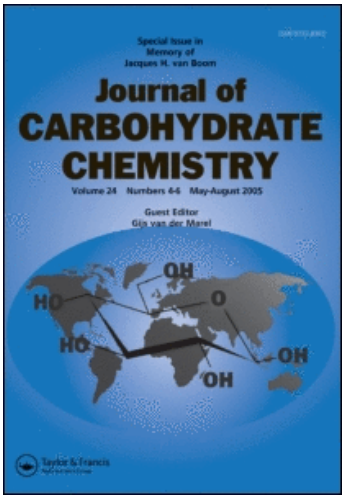

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Total Synthesis of Antibiotic A23187 (Calcimycin) from D-Glucose: Communication

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Communication

TOTAL SYNTHESIS OF ANTIBIOTIC A23187 (CALCIMYCIN) FROM D-GLUCOSE

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Antibiotic A23187 1[1] is a cation ionophore highly specific for Ca^{2+}. Because of its unique dioxaspiro ring structure as well as its biological activities,[2] several synthetic approaches to the compound have been reported.[3] We report here the first example of the total synthesis of 1 based on the use of a carbohydrate template.[4] The target structure 1 was synthesized from the chiral synthons or "chirons"[5] 5 and 6 via a key intermediate 4, as shown in Scheme I. A thermodynamically controlled, acid catalyzed ring closure of 4 was expected to provide a correct configuration at the spiro center C-14 according to the anomeric effect.[6] The two chirons 5 and 6 were prepared from D-glucose via the same intermediate 9 as follows (Scheme II).

Methyl 3,4-dideoxy-α-D-erythro-hex-3-enopyranoside 7,[7] obtainable in 4 steps from methyl α-D-glucopyranoside, was selectively oxidized and protected to give an α,β-unsaturated ketone 8 (86%). Addition of lithium dimethylcuprate to the enone system of 8 proceeded stereoselectively (>95%) to afford 9.[8] Reduction of the ketonic group and subsequent benzylation produced a diastereomeric mixture of 10 (72%). After removal of the ethoxyethyl group from 10 (86%), trifluoromethanesulfonylation and displacement with cyanide afforded the nitrile 11 in 87% yield. Methanolysis of 11 afforded the methyl ester 12, which was then

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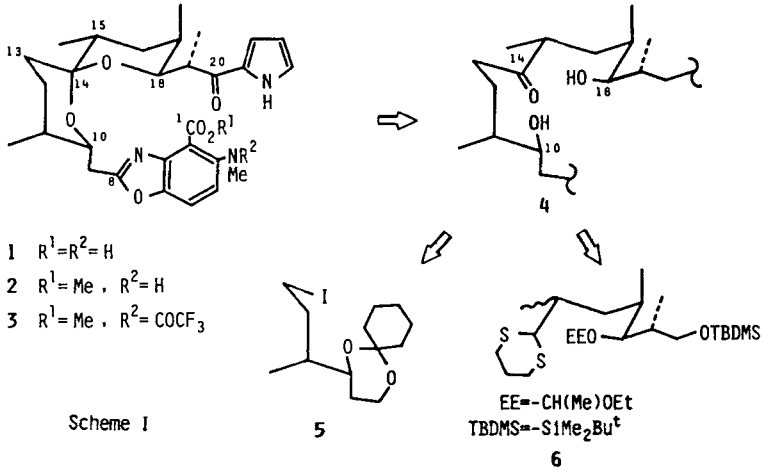
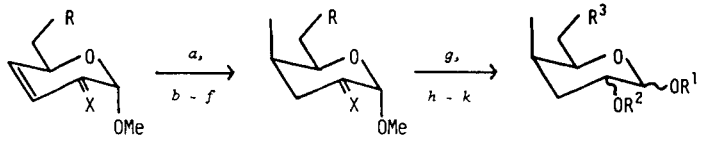


Scheme I

reduced to the alcohol 13 (84% from 11). The vicinal glycol 14, generated through deprotective processes, was cleaved by periodate oxidation and then reduced to the triol 15. Selective blocking of the 1,3-diol with cyclohexylidene gave a homogeneous mono-alcohol 16 ($[\alpha]_D^{26}$ +6.2°, C=0.68, $CHCl_3$: 43% from 13) after silica gel chromatography. Treatment of 16 with 2,4,5-triiodoimidazole-Ph_3P in toluene under reflux afforded the iodo derivative[9] corresponding to the chiron 5 ($[\alpha]_D^{26}$ +18.4°, C=0.6, $CHCl_3$; 69%), and representing the C8-C13 framework. The other chiron 6 was synthesized via a synthetic intermediate 19[10] in the following way. Wittig methylenation of 9 gave 17 (80%) which was hydrogenated to afford a diastereomeric mixture of dimethyl compounds 18. Replacement of ethoxyethyl group by the tosyl group facilitated the separation of the diastereomers by medium pressure column chromatography to give 19 (58% from 17). A further transformation of 19 to the chiron 6, involving highly stereoselective methylation of the bicyclic intermediate 20 into 21, was achieved as described in the previous paper.[10]

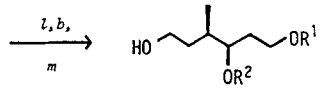
The coupling of two chirons 5 and 6 was performed in the presence of t-BuLi in hexane-HMPA to give 22 in 70% yield.



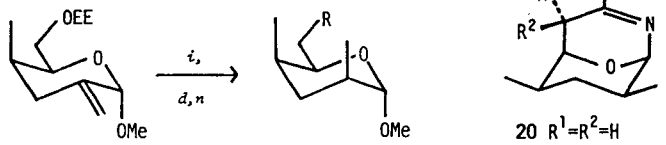
7 R=OH, X=H,OH (α)
8 R=OEE, X=O

9 R=OEE, X=O
10 R=OEE, X=H,OBn
11 R=CN, X=H,OBn

12 R^1=Me, R^2=Bn, R^3=CO_2Me
13 R^1=Me, R^2=Bn, R^3=CH_2OH
14 R^1=R^2=H, R^3=CH_2OH



15 R^1=R^2=H
16 R^1,R^2=cyclohexylidene



17

18 R=OEE
19 R=OTs

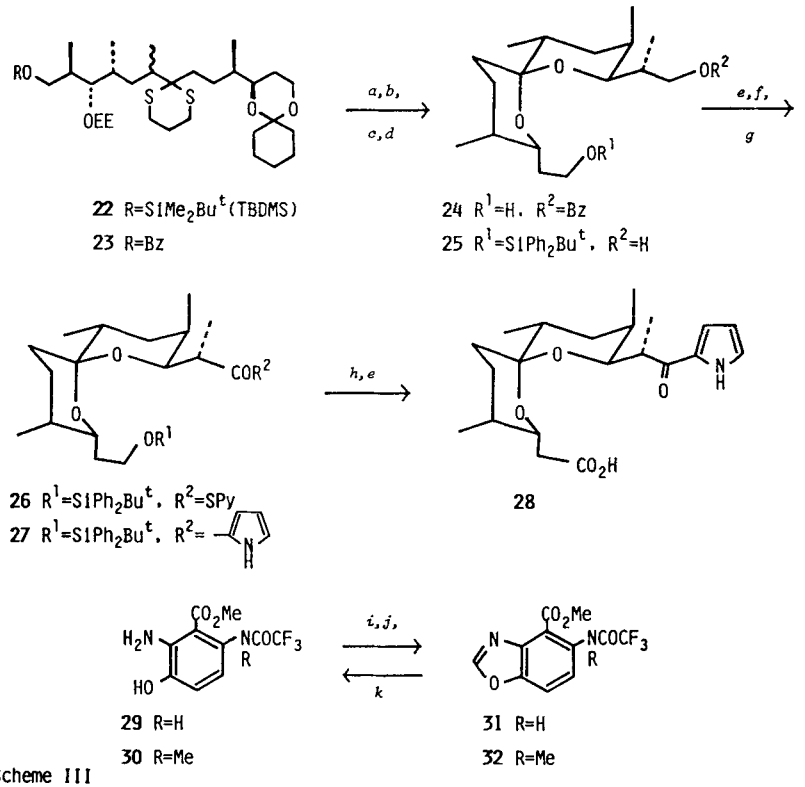
20 R^1=R^2=H
21 R^1=Me, R^2=H

Scheme II

[a] $LiMe_2Cu$, ether, -78°. [b] $NaBH_4$, EtOH. [c] BnBr, NaH, DMF. [d] p-TsOH, MeOH. [e] $(CF_3SO_2)_2O$, i-Pr_2EtN, CH_2Cl_2, -10°. [f] NaCN, DMF, room temperature, 30min. [g] HCl-MeOH, -8°, 2days; then MeOH-ether, reflux, 4h. [h] $LiAlH_4$, ether. [i] H_2(3.5Kg/cm^2), 10%Pd-C, EtOAc. [j] Ac_2O, BF_3OEt_2. [k] NaOMe, MeOH. [l] $NaIO_4$, EtOH. [m] 1,1-dimethoxycyclohexane, CSA, DMF; then 50%AcOH*aq*, ether. [n] p-TsCl, pyridine.

Desilylation (Bu_4NF, THF) of 22, followed by benzoylation (BzCl, pyridine), gave a 71% yield of 23. Hg^{2+} catalyzed hydrolysis of 23 and subsequent acid treatment gave a spiroketal 24[11] as the sole product ($[\alpha]_D^{26}$ +44.9°, C=0.49, $CHCl_3$; 66% overall yield from 23).

In order to complete the synthesis of 1, two heteroaromatic rings were introduced in the following way.[12] Silylation of 24 and then debenzoylation afforded 25, which was oxidized and subsequently transformed[13] into the pyridylthiol ester 26 ($[\alpha]_D^{26}$ +49.7°, C=0.62, $CHCl_3$; 43% overall yield from 24). Regioselective condensation of 26 with 3 equivalents of pyrrolemagnesium



22 R=SiMe$_2$Bu^t(TBDMS)
23 R=Bz

24 R^1=H, R^2=Bz
25 R^1=SiPh$_2$Bu^t, R^2=H

26 R^1=SiPh$_2$Bu^t, R^2=SPy
27 R^1=SiPh$_2$Bu^t, R^2=

28

29 R=H
30 R=Me

31 R=H
32 R=Me

Scheme III

[a] $HgCl_2$, $CaCO_3$, $aq CH_3CN$. [b] H_3PO_4-aqTHF, reflux, 20h. [c] t-$BuPh_2SiCl$, imidazole, DMF. [d] K_2CO_3, MeOH. [e] 8N-Jones reagent, acetone. [f] $(PyS)_2$, Ph_3P, CH_2Cl_2. [g] pyrrylmagnesium bromide, CuI, THF-ether, 0°. [h] n-Bu_4NF, THF. [i] $CH(OMe)_3$, p-TsOH, DMF. [j] MeI, K_2CO_3, acetone. [k] dil.HCl, 90°, 30min; then $aq Na_2CO_3$.

bromide[14] in the presence of CuI (1.5eq) in 1:1 THF-Et_2O at 0° afforded an 80% yield of a crystalline 27 (mp 102-103°, $[\alpha]_D^{26}$ +57.4°, C=0.195, $CHCl_3$).

The appropriately substituted aminophenol 30 (mp 121-121.5°) was prepared from 29[2a,f] in 3 steps; (i) selective protection of the adjacent aminophenolic function as an oxazole ring to give 31 (94%), (ii) methylation of 31 to give 32 (94%) and (iii) hydrolysis of the oxazole ring (68%). Desilylation (92%) of 27 and Jones

oxidation (84%) gave 28[11] ($[\alpha]_D^{26}$ +120.9°, C=0.88, $CHCl_3$), which was further converted into the mixed anhydride by treatment with $ClCO_2Et$-Et_3N in CH_2Cl_2 for 0.5h at 0° and immediately condensed with 30 in THF. The initial acylation took place at the phenolic oxygen but during chromatography over silica gel the acyl group migrated to give the amide, which was refluxed in $Cl(CH_2)_2Cl$ in the presence of pyridinium p-toluenesulfonate to give the benzoxazole 3. Finally, treatment of 3 with Bu_4NF afforded A23187 methyl ester 2[11] in 24% overall yield from 28. The synthetic 2 was identical in all respects (IR, 400MHz-NMR, high resolution MS, CD, HPLC) with the authentic sample prepared from the natural product 1 (CH_2N_2, ether). Hydrolysis of 2 to the free acid 1 has been described previously.[3a]

In conclusion, the fully stereocontrolled synthesis of A23187 by using the chirons derived from D-glucose is described. This approach may be versatile enough to be applicable to the synthesis of various analogs[15] of A23187.

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