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Asymmetric Heck Reaction: A Catalytic Asymmetric Synthesis of the Key Intermediate of (–)-Oppositol and (–)-Prepinnaterpene

Yoshihiro Sato,[a] Miwako Mori,[a] and Masakatsu Shibasaki*[b]

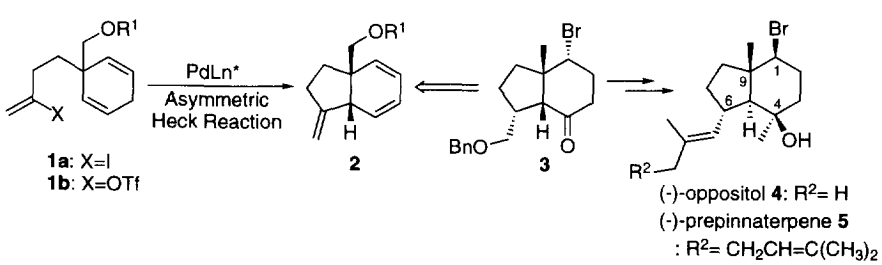
[a] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan
[b] Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: A catalytic asymmetric synthesis of the key intermediate of (–)-oppositol **4** and (–)-prepinnaterpene **5**, brominated terpenes isolated from the marine red algae, has been achieved from *cis*-hydrindane derivative **2** obtained by an asymmetric Heck reaction.

We have recently reported the first example of an asymmetric Heck reaction, and succeeded in demonstrating the efficiency of this reaction in the preparation of various optically active compounds and biologically active substances.[1,2] This asymmetric Heck reaction was also useful for the catalytic asymmetric synthesis of *cis*-hydrindane derivatives, giving **2** in up to 86% ee in the reaction of **1a** in the presence of Ag_3PO_4 or **1b** without silver salts.[1e] Here we would like to report a catalytic asymmetric synthesis of the key intermediate of (–)-oppositol **4** and (–)-prepinnaterpene **5** from the optically active *cis*-hydrindane derivative **2** obtained by the asymmetric Heck reaction.

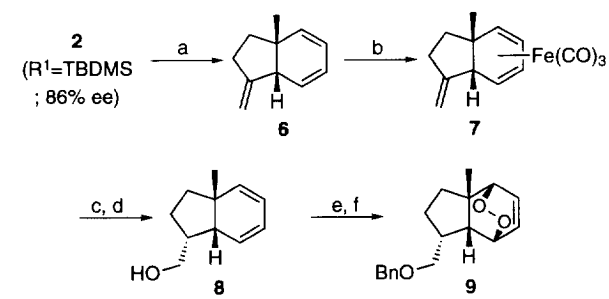
(–)-Oppositol **4** and (–)-prepinnaterpene **5** are brominated terpenes isolated from *Laurencia subopposita* Setchell and *Laurencia pinnata* Yamada, respectively.[3a,b] These compounds possess a unique bicyclic skeleton with five stereogenic centers and a bromine atom at the C1 position. The syntheses of (±)-**4**[4a,b] and (±)-**5**[4b] have already been reported, in which Masamune *et al.* have achieved total synthesis of (±)-**4** and (±)-**5** *via* 1α-bromide **3**.[4b] In order to demonstrate the availability of **2** as a chiral building block in the synthesis of a natural product having a 6-5 ring system, we sought its application in the synthesis of (–)-**4** and (–)-**5** by conversion of **2** to the key intermediate **3**. (Scheme 1)

Scheme 1



Deprotection of TBDMS group in (+)-**2** {R=TBDMS, $[\alpha]_D^{20}$ +295.3 (*c* 1.45, $CHCl_3$) (86% ee)} is followed by treatment with *p*-TsCl and pyridine, then by reduction with lithium triethylborohydride to afford **6** in 90% yield (3 steps). Several attempts to convert **6** directly into **8** by hydroboration gave only complex mixtures, which indicated that the conjugated diene moiety was more reactive to the borane reagent than the *exo*-olefin of the cyclopentane ring in **6**. Thus, **6** was treated with $Fe_2(CO)_9$ to protect conjugated diene moiety[5] producing diene-$Fe(CO)_3$ complex **7** in 73% yield as a single isomer. Treatment of **7** with BH_3·THF successfully gave the alcohol stereoselectively in 77% yield and subsequently deprotection of $Fe(CO)_3$ complex by exposure to $FeCl_3$-H_2SO_4[6] provided **8** in 74% yield.[7] After protection of α-hydroxymethyl group in **8**, photoperoxidation of the resulting benzyl ether (O_2, halogen lamp irradiation, 3 mol % rose bengal, ^{i}PrOH) afforded endoperoxide **9** in 83% yield as the sole product. (Scheme 2)

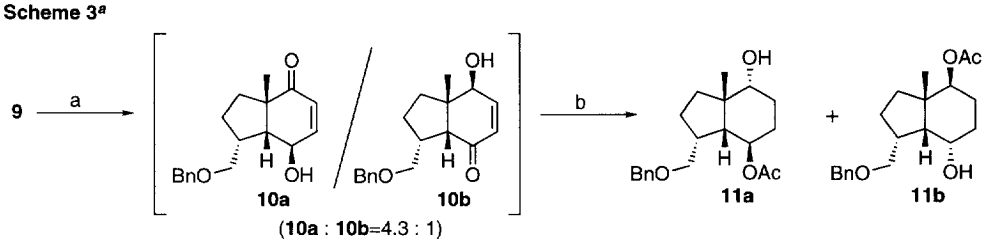
Scheme 2[a]



[a] Reaction Conditions: (a) TBAF, THF, 23 °C; TsCl, pyridine, CH_2Cl_2, DMAP, 23 °C; $LiEt_3BH$, THF, 0~23 °C (90%, 3 steps); (b) $Fe_2(CO)_9$, THF, 40 °C (73%); (c) BH_3·THF, THF, 0 °C; H_2O_2/NaOH (77%); (d) $FeCl_3$, H_2SO_4, EtOH, 0~23 °C (74%); (e) BnBr, NaH, DMF (79%); (f) O_2, hν, ^{i}PrOH (83%).

When **9** was treated with an excess of Et_3N in CH_2Cl_2 at room temperature, cleavage of the endoperoxide occurred, producing predominantly the desired hydroxyenone **10a**.[8] After acetylation of the mixture of **10a** and **10b**, followed by reduction with sodium borohydride, the resulting alcohols were separated into **11a** (63%, 2 steps) and **11b** (16%, 2 steps). (Scheme 3)

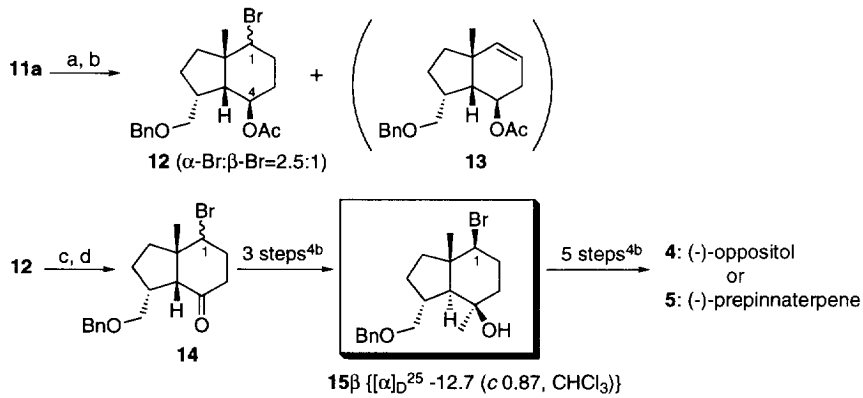
Scheme 3[a]



[a] Reaction Conditions: (a) Et_3N, CH_2Cl_2, 23 °C (**10a**+**10b**, 85%); (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 23 °C; $NaBH_4$, EtOH, 23 °C (**11a**: 63%, **11b**: 16%, 2 steps, respectively).

Although substitution of the hydroxy group in **11a** for a bromine atom under the various conditions was examined, brominated hydrindane **12** was not obtained. However, after mesylation of **11a**, treatment with tetrabutylammonium bromide in toluene at 70 °C gave **12** in a ratio of 2.5:1 (α-Br:β-Br, 55%) with eliminated product **13** (37%). Deprotection of acetyl group in **12** followed by oxidation with PCC afforded **14** in 84% yield (2 steps), which is Masamune's key intermediate of (±)-oppositol and (±)-prepinnaterpene.[10] Transformation of **14** into **15β** was achieved in three steps acoording to the literature,[4b] which involved synthetically significant conversion of *cis*-hydrindane to *trans*-one: (1) epimerization at C5 position by acidic conditions, affording the *trans*-hydrindanone; (2) stereoselective methylation by MeLi; (3) conversion of a mixture of α- and β-bromide to equatorially oriented β-one by treatment with tetrabutylammonium bromide, giving **15β**.[11] (Scheme 4)

Scheme 4[a]



[a] Reaction Conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C (95%); (b) Bu_4NBr,toluene, 70°C (**12**: 55%); (c) $LiAlH_4$, Et_2O, -30 °C; (d) PCC, MS 4A, CH_2Cl_2, 23 °C (84%, 2 steps).

In conclusion, we have achieved a formal total synthesis of (–)-oppositol **4** and (–)-prepinnaterpene **5** by conversion of (+)-**2** {R=TBDMS, $[\alpha]_D^{20}$ +295.3 (*c* 1.45, CHCl3)(86% ee)} to a key intermediate (–)-**15β** {$[\alpha]_D^{25}$ –12.7 (*c* 0.87, CHCl3)}. These results enable the transformation of *cis*-hydrindane derivatives, obtained by the asymmetric Heck reaction, into *trans*-ones, as well as the first synthetic route to optically active **4** and **5**.

Acknowledgements

We thank Dr. A. Fukuzawa for his generous donations of spectra of compound **3** (1α-bromide) and its epimer with respect to C5 position (*trans*-hidrindanone). Partial financial support for this work was provided by the Akiyama Foundation, which is gratefully acknowledged.

EXPERIMENTAL SECTION

General Methods All manipulations were performed under an argon atmosphere unless otherwise mentioned. Solvents were distilled under an argon atmosphere from sodium-benzophenone (THF, Et_2O, toluene) or CaH_2 (CH_2Cl_2, DMF). All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70~230 mesh or 230~400 mesh) using the indicated solvent. Infrared (IR) spectra were measuered on a Perkin Elmer FT-IR 1605. ^{1}H-NMR spectra were recorded with a JEOL JNM-EX 270 (270 MHz) or Bruker ARX-500 (500 MHz). Mass spectra (MS) were obtained with a JEOL JMS-DX 303 (EI-MS) or JMS-HX 110 (FAB-MS). Optical rotation was measured on a JASCO DIP-370.

Triene 6. To a solution of (+)-**2** (3.42 g, 12.4 mmol) in THF (40 ml) was added tetrabutylammonium fluoride (1 *M* in THF, 18.5 ml, 18.5 mmol) at 0 °C. After stirring at 23 °C for 3 h, the reaction mixture was quenched by the addition of brine, followed by extraction of the mixture with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 3:1) to give the alcohol (2.01 g, 100%) as a colorless oil: IR (neat) 3350, 1650, 1070, 1030, 1005, 875 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.40~1.85 (m, 3 H), 2.15~2.50 (m, 2 H), 3.10 (bs, 1 H), 3.39 (dd, *J*=10.6, 7.0 Hz, 1 H), 3.49 (dd, *J*=10.6, 4.4 Hz, 1 H), 4.88~4.97 (m, 2 H), 5.49 (bd, *J*=9.5 Hz, 1 H), 5.82~5.87 (m, 2 H), 5.96~6.04 (m, 1 H); MS m/z 162 (M^+), 144 (M^+-H_2O), 131 (bp), 116, 91; HR-MS (M^+) calcd for $C_{11}H_{14}O$ 162.1045, found 162.1037; $[\alpha]_D^{19}$ +422.4 (*c* 1.10, $CHCl_3$) (86% ee).

To a solution of the alcohol (1.42 g, 8.7 mmol) in CH_2Cl_2 (25 ml) were added pyridine (6.3 ml, 78 mmol), *p*-toluenesulfonyl chloride (5.00 g, 26.2 mmol) and 4-dimethylaminopyridine (573 mg, 4.7 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 48 h, and quenched by the addition of brine at 0 °C followed by extraction of the mixture with AcOEt. The organic layer was washed with 10% HCl and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 4:1) to afford the tosylate (2.61 g, 94%) as a colorless oil: IR (neat) 2946, 1655, 1599, 1360, 1177, 1098, 949 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.50~2.10 (m, 2 H), 2.10~2.50 (m, 2 H), 2.45 (s, 3 H), 2.93 (bs,1 H), 3.74 (d, *J*=9.5 Hz, 1 H), 3.85 (d, *J*=9.5 Hz, 1 H), 4.75~4.95 (m, 2 H), 5.25~5.45 (m, 1 H), 5.60~6.00 (m, 3 H), 7.34 (d, *J*=8.2 Hz, 2 H), 7.77 (d, *J*=8.2 Hz, 2 H); MS m/z 316 (M^+), 172, 155, 144, 131 (bp), 115, 91; HR-MS (M^+) calcd for $C_{18}H_{20}O_3S$ 316.1133, found 316.1109; $[\alpha]_D^{20}$ +262.9 (*c* 0.72, $CHCl_3$) (86% ee).

To a stirred solution of the tosylate (149 mg, 0.47 mmol) in THF (4.7 ml) was added dropwise lithium triethylborohydride (1 *M* in THF, 7.1 ml, 7.1 mmol) at 0 °C, and the reaction mixture was stirred at 23 °C for 24 h. To the reaction mixture was added 3N NaOH aq (2.8 ml, 8.4 mmol) and 35% H_2O_2 (0.7 ml, 7.2 mmol) at 0 °C. The resultant mixture was stirred at 23 °C for 1 h, and extracted with Et_2O. The organic layer was washed with 10% $Na_2S_2O_3$ aq and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane) to give **6** (66 mg, 96%) as a volatile colorless oil: IR (neat) 2951, 1653, 1456, 1372 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.55~1.70 (m, 1 H), 1.71~1.83 (m, 1 H), 2.15~2.45 (m, 2 H), 2.74~2.82 (m, 1 H), 4.85~4.96 (m, 2 H), 5.47~5.56 (m, 1 H), 5.73~5.86 (m, 3 H); MS m/z 146 (M^+), 131 (bp), 117, 105, 91; HR-MS (M^+) calcd for $C_{11}H_{14}$ 146.1095, found 146.1109; $[\alpha]_D^{20}$ +278.8 (*c* 0.53, $CHCl_3$) (86% ee).

Diene–Fe(CO)3 complex 7. To a stirred solution of **6** (1.40 g, 9.6 mmol) in THF (48 ml) was added $Fe_2(CO)_9$ (17.50 g, 48.1 mmol) in one portion at 23 °C, and the reaction mixture was stirred for 7 h while maintaining the temperature between 35 and 40 °C in an efficient fume hood. After cooling to room

temperature, the reaction mixture was diluted with Et_2O and filtered through a column of alumina (aluminum oxide, standardized, activity II-III). The filtrate was concentrated in vacuo in an efficient fume hood. The residue was purified by silica gel chromatography (hexane) to give **7** (1.99 g, 73%) as a yellow oil: IR (neat) 2042, 1964, 1654, 1452 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.17 (s, 3 H), 1.36~1.70 (m, 2 H), 2.00~2.20 (m, 1 H), 2.25~2.40 (m, 1 H), 2.41~2.48 (m, 1 H), 3.03 (dd, *J*=6.5, 1.2 Hz, 1 H), 3.09~3.17 (m, 1 H), 4.68~4.72 (m, 2 H), 5.28~5.43 (m, 2 H); MS m/z 286 (M^+), 258, 230, 202, 184 (bp), 148; HR-MS (M^+) calcd for $C_{14}H_{14}FeO_3$ 286.0293, found 286.0290; $[\alpha]_D^{20}$ +104.5 (*c* 0.40, $CHCl_3$) (86% ee).

Alcohol 8. To a solution of **7** (1.99 g, 7.0 mmol) in THF (35 ml) was added BH_3·THF (1.1 *M* in THF, 18.0 ml, 19.8 mmol) at -20 °C, and the reaction mixture was stirred at the same temperature for 6 h. To the reaction mixture were added dropwise 6N NaOH aq (27 ml, 162 mmol) and 35% H_2O_2 (23 ml, 203 mmol) at -20 °C. The resultant mixture was stirred at 0 °C for 30 min, then at 23 °C for 1 h, and extracted with Et_2O. The organic layer was washed with 10% $Na_2S_2O_3$ aq and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 6:1) to give the alcohol (1.64 g, 77%) as a yellow oil: IR (neat) 3334, 2042, 1964, 1448, 1016 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.15~1.60 (m, 4 H), 1.90~2.10 (m, 1 H), 2.20~2.30 (m, 1 H), 3.00~3.10 (m, 2 H), 3.55~3.80 (m, 2 H), 5.23 (ddd, *J*=6.7, 4.1, 1.8 Hz, 1 H), 5.48 (ddd, *J*=6.8, 4.1, 1.6 Hz, 1 H); MS m/z 304 (M^+), 276, 248, 220, 205 (bp), 184, 165, 148, 128, 91; HR-MS(M^+) calcd for $C_{14}H_{16}FeO_4$ 304.0398, found 304.0390; $[\alpha]_D^{20}$ +61.5 (*c* 0.49, $CHCl_3$) (86% ee).

To a solution of the alcohol (1.64 g, 5.4 mmol) in EtOH (160 ml) were added conc. H_2SO_4 (20 ml) and a solution of anhydrous $FeCl_3$ (13.1 g, 80.9 mmol) in EtOH (40 ml) at 0 °C. The reaction mixture was stirred at 23 °C for 6 h, poured into ice-cold water, and extracted with Et_2O. The organic layer was washed with sat. aq $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 7:1) to afford **8** (655 mg, 74%) as a colorless oil: IR (neat) 3350, 1650, 1580, 1450, 1100, 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.20~1.32 (m, 1 H), 1.44 (bs, 1 H), 1.54~1.62 (m, 1 H), 1.66~1.78 (m, 2 H), 2.40~2.50 (m, 2 H), 3.48 (dd, *J*=11.1, 4.9 Hz, 1 H), 3.59 (dd, *J*=11.1, 6.2 Hz, 1 H), 5.47 (d, *J*=9.6 Hz, 1 H), 5.75 (dd, *J*=9.6, 5.2 Hz, 1 H), 5.78 (dd, *J*=9.6, 4.3 Hz, 1 H), 5.93 (dd, *J*=9.6, 5.2 Hz, 1 H); MS m/z 164 (M^+), 149, 146, 133, 131, 118, 105, 91 (bp); HR-MS (M^+) calcd for $C_{11}H_{16}O$ 164.1201, found 164.1177; $[\alpha]_D^{20}$ +258.1 (*c* 0.56, $CHCl_3$) (86% ee).

Endoperoxide 9. A solution of **8** (42 mg, 0.26 mmol) in DMF (3.5 ml) was added to a suspension of NaH (51 mg, 60% wt dispersion in mineral oil, 1.3 mmol) in DMF (0.5 ml) at 0 °C, and the mixture was stirred at 0 °C for 1 h. To this mixture was added benzyl bromide (60 μl, 0.51 mmol) at 0 °C, and the mixture was stirred at 23 °C for 7 h. The reaction mixture was quenched by the addition of sat. aq NH_4Cl at 0 °C, followed by extraction of the mixture with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane-Et_2O, 20:1) to give the bezyl ether (30 mg, 79%) as a colorless oil: IR (neat) 1600, 1580, 1450, 1360, 1200, 1100, 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.15~1.25 (m, 1 H), 1.54 (ddd, *J*=12.1, 9.3, 7.1 Hz, 1 H), 1.67 (ddd, *J*=12.1, 7.2, 4.4 Hz, 1 H), 1.72~1.80 (m, 1 H), 2.50 (ddd, *J*=9.4, 5.1, 1.2 Hz, 1 H), 2.53~2.60 (m, 1 H), 3.32 (dd, *J*=9.0, 6.8 Hz, 1 H), 3.41 (dd, *J*=9.0, 7.6 Hz, 1 H), 4.43 (d, *J*=11.9 Hz, 1 H), 4.47 (d, *J*=11.9 Hz, 1 H), 5.40 (d, *J*=9.6 Hz, 1 H), 5.67 (dd, *J*=9.0, 5.1 Hz, 1 H), 5.69 (dd, *J*=9.0, 5.3 Hz, 1 H), 5.84 (dd, *J*=9.6, 5.3 Hz, 1 H), 7.25~7.38 (m, 5 H); MS m/z 254 (M^+), 163, 145, 135, 133, 117, 105, 91 (bp); HR-MS (M^+) calcd for $C_{18}H_{22}O$ 254.1670, found 254.1672; $[\alpha]_D^{20}$ +27.2 (*c* 0.47, $CHCl_3$) (86% ee).

A stirred solution of the benzyl ether (44 mg, 0.17 mmol) in 2-propanol (19 ml) and rose bengal (8.8 mg, 8.6 μmol) was irradiated with a 150 W halogen lamp at 23 °C for 11 h under an atmosphere of oxygen. The mixture was placed on a column of silica gel and eluted with Et_2O. The combined eluates were concentrated, and the residue was purified by silica gel chromatography (hexane-AcOEt, 10:1) to give **9** (41 mg, 83%) as a colorless oil: IR (neat) 3050, 1450, 1365, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20~1.65 (m, 4 H), 1.35 (s, 3 H), 2.37 (dd, *J*=8.8, 3.9 Hz, 1 H), 2.45~2.55 (m, 1 H), 3.33 (dd, *J*=9.4, 8.8 Hz, 1 H), 3.45 (dd, *J*=9.4, 5.6 Hz, 1 H), 4.27 (dt, *J*=6.2, 1.6 Hz, 1 H), 4.46 (d, *J*=11.9 Hz, 1 H), 4.52 (d, *J*=11.9 Hz, 1 H), 4.58~4.62 (m, 1 H), 6.50 (ddd, *J*=8.3, 6.0, 1.6 Hz, 1 H), 6.61 (ddd, *J*=8.3, 6.2, 1.8 Hz, 1 H), 7.25~7.45 (m, 5 H); FAB-MS m/z 287 (M^++H), 254 (M^+-O_2), 195 (M^+-Bn), 179, 154 (bp); FAB-HR-MS (M^++H) calcd for $C_{18}H_{23}O_3$ 287.1647, found 287.1634; $[\alpha]_D^{20}$ +13.5 (*c* 0.72, $CHCl_3$) (86% ee).

Acetate 11a. To a solution of **9** (1.21 g, 4.2 mmol) in CH_2Cl_2 (42 ml) was added Et_3N (11.7 ml, 83.9 mmol) at 23 °C, and the mixture was stirred for 90 h while maintaining the temperature between 30 and 35 °C. The reaction mixture was diluted with CH_2Cl_2, washed with 2% HCl and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 2:1) to give a colorless oil (1.02 g, 85%), which was shown by NMR analysis to be a mixture of **10a** and **10b** (ratio of 4.3:1). To a solution of the mixture of **10a** and **10b** (311 mg, 1.1 mmol) in CH_2Cl_2 (5 ml) were added pyridine (0.44 ml, 5.4 mmol), Ac_2O (0.31 ml, 3.3 ml) and 4-dimethylaminopyridine (6.6 mg, 0.05 mmol), and the mixture was stirred at 23 °C for 9 h. To the reaction mixture was added sat. aq NH_4Cl, and the resultant mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4 and concentrated. The residual oil was dissolved in EtOH (11 ml), and $NaBH_4$ (206 mg, 5.4 mmol) was added at 0 °C, and the mixture was stirred at 23 °C for 2 h. To the reaction mixture were successively added acetone and brine at 0 °C, and the resultant mixture was extracted with AcOEt, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel flash chromatography to give **11a** (228 mg, 63%, 2 steps) as a colorless crystal and **11b** (59 mg, 16%, 2 steps) as a colorless oil, respectively;

11a: IR (neat) 3450, 1730, 1450, 1360, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.20~1.33 (m, 2 H), 1.48~1.62 (m, 3 H), 1.73~1.81 (m, 3 H), 1.91 (s, 3 H), 1.98~2.11 (m, 2 H), 2.61~2.71 (m, 1 H), 3.10 (dd, *J*=8.9, 8.8 Hz, 1 H), 3.55 (dd, *J*=11.5, 4.7 Hz, 1 H), 3.59 (dd, *J*=8.8, 5.2 Hz, 1 H), 4.45 (d, *J*=12.0 Hz, 1 H), 4.49 (d, *J*=12.0 Hz, 1 H), 4.54 (ddd, *J*=11.0, 11.0, 4.6 Hz, 1 H), 7.20~7.40 (m, 5 H); MS m/z 289 (M^+-Ac), 272 (M^+-AcOH), 254, 181, 163, 91 (bp), 81; HR-MS (M^+-AcOH) calcd for $C_{18}H_{24}O_2$ 272.1777, found 272.1794; $[\alpha]_D^{20}$ -26.0 (*c* 0.67, $CHCl_3$) (86% ee); mp 119.0-120.0 °C.

11b: IR (neat) 3446, 1736, 1454, 1248 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.15~2.10 (m, 9 H), 2.04 (s, 3 H), 2.55~2.75 (m, 1 H), 3.52~3.65 (m, 1 H), 3.75 (dd, *J*=9.7, 9.7 Hz, 1 H), 3.85~4.00 (m, 1 H), 4.32~4.60 (m, 1 H), 4.51 (d, *J*=11.7 Hz, 1 H), 4.59 (d, *J*=11.7 Hz, 1 H), 4.78~4.90 (m, 1 H), 7.20~7.40 (m, 5 H); MS m/z 332 (M^+), 314, 272, 254, 181, 163, 133, 91 (bp); HR-MS (M^+) calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1987; $[\alpha]_D^{20}$ -4.2 (*c* 2.3, $CHCl_3$) (86% ee).

Bromide 12. To a stirred solution of **11a** (250 mg, 0.75 mmol) in CH_2Cl_2 (10 ml) were added Et_3N (0.53 ml, 3.8 mmol) and methanesulfonyl chloride (0.18 ml, 2.3 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture was added sat. aq $NaHCO_3$, and the aqueous layer was extracted with AcOEt, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 2:1) to afford the mesylate (295 mg, 95%) as a colorless crystal: IR (neat) 1725, 1345, 1250, 1175 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.28~1.38 (m, 2 H), 1.52~1.62 (m, 1 H), 1.79~1.91 (m, 3 H), 1.92 (s, 3 H), 2.02~2.13 (m, 3 H), 2.62~2.71 (m, 1 H), 3.01 (s, 3 H), 3.10 (dd, *J*=8.9, 8.8 Hz, 1 H), 3.57 (dd, *J*=8.8, 5.3 Hz, 1 H), 4.44 (d, *J*=12.0 Hz, 1 H), 4.48 (d, *J*=12.0 Hz, 1 H), 4.55 (ddd, *J*=11.0, 10.4, 4.4 Hz, 1 H), 4.62 (dd, *J*=11.8, 4.8 Hz, 1 H), 7.26~7.36 (m, 5

H); MS m/z 410 (M^+), 254 (M^+-AcOH-MsOH), 163, 148, 133, 91 (bp); HR-MS (m/z 254) calcd for $C_{18}H_{22}O$ 254.1671, found 254.1643; $[\alpha]_D^{20}$ -26.7 (*c* 0.50, $CHCl_3$) (86% ee); mp 127.5-128.5 °C.

A mixture of the mesylate(78 mg, 0.19 mmol) and Bu_4NBr (619 mg, 1.9 mmol) in toluene (5 ml) was stirred at 70 °C for 10 days. After cooling to room temperature, the reaction mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt, 30:1) to give **12** (41.3 mg, 55%) as a colorless oil, which was shown by NMR analysis to be a mixture of α-bromide and β-bromide at C1 position of **12** (ratio of 5:2): IR (neat) 1730, 1450, 1380, 1360, 1240, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24 (s, 6/7 Hβ), 1.28 (s, 15/7 H_α), 1.30~1.60 (m, total 3 H), 1.80 ~1.91 (m, total 2 H), 1.91 (s, 15/7 H_α), 1.97 (s, 6/7 Hβ), 1.98~2.18 (m, total 4 H), 2.55~2.65 (m, 2/7 Hβ), 2.70~2.79 (m, 5/7 H_α), 3.08 (dd, *J*=8.9, 8.8 Hz, 5/7 H_α), 3.17 (dd, *J*=8.7, 8.6 Hz, 2/7 Hβ), 3.56 (dd, *J*=8.7, 5.4 Hz, 2/7 Hβ), 3.57 (dd, *J*=8.8, 5.1 Hz, 5/7 H_α), 4.04 (dd, *J*=12.4, 4.7 Hz, 5/7 H_α), 4.31 (bt, *J*=4.6 Hz, 2/7 Hβ), 4,44 (d, *J*=12.1 Hz, 5/7 H_α), 4.45 (d, *J*=12.0 Hz, 2/7 Hβ), 4.48 (d, *J*=12.1 Hz, 5/7 H_α), 4.49 (d, *J*=12.0 Hz, 2/7 Hβ), 4.60 (ddd, *J*=11.0, 10.8, 4.7 Hz, 5/7 H_α), 4.78~4.83 (m, 2/7 Hβ), 7.20~7.40 (m, total 5 H) [The protons assigned to α-bromide **12** or β-bromide **12** are indicated as H_α or Hβ, respectively.]; MS m/z 396 and 394 (M^+), 353 and 351 (M^+-Ac), 336 and 334 (M^+-AcOH), 255, 245 and 243, 149, 91 (bp); HR-MS (M^+-AcOH 334) calcd for $C_{18}H_{23}{}^{79}BrO$ 334.0933, found 334.0941.

***cis*-Hydrindanone 14.** To a suspension of $LiAlH_4$ (10 mg, 0.27 mmol) in Et_2O (2.0 ml) was added a solution of **12** (85 mg, 0.22 mmol) in Et_2O (2.0 ml) at -30 °C, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture were successively added AcOEt and $Na_2SO_4 \cdot 10H_2O$ at -30 °C, and the mixture was stirred at room temperature for several hours. The resultant mixture was filtered through Celite, and the filtrate was concentrated. The residual crude alcohol (77 mg) was dissolved in CH_2Cl_2 (5.0 ml), then PCC (142 mg, 0.66 mmol) and MS 4A (586 mg) were added at 0 °C, and the mixture was stirred at 23 °C for 1 h. The reaction mixture was filtered through Florisil, and the filtrate was concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt, 10:1) to give the *cis*-hydrindanone **14** (64 mg, 84%, 2 steps) as a colorless oil, which was shown by NMR analysis to be a mixture of α-bromide and β-bromide at C1 position of **14** (ratio of 5:2): IR (neat) 1712, 1453, 1113 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (s, 6/7 Hβ), 1.31 (s, 15/7 H_α), 1.38~1.55 (m, 5/7 H_α), 1.60~1.71 (m, 5/7 H_α), 1.83~1.91 (m, 4/7 Hβ), 1.92~2.12 (m, 4/7 Hβ and 10/7 H_α), 2.25~2.45 (m, total 4 H), 2.56 (d, *J*=7.8 Hz, 5/7 H_α), 2.65~2.75 (m, 4/7 Hβ and 5/7 H_α), 3.43 (dd, *J*=9.6, 4.0 Hz, 2/7 Hβ), 3.47 (dd, *J*=9.6, 3.5 Hz, 2/7 Hβ), 3.65 (dd, *J*=9.2, 6.3 Hz, 5/7 H_α), 3.77 (dd, *J*=9.2, 4.8 Hz, 5/7 H_α), 4.26 (dd, *J*=10.6, 4.7 Hz, 5/7 Hα), 4.37 (d, *J*=11.2 Hz, 2/7 Hβ), 4.40 (d, *J*=11.2 Hz, 2/7 Hβ), 4.42 (bs, 10/7 H_α), 4.61 (dd, *J*=10.7, 4.2 Hz, 2/7 Hβ), 7.20~7.40 (m, total 5H) [The protons assigned to α-bromide **14** or β-bromide **14** are indicated as H_α or Hβ, respectively.]; MS m/z 352 and 350 (M^+), 270 (M^+-HBr), 261 and 259 (M^+-Bn), 245 and 243 (M^+-OBn), 231 and 229, 133, 91 (bp); HR-MS (M^+ 352) calcd for $C_{18}H_{23}{}^{81}BrO_2$ 352.0861, found 352.0841.

Conversion of 14 into the intermediate of (–)-oppositol and (–)-prepinnaterpene (15β). To a solution of **14** (64 mg, 0.18 mmol) in CH_2Cl_2 (5.0 ml) was added *p*-TsOH·H_2O (7 mg, 0.036 mmol) at 23 °C, and the mixture was stirred at the same temperature for 16 h. The reaction mixture was diluted with AcOEt, washed with sat. aq $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane-AcOEt, 10:1) to give the *trans*-hydrindanone (54 mg, 86%) as a colorless oil, which was shown by NMR analysis to be a mixture of α-bromide and β-bromide (ratio of 5:2). The *trans*-hydrindanone (53 mg, 0.15 mmol) was dissolved in Et_2O (92.0 ml), and MeLi (1.1 *M* in Et_2O, 0.27 ml, 0.30 mmol) was added at -20 °C, and the mixture was stirred at the same temperature for 2.5 h. The reaction mixture was quenched by the addition of sat. aq NH_4Cl at -20 °C, followed by extraction of the

resultant mixture with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt, 4:1) to afford **15** (49 mg, 89%) as a colorless oil, which was shown by NMR analysis to be a mixture of α-bromide and β-bromide at C1 position of **15** (ratio of 5:2). To a solution of **15** (21 mg, 0.056 mmol) in xylene (0.5 ml) was added Bu_4NBr (188 mg, 0.58 mmol) at room temperature, and the mixture was stirred at 145 °C for 14 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt, 5:1) to give the key intermediate **15**β (9 mg, 42%) as a colorless oil: IR (neat) 3472, 1454, 1364, 1102 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.19 (s, 3 H), 1.25~1.33 (m, 1 H), 1.37 (d, *J*=11.2 Hz, 1 H), 1.49 (ddd, *J*=12.7, 12.5, 5.0 Hz, 1 H), 1.54~1.67 (m, 3 H), 1.91~2.03 (m, 2 H), 2.32 (ddd, *J*=26.2, 13.4, 4.7 Hz, 1 H), 2.43 (dddd, *J*=16.4, 11.2, 6.1, 3.5 Hz, 1 H), 3.44 (dd, *J*=9.1, 6.1 Hz, 1 H), 3.63 (dd, *J*=9.1, 3.5 Hz, 1 H), 3.99 (dd, *J*=12.5, 4.0 Hz, 1 H), 4.48 (d, *J*=12.0 Hz, 1 H), 4.52 (d, *J*=12.0 Hz, 1 H), 7.20~7.40 (m, 5 H); MS m/z 353 and 351 (M^+-Me), 286 (M^+-HBr), 268 (M^+-HBr-H_2O), 247 and 245, 229 and 227, 195, 177, 163, 147, 119, 107, 91 (bp); HR-MS (M^+-Me) calcd for $C_{18}H_{24}{}^{81}BrO_2$ 353.0939, found 353.0967, calcd for $C_{18}H_{24}{}^{79}BrO_2$ 351.0960, found 351.0981; $[\alpha]_D{}^{25}$ -12.7 (*c* 0.87, $CHCl_3$) (86% ee).

Silyl ether 17a. To a solution of the mixture of **10a** and **10b** (42 mg, 0.15 mmol) in CH_2Cl_2 (2.0 ml) were added 2,6-lutidine (65 μl, 0.56 mmol) and Et_3SiOTf (65 μl, 0.29 mmol) at -20 °C, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture was added sat. aq $NaHCO_3$ at -20 °C, and the solution was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane-AcOEt, 30:1) to give **17a** (46 mg, 79%) as a colorless oil and **17b** (11 mg, 19%) as a colorless oil, respectively;

17a: IR (neat) 1680, 1450, 1380, 1240, 1070, 1040, 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.60 (q, *J*=7.9 Hz, 6 H), 0.95 (t, *J*=7.9 Hz, 9 H), 1.20~1.30 (m, 1 H), 1.34 (s, 3 H), 1.43 (ddd, *J*=13.2, 9.5, 7.5 Hz, 1 H), 1.80~1.88 (m, 1 H), 2.26~2.35 (m, 2 H), 2.55~2.63 (m, 1 H), 3.16 (dd, *J*=9.5, 6.5 Hz, 1 H), 3.20 (dd, *J*=9.5, 8.5 Hz, 1 H), 4.32 (d, *J*=11.8 Hz, 1 H), 4.39 (d, *J*=11.8 Hz, 1 H), 4.73 (dd, *J*=4.6, 2.4 Hz, 1 H), 5.89 (d, *J*=10.1 Hz, 1 H), 6.64 (ddd, *J*=10.1, 4.6, 1.2 Hz, 1 H), 7.25~7.30 (m, 3 H), 7.30~7.35 (m, 2 H); MS m/z 400 (M^+), 371, 279, 265, 221, 198, 177, 167, 149, 91 (bp); HR-MS (M^+) calcd for $C_{24}H_{36}O_3Si$ 400.2434, found 400.2426; $[\alpha]_D{}^{20}$ -71.8 (*c* 0.450, $CHCl_3$) (86% ee).

17b: IR (neat) 1665, 1455, 1380, 1240, 1100, 1050, 1030, 1010 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.52 (q, *J*=8.0 Hz, 6 H), 0.92 (t, *J*=8.0 Hz, 9 H), 1.07 (s, 3 H), 1.25~1.32 (m, 1 H), 1.77~1.97 (m, 3 H), 2.50 (d, *J*=12.3 Hz, 1 H), 2.70~2.80 (m, 1 H), 3.39 (d, *J*=3.6 Hz, 2 H), 4.24 (d, *J*=11.9 Hz, 1 H), 4.27 (d, *J*=11.9 Hz, 1H), 4.58 (bt, *J*=2.1 Hz, 1 H), 5.82 (dd, *J*=10.1, 2.3 Hz, 1 H), 6.49 (dd, *J*=10.1, 1.7 Hz, 1 H), 7.20~7.35 (m, 5 H); MS m/z 400 (M^+), 309, 292, 280, 265, 239, 198, 177, 163, 149, 115, 91 (bp); HR-MS (M^+) calcd for $C_{24}H_{36}O_2Si$ 400.2434, found 400.2448; $[\alpha]_D{}^{20}$ +72.4 (*c* 0.44, $CHCl_3$) (86% ee).

Benzoate 18. To a solution of **17a** (46 mg, 0.11 mmol) in THF (2.0 ml) was added tetrabutylammonium fluoride (1 *M* in THF, 0.17 ml, 0.17 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched by the addition of brine, followed by extraction of the mixture with AcOEt, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residual crude alcohol was dissolved in CH_2Cl_2 (2.0 ml), and to the mixture were added pyridine (50 μl, 0.62 mmol), benzoyl chloride (40 μl, 0.34 mmol) and a catalytic amount of 4-dimethylaminopyridine at 0 °C. After stirring at 23 °C for 4 h, sat. aq NH_4Cl was added to the reaction mixture, and the resultant mixture was extracted with AcOEt. The organic layer was washed with sat. aq $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the sovent, the residue was purified by silica gel chromatography (hexane-AcOEt, 3:1) to give **18** (30 mg, 69%, 2 steps) as a colorless oil: IR (neat) 1720, 1680, 1450, 1260, 1100, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 3

H), 1.41~1.48 (m, 1 H), 1.52~1.61 (m, 1 H), 1.90~1.20 (m, 1 H), 2.25 (ddd, *J*=13.4, 9.7, 5.8 Hz, 1 H), 2.61 (dd, *J*=7.2, 4.7 Hz, 1 H), 2.70~2.80 (m, 1 H), 3.25 (dd, *J*=9.4, 6.2 Hz, 1H), 3.31 (dd, *J*=9.4, 8.1 Hz, 1 H), 4.26 (d, *J*=11.9 Hz, 1 H), 4.31 (d, *J*=11.9 Hz, 1 H), 5.92~5.96 (m, 1 H), 6.05 (dd, *J*=10.1, 1.1 Hz, 1 H), 6.80 (dd, *J*=10.1, 3.6 Hz, 1 H), 7.18~7.33 (m, 5 H), 7.44 (bt, *J*=8.0 Hz, 2 H), 7.58 (bt, *J*=8.0 Hz, 1 H), 8.03 (bd, *J*=8.0 Hz, 2 H); MS m/z 390 (M^+), 299 (M^+-Bn), 282, 268, 177, 162, 147, 105 (bp), 91, 77; HR-MS (M^+) calcd for $C_{25}H_{26}O_4$ 390.1831, found 390.1840. The CD spectrum of **18** showed a negative Cotton effect at 235 nm.

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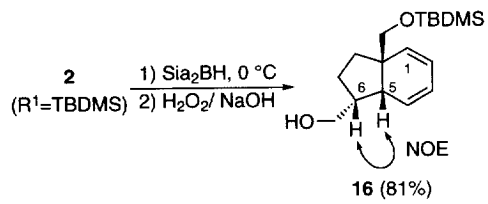
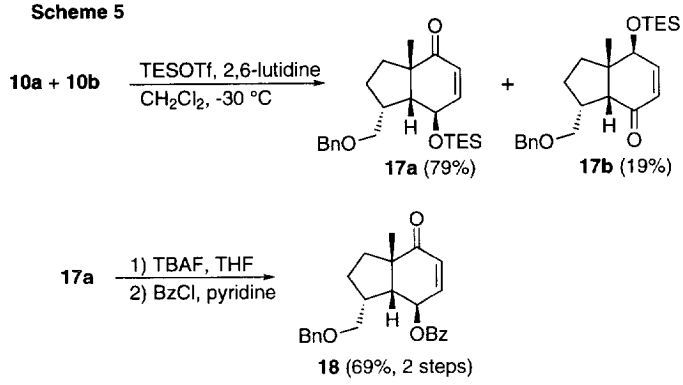
(7) Hydroboration of **2** (R^1=TBDMS) using Sia_2BH proceeded stereoselectively to produce **16** as a single isomer, whose stereochemistry of the hydroxymethyl group at C6 position was determined unequivocally by the ^{1}H-NMR spectrum (NOESY) of **16**.[1e] On the basis of this result, the stereochemistry of the

hydroxymethyl group in **8** was presumed to be an α-configuration at this stage, which was confirmed ultimately by comparison of the ^{1}H-NMR spectrum of **14** with that of α-bromide **3**.



(8) The stereochemistry of endoperoxide **9** was determined as follows (Scheme 5); After protection of a mixture **10a** and **10b** with triethylsilyl group, the resulting silyl ethers were easily separated into **17a** and **17b** by silica gel column chromatography. The silyl ether **17a** was converted into benzoate **18**. The CD spectrum of **18** showed a negative Cotton effect at 235 nm, which indicates that the stereochemistry of benzoyloxy group at C4 position in **18** is a β-configuration according to the CD exciton chirality method[9] in the allyl benzoate system.

Scheme 5



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(10) Compound **14** was obtained as a mixture of 1α-bromide and 1β-bromide (ratio of 2.5:1), while the key intermediate **3**, reported by Masamune *et al.*,[4b] was 1α-bromide.

(11) It was reported that treatment of **15**α, which possessed the axially oriented bromine atom at the C1 position, with tetrabutylammonium bromide in toluene at 115 °C for 2 days afforded equatorially brominated epimer **15**β in 55% yield.[4b] According to their procedure, treatment of a mixture of **15**α and **15**β (ratio of 2.5:1) with tetrabutylammonium bromide (5~10 eq) in toluene at 115 °C for 4 days or 8 days afforded the mixture of **15**α and **15**β in 60% yield (ratio of 1:5.9) or in 42% yield (ratio of 1:9.5), respectively. When this mixture was treated with tetrabutylammonium bromide in xylene at 145 °C for 12 h, a satisfactory result was obtained, giving **15**β in a ratio of 17:1 (**15**β:**15**α) in 42% yield.

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