CROATICA CHEMICA ACTA CCACAA 58 (4) 681—698 (1985)

CCA-1615

YU ISSN 0011-1643
UDC 547.474.4
Original Scientific Paper

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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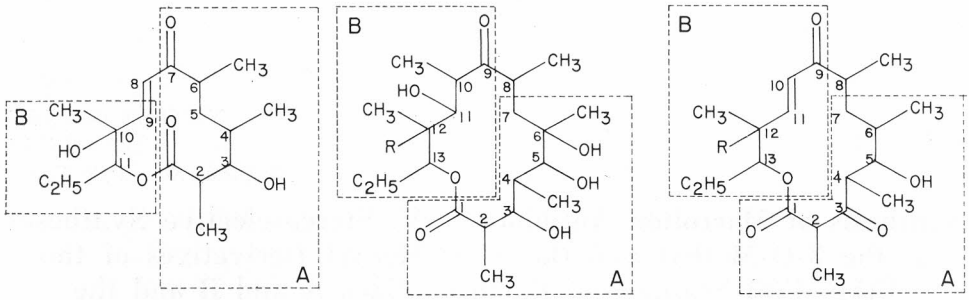
Received June 13, 1985

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 sp^2 (C=O and C=C) carbon atoms of a glycopranoside 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-*O*, 4-*C*-tri-methyl-β-L-*ido*-heptopyranosid-6-ulose and methyl 2,6,7-trideoxy-2-*C*, 3-*O*, 4-*C*-trimethyl-α-D-*gluco*heptopyranoside, 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[5], 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, pikromycin 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)]. Consequenatly, 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

Scheme 1



I, aglycone of methymycin (methynolide)

II, R=OH: aglycone of erythromycin A (erythronolide A)

III, R=H : aglycone of erythromycin B (erythronolide B)

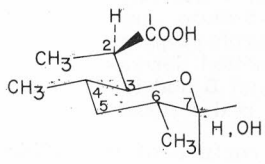
IV, R=OH: aglycone of pikromycin (pikronolide)

V, R=H : aglycone of narbomycin (narbonolide)

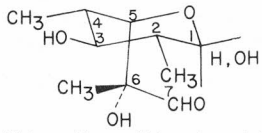
macrolide aglycone. An important advantage of dissecting the macrocyclic lactone rings, as depicted in Scheme 1, is that it produces constitutionally and stereochemically similar fragments. This becomes particularly evident if segments A and B of methynolide, erythronolides A and B, pikronolide and narbonolide are represented in the form of carbohydrate pyranosides (Scheme 2).

Scheme 2

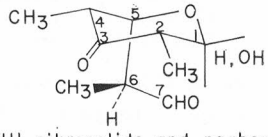
Segments A



VI, methynolide

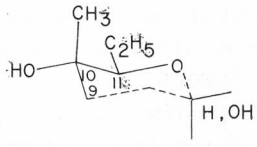


VII, erythronolides A and B

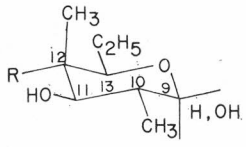


VIII, pikronolide and narbonolide

Segments B

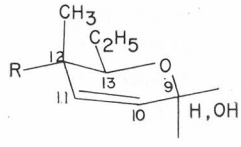


IX, methynolide



X, R = OH: erythronolide A

XI, R = H : erythronolide B



XII, R = OH: pikronolide

XIII, R = H : narbonolide

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 $^4C_1$ conformation of a pyranoside-like strukcture. 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 methynolide, 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 glycopyranosides (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 transformtaions 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-glucopyranose 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-glucopyranose 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 addtion of organometallic reagents (methyllithium and 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 methyllithium 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 methyllithium 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 methyllithium and thus

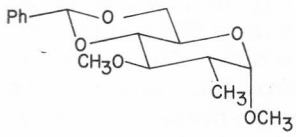
the stereochemical outcome of the addition. A fuller account of these studies and the proposed rationalization of the obtained results has been published.[8]

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[9,10] it was reported that the ^{13}C chemical shift of an axial methyl group is shifted by ca. 6 ppm towards the higher magnetic field, as compared to the ^{13}C chemical shift of an equatorial methyl group. This observation prompted us to investigate whether the ^{13}C 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 ^{13}C 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]

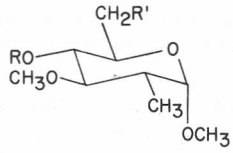
The above findings immediately raised the question as to wheter the anomeric configuration could control the stereochemistry of addition to all sp^2 carbon atoms of a glycopyranoside ring, and particularly to the C(2), and the C(4) and C(5) carbons[12]. It was reported that the complex metal hydride reduction of a β-D-*lyxo*-hexapyranoside derivative gave the corresponding β-D-talopyranoside derivative[16], whereas an α-D-*arabino*-hexopyranoside-2--ulose derivative, under simliar reaction conditions, gave the corresponding α-D-glucopyranoside derivative as the only product[17]. Our own investigation showed that the stereochemistry of sodium borohydride reduction of methyl α- and β-D-*arabino*-hexopyranisid-2-ulose derivatives strongly depended upon the anomeric configuration[18]. Furthermore, very high stereoselectivity was observed in catalytic hydrogenation of methyl β-D-*arabino*-hexopyranosidulose[19] and methyl 3,4,6-trio-*O*-benzyl-β-D-*arabino*-hexopyranosidulose[20]. 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-*arabino*-hexopyranoside derivatives[21]. 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-*arabino*--hexopyranoside 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-*arabino*-hexopyranoside 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 D-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[22] 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[23].

The finding that configuration of the aglycone group of a glucopyranoside effectively controls the stereochemistry of various addition reactions to sp^2 (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.



XIV



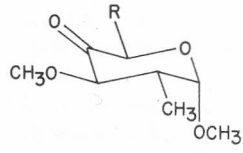
XV, R = PhCO ; R' = Br

XVI, R = H ; R' = CH_3SOCH_2

XVII, R = H ; R' = CH_3

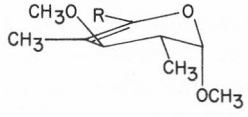
XXI, R = H ; R' = OH

XXII, R = H ; R' = Ph_3CO

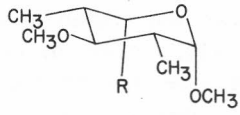


XVIII, R = CH_2CH_3

XXIII, R = CH_2OCPh_3



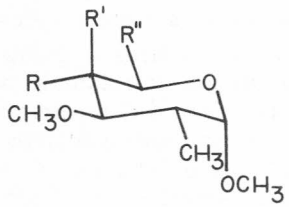
XXXI, R = $COCH_3$



XXXII, R = $COCH_3$

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[24].

The oxidative debenzylidenation of the 4,6-*O*-benzylidene derivative *XIV*[21] with *N*-bromosuccinimide in refluxing carbontetrachloride[26] gave, in quantitative yield[27], methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-*C*, 3-*O*-dimethyl-α--D-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-D-*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-D-*gluco*heptopyranoside, *XVII*, as a colorless syrup in 92% yield. The oxidation of *XVII* with dipyridine chromium (VI) oxide in methylene chloride[28] gave, as a colorless syrup, the corresponding methyl 2,6,7-trideoxy-2-*C*, 3-*O*-dimethyl-α-D-*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-α-D-*gluco*heptopyranoside, *XIX*, in 63% yield. It is interesting to note that the D-galacto derivative, *XX*, (the C(4) epimer of *XIX*) was obtained in 21% yield, a rather surprising result in view of our previous findings[8]. It seems that the stereoselectivity of the addition



XIX, R=OH; R'=CH_3; R"=C_2H_5

XX, R=CH_3; R'=OH; R"=C_2H_5

XXIV, R=OH; R'=CH_3; R"=CH_2OCPh_3

XXV, R=CH_3; R'=OH; R"=CH_2OCPh_3

XXVI, R=OCH_3; R'=CH_3; R"=CH_2OCPh_3

XXVII, R=OCH_3; R'=CH_3; R"=CH_2OH

XXVIII, R=OCH_3; R'=CH_3; R"=CHO

XXIX, R=OCH_3; R'=CH_3; R"=$CH(OH)CH_3$

XXX, R=OCH_3; R'=CH_3; R"=$COCH_3$

XXXIII, R=CH_3; R'=OCH_3; R"=CH_2OCPh_3

XXXIV, R=CH_3; R'=OCH_3; R"=CH_2OH

XXXV, R=CH_3; R'=OCH_3; R"=CHO

XXXVI, R=CH_3; R'=OCH_3; R"=$CH(OH)CH_3$

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.

Debenzylidenation 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*-tritylderivative *XXII* with 10 : 7 dimethylsulfoxide-acetic anhydride solution at 60°, gave methyl 2-deoxy-2-*C*, 3-*O*-dimethyl-6-*O*-triphenylmethyl-α-D-*xylo*hexopyranosid-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-galactopyranoside *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[29] gave, in 85% yield, methyl 2-deoxy-2-*C*, 3-*O*, 4-*C*, 4-*O*-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[30]. The oxidation of the primary C(6) hydroxyl group of *XXVII* with dipyridine chromium (VI) oxide in methylene chloride[28] gave the corresponding 6-aldehyde, *XXVIII*, in 90% yield[32]. 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[33] strongly suggested that, prior to the actual addition of methylmagnesium iodide to the electrophilic sp^2 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 L-ido derivative *XXXII*, representing the 3-*O*-methyl derivative of the C(1)—C(6) 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 earlier[22,23], and also on more recent results[25].

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. ^{1}H 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-Dimethyl-α-D-glucopyranoside (XV)

N-Bromosuccinimide (375 mg; 2.11 mmol) and $BaCO_3$ (200 mg) were added to a suspension of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*, 3-*O*-dimethyl-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 ($BaCO_3$ and succinimide) were filtered off and washed with carbon tetrachloride (50 ml). The combined filtrate was evaporated in vacuo and the dry residue (605 mg) was chromatographed on silica gel (10 g). Elution with benzene gave pure (*XV*) as a white crystalline solid (519 mg; 82%). An analytical sample was obtained by recrystallization from hexane: large, lustrous needles, m. p. 106—106.5 °C, $[\alpha]_D^{27} + 87°$ ($c = 1.10$, $CHCl_3$), IR ($CHCl_3$): 1720 and 1265 (C=O and C—O stretch, benzoate) and 1245 cm^{-1} (CH_2 wag., CH_2—Br); ^{1}H-NMR ($CDCl_3$): δ 8.07 (d, $J = 7.33$ Hz, 2, benzoate *ortho*-hydrogens), 7.58 (d × d, $J_1 = 7.33$ and $J_2 = 7.92$ Hz, 1, benzoate *para*-hydrogen), 7.46 (d × d, $J_1 = 7.32$ and $J_2 = 7.93$ Hz, 2, benzoate *meta*-hydrogens), 5.07 [d × d, $J_{3,4} = 9.16$ and $J_{4,5} = 9.77$ Hz 1, H(4)], 4.63 [d, $J_{1,2} = 3.05$ Hz 1, H(1)], 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, $J_{2,CH_3} = 6.71$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_{16}H_{21}O_5Br$ (373.26) calc'd.: C 51.48; H 5.67%
found: C 51.60; H 5.78%

Methyl 2,6,7-Trideoxy-2-C, 3-O-dimethyl-7-sulfoxymethyl-α-D-glucoheptopyranoside (XVI)

A 5 ml round bottom flask, containing a 57% oil suspension of sodium hydride (120 mg; ca. 2.9 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 coolung 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 Na_2SO_4 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°; $[\alpha]_D^{27}$ + 141° (c = 1.01, $CHCl_3$); IR ($CHCl_3$) 3570 (free OH stretch), 3340 (broad absorption, hydrogen bonded OH), and 1035 cm^{-1} (S=O stretch); ^{1}H-NMR ($CDCl_3$) δ 4.47 [d, $J_{1,2}$ = 3.66 Hz, 1, H(1)], 4.17 (d, J = 4.27 Hz, 1, OH), 3.65—3.50 [m, 1, H(5)], 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(3)], 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(2)], 1.02 [d, J_{2,CH_3} = 6.71 Hz, 1, C(2) methyl hydrogens].

Anal. $C_{11}H_{22}O_5S$ (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-α-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: $[\alpha]_D^{27}$ + 172° (c = 0.88, $CHCl_3$); IR ($CHCl_3$) 3580 (free OH) and 3440 cm^{-1} (broad absorption, hydrogen bonded OH); ^{1}H-NMR ($CDCl_3$) δ 4.48 [d, $J_{1,2}$ = 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, $J_{1,2}$ = 3.66, J_{2,CH_3} = 6.71, and $J_{2,3}$ = 10.38 Hz, 1, H(2)], 1.51—1.39 [m, 1, H′(6)], 1.04 [d, J_{2,CH_3} = 6.71 Hz, 3, C(2) methyl hydrogens], 1.00 [t, $J_{6,7}$ = 7.32 Hz, 3, H(7)].

Anal. $C_{10}H_{20}O_4$ (204.27) calc'd.: C 58.80; H 9.87%
found: C 58.61; H 9.89%

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

Methyl 2,6,7-trideoxy-2-*C*, 3-*O*-dimethyl-*α*-D-*gluco*-heptopyranoside (*XVII*) (103 mg; 0.5 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 $NaHCO_3$ 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 $NaHCO_3$ 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 Na_2SO_4, 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 D-*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-gluco-heptopyranoside (XIX)

To a cold (—80 °C) etheral solution (10 ml) of α-D-*xylo*heptopyranosid-4-ulose *XVIII* (280 mg; 1.38 mmol), an etheral solution of methyllithium was added (1.0 ml of ca. 1.4 molar solution, corresponding to ca. 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 Na_2SO_4 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-*gluco*heptopyranoside *XIX* (190 mg; 63%); a syrup, $[\alpha]_D^{27} + 179°$ ($c = 0.82$, $CHCl_3$); IR ($CHCl_3$) 3580 cm^{-1} (free OH stetch); ^{1}H-NMR ($CDCl_3$): δ 4.45 [d, $J_{1,2} = 3.66$ Hz, 1, H(1)], 3.55 [s, 3, C(3) methoxy hydrogens]; 3.38 [d, $J_{5,6} = 10.99$ and $J_{5,6'} = 0$ Hz, 1, H(5)], 3.30 [s, 3, C(1) methoxy hydrogens], 3.10 [d, $J_{2,3} = 10.99$ Hz, 1, H(3)], 1.72 [m, $J_{5,6} = 10.99$, $J_{5,6'} = 0$, $J_{6,7} = J_{6'7} = 6.71$ Hz, 2, H(6) and H'(6)], 1.35 [m, $J_{1,2} = 3.66$, $J_{2,3} = 10.99$, and $J_{2,CH_3} = 7.33$ Hz, 1, H(2)], 1.12 [s, 3, C(4) methyl hydrogens], 1.02 [d, $J_{2,CH_3} = 7.33$ Hz, 3, C(2) methyl hydrogens], 1.02 [t, $J_{6,7} = J_{6'7} = 7.33$ Hz, 3, H(7)].

Anal. $C_{11}H_{24}O_4$ (220.31) calc'd.: C 60.52; H 10.16%
found: C 60.37; H 10.30%

The more polar fraction, identified as methyl 2,6,7-trideoxy-2-*C*, 3-*O*, 4-*C*-trimethyl-α-D-*galacto* heptopyranoside *XX*, [the C(4) epimer of *XIX*] was obtained as a white crystalline material (64 mg; 21%) with a m. p. 49—50°; $[\alpha]_D^{27} + 178°$ ($c = 0.20$, $CHCl_3$); IR ($CHCl_3$) 3560 cm^{-1} (free OH stretch); ^{1}H-NMR ($CDCl_3$ δ 4.54 [d, $J_{1,2} = 3.66$ Hz, 1, H(1)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.37 [dxd, $J_{5,6} = 4.56$ and $J_{5,6'} = 8.26$ Hz, 1, H(5)], 3.32 [s, 3, C(1) methoxy hydrogens], 2.94 [d, $J_{2,3} = 10.99$ Hz, 1, H(3)] 2.06 [m, $J_{1,2} = 3.66$, $J_{2,3} = 10.99$, and $J_{2,CH_3} = 7.32$ Hz, 1, H(2)], 1.67 and 1.64 [m, $J_{5,6} = 4.56$, $J_{5,6'} = 8.26$, $J_{6,6'} = 7.33$, and $J_{6,7} = 7.94$ Hz, 2, H(6) and H'(6)], 1.18 [s, 3, C(4) methyl hydrogens], 1.02 [d, $J_{2,CH_3} = 7.32$ Hz, 3, C(2) methyl hydrogens], 1.01 [t, $J_{6,7} = 7.94$ Hz, 3, H(7)].

Anal. $C_{11}H_{24}O_4$ (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-ethanol and 5 : 1 benzene-ethanol) methyl 2-deoxy-2-*C*, 3-*O*-dimetyl-α-D-glucopyranoside *XXI* was obtained as a colorless syrup (3.5 g; 100%), $[\alpha]_D^{27} + 168°$ ($c = 1.03$, $CHCl_3$); IR ($CHCl_3$): 3580 (free OH stretch) and 3420 cm^{-1} (broad absorption, hydrogen bonded OH); ^{1}H-NMR ($CDCl_3$): δ 4.52 [d, $J_{1,2} = 3.05$, 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], 3.28 [dxd, $J_{2,3} = 10.38$ and $J_{3,4} = 7.94$ Hz, 1, H(3)], 1.78 [m, $J_{1,2} = 3.05$, $J_{2,3} = 10,38$, and $J_{2,CH_3} = 7.33$ Hz, 1, H(2)], 1.03 [d, $J_{2,CH_3} = 7.33$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_9H_{18}O_5$ (206.24) calc'd.: C 52.41; H 8.80%
found: C 52.67; 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*-dimetyl-α-D-glucopyranoside, *XXI*, (3.0 g; 14.5 mmol) and triphenylmetyl chloride (9.0 g; 32.3

mmol) was kept at room temperature for 24 hrs. Pyridine was evaporated in vacuo and the residue was chromatographed on silica gel (90 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, $[\alpha]_D^{27} + 70°$ (c = = 1.17, $CHCl_3$); IR ($CHCl_3$) 3560 and 3480 (free and hydrogen bonded OH stretch), 3040 (aromatic CH stretch) and 1590 cm^{-1} (aromatic C = C stretch); ^{1}H-NMR ($CDCl_3$: δ 7.46 [d, J = 7.94 Hz, 6, *meta*-hydrogens of triphenylmethyl group)], 7.28 [dxd, J = 7.33 Hz, 6, *ortho*-hydrogens of triphenylmethyl group), 7.21 (t, J = 7.33 Hz, 3, *para*-hydrogens of triphenylmethyl group), 4.50 [d, $J_{1,2}$ = 3.05 Hz, 1, H(1)], 3.68 [m, $J_{5,6} = J_{5,6'}$ = 4.88 and $J_{4,5}$ = 9.77 Hz, 1, H(5)], 3.51 [s, 3, C(3) methoxy hydrogens], 3.48 [dxd, $J_{3,4}$ = 9.16 and $J_{4,5}$ = 9.77 Hz, 1, H(4)], 3.37 [d, $J_{5,6} = J_{5,6'}$ = 4.88 Hz, 2, H(6) and H'(6)], 3.32 [s, 3, C(1) methoxy hydrogens], 3.17 [dxd, $J_{2,3}$ = 10.38 and $J_{3,4}$ = 9.16 Hz, 1, H(3)], 2.79 (d, J = 2.44 Hz, OH), 1.75 [m, $J_{1,2}$ = 3.05, $J_{2,3}$ = 10.38, and J_{2,CH_3} = 6.71 Hz, 1, H(2)], 1.02 [d, J_{2,CH_3} = 6.71 Hz, 3, C(2) methyl hydrogens].

Anal. $C_{28}H_{32}O_5$ (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 D-*xylo*-hexopyranoside-4-ulose *XXIII*. An analytical sample was obtained by recrystallization from isopropyl ether, m. p. 135—136 °C, $[\alpha]_D^{27} + 135°$ (c = 1.21, $CHCl_3$); IR ($CHCl_3$): 3045 and 1590 (aromatic CH and C=C stretch) and 1728 cm^{-1} (C=O stretch); ^{1}H-NMR ($CDCl_3$): δ 7.6—7.1 (m, 15, triphenylmethyl hydrogens), 4.78 [d, $J_{1,2}$ = 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(1) methoxy hydrogens], 2.27 [broad m, 1, H(2)], 1.10 [d, J = 6.5 Hz, 3, C(2) methyl hydrogens].

Anal. $C_{28}H_{30}O_5$ (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-pyranoside (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 ethereal layer separated from the aqueous layer in a separatory funnel and the equeous layer extracted with three 30-ml portions of ether. The combined ethereal extract was washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 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 D-*gluco*-derivative *XXIV* (776 mg; 75%) was a white crystalline solid which, after recrystallization from hexane, melted at 109—110 °C; $[\alpha]_D^{27} + 56°$ (c = 0.97, $CHCl_3$); IR ($CHCl_3$) 3500 (broad absorption, hydrogen bonded OH) 3050 and 1590 cm^{-1} (aromatic CH and C=C stretch); ^{1}H-NMR ($CDCl_3$): δ 7.45 (d, J = 7.32 Hz, 6, *ortho*-hydrogens of triphenylmethyl group), 7.30 (t, J = 7.32 Hz, 6, *meta*-hydrogens of triphenylmethyl group), 7.22 (dxd, J_1 = 6.71 and J_2 = 7.33 Hz, 3, *para*-hydrogens of triphenylmethyl group), 4.44 [d, $J_{1,2}$ = 3.66 Hz, 1, H(1)], 3.84 [dxd, $J_{5,6}$ = 6.71 and $J_{5,6'}$ = 6.10 Hz, 1, H(5)], 3.56 [s, 3, C(3) methoxy hydrogens], 3.39 and 3.26 [m, $J_{5,6}$ = 6.71, $J_{5,6'}$ = 9.10, and $J_{6,6'}$ = 9.16 Hz, 2, H(6) and H'(6)], 3.33 (s, 3, C(1) methoxy hydrogens), 3.17 (d,

$J_{2,3}$ = 11.60 Hz, 1, H(3)], 1.64 [m, $J_{1,2}$ = 3.66, $J_{2,3}$ = 11.60, and J_{2,CH_3} = 5.49 Hz, 1, H(2)], 0.98 [d, J_{2,CH_3} = 5.49 Hz, 3, C(2) methyl hydrogens], 0.97 [s, 3, C(4) methyl hydrogens]

Anal. $C_{29}H_{34}O_5$ (462.59) calc'd.: C 75.30; H 7.41%
found: C 75.45; H 7.56%

The D-*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, $[\alpha]_D^{27}$ + 84° (*c* = 0.97, $CHCl_3$); IR ($CHCl_3$) 3550 (broad absorption, hydrogen bonded OH), 3045 and 1590 cm^{-1} (aromatic CH and C=C stretch); ^{1}H-NMR ($CDCl_3$): δ 7.52 [d, J = 7.32 Hz, 6, *ortho*-hydrogens of triphenylmethyl group), 7.30 [dxd, J_1 = 7.94 and J_2 = 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, $J_{1,2}$ = 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, $J_{2,3}$ = 10.99 Hz, 1, H(3)], 2.53 (s, 1, OH), 2.17 [m, $J_{1,2}$ = 3.66, $J_{2,3}$ = 10.99 and J_{2,CH_3} = 5.49 Hz, 1, H(2)], 1.06 [d, J_{2,CH_3} = 5.49 Hz, 3, C(2) methyl hydrogens], 1.05 [s, 3, C(4) methyl hydrogens].

Anal. $C_{29}H_{34}O_5$ 462.59) calc'd.: C 75.30; H 7.41%
found: C 75.35; H 7.50%

*Methyl 2-Deoxy-2-*C*, 3-*O*, 4-*C*, 4-*O*-tetramethyl-6-*O*-triphenylmethyl-α-*D*-glucopryranoside* (XXVI)

To a cold (0°) solution of the D-*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 Na_2SO_4, and evaporated in vacuo. The crystalline residue yielded after recrystallization from acetone-hexane pure 4-*O*-methyl-D-*gluco* derivative *XXVI* (3.2 g; 85%) as a white crystalline solid, m. p. 154.5—155.5 °C; $[\alpha]_D^{27}$ + 68° (*c* = 1.19, $CHCl_3$); IR ($CHCl_3$) 3050 and 1590 cm^{-1} (aromatic CH and C=C stretch); ^{1}H-NMR ($CDCl_3$): δ 7.49 (d, J = 7.32 Hz, 6, *ortho*-hydrogens of triphenylmethyl group). 7.28 (dxd, J_1 = 7.32 and J_2 = 7.93 Hz, 6, *meta*-hydrogens of triphenylmethyl group), 7.20 (t, J = 7.32 Hz, 3, *para*-hydrogens of triphenylmethyl group), 4.56 [d, $J_{1,2}$ = 3.66 Hz, 1, H(1)], 4.04 [dxd, $J_{5,6}$ = 5.99 and $J_{5,6'}$ = 2.50 Hz, 1, H(5)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.49 [s, 3, C(1) methoxy hydrogens], 3.37 [d, $J_{2,3}$ = 10.99 Hz, 1, H(3)], 3.22 [m, $J_{5,6}$ = 5.99 and $J_{5,6}$ = 2.50 Hz, 2, H(6) and H'(6)], 3.10 [s, 3, C(4) methoxy hydrogens], 1.77 [m, $J_{1,2}$ = 3.66, $J_{2,3}$ = 10.99, and J_{2,CH_3} = 6.71 Hz, 1, H(2)], 1.03 [d, J_{2,CH_3} = 6.71 Hz, 3, C(2) methyl hydrogens], 0.95 [s, 3, C(4) methyl hydrogens].

Anal. $C_{30}H_{36}O_5$ (476.62) calc'd.: C 75.60; H 7.61%
found: C 75.74; H 7.79%

*Methyl 2-Deoxy-2-*C*, 3-*O*, 4-*C*, 4-*O*-tetramethyl-α-*D*-glucopyranoside* (XXVII)

An ethanolic solution (150 ml) of the triphenylmethyl derivative *XXVI* (2.0 g; 4.2 mmol) was hydrogenated in the presence of 10% Pd—C (500 mg) at atmospheric pressure. After 4 hrs of vigorous stirring, the consumption of hydrogen ceased. The catalyst was filtered off through a layer of Celite, washed with ethanol and the combined filtrate was evaporated in vacuo. The syrupy residue was chromatographed on silica gel (100 g). Elution with 9 : 1 benzene-ethylacetate (or 4 : 1 hexane-acetone) gave chromatographically pure detritylated product *XXVII* (980 mg; 100%) as a syrup; $[\alpha]_D^{27}$ + 167° (*c* = 1.10, $CHCl_3$); IR ($CHCl_3$): 3580 and 3450 cm^{-1} (free and hydrogen bonded OH); ^{1}H-NMR ($CDCl_3$); δ 4.48 [d, $J_{1,2}$ = 3.05 Hz, 1, H(1)], 3.84—3.74 [m, 2, H(6) and H'(6)], 3.68—3.58 [m, 1, H(5)], 3.54 [s, 3, C(3) methoxy hydrogens], 3.40 [s, 3, C(4) methoxy hydrogens], 3.37 [m, 1, H(3)], 3.34

[s, 3, C(1) methoxy hydrogens], 2.55 [broad s, 1, OH], 1.77 [m, $J_{1,2} = 3.05$ and $J_{2,CH_3} = 6.71$ Hz, 1, H(2)], 1.16 [s, 3, C(4) methyl hydrogens], 1.02 [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 56.16; H 9.64%

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

Dipyridine chomium (*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 $NaHCO_3$ 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 Na_2SO_4, 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* (324 mg; 90%) (a colorless syrup) was, according to TLC. (9 : 1 benzene-ethyl acetate), better than 95% pure; ^{1}H-NMR ($CDCl_3$) δ: 9.80 [s, 1, H(6) aldehydo hydrogen], 4.59 [d, $J_{1,2} = 3.5$ 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, $J_{2,CH_3} = 6.5$ 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-α-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 etheral solution (2.0 ml) of D-*gluco*-hexodialdo-1,5-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 etheral 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 Na_2SO_4, 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) a chromatographically homogeneous product: $[\alpha]_D^{27} + 154^\circ$; IR ($CHCl_3$) 3560 cm^{-1} (free OH stretch); ^{1}H-NMR ($CDCl_3$) δ: 4.53 [d, $J_{1,2} = 3.05$ 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, $J_{5,6} = 3.66$ and $J_{6,7} = 6.10$ Hz, 1, H(6)], 3.34 [s, 3, C(3) methoxy hydrogens], 3.20 [d, $J_{2,3} = 10.99$ Hz, 1, H(3)], 2.43 [broad s, 1, OH), 1.79 [m, $J_{1,2} = 3.05$, $J_{2,3} = 10.99$, and $J_{2,CH_3} = 6.72$ Hz, 1, H(2)], 1.28 [d, $J_{6,7} = 6.10$ Hz, 3, H(7)], 1.25 [s, 3, C(4) methyl hydrogens], 1.10 [d, $J_{2,CH_3} = 6.72$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_{12}H_{24}O_5$ (248.32) calc'd.: C 58.04; H 9.74%
found: C 58.35; H 10.06%

Methyl 2,7-Dedeoxy-2-C, 3-O, 4-C, 4-O-tetramethyl-α-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-α-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 $NaHCO_3$ 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 Na_2SO_4 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 ($CHCl_3$): 1710 cm^{-1} (C=O stretch); ^{1}H-NMR ($CDCl_3$) δ: 4.57 [d, $J_{1,2} = 3.66$ 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, $J_{2,3} = 11.60$ Hz, 1, H(3)], 3.32 [s, 3, C(1) methoxy hydrogens], 2.26 [s, 3, H(7)], 1.80 [m, $J_{1,2} = 3.66$, $J_{2,3} = 11.60$, and $J_{2,CH_3} = 6.71$ Hz, 1, H(2)], 1.17 [s, 3, C(4) methyl hydrogens], 1.01 [d, $J_{2,CH_3} = 6.71$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_{12}H_{22}O_5$ (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 (*XXX*) (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 Na_2SO_4, evaporated in vacuo. The dry residue (87 mg; 85%), a syrup, was chromatographically homogeneous *XXXI*. IR ($CHCl_3$): 1690 cm^{-1} (C=O stretch, α,β-unsaturated ketone); ^{1}H-NMR ($CDCl_3$) δ: 4.77 [d, $J_{1,2} = 2.1$ 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, $J_{2,CH_3} = 6.8$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_{11}H_{18}O_4$ (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 aded 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 Na_2SO_4 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; $[\alpha]_D^{27} + 61°$ (c = 1.10, $CHCl_3$); IR ($CHCl_3$): 3045 and 1590 cm^{-1} (aromatic CH and C=C stretch); ^{1}H-NMR ($CDCl_3$) δ: 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, $J_{1,2}$ = 3.05 Hz, 1, H(1)], 3.71 [m, 1, H(5)], 3.46 [s, 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], 2.98 [d, $J_{2,3}$ = 10.99 Hz, 1, H(3)], 2.22 [m, $J_{1,2}$ = 3.05, $J_{2,3}$ = 10.99, and J_{2,CH_3} = 6.71 Hz, 1, H(2)], 1.11 [s, 3, C(4) methyl hydrogens], 1.01 [d, J_{2,CH_3} = 6.71 Hz, 3, C(2) methyl hydrogens].

Anal. $C_{30}H_{36}O_5$ (476.62) calc'd.: C 75.60; H 7.61%
found: C 75.48; H 7.49%

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

An ethanolic solution (20 ml) of the 6-*O*-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; $[\alpha]_D^{27} + 152°$ (c = = 0.74, $CHCl_3$), IR ($CHCl_3$): 3580 and 3430 (free and hydrogen bonded OH stretch); ^{1}H-NMR ($CDCl_3$) δ: 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)], 3.73 [m, $J_{5,6'}$ = 3.05 and $J_{6,6'}$ = 11.60 Hz, 1, H'(6)], 3.55 [dxd, $J_{5,6}$ = 6.71 and $J_{5,6'}$ = 3.05 Hz, 1, H(5)], 3.49 [s, 3, C(3) methoxy hydrogens], 3.44 [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-*O*-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-*O*-tetramethyl-α-D-galactopyranoside *XXXIV* (160 mg; 0.68 mmole), 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; 85%), 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-*O*-tetramethyl-L-glucero-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 etheral 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 NH_4Cl 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 Na_2SO_4 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). $[\alpha]_D^{27} + 144°$ ($c = 0.99$, $CHCl_3$); IR ($CHCl_3$): 3430 cm^{-1} (broad absorption, hydrogen bonded OH stretch); ^{1}H-NMR ($CHCl_3$) δ: 4.68 [d, $J_{1,2} = 3.05$ Hz, 1 H(1)], 4.42 [s, 1, OH], 4.27 [dxd, $J_{6,7} = 6.10$ and $J_{5,6} = 0$ 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, $J_{2,3} = 10.99$ Hz, 1, H(3)], 2.30 [m, $J_{1,2} = 3.05$, $J_{2,3} = 10.99$, and $J_{2,CH_3} = 6.71$ Hz, 1, H(2)], 1.39 [s, 3, C(4) methyl hydrogens], 1.24 [d, $J_{6,7} = 6.10$ Hz, 3, H(7)], 1.02 [d, $J_{2,CH_3} = 6.71$ Hz, 3, C(2) methyl hydrogens].

Anal. $C_{12}H_{24}O_5$ (248.32) calc'd.: C 58.04; H 9.74%
found: C 58.01; H 10.02%

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SAŽETAK

Sinteza makrolidnih antibiotika. IV. Stereoselektivna sinteza 3-*O*-metil i 11-*O*-metil derivata C(1)—C(6) segmenta eritronolida A i B te C(9)—C(15) segmenta eritronolida A

M. Miljković, T. C. Choong i Dj. Glišin

Saznanje da su reakcije adicije sp^2 (C=O i C=C) ugljikovih atoma u ugljikohidratnom 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-*O*, 4-*C*, 6-*C*-tetrametil-6-okso-β-L-idopiranozida i metil 2,6-dideoksi-2-*C*, 3-*O*, 4-*C*, 6-*C*-tetrametil-α-D-glukopiranozida koji predstavljaju 3-*O*-metil i 11-*O*-metil derivate C(1)—C(6) segmenta eritronolida A i B te C(9)—C(15) segment eritronolida A.