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Journal of Molecular Catalysis B: Enzymatic 22 (2003) 161–172
JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC
www.elsevier.com/locate/molcatb

Total synthesis of (−)-(8*R*, 10*S*)- and (+)-(8*S*, 10*R*)-8-hydroxypolypoda-13,17,21-triene based on enzymatic resolution

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Received 14 January 2003; received in revised form 3 February 2003; accepted 19 February 2003

Abstract

The total synthesis of (−)-(8*R*, 10*S*)- and (+)-(8*S*, 10*R*)-8-hydroxypolypoda-13,17,21-triene (**1**) was achieved based on the kinetic resolution of (±)-epoxy-albicanol (**3**) using lipase. The absolute structure of natural product (**1**) was synthetically again confirmed to be (5*S*, 8*R*, 9*R*, 10*S*)-8-hydroxypolypoda-13,17,21-triene.

Keywords: Lipase; *Candida rugosa*; Enzymatic resolution; Enantioselective acetylation; Total synthesis

1. Introduction

Novel triterpene alcohol 8α-hydroxypolypoda-13, 17,21-triene (**1**) was isolated from a fern, *Polypodiodes fomtosana* [1]. The occurrence of this type of alcohol from nature is important from the mechanistic point of view of the biosynthesis of lanosterol from 2,3-oxidosqualene via a cationic intermediate. The structure of **1** including its absolute configuration has been elucidated as 8α-hydroxypolypoda-13,17,21-triene on the basis of spectral and chemical evidences [1]. Total synthesis of (±)-**1** was achieved based on the mercury(II) trifluoromethanesulphonate–amine complex-induced cyclization [2]. In order to reconfirm the absolute structure of natural product (**1**), the synthesis of both enantiomers of **1** was necessitated because of the low value of optical rotation ($[\alpha]_D$ − 0.9) [1]. The key optically active intermediate for the synthesis of (−)-**1** and (+)-*ent*-**1** appeared to be (10*S*)-epoxy-alcohol (**3**) and (10*R*)-**3**, respectively, which can be obtained based on the enzymatic resolution of racemic (±)-**3** produced by epoxidation of (±)-albicanol (**2**) [3] (Scheme 1).

An outline of the synthesis of (8*R*, 10*S*)-8-hydroxypolypoda-13,17,21-triene (**1**) from chiral epoxy alcohol (10*S*)-**3** is depicted in Scheme 2, which involves three carbons elongation by Wittig condensation, the preparation of α,β-unsaturated ester **10** by the second Wittig condensation followed by coupling reaction of the sulfone **13** and *trans*-geranylbromide. The synthesis of (+)-*ent*-**1** from (10*R*)-**3** is fundamentally carried out in the same way as for the synthesis of (8*R*, 10*S*)-**1** and the synthetic scheme of *ent*-**1** was omitted. In this paper, we describe the first synthesis of (8*R*, 10*S*)- and (8*S*, 10*R*)-8-hydroxypolypoda-13,17,21-triene (**1**)

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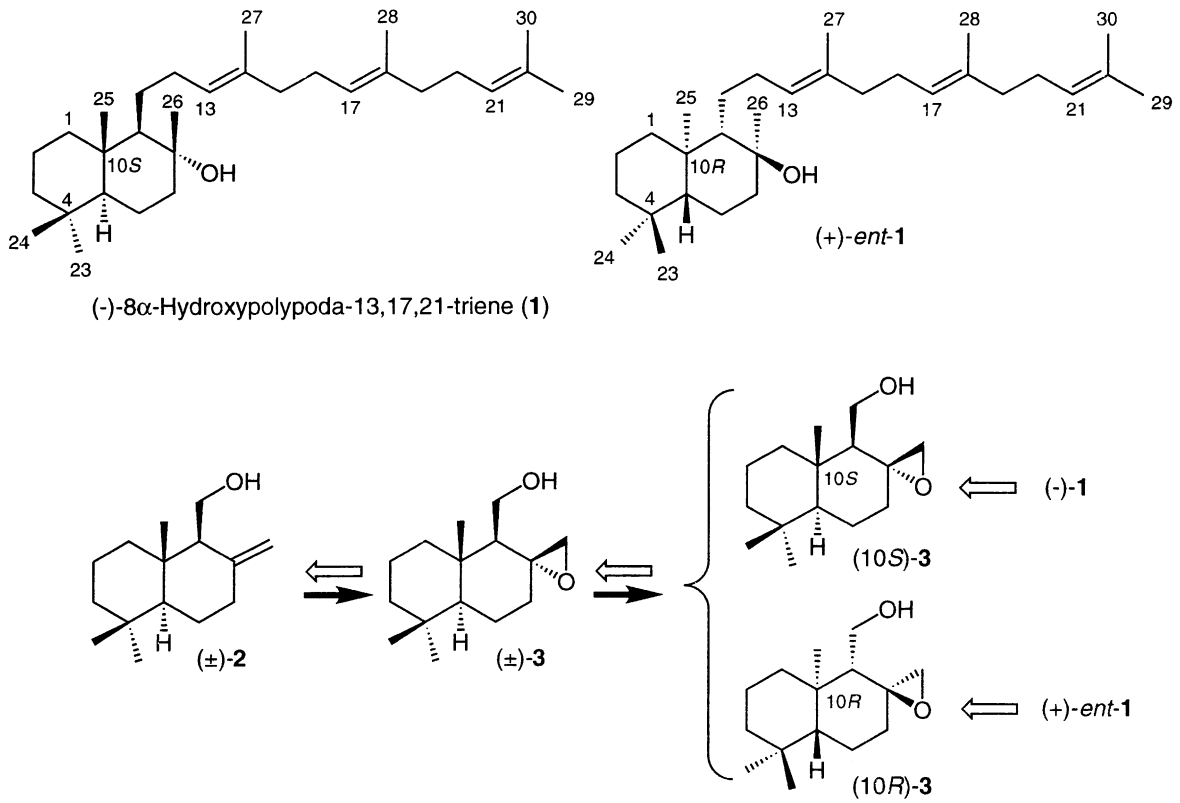
doi:10.1016/S1381-1177(03)00028-6



Scheme 1.

based on the kinetic resolution of (±)-epoxy-albicanol (**3**) using lipase.

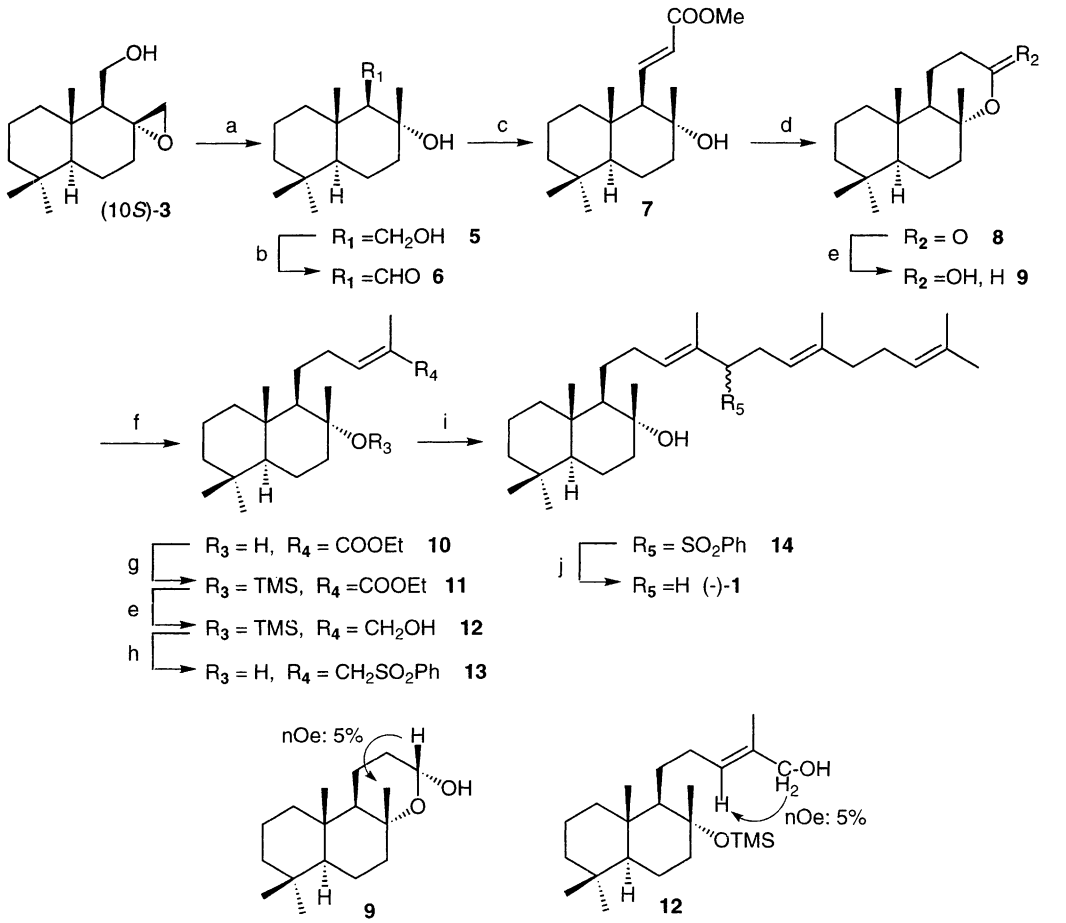
2. Methods and results

2.1. Analytical methods

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. High-resolution mass spectra (HRMS) and 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.

2.2. Epoxidation of (±)-albicanol (2)-(synthesis of (±)-3)

A mixture of (±)-albicanol (**2**) [4] (15.1 g, 68 mmol) and *m*-chloroperbenzoic acid (MCPBA, 19.9 g, 116 mmol) in CH_2Cl_2 (200 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with ether and the organic layer was washed with 10% aqueous $Na_2S_2O_3$, 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (150 g, *n*-hexane:AcOEt = 20:1) to give a colorless plate (±)-**3** (15.86 g, 98%). Recrystallization of (±)-**3** from *n*-hexane provided a colorless plate (±)-**3**. (±)-**3**: mp 58 °C. NMR data of (±)-**3** were identical with those of the reported (−)-**3** [3].



a; $LiAlH_4$ / Et_2O b; $(COCl)_2$ / DMSO c; Ph_3P=CHCOOMe / benzene d; H_2 / 20% $Pd(OH)_2$-C / MeOH
e; $HAl(i\text{-}Bu)_2$ / toluene f; Ph_3P=C(Me)COOEt / benzene g; TMSOTf /$(i\text{-}Pr)_2NEt$ / Et_3N
h; 1) MsCl / LiCl / 2,6-luthidine / $NaHCO_3$ / DMF 2) $PhSO_2Na{\cdot}2H_2O$ / DMF
i; LDA / *trans*-geranylbromide / THF j; 5% Na-Hg / MeOH

Scheme 2.

2.3. Acetylation of (±)-3

A solution of (±)-**3** (195 mg, 0.82 mmol) in pyridine (1 ml), 4-*N*,*N*-dimethylaminpyridine (DMAP, 30 mg, 0.2 mmol) was treated with Ac_2O (0.2 g, 2 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt = 20:1) to give a colorless oil (±)-**4** (219 mg, 95%). (±)-**4**: IR (neat): 1735 cm^{-1} (OAc); NMR: δ 0.84 (3H, s), 0.89 (3H, s), 0.91 (3H, s), 1.08 (1H, dd, J = 2.5, 12 Hz), 1.16–1.24 (2H, m), 1.38–1.63 (6H, m), 1.79–1.98 (3H, m), 2.01 (3H, s), 2.56 (1H, dd, J = 1, 4 Hz), 2.64 (1H, dd, J = 2, 4 Hz), 3.75 (1H, dd, J = 3.5, 11.5 Hz), 3.96 (1H, dd, J = 6, 11.5 Hz). Anal. found: C, 72.77; H, 9.83. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%. FAB MS *m*/*z*: 281 ($M^+ + 1$).

2.4. (R)-MTPA ester formation from (±)-3

For the purpose of determining the enantiomeric excess (ee) of the enzymatic reaction products, racemate (±)-**3** was converted to the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate (*R*)-MTPA esters). To a stirred solution of (±)-**3** (112 mg, 0.47 mmol) in pyridine (2 ml) was added (S)-α-methoxy-α-tifluoromethylphenylacetyl chloride [5,6] ((*S*)-MTPACl; 131 mg, 0.55 mmol) and DMAP (60 mg), and the whole was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 2 M aqueous HCl, 7% aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 20: 1) to give a diastereomeric mixture of (10*S*)-(*R*)- and (10*R*)-(*R*)-MTPA esters (211 mg, 99%). The signal due to the methoxyl proton appeared in distinctly different fields [(*R*)-MTPA esters from (±)-**3**: 3.52 (d, $J = 0.5$ Hz) and 3.55 (s) of the 400 MHz NMR spectrum. Diastereomeric mixture of (10*S*)-(R)- and (10*R*)-(*R*)-MTPA esters: FAB MS *m/z*: 455 ($M^+ + 1$).

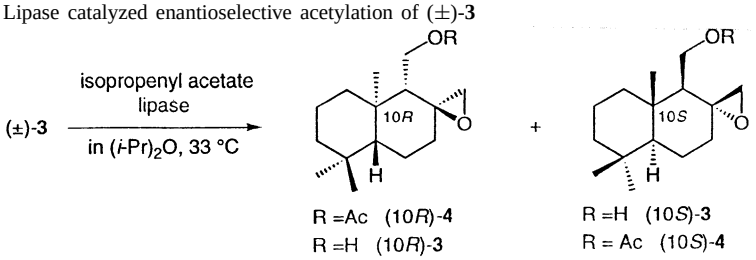
2.5. Enantioselective acetylation of (±)-3

From a screening experiment using various kinds of lipase, the effective lipases were as follows: MY-30 from *Candida rugosa*, PL-266 from *Alcaigenes* sp., Amano P from *Pseudomonas* sp. Enzymatic acetylation of (±)-**3** was performed under the following condition (entries 1–5). Determination of the enantiomeric excess (ee) of the enzymatic reaction products was carried out by the method mentioned in Section 2.6 in this text. The results were shown in Table 1.

(1) Table 1, entry 1: A suspension of (±)-**3** (149 mg, 0.63 mmol), isopropenyl acetate (586 mg, 6 mmol) and lipase MY-30 (300 mg) in diisopropyl ether (30 ml) was incubated at 33 °C for 4 days. After the reaction mixture was filtered, the precipitate was washed with AcOEt. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (10 g) to give (+)-**4** (91 mg, 52%, $[\alpha]_D^{27}$ +12.8 ($c = 1.04$, $CHCl_3$); corresponds to 83% ee) from *n*-hexane: AcOEt = 20:1 eluate and (−)-**3** (64 mg, 43%, $[\alpha]_D^{26}$ − 26.9 ($c = 0.92$, $CHCl_3$); corresponds to >99% ee) from *n*-hexane EtOAc = 10:1 eluate, respectively.

(2) Table 1, entry 2: A suspension of (±)-**3** (145 mg, 0.61 mmol), isopropenyl acetate (305 mg, 3.1 mmol) and lipase PL-266 (152 mg) in diisopropyl ether (30 ml) was incubated at 33 °C for 1 day. The reaction mixture was worked up in the same way as entry 1 to give (−)-**4** (73 mg, 43%, $[\alpha]_D^{25}$ − 15.2 ($c = 1.09$, $CHCl_3$): corresponds to 91% ee) and (+)-**3** (58 mg, 40%, $[\alpha]_D^{27}$ +26.1 ($c = 1.10$, $CHCl_3$); corresponds to >99% ee).

Table 1
Lipase catalyzed enantioselective acetylation of (±)-**3**



Entry	Substrate (g)	Lipase	Time (day)	Product	
1	(±)-**3** (0.149)	MY-30	4	(+)-(10*R*)-**4** (52%, 83% ee)	(−)-(10*S*)-**3** (43%, >99% ee)
2	(±)-**3** (0.145)	PL-266	1	(−)-(10*S*)-**4** (43%, 91% ee)	(+)-(10*R*)-**3** (40%, >99% ee)
3	(±)-**3** (0.186)	Amano P	16	(−)-(10*S*)-**4** (44%, 90% ee)	(+)-(10*R*)-**3** (40%, >99% ee)
4	(±)-**3** (15.383)	MY-30	2	(+)-(10*R*)-**4** (48%, 98% ee)	(−)-(10*S*)-**3** (50%, 91-% ee)
5	(−)-**3** (91% ee, 7.713)	MY-30	2	(−)-(10 *S*)-**4** (10%, 11% ee)	(−)-(10*S*)-**3** (80%, >99% ee)

(3) Table 1, entry 3: A suspension of (±)-**3** (186 mg, 0.78 mmol), isopropenyl acetate (271 mg, 2.8 mmol) and lipase Amano P (164 mg) in diisopropyl ether (30 ml) was incubated at 33 °C for 16 days. The reaction mixture was worked up in the same way as entry 1 to give (−)-**4** (96 mg, 44%, >90% ee) and (+)-**3** (74 mg, 40%, >99% ee).
(4) Table 1, entry 4: A suspension of (±)-**3** (15.383 g, 64.5 mmol), isopropenyl acetate (15 g, 150 mmol) and lipase MY-30 (8 g) in diisopropyl ether (400 ml) was incubated at 33 °C for 2 days. The reaction mixture was worked up in the same way as entry 1 to give (+)-**4** (8.639 g, 48%, $[\alpha]_D^{25}$ + 16.5 (c = 0.98, $CHCl_3$); corresponds to 98% ee) and (−)-**3** (7.744 g, 50%, 91% ee).
(5) Table 1, entry 5: A suspension of (−)-**3** (91% ee, 7.713 g, 32.4 mmol), isopropenylacetate (8 g, 2.8 mmol) and lipase MY-30 (4.03 g) in diisopropyl ether (150 ml) was again incubated at 33 °C for 2 days. The reaction mixture was worked up in the same way as entry 1 to give (−)-**4** (907 mg, 10, 11% ee) and (−)-**3** (6.151 g, 80%, >99% ee).

In the case of using MY-30, (+)-acetate **4** and unchanged (−)-**3** were obtained (entry 1), while PL-266 and Amano P afforded (−)-acetate **4** and unchanged (+)-**3** (entries 2 and 3). The absolute configuration at the C_{10}-position of (−)-**3** ($[\alpha]_D$ − 26.9 (c = 0.92, $CHCl_3$); entry 1) was determined to be *S* by the direct comparison with the sign of $[\alpha]_D$ of the reported (−)-(10*S*)-**3** ($[\alpha]_D$ − 28.8 (c = 1.0, $CHCl_3$)) [3], thence that of (+)-**4** was confirmed to be *R*.

2.6. General procedure of (R)-MTPA ester formation from enzymatic reaction products (alcohol and acetate)

(1) To a stirred solution of alcohol (ca. 20 mg) in pyridine (0.5 ml) was added (*S*)-MTPACl (ca. 30 mg) and DMAP (15 mg), and the whole was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as Section 2.4. to give quantitatively the corresponding (*R*)-MTPA ester. NMR analysis of the resulting (*R*)-MTPA ester made it possible to determine an ee of the optically active alcohol.
(2) Alkaline hydrolysis of acetate (73–96 mg) with K_2CO_3 in MeOH (ml) gave quantitatively the corresponding alcohol. To a stirred solution of the resulting alcohol (ca. 20 mg) in pyridine (0.5 ml) was added (S)-MTPACl (ca. 30 mg) and DMAP (15 mg), and the whole was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as (1) to give quantitatively the corresponding (*R*)-MTPA ester. NMR analysis of the resulting (*R*)-MTPA ester made it possible to determine an ee of the optically active acetate.

2.7. Alkaline hydrolysis of (+)-acetate (4)

A suspension of(+)-**4** (98% ee; 8.639 g. 30.8 mmol) and K_2CO_3 (5.23 g, 37.8 mmol) in MeOH (150 ml) was stirred for 6 h at room temperature. The reaction mixture was concentrated and the residue was diluted with brine and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue which was chromatographed on silica gel (100 g, *n*-hexane:AcOEt = 5:1) to give a colorless plate (+)-**3** (7.253 g, 98%). Recrystallization of (+)-**3** (98% ee) from *n*-hexane/AcOEt afforded enantiomerically pure colorless plate (+)-**3** (6.62 g, 90%). NMR data of were identical with those of the reported (−)-**3** [3].

2.8. $LiAlH_4$ reduction of (−)-(10S)-epoxy alcohol (3)

To a suspension of $LiAlH_4$ (1.02 g, 27 mmol) in Et_2O (40 ml), a solution of (−)-(10*S*)-**3** (5.272 g, 22.1 mmol) in Et_2O (10 ml) at 0 °C was added and the whole 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 crude crystal which was recrystallized from *n*-hexane/AcOEt to give a colorless powder (10*S*)-**5** (3.315 g). The mother liquor part was chromatographed on silica gel (50 g, *n*-hexane:AcOEt = 1:1) to give (10*S*)-**5** (1.948 g total weight; 5.263 g, 99%). (10*S*)-**5**: mp 127 °C. 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(911, 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. found: C, 75.02; H, 11.77. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%. FAB MS *m*/*z*: 241 ($M^+ + 1$).

2.9. $LiAlH_4$ reduction of (+)-(10R)-epoxy-alcohol (3)

To a suspension of $LiAlH_4$ (1.0 g, 22.4 mmol) in Et_2O (50 ml), a solution of (+)-**3** (5.33 g, 22.4 mmol) in Et_2O (50 ml) at 0 °C was added and the whole was stirred for 1.5 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of (10*S*)-**5** to afford (10*R*)-**5** (4.915 g, 91%). NMR data of (10*R*)-**5** were identical with those of (10*S*)-**5**.

2.10. Swern oxidation of (10S)-5

To a solution of dimethyl sulfoxide (DMSO; 7.65 g, 98 mmol) in CH_2Cl_2 (40 ml) was added oxalyl chloride (4.2 ml, 49 mmol) at −78 °C and the reaction mixture was stirred for 0.5 h. A solution of (10*S*)-**5** (4.445 g, 18.5 mmol) in CH_2Cl_2 (25 ml) was added to the above reaction mixture and the whole mixture was stirred for 0.5 h. Et_3N (30 ml, 228 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 (100 g, *n*-hexane:AcOEt = 5:1) to give a colorless oil (+)-**6** (3.835 g, 87%). (+)-**6**: IR (neat): 3340, 1738 cm^{-1}; $[\alpha]_D^{22} + 39.2$ ($c = 0.65$, $CHCl_3$); ^{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. found: C, 76.21; H, 11.02. Calcd. for $C_{15}H_{26}O_2$: C, 75.58;H, 10.99%.

2.11. Swern oxidation of (10R)-5

To a solution of dimethyl sulfoxide ($DMSO_4$ 6.3 g, 80 mmol) in CH_2Cl_2 (20 ml) was added oxalyl chloride (3.5 ml, 41 mmol) at −78 °C and the reaction mixture was stirred for 0.5 h. A solution of (10*R*)-**5** (4.865 g, 20.2 mmol) in CH_2Cl_2 (25 ml) was added to the above reaction mixture and the whole mixture was stirred for 0.5 h. Et_3N (20 ml, 155 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 worked up in the same way as for the preparation of (+)-**6** to afford (−)-**6** (4.62 g, 95%). $[\alpha]_D^{27} - 38.2$ ($c = 0.84$, $CHCl_3$). NMR data of (−)-**6** were identical with those of (+)-**6**.

2.12. Wittig condensation of (+)-6

To a solution of (+)-**6** (4.226 g, 17.7 mmol) in benzene (100 ml) was added a solution of methyl (triphenylphosphoranylidene) acetate (Ph_3P = CHCOOMe; 29.93 g, 89 mmol) in benzene (30 ml) and the whole was refluxed for 12 h with stirring. The reaction mixture was evaporated to give a residue, which was diluted with *n*-hexane. The precipitate was filtered off and the filtrate was again evaporated to give a crude crystal, which was recrystallized from *n*-hexane to afford colorless needles (+)-**7** (1.077 g). The mother liquor part was chromatographed on silica gel (40 g, *n*-hexane:AcOEt = 5: 1) to give a colorless crystal (+)-**7** (1.001 g, total; 2.09 g, 40%). (+)-**7**: mp 112 °C. IR (KBr): 3328, 1720 cm^{-1}; $[\alpha]_D^{24} + 13.2$ ($c = 1.29$, $CHCl_3$); ^{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, 5), 5.91 (1H, d, $J = 15.5$ Hz), 6.98 (1H, dd, $J = 11$, 15.5 Hz). ^{13}C-NMR: 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. found: C, 73.34; H, 10.52. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%. FAB MS *m*/*z*: 294 (M^+).

2.13. Wittig condensation of (−)-6

To a solution of (−)-**6** (4.62 g, 19.3 mmol) in benzene (100 ml) was added a solution of Ph_3P = CHCOOMe (41.23 g, 123.5 mmol) in benzene (100 ml) and the whole was refluxed for 12 h with stirring. The reaction mixture was worked up in the same

way as for the preparation of (+)-**7** to afford (−)-**7** (2.20 g, 42%). $[\alpha]_D^{27}$ − 13.4 (c = 1.19, $CHCl_3$). NMR data of (−)-**7** were identical with those of (+)-**7**.

2.14. Catalytic hydrogenation of (+)-7

A solution of (+)-**7** (2.825 g, 9.6 mmol) in MeOH (20 ml) was hydrogenated over 20% Pd–C (500 mg) at room temperature under 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 (50 g, *n*-hexane:AcOEt = 5:1) to give (+)-**8** (2.343 g, 92%). Recrystallization of (+)-**8** from *n*-hexane gave colorless plate: (+)-**8**: mp 143 °C. IR (KBr): 1740 cm^{-1}; $[\alpha]_D^{24}$ + 28.9 (c = 0.84, $CHCl_3$); ^{1}H-NMR: δ 0.79 (3H, s), 0.82 (3H, s), 0.87 (3H, s), 0.92 (1H, dt, J = 4, 14 Hz), 0.99 (1H, dd, J = 2.5, 12 Hz), 1.10–1.49 (5H, m), 1.36 (3H, s), 1.53–1.83 (6H, m), 2.00 (1H, dt, J = 3, 12.5 Hz), 2.51 (1H, ddd, J = 8.5, 9, 18.5 Hz), 2.65 (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 (**4**), 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. found: C, 77.34: H, 10.82. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%. FAB MS *m/z*: 265 (M^+ + 1).

2.15. Catalytic hydrogenation of (−)-7

A solution of (−)-**7** (3.573 g, 12.1 mmol) in MeOH (30 ml) was hydrogenated over 20% Pd–C (500 mg) at room temperature under atmospheric pressure of hydrogen. The reaction mixture was worked up in the same way as for the preparation of (+)-**8** to afford (−)-**8** (2.604 g, 81%). $[\alpha]_D^{26}$ −28.7 (c = 0.97, $CHCl_3$). NMR data of (−)-**8** were identical with those of (+)-**8**.

2.16. Dibal-H reduction of (+)-8

To a solution of (+)-**8** (2.317 g, 8.8 mmol) in toluene (10 ml) was added 1 M diisobutylaluminum hydride ((HAl(iso-Bu)$_2$: Dibal-H) in toluene (18 ml, 18 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. After addition of MeOH (5 ml), the reaction mixture was diluted with 10% aqueous sodium–potassium tartarate and 2 M aqueous NaOH, and extracted with ether. 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 (30 g, *n*-hexane:AcOEt = 5:1) to give (−)-**9** (1.895 g, 81%). Recrystallization of (−)-**9** from *n*-hexane to afford colorless plate (−)-**9**. The stereochemistry of (−)-**9** was confirmed by the fact that nuclear Overhauser effect (nOe) enhancement (5%) was observed between C_8-methyl group and the lactol proton (C_{13}–H). (−)-**9**: mp l96 °C. IR (KBr): 3372 cm^{-1}; $[\alpha]_D^{25}$ − 8.0 (c = 0.2, $CHCl_3$); ^{1}H-NMR: δ 0.72 (3H, s), 0.77 (3H, s), 0.84 (3H, s), 0.82–0.93 (1H, m), 0.93 (1H, dd, J = 2.5, 12 Hz), 1.13 (1H, dd, J = 4, 13 Hz), 1.21–1.69 (11H, m), 1.25 (3H, s), 1.78 (1H, dt, J = 3, 12.5 Hz), 1.99 (1H, ddd, J = 2.5, 6, 12.5 Hz), 2.93 (1H, br s, disappeared with D_2O), 4.96 (1H, ddd, J = 3, 7, 9.5 Hz). Anal. found: C, 76.94; H, 11.55. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%. FAB MS *m/z*: 267 (M^+ + 1).

2.17. Dibal-H reduction of (−)-8

To a solution of (−)-**8** (0.87 g, 3.3 mmol) in toluene (10 ml) was added 1 M Dibal-H in toluene (6.5 ml, 6.5 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. The reaction mixture was worked up in the same way as for the preparation of (−)-**9** to afford (+)-**9** (0.644 g, 73%). $[\alpha]_D^{25}$ +9.0 (c = 0.28, $CHCl_3$). NMR data of (−)-**9** were identical with those of (+)-**9**.

2.18. Wittig condensation of (−)-9

To a solution of (−)-**9** (1.895 g, 7.1 mmol) in benzene (50 ml) was added ethyl 2-(triphenylphosphoranylidene)propionate (Ph_3P = C(Me)COOEt; 7.72 g, 14.2 mmol) and the whole was refluxed for 2 h with stirring. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane:AcOEt = 50:(**1**) to give a colorless crystal (+)-**10** (2.09 g, 83%). Recrystallization of (+)-**10** from *n*-hexane to give a colorless powder. (+)-**10**: mp 83 °C. IR (KBr): 3504, 1702 cm^{-1}; $[\alpha]_D^{24}$ + 5.4 (c = 0.7, $CHCl_3$); ^{1}H-NMR: 0.76 (6H, s), 0.84 (3H, s), 0.89 (1H, dd, J = 2.5, 12.5 Hz), 0.94 (1H, dt, J = 4, 12 Hz), 1.04–1.16 (3H, m), 1.12 (3H, s), 1.21–1.25 (2H, m) 1.26 (3H, t, J = 7 Hz), 1.32–1.44 (4H, m), 1.4–1.67 (4H, m), 1.80 (3H, br s), 1.85 (1H, dt, J = 3, 12.5 Hz), 2.15–2.34 (1H, m), 4.13 (2H, q, J = 7 Hz), 6.76 (1H, dt, J = 1, 7 Hz).

^{13}C-NMR: δ 12.6 (q), 14.4 (q), 15.5 (q), 18.6 (t), 20.7 (t), 21.6 (q), 24.0 (q), 24.5 (t), 32.2 (t), 33.3 (s), 33.5 (q), 39.2 (s), 39.8 (t), 42.0 (t), 44.8 (t), 56.1 (d), 60.4 (t), 61.6 (d), 74.2 (s), 127.3 (s), 142.5 (d), 168.1 (s). Anal. found: C, 75.33; H, 11.22. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93%. FAB MS *m/z*: 351 ($M^+ + 1$).

2.19. Wittig condensation of (+)-9

To a solution of (+)-**9** (0.644 g, 2.41 mmol) in benzene (20 ml) was added Ph_3P = C(Me)COOEt (2.25 g, 6.2 mmol) and the whole was refluxed for 0.5 h with stirring. The reaction mixture was worked up in the same way as for the preparation of (+)-**10** to afford (−)-**10** (0.815 g, 96%). $[\alpha]_D^{26}$ − 7.4 (c = 0.78, $CHCl_3$). NMR data of (−)-**10** were identical with those of (+)-**10**.

2.20. Silylation of (+)-10

A mixture of (+)-**10** (1.75 g, 5 mmol), trimethylsilyl trifluoromethanesulfonate (TMSOTf; 4 ml, 22 mmol), diisopropylethylamine ((*iso*-Pr)$_2$NEt; 8 ml, 43 mmol) and Et_3N (8 ml, 58 mmol) was stirred for 0.5 h at room temperature. The reaction mixture was diluted with 10% aqueous NH_4CI and extracted with ether. 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 (50 g, *n*-hexane:AcOEt = 50: 1) to give a colorless oil (+)-**11** (2.09 g, 97%). (+)-**11**: IR (neat): 1706 cm^{-1}; $[\alpha]_D^{26}$ + 108 (c = 0.7, $CHCl_3$); ^{1}H-NMR: δ 0.07 (9H, s), 0.74 (3H, s), 0.75 (3H, s), 0.83 (3H, s), 0.82–0.97 (2H, m), 1.08–1.66 (8H, m), 1.14 (3H, s), 1.27 (3H, t, J = 7 Hz), 1.53 (3H, s), 1.81 (3H, s), 1.88 (1H, dt, J = 2.5, 12 Hz), 2.08–2.18 (1H, m), 2.27–2.37 (1H, m), 4.16 (2H, dt, J = 1.5, 7 Hz), 6.76 (1H, dt, J = 1.5, 7 Hz). Anal. found: C, 71.13; H, 11.04. Calcd for $C_{25}H_{46}O_3$ Si: C, 71.03; H, 10.97%. FAB MS *m/z*: 423 $M^+ + 1$).

2.21. Silylation of (−)-10

A mixture of (−)-**10** (0.494 g, 1.4 mmol), TMSOTf (1.3 ml, 7.2 mmol), (*iso*-Pr)$_2$NEt (5 ml, 28.7 mmol) and Et_3N (5 ml, 38.6 mmol) was stirred for 0.5 h at room temperature. The reaction mixture was worked up in the same way as for the preparation of (+)-**11** to afford (−)-**11** (0.596 g, 99%). $[\alpha]_D^{26}$ − 13.5 (c = 1.0, $CHCl_3$). NMR data of (−)-**11** were identical with those of (+)-**11**.

2.22. Dibal-H reduction of (+)-11

To a solution of (+)-**11** (2.05 g, 4.8 mmol) in toluene (40 ml) was added 1 M Dibal-H in toluene (20 ml, 20 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. After addition of MeOH (5 ml), the reaction mixture was diluted with 2 M aqueous NaOH, and extracted with ether. 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 (50 g, *n*-hexane:AcOEt = 20: 1) to give a colorless oil (+)-**12** (1.75 g, 94%). The *trans*-geometry of **12** was confirmed by the fact that (nOe enhancement (5%) was observed between the newly generated methylene proton and the olefin proton. (+)-**12**: IR (neat): 3406 cm^{-1}; $[\alpha]_D^{25}$ + 4.8 (c = 1.03, $CHCl_3$); ^{1}H-NMR: δ 0.09 (9H, s), 0.73 (3H, s), 0.74 (3H, s), 0.83 (3H, s), 0.88–0.96 (2H, m), 1.07–1.24 (3H, m), 1.13 (3H, s), 1.32–1.64 (8H, m), 1.64 (3H, s), 1.83–1.88 (2H, m), 1.93–2.04 (1H, m), 2.11–2.20 (1H, m), 3.97 (2H, br s), 5.42 (1H, t, J = 7 Hz). ^{13}C-NMR: δ 3.12 (q), 13.9 (q), 15.7 (q), 18.6 (t), 20.7 (t), 21.6 (q), 24.8 (t), 25.9 (q), 31.5 (t), 33.3 (s), 33.5 (q), 39.0 (s), 39.9 (t), 42.1 (t), 44.5 (t), 56.0 (d), 62.0 (d), 69.2 (t), 77.9 (s), 127.5 (d), 133.7 (s). Anal. found: C, 72.88; H, 11.69. Calcd for $C_{23}H_{44}O_2Si$: C, 72.57; H, 11.65%. FAB MS *m/z*: 381 ($M^+ + 1$).

2.23. Dibal-H reduction of (−)-11

To a solution of (−)-**11** (0.82 g, 1.9 mmol) in toluene (20 ml) was added 1 M Dibal-H in toluene (8 ml, 8 mmol) at −78 °C, the whole was stirred for 30 min at the same temperature. The reaction mixture was worked up in the same way as for the preparation of (+)-**12** to afford (−)-**12** (0.629 g, 85%). $[\alpha]_D^{24}$ − 4.2 (c = 0.85, $CHCl_3$). NMR data of (−)-**12** were identical with those of (+)-**12**.

2.24. Conversion of (+)-12 into sulfone (10S)-13

(1) To a solution of (+)-**12** (1.715 g, 4.5 mmol) in DMF (25 ml) was added mesyl chloride (MsCl;

3.1 g, 27 mmol), 2.6-lutidine (2 ml, 17 mmol), $NaHCO_3$ (116 mg, 1.4 mmol), and LiCl (0.587 g, 14 mmol) at 0 °C and the whole was stirred for 30 min at the same temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was washed with 10% aqueous $CuSO_4$ and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude chloride (1.92 g).

(2) To a solution of crude chloride (1.92 g) in DMF (30 ml) was added $PhSO_2Na{\cdot}2H_2O$ (4.53 g, 22.6 mmol) at room temperature and the whole was stirred for 1 h at 60 °C. The reaction rnixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (30 g, *n*-hexane: AcOEt = 10:1) to afford a colorless oil (10*S*)-**13** (1.072 g, 55%). (10*S*)-**13**: IR (neat): 3078, 1362 cm^{-1}; ^{1}H-NMR: δ 0.78 (6H, s), 0.85 (3H, s), 0.84–1.03 (3H, m), 1.01 (3H, s), 1.01–1.70 (11H, m), 1.72 (3H, s), 1.85 (1H, dt, J = 3, 12.5 Hz), 2.05–2.16 (2H, m), 3.76 (2H, s), 5.66 (1H, t, J = 6.5 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.55 (2H, d, J = 7.5 Hz). Anal. found: C, 72.42: H, 9.66. Calcd for $C_{26}H_{40}O_3S$: C, 72.18; H, 9.32%. FAB MS *m*/*z*: 433 ($M^+ + 1$).

2.25. Conversion of (−)-12 into sulfone (10R)-13

(1) To a solution of (−)-**12** (0.679 g, 1.8 mmol) in DMF (20 ml) was added MsCl (1.1 g, 9.6 mmol), 2.6-lutidine (0.6 ml, 5.1 mmol), $NaHCO_3$ (0.456 g, 5.4 mmol), and LiCi (0.222 g, 5.2 mmol) at 0 °C and the whole was stirred for 30 min at the same temperature. The reaction mixture was worked up in the same way as 3.16 to afford a crude chloride (0.889 g).

(2) To a solution of crude chloride in THF (10 ml) was added $PhSO_2Na{\cdot}2H_2O$ (0.816 g, 4 mmol) at room temperature and the whole was refluxed with stirring for 12 h. The reaction mixture was worked up in the same way as for the preparation of (10*S*)-**13** to afford (10*R*)-**13** (0.437 g, 57%). NMR data of (10*R*)-**13** were identical with those of (10*S*)-**13**.

2.26. (8R, 10S)-8-hydroxypolypoda-13,17,2]-triene (1)

(1) *n*-Butyllithium (*n*-BuLi, 1.6 M in hexane, 0.8 ml, 1.28 mmol) was added to a stirred solution of dilsopropylamine (0.107 g, 1.05 mmol) in THF (1 ml) at 78 °C under an argon atmosphere and the mixture was stirred for 15 min at the same temperature. A solution of (10*S*)-**13** (0.114 g, 0.26 mmol) in THF (1 ml) was added to the resulting LDA-THF solution and the whole mixture was stirred for 15 min at the same temperature. To the above reaction mixture was added a solution of *trans*-geranylbromide (0.242 g, 1.12 mmol) in THF (1 ml) and the whole mixture was stirred for 15 min at −78 °C, for 30 min at −20 °C and for 30 min at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt = 2:1) to afford **14** as a homogeneous oil (66 mg, 44%). **14**: IR (neat): 3074, 1366 cm^{-1}; FAB MS *m*/*z*: 569 ($M^+ + 1$).

(2) A mixture of 14 (66 mg, 0.12 mmol) and 5% Na-Hg (0.7 g, 0.17 mmol) in MeOH (10 ml) was refluxed for 12 h with stirring. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane-AcOEt = 10:1) to give a colorless oil (−)-**1** (21 mg, 42%). (−)-**1**: IR (neat): 3540 cm^{-1}; $[a]_D^{24}$ − 0.6 (c = 0.75, $CHCl_3$); ^{1}H-NMR: δ 0.79 (3H, s), 0.79 (3H, s), 0.87 (3H, s), 1.06–1.36 (3H, m), 1.38–1.81 (23H, m), 1.60 (3H, s), 1.61 (6H, s), 1.62 (3H, s), 1.69 (3H, s), 5, 03 (1H, br t, J = 6 Hz), 5.06 (1H, br t, J = 6 Hz), 5.19 (1H, br t, J = 6 Hz). ^{13}C-NMR: δ 15.2 (q), 16.0 (q), 16.1 (q), 17.6 (q), 18.8 (t), 20.7 (t), 22.0 (t), 23.8 (q), 25.6 (t), 25.7 (q), 26.6 (t), 26.7 (t), 31.6 (t), 33.3 (s), 33.3 (q), 39.2 (s), 39.6 (t), 39.7 (t), 39.8 (t), 42.2 (t), 44.4 (t), 56.3 (d), 61.7 (d), 74.1 (s), 124.4 (d), 124.5 (d), 125.0 (d), 130.3 (s), 135.1 (s), 135.2 (s). Anal. found: C, 84.33; H, 12.43. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.22%. FAB MS *m*/*z*: 429 ($M^+ + 1$). Spectral data

(^{1}H-NMR and ^{13}C-NMR) were identical with those ($[\alpha]_D^{23} - 0.9$ ($c = 0.4$, $CHCl_3$)) of reported (−)-**1** [1].

2.27. (8S, 10R)-8-hydroxypolypoda-13,17,21-triene (**1**)-((+)-ent-**1**)

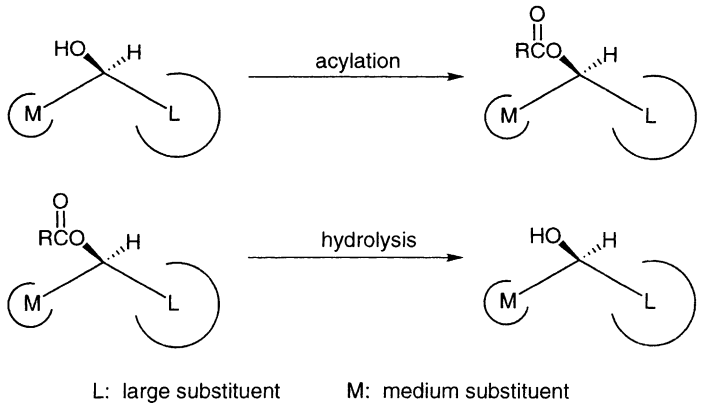
(1) *n*-Butyllithium (*n*-BuLi, 1.6 M in hexane, 1 ml, 1.6 mmol) was added to a stirred solution of diisopropylamine (0.131 g, 0.94 mmol) in THF (1 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 15 min at the same temperature. A solution of (10*R*)-**13** (0.110 g, 0.26 mmol) in THF (1 ml) was added to the resulting LDA-THF solution and the whole mixture was stirred for 15 min at the same temperature. To the above reaction mixture was added a solution of *trans*-geranylbromide (0.237 g, 1.1 mmol) in THF (1 ml) and the whole mixture was stirred for 15 min at −78 °C, for 30 min at −20 °C and for 30 min at room temperature. The reaction mixture was worked up in the same way as for 3.17 to afford a crude sulfone (88 mg).

(2) A mixture of **14** (73 mg, 0.13 mmol) and 5% Na–Hg (0.82 g, 0.2 mmol) in MeOH (10 ml) was refluxed for 12 h with stirring. The reaction mixture was worked up in the same way as for the preparation of (−)-**1** to afford (+)-**1** (22 mg, 40%). $[\alpha]_D^{24} + 0.5$ ($c = 0.72$, $CHCl_3$). NMR data of (+)-**1** were identical with those of (−)-**1**. FAB MS *m*/*z*: 429 ($M^+ + 1$).

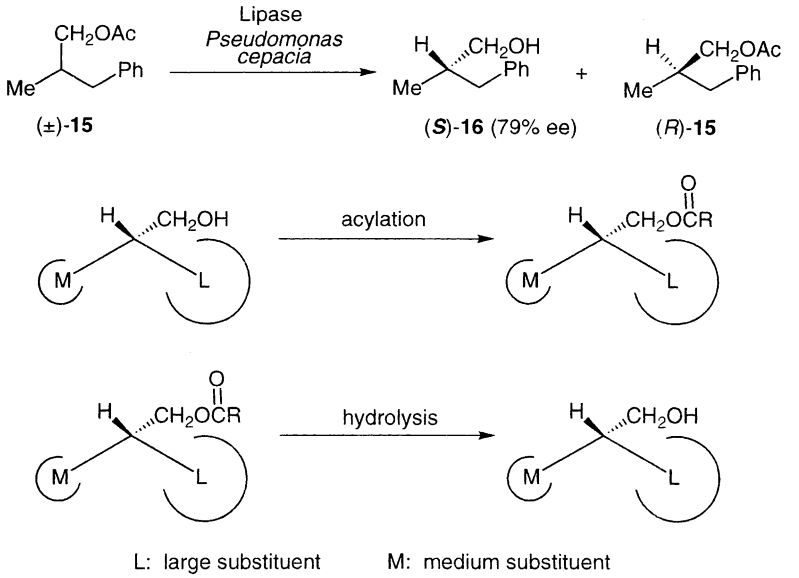
3. Discussion

Although lipases are widely used as enantioselective hydrolysis or transesterification catalysts, the structural basis for this enantioselectivity were unknown so far. The specificity of lipase from *C. rugosa* has established a simple empirical rule that predicts its enantiopreference toward secondary alcohols [7,8]. When the secondary oxygen functional group (hydroxy group or acyloxy group) exists forward with plane of the page, the favored enantiomer bears a large substituent (L) on the right, and a medium substituent (M) on the left (Scheme 3).

The structures of more than 10 different lipases including transition state analogues have been determined by X-ray crystallographic analysis [9–15]. These structures show an alcohol binding site with two pockets which is consistent with the empirical rule in Scheme 3. One pocket is large, bound with hydrophobic site and open to the solvent. The other pocket is medium-sized and contains polar as well as hydrophobic site. On the other hand, explanation concerning the molecular recognition of primary alcohols has been more difficult. Most lipases indicate low enantioselectivity toward primary alcohols. Only lipase from *Pseudomonas cepacia* (PCL) and lipase from porcine pancreas (PPL) show moderate to high enantioselectivity toward a wide range of primary alcohols, but even for these the enantioselectivity is usually lower than toward secondary alcohols. Lipase from *P. cepacia* (PCL) catalyzes the enantioselective hydrolysis of the (±)-**15** to afford (*S*)-alcohol **16** (79%



Scheme 3.



Scheme 4.

ee) and unchanged (*R*)-**15** (ee; nd) (Scheme 4) [16]. The empirical rule summarize the enantioperference of PCL toward primary alcohol or its acylated derivative as shown in Scheme 4 [16,17]. When the hydroxy methyl (–CH_2OH) or acyloxy methyl–CH_2OCOR) groups exist back with the plane of the page, the favored enantiomer bears a large substituent (L) on the right, and a medium substituent (M) on the left.

In the present case, the recognition of both substituent L and M in the substrate (+)-**3** by lipase is considered to be difficult and thence enantiopreference toward primary alcohol is depended upon the used lipase. It is worth noting that the preparation of both (10*S*)- and (10*R*)-**3** possessing high enantiomeric excess was achieved based on lipase catalyzed esterification.

4. Conclusion

The first synthesis of (8*R*, 10*S*)- and (8*S*, 10*R*)-8-hydroxypolypoda-13,17,21-triene (**1**) was achieved based on the kinetic resolution of (±)-epoxy-albicanol (**3**) using lipase and the absolute structure of natural product (**1**) was synthetically again confirmed to be (5*S*, 8*R*, 9*R*, 10*S*)-8-hydroxypolypoda-13,17,21-triene.

Acknowledgements

The authors are grateful to Meito Sangyo Co. Ltd. (Japan) for providing the lipases “MY-30 and PL-266”, and Amano Enzymes Co. Ltd. (Japan) for providing the lipases “A ano P”.

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