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Practical Synthesis of Ambrox® from Farnesyl Acetate Involving Lipase Catalyzed Resolution

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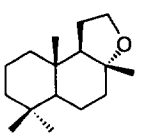
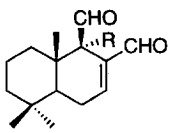
Abstract: Enantiomerically pure Ambrox® was synthesized from (–)-13,14,15,16-tetranor-8α,12-labdanediol, which was prepared by lipase catalyzed kinetic resolution of (±)-drimane-8,11-diol.

To date, much attention has been paid to the synthesis of ambergris-fragrance Ambrox®[1a-g] and other drimane sesquiterpenes[2] due to their wide range of biological activities, however, few useful asymmetric syntheses have been reported.[1a] Most early works were preparations by degradation of the naturally occurring sesquiterpenes or diterpenes.[3a-e]

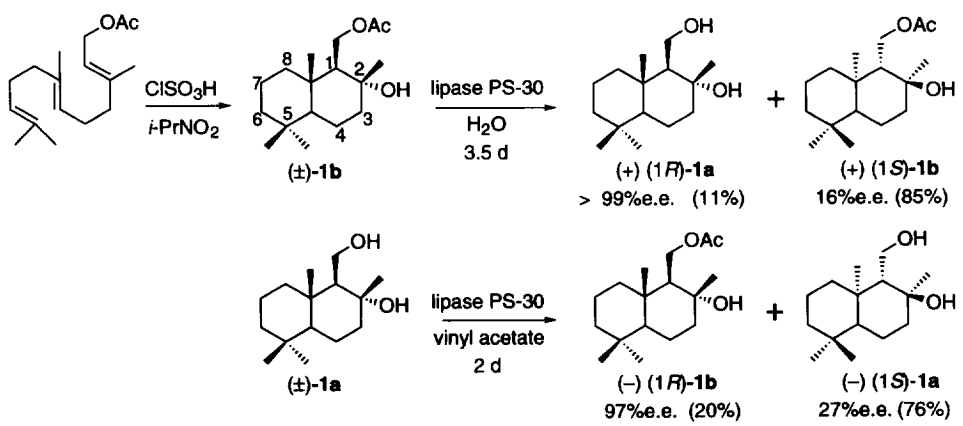


Ambrox®



R = H, Polygodial
R = OH, Warburganal

In this paper we report the synthesis of Ambrox® using the enzymatic preparation of (+)-drimanediol [(+) (1*R*)-**1a**] or (–)-13,14,15,16-tetranor-8α,12-labdanediol [(–) (1*R*)-**2a**] in key steps. The former compound (+) (1*R*)-**1a** was an important synthetic intermediate for the famous antifeedants polygodial and warburganal,[3a-b] and the latter compound (–) (1*R*)-**2a** was that for a commercial tenacious ambergris-type perfumery Ambrox®.[3d]



Scheme 1

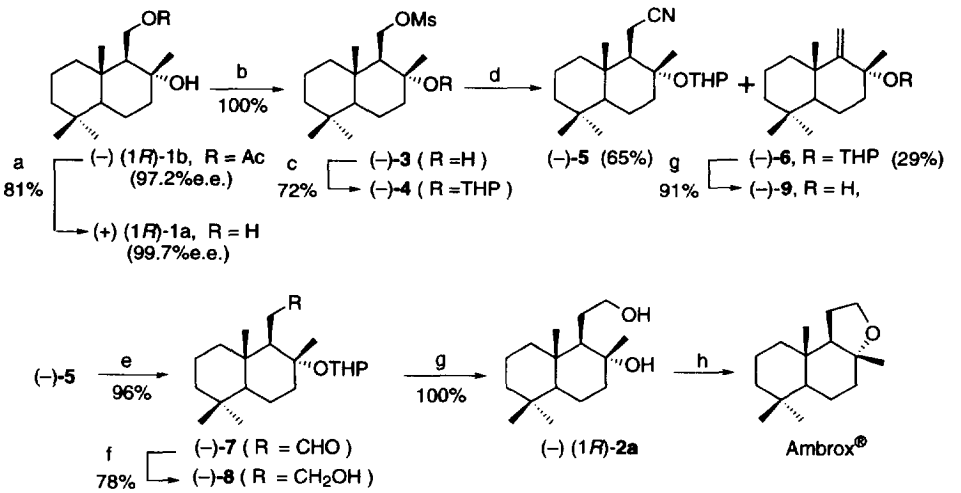
Table 1. Optical Resolution of (±)-**1a** by Repeating Lipase Catalyzed Acetylation [a]

Substrate	Time (d)	(–) (1*R*)-**1b** (%)	e.e.[b](%)	(–) (1*S*)-**1a** (%)	e.e.[b](%)
(±)-**1a**	2	20	97	76	27
(–) (1*S*)-**1a**[c] (27%e.e.)	3.5	13	68	70	50
(–) (1*S*)-**1a**[c] (50%e.e.)	2	21	55	72	89

a. Substrate (0.2 M), vinyl acetate (0.8 M) and Lipase PS-30 (5 mg/ml) in *i*-Pr2O-benzene (1:1) at 30°C.
b. Calculated by the specific rotation values. c. Recovered substrate

Racemic substrates (±)-**1a** and its monoacetate (±)-**1b** prepared by cyclization of farnesyl acetate with chlorosulfonic acid[4] were subjected to screening of enzymatic resolution. We used commercially available lipases (Amano and Nagase) and amylases (Nagase). Among them, lipase PS-30 (*Pseudomonas* sp., Amano) exhibited the best results (Scheme 1). Hydrolysis of (±)-**1b** gave enantiomerically pure (+) (1*R*)-**1a** [11%, >99%e.e., determined by ^{1}H NMR and HPLC (CHIRALCEL OD) analyses of the corresponding (*S*)-MTPA ester of the primary hydroxyl group], but the reaction rate was quite slow. On the other hand, the lipase catalyzed acetylation of (±)-**1a** proceeded faster to afford (–) (1*R*)-**1b** (20%, 97%e.e.). The absolute stereochemistry of (+) (1*R*)-**1a** was confirmed by comparing the sign of the specific rotation value with that reported.[3e] The acetylation product (–) (1*R*)-**1b** was deacetylated by $LiAlH_4$ reduction and recrystallized to give enantiomerically pure (+) (1*R*)-**1a** (99.7%e.e.). The repeated acetylations of the recovered substrate (–) (1*S*)-**1a** gave (–) (1*R*)-**1b** and (–) (1*S*)-**1a** (89%e.e.) as shown in Table 1. The recrystallization of (–) (1*S*)-**1a** (89%e.e.) from *i*-Pr_2O gave enantiomerically pure (–) (1*S*)-**1a**. The optical yield of (–) (1*R*)-**1b** and (–) (1*S*)-**1a** were 76% and 76% respectively.

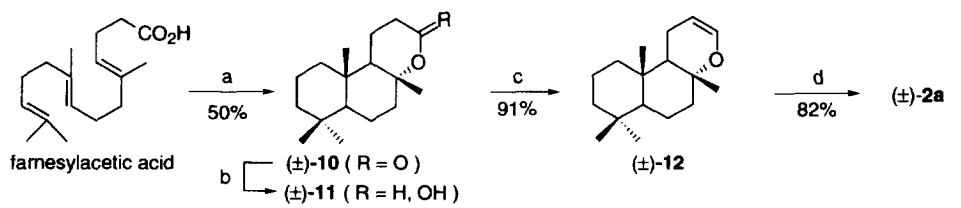
The one carbon elongation of enantiomerically pure (+) (1*R*)-**1a** gave the compound (–) (1*R*)-**2a** as shown in Scheme 2. The diol (+) (1*R*)-**1a** was converted to mesylate (–)-**4** and the tertiary hydroxyl group of **4** was protected as THP ether. We found that cyanization of (–)-**4** with NaCN in the presence of crown ether gave nitrile [(–)-**5**], although the elimination byproduct [(–)-**6**] was observed. Treatment of (–)-**6** with bis(trimethylsilyl) sulfate [$(TMS)_2SO_4$][5] afforded the sporogenic compound (–)-drim-9(11)en-8-ol [(–)-**9**] which was isolated from the fungus *Aspergillus oryzae*.[6] The nitrile (–)-**5** was then treated with diisobutylaluminium hydride (DIBAL) to give aldehyde (–)-**7**, which was further reduced with $LiAlH_4$ to yield alcohol (–)-**8**. Deprotection of (–)-**8** with various acidic media [*p*-toluenesulfonic acid (TsOH) or pyridinium *p*-toluenesulfonate] unsuccessfully gave dehydrated products of the tertial hydroxyl group. Heating (–)-**8** in xylene at 120°C for 48 h gave the corresponding alcohol (–) (1*R*)-**2a** only in a 48% yield. Satisfactorily treatment with catalytic amount of $(TMS)_2SO_4$ gave a quantitative yield of (–) (1*R*)-**2a**. Treatment of (–)(1*R*)-**2a** with *p*-toluenesulfonyl chloride (TsCl) in pyridine by Barrero's protocol afforded (–)-Ambrox®.[3d] The overall yield was 35% in 7 steps from (+) (1*R*)-**1a**.



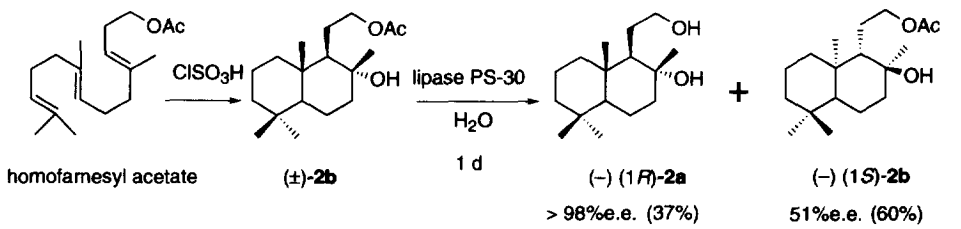
a; $LiAlH_4/Et_2O$ then recrystallization b; MsCl/Py c; DHP/TsOH/CH_2Cl_2 d; NaCN/18-crown-6/DMSO
e; DIBAL/CH_2Cl_2 f; $LiAlH_4/Et_2O$ g; $(TMS)_2SO_4$ h; TsCl/Py

Scheme 2

Furthermore, we attempted the lipase PS-30 catalyzed kinetic resolution of (±)-**2a** or its monoacetate (±)-**2b**. (±)-Ambreinolide [(±)-**10**] prepared by the cyclization of farnesylacetic acid with chlorosulfonic acid [7] was reduced with DIBAL to give lactol (±)-**11**. Isomers arising from the cyclization could be removed by recrystallization of (±)-**11**. Dehydration of (±)-**11** with TsCl in pyridine followed by ozonolysis and reduction with $NaBH_4$ led to (±)-**2a**. The monoacetate (±)-**2b** was also prepared from homofarnesyl acetate.[4]



a; $ClSO_3H/i\text{-}PrNO_2$ b; DIBAL/CH_2Cl_2 c; TsCl/Py d; O_3/MeOH then $NaBH_4$



Scheme 3

Although asymmetric acetylation of (±)-**2a** using lipase PS-30 was unsuccessful (12%e.e.), asymmetric hydrolysis of (±)-**2b** proceeded satisfactorily to give (–) (1*R*)-**2a** (98%e.e., enantiomeric purities were determined as mentioned above) (Scheme 3)

In summary, we have developed an efficient synthesis of enantiomerically pure Ambrox® based on lipase catalyzed resolution. The enantiomerically pure intermediates, (+)-drimane-8,11-diol and (–)-13,14,15,16-tetranor-8a,12-labdanediol will serve as valuable intermediates in the synthesis of chiral terpenoids.

Experimental

General. All melting point (mp) values are uncorrected. ^{1}H NMR spectra were recorded on JEOL GSX-270 (270 MHz) and JEOL JMA-5600 (400 MHz) spectrometers in $CDCl_3$. IR spectra were recorded on a JEOL JMS HX-105 spectrometer. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-4 polarimeter.

Kinetic Acetylation of Racemic Drimane-8,11-diol [(±)-1a]. A suspension of (±)-**1a** (1.80 g, 7.50 mmol), vinyl acetate (2.9 ml, 2.7 g, 31 mmol) and lipase PS-30 (*Pseudomonas* sp., Amano, 0.20 g) in *i*-Pr_2O-benzene (40 ml, 1:1) was stirred at 30°C for 2 d. After the reaction mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed on silica gel (hexane-EtOAc = 2:1 - 1:2) to give acetate (–) (1*R*)-**1b** (0.423 g, 20.0%, 97.2%e.e.) and alcohol (–) (1*S*)-**1a** (1.36 g, 75.5%, 27%e.e.). The enantiomeric purity of (–) (1*R*)-**1b** was determined by ^{1}H NMR and HPLC analyses after the reduction with $LiAlH_4$ and transformation to the corresponding mono-(*S*)-MTPA ester of the primary hydroxyl group. And the enantiomeric purity of the non-acetylated product (–) (1*S*)-**1a** {$[\alpha]_D^{21}$ –1.1 (*c* 1.3)} was calculated by comparing the specific rotation value with that reported of (+) (1*R*)-**1a** {lit.[3e] $[\alpha]_D^{26}$ +4.2 (*c* 1.3)}.

(–)-11-Acetoxy-8α-drimanol [(1*R*,2*R*,4a*S*,8a*S*)-(–)-(1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-hydroxy-2,5,5,8a-tetramethyl-1-naphthyl)methyl Acetate] [(–)-1b]: mp 83°C; $[\alpha]_D^{21}$ –8.5 (*c* 1.00) {lit.[8] $[\alpha]_D^{20}$ –9 (*c* 0.53)}; IR (KBr): 3480 cm^{-1} (s, OH), 1710 (s, C=O), 1260 (s, O-Ac), 938 (s); ^{1}H NMR (400 MHz): δ 0.81 (3H, s, 5-CH_3), 0.86 (3H, s, 5-CH_3), 0.88 (3H, s, 8a-CH_3), 1.18 (3H, s, 2-CH_3), 0.9-1.7 (11H, m) 1.89 (1H, dt, 3.3, 12.5, 6-H_{aq}), 2.05 (3H, s, Ac H), 2.38 (1H, br., OH), 4.24 (1H, dd, 5.1, 11.7, C<u>H</u>H–OAc), 4.36 (1H, dd, 4.4, 11.7, CH<u>H</u>–OAc); *Anal.* Found: C, 72.06; H, 10.41. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71%; HPLC [(*S*)-MTPA ester]: 97.2%e.e., CHIRALCEL OD (hexane-*i*-PrOH = 2:1, 1.0 ml/min), t_R = 3.5 min (98.6%) and 3.9 min (1.4%).

(+)-Drimane-8,11-diol [(1*R*,2*R*,4a*S*,8a*S*)-(+)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-hydroxy-2,5,5,8a-tetramethyl-1-naphthalenemethanol] [(+) (1*R*)-1a]. (–) (1*R*)-**1b** (0.400 g, 1.42

mmol) was reduced with $LiAlH_4$ in the usual manner to give (+) (1*R*)-**1a** (0.314 g, 92.2%) as white crystals; these were further recrytstallized with hexane-*i*-Pr_2O to raise enantiomeric purity (99.7%e.e.): mp 126-128°C (hexane-*i*-Pr_2O); $[\alpha]_D^{21}$ +5.5 (*c* 0.50); IR (KBr): 3350 cm^{-1} (br. s, OH), 1128 [s,$S(=O)_2$], 1020 [s, $S(=O)_2$], 940 (m); ^1H NMR (270 MHz): δ 0.79 [6H, s, 5-$(CH_3)_2$], 0.88 (3H, s, 8a-CH_3), 1.35 (3H, s, 2-CH_3), 0.9-1.8 (m, 12H), 1.89 (1H, dt, 3.2, 12.2, 6-H_{eq}), 2.8-3.3 (br., OH), 3.92 (2H, d, 6.8, CH_2OH); *Anal.* Found: C, 74.60; H, 11.47. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%).

Kinetic Hydrolysis of Racemic 11-acetoxy-8α-drimanol [(±)-1b]. A suspension of (±)-**1b** (0.200 g, 0.709 mmol), 0.2% aq. tween®80 (0.1 ml) and lipase PS-30 (0.10 g) in 0.1 M phosphate buffer (pH 7.0, 10 ml) and benzene (1 ml) was stirred at 30°C for 3.5 d. After the reaction mixture was filtered through a Celite pad, the filtrate was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The mixture was chromatographed on silica gel to give diol (+) (1*R*)-**1a** (0.019 g, 11%, >99%e.e.) and acetate (+) (1*S*)-**1b** (0.170 g, 85.0%, 16%e.e.). In the same manner as kinetic acetylation of (±)-**1a**, the enantiomeric purity of the hydrolyzed product (+) (1*R*)-**1a** was determined by ^1H NMR and HPLC analyses and the enantiomeric purity of non-hydrolyzed product (+) (1*S*) **1b** {$[\alpha]_D^{21}$ +1.4 (*c* 0.53)} was calculated by comparing the specific rotation value with that reported of (–) (1*R*)-**1b** {lit.[8] $[\alpha]_D^{20}$ –9 (*c* 0.53)}.

(1*R*,2*R*, 4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-1-[(methanesulfonyloxy)methyl]-2,5,5,8a-tetramethylnaphthalen-2-ol [(–)-3]. To a solution of (+) (1*R*)-**1a** (0.145 g, 0.604 mmol) in pyridine (2 ml) was added dropwise methanesulfonyl chloride (MsCl) (0.056 ml, 0.72 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h and diluted with Et_2O. The organic phase was washed successively with aq. $CuSO_4$, H_2O and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil; that was filtered through a short silica gel column with hexane-EtOAc (1:1) to give (–)-**3** (0.192 g, 100%) as a colorless oil: $[\alpha]_D^{21}$ –18.4 (*c* 1.92); IR (film): 3525 cm^{-1} (br. s, OH), 1350 [s, $S(=O)_2$], 1170 [s, $S(=O)_2$]; ^1H NMR (400 MHz): δ 0.82 (3H, s, 5-CH_3), 0.89 (3H, s, 5-CH_3), 0.90 (3H, s, 8a-CH_3), 1.17 (3H, s, 2-CH_3), 0.85-1.8 (12H, m), 1.92 (1H, dt, 3.3, 12.5, 6-H_{eq}), 3.04 (3H, s, S–CH_3), 4.35 (1H, dd, 5.7, 10.4, C<u>H</u>H–OMs), 4.58, (1H, dd, 2.8, 10.4, CH<u>H</u>–OMs; MS m/z (relative intensity): 303 ([M–CH_3]$^+$, 97), 239 ([M–Ms]$^+$, 100%).

(1*R*, 2*R*,4a*S*,8a*S*)-(–)-(1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethyl-naphthyl)methyl Methanesulfonate [(–)-4]. A solution of (–)-**3** (0.192 g, 0.604

mmol), 3,4-dihydro-2*H*-pyran (0.16 ml, 1.8 mmol) and catalytic amount of TsOH in CH_2Cl_2 (10 ml) was stirred at 0°C for 1 h. Then the reaction mixture was washed successively with aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil; that was chromatographed on silica gel (hexane-EtOAc = 4:1-3:1) to give (–)-**4** (0.175 g, 72.1%) as a 1.1:1 mixture of diastereomers: $[\alpha]_D^{21}$ –28.7 (*c* 1.75); IR (film): 1350 cm^{-1} [s, $S(=O)_2$], 1170 [s, $S(=O)_2$], 1120 (m, C-O), 1070 (s, C–O); ^1H NMR (400 MHz): δ 0.81 and 0.87 [6H in total, s each, 5-$(CH_3)_2$], 0.92 and 0.93 (3H, in total, s each, 8a-CH_3), 1.12 and 1.18 (3H, in total, s each, 2–CH_3), 1.1-2.0 (18H, m) 3.01 and 3.02 (3H in total, s each, S–CH_3), 3.43-3.51 (1H, m, C<u>H</u>H–O) 3.90-3.98 (1H, m, CH<u>H</u>–O), 4.27 (1H, dd, 6.4, 10.1, C<u>H</u>H–OMs), 4.54 and 4.62 (1H in total, dd each, 1.5, 10.0, CH<u>H</u>–OMs), 4.79-4.87 (1H, m, O–CH–O); MS m/z: 403 (M^++1, 10), 301 ([M–OTHP]$^+$, 18), 205 (100%); *Anal.* Found: C, 62.57; H, 9.56. Calcd. for $C_{21}H_{38}O_5S$: C, 62.65; H, 9.51%.

(1*R*,2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethyl-1-naphthaleneacetonitrile [(–)-5] and (2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethyl-1-methylenenaphthalene [(–)-6]. NaCN (0.100 g, 2.04 mmol) and 18-crown-6-ether were added to a solution of (–)-**4** (0.174 g, 0.432 mmol) in DMSO (10 ml), and the mixture was stirred for 12 h at 85°C. After the reaction mixture was cooled and filtered, the filtrate was extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 8:1-4:1) to give (–)-**5** (0.094 g, 65%) as a 1.1:1 mixture of diastereomers and (–)-**6** (0.038 g, 29%).

(–)-**5**: $[\alpha]_D^{21}$ –8.3 (*c* 0.70); IR (film): 2220 cm^{-1}(m, C≡N), 1125 (m, C–O), 1070 (s, C–O), 1025 (s, C–O); ^1H NMR (400 MHz): δ 0.80 and 0.88 [6H in total, s each, 5-$(CH_3)_2$], 0.84 and 0.85 (3H in total, s, each, 8a-CH_3), 0.96-1.02 (1H in total, m each), 1.09 and 1.15 (3H in total, s each, 2-CH_3), 1.17-2.0 (17H, m), 2.17 (1H, dd, 7.70, 17.22, C<u>H</u>H–C≡N), 2.61 and 2.69 (1H in total, dd each, 3.21, 17.88, CH<u>H</u>–C≡N), 3.44-3.53 (1H, m, C<u>H</u>H–O), 3.89-4.02 (1H, m, CH<u>H</u>–O), 4.80-4.90 (1H, m, O–CH–O); *Anal.* Found: C, 75.14; H, 10.52; N, 4.08. Calcd. for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20%.

(–)-**6**: $[\alpha]_D^{21}$ –43.9 (*c* 0.38); IR (film): 1622 cm^{-1} (m, C=C), 1125 (m, C–O), 1070 (s, C–O), 902 (s, C=H_2); ^1H NMR (400MHz): δ 0.84 and 0.84 (3H in total, s each, 5-CH_3), 0.86 and 0.88 (3H in total, s each, 5-CH_3), 1.09 and 1.10 (3H in total, s each, 8a-CH_3), 1.39 and 1.44 (3H in total, s each, 2-CH_3), 1.0-1.95 (17H, m), 3.40-3.50 (1H, m, C<u>H</u>H–O), 3.91- 4.00 (1H, m, CH<u>H</u>–O), 4.64-4.68 and 4.71-4.75 (1H in total, m each, O–CH–O), 4.90 and 5.11 (1H in total, s each, C=<u>H</u>H), 5.05 and 5.21 (1H in total, s each, C=H<u>H</u>); MS m/z: 305 (M^+–1), 205 ([M–OTHP]$^+$).

(–)-Drim-9(11)-en-8-ol [(2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2,5,5,8a-tetramethyl-1-methylenenaphthalen-2-ol] [(–)-9]. To a solution of (–)-**6** (0.038 g, 0.12 mmol) in MeOH was added bis(trimethylsilyl) sulfate (2 mg) in dichloroethane (0.1 ml), and the reaction mixture was stirred at room temperature for 2 min. After pyridine (0.02 ml) was added to the mixture, it was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 10:1-6:1) to give (–)-**9** (0.025 g, 91%) as white crystals: mp 58-59°C (hexane-Et_2O); $[\alpha]_D^{21}$ –27.8 (*c* 1.2); IR (KBr): 3375 cm^{-1} (br. s, OH), 1620 (m, C=C), 1460 (s), 1370 (s), 1080 (s, C–O), 902 (s, $=CH_2$); ^1H NMR (270 MHz): δ 0.85 (3H, s, 5-CH_3), 0.88 (3H, s, 5-CH_3), 1.09 (3H, s, 8a-CH_3), 1.41 (3H, s, 2-CH_3), 0.9-1.85 (12H, m), 4.84 (1H, s, C=C<u>H</u>H), 5.22 (1H, s, C=H<u>H</u>); HRMS: Found: 222.1978. Calcd. for $C_{15}H_{26}O$ (M^+): 222.1984.

(1*R*,2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethyl-1-naphthaleneacetaldehyde [(–)-7]. To a solution of (–)-**6** (0.072 g, 0.22 mmol) in toluene (5 ml) was added DIBAL (0.1 M in toluene, 0.37 ml, 0.37 mmol) at –10°C under argon. After stirring for 1 h, the mixture was quenched with 1 M aq. tartaric acid (2 ml) and diluted with Et_2O (20 ml). The organic phase was separated, washed with aq. potassium sodium tartrate and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 6:1-4:1) to give (–)-**7** (0.070 g, 96%) as a 1.1:1 mixture of diastereomers: $[\alpha]_D^{21}$ –28.1 (*c* 0.70); IR (film): 1720 cm^{-1} (C=O), 1125 (s, C–O); ^1H NMR (400 MHz): δ 0.80 and 0.88 [6H in total, s each, 5-$(CH_3)_2$], 0.83 and 0.84 (3H in total, s each, 8a-CH_3), 1.18 and 1.24 (3H in total, s each, 2-CH_3), 0.9-2.1 (17H, m), 2.23-2.45 (2H, m, CHH–CHO), 2.57 and 2.62 (1H in total, dd each, 2.6, 6.1), 3.39-3.51 (1H, m, C<u>H</u>H–O), 3.79-3.93 (1H, m, CH<u>H</u>–O), 4.77 and 4.90 (1H in total, m each, O–CH–O), 9.59 and 9.70 (1H in total, m each, CHO); MS m/z: 306 ([M–CHO]$^+$–1, 38), 199 (40), 153 (100%).

(1*R*,2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethyl-1-naphthaleneethanol [(–)-8]. To a stirred suspension of $LiAlH_4$ (0.010 g, 0.26 mmol) in Et_2O (2 ml) was added a solution of (–)-**7** (0.070 g, 0.21 mmol) in Et_2O (0.5 ml). The reaction mixture was stirred for 3 h at room temperature, cooled to 0°C, quenched by addition of wet Et_2O followed by H_2O and washed successively with 1 N HCl, aq. $NaHCO_3$ and H_2O. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 3:1-1:1) to give (–)-**8** (0.055 g, 78%) as a 1.1:1 mixture of diastereomers: $[\alpha]_D^{21}$ –22.9 (*c* 0.55); IR (film): 3430 cm^{-1} (br. s, OH), 1125 (s, C–O); ^1H NMR (400 MHz): δ 0.79 (3H, s, 5-CH_3), 0.83 (3H, s, 5-CH_3), 0.87

(3H, s, 8a-CH_3), 1.19 and 1.28 (3H in total, s each, 2-CH_3), 1.1-2.1 (18H, m), 3.32-3.53 (3H, m, CHHOH), 3.68-3.81 (1H, m,CHH–O), 3.89-3.99 (1H, m, CHH–O), 4.89 (1H, m, O–CH–O); HRMS: Found: 237.2221. Calcd. for $C_{16}H_{29}O$ (M–OTHP]$^+$): 237.2218.

(–)-13,14,15,16-Tetranor-8α,12-labdanediol [(1*R*, 2*R*,4a*S*,8a*S*)-(–)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2,5,5,8a-tetramethyl-1-naphthaleneethanol] [(–) (1*R*)-2a]. In the same manner as THP-deprotection of (–)-**6**, treatment of (–)-**8** (0.055 g, 0.16 mmol) yielded (–) (1*R*)-**2a** (0.041 g, quant.) as white crystals: mp 132-133°C (hexane-Et_2O); $[\alpha]_D^{21}$ –16.3 (*c* 0.41); IR (KBr): 3200 (br. s,.OH), 1085 (s, C–O), 1050 (s, C–O); ^{1}H NMR (400 MHz): δ 0.80 [6H, s, 5-$(CH_3)_2$], 0.88 (3H, s, 8a-CH_3), 1.20 (3H, s, 2-CH_3), 0.9-1.7 (14H, m), 1.90 (1H, dt, 3.3, 12.5, 6-H), 2.4-2.8 (1H, br, OH), 3.48 (1H, m, CHH–OH), 3.79 (1H, dt, 4.4, 10.3, CHH-OH); *Anal.* Found: C, 75.33; H, 11.51. Calcd. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%.

(±)-Ambreinolide [(4a*R,6a*S**,10a*S**,10b*R**)-2,3,4a,5,6,6a,7,8,9,10,10a,10b-Dodecahydro-4a,7,7,10a-tetramethyl-naphtho[2,1-b]pyran-3-one] [(±)-10].** Several recryctallizations from hexane-EtOAc after chlorosulfonic acid cyclization of farnesyl acetic acid[7] afforded pure (±)-**10** as colorless prisms: mp 138-140°C; IR (KBr): 1738 cm^{-1} (s, C=O), 1190 (m), 1159 (m), 1125 (s, C–O), 1043 (s, C–O), 970 (s); ^{1}H NMR (400 MHz): δ 0.82 (3H, s, 7-CH_3), 0.85 (3H, s, 7-CH_3), 0.90 (3H, s, 10a-CH_3), 1.38 (3H, s, 4a-CH_3), 0.9-1.75 (13H, m), 2.03 (1H, dt, 3.2, 12.8, 8-H_{eq}), 2.54 [1H, ddd, 8.4, 9.2, 9.3, CHHC(=O)], 2.67(1H, ddd, 2.9, 8.5, 18.8, CHHC=O); HRMS: Found: 265.2169. Calcd. for $C_{17}H_{29}O_2$ (M+1): 265.2168.

(4a*R,6a*S**,10a*S**,10b*R**)-2,3,4a,5,6,6a,7,8,9,10,10a,10b-Dodecahydro-4a,7,7,10a-tetramethyl-naphtho[2,1-b]pyran-3-ol [(±)-11].** To a solution of (±)-**10** containing isomers (prepared from farnesylacetic acid as previously reported,[7] (2.64 g, 10.0 mmol) in toluene (20 ml) was added DIBAL (1.0 M in toluene, 11 ml, 11 mmol) at –78°C under argon. After stirring for 1 h, the mixture was added subsequently MeOH (1 ml) and aq. sodium tartrate and stirred for 2 h at room temperature. The resulting clear solution was extracted with benzene. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residual solid was recrystallized from benzene to give (±)–**11** (2.21 g, 50.4% from farnesylacetic acid) as colorless crystals: mp 195°C; IR (KBr): 3370 (br. s, OH), 1120 (s, C–O), 1055 (s, C–O) cm^{-1}; ^{1}H NMR (400 MHz): δ 0.74 and 0.74 (3H in total, s each, 7-CH_3), 0.80 (3H, s, 7-CH_3), 0.87 (3H, s, 10a-CH_3), 1.28 and 1.28 (3H in total, s each, 4a-CH_3), 1.1-1.75 (14H, m), 1.81 (1H, dt, 3.1, 12.5), 1.99-2.05 (1H, m), 2.65 (1H, br, OH), 4.98 (1H, ddd, 2.6, 7.1, 8.4,

CH–OH); *Anal.* Found: C, 76.23; H, 11.24. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%.

(4a*R,6a*S**,10a*S**,10b*R**)-4a,5,6,6a,7,8,9,10,10a,10b-Decahydro-4a,7,7,10a-tetramethyl-naphtho[2,1-b]pyran [(±)-12].** A stirred solution of (±)-**11** (1.33 g, 5.00 mmol), pyridine (10 ml) and TsCl (1.14 g, 6.00 mmol) was kept at 35°C for 12 h. After H_2O (1 ml) was added to this, the resulting mixture was diluted with Et_2O. Then the organic phase and successively washed with H_2O, 1 N HCl, aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 50:1-20:1) to give (±)-**12** (1.13 g, 91.1%) as white crystals: mp 86-87°C (hexane); IR (KBr): 3060 cm^{-1}[s, (C=C)-H], 1655 (s, C=C), 1458 (s), 1440 (s), 1095 (s), 1050 (s, C–O), 1378 (s); ^1H NMR (400 MHz): δ 0.82 [6H, s, 7-$(CH_3)_2$], 0.88 (3H, s, 10a-CH_3), 1.19 (3H, s, 4a-CH_3), 1.92 (1H, dt, 3.3, 12.5, 8-H_{eq}), 1.1-1.9 (13H, m), 4.64 (1H, dt, 2.2, 5.6, O–CH=CH), 6.20 (1H, dt, 1.8, 5.9, O–CH=CH); HRMS: Calcd. for $C_{17}H_{29}O$ (M+1): 249.2218. Found: 249.2219.

(±)-13,14,15,16-Tetranor-8α,12-labdanediol [(1*R,2*R**,4a*S**,8a*S**)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-hydroxy-2,5,5,8a-tetramethyl-1-naphthaleneethanol] [(±)-2a].** A solution of (±)-**12** (0.248 g, 1.00 mmol) in MeOH (10 ml) was ozonized at –20°C. Then $NaBH_4$ (0.1 g) was added, and the stirred mixture was allowed to warm up to room temperature. After most of MeOH was evaporated, the mixture was added H_2O and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc =1.5:1-1:2) to give (±)-**2a** (0.209 g, 82.3%) as white crystals; mp 130°C (hexane-Et_2O).

(±)-13,14,15,16-Tetranor-12-acetoxy-8α-labdanol [(1*R,2*R**,4a*S**,8a*S**)-2-(1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthyl)ethyl acetate] [(±)-2b].** The primary hydroxyl group of (±)-**2a** (0.127 g, 0.500 mmol) was acetylated with acetic anhydride in pyridine in the usual manner to give (±)-**13** (0.146 g, 98.6%): IR (film): 3480 cm^{-1} (br. s, OH), 1737 (s, C=O), 1245 (s, O–Ac), 1075 (s, C–O), 1035 (s, C–O), 940 (m); ^1H NMR (400 MHz): δ 0.79 [6H, s, 5-$(CH_3)_2$], 0.88 (3H, s, 8a-CH_3), 1.17 (3H, s, 2-CH_3), 0.9-1.8 (14H, m), 1.90 (1H, dt, 2.94, 12.1, 6-H_{eq}), 2.05 (3H, s, Ac H), 4.06 -4.19 (2H, m, CH_2–OAc); MS m/z: 296 (M^+, 12), 279 ([M–OH]$^+$, 22), 219 (100%).

Kinetic Hydrolysis of Racemic 13,14,15,16-Tetranor-12-acetoxy-8a-labdanol [(±)-2b]. A suspension of (±)-**2b** (0.075 g, 0.25 mmol), 0.2% aq. tween®80 (0.1 ml) and lipase PS-30 (0.05 g) in 0.1 M phosphate buffer (3 ml) and CH_2Cl_2 (0.5 ml) was stirred at 30°C for 1 d. After the mixture was filtered through a Celite pad, the filtrate was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and

evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 2:1-1:2) to give diol (–) (1*R*)-**2a** (0.024 g, 37%, 98.0%e.e.) and acetate (–) (1*S*)-**2b** (0.045 g, 60%, 51%e.e.). The enantiomeric purity of (–) (1*R*)-**2a** was determined by ^{1}H NMR and HPLC analyses of the corresponding mono-(*S*)-MTPA ester of the primary hydroxyl group. HPLC [(*S*)-MTPA ester]: 98.0%e.e., CHIRALCEL OD (hexane-*i*-PrOH = 50:1, 1.0 ml/min), t_R = 10.9 min (99.0%) and 14.0 min (1.0%). The enantiomeric purity of the non-hydrolyzed product (–) (1*S*)-**2b** was calculated by comparing the specific rotation value of the corresponding diol (+) (1*S*)-**2a** {$[\alpha]_D^{21}$ +7.7} (given by $LiAlH_4$ reduction) with that reported of (–) (1*R*)-**2a** {lit.[3d] $[\alpha]_D$ –15 (*c* 1)}, because the optical rotation value of enantiomerically pure (+) (1*R*)-**2b** is very small {lit.[1a] $[\alpha]_D^{21}$ +1.06 (*c* 1.0)}.

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