Highly Stereocontrolled Total Synthesis of the Polyether Antibiotic Salinomycin. III. Total Synthesis of Salinomycin *via* Coupling of C1—C9, C10—C17, and C18—C30 Segments[1,2]

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The polyether antibiotic salinomycin was synthesized *via* coupling between the C10—C17 aldehyde, (2*R*,4*S*,5*S*,6*S*,7*R*)-6-ethyl-5,7-isopropylidenedioxy-2,4-dimethylnonanal, and C18—C30 acetylenes, for example, (3*R*,4*R*,7*S*)-4,7-bis(*tert*-butyldimethylsilyloxy)-7-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-3-(4-methoxybenzyloxy)oct-1-yne, followed by the aldol condensation with the C1—C9 segment, (*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-formylethyl]-5-methyltetrahydropyran-2-yl]butanoic acid. In this total synthesis, protection of hydroxy groups with the 4-methoxybenzyl group played an important role.

Keywords polyether antibiotic; salinomycin; total synthesis; stereocontrolled synthesis; aldol condensation; protection of hydroxy group; 4-methoxybenzyl

Highly stereoselective syntheses of the C1—C9 (**2**), C10—C17 (**3**), and C18—C30 segments (**4**, **5**) required for the total synthesis of salinomycin (**1**) starting from D-glucose, D-mannitol, and ethyl L-lactate by means of some selective reactions and the use of suitable protecting groups, in particular benzyl-type protecting groups,[3] were described in the preceding papers.[1,4] We report here a rather facile total synthesis of **1**, consisting of three parts: 1) synthesis of the C10—C30 segment (**6**),[2a] Kishi's intermediate of **1**,[5] from **5** and the aldehyde (**7**) corresponding to **3**; 2) total synthesis of **1** from **2**, **7**, and the third C18—C30 segment (**8**)[2b]; 3) an improved synthesis of **1** from **2**, **7**, and the fourth C18—C30 segment (**9**).[2b]

Synthesis of the C20-*O*-Acetyl C10—C30 Segment (6), a Formal Total Synthesis of Salinomycin (1)[2a] Since all attempts to condense the C10—C17 lactone (**3**)[4] with the second acetylenic C18—C30 segment (**5**)[1] were unsuccessful, **3** was replaced by the more reactive aldehyde (**7**). Compound **10**, the final intermediate to **3** from D-glucose,[4] was reduced to the triol with calcium borohydride. The 1,3-diol group of the triol was protected as an acetonide, and then Swern oxidation of the remaining primary alcohol gave the aldehyde (**7**), which was coupled with the acetylene (**5**) in the presence of *n*-butyllithium (*n*-BuLi) at −78 °C. The coupling proceeded quite smoothly to give an acetylene-alcohol, which was readily oxidized with manganese dioxide to the ynone (**11**). When **11** was treated with a catalytic amount of camphorsulfonic acid (CSA) in methanol, deprotection of the isopropylidene group followed by intramolecular ketalization occurred to give the bisketal as a mixture of four diastereoisomers with respect to the C17 and C21 positions.[6,7] The mixture was separable chromatographically into each isomer after conversion to the monoacetate (**12**).

Although no reduction of **12** occurred with Lindlar catalyst in the presence of quinoline under usual conditions probably because of steric hinderance, the catalyst in the absence of quinoline was effective for the conversion of the triple bond in **12** to a double bond. However, since the four isomers of **12** have quite different reactivities, better results were obtained when each isomer was reduced separately. Actually, the four isomers of the monoacetate, **12a**, **12b**, **12c**, and **12d**, isolated in the ratio of 1.0 : 2.8 : 3.8 : 1.3, were converted to the corresponding *Z*-olefins, **13a**, **13b**, **13c**, and **13d** in 100, 72, 78, and 0% yields, respectively, and the combined yield of **13** was 68%.

On treatment with 80% aqueous acetic acid at room temperature, **13** cyclized quite smoothly to give the bisspiroketal. After removal of the acetyl protection with potassium hydroxide, the resulting secondary alcohol was oxidized with pyridinium chlorochromate (PCC) to give the ketone (**14**) as a *ca.* 1 : 1 mixture of two diastereoisomers again with respect to the C17 and C21 positions. The ketone (**14**) has all the rings and chiral centers with correct configurations necessary for **6**, except at the C17 and C21 bisspiroketal positions.[7]

When **14** was treated with a large excess of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at room temperature, removal of the 4-methoxybenzyl (MPM) group[3,8] occurred within a few minutes and then the benzyl (Bn) protecting

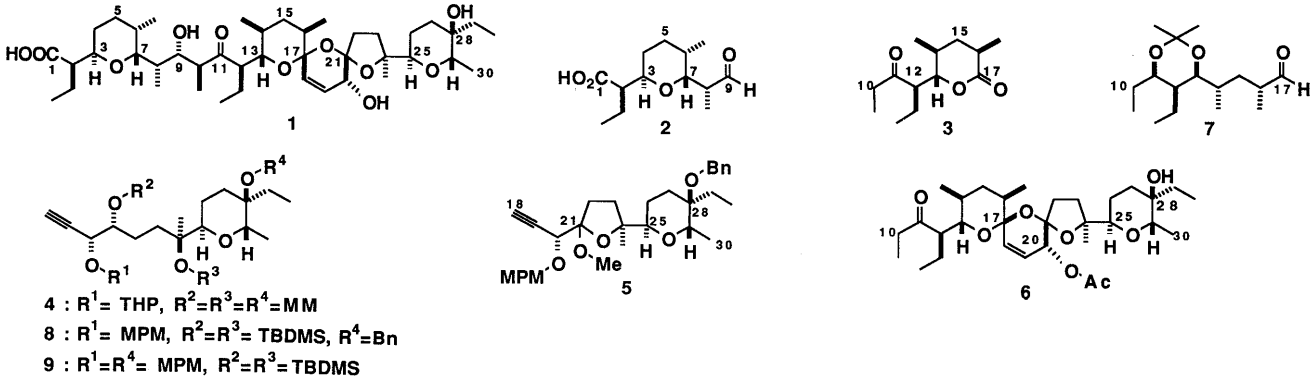
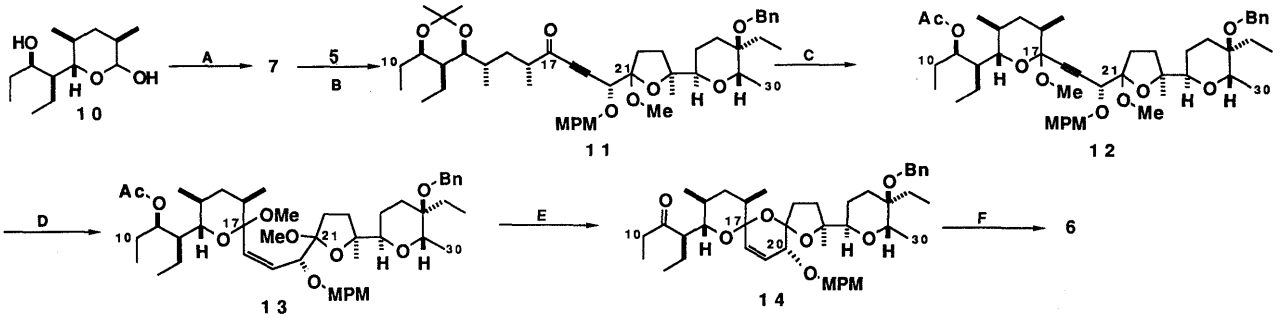
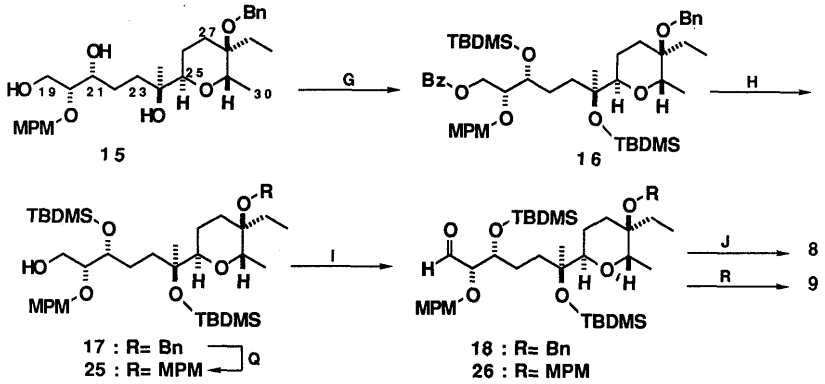


Chart 1



(A) 1) $Ca(BH_4)_2$, THF; 2) $Me_2C(OMe)_2$, CSA, C_6H_6; 3) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (B) 1) *n*-BuLi, THF, −78 °C; 2) MnO_2, CH_2Cl_2 (C) 1) CSA, MeOH; 2) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (D) Lindlar catalyst, H_2, MeOH (AcOH) (E) 1) 80% AcOH; 2) KOH, MeOH–H_2O, 60—70 °C; 3) PCC, MS, CH_2Cl_2 (F) 1) DDQ, CH_2Cl_2–H_2O (10:1); 2) Ac_2O, Et_3N, DMAP, CH_2Cl_2; 3) CSA, CH_2Cl_2

Chart 2



(G) 1) BzCl, Py, CH_2Cl_2, 0 °C; 2) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C (H) KOH, MeOH, 55 °C (I) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N (J) 1) $PhHgCBrCl_2$, Ph_3P, C_6H_6, reflux; 2) *n*-BuLi, THF, −78 °C (Q) 1) Raney Ni, H_2, EtOH, 60 °C; 2) $Me_2C(OMe)_2$, CSA, C_6H_6, r.t.; 3) MPMCl, NaH, DMF, r.t.; 4) CSA, MeOH, r.t. (R) 1) CBr_4, Ph_3P, CH_2Cl_2, −78 °C; 2) LDA, THF, −30 °C
r.t. = room temperature

Chart 3

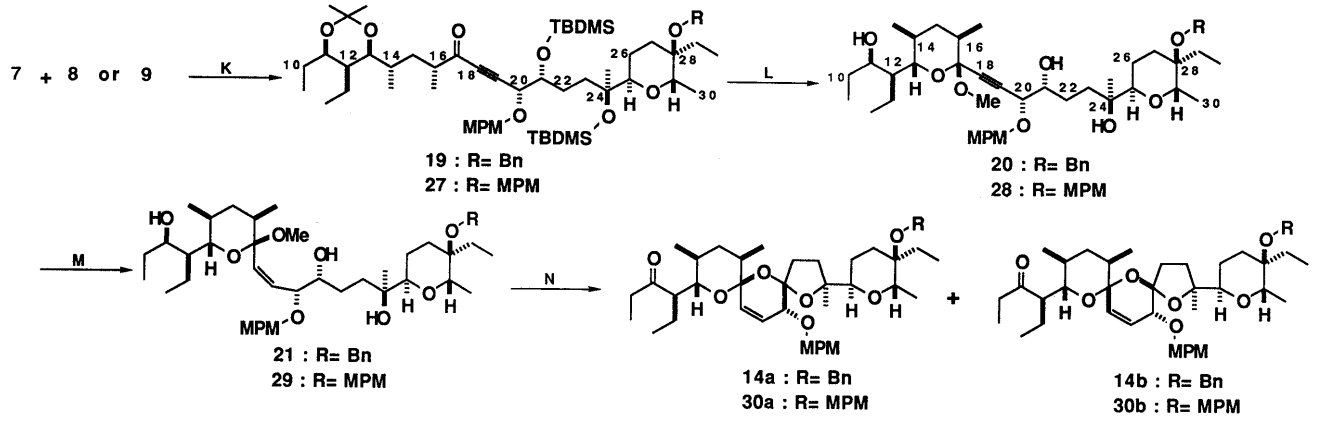
group for the tertiary alcohol[3,9] was gradually removed. After acetylation of the secondary alcohol of the resulting diol with acetic anhydride in the presence of dimethylaminopyridine (DMAP), the monoacetate was treated with CSA in dichloromethane at room temperature. Acid-catalyzed isomerization at the C17 and C21 bisspiroketal positions occurred to give the expected C10—C30 segment (**6**) with C17-*epi* configuration,[10] which was identical, in terms of its infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS), with an authentic sample derived from natural salinomycin (**1**).[5,11]

Total Synthesis of Salinomycin (1)[2b] As described above, **6** was synthesized from D-glucose, *etc.*, *via* **5**; however, since **5** was a *ca.* 1:1 mixture of two stereoisomers with respect to the C21-acetal position, all intermediates from **5** to **6** were complex stereoisomeric mixtures, whose structural characterization was sometimes quite difficult. A new single C18—C30 segment (**8**) without the C21-acetal group was expected to be a more convenient intermediate.[2b]

The primary alcohol of the triol (**15**)[1] was selectively benzoylated, and the remaining two alcohols were protected with *tert*-butyldimethylsilyl (TBDMS) groups in the usual way to give **16**. Alkaline hydrolysis of the benzoate gave the alcohol (**17**), which was readily converted to the aldehyde (**18**) by Swern oxidation. Treatment of **18** with bromodichloromethylphenylmercury and triphenylphosphine gave the dichloroolefin in excellent yield, and this was dechlorinated with *n*-BuLi to give the third acetylenic C18—C30 segment (**8**) as the sole product.[12]

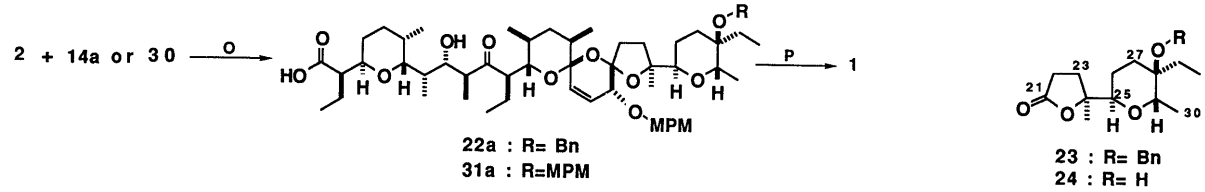
Coupling of **8** with **7** in the presence of *n*-BuLi followed by oxidation as described above for **11** gave the ynone (**19**), which was treated with a small amount of CSA in methanol to remove the isopropylidene protection and then with tetra-*n*-butylammonium fluoride to deprotect the silyl groups. The resulting acetal (**20**) was a 4:1 stereoisomeric mixture with respect to the C17 acetal position and used for further reactions without separation into isomers, because their reactivities toward the reduction with Lindlar catalyst were about the same, being quite different from those of the isomers of **12**. Partial hydrogenation of the acetylene of **20** proceeded rather rapidly in the presence of Lindlar catalyst and the expected *cis*-olefin (**21**) was isolated in high yield. Swern oxidation of the secondary alcohols of **21** followed by treatment with CSA in dichloromethane gave the expected C10—C30 segment (**14**), which was a separable 1:1.1 mixture of stereoisomers with respect to the C17 and C21 positions, **14a** and **14b**.[13]

Although **14a** and **14b** were converted into **1** in the same way, the synthesis from **14a** is described here (for the synthesis from **14b**, see Experimental). When the magnesium enolate of **14a** prepared with dicyclohexylaminomagnesium bromide was coupled with the C1—C9 segment (**2**) in tetrahydrofuran (THF) at −55 °C,[5] only the expected



(K) 1)*n*-BuLi, THF. −78 °C; 2) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N (L) 1) CSA, MeOH; 2) *n*-Bu_4NF, dioxane–THF, 65 °C (M) Lindlar catalyst, H_2, MeOH (N) 1) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; 2) CSA, CH_2Cl_2

Chart 4



(O) $(C_6H_{11})_2NMgBr$, THF, −55 °C (P) from **22a** DDQ, CH_2Cl_2–buffer (pH 6.86) (P) from **31a** 1) DDQ, CH_2Cl_2–H_2O; 2) TFA, MS, CH_2Cl_2

Chart 5

aldol product (**22a**) was obtained, though the yield was unsatisfactory. Finally, **22a** was treated with a large excess of DDQ to remove both the MPM and Bn protecting groups. Removal of the C20-*O*-MPM group occurred within a few minutes,[3,8] and then the C28-*O*-Bn group was slowly removed with simultaneous isomerization at the C17 ketal position to afford **1** itself. However, the yield was very poor, because when the C20-*O*-protecting group was removed, the C20 free-hydroxy compound was unexpectedly labile toward DDQ and a noticeable radical cleavage between C20 and C21 positions probably occurred to give the lactone (**23**) in 46% yield. Actually, **1** underwent this interesting cleavage. Addition of DDQ to a solution of **1** in methylene chloride produced immediately a light red color owing to the formation of a charge-transfer complex between electron-denating **1** and DDQ, and then the color faded slowly to afford the C21—C30 segment (**24**).[1,14] Prolonged treatment of **22** with DDQ was clearly responsible for this undesirable cleavage. In order to overcome such a side reaction, we decided to replace the C28-*O*-Bn protecting group by an MPM group, which was expected to be removed within a few minutes with DDQ.

Improved Synthesis of Salinomycin (1)[2b] The C28-*O*-Bn group of **17** was selectively removed by catalytic hydrogenation in the presence of Raney nickel[3,15] and replaced by the MPM group to give **25** in a conventional way *via* selective protection of the primary alcohol with a methoxypropyl group, MPM protection of the tertiary alcohol, and removal of the methoxypropyl protection. Oxidation of **25** gave the aldehyde (**26**), which was converted to the fourth acetylenic C18—C30 segment (**9**) *via* a dibromoolefin.[16] The acetylene (**9**) was condensed with the aldehyde (**7**) and the resulting ynone (**27**) was converted to the new C10—C30 segment (**30**) as a stereoisomeric mixture of **30a** and **30b**[13] *via* **28** and **29** by a method virtually identical with that described for **14** without any difficulty.

Although, in analogy with **14a** and **14b**, both **30a** and **30b** were converted to **1** in the same way, conversion of **30a** into **1** is described here (for the conversion from **30b** to **1**, see Experimental). After coupling of the magnesium enolate of **30a** with **2** as described for **22a**, the resulting 20,28-di-*O*-MPM compound (**31a**) was treated with DDQ at room temperature. Deprotection of both MPM groups occurred quite rapidly, and was completed within only 10 min without epimerization at the C17 ketal position to give 17-episalinomycin in excellent yield, treatment of which with trifluoroacetic acid in the presence of molecular sieves readily gave salinomycin (**1**), which was identical, in terms of its melting point, optical rotation and spectral data (IR, NMR, and MS), with the natural product.

Experimental

Physical data were measured as described in the previous paper.[4]

(2*R*,4*S*,5*S*,6*S*,7*R*)-6-Ethyl-5,7-isopropylidenedioxy-2,4-dimethylnonanal (7) $NaBH_4$ (56 mg, 1.47 mmol) was added to a stirred solution of $CaCl_2$ (91 mg, 0.816 mmol) in EtOH (3 ml) at −15 °C. The mixture was stirred at room temperature for 1 h, then a solution of **10** (47 mg, 0.204 mmol) in EtOH (1 ml) was added dropwise and the stirring was continued for 1.5 h. Insoluble materials were removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was treated with 2 N HCl (5 ml). The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (CH_2Cl_2–MeOH, 10:1) to give the triol (46 mg, 97%), as a colorless oil.

A solution of the above triol (41 mg, 0.176 mmol), 2,2-dimethoxypropane (0.8 ml) and CSA (5 mg) in benzene (2.0 ml) was stirred at room temperature for 6 h. The reaction mixture was quenched with Et_3N (0.3 ml), and extracted with CH_2Cl_2. The extract was washed with 1 N HCl, brine, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column

(hexane–EtOAc, 3:1) to give the acetonide as a colorless oil (39 mg, 81%).

A solution of dimethyl sulfoxide (DMSO) (51 μl, 0.72 mmol), in CH_2Cl_2 (0.9 ml) was added dropwise to a stirred solution of $(COCl)_2$ (48 μl, 0.55 mmol) in CH_2Cl_2 (0.5 ml) at −78 °C under argon. After 7 min, a solution of the above alcohol (50 mg, 0.18 mmol) in CH_2Cl_2 (2.0 ml) was added, and the reaction mixture was stirred at −75 °C for 10 min. Et_3N (199 μl, 1.43 mmol) was then added dropwise. After 20 min, the mixture was allowed to warm to −15 °C, diluted with Et_2O (40 ml), washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (EtOAc–hexane, 1:7) to give **7** as a colorless oil (46 mg, 93%). $[\alpha]_D^{20}$ −18° (c=1.04). IR ν_{max} cm^{-1}: 2700, 1720. ^{1}H-NMR δ: 0.77 (3H, d, J=6.5 Hz), 0.85 (3H, t, J=7.0 Hz), 0.90 (3H, t, J=7.5 Hz), 1.03 (3H, d, J=7.0 Hz), 1.26 (3H, s), 1.30 (3H, s), 1.13—1.78 (7H, m), 2.03 (1H, ddd, J=4.5, 9.0, 13.5 Hz), 2.28—2.58 (1H, m), 3.31 (1H, dd, J=2.0, 9.5 Hz), 3.60 (1H, dt, J=2.0, 8.5 Hz), 9.48 (1H, d, J=3.0 Hz). MS m/z (relative intensity): 255 (M^+ −15, 18), 195 (11), 177 (11), 137 (16), 129 (41), 59 (100). Exact MS m/z Calcd for $C_{15}H_{27}O_3$ (M^+ −15): 255.1957. Found: 255.1962.

(1*R*,5*R*,7*S*,8*S*,9*S*,10*R*)-1-[(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]-9-ethyl-8,10-isopropylidenedioxy-1-(4-methoxybenzyloxy)-5,7-dimethyldodec-2-yn-4-one (11)** A solution of **5** (92 mg, 0.176 mmol) in THF (0.8 ml) was treated with a 1.6 M solution of *n*-BuLi in hexane (0.11 ml, 0.176 mmol) at −78 °C for 1 h under argon, and a solution of **7** (35 mg, 0.129 mmol) in THF (0.8 ml) was added dropwise. The reaction mixture was allowed to warm gradually to −20 °C during 2 h, then quenched with saturated NH_4Cl, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (hexane–EtOAc, 4:1) to give the hydroxyacetylene as a colorless oil (82 mg, 80%). IR ν_{max} cm^{-1}: 3400, 1610, 1585. MS m/z (relative intensity): 777 (M^+ −15, 1.4), 701 (1.1), 687 (4), 559 (5), 368 (11), 347 (42), 257 (67), 239 (27), 121 (100), 91 (39). Exact MS m/z Calcd for $C_{33}H_{51}O_7$ (M^+ −233): 559.3662. Found: 559.3638.

A solution of the above hydroxyacetylene (50 mg, 0.063 mmol) in CH_2Cl_2 (1.6 ml) was stirred in the presence of MnO_2 (160 mg, 1.8 mmol) at room temperature for 18 h. After removal of inorganic salts by filtration, the filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (hexane–EtOAc, 3:1) to give the ynone (**11**) as a colorless oil (50 mg, 100%). IR ν_{max} cm^{-1}: 2205, 1670, 1615, 1585. ^{1}H-NMR δ: 0.83 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=7.5 Hz), 0.91 (3H, t, J=7.5 Hz), 0.96 (3H, t, J=7.5 Hz), 1.18 (3H, s), 1.21 (3H, d, J=7.0 Hz), 1.25 (3H, d, J=7.0 Hz), 1.31 (3H, s), 1.35 (3H, s), 1.31—2.25 (17H, m), 2.36 (1H, dt, J=12.5, 9.0 Hz), 2.81 (1H, dt, J=7.0, 5.5 Hz), 3.30 (3H, s), 3.57 (1H, dd, J=2.0, 10.0 Hz), 3.52 (1H, dd, J=2.5, 12.0 Hz), 3.66 (1H, ddd, J=2.0, 6.0, 8.0 Hz), 3.80 (3H, s), 4.12 (1H, q, J=7.0 Hz), 4.32 (1H, d, J=11.0 Hz), 4.39 (1H, s), 4.44 (1H, d, J=11.0 Hz), 4.52 (1H, d, J=11.0 Hz), 4.74 (1H, d, J=11.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.24—7.42 (7H, m). MS (relative intensity): 775 (M^+ −15, 13), 557 (7), 368 (7), 347 (98), 257 (6), 239 (33), 121 (100), 91 (56). Exact MS m/z Calcd for $C_{33}H_{49}O_7$ (M^+ −233): 557.3474. Found: 557.3481.

(*R*)-1-[(2*R,3*R*,5*R*,6*S*)-6-[(1*R*,2*R*)-2-Acetoxy-1-ethylbutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-3-[(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]-3-(4-methoxybenzyloxy)prop-1-yne (12)** A solution of **11** (41 mg, 0.0518 mmol) and CSA (8 mg) in MeOH (5.0 ml) was stirred at room temperature for 40 min. After neutralization with Et_3N (0.1 ml), the reaction mixture was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2:3) to give an alcohol (38 mg, 96%).

The above alcohol (38 mg, 0.0497 mmol) was treated with Ac_2O (70 μl), Et_3N (0.1 ml), and DMAP (5 mg) in CH_2Cl_2 (5.0 ml) at room temperature for 30 min. After addition of MeOH, the reaction mixture was evaporated *in vacuo* and the residue was chromatographed on a short silica gel column (EtOAc–hexane, 2:3) to give **12** as a colorless oil (32.2 mg, 85%). MS m/z (relative intensity): 774 (M^+ −32, 0.5), 743 (4), 621 (5), 541 (5), 513 (15), 437 (45), 361 (11), 347 (44), 329 (7), 285 (19), 239 (17), 121 (100), 91 (61). Exact MS m/z Calcd For $C_{47}H_{66}O_9$ (M^+ −32): 774.4728. Found: 774.4711.

Four isomers of **12** were separated by a silica gel thin layer chromatography (TLC) (Et_2O–hexane, 1:2). **12a** (3.6 mg, 90%): ^{1}H-NMR δ: 0.78 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=7.5 Hz), 0.88 (3H, t, J=7.5 Hz), 0.98 (3H, t, J=7.5 Hz), 0.99 (3H, d, J=6.5 Hz), 1.19 (3H, s), 1.25 (3H, d, J=7.0 Hz), 1.31—2.41 (19H, m), 2.05 (3H, s), 3.30 (3H, s), 3.39 (3H, s), 3.40 (1H, dd, J=2.0, 10.0 Hz), 3.53 (1H, dd, J=2.0, 11.5 Hz), 3.81 (3H, s), 4.11 (1H, q, J=7.0 Hz), 4.31 (1H, s), 4.31 (1H, d, J=11.0 Hz), 4.45 (1H, d, J=11.0 Hz), 4.52 (1H, d, J=11.5 Hz), 4.73 (1H, d, J=11.5 Hz), 5.03 (1H, ddd, J=4.0, 6.5, 7.5 Hz), 6.87 (2H, d, J=9.0 Hz), 7.24—7.43 (7H, m). **12b** (10.2 mg, 25.5%): ^{1}H-NMR δ: 0.77 (3H, d, J=6.0 Hz), 0.85 (3H, t, J=7.5 Hz), 0.88 (3H, t, J=7.5 Hz), 0.97 (3H, d, J=6.0 Hz), 0.98 (3H, t, J=7.5 Hz), 1.20 (3H, s), 1.25 (3H, d, J=7.0 Hz), 1.30—2.47 (19H, m), 1.97 (3H, s), 3.29 (3H, s), 3.46 (3H, s), 3.53 (1H, dd, J=2.0, 11.5 Hz), 3.60 (1H, dd, J=1.0, 10.5 Hz), 3.81 (3H, s), 4.12 (1H, q, J=7.0 Hz), 4.32 (1H, d, J=11.0 Hz), 4.44 (1H, d, J=11.0 Hz), 4.35 (1H, s), 4.52 (1H, d, J=11.5 Hz), 4.76 (1H, d, J=11.5 Hz), 4.97 (1H, ddd, J=3.5, 6.0, 10.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.24—7.43 (7H, m). **12c** (13.6 mg, 34%): ^{1}H-NMR δ: 0.81 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=7.5 Hz), 0.90 (3H, t, J=7.5 Hz), 0.99 (3H, t, J=7.5 Hz), 1.04 (3H, d, J=7.0 Hz), 1.18 (3H, d, J=7.0 Hz), 1.27 (3H, s), 1.36—2.35 (19H, m), 2.07 (3H, s), 3.04 (3H, s), 3.36—3.46 (2H, m), 3.43 (3H, s), 3.81 (3H, s), 4.07 (1H, q, J=7.0 Hz), 4.25 (1H, s), 4.30 (1H, d, J=11.0 Hz), 4.12 (1H, d, J=11.0 Hz), 4.56 (1H, d, J=11.5 Hz), 4.77 (1H, d, J=11.5 Hz), 5.07 (1H, ddd, J=4.5, 7.0, 8.0 Hz), 6.89 (2H, d, J=9.0 Hz), 7.23—7.41 (7H, m). **12d** (4.8 mg, 12%): ^{1}H-NMR δ: 0.81 (3H, d, J=6.0 Hz), 0.86 (3H, t, J=7.5 Hz), 0.88 (3H, d, J=7.0 Hz), 0.99 (3H, t, J=7.5 Hz), 1.00 (3H, d, J=6.0 Hz), 1.16 (3H, d, J=7.0 Hz), 1.28 (3H, s), 1.92 (3H, s), 1.33—2.36 (19H, m), 3.08 (3H, s), 3.41 (1H, dd, J=2.0, 11.5 Hz), 3.49 (3H, s), 3.72 (1H, dd, J=1.0, 10.0 Hz), 3.81 (3H, s), 4.05 (1H, q, J=6.0 Hz), 4.29 (1H, d, J=11.0 Hz), 4.29 (1H, s), 4.41 (1H, d, J=11.0 Hz), 4.60 (1H, d, J=12.0 Hz), 4.81 (1H, d, J=12.0 Hz), 4.99 (1H, ddd, J=3.0, 6.0, 9.0 Hz), 6.88 (2H, d, J=9.0 Hz), 7.23—7.40 (7H, m).

(1*Z*,3*R*)-1-[(2*R,3*R*,5*R*,6*S*)-6-[(1*R*,2*R*)-2-Acetoxy-1-ethylbutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-3-[(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]-3-(4-methoxybenzyloxy)prop-1-ene (13)** a) Reduction of **12a**: A solution of **12a** (2.5 mg, 3.1 μmol) in MeOH (1.0 ml) was hydrogenated in the presence of Lindler catalyst (15 mg) at ordinary temperature and pressure for 30 min. After removal of the catalyst, the filtrate was evaporated *in vacuo* and the residue was applied to a short silica gel column (EtOAc–hexane, 2:3) to give **13a** as a colorless oil (2.5 mg, 100%). ^{1}H-NMR δ: 0.82 (3H, d, J=6.0 Hz), 0.84 (3H, d, J=6.5 Hz), 0.89 (3H, t, J=7.0 Hz), 0.90 (3H, t, J=6.5 Hz), 1.00 (3H, t, J=7.5 Hz), 1.20 (3H, s), 1.27 (3H, d, J=7.0 Hz), 1.36—2.13 (18H, m), 2.04 (3H, s), 2.30—2.43 (1H, m), 3.21 (3H, s), 3.28 (3H, s), 3.46 (1H, dd, J=1.0, 10.0 Hz), 3.52 (1H, dd, J=2.0, 11.5 Hz), 3.79 (3H, s), 4.12 (1H, q, J=7.0 Hz), 4.33 (1H, d, J=11.0 Hz), 4.46 (1H, d, J=11.0 Hz), 4.57 (1H, d, J=11.0 Hz), 4.68 (1H, d, J=11.0 Hz), 5.06 (1H, d, J=9.5 Hz), 5.03—5.09 (1H, m), 5.55 (1H, dd, J=9.5, 12.5 Hz), 5.64 (1H, d, J=12.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.24—7.44 (7H, m). MS m/z (relative intensity): 744 (M^+ −64, 1), 640 (3), 623 (2), 609 (12), 499 (2), 437 (4), 347 (10), 121 (100), 91 (90). Exact MS m/z Calcd for $C_{46}H_{64}O_8$ (M^+ −64): 744.4568. Found: 744.4605.

b) Reduction of **12b**: A solution of **12b** (3.6 mg, 4.46 mol) in MeOH (1.0 ml) containing AcOH (0.1% w/w) was hydrogenated in the presence of Lindlar catalyst (8 mg) at 50 °C for 7.5 h. Work-up as described for **13a** gave **13b** as a colorless oil (2.6 mg, 72%).

c) Reduction of **12c**: A solution of **12c** (19 mg, 0.0235 mmol) in MeOH (2.0 ml) was hydrogenated in the presence of Lindlar catalyst (50 mg) at room temperature for 8.5 h. Work-up as described for **13a** gave **13c** as a colorless oil (15 mg, 78%). ^{1}H-NMR δ: 0.81 (3H, t, J=7.0 Hz), 0.81 (3H, d, J=6.0 Hz), 0.83 (3H, d, J=7.0 Hz), 0.86 (3H, t, J=7.5 Hz), 0.96 (3H, d, J=6.5 Hz), 1.01 (3H, t, J=7.5 Hz), 1.32 (3H, s), 1.15—1.85 (17H, m), 2.03—2.17 (1H, m), 2.07 (3H, s), 2.29—2.42 (1H, m), 3.23 (3H, s), 3.29 (3H, s), 3.42 (1H, dd, J=2.4, 11.0 Hz), 3.53 (1H, dd, J=1.0, 10.5 Hz), 3.80 (3H, s), 3.93 (1H, q, J=7.0 Hz), 4.25 (1H, d, J=11.0 Hz), 4.30 (1H, d, J=10.0 Hz), 4.37 (1H, d, J=11.0 Hz), 4.43 (1H, d, J=10.0 Hz), 4.90 (1H, dd, J=3.5, 5.5 Hz), 5.06 (1H, dt, J=3.0, 8.0 Hz), 5.66 (1H, d, J=5.5 Hz), 5.67 (1H, d, J=3.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25—7.39 (7H, m).

(2*S*,5*S,7*S**,9*S*,10*S*,12*R*,13*Z*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-9-[(*R*)-1-ethyl-2-oxobutyl]-15-(4-methoxybenzyloxy)-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (14)** a) A solution of **13** (22.2 mg, 0.027 mmol) in 80% AcOH (4.0 ml) was stirred at room temperature for 12 h. The reaction mixture was diluted with Et_2O, washed with 10% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was applied to a silica gel column (EtOAc–hexane, 1:4) to give the bisspiroketal as a colorless oil (14.4 mg, 69%). MS m/z (relative intensity): 762 (M^+, 0.3), 733 (0.8), 703 (0.3), 655 (0.3), 641 (2), 626 (2), 624 (2), 619 (2), 608 (0.6), 606 (0.5), 529 (9), 430 (28), 401 (7), 393 (7), 309 (35), 249 (15), 165 (11), 137 (8), 121 (100), 91 (23). Exact MS m/z Calcd for $C_{38}H_{57}O_8$ (M^+ −121): 641.4057. Found:

641.4053.

The above bisspiroketal (14.0 mg, 0.0183 mmol) was treated with 2 N KOH (0.5 ml) in MeOH (4.0 ml) at 70 °C for 8 h. The reaction mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was applied to a short silica gel column (EtOAc–hexane, 1 : 1) to give the alcohol as a colorless oil (13.0 mg, 98%). MS *m/z* (relative intensity): 720 (M^+, 0.3), 702 (41), 691 (4), 662 (0.5), 619 (4), 599 (4), 584 (6.5), 487 (8), 437 (5), 388 (33), 350 (6.5), 267 (40), 122 (100), 91 (26), 57 (8). Exact MS *m/z* Calcd for $C_{36}H_{55}O_7$ ($M^+ - 121$): 599.3951. Found: 599.3932. The alcohol was a stereoisomeric mixture of alcohol-a, -b, and -c, which were separated by silica gel TLC (EtOAc–hexane, 1 : 3). Alcohol-a (5.6 mg, 42%): ^{1}H-NMR δ: 0.81 (3H, t, J=7.0 Hz), 0.86 (3H, d, J=7.5 Hz), 0.91 (3H, t, J=7.5 Hz), 0.95 (3H, d, J=7.0 Hz), 0.99 (3H, t, J=7.5 Hz), 1.23 (3H, s), 1.30 (3H, d, J=7.0 Hz), 1.48—2.45 (19H, m), 3.24 (1H, br s), 3.64—3.85 (3H, m), 3.79 (3H, s), 4.11 (1H, q, J=7.0 Hz), 4.31 (1H, dd, J=2.0, 2.5 Hz), 4.34 (1H, d, J=11.0 Hz), 4.48 (1H, d, J=11.0 Hz), 4.53 (1H, d, J=11.0 Hz), 4.73 (1H, d, J=11.0 Hz), 5.72 (1H, dd, J=2.5, 10.5 Hz), 5.99 (1H, dd, J=2.0, 10.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.24—7.41 (7H, m). Alcohol-b (3.0 mg, 23%): ^{1}H-NMR δ: 0.84—1.05 (15H, m), 1.18 (3H, d, J=7.0 Hz), 1.38 (3H, s), 1.54—2.30 (20H, m), 3.40—3.90 (4H, m), 3.80 (3H, s), 4.07 (1H, q, J=7.0 Hz), 4.28 (1H, d, J=11.0 Hz), 4.32 (1H, d, J=11.0 Hz), 4.66 (2H, s), 5.63 (1H, d, J=10.0 Hz), 5.97 (1H, dd, J=4.5, 10.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.24—7.38 (7H, m). Alcohol-c (4.4 mg, 33%): ^{1}H-NMR δ: 0.78 (3H, t, J=7.0 Hz), 0.83 (3H, d, J=7.0 Hz), 0.91 (3H, t, J=7.0 Hz), 0.92 (3H, d, J=7.0 Hz), 1.02 (3H, t, J=7.0 Hz), 1.25 (3H, d, J=7.0 Hz), 1.26 (3H, s), 1.32—2.34 (19H, m), 2.20 (1H, d, J=2.0 Hz), 3.31 (1H, dd, J=2.0, 11.0 Hz), 3.42—3.71 (2H, m), 3.80 (3H, s), 3.97 (1H, t, J=2.0 Hz), 4.10 (1H, q, J=7.0 Hz), 4.31 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=11.5 Hz), 4.55 (1H, d, J=11.5 Hz), 4.80 (1H, d, J=11.5 Hz), 5.80—6.00 (2H, m), 6.86 (2H, d, J=9.0 Hz), 7.24—7.40 (7H, m).

The above alcohol mixture (5.6 mg, 7.76 μmol), powdered molecular sieves 3 Å (7.0 mg), and PCC (7.0 mg) in CH_2Cl_2 (0.3 ml) were stirred at room temperature for 4 h. The reaction mixture was applied to a short silica gel column (EtOAc–hexane, 2 : 3) to give **14** as a colorless oil (4.5 mg, 81%). MS *m/z* (relative intensity): 619 ($M^+ - 99$, 0.2), 597 (0.1), 582 (0.4), 485 (1), 469 (1), 386 (8), 257 (2.5), 265 (12), 209 (2.5), 191 (5.5), 165 (21), 121 (100), 91 (23), 57 (20). Exact MS *m/z* Calcd for $C_{36}H_{55}O_7$ ($M^+ - 121$): 597.3794. Found: 597.3773.

b) Compound **21** (20 mg, 0.0261 mmol) was oxidized with $(COCl)_2$ (23 μl, 0.26 mmol), DMSO (24 μl, 0.338 mmol), and Et_3N (94 μl, 0.67 mmol) in CH_2Cl_2 (2.4 ml) as described for **7** to give the ketone as a colorless oil (17 mg, 85%).

A solution of the above ketone (5.0 mg, 6.57 μmol) and CSA (0.3 mg) in CH_2Cl_2 (0.3 ml) was stirred at room temperature for 15 min. After neutralization with Et_3N (0.1 ml), the mixture was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to give the (5*S*,7*S*) compound (**14a**) (1.5 mg, 31%) and (5*R*,7*R*) compound (**14b**) (1.5 mg, 31%). **14a**: $[\alpha]_D^{17}$ −51° (c=0.44). IR ν_{max} cm^{-1}: 1715, 1615, 1590. ^{1}H-NMR δ: 0.78 (3H, d, J=6.5 Hz), 0.81 (3H, t, J=7.5 Hz), 0.87 (3H, d, J=6.5 Hz), 0.91 (3H, t, J=7.5 Hz), 1.01 (3H, t, J=7.5 Hz), 1.24 (3H, s), 1.31 (3H, d, J=6.5 Hz), 1.32—2.40 (17H, m), 2.02 (1H, dt, J=10.5, 3.0 Hz), 2.79 (1H, dq, J=18.0, 7.5 Hz), 3.73 (1H, dd, J=2.0, 11.5 Hz), 3.80 (3H, s), 3.93 (1H, dd, J=3.0, 10.5 Hz), 4.15 (1H, dd, J=2.0, 3.0 Hz), 4.20 (1H, q, J=6.5 Hz), 4.36 (1H, d, J=10.5 Hz), 4.47 (1H, d, J=10.5 Hz), 4.51 (1H, d, J=11.0 Hz), 4.71 (1H, d, J=11.0 Hz), 5.69 (1H, dd, J=3.0, 10.0 Hz), 7.48 (1H, dd, J=2.0, 10.0 Hz), 6.87 (2H, d, J=8.5 Hz), 7.25—7.44 (7H, m). **14b**: $[\alpha]_D^{17}$ −35° (c=2.04). IR ν_{max} cm^{-1}: 1710, 1700, 1610, 1585. ^{1}H-NMR δ: 0.81—0.90 (12H, m), 0.10 (3H, t, J=7.5 Hz), 1.18 (3H, d, J=7.0 Hz), 1.37 (3H, s), 1.27—1.88 (14H, m), 2.15—2.23 (2H, m), 2.46 (1H, dq, J=18.0, 7.0 Hz), 2.52 (1H, dt, J=9.5, 3.0 Hz), 2.62 (1H, dq, J=18.0, 7.5 Hz), 3.48 (1H, dd, J=2.0, 11.5 Hz), 3.55 (1H, d, J=5.0 Hz), 3.79 (1H, dd, J=3.0, 9.0 Hz), 3.80 (3H, s), 4.06 (1H, q, J=7.0 Hz), 4.30 (1H, d, J=11.0 Hz), 4.41 (1H, d, J=11.0 Hz), 4.63 (1H, d, J=12.5 Hz), 4.70 (1H, d, J=12.5 Hz), 5.60 (1H, d, J=10.0 Hz), 5.93 (1H, dd, J=5.0, 10.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.24—7.41 (7H, m).

(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 (6) A solution of **14** (12 mg, 16.6 μmol) and DDQ (46 mg, 203 μmol) in CH_2Cl_2 (0.8 ml) and H_2O (0.08 ml) was stirred at room temperature for 2 h. After addition of 10% $NaHCO_3$ (0.1 ml), the mixture was diluted with Et_2O (30 ml), washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was applied to a short silica gel column (EtOAc–hexane, 2 : 3) to give the diol as a colorless oil (4.5 mg, 53%).

The diol was acetylated with Ac_2O (50 μl), Et_3N (0.1 ml), and DMAP (3 mg) in CH_2Cl_2 (2.0 ml) to give the acetate (5.0 mg), which was treated with CSA (3 mg) in CH_2Cl_2 (0.6 ml) at room temperature for 1.2 h. After addition of Et_3N, the mixture was evaporated *in vacuo* and subjected to silica gel TLC (EtOAc–hexane, 2 : 3) to give **6** as a colorless oil (3.5 mg, 70%). IR ν_{max} cm^{-1}: 3525, 1730, 1710, 1700. ^{1}H-NMR δ: 0.81—0.88 (9H, m), 0.91 (3H, t, J=7.0 Hz), 1.00 (3H, t, J=7.5 Hz), 1.18 (3H, d, J=7.0 Hz), 1.37 (3H, s), 1.47—1.89 (16H, m), 2.06 (3H, s), 2.31 (1H, dt, J=3.0, 7.5 Hz), 2.41—2.67 (2H, m), 2.74 (1H, br s), 3.35 (1H, dd, J=1.5, 10.0 Hz), 3.75 (1H, q, J=7.0 Hz), 3.78 (1H, dd, J=3.0, 8.0 Hz), 4.97 (1H, d, J=6.0 Hz), 5.71 (1H, d, J=10.5 Hz), 5.99 (1H, dd, J=6.0, 10.5 Hz). MS *m/z* (relative intensity): 550 (M^+, 2), 532 (1), 521 (0.9), 508 (6), 490 (19), 407 (22), 347 (29), 308 (35), 291 (13), 266 (46), 247 (25), 57 (100), 43 (54). Exact MS *m/z* Calcd for $C_{31}H_{50}O_8$ (M^+): 550.3509. Found: 550.3489.

(2*R*,3*R*,6*S*)-1-Benzoyloxy-6-[(2*R*,5*R*,6*S*)5-benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-3,6-bis(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)-heptane (16) A solution of benzoyl chloride (169 mg, 1.20 mmol) was added dropwise to a stirred solution of **15** (499 mg, 0.966 mmol) in CH_2Cl_2 (5 ml) and pyridine (7 ml) at 0 °C. After 4 h, the solution was diluted with CH_2Cl_2 (30 ml), washed with H_2O, 4 N HCl, 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (hexane–EtOAc, 2 : 1) to give the monobenzoate (371 mg, 64%) and the dibenzoate (218 mg, 32%) as colorless oils. The monobenzoate: $[\alpha]_D^{27}$ −2.6° (c=1.0). IR ν_{max} cm^{-1}: 3150—3550. 1710, 1610, 1580. ^{1}H-NMR δ: 0.88 (3H, t, J=7.5 Hz), 1.13 (3H, s), 1.24 (3H, d, J=7.0 Hz), 1.37—1.97 (10H, m), 2.44 (1H, br s), 2.64 (1H, br s), 3.42 (1H, dd, J=2.0, 11.5 Hz), 3.61 (1H, dt, J=10.5, 5.0 Hz), 3.69—3.75 (1H, m), 3.78 (3H, s), 4.11 (1H, q, J=7.0 Hz), 4.31 (1H, d, J=10.5 Hz), 4.39 (1H, d, J=10.5 Hz), 4.42 (1H, dd, J=5.5, 11.5 Hz), 4.54 (1H, d, J=11.0 Hz), 4.56 (1H, dd, J=5.0, 11.5 Hz), 4.74 (1H, d, J=11.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.20—7.57 (10H, m), 8.00—8.04 (2H, m). MS *m/z* (relative intensity): 602 ($M^+ - 18$, 0.2), 557 (0.2), 511 (0.8), 450 (0.7), 373 (10), 121 (100), 105 (12), 91 (32). Exact MS *m/z* Calcd for $C_{37}H_{46}O_7$ ($M^+ - 18$): 602.3246. Found: 602.3186.

tert-Butyldimethylsilyl chloride (263 mg, 0.996 mmol) was added to a stirred solution of the above monobenzoate (200 mg, 0.322 mmol) and Et_3N (302 mg, 3.0 mmol) in CH_2Cl_2 (5 ml) at 0 °C under argon. After 30 min, the solution was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (hexane–EtOAc, 10 : 1) to give the disilylate (**16**) as a colorless oil (273 mg, 100%), $[\alpha]_D^{27}$ +22° (c=1.04). IR ν_{max} cm^{-1}: 1715, 1610, 1580. ^{1}H-NMR δ: 0.00 (3H, s), 0.04 (3H, s), 0.56 (3H, s), 0.10 (3H, s), 0.84 (9H, s), 0.85 (3H, t, J=7.0 Hz), 0.87 (9H, s), 1.16 (3H, d, J=7.0 Hz), 1.21 (3H, s), 1.25—1.98 (10H, m), 3.45 (1H, dd, J=2.0, 11.5 Hz), 3.68—3.78 (2H, m), 3.77 (3H, s), 4.03 (1H, q, J=7.0 Hz), 4.32 (1H, d, J=11.0 Hz), 4.39 (1H, dd, J=7.5, 11.5 Hz), 4.42 (1H, d, J=11.0 Hz), 4.56 (1H, d, J=11.5 Hz), 4.61 (1H, d, J=11.5 Hz), 4.65 (1H, dd, J=2.5, 11.5 Hz), 6.80 (2H, d, J=8.5 Hz), 7.22—7.56 (10H, m), 8.02 (2H, dd, J=1.5, 7.5 Hz). MS *m/z* (relative intensity): 563 ($M^+ - 285$, 0.3), 483 (2.5), 431 (0.6), 323 (0.6), 211 (4), 171 (2.5), 121 (100), 91 (15). FD-MS *m/z*: 849 ($M^+ + 1$, 50), 848 (M^+, 32), 791 (100). Exact MS *m/z* Calcd for $C_{28}H_{39}O_5Si$ ($M^+ - 365$): 483.2569. Found: 483.2576.

(2*R*,3*R*,6*S*)-6-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-3,6-bis(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)heptan-1-ol (17) A solution of KOH (100 mg) in H_2O (2 ml) was added to a stirred solution of **16** (273 mg, 0.321 mmol) in MeOH (15 ml) at room temperature. The solution was stirred at 55 °C for 30 min, then concentrated *in vacuo*, diluted with CH_2Cl_2 (30 ml), washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane–EtOAc, 6 : 1) to give the alcohol (**17**) as a colorless oil (227 mg, 95%), $[\alpha]_D^{28}$ +25° (c=0.92). ^{1}H-NMR δ: 0.03 (3H, s), 0.04 (3H, s), 0.05 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 0.86 (3H, t, J=6.5 Hz), 0.87 (9H, s), 1.19 (3H, d, J=7.0 Hz), 1.21 (3H, s), 1.43—1.95 (10H, m), 2.16 (1H, dd, J=5.5, 7.0 Hz), 3.44 (1H, dd, J=2.0, 11.5 Hz), 3.51 (1H, dt, J=6.5, 4.5 Hz), 3.66 (1H, ddd, J=5.0, 7.0, 12.0 Hz), 3.77—3.85 (2H, m), 3.80 (3H, s), 4.05 (1H, q, J=7.5 Hz), 4.32 (1H, d, J=11.0 Hz), 4.42 (1H, d, J=11.0 Hz), 4.48 (1H, d, J=11.5 Hz), 4.57 (1H, d, J=11.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.23—7.43 (7H, m). MS *m/z* (relative intensity): 687 ($M^+ - 57$, 0.1), 579 (0.1), 555 (0.5), 447 (0.3), 431 (0.4), 323 (0.8), 211 (2), 171 (3), 121 (100), 91 (14), 73 (8). Exact MS *m/z* Calcd for $C_{26}H_{43}O_3Si$ ($M^+ - 313$): 431.2984. Found: 431.2994.

(2*S*,3*R*,6*R*)-6-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-3,6-bis(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)heptanal (18) Compound **17** (223 mg, 0.301 mmol) was oxidized with DMSO (128 μl, 1.80 mmol), $(COCl)_2$ (105 μl, 1.20 mmol), and Et_3N (0.503 ml, 3.61 mmol) in CH_2Cl_2 (9 ml) as described for **7** to give the aldehyde (**18**) as a

colorless oil (222 mg, 99%). IR ν_{max} cm^{-1}: 2850, 1730, 1685, 1615. ^{1}H-NMR δ: −0.02 (3H, s), 0.03 (3H, s), 0.04 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 0.86 (9H, s), 0.83—0.86 (3H, m), 1.18 (3H, s), 1.19 (3H, d, J=6.0 Hz), 1.36—1.97 (10H, m), 3.40 (1H, dd, J=2.0, 11.0 Hz), 3.72 (1H, dd, J=1.5, 4.5 Hz), 3.78 (3H, s), 3.86 (1H, ddd, J=4.5, 8.0, 13.0 Hz), 4.03 (1H, q, J=6.0 Hz), 4.31 (1H, d, J=11.0 Hz), 4.41 (1H, d, J=11.0 Hz), 4.45 (1H, d, J=11.5 Hz), 4.65 (1H, d, J=11.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.24—7.42 (7H, m), 9.75 (1H, d, J=1.5 Hz).

(3*R*,4*R*,7*S*)-7-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-4,7-bis(*tert*-butyldimethylsilyloxy)-2-(4-methoxybenzyloxy)oct-1-yne (8) A solution of **18** (215 mg, 0.289 mmol), triphenylphosphine (27 mg, 0.867 mmol) and bromodichloromethylphenylmercury (381 mg, 0.867 mmol) in benzene (8 ml) was stirred at 80 °C for 30 min under argon. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in *n*-hexane–EtOAc (7 : 1, 60 ml); insoluble materials were removed by filtration. The filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (hexane–EtOAc, 13 : 1) to give the dichloroolefin as a colorless oil (224 mg, 96%). $[\alpha]_D^{27.5}$ +9° (c=1.48). ^{1}H-NMR δ: −0.02 (3H, s), 0.01 (3H, s), 0.05 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 0.85 (3H, t, J=7.0 Hz), 0.86 (9H, s), 1.18 (3H, s), 1.19 (3H, d, J=6.5 Hz), 1.33—1.58 (7H, m), 1.64—1.73 (2H, m), 1.91—1.96 (1H, m), 3.39 (1H, dd, J=2.0, 11.5 Hz), 3.63—3.67 (1H, m), 3.79 (3H, s), 4.04 (1H, q, J=6.5 Hz), 4.08 (1H, dd, J=5.0, 9.0 Hz), 4.32 (2H, d, J=11.5 Hz), 4.42 (1H, d, J=11.5 Hz), 4.51 (1H, d, J=11.5 Hz), 5.92 (1H, d, J=9.0 Hz), 6.85 (2H, d, J=8.5 Hz), 7.23—7.43 (7H, m). MS m/z (relative intensity): 563 (M^+−245, 0.1), 523 (0.1), 431 (15), 323 (2), 211 (3), 171 (4), 121 (100), 91 (20), 73 (11). FD-MS m/z: 808 (M^+), 810, 812. Exact MS m/z Calcd for $C_{26}H_{43}O_3Si$ (M^+−377): 431.2984. Found: 431.3007.

A 1.6 M solution of *n*-BuLi in *n*-hexane (0.508 ml, 0.813 mmol) was added to a stirred solution of the above dichloroolefin (220 mg, 0.271 mmol) in THF (7 ml) at −78 °C under argon. After 30 min, the reaction mixture was allowed to warm to −20 °C, poured into saturated NH_4Cl with crushed ice, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (hexane–Et_2O, 10 : 1) to give the acetylene (**8**) as a colorless oil (169 mg, 84%). $[\alpha]_D^{28}$ −12° (c=1.00). IR ν_{max} cm^{-1}: 3300, 2115, 1615, 1585. ^{1}H-NMR δ: −0.04 (3H, s), 0.01 (3H, s), 0.05 (3H, s), 0.09 (3H, s), 0.84 (9H, s), 0.86 (9H, s), 0.84—0.89 (3H, m), 1.20 (3H, s), 1.21 (3H, d, J=6.0 Hz), 1.25—1.96 (10H, m), 2.39 (1H, d, J=2.0 Hz), 3.44 (1H, dd, J=2.0, 12.0 Hz), 3.66 (1H, ddd, J=3.5, 5.5, 9.0 Hz), 3.80 (3H, s), 3.98 (1H, dd, J=2.0, 5.5 Hz), 4.04 (1H, q, J=6.0 Hz), 4.32 (1H, d, J=11.0 Hz), 4.41 (1H, d, J=11.5 Hz), 4.42 (1H, d, J=11.0 Hz), 4.75 (1H, d, J=11.5 Hz), 6.85 (2H, d, J=9.0 Hz), 7.23—7.43 (7H, m). MS m/z (relative intensity): 519 (M^+−219, 0.1), 431 (0.7), 373 (1), 323 (1), 211 (3), 171 (3), 121 (100), 91 (16), 73 (10). Exact MS m/z Calcd for $C_{26}H_{43}O_3Si$ (M^+−307): 432.2984. Found: 431.2977.

(2*S*,5*R*,6*R*,10*R*,12*S*,13*S*,14*S*,15*R*)-2-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-2,5-bis(*tert*-butyldimethylsilyloxy)-13,15-isopropylidenedioxy-6-(4-methoxybenzyloxy)-10,12-dimethylheptadec-7-yn-9-one (19) A solution of **8** (169 mg, 0.229 mmol) in THF (1.3 ml) was treated with a 1.6 M *n*-BuLi solution (136 μl, 0.218 mmol) in *n*-hexane at −78 °C for 30 min under argon, and then a solution of **7** (59 mg, 0.218 mmol) in THF (1.0 ml) was added dropwise. The reaction mixture was allowed to warm gradually to 0 °C during 3 h, then quenched with saturated NH_4Cl, and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (Et_2O–hexane, 1 : 5) to give the hydroxyacetylene as a colorless oil (131 mg, 60%).

The hydroxyacetylene (105 mg, 0.104 mmol) was oxidized with $(COCl)_2$ (40 μl, 0.459 mmol), DMSO (49 μl, 0.689 mmol and Et_3N (190 μl, 1.36 mmol) at −78 °C as described for **7** to give **19** as a colorless oil (95 mg, 91%). $[\alpha]_D^{12.5}$ −17° (c=1.0). IR ν_{max} cm^{-1}: 2200, 1670, 1605, 1592. ^{1}H-NMR δ: −0.04 (3H, s), 0.02 (3H, s), 0.05 (3H, s), 0.08 (3H, s), 0.82—0.88 (21H, m), 0.92 (3H, t, J=7.5 Hz), 0.96 (3H, t, J=7.5 Hz), 1.17 (3H, d, J=7.0 Hz), 1.19 (3H, s), 1.22 (6H, d, J=7.0 Hz), 1.33 (3H, s), 1.37 (3H, s), 1.39—1.90 (17H, m), 2.21 (1H, ddd, J=5.0, 8.5, 14.0 Hz), 2.73—2.87 (1H, m), 3.38 (1H, dd, J=2.0, 11.0 Hz), 3.42 (1H, dd, J=2.0, 12.0 Hz), 3.63—3.74 (2H, m), 3.79 (3H, s), 4.03 (1H, q, J=7.0 Hz), 4.17 (1H, d, J=5.0 Hz), 4.31 (1H, d, J=11.0 Hz), 4.40 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.0 Hz), 4.75 (1H, d, J=11.5 Hz), 6.85 (2H, d, J=9.0 Hz), 7.23—7.41 (7H, m). MS m/z (relative intensity): 896 (M^+−110, 0.2), 783 (0.1), 697 (0.3), 583 (0.7), 431 (2), 323 (3), 211 (7), 171 (6), 121 (100), 91 (10), 73 (11). Exact MS m/z Calcd for $C_{26}H_{43}O_3Si$ (M^+−575): 431.2984. Found: 431.3006.

(2*S*,5*R*,6*R*)-2-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-8-[(2*R,3*R*,5*S*,6*S*)-6-[(1*S*,2*R*)-1-ethyl-2-hydroxybutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-6-(4-methoxybenzyloxy)oct-7-yne-2,5-diol (20)** A solution of **19** (95 mg, 0.094 mmol) and CSA (15 mg) in MeOH (8 ml) was stirred at room temperature for 4 h. Et_3N (0.1 ml) was added, and the reaction mixture was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2 (30 ml). This solution was washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo* to leave a colorless oil, which was used for the next reaction without further purification.

A 1.0 M *n*-Bu_4NF solution (566 μl) in THF was added to a stirred solution of the above oil (92 mg) in dioxane (0.6 ml). After 5 h at 70 °C, the reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on a short silica gel column (EtOAc–hexane, 2 : 3) to give **20** as a colorless oil (62 mg, 86%). ^{1}H-NMR δ: 0.82—1.04 (15H, m), 1.11 (3H, s), 1.24 (3H, d, J=7.0 Hz), 1.30—1.95 (19H, m), 2.49 (1H, br s), 2.68 (1H, br s), 2.88 (1H, br s), 3.40 (2.4H, s), 3.45 (0.6H, s), 3.46 (1H, dd, J=2.0, 13.0 Hz), 3.67—3.78 (3H, m), 3.80 (3H, s), 3.92 (0.8H, d, J=7.5 Hz), 4.03 (0.2H, d, J=7.0 Hz), 4.11 (1H, d, J=7.0 Hz), 4.31 (1H, d, J=11.0 Hz), 4.39 (1H, d, J=11.0 Hz), 4.42 (0.8H, d, J=11.5 Hz), 4.47 (0.2H, d, J=11.0 Hz), 4.74 (0.8H, d, J=11.5 Hz), 4.79 (0.2H, d, J=11.0 Hz), 6.86—6.91 (2H, m), 7.23—7.41 (7H, m). MS m/z (relative intensity): 702 (M^+−50, 0.2), 566 (0.6), 469 (0.9), 439 (1.5), 317 (3.5), 209 (13), 121 (100), 91 (28). Exact MS m/z Calcd for $C_{28}H_{39}O_4$ (M^+−313): 439.2851. Found: 439.2855.

(2*S*,5*R*,6*R*,7*Z*)-2-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-8-[(2*R,3*R*,5*S*,6*S*)-6-[(1*S*,2*R*)-1-ethyl-2-hydroxybutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-6-(4-methoxybenzyloxy)oct-7-ene-2,5-diol (21)** A solution of **20** (49 mg, 0.064 mmol) in MeOH (4.0 ml) was hydrogenated in the presence of Lindlar catalyst (45 mg) at ordinary temperature and pressure for 13 min. After removal of the catalyst, the filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (Et_2O–hexane, 1 : 2) to give two fractions. The first fraction gave the (2*R*) compound (**21a**) as a colorless oil (34.4 mg, 70%). Diacetate: ^{1}H-NMR δ: 0.76 (3H, d, J=6.0 Hz), 0.80—0.98 (12H, m), 1.21 (3H, s), 1.23 (3H, d, J=7.0 Hz), 1.25—1.99 (19H, m), 2.03 (3H, s), 2.04 (3H, s), 2.67 (1H, br s), 3.19 (3H, s), 3.36 (1H, dd, J=2.0, 11.5 Hz), 3.47 (1H, dd, J=1.0, 10.0 Hz), 3.79 (3H, s), 4.10 (1H, q, J=7.0 Hz), 4.30 (1H, d, J=10.5 Hz), 4.30 (1H, d, J=12.0 Hz), 4.38 (1H, d, J=10.5 Hz), 4.58 (1H, d, J=12.0 Hz), 4.72 (1H, dd, J=4.0, 9.5 Hz), 4.96—5.11 (2H, m), 5.42 (1H, dd, J=9.5, 12.5 Hz), 5.61 (1H, d, J=12.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.22—7.40 (7H, m). MS m/z (relative intensity): 534 (M^+−304, 0.8), 241 (18), 181 (16), 163 (11), 135 (13), 121 (100), 91 (19), 43 (18). Exact MS m/z Calcd for $C_{31}H_{50}O_7$ (M^+−304): 534.3559. Found: 534.3581.

The second fraction gave the (2*S*) compound (**21b**) as a colorless oil (8.6 mg, 17.5%). Diacetate: ^{1}H-NMR δ: 0.78—0.92 (12H, m), 0.98 (3H, t, J=7.5 Hz), 1.12 (3H, s), 1.23 (3H, d, J=7.0 Hz), 1.25—1.99 (19H, m), 2.03 (6H, s), 2.49 (1H, br s), 3.18 (3H, s), 3.36 (1H, dd, J=2.0, 11.5 Hz), 3.49 (1H, dd, J=1.0, 10.5 Hz), 3.78 (3H, s), 4.12 (1H, q, J=7.0 Hz), 4.30 (1H, d, J=10.5 Hz), 4.32 (1H, d, J=11.5 Hz), 4.38 (1H, d, J=10.5 Hz), 4.52 (1H, d, J=11.5 Hz), 4.91—5.01 (3H, m), 5.57 (1H, dd, J=8.5, 13.0 Hz), 5.86 (1H, d, J=13.0 Hz), 6.84 (2H, d, J=9.0 Hz), 7.24—7.37 (7H, m). MS m/z (relative intensity): 534 (M^+−304, 0.4), 241 (10), 181 (10), 121 (100), 91 (33), 43 (16).

17-*epi*-20-*O*-(4-Methoxybenzyl)-28-*O*-benzylsalinomycin (22a) A solution of **14a** (102 mg, 0.142 mmol) in THF (4.0 ml) was added dropwise to a stirred 1.06 M THF solution of $(C_6H_{11})_2NMgBr$ (0.6 ml), prepared from a 1.36 M THF solution of EtMgBr and dicyclohexylamine at 50 °C under argon, at −55 °C. After 15 min, a solution of **2** (32 mg, 0.132 mmol) in THF (2.0 ml) was added, and the reaction mixture was allowed to warm to −30 °C during 1.2 h. After addition of saturated NH_4Cl at −30 °C, the mixture was extracted with Et_2O. The extract was washed with 0.5 N HCl and brine, and evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3 then MeOH–CH_2Cl_2, 1 : 10) to give recovered **14a** (55 mg, 54%), **22a** as a colorless viscous oil (40 mg, 32%), and recovered **2** (18 mg, 56%). Compound **22a**: $[\alpha]_D^{25}$ −66° (c=0.36). IR ν_{max} cm^{-1}: 3500, 1710, 1700, 1612, 1585. ^{1}H-NMR δ: 0.75 (3H, d, J=6.5 Hz), 0.81—0.88 (18H, m), 0.93 (3H, t, J=7.5 Hz), 1.20 (3H, d, J=6.5 Hz), 1.26 (3H, s), 1.28—1.91 (23H, m), 2.16—2.17 (1H, m), 2.78—3.02 (4H, m), 3.43 (1H, dd, J=2.5, 11.5 Hz), 3.60 (1H, d, J=5.0 Hz), 3.66 (1H, dd, J=1.5, 10.0 Hz), 3.80 (3H, s), 3.86 (1H, d, J=11.0 Hz), 3.98—4.06 (3H, m), 4.28 (1H, d, J=11.0 Hz), 4.40 (1H, d, J=11.0 Hz), 4.61 (1H, d, J=12.0 Hz), 4.73 (1H, d, J=12.0 Hz), 5.62 (1H, d, J=10.0 Hz), 5.95 (1H, dd, J=5.0, 10.0 Hz), 6.85 (2H, d, J=9.0 Hz), 7.22—7.39 (7H, m). MS m/z (relative intensity): 700 (M^+−260, 0.4), 682 (0.5), 576 (2), 575 (2), 471 (2), 437 (11), 386 (2), 329 (4), 265 (6), 165 (19), 121 (100), 91 (48), 57 (26). Exact m/z Calcd for $C_{28}H_{37}O_4$ (M^+−523): 437.2694. Found: 437.2675.

21-*epi*-20-*O*-(4-Methoxybenzyl)-28-*O*-benzylsalinomycin (22b) Compound **14b** (36 mg, 0.05 mmol) and **2** (18 mg, 0.074 mmol) were condensed in the presence of a 1.03 M THF solution of $(C_6H_{11})_2NMgBr$ (0.397 ml) as described for **22a** to give recovered **14b** (24 mg, 67%), **22b** (10 mg, 21%), and recovered **2** (13 mg, 72%). Compound **22b**: $[\alpha]_D^{16.5}$ −78° (c=0.4). IR ν_{max} cm^{-1}: 3500, 1705, 1615, 1590. ^{1}H-NMR δ: 0.68 (6H, t, J=7.0 Hz), 0.76—0.84 (12H, m), 0.84 (3H, t, J=7.5 Hz), 0.85 (3H, t, J=7.0 Hz), 1.18 (3H, s), 1.21 (3H, d, J=7.0 Hz), 1.28—2.09 (22H, m), 2.17—2.31 (2H, m), 2.70—3.74 (1H, m), 2.82 (1H, dt, J=4.0, 11.0 Hz), 2.97 (1H, ddd, J=7.0, 10.0, 13.5 Hz), 3.23 (1H, br s), 3.55 (1H, dd, J=1.5, 9.5 Hz), 3.34 (1H, dd, J=3.0, 11.0 Hz), 3.73 (3H, s), 3.76 (1H, dd, J=1.5, 9.0 Hz), 1.96 (1H, dd, J=5.0, 11.0 Hz), 3.97 (1H, dd, J=1.0, 9.5 Hz), 4.02 (1H, q, J=7.0 Hz), 4.25 (1H, d, J=10.5 Hz), 4.25 (1H, dd, J=2.0, 2.5 Hz), 4.32 (1H, d, J=10.5 Hz), 4.53 (1H, d, J=11.0 Hz), 4.65 (1H, d, J=11.0 Hz), 5.64 (1H, dd, J=2.0, 9.5 Hz), 5.94 (1H, dd, J=2.5, 9.5 Hz), 6.80 (2H, d, J=9.0 Hz), 7.15—7.34 (7H, m). MS m/z (relative intensity): 700 (M^+ −260, 0.2), 682 (0.4), 576 (2), 575 (2), 471 (1), 437 (3), 386 (14), 265 (10), 165 (10), 121 (100), 91 (37), 57 (28). Exact MS m/z Calcd for $C_{28}H_{37}O_4$ (M^+ −523): 437.2694. Found: 437.2687.

(2*R*,3*R*,6*S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-6-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-2-(4-methoxybenzyloxy)heptan-1-ol (25) A solution of **17** (209 mg, 0.28 mmol) in EtOH (1.0 ml) was hydrogenated in the presence of Raney Ni (W-2) (4.0 ml) at 60 °C for 16 h. After removal of the catalyst, the filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (EtOAc–hexane 1 : 4) to give an diol as a colorless oil (174 mg, 95%). $[\alpha]_D^{15.5}$ +18° (c=1.0). ^{1}H-NMR δ: 0.03 (3H, s), 0.04 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.86 (9H, s), 0.88 (9H, s), 0.91 (3H, t, J=7.5 Hz), 1.17 (3H, d, J=6.5 Hz), 1.20 (3H, s), 1.25—1.75 (10H, m), 2.14 (1H, t, J=5.0 Hz), 2.64 (1H, br s), 3.37 (1H, dd, J=2.0, 11.0 Hz), 3.51 (1H, dt, J=7.0, 5.0 Hz), 3.60—3.78 (4H, m), 3.81 (3H, s), 4.49 (1H, d, J=11.5 Hz), 4.56 (1H, d, J=11.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz). MS m/z (relative intensity): 597 (M^+ −57, 0.1), 465 (0.4), 341 (0.6), 209 (2), 171 (3), 143 (2), 121 (100), 73 (7). Exact MS m/z Calcd for $C_{31}H_{57}O_7Si$ (M^+ −57): 597.3646. Found: 597.3665.

A solution of the above diol (140 mg, 0.214 mmol), 2,2-dimethoxypropane (2.0 ml), and CSA (20 mg) in benzene (5 ml) was stirred at room temperature for 15 min. After neutralization with Et_3N, the reaction mixture was evaporated *in vacuo* and chromatographed on a short silica gel column (EtOAc–hexane, 1 : 3) to give the mono-2-methoxyisopropyl ether (143 mg, 93%).

A solution of the above ether (143 mg, 0.197 mmol) in DMF (2.6 ml) was added dropwise to a stirred suspension of NaH (28 mg, 1.18 mmol) in DMF (0.6 ml) under argon. After evolution of H_2 had ceased, the solution was treated with MPM chloride (166 μl, 1.18 mmol) at 50 °C for 2 h. Et_2NH (0.8 ml) was added, and the stirring was continued at room temperature for 1 h. The reaction mixture was poured into cold H_2O, and extracted with Et_2O. The extract was washed with 1 N HCl, 10% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was treated with CSA (20 mg) in MeOH (8 ml) at room temperature for 15 min. After neutralization with Et_3N, the reaction mixture was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to give **25** as a colorless oil (104 mg, 68%) and recovered diol (20 mg, 16%). Compound **25**: $[\alpha]_D^{17}$ +29° (c=1.04). ^{1}H-NMR δ: 0.03 (3H, s), 0.04 (3H, s), 0.05 (3H, s), 0.09 (3H, s), 0.84 (9H, s), 0.86 (3H, t, J=7.0 Hz), 0.88 (9H, s), 1.18 (3H, d, J=7.0 Hz), 1.21 (3H, s), 1.43—1.95 (10H, m), 2.16 (1H, t, J=6.0 Hz), 3.43 (1H, dd, J=2.0, 10.5 Hz), 3.51 (1H, dt, J=7.0, 4.5 Hz), 3.66 (1H, ddd, J=5.0, 6.5, 11.5 Hz), 3.74—3.85 (2H, m), 3.80 (6H, s), 4.03 (1H, q, J=7.0 Hz), 4.24 (1H, d, J=10.5 Hz), 4.34 (1H, d, J=10.5 Hz), 4.48 (1H, d, J=11.5 Hz), 4.57 (1H, d, J=11.5 Hz), 6.86 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.0 Hz), 7.24 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.0 Hz). MS m/z (relative intensity): 585 (M^+ −189, 0.1), 521 (0.3), 385 (0.5), 291 (0.6), 241 (1), 121 (100), 73 (5). Exact MS m/z Calcd for $C_{21}H_{41}O_4Si$ (M^+ −389): 385.2776. Found: 385.2766.

(2*S*,3*R*,6*S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-6-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-2-(4-methoxybenzyloxy)heptanal (26) Compound **25** (62 mg, 0.080 mmol) was oxidized with $(COCl)_2$ (28 μl, 0.321 mmol), DMSO (32 μl, 0.451 mmol), and Et_3N (125 μl, 0.897 mmol) as described for **7** to give **26** as a colorless oil (62 mg, 100%). IR ν_{max} cm^{-1}: 2850, 1730, 1615, 1585. ^{1}H-NMR δ: −0.02 (3H, s), 0.03 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 0.86 (9H, s), 0.83—0.86 (3H, m), 1.18 (3H, d, J=6.5 Hz), 1.18 (3H, s), 1.25—1.95 (10H, m), 3.39 (1H, dd, J=2.0, 11.5 Hz), 3.72 (1H, dd, J=1.5, 4.5 Hz), 4.78 (3H, s), 3.79 (3H, s), 3.85—3.93 (1H, m), 4.01 (1H, q, J=6.5 Hz), 4.23 (1H, d, J=10.5 Hz), 4.33 (1H, d, J=10.5 Hz), 4.46 (1H, d, J=11.5 Hz), 4.64 (1H, d, J=11.5 Hz), 6.85 (2H, d, J=8.5 Hz), 6.86 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.31 (2H, d, J=8.5 Hz), 9.75 (1H, d, J=1.5 Hz).

(3*R*,4*R*,7*S*)-4,7-Bis(*tert*-butyldimethylsilyloxy)-7-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-3-(4-methoxybenzyloxy)oct-1-yne (9) A solution of **26** (59 mg, 0.076 mmol) in CH_2Cl_2 (3.0 ml) was added to a stirred solution of Ph_3P (260 mg, 0.991 mmol) and CBr_4 (159 mg, 0.479 mmol) in CH_2Cl_2 (4.5 ml) at −78 °C under argon. After 20 min, saturated $NaHCO_3$ was added. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), evaporated *in vacuo*, and chromatographed on a silica gel column (EtOAc–hexane, 1 : 5) to give the dibromoolefin as a colorless oil (62 mg, 88%). $[\alpha]_D^{21}$ +9° (c=2.48). ^{1}H-NMR δ: 0.00 (3H, s), 0.02 (3H, s), 0.05 (3H, s), 0.09 (3H, s), 0.85 (9H, s), 0.86 (3H, t, J=6.5 Hz), 0.87 (9H, s), 1.18 (3H, s), 1.18 (3H, t, J=6.5 Hz), 1.36—1.76 (9H, m), 1.88—1.93 (1H, m), 3.34 (1H, dd, J=2.0, 11.0 Hz), 3.63—3.68 (1H, m), 3.78 (3H, s), 3.79 (3H, s), 3.97 (1H, dd, J=5.0, 9.0 Hz), 4.03 (1H, q, J=6.5 Hz), 4.24 (1H, d, J=10.5 Hz), 4.33 (1H, d, J=10.5 Hz), 4.34 (1H, d, J=10.5), 4.53 (1H, d, J=10.5 Hz), 6.47 (1H, d, J=9.0 Hz), 6.85 (2H, d, J=9.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.32 (2H, d, J=9.0 Hz). MS m/z (relative intensity): 613 (M^+ −316, 0.2), 533 (0.2), 461 (0.4), 329 (0.7), 291 (1.5), 241 (0.8), 171 (1.5), 121 (100), 73 (7). Exact MS m/z Calcd for $C_{27}H_{45}O_4Si$ (M^+ −468): 461.3090. Found: 461.3105. Found: 461.3105.

A solution of the above dibromoolefin (61 mg, 0.066 mmol) in THF (3.0 ml) was treated with lithium diisopropyl amide (LDA), prepared from iso-Pr_2NH (185 μl, 1.32 mmol) and *n*-BuLi (1.6 M solution in *n*-hexane, 815 μl) in THF (6.5 ml) at −78 °C under argon, at −70 °C for 40 min. After addition of 10% $NaHCO_3$ at −40 °C, the reaction mixture was extracted with Et_2O. The extract was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 10) to give **9** as a colorless oil (42 mg, 83%). $[\alpha]_D^{15.5}$ −9° (c=1.66). IR ν_{max} cm^{-1}: 3290, 1615, 1885. ^{1}H-NMR δ: −0.04 (3H, s), 0.01 (3H, s), 0.05 (3H, s), 0.10 (3H, s), 0.84 (9H, s), 0.86 (9H, s), 0.84—0.89 (3H, m), 1.20 (3H, s), 1.20 (3H, d, J=7.0 Hz), 1.25—1.96 (10H, m), 2.39 (1H, d, J=2.0 Hz), 3.44 (1H, dd, J=2.0, 11.0 Hz), 3.66 (1H, ddd, J=3.0, 5.5, 9.0 Hz), 3.79 (3H, s), 3.80 (3H, s), 3.98 (1H, dd, J=2.0, 5.5 Hz), 4.03 (1H, q, J=7.0 Hz), 4.24 (1H, d, J=10.5 Hz), 4.35 (1H, d, J=10.5 Hz), 4.41 (1H, d, J=11.5 Hz), 4.76 (1H, d, J=11.5 Hz), 6.85 (4H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz). MS m/z (relative intensity): 515 (M^+ −253, 0.1), 453 (0.6), 379 (0.3), 373 (0.6), 291 (0.9), 241 (1.2), 121 (100), 73 (5.5). Exact MS m/z Calcd for $C_{28}H_{41}O_3Si$ (M^+ −315): 453.2827. Found: 453.2847.

(2*S*,5*R*,6*R*,10*R*,12*S*,13*S*,14*S*,15*R*)-2,6-Bis(*tert*-butyldimethylsilyloxy)-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-13,15-isopropylidenedioxy-10,12-dimethylheptadec-7-yn-9-one (27) A solution of **9** (40 mg, 0.052 mmol) in Et_2O (0.2 ml) was treated with a 1.6 M *n*-BuLi solution (32 μl, 0.512 mmol) in *n*-hexane at −78 °C for 40 min under argon, and then a solution of **7** (8 mg, 0.0296 mmol) in Et_2O (0.6 ml) was added dropwise. The reaction mixture was allowed to warm to −15 °C during 2 h, and quenched with saturated NH_4Cl. Work-up as described for **19** gave the hydroxyacetylene as a colorless oil (23 mg, 56%).

The hydroxyacetylene (25 mg, 0.024 mmol) was oxidized with $(COCl)_2$ (10 μl, 0.115 mmol), DMSO (11 μl, 0.156 mmol) and Et_3N (43 μl, 0.312 mmol) in CH_2Cl_2 (2.0 ml) as described for **18** to give **27** as a colorless, viscous oil (23 mg, 92%). $[\alpha]_D^{22}$ −18° (c=0.88). IR ν_{max} cm^{-1}: 2210, 1685, 1619, 1590. ^{1}H-NMR δ: −0.04 (3H, s), 0.02 (3H, s), 0.05 (3H, s), 0.08 (3H, s), 0.82—0.89 (21H, m), 0.91 (3H, t, J=7.5 Hz), 0.97 (3H, t, J=7.5 Hz), 1.16 (3H, d, J=6.5 Hz), 1.19 (3H, s), 1.22 (6H, d, J=7.0 Hz), 1.33 (3H, s), 1.36 (3H, s), 1.30—1.90 (17H, m), 2.21 (1H, ddd, J=5.0, 8.5, 14.0 Hz), 2.76—2.84 (1H, m), 3.34 (1H, dd, J=2.0, 10.0 Hz), 3.42 (1H, dd, J=2.0, 10.0 Hz), 3.63—3.73 (2H, m), 3.79 (6H, s), 4.01 (1H, q, J=7.0 Hz), 4.17 (1H, d, J=5.0 Hz), 4.23 (1H, d, J=10.5 Hz), 4.32 (1H, d, J=10.5 Hz), 4.40 (1H, d, J=11.5 Hz), 4.75 (1H, d, J=11.5 Hz), 6.85 (4H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz). MS m/z (relative intensity): 697 (M^+ −339, 0.1), 583 (0.3), 461 (0.4), 291 (1), 241 (3), 171 (2.5), 121 (100), 73 (5). Exact MS m/z Calcd for $C_{27}H_{45}OSi$ (M^+ −575): 461.3090. Found: 461.3075.

(2*S*,5*R*,6*R*)-8-[(2*R,3*R*,5*S*,6*S*)-6-[(1*S*,2*R*)-1-Ethyl-2-hydroxybutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-6-(4-methoxybenzyloxy)oct-7-yne-2,5-diol (28)** Compound **27** (21 mg, 0.0202 mmol) was treated with CSA (5.0 mg) in MeOH (3.0 ml) at room temperature for 110 min. The resulting oil was treated with a 1.0 M *n*-Bu_4NF solution (0.1 ml) in THF as described for **20** to give **28** as a colorless oil (16 mg, 100%). ^{1}H-NMR δ: 0.82—1.04 (15H, m), 1.11 (3H, s), 1.23 (3H, d, J=7.0 Hz), 1.30—1.94 (19H, m), 2.60 (1H, br s), 2.68 (1H, br s), 2.88 (1H,

br s), 3.40 (2H, s), 3.46 (1H, dd, J=2.0, 13.0 Hz), 3.45 (1H, s), 3.67—3.73 (3H, m), 3.77 (3H, s), 3.80 (3H, s), 3.93 (0.67H, d, J=7.5 Hz), 4.04 (0.33H, d, J=7.0 Hz), 4.08 (1H, q, J=7.0 Hz), 4.23 (1H, d, J=10.5 Hz), 4.32 (1H, d, J=10.5 Hz), 4.43 (0.67H, d, J=11.0 Hz), 4.47 (0.33H, d, J=11.0 Hz), 4.74 (0.67H, d, J=11.0 Hz), 4.79 (0.33H, d, J=11.0 Hz), 6.86 (2H, d, J=8.5 Hz), 6.88 (2H, d, J=9.0 Hz), 7.25—7.33 (4H, m). MS m/z (relative intensity): 614 (M^+-168, 0.1), 476 (0.5), 439 (0.6), 227 (2), 209 (2), 121 (100). Exact MS m/z Calcd for $C_{28}H_{39}O_4$ (M^+-343): 439.2851. Found: 439.2854.

(2*S*,5*R*,6*R*,7*Z*)-8-[(2*R,3*R*,5*S*,6*S*)-6-[(1*S*,2*R*)-1-Ethyl-2-hydroxybutyl]-2-methoxy-3,5-dimethyltetrahydropyran-2-yl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-6-(4-methoxybenzyloxy)oct-7-ene-2,5-diol (29)** Compound **28** (6.8 mg, 8.68 μmol) was hydrogenated in the presence of Lindlar catalyst (5 mg) in MeOH (1.0 ml) as described for **21** to give the (2*R*) compound (**29a**) (4.8 mg, 71%) and the (2*S*) compound (**29b**) (1.2 mg, 18%). Diacetate of **29a**: ^{1}H-NMR δ: 0.76 (3H, d, J=6.0 Hz), 0.80—0.98 (12H, m), 1.12 (3H, s), 1.22 (3H, d, J=6.5 Hz), 1.25—1.99 (20H, m), 2.03 (3H, s), 2.05 (3H, s), 3.19 (3H, s), 3.36 (1H, dd, J=2.0, 10.5 Hz), 3.47 (1H, dd, J=1.0, 9.5 Hz), 3.79 (6H, s), 4.08 (1H, q, J=6.5 Hz), 4.22 (1H, d, J=12.0 Hz), 4.30 (2H, d, J=12.0 Hz), 4.59 (1H, d, J=12.0 Hz), 4.72 (1H, dd, J=4.0, 9.5 Hz), 4.96—5.10 (2H, m), 5.43 (1H, dd, J=9.5, 13.0 Hz), 5.61 (1H, d, J=13.0 Hz), 6.86 (2H, d, J=8.5 Hz), 6.89 (2H, d, J=9.0 Hz), 7.23 (2H, d, J=9.0 Hz), 7.30 (2H, d, J=8.5 Hz). Diacetate of **29b**: ^{1}H-NMR δ: 0.84—0.96 (15H, m), 1.11 (3H, s), 1.21 (3H, d, J=7.0 Hz), 1.25—1.99 (20H, m), 2.04 (3H, s), 2.05 (3H, s), 3.35 (1H, dd, J=2.0, 11.5 Hz), 3.45 (3H, s), 3.53 (1H, dd, J=3.5, 8.0 Hz), 3.78 (6H, s), 4.08 (1H, q, J=7.0 Hz), 4.22 (1H, d, J=10.5 Hz), 4.30 (1H, d, J=10.5 Hz), 4.16 (1H, d, J=12.0 Hz), 4.53 (1H, d, J=12.0 Hz), 4.77 (1H, dd, J=5.0, 10.0 Hz), 5.00—5.05 (2H, m), 5.23 (1H, dd, J=10.0, 12.0 Hz), 6.23 (1H, d, J=12.0 Hz), 6.83 (2H, d, J=8.5 Hz), 6.88 (2H, d, J=8.5), 7.22 (2H, d, J=8.5 Hz), 7.30 (2H, d, J=8.5 Hz).

(2*S*,5*S,7*S**,9*S*,10*S*,12*R*,13*Z*,15*R*)-9-[(*R*)-1-Ethyl-2-oxobutyl]-2-[(2*R*,5*R*,6*S*)-5-ethyl-5-(4-methoxybenzyloxy)-6-methyltetrahydropyran-2-yl]-15-(4-methoxybenzyloxy)-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene (30)** Compound **29** (7.0 mg, 9.13 μmol) was oxidized with $(COCl)_2$ (15 μl, 0.172 mmol), DMSO (18 μl, 0.253 mmol) and Et_3N (73 μl, 0.524 mmol) to give the ketone (8.0 mg), which was treated with CSA (5 mg) in CH_2Cl_2 (4.0 ml) as described for **14** to give the (5*S*,7*S*) compound (**30a**) (1.2 mg, 18%) and the (5*R*,7*R*) compound (**30b**) (2.4 mg, 36%). **30a**: $[\alpha]_D^{17.5}$ −60° (c=0.44). IR ν_{max} cm^{-1}: 1710, 1700, 1615, 1585. ^{1}H-NMR δ: 0.81—0.90 (12H, m), 1.00 (3H, t, J=7.5 Hz), 1.18 (3H, d, J=7.0 Hz), 1.37 (3H, s), 1.40—1.89 (14H, m), 2.15—2.23 (2H, m), 2.42 (1H, dq, J=18.0, 7.0 Hz), 2.52 (1H, dt, J=10.5, 3.0 Hz), 2.59 (1H, dq, J=18.0, 7.0 Hz), 3.48 (1H, dd, J=2.0, 11.5 Hz), 3.55 (1H, d, J=5.0 Hz), 3.79 (3H, s), 3.80 (3H, s), 3.77—3.81 (1H, m), 4.06 (1H, q, J=7.0 Hz), 4.22 (1H, d, J=10.5 Hz), 4.34 (1H, d, J=10.5 Hz), 4.62 (1H, d, J=12.0 Hz), 4.70 (1H, d, J=12.0 Hz), 5.60 (1H, d, J=10.5 Hz), 5.93 (1H, dd, J=5.0, 10.5 Hz), 6.84 (2H, d, J=8.5 Hz), 6.86 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.30 (2H, d, J=8.5 Hz). **30b**: $[\alpha]_D^{17.5}$ −79° (c=0.4). IR ν_{max} cm^{-1}: 1710, 1610, 1585. ^{1}H-NMR δ: 0.78 (3H, d, J=6.5 Hz), 0.81 (3H, t, J=7.5 Hz), 0.87 (3H, d, J=6.5 Hz), 0.90 (3H, t, J=7.5 Hz), 1.02 (3H, t, J=7.0 Hz), 1.24 (3H, s), 1.30 (3H, d, J=6.5 Hz), 1.35—2.30 (18H, m), 2.38 (1H, dq, J=18.0, 7.5 Hz), 2.51 (1H, dt, J=10.5, 3.0 Hz), 2.79 (1H, dq, J=18.0, 7.5 Hz), 3.72 (1H, dd, J=2.0, 11.0 Hz), 3.80 (6H, s), 3.93 (1H, dd, J=3.0, 10.0 Hz), 4.14 (1H, q, J=6.5 Hz), 4.17 (1H, dd, J=2.0, 3.0 Hz), 4.28 (1H, d, J=10.5 Hz), 4.40 (1H, d, J=10.5 Hz), 4.52 (1H, d, J=11.0 Hz), 4.71 (1H, d, J=11.0 Hz), 5.69 (1H, dd, J=3.0, 10.0 Hz), 5.98 (1H, dd, J=2.0, 10.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.31 (2H, d, J=9.0 Hz), 7.34 (2H, d, J=9.0 Hz).

17-*epi*-20,28-Bis-*O*-(4-methoxybenzyl)salinomycin (31a) Compound **30a** (43 mg, 0.0574 mmol) and **2** (22 mg, 0.0905 mmol) in THF (5.0 ml) were condensed in the presence of $(C_6H_{11})_2$NMgBr (1.04 M in THF, 0.51 μl) as described for **22a** to give recovered **30a** (33 mg, 77%) and **2** (17 mg, 77%) and **31a** (13 mg, 23%). $[\alpha]_D^{25}$ −81° (c=0.52). IR ν_{max} cm^{-1}: 3500, 1710, 1615, 1588. ^{1}H-NMR δ: 0.75 (3H, d, J=7.0 Hz), 0.84—0.92 (18H, m), 0.94 (3H, d, J=6.5 Hz), 1.19 (3H, d, J=7.0 Hz), 1.42 (3H, s), 1.28—1.89 (23H, m), 2.13—2.20 (1H, m), 2.71—2.81 (2H, m), 2.95 (1H, dt, J=4.5, 11.0 Hz), 3.02 (1H, ddd, J=7.5, 10.5, 15.5 Hz), 3.41 (1H, dd, J=2.5, 12.0 Hz), 3.62 (1H, d, J=5.0 Hz), 3.66 (1H, dd, J=2.0, 10.0 Hz), 3.79 (3H, s), 3.80 (3H, s), 3.85 (1H, dd, J=1.0, 10.0 Hz), 3.97—4.08 (3H, m), 4.20 (1H, d, J=10.5 Hz), 4.33 (1H, d, J=10.5 Hz), 4.62 (1H, d, J=12.0 Hz), 4.72 (1H, d, J=12.0 Hz), 5.62 (1H, d, J=10.0 Hz), 5.95 (1H, dd, J=5.0, 10.0 Hz), 6.84 (2H, d, J=8.5 Hz), 6.85 (2H, d, J=8.5 Hz), 7.29 (4H, d, J=8.5 Hz). MS m/z (relative intensity): 730 (M^+-260, 0.1), 576 (0.3), 467 (5.5), 386 (0.5), 265 (1.5), 165 (5), 121 (100), 57 (10). Exact MS m/z Calcd for $C_{29}H_{39}O_5$ (M^+-523): 467.2800. Found: 467.2813.

21-*epi*-20,28-Bis-*O*-(4-methoxybenzyl)salinomycin (31b) Compound **30b** (43 mg, 0.574 mmol) and **2** (40 mg, 0.165 mmol) in THF (3.0 ml) were condensed with $(C_6H_{11})_2$NMgBr (1.06 M in THF, 0.374 ml) as described for **22a** to give recovered **30b** (16 mg, 37%) and **2** (25 mg, 62.5%) and **31b** (20 mg, 35%), $[\alpha]_D^{29}$ −77° (c=0.7). IR ν_{max} cm^{-1}: 3500, 1710, 1615, 1585. ^{1}H-NMR δ: 0.75 (6H, t, J=7.5 Hz), 0.84—0.96 (18H, m), 1.25 (3H, s), 1.26 (3H, d, J=8.5 Hz), 1.21—2.37 (24H, m), 2.72—2.78 (1H, m), 2.88 (1H, dt, J=4.0, 11.0 Hz), 3.05 (1H, ddd, J=8.0, 11.0, 15.0 Hz), 3.31 (1H, br s), 3.61 (1H, dd, J=1.5, 9.5 Hz), 3.70 (1H, dd, J=3.5, 11.0 Hz), 3.79 (3H, s), 3.80 (3H, s), 3.85 (1H, dd, J=1.0, 11.0 Hz), 3.94—4.16 (3H, m), 4.25 (1H, d, J=10.5 Hz), 4.31 (1H, d, J=10.5 Hz), 4.38 (1H, dd, J=2.0, 2.5 Hz), 4.61 (1H, d, J=11.5 Hz), 4.74 (1H, d, J=11.5 Hz), 5.71 (1H, dd, J=2.0, 10.0 Hz), 6.00 (1H, dd, J=2.5, 10.0 Hz), 6.84 (2H, d, J=8.5 Hz), 6.87 (2H, d, J=8.5 Hz), 7.30 (4H, d, J=8.5 Hz). MS m/z (relative intensity): 648 (M^+-342, 0.1), 576 (0.6), 474 (1.5), 467 (2.5), 386 (2.5), 265 (4.5), 165 (8), 121 (100), 57 (13). Exact MS m/z Calcd for $C_{29}H_{39}O_5$ (M^+-523): 467.2800. Found: 467.2791.

Salinomycin (**1**): a) A 0.05 M phosphate buffer (pH 6.86) (40 μl) and DDQ (42 mg, 0.185 mmol) were added to a stirred solution of **22a** (8.5 mg, 8.8 μmol) in CH_2Cl_2 (0.4 ml) at room temperature. After 1.5 h, the reaction mixture was quenched with saturated $NaHCO_3$, and extracted with Et_2O. The extract was washed with 0.5 N HCl and brine, and evaporated *in vacuo*, and the residue was subjected to a silica gel TLC (EtOAc–hexane, 1 : 1) to give **1** (1.0 mg, 15%) and a mixture of 28-*O*-benzylsalinomycin and 17-*epi*-28-*O*-benzylsalinomycin (3.7 mg, 44%).

b) Compound **22b** (9.0 mg, 9.4 μmol) in CH_2Cl_2 (0.8 ml) was treated with DDQ (27 mg, 0.119 mmol) and the pH 6.86 buffer (0.2 ml) as described above to give **1** (1.1 mg, 16%) and a mixture of 28-*O*-benzylsalinomycin and 21-*epi*-28-*O*-benzylsalinomycin (3.6 mg, 40%).

c) A solution of **31a** (5.8 mg, 5.86 μmol) in CH_2Cl_2 (0.4 ml) and H_2O (0.04 ml) was stirred in the presence of DDQ (5.7 mg, 25 μmol) at room temperature for 10 min. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with Et_2O. The extract was evaporated *in vacuo*, and the residue was applied to a silica gel column (EtOAc–hexane, 1 : 1) to give 17-episalinomycin as a colorless, viscous oil (4.3 mg, 95%), which (4.0 mg, 5.18 μmol) was dissolved in CH_2Cl_2 (3 ml), and stirred with molecular sieves 3 Å (10 mg) and trifluoroacetic acid (TFA) (3 μl) at room temperature for 20 min. The reaction mixture was neutralized with Et_3N, diluted with CH_2Cl_2, washed with 10% $NaHCO_3$, H_2O, 1 N HCl and brine, and evaporated *in vacuo*, and the residue was applied to a silica gel column (EtOAc–hexane, 2 : 1) to give **1** as a colorless, amorphous solid (2.8 mg, 72%), mp 110.5—111.5 °C (lit.[17] 112.5—113.5 °C). $[\alpha]_D^{20}$ −61° (c=0.11 in MeOH) (lit.[17] $[\alpha]_D^{25}$ −63° (EtOH). IR ν_{max} cm^{-1}: 3450, 1710. ^{1}H-NMR δ: 0.71 (3H, t, J=7.0 Hz), 0.73 (3H, d, J=7.0 Hz), 0.78 (3H, d, J=7.5 Hz), 0.81 (3H, d, J=7.0 Hz), 0.89 (3H, t, J=7.5 Hz), 0.91 (3H, d, J=6.5 Hz), 0.91 (3H, d, J=7.5 Hz), 0.96 (3H, t, J=7.5 Hz), 1.24 (3H, d, J=7.0 Hz), 1.48 (3H, s), 1.33—2.46 (25H, m), 2.60—2.95 (3H, m), 3.64 (1H, dd, J=2.0, 10.5 Hz), 3.83 (1H, q, J=7.0 Hz), 3.87—4.03 (4H, m), 4.17 (1H, dd, J=2.0, 10.0 Hz), 5.98)1H, d, J=10.5 Hz), 6.03 (1H, d, J=10.5 Hz). MS m/z (relative intensity): 750 (M^+, 0.9), 746 (1.1), 743 (0.9), 732 (18), 617 (13), 559 (15), 530 (22), 508 (31), 490 (11), 431 (8), 347 (11), 343 (15), 57 (100), 43 (86).

d) Compound **31b** (10 mg, 10.1 μmol) in CH_2Cl_2 (0.4 ml) and H_2O (0.04 ml) was treated with DDQ (9.2 mg, 40.3 μmol) at room temperature for 10 min to give 21-episalinomycin as a colorless, viscous oil (6.6 mg, 85%), a solution of which (4.8 mg, 6.21 μmol) in CH_2Cl_2 (3.0 ml) was treated with TFA (3 μl) and molecular sieves 3Å (15 mg) as described above to give **1** as a colorless, amorphous solid (2.8 mg, 61%). $[\alpha]_D^{16}$ −64° (c=0.11 in MeOH).

References and Notes

1) Chiral Synthesis of Polyketide-Derived Natural Products. XXV. For part XXIV, see: K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1705 (1989).
2) Preliminry reports of this work: *a*) K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, **28**, 3253 (1987); *b*) K. Horita, Y. Oikawa, S. Nagato and O. Yonemitsu, *ibid.*, **29**, 5143 (1988).
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6) Unless otherwise noted, the numberings are bsed on that of salino-

mycin (**1**).
7) Under acidic conditions, the configurations at the C17 and C21 acetal positions were always changeable in the ratio reflecting the thermodynamical stability of each isomer, which was probably determined by the combination of three effects (anomeric effect, dipole–dipole interaction among oxygen atoms, and hydrogen bonding). Similarly, the stability of each isomer of **6**, **30** and **1** seemed to vary with change in the combination of the three effects reflecting delicate structural changes.[5] *Cf.* R. Baker, M. A. Brimble and J. A. Robinson, *Tetrahedron Lett.*, **26**, 2115 (1985).
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13) The structures of **14a** and **30a** were easily confirmed by the conversion of **6** derived from natural salinomycin (**1**) into **14a** and **30a**. The structure of **14b** was estimated as follows: DDQ oxidation of **14b** followed by monoacetylation gave a stereoisomer (i) of **6**, whose NMR spectrum showed a W-shaped coupling between H_a and H_b ($J=2.0$ Hz). Among four possible compounds, i was neither **6** nor ii, also derived from natural **1**,[11] and according to a model inspection the angle between H_a and H_b in iii was about 90°. Therefore, the structure of i must be correct as shown. The structure of **30b** was estimated in the same way.

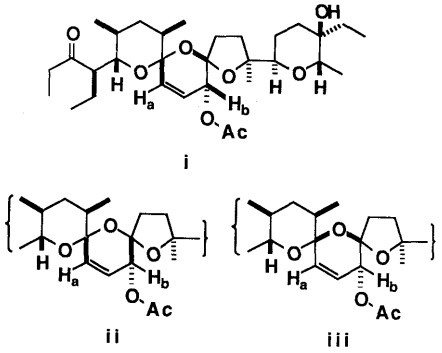

Chart 6

14) Y. Oikawa, K. Horita and O. Yonemitsu, *Tetrahedron Lett.*, **26**, 1541 (1985).
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