Synthesis of Macrolide Antibiotics. IV. Stereoselective Syntheses of the 3-O-Methyl and the 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, Respectively. 1-4

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By appropriate dissection of the macrocyclic lactone ring of methymycin erythromycins A and B, picromycin and narbomycin, carbohydrate-like structural segments were obtained. The finding that the anomeric configuration of a glycopyranoside effectively controls the stereochemistry of various addition reactions to sp² (C=O and C=C) carbon atoms of a glycopyranoside ring led to the development of a general stereoselective approach for the synthesis of the chiral carbon framework of the polyoxomacrolide aglycones of methymycin, erythromycin A and B, picromycin and narbomycin. Stereoselective synthesis of methyl 2,4,7-trideoxy-2-C, 3-0, 4-C-tri-methyl-β-D-idopyranosid-6-ulose and methyl 2,6,7-trideoxy-2-C, 3-O, 4-C-tri-methyl-α-D-glucopyranoside, representing the 3-O-methyl and the 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, respectively, is described.

The striking resemblance of the macrocyclic ring structure of macrolide antibiotics to branched chain sugars 3, the realization that some 12- and 14-membered macrocyclic lactone rings can be dissected into two hexose-like structural fragments and the fact that the chemical transformations of sugar molecules often proceed highly stereoselectively prompted us to investigate the possibility of stereoselective synthesis of some of these stereochemically highly complex natural products from carbohydrate precursors.

Dissection of the macrocyclic lactone ring of erythromycins A and B, picromycin and narbomycin, as depicted in Scheme 1, affords, in each case, two seven carbon atom segments: A, consisting of [C(1)—C(7)], and B, consisting of the [C(9)—C(14)] carbon atoms. A similar dissection of the macrocyclic lactone ring of methymycin affords a seven carbon atom segment A, consisting of the [C(1)—C(7)] carbons and B consisting of only five carbon atoms-[C(9)—C(13)]. Consequently, the construction of the carbon skeleton of macrolides I—V (Scheme 1) from the corresponding segments would require that the C(8) carbon atom be introduced either immediately before, or during the coupling of the two segments into the open-chain precursor of a given
macrolide aglycone. An important advantage of dissecting the macrocyclic lactone rings, as depicted in Scheme 1, is that it produces constitutionally and stereochemically similar fragments. This becomes particularly evident if segments A and B of methynolide, erythronolides A and B, pikronolide and narbonolide are represented in the form of carbohydrate pyranosides (Scheme 2).

Segment A of all five macrolide aglycones (VI, VII, and VIII in Scheme 2) has two structurally identical carbon atoms: the C(2) and the C(4) carbons in VII and VIII, and the C(4) and the C(6) carbons in VI. All these carbon atoms have an equatorially oriented methyl group when represented in the 1C1 conformation of a pyranoside-like structure. The C(3) carbon atom in
VII and VIII is oxygenated, whereas its counterpart C(5) in VI is not bonded to oxygen. Finally, the side chain in VII and VIII, consisting of the C(6) and C(7) carbon atoms of macrolide aglycones II—V, is axially oriented and in the cis configuration with respect to the C(4) methyl group; however, in VI, the side chain, consisting of the C(1) and the C(2) carbon atoms of methylnolide, is equatorially oriented and is in the trans configuration with respect to the C(4) methyl group.

Segment B of all five macrolide aglycones (IX—XIII) has as common structural features the same side chain (ethyl group) and one configurationally identical carbon atom: the C(13) carbon in X—XIII and the C(11) carbon in IX. Further, the C(12) carbon in X and XII, the C(10) carbon in IX, as well as the C(12) carbon in XI and XIII are structurally identical. It is important to note that the axially oriented C(10) methyl group in IX and the C(12) methyl group in X—XIII are in the cis configuration with respect to the equatorially oriented C(11) and/or C(13) ethyl group.

Because of these constitutional and stereochemical similarities, we became interested in developing a general approach for the stereoselective preparation of the above synthons from an appropriate carbohydrate precursor(s). By comparing the structures of readily available hexoses with the eight segments (VI—XIII) depicted in Scheme 2, D-glucose seemed best suited to be used as starting material. This conclusion was based on the following two reasons: First, D-glucopyranose is the only hexose without an axial substituent. This is very important because the presence of an axial group would limit the number of strategies which one could adopt for stereoselective conversion of the various carbohydrate carbon atoms into the skeletal carbons of synthons VI—XIII. Second, the absolute configuration of the C(3) carbon of d-glucose is identical to that of the C(3) carbon of VII and the C(11) carbon of X and XI, and the absolute configuration of the C(5) carbon of D-glucose is identical to the absolute configuration of the C(3) carbon of VI, the C(11) carbon of IX, and the C(13) carbon of X—XIII.

If one compares the structure of D-glucopyranose with the structures of segments A and B of erythronolide A, represented as glucopyranosides (synthons VII and X, respectively), it becomes apparent that the stereoselective conversion of D-glucose into synthons VII and X requires the following transformations:

1) Replacement of the primary C(6) hydroxyl group of a D-glucopyranoside derivative with a methyl group, resulting in the 6-deoxy-6-C-methyl homolog of D-glucopyranoside [synthesis of the side chain (ethyl group) of synthon X, representing the C(14) and C(15) carbon atoms of erythronolide A].

2) Introduction of an axial methyl group at the C(4) carbon atom of a D-glucopyranoside derivative resulting in a branched-chain sugar in which the C(4) quaternary carbon has the (S) configuration [synthesis of the C(12) carbon of erythronolide A].

3) Replacement of the equatorially oriented C(2) hydroxyl group of a D-glucopyranoside with an equatorially oriented methyl group [synthesis of the C(2) and the C(10) carbon atoms of erythronolide A, both having the (R) configuration].
4) Inversion of the configuration of the C(5) carbon of a D-glucopyranoside derivative, resulting in the formation of the corresponding L-idopyranoside derivative [synthesis of the C(5) carbon atom of erythronolide A].

5) Replacement of the equatorial C(4) hydroxyl group of a D-glucopyranoside derivative with an equatorial methyl group, resulting in a 4-deoxy-4-C-methyl branched-chain sugar [synthesis of the C(4) carbon of erythronolide A].

6) Addition of an alkyl group to the exocyclic C(6) carbonyl carbon of a 7-deoxy-L-ido-heptopyranosid-6-ulose derivative, resulting in a chiral C(6) tertiary alcohol having the (R) configuration [synthesis of the C(6) carbon of erythronolide A].

Except for the replacement of the primary C(6) hydroxyl group with a methyl group (reaction 1), all other chemical transformations of D-glucose ought to be highly stereoselective if an effective synthesis of synthons VII and X is to be accomplished from an appropriate D-glucopyranoside derivative. Consequently, the above goal can be achieved only by finding a way of efficiently controlling the stereochemical outcome of reactions 2 through 6.

At the time we started this investigation in late 1972, the stereoselective synthesis of the quaternary C(12) carbon of erythronolide A seemed to be the most challenging problem since it required the introduction of a thermodynamically less favored axial methyl group at the C(4) carbon of a D-glucopyranoside derivative. Thus, we began our work on the stereoselective synthesis of erythronolide A (and possibly other macrolides) from D-glucose by undertaking a study of the stereochemistry of the addition of organometallic reagents (methylmagnesium halides) to the C(4) carbonyl carbon of various methyl D-glucopyranosid-4-ulose derivatives. The goal was to achieve the stereoselective synthesis of the thermodynamically less favored C(4) (S) epimer.

Addition of the methyl group of methylmagnesium iodide to α- and β-anomers of methyl D-glucopyranosid-4-ulose derivatives proceeded, as expected, from the equatorial direction, giving as the exclusive (or under certain experimental conditions, predominant) product the (R) epimer having the C(4) methyl group equatorially oriented. However, the stereoselectivity of this addition was to a variable extent affected by the reaction temperature, by the nature of the solvent, and by the nature of the halogen atom. Thus, partial, and in some instances, complete loss of stereoselectivity was observed at elevated reaction temperatures, when tetrahydrofuran was added to ether as a cosolvent, and when the iodide of the Grignard reagent was replaced by chloride.

Contrary to these results, the stereoselectivity of addition of methylmagnesium to the C(4) carbonyl carbon of the α- and β-anomers of various methyl D-glucopyranosid-4-ulose derivatives strongly depended upon the anomeric configuration. Thus, the addition of methylmagnesium to the C(4) carbonyl carbon of the α-anomer of various D-glucopyranosid-4-uloses proceeded exclusively from the axial direction, yielding as the only isolable product the C(4)(S) epimer. However, the β-anomers gave, under identical experimental conditions, both C(4) epimers, suggesting a unique role for the axially oriented glycosidic oxygen in controlling the direction of approach of methylmagnesium and thus
the stereochemical outcome of the addition. A fuller account of these studies and the proposed rationalization of the obtained results has been published. 8

Configurational determination of the quarternary carbon atom of branched-chain sugars posed, at the time of these studies, a serious problem, since there was no single physico-chemical method available by which one could make an unequivocal configurational assignment of the branching carbon. In searching for such a method, studies of the conformational equilibrium of methylcyclohexane by carbon-13 NMR spectroscopy, published a few years earlier, came to our attention. In these publications, it was reported that the 13C chemical shift of an axial methyl group is shifted by ca. 6 ppm towards the higher magnetic field, as compared to the 13C chemical shift of an equatorial methyl group. This observation prompted us to investigate whether the 13C chemical shifts of axial and equatorial methyl groups bonded to the quaternary carbon atom of branched-chain sugars could be used for configurational determination. The study which followed established that the 13C chemical shift of axial and equatorial methyl groups bonded to quaternary carbon atom can indeed be utilized for configurational assignment of the branching carbon atom having a branched-chain methyl group, or for any other carbon distinguishable by C-13 NMR spectroscopy. A fuller account of this investigation was published elsewhere. 11

The above findings immediately raised the question as to whether the anomeric configuration could control the stereochemistry of addition to all sp2 carbon atoms of a glycopyranoside ring, and particularly to the C(2), and the C(4) and C(5) carbons. It was reported that the complex metal hydride reduction of a β-d-Lyxo-hexapyranoside derivative gave the corresponding β-d-talopyranoside derivative, whereas an α-d-arabinohexopyranoside-2-uloside derivative, under similar reaction conditions, gave the corresponding α-d-glucopyranoside derivative as the only product. Our own investigation showed that the stereochemistry of sodium borohydride reduction of methyl α- and β-d-arabinohexopyranosid-2-ulose derivatives strongly depended upon the anomeric configuration. Furthermore, very high stereoselectivity was observed in catalytic hydrogenation of methyl β-d-arabino-hexopyranosidulose and methyl 3,4,6-trio-O-benzyl-β-d-arabinohexopyranosidulose. Prompted by these studies, we studied the influence of anomeric configuration upon the stereochemistry of hydrogenation of the C(2) methylene group of methyl 2-deoxy-2-C-methylene-α- and β-d-arabinohexopyranoside derivatives. This investigation was undertaken in an attempt to stereoselectively synthesize the C(2) and the C(10) carbon of erythronolide A from a d-glucose derivative. The reaction scheme requires the replacement of the equatorial C(2) hydroxyl group of a d-glucopyranoside derivative with an equatorially oriented methyl group. Catalytic hydrogenation of methyl 2-deoxy-2-C-methylene-β-d-arabinohexopyranoside gave the corresponding 2-deoxy-2-C-methyl branched-chain sugar, having the C(2) methyl group axially oriented as the only product. However, contrary to expectation, and to our disappointment, catalytic hydrogenation of methyl 2-deoxy-2-C-methylene-α-d-arabinohexopyranoside derivative was much less stereoselective [equatorial to axial C(2) methyl group ratio was 3 : 1] and seemingly depended only upon the nature of both the catalyst and the solvent.
Synthesis of the C(4) and C(5) carbons of erythronolide A required the replacement of the equatorial C(4) hydroxyl group of a D-glucopyranoside derivative with an equatorial methyl group and inversion of the configuration of the C(5) carbon of a α-glucopyranoside. The cis orientation of the two substituents at the C(4) and C(5) carbons suggested that both transformations could be accomplished in a single step by catalytic hydrogenation of the corresponding C(4)–C(5) unsaturated carbohydrate. This strategy was based on the findings of Schmidt and Neukom who have shown that catalytic hydrogenation of the C(4)–C(5) double bond of a glycopyranoside is highly stereoselective and strongly dependent upon the anomeric configuration. Thus, the α-anomers of the C(4)–C(5) unsaturated sugars gave L-ido derivatives, whereas the corresponding β-anomers gave D-glucose derivatives as predominant products.

The finding that configuration of the aglycone group of a glucopyranoside effectively controls the stereochemistry of various addition reactions to sp² (C=O and C=C) carbon atoms of a glycopyranoside ring permitted us to develop a general, stereoselective approach for the synthesis from a D-glucose, of the chiral carbon framework of the polyoxomacrolide aglycones of methymycin, erythromycins A and B, pikromycin and narbomycin.

We wish here to report the stereoselective syntheses of methyl 2,4,7-trideoxy-2-C, 3-O,4-C-trimethyl-β-L-ido-heptopyranosid-6-ulose XXXII and methyl 2,6,7-trideoxy-2-C, 3-O,4-C-trimethyl-α-D-gluco-heptopyranoside XIX, representing the 3-O-methyl derivative of the C(1)–C(6) segment of erythronolides A and B and the 11-O-methyl derivative of the C(9)–C(15) segment of erythronolide A, respectively.
The oxidative debenzylenedensation of the 4,6-O-benzylidene derivative XIV21 with N-bromosuccinimide in refluxing carbontetrachloride26 gave, in quantitative yield27, methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-2-C, 3-O-dimethyl-α-β-glucopyranoside, XV. The displacement of the 6-bromo group with a carbanion as the nucleophile was effected by reacting XV in tetrahydrofuran-dimethylsulfoxide solution with methylsulfinylmethide sodium at -20°C, whereby methyl 2,6,7-trIDEOXY-2-C,3-O-DIMETHYL-7-SULFOXYMETHYL-α-β-GLUCO-HEPTOPYRANOSIDE, XVI, was obtained in 79% yield. Refluxing of an ethanolic solution of XVI with an excess of freshly prepared W-2 Raney-Ni afforded methyl 2,6,7-trIDEOXY-2-C, 3-O-DIMETHYL-α-β-P-GLOUCOHEPTOPYRANOSIDE, XVII, as a colorless syrup in 92% yield. The oxidation of XVII with dipyridine chromium (VI) oxide in methylene chloride28 gave, as a colorless syrup, the corresponding methyl 2,6,7-trIDEOXY-2-C, 3-O-DIMETHYL-α-β-XYLO-HEPTOPYRANOSID-4-ULOSE XVIII in 65% yield. Due to its instability, the ulose XVIII was characterized only spectroscopically. The addition of methyllithium to the C(4) carbonyl carbon of XVIII in anhydrous ether at -80°C gave the corresponding methyl 2,6,7-trIDEOXY-2-C, 3-O-4-C-TRIMETHYL-P-GLOUCOHEPTOPYRANOSIDE, XIX, in 63% yield. It is interesting to note that the β-galacto derivative, XX, (the C(4) epimer of XIX) was obtained in 21% yield, a rather surprising result in view of our previous findings8. It seems that the stereoselectivity of the addition
of methyllithium to the C(4) carbonyl carbon of a glycopyranoside-4-ulose derivative is considerably reduced when the corresponding 2-deoxy analog is used.

Debenzylidenaion of the 4,6-O-benzylidene derivative XIV by catalytic hydrogenation in ethanol, using 10% Pd—C as the catalyst, afforded methyl 2-deoxy-2-C, 3-O-dimethyl-α-D-glucopyranoside, XXI, in quantitative yield. Selective tritylation of the primary hydroxyl group of XXI with triphenylmethyl chloride (trityl chloride) in pyridine gave the corresponding 6-O-trityl derivative XXII, in 95% yield. The oxidation of the 6-O-trityl derivative XXII with 10:7 dimethylsulfoxide-acetic anhydride solution at 60°, gave methyl 2-deoxy-2-C, 3-O-dimethyl-6-O-triphenylmethyl-α-D-xyllohexopyranosid-4-ulose, XXIII, in 98% yield. The reaction of the 4-ulose XXIII, with methyllithium in ether at —80°C gave methyl 2-deoxy-2-C, 3-O, 4-C trimethyl-6-O-triphenylmethyl-α-D-glucopyranoside, XXIV, in 75% yield. It should be noted that the C(4) epimer of XXIV, methyl 2-deoxy-2-C, 3-O, 4-C-trimethyl-6-O-triphenylmethyl-α-D-galactopyranosid-4-ulose, XXV, was again obtained in a rather high yield (23%). The axial to equatorial ratio of addition being thus, similar to the addition of methyllithium to the 4-ulose XVIII, 3:1. It is obvious that the loss of oxygen at the C(6) carbon has no effect upon the stereochemical outcome of the addition. The two C(4) epimers, XXIV and XXV, as well as the C(4) epimers XIX and XX, were readily separated by chromatography on silica gel using 9:1 benzene-ethyl acetate as eluant.

Methylation of the tertiary C(4) hydroxyl group of XXIV with methyl-iodide-sodium hydride in N,N-dimethylformamide solution gave, in 85% yield, methyl 2-deoxy-2-C, 3-O, 4-C tetramethyl-6-O-triphenylmethyl-α-D-glucopyranoside, XXVI. Catalytic hydrogenation of an ethanolic solution of 4-O-methyl derivative XXVI, using 10% Pd—C as the catalyst, gave the detritylated product, XXVII, in quantitative yield. The oxidation of the primary C(6) hydroxyl group of XXVII with dipyridine chromium (VI) oxide in methylene chloride gave the corresponding 6-aldehyde, XXVIII, in 90% yield. The addition of methylmagnesium iodide to the C(6) carbonyl group of XXVIII gave the corresponding secondary alcohol XXIX, in 84% yield.

It is interesting to note that the addition of Grignard reagent to the exocyclic C(6) carbonyl carbon of XXVIII proceeded highly stereoselectively, giving (according to TLC in several solvent systems) only one stereoisomer. The configuration of the new chiral carbon has not been determined thus far, but based on the following arguments the (S) configuration was tentatively assigned to the C(6) carbon of XXIX. Numerous studies of the addition of Grignard reagent to the exocyclic carbonyl group in dialdehydo sugars strongly suggested that, prior to the actual addition of methylmagnesium iodide to the electrophilic sp² carbonyl carbon, the magnesium atom forms, a chelate complex with the carbonyl oxygen and the carbohydrate ring oxygen. The carbonyl group is oriented so that its oxygen atom is at the closest possible distance to the carbohydrate ring oxygen. The electronegative methyl group of methylmagnesium iodide can then be expected to approach the chelated carbonyl group from a direction that will give rise to the least amount of non-bonded steric interactions in the transition state, which, in turn, should result in the (S) configuration of the C(6) carbon of XXIX.
The oxidation of XXIX with the dipyridine chromium(VI) oxide complex in methylene chloride afforded the 6-keto derivative, XXX, in 95% yield; this could be isolated by chromatography on silica gel. Treatment of the β-alkoxy ketone, XXX, in 1:1 aqueous methanol with sodium hydroxide effected a very smooth β-elimination of the C(4) methoxy group, yielding the C(4)→C(5) unsaturated sugar XXXI, in 85% yield. Catalytic hydrogenation of the C(4)→C(5) double bond of XXXI in ethanol, using 10% Pd—C as the catalyst, afforded (in 90% yield) the corresponding 1-idoo derivative XXXII, representing the 3-O-methyl derivative of the C(1)→C(5) segment of erythronolides A and B. It should be noted that the configurations of the C(4) and C(5) carbons of XXXII are tentatively as (S) and (R), respectively, based on the rationalization given earlier22,23, and also on more recent results24.

EXPERIMENTAL

General

The silica gel used for column chromatography was E. Merck (Darmstadt, W. Germany) silica gel, particle size < 0.063 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0 cm cell. Infrared spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. 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).  

Methyl 4-O-Benzoyl-6-bromo-2,6-dideoxy-2-C 3-O-Methyl-a-D-glucopyranoside (XV)

N-Bromosuccinimide (375 mg; 2.11 mmol) and BaCO₃ (200 mg) were added to a suspension of methyl 4,6-0-benzylidene-2-deoxy-2-C, 3-O-methyl-α-D-glucopyranoside (XIV) (500 mg; 1.70 mmol) in carbon tetrachloride (25 ml) and the vigorously stirred mixture was heated at reflux for 1 hr. The solids (BaCO₃ and succinimide) were filtered off and washed with carbon tetrachloride (50 ml). The combined filtrate was evaporated in vacuo and the dry residue (505 mg) was chromatographed on silica gel (10 g). Elution with benzene gave pure (XV) as a white crystalline solid (519 mg; 82% yield). An analytical sample was obtained by recrystallization from hexane: large, lustrous needles, m. p. 106-106.5°C, [α]₀²⁷ + 87° (c = 1.10, CHCl₃), IR (CHCl₃): 1720 and 1265 (C=O and C-O stretch, benzoate) and 1245 cm⁻¹ (CH₂ wagg., CH₂-Br); 1H-NMR (CDCl₃): δ 8.07 (d, J₁ = 7.33 Hz, 2, benzoate ortho-hydrogens), 7.58 (d × d, J₁ = 7.33 and J₂ = 7.92 Hz, 1, benzoate para-hydrogen), 7.46 (d × d, J₁ = 7.33 and J₂ = 7.93 Hz, 2, benzoate meta-hydrogens), 5.07 [d × d, J₃.4 = 9.16 and J₄.5 = 9.77 Hz 1, H(4] 4.63 [d, J₁₂ = 3.05 Hz 1, H(2)], 4.01 [m, 1, H(5)], 3.53-3.40 [m, 3, H(3), H(6), and H'(6)], 3.43 [s, 3, C(3) methoxy hydrogens] 3.37 [s, 3, C(1) methoxy hydrogens'], 1.96 [m, 1, H(2)], and 1.05 [d, J₂, CH₃ = 6.71 Hz, 3, C(2) methyl hydrogens].

Anal. C₁₆H₂₁O₅Br (373.26) calc’d.: C 51.48; H 5.67% found: C 51.60; H 5.78%  

Methyl 2,6,7-Trimethoxy-2-C, 3-O-methyl-7-sulfoxymethyl-α-D-glucopyranoside (XVI)

A 5 ml round bottom flask, containing a 37% oil suspension of sodium hydride (120 mg; ca. 5.5 mmol) and a small magnetic stirring bar, was capped with a serum bottle cap and the cap was pierced by two hypodermic syringe needles. After flushing the reaction flask with dry nitrogen by attaching a source of dry nitrogen to one needle, dry dimethylsulfoxide (1.0 ml; ca. 12 mmol) was added via syringe through the needle which served as the nitrogen outlet and the suspension was stirred at 70—75°C until evolution of hydrogen ceased (ca. 1 hr). After cooling the mixture to 10°C (ice-salt bath), dry tetrahydrofuran (1 ml) and a solution of the 6-bromo derivative XV (187 mg; 0.5 mmol) in anhydrous tetrahydrofuran (1 ml)
was added (as described for dimethylsulfoxide) and the mixture was stirred at -10°C for 2 hrs. The reaction mixture was transferred to a separatory funnel with water (10 ml), and the aqueous solution extracted with three 10 ml portions of chloroform. The combined chloroform extract was dried over anhydrous Na2SO4 and evaporated in vacuo. The residue was chromatographed on silica gel (10 g). Elution with 5:1 benzene-ethanol afforded XVI as a white crystalline solid (93 mg; 70%). An analytical sample was obtained by recrystallization of this material from acetone-isopropyl ether: fine lustrous needles; m. p. 83.5°-84.5°; [α]n27 +141° (c = 1.01, CHCl3); IR (CHCl3) 3570 (free OH stretch), 3340 (broad absorption, hydrogen bonded OH), and 1035 cm⁻¹ (S=O stretch); 1H-NMR (CDCl3), δ 4.47 [d, J1.2 = 3.66 Hz, 1, H(1)], 4.17 [d, J = 4.27 Hz, 1, OH], 3.55-3.50 [m, 1, H(3)], 3.56 [s, 3, C(3) methoxy hydrogens], 3.31 [s, 3, C(1) methoxy hydrogens], 3.28-3.21 [m, 1, H(4)], 3.18-3.12 [m, 1, H(5)], 3.01-2.90 [m, 1, H(7)], 2.87-2.77 [m, 1, H(7)], 2.61 (s, 3, methylsulfinyl hydrogens), 2.38-2.26 [m, 1, H(6)], 1.96-1.82 [m, 1, H(6)], 1.80-1.69 [m, 1, H(6)], 1.02 [d, J2.3 = 6.71 Hz, 1, C(2) methyl hydrogens].

Anal. C11H22O5S (266.36) calc’d.: C 49.60; H 8.33%
found: C 49.60; H 8.34%

Methyl 2,6,7-Trideoxy-2-C, 3-O-dimethyl-a-D-gluco-heptopyranoside (XVII)

To a solution of 7-sulfoxymethyl derivative XVI (86 mg; 0.32 mmol) in 96% aqueous ethanol (20 ml), a large excess (ca. 500 mg) of Raney-Ni (W-2) was added and the vigorously stirred mixture was heated at reflux for 24 hr. The catalyst was removed by filtration through a layer of «Celite» (Johns-Manville, Denver, Colorado, USA) and successively washed with ethanol (20 ml), ethylacetate (20 ml) and chloroform (20 ml). The combined filtrate was evaporated in vacuo and the residue chromatographed on silica gel (10 g). Elution with 9:1 benzene-ethyl acetate gave chromatographically pure XVII (61 mg; 93%) as a colorless syrup: [α]n27 +172° (c = 0.88, CHCl3); IR (CHCl3) 3580 (free OH) and 3440 cm⁻¹ (broad absorption, hydrogen bonded OH); 1H-NMR (CDCl3), δ 4.48 [d, J1.2 = 3.66 Hz, 1, H(1)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.46-3.40 [m, 1, H(4)], 3.32 [s, 3, C(1) methoxy hydrogens], 3.27-3.15 [m, 2, H(3) and H(5)], 2.80 (broad s, 1, OH), 1.96-1.85 [m, 1, H(6)], 1.83-1.75 (m, J2.CHS = 3.66, J2.3 = 10.38 Hz, 1, H(2)], 1.51-1.39 [m, 1, H'(6)], 1.04 (d, J6.CH3 = 6.71 Hz, 3, C(2) methyl hydrogens), 1.00 [t, J6.CH3 = 7.32 Hz, 3, H(7)].

Anal. C10H20O4 (204.27) calc’d.: C 58.86; H 9.87%
found: C 58.61; H 9.89%

Methyl 2,6,7-Trideoxy-2-C, 3-O-dimethyl-a-D-xylo-heptopyranosid-4-ulose (XVIII)

Methyl 2,6,7-trIDEOXY-2-C, 3-O-dimethyl-a-D-xylo-heptopyranosid-4-ulose (XVIII) (103 mg; 0.55 mmol) dissolved in anhydrous methylene chloride (0.5 ml) was added in one portion to a deep red solution of dipyridine chromium (VI) oxide (775 mg; 3.0 mmol) in anhydrous methylene chloride (15 ml). The mixture was vigorously stirred at room temperature for 10 min in a strictly anhydrous atmosphere and the supernatant was decanted into a separatory funnel containing a saturated aqueous NaHCO3 solution (15 ml). The dark reddish-brown residue which remained in the reaction flask was washed with several 15 ml portions of methylene chloride, and each washing was decanted into the same NaHCO3 solution. The two layers in the separatory funnel were then thoroughly shaken and the methylene chloride layer was separated; the aqueous layer was extracted with two additional 15 ml portions of methylene chloride, and the combined methylene chloride extract was, after drying over anhydrous Na2SO4, evaporated in vacuo (the water bath temperature was kept at 30°C). The residue was chromatographed on silica gel (10 g). Elution with 9:1 benzene-ethyl acetate gave chromatographically homogeneous a-xylo-heptopyranosid-4-ulose XVIII (66 mg; 65%) as a colorless syrup. Because of its instability, this product was not characterized by microanalysis.
Methyl 2,6,7-Trideoxy-2-C, 3-O, 4-C-trimethyl-α-D-glucopyranoside

(XIX)

To a cold (-80 °C) etheral solution (10 ml) of α-ν-xyloheptopyranosid-4-ulose XVIII (280 mg; 1.38 mmol), an etheral solution of methyl lithium was added (1.0 ml of ea. 1.4 molar solution, corresponding to ea. 1.4 mmol). After stirring the reaction mixture for 5 hrs at -80°, water was added and the etheral layer separated in a separatory funnel. The aqueous layer was extracted with three 30 ml portions of ether, and the combined etheral extract washed with brine, dried over anhydrous Na₂SO₄ and evaporated in vacuo. The syrupy residue was chromatographed on silica gel (100 g). Elution with 9:1 benzene-ethyl acetate gave two pure fractions. The less polar fraction was the predominant reaction product and was identified as methyl 2,6,7-trideoxy-2-C, 3-O, 4-C-trimethyl-α-D-glucopyranoside (XIX) (190 mg; 63 %); a syrup, [α]₂₇₅ +179° (e = 0.82, CHCl₃); IR (CHCl₃) 3580 cm⁻¹ (free OH stretch); ¹H-NMR (CDCl₃): δ 4.45 [d, J₂,3 = 3.66 Hz, 1, H(1)], 3.55 [s, 3, C(3) methoxy hydrogens]; 3.38 [d, J5.6 = 10.99 and J5.6' = 0 Hz, 1, H(5)], 3.30 [s, 3, C(1) methoxy hydrogens], 3.10 [d, J₂,3 = 10.99 Hz, 1, H(3)], 1.72 [m, J₆,₇ = 6.71 Hz, 2, H(6) and H'(6)], 1.53 [m, J₆,₇ = 5.6, J₂,CH₃ = 7.33 Hz, 1, H(2)], 1.12 [s, 3, C(4) methyl hydrogens].

Anal. C₁₁H₂₄O₄ (220.31) calc’d.: C 60.52; H 10.16%; found: C 60.37; H 10.30%

To the more polar fraction, identified as methyl 2,6,7-trideoxy-2-C, 3-O, 4-C-trimethyl-β-D-lyxofuranoside [the C(4) epimer of XIX] was obtained as a white crystalline material (64 mg; 21 %); m.p. 49-50°; [α]₂₇₅ +178° (c = 0.20, CHCl₃); IR (CHCl₃) 3560 cm⁻¹ (free OH stretch); ¹H-NMR (CDCl₃): δ 4.54 [d, J₂,3 = 3.05, 1, H(1)], 4.14 (broad s, 1, OH), 3.82 [broad s, 2, H(4) and H(5)], 3.57 [s, 3, C(3) methoxy hydrogens], 3.56 [m, 2, H(6) and H'(6)], 3.40 (broad s, 1, OH), 3.33 [s, 3, C(1) methoxy hydrogens], 2.94 [d, J₂,3 = 10.59 Hz, 1, H(3)], 2.06 [m, J₁₂,₁₃ = 3.66, J₂,₃ = 10.99, and J₂,CH₃ = 7.32 Hz, 1, H(2)], 1.67 and 1.64 [m, J₆,₇ = 4.56, J₂,₆,₇ = 8.26, J₆,₇ = 7.94 Hz, 2, H(6) and H'(6)], 1.18 [s, 3, C(4) methyl hydrogens], 1.02 [t, J₆,₇ = 7.94 Hz, 3, H(7)].

Anal. C₁₁H₂₄O₄ (220.31) calc’d.: C 60.52; H 10.16%; found: C 60.50; H 10.34%

Methyl 2-Deoxy-2-C, 3-O-dimethyl-α-D-glucopyranoside

(XXI)

An ethanolic solution (150 ml) of methyl 4,6-O-benzylidene-2-deoxy-2-C,3-O-dimethyl-α-D-glucopyranoside XIV (5.0 g; 17 mmol) was hydrogenated at atmospheric pressure in the presence of 10% Pd-C (0.7 g). After the absorption of hydrogen ceased (ca 4 hr), the catalyst was filtered off through a layer of Celite and washed with ethanol. The combined filtrate was evaporated in vacuo. Chromatographically pure (according to TLC in three solvent systems: 9:1 benzene-methanol, 9:1 benzene-ethyl alcohol and 5:1 benzene-ethanol) methyl 2-deoxy-2-C, 3-O-dimethyl-α-D-glucopyranoside (XXI) was obtained as a colorless syrup (3.5 g; 100%); [α]₂₇₅ +168° (c = 0.20, CHCl₃); IR (CHCl₃): 3580 cm⁻¹ (free OH stretch); ¹H-NMR (CDCl₃): 4.52 [d, J₂,₃ = 3.05, 1, H(1)], 4.14 (broad s, 1, OH), 3.82 [broad s, 2, H(4) and H(5)], 3.57 [s, 3, C(3) methoxy hydrogens], 3.56 [m, 2, H(6) and H'(6)], 3.40 (broad s, 1, OH), 3.33 [s, 3, C(1) methoxy hydrogens], 2.98 [d, J₂,₃ = 10.38 Hz, 1, H(3)], 2.06 [m, J₁₂,₁₃ = 3.66, J₂,₃ = 10.99, and J₂,CH₃ = 7.32 Hz, 1, H(2)], 1.78 [m, J₆,₇ = 3.05, J₂,₆,₇ = 10.38, and J₂,CH₃ = 7.33 Hz, 1, H(2)], 1.03 [d, J₂,CH₃ = 7.33 Hz, 3, C(2) methyl hydrogens].

Anal. C₁₁H₁₄O₅ (206.24) calc’d.: C 52.41; H 8.80%; found: C 52.87; H 8.75%

Methyl 2-Deoxy-2-C, 3-O-dimethyl-6-O-triphenylmethyl-α-D-glucopyranoside

(XXII)

A pyridine solution (50 ml) containing methyl 2-deoxy-2-C,3-O-dimethyl-α-D-glucopyranoside, XXI (9.0 g; 45 mmol) and triphenylmethyl chloride (9.0 g; 32.3
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mmol) was kept at room temperature for 24 hrs. Pyridine was evaporated in vacuo and the residue was chromatographed on silica gel (80 g). Elution with 98:2 benzene-methanol gave the crystalline and chromatographically homogeneous 6-O-triphenylmethyl derivative XXII (6.2 g; 95%). An analytical sample was obtained by recrystallization from hexane, white needles, m. p. 105–106.5 °C, [α]D27 +70° (ε = 1.17, CHCl3); IR (CHCl3) 3560 and 3480 (free and hydrogen bond ed OH stretch), 3040 (aromatic CH stretch) and 1590 cm⁻¹ (aromatic C=C stretch): lH-NMR (CDCl3: 07.46 [d, J = 7.94 Hz, 6, meta-hydrogens of triphenylmethyl group], 7.28 [dxd, J = 7.53 Hz, 6, ortho-hydrogens of triphenylmethyl group], 7.21 (t, J = 7.53 Hz, 3, para-hydrogens of triphenylmethyl group), 4.50 [d, J1.2 = 3.05 Hz, 1, H(1)], 3.68 [m, J5.6 = J5.6· = 4.88 and J4.5 = 9.77 Hz, 1, H(5)], 3.51 [s, 3, C(3) methoxy hydrogens], 3.48 [dxd, J3.4 = 9.16 and J4.5 = 9.77 Hz, 1, H(6)], 3.32 [s, 3, C(3) methoxy hydrogens], 2.79 (d, J = 2.44 Hz, OH), 1.75 (m, J1.2 = 3.05, J2.3 = 10.38, and J2, CH3 = 6.71 Hz, 1, H(2)], 1.02 [d, J2, CH3 = 6.71 Hz, 3, C(2) methyl hydrogens].

Anal. C28H32O5 (448.57) calc'd.: C 74.97; H 7.19%. Found: C 74.87; H 7.23%.

Methyl 2-Deoxy-2-C, 3-O-dimethyl-6-O-triphenylmethyl-α-D-xylo-hexo-
-pyranosid-4-ulose (XXIII)

The 6-O-Triphenylmethyl derivative (XXII) (7.0 g; 15.6 mmol) was dissolved in 10:7 dimethylsulfoxide-acetic anhydride mixture (10 ml) and the solution was kept at 60° for 2 hrs. Evaporation in high vacuum at temperatures below 60° gave a white crystalline solid (6.8 g; 98%), which was the chromatographically pure α-D-xylo-hexopyranosid-4-ulose XXIII. An analytical sample was obtained by recrystallization from isopropyl ether, m. p. 135–136°C, [α]D27 +135° (ε = 1.21, CHCl3); IR (CHCl3): 3045 and 1590 (aromatic CH and C=C stretch) and 1728 cm⁻¹ (C=O stretch); lH-NMR (CDCl3): 07.6–7.1 (m, 15, triphenylmethyl hydrogens), 4.78 [d, J1.2 = 3.5 Hz, 1, H(1)], 4.43–4.20 [m, 1 H(5)], 3.9–3.2 [m, 3, H(3), H(6), and H'(6)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.45 [s, 3, C(l) methoxy hydrogens], 2.27 (broad m, 1, H(2)], 1.10 [d, J = 6.5 Hz, 3, C(2) methyl hydrogens].

Anal. C26H32O5 (446.55) calc'd.: C 75.31; H 6.77%. Found: C 75.37; H 6.78%.

Methyl 2-Deoxy-2-C, 3-O, 4-C-trimethyl-6-O-triphenylmethyl-α-D-gluco-pyranosid-4-ulose (XXIV)

To a cold (−80°C) solution of hexopyranosid-4-ulose XXIII (1.0 g; 2.24 mmol) in anhydrous ether (25 ml), an ethereal solution of methyllithium (5 ml of 1.8 molar solution corresponding to ca. 9.0 mmol) was added and the mixture was stirred for 4.5 hrs at −80°C. After an additional amount (2 ml) of methyllithium solution was added, the stirring was continued for another 1.5 hrs. Water (25 ml) was then added, the etheral layer separated from the aqueous layer in a separatory funnel and the equeous layer extracted with three 30-ml portions of ether. The combined etheral extract was washed with saturated aqueous NaCl solution, dried over anhydrous Na2SO4 and evaporated in vacuo. The residue was chromatographed on silica gel (55 g). Elution with 9:1 benzene-ethyl acetate gave two pure fractions identified as the C(4) epimers XXIV and XXV. The α-D-gluco-derivative XXIV (776 mg; 79%) was a white crystalline solid which, after recrystallization from hexane, melted at 109–110°C; [α]D27 +66° (ε = 0.97, CHCl3); IR (CHCl3) 3500 (broad absorption, hydrogen bonded OH) 3030 and 1590 cm⁻¹ (aromatic CH and C=C stretch); 1H-NMR (CDCl3): δ 7.45 (d, J = 7.32 Hz, 6, ortho-hydrogens of triphenylmethyl group), 7.30 (d, J = 7.32 Hz, 6, meta-hydrogens of triphenylmethyl group), 7.22 (dxd, J1 = 6.71 Hz, J2 = 7.33 Hz, 3, para-hydrogens of triphenylmethyl group), 4.44 (d, J1,2 = 3.66 Hz, 1, H(1)], 3.84 (dxd, J4,5 = 6.71 Hz, and J4,6 = 6.10 Hz, 1, H(5)], 3.56 (s, 3, C(3) methoxy hydrogens), 3.33 (s, 3, C(1) methoxy hydrogens), 3.17 (6,
J₂,₃ = 11.60 Hz, 1, H(3)], 1.64 [m, J₁,₂ = 3.66, J₂,₃ = 11.60, and J₂,CH₃ = 5.49 Hz, 1, H(2)], 0.98 [d, J₂,CH₃ = 5.49 Hz, 3, C(2) methyl hydrogens], 0.87 [s, 3, C(4) methyl hydrogens]

Anal. C₂₉H₃₄O₅ (462.59) calc'd.: C 75.30; H 7.41%
found: C 75.45; H 7.56%

The α-galacto derivative XXV (243 mg; 23.5% was obtained as a white crystalline material, which after recrystallization from acetone-hexane melted at 133–134°C, [a]D +84° (c = 0.97, CHCl₃); IR (CHCl₃) 3550 (broad absorption, hydrogen bond ed OH), 3045 and 1590 cm⁻¹ (aromatic CH and C=C stretch); ¹H-NMR (CDCl₃): δ 7.52 [d, J = 7.32 Hz, 6, ortho-hydrogens of triphenylmethyl group), 7.30 [dx, J₁ = 7.94 and J₂ = 7.32 Hz, 6, meta-hydrogens of triphenylmethyl group], 7.22 [d, J = 7.32 Hz, 3, para-hydrogens of triphenylmethyl group], 4.67 [d, J₁,₂ = 3.66 Hz, 1, H(1)], 3.72 [m, 1, H(5)], 3.51 [s, 3, C(3) methoxy hydrogens], 3.47 [s, 3, C(1) methoxy hydrogens], 3.46 [m, 2, H(6) and H'(6)], 2.94 [d, J₂,CH₃ = 5.49 Hz, 1, H(2)], 2.53 [s, 3, C(4) methyl hydrogens].

Anal. C₂₉H₃₄O₅ (462.59) calc'd.: C 75.30; H 7.41%
found: C 75.45; H 7.56%

Methyl 2-Deoxy-2-C₃,3-O,4-C₄,4-O-tetramethyl-α-D-glucopyranoside (XXVI)

To a cold (0°C) solution of the α-gluco-derivative XXIV (3.68 g; 7.95 mmol) in anhydrous N,N-dimethylformamide (120 ml), sodium hydride (3.0 g of 57% oil suspension; ca. 71 mmol) was added and the obtained mixture was stirred for 1 hrs at 0°C. Freshly distilled methyl iodide (3.0 ml; 48 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The excess of sodium hydride was destroyed by adding methanol (15 ml) and the solvents were evaporated in vacuo. The residue was transferred to a separatory funnel with 1:1 water-chloroform (300 ml) and the chloroform layer separated after shaking. The aqueous layer was extracted with two more 150-ml portions of chloroform, and the combined chloroform extract was washed with water (50 ml), dried over anhydrous Na₂SO₄, and evaporated in vacuo. The crystalline residue yielded after recrystallization from acetone-hexane pure 4-O-methyl-α-D-glucopyranoside derivative XXVI (3.2 g; 85%) as a white crystalline solid, m. p. 154.5–155.5°C; [a]D +68° (c = 1.19, CHCl₃); IR (CHCl₃): 3050 and 1590 cm⁻¹ (aromatic CH and C=C stretch); ¹H-NMR (CDCl₃): δ 4.48 [d, J₁ = 3.05 Hz, 1, H(1)], 3.84-3.74 [m, 3, C(4) methyl hydrogens], 3.70-3.60 [m, 1, H(3)], 3.68-3.58 [m, 1, H(5)], 3.54 [s, 3, C(4) methoxy hydrogens], 3.40 [s, 3, C(4) methoxy hydrogens], 3.37 [d, J₂,CH₃ = 6.71 Hz, 3, C(2) methyl hydrogens], 0.95 [s, 3, C(4) methyl hydrogens].

Anal. C₃₀H₃₆O₅ (476.62) calc'd.: C 75.60; H 7.61%
found: C 75.74; H 7.79%
[s, 3, C(1) methoxy hydrogens], 2.55 [broad s, 1, OH], 1.77 [m, J1,2 = 3.05 and J2,3 = 6.71 Hz, 1, H(2)], 1.16 [s, 3, C(4) methyl hydrogens], 1.02 [d, J2,3 = 3.05 Hz, 3, C(2), methyl hydrogens].

Anal. C14H22O5 (234.30) calc'd.: C 56.39; H 9.47% found: C 56.16; H 9.64%

**Methyl 2-Deoxy-2-C,3-O,4-C,4-O-tetramethyl-a-D-gluco-hexodialdo-1,5-pyranoside (XXVIII)**

Dipyridine chromium (VI) oxide (2.34 g; 9.3 mmol) was added to a vigorously stirred anhydrous methylene chloride (150 ml) and the stirring was continued for 5 min at room temperature whereby a deep red solution was obtained. Methylene chloride solution (0.5 ml) of XXVII (363 mg; 1.5 mmol) was then added and the reaction mixture vigorously stirred for 5—10 min. at room temperature, after which the organic phase was decanted into a separatory funnel containing saturated aqueous NaHCO3 solution (50 ml). After shaking, the methylene chloride layer was separated, and the aqueous layer extracted with three 50-ml portions of methylene chloride. The combined extract was, after drying over anhydrous Na2SO4, evaporated in vacuo. The crude product, which still contained traces of pyridine, was dried for an additional 10 min at room temperature in high vacuum. The dialdo sugar XXVIII (294 mg; 90%) (a colorless syrup) was, according to TLC. (9: 1 benzene-ethyl acetate), better than 95% pure: 'H-NMR (CDCl3) δ: 9.80 [s, 1, H(6) aldehydo hydrogen], 4.59 [d, J1,2 = 3.5 Hz, 1, H(1)], 4.22 [s, 1, H(5)], 3.52 [s, 3, C(3) methoxy hydrogens], 3.46 [s, 3, C(4) methoxy hydrogens], 3.29 [s, 3, C(1) methoxy hydrogens], 1.76 [m, 1, H(2)], 1.21 [s, 3, C(4) methyl hydrogens], 1.01 [d, J2,CH3 = 6.5 Hz, 3, C(2) methyl hydrogens]. Due to its instability, no attempt was made to characterize this product by microanalysis.

**Methyl 2,7-Dideoxy-2-C,3-O,4-C,4-O-tetramethyl-L-glycero-a-D-gluco-heptopyranoside (XXIX)**

To an ethereal solution (30 ml) of methylmagnesium iodide (obtained from Mg turning (200 mg; 8.23 mmol) and methyl iodide (1.5 ml; 24.10 mmol)), an ethereal solution (2.0 ml) of D-gluco-hexodialdo-L,5-pyranoside XXVIII (500 mg; 2.1 mmol) was added and the mixture stirred at room temperature for 30 min. Aqueous ammonium chloride solution (30 ml) was then added and the ether layer separated from the aqueous layer in a separatory funnel. The aqueous layer was extracted with three 30 ml portions of ether and the combined etheral extract, after drying over anhydrous Na2SO4, evaporated in vacuo. The residue (450 mg; 84%), a syrup assumed (vide supra) to be the L-glycero-epimer XXIX was according to TLC (9 :1 benzene-ethyl acetate), IR (CHCl3) 3560 cm⁻¹ (free OH stretch); 'H-NMR (CDCl3) δ: 4.53 [d, J1,2 = 3.05 Hz, 1, H(1)], 4.02 [broad singlet, 1, H(5)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.40 [s, 3, C(4) methoxy hydrogens], 3.39 [m, J6.6 = 3.66 and J7.7 = 6.10 Hz, 1, H(6)], 3.34 [s, 3, C(3) methoxy hydrogens], 3.20 [d, J2,3 = 10.99 Hz, 1, H(3)], 2.43 [broad s, 1, OH), 1.79 [m, J1,2 = 3.05, J2,3 = 10.99, and J3,4 = 6.72 Hz, 1, H(2)], 1.28 [d, J6.7 = 6.10 Hz, 3, H(7)], 1.25 [s, 3, C(4) methyl hydrogens], 1.10 [d, J2,3 = 6.72 Hz, 3, C(2) methyl hydrogens].

Anal. C12H24O5 (248.32) calc'd.: C 58.04; H 9.74% found: C 58.33; H 19.06%

**Methyl 2,7-Dideoxy-2-C,3-O,4-C,4-O-tetramethyl-L-glycero-a-D-gluco-heptopyranosid-6-ulose (XXX)**

Dipyridinium chromium (VI) oxide (762 mg; 3.05 mmol) was added to vigorously stirred anhydrous methylene chloride (150 ml), and to the deep red solution, obtained after stirring at room temperature for 5 min, a methylene chloride solution (0.5 ml) of methyl l-glycero-a-D-gluco-heptopyranoside XXIX (126 mg; 0.51 mmol) was added. After stirring the reaction mixture for 5—10 min at room temperature, the
organic layer was decanted into a separatory funnel containing a saturated aqueous NaHCO₃ solution (15 ml). After shaking, the organic layer was separated and the aqueous layer extracted with two 15 ml portions of methylene chloride. The combined methylene chloride extract was dried over anhydrous Na₂SO₄ and evaporated in vacuo. The dry residue was chromatographed on silica gel (10 g). Elution with 6:1 benzene-ethyl acetate (or 4:1 hexane-acetone) gave chromatographically pure (TLC.: using 4:1 hexane-acetone) α-D-gluco-heptopyranosid-6-ulose, XXX, as a colorless syrup, IR (CHCl₃): 1710 cm⁻¹ (C=O stretch); ¹H-NMR (CDCl₃) δ: 4.57 [d, J₁ = 3.66 Hz, 1, H(1)], 4.26 [s, 1, C(5)], 3.56 [s, 3, C(3) methoxy hydrogens], 3.46 [s, 3, C(4) methoxy hydrogens], 3.41 [d, J₂,CH₃ = 3.66 Hz, 1, H(2)], 1.17 [s, 3, C(4) methyl hydrogens], 0.92 [d, J₂,CH₃ = 6.8 Hz, 3, C(2) methyl hydrogens].

Anal. C₁₂H₂₂O₅ (246.31) calc’d.: C 58.51; H 9.00%; found: C 58.37; H 9.22%.

Methyl 2,4,7-Trideoxy-2-C, 3-O, 4-C-trimethyl-β-L-threo-hept-4-enopyranoside-6-ulose (XXXI)

Methyl 2,7-dideoxy-2-C, 3-O, 4-C, 4-O-tetramethyl-α-D-gluco-heptopyranosid-6-ulose (XXXI) (118 mg; 0.48 mmol) was dissolved in a 50% aqueous methanolic sodium hydroxide solution (2 ml) (containing 100 mg of NaOH) and the mixture was stirred for 3 hrs at 50 °C. The reaction mixture was then diluted with water (10 ml) and extracted with three 15 ml portions of chloroform. The combined chloroform extract was, after drying over anhydrous Na₂SO₄, evaporated in vacuo. The dry residue (87 mg; 85%), a syrup, was chromatographically homogeneous. IR (CHCl₃): 1690 cm⁻¹ (C=O stretch, α,β-unsaturated ketone); ¹H-NMR (CDCl₃) δ: 4.77 [d, J₁,CH₂ = 2.1 Hz, 1, H(1)], 3.52 [s, 3, C(3) methoxy hydrogens], 3.37 [s, 3, C(1) methoxy hydrogens], 2.27 [s, 3, H(7)], 2.01 [s, 3, C(4) methyl hydrogens], 0.92 [d, J₂,CH₃ = 6.8 Hz, 3, C(2) methyl hydrogens].

Anal. C₁₁H₁₇O₄ (214.26) calc’d.: C 61.66; H 8.47%; found: C 61.41; H 8.74%.

Methyl 2,4,7-Trideoxy-2-C, 3-O, 4-C-trimethyl-β-L-ido-heptopyranosid-6-ulose (XXXII)

An ethanolic solution (10 ml) of β-L-threo-hept-4-enopyranosid-6-ulose XXXI (50 mg; 0.23 mmol) was hydrogenated in the presence of 10% Pd-C (15 mg) at room temperature and atmospheric pressure. After vigorous stirring overnight, the catalyst was filtered off through a layer of Celite and washed with several 5 ml portions of ethanol. The combined filtrate was evaporated in vacuo and the dry residue was chromatographed on silica gel (10 g). Elution with 9:1 benzene-ethyl acetate afforded chromatographically homogeneous β-L-ido-heptopyranosid-6-ulose (XXXII) (45 mg; 90%) as a colorless syrup.

Methyl 2-deoxy-2-C, 3-O, 4-C, 4-O-tetramethyl-6-O-triphenylmethyl-α-D-galactopyranoside (XXXIII)

To a cold (0 °C) N,N-dimethylformamide solution (20 ml) of methyl 2-deoxy-2-C, 3-O, 4-C-trimethyl-6-O-triphenylmethyl-α-D-galactopyranoside (XXV) (666 mg; 1.44 mmol), sodium hydride (500 mg of 57% oil suspension; ca. 12 mmol) was added and the obtained suspension was stirred for 1 hr. Methyl iodide (1.0 ml; ca. 16 mmol) was then added and the reaction mixture stirred at room temperature overnight. The excess sodium hydride was destroyed by adding methanol (5 ml). After the solvents were evaporated in vacuo, the dry residue was transferred into a separatory funnel with a 1:1 chloroform-water mixture (100 ml); after shaking, the chloroform layer was separated. The aqueous layer was extracted with two 50 ml portions of chloroform, the combined chloroform extract was washed with water (20 ml), dried over anhydrous Na₂SO₄ and evaporated in vacuo. The
crude product (674 mg) was chromatographed on silica gel. Elution with benzene, followed by 99:1 benzene-ethyl acetate, gave pure, crystalline 4-O-methyl-α-D-galactopyranoside [XXXIII] (600 mg; 87%). An analytical sample was prepared by recrystallization from acetone-hexane: white crystals, m. p. 137-138°C; [α]_D +6.1° (c = 1.10, CHCl_3); IR (CHCl_3): 3045 and 1590 cm⁻¹ (aromatic CH and C=C stretch); 1H-NMR (CDCl_3): 7.47 (d, J = 7.94 Hz, 6, ortho-hydrogens of triphenylmethyl group), 7.27 (dxd, J_1 = 7.32 and J_2 = 7.93 Hz, 6, meta-hydrogens of the triphenylmethyl group), 7.20 (dxd, J_1 = 7.32 and J_2 = 6.71 Hz, 3, para-hydrogens of the triphenylmethyl group), 4.61 [d, J_1,2 = 3.06 Hz, 1, H(1)], 3.71 [m, 3, C(3) methoxy hydrogens], 3.45 [s, 3, C(1) methoxy hydrogens], 3.40-3.25 [m, 2, H(6) and H'(6)], 3.22 [s, 3, C(4) methoxy hydrogens].

Anal. C_{30}H_{30}O_8 (476.62) calc'd.: C 75.60; H 7.61% found: C 75.48; H 7.49%.

Methyl 2-Deoxy-2-C,3-,4-,4-0-tetramethyl-β-L-galactopyranoside (XXXIV)

An ethanolic solution (20 ml) of the 6-0-triphenylmethyl derivative XXXIII (600 mg; 1.26 mmol) was hydrogenated overnight in the presence of 10% Pd-C (60 mg) at room temperature and atmospheric pressure. The catalyst was filtered off, washed with several 5 ml portions of ethanol and the combined filtrate was evaporated in vacuo. The dry residue was chromatographed on silica gel (30 g). Elution with 3:1 hexane-acetone (or 5:1 benzene-ethyl acetate) gave chromatographically pure (TLC in 3:1 hexane-acetone, 9:1 benzene ethyl acetate, 95:5 benzene-ethanol) detritylated XXXIV (295 mg; 100%) as a syrup; [α]_D +152° (c = 0.74, CHCl_3), IR (CHCl_3): 3580 and 3430 (free and hydrogen bonded OH stretch); 1H-NMR (CDCl_3): 4.65 [d, J_1,2 = 3.66 Hz, 1, H(1)], 3.94 [dxd, J_5,6 = 6.71 and J_6,6' = 11.60 Hz, 1, H(6)], 3.72 [s, 3, C(3) methoxy hydrogens], 3.45 [s, 3, C(1) methoxy hydrogens], 3.34 [s, 3, C(4) methoxy hydrogens], 3.02 [d, J_2,3 = 11.60 Hz, 1, H(3)], 2.87 (broad s, 1, OH), 2.30 [m, J_1,2 = 3.66, J_2,3 = 11.60, and J_2,CH_3 = 6.71 Hz, 1, H(2)], 1.32 [s, 3, C(4) methyl hydrogens], 1.03 [d, J_2,CH_3 = 6.71 Hz, 3, C(2) methyl hydrogens].

Anal. C_{11}H_{22}O_5 (234.30) calc'd.: C 56.39; H 9.47% found: C 56.18; H 9.29%.

Methyl 2-Deoxy-2-C,3-O,4-C,4-0-tetramethyl-α-D-galacto-hexodialdo-1,5-pyranoside (XXXV)

Dipyridine chromium (VI) oxide (1.3 g; 4.6 mmol) was dissolved, under strictly anhydrous conditions, in anhydrous methylene chloride (100 ml) by vigorously stirring the mixture at room temperature for 5 min. To the obtained deep red solution, methyl 2-deoxy-2-C,3-O,4-C,4-0-tetramethyl-α-D-galactopyranoside XXXIV (160 mg; 0.68 mmol), dissolved in anhydrous methylene chloride (0.5 ml), was added in one portion. After stirring the reaction mixture at room temperature for 5 min, the organic layer was decanted into a separatory funnel containing a saturated aqueous NaHCO_3 solution (50 ml), and the two layers were thoroughly mixed by shaking. The organic layer was separated and the aqueous layer extracted with three 50 ml portions of methylene chloride. The combined methylene chloride extract was dried over anhydrous Na_2SO_4 and the evaporated in vacuo. The crude product (134 mg; 65%), a colorless syrup, was, according to TLC (9:1 benzene-ethyl acetate) chromatographically homogeneous. Due to its instability, the product XXXV was immediately used without further characterization.

Methyl 2,7-dideoxy-2-C,3-O,4-C,4-0-tetramethyl-γ-l-gluco-α-D-galactoheptopyranoside (XXXVI)

To an etheral solution (10 ml) of methylmagnesium iodide (obtained from 40 mg of Mg turnings and 0.3 ml of methyl iodide), an ethereal solution (1 ml) of α-D-galacto-hexodialdo-1,5-pyranoside (XXXV) (134 mg; 0.58 mmol) was added in one
portion and the mixture was stirred at room temperature for 30 min. Aqueous NH₄Cl solution (2M; 10 ml) was then added and the mixture was transferred to a separatory funnel. After shaking, the etheral layer was separated and the aqueous layer extracted with three 20-ml portions of ether. The combined etheral extract was dried over anhydrous Na₂SO₄ and evaporated in vacuo. The residue was chromatographed on silica gel (7 g). Elution with 4:1 chloroform-ethyl acetate gave methyl L-glycero-α-D-galacto-heptopyranoside XXXVI (122 mg; 85%) as a colorless syrup, which solidified, m.p. 44-45°C. The chromatographically homogeneous XXXVI (according to TLC in: 4:1 chloroform-ethyl acetate, 9:1 benzene-ethyl acetate, 4:1 hexane-acetone, and 9:1 benzene-ethanol) was not recrystallized since the chromatographically purified product was spectroscopically pure. It gave good microanalysis and was easily soluble in all examined solvents (from hexane to methanol). 

\[ [\alpha]_D^{27} +144^\circ \ (c = 0.99, CHCl_3); \] 
\[ \text{IR} \ (\text{CHCl}_3): 3430 \text{ cm}^{-1} \ (\text{broad absorption, hydrogen bonded OH stretch}); \]
\[ \text{H-NMR} \ (\text{CHCl}_3): \]
\[ \delta 4.68 \ [d, J_{1,2} = 3.05 \text{ Hz}, 1, H(1)], \]
\[ 4.42 \ [s, 1, OH], \]
\[ 4.27 \ [d, x_7 = 6.10 \text{ and } J_{5,6} = 0 \text{ Hz}, 1, H(6)], \]
\[ 3.48 \ [s, 3, C(3) methoxy hydrogens], \]
\[ 3.47 \ [s, 3, C(1) methoxy hydrogens], \]
\[ 3.33 \ [s, 3, C(4) methoxy hydrogens], \]
\[ 3.23 \ [s, 1, H(5)], \]
\[ 2.98 \ [d, J_{3,4} = 10.99 \text{ Hz}, 1, H(3)], \]
\[ 2.30 \ [m, J_{1,2} = 3.05, J_{2,3} = 10.99, \text{ and } J_{2,3} = 6.71 \text{ Hz}, 1, H(2)], \]
\[ 1.39 \ [d, J_{5,6} = 6.71 \text{ Hz}, 1, C(2) methyl hydrogens], \]
\[ 1.02 \ [d, J_{5,6} = 6.71 \text{ Hz}, 3, C(2) methyl hydrogens]. \]

Anal. C_{12}H_{24}O_{2} (248.32) calc'd.: C 58.04; H 9.74%;
found: C 58.01; H 10.02%.

REFERENCES
1. Dedicated to Prof. Mihailo Lj. Mihailović on the occasion of his 60th birthday.
3. This work was supported in part by the National Science Foundation, CHE75-17782 and the National Cancer Institute, CA 15483.
5. The carbohydrate-like structure of the macrocyclic lactone ring of macrolide antibiotics, noticed by Woodward, became particularly evident during later structural studies. The large number of fragments obtained by chemical degradation of macrolide aglycones so strongly resembled carbohydrates in their appearance, conformational behavior and optical rotatory power that they were termed »semisynthetic sugars«.
6. R. B. Woodward, Angew. Chem. 69 (1957) 50. Here, Woodward introduced the word »macrolides« to describe a new class of lipophilic basic antibiotics, all highly active against gram-positive bacteria, and exclusively produced by Actinomycetes which, as a common structural feature, have a polysubstituted macrocyclic lactone ring. In the same paper, he describes magnamycin (carbo-
mycin) as a giant sugar having at the same time the properties of a long-chain aliphatic acid.
12. The addition of organometallic reagents to the C(3) carbon of alkyl hexopy-
ranoside-3-uloses has been the subject of several studies. It has been stated in all of them that the anomeric configuration of aglycone effectively controls the stereochemistry of these nucleophilic additions.
SINTEZA MAKROLIDNIH ANTIBIOTIKA. IV. STEREOSELEKTIVNA SINTEZA 3-0-METIL I 11-O-METIL DERIVATA C(1)-C(6) SEGMENTA ERYTRONOLIDA A I B TE C(9)-C(15) SEGMENTA ERYTRONOLIDA A

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Saznanje da su reakcije adicije Sp2 (C=O i C=C) ugljikovih atoma u ugljihidratnom prstenu ovisne o anomernoj konfiguraciji glikopiranozida omogućilo je stereoselektivnu sintezu kiralnih ugljikovih skeleta polioksomakrolidnih aglikona metimicina, eritromicina A i B, pikromicina i narbomicina.

U radu su opisane stereoselektivne sinteze metil 2,6-dideoksi-2-C, 3-0, 4-C, 6-C-tetrametil-6-okso-8-L-idopiranozida i metil 2,6-dideoksi-2-C, 3-0, 4-C, 6-C-tetrametil-α-D-glukopiranozida koji predstavljaju 3-0-metil i 11-0-metil derivate C(1)-C(6) segmenata eritronolida A i B te C(9)-C(15) segmenta eritronolida A.