Chemoenzymatic Synthesis of (+)-α-Polypodatetraene and Methyl (5*R*,10*R*,13*R*)-Labda-8-en-15-oate

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Received September 13, 2007; accepted October 15, 2007; published online October 15, 2007

The reported enzymatic resolution products {acetate of (1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal} (8a*S*)-5 (>99% ee)] and [(1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal (8a*R*)-4 (98% ee) were converted to (+)-α-polypodatetraene (1) and methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate (2), respectively. For the synthesis of (5*R*,10*R*,13*R*)-2, chiral isoprene congener (3*S*)-26 corresponding to the right part of 2 was synthesized based on the lipase-assisted resolution of (±)-2-methyl-3- (*p*-methoxyphenyl)propanol (17).

Key words (+)-α-polypodatetraene; methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate; total synthesis

The chiral structural unit **A** possessing decaline ring system attached with three methyl group is the important nuclei found in a variety of natural products such as drimane sesquiterpenes and other terpenes. Among them, (+)-α-polypodatetraene (**1**)[1] and methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**2**)[2] are typical compounds (Chart 1). For the synthesis of these compounds, (8a*S*)- and (8a*R*)-β-keto esters (**3**) are the desirable compound as starting material. We already reported that lipase-assisted resolution of racemic primary alcohol (±)-**4** derived from (±)-**3** gave (8a*S*)-acetate **5** (49%, >99% ee) and (8a*R*)-primary alcohol **4** (49%, 98% ee).[3] This enzymatic resolution was found to be effective and the *E*-value of this resolution was estimated to be 921. Conversion of (8a*S*)-**5** to a hydroxyl-ketone (8a*S*)-**6** was achieved,[3] while the synthesis of (8a*R*)-bicyclofarnesol (**7**) from (8a*R*)-**4** *via* (8a*R*)-β-keto ester (**3**) was also reported by us.[4] Herein we report the concise synthesis of (+)-α-polypodatetraene (**1**) from (8a*S*)-acetate **5** and (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**2**) from (8a*R*)-bicyclofarnesol (**7**).

Synthesis of (+)-α-Polypodatetraene (1) Polypodanes constitute a new class of bicyclic terpenoids and their occurrence in nature is important for the mechanistic study of the biosynthesis of polycyclic triterpenoids. (+)-α-Polypodatetraene (**1**) is the first compound of this class and was isolated from the fresh leaves of *Polypodium fauriei* and *Lemmaphyllum microphyllum*.[1] Total synthesis of (±)-**1** was reported based on mercury(II)trifluoromethanesulphonate-amine complex-induced olefin cyclization,[5] while stepwise synthesis of (+)-α-polypodatetraene (**1**) from (+)-(8s*S*)-albicanol (**10**) was reported by us.[6] Straightforward synthesis of (+)-α-polypodatetraene (**1**) from (8a*S*)-**6** was shown in Chart 2.

Silylation of (8a*S*)-**6** followed by Wittig olefination gave a silyl ether (8a*S*)-**9** which was treated with tetrabutylammonium fluoride (TBAF) provided (+)-(8a*S*)-albicanol (**10**) in 75% overall yield from (8a*S*)-**6**. The physical data (mp 70 °C, $[\alpha]_D^{24}$ +12.8° (c=1.14, $CHCl_3$) and ^{1}H-NMR) of the synthetic (8a*S*)-**10** were identical with those (mp 68—69 °C,[7] $[\alpha]_D$ +13.0° (c=0.6, $CHCl_3$)[7] and ^{1}H-NMR[8]) of the reported (8a*S*)-**10**. Mesylation of (8a*S*)-**10** followed by the treatment with benzenethiolate ion (PhS^-Na^+) gave sulfide (8a*S*)-**12** in 74% overall yield from (8a*S*)-**10**. Oxidation of (8a*S*)-**12** with 30% H_2O_2 in the presence of

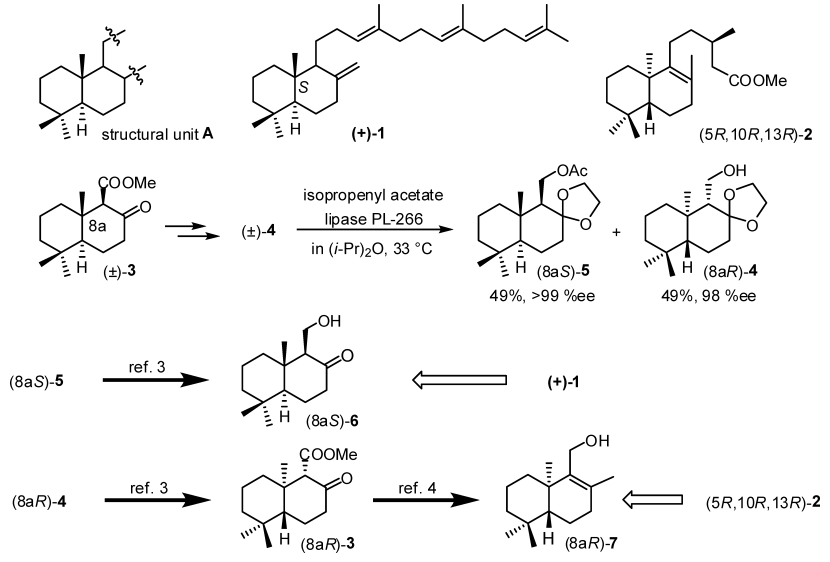

Chart 1

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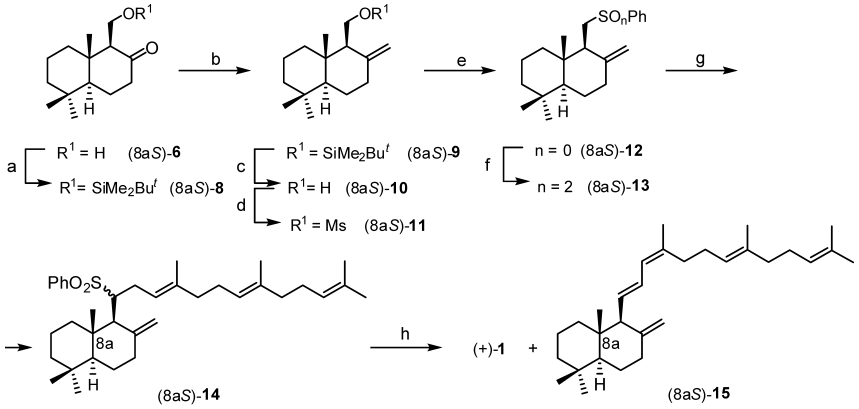
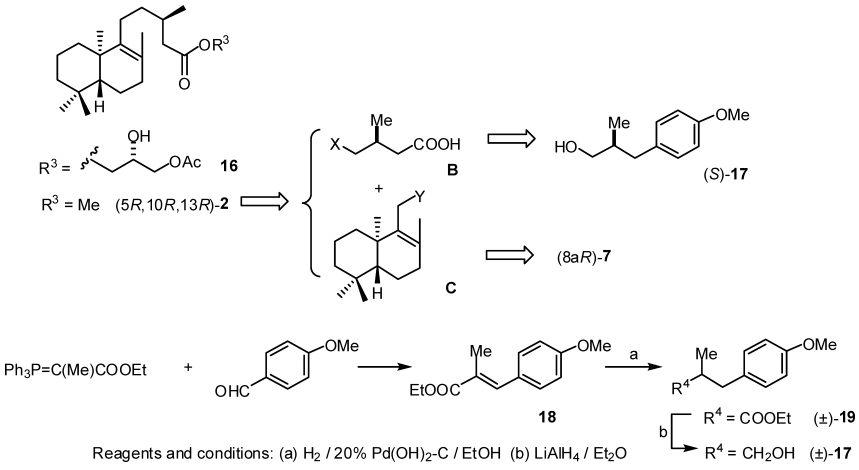


Reagents and conditions: (a) ^{t}BuMe$_2$SiCl / imidazole/ DMF (b) Ph_3P^+-Me Br^- / $NaNH_2$ / toluene
(c) $Bu_4N^+F^-$ (TBAF) / THF (d) MsCl / 4-DMAP / pyridine (e) PhSH / NaH / DMSO
(f) 30% H_2O_2 / $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ / EtOH (g) 1) *i*-Pr_2NLi (LDA) / THF 2) (*E*,*E*)-farnesyl bromide
(h) 5% Na-Hg / MeOH

Chart 2



Reagents and conditions: (a) H_2 / 20% $Pd(OH)_2$-C / EtOH (b) $LiAlH_4$ / Et_2O

Chart 3

$Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ afforded sulfone (8a*S*)-**13** in 90% yield. By applying the reported procedure,[5] (8a*S*)-**13** was lithiated with LDA followed by treatment with (*E*,*E*)-farnesyl bromide to give a diastereomeric mixture of (8a*S*)-**14** in 83% yield. Treatment of (8a*S*)-**14** with 5% Na–Hg gave (+)-α-polypodatetraene (**1**, $[\alpha]_D^{21}$ +26.0° (*c*=0.99, $CHCl_3$), 44% yield) and a conjugated diene ((8a*S*)-**15**, $[\alpha]_D^{21}$ +21.6° (*c*=0.94, $CHCl_3$), 27% yield). (11*E*)-Geometry of **15** was confirmed by NMR analysis due to $J_{11,12}$ coupling constant (15 Hz). The physical data ($[\alpha]_D^{24}$ and ^{1}H-NMR) of the synthetic (+)-**1** were identical with those ($[\alpha]_D$ +27.4° (*c*=0.4, $CHCl_3$) and ^{1}H-NMR) of the reported (+)-**1**.[1]

Synthesis of Methyl (5*R*,10*R*,13*R*)-Labda-8-en-15-oate (2) Marine dorid nudibranchs are known to contain terpenoid glyceryl esters in their mantle. Among them, a single specimen of the Antractic nudibranch *Austrodoris kerguelensis* contained two major glyceride ester, 2′-acetoxyglyceryl (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**16**) and 3′-acetoxyglyceryl (5*R*,10*R*,13*R*)-labda-8-en-15-oate.[2] These terpenoid glyceryl esters are potent activators of protein kinase C and very active in a regenerative test with the fresh water hydrozoan *Hydra vulgaris*.[9] Synthesis of a mixture of (5*S*,10*S*,13*S*)-labda-8-en-15-oate (**2**) and another two regioisomers was achieved by the dehydration of natural methyl labdanolate.[10] We first tried to synthesize (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**2**) corresponding to the left carboxylic acid part of **16**. Retrosynthesis of (5*R*,10*R*,13*R*)-**2** was shown in Chart 3.

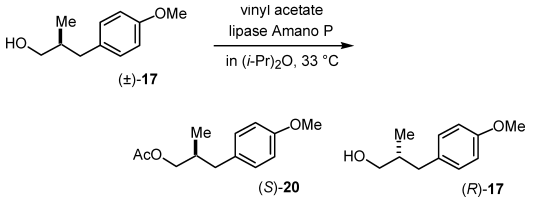
Target molecule **2** could be obtained by coupling reaction of chiral isoprene unit **B** and (8a*R*)-bicyclofarnesyl part **C**. Synthesis of chiral isoprene unit **B** could be achieved by the oxidative cleavage of the *p*-methoxyphenyl moiety of chiral alcohol (*S*)-**17**, which could be obtained by lipase-assisted resolution of (±)-**17**. On the other hand, (8a*R*)-bicyclofarnesyl part **C** could be obtained from the reported (8a*R*)-bicyclofarnesol (**7**). The synthesis of substrate (±)-**17** for enzymatic resolution was shown in Chart 3. Wittig reaction of *p*-anisole with (ethoxycarbonylethylidene)triphenylphosphorane gave α,β-unsaturated ester (**18**) in 99% yield, which was subjected to catalytic hydrogenation to afford (±)-**19** in 97% yield. $LiAlH_4$ reduction of (±)-**19** gave the desired primary alcohol (±)-**17** in 93% yield. For the purpose of the determination of enantiomeric excess (ee) of enzymatic reaction product, the racemate (±)-**17** was analyzed to provide well separated peaks (33.5, 40.4 min) corresponding to the enantiomers using Chiralcel AD (250 mm×4.6 mm)

under the following analytical conditions (eluent, *n*-hexane/EtOH=100 : 1; detection, UV at 254 nm; flow rate, 1 ml/1 min). Initially, (±)-**17** was subjected to a screening experiment using several kinds of commercially available lipases. Among them, lipase Amano P from *Pseudomonas* sp. was found to give an acetate (*S*)-**20** (42% yield) and unchanged (+)-**17** (54% yield, $[\alpha]_D^{27}$ +10.1° (*c*=0.66, $CHCl_3$) corresponds to 78% ee) in the presence of vinyl acetate as an acyl donor as shown in Table 1 (entry 1).

The ee of the (+)-**17** was determined by HPLC analysis on a Chiralcel AD. The absolute structure of (+)-**17** was confirmed to be *R*-configuration in comparison to a specific rotation ($[\alpha]_D^{25}$ −11.9° (*c*=1.02, $CHCl_3$) corresponds to >99% ee) of the reported (*S*)-**17**.[11] Deprotection of the acetate (**20**) with K_2CO_3 in MeOH gave the (−)-**17** ($[\alpha]_D^{25}$ −12.5° (*c*=0.67, $CHCl_3$) corresponds to >99% ee by HPLC analysis), thence the absolute structure of the acetate (**20**) was confirmed to be *S*-configuration. The 78% ee of (+)-**17** was again subjected to enzymatic acetylation to afford (*S*)-**20** (15% yield, 29% ee) and unchanged (*R*)-**17** (84% yield, >99%) as shown in Table 1 (entry 2). Then the synthesis of (5*R*,10*R*,13*R*)-**2** from (*S*)-**20** was shown in Chart 4.

Thus obtained (*S*)-**20** was converted into the desired tetrahydropyranyl (THP) ether (3*S*)-**26** by the reported procedure[11] in 52% overall yield (7 steps) as shown in Chart 4. On the other hand, (8a*R*)-bicyclofarnesyl bromide (**27**) was obtained by treatment of the reported (8a*R*)-bicyclofarnesol (**7**)[4] with PBr_3. The anion of (3*S*)-**26** generated by treatment with lithium diisopropylamide (LDA) in the presence of hexamethylphosphoramide (HMPA) was subjected to alkylation with the above bromide (8a*R*)-**27** to give a diastereomeric mixture of coupling product **28** in 70% yield. Reduction of **28** with Na/Hg in MeOH followed by deprotection of the THP group with pyridinium *p*-toluenesulfonate (PPTS) provided alcohol (5*R*,10*R*,13*R*)-**30** ($[\alpha]_D^{18}$ −63.0° (*c*=0.84, $CHCl_3$)) in 20% overall yield. Jones oxidation of (5*R*,10*R*,13*R*)-**30** followed by treatment with CH_2N_2–ether solution gave (5*R*,10*R*,13*R*)-**2** ($[\alpha]_D^{21}$ −63.6° (*c*=0.80, $CHCl_3$)) in 49% overall yield. The specific rotation and ^{1}H-NMR of synthetic (5*R*,10*R*,13*R*)-**2** were consistent with those ($[\alpha]_D$ −49° (*c*=0.21, $CHCl_3$)) of the reported (5*R*,10*R*,13*R*)-**2**.[2]

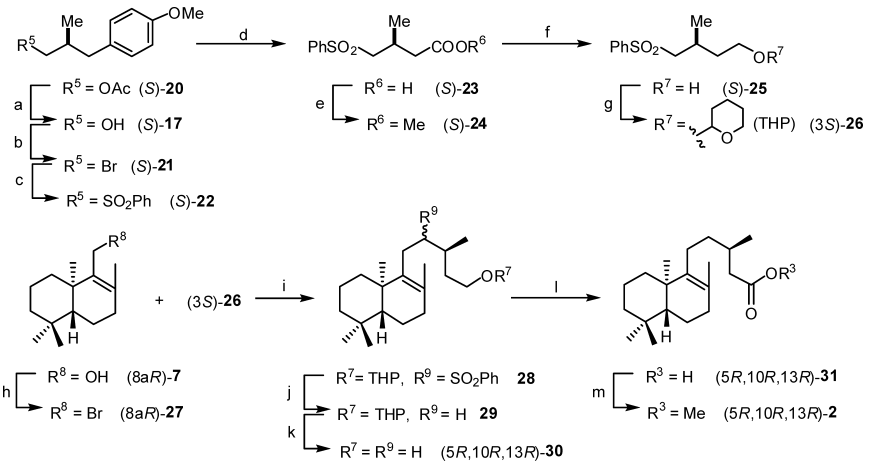
Table 1.



Entry	Substrate	Products	
1	(±)-**17**	(*S*)-**20** (42%, >99% ee)	(*R*)-**17** (54%, 78% ee)
2	(*R*)-**17** (78% ee)	(*S*)-**20** (15%, 29% ee)	(*R*)-**17** (84%, >99% ee)

Discussion

Although lipases are widely used as enantioselective hydrolysis or transesterification catalysts, the structural basis for this enantioselectivity were unknown so far. The enantiopreference toward secondary alcohols by lipase from *Candida rugosa* has established a simple empirical rule.[12,13] 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. The empirical rule summarize the enantioperference of PCL toward primary alcohol or its acylated derivative as shown in Chart 5.[14,15] 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, prediction of enantioperference toward primary alcohol (±)-**17** was fairly explained by the empirical rule. It is worth noting that the preparation of both (*S*)-**20** and (*R*)-**17** possessing high enantiomeric excess was achieved based on lipase catalyzed esterification.



Reagents and conditions: (a) K_2CO_3 / MeOH (b) CBr_4 / Ph_3P / THF (c) $PhSO_2Na{\cdot}2H_2O$ / DMF
(d) 1) O_3 / AcOEt 2) 30% H_2O_2 (e) CH_2N_2 / Et_2O (f) $LiBH_4$ / THF (g) 3,4-dihydropyran / PPTS / CH_2Cl_2
(h) PBr_3 / pyridine / Et_2O (i) LDA / HMPA / THF (j) 5% Na-Hg / Na_2HPO_4 / MeOH
(k) PPTS / MeOH (l) CrO_3 / H^+ / acetone (m) CH_2N_2 / Et_2O

Chart 4

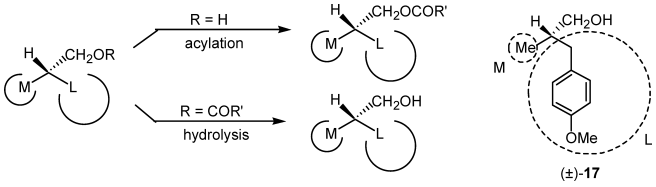


Chart 5

Conclusion

The reported enzymatic resolution products {acetate of (1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal} (8a*S*)-**5** (>99% ee)] and [(1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-*trans*-naphthalene-1-methanol-2-ethylene acetal (8a*R*)-**4** (98% ee) were converted to (+)-α-polypodatetraene (**1**) and methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**2**), respectively. For the synthesis of (5*R*,10*R*,13*R*)-**2**, chiral isoprene congener (3*S*)-**26** corresponding to the right part of **2** was synthesized based on the lipase-assisted resolution of (±)-2-methyl-3-(*p*-methoxyphenyl)propanol (**17**).

Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL EX 400 spectrometer. Spectra were taken with 5—10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. The mass spectra, FAB and EI, were obtained with a JEOL JMS-600 H (matrix; glycerol, *m*-nitrobenzyl alcohol) or a JEOL JMS-AM II 50 spectrometer, respectively. IR spectra were recorded on 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.

(8a*S*)-Albicanol (10) 1) To a solution of the reported (8a*S*)-**6** (9.42 g, 42.0 mmol) in DMF (100 ml) was added *tert*-butyldimethylsilyl chloride (TBDMSCl, 7.60 g, 50.4 mmol) and imidazole (5.70 g, 83.7 mmol) at 0 °C and whole mixture was stirred for 1 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude silyl ether (8a*S*)-**8** (14.4 g), which was used for the next reaction without further purification. 2) A mixture of methyltriphenylphosphonium bromide (Ph_3P^+-Me Br^-, 75.0 g, 210 mmol) and sodium amide ($NaNH_2$, 8.03 g, 206 mmol) in toluene (500 ml) was refluxed with stirring for 3 h under argon atmosphere. To a solution of crude (8a*S*)-**8** (14.4 g) in toluene (50.0 ml) was added the above yellow solution ($Ph_3P{=}CH_2$, *ca.* 500 ml) and the whole mixture was stirred for 9 h at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil (8a*S*)-**9**, which was used for the next reaction without further purification. 3) To a solution of crude (8a*S*)-**9** in THF (200 ml) was added 1 M tetrabutylammonium fluoride ($Bu_4N^+F^-$, TBAF) in THF solution (84.0 ml, 84.0 mmol) and the whole mixture was stirred for 12 h at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil (8a*S*)-**9**, which was chromatographed on silica gel (100 g, *n*-hexane : AcOEt = 10 : 1) to give (8a*S*)-**10** (7.05 g, 75%). (8a*S*)-**10**: mp 70 °C (colorless needles from *n*-hexane), $[\alpha]_D^{24}$ +12.8° (c=1.14, $CHCl_3$), ^{1}H-NMR data of (8a*S*)-**10** were identical with those of the reported (8a*S*)-**10**.[8] *Anal*. Calcd for $C_{15}H_{22}O$: C, 81.02; H, 11.79. Found: C, 81.19; H, 11.97.

(8a*S*)-Albicanyl Phenyl Sulfide (12) 1) To a solution of (8a*S*)-**10** (1.00 g, 4.50 mmol) in pyridine (15.0 ml) was added methanesulfonyl chloride (MsCl, 0.620 g, 5.40 mmol) and 4-dimethylaminopyridine (DMAP, 0.060 g, 0.500 mmol) at 0 °C, and the whole mixture was stirred for 2 h at rt. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude mesylate (8a*S*)-**11**, which was used for the next reaction without further purification. 2) 55% NaH in oil (0.870 g, 19.9 mmol) was washed with *n*-hexane. To a mixture of NaH in DMSO (10.0 ml) was added a solution of the above mesylate (8a*S*)-**11** in DMSO (10.0 ml) and thiophenol (PhSH, 2.20 g, 20.0 mmol). The whole mixture was stirred for 20 min at rt and for 12 h at 100 °C. The reaction mixture was diluted with 2 M aqueous NaOH and extracted with Et_2O. 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 (30.0 g, *n*-hexane) to afford (8a*S*)-**12** (1.05 g, 74%) as a colorless oil. (8a*S*)-**12**: $[\alpha]_D^{27}$ +164.6° (c=0.41, $CHCl_3$). IR (KBr): 1647, 1452 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 0.81 (3H, s), 0.87 (3H, s), 1.08—1.23 (3H, m), 1.28—1.43 (2H, m), 1.45—1.65 (2H, m), 1.69—1.81 (2H, m), 2.00—2.09 (2H, m), 2.43 (1H, ddd, J=2, 4, 15 Hz), 2.98 (1H, t, J=12 Hz), 3.17 (1H, dd, J=2, 12 Hz), 4.67 (1H, s), 4.96 (1H, s), 7.15 (1H, t, J=8 Hz), 7.23—7.35 (4H, m). ^{13}C-NMR: δ 14.5 (q), 19.2 (t), 21.7 (q), 24.1 (t), 29.9 (t), 33.5 (q), 33.6 (s), 37.7 (t), 39.1 (t), 40.2 (s), 41.9 (t), 55.1 (d), 56.9 (d), 107.8 (t), 125.5 (d), 128.6 (2C, d), 128.8 (2C, d), 138.4 (s), 147.2 (s). *Anal.* Calcd for $C_{21}H_{30}S$: C, 80.19; H, 9.61. Found: C, 80.09; H, 9.62.

(8a*S*)-Albicanyl Phenyl Sulfone (13) To a solution of (8a*S*)-**12** (0.500 g, 1.60 mmol) in EtOH (5.00 ml) was added $Mo_7O_{24}(NH_4)_6\cdot 4H_2O$ (0.187 g, 0.150 mmol) and 30% H_2O_2 (1.40 ml) at 0 °C and the whole mixture was stirred for 3 h at rt. The reaction mixture was diluted with 10% aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30.0 g, *n*-hexane : AcOEt = 30 : 1) to afford (8a*S*)-**13** (0.498 g, 90%). (8a*S*)-**13**: mp 111 °C (colorless needles from *n*-hexane), $[\alpha]_D^{26}$ +28.1° (c=0.99, $CHCl_3$). IR (KBr): 1647, 1308, 1151 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.58 (3H, s), 0.74 (3H, s), 0.84 (3H, s), 1.09—1.30 (3H, m), 1.32—1.39 (2H, m), 1.42—1.57 (3H, m), 1.66—1.74 (1H, m), 1.91—1.97 (1H, m), 2.29—2.38 (2H, m), 3.20 (1H, dd, J=1, 15 Hz), 3.33 (1H, dd, J=9, 15 Hz), 4.43 (1H, s), 4.72 (1H, s), 7.47—7.54 (2H, m), 7.56—7.61 (1H, m), 7.83—7.86 (2H, m). ^{13}C-NMR: δ 14.9 (q), 19.0 (t), 21.5 (q), 23.8 (t), 33.3 (q), 33.6 (s), 37.4 (t), 38.4 (t), 39.8 (s), 41.6 (t), 50.6 (d), 52.2 (t), 55.1 (d), 107.7 (t), 128.1 (d), 129.0 (2C, d), 133.4 (2C, d), 140.0 (s), 145.6 (s). *Anal.* Calcd for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.73. Found: C, 72.72; H, 8.68.

(+)-α-Polypodatetraene (1) 1) 2.6 M *n*-butyllithium (*n*-BuLi) in hexame solution (1.90 ml, 4.90 mmol) was added to a stirred solution of diisopropylamine (0.490 g, 4.80 mmol) in THF (1.50 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 15 min at the same temperature. A solution of (8a*S*)-**13** (0.570 g, 1.60 mmol) in THF (1.50 ml) was added to the above 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 (*E*,*E*)-farnesyl bromide (0.254 g, 0.890 mmol) in THF (1.00 ml) and the whole mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (45.0 g, *n*-hexane : AcOEt = 100 : 1) to afford a diastereomeric mixture of (8a*S*)-**14** (0.752 g, 83%) as a colorless oil. 2) A mixture of (8a*S*)-**14** (0.746 g, 1.40 mmol) and 5% Na–Hg (6.04 g) in MeOH (10.0 ml) was refluxed for 24 h with stirring. The reaction mixture was evaporated to give a residue, which was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (45.0 g, *n*-hexane) to afford (+)-**1** (0.245 g, 44%) as a colorless oil and (8a*S*)-**15** (0.150 g, 27%) as a colorless oil in elution order. (+)-**1**: $[\alpha]_D^{21}$ +26.0° (c=0.99, $CHCl_3$). FAB-MS m/z: 411 (M^++1). ^{1}H- and ^{13}C-NMR data of (+)-**1** were identical with those of the previously reported data of (+)-**1**.[1] (8a*S*)-**15**: $[\alpha]_D^{21}$ +21.6° (c=0.94, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s), 0.82 (3H, s), 0.87 (3H, s), 0.90—1.04 (1H, m), 1.07 (1H, dd, J=2, 12 Hz), 1.11—1.54 (8H, m), 1.59 (6H, s), 1.66 (3H, s), 1.72 (3H, s), 1.91—2.19 (8H, m), 2.30—2.36 (1H, m), 2.38—2.46 (1H, m), 4.50 (1H, d, J=2 Hz), 4.71 (1H, d, J=2 Hz), 5.03—5.17 (2H, m), 5.59 (1H, dd, J=10, 15 Hz), 5.85 (1H, d, J=11 Hz), 6.18 (1H, dd, J=11, 15 Hz). EI-MS m/z: 408 (M^+).

(±)-2-Methyl-3-(*p*-methoxyphenyl)propanol (17) 1) A mixture of *p*-anisole (1.00 g, 7.40 mmol) and (ethoxycarbonylethylidene)triphenyl phosphorane (5.31 g, 14.7 mmol) in benzene (20.0 ml) was refluxed for 12 h with stirring. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Evaporation of organic solvent gave a crude oil which was chromatographed on silica gel (40.0 g, *n*-hexane : AcOEt = 10 : 1) to afford **18** (1.61 g, 99% yield) as a homogeneous oil. IR (neat) 1703 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=7.1 Hz), 2.11 (3H, s), 3.81 (3H, s), 4.25 (2H, q, J=7.1 Hz), 6.90 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.8 Hz), 7.62 (1H, s). ^{13}C-NMR: δ 14.0 (q), 14.1 (q), 55.3 (q), 60.7 (t), 113.8 (2C, d), 126.4 (s), 128.5 (s), 131.4 (2C, d), 138.3 (d), 159.6 (s), 168.9 (s). 2) A solution of **18** (0.500 g, 2.30 mmol) in EtOH (10.0 ml)

was subjected to hydrogenation at ordinary temperature and pressure in the presence of 20% $Pd(OH)_2$–C (0.05 g). After hydrogen absoprption had ceased, the catalyst was filtered with the aid of celite and the filtrate was evaporated. The residue was chromatographyed on silicagel (20.0 g, *n*-hexane : AcOEt=10 : 1) to afford (±)-**19** (0.493 g, 97% yield) as a homogeneous oil. IR (neat) 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=7 Hz), 1.17 (3H, d, J=7 Hz), 2.56—2.70 (2H, m), 2.92 (1H, dd, J=13, 7 Hz), 3.76 (3H, s), 4.07 (2H, q, J=7 Hz), 6.80 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz). ^{13}C-NMR: δ 14.2 (q), 16.7 (q), 38.9 (t), 41.7 (d), 55.2 (q), 60.2 (t), 113.7 (2C, d), 129.9 (2C, d), 131.5 (s), 158.1 (s), 176.1 (s). HR-MS (EI) Calcd for $C_{13}H_{18}O_3$: 222.1307. Found: 222.1256. 3) A solution of (±)-**19** (0.493 g, 2.20 mmol) in Et_2O (10.0 ml) was added to a suspension of $LiAlH_4$ (0.133 g) in Et_2O (10 ml) at 0 °C. The whole mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with 2 M aqueous HCl and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a crude oil which was chromatographed on silica gel (20.0 g, *n*-hexane : AcOEt=5 : 1) to afford (±)-**17** (0.373 g, 93% yield) as a colorless oil. IR (neat) 3379 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.8 Hz), 1.90—1.97 (2H, m), 2.35 (1H, dd, J=8.3, 13.7 Hz), 2.68 (1H, dd, J=6.4, 13.7 Hz), 3.43 (1H, dd, J=6.4, 10.7 Hz), 3.50 (1H, dd, J=6.4, 10.7 Hz), 3.77 (3H, s), 6.82 (2H, d, J=8.3 Hz), 7.07 (2H, d, J=8.3 Hz). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.30; H, 9.13. EI-MS m/z 180 (M^+). The racemate (±)-**17** was analyzed to provide well separated peaks (33.5, 40.4 min) corresponding to the enantiomers using Chiralcel AD (250 mm×4.6 mm) under the following analytical conditions (eluent, *n*-hexane/EtOH=100 : 1; detection, UV at 254 nm; flow rate, 1 ml/1 min).

Enantioselective Acetylation of (±)-17 with Lipase Amano P 1) (Entry 1) A suspension of (±)-**17** (3.88 g, 21.6 mmol), lipase Amano P (1.50 g) and vinyl acetate (4.00 g) in diisopropyl ether (150 ml) was incubated at 33 °C for 1 h. 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 (90 g) to give (*S*)-**20** (2.04 g, 42% yield) as a colorless oil from *n*-hexane : AcOEt=10 : 1 eluent, and (*R*)-**17** (2.12 g, 54% yield) from *n*-hexane : AcOEt=5 : 1 eluent. (*R*)-**17**: $[\alpha]_D^{27}$ +10.1° (c=0.66, $CHCl_3$) corresponds to 78% ee. t_R=33.5 min (89%) and t_R=40.4 min (11%). 2) A suspension of (*S*)-**20** (2.04 g, 9.2 mmol) and K_2CO_3 (1.92 g, 13.9 mmol) in MeOH (20.0 ml) was stirred for 1 h at room temperature. The reaction mixture was evaporated, diluted with saturated brine and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (40.0 g) to give (*S*)-**17** (1.63 g, 98% yield) from *n*-hexane : AcOEt=5 : 1 eluent. (*S*)-**17**: $[\alpha]_D^{25}$ −12.5° (c=0.67, $CHCl_3$) corresponds to >99% ee. t_R=33.5 min (<1%) and t_R=40.4 min (>99%). 3) (Entry 2) A suspension of 78% ee of (*R*)-**17** (2.12 g, 12 mmol), lipase (1.01 g) and vinyl acetate (2.50 g) in diisopropyl ether (4.0 ml) was incubated at 33 °C for 90 min. The reaction mixture was worked up in the same way as entry 1 to afford (*S*)-**20** (0.410 g, 15%) and (*R*)-**17** (84%, >99% ee). (*R*)-**17**: $[\alpha]_D^{25}$ +12.9° (c=0.96, $CHCl_3$) corresponds to >99% ee. t_R=33.5 min (>99%) and t_R=40.4 min (<1%). 4) A suspension of (*S*)-**20** (0.410 g, 1.0 mmol) and K_2CO_3 (0.384 g, 2.80 mmol) in MeOH (10 ml) was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as entry 2 to afford (*S*)-**17** (0.310 g, 93%). (*S*)-**17**: 29% ee. t_R=33.5 min (35.5%) and t_R=40.4 min (64.5%).

(*S*)-1-Bromo-2-methyl-3-*p*-methoxyphenylpropanol (21) Triphenylphosphine (Ph_3P, 0.295 g, 1.12 mmol) and CBr_4 (0.372 g, 1.12 mmol) were added to a solution of (*S*)-**17** (0.126 g, 0.7 mmol) in THF (2.00 ml) and the resulting solution was stirred for 15 min at room temperature. The reaction mixture was diluted with saturated brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (15.0 g, *n*-hexane : AcOEt=5 : 1) to give (*S*)-**21** as a homogeneous oil (0.168 g, 98% yield). (*S*)-**21**: $[\alpha]_D^{23}$ +28.3° (c=1.21, $CHCl_3$). Spectral data (IR and ^{1}H-NMR) were identical with those of reported (*S*)-**21**.[6]

(*S*)-2-Methyl-3-(*p*-methoxyphenyl)-1-phenylsulfonylpropane (22) A mixture of (*S*)-**21** (1.54 g, 6.34 mmol) and sodium benzenesulfinate ($PhSO_2Na \cdot 2H_2O$, 5.03 g, 25.1 mmol) in dimethylforamide (DMF, 30.0 ml) was heated at 100 °C for 1 h with stirring, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford a crude product which was chromatographed on silica gel (30.0 g, *n*-hexane : AcOEt=5 : 1) to give (*S*)-**22** as a homogeneous oil (1.55 g, 80% yield). Spectral data (IR, ^{1}H-NMR) were identical with those of reported (*S*)-**22**.[6]

Methyl (*S*)-3-Methyl-4-phenylsulfonylbutanoate (24) Ozone was passed through a solution of (*S*)-**23** (1.52 g, 4.98 mmol) in AcOEt (20.0 ml) at −78 °C for 2.5 h, then 30% aqueous H_2O_2 (10.0 ml) was added to the ozonolyzed product. The reaction mixture was stirred for 10 min at room temperature, then diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford a crude product (**23**) which was treated with CH_2N_2 in Et_2O to provide an oily product. This was subjected to chromatographic separation on silica gel (50.0 g, *n*-hexane : AcOEt=5 : 1) to give (*S*)-**24** as a homogeneous oil (1.06 g, 83% overall yield). Spectral data (IR, ^{1}H-NMR) were identical with those of reported (*S*)-**24**.[6]

(*S*)-3-Methyl-4-phenylsulfonylbutanol (25) $LiBH_4$ (0.157 g, 7.21 mmol) was added to a solution of (*S*)-**24** (1.06 g, 4.15 mmol) in THF (20.0 ml) at 0 °C and the whole was stirred for 12 h at 60 °C. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine, dried over $MgSO_4$ and evaporated to afford acrude product which was chromatographed on silica gel (30.0 g, *n*-hexane : AcOEt=1 : 2) to give (*S*)-**25** as a homogeneous oil (0.812 g, 86% yield). Spectral data (IR, ^{1}H-NMR) were identical with those of reported (*S*)-**25**.[6]

(3*S*)-3-Methyl-4-phenylsulfonylbutyltetrahydropyranyl Ether (26) A mixture of (*S*)-**25** (0.109 g, 0.470 mmol), 3,4-dihydropyran (DHP) (0.108 g, 1.28 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.011 g, 0.043 mmol) in CH_2Cl_2 (2.00 ml) was stirred for 12 h at room temperature. The reaction mixture was washed with aqueous $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. The organic layer was evaporated to afford a crude product which was chromatographed on silica gel (15.0 g, *n*-hexane : AcOEt=4 : 1) to give (3*S*)-**26** as a homogeneous oil (0.142 g, 95% yield). Spectral data (IR, ^{1}H-NMR) were identical with those of reported (3*S*)-**26**.[6]

(8a*R*)-Cyclofarnesyl Bromide (27) To a solution of (8a*R*)-cyclofarnesol (**7**) (0.590 g, 2.65 mmol) and pyridine (0.190 g, 2.40 mmol) in Et_2O (5.00 ml) was added phosphorus tribromide (PBr_3; 0.300 ml, 312 mmol) at 0 °C and the reaction mixture was stirred for 10 min. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to give a crude ((8a*R*)-**27**, 0.734 g), which was used for the next reaction without further purification.

(5*R*,10*R*,13*R*)-Labda-8-en-15-ol (30) 1) *n*-Butyllithium (*n*-BuLi, 1 M in hexane, 4.20 ml, 4.20 mmol) was added to a stirred solution of diisopropylamine (4.00 ml) in THF (5.00 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min at the same temperature. To a solution of (3*S*)-**26** (0.403 g, 1.29 mmol) in THF (5.00 ml) at −78 °C was added the above LDA-THF solution (4.00 ml) and HMPA (4.00 ml). The whole was stirred for 1 h at −78 °C, then a solution of (*R*)-bromide (**27**, 0.734 g, 2.57 mmol) in THF (5.00 ml) was added at the same temperature. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with saturated brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (50.0 g, *n*-hexane : AcOEt=10 : 1) to afford **28** (0.469 g, 70%) as amorphous. **28**: FAB-MS: (m/z) 539 ($M+Na)^+$. 2) To a solution of **28** (0.469 g, 0.9 mmol) in THF (3 ml) and MeOH (6.00 ml) were added Na_2HPO_4 (6.74 g, 18.8 mmol) and 5% Na–Hg (26.9 g, 120 mmol) and whole mixture was stirred for 2 d at 80 °C. The reaction mixture was filtered with the aid of Celite and filtrate was condensed. The residue was treated with 2 M aqueous NaOH and extracted with Et_2O. The organic layer was washed with saturated with brine and dried over $MgSO_4$. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (10.0 g, *n*-hexane : AcOEt=50 : 1) to afford **29** (0.283 g, 83%) as a homogeneous oil. **29**: EI-MS: (m/z) 376 (M^+). 3) A mixture of **29** (0.260 g, 0.69 mmol), PPTS (0.292 g, 1.16 mmol) in MeOH (5 ml) was stirred for 12 h at 40 °C. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was evaporated to afford a crude product which was chromatographed on silica gel (10.0 g, *n*-hexane : AcOEt=15 : 1) to give (5*R*,10*R*,13*R*)-**30** (0.051 g, 25%) as a homogeneous oil. (5*R*,10*R*,13*R*)-**30**: $[\alpha]_D^{18}$ −63.0° (c=0.84, $CHCl_3$). IR (neat): 3328 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s), 0.85 (3H, s), 0.91 (3H, d, J=6 Hz), 0.91 (3H, s), 1.04—1.25 (5H, m), 1.28—1.47 (6H, m), 1.52 (3H, s), 1.55—1.66 (3H, m), 1.70—1.80 (1H, m), 1.91—2.19 (4H, m), 3.61—3.72 (2H, m). ^{13}C-NMR: δ 19.1 (t), 19.1 (t), 19.5 (q), 19.5 (q), 20.1 (q), 21.7 (q), 25.5 (t), 30.7 (d), 33.3 (q), 33.3 (s), 33.6 (t), 37.0 (t), 37.8 (t), 39.0 (s), 39.9 (t), 41.8 (t), 51.9 (d), 61.3 (t), 125.3 (s), 141.0 (s). HR-MS (EI) Calcd for $C_{20}H_{36}O$: 292.2766. Found: 292.2778.

Methyl (5*R*,10*R*,13*R*)-Labda-8-en-15-oate (2) To a solution of (5*R*,10*R*,13*R*)-**30** (0.052 g, 0.17 mmol) in acetone (3.00 ml) was added Jones

reagent (0.10 ml) at 0 °C and whole mixture was stirred for 10 min at the same temperature. To the reaction mixture was added *iso*-PrOH (1.00 ml) and whole mixture was stirred for 15 min. The reaction mixture was condensed, diluted with brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Removal of the organic solvent gave a crude carboxylic acid (**31**, 0.052 g), which was treated with CH_2N_2–ether solution to afford a crude residue. This was chromatographed on silica gel (5.00 g, *n*-hexane : AcOEt = 100 : 1) to provide (5*R*,10*R*,13*R*)-**2** (0.027 g, 49%) as a colorless oil. (5*R*,10*R*,13*R*)-**2**: $[\alpha]_D^{21}$ −63.6° (*c* = 0.80, $CHCl_3$). IR (neat): 1741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, s), 0.85 (3H, s), 0.91 (3H, s), 0.94 (3H, d, *J* = 6.6 Hz), 1.05—1.14 (3H, m), 1.23—1.59 (8H, m), 1.52 (3H, s), 1.70—1.75 (1H, m), 1.88—2.14 (4H, m), 2.12 (1H, dd, *J* = 15, 8 Hz), 2.31 (1H, dd, *J* = 15, 6 Hz), 3.66 (3H, s). ^{13}C-NMR: δ 19.1 (t), 19.1 (t), 19.4 (q), 19.6 (q), 20.1 (q), 21.7 (q), 25.5 (t), 31.4 (d), 33.3 (q), 33.6 (t), 37.0 (t), 37.3 (t), 39.0 (s), 41.5 (t), 41.8 (t), 51.3 (q), 51.9 (d), 125.6 (s), 126.4 (s), 140.6 (s), 173.7 (s). HR-MS (EI) Calcd for $C_{21}H_{36}O_2$: 320.2715. Found: 320.2725.

References and Notes

1) Shiojima K., Arai Y., Masuda K., Kamada T., Ageta H., *Tetrahedron Lett.*, **24**, 5733—5736 (1983).
2) Davies-Coleman M. T., Faulkner D. J., *Tetrahedron*, **47**, 9743—9750 (1991). Carbon number of compound (**2**) was employed based on steroid skeleton.
3) Amano Y., Kinoshita M., Akita H., *J. Mol. Catalysis B: Enzymatic*, **32**, 141—148 (2005). Carbon number of (8a*S*)- and (8a*R*)-**3** was employed based on the decaline structure.
4) Arima Y., Kinoshita M., Akita H., *Tetrahedron: Asymmetry*, **18**, 1701—1711 (2007).
5) Nishizawa M., Nishide H., Hayashi Y., *J. Chem. Soc.*, *Chem. Commun.*, **1984**, 467—468.
6) Kinoshita M., Ohtsuka M., Nakamura D., Akita H., *Chem. Pharm. Bull.*, **50**, 930—934 (2002).
7) Hellou J., Andersen R. J., Thompson J. E., *Tetrahedron*, **38**, 1875—1879 (1982).
8) Akita H., Nozawa M., Mitsuda A., Ohsawa H., *Tetrahedron: Asymmetry*, **11**, 1375—1388 (2000).
9) Gavagnin M., Napoli A. D., Cimino G., Iken K., Avila C., Garcia F. J., *Tetrahedron: Asymmetry*, **10**, 2647—2650 (1999).
10) Vlad P. F., Ungur N. D., Aricu A. N., Andreeva I. Y., *Russian Chem. Bull.*, **46**, 767—770 (1997).
11) Nozawa M., Takahashi K., Kato K., Akita H., *Chem. Pharm. Bull.*, **48**, 272—277 (2000).
12) Kazlauskas R. J., Weissfloch A. N. E., Rappaport A. T., Cuccia L. A., *J. Org. Chem.*, **56**, 2656—2665 (1991).
13) Cygler M., Grochulski P., Karlauskas R. J., Schrag J. D., Bouthillier F., Rubin B., Serreqi A. N., Gupta A. K., *J. Am. Chem. Soc.*, **116**, 3180—3186 (1994).
14) Weissfloch A. N. E., Kazlauskas R. J., *J. Org. Chem.*, **60**, 6959—6969 (1995).
15) Tuomi W. V., Kazlauskas R. J., *J. Org. Chem.*, **64**, 2638—2647 (1999).