Alternative Syntheses of the C9—C15 and C1—C5 Segments of Erythronolide A *via* Regio- and Stereo-Selective Reductive Ring Opening of 2,3-Epoxy Alcohols[1)]

Hitoshi TONE, Masataka HIKOTA, Tatsuo HAMADA, Takao NISHI, Yuji OIKAWA and Osamu YONEMITSU*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kitaku, Sapporo 060, Japan. *Received August 26, 1988*

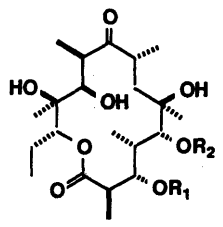
Improved syntheses are described of two segments required for the total synthesis of (9*S*)-9-dihydroerythronolide A, *i.e.*, (2*S*,3*R*,4*S*,5*R*)-2,4-dimethyl-5-(4-methoxybenzyloxy)heptane-1,3,4-triol corresponding to the C9—C15 subunit and (2*S*,3*R*,4*R*)-5-benzyloxy-2,3-dimethylpentane-1,4-diol corresponding to the C1—C5 subunit, *via* regio- and stereo-selective reduction of 2,3-epoxy alcohols.

Keywords macrolide antibiotic; erythromycin A; aglycone; erythronolide A; D-glucose; 2,3-epoxy alcohol; stereoselective reduction; protecting group; segment synthesis

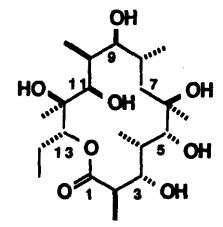
Because of their complex chemical structures as well as significant biological and pharmacological activities, polyketide-derived natural products such as macrolide and polyether antibiotics with multiple chiral centers have received much recent synthetic attention, and many modern synthetic methodologies have been developed during rather formidable total syntheses of such complex compounds. Recently we also planned to synthesize a series of representative natural products mainly from D-glucose by a common methodology consisting of means of selective use of benzyl-type protecting groups[2)] as well as stereochemical control in both cyclic and acyclic systems, and we reported highly stereoselective syntheses of macrolide aglycones (methynolide,[3)] pikronolide,[4)] tylonolide[5)]) and a polyether salinomycin.[1,6)] Our synthetic methodology has now been applied to one of several plans for the synthesis of erythromycin A (**1**), which is still a challenging target for modern synthetic chemists[7)] as well as an important therapeutic agent. We have achieved a total synthesis of (9*S*)-9-dihydroerythronolide A (**3**), which has already been converted to **2**[7d)] and **1**.[7b)] We describe alternative syntheses of the C9—C15 (**4**) and C1—C5 segments (**5**) of **3** in the present paper, Wittig–Horner coupling of the C1—C6 and C7—C15 segments in the following paper,[8)] and the total synthesis in the third paper.[9)]

Recently the C9—C15 segment (**4**)[10)] was synthesized from D-glucose *via* the diol (**6**) using kinetic acetalization[11)] and reduction with aluminum hydride. However, this method required some improvements, because some intermediates were too labile even to a trace of acid. In this paper we describe two new syntheses of **4**. One is a slightly modified but more convenient method, and the other is a simpler method starting from propionaldehyde.

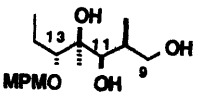
Although the C1—C5 segment (**5**) was also synthesized from D-glucose,[12)] a convenient method starting from methallyl alcohol is presented here.



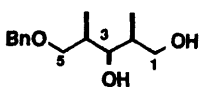
1 : R_1=L-cladinosyl
R_2=D-desosaminyl
2 : R_1, R_2=H



3



4



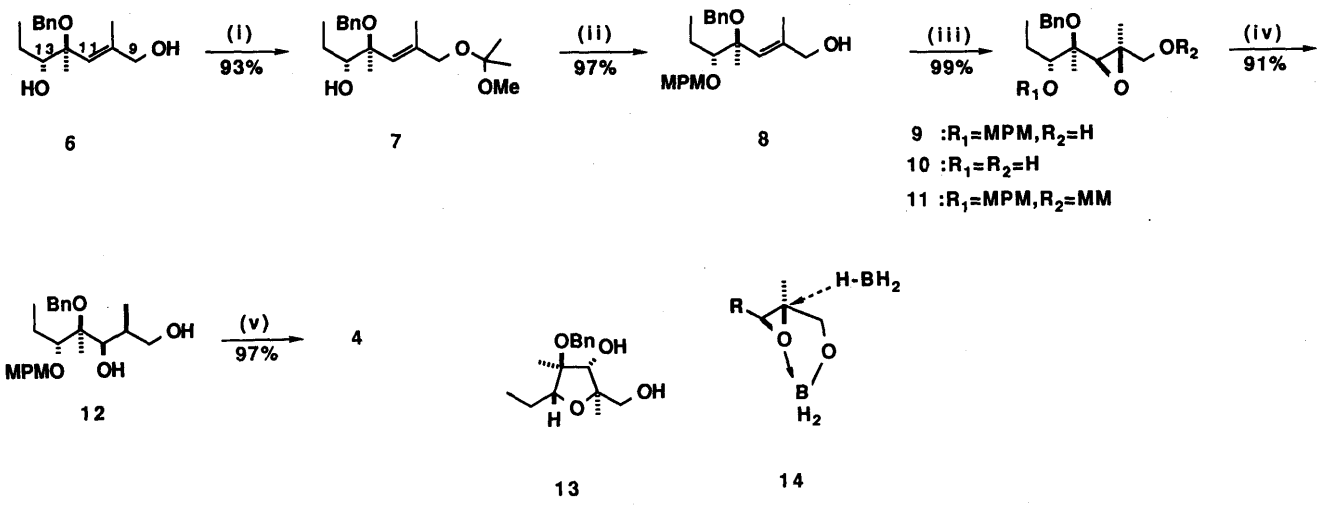
5

Chart 1

Results and Discussion

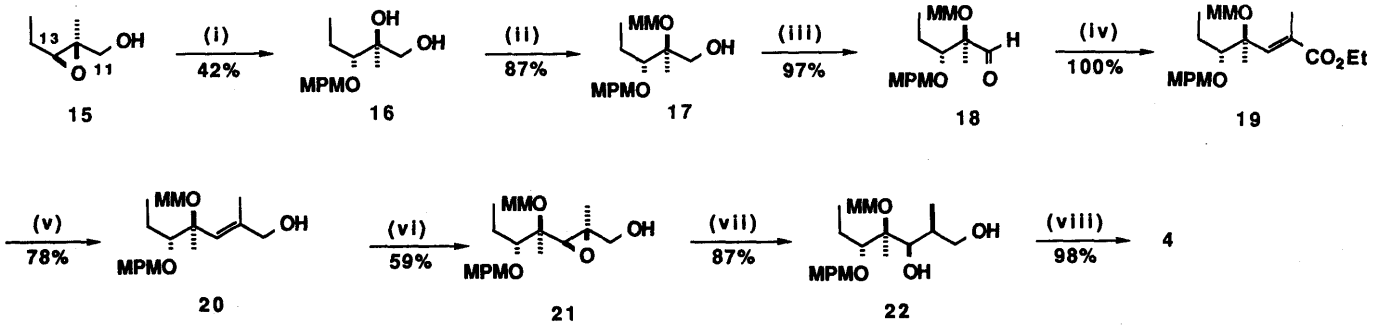
An Improved Synthesis of 4 from D-Glucose *via* 6 The 9,13-diol (**6**)[13)] was readily converted to the allyl alcohol (**8**) *via* three conventional reactions, selective protection of the primary alcohol with a *tert*-butyldimethylsilyl (TBDMS) group, *p*-methoxybenzyl (MPM) protection[2a,d)] of the remaining secondary alcohol, and removal of the TBDMS group with tetra-*n*-butylammonium fluoride. However, the overall yield was only 43%, because formation of a di-MPM compound was unavoidable during the second reaction with loss of the TBDMS group. Therefore, the protecting group of the primary alcohol was changed to an acid-sensitive methoxyisopropyl (MIP) group. The MIP protection with dimethoxypropane[14)] is usually highly selective toward primary alcohols and stable under chromatographic conditions on silica gel as well as to alkali treatment.[4,5)] Treatment of **6** with dimethoxypropane in the presence of camphorosulfonic acid (CSA) gave **7**, which was treated with MPM chloride in the presence of sodium hydride,[2a,d)] then with 10% hydrochloric acid to recover the primary alcohol, and the allyl alcohol (**8**) was isolated in excellent yield. Stereo-selective epoxidation of **8** with *m*-chloroperbenzoic acid (*m*-CPBA) proceeded smoothly at 0 °C to give the expected epoxy alcohol (**9**) in quantitative yield with excellent selectivity (20 : 1).[12,15,16)]

Regio- and stereo-selective reductive ring opening of **9** to **12** was crucial. When **9** was treated with lithium aluminum hydride (LAH) and aluminum chloride in ether,[17)] diisobutylaluminum hydride (DIBAH) in dichloromethane,[18)] or sodium cyanoborohydride ($NaBH_3CN$) in the presence of boron trifluoride etherate ($BF_3 \cdot Et_2O$) in tetrahydrofuran (THF) as described in the following paper,[8,19)] unfortunately **13** was mainly obtained *via* the recyclization of **9** catalyzed by a strong Lewis acid. In order to avoid such a side reaction, **9** was first treated with $NaBH_3CN$ and then



(i) $Me_2C(OMe)_2$, CSA, benzene, r.t., 10 min; (ii) a) MPMCl, NaH, DMF, r.t., 24 h, b) 10% HCl, CH_2Cl_2; (iii) *m*-CPBA, CH_2Cl_2, 0 °C, 3 h; (iv) B_2H_6, HMPA–THF (1 : 2), r.t., 10 h; (v) Raney Ni (W-2), H_2, EtOH, r.t., 2 h.

Chart 2



(i) MPMOH, Ti(iso-PrO)$_4$, benzene, r.t., 45 h; (ii) a) Ac_2O, Et_3N, DMAP, r.t., 1 h, b) MMCl, iso-Pr_2EtN, CH_2Cl_2, 45 °C, 8 h, c) 1 N NaOH, MeOH, r.t., 75 min; (iii) PCC, MS 3A, CH_2Cl_2, r.t., 2 h; (iv) $Ph_3P{=}CMeCO_2Et$, EDC, reflux, 96 h; (v) $LiAlH_4$, Et_2O, −15 °C, 80 min; (vi) *m*-CPBA, CH_2Cl_2, −20 °C, 2 h; (vii) B_2H_6, HMPA–THF (1 : 3), r.t., 14 h; (viii) 67% AcOH, r.t., 46 h.

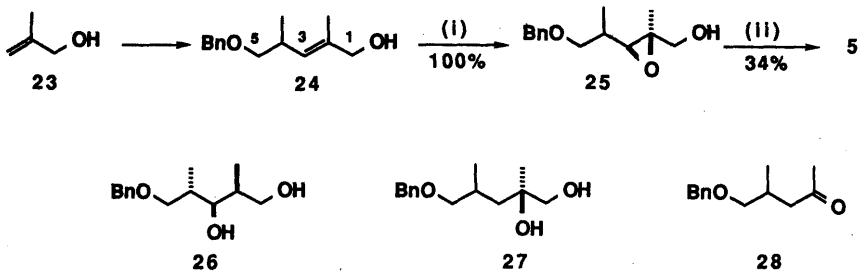
Chart 3

diborane (B_2H_6) in hexamethyl phosphoramide (HMPA)–THF[20] to give only **12** in high yield. However, reduction with only a large excess of B_2H_6 in HMPA–THF (1 : 2), namely, in the absence of $NaBH_3CN$, gave almost the same result. Because methoxymethyl (MM)-protected **11** was recovered unchanged under the same conditions, the completely regio- and stereoselective reduction of the 2,3-epoxy alcohol (**9**) can be explained as a reaction *via* a controlled transition state such as **14**, in which B_2H_6 probably acted as both a weak Lewis acid and a reductant.[21]

The benzyl group of **12** was selectively removed by means of a catalytic hydrogenation with Raney nickel recently developed in this laboratory[2c,d] to give the C9—C15 segment (**4**) in almost quantitative yield. The overall yield of **4** from **6** was 70—73%, whereas it was 33% in the previous method.[10]

Synthesis of 4 from Propionaldehyde *via* 15 The other simpler synthesis of **4** is as follows. The epoxy alcohol (**15**),[24a] derived readily from propionaldehyde *via* the Sharpless asymmetric epoxidation,[24] was treated with MPM alcohol in the presence of titanium (IV) isopropoxide,[25] and regioselective ring opening occurred to give mainly the 13-*O*-MPM compound (**16**), though both the yield and selectivity (8.7 : 1) were unsatisfactory. Since **16** was unable to be separated from its regioisomer, purification of the product was achieved after its conversion into **17** *via* three conventional reactions, selective acetylation of the primary alcohol, MM protection of the remaining tertiary alcohol, and removal of the acetyl protection. Purified **17** obtained by column chromatography was oxidized with pyridinium chlorochromate (PCC) to give the aldehyde (**18**) almost quantitatively. When **18** was treated with a stable ylide[26] in refluxing ethylene dichloride (EDC), a smooth Wittig reaction proceeded to give the expected (*E*)-α,β-unsaturated ester (**19**), which was reduced with LAH into the (*E*)-allyl alcohol (**20**). Epoxidation of **20** with *m*-CPBA[15] took place very smoothly to give the epoxide (**21**), but in contrast with the case of formation of **9** and **10**, the stereoselectivity was unexpectedly poor (3 : 2), though **21** was still the major product, which was easily separated from its isomer by column chromatography. The reductive ring opening of **21** with B_2H_6 in HMPA–THF, however, proceeded with complete regio- and stereo-selectivities to give the expected diol (**22**), which was readily converted to the C9—C15 segment (**4**) by removal of the MM protecting group with 67% acetic acid.

A Convenient Synthesis of 5 from Methallyl Alcohol (23) *via* 24 We have already reported the synthesis of the C1—



(i) L(+)-DET, Ti(iso-PrO)$_4$, *tert*-BuOOH, CH_2Cl_2, −60— −10 °C, 2.5 h; (ii) B_2H_6, HMPA–THF (1 : 2), r.t., 8 h.

Chart 4

C5 segment (**5**) starting from D-glucose, though rather many steps were required.[12] A more convenient and practical synthesis of **5** is as follows. The racemic allyl alcohol (**24**),[15] derived from methallyl alcohol (**23**) *via* five conventional reaction steps, was subjected to the Sharpless asymmetric epoxidation,[24] and a 1 : 1 diastereoisomeric mixture (with respect to C4) of epoxy alcohols (**25**) was obtained in quantitative yield. The reductive ring opening of the inseparable mixture (**25**) with B_2H_6 in HMPA–THF gave a mixture of diols, **5**, **26**, and **27** (1 : 1 with respect to C4). Treatment with sodium periodate followed by column chromatography gave **5**, **26**, and **28** in 34, 35, and 18% yields, respectively. Although the regioselectivity of the reductive ring opening of **25** into 1,3-diols (**5**, **26**) and 1,2-diols (**27**) was unsatisfactory (3.8 : 1), this synthetic method of **5** is practically useful, because **5** was synthesized in a rather large amount by only a seven-step conversion of methallyl alcohol and was readily separable from its isomers (**26**, **27**).[27]

Experimental

Unless otherwise noted, physical data were measured as follows. Melting points were measured on a Yamato MP-1 micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrophotometer. Low- and high-resolution mass spectra (MS) were taken on a JEOL JMS D-300 or JEOL JMS-01SG spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM FX-100, JEOL JNM GX-270, or JEOL JNM GX-500 instrument.

(2*E*,4*S*,5*R*)-4-Benzyloxy-5-hydroxy-1-(1-methoxy-1-methylethyl)-2,4-dimethyl-2-heptene (7) A solution of CSA (10-camphorsulfonic acid) (5 mg) in benzene (10 ml) was added to a stirred solution of **6** (2.64 g, 10 mmol) in dimethoxypropane (50 ml) and benzene (50 ml) at room temperature. After 10 min, Et_3N (10 ml) was added, and the reaction mixture was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with *n*-hexane–EtOAc (2 : 1) as the eluent to give **7** as a colorless oil (3.12 g, 93%). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J = 7.0 Hz), 1.20—2.00 (2H, m), 1.37 (3H, s), 1.82 (3H, br s), 2.20 (1H, d, J = 4.0 Hz), 3.21 (3H, s), 3.54 (1H, d, J = 10.0 Hz), 3.85 (2H, s), 4.36 (1H, d, J = 11.0 Hz), 4.54 (1H, d, J = 11.0 Hz), 5.47 (1H, br s), 7.31 (5H, s).

(2*E*,4*S*,5*R*)-4-Benzyloxy-2,4-dimethyl-5-(4-methoxybenzyloxy)hepta-2-en-1-ol (8) A solution of **7** (3.12 g, 9.29 mmol) was added to a stirred suspension of NaH (1.2 g, 50 mmol) in dimethylformamide (DMF) (100 ml). After evolution of H_2 had ceased, MPMCl (4-methoxybenzyl chloride) (4.7 g, 30 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h and then treated with Et_2NH (5 ml). After 5 h, the reaction mixture was poured into cold aqueous NH_4Cl and extracted with Et_2O. The extract was washed with brine, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml) and stirred with 10% HCl (30 ml) at room temperature for 30 min. The CH_2Cl_2 layer was separated, washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1) as the eluent to give **8** as a colorless oil (3.45 g, 97%). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J = 7.5 Hz), 1.20—2.00 (2H, m), 1.39 (3H, s), 1.83 (3H, d, J = 1.0 Hz), 3.48 (1H, dd, J = 6.5, 2.5 Hz), 3.79 (3H, s), 4.00 (2H, d, J = 4.0 Hz), 4.34 (1H, d, J = 11.0 Hz), 4.40 (1H, d, J = 11.0 Hz), 4.55 (2H, s), 5.48 (1H, q, J = 1.0 Hz), 6.86 (2H, d, J = 8.5 Hz), 7.24 (2H, d, J = 8.5 Hz), 7.31 (5H, s). MS m/z (relative intensity): 353 ($M^+ - 31$, 0.4), 276 (0.3), 233 (0.6), 211 (1.9), 205 (16), 145 (23), 121 (84), 91 (100). *Anal.* Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.44. Exact MS m/z Calcd for $C_{23}H_{29}O_3$ ($M^+ - 31$): 353.2115. Found: 353.2122.

(2*S*,3*R*,4*R*,5*R*)-4-Benzyloxy-2,4-dimethyl-2,3-epoxy-5-(4-methoxybenzyloxy)heptan-1-ol (9) *m*-CPBA (2.16 g, 10.6 mmol) was added to a stirred solution of **8** (3.40 g, 8.85 mmol) in CH_2Cl_2 (150 ml) at −20 °C. After 7 h, the solution was warmed to 0 °C and stirred for 3 h. The reaction mixture was washed successively with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1) as the eluent to give the epoxide (**9**) as a colorless oil (3.51 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J = 7.5 Hz), 1.28 (3H, s), 1.31 (3H, s), 1.30—2.10 (3H, m), 3.27 (1H, s), 3.47 (1H, dd, J = 8.5, 3.0 Hz), 3.50—3.70 (2H, m), 3.80 (3H, s), 4.77 (2H, s), 4.69 (2H, s), 6.86 (2H, d, J = 9.0 Hz), 7.26 (2H, d, J = 9.0 Hz), 7.31 (5H, br s). MS m/z (relative intensity): 369 ($M^+ - 15$, 0.35), 309 (1.0), 249 (7.0), 369 (6.5), 121 (100), 91 (87). *Anal.* Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.66; H, 8.16. Exact MS m/z Calcd for $C_{23}H_{29}O_4$ ($M^+ - 15$): 369.2065. Found: 369.2046.

(2*S*,3*S*,4*R*,5*R*)-4-Benzyloxy-2,4-dimethyl-2,3-epoxy-5-(4-methoxybenzyloxy)-1-methoxymethoxyheptane (11) A solution of **9** (19 mg, 0.047 mmol), chloromethyl methyl ether (11.4 mg, 0.142 mmol) and diisopropylethylamine (42.9 mg, 0.332 mmol) in CH_2Cl_2 (0.4 ml) was stirred at room temperature overnight. The solution was treated with MeOH and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (4 : 1) as the eluent to give **11** as a colorless oil (16.3 mg, 77%). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J = 7.5 Hz), 1.28 (3H, s), 1.36 (3H, s), 1.10—2.00 (2H, m), 3.16 (1H, s), 3.20—3.60 (3H, m), 3.36 (3H, s), 3.81 (3H, s), 4.60 (2H, s), 4.63 (2H, s), 4.69 (2H, s), 6.87 (2H, d, J = 9.0 Hz), 7.28 (2H, d, J = 9.0 Hz), 7.32 (5H, s). MS m/z (relative intensity) 369 ($M^+ - 75$, 0.2), 311 (0.3), 233 (0.8), 211 (5.9), 121 (100), 91 (68). Exact MS m/z Calcd for $C_{23}H_{29}O_4$ ($M^+ - 75$): 369.2065. Found: 369.2085.

(2*S*,3*R*,4*S*,5*R*)-4-Benzyloxy-2,4-dimethyl-5-(4-methoxybenzyloxy)-heptane-1,3-diol (12) A 1.0 M solution of B_2H_6 in THF (50 ml, 50 mmol) was added dropwise to a stirred solution of **9** (3.46 g, 8.65 mmol) in THF (50 ml) and HMPA (50 ml) at −20 °C. After 10 h at room temperature, the reaction mixture was diluted with Et_2O, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1) as the eluent to give the diol (**12**) as a colorless oil (3.16 g, 91%). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, J = 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 1.33 (3H, s), 1.50—2.10 (3H, m), 2.20—2.70 (1H, m), 3.40—3.80 (3H, m), 3.79 (3H, s), 3.92 (1H, dd, J = 5.5, 3.5 Hz), 4.56 (2H, s), 4.55 (1H, d, J = 11.0 Hz), 4.68 (1H, d, J = 11.0 Hz), 6.84 (2H, d, J = 9.0 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.33 (5H, s). MS m/z (relative intensity): 313 ($M^+ - 89$, 0.25), 223 (3.5), 211 (10), 121 (100), 115 (45), 91 (90). *Anal.* Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.36; H, 8.61. Exact MS m/z Calcd for $C_{20}H_{25}O_3$ ($M^+ - 89$): 313.1800. Found: 313.1803.

(2*S*,3*R*,4*S*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)heptane-1,3,4-triol (4) (a) A solution of **12** (2.73 g, 6.79 mmol) in EtOH (70 ml) was hydrogenated in the presence of Raney Ni W-2 (20 ml) at ordinary temperature and pressure for 7 h. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 1) as the eluent to give the

triol (**4**) as a colorless oil (2.06 g, 97%), which gradually solidified, mp 61—62 °C (from ether–hexane). $[\alpha]_D^{22}$ +23.7° (c=0.46, $CHCl_3$) [lit.,[10] mp 63—64 °C. $[\alpha]_D^{16}$ +23° (c=1.20, $CHCl_3$)].

(b) A solution of **22** (34.3 mg, 0.0964 mmol) in AcOH (1.6 ml) and H_2O (0.8 ml) was stirred at room temperature for 46 h. After dilution with H_2O, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), evaporated *in vacuo* to give **4** as a colorless oil (29.6 mg, 98%).

(2*S*,3*R*)-3-(4-Methoxybenzyloxy)-2-methylpentane-1,2-diol (16) Ti(iso-PrO)$_4$ (210 μl, 0.704 mmol) was added dropwise to a stirred solution of **15** (54.5 mg, 0.47 mmol) and 4-methoxybenzyl alcohol (MPMOH) (293 μl, 2.35 mmol) in benzene (2 ml) at room temperature. After 45 h, Et_2O (60 ml) and 5% H_2SO_4 (12 ml) were added, and the mixture was vigorously stirred for 2 h. The Et_2O layer was separated, washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1) as the eluent to give the diol (**16**) as a colorless oil (93 mg, 42%). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.0 Hz), 1.10 (3H, s), 1.38—1.92 (2H, m), 2.66 (1H, s), 2.85 (1H, s), 3.35 (1H, dd, J=8.0, 4.0 Hz), 3.77 (2H, d, J=11.0 Hz), 3.80 (3H, s), 4.55, 4.65 (1H each, ABq, J=10.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz).

(2*S*,3*R*)-3-(4-Methoxybenzyloxy)-2-methoxymethoxy-2-methylpentan-1-ol (17) Et_3N (0.2 ml, 1.42 mmol), DMAP (1.5 mg), and Ac_2O (0.1 ml, 1.06 mmol) were added to a stirred solution of **16** (26.2 mg, 0.103 mmol) in CH_2Cl_2 (5 ml) at room temperature. After 1 h, MeOH was added, and the stirring was continued for 30 min. The solution was diluted with Et_2O, washed successively with aqueous $KHSO_4$, brine, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave an oil, which was dissolved in CH_2Cl_2 (2 ml). Diisopropylethyl amine (495 μl, 2.84 mmol) and methoxymethyl chloride (108 μl, 1.42 mmol) were added dropwise, and the solution was stirred at 45 °C for 8 h. MeOH was added at room temperature, and the stirring was continued for 30 min. The reaction mixture was diluted with Et_2O, washed with aqueous $KHSO_4$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave a pale yellow oil, which was dissolved in MeOH (4 ml). After addition of 1 N NaOH (0.6 ml), the solution was stirred for 75 min at room temperature, diluted with Et_2O, washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1) as the eluent to give the alcohol (**17**) as a colorless oil (26.8 mg, 87%). IR ν_{max}^{neat} cm^{-1}: 3460. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.0 Hz), 1.12 (3H, s), 1.34—1.88 (2H, m), 3.24 (1H, t, J=7.0 Hz), 3.43 (3H, s), 3.46 (1H, dd, J=8.5, 3.5 Hz), 3.61 (1H, d, J=2.0 Hz), 3.68 (1H, d, J=4.0 Hz), 3.79 (3H, s), 4.53, 4.68 (1H each, ABq, J=10.5 Hz), 4.69, 4.82 (1H each, ABq, J=7.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.28 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 267 (M^+ − 31, 0.1), 266 (0.8), 253 (2.1), 166 (5.8), 137 (12), 121 (100). ($[\alpha]_D^{15}$ −12.6° (c=1.52, $CHCl_3$). Exact MS m/z Calcd for $C_{15}H_{22}O_4$ (M^+ − 32): 266.1519. Found: 266.1520.

(2*R*,3*R*)-3-(4-Methoxybenzyloxy)-2-methoxymethoxy-2-methylpentanal (18) Pulverized molecular sieves 3A (0.64 g) and PCC (905 mg, 4.20 mmol) were added to a stirred solution of **17** (250 mg, 0.839 mmol) in CH_2Cl_2 (30 ml) at room temperature. After 2 h, the reaction mixture was diluted with Et_2O and filtered with the aid of Celite. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column with Et_2O as the eluent to give the aldehyde (**18**) as a colorless oil (242 mg, 97%). IR ν_{max}^{neat} cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz), 1.32 (3H, s), 1.44—1.80 (2H, m), 3.38 (3H, s), 3.53 (1H, dd, J=7.5, 4.5 Hz), 3.79 (3H, s), 4.53 (2H, s), 4.60, 4.84 (1H each, ABq, J=7.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 9.58 (1H, s). MS m/z (relative intensity): 264 (M^+ − 32, 03), 251 (1.7), 217 (1.4), 137 (4.5), 121 (100). $[\alpha]_D^{15}$ +3.9° (c=1.08, $CHCl_3$). Exact MS m/z Calcd for $C_{15}H_{20}O_4$ (M^+ − 32): 264.1351. Found: 264.1348.

Ethyl (2*E*,4*S*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-4-methoxymethoxyhept-2-enoate (19) A solution of **18** (234 mg, 0.791 mmol) and α-ethoxycarbonylethylidenetriphenylphosphorane (1.72 g, 4.75 mmol) in EDC (20 ml) was stirred and heated under reflux for 76 h. The phosphorane (0.57 g, 1.58 mmol) was again added, and the solution was refluxed for 20 h and then evaporated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2 as the eluent to give the ester (**19**) as a colorless oil (320 mg, 100%). IR ν_{max}^{neat} cm^{-1}: 1710, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.0 Hz), 1.30 (3H, t, J=7.0 Hz), 1.43 (3H, s), 2.01 (3H, d, J=1.5 Hz), 3.38 (3H, s), 3.41 (1H, dd, J=11.5, 2.5 Hz), 3.79 (3H, s), 4.20 (2H, q, J=7.0 Hz), 4.50 (2H, s), 4.62, 4.72 (1H each, ABq, J=7.0 Hz), 6.79 (1H, d, J=1.5 Hz), 6.84 (2H, d, J=8.0 Hz), 7.23 (2H, d, J=8.0 Hz). $[\alpha]_D^{22}$ +1.3° (c=2.90, $CHCl_3$).

(2*E*,4*S*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-4-methoxymethoxyhept-2-en-1-ol (20) $LiAlH_4$ (7.2 mg, 0.19 mmol) was added to a stirred solution of **19** (29.8 mg, 0.0784 mmol) in Et_2O (5 ml) at −15—−10 °C. After 80 min, H_2O (0.1 ml) was added, and the reaction mixture was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (4 : 1) as the eluent to give the alcohol (**20**) as a colorless oil (20.5 mg, 78%). IR ν_{max}^{neat} cm^{-1}: 3450. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz), 1.38 (3H, s), 1.80 (3H, s), 3.37 (1H, dd, J=9.0, 3.0 Hz), 3.37 (3H, s), 3.79 (3H, s), 3.95 (2H, s), 4.54 (2H, s), 4.61, 4.77 (1H each, ABq, J=7.5 Hz), 5.47 (1H, s), 6.85 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz). $[\alpha]_D^{24}$ +26.7° (c=1.44, $CHCl_3$).

(2*S*,3*R*,4*S*,5*R*)-2,4-Dimethyl-2,3-epoxy-5-(4-methoxybenzyloxy)-4-methoxymethoxyheptan-1-ol (21) *m*-CPBA (51 mg, 0.24 mmol) was added at once to a stirred solution of **20** (73.9 mg, 0.219 mmol) in CH_2Cl_2 (5 ml) at −20 °C. The solution was stirred at −20—−10 °C for 2 h, then diluted with CH_2Cl_2, washed successively with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (3 : 1→2 : 1) as the eluent to give the β-epoxide (**21**) and the (2*R*,3*S*)-α-epoxide (**21′**) as colorless oils, (44.4 mg, 59%) and (28.6 mg, 37%), respectively. The β-epoxide (**21**): ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.0 Hz), 1.25 (3H, s), 1.33 (3H, s), 1.40—1.92 (2H, m), 3.20 (1H, s), 3.35 (1H, dd, J=9.0, 3.0 Hz), 3.39 (3H, s), 3.54 (1H, d, J=7.5 Hz), 3.56 (1H, d, J=5.0 Hz), 3.80 (3H, s), 4.57 (2H, s), 4.83, 4.95 (1H each, ABq, J=7.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz). The α-epoxide (**21′**): ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.5 Hz), 1.41 (3H, s), 1.53 (3H, s), 1.50—2.0 (2H, m), 3.15 (1H, s), 3.31 (1H, dd, J=8.5, 3.5 Hz), 3.37 (3H, s), 3.52 (1H, d, J=5.0 Hz), 3.53 (1H, d, J=7.5 Hz), 3.80 (3H, s), 4.57 (2H, t, J=8.5 Hz), 4.66, 4.92 (1H each, ABq, J=7.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz).

(2*S*,3*R*,4*S*,5*R*)-2,4-Dimethyl-5-(4-methoxybenzyloxy)-4-methoxymethoxyheptane-1,3-diol (22) A 1.0 M solution of B_2H_6 in THF (2.24 ml, 2.24 mmol) was added dropwise to a stirred solution of **21** (39.5 mg, 0.112 mmol) in HMPA (1 ml) and THF (1 ml) at −14 °C under argon, and the solution was stirred at room temperature for 14 h. After addition of H_2O, the reaction mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column with *n*-hexane–EtOAc (2 : 1) as the eluent to give the diol (**22**) as a colorless oil (34.3 mg, 87%). IR ν_{max}^{neat} cm^{-1}: 3450. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, J=7.0 Hz), 1.06 (3H, t, J=7.0 Hz), 1.28 (3H, s), 1.66 (2H, quint, J=7.0 Hz), 1.60—2.10 (1H; m), 2.70 (1H, s), 3.42 (3H, s), 3.48—3.74 (3H, m), 3.80 (3H, s), 3.85 (2H, s), 4.58 (2H, s), 4.72, 4.88 (1H each, ABq, J=7.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.27 (2H, d, J=9.0 Hz). $[\alpha]_D^{22}$ −9.7° (c=0.57, $CHCl_3$).

(2*S*,3*S*,4*RS*)-5-Benzyloxy-2,4-dimethyl-2,3-epoxypentan-1-ol (25) A solution of L(+)-DET (14.4 g, 69.6 mmol) in CH_2Cl_2 (40 ml) and then a solution of **24** (23.4 g, 107 mmol) in CH_2Cl_2 (80 ml) were added dropwise to a stirred solution of Ti(iso-PrO)$_4$ (17.3 ml, 57.8 mmol) in CH_2Cl_2 (400 ml) at −60—−55 °C. After 10 min, a 3.0 M solution of *tert*-BuOOH in toluene (8.0 ml, 214 mmol) was added dropwise. The resulting solution was allowed to warm to −10 °C over a period of 2.5 h and then poured into an ice-cooled stirred solution of $FeSO_4$–$7H_2O$ (98.2 g, 353 mmol) and tartaric acid (21.5 g, 143 mmol) in H_2O (500 ml). The reaction mixture was allowed to warm to room temperature over a period of 1 h. The CH_2Cl_2 layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in Et_2O (700 ml) and stirred with 1 N NaOH (214 ml) at 0 °C for 1 h. The Et_2O layer was separated, washed with brine, dried (Na_2SO_4), and evaporated to leave the epoxide (**25**) (1 : 1 mixture of 4*R* and 4*S*) as a colorless oil (25.3 g, 100%). A part of the product (**25**) was chromatographed on a silica gel column with *n*-hexane–EtOAc (6 : 1→3 : 2) as the eluent to give two fractions.

The first fraction was the oily (4*R*)-pentanol (**25a**). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, d, J=7.0 Hz), 1.29 (3H, s), 1.50—2.10 (2H, m), 2.84 (1H, d, J=9.0 Hz), 3.31 (1H, dd, J=9.0, 7.5 Hz), 3.46 (1H, dd, J=9.0, 6.0 Hz), 3.40—3.90 (2H, m), 4.49 (2H, s), 7.31 (5H, s). MS m/z (relative intensity): 201 (M^+ − 35, 0.16), 187 (1.7), 115 (4.0), 107 (16), 91 (100). Exact MS m/z Calcd for $C_{13}H_{15}O$ (M^+ − 49): 187.1123. Found: 187.1120.

The second fraction was the oily (4*S*)-pentanol (**25b**). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=7.0 Hz), 1.31 (3H, s), 1.50—2.10 (3H, m), 2.92 (1H, d, J=9.5 Hz), 3.47 (1H, dd, J=9.0, 6.0 Hz), 3.55 (1H, dd, J=9.0, 4.0 Hz), 3.60—3.90 (4H, m), 4.55 (2H, s), 7.33 (5H, s). MS m/z (relative intensity): 218 (M^+ − 18, 0.15), 201 (0.15), 187 (1.6), 115 (1.7), 112 (2.1), 107 (23), 91 (100). Exact MS m/z Calcd for $C_{13}H_{15}O$ (M^+ − 49): 187.1123. Found: 187.1106.

(2*S*,3*R*,4*R*)-5-Benzyloxy-2,4-dimethylpentane-1,3-diol (5), (2*S*,3*R*,4*S*)-5-Benzyloxy-2,3-dimethylpentane-1,4-diol (26) and (2*RS*)-1-Benzyloxy-2-

methylpentan-4-one (28) A 1.0 M solution of B_2H_6 in THF (30 ml, 30 mmol) was added to a stirred solution of the (4*RS*)-pentanol (**25**) (3.70 g, 15.7 mmol) in THF (30 ml) and HMPA (30 ml) at room temperature. After 8 h, MeOH was added at 0 °C, then the reaction mixture was evaporated under reduced pressure to leave an oil, which was dissolved in a 1% AcOH solution in MeOH, and the solvent was evaporated off. This AcOH–MeOH treatment was repeated three times. The residue was dissolved in EtOAc, and this solution was washed successively with 1 N HCl, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave a mixture of the diols. A solution of $NaIO_4$ (3 g, 14 mmol) in H_2O (30 ml) was added to a stirred solution of the mixture of the diols in MeOH (60 ml) at room temperature. After 1 h, the reaction mixture was evaporated *in vacuo*. The residue was extracted with CH_2Cl_2, and the extract was dried ($MgSO_4$) and evaporated to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–EtOAc (10 : 1) as the eluent. The first fraction was the oily ketone (**28**) (581 mg, 18%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7.0 Hz), 2.10 (3H, s), 2.10—2.80 (3H, m), 3.24 (1H, dd, J=10.0, 6.0 Hz), 3.36 (1H, dd, J=10.0, 5.5 Hz), 4.48 (2H, s), 7.31 (5H, s).

The second fraction was the solid (4*S*)-diol (**26**) (1.31 g, 35%), which was recrystallized from *n*-hexane–EtOAc to give colorless fine needles, mp 60—61 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, d, J=7.0 Hz), 0.97 (3H, d, J=7.0 Hz), 1.50—2.20 (2H, m), 3.40—3.90 (5H, m), 4.52 (2H, s), 7.32 (5H, s). MS *m/z* (relative intensity): 238 (M^+, 0.15), 220 (0.7), 179 (2.8), 132 (5.5), 129 (3.7), 114 (17), 108 (40), 107 (29), 91 (100). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.51; H, 9.48. Exact MS *m/z* Calcd for $C_{14}H_{22}O_3$ (M^+): 238.1569. Found: 238.1529.

The third fraction was the solid (4*S*)-diol (**5**) (1.27 g, 34%), which was recrystallized from *n*-hexane–EtOAc to give colorless prisms, mp 51—52 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=7.0 Hz), 1.60—2.20 (2H, m), 3.47 (2H, d, J=5.0 Hz), 3.63 (2H, d, J=5.0 Hz), 3.77 (1H, t, J=5.0 Hz), 4.50 (2H, s), 7.32 (5H, s). MS *m/z* (relative intensity): 220 ($M^+ - 18$, 2.9), 178 (3.8), 160 (1.3), 147 (3.0), 114 (14.5), 108 (47), 91 (100). $[\alpha]_D^{17}$ +0.9° (c=1.00, EtOH). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.59; H, 9.24. Found: C, 70.47; H, 9.49. Exact MS *m/z* Calcd for $C_{14}H_{20}O_2$ ($M^+ - 18$): 220.1463. Found: 220.1468.

References and Notes

1) Chiral synthesis of polyketide-derived natural products. 20. For part 19, see: K. Horita, Y. Oikawa, S. Nagato and O. Yonemitsu, *Tetrahedron Lett.*, **29**, 5143 (1988).
2) *a*) Y. Oikawa, Y. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982); *b*) T. Oikawa, T. Tanaka, K. Horita, T. Yoshioka and O. Yonemitsu, *ibid.*, **25**, 5393 (1984); *c*) Y. Oikawa, T. Tanaka, K. Horita and O. Yonemitsu, *ibid.*, **25**, 5397 (1984); *d*) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, *Tetrahedron*, **42**, 3021 (1986).
3) *a*) Y. Oikawa, T. Tanaka and O. Yonemitsu, *Tetrahedron Lett.*, **27**, 3647 (1986); *b*) Y. Oikawa, T. Tanaka, T. Hamada and O. Yonemitsu, *Chem. Pharm. Bull.*, **35**, 2196 (1987); *c*) T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada and O. Yonemitsu, *ibid.*, **35**, 2203 (1987).
4) N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 4645 (1986); N. Nakajima, T. Tanaka, T. Hamada, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, **35**, 2228 (1987).
5) T. Tanaka, Y. Oikawa, T. Hamada and O. Yonemitsu, *Tetrahedron Lett.*, **27**, 3651 (1986); *idem, Chem. Pharm. Bull.*, **35**, 2219 (1987).
6) K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, **28**, 3253 (1987).
7) Successful total synthetic studies directed toward **1**, **2**, and **3**: *a*) E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar and J. R. Falk, *J. Am. Chem. Soc.*, **101**, 7131 (1979); *b*) R. B. Woodward, *et al.*, *ibid.*, **103**, 3210, 3213, 3215 (1981); *c*) B. Bernet, P. M. Bishop, M. Caron, T. Kawamata, B. L. Roy, L. Ruest, G. Sauve, P. Soucy and P. Deslongchamps, *Can. J. Chem.*, **63**, 2810, 2814, 2818 (1985); *d*) M. Kinoshita, M. Arai, K. Tomooka and M. Nakata, *Tetrahedron Lett.*, **27**, 1811, 1815 (1986); *e*) G. Stork and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **109**, 1565 (1987); *f*) H. Tone, T. Nishi, Y. Oikawa, M. Hikota and O. Yonemitsu, *Tetrahedron Lett.*, **28**, 4569 (1987); *g*) T. Nakata, M. Fukui and T. Oishi, *ibid.*, **29**, 2219, 2223 (1988).
8) H. Tone, T. Nishi, Y. Oikawa, M. Hikota and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1160 (1989).
9) H. Tone, T. Nishi, Y. Oikawa, M. Hikota and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1167 (1989).
10) Y. Oikawa, T. Nishi and O. Yonemitsu, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 7.
11) Y. Oikawa, T. Nishi and O. Yonemitsu, *Tetrahedron Lett.*, **24**, 4037 (1983).
12) Y. Oikawa, T. Nishi and O. Yonemitsu, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 19.
13) Unless otherwise noted, the numberings are based on that of **3**.
14) P. L. Barili, G. Berti, G. Catelani, F. Colonna and A. Marra, *Tetrahedron Lett.*, **27**, 2307 (1986).
15) M. R. Johnson and Y. Kishi, *Tetrahedron Lett.*, **1979**, 4347.
16) Epoxidation of **6** itself with *m*-CPBA gave **10** with 16 : 1 stereoselection in 76% yield. Three-step conversion of **10** gave **4** in 43% overall yield.[10] However, acid-catalyzed recyclization of **10** occurred quite easily to give the undesired tetrahydrofuran (**13**)[10] even in the presence of a trace of acid.
17) N. M. Yoon and H. C. Brown, *J. Am. Chem. Soc.*, **90**, 2927 (1968).
18) J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, **23**, 2719 (1982).
19) *Cf.* R. O. Hutchins, I. M. Taffer and W. Burgoyne, *J. Org. Chem.*, **46**, 5214 (1981).
20) *Cf.* H. Iio, M. Isobe, T. Kawai and T. Goto, *J. Am. Chem. Soc.*, **101**, 6076 (1979).
21) When **9** was treated with B_2H_6 in THF at room temperature, very slow reactions occurred to give a small amount of a complex mixture of products. Reduction of 2,3-unsubstituted 2,3-epoxy alcohols with sodium bis-(2-methoxyethoxy)aluminium hydride (Red-al) gave mainly 1,3-diols,[18,22] whereas a 2-methyl-2,3-epoxy alcohol was reported to give a 1,2-diol.[22b] However, Yamaguchi *et al.* obtained the expected 1,3-diols from 2-substituted 2,3-epoxy alcohols by the Red-al reduction, though the reaction required rather a long time, in the course of the total synthesis of protomycinolide IV.[23] Unfortunately, in the case of **9**, loss of the MPM and benzyl groups occurred in preference to the reduction of the epoxide ring.
22) *a*) P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless and S. M. Viti, *J. Org. Chem.*, **47**, 1378 (1982); *b*) S. M. Viti, *Tetrahedron Lett.*, **23**, 4541 (1982).
23) M. Honda, T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 3857 (1984).
24) *a*) B. E. Rossiter, T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 464 (1981); *b*) T. Katsuki and K. B. Sharpless, *ibid.*, **102**, 5974 (1980); *c*) C. H. Behrens and K. B. Sharpless, *Aldrichim. Acta*, **16**, 67 (1983).
25) *Cf.* M. Caron and K. B. Sharpless, *J. Org. Chem.*, **50**, 1557 (1985); J. M. Klunder, S. Y. Ko and K. B. Sharpless, *ibid.*, **51**, 3710 (1986); S. Y. Ko and K. B. Sharpless, *ibid.*, **51**, 5413 (1986); S. Y. Ko, H. Masamune and K. B. Sharpless, *ibid.*, **52**, 667 (1987).
26) O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).
27) 1,3-Diols (**5**, **26**) were more easily separated from 1,2-diol (**27**) by silica gel column chromatography after **27** was oxidized to the ketone (**28**) (see Experimental).