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SYNTHESIS OF MACROLIDE ANTIBIOTICS. 2. SYNTHESIS OF THE C_9-C_{13} SEGMENTS OF ERYTHRONOLIDES A, B AND OLEANDONOLIDE

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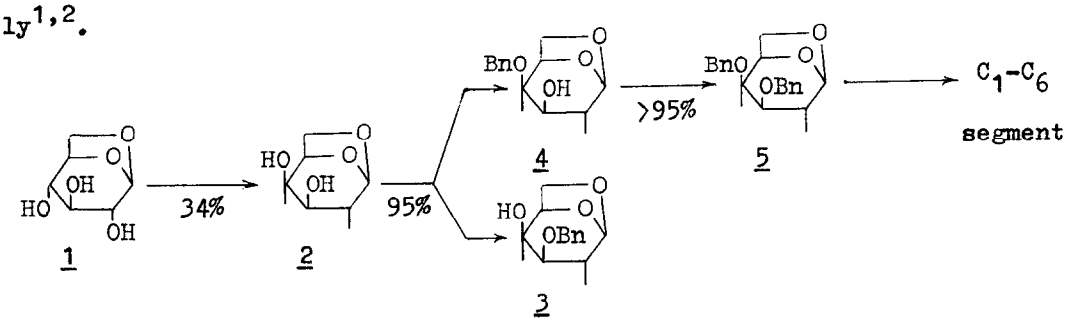
Abstract. The C_9-C_{13} segments of some 14-membered macrolide antibiotics have been synthesized from levoglucosan.

In preceding paper[1] we have reported the synthesis of C_1-C_6 segment of a number of structurally related 14-membered macrolide antibiotics. Here we describe the synthesis of C_9-C_{13} segments of some antibiotics of this group.

The key compound - 1,6-anhydro-2-deoxy-2,4-di-C-methyl-β-D-galactopyranose 2 have been synthesized from levoglucosan 1 in 34% overall yield as described previously[1,2].

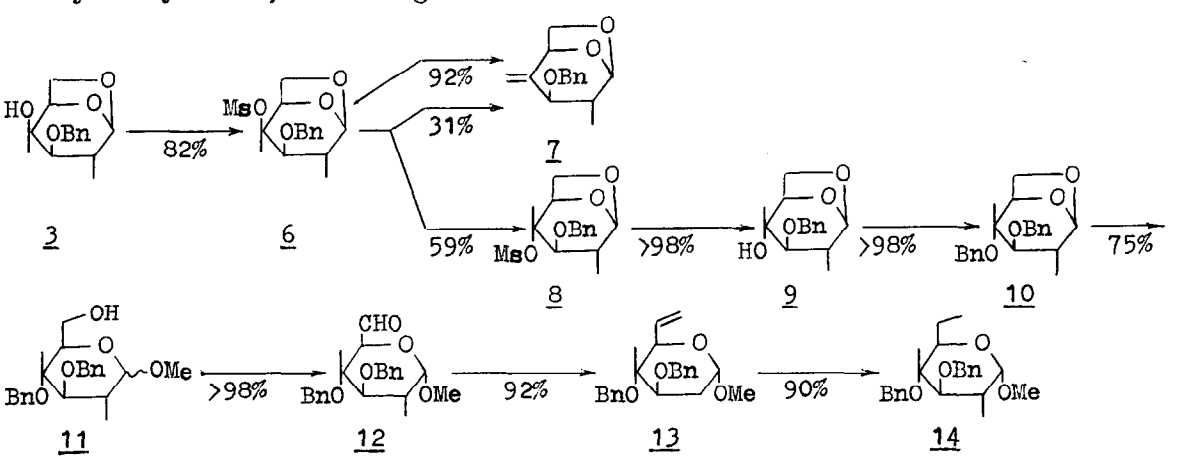


Monobenzylation of glycol 2 (1.05 eq CH_3SOCH_2Na, 1.05 eq BnCl) led mainly to 3-O-benzyl ether 3 [mp 57.5-58°(pentane); $[\alpha]_D$ -89.0°; pmr: 5.22(s, H-1), 3.88 (broad s, H-3)] contaminated with ca. 5-10% of 4-O-benzyl derivative 4 (syrup;

$[\alpha]_D$ -18.3°). Crystallization of the mixture from ether-hexane gave pure 3. Mother liquors contained both 3 and 4 was repeatedly benzylated (NaH/DMF, BnCl) to give 5 which was used in the synthesis of the C_1-C_6 segment of macrolides as described[1].

Mesylation of 3 (Ms_2O-Py, CH_2Cl_2, 20°, 48 h) afforded 6 [mp 63-63.5°(ether); $[\alpha]_D$ -55.0°; pmr: 1.45(s, CH_3-4), 3.72(s, H-3)] which was isomerized by heating (20 h) in nitromethane solution in presence of powdered molecular sieves 4 Å as a proton scavenger to give the mixture of 7 (syrup; $[\alpha]_D$ -4.9°)[3] and isomeric mesylate 8 [mp 63.5-64°(ether-pentane); $[\alpha]_D$ +4.6°; pmr: 1.50(s, CH_3-4), 3.45(d, $J_{2,3}$=3.5 Hz, H-3)].

Demesylation of 8 ($LiAlH_4$/ether) followed by alkylation (NaH/DMF, BnCl) led to dibenzyl ether 10 (syrup; $[\alpha]_D$ -22.9°). Methanolysis of 10 (10% HCl/MeOH, 20°) gave difficult-to-separate mixture of methyl α- and β-glycosides 11 which was oxidized by DMSO-$(COCl)_2$[5]. Resulted α- and β-anomers of aldehydo derivative 12 were separated by column chromatography and the former[6] was transformed via Wittig reaction (2 eq Ph_3PCH_2, benzene, reflux, 10 min) into vinylic compound 13 (syrup; $[\alpha]_D$ +138°). Reduction of the double bond by $LiAlH_4$-$CoCl_2$[7] afforded 14 [syrup; $[\alpha]_D$ +107°; pmr: 1.00(t, J=7.2 Hz), 1.05(d, J=7.5 Hz), 1.33(s), 3.65(d, $J_{2,3}$=8.5 Hz, H-3), 4.78(d, $J_{1,2}$=5 Hz, H-1)] which represents the C_9-C_{13} segment of erythromycins A, C and megalomicin A.



Dehydromesylation of 6 (i-Pr_2NEt, CH_3NO_2) led to methylene derivative 7 in good yield. Treatment of 7 with $LiAlH_4$ - transition metal halide ($FeCl_3$, $CoCl_2$, $NiCl_2$)[7] produced the mixture of 1,6-anhydro-2,4-dideoxy-2,4-di-C-methyl-β-D-galactopyranose 15 [syrup; $[\alpha]_D$ -64.9°; pmr: 0.95(d, J=7.5 Hz), 0.98(d, J=7.6 Hz),

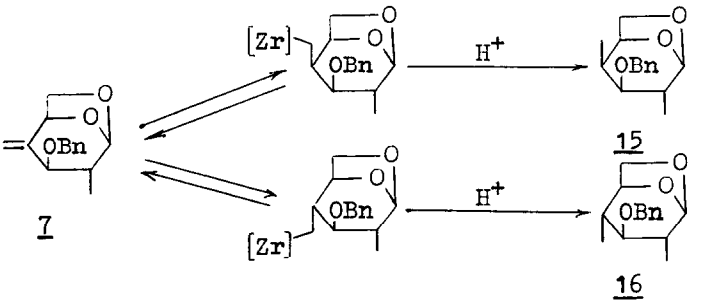
3.20(d, J=4.5 Hz, H-3)] and its gluco isomer 16 in about 3:7 ratio.

Although few data are available[7,8] about the mechanism of this reaction it seems likely to involve the generation of π-bonded low-valent transition metal hydride complex, olefine insertion into metal - hydrogen bond and reductive elimination thus producing the alkane and regenerating catalytically active species.

Stereochemistry of the such hydrogenation have to be controlled by reagent approach. It should be noted that the catalytic (Ni-Re, Pd/C) reduction of 3-O-methyl analogue of 7 led exclusively (or predominantly) to gluco isomer[4].

In contrast, the thermodynamically controlled reaction must lead to galacto isomer 15.

Indeed making use the reversibility of hydrozirkonation[9] we succeeded in selective hydrogenation of 7 into 15 by means of hydrozirkonation (1 eq $Cp_2Zr(H)Cl$, benzene, reflux, 15 min) followed by protolysis (0.1 N HCl, 20°). The reaction is rather selective (15 to 16 ratio is about 12) and it seems likely to represent the new general method of synthesis of deoxy branched-chain sugars[10]. Hydrozirkonation is reversible and conversion of 7 depends on conditions (63% in those mentioned above).

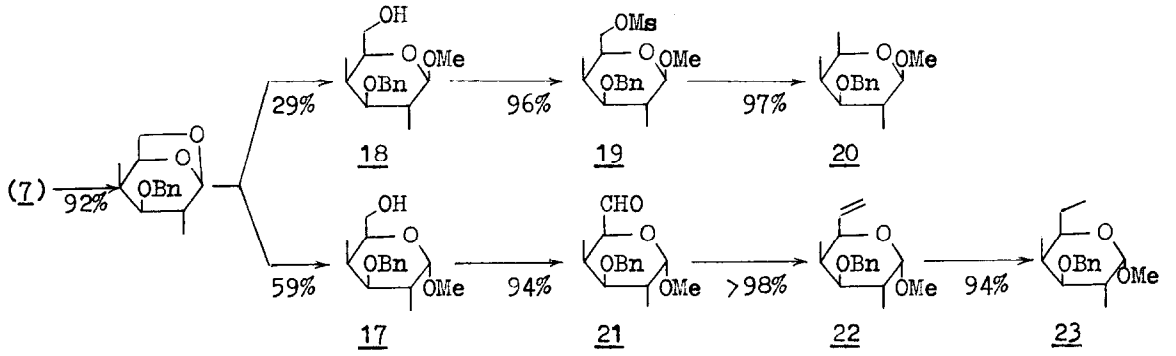


Methanolysis of 15 (10% HCl/MeOH, 20°, 0.5 h) led to the mixture of methyl α- (17) [mp 71.5-72°(hexane); $[\alpha]_D$+192°; pmr: 3.57(dd, $J_{2,3}$=10,5 Hz, $J_{3,4}$=4.5Hz, H-3), 4.57(d, $J_{1,2}$=3 Hz, H-1)] and β- (18) glycosides [mp 81.5-82°(hexane); $[\alpha]_D$ +59.8°; pmr: 3.16(dd, $J_{2,3}$=10.5 Hz, $J_{3,4}$=4.5 Hz, H-3), 3.95(d, $J_{1,2}$=8.5 Hz, H-1)] which was separated by column chromatography and used independently[6].

Mesylation of 18 (MsCl-Et_3N, CH_2Cl_2)[11] afforded 19 [mp 90.5-91°(ether-pentane); $[\alpha]_D$+37.2°] which was reduced by $LiBHEt_3$ (THF, reflux, 1 h) to provide 20 [mp 63-64°(pentane); $[\alpha]_D$+60.0°; pmr: 0.94(d, J=7 Hz), 1.02(d, J=7 Hz), 1.27 (d, J=7 Hz), 3.15(dd, $J_{2,3}$=10.5 Hz, $J_{3,4}$=4.5 Hz, H-3), 3.52(dq, $J_{4,5}$=2 Hz, H-5), 3.88(d, $J_{1,2}$=8.5 Hz, H-1)] which represents specifically protected C_9-C_{13} segment

of oleandomycin and O-demethyloleandomycin.

Oxidation of 17 by DMSO-$(COCl)_2$[5] led to aldehyde 21 [mp 72.5-73.5°(pentane); $[\alpha]_D$ +193°] which was transformed into 22 (syrup; $[\alpha]_D$ +193°) via Wittig reaction (2 eq Ph_3CH_2, benzene, reflux, 10 min). Reduction of the double bond by $LiAlH_4$-$CoCl_2$[7] finished the synthesis of 23 [syrup; $[\alpha]_D$ +192°; pmr: 0.92(d, J=7 Hz), 0.95 (t, J=7.5 Hz), 1.00(d, J=7 Hz), 3.66(dt, $J_{4,5}$=3.5 Hz, H-5), 4.52(d, $J_{1,2}$=3.5 Hz, H-1)] which represents the C_9-C_{13} segment of erythromycin B.



REFERENCES AND NOTES

1. See preceding communication in this issue.
2. All new crystalline compounds gave correct microanalyses; melting points are uncorrected, optical rotation were mesured at 20±2° in chloroform (c~1), pmr spectra were recorded in $CDCl_3$ (δ scale).
3. ^1H and ^{13}C nmr spectra are analogous to those of 3-O-methyl derivative described earlier[4].
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6. Although it is not essential for further transformations, the individual anomers were used to simplify the spectral information.
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