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Synthesis of (+)-Ambrein

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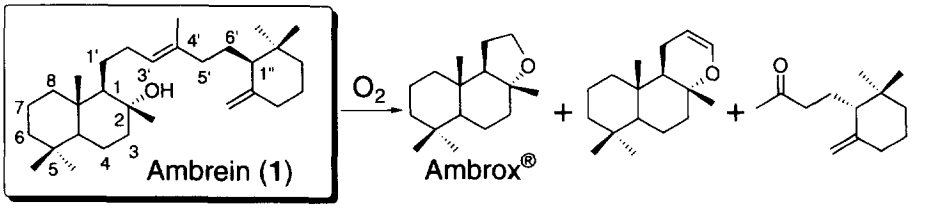
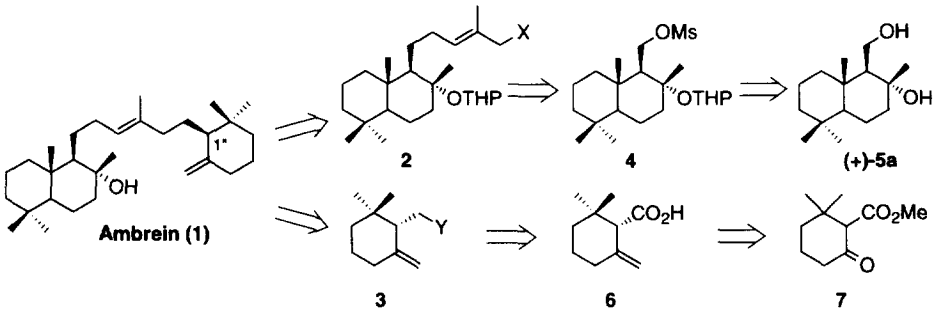
Abstract: Enantiomerically pure (+)-Ambrein was synthesized from (+)-drimane-8,11-diol prepared via lipase catalyzed kinetic resolution, and easily prepared (+)-γ-cyclogeraniol.

Ambergris, a metabolite of the sperm whale, is one of the most important animal perfumes. (+)-Ambrein, the major constituent of ambergris, is decomposed by the exposure to air and sunlight to give some odorous compounds (Scheme 1).[1] The unique fragrance properties are related principally to (–)-Ambrox®, of which we have reported useful asymmetric syntheses.[2] Nowadays, fragrance companies are interested in the release of ambergris scent by the artificial degradation of (+)-ambrein. However, it has become very hard to obtain ambergris under the prohibition of commercial whaling. Although two publications[3a,4] have appeared on the (+)-ambrein, both of them



Scheme 1. Air degradation of Ambrein (1)

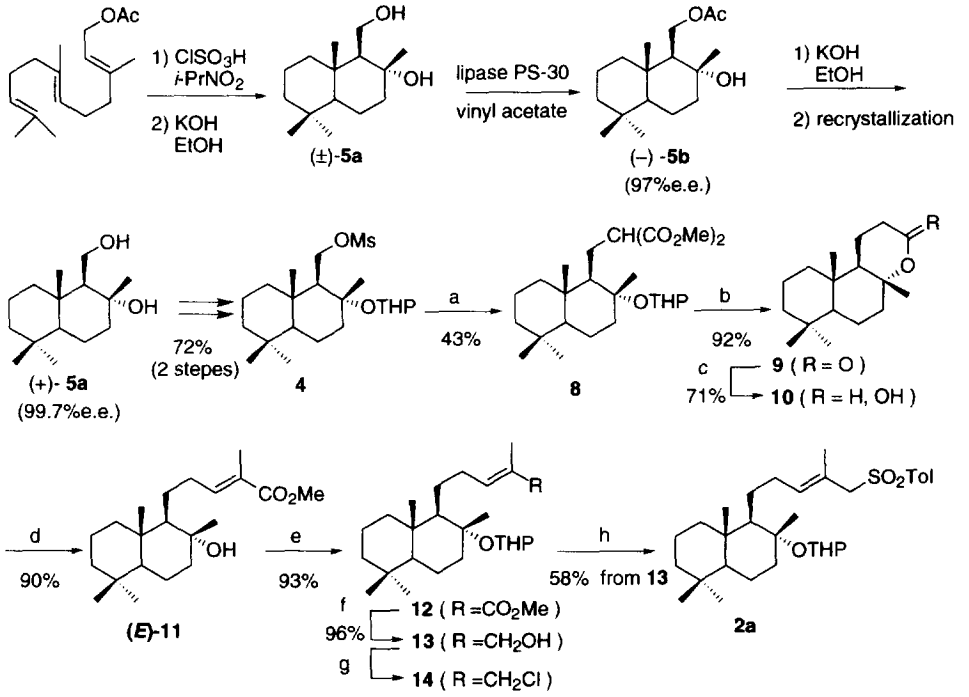
had problems especially in the construction of γ-cyclogeranyl part. Mori and Tamura reported the total synthesis of **1** in 1990.[3a] They concentrated their effort on the synthesis of chiral γ-homocyclogeraniol.[3a,3b] At the same time, we also reported the synthesis of the (1"*RS*)-diastereomers of **1** through the use of (±)-γ-cyclogeraniol.[4] According to certain literatures, although efficient syntheses of (±)-γ-cyclogeranyl compounds were reported,[5a,5b] there were some problems in the preparation of their stating materials. Fehr *et al.* obtained their starting material, β-cyclogeranate



Scheme 2 Retrosynthesis of Ambrein 1

by the imperfect isomerization of α-cyclogeranate.[5a] Stella's starting material, 3,3-dimethyl-1-bromomethyl-1-cyclohexene was prepared in many steps.[5b] We found that methyl (±)-γ-cyclogeranate can be synthesized from the easily prepared β–ketoester **7** in one step.[6] We also found more efficient synthesis of the bicyclic intermediate (+)-ambreinolide (**9**) via lipase catalyzed kinetic resolution[2] than the skillful optical resolution of (+)-ambreinolide (**9**) itself in our previous work.[4] In this paper we report a new synthetic route for (+)-ambrein.

Scheme 2 shows our synthetic plan for (+)-ambrein (**1**). The target **1** can be disconnected into two synthesis convergent **2** and **3**. The compound **2** will be synthesized from **4**, which we prepared from the diol (+)-**5a** in connection with our synthesis of (–)-Ambrox®. The diol (+)-**5a** is an important chiral building block prepared by lipase catalyzed resolution.[2] The halide **3** will be derived from (+)-**6** which can be prepared by the optical resolution of (±)-**6** according to Takáes-Novák's protocol.[5a] γ-Cyclogeranic acid [(±)-**6**] was obtained efficiently via Wittig reaction of the β–ketoester **7**.

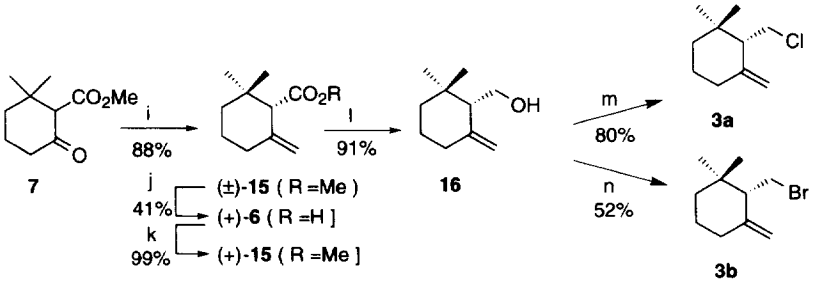


Scheme 3. Synthesis of the bicyclic building block 2

Scheme 3 shows the synthetic route leading to **2**. The methods for preparing enantiomerically pure **4** had already been established.[2] Coupling of **4** with dimethyl malonate gave the diester **8** along with an elimination by-product[7]. Saponification of **8** followed by decarboxylation gave (+)-

ambreinolide (**9**) directly. The lactone **9** was reduced with DIBAL to give the lactol **10**. The condensation of **10** with 1-(methoxycarbonyl)ethylidenetriphenylphosphorane in boiling benzene gave the unsaturated ester **11**, the *E*/*Z* ratio[8a-c,4] of which was 18/1. These geometrical isomers were separated by silica gel column chromatography and recrystallization to give the *E*-isomer **11**, which was converted to the THP ether **12**. The compound **12** was reduced with $LiAlH_4$ to afford **13** without 1,4-reduction. For coupling reaction with the γ-cyclogeranyl halide, we used the Grignard reaction in our previous work.[4] However, there were technical difficulties in the preparation of the γ-cyclogeranylmagnesium halide. After trial and error we chose the tolylsulfone alkylation-desulfonylation strategy. Accordingly, the alcohol **13** was converted to the chloride **14** under Collington and Meyers condition.[9] Treatment of the compound **14** with sodium tolylsulfinate in *N*,*N*-dimethylformamide (DMF) afforded the allylic sulfone **2a**.

Scheme 4 shows the synthetic route of the monocyclic building block **3**. The β–ketoester **7**[6] easily prepared from mesityl oxide and dimethyl malonate was treated with a salt-free Wittig reagent to give methyl (±)-γ-cyclogeranate [(±)-**15**]. Mild saponification of (±)-**15** and optical resolution of γ-cyclogeranic acid [(±)-**6**] with (*S*)-1-phenylethylamine by Takáes-Novák's protocol[5a] gave (+)-**6**. The compound (+)-**6** was transformed to the enantiomerically pure alcohol **16** [>99%e.e., determined by ^1H NMR analysis of the corresponding (*S*)-MTPA ester]. The absolute stereochemistry of it was confirmed by comparing the sign of the specific rotation value with that reported.[5a] The alcohol **16** was converted to the chloride **3a** or the bromide **3b**.



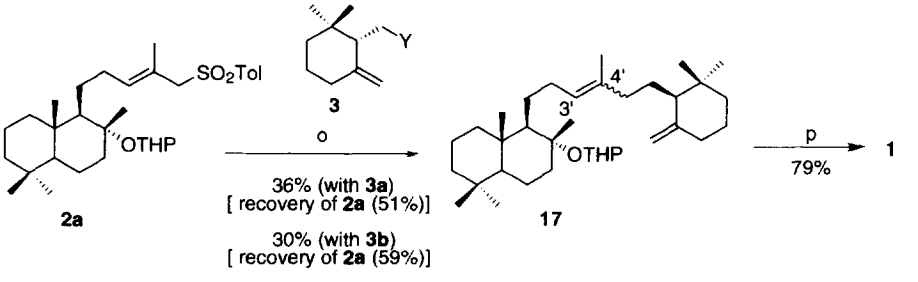
i; $Ph_3P^+MeBr^-$, KO*t*-Bu / toluene j; PhSH, KOH / DMF then (*S*)-1-phenylethylamine
k; CH_2N_2 l; $LiAlH_4$ / Et_2O m; CCl_4 / trioctylphosphine n; MsCl / Py then NaBr / DMF

Scheme 4. Synthesis of monocyclic building block 3

The next stage was the coupling of the bicyclic building block **2a** and the monocyclic building block **3** (**3a** or **3b**). The carbanion generated from the compound **2a** by the treatment with butyllithium (BuLi) was alkylated with the compound **3a** or **3b** to give the condensed products, which were desulfonylated immediately by Inomata's method[10] with 4 equiv. of $LiBHEt_3$ in the presence of 10 mol% of [$PdCl_2$(dppp)] in THF to give crude ambrein-THP ethers **17**. The product **17** of this reductive desulfonylation contained a small amount of the *Z*-isomer (*E*/*Z*=10/1). The desulfonylation procedures using Na (Hg) and Li-$EtNH_2$ were accompanied by a migration of the double bond to give a 4'-(*E*)-isomer (38% and 27%). Finally, (+)-ambrein (**1**) was obtained after deprotection of **17** with bis(trimethylsilyl)sulfate [$(TMS)_2SO_4$][11] and the removal of the *Z*-isomer by

preparative TLC. The spectral data and physical properties of synthetic **1** were identical with those of natural **1**.

In summary, we have synthesized enantiomerically pure (+)-ambrein from (+)-drimane-8,11-diol prepared via the lipase catalyzed kinetic resolution, and easily prepared (+)-γ-cyclogeraniol. This will serve practical and academic purposes on the degradation pathway of ambergris.



Scheme 5. The Coupling of the bycyclic building block 2a and the monocyclic building block 3

Experimental

General. All melting point (mp) values are uncorrected. ^{1}H NMR spectra were recorded on Varian GEMINI 2000 (300 MHz) and JEOL JMA-5600 (400 MHz) spectrometers in $CDCl_3$. IR spectra were taken with a JASCO IR-810 infrared spectrometer. MS spectra were recorded with a JEOL JMS HX-105, JMS AM-150 and JMS-DX-303 instruments. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-4 polarimeter.

(+)-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} (9). Dimethyl malonate (0.330 g, 2.50 mmol) was added to a solution of NaOMe (0.148 g, 2.74 mmol) in MeOH (5 ml) at room temperature and the mixture was stirred for 30 min at 30°C. Then mesylate **4** (0.403 g, 1.00 mmol) in hexamethylphosphoric triamide (HMPA) (8 ml) and 18-crown-6-ether were added and the stirring was continued for 12 h at 68°C. The reaction mixture was cooled and poured into aq. NH_4Cl and extracted with Et_2O. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 10:1-5:1) to give **8** (0.189 g, 43%) as a 1.2:1 mixture of diastereomers and elimination by-product[7] (0.095 g, 31%). To a solution of KOH (0.085 g, 1.5 mmol) in EtOH (3 ml), The above product **8** (0.189 g, 0.431 mmol) in EtOH (2 ml) was added and the stirring was continued for 1.5 h at 55°C. The reaction mixture was cooled and poured into 1 N HCl and extracted with Et_2O. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in toluene (5 ml) and stirred for 5 min at 95°C. The reaction mixture was evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 6:1-2:1) to give **9**

(0.105 g, 92.1%).
8; IR (film): 1738 cm^{-1} (s, C=O), 1150 (m, C–O), 1020 (m, C–O). ^1H NMR (300 MHz): δ 0.77 and 0.78 (3H in total, s each, CH_3), 0.81 (3H, s, CH_3), 0.85 and 0.85 (3H in total, s each, CH_3), 1.23 and 1.31 (3H in total, s each, CH_3), 1.1-2.1 (21H, m), 3.41-3.50 (1H, m, C<u>H</u>H–O), 3.71 and 3.73 (3H in total, s each, CO_2–CH_3), 3.73 and 3.75 (3H in total, s each, CO_2–CH_3), 3.82-3.87 and 3.90-3.95 (1H, m, CH<u>H</u>–O), 4.06-4.09 and 4.16-4.19 [1H in total, m each, C<u>H</u>–$(CO_2CH_3)_2$], 4.83 and 4.86 (1H in total, m each, O–CH–O).

9; mp 142-143°C, $[\alpha]_D^{21}$ +34.5 (*c* 1.00). IR (KBr): 1738 cm^{-1} (s, C=O), 1190 (m), 1159 (m), 1125 (s, C–O), 1043 (s, C–O), 970 (s). ^1H NMR (400 MHz): δ 0.82 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.38 (3H, s, CH_3), 0.9-1.75 (13H, m), 2.03 (1H, dt, *J*= 3.2, 12.8 Hz), 2.54 [1H, ddd, *J* = 8.4, 9.2, 9.3 Hz, C<u>H</u>HC(=O)], 2.67 [1H, ddd, *J* = 2.9, 8.5, 18.8 Hz, CH<u>H</u>(C=O)]. HRFABms: 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 (10). To a solution of **9** (0.377 g, 1.43 mmol) in toluene (20 ml) was added DIBAL (1.0 M in toluene, 1.6 ml, 1.6 mmol) at –65°C under argon. After stirring for 1 h, to this was added subsequently MeOH (0.1 ml) and aq. sodium tartrate and the mixture was stirred for 2 h at room temperature. The resulting clear solution was extracted with chloroform. 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 **10** (0.270 g, 71.1%) as colorless crystals; mp 196-197°C, $[\alpha]_D^{21}$ –9.2 (*c* 0.2). IR (KBr): 3370 (br. s, OH), 1120 (s, C–O), 1055 (s, C–O) cm^{-1}. ^1H NMR (400 MHz): δ 0.74 and 0.74 (3H in total, s each, CH_3), 0.80 (3H, s, CH_3), 0.87 (3H, s, CH_3), 1.28 and 1.28 (3H in total, s each, CH_3), 1.1-1.75 (14H, m), 1.81 (1H, dt, *J* = 3.1, 12.5 Hz), 1.99-2.05 (1H, m), 2.65 (1H, br, OH), 4.98 (1H, ddd, *J* = 2.6, 7.1, 8.4 Hz, C<u>H</u>–OH). *Anal.* Found: C, 76.23; H, 11.24. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%.

(1*R*,2*R*,4a*S*,8a*S*,3'*E*)-(+)-1-[4'-Carboxymethyl-4'-methyl-3-hexenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2,5,5,8a-tetramethylnaphthalen-2-ol [(*E*)-11]. A solution of **10** (0.793 g, 2.98 mmol) and 1-(methoxycarbonyl)ethylidenetriphenylphosphorane (1.5 g, 4.3 mmol) in benzene (15 ml) was stirred for 15 h at 70°C and the reaction mixture was evaporated under reduced pressure. Most of the Ph_3PO was removed as a precipitate by recrystallization (toluene-hexane). The resulting residue was chromatographed on silica gel (hexane-EtOAc = 10:1-4:1) and recryctalizatiuon (*i*-Pr_2O-hexane) to give **(*E*)-11** (0.903 g, 90.1%) as white crystals; mp 85°C, $[\alpha]_D^{21}$ +5.8 (*c* 1.05). IR (KBr): 3500 (br. s, OH), 1705 (s, C=O). ^1H NMR (400 MHz): δ 0.77 (6H, s, CH_3), 0.87 (3H, s, CH_3), 1.15 (3H, s, CH_3), 0.9-1.75 (14H, m), 1.83 (3H, d, *J* = 1.4 Hz, CH=C–C<u>H</u>$_3$), 1.84 (1H, dt, *J* = 3.3, 12.4 Hz), 2.17-2.32 (2H, m, C<u>H</u>$_2$–CH=C), 3.73 (3H,s, CO_2-C<u>H</u>$_3$), 6.80 (1H, dt, *J* = 1.7, 7.0 Hz, CH_2–C<u>H</u>=C). HRFABms: Found: 319.2658. Calcd. for $C_{21}H_{25}O_2$ (M–OH): 319.2637. *Anal.* Found: C, 75.05; H, 11.01. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78%.

(*Z*)-11; ^1H NMR (300 MHz): δ 0.78 (6H, s, CH_3), 0.87 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.89 (3H, d, *J* = 1.4 Hz, CH=C–C<u>H</u>$_3$), 0.9-2.0 (15H, m), 2.18-2.40 (2H, m, C<u>H</u>$_2$–CH=C), 3.72 (3H, s, CO_2-C<u>H</u>$_3$), 6.01 (1H, dt, *J* = 1.7, 8.0 Hz, CH_2–C<u>H</u>=C).

(1*R*,2*R*,4a*S*,8a*S*,3'*E*)-(+)-1-[4'-Carboxymethyl-4'-methyl-3-penenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethylnaphthalene (12). A solution of (*E*)-**11** (0.338 g, 1.00 mmol), 3,4-dihydro-2*H*-pyran (0.32 ml, 3.5 mmol) and catalytic amount of TsOH in CH_2Cl_2 (40 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, which was chromatographed on silica gel (hexane-EtOAc = 20:1-8:1) to give **12** (0.392 g, 92.7%) as a 1:1 mixture of diastereomers;$[\alpha]_D^{21}$ +2.7 (*c* 1.06). IR (KBr): 1710 (s, C=O), 1120 (s, C–O), 1070 (s, C–O), 1025 (s, C–O). ^{1}H NMR (300 MHz): δ 0.77 and 0.78 (3H in total, s each, CH_3), 0.80 and 0.81 (3H in total, s each, CH_3), 0.85 and 0.85 (3H in total, s each, CH_3), 1.13 and 1.21 (3H in total, s each, CH_3), 1.82 (3H, CH=C–C$\underline{H}_3$), 0.9-2.0 (20H, m), 2.10-2.50 (2H, m, C$\underline{H}_2$–CH=C), 3.38-3.47 (1H, m, C$\underline{H}$H–O), 3.73 and 3.73 (3H in total, s each, CO_2–CH_3), 3.82-3.98 (1H, m, CH$\underline{H}$–O), 4.80 and 4.89 (1H in total, m each, O–CH–O), 6.80 (1H, m, CH_2–C$\underline{H}$=C). HRFABms: Found: 319.2641. Calcd. for $C_{21}H_{35}O_2$ (M–OTHP): 319.2637. *Anal.* Found: C, 74.39; H, 10.64. Calcd. for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54%.

(1*R*,2*R*,4a*S*,8a*S*,3'*E*)-(+)-1-[5'-Hydroxy-4'-methyl-3-pentenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethylnaphthalene (13). **12** (0.392 g, 0.932 mmol) was reduced with $LiAlH_4$ in the usual manner and chromatographed on silica gel (hexane-EtOAc = 10:1-4:1) to give **13** (0.352 g, 96.2%) as a 1:1 mixture of diastereomers; $[\alpha]_D^{21}$ –5.9 (*c* 0.95). IR (film): 3400 cm^{-1} (br. s, OH), 1125 (s, C–O), 1070 (m, C–O), 1020 (s, C–O). ^{1}H NMR (300 MHz): δ 0.77 and 0.78 (3H in total, s each, CH_3), 0.80 and 0.81 (3H in total, s each, CH_3), 0.85 and 0.89 (3H in total, s each, CH_3), 1.12 and 1.19 (3H in total, s each, CH_3), 1.64 (3H, s, CH=C–C$\underline{H}_3$), 0.9-2.4 (23H, m), 3.39-3.51 (1H, m, C$\underline{H}$H–O), 3.84-4.02 (3H, m, CH$\underline{H}$–O and C$\underline{H}_2$OH), 4.78 and 4.89 (1H in total, m each, O–CH–O), 5.45 (1H, m, CH_2–C$\underline{H}$=C). HRFABms: Found: 291.2708. Calcd. for $C_{20}H_{35}O$ (M–OTHP): 291.2688. *Anal.* Found: C, 75.92; H, 11.23. Calcd. for $C_{25}H_{44}O_3$: C, 76.48; H, 11.30%.

(1*R*,2*R*,4a*S*,8a*S*,3'*E*)-(+)-1-[5'-Tolylsulfonyl-4'-methyl-3-pentenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethylnaphthalene (2a). To a cooled (0°C) solution of LiCl (0.095 g, 2.2 mmol) and $NaHCO_3$ (0.20 g) in DMF (15 ml) was added a solution of **13** (0.274 g, 0.698 mmol) in 2,6-lutidine (0.35 ml, 3.0 mmol) and DMF (1 ml). After 50 min, methanesulfonyl chloride (0.16 ml, 2.1 mmol) was added and the resulting slurry was stirred at 0°C for 2.5 h. Then water and Et_2O were added and extracted with Et_2O. The organic phase was successively washed with H_2O, aq. $CuSO_4$, H_2O and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil. The residue was immediately purified by preparative TLC (hexane-EtOAc = 5:1) and dissolved in DMF (5 ml). To the solution sodium *p*-toluenesulfinate ($TolSO_2Na$, 0.35 g, 2.0 mmol) was added and the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was poured into water and extracted with Et_2O. The organic phase was successively washed with H_2O and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 12:1-5:1) to give **2a** (0.213 g, 57.5% from **13**).

14; IR (film): 1670 (w, C=C), 820 (m, C=C).

2a; $[\alpha]_D^{21}$ +0.6 (*c* 0.64). IR (film): 1620 (m, C=C), 1340 cm^{-1} [s, $S(=O)_2$], 1155 [s, $S(=O)_2$], 840 (m, aromatic). ^1H NMR (300 MHz): δ 0.77 (6H, CH_3), 0.84 and 0.85 (3H in total, s each, CH_3), 1.09 and 1.16 (3H in total, s each, CH_3), 1.73 and 1.75 (3H in total, s each, CH=C–C$\underline{H}_3$), 0.9-2.2 (22H, m) 2.42 (3H, s, Ph-CH_3), 3.38-3.48 (1H, m, C$\underline{H}$H–O), 3.68 (2H, s, CH_2SO_2Tol), 3.80-3.96 (1H, m, CH$\underline{H}$–O), 4.76 and 4.85 (1H in total, m each, O–CH–O), 5.02 (1H, m, CH_2–C$\underline{H}$=C), 7.28-7.34 (2H, m, aromatic) 7.70 and 7.72 (2H in total, d, *J* = 8.5 Hz, aromatic). HRFABms: Found: 429.2834. Calcd. for $C_{27}H_{41}O_2S$ (M–OTHP): 429.2827. *Anal.* Found: C, 72.41; H, 9.56. Calcd. for $C_{32}H_{50}O_4S$: C, 72.41; H, 9.49%.

Methyl (±)-2,2-Dimethyl-6-methylene-1-cyclohexanecarboxylate [(±)-15]. A solution of $Ph_3P^+MeBr^-$ (52.5 g, 147 mmol) and potassium *tert*-butoxide (KO*t*-Bu) (17.5 g, 156 mmol) in toluene (350 ml) was heated under reflux for 3 h. After the suspension had settled for 3h at room temperature, the supernatant solution was added to a solution of **7** (12.5 g, 67.8 mmol) in toluene (80 ml). The reaction mixture was stirred at room temperature. Further ylide was extracted with toluene (200 ml) by stirring and settlement for 2 h. The ylide was added till the disappearing rate of the yellow ylide color became slow during 4 h. Then the stirring was continued for 30 min and the mixture was poured into water and extracted with Et_2O. The organic phase was successively washed with H_2O, aq. NH_4Cl and brine, dried over $MgSO_4$ and evaporated under reduced pressure. Most of the Ph_3PO was removed as a precipitate by recrystallization (toluene-hexane) and purified by chromatography on silica gel (pentane-Et_2O = 100:1-80:1) and distillation (105°C, 30 mmHg) to give **(±)-15** (10.9 g, 88.1%). IR (film): 3070 cm^{-1} [w, (C=)C–H], 1740 (s, C=O), 1650 (m, C=C), 895 (m, $C=CH_2$). ^1H NMR (400 MHz): δ 0.93 (3H, CH_3) and 0.97 (3H, CH_3), 1.20-1.30 (1H, m), 1.45-1.70 (2H, m), 1.79-1.89 (1H, m), 2.07-2.16(1H, m), 2.42-2.51 (1H,m), 2.89 (1H, s), 3.65 (3H, s), 4.73 (1H, s, C=C$\underline{H}$H), 4.85 (1H, s, C=CH$\underline{H}$). HREIms: Found: 182.1298. Calcd. for $C_{11}H_{18}O_2$ (M): 182.1307.

(1*S*)-(+)-2,2-Dimethyl-6-methylene-1-cyclohexanecarboxylic Acid [(+)-6]. The protocol of Takáes-Novák was followed[5a]; mp 63°C, $[\alpha]_D^{21}$ +125.0 (*c* 0.11). IR (KBr): 2950 cm^{-1} (br. s, C=O), 1700 (s, C=O), 900 (s, $C=CH_2$). ^1H NMR (300 MHz): δ 0.95 (3H, CH_3), 1.03 (3H, CH_3), 1.20-1.29 (1H, m), 1.44-1.70 (2H, m), 1.79-1.92 (1H, m), 2.08-2.18 (1H, m), 2.41-2.54 (1H,m), 2.89 (1H,s), 4.82 (1H, s, C=C$\underline{H}$H), 4.90 (1H, s, C=CH$\underline{H}$), 9.9-11.0 (1H, br, CO_2H). HREIms: Found: 168.1103. Calcd. for $C_{10}H_{16}O_2$ (M): 168.1151.

Methyl (1*S*)-(+)-2,2-Dimethyl-6-methylene-1-cyclohexanecarboxylate [(+)-15]. **(+)-6** (0.167 g, 0.993 mmol) was treated with diazomethane in the usual manner and chromatographed on silica gel (pentane-Et_2O = 100:1-80:1) to give **(+)-15** (0.180 g, 99.4%); $[\alpha]_D^{21}$ +101.3 (*c* 0.10).

(1*S*)-(+)-2,2-Dimethyl-6-methylene-1-cyclohexanemethanol (16). **(+)-15** (0.180 g, 0.988 mmol) was reduced with $LiAlH_4$ in the usual manner and chromatographed on silica gel (pentane-Et_2O = 10:1-4:1) to give **16** (0.138 g, 90.6%); $[\alpha]_D^{21}$ +23.7 (*c* 0.31). IR (film): 3375 cm^{-1} (br. s, OH), 3070 [w, (C=)C–H], 1645 (m, C=C), 885 (s, $C=CH_2$). ^1H NMR (300 MHz): δ 0.87 (3H, CH_3), 0.96 (3H, CH_3), 1.20-1.62 (4H, m), 2.04 (1H, dd, *J* = 4.7, 10.9 Hz), 2.08-2.15 (2H, m), 3.64 (1H, t, *J* = 10.4, C$\underline{H}$HOH), 3.72 (1H, dd, *J* = 4.7, 10.4 Hz, CH$\underline{H}$OH), 4.76 (1H, m,

C=CHH), 4.96 (1H, m, C=CHH). EIms m/z (relative intensity): 154 (M^+, 5), 136 ([$M-H_2O$]$^+$, 58), 69 (100%).

3,5-Dinitrobenzoate of 16. mp 76°C, $[\alpha]_D^{21}$ −7.8 (*c* 0.67). IR (KBr): 3090 cm^{-1} [s, (C=)C–H], 1725 (s, C=O), 1645 (m, C=C), 885 (s, C=CH_2). ^{1}H NMR (300 MHz): δ 0.97 (3H, CH_3), 1.05 (3H, CH_3), 1.34-1.66 (4H, m), 2.10-2.43 (3H, m), 4.61 (2H, d, *J*=7.7 Hz, CH_2Ph), 4.69 (1H, s, C=CHH), 4.87 (1H, s, C=CHH), 9.12 (2H, d, *J*= 1.9 Hz, aromatic), 9.12 (1H, t, *J*= 1.9 Hz, aromatic). HRFABms: Found: 349.1414. Calcd. for $C_{17}H_{21}N_2O_6$ (M+1): 349.1400. *Anal.* Found: C, 58.65; H, 5.84; N, 8.03. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04%.

(1*S*)-2,2-dimethyl-6-methylene-1-[1'-(chloro)methyl]cyclohexane (3a). **16** (1.54 g, 10.0 mol) was converted by the procedure of Hooz and Gilani[12], although the reaction temperature was 75°C to give **3a** (1.38 g, 80.0%); bp 70°C (45 mmHg). IR (film): 3070 cm^{-1} [w, (C=)C–H], 1645 (m, C=C), 895 (s, C=CH_2). ^{1}H NMR (300 MHz): δ 0.86 (3H, CH_3), 1.00 (3H, CH_3), 1.25-1.66 (4H, m), 2.02-2.20 (3H, m), 3.58 (1H, t, *J*= 11.0, CHHCl), 3.78 (1H, dd, *J*= 3.6, 11.0 Hz, CHHCl), 4.72 (1H, s, C=CHH), 4.94 (1H, s, C=CHH). EIms m/z (relative intensity): 174 (M^++2, 4), 172 (M^+, 12), 69 (100%).

(1*S*)-2,2-dimethyl-6-methylene-1-[1'-(bromo)methyl]cyclohexane (3b). To a solution of **16** (3.09 g, 20.0 mmol) in pyridine (10 ml) was added MsCl (2.3 ml, 30.0 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 a colorless oil. To a solution of the residue in DMF (10 ml) was added NaBr (4.0 g, 39 mmol), and the mixture was stirred for 5 h at 90°C. After the reaction mixture was cooled and extracted with Et_2O. The organic phase was washed with brine, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (pentane only) and distillation (105°C, 40 mmHg) to give **3b** (2.27 g, 52.2% from **16**).

Methanesulfonate of 16; IR (film): 3075 cm^{-1} [w, (C=)C–H], 1650 (m, C=C), 1360 [s, $S(=O)_2$], 1175 [s, $S(=O)_2$], 895 (s, C=CH_2). ^{1}H NMR (300 MHz): δ 0.88 (3H, CH_3), 1.01 (3H, CH_3), 1.25-1.62 (4H, m), 2.03-2.28 (3H, m), 2.99 (3H, SO_2CH_3), 4.33 (1H, t, *J* = 9.9 Hz, CHHOMs), 4.43 (1H, dd, *J* = 4.7, 9.9 Hz, CHHOMs), 4.70 (1H, s, C=CHH), 4.91 (1H, s, C=CHH).

3b; IR (film): 3075 cm^{-1} [w, (C=)C–H], 1645 (m, C=C), 895 (s, C=CH_2). ^{1}H NMR (300 MHz): δ 0.86 (3H, CH_3), 1.01 (3H, CH_3), 1.24-1.60 (4H, m), 2.02-2.25 (3H, m), 3.43 (1H, dd, *J*= 10.2, 10.2 Hz, CHHBr), 3.71 (1H, dd, *J*= 3.6, 10.2 Hz, CHHBr), 4.70 (1H, s, C=CHH), 4.94 (1H, s, C=CHH). EIms m/z (relative intensity): 218 (M^++2, 5), 216 (M^+, 5), 137 ([M–Br]$^+$, 82), 81 (100%).

(1*R*,2*R*,4a*S*,8a*S*,3'*E*,1"*S*)-(+)-1-[6'-(2",2"-Dimethyl-6"-methylenecyclohexyl-4'-methyl-3-hexenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-tetrahydropyranyloxy-2,5,5,8a-tetramethylnaphthalene (17). BuLi (1.6 M in hexane, 0.48 ml, 0.76 mmol) was added dropwise to a solution of **2a** (0.336 g, 0.633 mmol) in THF (1.5 ml) and HMPA (1.5 ml) at −30°C and the reaction mixture was stirred for 15 min. To the mixture at −30°C was added bromide

3b (0.22 g, 1.0 mmol) in THF (0.1 ml). This mixture was stirred and allowed to warm to 10°C during 3 h. Then it was poured into aq. NH_4Cl and extracted with Et_2O. The organic phase was successively washed with H_2O, aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 10:1-5:1) to give coupling products (0.135 g, *ca* 32%) as a mixture of diastereomers and recovered **2a** (0.197 g, 58.6%). To a solution of the coupling products and 10 mol% of $[PdCl_2(dppp)]$ in THF (3 ml) was added $LiHBEt_3$ (1.0 M in THF, 0.81 ml, 0.81 mmol) at 0°C. After stirring for 8h at 0°C, the mixture was treated with 3 M NaOH (1.5 ml) and a small amount of aq. KCN with stirring for 30 min followed by addition of NaCl and extraction with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane-EtOAc = 100:1-50:1) to give **17** (0.098 g, 30% from **2a**).

In the same manner as above, the coupling of **2a** (0.119 g, 0.224 mmol) with chloride **3a** (0.086 g, 0.5 mmol) and desulfonylation gave **17** (0.041 g, 36% from **2a**); $[\alpha]_D^{21}$ +8.0 (*c* 0.25). IR (film): 3070 cm^{-1} [w, (C=)C–H], 1645 (w, C=C), 1125 (m, C–O), 1020 (m, C–O,) 885 (m, $C=CH_2$). ^1H NMR (300 MHz): δ 0.78 and 0.79 (3H in total, s each, CH_3), 0.81 and 0.82 (3H in total, s each, CH_3), 0.84 (3H, s, CH_3), 0.86 and 0.86 (3H in total, s each, CH_3), 0.92 (3H, s, CH_3), 1.15 and 1.21 (3H in total, s each, CH_3), 1.60 (3H, s, CH=C–C$\underline{H}_3$), 0.9-2.15 (33H, m), 3.43-3.51 (1H, m, C$\underline{H}$H–O), 3.93-4.00 (1H, m, CH$\underline{H}$–O), 4.55 (1H, d, 2.4, C=C$\underline{H}$H), 4.75 (1H, m, C=CH$\underline{H}$), 4.84 and 4.92 (1H in total, m each, O–CH–O), 5.15 (1H, m, CH_2–C$\underline{H}$=C). HRFABms: Found: 411.3991. Calcd. for $C_{30}H_{51}$ (M–OTHP): 411.3991. *Anal.* Found: C, 82.01; H, 11.62. Calcd. for $C_{35}H_{60}O_2$: C, 81.97; H, 11.79%.

(+)-Ambrein {(1*R*,2*R*,4a*S*,8a*S*,3'*E*,1"*S*)-(+)-1-[6'-(2",2"-Dimethlyl-6"-mehylenecyclohexyl-4'-methyl-3-hexenyl]-1,2,3,4,4a,5,6,7,8,8a-decahydro-2,5,5,8a-tetramethyl-2-naphthalenol} (1). To a solution of **17** (0.050 g, 0.097 mmol) in MeOH (1 ml) was added bis(trimethylsilyl) sulfate (1 mg) in dichloroethane (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 purified by preparative TLC (hexane-EtOAc = 10:1) to give **1** (0.033 g, 79%); mp 81-82°C (lit.[3] mp 81.5-82.5), $[\alpha]_D^{21}$ +17.2 (*c* 0.20) {lit.[3] $[\alpha]_D$ +18.7 (*c* 0.63)}. IR (KBr): 3400 cm^{-1} (br. s, OH), 3075 [w, (C=)C–H], 1650 (w, C=C), 890 (s, $C=CH_2$). ^1H NMR (300 MHz): δ 0.78 (6H, s, CH_3), 0.83 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.60 (3H, s, CH=C–C$\underline{H}_3$), 0.9-2.12 (28H, m), 4.53 (1H, s, C=C$\underline{H}$H), 4.74 (1H, s, C=CH$\underline{H}$), 5.15 (1H, dt, *J* = 1.1, 7.1 Hz, CH_2–C$\underline{H}$=C). HRFABms: Found: 411.4003. Calcd. for $C_{30}H_{51}$ (M–OH): 411.3991. *Anal.* Found: C, 84.02; H, 12.39. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.22%.

(*Z*)-isomer; ^1H NMR (300 MHz): δ 0.78 (6H, s, CH_3), 0.83 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.61 (3H, s, CH=C–C$\underline{H}_3$), 0.9-2.12 (28H, m) 4.54 (1H, m, C=C$\underline{H}$H), 4.74 (1H, m, C=CH$\underline{H}$), 5.10 (1H, m, CH_2–C$\underline{H}$=C).

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