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New total synthesis of (+)-ambrein

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Abstract—The convergent synthesis of (+)-ambrein **1** was achieved based on a modified Julia coupling reaction between aldehyde **14** corresponding to the left-half **A** and sulfone **25a** or **25b** corresponding to the right-half **B**. Aldehyde **14** was synthesized in 14% overall yield (nine steps) from the enzymatic resolution product, epoxy alcohol (8a*S*)-**2**. Sulfone **25a** or **25b** was synthesized in 11 steps (**25a**: 41% overall yield, **25b**: 56% overall yield) from the enzymatic resolution product, (1*S*,6*S*)-2,2-dimethyl-6-hydroxyhexane-1-carboxylate **4**.

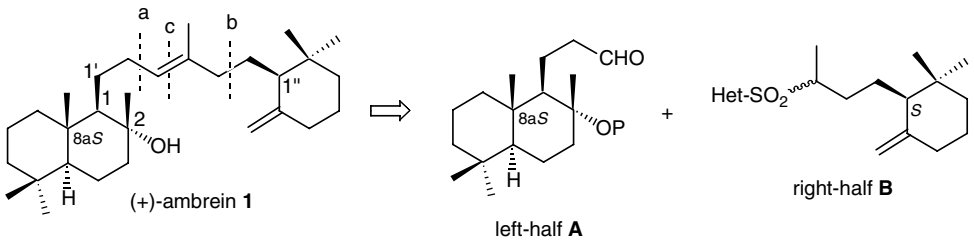
1. Introduction

(+)-Ambrein **1** is a major constituent of ambergris, which is a metabolite of the sperm whale, and is used for the production of expensive perfumes.[1] However, the supply of ambergris has become very difficult, as commercial whaling is prohibited, and thus the development of efficient synthesis of (+)-**1** is strongly desirable. Herein, we report a new total synthesis of (+)-**1** based on convergent synthesis via the modified Julia coupling method. The synthetic approach can be carried out by way of two published routes. One is accomplished based on the carbon–carbon bond formation at the dotted line a by the method of Negishi via the organoalane,[2] in the other route, the carbon–carbon bond formation at the dotted line b is accomplished based on alkylation of the allyl-sulfone congener.[3] Our synthetic plan for (+)-ambrein **1** is based on the double bond formation between the left-half **A** and the right-half **B** at the dotted line c by the modified Julia coupling method,[4] as shown in Scheme 1.

In order to make two chiral building blocks, left-half (8a*S*)-**A** and right-half (*S*)-**B**, both chiral (8a*S*)-epoxy alcohol **2** and (1*S*,2*S*)-β-hydroxy ester **4** appear to be useful starting materials, respectively. Both (8a*S*)-**2**[5] and (1*S*,2*S*)-**4**[6] were effectively obtained based on the lipase-catalyzed asymmetric acetylation of (±)-**2** and (±)-**4**, respectively, as shown in Scheme 2. Furthermore, enrichment of the enantiomeric excess (ee) of the chiral synthons (8a*S*)-**2** and (1*S*,2*S*)-**4** was achieved by repeated enzymatic reactions.

2. Synthesis of left-half A 14

Reduction of enantiomerically pure (8a*S*)-**2** followed by Swern's oxidation gave aldehyde **7** in 86% yield (two



Scheme 1.

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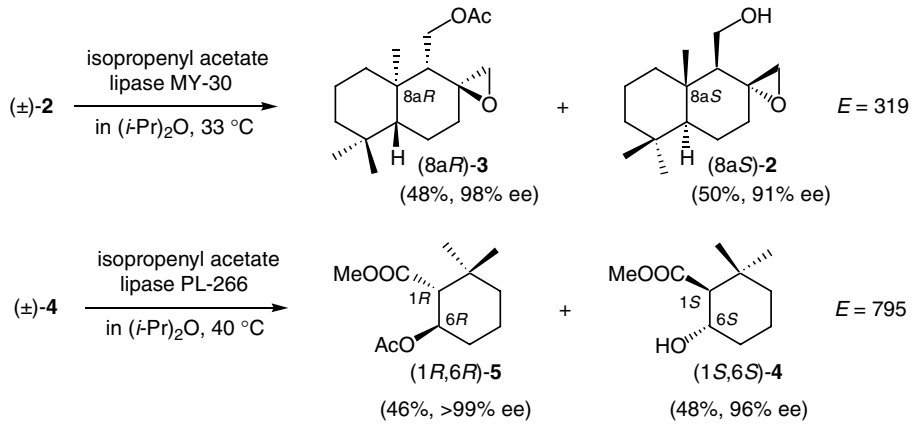


Scheme 2.

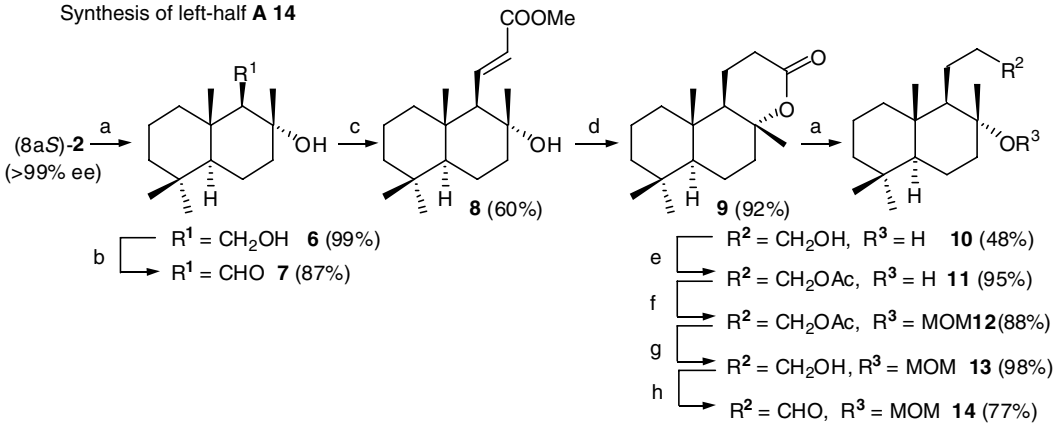
steps), which was subjected to Wittig reaction to afford α,β-unsaturated ester **8** in 60% yield. Catalytic hydrogenation of **8** followed by $LiAlH_4$ reduction provided diol **10** in 44% overall yield (two steps). The low yield of **10** could be explained by the production of a dehydration product (46% yield) in the process of $LiAlH_4$ reduction followed by silica gel column chromatography. Selective acetylation of the primary hydroxyl group in **10** followed by treatment with methoxymethyl chloride (MOM-Cl) gave MOM ether **12** in 83% overall yield (two steps). Treatment of **12** with K_2CO_3 gave MOM-alcohol **13** in 98% yield, which was subjected to oxidation with PDC to afford the desired aldehyde **14** in 77% yield (Scheme 3).

3. Synthesis of right-half B (25a or 25b)

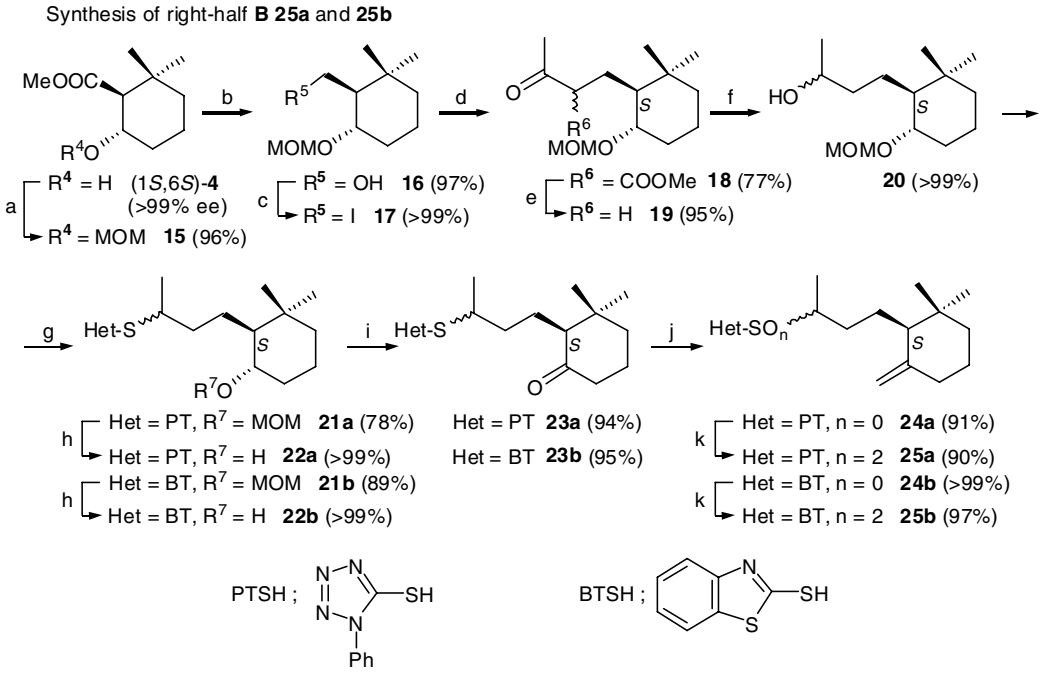
Treatment of enantiomerically pure (1*S*,6*S*)-**4** with MOM-Cl gave the corresponding MOM-ether **15** in 96% yield, which was reduced with $LiAlH_4$ to afford alcohol **16** in 97% yield. After conversion of **16** into iodide **17** in 95% yield, **17** was subjected to acetoacetic ester synthesis to provide a 1:1 diastereomeric mixture of acetoacetic ester congener **18** (77% yield). Alkaline hydrolysis of **18** followed by decarboxylation gave methyl ketone **19** in 95% yield, which was reduced with $NaBH_4$ to give quantitatively a 3:2 diastereomeric mixture of **20**. Treatment of **20** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) or 2-mercaptobenzothiazole (BTSH) in the presence of triphenylphosphine and diethylazodicarboxylate gave the corresponding sulfide, a 3:7 diastereomeric mixture of **21a** (78% yield) or a 2:3 diastereomeric mixture of **21b** (89% yield), respectively. Deprotection of the MOM group in **21a** or **21b** quantitatively gave the corresponding alcohol a 3:7 diastereomeric mixture of **22a** or a 2:3 diastereomeric mixture of **22b**, respectively. PCC oxidation of **22a** or **22b** afforded the corresponding ketone a 3:7 diastereomeric mixture of **23a** (94% yield) or a 2:3 diastereomeric mixture of **23b** (95% yield), respectively. Treatment of **23a** or **23b** with triphenylmethylphosphonium iodide in the presence of *tert*-BuOK provided the corresponding *exo*-olefin a 3:7 diastereomeric mixture of **24a** (91% yield) or a 2:3 diastereomeric mixture of **24b** (>99% yield), respectively. Oxidation of **23a** or **23b** with 30% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ gave the corresponding sulfone **4** a 3:7 diastereomeric mixture of **25a** (90% yield) or a 2:3 diastereomeric mixture of **25b** (97% yield), respectively (Scheme 4).

4. Modified Julia coupling of aldehyde 14 with sulfone 25a or 25b

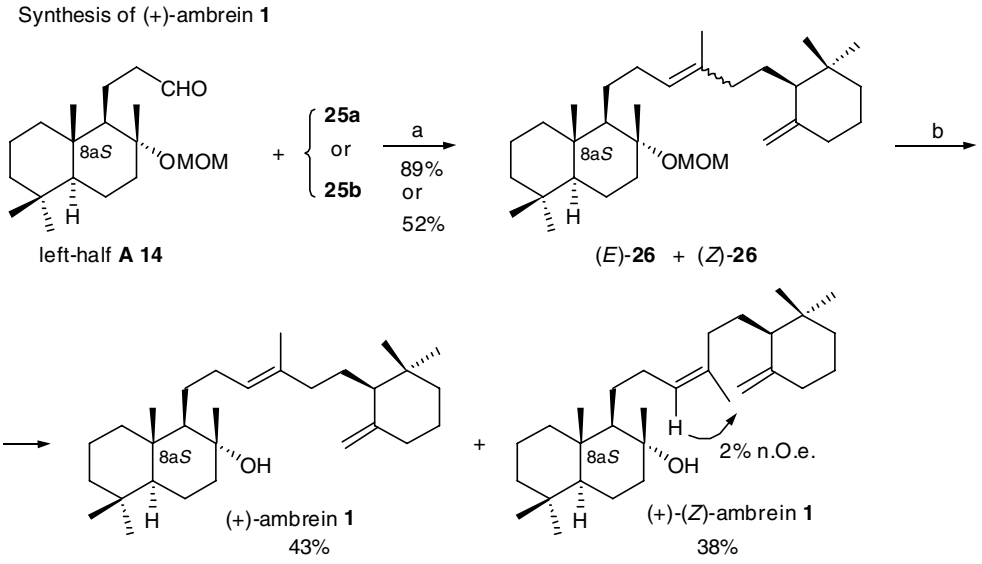
The modified Julia coupling of aldehyde **14** with sulfone **25a** or **25b** was carried out. The reaction of **14** and **25a** in



Scheme 3. Reagents and conditions: (a) $LiAlH_4/Et_2O$; (b) $(COCl)_2$/DMSO; (c) $Ph_3P{=}CHCOOMe$/PhH; (d) H_2/20% $Pd(OH)_2$–C/MeOH; (e) Ac_2O/DMAP/pyridine; (f) MOM–Cl/*i*-Pr_2NEt; (g) K_2CO_3/MeOH; (h) PDC/CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) MOM–Cl/*i*-Pr_2NEt/DMF; (b) $LiAlH_4/Et_2O$; (c) I_2/Ph_3P/imidazole/THF; (d) CH_3COCH_2COOMe/NaOMe/MeOH, 90 °C; (e) 6 M NaOH, 100 °C; (f) $NaBH_4$/MeOH; (g) PTSH/DEAD/Ph_3P/THF or BTSH/DEAD/Ph_3P/THF; (h) concd HCl/MeOH; (i) PCC; (j) (1) $Ph_3P^+CH_3Br^-$/*t*-BuO^-K^+/toluene; (k) 30% $H_2O_2/Mo_7O_{24}(NH_4)\cdot 6H_2O$/EtOH.



Scheme 5. Reagents and conditions: (a) LHMDS/THF; (b) 2 M HCl/80% AcOH.

the presence of 1 M solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF gave a mixture ($E/Z = 1/1$) of **26** in 89% yield. Deprotection of the MOM group in **26** with acid gave (*E*)-**1** (43% yield) and (*Z*)-**1** {38% yield, $[\alpha]_D = +5.9$ (*c* 1.07, EtOH)}. The physico-chemical data ($[\alpha]_D$, mp, ^1H and ^{13}C NMR) of the synthetic (*E*)-**1** {mp 82 °C, $[\alpha]_D = +18.9$ (*c* 0.47, EtOH)} were identical with those {mp 80.5–82 °C,[2] mp 81–82 °C,[3] $[\alpha]_D = +18.3$ (*c* 0.63, EtOH)[2]} of natural (+)-ambrein **1**. The geometry of (*Z*)-**1** was confirmed by NOE study as shown in Scheme 5. The reaction of **14** and **25b** in the presence of a 1 M solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF gave a mixture ($E/Z = 1/1$) of **26** in 52% yield (Scheme 5). Although the solvent effect should be studied to improve the stereoselectivity in the key Julia coupling, this trial was not carried out at the present stage. No stereoselectivity in the synthesis of trisubstituted alkene from secondary alkyl heteroarylsulfones and aldehydes was reported.[7,8]

5. Conclusion

The convergent synthesis of (+)-ambrein **1** was achieved based on the modified Julia coupling reaction between

aldehyde **14** corresponding to the left-half **A** and sulfone **25a** or **25b** corresponding to the right-half **B**. Aldehyde **14** was synthesized in 14.4% overall yield (nine steps) from the enzymatic resolution product, (1*R*,2*R*,4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*),2′-oxirane]-methanol **2**. Sulfone **25a** or **25b** was synthesized in 11 steps (**25a**: 41% overall yield, **25b**: 56% overall yield) from the enzymatic resolution product, (1*S*,6*S*)-2,2-dimethyl-6-hydroxyhexane-1-carboxylate **4**.

6. Methods and results

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. 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.

6.1. (+)-Driman-8,11-diol 6

To a suspension of $LiAlH_4$ (4.09 g, 110 mmol) in Et_2O (160 ml) was added a solution of (−)-(8a*S*)-**2** (21.09 g, 89 mmol) in Et_2O (40 ml) at 0 °C and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and filtered with the aid of Celite. The filtrate was extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave crude crystals, which were recrystallized from *n*-hexane/AcOEt to give a colorless powder (8a*S*)-**6** (13.26 g). The mother liquor was chromatographed on silica gel (120 g, *n*-hexane–AcOEt = 1:1) to give (8a*S*)-**6** (8.00 g, total weight; 21.26 g, 99%). Compound (8a*S*)-**6**: mp 127 °C; $[\alpha]_D^{26} = +3.5$ (*c* 0.72, $CHCl_3$); IR (KBr): 3350 cm^{-1} (OH); NMR: δ 0.76 (6H, s), 0.86 (3H, s), 0.96 (1H, dd, $J = 2$, 12 Hz), 1.04–1.66 (9H, m), 1.32 (3H, br s), 1.69–1.75 (1H, m), 1.86 (1H, dt, $J = 3$, 12.5 Hz), 2.90 (1H, br s; disappeared with D_2O), 2.98 (1H, br s; disappeared with D_2O), 3.89 (2H, d, $J = 7$ Hz). ^{13}C NMR: δ 16.2 (q), 18.7 (t), 20.3 (t), 21.7 (q), 24.4 (q), 33.4 (s), 33.6 (q), 37.6 (s), 40.1 (t), 41.8 (t), 44.4 (t), 56.0 (d), 60.5 (d), 61.1 (t), 75.0 (s). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.02; H, 11.77. FAB MS *m*/*z*: 241 (M^++1).

6.2. (1*R*,2*R*,4a*S*,8a*S*)-(+)-2-Hydroxy-1,2,3,4,4a,5,6,7,8,8a-decahydro-2,5,5,8a-tetramethyl-naphthalene-1-aldehyde 7

To a solution of dimethyl sulfoxide (DMSO; 30.6 g, 390 mmol) in CH_2Cl_2 (160 ml) was added oxalyl chloride (16.6 ml, 200 mmol) at −78 °C and the reaction mixture was stirred for 0.5 h. A solution of (10*S*)-**6** (17.78 g, 74 mmol) in CH_2Cl_2 (100 ml) was added to the above reaction mixture and the whole mixture was stirred for 0.5 h. Et_3N (118 ml, 846 mmol) was added to the above reaction mixture and the whole mixture was stirred for 0.5 h at room temperature. The reaction mixture was diluted with ice-water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (300 g, *n*-hexane–AcOEt = 5:1) to give a colorless oil (+)-**7** (15.34 g, 87%). Compound (+)-**7**: $[\alpha]_D^{22} = +39.2$ (*c* 0.65, $CHCl_3$); IR (neat): 3340, 1738 cm^{-1}; ^{1}H NMR: δ 0.80 (3H, s), 0.86 (3H, s), 0.94 (1H, dd, $J = 2.5$, 12 Hz), 1.09 (3H, s), 1.14–1.51 (6H, m), 1.35 (3H, s), 1.59–1.72 (2H, m), 1.79 (1H, dd, $J = 3$, 12.5 Hz), 1.91–1.96 (1H, m), 2.05 (1H, br s), 3.11 (1H, br s), 9.99 (1H, d, $J = 1.5$ Hz). ^{13}C NMR: δ 17.7 (q), 18.3 (t), 20.0 (q), 21.5 (q), 25.4 (q), 33.3 (s), 33.4 (q), 37.4 (s), 39.8 (t), 41.7 (t), 42.7 (t), 55.2 (d), 71.3 (d), 72.7 (s), 207.7 (d). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 76.21; H, 11.02.

6.3. Wittig condensation of (+)-7

To a solution of (+)-**7** (0.836 g, 3.5 mmol) in benzene (15 ml) was added methyl(triphenylphosphoranylidene) acetate ($Ph_3P{=}CHCOOMe$; 2.92 g, 8.7 mmol) and the whole mixture was refluxed for 24 h with stirring. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt = 10:1) to give colorless crystal (+)-**8** (0.621 g, 60%). Compound (+)-**8**: mp 112 °C (colorless needles from *n*-hexane); $[\alpha]_D^{26} = -28.7$ (*c* 0.97, $CHCl_3$); IR (KBr): 3328, 1720 cm^{-1}; ^{1}H NMR: δ 0.80 (3H, s), 0.86 (3H, s), 0.84–0.88 (1H, m), 0.90 (1H, dd, $J = 4$, 12 Hz), 0.96 (3H, s), 1.12 (1H, dt, $J = 4$, 13.5 Hz), 1.23 (3H, s), 1.26–1.61 (7H, m), 1.65–1.71 (1H, m), 1.90 (1H, dt, $J = 3.5$, 12.5 Hz), 1.94 (1H, d, $J = 11$ Hz), 3.72 (3H, s), 5.91 (1H, d, $J = 15.5$ Hz), 6.98 (1H, dd, $J = 11$, 15.5 Hz). ^{13}C NMR: δ 16.0 (q), 18.4 (t), 20.2 (t), 21.7 (q), 25.1 (q), 33.4 (s), 33.4 (q), 37.8 (s), 40.9 (t), 41.9 (t), 42.8 (t), 51.5 (q), 55.5 (d), 65.7 (d), 72.2 (s), 125.5 (d), 146.0 (d), 166.0 (s). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.52. FAB MS *m*/*z*: 294 (M^+).

6.4. (+)-Ambreinolide 9

A solution of (+)-**8** (5.650 g, 19 mmol) in MeOH (40 ml) was hydrogenated over 20% Pd–C (1 g) at room temperature under an atmospheric pressure of hydrogen. After removal of the catalyst by filtration with the aid of Celite, the filtrate was evaporated to give a residue. It was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 5:1) to give (+)-**9** (4.707 g, 92%). Recrystallization of (+)-**9** from *n*-hexane gave colorless plate: (+)-**9**: mp 127 °C; $[\alpha]_D^{24} = +28.9$ (*c* 0.84, $CHCl_3$); IR (KBr): 1740 cm^{-1}; ^{1}H NMR: δ 0.76–0.96 (m, 2H), 0.79 (3H, s), 0.81 (3H, s), 0.86 (3H, s), 0.98 (1H, dd, $J = 2$, 12 Hz), 1.10–1.49 (5H, m), 1.35 (3H, s), 1.53–1.83 (6H, m), 2.00 (1H, dt, $J = 3$, 12.5 Hz), 2.51 (1H, dt, $J = 8.5$, 18.0 Hz), 2.64 (1H, ddd, $J = 3$, 8.5, 18.5 Hz). ^{13}C NMR: δ 15.2 (q), 15.9 (t), 18.5 (t), 19.7 (t), 21.6 (q), 23.0 (q), 29.0 (t), 33.3 (s), 33.4 (q), 37.3 (s), 39.2 (t), 41.3 (t), 41.8 (t), 53.6 (d), 56.0 (d), 83.8 (s), 171.3 (s). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H,

10.67. Found: C, 77.34; H, 10.82. FAB MS *m*/*z*: 265 (M^++1).

6.5. (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-naphthalene-propanol 10

To a suspension of $LiAlH_4$ (0.162 g, 4.3 mmol) in Et_2O (80 ml) was added a solution of (+)-**9** (0.943 g, 3.8 mmol) in Et_2O (35 ml) at 0 °C and the whole mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and filtered with the aid of Celite. The filtrate was then extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt = 1:1) to give (−)-**10** (0.464 g, 48%). Compound (−)-**10**: mp 133–133.5 °C (colorless needles from AcOEt); $[\alpha]_D^{27} = -7.3$ (*c* 0.82, $CHCl_3$); IR (KBr): 3395 cm^{-1} (OH); NMR: δ 0.77 (3H, s), 0.78 (3H, s), 0.85 (3H, s), 0.87–1.00 (2H, m), 1.07–1.17 (1H, m), 1.14 (3H, s), 1.18–1.31 (2H, m), 1.31–1.46 (4H, m), 1.46–1.63 (5H, m), 1.63–1.74 (1H, m), 1.82 (1H, dt, $J = 3$, 12 Hz), 1.95 (1H, br s; disappeared with D_2O), 3.60 (1H, dt, $J = 5$, 10 Hz), 3.70 (1H, ddd, $J = 4$, 5, 11 Hz). ^{13}C NMR: δ 15.4 (q), 18.5 (q), 20.7 (t, t), 21.6 (q), 24.6 (q), 33.3 (s), 33.5 (q), 34.3 (t), 39.2 (s), 39.8 (t), 42.0 (t), 44.3 (t), 56.1 (d), 59.0 (d), 61.8 (t), 74.6 (s). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 11.92. Found: C, 75.62; H, 12.03.

6.6. (1*R*,2*R*,4a*S*,8a*S*)-(−)-1-(3′-Acetoxypropyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalene 11

A mixture of (−)-**10** (0.415 g, 1.54 mmol), Ac_2O (0.199 g, 1.95 mmol) and 4-dimethylaminopyridine (DMAP; 0.019 g, 0.15 mmol) in pyridine (5 ml) was stirred for 3 h at room temperature. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (15 g, *n*-hexane–AcOEt = 5:1) to afford (−)-**11** (0.456 g, 95%) as a colorless oil. Compound (−)-**11**; $[\alpha]_D^{22} = -1.9$ (*c* 0.87, $CHCl_3$); IR (neat): 3489, 1733, 1248 cm^{-1}; ^1H NMR: δ 0.76 (3H, s), 0.84 (3H, s), 0.86–0.95 (2H, m), 1.04 (1H, t, $J = 4$ Hz), 1.06–1.19 (2H, m), 1.11 (3H, s), 1.21–1.31 (2H, m), 1.31–1.38 (2H, m), 1.38–1.47 (2H, m), 1.50–1.78 (5H, m), 1.84 (1H, dt, $J = 3$, 12 Hz), 2.02 (3H, s), 4.02 (1H, dt, $J = 7$, 14 Hz), 4.04 (1H, dt, $J = 7$, 14 Hz). ^{13}C NMR: δ 15.5 (q), 18.6 (q), 20.7 (t), 21.2 (q), 21.6 (q), 21.7 (t), 24.1 (q), 32.0 (t), 33.3 (s), 33.5 (q), 39.2 (s), 39.8 (t), 42.0 (t), 44.7 (t), 56.1 (d), 61.6 (d), 65.0 (t), 74.1 (s), 170.9 (s). Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.76; H, 11.06.

6.7. (1*R*,2*R*,4a*S*,8a*S*)-(−)-1-(3′-Acetoxypropyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-(methoxymethyloxy)-2,5,5,8a-tetramethylnaphthalene 12

A mixture of (−)-**11** (0.416 g, 1.34 mmol), chloromethylmethyl ether (MOM-Cl; 0.33 g, 4.09 mmol) and *N*,*N*-diisopropylethylamine (0.359 g, 2.78 mmol) in DMF (5 ml) was stirred for 1 h at 80 °C. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was then dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (15 g, *n*-hexane–AcOEt = 10:1) to afford (−)-**12** (0.419 g, 88%) as a colorless oil. Compound (−)-**12**; $[\alpha]_D^{24} = -17.3$ (*c* 0.79, $CHCl_3$); IR (neat): 1739, 1242, 1144 cm^{-1}; ^1H NMR: δ 0.75 (3H, s), 0.79 (3H, s), 0.83 (3H, s), 0.86–0.97 (2H, m), 1.06–1.28 (4H, m), 1.15 (3H, s), 1.30–1.56 (5H, m), 1.56–1.80 (4H, m), 1.91 (1H, dt, $J = 3.5$, 12 Hz), 2.00 (3H, s), 3.31 (3H, s), 3.98 (1H, dt, $J = 7$, 13 Hz), 4.03 (1H, dt, $J = 7$, 13 Hz), 4.60 (1H, d, $J = 7.5$ Hz), 4.72 (1H, d, $J = 7.5$ Hz). ^{13}C NMR: δ 15.8 (q), 18.5 (q), 20.1 (t), 20.7 (q), 21.2 (q), 21.6 (q), 22.1 (t), 31.8 (t), 33.3 (s), 33.4 (q), 39.2 (s), 39.8 (t), 40.0 (t), 40.2 (t), 42.0 (t), 55.0 (q), 56.0 (d), 59.5 (d), 65.2 (t), 80.0 (s), 89.6 (t), 170.9 (s). Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H, 11.04. Found: C, 71.66; H, 10.93.

6.8. (1*R*,2*R*,4a*S*,8a*S*)-(−)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-(methoxymethyloxy)-2,5,5,8a-tetramethyl-1-naphthalene-propanol 13

A mixture of (−)-**12** (0.403 g, 1.14 mmol) and K_2CO_3 (0.189 g, 1.37 mmol) in MeOH (10 ml) was stirred for 2.5 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (15 g, *n*-hexane–AcOEt = 5:1) to afford (−)-**13** (0.349 g, 98%) as a colorless oil. Compound (−)-**13**; $[\alpha]_D^{25} = -29.7$ (*c* 0.96, $CHCl_3$); IR (neat): 3413, 1143 cm^{-1}; ^1H NMR: δ 0.75 (3H, s), 0.81 (3H, s), 0.83 (3H, s), 0.88–1.01 (2H, m), 1.16 (3H, s), 1.11 (1H, dt, $J = 4$, 11 Hz), 1.22 (1H, dt, $J = 3$, 13 Hz), 1.30–1.43 (4H, m), 1.45–1.74 (7H, m), 1.96 (1H, dt, $J = 3$, 12 Hz), 3.04 (1H, br s; disappeared with D_2O), 3.33 (3H, s), 3.57 (1H, dt, $J = 5$, 10 Hz with D_2O), 3.67 (1H, ddd, $J = 4$, 8, 12 Hz with D_2O), 4.67 (1H, d, $J = 7$ Hz), 4.71 (1H, d, $J = 7$ Hz). ^{13}C NMR: δ 15.7 (q), 18.4 (t), 20.1 (t), 20.2 (q), 21.1 (t), 21.6 (q), 33.2 (s), 33.4 (q), 34.2 (t), 39.3 (s), 40.0 (t), 40.1 (t), 42.0 (t), 55.3 (q), 55.9 (d), 57.9 (d), 62.1 (t), 81.0 (s), 89.7 (t). Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.99; H, 11.67.

6.9. (1*R*,2*R*,4a*S*,8a*S*)-(−)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-2-(methoxymethyloxy)-2,5,5,8a-tetramethyl-1-naphthalene-propanal 14

A mixture of (−)-**13** (0.332 g, 1.06 mmol), Florisil (1.17 g) and pyridinium dichromate (PDC; 1.17 g, 31 mmol) in CH_2Cl_2 (10 ml) was stirred for 3.5 h at 40 °C. The reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a residue, which was chromatographed on silica gel (15 g, *n*-hexane–AcOEt = 10:1) to afford (−)-**14** (0.252 g, 77%) as a colorless oil. Compound (−)-**14**; $[\alpha]_D^{26} = -5.2$ (*c* 0.99, $CHCl_3$); IR (neat): 1724, 1143 cm^{-1}; ^1H NMR: δ 0.75 (3H, s), 0.80 (3H, s), 0.82 (3H, s), 0.85–0.94 (2H, m), 1.06–1.25 (3H, m), 1.17 (3H, s), 1.30–1.43 (2H, m), 1.43–1.66 (5H, m), 1.68–1.82 (1H, m), 1.93 (1H, dt, $J = 3$, 12 Hz), 2.44 (1H, dddd, $J = 2$, 8, 9, 17 Hz), 2.56 (1H, dddd, $J = 2$, 7, 9, 17 Hz), 3.28 (3H, d, $J = 1$ Hz), 4.61 (1H, dd, $J = 1$, 7 Hz), 4.71 (1H, dd,

$J = 1$, 7 Hz), 9.69 (1H, d, $J = 2$ Hz). ^{13}C NMR: δ 15.7 (q), 18.1 (t), 18.5 (t), 20.0 (t), 20.5 (q), 21.6 (q), 33.2 (s), 33.4 (q), 39.2 (s), 39.9 (t), 40.2 (t), 41.9 (t), 47.1 (t), 55.1 (q), 55.9 (d), 59.3 (d), 80.2 (s), 89.6 (t), 203.3 (d). Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.87; H, 11.29.

6.10. (1*S*,6*S*)-(−)-2,2-Dimethyl-1-methoxycarbonyl-6-methoxymethyloxycyclohexane 15

To a solution of (+)-**4** (5.75 g, 30.9 mmol) in DMF (50 ml) was added chloromethylmethyl ether (MOM-Cl; 4.97 g, 61.7 mmol), *N*,*N*-diisopropylethylamine (4.00 g, 30.9 mmol) and Et_3N (3.12 g, 30.9 mmol) and the whole mixture was stirred for 2.5 h at 80 °C. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (70 g, *n*-hexane–AcOEt = 50:1) to afford (−)-**15** (6.817 g, 96%) as a colorless oil. Compound (−)-**15**; $[\alpha]_D^{26} = -0.9$ (*c* 1.15, $CHCl_3$); IR (neat): 1736, 1141 cm^{-1}; ^{1}H NMR: δ 0.92 (3H, s), 0.94 (3H, s), 1.07–1.24 (2H, m), 1.34 (1H, ddt, $J = 1$, 3.5, 13.5 Hz), 1.45 (1H, qt, $J = 3.5$, 13.5 Hz), 1.53–1.61 (1H, m), 2.10–2.17 (1H, m), 2.18 (1H, d, $J = 12$ Hz), 3.29 (3H, s), 3.65 (3H, s), 3.84 (1H, dt, $J = 6$, 12 Hz), 4.58 (1H, d, $J = 9$ Hz), 4.61 (1H, d, $J = 9$ Hz). ^{13}C NMR: δ 20.2 (t), 21.6 (q), 31.1 (q), 32.2 (t), 34.8 (s), 40.3 (t), 51.0 (q), 55.4 (q), 59.6 (d), 76.7 (d), 95.6 (t), 173.3 (s). Anal. Calcd for $C_{12}H_{22}O_3$: C, 62.53; H, 9.63. Found: C, 62.29; H, 9.71.

6.11. (1*R*,6*S*)-(+)-2,2-Dimethyl-1-hydroxymethyl-6-methoxymethyloxycyclohexane 16

To a suspension of $LiAlH_4$ (2.27 g, 59.8 mmol) in Et_2O (70 ml) was added a solution of (1*S*,6*S*)-**15** (6.816 g, 29.6 mmol) in Et_2O (30 ml) at 0 °C and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with 2 M aqueous NaOH and filtered with the aid of Celite. The filtrate was extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a residue, which was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 5:1) to give (+)-**16** (5.805 g, 97%). Compound (+)-**16**: $[\alpha]_D^{24} = +100.8$ (*c* 0.35, $CHCl_3$); IR (neat): 3500, 1147 cm^{-1}; ^{1}H NMR: δ 0.76 (3H, s), 1.02 (3H, s), 1.13–1.45 (5H, m), 1.57 (1H, dquinted, $J = 3.5$, 14 Hz), 2.08–2.14 (1H, m), 3.22 (1H, dd, $J = 2$, 11 Hz; disappeared with D_2O), 3.39 (3H, s), 3.61 (1H, ddd, $J = 2$, 7.5, 11 Hz; disappeared with D_2O), 3.69 (1H, dt, $J = 4$, 11 Hz), 3.80 (1H, dt, $J = 2$, 11 Hz; 1H, dd, $J = 2$, 11 Hz with D_2O), 4.59 (1H, d, $J = 7$ Hz), 4.80 (1H, d, $J = 7$ Hz). ^{13}C NMR: δ 20.5 (t), 21.0 (q), 30.8 (q), 32.2 (t), 34.4 (s), 41.1 (t), 54.1 (d), 55.9 (q), 63.6 (t), 79.3 (d), 94.5 (t). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.37; H, 10.90.

6.12. (1*S*,6*S*)-(+)-2,2-Dimethyl-1-iodomethyl-6-methoxymethyloxycyclohexane 17

To a solution of (1*S*,6*S*)-**16** (5.742 g, 28.4 mmol) in THF (50 ml) was added Ph_3P (8.95 g, 34.1 mmol), imidazole (3.86 g, 56.8 mmol) and I_2 (8.63 g, 34.1 mmol) at 0 °C and the whole mixture was stirred for 7 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 50:1) to give iodide **17** (8.78 g, >99%) as a colorless oil. Iodide **17**: $[\alpha]_D^{24} = +10.9$ (*c* 0.84, $CHCl_3$); IR (neat): 1145 cm^{-1}; NMR: δ 0.86 (3H, s), 1.03 (3H, s), 1.15 (1H, dt, $J = 4$, 13 Hz), 1.21–1.32 (1H, m), 1.37 (1H, tq, $J = 3.5$, 13 Hz), 1.46–1.56 (2H, m), 2.05–2.13 (1H, m), 3.19 (1H, dd, $J = 4$, 10.5 Hz), 3.33–3.41 (2H, m), 3.38 (3H, s), 4.69 (1H, d, $J = 7$ Hz), 4.71 (1H, d, $J = 7$ Hz). ^{13}C NMR: δ 2.9 (t), 20.0 (t), 21.0 (q), 30.7 (q), 33.1 (t), 36.2 (s), 41.6 (t), 53.7 (d), 55.9 (q), 78.5 (d), 96.1 (t). Anal. Calcd for $C_{11}H_{21}IO_2$: C, 42.32; H, 6.78. Found: C, 42.44; H, 6.78.

6.13. (1*S*,6*S*)-2,2-Dimethyl-1-(2′-methoxycarbonyl-3′-oxobutyl)-6-methoxymethyloxy-cyclohexane 18

To a solution of methyl acetoacetate (3.90 g, 34 ml) and NaOMe (prepared from Na 0.2 g) in MeOH (10 ml) was added a solution of iodide **17** (2.004 g, 6.4 mmol) in MeOH (5 ml) and the whole mixture was stirred for 1 h at 60 °C and 12 h at 90 °C. The reaction mixture was evaporated and diluted with brine, and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (30 g, *n*-hexane–AcOEt = 10:1) to give a 1:1 diastereomeric mixture of β-keto ester congener **18** (1.486 g, 77%) as a colorless oil. β-Keto ester congener **18**; IR (neat): 1744, 1716 cm^{-1}; ^{1}H NMR: δ 0.77 (3H, s), 0.88 (1.5H, s), 0.91 (1.5H, s), 0.92–1.18 (2H, m), 1.26–1.44 (2H, m), 1.46–1.68 (3H, m), 1.97–2.10 (2H, m), 2.18 (1.5H, s), 2.23 (1.5H, s), 3.29 (1.5H, s), 3.32 (1.5H, s), 3.37 (1H, dt, $J = 4$, 10 Hz), 3.67 (1.5H, s), 3.71 (1.5H, s), 3.97 (0.5H, dd, $J = 3.5$, 10.5 Hz), 4.06 (0.5H, dd, $J = 4$, 10.5 Hz), 4.54 (0.5H, d, $J = 7$ Hz), 4.55 (0.5H, d, $J = 7$ Hz), 4.67 (0.5H, d, $J = 7$ Hz), 4.69 (0.5H, d, $J = 7$ Hz). Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.98; H, 9.39. Found: C, 63.90; H, 9.61.

6.14. (1*S*,6*S*)-(+)-2,2-Dimethyl-1-(3′-oxobutyl)-6-methoxymethyloxycyclohexane 19

A mixture of the above diastereomeric mixture **18** (4.811 g, 16 mmol) and 6 M aqueous NaOH (15 ml) in MeOH (40 ml) was stirred for 7.5 h at 100 °C. The reaction mixture was evaporated under reduced pressure at room temperature to give a residue which was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (80 g, *n*-hexane–AcOEt = 10:1) to give methyl ketone **19** (3.694 g, 95%) as a colorless oil. Compound **19**; $[\alpha]_D^{26} = +34.0$ (*c* 1.02, $CHCl_3$); IR (neat): 1715, 1146 cm^{-1}; ^{1}H NMR: δ 0.75 (3H, s), 0.90 (3H, s), 0.93 (1H, ddd, $J = 2$, 7, 10.5 Hz), 1.04–1.17 (2H, m), 1.25–1.31 (1H, m), 1.33–1.45 (2H, m), 1.46–1.54 (1H, m), 1.64–1.74 (1H, m), 2.00–2.06 (1H, m), 2.07 (3H, s), 2.46 (1H, ddd, $J = 6$, 11, 17 Hz), 2.75 (1H, ddd, $J = 5$, 11, 17 Hz), 3.30 (3H, s), 3.29–3.35 (1H, m), 4.53 (1H, d, $J = 7$ Hz), 4.68 (1H, d, $J = 7$ Hz). ^{13}C NMR: δ 20.3 (q), 20.5 (t), 23.1 (t), 30.0 (q), 30.6 (q), 33.1 (t), 35.5 (s), 41.1 (t), 46.1 (t), 51.6 (d), 55.6 (q), 80.0 (d), 95.3

(t), 209.2 (s). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.13; H, 10.96.

6.15. (1*S*,6*S*)-2,2-Dimethyl-1-(3′-hydroxybutyl)-6-methoxymethyloxycyclohexane 20

To a suspension of $NaBH_4$ (1.769 g, 46.1 mmol) in MeOH (30 ml) was added a solution of **19** (3.655 g, 15.1 mmol) in MeOH (15 ml) at −78 °C and the whole mixture was stirred for 2.5 h at the same temperature. Acetone (10 ml) was added to the above mixture and the whole mixture was stirred for 10 min. The reaction mixture was evaporated to give a residue which was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt = 5:1) to give a 3:2 diastereomeric mixture of **20** (3.686 g, >99%) as a colorless oil. Compound **20**: IR (neat): 3421, 1145 cm^{-1}; NMR: δ 0.73 (1.8H, s), 0.75 (1.2H, s), 0.87 (1.2H, s), 0.89 (1.8H, s), 0.99–1.10 (2H, m), 1.11 (1.8H, d, $J = 6$ Hz), 1.12 (1.2H, d, $J = 6$ Hz), 1.14–1.22 (1H, m), 1.23–1.66 (7H, m), 2.00–2.10 (1H, m), 2.56 (1H, br s; disappeared with D_2O), 3.25–3.33 (1H, m), 3.34 (1.8H, s), 3.35 (1.2H, s), 3.67–3.83 (1H, m), 4.56 (0.4H, d, $J = 7$ Hz), 4.58 (0.6H, d, $J = 7$ Hz), 4.71 (0.6H, d, $J = 7$ Hz), 4.72 (0.4H, d, $J = 7$ Hz). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.27; H, 11.49.

6.16. (1*S*,6*S*)-(+)-2,2-Dimethyl-1-[3′-(1″-phenyl-1″*H*-tetrazole-5″-sulfanyl)butyl]-6-methoxymethyloxycyclohexane 21a

To a solution of (1*S*,6*S*)-**20** (3.548 g, 14.5 mmol) in THF (30 ml) were added Ph_3P (7.62 g, 29.0 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (5.18 g, 29.0 mmol) and 40% diethyl azodicarboxylate in toluene solution (11 ml, 21.8 mmol) at 0 °C and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 20:1) to give a 3:7 diastereomeric mixture of **21a** (4.613 g, 78%) as a colorless oil. Compound **21a**: IR (neat): 1499, 762, 694 cm^{-1}; NMR: δ 0.74 (3H, s), 0.87 (0.9H, s), 0.89 (2.1H, s), 0.94–1.00 (1H, m), 1.10–1.60 (7H, m), 1.50 (3H, d, $J = 6.5$ Hz), 1.64–1.76 (1H, m), 1.98–2.10 (2H, m), 3.30–3.38 (1H, m), 3.35 (3H, s), 3.36 (3H, s), 3.98–4.07 (1H, m), 4.49 (0.7H, d, $J = 7$ Hz), 4.61 (0.3H, d, $J = 7$ Hz), 4.72 (0.7H, d, $J = 7$ Hz), 4.76 (0.3H, d, $J = 7$ Hz), 7.47–7.57 (3H, m), 7.93 (2H, d, $J = 6.5$ Hz). Anal. Calcd for $C_{21}H_{32}N_4O_2S$: C, 62.34; H, 7.97; N, 13.85. Found: C, 62.15; H, 8.05; N,14.15. FAB MS *m*/*z*: 405 (M^++1).

6.17. (1*S*,6*S*)-2,2-Dimethyl-6-hydroxy-1-[3′-(1″-phenyl-1″*H*-tetrazole-5″-sulfanyl)butyl]-cyclohexane 22a

A solution of (1*S*,2*S*)-**21a** (4.574 g, 11.3 mmol) and concd HCl (7 ml) in MeOH (30 ml) was stirred for 90 min at 60 °C. The reaction mixture was evaporated under reduced pressure to give a residue, which was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt = 2:1) to give a 3:7 diastereomeric mixture of alcohol **22a** (4.065 g, >99%) as a colorless oil. Alcohol: IR (neat): 3428, 1495, 763, 690 cm^{-1}; ^1H NMR: δ 0.74 (3H, s), 0.83–0.93 (1H, m), 0.87 (0.9H, s), 0.89 (2.1H, s), 1.11–1.23 (2H, m), 1.27–1.33 (1H, m), 1.37–1.65 (5H, m), 1.48 (2.1H, d, $J = 7$ Hz), 1.49 (0.9H, d, $J = 7$ Hz), 1.84–2.00 (3H, m), 3.38–3.48 (1H, m), 3.95–4.05 (1H, m), 7.48–7.57 (5H, m). Anal. Calcd for $C_{19}H_{28}N_4OS$: C, 63.30; H, 7.83; N, 15.54. Found: C, 63.80; H, 7.92; N,15.43. FAB MS *m*/*z*: 361 (M^++1).

6.18. (*S*)-2,2-Dimethyl-1-[3′-(1″-phenyl-1″*H*-tetrazole-5″-sulfanyl)butyl]-6-oxocyclohexane 23a

A mixture of the above alcohol (4.062 g, 11.2 mmol), Florisil (3.8 g) and pyridinium chlorochromate (PCC; 3.69 g, 16.5 mmol) in CH_2Cl_2 (60 ml) was stirred for 6 h at room temperature. The reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane–AcOEt = 2:1) to afford a 3:7 diastereomeric mixture of **23a** (3.796 g, 94%) as a colorless oil. Compound **23a**; IR (neat): 1705, 1497, 762, 691 cm^{-1}; NMR: δ 0.70 (3H, s), 0.96 (0.9H, s), 1.01 (2.1H, s), 1.34–1.42 (1H, m), 1.46 (2.1H, d, $J = 7$ Hz), 1.47 (0.9H, d, $J = 7$ Hz), 1.49–1.90 (7H, m), 2.08 (0.3H, dd, $J = 10$, 1 Hz), 2.12 (0.7H, dd, $J = 10.5$, 1.5 Hz), 2.18–2.31 (2H, m), 3.91–4.01 (1H, m), 7.46–7.55 (5H, m). Anal. Calcd for $C_{19}H_{26}N_4OS$: C, 63.65; H, 7.31; N, 15.63. Found: C, 63.82; H, 7.37; N, 15.87. FAB MS *m*/*z*: 359 (M^++1).

6.19. (*S*)-2,2-Dimethyl-6-methylene-1-[3′-(1″-phenyl-1″*H*-tetrazole-5″-sulfanyl)butyl] cyclohexane 24a

To a suspension of methyltriphenylphosphonium bromide (4.39 g, 12 mmol) in toluene (25 ml) was added *t*-BuOK (1.30 g, 12 mmol) and the whole mixture was stirred for 3.5 h at 140 °C. After the suspension settled, the decanted yellow solution ($Ph_3P{=}CH_2$) was poured into **23a** (1.289 g, 3.6 mmol) in toluene (5 ml) and the whole mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was then dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt = 10:1) to give a 3:7 diastereomeric mixture of *exo*-olefine **24a** (1.167 g, 91%) as a colorless oil. Compound **24a**: IR (neat): 1643, 1497, 760, 690 cm^{-1}; ^1H NMR: δ 0.78 (0.9H, s), 0.80 (2.1H, s), 0.87 (0.9H, s), 0.89 (2.1H, s), 1.15–1.21 (1H, m), 1.37–1.70 (8H, m), 1.47 (2.1H, d, $J = 6.5$ Hz), 1.49 (0.9H, d, $J = 6.5$ Hz), 1.95–1.98 (2H, m), 3.97–4.07 (1H, m), 4.49 (0.7H, d, $J = 2$ Hz), 4.51 (0.3H, d, $J = 2$ Hz), 4.71 (0.7H, dd, $J = 1$, 2 Hz), 4.73 (0.3H, dd, $J = 1$, 2 Hz), 7.48–7.56 (5H, m). Anal. Calcd for $C_{20}H_{28}N_4S$: C, 67.38; H, 7.92; N, 15.71. Found: C, 67.98; H, 8.10; N, 15.50. FAB MS *m*/*z*: 357 (M^++1).

6.20. (*S*)-2,2-Dimethyl-6-methylene-1-[3′-(1″-phenyl-1″*H*-tetrazole-5″-sulfonyl)butyl]cyclohexane 25a

To a solution of **24a** (1.141 g, 3.2 mmol) in EtOH (10 ml) were added $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (0.40 g, 0.32 mmol) and

30% H_2O_2 (1.8 ml) at 0 °C and the whole mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane–AcOEt = 10:1) to afford a 3:7 diastereomeric mixture of **25a** (1.120 g, 90%). Recrystallization of **25a** from *n*-hexane provided colorless crystals. Compound **25b**: mp 97–99 °C; IR (neat): 1646, 1499, 1337, 1150, 756, 689 cm^{-1}; ^1H NMR: δ 0.80 (0.9H, s), 0.81 (2.1H, s), 0.89 (0.9H, s), 0.90 (2.1H, s), 1.16–1.23 (1H, m), 1.32–1.70 (8H, m), 1.46 (2.1H, d, $J = 7$ Hz), 1.48 (0.9H, d, $J = 7$ Hz), 1.94–2.00 (2H, m), 3.77–3.88 (1H, m), 4.49 (1H, d, $J = 2$ Hz), 4.72–4.74 (1H, m), 7.53–7.64 (5H, m). Anal. Calcd for $C_{20}H_{28}N_4O_2S$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.99; H, 7.19; N, 14.47. FAB-MS *m*/*z*: 389 (M^++1).

6.21. (1*S*,6*S*)-(+)-2,2-Dimethyl-1-[3′-(benzothiazole-2″-sulfanyl)butyl]-6-methoxymethyloxy-cyclohexane 21b

To a solution of (1*S*,6*S*)-**20** (0.604 g, 2.5 mmol) in THF (10 ml) were added Ph_3P (1.296 g, 5.0 mmol), 2-mercaptobenzothiazole (0.829 g, 5.0 mmol) and diethyl azodicarboxylate (0.74 ml, 3.8 mmol) at 0 °C and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane–AcOEt = 50:1) to give a 2:3 diastereomeric mixture of **21b** (0.869 g, 89%) as a colorless oil. Compound **21b**: IR (neat): 1427, 1145 cm^{-1}; NMR: δ 0.66 (1.2H, s), 0.67 (1.8H, s), 0.81 (1.2H, s), 0.84 (1.8H, s), 0.84–0.92 (1H, m), 0.98–1.12 (2H, m), 1.13–1.38 (3H, m), 1.40 (1.8H, d, $J = 6$ Hz), 1.41 (1.2H, d, $J = 6$ Hz), 1.43–1.57 (2H, m), 1.58–1.69 (1H, m), 1.88–2.03 (2H, m), 3.17–3.26 (1H, m), 3.23 (1.8H, s), 3.27 (1.2H, s), 3.82 (1H, sextet, $J = 6$ Hz), 4.47 (0.6H, d, $J = 7$ Hz), 4.58 (0.4H, d, $J = 7$ Hz), 4.58 (0.6H, d, $J = 7$ Hz), 4.63 (0.4H, d, $J = 7$ Hz), 7.17 (0.6H, t, $J = 7$ Hz), 7.25 (0.4H, t, $J = 7$ Hz), 7.29 (0.6H, t, $J = 7$ Hz), 7.35 (0.4H, t, $J = 7$ Hz), 7.63 (0.6H, d, $J = 7$ Hz), 7.66 (0.4H, d, $J = 7$ Hz), 7.74 (0.6H, d, $J = 7$ Hz), 7.83 (0.4H, d, $J = 7$ Hz). Anal. Calcd for $C_{21}H_{31}NO_2S_2$: C, 64.08; H, 7.94; N, 3.56. Found: C, 63.88; H, 7.97; N,3.59. FAB-MS *m*/*z*: 393 (M^++1).

6.22. (1*S*,6*S*)-2,2-Dimethyl-1-[3′-(benzothiazole-2″-sulfanyl)butyl]-6-hydroxycyclohexane 22b

A solution of (1*S*,6*S*)-**21b** (3.995 g, 10.0 mmol) and concd HCl (3.5 ml) in MeOH (70 ml) was stirred for 90 min at 60 °C. The reaction mixture was evaporated under reduced pressure to give a residue, which was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue which was chromatographed on silica gel (80 g, *n*-hexane–AcOEt = 10:1) to give a 2:3 diastereomeric mixture of alcohol **22b** (3.548 g, >99%) as a colorless oil. Compound **22b**: IR (neat): 3394 cm^{-1}; NMR: δ 0.77 (3H, s), 0.89 (1.2H, s), 0.93 (1.8H, s), 0.86–0.98 (1H, m), 1.11–1.35 (2H, m), 1.38–1.47 (1H, m), 1.48 (1.8H, d, $J = 7$ Hz), 1.50 (1.2H, d, $J = 7$ Hz), 1.51–1.59 (2H, m), 1.59–1.78 (2H, m), 1.84 (1H, br s; disappeared with D_2O), 1.87–2.18 (3H, m), 3.42–3.51 (1H, m), 3.86 (0.4H, sextet, $J = 7$ Hz), 3.94 (0.6H, sextet, $J = 7$ Hz), 7.27 (1H, t, $J = 8$ Hz), 7.39 (1H, t, $J = 8$ Hz), 7.73 (1H, d, $J = 7$ Hz), 7.86 (0.6H, d, $J = 8$ Hz), 7.88 (0.4H, d, $J = 8$ Hz). Anal. Calcd for $C_{19}H_{27}NOS_2$: C, 65.28; H, 7.79; N, 4.01. Found: C, 65.13; H, 7.93; N,3.91. FAB-MS *m*/*z*: 350 (M^++1).

6.23. (*S*)-2,2-Dimethyl-1-[3′-(benzothiazole-2″-sulfanyl)-butyl]-6-oxocyclohexane 23b

A mixture of **22b** (3.653 g, 10.0 mmol), Florisil (3.38 g) and pyridinium chlorochromate (PCC; 3.379 g, 16.0 mmol) in CH_2Cl_2 (50 ml) was stirred for 12 h at room temperature. The reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane–AcOEt = 20:1) to afford a 2:3 diastereomeric mixture of **23b** (3.443 g, 95%) as a colorless oil. Compound **23b**: IR (neat): 1707 cm^{-1}; NMR: δ 0.74 (1.8H, s), 0.75 (1.2H, s), 0.99 (1.2H, s), 1.04 (1.8H, s), 1.49 (1.2H, d, $J = 7$ Hz), 1.50 (1.8H, d, $J = 7$ Hz), 1.46–1.93 (8H, m), 2.08-2.15 (1.2H, m), 2.19-2.37 (1.8H, m), 3.91 (0.67H, sextet, $J = 7$ Hz), 3.97 (0.33H, sextet, $J = 7$ Hz), 7.26 (1H, t, $J = 8$ Hz), 7.38 (1H, t, $J = 8$ Hz), 7.73 (1H, t, $J = 8$ Hz), 7.84 (1H, t, $J = 8$ Hz). Anal. Calcd for $C_{19}H_{25}NOS_2$: C, 65.66; H, 7.25; N, 4.03. Found: C, 65.81; H, 7.24; N, 4.00. FAB MS *m*/*z*: 348 (M^++1).

6.24. (*S*)-2,2-Dimethyl-1-[3′-(benzothiazole-2″-sulfanyl)-butyl]-6-methylenecyclohexane 24b

To a suspension of methyltriphenylphosphonium bromide (10.62 g, 30 mmol) in toluene (100 ml) was added *t*-BuOK (3.374 g, 30 mmol) and the whole mixture was stirred for 12 h at 140 °C. After the suspension settled, the decanted yellow solution ($Ph_3P{=}CH_2$) was poured into **23b** (3.553 g, 10 mmol) in toluene (15 ml) and the whole mixture was stirred for 90 min at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 30:1) to give a 2:3 diastereomeric mixture of *exo*-olefine **24b** (3.532 g, >99%) as a colorless oil. Compound **24b**: IR (neat): 1644 cm^{-1}; ^1H NMR: δ 0.80 (1.2H, s), 0.83 (1.8H, s), 0.89 (1.2H, s), 0.91 (1.8H, s), 1.15–1.28 (1H, m), 1.49 (1.8H, d, $J = 7$ Hz), 1.50 (1.2H, d, $J = 7$ Hz), 1.40–1.70 (8H, m), 1.93–2.09 (2H, m), 3.89–3.90 (1H, m), 4.53 (0.6H, br s), 4.56 (0.4H, br s), 4.73 (0.6H, br s), 4.74 (0.4H, br s), 7.25–7.35 (1H, m), 7.39 (1H, t, $J = 8$ Hz), 7.73 (1H, d, $J = 2$ Hz), 7.85 (1H, d, $J = 8$ Hz). FAB-MS *m*/*z*: 346 (M^++1).

6.25. (*S*)-2,2-Dimethyl-1-[3′-(benzothiazole-2″-sulfonyl)-butyl]-6-methylenecyclohexane 25b

To a solution of **24b** (3.532 g, 10.2 mmol) in EtOH (30 ml) were added $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (1.033 g, 84 mmol) and 30% H_2O_2 (6 ml) at 0 °C and the whole mixture was stirred

for 12 h at room temperature. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (100 g, *n*-hexane–AcOEt = 20:1) to afford a 2:3 diastereomeric mixture of **25b** (3.740 g, 97%) as a colorless oil. Compound **25b**: IR (neat): 1376 cm^{-1}; ^1H NMR: δ 0.67 (1.2H, s), 0.68 (1.8H, s), 0.77 (3H, s), 1.02–1.12 (1H, m), 1.32 (1.8H, d, $J = 7$ Hz), 1.33 (1.2H, d, $J = 7$ Hz), 1.22–1.60 (7H, m), 1.72–2.06 (3H, m), 3.43–3.55 (1H, m), 4.34 (1H, br s), 4.53 (1H, br s), 7.47 (1H, t, $J = 8$ Hz), 7.52 (1H, t, $J = 8$ Hz), 7.90 (1H, d, $J = 8$ Hz), 8.10 (1H, d, $J = 8$ Hz). Anal. Calcd for $C_{20}H_{27}NO_2S_2$: C, 63.92; H, 7.21; N, 3.71. Found: C, 63.90; H, 7.40; N, 3.73. FAB MS *m*/*z*: 378 (M^++1).

6.26. Modified Julia coupling of (−)-14 and 25a

To a solution of **25a** (0.251 g, 0.64 mmol) in THF (1.5 ml) was added lithium bis(trimethylsilyl)amide (1 M solution in THF, 0.7 ml, 0.7 mmol) at −78 °C under an argon atmosphere and the whole mixture was stirred for 20 min at the same temperature. A solution of (−)-**14** (0.220 g, 0.71 mmol) in THF (1.5 ml) was added to the above reaction mixture at 0 °C and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product which was chromatographed on silica gel (12 g, *n*-hexane–AcOEt = 50:1) to give a 1:1 mixture (0.27 g, 88%) of (*E*)-**26** and (*Z*)-**26** as a colorless oil. Compounds (*E*)-**26** and (*Z*)-**26**: IR (neat): 1148 cm^{-1}; ^1H NMR: δ 0.76 (3H, s), 0.78 (1.5H, s), 0.79 (1.5H, s), 0.80 (1.5H, s), 0.81 (1.5H, s), 0.84 (3H, s), 0.85–1.00 (2H, m), 0.89 (1.5H, s), 0.90 (1.5H, s), 1.09–1.27 (6H, m), 1.15 (1.5H, s), 1.17 (1.5H, s), 1.33–1.74 (13H, m), 1.57 (1.5H, s), 1.65 (1.5H, s), 1.76–2.12 (6H, m), 3.32 (3H, s), 4.52 (0.5H, br d, $J = 2$ Hz), 4.54 (0.5H, br d, $J = 2$ Hz), 4.61 (1H, dd, $J = 7$, 8 Hz), 4.73 (0.5H, br s), 4.74 (0.5H, br s), 4.75 (1H, dd, $J = 5$, 8 Hz), 5.12 (1H, d, $J = 7.5$ Hz). Anal. Calcd for $C_{32}H_{56}O_2$: C, 81.29; H, 11.94. Found: C, 80.90; H, 11.95. FAB MS *m*/*z*: 495 (M^++Na).

6.27. (+)-(*E*)-Ambrein 1 and (+)-(*Z*)-ambrein 1

To a solution of the above mixture (0.098 g, 0.21 mmol) 80% aqueous AcOH (3 ml) in THF (1.5 ml) was gradually added 2 M HCl (0.5 ml) at room temperature and the whole mixture was stirred for 12 h at the same temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ 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 a mixture of (*E*)- and (*Z*)-**1**. Compound (*E*)-**1**; R_f value in silica gel thin layer chromatography (60 F_{254}, *n*-hexane–AcOEt = 4:1): 0.85, (*Z*)-**1**; R_f value in silica gel thin layer chromatography (60 F_{254}, *n*-hexane–AcOEt = 4:1): 0.79. This mixture was again chromatographed on silica gel (10 g, benzene–AcOEt = 60:1) to give (+)-(*E*)-**1** (0.038 g, 43%) and (+)-(*Z*)-**1** (0.034 g, 38%) in elution order. Compound (+)-(*E*)-Ambrein **1**; mp 82 °C (*n*-hexane); $[\alpha]_D^{24} = +18.9$ (*c* 0.47, EtOH); IR (neat): 3450 cm^{-1}; NMR: δ 0.76 (6H, s), 0.81 (3H, s), 0.84 (3H, s), 0.86–1.03 (2H, m), 0.89 (3H, s), 1.08–1.13 (1H, m), 1.11 (3H, s), 1.15–1.76 (18H, m), 1.58 (3H, s), 1.85 (1H, dt, $J = 3$, 12 Hz), 1.88–2.08 (5H, m), 4.51 (1H, d, $J = 2.5$ Hz), 4.73 (1H, br s), 5.13 (1H, t, $J = 7$ Hz). ^{13}C NMR: δ 15.6 (q), 16.5 (q), 18.6 (t), 20.7 (t), 21.7 (q), 23.9 (t), 23.9 (q), 25.0 (t), 25.7 (t), 26.4 (q), 28.6 (q), 31.6 (t), 32.6 (t), 33.4 (s), 33.5 (q), 35.0 (s), 36.4 (t), 38.4 (t), 39.2 (s), 39.8 (t), 42.1 (t), 44.6 (t), 53.8 (d), 56.2 (d), 61.5 (d), 74.1 (s), 108.7 (t), 124.5 (d), 135.7 (s), 149.2 (s). Anal. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.99; H, 12.21. (+)-(*Z*)-Ambrein **1**; colorless oil; $[\alpha]_D^{24} = +5.9$ (*c* 1.07, EtOH); NMR: δ 0.75 (6H, s), 0.76 (3H, s), 0.81 (3H, s), 0.85 (3H, s), 0.88–1.00 (2H, m), 0.89 (3H, s), 1.09 (3H, s), 1.10–1.29 (6H, m), 1.31–1.56 (7H, m), 1.58–1.69 (4H, m), 1.66 (3H, s), 1.74–2.10 (7H, m), 4.52 (1H, d, $J = 3$ Hz), 4.75 (1H, br s), 5.14 (1H, t, $J = 8$ Hz). ^{13}C NMR: δ 15.6 (q), 18.7 (t), 20.7 (t), 21.6 (q), 23.6 (q), 23.8 (t), 23.9 (q), 25.2 (t), 26.0 (t), 26.3 (q), 28.6 (q), 30.9 (t), 31.6 (t), 32.7 (t), 33.4 (s), 33.5 (q), 3.50 (s), 36.4 (t), 39.2 (s), 39.2 (t), 42.1 (t), 44.6 (t), 54.3 (d), 56.2 (d), 61.7 (d), 74.0 (s), 108.8 (t), 125.4 (d), 136.0 (s), 149.1 (s). Anal. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.21; H, 12.20.

6.28. Modified Julia coupling of (−)-14 and 25b

To a solution of **25b** (0.100 g, 0.26 mmol) in THF (1.0 ml) was added lithium bis(trimethylsilyl)amide (1 M solution in THF, 0.3 ml, 0.3 mmol) at −78 °C under an argon atmosphere and the whole mixture was stirred for 30 min at the same temperature. A solution of (−)-**14** (0.080 g, 0.26 mmol) in THF (1.0 ml) was added to the above reaction mixture at 0 °C and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude product which was chromatographed on silica gel (13 g, *n*-hexane–AcOEt = 50:1) to give a 1:1 mixture (0.065 g, 52%) of (*E*)-**26** and (*Z*)-**26** as a colorless oil.

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