Total Synthesis of (+)-Polyoxin J starting from *myo*-Inositol

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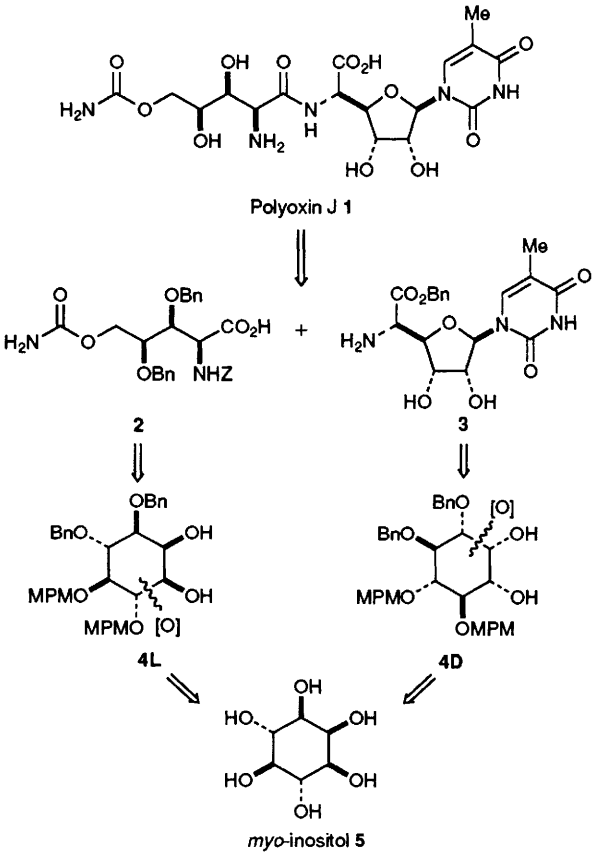
The total synthesis of the antifungal antibiotic, polyoxin J **1** starting from *myo*-inositol is described; the two key components, **2** and **3**, were prepared from a pair of optically resolved *myo*-inositol derivatives **4L** and **4D**, respectively, using a highly regioselective Baeyer–Villiger reaction, and finally coupled to complete the total synthesis.

Selectively protected and enantiomerically pure cyclitol derivatives are potentially useful chiral building blocks in natural product synthesis.[1] Given that regioselective cleavage of the cyclohexane ring is possible, its synthetic potential is even further extended; an array of chiral centres on the ring could be transferred to the stereogenic centres of acyclic or heterocyclic compounds.[1b,2] We now report successful implementation of this strategy to the total synthesis of polyoxin J **1**,[3–5] one of the components of the polyoxin complex, a class of antifungal compounds with a novel biological activity (chitin synthetase inhibitor),[6] starting from naturally abundant cyclitol, *myo*-inositol **5**. The key features in this synthesis involve (*i*) facile optical resolution of the *myo*-inositol derivative to give chiral, non-racemic **4L** and **4D**; (*ii*) conversion of **4L** into the side chain portion **2**, and **4D** into the nucleoside portion **3**, by regioselective Baeyer–Villiger cleavage of the cyclohexane ring (Scheme 1).

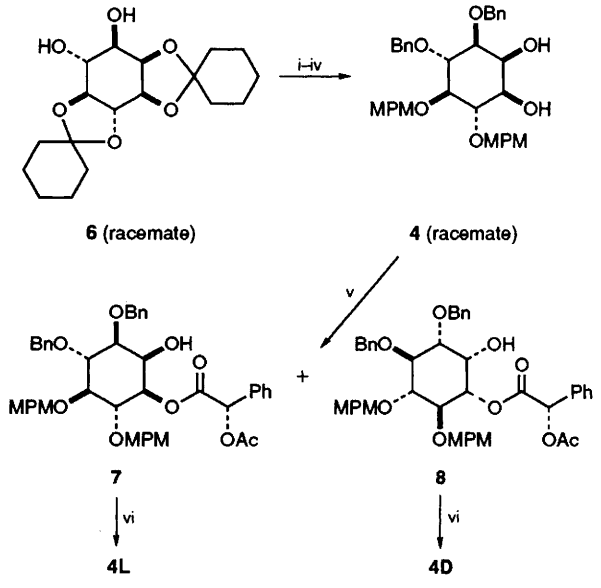
The known racemic diol **6**,[7] prepared from **5** in one step, was converted into **4**† in four steps (38% overall yield) (Scheme 2). The equatorial hydroxy group in racemic **4** was selectively acylated by a treatment with an equimolar amount of L-*O*-acetyl mandelic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to provide a pair of chiral diastereoisomers, **7** and **8**, which were easily separated by silica gel chromatography [R_f 0.46 for **7**, 0.57 for **8** on TLC (EtOAc–toluene 1:3)], in 34 and 31% isolated yields, respectively. Deacylation of **7** gave **4L** {$[\alpha]^{24}_D$ −16 (*c* 1, $CHCl_3$)} and that of **8** afforded the enantiomer **4D** {$[\alpha]^{24}_D$ +16 (*c* 1, $CHCl_3$)} both in quantitative yield.‡

Synthesis of the side chain **2** employed the enantiomer **4L**, which was selectively acylated at an equatorial hydroxy group with benzoyl chloride (1.1 molar equiv.) to give **9** in 73% yield (Scheme 3). Treatment of **9** with methanesulfonyl chloride and subsequent azidolysis provided **10**, the benzoyl group of which was removed to afford **11** in 83% overall yield. Baeyer–Villiger reaction of ketone **12**, prepared from **11** by Moffatt oxidation, proceeded highly regioselectively,§ and gave seven-membered lactone **13** exclusively. Without isolation, **13** was reduced with $NaBH_4$ in MeOH in the presence of catalytic amount of MeONa to give **14**, which was further reduced with lithium aluminum hydride, followd by treatment with benzyl chloroformate to provide **15** in 83% overall yield from **11**. After the formation of *N*,*O*-acetal, the *O*-MPM group was removed to give **16** in 58% yield. Glycol cleavage of **16** with lead tetraacetate in benzene followed by reductive work up and carbamoylation gave the carbamate **17** in 69% yield from **16**. Removal of the *N*,*O*-acetal group and subsequent oxidation afforded protected 5-*O*-carbamoyl polyoxamic acid **2**[4] in 90% (18% overall from **4L**) yield.

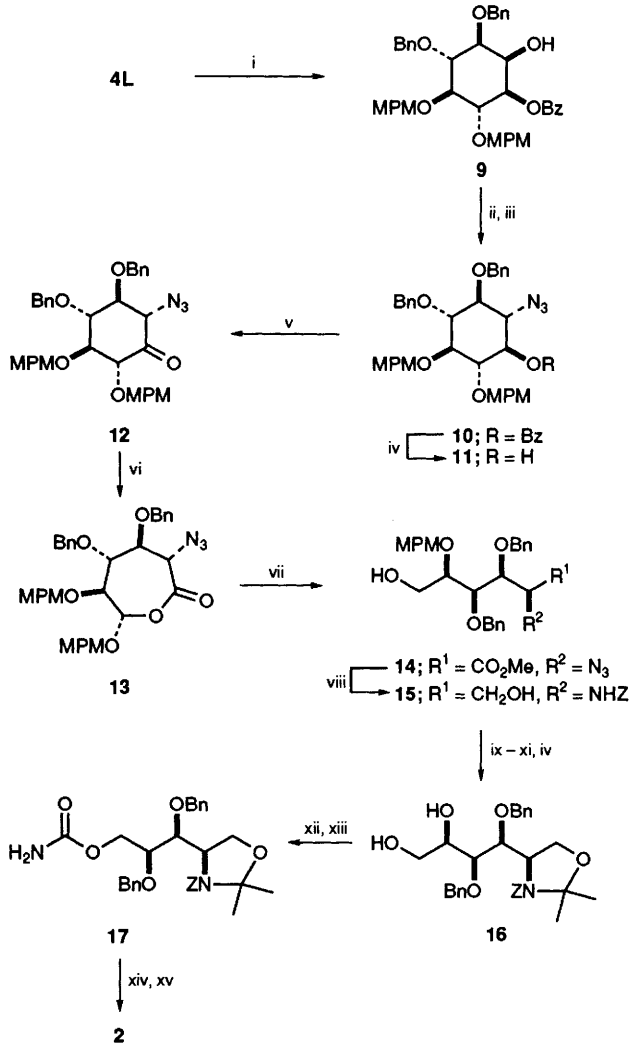
Preparation of nucleoside portion **3** started from the enantiomer **4D**, the equatorial hydroxy group was selectively benzoylated followed by oxidation with pyridinium dichromate (PDC) to give ketone **18** in 70% yield (Scheme 4). Baeyer–Villiger reaction of **18** with *m*-chloroperbenzoic acid (*m*CPBA) again proceeded in a regioselective manner§ and afforded **19**. When **19** was treated with $HC(OMe)_3$ and



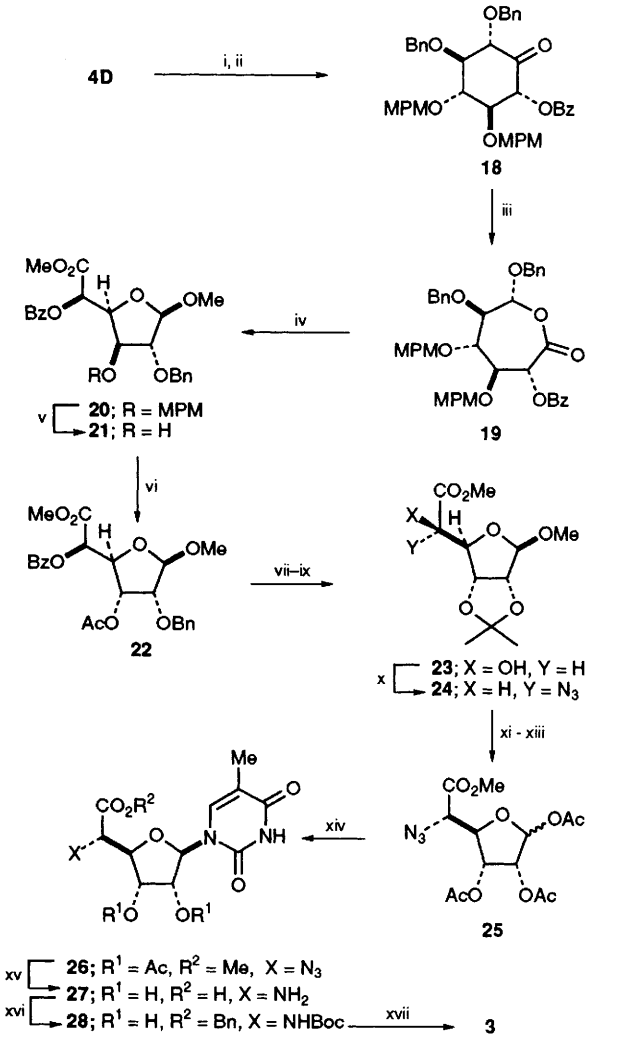
Scheme 1 Bn = $PhCH_2$, Z = $PhCH_2OC(O)$, MPM = (*p*-OMe)-$C_6H_4CH_2$



Scheme 2 *Reagents and conditions*: i, NaH, BnBr, *N*,*N*-dimethylformamide (DMF); ii, TsOH (5 mol%), EtOH, room temp.; iii, NaH, MPMCl, DMF; iv, AcOH–H_2O (4:1), 80 °C; v, L-*O*-acetylmandelic acid, DCC, DMAP, CH_2Cl_2, −15 °C; vi, MeONa, MeOH, 0 °C

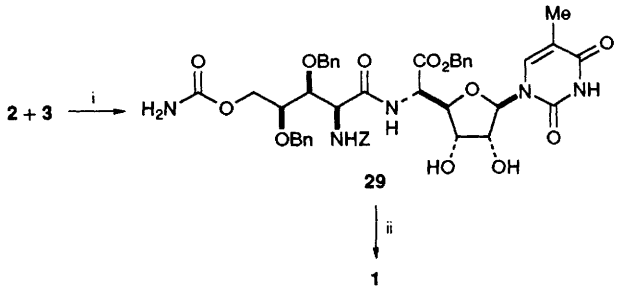


Scheme 3 *Reagents and conditions*: i, BzCl, DMAP, pyridine, room temp.; ii, $MeSO_2Cl$, pyridine, 50 °C.; iii, NaN_3, DMF, 80 °C; iv, MeONa, MeOH; v, dimethylsulfoxide, DCC, TFA, pyridine, benzene, room temp.; vi, *m*CPBA, $KHCO_3$, $(CH_2Cl)_2$, 0 °C; vii, $NaBH_4$, MeONa, MeOH, 0 °C; viii, lithium aluminum hydride, diethyl ether then ZCl, $NaHCO_3$, tetrahydrofuran (THF)–H_2O; ix, $CH_2(OMe)_2$, TsOH, DMF; x, Ac_2O, pyridine; xi, DDQ, CH_2Cl_2–H_2O; xii, $Pb(OAc)_4$, benzene, room temp., then $NaBH_4$, MeOH; xiii, 4-nitrophenyl chloroformate then NH_3–MeOH, CH_2Cl_2; xiv, TsOH, MeOH, room temp.; xv, Jones reagent (CrO_3 in dil. H_2SO_4), acetone, 0 °C Bz = PhC(O)



Scheme 4 *Reagents and conditions*: i, BzCl, DMAP, pyridine; ii, PDC, molecular sieves 4A, CH_2Cl_2; iii, *m*CPBA, $KHCO_3$, $(CH_2Cl)_2$, 0 °C; iv, TsOH, $HC(OMe)_3$, MeOH, room temp. then MeI, $NaHCO_3$, DMF; v, DDQ, CH_2Cl_2–H_2O, room temp.; vi, $(CF_3SO_2)_2O$ (Tf_2O), pyridine, CH_2Cl_2, 0 °C then AcOK, DMF, 5 °C; vii, MeONa, MeOH; viii, H_2, $Pd(OH)_2$, EtOH; ix, $MeC(OMe)_2$, TsOH, DMF, room temp.; x, Tf_2O, pyridine, CH_2Cl_2, 0 °C then NaN_3, DMF, room temp.; xi, Dowex 50w X8, MeOH, room temp.; xii, Ac_2O, pyridine; xiii, Ac_2O, H_2SO_4, CH_2Cl_2-AcOH; xiv, 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, $Me_3SiOSO_2CF_3$, CH_2Cl_2, room temp.; xv, H_2, 5% Pd–$BaSO_4$, dioxane–H_2O then 1 mol dm^{-3} $Ba(OH)_2$, H_2O–dioxane, room temp.; xvi, di-*tert*-butyl dicarbonate, K_2CO_3, dioxane–H_2O then BnBr, $NaHCO_3$, DMF, room temp.; xvii, TFA, EtOAc, 0 °C

methanol in the presence of toluene-*p*-sulfonic acid (TsOH), opening of the lactone ring and subsequent furanoside formation with loss of *O*-MPM group at 3-C position in **19** took place to provide methyl α-furanoside **20** (54% from **18**) and its β-anomer (29% from **18**) after methyl ester formation. The *O*-MPM group in **20** was deprotected to give **21** (70%), which was then converted into the inverted acetate **22** *via* the derived triflate intermediate (55% yield). Removal of the benzyl and acyl protecting groups in **22** followed by acetal formation gave **23** (53%). Treatment of **23** with $(CF_3SO_2)_2O$ and subsequent azidolysis of the resulting triflate afforded **24**¶ in 66% yield. Exchange of the protecting group in **24** was accomplished by the literature procedure[5b] to afford acetate **25**¶ (81% yield), which was subjected to Vorbrüggen condensation[8] with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine,[9] to provide β-nucleoside **26** in 93% yield. Hydrogenolysis of **26** and subsequent basic hydrolysis afforded deoxypolyoxin C[5a,c,d] **27** (76%), which was converted into the protected derivative **28** (100%). Treatment of **28** with trifluoroacetic



Scheme 5 *Reagents and conditions*: i, $(EtO)_2P(O)CN$, Et_3N, DMF, room temp.; ii, H_2, 10% Pd-C, MeOH–H_2O

acid (TFA) gave **3** (as its TFA salt) in a quantitative yield (2.9% overall yield from **4D**).

Coupling of **2** and **3** was conducted under conditions of Shioiri *et al.*[10] and the condensate **29** was obtained in 54% yield. Hydrogenolysis of **29**, followed by purification with avicel column chromatography provided **1** as an amorphous solid in 73% yield.‖ The ^{1}H NMR spectrum of **1** [270 MHz, in 3 wt% DCl–D_2O] was identical with that of the authentic polyoxin J, kindly provided by Professors Kuzuhara and Isono,** and the physical properties of synthetic **1** {mp 200–210 °C (decomp.), [authentic sample, mp 198–208 °C (decomp.)]; $[\alpha]^{23}_D$ +35 (*c* 0.8, H_2O), lit[4] $[\alpha]^{23}_D$ +33 (*c* 0.75, H_2O)]} showed a good accord with those of the authentic sample.

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Footnotes

† All new compounds described in this communication were homogeneous on TLC and spectrometric analyses; no epimerisation at carbons adjacent to the carbonyl group was observed during this synthesis.

‡ The absolute configuration and the optical purity of **4L** and **4D** were confirmed by their transformation into the known compounds, 1L- and 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol,[11] respectively, in the following four-step reaction; (*i*) acetonide formation [$H_2C(OMe)_2$, TsOH]; (*ii*) removal of *O*-MPM group [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), aqueous CH_2Cl_2]; (*iii*) benzylation [NaH, benzyl bromide]; (*iv*) acid hydrolysis of the acetonide group [TsOH, MeOH, room temp.]. For 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol prepared from **4L**: mp 144–145 °C; $[\alpha]^{23}_D$ − 24 (*c* 1, $CHCl_3$), lit.[11] mp 141–143 °C, $[\alpha]^{20}_D$ − 24.3 (*c* 1.3, $CHCl_3$). For 1D-isomer prepared from **4D**: mp 144–145 °C; $[\alpha]^{24}_D$ +25 (*c* 1, $CHCl_3$), lit.[11] mp 140–142 °C, $[\alpha]^{20}_D$ + 25.0 (*c* 0.18, $CHCl_3$).

§ The electronic control may account for the observed regioselectivity in Baeyer–Villiger reaction of the ketone **12** and **18**. The carbon with a more electron donating substituent (*p*-methoxybenzyloxy or benzyloxy) underwent 1,2-migration to the adjacent oxygen atom. See also ref. 2(*a*) and 12.

¶ This compound has been synthesized from D-ribose by Barrett and Lebold in their synthesis of polyoxin C.[5b] the spectral data showed a full accord with that reported in the literature.

‖ This sequence provided 20 mg of polyoxin J **1**.

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