Enzymatic Hydrolysis of *meso*(*syn*-*syn*)-1,3,5-Triacetoxy-2,4-dimethylpentane and Acetylation of *meso*(*syn*-*syn*)-3-Benzyloxy-2,4-dimethylpentane-1,5-diol by Lipase

Shinji NAGUMO, Takayuki ARAI, and Hiroyuki AKITA*

School of Pharmaceutical Science, Toho University, 2–2–1 Miyama, Funabashi, Chiba 274, Japan.

Received December 11, 1995; accepted February 7, 1996

Chiral inductions of *meso* triacetate (4) and *meso* diol (15) were carried out on the basis of enzymatic reaction using lipase to give chiral synthons having three consecutive chiral centers with high enantiomeric excess.

Key words *meso*(*syn*-*syn*)-1,3,5-triacetoxy-2,4-dimethylpentane: *meso*(*syn*-*syn*)-3-benzyloxy-2,4-dimethylpentane-1,5-diol; enzymatic hydrolysis; enzymatic acetylation

Many macrolide antibiotics[1] and ionophores[2] possess a straight-chain portion bearing methyl and hydroxy groups. Consequently, the control of stereochemistry is an important problem in the synthesis of these compounds. The spiroketal compound A, which is regarded as an essential chiral building block for the synthesis of tautomycin,[3] can be retro-synthetically divided into an acetone unit and two chiral parts (B and C). We have already synthesized several chiral synthons corresponding to C, in which methyl and hydroxy groups are consecutively arranged with *anti* configuration, based on kinetic resolution using lipase.[4] We wish to report here the lipase-catalyzed hydrolysis of *meso* triacetate (**4**) and acetylation of *meso* triol (**1**) or *meso* diol (**15**) for the purpose of the synthesis of chiral part B.

First, enzymatic acetylation of the triol **1** and hydrolysis of the triacetate **4** were carried out. The triol **1** was prepared according to Harada's method[5] and the triacetate **4** was obtained by acetylation (81%) of **1**. Based on a screening experiment, the lipase Lilipase B4 from *Rhizopus japonicus* was selected as a catalyst. Treatment of **1** with Lilipase B4 in the presence of vinyl acetate proceeded smoothly to afford the (+)-diol (**2**) (56%, 53% ee) along with the alcohol (**3**) (12%) and recovered **1** (31%) after 1 d. On the other hand, enzymatic hydrolysis of **4** with the lipase in water-saturated isopropyl ether at 33 °C gave the (+)-alcohol (**5**) (28%) in high enantiomeric excess (93% ee) along with recovered **4** (63%), but the reaction rate was very slow. In order to increase the reaction rate, **4** was treated with Lilipase B4 at 70 °C for 2 d to give (+)-**5** in 39% yield along with recovered **4** (58%). Acceleration of reaction rate was observed but the enantiomeric excess markedly declined. The values of enantiomeric excess of (+)-**2** and (+)-**5** were determined by HPLC analysis of the corresponding benzoates (+)-(**7**) and (−)-(**6**) using a chiral column.

For determination of their absolute configuration, (+)-**2** and (+)-**5** were converted into the alcohol (**9**), whose optical rotation and absolute configuration had been already established.[6] Acetalization (94%) of (+)-**2** followed by hydrolysis (97%) afforded (−)-**9** ($[\alpha]_D^{23}$ −4.2° (c=1.73, $CHCl_3$)). Meanwhile, protection (96%) of (+)-**5** with *tert*-butyldimethylsilyl chloride (TBDMSCl) followed by hydrolysis (93%) gave a (+)-diol (**11**). Acetalization (80%) of (+)-**11** followed by desilylation (90%) provided (−)-**9** ($[\alpha]_D^{23}$ −6.7° (c=1.12, $CHCl_3$)). The signs of their optical rotations were the same as that of (1*R*,4S,5*S*)-**9** ($[\alpha]_D^{22}$ −7.1° (c=1.39, $CHCl_3$)) reported by Born and Tamm.[6] Thus, the absolute configurations of (+)-**2** and (+)-**5** were determined to be (2*S*,3*R*,4*R*) and (2*R*,3*S*,4*S*), respectively.

These findings implied that i) acetylation was much faster than hydrolysis, ii) the presence of the free secondary alcohol appeared to favor low enantioselectivity. We then tried asymmetric acetylation of a meso diol **15**, whose secondary alcohol was protected by a benzyl group. Selective protection of the primary alcohol of **1** with TBDMSCl gave a silyl ether (**13**) in 80% yield. Benzylation of **13** followed by treatment with tetrabutylammonium fluoride (TBAF) afforded the desired diol **15** in 58%

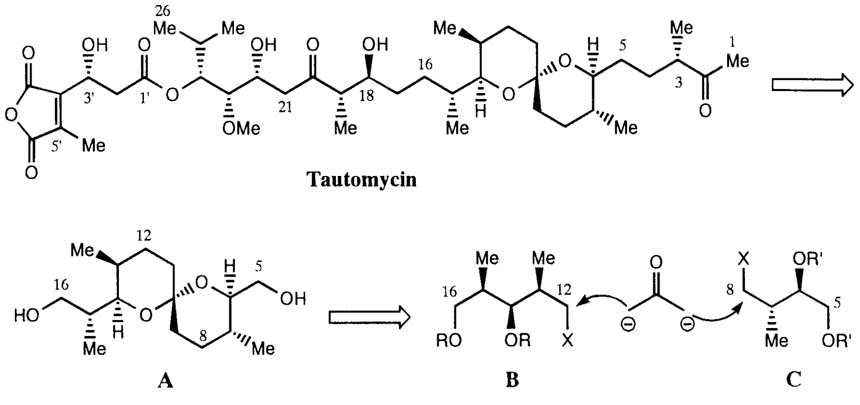
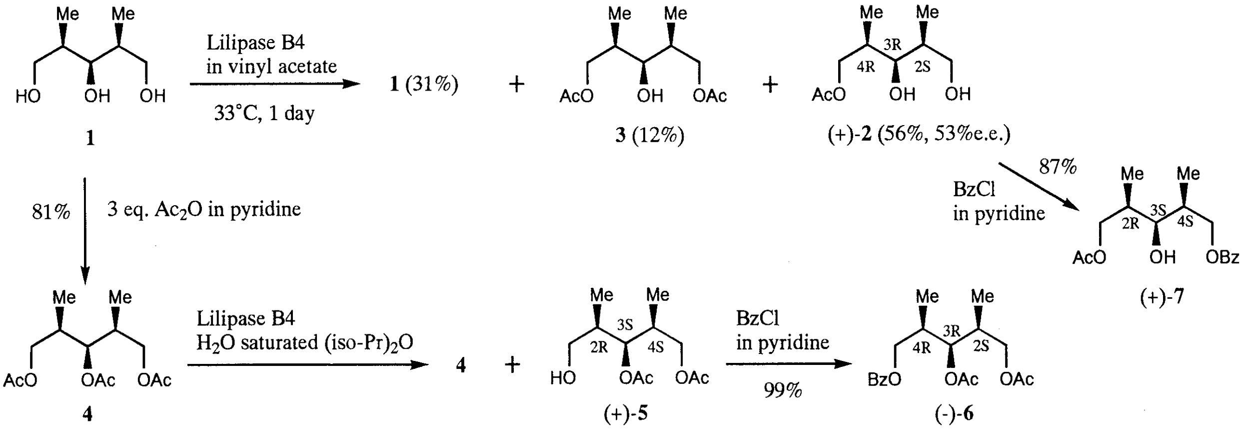


Chart 1

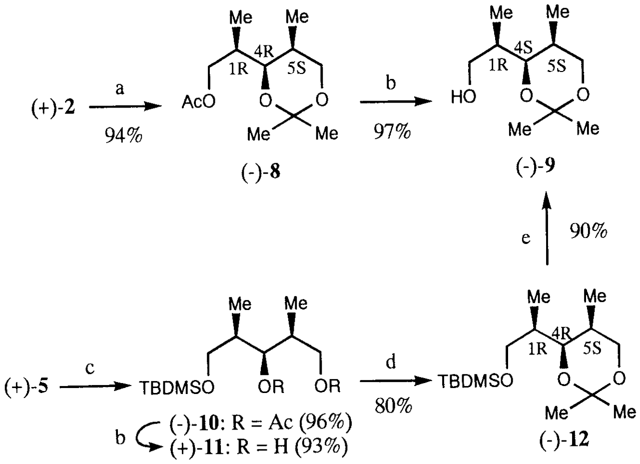
---

* To whom correspondence should be addressed.



Temperature	Reaction time	4	(+)-5
33°C	10 days	63%	28% (93%e.e.)
70°C	2 days	58%	39% (76%e.e.)

Chart 2



Reagents: a) $(MeO)_2CMe_2$, TsOH in acetone; b) K_2CO_3 in MeOH; c) TBDMSCl, imidazole in DMF; d) $(MeO)_2CMe_2$, CSA in benzene; e) TBAF in THF.

Chart 3

overall yield. Enzymatic acetylation of **15** with Lilipase B4 in the presence of vinyl acetate proceeded smoothly. Contrary to our expectation, the enantiomeric excess of a (−)-monoacetate (**16**) was inadequate. In a screening experiment, the lipase from *Porcine Pancreas* (PPL) was found to promote the acetylation of **15**. Thus, exposure of **15** to the lipase "PPL" in vinyl acetate at 33 °C gave (−)-**16** with high enantiomeric excess (95% ee) in 87% yield after 2 d. The absolute configuration of (−)-**16** was determined to be 2*S*, 3*R*, 4*R* by chemical conversion into the above-mentioned (+)-**2**. In conclusion, the synthesis of (−)-**16**, regarded as a useful chiral synthon for the synthesis of the C_{12}–C_{16} moiety of tautomycin, was achieved with high enantiomeric excess by using an enzymatic reaction.

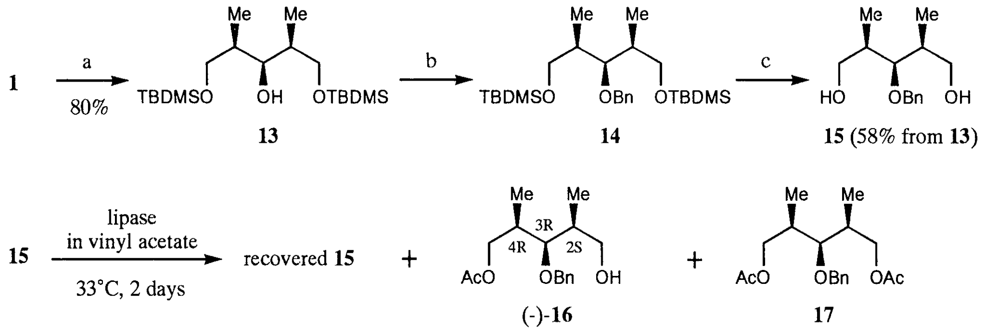
Experimental

Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained on a JASCO FT/IR-300 spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL JNM-EX400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d). triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were obtained on a JEOL JMS-D300 or JEOL LMS-DX303 spectrometer. For column chromatography, Silica gel 60 (Merck 7734) was employed. The HPLC system was composed of two SSC instruments (UV detector 3000B and flow system 3100). Chiralcel OD (4.6 x 250 mm) was used as a chiral column.

(2*S*,3*R*,4*R*)-5-Acetoxy-2,4-dimethylpentane-1,3-diol ((+)-2) and *meso*-(*syn*-*syn*)-1,5-Diacetoxy-2,4-dimethylpentan-3-ol (3) A mixture of **1** (210 mg, 1.42 mmol), lipase Lilipase B4 (140 mg) and vinyl acetate (30 ml) was incubated at 33 °C for 1 d. The reaction mixture was filtered and the filtrate was concentrated to give a crude product, which was purified by column chromatography on silica gel to give (+)-**2** (151 mg, 0.795 mmol, 56%) as a colorless oil, along with recovered **1** (64.8 mg, 0.438 mmol, 31%) and **3** (39.4 mg, 0.170 mmol, 12%). The enantiomeric excess of (+)-**2** was calculated by HPLC analysis of the readily obtainable benzoate (+)-(**7**) on a chiral column (Chiralcel OD, 4.6 × 250 mm). (+)-(**2**): $[\alpha]_D^{21}$ +3.6° (c=1.52, $CHCl_3$). IR (neat): 3410, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.10 (1H, dd, J=11.2, 5.9 Hz), 3.92 (1H, dd, J=15.1, 5.9 Hz), 3.69—3.62 (3H, m), 2.61 (1H, br s), 2.33 (1H, br s), 2.07 (3H, s), 1.99 (1H, m), 1.82 (1H, m), 1.04 (3H, d, J=6.8 Hz), 1.01 (3H, d, J=7.3 Hz). FAB-MS m/z: 191 (M^++1). *Anal.* Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 55.52; H, 9.72. **3**: IR (neat): 3495, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.13 (2H, dd, J=11.2, 6.4 Hz), 3.90 (2H, dd, J=11.2, 5.9 Hz), 3.44 (1H, t, J=5.9 Hz), 2.07 (6H, s), 1.97 (2H, m), 1.31 (1H, br s), 1.00 (6H, d, J=6.8 Hz). FAB-MS m/z: 233 (M^++1).

***meso*(*syn*-*syn*)-1,3,5-Triacetoxy-2,4-dimethylpentane (4)** Acetic anhydride (20 ml) was added to a solution of **1** (1.72 g, 11.6 mmol) in pyridine (30 ml) and the reaction mixture was stirred for 3 h at room temperature. Ether and 7% aqueous $NaHCO_3$ were added to the mixture. After extraction, the organic layer was washed with 2 N HCl, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give **4** (2.58 g, 0.942 mmol, 81%) as a colorless oil, IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.04 (1H, t, J=5.9 Hz), 3.98 (2H, dd, J=11.2, 6.8 Hz), 3.90 (2H, dd, J=11.2, 5.9 Hz), 2.13 (2H, m), 2.07 (3H, s), 2.06 (6H, s), 0.96 (6H, d, J=6.8 Hz). FAB-MS m/z: 275 (M^++1). *Anal.* Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 57.05; H, 8.27.

(2*R*,3*S*,4*S*)-3,5-Diacetoxy-2,4-dimethyl-1-pentanol ((+)-5) A mixture of **4** (1.03 g, 3.76 mmol), lipase Lilipase B4 (500 mg) and H_2O-saturated isopropyl ether (100 ml) was incubated at 33 °C for 10 d. The reaction mixture was filtered and the filtrate was concentrated to give a crude product, which was purified by column chromatography on silica gel to give (+)-**5** (245 mg, 1.06 mmol, 28%) as a colorless oil, along with recovered **4** (651 mg, 2.38 mmol, 63%). $[\alpha]_D^{23}$ +8.4° (c =2.15, $CHCl_3$). IR (neat): 3460, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.02 (1H, dd, J=7.8, 3.4 Hz), 4.04 (1H, dd, J=11.2, 5.4 Hz), 3.93 (1H, dd, J=11.2, 5.9 Hz), 3.46 (1H, m), 3.25 (1H, m), 2.56 (1H, dd, J=8.8, 4.9 Hz), 2.18 (1H, m), 2.12 (3H, s), 2.07 (3H, s), 2.00 (1H, m), 0.99 (3H, d, J=6.8 Hz),



(-)-16 17

Lipase	Reaction time	15	(-)-16	17
Lilipase B4	3 days	33%	57% (71%e.e.)	9%
PPL	2 days	3%	87% (95%e.e.)	9%

(-)-**16** $\xrightarrow[99\%]{\text{d}}$ (+)-**2**

Reagents: a) TBDMSCl, imidazole in DMF b) BnBr, NaH in DMF c) Bu_4NF in THF d) H_2, 20% $Pd(OH)_2$-C in MeOH

Chart 4

0.85 (3H, d, J=7.3 Hz). FAB-MS m/z: 233 (M^++1). *Anal.* Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.70; H, 8.82.

(2*S*,3*R*,4*R*)-1,3-Diacetoxy-5-benzoyloxy-2,4-dimethylpentane ((−)-6) Benzoyl chloride (0.01 ml) was added to a solution of (+)-**5** (11.7 mg, 0.0504 mmol) in pyridine (0.2 ml) and the reaction mixture was stirred for 30 min at room temperature. Ether and 7% aqueous $NaHCO_3$ were added. The organic layer was washed with 2 N HCl, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**6** (16.8 mg, 0.0499 mmol, 99%) as a colorless oil, $[\alpha]_D^{21}$ −13.0° (c=1.45, $CHCl_3$). IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.05 (2H, m), 7.57 (1H, m), 7.45 (2H, m), 5.20 (1H, t, J=5.9 Hz), 4.24 (1H, dd, J=11.2, 5.9 Hz), 4.19 (1H, dd, J=11.2, 6.4 Hz), 3.98 (1H, dd, J=10.8, 6.8 Hz), 3.91 (1H, dd, J=10.8, 5.4 Hz), 2.33—2.18 (2H, m), 2.09 (3H, s), 1.99 (3H, s), 1.06 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.8 Hz). FAB-MS m/z: 337 (M^++1). *Anal.* Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.30.

(2*R*,3*S*,4*S*)-1-Acetoxy-5-benzoyloxy-2,4-dimethylpentan-3-ol ((+)-7) Benzoyl chloride (0.03 ml) was added to a solution of (+)-**2** (25.6 mg, 0.135 mmol) in pyridine (0.5 ml) and the reaction mixture was stirred for 3 h at room temperature. Ether and 7% aqueous $NaHCO_3$ were added to the mixture. After extraction, the organic layer was washed with 2 N HCl, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (+)-**7** (34.4 mg, 0.117 mmol, 87%) as a colorless oil, $[\alpha]_D^{21}$ +1.1° (c=1.70, $CHCl_3$). IR (neat): 3510, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.03 (2H, m), 7.57 (1H, m), 7.45 (2H, m), 4.39 (1H, dd, J=11.0, 6.6 Hz), 4.19—4.13 (2H, m), 3.92 (1H, dd, J=11.0, 5.5 Hz), 3.56 (1H, t, J=5.5 Hz), 2.19—2.01 (3H, m), 2.00 (3H, s), 1.11 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz). FAB-MS m/z: 295 (M^++1). *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 64.27; H, 7.19. Found: C, 64.77; H, 7.66.

(4*R*,5*S*)-4-[(1*R*)-2-Acetoxy-1-methylethyl]-2,2,5-trimethyl-1,3-dioxne ((−)-8) A trace of TsOH was added to a mixture of (+)-**2** (29.2 mg, 0.154 mmol), 2,2-dimethoxypropane (0.5 ml) and acetone (0.5 ml) and the reaction mixture was stirred for 1 h at room temperature. Ether and 7% aqueous $NaHCO_3$ were added to the mixture. After extraction, the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**8** (33.2 mg, 0.144 mmol, 94%) as a colorless oil, $[\alpha]_D^{23}$ −2.2° (c=1.48, $CHCl_3$). IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.10—4.02 (2H, m), 3.89 (1H, dd, J=11.2, 6.4 Hz), 3.66 (1H, dd, J=9.8, 2.4 Hz), 3.59 (1H, dd, J=11.2, 2.0 Hz), 2.07 (3H, s), 1.90 (1H, m), 1.54 (1H, m), 1.42 (3H, s), 1.40 (3H, s), 1.10 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=6.4 Hz). FAB-MS m/z: 231 (M^++1). *Anal.* Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.22; H, 9.88.

(4*S*,5*S*)-4-[(1*R*)-2-Hydroxy-1-methylethyl]-2,2,5-trimethyl-1,3-dioxane ((−)-9) A solution of (−)-**8** (29.8 mg, 0.130 mmol) in MeOH (1 ml) was treated with K_2CO_3 (5 mg) and the reaction mixture was stirred for 30 min at room temperature. Ether and brine were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**9** (23.7 mg, 0.126 mmol, 97%) as a colorless oil, $[\alpha]_D^{22}$ −4.2° (c=1.73, $CHCl_3$). IR (neat): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.09 (1H, dd, J=11.5, 2.5 Hz), 3.76 (1H, dd, J=9.5, 2.0 Hz), 3.63 (1H, dd, J=10.7, 4.4 Hz), 3.58 (1H, dd, J=11.5, 2.0 Hz), 3.53 (1H, dd, J=10.7, 5.4 Hz), 1.75 (1H, m), 1.60 (1H, m), 1.43 (3H, s), 1.40 (3H, s), 1.11 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.4 Hz). FAB-MS m/z: 189 (M^++1). *Anal.* Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.59; H, 10.94.

(2*S*,3*R*,4*R*)-1,3-Diacetoxy-5-(*tert*-Butyldimethylsilyl)oxy-2,4-dimethylpentane ((−)-10) Imidazole (230 mg, 3.38 mmol) was added to a mixture of (+)-**5** (270 mg, 1.16 mmol), TBDMSCl (260 mg, 1.73 mmol) and *N*,*N*-dimethylformamide (DMF) (3 ml) imidazole (230 mg, 3.38 mmol) under ice cooling and the reaction mixture was stirred for 1 h at room temperature. Ether and brine were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**10** (386 mg, 1.11 mmol, 96%) as a colorless oil, $[\alpha]_D^{22}$ −8.3° (c=1.18, $CHCl_3$). IR (neat): 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.07 (1H, dd, J=6.4, 4.9 Hz), 3.95 (1H, dd, J=11.0, 7.0 Hz), 3.86 (1H, dd, J=11.0, 6.0 Hz), 3.49 (1H, dd, J=10.0, 5.9 Hz), 3.45 (1H, dd, J=10.0, 5.9 Hz), 2.19 (1H, m), 2.05 (3H, s), 2.04 (3H, s), 1.91 (1H, m), 0.94 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=5.9 Hz), 0.89 (9H, s), 0.04 (6H, s). FAB-MS m/z: 347 (M^++1). *Anal.* Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 58.41; H, 10.08.

(2*S*,3*R*,4*R*)-5-(*tert*-Butyldimethylsilyl)oxy-2,4-dimethylpentane-1,3-diol ((+)-11) A solution of (−)-**10** (356 mg, 1.03 mmol) in MeOH (5 ml) was treated with K_2CO_3 (350 mg) and the reaction mixture was stirred for 30 min at room temperature. Ether and brine were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (+)-**11** (252 mg, 0.96 mmol, 93%) as a colorless oil, $[\alpha]_D^{22}$ +3.8° (c=1.43, $CHCl_3$). IR (neat): 3375 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.78 (1H, t, J=4.9 Hz), 3.73—3.60 (4H, m), 3.04 (1H, br s), 2.11 (1H, br s), 1.86—1.80 (2H, m), 1.04 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz), 0.90 (9H, s), 0.06 (6H, s). FAB-MS m/z: 263 (M^++1). *Anal.* Calcd for $C_{13}H_{30}O_3Si$: C, 59.49; H, 11.52. Found: C, 58.87; H, 11.83.

(4*R*,5*S*)-4-[(1*R*)-2-(*tert*-Butyldimethylsilyl)oxy-1-methylethyl]-2,2,5-trimethyl-1,3-dioxane ((−)-12) (+)-Camphorsulfonic acid ((+)-CSA) (20 mg) was added to a mixture of (+)-**11** (233 mg, 0.888 mmol), 2,2-dimethoxypropane (2 ml) and benzene (3 ml) and the reaction mixture was stirred for 12 h at room temperature. Ether and 7% aqueous $NaHCO_3$ were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**12** (214 mg, 0.707 mmol, 80%) as a colorless oil, $[\alpha]_D^{22}$ −8.2° (c=1.44, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 4.07 (1H, dd, J=11.2, 2.9 Hz), 3.72 (1H, dd, J=9.8, 2.4 Hz), 3.58 (1H, dd, J=11.2, 1.5 Hz), 3.47 (2H, d, J=4.4 Hz), 1.71—1.60 (2H, m), 1.42 (3H, s), 1.40 (3H, s), 1.10 (3H, d, J=7.3 Hz), 0.97 (3H, d, J=6.8 Hz), 0.89 (9H, s), 0.03 (6H, s). FAB-MS m/z: 303 (M^++1). *Anal.* Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.40; H, 11.65.

Desilylation of (−)-12 TBAF (340 mg, 1.30 mmol) was added to a solution of (−)-**12** (195 mg, 0.645 mmol) in THF (3 ml) and the reaction mixture was stirred for 1 h at room temperature. Ether and brine were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give (−)-**9** (109 mg, 0.580 mmol, 90%) as a colorless oil, $[\alpha]_D^{23}$ −6.7 (c=1.12,

$CHCl_3$).

***meso*(*syn*-*syn*)-1,5-Di(*tert*-butyldimethylsilyl)oxy-2,4-dimethylpentan-3-ol (13)** Imidazole (19.9 g, 293 mmol) was added to a mixture of **1** (14.4 g, 97.3 mmol), TBDMSCl (33.8 g, 224 mmol) and DMF (200 ml) under ice cooling and the reaction mixture was stirred for 3 h at room temperature. Ether and brine were added. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to give **13** (29.3 g, 77.8 mmol, 80%) as a colorless oil. IR (neat): 3520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (1H, t, $J=2.4$ Hz), 3.64 (2H, dd, $J=9.8$, 4.4 Hz), 3.55 (2H, dd, $J=9.8$, 4.9 Hz), 1.80 (2H, m), 1.00 (6H, d, $J=6.8$ Hz), 0.89 (18H, s), 0.05 (12H, s). FAB-MS *m/z*: 377 ($M^+ + 1$). *Anal.* Calcd for $C_{19}H_{44}O_3Si_2$: C, 60.57; H, 11.77. Found: C, 60.79; H, 11.69.

***meso*(*syn*-*syn*)-3-Benzyloxy-2,4-dimethylpentane-1,5-diol (15)** Benzyl bromide (20.4 g, 119 mmol) was added to a mixture of **13** (30.0 g, 79.6 mmol), 60% NaH (4.80 g, 120 mmol) and DMF (200 ml), and the reaction mixture was stirred for 12 h at room temperature. Ether and brine were added under ice cooling, and the organic layer was dried over $MgSO_4$ and concentrated. The crude **14** was taken up in THF (200 ml), TBAF (62.4 g, 239 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. Ether and brine were added and the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel and further recrystallized from acetone to give **15** (11.0 g, 46.2 mmol, 58%) as white needles: mp 83—84 °C. IR (Nujol): 3230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.35—7.25 (5H, m), 4.62 (2H, s), 3.64 (1H, t, $J=4.9$ Hz), 3.57 (4H, d, $J=5.4$ Hz), 2.72 (2H, br s), 2.00 (2H, m), 1.00 (6H, d, $J=7.3$ Hz). FAB-MS *m/z*: 239 ($M^+ + 1$). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.37; H, 9.47.

(2*S*,3*R*,4*R*)-5-Acetoxy-3-benzyloxy-2,4-dimethylpentanol ((−)-16) and *meso*(*syn*-*syn*)-3-Benzyloxy-1,5-diacetoxy-2,4-dimethylpentane (17) A mixture of **15** (223 mg, 0.852 mmol), lipase PPL (140 mg) and vinyl acetate (30 ml) was incubated at 33 °C for 2 d. The reaction mixture was filtered and the filtrate was concentrated to give a crude product, which was purified by column chromatography on silica gel to give (−)-**16** (227 mg, 0.811 mmol, 87%) as a colorless oil, along with recovered **15** (5.6 mg, 0.024 mmol, 3%) and **17** (24.7 mg, 0.077 mmol, 9%). The enantiomeric excess of (−)-**16** was calculated by HPLC analysis using a chiral column (Chiralcel OD, 4.6 × 250 mm). (−)-**16**: $[\alpha]_D^{21}$ −8.3° ($c=1.08$, $CHCl_3$). IR (neat): 3445, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.35—7.27 (5H, m), 4.61 (1H, d, $J=11.2$ Hz), 4.58 (1H, d, $J=11.2$ Hz), 4.04 (1H, dd, $J=10.8$, 6.4 Hz), 3.98 (1H, dd, $J=10.8$, 6.4 Hz), 3.63 (1H, dd, $J=10.8$, 6.8 Hz), 3.56 (1H, dd, $J=10.8$, 5.4 Hz), 3.53 (1H, t, $J=4.9$ Hz), 2.17—1.99 (3H, m), 2.06 (3H, s), 1.05 (3H, d, $J=6.8$ Hz), 0.98 (3H, d, $J=6.8$ Hz). FAB-MS *m/z*: 281 ($M^+ + 1$). *Anal.* Calcd for $C_{16}H_{24}O_4$: C, 68.54. H, 8.63. Found: C, 68.27; H, 8.84. **17**: IR (neat): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.26 (5H, m), 4.56 (2H, s), 4.04 (2H, dd, $J=11.2$, 6.4 Hz), 3.98 (1H, dd, $J=11.2$, 6.4 Hz), 3.41 (1H, t, $J=5.4$ Hz), 2.13—2.07 (2H, m), 2.06 (6H, s), 1.03 (6H, d, $J=6.8$ Hz). FAB-MS *m/z*: 323 ($M^+ + 1$).

References and Notes

1) O'Hagan D., *Nat. Prod. Rep.*, **12**, 1 (1995).

2) Dutton C. J., Banks B. J., Cooper C. B., *Nat. Prod. Rep.*, **12**, 165 (1995).

3) *a*) For isolation: Cheng X.-C., Kihara T., Kusakabe H., Magae J., Kobayashi Y., Fang R.-P., Ni Z.-F., Shen Y.-C., Ko K., Yamaguchi I., Isono K., *J. Antibiot.*, **40**, 907 (1987); *b*) For structure: Cheng X.-C., Ubukata M., Isono K., *ibid.*, **43**, 809 (1990); *c*) For absolute configuration: Ubukata M., Cheng X.-C., Isobe M., Isono K., *J. Chem. Soc., Perkin Trans. 1*, **1993**, 617; *d*) For biological activity: Hori M., Magae J., Han Y.-G., Karaki H., Hartshorne D. J., *FEBS Lett.*, **285**, 145 (1991); Magae J., Watanabe C., Osada H., Cheng X.-C., Isono K., *J. Antibiot.*, **41**, 932 (1988); Magae J., Hino A., Isono K., Nagai K., *ibid.*, **45**, 246 (1992); Kurisaki T., Magae J., Isono K., Nagai K., Yamasaki M., *ibid.*, **45**, 252 (1992); *e*) For synthesis: Oikawa H., Oikawa M., Ueno T., Ichihara A., *Tetrahedron Lett.*, **35**, 4809 (1994); Oikawa M., Ueno T., Oikawa H., Ichihara A., *J. Org. Chem.*, **60**, 5048 (1995); Ichikawa Y., Katsunori T., Jiang Y., Naganawa A., Isobe M., *Tetrahedron Lett.*, **36**, 7101 (1995).

4) Akita H., Matsukura H., Oishi T., *Tetrahedron Lett.*, **27**, 5241 (1986); Akita H., Chen C.-Y., Uchida K., *Tetrahedron: Asymmetry*, **6**, 2131 (1995).

5) For synthesis of **1**: Harada T., Wada I., Uchimura J., Inoue A., Tanaka S., Oku A., *Tetrahedron Lett.*, **32**, 1219 (1991).

6) Born M., Tamm C., *Tetrahedron Lett.*, **30**, 2083 (1989).