SYNTHESIS OF MACROLIDE ANTIBIOTICS.

11.* RETROSYNTHETIC ANALYSIS OF ERYTHRONOLIDE B AND SYNTHESIS OF THE CYCLIC FORM OF THE C^1–C^6 FRAGMENT OF ERYTHRONOLIDES A AND B

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Following a program adopted in our laboratory directed to the total synthesis of macrolide antibiotics from carbohydrates [2] we have developed a detailed strategy for the synthesis of erythronolide B, an aglycone of one of the components of the erythromycin complex – erythromycin B.

It was proposed to carry out the synthesis of erythronolide B (I) (scheme 1) via the 9-(S)-dihydro derivative (II), in which the hydroxyl group at C^9 can be further selectively oxidized [3]. Thus, the bis(cyclo)acetal derivative (III) may be used for the macrolactonization stage, which should ensure the fixation of the conformation of the carbon chain of the seco-acid, required for the successful formation of the macrocycle (cf. [4, 5]). The predecessors for compound (III) can be the derivatives (IV) or (V), in which the C^1 carboxyl group is masked over the whole course of this synthesis, in the first case, in the form of a relatively inert carbon–carbon double bond, and in the second case, in the form of a glycoside. The use of compounds (IV) or (V) as key intermediates in the synthesis of erythronolide B involves differences in the time of transition from the cyclic form of the fragments to an acyclic one. As shall be shown in later publications, in the case of (IV), this transition proceeds at the fragment level, whereas when (V) is used, it occurs after their coupling.

We have previously found the optimal C^1–C^6 and C^9–C^{13} fragments and developed a method for constructing their correct stereochemistry. Working with these fragments is possible when the desired end structures (IV) and (V) are uncoupled at the C^6–C^7 and C^8–C^9 bonds. During the initial uncoupling at the C^8–C^9 bond (path A), we obtain the C^9–C^{13} fragment in the form of aldehyde (VI) and esters (VII) and (VIII), respectively, the further uncoupling of which at the C^6–C^7 bond leads to the C^1–C^6 fragment in the form of methyl ketones (IX) and (X).

During the initial uncoupling of the intermediate compounds (IV) and (V) at the C^6–C^7 bonds (path B), we obtain the same C^1–C^6 fragments in the form of methyl ketones (IX) and (X) and C^7–C^{13} fragment (XI) in the form of an organometallic derivative, retrosynthetically reduced to C^9–C^{13} fragment – aldehyde (VI). The synthesis of the C^9–C^{13} fragment (VI) (R = Bn) and C^1–C^6 fragment in the form of ester (XII) has been carried out by us previously [2, 6].

At this stage of the planned synthesis of erythronolide B, it is necessary to carry out the synthesis of the C^1–C^6 fragment in the form of methyl ketones (IX) and (X), and to further propagate the C^7–C^8 section of the chain in order to obtain the C^1–C^8 fragments (VII) and (VIII). The subsequent addition of these fragments to C^9–C^{13} fragment (VI) should lead to the seco-acid derivatives of erythronolide B (IV) and (V).

It should be noted that the most difficult step in the realization of the above schemes of synthesis is the construction of the correct stereochemistry of the C^6, C^8, and C^9 centers in intermediates (IV) and (V), since there is only an acyclic stereocontrol in the propagation and coupling processes of the fragments, and this is quite difficult to predict on the basis of the available literature data. It was therefore decided to investigate the two paths of synthesis of erythronolide B.

*For previous communication, see [1].

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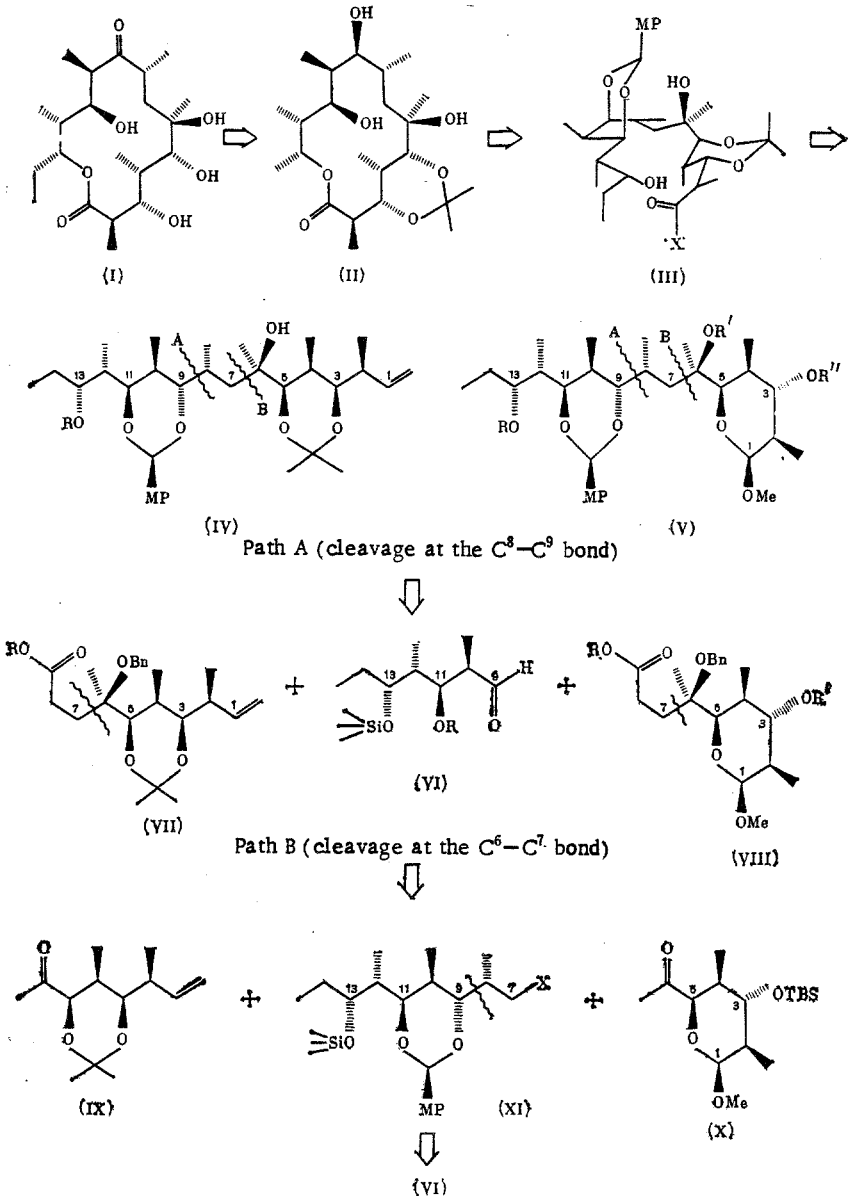
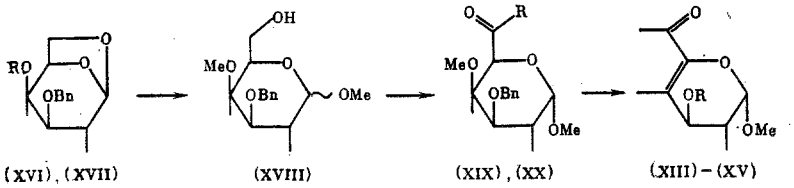
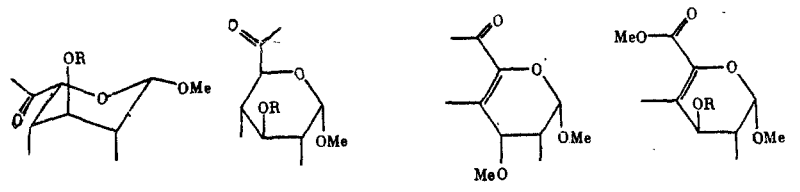
Scheme 1



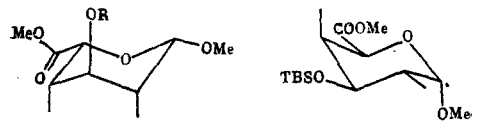
MP = *p*-$MeOC_6H_4$; Bn = $PhCH_2$; TBS = *t*-$BuMe_2Si$

Path A was first investigated using the cyclic form of the C^1–C^6 fragment (X), whose synthesis we describe in the present publication. In the subsequent publications, we shall describe the synthesis of this fragment in an acyclic form (IX) and the synthesis of the C^1–C^8 fragments (VII) and (VIII), the coupling of the latter with the previously described [6] C^9–C^{13} fragment (VI) (R = Bn) (path A), and finally, the completion of the synthesis of erythronolide B by an alternate scheme (path C).

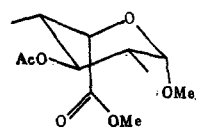




(XXII), (X) (XXIV), (XXVI) (XXIII) (XXI), (XXIX)–(XXXI)



(XII), (XXVII) (XXXII) (XXXIII)



(XXVIII)

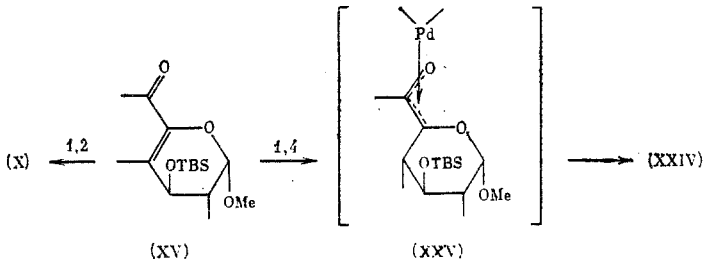
R = H (XVI), Me (XVII); R = H (XIX), Me (XX); R = Bn (XIII), H (XIV), TBS (XV): R = H (XXII), TBS (X); R = TBS (XXIV), H (XXVI); R = Bn (XXI), TBS (XXIX), Ac (XXX), H (XXXI); R = MEM (XII), TBS (XXVII)

We have previously synthesized the C^1–C^6 fragment of erythronolides A and B in the form of ester (XII), the stereochemistry of which corresponded to the stereochemistry of the C^2–C^5 section of the chain of the antibiotics. We therefore first attempted to obtain ketone (X) by a similar scheme [2], the critical stage of which is the catalytic hydrogenation of $\Delta^{4,5}$-unsaturated compounds of type (XIII)-(XV). The required compounds (XIII)-(XV) were obtained from the previously described [2] tertiary alcohol (XVI). Ester (XVII), synthesized by methylation of (XVI), was further subjected to methanolysis, and the mixture of the thus formed methylglycosides (XVIII) was separated chromatographically. Thus, the β-anomer was converted by repeated methanolysis into α-(XVIII), the overall yield of which was 74%, based on alcohol (XVI). The exclusive use of α-(XVIII) in the further synthesis was due to the decisive influence of the configuration of the C^1 center on the stereochemical result of the hydrogenation of the double bond [2] (scheme 2).

The oxidation of the α-anomer of (XVIII) according to Swern [7] gave aldehyde (XIX), which was entered into reaction with MeMgBr, and the mixture of the secondary alcohols formed was oxidized under the same conditions to methyl ketone (XX). Boiling of the latter in a methanol solution of MeONa led to the formation in quantitative yield of the unsaturated ketone (XIII) the structure of which can be deduced from the analysis of its PMR spectrum (see the experimental part). Attempts to remove the benzyl protecting group in (XIII) by hydrogenolysis under conditions used for the debenzylation of the unsaturated ester (XXI) [2] (Pd/C, H_2, MeOH, 40°C) led to a mixture of ketones (XIV) (48%), (XXII) (2.5%), and (XXIII) (32%). Ketone (XXIII) is a product of nucleophilic substitution of the benzyl group in the allylic position by methanol.

The selective debenzylation of (XIII) could be accomplished in quantitative yield by the action of the Pd/C–cyclohexene system [8] in boiling methanol (per weight ratio Pd/C:(XIII) = 4:1). Silylation of the thus obtained α,β-unsaturated ketone (XIV) led to the formation of silyl ester (XV), the catalytic hydrogenation of which, however, does not proceed unequivocally, and leads to a mixture of the desired ketone (X) (36%) and a D-gluco isomer (XXIV) (35%). Their structure follows from the analysis of the PMR spectra of ((X) – $J_{1,2}$ = 3, $J_{2,3} = J_{3,4}$ = 2.5, $J_{4,5}$ = 3.5 Hz; (XXIV) – $J_{1,2}$ = 3, $J_{2,3} = J_{3,4}$ = 9.5, $J_{4,5}$ = 10.5 Hz). It is clear that during the hydrogenation (XV), two parallel processes take place: the stereospecific addition of hydrogen at the double bond, controlled by an axial methoxyl group at C^1 leads to the desired product (X). A similar selective 1,4-addition leads to a π-oxoallyl intermediate (XXV), which rapidly transforms into the thermodynamically more favorable D-gluco isomer (XXIV) (see top of following page).

The catalytic hydrogenation of enone (XIV) also does not proceed unequivocally. A mixture is formed of the required L-ido isomer (XXII) (60%) ($J_{1,2}$ = 3.5, $J_{2,3} = J_{3,4}$ = 4, $J_{4,5}$ = 3.5 Hz) and the D-gluco isomer (XXVI) (24%) ($J_{1,2}$ = 3.3, $J_{2,3} = J_{3,4}$ = 9.5, $J_{4,5}$ = 10.5 Hz).



(XV) (XXV)

Attempts to use other catalysts (Ni/Ra; Pt, $Pd/BaSO_4$) also did not lead to increased selectivity of the hydrogenation of the double bond in derivatives (XIV) and (XV).

We therefore studied the possibility of obtaining ketone (X) via the esters of L-iduronic acid of type (XII), (XXVII), and (XXVIII). For this purpose, we studied the hydrogenation of unsaturated esters (XXIX) and (XXX), which are obtained by the silylation and acetylation of compound (XXXI), previously described by us in [2]. It was found that, as in the case of the methyl ketone analog (XV), the hydrogenation of 3-O-TBS-derivative (XXIX) does not proceed unequivocally and leads to a mixture of the D-galacto isomer (XXXII) (53%) ($J_{1,2}$ = 3.5, $J_{2,3}$ = 10.6, $J_{3,4}$ = 5, $J_{4,5}$ = 4.5 Hz) and the required isomer (XXVII) (43%) ($J_{1,2} = J_{2,3} = J_{3,4} = J_{4,5}$ = 3.5 Hz). The ratio of the products can be radically changed in favor of the required L-ido isomer, by using 3-O-acetyl derivative (XXX), from which compound (XXVIII) was obtained in quantitative yield.

The complexity of the transition from ester (XXVIII) to ketone (X) consists in that by the action of basic agents, the derivatives of L-iduronic acid readily isomerize at the C^5 center forming the more favorable D-gluco derivatives [9]. Therefore, to transform esters of the type of (XXVIII) into methyl ketone (X), we used a new general method of synthesis of ketones, including the configurationally unstable ones, that we have previously developed [10], by direct conversion of esters into seleno esters. For this purpose, ester (XXVIII) was held in ether solution of dimethyl aluminum selenide for 50 h, the acetyl group was thus removed, and the seleno ester (XXXIII) was formed in 93% yield. Its $^1C_4$-conformation was confirmed by the PMR ($J_{1,2} = J_{2,3} = J_{3,4}$ = 3, $J_{4,5}$ = 3.5 Hz). Methyl ketone (XXII) was formed in good yield by the action of an excess of lithium dimethyl cuprate on the seleno ester (XXXIII), and was converted into the desired compound (X).

EXPERIMENTAL

The PMR spectra were run on a "Bruker WM-250" spectrometer (solutions in $CDCl_3$). The chemical shifts are given in ppm in a δ scale. The specific optical rotation was measured in $CHCl_3$ on a "Perkin–Elmer-141" polarimeter. The course of the reaction was monitored by TLC on Kieselguhr-60 silica gel plates and by HPLC on a Lichrosorb Si-60 column using an "Altex 153" UV-detector. The absolute solvents were obtained by distillation in an argon atmosphere over the corresponding drying agents directly before use. Benzene, pyridine, hexane, diisopropylamine, DMSO, and triethylamine were distilled, first over P_2O_5, and then over CaH_2.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-methyl-β-D-galactopyranose (XVII). A solution of 11.3 g (42.8 mmoles) of (XVI) in 15 ml of DMF was added with stirring to 4.8 g of a 50% suspension of NaH (100 mmoles) in 20 ml of DMF. The mixture was stirred for 30 min, and 4 ml (64 mmoles) of MeI were added. The mixture was stirred for another hour then decomposed by MeOH and water, and extracted with $CHCl_3$. The extract was washed with water, and a saturated aqueous NaCl solution, dried over Na_2SO_4, evaporated and the residue was chromatographed in a heptane–ether (1:1) system. The yield of (XVII) was 11.4 g (96%), mp 58-58.5°C (ether), $[\alpha]_D^{23}$ −59.6° (C 6.45). PMR spectrum: 1.05 d (3H, $J_{CH_3,2}$ = 7.7 Hz, CH_3 at C^2), 1.41 s (3H, CH_3 at C^2), 1.41 s (3H, CH_3 at C^4), 2.20 br. q (1H, H^2), 3.20 s (3H, OMe), 3.22 br. s (1H, H^3), 3.62 d. d (1H, $J_{6\ exo,\ 6\ endo}$ = 7, $J_{6\ exo,5}$ = 5.5 Hz, $H^{6\ exo}$), 4.02 d.d.d.d (1H, $J_{5,6\ endo} = J_{5,1} = J_{5,3}$ = 1 Hz, H^5), 4.39 d and 4.66 d (2H, AB system, J_{gem} = 12 Hz, OCH_2Ph), 4.60 d.d. (1H, $H^{6\ endo}$), 5.23 br. d. d (1H, H^1), 7.30-7.40 m (5H, C_6H_5).

Methyl-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-methyl-α,β-D-galactopyranoside (XVIII). An 8.77 g portion (31.5 mmole) of (XVII) was dissolved in 47 ml of a 16% solution of H_2SO_4 in MeOH. The mixture was heated at 75°C for 2 h, then was neutralized by the addition of $NaHCO_3$, and evaporated. The residue was diluted with $CHCl_3$, the solution was washed with water and with a saturated NaCl aqueous solution, dried over Na_2SO_4, evaporated, and the residue was

chromatographed in a benzene–ethyl acetate (EA) (4:1) system. The yield of α-glycoside (XVIII) was 6.19 g (63%), mp 64.5-65°C, (pentane–ether, 4:1), $[\alpha]_D^{23}$ +119.6° (C 0.5); the yield of β-glycoside (XVIII) was 1.55 g (16%), syrup, $[\alpha]_D^{23}$ −7.2° (C 2.0). PMR spectrum for α-(XVIII): 1.07 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.30 s (3H, CH_3 at C^4), 2.42 d.d.q (1H, $J_{2,3}$ = 10.5, $J_{2,1}$ = 3.5 Hz, H^2), 2.95 br. d, (1H, $J_{OH,6\ endo}$ = 9 Hz, OH at C^6), 3.34 d (1H, H^3), 3.36 s (3H, OMe at C^4), 3.46 e (3H, OMe at C^1), 3.58 d.d. (1H, $J_{5,6\ endo}$ = 3, $J_{5,6\ exo}$ = 6 Hz, H^5) 3.74 d.d.d (1H, $J_{6\ exo,\ 6\ endo}$ = 11.5 Hz, $H^{6\ endo}$), 3.94 d.d. (1H, $H^{6\ exo}$), 4.57 d and 4.68 d (2H, AB system, J_{gem} = 11 Hz, OCH_2Ph), 4.68 d (1H, H^1), 7.30-7.40 m (5H, C_6H_5). Found, %: C 66.14, H 8.62. $C_{17}H_{26}O_5$. Calculated, %: C 65.78, H 8.44.

A 1.55 g portion (4.99 mmoles) of β-glycoside (XVIII) was dissolved in 10 ml of 3% solution of HCl in MeOH, and the mixture was allowed to stand at ~20°C for 2 h. It was neutralized with excess Et_3N, evaporated, and the residue was chromatographed in a benzene–EA (4:1) system. The yield of α-glycoside (XVIII) was 1.08 g (69%).

Methyl-2-desoxy-2,4-di-C-methyl-3-O-benzyl-4-O-methyl-6-oxo-α-D-galactopyranoside (XIX). A 2.58 ml portion of a 1.5 M solution of DMSO in CH_2Cl_2 (3.87 mmoles) was added at −60°C to 5.15 ml of a solution of $(COCl)_2$ in CH_2Cl_2 (3.09 mmoles). The mixture was stirred for 10 min, a solution of 0.475 g (1.577 mmole) of (XVIII) in 3 ml of CH_2Cl_2 was added, and after stirring for 15 min, 1.1 ml of Et_3N was added. The means of cooling was removed, and 10 ml of 1 M HCl solution was added at 0°C. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined extract was washed with water and a saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The residue was recrystallized from pentane to yield 0.448 g (92%) of (XIX), mp 69.5-70°C, $[\alpha]_D^{22}$ +61.8°(C 0.83). PMR spectrum: 1.0 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.32 s (3H, CH_3 at C^4) 3.40 d.d.q (1H, $J_{2,1}$ = 3.5, $J_{2,3}$ = 10.5 Hz, H^2), 3.28 s (3H, OMe at C^4), 3.30 d (1H, H^3), 3.32 s (3H, OMe at C^1), 3.72 d (1H, $J_{5,CHO}$ = 2 Hz, H^5) 4.53 d and 4.59 d (2H, AB-system, J_{gem} = 11 Hz, OCH_2Ph), 4.68 d (1H, H^1), 7.25-7.30 m (5H, C_6H_5), 8.66 d (1H, CHO). Found, %: C 66.48, H 8.05. $C_{17}H_{24}O_5$. Calculated, %: C 66.21, H 7.84.

Methyl-2,7-didesoxy-2,4-di-C-methyl-3-O-benzyl-4-O-methyl-6-oxo-α-D-galactoheptopyranoside (XX). A 0.5 ml portion of a 2.5 M solution of MeMgCl in THF (1.25 mmoles) was added at −80°C to a solution of 0.377 g (1.224 mmoles) of (XIX) in 2 ml of abs. THF. The mixture was allowed to stand for 5 min, and then was decomposed with saturated NH_4Cl solution. The precipitate was filtered, and washed with ether, and the solution was dried by azeotropic distillation with benzene. The residue was oxidized in a similar way as described above for (XVIII) with the same quantities of reagents. The yield of (XX) was 0.36 g (93%), mp 64.5-65°C (pentane), $[\alpha]_D^{22}$ +27.3° (C 1.0). PMR spectrum: 1.07 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.33 s (3H, CH_3 at C^4), 2.28 s (3H, CH_3 at C^6), 2.46 d.d.q (1H, $J_{3,2}$ = 10, $J_{2,1}$ = 3.5 Hz, H^2), 3.33 s (3H, OMe at C^4), 3.36 d (1H, H^3), 3.40 s (3H, OMe at C^1), 3.83 s (1H, H^5), 4.62 s (2H, OCH_2Ph), 4.70 d (1H, H^1), 7.30-7.40 m (5H, C_6H_5). Found, %: C 67.37, H 8.29. $C_{18}H_{26}O_5$. Calculated, %: C 67.06, H 8.13.

Methyl-2,7-didesoxy-2,4-di-C-methyl-3-O-benzyl-6-oxo-β-L-threo-hept-4-enopyranoside (XIII). A 9.13 g portion (28.35 mmoles) of (XX) in 45 ml of a solution of MeONa in MeOH (obtained by dissolving 1.2 g of Na in 50 ml of MeOH) was boiled for 1 h. The mixture was cooled, and after adding solid CO_2 and then water, it was extracted with $CHCl_3$. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, and evaporated. The yield of (XIII) was 8.4 g (100%), syrup, $[\alpha]_D^{23}$ +117.7° (C 1.0). PMR spectrum: 0.92 d (3H, $J_{CH_3,2}$ = 7.0 Hz, CH_3 at C^2), 2.02 d (3H, $J_{CH_3,3}$ = 0.5 Hz, CH_3 at C^4), 2.25 d.d.q (1H, $J_{2,1}$ = 2.0, $J_{2,3}$ = 4 Hz, H^2), 2.30 s (3H, CH_3 at C^6), 3.57 s (3H, OMe at C^1), 3.58 d.d (1H, H^3), 4.52 d and 4.66 d (2H, AB-system, J_{gem} = 11 Hz, OCH_2Ph), 4.82 d (1H, H^1), 7.30-7.40 m (5H, C_6H_5).

Hydrogenolysis of Compound (XIII). a. A solution of 8.4 g of (XIII) in 50 ml of MeOH was hydrogenated over Pd/C for 20 h at 40°C. The catalyst was filtered off and washed with MeOH, the solution was evaporated, and the residue was chromatographed in a heptane–EA (4:1) system. The yield of (XXIII) was 1.94 g (32%), syrup, $[\alpha]_D^{22}$ +108.8° (C 1.0); (XIV) 2.72 g (48%), mp 80-80.5°C (pentane–ether, 1:1), $[\alpha]_D^{23}$ +118.6° (C 1.0), and the yield of (XXII) was 0.143 g (2.5%), syrup, $[\alpha]_D^{22}$ +107.5° (C 1.0). PMR spectrum of (XXIII): 0.83 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.95 d (3H, $J_{CH_3,3}$ = 0.6 Hz, CH_3 at C^4), 2.10 d.d.q (1H, $J_{2,3}$ = 4.5, $J_{2,1}$ =

2.5 Hz, H^2), 2.22 s (3H, CH_3 at C^6), 3.30 d.d (1H, H^3), 3.33 s (3H, MeO at C^3), 3.48 s (3H, MeO at C^1), 4.69 (1H, H^1); (XIV): 1.0 d (3H, $J_{CH_3,2}$ = 6.5 Hz, CH_3 at C^2), 1.97 d.d.q (1H, $J_{2,1}$ = 2.5, $J_{2,3}$ = 6.5 Hz, H^2), 2.07 d (3H, $J_{CH_3,4}$ = 1.0 Hz, CH_3 at C^4), 2.31 s (3H, CH_3 at C^6), 3.52 s (3H, MeO at C^1, 3.84 d.d (1H, H^3), 4.82 d (1H, H^1); (XXII): 0.96 d (3H, $J_{CH_3,4}$ = 7.0 Hz, CH_3 at C^4), 0.98 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 1.83 d.d.q (1H, $J_{1,2}$ = 3.0, $J_{2,3}$ = 4 Hz, H^2), 1.97 d.d.q (1H, 1H, $J_{3,4}$ = 4, $J_{4,5}$ = 3.5 Hz, H^4), 2.19 s (3H, CH_3 at C^6), 3.46 s (3H, MeO at C^1), 3.79 d.d (1H, H^3), 4.24 d (1H, H^5). 4.67 d (1H, H^1).

b. A mixture of 0.1 g (0.345 mmole) of (XIII), 0.4 g of Pd/C, 1 ml of MeOH, and 1 ml of cyclohexene was boiled and stirred for 20 min. It was then filtered, the precipitate was washed with MeOH, the filtrate evaporated, and the residue was chromatographed in a heptane: EA (2:1) system. The yield of (XVI) was 0.07 g (100%).

Methyl-2,7-didesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-6-oxo-β-L-threo-hept-4-enopyranoside (XV). A 0.34 g portion (5 mmoles) of imidazole and 0.302 g (2 mmoles) of tert-butyldimethylsilyl chloride were added to a solution of 0.2 g (1 mmole) of (XIV) in 2 ml of DMF. The mixture was allowed to stand at ~20°C for 48 h, and then was decomposed with water and extracted with ether. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–ether (9:1) system. The yield of (XV) was 0.289 g (92%), syrup, $[\alpha]_D^{22}$ +101° (C 1.08). PMR spectrum: 0.1 s and 0.12 s (6H, $OSiMe_2Bu$-t), 0.82 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 0.9 s (9H, $OSiMe_2Bu$-t), 1.95 d.d.q (1H, $J_{2,1}$ = 2.0, $J_{2,3}$ = 3 Hz, H^2), 2.0 br. s (3H, CH_3 at C^4), 2.20 s (3H, CH_3 at C^6), 3.58 s (3H, MeO at C^1), 3.7 br. d (1H, H^3), 4.8 d (1H, H^1).

Methyl-2,4,7-tridesoxy-2,4-di-C-methyl-6-oxo-α-D-glucoheptopyranoside (XXVI) and Methyl-2,4,7-tridesoxy-2,4-di-C-methyl-6-oxo-β-L-ido-heptopyranoside (XXII). A solution of 3.23 g (16.135 mmoles) of (XIV) was hydrogenated over 10 g Pd/C at 40°C for 30 h. The catalyst was filtered off and washed with MeOH, the filtrate was evaporated, and the residue was chromatographed in a benzene–EA (3:1) system. The yield of (XXVI) was 0.782 g (24%), syrup, $[\alpha]_D^{23}$ +86° (C 1.0), and of (XXII) 1.95 g (60%). PMR spectrum for (XXVI): 0.97 d and 1.05 d (6H, $J_{CH_3,2}$ = $J_{CH_3,4}$ = 6.5 Hz, CH_3 at C^2 and C^4), 1.59 d.d.q (1H, $J_{4,3}$ = 9.5, $J_{4,5}$ = 10.5 Hz, H^4), 1.78 d.d.q (1H, $J_{2,1}$ = 3.2, $J_{2,3}$ = 9.5 Hz, H^2), 2.22 s (3H, CH_3 at C^6), 3.32 s (3H, MeO at C^1), 3.34 d.d (1H, H^3), 3.78 d (1H, H^5), 4.65 d (1H, H^1).

Methyl-2,4,7-tridesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-6-oxo-α-D-glucoheptopyranoside (XXIV) and Methyl-2,4,7-tridesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-6-oxo-β-L-ido-heptopyranoside (X). A solution of 0.234 g (0.745 mmole) of (XV) was hydrogenated over 0.15 g of Pd/C at 40°C for 1 h. The catalyst was filtered off and washed with MeOH, the filtrate was evaporated and the residue was chromatographed in a heptane–ether (4:1) system. The yield of (XXIV) was 0.82 g (35%), syrup, $[\alpha]_D^{22}$ +17° (C 1.0), (X) 0.085 g (36%). PMR spectrum of (XXIV): 0.06 s and 0.08 s (6H, $OSi\underline{Me}_2Bu$-t), 0.85 d and 0.96 d (6H, $J_{CH_3,2}$ = $J_{CH_3,4}$ = 6.7 Hz, CH_3 at C^2 and C^4), 0.9 s (9H, $OSiMe_2\underline{Bu}$-t), 1.78 d.d.q (1H, $J_{1,2}$ = 3, $J_{2,3}$ = 9.5 Hz, H^2), 1.58 d.d.q (1H, $J_{4,5}$ = 10.5, $J_{4,3}$ = 9.5 Hz, H^4), 2.20 s (3H, CH_3 at C^6), 3.31 s (3H, MeO at C^1), 3.40 d.d (1H, H^3), 3.76 d (1H, H^5), 4.61 d (1H, H^1).

Methyl-2-desoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-5-methoxycarbonyl-β-L'-threo-pent-4-enopyranoside (XXIX). A 10.3 g portion (150 mmoles) of imidazole and 9.1 g (60 mmoles) of tert-butyldimethylsilyl chloride was added to a solution of 10.0 g (46.29 mmoles) of (XXXI) in 100 ml of DMF. The mixture was allowed to stand for 22 h at 20°C, then was poured into water and extracted with $CHCl_3$. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in benzene. The yield of (XXIX) was 14.0 g (91%), syrup, $[\alpha]_D^{23}$ +159° (C 1.1). PMR spectrum: 0.1 s and 0.14 s (6H, $OSi\underline{Me}_2Bu$-t), 0.87 d (3H, $J_{CH_3,2}$ = 7 Hz, CH_3 at C^2), 0.9 s (9H, $OSiMe_2\underline{Bu}$-t), 1.95 d.d.q (1H, $J_{2,1}$ = 2, $J_{2,3}$ = 3.6 Hz, H^2), 2.0 br. s (3H, CH_3 at C^4), 3.55 s (3H, MeO at C^1), 3.74 br. d (1H, H^3), 3.79 s (3H, MeO at C^6), 4.89 d (1H, H^1).

Methyl (methyl-2,4-didesoxy-2,4-di-C-methyl-3-O-tert-butyl-dimethylsilyl-β-L-idopyranosyl)uronate (XXVII) and Methyl (methyl-2,4-didesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-α-D-galactopyranosyl)uronate (XXXII). A solution of 0.158 g (0.478 mmole) of (XXIX) in 5 ml of MeOH was hydrogenated over 0.1 g of Pd/C at 40°C for 10 h. The catalyst was filtered off and washed with MeOH, the filtrate was evaporated, and the residue was chromatographed in the heptane–EA (4:1) system. The yield of (XXVII) was 0.068 g (43%), syrup $[\alpha]_D^{22}$ +135° (C

1.2). The yield of (XXXII) was 0.085 g (53%), syrup $[\alpha]_D^{22}$ +120° (C 1.0). PMR spectrum of (XXVII): 0.07 s and 0.09 s (6H, $OSiMe_2Bu$-t), 0.88 s (9H, $OSiMe_2Bu$-t), 0.98 d and 1.01 d (6H, $J_{CH_3,4} = J_{CH_3,2} = 8.7$ Hz, CH_3 at C^2 and C^4), 1.82 d.d.q (1H, $J_{2,3} = J_{2,1} = 3.5$ Hz, H^2), 1.96 d.d.q (1H, $J_{4,5} = J_{3,4} = 3.5$ Hz, H^4), 3.5 s (3H, MeO at C^1), 3.78 m (4H, MeO at C^6 and H^3), 4.51 d (1H, H^5), 4.67 d (1H, H^1). PMR spectrum of (XXXII): 0.09 s (6H, $OSiMe_2Bu$-t), 0.9 s (9H, $OSiMe_2Bu$-t), 0.91 d, (6H, $J_{CH_3,2} = 3.5$ Hz, H^2), 2.23 d.d.q (1H, $J_{4,3} = 5$, $J_{4,5} = 2.5$ Hz, H^4), 3.35 s (3H, MeO at C^1), 3.80 s (3H, MeO at C^6), 3.85 d.d (1H, H^3), 4.48 d (1H, H^5), 4.67 d (1H, H^1).

Methyl-2-desoxy-2,4-di-C-methyl-3-O-acetyl-5-methoxycarbonyl-β-L-threo-pent-4-enopyranoside (XXX). A 12 ml portion (87 mmoles) of Et_3N, 2.95 ml (34.8 mmoles) of Ac_2O and 15 mg of 4-dimethylaminopyridine was added to a solution of 3.76 g (17.4 mmoles) of (XXXI) in 75 ml of CH_2Cl_2. The mixture was allowed to stand for 2 h at ~20°C, and then was decomposed by 1 M HCl solution and extracted with $CHCl_3$. The extract was washed with a saturated solution of $NaHCO_3$ and NaCl, and dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (9:1) system. The yield of (XXX) was 4.2 g (93%), syrup, $[\alpha]_D^{23}$ +258.8° (C 1.02). PMR spectrum: 0.93 d (3H, $J_{CH_3,2} = 7$ Hz, CH_3 at C^2), 1.91 d (3H, $J_{CH_3,3} = 1$ Hz, CH_3 at C^4), 2.07 d.d.q (1H, $J_{1,2} = 2.5$, $J_{2,3} = 7$ Hz, H^2), 2.10 s (3H, $OCOCH_3$ at C^3), 3.50 s (3H, MeO at C^1), 3.80 s (3H, MeO at C^6), 4.79 d (1H, H^1), 5.24 d.d (1H, H^3).

Methyl (methyl-2,4-di-C-methyl-3-O-acetyl-β-L-idopyranosyl)uronate (XXVIII). A solution of 4.2 g (16.2 mmoles) of (XXX) in 50 ml of MeOH was hydrogenated over 1.5 g of Pd/C at 40°C for 30 h. The catalyst was filtered off, washed with MeOH, the filtrate was evaporated, and the residue was recrystallized from ether. Yield 4.21 g (100%), mp 104-105°C, $[\alpha]_D^{22}$ +235° (C 1.0). PMR spectrum: 0.96 d (3H, $J_{CH_3,2} = 7$ Hz, CH_3 at C^2), 1.04 d (3H, $J_{CH_3,4} = 7$ Hz, CH_3 at C^4), 1.90 d.d.q (1H, $J_{2,1} = 3.2$, $J_{2,3} = 6.0$ Hz, H^2), 2.04 s (3H, $OCOCH_3$ at C^3), 2.10 d.d.q (1H, $J_{4,5} = 4$, $J_{4,3} = 6$ Hz, H^4), 3.40 s (3H, MeO at C^1), 3.72 s (3H, MeO at C^6), 4.32 d (1H, H^5), 4.6 d (1H, H^1), 5.07 d.d (1H, H^3).

Methyl (methyl-2,4-didesoxy-2,4-di-C-methyl-β-L-idopyranosylseleno)uronate (XXXIII). A 1.42 ml portion of a 2N solution (2.84 mmoles, 2.5 eq.) of $Me_2AlSeMe$ in toluene was added at −10°C to a solution of 0.148 g (0.569 mmole) of (XXVIII) in 3 ml of abs. ether. The mixture was allowed to stand for 50 h at ~20°C, then was decomposed with an excess of $Na_2SO_4 \cdot 10H_2O$ and filtered. The precipitate was washed with $CHCl_3$, the filtrate was evaporated and the residue was chromatographed in a heptane–EA (3:1) system. Yield, 0.147 g (93%), syrup, $[\alpha]_D^{22}$ +146° (C 1.91). PMR spectrum: 1.02 d and 1.06 d (6H, $J_{CH_3,2} = J_{CH_3,4} = 7$ Hz, CH_3 at C^2 and C^4), 1.95 d.d.q (1H, $J_{2,1} = J_{2,3} = 3$ Hz, H^2), 2.10 m (1H, $J_{4,3} = 3$, $J_{4,5} = 3.5$ Hz, H^4), 2.14 s (3H, COSeMe), 3.56 s (3H, MeO at C^1), 3.81 d.d (1H, H^3), 4.4 d (1H, H^5), 4.80 d (1H, H^1).

Methyl-2,4,7 tridideoxy-2,4-di-C-methyl-6-oxo-β-L-idoheptopyranoside (XXVI).* A 1.98 ml portion of 1.56 N solution of MeLi in ether (3.09 mmoles) was added at −35°C to a suspension of 0.222 g (1.547 mmole) of CuBr in 5 ml of ether. The mixture was stirred for 10 min, cooled to −78°C, and a solution of 0.115 g (0.409 mmole) of (XXXIII) in 5 ml of ether was added. The mixture was allowed to stand for 10 min, and then was decomposed with saturated NH_4Cl, filtered through Celite, and extracted with ether. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (3:1) system. Yield 0.081 g (98%).

Methyl-2,4,7-tridesoxy-2,4-di-C-methyl-3-O-tert-butyldimethyl-6-oxo-β-L-idoheptopyranoside (X). A 0.12 g portion (2 mmoles) of imidazole and 0.105 g (0.7 mmole) of tert-butyldimethylsilyl chloride were added to a solution of 0.0444 g (0.22 mmole of (XXII) in 1 ml of DMF. The mixture was allowed to stand for 12 h at ~20°C, then was diluted with water and extracted with ether. The extract was washed with water and a saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed in a heptane–ether (9:1) system. The yield of (X) was 0.068 g (98%), syrup, $[\alpha]_D^{23}$ +87°C (C 1.13). PMR spectrum: 0.07 s (6H, $OSiMe_2Bu$-t), 0.89 s (9H, $OSiMe_2Bu$-t), 0.93 d and 1.01 d (6H, $J_{CH_3,2} = J_{CH_3,4} = 7.2$ Hz, CH_3 at C^2 and C^4), 1.96 d.d.q (1H, $J_{1,2} = 3$, $J_{2,3} = 2.5$ Hz, H^2), 2.0 d.d.q (1H, $J_{4,5} = 3.5$, $J_{4,3} = 2.5$ Hz, H^4), 2.25 s (3H, CH_3 at C^6), 3.55 s (3H, MeO at C^1), 3.72 d.d (1H, H^3), 4.32 d (1H, H^5), 4.71 d (1H, H^1).

*As in Russian Original – Editor.

CONCLUSIONS

1. The general strategy for the synthesis of erythronolide B from levoglucosan was analyzed.

2. The stereochemistry of the hydrogenation of the double bond in certain $\Delta^{4,5}$-enopyranosides was investigated.

3. The synthesis of methyl-2,4,7-tridesoxy-2,4-di-C-methyl-3-O-tert-butyldimethylsilyl-6-oxo-β-L-idoheptopyranoside, the C^1–C^6 fragment of erythronolides A and B, was carried out.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

12.* SYNTHESIS OF C^1–C^8 FRAGMENTS OF ERYTHRONOLIDES A AND B

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We have already discussed [1] the possible scheme of preparation of erythronolide B from levoglucosan via seco-acid derivatives of erythronolide B (I) or (II), which were retrosynthetically reduced to fragments C^1–C^8 (IV) and (V) and C^9–C^{13} (III). Further retrosynthetic analysis of (IV) and (V) leads the C^1–C^6 fragments (VI) and (VII). We have already described the synthesis of fragments (III) [2] and (VII) [1]. In accordance with the accepted scheme [1], we describe in the present work the synthesis of the C^1–C^6 fragment in the acyclic form (VI) and two forms of the C^1–C^6 fragment (IV) and (V) (scheme 1).

The stereochemistry of the C^2–C^4 section of the chain of compound (VI) (scheme 2) coincides with that of the C^2–C^4 part of the 1,6-anhydro derivative (VIII) that we previously obtained from levoglucosan in five steps in an overall yield of 54% [3]. To pass from the bicyclic derivative (VIII) to the acyclic compound (VI), the C^1-center must be masked by a group which is relatively inert under the experimental conditions of subsequent synthesis, the chain at the C^6 atom must be extended by one carbon unit, and lastly, the configuration of the C^5-center has to be inverted (see top of following page).

The consecutive mercaptolysis of compound (VIII) [4], the selective acetylation of the primary hydroxyl in the triol formed (Ac_2O, Py) and setting up of the 3,5-O-isopropylidene protection carried out without separation of the intermediate products, resulted in the formation of derivative (IX) in 67% yield. The hydrolysis of (IX) under mild conditions [5] gives in a high yield aldehyde (X), which was entered into the reaction with Ph_3PCH_2. Thus,

*For previous communication, see [1].

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