SYNTHESIS OF MACROLIDE ANTIBIOTICS

COMMUNICATION 3.* SYNTHESIS OF THE C^9-C^{13} FRAGMENTS OF OLEANDONOLIDE AND ERYTHRONOLIDE B

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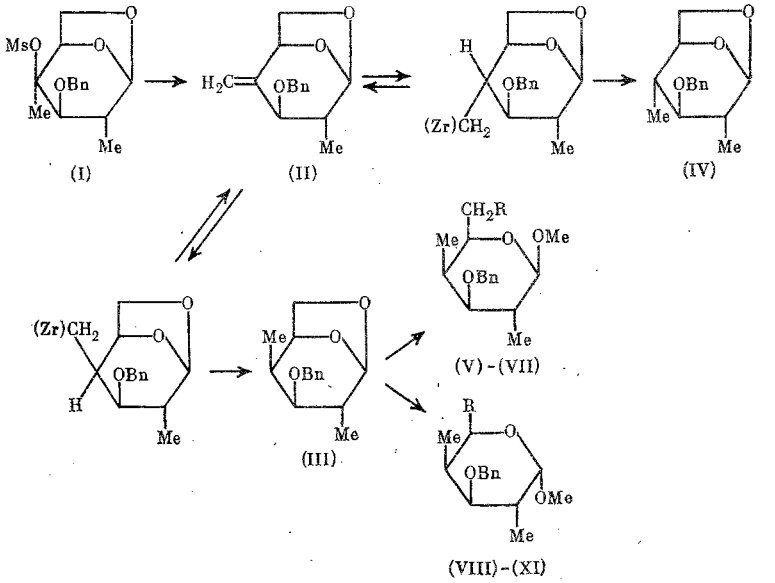
In the preceding communication [2], we described numerous attempts to synthesize the C^9-C^{13} fragments of oleandonolide and erythronolide B by the direct deoxygenation of the mesylate (I) and other compounds. We here present a route for the synthesis of the C^9-C^{13} fragments of these antibiotics from the methylene derivative (II), obtained by the epimerization of (I). It has been found that the yield of (II) can be increased considerably (up to 92%) by boiling (I) in nitromethane in the presence of bisisopropylethylamine. The structure of (II) is confirmed by comparison of its spectra with those of the 3-O-methyl analog [3]. Both the proton and ^{13}C NMR spectra of these compounds correspond closely, bearing in mind the different nature of the substituents at O^3.

As will be seen from the reaction sequence given below, in order to convert (II) into the C^9-C^{13} fragment of oleandonolide (VII) and erythronolide B (XI), it is necessary to reduce the double bond in such a way that the galacto-isomer (III) is formed, and then to extend the chain at C^6 by one carbon atom [for the erythronolide B fragment (XI)], or to reduce the primary alcohol group to methyl [for the oleandonolide fragment (VII)].

It has been shown [3] that the catalytic hydrogenation of the 3-O-methyl analog of (II) over Ni/Re or Pd/C affords preferentially the gluco-isomer. On the other hand, thermodynamically controlled hydrometallation should lead to the preferential formation of the galacto-isomer (III). It is known that $Cp_2Zr(H)Cl$ rapidly and (what is particularly important) reversibly adds to olefins [4]. Making use of this approach, we have succeeded in carrying out the sterically directed reduction of the double bond in (II) by hydrozirconization, followed by mild protolysis. This reaction led to the preferential formation of the thermodynamically more stable galacto-isomer [ratio of (III) : (IV) = 12 :1]. At a conversion of 63%, the yield of (III) was 92%.



R = OH (V), OMS (VI), H (VII), CH_2OH (VIII), CHO (IX), CH_2=CH (X), C_2H_5 (XI)

The PMR spectrum of the gluco-isomer (IV) is similar to that of its 3-O-methyl analog [3]. In comparing

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the PMR spectra of (III) and (IV), attention is drawn to the multiplicity of the H^3 proton. In (IV), this is a broadened singlet with $J_{2,3} = J_{3,4} = 1$ Hz, but in (III) it is a resolved doublet with $J_{3,4} = 4.5$ Hz, confirming its galacto-configuration.

Methanolysis of (III) afforded a mixture of the α-(VIII) and β-methylglucosides (V), which were separated chromatographically, and in order to facilitate evaluation of the spectral data these were subsequently utilized separately. Confirmation of the structures of (V) and (VIII) was provided by an examination of their PMR spectra. In the spectrum of isomer (VIII), the H^1 proton appears at 4.57 ppm, with $J_{1,2} = 3$ Hz, whereas in the case of (V) it is seen at 3.94 ppm, with $J_{1,2} = 8.5$ Hz.

Mesylation of (V) with $MsCl-Et_3N$ [5] gave the mesylate (VI), an attempt to reduce which with $LiAlH_4$ resulted in regeneration of the starting material (V). However, reduction of (VI) with $LiBHEt_3$ [6] gave methyl-2,4,6-tridesoxy-2,4-di-C-methyl-3-O-benzyl-β-D-galactopyranoside (VII) in high yield, this constituting a specifically protected C^9-C^{13} fragment of the antibiotics oleandomycin and O-demethyloleandomycin.

Oxidation of (VIII) with $DMSO-(COCl)_2$ [7] gave the aldehyde (IX), as shown by the occurrence in the PMR spectrum of a signal at 9.66 ppm. The aldehyde (IX) was subjected to the Wittig reaction, and the resulting vinyl derivative (X) (δ 6.1, 5.76, and 5.6 ppm $-CH=CH_2$) was reduced with $LiAlH_4-CoCl_2$ [8] to give high yields of methyl-2,4-tridesoxy-2,4,6-tri-C-methyl-3-O-benzyl-α-D-galactopyranoside (XI), which is a specifically protected C^9-C^{13} fragment of erythromycin B.

EXPERIMENTAL

PMR spectra were obtained on Tesla BS-497 and Bruker WN-250 instruments, and ^{13}C NMR spectra on Bruker WP-60 and Bruker WP-250 instruments ($CDCl_3$ solutions, internal standard TMS, δ, J in Hz). Specific rotations were measured on a Perkin-Elmer M141 polarimeter, in chloroform. TLC was carried out on silica gel L (5-40 mμ), and GLC on a Biokhrom-21 (OV-101 glass capillary column, length 50 m). Column chromatography was carried out on Silpearl silica gel (25-40 mμ), using continuous linear solvent gradients (benzene, ether, and light petroleum) and an overpressure of 0.5-1.2 atm.

1,6-Anhydro-2-desoxy-2-C-methyl-3-O-benzyl-4-methylene-β-D-xylohexapyranose (II). A solution of 0.32 g (0.94 mmole) of (I) and 0.35 g (2.7 mmole) of $i\text{-}Pr_2NEt$ in 5 ml of $MeNO_2$ was boiled for 32 h, the solution evaporated, and the residue chromatographed. Yield, 0.204 g (92%), syrup, $[\alpha]_D^{22} -4.9°$ (c, 10). PMR spectrum (δ, ppm): 5.0 d (1H, H^1, $J_{1,2} = 1$ Hz), 2.22 q (1H, H^2, $J_{2,CH_3} = 7$ Hz), 3.55 m (1H, H^3), 4.17 d (1H, H^5, $J_{5,6\ exo} = 5.5$ Hz), 3.73 d.d (1H, $H^{6\ exo}$, $J_{6,6'} = 7$ Hz), 4.67 d (1H, $H^{6\ endo}$), 5.25 and 5.28 broadened s (2H, $=CH_2$), 4.43 q (2H, CH_2Ph), 7.28 s (5H, C_6H_5), 0.92 d (3H, CH_3 at C^2). ^{13}C NMR spectrum (δ, ppm): 104.1 (C^1), 42.2 (C^2), 79.9 (C^3), 140.6 (C^4), 77.5 (C^5). 67.4 (C^6), 69.6 (CH_2Ph), 14.8 (CH_3 at C^2), 117.0 ($=CH_2$), 138.3, 128.5, 127.6 (C_6H_5).

1,6-Anhydro-2,4-didesoxy-2,4-di-C-methyl-3-O-benzyl-β-D-galacto- (III) and glucopyranose (IV). To a stirred suspension of 1.67 g (6.1 mmole) of $Cp_2Zr(H)Cl$ [9] in 20 ml of dry benzene was added under argon 1.35 g (5.5 mmole) of (II) in 8 ml of benzene. When the solid $Cp_2Zr(H)Cl$ had dissolved (5-10 min), the mixture was hydrolyzed with 10 ml of 1 N HCl at 20°C, the aqueous layer extracted with benzene (2 × 10 ml), the organic layer washed with saturated solutions of $NaHCO_3$ (2 × 20 ml) and NaCl (2 × 20 ml), dried over Na_2SO_4, evaporated, and the residue chromatographed. Yield, 0.74 g (54%) of (III), syrup, $[\alpha]_D^{22} -64.9°$ (c, 1.0), $R_f = 1.2$ [relative to (II), benzene-ether, 3:1]. PMR spectra (δ, ppm): 5.28 d (1H, H^1, $J_{1,2} = 1$ Hz), 2.2 m (2H, H^2, H^4), 3.20 d (1H, H^3, $J_{3,4} = 4.5$ Hz), 4.14 t (1H, H^5, $J_{5,6\ exo} = 5.5$ Hz), 4.33 d (1H, $H^{6\ endo}$, $J_{6,6'} = 6.5$ Hz), 3.57 d.d (1H, $H^{6\ exo}$), 4.47 q (2H, CH_2Ph), 7.31 s (5H, C_6H_5), 0.95 d (3H, $J_{2,CH_3} = 6.5$ Hz, CH_3 at C^2), 0.98 d (3H, $J_{4,CH_3} = 6.5$ Hz, CH_3 at C^4).

Yield of (IV), 0.07 g (5%), R_f 1.05. PMR spectrum (δ, ppm): 5.27 d (1H, H^1, $J_{1,2} = 1$ Hz), 2.0 and 1.94 m (2H, H^2, H^4), 3.05 broadened s (1H, H^3, $J_{2,3} = J_{3,4} = 1$ Hz), 4.25 d (2H, H^5, $H^{6\ endo}$, $J_{5,6\ exo} = 5.5$ Hz), 3.74 d.d (1H, $H^{6\ exo}$, $J_{6,6'} = 6.5$ Hz), 4.49 s (2H, CH_2Ph), 7.31 s (5H, C_6H_5), 1.04 d and 1.19 d (6H, CH_3 at C^2 and C^4, $J_{2,CH_3} = J_{4,CH_3} = 7.5$ Hz). There was isolated 0.405 g (30%) of (II).

Methyl 2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-α- (VIII) and β-D-galactopyranoside. A solution of 0.735 g (2.96 mmole) of (III) in 7 ml of a 10% solution of HCl in MeOH was kept at 20°C for 40 min, then 30 ml of dry ether was added, the mixture neutralized with gaseous NH_3, the NH_4Cl filtered off, evaporated, and the residue chromatographed to give 0.49 g (59%) of (VIII), mp 71.5-72°C (hexane), $[\alpha]_D^{22} +192°$ (c, 0.96), R_f 1.3 [relative to (V)]. PMR spectrum (δ, ppm): 4.57 d (1H, H^1, $J_{1,2} = 3$ Hz), 2.0 m (3H, H^2, H^4, OH), 3.58 d.d (1H, H^3, $J_{2,3} = 11$ Hz; $J_{3,4} = 4.7$ Hz), 3.4-4.0, ABC system (3H, H^5, H^{6} exo, H^{6} endo), 3.32 s (3H, OMe), 4.48 q (2H, CH_2Ph), 7.3 s (5H, C_6H_5), 0.92 d and 1.02 d (6H, $J_{2,CH_3} = J_{4,CH_3} = 7.5$ Hz, CH_3 at C^2, C^4). Found: 68.29, H 8.45%, $C_{15}H_{20}O_3$. Calculated: C 68.57; H 8.57%.

Yield of (V), 0.244 g (29%), mp 81.5-82°C (hexane), $[\alpha]_D^{22}$ +59.8° (c, 0.8), R_f = 1. PMR spectrum (δ, ppm): 3.94 d (1H, H^1, $J_{1,2}$ = 8.5 Hz), 1.8 and 2.2 m (3H, H^2, H^4, OH), 3.17 d.d (1H, H^3, $J_{2,3}$ = 11 Hz, $J_{3,4}$ = 5 Hz), 3.4-4.0, ABC system (3H, H^5, $H^{6\,exo}$, $H^{6\,endo}$), 1.01 and 0.90 d and d (6H, $J_{2,CH_3} = J_{4,CH_3}$ = 7.5 Hz, CH_3 at C^2 and C^4), 4.49 q (2H, CH_2Ph), 7.30 s (5H, C_6H_5), 3.51 s (3H, OMe). Found: 68.31; H 8.45% $C_{15}H_{20}O_3$. Calculated: C 68.57; H 8.57%.

Methyl 2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-6-O-mesyl-β-D-galactopyranoside (VI). To a solution of 0.228 g (0.815 mmole) of (V) and 0.225 ml (1.63 mmole) of Et_3N in 4 ml of dry CH_2Cl_2 was added at −10°C over 5 min a solution of 0.14 g (1.23 mmole) of MSCl in 1 ml of CH_2Cl_2. After 15 min, 10 ml of water was added. The organic layer was washed with 1 N HCl (1 × 5 ml), saturated solutions of $NaHCO_3$ and NaCl, evaporated, and the residue recrystallized from ether−pentane (1:2). Yield 0.28 g (96%), mp 90.5-91°C, $[\alpha]_D^{22}$ +37.5° (c, 0.86) Found: C 56.72; H 7.08% $C_{17}H_{26}O_6S$. Calculated: C 57.00; H 7.26%.

IMethyl 2,4,6-Tridesoxy-2,4-di-C-methyl-3-O-benzyl-β-D-galactopyranoside (VII). To a solution of 0.275 g (0.77 mole) of (VI) in 5 ml of THF was added 2.5 ml of an 0.975 N solution of $LiBHEt_3$ in THF (2.44 mmole), the mixture boiled under argon for 1 h, decomposed with 3N NaOH, then 1.6 ml of 30% H_2O_2 added gradually. The mixture was stirred for 1 h, 25 ml of water added, and extracted with pentane (5 × 30 ml). The extract was dried over Na_2SO_4 and evaporated to give 0.198 g (97%), mp 63-64°C (pentane), $[\alpha]_D^{22}$ +60.0° (c, 2.0). PMR spectrum (δ, ppm): 3.88 d (1H, H^1, $J_{1,2}$ = 8.5 Hz), 1.5-2.1 m (2H, H^2, H^4), 3.16 d.d (1H, H^3, $J_{2,3}$ = 11 Hz; $J_{3,4}$ = 5 Hz), 3.5 m (6H, H^5, $H^{6\,exo}$, $H^{6\,endo}$, OMe), 0.94, 1.01, 1.23 d (9H, $J_{2,CH_3} = J_{4,CH_3} = J_{5,CH_3}$ = 7.5 Hz, CH_3 at C^2, C^4, C^5), 4.49 q (2H, CH_2Ph), 7.30 s (C_6H_5). Found: C 73.12; H 9.26%, $C_{16}H_{24}O_3$. Calculated: C 73.38; H 9.35%.

Methyl 2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-6-oxo-α-D-galactopyranoside (IX). To 0.131 g (1.2 mmole) of $(COCl)_2$ in 2 ml of dry CH_2Cl_2 was added with stirring and cooling at −60°C over 5 min 0.19 g (2.4 mmole) of DMSO in 1 ml of CH_2Cl_2. The mixture was stirred for 10 min, then 0.28 g (1 mmole) of (VIII) in 1 ml of CH_2Cl_2 was added over 5 min, and stirring continued for 15 min. Et_3N (0.7 ml, 5 mmole) was added, and the mixture allowed to warm up to 20°C, diluted with 20 ml of CH_2Cl_2, washed with 1 N HCl and with saturated solutions of $NaHCO_3$ and NaCl, dried, and evaporated. Yield, 0.27 g (100%), mp 72.5-73.5°C (pentane), $[\alpha]_D^{23}$ +192° (c, 0.88). PMR spectrum (δ, ppm): 4.70 d (1H, H^1, $J_{1,2}$ = 3 Hz), 2.0 m (1H, H^2), 3.60 d.d (1H, H^3, $J_{2,3}$ = 11 Hz; $J_{3,4}$ = 5 Hz), 2.61 m (1H, H^4), 4.23 d (1H, H^5, $J_{4,5}$ = 2.5 Hz), 9.66 s (1H, H^6), 4.49 q (2H, CH_2Ph), 7.30 s (5H, C_6H_5), 3.32 s (3H, OMe), 0.93 and 1.01 d (6H, $J_{2,CH_3} = J_{4,CH_3}$ = 7.5 Hz, CH_3 at C^2, C^4). Found: C 68.78; H 7.85%. $C_{16}H_{22}O_4$. Calculated: C 69.06; H 7.91%.

Methyl 2,4-Didesoxy-2,4-di-C-methyl-3-O-benzyl-6-methylene-α-D-galactopyranoside (X). To a suspension of 0.725 g (2.03 mmole) of triphenylphosphonium bromide in 10 ml of dry benzene was added with stirring at 20°C 1.8 ml of a 1.12 N solution of n-butyllithium (2.03 mmole), stirred for 15 min, and a solution of 0.257 g (0.925 mmole) of (IX) in 2 ml of dry benzene added at 80°C. The mixture was boiled for 10 min, cooled, 5 ml of acetone added, filtered through silica gel, washed with benzene, and evaporated. Yield 0.25 g (98.5%), syrup, $[\alpha]_D^{22}$ +193°C (c, 0.82). PMR spectrum (δ, ppm): 4.59 d (1H, H^1, $J_{1,2}$ = 3 Hz), 2.1 m (2H, H^2, H^4), 3.62 d.d (1H, H^3, $J_{2,3}$ = 11 Hz; $J_{3,4}$ = 5 Hz), 4.35 m (1H, H^5, $J_{4,5}$ = 2.5 Hz), 6.1 m (1H, H^6), 5.76 and 5.6 m (2H, CH_2=), 4.50 q (2H, CH_2Ph), 7.3 s (5H, C_6H_5), 0.92 and 1.0 d (6H, $J_{2,CH_3} = J_{4,CH_3}$ = 7.5 Hz, CH_3 at C^2, C^4), 3.3 s (3H, OMe).

Methyl 2,4,6-Tridesoxy-2,4,6-tri-C-methyl-3-O-benzyl-α-D-galactopyranoside (XI). To a solution of 0.244 g (0.89 mmole) of (X) and 0.116 g (0.89 mmole) of $CoCl_4$ in 4 ml of dry THF was added with stirring and cooling at −78°C 0.5 ml of a 1.18 M solution of $LiAlH_4$ in THF. The mixture was stirred at −78°C for 10 min, the cooling bath removed, and stirring continued for a further 30 min. Water (5 ml) was then added, filtered through Celite, and washed with CH_2Cl_2. The organic layer (30 ml) was washed with water and saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue chromatographed. Yield, 0.186 g (75%), syrup, $[\alpha]_D^{20}$ +192° (c, 0.92). PMR spectrum (δ, ppm): 4.52 d (1H, H^2, $J_{1,2}$ = 3 Hz), 1.20-2.20 m (4H, H^2, H^4, H^6, H^6), 3.55 d.d (1H, H^3, $J_{2,3}$ = 11 Hz; $J_{3,4}$ = 5 Hz), 3.66 m (1H, H^5, $J_{5,6}$ = 6 Hz), 4.49 q (2H, CH_2Ph), 7.35 s (5H, C_6H_5), 0.92, 0.95, 1.0 d.t.d (9H, CH_3 at C^2, C^4, C^6), 3.30 s (3H, OMe).

CONCLUSIONS

Using $Cp_2Zr(H)Cl$, 1,6-anhydro-2-desoxy-2-C-methyl-3-O-benzyl-4-methylene-β-D-xylohexapyranose has been reduced with a high degree of stereospecificity to 1,6-anhydro-2,4-didesoxy-2,4-di-C-methyl-3-O-benzyl-β-D-galactopyranose, which was then converted into the C^9−C^{13} fragments of erythronolide B and oleandonolide.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS

COMMUNICATION 4.* SYNTHESIS OF THE $C^{11}-C^{13}$ FRAGMENT OF NARBOMYCIN

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The antibiotics narbomycin (I) and picromycin (II) stand apart in the group of 14-membered macrolide antibiotics [2]. Unique features of their structure include the presence of a double bond at $C^{10}-C^{11}$, and a keto group at C^3, which accordingly require modifications in the overall strategy for their synthesis [3]. In order to accomplish this, it is convenient to divide the antibiotic molecule into three fragments: C^1-C^6, C^7-C^{10}, and $C^{11}-C^{13}$. The synthesis of the first of these, namely the C^1-C^6 fragment of the 14-membered macrolide antibiotics, has been reported [3, 4]. This synthesis, with slight modifications to enable introduction of a keto group at C^3, may also be employed for the preparation of the C^1-C^6 fragments of these antibiotics.

We here report the synthesis of the $C^{11}-C^{13}$ fragment of narbomycin from the α-oxide (IV), which can be obtained in two steps from levoglucosan (III) [5]. Reaction of (IV) with methylmagnesium chloride in the presence of CuCl gave good yields of the C-methyldesoxy derivative (V), the structure of which was established by its PMR and ^{13}C NMR spectra [6]. The positions of the signals, their multiplicity, and low spin–spin coupling constants due to the equatorial protons H^2, H^3, and H^4, are in accordance with the expected structure. Treatment of (V) with MeONa readily affords the α-oxide (VI), the ^{13}C NMR spectrum of which fully corresponds to that described previously for that of an oxide of analogous structure [7], with a correction for the methyl group at C^4. Reduction of (VI) with $LiAlH_4$ in ether proceeded smoothly to give exclusively the 2,4-didesoxy derivative (VII), which is the key intermediate in the synthesis of the $C^{11}-C^{13}$ fragment of narbomycin. Its structure follows from the PMR and ^{13}C NMR spectra of (VII)-(IX). The position of the new desoxy unit is shown by the high-field shift of the C^2 and C^4 signals in the ^{13}C NMR spectrum of (VIII) and (IX). The stereochemistry at C^3 follows from the multiplicity of H^3 and the small spin–spin coupling constants, due to the equatorial disposition of the neighboring protons ($J_{2a,3} = 5.2$, $J_{2e,3} = 1$, $J_{3,4} = 1$-2 Hz).

The stereochemistry at C^3 and C^4 in (VI) corresponds to the stereochemistry at C^{12} and C^{13} in narbomycin (I) with reference to the C^6 of levoglucosan. In order to convert (VII) into the $C^{11}-C^{13}$ fragment of narbomycin, it is necessary to reduce the aldehyde group to methyl, and to shorten the chain by one unit from the opposite end. To this end, (VII) was treated with ethyl mercaptan and $Et_2O \cdot BF_3$ at 0°C [8]. The resulting ethyl mercaptal (X) was unstable on keeping, readily rearranging to the ethylthioglucoside, and it was therefore desulfurized immediately by boiling with Raney nickel in alcohol [9], and the resulting triol, chromatographic purification of which was difficult, was converted into the isopropylidene derivative (XI), isolated in an overall yield of 96%. The structures of (X), (XI), and the benzoate (XII), obtained in the usual way from (XI), were in good agreement with their ^{13}C NMR spectra. The presence of the ethylmercaptal group is shown by the occurrence of signals for C^1 (48.8 ppm) and the SEt group (24.3, 23.8, and 14.5 ppm, double intensity). Following desulfurization and subsequent acetonization, the C^1 signal is shifted to higher field (10.3 ppm). Similarly, the C^2 signal is shifted to high field (39.5 → 26.9 ppm), since the nature of its substituent is changed ($CH(SEt)_2 \rightarrow CH_3$). It is easy to de-

* For communication 3, see [1].

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