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TETRAHEDRON: *ASYMMETRY*

Synthesis of decalin type chiral synthons based on enzymatic functionalisation and their application to the synthesis of (−)-ambrox and (+)-zonarol

Hiroyuki Akita,* Masako Nozawa and Hiroyo Shimizu

School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract

Stereoselective syntheses of (−)-ambrox **2** and (+)-zonarol **3** were achieved based on the enzymatic syntheses of (8a*S*)- and (8a*R*)-decalin-type 1,3-diols **1**, respectively. Non-racemic intermediates such as (8a*S*)-**1** and (8a*R*)-**1** were obtained based on the enantioselective hydrolyses of the phenolic acetal derivative (±)-**7** by acylase I.

1. Introduction

In the field of the synthesis of optically and biologically active drimane sesquiterpenes and their related compounds, the use of the optically active and functionalized decalin derivatives is known to be advantageous.[1] The optically active 1,3-diols (8a*S*)-**1** and (8a*R*)-**1** seem to be important chiral synthons for the synthesis of ambergris-fragrance (−)-ambrox **2**[2] and fungitoxic hydroquinone (+)-zonarol **3**,[3] respectively.

Enantioselective and regioselective acetylation of (±)-**1** with the lipase 'Godo E-4' from *Pseudomonas* sp. in the presence of isopropenyl acetate was reported to give four kinds of optically active compounds (8a*S*)-**4**, (8a*S*)-**5**, (8a*S*)-**6** and (8a*R*)-**1** because (±)-**1** has two reaction sites for acetylation.[4] This problem could be overcome by converting two reaction sites to one reaction site in the substrate. This synthetic strategy could be realised by the formation of a phenolic acetal (±)-**7** which corresponds to the masked 1,3-diol structure. The newly introduced bulky naphthyl group in the substrate (±)-**7** is situated with the thermodynamically stable equatorial conformation shown in Scheme 1. We now report the stereoselective synthesis of the phenolic acetal (±)-**7** (Scheme 2) followed by chiral induction using an enzyme and

* Corresponding author. E-mail: akita@phar.toho-u.ac.jp

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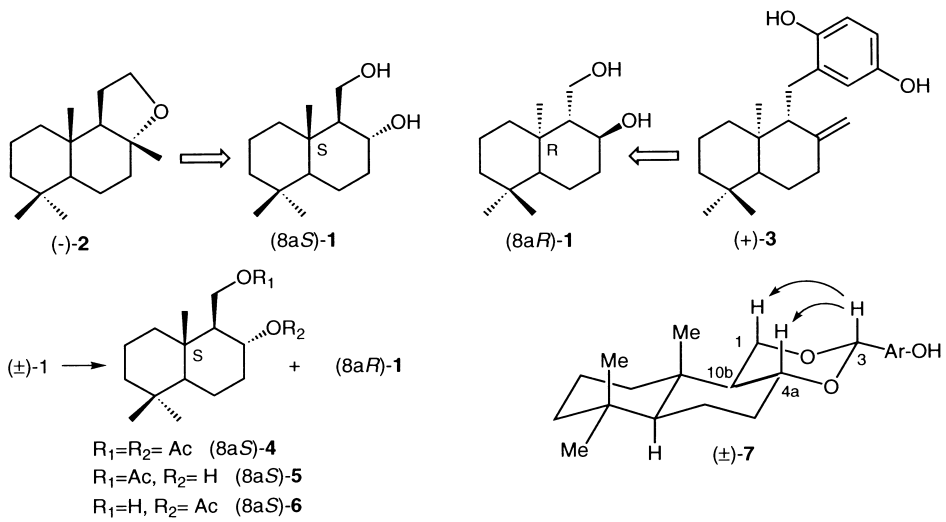
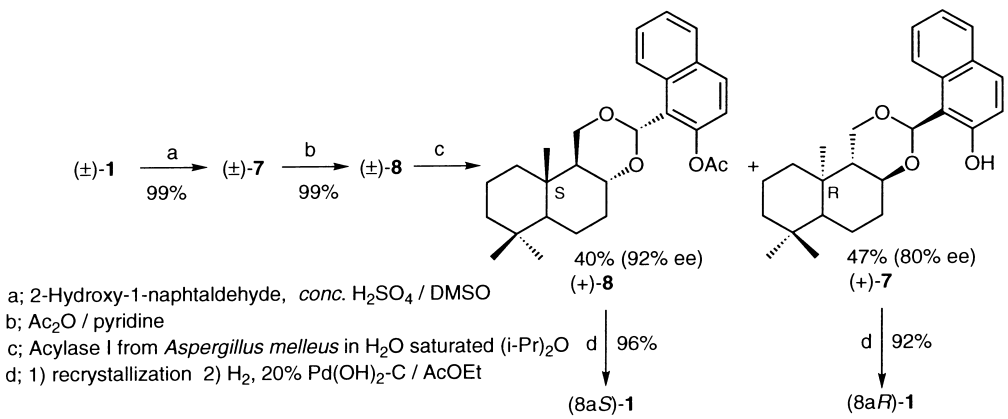
asymmetric synthesis of (−)-**2** and (+)-**3** from the enzymatic reaction products, (8a*S*)-**1** and (8a*R*)-**1**, respectively.



Scheme 1.



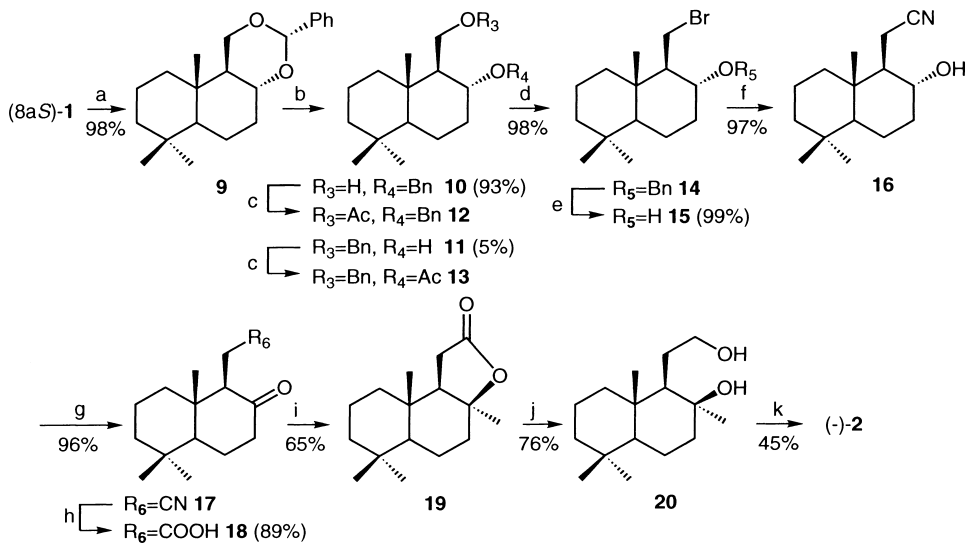
Scheme 2.

2. Results and discussion

The reaction of (±)-**1** and 2-hydroxy-1-naphthaldehyde gave the phenolic acetal (±)-(**7**) as a single diastereomer in quantitative yield whose acetylation afforded the corresponding acetate (±)-**8** in 99% yield (Scheme 2). The stereochemistry of (±)-**7** was confirmed by difference nuclear Overhauser effect (NOE) spectra. The observation of NOE enhancement for the newly generated methine proton C_3-axial proton/C_{4a}-axial proton (13.4%) and C_3-axial proton/C_1-axial proton (6.5%) as shown in Scheme 1 indicated that the newly introduced naphthyl group is located in the equatorial position. From a screening experiment using various kinds of lipase and acylase, a commerically available acylase I (No. A-2156) from *Aspergillus melleus* was found to be effective. When the phenolic acetate (±)-**8** was exposed to the acylase I in water-saturated diisopropyl ether, hydrolyzed product (+)-**7** (47%, 80% ee) and unchanged (+)-**8** (40%, 92% ee) were obtained. An enantiomeric excess of both materials was improved to give

enantiomerically pure (+)-**7**; $[\alpha]_D$ +10.3 (c=1.10, CH_2Cl_2) and (+)-**8**; $[\alpha]_D$ +9.0 (c=1.15, $CHCl_3$) by recrystallization. The enantiomeric purity of the enzymatic reaction products was determined by HPLC on a Chiralcel AD column (250 mm×4.6 mm). In order to confirm the absolute configurations of (+)-**8**, it was subjected to a catalytic hydrogenation to provide the (−)-1,3-diol **1** ($[\alpha]_D$ −2.8 (c=1.61, MeOH)), whose sign of $[\alpha]_D$ was the same as that ($[\alpha]_D$ −2.26 (c=1.06, MeOH)) of the known (−)-(8a*S*)-1,3-diol (**1**) previously reported.[4] The phenol (+)-**7** was also converted into the (+)-1,3-diol **1** ($[\alpha]_D$ +2.8 (c=1.04, MeOH)). Consequently, absolute configurations at the C_{10a}-position of (+)-**8** and (+)-**7** were determined to be *S* and *R*, respectively.

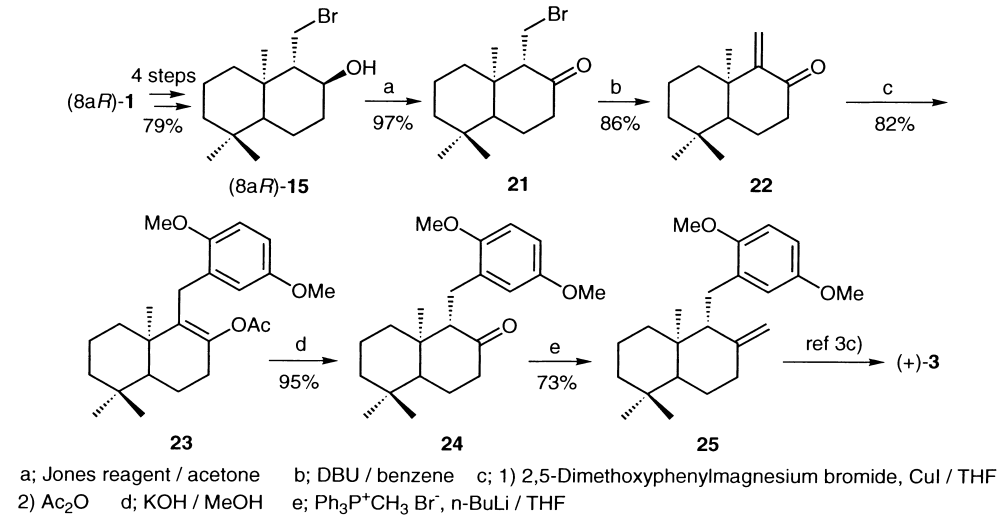
Treatment of (8a*S*)-**1** with benzaldehyde in the presence of a catalytic amount of conc. H_2SO_4 afforded acetal **9** exclusively in 98% yield, which was reduced with a mixed reducing reagent [$LiAlH_4$ (1 equiv.)–$AlCl_3$ (4 equiv.)][5] to provide selectively primary alcohol **10** (93% yield) along with a small amount of secondary alcohol **11** (5% yield) (Scheme 3). The structure of both alcohols was confirmed by derivation to the corresponding acetates **12** and **13**, respectively. Conversion of **10** by treatment with CBr_4 and Ph_3P into the bromide **14** (98% yield) followed by catalytic reduction gave the 1,3-bromohydrin **15** (99% yield). Treatment of **15** with NaCN provided nitrile **16** (97% yield), which was oxidized with Jones reagent to afford keto-nitrile **17** (96% yield).[6] Hydrolysis of **17** gave the β-keto-acid **18** (89% yield), which was reacted with MeLi followed by treatment with *p*-TsOH to provide the δ-lactone **19** (65% yield). Reduction of **19** yielded the diol **20** (76% yield) which was reacted with *p*-TsOH in $MeNO_2$ to provide the (−)-ambrox **2** (45% yield, mp 75–76°C, $[\alpha]_D$ −22.3 (c=1.30, $CHCl_3$)) whose spectral data (mp, $[\alpha]_D$, ^1H NMR and ^{13}C NMR) were identical to those (mp 75–76°C,[2n] $[\alpha]_D$ −22.1 (c=0.68, $CHCl_3$),[2i] ^1H NMR[2i] and ^{13}C NMR[2i]) reported for (−)-**2**.[2i]



Scheme 3.

A formal total synthesis of (+)-zonarol **3** from (8a*R*)-**1** was then carried out. The (8a*R*)-**1** was converted into the 1,3-bromohydrin (8a*R*)-**15** in 79% overall yield in the same way as in the conversion of (8a*S*)-**1** to (8a*S*)-**15**. Oxidation of (8a*R*)-**15** gave the bromo-ketone **21** (97% yield) which was treated with

1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the desired α,β-unsaturated ketone **22** (86% yield). Michael addition of **22** with the 2,5-dimethoxyphenyl Grignard reagent in the presence of CuI followed by treatment with Ac_2O provided an enol acetate **23** (82% yield), which was hydrolyzed to the ketone **24** (95% yield, $[\alpha]_D$ +56.3 (c=1.37, $CHCl_3$)). Wittig reaction of **24** with phosphonium salt in the presence of n-BuLi afforded the exo-olefin **25** (73% yield, $[\alpha]_D$ +27.9 (c=1.06, $CHCl_3$)) whose spectral data ($[\alpha]_D$, NMR) were identical with those ($[\alpha]_D$ +28.9 (c=0.89, $CHCl_3$)),[3c] NMR[3c]) of the reported olefin (+)-**25**.[3c] The total synthesis of (+)-zonarol **3** from (8a*R*)-**25** has been already achieved by Mori (Scheme 4).[3c]



Scheme 4.

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained using a JEOL JMS-DX 303 spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

3.2. 1-[(3S,4aR*,6aS*,10aS*,10bS*)-Decahydro-7,7,10a-trimethyl-1H-naphtho-[2,1-d][1,3]-dioxin-3-yl]-2-naphthol (±)-7*

A small amount of conc. H_2SO_4 (2 ml) was added to a solution of (±)-**1**[4] (513 mg, 2.27 mmol), 2-hydroxy-1-naphthaldehyde (428 mg, 2.48 mmol) in DMSO (20 ml) at 0°C, and the whole mixture was stirred at rt for 1 h, and then diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (25 g, n-hexane:AcOEt=10:1) to give (±)-**7** as crystals. Recrystallization from n-hexane:$CHCl_3$ gave (±)-**7** (863

mg, 99%) as colorless plates. (±)-**7**: Mp 229°C; IR (KBr): 3274 cm^{-1} (OH); ^1H NMR: δ 0.86 (3H, s), 0.91 (3H, s), 0.99 (3H, s), 1.04–1.66 (10H, m), 1.76–1.82 (1H, m), 2.14–2.20 (1H, m), 3.94 (1H, t, *J*=11 Hz), 4.02 (1H, dt, *J*=5, 11 Hz), 4.32 (1H, dd, *J*=4, 11 Hz), 6.33 (1H, s), 7.10 (1H, d, *J*=9 Hz), 7.30 (1H, dt, *J*=1, 8 Hz), 7.45 (1H, dt, *J*=1, 8 Hz), 7.70 (1H, d, *J*=9 Hz), 7.71 (1H, d, *J*=8 Hz), 7.76 (1H, d, *J*=8 Hz), 9.19 (1H, s). ^{13}C NMR: δ 15.0 (q), 18.2 (t), 20.3 (t), 21.7 (q), 32.8 (t), 33.1 (s), 33.4 (q), 36.3 (s), 38.3 (t), 41.8 (t), 52.2 (d), 54.6 (d), 67.8 (t), 77.8 (d), 101.0 (d), 111.6 (s), 119.7 (d), 121.4 (d), 122.9 (d), 126.8 (d), 128.6 (d), 128.6 (s), 131.1 (d), 131.8 (s), 154.6 (s). Anal. found: C, 79.07; H, 8.37. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48%. FAB MS m/z: 381 (M^++1). The racemate (±)-**7** was analyzed to provide well separated peaks (16 and 18 min) of each enantiomer using a Chiralcel AD column under the following analytical conditions (eluent, n-hexane:EtOH=50:1); detection, UV at 254 nm; flow rate, 1.0 ml/min).

3.3. 2-Acetoxy-1-[(3S,4aR*,6aS*,10aS*,10bS*)-decahydro-7,7,10a-trimethyl-1H-naphtho-[2,1-d]-[1,3]-dioxin-3-yl]-2-naphthalene (±)-**8***

A mixture of (±)-**7** (665 mg, 1.75 mmol), Ac_2O (814 mg, 7.98 mmol), *p*-dimethylaminopyridine (DMAP, 33 mg, 0.27 mmol) in pyridine (15 ml) was stirred at rt for 1 h, and then diluted with saturated brine and extracted with ether. The organic layer was washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. The organic layer was evaporated and chromatographed on silica gel (25 g, n-hexane:AcOEt=20:1) to afford crystals which were recrystallized from n-hexane:AcOEt to provide (±)-**8** (738 mg, 99%) as colorless needles. (±)-**8**: Mp 139°C; IR (KBr): 1759 cm^{-1} (OAc); ^1H NMR: δ 0.85 (3H, s), 0.92 (3H, s), 0.99 (3H, s), 1.11–1.82 (11H, m), 2.08–2.16 (1H, m), 2.39 (3H, s), 3.80 (1H, t, *J*=11 Hz), 3.88 (1H, dt, *J*=5, 11 Hz), 4.28 (1H, dd, *J*=4, 11 Hz), 6.10 (1H, s), 7.13 (1H, d, *J*=9 Hz), 7.42 (1H, dt, *J*=1, 8 Hz), 7.50 (1H, dt, *J*=1, 8 Hz), 7.76 (1H, dd, *J*=1, 8 Hz), 7.79 (1H, d, *J*=8 Hz), 8.75 (1H, dd, *J*=1, 9 Hz). ^{13}C NMR: δ 15.1 (q), 18.3 (t), 20.4 (t), 21.1 (q), 21.7 (q), 32.9 (t), 33.2 (s), 33.5 (q), 36.3 (s), 38.4 (t), 41.9 (t), 52.4 (d), 54.8 (d), 68.1 (t), 77.7 (d), 97.9 (d), 121.3 (d), 123.8 (s), 125.5 (d), 126.4 (d), 126.7 (d), 128.1 (d), 130.8 (d), 131.5 (s), 132.5 (s), 146.3 (s), 169.3 (s). FAB MS m/z: 423 (M^++1). Anal. found: C, 76.36; H, 8.23. Calcd. for $C_{27}H_{34}O_4$: C, 76.07; H, 8.35%. The racemate (±)-**8** was analyzed to provide well separated peaks (8 and 13 min) of each enantiomer using a Chiralcel AD column under the following analytical conditions (eluent, n-hexane:EtOH=10:1); detection, UV at 254 nm; flow rate, 1.0 ml/min).

*3.4. Enantioselective hydrolysis of (±)-**8***

A suspension of (±)-**8** (*ca*. 100 mg) and acylase I (*ca*. 100 mg) in water-saturated diisopropyl ether (20 ml) was incubated at 33°C for 2 days. This reaction was carried out seventeen times (total amount of (±)-**8** was 1.748 g, 4.14 mmol). After the reaction mixture was filtered, the precipitate was washed with diisopropyl ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (50 g) to give phenol (+)-(10a*R*)-**7** (740 mg, 47%, 80% ee) from n-hexane:-AcOEt (20:1) eluate and acetate (+)-(10a*S*)-**8** (699 mg, 40%, 92% ee) from n-hexane:AcOEt (10:1) eluate, respectively. Both fractions were recrystalized from n-hexane:AcOEt to give enantiomerically pure (+)-(10a*R*)-**7** as colorless needles and enantiomerically pure (+)-(10a*S*)-**8** as colorless plates. (+)-(10a*R*)-**7**: Mp 232–233°C; $[\alpha]_D^{27}$ +10.3 (c=1.1, CH_2Cl_2). (+)-(10a*S*)-**8**: Mp 142–142.5°C; $[\alpha]_D^{29}$ +9.0 (c=1.15, $CHCl_3$). The retention times of (+)-(10a*R*)-**7** and (+)-(10a*S*)-**8** were 18 and 8 min by means of HPLC analysis, respectively.

3.5. (−)-(1S,2R,4aS,8aS)-2-Hydroxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (−)-(8aS)-1

A mixture of (+)-(10a*S*)-**8** (1.835 g, 4.34 mmol) and 20% $Pd(OH)_2$–C (900 mg) in MeOH (20 ml) was subjected to catalytic hydrogenation at ambient temperature and the reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a crude product, which was chromatographed on silica gel (30 g, n-hexane:AcOEt=1:1) to provide (8a*S*)-**1** (947 mg, 96%). Recrystallization from n-hexane gave (8a*S*)-**1** as colorless plates. (−)-(8a*S*)-**1**: Mp 84.5–85°C; $[\alpha]_D^{27}$ −2.8 (c=1.61, MeOH). The spectral data of (−)-(8a*S*)-**1** were identical to those of the reported (−)-(8a*S*)-**1**.[4]

3.6. (+)-(1R,2S,4aR,8aR)-2-Hydroxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (+)-(8aR)-1

A mixture of (+)-(10a*R*)-**7** (983 mg, 2.58 mmol) and 20% $Pd(OH)_2$–C (980 mg) in AcOEt (10 ml) was subjected to catalytic hydrogenation at ambient temperature. The reaction mixture was worked up in the same way as for the preparation of (−)-(8a*S*)-**1** and gave (+)-(8a*R*)-**1** (541 mg, 92%) as colorless plates. (+)-(8a*R*)-**1**: Mp 86.5°C; $[\alpha]_D^{21}$ +2.8 (c=1.04, MeOH). The spectral data of (+)-(8a*R*)-**1** were identical to those of the reported (−)-(8a*S*)-**1**.[4]

3.7. (−)-[(3S,4aR,6aS,10aS,10bS)-Decahydro-7,7,10a-trimethyl-1H-naphtho-[2,1-d][1,3]-dioxin-3-yl]-benzene (−)-9

A small amount of conc. H_2SO_4 (15 drops) was added to a solution of (−)-(8a*S*)-**1** (338 mg, 1.5 mmol), benzaldehyde (462 mg, 4.36 mmol) in DMSO (3 ml) at 0°C and the whole mixture was stirred at rt for 30 min, and then diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated to give a residue. To a solution of the residue in a mixed solvent [H_2O (1 ml)–DMSO (1 ml)] was added $NaHSO_3$ (548 mg, 5.27 mmol) at rt and the whole mixture was stirred at rt for 12 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (15 g, n-hexane:AcOEt=20:1) to afford (−)-(10a*S*)-**9** as crystals. Recrystallization from n-hexane gave (−)-(10a*S*)-**9** (463 mg, 98%) as colorless needles. (−)-(10a*S*)-**9**: Mp 98.5–99°C; $[\alpha]_D^{23}$ −9.5 (c=1.12, $CHCl_3$); IR (KBr): 1041 cm^{-1}; ^1H NMR: δ 0.85 (3H, s), 0.89 (3H, s), 0.94 (3H, s), 1.01–1.62 (10H, m), 1.73–1.79 (1H, m), 2.09–2.14 (1H, m), 3.78 (1H, t, *J*=11 Hz), 3.85 (1H, dt, *J*=5, 11 Hz), 4.21 (1H, dd, *J*=4, 11 Hz), 5.46 (1H, s), 7.28–7.34 (3H, m), 7.46–7.49 (2H, m). Anal. found: C, 80.58; H, 9.39. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62%. FAB MS m/z: 315 (M^++1).

3.8. (−)-(1S,2R,4aS,8aS)-2-Benzyloxy-decahydro-5,5,8a-trimethyl-1-naphthylmethanol (−)-(8aS)-10 and (+)-(1R,2R,4aS,8aS)-1-benzyloxy-2-hydroxy-decahydro-5,5,8a-trimethylnaphthalene (+)-(8aS)-11

To a solution of (−)-(10a*S*)-**9** (359 mg, 1.14 mmol) in Et_2O (10 ml) at −20°C was added $LiAlH_4$ (51 mg, 1.35 mmol) and the whole mixture was stirred for 10 min. $AlCl_3$ (734 mg, 5.52 mmol) was added to the above mixture which was then stirred at −20°C for 30 min. The reaction mixture was diluted with H_2O, acidified with 2 M aqueous HCl and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (15 g, n-hexane:AcOEt=20:1) to give (−)-(8a*S*)-**10** (336 mg, 93%) as crystals and (+)-(8a*S*)-**11** (18 mg, 5%) as a colorless oil, respectively. Recrystallization of the former from n-hexane gave (−)-(8a*S*)-**10** as colorless plates. (−)-(8a*S*)-**10**: Mp 110.5–111°C; $[\alpha]_D^{23}$ −67.0 (c=1.08, $CHCl_3$); IR (KBr): 3479 cm^{-1} (OH); ^1H NMR: δ 0.75 (3H, s), 0.79 (3H, s), 0.88 (3H, s), 0.90–1.58 (9H,

m), 1.71–1.85 (2H, m), 2.30–2.36 (1H, m), 3.39 (1H, d, *J*=11 Hz, OH), 3.59 (1H, dd, *J*=8, 11 Hz), 3.64 (1H, dt, *J*=5, 11 Hz), 3.78 (1H, t, *J*=11 Hz), 4.44 (1H, d, *J*=11.5 Hz), 4.70 (1H, d, *J*=11.5 Hz), 7.26–7.37 (5H, m). Anal. found: C, 79.98; H, 10.04. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%. FAB MS m/z: 317 (M^++1). (+)-(8a*S*)-**11**: $[\alpha]_D^{22}$ +32.5 (c=1.36, $CHCl_3$); IR (KBr): 3480 cm^{-1} (OH); ^{1}H NMR: δ 0.80 (3H, s), 0.81 (3H, s), 0.88 (3H, s), 0.91–1.75 (11H, m), 2.05–2.12 (1H, m), 3.61 (1H, t, *J*=9 Hz), 3.82 (1H, dt, *J*=5, 10.5 Hz), 3.85 (1H, dd, *J*=3, 9 Hz), 4.05 (1H, br s), 4.51 (2H, s), 7.26–7.36 (5H, m). Anal. found: C, 79.73; H, 10.08. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%. FAB MS m/z: 317 (M^++1).

*3.9. Acetylation of (−)-(8a*S*)-**10***

The primary hydroxyl group of (−)-(8a*S*)-**10** (95 mg, 0.3 mmol) was acetylated with Ac_2O (45 mg, 0.44 mmol) in pyridine (2 ml) in the usual manner to give (8a*S*)-**12** (103 mg, 96%) as a colorless oil. (8a*S*)-**12**: IR (KBr): 1738 cm^{-1} (OAc); ^{1}H NMR: δ 0.82 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.90–1.77 (11H, m), 1.95 (3H, s), 2.32–2.37 (1H, m), 3.42–3.50 (1H, m), 4.26 (1H, dd, *J*=4, 11 Hz), 4.30 (1H, dd, *J*=3, 11 Hz), 4.38 (1H, d, *J*=12 Hz), 4.63 (1H, d, *J*=12 Hz), 7.22–7.35 (5H, m). FAB MS m/z: 359 (M^++1).

*3.10. Acetylation of (+)-(8a*R*)-**11***

The secondary hydroxyl group of (+)-(8a*R*)-**11** (95 mg, 0.3 mmol) was acetylated with Ac_2O (45 mg, 0.44 mmol), DMAP (12 mg, 0.1 mmol) in pyridine (2 ml) in the usual manner to give (8a*R*)-**13** (106 mg, 99%) as a colorless oil. (8a*R*)-**13**: IR (neat): 1736 cm^{-1} (OAc); ^{1}H NMR: δ 0.81 (3H, s), 0.87 (3H, s), 0.91 (3H, s), 0.92–1.83 (11H, m), 2.09–2.15 (1H, m), 1.91 (3H, s), 3.39 (1H, dd, *J*=3.5, 10 Hz), 3.52 (1H, dd, *J*=4, 10 Hz), 4.38 (1H, d, *J*=11 Hz), 4.42 (1H, d, *J*=11 Hz), 4.95 (1H, dt, *J*=5.5, 11 Hz), 7.23–7.34 (5H, m). Anal. found: C, 77.32; H, 9.09. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56%. FAB MS m/z: 359 (M^++1).

*3.11. (−)-(1*R*,2*S*,4a*S*,8a*S*)-2-Benzyloxy-1-bromomethyl-decahydro-5,5,8a-trimethylnaphthalene (−)-(8a*S*)-**14***

To a solution of (−)-(8a*S*)-**10** (316 mg, 1 mmol) in THF (5 ml) at 0°C was added CBr_4 (657 mg, 1.98 mmol) and Ph_3P (521 mg, 1.99 mmol) and the whole mixture was stirred at rt for 15 min. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (10 g, n-hexane:AcOEt=50:1) to give (−)-(8a*S*)-**14** (370 mg, 98%) as crystals. Recrystallization from n-hexane afforded (−)-(8a*S*)-**14** as colorless needles. (−)-(8a*S*)-**14**: Mp 67.5–68°C; $[\alpha]_D^{21}$ −45.7 (c=1.16, $CHCl_3$); IR (neat): 1071 cm^{-1}; ^{1}H NMR: δ 0.82 (3H, s), 0.87 (3H, s), 0.94 (3H, s), 0.87–1.61 (10H, m), 1.66–1.74 (1H, m), 1.80–1.86 (1H, m), 2.01–2.05 (1H, m), 2.43–2.48 (1H, m), 3.42–3.50 (1H, m), 3.56 (1H, dd, *J*=2.5, 10.5 Hz), 3.66 (1H, dd, *J*=4, 10.5 Hz), 7.24–7.43 (5H, m). Anal. found: C, 66.85; H, 7.73. Calcd. for $C_{21}H_{31}OBr$: C, 66.49; H, 8.24%. FAB MS m/z: 379 (M^++1).

3.12. (−)-(1R,2R,4aS,8aS)-1-Bromomethyl-2-hydroxy-decahydro-5,5,8a-trimethylnaphthalene (−)-(8aS)-15

A mixture of (−)-(8a*S*)-**14** (1.123 g, 2.96 mmol) and 20% $Pd(OH)_2$–C (1 g) in AcOEt (10 ml) was subjected to catalytic hydrogenation at ambient temperature and the reaction mixture was worked up in the same way as (8a*S*)-**1** to give a residue which was chromatographed on silica gel (20 g, n-hexane:AcOEt=20:1) to provide (−)-(8a*S*)-**15** (855 mg, 99%) as a colorless oil. (−)-(8a*S*)-**15**: $[\alpha]_D^{24}$ −16.3 (c=1.36, $CHCl_3$); IR (neat): 3351 cm^{-1} (OH); ^1H NMR: δ 0.81 (3H, s), 0.87 (3H, s), 0.89 (3H, s), 1.08–1.61 (8H, m), 1.67–1.71 (2H, m), 1.79–1.84 (1H, m), 2.11–2.17 (1H, m), 3.58 (1H, dd, *J*=3.5, 11 Hz), 3.63 (1H, dd, *J*=4, 11 Hz), 3.68 (1H, ddd, *J*=5, 11, 11 Hz). Anal. found: C, 58.77; H, 8.44. Calcd. for $C_{14}H_{25}OBr$: C, 58.13; H, 8.71%. FAB MS m/z: 271 (M^++1–H_2O).

3.13. (−)-(1R,2R,4aS,8aS)-2-Hydroxy-decahydro-5,5,8a-trimethyl-1-naphthaleneacetonitrile (−)-(8aS)-16

To a solution of (−)-(8a*S*)-**15** (199 mg, 0.68 mmol) in DMSO (2 ml) was added NaCN (51 mg, 1.04 mmol) and the mixture was stirred at 40°C for 12 h. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue which was chromatographed on silica gel (10 g, n-hexane:AcOEt=5:1) to yield (−)-(8a*S*)-**16** (156 mg, 97%) as crystals. Recrystallization from n-hexane afforded (−)-(8a*S*)-**16** as colorless plates. (−)-(8a*S*)-**16**: Mp 59°C; $[\alpha]_D^{22}$ −17.6 (c=1.50, $CHCl_3$); IR (neat): 3433 cm^{-1} (OH), 2245 cm^{-1} (CN); ^1H NMR: δ 0.82 (3H, s), 0.88 (3H, s), 0.89 (3H, s), 0.90–1.75 (11H, m), 2.13–2.18 (1H, m), 2.48 (2H, d, *J*=5 Hz), 3.57–3.66 (1H, m). Anal. found: C, 76.82; H, 10.79; N, 5.64. Calcd. for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95%. FAB MS m/z: 236 (M^++1).

3.14. (−)-(1R,4aS,8aS)-2-Oxo-decahydro-5,5,8a-trimethyl-1-naphthaleneacetonitrile (−)-(8aS)-17

A mixture of (−)-(8a*S*)-**16** (172 mg, 0.73 mmol) in acetone (5 ml) at 0°C was oxidized with Jones reagent (20 drops) in the usual manner to give (−)-(8a*S*)-**17** (165 mg, 96%) as a colorless oil. (−)-(8a*S*)-**17**: $[\alpha]_D^{23}$ −43.4 (c=1.11, $CHCl_3$). The spectral data (IR and ^1H NMR) were identical to those of the reported (−)-(8a*S*)-**17**.[4]

3.15. (−)-(1R,4aS,8aS)-2-Oxo-decahydro-5,5,8a-trimethyl-1-naphthaleneacetic acid (−)-(8aS)-18

A mixture of (−)-(8a*S*)-**17** (165 mg, 0.708 mmol), 6 M aqueous NaOH (2 ml) in MeOH (2 ml) was refluxed for 1 h. The reaction mixture was acidified with 2 M aqueous HCl and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed on silica gel (10 g, n-hexane:AcOEt=1:1) to give (−)-(8a*S*)-**18** (159 mg, 89%) as crystals. Recrystallization from n-hexane afforded (−)-(8a*S*)-**18** as colorless needles. (−)-(8a*S*)-**18**: Mp 124°C; $[\alpha]_D^{22}$ −81.9 (c=1.30, $CHCl_3$); IR (KBr): 1712 cm^{-1} (COOH); ^1H NMR: δ 0.73 (3H, s), 0.86 (3H, s), 0.98 (3H, s), 1.21–1.72 (8H, m), 2.02–2.50 (4H, m), 2.70–2.78 (2H, m). Anal. found: C, 71.17; H, 9.46. Calcd. for $C_{15}H_{24}O_3$: C, 71.40; H, 9.59%. FAB MS m/z: 251 (M^+−1).

3.16. (−)-(3a*S*,5a*S*,9a*S*,9b*R*)-3a,4,5,5a,6,7,8,9,9a,9b-Decahydro-3a,6,6,9a-tetramethyl-naphtho-[1,2-d]furan-2(1H)-one (−)-(9a*S*)-**19**

To a solution of (−)-(8a*S*)-**18** (227 mg, 0.90 mmol) in a mixed solvent (Et_2O (1 ml) and THF (2 ml)) at −70°C was added MeLi (1.4 M in Et_2O, 1.3 ml, 1.82 mmol) and the whole mixture was stirred at −70°C for 1 h and at 0°C for 30 min. The reaction mixture was diluted with saturated brine and acidified with 2 M aqueous HCl, extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. A mixture of the residue and *p*-TsOH·H_2O (150 mg, 0.87 mmol) in toluene (3 ml) was refluxed for 30 min. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, n-hexane:AcOEt=10:1) to yield (−)-(9a*S*)-**19** (148 mg, 65%) as crystals. Recrystallization from n-hexane afforded (−)-(9a*S*)-**19** as colorless plates. (−)-(9a*S*)-**19**: Mp 106°C; $[\alpha]_D^{24}$ −163.9 (c=0.213, $CHCl_3$); IR (KBr): 1767 cm^{-1} (γ-lactone); ^1H NMR: δ 0.87 (3H, s), 0.90 (3H, s), 0.91 (3H, s), 0.85–1.65 (10H, m), 1.32 (3H, s), 1.76 (1H, d, *J*=8 Hz), 2.31 (1H, ddd, *J*=3, 5, 15 Hz), 2.38 (1H, d, *J*=18 Hz), 2.72 (1H, dd, *J*=8, 18 Hz). Anal. found: C, 76.82; H, 10.35. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%. FAB MS m/z: 251 (M^++1).

3.17. (+)-(1R,2S,4aS,8aS)-2-Hydroxy-decahydro-2,5,5,8a-tetramethyl-1-naphthaleneethanol (−)-(8a*S*)-**20**

A mixture of (9a*S*)-**19** (148 mg, 0.593 mmol), $LiAlH_4$ (57 mg, 1.49 mmol) in Et_2O (3 ml) was stirred at rt for 30 min. The reaction mixture was quenched with saturated brine and acidified with 2 M aqueous HCl, extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, n-hexane:AcOEt=1:1) to provide (−)-(8a*S*)-**20** (114 mg, 76%) as crystals. Recrystallization from AcOEt gave (−)-(8a*S*)-**20** as colorless needles. (−)-(8a*S*)-**20**: Mp 186°C; $[\alpha]_D^{22}$ +15.1 (c=1.06, $CHCl_3$); IR (KBr): 3338 cm^{-1} (OH); ^1H NMR: δ 0.83 (6H, s), 0.87 (3H, s), 0.97 (3H, s), 1.14 (3H, s), 0.78–1.78 (14H, m), 3.54–3.69 (2H, m). ^{13}C NMR: δ 15.1 (q), 18.1 (t), 18.3 (t), 21.7 (q), 28.7 (t), 30.7 (q), 33.3 (s), 33.4 (q), 38.5 (s), 39.3 (t), 42.0 (t), 42.3 (t), 54.7 (d), 55.9 (d), 64.9 (t), 72.9 (s). Anal. found: C, 75.57; H, 11.64. Calcd. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%.

3.18. (−)-Ambrox (−)-**2**

A mixture of (8a*S*)-**20** (112 mg, 0.44 mmol) and *p*-TsOH·H_2O (14.4 mg, 0.08 mmol) in $MeNO_2$ (2 ml) was stirred at 40°C for 5 min. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g, n-hexane:AcOEt=50:1) to give (−)-**2** (47 mg, 45%) as crystals. Recrystallization from EtOH gave (−)-**2** as colorless plates. (−)-**2**: Mp 75–76°C; $[\alpha]_D^{23}$ −22.3 (c=1.30, $CHCl_3$). FAB MS m/z: 221 (M^+−Me, 20). ^{13}C NMR: δ 15.1 (q), 18.4 (t), 20.7 (t), 21.2 (q), 21.2 (q), 22.7 (t), 33.1 (s), 33.6 (q), 36.2 (s), 39.8 (t), 40.0 (t), 42.4 (t), 57.3 (d), 60.1 (d), 65.0 (t), 79.9 (s). The spectral data (IR and ^1H NMR) were identical with those of the reported (−)-**2**.

3.19. (+)-(1S,2S,4aR,8aR)-1-Bromomethyl-2-hydroxy-decahydro-5,5,8a-trimethylnaphthalene (+)-(8a*R*)-**15**

The bromohydrin (8a*R*)-**15** was obtained in 79% overall yield from (8a*R*)-**1** in the same way as for the conversion of (8a*S*)-**1** to (8a*S*)-**15**. (8a*R*)-**15**: $[\alpha]_D^{22}$ +16.1 (c=1.34, $CHCl_3$).

3.20. (+)-(1S,4aR,8aR)-1-Bromomethyl-2-oxo-decahydro-5,5,8a-trimethylnaphthalene (+)-(8aR)-21

A mixture of (+)-(8a*R*)-**15** (465 mg, 1.61 mmol) in acetone (10 ml) at 0°C was oxidized with Jones reagent (1 ml) in the usual manner to give (+)-(8a*R*)-**21** (448 mg, 97%) as a colorless oil. (+)-(8a*R*)-**21**: $[\alpha]_D^{25}$ +16.8 (c=1.30, $CHCl_3$); IR (neat): 1718 cm^{-1} (ketone); ^1H NMR: δ 0.72 (3H, s), 0.84 (3H, s), 0.96 (3H, s), 1.23–1.78 (7H, m), 1.65 (1H, dq, *J*=5, 13 Hz), 2.08 (1H, ddt, *J*=2, 7, 13 Hz), 2.38 (1H, ddd, *J*=1, 7, 13 Hz), 2.50 (1H, ddd, *J*=2, 5, 13 Hz), 2.74 (1H, dd, *J*=2.5, 9.5 Hz), 3.33 (1H, dd, *J*=2.5, 9.5 Hz), 3.73 (1H, t, *J*=9.5 Hz).

3.21. (−)-(4aR,8aR)-1-(2,5-Dimethoxyphenyl)methyl-2-acetoxy-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene (−)-(8aR)-23

(i) A mixture of (+)-(8a*R*)-**21** (428 mg, 1.49 mmol), DBU (455 mg, 3 mmol) in benzene (5 ml) was stirred at rt for 30 min. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (5 g, n-hexane:AcOEt=20:1) to give (8a*R*)-**22** (263 mg, 86%) as a colorless oil. (ii) A mixture of Mg (154 mg, 6.33 mmol) and 2,5-dimethoxybromobenzene (1.399 g, 6.45 mmol) in THF (15 ml) was refluxed for 2 h under Argon. The generated Grignard reagent was added dropwise to CuI (364 mg, 1.91 mmol) at 0°C under Ar and the whole miture was stirred at 0°C for 10 min. A solution of (8a*R*)-**22** (263 mg, 1.28 mmol) in THF (5 ml) was added stepwise to the above cuprate reagent at 0°C for 15 min and the whole mixture was stirred at rt for 1 h. After cooling, Ac_2O (1 ml, 10.9 mmol) was added to the stirred mixture to quench the enolate and stirring was continued for 20 min at rt. The reaction mixture was diluted with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave a residue which was chromatographed on silica gel (50 g, n-hexane:AcOEt=30:1) to give (8a*R*)-**23** (404 mg, 82%) as a pale yellow oil. (−)-(8a*R*)-**23**: $[\alpha]_D^{26}$ −102.4 (c=1.42, $CHCl_3$); IR (neat): 1747 cm^{-1} (OAc); ^1H NMR: δ 0.84 (3H, s), 0.92 (3H, s), 1.07 (3H, s), 0.95–1.85 (9H, m), 1.90 (3H, s), 2.21 (1H, dd, *J*=7, 17 Hz), 2.49 (1H, ddd, *J*=10, 11, 17 Hz), 3.24 (1H, d, *J*=18 Hz), 3.30 (1H, d, *J*=18 Hz), 3.75 (3H, s), 3.79 (3H, s), 6.65 (1H, dd, *J*=3, 8.5 Hz), 6.73 (1H, d, *J*=8.5 Hz), 6.77 (1H, d, *J*=3 Hz). ^{13}C NMR: δ 18.7 (t), 18.7 (t), 20.5 (q), 20.9 (q), 21.7 (q), 24.2 (t), 28.0 (t), 33.3 (q), 33.3 (s), 35.9 (t), 38.7 (s), 41.6 (t), 51.2 (d), 55.7 (q), 56.0 (d), 110.5 (d), 110.8 (d), 115.6 (d), 130.2 (s), 132.2 (s), 145.0 (s), 151.1 (s), 153.5 (s), 169.3 (s). Anal. found: C, 74.52; H, 8.68. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87%. FAB MS m/z: 386 (M^+).

3.22. (+)-(1S,4aR,8aR)-1-(2,5-Dimethoxyphenyl)methyl-2-oxo-5,5,8a-decahydro-trimethylnaphthalene (+)-(8aR)-24

A mixture of (8a*R*)-**23** (371 mg, 0.96 mmol) and KOH (1 g) in MeOH (9 ml) was stirred at rt for 6 h. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (15 g, n-hexane:AcOEt=20:1) to afford (8a*R*)-**24** (314 mg, 95%) as crystals. Recrystallization from n-hexane gave (8a*R*)-**24** as colorless prisms. (+)-(8a*R*)-**24**: Mp 108°C; $[\alpha]_D^{24}$ +56.3 (c=1.37, $CHCl_3$); IR (KBr): 1709 cm^{-1} (ketone); ^1H NMR: δ 0.80 (3H, s), 0.86 (3H, s), 0.96 (3H, s), 1.22–1.67 (7H, m), 1.93–2.06 (2H, m), 2.23 (1H, ddt, *J*=1, 6, 13 Hz), 2.36 (1H, ddd, *J*=2.5, 5, 13 Hz), 2.47 (1H, br. d, *J*=9 Hz), 2.66 (1H, dd, *J*=1, 13 Hz), 2.88 (1H, dd, *J*=9, 13 Hz), 3.74 (3H, s), 3.76 (3H, s), 6.64 (1H, dd, *J*=3, 8.5 Hz), 6.70 (1H, d, *J*=8.5 Hz), 6.90 (1H, d, *J*=3 Hz). ^{13}C NMR: δ 14.6 (q), 19.1 (t), 21.7 (q), 22.9 (t), 24.2 (t), 33.5 (q), 33.8 (s), 38.9 (t), 42.0 (t), 42.7 (t), 43.4 (s), 54.3 (d), 55.6 (q), 55.8 (q), 64.2 (d), 110.0 (d), 111.2 (d),

117.7 (d), 131.7 (s), 151.6 (s), 153.2 (s), 211.6 (s). Anal. found: C, 77.19; H, 9.02. Calcd. for $C_{22}H_{32}O_3$: C, 76.71; H, 9.36%. FAB MS m/z: 344 (M^+).

*3.23. (+)-Zonarol dimethyl ether (+)-(8a*R*)-**25***

n-BuLi (1.6 M in n-hexane, 0.6 ml, 0.96 mmol) was added to a suspension of $Ph_3P^+MeBr^-$ (685 mg, 1.92 mmol) in THF (10 ml) at −78°C under Argon and the whole mixture was stirred for 30 min. A solution of (8a*R*)-**24** (263 mg, 0.76 mmol) in THF (2 ml) was added to the above reaction mixture at 0°C and the whole mixture was stirred at 80°C for 2 days. The reaction mixture was diluted with saturated brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (15 g, n-hexane:AcOEt=50:1) to afford (8a*R*)-**25** (190 mg, 73%) as a colorless oil. (+)-(8a*R*)-**25**: $[\alpha]_D^{26}$ +27.9 (c=1.06, $CHCl_3$); ^{1}H NMR: δ 0.82 (3H, s), 0.84 (3H, s), 0.89 (3H, s), 1.12–1.67 (7H, m), 1.71–1.76 (1H, m), 1.85–1.91 (1H, m), 2.00 (1H, dt, *J*=5, 13 Hz), 2.20 (1H, d, *J*=7 Hz), 2.35 (1H, ddd, *J*=2.5, 6.5, 13 Hz), 2.74 (2H, d, *J*=7 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.61 (1H, d, *J*=1.5 Hz), 4.74 (1H, d, *J*=1.5 Hz), 6.63 (1H, dd, *J*=3, 9 Hz), 6.73 (1H, d, *J*=9 Hz), 6.72 (1H, d, *J*=3 Hz). ^{13}C NMR: δ 14.6 (q), 19.5 (t), 21.8 (q), 23.3 (t), 24.4 (t), 33.7 (q), 33.7 (s), 38.3 (t), 39.2 (t), 39.9 (s), 42.2 (t), 55.6 (q), 55.7 (d), 55.9 (q), 56.0 (d), 107.7 (t), 109.7 (d), 110.8 (d), 116.3 (d), 132.1 (s), 148.3 (s), 151.8 (s), 153.3 (s). Anal. found: C, 80.93; H, 9.88. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00%. FAB MS m/z: 342 (M^+).

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6. The overall yield of (8a*S*)-**17** was improved to 82% in 6 steps from (8a*S*)-**1** in the present case while that of (8a*S*)-**17** was 39% in 4 steps from (8a*S*)-**1** in the previously reported synthetic route.[4]