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SYNTHESIS OF BOTH THE ENANTIOMERS OF POLYGODIAL, AN INSECT ANTIFEEDANT SESQUITERPENE†

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Abstract---Both the natural and unnatural enantiomers of polygodial, an insect antifeedant sesquiterpene of the drimane family, were synthesized starting from (S)-3-hydroxy-2,2-dimethylcyclohexanone as a single chiral source.

Polygodial **1** is a hot-tasting sesquiterpene first isolated from Polygonum hydropiper, water-pepper in English or yanagi-tade in Japanese.[1,2] It has also been isolated from Warburgia stuhlmannii and shown to possess antifeedant activity against African crop pest insects such as the army worms Spodoptera littoralis and S. exempta.[3] Recent work revealed that nudibranch molluscs contain polygodial **1** as a chemical defense substance.[4,5] Revival of interest in the synthesis of drimanic sesquiterpenes is due largely to Kubo and Nakanishi's discovery of the antifeedant activity shown by polygodial and warburganal.[3]

Racemic polygodial (±)-**1** has been synthesized several times to date.[6~8] However, no synthesis of the enantiomers of **1** has been reported. The only existing synthesis of an enantiomer of a drimanic antifeedant is that of (-)-warburganal from (-)-abietic acid.[9] Some timely information kindly given to one of us (K. M.) by Dr. J. A. Pickett of Rothamsted Experimental Station prompted us to undertake a project to synthesize both the natural and unnatural enantiomers of polygodial (**1** and **1'**). According to Pickett, the natural enantiomer **1** is an active insect antifeedant with no phytotoxicity. The synthetic racemate (±)-**1**, on the other hand, shows phytotoxicity together with the expected antifeedant activity. This implies that the phytotoxicity might be due to the unnatural enantiomer **1'** of polygodial[10] and it was to prove this hypothesis that both the enantiomers of polygodial were synthesized. A second driving force for our chiral synthesis of **1** and **1'** was Kubo's report that the specific absolute stereochemistry of an antifeedant appears to govern the hotness of its taste.[11] Synthesis of the unnatural isomer **1'** would prove or disprove his proposal.

Our synthetic plan is shown in Fig. 1. The strategy is to employ the OH group of **A** as the handle to facilitate the chiral synthesis. Microbial reduction of **2** employing Kloeckera magna ATCC 20109[12] is known to give (S)-**3a**. We have recently found that the

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above conversion can be achieved simply by using baker's yeast.[13] Thus, **3a** serves as a readily available chiral starting material. The (S)-ketol **3a** gives **A** through a multi-step sequence. A Diels-Alder reaction between **A** and **B** is expected to give either **C** or a mixture of **C** and **D**. Only **C** will be produced, if the influence of the OH group of **A** on the steric course of the Diels-Alder reaction is great enough to give a single product with an eq OH group. Then **C** affords (-)-polygodial **1** after several steps including deoxygenation at C-3. In the same manner, for the synthesis of (+)-polygodial **1'**, (R)-**3a** can be the starting material. However, the key Diels-Alder reaction was surprisingly non-diastereoselective, furnishing a mixture of **C** and **D**. This seemingly disappointing non-selectivity turned out to be beneficial to us as detailed below.

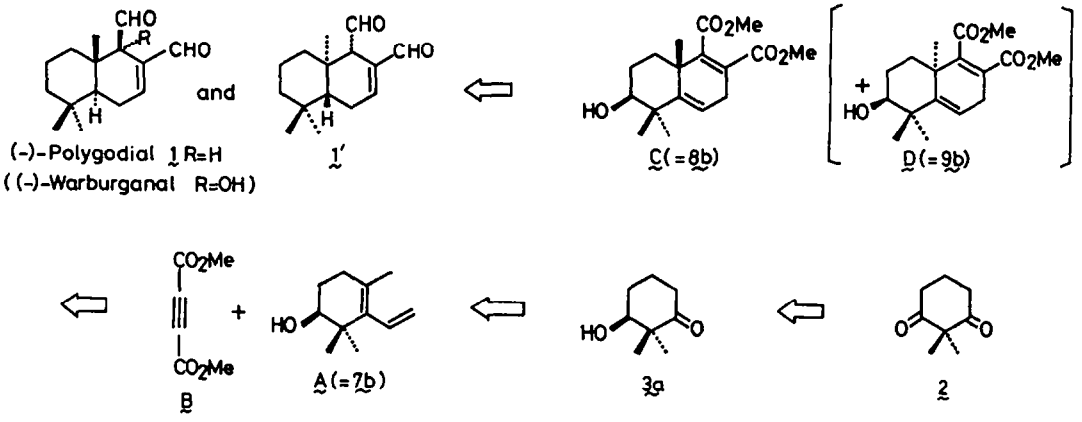

Fig. 1. Synthetic plan.

The first stage of our work was the construction of the drimane skeleton as shown in Fig. 2. The Diels-Alder approach to drimanic sesquiterpenes was first adopted by Brieger,[14] and widely employed by later workers such as Nakanishi,[15] Lallemand,[7] Ley,[8] and Snowden.[16] The preparation of a diene **7a** and **7b** required for the Diels-Alder reaction started from (S)-3-hydroxy-2,2-dimethylcyclohexanone **3a**, whose optical purity was determined to be 97 % e.e. by the HPLC analysis of the corresponding (R)-MTPA ester **3b**. After protecting the OH group of **3a** as a silyl ether, the resulting **3c** was methylated with MeI and $LiN(i\text{-}Pr)_2$ to give **4** in 72 % yield from **3a**. The ketone **4** was converted to the desired diene **7a** by the method of Ley.[8] Thus, **4** was treated with $HC{\equiv}CNa$ in liq NH_3 to give **5**, whose dehydration by heating with $CuSO_4$ in xylene yielded **6**. Semi-hydrogenation of **6** over $Pd\text{-}CaCO_3$ in the presence of quinoline gave **7a**, $[\alpha]_D^{21}$ -31.4° (n-pentane), in 50.5 % overall yield from **4**.

The Diels-Alder reaction of **7a** with $MeO_2C{\cdot}C{\equiv}C{\cdot}CO_2Me$ **B** was effected by heating the neat mixture at 110° for 30 h. The reaction was not diastereoselective but yielded a mixture of **8a** and **9a**. Although the presence of both **8a** and **9a** was discernible by scrutinizing the ^{1}H-NMR spectrum of the mixture, **8a** and **9a** were inseparable even by TLC. The mixture was therefore treated with HF in aq MeCN to remove the silyl protective group. Fortunately, the diastereomeric hydroxy esters **8b** and **9b** could be separated by medium pressure LC to give **8b**, m.p. 118~119°, $[\alpha]_D^{21.5}$ -30.7° ($CHCl_3$), and **9b**, m.p. 104.5~105.6°, $[\alpha]_D^{21}$ +39.9° ($CHCl_3$), in 26 % yield of each from **7a**. The structural assignments of the two isomers were based on the inspection of their ^{1}H-NMR spectra: the CHOH proton of **8b** showed the $W_{1/2}$ value of 18 Hz, while the $W_{1/2}$ value of the CHOH proton of **9b** was 9 Hz. The result clearly indicated that the cycloaddition was entirely non-diastereoselective, giving **8a** and **9a** in 1:1 ratio. We then thought that the diastereoselectivity of the reaction might be modified by employing the dienol **7b** for the cycloaddition. Treatment of **7a** with HF in aq MeCN gave **7b**, $[\alpha]_D^{18}$ -53.4° (ether), in 74 % yield. The

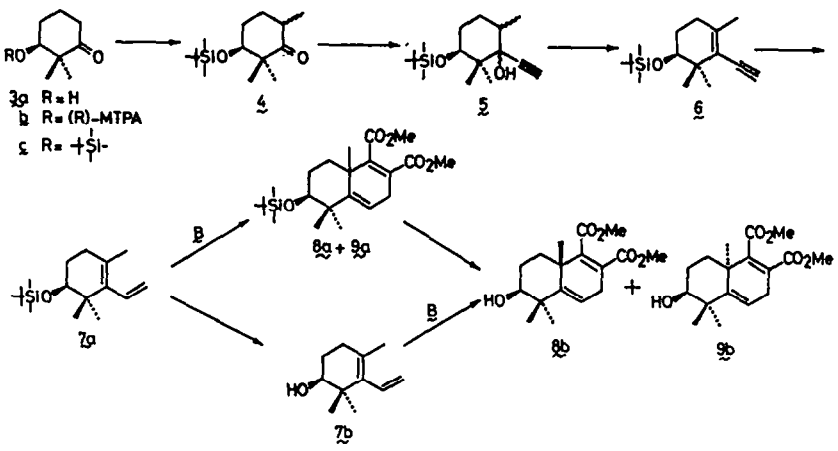

Fig. 2. Construction of the drimane skeleton.

Diels-Alder reaction of **7b** with **B** was executed similarly as before at 110° for 30 h. The product was again a mixture, which could be purified by medium pressure LC to give **8b** (32 % yield) and **9b** (35 % yield). In this case, too, the reaction proceeded without any substantial diastereoselectivity. This result may be the reflection of the lack of energy difference between two possible conformers (ax OR or eq OR) of **7a** (or **7b**) at the reaction temp. The lack of diastereoselectivity, however, was quite fortunate for our purpose, because it enabled us to prepare both the enantiomers of polygodial(1 and 1') from a single chiral precursor [(S)-**3a**]. The overall yield of **8b** from **3a** via **7b** was 8.6 % and that of **9b** was 9.4 %.

The second stage of the synthesis was the reduction of the Diels-Alder adducts **8b** and **9b** to diastereomeric trans-octalin esters **10a** and **12** as shown in Fig. 3. We first attempted the reduction of **8b** according to Ley's procedure which worked satisfactorily in his synthesis of (±)-polygodial.[8] Hydrogenation of **8b** over Pd-C in the presence of HCl in

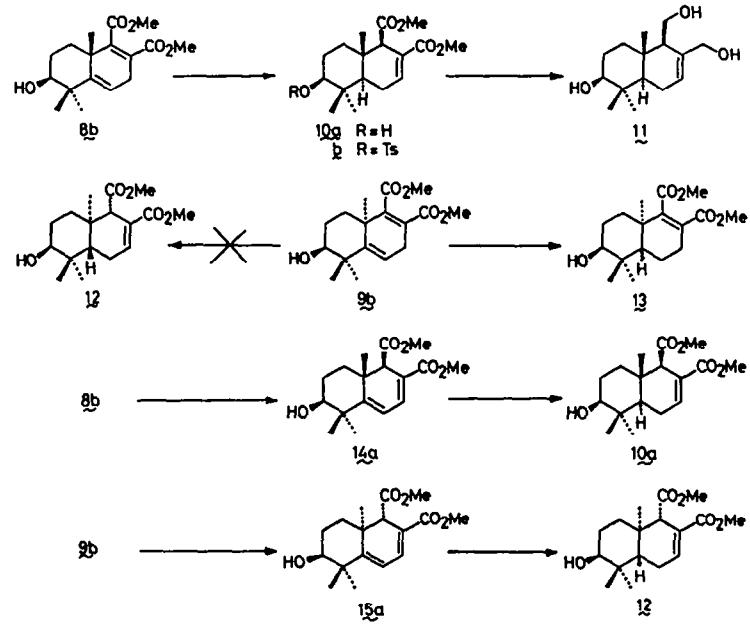

Fig. 3. Reduction of **8b** and **9b** to **10a** and **12**.

MeOH afforded **10a** in 63 % yield in one occasion. In our hands, however, the reduction of the dienol **8b** was found to be difficult to reproduce after several trials. In addition, conventional deoxygenation of **10a** *via* **10b** was unsuccessful. Indeed, **11** was the sole product when **10b** was reduced with LAH. Reduction of **9b** was attempted in the same manner as for **8b** according to Ley.[8] In this particular case, the product was not the expected **12**, but **13** with no olefinic proton in its ^{1}H-NMR spectrum. Definite configuration could not be assigned to the angular proton at C-5 of **13**.

A successful procedure for obtaining the trisubstituted olefinic esters **10a** and **12** was finally devised as follows. Treatment of **8b** with DBU in refluxing THF gave an isomeric conjugated diene ester **14a**, which was hydrogenated over Pd-C to give **10a** in 80 % yield from **8b**. Similarly, **9b** was treated with DBU in refluxing THF to give **15a**, whose hydrogenation gave **12** in 89 % yield from **9b**. The above-described isomerization-hydrogenation strategy was first adopted by Lallemand employing LiN(*i*-Pr)$_2$ as the base for isomerization. Our procedure to use DBU as the base was simpler and reproducible. Inspection of the ^{1}H-NMR spectra of **10a** and **12** confirmed the assigned stereochemistry at C-9 (see Experimental).[cf.7]

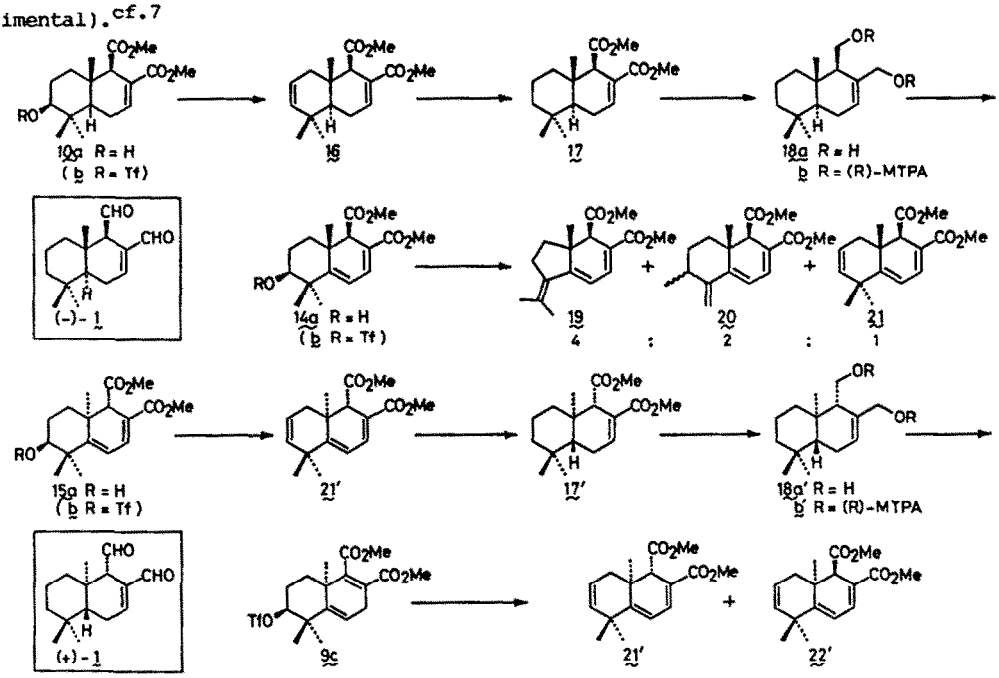

Fig. 4. Synthesis of the enantiomers of polygodial.

The third and the final stage of the synthesis was conversion of the hydroxy esters **10a** and **15a** to the enantiomers of polygodial as shown in Fig. 4. Treatment of **10a** with CF_3SO_2Cl (=TfCl) and 4-(N,N-dimethylamino)pyridine (DMAP) in CH_2Cl_2 (0°, 15 min; room temp, 15 min) furnished **16** in 86 % yield *via* **10b**. Hydrogenation of **16** over Pd-C gave **17**, m.p. 88.1~89.0°, $[\alpha]_D^{22}$ -31.5° ($CHCl_3$), in 89 % yield. Reduction of **17** with LAH afforded **18a**, m.p. 69.5~70.5°, $[\alpha]_D^{22}$ -6.3° ($CHCl_3$), in 82 % yield. Its *bis*-(*R*)-MTPA ester **18b** was analyzed by HPLC to reveal the optical purity of **18a** as ~100 % e.e. Swern oxidation[17] of **18a** gave (-)-polygodial **1**, m.p. 56.9~57.3°, $[\alpha]_D^{22.5}$ -133° (EtOH) [lit.[2] m.p. 57°, $[\alpha]_D^{24}$ -131° (EtOH)] in 63 % yield. The spectral properties of (-)-**1** were identical with those previously reported for natural polygodial[1,2] or for the racemate.[7,8] The overall yield of (-)-polygodial **1** from **3a** was 3.0 % in 13 steps. Prior to the successful synthesis of (-)-**1**, an attempt was made to obtain **21** directly from **14a**. When **14a** was treated with TfCl and DMAP in CH_2Cl_2, however, a complex mixture resulted owing to cationic

skeletal rearrangements via **14b**. The products were shown to be **19**, **20**, and **21**, the desired **21** having been only 14 % of the total products. This was not unexpected, because of the eq orientation of the OH group of **14a**. The successful elimination of the eq OH group of **10a** to give **16** without rearrangement must be considered exceptional.

In the case of **15a**, smooth elimination of an ax OH group at C-3 position took place when **15a** was treated with TfCl and DMAP in CH_2Cl_2 to give **21'**, m.p. 64.0~64.5°, $[\alpha]_D^{21}$ +244° ($CHCl_3$), in 81 % yield via **15b**. Hydrogenation of **21'** over Pd-C afforded **17'**, m.p. 88.2~88.9°, $[\alpha]_D^{21}$ +33.1° ($CHCl_3$), in 70 % yield. Treatment of **17'** with LAH gave **18a'**, m.p. 69.0~70.0°, $[\alpha]_D^{22}$ +6.5° ($CHCl_3$), in 80 % yield. The HPLC analysis of the corresponding bis-(R)-MTPA ester **18b'** confirmed the optical purity of **18a'** as ~100 % e.e. Finally **18a'** furnished the unnatural (+)-polygodial **1'**, m.p. 57.0~57.5°, $[\alpha]_D^{22.5}$ +135° (EtOH), in 72 % yield. Its spectral properties were identical with those of (-)-**1**. The overall yield of (+)-polygodial **1'** from **3a** was 2.9 % in 12 steps. Prior to the above described success, we attempted the direct preparation of **21'** by treating **9c** with $(n\text{-}Bu)_4NBr$ and DBU.[cf.18] Although both the elimination of TfOH and the conjugation of the ring B diene system took place, concomittant epimerization at C-9 invalidated our attempt, and the product was found to be a mixture of **21'** and **22'** (1:4).

After the completion of the synthesis, we examined the human taste of the enantiomers of polygodial. Both **1** and **1'** were strongly pungent to human taste as tested by the tongues of K. M. and his collaborators. The antifeedant as well as phytotoxic activity of **1** and **1'** are now being examined by Dr. J. A. Pickett.

In conclusion, the first synthesis of both the natural and unnatural enantiomers (**1** and **1'**) of polygodial was accomplished starting from a single chiral source readily obtainable by microbial reduction of a prochiral ketone **2**.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JMN FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-300 spectrometer at 70 eV.

(S)-3-t-Butyldimethylsilyloxy-2,2-dimethylcyclohexanone **3c**. To a stirred soln of **3a** (97 % e.e., 7.10 g, 49.9 mmol) and imidazole (10.0 g, 147 mmol) in dry DMF (100 ml) was added t-$BuMe_2SiCl$ (11.0 g, 73.0 mmol) at room temp. The mixture was stirred for 18 h at 40°, poured into ice-water, and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) and the resulting crude **3c** was distilled to give 10.3 g (81 %) of **3c**, b.p. 91~94°/1.5 Torr; n_D^{21} 1.4540; $[\alpha]_D^{21}$ +22.1° (c=1.47, $CHCl_3$); νmax 1710 (s), 1250 (s), 1075 (s) cm^{-1}; δ (CCl_4) 0.03 (6H, s), 0.87 (9H, s), 1.00 (3H, s), 1.04 (3H, s), 1.20~2.00 (4H, m), 2.00~2.50 (2H, m), 3.60 (1H, m). (Found: C, 65.49; H, 11.06. Calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.06 %).

(3S)-3-t-Butyldimethylsilyloxy-2,2,6-trimethylcyclohexanone **4**. A soln of LDA was prepared by the dropwise addition of n-BuLi soln (1.60 M, in n-hexane, 25.1 ml, 40.2 mmol) to a stirred and cooled soln of i-Pr_2NH (5.90 ml, 42.2 mmol) in dry THF (23 ml) at -60~-45° under Ar. HMPA (14 ml, 80.5 mmol) was added to the mixture at -60°. The mixture was warmed to -20° to make it a homogeneous soln. To the stirred and cooled LDA soln, a soln of **3c** (9.80 g, 38.2 mmol) in dry THF (20 ml) was added dropwise at -60~-50°. The mixture was stirred for 30 min at -78°. To the stirred and cooled soln was added dropwise MeI (93 % purity, d=2.28; 2.8 ml, 41.8 mmol) at -78°. After the addition, the reaction temp was raised to -5°, and the stirring was continued for 30 min at -5~0°. The mixture was poured into water and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 (Merck Kieselgel 60) chromatography followed by distillation to give 9.21 g (89 %) of **4**, b.p. 103~111°/5 Torr; n_D^{24} 1.4568; $[\alpha]_D^{24}$ +13.7° (c=1.12, $CHCl_3$); νmax 1715 (s), 1255 (s), 1080 (s), 1030 (s), 890 (m) 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.02 (3.8H, s), 0.05 (2.2H, s), 0.84 (5.7H, s), 0.88 (3.3H, s), 0.80~1.10 (9H, m), 1.40~2.10 (4H, m), 2.10~2.90 (1H, m), 3.40 (0.36H, t, J=7 Hz), 3.75 (0.64H, m). (Found: C, 66.34; H, 11.10. Calc for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18 %).

(3S)-3-t-Butyldimethylsilyloxy-1-ethynyl-2,2,6-trimethylcyclohexanol **5**. Acetylene was bubbled into a stirred and cooled suspension of sodamide [from 2.3 g (0.1 g atom) of Na] in liq. NH_3 (150 ml) for 30 min. To the suspension was added dropwise a soln of **4** in dry ether (15 ml) at -78° with stirring, and the stirring was continued for 2.5 h at -33°. The

reaction was quenched by adding solid NH_4Cl (10 g), and after 10 min at -33°, ether (20 ml) was added and the ammonia was evaporated by heating with a warm-water bath. The residue was filtered and the filter cake was washed with ether. The combined filtrate and washings were concentrated *in vacuo*. The residue was chromatographed over neutral Al_2O_3 (grade II) to give 9.98 g (99 %) of **5**, νmax 3500 (m), 3310 (m), 2090 (w), 1095 (s), 1025 (s), 830 (s) cm^{-1}; δ (CCl_4) 0.02 and 0.03 (total 6H, two s), 0.85 (9H, s), 0.80 1.10 (9H, m), 1.00~2.20 (6H, m), 2.40 (1H, s), 3.60 (1H, m). This was employed in the next step without further purification.

(S)-4-t-Butyldimethylsilyoxy-2-ethynyl-1,3,3-trimethylcyclohexene **6**. To a soln of **5** (9.98 g, 33.7 mmol) in distilled xylene (100 ml) was added anhyd $CuSO_4$ powder (1.1 g) and the suspension was refluxed using Dean-Stark trap under Ar for 20 h. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed over neutral Al_2O_3 (grade II) and the resulting crude **6** was distilled to give 4.82 g (51 %) of **6**, b.p. 91~93°/0.2 Torr; $n_D^{16.5}$ 1.4779; $[\alpha]_D^{16.5}$ -27.0° (c=1.94, *n*-pentane); νmax 3330 (s), 2100 (w), 1635 (w), 1430 (m), 1255 (s), 1120 (s), 1070 (s), 890 (s), 840 (s), 775 (s), 675 (m) cm^{-1}; δ ($CDCl_3$) 0.07 (6H, s), 0.90 (9H, s), 1.04 (3H, s), 1.13 (3H, s), 1.20~2.50 (4H, m), 1.88 (3H, s), 3.00 (1H, s), 3.50 (1H, t, J= 6Hz). (Found: *m/z* 221.1362. Calc for $C_{13}H_{21}OSi$: 221.1362).

(S)-4-t-Butyldimethylsilyloxy-2-vinyl-1,3,3-trimethylcyclohexene **7a**. 5 % Pd-$CaCO_3$ (0.5 g) and quinoline (0.35 ml) were added to a soln of **6** (3.0 g, 10.8 mmol) in *n*-pentane (150 ml). The mixture was stirred under H_2 at room temp until **6** disappeared on TLC. It was then filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed over neutral Al_2O_3 (grade II) to give 3.08 g (quant.) of **7a**, n_D^{21} 1.4705; $[\alpha]_D^{21}$ -31.4° (c=1.17, *n*-pentane); νmax 3090 (w), 1620 (w), 1250 (s), 1110 (s), 1085 (s), 1005 (m), 915 (m), 835 (s) cm^{-1}; δ (CCl_4) 0.03 (3H, s), 0.04 (3H, s), 0.94 (15H, s), 1.30~1.90 (2H, m), 1.68 (3H, s), 1.90~2.40 (2H, m), 3.49 (1H, m), 4.92 (1H, dd, J= 3, 18Hz), 5.21 (1H, dd, J= 3, 11Hz), 6.05 (1H, dd, J= 11, 18Hz). (Found: C, 72.96; H, 11.30. Calc for $C_{17}H_{32}OSi$: C, 72.79; H, 11.50 %).

Diels-Alder reaction (route A): A diastereomeric mixture of dimethyl (6S)-6-t-butyldimethylsilyloxy-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **8a** and **9a**. A mixture of the diene **7a** (3.0 g, 10.7 mmol) and freshly distilled dimethyl acetylenedicarboxylate (2.0 ml, 16.3 mmol) was heated under Ar in a sealed tube at 110° for 30 h. After cooling, the reaction mixture was chromatographed over neutral Al_2O_3 (grade IV) to give 3.50 g of the mixture of **8a**, **9a** and a small amount of dimethyl acetylenedicarboxylate. Since 0.60 g of **7a** was recovered, the yield of the crude mixture of **8a** and **9a** was 97 %. The oily mixture of **8a** and **9a** was used in the next step without further purification and showed the following physical properties: νmax 1735 (s), 1680 (w), 1645 (w), 1260 (s), 1120 (s), 1095 (s), 1040 (s), 940 (m), 890 (s), 840 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.03 (6H, s), 0.85 (4.5H, s), 0.91 (4.5H, s), 1.10 (3H, s), 1.14 (1.5H, s), 1.17 (1.5H, s), 1.43 (3H, s), 1.10~2.30 (4H, m), 2.76 (0.5H, dd, J= 3, 23Hz), 2.80 (0.5H, dd, J= 3, 23Hz), 3.15 (1H, dd, J= 5, 23Hz), 3.27 (0.5H, m), 3.48 (0.5H, m), 3.74 (3H, s), 3.78 (1.5H, s), 3.80 (1.5H, s), 5.64 (0.5H, dd, J=3, 5 Hz), 5.77 (0.5H, dd, J=3, 5 Hz).

Dimethyl (6S,8aS)-3,5,6,7,8,8a-hexahydro-6-hydroxy-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **8b** and (6S,8aR)-isomer **9b**. A soln of the crude mixture of **8a** and **9a** (3.40 g, 8.0 mmol) in 46 % aq. HF-MeCN (1:60, 100 ml) was stirred for 1 h 40 min at room temp. Subsequently $NaHCO_3$ powder (5 g) was added to the stirred soln. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by medium pressure LC employing a Merck Lobar®column (Grösse C). Elution with *n*-pentane-ether (3:2) gave less polar **8b** [672 mg (27 %) of prisms after recrystallization from *n*-pentane-ether (3:10)], m.p. 118.0~119.0°; $[\alpha]_D^{21.5}$ -30.7° (c=1.15, $CHCl_3$); νmax 3590 (m), 1735 (s), 1715 (s), 1670 (w), 1640 (w), 1270 (s), 1255 (s), 1205 (m), 1080 (m), 1070 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.14 (3H, s), 1.22 (3H, s), 1.43 (3H, s), 1.20~2.00 (5H, m), 2.85 (1H, dd, J=2.6, 22.7 Hz), 3.13 (1H, dd, J=5.3, 22.7 Hz), 3.31 (1H, br), 3.74 (3H, s), 3.80 (3H, s), 5.80 (1H, dd, J=2.6, 5.3 Hz). (Found: C, 66.48; H, 7.80. Calc for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85 %). Further elution gave more polar **9b** [676 mg (27 %) of needles after recrystallization from *n*-pentane-ether (1:1)], m.p. 104.5~105.6°; $[\alpha]_D^{21}$ +39.9° (c=1.90, $CHCl_3$); νmax 3330 (m), 1740 (s), 1720 (s), 1660 (w), 1630 (w), 1255 (s), 1200 (m), 1060 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.22 (6H, s), 1.47 (3H, s), 1.00~2.20 (5H, m), 2.83 (1H, dd, J=2.5, 22.5 Hz), 3.17 (1H, dd, J=5.3, 22.5 Hz), 3.54 (1H, br), 3.74 (3H, s), 3.80 (3H, s), 5.75 (1H, dd, J= 2.5, 5.3 Hz). (Found: C, 65.89; H, 7.63. Calc for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85 %).

Diels-Alder reaction (route B): (S)-3-Ethenyl-2,2,4-trimethyl-3-cyclohexenol **7b**. A soln of the silyl ether **7a** (1.33 g, 4.74 mmol) in 46 % aq HF-MeCN (1:60, 70 ml) was stirred at room temp for 1 h. Subsequently Et_3N (4.5 ml) was added to the reaction mixture and the resulting soln was concentrated *in vacuo*. The residue was diluted with ether and filtered through neutral Al_2O_3 (grade IV) column. The column was washed with ether. The combined filtrate and washings were concentrated and the residue was distilled to give 584 mg (74 %) of **7b**, b.p. 115~118°/13 Torr; n_D^{18} 1.5035; $[\alpha]_D^{18}$ -53.4° (c=1.34, ether); νmax 3410 (m), 3100 (w), 2990 (s), 1620 (w), 1050 (s), 1005 (s), 920 (s) cm^{-1}; δ (CCl_4) 0.95 (3H, s), 1.01 (3H, s), 1.65 (3H, s), 1.30~1.90 (3H, m), 1.90~2.40 (2H, m), 3.40 (1H, m), 4.95 (1H, dd, J=3, 18 Hz), 5.23 (1H, dd, J=3, 12 Hz), 6.11 (1H, dd, J=12, 18 Hz). (Found: *m/z* 166.1371. Calc for $C_{11}H_{18}O$: 166.1358).

Diels-Alder reaction of **3b** with dimethyl acetylenedicarboxylate to provide **8b** and **9b**. The diene **7b** (560 mg, 3.37 mmol) was heated with 1.0 ml (8.1 mmol) of dimethyl acetylenedicarboxylate under Ar in a sealed tube for 30 h at 110°. After cooling, the mixture was chromatographed over SiO_2 (Merck Kieselgel 60) to recover the unreacted **3b** (87 mg, 16 %) and to give the mixture of **8b** and **9b**. The mixture was further purified by medium pressure LC followed by recrystallization as mentioned in route A to give 277 mg (32 %) of **8b** and 311 mg (30 %) of **9b**. Their IR and ^1H-NMR data were identical with those of **8b** and **9b** prepared *via* route A, respectively.

Dimethyl (1R,6S,8aR)-1,5,6,7,8,8a-hexahydro-6-hydroxy-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **14a**. A soln of **8b** (502 mg, 1.63 mmol) and DBU (100 μl 1) in dry THF (15 ml) was stirred and heated under reflux under Ar for 3 h. After cooling, the mixture was concentrated *in vacuo*. The residue was diluted with ether and filtered through SiO_2 (2 g) to remove DBU. The column was washed with ether. The combined filtrate and washings were concentrated *in vacuo* to give 520 mg of crude

14a as a colorless oil, νmax 3550 (m), 1740 (s), 1715 (s), 1640 (w), 1570 (m), 1275 (s) cm^{-1}; δ (CCl_4) 1.09 (6H, s), 1.20 (3H, s), 1.30~2.00 (4H, m), 2.41 (1H, br), 3.18 (1H, d, J=3 Hz), 3.30 (1H, m), 3.62 (3H, s), 3.65 (3H, s), 6.02 (1H, d, J=7 Hz), 6.87 (1H, dd, J=3, 7 Hz). This was employed in the next step without further purification.

Dimethyl (1R,4aR,6S,8aS)-1,4,4a,5,6,7,8,8a-octahydro-6-hydroxy-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **10a**. 10 % Pd-C (50 mg) was added to a soln of crude **14a** (520 mg, 1.69 mmol) in MeOH (20 ml) and the suspension was stirred under H_2 at room temp until **14a** disappeared on monitoring TLC. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) and the resulting crude **10a** was recrystallized from n-pentane-ether (4:1) to give 308 mg of **10a** as prisms. Chromatography of the mother liquor provided a further 98 mg of **10a** (total yield 80 % from **8b**), m.p. 76.0~77.0°; $[\alpha]_D^{20.5}$ -20.6° (c=1.82, $CHCl_3$); νmax 3550 (s), 1740 (s), 1710 (s), 1670 (m), 1265 (s), 1055 (s), 840 (w) cm^{-1}; δ ($CDCl_3$) 0.89 (3H, s), 0.91 (3H, s), 1.01 (3H, s), 1.00~2.00 (6H, m), 2.00~2.50 (2H, m), 3.15 (1H, m), 3.25 (1H, br), 3.66 (3H, s), 3.68 (3H, s), 7.05 (1H, m). (Found: C, 65.59; H, 8.33. Calc for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44 %).

Dimethyl (1R,4aS,8aS)-1,4,4a,5,8,8a-hexahydro-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **16**. To a stirred and ice-cooled soln of **10a** (250 mg, 0.805 mmol) and DMAP (590 mg, 4.83 mmol) in dry CH_2Cl_2 (7.5 ml) was added TfCl (214 μl, 2.01 mmol) slowly and dropwise under Ar. The stirring was continued for 15 min at 0° and for 15 min at room temp. The mixture was poured into water and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji-Davison, BW-820 MH) to give 202 mg (86 %) of **16** as a pale yellow oil. This was employed in the next step without further purification and showed the following physical properties: νmax 1740 (s), 1720 (s), 1660 (m), 1430 (s), 1260 (s), 730 (m) cm^{-1}; δ ($CDCl_3$) 0.87 (3H, s), 0.97 (3H, s), 1.00 (3H, s), 1.67 (1H, m), 1.90~2.60 (4H, m), 3.27 (1H, m), 3.68 (3H, s), 3.70 (3H, s), 3.20~3.80 (2H, m), 7.11 (1H, m).

Dimethyl (1R,4aS,8aS)-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **17**. 10 % Pd-C (10 mg) was added to a soln of **16** (200 mg, 0.68 mmol) in MeOH (10 ml) and the suspension was stirred under H_2 at room temp. The reaction was monitored by GLC for the disappearance of **16** and the formation of the desired product **17**. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji-Davison, BW-820 MH) and the resulting crude **17** was recrystallized from n-hexane to give 99 mg of **17** as rods. Chromatography of the mother liquor provided a further 80 mg of **17** (total yield 89 %), m.p. 88.1~89.1°; $[\alpha]_D^{22}$ -31.5° (c=1.25, $CHCl_3$); νmax 1725 (s), 1660 (m), 1280 (s), 1260 (s), 1205 (s), 1180 (s), 1080 (m), 830 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.88 (3H, s), 0.90 (3H, s), 0.93 (3H, s), 1.24 (1H, dd, J=5.8, 11.0 Hz), 1.10~1.70 (5H, m), 1.85 (1H, dm, J= 12.0 Hz), 2.00~2.50 (2H, m), 3.20 (1H, m), 3.66 (3H, s), 3.70 (3H, s), 7.05 (1H, m). (Found: C, 69.39; H, 8.90. Calc for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90 %).

(1R,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-1,2-bis(hydroxymethyl)-5,5,8a-trimethylnaphthalene **18a**. To a stirred and ice-cooled suspension of LAH (20 mg, 0.527 mmol) in dry ether (4 ml) was added dropwise a soln of **17** (79 mg, 0.268 mmol) in dry ether (1 ml) under Ar. The stirring was continued for 30 min at 0°. The mixture was poured into 5 % aq H_2SO_4 (5 ml)-ice and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji-Davison, BW-820 MH) and recrystallized from n-hexane to give 52.6 mg (82 %) of **18a** as rods, m.p. 69.5~70.5°; $[\alpha]_D^{22}$ -6.3° (c=0.96, $CHCl_3$); νmax 3310 (s), 1670 (w), 1390 (s), 1370 (s), 1050 (s), 990 (s), 950 (s), 840 (m) cm^{-1}; δ (100 MHz, $CDCl_3$, after D_2O exchange) 0.75 (3H, s), 0.87 (6H, s), 0.90~1.80 (7H, m), 1.80~2.30 (3H, m), 3.64 (1H, dd, J=7.9, 10.9 Hz), 3.87 (1H, dd, J=2.3, 10.9 Hz), 3.94 (1H, d, J=12.0 Hz), 4.31 (1H, d, J=12.0 Hz), 5.77 (1H, m). (Found: C, 75.39; H, 10.94. Calc for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99 %). The optical purity of **18a** was shown to be ~100 % by HPLC analysis of its bis-(R)-MTPA ester **18b** prepared as usual: HPLC (Column, NUCLEOSIL®50-5, 25 cm x 4.6 mm ϕ; Solvent, n-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detected at 254 nm) Rt 36.2 min (single peak).

(1R,4aS,8aS)-1,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalene-1,2-dicarbaldehyde (Polygodial) (-)-**1**. A soln of the Swern reagent was prepared by the dropwise addition of a soln of DMSO (197 μl, 2.77 mmol) in dry CH_2Cl_2 (0.4 ml) to a stirred and cooled soln of $(COCl)_2$ (119 μl, 1.39 mmol) in dry CH_2Cl_2 (3 ml) at -50° under Ar. To the stirred and cooled soln of the Swern reagent was added dropwise a soln of **18a** (40 mg, 0.168 mmol) in dry CH_2Cl_2 (0.8 ml) at -50°. The mixture was stirred for 1 h at -50°. Et_3N (258 μl, 1.85 mmol) was added to the mixture and the temp was allowed to rise gradually to room temp during 1 h. The reaction mixture was poured into water and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (Fuji-Davison, BW-820 MH) to give 32 mg of crude (-)-**1**. This was recrystallized from n-hexane to give 24.6 mg (63 %) of (-) -**1** as needles, m.p. 56.9~57.3°; $[\alpha]_D^{22.5}$ -133° (c=0.88, EtOH); νmax 2850 (w), 2750 (w), 1725 (s), 1710 (m), 1685 (s), 1650 (m), 980 (w), 840 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.93 (3H, s), 0.95 (3H, s), 0.96 (3H, s), 1.27 (1H, dd, J=5.7, 10.9 Hz), 1.00~2.00 (6H, m), 2.35 (1H, dddd, J=2.8, 3.7, 10.9, 20.2 Hz), 2.48 (1H, ddt, J=2.3, 20.2, 5.5 Hz), 2.81 (1H, m), 7.13 (1H, m), 9.47 (1H, s), 9.54 (1H, d, J=4.4 Hz); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 15.24, 18.02, 21.91, 25.21, 33.08 (s and q overlap in the OFR decoupled spectrum), 36.86, 39.55, 41.71, 48.97, 60.29, 138.24, 154.27, 193.18, 201.86; MS: m/z 234 (M^+, 4 %), 206 (100 %, base peak), 191 (48 %), 121 (90 %), 109 (80 %). (Found: C, 76.94; H, 9.31. Calc for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46 %). The spectral properties listed above were in good accord with those reported for (-)-1[1,2] or (±)-1.[7,8]

Dimethyl (1R,6S,8aS)-1,5,6,7,8,8a-hexahydro-6-hydroxy-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **15a**. In the same manner as described for the preparation of **14a**, **9b** (514 mg, 1.67 mmol) was treated with DBU to give crude **15a**. Recrystallization of the crude product from n-hexane-ether (1:1) gave 487 mg (95 %) of pure **15a** as plates, m.p. 152.5~153.5°; $[\alpha]_D^{21}$ +230° (c=1.60, $CHCl_3$); νmax 3550 (m), 1735 (s), 1700 (s), 1635 (w), 1570 (s), 1280 (s) cm^{-1}; δ ($CDCl_3$) 1.15 (3H, s), 1.19 (3H, s), 1.22 (3H, s), 1.00~2.30 (5H, m), 3.40 (1H, d, J=3 Hz), 3.55 (1H, m), 3.68 (6H, s), 6.00 (1H, d, J=6 Hz), 6.94 (1H, dd, J=3, 6 Hz). (Found: C, 66.22; H, 7.79. Calc for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85 %).

Dimethyl (1*S*,8a*S*)-1,5,8,8a-tetrahydro-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **21'**. In the same manner as described for the preparation of **16**, **15a** (424 mg, 1.37 mmol) was treated with TfCl and DMAP to give crude **21'**. The crude product was chromatographed (SiO_2) and recrystallized from *n*-hexane-EtOAc (20:1) to give 322 mg (81 %) of pure **21'** as rods, m.p. 64.0~64.5°; $[\alpha]_D^{21}$ +244° (c=1.14, $CHCl_3$); νmax 1735 (s), 1710 (s), 1660 (w), 1640 (w), 1580 (m), 1275 (s), 715 (m) cm^{-1}; δ ($CDCl_3$) 1.08 (3H, s), 1.15 (3H, s), 1.21 (3H, s), 1.90~2.30 (2H, m), 3.50 (1H, d, J=3 Hz), 3.68 (6H, s), 3.20~3.80 (2H, m), 5.95 (1H, d, J= 6 Hz), 6.95 (1H, dd, J=3, 6 Hz). (Found: C, 70.46; H, 7.68 . Calc for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64 %).

Dimethyl (1*S*,4a*R*,8a*R*)-1,4,4a,5,6,7,8,8a-octahydro-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **17'**. 10 % Pd-C (15 mg) was added to a soln of **21'** (300 mg, 1.03 mmol) in MeOH (20 ml) and the suspension was stirred under H_2 at room temp until the starting material **21'** and a partly reduced product disappeared on GLC. (The double bond at C-4(4a) was hydrogenated first.) The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Fuji-Davison, BW-820 MH) and the resulting crude **17'** was recrystallized from *n*-hexane to give pure **17'** (194 mg) as rods. Chromatographic purification of the mother liquor followed by recrystallization provided a further 20 mg of **17'** (total yield 70 %), m.p. 88.2~88.9°; $[\alpha]_D^{21}$ +33.1° (c=1.24, $CHCl_3$). Its IR and ^{1}H-NMR spectra were identical with those of **17**. (Found: C, 69.25; H, 8.87. Calc for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90 %).

(1*S*,4a*R*,8a*R*)-1,4,4a,5,6,7,8,8a-Octahydro-1,2-bis(hydroxymethyl)-5,5,8a-trimethylnaphthalene **18a'**. In the same manner as described for the preparation of **18a**, **17'** (170 mg, 0.577 mmol) was reduced to give 110 mg (80 %) of **18a'** as rods, m.p. 69.0~70.0°; $[\alpha]_D^{22}$ +6.5° (c=0.83, $CHCl_3$). Its IR and ^{1}H-NMR spectra were identical with those of **18a**. (Found: C, 75.60; H, 10.91. Calc for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99 %). The optical purity of **18a'** was shown to be ~100 % by HPLC analysis of its bis-(*R*)-MTPA ester **18b'** prepared as usual: HPLC (Column, NUCLEOSIL®50-5, 25 cm x 4.6 mm φ ; Solvent, *n*-hexane-THF-MeOH (10000:100:1), 1.1 ml/min; Detected at 254 nm) Rt 33.0 min (single peak).

(1*S*,4a*R*,8a*R*)-1,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalene-1,2-dicarbaldehyde (The enantiomer of natural Polygodial) (+)-**1'**. In the same manner as described for the preparation of (-)-**1**, 110 mg (0.461 mmol) of (+)-**18a'** afforded 78 mg (72 %) of (+)-**1'** as needles, m.p. 57.0~57.5°; $[\alpha]_D^{22.5}$ +135° (c=0.92, EtOH). Its IR, ^{1}H- and ^{13}C-NMR and mass spectral data were identical with those of (-)-**1**. (Found: C, 76.81; H, 9.38. Calc for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46 %).

Direct preparation of **10a** from **8b** employing Ley's procedure. 10 % Pd-C (5 mg) was added to a soln of **8b** (47 mg, 0.15 mmol) in 0.05 % conc HCl-MeOH (7 ml). The suspension was stirred under H_2 at room temp until **8b** disappeared on monitoring by TLC. To the soln was added $NaHCO_3$ powder (0.1 g) and the mixture was filtered through Celite, and the Celite layer was washed with ether. The combined filtrate and washings were concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 30 mg (63 %) of **10a** as an oil. The ^{1}H-NMR spectral data of **10a** were identical with those of **10a** obtained *via* two-step procedure described above.

(1*R*,4a*R*,6*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-1,2-hydroxymethyl-5,5,8a-trimethylnaphthalene **11**. To a stirred soln of **10a** (5.8 mg, 0.017 mmol) in dry C_5H_5N (0.5 ml) was added TsCl (10 mg, 0.052 mmol) and the mixture was stirred overnight at room temp. The mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude **10b** (9.0 mg), νmax 1740 (s), 1720 (s), 1660 (w), 1600 (w), 1355 (s), 1260 (s), 1190 (s), 1170 (s) cm^{-1}. To a stirred and ice-cooled soln of **10b** (9.0 mg) in dry ether (1 ml) was added LAH (10 mg, 0.26 mmol) and the mixture was stirred overnight at room temp. The mixture was poured into 5 % aq H_2SO_4-ice and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried (Na_2SO_4) and concentrated *in vacuo*. A main product was isolated by prep TLC (Merck Kieselgel 60 F-254) and identified as **11** by comparing its ^{1}H-NMR data with those reported for (±)-**11** by Ley *et al.*[8] (1.5 mg of solid, 34 % from **10a**), νmax 3350 (s), 1675 (w), 1095 (m), 1060 (s), 1020 (s), 995 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.77 (3H, s), 0.86 (3H, s), 0.99 (3H, s), 1.00~1.90 (5H, m), 1.90~2.20 (4H, m), 2.80 (2H, br), 3.30 (1H, m), 3.70 (1H, dd, J=7.5, 10.6 Hz), 3.70~4.10 (2H, m), 4.33 (1H, d, J=12.0 Hz), 5.82 (1H, m).

Direct hydrogenation of **9b** employing Ley's procedure (to give **13**). In the same manner as described for the direct preparation of **10a** from **8b**, **9b** (16 mg, 0.052 mmol) was hydrogenated only to give oily **13** (14 mg, 87 %) as the main product, νmax 3570 (m), 1725 (s), 1640 (m), 1255 (s), 1030 (m), 735 (m) cm^{-1}; δ ($CDCl_3$) 0.86 (3H, s), 1.01 (3H, s), 1.20 (3H, s), 1.00~2.70(10H, m), 3.21 (1H, m), 3.62 (3H, s), 3.73 (3H, s).

Dimethyl (1*S*,4a*S*,6*S*,8a*R*)-1,4,4a,5,6,7,8,8a-octahydro-6-hydroxy-5,5,8a-trimethylnaphthalene-1,2-dicarboxylate **12**. In the same manner as described for the preparation of **10a** from **14a**, **15a** (20 mg, 0.065 mmol) was hydrogenated to give crude **12**, which was purified by prep TLC (Merck Kieselgel 60 F-254) followed by recrystallization from *n*-hexane-ether (3:1) to give 19 mg (94 %) of pure **12** as needles, mp 144.5~145.0°; νmax 3540 (s), 1720 (s, sh), 1710 (s), 1660 (m), 1265 (s), 1070 (m), 830 (m) cm^{-1}; δ ($CDCl_3$) 0.94 (3H, s), 1.00 (3H, s), 1.02 (3H, s), 1.00~2.00 (6H, m), 2.00~2.50 (2H, m), 3.31 (1H, m), 3.48 (1H, br), 3.70 (3H, s), 3.72 (3H, s), 7.09 (1H, m).

Dehydration and isomerization of **9b** to give **22'** (and **21'**). To a stirred soln of **9b** (36 mg, 0.12 mmol) in dry C_5H_5N (0.5 ml) was added dropwise TfCl (26 μl, 0.24 mmol) and the mixture was stirred overnight at room temp. It was poured into water and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC (Merck Kieselgel 60 F-254) to give 35 mg (82 %) of **9c**; νmax 1730 (s), 1670 (w), 1640 (w), 1200 (s), 1130 (s), 800 (m) cm^{-1}. A soln of **9c** (33 mg, 0.075 mmol), (n-Bu)$_4$NBr (120 mg, 0.37 mmol) and DBU (67 μl, 0.45 mmol) in dry THF (1 ml) was stirred and heated under reflux for 5 h under Ar. The mixture was filtered through SiO_2 (1 g, Merck Kieselgel 60) and the column was washed with ether. The combined filtrate and washings were concentrated *in vacuo*. The residue was purified by prep TLC (Merck Kieselgel 60 F-254) to give 20 mg (85

%) of **22'**; νmax 1740 (s), 1715 (s), 1650 (w), 720 (m) cm^{-1}; δ ($CDCl_3$) 1.14 (6H, s), 1.22 (3H, s), 1.80~2.20 (2H, m), 3.43 (1H, s), 3.60 (3H, s), 3.72 (3H, s), 5.20~5.80 (2H, m), 5.98 (1H, d, J=6 Hz), 7.18 (1H, d, J=6 Hz). Weak signals at 1.09 (s), 3.69 (s), 6.96 (dd) indicate the presence of **21'** in the ratio **22'**:**21'**=4:1.

Treatment of **14a** with TfCl and DMAP (to give **19**, **20**, and **21**). To a stirred and ice-cooled soln of **14a** (32 mg, 0.10 mmol) and DMAP (36 mg, 0.29 mmol) in dry CH_2Cl_2 (1.5 ml) was added dropwise TfCl (36 μl, 0.33 mmol) and the mixture was stirred at room temp for 1 h. The mixture was filtered through SiO_2 (1 g) and the SiO_2 column was washed with ether. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 10 mg (33 %) of the mixture of **20** and **21** (2:1) and 14 mg (46 %) of **19**. They showed the following spectral properties, **20** + **21**: νmax 3100 (w), 2980 (s), 2890 (m), 1740 (s), 1715 (s), 1640 (w), 1615 (w), 1440 (s), 1275 (s), 900 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.99 (2H, s), 1.06 (2H, d, J=6.6 Hz), 1.11 (1H, s), 1.19 (1H, s), 1.26 (1H, s), 1.20~2.00 (2.7H, m), 2.00~2.25 (0.67H, m), 2.65 (0.67H, m), 3.56 (1H, d, J=2.9 Hz), 3.73 (6H, s), 4.88 (0.67H, d, J=2.5 Hz), 5.09 (0.67H, d, J=2.5 Hz), 5.30~5.80 (0.67H, m), 6.00 (0.33H, d, J=12.2 Hz), 6.08 (0.67H, d, J=12.2 Hz), 6.93 (0.67H, dd, J=2.9, 12.2 Hz), 6.98 (0.33H, dd, J=2.9, 12.2 Hz). **19**: νmax 2970 (s), 1740 (s), 1710 (s), 1615 (w), 1265 (s), 840 (m), 765 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.03 (3H, s), 1.15 (1H, m), 1.80 (3H, s), 1.85 (3H, s), 1.60~2.50 (3H, m), 3.48 (1H, d, J=2.8 Hz), 3.73 (6H, s), 5.88 (1H, d, J=6.4 Hz), 7.05 (1H, dd, J=2.8, 6.4 Hz).

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