Total Synthesis of a Macrocyclic Lactone Antibiotic A26771B and Its Isomers Using Carbohydrates

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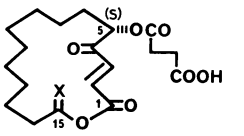
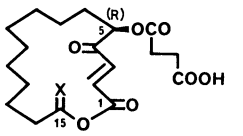
Total synthesis and antibacterial activities of a macrocyclic lactone antibiotic A26771B (**1**) and all its isomers (**2**, **3**, and **4**) are discussed. The starting 8,9,10,12-tetra-*O*-benzyl-2,3,4,5,11-pentadeoxy-*aldehydo*-D-*xylo*-(*E*)-6-dodecenose derived from D-glucose reacted with racemic Wittig reagent, (3-hydroxybutyl)triphenylphosphonium iodide to give 1,3,4,5-tetra-*O*-benzyl-2,8,9,10,11,14,16-heptadeoxy-DL-*glycero*-L-*xylo*-hexadeca-6,12-dienitol, which was in turn converted into methyl 15-*O*-acetyl-6,7,8,9,10,11,12,13,14,16-decadeoxy-4,5-*O*-isopropylidene-DL-*glycero*-L-*threo*-(*E*)-2-hexadecenonate (**13**) through effective oxidation and β-elimination. Saponification followed by Yamaguchi's lactonization of **13** afforded two diastereomeric 16-membered-ring lactones which were converted into (5*S*, 15*R*)-A26771B (**1**) and its (5*S*, 15*S*)-diastereomer (**2**) by successive deacetonation, selective succinylation and oxidation. The other starting 2,3,4,6-tetra-*O*-benzyl-5-deoxy-*aldehydo*-D-*lyxo*-hexose, which was prepared from 2-deoxy-D-glucose, reacted with a Wittig reagent to give 8,9,10,12-tetra-*O*-benzyl-2,3,4,5,11-pentadeoxy-*aldehydo*-D-*lyxo*-6-dodecenose (**20**) followed by hydrolysis. Similar reaction sequence from **20** with the aforesaid series for **1** and **2** afforded the (5*R*, 15*R*)-isomer (**3**) and (5*R*, 15*S*)-isomer (**4**).

A 16-membered macrocyclic lactone antibiotic A26771B (**1**), produced by *Penicillium turbatum*, possesses a novel structure and an interesting antibacterial activity.[1] The first stereospecific total synthesis and the absolute configuration of **1** were disclosed in our laboratories[2] and followed by the elegant synthesis of the racemate by Takei *et al.*[3] The previous stereospecific synthesis was based on a convergent scheme involving both optically pure C-1—C-12 and C-13—C-16 portions, which were derived from D-glucose. Herein we describe in detail, the total synthesis of the antibiotic A26771B [(5*S*,15*R*)-isomer (**1**)], its diastereomers [(5*S*,15*S*)-isomer (**2**) and (5*R*,15*R*)-isomer (**3**)] and enantiomer [(5*R*,15*S*)-isomer (**4**)] in order to further study their structure-activity relationships. The key step was effective separation of the (15*R*)- and (15*S*)-diastereomers after coupling a racemic C-13—C-16 portion (**8**) to an optically active C-1—C-12 portion (**7** or **20**). The latter portion was in turn prepared from D-glucose derivatives, because the C-5 positions of **1** (or **2**) and **3** (or **4**) were stereochemically corresponding to C-2 position of 5-deoxy-D-glucose and C-5 position of 2-deoxy-D-glucose, respectively.



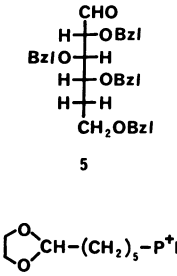
1: X = (R)-Me, H (A26771B)

2: X = (S)-H, Me



3: X = (R)-Me, H

4: X = (S)-H, Me



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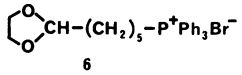

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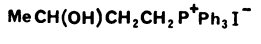

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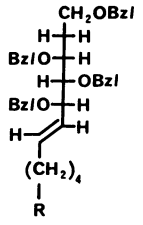
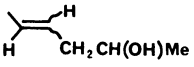
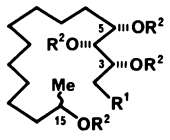


7: R = CHO

9: R = 

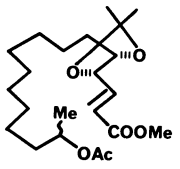
The synthesis of the antibiotic A26771B (**1**) and its (5*S*,15*S*)-diastereomer (**2**) was initiated from the C-1—C-12 portion (**7**), which was obtained from 2,3,4,6-tetra-*O*-benzyl-5-deoxy-*aldehydo*-D-*xylo*-hexose (**5**) and [5-(1,3-dioxolan-2-yl)pentyl]triphenylphosphonium bromide (**6**) by Wittig reaction and subsequent hydrolysis as described in the previous paper.[2] The second Wittig reagent **8** was prepared by a three-step sequence from 1,3-butanediol in a 72% yield. Reaction of **7** with the reactive ylide formed from **8** afforded a 1 : 1 mixture of the two diastereomeric 16-carbon products, 1,3,4,5-tetra-*O*-benzyl-2,8,9,10,11,14,16-heptadeoxy-DL-*glycero*-L-*xylo*-hexadeca-6,12-dienitol (**9**) in a 67% yield. The separation of the diastereomers was not overcome at this stage but done after lactonization as described later on. Catalytic reduction of **9** with hydrogen and palladium black gave the saturated alcohol **10**, which was selectively *t*-butyldimethylsilylated and then totally acetylated to afford the fully masked product **11**. Desilylation of **11** with difluoroacetic acid followed by successive catalytic oxidation of the resulting alcohol and esterification with diazomethane gave the methyl ester, methyl 3,4,5,15-tetra-*O*-acetyl-2,6,7,8,9,10,11,-12,13,14,16-undecadeoxy-DL-*glycero*-L-*xylo*-hexadeconate (**12**). Selective deacetylation of **12** accompanying the desired β-elimination with 4.5 equiv. of potassium *t*-butoxide and 2 equiv. of water followed by acetonation with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone gave the α,β-unsaturated ester, methyl 15-*O*-acetyl-6,7,8,9,10,11,12,13,14,16-decadeoxy-4,5-*O*-isopropylidene-DL-*glycero*-L-*threo*-(*E*)-2-hexadecenonate (**13**). Without water, the above-mentioned reaction gave a very low yield of the elimination product. The *E*-stereochemistry was defined by the 16 Hz coupling



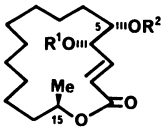
10 : $R^1 = CH_2OH$, $R^2 = H$

11 : $R^1 = CH_2OSiMe_2Bu^t$, $R^2 = Ac$

12 : $R^1 = COOMe$, $R^2 = Ac$

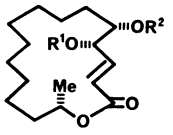


13



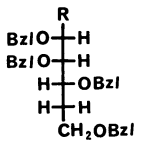
14 : $R^1, R^2 =$ 

16 : $R^1 = R^2 = H$



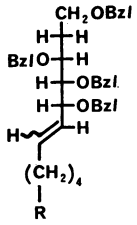
15 : $R^1, R^2 =$ 

17 : $R^1 = R^2 = H$

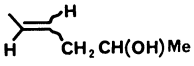


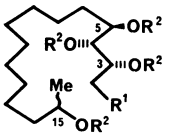
18 : $R = CH_2OTr$

19 : $R = CHO$



20 : $R = CHO$

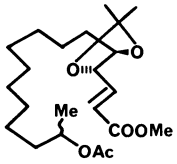
21 : $R =$ 



22 : $R^1 = CH_2OH$, $R^2 = H$

23 : $R^1 = CH_2OSiMe_2Bu^t$, $R^2 = Ac$

24 : $R^1 = COOMe$, $R^2 = Ac$



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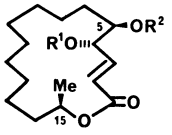
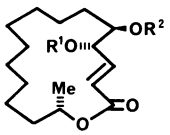


26 : $R^1, R^2 =$ 

28 : $R^1 = R^2 = H$



27 : $R^1, R^2 =$ 

29 : $R^1 = R^2 = H$

constant of the vinylic protons. When treated with lithium hydroxide in 50% aqueous THF, **13** quantitatively furnished the corresponding hydroxy acid, which was submitted to lactonization. Yamaguchi's method[4] among others gave the best yield of the desired lactones **14** and **15**. Namely, the hydroxy acid reacted with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine in THF to give the corresponding mixed anhydride, which was treated with 4-dimethylaminopyridine in toluene at 95 °C. The two diastereomeric 16-membered-ring lactones **14** and **15** were obtained and separated in 45% and 40% yields by silica gel column chromatography. The lactone **14** was identical in all respects with a sample of the same structure stereospecifically synthesized from D-glucose as previously described,[2] and convertible into the antibiotic A26771B (**1**). Therefore, **14** and **15** were found to be (4*S*,5*S*,15*R*)- and (4*S*,5*S*,15*S*)-isomers, respectively. Hydrolysis of **14** and **15** with difluoroacetic acid in aqueous MeOH gave the diols, 6,7,8,9,10,11,12,13,14,16-decadeoxy-D-*glycero*-L-*threo*-(*E*)-2-hexadecenono-1,15-lactone (**16**) and the L-*glycero*-L-*threo*-isomer (**17**) in 94% and 92% yields, respectively. Selective succinylation of **16** and **17** with succinic anhydride and *N*,*N*-diisopropylethylamine in CCl_4 gave predominantly 5-*O*-succinyl compounds, which were oxidized with acetic anhydride and DMSO to afford (5*S*,15*R*)-A26771B (**1**) and the (5*S*,15*S*)-isomer (**2**) in 70% and 73% yields, respectively. The synthetic product **1** thus obtained was identical both spectroscopically and chromatographically with an authentic sample of the natural antibiotic.

Subsequently, the (5*R*,15*R*)- and (5*R*,15*S*)-isomers (**3** and **4**) were synthesized by the similar strategy to the aforesaid. The starting 2,3,4,6-tetra-*O*-benzyl-1-*O*-trityl-5-deoxy-D-*lyxo*-hexose (**18**) was prepared from 2-deoxy-D-glucose successively by tritylation, $NaBH_4$ reduction and benzylation in a 65% yield. Detritylation of **18** with 90% trifluoroacetic acid followed by oxidation with trifluoroacetic anhydride and DMSO in dichloromethane gave 2,3,4,6-tetra-*O*-benzyl-5-deoxy-*aldehydo*-D-*lyxo*-hexose (**19**), in a 78% yield, which had the opposite configuration only at the C-2 position in comparison with **5**. The Wittig reaction of **19** with the ylide derived from **6**, followed by hydrolysis with 70% trifluoroacetic acid, gave the 12-carbon skeletal aldehyde **20** in an 82% yield. The second Wittig reaction of **20** with the ylide formed from **8** gave a 1 : 1 mixture of the two diastereomeric compounds, 1,3,4,5-tetra-*O*-benzyl-2,8,9,10,11,14,16-heptadeoxy-DL-*glycero*-D-*arabino*-hexadeca-6,12-dienitol (**21**). Reduction of **21** to give **22**, followed by successive silylation and acetylation, afforded **23**, which was in turn converted into the corresponding methyl ester **24** as efficiently as described in the preparation for **12**. Selective deacetylation with β-elimination of **24**, followed by acetonation gave methyl 15-*O*-acetyl-6, 7, 8, 9, 10, 11, 12, 13, 14, 16-decadeoxy-4,5-*O*-isopropylidene-DL-*glycero*-D-*erythro*-(*E*)-2-hexadecenonate (**25**) as described in the preparation for **13**. Saponification of **25** with LiOH gave the corresponding hydroxy acid, which was cyclized as described for the preparation of **14** and **15** to afford, after column chromatography, the two diastereomeric lactones **26** [(4*S*,5*R*,15*R*)-isomer] and **27** [(4*S*,5*R*,15*S*)-isomer] in 47% and 39% yields. The independent conversion of the diastereomers **26** and **27** into the optically pure (5*R*,15*R*)-isomer (**3**) and (5*R*,15*S*)-isomer (**4**) involved the same reagents and reaction conditions through **28** and **29** as mentioned in the scheme for the aforesaid compounds **1** and **2**, and gave similar yields. Conclusive evidence for the stereochemical assignments at the C-5

TABLE 1. MINIMAL INHIBITORY CONCENTRATION (mcg/ml) OF THE PRODUCTS

	A26771B	1	2	3	4
Staph. aureus 193	6.25	6.25	12.5	1.56	6.25
Staph. aureus 209P	6.25	6.25	12.5	3.12	6.25
Staph. aureus MS9610	6.25	6.25	12.5	3.12	3.12
Staph. aureus MS9351	6.25	6.25	12.5	3.12	6.25
Staph. aureus MS9861	6.25	6.25	12.5	1.56	6.25
Staph. aureus MS10225	6.25	6.25	12.5	3.12	6.25
Staph. aureus MS10246	6.25	6.25	12.5	3.12	6.25
Sarcina lutea PCI1001	6.25	6.25	12.5	6.25	12.5
B. subtilis B-558	50	50	50	50	50
E. coli NIHJ	>50	>50	>50	>50	>50

and C-15 positions was provided by identification of **4** with the natural antibiotic A26771B (**1**) in all respects except for the sign of the optical rotation.

Biological investigation of the natural antibiotic A26771B and synthetic products **1**, **2**, **3**, and **4** revealed (Table 1) that all products exhibited in vitro antibiotic activities against Gram-positive and macrolide-resistant Gram-positive bacteria and the (5*R*,15*R*)-isomer **3** was approximately twice as active as A26771B (**1**). This lack of the essential stereochemical requirement for the antibiotic activity of this class of novel compounds was the most striking aspect, suggesting pliable possibility in chemical modification of macrolide antibiotics.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR and UV spectra were recorded on Hitachi Perkin-Elmer 225 and JASCO UV IDEC-1 spectrometers, respectively, and ^{1}H-NMR spectra in $CDCl_3$ with TMS as internal standard on a Varian EM-390 (90 MHz) or a Bruker WM 250 spectrometer (250 MHz). Optical rotations were measured on a Carl Zeiss photoelectric polarimeter. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 and Wakogel C-200, respectively. In general, evaporation was carried out under reduced pressure below 30 °C.

*(3-Hydroxybutyl)triphenylphosphonium Iodide (**8**).* To a stirred and ice-cooled solution of 1,3-butanediol (5.0 g, 55 mmol) in acetonitrile (75 ml) were added *p*-toleunesulfonyl chloride (10 g) and triethylamine (10 ml), and stirring at room temperature was continued for 2.5 h. The resulting solution was partitioned between ether and water, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ and NaCl solutions, dried and evaporated to a residue, which was chromatographed on silica gel (250 g) with 3 : 2 hexane–ethyl acetate to give a syrup of the corresponding tosylate (11 g, 82%).

To a solution of the tosylate (11 g) in acetone (110 ml) was added NaI (12.7 g), and the solution was stirred at 60 °C for 1 h. The precipitated salt was filtered and the filtrate was evaporated to a residue, which was partitioned between benzene and water. The organic layer was dried and evaporated to give a syrup of the iodo compound.

A solution of the syrup in benzene (40 ml) was stirred with triphenylphosphine (14 g) at 80 °C for 20 h under argon. The precipitated product was filtered and recrystallized from methanol–ethyl acetate to give needles of **8** (18.2 g, 90%): mp 149—152 °C.

Found: C, 56.97; H, 5.20; I, 27.61%. Calcd for $C_{22}H_{24}$-OIP: C, 57.16; H, 5.23; I, 27.45%.

*1,3,4,5-Tetra-*O*-benzyl-2,8,9,10,11,14,16-heptadeoxy-*DL*-glycero-*L*-xylo-hexadeca-6,12-dienitol (**9**).* To a suspension of **8** (5.4 g, 11.7 mmol) in dry THF (54 ml) were added with stirring at room temperature, under argon, 2M sodium methylsulfinylmethanide solution prepared *in situ* from NaH (199 mg, 8.29 mmol) and DMSO (4.14 ml), and then a 1.6 M butyllithium solution in hexane (6.23 ml, 10 mmol). After 5 min, to the resulting orange solution was added a solution of **7** (3.57 g, 5.88 mmol) in dry THF (18 ml) with stirring, and stirring at room temperature was continued for 0.5 h. The reaction solution was diluted with water and extracted with ether. The combined extracts were then evaporated, and the residue was chromatographed on silica gel (300 g) with 4 : 1 hexane–ethyl acetate to give a colorless syrup of **9** (2.57 g, 67%): R_f 0.20 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{15}$ +45° (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ=1.13 and 1.18 (3H in total, each d, Me-15, $J_{15,Me}$=6 Hz), 3.50 (2H, t, H-1, $J_{1,2}$= 6 Hz), 3.53—4.05 (4H, m, H-3,4,5 and 15), 4.21—4.80 (8H, m, PhC$\underline{H_2}$O×4), 5.34—5.78 (4H, m, H-6,7,12 and 13), 7.33 (20H, s, Ph×4).

Found: C, 80.01; H, 8.17%. Calcd for $C_{44}H_{54}O_5$: C, 79.72; H, 8.21%.

*3,4,5,15-Tetra-*O*-acetyl-1-*O*-(t-butyldimethylsilyl)-2,6,7,8,9,10,-11,12,13,14,16-undecadeoxy-*DL*-glycero-*L*-xylo-hexadecitol (**11**).* A solution of **9** (547 mg) in methanol (8 ml) was shaken with palladium black and 3-atm hydrogen at room temperature for 15 h, filtered and evaporated to give a crude solid (250 mg) of **10**: R_f 0.25 (6 : 1 chloroform–methanol).

To a stirred solution of crude **10** (250 mg) in dry pyridine (2.5 ml) was added *t*-butyldimethylsilyl chlorde (150 mg), and the solution was kept at room temperature. After 3 h, TLC indicated the absence of starting material. Acetic anhydride (0.67 ml) was added and the mixture stirred overnight at room temperature. After addition of EtOH, the solution was evaporated and the residue was dissolved in ethyl acetate. The solution was washed successively with saturated aqueous $NaHCO_3$ and NaCl solutions, dried, and evaporated. The residue was chromatographed on silica gel (25 g) with 5 : 1 hexane–ethyl acetate to give a syrup of **11** (370 mg, 77% from **9**): R_f 0.37 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{17}$ 0° (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ=0.05 (6H, s, Me_2Si), 0.88 (9H, s, *t*-BuSi), 1.20 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 2.02, 2.05, and 2.08 (12H in total, each s, OAc×4), 3.62 (2H, t, H-1, $J_{1,2}$=6 Hz).

Found: C, 61.10; H, 9.32%. Calcd for $C_{30}H_{56}O_9Si$: C, 61.19; H, 9.59%.

*Methyl 3,4,5,15-Tetra-*O*-acetyl-2,6,7,8,9,10,11,12,13,14,16-undecadeoxy-*DL*-glycero-*L*-xylo-hexadeconate (**12**).* To a solution of **11** (340 mg, 0.577 mmol) in acetonitrile (10 ml) was added 0.08 M difluoroacetic acid solution in 50% aqueous acetonitrile (5.1 ml), and the solution was left at 50 °C for 5 h,

neutralized with a saturated aqueous $NaHCO_3$ solution and then extracted with ether. The combined extracts were washed with a saturated aqueous NaCl solution, dried, and evaporated to give a syrup of the crude alcohol (274 mg): R_f 0.13 (3 : 2 hexane–ethyl acetate).

Subsequently, gaseous oxygen (600 ml/min) was bubbled into a solution of the syrup (274 mg) in 75% aqueous dioxane at 85 °C for 5 h in the presence of platinum black (150 mg).

The mixture was filtered, and the filtrate was evaporated to give a residue of the carboxylic acid.

The residue was dissolved in ether (5 ml), and an excess of etheral diazomethane solution was added. The resulting yellowish solution was stirred for 0.5 h at room temperature and then evaporated to the residue, which was chromatographed on silica gel (20 g) with 2 : 1 hexane–ethyl acetate to give a syrup of **12** (250 mg, 86% from **11**): R_f 0.24 (3 : 2 hexane–ethyl acetate); $[\alpha]_D^{16}$ +15° (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ=1.23 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 2.02, 2.05 and 2.08 (12H in total, each s, OAc×4), 2.60 (2H, d, H-2, $J_{2,3}$=6 Hz), 3.68 (3H, s, COOMe).

Found: C, 59.71; H, 8.21%. Calcd for $C_{25}H_{42}O_{10}$: C, 59.74; H, 8.42%.

*Methyl 15-O-Acetyl-6,7,8,9,10,11,12,13,14,16-decadeoxy-4,5-O-isopropylidene-*DL-glycero-L-threo-*(E)-2-hexadecenonate (**13**).* To a solution of **12** (330 mg) in *t*-butyl alcohol (9.9 ml) were added water (0.024 ml) and 0.5 M potassium *t*-butoxide solution in *t*-butyl alcohol (14.8 ml) at room temperature. After 2 min, the reaction solution was neutralized with Dowex 50WX8 (H type) and filtered. The filtrate was evaporated to a residue, which was chromatographed on silica gel (15 g) with 1 : 1 hexane–ethyl acetate to give a syrup of the (*E*)-unsaturated ester (115 mg, 49%).

A solution of the syrup (84 mg) in dry acetone (1.7 ml) was stirred with 2,2-dimethoxypropane (3.4 ml) in the presence of TsOH (4.2 mg) at room temperature for 1.5 h, neutralized with triethylamine and then evaporated to a residue. The residue was partitioned between chloroform and water, and the combined organic layers were evaporated to give a syrup, which was chromatographed on silica gel (10 g) with 5 : 1 hexane–ethyl acetate to give a syrup of **13** (77 mg, 82%): R_f 0.36 (5 : 1 hexane–ethyl acetate); $[\alpha]_D^{18}$ −13° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 212 nm (ε 10200); ^{1}H-NMR δ=1.20 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.41 and 1.44 (each 3H, s, Me_2C), 2.03 (3H, s, OAc), 3.72 (1H, m, H-5), 3.77 (3H, s, COOMe), 4.10—4.20 (1H, m, H-4), 4.80—4.95 (1H, m, H-15), 6.13 (1H, dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=1.5 Hz), 6.89 (1H, dd, H-3, $J_{2,3}$=16 Hz, $J_{3,4}$=6 Hz).

Found: C, 66.52; H, 9.49%. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61%.

*6,7,8,9,10,11,12,13,14,16-Decadeoxy-4,5-O-isopropylidene-*D-glycero-L-threo-*(E)-2-hexadecenono-1,15-lactone (**14**) and* L-glycero-L-threo-*isomer (**15**).* A solution of **13** (132 mg, 0.33 mmol) in 50% aqueous THF (5.0 ml) was stirred with a 0.2 M LiOH solution in 50% aqueous THF (5.8 ml) at 30° for 2 d. The resulting solution was neutralized with Dowex 50WX8 (H type) to pH 4, and then filtered. The filtrate was extracted with ether. The extracts were washed with a saturated aqueous NaCl solution, dried and evaporated to give quantitatively the corresponding hydroxy acid (120 mg): R_f 0.29 (3 : 2 hexane–acetone).

To a mixture of the hydroxy acid (120 mg) and triethylamine (0.108 ml) in dry THF (1.2 ml) was added a solution of 2,4,6-trichlorobenzoyl chloride[4] (172 mg) in dry THF (1.7 ml), and the mixture was stirred for 1 h at room temperature. After removal of triethylamine hydrochloride under argon, the filtrate was diluted with dry toluene (175 ml). The resulting solution was added dropwise to the refluxing solution of 4-dimethylaminopyridine (258 mg) in dry toluene (35 ml) at 95 °C over a 6-h period with stirring under argon, and stirring at this temperature was continued for another 40 min. The reaction solution diluted with ether (500 ml) was washed successively with satu rated aqueous citric acid and $NaHCO_3$ solutions, dried, and then evaporated to give a residue. The residue was chromatographed on silica gel (15 g) with 20 : 1 hexane–ethyl acetate. The eluates between 57—78 ml (R_f 0.30 with 10 : 1 hexane–ethyl acetate) were collected and evaporated to give a solid. Recrystallization from acetone–ethanol–water afforded colorless needles of **14** (52 mg, 45%): mp 74—75 °C (lit,[2] mp 74—75 °C); $[\alpha]_D^{13}$ +7.0° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 212 nm (ε 10300); ^{1}H-NMR δ=1.27 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.42 (6H, s, Me_2C), 3.73 (1H, m, H-5), 4.12 (1H, dt, H-4, $J_{3,4}$=6.0 Hz, $J_{2,4}$=1.5 Hz), 5.03 (1H, m, H-15), 6.11 (1H, dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=1.5 Hz), 6.88 (1H, dd, H-3, $J_{2,3}$=16 Hz, $J_{3,4}$=6.0 Hz).

Found: C, 70.55; H, 9.77%. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%.

The other eluates between 80—105 ml (R_f 0.25 with 10 : 1 hexane–ethyl acetate) gave a colorless syrup of **15** (45 mg, 40%): $[\alpha]_D^{13}$ +52° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 211 nm (ε 9800); ^{1}H-NMR δ=1.26 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.46 (6H, s, Me_2C), 3.85 (1H, m, H-5), 4.05 (1H, dull t, H-4, J=8 Hz), 5.04 (1H, m, H-15), 6.07 (1H, dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=0.5 Hz), 6.76 (1H, dd, H-3, $J_{2,3}$=16 Hz, $J_{3,4}$=8 Hz).

Found: C, 70.63; H, 9.74%. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%.

*6,7,8,9,10,11,12,13,14,16-Decadeoxy-*D-glycero-L-threo-(E)-*2-hexadecenono-1,15-lactone (**16**).* A sample of **14** (33 mg) was dissolved in a mixture (0.5 ml) of difluoroacetic acid, methanol and water (4 : 3 : 1). The solution was stirred for 1 h at room temperature and then evaporated to a residue, which was chromatograhed on silica gel (3 g) with 3 : 1 hexane–acetone to give needles of **16** (27 mg, 94%): R_f 0.51 (3 : 2 hexane–acetone): mp 86—87 °C (lit,[2] 86—87 °C); $[\alpha]_D^{15}$ −43° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 214 nm (ε 10900).

Found: C, 67.55; H, 9.97%. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92%.

*6,7,8,9,10,11,12,13,14,16-Decadeoxy-*L-glycero-L-threo-(E)-*2-hexadecenono-1,15-lactone (**17**).* A sample of **15** (25 mg) was hydrolyzed by the procedure described in the preparation of **16** and then worked up to give a syrup of **17** (21 mg, 92%): R_f 0.49 (3 : 2 hexane–acetone); $[\alpha]_D^{15}$ +12.5° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 213 nm (ε 10600).

Found: C, 67.69; H, 10.01%. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92%.

*A26771B: 5-O-(3-Carboxypropionyl)-4-oxo-4,6,7,8,9,10,11,12,-13,14,16-undecadeoxy-*D-glycero-L-glycero-(E)-*2-hexadecenono-1,15-lactone (**1**).* To a suspension of **16** (19 mg, 0.067 mmol) in dry CCl_4 (0.95 ml) were added succinic anhydride (10 mg) and *N,N*-diisopropylethylamine (0.024 ml) under argon, and the mixture was stirred for 2 h at 50 °C. After addition of ethyl acetate and water, the aqueous layer was acidified to pH 1 with 1 M HCl. The organic layer was dried and then evaporated to a residue, which was purified by PLC with 8 : 1 chloroform–ethanol to give crude crystals of the corresponding succinate (19 mg): R_f 0.55 (8 : 1 chloroform–ethanol); mp 120—122 °C (hexane–ethyl acetate).

The crystals (9.0 mg) was dissolved in a mixture of acetic anhydride (0.064 ml) and dry DMSO (0.22 ml), and the solution was kept at 30 °C for 20 h. The resulting solution diluted with ethyl acetate was washed with water, dried and evaporated to a residue, which was purified by PLC with 8 : 1 chloroform–ethanol to give, after recrystallization from ethyl acetate–hexane, needles (6.1 mg, 51% from **16**) of A26771B

(**1**): R_f 0.57 (8 : 1 chloroform-ethanol); mp and mmp 125—126 °C (lit,[2]) mp 125—126 °C); $[\alpha]_D^{12}$ −13° (*c* 0.2, MeOH); UV_{max} (MeOH) 223 nm (ε 13300); IR (KBr) 1750, 1725, 1720, 1710, 1705 (succinyl ester, lactone) and ≈1645 (C=C) cm^{-1}; ^{1}H-NMR δ=1.30 (3H, d, Me-15, $J_{15,Me}$=6.5 Hz), 2.73 (4H, m, succinyl C$\underline{H}_2$-C$\underline{H}_2$), 5.15 (1H, m, H-15), 5.33 (1H, t, H-5, $J_{5,6}$=5.5 Hz), 6.75 and 7.22 (each 1H, AB-q, H-2 and 3, $J_{2,3}$=15.5 Hz). Its UV, IR, and ^{1}H-NMR spectra and TLC behavior were identical with those of an authentic sample of the natural product.

Found: C, 62.79; H, 8.05%. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%.

5-O-(3-Carboxypropionyl)-4-oxo-4,6,7,8,9,10,11,12,13,14,16-undecadeoxy-L-glycero-L-glycero-(E)-*2-hexadecenono-1,15-lactone* (***2***). Following the procedure described for **1**, from **17**, a syrup of **2** (9.7 mg, 51% from **17**) was obtained: R_f 0.57 (8 : 1 chloroform–ethanol); $[\alpha]_D^{17}$ +25° (*c* 0.2, MeOH); UV_{max} (MeOH) 223 nm (ε 10100); IR ($CHCl_3$) 1740, 1735, 1720, 1710, 1700 (succinyl ester, lactone) and ≈1620 (C=C) cm^{-1}; ^{1}H-NMR δ=1.29 (3H, d, Me-15, $J_{15,Me}$=6.5 Hz), 2.76 (4H, m, succinyl C$\underline{H}_2$-C$\underline{H}_2$), 5.09 (1H, m, H-15), 5.35 (1H, t, H-5, $J_{5,6}$=6 Hz), 6.76 and 7.16 (each 1H, AB-q, H-2 and 3, $J_{2,3}$=16 Hz).

Found: C, 62.69; H, 8.11%. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%.

2,3,4,6-Tetra-O-*benzyl-1*-O-*trityl-5-deoxy*-D-lyxo-*hexose* (***18***). To a stirred and ice-cooled solution of 2-deoxy-D-glucose (1.05 g, 6.4 mmol) in dry pyridine (10.5 ml) was added trityl chloride (1.96 g), and stirring was continued at room temperature for 15 h. After addition of a few drops of water, the resulting solution was evaporated to a residue, which was partitioned between ethyl acetate and a saturated aqueous NaCl solution. The organic layer was dried and evaporated to give quantitatively a crude solid of the *O*-trityl compound (2.7 g).

To a solution of this crude compound (24.7 g) in 80% aqueous ethanol (250 ml) was added $NaBH_4$ (2.3 g), and the solution was stirred for 1 h at room temperature. After neutralization with Dry Ice, the solution was evaporated to a residue, which was chromatographed twice on silica gel (400 g and 1 kg) with 5 : 1 and 10 : 1 chloroform–methanol, respectively, to give a pure syrup of the corresponding alcohol (22 g, 88%): $[\alpha]_D^{19}$ −2.5° (*c* 2.0, $CHCl_3$): ^{1}H-NMR δ=1.27—2.05 (2H, m, H-5), 2.93—4.20 (11H, m, H-1,2,3,4,6 and OH×4), 6.94—7.82 (15H, m, trityl).

Found: C, 73.70; H, 7.00%. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91%.

A solution of this alcohol (10 g) in dry THF (130 ml) was added to NaH (3 g), and the mixture was stirred at room temperature. After 1 h, benzyl bromide (14.6 ml) was added, and stirring at 50 °C was continued for another 2 h. The reaction mixture was partitioned between benzene and water, and the organic layer was washed with a saturated aqueous NaCl solution, dried and evaporated to a residue. The residue was chromatographed on silica gel (600 g) with 10 : 1 hexane-ethyl acetate to give a syrup of **18** (14 g, 65% from 2-deoxy-D-glucose): ^{1}H-NMR δ=1.75—1.95 (2H, m, H-5), 3.42 (2H, t, H-6, $J_{5,6}$=6.0 Hz), 3.47 (2H, d, H-1, $J_{1,2}$=6.0 Hz), 3.70—3.95 (3H, m, H-2,3 and 4), 4.28—4.79 (8H, m, PhC$\underline{H}_2$O×4), 6.95—7.55 (35H, m, Ph×7). Without further purification, the syrup was used for the next step.

2,3,4,6-Tetra-O-*benzyl-5-deoxy*-aldehydo-D-lyxo-*hexose* (***19***). An ice-cooled solution of **18** (11.5 g, 15 mmol) in 90% aqueous trifluoroacetic acid (50 ml) was stirred for 1 h, and then evaporated to a residue, which was partitioned between chloroform and a saturated aqueous $NaHCO_3$ solution. The organic layer was washed with a saturated aqueous NaCl solution, dried and evaporated to a residue, which was chromatographed on silica gel (600 g) with 10 : 1 benzene–ethyl acetate to give a syrup of the de-*O*-tritylated compound (7.50 g, 95%): R_f 0.11 (5 : 1 hexane–ethyl acetate); $[\alpha]_D^{19}$ +7.5° (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ=1.76—2.10 (2H, m, H-5), 2.10—2.34 (1H, m, OH-1), 3.50 (2H, t, H-6, $J_{5,6}$=6 Hz), 3.61—4.00 (5H, m, H-1,2,3 and 4), 4.40—4.79 (8H, m, PhC$\underline{H}_2$O×4), 7.30 (20H, m, Ph×4).

Found: C, 77.26; H, 7.27%. Calcd for $C_{34}H_{38}O_5$: C, 77.54; H, 7.24%.

A solution of the syrup (7.50 g, 14.2 mmol) in CH_2Cl_2 (14 ml) was added to a mixture of DMSO (2.0 ml), trifluoroacetic anhydride (3.0 g) and CH_2Cl_2 (14 ml) at −76° over a period of 15 min with stirring, and stirring at −76 °C was continued for another 1 h. After addition of triethylamine (5.7 ml) at this temperature, the resulting solution was partitioned between ethyl acetate and water. The organic layer washed successively with a saturated aqueous $NaHCO_3$ solution and water, dried, and evaporated to a residue, which was chromatographed on silica gel (200 g) with 5 : 1 hexane–ethyl acetate to give a syrup of **19** (6.12 g, 82%): R_f 0.35 (5 : 1 hexane–ethyl acetate); ^{1}H-NMR δ=1.80—2.20 (2H, m, H-5), 3.47 (2H, t H-6, $J_{5,6}$=6.0 Hz), 3.71—4.12 (3H, m, H-2,3 and 4), 4.32—4.84 (8H, m, PhC$\underline{H}_2$O×4), 7.30 (20H, s, Ph×4), 9.69 (1H, d, CHO, $J_{1,2}$=2 Hz). As this compound was considerably labile, it was used for the next step without further purification.

8,9,10,12-Tetra-O-*benzyl-2,3,4,5,11-pentadeoxy*-aldehydo-D-lyxo-*6-dodecenose* (***20***) *and Its Ethylene Acetal.* To an ice-cooled solution of **6** (11.3 g, 23.3 mmol) in dry THF (110 ml) was added, under argon, 2 M sodium methylsulfinylmethanide solution prepared *in situ* from NaH (533 mg) and DMSO (11.1 ml). After the solution had been stirred at room temperature for 0.5 h, to the resulting deep red solution was added a solution of **19** (6.12 g, 11.7 mmol) in dry THF (61 ml), and stirring at room temperature was continued for another 0.5 h. The reaction mixture was partitioned between ether and a saturated aqueous NaCl solution. The organic layer was evaporated to a residue, which was chromatographed on silica gel (700 g) with 5 : 1 hexane–ethyl acetate to give the ethylene acetal of **20** as a colorless syrup (7.14 g, 94%): R_f 0.52 (2 : 14 : 1 : 2 benzene–chloroform–ethyl acetate–hexane); $[\alpha]_D^{15}$ +2.5° (*c* 2.0, $CHCl_3$); ^{1}H-NMR δ=3.50 (2H, t, H-12, $J_{11,12}$=6.0 Hz), 3.70—3.95 (4H, m, C$\underline{H}_2$ of ethylene acetal).

Found: C, 77.75; H, 7.76%. Calcd for $C_{42}H_{50}O_6$: C, 77.51; H, 7.74%.

The syrup (6.52 g) was dissolved in 70% aqueous trifluoroacetic acid (32.5 ml) at 5 °C and the solution was kept at this temperature overnight. The resulting solution was partitioned between chloroform and a saturated aqueous $NaHCO_3$ solution, and the organic layer was washed with a saturated aqueous NaCl solution ,dried, and evaporated to a residue. The residue was chromatographed on silica gel (200 g) with 5 : 1 hexane–ethyl acetate to give a syrup of **20** (5.28 g, 87%): R_f 0.59 (2 : 14 : 1 : 2 benzene–chloroform–ethyl acetate–hexane). As this compound **20** was considerably labile, it was used for the next step without further characterization.

1,3,4,5-Tetra-O-*benzyl-2,8,9,10,11,14,16-heptadeoxy*-DL-glycero-D-arabino-*hexadeca-6,12-dienitol* (***21***). A sample of **20** (4.39 g, 7.24 mmol) was treated by the procedure described in the preparation of **9** and then worked up to give a syrup of **21** (3.2 g, 66%): R_f 0.20 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{16}$ +5.0° (*c* 1.0, $CHCl_3$); ^{1}H-NMR δ=1.18 and 1.20 (3H in total, each d, Me-15, $J_{15,Me}$=6.5 Hz). 3.47 (2H, t, H-1, $J_{1,2}$=6 Hz), 3.50—3.92 (4H, m, H-3,4,5 and 15), 4.12—4.85 (8H, m, PhC$\underline{H}_2$O×4), 5.35—5.90 (4H, m, H-6,7,12 and 13), 7.30 (20H, s, Ph×4).

Found: C, 80.00; H, 8.26%. Calcd for $C_{44}H_{54}O_5$: C, 79.72; H, 8.21%.

3,4,5,15-Tetra-O-*acetyl-1*-O-(t-*butyldimethylsilyl*)-*2,6,7,8,9,10,-11,12,13,14,16-undecadeoxy*-DL-glycero-D-arabino-*hexadecitol* (**23**). A sample of **21** (3.13 g, 4.72 mmol) was treated by the procedure described in the preparation of **11** through **10** and then worked up to give, through **22**, a syrup of **23** (2.17 g, 78%): R_f 0.44 (3 : 1 hexane–ethyl acetate); $[\alpha]_D^{17}$ +30° (*c* 1.0. $CHCl_3$); ^{1}H-NMR δ=0.02 (6H, s, Me_2Si), 0.85 (9H, s, *t*-BuSi), 1.19 (3H, d, Me-15, $J_{15,Me}$=6.0 Hz), 2.02, 2.05 and 2.08 (12H in total, each s, OAc×4), 3.65 (2H, t, H-1, $J_{1,2}$=6 Hz).

Found: C, 61.22; H, 9.26%. Calcd for $C_{30}H_{56}O_9Si$: C, 61.19; H, 9.59%.

Methyl 3,4,5,15-Tetra-O-*acetyl-2,6,7,8,9,10,11,12,13,14,16-undecadeoxy*-DL-glycero-D-arabino-*hexadeconate* (**24**). A sample of **23** (291 mg, 0.50 mmol) was treated by the procedure described in the preparation of **12** and then worked up to give a syrup of **24** (208 mg, 84%): R_f 0.20 (3 : 2 hexane–ethyl acetate); $[\alpha]_D^{15}$ +47° (*c* 1.0. $CHCl_3$); ^{1}H-NMR δ=1.20 (3H, d, Me-15, $J_{15,Me}$=6.0 Hz), 2.00, 2·03 and 2.11 (12H in total, each s, OAc×4), 2.52 (2H, d, H-2, $J_{2,3}$=6.0 Hz), 3.65 (3H, s, COOMe).

Found: C, 59.56; H, 8.20%. Calcd for $C_{25}H_{42}O_{10}$: C, 59.74; H, 8.42%.

Methyl 15-O-*Acetyl-6,7,8,9,10,11,12,13,14,16-decadeoxy-4,5*-O-*isopropylidene*-DL-glycero-D-erythro-(E)-*2-hexadecenonate* (**25**). A sample of **24** (271 mg, 0.54 mmol) was treated by the procedure described in the preparation of **13** and then worked up to give a syrup of **25** (91 mg, 42%): R_f 0.29 (5 : 1 hexane-ethyl acetate); $[\alpha]_D^{15}$ −7.5° (*c* 1.0, $CHCl_3$); UV_{max} (MeOH) 212 nm (ε 10800); ^{1}H-NMR δ=1.20 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.39 and 1.51 (each 3H, each s, Me_2C), 2.04 (3H, s, OAc), 3.77 (3H, s, COOMe), 4.16—4.28 (1H, m, H-5), 4.64 (1H, m, H-4), 4.80—4.95 (1H, m, H-15), 6.09 (1H, dd, H-2, $J_{2,3}$=15.5 Hz, $J_{2,4}$=1.5 Hz), 6.85 (1H, dd, H-3, $J_{2,3}$=15.5 Hz, $J_{3,4}$=6 Hz).

Found: C, 66.25; H, 9.84%. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61%.

6,7,8,9,10,11,12,13,14,16-Decadeoxy-4,5-O-*isopropylidene*-D-glycero-D-erythro-(E)-*2-hexadecenono-1,15-lactone* (**26**) *and* L-glycero-D-erythro-*isomer* (**27**). A sample of **25** (97 mg, 0.243 mmol) was treated by the procedure described in the preparation of **14** and **15**, and then worked up to give **26** (37 mg, 47%) and **27** (32 mg, 39%) having the R_f -values of 0.24 and 0.18 (10 : 1 hexane–ethyl acetate) respectively.

26: Needles from ether–hexane; mp 57—58 °C; $[\alpha]_D^{17}$ −60° (*c* 2.0, $CHCl_3$); UV_{max} (MeOH) 212 nm (ε 11700); ^{1}H-NMR δ=1.27 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.38 and 1.52 (each 3H, each s, Me_2C), 4.16—4.26 (1H, m, H-5), 4.64 (1H, dt, H-4, $J_{3,4}$=7 Hz, $J_{2,4}$=1 Hz), 5.08 (1H, m, H-15), 6.04 (1H, dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=1 Hz), 6.86 (1H, dd, H-3, $J_{2,3}$=16 Hz, $J_{3,4}$=7 Hz).

Found: C, 70.42; H, 9.85%. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%.

27: syrup; $[\alpha]_D^{17}$ +25° (*c* 2.0, $CHCl_3$); UV_{max} (MeOH) 212 nm (ε 11700); ^{1}H-NMR δ=1.27 (3H, d, Me-15, $J_{15,Me}$=6 Hz), 1.38 and 1.52 (each 3H, each s, Me_2C), 4.16—4.26 (1H, m, H-5), 4.61 (1H, dt, H-4, $J_{3,4}$=6.5 Hz, $J_{2,4}$=1 Hz), 5.07 (1H, m, H-15), 6.02 (1H, dd, H-2, $J_{2,3}$=16 Hz, $J_{2,4}$=1 Hz), 6.82 (1H, dd, H-3, $J_{2,3}$=16 Hz, $J_{3,4}$=6.5 Hz).

Found: C, 70.58; H, 9.76%. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%.

6,7,8,9,10,11,12,13,14,16-Decadeoxy-D-glycero-D-erythro-(E)-*2-hexadecenono-1,15-lactone* (**28**). A sample of **26** (44.5 mg) was hydrolyzed by the procedure described in the preparation of **16** and then worked up to give needles of **28** (36 mg, 92%): R_f 0.48 (3 : 2 hexane–acetone); mp 118—119 °C; $[\alpha]_D^{16}$ −49° (*c* 2.0, $CHCl_3$); UV_{max} (MeOH) 214 nm (ε 11000).

Found: C, 67.70; H, 9.91%. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92%.

6,7,8,9,10,11,12,13,14,16-Decadeoxy-L-glycero-D-erythro-(E)-*2-hexadecenono-1,15-lactone* (**29**). A sample of **27** (35 mg) was hydrolyzed by the procedure described in the preparation of **16** and then worked up to give needles of **29** (29 mg, 93%); R_f 0.49 (3 : 2 hexane–acetone); mp 87—89 °C; $[\alpha]_D^{12}$ +12° (*c* 2.0, $CHCl_3$); UV_{max} (MeOH) 214 nm (ε 10800).

Found: C, 67.64; H, 9.94%. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92%.

5-O-*(3-Carboxypropionyl)-4-oxo-4,6,7,8,9,10,11,12,13,14,16-undecadeoxy*-D-glycero-D-glycero-(E)-*2-hexadecenono-1,15-lactone* (**3**). Following the procedure described for **1**, from **28**, a syrup of **3** (9.5 mg, 50% from **28**) was obtained: R_f 0.57 (8 : 1 chloroform–ethanol); $[\alpha]_D^{16}$ −25° (*c* 0.2, MeOH). The UV, IR and ^{1}H-NMR spectra were identical with those of **2**,

Found: C, 62.65; H, 8.04%. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%.

5-O-*(3-Carboxypropionyl)-4-oxo-4,6,7,8,9,10,11,12,13,14,16-undecadeoxy*-L-glycero-D-glycero-(E)-*2-hexadecenono-1,15-lactone* (**4**). Following the procedure described for **1**, from **29**, needles of **4** (4.0 mg, 46% from **29**) were obtained: R_f 0.57 (8 : 1 chloroform–ethanol); $[\alpha]_D^{17}$ +13° (*c* 0.2, MeOH). The UV, IR, and ^{1}H-NMR spectra were identical with those of **1**.

Found: C, 62.74; H, 8.04%. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%.

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