

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

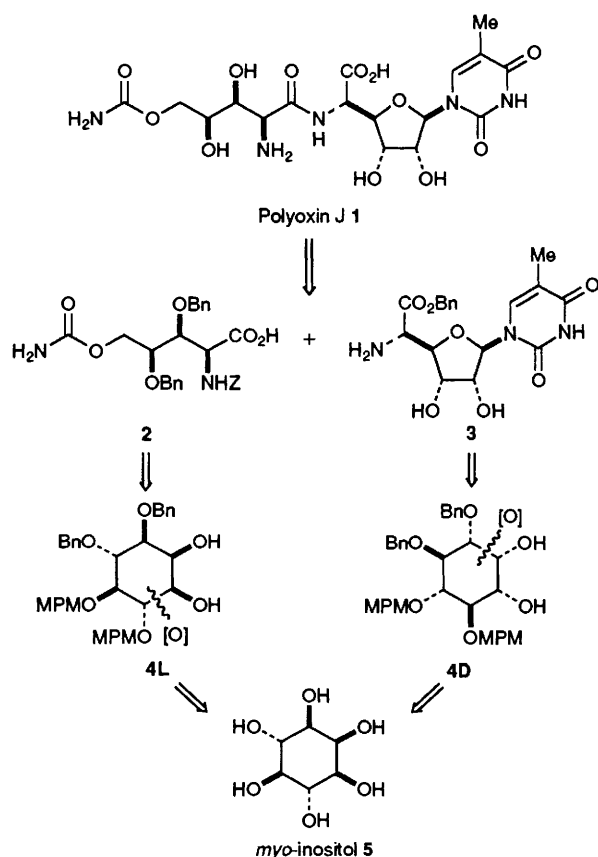
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The total synthesis of the antifungal antibiotic, polyoxin J **1** starting from *myo*-inositol is described; the two key components, **2** and **3**, were prepared from a pair of optically resolved *myo*-inositol derivatives **4L** and **4D**, respectively, 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

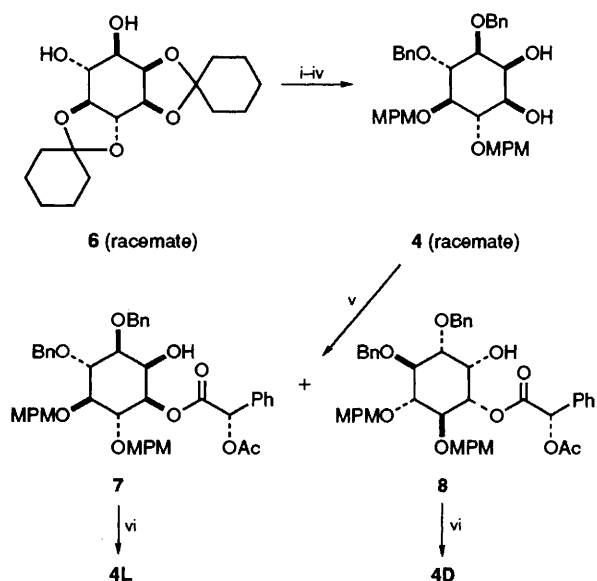


Scheme 1 Bn = PhCH₂, Z = PhCH₂OC(O), MPM = (*p*-OMe)-C₆H₄CH₂

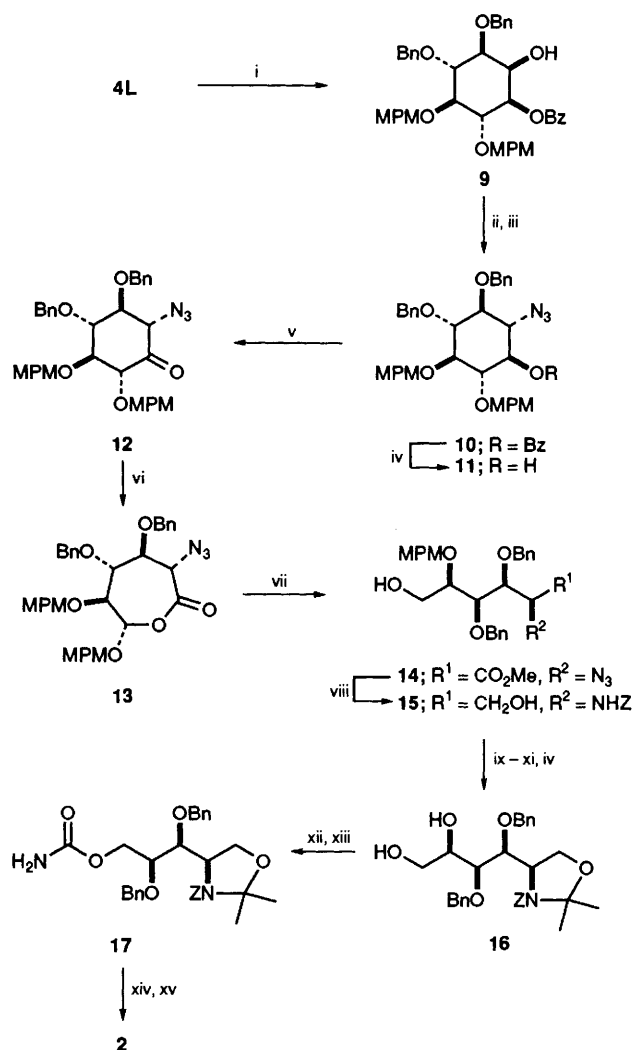
easily separated by silica gel chromatography [*R*_f 0.46 for **7**, 0.57 for **8** on TLC (EtOAc–toluene 1:3)], in 34 and 31% isolated yields, respectively. Deacylation of **7** gave **4L** {[α]_D²⁴ –16 (*c* 1, CHCl₃)} and that of **8** afforded the enantiomer **4D** {[α]_D²⁴ +16 (*c* 1, CHCl₃)} both 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 NaBH₄ in MeOH in the presence of catalytic amount of MeONa to give **14**, which was further reduced with lithium aluminum hydride, followed 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 **24** 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

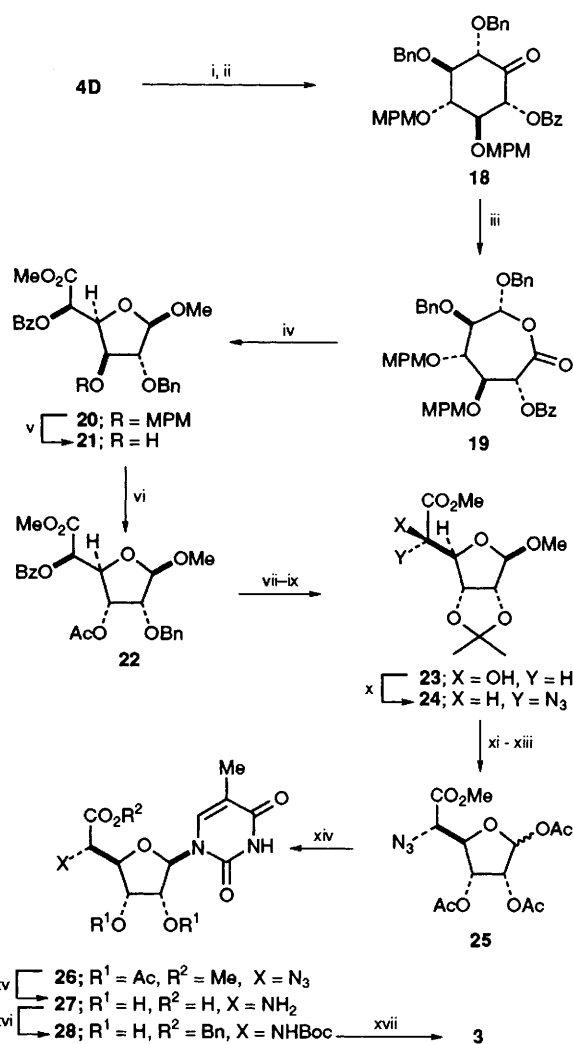


Scheme 2 Reagents and conditions: i, NaH, BnBr, *N,N*-dimethylformamide (DMF); ii, TsOH (5 mol%), EtOH, room temp.; iii, NaH, MPMCl, DMF; iv, AcOH–H₂O (4:1), 80 °C; v, *L*-*O*-acetylmandelic acid, DCC, DMAP, CH₂Cl₂, –15 °C; vi, MeONa, MeOH, 0 °C

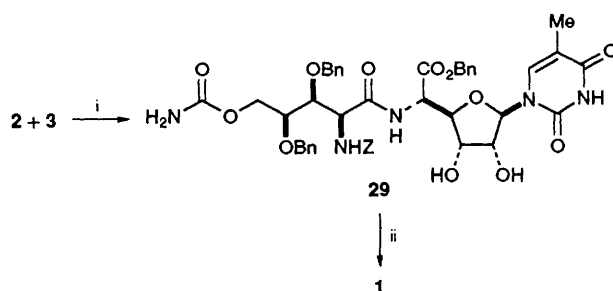


Scheme 3 Reagents and conditions: i, BzCl, DMAP, pyridine, room temp.; ii, MeSO₂Cl, pyridine, 50 °C; iii, NaN₃, DMF, 80 °C; iv, MeONa, MeOH; v, dimethylsulfoxide, DCC, TFA, pyridine, benzene, room temp.; vi, *m*CPBA, KHCO₃, (CH₂Cl)₂, 0 °C; vii, NaBH₄, MeONa, MeOH, 0 °C; viii, lithium aluminum hydride, diethyl ether then ZCl, NaHCO₃, tetrahydrofuran (THF)-H₂O; ix, CH₂(OMe)₂, TsOH, DMF; x, Ac₂O, pyridine; xi, DDQ, CH₂Cl₂-H₂O; xii, Pb(OAc)₄, benzene, room temp., then NaBH₄, MeOH; xiii, 4-nitrophenyl chloroformate then NH₃-MeOH, CH₂Cl₂; xiv, TsOH, MeOH, room temp.; xv, Jones reagent (CrO₃ in dil. H₂SO₄), acetone, 0 °C Bz = PhC(O)

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 (CF₃SO₂)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 condensation⁸ 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 4 Reagents and conditions: i, BzCl, DMAP, pyridine; ii, PDC, molecular sieves 4A, CH₂Cl₂; iii, *m*CPBA, KHCO₃, (CH₂Cl)₂, 0 °C; iv, TsOH, HC(OMe)₃, MeOH, room temp. then MeI, NaHCO₃, DMF; v, DDQ, CH₂Cl₂-H₂O, room temp.; vi, (CF₃SO₂)₂O (Tf₂O), pyridine, CH₂Cl₂, 0 °C then AcOK, DMF, 5 °C; vii, MeONa, MeOH; viii, H₂, Pd(OH)₂, EtOH; ix, MeC(OMe)₂, TsOH, DMF, room temp.; x, Tf₂O, pyridine, CH₂Cl₂, 0 °C then NaN₃, DMF, room temp.; xi, Dowex 50w X8, MeOH, room temp.; xii, Ac₂O, pyridine; xiii, Ac₂O, H₂SO₄, CH₂Cl₂-AcOH; xiv, 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, Me₃SiOSO₂CF₃, CH₂Cl₂, room temp.; xv, H₂, 5% Pd-BaSO₄, dioxane-H₂O then 1 mol dm⁻³ Ba(OH)₂, H₂O-dioxane, room temp.; xvi, di-*tert*-butyl dicarbonate, K₂CO₃, dioxane-H₂O then BnBr, NaHCO₃, DMF, room temp.; xvii, TFA, EtOAc, 0 °C



Scheme 5 Reagents and conditions: i, (EtO)₂P(O)CN, Et₃N, DMF, room temp.; ii, H₂, 10% Pd-C, MeOH-H₂O

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 ¹H NMR spectrum of **1** [270 MHz, in 3 wt% DCl-D₂O] 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.)]; [α]²³_D +35 (c 0.8, H₂O), lit.⁴ [α]²³_D +33 (c 0.75, H₂O)} 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-myco-inositol,¹¹ respectively, in the following four-step reaction; (i) acetonide formation [H₂C(OMe)₂, TsOH]; (ii) removal of O-MPM group [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), aqueous CH₂Cl₂]; (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-myco-inositol prepared from **4L**: mp 144–145 °C; [α]²³_D – 24 (c 1, CHCl₃), lit.¹¹ mp 141–143 °C, [α]²⁰_D – 24.3 (c 1.3, CHCl₃). For 1D-isomer prepared from **4D**: mp 144–145 °C; [α]²⁴_D +25 (c 1, CHCl₃), lit.¹¹ mp 140–142 °C, [α]²⁰_D + 25.0 (c 0.18, CHCl₃).

§ 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 benzyl-oxy) 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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