SYNTHESIS OF MACROLIDE ANTIBIOTICS

COMMUNICATION 1.* SYNTHESIS OF THE C^1-C^6 FRAGMENT OF 14-MEMBERED MACROLIDE ANTIBIOTICS

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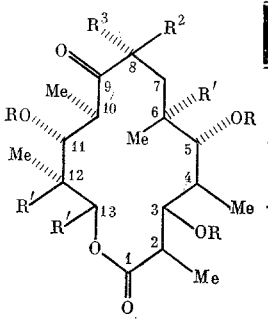
The use of carbohydrates as multichiral starting materials is currently one of the most promising approaches to the synthesis of naturally occurring compounds of a wide variety of types. Of special interest is the use of carbohydrates in the synthesis of macrolide antibiotics, which are specifically glycosylated polyhydroxylic macrocyclic lactones. Outstanding among these in terms of importance is the group of structurally related 14-membered macrolides, the structures of which have been proved by a combination of chemical, physicochemical, and biosynthetic studies [2].

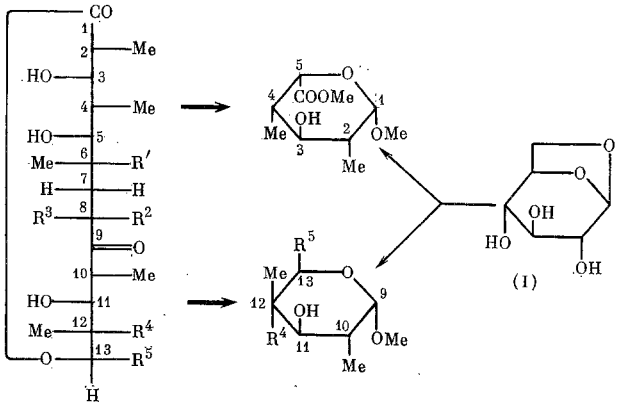


Antibiotic	R^1	R^2	R^3	R^4	R^5
Erythromycin A, C, megalomycin	OH	H	Me	OH	C_2H_5
Erythromycin B	OH	H	Me	H	C_2H_5
Oleandomycin, O-demethyl-oleandomycin	H	O—C(Me)—CH_2		H	Me

The total synthesis of these compounds would not only constitute a solution of a most difficult synthetic problem, but would also open up the possibility of systematic modification of this class of biologically active compounds which is important for the elucidation of the finer details of structure–activity relationships, and for the identification of practically important synthetic analogs.

In accordance with a program undertaken in our laboratory, aimed at the total synthesis of macrolide antibiotics, a general strategy was evolved, as follows.

1. The structures of the antibiotic aglycones were broken down into the C^1-C^6 and C^9-C^{13} fragments, synthesizable from sugars.



(I)

* For a brief communication, see [1].

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2. Since the stereochemistry of C^1-C^6 and $C^{10}-C^{11}$ is the same for all antiobiotics in the group under consideration, the synthetic scheme was selected in such a way as to utilize the maximum number of stages common to both fragments.

3. The synthesis should provide fragments with specifically protected hydroxyl groups, which must subsequently allow the selective glycosylation of the synthetic aglycone.

In this and the following communications, we give the results of the accomplishment of the first part of the program, namely the synthesis of the C^1-C^6 and C^9-C^{13} fragments as mentioned above, and other antibiotics of this group.

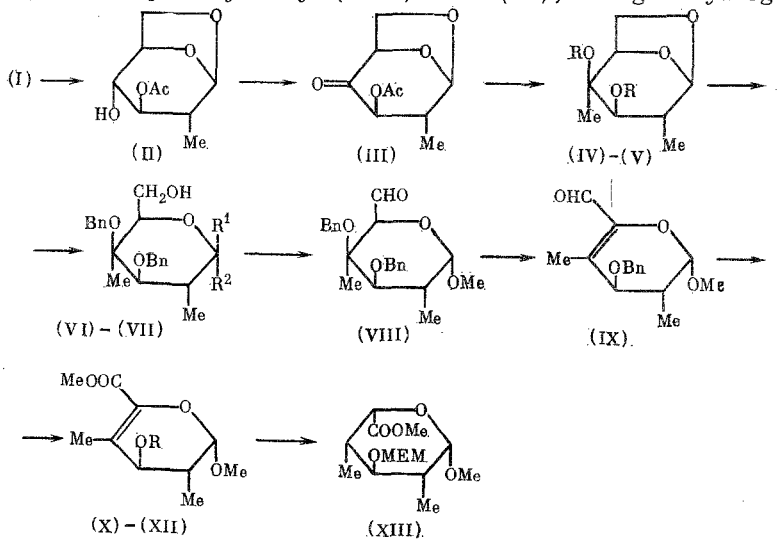
The starting material chosen for the synthesis was levoglucosan (I), the bicyclic skeleton of which ensures high regio- and stereoselectivity in the required transformations [3]. The key compound in the synthesis is 1,6-anhydro-2-desoxy-2,4-di-C-methyl-β-D-galactopyranose (IV), the synthesis of which was effected by a reaction sequence previously described by us [4, 5], with a few modifications. The most significant modification involved the use of the system $(COCl)_2$/DMSO [6] for the oxidation of the alcohol (III), which provided a convenient method for the preparation of substantial amounts of (IV).

Exhaustive benzylation of (IV) (NaH/DMF, BnCl) gave the dibenzyl ether (V), methanolysis of which afforded a mixture (9 : 2) of α-(VI) and β-methylglycosides (VII) which was separated chromatographically. The minor glycoside (VII) was anomerized to (VI). In the PMR spectra of both isomers, the H^3 protons gave a doublet with $J_{2,3} = 11$ Hz, showing the equatorial orientation of the substituents at C^2 and C^3. Comparison of the chemical shifts of the H^1 signals and the spin–spin coupling constant (SSCC) $J_{1,2}$ values [δ 4.67 ppm, $J_{1,2} = 3.5$ Hz for (VI) and δ 4.05 ppm, $J_{1,2} = 7$ Hz for (VII)] permits unambiguous assignment of the configuration of the anomeric center in these compounds. This is confirmed by a comparison of the chemical shifts of the C^1 signals in the ^{13}C NMR spectra [δ 102.5 ppm for (VI) and 106.3 ppm for (VII)].

In order to obtain the required stereochemistry at C^4 and C^5 in (V), corresponding to the stereochemistry of the C^1-C^6 fragment of the macrolides, we employed the route used previously for the O-methyl analogs [7]. For this purpose, the glycoside (VI) was oxidized by the system DMSO–$(COCl)_2$ [6] to give the aldehyde (VIII) in high yield, which on heating with aqueous-methanolic $Ca(OH)_2$ [7] was smoothly converted into the α,β-unsaturated aldehyde (IX). The PMR spectrum of (IX) was well resolved, and gave complete information on its structure. Thus, the signal for the Me group at C^4 occurs at low field (δ 2.12 ppm), and is split by coupling with H^3 ($J_{3,CH_3} = 1$ Hz). The aldehyde proton is seen as a singlet at low field (δ 9.79 ppm). This, together with the decrease in the SSCC as compared with (VI) ($J_{1,2} = 2.5$ Hz; $J_{2,3} = 6.8$ Hz) indicates considerable flattening of the pyranose ring, confirming the $\Delta^{4,5}$-ene structure of (IX).

Oxidation of (IX) by the method of Corey [8] (MeOH, KCN–AcOH, MnO_2) gave the α,β-unsaturated ether (X), as shown by the disappearance of the signal at 9.79 ppm and the appearance of a singlet due to the MeOOC group (δ 3.75 ppm).

Catalytic hydrogenation of (X) (Pd/C, MeOH) resulted in rapid uptake of one equivalent of hydrogen, following which the reaction slowed down considerably. The hydrogenation product [the debenzylated ether (XI)] was converted [9] into the β-methoxyethoxymethyl (MEM) ether (XII), and again hydrogenated



R = H (IV); R = Bn (V); R′ = H, R^2 = OMe (VI); R′ = OMe, R^2 = H (VII); R = Bn (X); R = H (XI); R = MEM (XII).

The resulting compound (XIII), after purification on a column of silica gel, from its PMR spectrum [the similar chemical shifts of the doublet for the methyl groups at C^2 and C^4 (δ 1.04 and 1.06 ppm), H^1 doublets (δ 4.66 ppm, $J_{1,2}$ = 3 Hz) and H^5 doublets (δ 4.47 ppm, $J_{4,5}$ = 3 Hz), and the singlets at 3.40 (anomeric methoxy), 3.48 (methoxy of the MEM group), and 3.76 ($COOCH_3$)] was methyl (methyl-2,4-didesoxy-2,4-di-C-methyl-3-O-MEM-β-L-idopyranosyl)uronate, a specifically protected C^1-C^6 fragment in the synthesis of the antibiotics listed in the table, namely lancomycin, picromycin, carbomycin, cromycin, and cromine [2]. In addition to the above findings, the structure of (XIII) was further corroborated by comparison with its 3-O-methyl analogs [6].

EXPERIMENTAL

PMR spectra were obtained on Tesla BS-497 and Bruker WM-250 instruments, and ^{13}C NMR spectra on Bruker WP-60 and Bruker WM-250 instruments ($CDCl_3$ solutions, internal standard TMS, δ = 0). IR spectra were recorded on a UR-20 in CCl_4, and UV spectra on a Specord UV-VIS. Specific rotations were measured on a Perkin–Elmer 141 polarimeter, in $CHCl_3$. The progress of the reactions was followed and the purity of the compounds obtained estimated by TLC on silica gel L (5-40 mμ) and GLC on LKhM-8MD (column packed with 3% SE-30 on Chromaton NAW-DMCS, l 2 m) and Biokhrom-21 (glass capillary column, OV-101, l 50 m) instruments. The mixtures were separated by column chromatography on Silpearl silica gel (25-40 mμ), using continuous linear solvent gradients and an overpressure of 0.5-1.2 atm.

The compounds were recrystallized several times at −60°C, the mother liquors evaporated, and following purification on silica gel columns the residues were precrystallized.

1,6-Anhydro-2-desoxy-2-C-methyl-3-O-acetyl-β-D-xylopyranosyl-4-ulose (III). To a solution of 5.35 ml (63.2 mmole) of $(COCl)_2$ in 145 ml of dry CH_2Cl_2 was added with stirring and cooling at −60°C over 15 min a solution of 9.8 ml (138 mmole) of dry DMSO in 30 ml of dry CH_2Cl_2. The mixture was stirred for a further 15 min; then at the same temperature there was added over 15 min a solution of 11.6 g (5.74 mmole) of (II) [4] in 60 ml of dry CH_2Cl_2. After 20 min, the mixture was treated with 19.7 ml (143 mmole) of triethylamine, the cooling bath removed, and the temperature brought to 0°C over 15 min. Water (180 ml) was added, the organic layer separated, and the aqueous layer washed with 100 ml of CH_2Cl_2. The combined organic extracts were washed with 1 N HCl (2 × 100 ml), water (100 ml), saturated sodium bicarbonate solution (2 × 100 ml), and saturated sodium chloride solution (2 × 100 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. Yield 11.0 g (96%), mp 72-74°C (ether), $[\alpha]_D^{21}$ −1.6° (c, 1.2). The glycol (IV) was obtained as in [5].

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-β-D-galactopyranose (V). A solution of 1.74 g (10 mmole) of (IV) in 30 ml of dry DMF was stirred for 1 h at ~ 20°C with 1 g of NaH, then 3 ml of benzyl chloride (BnCl) was added and stirring continued for a further 1 h. Excess NaH was decomposed with 5 ml of MeOH, and the mixture was poured into 100 ml of water and extracted with chloroform (3 × 50 ml). The organic extract was washed with water and saturated NaCl solution, dried over anhyd. Na_2SO_4, and evaporated to dryness. Yield 3.40 g (96%), mp 73-74°C (hexane), $[\alpha]_D^{21}$ −26.1° (c, 1.3). PMR spectrum (δ, ppm): 5.24 s (1H, H^1), 2.22 q (1H, J_{2,CH_3} = 7.5 Hz, H^2), 3.30 s (1H, H^3), 4.06 d (1H, $J_{5,6\,exo}$ = 5 Hz, H^5), 4.66 d (1H) (1H, $J_{6,6'}$ = 6 Hz, H^6), 3.60 d.d (1H, H^6), 4.48 s (2H, CH_2Ph at O^3), 4.58 AB (2H, CH_2Ph at O^4), 7.20 s (10H, Ph), 1.50 s (3H, CH_3 at C^4), 1.05 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.5 (C^1), 38.4 (C^2), 82.2 (C^3), 79.2 (C^4), 78.1 (C^5), 64.5 (C^6), 16.5 (CH_3 at C^2), 23.3 (CH_3 at C^4), 71.8 (CH_2Ph at C^3), 63.9 (CH_2Ph at C^4). Found: C 74.31; H 7.25%. $C_{22}H_{26}O_4$. Calculated: C 74.57; H 7.37%.

Methyl 2-Desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-α-D-galactopyranoside (VI) and Its Anomer (VII). a) A solution of 3.12 g (8.8 mmole) of (V) in 25 ml of a 20% solution of HCl in methanol was kept at 20°C for 2 h. It was then diluted with 50 ml of dry ether, and neutralized with gaseous NH_3. The precipitate of NH_4Cl was filtered off, the solution evaporated, and the residue chromatographed. Yield of the α-glycoside (VI), 2.2 g (65%), syrup, $[\alpha]_D^{23}$ +122.5° (c, 0.95), and of the β-glycoside (VII), 0.46 g (13.6%). PMR spectrum (δ, ppm) of (VI): 4.67 d (1H, $J_{1,2}$ = 3.5 Hz, H^1), 3.42 d (1H, $J_{2,3}$ = 11 Hz, H^3), and of (VII): 4.05 d (1H, $J_{1,2}$ = 8 Hz, H^1), 2.95 d (1H, $J_{2,3}$ = 11 Hz, H^3). ^{13}C NMR spectrum (δ, ppm): of (VI): 102.5 (C^1), 37.5 (C^2), 85.0 (C^3), 76.8 (C^5), 61.8 (C^6), 17.1 (CH_3 at C_2), 23.7 (CH_3 at C^4). 67.1 (CH_2Ph at C^4), 75.0 (CH_2Ph at O^3), 55.1 (OMe); and of (VII): 106.3 (C^1), 39.4 (C^2), 88.9 (C^3), 76.1 (C^4), 79.4 (C^5), 61.6 (C^6), 17.0 (CH_3 at C^2); 20.8 (CH_3 at C^4), 66.8 (CH_2Ph at O^4), 77.0 (CH_2Ph at O^3), 56.6 (OMe).

b) A solution of 0.46 g (1.3 mmole) of (VII) in 5 ml of a 3% solution of HCl in MeOH was kept at 20°C for 3 h. The solution was neutralized with Amberlite JRA-400 (CO_3^-), filtered, evaporated, and the residue chromatographed to give 0.32 g (70%) of (VI).

Methyl 2-Desoxy-2,4-di-C-methyl-3,4-di-O-benzyl-6-ozo-α-D-galactopyranoside (VIII). The oxidation of 3.4 g (8.8 mmole) of (VI) was carried out as described above with 1.72 g (22 mmole) of DMSO, 1.27 g (10

mmole) of $(COCl)_2$, and 5 ml of triethylamine, to give 3.30 g (98%) of a syrup, $[\alpha]_D^{23}$ +66.9° (c, 0.94). PMR spectrum (δ, ppm): 4.72 d (1H, $J_{1,2}$ = 3.5 Hz, H^1), 2.50 m (1H, H^2), 3.44 m (1H, $J_{2,3}$ = 11 Hz, H^3), 3.80 d (1H, $J_{5,6}$ = 2 Hz, H^5), 9.64 d (1H, H^6), 1.08 d (3H, J_{2,CH_3} = 7 Hz, CH_3 at C^2), 1.47 s (3H, CH_3 at C^4), 3.33 s (3H, OMe), 4.64 s (2H, CH_2Ph at O^3), 4.70 AB (2H, CH_2Ph at O^4), 7.2 and 7.31 s.s (5H, 5H, $2C_6H_5$).

Methyl 2-Desoxy-2,4-di-C-methyl-3-O-benzyl-6-oxo-$\Delta^{4,5}$-α-L-threopentapyranoside (IX). A solution of 3.3 g (8.7 mmole) of (VIII) in 30 ml of MeOH and 5 ml of saturated aqueous $Ca(OH)_2$ was boiled until starting material was no longer detected (~ 1 h). The mixture was cooled, neutralized with CO_2, filtered, evaporated, and the residue chromatographed to give 2.36 g (100%) of a syrup, $[\alpha]_D^{20}$ = 197° (c, 1.2). PMR spectrum (δ, ppm): 4.86 d (1H, $J_{1,2}$ = 2.5 Hz, H^1), 2.28 d.d.q (1H, J_{2,CH_3} = 6.8 Hz, H^2), 3.81 d.d ($J_{3,CH_3(4)}$ = 1 Hz, H^3), 9.79 s (1H, H^6), 1.02 d (3H, CH_3 at C_2), 2.12 d (3H, CH_3 at C^4), 3.50 s (3H, OMe), 4.60 s (2H, CH_2Ph at O^3), 7.37 s (5H, C_6H_5).

Methyl 2-Desoxy-2,4-di-C-methyl-3-O-benzyl-5-methoxycarbonyl-$\Delta^{4,5}$-α-L-threopentapyranoside (X). A mixture of 0.312 g (1.3 mmole) of (IX), 0.325 g (5.65 mmole) of KCN, 0.135 g (2.26 mmole) of AcOH, and 3 g of of activated MnO_2 in 15 ml of absolute methanol was stirred at 20°C for 12 h. The mixture was filtered, and the solid washed with chloroform. The solution was washed with water (2 × 20 ml) and saturated NaCl solution (2 × 20 ml), evaporated, and the residue chromatographed to give 0.293 g (85%), $[\alpha]_D^{20}$ +151° (c, 1.1). PMR spectrum (δ, ppm): 4.82 d (1H, $J_{1,2}$ = 2.5 Hz, H^1), 2.25 m (1H, H^2), 3.66 d (1H, $J_{2,3}$ = 5 Hz, H^3), 0.93 d (3H, J_2CH_3 = 8 Hz, CH_3 at C^2), 2.06 s (3H, CH_3 at C^4), 3.75 s (3H, COOMe), 3.52 s (3H, OMe), 4.55 s (2H, CH_2Ph), 7.28 s (5H, C_6H_5).

Methyl 2-Desoxy-2,4-di-C-methyl-5-methoxycarbonyl-$\Delta^{4,5}$-α-L-threopentapyranoside (XI). A solution of 1.76 g (5.8 mmole) of (X) in 15 ml of MeOH was hydrogenated over 1 g of 5% Pd/C for 1 h, filtered, and evaporated. Yield 1.22 g (98%), syrup, $[\alpha]_D^{21}$ +179° (c, 1.2). PMR spectrum (δ, ppm): 4.89 d (1H, $J_{1,2}$ = 2 Hz, H^1), 1.12 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2), 2.15 s (3H, CH_3 at C^4), 3.55 s (3H, OMe), 3.88s (3H, COOMe), 2.60 br. s (1H, OH).

Methyl 2-Desoxy-2,4-di-C-methyl-3-O-MEM-5-methoxycarbonyl-$\Delta^{4,5}$-α-L-threopentapyranoside (XII). To a solution of 0.635 g (5.1 mmole) of MEM-Cl in 10 ml of dry MeCN was added 0.54 g (5.35 mmole) of triethylamine, and the mixture kept overnight. Compound (XI) (0.736 g; 3.4 mmole) was then added, the mixture boiled for 12 h, poured into water (20 ml), extracted with chloroform (2 × 30 ml), and the extract washed with saturated NaCl, evaporated, and the residue chromatographed. Yield 0.91 g (81%), syrup, $[\alpha]_D^{24}$ +108.5° (c, 0.8). PMR spectrum (δ, ppm): 4.73 d (1H, $J_{1,2}$ = 2.5 Hz, H^1), 0.91 d (3H, J_{2,CH_3} = 7.5 Hz, CH_3 at C^2), 2.05 s (3H, CH_3 at C^4), 3.76, 3.37, 3.52 s. s. s (9H, COOMe, 2 OMe).

Methyl (Methyl 2,4-didesoxy-2,4-di-C-methyl-3-O-MEM-β-L-idopyranosyl)uronate (XIII). A solution of 0.7 g (2.3 mmole) of (XII) in 12 ml of MeOH was hydrogenated over 0.83 g of 5% Pd/C at 40°C for 10 h, and the catalyst filtered off, washed with MeOH, the filtrates evaporated, and the residue chromatographed. Yield 0.62 g (88%), syrup, $[\alpha]_D^{22}$ +70.5° (c, 1.0). PMR spectrum (δ, ppm): 4.66 d (1H, $J_{1,2}$ = 3 Hz, H^1), 2.0 m (2H, H^2, H^4), 4.47 d (1H, $J_{4,5}$ = 3.5 Hz, H^5), 1.04 and 1.06 d.d (6H, J_{2,CH_3} = J_{4,CH_3} = 7.5 Hz, CH_3 at C^2 and C^4), 3.40, 3.48, 3.76 s. s. s (9H, COOMe, 2 OMe).

CONCLUSIONS

1. A general strategy for the synthesis of 14-membered macrolide antibiotics from suger derivatives is discussed.

2. The synthesis has been carried out of the C^1-C^6 fragment common to the whole group of antibiotics, in 16 stages starting from levoglucosan, in an overall yield of 14%.

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