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STEREOSELECTIVE SYNTHESIS OF ERYTHRONOLIDE A BY EXTREMELY EFFICIENT LACTONIZATION BASED ON CONFORMATIONAL ADJUSTMENT AND HIGH ACTIVATION OF SECO-ACID[1]

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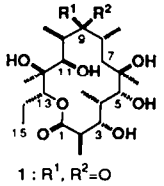
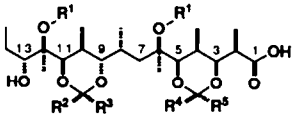
Abstract: C1-C5 sulfone (**11**) and C7-C15 aldehyde (**20**), synthesized stereoselectively from D-glucose, were coupled, and the C5 and C6 chiral centers were constructed taking advantage of the MPM (4-methoxybenzyl) type protecting group to give the seco-acid (**7**), which has 9,11-and 3,5-diols protected as the mesityl- and DMP (3,4-dimethoxyphenyl) acetals, respectively. When Yamaguchi's mixed anhydride of **7** was treated with a high concentration of DMAP at room temperature, a very rapid cyclization occurred and the 14-membered lactone (**8**) was isolated in almost quantitative yield. Deprotection of **8** readily gave 9-dihydroerythronolide A (**2**), which was converted to the title compound (**1**).

As part of our study directed toward the stereoselective synthesis of complex natural products such as a series of representative macrolide and polyether antibiotics, we recently reported the stereoselective synthesis of erythronolide A (**1**)[2] via macrolactonization of the seco-acid (**3**). Thus **3** synthesized starting from D-glucose failed to cyclize to the corresponding lactone by the Corey[2b,3] and Yamaguchi methods[4] using a high dilution technique, the latter method when augmented by a high concentration of DMAP, however, gave the lactone in poor yield (27%).[2f,g] This, together with the evidence shown by Woodward et al.,[5] indicates that unsuitably protected seco-acid derivatives are very difficult to cyclize even though they contain all the correct configurations. Recently, Stork and Rychnovsky clearly demonstrated that the 9, 11-acetaldehyde acetal (**4**) readily cyclized to the corresponding lactone, whereas the isomeric acetal (**5**) and the acetone acetal (**6**) failed to cyclize because only **4** has a favorable conformation of the C8-C11

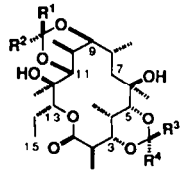
Fig 1.



1 : R^1, R^2=O
2 : R^1=OH, R^2=H



3 : R^1=MOM, R^2=R^3=R^4=R^5=Me
4 : R^1=R^3=H, R^2=R^4=R^5=Me
5 : R^1=R^2=H, R^3=R^4=R^5=Me
6 : R^1=H, R^2=R^3=R^4=R^5=Me
7 : R^1=R^3=R^5=H, R^2=Mes, R^4=DMP
Mes : 2,4,6-trimethylphenyl
DMP : 3,4-dimethoxyphenl



8 : R^1=R^3=H, R^2=Mes, R^4=DMP
9 : R^1=R^2=R^3=R^4=Me

Dedicated to Professor David Ollis on the occasion of his 65th birthday.

portion.[2e] Judging from these results, both a proper conformation and strong activation are crucial to achieving an efficient cyclization of seco-acid derivatives, and we decided to synthesize 7 for its promise as a cyclization substrate. The seco-acid (7) and its expected cyclization product (8) were first derived from natural erythromycin A and their conformations examined by comparing the coupling constants (J) (Table 1).[6] The one notable difference in the $J_{7,8}$ values

Table 1. Vicinal proton coupling constants (J;Hz) of the seco-acids (7, 6) and the corresponding lactones (8, 9)

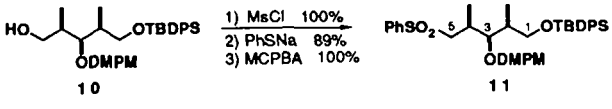
J_{H-H}	7	8	6	9
2-3	10.0	11.0	9.5	10.5
3-4	1.5	1.0	1.5	1.0
4-5	1.5	1.0	2.0	1.5
7-8	7.0;0	11.5;0	5.0; ND	11.0;0
8-9	11.5	11.0	6.5	11.0
9-10	0	0	2.5	0
10-11	2.0	1.5	4.0	1.5
13-14	10.5;1.5	11.5;2.0	11.0;1.5	11.0;2.5
14-15	7.5	7.5	7.5	7.5

revealed that for the lactonization of 7 into 8 only the rotation of the C7-C8 bond (the least substituted bond) appears necessary. On the other hand, the J values in the C7-C11 portion of 6 greatly differ from those of the corresponding lactone (9), and hence difficult conformational changes at the highly crowded positions are required for the cyclization of 6 into 9. We report here the stereoselective synthesis of the title compound through the extremely efficient macrolactonization of 7.[9]

Synthesis of C1-C5 (11) and C6-C15 Fragments (20)

The alcohol (10)[10] was converted to the sulfone (11) of C1-C5 fragment in excellent yield via three conventional reactions.

Scheme 1



10 11

The triol (12)[10] was converted to three types of 6-membered acetals: the mesitaldehyde acetal (13), the benzaldehyde acetal (16), and the acetone acetal (18) in the usual way, and their conformations were examined by NMR spectroscopy (coupling constants and NOE data) (Table 2) to reveal that the cyclic acetal of 13 exists in a chair conformation very similar to those of 7 and 8, whereas the acetals of 16 and 18 have unfavorable twist-boat conformations.[11] Treatment of

12 with mesitaldehyde dimethyl acetal directly gave the desired acetal (13), which was readily

Scheme 2

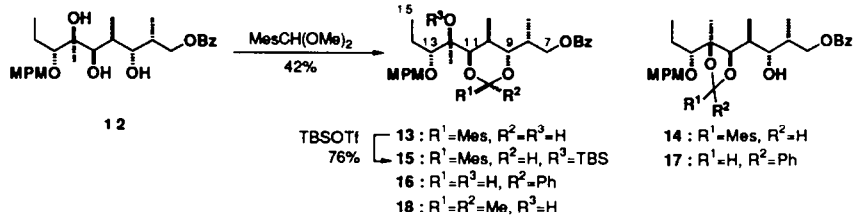
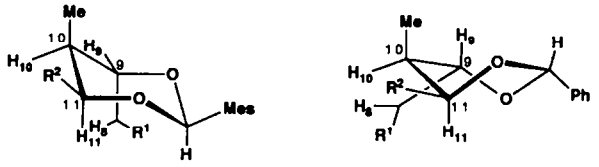


Fig 2.



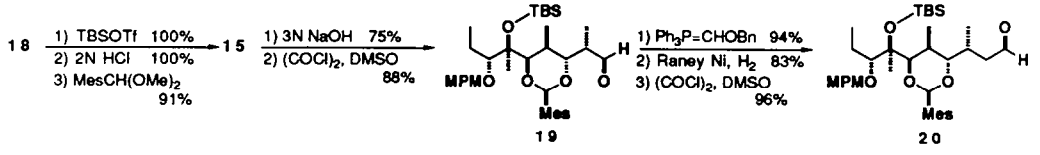
13 16

Table 2. Vicinal proton coupling constants (J;Hz) of the C7-C15 segments (13, 16, 18)

J_{H-H}	13	16	18
8-9	11.0	(4.5	(6.0
9-10	0	4.0)	4.0)
10-11	2.0	3.0	4.0

converted to 15. However, on the acetalization 13 was usually accompanied by the thermodynamically more stable 5-membered acetal (14). Therefore, 15 was synthesized from 18 without separation of isomers in excellent yield via three conventional reactions.[12] Alkaline hydrolysis of 15 followed by the Swern oxidation gave the aldehyde (19), which was converted to the homologous aldehyde (20) of C6-C15 fragment via the Wittig reaction, hydrogenation with Raney nickel,[13] and the Swern oxidation.

Scheme 3



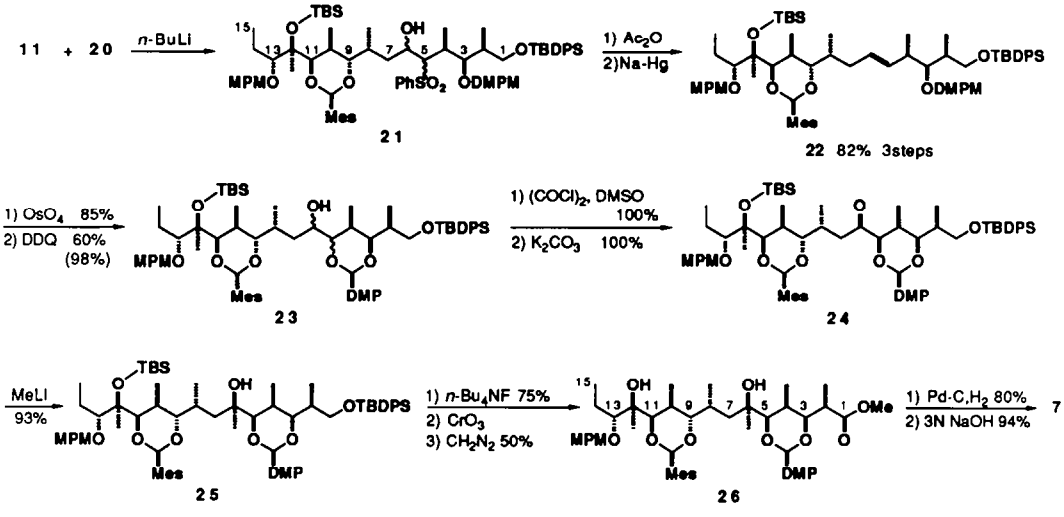
19 20

Synthesis of the Seco-Acid (7)

The anion of the sulfone (11) formed with n-butyllithium was condensed with the aldehyde (20) to give a mixture of hydroxysulfones (21), which was desulfonated[15] to give the 5,6-E-olefin

(**22**) in high yield. From the olefin the final C5 and C6 chiral centers were constructed highly stereoselectively taking advantage of the MPM (4-methoxybenzyl) type protecting groups[14,16] as follows. Oxidation of **22** with osmium tetroxide gave a mixture of diols (a:b=1.6:1), which was treated with DDQ to give the acetal (**23**)[16] still as a mixture with respect to the C5 and C6 positions, though having the same configuration (*R*) at the DMP (3,4-dimethoxyphenyl) attached position. A diastereoisomeric mixture (at C5) of 6-ketones produced by the Swern oxidation of **23** was treated with potassium carbonate at room temperature to primarily give the thermodynamically more stable isomer (**24**) with the desired C5 configuration (d.e. > 95%). The final chiral center at the C6 position was constructed by the Cram nonchelation addition of methyllithium at -78°C in THF to give **25** with 21:1 selectivity, although in ether the selectivity dropped to 2.4:1. For easy isolation of the pure seco-acid (**7**), **25** was once converted to the ester (**26**) by three conventional reactions, treatment with a fluoride anion, the Jones oxidation, and esterification with diazomethane. Finally, the MPM protecting group and the methyl ester were removed to give the seco-acid (**7**).

Scheme 4



Lactonization of the Seco-Acid (7)

In previous papers,[2f,g] we reported that the efficiency of the cyclization of **3** by the Yamaguchi method[4] was strongly dependent on the concentration of DMAP. When **7** was subjected to lactonization by the Corey method[2a,b,3] using a high dilution technique (Table 3, entry 1), the expected lactone (**8**) was obtained only in 6% yield, whereas in the presence of a highconcentration of DMAP (25 mM) the yield of **8** increased to 60% (entry 2). Yamaguchi's mixed anhydride[4] was much more reactive and gave **8** in excellent yield. However, since **7** was a substrate controlled to be conformationally favorable in advance, the high dilution method was thought unnecessary. Actually, when a benzene solution of the Corey active ester (10 mM) and DMAP (20 mM) was allowed to stand at room temperature for 10 days, **8** was isolated in 72% yield

(entry 5). At 80°C, the yield of **8** was improved to 92% (entry 6). Triethylamine used in place of DMAP was not effective (entry 4). The Keck method[2e,17] was more effective and gave **8** in 85% yield within 8 h at room temperature. Finally, the Yamaguchi method[4] gave the surprising result that when DMAP (2 equiv., 20 mM) was added all at once to a 10 mM xylene solution of the Yamaguchi mixed anhydride of **7** at room temperature, lactonization proceeded very rapidly and was completed within 8 min (checked by TLC) to give the lactone (**8**) in almost quantitative yield.

This extremely efficient means of lactonization can be explained in terms of reflection of both the suitable conformation and the high activation of the seco-acid (**7**). On the basis of the NOESY data (cross peaks from C6-Me to C4-Me and C8-Me), combined with the above *J* values, the conformation of **7** is distinct from that of **8** only at either side of the least substituted C7-

Scheme 5

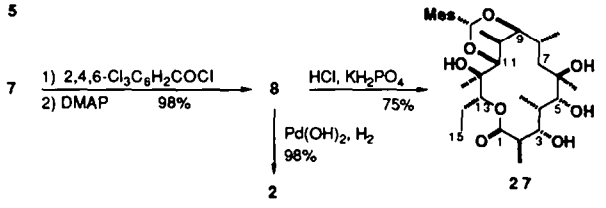


Table 3. Macrolactonization of the seco-acid (**7**) into the lactone (**8**)

Entry	Method	Base (mM)	Solvent	Temperature	Time	**8** Yield(%)
1	A[a]	---	toluene	reflux	72 h	6
2	A[a]	DMAP(25)	toluene	reflux	72 h	60
3	B[a]	DMAP(25)	toluene	reflux	72 h	92
4	A[b]	Et_3N(20)	benzene	room temp.	10 d	0[c]
5	A[b]	DMAP(20)	benzene	room temp.	10 d	74
6	A[b]	DMAP(20)	benzene	80°C	5 d	92
7	C[b]	DMAP(20)	CH_2Cl_2	room temp.	8 h	85
8	B[b]	DMAP(20)	xylene	room temp.	10 m	98

A: Mukaiyama-Corey's method.[2a,b,3]
B: Yamaguchi's method.[2f,g,4]
C: Keck's method.[2e,14]
[a] An active ester or anhydride (final concentration : 1.0 mM) was added very slowly to a refluxing toluene with or without DMAP over a period of 48 h.
[b] A solution of an active ester or anhydride (10 mM) and a base (20 mM) was allowed to stand at room temperature or 80°C.
[c] 96% of **7** was recovered.

methylene group. Hence, the cyclization of **7** into **8** probably took place quite smoothly via the rotation of the least hindered two bonds, the C7-C8 and the C6-C7 bonds. The activation effect of DMAP may be due to the formation of a more reactive acylpyridinium salt as earlier proposed by Steglich et al..[18,19] The difference in reactivity between the Yamaguchi method and the others may be explained in terms of the difference in rate and efficiency of the formation of the acylpyridinium salt.

Finally, both the protecting groups were smoothly removed by catalytic hydrogenation to give 9-dihydroerythronolide A (**2**), which was readily converted to the title compound (**1**).[2d] In contrast, the 3,5-O-DMP acetal was selectively hydrolyzed under buffered conditions to give **27**, which is a suitable substrate for glycosidation into erythromycin A.

Experimental

(2S,3R,4S)-3-(3,4-Dimethoxybenzyloxy)-1-[(1,1-dimethylethyl)diphenylsilyloxy]-2,4-(dimethyl-5-phenylsulfonylpentane (**11**). Et_3N (0.935 ml, 6.71 mmol) and methanesulfonyl chloride (0.173 ml, 2.24 mmol) were added to a stirred ice-cold solution of **10** (0.958 mg, 1.79 mmol) in CH_2Cl_2 (14 ml) under argon. The reaction mixture was stirred for 14 h at room temperature, then quenched with MeOH (1.0 ml), mixed with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*, then the residue was chromatographed on a silica gel column (hexane-EtOAc 4:1) to give *(2S,3R,4R)-3-(3,4-dimethoxybenzyloxy)-1-[(1,1-dimethylethyl)diphenylsilyloxy]-2,4-dimethyl-5-methylsulfonyloxypentane* as a colorless oil (1.05 g, 96%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.98 (3H, d, *J*=6.5Hz), 1.01 (3H, d, *J*=6.5Hz), 1.08 (9H, s), 1.95 (1H, dddq, *J*=5.0, 5.5, 7.0, 6.5Hz), 2.19 (1H, ddquint, *J*=5.0, 6.0, 6.5Hz), 2.94 (3H, s), 3.55 (1H, dd, *J*=5.5, 10.5Hz), 3.63 (1H, dd, *J*=7.0, 10.5Hz), 3.67 (1H, t, *J*=5.0Hz), 3.86 (3H, s), 3.87 (3H, s), 4.05 (1H, dd, *J*=6.0, 9.5Hz), 4.19 (1H, dd, *J*=6.5, 9.5Hz), 4.48 (1H, d, *J*=11.0Hz), 4.56 (1H, d, *J*=11.0Hz), 6.80-6.87 (3H, m), 7.34-7.47 (6H, m), 7.64-7.68 (4H, m). IR ν (neat) cm^{-1}: 3060, 2930, 2850, 1590, 1510, 1355, 1260, 1180, 1115, 960, 815, 740, 700. DI-MS *m/z*(%): 614 (M^+, 0.1), 463 (0.1), 462 (0.5), 461 (1.2), 151 (100). HR-MS: Calcd for $C_{28}H_{33}O_4Si$ [M^+-(MsOH,*t*Bu)]: 461.2148. Found: 461.2155. *Anal.* Calcd for $C_{33}H_{46}O_7SSi$: C, 64.46; H, 7.54; S, 5.21. Found: C, 64.45; H, 7.55; S, 5.14. $[\alpha]_D^{18}$-2.4° (c=1.244, $CHCl_3$).

Thiophenol (0.552 ml, 5.37 mmol) was added dropwise to a stirred suspension of 60% oil-dispersion of NaH (71.5mg, 1.79mmol) at room temperature under argon. After evolution of H_2 ceased, a solution of the above methanesulfonate (1.10g, 1.79 mmol) in THF (5.0 ml) and DMF (12.5 ml) were added. The reaction mixture was stirred for 45 min, then diluted with ether, washed several times with small amounts of H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column (hexane-EtOAc 10:1) to give *(2S,3R,4S)-3-(3,4-dimethoxybenzyloxy)-1-[(1,1-dimethylethyl)diphenylsilyloxy]-2,4-dimethyl-5-phenylthiopentane* as a colorless oil (1.002g, 89%). ^{1}H-NMR (100MHz, $CDCl_3$) δ: 0.93 (3H, d, *J*=7.0Hz), 1.06 (9H, s), 1.07 (3H, d, *J*=6.5Hz), 1.79-2.22 (2H, m), 2.77 (1H, dd, *J*=7.5, 12.5Hz), 3.03 (1H, dd, *J*=6.0, 12.5Hz), 3.50 (1H, dd, *J*=5.5, 11.5Hz), 3.58 (1H, dd, *J*=7.0, 11.5Hz), 3.70 (1H, t, *J*=5.0Hz), 3.83 (3H, s), 3.80 (3H, s), 4.51 (2H, s), 6.81 (3H, s), 7.08-7.46 (11H, m), 7.59-7.66 (4H, m). IR ν (neat) cm^{-1}: 3060, 2930, 2850, 1590, 1515, 1270, 1115, 1035, 825, 740, 700. DI-MS *m/z*(%): 628 (M^+, 0.3), 571 (0.3), 407 (0.3), 406 (0.7), 405

(2.0), 151 (100). HR-MS Calcd for $C_{34}H_{39}O_4SSi$ (M^+-*t*Bu): 571.2338. Found: 571.2355. *Anal.* Calcd for $C_{38}H_{48}O_4SSi$: C, 72.57; H, 7.69; S, 5.10. Found: C, 72.65; H, 7.73; S, 5.27. $[\alpha]_D^{18}$+1.51° (c=0.784, $CHCl_3$).

m-Chloroperbenzoic acid (0.875 g, 4.31 mmol) was added portionwise to a stirred ice-cold solution of the above thio ether (1.129 g, 1.795 mmol) in CH_2Cl_2 (40 ml) at room temperature. After 45 min, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated, then the residue was chromatographed on a silica gel column (hexane-EtOAc 4:1) to give **11** as a colorless oil (1.187 g, 100%). ^{1}H-NMR (100MHz, $CDCl_3$) δ: 0.79 (3H, d, *J*=7.0Hz), 1.04 (9H, s), 1.07 (3H, d, *J*=7.0Hz), 1.64-2.05 (1H, m), 2.28-2.68 (1H, m), 2.88 (1H, dd, *J*=9.0, 14.0Hz), 3.30 (1H, dd, *J*=3.0, 14.0Hz), 3.36-3.68 (3H, m), 3.81 (3H, s), 3.86 (3H, s), 4.36 (2H, s), 6.71 (3H, s), 7.32-7.68 (13H, m), 7.81-7.91 (2H, m). IR ν (neat) cm^{-1}: 3060, 2930, 2850, 1590, 1515, 1460, 1305, 1265, 1150, 1110, 1085, 1030, 735, 700. DI-MS *m/z*(%): 660 (M^+, 0.1), 606 (0.5), 604 (3.6), 603 (8.3), 151 (100). *Anal.* Calcd for $C_{38}H_{48}O_6SSi$: C, 69.06; H, 7.32; S, 4.85. Found: C, 68.95; H, 7.54; S, 4.58. $[\alpha]_D^{17.5}$+13.0° (c=1.39, $CHCl_3$).

(2R,3S,4S,5R,6R,7R)-1-Benzoyloxy-6-[(1,1-dimethylethyl)dimethylsilyloxy]-7-(4-methoxybenzyloxy)-2,4,6-trimethyl-3,5-(2,4,6-trimethylbenzylidenedioxy)nonane (**15**) 2,6-Di-*t*-butylpyridine (0.219 ml, 0.975 mmol) and *t*-butyldimethylsilyl triflate (0.15 ml, 0.65 mmol) were added dropwise to a stirred solution of the alcohol (**18**) (6.9 mg, 13 mol) in CH_2Cl_2 (1.0 ml). After 48 h, the reaction mixture was quenched with MeOH, and evaporated *in vacuo*, then the residue was chromatographed on a silica gel column (hexane-EtOAc 20:1) to give *(2R,3S,4S,5R,6R,7R)-1-benzoyloxy-6-[(1,1-dimethylethyl)dimethylsilyloxy]-3,5-isopropylidenedioxy-7-(4-methoxybenzyloxy)-2,4,6-trimethylnonane* as a colorless oil (8.5 mg, 100%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.00 (3H, d, *J*=7.0Hz), 1.02 (3H, t, *J*=7.5Hz), 1.03 (3H, d, *J*=7.0Hz), 1.30 (3H, s), 1.31 (3H, s), 1.35 (3H, s), 1.54-1.78 (2H, m), 1.80-1.93 (1H, m), 1.97-2.12 (1H, m), 3.30 (1H, dd, *J*=3.0, 9.0Hz), 3.44 (1H, dd, *J*=2.5, 7.5Hz), 3.76 (1H, d, *J*=4.5Hz), 3.80 (3H, s), 4.24 (1H, dd, *J*=6.5, 10.5Hz), 4.27 (1H, dd, *J*=7.5, 10.5Hz), 4.52 (1H, d, *J*=10.5Hz), 4.61 (1H, d, *J*=10.5Hz), 6.86 (2H, d, *J*=9.0Hz), 7.28 (2H, d, *J*=9.0Hz), 7.45 (2H, brt, *J*=7.5Hz), 7.58 (1H, t, *J*=7.5Hz), 8.04 (2H, d, *J*=7.5Hz). IR ν (neat) cm^{-1}: 3050, 2950, 1720, 1615, 1510, 1460, 1380, 1270, 1245, 1185, 1000, 835, 775, 710. DI-MS *m/z*(%): 513 [M^+-(*t*Bu,MeCOMe), 0.4], 449 (0.8), 391 (9.6), 121 (100), 105 (20). HR-MS Calcd for $C_{25}H_{41}O_5Si$ (M^+-MPMOCHEt): 449.2723. Found: 449.2716.

2N HCl (0.2 ml) was added to a stirred solution of the above silyl ether (4.8 mg, 7.6 μmol) in MeOH (1.4 ml) at room temperature. After 10 min, the solution was poured into ether, then the ether layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (hexane-EtOAc 5:1) to give *(2R,3S,4S,5R,6R,7R)-1-benzoyloxy-6-[(1,1-dimethylethyl)dimethylsilyloxy]-7-(4-methoxybenzyloxy)-2,4,6-trimethylnonane-3,5-diol* as a colorless oil (4.5 mg, 100%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.14 (3H, s), 0.17 (3H, s), 0.89 (9H, s), 0.97 (3H, d, *J*=6.5Hz), 1.01 (3H, d, *J*=7.0Hz), 1.06 (3H, t, *J*=7.5Hz), 1.30 (3H, s), 1.52-1.63 (1H, m), 1.71-1.85 (1H, m), 1.84-1.96 (1H, m), 2.11-2.23 (1H, m), 2.56 (1H, d, *J*=6.0Hz), 3.20 (1H, d, *J*=6.5Hz), 3.44 (1H, dd, *J*=2.5, 8.5Hz), 3.53-3.63 (1H, m), 3.79 (3H, s), 4.01 (1H, dd, *J*=1.5, 6.5Hz), 4.15 (1H, dd, *J*=6.0, 11.0Hz), 4.43 (1H, dd, *J*=7.5, 11.0Hz), 4.55 (2H, s), 6.86 (2H, d, *J*=8.5Hz), 7.25 (2H, d, *J*=8.5Hz), 7.40-7.47 (2H, m), 7.52-7.60 (2H, m), 8.01-8.07 (2H, m). IR ν (neat) cm^{-1}: 3580, 3530, 2950, 1720, 1620, 1515, 1465, 1280, 1250, 1115, 1005, 840, 780, 715. DI-MS *m/z*(%): 393 (6.6), 277 (10), 201 (8.0), 200 (10),

121 (100), 105 (28). HR-MS Calcd for $C_{21}H_{33}O_5Si$ [M^+-(MPMOCHEt,MeH)]: 393.2097. Found: 393.2107. $[\alpha]_D^{23}$-7.3° (c=0.18, $CHCl_3$).

Mesitaldehyde dimethyl acetal (28 μl, 0.15 mmol) and camphorsulfonic acid (0.7 mg, 3.0 μmol) was added to a stirred solution of the above diol (4.5 mg, 7.6 μmol) at room temperature under argon. After 2 h, the reaction mixture was quenched with Et_3N, and evaporated to leave an oil, which was chromatographed on a silica gel column (hexane-EtOAc 10:1) to give **15** as a colorless oil (5.0 mg, 91%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.07 (3H, s), 0.79 (9H, s), 1.02 (3H, t, *J*=7.5Hz), 1.21 (3H, d, *J*=6.5Hz), 1.35 (3H, s), 1.38 (3H, d, *J*=7.0Hz), 1.52-1.65 (1H, m), 1.65-1.80 (1H, m), 1.82-1.88 (1H, m), 2.24 (3H, s), 2.52 (6H, s), 2.77-2.90 (1H, m), 3.18 (1H, dd, *J*=2.5, 8.5Hz), 3.64 (1H, d, *J*=11.0Hz), 3.74 (3H, s), 4.00 (1H, d, *J*=2.0Hz), 4.19 (1H, dd, *J*=5.5, 11.5Hz), 4.35 (1H, dd, *J*=3.0, 11.5Hz), 4.54 (1H, d, *J*=11.0Hz), 4.57 (1H, d, *J*=11.0Hz), 6.06 (1H, s), 6.78-6.83 (4H, m), 7.22-7.26 (2H, m), 7.43-7.48 (2H, m), 7.55-7.61 (1H, m), 8.02-8.05 (2H, m). IR ν (neat) cm^{-1}: 2940, 2870, 1720, 1620, 1515, 1275, 1255, 1110, 835, 780, 715. DI-MS *m/z*(%): 718 (M^+, 0.1), 661 (0.5), 539 (3.9), 513 (0.9), 421 (1.2), 391 (3.5), 121 (100). HR-MS Calcd for $C_{32}H_{47}O_5Si$ (M^+ -MPMOCHEt): 539.3192. Found: 539.3208. *Anal.* Calcd for $C_{43}H_{62}O_7Si$: C, 71.82; H, 8.69. Found: C, 71.57; H, 8.69.

(2S,3R,4S,5R,6R,7R)-6-[(1,1-Dimethylethyl)dimethylsilyloxy]-7-(4-methoxybenzyloxy)-2,4,6-trimethyl-3,5-(2,4,6-trimethylbenzylidenedioxy)nonanal (**19**). 3N NaOH (0.4 ml) was added to a stirred solution of **15** (23.3 mg, 23.4 μmol) in EtOH (2.0 ml) at room temperature. After 4 h, CH_2Cl_2 was added, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (hexane-EtOAc 5:1) to give *(2R,3S,4S,5R,6R,7R)-6-[(1,1-dimethylethyl)dimethylsilyloxy]-7-(4-methoxybenzyloxy)-2,4,6-trimethyl-3,5-(2,4,6-trimethylbenzylidenedioxy)nonan-1-ol* as a colorless oil (15 mg, 75%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.08 (3H, s), 0.79 (9H, s), 1.03 (3H, t, *J*=7.5Hz), 1.07 (3H, d, *J*=7.0Hz), 1.30 (1H, t, *J*=5.0Hz), 1.36 (3H, s), 1.39 (3H, d, *J*=7.0Hz), 1.59 (1H, ddq, *J*=3.0, 14.5, 7.5Hz), 1.70 (1H, ddq, *J*=9.0, 14.5, 7.5Hz), 1.95 (1H, dq, *J*=2.0, 7.0Hz), 2.24 (3H, s), 2.50-2.64 (1H, m), 2.51 (6H, s), 3.21 (1H, dd, *J*=3.0, 9.0Hz), 3.49 (1H, d, *J*=11.0Hz), 3.49-3.51 (2H, m), 3.81 (3H, s), 4.03 (1H, d, *J*=2.0Hz), 4.58 (1H, d, *J*=10.5Hz), 4.64 (1H, d, *J*=10.5Hz), 6.07 (1H, s), 6.79 (2H, s), 6.88 (2H, d, *J*=9.0Hz), 7.29 (2H, d, *J*=9.0Hz). IR ν (neat) cm^{-1}: 3450, 2930, 1615, 1510, 1460, 1245, 1085, 1035, 835, 775. DI-MS *m/z*(%): 557 (M^+-*t*Bu, 0.1), 437 (0.2), 436 (0.6), 435 (1.6), 199 (1.8), 121 (100). HR-MS Calcd for $C_{33}H_{49}O_6Si$ (M^+-*t*Bu): 557.3299. Found: 557.3298. $[\alpha]_D^{18}$-41.9° (c=1.308, $CHCl_3$).

DMSO (13.3 μl, 187 μmol) was added dropwise to a stirred solution of oxalyl chloride (11.0 μl, 125 μmol) in CH_2Cl_2 (0.5 ml) at -80°C, and after 10 min, a solution of the above alcohol (7.1 mg, 11.5 μmol) in CH_2Cl_2 (0.75 ml) was added dropwise. The reaction mixture was stirred for 15 min, then Et_3N (70 μl, 501 μmol) was added, and after 10 min, the mixture was allowed to warm to -30°C, kept at this temperature for 1 h, and then poured into ether to stop the reaction. The ether solution was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated, then the residue was chromatographed on a silica gel column (hexane-EtOAc 20:1 ~ 10:1) to give **19** as a colorless oil (6.2 mg, 88%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.18 (3H, s), -0.07 (3H, s), 0.07 (9H, s), 1.02 (3H, t, *J*=7.5Hz), 1.24 (3H, d, *J*=7.0Hz), 1.35 (3H, s), 1.38 (3H, d, *J*=7.0Hz), 1.45-1.83 (3H, m), 2.24 (3H, s), 2.49 (6H, s), 3.11 (1H, dd, *J*=2.5, 9.0Hz), 3.39 (1H, ddq, *J*=3.0, 11.5, 7.0Hz), 3.81 (3H, s), 3.85 (1H, d, *J*=11.5Hz), 3.97 (1H, d, *J*=2.0Hz), 4.52 (1H, d, *J*=10.5Hz), 4.58 (1H, d, *J*=10.5Hz), 5.97 (1H, s), 6.80 (2H, s), 6.86 (2H, d,

J=8.5Hz), 7.25 (2H, d, *J*=8.5Hz), 9.57 (1H, d, *J*=3.0Hz). IR ν (neat) cm^{-1}: 2920, 2840, 1720, 1615, 1585, 1510, 1455, 1375, 1300, 1245, 1155, 1090, 1035, 990, 830, 770, 730. DI-MS *m/z*(%): 555 (M^+-*t*Bu, 0.6), 434 (0.8), 433 (2.7), 159 (12), 121 (100), 73 (12). HR-MS Calcd for $C_{32}H_{47}O_6Si$ (M^+-*t*Bu): 555.3141. Found: 555.3132. *Anal.* Calcd for $C_{36}H_{56}O_6Si$: C, 70.54; H, 9.20. Found: C, 70.42: H, 9.36.

(3R,4S,5S,6R,7R,8R)-7-[(1,1-Dimethylethyl)dimethylsilyloxy]-8-(4-methoxybenzyloxy)-3,5,7-trimethyl-4,6-(2,4,6-trimethylbenzylidenedioxy)decanal (**20**). A 1.6 M solution of *n*-butyllithium in hexane (2.27 ml, 3.63 mmol) was slowly added dropwise to a stirred suspension of benzyloxymethyltriphenylphosphonium chloride (1.726 g, 4.12 mmol) in THF at -78°C under argon. After 15 min, a solution of **19** (1.01 g, 1.64 mmol) in THF (18 ml) was added, then the reaction mixture was allowed to warm to room temperature during 1 h. After 10 h, the reaction mixture was quenched with H_2O, and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column (hexane-EtoAc 30:1) to give *(1EZ,3R,4S,5S,6R,7R,8R)-1-benzyloxy-7-[(1,1-dimethylethyl)dimethylsilyloxy]-8-(4-methoxybenzyloxy)-3,5,7-trimethyl-4,6-(2,4,6-trimethylbenzylidenedioxy)dec-1-ene* as a colorless oil (1.113 g, 94%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.17 (3H, s), -0.08 (3H, s), 0.79 (9H, s), 0.94 (0.6H, t, *J*=7.5Hz), 1.03 (2.4H, t, *J*=7.5Hz), 1.09 (0.6H, d, *J*=6.5Hz), 1.12 (2.4H, d, *J*=6.5Hz), 1.33 (2.4H, d, *J*=7.0Hz), 1.34 (0.6H, d, *J*=7.0Hz), 1.37 (3H, s), 1.45-1.93 (3H, m), 2.24 (3H, s), 2.51 (6H, s), 2.93-3.08 (1H, m), 3.10 (1H, dd, *J*=2.0, 9.0Hz), 3.31 (0.8H, d, *J*=11.0Hz), 3.36 (0.2H, d, *J*=11.0Hz), 3.80 (3H, s), 3.92 (0.8H, d, *J*=2.0Hz), 4.02 (0.2H, d, *J*=2.0Hz), 4.17 (0.2H, dd, *J*=6.0, 9.5Hz), 4.51 (0.2H, d, *J*=11.5Hz), 4.55 (0.2H, d, *J*=11.5Hz), 4.58 (1.6H, s), 4.62 (0.8H, dd, *J*=9.5, 12.5Hz), 4.67 (0.8H, d, *J*=12.0Hz), 4.73 (0.8H, d, *J*=12.0Hz), 4.77 (0.2H, d, *J*=12.5Hz), 4.90 (0.2H, d, *J*=12.5Hz), 6.05 (0.8H, s), 6.12 (0.2H, d, *J*=6.0Hz), 6.13 (0.2H, s), 6.44 (0.8H, d, *J*=12.5Hz), 6.80 (2H, s), 6.85 (2H, d, *J*=8.5Hz), 7.28-7.40 (7H, m). IR ν (neat) cm^{-1}: 2940, 2920, 2840, 1645, 1615, 1510, 1460, 1450, 1245, 1110, 1080, 1035, 835, 775. DI-MS *m/z*(%) 555 (M^+-BnOCH=CHCHMe, 0.4), 537 (0.2), 511 (0.2), 419 (0.2), 389 (2.8), 315 (8.1), 121 (100), 91 (24). HR-MS Calcd for $C_{33}H_{51}O_5Si$ (M^+-BnOCH=CHCHMe): 555.3506. Found: 555.3518. *Anal.* Calcd for $C_{44}H_{64}O_6Si$: C, 73.70; H, 8.99. Found: C, 73.61; H, 9.19.

A suspension of Raney Ni (W-2) in EtOH (10 ml) was added to a solution of the above olefin (1.067 g, 1.48 mmol) in EtOH (30 ml), and the mixture was vigorously stirred and hydrogenated for 24 h at room temperature, then diluted with CH_2Cl_2. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane-EtOAc 30:1) to give *(3R,4S,5S,6R,7R,8R)-7-[(1,1-dimethylethyl)dimethylsilyloxy]-8-(4-methoxybenzyloxy)-3,5,7-trimethyl-4,6-(2,4,6-trimethylbenzylidenedioxy)decan-1-ol* as a colorless oil (778 mg, 83%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.08 (3H, s), 0.79 (9H, s), 1.02 (3H, d, *J*=6.5Hz), 1.05 (3H, t, *J*=7.5Hz), 1.22-1.36 (1H, m), 1.36 (3H, s), 1.38 (3H, d, *J*=7.0Hz), 1.52-1.68 (3H, m), 1.64-1.82 (1H, m), 1.85 (1H, dq, *J*=2.0, 7.0Hz), 2.23 (3H, s), 2.40-2.54 (1H, m), 2.51 (6H, s), 3.20 (1H, dd, *J*=2.5, 9.0Hz), 3.30 (1H, d, *J*=11.0Hz), 3.54-3.78 (2H, m), 3.81 (3H, s), 4.00 (1H, d, *J*=2.0Hz), 4.58 (1H, d, *J*=10.5Hz), 4.65 (1H, d, *J*=10.5Hz), 6.03 (1H, s), 6.79 (2H, s), 6.88 (2H, d, *J*=8.5Hz), 7.29 (2H, d, *J*=8.5Hz). IR ν (neat) cm^{-1}: 3420, 2910, 2840, 1615, 1510, 1460, 1245, 1080, 1035, 830, 770, 730. DI-MS *m/z*(%): 451 (0.2), 450 (0.5), 449 (M^+-MPMOCHEt, 1.3), 301 (2.6), 159 (6.5), 121 (100). HR-MS Calcd for $C_{26}H_{45}O_4Si$ (M^+-MPMOCHEt): 449.3086. Found: 449.3075. $[\alpha]_D^{17.5}$ -29.5° (c=1.40, $CHCl_3$).

The above alcohol (388 mg, 0.617 mmol) was oxidized with oxalyl chloride (0.134 ml, 1.54

mmol), DMSO (0.131 ml, 2.46 mmol), and Et_3N (0.861 ml, 6.17 mmol) as described for **19** to give **20** as a colorless oil (372 mg, 96%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.15 (3H, s), -0.07 (3H, s), 0.80 (9H, s), 1.03 (3H, t, *J*=7.5Hz), 1.07 (3H, d, *J*=6.5Hz), 1.47-1.76 (3H, m), 2.16 (1H, ddd, *J*=3.0, 9.5, 17.0Hz), 2.24 (3H, s), 2.33 (1H, dd, *J*=3.5, 17.0Hz), 2.51 (6H, s), 2.88-3.01 (1H, m), 3.20 (2H, dd, *J*=3.0, 9.0Hz), 3.35 (1H, d, *J*=11.5Hz), 3.81 (6H, s), 4.00 (1H, d, *J*=2.0Hz), 4.57 (1H, d, *J*=11.0Hz), 4.60 (1H, d, *J*=11.0Hz), 6.06 (1H, s), 6.80 (2H, s), 6.86 (2H, d, *J*=8.5Hz), 7.25 (2H, d, *J*=8.5Hz), 9.61 (1H, d, *J*=3.0Hz). IR ν (neat) cm^{-1}: 2920, 2850, 1720, 1615, 1510, 1460, 1245, 1080, 830, 770. DI-MS *m/z*(%): 569 (M^+-*t*Bu, 0.1), 449 (0.2), 448 (0.6), 447 (1.7), 363 (0.8), 299 (3.9), 159 (14), 121 (100). HR-MS Calcd for $C_{33}H_{49}O_6Si$ (M^+-*t*Bu): 569.3297. Found: 569.3306. $[\alpha]_D^{17}$-40.9° (c=0.694, $CHCl_3$).

(2S,3S,4R,5E,8R,9S,10S,11R,12R,13R)-3-(3,4-Dimethoxybenzyloxy)-12-[(1,1-dimethylethyl)dimethylsilyloxy]-1-[(1,1-dimethylethyl)diphenylsilyloxy]-13-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadec-5-ene (**22**). A 1.60 M solution of *n*-butyllithium in hexane (0.462 ml, 0.74 mmol) was added dropwise to a stirred solution of **11** (489 mg, 0.74 mmol) in ether (8.0 ml) at -78°C under argon. After 20 min, to this carbanion solution a solution of **20** (364 mg, 0.58 mmol) in ether (7.0 ml) was added dropwise at -60°C. After 1 h, the reaction mixture was poured into ether, and the ether solution was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (hexane-EtOAc 5:1) to give **21** as a colorless oil (849 mg).

A solution of **21** (849 mg), Et_3N (0.917 ml, 6.59 mmol), Ac_2O (0.186 ml, 1.98 mmol) and 4-dimethylaminopyridine (20 mg) in CH_2Cl_2 (25 ml) was stirred at room temperature overnight under argon. After addition of MeOH, the reaction mixture was evaporated, and the residue was chromatographed on a silica gel column to give the acetate as a colorless oil (866 mg). At 1 h intervals, 5.2% Na-amalgam (2.5 g each) was added four times to a stirred solution of the above acetate (866 mg) in a 2:1 mixture of MeOH and EtOAc (24 ml) at -30°C. After 5 h, the reaction mixture was filtered with the aid of celite, and the filtrate was evaporated. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to leave a hard oil, which was chromatographed on a silica gel column (hexane-EtOAc 5:1) to give **22** as a colorless powder (542 mg, 82%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.08 (3H, s), 0.79 (9H, s), 0.84 (3H, d, *J*=6.5Hz), 1.00 (3H, d, *J*=6.0Hz), 1.02 (3H, t, *J*=7.0Hz), 1.06 (9H, s), 1.11 (3H, d, *J*=6.5Hz), 1.37 (3H, s), 1.38 (3H, d, *J*=7.0Hz), 1.46-1.62 (1H, m), 1.68-2.05 (4H, m), 2.10-2.23 (1H, m), 2.24 (3H, s), 2.39-2.42 (2H, m), 2.51 (6H, s), 3.17 (1H, dd, *J*=2.0, 9.5Hz), 3.32 (1H, d, *J*=11.0Hz), 3.49-3.60 (2H, m), 3.65 (1H, dd, *J*=8.5, 10.0Hz), 3.79 (3H, s), 3.83 (3H, s), 3.97 (1H, s), 4.53 (2H, s), 4.58 (2H, s), 5.32-5.39 (2H, m), 6.03 (1H, s), 6.76-6.89 (7H, m), 7.26 (2H, d, *J*=9.0Hz), 7.30-7.45 (6H, m), 7.61-7.67 (4H, m). IR ν (neat) cm^{-1}: 2950, 2925, 2850, 1610, 1585, 1515, 1480, 1245, 1110, 1080, 1030, 825, 735, 700. DI-MS *m/z*(%): 702 (0.4), 701 (0.7), 623 (0.2), 475 (0.3), 466 (0.3), 151 (100), 121 (83). FD-MS *m/z*(%): 1131 (38), 1130 (39), 1129 (74), 1128 (M^+, 100), 1073 (26), 1072 (58), 1071 (M^+-*t*Bu, 59), 951 (40), 520 (52). *Anal.* Calcd for $C_{69}H_{100}O_9Si_2$: C, 73.36; H, 8.92. Found: C, 73.32; H, 9.01.

(2S,3R,4S,5RS,6RS,8R,9S,10S,11R,12R,13R)-3,5-(3,4-Dimethoxybenzylidenedioxy)-12[(1,1-dimethylethyl)dimethylsilyloxy]-1-[(1,1-dimethylethyl)diphenylsilyloxy]-13-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadecan-6-ol (**23**) N-Methylmorpholine N-oxide (106 mg, 0.79 mmol) and OsO_4 (25 mg) were added to a stirred

solution of **22** (446 mg, 0.395 mmol) in acetone (24 ml) at room temperature. After 48 h, acetone, celite and aqueous $Na_2S_2O_4$ were successively added, and the mixture was filtered and washed with acetone several times. The combined filtrates were evaporated to leave a oil, which was chromatographed on a silica gel column (hexane-EtOAc 3:1) to give a 1.6:1 mixture of diols, *(2S,3R,4S,5RS,6RS,8R,9S,10S,11R,12R,13R)-3-(3,4-dimethoxybenzyloxy)-12-[(1,1-dimethylethyl)dimethylsilyloxy]-1-[(1,1-dimethylethyl)diphenylsilyloxy]-13-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadecane-5,6-diol* as a colorless hard oil (389 mg, 85%). FD-MS *m/z*(%): 1166 (10), 1165 (36), 1164 (53), 1163 (85), 1162 (M^+, 100), 1108 (38), 1107 (51), 1106 (68), 1105 (M^+-*t*Bu, 94), 985 (34), 121 (54). *Anal.* Calcd for $C_{69}H_{102}O_{11}Si_2$: C, 71.22; H, 8.83. Found: C, 70.98; H, 8.83.

5S,6S-diol (52% yield): ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.21 (3H, s), -0.11 (3H, s), 0.75 (9H, s), 0.88 (3H, d, *J*=6.5Hz), 0.91 (3H, t, *J*=7.5Hz), 1.01 (3H, d, *J*=6.5Hz), 1.06 (9H, s), 1.07 (3H, d, *J*=6.0Hz), 1.36 (3H, s), 1.36 (3H, d, *J*=6.5Hz), 1.46-1.77 (2H, m), 1.74-1.85 (1H, m), 1.92-2.06 (2H, m), 2.24 (3H, s), 2.31-2.50 (2H, m), 2.50 (6H, s), 3.11 (1H, dd, *J*=2.0, 9.0Hz), 3.36 (1H, d, *J*=10.5Hz), 3.51 (2H, d, *J*=6.5Hz), 3.60 (1H, d, *J*=10.0Hz), 3.65-3.78 (1H, m), 3.79 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 3.89-3.94 (2H, m), 4.36 (1H, d, *J*=11.0Hz), 4.44 (1H, s), 4.54 (2H, s), 4.61 (1H, d, *J*=11.0Hz), 6.00 (1H, s), 6.78 (5H, s), 6.85 (2H, d, *J*=8.5Hz), 7.26 (2H, d, *J*=8.5Hz), 7.33-7.44 (6H, m), 7.61-7.66 (4H, m). IR ν (neat) cm^{-1}: 3440, 2960, 2940, 2860, 1615, 1520, 1460, 1245, 1155, 1085, 1030, 830, 770, 735, 700.

5R,6R-diol (33% yield): ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.09 (3H, s), 0.78 (9H, s), 0.96 (3H, d, *J*=7.5Hz), 0.97 (3H, t, *J*=7.5Hz), 1.02 (3H, d, *J*=6.0Hz), 1.04 (3H, d, *J*=6.0Hz), 1.08 (9H, s), 1.26-1.40 (2H, m), 1.35 (3H, s), 1.36 (3H, d, *J*=6.5Hz), 1.59-1.86 (4H, m), 1.98-2.12 (1H, m), 2.20 (1H, d, *J*=5.0Hz), 2.24 (3H, s), 2.51 (6H, s), 2.59-2.75 (1H, m), 2.82 (1H, d, *J*=2.0Hz), 3.18 (1H, dd, *J*=2.5, 9.0Hz), 3.22 (1H, d, *J*=11.5Hz), 3.30 (1H, d, *J*=6.5Hz), 3.57-3.70 (3H, m), 3.72 (1H, t, *J*=4.5Hz), 3.79 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 4.03 (1H, s), 4.42 (1H, d, *J*=10.5Hz), 4.51 (1H, d, *J*=10.5Hz), 4.52 (1H, d, *J*=10.5Hz), 4.65 (1H, d, *J*=10.5Hz), 6.03 (1H, s), 6.79 (2H, s), 6.80 (3H, s), 6.87 (2H, d, *J*=9.0Hz), 7.29 (2H, d, *J*=9.0Hz), 7.34-7.48 (6H, m), 7.64-7.70 (4H, m). IR ν (neat) cm^{-1}: 3530, 2960, 2940, 2860, 1615, 1520, 1460, 1245, 1150, 1105, 1090, 1025, 830, 770, 735, 700.

DDQ (70.2 mg, 0.309 mmol) was added to a stirred ice-cold solution of the above diol mixture (360 mg, 0.309 mmol) in toluene (8.5 ml). After 3 h, saturated $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave an oil, which was chromatographed on a silica gel column (hexane-EtOAc 10:1~2:1) to give the recovered starting material (140 mg, 39%) and a mixture of **23a** and **23b** as a colorless hard oil (215 mg, 60%: 98% based on the consumed starting material). FD-MS *m/z*(%): 1164 (10), 1163 (43), 1162 (74), 1161 (76), 1160 (M^+, 100), 1105 (32), 1104 (37), 1103 (M^+-*t*Bu, 49), 983 (30), 982 (33), 121 (34). *Anal.* Calcd for $C_{69}H_{100}O_{11}Si_2$: C, 71.34; H, 8.68. Found: C, 71.18; H, 8.75.

5S,6S compound (**23a**): ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.17 (3H, s), -0.08 (3H, s), 0.78 (9H, s), 1.00 (3H, t, *J*=7.5Hz), 1.01 (3H, d, *J*=7.0Hz), 1.07 (12H, s), 1.20 (3H, d, *J*=7.0Hz), 1.29-1.45 (2H, m), 1.35 (3H, d, *J*=6.5Hz), 1.36 (3H, s), 1.45-1.65 (1H, m), 1.65-1.85 (2H, m), 1.85-2.10 (2H, m), 2.24 (3H, s), 2.50 (6H, s), 2.51 (1H, d, *J*=6.5Hz), 2.56-2.72 (1H, m), 3.17 (1H, dd, *J*=2.0, 9.0Hz), 3.48-3.60 (4H, m), 3.77 (3H, s), 3.82 (1H, d, *J*=9.0Hz), 3.89 (3H, s), 3,91 (3H, s), 3.93 (1H, s), 4.29-4.40 (1H, m), 4.55 (1H, d, *J*=10.5Hz), 4.60 (1H, d, *J*=10.5Hz), 5.74 (1H, s), 6.00 (1H, s), 6.79 (2H, s), 6.82-6.89 (3H, m), 7.03-7.06 (2H, m), 7.27

(2H, d, *J*=8.5Hz), 7.35-7.46 (6H, m), 7.63-7.66 (4H, m). IR ν (neat) cm^{-1}: 3530, 2950, 2920, 2850, 1610, 1515, 1105, 1080, 1025, 825, 770, 735, 700.

5R,6R compound (**23b**): ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.18 (3H, s), -0.09 (3H, s), 0.77 (9H, s), 0.91 (3H, d, *J*=6.5Hz), 1.01 (3H, t, *J*=7.5Hz), 1.06 (12H, s), 1.13 (3H, d, *J*=6.5Hz), 1.21-1.42 (2H, m), 1.37 (3H, s), 1.38 (3H, d, *J*=7.0Hz), 1.57-1.85 (5H, m), 1.90-2.05 (1H, m), 2.24 (3H, s), 2.52 (6H, s), 2.72-2.86 (1H, m), 3.15 (1H, dd, *J*=2.5, 9.0Hz), 3.27 (1H, d, *J*=11.5Hz), 3.48 (1H, dd, *J*=1.5, 9.0Hz), 3.57 (1H, dd, *J*=4.5, 10.5Hz), 3.60 (1H, dd, *J*=4.0, 10.5Hz), 3.67 (1H, d, *J*=10.0Hz), 3.78 (3H, s), 3.82-3.93 (1H, m), 3.89 (3H, s), 3.92 (3H, s), 4.02 (1H, s), 4.59 (2H, s), 5.52 (1H, s), 6.04 (1H, s), 6.79 (2H, s), 6.85 (2H, d, *J*=9.0Hz), 6.88 (1H, d, *J*=9.0Hz), 7.05-7.09 (2H, m), 7.27 (2H, d, *J*=9.0Hz), 7.36-7.45 (6H, m), 7.62-7.67 (4H, m). IR ν (neat) cm^{-1}: 3570, 2950, 2920, 2850, 1610, 1515, 1460, 1245, 1165, 1110, 1080, 1025, 830, 770, 735, 700.

(2S,3R,4S,5R,8R,9S,10S,11R,12R,13R)-3,5-(3,4-Dimethoxybenzylidenedioxy)-12-[(1,1-dimethylethyl)dimethylsilyloxy]-1-[(1,1-dimethylethyl)diphenylsilyloxy]-13-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadecan-6-one (**24**). The mixture of **23a** and **23b** (92 mg, 0.079 mmol) was oxidized with oxalyl chloride (20 μl, 0.23 mmol), DMSO (28 μl, 0.39 mmol) and Et_3N (99 μl, 0.71 mmol) in CH_2Cl_2 (3.0 ml) as described for **19** to give a mixture of C-6 ketones, which was dissolved in MeOH-THF (5:1) (3 ml). To this solution K_2CO_3 (25 mg) was added, and the mixture was stirred at room temperature for 3.5 h, then poured into CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and evapouated to leave an oil, which was chromatographed on a silica gel column (hexane-EtOAc 20:1) to give **24** as a colorless oil (90 mg, 98%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.18 (3H, s), -0.09 (3H, s), 0.78 (9H, s), 0.80 (3H, d, *J*=7.0Hz), 0.90 (3H, t, *J*=7.5Hz), 1.02 (3H, d, *J*=6.0Hz), 1.08 (9H, s), 1.15 (3H, d, *J*=6.5Hz), 1.34-1.47 (1H, m), 1.35 (3H, s), 1.36 (3H, d, *J*=6.5Hz), 1.66-1.80 (2H, m), 1.88-2.01 (1H, m), 2.23 (3H, s), 2.23 (3H, s), 2.28 (1H, d, *J*=18.5Hz), 2.50 (6H,s), 2.71 (1H, dd, *J*=10.0Hz, 18.5Hz), 2.95-3.09 (1H, m), 3.07 (1H, dd, *J*=2.5, 9.0Hz), 3.38 (1H, d, *J*=11.5Hz), 3.57 (1H, dd, *J*=5.0, 10.0Hz), 3.59 (1H, dd, *J*=4.0, 10.0Hz), 3.72 (1H, dd, *J*=2.0, 9.0Hz), 3.77 (3H, s), 3.90 (3H, s), 3.94 (1H, d, *J*=1.0Hz), 4.22 (1H, d, *J*=2.5Hz), 4.51 (2H, s), 5.52 (1H, s), 6.03 (1H, s), 6.78 (2H, s), 6.82 (2H, d, *J*=9.0Hz), 6.89 (1H, d, *J*=8.5Hz), 7.06 (1H, d, *J*=2.0Hz), 7.11 (1H, dd, *J*=2.0, 8.5Hz), 7.22 (2H, d, *J*=9.0Hz), 7.34-7.46 (6H, m), 7.62-7.70 (4H, m). IR ν (neat) cm^{-1}: 2925, 2850, 1715, 1615, 1510, 1460, 1245, 1165, 1110, 1085, 1035, 830, 775, 740, 700. FD-MS *m/z*(%): 1162 (15), 1161 (50), 1160 (60), 1159 (100), 1158 (M^+, 33), 1103 (37), 1102 (82), 1101 (62), 982 (34), 981 (47), 980 (36). $[\alpha]_D^{19}$+6.44° (c=1.596, EtOH).

(2S,3R,4S,5R,6R,8R,9S,10S,11R,12R,13R)-3,5-(3,4-Dimethoxybenzylidenedioxy)-12-[(1,1-dimethylethyl)dimethylsilyloxy]-1-[(1,1-dimethylethyl)diphenylsilyloxy]-13-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadecan-6-ol (**25**). A 1.4 M solution of methyllithium in ether (0.146 ml, 0.205 mmol) was added to a stirred solution of **24** (31.7 mg, 27 μmol) in THF (2.0 ml) at -78°C under argon. After 5 min, H_2O was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave an oil, which was chromatographed on a silica gel column (hexane-EtOAc 10:1) to give **25** as a colorless oil (28.5 mg, 89%) and its *6S-isomer* also as a colorless oil (1.4 mg, 4%). Physical data of **25**: ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.20 (3H, s), -0.11 (3H, s), 0.76 (9H, s), 0.82 (3H, t, *J*=7.0Hz), 1.06 (3H, d, *J*=7.0Hz), 1.08 (9H, s), 1.13 (3H, d, *J*=6.0Hz), 1.17 (3H, d, *J*=6.5Hz), 1.21-1.35 (1H, m), 1.24 (3H, s), 1.36 (3H, s), 1.37 (3H, d, *J*=6.0Hz), 1.48-1.79 (4H, m), 1.86-2.07 (2H, m), 2.23 (3H,

s), 2.28 (1H, s), 2.50 (6H, s), 2.52-2.65 (1H, m), 3.00 (1H, dd, *J*=1.5, 9.5Hz), 3.21 (1H, d, *J*=11.5Hz), 3.54 (1H, d, *J*=1.0Hz), 3.57-3.65 (2H, m), 3.69 (1H, dd, *J*=1.0, 10.0Hz), 3.79 (3H, s), 3.84 (3H, s), 3.90 (3H, s), 3.96 (1H, d, *J*=1.5Hz), 4.43 (1H, d, *J*=10.5Hz), 4.51 (1H, d, *J*=10.5Hz), 5.58 (1H, s), 5.93 (1H, s), 6.79 (2H, s), 6.82-6.88 (3H, m), 7.03-7.08 (2H, m), 7.26 (2H, d, *J*=9.0Hz), 7.36-7.49 (6H, m), 7.63-7.70 (4H, m). IR ν (neat) cm^{-1}: 3550, 2925, 2850, 1615, 1585, 1515, 1460, 1245, 1110, 1085, 1035, 825, 695. FD-MS *m/z*(%): 1177 (36), 1176 (40), 1175 (69), 1174 (M^+, 83), 1119 (37), 1118 (64), 1117 (M^+-*t*Bu, 100), 998 (34), 997 (67), 121 (49). *Anal.* Calcd for $C_{70}H_{102}O_{11}Si_2$: C, 71.51; H, 8.74. Found: C, 71.51; H, 8.77. $[\alpha]_D^{17}$-3.86° (c=1.096, MeOH). Physical data of *6S-isomer*: ^{1}H-NMR (270MHz, $CDCl_3$) δ: -0.16 (3H, s), -0.08 (3H, s), 0.78 (9H, s), 0.99 (3H, t, *J*=7.5Hz), 1.07 (9H, s), 1.09 (3H, d, *J*=7.0Hz), 1.15 (3H, d, *J*=6.0Hz), 1.21-1.27 (1H, m), 1.22 (3H, d, *J*=6.0Hz), 1.33 (3H, s), 1.34 (3H, d, *J*=7.0Hz), 1.37 (3H, s), 1.39-1.67 (3H, m), 1.66-1.85 (1H, m), 1.91-2.06 (2H,m), 2.19 (1H, s), 2.24 (3H, s), 2.52 (6H, s), 2.61-2.73 (1H, m), 3.14 (1H, d, *J*=9.0Hz), 3.25 (1H, d, *J*=11.5Hz), 3.44 (1H, s), 3,57 (1H, dd, *J*=4.0, 10.5Hz), 3.64 (1H, dd, *J*=4.5, 10.5Hz), 3.67 (1H, d, *J*=10.0Hz), 3.78 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 3.99 (1H, d, *J*=1.5Hz), 4.57 (2H, s), 5.59 (1H, s), 6.00 (1H, s), 6.79 (2H, s), 6.85 (2H, d, *J*=8.5Hz), 6.90 (1H, s), 7.04-7.11 (2H, m), 7.26 (2H, d, *J*=8.5Hz), 7.35-7.49 (6H, m), 7.62-7.68 (4H, m).

3,5-O-(3,4-Dimethoxybenzylidene)-13-O-(4-methoxybenzyl)-9,11-O-(2,4,6-trimethylbenzylidene)-(9S)-9-dihydroerythronolide A seco-acid methylester (**26**). A 1.0 M solution of tetra-*n*-butylammonium fluoride in THF (0.236 ml, 0.236 mmol) was added to a stirred solution of **25** (27.7 mg, 23.6 μmol) in HMPA (1.0 ml) at 60°C. After 48 h, the reaction mixture was diluted with ether, washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (hexane-EtOAc 2:1) to give *(2S,3R,4S,5R,6R,8R,9S,10S,11R,12R,13R)-3,5-(3,4-dimethoxybenzylidenedioxy)-13-(4methoxybenzyloxy)-2,4,6,8,10,12-hexamethyl-9,11-(2,4,6-trimethylbenzylidenedioxy)pentadecane-1,6,12-triol* as a colorless oil (14.5 mg, 75%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.98 (3H, t, *J*=7.5Hz), 1.03 (3H, s), 1.10 (3H, d, *J*=6.5Hz), 1.16 (6H, d, *J*=6.5Hz), 1.26 (3H, s), 1.34 (1H, dd, *J*=6.0, 14.5Hz), 1.40-1.52 (1H, m), 1.47 (3H, d, *J*=7.0Hz), 1.63 (1H, d, *J*=14.5Hz), 1.67-1.84 (2H, m), 1.86-1.95 (1H, m), 1.95-2.12 (2H, m), 2.10 (1H, s), 2.23 (1H, s), 2.26 (3H, s), 2.48 (6H, s), 2.50-2.64 (1H, m), 3.33 (1H, d, *J*=11.5Hz), 3.37 (1H, dd, *J*=2.5, 9.0Hz), 3.61 (1H, d, *J*=1.5Hz), 3.67 (2H, t, *J*=3.5Hz), 3.72 (1H, dd, *J*=1.5, 10.0Hz), 3.81 (3H, s), 3.89 (6H, s), 4.42 (1H, d, *J*=2.0Hz), 4.50 (2H, s), 5.58 (1H, s), 6.18 (1H, s), 6.85 (2H, s), 6.85-6.91 (3H, m), 7.00-7.06 (2H, m), 7.36 (2H, d, *J*=8.5Hz). IR ν (neat) cm^{-1}: 3540, 3450, 2920, 1615, 1510, 1455, 1260, 1245, 1160, 1100, 1030, 735. DI-MS *m/z*(%): 822 (M^+, 0.2), 687 (0.2), 686 (0.2), 643 (3.2), 495 (2.1), 329 (3.0), 311 (6.0), 121 (100). $[\alpha]_D^{24}$-30.4° (c=0.58, $CHCl_3$).

A 2.67 M solution of Jones reagent (82.9 μl, 221 μmol) was added dropwise to a stirred solution of the above alcohol (60.7 mg, 73.7 μmol) at -28°C, and the reaction mixture was gradually warm to -18°C during 1 h. Isopropanol (80 μl) was added to decompose the excess reagent, and the mixture was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the acid as a pale yellow oil (59.7 mg), which was chromatographed on a silica gel column (hexane-EtOAc 1:1 ~ CH_2Cl_2-EtOAc 1:1) to give a colorless oil. ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.98 (3H, t, *J*=7.5Hz), 1.05 (3H, s), 1.08 (3H, d, *J*=6.0Hz), 1.15-1.26 (1H, m), 1.20 (3H, d, *J*=6.0Hz), 1.21 (3H, s), 1.28-1.42 (1H, m), 1.37 (3H, d, *J*=7.0Hz), 1.47 (3H, d, *J*=7.0Hz), 1.57 (1H, d, *J*=14.5Hz), 1.71-1.90 (2H, m), 2.00-2.11 (1H, m), 2.26 (3H, s), 2.40-2.52 (1H, m), 2.50 (6H, s), 2.86 (1H, dq, *J*=10.5, 7.5Hz), 3.32 (1H, d, *J*=11.5Hz), 3.38 (1H, dd, *J*=3.0, 9.0Hz), 3.61 (1H, d, *J*=2.0Hz), 3.82-3.92 (1H, m), 3.84 (3H, s), 3.89 (6H, s),

4.35 (1H, d, *J*=2.0Hz), 4.48 (1H, d, *J*=10.5Hz), 4.53 (1H, d, *J*=10.5Hz), 5.58 (1H, s), 6.17 (1H, s), 6.83-6.93 (3H, m), 6.85 (2H, s), 6.90-7.05 (2H, m), 7.33 (2H, d, *J*=8.5Hz). DI-MS *m/z*(%): 837 (0.3), 836 (M^+, 0.5), 657 (0.9), 639 (0.6), 552 (0.8), 551 (0.8), 509 (5.7), 325 (7.3), 167 (28), 121 (100).

A solution of the crude acid (59.7 mg) in ether (3.0 ml) was treated with excess diazomethane in ether at room temperature for 3 min. The reaction mixture was evaporated, and the residue was chromatographed on a silica gel column (hexane-EtOAc 5:1~3:1) to give **26** as a colorless oil (31.4 mg, 50%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.96 (3H, t, *J*=7.5Hz), 1.00 (3H, s), 1.09 (3H, d, *J*=6.5Hz), 1.14 (3H, d, *J*=6.5Hz), 1.19-1.29 (1H, m), 1.29 (3H, s), 1.34 (3H, d, *J*=7.0Hz), 1.38-1.51 (1H, m), 1.46 (3H, d, *J*=7.0Hz), 1.68-1.90 (3H, m), 2.00-2.10 (1H, m), 2.13 (1H, s), 2.26 (3H, s), 2.47 (6H, s), 2.65-2.79 (1H, m), 2.83 (1H, dq, *J*=10.0, 7.0Hz), 3.33 (1H, d, *J*=10.5Hz), 3.36 (1H, dd, *J*=2.5, 9.5Hz), 3.60 (1H, d, *J*=2.0Hz), 3.74 (3H, s), 3.79 (3H, s), 3.85-3.92 (1H, m), 3.89 (6H, s), 4.44 (1H, s), 4.46 (1H, d, *J*=10.5Hz), 4.53 (1H, d, *J*=10.5Hz), 5.58 (1H, s), 6.19 (1H, s), 6.84 (2H, s), 6.84-6.87 (3H, m), 6.98-7.04 (2H, m), 7.38 (2H, d, *J*=8.5Hz). IR ν (neat) cm^{-1}: 3550, 2930, 1735, 1615, 1510, 1455, 1350, 1260, 1245, 1165, 1100, 1030, 970, 850, 735. DI-MS *m/z*(%): 852 (0.7), 851 (2.2), 850 (M^+, 3.9), 673 (3.3), 672 (12), 671 (28), 523 (20), 201 (30), 167 (48), 121 (100). *Anal.* Calcd for $C_{49}H_{70}O_{12}$: C, 69.15; H, 8.29. Found: C, 69.04; H, 8.31. $[\alpha]_D^{20}$-28.3° (c=0.636, $CHCl_3$).

3,5-O-(3,4-Dimethoxybenzylidene)-9,11-O-(2,4,6-trimethylbenzylidene)-(9S)-9-dihydroerythronolide A Seco-acid (**7**). A vigorously stirred solution of **26** (5.7 mg, 6.7 μmol) in EtOH (1.5 ml) was hydrogenated over 10% Pd-C (3.6 mg) at room temperature for 20 min. After the catalyst was removed by filtration, the filtrate was evaporated, and the residue was chromatographed on a silica gel column (hexane-EtOAc 3:1~3:2) to give *3,5-O-(3,4-dimethoxybenzylidene)-9,11-O-(2,4,6-trimethylbenzylidene)-(9S)-9-dihydroerythronolide A seco-acid methylester* as a colorless hard oil (3.9 mg, 80%). ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.99 (3H, s), 1.00 (3H, t, *J*=7.5Hz), 1.09 (3H, d, *J*=6.5Hz), 1.15 (3H, d, *J*=6.5Hz), 1.18-1.35 (2H, m), 1.27 (3H, s), 1.34 (3H, d, *J*=6.5Hz), 1.51 (3H, d, *J*=7.5Hz), 1.59-1.78 (2H, m), 1.85 (1H, tq, *J*=2.0, 6.5Hz), 1.96 (1H, dq, *J*=2.0, 7.5Hz), 2.18 (1H, d, *J*=10.0Hz), 2.25 (4H, s), 2.47-2.59 (1H, m), 2.51 (6H, s), 2.85 (1H, dq, *J*=6.5, 10.5Hz), 3.04 (1H, s), 3.22 (1H, ddd, *J*=1.5, 9.0, 10.0Hz), 3.30 (1H, d, *J*=11.5Hz), 3.62 (1H, d, *J*=2.0Hz), 3.74 (3H, s), 3.89 (3H, s), 3.89 (3H, s), 3.90 (1H, dd, *J*=2.0, 10.5Hz), 4.22 (1H, d, *J*=2.0Hz), 5.60 (1H, s), 6.07 (1H, s), 6.82 (2H, s), 6.87 (1H, d, *J*=8.0Hz), 7.00 (1H, d, *J*=2.0Hz), 7.04 (1H, dd, *J*=2.0, 8.0Hz). IR ν (neat) cm^{-1}: 3540, 3470, 2920, 2860, 1730, 1610, 1515, 1455, 1265, 1240, 1160, 1105, 1030, 980, 855, 735. DI-MS *m/z*(%): 732 (1.3), 731 (2.5), 730 (M^+, 5.5), 715 (0.5), 698 (0.7), 671 (7.1), 653 (1.3), 627 (2.1), 523 (7.2), 421 (9.1), 167 (79), 149 (100), 43 (88). *Anal.* Calcd for $C_{41}H_{62}O_{11}$: C, 67.37; H, 8.55. Found: C, 67.34; H, 8.69.

3N NaOH (0.2 ml) was added to a stirred solution of the above ester (22 mg, 30 μmol) in MeOH (1.5 ml) at room temperature. After 18 h, the reaction mixture was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and evaporated, then the residue was chromatographed on a silica gel column (CH_2Cl_2-MeOH 30:1) to give **7** as a colorless hard oil (20.4 mg, 94%). ^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.99 (3H, t, *J*=7.5Hz), 1.00 (3H, s), 1.11 (3H, d, *J*=6.5Hz), 1.19-1.34 (2H, m), 1.19 (3H, d, *J*=7.0Hz), 1.30 (3H, s), 1.39 (3H, d, *J*=6.5Hz), 1.51 (3H, d, *J*=7.0Hz), 1.64 (1H, d, *J*=14.0Hz), 1.64-1.77 (1H, m), 1.92-1.99 (2H, m), 2.25 (3H,s), 2.50-2.61 (1H, m), 2.51 (6H, s), 2.86 (1H, dq, *J*=10.0, 6.5Hz), 3.29 (1H, dd, *J*=1.5, 10.5Hz), 3.30 (1H, d, *J*=11.5Hz), 3.69 (1H, d, *J*=1.5Hz), 3.88-3.92 (1H, dd, *J*=1.5, 10.0Hz), 3.895 (3H, s), 3.900 (3H, s), 4.21 (1H, d, *J*=2.0Hz), 5.61 (1H, s), 6.08 (1H, s), 6.83 (2H, s), 6.88 (1H, d, *J*=8.5Hz), 7.01 (1H,

d, *J*=1.5Hz), 7.04 (1H, dd, *J*=1.5, 8.5Hz). IR ν (neat) cm^{-1}: 3600-2400, 2950, 1725, 1615, 1515, 1460, 1260, 1165, 1105, 1030, 975, 855, 735. DI-MS *m/z*(%): 718 (0.5), 717 (1.2), 716 (M^+, 3.0), 698 (0.9), 509 (3.5), 167 (48), 149 (69), 43 (100). $[\alpha]_D^{19}$-41.3° (c=0.776, $CHCl_3$).

3,5-O-(3,4-Dimethoxybenzylidene)-9,11-O-(2,4,6-trimethylbenzylidene)-(9S)-9-dihydroerythronolide A (**8**). Et_3N (3.1 μl, 21.8 μmol) and 2,4,6-trichlorobenzoyl chloride (4.7 mg, 19.1 μmol) was added to a stirred solution of **7** (13.1 mg, 18,2 μmol) in toluene (1.8 ml) at room temperature. After 48 h, 4-dimethylaminopyridine (4.4 mg, 36 μmol) was added, and the reaction mixture was stirred for 50 min, then evaporated *in vacuo*. The residue was chromatographed on a silica gel column (hexane-EtOAc 3:1) to give **8** as amorphous powder (12.5 mg, 98%), mp 140-143°C. ^{1}H-NMR (500MHz, $CDCl_3$) δ: 0.78 (3H, t, *J*=7.5Hz), 1.17 (3H,s), 1.18 (3H, d, *J*=6.5Hz), 1.26 (3H, d, *J*=6.5Hz), 1.27 (3H, d, *J*=6.5Hz), 1.35 (3H, s), 1.41 (1H, dd, *J*=11.5, 14.5Hz), 1.49 (3H, d, *J*=6.5Hz), 1.50 (1H, ddq, *J*=11.5, 14.5, 7.5Hz), 1.57 (1H, d, *J*=14.5Hz), 1.80 (1H, q, *J*=6.5Hz), 1.85 (1H, ddq, *J*=2.0, 14.5, 7.5Hz), 1.93 (1H, dq, *J*=1.5, 6.5Hz), 2.27 (3H, s), 2.35 (1H, s), 2.48-2.57 (1H, m), 2.57 (6H, s), 2.64 (1H, s), 2.90 (1H, dq, *J*=11.0, 6.5Hz), 3.34 (1H, d, *J*=11.0Hz), 3.66 (1H, d, *J*=1.5Hz), 3.88 (1H, dd, *J*=11.0, 6.5Hz), 3.90 (3H, s), 3.92 (3H, s), 4.09 (1H, d, *J*=1.0), 5.13 (1H, dd, *J*=2.0, 11.5Hz), 5.71 (1H, s), 6.17 (1H, s), 6.87 (2H, s), 6.90 (1H, d, *J*=8.5Hz), 7.06 (1H, d, *J*=2.0Hz), 7.10 (1H, dd, *J*=2.0, 8.5Hz). IR ν ($CHCl_3$) cm^{-1}: 3530, 2950, 2920, 1720, 1610, 1595, 1510, 1460, 1450, 1260, 1165, 955. DI-MS *m/z*(%): 701 (1.0), 700 (4.0), 699 (16), 698 (M^+, 34), 492 (6.0), 417 (13), 395 (9.0), 353 (10), 167 (82), 166 (81), 147 (51), 43(100). *Anal.* Calcd for $C_{40}H_{58}H_{10}$: C, 68.74; H, 8.36. Found: C, 68.67; H, 8.40. $[\alpha]_D^{24}$-12.4° (c=0.772, $CHCl_3$).

(9S)-9-Dihydroerythronolide A (**2**). A vigorously stirred solution of **8** (12.7 mg, 18.2 μmol) in EtOH (1.5 ml) was hydrogenated over 10% $Pd(OH)_2$-C (13.1 mg) at room temperature for 12 h. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*, then the residue was chromatographed on a silica gel column (hexane-EtOAc 1:1) to give **2** as a colorless fine needles (7.5 mg, 98%), mp 195-199°C. ^{1}H-NMR (270MHz, $CDCl_3$) δ: 0.90 (3H, t, *J*=7.5Hz), 1.03 (3H, d, *J*=7.0Hz), 1.05 (3H, s), 1.20 (1H, dd, *J*=12.5, 15.0Hz), 1.23 (3H, d, *J*=7.0Hz), 1.24 (3H, s), 1.29 (6H, d, *J*=7.0Hz), 1.43 (1H, dd, *J*=2.5, 15.0Hz), 1.47-1.64 (3H, m), 1.79 (1H, s), 1.94 (1H, ddq, *J*=2.0, 14.5, 7.5Hz), 2.01-2.17 (1H, brq, *J*=7.0Hz), 2.52 (1H, s), 2.80 (1H, dq, *J*=10.5, 7.0Hz), 2.92 (1H, s), 2.96 (1H, dt, *J*=2.0, 10.0Hz), 3.41 (1H, d, *J*=1.5Hz), 3.42 (1H, d, *J*=10.0Hz), 3.48 (1H, dd, *J*=1.5, 4.5Hz), 3.83-3.88 (1H, brd, *J*=10.5Hz), 3.94-3.97 (1H, brs), 4.25 (1H, d, *J*=4.5Hz), 4.61 (1H, dd, *J*=1.5, 11.0Hz). IR ν (KBr) cm^{-1}: 3480, 2970, 2930, 2800, 1710, 1455, 1350, 1190, 1085, 980. DI-MS *m/z*(%): 422 (M^++2, 0.2), 421 (M^++1, 0.6), 402 (0.3), 384 (2.1), 366 (2.0), 327 (7.7), 281 (7.2), 257 (10), 223 (25), 197 (33), 127 (39), 97 (46), 69 (50), 57 (48), 43 (100). HR-MS Calcd for $C_{21}H_{41}O_8$ (MH^+): 421.2801. Found: 421.2815. $[\alpha]_D^{20}$+9.2° (c=0.65, MeOH).

9,11-O-(2,4,6-Trimethylbenzylidene)-(9S)-9-dihydroerythronolide A (**27**). 5% KH_2PO_4 (0.2 ml) and 0.4N HCl (0.4 ml) were added to a stirred solution of **8** (30.2 mg, 0.043 mmol) at room temperature. After 24 h, the reaction mixture was poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($NaSO_4$), and evaporated, then the residue was chromatographed on a silica gel column (hexane-EtOAc 2:1) to give **27** as a colorless amorphous solid (17.8 mg, 75%), mp 146-152°C. ^{1}NMR (270MHz, $CDCl_3$) δ: 0.79 (3H, t, *J*=7.5Hz), 1.02 (3H, d, *J*=7.0Hz), 1.09 (3H, s), 1.22 (3H, d, *J*=6.0Hz), 1.24-1.35 (2H, m), 1.30 (3H, d, *J*=7.0Hz), 1.31 (3H, s), 1.45 (3H, d, *J*=6.5Hz), 1.46-1.73 (3H, m), 1.73-1.92 (2H, m), 2.26 (3H, s), 2.42-2.57 (1H, m), 2.57 (6H, s),

2.60 (1H, s), 2.73 (1H, dq, *J*=10.5, 6.5Hz), 3.04 (1H, s), 3.27 (1H, d, *J*=10.5Hz), 3.52 (1H, s), 3.64 (1H, d, *J*=2.0Hz), 4.04 (1H, d, *J*=10.5Hz), 4.09 (1H, s), 5.01 (1H, dd, *J*=2.0, 11.5Hz), 6.18 (1H, s), 6.85 (2H, s). IR ν ($CHCl_3$) cm^{-1}: 3350, 2980, 2945, 1725, 1615, 1455, 1285, 1100. DI-MS *m/z*(%): 551 (4.0), 550 (M^+, 10) 536 (1.4), 535 (3.9), 532 (1.3), 517 (1.3), 471 (1.3), 464 (1.3) 463 (1.3), 446 (2.5), 405 (5.3), 155 (37), 147 (86), 43 (100).

References and Notes

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5. Cyclization of seventeen variously protected seco-acid derivatives having correct configurations of all chiral centers into the corresponding macrolactones was attempted by Woodward et al., and only one among them gave a 9-dihydroerythronolide A derivative in reasonable yield (70%).[2b]
6. The conformation of **8** speculated from its NMR spectra including transannular NOE data (C4-H~C11-H, C5-H~C8-H) is consistent with the reported NMR[7] and X-ray data[8] of similar compounds.
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11. In analogy with the formation of **16**, treatment of a similar C7-C15 triol with acetaldehyde diethyl acetal gave mainly a 9,11-acetaldehyde acetal with a twist-boat conformation.[2e]
12. Different from **16**, **18**, and the acetaldehyde acetal, **13** and **15** in the chair forms must be thermodynamically more stable than in their twist-boat forms.
13. The Bn group was selectively removed without any detectable loss of the 13-MPM group.[14]
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19. After unsuccessful attempts to prove the acylpyridinium salt by NMR spectroscopy, indirect proof was obtained by TLC analysis on silica gel of the reaction mixture at regular time intervals. For example, after 1 min a main spot of the lactone (**8**) and two minor spots of the mixed anhydride and the seco-acid (**7**) were detected: the acylpyridinium salt was probably detected as **7** because it was too labile to exist under the TLC conditions. The two minor compounds disappeared with time, and after 8 min the lactone **8** was observed as a single spot.