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SYNTHESIS OF MACROLIDE ANTIBIOTICS. 3.REVISED SYNTHESIS OF C_9- C_{13} SEGMENT OF ERYTHRONOLIDE A.

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Abstract. The C_9- C_{13} segment of erythronolide A has been synthesized from levoglucosan.

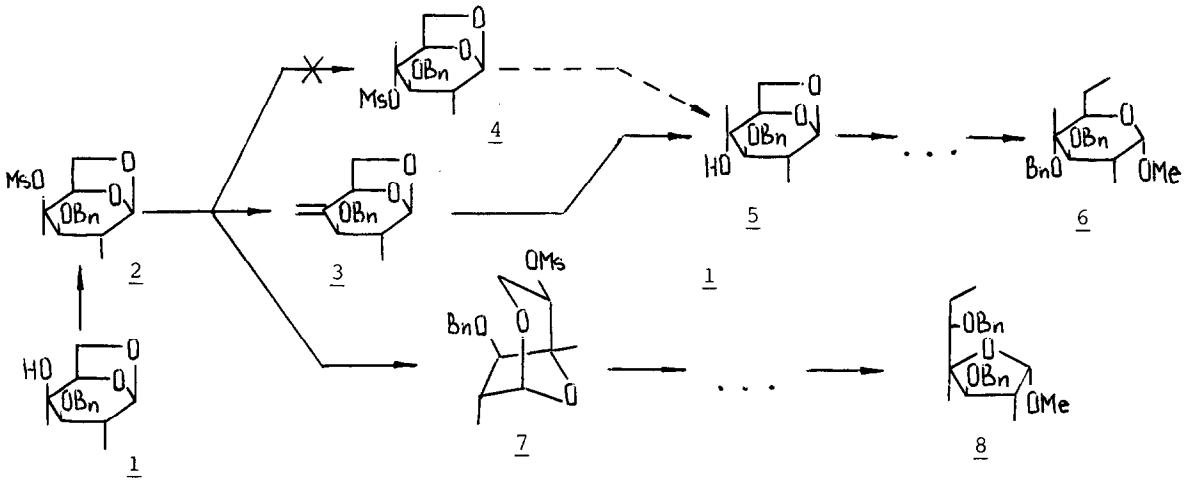
Recently we reported the synthesis of a number of C_9- C_{13} segments of 14-memberd macrolide antibiotics[1]. The key stage of the synthesis was the transformation of mesylate 2 which produced methylene derivative 3 and, we believed, the isomeric mesylate of the proposed structure 4, which was used in an intended synthesis of the C_9- C_{13} segment of erythronolide A.

Now as a result of a close reinvestigation of the reaction sequence 2 - 4 the structures of isomeric mesylate (and therefore synthesized segment) are revised.

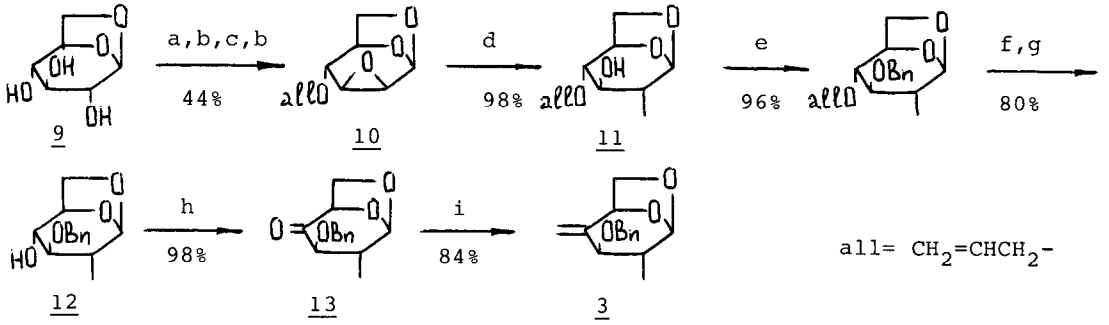
The attempt to synthesize the C_9- C_{13} segment of erythronolide A using epoxidation of the methylene compound 3 followed by the reductive oxirane ring opening led to two tertiary alcohols, one of which represents the starting alcohol 1. The other one, as should be expected from chemical reasons, must have the structure 5 suitable for the erythronolide A segment synthesis. Spectral data of the compound fit the sructure 5, but differ from those for alcohol produced by demesylation of isomeric mesylate of proposed structure 4[1].

These results initiated the reinvestigation of the synthesis of the C_9- C_{13} segment of erythronolide A using some additional chemical and spectroscopic experiments. It was found that the isomeric mesylate is, in fact, 1.6-anhydro-α-L-idofuranose 7[2] and, consequently,"the C_9- C_{13} segment of erythronolide A" reported earlier[1] had not the desired structure 6, but in fact the structure 8, which has the stereochemistry of 13-epi-C_9- C_{13} segment of erythronolide A.

At the same time, the structure of the alcohol 5 prepared by epoxidation--reduction sequence from 3 was confirmed by spectroscopy, including NOE, and, finally, proved by the X-ray analysis[3]. Alcohol 5 obtained in this way was used in the synthesis of the C_9- C_{13} segment of erythronolide A (6).



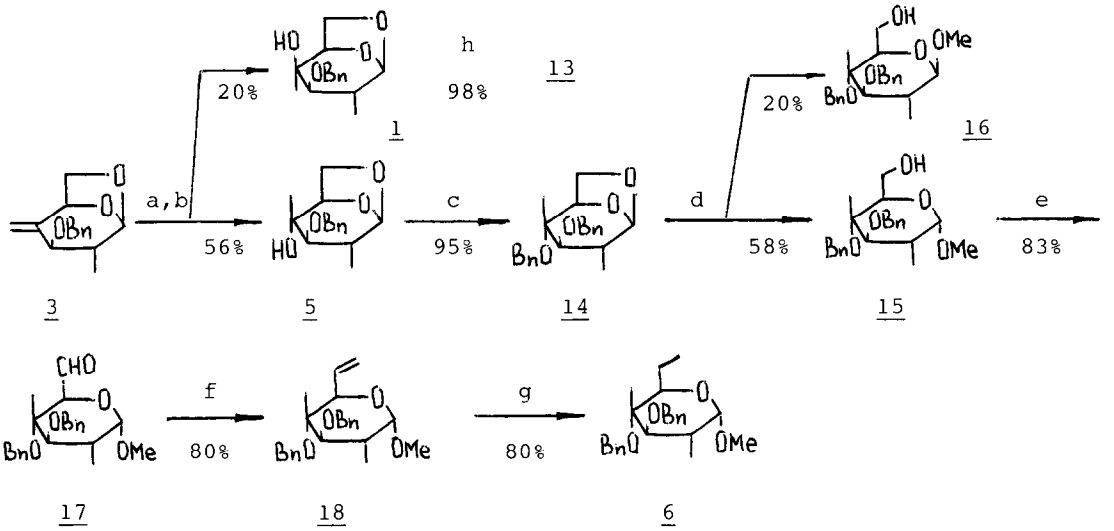
Successful transformations of the methylene derivative 3 into the C_9- C_{13} segment of erythronolide B, oleandonolide[1], and, recently, erythronolide A (vide infra) stimulated the search for its alternative synthesis. Using a suitable set of protecting groups the more convenient and effective synthesis of this key intermediate was achieved, starting from levoglucosan 9 (cf.1,4).



a. TsCl-Py; b.MeONa; c.allOH,TsOH/PhH,Δ; d.Me_2Mg/Et_2O,Δ; e.BnBr,NaH/DMF; f.t-BuOK/DMSO; g.$HgCl_2/Me_2CO-H_2O$; h.DMSO-$(COCl)_2$,Et_3N/CH_2Cl_2; i.Ph_3PCH_2/ /PhH,Δ.

The reaction of the known oxirane 10[5] with Me_2Mg (ether, reflux 12 hrs) led to alcohol 11[6] [syrup;$[\alpha]_D$ -44.7°; ^{1}H-NMR: 1.14(d,$J_{2,CH_3\text{-}2}$=7.1Hz, CH_3-2); 1.87 (broad q, H-2); 3.59(broad d, $J_{3,OH}$=6.5Hz, H-3)] in quantitative yield. Benzylation of 11 followed by removal of allylic protecting group[7] afforded alcohol 12 [syrup; $[\alpha]_D$ -41.1°;^{1}H-NMR: 2.57(OH); 3.70(broad d, $J_{4,OH}$=8.5Hz, H-4)]. Oxidation[8] of 12 produced ketone 13 [mp 66.0-66.5°C(ether-pentane); $[\alpha]_D$ +72.2°; ^{1}H-NMR: 1.89(dq,$J_{2,CH_3\text{-}2}$=7Hz, $J_{2,3}$=7.5Hz, H-2); 3.83(d, H-3); ^{13}C-NMR: 210.0(C-4)] which was subjected to a Wittig reaction with Ph_3PCH_2. The resulting methylene derivative 3 was identical in all respects with the compound obtained earlier[1]

and can be used in synthesis of the C_9- C_{13} segments of erythronolide B, oleandonolide[1] or erythronolide A as follows:



a.MCPBA/$CHCl_3$,Δ; b.$LiAlH_4$/THF; c.BnBr,NaH/DMF; d.20%HCl/MeOH,r.t.; e.DMSO-$(COCl)_2$,Et_3N/CH_2Cl_2; f.Ph_3PCH_2/PhH,Δ; g.$LiAlH_4$-$CoCl_2$/THF; h.MeMgBr/THF.

Epoxidation of 3 by MCPBA ($CHCl_3$,reflux 12 hrs) followed by oxirane reduction gave the mixture (26:74 by capillary GLC) of the known[1] 1 and its gluco-isomer 5 [syrup;$[\alpha]_D$ -87.0°;^{1}H-NMR: 1.12(d, J_{2,CH_3-2}=7.4Hz, CH_3-2); 1.23(s, CH_3-4); 3.13 (broad s, $J_{2,3}$=1Hz,H-3)] which was separated by chromatography. Moreover, galacto-isomer 1 can be obtained selectively with quantitative yield by the reaction of the ketone 13 with MeMgBr, and used in the synthesis of the C_1- C_6 segment of 14-membered macrolide antibiotics as described previously[4].

The isomer 5 possesses appropriate stereochemistry and was transformed into the C_9- C_{13} segment of erythronolide A by the reaction sequence described earlier[1] for 8.

Benzylation of 5 led to dibenzyl ether 14[3] [mp 100-100.5°C(ether-pentane); $[\alpha]_D$ -95.7°]which was subjected to methanolysis to afford the mixture of α-(15) [mp 83-83.5°C(ether-pentane);$[\alpha]_D$ +68.7°; ^{1}H-NMR: 3.37(s, OMe); 4.53(d, $J_{1,2}$=3.5Hz, H-1); 1.93(ddq, $J_{2,3}$=11Hz, J_{2,CH_3-2}=6.9Hz, H-2)] and β-(16) methyl-glycosides which was separated by chromatography[9]. Oxidation of 15[8] gave aldehyde 17[syrup;$[\alpha]_D$+137.3° ^{1}H-NMR: 9.82(s, CHO)] which was transformed into olefin 18 via a Wittig reaction. Reduction of double bond by $LiAlH_4$-$CoCl_2$[10] completed the synthesis of the C_9- C_{13} segment of erythronolide A (6)[11].

Thus, a synthesis of the uniformly protected C_9- C_{13} segments of erythronolide A as well as erythronolide B and oleandonolide[1] has been developed from a common intermediate, the methylene derivative 3.

The presently described synthesis of 3 is more effective than the one reported previously[1], and possesses considerable advantages.

REFERENCES AND NOTES

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6. Yields are not optimized, mp are uncorrected, specific rotation were mesured at 22±2° in chloroform (c~1), ^{1}H- and ^{13}C-NMR spectra were recorded on Brucker WM-250 spectrometer in $CDCl_3$ (δ scale).
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11. 6: syrup;$[\alpha]_D$ +74.7°; ^{1}H-NMR: 1.02(t, J_{6,CH_3-6}=7Hz, CH_3-6); 1.07(d, J_{2,CH_3-2}=6.5Hz, CH_3-2); 1.33(s, CH_3-4); 1.94(ddq, $J_{2,3}$=10.7Hz, $J_{1,2}$=3.6Hz, H-2); 3.74(d, H-3); 3.65(dd, $J_{5,6}$=10.4Hz, $J_{5,6'}$=1.8Hz, H-5); 1.80 and 1.44 (two ddq, $J_{6,6'}$=13.5Hz, H-6 and H-6'); 4.50(d, H-1); ^{13}C-NMR: 11.4, 11.7 and 13.1(Me-groups at C_6, C_2 and C_4); 21.2(C-6); 40.3(C-2); 54.7(OMe); 65.3(Ph$\underline{CH_2}$O-4); 73.9(Ph$\underline{CH_2}$O-3); 74.9(C-5); 79.3(C-4); 83.5 (C-3); 101.7 (C-1) plus signals of aromatic carbons.

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