CHEMICAL REVIEWS

REVIEW

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Isolation, Chemical, and Biotransformation Routes of Labdane-type Diterpenes

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CONTENTS

1. INTRODUCTION AND SCOPE

Small molecule natural products continue to provide an incomparable source of inspiration for advances in organic chemistry and disease treatment.[1−6] Labdane-type diterpenes are excellent examples of natural products with important pharmaceutical activities (see Figure 1). Many of these derivatives possess significant biological properties, such as antifungal and antibacterial,[7] antimutagenic,[8] cytotoxic,[9] anti-inflammatory, or analgesic activities.[10]

An initial literature survey revealed that different processes have been used for the total synthesis of labdane-type diterpenes. For instance, these molecules can be produced from synthetic monocyclic precursors, cyclic monoterpenoids, sesquiterpenoids, or by biomimetic cyclization of acyclic terpene precursors. Nevertheless, these synthetic routes

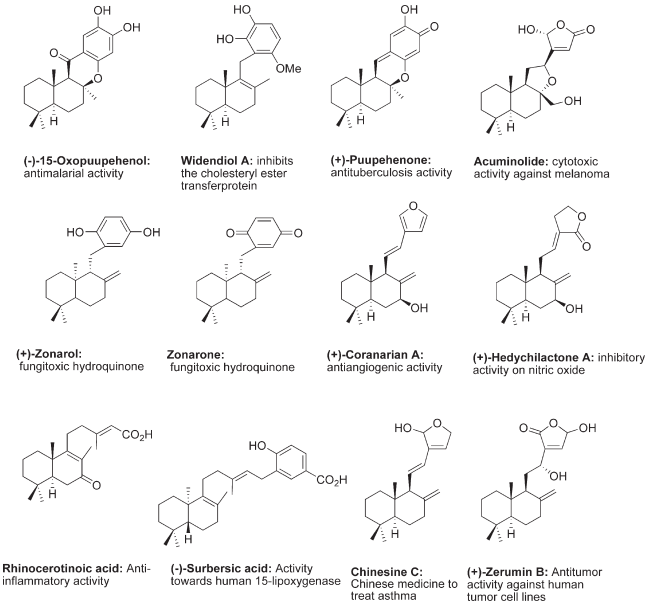

Figure 1. Representative bioactive compounds containing the bicyclic core of labdane-type diterpenes.

are generally complex and expensive due to their numerous reaction steps.

Besides, diverse publications reveal that labdane-type diterpenes are susceptible to biomanipulations producing important synthetic intermediates. On the other hand, several labdane-type diterpenes are quite abundant in nature and/or are commercially available, such as sclareol, sclareolide, larixol, ladanolic acid, or ozic acid (see Figure 2). Hence, they are useful starting materials for chemical or biotransformations.

Recent progress in the total synthesis and interconversions of labdane diterpenoids was partially compiled in a review by Awen et al.[11] Hanson has been publishing regular reviews covering primarily the isolation of naturally occurring labdanes.[12−14] To the best of our knowledge, these are the most recent reviews on labdane diterpenoids, but none of them describe the biotransformation of such compounds. Therefore, bearing in mind that in the last two decades there have been many new developments concerning the isolation, chemical, and biomanipulation of diterpenoids, particularly for labdanes, we provide an overview of the most significant advances described in the recent literature.

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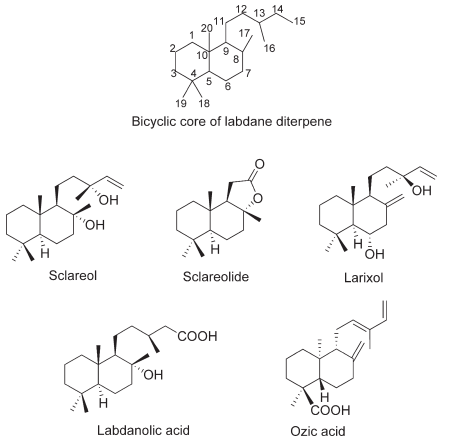


Figure 2. Bicyclic framework of labdane diterpenes (top, basic skeleton) with atom numbering and structure of five representative labdane-type diterpenes.

In the section on chemical manipulation, we emphasize attractive methodologies for the production of pharmacologically active compounds. Their total synthesis is not covered in this Review, as we chose to focus exclusively on synthetic transformations of naturally abundant labdanes.

2. ISOLATION AND CHEMICAL MANIPULATION

2.1. Sclareol

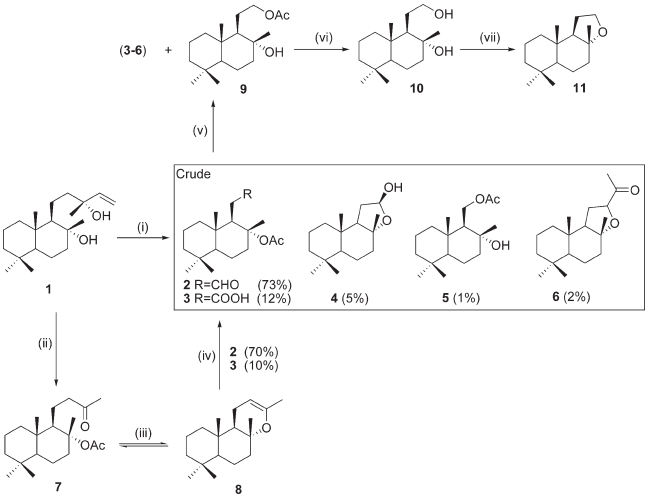
(−)-Sclareol (**1**) is a commercially available labdane isolated from *Salvia sclarea*. This derivative has been used as a starting material for different terpenoid syntheses, particularly for compounds that do not have functional groups in the left ring of the decalin core. Ambergris, a metabolic product of sperm whales, has been used in the past as a valuable constituent of fine fragrances.[15] Although natural ambergris is no longer used, there is demand for perfume ingredients with ambergris-type odors. One of the most commercially important synthetic ingredients is (−)-norlabdane oxide **11** ((−)-dodecahydro-3*a*,6,6,9*a*-tetramethylnaphtho[2,1-*bl*]furan), more commonly known under the trade names Amberlyn (Quest), Ambrox (Firmenich), and Ambroxan (Henkel).[16] Ambrox occurs naturally in trace amounts and has been isolated mostly from ambergris,[17] the essential oils of *Salvia sclarea* L,[16] *Cistus ladaniferus* L,[15,16,18] and in the absolute of *Nicotiana tabacum*.[19]

In 1993, Barrero and co-workers described a novel and very attractive synthesis of (−)-ambrox (**11**) from (−)-sclareol (**1**).[20] The authors concluded that the critical step in the synthesis is the oxidative degradation of the side chain of sclareol. In that process, treatment of **1** with osmium tetroxide−sodium periodate in tetrahydrofuran solution at 45 °C afforded five products: the acetoxyaldehyde **2**, the acetoxyacid **3**, the hemiacetal **4**, and the minor products **5** and **6** (Scheme 1).

Before 1994, Barton and co-workers described a simple and high yielding (74% overall) synthesis of Ambrox (**11**), starting from (−)-sclareol (**1**) (Scheme 2).[21] The key step involves an unusual osmium-catalyzed rearrangement, which is dependent on the ratio of $OsO_4/NaIO_4$ and the pH of the solution. Reaction of **2** in a buffered *t*-butanol solution (pH ≈ 1.0) of osmium tetroxide and sodium periodate at room temperature, afforded after 5 h an epimeric mixture of the methyl ketones **6a** and **6b** in excellent yield (91% ratio 9:1). Baeyer−Villiger oxidation of the major epimer **6a** afforded acetate **12** in 89% yield. Quantitative conversion of **12** into **11** was achieved with $LiAlH_4$ in the presence of $BF_3 \cdot OEt_2$.

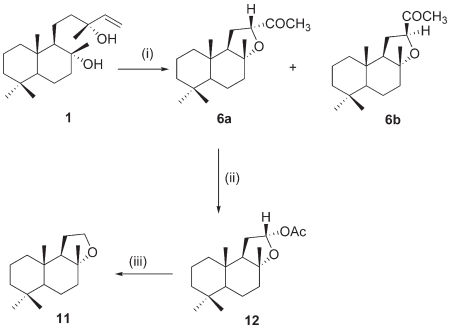
Although this route represents a simple and high yielding method for the preparation of **11**, the use of the expensive and toxic osmium tetroxide makes this synthetic sequence less attractive to industry.

Scheme 1. Synthetic Approach to Ambrox (11) from Sclareol (1)[a]



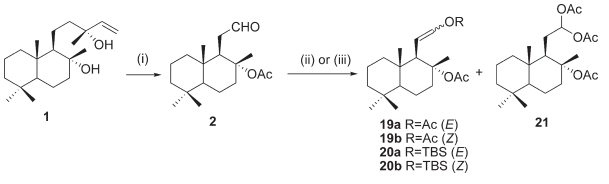
[a] (i) $OsO_4/NaIO_4$, THF, 45 °C, 6 h. (ii) $OsO_4/NaIO_4$, THF, 10 °C. (iii) Δ/benzene. (iv) $OsO_4/NaIO_4$, THF, 10 °C. (v) $NaBH_4$, THF, 30 min. (vi) KOH, MeOH, 10%, room temperature, 2 h. (vii) TsCl, Py, 99%.

Scheme 2. A Different Approach for the Preparation of Ambrox (11) from Sclareol (1)[a]



[a] (i) OsO_4 (cat.)/$NaIO_4$, *t*-butanol, room temperature, pH = 1 (91% ratio of **6a**:**b**, 9:1). (ii) *m*-CPBA, NaOAc, dioxane, room temperature, 89%. (iii) $LiAlH_4/BF_3 \cdot OEt_2$, −78 °C.

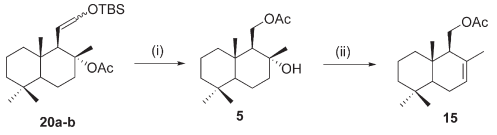
Scheme 3. Preparation of Enol Acetates 19a,b and 20a,b from Acetoxyaldehyde 2[a]



[a] (i)$OsO_4/NaIO_4$, Pr^iOH, 45 °C, 6 h, 73%. (ii) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18 h, 89%. (iii) TBSCl, NaH, THF, −78 °C, 4 h, 99%.

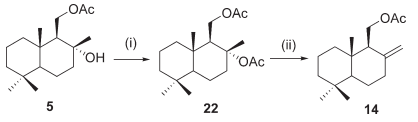
dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Scheme 4. Preparation of Drimenyl Acetate 15 from Silyl Enol Ethers 20a,b[a]



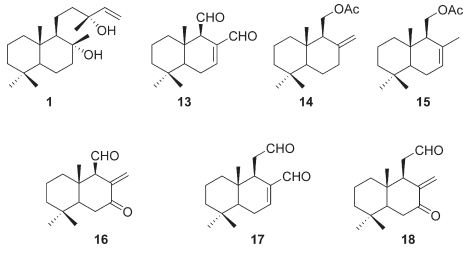
[a] (i) O_3, MeOH/CH_2Cl_2, −78 °C, 1 h; Me_2S, $NaBH_4$, MeOH, room temperature, 30 min, 95%. (ii) $SnCl_4$, CH_2Cl_2, −19 °C, dropwise 30 min, 61%.

Scheme 5. Preparation of Albicanyl Acetate 14 from Acetoxyalcohol 5[a]



[a] (i) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18 h, 92%. (ii) Collidine, reflux.

In 1995, Barrero et al. prepared drimenyl acetate (**15**), three drimanes, polygodial (**13**), albicanyl acetate (**14**), and 7-oxo-8,12-drimen-11-al (**16**), and two homodrimanes, 13,14,15,16-tetranorlabd-7-ene-12,17-dia1 (**17**) and 7-oxo-13,14,15,16-tetranorlabd-8(17)-en-12-al (**18**), from (−)-sclareol (**1**).[22]



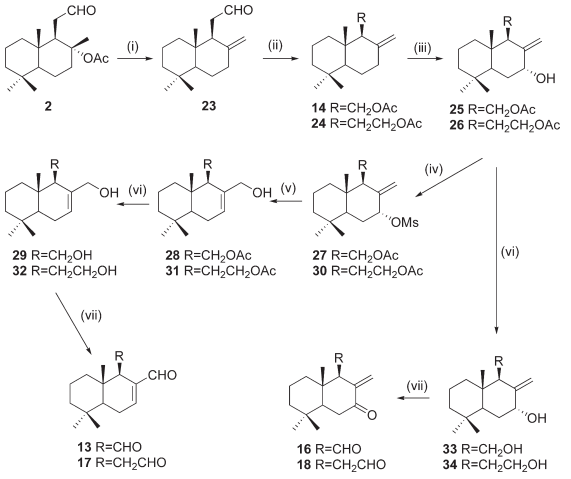
The large diversity of biological activities of several drimane sesquiterpenes,[23] such as compounds **13** to **18**, has stimulated many efforts toward their synthesis.[24] There have been diverse studies[25−33] on the mode of action of sesquiterpene drimane antifeedants, such as polygodial (**13**). A reactive enedial functionality, which blocks insect chemoreceptors, is a common feature in these compounds. Kubo et al.[31] and Ma[33] proposed that the enedial function reacts with a SH receptor group via a Michael addition. Sodano et al.[28] suggested that it is an NH_2 group of the receptor that reacts with the enedial group to form a pyrrole. Afterward, Lam et al.[27] isolated a pyrrole derivative, formed from reacting L-cysteine methyl ester with muzigadial, an antifeedant drimane, a finding that supports Sodano's hypothesis.

The oxidation of sclareol (**1**) was performed by Barrero and co-workers with osmium tetroxide−sodium periodate to form acetoxyaldehyde **2** in good yield. This acetoxyaldehyde was then transformed into biologically active drimanes **13**, **14**, and **16** and homodrimanes **17** and **18** (Schemes 3−6).[22]

The synthesis of drimanes involves shortening of the side chain of **2**, by oxidative degradation of the corresponding enol derivatives. The preparation of enol acetates from **2** (Scheme 3) led to a mixture of isomers **19a** and **19b** (ratio *E*/*Z* 3: 1) and the triacetate **21**. Treatment of **2** with *tert*-butyldimethylsilyl chloride in dichloromethane gave quantitative yields of the corresponding silyl enol ethers **20a** and **20b**.

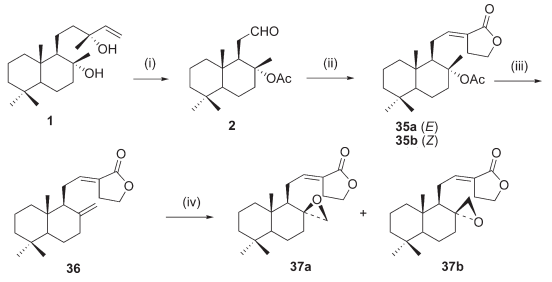
Reductive ozonolysis of silyl enol ethers **20a,b** was chosen by the authors as a degradation method for preparing biologically active drimanes. Thus, acetoxyalcohol **5** was obtained in high yields by ozonolysis of **20a,b** followed by reduction with $NaBH_4$. The use of $SnCl_4$ in dichloromethane

Scheme 6. Synthesis of Drimanes 13 and 16 and Homodrimanes 17 and 18[a]



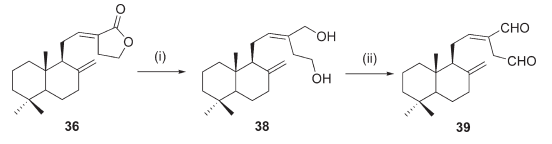
[a] (i) Collidine, 170 °C, 8 h, 60%. (ii) $NaBH_4$, MeOH, room temperature, 30 min, 93%; Ac_2O, Py, room temperature, 2 h, 94%. (iii) *t*-BuOOH, SeO_2, CH_2Cl_2, room temperature. (iv) MsCl, Py, room temperature. (v) NaOAc, acetone−H_2O, reflux. (vi) 2 N KOH/MeOH, room temperature. (vii) $(COCl)_2$/DMSO, CH_2Cl_2, Et_3N, −78 °C, 15 min.

Scheme 7. Synthesis of Galactones 37a and 37b from Sclareol (1)[a]



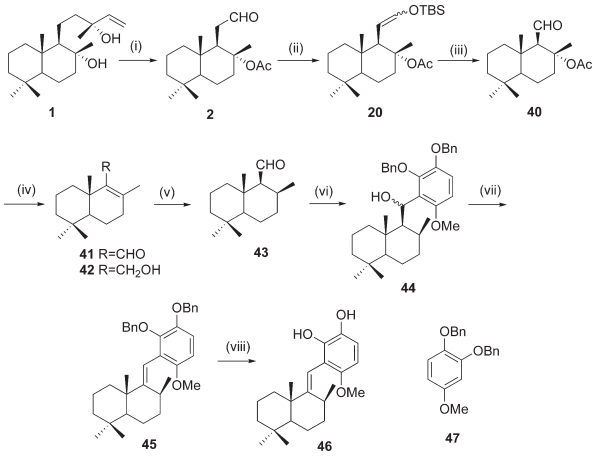
[a] (i) OsO_4/$NaIO_4$, *t*-butanol, THF, 25 °C, 5.5 h, 65%. (ii) Diethylphosphono-2-butyrolactone (1.0 equiv), NaH (1.2 equiv), dry toluene, 0 °C, 4 h; then 80 °C, 1 h, 67% (*E*/*Z* = 3/1). (iii) Quinoline, reflux, 2 h, 71%. (iv) *m*-CPBA (2.0 equiv), $CHCl_3$, 0 °C, overnight, 52%.

Scheme 8. Synthesis of (+)-Labdienedial (39) Starting from Derivative 36[a]



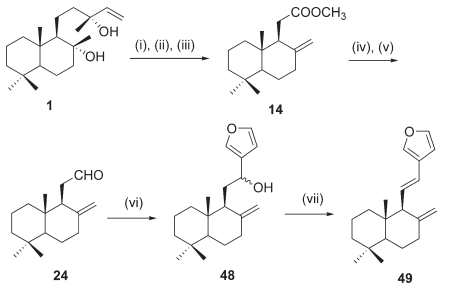
[a] (i) $LiAlH_4$ (5 equiv), Et_2O, room temperature, 2 h, 85%. (ii) PCC (2.5 equiv), CH_2Cl_2, room temperature, 50 min, 81%.

Scheme 9. Synthesis of Wiedendiol-B (46) from Sclareol (1)[a]



[a] (i) $OsO_4/NaIO_4$, Pr^iOH, 45 °C, 6 h, 73%. (ii) TBSCl, NaH, THF, −78 °C, 4 h, 99%. (iii) O_3, Me_2S, 93%. (iv) Collidine, 200 °C, 3 h, 78%. (v) H_2, Pd−C, MeOH−EtOAc (1:1), 0 °C, 1 h, 70%. (vi) **47**, *n*-BuLi, Et_2O−TMEDA (4:1), −40 to 0 °C, 1 h 30 min, 55%. (vii) TsOH, benzene, 35 °C, 13 h, 82%. (viii) H_2, Pd−C, MeOH−EtOAc (1:1), 0 °C, 2 h, 93%.

Scheme 10. Synthesis of (+)-Coronarin E (49) from Sclareol (1)[a]



[a] (i) $RuCl_3 \cdot H_2O$, $NaIO_4$, H_2O/CH_3CN, CCl_4, room temperature (acetoxyacid, 50%; sclareolide, 30%). (ii) Me_2SO_4, $LiOH \cdot H_2O$, DMF, room temperature, 99%. (iii) $KHCO_3$, DMSO, 150 °C (74%). (iv) $LiAlH_4$, THF or Et_2O, reflux, 97%. (v) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, room temperature or PCC/Alox B, CH_2Cl_2, 0 °C, room temperature (86−96%). (vi) 3-Furyllithium, THF, −78 °C (total 65%, relation 1:1). (vii) $Cl_3C-CO-CF_3$, pyridinium *p*-toluenesulfonate, benzene, reflux (50%).

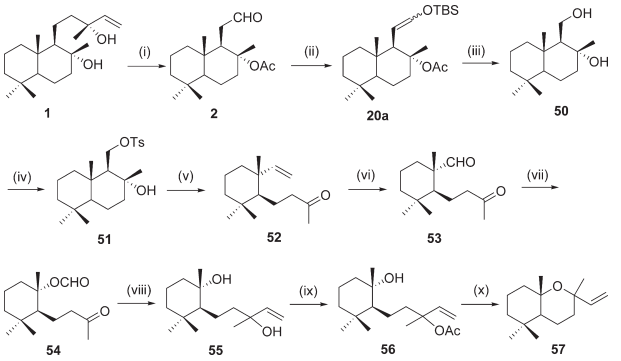
allowed the transformation of **5** into drimenyl acetate **15** (Scheme 4).[22]

Additionally, acetoxyalcohol **5** was transformed through its *O*-acetyl derivative into albicanyl acetate **14** (Scheme 5).[22]

Polygodial (**13**) and the homodrimane **17** were synthesized from albicanyl acetate (**14**) and its homologue **24**, respectively, by a five-step sequence. Also, drimane **16** and homodrimane **18** were obtained from **14** in high yields (about 90%) (Scheme 6).[22]

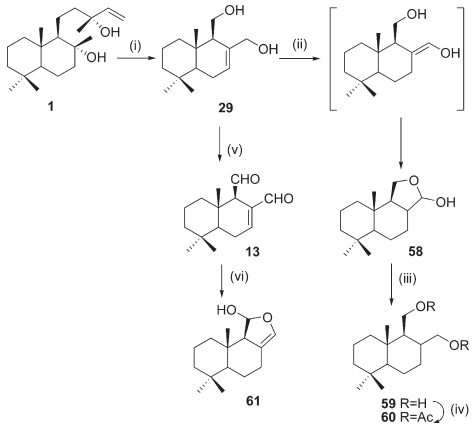
Two years later, Jung et al. synthesized three novel labdane-type diterpenes, (+)-galanolactone (**37a**), (−)-8-*epi*-galanolactone (**37b**), and (+)-labdienedial (**39**), in optically active forms, from (−)-sclareol (**1**) (Schemes 7 and 8).[34] These synthetic strategies made it possible to test further the biological activities of galanolactone and related compounds,

Scheme 11. Enantiospecific Synthesis of (−)-Caparrapi Oxide (57) from Sclareol (1)[a]



[a] (i,ii) See Scheme 3. (iii) (a) O_3, $MeOH/CH_2Cl_2$, −78 °C, 1 h; (b) $LiAlH_4$, THF, room temperature, 40 min, 95%. (iv) TsCl, 4-DMAP. (v) NaH, DME, reflux, 2.5 h, 95%. (vi) O_3, CH_2Cl_2, −78 C, 20 min; Ph_3P, −78 °C to room temperature, 14 h, 75%. (vii) MCPBA, CH_2Cl_2, room temperature, 5 days, 93%. (viii) $CH_2{=}CHMgBr$, Et_2O, 0 °C; room temperature, 20 min; 2 N KOH−MeOH, room temperature, 4 h (90%). (ix) Ac_2O, DMAP, Et_3N, THF, reflux, 4 days. (x) $PdCl_2$ $(CH_3CN)_2$, THF, room temperature, 12 h.

Scheme 12. Synthesis of Drimanes 60 and 61 from Sclareol (1)[a]



[a] (i) See Schemes 3 and 6. (ii) H_2, Raney Ni, THF, room temperature, 72 h, 85%. (iii) $NaBH_4$, EtOH, room temperature, 45 min (97%). (iv) Ac_2O, Py, room temperature, 1 h (99%). (v) $(COCl)_2$/DMSO, CH_2Cl_2, Et_3N, −78 °C, 15 min. (vi) H_2, Raney Ni, THF, room temperature, 1 h, 95%.

and to establish the labdane structure as a new scaffold for agrochemicals.

In 1997, Barrero et al. described the first enantiospecific synthesis of the cholesteryl ester transfer protein inhibitor wiedendiol-B (**46**) from (−)-sclareol (**1**). The synthetic strategy used by the authors was based on the reaction of drimanic aldehyde **43** with an organolithium reagent derived from **47** (see Scheme 9).[35]

In 1998, the first synthesis of (+)-coronarin E (**49**) was achieved in seven steps from (−)-sclareol (**1**) by Seifert and coworkers (see Scheme 10).[36] (+)-Coronarin E has been isolated essentially from the rhizomes of the Brazilian medical plant *Hedychium coronarium* (Zingiberaceae).[37] However, this compound can be also obtained from other plants, such as *Alpinia*

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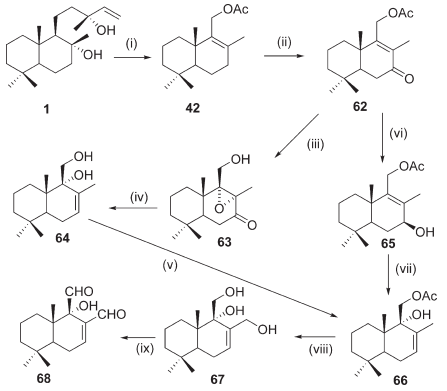
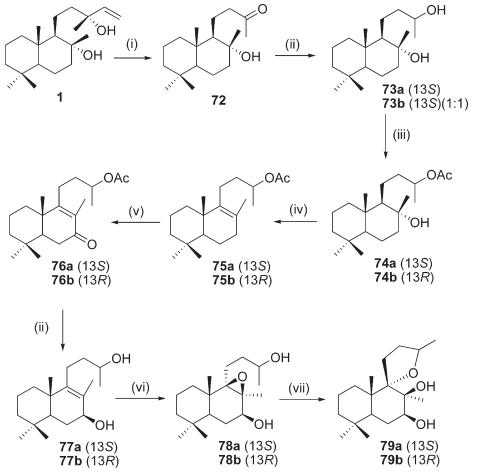
Scheme 13. Synthesis of Warburganal 68 from Sclareol (1)[a]



[a] (i) See Schemes 3 and 4 (preparation of compound **15**). (ii) Na_2CrO_4, Ac_2O, AcOH, NaOAc, 70 °C, 3.5 h, 91%. (iii) H_2O_2, NaOH, room temperature, 5 h, 88%. (iv) NH_2NH_2, AcOH, reflux, 30 min, 95%. (v) Ac_2O, Py, 92%. (vi) $NaBH_4$, EtOH, 0 °C, 96%. (vii) MsCl, Et_3N, DMAP, H_2O, THF, reflux, 1 h, 81%. (viii) SeO_2, dioxan, 100 °C, 2 h; KOH, MeOH, room temperature, 1 h, 71%. (ix) Oxidation (Swern reagent).

Scheme 14. Synthesis of Grindelic Acid Derivatives 79a,b from Sclareol (1)[a]

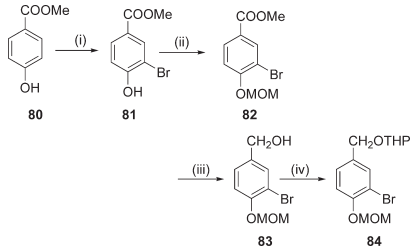


[a] (i) $KMnO_4$, acetone, $MgSO_4$, room temperature, 6 h. (ii) $LiAlH_4$, ether, room temperature, 2 h. (iii) Ac_2O, Py, room temperature, 12 h. (iv) I_2, C_6H_6, 80 °C, 2 h. (v) Na_2CrO_4, Ac_2O, AcOH, 60 °C, 2 h. (vi) *m*-CPBA, DCM, room temperature, 2 h. (vii) CSA, DCM, room temperature, 7 h.

chinensis,[38] *Alpinia zurumbet*,[39] *Alpinia javanica*,[40] or *Hedychium acuminatum*.[41] The Seifert synthesis is reasonably efficient, thereby providing a valuable alternative source of this natural product.

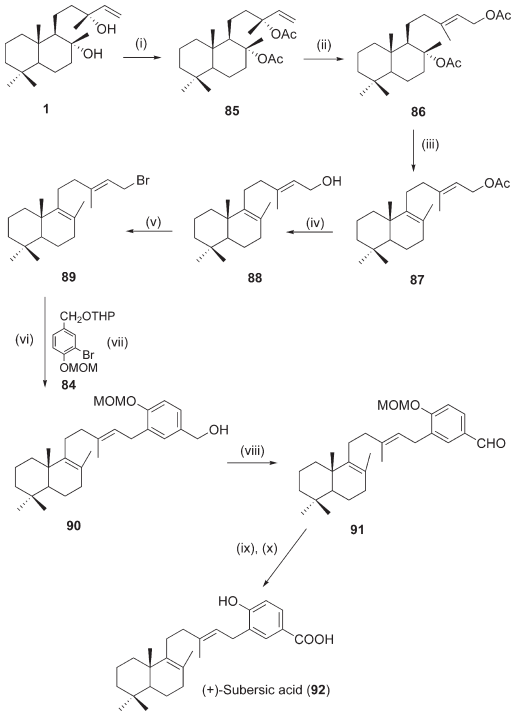
Also in 1998, Barrero and co-workers described a new and efficient strategy for carrying out the synthesis of monocarbocyclic terpenoids from (−)-sclareol (**1**).[42] The key steps are (i) Grob scission of 11-*p*-toluene-sulfonyloxydriman-7α-ol (**51**) to give the tobacco *seco*-sesquiterpene **52**, and (ii) a regioselective Baeyer−Villiger oxidation of keto-aldehyde **53** to give the corresponding formate **54**. In the same article,[42] the first synthesis of the acid-sensitive (−)-caparrapi oxide (**57**) is reported (Scheme 11).

Scheme 15. Synthesis of the Aromatic Unit 84 from Methyl 4-Hydroxybenzoate (80)[a]



[a] (i) Br_2, DCM, room temperature, 24 h, 95%. (ii) Dimethoxymethane, P_2O_5, $CHCl_3$, room temperature, 10 min, 99%. (iii) DIBAL-H, DCM, −78 °C, 1 h, 99%. (iv) DHP, HCl/dioxane 4 M, room temperature, 10 min, 99%.

Scheme 16. Synthesis of (+)-Subersic Acid (92) from Sclareol (1)[a]

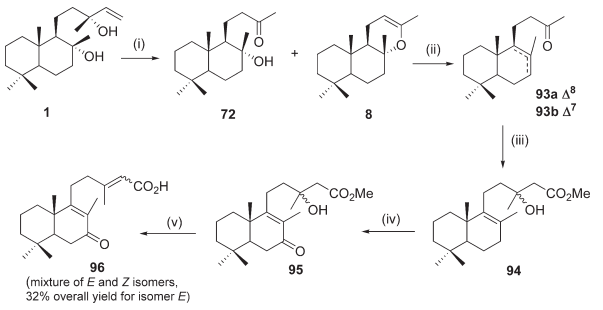


[a] (i) AcCl, *N*,*N*-dimethylaniline, DCM, room temperature, 24 h, 97%. (ii) $PdCl_2(MeCN)_2$, THF, room temperature, 4 h, 92%. (iii) HI, C_6H_6, room temperature, 11 h, 48%. (iv) K_2CO_3/MeOH 3%, room temperature, 98%. (v) CBr_4, PPh_3, DCM, 0 °C, 10 min, 90%. (vi) **84**, *t*-BuLi, THF, −78 °C to room temperature, 3 h. (vii) *p*-TsOH, MeOH, room temperature, 1 h, 26% (from 89). (viii) MnO_2, DCM, room temperature, 3 h, 85%. (ix) $NaClO_2$, *t*-BuOH, room temperature, 2 h. (x) HCl 6 M, THF, 45 °C, 3 h, 47% (from **91**).

One year later, the same research group reported the preparation of the drimanes 11,12-diacetoxydrimane (**60**) and 11,12-epoxydrim-8,12-en-11-ol (**61**) (Scheme 12) and described two efficient new routes to the potent bioactive drimane warburganal (**68**) (11 steps, 25% overall yield and 12 steps, 24% overall yield) from (−)-sclareol (**1**) (Scheme 13).[43] The chemistry developed by Barrero et al. constitutes a major advance in the synthesis of these important compounds.

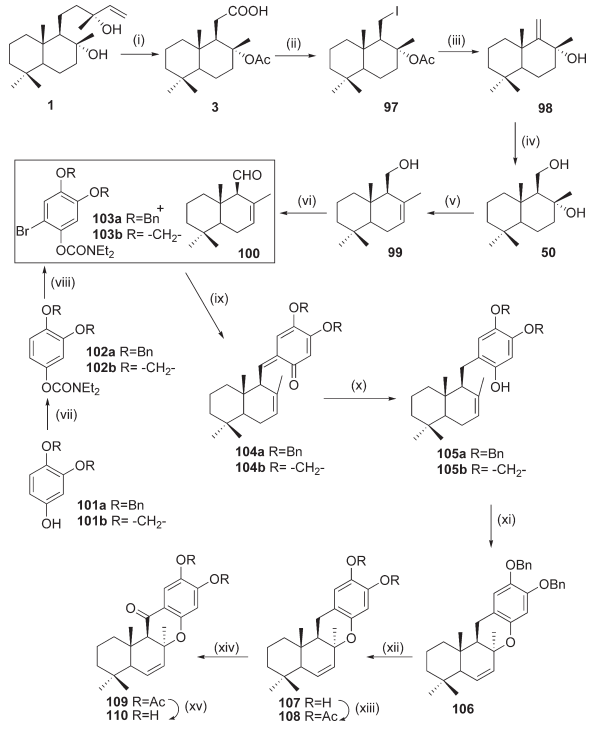
dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Scheme 17. Synthesis of *E*-Rhinocerotinoic Acid (96) from Sclareol (1)[a]



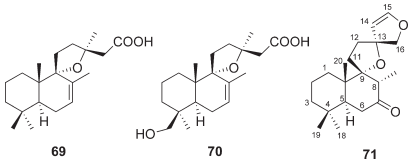
[a] (i) $KMnO_4$, acetone, <15 °C. (ii) I_2 (0.05 equiv), benzene, reflux, 6 h. (iii) Zn, $BrCH_2CO_2Me$, benzene−Et2O (5:2), reflux, 2 h. (iv) CrO_3·2Py, DCM, 0 °C to room temperature, 48 h. (v) $POCl_3$, pyridine.

Scheme 18. Synthesis of (−)-15-Oxopuupehenol (110) from Sclareol (1)[a]



[a] (i) (a) OsO_4, $NaIO_4$, *t*-BuOH, 45 °C, 6 h; (b) Jones' oxidation, acetone, 0 °C, 45 min, 75% overall yield. (ii) $Pb(OAc)_4$ (1.2 equiv), C_6H_6, I_2, *hν*, 50−60 °C, 4 h, quantitative. (iii) *t*-BuOK, DMSO, H_2O, room temperature, 6 h, 85%. (iv) B_2H_6, THF, 0 °C, 2 h; NaOH, H_2O_2, EtOH, H_2O, room temperature, 12 h, 94%. (v) DEAD, PPh_3, benzene, room temperature, 1 h, 92%. (vi) PCC, DCM, room temperature, 1 h, 71%. (vii) $ClCONEt_2$, pyridine, reflux, 24 h, (89/92%). (viii) NBS, CCl_4, silica gel, room temperature, 1 h (93/90%). (ix) *t*-BuLi, THF, 30 min; −80 °C, 30 min (87/83%). (x) Raney Ni, THF, room temperature, 30 min (98/96%). (xi) $PdCl_2$, cat. $Pd(OAc)_2$, MeOH−H_2O (99:1), 40 °C, 48 h, 91%. (xii) H_2, Pd/C, EtOAc, room temperature, 48 h, 99%. (xiii) AcO, pyridine, DMAP, room temperature, 4 h, 95%. (xiv) Na_2CrO_4, NaOAc, Ac_2O, C_6H_6, 70 °C, 5 h, 96%. (xv) $NaHCO_3$, DMF, 80 °C, 8 h, 67%.

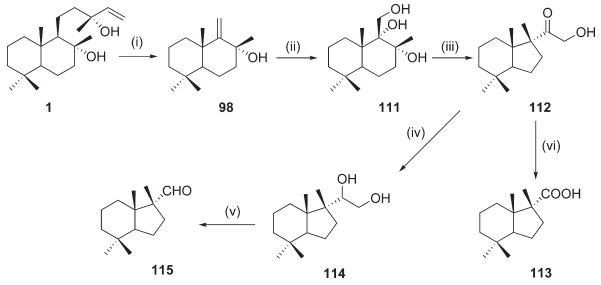
Several natural products, especially bicyclic diterpenes of the labdane class, possess an oxygenated bridge (C9−C13), for instance, grindelic acid (**69**), 19-hydroxygrindelic acid (**70**),[44] prehispanolone (**71**),[45] and many other compounds isolated from the Labiatae or Lamiaceae.



In 2001, Urones and co-workers described a new strategy for acid-catalyzed intramolecular epoxide ring-opening for preparing grindelic acid derivatives, such as compounds **79a**,**b**.[46] In this work, sclareol (**1**) is used as starting material (Scheme 14).

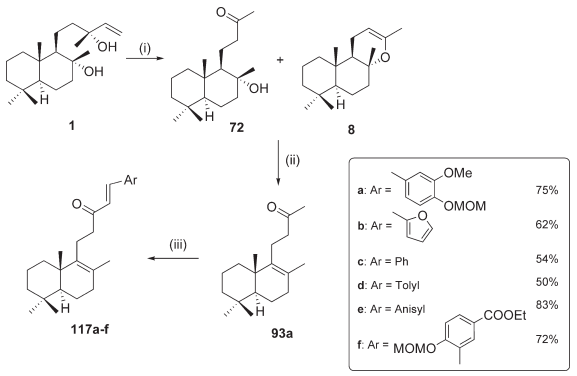
In 2003, Pilar Basabe and co-workers reported a short and efficient synthesis of (+)-subersic acids starting from (−)-sclareol (Scheme 16).[47] The key step of the synthesis is the coupling of the diterpene part with the lithiated arene unit **84** prepared independently (Schemes 15 and 16). Subersic acid (**92**) was isolated from the sponge Suberea sp. by Crews and co-workers.[48] This natural product is an inhibitor of human 15-lipoxygenase, a property that motivated research to discover new marine sponge-derived bioactive compounds.

Scheme 19. Synthesis of (+)-Austrodoral (115) and (+)-Austrodoric Acid (113) from Sclareol (1)[a]



[a] (i) See Scheme 18, three steps. (ii) OsO_4, H_2O, *t*-BuOH, trimethylamine *N*-oxide, pyridine, reflux, 24 h, 87%. (iii) BF_3·OEt_2, DCM, 0 °C to room temperature, 20 min, 95%. (iv) $NaBH_4$, EtOH, room temperature, 15 min, 97%. (v) $Pb(OAc)_4$, DCM, room temperature, 45 min, 92%. (vi) $NaIO_4$, *t*-BuOH−H_2O, reflux, 12 h, 91%.

Scheme 20. Synthesis of (+)-Subersic Acid Analogues (117a−f) from Sclareol (1)[a]



[a] (i) $KMnO_4$, acetone, 80%. (ii) I_2, Δ, benzene, 70%. (iii) Claisen−Schmidt, Ar−CHO.

In 2001, Urones and co-workers described a new strategy for acid-catalyzed intramolecular epoxide ring-opening for preparing grindelic acid derivatives, such as compounds **79a**,**b**.[46] In this work, sclareol (**1**) is used as starting material (Scheme 14).

In 2003, Pilar Basabe and co-workers reported a short and efficient synthesis of (+)-subersic acids starting from (−)-sclareol (Scheme 16).[47] The key step of the synthesis is the coupling of the diterpene part with the lithiated arene unit **84** prepared independently (Schemes 15 and 16). Subersic acid (**92**) was isolated from the sponge Suberea sp. by Crews and co-workers.[48] This natural product is an inhibitor of human 15-lipoxygenase, a property that motivated research to discover new marine sponge-derived bioactive compounds.

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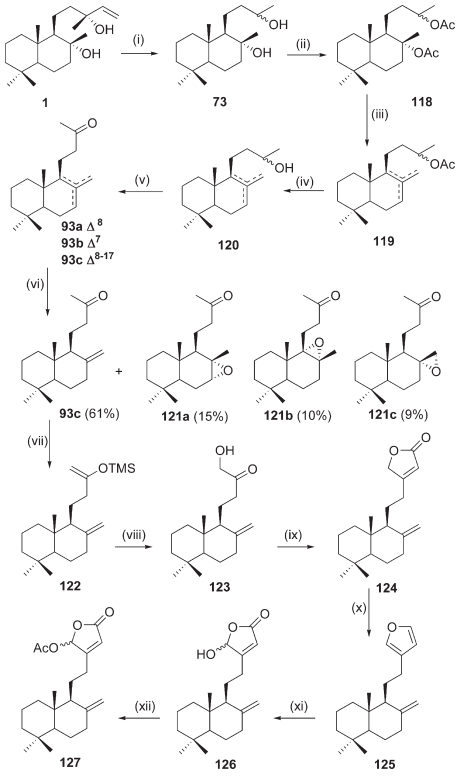
Scheme 21. Synthesis of (+)-Lagerstronolide (127) from Sclareol (1)[a]



[a] (i) $KMnO_4$, acetone, $MgSO_4$, room temperature, 6 h. (ii) AcCl, *N*,*N*-dimethylaniline, DCM. (iii) SiO_2, 100 °C, 90%. (iv) K_2CO_3/MeOH 3%, 90%. (v) TPAP, NMO, DCM, molecular sieves 3 Å, 100 °C. (vi) *m*-CPBA, DCM. (vii) LDA, TMSCl, THF, −78 °C, 100%. (viii) *m*-CPBA, DCM, 90%. (ix) $PH_3{=}P{=}C{=}C{=}O$, benzene, 90 °C, 60%. (x) DIBAL-H, DCM, −78 °C and then SiO_2, 70%. (xi) $^1O_2$, Rose Bengal, DCM, −78 °C, 86%. (xii) Ac_2O, pyridine, 92%.

In the same year, Douglas Rivett and collaborators described an elegant process for the stereoselective synthesis of *E*-rhinocerotinoic acid (**96**) from (−)-sclareol (**1**) in an overall yield of 32% (Scheme 17).[49] Rhinocerotinoic acid was originally obtained by Dekker et al.[50] from the plant *Elytropappus rhinocerotis* and was shown to have anti-inflammatory properties. Rivett's synthesis constitutes a significant improvement over a previous route to this anti-inflammatory compound.

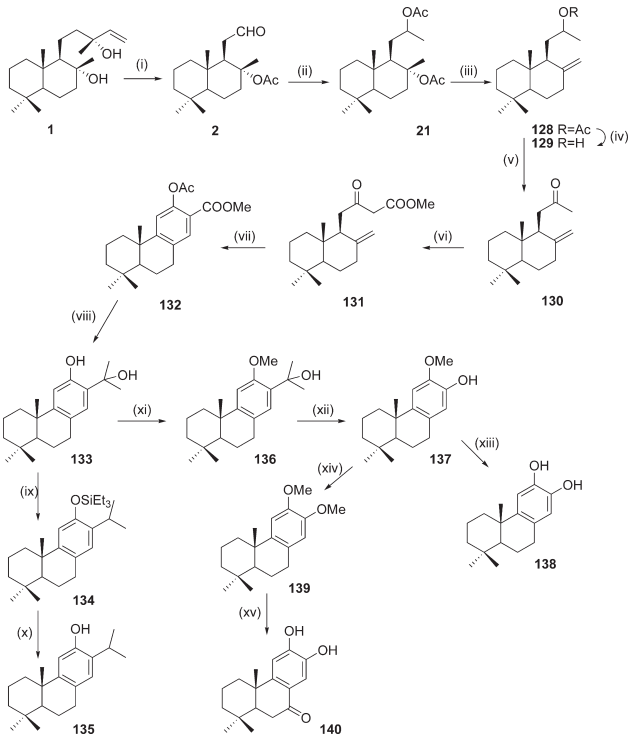
In 2005, Alvarez-Manzaneda et al. described for the first time the enantiospecific synthesis of the antitumor and antimalarial marine sponge metabolite (−)-15-oxopuupehenol (**110**) from (−)-sclareol (**1**) (Scheme 18).[51]

The synthetic process reported involved a new route toward puupehenone-related bioactive metabolites, based on palladium-(II)-mediated diastereoselective cyclization of a drimenylphenol. In addition, a new synthon, **103a**, was prepared from 3,4-bis(benzyloxy)phenol in two steps and 83% overall yield (Scheme 18).

In the same year, the research group of Alvarez-Manzaneda described the first synthesis of the marine *nor*-sesquiterpenes (+)-austrodoral (**115**) and (+)-austrodoric acid (**113**) from (−)-sclareol (**1**).[52]

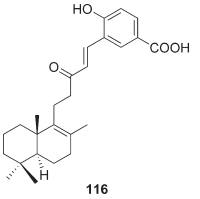
The synthesis of these natural products begins with the transformation of sclareol into 9,11-drimen-8α-ol (**98**). Subsequent conversion of **98** into (+)-austrodoral (**115**) and (+)-austrodoric acid (**113**) via triol **111** was then achived (Scheme 19). Alvarez-Manzaneda and co-workers assumed that the short synthetic procedure, involving high-yield steps and stereoselective processes, made it possible to prepare large amounts of **115** and thus elaborate bicyclic chiral synthons to gain access to other interesting metabolites.

Scheme 22. Synthesis of the Antitumor Derivatives (+)-7-Deoxynimbidiol (138), (+)-Nimbidiol (140), and Terpenoid 135 from Sclareol (1)[a]



[a] (i) OsO_4, 0.2%, $NaIO_4$, *t*-BuOH, 45 °C, 3 h. (ii) (a) MeMgBr, Et_2O, 0 °C, 30 min, 92%; (b) AcCl, dimethylaniline, room temperature, 14 h, 92%. (iii) Collidine, reflux, 15 h, 94%. (iv) KOH, MeOH, room temperature, 1 h, 98%. (v) Jones, acetone, 0 °C, 15 min, 90%. (vi) $(MeO)_2CO$, NaH, benzene, reflux, 4 h, 87%. (vii) $Mn(OAc)_3{\cdot}2H_2O$ (4 equiv), LiCl (3 equiv), Ac_2O, 120 °C, 75%. (viii) MeMgBr exc., Et_2O, 0 °C, 15 min, HCl (dil.), 89%. (ix) Et_3SiH, CF_3COOH, DCM, −40 °C, 30 min, 91%. (x) TBAF, THF, room temperature, 15 min, 97%. (xi) MeI, K_2CO_3, reflux, 12 h, 93%. (xii) H_2O_2 (30%), $BF_3{\cdot}OEt_2$, DCM, 0 °C to room temperature, 3 h, 84%. (xiii) BBr_3, DCM, 0 °C, 1 h, 93%. (xiv) MeI, K_2CO_3, acetone, reflux, 18 h, 90%. (xv) PCC, BBr_3, Ac_2O, 55% (overall).

In 2006, Fekih and colleagues reported a straightforward route to various analogues of (+)-subersic acid (**116**) from (−)-sclareol (**1**) (see Scheme 20).[53]



The synthesis started with classical oxidative degradation of (−)-sclareol (**1**) using 3.9 equiv of potassium permanganate to yield a (9:1) mixture of 8α-hydroxy-14,15-bisnorlabdan-13-one

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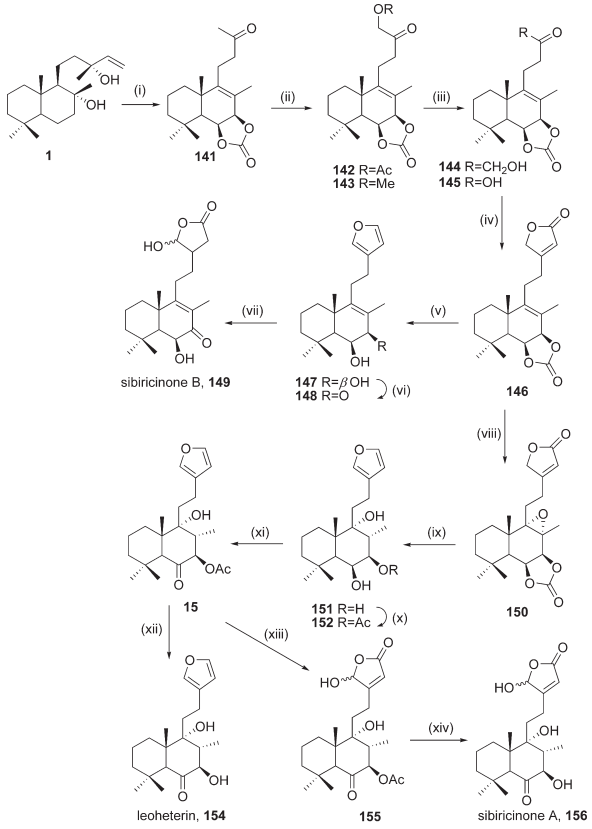
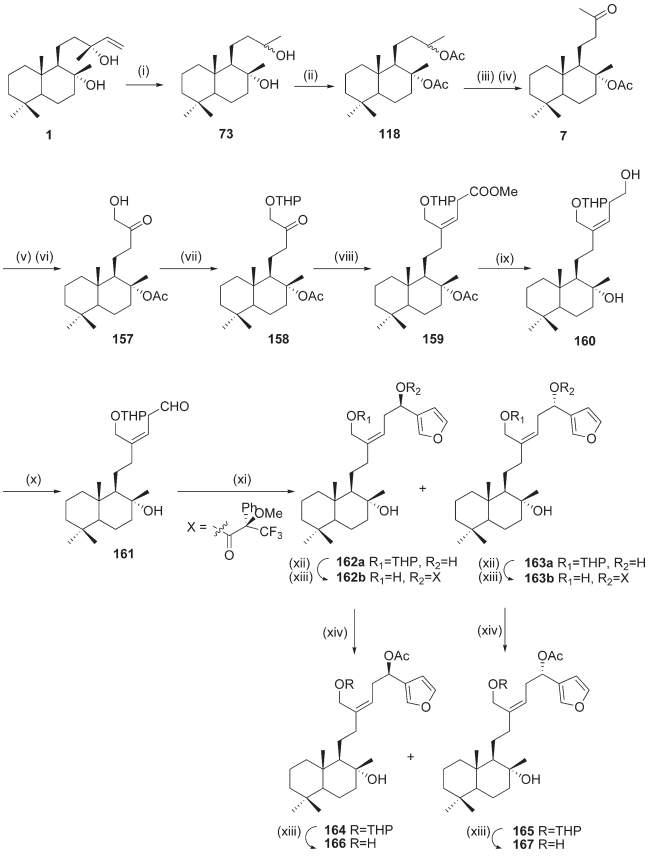
Scheme 23. Synthesis of the Labdemolides, Sibiricinone A (156) and Sibiricinone B (149), and the Furo-Labdane Leoheterin (154) from Ketone 141[a]



[a] (i) Reference 61. (ii) $Pb(OAc)_4$, $BF_3 \cdot Et_2O$, MeOH, C_6H_6, room temperature, 50 min (**142**, 60%; **143**, 21%). (iii) K_2CO_3, MeOH, room temperature, 20 min (**144**, 81%; **145**, 13% from **142**). (iv) $Ph_3P{=}C{=}C{=}O$, C_6H_6, 85 °C, 40 min (84% from **144**). (v) (a) DIBAL-H, DCM, −78 °C, 30 min; (b) LAH, Et_2O, room temperature, 1 h, 91%. (vi) MnO_2, DCM, room temperature, 2.5 h, 89%. (vii) $^1O_2$, Rose Bengal, DIPEA, DCM, −78 °C, 2.5 h, 85%. (viii) *m*-CPBA, DCM, room temperature, 40 h, 98%. (ix) (a) DIBAL-H, DCM, −78 °C, 30 min; (b) LAH, THF, 50 °C, 24 h, 70%. (x) Ac_2O, Py, room temperature, 18 h, 98%. (xi) TPAP, NMO, sieves, DCM, room temperature, 3 h, 86%. (xii) K_2CO_3, MeOH, room temperature, 50 min, 99%. (xiii) $^1O_2$, Rose Bengal, DIPEA, DCM, −78 °C, 5 h, 92%. (xiv) K_2CO_3, MeOH, room temperature, 1 h, 97%.

Scheme 24. Synthetic Approach to Derivatives 166 and 167 from Sclareol (1)[a]



[a] (i) $KMnO_4$, acetone, $MgSO_4$, room temperature, 6 h. (ii) AcCl, *N*,*N*-dimethylaniline, DCM. (iii) K_2CO_3, MeOH 3%, 6 h. (iv) TPAP, NMO, DCM, 6 h, 100%. (v) LDA, TMSCl, THF, −78 °C, 3 h. (vi) OsO_4, NMO, *t*-BuOH/THF/H_2O, 24 h, 95%. (vii) DHP, *p*-TsOH, benzene, 30 min, 100%. (viii) (2-Carboxyethyl)triphenylphosphonium bromide, *n*-BuLi, THF/DMSO, −5 °C, then MeI, 70%. (ix) LAH, Et_2O, 0 °C, 97%. (x) Dess−Martin periodinane, DCM, 100%. (xi) 3-Bromofuran, *n*-BuLi, Et_2O, −78 °C. (xii) (+)-MTPA, DMAP, DCC, DCM. (xiii) Cat. *p*-TsOH/MeOH. (xiv) Ac_2O, pyr.

72 and 8α,13-epoxy-14,15-bisnorlabd-12-ene **8** in 80% yield. Subsequently, by using the optimized iodine catalyzed dehydration procedure, the mixture of compounds **72** and **8** was converted in good yield (70%) into the Δ^8-unsaturated ketone **93a**. The reaction of **93a** with aromatic aldehydes using Claisen-Schmidt condensation gave different analogues of (+)-subersic acid (see structures **117a**−**f**, Scheme 20).

In 2007, Pilar Basabe and co-workers reported the synthesis of γ-acetoxybutenolide (+)-lagerstronolide (**127**) from (−)-sclareol, in an overall yield of 10% (Scheme 21).[54] (+)-Lagerstronolide is a molecule isolated from the plant *Lagerstreomia lancasteri*, which contains a unit of γ-hydroxybutenolide.[55,56] This functional group is present in diverse derivatives with important biologic activities, such as luffolide (anti-inflammatory activity),[57] dysidiolide (which is an inhibitor of the cdc25A protein phosphatase),[58] and its analogues (which have antitumor properties).[59] Although the route to **127** involves 12 reaction steps, as shown in Scheme 21, it is very elegant.

In the same year, Alvarez-Manzaneda and co-workers described a very interesting strategy toward abietane and podocarpane-type diterpenes. Podocarpane diterpenes are interesting metabolites from a biosynthetic point-of-view, as they do not occur extensively in nature. By using a new strategy, the synthesis of the antitumor (+)-7-deoxynimbidiol (**138**), (+)-nimbidiol (**140**), and natural terpenoid **135** was achieved from (−)-sclareol (see Scheme 22).[60]

In 2008, Marcos and collaborators synthesized two labdemolides, sibiricinone A (**156**) and sibiricinone B (**149**), and the furo-labdane leoheterin (**154**) from (−)-sclareol (**1**). The strategy was previously developed in Marcos' laboratory for the synthesis of α-*cis*, β-*cis*, or *trans* labdane-ring B diols.[61] In this manner, ketone **141** was produced,[61] which is the key intermediate in the synthesis of diterpenes **149**, **154**, and **156** (Scheme 23).[62]

Sibiricinone A (**156**) and sibiricinone B (**149**) are two labdanes isolated from *Leonorus sibericus* L., which is commonly referred to

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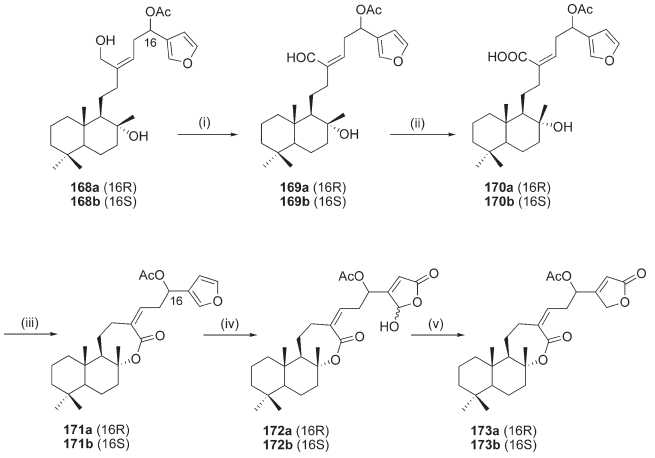
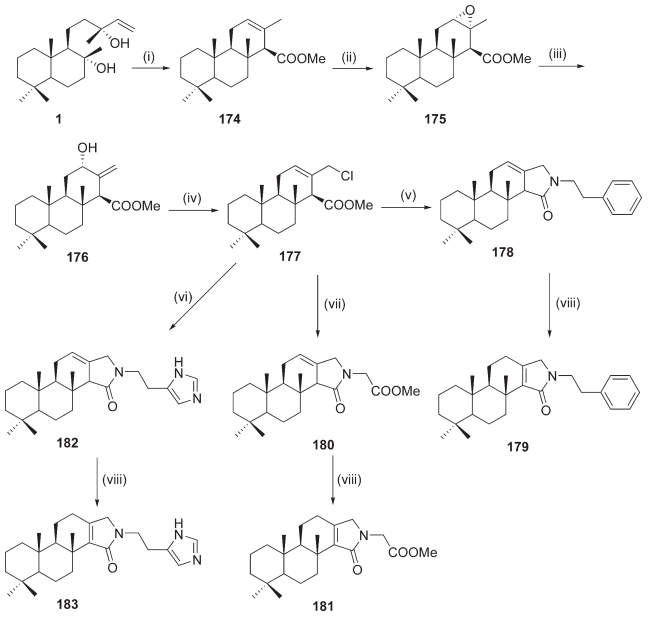
Scheme 25. Synthesis of (+)-Luffalactone (173a) and 16-*epi*-Luffalactone (173b)[a]



[a] (i) Dess−Martin periodinane, DCM. (ii) $NaClO_2$ 5%, *t*-BuOH, NaH_2PO_4, 2-methyl-2-butene. (iii) 2,4,6-Trichlorobenzoylchloride, Et_3N, toluene, then DMAP. (iv) O_2, Rose Bengal, *hν*, DCM. (v) $NaBH_4$, EtOH.

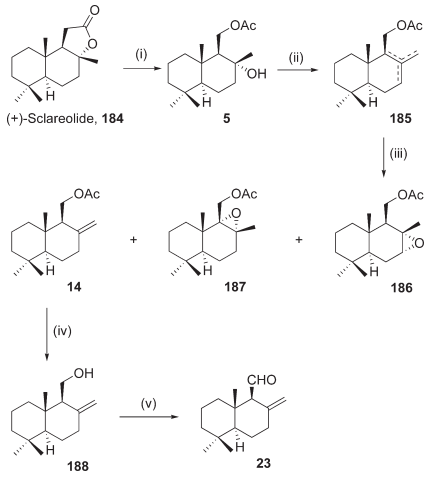
Scheme 26. Synthetic Approach to Nitrogenated Spongianes 179, 181, and 183 from Sclareol (1)[a]



[a] (i) Reference 75. (ii) *m*-CPBA, DCM, 0 °C, 2 h, 78%. (iii) $(i\text{-PrO})_3Al$, toluene, 110 °C, 12 h, 86%. (iv) $SOCl_2$, benzene, 0 °C, 15 min, 52%. (v) B-phenylethylamine, NaCN, 45 °C, 24 h, 81%. (vi) Histamine, MeOH, 80 °C, 24 h, 42%. (vii) Glycine methyl ester hydrochloride, MeOH, Et_3N, 80 °C, 24 h, 38%. (viii) 10% KOH/MeOH, room temperature, 82% **179**, 91% **183**, 93% **181**.

as "mother-wort" in the West Indies, where it is used as a cough syrup and antipyretic for the treatment of malaria. The juice of the fresh plant is used to treat hemoptysis, edema, gout, and arthritis.[63] Leoheterin (**154**) is a furo-labdane isolated from *Leonorus heterophyllus*.[64] Such compounds are very abundant in plants of this genus.[65]

Scheme 27. Synthesis of Aldehyde 23 from Sclareolide (184)[a]



[a] (i) (a) MeLi, Et_2O, room temperature; (b) H_2O_2 50%, $(CF_3CO)_2O$, $NaHCO_3$/DCM, 75%. (ii) 2.5 equiv of $SOCl_2$, 1 equiv of 4-DMAP, pryidine, −30 to 0 °C, 1 h. (iii) 0.375 equiv of *m*-CPBA, DCM−5% aq $NaHCO_3$ (1:1), 0 °C, 1 h (60% for two steps). (iv) 3 equiv of KOH, MeOH, room temperature, 1 h, 100%. (v) 2 equiv of PDC, DCM, 0 °C to room temperature, 4 h, 84%.

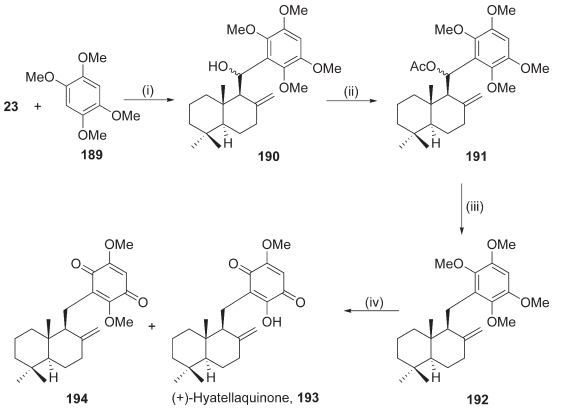
Recently, Pilar Basabe and co-workers described the first synthesis of the marine metabolite (+)-luffalactone (**173a**) and its epimer 16-*epi*-luffalactone (**173b**), starting from sclareol (**1**).[66] Their first synthetic approach involves production of intermediates **166** and **167** in a complex sequence of 15 steps (see Scheme 24). With **166** and **167** in hand, five more steps were needed to reach the target molecules **173a** and **173b** (Scheme 25). Oxidation of **166** and **167** to the corresponding acids required two steps. Lactonization of **170a** and **170b** was achieved by exposure to 2,4,6-trichlorobenzoyl chloride and Et_3N in toluene, and then with DMAP, giving lactones **171a** and **171b** in 88% and 78% yield, respectively. Conversion of the furan ring into the γ-hydroxybutenolide was carried out using Faulkner's method. Thus, photosensitized oxygenation of **171a** and **171b** in the presence of Hünig's base gave the hydroxybutenolides **172a** (69%) and **172b** (79%). Ultimately, the authors transformed the γ-hydroxybutenolide into γ-butenolides by reduction with $NaBH_4$.

In 2010, the same authors described an expeditious synthesis of three nitrogenated spongianes starting from sclareol (**1**).[67] Spongianes are a group of tetracyclic diterpenes isolated from marine organisms,[68−71] some of which display an interesting range of biological activities.[72−75] Specifically, the authors presented the synthesis of 4-methyldecarboxyhaumanamide (**179**) and 4-methyldecarboxy-spongolactams A (**183**) and C (**181**) (Scheme 26).[67] The synthetic route offers an alternative means to introduce a nitrogen heteroatom into a carbon framework, involving condensation of the allylic halide/ester with an amine, followed by isomerization of the olefin. The key intermediate in the synthesis of spongianes is the halogenated compound (**177**) (Scheme 26).

2.2. Sclareolide

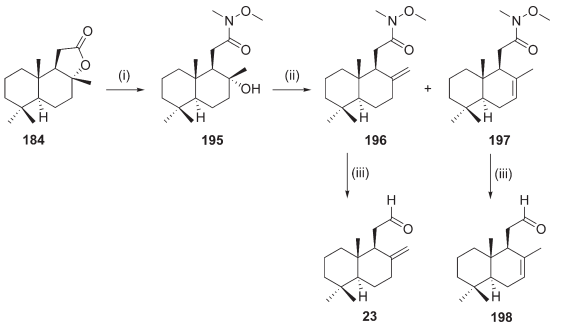
Sclareolide (**184**) is mainly used in the synthesis of the commercially important perfume component Ambrox.[76−78] Apart from this application, sclareolide has also been found to be a useful supplement for weight loss.[79] It was shown to help maintain or build lean body mass.[80]

Scheme 28. Synthesis of (+)-Hyatellaquinone (193) from Aldeyde 23[a]



[a] (i) 3 equiv of **189**, 2.5 equiv of BuLi, THF, 0 °C, 30 min, then 1 equiv of **23**, THF, room temperature, 30 min, 74%. (ii) Ac_2O, cat. 4-DMAP, pryidine, room temperature, 24 h. (iii) 10 equiv of Li, liqud NH_3, THF, −78 °C, 15 min, 93% (for two steps). (iv) 2.5 equiv of CAN, CH_3CN-H_2O, 0 °C to room temperature, 4 h, 58% for **193**.

Scheme 29. Synthesis of γ-Bicyclohomofarnesal (23) and Its *endo*-Isomer (198) from Sclareolide (184)[a]



[a] (i) MeONHMe, Me_3Al, DCM, 0 °C to room temperature, 88%. (ii) $SOCl_2$/py, 0 °C, 60% for **196**, 32% for **197**. (iii) $LiAlH_4$/THF, H_2O, 89% for **23**, 91% for **198**.

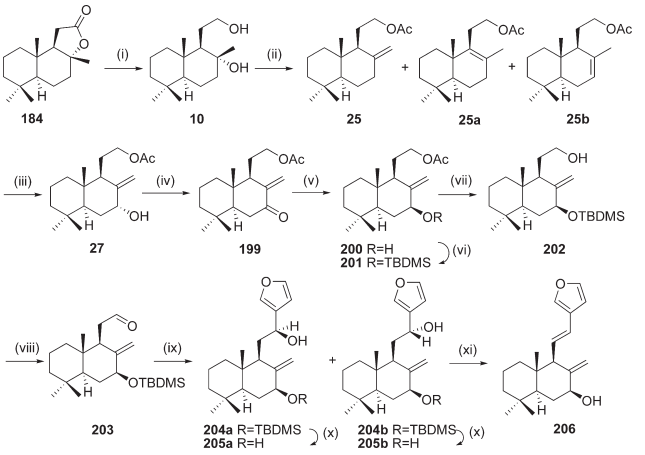
Like (−)-sclareol, sclareolide is a commercially available compound obtained from *Salvia sclarea*, although in much smaller amounts than sclareol. Alternatively, sclareolide is produced by semisynthesis from sclareol.

In the past decade, many important new methods for the chemical manipulation of sclareolide have been reported in the literature.

Thus, in 1999, Mohammad Samadi and collegues described the synthesis of (+)-hyatellaquinone (**193**) from (+)-sclareolide (**184**).[81,82] The strategy adopted by the authors was divided in two synthetic sequences: first, production of aldehyde **23** from (+)-sclareolide (Scheme 27); and, second, coupling of aldehyde **23** with the lithium anion of 1,2,4,5-tetramethoxybenzene (**189**) as precursor of the quinone moiety (Scheme 28).

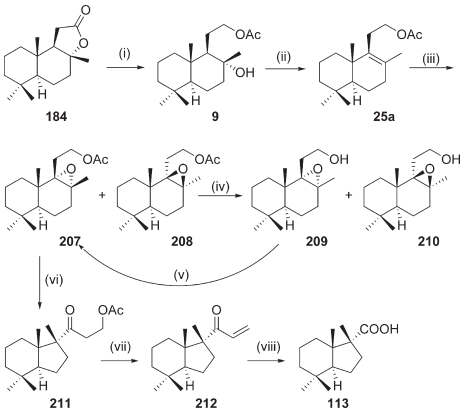
In 2002, Maria de la Torre and co-workers described a very simple route for converting sclareolide (**184**) to γ-bicyclohomofarnesal (**23**) and its *endo*-isomer (**198**) (Scheme 29).[83] γ-Bicyclohomofarnesal (Ambral, **23**) is a strong ambergris odorant with fine tonality and a versatile synthetic intermediate.[84] For instance, this aldehyde is a key intermediate in the preparation

Scheme 30. Synthesis of Coronarin A (206) from Sclareolide (184)[a]



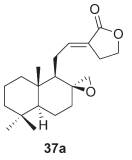
[a] (i) LAH, THF, reflux, 5 h, 97%. (ii) Ac_2O, collidine, reflux, 16 h, 85%. (iii) SeO_2, *t*-BuOOH, methylene chloride, room temperature, 2 h, 45%. (iv) PCC, methylene chloride, room temperature, 3 h, 75%. (v) $NaBH_4$, MeOH, room temperature, 1 h, 98%. (vi) TBDMSCl, $AgNO_3$, DMF, room temperature, 1 h, 89%. (vii) Na_2CO_3, MeOH, room temperature, 2 h, 92%. (viii) PCC, methylene chloride, room temperature, 3 h, 98%. (ix) 3-Bromofuran, *n*-BuLi, THF, −78 °C to room temperature, 72%, **204a**:**204b** = 3:1. (x) $CuCl_2 \cdot 2H_2O$ (5 mmol %), acetone/H_2O (95:5), reflux, 90%. (xi) 2,6-Lutidine, MsCl, MC, room temperature, 24 h and then gently warming to evaporate solvent, 68%.

Scheme 31. Synthesis of Austrodoric Acid (113) from Sclareolide (184)[a]



[a] (i) Reference 84. (ii) I_2/C_6H_6, reflux, 90%. (iii) *m*-CPBA, 0 °C, 90%. (iv) K_2CO_3/MeOH, room temperature, 2 h, 89%. (v) Ac_2O/Py, room temperature, 97%. (vi) Tris-(*p*-bromo-phenyl)-aminium cation/$SbCl_6$, room temperature, 45%. (vii) NaH, THF, 52%. (viii) OsO_4, $NaIO_4$, 70%.

of (−)-Ambrox and others terpene derivatives such as (+)-galanolactone **37a**.[85]



Compounds **23** and **198** were prepared in 47% and 26% overall yield, respectively, by a three-step sequence. The synthetic

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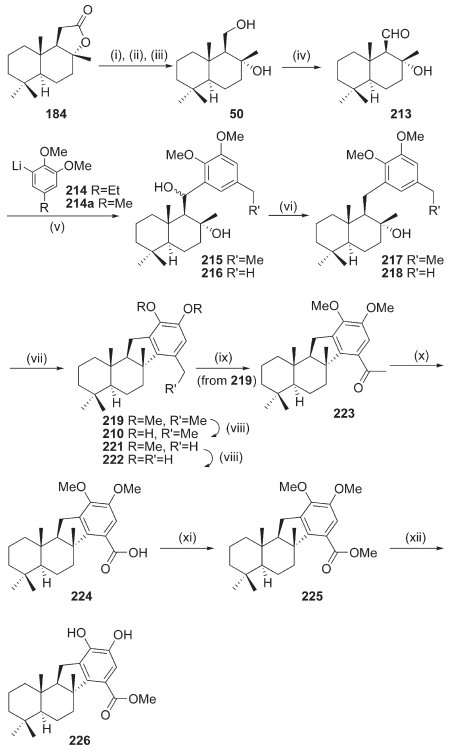
Scheme 32. Synthesis of Pelorol (226) from Sclareolide (184)[a]



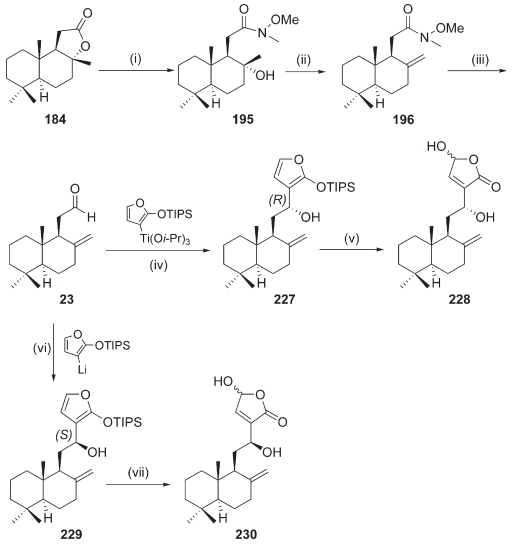
[a] (i) MeLi, Et_2O, room temperature. (ii) $(CF_3CO)_2O$, H_2O_2, $NaHCO_3$, DCM, room temperature. (iii) KOH, MeOH, room temperature. (iv) $(COCl)_2$, DMSO, TEA, −78 °C to room temperature, 20 min. (v) THF, −78 °C. (vi) H_2, Pd/C, EtOAc, room temperature. (vii) $SnCl_4$, DCM, −20 °C. (viii) **219** to **220**, BBr_3, room temperature; **221** to **222**, BBr_3, room temperature. (ix) PCC, 40 °C, 20 h, 53%. (x) Br_2, NaOH, 40 °C. (xi) MeI, K_2CO_3, DMF, room temperature. (xii) BI_3, DCM, −78 °C, 30 min.

procedure described involves the preparation of Weinreb's amide **195**, dehydration of the tertiary alcohol to form compounds **196** and **197**, and reduction with $LiAlH_4$ (see Scheme 29). It should be mentioned, however, that the regioselectivity of dehydration is modest (ca. 2:1 in favor of **196**), thereby compromising the overall efficiency of this route.

In 2003, Seokjoon Lee and co-workers reported the synthesis of coronarin A (**206**) from (+)-sclareolide (**184**) (Scheme 30).[86] Coronarin A (**206**) is a furanolabdane diterpenoid, which can be isolated from rhizomes of the Brazilian antirheumatic medicinal plant, *Hedychium coronarium* (Zingiberaceae).[9] This compound exhibts a significant cytotoxic effect against V-79 cells and sarcoma 180 ascites in mice.[37]

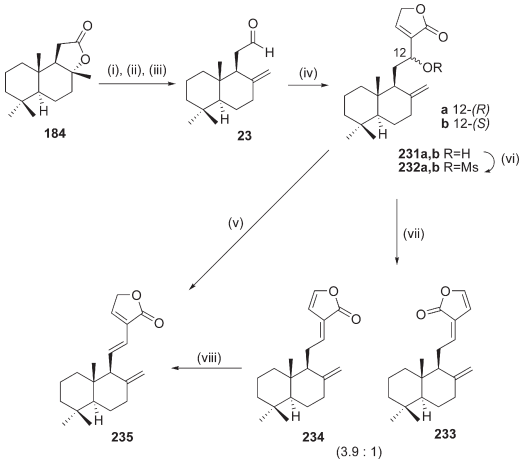
One year later, Gavagnin and colleagues described the synthesis of the *nor*-sesquiterpene austrodoric acid (**113**) from (+)-sclareolide (**184**).[87] The synthetic procedure developed for the preparation of this marine natural product is presented in Scheme 31. Austrodoric acid **113** was recently isolated from the skin extract of Antarctic dorid nudibranch *Austrodoris kerguelenensis*.[88] Extraordinarily, this compound possesses a bicyclic structure with a unique carbon backbone, which could biogenetically arise from a drimanic-like framework by a ring contraction process. In the strategy developed by the authors to synthesize **113**, the key step was ring contraction of the homodrimanic epoxide **207** followed

Scheme 33. Synthesis of (+)-Zerumin B (230) from Sclareolide (184)[a]



[a] (i) MeNHOMe·HCl, Me_3Al, 87%. (ii) $SOCl_2$, py, DCM, −78 °C, 88%. (iii) DIBAL-H, −78 °C, 93%. (iv) Et_2O, −110 °C, 72%. (v) Dimethyldioxirane, H_3O^+, 94%. (vi) THF, −78 °C, 65%. (vii) Dimethyldioxirane, H_3O^+, 93%.

Scheme 34. Synthesis of Villosin (235) from Sclareolide (184)[a]



[a] (i) MeNHOMe·HCl, Me_3Al, 87%. (ii) $SOCl_2$, py, DCM, −78 °C, 88%. (iii) DIBAL-H, −78 °C, 93% (see Scheme 33). (iv) 2-(5*H*)Furanone, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, then **23**, −78 °C, 2 h, 95%. (v) Al_2O_3 (1.5 equiv), pyridine, reflux, 8 h, 89%. (vi) MsCl (4 equiv), Et_3N or *i*-Pr_2NEt (4 equiv), CH_2Cl_2, −78 to 0 °C, 1 h. (vii) *i*-Pr_2NEt (5 equiv), CH_2Cl_2, room temperature, 2 h, 63% for **234**, ca. 8% for **235** (two steps). (viii) DBU (ca. 2 equiv), CH_2Cl_2, room temperature, 15−20 min, 90%.

by cleavage of the side chain. Derivative **207** was obtained from (+)-sclareolide (**184**) via acetate **9**.[89]

In 2005, Andersen and co-workers developed a new strategy to synthesize the meroterpenoid pelorol (**226**, Scheme 32), an activator of the inositol-5-phosphatase SHIP.[90] Pelorol had been isolated before from the sponge *Dactylospongia elegans* in Andersen's laboratory, but the characterization of this compound was not

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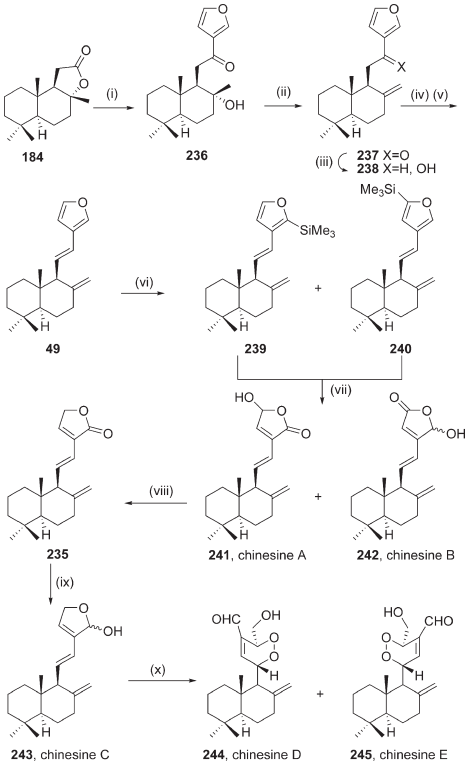
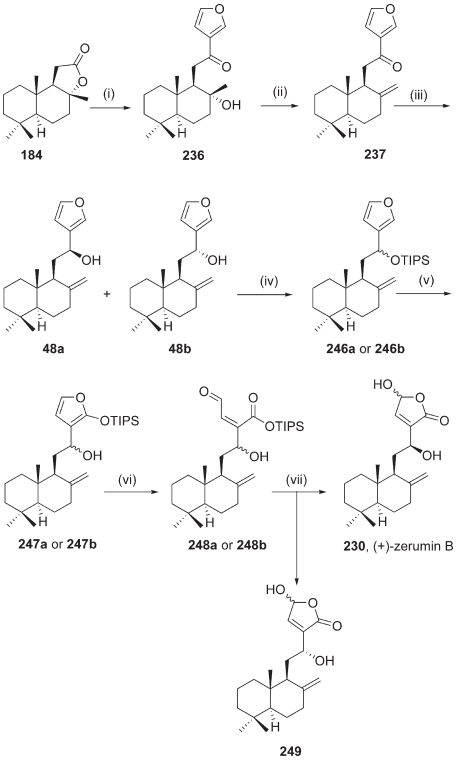
Scheme 35. Synthesis of Coronarin E (49) and Chinesines A−E from Sclareolide (184)[a]



[a] (i) 3-Bromofuran, *n*-BuLi, 85%. (ii) Pyridine, $SOCl_2$, 95%. (iii) $LiAlH_4$, 97%. (iv) PPh_3, Br_2, Et_3N. (v) DBU, 57% (over steps iv and v). (vi) *n*-BuLi, Me_3SiCl. (vii) O_2, methylene blue, *hν*. (viii) $NaBH_4$, 92%. (ix) DIBAL-H, 96%. (x) O_2, methylene blue, *hν*, 60%.

Scheme 36. Novel Synthesis of (+)-Zerumin B (230) from Sclareolide (184)[a]



[a] (i) 3-Bromofuran, *n*-BuLi, 85%. (ii) Pyridine, $SOCl_2$, 95%. (iii) $LiAlH_4$, 97%. (iv) 2,6-Lutidine, TIPSOTf, 91% for **246a**, 90% for **246b**. (v) *n*-BuLi, HMPA, 90% for **247a**, 91% for **247b**. (vi) O_2, methylene blue, *hν*. (vii) H_2O, silica gel.

complete at that time. The authors reported that the reduced quantity of pelorol (**226**) available from the sponge *D. elegans* was inadequate to support detailed in vitro and in vivo evaluation of its ability to activate SHIP. To satisfy the need for additional material, confirm the absolute configuration of the natural product, and generate analogues for SAR, the synthesis of pelorol (**226**) from (+)-sclareolide (**184**) was undertaken.[90]

One year later, Boukouvalas and co-workers described the development of important new methodology in the context of the first synthesis of the antitumor diterpenoid (+)-zerumin B (**230**, Scheme 33).[91] (+)-Zerumin B is a bioactive diterpenoid isolated in 1996 from the Chinese medicinal plant *Alpinia zerumbet*[39] and more recently from *Curcuma mangga*, a popular vegetable that is also used in Asian folk medicine for alleviating stomach ache, chest pain, and fever, and in postpartum care to aid womb healing.[92] By using a substantially improved modification[91] of the de la Torre method,[83] aldehyde **23** was prepared from sclareolide (**184**) via highly regioselective dehydration of alcohol **195** to **196**, and Weinreb's amide reduction using DIBAL-H (see Scheme 33). Reaction of 3-lithio-2-triisopropylsilyloxyfuran with **23** (THF, −78 °C) provided the separable C12 (*R*) and (*S*) epimers **227** and **229** in a modest 2.2:1 ratio. Importantly, however, when the authors performed the reaction at −110 °C in diethyl ether, by using a organotitanium reagent (see Scheme 33), a significant improved diastereoselectivity in the opposite direction (1:6.4) was achieved, delivering the C12-(*R*)-isomer (**227**) in 72% yield after chromatography. Reaction of the individual isomers **227** and **229** to dimethyldioxirane in acetone and subsequent quenching with Amberlyst-15/aq acetone led exclusively to the corresponding γ-hydroxybutenolides **228** and **230**.

In 2007, the Boukouvalas group reported a new strategy that enables a short, highly regio- and stereoselective synthesis of villosin (**235**) form sclareolide (**184**) (see Scheme 34).[93] Villosin is a labdane diterpenoid originally obtained from *Hedychium coronarium* (Zingiberaceae),[94] a medicinal plant used in many countries for treating diseases such as headache, fever, and rheumatism.[95] Subsequently, this compound was isolated from the related herbs *Hedychium villosum* (hence the name villosin)[96] and *Hedychium forrestii*.[97] Recently, it was found that villosin exhibits potent cytotoxic activity against human small cell lung cancer cells (NCI-H187) with exceptionally high selectivity.[98] The Boukouvalas synthesis of villosin demonstrates a new and efficient pathway to (*E*)-3-(1-alkenyl)-2(5*H*)-furanones from aldehydes.[93] In addition, the villosin isomer (*E*)-labda-8(17), 12,14-trien-15(16)-olide (**234**) was synthesized for the first time, en route to villosin.[93] Note that the Boukouvalas modification[91] of the de la Torre route[83] has now become the method of choice for making aldehyde **23** from sclareolide.[99]

In the same year, Margaros and Vassilikogiannakis described a new strategy to synthesize coronarin E (**49**) and chinesines A−E (**242**, **242**, **243**−**245**), starting from (+)-sclareolide (**184**) (Scheme 35).[100] Through the synthetic procedure, derivative **184** was converted into coronarin E (**49**) in five steps. First, 3-lithiofuran, obtained from 3-bromofuran upon treatment with *n*-BuLi, was used to open sclareolide lactone moiety giving

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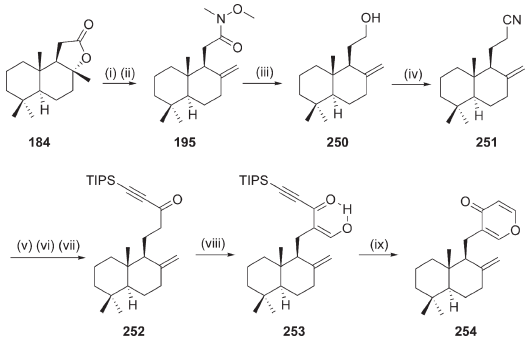
Scheme 37. Synthesis of Ottensinin (254) from Sclareolide (184)[a]



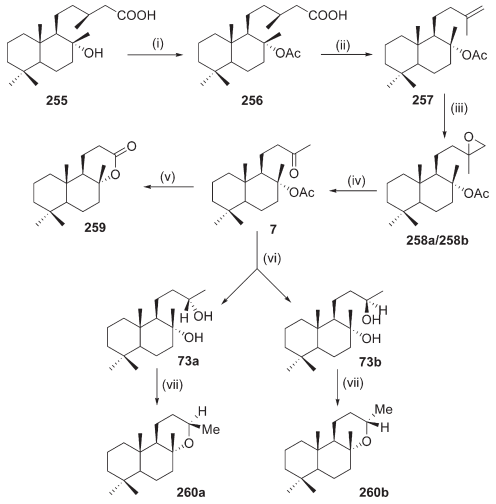
[a] (i) MeNHOMe·HCl, Me_3Al, 87%. (ii) $SOCl_2$, py, DCM, −78 °C, 88%. (iii) LiH_2NBH_3, THF, 0 °C to room temperature, 83%. (iv) 2-Hydroxy-2-methylpropanenitrile, DEAD, Ph_3P, 0 °C to room temperature, 85%. (v) DIBAL-H, PhMe, −78 °C, 93%. (vi) TIPSCCLi, THF, −78 to 0 °C, 94%. (vii) PCC, SiO_2, DCM, 96%. (viii) LHMDS, Et_2O, −78 to 0 °C, then TFEF (2,2,2-trifluoroethyl formate), −78 °C, 96%. (ix) CsF, TBAF, THF, reflux, 62%.

hydroxyketone (**236**). Next, compound **236** was dehydrated by using a combination of $SOCl_2$ and pyridine to form derivative **237** with the exocyclic double bond. Subsequently, furylic ketone **237** was reduced to the diastereomeric mixture of alcohols **238** with $LiAlH_4$. Finally, the alcohols were converted into the corresponding bromides followed by elimination under basic conditions, affording coronarin E (**49**) in 57% yield. This molecule was then used to produce chinesines A−E in a process that uses two different types of reaction of singlet oxygen ($^1O_2$) (see Scheme 35).

In 2008, the same authors reported a new synthesis of (+)-zerumin B (**230**) by a short but nonstereoselective route from (+)-sclareolide (**184**) (Scheme 36).[101] As described earlier, the first total synthesis of this interesting bioactive diterpenoid was reported by Boukouvalas and co-workers also starting from compound **184**.[91] Stereoselective addition of a silyloxyfuran reagent to an aldehyde and regiospecific silyloxyfuran oxyfunctionalization lie at the heart of the Boukouvalas synthesis. On the other hand, the key step in the synthetic developed by Margaros and Vassilikogiannakis is the regioselective formation of the α-substituted γ-hydroxy-butenolide moiety of zerumin B. This was achieved by means of a [1,4] O→C triisopropylsilyl migration followed by single oxygen ($^1O_2$) oxidation of the resulting 2-triisopropylsilyl-3-(α-hydroxy)-alkylfuran (Scheme 36).

First, a new protocol was developed for the conversion of (+)-sclareolide (**184**) into furan **48a,b** in just three high-yielding steps. Next, with the diastomeric alcohols **48a** and **48b** in hand, the authors proceeded to the silylation of the hydroxyl group under standard conditions (2,6-lutidine, TIPSOTf) to provide triisopropylsilyl ethers **246a** and **246b** in 91% and 90% yield, respectively. Treatment of derivatives **246a** or **246b** with *n*-BuLi in the presence of HMPA (hexamethylphosphoramide) cleanly transformed them to the corresponding 2-triisopropylsilyl-3-(α-hydroxy)alkylfurans **247a** or **247b**. Following irradiation (visible ligth) of a DCM solution of **247a** and **247b**, containing catalytic amounts of methylene blue (10^{-4} M), with O_2 bubbling through it, for 1 min, resulted in the complete consumption of the starting materials to form silyl esters **248a** and **248b**. Finally, hydrolysis of

Scheme 38. Synthesis of Oxides 260a and 260b from Labdanolic Acid (255)[a]



[a] (i) Ac_2O, Et_3N, DMAP, 70%. (ii) LTA, C_6H_6, $Cu(OAc)_2$, 60%. (iii) *m*-CPBA, 90%. (iv) HIO_4, Me_2CO, 93%. (v) Br_2, OH^-, 93%. (vi) LAH, 97%. (vii) MsCl, Py, 65%.

esters in situ yielded the corresponding γ-hydroxybutenolides, (+)-12-*epi*-zerumin B (**249**) and (+)-zerumin B (**230**).

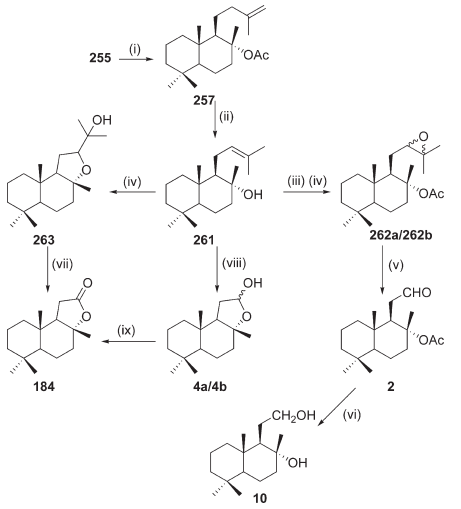
Also in 2008, Boukouvalas and Wang described an innovative strategy for the synthesis of a novel labdane diterpenoid, ottensinin (**254**).[102] The authors deduced the correct structure (**254**) of this natural product by careful analysis of the reported NMR data. Structure **254**, which features an unprecedented rarranged labdane skeleton, was proven by synthesis from sclareolide (nine steps, 27% overall yield) (Scheme 37) and was further confirmed by X-ray diffraction analysis.[102] The synthesis started with a two-step conversion of sclareolide to the Weinreb's amide (**195**). Next, the desired reduction was achieved by recourse to Meyers' in situ generated lithium amidotrihydroborate (LiH_2NBH_3, LAB) to give alcohol **250**. This alcohol was subsequently submitted to the Mitsunobu−Wilk procedure,[103] generating nitrile **251** in good yield. Nitrile **251** was then reduced to the aldehyde, followed by acetylide addition and oxidation of the resulting alcohol epimers to afford compound **252**. After sequential treatment of **252** with LHMDS and 2,2,2-trifluoroethyl formate (TFEF) enol, **253** was generated as a single isomer in nearly quantitative yield. Heating **253** with a mixture of CsF and TBAF in THF accomplished both desilylation and cyclization affording ottensinin (**254**).

2.3. Labdanolic Acid

Labdanolic acid (**255**) is the main component of the acid fraction of *Cistus ladaniferus* obtained from an extract of the plant. *Cistus ladaniferus* (rock rose), called "esteva" in Portugal, is a wild, persistent shrub, which is widespread in many Mediterranean countries, such as Portugal, Spain, France, Greece, and Morocco. From the extract of this plant have been identified **186** compounds, including fragrances such as ambrox and various diterpenes.[104,105] Labdanoic acid[106] (Figure 2) is a major compound, which has been isolated in large amounts (1.1 g of labdanolic acid from 100 g of air-dried twigs, corresponding to less than 10% of the twigs of an average plant) simply by sequential extraction with diethyl ether aqueous base, followed by conventional column chromatography.[107]

dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Scheme 39. Synthesis of Ambroxdiol (10) and 12-*nor*-Ambreinolide (Sclareolide, 184) from Labdanolic Acid (255)[a]



[a] (i) See Scheme 38. (ii) Li, ethylenediamine, 92%. (iii) MeCOCl, *N*,*N*-dimethylaniline, 87%. (iv) *m*-CPBA, 68%. (v) HIO_4, 98%. (vi) LAH, 94%. (vii) Na_2CrO_4, 99%. (viii) O_3, 96%. (ix) Jones reagent, 70%.

In recent years, a significant amount of work on the chemical manipulation of labdanolic acid has been published. This section covers only the most representative transformations of this labdane.

In 1992, Urones and co-workers, following their studies on the transformation of the main components of *Cistus ladaniferus* to obtain derivatives with amber odor, reported the conversion of labdanolic acid into oxides **260a** and **260b** (Scheme 38), ambroxdiol **10**, and sclareolide (**184**) (Scheme 39).[108]

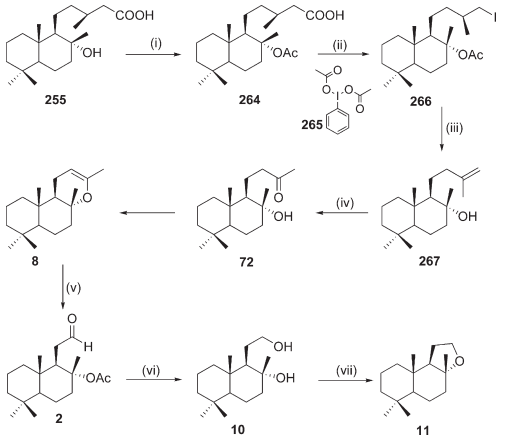
Initially, treatment of labdanolic acid (**255**) with Ac_2O/Et_3N/DMAP at 35−40 °C produced the acetyl derivative (**256**) in 70% yield (Scheme 38). Decarboxylation of **256** with LTA/$(Cu(OAc)_2$ produced the alkene 257 in 60% yield. Upon treatment of **257** with *m*-CPBA, a mixture of epoxides **258a**/**258b** was obtained. This mixture was then treated with periodic acid to give a crystalline product (**7**) with amber odor.

Ketone **7** was the starting material for preparing oxides **260a** and **260b**. Reaction of **7** with Br_2 in basic medium formed lactone **259**, ambreinolide, which is the precursor of the corresponding oxide with amber odor. Alternatively, when **7** was submitted to reduction conditions with lithium aluminum hydride (LAH), a mixture of diols, **73a** and **73b**, separable by column chromatography, was obtained. Cyclization of derivatives **73a** and **73b** led to oxides **260a** and **260b** in reasonable yields (Scheme 38).

The 12-*nor*-ambreinolide **184** and ambroxdiol **10** (Scheme 39) were synthesized from intermediate **261**, which is obtained from **257** after isomerization of the double bond with lithium/ethylenediamine.

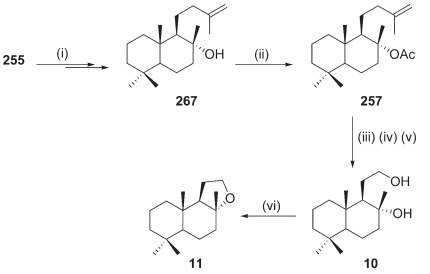
When **261** was subjected to epoxidation with *m*-CPBA, the tetrahydrofuran derivative **263** was obtained. Subsequent oxidation of **263** with Na_2CrO_4 led to 12-*nor*-ambreinolide (sclareolide, **184**) in quantitative yield. At the same time, the authors had developed a novel route to **184** by transformation of derivative **261** to lactols **4a**/**4b** by ozonolysis. Oxidation of the lactols with Jones reagent led to the formation of **184**.

Scheme 40. Synthesis of Ambrox (11) from Labdanolic Acid (255)[a]



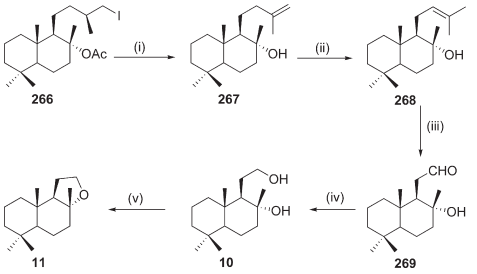
[a] (i) AcCl, *N*,*N*-dimethylaniline. (ii) IBDA (**265**), I_2, CCl_4, $h\nu$, Δ, 76%. (iii) *t*-BuOK, THF, 74%. (iv) O_3, MeOH/DCM (1:5), −78 °C, PPh_3, 44%. (v) O_3, DCM, py, −78 °C. (vi) $LiAlH_4$, THF, 60%. (vii) *p*-TsOH, CH_3NO_2, 87%.

Scheme 41. A Different Approach to the Synthesis of Ambrox (11) from Labdanolic Acid (255) (Based on Scheme 40)[a]



[a] (i) See Scheme 40. (ii) AcCl, *N*,*N*-dimethylaniline, 83%. (iii) O_3, MeOH/DCM (1:5), −78 °C. (iv) Ac_2O, NEt_3, DMAP. (v) $LiAlH_4$, THF, 89%. (vi) *p*-TsOH, CH_3NO_2, 87%.

Scheme 42. Alternative Approach to the Synthesis of Ambrox (11) from Labdanolic Acid (255) (Based on Scheme 40)[a]

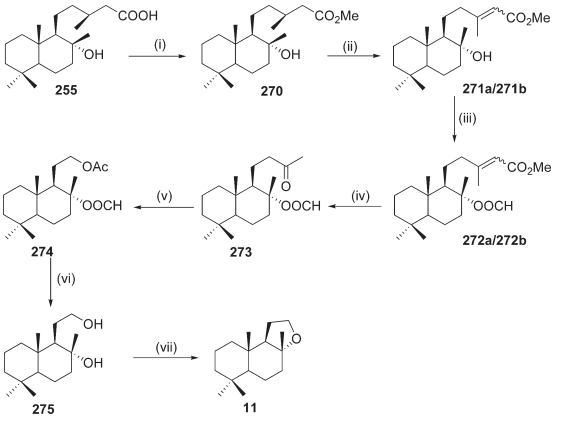


[a] (i) *t*-BuOK, THF, 74%. (ii) Δ, 78%. (iii) O_3, MeOH/DCM (3:1), −78 °C. (iv) $NaBH_4$, 92%. (v) *p*-TsOH, CH_3NO_2, 87%.

In 2001, de Groot and co-workers described three attractive routes to Ambrox (**11**) from labdanolic acid (**255**). In all of these routes, the key step is the iododecarboxylation of labdanolic acid (Schemes 40−42).[109]

dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Scheme 43. Synthetic Approach to Ambrox (11) from Labdanolic Acid (255)[a]



[a] (i) *N*-Methyl-*N*-nitrosotoluene-4-sulfonamide, DOH (2 N, MeOH). (ii) LDA, THF, Ph_2Se_2, −78 °C, H_2O_2, 94%. (iii) HCOOH−Ac_2O, 93%. (iv) $KMnO_4$, $MgSO_4$, acetone, 88%. (v) *m*-CPBA, DCM, 96%. (vi) KOH, MeOH, 59%. (vii) *p*-TsOH, $MeNO_2$, 75%.

Labdanoic acid was obtained from air-dried twigs and leaves of the *Cistus ladaniferus* soaked in *n*-hexane, to give after evaporation of the solvent a sticky labdanum gum. This gum was then purified by extraction of an etheral solution with aq base. Acidification gave crude labdanolic acid (**255**), which was further purified by conversion of the $C_{(8)}$ tertiary hydroxyl group to its acetate **264** (obtained in 35−45% based upon crude acidic material).

Iododecarboxylation of **264** with iodobenzenediacetate (IBDA) and iodine under irradiation with a tungsten lamp delivered iodide **266** in 76% yield (Scheme 40).

Compound **266** was immediately treated with potassium *tert*-butoxide in THF at room temperature to achieve both dehydroiodination and hydrolysis of the acetate group, thereby providing alcohol **267** in 74% yield. Ozonolysis of the double bond of **267** and reduction of the intermediate ozonides gave the methyl ketone **72**, which immediately cyclized into sclareol oxide (**8**). Subsequent ozonolysis of the enol ether moiety and reduction of the aldehyde and acetate groups afforded the diol **10** in 60% overall yield (from **267**). Treatment of **10** with *p*-toluenesulfonic acid in nitromethane gave Ambrox (**11**) in 87% yield.

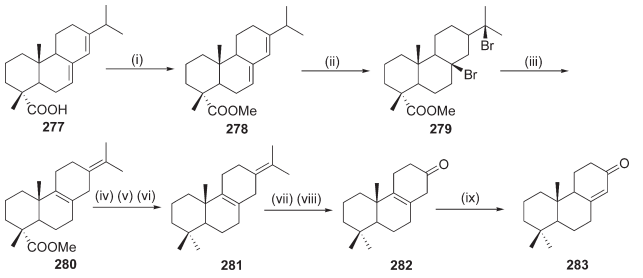
In a second approach, the ozonolysis product of **257** was subjected to Criegee rearrangement. After reduction of the so obtained intermediate with lithium aluminum hydride, compound **10** was obtained in 89% overall yield. This diol was then transformed to Ambrox (**11**) (Scheme 41).

The third route investigated is a modification of the first route (Scheme 40). In the first route, it was shown that treatment of **266** with *t*-BuOK at room temperature afforded compound **267**. When the dehydroiodination was performed using the same base in refluxing THF (or DMSO at room temperature), the intermediate **267** isomerized in situ to **268** (Scheme 42). Ozonolysis of the double bond and reduction of the intermediate ozonides with sodium borohydride ($NaBH_4$) gave diol **10** in 92% overall yield.

In 2002, Altarejos and collegues reported a novel six-step route to Ambrox (**11**) starting also from labdanolic acid (33% overall yield, Scheme 43).[107] This route involves α,β-dehydrogenation of methyl labdanolate (**270**), subsequent oxidative degradation of the side chain, and final stereoselective formation of the tetrahydrofuran ring. Labdanolic acid was obtained from an ethereal extract of wild-grown *Cistus ladaniferus*, harvested on the northwest of Jaén province (Spain). An extract was prepared by simply soaking the plant material in Et_2O for 1 day at room temperature. Pure labdanolic acid was isolated by column chromatography.

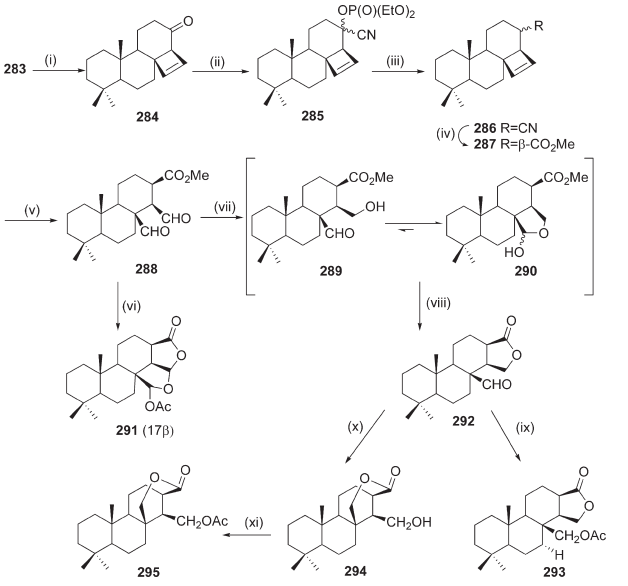
The abundance of *Cistus ladaniferus* (rock rose) in European countries is vital for the regular isolation of labdanolic acid for the purpose of producing valuable molecules.

Scheme 44. Synthesis of Derivative 283 from (−)-Abietic Acid (277)[a]



[a] (i) MeI, K_2CO_3, acetone, reflux, 24 h, 90%. (ii) HBr, AcOH, 42%. (iii) $LiOH·2H_2O$, DMF, 80 °C, 71%. (iv) Sodium bis(2-ethoxymethoxy)aluminium hydride, toluene. (v) TsCl, pyridine. (vi) NaI, Zn, hexamethylphosphoro-triamide, 55% (three steps). (vii) O_3, DCM/EtOAc, 78 °C. (viii) Me_2S, 79% (two steps). (ix) HCl, MeOH, 80%.

Scheme 45. Synthetic Approach to Spongiane Diterpenes 291−293 and 295 from Podocarpenone (283)[a]



[a] (i) C_2H_2, acetone, *hv*. (ii) $(EtO)_2P(O)CN$, Li, THF/DCM. (iii) SmI_2, *t*-BuOH, THF. (iv) KOH, $HO(CH_2)_2OEt$, 110 °C; Me_2SO_4, DMF. (v) O_3, DCM, −78 °C; Me_2S. (vi) AcOH, Ac_2O, H_2SO_4 cat., 65 °C, 17 h. (vii) $NaBH_4$, MeOH, 0 °C. (viii) PTSA, C_6H_6, reflux. (ix) $BF_3·OEt_2$, AcCl, Bu_3SnH, $PhCH_3$, −78 °C. (x) $NaBH_4$, MeOH, 0 °C. (xi) Ac_2O, 4-pyrrolidinopyridine.

2.4. Abietic Acid

Abietic acid (**277**, Scheme 44) is readily available from a resin produced by *Pinus elliottii*.[110] This natural product as been used

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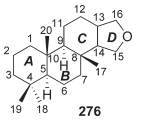
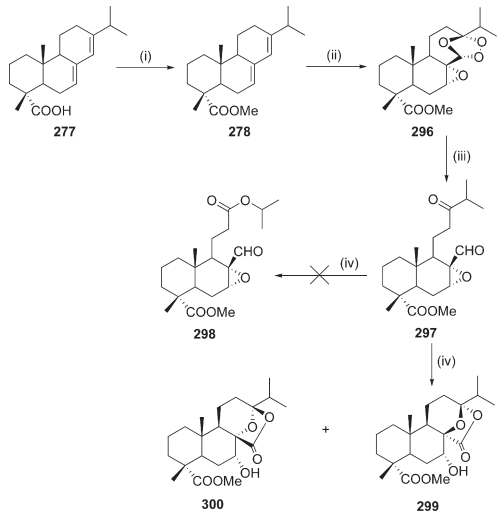


276

Figure 3. Carbon framework of spongian family (skeleton).

Scheme 46. Synthesis of Tetracyclic Compounds 299 and 300 from Abietic Acid (277)[a]



[a] (i) CH_2N_2, Et_2O, 0 °C, 100%. (ii) O_3, DCM, −78 °C, 78%. (iii) PPh_3, DCM, room temperature, 12 h, 80%. (iv) Baeyer−Villiger, *m*-CPBA.

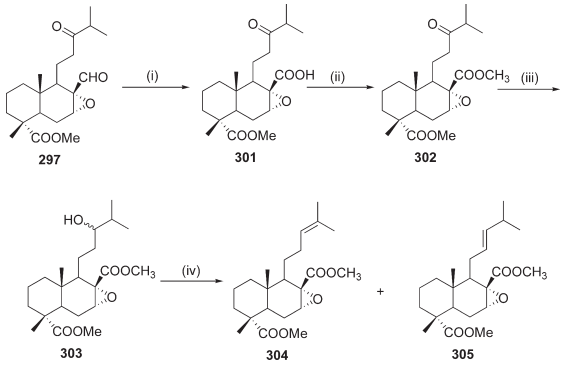
as a chemical defense against insect and pathogenic fungi and bacteria.[111]

In the past decade, several chemical transformations of abietic acid were carried out with a view to produce new derivatives and important synthetic intermediates. Some of the most recent and important work in this area is presented below.

In 2003, Manuel Arnó and co-workers described a new strategy for the synthesis of four spongiane diterpenes (**291**−**293** and **295**) via a common intermediate (**288**). This intermediate was previously prepared in five synthetic steps from (+)-podocarp-8(14)-en-13-one **269**, easily available from commercial (−)-abietic acid (**277**) (see Schemes 44 and 45).[112,113] Among the numerous bioactive substances isolated from sponges and nudibranchs,[114] the spongiane family[115] comprises a group of tetracyclic and pentacyclic metabolites characterized by the carbon framework (**276**, Figure 3). Since their discovery by Minale and co-workers in 1974,[116] these compounds have attracted the interest of synthetic chemists and biologists because of their wide spectrum of biological activities. These include antifungal, antimicrobial, antifeedant, antiviral, and antitumor properties, as well as PLA2 inhibition.[117−121] To date, there are around 70 known members of this family, which mainly differ in the extent of oxidation at C17 and C19 and the oxidation pattern on rings A−D.[122] Through the synthesis of spongiane diterpenes **291**−**293** and **295** from (−)-abietic acid, Manuel Arnó and collegues made a great contribution to this field.

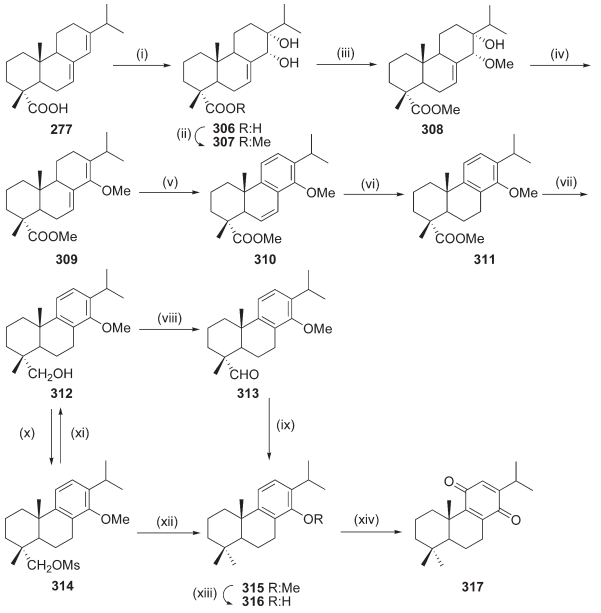
In the same year, Imamura and co-workers described several transformations of the C-ring of abietic acid in the context of the preparation of some new chiral synthons.[123] First, abietic acid was transformed to its methyl ester (**278**), which upon ozonolysis furnished compound **296** (Scheme 46). In an attempt to cleave the side chain of bicyclic intermediate **297**, this compound was submitted to a Baeyer−Villiger reaction with *m*-CPBA. Two compounds were isolated from the crude reaction mixture and were spectroscopically characterized as the tetracyclic compounds **299** (50%) and **300** (33%), instead of the expected product **298** (see Scheme 46).

Scheme 47. Synthetic Approach to Chiral Synthons 304/305 from Intermediate 297[a]



[a] (i) Jones reagent, Et_2O, 0 °C, 74%. (ii) CH_2N_2, Et_2O, 0 °C, 100%. (iii) $NaBH_4$, MeOH, 80%. (iv) MsCl, py, DBU-Bz, 54% (**304**/**305** (88:12)).

Scheme 48. Synthetic Approach to Antileishmanial 12-Deoxyroyleanone (317) from Abietic Acid (277)[a]



[a] (i) ac. OsO_4 0.2%, Me_3NO, pyridine, *t*-BuOH, Ar, reflux, 7 days. (ii) MeI, K_2CO_3, acetone, reflux, 24 h, 90% from **306**. (iii) NaH, THF, MeI, 0 °C, 2 h, 96%. (iv) $SOCl_2$, Et_3N, DCM, −78 °C, 20 min, 74%. (v) Br_2, CCl_4, $CaCO_3$, reflux, 12 h, 70%. (vi) H_2, Pd/C, MeOH, room temperature, 3 h, 96%. (vii) $LiAlH_4$, THF, room temperature, 3 h, 95%. (viii) PCC, DCM, room temperature, 1 h, 70%. (ix) NH_2NH_2, KOH, ethyleneglycol−ethyleneglycol dimethyl-ether 3:2, 190 °C, 3 days, 70%. (x) MsCl, Et_3N, DCM, 0 °C to room temperature, 4 h, 93%. (xi) $LiAlH_4$, THF, reflux, 24 h, 95%. (xii) Zn, NaI, HMPA, 110 °C, 3 days, 75%. (xiii) BBr_3, DCM, −10 °C, 30 min, 95%. (xiv) $(KSO_3)_2NO$, MeOH, room temperature, 4 h, 91%.

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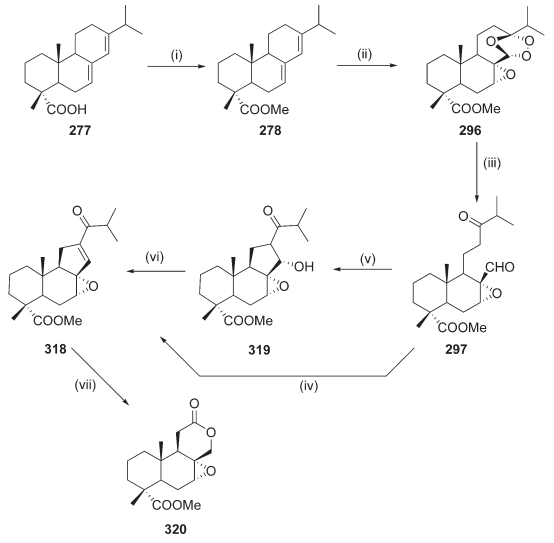
Scheme 49. Synthetic Approach to the Analogue of Homosesquiterpene Oidiolactone (320) from Abietic Acid (277)[a]



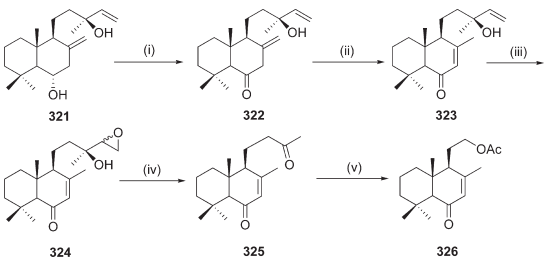
[a] (i) CH_2N_2, Et_2O, 0 °C, 100%. (ii) O_3, DCM, −78 °C, 78%. (iii) PPh_3, DCM, room temperature, 12 h, 80%. (iv) LDA, TMSCl, THF, −78 °C, 12%. (v) MeO^-Na^+/MeOH, room temperature, 56%. (vi) $(F_3CCO)_2O$, DCM, Na_2CO_3, 58%. (vii) (a) O_3, DCM, −78 °C; (b) $NaBH_4$, MeOH; (c) $NaIO_4$, room temperature, 17% (three steps).

In view of these findings, the authors decided to study an alternative approach, starting with **297**[124] to cleave its side chain. Thus, reduction of derivative **302** with $NaBH_4$/MeOH furnished an inseparable mixture of epimeric alchols **303** in 80% yield. Dehydration of **303**, followed by treatment with DBU-Bz, furnished a mixture of new chiral synthons **304**/**305** (88:12) in 54% yield (Scheme 47).

One year later, Alvarez-Manzaneda Roldan and co-workers described the first synthesis of antileishmanial 12-deoxyroyleanone (**317**) starting from abietic acid (**277**).[125] 12-Deoxyroyleanone was obtained in 11 steps and 25% overall yield (Scheme 48). Initially, abietic acid was efficiently converted to diol **306**. After esterification, the secondary hydroxyl group was methylated, affording derivative **308**, which underwent regioselective dehydration upon treating with thionyl chloride and triethylamine. The resulting methoxydiene **309** was converted to dehydroabietic acid derivative **310** by treatment with bromine in carbon tetrachloride. Subsequent hydrogenation gave methyl 14-methoxy-dehydroabietate (**311**). Treatment of **311** with lithium aluminum hydride gave alcohol **312**, which was then oxidized to aldehyde **313**. This aldehyde was converted to **315** under the Wolff−Kishner conditions. A different method for converting **312** into **315**, via the mesylate **314**, was also explored. It was found, however, when **315** was treated with lithium aluminum hydride, **312** was regenerated. Even so, compound **315** was eventually obtained by treating **314** with zinc and sodium iodide. Finally, demethylation gave phenol **316**, which was converted into 12-deoxyroyleanone (**317**) upon treatment with potassium nitrosodisulfonate.

Continuing their studies, Imamura and collegues reported in 2005 the synthesis of a new analogue of homosesquiterpene oidiolactone (**320**), starting from abietic acid (**277**) (Scheme 49).[126] This analogue was prepared in eight steps and an overall yield of 5.5%. The synthesis began with the preparation of polyoxygenated compound **297** from **277** in three steps. Reaction of **297** with LDA/TMSCl at −78 °C furnished a mixture of compounds from which the intermolecular aldol-dehydration product **318** was isolated in a poor yield (12%). In a different approach, compound **318** was synthesized from **297** in two steps (32% overall yield), via aldol-adduct **319**. Finally, ozonolysis of **318** followed by reductive treatment with $NaBH_4$ led to a complex mixture of products, from which compound **320** was obtained after column chromatography in 17% yield (over three steps).

Scheme 50. Synthetic Approach to Ester 326 (Intermediate for the Synthesis of Polyhydroxylated Labdane Diterpenes) from Larixol (321)[a]



[a] (i) Dess−Martin periodinane, 1 equiv, DCM, 1 h, room temperature, then ether, NaOH (aq), 1 h, 95%. (ii) 1 N, methanolic NaOMe, 1 h, room temperature, 98%. (iii) *t*-BuOOH, $VO(acac)_2$, lutidine, 38 °C, 12 h, 93%. (iv) HIO_4, 1 equiv, THF, H_2O, room temperature, 3 h, 60%. (v) *m*-CPBA, 1.5 equiv, $BF_3 \cdot OEt_2$, 1.5 equiv, DCM, 48 h, 30%.

2.5. Larixol

Larixol (**321**) has been isolated as its acetate from the turpentine oil of *Larix deciduaj*, *L. europea*, and *L. sibirica*.[127,128] Its structure has been determined by Norin et al.,[129] and the absolute configuration of the side-chain was defined as 13-(*S*).[130,131] Larixol has been very useful in the preparation of important intermediates for the synthesis of different diterpenes.

Once again, we describe here the most relevant chemical transformations of larixol reported in recent years.

In 1996, Khuoug-Huu and colleagues reported a reaction sequence for the degradation of the side-chain of larixol (**321**, Scheme 50), isolated from the turpentine oil of *Larix europea*. This sequence provides ester **326**, a useful intermediate for the synthesis of polyhydroxylated labdane diterpenes.

Oxidation of larixol with Dess−Martin periodinane[132] led to ketone **322**, which was transformed to conjugated ketone **323** using methanolic sodium methoxide (93% for two steps). The 14−15 double bond was selectively epoxidized with *t*-butyl hydroperoxide in the presence of $VO(acac)_2$ according to Sharpless' procedure. A mixture of diastereomeric epoxides **324a,b** was obtained in a 7/3 ratio (93%). Epoxidation with *m*-CPBA furnished a 1:1 mixture of diastereomers, although some epoxidation of the 7−8 double bond also occurred. Periodic acid oxidation of epoxides **324a,b** gave diketone **325** in 60% yield. Baeyer−Villiger oxidation of **325** furnished the acetate **326** in a moderate yield (30%) together with unreacted starting material (ca. 50%) (Scheme 50).

In 2001, Aede de Groot and co-workers described the synthesis of several Ambrox-like compounds starting from (+)-larixol (**321**).[133] For example, Δ^6-Ambroxene (**330**) was prepared in 37% overall yield, as depicted in Scheme 51.

The success of the cyclization reaction (step x, Scheme 51) encouraged the authors to develop a better synthesis of diol **329**.

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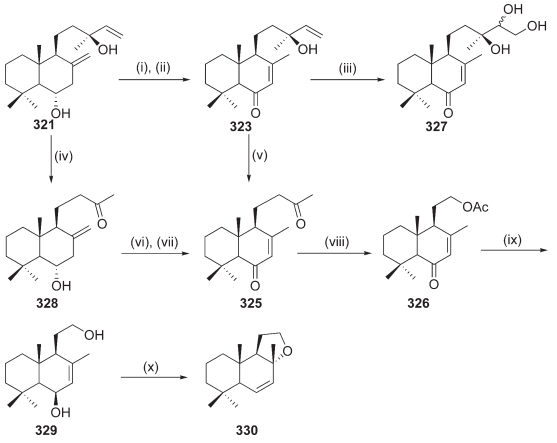
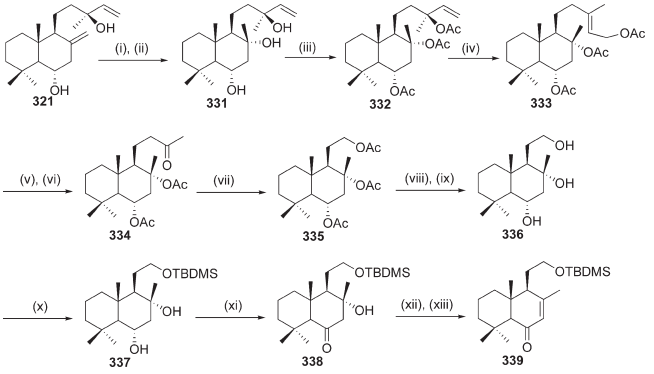
Scheme 51. Synthetic Approach to Δ^6-Ambroxene (330) from (+)-Larixol (321)[a]



[a] (i) PCC, DCM, 95%. (ii) NaOMe, MeOH, 98%. (iii) $KMnO_4$, BTEACl, DCM, 0 °C to room temperature, 56%. (iv) $KMnO_4$, benzyltriethylammonium chloride (BTEACl), DCM, 0 °C to room temperature, 68%. (v) $KMnO_4$, BTEACl, DCM, room temperature, sonication, 68%. (vi) PCC, DCM, 89%. (vii) NaOMe, MeOH, 92%. (viii) *m*-CPBA, $BF_3 \cdot OEt_2$, 30%. (ix) $LiAlH_4$, THF, 0 °C to room temperature. (x) *p*-TsOH, CH_3NO_2, 37% (two steps).

Scheme 52. Synthetic Approach to the Enone 339, a Precursor of Diol 329 (See Scheme 51)[a]

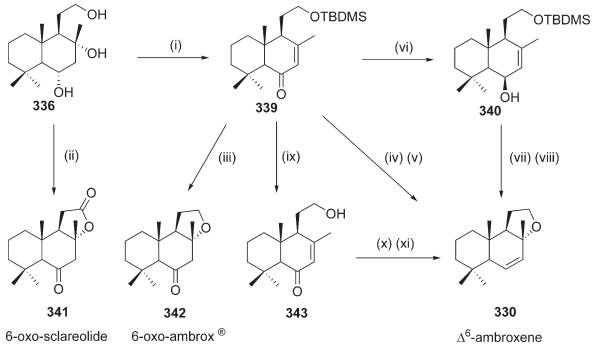


[a] (i) Oxone, acetone, H_2O, DCM, [18]crown-6, $NaHCO_3$, 0 °C, 81%. (ii) $LiAlH_4$, THF, 0 °C to room temperature, 94%. (iii) AcCl, *N*,*N*-dimethylaniline, 93%. (iv) $PdCl_2(CH_3CN)_2$, THF, 98%. (v) O_3, DCM/MeOH (1:1), −78 °C. (vi) PPh_3, −78 °C, 95% (two steps). (vii) *m*-CPBA, DCM, 83%. (viii) $LiAlH_4$, THF, 0 °C to room temperature, 94%. (ix) NaOMe, MeOH, 85%. (x) TBDMSiCl, DMF, imidazole, N_2, 95%. (xi) PDC, DCM, 3 Å molecular sieves, 86%. (xii) $SOCl_2$, Py, DMAP, 0 °C to room temperature. (xiii) NaOMe, MeOH, 82% (two steps).

An alternative route to a precursor of **329**, enone **339**, is shown in Scheme 52. This route makes use of a modified procedure of previously described methodology[134] for the oxidative breakdown of the side chain of larixol to a hydroxyethyl group. Enone **339** is also an important intermediate in the synthesis of the polyoxygenated diterpenes crotomachlin and 8-*epi*-crotomachlin.[135]

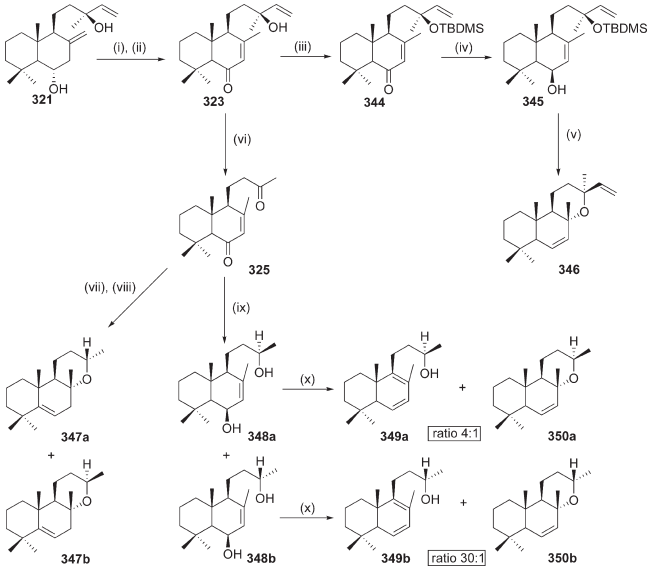
Furthermore, intermediates **336** and **339** are good starting points for the synthesis of C6-modified Ambrox-like compounds (Scheme 53). A selective synthesis of Δ^6-Ambroxene (**330**) from enone **339** proved to be possible in one-pot fashion, although a two-step route gave better results. Reaction of **339** with $LiAlH_4$ accomplished both carbonyl reduction and removal of the silyl propecting group, giving a diol that underwent acid-catalyzed cyclization to **330** in a moderate 40% yield. Alternatively, enone **339** was reduced to alcohol **340** with DIBAL-H in 90% yield. Desilylation of **340** with TBAF,[135] and subsequent acid-catalyzed cyclization, gave **330** in 78% overall yield (from **339**). When desilylation was performed before reducion, the overall yield of **330** was slightly lower (71%, Scheme 53).

Scheme 53. Synthesis of C6-Modified Ambrox-like Compounds from Triol 336 and Enone 339[a]



[a] (i) See Scheme 52. (ii) PCC, DCM, 76%. (iii) TBAF, dry THF, 18 h, 59%. (iv) $LiAlH_4$, dry THF, 0 °C to room temperature. (v) *p*-TsOH, CH_3NO_2, 40% (two steps). (vi) DIBAL-H, dry THF, 0 °C, N_2, 90%. (vii) TBAF, dry THF. (viii) *p*-TsOH, CH_3NO_2, 87% (two steps). (ix) TBAF, dry THF, 1 h, 93%. (x) DIBAL-H, dry THF, 0 °C, N_2. (xi) *p*-TsOH, CH_3NO_2, 71% (two steps).

Scheme 54. Synthetic Approach to Ambra Oxide Related Compounds 346, 347a,b, and 350a,b from (+)-Larixol (321)[a]



[a] (i) PCC, DCM, 95%. (ii) $NaOCH_3$, MeOH, 98%. (iii) TBDMSiCl, DMF, imidazole, 70 °C, 3 days, 92%. (iv) DIBAL-H, toluene, −78 °C, 98%. (v) (a) HF (50% aq sol.), MeCN; (b) SiO_2, 67%. (vi) $KMnO_4$, benzyltriethylammonium chloride, DCM, room temperature, 68%. (vii) DIBAL-H, toluene, −78 °C, HCl, H_2O. (viii) *p*-TsOH, CH_3NO_2, 29%. (ix) DIBAL-H, toluene, −78 °C, NaOH, H_2O, 78%. (x) HCl (aq) 4 M, Et_2O, 80−95%.

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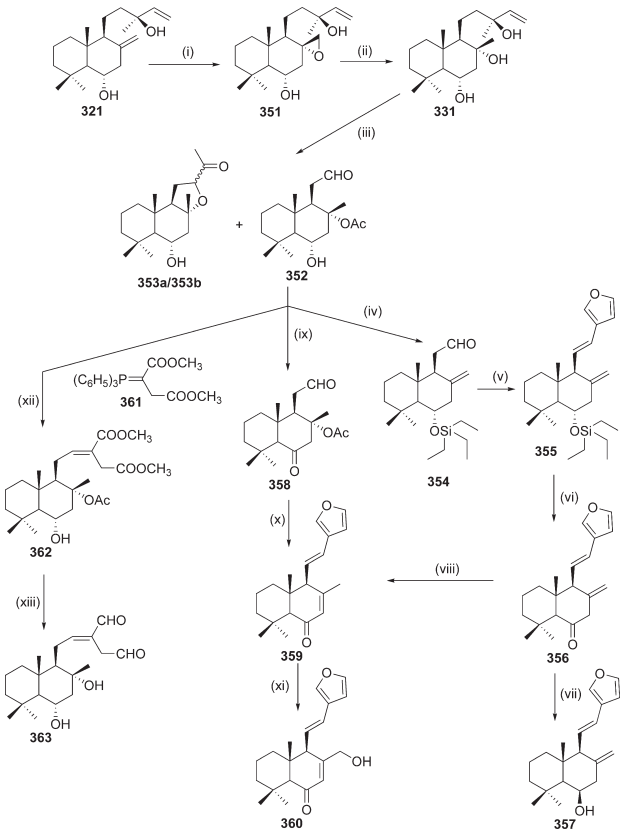
Scheme 55. Synthetic Approach to Furan (357, 359, 360) and 1,4-Enedial (363) Labdane-type Diterpenes Starting from (+)-Larixol (321)[a]



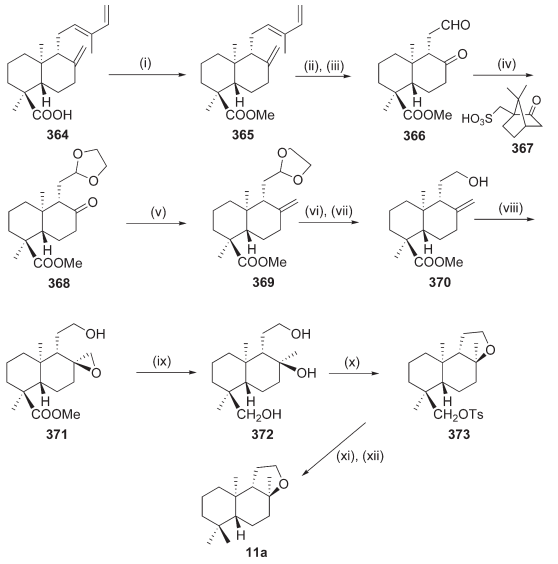
[a] (i) Oxone, acetone, H_2O, DCM, [18]crown-6, $NaHCO_3$, 0 °C, 68%. (ii) $LiAlH_4$, THF, 0 °C to room temperature, 94%. (iii) OsO_4 (cat.), $NaIO_4$, THF, 80−90%, **353a**,**b**:**352** = 1:2.2. (iv) (a) Et_3SiCl, DMAP (cat.), py, 8 h, 94%; (b) 2,4,6-collidine as solvent, 170 °C, 12 h, 79%. (v) (a) 3-Furyllithium, −78 °C, 2 h, 68%; (b) 2,6-lutidine (7 equiv), DCM, MsCl (3 equiv), room temperature, 18 h, 68%. (vi) (a) AcOH, THF−H_2O (5:1:3), room temperature, overnight, 95%; (b) IBX (3 equiv), AcOEt, 60 °C, 3 h, 85%. (vii) THF, −78 °C, DIBAL-H (6 equiv), 2 h, 95%. (viii) MeONa (0.2 M in MeOH), 2 h, quant. (ix) (a) IBX (3 equiv), AcOEt, 70 °C, 3 h, 84%; (b) 2,4,6-collidine, 160 °C, 12 h, 90%. (x) (a) 3-Furyllithium, −78 °C; (b) 2,6-lutidine, MsCl, 59% (two steps). (xi) (a) SeO_2 (1.5 equiv), dioxane, 80 °C, 8 h; (b) $NaBH_4$, EtOH, −78 °C, 60 °C, two steps. (xii) **361** 65%. (xiii) LAH, then IBX, 56% overall.

In 2002, the same research group reported the synthesis of several Δ^6-ambra oxide analogues, such as derivatives **346**, **347a**,**b**, and **350a**,**b**, from (+)-larixol using similar chemistry (Scheme 54).[136]

In 2005, Morin and co-workers described the synthesis of three labdane furans (**357**, **359**, **360**) and a 1,4-enedial (**363**) from (+)-larixol (Scheme 55).[137] Larixol was converted in five steps to aldehyde **354**. Addition of 3-furyl lithium to this aldehyde and formal dehydration of the resulting alcohol mixture provided furanolabdane **355**, which was subsequently transformed to relay intermediate **356** by desilylation and alcohol oxidation.

This intermediate was readily converted to hedychenone (**359**), by base-induced isomerization, and to yunnancoronarin A (**357**) upon DIBAL reduction. An alternative route to hedychenone (**359**) from **352** entailed oxidation and double-bond isomerization to form enone **358**. Interestingly, addition of 3-furyl lithium occurred preferentially on the aldehyde group to afford **359** after mesylation/elimination. Thus, hedychenone was obtained in four steps from **352** (22% overall yield from larixol). In addition, yunnancoronarin D (**360**) was synthesized from **359** in two steps: oxidation of the allylic methyl group followed by reduction of the resulting aldehyde. 1,4-Enedial **363** was also synthesized from **352** via stereoselective Wittig reaction with ylide **361** (Scheme 55).

Scheme 56. Synthesis of *ent*-Ambrox (11a) from (−)-Ozic Acid (364)[a]



[a] (i) Diazomethane. (ii) O_3, DCM, −78 °C. (iii) PPh_3, room temperature, 85%. (iv) Camphorsulfonic acid (**367**), $HO(CH_2)_2OH$ benzene, reflux, 90%. (v) Zn, $TiCl_4$, CH_2Br_2, DCM, room temperature, 73%. (vi) THF, HCl 1%, room temperature. (vii) $NaBH_4$, MeOH, room temperature, 81%. (viii) *m*-CPBA, DCM, room temperature, 90%. (ix) $LiAlH_4$, THF, reflux, 86%. (x) TsCl, Py, room temperature, 62%. (xi) NaI, Zn, DMF, 120 °C. (xii) *m*-CPBA, DCM, room temperature, 58% (two steps).

2.6. Ozic Acid

(−)-Ozic acid (**364**, Scheme 56) is the main component of the seedpod extract of *Hymenaea courbaril* var. *altissima*[138] and can be readily obtained as its methyl ester **365**, after esterification with diazomethane. The most important use of ozic acid is as starting labdane for the synthesis of *ent*-Ambrox. To the best of our knowledge, work on the chemical manipulation of ozic acid has been very limited. Thus, our discussion is confined to the synthesis of *ent*-Ambrox, reported by Paulo Imamura and co-workers in 2003.[139] Imamura's 12-step synthesis of *ent*-Ambrox (**11a**) from (−)-ozic acid is shown in Scheme 56. The first step involves conversion to methyl ester **365**. Reaction of **365** with a stream of ozone, followed by treatment with PPh_3, furnished the corresponding keto-aldehyde **366** in 85% yield. Treatment of **366** with ethylene glycol and camphorsulfonic acid (**367**) gave acetal **368**, which was converted to *ent*-Ambrox (**11a**) in eight straightforward steps (58% overall yield, Scheme 56).

3. BIOTRANSFORMATION

3.1. Sclareol

In general, the microorganisms studied in the biotransformation of sclareol were able to biotransform this diterpene in a few days (2−8 days). *Cunninghamella echinulata* NRRL 3655, *Mucor plumbeus* ATCC 4740, and *Rhodococcus erythropolis* JTS-131

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were the best microorganisms, with 1, 2, and 2 days, respectively, whereas *Fusarium lini* was the slowest needing 8 days. Excluding *R. erythropolis* and *F. lini*, all of the others presented in the literature (*Aspergillus alliaceus* NRRL 2315, *Aspergillus niger*, *Aspergillus ochraceus* ATCC 1009, *Cunninghamella echinulata* NRRL 3655, *Cunninghamella elegans*, *Cunninghamella* species NRRL 5695, *Curvularia lunata* NRRL 2380, *Mortierella ramanniana* MMP 17, *Mortierella isabellina* MMP 108, *Rhizopus arrhizus* ATCC 11145, *Rhizopus stolonifer*, and *Sporotrichum exile* QM 1250) led to formation of compounds **374**−**376** (see Table 1). The best reported yields were 74%, by using *Rhizopus stolonifer* to form 18-hydroxysclareol (**376**),[140] achieved during a research project developed by Díez and co-workers in 2005, and 84% with the microorganism *Mucor plumbeus* ATCC MMP 117, forming 3β-hydroxysclareol (**374**), in the course of a study conducted by Aranda in 1991.[141] *Cunninghamella* species NRRL 5695 also produced compounds **374** and **376** in reasonable yields (50% and 36%, respectively).[141] 6α-Hydroxysclareol (**375**) was also a very common product within the tested microorganisms, with the exception of *Cunninghamella elegans*, *Cunninghamella* species NRRL 5695, *Rhodococcus erythropolis* JTS-131, and *Fusarium lini* (Table 1).[141] The formation of bioproducts depends on the growing conditions of the microorganism. In a different study, carried out by Choudhary and colleagues in 2006, it was shown that the use of *Rhizopus stolonifer* gives two new products: (6α)-6,18-dihydroxysclareol (**377**) and (11*S*)-11,18-dihydroxysclareol (**378**) in 3.2% and 4.6% yield, respectively (Table 2).[142] It was also observed that *Fusarium lini* converted sclareol into 1β-hydroxysclareol (**381**) and (12*S*)-12-hydroxysclareol (**382**) in 1.3% and 1% yield, respectively (Table 2).[142] In 1983, Hieda and co-workers found that the microorganism *Rhodococcus erythro-*

Table 1. Predominant Products Resulting from Biotransformation of Sclareol (1)

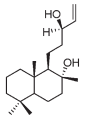
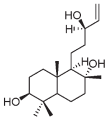
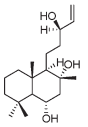
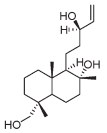
Substrate	Observed Products		
			
Sclareol **1**	**374**	**375**	**376**

Table 2. Biotransformation of Sclareol (1) Using the Microorganisms *Rhizopus stolonifer*, *Rhodococcus erythropolis* JTS-131, and *Fusarium lini* (Percentages Shown in the Table Represent the Yield Achieved for Each Molecule)

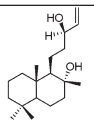
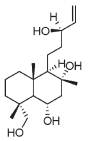
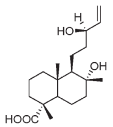
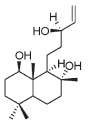
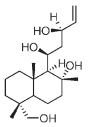
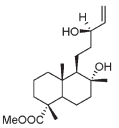
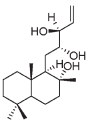
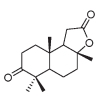
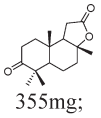
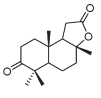
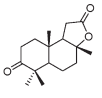
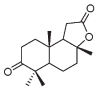
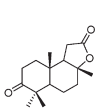
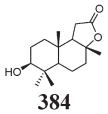
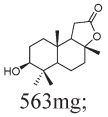
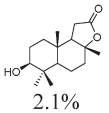
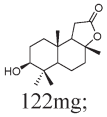
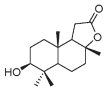
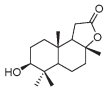
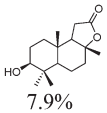
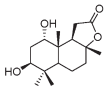
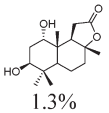
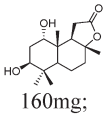
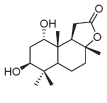
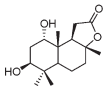
Substrate	Observed Products		
	R. stolonifer (6 days)[142]	*R. erythropolis* JTS- 131 (2 days)[143]	*F. lini* (8 days)[142]
 Sclareol **1**	 3.2% **377**	 **379**	 1.3% **381**
	 4.6% **378**	 **380**	 1.0% **382**

Table 3. Predominant Products Formed by Biotransformation of Sclareolide (184) Using the Following Microorganisms: *Aspergillus niger*, *Cephalosporium aphidicola* (1.5 g), *Cunninghamella elegans*, *Curvularia lunata* (1 g), *Fusarium lini*, *Gibberella fujikuroi*, and *Mucor plumbeus* (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Percentage/Mass Shown in the Table Represents the Yield/Amount Achieved for Each Molecule)

Substrate	Observed Products						
	A. niger ATCC 10549 (10 days)[145]	*C. aphidicola* (10 days)[144]	*C. elegans* (12 days)[146]	*C. lunata* NRRL 2178 (10 days)[145]	*F. lini* NRRL 68751 (10 days)[145]	*G. fujikuroi* (10 days)[145]	*M. plumbeus* (2 days)[141]
 Sclareolide **184**	 **383**	 355mg; 23,6% **383**	 13.5% **383**	 87mg; 7,3% **383**	–	 **383**	 3.2% **383**
	 **384**	 563mg; 37,5% **384**	 2.1% **384**	 122mg; 11,5% **384**	 **384**	 **384**	 7.9% **384**
	 **385**	–	 1.3% **385**	 160mg; 13,3% **385**	 **385**	 **385**	–

dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Table 4. Less-Predominant Products from Biotransformation of Sclareolide (184) Using the Microorganisms *Aspergillus niger*, *Cephalosporium aphidicola* (1.5 g), *Cunninghamella elegans*, *Curvularia lunata* (1 g), *Gibberella fujikuroi*, and *Mucor plumbeus* (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Percentage/Mass Shown in the Table Represents the Yield/Amount Achieved for Each Molecule)

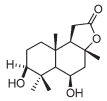
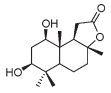
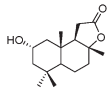
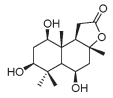
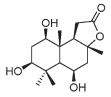
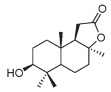
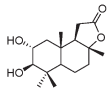
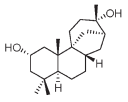
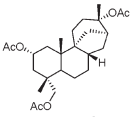
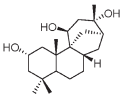
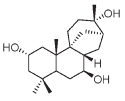
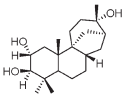
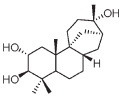
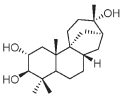
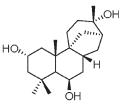
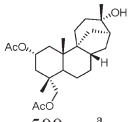
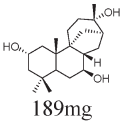
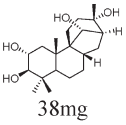
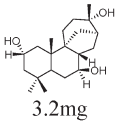
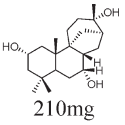
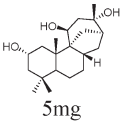
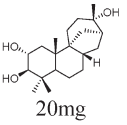
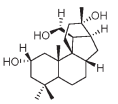
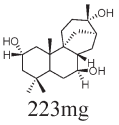
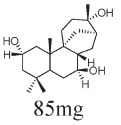
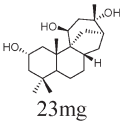
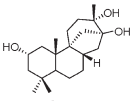
Substrate	Observed Products					
	G. fujikuroi (10 days)[145]	*M. plumbeus* (2 days)[141]	*C. aphidicola* (10 days)[144]	*A. niger* ATCC 10549 (10 days)[145]	*C. lunata* NRRL 2178 (10 days)[145]	*C. elegans* (12 days)[146]
 Sclareolide **184**	 **386**	 2.5% **387**	 382mg; 25,5% **388**	 **386**	 93mg **390**	 53% **391**
–	–	–	–	 **389**	 70mg **389**	 2.7% **392**
–	–	–	–	–	–	 23.6% **393**

Table 5. Biotransformation of Stemodin (395) Using the Microorganisms *Mucor plumbeus* (500 mg), *Beauveria bassiana* (1 g), *Cunninghamella echinulata* (1 g), *Phanerochaete chrysosporium* (1 g), *Whetzelinia sclerotiorum* (1 g), *Rhizopus oryzae* (1 g), and *Aspergillus niger* (500 mg) (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Percentage/Mass Shown in the Table Represents the Yield/Amount Achieved for Each Molecule)

Substrate	Observed Products						
	B. bassiana ATCC 7159 (14 days)[151]	*W. sclerotiorum* ATCC 18687 (10 days)[148]	*R. oryzae* (5 days)[150]	*A. niger* ATCC 9142 (10days)[152]	*C. echinulata* var. *elegans* ATCC 8688a (10 days)[149]	*P. chrysosporium* ATCC 24725 (10days)[149]	*M. plumbeus* ATCC 4740 (10 days)[148]
 Stemodin **395**	 64mg [a] **396**	 26mg **398**	 76mg **399**	 97mg **401**	 88mg **404**	 7mg **404**	 22mg **406**
	 500mg [a] **397**	 189mg **399**	 38mg **400**	 3.2mg **402**	 210mg **405**	 5mg **398**	 20mg **404**
–	–	–	–	 **403**	 223mg **402**	 85mg **402**	 23mg **398**
–	–	–	–	–	–	–	 9mg **407**

[a] The partially purified metabolites were acetylated using standard conditions to afford products **396** and **397**.

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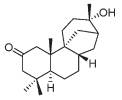
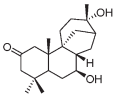
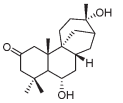
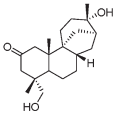
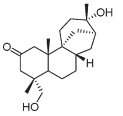
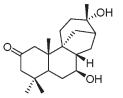
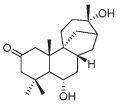
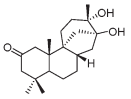
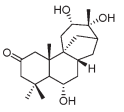
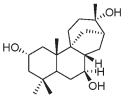
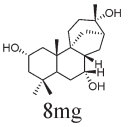
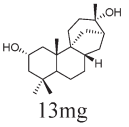
Table 6. Biotransformation of Stemodinone (408) Using the Microorganisms *Mucor plumbeus* (1 g), *Beauveria bassiana* (1 g), *Cunninghamella echinulata* (480 mg), *Phanerochaete chrysosporium* (500 mg), *Whetzelinia sclerotiorum* (500 mg), and *Rhizopus oryzae* (1 g) (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)

Substrate	Observed Products					
 Stemodinone **408**	*C. echinulata var.* elegans ATCC 8688a (10 days)[149]	*M. plumbeus* ATCC 4740 (10 days)[148]	*B. bassiana* ATCC 7159 (14 days)[151]	*P. chrysosporium* ATCC 24725 (10days)[149]	*W. sclerotiorum* ATCC 18687 (10 days)[148]	*R. oryzae* ATCC 11145 (5 days)[150]
	 38mg **409**	 125mg **414**	 258mg **416**	 52mg **416**	 108mg **409**	 14.3mg **414**
	 56mg **410**	 6mg **415**	–	–	–	–
	 8mg **411**	–	–	–	–	–
	 8mg **412**	–	–	–	–	–
	 13mg **413**	–	–	–	–	–

polis JTS-131 produces two exclusive products from sclareol, 13β-hydroxylabd-14-en-18-oic acid (**379**) and 13β-hydroxylabd-14-en-18-oic acid methyl ester (**380**), in about 2 days (Table 2).[143]

3.2. Sclareolide

The products of the most significant biotransformations of sclareolide are presented in Table 3 (predominant products) and Table 4 (less predominant products). The seven microorganisms tried afforded conversion of the substrate in 10 or 12 days, with the exception of *Mucor plumbeus*, which needed only 2 days to produce 3-oxo-sclareolide (**383**), 3β-hydroxysclareolide (**384**), and 1β-hydroxysclareolide (**387**) in 3.2%, 7.9%, and 2.5% yield, respectively. These results were reported by Aranda and colleagues in 1991.[141] Compound **387** was obtained exclusively with *Mucor plumbeus*. On the other hand, derivatives **383** and **384** were very common from the tested fungi and were produced in more reasonable yields during studies completed by Hanson and Truneh in 1996, using the microorganism *Cephalosporium aphidicola* (23.6% for **383** and 37.5% for **384**, Table 3).[144]

The compound 1α,3β-dyhydroxysclareolide (**385**) was also a common sclareolide-derived compound, as demonstrated by Rahman and co-workers in 1997 and more recently by Choudhary and colleagues.[145,146] However, 3β,6β-dihydroxysclareolide (**388**), 1β,3β-dihydroxysclareolide (**390**), 2α-hydroxysclareolide (**391**), 3β-hydroxy-8-episclareolide (**392**), and 2α,3β-dihydroxysclareolide (**393**) were each produced by only one of the microorganisms investigated (Table 4).[144−146] These molecules result from mono- or dihydroxylations, with the exception of compound **392** that was formed by ether bond cleavage and inversion of configuration. This is a rare transformation and was performed by the microorganism *Cunninghamella elegans* in a 2.7% yield.[146] In 1996, Hanson's group, followed by Rahman and collaborators 1 year later, both established that compounds **388** and **393** were formed by *Cephalosporium aphidicola* (25.5%) and *Cunninghamella elegans* (23.6%), respectively.[144,146] As far as we know, the first microorganism was the one giving the best yields. *Pleurotus ostreatus* NRRL 4590 was also tried for the biotransformation sclareolide, but proved ineffective.[145]

3.3. Stemodin

Stemodia maritima is a plant that grows on saline soil and contains several compounds structurally similar to aphidicolin

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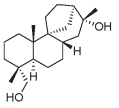
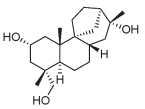
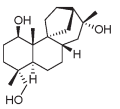
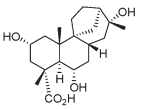
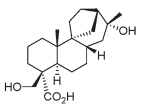
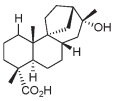
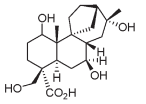
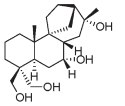
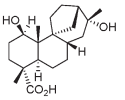
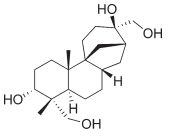
Table 7. Biotransformation of Stemarin (417) Using the Microorganisms *Mucor plumbeus* (1 g), *Beauveria bassiana* (1 g), *Cunninghamella echinulata* (100 mg), and *Aspergillus niger* (1g) (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)

Substrate	Observed Products			
 Stemarin **417**	*M. plumbeus* ATCC 4740 (10 days)[148]	*B. bassiana* ATCC 7159 (14 days)[151]	*C. echinulata* var. *elegans* ATCC 8688a (10 days)[149]	*A. niger* ATCC 9142 (10days)[152]
	 547mg **418**	 24.5mg **419**	 5mg **421**	 47.5mg **422**
–	–	 14mg **420**	–	 30.4mg **423**
–	–	–	–	 30mg **424**
–	–	–	–	 10.3mg **425**

(**394**), a known antiviral agent. These compounds are stemodin, stemodinone, and stemarin, for instance. Some of them have already been demonstrated to have antiviral properties.[147]


Aphidicolin, **394**

The products of biotransformation of stemodin (**395**) are shown in Table 5. All of the experimented microorganisms took 10 or more days to transform this substrate, with exception of *Rhizopus oryzae*.[148−152] In 2005, Chen and co-workers and in 2006, Lamm and co-workers found that the microorganisms *Whetzelinia sclerotiorum* ATCC 18687 and *Cunninghamella echinulata* var. *elegans* ATCC 8688a produced 2a,11b,13-trihydroxystemodane (**398**) and 2α,3β,13 trihydroxystemodane (**404**) in 4.9% and 8.4%, respectively.[148,149] These are the highest yields reported for this type of transformation. *Cunninghamella echinulata* var. *elegans* ATCC 8688a also produced 2α,7α, 13-trihydroxystemodane (**405**) and 2α,7β,13-trihydroxystemodane (**402**) stereoisomers. Compound **402** was also produced by *Phanerochaete chrysosporium* ATCC 24725 and *Aspergillus niger* ATCC 9142 in the same study.[149,152] At the same time, Chen and colleagues reported that *Mucor plumbeus* ATCC 4740 converts stemodin to compounds **398** and **404**, together with two additional products: 2α,6β,13-trihydroxystemodane (**406**) and 2α,13,14-trihydroxystemodane (**407**).[148] In 2004, Martin and co-workers reported that 2α,7β-13(*S*)-trihydroxystemodane (**399**) was produced by both *Whetzelinia sclerotiorum* ATCC 18687 and *Rhizopus oryzae*, in 35.9% and 7.2% yield, respectively. The last microorganism also converted stemodin to 2α,3β,13(*S*),16α-tetrahydroxystemodane (**400**), which was not formed by any of the other microorganisms tested to date.[150] Besides, during the investigation of biotransformation of diterpenes and terpene derivatives, Reese's group found that *Beauveria bassiana* ATCC 7159 produced a metabolite from stemodin, which, on acetylation using standard conditions, afforded 2α,13,18-triacetoxystemodane (**396**) and 2α,18-diacetoxy-13-hydroxystemodane (**397**), with the latter produced in 53% yield.[151] The same authors demonstrated that the microorganism *Aspergillus niger* ATCC 7159 converted stemodin to compounds **401**−**403**.[152]

3.4. Stemodinone

Products obtained from biotransformation of stemodinone (**408**) are listed in Table 6. *Rhizopus oryzae* was the

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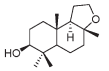
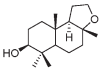
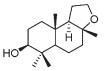
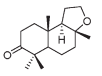
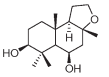
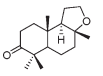
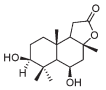
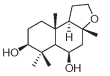
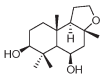
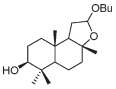
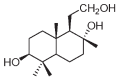
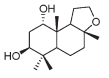
Table 8. Biotransformation of Ambrox (11) Using the Microorganisms *Actinidia deliciosa*, *Cephalosporium aphidicola* (2 g), *Fusarium lini* (600 mg), and *Rhizopus stolonifer* (600 mg) (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Percentage/Mass Shown in the Table Represents the Yield/Amount Achieved for Each Molecule)

Substrate	Observed Products			
 Ambrox **11**	*A. deliciosa* (15 days)[154]	*C. aphidicola* (10 days)[144]	*F. lini* NRRL 68751 (8 days)[146]	*R. stolonifer* ATCC 10404 (12 days)[146]
	 4.1% **426**	 360mg **426**	 16.4mg **428**	 6.3mg **426**
	 8.2% **427**	 131mg **429**	 19.1mg **434**	 7.9mg **427**
	 9.5% **428**	 178mg **432**	 8.2mg **435**	 11.4mg **429**
	 10.5% **429**	 174mg **433**	 27.8mg **436**	 28.1mg **437**
	 15.7% **430**	–	–	–
	 10.1% **431**	–	–	–

quickest microorganism to transform this substrate. As for stemodin (Table 5), it was converted to stemodinone in about 5 days.

In 2004, Martin and collaborators revealed that this microorganism catalyzed the production of a unique compound named 6α,13-hydroxystemodan-2-one (**414**).[150] Almost at the same time, Chen and co-workers[148] and Lamm's group[149] found that other microorganisms, such as *Whetzelinia sclerotiorum* ATCC 18687 and *Phanerochaete chrysosporium* ATCC 2472, needed at least 10 days to modify the substrate and furnish a single product in each case: 7β,13-hydroxystemodan-2-one (**409**)[148] and 13,18-dihydroxystemodan-2-one (**416**), respectively.[149] Besides, Buchanan and Reese have shown that the microorganism *Beauveria bassiana* needed a longer period of 14 days to modify stemodinone into compound **416** (25.8%).[151] During their studies, Chen[148] and Lamm[149] also verified that microorganism *Mucor plumbeus* ATCC 4740 transformed stemodinone to two compounds, whereas *Cunninghamella echinulata* formed five compounds, two of them being stereoisomers.

3.5. Stemarin

The transformation of stemarin (**417**) by different microorganisms also required longer periods (10 days or more, Table 7).

This molecule underwent mono- or dihydroxylations or oxidation to a carboxylic acid. The best yield was achieved in 2005 by Chen and co-workers, by using *Mucor plumbeus* ATCC 4740 microorganism, which afforded 2α,13,19-trihydroxystemarane (**418**).[148] In 2006, Lamm and colleagues discovered that *Cunninghamella echinulata* var. *elegans* hydroxylated position C2 and oxidized position C19 of stemarin, to give 2α,13-dihydroxystemaran-19-oic acid (**421**).[149] In addition, Buchanan and Chen found that microorganisms *Beauveria bassiana* ATCC 7159 and *Aspergilus niger* ATCC 9142 produce carboxylic acids (**420**, **422**, **423**, **425**) as well.[151,150] The last microorganism was also capable of producing 7α,13,18,19-tetrahydroxystemarane (**424**).[152]

3.6. Ambrox

Ambrox (**11**) has a very strong amber-like odor and originates from oxidative decomposition of ambrein, a major

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Table 9. Biotransformation of 18-Hydroxymanoyl Oxide (439) by *Mucor plumbeus* CMI 116688 (300 mg) and *Gibberelia fujikuroi* (240 mg) (Only the Compounds Marked with "*" Were Produced by *Gibberella fujikuroi*; Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)[156,158]

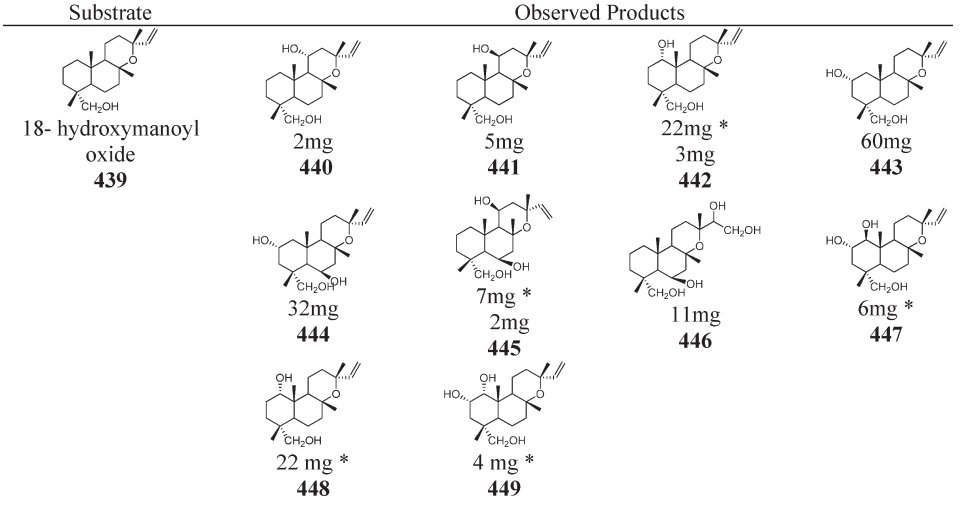
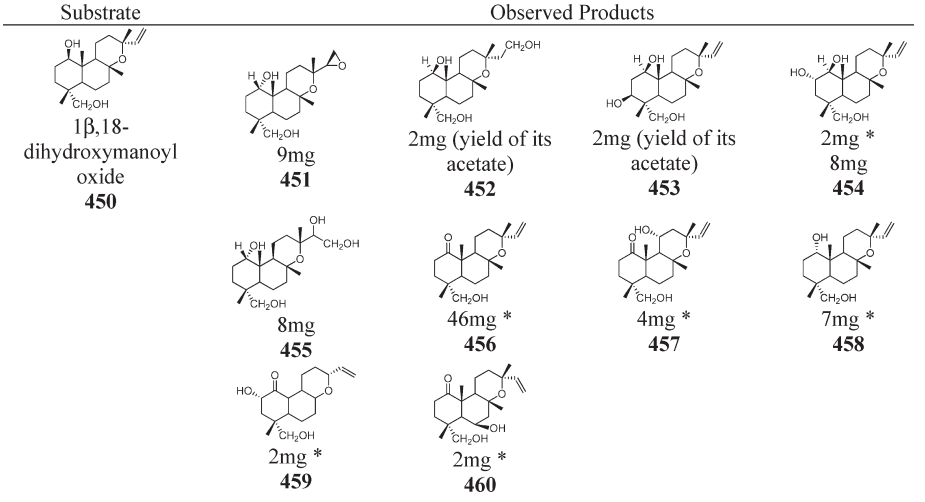


Table 10. Biotransformation of 1*β*,18-Dihydroxymanoyl Oxide (350) by *Mucor plumbeus* CMI 116688 (230 mg) and *Gibberelia fujikuroi* (210 mg) (Only the Compounds Marked with "*" Were Produced by *Gibberella fujikuroi*; Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)[156,158]



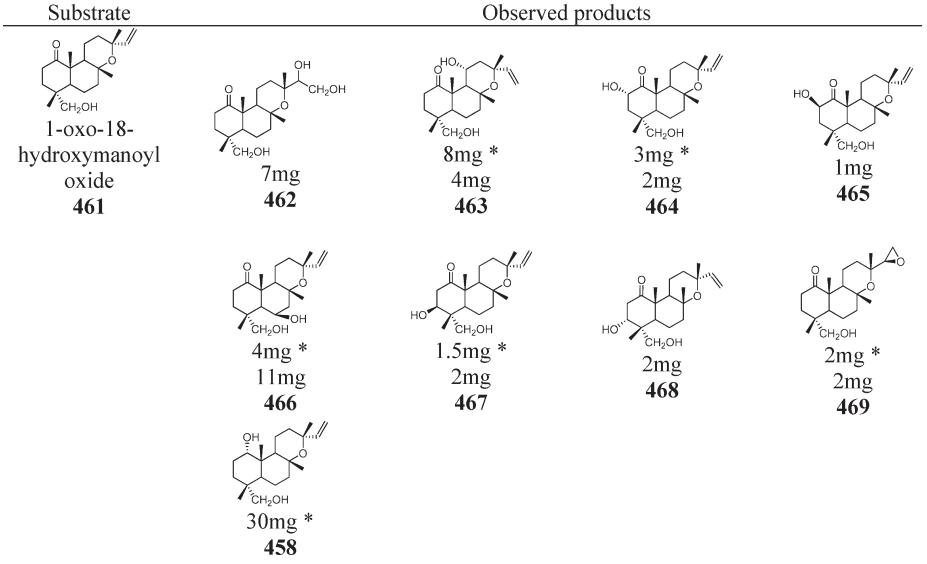
constituent of ambergris. Ambrein is obtained from the sperm whale and is one of the most valuable animal perfumes.[153]

Bioconversion of Ambrox also took long periods (8 days or more), and the products formed varied within the group of tested microorganisms, despite the fact that 3*β*-ambrox (**426**), 3-oxo-ambrox (**427**), 1α-ambrox (**428**), and 3*β*,6*β*-dihydroxyambrox (**429**) were formed by 3, 2, 2, and 3 microorganisms, respectively (Table 8).

In 1996, Hanson and Truneh reported the formation of 3*β*,6*β*-dihydroxylactone **432** from Ambrox, with the microorganism *Cephalosporium aphidicola*.[144] In 2004, Choudhary and co-workers found that 3-oxo-ambrox (**427**) was formed together with three others products (**426**, **429**, **437**) by biotransformation of Ambrox with the microorganism *Rhizopus stolonifer*.[146] This microorganism was the only one to cleave the ether bond to transform the substrate into 13,14,15,16-tetranorlabdane-3,8,12-triol (**437**). In no other work was observed this type of Ambrox biomodification.[146] Two years later, Nasib and colleagues confirmed the formation of 3-oxo-ambrox (**427**) using *Actinidia deliciosa*.[154] In this, compound **427** was isolated from a mixture of six molecules (structures **426**−**431**). Apart from the 3-oxo-ambrox derivative, all of the other modifications observed

dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

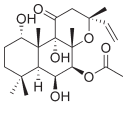
Table 11. Biotransformation of 1-Oxo-18- hydroxymanoyl Oxide (461) by *Mucor plumbeus* CMI 116688 (200 mg) and *Gibberella fujikuroi* (300 mg) (Only the Compounds Marked with "*" were Produced by *Gibberella fujikuroi*; Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)[156,158]



by the authors during the same study were mono- or dihydroxylations. The hydroxylated product obtained with the best yield was 1α,3β-dihydroxyambrox (**430**) from *Actinidia deliciosa* (15.7%).[154]

3.7. Manoyl Oxide Derivatives

Some manoyl oxide derivatives, such as 18-hydroxymanoyl oxide (jhanol, **439**, Table 9) and 1β,18-dihydroxymanoyl oxide (jhanidiol, **450**, Table 10), can be isolated from *Eupatorium jhanii*, a plant growing in the Andean region of Venezuela. The compound 1-oxo-18-hydroxymanoyl oxide (1-oxo-jhanol, **461**, Table 11) can be obtained by transformation of jhanol or jhanidiol.[156,157] These compounds have similarities with forskolin (**438**), a major component of the extract from the roots of *Plectranthus barbatus* Andrews, which has shown blood pressure lowering activity in laboratory animals.[157] Therefore, the biotransformation of these compounds may lead to the discovery of new molecules with potentially better pharmacological profiles.



Forskolin, **438**

A common biotransformation pathway of manoyl oxide derivates involves the introduction of hydroxyl groups (Tables 9−11). However, we can highlight some other interesting transformations, such as dismantling of the double-bond to create dihydroxylated carbons (**446**, **455**, **462**) or an epoxy function (**451**, **469**). The most promising results in this were reported by Fraga and co-workers.[156,158]

During their studies with 18-hydroxymanoyl oxide (**439**), 1β,18-dihydroxymanoyl oxide (**450**), and 1-oxo-18-hydroxymanoyl oxide (**461**), the authors concluded that the formation of dihydroxylated carbons was only achieved by the *Mucor plumbeus*, but not by *Gibberella fujikuroi*, while the epoxy function was installed by both microorganisms. In addition, it was observed that *Aspergillus niger* seems to hydroxylate 18-hydroxymanoyl oxide preferentially at C2(α) and C6(β) positions to form compounds **443**, **444**, and **446**, whereas *Gibberella fujikuroi* prefers to hydroxylate C1(α), forming structures **442**, **448**, and **449** (see Table 9). In the case of 1β,18-dihydroxymanoyl oxide, *Gibberella fujikuroi* oxidized preferentially the 1β-hydroxyl to an oxo group to form compounds **456**, **457**, **459**, and **460** (see Table 10). In the course of the incubation of 1-oxo-18-hydroxymanoyl oxide, the authors observed that hydroxylation occurred exclusively at C3(β) position (**468**) when *Mucor plumbeus* was used (Table 11).

Ribenone (**470**, Table 12), a distinct manoyl oxide, is isolated from *Sideritis canariensis*, and it is a derivative from the enantiomer series. The purpose of using this compound in biotransformation studies is to obtain substances with functionality similar to forskolin (**438**), although being an enantioner.[161] In 1999 and 2001, Fraga et al. reported that the microorganisms *Mucor plumbeus* and *Gibberella fujikuroi* were able to metabolize ribenone to produce a wide range of compounds (Table 12).[159,160] The formation of a new double bond was observed in three different derivatives: 3-oxo-1-en-*ent*-13-*epi*-manoyl oxide (**471**), 12β-hydroxyl-3-oxo-1-en-*ent*-13-*epi*-manoyl oxide (**472**), and 3-oxo-1-en-14*S*,15-epoxy-*ent*-13-*epi*-manoyl oxide (**482**). However, only compound **471** was produced by *Gibberella fujikuroi*. Compound **482** also contains an epoxy group, as well as 11β-hydroxy-3-oxo-14*S*(*R*),15-epoxy-*ent*-13-*epi*-manoyl oxide (**483**/**484**), 1α-hydroxyl-3-oxo-14*S*,15-epoxy-*ent*-13-*epi*-manoyl oxide (**485**), 6α-hydroxyl-3-oxo-14*S*,15-epoxy-*ent*-13-*epi*-manoyl oxide (**486**), 6β-hydroxyl-3-oxo-14*S*,15-*ent*-13-*epi*-manoyl oxide (**487**), 12β-hydroxyl-3-oxo-14*S*(*R*),15-epoxy-*ent*-13-*epi*-manoyl oxide (**488**/**489**), 7α-hydroxyl-3-oxo-14*R*(*S*),15-epoxy-*ent*-13-*epi*-manoyl

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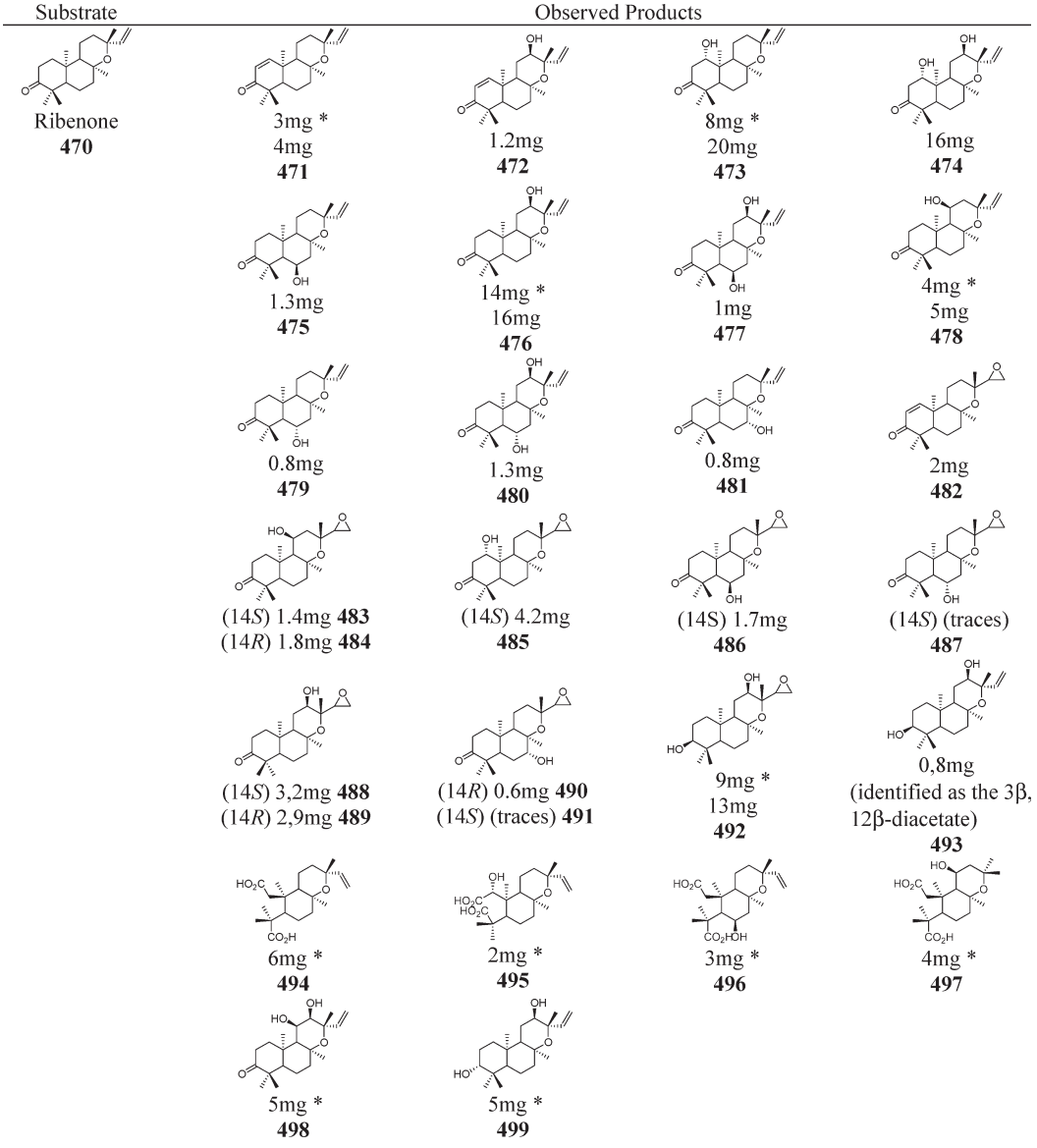
Table 12. Biotransformation of Ribenone (470) by *Mucor plumbeus* (260 mg) and *Gibberella fujikuroi* (220 mg) (Just the Compounds Assigned with "*" Were Produced by *Gibberella fujikuroi*; Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)[159,160]



oxide (**490**/**491**), and 3*β*,12*β*-dihydroxy-ent-13-*epi*-manoyl oxide (**492**).[159] From all of these compounds with an epoxy group, just compound **492** was synthesized by *Gibberella fujikuroi*.[160] The remaining products arise by monohydroxylations (**473**, **475**, **476**, **478**, **479**, **481**) or dihydroxylations (**474**, **477**, **480**, **493**).

Compounds **473**, **474**, and **476** were preferred for *Mucor plumbeus* and *Gibberella fujikuroi*. Moreover, the latter formed some exclusive compounds (**494**−**499**).[160] The novelty of some of these compounds is that they are carboxylic acids: *ent*-2,3-*seco*-13-*epi*-manoyl oxide-2,3-dioic acid (**494**), *ent*-1*β*-hydroxy-2,3-*seco*-13-*epi*-manoyl oxide-dioic acid (**495**), *ent*-6α-hydroxy-2,3-*seco*-13-*epi*-manoyl oxide-dioic acid (**496**), and *ent*-11α-hydroxy-2,3-*seco*-13-*epi*-manoyl oxide-dioic acid (**497**). Unfortunately, none of them are produced in reasonable yields.

3.8. Isocupresic Acid

Isocupressic acid (**500**) is found in species of *Pinus*. Terpenes of this kind can be transformed after ingestion to generate compounds of different activity. Microbial transformation of isocupressic acid is a useful approach to predict oxidative mammalian biotransformation of this compound.[162]

The most important research in this area was reported in 1998 by Lin and Rosazza. The authors concluded that isocupressic acid is transformed by *Nocardia aurantia* ATCC 12674, *Cunninghamella elegans* (−)NRRL 1393, and *Mucor*

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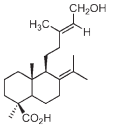
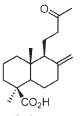
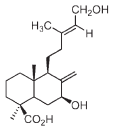
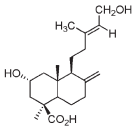
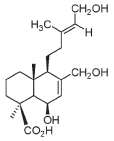
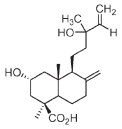
mucedo ATCC 20094 (Table 13).[162] The first simply produced compound **501**, whereas *Cunninghamella elegans* afforded 7α-hydroxyisocupressic acid (**502**) and labda-7,13(*E*)-diene-6α,15,-17-triol-19-oic acid (**503**) and *Mucor mucedo* gave 2*R*-hydroxyisocupressic acid (**504**) and labda-8(17),14-diene-2*R*,13-diol-19-oic acid (**505**). *Nocardia aurantia* seems the best among these three because it produced only one product with a higher yield than those achieved with the other microorganisms.

Table 13. Biotransformation of Isocupressic Acid (500) by *Nocardia aurantia* ATCC 12674 (200 mg), *Cunninghamella elegans* NRRL 1393 (200 mg), and *Mucor mucedo* ATCC 20094 (200 mg) (Mass in Brackets Corresponds to the Amount of Starting Material Used with Specific Microorganism; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)[162]

Substrate	Observed Products		
	Nocardia aurantia ATCC 12674 (6 days)	*Cunninghamella elegans NRRL 1393* (3 days)	*Mucor mucedo* ATCC 20094 (1 day)
 Isocupressic acid **500**	 34mg **501**	 7mg **502**	 5mg **504**
		 2mg **503**	 6mg **505**

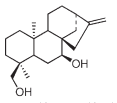
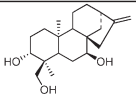
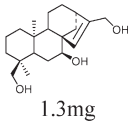
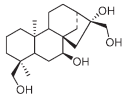
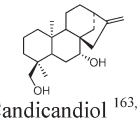
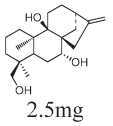
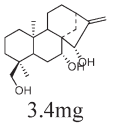
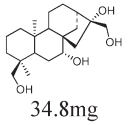
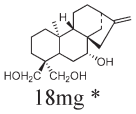
3.9. Epicandicandiol and Candicandiol

The diterpenes epicandicandiol (**506**) and candicandiol (**507**) are isomers and can be obtained from *Sideritis candicans* and other species from this genus.[163] Products obtained from biotransformation of epicandicandiol and candicandiol are shown in Table 14. In 2003, Fraga and co-workers reported that epicandicandiol was transformed by *Mucor plumbeus* by addition of hydroxyl group(s) to form 3α,7β, 18-trihydroxy-*ent*-kaur-16-ene (**508**), sideritrol (**509**), and 7β,16α,17,18-tetrahydroxy-*ent*-kaurane (**510**) (Table 14).[163] During the same study, candicandiol produced 7α,9β,18-trihydroxy-*ent*-kaur-16-ene (**511**), 7α,15α,18-trihydroxy-*ent*-kaur-16-ene (**512**), and 7α,16α,17,18-tetrahydroxy-*ent*-kaurane (**513**), suggesting that a simple spatial changing of the hydroxyl group at position C7 is sufficient to alter the way substrates bind to oxidative enzymes, resulting in a different hydroxylation pattern.[163] In a different investigation, the same research group revealed that a new compound was produced from candicandiol with *Gibberella fujikuroi*, 18,19-dihydroxycandicandiol (**514**).[164]

3.10. Cedrol

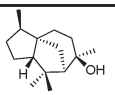
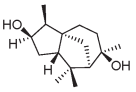
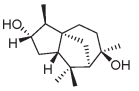
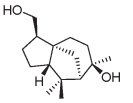
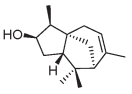
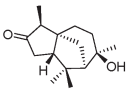
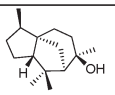
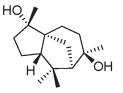
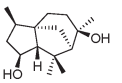
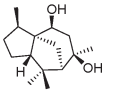
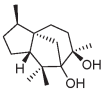
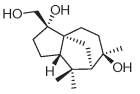
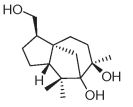
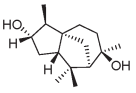
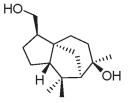
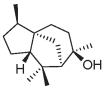
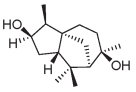
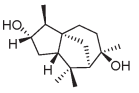
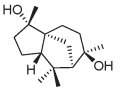
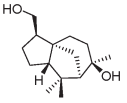
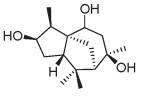
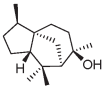
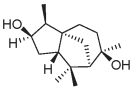
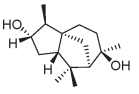
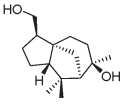
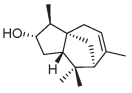
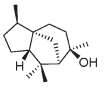
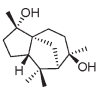
Cedrol (**515**) can be extracted from the volatile oil of *Juniperus* sp. Microbial transformation of cedrol is interesting due to the fact that analogues of this molecule are promising compounds for the perfume industry.[165] Cedrol has already been studied in many biotransformations using a significant number of microorganisms.[166−168] The number of products derived from cedrol is considerable, as we can observe in Table 15 which summarizes the structures of compounds obtained within the most significant investigations carried out with this sesquiterpene. Some of them were predominantly obtained, such as compounds 3β-hydroxycedrol (**516**), 3α-hydroxycedrol (**517**), and 12- hydroxycedrol (**518**), which were produced by the microorganisms *Curvularia lunata*, *Mucor plumbeus*, and *Glomerella cingulata*.[165−167] *Mucor plumbeus* afforded a mixture of compounds **516** and **517** in a reasonable yield of 67%. The compound 3-oxo-cedrol was synthesized by *Curvularia lunata*, but only in the presence of potato

Table 14. Biotransformation of Epicandicandiol (506) (140 mg) and Candicandiol (507) (230.8 mg) by *Mucor plumbeus*, and Biotransformation of Candicandiol (400 mg) by *Gibberella fujikuroi* (Compound Assigned by "*") (Amounts in Brackets Correspond to the Amount of Starting Material Used by Specific Microorganism; Substrates were Left with the Microorganisms for a Period of 6 days; Mass Shown in the Table Represents the Amount Achieved for Each Molecule)

Substrate	Observed Products		
 Epicandicandiol [165] **506**	 7.1mg **508**	 1.3mg **509**	 20.2mg **510**
 Candicandiol [163,164] **507**	 2.5mg **511**	 3.4mg **512**	 34.8mg **513**
	 18mg * **514**		

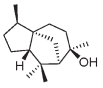
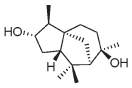
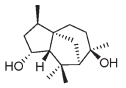
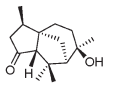
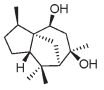
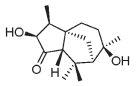
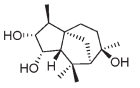
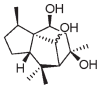
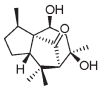
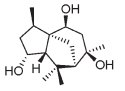
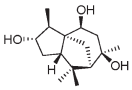
dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Table 15. Biotransformation of Cedrol (515) by *Curvularia lunata*, *Mucor plumbeus*, *Glomerella cingulata*, *Streptomyces griseus*, and *Bacillus cereus* (Percentage/Mass Shown in the Table Represents the Yield/Amount Achieved for Each Molecule)

Substrate	Observed Products		
 Cedrol, **515** (*Curvularia lunata* ATCC 12017 – potato dextrose broth, 14 days)[165]	 **516**	 **517**	 **518**
	 **519**	 **520**	
 Cedrol, **515** (*Curvularia lunata* ATCC 12017, beef extract medium, 14 days)[165]	 **521**	 **522**	 **523**
	 **524**	 **525**	 **526**
	 **517**	 **518**	
 Cedrol, **515** (*Mucor plumbeus* – glucose, 6 days)[166]	 mixture 1+2: 1:1; 67% **516**	 mixture 1+2: 1:1; 67% **517**	 3% **521**
	 2% **518**	 1.5% **527**	
 Cedrol, **515** (*Glomerella cingulata* – saccharose & glucose, 14 days)[167]	 10-12% at day 8 **516**	 30% at day 10, decreased afterwards **517**	 10-12% at day 8 **518**
	 10% at day 14 **528**		
 Cedrol, **515** (*Bacillus cereus* UI 1477 (NRRL B-14591)- Soybean meal/glucose, 1 day)[168]	 1.5g/13mg **529**		

dx.doi.org/10.1021/cr100258k |*Chem. Rev.* 2011, 111, 4418–4452

Table 15. Continued

Substrate	Observed Products		
 Cedrol, **515** (*Streptomyces griseus* ATCC 10137- Soybean meal/glucose, 2 days)[168]	 20% **530**	 20% **531**	 1% **532**
	 9% **533**	 1% **534**	 1% **535**
	 (**536**+**537**+**538** >30%) **536**	 **537**	 **538**
	 (20%) **539**		

dextrose broth, suggesting that the type of growth medium is an important factor for biotransformation. Other ketone products were 4-oxocedrol (**532**) and 4-oxo-3*S*-hydroxycedrol (**534**) from *Streptomyces griseus*.[168] 8-Cedren-3α-ol (**528**) and 3*β*-hydroxycedrene (**519**) were produced by *Glomerella cingulata* and *Curvularia lunata*, respectively. However, most of the new compounds were due to mono- (**516**, **517**, **518**, **521**−**524**, **530**, **531**, **535**, **538**, **539**) or dihydroxylations (**525**, **526**, **528**, **535**−**537**).[165−168]

4. CONCLUSIONS AND FUTURE PROSPECTS

In this Review, we have highlighted the use of a series of labdane-type diterpenes as starting materials for the preparation of numerous valuable molecules. We focused on the chemical and biomanipulation of labdanes that are accessible from natural sources.

Over the past few years, diverse synthetic strategies involving naturally occurring labdane-diterpenes, such as sclareol, sclareolide, labdanolic acid, abietic acid, larixol, or ozic acid, have been explored, with the purpose of establishing attractive methodologies for the production of fine chemicals, including pharmacologically active compounds, their synthetic precursors, and some interesting naturally occurring substances.

Starting from sclareol, a number of important molecules have been synthesized such as Ambrox, warburganal, galactones, wiedendiol-B, (+)-coronarin E, grindelic acid derivatives, (+)-subersic acid, *E*-rhinocerotinoic acid, (−)-15-oxopuupehenol (important antitumoral and antimalarial activity), (+)-lagerstronolide, (+)-7-deoxynimbidiol (antitumoral activty), or sibiricinone A (antimalarial activity). Sclareolide has also been proven an excellent starting point for the synthesis of medicinally and/or structurally important natural products, including coronarin A, austrodoric acid, pelorol, (+)-zerumin B, villosin, and chinesines A−E. Labdanolic and abietic acid have been useful for preparing mainly ambrox-type compounds.

Concerning the biomanipulation of diterpenoids, different microorganisms have been studied with the aim of producing new molecules that are not readily accessible by chemical synthesis. Among the most frequently used microorganisms are *Mucor plumbeus*, *Gibberella fujikuroi*, and *Aspergillus niger* (Table 16). The number of products resulting from biotransformation seems to vary with the microorganism, as well as the substrate. With few exceptions, product yields are generally low. For instance, biotransformation of sclareolide with *Cephalosporium aphidicola*[144] afforded three compounds in 24%, 26%, and 38% yield, while the same substrate gave two compounds in yields of 24% and 53% with *Cunninghamella elegans*.[144] It is also important to highlight that the performance of biotransformation can depend on the microorganism's growing conditions as seen in Table 15.

The main structural modification observed is the addition of hydroxyl groups (Table 16), and the position on the molecule where this occurs depends on both the substrate and the microorganism. This is due to the presence of different enzymes in the various microorganisms, having different specificities toward substrates. Some fungi seem to hydroxylate preferentially certain positions of labdane-diterpenes. Besides addition of hydroxyl groups to substrates, some microorganisms are able to perform other modifications, such as oxidation of methyl groups to carboxylic acids, esters or ketones, ether bond cleavage, or

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Table 16. Summary of the Microorganisms Already Experimented for Biotransformation and Their Relative Percentage within the Presented Studies, the Minimum and Maximum Days Used for Reaction to Occur, the Minimum and Maximum Number of Final Products, Indication of the Ones That Have Ever Produced Molecules in Reasonable Yields (>15−20%), and the Known Modification They Induced in the Substrates

microorganism	% use	reaction days	number of products	existence of products with reasonable yields	modifications
Mucor plumbeus	19%	2−14	1−20	yes	hydroxylation (C6 preferentially)
					attack of ketones
					formation of an epoxy ring
Gibberella fujikuroi	12%	6−10	1−11		hydroxylation
					formation of carboxylic acids
					attack of ketones
Aspergillus niger	10%	10−14	1−4		hydroxylation (C18 preferentially)
					formation of carboxylic acids
					formation of ketones
Beauveria bassiana	6%	14	1−2	yes	hydroxylation
					formation of carboxylic acids
Cunnighamella echinulata var. *elegans*	6%	10	1−5	yes	hydroxylation (C2 and C7 preferentially)
					formation of carboxylic acids
					attack of ketones
Fusarium lini	6%	8−10	2−4		hydroxylation (C1 preferentially)
Cephalosporium aphidicola	4%	10	3−4	yes	hydroxylation (C3 preferentially)
					formation of ketones
Cunninghamella elegans	4%	3−14	2−6	yes	hydroxylation
					ether bond cleavage and inversion of configuration
Curvularia lunata	4%	10−14	5−8		hydroxylation
Rhizopus stolonifer	4%	6−12	4−5	yes	hydroxylation (C6 preferentially)
					cleavage of the ether ring
Phanerochaete chrysosporium	4%	10	1−3		hydroxylation
Rhizopus oryzae	4%	5	1−2		hydroxylation
Whetzelinia sclerotiorum	4%	10	1−2	yes	hydroxylation (C7 preferentially)
Actinidia deliciosa	2%	15	6		hydroxylation
Bacillus cereus	2%	1	1		hydroxylation
Debarryomyces hansenii	2%	14	1	yes	hydroxylation
					formation of ketones
Glomerella cingulata	2%	14	4		hydroxylation
Mucor mucedo	2%	1	2		hydroxylation
Nocardia aurantia	2%	6	1	yes	hydroxylation
					formation of ketones
Rhodococcus erythropolis	2%	2	2		hydroxylation
					formation of carboxylic acids and ester
Streptomyces griseus	2%	2	10	yes	hydroxylation
					formation of ketones

even epoxide formation. Carboxylic acids were obtained with 5 out of 21 microorganisms reviewed (Table 16). Some microorganisms were able to form ketones from different labdanes.

We believe it is preferable to use microorganisms with a short biotransformation time; however, it is also desirable to choose microorganisms that produce as few products as possible to facilitate their isolation. Protection of labile groups on the starting labdane can be a good way to minimize the number of products and improve yields. Additional fungal and bacterial strains need to be explored.

The significant advances in the field of chemical and biological manipulation of labdanes documented here demonstrate the numerous useful transformations that these undergo, and the need for continued work in this area. It is hoped that this Review will not only inspire future researchers to make new discoveries, but also drive others to employ natural molecular resources as synthons in their own research.

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BIOGRAPHIES

Dr. Luís M. T. Frija was born in 1979 in Alenquer (Portugal). He received his B.Sc. in Chemistry from the University of Algarve in 2002 and his Ph.D. in Organic Chemistry from the same university in 2008 (M. Lurdes S. Cristiano). Part of the studies he performed during his Ph.D. program were developed in the University of Coimbra (Laboratory for Molecular Cryospectroscopy and Biospectroscopy (LMCB), Department of Chemistry) in the research group of Professor Rui Fausto. His research interests were initially mainly devoted to the design and synthesis of heteroaromatic compounds, such as tetrazoles and benzisothiazoles, of biological and/or pharmacological interest and to the study of their photoreactivity and spectroscopic properties. He worked for two years (2009−2010) as postdoctoral research fellow at the Instituto Superior Técnico-Technical University of Lisbon (Carlos A. M. Afonso). In 2011, he moved to Faculty of Pharmacy−Lisbon University as postdoctoral fellow and he is working on the development of novel and efficient protocols for synthetic transformations of Portuguese natural resources derived from *Cistus ladaniferus*.

Dr. Raquel Frade graduated in Biological Engineering from Instituto Superior Técnico of Lisbon in 2002 and received her Ph.D. in Biology in 2006 from the University of St. Andrews in Scotland, under the supervision of Prof. Ronald Thomas Hay. She worked for 2 years in the Institute of Experimental Biology and Technology in Oeiras, Portugal, where she performed bioactivity studies in human cell lines. She worked in Institute Superior Técnico on biotransformation studies using compounds extracted from *Cistus ladaniferus* plant and from other naturally occurring substances. She also performed toxicity evaluation of new ionic liquids and new rhodium complexes. At the present, she owns a Postdoctoral position in Faculty of Pharmacy-University of Lisbon, and her main task is the investigation of the bioactivity of new molecules.

Dr. Carlos A. M. Afonso graduated from University of Coimbra (1984), and he joined the New University of Lisbon as a teaching assistant and received his Ph.D. in 1990 under the supervision of Professor C. D. Maycock where he became assistant professor. He worked for one year as postdoctoral fellow at the Imperial College of Science Technology and Medicine under the supervision of Professor W. B. Motherwell (1990) and one more academic year of sabbatical leave (1997−1998) at the University of Bath, U.K. (Professor J. Williams), and at the University of Toronto (Professor R. Batey). In 2004, he moved to Instituto Superior Técnico of the Technical University of Lisbon as associate professor, and in 2008, he received his Agregação. In 2010, he moved to Faculty of Pharmacy − Lisbon University as full professor. His research focuses on the development of more sustainable methodologies in asymmetric organic transformations and the development and application of new ionic liquids.

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