Synthesis of *d,l*-Norlabdane Oxide and Related Odorants: An Intramolecular Radical Approach

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A cascade radical approach to *d,l*-norlabdane oxide and related odorants is reported. Oxidative radical cyclization of polyene **4** with Mn(III) and Cu(II) afforded exclusively bicycle **3**, which upon acid treatment gave tricycle **2** possessing the norlabdane oxide skeleton with a modified A-ring system. Tricycle **2** was ultimately converted to *d,l*-norlabdane oxide **1** and to several new A-ring labdane oxides as potential odorants.

Introduction

Ambergris[1] is a metabolite of blue sperm whale (*Physeter macrocephalus* L.) and accumulates as concretions in the gut. A naturally occurring fragrance, (−)-norlabdane oxide **1**,[2] produced during the aging process of ambergris with sunlight and air, is highly valued in the perfumery industry. Owing to its unique olfactive and fixative properties and a diminished availability from a natural source, a number of synthetic approaches have been developed toward **1** and racemic norlabdane oxide, the odor[3] of which is slightly different from that of the natural enantiomer. Since its first synthesis[4] in 1950, the major efforts targeted toward the synthesis of **1** have focused on the use of optically active terpenoids,[5] as starting materials, that possess several of the contiguous chiral centers present in the natural product. Recent reports have shown that naturally occurring sclareol[6] and communic acids[7] are the most attractive precursors for the preparation of **1**. Of these, sclareol, readily available from clary sage, appears to be the most ideal. The synthesis of both enantiomers of norlabdane oxide from geranylacetone[8] involving an optical resolution step and several strategies,[9] including a biomimetic-like[10] approach to racemic norlabdane oxide, have also been reported.

Results and Discussion

Specific odorants of the labdane oxide type are not only valuable in perfumery[1] but as additives to tobacco.[11] Our interest in this area was to develop a radical strategy that might provide an alternative cascade route to known and possibly new olfactory agents. Retrosynthetic analysis of **1** (Scheme 1) suggests that radical cyclization of polyene **4** with Mn(III) and Cu(II) could provide an indirect entry to tricycle **2** via a kinetic acid-catalyzed cyclization of **3**. Alternatively, stereospecific cyclization of **4** with 2 equiv of Mn(III) could in theory provide a direct one-step entry to **2** (vide infra), which in turn could serve as a common intermediate to known and to new functionalized A-ring norlabdane oxides as potential

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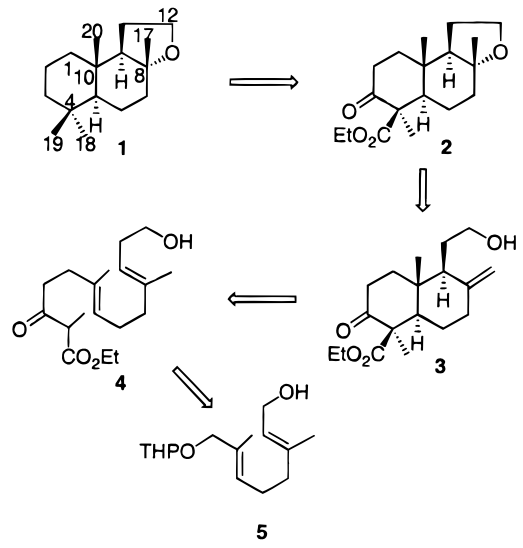
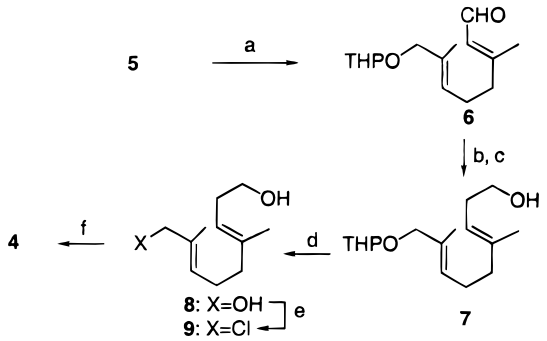
Scheme 1



Scheme 2[a]



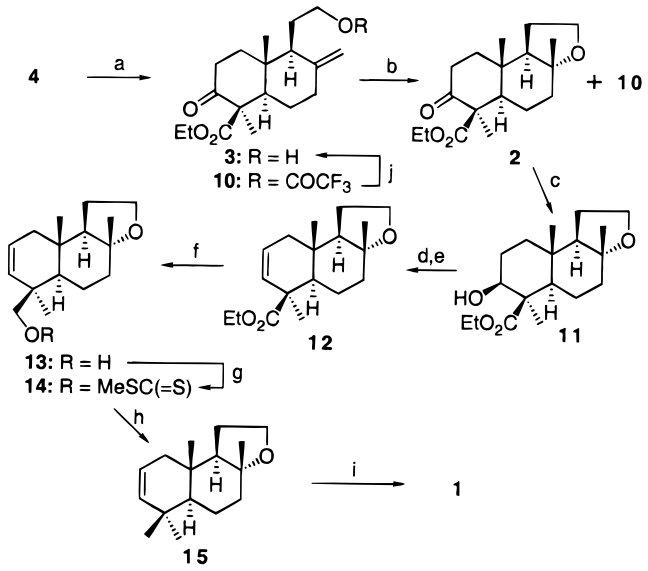
[a] Key: (a) Swern oxidation, −60 °C, N_2; (b) $Ph_3P{=}CH_2$, THF, −78 °C; (c) $(Me_2CHCHMe)_2BH$, THF, −10 °C, N_2, then aq NaOH, H_2O_2; (d) MeOH, *p*-TsOH·H_2O, rt; (e) NCS, DMS, CH_2Cl_2, −20 °C; (f) 5 equiv $LiCH_2C(O)CMe(Na)CO_2Et$, THF, 0 °C, then 10% HCl.

olfactory agents. We describe herein the application of the proposed radical methodology in the synthesis of racemic **1** and related norlabdane oxides.

The synthesis of polyene **4** from alcohol **5**[12] is shown in Scheme 2. Swern oxidation of **5** afforded aldehyde **6** in quantitative yield. Wittig reaction of **6** with triphenylphosphonium methylide followed by hydroboration of the resulting triene with disiamylborane and subsequent oxidation with basic hydrogen peroxide gave the one carbon extended alcohol **7** in 87% yield (two steps). Cleavage of the THP protecting group in **7** afforded diol **8** (97%), which was converted to the corresponding allyl chloride **9** (84%) by reaction of **8** with NCS and DMS.[13] Reaction of **9** with the dianion of ethyl 2-methylacetoacetate (5 equiv) followed by acidification gave polyene **4** (85%), after chromatography.

Oxidative free-radical[14] cyclization of **4** (Scheme 3) with a 2:1 ratio of $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OAc)_2{\cdot}H_2O$[15] in an 0.1 M solution of deaerated acetic acid afforded exclu-

Scheme 3[a]



[a] Key: (a) $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, HOAc; (b) CF_3CO_2H, rt; (c) $NaBH_4$, EtOH; (d) CF_3SO_2Cl, 4-DMAP, CH_2Cl_2, 0 °C; (e) 4-DMAP, CH_2Cl_2, Δ; (f) LAH, THF, Δ, then satd Na_2SO_4; (g) CS_2, DBN, DMF, rt, then MeI; (h) *n*-Bu_3SnH, xylene, Δ; (i) Pd/C, H_2; (j) EtOH, K_2CO_3.

sively the exocyclic product **3** in 58% yield. None of the endocyclic isomer was detected (vide infra). Attempted cyclization of **3** with *p*-TsOH·H_2O in nitromethane gave only 7% of desired tricycle **2** along with 59% of recovered starting materal and an unidentified faster moving compound(s). Fortunately cyclization of **3** with trifluoroacetic acid gave **2** (55%) and crude ester **10** (38%), which was hydrolyzed back to **3** and recyclized to afford **2** in 72% overall yield. It is noteworthy that cyclization of **3** could not be achieved with 90% aqueous trifluoroacetic acid.

The assignment of each proton and carbon resonance signal in **2** was determined from a series of 2D COSY, long-range COSY, HMQC, and HMBC correlations. The relative stereochemistry shown in **2** was consistent with the following 2D NOESY and 1D NOEDS results: The C-10 Me (δ 0.99) showed NOE enhancements to the C-8 Me (δ 1.15), the H_{2ax} proton (δ 2.99), the H_{1eq} proton (δ 1.85), the methyleneoxy protons of the ester (δ 4.15), the H_{6ax} proton (δ 2.07), and the H_{11ax} proton (δ 1.80). The C-8 Me showed enhancements to the C-10 Me, H_{12ax}, H_{11ax}, H_{6ax}, and 7_{eq} protons. These results confirmed the stereochemistry depicted in **2**.

The prevalant olfactory properties[1] of (−)-norlabdane oxide **1** are presumably due to the axial disposition of three methyl groups. Keeping this in mind, tricycle **2**, having a functionalized A-ring and three suitably disposed axial groups, presents an ideal synthon for elaboration to known as well as to potentially new odorants possessing the desired norlabdane skeleton. The synthesis of *d,l*-norlabdane oxide **1** from tricycle **2** was realized in the following manner. Hydride reduction of **2** with $NaBH_4$ gave alcohol **11** (91%). Subsequent reaction of **11** with trifluoromethanesulfonyl chloride in the presence of 4-DMAP followed by treatment of the resulting sulfonate with 4-DMAP in refluxing CH_2Cl_2 afforded

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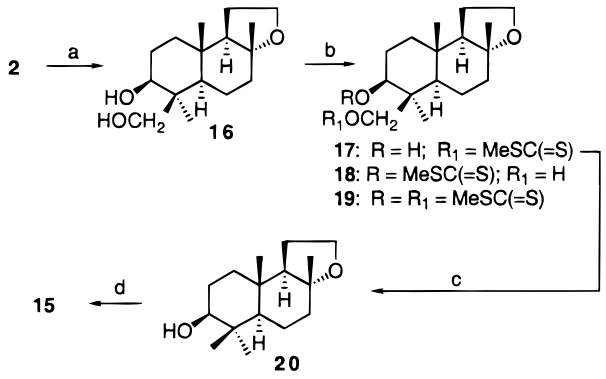
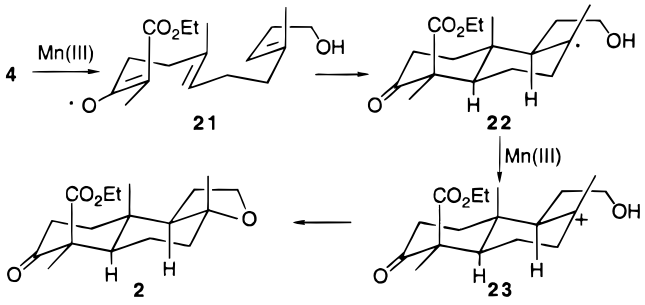
Scheme 4[a]



[a] Key: (a) LAH, THF, Δ, then satd Na_2SO_4; (b) CS_2, DBN, DMF, N_2, then MeI; (c) *n*-Bu_3SnH, xylene, Δ; (d) CF_3SO_2Cl, 4-DMAP, CH_2Cl_2, 0 °C, N_2.

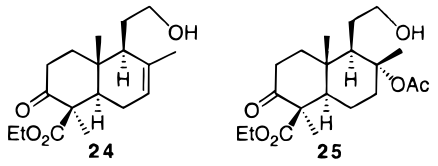
Scheme 5



12 (83%). Reduction of **12** with LAH yielded alcohol **13** (95%). Deoxygenation of **13** was effected in two steps using the procedure developed by Barton.[16] Thus, alcohol **13** was converted to dithiocarbonate **14** (94%) and treatment of **14** with *n*-Bu_3SnH afforded *d,l*-2-norlabdene oxide **15** in 78% yield along with a trace amount of **13**. Catalytic reduction of **15** with H_2 in the presence of 5% Pd/C gave a quantitative yield of *d,l*-**1**, the ^1H and ^{13}C NMR spectra of which were identical to those of (−)-**1**.

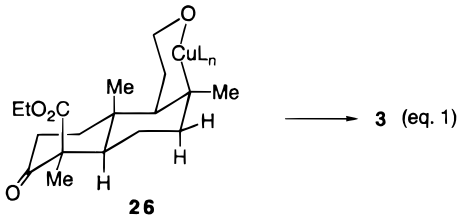
Of the modified A-ring compounds **11**−**15**, *d,l*-2-norlabdene oxide **15** possessed a fragrance most paralleling that of (−)-**1**. Hence, an alternative route to *d,l*-**15** was explored, as projected in Scheme 4**.** Hydride reduction of keto ester **2** with LAH yielded diol **16** (95%). Reaction of **16** with CS_2 in the presence of DBU followed by methylation with methyl iodide gave monodithiocarbonate **17** in 62% yield, after chromatography, along with the bisdithiocarbonate **19** and the 3*β*-monodithiocarbonate **18**. Subsequent treatment of **17** with *n*-Bu_3SnH[16] gave *d,l*-**20**[11] in 91% yield. It is noted that (−)-norlabdane-3*β*-ol oxide **20**, obtained from a fermentation process, and the corresponding ketone are valued as odorants in tobacco.[11] Reaction of **20** with CF_3SO_2Cl in the presence of 4-DMAP afforded directly *d,l*-**15** (97%).

In theory, one might postulate that tricycle **2** (Scheme 5) might be obtained directly from the oxidative free-radical cyclization of polyene **4** using excess $Mn(OAc)_3 \cdot 2H_2O$. Here, it might be anticipated that the derived tertiary radical **22** resulting from the second endo trig cyclization would be oxidized by an additional equivalent of Mn(III) to give the tertiary carbocation **23**. Under kinetic conditions, intermediate **23** could in turn be trapped intramolecularly by the alcohol group to afford tricycle **2**. Indeed, this postulation is intriguing, but in reality oxidative radical cyclization of **4** in the presence of 3 equiv of Mn(III) gave only 11% of **2**, 35% of an approximate 87:13 ratio of **3** and the corresponding Δ^7-isomer **24**, and acetate **25** (10%), after chromatography.

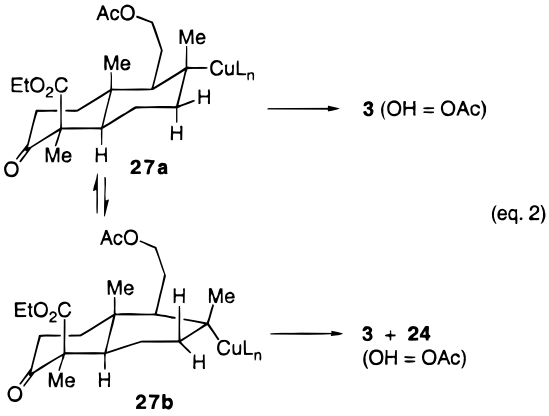


Acetate **25** was converted into **2** in the following manner. Hydrolysis of **25** with EtOH in the presence of K_2CO_3 afforded an intermediate diol which upon treatment with *p*-TsOH·H_2O in nitromethane gave **2** (70%, two steps).

It is noteworthy that cyclization of polyene **4** with Mn(III) in tandem with Cu(II) (vide supra*)* differs dramatically from that with Mn(III). The exclusive formation of the exo product **3** in the former case maybe due to an interelectron-transfer process[17] involving intermediate **26** (eq 1) resulting from intramolecular complexation of the



alcohol group with the copper species. Here, synchronous electron-transfer to copper and *β*-hydrogen elimination in the product-forming step may only be possible from the methyl group, since the C−Cu and C−H bonds should be aligned syn for smooth *β*-H elimination. The exclusion of the endo isomer **24** in this case may simply reflect the fact that the C−Cu and C_7−H bond cannot align in a syn fashion for *β*-H elimination to occur, since alcohol complexation locks the conformation. In support of this rationale, it was noted that cyclization of the corresponding acetate of **4** afforded a 67:33 ratio of acetates **3** and **24**. With the alcohol blocked as an acetate, the copper should come in from the less sterically hindered α-face of **22** (OH = OAc, Scheme 5). Here, syn *β*-hydrogen elimination via **27a** or **27b** (eq 2) could occur to afford exo and endo acetate products **3** and **24**, respectively.



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Conclusion

A stereoselective radical cascade approach to norlabdane oxides has been demonstrated. The distinct regiospecificity derived from the radical cyclization of polyene **4** with Mn(III) and Cu(II) versus that obtained from the corresponding acetate of **4** is also noteworthy.

Experimental Section

General Procedures. NMR spectra were obtained at 200 and 500 MHz. Elemental analyses were obtained from Galbraith Laboratories. HRMS analyses were obtained from the Mass Spectroscopy Facilities at UNC−CH and Duke. All melting points are uncorrected. Preparative chromatography was performed on Merck silica gel G 60 (70−230 mesh) and Merck silica gel G (230−400 mesh, for pressure chromatography). TLC was preformed with Sybron/Brinkmann silica gel G/UV 254 plates, 0.25 mm (analytical). Compounds on chromatography plates were visualized by spraying with 4% phosphomolybdic acid in isopropyl alcohol followed by heating. THF was distilled from sodium benzophenone ketyl. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted.

(2*E*,6*E*)-3,7-Dimethyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6-octadien-1-ol (5). Anhydrous K_2CO_3 (12.2 g, 88 mmol) was added to (2*E*,6*E*)-3,7-dimethyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6-octadienyl acetate[12] (52.1 g, 176 mmol) in absolute MeOH (95 mL) and the reaction mixture was stirred overnight at room temperature and then diluted with H_2O. The resulting mixture was extracted with CH_2Cl_2. The organic solution was washed with H_2O and brine. After back-washing of the aqueous solution with CH_2Cl_2, the organic solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (200 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 40.6 g (91%) of **5**: ^{1}H NMR ($CDCl_3$) δ 5.33−5.48 (m, 2H), 4.57−4.66 (m, 1H), 4.03−4.22 (m, 3H), 3.79−3.95 (m, 2H), 3.45−3.58 (m, 1H), 2.00−2.28 (m, 4H), 1.67 (s) and 1.48−1.95 (m) [13H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 138.8, 132.0, 127.7, 123.9, 96.9, 72.8, 61.9, 59.2, 39.0, 30.5, 25.8, 25.4, 19.3, 16.1, 14.0.

(2*E*,6*E*)-3,7-Dimethyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6-octadienal (6). Dry DMSO (7.4 g, 6.7 mL, 94.7 mmol) in dry CH_2Cl_2 (10 mL) was added to oxalyl chloride (5.8 g, 4.0 mL, 45.7 mmol) in dry CH_2Cl_2 (110 mL) at −60 °C over 20 min under N_2. After stirring for 5 min, alcohol **5** (10.0 g, 39.4 mmol) in dry CH_2Cl_2 (5 mL) *was added dropwise over 5 min* and the reaction mixture was stirred for an additional 15 min. Et_3N (20.3 g, 28 mL, 201 mmol) was added at −60 °C over 10 min and stirring was continued for 20 min. The reaction mixture was quenched with H_2O, allowed to come to room temperature, and extracted with CH_2Cl_2. The organic solution was washed with brine, and after back-washing of the aqueous solution, the organic solution was dried (Na_2SO_4), concentrated in vacuo at 35 mm and then at 0.4 mm to give 100% of crude **6**: ^{1}H NMR ($CDCl_3$) δ 10.0 (d, 1H, J = 8.0 Hz), 5.89 (dd, 1H, J = 0.9, 8.1 Hz), 5.35−5.47 (m, 1H), 4.59 (t, 1H, J = 3.3 Hz), 4.10 (d, 1H, J = 11.6 Hz), 3.84 (d, J = 11.6 Hz) and 3.80−3.94 (m) [2H], 3.44−3.58 (m, 1H), 2.29 (s) and 2.27-(s) [4H], 2.18 (s, 3H), 1.67 (s) and 1.45−1.94 (m) [9H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 191.2, 163.4, 133.4, 127.4, 125.5, 97.6, 72.5, 62.2, 40.1, 30.6, 25.4, 25.3, 19.5, 17.6, 14.1; IR (neat) 1675 cm^{-1}. Crude **6** was not characterized further but submitted directly to the Wittig reaction.

(3*E*,7*E*)-4,8-Dimethyl-9-[(2-tetrahydropyranyl)oxy]-3,7-nonadien-1-ol (7). *n*-BuLi (2.6 M in hexane, 20.5 mL, 53.3 mmol) was added to methyltriphenylphosphonium bromide (18.7 g, 52.3 mmol) in dry THF (250 mL) at −78 °C under N_2 over 30 min and the reaction mixture was stirred for 2 h. Crude aldehyde **6** (9.9 g, 39.3 mmol) in dry THF (5 mL) was added over 10 min and stirring was continued at −78 °C for 4 h. The reaction mixture was then allowed to warm to room temperature, quenched with H_2O (200 mL), and extracted with hexanes. The organic solution was washed with H_2O and brine, and after back-washing of the aqueous solution with CH_2Cl_2, the combined organic solution was dried (Na_2SO_4) and concentrated in vacuo to give 11.7 g of an oil. Chromatography on silica gel (80 g, 70−230 mesh) eluting with hexanes and ethyl acetate−hexanes gave 8.1 g (83%) of (2*E*,6*E*)-2,6-dimethyl-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,6,8-octatriene: ^{1}H NMR ($CDCl_3$) δ 6.57 (m, 1H), 5.86 (d, 1H, J = 10.9 Hz), 5.42 (m, 1H), 5.05 (m, 2H), 4.60 (t, 1H, J = 3.3 Hz), 4.10 (d, 1H, J = 11.5 Hz), 3.85 (d, J = 11.5 Hz) and 3.81−3.96 (m) [2H], 3.43−3.57 (m, 1H), 2.03−2.28 (m, 4H), 1.77 (s), 1.67 (s) and 1.44−1.95 (m) [12H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 139.0, 133.2, 132.1, 127.3, 125.6, 114.7, 97.3, 72.7, 62.1, 39.4, 30.6, 26.0, 25.4, 19.5, 16.6, 14.0. The triene was not characterized further but submitted directly to the hydroboration oxidation reaction.

Triene (7.76 g, 31.0 mmol) in dry THF (9 mL) was added slowly to a freshly prepared solution of disiamylborane (0.5 M in THF, 137 mL, 68.5 mmol) at −10 °C under N_2. The reaction mixture was stirred for 5 h between −5 and −10 °C and then carefully quenched with sequential addition of water (22.9 mL), 3 M NaOH (22.9 mL), and 30% aqueous H_2O_2 (22.3 mL). The heterogeneous mixture was vigorously stirred for 9 h and diluted with Et_2O. The organic solution was washed with H_2O and brine. After back-washing of the aqueous solution with CH_2Cl_2, the combined organic solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (66 g, 70−230 mesh) and elution with ethyl acetate−hexanes gave 7.2 g (87%) of **7**: ^{1}H NMR ($CDCl_3$) δ 5.35−5.48 (m, 1H), 5.08−5.21 (m, 1H), 4.61 (t, 1H, J = 3.3 Hz), 4.10 (d, 1H, J = 11.5 Hz), 3.84 (d, J = 11.5 Hz) and 3.80−3.97 (m) [2H], 3.45−3.69 (m, 3H), 2.02−2.36 (m, 7H), 1.65 (s) and 1.47−1.91 (m) [12H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 138.2, 132.0, 127.7, 120.4, 97.3, 72.9, 62.4, 62.1, 39.3, 31.5, 30.6, 26.1, 25.5, 19.4, 16.1, 14.0; IR (neat) 3423 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.73; H, 10.48.

(2*E*,6*E*)-2,6-Dimethyl-2,6-nonadien-1,9-diol (8) *p*-TsOH·H_2O (12.6 g, 66.2 mmol) was added in several portions to tetrahydropyran **7** (21.8 g, 81.3 mmol) in absolute MeOH (480 mL) and the reaction mixture was stirred at room temperature for 6 h. 3% NaOH (200 mL) was added and the resulting solution was extracted with CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (100 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 14.6 g (97%) of **8**: ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 1H), 5.13 (m, 1H), 3.97 (s, 2H), 3.60 (t, 2H, J = 6.2 Hz), 1.84−2.33 (m, 8H), 1.65 (s) and 1.63 (s) [6H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 138.1, 135.2, 125.7, 120.8, 68.8, 62.2, 39.3, 31.2, 25.7, 16.0, 13.7; IR (neat) 3331 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.69; H, 11.15.

(3*E*,7*E*)-9-Chloro-4,8-dimethyl-3,7-nonadien-1-ol (9). DMS (2.37 g, 2.8 mL, 38.1 mmol) was added to NCS (4.72 g, 35.3 mmol) in dry CH_2Cl_2 (120 mL) at 0 °C under N_2 over 20 min. A white suspension was formed after 15 min and the reaction mixture was then cooled to −20 °C. Diol **8** (5.0 g, 27.2 mmol) in dry CH_2Cl_2 (20 mL) was added over 10 min and after 15 min at −20 °C the reaction mixture was warmed to 0 °C and stirred for 2.5 h. Cold brine (200 mL) was added and the resulting mixture was extracted with CH_2Cl_2. The organic solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (50 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 4.6 g (84%) of **9**: ^{1}H NMR ($CDCl_3$) δ 5.50 (t, 1H, J = 6.3 Hz), 5.14 (m, 1H), 4.01 (s, 2H), 3.62 (t, 2H, J = 6.5 Hz), 2.02−2.36 (m, 7H), 1.74 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 137.9, 131.9, 130.4, 120.5, 62.4, 52.4, 38.9, 31.5, 26.4, 16.1, 14.1; IR (neat) 3355 cm^{-1}. Anal. Calcd for $C_{11}H_{19}OCl$: C, 65.17; H, 9.45. Found: C, 65.26; H, 9.79.

Ethyl (6*E*,10*E*)-13-Hydroxy-2,10-dimethyl-3-oxo-6,10-tridecadienoate (4). Ethyl 2-methylacetoacetate (23.8 g, 165 mmol) in dry THF (110 mL) was added to a suspension of NaH (60% in mineral oil, 6.75 g, 169 mmol) in dry THF (380 mL) at 0 °C under N_2 over 1 h. *n*-BuLi (2.6 M in hexanes, 64.9 mL, 169 mmol) was then added over 45 min and stirring was continued for 1.5 h. Chloride **9** (6.7 g, 33.1 mmol) in dry THF (50 mL) was added at 0 °C over 20 min and stirring was

continued for 2 h followed by neutralization with 10% HCl. The mixture was diluted with CH_2Cl_2 (300 mL) and then washed with saturated $NaHCO_3$, H_2O, and brine. The organic solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (140 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 8.8 g (85%) of **4**: ^{1}H NMR ($CDCl_3$) δ 12.73 (br s, 0.15H), 4.52−4.60 (m, 2H), 4.19 (q, 2H, J = 7.1 Hz), 3.62(t, 2H, J = 6.4 Hz), 3.52 (q, 0.85H, J = 7.1 Hz), 2.24−2.49 (m, 2H), 2.09−2.20 (m, 4H), 1.96−2.08 (m, 4H), 1.64 (s), 1.60 (s) and (HO) [7H], 1.33 (d, J = 7.1 Hz) and 1.27 (t, J = 7.1 Hz) [6H]; ^{13}C NMR ($CDCl_3$, 77.0) δ 205.5, 170.6, 138.3, 133.5, 124.8, 120.2, 62.4, 61.3, 52.9, 40.0, 39.6, 33.2, 31.4, 26.3, 16.1, 16.0, 14.1, 12.7; HRMS calc for C_{18} $H_{30}O_4$ (M^+) 310.2144, found 310.2148. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.01; H, 9.93. The carbon value for **4** was always slightly lower than the theoretical value.

(*d*,*l*)-[1*R*-(1α,4aα,8a*β*)]-5-(2-Hydoxyethyl)-1,4a-dimethyl-6-methylene-2-oxo-1,4,4a,5,8,8a-hexahydro-1-naphthylcarboxylic Acid, Ethyl Ester (3). $Mn(OAc)_3{\cdot}2H_2O$ (7.54 g, 28.1 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (2.81 g, 14.1 mmol) were added to keto ester **4** (4.36 g, 14.1 mmol) in deaerated HOAc (140 mL) at room temperature under Ar. The reaction mixture was stirred for 14 h and then passed through a Celite pad by washing with CH_2Cl_2 (200 mL). The organic solution was washed with H_2O and then back-washed with CH_2Cl_2. The combined organic solution was neutralized with 0.1 N NaOH (400 mL) and then washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (50 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 2.5 g (58%) of **3**: ^{1}H NMR ($CDCl_3$) δ 4.92 (s, 1H), 4.61 (s, 1H), 4.00−4.23 (m, 2H), 3.68−3.81 (m, 1H), 3.42−3.58 (m, 1H), 2.96 (6 line ddd, 1H, J = 6.2, 14.8, 14.8 Hz), 2.34−2.52 (m, 2H), 2.13 (ddd, 1H, J = 2.6, 6.2, 13.2 Hz), 1.34 (s, 3H), 1.23 (t, 3H, J = 7.2 Hz), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 208.7, 173.2, 146.7, 107.7, 61.8, 61.1, 57.5, 57.2, 51.0, 39.5, 38.8, 38.0, 37.1, 27.4, 26.1, 21.2, 13.6, 12.5. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.29; H, 9.48.

(*d*,*l*)-Ethyl 8α,12-Epoxy-3-oxo-13,14,15,16-tetranorlabdan-19-oate (2). From Acid-Catalyzed Cyclization. Keto ester **3** (483 mg, 1.57 mmol) in CF_3CO_2H (12 mL) was stirred at room temperature for 1 h and then diluted with CH_2Cl_2 (30 mL). The solution was washed with H_2O, neutralized with saturated $NaHCO_3$ (pH 7), and washed with brine. After back-washing, the organic solution was dried (Na_2SO_4) and concentrated in vacuo to give a thick oil. Chromatography on silica gel (20 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 264 mg of **2** [mp 54−56 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.15 (m, 2H), 3.94 (m, H_{12ax}, 1H), 3.85 (apparent dd, H_{12eq}, 1H, J = 8.2, 16.5 Hz), 2.99 (6 line ddd, H_{2ax}, 1H, J = 6.6, 14.7, 14.7 Hz), 2.43 (dq, H_{2eq}, 1H, J = ∼2.2, 15 Hz), 2.07 (m, H_{6ax}, 1H), 2.00 (dt, $H_{7eq,}$ 1H, J = ∼ 3.2, 11.9 Hz), 1.95 (dq, H_{6eq}, 1H, J = ∼3.2, 14.4 Hz), ∼1.85 (m, H_{1eq}, 1H), ∼1.81 (m, H_{11ax}, H_{11eq}, 2H), 1.48 (6 line ddd, 1H, H_{1ax}, J = ∼ 4.7, 13.8, 13.8 Hz), 1.38 (s, C-4 Me) and 1.32−1.41 (m, H_{7ax}, H_{9ax}, H_{5ax}) [6H], 1.27 (t, 3H, J = 7.2 Hz), 1.15 (s, C-8 Me, 3H), 0.99 (s, C-10 Me, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz, 77.0) δ 207.74 (C3), 173.43 (ester CO), 79.43 (C8), 64.74 (C12), 61.13 (ethyl CH_2), 59.17 (C9), 57.61 (C4), 57.55 (C5), 40.21 (C1), 39.05 (C7), 36.48 (C10), 36.39 (C2), 22.81 (C1), 22.47 (C6), 21.07 (4 Me), 20.73 (8 Me), 13.94 (ethyl Me), 12.52 (10 Me); IR (KBr) 1713 (br) cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.31.] and 243 mg of crude **10** along with a small amount of isomeric material. Anhydrous K_2CO_3 (249 mg, 1.8 mmol) was added to **10** (243 mg) in absolute EtOH (5 mL) and the reaction mixture was stirred for 30 min at room temperature and then diluted with CH_2Cl_2. The solution was washed with H_2O and brine, and after back-washing, the organic solution was dried (Na_2SO_4) and concentrated in vacuo at 35 mm and then at 0.5 mm to give 185 mg of crude alcohol(s), which was submitted directly to cyclization. The alcohol(s) (185 mg) in CF_3CO_2H (4.5 mL) was stirred at room temperature for 1 h. Workup as described above and chromatography on silica gel (8 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave an additional 85 mg of **2**. The total yield of **2** was 72%.

(*d*,*l*)-Ethyl 8α,12-Epoxy-3*β*-hydroxy-13,14,15,16-tetranorlabdane-19-oate (11). $NaBH_4$ (91.1 mg, 2.40 mmol) was added in small portions to keto ester **2** (246 mg, 0.799 mmol) in EtOH (6 mL) at 0 °C over 10 min. The reaction mixture was stirred for 30 min and then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). After separation of the two phases, the aqueous solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a solid. Trituration of the solid with hexanes gave 205 mg of **11**: mp 139−140 °C. Recrystallization of the solid from the filtrate with a 1:1 mixture of CH_2Cl_2 and hexanes gave an additional 21 mg of **11** (mp 139.5−140.6 °C) for a total yield of 91%. For **11**: ^{1}H NMR ($CDCl_3$) δ 4.15 (q, 2H, J = 7.1 Hz), 3.76−3.98 (m, 2H), 3.45 (d, 1H, J = 12 Hz), 3.10 (6 line ddd, 1H, J = 4.8, 12.0, 12.0 Hz), 1.42 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz), 1.09 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 177.6, 79.3, 78.4, 64.8, 60.3, 59.6, 56.3, 58.7, 39.3, 38.8, 36.3, 28.0, 23.6, 22.7, 22.2, 20.6, 14.0, 12.6; IR (KBr) 3524, 1711 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.55; H, 9.83.

(*d*,*l*)-Ethyl 13,14,15,16-Tetranor-8α,12-epoxy-4-labden-19-oate (12). Trifluoromethanesulfonyl chloride (201 mg, 127 uL, 1.20 mmol) was added dropwise to alcohol **11** (149 mg, 0.481 mmol) and 4-DMAP (352 mg, 2.88 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under N_2. The reaction mixture was stirred for 9 h at 0 °C and then washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to give an oil. 4-DMAP (180 mg, 1.48 mmol) was added to the oil in dry CH_2Cl_2 (15 mL) and the reaction mixture was refluxed overnight. TLC analysis showed that the reaction was incomplete. 4-DMAP (180 mg) was then added and refluxing was continued for 10 h. The reaction mixture was washed with H_2O, saturated $NaHCO_3$, and brine. After back-washing of the aqueous solutions, the organic solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (8 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 116 mg (83%) of **12**: mp 46.5−47.9 °C; ^{1}H NMR ($CDCl_3$) δ 5.63 (s, 2H), 4.11 (q, 2H, J = 7.1 Hz), 3.78−4.01 (m, 2H), 1.32 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz) 1.09 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 175.3, 132.0, 123.6, 79.4, 64.8, 60.3, 58.7, 53.8, 44.8, 40.9, 39.1, 35.1, 27.8, 22.9, 22.4, 20.0, 14.1, 13.9; IR (KBr) 1725, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.88; H, 9.80.

(*d*,*l*)-13,14,15,16-Tetranor-8α-12-epoxy-2-labden-19-ol (13). Ester **12** (99.6 mg, 0.341 mmol) in dry THF (6 mL) was added dropwise to a suspension of LAH (19.4 mg, 0.511 mmol) in dry THF (6 mL) at room temperature. The reaction mixture was refluxed for 40 min and cooled to 0 °C, and excess LAH was destroyed with saturated Na_2SO_4 (10 mL). After extraction with CH_2Cl_2, back-washing, and drying (Na_2SO_4), the combined organic solution was concentrated in vacuo. Chromatography on silica gel (2.5 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 81.2 mg (95%) of **13**: mp 116.0−117.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.61 (s, 2H), 3.78−4.01 (m, 2H), 3.69 (d, 1H, J = 10.8 Hz), 3.53 (d, 1H, J = 10.8 Hz), 1.68−2.05 (m, 6H), 1.18−1.51 (m, 5H), 1.11 (s) and 1.10 (s) [6H], 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 133.1, 124.2, 79.6, 66.6, 64.8, 58.9, 53.3, 40.7, 39.3, 39.3, 35.1, 25.7, 22.8, 21.2, 20.5, 15.8. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.51; H, 10.65.

(*d*,*l*)-*S*-Methyl 13,14,15,16-Tetranor-8α,12-epoxy-2-labden-19-dithiocarbonate (14). Carbon disulfide (1.6 mL) was added dropwise to alcohol **13** (70 mg, 0.28 mmol) and DBN (121.7 mg, 0.98 mmol) in dry DMF (2.5 mL) at room temperature under N_2. The red-orange reaction mixture was stirred at room temperature for 30 min. Methyl iodide (2.7 mL) was added dropwise and stirring was continued for 30 min. The reaction mixture was concentrated in vacuo and then diluted with CH_2Cl_2 (20 mL). The organic solution was washed with H_2O, brine, dried (Na_2SO_4), and concentration in vacuo gave an oil. Chromatography on silica gel (3 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 89 mg (94%) of **14**: mp 105.1−106.8 °C; ^{1}H NMR ($CDCl_3$) δ 5.25−5.71 (m, 2H), 4.60 (d, 1H, J = 10.8 Hz), 4.52 (d, 1H, J = 10.8

Hz), 3.77−4.10 (m, 2H), 2.58 (s, 3H), 1.70−2.07 (m, 6H), 1.31−1.54 (m, 4H), 1.18 (s, 3H), 1.11 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 215.9, 132.3, 124.8, 79.4, 64.8, 58.8, 53.2, 40.5, 39.2, 38.1, 35.0, 26.5, 22.7, 21.4, 20.5, 18.9, 15.6. Anal. Calcd for $C_{18}H_{28}O_2S_2$: C, 63.49; H, 8.29. Found: C, 63.66; H, 8.42.

(*d*,*l*)-13,14,15,16-Tetranor-8α,12-epoxy-2-labdene (15). From Tin Hydride Reduction. Thionoester **14** (81.2 mg, 0.239 mmol) in dry, deaerated xylene (9 mL) was added to a refluxing solution of *n*-Bu_3SnH (105 mg, 0.36 (mmol) in dry, deaerated xylene (15.8 mL) under Ar over 30 min. The reaction mixture was refluxed for 4.5 h and then concentrated in vacuo to give an oil. Chromatography on silica gel (5 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 29 mg (52%)[18] of **15** [mp 63.0−63.6 °C; ^{1}H NMR ($CDCl_3$) δ 5.37−5.52 (m, 2H), 3.78−4.01 (m, 2H), 1.94−2.03 (m, 1H), 1.68−1.87 (m, 5H), 1.22−1.51 (m, 4H), 1.11 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 138.6, 121.2, 79.8, 64.9, 58.8, 52.8, 40.5, 39.1, 35.2, 34.5, 31.9, 22.7, 22.2, 21.5, 20.5, 15.2. HRMS calculated for $C_{16}H_{26}O$ (M^+) 234.1983, found 234.1969.], 10 mg of recovered **14** along with 6.9 mg of alcohol **13**, and a trace amount of a bicyclic compound.[19]

A similar experiment using thionoester **14** (17.6 mg, 0.052 mmol) and *n*-Bu_3SnH (22.6 mg, 0.078 mmol) in xylene gave 9.4 mg (78%) of **15**, after general workup, careful removal of the xylene in vacuo, and chromatography.

(*d*,*l*)-8α,12-Epoxy-13,14,15,16-tetranorlabdane (1). From Catalytic Hydrogenation. Pd/C (5%, 1.4 mg) was added to **15** (8.0 mg, 0.0342 mmol) in MeOH (1 mL) and the resulting heterogeneous mixture was treated with H_2 at 1 atm. The reaction mixture was filtered through Celite and the residue was washed with additional MeOH. After removal of the MeOH in vacuo, the residue was dissolved in CH_2Cl_2 and dried (Na_2SO_4). Removal of the solvent gave 8.0 mg (100%) of *d*,*l*-**1**: ^{1}H NMR ($CDCl_3$) δ 3.75−3.99 (m, 2H), 1.09 (s, 3H), 0.88 (s, 3H), 0.83 (s, 6H); ^{13}C NMR ($CDCl_3$, 77.00) δ 39.91 (C-1 or C-7), 18.38 (C-2), 42.40 (C-3), 33.05 (C-4), 57.21 (C-5), 20.63 (C-6), 39.70 (C-7 or C-1), 79.90 (C-8), 60.08 (C-9), 36.15 (C-10), 22.61 (C-11), 64.97 (C-12), 21.12 (C-17or C-19), 33.57 (C-18), 21.12 (C-19 or C-17), 15.03 (C-20). The ^{1}H NMR spectrum of *d*,*l*-**1** was identical to the proton spectrum of (−)-ambroxide purchased from Aldrich. The ^{13}C NMR spectrum *d*,*l*-**1** was identical to the ^{13}C NMR spectrum reported for ambrox.[6e]

(*d*,*l*)-13,14,15,16-Tetranor-8α,12-epoxy-3,19-labdanediol (16). Keto ester **2** (102 mg, 0.33 mmol) in dry THF (3.5 mL) was added dropwise to a suspension of LAH (37.8 mg, 0.99 mmol) in dry THF (3.5 mL) at room temperature. The reaction mixture was refluxed for 40 min. Excess LAH was destroyed by addition of saturated Na_2SO_4 (5 mL) at 0 °C. The reaction was diluted with H_2O and then extracted with $CHCl_3$. The organic solution was dried (Na_2SO_4) and concentration in vacuo gave a solid. Trituration with hexanes gave 84 mg (95%) of **16**: mp 184−184.5 °C (1:1 CH_2Cl_2−EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.19 (H-19, d, 1H, J = 11.1 Hz), 3.76−3.99 (H-12, m, 2H), 3.30−3.53 (H-19, H-3, m, 2H), 2.78 (OH, br d, 1H), 2.53 (OH, br d, 1H), 1.25 (8-Me, s, 3H), 1.06 (4-Me, s, 3H), 0.80 (10-Me, s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 80.9, 79.6, 64.9, 64.0, 59.9, 56.4, 42.7, 39.6, 37.8, 35.6, 27.5, 22.8, 22.7, 20.9, 20.4, 15.4. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.28; H, 10.69.

(*d*,*l*)-*S*-Methyl 8α,12-Epoxy-3β-hydroxy-13,14,15,16-tetranorlabdan-19-yl Dithiocarbonate (17), (*d*,*l*)-*S*-Methyl 8α,12-Epoxy-19-hydroxy-13,14,15,16-tetranorlabdan-3β-yl Dithiocarbonate (18), and (*d*,*l*)-8α,12-Epoxy-3β-[(*S*-methyl) dithiocarbonoxy]-19-[(*S*-methyl) dithiocarbonoxy]-13,14,15,16-tetranorlabdane (19). CS_2 (1.14 g, 0.9 mL, 15.0 mmol) was added to diol **16** (48 mg, 0.18 mmol) and DBN (38 mg, 0.306 mmol) in dry DMF (1 mL) at room temperature under N_2 over 5 min. The red-orange reaction solution was stirred for an additional 30 min. CH_3I (4.1 g, 1.8 mL, 29 mmol) was added over 5 min and stirring was continued for 15 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1% HCl, saturated $NaHCO_3$, and brine. After back-washing, the organic solution was dried (Na_2SO_4) and concentrated in vacuo to give a solid. Chromatography on silica gel (3 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 10.6 mg (13%) of **19** [mp 183.0−184.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.49 (dd, 1H, J = 4.8, 11.7 Hz), 4.87 (d, 1H, J = 11.6 Hz), 4.79 (d, 1H, J = 11.6 Hz), 3.78−4.01 (m, 2H), 2.59 (s, 3H), 2.57 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 215.9, 215.8, 89.5, 79.5, 75.1, 64.9, 59.9, 56.6, 42.4, 39.7, 37.8, 35.8, 22.9, 22.8, 22.6, 21.5, 20.6, 19.0, 19.0, 14.8; Anal. Calcd. for $C_{20}H_{32}O_3S_4$: C, 53.53; H, 7.19. Found: C, 53.26; H, 7.36.] and 53 mg (82%) of an approximate 77:23 mixture of **17**:**18** as determined by ^{1}H NMR from integration of the δ 5.49 and δ 3.38 resonance signals. Recrystallization of the mixture gave 40 mg (62%) of **17**: mp 168.5−170.8 °C; ^{1}H NMR ($CDCl_3$) δ 4.80 (d, 1H, J = 11.6 Hz), 4.71 (d, 1H, J = 11.6 Hz), 3.77−4.00 (m, 2H), 3.32−3.47 (m, 1H), 2.58 (s, 3H), 1.24 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 215.9, 79.5, 79.0, 75.7, 64.9, 60.1, 56.3, 42.6, 39.8, 38.1, 35.8, 27.1, 22.9, 22.8, 21.4, 20.8, 19.0, 14.9. Anal. Calcd for $C_{18}H_{30}O_3S_2$: C, 60.30; H, 8.43. Found: C, 60.02; H, 8.56. For **18** (approximately 85% pure): ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 0.88 (s, 3H).

A similar experiment using diol **16** (54 mg, 0.20 mmol), DBN (97 mg, 0.78 mmol) in DMF (1 mL), CS_2 (1 mL), and MeI (2 mL) gave 27 mg (30%) of **19**: mp 182.2−183.5 °C (from chromatography). A second chromatography and recrystallization of a mixture of **17** and **18** from CH_2Cl_2−hexanes gave 19.2 mg (27%) of pure **17** and 20.2 mg of a 51:49 mixture of **17** and **18.**

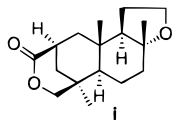
(*d*,*l*)-8α,12-Epoxy-3β-hydroxy-13,14,15,16-tetranorlabdane (20). Thionoester **17** (35.1 mg, 0.098 mmol) in dry, deaerated xylene (3 mL) was added to a refluxing solution of *n*-Bu_3SnH (45.6 mg, 0.157 mmol) in deaerated xylene (6.7 mL) over 10 min under Ar. The reaction mixture was refluxed for 4.5 h with stirring and then concentrated in vacuo to give a solid. The solid was washed with hexanes to give 22.5 mg (91%) of **20**: mp 164.0−165.5 °C; lit.[11] mp 162.0−163.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.75−3.98 (m, 2H), 3.19−3.33 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.85 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 77.0) δ 79.7, 79.0, 64.9, 60.0, 56.0, 39.5, 38.7, 38.1, 35.9, 28.2, 27.2, 22.6, 21.1, 20.4, 15.2, 15.1.

(*d*,*l*)-13,14,15,16-Tetranor-8α,12-epoxy-2-labdene (15). Trifluoromethanesulfonyl chloride (22.8 mg, 14.4 μL, 0.135 mmol) was added dropwise to alcohol **20** (13.6 mg, 0.054 mmol) and 4-DMAP (39.5 mg, 0.324 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 7 h and then diluted with CH_2Cl_2 (5 mL). The solution was washed with H_2O and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to give an oil. Chromatography on silica gel (2.5 g, 230−400 mesh) eluting with hexanes and ethyl acetate−hexanes gave 12.3 mg (98%) of **15**. The ^{1}H NMR spectrum of **15** was identical to the spectrum of **15** obtained from tin hydride reduction of **14**.

(*d*,*l*)-Ethyl 8α,12-Epoxy-3-oxo-13,14,15,16-tetranorlabdan-19-oate (2), (*d*,*l*)-Ethyl 13,14,15,16-Tetranor-3-oxo-7- and -8- (17)-labden-19-oates (3 and 24), and (*d*,*l*)-Ethyl 13,14,15,16-Tetranor-8-acetoxy-12-hydroxy-3-oxolabdan-19-oates (25). Cyclization with Excess Mn(III). $Mn(OAc)_3 \cdot H_2O$ (3.61 g, 13.5 mmol) was added to keto ester **4** (1.4 g, 4.5 mmol) in deaerated HOAc (45 mL) at room temperature under Ar. The reaction mixture was stirred overnight and general workup followed by chromatography on silica gel (32 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 146 mg (11%) of **2** (mp 54−56 °C), 487 mg (35%) of an approximate 87:13 ratio of **3** and isomer **24**, and 202 mg (10%) of acetate **25**. The ^{1}H NMR spectrum of **2** was identical to the proton

(18) Compound **15** is quite volatile and care must be exercised on removal of the solvent. Here the moderate yield (52%) was due to loss of product under vacuum.

(19) A trace amount of a bicyclic compound was also isolated. It has not been fully characterized and has been tentatively assigned as structure **i**.



i

spectrum of **2** obtained from the acid-catalyzed cyclization of **3**. For **25**: ^{1}H NMR ($CDCl_3$) δ 4.02−4.20 (m, 2H), 3.52−3.71 (distorted t, 2H), 2.92 (6 line ddd, 1H, J = 6.3, 14.8 Hz) and 2.71−3.02 (m) [2H], 2.38 (ddd, 1H, J = 3.3, 12.5 Hz), 1.93 (s, 3H), 1.52 (s, 3H), 1.23 (t, 3H), 0.97 (s, 3H).

Anhydrous K_2CO_3 (182 mg) was added to acetate **25** (155 mg) in EtOH (1.5 mL) and the reaction mixture was stirred for 6 h. General workup and chromatography on silica gel (6 g, 70−230 mesh) eluting with ethyl acetate−hexanes gave 83 mg of a diol: ^{1}H NMR ($CDCl_3$) δ 4.03−4.21 (m, 2H), 3.79 (distorted dt, 1H, J = 4.4, ~9.0 Hz), 3.45 (6 line ddd, 1H, J = 4.3, 9.8 Hz), 3.23 (br s, OH, 1H), 2.94 (6 line ddd, 1H, J = 6.4, 14.8, 14.8 Hz), 2.39 (ddd, 1H, J = 2.4, 4.7, 15.0 Hz), 1.36 (s, 3H), 1.25 (s) and 1.25 (t, J = 7.1 Hz) [6H], 0.94 (s, 3H). *p*-TsOH·H_2O (16.4 mg) was added to the diol (83 mg, 0.254 mmol) in dry CH_3NO_2 (4.8 mL). The reaction mixture was stirred at room temperature for 20 h and then diluted with CH_2Cl_2 (5 mL). The organic solution was washed with saturated $NaHCO_3$, H_2O, and brine, and after back-washing of the aqueous solutions, the organic solution was dried (Na_2SO_4) and concentrated in vacuo to give 55 mg (70%) of **2**. The ^{1}H NMR spectrum of **2** was identical to the proton spectrum of **2** obtained from the radical cyclization of **4** and that of **2** obtained from the acid (CF_3CO_2H) catalyzed cyclization of **3**.

A reaction using keto ester **4** (295 mg, 0.95 mmol), $Mn(OAc)_3$·$2H_2O$ (765 mg, 2.86 mmol), and NaOAc (312 mg, 3.81 mmol) in HOAc (9.5 mL) under Ar with stirring overnight gave 20 mg (7%) of **2**, 103 mg (35%) of a mixture of **3** and **24**, and 35 mg (12%) of **25**, after chromatography on silica gel (12 g, 70−230 mesh) eluting with ethyl acetate−hexanes.

Keto Ester 2. From Attempted Cyclization of 3 with *p*-TsOH·H_2O in Nitromethane. *p*-TsOH·H_2O (13.1 mg, 0.069 mmol) was added to alcohol **3** (63 mg, 0.205 mmol) in CH_3NO_2 (3.8 mL) and the reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2 (10 mL). The organic solution was washed with saturated $NaHCO_3$, and after back-washing, the combined CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil. Chromatography on silica gel (3 g, 230−400 mesh) eluting with ethyl acetate−hexanes gave 4.2 mg (7%) of **2** and 20.3 mg of an unidentified faster moving compound(s) along with 37 mg (59%) of recovered **3**.

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Supporting Information Available: ^{1}H NMR spectra of **4**, **6**, **25**, the intermediate triene and diol, and the ^{13}C NMR spectra of **4**, **6**, and triene (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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