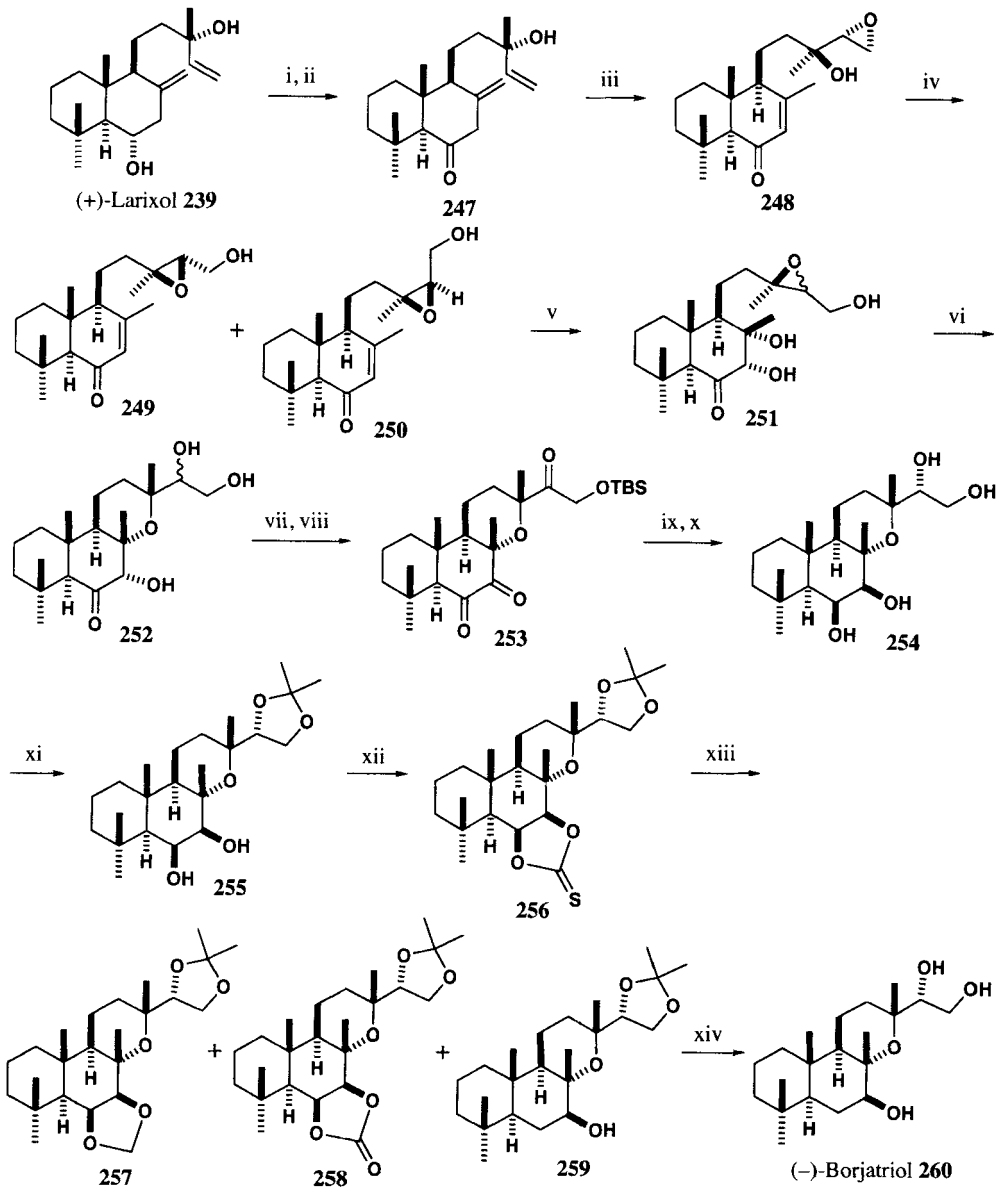
A practical transformation of larixyl acetate (**243**) was reported.[34] CrO_3 oxidation of the side-chain of larixyl acetate (**243**) provided the methylketone **244** selectively, which was oxidized through the iodoform reaction to give carboxylic acid **245**. Esterification with MeI and DBU gave the acetoxy-ester **246** which would be a good precursor for further transformations (*Scheme 32*).



i) CrO_3, HOAc; ii) KI, I_2, KOH; iii) MeI, DBU.

Scheme 32

(–)-Borjatriol (**260**) isolated from *Sideritis mugronensis*, shows anti-inflammatory property. Enone **247** was prepared by a Dess-Martin periodinane oxidation of (+)-larixol (**239**) and subsequent base-catalyzed isomerization. Epoxidation of **247** with TBHP in the presence of $VO(acac)_2$ provided a mixture of diastereomeric epoxides, which were transformed into internal epoxides by a Payne rearrangement. OsO_4 *bis*-hydroxylation proceeded selectively from the less hindered α-face. Acid catalyzed opening of the epoxide ring provided tetrahydropyran ring. The triketone **253** was obtained by oxidation *via* the Dess-Martin periodinane method followed by $Na_2S_2O_7$. The two hydroxy groups at C-6 and C-7 of **254** were generated by $NaBH_4$ reduction. The diol of the side-chain was protected as acetonide whereas the hydroxy group at C-6 and C-7 were protected as the thiocarbonate. Reduction of this compound with *n*-Bu_3SnH resulted in the selective removal of the hydroxy group at C-6. Subsequent deprotection completed the synthesis of the target molecule **260** (*Scheme 33*).[35]

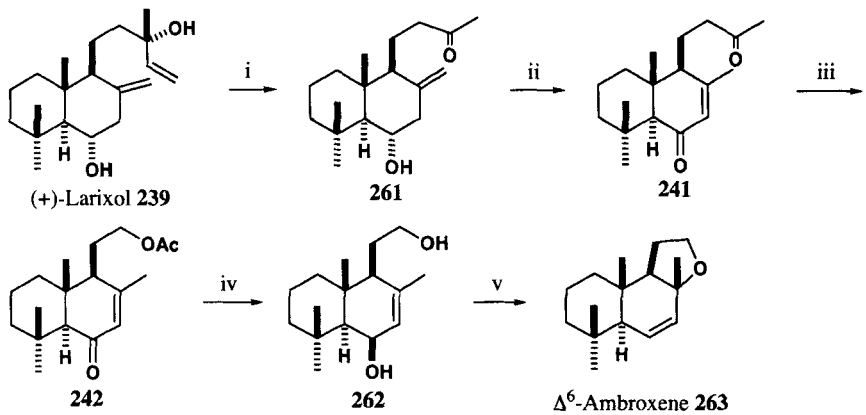


i) Dess-Martin periodnane; ii) NaOMe; iii) *t*-BuOOH, $VO(acac)_2$, lutidine; iv) NaOH, *t*-BuOH; v) NMO, OsO_4, *t*-BuOH; vi) CSA; vii) TBDMSCl, imidazole; viii) Dess-Martin periodinane, pyr, $Na_2S_2O_7$; ix) *n*-Bu_4F, THF; x) $NaBH_4$; xi) dimethoxypropane, CSA; xii) thiocarbonyldiimidazole, DBU; xiii) *n*-Bu_3SnH; xiv) CSA, MeOH.

Scheme 33

(+)-Larixol (**239**) was transformed into Δ^6-ambroxene (**263**). The side-chain of (+)-larixol (**239**) was cleaved with $KMnO_4$ to give the methylketone **261**. PCC oxidation of the alcohol at C-6 and subsequent base-catalyzed isomerization of the double bond gave enone **241**. Baeyer-Villiger reaction provided acetate **242** in moderate yield, which was reduced with

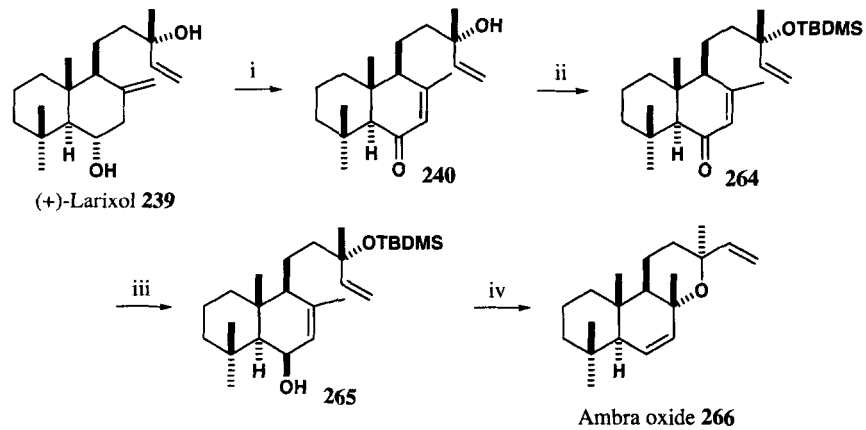
$LiAlH_4$. Acid-catalyzed cyclodehydration *via* ionization of the C(6)-allylic alcohol gave in moderate yield Δ^6-ambroxene (**263**), which has a pleasant ambrox-like odor. Improvement of the low yields in Baeyer-Villiger reaction and cyclization are required for commercial production (*Scheme 34*).[36]



i) $KMnO_4$, BTEACl; ii) PCC, NaOMe-MeOH; iii) MCPBA, BF_3•OEt_2; iv) LAH; v) PTSA, CH_3NO_2.

Scheme 34

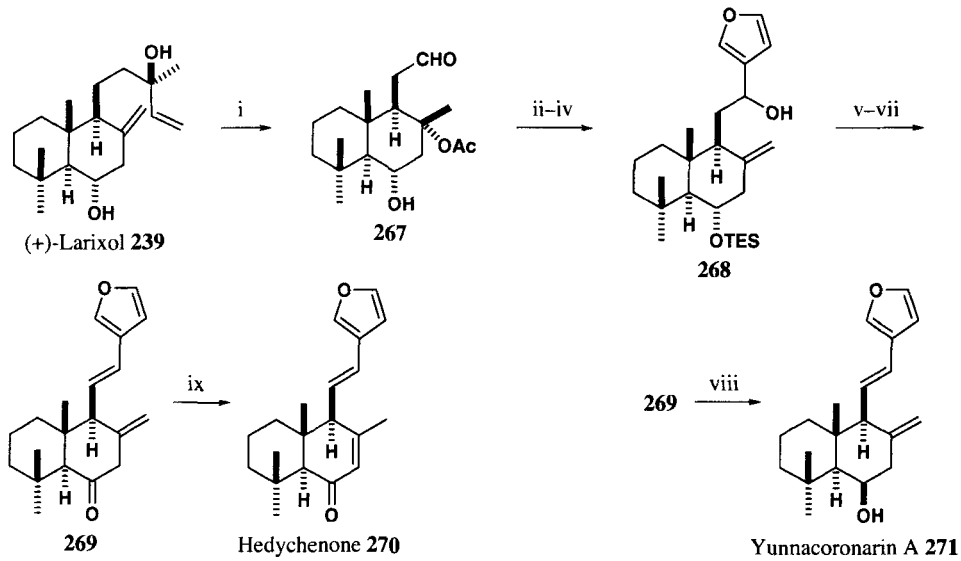
The synthetic study of Δ^6-ambroxene (**263**) cited above was extended to the synthesis of Δ^6-ambra oxide (**266**). The enone **240** was synthesized from (+)-larixol (**239**) by oxidation and isomerization. Reduction by DIBAL-H afforded the axial alcohol **265** selectively. After deprotection of TBDMS group, cyclodehydration proceeded during SiO_2 flash column chromatography to provide ambra oxide (**266**) in good yield. Several other derivatives have also been synthesized (*Scheme 35*).[37]



i) PCC then NaOMe-MeOH; ii) TBDMSCl, DMF, imidazole; iii) DIBAL; iv) HF then SiO_2.

Scheme 35

Hedychenone (**270**) and yunnancoronarin A (**271**) were isolated from the rhizomes of *Hedychium spicatum*. (+)-Larixol (**239**) was transformed into the aldehyde **267** by known steps involving OsO_4 oxidation of the side-chain. After protection of the hydroxy group at C-6, pyrolysis in collidine gave *exo*-methylenedecaline. Addition of 3-furyllithium provided a 1:1 mixture of epimeric alcohols **268**, which were mesylated in the presence of a base to give elimination product. Deprotection and subsequent oxidation afforded compound **269**, which was transformed into hedychenone (**270**) and yunnancoronarin A **271** (*Scheme 36*) .[38]

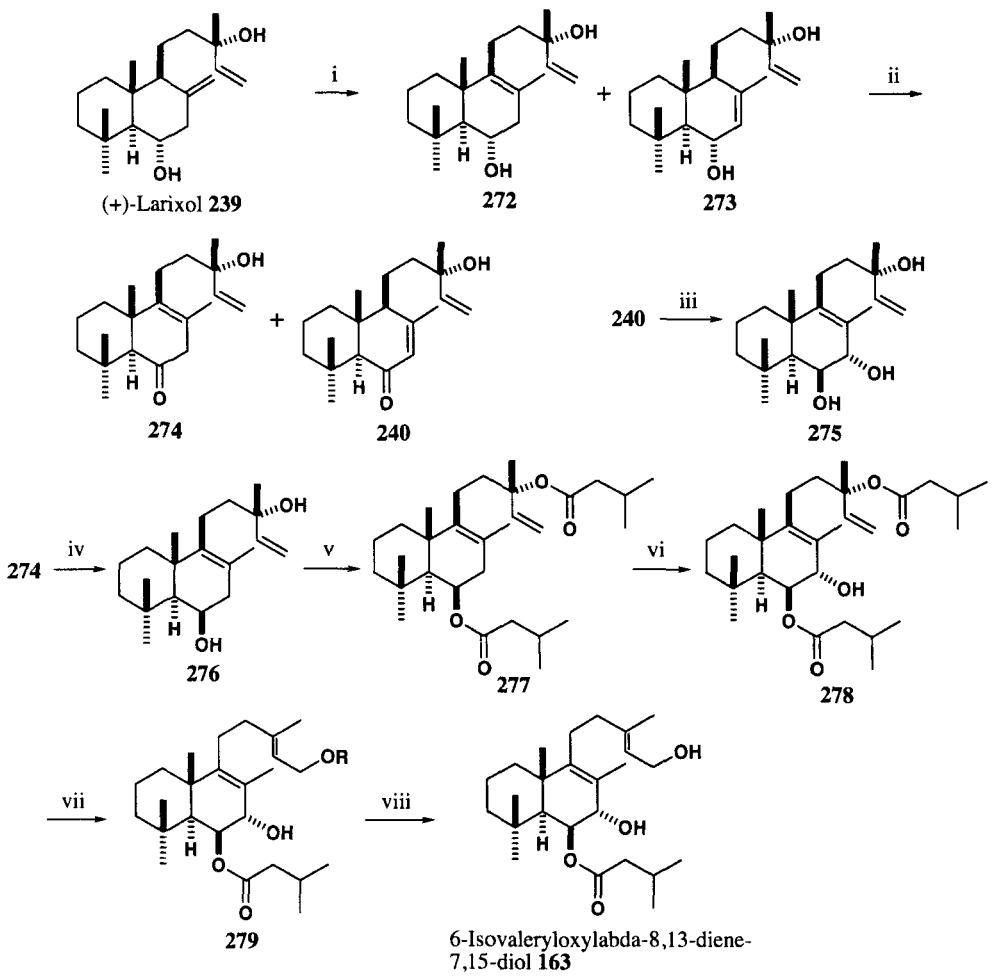


i) known; ii) TESCl, DMAP; iii) 2,4,6-collidine, 170°C; iv) 3-furyllithium; v) 2,6-lutidine, MsCl; vi) HOAc; vii) IBX, AcOEt; viii) DIBAL-H; ix) NaOMe, MeOH.

Scheme 36

The mucus of *Trimusculus reticulatus* metabolizes (+)-6β-isovaleryloxylabda-8,13-diene-7α,15-diol (**163**), which exhibits potent repellent activity against starfish. An 18-step synthesis of **163** in racemic form had been reported (*Scheme 17*).[19]

Morin *et al.*[39] accomplished its synthesis starting from (+)-larixol (**239**), thereby establishing absolute stereostructure. Isomerization of the *exo*-methylene of larixol (**239**) was carried out by lithium in ethylenediamine to give a mixture of *endo*-Δ^6- and Δ^7-isomers, which were oxidized by *o*-iodoxybenzoic acid (IBX) to give separable Δ^7-enone **274** and Δ^6-enone as a major and as a minor isomers of **240**. Reduction of Δ^7-enone **274** followed by acylation with isovalerylchloride provided the *bis*-ester **277**. Allylic oxidation at C-6 was carried out by SeO_2 to give the α-alcohol selectively. Finally, palladium catalyzed allylic rearrangement and subsequent hydrolysis completed the synthesis of the natural product **163** in an optically active form (*Scheme 37*).



i) $H_2NCH_2CH_2NH_2$, Li; ii) IBX; iii) SeO_2, $NaBH_4$; iv) LAH; v) isovaleryl-Cl, pyr, DMAP; vi) SeO_2; vii) $(PhCN)_2PdCl_2$; viii) K_2CO_3.

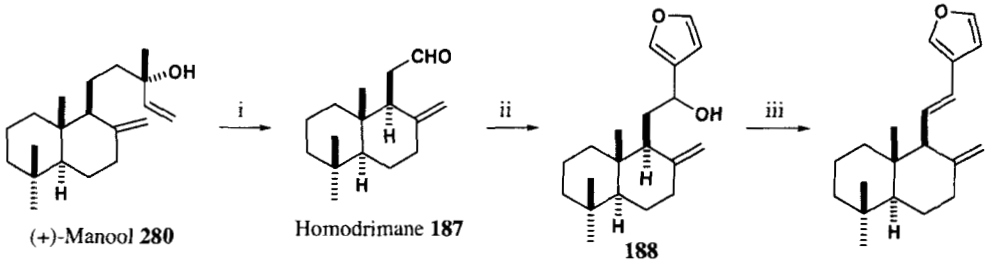
Scheme 37

Manool (**280**) is also a good starting material for synthetic transformation into labdane diterpenoids.

An alternative synthesis of (+)-coronarin E (**149**) and related compounds was achieved from (+)-manool (**280**). The side-chain of (+)-manool (**280**) was cleaved by $KMnO_4$ to give the methylketone, which was further oxidized by oxygen and *t*-BuOK. Resulting carboxylic acid was reduced and then oxidized by tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholin-*N*-oxide (NMO) to give homodrimane (**187**). Addition of 3-furyllithium and subsequent dehydration afforded (+)-coronarin E (**149**) (*Scheme 38*).[40]

Enantiomers of (+)-15,16-epoxy-8(17),13(16),14-labdatriene (coronarin E) (**149**) and (+)-labda-8(17),13(Z)-diene-15,16-diol (**283**) were isolated from terrestrial plant *Blephar-*

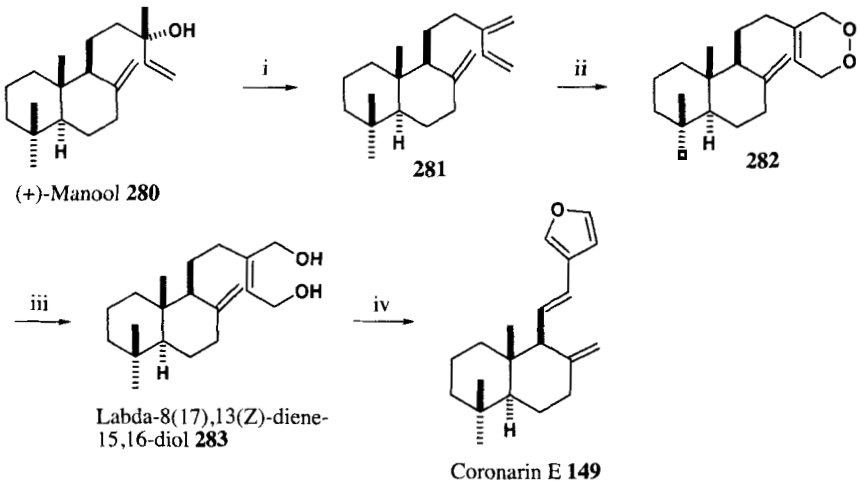
ispermum zanguebaricum. Dehydration of manool (**280**) provided sclarene (**281**), which was irradiated in the presence of oxygen and *meso*-tetraphenylporphine to give the peroxide **282**.



i) 4 steps, known; ii) 3-lithiofuran; iii) $MeSO_2Cl$, 2,6-lutidine.

Scheme 38

Reduction of the peroxide with $LiAlH_4$ produced the diol **283**, which was oxidized by PCC to afford furanolabdane **149**. Since these compounds exhibited opposite sign of optical rotation, the natural products were enantiomeric to these compounds (*Scheme 39*).[41]



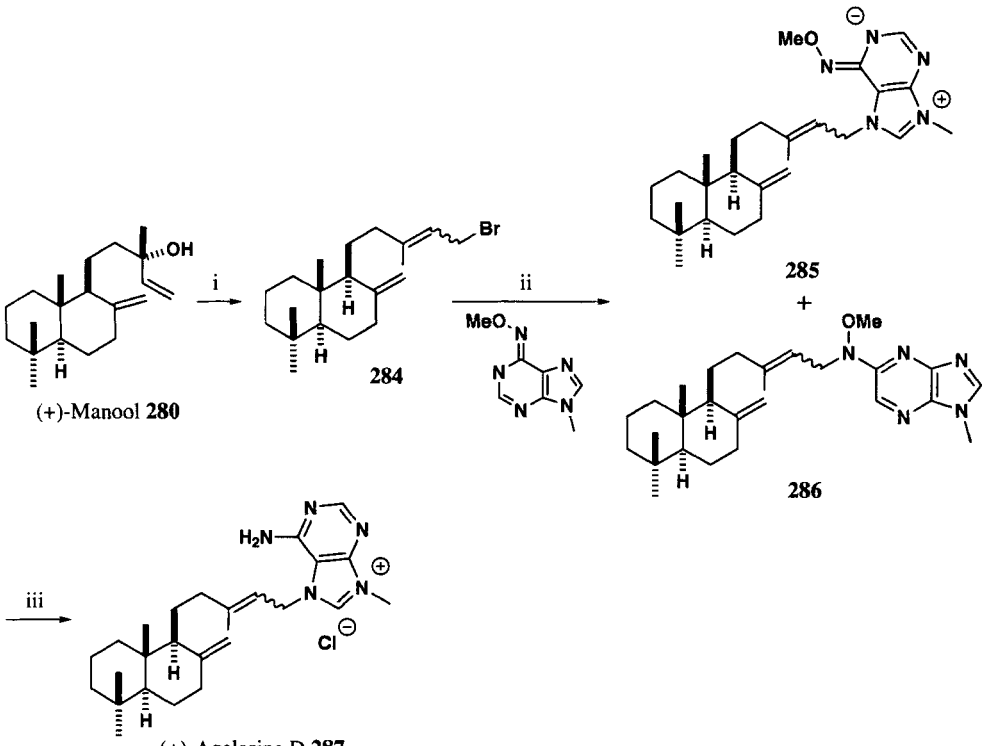
i) PTSA, THF, reflux; ii) O_2, *meso*-tetraphenylporphine, CCl_4, 5% MeOH; iii) LAH, THF, reflux; iv) PCC, CH_2Cl_2, r.t.

Scheme 39

(+)-Agelasine D (**287**) isolated from the marine sponge, *Agelas nakamurai* presents antimicrobial and cytotoxic effects along with contractive responses of smooth muscles and inhibition of Na, K-ATPase. Treatment of (+)-manool (**280**) with phosphorous tribromide gave the allylic bromide **284** as a mixture of *E*/*Z*-double bond isomers.

Alkylation of methoxyadenine provided the desired compound **285** as a major product, which was deprotected by Zn/AcOH to furnish (+)-agelasine D (**287**) for the first time (*Scheme 40*).[42]

(+)-Limonidilactone (**298**) was isolated from the leaves of *Vitex limonifolia*, in which absolute stereostructure is yet to be assigned. Zamoranic acid (**288**), a major component of

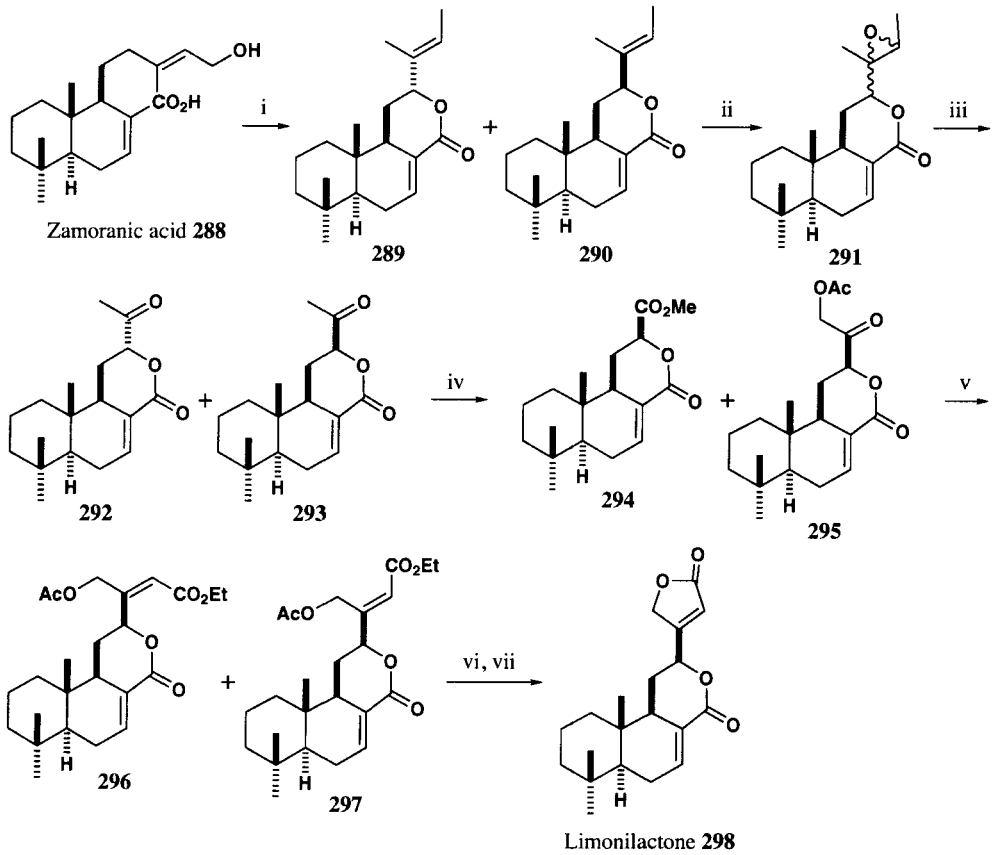


i)PBr_3, pyr; ii) CH_2Cl_2, MeOH, aq. NH_3, SiO_2; iii) Zn, HOAc, MeOH, H_2O.

Scheme 40

Halimium viscosum, was used as a starting material. Acid-catalyzed lactonization provided lactone **290** with high diastereoselectivity (95/5). Regioselective epoxidation followed by treatment with periodic acid resulted in the cleavage of the side-chain to give the methylketones **292** and **293**. Butenolide moiety was introduced by oxidation with $Pb(OAc)_4$, Wittig condensation and subsequent acid-catalyzed lactonization. Thus, an antipode of the natural product **298** was synthesized in 6 steps with an overall yield of 25% and the absolute stereochemistry of the natural product **298** was established to belong to antipodal series (*Scheme 41*).[43]

13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid (**304**) isolated from the chopped stem bark of *Thuja standishii* as a minor component, has the most potent activity among the isolated diterpenoids towards the prevention of incipient carcinogenesis. Since this compound is in short supply from natural sources, an efficient synthesis would be highly useful in order to further evaluate its compound potential as a cancer chemo-preventive agent. *trans*-Communic acid (**299**) isolated as the major component (*ca.* 10 g) from the stem bark (*ca.* 5 kg) of *Thuja standishii*, was converted into di-nor-labdadienoic acid (**304**) (*Scheme 42*). Esterification of *trans*-communic acid (**299**) followed by MCPBA oxidation provided the 12-epoxide selectively, which was cleaved by HIO_4 to give the aldehyde **300**. Elongation of the aldehyde group was



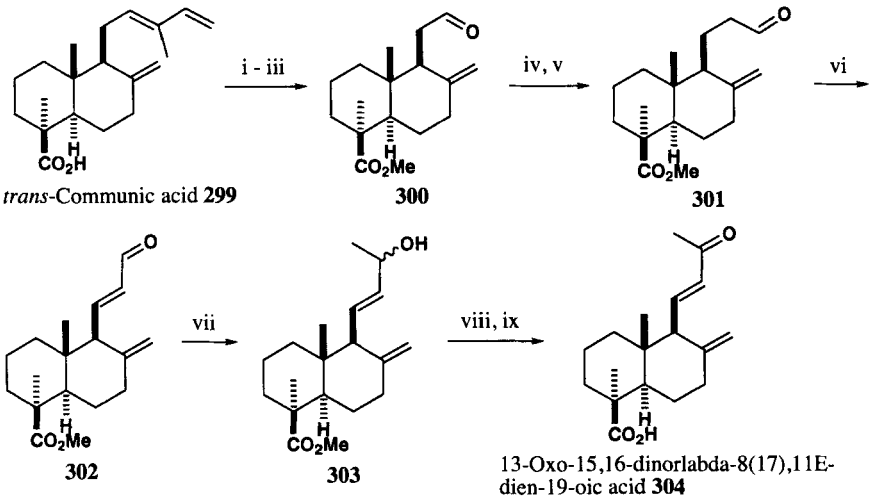
i) PTSA, benzene; ii) MCPBA, CH_2Cl_2; iii) H_5IO_6, THF : H_2O (2:1); iv) lead (IV) tetraacetate, benzene, BF_3•Et_2O, MeOH; v) Ph_3PCHCO_2Et, benzene, reflux; vi) acetone, H_2O, PTSA; vii) PTSA, MeOH.

Scheme 41

carried out by Wittig condensation and hydrolysis. α,β-Unsaturation was introduced by phenylselenylation and elimination. After addition of MeLi, the ester was hydrolyzed with lithium dodecanethiolate, an odorless procedure developed by the authors, to give the acid. PDC oxidation afforded the desired natural product **304** in 38% overall yield.[44]

Andrographolide (**305**) is the major constituent of the Indian medicinal plant *Andrographis paniculata*. It was transformed into the aldehyde **308** by cleavage of the side-chain after protection as an acetonide followed by elimination of acetic acid. Reaction of the aldehyde **308** with various heterocyclic nucleophiles led to a variety of labdane type derivatives, which were evaluated for their *in vitro* cytotoxicity against human cancer cell lines (*Scheme 43*).[45]

8,13-Epoxy-3β-hydroxylabd-14-en-2-one (**310**), isolated from the wood of *Lagarostrobes colensoi*, was transformed into 8α-acetoxy-2β,3β-dihydroxy-13,14,15,16-tetranorlabdan-12-oic acid (**313**), a potentially useful intermediate for the synthesis of γ-bicyclofarnesal odorants. Reduction with Red-Al gave the 2β,3β-diol, which was protected as an acetonide

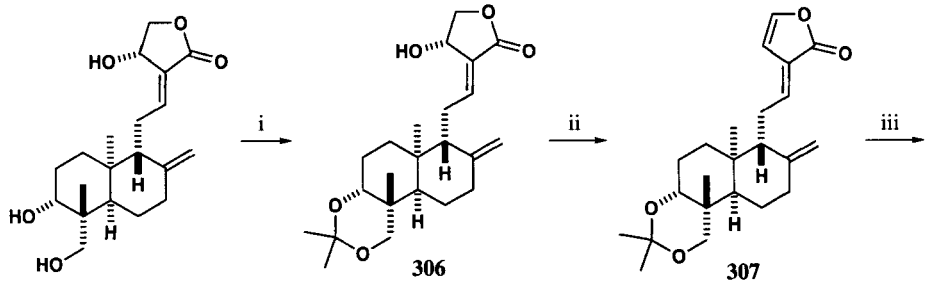


trans-Communic acid **299** **300** **301**

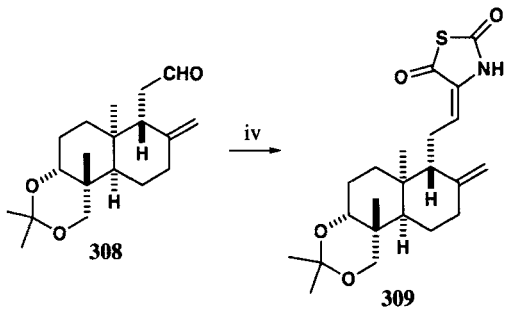
302 **303** 13-Oxo-15,16-dinorlabda-8(17),11E-dien-19-oic acid **304**

i) CH_2N_2; ii) MCPBA; iii) HIO_4; iv) $Ph_3P^+CH_2OMe$, *t*-BuOK; v) PPTS; vi) PhSeCl, *t*-BuOK, then H_2O_2; vii) MeMgBr; viii) dodecanthiol, *n*-BuLi, HMPA; ix) PDC, 38% overall yield.

Scheme 42



Andrographolide **305** **306** **307**

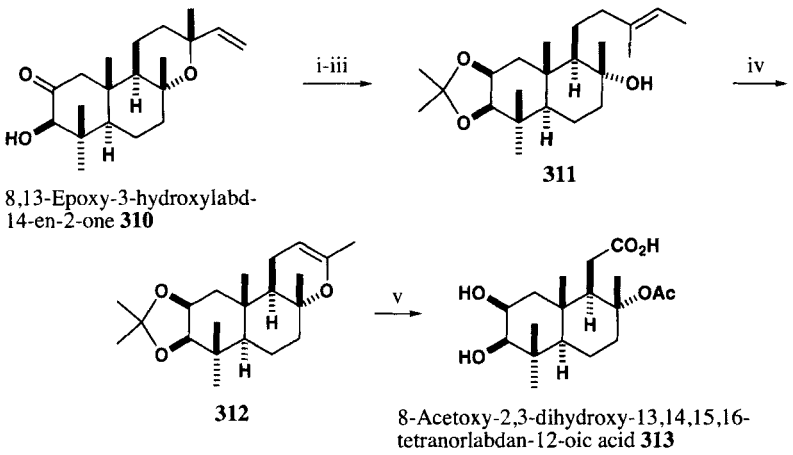


308 **309**

i) 2,2-dimethoxypropane, PPTS; ii) Ac_2O, Et_3N, DCM, DMAP; iii) $KMnO_4$; iv) rodanine, thiazolidinedione, oxindole, β-alanine, reflux.

Scheme 43

311. Cleavage of the pyran ring was effected via Birch reduction to give olefins as a mixture of *E/Z* isomers. Ozonolysis provided mainly the enol ether, which was treated with MCPBA to give the desired compound **313** (*Scheme 44*).[46]



8,13-Epoxy-3-hydroxylabd-14-en-2-one **310**

311

312

8-Acetoxy-2,3-dihydroxy-13,14,15,16-tetranorlabdan-12-oic acid **313**

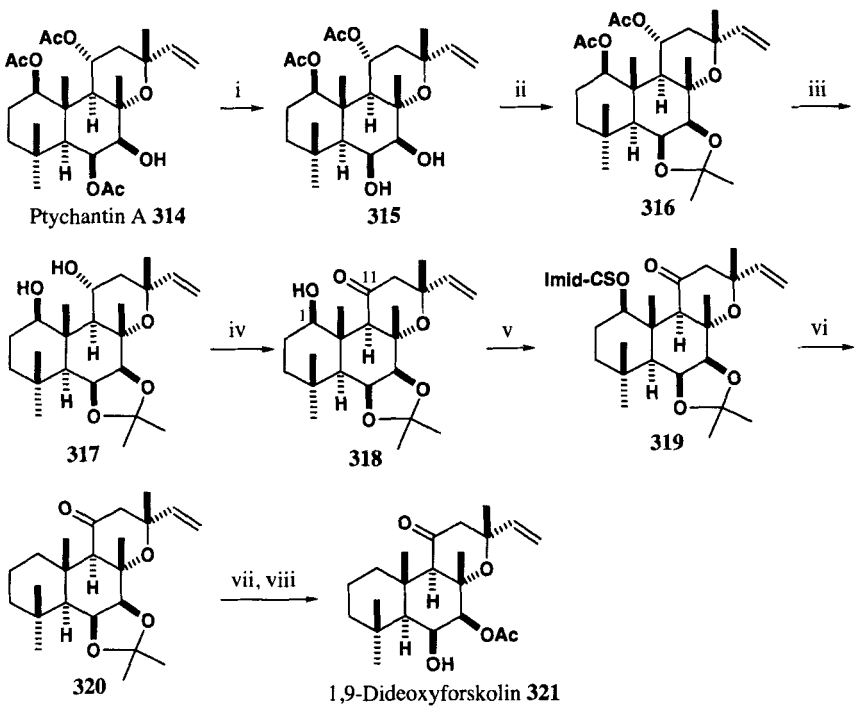
i) Red-Al; ii) acetone, PTSA; iii) Li/liq. NH_3; iv) O_3, CH_2Cl_2; v) MCPBA, buffer.

Scheme 44

Forskolin (**24**) isolated from the Indian herb *Coleus forskolli* displays efficient blood pressure lowering and cardio-protective properties based on activation of adenylate cyclase. From 1980 to mid 1990, a large number of synthetic efforts were undertaken and the groups of Ziegler,[47a] Hashimoto[47b] and Corey[47c] succeeded in the total synthesis of forskolin (**24**), though as racemates. Somewhat later, Lett and coworkers[3-5] also completed a total synthesis of racemates of **24**. Due to its intriguing physiological activity, forskolin (**24**) still attracts much attention for the study of physiological phenomena based on the activity of adenylate cyclase. 1,9-Dideoxyforskolin (**321**), a second major constituent of *C. forskoli*, exhibits strong inhibitory activity to glucose transport in rat's adipocytes. In 1994, Hashimoto and Asakawa isolated ptychantins from the liverwort *Ptychantus striatus* in high yield (6.7 g from 1 kg of dry plant). Ptychantins have the same ring framework and the same absolute stereostructure and similar oxygenated functionalities as forskolins.

Transformation into forskolins has started from ptychantin A (**314**) leading to ketone **318**, a common synthetic intermediate for 1,9-dideoxyforskolin (**321**) and forskolin (**24**) (*Scheme 45*).

Selective hydrolysis of the acetoxy group at C-6 and subsequent protection of the diol gave acetonide **316**. Reduction with $LiAlH_4$ gave 1,11-diol **317**, in which the less hindered hydroxy group at C-11 was selectively oxidized with PCC to give the 11-keto alcohol **318**. Transformation into 1,9-dideoxyforskolin (**321**) was carried out at first. Deoxygenation of **318** at C-1 was accomplished by Barton's radical protocol, in order to avoid epimerization at C-9 of **318**. The thiocarbonylimidazolide was prepared by solid state reaction with thiocarbonyldiimidazole since no base was required for the transformation. Radical cleavage by $(n\text{-Bu})_3SnH$ followed by hydrolysis of acetonide **320** and selective acetylation at C-7 furnished the 1,9-dideoxyforskolin (**321**) in 37% overall yield in 8 steps from ptychantin A (**314**).[48]



Ptychantin A **314** **315** **316**

317 **318** **319**

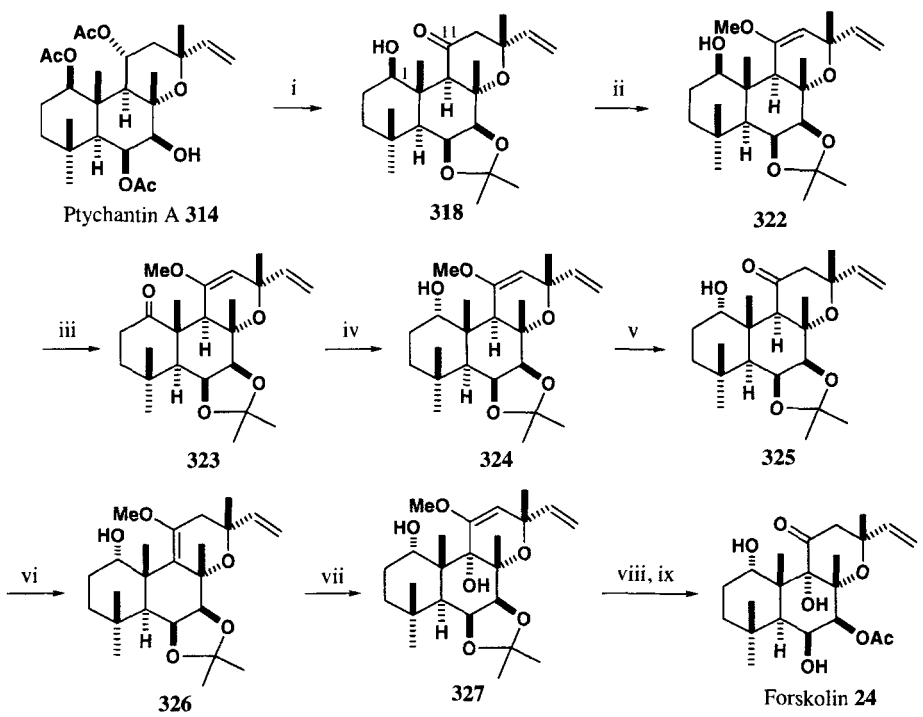
320 1,9-Dideoxyforskolin **321**

i) KOH/MeOH, r.t.; ii) 2,2-dimethoxypropane, PTSA; iii) LAH, Et_2O; iv) PCC, AcONa, CH_2Cl_2; v) thiocarbonyldiimidazolide, DMAP, solid state; vi) AIBN, *n*-Bu_3SnH, toluene,100 ~ 120°C; vii) 10% $HClO_4$/THF (1 : 2), r.t., 7 days; viii) Ac_2O, pyr, DMAP, 0°C.

Scheme 45

For our forskolin (**24**) synthesis, inversion of configuration at C-1 and introduction of the hydroxy group at C-9 are the major issue to be solved. The carbonyl group at C-11 of ketone **318** was protected as $\Delta^{11,12}$-enol ether. Oxidation at C-1 of enol ether **322** was successful only by Sarret reagent. Reduction of ketone **323** with Na in *t*-BuOH provided the desired α-axial alcohol **324** probably due to *peri* steric repulsion by the methoxy group at C-11. Different from β-equatorial alcohol **318**, treatment of the α-axial alcohol **325** with KH and Me_2SO_4 afforded the $\Delta^{9,11}$-enol ether **326**, which was treated with MCPBA to give the 9-α-hydroxy- $\Delta^{11,12}$-enol ether **327**. Hydrolysis of the enol ether and acetonide and selective acetylation furnished forskolin (**24**) in natural enantiomeric form in 12% overall yield from ptychantin A (**314**) (*Scheme 46*).[49]

Because of the importance of ambrox (**74**) in the fragrance industry, various synthetic efforts toward a more efficient route have been made. At the same time, several derivatives have been synthesized in anticipation better ambergris fragrance. de Groot *et al.* corroborated various efforts in this area. Labdanolic acid (**328**), a main diterpenoid of the acid fraction of non-polar extracts of *Cistus ladaniferus* L., was purified after acetylation. Photochemical iodination with iodobenzenediacetate and subsequent elimination afforded the terminal olefin **331**, which was



i) see *Scheme 45*; ii) KH, Me_2SO_4, THF; iii) CrO_3•2pyr, CH_2Cl_2; iv) Na, *t*-BuOH, r.t., 22 h; v) 1% HCl/THF (1 : 10); vi) KH, Me_2SO_4, THF; vii) MCPBA, CH_2Cl_2; viii) $HClO_4$; ix) Ac_2O, pyr, DMAP.

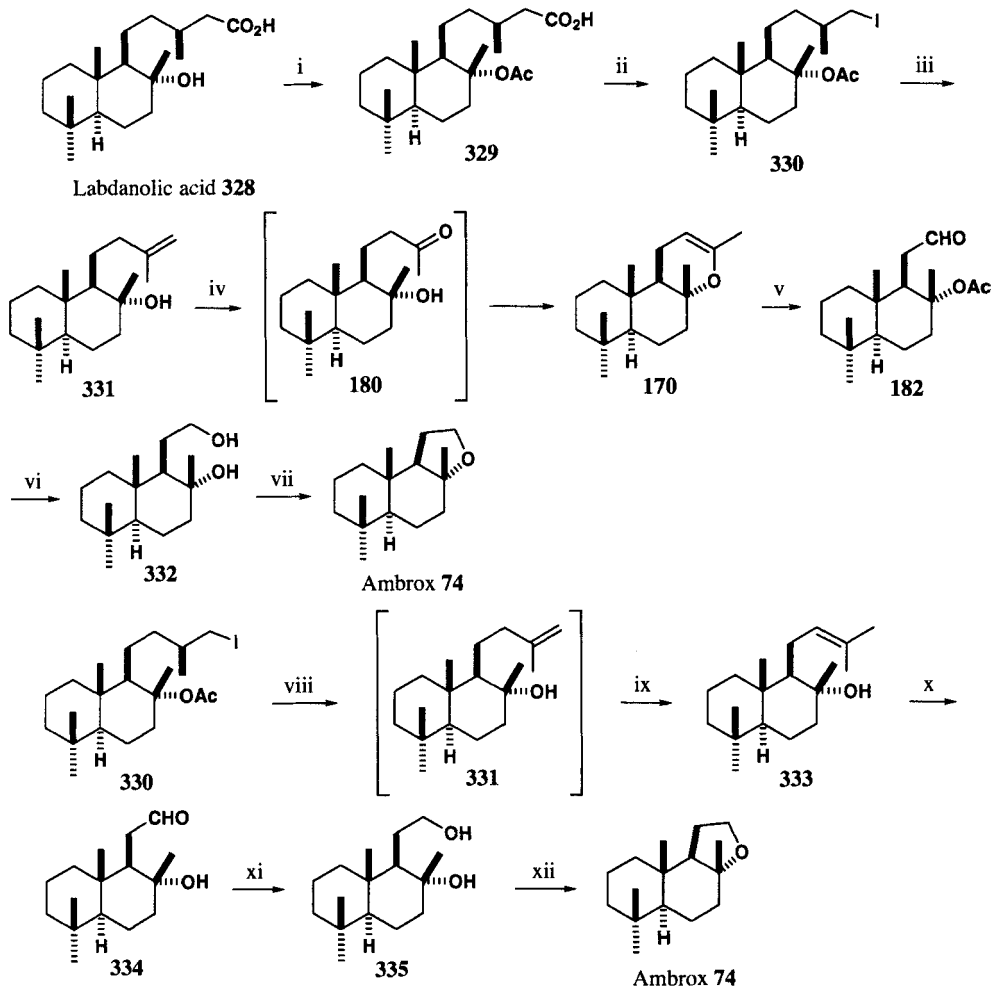
Scheme 46

cleaved by ozonolysis to give sclareol oxide (**170**). Further ozonolysis followed by hydride reduction provided the diol **332**. Acid-catalyzed cyclodehydration furnished ambrox (**74**) (*Scheme 47*).

Alternatively, treatment of the iodoacetate **330** with a large excess of *t*-BuOK in dimethyl sulfoxide (DMSO) resulted in the isomerization of the internal double bond. Ozonolysis, hydride reduction and cyclization furnished ambrox (**74**) in 47% overall yield from acetoxylabdanolic acid (**329**). If the cost of the iodination process could be minimized, the present protocol would be industrially useful.[50]

Ambrox (**74**) was also synthesized from methyl labdanolate (**336**) (*Scheme 48*). After introduction of unsaturation by phenylselenylation and oxidative elimination of the side-chain, the double bond was cleaved by $KMnO_4$ oxidation. Baeyer-Villiger reaction of resulting methyl ketone **339** provided acetate **340**, which was then converted to ambrox **74** in 33% overall yield from methyl labdanolate (**336**) in a six-step procedure (*Scheme 48*).[51]

Ent-Ambrox (**346**) was synthesized from copalic acid (**341**). Epoxidation of the *exo*-methylene by MCPBA proceeded from the less hindered β-face of the molecule. Ozonolysis followed by Baeyer-Villiger reaction gave the epoxy acetate **344**. Reduction and subsequent



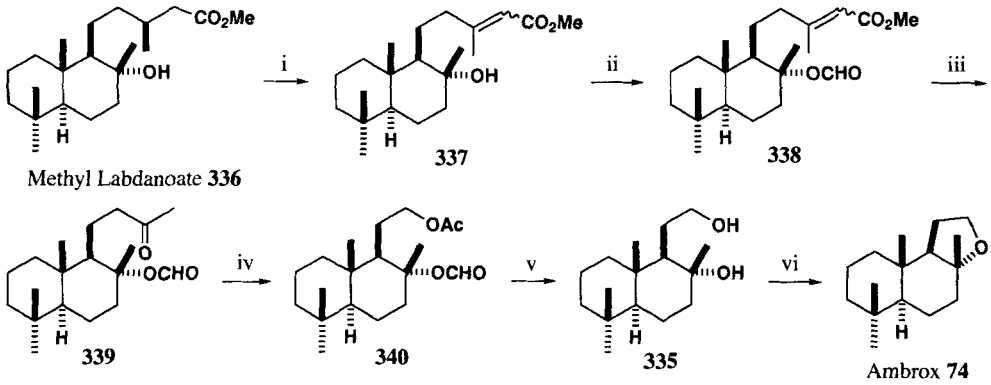
i) AcCl, *N,N*-dimethylaniline; ii) IBDA, I_2, CCl_4, hv; iii) *t*-BuOK, THF; iv) O_3, MeOH, CH_2Cl_2, Ph_3P; v) O_3, CH_2Cl_2, pyr; vi) LAH, THF; vii) PTSA, $MeNO_2$; viii) *t*-BuOK, THF; ix) heat; x) O_3, MeOH, CH_2Cl_2, $NaBH_4$; xii) PTSA, CH_3NO_2.

Scheme 47

cyclization afforded *ent*-ambrox (**346**). Related tetrahydropyran derivatives **349** and **350** were also synthesized (*Scheme 49*)[52]

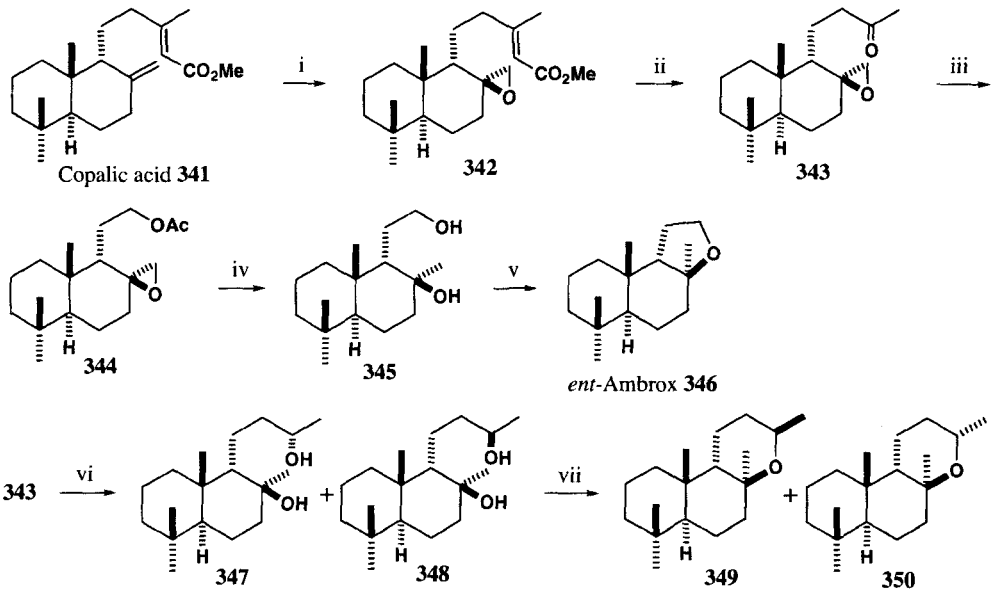
Indium chloride ($InCl_3$) mediated coupling of 4-benzyloxystannane with racemic drimenal **76** provided the coupling product **352** as a single isomer, in which a six membered cyclic transition state was proposed. The product **352** is expected to be a potential intermediate for the synthesis of forskolin (**24**) (*Scheme 50*).[53]

One of the labdane derivatives was transformed into α-epoxide **354**, which was treated with TMSOTf to give the tetrahydropyran ring **355** similar to forskolin C ring with retention of configuration at C-8 (*Scheme 51*).[54]



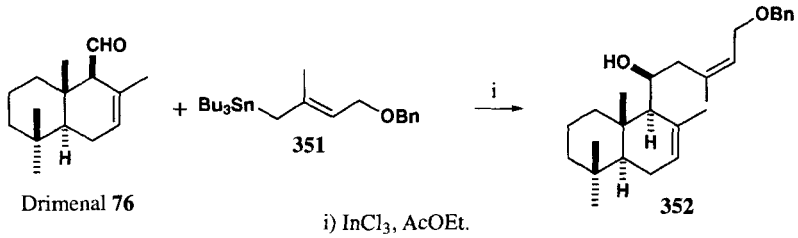
i) LDA, THF, Ph_2Se_2; ii) HCO_2H, Ac_2O; iii) $KMnO_4$, $MgSO_4$, acetone; iv) MCPBA, CH_2Cl_2; v) KOH, MeOH; vi) PTSA, $MeNO_2$.

Scheme 48



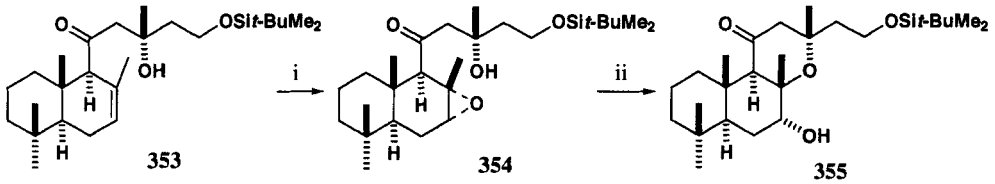
i) MCPBA; ii) O_3, Me_2S; iii) MCPBA; iv) LAH; v) MsCl, pyr; vi) LAH; vii) MsCl, pyr.

Scheme 49



i) $InCl_3$, AcOEt.

Scheme 50



i) MCPBA; ii) TMSOTf.

Scheme 51

II. CONCLUSION

Labdane diterpenoids are the most common types of diterpenoids isolated in minute amounts from higher plants. Owing to their significant antimutagenic, antibacterial and anti-fungal activities, increasing number of attempts are being made towards the synthesis of these compounds. The period under review had a proliferation of publications on the semi-synthesis of labdane derivatives from other natural products. These syntheses allow further investigations of the structure and their structure-activity relationships.

REFERENCES

1. (a) J. I. G. Cadogan, S. V. Ley, G. Pattenden, R. A. Raphael and C. W. Rees, Chapman & Hall, London, Dictionary of Organic Compound, 1996. (b) J. R. Hanson, *Nat. Prod. Rep.*, **16**, 209 (1999) . (c) J. R. Hanson, *Nat. Prod. Rep.*, **18**, 88 (2001). (d) J. R. Hanson, *Nat. Prod. Rep.*, **17**, 165 (2000).

2. (a) J. Mann, R. S. Davison, J. B. Hobbs, D. V. Banthorpe and J. B. Harborne, Natural Products: Their Chemistry and Biological Significance; Longman Group Ltd.: NewYork, 1994. (b) T. Matsuda, M. Kuroyanagi, S. Sugiyama, K. Umehara, A. Ueno and K. Nishi, *Chem. Pharm. Bull.*, **42**, 1216 (1994). (c) M. Miyazawa, H. Shimamura, S. Nakamura and H. Kameoka, *J. Agric. Food Chem.*, **43**, 3012 (1995). (d) M. Singh, M. Pal, and R. P. Sharma, *Planta Med.*, ***65***, 2 (1999). (e) H. Itokawa, H. Morita, I. Katou, K. Takeya, A. J. Cavalheiro, R. C. B. de Oliveira, M. Ishige and M. Motidome, *Planta Med.*, **54**, 311 (1988). (f) R. C. Srimal, S. C. Sharma and J. S. Tandon, *Indian J. Pharmacol, **16***, 143 (1984). (g) H. Itokawa and H. Morita, *Planta Med.*, ***54***, 117 (1988). (h) K. Dimas, C. Demetzos, M. Marsellos, R. Sotiriadou, M. Malamas and D. Kokki-nopoulos, *Planta Med.*, **64**, 208 (1998).

3. B. Delpech, D. Calvo and R. Lett, *Tetrahedron Lett.*, **37**, 1015 (1996).

4. B. Delpech, D. Calvo and R. Lett, *Tetrahedron Lett.*, **37**, 1019 (1996).

5. D. Calvo, M. Port, B. Delpech and R. Lett, *Tetrahedron Lett.*, **37**, 1023 (1996).

6. (a) N. Furuichi, T. Hata, H. Soetjipto, M. Kato and S. Katsumura, *Tetrahedron*, **57**, 8425 (2001). (b) K. Shishido, Y. Tokunaga, N. Omachi, K. Hiroya and K. Fukumoto, *J. Chem. Soc., Perkin Trans 1*, 2481 (**1997**).

7. (a) H. Iio, M. Monden, K. Okada and T. Tokoroyama, *Chem Commun.*, 358 (**1987**). (b) M. Ohba, K. Iizuka, H. Ishibashi and T. Fujii, *Tetrahedron*, **53**, 16977 (1997).

8. (a) D. L. Commins and A. Dehghani, *Tetrahedron Lett.*, **33**, 6299 (1992). (b) P. A. Grieco and Y. Yokoyama, *J. Am. Chem. Soc.*, **99**, 5210 (1977). (c) A. Abad, C. Agullo, M. Arno, A. Cantin, A. C. Cunat, B. Meseguer and R. J. Zaragoza, *J. Chem. Soc., Perkin Trans. 1*, 1837 (**1997**).

9. U. Hersel, M. Steck and K. Seifert, *Eur. J. Org. Chem.*, 1609 (**2000**).

10. P. A. Zoretic and H. Fang, *J. Org. Chem.*, **63**, 4779 (1998).

11. A. Anikin, M. Maslov, J. Sieler, S. Blaurock, J. Baldamus, L. Hennig, M. Findeisen, G. Reinhardt, R. Oehme and P. Welzel, *Tetrahedron*, **59**, 5295 (2003).

12. J. Justicia, J. E. Oltra and J. M. Cuerva, *Tetrahedron Lett.*, **45**, 4293 (2004).

13. J. H. Yang and W. D. Z. Li, *Chinese Chem. Lett.*, **16**, 293 (2005), *Chem. Abst.*, **144**:150493 (2005).

14. L. A. Paquette and H.-L. Wang, *J. Org. Chem.*, **61**, 5352 (1996); L. A. Paquette and H. -L. Wang, *Tetrahedron Lett.*, **36**, 6005 (1995).

15. A. Pemp and K. Seifert, *Tetrahedron Lett.*, **38**, 2081 (1997).

16. W. S. Cheung and H. N. C. Wong, *Tetrahedron Lett.*, **39**, 6521 (1998).

17. H. Hagiwara, F. Takeuchi, M. Nozawa, T. Hoshi and T. Suzuki, *Tetrahedron*, **60**, 1983 (2004); H. Hagiwara, F. Takeuchi, T. Hoshi, T. Suzuki and M. Ando, *Tetrahedron Lett.*, **42**, 7629 (2001).

18. (a) M. Kolympadi, M. Liapis and V. Ragoussis, *Tetrahedron*, **61**, 2003 (2005). (b) M. Müller, J. Schröder, C. Magg and K. Seifert, *Tetrahedron Lett.*, **39**, 4655 (1998).

19. W.-G. Gao, K. Sakaguchi, S. Isoe and Y. Ohfune, *Tetrahedron Lett.*, **37**, 7071 (1996).

20. T. Teramoto, T. Yuno, H. Morita, S. Katsumura, K. Sakaguchi and S. Isoe, *Synlett*, 141 (**1996**).

21. J. G. Urones, A. Jorge, I. S. Marcos, P. Basabe, D. Diez, N. M. Garrido and A. M. Lithgow, *Tetrahedron Lett.*, **37**, 1659 (1996); I. S. Marcos, P. Basabe, M. Laderas, D. Diez, A. Jorge, J. M. Rodilla, R. F. Moro, A. M. Lithgow, I. G. Barata and J. G. Urones, *Tetrahedron*, **59**, 2333 (2003); I. S. Marcos, M. Laderas, D. Diez, P. Basabe, R. F. Moro, N. M. Garrido and J. G. Urones, *Tetrahedron Lett.*, **44**, 5419 (2003).

22. M. Jung, S. Lee and B. Yoon, *Tetrahedron Lett.*, **38**, 2871 (1997).

23. M. Jung, I. Ko and S. Lee, *J. Nat. Prod.*, **61**, 1394 (1998).

24. M. Miller, J. Schroeder, C. Magg and K. Seifert, *Tetrahedron Lett.*, **39,** 4655 (1998).

25. C. A. Gray, M. T. Davies-Coleman and D. E. A. Rivett, *Tetrahedron,* **59**, 165 (2003).

26. F. Chauvet, I. Coste-Maniere, P. Martres, P. Perfetti, B. Waegell and J.-P. Zahra, *Tetrahedron Lett.*, **37**, 3695 (1996).

27. J. Moulines, A.-M. Lamidey and V. Desvergnes-Breuil, *Synth. Commun.*, **31**,749 (2001).

28. P. A. Zoretic and H. Fang, *J. Org. Chem.*, **63**, 1156 (1998).

29. M. C. de la Torre, I. Garcia and M. A. Sierra, *J. Nat. Prod.*, **65**, 661 (2002).

30. S. Rosselli, M. Bruno, I. Pibiri and F. Piozzi, *Eur. J. Org. Chem.*, **24**, 4169 (2002).

31. M. C. de la Torre and I. Garcia, *J. Org. Chem.*, **68**, 6611 (2003).

32. S. Oh, I. H. Jeong, W.-S. Shin, Q. Wang and S. Lee, *Bioorg. & Med. Chem. Lett.*, **16**, 1656 (2006).

33. D. Herlem, J. Ouazzani and F. Khuong-Huu, *Tetrahedron Lett.*, **37**, 1241 (1996).

34. C. Morin and N. Nedjar, *Tetrahedron Lett.*, **37**, 4705 (1996).

35. D. Herlem and F. Khuong-Huu, *Tetrahdron*, **53**, 673 (1997).

36. M. G. Bolster, B. M. F. Lagnel, B. J. M. Jansen, C. Morin and A. de Groot, *Tetrahedron*, **57**, 8369 (2001).

37. M. G. Bolster, B. J. M. Jansen and A. de Groot, *Tetrahedron*, **58**, 5275 (2002).

38. J. Aslaoui, H. Li and C. Morin, *Tetrahedron Lett.*, **46**, 1713 (2005).

39. A. Pathak, J. Aslaoui and C. Morin, *J. Org. Chem.*, **70**, 4184 (2005).

40. J. Villamizar, J. Fuentes, F. Salazar, E. Tropper and R. Alonso, *J. Nat. Prod.*, **66**, 1623 (2003).

41. (a) J. Villamizar, F. Salazar, J. Fuentes, E. Tropper and R. Alonso, *J. Chem. Res., Synopses,* 504 (2003), *Chem. Abst.*, **142**:6673 (2004). (b) J. Villamizar, J. Fuentes, F. Salazar, E. Tropper and R. Alonso, *J. Natural Products*, **66**, 1623 (2003).

42. B. T. Utenova and L.-L. Gundersen, *Tetrahedron Lett.*, **45**, 4233 (2004).

43. I. S. Marcos, R. F. Moro, S. Carballares M. and J. G. Urones, *Tetrahedron Lett.*, **40**, 2615 (1999).

44. T. Katoh, R. Tanaka, M. Takeo, K. Nishide and M. Node, *Chem. Pharm. Bull.*, **50**, 1625 (2002).

45. S. Nanduri, V. K. Nyavanandi, S. S. R. Thunuguntla, M. Velisoju, S. Kasu, S. Rajagopal, R. A. Kumar, R. Rajagopalan and J. Iqbal, *Tetrahedron Lett.*, **45**, 4883 (2004).

46. R. C. Cambie and D. R. Stewart, *Synth. Commun.*, **28**, 659 (1998).

47. (a) F. E. Ziegler, B. H.Jaynes and M. T. Saindane, *Tetrahedron Lett.*, **26**, 3307 (1985). (b) S. Hashimoto, S. Sakata, M. Sonegawa and S. Ikegami, *J. Am. Chem. Soc.*, **110**, 3670 (1988). (c) E. J. Corey, J. P. Da Silva and J. C. Rohloft, *J. Am. Chem. Soc.*, **110**, 3672 (1988).

48. H. Hagiwara, F. Takeuchi, T. Hoshi, T. Suzuki, T. Hashimoto and Y. Asakawa, *Tetrahedron Lett.*, **44**, 2305 (2003).

49. H. Hagiwara, F. Takeuchi, M. Kudou, T. Hoshi, T. Suzuki, T. Hashimoto and Y. Asakawa, *J. Org. Chem.*, **71**, 4619 (2006).

50. M. G. Bolster, B. J. M. Jansen and A. de Groot, *Tetrahedron*, **57**, 5657 (2001).

51. J. M. Castro, S. Salido, J. Altarejos, M. Nogueras and A. Sánchez, *Tetrahedron*, **58**, 5941 (2002).

52. F. M. N. Nunes and P. M. Imamura, *J. Braz. Chem. Soc.*, **7**, 181 (1996), *Chem. Abstr.*, **125**:329073 (1996).

53. D. Behnke, S. Hamm, L. Hennig and P. Welzel, *Tetrahedron Lett.*, **38**, 7059 (1997).

54. S. Hamm, S. Zimmermann, L. Hennig, D. Muller and P. Welzel, *Tetrahedron Lett.*, **40**, 9225 (1999).

(Received October 3, 2007; in final form February 21, 2008)