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SYNTHETIC STUDIES ON ANTIBIOTIC A23187 I. CHIRAL SYNTHONS FOR C9-C13 AND C14-C20

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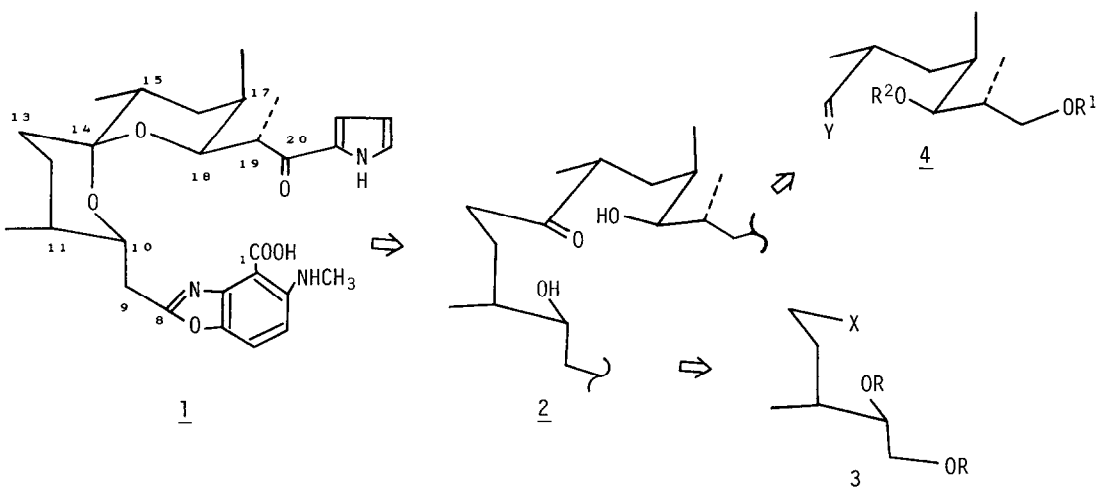
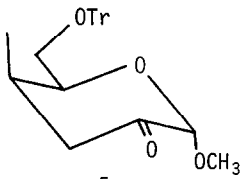
Summary: Chiral synthons 3 and 4 for the synthesis of antibiotic A23187 1 were prepared from methyl α-*D*-glucopyranoside.

Extensive use of carbohydrate synthons have appeared in the synthesis of highly functionalized molecules such as macrolides[1] and polyethers.[2] As part of our project[3] on the synthesis of biologically active substances via carbohydrate synthons, our attention was now focussed on the polyether antibiotic A23187 1 which is a divalent cation ionophore isolated from cultures of *Streptomyces chartreusensis*. The structural feature of the nitrogen-containing molecule,[4] as well as its remarkable bio-activities,[5] has aroused interest of a number of chemists.[6] We describe here our synthetic approach to the chiral part of the molecule 1.



All chiral centers of 1 are located around the structurally unique 1,7-dioxaspiro[5.5]undecane ring. A synthetically plausible precursor of the dioxasprane is keto diol 2, which may be retrosynthesized into two synthons 3 and 4 representing C9-C13 and C14-C20 frameworks respectively. The ketone 5 (m.p. 169-172°, $[\alpha]_D^{18}$ +25.7 $CHCl_3$), obtainable from methyl α-*D*-glucopyranoside,[7] provides us with the appropriate arrangement of substituents existing in both synthons. Reduction ($NaBH_4$, THF-EtOH) of 5 gave quantitatively the hydroxyl compound 6 as a mixture of α- and β-isomers (α/β = 4/1).[8,9] Detritylation and the simultaneous cleavage



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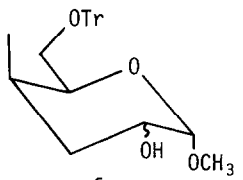

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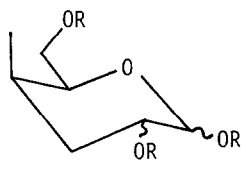
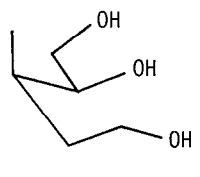


7 R = Ac
8 R = H



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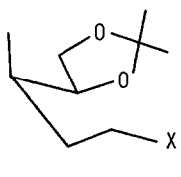
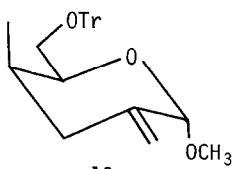


10 X = OH
11 X = OTs



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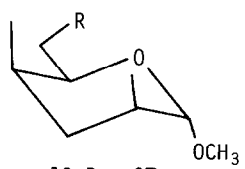
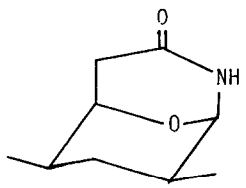


13 R = OTr
14 R = OH
15 R = OTs
16 R = CN
17 R = $CONH_2$



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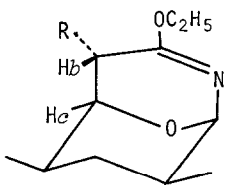
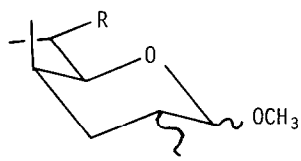
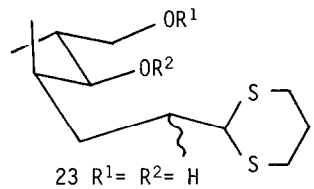


19 R = Hα
20 R = CH_3



21 R = $CO_2C_2H_5$
22 R = CH_2OH



23 R^1= R^2= H
24 R^1= $SiMe_2Bu^t$, R^2= H

of the glycosyl linkage were effected by acetolysis (Ac_2O, $BF_3{\cdot}OEt_2$, room temp. overnight).

After saponification (1% NaOMe-MeOH, then HCl) of triacetate 7, periodate oxidation ($NaIO_4$, EtOH, 0°-room temp. 1h) of crude 8 was followed by reduction with $NaBH_4$ (0°-room temp. 2h) to afford a crude triol 9, which, without purification, was further converted to the isopropylidene derivative 10, ($Me_2C(OMe)_2$, acetone, H^+(resin), 26 % from 5), $[\alpha]_D^{23}$ +16.8 ($CHCl_3$), ν_{max}3400cm^{-1}, δ($CDCl_3$) 0.98(3H,d,J=7Hz),1.34(3H,s),1.40(3H,s). The corresponding tosylate 11, $[\alpha]_D^{23}$ +8.3 ($CHCl_3$), δ($CDCl_3$) 0.88(3H,d,J=7Hz),1.30(3H,s),1.37(3H,s),2.43(3H,s),7.32(2H,d,J=9Hz),7.78(2H,d, J=9Hz), prepared in the usual way (p-TsCl, pyridine), was heated with NaI (acetone, 1h) to produce an oily iodide 3 (R = isopropylidene, X = I, 78 % from 10), $[\alpha]_D^{26}$ +29.6 ($CHCl_3$), δ($CDCl_3$) 0.96(3H,d,J=6Hz),1.34(3H,s),1.40(3H,s). Another chiral synthon 4 was also synthesized from 5 as described below. Methylenation ($Ph_3P{=}CH_2$, THF, 0°-room temp. overnight) of 5 gave 12, m.p. 166°, $[\alpha]_D^{22}$ +35.0 ($CHCl_3$), δ($CDCl_3$)0.66(3H,d,J=7Hz),3.44(3H,s),4.24(1H,m),4.85(1H,s),4.89(1H,d, J=9Hz),7.20-7.55(15H,m), which was hydrogenated (Pd-C, EtOAc, H_2,3-3.5Kg/cm^2) to afford cis dimethyl compound 13 as the predominant product, (13/isomers = 3-3.5/1, 72 % from 5), m.p. 143-143.5°, $[\alpha]_D^{22}$ +30.4 ($CHCl_3$),^{1}H-δ($CDCl_3$)0.70(3H,d,J=6.5Hz),0.94(3H,d,J=6.5Hz),3.46(3H,s),4.08(1H

m),4.26(1H,d,J=6Hz),7.20-7.55(15H,m), ^{13}C-$\delta(CDCl_3)$15.9,18.3,30.6,33.7,34.6,55.3,63.0,71.9,86.6, 104.2,126.8,127.7,128.7,144.0. A comparison of ^1H and ^{13}C NMR spectra of 13 with those of the reported material,[10] prepared from *D*-glucose via a different synthetic route, proved their identity. Trityl group was removed reductively (Na, NH_3,THF, NH_4Cl) to give 14 (83 %), m.p.45-46.5°, $[\alpha]_D^{25}$ +101.7 ($CHCl_3$) which upon tosylation (p-TsCl, pyridine) was quantitatively converted to 15, $[\alpha]_D^{22}$ +57.0 ($CHCl_3$), $\delta(CDCl_3)$0.84(3H,d,J=6.5Hz),0.95(3H,d,J=7Hz),2.43(3H,s),3.31(3H,s), 4.07(2H,br.s),4.17(1H,d,J=6Hz),7.30(2H,d,J=9Hz),7.78(2H,d,J=9Hz). Displacement of the tosylate 15 by cyanide (NaCN, DMF, 85°, 8h) was effected in the presence of n-Bu_4NBr (2 mol eq.). The obtained crude nitrile 16, ν_{max}2260cm^{-1}, without purification, was hydrolized (30% H_2O_2, acetone, aq.Na_2CO_3, room temp. 4days) to give the corresponding amide 17 (40 % from 15), m.p. 162-163°, $[\alpha]_D^{23}$ +123.5 ($CHCl_3$), $\delta(CDCl_3)$0.90(3H,d,J=6.5Hz),0.98(3H,d,J=6Hz),3.40(3H,s),4.26(1H,d,J=6Hz), 5.8-6.7(2H, br). Heating of 17 in toluene with p-TsOH or $CuSO_4 \cdot 5H_2O$ caused cyclization with loss of MeOH to produce 18, m.p. 144°, $[\alpha]_D^{20}$ -177.7 ($CHCl_3$), $\delta(CDCl_3)$0.86(6H,d,J=7Hz),2.29(1H, d,J=18Hz),2.65(1H,dd,J=18,8Hz),4.08(1H,dd,J=8,5Hz),4.82(1H,t,J=3Hz),7.60(1H,br), in high yield![11]

By treatment with Et_3OBF_4 in CH_2Cl_2, the lactam 18 was converted to the iminoether 19 (80 %), $\delta(CDCl_3)$0.83(3H,d,J=7Hz),0.90(3H,d,J=7Hz),1.30(3H,t,J=7Hz),1.98(H*b*,d, J*ab*=18Hz),2.53(H*a*,dd, J*ab*=18, J*ac*=7Hz),4.10(2H,q,J=7Hz),5.13(1H,d,J=3.5Hz). Stereoselective alkylation of the active methylene (LDA, CH_3I, THF, -78°- -40°) was achieved exclusively at the less hindered side and 20 was obtained as the sole product quantitatively, $[\alpha]_D^{22}$ -90.5 ($CHCl_3$), $\delta(CDCl_3)$0.83(3H,d,J=7 Hz),0.88(3H,d,J=7Hz),1.27(3H,t,J=7Hz),1.29(3H,d,J=7Hz),3.55(H*a*,d,J=4.5Hz),4.08(2H,q,J=7Hz),5.10 (1H,d,J=3.5Hz). The disappearance of H*a*-proton in 20 was confirmed by a careful examination of the NMR spectrum. The imino-linkage of 20 was hydrolized in an acidic condition (5% H_2SO_4- 80% aq.MeOH, 60°, 8h) and the obtained crude ester 21 was reduced with $LiAlH_4$ (ether, reflux, 3h) to give a mixture of diastereomers 22, ν_{max}3450cm^{-1}. NMR spectrum of the mixture 22 ($CDCl_3$) showed nearly equal magnitude of two doublets due to acetal protons at δ3.90(J=8Hz) and at δ 4.45(J=3Hz). The existence of an axial proton at C(2), supported by the coupling constant of the higher field signal (δ3.90), indicated that epimerization of C(2) methyl group had taken place at least in half of the substrate during the above transformation. The exact proportion of the epimerized product was determined in the following step. The mixture 22 was treated with 1,3-propanedithiol and $BF_3 \cdot OEt_2$ (CH_2Cl_2, room temp. overnight) affording the dithioacetal 23 (55 % from 20), $[\alpha]_D^{26}$ -1.4 ($CHCl_3$), ν_{max}3450cm^{-1}, $\delta(CDCl_3)$0.83(3H,d,J=6Hz),0.86(3H,d,J=6Hz), 1.07(3H,d,J=6Hz), ~2.9(4H,m), 4.11(1H,d,J=4Hz). VPC-MS analysis of the corresponding bis-trimethylsilyl derivative of 23 indicated 25 % of contamination with a diastereomer.[12]

Selective protection (*t*-$BuMe_2SiCl$, imidazole, DMF, 0°, 2h) of the primary hydroxyl group of 23 was carried out to give 24 (89 %), $[\alpha]_D^{28}$ -10.7 ($CHCl_3$), ν_{max}3500cm^{-1}, $\delta(CDCl_3)$0.08 (6H,s) 0.88(9H,s),1.06(3H,d,J=7Hz),~2.9(4H,m),4.10(1H,d,J=4Hz), which was finally converted to the ethoxyethyl ether, synthon 4 (R^1 = $SiMe_2Bu^t$, R^2 = CH(OEt)Me, Y = -$S(CH_2)_3S$-), (ethyl vinyl ether, pyridinium p-tosylate, CH_2Cl_2, room temp., 7h, 88 % yield), $[\alpha]_D^{28}$ +27.6 ($CHCl_3$), $\delta(CDCl_3)$ 0.08(6H,s),0.88(9H,s),2.85(4H,m),4.08&4.12(1H,dx2,J=4Hz),4.64(1H,m).

In conclusion, all chiralities present in 1 except for C14 were successfully accommodated into two synthons 3 and 4 in a stereocontrolled way starting from methyl α-*D*-glucopyranoside.

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References and Notes

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11. Shorter period of reaction led to isolation of the intermediate glycal formed by the elimination of MeOH from 17.
12. Equilibration of the diastereomeric C15 methyl group of 1 under acidic condition was announced; see 6 a).

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