# SYNTHESIS OF MACROCYCLIC ANTIBIOTICS.

# 9.* SYNTHESIS OF THE $C^9$–$C^{13}$ FRAGMENTS OF 12-EPINEOMETHINOLIDE AND METHINOLIDE

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In the complete stereodirected synthesis of 12-membered macrocyclic antibiotics, which comprise three representatives (methimycin, US-17, and neomethimycin), until recently the principal approach was the preparation of the chiral fragments by the resolutions of racemates. Another route was developed simultaneously, in which carbohydrates were used in the synthesis of these fragments. For example, there have been reports of the synthesis of the $C^1$–$C^7$ fragment (the Prelog–Djerassi lactone) [2-5] and the $C^9$–$C^{13}$ fragments of methimycin and the antibiotic US-17 [6, 7] from carbohydrate derivatives. We here describe the preparation of the $C^9$–$C^{13}$ fragment of 12-epineomethinolide and a new, more convenient synthesis of the $C^9$–$C^{13}$ fragment of methimycin.

The starting material for the synthesis of the $C^9$–$C^{13}$ fragment of 12-epineomethinolide (XI) was the known epoxide (I), obtained from levoglucosan in four steps, in an overall yield of 40% [7]. In accordance with the synthetic route adopted for the synthesis of (XI), the first step requires fission of the epoxide in (I) at $C^2$ in order to obtain (see Diagram 1) (II), in which the configuration of the centers $C^2$, $C^3$, and $C^4$ is in full accordance with centers $C^{12}$, $C^{11}$, and $C^{10}$ in 12-epineomethinolide. It was also necessary to retain the hydroxyl group at $C^3$, which was subsequently to be used in the macrolactonization (at $C^{11}$) in the free state, and that at $C^2$ (center $C^{12}$) in the protected state.

Reaction of the epoxide (I) with $PcCH_2ONa$ gave the alcohol (II) in 50% yield, which was then converted into the acetate (III). Cleavage of the oxirane (II) proceeded strictly regioselectively, no D-altroisomer (cleavage at $C^3$) being found. The structure of the alcohol (II) follows from a comparison of its $^{13}C$ NMR spectrum with that of its acetate (III). Thus, on acetylation shifts of the signals for the carbon atoms to higher field (β-effect) was observed only for $C^2$ ($\Delta\delta$ 3.3 ppm) and $C^4$ ($\Delta\delta$ 2.4 ppm), whereas the position of the signal for $C^1$ remained virtually unchanged. The small coupling constants ($J_{2,3}$ = 1.5, $J_{3,4}$ = 1 Hz) also indicate the D-glucone configuraiotn of the alcohol (II).

The next step in the synthesis consists in the cleavage of the 1,6-anhydro-ring followed by deoxygenation at $C^4$. The best method for the first step was found to be acetolysis of the alcohol (II). Subsequent removal of the O-acetyl groups, reduction with $NaBH_4$, and acetonation gave 60% of a mixture of polyols (IV) and (V), the latter predominating. The structures of these compounds and the others shown in Scheme 1 were established by $^{13}C$ NMR spectroscopy.

In the spectra of (IV) and (V), it was easily possible to identify the signals of atoms assigned to the same structural elements; $C^4$, $C^5$, $C^6$, Me-4, and $CMe_2$ groups of the dioxolane ring [8]. The chemical shifts of the carbon atoms comprising the 1,3-dioxolane ring ($C^1$, $C^2$, $C^3$, and the $CMe_2$ group) were in full agreement with the literautre values for 4,6-O-isopropylidene derivatives of hexoses [9], in which a substantial high-field shift of all the carbon atoms present in this ring is also seen. Examination of the PMR spectrum of (V) leads to the conclusion that the 1,3-dioxolane ring therein possesses the conformation (Va), since only in this case is a small coupling constant found between the protons at $C^2$, $C^1$, and $C^3$.

*For Communication 8, see [1].

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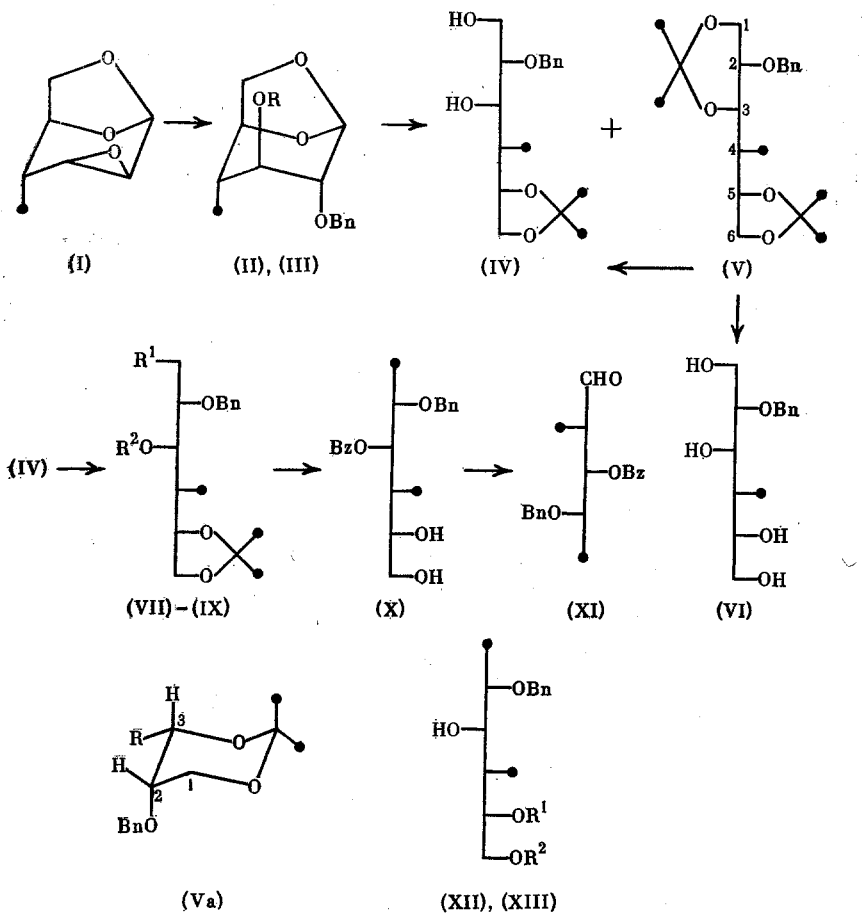
Scheme 1



R = H (II); Ac (III); $R^1$ = TsO, $R^2$ = H (VII); $R^1$ = $R^2$ = H (VIII); $R^1$ = H, $R^2$ = Bz (IX); $R^1$ = H, $R^2$ = $CHMe_2$ (XII); $R^1$ = $CHMe_2$, $R^2$ = H (XIII).

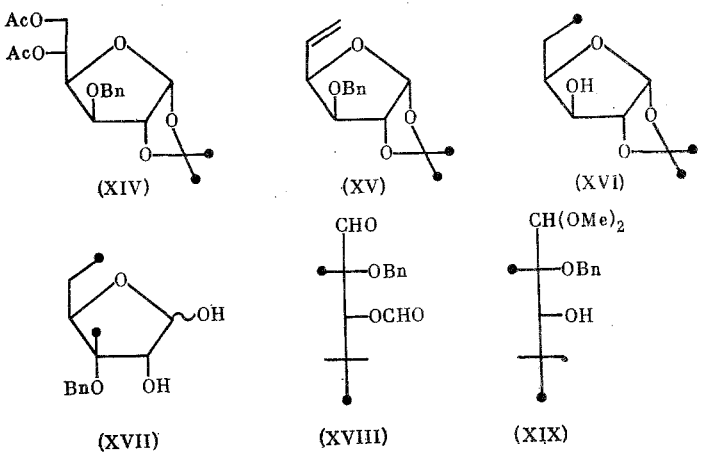
The preferentially formed acetonide (V) was then converted into the monoacetonide (IV) by methanolysis in 5% acetic acid in 63% yield, the overall yield from the alcohol (II) reaching 50%. Small amounts of the polyol (VI) are also formed, which may be used again in this reaction sequence. The structure of the polyol (VI) was established by comparing the $^{13}C$ NMR spectra of (VI) and its analog (IV). The signals for $C^1$,$C^2$, $C^3$, $C^4$, and Me-4 in these compounds were nearly identical. The differences in their spectra were due to the absence of the $CMe_2$ group in (VI), as a result of which the signals for $C^5$ and $C^6$ were shifted to higher field.

The next stage, monotosylation of the acetonide (VI), resulted in the preferential formation of (VII), the spectrum of which differed from that of (IV) only for $C^1$ (61.2 → 69.4 ppm) and $C^2$ ($\Delta\delta$ 2.5 ppm). Reduction of the tosylate (VII) gave high yields of the desoxy-compound (VIII), in the $^{13}C$ NMR spectrum of which the signal for $C^1$ was shifted to higher field (69.9 → 15.5 ppm) the signal for $C^2$ being shifted similarly (278.3 → 77.2 ppm). More vigorous reduction of the tosylate (VII) resulted in partial opening of the dioxolane ring to give the isopropyl ethers (XII) and (XIII), the structures of which were established by their $^{13}C$ NMR spectra (see Experimental).

Conversion of the acetonide (VIII) into the $C^9$–$C^{13}$ fragment of 12-epineomethinolide (XI) was effected by a method described by us previously [7]. For this purpose, the benzoate (IX) obtained from (VIII) was hydrolyzed to (X), followed by oxidation [10] of the cis-glycol grouping to give (XI), which is the $C^9$–$C^{13}$ fragment of 12-epineomethinolide. The PMR spectrum of the latter showed a signal at 9.8 ppm for the aldehyde proton, and in the $^{13}C$ NMR spectrum the aldehyde function corresponded to the signal at 201.2 ppm. The remaining signals in both the PMR and $^{13}C$ NMR spectra were in complete accordance with the assumed structure of the fragment (XI). The system of functional and protecting groups in the aldehyde (XI) is most convenient for subsequent condensation with the $C^1$–$C^8$ fragment of the 12-membered macrocycles.

In a new synthesis of the $C^9$–$C^{13}$ fragment of methinolide (XIX), which can also serve as the $C^{11}$–$C^{15}$ fragment of picronolide, the starting material was the D-glucofuranose derivative (XIV) [11].

Scheme 2




The furanose (XVII) was obtained in a yield of 39%, calculated on (XIV), via compounds (XIV)-(XVII), the synthesis of which has been fully described [12-14]. This furanose was oxidized with n-$Bu_4NIO_4$ [10] to give a high yield of the formate (XVIII), which which the acetal (XIX) was readily obtained (scheme 2). This compound is more successful in respect of its functional and protective groups for the $C^9$–$C^{13}$ fragment of methinolide (cf. [6]). The presence of the aldehyde group in (XVIII) and (XIX) is shown by the signal at 202.6 ppm in the $^{13}C$ NMR spectra, shifted to higher field (110.4 ppm) on acetalization.

## EXPERIMENTAL

PMR and $^{13}C$ NMR spectra were obtained on a Bruker WM-250 instrument (solutions in $CDCl_3$, internal standard TMS, δ, ppm; J, Hz). Specific rotations were measured on a Perkin-Elmer-141M polarimeter in chloroform. TLC was carried out on silica gel L (5-40 mμ), and column chromatography on Silpearl (25-40 mμ) using continuous gradients of benzene–ether, and excess pressures up to 1 atmosphere.

1,6-Anhydro-4-desoxy-4-C-methyl-2-O-benzyl-β-D-glucopyranose (II). A solution of 12.5 g (80 mmole) of (I) [7] in 30 ml of benzyl alcohol was added to a solution of 5.8 g (240 mmole) of NaH in 100 ml of benzyl alcohol. The mixture was heated for 10 h at 95°C, cooled, treated with solid $CO_2$, diluted with 400 ml of chloroform, washed with a saturated solution of NaCl, evaporated, excess benzyl alcohol distilled off under reduced pressure (85-90°C/9 mm), and the residue chromatographed. Yield 11 g (60%), mp 80-81°C (ether–hexane), $[\alpha]_D^{20}$ −54.8°, (C 1.0). $^{13}C$ NMR spectrum: 100.9 ($C^1$), 79.4 ($C^2$), 71.4 ($C^3$), 39.2 ($C^4$), 76.8 ($C^5$), 68.0 ($C^6$), 17.6 (Me-4), 71.9 ($\underline{C}H_2Ph$), 138.1-127.7 ($C_6H_5$).

The acetate (II) was obtained in the usual way by acetylation in acetic anhydride-pyridine. It was purified by chromatography and obtained as a syrup, $[\alpha]_D^{20}$ −102.6° (C 2.0). $^{13}C$ NMR spectrum: 100.5 ($C^1$), 76.1 ($C^2$), 71.8 ($C^3$), 36.8 ($C^4$), 76.1 ($C^5$), 67.3 ($C^6$), 17.3 (Me-4), 21.2 ($\underline{C}H_2CO$), 170.0 ($CH_3\underline{C}O$), 71.9 ($CH_2Ph$), 138.0-127.8 ($C_6H_5$). PMR spectrum: 5.36 s (1H, $H^1$), 3.22 d (1H, $H^2$, $J_{2,3}$ = 1.5), 4.74 t (1H, $H^3$, $J_{3,4}$ = 1), 1.8 m (1H, $H^4$, $J_{4,Me}$ = 7.5), 4.28 d (1H, $H^5$, $J_{5,6exo}$ = 5), 4.05 d (1H, $H^{6endo}$, $J_{6,6}$ = 7), 3.72 d.d (1H, $H^{6exo}$), 4.70 d.d (2H, AB-system, $J_{gem}$ = 11, $C\underline{H}_2Ph$), 7.35 m (5H, $C_6H_5$), 2.05 s (3H, $CH_3CO$), 1.33 d (3H, Me-4).

2-O-Benzyl-4-desoxy-4-C-methyl-1,3:5,6-di-O-isopropylidene-D-sorbitol (V) and 2-O-Benzyl-4-desoxy-4-C-methyl-5,6-O-isopropylidene-D-sorbitol (IV). To a solution of 9.3 g (37 mmole) of (II) in 35 ml of $Ac_2O$ was added 0.1 ml of sulfuric acid, and after 10 min the mixture was poured on to ice, stirred at ∿20°C for 10 h, extracted with chloroform, and the extract washed with saturated $NaHCO_3$ solution and evaporated. The residue was dissolved in 50 ml of methanol, 0.1 g of Na added, and the mixture stirred for 2 h. It was then concentrated to 25 ml, and 25 ml of water added followed by 3 g of $NaBH_4$. After 3 h, the mixture was treated with KU-2 ($H^+$), evaporated several times with methanol, and then

with toluene. The residue was dissolved in 30 ml of acetone, 0.5 mg of $TsOH \cdot H_2O$ and 20 ml of dimethoxypropane added, and the mixture stirred for 3 h. It was then diluted with 300 ml of chloroform, washed with 300 ml of sat. $NaHCO_3$ solution, evaporated, and the residue chromatographed to give 5.05 g (40.5%) of (V) as a syrup, $[\alpha]_D^{20}$ +42.7° (C 3.0). $^{13}C$ NMR spectrum: 61.6 ($C^1$), 72.5 ($C^2$), 73.0 ($C^3$), 37.2 ($C^4$), 77.9 ($C^5$), 67.8 ($C^6$), 11.0 (Me-4), 70.8 ($\underline{C}H_2Ph$), 138.5-127.5 ($C_6H_5$), 108.6, 26.7, 25.8 ($CMe_2$-5,6), 98.7, 28.9, 19.2 ($CMe_2$-1,3). PMR spectrum: 4.0-3.8 m (4H, $H^1$, $H^{1'}$, $H^5$, $H^6$, $J_{1,1'} = J_{6,6'} = 12.5$; $J_{1,2} = J_{1',2} = 2.5$; $J_{5,6} = 6$; $J_{5,6} = 7.5$), 3.4 d.d.d (1H, $H^2$, $J_{2,3} = 2$), 3.72 d.d (1H, $H^3$, $J_{3,4} = 7$), 3.55 m (1H, $H^6$), 2.18 d.d.q (1H, $H^4$, $J_{4,Me\text{-}4} = 7$; $J_{4,5} = 6$), 0.9 d (3H, Me-4), 1.42 and 1.38 s (6H, $CMe_2$-1,3), 1.33 and 1.28 s (6H, $CMe_2$-5,6), 4.58 and 4.40 d (2H, $CH_2Ph$, $J_{gem} = 12$), 7.40-7.20 m (5H, $C_6H_5$).

Yield of (IV), 2.5 g (21.1%), syrup, $[\alpha]_D^{20}$ +19.2° (C 3.0). $^{13}C$ NMR spectrum: 61.2 ($C^1$), 80.8 ($C^2$), 71.3 ($C^3$), 38.4 ($C^4$), 77.7 ($C^5$), 67.5 ($C^6$), 72.3 ($\underline{C}H_2Ph$), 138.0-127.5 ($C_6H_5$), 9.2 (Me-4), 108.3, 26.4, 25.4 ($CMe_2$-5,6).

2-O-Benzyl-4-desoxy-4-C-methyl-5,6-O-isopropylidene-D-sorbitol (IV) and 2-O-Benzyl-4-desoxy-4-C-methyl-D-sorbutol (VI). To a solution of 5.05 g (14 mmole) of (V) in 50 ml of methanol was added 2.1 ml of acetic acid, and the mixture boiled for 5 h. It was then neutralized with saturated $NaHCO_3$ solution, evaporated to dryness, and the residue chromatographed to give 3.05 g (63.2%) of (IV) and 0.923 g (23.6%) of (VI), mp 68-70°C (ethyl acetate–hexane), $[\alpha]_D^{20}$ +21.8° (C 0.5). $^{13}C$ NMR spectrum: 60.4 ($C^1$), 81.7 ($C^2$), 70.1 ($C^3$), 37.0 ($C^4$), 74.2 ($C^5$), 64.8 ($C^6$), 10.0 (Me-4), 72.9 ($\underline{C}H_2Ph$), 138.1-128.2 ($C_6H_5$).

1-O-Tosyl-2-O-Benzyl-4-desoxy-4-C-methyl-5,6-O-isopropylidene-D-sorbitol (VII). To a solution of 5.1 g (16.6 mmole) of (IV) in 50 ml of pyridine was added 3.8 g (20 mmole) of TsCl. The mixture was kept at ∿20°C for 20 h, poured into 100 ml of water, and extracted with chloroform. The extract was washed with water, 2 N $H_2SO_4$, water, and saturated $NaHCO_3$ solution, dried over $Na_2SO_4$, and evaporated to give 7 h (91%) of product. Part of the material was purified by chromatography to give a syrup, $[\alpha]_D^{20}$ +25.4° (C 1.0). $^{13}C$ NMR spectrum: 69.4 ($C^1$), 78.3 ($C^2$), 71.4 ($C^3$), 38.9 ($C^4$), 77.9 ($C^5$), 68.2 ($C^6$), 10.0 (Me-4), 108.8, 26.8, 25.7 ($CMe_2$-5,6), 21.6 ($\underline{C}H_3C_6H_4SO_2$-), 145.0-128.0 ($C_6H_5$, $C_6H_4$).

1,4-Didesoxy-4-C-methyl-2-O-benzyl-5,6-di-O-isopropylidene-D-sorbitol (VIII). a) The tosylate (VII), obtained from 5.1 g (16.5 mmole) of the diol (IV), was dissolved without further purification in 100 ml of a 1:1 mixture of dichloromethane and ether, 2 g (52.6 mmole) of $LiAlH_4$ added, and the mixture boiled for 4 h. It was then decomposed with 2 ml of water, 6 ml of 3 N KOH and 2 ml of water added, filtered through a layer of $SiO_2$, washed with acetone, evaporated, and the residue chromatographed to give 1.4 g (30%) of (VIII) as a syrup, $[\alpha]_D^{21}$ +32.0° (C 4.5). $^{13}C$ NMR spectrum: 15.5 ($C^1$), 77.2 ($C^2$), 74.6 ($C^3$), 38.8 ($C^4$), 78.0 ($C^5$), 67.7 ($C^6$), 8.3 (Me-4), 71.0 ($\underline{C}H_2Ph$), 138.7-127.5 ($C_6H_5$), 108.3, 26.8, 25.7 ($CMe_2$). Yield of (XII), 1.0 g (22%), syrup, $R_f$ 0.70 (benzene–ether, 2:1). $^{13}C$ NMR spectrum: 15.4 ($C^1$), 77.5 ($C^2$), 74.4 ($C^3$), 36.0 ($C^4$), 73.2 ($C^5$), 70.2 ($C^6$), 71.8 ($\underline{C}HMe_2$), 22.0 and 22.1 ($CH\underline{C}H_3$), 9.7 (Me-4), 71.1 ($\underline{C}H_2Ph$), 138.6-127.6 ($C_6H_5$). Yield of (XIII) 1.0 g (22%), $R_f$ 0.64 (benzene–ether, 2:1). $^{13}C$ NMR spectrum: 15.5 ($C^1$), 77.7 ($C^2$), 74.2 ($C^3$), 35.8 ($C^4$), 79.4 ($C^5$), 61.8 ($C^6$), 70.9 ($\underline{C}HMe_2$), 23.1 and 22.4 ($CH\underline{C}H_3$), 8.8 (Me-4), 71.2 ($\underline{C}H_2Ph$), 138.5-127.7 ($C_6H_5$).

b) The tosylate (VII) (0.66 g, 1.42 mmole) was dissolved in 10 ml of a 1:1 mixture of dichloromethane and THF, and 0.2 g (5.6 mmole) of $LiAlH_4$ added. The mixture was stirred at ∿20°C for 5 h, then 1 ml of water was added, filtered through a layer of $SiO_2$, washed with acetone, evaporated, and the residue chromatographed to give 0.36 g (86%) of (VIII).

1,4-Didesoxy-4-C-methyl-2-O-Benzyl-3-O-benzoyl-5,6-O-isopropylidene-D-sorbitol (IX). To a solution of 1.08 g (3.66 mmole) of (VIII) in 10 ml of pyridine was added at 0°C 3 ml of benzoyl chloride. The mixture was kept for 3 h at ∿20°C, poured on to ice, and after 1 h extracted with chloroform. The extract was washed with water, 2 N sulfuric acid, water, sat. $NaHCO_3$ solution, and water, dried over $Na_2SO_4$, evaporated, and the residue chromatographed to give 1.35 g (95%) of a syrup, $[\alpha]_D^{20}$ −2.6° (C 1.0). $^{13}C$ NMR spectrum: 16.1 ($C^1$), 75.3 ($C^2$), 76.4 ($C^3$), 37.4 ($C^4$), 77.6 ($C^5$), 67.1 ($C^6$), 9.9 (Me-4), 108.6, 26.7, 25.5 ($CMe_2$), 71.1 ($\underline{C}H_2Ph$), 162.4 ($\underline{C}OPh$), 138.6-127.4 ($C_6H_5$).

1,4-Didesoxy-4-C-methyl-2-O-benzyl-3-O-benzoyl-D-sorbitol (X). The acetonide (IX) (0.45 g, 1.11 mmole) was dissolved in 10 ml of methanol, 6 ml of acetic acid added, and the mixture

boiled for 6 h. It was then evaporated several times with toluene, and the residue chromatographed to give 0.27 g (67.5%) of a syrup, $[\alpha]_D^{25}$ +22.3° (C 1.0). $^{13}$C NMR spectrum: 16.1 ($C^1$), 77.6 ($C^2$), 75.5 ($C^3$), 37.2 ($C^4$), 71.3 ($C^5$), 64.2 ($C^6$), 72.7 ($\underline{C}H_2Ph$), 10.2 (Me-4), 167.4 ($\underline{C}OPh$), 138.3-127.5 ($C_6H_5$).

2,5-Didesoxy-2-C-methyl-3-O-benzoyl-4-O-benzyl-al-L-xylose (XI). The diol (X) (0.27 g, 0.75 mmole) was stirred in a mixture of acetone and water (7:3) with 0.91 g (2.1 mmole) of N-$Bu_4NIO_4$ at ∿20°C. After 2 h the acetone was evaporated, 30 ml of benzene added, washed with water, filtered through a layer of silica, washed with benzene followed by ether, the solvent removed, and the residue chromatographed to give 0.23 g (95%) of a syrup, $[\alpha]_D^{25}$ +22.0° (C 1.0). PMR spectrum: 9.8 d (1H, $H^1$, $J_{1,2}$ = 1), 2.86 d.d.q (1H, $H^2$, $J_{2,Me\text{-}2}$ = 7; $J_{2,3}$ = 6), 5.5 d.d (1H, $H^3$, $J_{3,4}$ = 4), 3.88 d.q (1H, $H^4$, $J_{4,5}$ = 6), 1.28 d (3H, $H^5$), 1.12 d (3H, Me-2), 4.60 and 4.45 d (2H, $C\underline{H}_2Ph$, $J_{gem}$ = 12), 8.1-7.2 m (10H, $C_6H_5$). $^{13}$C NMR spectrum: 201.2 ($C^1$), 47.4 ($C^2$), 73.0 ($C^3$), 76.2 ($C^4$), 15.4 ($C^5$), 9.9 (Me-2), 71.7 ($\underline{C}H_2Ph$), 166.0 ($\underline{C}OPh$), 137.8-127.8 ($C_6H_5$).

4,5-Didesoxy-2-C-methyl-2-O-benzyl-3-O-formyl-D-erythro-al-pentose (XVIII). The hexose (XVII) (6 g, 24 mmole) [$^{13}$C NMR spectrum: α −96.0 ($C^1$), 75.6 ($C^2$), 82.8 ($C^3$), 82.5 ($C^4$), 16.0 ($C^5$), 10.8 ($C^6$), 24.2 (Me-2), 65.9 ($\underline{C}H_2Ph$), 137.9-127.6 ($C_6H_5$). β − 102.1 ($C^1$), 81.0 ($C^2$), 82.0 ($C^3$), 84.3 ($C^4$), 16.3 ($C^5$), 11.0 ($C^6$), 24.7 (Me-3), 65.7 ($\underline{C}H_2Ph$), 138.2-127.6 ($C_6H_5$)] in 50 ml of a mixture of acetone and water (7:3) was stirred with 13 g (30 mmole) of N-$Bu_4NIO_4$ at ∿20°C for 3 h. The mixture was diluted with 50 ml of water, extracted with benzene (4 × 50 ml), the benzene layer was washed with water, evaporated, and the residue chromatographed to give 4.9 g (81%) of a syrup, $[\alpha]_D^{20}$ +58.2° (C 1.2, benzene). $^{13}$C NMR spectrum: 202.6 ($C^1$), 83.4 ($C^2$), 76.0 ($C^3$), 14.2 ($C^4$), 10.3 ($C^5$), 22.2 (Me-2), 160.4 (OCHO), 66.3 ($\underline{C}H_2Ph$), 138.0-127.4 ($C_6H_5$).

4,5-Didesoxy-2-methyl-2-O-benzyl-D-erythro-al-pentose Dimethyl Acetal (XIX). To 4.25 g (17 mmole) of (XVII) in 50 ml of methanol was added 0.2 g of TsOH and 10 g of molecular sieve 4 Å. The mixture was boiled for 0.5 h, neutralized with saturated $NaHCO_3$ solutions, evaporated, and the residue chromatographed to give 4.3 g (93%) of a syrup, $[\alpha]_D^{20}$ +74.0° (C 2.0). $^{13}$C NMR spectrum: 110.4 ($C^1$), 80.7 ($C^2$), 76.4 ($C^3$), 13.2 ($C^4$), 11.3 ($C^5$), 23.9 (Me2), 65.4 ($\underline{C}H_2Ph$), 139.6-127.2 ($C_6H_5$), 58.7 and 57.2 (OMe).

## CONCLUSIONS

1. Starting from levoglucosan, the $C^9$–$C^{13}$ fragment of 12-epineomethinolide has been synthesized in 15 steps (yield 4.5%).

2. The $C^9$–$C^{13}$ fragment of methinolide has been synthesized by a new route in a yield of 29.4% based on 1,2-O-isopropylidene-3-O-benzyl-5,6-di-O-acetyl-α-D-glucofuranose.

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