Pergamon

Tetrahedron, Vol. 52, No. 2, pp. 531-550, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)00905-1

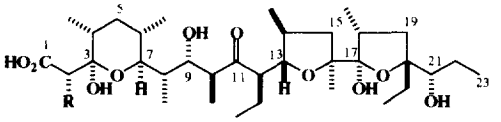
STEREOSELECTIVE TOTAL SYNTHESIS OF LYSOCELLIN, THE REPRESENTATIVE POLYETHER ANTIBIOTIC OF THE LYSOCELLIN FAMILY. PART 1. SYNTHESIS OF C1-C9 AND C16-C23 SUBUNITS[1]

Kiyoshi Horita,* Takayuki Inoue, Kazuhiro Tanaka, and Osamu Yonemitsu*[2]

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

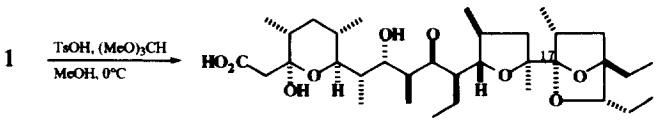
Abstract: The C1-C9 (**4**) and C16-C23 subunits (**9**) of lysocellin (**1**), a representative polyether antibiotic, were synthesized stereoselectively from D-glucose and D-mannitol. Stereocontrolled hydroboration, Michael reaction, Grignard reaction, *etc.* were successfully applied.

It is well known that polyether antibiotics play an important role in liquid membrane transport of various metal cations and organic ammonium ions as naturally occurring ionophores, and some of them are widely utilized as an anticoccidial agent in the poultry industry.[3] In addition to the biological importance, most polyether antibiotics have a formidable molecular complexity, and hence, particular attention of their synthesis has been focused by many organic chemists.[4] In connection with our continuing interest in the synthetic study of polyketide-derived natural products, we have reported stereoselective total synthesis of some typical polyether antibiotics, and as an extension the present report describes the synthesis of lysocellin **1**.[5]



1: R=H Lysocellin
2: R=Me Ferensimycin

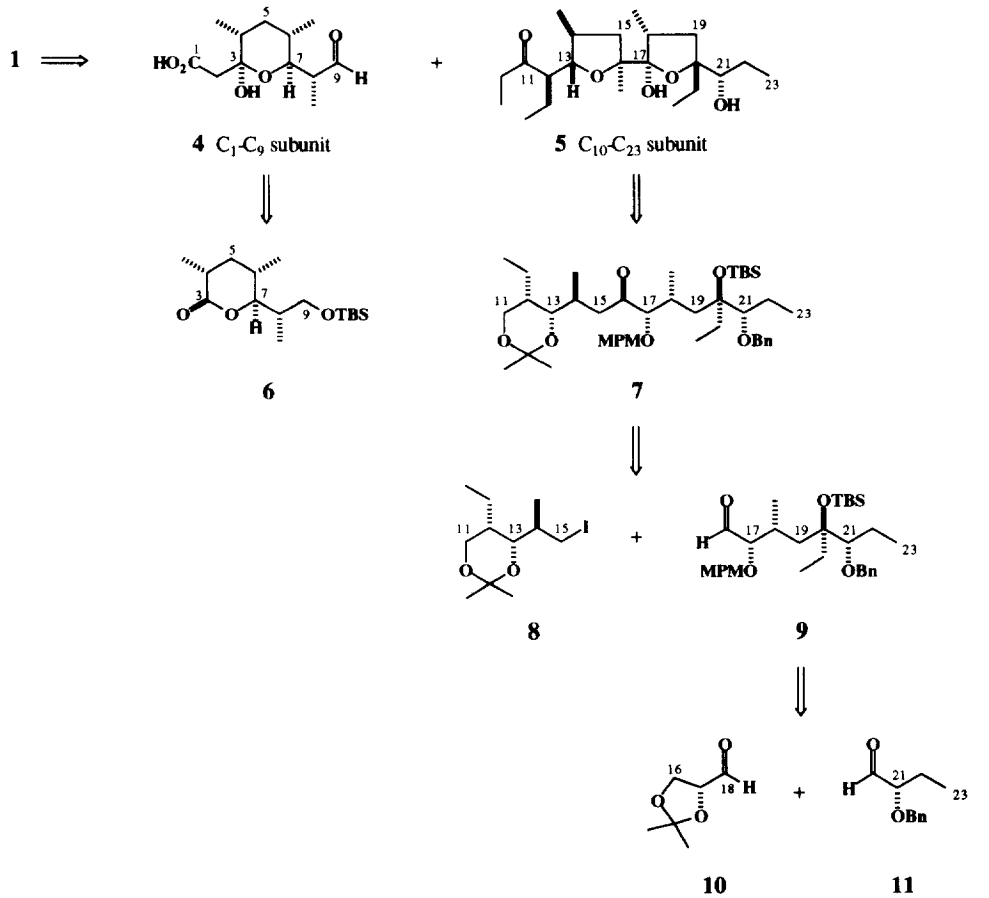
Lysocellin (**1**), the first and representative member of the lysocellin family, was isolated from *Streptomyces cacaoi* var. *asoensis* in 1975 and showed antibacterial and antifungal activities.[6] The relative and absolute configuration of **1** was determined by three-dimensional X-ray diffraction analysis of the silver salt.[7] Recently, an elegant achievement of the total synthesis of ferensimycin B (**2**), a member of the lysocellin family, was reported by Evans *et al*,[4r] as an application of their methodology established in the synthesis of X-206[4p] *etc.* Several years ago, we decided to choose **1** as one of quite appropriate target molecules for an extension of our methodolgy developed in the synthesis of polyether and macrolide antibiotics. The stereoselective synthesis of **1** raises three key issues. The first is how to construct many stereogenic centers by means of cyclic and acyclic stereocontrol. The second is selection of appropriate protecting groups for many hydroxy groups. Finally, stereoselective preparation of substituted tetrahydrofuran, γ-lactol, and δ-lactol rings is very important. In particular, special care for the preparation of the C17-C20[8] lactol has to be exercised to prevent a serious side reaction, easy formation of an anhydro compound such as **3** even under mild acidic conditions.[4r,9] We report



3

here the first total synthesis of **1**, detailing the stereocontrolled synthesis of two important subunits corresponding to C1-C9 (**4**) and C16-C23 parts (**9**) of **1** in this paper,[5a] and the total synthesis of **1** in the succeeding paper.[5b]

Retrosynthetic disconnection of **1** is shown in scheme 1. The synthesis of **1** *via* the final aldol condensation between aldehyde (**4**) (C1-C9 subunit) and ethyl ketone (**5**) (C10-C23 subunit) under Kishi's conditions[4g] was obviously the first choice, in analogy with the synthesis of many other polyether antibiotics. Aldehyde (**4**) can be synthesized from Prelog-Djerrasi lactone derivative (**6**)[10] by the introduction of an acetic acid unit at the ester position. Iodide (**8**)[11] and aldehyde (**9**) were expected to provide suitable building blocks for the synthesis of **5** *via* an intermediary ketone (**7**). Finally, **9** was retrosynthetically divided into the known two compounds, **10**[12] and **11**,[13] in which the C21 hydroxy group would be protected with a benzyl group in order to avoid the

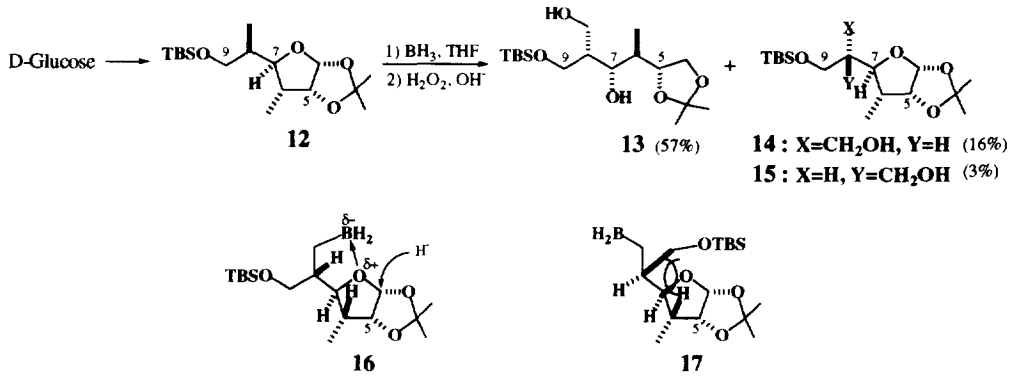


Scheme 1

above-mentioned side reaction.[4r,9] Since **8** and the corresponding sulfoxide and sulfone were already synthesized from D-glucose in our synthetic study of polyether antibiotics isolasalocid A and lasalocid A,[11] the subject in this report was highly stereoselective synthesis of **4** and **9**.

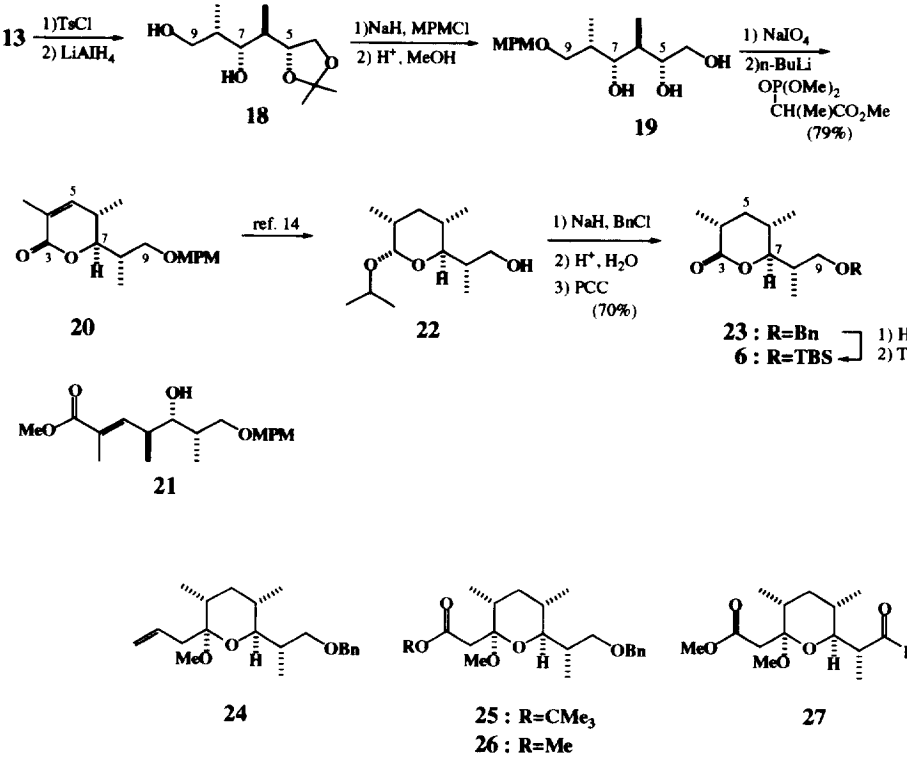
Synthesis of C1-C9 subunit (4)

The C1-C9 subunit (**4**) was anticipated to be synthesized by the introduction of two carbon unit to the C3 ester carbonyl position of the Prelog-Djerassi lactone derivative (**6**) synthesized from D-glucose *via* the dihydro lactol derivative (**22**),[14] which was previously synthesized as a key intermediate in our efficient and convergent synthesis of methynolide, the aglycone of 12-membered macrolide methymycin. When **12**,[14] easily derived from D-glucose, was treated with diborane and then alkaline *tert*-butylhydroperoxide under usual conditions, an 11 : 1 mixture of **14** and **15** was obtained.[14] The former (**14**) was converted to **22**. In this process hydrolysis of the 5-membered acetonide in bicyclic system required rather strong acidic conditions, which sometimes caused overreactions. Treatment of **12** with a large excess of diborane at room temperature overnight gave diol (**13**) as the main product, which was easily separable from **14** and **15**. Hydrolysis of the acetonide of **13** was expected to proceed under mild acidic conditions. This stereoselective overreductive cleavage of the furanose ring can be explained as follows. Hydrobration of **12** proceeded according to Still's model[15] to give mainly **16**, which was then attacked by another diborane to cleave the furanose ring, and **13** was mainly obtained. No reductive cleavage of **17** leading to an isomer of **13** at the C8 postion occurred probably because of steric hinderance by the *tert*-butyldimethylsilyl (TBS) group.

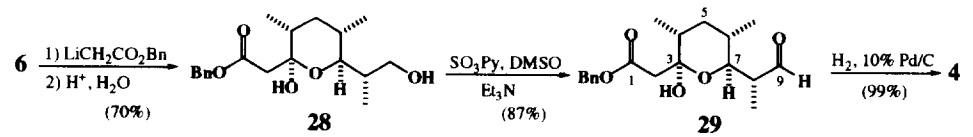


The primary alcohol of **13** was tosylated and then reduced with lithium aluminum hydride ($LiAlH_4$) to give **18**, which was readily converted to **19** *via* 4-methoxybenzyl (MPM) protection and hydrolysis of the acetonide group with dilute sulfuric acid in methanol at room temperature. After cleavage of the vicinal diol of **19** with sodium periodate, the resulting aldehyde was treated with the salt of dimethyl 1-methoxycarbonylethylphosphonate generated with soduim hydride in tetrahydrofuran at -80 °C to give a 6.8 : 1 mixture of α,β-unsaturated-δ-lactone (**20**)[14] and (*E*)-α,β-unsaturated ester (**21**) in 93% yield. Use of *n*-butyllithium instead of sodium hydride improved remarkably the selectivity to get **20**, namely, the ratio of **20** to **21** was 26 : 1.

Conversion of **20** into **22** was carried out according to the published procedures.[14] After protection of the primary alcohol of **22** with a benzyl group, hydrolysis of the acetal, followed by oxidation with pyridinium



chlorochromate gave **23**.[16] In order to introduce an acetic acid unit at the carbonyl position of **23**, three compounds, **24**, **25**, and **26**, were synthesized in good yields. However, all attempts of their conversion into **4** were unsuccessful, althongh it was possible to lead **26** to **27**,[4r] which was completely identical with a product in the degradation study of **1** (*vide infra*). Therefore, the benzyl protecting group of **23** was replaced by a TBS group to give **6**,[10] which was readily converted to **28** by treatment with the lithium salt of benzyl acetate generated with lithium diisopropylamide in tetrahydrofuran at -78 °C and subsequent acid hydrolysis. Finally, the primary alcohol of **28** was oxidized with sulfur trioxide pyridine complex[17] to aldehyde (**29**), which was easily converted to the C1-C9 subunit (**4**) in almost quantitative yield by hydrogenation over 10% palladium on charcoal in ethyl acetate.

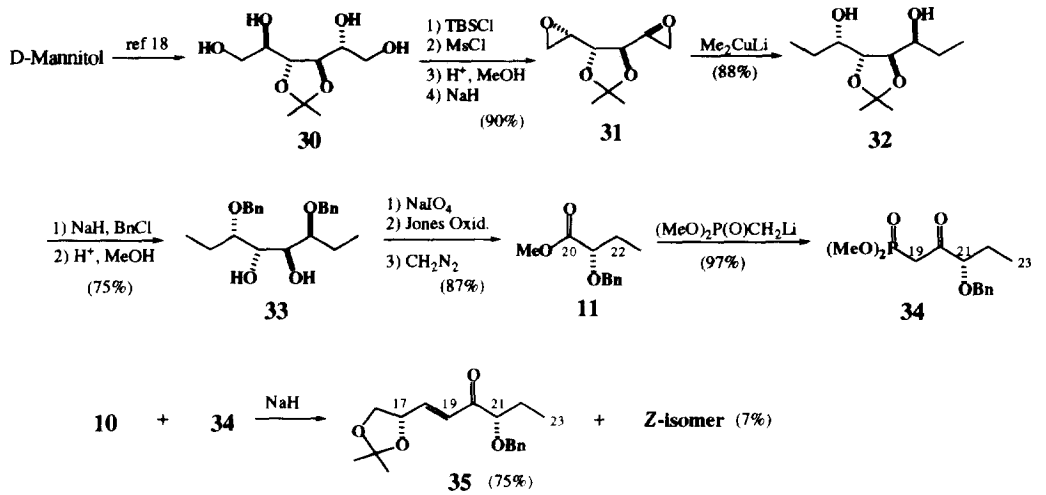


Synthesis of C16-C23 subunit (9)

The C16-C23 subunit **9** with four asymmetric centers was synthesized from D-mannitol *via* α,β-unsaturated ketone (**35**), prepared by coupling between D-glyceraldehyde (**10**)[12] and β-ketophosphonate (**34**). The main issue for the synthesis of **9** was protection of the C21 hydroxy group and stereocontrolled construction of C18

and C20 chiral centers.

Compound **34** was readily synthesized from the known ester (**11**),[13] which was prepared quite conveniently from D-mannitol in this work. Tetraol (**30**),[18] readily prepared from D-mannitol, was converted to diepoxide (**31**) *via* four conventional reactions; TBS protection of the primary alcohols, treatment with mesyl (Ms) chloride, removal of the TBS groups, and treatment with sodium hydride. When **31** was treated with lithium dimethyl cuprate in ether at - 20 °C, regioselective methylation proceeded smoothly to give **32** in good yield. The secondary alcohols corresponding to the C21 position of **32** were protected with a benzyl group in order to avoid the side reaction, namely formation of a bicyclic acetal such as **3** as described above, and then the acetonide was hydrolyzed to give **33**. Periodate oxidation, followed by Jones oxidation gave a carboxylic acid, which was readily converted to methyl ester (**11**). Treatmeut of **11** with the lithium salt of dimethyl methanephosphonate in the usual way gave β-ketophosphonate (**34**). Wittig-Horner codensation between **10** and **34** yielded (*E*)-enone (**35**) with 11 : 1 selectivity.



For the purpose of construction of the C18 chiral center, Michael addition mainly with lithium dimethyl cuprate was examined under various conditions, and several results are shown in Table 1. When **35** was treated with the cuprate in ether, 1,4-addition proceeded efficiently to give manily the expected C18-(*R*) isomer (**36**), though its stereoselectivity to undesired C18-(*S*) isomer (**37**) was only 2.3 : 1. In a mixture of tetrahydrofuran and ether, the selectivity was improved to 6.3 : 1 (entry 2). In the presence of magnesium bromide, the ratio of **36** to **37** was reversed to 1 : 5.8 (entry 3). Tetra-*n*-butylammonium dimethyl cuprate[19] gave only poor result

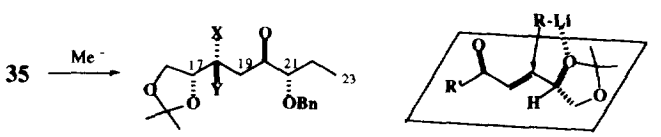
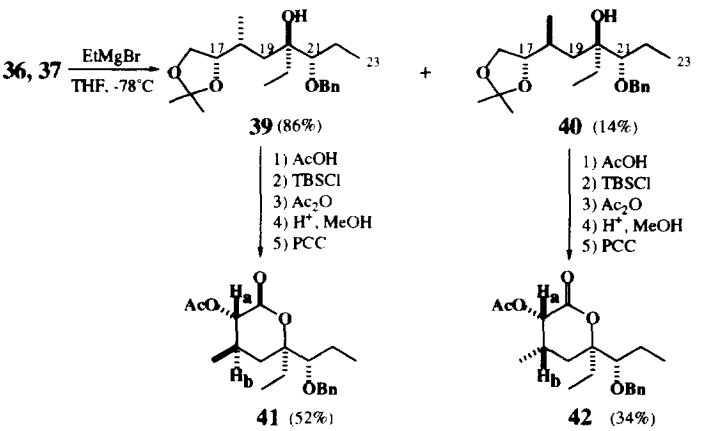


Table 1. Michael addition (methylation) of *E*-enone (**35**)

entry	reagent	conditions	yield (%)	ratio **36** : **37**
1	Me_2CuLi	Et_2O, -20°C, 20min	90	2.3 : 1
2	Me_2CuLi	THF-Et_2O, -80°C→-20°C, 2h	88	6.3 : 1
3	Me_2CuLi	THF, -20°C, $MgBr_2$, 40min	92	1 : 5.8
4	Me_2CuNBu_4	THF, -20°C, 30min	98	1.6 : 1
5	$MeNBu_4$	THF, -20°C, 30min	63[a]	6.6 : 1

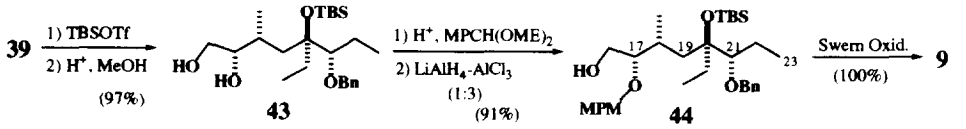
[a] Yield of 1,2-addition product : 37%

with 1.6 : 1 ratio (entry 4). A better selectivity (6.6 : 1) of **36** was obtained on treatment with a naked anion prepared *in situ* from methyllithium and tetra-*n*-butylammonium bromide,[19] but a considerable amount (37%) of 1,2-adduct was concomitantly formed (entry 5). The (*R*)-selectivity of the 1,4-addition of lithium dimethyl cuprate can be explained by Leonard's model[20] (**38**), that is, chelation of lithium ion to an oxygen atom of the dioxolan ring may control the face of the double bond attacked by methyl anion, giving mainly the (*R*)-isomer (**36**).



Since it was quite difficult to separate **36** from **37**, a 6.3 : 1 mixture of **36** and **37** was subjected to the next Grignard reaction. When the mixture was treated with ethylmagnesium bromide in tetrahydrofuran at -78 °C, a chelation-controlled reaction[21] proceeded with complete stereoselectivity to give a mixture of **39** and **40**, which were easily separated by silica gel column chromatography. The stuctures of **39** and **40** were easily determined after conversion to **41** and **42**, respectively. The coupling constant between Ha and Hb of **41** is 11.5 Hz (axial-axial), while that of **42** is 5.0 Hz (axial-equatorial).

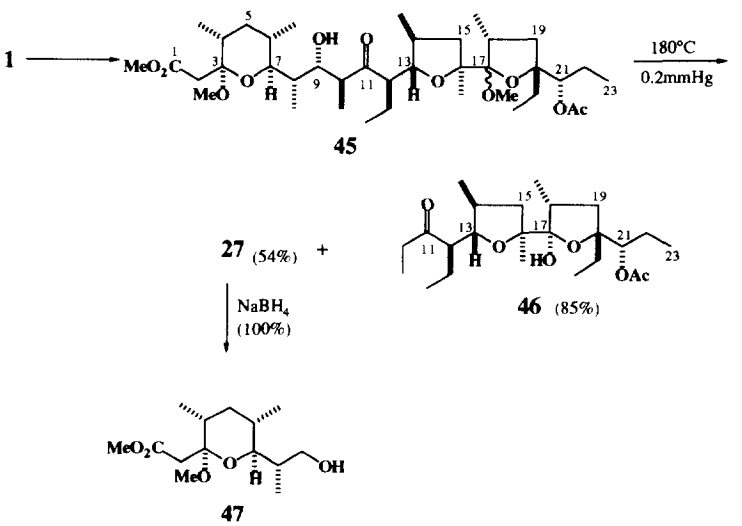
Finally, **39** was smoothly converted to the C16-C23 subunit (**9**) *via* a series of conventional reactions. After protection of the C20 alcohol with a TBS group, the acetonide was hydrolyzed to give diol (**43**), which was protected again by a 4-methoxybenzylidene group. On treatment with a 3 : 1 mixture of aluminum chloride and $LiAlH_4$ at - 50°C, reductive ring opening of the MP acetal proceeded regioselectively to give MPM ether (**44**) with 13 : 1 selectivity. Swern oxidation[22] of the primary alcohol of **44** gave aldehyde (**9**: C16-C23 subunit) in quantitative yield.



In the succeeding paper, we will report the coupling of **4**, **8**, and **9** to complete the total synthesis of lysocellin (**1**).

Degradation study of lysocellin (1)

Lysocellin (**1**) was converted to 21-O-acetyllysocellin methyl ester[9] and subsequently to **45**, which was subjected to pyrolysis at 180 °C under reduced pressure at 0.1 mm Hg to proceed retro-aldol cleavage,[4m,r] and aldehyde (**27**) and ethyl ketone (**46**) were isolated in good yields. This aldehyde (**27**) was completely identical with the synthetic compound described above in terms of optical rotation and spectra data (IR, NMR, MS), and converted to more stable alcohol (**47**) by reduction with sodium borohydride.



Experimental

(2*S*,3*S*,4*R*)-2-*tert*-Butyldimethylsilyloxymethyl-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]pentane-1,3-diol (13)

A 1.0M solution of BH_3 (4.6ml) in THF was added dropwise to a stirred solution of **12**[14] (500mg, 1.52mmol) in THF (1.5ml) at -20°C under argon. After 2 hr, the reaction mixture was allowed to warm to room temperature, and the stirring was continued for 19 hr. After 4N NaOH (1.8ml) and 70% tert-BuOOH (0.69ml) were added, the mixture was stirred vigorously for 3 hr, and then extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 2:1) to give three fraction as colorless oils. The first fraction was **15**[14] (14mg, 3%), the second

fraction was **14**[14] (82mg, 16%), and the third fraction was **13** (300mg, 57%). $[\alpha]_D^{20}$ -5.4° (c=1.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) d: 0.08 (s, 6H), 0.78 (d, 3H, *J*=7.0Hz), 0.90 (s, 9H), 1.37 (s, 3H), 1.41 (s, 3H), 1.81-2.03 (m, 2H), 3.22-3.34 (m, 1H), 3.67 (t, 1H, *J*=8.0Hz), 3.79-4.07 (m, 6H), 4.14 (dd, 1H, *J*=8.0, 6.0Hz), 4.27 (brs, 1H). EI-MS *m/z* (%): 333 (M^+-15, 10), 275 (1.3), 241 (1.5), 233 (34), 219 (6.7), 215 (7.5), 75 (100). HR-MS Calcd for $C_{16}H_{33}O_5Si$: 333.2099. Found: 333.2091.

(2*S*,3*S*,4*R*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylpentane-1,3-diol (18)

Pyridine (50ml) and TsCl (16.5g, 87mmol) were added to a stirred solution of **13** (28.7g, 82mmol) in CH_2Cl_2 (100ml) at 0°C. After 41 hr at room temperature, a 1:1 mixture (200ml) of THF and H_2O was added, and the stirring was continued for 1 hr. The mixture was extracted with CH_2Cl_2. The extract was washed with 2N HCl, H_2O, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave the tosylate as a colorless oil (42.6g), which was dissolved in dry ether (200ml). The ether solution was added dropwise to a stirred suspension of $LiAlH_4$ (4.0g, 105mmol) in ether (300ml) at 0°C. After 18 hr at room temperature, the excess reagent was decomposed with MeOH at 0°C, then H_2O (4ml), 15% NaOH (4ml) and H_2O (12ml) were added successively, and the stirring was continued for 1 hr. $MgSO_4$ was added to dry the solution, and after 30 min, the mixture was filtered. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 1:1) to give **18** (13.7g, 77%). Recrystallization from *n*-hexane gave colorless needles, mp 66.5-67.0°C. $[\alpha]_D^{22.5}$ +5.6° (c=1.21, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.74 (d, 3H, *J*=6.5Hz), 0.98 (d, 3H, *J*=7.5Hz), 1.38 (s, 3H), 1.43 (s, 3H), 1.66-1.81 (m, 2H), 3.66 (t, 1H, *J*=8.0Hz), 3.67 (dd, 1H, *J*= 10.5, 5.5Hz), 3.77-3.85 (m, 2H), 4.00 (ddd, 1H, *J*=9.0, 8.0, 6.0Hz), 4.16 (dd, 1H, *J*= 8.0, 6.0Hz). EI-MS *m/z* (%): 203 (M^+-15, 11), 159 (6.9), 143 (19), 101 (94), 59 (98), 43 (100). HR-MS Calcd for $C_{10}H_{19}O_4$: 203.1285. Found: 203.1295. *Anal* Calcd for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.37; H, 10.17.

2*R*,3*R*,4*R*,5*S*)-5-(4-Methoxybenzyloxymethyl)-3-methylhexane-1,2,4-triol (19)

A solution of **18** (9.4g, 43mmol) in THF (110ml) was added to a stirred suspension of NaH (60% oil dispersion, 5.2g, 130mmol, washed with *n*-hexane) in THF (30ml) at room temperature. After 2 hr, MPM chloride (7.6ml, 51.9mmol) was added, and the stirring was continued for 28 hr. Et_2NH (10ml) was added, and the resulting mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give (2*S*,3*R*,4*R*)-4-(1,3-dioxolan-4-yl)-1-(4-methoxybenzyloxymethyl)-2-methylpentan-3-ol as a colorless oil (10.3g, 71%). $[\alpha]_D^{22.5}$ -2.6° (c=0.91, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.74 (d, 3H, *J*=7.0Hz), 0.90 (d, 3H, *J*=7.0Hz), 1.37 (s, 3H), 1.42 (s, 3H), 1.73-1.95 (m, 2H), 3.40 (dd, 1H, *J*=9.0, 6.0Hz), 3.56 (dd, 1H, *J*=9.0, 7.0Hz), 3.61-3.73 (m, 2H), 3.80 (s, 3H), 3.80-3.81 (m, 1H), 4.02-4.15 (m, 2H), 4.43 (d, 1H, *J*=11.5Hz), 4.50 (d, 1H, *J*=11.5Hz), 6.88 (d, 2H, *J*=9.0Hz), 7.27 (d, 2H, *J*=9.0Hz). EI-MS *m/z* (%): 338 (M^+, 0.2), 280 (1.1), 262 (0.6), 217 (0.6), 207 (1.1), 159 (6.5), 137 (44), 121 (100), 101 (21). HR-MS Calcd for $C_{19}H_{30}O_5$: 338.2095. Found: 338.2118.

2N H_2SO_4 (6ml) was added to a stirred solution of the alcohol (10.3g, 30.4mmol) in MeOH (80ml) at room temperature. After 23 hr, the reaction mixture was neutralized with $NaHCO_3$ and concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1-2:1) to give the recovered alcohol (0.3g, 3%) and **19** as a colorless oil (7.6g, 85%). $[\alpha]_D^{22.5}$ -9.8° (c=0.85, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H, *J*=7.0Hz), 1.00 (d, 3H, *J*=7.0Hz), 1.71-1.97 (m, 2H), 2.66-2.78 (m, 1H), 3.55 (dd, 1H, *J*=9.0, 4.0Hz), 3.65 (dd, 1H, *J*=9.0, 3.5Hz), 3.52-3.77 (m, 3H), 3.81 (s, 3H), 3.85 (dd, 1H, *J*=9.5, 1.5Hz),

3.98 (bs, 1H), 4.43 (d, 1H, *J*=11.5Hz), 4.48 (d, 1H, *J*=11.5Hz), 4.61 (bs, 1H), 6.89 (d, 2H, *J*=9.0Hz), 7.23 (d, 2H, *J*=9.0Hz). EI-MS *m/z* (%): 298 (M^+, 0.8), 220 (0.7), 190 (0.6), 162 (1.9), 150 (4.5), 137 (36), 121 (100). HR-MS Calcd for $C_{16}H_{26}O_5$: 298.1782. Found: 298.1769.

(2*Z*,4*S*,5*S*,6*S*)-5-Hyroxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylhept-2-enoic Acid δ-Lactone (20)

A solution of $NaIO_4$ (5.5g, 25.7mmol) in H_2O (18ml) was added to a stirred solution of **19** (3.8g, 12.7mmol) in MeOH (30ml) at room temperature. After 2 hr, the insoluble materials were filtered off, and the filtrate was concentrated *in vacuo*. The residual aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave (2*R*,3*R*,4*S*)-3-hydroxy-4-(4-methoxyphenyl)methyl-2-methylpentanal as a colorless oil (3.4g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (d, 3H, *J*=7.0Hz), 1.03 (d, 3H, *J*=7.0Hz), 1.65-2.08 (m, 1H), 2.31-2.72 (m, 1H), 3.01 (d, 1H, *J*=3.0Hz), 3.54 (d, 2H, *J*=4.5Hz), 3.81 (s, 3H), 3.89-4.08 (m, 1H), 4.44 (s, 2H), 6.88 (d, 2H, *J*=8.5Hz), 7.24 (d, 2H, *J*=8.5Hz), 9.79 (d, 1H, *J*=2.0Hz).

A 1.6M hexane solution of *n*-BuLi (0.22ml, 0.35mmol) was added dropwise to a stirred solution of dimethyl methoxycarbonylethylphosphonate (81mg, 0.41mmol) in THF (0.7ml) at -80°C under argon. After 1 hr, a solution of the above aldehyde (37mg, 0.139mmol) in THF (0.7ml) was added dropwise, and the stirring was continued for 1 hr. The reaction mixture was allowed to warm to room temperature, then poured into saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:2) to give colorless oils of **20** (33mg 79%) and methyl (2*E*,4*S*,5*S*,6*S*)-2,4-dimethyl-5-hydroxy-6-(4-methoxybenzyloxymethyl)hept-2-enoate (**21**) (1.2mg, 3%). **20**: $[\alpha]_D^{21}$ +42° (c=1.43, $CHCl_3$). IR (neat) ν (cm^{-1}): 1715. **21**: ^{1}H-NMR ($CDCl_3$) δ: 0.93 (d, 3H, *J*=7.0Hz), 1.00 (d, 3H, *J*=7.0Hz), 1.87(d, 3H, *J*=1.5Hz), 1.81-2.15 (m, 1H), 2.52-2.84 (m, 2H), 3.45 (d, 2H, *J*=5.0Hz), 3.59-3.89 (m, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 4.43 (s, 2H), 6.76 (dq, 1H, *J*=10.0, 1.5Hz), 6.87 (d, 2H, *J*=8.5Hz), 7.24 (d, 2H, *J*=8.5Hz).

(2*R*,4*S*,5*S*,6*S*)-7-Benzyloxy-5-hydroxy-2,4,6-trimethylheptanoic Acid δ-Lactone (23)

A solution of **22** (163mg, 708μmol) in THF (0.7ml) was added dropwise to a stirred suspension of NaH (60% oil dispersion, 43mg, 1.08mmol, washed with *n*-hexane) in THF (1ml) at room temperature under argon. After 1 hr, benzyl chloride (106μl, 0.92mmol) was added, the stirring was continued for 17 hr, and then Et_2NH (0.3ml) was added to quench the reaction. The mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (benzene) to give (2*S*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-benzyloxyprop-2-yl)]-3,5-dimethyl-2-isopropoxytetrahydropyran as a colorless oil (226mg, 100%). $[\alpha]_D^{15.5}$ +90° (c=1.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.0Hz), 0.81 (d, 3H, *J*=6.0Hz), 0.89 (d, 3H, *J*=7.0Hz), 1.06 (d, 3H, *J*=6.5Hz), 1.13 (d, 3H, *J*=6.5Hz), 1.27 (q, 1H, *J*=12.5Hz), 1.40 (dt, 1H, *J*=12.5, 4.0Hz), 1.57-1.78 (m, 2H), 2.08 (dtq, 1H, *J*=2.0, 7.0, 7.0Hz), 3.34 (dd, 1H, *J*=9.0, 7.0Hz), 3.51 (dd, 1H, *J*=9.0, 7.0Hz), 3.57 (dd, 1H, *J*=10.5, 2.0Hz), 3.80 (sept, 1H, *J*=6.5Hz), 4.45 (d, 1H, *J*=12.0Hz), 4.54 (d, 1H, *J*=12.0Hz), 4.62 (d, 1H, *J*=3.5Hz), 7.27-7.37 (m, 5H). EI-MS *m/z* (%): 320 (M^+, 1.1), 278 (2.3), 260 (8.3), 100 (72), 91 (100), 58 (57). HR-MS Calcd for $C_{20}H_{32}O_3$: 320.2353. Found: 320.2355.

A solution of the above benzyl ether (98mg, 306μmol) and 1N H_2SO_4 (0.6ml) in dioxane (0.9ml) was stirred at 50°C for 3.5 hr. After neutralization with $NaHCO_3$, the mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give the recovered starting material (23mg, 23%) and a mixture of hemiacetals as a colorless oil (65mg, 76%; 99% based on the consumed starting material). IR (neat) ν (cm^{-1}): 3400. EI-MS

m/z (%): 278 (M^+, 0.1), 260 (14), 187 (8.6), 169 (9.3), 91 (100), 69 (21). HR-MS Calcd for $C_{17}H_{24}O_2$: 260.1778. Found: 260.1763.

Powdered 3Å molecular sieves (148mg) and PCC (148mg, 687μmol) were added to a stirred solution of the above hemiacetals (137mg, 492μmol) in CH_2Cl_2 (1.5ml) at room temperature. After 2 hr, the reaction mixture was passed through a short silica gel column (*n*-hexane-EtOAc 3:2), and the eluate was again chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give **23** as a colorless oil (125mg, 92%). $[\alpha]_D^{15.5}$ +56° (c=1.20, $CHCl_3$). IR (neat) ν (cm^{-1}): 1735. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (d, 3H, *J*=7.0Hz), 0.96 (d, 3H, *J*=6.5Hz), 1.28 (d, 3H, *J*=7.5Hz), 1.38 (dt, 1H, *J*=13.5, 12.5Hz), 1.86-1.97 (m, 2H), 2.11 (dddq, 1H, *J*=9.0, 6.0, 1.5, 6.5Hz), 2.44-2.53 (m, 1H), 3.40 (dd, 1H, *J*=9.0, 6.0Hz), 3.61 (t, 1H, *J*=9.0Hz), 4.21 (dd, 1H, *J*=10.5, 1.5Hz), 4.49 (d, 1H, *J*=12.0Hz), 4.56 (d, 1H, *J*=12.0Hz), 7.25-7.38 (m, 5H). EI-MS *m/z* (%): 276 (M^+, 21), 230 (3.8), 187 (2.8), 170 (15), 128 (40), 107 (19), 97 (40), 91 (100), 83 (61). HR-MS Calcd for $C_{17}H_{24}O_3$: 276.1727. Found: 276.1720.

(2*R*,4*S*,5*S*,6*S*)-7-*tert*-Butyldimethylsilyloxy-5-hydroxy-2,4,6-trimethylheptanoic Acid δ-Lactone (6)

A solution of **23** (2.4g, 8.68mmol) in EtOAc was hydrogenated in the presence of $Pd(OH)_2$ (150mg) at room temperature for 3 hr. Work-up as usual and chromatography on a silica gel column (*n*-hexane-Et_2O 4.5:1) gave 7-hydroxy compound (1.55g, 96%).

Imidazole (545mg, 8.0mmol) and TBS chloride (573mg, 3.8mmol) were added to a stirred solution of the above alcohol (590mg, 3.17mmol) in CH_2Cl_2 (20ml) at 0°C under argon. After 1 hr at room temperature, MeOH and CH_2Cl_2 were added, and the mixture was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **6** as a colorless oil (845mg, 89%). $[\alpha]_D^{25}$ +54° (c=1.12, $CHCl_3$). IR (neat) ν (cm^{-1}): 1740. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 6H), 0.84 (d, 3H, *J*=7.0Hz), 0.89 (s, 9H), 0.96 (d, 3H, *J*=6.5Hz), 1.28 (d, 3H, *J*=7.5Hz), 1.84 (t, 1H, *J*=13.0Hz), 1.84-1.97 (m, 3H), 2.42-2.52 (m, 1H), 3.49 (dd, 1H, *J*=6.0, 10.5Hz), 3.67 (dd, 1H, *J*=8.5, 9.5Hz), 4.18 (dd, 1H, *J*=1.5, 10.5Hz). FAB-MS *m/z* (%): 301 (M^++1, 100), 299 (8.6), 255 (8.3), 243 (68), 225 (9.1), 213 (31), 169 (46), 154 (12), 151 (15), 137 (17), 136 (14), 123 (24), 89 (18), 75 (20), 73 (32). HR-MS Calcd for $C_{16}H_{33}O_3Si$ (MH^+): 301.2201. Found: 301.2185.

(2*S*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-Benzyloxyprop-2-yl]-3,5-dimethyl-2-methoxy-2-(prop-1-en-3-yl)tetrahydropyran (24)

A 0.19M ether solution of allylmagnesium bromide (0.55ml, 0.105mmol) was dissolved in anhydrous ether (0.5ml) and then added dropwise to a stirred solution of **23** (22mg, 0.08mmol) in ether (1.5ml) at -80 °C under argon. After 2 hr, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give (2*R*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-benzyloxyprop-2-yl]-3,5-dimethyl-2-hydroxy-2-(prop-1-en-3-yl)tetrahydropyran as a colorless oil (23mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.5Hz), 0.84 (d, 3H, *J*=6.5Hz), 0.89 (d, 3H, *J*=6.5Hz), 1.30 (dt, 1H, *J*=13.0, 12.0Hz), 1.46 (dt, 1H, *J*=13.0, 4.0Hz), 1.50-1.68 (m, 2H), 1.83 (brs, 1H), 2.06 (dddq, 1H, *J*=8.0, 6.5, 2.0, 6.5Hz), 2.18-2.37 (m, 2H), 3.29 (dd, 1H, *J*=9.0, 6.5Hz), 3.47 (dd, 1H, *J*=9.0, 8.0Hz), 3.61 (dd, 1H, *J*=1.05, 2.0Hz), 4.42 (d, 1H, *J*=12.0Hz), 4.54 (d, 1H, *J*=12.0Hz), 5.03-5.14 (m, 2H), 5.79 (dddd, 1H, *J* =17.5, 9.5, 8.0, 6.5Hz), 7.22-7.40 (m, 5H).

$CH(OMe)_3$ (0.2 ml) and camphorsulfonic acid (CSA) were added to a stirred solution of the above hemiacetal (23 mg, 72 μmol) in CH_2Cl_2 (0.2 ml) and MeOH (0.2 ml) at room temperature. After 1.5 hr, the reaction mixture was neutralized with Et_3N and then evaporated *in vacuo* to leave an oil, which was chromatographed on a silica

gel columm (*n*-hexane-EtOAc 7:1) to give **24** (16 mg, 67%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H, *J*=6.0Hz), 0.83 (d, 3H, *J*=6.5Hz), 0.88 (d, 3H, *J*=7.0Hz), 1.22-2.68 (m, 7H), 3.14 (s, 3H), 3.38 (dd, 1H, *J*=8.5, 6.5Hz), 3.40 (dd, 1H, *J*=10.5, 2.0Hz), 3.61 (dd, 1H, *J*=8.5, 8.0Hz), 4.49 (s, 2H), 4.91-5.22 (m, 2H), 5.59-6.03 (m, 1H), 7.21-7.47 (m, 5H).

(2*S*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-Benzyloxyprop-2-yl]-2-*tert*-butoxycarbonylmethyl-3,5-dimethyl-2-methoxytetrahydropyran (25)

A 1.5M hexane solntion of *n*-BuLi (173μl, 0.26mmol) was added dropwise to a stirred solntion of *i*-Pr_2NH (38μl, 0.27mmol) in THF (0.3ml) at -85°C under argon. After 1 hr, *tert*-butyl acetate (37μl, 0.275 mmol) was added and the stirring was continued for 1 hr, then **23** (25mg, 90μmol) was added. After 1 hr, the reaction mixture was poured into saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give (2*R*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-benzyloxyprop-2-yl]-2-*tert*-butoxycarbonylmethyl-3,5-dimethyl-2-hydroxytetrahydropyran as a colorless oil (29mg, 82%). ^{1}H-NMR ($CDCl_3$) δ : 0.79 (d, 3H, *J*=6.5Hz), 0.86 (d, 3H, *J*=6.5Hz), 0.90 (d, 3H, *J*=6.5Hz), 1.28-1.61 (m, 4H), 1.45 (s, 9H), 1.96-2.11 (m, 1H), 2.31 (d, 1H, *J*=15.0Hz), 2.65 (d, 1H, *J*=15.0Hz), 3.29 (dd, 1H, *J*=9.0, 7.5Hz), 3.43 (dd, 1H, *J*=9.0, 7.0Hz), 3.69 (dd, 1H, *J*=10.0, 2.0Hz), 4.42 (d, 1H, *J*=12.0Hz), 4.53 (d, 1H, *J*=12.0Hz), 4.90 (d, 1H, *J*=1.5Hz), 7.24-7.36 (m, 5H).

The above hemiacetal (17mg, 43μmol) was methylated as described for **24** to give **25** as a colorless oil (15 mg, 86%). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.5Hz), 0.88 (d, 3H, *J*=7.0Hz), 0.93 (d, 3H, *J*=7.0Hz), 1.28-1.42 (m, 2H), 1.44 (s, 9H), 1.51-1.68 (m, 1H), 1.95-2.14 (m, 2H), 2.42 (d, 1H, *J*=12.5Hz), 2.63 (d, 1H, *J*=12.5Hz), 3.14 (s, 3H), 3.37 (dd, 1H, *J*=9.0, 6.5Hz), 3.39 (dd, 1H, *J*=10.5, 2.0Hz), 3.62 (dd, 1H, *J*=9.0, 8.0Hz), 4.44 (d, 1H, *J*=12.0Hz), 4.53 (d, 1H, *J*=12.0Hz), 7.21-7.40 (m, 5H).

(2*S*,3*R*,5*S*,6*S*)-6-[(2*S*)-Benzyloxyprop-2-yl]-3,5-dimethyl-2-methoxy-2-methoxycarbonylmethyltetrahydropyran (26)

A 1.54M hexane solution of *n*-BuLi (1.9ml, 2.93mmol) was added dropwise to a stirred solution of *i*-Pr_2NH (423μl, 3.02mmol) in THF (0.5ml) at -50°C under argon. After 30 min, AcOH (163μl, 2.85mmol) and HMPA (518μl, 2.98mmol) were added, and the stirring was continued for 30 min, then a solution of **23** (83 mg, 0.3mmol) in THF (1ml) was added at -80°C. The reaction mixture was gradually warmed to room temperature during 19 hr, then poured into cold saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was treated with excess CH_2N_2 in ether. After evaporation of the solvent, the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give the recovered **23** (34mg, 41%) and (2*R*,3*R*,5*S*,6*S*)-6-[(2*S*)-benzyloxyprop-2-yl]-3,5-dimethyl-2-hydroxy-2-methoxycarbonylmethyltetrahydropyran as a colorless oil (40mg, 38%). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.0Hz), 0.83 (d, 3H, *J*=7.0Hz), 0.92 (d, 3H, *J*=6.5Hz), 1.14-1.69 (m, 4H), 1.92-2.10 (m, 1H), 2.44 (d, 1H, *J*=14.5Hz), 2.70 (d, 1H, *J*=14.5Hz), 3.24 (dd, 1H, *J*=9.0, 7.5Hz), 3.35 (dd, 1H, *J*=9.0, 7.0Hz), 3.62 (s, 3H), 3.68 (dd, 1H, *J*=10.5, 2.0Hz), 4.42 (d, 1H, *J*=11.5Hz), 4.46 (d, 1H, *J*=1.5Hz), 4.55 (d, 1H, *J*=11.5Hz), 7.21-7.40 (m, 5H). EI-MS *m/z* (%): 332 (M^+-18, 12), 241 (4.1), 226 (2.1), 211 (2.8), 209 (6.0), 190 (7.4), 187 (7.3), 183 (6.7), 130 (48), 91 (100), 69 (22). HR-MS Calcd for $C_{20}H_{28}O_4$: 332.1989. Found: 332.1975.

The above hemiacetal (38mg, 108μmol) was methylated as described for **24** to give **26** (37mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H, *J*=6.5Hz), 0.82 (d, 3H, *J*=7.0Hz), 0.92 (d, 3H, *J*=6.5Hz), 1.23-1.47 (m, 3H), 1.15-2.15 (m, 2H), 2.51 (d, 1H, *J*=13.0Hz), 2.74 (d, 1H, *J*=13.0Hz), 3.17 (s, 3H), 3.35 (dd, 1H, *J*=9.0, 6.0Hz), 3.38 (dd, 1H, *J*=10.5, 2.0Hz), 3.59 (t, 1H, *J*=9.0Hz), 3.64 (s, 3H), 4.46 (d, 1H, *J*=12.0Hz), 4.51 (d, 1H, *J*=12.0Hz),

7.24-7.39 (m, 5H). EI-MS *m/z* (%): 333 (2.7), 332 (M^+-32, 6.0), 301 (0.6), 291 (0.9), 241 (2.1), 232 (2.1), 223 (4.2), 190 (12), 144 (22), 91 (100), 69 (23). HR-MS Calcd for $C_{20}H_{28}O_4$: 332.1989. Found: 332.1973.

(2*R*)-[(2*S*,3*R*,5*S*,6*S*)-3,5-Dimethyl-2-methoxy-2-methoxycarbonylmethyltetrahydropyran-6-yl]-2-propanal (27)

A solution of **26** (8.7mg, 24μmol) in MeOH (0.3ml) was hydrogenated over $Pd(OH)_2$ (8mg) at room temperature for 2 hr. After removal of the catalyst by filtration, the solvent was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give an alcohol as a colorless oil (6.0mg, 91%), which was dissolved in CH_2Cl_2 (0.6ml), and then 3Å molecular sieves (11mg) and PDC (11mg) were added at room temperature. After 4 hr, the reaction mixture was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give **27** as a colorless oil (5.1mg, 86%). $[\alpha]_D^{16}$ +115° (c=0.29, $CHCl_3$). IR (neat) ν (cm^{-1}): 2710, 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (d, 3H, *J*=6.5Hz), 0.92 (d, 3H, *J*=7.0Hz), 1.10 (d, 3H, *J*=7.0Hz), 1.38 (dt, 1H, *J*=13.0, 12.0Hz), 1.47 (dt, 1H, *J*=13.0, 4.5Hz), 1.65 (dddq, 1H, *J*=12.0, 10.5, 4.5, 6.5Hz), 2.06 (ddq,1H, *J*=12.0, 4.5, 7.0Hz), 2.47 (dq, 1H, *J*=2.5, 7.0Hz), 2.49 (d, 1H, *J*=13.0Hz), 2.70 (d, 1H, *J*=13.0Hz), 3.17 (s, 3H), 3.64 (s, 3H), 3.78 (dd, 1H, *J*=10.5, 2.5Hz), 9.74 (s, 1H). EI-MS *m/z* (%): 241 (M^+-31, 9.2), 212 (2.7), 199 (5.3), 194 (3.3), 183 (7.9), 167 (4.7), 144 (17), 133 (100), 101 (63), 69 (58). HR-MS Calcd for $C_{13}H_{21}O_4$: 241.1441. Found: 241.1436.

Benzyl 2-{(2*S*,3*R*,5*S*,6*S*)-3,5-Dimethyl-2-hydroxy-6-[(2*S*)-1-hydroxyprop-2-yl]tetrahydropyran-2-yl}-acetate (28)

A solution of freshly distilled BnOAc (616mg, 4.1mmol) in THF (3ml) was added dropwise to a stirred solution of LDA (3.99mmol) in THF (5.0ml), prepared from *n*-BuLi (1.6M *n*-hexane solution, 2.5ml, 3.99 mmol) and freshly distilled *i*-Pr_2NH (597μl, 4.26mmol), at -78°C under argon. After 30 min, a solution of **6** (400mg, 1.33mmol) in THF (10ml) was added dropwise. The mixture was stirred for 1 hr at -78°C, then poured into saturated aqueous NH_4Cl with crushed ice, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give crude benzyl 2-{(2*S*,3*R*,5*S*,6*S*)-6-[(2*S*)-1-*tert*-butyldimethylsilyloxyprop-2-yl]-3,5-dimethyl-2-hydroxytetrahydropyran-2-yl}acetate as a colorless oil, which was stirred with 1N H_2SO_4 (2ml) in THF (6ml) at room temperature for 3 hr. The reaction mixture was diluted with ether (20ml) washed with H_2O, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 2.5:1) to give **28** as a colorless oil (315mg, 70%). $[\alpha]_D^{26}$ +47° (c=0.8, $CHCl_3$). IR (neat) ν (cm^{-1}): 3480, 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.5Hz), 0.88 (d, 3H, *J*=7.0Hz), 0.92 (d, 3H, *J*=7.0Hz), 1.37 (dt, 1H, *J*=13.0, 12.0Hz), 1.46 (dt, 1H, *J*=13.0, 4.0Hz), 1.53-1.65 (m, 2H), 1.83-1.88 (m, 1H), 1.90-2.30 (brs, 1H), 2.54 (d, 1H, *J*=15.0Hz), 2.81 (d, 1H, *J*=15.0Hz), 3.48 (dd, 1H, *J*=6.0, 5.5Hz), 3.77 (dd, 1H, *J*=10.5, 4.5Hz), 3.78 (dd, 1H, *J*=10.5, 2.0Hz), 4.62 (brs, 1H), 5.13 (d, 1H, *J*=12.0Hz), 5.20 (d, 1H, *J*=12.0Hz), 7.31-7.39 (m, 5H). FAB-MS *m/z* (%): 319 (M^+-17, 100), 301 (5.8), 211 (9.0), 185 (5.2), 169 (5.3), 154 (14), 137 (11), 136 (10), 91 (69). HR-MS Calcd for $C_{19}H_{27}O_4$: 319.1911. Found: 319.1911.

Benzyl 2-{(2*S*,3*R*,5*S*,6*S*)-3,5-Dimethy-2-hydroxy-6-[(2*S*)-1-oxoprop-2-yl]tetrahydropyran-2-yl}acetate (29)

Pyridine·SO_3 complex (236mg, 1.49mmol) was added portionwise to a stirred solution of **28** (100mg, 297μmol) and Et_3N (207μl, 1.48mmol) in DMSO (1.6ml) and CH_2Cl_2 (1ml) at 0°C, and the mixture was allowed to warm to room temperature. After 1 hr, the mixture was diluted with ether (30ml), washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel (*n*-hexane-ether 2:1) to give **29** as a colorless oil (81.8mg, 87%). $[\alpha]_D^{26}$ +0.9° (c=1.2, $CHCl_3$). IR (neat) ν (cm^{-1}): 3300, 1710. ^{1}H-NMR

($CDCl_3$) δ: 0.85 (d, 3H, *J*=7.0Hz), 0.92 (d, 3H, *J*=7.0Hz), 1.02 (d, 3H, *J*=7.0Hz), 1.41-1.68 (m, 4H), 2.47 (d, 1H, *J*=14.5Hz), 2.48 (dq, 1H, *J*=3.0, 7.0Hz), 2.72 (d, 1H, *J*=14.5Hz), 4.18 (dd, 1H, *J*=10.5, 3.0Hz), 4.81 (d, 1H, *J*=1.5Hz), 5.06 (d, 1H, *J*=11.5Hz), 5.11 (d, 1H, *J*=11.5Hz), 7.32-7.40 (m, 5H), 9.54 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 6.0, 16.5, 16.8, 31.8, 36.2, 39.0, 42.7, 47.1, 66.9, 73.7, 97.6, 128.4, 128.6, 135.3, 172.6, 204.3. FAB-MS *m/z* (%): 317 (M^+-17, 55), 307 (43), 289 (24), 154 (100), 136 (65), 107 (16), 91 (50), 77 (13). HR-MS Calcd for $C_{19}H_{25}O_4$ (M^+-17): 317.1754. Found: 317.1768.

2-{(2*S*,3*R*,5*S*,6*S*)-3,5-Dimethyl-2-hydroxy-6-[(2*S*)-1-oxoprop-2-yl]tetrahydropyran-2-yl}acetic Acid (4)

The above ester (**29**) (86mg, 257μmol) was hydrogenated in EtOAc (2ml) over 10% Pd-C (40mg). Work-up gave **4** as a colorless solid (59mg, 99%), mp 55-56 °C. $[\alpha]_D^{29}$ -2.2° (c=0.544, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 3450, 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (d, 3H, *J*=7.0Hz), 0.91 (d, 3H, *J*=7.0Hz), 1.02 (d, 3H, *J*=7.0Hz), 1.40-1.69 (m, 4H), 2.37 (d, 1H, *J*=15.0Hz), 2.53 (dq, 1H, *J*=7.0, 2.5Hz), 2.71 (d, 1H, *J*=15.0Hz), 4.19 (dd, 1H, *J*=10.5, 2.5Hz), 4.91 (brs, 2H), 9.54 (s, 1H). FAB-MS *m/z* (%): 227 (M^+-17, 88), 183 (62), 169 (25), 163 (15), 154 (100), 149 (20), 136 (61), 123 (14), 107 (20), 89 (16). HR-MS Calcd for $C_{12}H_{19}O_4$ (M^+-17): 227.1285. Found: 227.1301. *Anal* Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.10.

(2*S*,3*R*,4*R*,5*S*)-1,2-5,6-Diepoxy-3,4-isopropylidenedioxyhexane (31)

A solution of TBS chloride (76.0g, 504mmol) in CH_2Cl_2 (150ml) was added dropwise to a stirred solution of **30** (55.2g, 248mmol) and imidazole (38.0g, 558mmol) in CH_2Cl_2 (300ml) at 0°C. After 2 hr, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give a disilyl compound as a colorless oil (112.0g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.09 (s, 12H), 0.91 (s, 18H), 1.36 (s, 6H), 3.35 (brs, 2H), 3.53-3.98 (m, 8H).

Ms chloride (62.5g, 546mmol) was added slowly to a stirred solution of the disilyl compound (112g, 248mmol) and Et_3N (77ml, 552mmol) in CH_2Cl_2 (300ml) at 0°C. After 30 min, H_2O (50ml) and THF (200ml) were added, and the mixture was vigorously stirred for 30 min. The organic layer was separated, washed with 1N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave a dimesylate as a pale yellow oil (149.4g). TsOH (8.8g) was added to a stirred solution of the dimesylate (149.4g) in MeOH (900ml) at room temperature. After 2.5 hr, the reaction mixture was neutralized with Et_3N, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3.5:1) to give a diol as a pale yellow oil (93.3g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 6H), 1.60-2.60 (m, 2H), 3.19 (s, 6H), 3.88 (dd, 2H, *J*=12.0, 6.0Hz), 4.05 (dd, 2H, *J*=12.0, 4.0Hz), 4.35 (dd, 2H, *J*=4.0, 1.5Hz), 4.70-4.90 (m, 2H).

A solution of the diol (93.3g, 247mmol) in THF (200ml) was added dropwise to a stirred suspension of NaH (60% oil dispersion, 33.0g, washed with *n*-hexane) in THF (600ml) at 0°C under argon. After 23 hr at room temperature, the reaction mixtwre was poured into ice-H_2O, and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 2:1) to give **31** as colorless crystals (41.9g, 91%). mp 70-71 °C (from *n*-hexane, colorless fine plates). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (s, 6H), 2.75 (dd, 2H, *J*=5.0, 2.5Hz), 2.85 (dd, 2H, *J*=5.0, 4.0Hz), 3.06-3.10 (m, 2H), 3.86 (dd, 2H, *J*=3.5, 1.5Hz). EI-MS *m/z* (%): 171 (M^+-15, 33), 143 (1.1), 111 (6.6), 59 (36), 43 (100). HR-MS Calcd for $C_8H_{11}O_4$: 171.0658. Found: 171.0647. *Anal* Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.95; H, 7.68.

(3*S*,4*R*,5*R*,6*S*)-4,5-Isopropylidenedioxyoctane-3,5-diol (32)

A 1.4M ether solution of MeLi (953ml, 1.334mol) was added dropwise to a stirred suspension of CuI (127.0g,

667mmol) in ether (80ml) at -20°C. After 2 hr at -10°C, the mixture was cooled at -30°C, and a solution of **31** (41.4g, 222mmol) in ether (80ml) and THF (80ml) was added. After being stirred at -20°C for 3 hr, the reaction mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:2) to give **32** as a colorless oil (42.8g, 88%). $[\alpha]_D^{22.5}$+16° (c=1.30, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (t, 6H, *J*=7.5Hz), 1.43 (s, 6H), 1.56 (dq, 4H, *J*=14.5, 7.5Hz), 1.99 (d, 2H, *J*=9.0Hz), 3.38-3.46 (m, 2H), 3.93 (dd, 2H, *J*=1.5, 1.0Hz). EI-MS *m/z* (%): 203 (M^+-15, 11), 189 (0.5), 159 (15), 125 (69), 101 (43), 59 (100), 57 (61). HR-MS Calcd for $C_{10}H_{19}O_4$: 203.1285 Found: 203.1284.

(3*S*,4*R*,5*R*,6*S*)-3,6-Dibenzyloxyoctane-4,5-diol (33)

A solution of **32** (35.0g, 160mmol) in THF (250ml) was added dropwise to a stirred suspeusion of NaH (60% oil dispersion, 16.0g, washed with *n*-hexane) in DMSO (250ml) at room temperature. After 2 hr, benzyl chloride (41ml, 356mmol) was added, and the stirring was continued for 5 hr. The reaction mixture was quenched by addition of Et_3N (50ml), then poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give a dibenzylate as a colorless oil (64.2g, 100%).

2N H_2SO_4 (70ml) was added to a stirred solution of the dibenzylate (64.2g, 161mmol) in MeOH (400ml) at room temperature. After 90 hr, the reaction mixture was neutralized with $NaHCO_3$ and dilute aqueous NaOH, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and vigorously stirred with $MgSO_4$ for 1 hr, then insoluble materials were filtered off, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 2.5:1) to give the recovered starting material (10.3g) and **33** as colorless crystals (43.1g, 75%), mp 44-45 °C (fine needles). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 6H, *J*=7.5Hz), 1.54-1.85 (m, 4H), 2.80 (d, 2H, *J*=4.5Hz), 3.45-3.56 (m, 2H), 3.62-3.70 (m, 2H), 4.49 (d, 2H, *J*=11.0Hz), 4.66 (d, 2H, *J*=11.0Hz), 7.22-7.44 (m, 10H). EI-MS *m/z* (%): 267 (M^+-91, 1.4), 163 (2.5), 161 (2.1), 149 (7.8), 91 (100). HR-MS Calcd for $C_{15}H_{23}O_4$: 267.1598. Found: 267.1592. *Anal* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.65; H, 8.37.

Methyl (2*S*)-2-Benzyloxybutanoate (11)

A solution of $NaIO_4$ (14.0g, 65.5mmol) in H_2O (10ml) was added to a stirred solution of **33** (12.0g, 33.5mmol) in THF (50ml) at room temperature. After 3 hr, insoluble materials were filtered off, and the filtrate was concentrated *in vacuo* to remove most THF. The residual aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an aldehyde as a colorless oil (12.0g, 100%).

A 2.67M Jones reagent (50ml) was added to a stirred solution of the aldehyde (12.0g, 67mmol) in acetone (200ml) at -20°C. After 45 min, the excess reagent was quenched with *i*-PrOH, and CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was treated with an ether solution of excess CH_2N_2. The solution was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 2:1) to leave **11** as a colorless oil (12.1g, 87%). $[\alpha]_D^{23}$ -94° (c=1.60, $CHCl_3$). IR (neat) ν (cm^{-1}): 1755. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (t, 3H, *J*=7.5Hz), 1.68-1.89 (m, 2H), 3.75 (s, 3H), 3.90 (dd, 1H, *J*=7.0, 5.5Hz), 4.42 (d, 1H, *J*=11.5Hz), 4.71 (d, 1H, *J*=11.5Hz), 7.25-7.41 (m, 5H). EI-MS *m/z* (%): 208 (M^+, 0.3), 159 (1.0), 149 (3.3), 136 (1.3), 129 (2.4), 102 (33), 91 (100). HR-MS Calcd for $C_{12}H_{16}O_3$: 208.1100. Found: 208.1127.

Dimethyl (3*S*)-3-Benzyloxy-2-oxopentylphosphonate (34)

A 1.6M hexane solution of *n*-BuLi (57ml) was slowly added dropwise to a stirred solution of dimethyl methanephosphonate (13ml, 120mmol) in THF (70ml) at -80°C under argon. After 30 min, a solution of **11** (8.8g, 42mmol) in THF (50ml) was added dropwise. The reaction mixture was warmed to -30°C during 1.5 hr, then poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (EtOAc) to give **34** as a colorless oil (12.3g, 97%). $[\alpha]_D^{23}$ -35° (c=1.04, $CHCl_3$). IR (neat) ν (cm^{-1}): 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, *J*=7.5Hz), 1.74 (dq, 2H, *J*=7.5, 6.5Hz), 3.19 (dd, 1H, *J*=19.0, 14.5Hz), 3.27 (dd, 1H, *J*=18.5, 14.5Hz), 3.75 (d, 3H, *J*=3.5Hz), 3.79 (d, 3H, *J*=3.5Hz), 3.87 (t, 1H, *J*=6.5Hz), 4.47 (d, 1H, *J*=11.5Hz), 4.63 (d, 1H, *J*=11.5Hz), 7.29-7.36 (m, 5H). EI-MS *m/z* (%): 301 (MH^+, 0.2), 242 (1.4), 214 (17), 209 (0.9), 151 (44), 91 (100). HR-MS Calcd for $C_{14}H_{22}O_5P$: 301.1206. Found: 301.1218.

(1*E*,4*S*)-4-Benzyloxy-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]hex-1-en-3-one (35)

A solution of **34** (100mg, 0.333mmol) in THF (0.3ml) was added dropwise to a stirred suspension of NaH (60% dispersion, 13mg, 0.325mmol, washed with *n*-hexane) in DMSO (0.3ml) at 0°C under argon. After 10 min, the reaction mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. A solution of **10** (39mg, 0.3mmol) in THF (0.3ml) was added dropwise at 0°C. After being stirred for 2 hr, the reaction mixture was poured into ice-cold saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give colorless oils of **35** (68mg, 75%) and its *Z*-isomer (6mg, 7%). **35**: $[\alpha]_D^{16}$ -40° (c=1.06, $CHCl_3$). IR (neat) ν (cm^{-1}): 1690, 1620. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J*=7.5Hz), 1.41 (s, 3H), 1.45 (s, 3H), 1.67-1.79 (m, 2H), 3.67 (dd, 1H, *J*=8.0, 7.0Hz), 3.85 (dd, 1H, *J*=7.0, 6.0Hz), 4.18 (dd, 1H, *J*=8.0, 6.5Hz), 4.40 (d, 1H, *J*=11.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.68 (dddd, 1H, *J*=8.0, 6.0, 5.5, 1.5Hz), 6.76 (dd, 1H, *J*=16.0, 1.5Hz), 6.94 (dd, 1H, *J*=16.0, 5.5Hz), 7.31-7.35 (m, 5H). EI-MS *m/z* (%): 289 (M^+-15, 1.1), 229 (0.5), 203 (3.3), 149 (14), 97 (17), 91 (100). HR-MS Calcd for $C_{17}H_{21}O_4$: 289.1441. Found: 289.1458. *Z*-isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J*=7.5Hz), 1.40 (s, 3H), 1.46 (s, 3H), 1.59-1.82 (m, 2H), 3.58 (dd, 1H, *J*=8.5, 6.5Hz), 3.75 (t, 1H, *J*=6.5Hz), 4.46 (dd, 1H, *J*=8.0, 7.0Hz), 4.39 (d, 1H, *J*=11.5Hz), 4.59 (d, 1H, *J*=11.5Hz), 5.35 (dddd, 1H, *J*=8.5, 6.5, 5.5, 1.0Hz), 6.38 (dd, 1H, *J*=11.5, 5.5Hz), 6.61 (dd, 1H, *J*=11.5, 1.0Hz), 7.23-7.42 (m, 5H).

(2*R*,5*S*)-5-Benzyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]heptan-4-one (36) and (2*S*,5*S*)-5-Benzyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]heptan-4-one (37)

A 1.4M ether solution of MeLi (32ml, 45mmol) was added dropwise to a stirred suspension of CuI (4.4g, 23mmol) in THF (50ml) at -20°C under argon. After 2 hr, the mixture was cooled to -78°C, and a solution of **35** (2.0g, 6.57mmol) in THF (25ml) was added dropwise. The reaction mixture was gradually warmed to -20°C during 2 hr, then poured into ice-cold saturated aqueous NH_4Cl, and after removal of insoluble materials by filtration, the filtrate was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give a 6.3:1 mixture of **36** and **37** [determined by ^{1}H-NMR signals at 4.44 (d, *J*=11.5Hz, 1H of benzylic protons) for **36** and 4.42 (d, *J*=11.5Hz, 1H of benzylic protons) for **37**] as a colorless oil (1.85g, 88%). IR (neat) ν (cm^{-1}): 1710. EI-MS *m/z* (%): 305 (M^+-15, 0.8), 233 (1.5), 213 (1.7), 214 (1.6), 171 (4.2), 149 (11), 113 (23), 91 (100). HR-MS Calcd for $C_{18}H_{25}O_4$: 305.1754. Found: 305.1765.

(2*R*,4*R*,5*S*)-5-Benzyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-ethylheptan-4-ol (39)

A solution of the mixture of **36** and **37** (1.8g, 5.61mmol) in THF (4ml) was added dropwise to a stirred

solution of EtMgBr prepared from Mg (682mg, 28mmol) and EtBr (2.2ml, 28mmol) in THF (14ml) at -78°C under argon. After 1 hr, the reaction mixture was allowed to warm to room temperature, then poured into ice-cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give colorless oils of **39** (1.68g, 86%) and its 2*S*-isomer (**40**: 280mg, 14%). **39**: $[\alpha]_D^{16}$ +17° (c=1.24, $CHCl_3$). IR (neat) ν (cm^{-1}): 3500. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.5Hz), 0.97 (d, 3H, *J*=7.0Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.14 (dd, 1H, *J*=14.5, 5.5Hz), 1.32 (s, 3H), 1.33 (s, 3H), 1.36-1.73 (m, 4H), 1.86 (dd, 1H, *J*=14.5, 4.5Hz), 2.14 (dtq, 1H, *J*=4.5, 5.5, 7.0Hz), 2.63-2.78 (bs, 1H), 3.34 (dd, 1H, *J*=8.5, 3.5Hz), 3.62 (t, 1H, *J*=8.0Hz), 3.93 (dd, 1H, *J*=8.0, 6.5Hz), 4.06 (ddd, 1H, *J*=8.0, 6.5, 5.5Hz), 4.67 (d, 1H, *J*=11.5Hz), 4.72 (d, 1H, *J*=11.5Hz), 7.27-7.37 (m, 5H). EI-MS *m/z* (%): 335 (M^+-15, 0.9), 263 (1.0), 227 (4.5), 201 (11), 143 (100), 91 (88). HR-MS Calcd for $C_{20}H_{31}O_4$: 335.2224. Found: 335.2229. **40**: ^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, 3H, *J*=7.0Hz), 0.91 (t, 3H, *J*=7.5Hz), 1.06 (t, 3H, *J*=7.5Hz), 1.36 (s, 3H), 1.37 (s, 3H), 1.65 (dd, 1H, *J*=14.5, 6.0Hz), 1.41-1.78 (m, 5H), 1.87-2.04 (m, 1H), 3.34 (dd, 1H, *J*=8.0, 3.5Hz), 3.34 (brs, 1H), 3.54 (t, 1H, *J*=8.0Hz), 3.75 (dt, 1H, *J*=6.0, 8.0Hz), 4.04 (dd, 1H, *J*=8.0, 6.0Hz), 4.63 (d, 1H, *J*=11.5Hz), 4.72 (d, 1H, *J*=11.5Hz), 4.72 (d, 1H, *J*=11.5Hz), 7.22-7.41 (m, 5H).

(2*S*,3*R*,5*R*,6*S*)-2-Acetoxy-6-benzyloxy-5-ethyl-5-hydroxy-3-methyloctanoic Acid δ-Lactone (41)

39 (689mg, 1.97mmol) in 70% AcOH was stirred at room temperature for 5 hr. After neutralization with $NaHCO_3$, the reaction mixture was evaporated *in vacuo*. To the residue were added CH_2Cl_2 and $MgSO_4$, and the mixture was vigorously stirred for 1 hr. After filtration, the filtrate was chromatographed on a silica gel column (*n*-hexane-EtOAc 1:2) to give a triol as a colorless oil (521mg, 85%). TBS chloride (275mg, 1.82mmol) was added to a stirred solution of the triol (517mg, 1.67mmol) and imidazole (136mg, 2.0mmol) in CH_2Cl_2 (2ml) at room temperature. After 1 hr, the reaction mixture was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give (3*S*,4*R*,6*R*,7*S*)-3-benzyloxy-8-*tert*-butyldimethylsilyloxy-4-ethyl-6-methyloctane-4,7-diol as a colorless oil (648mg, 92%). $[\alpha]_D^{16}$ +9.2° (c=0.80, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 6H), 0.89 (s, 9H), 0.89 (t, 3H, *J*=7.5Hz), 0.94 (d, 3H, *J*=7.5Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.19 (dd, 1H, *J*=14.5, 4.0Hz), 1.53 (dq, 1H, *J*=29.5, 7.5Hz), 1.53-1.67 (m, 3H), 1.72 (dq, 1H, *J*=29.5, 7.5Hz), 1.88 (dd, 1H, *J*=14.5, 8.0Hz), 1.99-2.16 (m, 1H), 2.93-3.26 (9m, 1H), 3.32 (dd, 1H, *J*=8.5, 3.5Hz), 3.58 (dd, 1H, *J*=10.0, 4.0Hz), 3.63 (dd, 1H, *J*=10.0, 4.0Hz), 3.68-3.77 (m, 1H), 5.30 (s, 2H), 7.23-7.42 (m, 5H). EI-MS *m/z* (%): 377 (0.3), 349 (M^+-75, 0.4), 257 (38), 185 (45), 91 (100). HR-MS Calcd for $C_{20}H_{33}O_3Si$: 349.2201. Found: 349.2191.

Et_3N (0.38ml, 2.73mmol), DMAP (12mg), and Ac_2O (64μl, 678μmol) were added to a stirred solution of the above silylate (116mg, 273μmol) in CH_2Cl_2 (0.5ml) at room temperature. After 1 hr, MeOH (1ml) was added to decompose excess Ac_2O, and the reaction mixture was evaporated *in vacuo* to leave an oil (218mg), which was dissolved in THF (1.5ml). After addition of 1N HCl (0.6ml), MeOH was added until the solution became clear. After being stirred for 3 hr, $NaHCO_3$ and H_2O were added, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc) to give a diol as a colorless oil (86mg, 89%). Molecular sieves 3Å (22mg) and PCC (22mg, 102μmol) were added to a stirred solution of the diol (12mg, 34μmol) in CH_2Cl_2 (0.3ml) at room temperature. After 1 hr, the reaction mixture was chromatographed on a silica gel column (*n*-hexane-EtOAc 1:2) to give **41** as a colorless oil (8.8mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=6.0Hz), 0.95 (d, 3H, *J*=7.5Hz), 0.96 (t, 3H, *J*=7.5Hz), 1.15-1.46 (m, 2H), 1.53 (dq, 1H, *J*=22.0, 7.5Hz), 1.58 (dd, 1H, *J*=13.5, 4.0Hz), 1.77 (dq, 1H, *J*=22.0, 7.5Hz), 2.00 (t, 1H, *J*=13.5Hz), 2.08-2.28 (m, 1H), 2.10 (s, 3H),

3.36 (dd, 1H, *J*=9.5, 3.0Hz), 4.40 (d, 1H, *J*=10.5Hz), 4.60 (d, 1H, *J*=10.5Hz), 4.86 (d, 1H, *J*=11.5Hz), 7.16-7.35 (m, 5H). EI-MS *m/z* (%): 349 (MH^+, 0.2), 319 (M^+ -29, 0.1), 291 (0.2), 290 (0.2), 289 (0.1), 230 (0.3), 199 (23), 157 (33), 129 (48), 111 (67), 91 (100), 43 (78). HR-MS Calcd for $C_{18}H_{23}O_5$: 319.1547. Found: 319.1539.

(2*S*,3*S*,5*R*,6*S*)-2-Acetoxy-6-benzyl-5-ethyl-5-hydroxy-3-methyloctanoic Acid δ-Lactone (42)

42 (3.6mg, 34% overall yield) was obtained from **40** as described for **41**. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (d, 3H, *J*=7.0Hz), 1.03 (t, 3H, *J*=7.5Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.33-1.63 (m, 2H), 1.62 (dd, 1H, *J*=14.0, 5.5Hz), 1.65 (dq, 1H, *J*=22.0, 7.5Hz), 1.78 (dq, 1H, *J*=22.0, 7.5Hz), 2.09 (dd, 1H, *J*=14.0, 5.0Hz), 2.13 (s, 3H), 2.42-2.61 (m, 1H), 3.43 (dd, 1H, *J*=9.0, 3.5Hz), 4.44 (d, 1H, *J*=10.5Hz), 4.65 (d, 1H, *J*=10.5Hz), 5.47 (d, 1H, *J*=5.0Hz), 7.28-7.38 (m, 5H). EI-MS *m/z* (%): 347 (M^+-1, 0.1), 319 (0.1), 290 (0.3), 230 (0.6), 199 (21), 157 (26), 129 (52), 111 (88), 91 (100), 43 (55). HR-MS Calcd for $C_{20}H_{27}O_5$: 347.1860. Found: 347.1859.

(2*S*,3*R*,5*R*,6*S*)-6-Benzyloxy-5-*tert*-butyldimethylsilyloxy-5-ethyl-3-methyloctane-1,2-diol (43)

TBS-triflate (14.1ml, 6.1mmol) was carefully added dropwise to a stirred solution of **39** (415mg, 1.18mmol) and Et_3N (3.3ml, 23.7mmol) in CH_2Cl_2 (10ml) at 0°C under argon. After 18 hr at room temperature, H_2O was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give (2*S*,4*R*,5*S*)-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)]-4-ethylheptane as a colorless oil (548mg, 100%). $[\alpha]_D^{20}$ +3.9° (c=0.36, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.89 (t, 3H, *J*=7.5Hz), 1.02 (d, 3H, *J*=7.0Hz), 1.05 (t, 3H, *J*=7.5Hz), 1.32 (s, 3H), 1.40 (s, 3H), 1.52-1.69 (m, 4H), 1.75-1.96 (m, 3H), 3.15 (dd, 1H, *J*=7.5, 3.5Hz), 3.63 (t, 1H, *J*=7.5Hz), 3.93 (dd, 1H, *J*=7.5, 6.5Hz), 4.01 (ddd, 1H, *J*=7.5, 6.5, 5.0Hz), 4.54 (d, 1H, *J*=11.0Hz), 4.68 (d, 1H, *J*=11.0Hz), 7.28-7.36 (m, 5H). EI-MS *m/z* (%): 449 (M^+-15, 0.7), 377 (0.4), 349 (1.8), 315 (17), 125 (10), 91 (100), 73 (34), 57 (11). HR-MS Calcd for $C_{26}H_{45}O_4Si$: 449.3090. Found: 449.3083.

A solution of the above TBS compound (1.64g, 3.48mmol) in THF (30ml) containing 1N H_2SO_4 (15ml) and MeOH (7ml) was stirred at room temperature for 39 hr. The reaction mixture was neutralized with $NaHCO_3$ and aqueous NaOH, and concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 1:2) to give **43** as a colorless oil (1.45g, 97%). $[\alpha]_D^{18}$ -3.0° (c=0.24, $CHCl_3$). IR (neat) ν (cm^{-1}): 3350. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.88 (t, 3H, *J*=7.5Hz), 0.93 (d, 3H, *J*=7.0Hz), 1.07 (t, 3H, *J*=7.5Hz), 1.24 (dd, 1H, *J*=14.5, 5.5Hz), 1.55 (dq, 1H, *J*=15.0, 7.5Hz), 1.66 (dq, 1H, *J*=15.0, 7.5Hz), 1.77-1.97 (m, 6H), 3.17 (dd, 1H, *J*=7.0, 3.5Hz), 3.52-3.58 (m, 2H), 3.72-3.78 (m, 1H), 4.50 (d, 1H, *J*=11.0Hz), 4.69 (d, 1H, *J*=11.0Hz), 7.27-7.35 (m, 5H). EI-MS *m/z* (%): 349 (M^+-75, 0.2), 321 (1.1), 285 (0.4), 275 (0.7), 259 (3.9), 241 (2.6), 185 (8.9), 143 (78), 91 (100), 75 (20), 73 (29), 57 (20). HR-MS Calcd for $C_{20}H_{33}O_3Si$: 349.2201. Found: 349.2178.

(2*S*,3*R*,5*R*,6*S*)-6-Benzyloxy-5-*tert*-butyldimethylsilyloxy-5-ethyl-2-(4-methoxybenzyloxy)-3-methyloctan-1-ol (44)

p-Anisaldehyde dimethyl acetal (85%, 241mg, 1.12mmol) and PPTS (15mg) were added to a stirred solution of **43** (319mg, 0.75mmol) in CH_2Cl_2 (3ml) at room temperature. After 1 hr, the reaction mixture was neutralized with Et_3N (1ml), and concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give (2*R*,4*R*,5*S*)-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-2-[(2*RS*,4*S*)-(4-methoxyphenyl)-1,3-dioxolan-4-yl]heptane as a colorless oil (406mg, 100%). EI-MS *m/z* (%): 485 (M^+-57, 2.8), 393 (12), 257 (12), 241 (7.7), 185 (7.1), 173 (18), 167 (5.4), 135 (19), 121 (14), 109 (5.5), 91 (100), 73 (48),

57 (17). HR-MS Calcd for $C_{38}H_{41}O_5Si$: 485.2726. Found: 485.2726.

$LiAlH_4$ (17mg, 0.45mmol) was added to a stirred solution of $AlCl_3$ (180mg, 1.35mmol) in ether (1ml) at 0°C under argon. After 30 min, the mixture was cooled to -50°C, and a solution of the above acetal (122mg, 0.255mmol) in ether (1ml) was added dropwise. After 10 min, 15% NaOH (1ml) was added to quench the reaction, then the reaction mixture was acidified with 1N HCl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-ether 1:1) to give colorless oils of **44** (112mg, 91%) and 1-MPM isomer (8.1mg, 7%). **44**: $[\alpha]_D^{20}$ +13° (c=0.82, $CHCl_3$). IR (neat) ν (cm^{-1}): 3420. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.90 (t, 3H, *J*=7.5Hz), 1.03 (d, 3H, *J*=7.0Hz), 1.06 (t, 3H, *J*=7.5Hz), 1.34 (dd, 1H, *J*=14.5, 8.0Hz), 1.55-1.92 (m, 6H), 2.01-2.06 (m, 1H), 3.16 (dd, 1H, *J*=7.5, 3.0Hz), 3.45 (dt, 1H, *J*=3.5, 6.0Hz), 3.55-3.67 (m, 2H), 3.81 (s, 3H), 4.47 (d, 1H, *J*=11.5Hz), 4.54 (d, 1H, *J*=11.5Hz), 4.60 (d, 1H, *J*=11.5Hz), 4.60 (d, 1H, *J*=11.5Hz), 4.69 (d, 1H, *J*=11.5Hz), 6.88 (d, 2H, *J*=8.5Hz), 7.26 (d, 2H, *J*=8.5Hz), 7.29-7.37 (m, 5H). EI-MS *m/z* (%): (M^+-223, 0.3), 304 (0.1), 263 (2.5), 211 (1.8), 173 (0.8), 145 (1.0), 121 (100), 91 (18), 73 (5.8), 57 (2.2). HR-MS Calcd for $C_{19}H_{33}O_2Si$: 321.2252. Found: 321.2250.

(2*S*,3*R*,5*R*,6*S*)-6-Benzyloxy-5-*tert*-butyldimetylsilyloxy-5-ethyl-2-(4-methoxybenzyloxy)-3-methyloctanal (9)

A solution of DMSO (136μl, 1.92mmol) in CH_2Cl_2 (1ml) and then a solution of **44** (174mg, 0.319mmol) in CH_2Cl_2 (2ml) were slowly added dropwise to a stirred solution of oxalyl chloride (84ml, 0.963mmol) in CH_2Cl_2 (1ml) at -90°C under argon. After 5 min, Et_3N (356μl, 2.55mmol) was added dropwise, and the reaction mixture was allowed to warm to -30°C. Ether was added, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave **9** as a colorless oil (173mg, 100%). $[\alpha]_D^{20}$ -21° (c=0.72, $CHCl_3$). IR (neat) ν (cm^{-1}): 3000, 2875, 2860, 2825, 2650, 1730, 1610, 1580, 1510, 1460. ^{1}H-NMR (C_6D_6) δ: 0.20 (s, 3H), 0.22 (s, 3H), 0.82 (t, 3H, *J*=7.5Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.10 (d, 3H, *J*=7.0Hz), 1.13-1.17 (m, 1H), 1.36 (dd, 1H, *J*=6.0, 14.5Hz), 1.55-1.96 (m, 5H), 3.04 (dd, 1H, *J*=3.5, 7.5Hz), 3.34 (s, 3H), 3.80 (dd, 1H, *J*=1.5, 3.5Hz), 4.29 (d, 1H, *J*=11.5Hz), 4.38 (d, 1H, *J*=11.5Hz), 4.53 (d, 1H, *J*=11.5Hz), 4.61 (d, 1H, *J*=11.5Hz), 6.80-6.88 (m, 2H), 7.11-7.27 (m, 5H), 7.36-7.39 (m, 2H), 9.71 (d, 1H, *J*=1.5Hz). EI-MS *m/z* (%): 513 (M^+ -29, 0.9), 393 (1.0), 279 (2.2), 257 (2.0), 243 (2.0), 211 (4.9), 167 (3.4), 149 (6.4), 121 (100), 91 (30). HR-MS Calcd for $C_{30}H_{45}O_5Si$: 513.3025. Found: 513.3061.

Methyl {2*R*,3*R*,5*S*,6*S*,6[1*S*,2*S*,3*S*,5*R*,5(2*R*,3*R*,5*R*,5(2*RS*,3*R*,5*R*,5(1*S*)))]}-2-{6-[5-(5-(5-(1-Acetoxy)propyl-5-ethyl-2-metoxy-3-methyltetrahydrofuran-2-yl)-3,5-dimethyltetrahydrofuran-2-yl)-1,3-dimethyl-2-hydroxy-4-oxoheptyl]-3,5-dimethyl-2-methoxytetrahydropyran-2-yl}acetate (45)

21-O-Acetyllysocellin methyl ester[9] (321mg, 0.467mmol) was treated with (±)-10-camphorsulfonic acid (5mg, 25μmol) in MeOH (5.0ml) for 15 min at room temprature. The reaction mixture was neutralized with Et_3N (0.3ml) and concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give **45** as a colorless oil (315mg, 94%). IR (neat) ν (cm^{-1}): 3510, 2960, 2925, 2870, 1735, 1700, 1455, 1430. FAB-MS *m/z* (%): 681 (M^+ -32, 9.8), 649 (14), 631 (9.0), 607 (3.6), 589 (6.5), 451 (5.8), 438 (13), 419 (9.7), 351 (13), 341 (15), 309 (25), 297 (10), 267 (20), 251 (31), 249 (42), 243 (100), 207 (29), 191 (22), 183 (69), 169 (44), 151 (42), 139 (22), 123 (31), 95 (21), 57 (23), 43 (21). HR-MS Calcd for $C_{38}H_{65}O_{10}$: 681.4582. Found: 681.4526.

Degradation of 45 to {4*R*,4(2*S*,3*S*,5*R*),5[(2*R*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Acetoxy)propyl-5-ethyl-2-hydroxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (46) and 27

45 (315mg, 0.44mmol) was pyrolyzed at 180 ℃ under reduced pressure (0.2mmHg) using a Kugelroh apparatus gave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6.5:1) to give **46** (159mg, 85%) and **27** (65mg, 54%) as colorless oils. **46**: IR (neat) ν (cm^{-1}): 3500, 2970, 2920, 2860, 1705, 1455, 1430. ^{1}H-NMR ($CDCl_3$) δ: 0.81-1.08 (m, 18H), 1,13 (s, 1.5H), 1.29 (s, 1.5H), 1.42-2.24 (m, 12H), 2.06 (s, 1.5H), 2.07 (s, 1.5H), 2.38-2.69 (m, 3H), 3.33 (s, 1H), 3.54 (dd, 0.5H, *J*=8.0, 6.0H), 3.65 (dd, 0.5H, *J*=10.0, 5.0H), 4.91-5.30 (m, 1H). EI-MS *m/z* (%): 408 (M^+ -18, 5.7), 319 (6.4), 307 (4.7), 251 (3.5), 243 (10), 207 (15), 197 (31), 183 (13), 169 (8.5), 151 (14), 57 (100), 43 (54). HR-MS Calcd for $C_{24}H_{40}O_5$: 408.2874. Found: 408.2868.

Methyl 2-{(2R,3R,5S,6S)-3,5-Dimethyl-2-methoxy-6-[(1S)-2-hydroxy-1-methylethyl]tetrahydropyran-2-yl}acetate (47)

The aldehyde (**27**) (65mg, 0.24mmol) was reduced with $NaBH_4$ (17mg, 0.44mmol) in MeOH (1.5ml) at 0°C for 15 min to give **47** as a colorless oil (66mg, 100%). $[\alpha]_D^{20}$ +30° (c=0.90, $CHCl_3$). IR (neat), ν (cm^{-1}): 3475, 2980, 2950, 1745, 1470, 1445. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H, *J*=6.5Hz), 0.93 (d, 3H, *J*=7.0Hz), 0.95 (d, 3H, *J*=7.5Hz), 1.33 (dt, 1H, *J*= 13.0, 11.5Hz), 1.43 (dt, 1H, *J*=13.0, 4.0Hz), 1.55-1.63 (m, 1H), 1.84-1.89 (m, 1H), 1.97-2.05 (m, 1H), 2.53 (d, 1H, *J*=13.0Hz), 2.70-2.75 (brs, 1H), 2.77 (d, 1H, *J*=13.0 Hz), 3.25 (s, 3H), 3.41 (dd, 1H, *J*= 10.5, 2.5Hz), 3.68 (s, 3H), 3.64-3.68 (m, 1H), 3.81 (dd, 1H, *J*=10.5, 2.5Hz). FAB-MS *m/z* (%): 243 (M^+ -31, 100), 225 (13), 211 (14), 207 (13), 169 (14), 154 (37), 137 (24), 136 (28). HR-MS Calcd for $C_{13}H_{23}O_4$: 243.1598. Found: 243.1607.

Acknowledgment — We are grateful to the Tokyo Research Laboratory of Kaken Pharmaceutical Co. for the generous gift of lysocellin.

References and Notes

1. Chiral synthesis of polyketide-derived natural products, 51. For part 50, see: K. Horita, S. Hachiya, K. Ogihara, Y. Yoshida, M. Nagasawa, and O.Yonemitsu, *Heterocycls.*, in press.
2. Present address: Department of Chemistry, Okayama University of Science, Okayama 700, Japan.
3. J. W. Westley, *Polyether Antibiotics. Naturally Occurring Acid Ionophores. Vol. 1; Biology*, Marcel Dekker Inc., New York, 1982.
4. Total synthesis of polyether antibiotics. Calcimycin: a) D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *J. Am. Chem. Soc.*, **101**, 6789 (1979); b) G. R. Martinez, P. A. Grieco, E. Williams, K. Kanai, and C. V. Srinivasan, *Ibid.*, **104**, 1436 (1982); c) Y. Nakahara, A. Fujita, K. Beppu, and T. Ogawa, *Tetrahedron*, **42**, 6465 (1986); d) D. P. Negri and Y. Kishi, *Tetrahedron Lett.*, **28**, 1063 (1987). Monensin: e) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C. -L. J. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 262 (1979); f) W. C. Still, J. McDonald, and D. Collum, *Ibid.*, **102**, 2117 (1980). Lasalocid A: g) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *Ibid.*, **100**, 2933 (1978); h) R. E. Ireland, S. Thaisrivongs, and C. S. Wilcox, *Ibid.*,**102**, 1155 (1980); i) R. E. Ireland, R. C. Anderson, A. R. Bodoud, B. J. Fitzsimmons, G. J. McGarrey, S. Thaisrivongs, and S. C. Wilcox, *Ibid.*, **105**, 1988 (1983); j) I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, **31**, 6035 (1990); k) K. Horita, I. Noda, K. Tanaka, Y. Oikawa, and O. Yonemitsu, *Tetrahedron*, **49**, 5997 (1993). Narasin: l) Y. Kishi, *Aldrichim. Acta*, **13**, 23 (1980). Salinomycin: m) Y. Kishi, S. Hatakeyama, and M. D. Lewis, "Front. Chem. Plenary Keynote Lect. IUPAC Congr. 28th, 1981," ed by K. J. Laidler, Pergamon Press, Oxford, 1982, pp

287-304; n) K. Horita, Y. Oikawa, S. Nagato, and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1717 (1989); o) R. C. D. Brown and P. J. Kocienski, *Synlett*, 417 (1994). X-206: p) D. A. Evans, S. L. Bender, and J. Morris, *J. Am. Chem. Soc.*, **110**, 2506 (1988). Ionomysin: q) D. A. Evans, R. L. Dow, T. L. Shin, J. M. Takacs, and R Zahler, *Ibid.*, **112**, 5290 (1990). Ferensimysin B: r) D. A. Evans, R. P. Polmazek, K. M. DeVries, D. E.Guinn, and D. J. Mathre, *Ibid.*, **113**, 7613 (1991). Lonomycin A: s) D. A. Evans, A. M. Ratz, B. E. Huff, and G. S. Sheppard, *J. Am. Chem. Soc.*, **117**, 3448 (1995).

5. The preliminary reports of this work: a) K. Horita, T. Inoue, K. Tanaka, and O. Yonemitsu, *Tetrahedron Lett.*, **33**, 5537 (1992); b) K. Horita, K. Tanaka, T. Inoue, and O. Yonemitsu, *Ibid.*, **33**, 5541 (1992).
6. a) E. Ebata, H. Kasahara, K. Sekine, and Y. Inoue, *J. Antibiot.*, **28**, 118 (1975); b) N. Otake, M. Naenuma, H. Kinashi, S. Sato, and Y. Saito, *J. Chem. Soc. Chem. Commun.*, **1975**, 92.
7. M. Koenuma, H. Kinashi, N. Otake, S. Seto, and Y. Saito, *Acta Crystallogr. Sect. B*, **32**, 1267 (1976).
8. Unless otherwise noted, numbering is based on that of lysocellin (**1**).
9. M. Koenuma and N. Otake, *J. Antibiot.*, **30**, 819 (1977).
10. Racemic **6**: P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc.*, **101**, 4749 (1979).
11. K. Horita, I. Noda, K. Tanaka, Y. Oikawa, and O. Yonemitsu, *Tetrahedron*, in press.
12. E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).
13. Y. Kato, H. Ohta, and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 1303 (1987).
14. Y. Oikawa, T. Tanaka, K. Horita, I. Noda, N. Nakajima, N. Kakusawa, T. Hamada, and O. Yonemitsu, *Chem. Pharm. Bull.*, **35**, 2184 (1987).
15. W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, **105**, 2487 (1983).
16. Recemic **23** : P. G. M. Wutz, M. L. Obrzut, and P. A. Thompson, *Tetrahedron Lett.*, **25**, 4051 (1984).
17. J. R. Parikh and W. E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
18. L. F. Wiggins, *J. Chem. Soc.*, **1946**, 13.
19. Y. Yamamoto and K. Matsuoka, *J. Chem. Soc., Chem. Commun.*, **1987**, 923.
20. J. Leonard and G. Ryan, *Tetrahedron Lett.*, **28**, 2525 (1987).
21. a) W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, **21**, 1031 (1980); b) M. T. Reetz. *Ang. Chem. Int. Ed. Engl.*, **23**, 556 (1984); c)Y. Oikawa, K. Horita, and O. Yonemitsu, *Tetrahedron Lett.*, **26**, 1541 (1985).
22. A. J. Mancuso and D. Swern, *Synthesis*, **1981**, 165.
23. a) R. Bernardi, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, **22**, 4021 (1981); b) T. Suami, K. Tadano, Y. Iimura, and H. Yokoo, *J. Carbohydr. Chem.*, **5**, 1 (1986).

(*Received in Japan* 27 *July* 1995; *accepted* 9 *October* 1995)