Pergamon

Tetrahedron Vol. 51, No. 18, pp. 5315-5330, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00215-4

Total Synthesis of the Polyene Macrolide Antibiotic Roxaticin. II. Total Synthesis of Roxaticin

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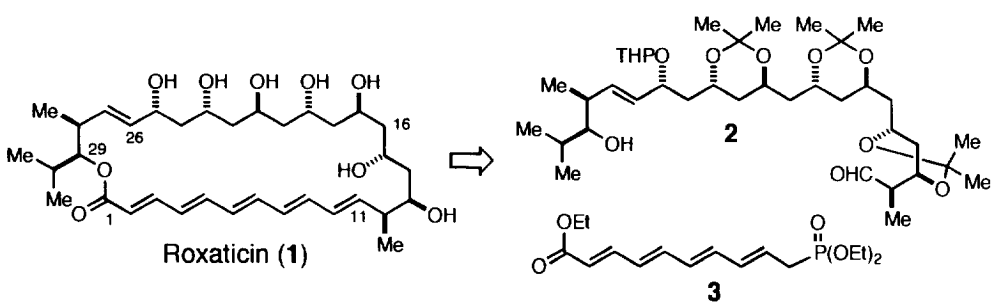
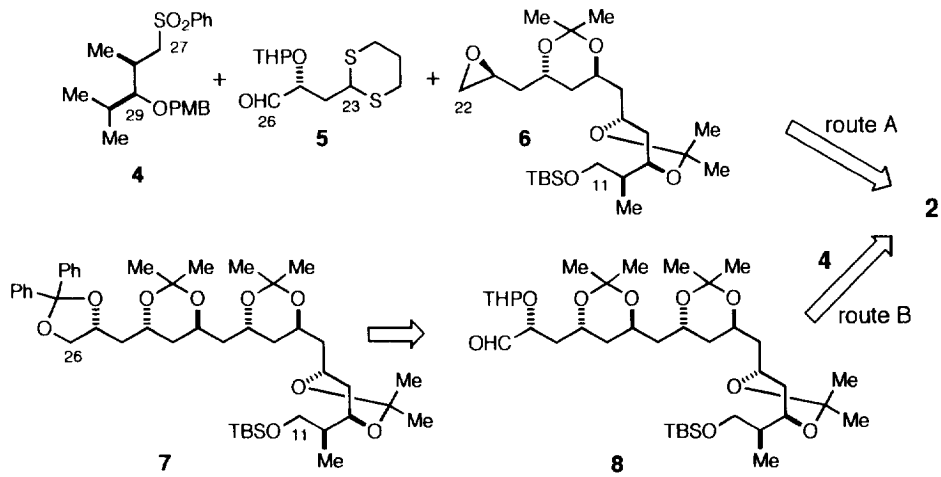
Abstract: Roxaticin has been synthesized in a convergent manner from the polyol segment **2**, which was prepared by the Julia coupling reaction of sulfone **4** and aldehyde **8**, and the polyene phosphonate **3**. The cyclization was achieved by macrolactonization.

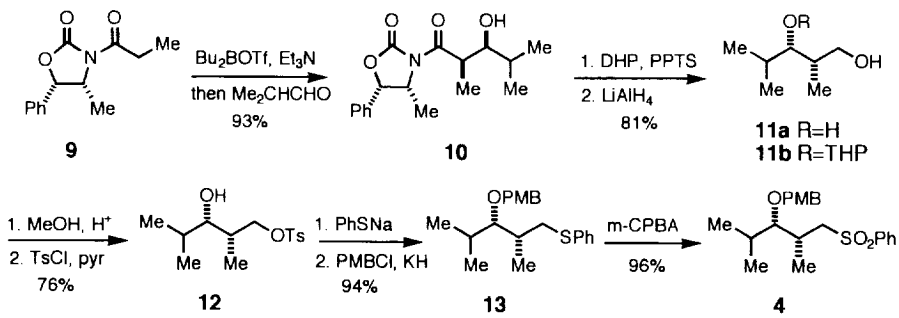
In a preceding paper,[1] we discussed the retrosynthetic analysis of roxaticin (**1**)[2] and the stereocontrolled synthesis of the key C11-C26 polyol segment required for the total synthesis of this target molecule using four-carbon chain extension methodology.[3] In this paper, we describe the further elaboration of the polyol segment and the total synthesis of roxaticin.[4] According to the synthetic plan, we divided roxaticin into two segments, **2** and **3**. The C11-C29 polyol chain **2** could be prepared from two fragments, **4** and **8**, and the light sensitive polyene portion **3** was introduced in the final stage. This approach involved the formation of a macrocyclic ring by lactonization.



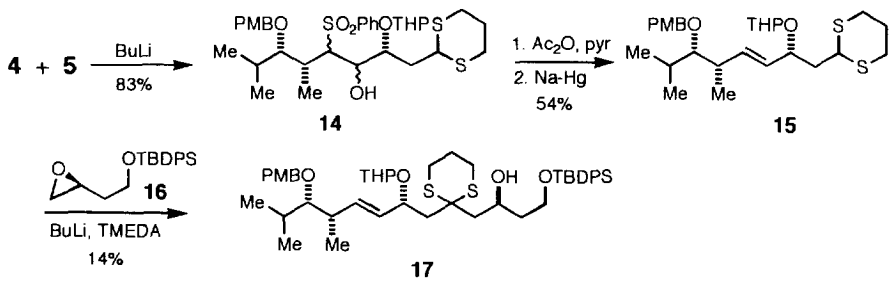
Synthesis of the C11-C29 Polyol Segment 2. We initially planned two approaches for the synthesis of the advanced intermediate **2**; one was designed to couple sulfone **4** and aldehyde **5** followed by epoxide **6** (route A), and the other involved the transformation of **7** into aldehyde **8** and its condensation with sulfone **4** (route B). The syntheses of segments **6** and **7** were detailed in a preceding paper.[1] The sulfone **4**[5] was prepared by starting with the Evans' asymmetric aldol method[6] using **9** and isobutyraldehyde. Protection of the hydroxyl group of **10**, obtained with 99% enantiomeric excess, with a *p*-methoxybenzyl (PMB) group under basic and acidic conditions[7] was unsuccessful, giving the desired product only in low yield. The hydroxyl group



seemed to be hindered by the methyl and isopropyl groups. Reductive removal of the chiral auxiliary with $LiAlH_4$ leading to diol **11a** also failed and the product obtained was a decarbonylated compound. The aldol **10** was then protected with a tetrahydropyranyl (THP) group and reduced with $LiAlH_4$ to give **11b** in 81% overall yield. After methanolysis of the THP group, the primary hydroxyl group of **11a** was replaced by a phenylthio group via tosylate **12** and the remaining hydroxyl was protected as a PMB ether using potassium hydride and *p*-methoxybenzyl chloride. Oxidation of sulfide **13** with *m*-chloroperbenzoic acid produced the desired sulfone **4** in 69% overall yield from **11**.

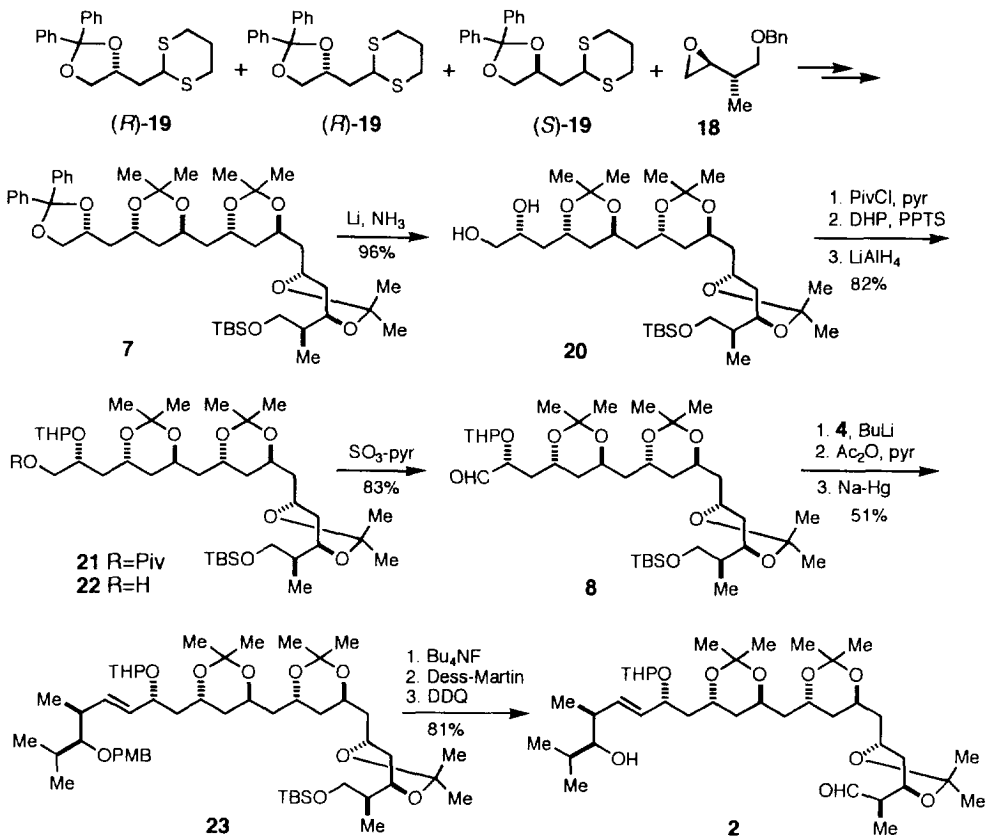


We first tried the sulfone anion (Julia) coupling[8] of sulfone **4** with aldehyde **5**, prepared from (*S*)-*t*-butyldiphenylsilylglycidol and 1,3-dithiane in four steps, giving a mixture of β-hydroxy sulfones **14** in 83% yield. The product was transformed into the *trans*-olefin **15** by acetylation followed by reductive elimination with sodium amalgam in 54% overall yield. Before proceeding to the synthesis of **2** by route A, we examined the coupling reaction of dithiane **15** and the model epoxide **16**. Deprotonation of **15** with *n*-BuLi in THF at -30°C for 2h was found to be unacceptably slow, but the addition of TMEDA as a co-solvent and a prolonged reaction time (12h) improved the deprotonation up to 90% after quenching with D_2O. However, much to our



disappointment, the coupling reaction of the lithiated **15** with **16** under the above conditions was very slow and only a 14% yield of **17** was obtained along with variable amounts of lower Rf products. All our efforts, such as changing the protecting groups from THP in **15** to triethylsilyl or benzyl groups and the bases from *n*-BuLi to *s*- or *t*-BuLi, did not improve the yield of the coupling reactions.

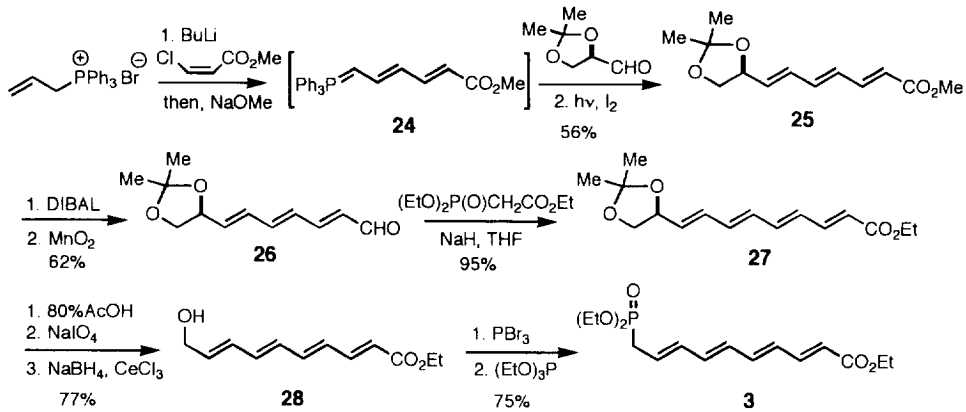
In order to circumvent the encountered difficulties, we tried an alternative approach employing the C11-C26 segment **7**, which was prepared in an enantiomerically pure form as



described in a previous paper.[1] Four-carbon unit derivatives **18**, (*R*)-**19**, and (*S*)-**19** were successively coupled using lithiodithiane alkylations followed by 1,3-asymmetric reductions that allowed the stereoselective construction of segment **7** containing eight chiral centers. The treatment of **7** with lithium in ammonia resulted in the cleavage of the diphenylmethylene ketal in 96% yield. Selective protection of the resulting diol **20** with pivaloyl chloride followed by dihydropyran gave **21** as an inseparable mixture of isomers of the anomeric centers of the THP ether (ca. 1:1 by ^{1}H NMR analysis), and subsequent reduction with $LiAlH_4$ yielded **22** in 82% overall yield. At this stage, the stereoisomers were separated by flash chromatography. Although both isomers were good candidates for further elaboration, the less polar isomer was used in subsequent sequences to allow for unequivocal spectral characterization of the synthetic intermediates. The oxidation of alcohol **22** with a sulfur trioxide-pyridine complex[9] produced the desired aldehyde **8** in 83% yield.

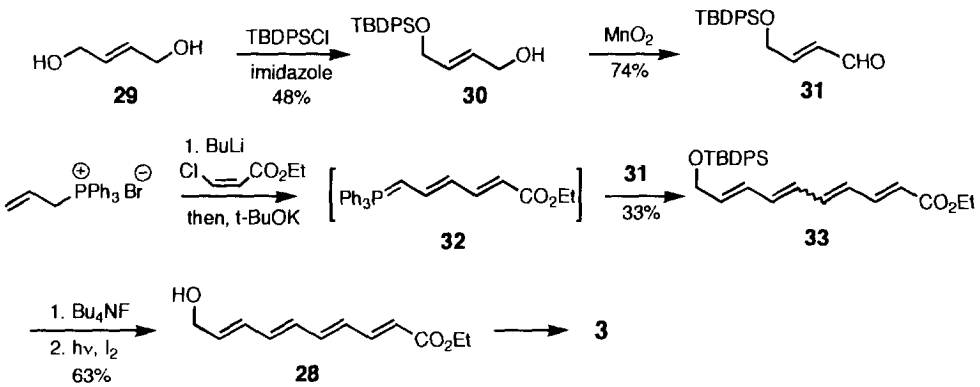
With two segments, **4** and **8**, available, we then turned our attention to constructing the whole polyol chain of roxaticin. The plan for construction of the C26-C27 *trans*-disubstituted olefin was based on the Julia coupling.[8] This sequence was initiated by the reaction of the sulfone anion generated from **4** with aldehyde **8**. The condensation proceeded uneventfully to produce a mixture of β-hydroxy sulfones which was then acetylated, and the product was subjected to reductive elimination with sodium amalgam. The coupled product **23** was obtained in 51% overall yield after chromatographic separation of a 9:1 mixture of *E* and *Z* isomers estimated by ^{1}H NMR analysis. Deprotection of the *t*-butyldimethylsilyl group of **23** by tetra-*n*-butylammonium fluoride followed by the oxidation with the Dess-Martin periodinane[10] gave a PMB-protected aldehyde. Finally, oxidative removal of the PMB group with DDQ[11] afforded the C11-C29 polyol segment **2** in 81% overall yield from **23**.

Synthesis of the Tetraene Phosphonate 3.[5] Many efforts have been devoted to the synthesis of polyenes over the years and incorporating diverse functionalities have fostered a number of recent studies in this area.[12] Hanessian has reported the synthesis of the bifunctional all-*trans* tetraene **27**[13] by the reactions of 2,3-O-isopropylidene-D-glyceraldehyde with formylmethylenetriphenylphosphorane followed by a Wittig reagent developed by Vedejs



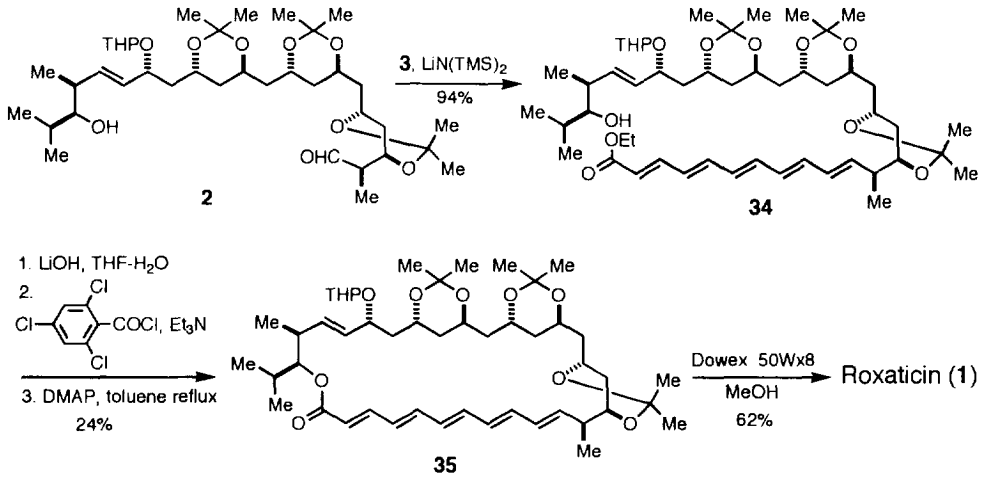
and Bershas.[14] Although we initially prepared **27** by this route, separation of the product from the recovered pentenal in the second step was difficult and the yield was only 30%. However, changing the order of coupling reagents improved the yield. Thus, the Wittig reaction of 2,3-O-isopropylidene-*D*-glyceraldehyde with Vedejs reagent (**24**)[14] gave a 1:2 mixture of *E* and *Z* olefins and photochemical isomerization in the presence of a catalytic amount of iodine afforded the all-*trans* triene ester **25** in 56% overall yield. Reduction of the ester with diisobutylaluminum hydride followed by oxidation with MnO_2 gave aldehyde **26** (62%), which was treated with sodio triethylphosphonoacetate in THF, leading to tetraene ester **27** in 95% yield. Small amounts of the *Z* isomer of the newly generated double bond in this reaction were removed by chromatography. Compound **27** was then converted to hydroxy ester **28** by deacetonization (80% AcOH) followed by oxidative cleavage of the resulting diol ($NaIO_4$) and reduction ($NaBH_4$-$CeCl_3$)[15] in 77% overall yield. Finally, bromination of the alcohol with PBr_3 and reaction with triethyl phosphite gave the desired tetraene phosphonate **3** in 75% yield. Although the phosphonate **3** was synthesized as stated above, the approach was still frustrating because it required two C-C bond formations and one C-C bond cleavage.

We explored an alternative procedure for the preparation of phosphonate **3**. Monoprotection of *trans*-butene-1,4-diol (**29**)[16] with *t*-butydiphenylchlorosilane and oxidation with MnO_2 gave the unsaturated aldehyde **31**. The Wittig reaction of **31** with Vedejs reagent **32**[14] gave the unstable tetraene ester **33** (33%) as a mixture of *E* and *Z* isomers after quick purification by flash chromatography. The tetraene gradually decomposed on standing to liberate *t*-butyldiphenylsilanol. Immediate desilylation and subsequent photochemical isomerization provided the all-*trans* tetraene alcohol **28** in 63% overall yield. Compound **28** was converted to the desired polyene segment **3** in two steps as previously described.



Synthesis of Roxaticin. The stage was now set for the serious issues of coupling between the polyol segment **2** and the polyene segment **3** and constructing the macrocyclic ring of roxaticin (**1**). Although the reactivity of the C29 hydroxyl group had decreased due to the presence of the adjacent methyl and bulky isopropyl substituents, we considered that the macrolactonization of seco-acid could be possible because a similar cyclization was reported in

the Schreiber's synthesis of mycoticin A.[5] The treatment of aldehyde **2** with three equivalents of the phosphonate anion generated from **3** and lithium hexamethyldisilazide cleanly effected oxo-pentaene formation to give the protected seco-ester **34** in 94% yield. The seco-ester was light-sensitive thus gradually producing a mixture of olefin isomers and, in addition, decomposed slowly in a chloroform solution. Therefore, subsequent experiments were performed under protection from light. Macrolactonization of the seco-acid, obtained by hydrolysis of the ethyl ester, was achieved using the Yamaguchi method[17] modified by Yonemitsu.[18] A THF solution of a mixed anhydride, prepared from the seco-acid and 2,4,6-trichlorobenzoyl chloride, was added using a syringe pump over a period of 4h to a refluxing toluene solution containing a large excess of 4-dimethylaminopyridine. The macrolactone **35** was isolated in 24% yield. Final deprotection with acid-resin in methanol followed by purification using preparative reverse-phase TLC afforded the synthetic roxaticin (**1**), $[\alpha]_D$+7.14° (c 0.28, dioxane), [lit.[2] $[\alpha]_D$ +8.63° (c=0.15)]. The ^{1}H NMR spectrum and TLC mobility were identical with those reported for natural roxaticin.[2,4b]



Conclusion. The total synthesis of the polyene macrolide antibiotic, roxaticin, has been achieved. The work described herein relied heavily upon the efficient 1,3-polyol synthesis in an iterative fashion using four-carbon units. The application of this methodology should be useful for preparing analogous natural products.

Experimental

General Methods. See ref. 1.

(2*S*,3*S*)-2,4-Dimethylpentane-1,3-diol (11a). A solution of **10**[5] (1.02g, 3.33mmol), dihydropyran (0.364ml, 3.99mmol), and pyridinium *p*-toluenesulfonate (42mg) in CH_2Cl_2 (20ml) was stirred at room temperature for 3.5h and then the mixture was extracted with ether. The extract was washed with aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was purified by flash chromatography (12% EtOAc/hexane) to give a THP ether (1.16g, 90%).

A stirred suspension of $LiAlH_4$ (376mg, 9.90mmol) in dry THF (20ml) was cooled to 0°C and a solution of the THP ether (1.28g, 3.30mmol) in dry THF (3ml) was added. The suspension was stirred at 0°C for 4h and then excess $LiAlH_4$ was decomposed with 3N NaOH. The organic layer was separated and the precipitates were washed with EtOAc. The combined organic layers were concentrated and purified by flash chromatography (16% EtOAc/hexane) to afford **11b** (648mg, 91%).

A mixture of **11b** (666mg, 3.08mmol) and Amberlyst-15 (1.0g) in MeOH (30ml) was stirred at 45°C for 4h and then filtered. Concentration of the filtrate and purification of the residue by flash chromatography (64% EtOAc/hexane) gave **11a** (334mg, 82%) as a colorless oil. $[\alpha]_D^{25}$+7.63° (c=0.31, $CHCl_3$). IR ($CHCl_3$): 3630, 3440, 1480, 1390, 1070, 970cm^{-1}. ^{1}H NMR (270MHz) δ: 0.86 (3H, d, *J*=6.7 Hz), 0.96 (3H, d, *J*=7.1Hz), 1.01 (3H, d, *J*=6.4Hz), 1.71 (1H, m), 1.87 (1H, m), 2.14 (2H, br, OH), 3.42 (1H, dd, *J*=9.1, 2.4Hz), 3.71 (1H, dd, *J*=10.4, 5.0Hz), 3.77 (1H, dd, *J*=10.4, 4.0Hz). EIMS *m/z*: 132 (M^+).

(2*R*,3*S*)-3-[(*p*-methoxylbenzy)oxy]-2,4-Dimethyl-1-phenylthiopentane (13). A mixture of **11a** (1.22g, 9.24mmol), *p*-toluenesulfonyl chloride (2.29g, 12.01mmol), and 4-dimethylaminopyridine (50mg) in CH_2Cl_2 (37ml) and triethylamine (2.6ml, 18.48mmol) was stirred at 0°C for 4h and then extracted with EtOAc . The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (25% EtOAc/hexane) gave **12** (2.46g, 93%).

A mixture of thiophenol (1.76ml, 17.18mmol) and EtONa (1.05g, 15.46mmol) in EtOH (60ml) was stirred at room temperature for 30min, and to this mixture was added a solution of **12** (2.46g, 8.58mmol) in EtOH (5ml). The reaction mixture was stirred at 55°C for 2h and concentrated. The residue was purified by flash chromatography (15% EtOAc/hexane) to give a sulfide (1.82g, 95%). $[\alpha]_D^{25}$+19.6° (c=0.87, $CHCl_3$). IR ($CHCl_3$): 3630, 3460, 1590, 1480, 1390, 1220, 1100, 980, 700cm^{-1}. ^{1}H NMR (270MHz) δ: 0.81 (3H, d, *J*=6.7Hz), 0.99 (6H, d, *J*=6.7Hz), 1.40 (1H, d, *J*=5.4Hz, OH), 1.70 (1H, m), 1.94 (1H, m), 2.90 (1H, dd, *J*=12.8, 6.7Hz), 3.05 (1H, dd, *J*=12.8, 7.4Hz), 3.38 (1H, m), 7.16-7.36 (5H, m). EIMS *m/z*: 224 (M^+).

To a stirred solution of the sulfide (1.80g, 8.05mmol) in dry THF (40ml) were added *p*-methoxybenzyl chloride (1.4ml, 10.46mmol) and excess KH, and the mixture was stirred at room temperature for 3h. Excess KH was decomposed with MeOH and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (4% EtOAc/hexane) gave **13** (2.73g, 99%) as a colorless oil. $[\alpha]_D^{25}$+41.9° (c=0.51, $CHCl_3$). IR ($CHCl_3$): 1610, 1510, 1470, 1300, 1250, 1180, 1070, 1040, 830, 700cm^{-1}. ^{1}H NMR (270MHz) δ: 0.84 (3H, d, *J*=6.7Hz), 1.02 (3H, d, *J*=6.7Hz), 1.03 (3H, d, *J*=7.1Hz), 1.87 (1H, m), 1.97 (1H, m), 2.84 (1H, dd, *J*=12.4, 6.4Hz), 2.99 (1H, dd, *J*=12.4, 7.1Hz), 3.25 (1H, dd, *J*=8.1, 3.0Hz), 6.86 (2H, d, *J*=8.4Hz), 7.10-7.37 (5H, m), 7.27 (2H, d, *J*=8.4Hz). EIMS *m/z*: 344 (M^+).

(2*R*,3*S*)-3-[(*p*-methoxylbenzy)oxy]-2,4-Dimethyl-1-phenylsulfonylpentane (4). A mixture of **13** (2.73g, 7.94mmol) and *m*-chloroperbenzoic acid (3.60g, 16.67mmol) in CH_2Cl_2 (60ml) was stirred at room temperature for 30min, and then the excess reagent was decomposed with 0.1N $Na_2S_2O_3$ (1.0ml). The reaction mixture was filtered and the filtrate was concentrated. The residue was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc/hexane) gave **4** (2.86g, 96%) as a colorless oil. $[\alpha]_D^{25}$+8.09° (c=0.53, $CHCl_3$). IR ($CHCl_3$): 1610, 1520, 1470, 1300, 1250, 1150, 1090, 1040, 830cm^{-1}. ^{1}H NMR (270MHz) δ: 0.89 (3H, d, *J*=6.7Hz), 0.98 (3H, d, *J*=6.4Hz), 1.05 (3H, d, *J*=7.1Hz), 1.81 (1H,m),

2.45 (1H, m), 2.89 (1H, dd, J=14.1, 6.7Hz), 3.19 (1H, dd, J=9.7, 2.4Hz), 3.20 (1H, dd, J=14.1, 5.4Hz), 3.79 (3H, s), 4.41 (1H, d, J=11.1Hz), 4.54 (1H, d, J=11.1Hz), 6.84 (2H, d, J=8.7Hz), 7.22 (2H, d, J=8.7Hz), 7.53-7.67 (3H, m), 7.86 (2H, dd, J=8.7, 1.7Hz). ^{13}C NMR (100MHz) δ: 14.53, 19.36, 19.95, 30.72, 30.85, 55.24, 60.29, 74.10, 86.50, 113.74, 127.79, 129.13, 129.24, 130.87, 133.50, 140.08, 159.11. HREIMS m/z: calcd for $C_{21}H_{28}O_4S$: 376.1707; found: 376.1741.

(2*R*,4*R*,6*S*,8*R*,10*R*,12*R*,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-4,6;8,10;12,14-tris-O-isopropylidene-15-methylhexadecane-1,2,4,6,8,10,12,14-octol (20). Lithium (122mg, 17.52mmol) was added to liquid ammonia (14ml) and dry EtOH (2ml) at -78°C under an argon atmosphere and the mixture was stirred for 30min. To this solution was added a solution of **7** (1.41g, 1.46mmol) in dry THF (6ml) and the mixture was stirred at the same temperature for 40min. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was warmed gradually to room temperature. The residue was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (65% EtOAc/hexane) gave **20** (862mg, 96%) as a colorless oil. $[\alpha]_D^{25}$+16.0° (c=0.43, $CHCl_3$). IR ($CHCl_3$): 3470, 1460, 1380, 1210, 1170, 1100, 1030, 940, 840cm^{-1}. ^{1}H NMR (270MHz) δ: 0.03 (6H, s), 0.86 (3H, d, J=7.1Hz), 0.89 (9H, s), 1.18 (1H, ddd, J=12.4, 7.8, 7.8Hz), 1.33 (6H, s), 1.35 (6H, s), 1.39 (6H, s), 1.40-1.75 (12H, m), 1.79 (1H, m), 3.44-3.64 (6H, m), 3.79 (1H, m), 3.85-4.14 (6H, m). ^{13}C NMR (100MHz) δ: -5.49, 12.26, 18.23, 19.73, 24.72, 24.78, 25.86, 30.18, 33.48, 38.63, 38.92, 40.67, 41.90, 42.31, 62.57, 62.70, 62.95, 63.91, 65.73, 66.43, 67.12, 69.44, 71.76, 98.22, 100.27, 100.69. FABMS m/z: 641 (MNa^+), 619 (MH^+).

(2*R*,4*R*,6*S*,8*R*,10*R*,12*R*,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-4,6;8,10;12,14-tris-O-isopropylidene-15-methyl-2-O-(tetrahydro-2*H*-pyran-2-yl)-hexadecane-1,2,4,6,8,10,12,14-octol (22). A mixture of **20** (862mg, 1.39mmol) and pivaloyl chloride (0.205ml, 1.167mmol) in pyridine (6ml) was stirred at 0°C for 3h. After addition of MeOH (0.2ml), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (22% EtOAc/hexane) to give a pivalate (884mg, 90%). $[\alpha]_D^{25}$+15.9° (c=0.41, $CHCl_3$). IR ($CHCl_3$): 3460, 1720, 1460, 1380, 1210, 1160, 1030, 940, 840cm^{-1}. ^{1}H NMR (270MHz) δ: 0.03 (6H, s), 0.86 (3H, d, J=7.1Hz), 0.89 (9H, s), 1.16 (1H, m), 1.22 (9H, s), 1.33 (6H, s), 1.35 (6H, s), 1.39 (6H, s), 1.40-1.75 (11H, m), 1.83 (1H, m), 3.53 (1H, dd, J=9.8, 4.7Hz), 3.59 (1H, m), 3.60 (1H, dd, J=9.8, 3.4Hz), 3.79 (1H, m), 3.91-4.16 (7H, m), 4.03 (1H, s, OH). ^{13}C NMR (100MHz) δ: -5.49, 12.26, 18.23, 19.73, 24.73, 24.81, 25.86, 27.17, 30.19, 33.49, 38.64, 38.80, 38.92, 38.97, 40.69, 41.90, 42.31, 62.57, 62.65, 62.95, 63.92, 65.73, 67.02, 67.82, 69.45, 69.66, 98.22, 100.28, 100.70.

A mixture of the pivalate (332mg, 0.47mmol), dihydropyran (0.065ml, 0.71mmol), and pyridinium p-toluenesulfonate (10mg) in CH_2Cl_2 (3ml) was stirred at room temperature for 2h. After addition of triethylamine (0.1ml), the reaction mixture was concentrated. Purification by flash chromatography (15% EtOAc/hexane) gave **21** (355mg, 95%) as a colorless oil. FABMS m/z: 787 (MH^+).

To a stirred solution of **21** (1.00g, 1.27mmol) in dry ether (20ml) at 0°C was added $LiAlH_4$ (60mg, 1.58mmol) and the suspension was stirred for 30min. The reaction was quenched with water (0.5ml). After being stirred for 10min at room temperature, the organic layer was separated, dried, and concentrated. The residue was subjected to flash chromatography (32% EtOAc/hexane). The THP anomers of **22** were isolated in a combined yield of 96%.

Less Polar Isomer of 22. This isomer, with R_f=0.34 (40% EtOAc/hexane), was isolated as a colorless oil (408mg, 44%). $[\alpha]_D^{25}$+1.49° (c=0.55, $CHCl_3$). IR ($CHCl_3$): 3460, 1465, 1440, 1380, 1220, 1170, 1030, 840cm^{-1}. ^{1}H NMR (400MHz) δ: 0.01 (6H, s), 0.85 (3H, d, *J*=7.1Hz), 0.87 (9H, s), 1.15 (1H, ddd, *J*=12.2, 11.7, 11.7Hz), 1.31 (3H, s), 1.32 (6H, s), 1.33 (3H, s), 1.34 (3H, s), 1.38 (3H, s), 1.43-1.65 (15H, m), 1.72-1.87 (3H, m), 2.16 (1H, s, OH), 3.51 (1H, dd, *J*=9.5, 6.1Hz), 3.54 (3H, m), 3.58 (1H, dd, *J*=9.5, 5.1Hz), 3.77 (2H, m), 3.75-4.03 (6H, m), 4.49 (1H, m). ^{13}C NMR (100MHz) δ: -5.49, 12.27, 18.24, 19.73, 20.95, 24.59, 24.73, 24.81, 25.03, 25.87, 30.19, 31.48, 33.49, 38.10, 38.67, 38.94, 40.69, 41.96, 42.32, 62.65, 62.65, 62.96, 63.51, 63.92, 64.71, 65.53, 65.75, 69.45, 79.51, 98.22, 100.27, 100.40, 100.88. HRFABMS *m/z*: calcd for $C_{37}H_{71}O_{10}Si$ (MH^+): 703.4812; found: 703.4837.

More Polar Isomer of 22. This isomer, with R_f=0.26 (40% EtOAc/hexane), was isolated as a colorless oil (479mg, 51%). $[\alpha]_D^{25}$+41.4° (c=0.37, $CHCl_3$). IR ($CHCl_3$): 3460, 1465, 1440, 1380, 1220, 1170, 1030, 840cm^{-1}. ^{1}H NMR (400MHz) δ: 0.01 (6H, s), 0.85 (3H, d, *J*=7.1Hz), 0.87 (9H, s), 1.15 (1H, ddd, *J*=12.2, 11.7, 11.7Hz), 1.26 (1H, m), 1.31 (9H, s), 1.34 (6H, s), 1.38 (3H, s), 1.44-1.65 (11H, m), 1.68-1.92 (6H, m), 2.69 (1H, br, OH), 3.50 (1H, m), 3.52 (1H, dd, *J*=9.5, 4.4Hz), 3.55 (1H, dd, *J*=11.0, 4.6Hz), 3.58 (1H, dd, *J*=9.5, 5.4Hz), 3.65 (1H, dd, *J*=11.0, 6.9Hz), 3.78 (1H, m), 3.85-4.07 (7H, m), 4.69 (1H, t, *J*=4.9Hz). ^{13}C NMR (100MHz) δ: -5.48, 12.27, 18.24, 19.74, 20.05, 24.66, 24.73, 24.79, 25.32, 25.87, 30.19, 31.08, 33.49, 37.91, 38.67, 38.83, 40.69, 41.94, 42.32, 62.64, 62.76, 62.96, 63.14, 63.24, 63.29, 63.92, 65.75, 69.45, 74.53, 98.24, 98,32, 100.28, 100.47. FABMS *m/z*: 703 (MH^+).

(2*R*,4*R*,6*S*,8*R*,10*R*,12*R*,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6,8,10,12,14-heptahydroxy-4,6;8,10;12,14-tris-O-isopropylidene-15-methyl-2-O-(tetrahydro-2*H*-pyran-2-yl)-hexadecanal (8). To a solution of the less polar isomer of **22** (406mg, 0.58mmol) in DMSO (2.0ml) were added triethylamine (0.767ml, 5.78mmol) and a solution of pyridine-SO_3 complex (552mg, 3.47mmol) in DMSO (1.2ml). The mixture was stirred at room temperature for 3h and then extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (20% EtOAc/hexane) gave **8** (335mg, 83%) as a colorless oil. $[\alpha]_D^{25}$-0.66° (c=0.53, $CHCl_3$). IR ($CHCl_3$): 1730, 1460, 1380, 1220, 1170, 1140, 1080, 1030, 840cm^{-1}. ^{1}H NMR (400MHz) δ: 0.02 (6H, s), 0.85 (3H, d, *J*=7.1Hz), 0.88 (9H, s), 1.16 (1H, ddd, *J*=12.4, 11.7, 11.7Hz), 1.29 (3H, s), 1.31 (6H, s), 1.33 (6H, s), 1.38 (3H, s), 1.42-1.68 (11H, m), 1.69-1.94 (7H, m), 3.47 (1H, m), 3.52 (1H, dd, *J*=9.7, 4.7Hz), 3.59 (1H, dd, *J*=9.7, 5.0Hz), 3.77 (1H, m), 3.86-4.03 (7H, m), 4.60 (1H, m), 9.62 (1H, d, *J*=2.0Hz). ^{13}C NMR (100MHz) δ: -5.49, 12.27, 18.24, 19.74, 19.86, 24.52, 24.72, 24.81, 25.19, 25.87, 30.19, 30.68, 33.49, 37.29, 38.50, 38.67, 40.69, 41.94, 42.32, 62.08, 62.65, 62.70, 62.95, 63.40, 63.92, 65.73, 69.44, 79.80, 98.22, 99.80, 100.27, 100.67, 203.21. FABMS *m/z*: 701 (MH^+).

(2*S*,3*R*,5*R*,7*R*,9*R*,11*S*,13*R*,15*R*,18*S*,19*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,5;7,9;11,13-tris-O-isopropylidene-19-[(4-methoxybenzyl)oxy]-2,18,20-trimethyl-15-O-(tetrahydro-2*H*-pyran-2-yl)-16-henicosene-3,5,7,9,11,13,15-heptol (23). A solution of **4** (360mg, 0.96mmol) in dry THF (5ml) under argon was cooled to -78°C and 1.6M *n*-BuLi in hexane (0.57ml, 0.91mmol) was added. After being stirred for 1h, a solution of **8** (335mg, 0.48mmol) in dry THF (0.5ml) was added and the reaction mixture was stirred at -78°C for 2h. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (25-40% EtOAc/hexane) gave a mixture of hydroxy sulfones (453mg, 88%).

A solution of the hydroxy sulfones (453mg) in pyridine (1.0ml) and acetic anhydride (0.5ml) was stirred at room temperature for 8h and then the solvents were evaporated in vacuo. Purification by flash chromatography (30% EtOAc/hexane) afforded a mixture of acetoxy sulfones (443mg, 94%).

To a cooled (-20°C), stirred solution of the acetoxy sulfones (443mg, 0.396mmol) in dry THF (6.4ml) and MeOH (1.6ml) were added Na_2HPO_4 (112mg) and 5% Na-Hg (1.82g), and the resulting mixture was stirred at -20°C for 3h. The reaction mixture was diluted with ether (20ml) and filtered through a short pad of Celite. The filtrate was then extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (14% EtOAc/hexane) gave **23** (223mg, 62%) as a colorless oil. $[\alpha]_D^{25}$-6.79° (c=0.36, $CHCl_3$). IR ($CHCl_3$): 1620, 1520, 1460, 1380, 1250, 1180, 1100, 1030, 840cm^{-1}. ^{1}H NMR (400MHz) δ: 0.02 (6H, s), 0.87 (3H, d, *J*=7.1Hz), 0.88 (9H, s), 0.92 (3H, d, *J*=6.8Hz), 0.95 (3H, d, *J*=6.8Hz), 1.08 (3H, d, *J*=6.8Hz), 1.16 (1H, q, *J*=12.4Hz), 1.28 (3H, s), 1.31 (6H, s), 1.32 (6H, s), 1.34 (3H, s), 1.38 (3H, s), 1.41-1.71 (15H, m), 1.72-1.92 (4H, m), 2.45 (1H, m), 2.97 (1H, dd, *J*=5.9, 5.4Hz), 3.40 (1H, m), 3.53 (1H, dd, *J*=9.8, 4.6Hz), 3.59 (1H, dd, *J*=9.8, 5.4Hz), 3.79 (3H, s), 3.76-3.88 (3H, m), 3.90-4.03 (4H, m), 4.11 (1H, m), 4.45 (1H, d, *J*=10.7Hz), 4.53 (1H, d, *J*=10.7Hz), 4.66 (1H, br s), 5.49 (1H, dd, *J*=15.4, 7.6Hz), 5.66 (1H, dd, *J*=15.4, 7.6Hz), 6.85 (2H, d, *J*=8.1Hz), 7.27 (2H, d, *J*=8.1Hz). ^{13}C NMR (100MHz) δ: -5.48, 12.27, 16.02, 17.17, 18.25, 19.74, 20.64, 24.75, 24.82, 24.87, 25.45, 25.87, 30.21, 30.98, 33.51, 38.70, 39.13, 39.68, 40.70, 41.62, 41.99, 42.34, 55.25, 62.48, 62.67, 62.97, 63.50, 63.94, 65.75, 69.45, 74.75, 75.50, 88.33, 97.78, 98.24, 100.29, 100.30, 113.66, 129.12, 130.29, 131.31, 135.85, 159.00. HRFABMS *m/z*: calcd for $C_{52}H_{91}O_{11}Si$ (MH^+): 919.6325; found: 919.6307.

(2*S*,3*R*,5*R*,7*R*,9*R*,11*S*,13*R*,15*R*,18*S*,19*S*)-3,5,7,9,11,13,15,19-octahydroxy-3,5;7,9;11,13-tris-O-isopropylidene-2,18,20-trimethyl-15-O-(tetrahydro-2*H*-pyran-2-yl)-16-henicosenal (2). A solution of **23** (224mg, 0.244mmol) in dry THF (4.0ml) was treated with 1.0M Bu_4NF in THF (0.29ml, 0.29mmol) and the reaction mixture was stirred at room temperature for 17h. The mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (40% EtOAc/hexane) afford an alcohol (196mg, 100%) as a colorless oil. $[\alpha]_D^{25}$-5.87° (c=0.94, $CHCl_3$). IR ($CHCl_3$): 3500, 1620, 1520, 1460, 1390, 1250, 1180, 1120, 1040cm^{-1}. ^{1}H NMR (400MHz) δ: 0.85 (3H, d, *J*=7.1Hz), 0.92 (3H, d, *J*=6.6Hz), 0.95 (3H, d, *J*=6.8Hz), 1.09 (3H, d, *J*=6.8Hz), 1.26 (1H, m), 1.29 (3H, s), 1.31 (3H, s), 1.33 (6H, s), 1.37 (3H, s), 1.44 (3H, s), 1.45-1.93 (19H, m), 2.44 (1H, m), 2.98 (1H, dd, *J*=6.1, 5.1Hz), 3.41 (1H, ddd, *J*=11.2, 5.1, 5.1Hz), 3.60 (2H, m), 3.73-3.87 (3H, m), 3.80 (3H, s), 3.98 (4H, m), 4.12 (1H, m), 4.46 (1H, d, *J*=10.5Hz), 4.54 (1H, d, *J*=10.5Hz), 4.66 (1H, m), 5.50 (1H, dd, *J*=15.6, 7.6Hz), 5.66 (1H, dd, *J*=15.6, 7.8Hz), 6.86 (2H, d, *J*=8.3Hz), 7.27 (2H, d, *J*=8.3Hz). ^{13}C NMR (100MHz) δ: 12.90, 16.05, 17.19, 19.74, 20.62, 24.78, 24.85, 24.89, 25.46, 30.18, 31.00, 34.79, 38.69, 39.14, 39.70, 40.38, 41.67, 42.02, 42.08, 55.25, 62.48, 62.68, 62.89, 63.51, 65.73, 67.60, 75.13, 75.50, 76.56, 77.20, 88.36, 97.78, 98.51, 100.29, 100.30, 113.69, 129.11, 130.30, 131.34, 135.85, 159.03. FABMS *m/z*: 805 (MH^+).

To a stirred solution of the alcohol (179mg, 0.223mmol) in dry CH_2Cl_2 (5ml) were added pyridine (20μl) and the Dess-Martin periodinane (189mg, 0.445mmol), and the suspension was stirred at room temperature for 30min. The reaction mixture was extracted with ether, and the extract was washed with 1N NaOH, water, and brine, dried, and concentrated. The residue was purified by flash chromatography (30% EtOAc/hexane) to afford an aldehyde (166mg, 93%) as a colorless oil. $[\alpha]_D^{25}$

-16.4° (c=1.0, $CHCl_3$). IR ($CHCl_3$): 1725, 1610, 1515, 1460, 1380, 1250, 1170, 1130, 1035cm^{-1}. ^{1}H NMR (400MHz) δ: 0.92 (3H, d, *J*=7.0Hz), 0.95 (3H, d, *J*=7.0Hz), 1.05 (3H, d, *J*=7.0Hz), 1.09 (3H, d, *J*=6.6Hz), 1.29 (3H, s), 1.32 (3H, s), 1.33 (6H, s), 1.35 (3H, s), 1.42 (3H, s), 1.45-1.72 (16H, m), 1.74-1.93 (4H, m), 2.43 (2H, m), 2.98 (1H, dd, *J*=6.5, 5.1Hz), 3.40 (1H, m), 3.80 (3H, s), 3.82 (2H, m), 3.99 (4H, m), 4.60 (1H, m), 4.11 (1H, m), 4.46 (1H, d, *J*=10.6Hz), 4.54 (1H, d, *J*=10.6Hz), 4.67 (1H, t, *J*=4.4Hz), 5.49 (1H, dd, *J*=15.3, 7.0Hz), 5.66 (1H, dd, *J*=15.3, 7.3Hz), 6.86 (2H, d, *J*=8.8Hz), 7.28 (2H, d, *J*=8.8Hz), 9.74 (1H, d, *J*=2.2Hz). ^{13}C NMR (100MHz) δ: 9.66, 16.04, 17.16, 19.60, 19.73, 20.62, 24.75, 24.82, 24.88, 25.45, 29.96, 30.98, 38.64, 39.11, 39.68, 41.62, 41.97, 42.02, 51.00, 55.25, 62.49, 62.64, 62.81, 63.50, 65.56, 70.17, 74.75, 75.50, 88.33, 97.78, 98.65, 100.29, 100.30, 113.66, 129.12, 130.27, 131.29, 135.85, 159.00, 204.39. FABMS *m/z*: 803 (MH^+).

DDQ (60mg, 0.264mmol) was added to a stirred solution of the aldehyde (165mg, 0.206mmol) in CH_2Cl_2 (6.3ml) and water (0.35ml) at 0°C. After being stirred for 2h, saturated aqueous $NaHCO_3$ (2ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was washed with water, dried, and concentrated. Purification by flash chromatography (30% EtOAc/hexane) provided **2** (122mg, 87%) as a colorless oil. $[\alpha]D^{25}$-29.0° (c=0.87, $CHCl_3$). IR ($CHCl_3$): 3450, 1725, 1460, 1385, 1220, 1170, 1130, 1020, 980cm^{-1}. ^{1}H NMR (400MHz) δ: 0.87 (3H, d, *J*=6.6Hz), 0.99 (3H, d, *J*=6.6Hz), 1.00 (3H, d, *J*=6.2Hz), 1.05 (3H, d, *J*=7.0Hz), 1.28 (3H, s), 1.33 (9H, s), 1.35 (3H, s), 1.42 (3H, s), 1.47-1.73 (16H, m), 1.80 (1H, m), 1.83 (1H, m), 1.91 (1H, m), 2.41 (2H, m), 3.13 (1H, dd, *J*=8.1, 3.3Hz), 3.45 (1H, m), 3.79 (1H, m), 3.87 (1H, ddd, *J*=9.9, 9.9, 1.5Hz), 3.94-4.09 (6H, m), 4.70 (1H, t, *J*=3.7Hz), 5.50 (1H, dd, *J*=15.4, 8.4Hz), 5.67 (1H, dd, *J*=15.4, 5.9Hz), 9.74 (1H, d, *J*=2.2Hz). ^{13}C NMR (100MHz) δ: 9.66, 10.85, 19.12, 19.25, 19.38, 19.60, 24.75, 24.80, 25.30, 29.96, 30.59, 31.19, 33.84, 37.75, 38.64, 39.01, 41.37, 41.96, 42.02, 50.96, 61.94, 62.65, 62.70, 62.81, 63.32, 65.56, 70.17, 78.55, 78.88, 98.63, 98.88, 100.29, 100.37, 132.40, 136.05, 204.39. HRFABMS *m/z*: calcd for $C_{38}H_{67}O_{10}$ (MH^+): 683.4730; found: 683.4759.

Methyl (2*E*,4*E*,6*E*,8*S*)-8,9-Isopropylidenedioxy-2,4,6-nonatrienoate (25). A stirred suspension of allyltriphenylphosphonium bromide (14.71g, 38.38mmol) in dry THF (160ml) was treated with 1.6M *n*-BuLi in hexane (24.0ml, 38.38mmol) at 0°C under an argon atmosphere. After being stirred at 0°C for 25min, methyl (*E*)-3-chloroacrylate (3.90ml, 38.38mmol) was added and the mixture was stirred at room temperature for 90min. The reaction mixture was cooled to 0°C and a solution of 28% MeONa in MeOH (8.0ml, 38.38mmol) was added. The mixture was allowed to stir at 0°C for 30min and then a solution of (*S*)-2,3-O-isopropylidene-*D*-glyceraldehyde (3.84g, 29.52mmol) in dry THF (5ml) was added, immediately followed by the addition of 2,6-di-*t*-butylphenol (50mg). After being stirred at room temperature for 17h, the reaction was quenched with saturated aqueous NH_4Cl and the whole was concentrated. The residue was extracted with ether, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (12% EtOAc/hexane) afforded a *E* and *Z* mixture of triene esters (4.75g, 68%).

A solution of this mixture (6.16g, 25.86mmol) and a trace amount of I_2 in CH_2Cl_2 (45ml) was irradiated with a 300-W sunlamp for 1.5h. The solution was diluted with CH_2Cl_2 (100ml), washed with aqueous $Na_2S_2O_3$, dried, and concentrated. Purification by flash chromatography (9% EtOAc/hexane) gave **25** (5.01g, 82%) as a yellow oil. ^{1}H NMR (270MHz) δ: 1.40 (3H, s), 1.44 (3H, s), 3.62 (1H, dd, *J*=8.1, 7.7Hz), 3.75 (3H, s), 4.13 (1H, dd, *J*=8.1, 6.1Hz), 4.60 (1H, q, *J*=7.1Hz), 5.87 (1H, dd,

J=14.8, 7.4Hz), 5.90 (1H, d, *J*=15.5Hz), 6.33 (1H, dd, *J*=14.8, 11.1Hz), 6.39 (1H, dd, *J*=14.8, 10.8Hz), 6.55 (1H, dd, *J*=14.8, 10.8Hz), 7.30 (1H, dd, *J*=15.5, 11.1Hz). ^{13}C NMR (100MHz) δ: 25.80, 26.57, 51.52, 69.31, 76.34, 109.61, 121.22, 130.80, 131.95, 134.83, 139.18, 144.12, 167.29. EIMS *m/z*: 223 (M^+-CH_3).

(2*E*,4*E*,6*E*,8*S*)-8,9-Isopropylidenedioxy-2,4,6-nonatrienal (26). To a stirred solution of **25** (5.01g, 21.5mmol) in dry CH_2Cl_2 (100ml) at -78°C under argon was added 1.02M diisobutylaluminum hydride in hexane (44.3ml, 45.2mmol). After being stirred at -78°C for 20min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was warmed to room temperature and the stirring was continued for 30min. The organic phase was separated and concentrated. Purification by flash chromatography (30% EtOAc/hexane) gave an alcohol (3.70g, 82%).

A mixture of the alcohol (3.17g, 15.08mmol) and activated MnO_2 (19.67g, 226mmol) in acetone (100ml) was stirred vigorously for 40h at room temperature. The mixture was filtered and the filtrate was concentrated. Purification by flash chromatography (24% EtOAc/hexane) afforded **26** (2.35g, 75%) as a yellow oil. ^{1}H NMR (270MHz) δ: 1.41 (3H, s), 1.45 (3H, s), 3.64 (1H, dd, *J*=8.4, 7.4Hz), 4.15 (1H, dd, *J*=8.4, 6.4Hz), 4.62 (1H, q, *J*=7.1Hz), 5.96 (1H, dd, *J*=15.1, 7.1Hz), 6.18 (1H, dd, *J*=15.5, 8.1Hz), 6.44 (1H, dd, *J*=15.1, 11.1Hz), 6.46 (1H, dd, *J*=15.1, 11.1Hz), 6.67 (1H, dd, *J*=15.1, 11.1Hz), 7.13 (1H, dd, *J*=15.5, 11.1Hz), 9.58 (1H, d, *J*=8.1Hz). ^{13}C NMR (100MHz) δ: 25.76, 26.56, 69.25, 76.17, 109.72, 130.71, 131.54, 131.85, 136.52, 140.94, 151.20, 193.40. FABMS *m/z*: 209 (MH^+).

Ethyl (2*E*,4*E*,6*E*,8*E*,10*S*)-10,11-Isopropylidenedioxy-2,4,6,8-undecatrienoate (27). To stirred suspension of NaH (50% in mineral oil, 442mg, 11.06mmol) in dry THF (90ml) at 0°C was added triethyl phosphonoacetate (2.21ml, 11.06mmol). After being stirred for 50min, a solution of **26** (2.09g, 10.05mmol) in dry THF (10ml) was added and the stirring was continued at 0°C for 1.5h. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was concentrated and extracted with ether. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (12% EtOAc/hexane) gave **27** (2.66g, 95%) as a yellow solid. IR ($CHCl_3$): 1700, 1620, 1600, 1370, 1300, 1210, 1060, 1010, 870cm^{-1}. ^{1}H NMR (270MHz) δ: 1.30 (3H, t, *J*=7.1Hz), 1.40 (3H, s), 1.44 (3H, s), 3.61 (1H, dd, *J*=8.1, 7.7Hz), 4.11 (1H, dd, *J*=8.1, 6.1Hz), 4.20 (2H, q, *J*=7.1Hz), 4.58 (1H, q, *J*=7.7Hz), 5.78 (1H, dd, *J*=14.1, 7.7Hz), 5.88 (1H, d, *J*=15.1Hz), 6.25-6.46 (4H, m), 6.58 (1H, dd, *J*=15.1, 10.1Hz), 7.31 (1H, dd, *J*=15.1, 11.1Hz). ^{13}C NMR (100MHz) δ: 14.26, 25.83, 26.60, 60.26, 69.38, 76.59, 109.49, 121.15, 130.67, 132.72, 132.75, 132.78, 135.48, 140.02, 144.05, 166.98. FABMS *m/z*: 265 (MH^+).

Ethyl (2*E*,4*E*,6*E*,8*E*)-10-Hydroxy-2,4,6,8-decatrienoate (28). A solution of **27** (2.65g, 9.55mmol) in 80% AcOH (40ml) was stirred at room temperature for 15h. The reaction was quenched with 27% aqueous NH_3 and the mixture was extracted with EtOAc. The extract was washed water and brine, dried, and concentrated. Purification by flash chromatography (70% EtOAc/hexane) afforded a diol ester (2.15g, 95%).

A mixture of the diol ester (2.15g, 9.03mmol) and $NaIO_4$ (2.32g, 10.84mmol) in THF (24ml) and water (16ml) was stirred vigorously at room temperature for 15min. The mixture was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (25% EtOAc/hexane) to give an aldehyde (1.70g, 91%). IR ($CHCl_3$): 1700, 1675, 1625, 1365, 1270, 1225, 1010cm^{-1}. ^{1}H NMR (400MHz) δ: 1.31 (3H, t, *J*=7.0Hz), 4.23 (2H, q, *J*=7.0Hz), 6.00 (1H, d, *J*=15.4Hz), 6.23 (1H, dd, *J*=15.0, 7.7Hz), 6.55 (1H, dd, *J*=14.3, 11.0Hz), 6.61 (1H, dd, *J*=14.6, 11.0Hz), 6.65 (1H, dd, *J*=14.3, 10.6Hz), 6.74 (1H, dd, *J*=14.6, 10.6Hz), 7.16 (1H, dd, *J*=15.4,

11.0Hz), 7.33 (1H, dd, J=15.0, 11.0Hz), 9.60 (1H, d, J=7.7Hz). ^{13}C NMR (100MHz) δ: 14.23, 60.54, 123.78, 132.62, 133.66, 134.94, 138.37, 140.68, 143.00, 150.40, 166.54, 193.24. FABMS m/z: 207 (MH^+).

A solution of the aldehyde (1.69g, 8.23mmol) in EtOH (20ml) was added to a stirred mixture of $NaBH_4$ (342mg, 9.05mmol) and $CeCl_3 \cdot 7H_2O$ (3.07g, 8.23mmol) in EtOH (80ml) at 0°C. The mixture was stirred for 20min and then extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (32% EtOAc/hexane) afforded **28** (1.52g, 89%) as a yellow solid. IR ($CHCl_3$): 3600, 3470, 1695, 1620, 1595, 1365, 1300, 1240, 1120, 1005cm^{-1}. ^{1}H NMR (400MHz) δ: 1.29 (3H, t, J=7.1Hz), 1.94 (1H, br, OH), 4.20 (2H, q, J=7.1Hz), 4.24 (2H, d, J=5.6Hz), 5.87 (1H, d, J=15.4Hz), 5.96 (1H, dt, J=14.4, 5.6Hz), 6.29 (1H, dd, J=14.4, 10.7Hz), 6.34 (2H, m), 6.41 (1H, dd, J=14.4, 10.5Hz), 6.58 (1H, dd, J=14.4, 10.7Hz), 7.31 (1H, dd, J=15.4, 11.5Hz). ^{13}C NMR (100MHz) δ: 14.26, 60.30, 63.06, 120.83, 130.20, 130.52, 131.89, 135.02, 136.13, 140.36, 144.26, 167.14. FABMS m/z: 209 (MH^+).

Ethyl (2*E*,4*E*,6*E*,8*E*)-10-Diethoxyphosphoryl-2,4,6,8-decatetraenoate (3). To a solution of **28** (1.26g, 6.08mmol) in CH_2Cl_2 (20ml) at 0°C were added pyridine (0.05ml) and PBr_3 (0.87ml, 9.12mmol). The mixture was stirred for 30min and then water was added. The whole was extracted with ether, and the extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The bromide (1.59g) thus obtained was employed without further purification.

A solution of the bromide (1.59g, 5.89mmol) and triethyl phosphite (2.5ml, 14.44mmol) in toluene (40ml) was refluxed for 8h. After cooling the reaction to ambient temperature, the solution was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (25% EtOAc/hexane) gave **3** (1.50g, 75% overall yield) as a yellow solid. IR ($CHCl_3$): 1700, 1620, 1595, 1370, 1300, 1250, 1025, 965cm^{-1}. ^{1}H NMR (400MHz) δ: 1.30 (3H, t, J=7.1Hz), 1.31 (6H, t, J=7.1Hz), 2.69 (2H, dd, $J_{H\text{-}P}$=23.0, $J_{H\text{-}H}$=7.6Hz), 4.09 (2H, q, J=7.1Hz), 4.10 (2H, q, J=7.1Hz), 4.20 (2H, q, J=7.1Hz), 5.77 (1H, m), 5.87 (1H, d, J=15.1Hz), 6.20-6.36 (3H, m), 6.39 (1H, dd, d, J=14.9, 10.8Hz), 6.57 (1H, dd, J=14.9, 11.0Hz), 7.31 (1H, dd, J=15.1, 11.5Hz). ^{13}C NMR (100MHz) δ: 14.26, 16.39, 16.44, 31.08 (d, $J_{C\text{-}P}$=40.9Hz), 60.25, 62.01, 62.08, 120.83, 125.13 (d, $J_{C\text{-}P}$ =13.2Hz), 131.43 (d, $J_{C\text{-}P}$=5.8Hz), 134.69 (d, $J_{C\text{-}P}$=16.1Hz), 136.05 (d, $J_{C\text{-}P}$=4.9Hz), 140.29, 144.18, 167.05. HRFABMS m/z: calcd for $C_{16}H_{26}O_5P$ (MH^+): 329.1516; found: 329.1552.

(2*E*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-butenal (31). A mixture of (*E*)-2-butene-1,4-diol (1.29g, 14.66mmol), imidazole (2.19g, 32.25mmol), and *t*-butyldiphenylchlorosilane (3.63g, 13.19 mmol) was stirred at 0°C for 15h. The mixture was extracted with ether, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (15% EtOAc/hexane) gave **30** (2.34g, 48%). The MnO_2 oxidation of the above obtained **30** was carried out in the same manner as described for **26** to give **31** (1.37g, 74%) as a solid. IR ($CHCl_3$): 1690, 1435, 1120, 970cm^{-1}. ^{1}H NMR (270MHz) δ: 1.08 (9H, s), 4.45 (2H, dd, J=3.0, 2.0Hz), 6.57 (1H, dddd, J=15.5, 8.1, 2.0, 2.0Hz), 6.85 (1H, ddd, J=15.5, 3.0, 3.0Hz), 7.36-7.48 (6H, m), 7.64-7.73 (4H, m), 9.60 (1H, d, J=8.1Hz).

Preparation of 28 via 33. The procedure for the preparation of **25** was employed with allyltriphenylphosphonium bromide (920mg, 2.4mmol), 1.6M *n*-BuLi in hexane (1.5ml, 2.4mmol), ethyl (*E*)-3-chloroacrylate (0.27ml, 2.4mmol), t-BuOK (268mg, 2.4mmol), and **31** (660mg, 2.0mmol).

Purification of the crude product by flash chromatography (7% EtOAc/hexane) gave **33** (298mg, 33%) as a 1:1.5 mixture of E and Z isomers.

To a solution of **33** (298mg, 0.659mmol) in THF (10ml) was added 1M Bu_4NF in THF (0.79ml, 0.79mmol), and the solution was stirred at room temperature for 1h. The reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and evaporated to give a mixture of hydroxy esters. The photochemical isomerization of the hydroxy esters was carried out in the same manner as described for the preparation of **25** to afford **28** (86.4mg, 63%).

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*R*,17*R*,19*R*,21*S*,23*R*,25*R*,26*E*,28*S*,29*S*)-12,15,17,19,21,23,25,29-octahydroxy-13,15;17,19;21,23-tris-O-isopropylidene-12,28,30-trimethyl-25-O-(tetrahydro-2*H*-pyran-2-yl)-2,4,6,8,10-hentriacontapentaenoate (34). To a solution of hexamethyldisilazane (97.4μl, 0.462mmol) in dry THF (2ml) at -78°C under an argon atmosphere was added 1.6M *n*-BuLi in hexane (290μl, 0.462mmol). The resulting solution was stirred for 5min at -78°C and then for 15min at 0°C, and was recooled to -78°C. To this solution was added a solution of **3** (152mg, 0.462mmol) in dry THF (1.5ml). The mixture was stirred for an additional 15min at -78°C in the dark, and a solution of **2** (105mg, 0.154mmol) in dry THF (1.5ml) was added. The reaction mixture was stirred for 30min at -78°C and was gradually warmed to 0°C over a 30-min period. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with ether. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (30% EtOAc/hexane) afforded **34** (124mg, 94%) as a yellow solid. $[\alpha]_D^{25}$-11.3° (c=0.40, $CHCl_3$). IR ($CHCl_3$): 3450, 1700, 1620, 1575, 1380, 1220, 1130, 1010cm^{-1}. ^{1}H NMR (400MHz) δ: 0.87 (3H, d, *J*=6.8Hz), 0.98 (3H, d, *J*=6.8Hz), 1.00 (3H, d, *J*=6.4Hz), 1.03 (3H, d, *J*=6.8Hz), 1.28 (3H, t, *J*=7.1Hz), 1.29 (3H, s), 1.31 (9H, s), 1.36 (3H, s), 1.40 (3H, s), 1.42-1.73 (16H, m), 1.79 (2H, m), 1.91 (1H, m), 2.30 (1H, m), 2.38 (1H, m), 2.40 (1H, br, OH), 3.12 (1H, dd, *J*=8.1, 4.4Hz), 3.45 (1H, m), 3.72 (1H, m), 3.78 (1H, m), 3.86 (1H, m), 3.90-4.03 (4H, m), 4.06 (1H, m), 4.20 (2H, q, *J*=7.1Hz), 4.70 (1H, br s), 5.50 (1H, dd, *J*=15.6, 8.3Hz), 5.67 (1H, dd, *J*=15.6, 5.9Hz), 5.18 (1H, dd, *J*=15.1, 8.3Hz), 5.86 (1H, d, *J*=15.1Hz), 6.12 (1H, dd, *J*=15.1, 10.5Hz), 6.21 (1H, dd, *J*=14.7, 10.7Hz), 6.25-6.36 (3H, m), 6.42 (1H, dd, *J*=14.6, 10.7Hz), 6.59 (1H, dd, *J*=14.7, 11.0Hz), 7.32 (1H, dd, *J*=15.1, 11.0Hz). ^{13}C NMR (100MHz) δ: 10.84, 14.33, 15.44, 19.13, 19.31, 19.40, 19.73, 24.78, 24.83, 24.83, 25.34, 29.70, 30.14, 30.62, 31.29, 33.32, 37.77, 38.71, 39.04, 41.39, 41.85, 42.01, 42.12, 60.25, 61.97, 62.69, 62.73, 62.92, 63.34, 65.66, 72.47, 78.60, 78.90, 98.43, 98.90, 100.30, 100.41, 120.38, 129.56, 130.42, 130.72, 131.26, 132.44, 135.96, 136.09, 137.40, 138.87, 140.82, 144.45, 167.19. FABMS *m/z*: 879 (MNa^+), 857 (MH^+).

13,15;17,19;21,23-Tris-O-isopropylidene-25-O-(tetrahydro-2*H*-pyran-2-yl)-roxaticin (35). A solution of **34** (32.8mg, 0.038mmol) in 4:1:1 THF/MeOH/H_2O (1.6ml) was treated with 1H LiOH (0.2ml, 0.20mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 8h in the dark. The mixture was diluted with saturated aqueous NH_4Cl (5ml) and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The protected seco-acid (31.7mg, 100%) obtained as a yellow oil, R_f=0.47 (60% EtOAc/hexane), was azeotropically dried by addition and evaporation of two 5ml-portions of dry benzene. This material was employed directly in the next reaction.

To a stirred solution of the seco-acid (31.7mg, 0.038mmol) in dry THF (2ml) under argon were added triethylamine (10.2μl, 0.076mmol) and 2,4,6-trichlorobenzoyl chloride (9.0μl, 0.057mmol). The

yellow solution was stirred at room temperature for 2h in the dark and then diluted with dry toluene (8ml). This solution was added over a period of 4h using a syringe pump to a refluxing solution of dry toluene (74ml) containing 4-dimethylaminopyridine (186mg, 1.52mmol), and the refluxing was continued for an additional 1h. The yellow solution was directly subjected to flash chromatography, eluting with 50% EtOAc/hexane to give a mixture of cyclized products (34.8mg). Preparative thin-layer chromatography (200x200x0.25mm, three plates, 30% EtOAc/hexane) of the mixture provided the macrocyclic lactone **35** (7.4mg, 24%), R_f=0.39 (30% EtOAc/hexane). $[\alpha]_D^{25}$+54.6° (c=0.11, $CHCl_3$). IR ($CHCl_3$): 1700, 1620, 1580, 1385, 1220, 1170, 1135, 1015cm^{-1}. ^{1}H NMR (400MHz) δ: 0.91 (3H, d, *J*=6.6Hz), 0.95 (3H, d, *J*=6.8Hz), 1.05 (3H, d, *J*=7.1Hz), 1.07 (3H, d, *J*=6.8Hz), 1.20 (3H, s), 1.26 (3H, s), 1.26 (3H, s), 1.27 (3H, s), 1.28 (3H, s), 1.30 (3H, s), 1.32-1.70 (15H, m), 1.72-1.97 (4H, m), 2.46 (1H, m), 2.60 (1H, m), 3.42 (1H, m), 3.77-4.02 (6H, m), 4.07 (1H, m), 4.63 (1H, t, *J*=3.5Hz), 4.79 (1H, dd, *J*=9.5, 2.4Hz), 5.49 (1H, dd, *J*=15.9, 4.4Hz), 5.69 (1H, dd, *J*=15.9, 5.9Hz), 5.75 (1H, dd, *J*=15.6, 7.1Hz), 5.83 (1H, d, *J*=15.1Hz), 6.13 (1H, dd, *J*=15.6, 10.0Hz), 6.23 (1H, dd, *J*=14.4, 9.8Hz), 6.26-6.34 (3H, m), 6.39 (1H, dd, *J*=14.7, 10.0Hz), 6.57 (1H, dd, *J*=14.9, 10.7Hz), 7.26 (1H, dd, *J*=15.1, 11.2Hz). ^{13}C NMR (100MHz, C_6D_6) δ: 11.62, 14.22, 18.92, 19.72, 19.82, 20.05, 24.84, 24.84, 24.89, 25.38, 25.59, 26.05, 29.95, 30.48, 31.19, 31.32, 37.12, 39.79, 40.95, 41.84, 42.56, 43.36, 62.09, 63.07, 63.26, 63.83, 64.82, 66.92, 71.66, 74.32, 80.08, 97.82, 98.62, 100.23, 100.25, 121.81, 130.05, 131.12, 131.37, 131.44, 132.09, 132.19, 134.99, 136.49, 137.55, 140.00, 144.19, 166.40. HRFABMS *m/z*: calcd for $C_{48}H_{74}O_{10}Na$ (MNa^+): 833.5175; found: 833.5139.

Roxaticin (1). A solution of protected roxaticin **35** (7.4mg, 9.1μmol) in MeOH (5ml) was treated with Dowex 50Wx8 acidic resin in the dark under an argon atmosphere. After being stirred for 4h, the mixture was filtered and concentrated to give 5.4mg of crude roxaticin. Purification by preparative reverse-phase thin-layer chromatography (RP-18, 100x100x0.25mm, two plates, 10% H_2O/MeOH) gave roxaticin (3.4mg, 62%) as a yellow solid. $[\alpha]_D^{25}$+7.14° (c=0.28, $CHCl_3$). IR (KBr): 3400, 1705, 1625, 1580, 1385, 1305, 1265, 1135, 1025cm^{-1}. ^{1}H NMR (400MHz, DMSO-d_6) δ: 0.84 (3H, d, *J*=6.6Hz), 0.93 (3H, d, *J*=6.6Hz), 0.99 (3H, d, *J*=6.7Hz), 1.01 (3H, d, *J*=6.8Hz), 1.00-1.40 (10H, m), 1.49 (2H, m), 1.87 (1H, m), 2.55 (2H, m), 3.42 (1H, m), 3.71-3.98 (5H, m), 3.87 (1H, d, *J*=4.6Hz, OH), 3.93 (1H, d, *J*=5.6Hz, OH), 4.12 (1H, d, *J*=5.1Hz, OH), 4.15 (1H, m), 4.21 (1H, d, *J*=5.4Hz, OH), 4.36 (1H, d, *J*=3.9Hz, OH), 4.59 (1H, d, *J*=2.9Hz, OH), 4.66 (1H, dd, *J*=9.5, 2.5Hz), 4.99 (1H, s, OH), 5.35 (1H, dd, *J*=16.4, 3.6Hz), 5.55 (1H, dd, *J*=15.4, 5.1Hz), 5.83 (1H, d, *J*=15.1Hz), 5.89 (1H, dd, *J*=15.1, 7.3Hz), 6.12 (1H, dd, *J*=15.4, 10.7Hz), 6.25-6.43 (4H, m), 6.48 (1H, dd, *J*=15.1, 10.7Hz), 6.70 (1H, dd, *J*=14.4, 11.2Hz), 7.12 (1H, dd, *J*=15.4, 11.7Hz). ^{13}C NMR (100MHz, DMSO-d_6) δ: 10.79, 13.66, 18.74, 19.65, 28.81, 35.66, 40.94, 42.56, 44.33, 44.44, 46.65, 46.65, 47.30, 62.37, 62.91, 64.25, 64.92, 67.71, 69.77, 71.02, 79.30, 120.19, 128.72, 129.07, 129.36, 130.45, 130.98, 133.08, 135.71, 137.59, 139.18, 141.12, 144.55, 166.06. HRFABMS *m/z*: calcd for $C_{34}H_{54}O_9Na$ (MNa^+): 629.3662; found: 629.3697.

Acknowledgment. We thank Professor Scott D. Rychnovsky of University of Minnesota for the generous gift of the ^{1}H NMR spectra of synthetic (-)-roxaticin and natural (+)-roxaticin.

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(*Received in Japan* 10 *February* 1995; *accepted* 9 *March* 1995)