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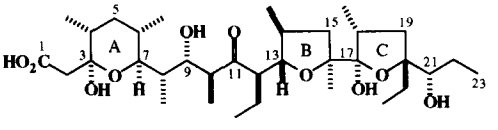
STEREOSELECTIVE TOTAL SYNTHESIS OF LYSOCELLIN, THE REPRESENTATIVE POLYETHER ANTIBIOTIC OF THE LYSOCELLIN FAMILY. PART 2. SYNTHESIS OF C10-C23 SUBUNIT VIA CONSTRUCTION OF TWO RINGS (B AND C) AND ITS CONDENSATION WITH C1-C9 SUBUNIT TO ACHIEVE THE TOTAL SYNTHESIS OF LYSOCELLIN [1]

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

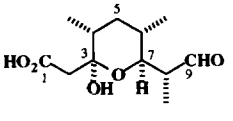
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract: Stereoselective total synthesis of lysocellin (**1**), a representative polyether antibiotic, was achieved *via* coustruction of substituted tetrahydrofuran and γ-lactol rings and final aldol condensation

Our continuing interest in the stereoselective synthesis of naturally occurring polyketide compounds with complex structures such as polyether and macrolide antibiotics has naturally led us to carry out the total synthesis of lysocellin (**1**), the representative polyether antibiotic in the lysocellin family. In the preceding paper,[1] we reported that two important subunits, **2** and **3**, corresponding to the C1-C9 and C16-C23 parts of **1**, respectively,



Lysocellin (1)



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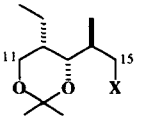
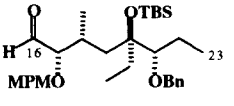


4 : X = SO_2Ph
5 : X = SOPh
6 : X = I



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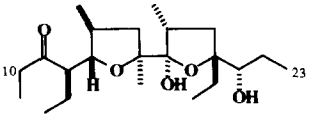

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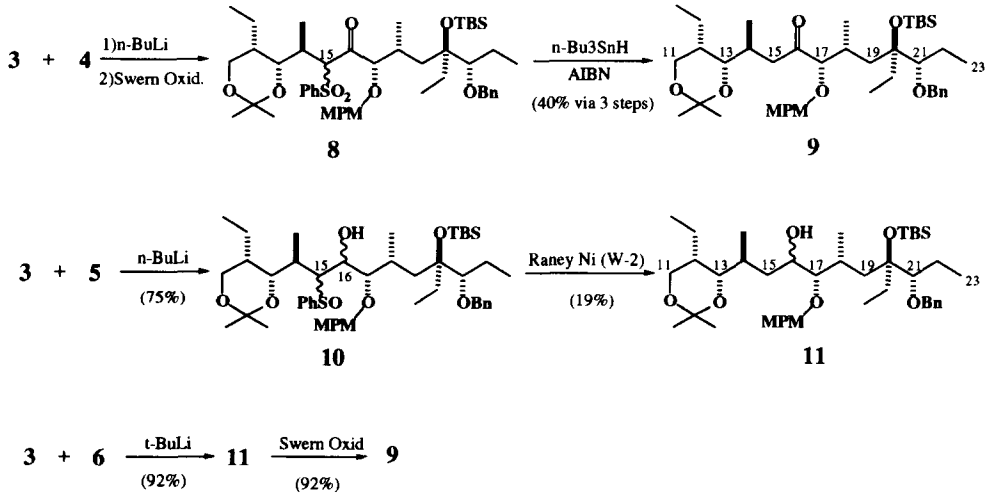
were synthesized rather efficiently by virtue of stereocontrolled hydroboration, Michael, and Grignard reactions. As shown in the preceding paper,[1] the key steps for completing the total synthesis of **1** arising from the retrosynthetic disconnection were presumed to be: 1) coupling of **3** with C11-C15 subunit such as **4**, **5**, and **6**; 2) stereoselective construction of B and C rings; and final aldol condensation between C1-C9 aldehyde (**2**) and C10-C23 ethyl ketone (**7**). In the present paper, we report an achievement of the first total synthesis of **1** through these key steps.

Coupling of C16-C23 subunit (3) with C11-C15 subunit (4-6)

Since a **4-6** type of subunit having three contiguous chiral centers substituted with ethyl, hydroxy, and methyl groups is one of the primary building blocks of polyether antibiotics, we recently reported a good method for these subunits starting from D-glucose in the course of the total synthesis of polyether antibiotics isolasalocid A and lasalocid A,[3] and more recently an improved method starting from methyl (*S*)-3-hydroxy-2-methylpropionate was also completed.[4] In order to synthesize a key intermediate, C11-C23 ketone (**9**), coupling of **3** with sulfone (**4**) was first examined. When **3** was allowed to react with the lithium salt of **4**, the coupling proceeded smoothly to give a mixture of hydroxysulfones, which was oxidized under Swern's conditions to give **8** as a mixture of two stereoisomers with respect to the C15 sulfone position.[5] Desulfurization of **8**, however, was quite difficult. All attemps to remove the sulfone group were unsuccessful, exccpt for a radical reaction, which proceeded with tri-*n*-butyltin hydride in the presence of 2,2-azobisisobutyronitrile (AIBN) at 80 °C, although the yield of expected **9** was only 40%. Coupling with sulfoxide (**5**) also gave poor results. Treatmeut of **3** with the lithium salt of **5** gave a complex mixture of stereoisomers of **10** with respect to the C15, C16, and sulfoxide positions. The mixture of **10** was then desulfurized with Reney nickel to give a mixture of two stereoisomers of **11** in only 19% yield. These two methods *via* coupling with **4** and **5** were practically not useful. Finally, coupling using iodide (**6**) was examined. No reaction of **3** with a Grignard reagent prepared from **6** occurred at -78 °C, and **3** was completely recovered. However, when **3** was treated with an alkyllithium



prepared from **6** and *tert*-butyllithium at -78 °C,[6] the coupling was completed within 1 hour to give **11** as a 1 : 1 isomeric mixture in excellent yield. Swern oxidation of **11** readily gave **9**.

Construction of the B ring. Synthesis of C11-C23 subunit (15)

Among many methods available for the stereocontrolled construction of substituted tetrahydrofuran rings,[3,7] we selected Kishi's epoxide method,[8] which was presumed to be most reliable for the B ring construction. When **9** was treated with methylmagnesium iodide in ether, a chelation controlled addition of the Grignard reagent proceeded with complete stereoselectivity to give only **12**, which was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to remove the 4-methoxybenzyl (MPM) protecting group, but on account of an adjacent hydroxy group, a 4-methoxybenzoate *via* an acetal was mainly obtained.[9] The subsequent reduction with lithium aluminum hydride (LAH) readily gave C16,C17-diol, and then the C17 secondary alcohol was selectively mesylated to give **13**. After hydrolysis of the isopropylidene group, treatment with potassium carbonate at room temperature gave epoxide (**14**), which, without purification, was treated with (±)-10-camphorsulfonic acid (CSA) at room temperature. An acid-catalyzed recyclization of epoxyalcohol (**14**) into the expected tetrahydrofuran (**15**) proceeded rapidly with complete stereoselectivity. After conversion to its diacetate (**16**), the configuration was confirmed by NOESY measurements as shown in Figure 1. Thus the stereoselective construction of the B ring was completed.

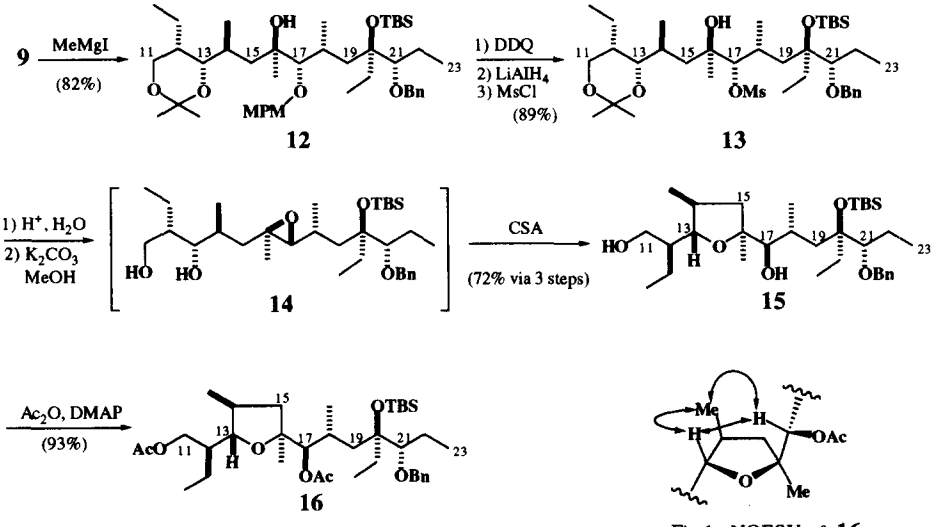


Fig 1. NOESY of **16**

Synthesis of ethyl ketone (7: C10-C23 subunit) *via* construction of the C ring

Conversion of **15** into C10-C23 ethyl ketone (**7**),[10] one of the two final intermediates for the total synthesis of **1**, was completed through several reactions including introduction of the C10 part and stereoselective construction of C17-C20 γ-lactol ring (C ring), the latter of which was a crucial step. In order to introduce the

C10 part, the secondary alcohol of **15** was first protected as an acetate (**17**) *via* three conventional reactions; *tert*-butyldimethylsilyl (TBS) protection of the primary alcohol, acetylation of the secondary alcohol, and recovery of the primary alcohol by selective hydrolysis. Successive three reactions; Swern oxidation of the primary alcohol, Grignard reaction with ethylmagnesium bromide, and removal of the TBS group with tetra-*n*-butylammonium fluoride gave triol (**18**).

Oxidation of **18** with pyridinium chlorochromate (PCC) in the presence of molecular sieves gave γ-lactols (**19**, **20**) as a *ca.* 1 : 1 mixture of two diastereoisomers with respect to the C17 hydroxy group. However, when the inseparable mixture of **19** and **20** was treated with 1N sulfuric acid in aqueous tetrahydrofuran at room temperature, the desired lactol (**19**) with correct stereochemistry of **1** was obtained as the sole product. This successful acid-catalyzed isomerization at the lactol position can be explained in terms of thermodynamic

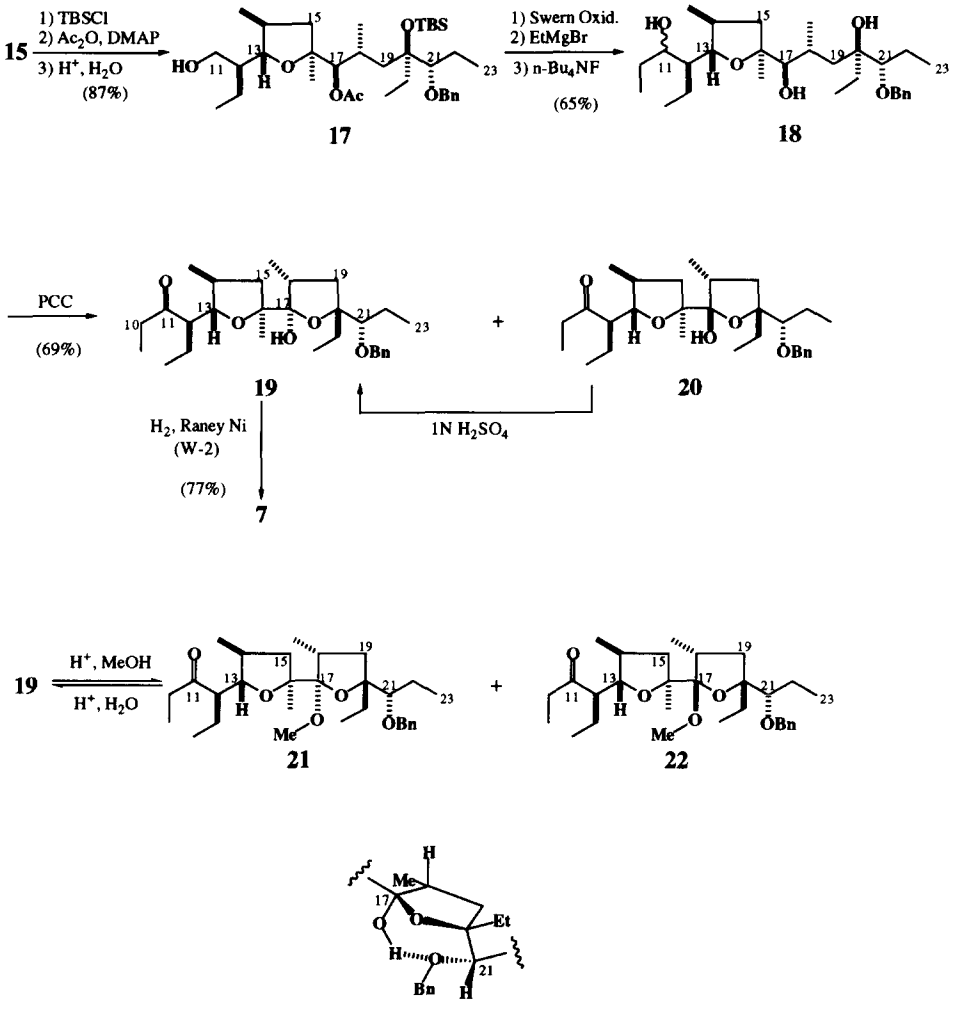


Fig 2.

stabilization of **19** owing to the hydrogen bonding effect as shown in Figure 2. The following evidence supported the above explanation. First, on treatment with CSA in anhydrous methanol at room temperature, **19** was converted to a 1 : 1 mixture of two diastereoisomers of acetals (**21**, **22**), which was, however, readily returned to only the starting γ-lactol (**19**) by the treatment with dilute sulfuric acid under the conditions described adove. Second, the ^{1}H-NMR signal of C17 hydroxy group in **19** appeared at δ 3.67 ppm regardless of concentration of **19** in deutrochloroform. Finally, the benzyl protection of **19** was removed by catalytic hydrogenation over Raney nickel in ethanol to give the expected C10-C23 subunit (**7**)[10] in good yield. The structures of **19** and **7**[10] were confirmed by direct comparison with authentic samples derived from retro-aldol reaction products of **1** (*vide infra*). It should be emphasized that the benzyl group was the best choice for the protection of the C21 hydroxy group in order to prevent a serious side reaction forming an anhydro compound which was readily obtained by reactions not only under mild acidic conditions as described in the preceding report[1] but also under mild alkaline conditions even such as catalytic hydrogenation over palladium hydroxide.

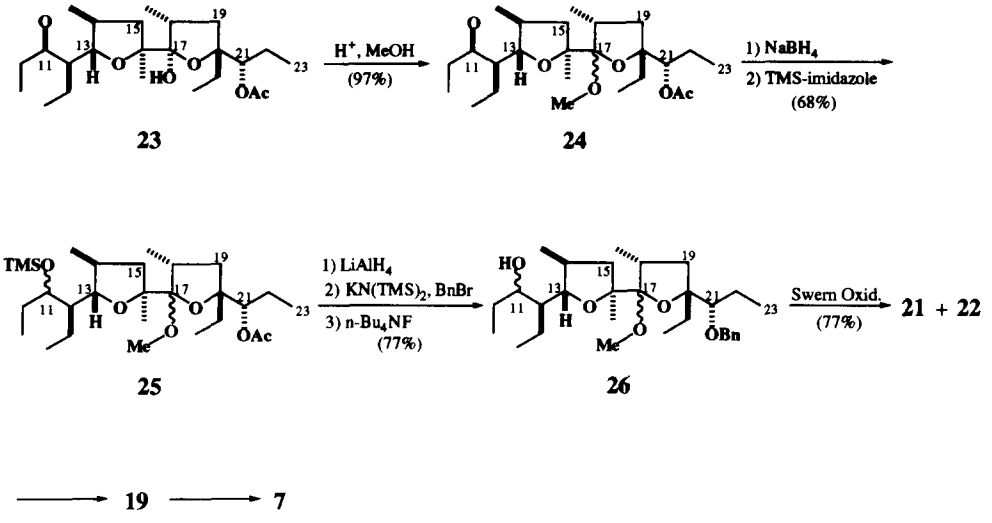
Total synthesis of lysocellin (1)

The synthesis of **1** *via* aldol condensation between C1-C9 aldehyde (**2**) and C10-C23 ethyl ketone (**7**) was finally achieved as follows. After treatment of **7** with a large excess lithium diisopropylamide (LDA) (5 equiv.) at - 78 °C, the resulting lithium enolate was converted by the addition of zinc chloride to the zinc enolate,[8a, 10] which was subjected to the condensation with **2** to give a coupling product as a mixture of four diastereoisomers in 44% yield. The major isomer (22%), which had the highest Rf value on a silica gel thin-layer chromatogram, was converted to the sodium salt, which was identical, in terms of its mixed melting point, optical rotation, and IR and ^{1}H-NMR spectra, with the sodium salt of naturally occurring lysocellin (**1**).[11]

$$\mathbf{2} + \mathbf{7} \xrightarrow[(22\%)]{\text{LDA,ZnCl}_2} \mathbf{1}^- \mathbf{Na}^+$$

A degradation study

The C17 hemi-acetal hydroxy group of ethyl ketone (**23**),[1] one of pyrolytic retro-aldol reaction products of a lysocellin derivative, was first methylated to **24**, and then the C11 ketone was reduced to give a complex mixture of C11 hydroxy, C17 methoxy compounds, which was readily converted to **25** by the treatment with trimethylsilylimidazole.[12] Treatment of **25** with LAH in ether at - 78 °C gave a C21 hydroxy compound,[13] which was protected as a benzyl ether, and then treated with tetra-*n*-butylammonium fluoride to give **26**. Swern oxidation of **26** gave a 1 : 1 mixture of **21** and **22**. This mixture was converted to **7** *via* **19** as described above. Compounds **7**, **19**, **21**, and **22** were identical with the corresponding synthetic compounds, respectively, in terms of their spectral data.



Experimental

(2*S*,5*S*,6*R*,8*R*,9*S*)-9-Benzyloxy-8-*tert*-butyldimethylsilyloxy-2-[(4*S*,5*S*)-2,2-dimethyl-5-ethyl-1,3-dioxan-4-yl)-8-ethyl-5-(4-methoxybenzyloxy)-6-methylundecan-4-one (9)

(a) A 1.6M *n*-hexane solution of *n*-BuLi (0.16ml, 224μmol) was added dropwise to a stirred solution of **4** (78mg, 239μmol) in ether (1.5ml) at -78°C under argon. After 2 hr, a solution of **3** (30mg, 55μmol) in ether (1ml) was added, and the reaction mixture was stirred -55°C for 2 hr, then poured into saturated aqueous NH_4Cl, and evaporated to leave a colorless oil (88mg), which was dissolved in CH_2Cl_2 (1ml) and added dropwise to a stirred solution of oxalyl chloride (80μl, 0.92mmol) and DMSO (131μl, 1.84mmol) in CH_2Cl_2 (2ml) at -78 °C. After 20 min, Et_3N (320μl, 2.3mmol) was added dropwise, and the mixture was allowed to warm to -30°C, and then diluted with ether. The ether layer 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 4:1) to give a mixture of **8** and recovered **4** as a colorless oil (64mg), which was dissolved in benzene (1.2ml). *n*-Bu_3SnH (54μl, 0.2mmol) and AIBN (25mg) were added to the benzene solution. The mixture was heated at 80°C for 5 hr, then allowed to cool to room temperature, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **9** as a colorless oil (16mg, 40%). IR (neat) ν (cm^{-1}): 1720. ^{1}H-NMR (C_6D_6) δ: 0.27 (s, 3H), 0.28 (s, 3H), 0.89 (t, 9H, *J*=7.5Hz), 1.07 (d, 3H, *J*=7.5Hz), 1.11 (s, 9H), 1.22 (d, 3H, *J*=7.0Hz), 1.40 (s, 3H), 1.53 (s, 3H), 1.63-1.76 (m, 2H), 1.83-2.04 (m, 4H), 2.54-2.60 (m, 2H), 3.07 (dd, 1H, *J*=17.0, 2.0Hz), 3.13 (dd, 1H, *J*=7.0, 3.5Hz), 3.35 (s, 3H), 3.54 (dd, 1H, *J*=9.5, 2.0Hz), 3.68 (dd, 1H, *J*=11.5, 2.0Hz), 3.82 (dd, 1H, *J*=11.5, 2.0Hz), 4.04 (d, 1H, *J*=3.5Hz), 4.30 (d, 1H, *J*=11.5Hz), 4.44 (d, 1H, *J*=11.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.75 (d, 1H, *J*=11.5Hz), 6.84-6.89 (m, 2H), 7.12-7.28 (m, 3H), 7.34-7.42 (m, 4H).

(b)DMSO (95μl, 1.34mmol) and then a solution of **11** (vide infra) (50mg, 68μmol) in CH_2Cl_2 (1ml) were added dropwise to a stirred solution of oxalyl chloride (58μl, 0.69mmol) at -78°C under argon. After 20 min,

Et_3N (233μl, 1.67mmol) was slowly added dropwise, and the mixture was allowed to warm to room temperature. After addition of ether, the ether solution was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **9** as a colorless oil (45mg, 92%).

(2*S*,4*RS*,5*S*,6*R*,8*R*,9*S*)-9-Benzyloxy-8-*tert*-butyldimethylsilyloxy-2-[(4*S*,5*S*)-2,2-dimethyl-5-ethyl-1,3-dioxan-4-yl]-8-ethyl-5-(4-methoxybenzyloxy)-6-methylundecan-4-ol (11)

(a) A 1.6M *n*-hexane solution of *n*-BuLi (0.46ml, 0.74mmol) was added dropwise to a stirred solution of **5** (260mg, 0.74mmol) in ether (3ml) at -78°C under argon. After 1 hr, a solution of **3** (160mg, 0.295mmol) in ether (2ml) was added, and the stirring was coutinued for 3 hr at -78°C. The reaction mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (benzene-EtOAc 7:1) to give **10** as a colorless oil (192mg, 75%). A solution of **10** (21mg, 24μmol) in EtOH (0.2ml) was stirred with Raney Ni W-2 (EtOH suspension 0.2ml) for 6 hr at room temperature. After filtration, the filtrate was evaporated *in vacuo* to leave on oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give **11** as a colorless oil (3.4mg, 19%). EI-MS *m/z* (%): 727 (M^+-1, 0.2), 489 (0.8), 351 (1.5), 154 (37), 121 (100), 91 (67). HR-MS Calcd for $C_{43}H_{71}O_7Si$: 727.4973. Found: 727.4929.

(b) A 1.9M pentane solution of *t*-BuLi (0.91ml, 1.73mmol) was added dropwise to a stirred solution of **6** (300mg, 0.96mmol) in ether at -78°C under urgon. After 30 min, a solution of **3** (260mg, 479μmol) in ether (3ml) was added, and the stirring was continued for 1 hr. The reaction mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **11** as a colorless oil (319mg, 92%).

(2*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Benzyloxy-8-*tert*-butyldimethylsilyloxy-4,6-dimethyl-2-[(4*S*,5*S*)- 2,2-dimethyl-5-ethyl-1,3-dioxan-4-yl]-8-ethyl-5-(4-methoxybenzyloxy)undecan-4-ol (12)

A solution of **9** (180mg, 248μmol) in ether (2ml) was added dropwise to a stirred solution of MeMgI prepared from Mg (60mg, 2.48mmol) and MeI (154μl, 2.48mmol) in ether (3ml) at -78°C under argon. After 1 hr, the reaction mixture was allowed to warm to -20°C, and the stirring was continued for 1 hr. The mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **12** as a colorless oil (151mg, 82%). $[\alpha]_D^{22}$ +1.4° (c=0.58, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.09 (s, 3H), 0.82 (d, 3H, *J*=7.0Hz), 0.88 (s, 9H), 0.94 (t, 3H, *J*=7.5Hz), 0.95 (t, 3H, *J*=7.5Hz), 1.06 (d, 3H, *J*=7.0Hz), 1.12 (s, 3H), 1.17-1.93 (m, 13H), 1.38 (s, 3H), 1.44 (s, 3H), 2.18-2.25 (m, 1H), 3.29 (dd, 1H, *J*=9.0, 3.0Hz), 3.46 (dd, 1H, *J*=10.0, 2.0Hz), 3.81 (s, 3H), 3.85 (dd, 1H, *J*=12.0, 2.0Hz), 3.89 (dd, 1H, *J*=12.0, 2.0Hz), 3.95 (s, 1H), 4.44 (d, 1H, *J*=11.0Hz), 4.60 (d, 1H, *J*=11.0Hz), 4.67 (d, 2H, *J*=11.0Hz), 6.84-6.90 (m, 2H), 7.24-7.38 (m, 7H). EI-MS *m/z* (%): 741 (M^+-1, 0.1), 611 (0.2), 213 (6.4), 171 (8.2), 121 (100), 91 (28), 73 (15). HR-MS Calcd for $C_{44}H_{73}O_7Si$: 741.5130. Found: 741.5070.

(2*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-Benzyloxy-8-*tert*-butyldimethylsilyloxy-4,6-dimethyl-2-[(4*S*,5*S*)-2,2-dimethyl-5-ethyl-1,3-dioxan-4-yl]-8-ethyl-5-methylsulfonyloxyundecan-4-ol (13)

DDQ (99mg, 437μmol) was added to a stirred solution of **12** (147mg, 199μmol) in CH_2Cl_2 (4ml) and H_2O (0.2ml) at 0°C. After 20 min, $NaHCO_3$ was added, then the mixture was poured into H_2O, and extracted with

ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil (138mg), which was dissolved in ether (4ml) and reduced with $LiAlH_4$ (14mg, 364μmol) at 0°C for 1 hr. Work-up as usual and chromatography on a silica gel column (*n*-hexane-EtOAc 4:1) gave (2*S*,4*R*,5*S*,6*R*,8*R*,9*S*)-9-benzyloxy-8-*tert*-butyldimethylsilyloxy-4,6-dimethyl-2-[(4*S*,5*S*)-2,2-dimethyl-5-ethyl-1,3-dioxan-4-yl]-8-ethylundecane-4,5-diol as a colorless oil (109mg, 89%). $[\alpha]_D^{23}$ -12° (c=0.452, acetone). ^{1}H-NMR (C_6D_6) δ: 0.25 (s, 3H), 0.30 (s, 3H), 0.89 (t, 3H, *J*=7.5Hz), 0.98 (d, 3H, *J*=7.0Hz), 1.01 (t, 3H, *J*=7.5Hz), 1.10 (s, 9H), 1.11 (t, 3H, *J*=7.5Hz), 1.22-1.54 (m, 3H), 1.28 (d, 3H, *J*=6.5Hz), 1.34 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 1.66-2.13 (m, 10H), 2.36-2.41 (m, 1H), 2.98 (s, 1H), 3.24 (dd, 1H, *J*=7.5, 3.5Hz), 3.31 (dd, 1H, *J*=10.0, 2.0Hz), 3.63 (dd, 1H, *J*=12.0, 1.5Hz), 3.65 (s, 1H), 3.79 (dd, 1H, *J*=12.0, 1.5Hz), 4.49 (d, 1H, *J*=11.5Hz), 4.61 (d, 1H, *J*=11.5Hz), 7.12-7.28 (m, 3H), 7.41-7.43 (m, 2H). EI-MS *m/z* (%): 623 (M^++1, 0.5), 473 (3.9), 213 (15), 154 (28), 136 (29), 91 (100), 73 (46). HR-MS Calcd for $C_{36}H_{67}O_6Si$: 623.4711. Found: 623.4682.

Mesyl chloride (15μl, 202μmol) was added to a stirred solution of the above diol (105mg, 169μmol) in pyridine (1ml) at 0°C. After 10 hr, H_2O was added, and the mixture was extracted with ether. The extract was successively washed with H_2O, 1N HCl, H_2O, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **13** as a colorless oil (118mg, 100%). $[\alpha]_D^{22}$ -8.7° (c=0.96, EtOH). ^{1}H-NMR (C_6D_6) δ: 0.28 (s, 3H), 0.35 (s, 3H), 0.86 (t, 3H, *J*=7.5Hz), 0.96 (t, 3H, *J*=7.0Hz), 0.99 (d, 3H, *J*=7.0Hz), 1.11 (s, 9H), 1.12 (t, 3H, *J*=7.5Hz), 1.26 (s, 3H), 1.33 (d, 3H, *J*=7.0Hz), 1.38 (s, 3H), 1.45 (s, 3H), 1.51-1.75 (m, 4H), 1.77-2.17 (m, 7H), 2.10-2.20 (m, 1H), 2.22 (dd, 1H, *J*=14.5, 3.5Hz), 2.49 (s, 3H), 2.75-2.88 (m, 1H), 3.24 (dd, 1H, *J*=10.0, 2.0Hz), 3.35 (dd, 1H, *J*=8.5, 3.0Hz), 3.55 (dd, 1H, *J*=11.5, 1.5Hz), 3.73 (dd, 1H, *J*=11.5, 1.5Hz), 4.98 (d, 1H, *J*=1.5Hz), 7.14-7.29 (m, 3H), 7.46-7.49 (m, 2H). EI-MS *m/z* : 643 (M^+-57), 461, 419, 365, 307, 213, 91. HR-MS Calcd for $C_{33}H_{59}O_8SSi$: 643.3703. Found: 643.3720.

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-5-Benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-1-hydroxy-2-methylhepthyl]-3,5-dimethyltetrahydrofuran-2-yl}butan-1-ol (15)

1N H_2SO_4 (2ml) was added to a stirred solution of **13** (110mg, 157μmol) in THF (5ml) at room temperature. After 24 hr, the reaction mixture was neutralized with $NaHCO_3$ and concentrated *in vacuo*. The residue was dissolved in MeOH (5ml) and treated with K_2CO_3 (50mg) for 1 hr. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave epoxide (**14**) (67mg), which was unstable and dissolved in CH_2Cl_2 (2ml), and CSA (10mg) was added. After being stirred for 30 min at room temperature, 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 3:1) to give **15** as a colorless oil (64mg, 72%). $[\alpha]_D^{20}$ +4.8° (c=0.99, $CHCl_3$). ^{1}H-NMR (C_6D_6) δ: 0.24 (s, 3H), 0.27 (s, 3H), 0.80 (d, 3H, *J*=6.0Hz), 0.86 (t, 3H, *J*=7.5Hz), 1.00 (t, 3H, *J*=7.5Hz), 1.05 (t, 3H, *J*=7.5Hz), 1.09 (s, 9H), 1.22 (d, 3H, *J*=7.0Hz), 1.24 (s, 3H), 1.32-1.41 (m, 4H), 1.57-1.75 (m, 4H), 1.87-2.10 (m, 6H), 3.04 (dd, 2H, *J*=6.5, 3.5Hz), 3.23 (d, 1H, *J*=8.0Hz), 3.58 (dd, 1H, *J*=9.5, 2.5Hz), 3.74 (dd, 1H, *J*=11.0, 2.5Hz), 3.81-3.95 (m, 1H), 4.32 (d, 1H, *J*=11.0Hz), 4.53 (d, 1H, *J*=11.0Hz), 7.13-7.28 (m, 3H), 7.35-7.49 (m, 2H). EI-MS *m/z* (%): 507 (M^+-57, 0.1), 283 (46), 171 (100), 91 (98), 57 (26), 43 (47). HR-MS Calcd for $C_{29}H_{51}O_5Si$: 507.3509. Found: 507.3553.

(2*S*)-1-Acetoxy-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*S*,4*R*,5*S*)-1-acetoxy-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-2-methylhepthyl]-3,5-dimethyltetrahydrofuran-2-yl}butane (16)

A solution of **15** (14mg, 25μmol), Et_3N (60μl, 0.43mmol), DMAP (3mg, 25μmol), and Ac_2O (20μl, 212μmol) in CH_2Cl_2 (0.2ml) was stirred at room temperature for 20 min. After addition of MeOH, the mixture was concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **16** as a colorless oil (15mg, 93%). ^{1}H-NMR (C_6H_6) δ: 0.23 (s, 3H), 0.26 (s, 3H), 0.82 (d, 3H, *J*=6.0Hz), 0.92 (t, 3H, *J*=7.5Hz), 0.93 (t, 3H, *J*=7.0Hz), 0.96 (t, 3H, *J*=7.5Hz), 1.09 (s, 9H), 1.22-2.11 (m, 1H), 3.12 (dd, 1H, *J*=6.5, 3.5Hz), 3.59 (dd, 1H, *J*=9.5, 3.5Hz), 4.22 (dd, 1H, *J*=11.0, 6.5Hz), 4.29 (dd, 1H, *J*=11.0, 5.5Hz), 4.43 (d, 1H, *J*=11.0Hz), 4.58 (d, 1H, *J*=11.0Hz), 5.02 (d, 1H, *J*=7.5Hz), 7.12-7.42 (m, 5H).

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-1-Acetoxy-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-2-methylhepthyl]-3,5-dimethyltetrahydrofuran-2-yl]}butan-1-ol (17)

Imidazole (21mg, 318μmol) and TBS chloride (12mg, 80μmol) were added to a stirred solution of **15** (43mg, 76μmol) in CH_2Cl_2 (1ml) at 0°C under argon. After 1 hr at room temperature, MeOH was added, and the reaction mixture was diluted with ether, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8:1) to give (2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-1-hydroxy-2-methylheptyl]-3,5-dimethyltetrahydrofuran-2-yl}-1-*tert*-butyldimethylsilyloxybutane as a colorless oil (48mg, 93%). $[\alpha]_D^{20}$ +11° (c=1.02, $CHCl_3$). ^{1}H-NMR (C_6D_6) δ: 0.03 (s, 6H), 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 0.88 (t, 3H, *J*=6.5Hz), 0.94 (t, 6H, *J*=6.5Hz), 1.06 (s, 3H), 1.06 (d, 3H, *J*=7.0Hz), 1.10 (d, 3H, *J*=6.5Hz), 1.18-1.66 (m, 6H), 1.79-2.11 (m, 7H), 2.87 (d, 1H, *J*=3.0Hz), 3.11-3.16 (m, 2H), 3.51 (d, 1H, *J*=10.0Hz), 3.53 (dd, 1H, *J*=10.0, 4.0Hz), 3.64 (dd, 1H, *J*=10.0, 5.0Hz), 4.48 (d, 1H, *J*=11.0Hz), 4.68 (d, 1H, *J*=11.0Hz), 7.25-7.34 (m, 5H). EI-MS *m/z* (%): 603 (M^+-75, 0.3), 547 (0.2), 513 (1.0), 397 (38), 285 (38), 153 (42), 99 (37), 91 (100), 73 (54), 57 (28), 43 (24). HR-MS Calcd for $C_{35}H_{63}O_4Si_2$: 603.4268. Found: 603.4284.

The above alcohol (39mg, 58μmol) in CH_2Cl_2 (0.8ml) was acetylated with Ac_2O (55μl, 0.59mmol) in the presence of Et_3N (0.33ml, 2.36mmol) and DMAP (10mg) as described for **16** to give (2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-1-acetoxy-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-2-methylheptyl]-3,5-dimethyltetrahydrofuran-2-yl}-1-*tert*-butyldimethylsilyloxybutane as a colorless oil (40mg, 96%). $[\alpha]_D^{20}$ +11° (c=0.58, $CHCl_3$). ^{1}H-NMR (C_6D_6) δ: 0.14 (s, 3H), 0.16 (s, 3H), 0.25 (s, 3H), 0.27 (s, 3H), 0.93 (t, 3H, *J*=7.5Hz), 0.94 (d, 3H, *J*=6.5Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.04 (s, 9H), 1.08 (t, 3H, *J*=7.5Hz), 1.11 (s, 9H), 1.34 (s, 3H), 1.38 (d, 3H, *J*=6.5Hz), 1.95 (s, 3H), 1.27-2.07 (m, 12H), 2.37 (m, 1H), 3.70 (dd, 1H, *J*=10.0, 6.0Hz), 3.75 (dd, 1H, *J*=10.0, 3.0Hz), 3.80 (dd, 1H, *J*=10.0, 5.0Hz), 4.42 (d, 1H, *J*=11.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 5.07 (d, 1H, *J*=8.0Hz), 7.13-7.29 (m, 3H), 7.39 (m, 2H). EI-MS *m/z* (%): 663 (M^+-57, 0.3), 603 (2.5), 571 (5.8), 383 (23), 285 (56) 213 (57), 153 (42), 99 (37), 91 (100), 73 (56), 57 (20), 43 (28). HR-MS Calcd for $C_{37}H_{67}O_6Si_2$: 663.4480. Found: 663.4479.

1N HCl (0.4ml) was added to a stirred solution of the above silyl ether (39mg, 54μmol) at room temperature. After 4 hr, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel (*n*-hexane-EtOAc 4:1) to give **17** as a colorless oil (32mg, 97%). $[\alpha]_D^{20}$ +10° (c=0.49, $CHCl_3$). ^{1}H-NMR (C_6D_6) δ: 0.22 (s, 3H), 0.25 (s, 3H), 0.75 (d, 3H, *J*=6.0Hz), 0.90 (t, 3H, *J*=7.5Hz), 0.99 (t, 3H, *J*=7.5Hz), 1.09 (t, 3H, *J*=7.5Hz), 1.09 (s, 9H), 1.23 (s, 3H), 1.26 (d, 3H, *J*=6.5Hz), 1.30-1.44 (m, 4H), 1.56-1.77 (m, 6H), 1.93 (s, 3H), 1.86-2.04 (m, 3H), 2.22-2.33 (m, 2H), 3.09 (dd, 1H, *J*=6.5, 3.5Hz), 3.56 (dd, 1H, *J*=10.0, 2.5Hz), 3.70 (ddd, 1H, *J*=10.5, 3.0, 2.5Hz), 3.82 (ddd, 1H, *J*=10.5, 8.0, 5.0Hz), 4.57 (d, 1H, *J*=11.5Hz), 5.03 (d, 1H, *J*=7.5Hz),

7.12-7.29 (m, 3H), 7.39-7.42 (m, 2H). EI-MS *m/z* (%): 533 (M^+-73, 0.4), 457 (8.6), 397 (25), 213 (54), 171 (97), 91 (100), 73 (38), 43 (50). HR-MS Calcd for $C_{31}H_{53}O_5Si$: 533.3665. Found: 533.3658.

(3*RS*,4*S*)-4-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-5-Benzyloxy-1,4-dihydroxy-4-ethyl-2-methylheptyl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-ol (18)

17 (20mg, 32μmol) in CH_2Cl_2 (1ml) was oxidized with DMSO (46μl, 648μmol) and oxalyl chloride (28μl, 324μmol) in CH_2Cl_2 (0.6ml) at -78°C as described for **12** to give (2*R*)-2-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-1-acetoxy-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-2-methylheptyl]-3,5-dimethyl- tetrahydrofuran-2-yl}butanal as a colorless oil (19mg, 97%). IR (neat) ν (cm^{-1}): 1730. ^{1}H-NMR (C_6D_6) δ: 0.23 (s, 3H), 0.27 (s, 3H), 0.70 (t, 3H, *J*=6.0Hz), 0.87 (t, 3H, *J*=7.5Hz), 0.96 (t, 3H, *J*=7.0Hz), 1.09 (t, 3H, *J*=7.5Hz), 1.10 (s, 9H), 1.22 (s, 3H), 1.27 (d, 3H, *J*=6.5Hz), 1.31-2.09 (m, 12H), 1.91 (s, 3H), 2.26-2.34 (m, 1H), 3.10 (dd, 1H, *J*=7.0, 3.5Hz), 3.59 (dd, 1H, *J*=9.5, 4.5Hz), 4.41 (d, 1H, *J*=11.0Hz), 4.57 (d, 1H, *J*=11.0Hz), 4.98 (d, 1H, *J*=8.0Hz), 7.15-7.29 (m, 3H), 7.39-7.42 (m, 2H), 9.58 (d, 1H, *J*=3.0Hz).

A solution of the above aldehyde (19mg, 31μmol) in THF (0.5ml) was added dropwise to a solution of EtMgBr prepared from Mg (15mg, 629μmol) and EtBr (47μl, 629μmol) in THF (1ml) at -78°C under argon. After 1 hr, the reaction mixture was allowed to warm to -20°C, and the stirring was continued for 1 hr. The reaction mixture was poured into cold saturated aqueous NH_4Cl, and extracted with ether. The extract was evaporated and the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give (3*RS*,4*S*)-4-{(2*S*,3*S*,5*S*)-5-[(1*R*,2*R*,4*R*,5*S*)-5-benzyloxy-4-*tert*-butyldimethylsilyloxy-4-ethyl-1-hydroxy-2-methylheptyl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-ol as a colorless oil (14mg, 75%). ^{1}H-NMR (C_6D_6) δ: 0.23 (s, 3H), 0.26 (s, 3H), 0.81 (t, 3H, *J*=7.5Hz), 0.84 (d, 3H, *J*=5.5Hz), 1.03 (t, 3H, *J*=7.5Hz), 1.04 (t, 3H, *J*=7.5Hz), 1.09 (s, 9H), 1.14 (t, 3H, *J*=7.5Hz), 1.21 (d, 3H, *J*=7.0Hz), 1.25 (s, 3H), 1.30-2.09 (m, 17H), 3.02 (dd, 1H, *J*=6.5, 4.0Hz), 3.17-3.23 (m, 1H), 3.55-3.58 (brd, 1H), 3.75-3.80 (m, 1H), 4.30 (d, 1H, *J*=11.0Hz), 4.52 (d, 1H, *J*=11.0Hz), 7.12-7.28 (m, 3H), 7.35-7.38 (m, 2H). EI-MS *m/z* (%): 557 (M^+-35, 0.3), 425 (2.9), 335 (4.4), 311 (40), 199 (42), 91 (100), 57 (34). HR-MS Calcd for $C_{35}H_{61}O_3Si$: 557.4393. Found: 557.4346.

1M solution of *n*-Bu_4NF in THF (22μl, 22μmol) was added to a stirred solution of the above alcohol (11mg, 19μmol) in DMF (0.3ml) at room temperature under argon. After 4 hr, the reaction mixture was poured into H_2O, and extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give **18** as a colorless oil (8.0mg, 90%). ^{1}H-NMR (C_6D_6) δ: 0.81 (d, 3H, *J*=6.0Hz), 0.86 (t, 3H, *J*=7.5Hz), 1.02 (t, 6H, *J*=7.5Hz), 1.12 (t, 3H, *J*=7.5Hz), 1.14 (d, 3H, *J*=6.5Hz), 1.21 (s, 3H), 1.28 (m, 10H), 1.63-1.95 (m, 6H), 2.05-2.15 (m, 2H), 3.08 (d, 1H, *J*=8.5Hz), 3.20 (t, 1H, *J*=6.0Hz), 3.51 (dd, 1H, *J*=9.5, 2.0Hz), 3.75 (ddd, 1H, *J*=9.0, 5.0, 2.0Hz), 4.54 (s, 2H), 7.11-7.25 (m, 3H), 7.32-7.35 (m, 2H). EI-MS *m/z* (%): 479 (M^++1, 0.5), 461 (M^+-17, 0.4), 323 (2.3), 311 (47), 199 (52), 91 (100). HR-MS Calcd for $C_{29}H_{51}O_5$: 479.3739. Found: 479.3731.

{4*R*,4(2*S*,3*S*,5*R*),5[(2*R*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Benzyloxy)propyl-5-ethyl-2-hydroxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (19)

(a) The triol (**18**) (10mg, 22μmol) was treated with PCC (10mg, 46μmol) in CH_2Cl_2(1.2ml) in the presence of powdered 3Å molecular sieves (5.0mg) for 45 min at room temperature. The reaction mixture was passed through a silica gel column (*n*-hexane-EtOAc 5:1) to give **19** and **20** (6.9mg, 69%) as a inseparable mixture. 1N H_2SO_4 (0.1ml) was added into **19** and **20** in THF (0.4ml) under cooling with ice bath. The mixture was stirred for 20 min, then neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4,

and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-Et_2O 7:1) to give **19** as a colorless oil (4.8mg, 70%). $[\alpha]_D^{20}$ +7.0° (c=0.16, $CHCl_3$). IR (neat) ν (cm^{-1}): 3410, 2950, 2925, 2775, 1710, 1460, 1450. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (d, 3H, *J*=7.5Hz), 0.91 (t, 3H, *J*=7.5Hz), 0.95 (d, 3H, *J* =6.5Hz), 1.00 (t, 3H, *J* =7.5Hz), 1.01 (t, 3H, *J* =7.5Hz), 1.03 (d, 3H, *J* =6.5Hz), 1.18 (s, 3H), 1.36~1.48 (m, 2H), 1.51~1.60 (m, 4H), 1.70~1.80 (m, 2H), 1.87 (t, 1H, *J* =12.0Hz), 2.06~2.12 (m, 1H), 2.15 (t, 1H, *J* =11.0Hz), 2.29~2.36 (m, 1H), 2.42 (dq, 1H, *J* =18.5, 7.5Hz), 2.58~2.63 (m, 1H), 2.61 (dq, 1H, *J* =18.5, 7.5Hz), 3.39 (dd, 1H, *J* =8.5, 3.0Hz), 3.65 (s, 1H), 3.68 (dd, 1H, *J* =9.5, 5.5Hz), 4.57 (d, 1H, *J* =10.5Hz), 4.71 (d, 1H, *J* =10.5Hz), 7.28~7.41 (m, 5H). FAB-MS *m/z* (%): 457 (M^+-17, 100), 391 (6.4), 367 (10), 351 (18), 325 (6.3), 307 (9.6), 267 (12), 249 (9.7), 225 (18), 197 (11), 169 (17), 141 (19), 91 (98), 57 (33). HR-MS Calcd for $C_{29}H_{45}O_4$: 457.3320. Found: 457.3313.

(b) A mixture of **21** and **22** (61mg, 0.125mmol) was treated with 2N H_2SO_4 (1.3ml) in THF (4.0ml) for 30 min at room temperature under cooling with ice bath. After being neutralized with $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-Et_2O 7:1) to give **19** (40mg, 67%) as a single product.

{4*R*,4(2*S*,3*S*,5*R*),5[(2*R*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Benzyloxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (21) and {4*R*,4(2*S*,3*S*,5*R*),5[(2*S*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Benzyloxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (22)

(a) The alcohol (**19**) (4.0mg, 7.3μmol) was treated with CSA (2.0mg, 8.6μmol) in anhydrous MeOH (1.0ml) for 30 min at room temperature. After being neutralized with Et_3N, the solution was diluted with Et_2O (30ml), then washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residual oil was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give an inseparable 1:1 mixture of **21** and **22** (4.0mg, 98%). IR (neat) ν (cm^{-1}): 2950, 2925, 2860, 1710, 1455, 1450. ^{1}H-NMR (C_6D_6) δ: 0.84~0.96 (m, 9H) 1.05~1.21 (m, 9H), 1.13 (s, 3/2H), 1.28 (s, 3/2 Hz), 1.33~2.19 (m, 9H) 2.26~2.19 (m, 3H), 2.46~2.64 (m, 3H), 3.20 (s, 3/2H), 3.44 (dd, 1/2H, *J*=8.5, 3.0Hz), 3.54 (s, 3/2H), 3.62 (dd, 1/2H, *J*=9.5, 5.5Hz), 3.83~3.98 (m, 1H), 4.57 (d, 1/2H, *J* =11.5Hz), 4.62 (d, 1/2H, *J*=11.5Hz), 4.69 (d, 1/2H, *J* =11.5Hz), 4.77 (d, 1/2H, *J* =11.5Hz), 7.12~7.26 (m, 5H). FAB-MS *m/z* (%): 457 (M^+-31, 14), 391 (3.6), 359 (4.3), 349 (4.1), 339 (5.7), 307 (9.6), 291 (20), 249 (6.1), 219 (7.0), 207 (17), 197 (67), 183 (13), 154 (46), 136 (40), 91 (100), 57 (38). HR-MS Calcd for $C_{29}H_{45}O_4$: 457.3320. Found: 457.3333.

(b) To an oxalyl chloride (71μl, 0.82mmol) in anhydrous CH_2Cl_2 (1.5ml) was added dropwise DMSO (69ml, 0.978mmol) in anhydrous CH_2Cl_2 (2.0ml) at -78 °C under argon. After 7 min, **26** (80mg, 0.163mmol) in anhydrous CH_2Cl_2 (2.0ml) was added. After 10 min, Et_3N (273ml, 1.96mmol) was slowly added into the resulting suspension. The mixture was stirred for 15 min and then allowed to warm to -30°C over 15 min, then diluted with Et_2O (40ml), and washed with H_2O and brine. The organic layer was separated, dried over Na_2SO_4 and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-Et_2O 7:1) to give **21** and **22** as a mixture (61mg, 77%).

{4*R*,4(2*S*,3*S*,5*R*),5[(2*R*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Benzyloxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (7)

An EtOH(1ml) solution of **19** (37mg, 78μmol) was hydrogenated in the presence of Raney Ni W-2 (2.0 ml of EtOH suspension) for 4 hr at room temperature. After the catalyst was removed by filtration, the filtrate was

evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-Et_2O 3:1) to give **7** as a colorless oil (23mg, 77%). $[a]_D^{25}$ -17° (c 0.72, CH_2Cl_2). IR (neat) n (cm^{-1}): 3450, 2960, 2925, 2875, 1705, 1460, 1410, 1375. ^{1}H-NMR (C_6D_6) d: 0.84 (t, 3H, *J*=7.5Hz), 0.91 (t, 3H, *J*=7.5Hz), 0.95 (d, 3H, *J*=6.5Hz), 1.02 (t, 3H, *J*=7.5Hz), 1.03 (t, 3H, *J*=7.5Hz), 1.16 (s, 3H), 1.38~1.61 (m, 7H), 1.72~1.79 (m, 2H), 2.00 (t, 1H, *J*=12.0Hz), 2.07 (t, 1H, *J*=12.0Hz), 2.12~2.22 (m, 2H), 2.39 (dq, 1H, *J*=18.0, 7.5Hz), 2.59 (dq, 1H, *J*=18.0, 7.5Hz), 2.64~2.70 (m, 1H), 3.60~3.62 (brs, 2H), 3.73 (dd, 1H, *J*=10.0, 5.5Hz). ^{13}C-NMR ($CDCl_3$) d: 7.4, 7.5, 10.9, 12.5, 14.1, 16.2, 21.1, 24.7, 30.4, 36.5, 37.2, 37.7, 38.1, 42.4, 57.3, 73.0, 85.0, 86.8, 88.2, 107.8, 213.6. EI-MS *m/z* (%): 367 (M^+-17, 0.6), 337 (0.7), 325 (5.7), 307 (5.9), 267 (0.8), 243 (1.6), 225 (18), 207 (8.8), 197 (19), 187 (12), 169 (31), 141 (41), 57 (100), 43 (29). HR-MS Calcd for $C_{22}H_{39}O_4$: 367.2838. Found: 367.2849.

{4*R*,4(2*S*,3*S*,5*R*),5[(2*RS*,3*R*,5*R*),5(1*S*)]}-4-{5-[5-(1-Acetoxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-one (24)

A solution of **23** (140mg, 0.329mmol) and CSA (5.0mg, 21.5mmol) in anhydrous MeOH (3.0 ml) was stirred for 4 hr at room temperature. After addition of Et_3N, the solution was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1) to give **24** as a 1:1 diastereomeric mixture (145mg, 97%). IR (neat) n (cm^{-1}): 2960, 2925, 2875, 1735, 1705, 1455, 1405, 1375. ^{1}H-NMR ($CDCl_3$) d: 0.76~1.04 (m, 18H), 1.03 (s, 3/2H), 1.08 (s, 3/2H), 1.25~2.30 (m, 14H), 2.05 (s, 3/2H), 2.08 (s, 3/2H), 2.30~2.81 (m, 3H), 3.20 (s, 3/2H), 3.33 (s, 3/2H), 3.40 (dd, 1/2H, *J*=7.0, 3.5Hz), 3.64 (dd,1/2H, *J* =9.5, 5.5Hz), 4.97 (dd, 1/2H, *J* =9.5, 3.0Hz), 4.99 (dd, 1/2H, *J*=10.0, 3.0Hz). FAB-MS *m/z* (%): 409 (M^+-31, 94), 391 (6.4), 319 (8.5), 307 (12), 249 (17), 243 (90), 207 (22), 197 (100), 183 (47), 169 (36), 151 (29), 123 (29), 57 (53), 43 (21). HR-MS Calcd for $C_{24}H_{41}O_5$: 409.2956. Found: 409.2947.

{3*R*,4*RS*,3(2*S*,3*S*,5*R*),5[(2*R*,3*R*,5*R*),5(1*S*)]}-3-{5-[5-(1-Acetoxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}-4-trimethylsiloxyhexane (25)

A solution of **24** (190mg, 0.413mmol) and $NaBH_4$ (163 mg, 4.31 mmol) in MeOH (3.0ml) was stirred at -10 °C. After 2 hr, the solution was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-Et_2O 3:1) to give an alcohol (152mg, 80%). The alcohol (152mg, 0.343mmol) was immediately treated with 1-(trimethylsilyl)imidazole (280ml, 1.9mmol) at -20°C for 1 hr under argon. The excess reagent was quenched with MeOH, the solution evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 10:1) to give **25** as a colorless oil (150mg , 85%). IR (neat) n (cm^{-1}): 2965, 2920, 2865, 1735, 1450, 1410, 1365. ^{1}H-NMR ($CDCl_3$) d: 0.06~0.10 (m, 9H), 0.84~1.16 (m, 21H), 1.32~2.18 (m, 15H), 2.05~2.07 (m, 3H), 3.20~3.35 (m, 3H), 3.43~3.68 (m, 2H), 4.92~4.97 (m, 1H). FAB-MS *m/z* (%): 483 (M^+-31, 25), 423 (5.8), 393 (5.7), 333 (7.9), 291 (8.8), 271 (33), 243 (68), 213 (15), 201 (9.7), 183 (34), 169 (24), 163 (13), 151 (19), 131 (100), 123 (25), 73 (58), 57 (12), 43 (12). HR-MS Calcd for $C_{27}H_{51}O_5Si$: 483.3505. Found: 483.3471.

{3*R*,4*RS*,4(2*S*,3*S*,5*R*),5[(2*RS*,3*R*,5*S*),5(1*R*)]}-4-{5-[5-(1-Benzyloxy)propyl-5-ethyl-2-methoxy-3-methyltetrahydrofuran-2-yl]-3,5-dimethyltetrahydrofuran-2-yl}hexan-3-ol (26)

To $LiAlH_4$ (60mg, 1.52mmol) in Et_2O (2.0ml) was added dropwise a solution of **25** (150mg, 0.29mmol) in Et_2O (1.0ml) at -78°C under argon. The resulting mixture was allowed to warm to 0°C over 30 min. After the excess reagent was quenched with MeOH, the mixture was diluted with Et_2O (30ml), washed with 0.5N HCl, H_2O, 10% $NaHCO_3$, and brine, then dried over Na_2SO_4, and evaporated *in vacuo* to leave a crude product as an oil (131mg), which was subjected to the next reaction without further purification. The crude oil (131mg) was

treated with $KN(TMS)_2$ (843ml of 0.527M in THF, 0.44mmol) in anhydrous THF (2.5ml) for 15 min at -78°C under argon, and then benzyl bromide (53ml, 0.44mmol) was added. The resulting mixture was allowed to warm to -20°C over 1 hr, poured into cold aqueous NH_4Cl solution, and extracted with Et_2O (20ml x 3). The extract was washed with 0.5N HCl, H_2O, 10% $NaHCO_3$ and brine, then dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was treated with *n*-Bu_4NF (0.1ml of 1M THF solution, 0.1mmol) in THF (1.0ml) for 1 day at room temperature. After removal of the solvent *in vacuo*, the resulting crude oil was chromatographed on a silica gel column (*n*-hexane-Et_2O 10:1) to give **26** as a colorless oil (110mg, 77%). IR (neat) ν (cm^{-1}): 3450, 2965, 2920, 2865, 1430, 1410, 1345. FAB-MS *m/z* (%): 459 (M^+-32, 72), 351 (7.5), 309 (24), 291 (33), 199 (45), 183 (14), 154 (16), 141 (17), 123 (17), 91 (100). HR-MS Calcd for $C_{29}H_{47}O_4$: 459.3477. Found: 459.3501.

Lysocellin (1) Sodium Salt

A solution of **7** (25mg, 65μmol) in anhydrous THF (0.3ml) was added dropwise *via* a syringe over 5 min to a stirred solution of lithium diisopropyl amide (445 μl of 0.63M solution of anhydrous THF, 0.325mmol) at -78 °C. After 45 min, $ZnCl_2$ (0.31ml of 0.63M solution in dry THF) was added in one portion. The stirring was continued for 30 min, then **2** (5mg, 21.5μmol) in anhydrous THF (0.1ml) was added. After 15 min, the reaction mixture was quenched with excess 10% aqueous $NaHCO_3$, then allowed to warm to room temperature, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was purified by silica gel preparative thin-layer chromatography (MeOH-CH_2Cl_2-*n*-hexane-EtOAc 2:18:5:5) in twice developments to give **1** sodium salt (3.0 mg, 22%) as a colorless solid, mp 156~158°C (lit,[11c] mp 158-160°C).[14] $[\alpha]_D^{20}$ +10° (c=0.12, MeOH). IR (neat) ν (cm^{-1}): 3425, 3175, 2950, 2925, 2860, 1710, 1600, 1590, 1450. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.79 (t, 3H, *J*=7.5Hz), 0.80 (t, 3H, *J*=7.5Hz), 0.80 (d, 3H, *J*=7.0Hz), 0.89 (d, 3H, *J*=6.5Hz), 0.90 (d, 3H, *J*=6.5Hz), 0.90 (t, 3H, *J*=7.5Hz), 0.98 (d, 3H, *J*=6.5Hz), 0.99 (d, 3H, *J*=7.0Hz), 1.03 (d, 3H, *J*=7.0Hz), 1.19 (s, 3H), 1.23~1.68 (m, 10H),1.76~1.87 (m, 2H), 1.80 (dd, 1H, *J*=7.0, 3.0Hz), 1.91~2.11 (m, 4H), 2.17~2.27 (m, 1H), 2.45 (d, 1H, *J*=10.5Hz), 2.66 (d, 1H, *J*=12.5Hz), 2.71~2.76 (m, 1H), 3.45~3.50 (m, 1H), 3.75 (brs, 1H), 3.80 (dd, 1H, *J*=13.5, 3.5Hz), 3.94 (d, 1H, *J*=10.5Hz), 4.06 (d, 1H, *J*=10.5Hz), 4.36 (brs, 1H), 5.01 (brs, 1H), 7.70 (brs, 1H). EI-MS *m/z* (%): 457 (MH^+, 100), 607 (70.8), 589 (81.7), 493 (16.7), 429 (74.0), 407 (33.3). *Anal* calcd for $C_{34}H_{59}O_{10}Na$: C, 62.81; H, 9.15. Found: C, 62.55; H, 9.28.

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12. Treatment with trimethylsilyltriflate (TMSOTf) in CH_2Cl_2 in the presence of Et_3N gave a C17,18-anhydro compound with loss of MeOH in quantitative yield.
13. In THF or in ether at 0°C, concomitant loss of the TMS group was observed.
14. Three products (3mg, 22%) other than **1** sodium salt were isolated by silical gel thin-layer chromatography and each Mass fragmentation pattern was almost identical to that of **1** sodium salt.

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