

Synthesis of higher sugars as precursors for the synthesis of chiral polyhydroxylated macrocyclic lactones

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A general method for the synthesis of higher sugars that can be used as precursors for the synthesis of polyhydroxylated macrocyclic lactones (macrolides) was described. The extension of the carbohydrate chain of a hexopyranose was effected at its C(6) hydroxymethyl carbon by coupling of two carbohydrate precursors *via* Wittig reaction. In this way 6,7-dideoxy-2,3,4,5,8,9,10-hepta-*O*-methyl-11-*O*-triphenylmethyl-*D*-arabino-*D*-glucoundecanose diethyl dithioacetal (**1**) was synthesized as a model compound.

Keywords: higher sugars, sugar chain elongation, Wittig reaction, sugar phosphonium salts, polyhydroxylated macrocyclic lactones.

INTRODUCTION

A large number of natural products containing polyhydroxylated macrocyclic lactones (macrolides) has been isolated from natural sources. Thus polyhydroxylated macrocyclic lactones have been found in (1) *polyoxomacrolides* such as erythromycins A, B, and C, methymycin, picromycin, carbomycin (macrocyclic antibiotics), (2) *polyenemacrolides* (amphotericin), (3) *ansamycins* (ansamycin and maytansin), (4) *ionophoric* macrolides (nonactin), *etc.* Due to a highly complex stereochemistry of their carbon skeletons, the stereoselective synthesis of this class of natural products was elusive for many years since the synthetic organic chemist was faced with a myriad of extremely challenging problems such as the stereoselective synthesis of many chiral centers of a macrolide and the efficient lactonization of medium or large lacton rings.¹⁻³

Many approaches have been used for the synthesis of chiral carbon skeleton of polyhydroxylated macrocyclic lactones, all of which were based on a common strategy that consisted in conversion of a small and relatively simple achiral molecule into a large macrolide carbon skeleton *via* a series of stereocontrolled additions/condensations. Our approach was, however, radically different. Since it was well known that chemical transformations of various chiral carbons of a pyranoside ring proceed with a high stereoselectivity, we decided to attempt the

synthesis of the macrocyclic lactone ring of erythromycin A by coupling two segments each synthesized from D-glucose through a series of stereocontrolled transformations of selected carbon atoms of a glucopyranoside ring. After solving the stereoselective synthesis of key carbon atoms, which were the C(9)⁴ carbon of erythronolides A and B, and the C(2) and/or C(10) carbons of erythronolide A,⁵ and after developing a simple spectroscopic method for determination of configuration of quaternary carbon atoms of a glucopyranoside ring having as the branched chain⁶ the methyl group we then successfully highly stereoselectively and in good overall yield synthesized the 3-*O*-methyl and 11-*O*-methyl derivatives of the C(1)–C(6) segment of erythronolides A and B and the C(9)–C(15) segment of erythronolide A.⁸

We now want to report the results of our efforts directed towards developing a general method for the synthesis of higher sugars that can also be used as precursors for the synthesis of polyhydroxylated macrocyclic lactones (macrolides). The basic idea was the extension of the carbohydrate chain of a hexopyranose at its C(6) hydroxymethyl carbon *via* Wittig reaction.

As a model for our studies we chose the synthesis of 2(*R*), 3(*S*), 4(*R*), 5(*R*), 8(*R*), 9(*R*), 10(*R*)-hepta-*O*-methyl-undecanose (**1**) which was achieved by coupling segments *A* (an aldehydo sugar generated from a D-arabinose derivative) and *B* (a phosphonium salt generated from a D-glucose derivative).

Segment *A* was synthesized in the following way. D-Arabinose diethylthioacetal (**2**) was tritylated with triphenylmethyl chloride and pyridine. The 5-*O*-trityl derivative **3** was methylated with methyl iodide using either BaO/Ba(OH)₂ or

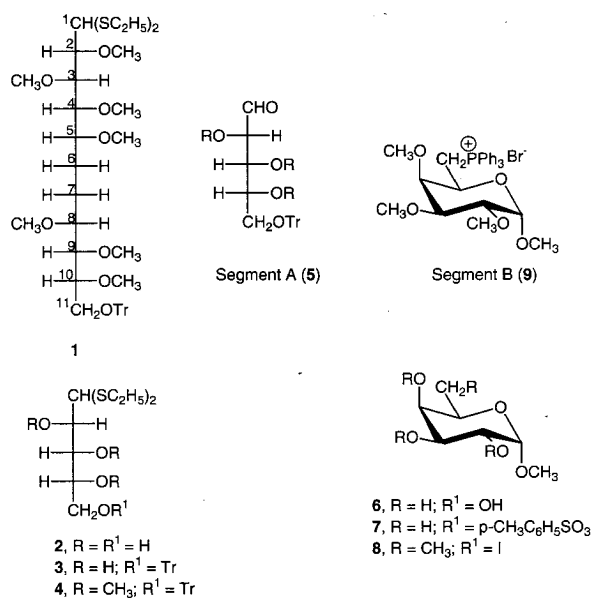


Fig. 1.

NaH as a base. The reaction was cleaner and resulted in a higher yield when NaH was used as a base. Diethyldithioacetal group of 2,3,4-tri-*O*-methyl-5-*O*-triphenylmethyl-D-arabinose diethyldithioacetal (**4**) was removed by either HgO/HgCl₂ or by the NBS method developed in our laboratory.⁹ Both methods gave the aldehydo arabinose derivative **5** in the same yield.

Segment B was synthesized as follows. Monotosylation of methyl α -D-glucopyranoside (**6**) with *p*-toluenesulfonyl chloride in pyridine¹⁰ afforded the crystalline 6-*O*-*p*-toluenesulfonyl derivative **7** in 70 % yield. Methylation of C-2, C-3, and C-4 hydroxyl groups and the nucleophilic displacement of the 6-*O*-*p*-toluenesulfonyl-

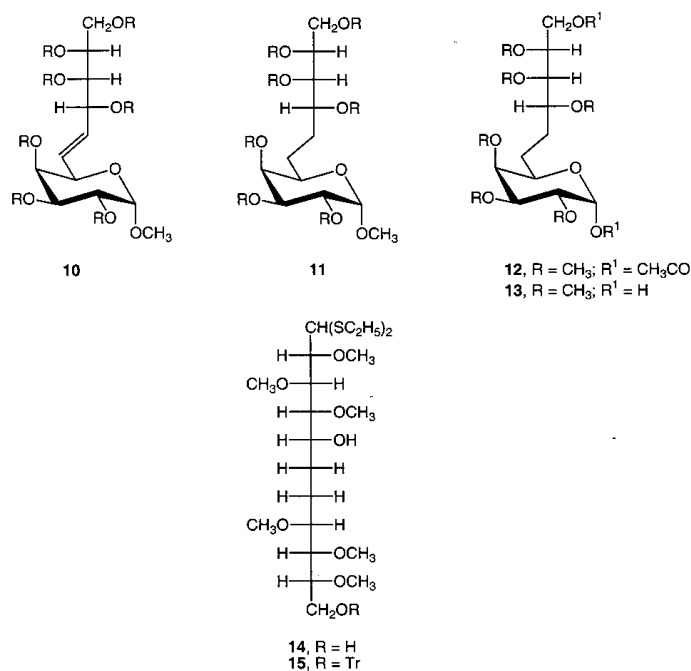


Fig. 2.

ate of **7** with iodine was effected in one step by treating **7** with methyl iodide, barium oxide and barium hydroxide in *N,N*-dimethylformamide as described by Stout.¹¹ In this way, methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl- α -D-glucopyranoside (**8**) was obtained in 84 % yield (after chromatography). It should be noted that this represented a significant improvement over previously published preparations (58 %¹¹ and 26 %¹²). Finally, heating of methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl- α -D-glucopyranoside with triphenylphosphine in tetramethylene sulfone for 72 h at 110 °C (a minor modification of the procedure described by Secríst¹³), gave crystalline methyl 6-deoxy-2,3,4-tri-*O*-methyl-6-triphenylphosphonio- α -D-glucopyranoside iodide (**9**) in 99 % yield.

Coupling of Segments A (2,3,4-tri-*O*-methyl-5-*O*-triphenylmethyl-aldehydo-D-arabinose (**5**)) and B (methyl 6-deoxy-2,3,4-tri-*O*-methyl-6-triphenylphosphonio- α -D-glucopyranoside (**9**)) was accomplished by using the protocol described by Secrist and Wu.¹⁰ A tetrahydrofuran solution of the aldehydo D-arabinose derivative **5** was added to a red colored ylide, generated by addition of 1 equivalent of *n*-butyllithium to the solution of phosphonium salt **9** in 2:1 (v/v) tetrahydrofuran-hexamethylphosphortriamide (HMPA) in a nitrogen atmosphere and at -60°C . After the addition the reaction mixture was allowed to warm up to room temperature over 45 min period. The obtained methyl 6,7-dideoxy-2,3,4,8,9,10-hexa-*O*-methyl-11-*O*-triphenylmethyl-D-arabino- α -D-glucoundec-6-ene-pyranoside (57 % yield) (**10**) was hydrogenated at the atmospheric pressure using 10 % Pt-C in 1:1 ethanol-ethyl acetate whereby methyl 6,7-dideoxy-2,3,4,8,9,10-hexa-*O*-methyl-11-*O*-triphenylmethyl-D-arabino-D-glucoundecapyranoside (**11**) was obtained in 90 % yield. Acetolysis of **11** with acetic anhydride-sulfuric acid at -20°C gave the corresponding 1,11-di-*O*-acetyl-6,7-dideoxy-2,3,4,8,9,10-hexa-*O*-methyl- α and β -D-arabino-D-glucoundecapyranoside (**12**) in 87 % yield (α to β ratio was 6.5:1, based on NMR). The hydrolysis of **12** with methanolic sodium hydroxide at -20°C gave, in a quantitative yield 6,7-dideoxy-2,3,4,8,9,10-hexa-*O*-methyl- α and β -D-arabino-D-glucoundecapyranose (**13**) which on treatment with ethanethiol and concentrated HCl at 0°C was converted into the corresponding dithioacetal **14**. The tritylation of **14** with triphenylmethyl chloride and pyridine at room temperature gave the 6,7-dideoxy-2,3,4,8,9,10-hexa-*O*-methyl-11-*O*-triphenylmethyl-D-arabino-D-glucoundecanose diethyl dithioacetal (**15**) in 86 % yield. Finally the methylation of **15** with methyl iodide-BaO/Ba(OH)₂ in *N,N*-dimethylformamide gave the 6,7-dideoxy-2,3,4,5,8,9,10-hepta-*O*-methyl-11-*O*-triphenylmethyl-D-arabino-D-glucoundecanose diethyl dithioacetal (**1**) in 70 % yield.

We would like to note that instead of synthesizing the 6,7-dideoxy sugar **11** we could have made the fully polyhydroxylated higher sugar by either a stereoselective or non-stereoselective hydroxylation of the 6,7-double bond in **10**. However, since we were interested in developing a general strategy for the synthesis of higher sugars, we decided, for the sake of simplicity, to hydrogenate the 6,7-double bond of **10**.

EXPERIMENTAL

The silica gel used for chromatography was E. Merck (Darmstadt, Germany) silica gel, particle size < 0.063 mm. The melting points are uncorrected. All reported yields represent the yields of pure compounds. Optical rotations were determined with Cary 60 spectropolarimeter in a 1.0 cm cell. Infrared spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267 and the individual absorptions are expressed in cm^{-1} . The ¹H-NMR spectra of deuteriochloroform solutions were recorded with Varian T-60 and Bruker WM-360 spectrometers, using tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in parts per million (ppm).

5-O-Triphenylmethyl-2,3,4-tri-O-methyl-D-arabinose diethyldithioacetal (4)

(a) Preparation with methyl iodide and BaO/Ba(OH)₂. To a stirred solution of 5-*O*-triphenylmethyl-D-arabinose diethyl dithioacetal (**3**) (6.40 g, 13 mmol) in *N,N*-dimethyl-formamide (50 mL)

were added BaO (17.7 g, 0.016 mol) and Ba(OH)₂ octahydrate (9.7 g, 31 mmol) and the mixture was cooled to 0 °C. Methyl iodide (4.0 mL, 64 mmol) was then added and the stirring was continued for 2 h at 0 °C and for an additional hour at room temperature. At this point TLC (using 4:1 hexane–acetone as eluent) showed the presence of one major product. The reaction mixture was diluted with chloroform (100 mL), filtered through a layer of Celite, and the insoluble solid was washed several times with chloroform (*ca.* 500 mL total). The combined filtrate was washed with 0.1 M HCl (200 mL), saturated aqueous NaHCO₃ solution (200 mL), and water (100 mL). The chloroform extract was dried over anhydrous MgSO₄, filtered and the filtrate evaporated on a rotary evaporator. The obtained orange syrup was chromatographed on silica gel (230 g). Elution with 50:1 benzene–ethyl acetate gave chromatographically homogeneous **4** (5.41 g, 78 %) as a colorless syrup. $[\alpha]_D^{27} - 1.8^\circ$ ($c = 1.69$, CHCl₃); ¹H-NMR (δ): 7.54–7.19 (*m*, 15H, aromatic H), 4.05 (*dx**d*, $J_{2,3} = 2.75$ and $J_{3,4} = 7.04$ Hz, 1, H-3), 4.04 (*d*, $J_{1,2} = 7.94$ Hz, 1, H-1), 3.59 (*dx**d*, $J_{1,2} = 7.94$ and $J_{2,3} = 2.75$ Hz, 1, H-2), 3.57, 3.45 and 3.28 (three *s*, 9, three methoxy groups), 3.53 (*dx**d*, $J_{4,5} = 2.44$ and $J_{5,5'} = 10.07$ Hz, H-5), 3.40 (*dx**d**d*, $J_{3,4} = 7.94$, $J_{4,5} = 2.44$, and $J_{4,5'} = 4.27$ Hz, 1, H-4), 3.10 (*dx**d*, $J_{4,5'} = 4.27$ and $J_{5,5'} = 10.07$ Hz, 1, H'-5), 2.82–2.62 (*m*, 4, methylene hydrogens from two ethylthio groups), 1.28 and 1.27 (two *dx**d*, $J' = 4.58$ and $J'' = 7.32$ Hz, 6, methyl hydrogens from two methyl groups).

Anal. Calcd. for C₃₁H₄₀O₄S₂: C, 68.85; H, 7.46. Found: C, 68.81; H, 7.41.

(b) *Preparation with methyl iodide and sodium hydride.* To an oil dispersion (55 %) of sodium hydride (278 mg, *ca.* 6.4 mmol) in a 35 mL two-neck round bottomed flask equipped with a magnetic stirring bar, pressure equalizing dropping funnel and a septum, washed with two 4-mL portions of hexane under a nitrogen atmosphere, a solution of 5-*O*-triphenylmethyl-*D*-arabinose diethyl dithioacetal (**3**) (740 mg, 1.49 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added dropwise with a constant stirring over a 20 min period. The stirring was continued for an additional hour at room temperature and the reaction mixture was cooled to 0 °C. Methyl iodide (0.83 mL, 13.37 mmol) was then added dropwise *via* a syringe over a 5 min period and the reaction mixture was stirred at 0 °C for additional 75 min. Since the TLC (using 20:1 benzene–ethyl acetate as eluent) showed at this point the presence of only one reaction product the reaction was stopped by adding excess of methanol. The reaction mixture was transferred to a 250 mL separatory funnel, water was added (50 mL) and the mixture was extracted with three 40 mL-portions of chloroform. The combined chloroform extract was washed with water, dried over anhydrous MgSO₄ filtered and evaporated on a rotary evaporator. The obtained crude product was chromatographed on silica gel (60 g). Elution with 50:1 benzene–ethyl acetate afforded chromatographically homogeneous **4** (727 mg, 90 %) as a colorless syrup.

2,3,4-Tri-*O*-methyl-5-*O*-triphenylmethyl-aldehydo-*D*-arabinose (**5**)

(a) *Preparation with HgCl₂/HgO.* A solution of 2,3,4-tri-*O*-methyl-5-*O*-triphenylmethyl-*D*-arabinose diethyl dithioacetal (**4**) (420 mg, 0.78 mmol) in 97:3 acetone–water (10 mL) was stirred with a 1:1 (w/w) mixture of HgCl₂ and HgO (1.2 g) for 30 min at 0 °C. Thin layer chromatography (using 4:1 hexane–acetone) indicated the presence of only one reaction product. The solids were filtered off and then washed with two 10 mL-portions of acetone. The combined filtrate and washings were evaporated on a rotary evaporator. The syrupy residue was dissolved in chloroform (10 mL), and the white precipitate formed was removed by filtration and washed with chloroform (10 mL). The combined filtrate was washed with two 30 mL-portions of 17 % aqueous KI solution and then with water (30 mL). After drying over anhydrous MgSO₄ the chloroform extract was filtered and the filtrate evaporated on a rotary evaporator. The obtained colorless syrup was chromatographed on silica gel (20 g). Elution with 15:1 benzene–ethyl acetate gave chromatographically homogeneous (**5**) (278 mg, 82 %) as a colorless syrup.

(b) *Preparation with N-bromosuccinimide.* 2,3,4-tri-*O*-methyl-5-*O*-triphenylmethyl-*D*-arabinose diethyl dithioacetal (**4**) (350 mg, 0.65 mmol) was dissolved in 97:3 acetone–water (3 mL) and solution was cooled to 0 °C. To the obtained solution an acetone solution (3 mL) of *N*-bromosuccinimide (350 mg, 1.94 mmol) was added with stirring, whereby the color of solution changed from colorless to orange. After stirring reaction solution for 7 min at 0 °C the TLC analysis (using 4:1

hexane–acetone as eluent) showed the presence of only one reaction product. The reaction was stopped by adding an excess of a 1:1 (w/w) mixture of solid $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ and stirring was continued for another 2 h. The solids were filtered off and washed with two 10 mL-portions of acetone. After evaporation of combined filtrate on a rotary evaporator the residue was dissolved in chloroform (50 mL) and washed with water (30 mL). The chloroform solution was then dried over anhydrous MgSO_4 , filtered and evaporated on a rotary evaporator. The obtained syrup was chromatographed on silica gel (16 g). Elution with 8:1 hexane–acetone gave chromatographically homogeneous **(5)** (232 mg, 82 %) as a colorless syrup. IR (cm^{-1}): 1725 (strong C=O stretch, aldehyde), 1095 (asymmetric C–O–C stretch). $^1\text{H-NMR}$: 9.87 (s, 1, H-1), 7.58–7.02 (m, 15, triphenylmethyl group), 4.02–2.90 (m, 5, H-2, H-3, H-4, H-5, H'-5), 3.45, 3.32, and 3.12 (three s, 9, three methoxy methyl groups).

Methyl 6-deoxy-2,3,4-tri-O-methyl-6-O-triphenylphosphonio- α -D-glucopyranoside iodide (9)

A solution of methyl 6-deoxy-6-iodo-2,3,4-tri-O-methyl- α -D-glucopyranoside (4.40 g, 12.7 mmol) and triphenyl phosphine (4.0 g, 15.3 mmol) in tetramethylene sulfone was stirred at 110 °C. TLC analysis (in 10:1 benzene–acetone as eluent) indicated that the reaction was complete after 3 days and that only one product was detectable. The solution was diluted with chloroform (25 mL) and dropwise added to vigorously stirred ethyl ether (1,200 mL). The precipitate was recrystallized from methanol–ethyl acetate resulting in colorless needle-like solid (7.65 g, 99 %), m.p. 214 °C (dec.). $[\alpha]_{\text{D}}^{27} + 78.08^\circ$ ($c = 1.56$, CHCl_3). $^1\text{H-NMR}$: 7.87–7.42 (m, 15H, triphenylmethyl group), 4.65 (d, 1H, $J_{1,2} = 3.42$ Hz, H-1), 4.59 (dxd, $J_{5,6} = 10.99$ and $J_{6,6'} = 16.11$ Hz, 1H, H-6), 3.85 (m, $J_{4,5} = 8.79$, $J_{5,6} = 10.99$, and $J_{5,6'} = 2.20$ Hz, 1H, H-5), 3.74, 3.56, and 3.48 (three s, 9H, three methyl groups), 3.63 (dxd, $J_{5,6'} = 2.20$, $J_{6,6'} = 16.11$ Hz, 1H, H'-6), 3.51 (t, $J_{3,4} = J_{4,5} = 8.79$ Hz, 1H, H-4), 3.39 (dxd, $J_{2,3} = 9.76$ and $J_{3,4} = 8.79$ Hz, 1H, H-3), 3.28 (dxd, $J_{1,2} = 3.42$ and $J_{2,3} = 9.76$ Hz, 1H, H-2), 2.63 (s, 3H, methyl group).

Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{IO}_5$: C, 55.27; H, 5.63. Found: C, 55.53; H, 5.87.

Methyl 6,7 dideoxy-2,3,4,8,9,10-hexa-O-methyl-11-O-triphenyl-methyl-D-arabino- α -D-glucoundec-6-enopyranoside (10)

A solution of methyl 6-deoxy-2,3,4-tri-O-methyl-6-triphenylphosphonio- α -D-glucopyranoside iodide **(9)** (2.52 g, 4.15 mmol) in 40 mL 2:1 (v/v) tetrahydrofuran–hexamethylphosphoramide was cooled to –55 °C (the salt does not completely dissolve) and under nitrogen atmosphere was added, *via* a syringe, 1 M *n*-butyllithium solution in tetrahydrofuran (4.6 mL, 4.6 mmol of *n*-butyllithium). In less than 1 min a tetrahydrofuran solution (5 mL) of 2,3,4-tri-O-methyl-5-triphenylmethyl-aldehyde-D-arabinose **(5)** (1.50 g, 3.46 mmol) was added and the solution was allowed to warm up to room temperature over a period of 45 min. TLC analysis (using 8:1 benzene acetone) indicated the presence of one major product ($R_f = 0.37$). The reaction mixture was evaporated on a rotary evaporator and the residue was diluted with 1:1 (v/v) petroleum ether–ethyl ether and washed with water. The organic extract was dried over anhydrous MgSO_4 , filtered and evaporated on a rotary evaporator yielding a yellow syrup which was chromatographed on silica gel (150 g). Elution with 15:1 benzene–ethyl acetate gave chromatographically homogeneous **10** (1.25 g, 57 %) which crystallized on standing. An analytical sample was prepared recrystallization from isopropyl ether, m.p. 149.5–150.5 °C. $[\alpha]_{\text{D}}^{27} + 0.46^\circ$ ($c = 0.95$, CHCl_3). $^1\text{H-NMR}$: 7.48–7.18 (m, 15H, triphenylmethyl group), 5.93–5.87 (m, 1H, olefinic H), 5.69–5.63 (m, 1H, olefinic H), 4.81 (d, $J_{1,2} = 3.42$ Hz, 1H, H-1), 4.42–4.35 (m, 2H, H-11, and H'-11), 3.65, 3.54, 3.52, 3.50, 3.40, 3.31, and 3.24 (seven s, 21H, seven methyl groups), 3.28–3.21 (m, 2H), 3.03–2.96 (m, 3H).

Anal. Calcd. for $\text{C}_{37}\text{H}_{48}\text{O}_9$: C, 69.79, H, 7.60. Found C, 69.93; H, 7.80.

Methyl 6,7-dideoxy-2,3,4,8,9,10-hexa-O-methyl-11-O-triphenylmethyl-D-arabino- α -D-glucoundecapyranside (11)

A solution of the olefin **10** (198 mg, 0.31 mmol) in 10 mL of 1:1 (v/v) ethanol–ethyl acetate was hydrogenated at atmospheric pressure and room temperature using 10 % Pt-C (49 mg) as the catalyst. The hydrogenation was stopped after the consumption of hydrogen ceased at which point the TLC

(using 8:1 benzene–acetone) showed the presence of only one product ($R_f = 0.27$). The catalyst was removed by filtration through a layer of celite and the solids were washed with several portion of solvent. The combined filtrate was evaporated on a rotary evaporator and the residue was chromatographed on silica gel (10 g). Elution with 8:1 benzene–acetone gave chromatographically homogeneous **11** (178 mg, 90 %) as a colorless syrup. $[\alpha]_D^{27} + 46.85^\circ$ ($c = 1.92$, CHCl_3). $^1\text{H-NMR}$: 7.52–7.20 (m , 15H, triphenylmethyl group), 4.77 (d , $J_{1,2} = 3.66$, 1H, H-1), 3.63, 3.59, 3.52, 3.46, 3.40, 3.39, and 3.26 (seven s , 21H, seven methyl groups), 3.21–3.18 (m , 2H), 3.12–3.08 (m , 2H), 2.88–2.82 (m , 2H), 1.97–1.90 (m , 2H, methylene group), 1.58–1.51 (m , 2H, methylene group).

Anal. Calcd. for $\text{C}_{37}\text{H}_{50}\text{O}_9$: C, 69.57; H, 7.89. Found: C, 69.36; H, 7.93.

1,11-Di-O-acetyl-6,7-dideoxy-2,3,4,8,9,10-hexa-O-methyl-D-arabino- α - and β -D-glucoundecapyranoside (12)

A solution of the hydrogenation product **11** (2.26 g, 3.54 mmol) in acetic anhydride (3 mL) was cooled to -20°C . With vigorous stirring, 1 mL-aliquots of an acid solution (freshly prepared and cooled to -20°C) containing concentrated sulfuric acid (0.94 mL, 17.7 mmol), acetic anhydride (20 mL), and acetic acid (20 mL) was added dropwise at 40 min intervals. After 8 h TLC analysis indicated the reaction was complete. Ice-water (150 mL) was then added and the reaction solution was stirred for an additional 4 h. The aqueous solution was extracted with six 80 mL-portions of chloroform and the combined chloroform fractions were washed with saturated aqueous NaHCO_3 solution (20 mL) and water (100 mL). The chloroform extract was dried over anhydrous MgSO_4 , filtered and evaporated on a rotary evaporator. The obtained syrup was chromatographed on silica gel (100 g). Elution with 6:1 hexane–acetone afforded two well separated anomers: β -anomer (191 mg, 11.6 %) and α -anomer (1.25 g, 75.8 %); total yield of acetolysis was 87.3 %, α : β ratio was 6.5:1.

α -Anomer (12 α). $[\alpha]_D^{27} + 83.55^\circ$ ($c = 0.90$, CHCl_3). IR: 1760 and 1740 (strong C=O stretch, acetates), 1235 (asym. ester C–O–C stretch, acetates). $^1\text{H-NMR}$: 6.25 (d , $J_{1,2} = 3.66$ Hz, 1H, H-1), 4.56 (dxd , $J_{10,11} = 2.69$ and $J_{11,11'} = 12.21$ Hz, 1H, H-11), 3.64, 3.59, 3.47, 3.46, 3.41, 3.41 (six s , 18H, six methyl groups), 3.51 ($dxdxd$, $J_{9,10} = 7.57$, $J_{10,11} = 2.68$, $J_{10,11'} = 4.40$ Hz, 1H, H-10), 3.26 (dxd , $J_{1,2} = 3.66$ and $J_{2,3} = 9.76$ Hz, 1H, H-2), 3.22 (dxd , $J_{8,9} = 2.69$ and $J_{9,10} = 7.57$ Hz, 1H, H-9), 2.91 (dxd , $J_{2,3} = 9.76$ and $J_{3,4} = 8.79$ Hz, 1H, H-3), 2.14 and 2.11 (two s , 6H, two acetates), 1.87–1.81 (m , 2H, methylene group), 1.61 (m , 2H, methylene group).

Anal. Calcd. for $\text{C}_{21}\text{H}_{38}\text{O}_{11}$: C, 54.07; H, 8.21. Found: C, 53.84; H, 8.39.

β -Anomer (12 β). $[\alpha]_D^{27} + 9.28^\circ$ ($c = 1.21$, CHCl_3). IR: 1755 and 1737 (strong C=O stretch, acetates), 1240–1205 (asym. C=O stretch, ester C–O–C stretch). $^1\text{H-NMR}$: 5.42 (d , $J_{1,2} = 8.06$ Hz, 1H, H-1), 4.56 (dxd , $J_{10,11} = 2.69$ and $J_{11,11'} = 12.21$, 1H, H-11), 4.09 (dxd , $J_{10,11'} = 4.40$ and $J_{11,11} = 12.21$ Hz, 1H, H-11), 3.64, 3.57, 3.55, 3.45, 3.41, 3.41 (six s , 18H, six methyl groups), 3.44–3.41 (m , 1H, H-10), 3.12 (dxd , $J_{1,2} = 8.06$ and $J_{2,3} = 9.28$, 1H, H-2), 2.89 (dxd , $J_{2,3} = 9.28$ and $J_{3,4} = 8.79$ Hz, 1H, H-3), 2.14 and 2.10 (two s , 6H, two acetates), 1.92–1.81 (m , 2H, methylene groups), 1.67–1.55 (m , 2H, methylene group).

Anal. Calcd. for $\text{C}_{21}\text{H}_{38}\text{O}_{11}$: C, 54.07; H, 8.21. Found: C, 53.80; H, 8.05.

6,7-Dideoxy-2,3,4,8,9,10-hexa-O-methyl-D-arabino-D-glucopyranose (13)

Mixture of α - and β -anomers, **12 α** and **12 β** , was dissolved in 80 % aqueous methanol, and after the solution was cooled to -20°C 0.5 M sodium hydroxide was added. Quantitative yield.

6,7-Dideoxy-2,3,4,8,9,10-hexa-O-methyl-D-arabino-D-glucoundecanose diethyl dithioacetal (14)

A mixture of 6,7-dideoxy-2,3,4,8,9,10-hexa-O-methyl- α - and β -D-glucoundecapyranose (**13**) (254 mg, 0.66 mmol) dissolved in concentrated HCl (1.0 mL) was cooled to 0°C and ethanethiol (1 mL) was added. The TLC analysis 1:1 benzene–acetone indicated that the reaction was complete after 1 h with one major product present ($R_f = 0.45$). The mixture was diluted with water (20 mL) and extracted with four 50 mL-portions of chloroform. The combined chloroform extracts were washed with saturated aqueous NaHCO_3 solution (100 mL) and water (100 mL). The chloroform extract was dried over anhydrous MgSO_4 , filtered and evaporated on a rotary evaporator. The obtained syrup was

chromatographed on silica gel (20 g). Elution with 3:1 benzene–acetone afforded chromatographically homogeneous **14** (264 mg, 81 %) as a colorless syrup. $[\alpha]_D^{27} + 24.14^\circ$ ($c = 3.62$, CHCl_3). $^1\text{H-NMR}$: 4.4–3.1 (*m*, 12H), 3.6–3.4 (six *s*, 18H, six methyl groups) 2.7 (*dxd*, 4H, two methylene groups from two ethylthio groups), 1.25 (*t*, 6H, two methyl groups from two ethylthio groups).

Anal. Calcd. for $\text{C}_{21}\text{H}_{44}\text{O}_8\text{S}_2$: C, 51.61; H, 9.07. Found: C, 51.79; H, 9.00.

6,7-Dideoxy-2,3,4,8,9,10-hexa-O-methyl-11-O-triphenylmethyl-D-arabino-D-glucoundecanose diethyl dithioacetal (15)

To a stirred solution of the dithioacetal **14** (1.35 g, 2.77 mmol) in anhydrous pyridine (40 mL) was added triphenylchloromethane (0.93 g, 3.32 mmol). TLC analysis (using 20:1 benzene–methanol as eluent) after 72 h at room temperature indicated the presence of one major product ($R_f = 0.35$). Pyridine was evaporated on a rotary evaporator and the residual syrup was chromatographed on silica gel (100 g). Elution with 50:1 benzene–methanol afforded chromatographically homogeneous **15** (1.73 g, 86 %) as a thick colorless syrup. $[\alpha]_D^{27} + 6.99^\circ$ ($c = 2.40$, CHCl_3). $^1\text{H-NMR}$: 7.6–7.2 (*m*, 15H, triphenylmethyl group), 4.3–3.1 (*m*, 11H), 3.6–3.2 (six *s*, 18H, six methyl groups), 2.7 (*dxd*, 4H, two methylene groups from two ethylthio groups), 2.0–1.5 (*m*, 4H, H-6, H'-6, H-7, and H'-7), 1.25 (*t*, 6H, two methyl groups from two ethylthio groups).

Anal. Calcd. for $\text{C}_{40}\text{H}_{58}\text{O}_8\text{S}_2$: C, 65.72; H, 8.00. Found: C, 65.77; H, 8.10.

6,7-Dideoxy-2,3,4,5,8,9,10-hepta-O-methyl-11-O-triphenylmethyl-D-arabino-D-glucoundecapyranose diethyl dithioacetal (1)

To a solution of 6,7-dideoxy-2,3,4,8,9,10-hexa-O-methyl-11-O-triphenylmethyl-D-arabino-D-glucoundecanose diethyl dithioacetal (**15**) (762 mg, 1.04 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) was added barium oxide (640 mg, 4.16 mmol) and barium hydroxide octahydrate (659 mg, 2.08 mmol). With constant stirring at room temperature, methyl iodide in 0.065 mL-aliquots (1.04 mmol) was being added at 1 h interval until TLC analysis (using 2:1 hexane–acetone as eluent) indicated the reaction was complete (7 h) with one major product ($R_f = 0.63$). The mixture was diluted with ice-water (200 mL) and extracted with six 75 mL-portions of chloroform. The combined chloroform extract was dried over anhydrous MgSO_4 , filtered and evaporated on a rotary evaporator. The orange syrup was chromatographed on silica gel (35 g). Elution with 6:1 hexane–acetone afforded chromatographically homogeneous **1** (544 mg, 70 %) as a colorless syrup. $[\alpha]_D^{27} - 2.08$ ($c = 1.85$, CHCl_3). $^1\text{H-NMR}$ 7.7–7.1 (*m*, 15H, triphenylmethyl group), 4.0 (*d*, 1H, H-1), 3.7–3.2 (seven *s*, 21H, seven methyl groups), 2.7 (*dxd*, 4H, two methylene groups from two ethylthio groups), 1.7 (broad *m*, 4H, H-6, H'-6, H-7, H'-7), 1.25 (*t*, 6H, two methyl groups from two ethylthio groups).

Anal. Calcd. for $\text{C}_{41}\text{H}_{60}\text{O}_8\text{S}_2$: C, 66.10; H, 8.12. Found: C, 65.95; H, 8.14.

ИЗВОД

СИНТЕЗА ВИШИХ ШЕЋЕРА КАО ПРЕКУРСОРА ЗА СИНТЕЗУ ХИРАЛНИХ ПОЛИ-ХИДРОКСИЛОВАНИХ МАКРОЦИКЛИЧНИХ ЛАКТОНА

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Описана је општа метода за синтезу виших шећера који се могу употребити као прекурсор за синтезу полихидроксилованих макроцикличних лактона (макролида). Продужење угљеничног низа шећерног скелета хексопиранозе извршено је на C(6) угљениковом атому хидроксиметил групе купловањем двају шећерних прекурсора помоћу Witting-ове реакције. На овај начин је синтетизован као модел једињења диетил дитиоацетал 6,7-дидеокси-2,3,4,5,8,9,10-хепта-метил-11-О-трифенилметил-D-арабино-D-глукоундеканоze(**1**).

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