2.78 ($COCH_2$). IR spectrum ($\nu[\delta]$, cm^{-1}): 2960 (CH_3), 2860 (CH_3, in $-OCH_3$), 1740 (C=O), [1460, 1375] (CH_3), [1300, 1255] (CH_2), 1200 (C–O), 1100 (Si–OCH_3), 690 (Si–O–C).

Trimethoxy(benzoyloxy)silane (IX). Mass spectrum, m/z (%): 242 (26), 211 (74), 210 (64), 180 (40), 167 (19), 137 (2), 136 (3), 122 (51), 121 (17), 105 (100), 91 (20), 90 (5), 77 (64). PMR spectrum (δ, ppm): 3.62 (CH_3O), ~7.10 (C_6H_5). IR spectrum ($\nu[\delta]$, cm^{-1}): 2955 (CH_3), 2860 (CH_3, in $-OCH_3$), 1690 (C=O), 1585, 1455 (C_6H_5), [1435] (CH_3), 1200 (C–O), 1175 (C_6H_5), 1100 (Si–OCH_3), 1030 (Si–O), [770, 710] (C_6H_5), 685 (Si–O–C).

Phenoxy(triacetoxy)silane (XI). IR spectrum ($\nu[\delta]$, cm^{-1}): 1720 (C=O), 1600, 1500 (C_6H_5), [1385] (CH_3), 1070 (Si–O), 1125 (C_6H_5), 1230 (C–O), [760, 695] (C_6H_5), 680 (Si–O–C).

CONCLUSIONS

Alkoxychlorosilanes react with trimethylacyloxysilanes to give the difficultly accessible alkoxy(acyloxy)silanes of general formula $(RO)_nSi(OCOR)_{4-n}$ (n = 1-3) in 60-80% yields.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

16.* SYNTHESIS OF ERYTHRONOLIDES A AND B BY A COUPLING SCHEME OF (C^5-C^9) + (C^3-C^4) + (C^1-C^2) + (C^{10}) + (C^{11}-C^{13}) FRAGMENTS AND SYNTHESIS OF THE C^5-C^9 FRAGMENT

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M. S. Ermolenko, and D. V. Yashunskii

UDC 542.91:547.455

In the preceding articles in this series [1, 2] we have described a stereodirected synthesis of erythronolide B, based on coupling of fragments in the (C^9-C^{13}) + (C^7-C^8) + (C^1-C^6) sequence.

The aim of the investigation described in the present and in the succeeding articles is to develop a new strategy of a stereodirected synthesis of aglycones of macrolide antibiotics of an erythromycin complex, based on the use of fragments obtained from carbohydrates, differing from the structure of fragments that we have previously used.

As a result of the structural uniformity of erythronolides A (I) and B (II), their synthesis can be directed through monotypic 9(S)-dihydro derivatives (III) and (IV), in which the hydroxyl group at C^9 can be selectively oxidized [3], so that they can be used at the stage of macrolactonization of bis(cyclo)acetal derivatives of type (V) and (VI), whose synthetic precursors are derivatives (VII) and (VIII). The dihydroxyl derivatives (VII) and (VIII) in turn can be obtained by selective reduction of β-hydroxy ketones (IX) and (X), which can be synthesized by an aldol addition of a Z(O)enolate of ketone (XV), which is a C^1-C^{10}-fragment common to erythronolides A and B, to alkoxyaldehydes (XI) and (XII), the synthesis of which from carbohydrates has already been described by us in [4, 5] (see scheme on following page).

Further retrosynthetic breaking up of the revealed C^1-C^{10}-fragment leads to a five-carbon C^5-C^9-fragment (XVII). It was decided to build on the C^2-C^5 chiral centers on transition from (XVII) to (XV) by successive addition of tri-n-butylcrotyltin (TBCT) to

*For previous communications, see [1].

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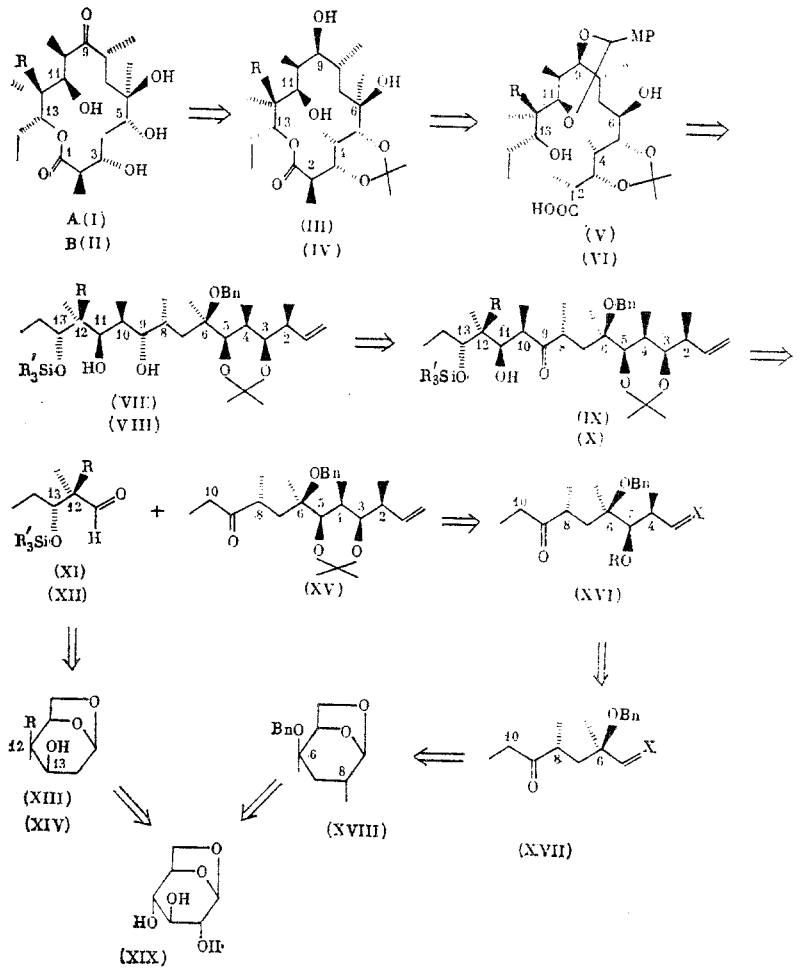
Scheme 1



A (I) : R = OH; B (II) : R = H; X = O; X = CH_2, R = H (XVI); X = O, X = CH_2 (XVII)

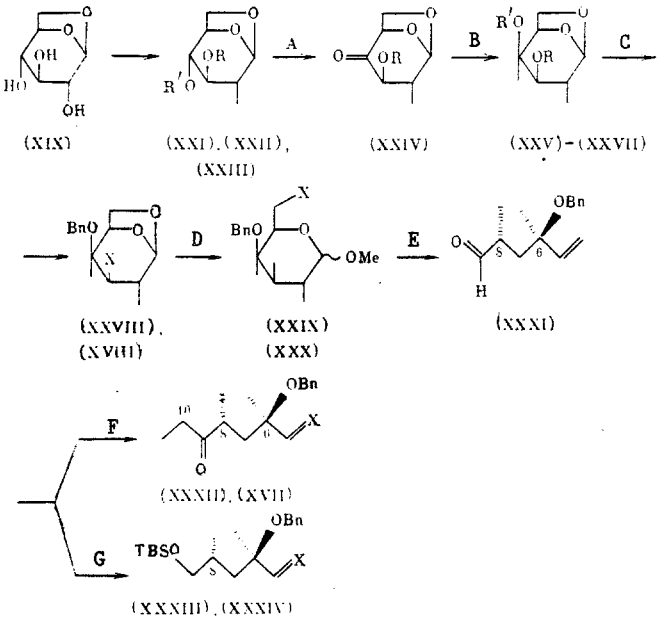
ketoaldehydes (XVII) and (XVI), whereby the homoallyl alcohol [structure (XVI), X = CH_2], formed in the reaction of TBCT with aldehyde (XVII), is a synthetic precursor of β-alkoxy-aldehyde (XVI), X = O.

The C^5-C^9 fragment (XVII), in turn, is retrosynthetically converted to the 1,6-anhydro derivative (XVIII) which can be obtained by stereospecific transformations of levoglucosan (XIX).

The synthesis of compound (XVIII) was accomplished via the bicyclic derivative (XXVI) (scheme 2), obtained from levoglucosan (XIX) by a method that we have previously developed for the synthesis of 3,4-di-O-benzyl analog of compound (XXVI) [6]. Treatment of compound (XXVI) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with wet CH_2Cl_2 [7] results in a selective removal of the p-methoxybenzyl (MPM) protecting group (see scheme on following page). The alcohol (XXVII) obtained is converted into derivative (XVIII) by free-radical deoxygenation of xanthate (XXVIII) [8]. Compound (XVIII) is a cyclic precursor of the C^5-C^9-fragment of erythronolides A and B.

The methanolysis of the desoxy derivative (XVIII) results in a mixture (9:2) of α- and β-methylglycosides (XXIX) in a high yield. This mixture was converted without separation into 6-desoxy-6-bromo-derivatives (XXX), which on boiling with an activated zinc dust in an i-PrOH–H_2O system (14:1) undergo reductive elimination with the formation of a single product, the unsaturated aldehyde (XXXI). It should be noted that carrying out of this reaction in a 96% EtOH or n-PrOH–H_2O (14:1) systems [9] was accompanied by the formation of considerable amounts of the corresponding dialkylacetals.

Scheme 2



X = O (XVII), H (XVIII); R = H, R′ = All (XXI); R = MPM, R′ = All (XXII); R = = MPM, R′ = H (XXIII); R = MPM (XXIV); R = MPM, R′ = H (XXV); R = MPM, R′ = Bn (XXVI); R = H, R′ = Bn (XXVII); X = OCS_2Me (XXVIII); X = OH (XXIX), Br (XXX), CH_2 (XXXII), (XXXIII), O (XXXIV).

A. $(COCl)_2$, DMSO, Et_3N—CH_2Cl_2—60°; B. 1) MeMgCl—THF, —40°; 2) NaH, BnBr—DMF; 3) DDQ — CH_2Cl_2/H_2O; C. 1) NaH, CS_2, MeI— THF; 2) *n*-Bu_3SnH, AIBN—$PhCH_3$; D. 1) 5% HCl—MeOH; 2) PPh_3, CBr_4—Py, 60°; E. Zn/H^+—*i*-PrOH—H_2O (14:1), boiling F. 1) EtMgBr— THF, —50°; 2) $(COCl)_2$, DMSO, Et_3N—CH_2Cl_2, —60°; 3) O_3—MeOH, —78°; G. 1) $LiAlH_4$—Et_2O, —50°; 2) TBSCl, imidazole—DMF; 3) O_3—CH_2Cl_2/Py, —78°.

Aldehyde (XXXI) was further converted into ketone (XXXII), the ozonolysis of the double bond in which led to ketoaldehyde (XVII). Taking into account the different reactivities of the keto- and aldehyde groups in derivative (XVII), we hoped to carry out the successive extension of the C^1-C^4-fragment of the carbon chain by a selective reaction of the TBCT with the aldehyde group. However, it was seen from even the first experiments that the reaction proceeds with respect to both of the carbonyl groups. This fact compelled us to change the tactic of the synthesis in some respects.

Aldehyde (XXXI) was converted in two stages into a silyl ether (XXXIII), the ozonolysis of the double bond in which resulted in aldehyde (XXXIV) in high yield, which is the C^5-C^9-fragment of erythronolides A and B. The use of aldehyde (XXXIV) in the synthesis of C^1-C^{10}-fragment (XV) will be discussed in the succeeding article.

EXPERIMENTAL

The PMR spectra were taken in $CDCl_3$ solutions on a "Bruker WM-250" spectrometer. The specific rotation was measured on a Perkin—Elmer M-141 polarimeter in $CHCl_3$. The course of the reactions was monitored by TLC on plates with silica gel from E. Merck. The compounds were purified and the reaction mixtures were separated by high performance liquid chromatography (HPLC) in a column with a Silpearl silica gel (25-40 μm).

Absolute solvents were obtained by distillation in argon atmosphere over the appropriate drying agents, directly before use. Benzene, pyridine, hexane, diisopropylamine, DMSO, and triethylamine were distilled over CaH_2. The ether and THF were held over the alkali and distilled over $LiAlH_4$. Methylene chloride CH_2Cl_2 was distilled first over P_2O_5, and then over powdered CaH_2.

1,6-Anhydro-2-desoxy-2-C-methyl-4-O-allyl-3-O-(4-methoxybenzyl)-β-D-glucopyranose (XXII). A solution of 0.4 g (2.03 mmoles) of (XXI) in 5 ml of DMF was stirred for 1.5 h with 0.974 g (4.06 mmoles) of NaH, 0.33 ml (2.45 mmoles) of 4-methoxybenzyl chloride was added, and the mixture was stirred for 2 h. The excess NaH was decomposed by MeOH, diluted

with water and extracted with (3 × 30 ml) of 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 (3:1) system. Yield, 0.619 g (95%), mp 37°C (heptane–EA, 10:1), $[\alpha]_D^{20} = -33.2°$ (C 1.0). PMR spectrum (δ, ppm, J, Hz): 5.3 d (1H, $J_{1,2}$ = 1.8, H^4), 1.97 br. q (1H, H^2), 3.29 m (1H, $J_{2,3} = J_{3,5}$ = 1.5, H^3), 3.38 br. s (1H, H^4), 4.58 br. d (1H, H^5), 4.12 d.d (1H, $J_{5,6}$ endo = 1.25, $J_{6,6}$ = 7, H^6 endo), 3.78 d.d (1H, $J_{5,6}$ exo = 6, H^6 exo), 4.45 d and 4.54 d (2H, AB-system, J_{gem} = 11.5, $CH_3OC_6H_4\underline{CH_2}O$), 4.25 d.t, 5.2 d.q, 5.27 d.q, 5.9 d.d.t (5H, CH_2=CH–CH_2O–), 1.06 d (3H, J_{2,CH_3} = 7, CH_3 at C^2), 3.81 s (3H, $CH_3OC_6H_4$) 6.88 m and 7.26 m (4H, aromatic protons). Found: C 67.12; H 7.47%. $C_{18}H_{24}O_5$. Calculated: C 67.47; H 7.55%.

1,6-Anhydro-2-desoxy-2-C-methyl-3-O-(4-methoxybenzyl)-β-D-glucopyranose (XXIII). A 0.27 g portion (2.32 mmoles) of t-BuOK was added in an argon atmosphere to a solution of 0.619 g (1.93 mmoles) of (XXII) in 4 ml of DMSO. The mixture was stirred for 2 h, poured into water, and extracted with $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was dissolved in 30 ml of an acetone–water (9:1) mixture, 0.616 g (1.93 mmoles of $Hg(OAc)_2$ was added, the mixture was stirred for 10 min, and evaporated. The residue was diluted with water and extracted with $CHCl_3$. The extract was washed with water, a 10% solution of KI, water, and a saturated solution of NaCl, dried over Na_2SO_4, evaporated and the residue was chromatographed in a heptane–EA (2:3) system. Yield, 0.483 g (90.6%), mp 91.5°C (ether), $[\alpha]_D^{20} = -41.8°$ (C 1.1). PMR spectrum (δ, ppm, J, Hz): 5.31 br. s (1H, H^1), 2.0 br. q (1H, H^2), 3.3 m (1H, $J_{3,2} = J_{3,4}$ = 1.5, H^3), 3.68 br.d (1H, $J_{OH,4}$ = 9, H^4), 4.5 m (1H, H^5), 4.25 d.d (1H, $J_{5,6}$ endo = 1.2, $J_{6,6}$ = 7, H^6 endo), 3.76 d.d (1H, $J_{5,6}$ exo = 6, H^6 exo), 1.1 d (3H, J_{2,CH_3} = 7.5, CH_3 at C^2), 3.81 s (3H, $\underline{CH_3}OC_6H_4CH_2O$), 4.46 d and 4.54 d (2H, AB-system, J_{gem} = 11, $CH_3OC_6H_4\underline{CH_2}O$), 6.80-7.20 m (4H, $CH_3\underline{OC_6H_4}CH_2O$). Found: C 64.17; H 7.36%. $C_{15}H_{20}O_5$. Calculated: C 64.26; H 7.19%.

1,6-Anhydro-2-desoxy-2-C-methyl-3-O-(4-methoxybenzyl)-β-D-xylo-hexapyranoz-4-ylose (XXIV). A solution of 3.51 ml (49.56 mmoles) of DMSO in 5 ml of CH_2Cl_2 was added at –60°C to a solution of 3.14 ml (24.78 mmoles) of $(COCl)_2$ in 30 ml of CH_2Cl_2, and the mixture was stirred for 10 min. A solution of 5.97 g (20.65 mmoles) of (XXIII) in 30 ml of CH_2Cl_2 was added, the mixture was stirred for 25 min, then 13.81 ml (99.12 mmoles) of Et_3N were added and the mixture was stirred for 5 min. The temperature was raised to 0°C and 105 ml of 1 N HCl were added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The extract was washed with water, a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was crystallized from ether, and the mother liquor was chromatographed in a heptane–EA (3:1) system. Yield, 5.56 g (97%), mp 81.5°C, $[\alpha]_D^{22} = +76.1°$ (C 2.35). PMR spectrum (δ, ppm, J, Hz): 5.35 s (1H, H^1), 1.87 d.q (1H, J_{2,CH_3} = 7, H^2), 3.81 d (1H, H^3), 4.65 br.d (1H, H^5), 3.96 d (1H, $J_{6,6}$ = 7, H^6 endo), 3.72 d.d (1H, $J_{5,6}$ = 5, H^6 exo), 1.2 d (3H, CH_3 at C^2), 3.81 s (3H, $\underline{CH_3}OC_6H_4CH_2O$), 4.42 d and 4.86 d (2H, J_{gem} = 11. AB-system, $CH_3OC_6H_4\underline{CH_2}O$), 6.89 m and 6.31 m (4H, $CH_3OC_6\underline{H_4}CH_2O$). Found: C 64.89; H 6.18%. $C_{15}H_{18}O_5$. Calculated: C 64.73; H 6.51%.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-(4-methoxybenzyl)-β-D-galactopyranose (XXV). An 11 ml portion of a 2 N solution of MeMgCl in THF was added at –40°C to a solution of 5.127 g (18.42 mmoles) of (XXIV) in 40 ml of THF. The mixture was stirred for 10 min, then heated to ~20°C and decomposed with a saturated solution of NH_4Cl. The precipitate was filtered and washed with ether. The filtrate was evaporated, and the residue was crystallized from hexane. Yield, 5.31 g (98%), mp 64.5°C, $[\alpha]_D^{20} = -85.3°$ (C 0.75). PMR spectrum (δ, ppm, J, Hz): 5.25 br.s (1H, H^1), 2.21 br.q (1H, H^2), 3.12 s (1H, H^3), 4.02 br.d (1H, H^5), 4.23 d (1H, $J_{6,6}$ = 7.5, H^6 endo), 3.63 d.d (1H, $J_{5,6}$ exo = 5.5, H^6 exo), 1.08 d (3H, J_{2,CH_3} = 7.5, CH_3 at C^2), 1.42 s (3H, CH_3 at C^4), 3.91 s (1H, OH at C^4), 4.32 d and 4.65 d (2H, J_{gem} = 11. AB-system, $CH_3OC_6H_4\underline{CH_2}O$), 3.8 s (3H, $\underline{CH_3}OC_6H_4CH_2O$), 6.9 m and 7.26 m (4H, $CH_3OC_6H_4CH_2O$). Found: C 65.23; H 7.64%. $C_{16}H_{22}O_6$. Calculated: C 65.28; H 7.53%.

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-3-O-(4-methoxybenzyl)-4-O-benzyl-β-D-galactopyranose (XXVI). A solution of 0.526 g (1.78 mmoles) of (XXV) in 5 ml of DMF was stirred for 1.5 h with 0.086 g (3.56 mmoles) of NaH. The mixture was cooled to 10°C, 0.364 g (2.136 mmoles) of BnBr was added, and the mixture was stirred for 2 h. The excess NaH was decomposed with MeOH, the mixture was diluted with water, and extracted with ether. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated.

The residue was chromatographed in a heptane–EA (3:1) system. Yield, 0.636 g (93%), syrup, $[\alpha]_D^{20} = -22.7°$ (C 4.15). PMR spectrum (δ, ppm, J, Hz): 5.38 br.s (1H, H^1), 2.37 br.q (1H, H^2), 3.43 br.s (1H, H^3), 4.21 br.d (1H, H^5), 4.79 d (1H, $J_{6,6} = 6.7$, H^6 endo), 3.73 d.d (1H, $J_{5,6\ exo} = 5.5$, H^6 exo), 1.2 d (3H, $J_{2,CH_3} = 8$, CH_3 at C^2), 1.61 s (3H, CH_3 at C^4), 3.88 s (3H, $\underline{CH_3}OC_6H_4CH_2O$), 4.4 d and 4.7 d (2H, $J_{gem} = 11$, AB-system, $CH_3OC_6H_4\underline{CH_2}O$), 4.5 m (2H, $J_{gem} = 10.5$ AB-system, $C_6H_5CH_2O$), 6.9 m and 7.35 m (9H, aromatic protons).

1,6-Anhydro-2-desoxy-2,4-di-C-methyl-4-O-benzyl-β-D-galactopyranose (XXVII). A 0.45 g portion (1.98 mmoles) of DDQ was added to a solution of 0.384 g (0.998 mmole) of (XXVI) in a mixture of 12 ml of CH_2Cl_2 and 0.6 ml of water. The mixture was stirred for 20 min, was then filtered through celite and the residue was washed with $CHCl_3$. The filtrate was washed with a saturated solution of $NaHCO_3$, water, and a saturated solution of NaCl, dried over Na_2SO_4, evaporated, and the residue was chromatographed in a heptane–EA (3:2) system. Yield, 0.224 g (85%), syrup, $[\alpha]_D^{20} = -14.8°$ (C 6.7). PMR spectrum (δ, ppm, J, Hz): 5.3 br.s (1H, H^5), 2.19 br.q (1H, H^2), 3.57 m (1H, $J_{2,3} = J_{3,5} = J_{1,3} = 1.5$, H^3), 4.24 br.d (1H, H^5), 4.42 d (1H, $J_{6,6} = 7.5$, H^6 endo), 3.64 d.d (1H, $J_{5,6\ exo} = 5.5$, H^6 exo), 1.11 d (3H, $J_{2,CH_3} = 7.5$, CH_3 at C^2), 1.56 s (3H, CH_3 at C^4), 4.5 d and 4.64 d (2H, AB-system, $C_6H_5\underline{CH_2}O$), 7.35 m (5H, $\underline{C_6H_5}CH_2O$).

1,6-Anhydro-2,3-didesoxy-2,4-di-C-methyl-4-O-benzyl-β-D-galactopyranose (XXIII). A solution of 4.81 g (18.2 mmoles) of (XXVII) in 80 ml of THF was stirred for 1 h with 0.873 g (36.4 mmoles) of NaH and 20 mg of imidazole, then 2.2 ml (36.4 mmoles) of CS_2 were added, and stirring was continued for 20 min. A 2.26 ml portion (36.4 mmoles) of MeI was added, and the mixture was stirred for 1 h. The excess NaH was decomposed with MeOH, the mixture was evaporated, water was added to the residue, and the mixture was extracted with 100 ml of $CHCl_3$. The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and evaporated. The residue was dissolved in 50 ml of $PhCH_3$ and 5.4 ml (20 mmoles) of Bu_3SnH were added. The mixture was heated to boiling and a few drops of a 10% solution of azoisobutyronitrile in $PhCH_3$ were added. At the end of a vigorous reaction, boiling was continued for 2 h. The mixture was evaporated, and the residue was chromatographed in a hexane–ether (0 → 30%) system. Yield, 3.88 g (86%), syrup, $[\alpha]_D^{20} = -16.6°$ (C 1.2). PMR spectrum (δ, ppm, J, Hz): 5.24 s (1H, H^1), 1.98 d.q (1H, H^2), 2.11 d.d (1H, $J_{3,3} = 13.0$, $J_{3e,2} = 7.2$, H^{3e}), 1.62 br.d (1H, H^{3a}), 4.18 br.d (1H, H^5), 4.37 d (1H, $J_{6,6} = 7.25$, H^6 endo), 3.69 d.d (1H, $J_{5,6} = 5$, H^6 exo), 1.1 d (3H, $J_{2,CH_3} = 7.2$, CH_3 at C^2), 1.6 s (3H, CH_3 at C^4), 4.42 d and 4.52 d (2H, $J_{gem} = 11$, AB system, $Ph\underline{CH_2}O$), 7.33 m (5H, $\underline{Ph}C_2O$).

Methyl-2,3-didesoxy-2,4-di-C-methyl-4-O-benzyl-α- and Methyl-2,3-didesoxy-2,4-di-C-methyl-4-O-benzyl-β-D-galactopyranosides (XXIX). A solution of 5.4 g (21.75 mmoles) of (XVIII) in 100 ml of a 5% solution of HCl in MeOH was allowed to stand for 12 h at 20°C. The mixture was poured into a 5% solution of $NaHCO_3$ and extracted with $CHCl_3$ (2 × 100 ml). The extract was washed with water and a saturated solution of NaCl, dried over Na_2SO_4 and evaporated. Yield 6 g (100%). A 120 mg portion of the anomers was chromatographed in a heptane–EA (1:1) system. The yield of the α-anomer was 85 mg (70%), and of the β-anomer 35 mg (30%). α-Anomer, syrup, $[\alpha]_D^{20} = +91.0°$ (C 1.2). PMR spectrum of α-anomer (δ, ppm, J, Hz): 4.61 d (1H, $J_{1,2} = 3.5$, H^1), 2.15 m (1H, H^2), 1.89 d.d (1H, $J_{3a,3e} = 14.5$, $J_{3e,2} = 4$, H^{3e}), 1.49 d.d (1H, $J_{3a,2} = 13.0$, H^{3a}), 3.59 d.d ($J_{5,6} = 5.5$ and 3, H^5), 4.1 d.d.d (1H, $J_{6',6} = 11.5$, $J_{6,OH} = 1.2$, H^6), 3.77 d.d.d (1H, $J_{6',OH} = 10$, $H^{6'}$), 2.9 d.d (1H, OH), 0.9 d (3H, $J_{2,CH_3} = 7$, CH_3 at C^2), 1.26 s (3H, CH_3 at C^4), 3.38 s (3H, MeO at C^1), 4.42 (2H, AB system, $C_6H_5\underline{CH_2}O$), 7.3 m (5H, $\underline{C_6H_5}CH_2O$). PMR spectrum of β-anomer (δ, ppm, J, Hz): 4.0 d (1H, $J_{1,2} = 8$, H^1), 1.9 m (1H, H^2), 2.15 d.d (1H, $J_{3,3} = 14.5$, $J_{3e,2} = 4$, H^{3e}), 1.11 d.d (1H, $J_{3a,2} = 12.5$, H^{3a}), 3.39 d.d (1H, $J_{5,6} = 6.7$, $J_{5,6'} = 3$, H^5), 4.1 d.d (1H, $J_{6,6'} = 11.5$, H^6), 3.8 m (1H, $H^{6'}$), 2.62 br.d (1H, OH), 0.92 d (3H, $J_{2,CH_3} = 6.7$, CH_3 at C^2), 1.21 s (3H, CH_3 at C^4), 3.52 s (3H, MeO at C^1), 4.41 (2H, AB system, $Ph\underline{CH_2}O$), 7.3 m (5H, $\underline{Ph}CH_2O$).

Methyl-2,3,6-tridesoxy-2,4-di-C-methyl-6-bromo-4-O-benzyl-α- and Methyl-2,3,6-tridesoxy-2,4-di-C-methyl-6-bromo-4-O-benzyl-β-D-galactopyranosides (XXX). A 1.19 g portion (4.56 mmoles) of PPh_3 and 1.54 g (4.56 mmoles) of CBr_4 were added to a solution of 0.64 g (2.28 mmoles) of a mixture of α,β-anomers (XXIX) in 10 ml of absolute pyridine. The reaction mixture was stirred for 3 h at 60°C and 1 ml of MeOH was added. The mixture was cooled, poured into 200 ml of 1 N HCl, 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 hexane–ether (9:1) system. Yield, 0.76 g (96.7%). α-Anomer, syrup, $[\alpha]_D^{20} =$

+95.2° (C 1.2). PMR spectrum (δ, ppm, J, Hz): 6.1 d (1H, $J_{1,2}$ = 3.2, H^1), 2.12 m (1H, H^2), 1.88 d.d (1H, $J_{3,3}$ = 14, $J_{3e,2}$ = 3.8, H^{3e}), 1.5 d.d (1H, $J_{3a,1}$ = 3, H^{3a}), 3.81 (1H, X-part of ABX system, H^5), 3.48 s (3H, MeO at C^1), 1.22 s (3H, CH_3 at C^4), 0.9 d (3H, J_{2,CH_3} = 7, CH_3 at C^2), 3.7 (2H, AB-part of ABX system, H^6, $H^{6'}$), 4.42 (2H, AB-system, $PhCH_2O$), 7.3 m, 5H, $PhCH_2O$). PMR spectrum of β-anomer (δ, ppm, J, Hz): 4.0 d (1H, $J_{1,2}$ = 8.5, H^1), 1.9 m (1H, H^2), 2.18 d.d (1H, $J_{3,3}$ = 15, $J_{3e,2}$ = 4, H^{3e}), 1.12 d.d (1H, $J_{3a,2}$ = 12.5, H^{3a}), 3.5 d.d (1H, $J_{5,6}$ = 2.5, $J_{5,6'}$ = 9, H^5), 6.8 d.d (1H, $J_{6,6'}$ = 11, H^6), 7.5 d.d (1H, H^6), 3.57 s (3H, MeO, at C^1), 1.22 s (3H, CH_3 at C^4), 0.94 d (3H, J_{2,CH_3} = 7, CH_3 at C^2), 4.42 (2H, AB-system, $PhCH_2O$), 7.32 m (5H, $PhCH_2O$).

(3R,5R)-3-Benzyloxy-6-tert-butyldimethylsiloxy-3,5-dimethylhex-1-ene (XXXIII). A 2.33 g portion (35.6 mmoles) of activated zinc dust was added to a solution of 0.245 g (0.7 mmole) of a mixture of bromides (XXX) in 8 ml of an i-PrOH-H_2O (14:1) mixture. The mixture was boiled for 1 h, then cooled, filtered through a celite layer, diluted with water, and extracted with ether (3 × 10 ml). The extract was dried over Na_2SO_4 and evaporated. The residue (0.158 g, 96%) was dissolved in 2 ml of ether, and 0.25 ml of 1 M solution of $LiAlH_4$ in THF was added at −50°C. The mixture was allowed to stand for 30 min, then heated to 0°C, and decomposed by $Na_2SO_4 \cdot 10H_2O$. The mixture was filtered through celite, the precipitate was washed with ether, and the filtrate was evaporated. The residue was dissolved in 1 ml of DMF and 0.19 g (1.26 mmoles) of TBSCl and 0.17 g (2.51 mmoles) of imidazole were added to the solution. The mixture was allowed to stand at ~20°C for 12 h. A 20 ml portion of water was added, and the mixture was extracted with ether (2 × 10 ml). 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 hexane–ethyl acetate (EA) (80:1) system. Yield 0.2 g (80%), syrup, $[\alpha]_D^{23}$ = −9.8° (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.025 s (6H, t-Bu$(CH_3)_2$-SiO), 0.9 s (9H, t-Bu$(CH_3)_2$SiO), 0.98 d (3H, J_{5,CH_3} = 6.5, CH_3 at C^5), 1.38 s (3H, CH_3 at C^3), 1.4 d.d (1H, $J_{4',4}$ = 13.5, $J_{4,5}$ = 6, H^4), 1.76 d.d (1H, $J_{4',5}$ = 4.5, $H^{4'}$), 1.84 m (1H, H^5), 3.34 d.d (1H, $J_{6',6}$ = 9, $J_{5,6}$ = 6.5, H^6), 3.53 d.d (1H, $J_{5,6'}$ = 5.7, H^6), 4.4 (2H, AB-system, $PhCH_2O$), 5.23 (multiplet center, 2H, AB part of ABX system, H^1, $H^{1'}$), 5.9 (1H, X-part of ABX-system, H^2), 7.34 m (5H, $PhCH_2O$).

(2R,4R)-2-Benzyloxy-5-tert-butyldimethylsiloxy-2,4-diemthylpentanal (XXXIV). A 1 ml portion of pyridine and a 1 ml of a 0.05% solution of Sudan (IV) dye in CH_2Cl_2 was added to a solution of 0.307 g (0.88 mmole) of (XXXIII) in 6.5 ml of CH_2Cl_2. The mixture was ozonized at −78°C up to disappearance of the indicator color, argon was bubbled for 10 min, and after 45 min, the mixture was heated to ~20°C, evaporated, and the residue was chromatographed in a hexane–ether system (3.5%). Yield, 0.264 g (85.5%) syrup, $[\alpha]_D^{20}$ = +19.2° (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.05 s (6H, t-Bu$(CH_3)_2$SiO), 0.9 s (9H, t-Bu$(CH_3)_2$-SiO), 0.96 d (3H, J_{4,CH_3} = 6.5, CH_3 at C^4), 1.38 s (3H, CH_3 at C^2), 1.5 d.d (1H, $J_{3,3}$ = 13.5, H^3), 1.92 m (multiplet center, 2H, $J_{3,4}$ = 5, H^3 and H^4), 3.36 d.d (1H, $J_{5,5}$ = 9.5, $J_{4,5}$ = 5.7, H^5), 4.6 d.d (1H, $J_{4,5}$ = 5.5, H^5), 4.5 (2H, AB-system, $PhCH_2O$), 7.36 m (5H, $PhCH_2O$), 9.65 s (1H, H^1).

(4R,6R)-6-Benzyloxy-4,6-dimethyl-oct-7-en-3-one (XXXII). A mixture of bromides (XXX), 0.72 g (2.1 mmoles) was treated with activated zinc dust in i-PrOH–H_2O (14:1) mixture, as shown for compound (XXXIII). The compound (XXXI) (0.445 g, 91%) obtained was dissolved without purification in 5 ml of ether, the solution was cooled to −50°C, and 1.1 ml of 1.99 N solution of ethylmagnesium bromide in THF was added. The mixture was stirred for 20 min, raising the temperature to −10°C, was then decomposed with a saturated solution of NH_4Cl, diluted with $CHCl_3$, and filtered through celite. The filtrate was evaporated, and the residue was chromatographed in a hexane–EA (3:1) system. The yield of the corresponding alcohols was 0.363 g (73%). They were oxidized according to Swern, and the ketone (XXXII) obtained was purified by chromatography in a hexane–EA (5:1) system. Yield, 0.342 g (94%), syrup, $[\alpha]_D^{20}$ = −10.1° (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.9 t (3H, CH_3CH_2), 1.09 d (3H, $J_{4,Me}$ = 7, Me at C^4), 1.36 s (3H, Me at C^6), 1.5 d.d (1H, $J_{5,5'}$ = 14, $J_{4,5}$ = 3, H^5), 2.4 m (3H, CH_3CH_2, $H^{5'}$), 2.84 d.d.q (1H, $J_{3,5}$ = 9, H^4), 4.33 s (2H, $PhCH_2O$), 5.15 d.d (1H, J_{gem} = 1.5, $J_{7',8'\ cis}$ = 11, $H^{8'}$ cis), 5.22 d.d (1H, $J_{7,8'trans}$ = 17.5, $H^{8'}$ trans), 5.78 d.d (1H, H^7), 7.3 m (5H, $PhCH_2O$).

(2R,4R)-2-Benzyloxy-2,4-dimetyl-5-oxoheptanal (XVII). A 0.342 g portion (1.3 mmoles) of (XXXII) was dissolved in 45 ml of MeOH, and the solution was ozonized at −78°C up to the appearance of a sky blue color in the solution. The solution was purged with oxygen to decoloration, 1 ml of dimethyl sulfide was added, and the mixture was heated in the course of 1 h to 20°C, was then evaporated, and the residue was chromatographed in a

hexane–EA (8:1) system. Yield, 0.269 g (78%), syrup, $[\alpha]_D^{20} = -11.4°$ (C 1.0). PMR spectrum (δ, ppm, J, Hz): 0.92 t (3H, CH_3CH_2), 1.1 d (3H, $J_{4,Me}$ = 7, Me at C^4), 1.38 s (3H, Me at C^2), 1.5 d.d (1H, $J_{3,3'}$ = 14, $J_{3,4}$ = 3, H^3), 2.44 m (3H, $CH_3\underline{CH_2}$, H^3), 2.85 d.d.q (1H, $J_{3,4}$ = 9.5, H^4), 4.42 s (2H, $Ph\underline{CH_2}O$), 7.35 m (5H, $\underline{Ph}CH_2O$), 9.52 s (1H, H^1).

CONCLUSIONS

A synthesis of a C^5-C^9-fragment common to erythronolides A and B was carried out starting from levoglucosan.

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SYNTHESIS OF MACROLIDE ANTIBIOTICS.

17.* SYNTHESIS OF THE C^1-C^{10}-FRAGMENT OF ERYTHRONOLIDES (A) AND (B)

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In the preceding article, the strategy was discussed of the stereodirected synthesis of erythronolides A and B in the sequence of coupling the $(C^5$-$C^9)$ + $(C^3$-$C_4)$ + $(C^1$-$C^2)$ + (C^{10}) + $(C^{11}$-$C^{13})$ fragments and also the synthesis of the C^5-$C^{9\dagger}$ fragment, the aldehyde (I), was described. The subject of the present article is the synthesis of the C^1-C^{10} fragment, the ketone (XX), from aldehyde (I).

It was proposed to carry out the extension of the C^1-C^4 fragment of the carbon chain and construction of the sequence of the C^2-C^5 chiral centers on transition from (I) to (XX) by adding tri-n-butylcrotyltin (TBCT) to aldehydes (I) and (XVI) in the presence of Lewis acids. The possibility of controlling the stereochemical result of this type of transformation by selecting the reaction promoters and suitable protecting groups in the substrates was demonstrated on the model of chiral α- and β-alkoxyaldehydes [2, 3].

Magnesium bromide $MgBr_2$ was chosen as a promoter for the addition of TBCT to aldehyde (I) [2], since the presence of an α-benzyloxy group in the molecule of the substrate opened up the possibility of the α-chelation of aldehyde (I) in the transition state, whereby the

*For previous communication, see [1].
†The numbering of the carbon atoms in the compounds described in the present article corresponds to the numbering of the erythronolide B carbon chain.

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