Tetrahedron Letters, Vol.22, No.43, pp 4315 - 4318, 1981
Printed in Great Britain

0040-4039/81/434315-04$02.00/0

SYNTHESIS OF MACROLIDE ANTIBIOTICS. 1. SYNTHESIS OF THE C_1-C_6 SEGMENT OF 14-MEMBERED MACROLIDE ANTIBIOTICS.

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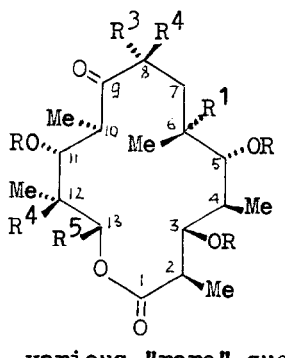
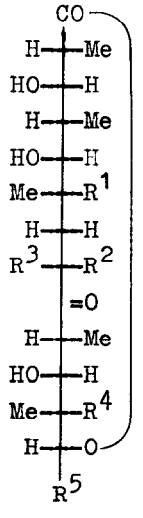
Abstract. The C_1-C_6 segment of a number of 14-membered macrolide antibiotics have been synthesized started from levoglucosan.

The employment of carbohydrates as a chiral precursors is one of the most promising directions in natural products synthesis. In accordance with our programme on utilization of carbohydrates for macrolide antibiotics construction we now report the synthesis of C_1-C_6 segment of a number of structurally related 14-membered macrolides[1].



R - various "rare" sugar units



Antibiotic	R^1	R^2	R^3	R^4	R^5
erythromycins A, C megalomicin A	OH	H	Me	OH	Et
erythromycin B	"	"	"	H	"
oleandomycin, O-demethyloleandomycin	H	O⟨—⟩CH_2	"		Me

Synthetic strategy, the programme base on, exploits the next principles

1. The structures of the antibiotics' aglycones are subdivided into C_1-C_6 and C_9-C_{13} segments are to be synthesized from carbohydrate(s).

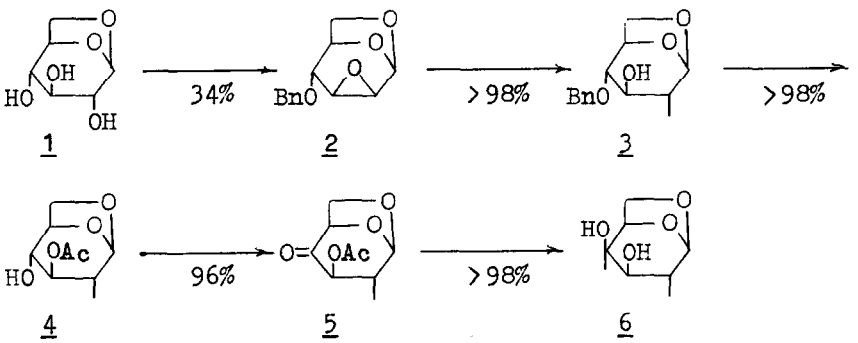
2. Since the configurations at C_2-C_3 and C_{10}-C_{11} are identical for all antibiotics under consideration the selecting synthetic scheme should provide the possibility to synthesize all the segments via uniform pathway in maximum common stages.

3. The hydroxyls in the segments have to be specifically protected in order to provide selective glycosidation of synthetic aglycones at the latest stages of the synthesis.

In this and followed papers we demonstrate the application of the above principles.

The synthesis of antibiotics under consideration starts from levoglucosan 1 whose bicyclic skeleton provides high regio- and stereoselectivity of reactions[2] and possesses the conformation convenient for desirable transformations.

The key compound in the synthesis - 1,6-anhydro-2-deoxy-2,4-di-C-methyl-β-D-galactopyranose 6 - was obtained according to the following sequence[3,4].



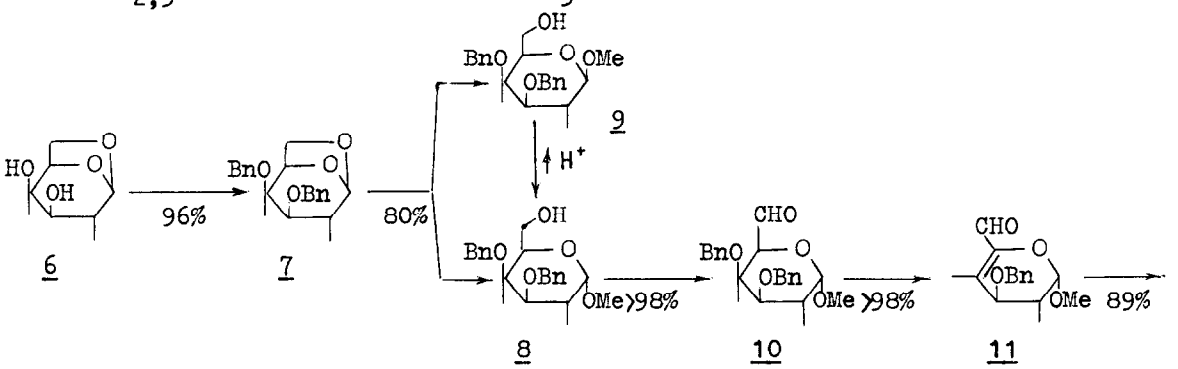
1 2 3 4 5 6

The reaction of the known oxirane 2[5] with Me_2Mg[6] (ether, reflux, 12 h) led selectively and practically quantitatively to the alcohol 3 [mp 80.5-81.5° (benzene-hexane); $[\alpha]_D$ -33.2°; pmr: 5.28(broad s, H-1), 3.28(broad s, H-3)]. Acetylation (Ac_2O-Py) followed by hydrogenolysis (5% Pd/C, MeOH) afforded 4 (syrup; $[\alpha]_D$ -51.2°). Oxidation of 4 with DMSO-$(COCl)_2$[7] (low temperature work-up was used to prevent isomerisation at C_3) provided ketone 5 [mp 72-74° (ether); $[\alpha]_D$ -1.6°; pmr: 5.35(s, H-1), 5.15(d, $J_{2,3}$=8.2 Hz, H-3)] which was converted into glycol 6

[syrup; $[\alpha]_D$ -26.0°; pmr: 5.28(broad s, H-1), 3.31(broad s, H-3)] by treatment with MeMgJ (3 eq, reflux, 1 h).

The exhaustive benzylation of 6 (NaH/DMF, BnCl) gave dibenzyl ether 7 [mp 73-74°(hexane); $[\alpha]_D$ -26.1°] which being treated with 20% HCl/MeOH (20°, 4 h) produced the mixture (9:2) of methyl α- (8) [syrup; $[\alpha]_D$ +123°; pmr: 4.67(d, $J_{1,2}$=3.5 Hz, H-1), 3.46(d, $J_{2,3}$=11 Hz, H-3)] and β- (9) glycosides. The latter was converted (3% HCl/MeOH, 20°) into 8. Oxidation of 8 as above[7] afforded aldehydo derivative 10 [syrup; $[\alpha]_D$ +66.5°; pmr: 4.72(d, $J_{1,2}$=3.2 Hz, H-1), 3.44(d, $J_{2,3}$=11 Hz, H-3), 3.80(d, $J_{5,CHO}$=2 Hz, H-5), 9.64(d, CHO)]. Heating of 10 with methanolic $Ca(OH)_2$[8] led to smooth elimination of benzyl alcohol with formation of α,β-unsaturated aldehyde 11 [syrup; $[\alpha]_D$ +197°; pmr: 4.86(d, $J_{1,2}$=2.5 Hz, H-1), 2.12(d, J_{3,CH_3-4}=1 Hz, CH_3-4), 3.81(dd, $J_{2,3}$=6.8 Hz, H-3), 9.79(s, CHO)].

The Corey oxidation[9] (MnO_2, KCN-AcOH, MeOH) of 11 gave rise to α,β-unsaturated ester 12 [syrup; $[\alpha]_D$ +151°; $\nu_{C=O}$ 1730 cm^{-1}; pmr: 4.82(d, $J_{1,2}$=2 Hz, H-1), 3.66(d, $J_{2,3}$=5 Hz, H-3), 3.75(s, $COOCH_3$)].



Upon catalytic hydrogenation (5% Pd/C, MeOH) 12 rapidly absorbed 1 equivalent of hydrogen whereafter the reaction practically stopped.

The resulted ester 13 (syrup; $[\alpha]_D$ +179°) was converted (MEM-NEt_3Cl, CH_3CN,

reflux, 12 h) into MEM[10] derivative 14 [syrup; $[\alpha]_D$ +109°; pmr: 2.05(d, J_{3,CH_3-4}= 0.7 Hz, CH_3-4), 3.37(s, $C\underline{H}_3OC_2H_4OCH_2$-), 3.54(s, OCH_3), 3.77(s, $COOCH_3$), 4.80(dd, $CH_3OC_2H_4OC\underline{H}_2$-)]. Hydrogenation of 14 (5% Pd/C, MeOH) gave mainly methyl(methyl-2,4-dideoxy-2,4-di-C-methyl-3-O-MEM-3-L-idopyranosyl)uronate 15 [syrup; $[\alpha]_D$+70.6°; pmr: 1.04(d, J=7 Hz), 1.06(d, J=7.5 Hz), 4.47(d, $J_{4,5}$=3.7 Hz, H-5), 4.66(d, $J_{1,2}$= 3 Hz, H-1), 4.79(s, $CH_3OC_2H_4OC\underline{H}_2$-)] which represents the specifically protected C_1-C_6 segment of a number of 14-membered macrolide antibiotics (besides those mentioned above also for construction of lakamycins, kujimycin A, narbomycin, picromycin, kromycin, kromin[1] and some related macrolides).

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(Received in UK 3 August 1981)