Highly Stereocontrolled Total Synthesis of the Polyether Antibiotic Salinomycin. IV. Chemical Degradation of Salinomycin for the Structure Confirmation of Synthetic Key Intermediates[1)]

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In order to confirm the structures of some key intermediates employed in the total synthesis of salinomycin (1), natural 1 was cleaved into C1—C9, C10—C30, C10—C17, C21—C30, and C19—C30 segments.

Keywords polyether antibiotic; salinomycin; chemical degradation; chemical correlation; retro-aldol reaction

As part of our synthetic study of a series of typical macrolide and polyether antibiotics by means of a common methodology, in the preceding papers[1,2)] we reported a highly stereocontrolled synthesis of salinomycin (**1**), in which benzyl-type protecting groups and some stereoselective reactions played important roles. However, in order to complete multistep syntheses of highly complex molecules such as **1**, it is crucial to prove unequivocally the structures and, in particular, configurations of key intermediates at several synthetic stages. The chemical correlation of the synthetic intermediates with segments derived from natural salinomycin (**1**) was expected to provide conclusive proof. We report here a chemical cleavage of **1** into the desired segments **2**, **3**, **4**, **5**, and **6** corresponding to the C1—C9,[2a)] C10—C30,[1)] C10—C17,[2a)] C21—C30,[2b)] and C19—C30[2b)] portions, respectively.

There have been two important precedents for the chemical cleavage of **1**. One is Kishi's thermal retro-aldol reaction of 20-*O*-acetylsalinomycin methyl ester (**7**) giving the aldehyde (**8**) and the ethyl ketone (**9**), as mentioned in his lecture on the first total synthesis of **1**.[3)] The other is the direct alkaline cleavage of **1** and isolation of the C21—C30 lactone (**5**).[4)] Nevertheless, it was necessary to establish a method which gave simultaneously more fragments from **1** by means of a series of cleavage reactions, in order to prove definitely the structures of key intermediates in our total

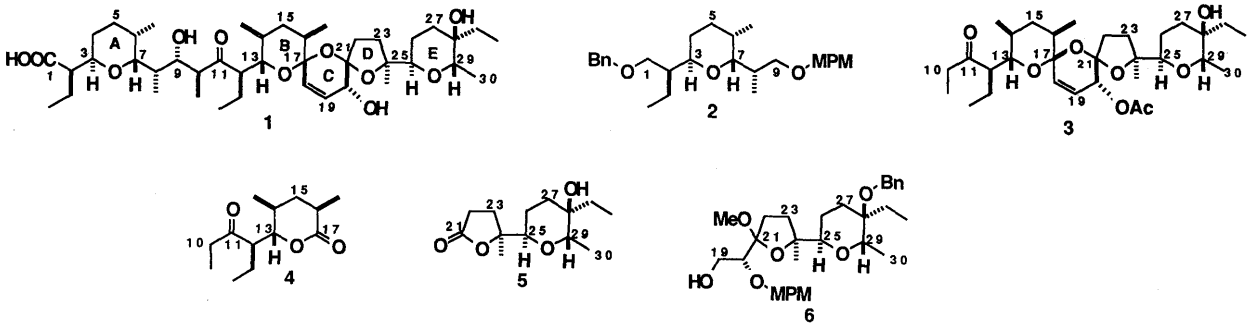
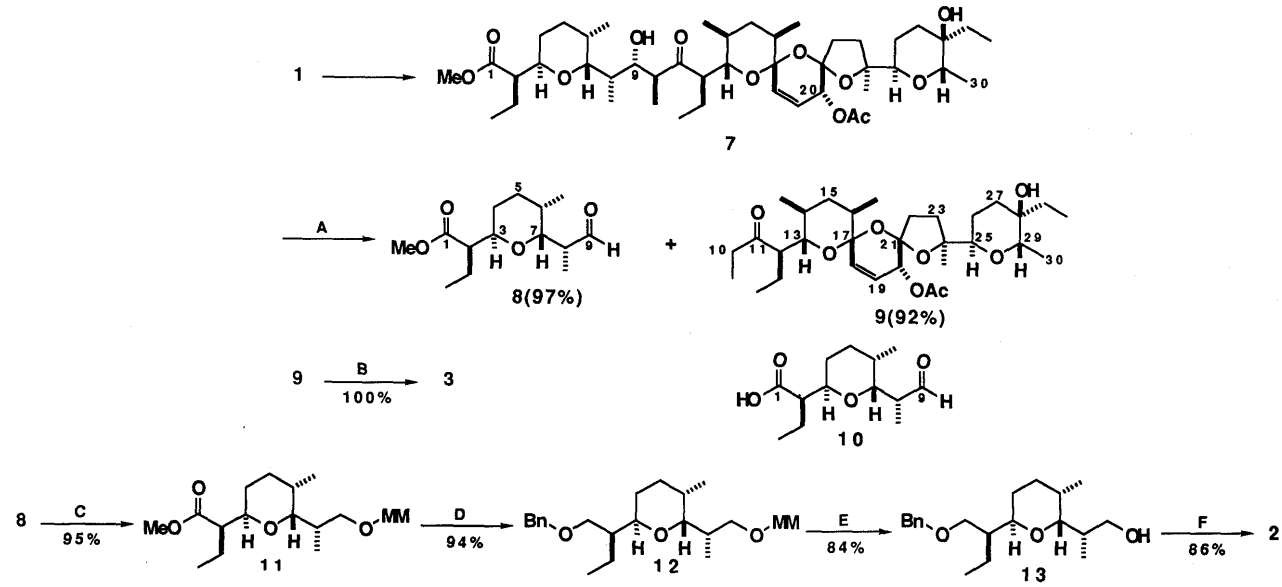


Chart 1



(A) 200°/5 mmHg (B) CSA, CH_2Cl_2 (C) 1) $NaBH_4$, MeOH, 0 °C; 2) MMCl, iso-Pr_2EtN, CH_2Cl_2 (D) 1) $LiAlH_4$, THF; 2) BnCl, NaH, DMSO, THF (E) 4 N HCl, THF (F) MPMCl, NaH, DMSO, YHF

Chart 2

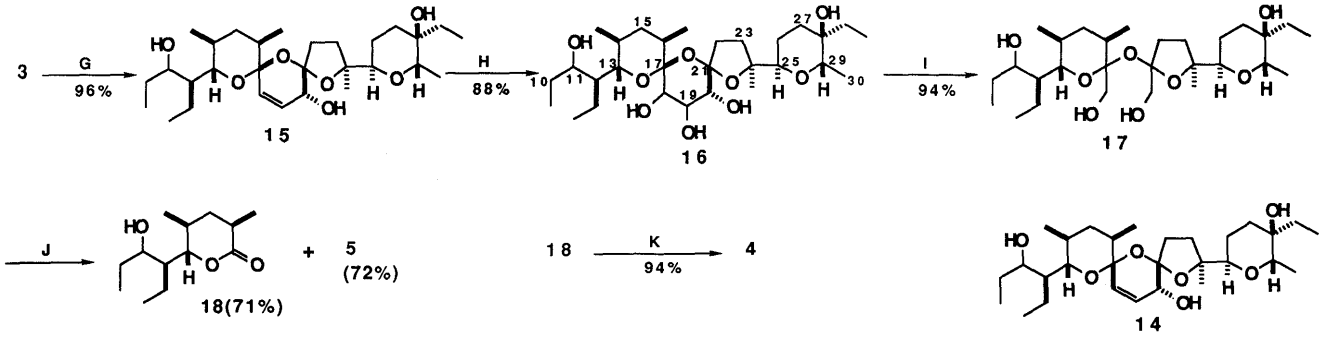
synthesis of **1**.

C10—C30 Segment (3) The C10—C30 segment (**3**) was prepared from **1** *via* **7** and **9** virtually according to the known method.[3,5] First, **1** was converted to **7** by treatment with diazomethane and then acetic anhydride.[5] When **7** was heated at 200 °C under reduced pressure, the retro-aldol reaction occurred quite smoothly to give **8** and **9** in excellent yields.[3] An acid-catalyzed isomerization at the C17 position[3,6] of **9** by treatment with camphorsulfonic acid (CSA) gave quantitatively the more stable 17-*epi*-ethyl ketone (**3**), which was identical, in terms of infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS), with the 17-*epi* compound (**3**) synthesized starting from D-glucose, D-mannitol, and ethyl L-lactate.[1]

C1—C9 Segment (2) For the purpose of establishing the structure of the synthetic C1—C9 subunit (**10**),[2a] **8** was next converted to the synthetic intermediates **13** and **2**. Reduction of **8** with sodium borohydride and protection of the resulting primary alcohol with a methoxymethyl (MM) group under usual conditions gave **11**,[3] which was reduced with lithium aluminum hydride and then treated with benzyl (Bn) chloride to give **12**. Deprotection of the MM group of **12** with hydrochloric acid gave **13**, and finally the primary alcohol of **13** was protected with a 4-methoxybenzyl (MPM) group[7] to give **2**. Compounds **13** and **2** were identical spectroscopically with the synthetic intermediates **13** and **2**, respectively, used for the synthesis of **10** from D-glucose.[2a]

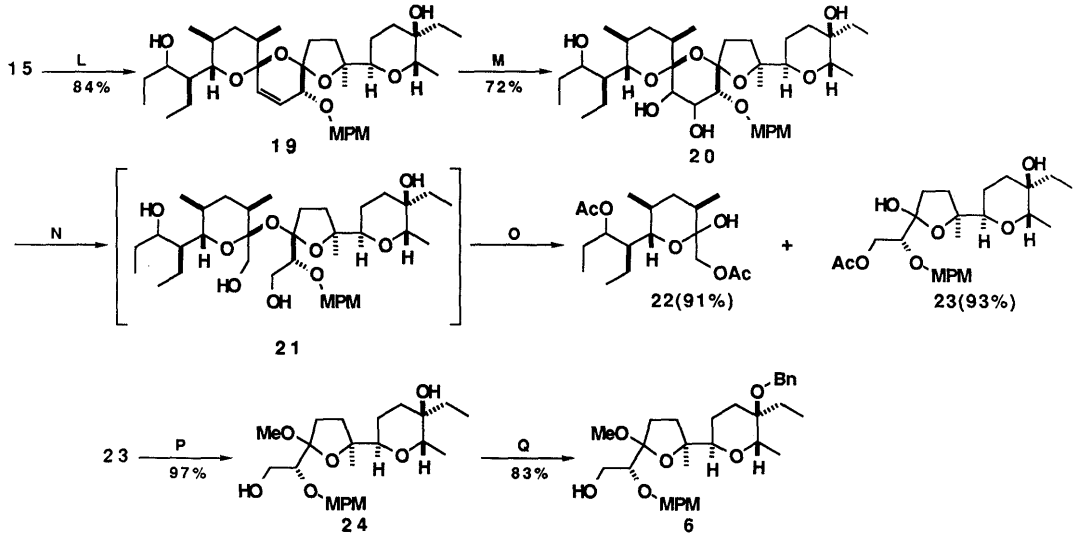
C10—C17 (4) and C21—C30 Segments (5) Although the C21—C30 segment (**5**) is obtainable by the alkaline degradation of **1**,[4] oxidative cleavage at the allyl acetate portion between C18 and C20 of the ethyl ketone (**9**) was tried in order to obtain both **5** and the C10—C17 segment (**4**) at the same time. However, all attempts to oxidize **9**, including after conversion to **14**, with ozone, osmium tetroxide, peracid, *etc.* were unsuccessful, and no expected products were isolated probably because the C18—C19 double bonds of **9** and **14** are buried in sterically crowded positions in the folded structures.[8]

The 17-*epi* compound (**3**) with a linear conformation was expected to be easily oxidized. Compound **3** was first reduced with sodium bis(methoxyethoxy)aluminum hydride (Red-Al) to the triol (**15**) (1.6 : 1.0 mixture with respect to the C11 position), which was treated with osmium tetroxide in the presence of excess *N*-methylmorpholine oxide (NMO) to give the expected pentaol (**16**) in high yield. Periodate oxidation of **16** followed by reduction of the resulting dialdehyde with sodium borohydride readily gave the tetraol (**17**) in excellent yield. The bis-acetal position of **17** was



(G) Red-Al, toluene, −70— −60 °C (H) OsO_4, NMO, MeCOMe–H_2O (I) 1) $NaIO_4$, MeOH; 2) $NaBH_4$, MeOH, 0 °C (J) 1) 1 N HCl, THF; 2) $NaIO_4$, THF–H_2O (K) PCC, MS, CH_2Cl_2

Chart 3



(L) MPMCl, NaH, DMF–THF (M) OsO_4, NMO, *tert*-BuOH–MeCOMe (N) 1) $Pb(PAc)_4$, C_6H_6; 2)$LiAlH_4$, THF, 0 °C (O) 1) Ac_2O, Et_3N, DMAP, CH_2Cl_2; 2) 1 N HCl, THF (P) 1) CSA, MeOH; 2) KOH, MeOH–H_2O (Q) 1) $(MeO)_2CMe_2$, CSA; 2) BnCl, NaH, DMF–THF, 50—60 °C; 3) CSA, MeOH

Chart 4

hydrolyzed with hydrochloric acid, and a mixture of the resulting two hemiacetals was oxidized with sodium periodate to give a mixture of the C21—C30 segment (**5**) and the hydroxylactone (**18**). Oxidation of **18** with pyridinium chlorochromate (PCC) readily gave the C10—C17 segment (**4**). Compounds **4** and **5** were identical, in terms of IR, NMR, and MS, with the synthetic subunits **4**[2a] and **5**,[2b] respectively.

C19—C30 Segment (6) Although the C21—C30 segment (**5**), derived from **1** by alkaline degradation[4] and also by the retro-aldol reaction followed by oxidative cleavage as described above, seemed to be a suitable intermediate, introduction of a three carbon unit (C18—C20) with correct C20 configuration was quite difficult,[2b] and therefore, we chose **6** as a more convenient intermediate, which was synthesized from D-glucose, D-mannitol, and L-lactic acid.[2b] In order to confirm the structure of synthesized **6**, the same compound was obtained from **1** as follows.

Compound **15** was first converted to **19**. Among the three hydroxy groups of **15**, the most reactive C20 hydroxy group was selectively protected with an MPM group in *N,N*-dimethyl dimethylformamide (DMF) and tetrahydrofuran (THF) (1 : 4), although in dimethyl sulfoxide (DMSO) a tri-MPM compound was obtained. The double bond of **19** was then oxidized with osmium tetroxide as described for **16**, and the resulting tetraol (**20**) was cleaved with lead (IV) acetate followed by reduction with lithium aluminum hydride to give **21**, which was too unstable to be isolated and was immediately acetylated to the triacetate. Hydrolysis of the bisacetal position of the triacetate with hydrochloric acid gave two hemiacetals **22** and **23** in excellent yields. The hemiacetal (**23**) was converted to the acetal by treatment with CSA in methanol, and alkaline hydrolysis of the acetyl protecting group gave the diol (**24**). Finally, **24** was converted to the expected C19—C30 segment (**6**) *via* three conventional reactions, an acetal protection of the primary alcohol, benzylation of the tertiary alcohol, and recovery of the primary alcohol. Spectral data of **6** were identical with those of **6** synthesized starting from D-glucose, D-mannitol, and L-lactic acid.[2b]

Experimental

Physical data were measured as described in the previous paper.[2a]

Pyrolysis of 7. Methyl (*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-Formylethyl]-5-methyltetrahydropyran-2-yl]butanoate (8) and (2*S*,5*S*,7*R*,9*S*,10*S*,12*R*,13*Z*,15*R*)-15-Acetoxy-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-9-[(*R*)-1-ethyl-2-oxobutyl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (9) The ester (**7**) (2.44 g, 3.03 mmol) was pyrolyzed at 200 °C under reduced pressure (0.5 mmHg) using a Kugelroh apparatus to yield two fractions. The first fraction gave **8** as a colorless oil (754 mg, 97%). IR ν_{max} cm^{-1}: 2725, 1720. ^{1}H-NMR δ: 0.90 (3H, t, J=7.5 Hz), 0.94 (3H, d, J=7.0 Hz), 0.98 (3H, d, J=7.0 Hz), 1.31—1.92 (7H, m), 2.93 (1H, ddq, J=3.5, 2.5, 7.5 Hz), 2.95 (1H, ddd, J=15.0, 9.0, 5.5 Hz), 3.67 (3H, s), 3.91 (1H, dd, J=10.5, 2.5 Hz), 3.85—4.02 (1H, m), 9.51 (1H, d, J=3.5 Hz). MS m/z (relative intensity): 256 (M$^+$, 0.6), 241 (0.5), 228 (4), 225 (7), 210 (10), 199 (11), 167 (22), 157 (52), 155 (33), 144 (28), 109 (49), 90 (50), 82 (100), 69 (42), 55 (35), 41 (50). Exact MS m/z Calcd for $C_{14}H_{24}O_4$ (M$^+$): 256.1676. Found: 256.1710. Compound **8** was immediately used for the next reaction.

The second fraction gave **9** as a colorless solid (1.53 g, 92%), which was purified through a short silica gel column (EtOAc–hexane, 2 : 3) to give pure **9** as colorless prisms, mp 183—184 °C. ^{1}H-NMR δ: 0.75 (3H, d, J=6.5 Hz), 0.81 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=7.5 Hz), 0.91 (3H, t, J=7.5 Hz), 1.01 (3H, t, J=7.0 Hz), 1.19 (3H, d, J=6.5 Hz), 1.31 (3H, s), 1.33—2.02 (15H, m), 2.12 (3H, s), 2.38 (1H, dt, J=9.5, 3.0 Hz), 2.44—2.67 (2H, m), 3.34 (1H, dd, J=9.0, 4.5 Hz), 3.62 (1H, dd, J=10.0, 3.5 Hz), 3.74 (1H, q, J=6.5 Hz), 5.26 (1H, dd, J=2.5, 1.5 Hz), 5.81 (1H, dd, J=11.0, 1.5 Hz), 6.19 (1H, dd, J=11.0, 2.5 Hz). MS m/z (relative intensity): 550 (M$^+$, 0.9), 523 (1.7), 508 (4.9), 490 (14), 462 (6.5), 407 (17), 347 (19), 308 (14), 291 (11), 266 (27), 57 (100). Exact MS m/z Calcd for $C_{31}H_{50}O_8$ (M$^+$): 550.3509. Found: 550.3284. *Anal.* Calcd for $C_{31}H_{50}O_8$: C, 67.01; H, 9.15. Found: C, 67.54: H, 9.13.

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,13*Z*,15*R*)-15-Acetoxy-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-9-[(*R*)-1-ethyl-2-oxobutyl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (3) DL-Camphor-10-sulfonic acid (CSA) (2.0 g, 8.61 mmol) was added to a stirred solution of **9** (15.0 g, 27.2 mmol) in CH_2Cl_2 (200 ml) at room temperature. After 2.7 h, the reaction mixture was neutralized with Et_3N (3.5 ml), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 5) to give **3** as a colorless, viscous oil (15.0 g, 100%).[1]

Methyl (*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*S*)-1-(methoxymethoxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butanoate (11) A solution of **8** (690 mg, 2.69 mmol) in MeOH (10 ml) was reduced with $NaBH_4$ (102 mg, 2.69 mmol) at room temperature for 15 min. The reaction mixture was acidified with 1 N HCl at 0 °C, and evaporated *in vacuo*. The residue was extracted with CH_2Cl_2. The extract was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to give an alcohol as a colorless viscous oil (695 mg, 100%). $[\alpha]_D^{17.5}$ −39° (c=1.12). ^{1}H-NMR δ: 0.78 (3H, d, J=7.0 Hz), 0.92 (3H, t, J=7.5 Hz), 0.96 (3H, d, J=7.0 Hz), 1.29—2.01 (8H, m), 3.08 (1H, dt, J=10.5, 5.0 Hz), 3.11 (1H, dd, J=9.0, 4.0 Hz), 3.39 (1H, dd, J=11.0, 6.5 Hz), 3.52 (1H, dd, J=11.0, 3.0 Hz), 3.61 (1H, dd, J=10.0, 2.0 Hz), 3.77 (3H, s), 4.03 (1H, dd, J=11.0, 5.5 Hz). MS m/z (relative intensity): 258 (M$^+$, 5.0), 240 (4.8), 227 (13), 199 (44), 167 (65), 157 (89), 69 (100). Exact MS m/z Calcd for $C_{14}H_{26}O_4$ (M$^+$): 258.1833. Found: 258.1813.

Diisopropylethylamine (478 mg, 3.70 mmol) and chloromethyl methyl ether (297 mg, 3.69 mmol) were added to a stirred solution of the above alcohol (680 mg, 2.63 mmol) in CH_2Cl_2 (5 ml) at room temperature under argon. After 1 d, the reaction mixture was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 4) to give **11** as a colorless oil (758 mg, 95%). $[\alpha]_D^{17.5}$ −53° (c=1.36). IR ν_{max} cm^{-1}: 1730. ^{1}H-NMR δ: 0.89 (3H, t, J=7.5 Hz), 0.88 (3H, d, J=6.5 Hz), 0.95 (3H, d, J=7.0 Hz), 1.36—2.04 (8H, m), 2.95 (1H, dt, J=5.0, 10.5 Hz), 3.06 (1H, t, J=10.0 Hz), 3.34 (3H, s), 3.34—3.41 (1H, m), 3.66 (1H, dd, J=10.0, 4.0 Hz), 3.72 (3H, s), 3.99 (1H, dd, J=11.0, 5.5 Hz), 4.61 (2H, s). MS m/z (relative intensity): 271 (M$^+$ −31, 30), 270 (20), 257 (25), 240 (14), 225 (20), 199 (96), 169 (26), 167 (87), 155 (12), 139 (27), 45 (100), 41 (100). FD-MS m/z (relative intensity): 302 (M$^+$, 100). Exact MS m/z Calcd for $C_{15}H_{27}O_4$ (M$^+$ −31): 270.1833. Found: 270.1835.

(*S*)-1-Benzyloxy-2-[(2*R*,5*S*,6*R*)-6-[(*S*)-1-(methoxymethoxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butane (12) A THF solution of **11** (1.7 g, 5.59 mmol) was reduced with $LiAlH_4$ (312 mg, 8.20 mmol) in the usual way to give the alcohol as a colorless oil (1.44 g, 94%). $[\alpha]_D^{17.5}$ −29° (c=1.08). ^{1}H-NMR δ: 0.89—0.99 (9H, m), 1.25—1.85 (9H, m), 2.34 (1H, t, J=6.0 Hz), 3.36 (3H, s), 3.41—3.75 (6H, m), 4.63 (2H, s). MS m/z (relative intensity): 274 (M$^+$, 0.1), 256 (0.5), 242 (4.2), 201 (20), 171 (26), 169 (33), 45 (100). Exact MS m/z Calcd for $C_{15}H_{30}O_4$ (M$^+$): 274.2146. Found: 274.2157.

A solution of the above alcohol (520 mg, 1.90 mmol) in THF (6 ml) was added to a vigorously stirred suspension of NaH (84 mg, 3.5 mmol) in DMSO (2 ml) at room temperature. After evolution of H_2 had ceased, benzyl chloride (BnCl) (288 mg, 2.27 mmol) was added. The reaction mixture was stirred at room temperature overnight, then poured into cold aqueous NH_4Cl, and extracted with ether. The exact was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 7) to give **12** as a colorless oil (700 mg, 100%). $[\alpha]_D^{17.5}$ −32° (c=0.88). ^{1}H-NMR δ: 0.88 (3H, t, J=8.0 Hz), 0.90 (3H, d, J=8.0 Hz), 0.97 (3H, d, J=7.0 Hz), 1.31—2.12 (9H, m), 3.32—3.60 (4H, m), 3.34 (3H, s), 3.70 (1H, dd, J=9.0, 3.0 Hz), 3.80 (1H, dd, J=10.5, 5.0 Hz), 4.47 (1H, d, J=12.0 Hz), 4.54 (1H, d, J=12.0 Hz), 4.54 (1H, d, J=6.5 Hz), 4.58 (1H, d, J=6.5 Hz), 7.33 (5H, s). MS m/z (relative intensity): 364 (M$^+$, 0.1), 332 (2.2), 319 (3.6), 302 (0.9), 91 (100). Exact MS m/z Calcd for $C_{22}H_{36}O_4$ (M$^+$): 364.2616. Found: 364.2608.

(*S*)-2-[(2*R*,3*S*,6*R*)-6-[(*S*)-1-(Benzyloxymethyl)propyl]-3-methyltetrahydropyran-2-yl]propan-1-ol (13) A 4 N HCl solution (3.5 ml) was added to a stirred solution of **12** (690 mg, 1.89 mmol) in THF (11 ml) at 50 °C. After 1 d, the solution was neutralized with $NaHCO_3$, and evaporated *in vacuo*. The residue was extracted with ether. The extract was dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 4) to give **13** as a colorless oil (512 mg, 84%).[2a]

(*S*)-1-Benzyloxy-2-[(2*R*,5*S*,6*R*)-6-[(*S*)-1-(4-methoxybenzyloxymethyl)-5-methyltetrahydropyran-2-yl]butane (2) A solution of **13** (250 mg, 0.78 mmol) in THF (3 ml) was added to a stirred suspension of NaH (26 mg, 1.09 mmol) in DMSO (1 ml) at room temperature under argon. After 45 min, 4-methoxybenzyl chloride (MPMCl) (158 mg, 1.01 mmol) was added. The

mixture was stirred for 3 h, then poured into cold saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 10) to give **2** as a colorless oil (296 mg, 86%).[2a)]

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,13*Z*,15*R*)-9-[(1*S*,2*R)-1-Ethyl-2-hydroxybutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol (15)** A solution of **3** (600 mg, 1.09 mmol) in toluene (15 ml) was added dropwise to a stirred 3.4 M toluene solution of sodium bis(methoxyethoxy)aluminum hydride (Red-Al) (3.1 ml, 11.2 mmol) diluted with toluene (25 ml) at −70 °C under argon. After 30 min, MeOH was added to decompose excess hydride at −70 °C. After addition of H_2O (6.5 ml) and 15% NaOH (4.0 ml), the mixture was stirred at 0 °C for 30 min, and then filtered through celite. The filtrate was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 1) to give **15** as a colorless amorphous solid (536 mg, 96%), mp 159—161 °C (from EtOAc–hexane). MS *m/z* (relative intensity): 510 (M^+, 1.1), 492 (28), 481 (5.2), 463 (6.9), 409 (7.8), 367 (14), 350 (11), 268 (100). Exact MS *m/z* Calcd for $C_{29}H_{50}O_7$ (M^+): 510.3559. Found: 510.3543. *Anal.* Calcd for $C_{29}H_{50}O_7$: C, 68.20; H, 9.87. Found: C, 68.34; H, 9.87.

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,13*R,14*R**,15*R*)-9-[(1*S*,2*R**)-1-Ethyl-2-hydroxybutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadecan-13,14,15-triol (16)** NMO (672 mg, 3.92 mmol) and OsO_4 (58 mg, 0.228 mmol) were added to a stirred solution of **15** (400 mg, 0.783 mmol) in acetone–H_2O (8 : 1) (18 ml) at room temperature. After 2 d, saturated $Na_2S_2O_4$ (3 ml) and celite (2 g) were added, and the mixture was stirred overnight and then filtered. The filtrate was evaporated *in vacuo*. The residue was extracted with CH_2Cl_2, successively washed with 1 N HCl, H_2O, 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (MeOH–CH_2Cl_2, 1 : 17) to give **16** as a colorless viscous oil (375 mg, 88%). MS *m/z* (relative intensity): 544 (M^+, 0.6), 527 (0.9), 508 (0.4), 497 (3.1), 484 (5.2), 401 (12), 383 (14), 365 (15), 343 (17), 285 (33), 256 (100), 242 (98). Exact MS *m/z* Calcd for $C_{29}H_{52}O_9$ (M^+): 544.3614. Found: 544.3632.

(2*R*,4*S*,5*S*,6*S*,7*R)-6-Ethyl-7-hydroxy-2,4-dimethylnonan-5-olide (18) and (*S*)-4-[(2*R*,5*R*,6*S*)-5-Ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-pentan-4-olide (5)** An aqueous solution (10 ml) of $NaIO_4$ (555 mg, 2.61 mmol) was added to a stirred solution of **16** (335 mg, 0.652 mmol) in MeOH (20 ml). The mixture was stirred at room temperature for 1 h, then cooled to 0 °C, and $NaBH_4$ (300 mg) was added. After 40 min, EtOH (50 ml) was added, and the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. Evaporation of the solvent left **17** as a colorless, amorphous solid (317 mg, 94%), mp 93—95 °C.

A stirred solution of **17** (963 mg, 1.86 mmol) in THF (16 ml) was treated with 1 N HCl (5.3 ml) at room temperature for 15 min, and then an aqueous solution (9 ml) of $NaIO_4$ (959 mg, 4.5 mmol) was added. After 6.5 h, the reaction mixture was neutralized with $NaHCO_3$ and insoluble materials were removed by filtration. The filtrate was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 1) to afford two fractions. The first fraction gave **18** as a colorless oil (302 mg, 71%). IR ν_{max} cm^{-1}: 3450, 1720. ^{1}H-NMR δ: 0.94—1.05 (9H, m), 1.28 (3H, d, J = 7.5 Hz), 1.34—1.64 (6H, m), 1.87—2.18 (3H, m), 2.40—2.62 (1H, m), 3.70—3.74 (1H, m), 4.19 (0.3H, d, J = 11.0 Hz), 4.43 (0.7H, d, J = 11.0 Hz). MS *m/z* (relative intensity): 210 (M^+ − 18, 0.3), 199 (4.0), 181 (9.0), 170 (24), 97 (100). Exact MS *m/z* Calcd for $C_{13}H_{22}O_2$ (M^+ − 18): 210.1621. Found: 210.1608.

The second fraction gave **5** as a colorless oil (327 mg, 72%).[2b)] $[\alpha]_D^{17.5}$ −26° (c = 2.64). Exact MS *m/z* Calcd for $C_{13}H_{22}O_4$ (M^+): 242.1519. Found: 242.1499.

(2*R*,4*S*,5*S*,6*R*)-6-Ethyl-2,4-dimethyl-7-oxononan-5-olide (4) Pulverized molecular sieves 3 Å (80 mg) and PCC (83 mg, 0.385 mmol) were added to a stirred solution of **18** (44 mg, 0.193 mmol) in CH_2Cl_2 (2 ml) at room temperature. After 3 h, the reaction mixture was filtered and the filtrate was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to give **4** as a colorless oil (41 mg, 94%).[2a)]

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,13*Z*,15*R*)-9-[(1*S*,2*R)-1-Ethyl-2-hydroxybutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-15-(4-methoxybenzyloxy)-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (19)** A solution of **15** (439.6 mg, 0.86 mmol) in THF (40 ml) was treated with NaH (61.9 mg, 2.58 mmol) in DMF (10 ml) and MPMCl (0.233 ml, 1.72 mmol) for 2 d as described for **2** to give **19** as a colorless oil (454.4 mg, 84%). MS *m/z* (relative intensity): 612 (M^+ − 18, 0.6), 529 (0.6), 487 (1.0), 388 (3.0), 267 (14), 121 (100). Exact MS *m/z* Calcd for $C_{37}H_{56}O_7$ (M^+ − 18): 612.4029. Found: 612.4038. *Anal.* Calcd for $C_{37}H_{58}O_8$: C, 70.44; H, 9.27. Found: C, 70.54; H, 9.31.

(2*S*,5*S*,7*S*,9*S*,10*S*,12*R*,13*R,14*R**,15*R*)-9-[(1*S*,2*R**)-1-Ethyl-2-hydroxybutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-15-(4-methoxybenzyloxy)-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadecan-13,14-diol (20)** A solution of **19** (454.4 mg, 0.72 mmol) in acetone (5 ml) and H_2O (2 ml) was oxidized with NMO (1.24 g, 7.2 mmol) and 2% OsO_4 in *tert*-BuOH (2 ml) at 35 °C for 8 h as described for **16** to give **20** as a colorless oil (343.5 mg, 72%). MS *m/z* (relative intensity): 521 (M^+ − 141, 0.7), 503 (1.1), 347 (2.6), 269 (5.2), 242 (21), 121 (100). *Anal.* Calcd for $C_{37}H_{60}O_{10}$: C, 66.84; H, 9.10. Found: C, 66.55; H, 9.23.

(2*R,3*R*,5*S*,6*S*)-6-[(1*S*,2*R**)-2-Acetoxy-1-ethylbutyl]-2-acetoxymethyl-3,5-dimethyltetrahydropyran-2-ol (22) and (2*S*,3*R*,6*R*)-6-[(2*S*,5*R**)-5-[(*R*)-1-2-Acetoxy-1-(4-methoxybenzyloxy)ethyl]-5-hydroxy-2-methyltetrahydrofuran-2-yl]-3-ethyl-2-methyltetrahydropyran-3-ol (23)** $Pb(OAc)_4$ (13.4 mg, 31 μmol) was added to a stirred solution of **20** (20.6 mg, 21 μmol) in benzene (1 ml) at room temperature. After 10 min, the reaction mixture was filtered. The filtrate was added dropwise to a stirred suspension of $LiAlH_4$ (90 mg, 2.38 mmol) in THF (2 ml) at 0 °C under argon. After 1 h, EtOAc (2 ml), 10% NaOH (0.1 ml), and H_2O (0.3 ml) were added. The reaction mixture was stirred for 30 min, then filtered through celite. The filtrate was evaporated *in vacuo* to leave **21** as an oil, which was dissolved in CH_2Cl_2 (1 ml) and treated with Et_3N (0.2 ml, 1.43 mmol), Ac_2O (0.1 ml, 1.06 mmol), and 4-dimethylaminopyridine (8 mg) at room temperature for 1 h. MeOH (0.1 ml) was added, and after 10 min, the reaction mixture was evaporated *in vacuo* and the residue was applied to a short silica gel column (EtOAc–hexane, 1 : 1→2 : 1). The eluate was evaporated *in vacuo*, dissolved in THF (0.8 ml), and stirred with 1 N HCl (0.4 ml) at room temperature for 2 h. The reaction mixture was neutralized with $NaHCO_3$, and extracted with ether. The extract was evaporated to leave an oil, which was dissolved in CH_2Cl_2 and subjected to silica gel thin layer chromatography (TLC) (EtOAc–hexane, 1 : 2) to give **22** (8.5 mg, 91%) and **23** (13.4 mg, 93%) as colorless oils. **22**: MS *m/z* (relative intensity): 327 (M^+ − 1, 6), 302 (0.7), 284 (1.5), 271 (6), 225 (2), 211 (15), 173 (27), 166 (9), 137 (19), 124 (40), 113 (36), 101 (47), 95 (28), 83 (31), 57 (35), 44 (100). Exact MS *m/z* Calcd for $C_{18}H_{31}O_5$ (M^+ − 1): 327.2173. Found: 327.2144. *Anal.* Calcd for $C_{18}H_{32}O_5$: C, 62.76; H, 9.36. Found: C, 63.02; H, 9.57. **23**: MS *m/z* (relative intensity): 449 (M^+ − 17, 2), 389 (2), 312 (10), 252 (22), 225 (23), 169 (22), 143 (63), 122 (93), 121 (100), 57 (58), 43 (100). Exact MS *m/z* Calcd for $C_{25}H_{37}O_7$ (M^+ − 17): 449.2542. Found: 449.2543.

(2*S*,3*R*,6*R*)-6-[(2*S*,5*R)-5-[(*R*)-1-2-Hydroxy-1-(4-methoxybenzyloxy)-ethyl]-5-methoxy-2-methyltetrahydrofuran-2-yl]-3-ethyl-2-methyltetrahydropyran-3-ol (24)** A solution of **23** (800 mg, 1.78 mmol) in MeOH (20 ml) was stirred with CSA (34.0 mg) at room temperature for 15 min. The reaction mixture was neutralized with Et_3N, and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3) to give the acetal as a colorless oil (800.0 mg, 97%). MS *m/z* (relative intensity): 389 (M^+ − 91, 0.1), 337 (0.9), 312 (1), 305 (0.5), 257 (17), 239 (7), 225 (12), 207 (7), 143 (11), 121 (100). Exact MS *m/z* Calcd for $C_{23}H_{33}O_5$ (M^+ − 91): 389.2330. Found: 389.2351.

A solution of KOH (1.20 g) in H_2O (10 ml) was added to a stirred solution of the above acetal (790 mg, 1.70 mmol) in MeOH (20 ml) at room temperature. After 20 min, the reaction mixture was evaporated *in vacuo*. The residue was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 2) to give **24** as a colorless oil (750.0 mg, 100%). MS *m/z* (relative intensity): 407 (M^+ − 31, 0.2), 347 (0.9), 329 (0.2), 295 (0.8), 277 (0.6), 270 (2.5), 257 (15), 239 (7), 225 (11), 207 (7), 143 (9), 121 (100). Exact MS *m/z* Calcd for $C_{23}H_{35}O_6$ (M^+ − 31): 407.2436. Found: 407.2445.

(*R*)-2-[(2*R,5*S*)-5-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-2-methoxy-5-methyltetrahydrofuran-2-yl]-2-(4-methoxybenzyloxy)ethan-1-ol (6)** A solution of **24** (750 mg, 1.71 mmol) in 2,2-dimethoxypropane (20 ml) was stirred with CSA (60 mg) at room temperature for 15 min, then neutralized with Et_3N, and evaporated *in vacuo*. The residue was extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3) to give the acetal as a colorless oil (837 mg, 96%).

A solution of the above acetal (837 mg, 1.64 mmol) in THF (8 ml) was added to a stirred suspension of NaH (118 mg, 4.92 mmol) in DMF (8 ml) at room temperature under argon. After 2 h, benzyl bromide (0.585 ml, 4.92 mmol) was added, and the mixture was stirred at 50—60 °C for 3 d. After being cooled to room temperature, the mixture was stirred with Et_2NH

(2 ml) for 30 min, poured into cold H_2O, extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 4) to give the benzyl ether (893 mg, 91%).

A solution of the above benzyl ether (893 mg, 1.49 mmol) in MeOH (20 ml) was stirred with CSA (40 mg) at room temperature for 20 min. After addition of Et_3N, the reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3) to give **6** as a colorless oil (745 mg, 95%).[2b] MS *m/z* (relative intensity): 497 ($M^+ - 31$, 0.2), 466 (0.6), 437 (10), 347 (12), 239 (6), 237 (6), 233 (8), 121 (100), 91 (67), 57 (7). Exact MS *m/z* Calcd for $C_{24}H_{37}O_7$ ($M^+ - 91$): 437.2542. Found: 437.2540.

References and Notes

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