Total Synthesis of (+)-Polyoxin J

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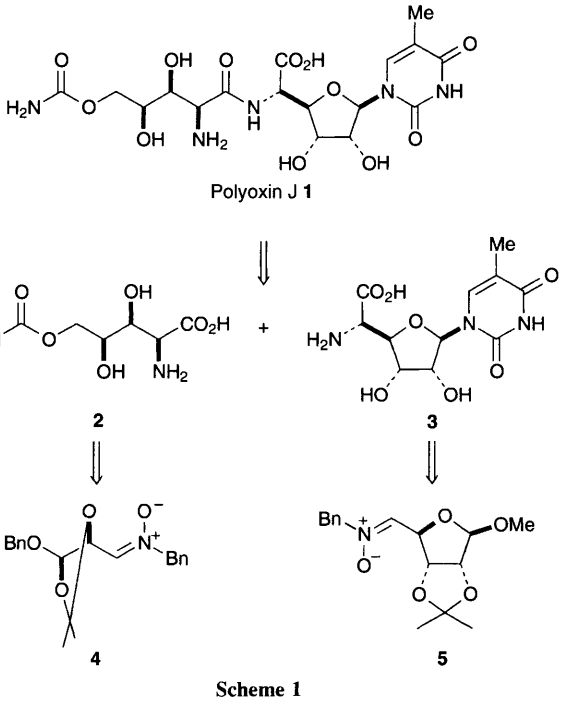
The antifungal antibiotic, polyoxin J **1**, has been obtained (46.4%) by the coupling of a protected derivative of 5-*O*-carbamoylpolyoxamic acid **2** with thymine polyoxin C **3** which were prepared by a stereoselective aminohomologation strategy of sugar aldehydes (L-threose and dialdo-D-ribofuranose) employing nitrones **4** and **5** as their iminium derivatives and furan as a carboxylate group equivalent.

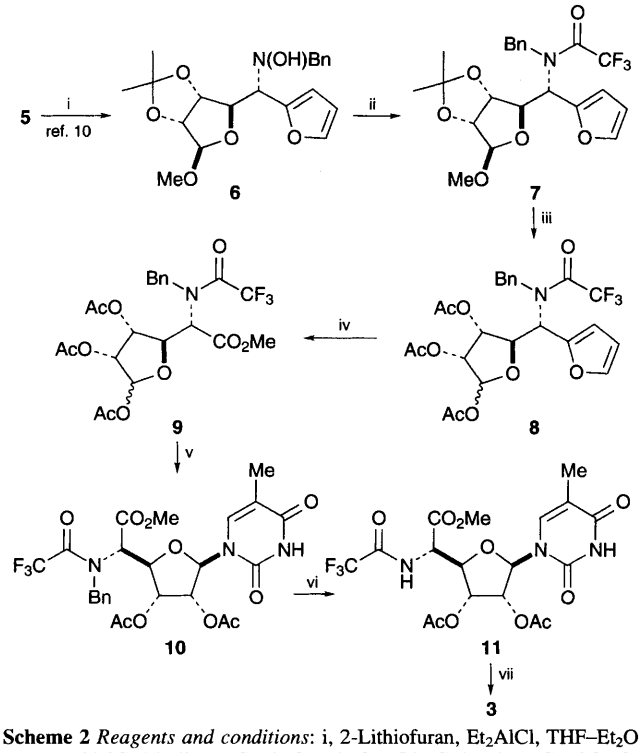
Polyoxin J **1** is one of the components of a wide class of peptidyl pyrimidine nucleoside antibiotics[1] which are attracting increasing interest as antifungal compounds[2] because of their ability to inhibit fungal cell wall chitin biosynthesis.[3] Two total syntheses of **1** have been reported with a twenty year gap between them,[4,5] both methods involving coupling of the key components of the molecule, 5-*O*-carbamoylpolyoxamic acid **2** and thymine polyoxin C **3** (Scheme 1). The efficient synthesis of protected derivatives of these compounds is *per se* an important issue which although addressed in various instances over the years,[6] still appears worth investigation. With the total synthesis of **1** and the development of a general synthetic method of the various components of the polyoxin complex as our goals, we studied new syntheses of **2** and **3** employing nitrones **4** and **5** derived from sugar aldehydes. A strategy for aldehyde homologation to the α-amino aldehyde and acid *via* addition of 2-thiazolyl-[7] (masked formyl) and 2-furyllithium[8] (masked carboxyl) to nitrones has been recently developed in our laboratories and its successful implementation to the synthesis of **2** and **3** has been described.[9,10] Here we report an improved reaction sequence leading to the nucleoside **3** and the coupling with an activated derivative of **2** to complete the total synthesis of polyoxin J **1**.

The diastereoselective addition (d.s. 82% of correct isomer) of 2-furyllithium to the ribofuranosyl nitrone **5** precomplexed with Et_2AlCl to give the hydroxylamine **6** (72%) has been previously described[10] (Scheme 2). Given the low yields of the reactions leading to **3**, particularly the anomeric acetolysis because of the competitive endocyclic mode of glycosyl cleavage,[11] compound **6** was elaborated as follows. The *N*-hydroxy group was removed *N*-benzylamino group was protected as the trifluoroacetamido derivative by treatment with trifluoroacetic anhydride in the presence of pyridine. In this way, amide **7** was obtained in 56% yield.† After deisopropylidenation of **7** by acid hydrolysis, treatment of the resulting furanose with acetic anhydride in the presence of pyridine gave the triacetate **8** (78%) as a mixture of α- and β-anomers (24 : 76). The carboxylic group was liberated from the furan ring of **8** by treatment with $RuCl_3$–$NaIO_4$. Without isolation, the carboxylic acid was converted by diazomethane into the methyl ribofuranosyl glycinate derivative **9** in 60% overall yield. This product was subjected to Vorbrüggen condensation[12] with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine to exclusively provide the β-nucleoside **10** (70%). *N*-Debenzylation of **10** by hydrogenolysis over $Pd(OH)_2$ gave **11** from which all the remaining protective groups were removed by treatment with lithium hydroxide in THF. The thymine polyoxin C **3** was thus isolated in 67% yield and 10.6% overall yield from the nitrone **5**. Synthetic **3** prepared by the above and earlier reaction sequence[10] showed identical characteristics which were in agreement with literature values.‡

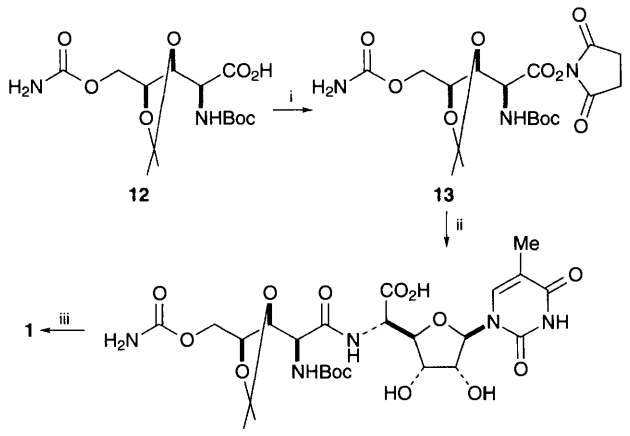
Successful coupling of **3** with a protected derivative of **2** was performed by the *N*,*N*-dicyclohexylcarbodiimide–*N*-hydroxysuccinimide (DCC–HOSu) active ester method[4] in Me_2SO and



Scheme 1



Scheme 2 *Reagents and conditions*: i, 2-Lithiofuran, Et_2AlCl, THF–Et_2O (1 : 1), −80 °C, 1 h; ii, Zn, $Cu(AcO)_2$, AcOH, 70 °C, 2 h then $(CF_3CO)_2O$, pyridine–CH_2Cl_2 (1 : 1), room temp., 3 h; iii, AcOH–HCl–H_2O (80 : 1 : 19), 70 °C, 4 h then Ac_2O, DMAP, pyridine, room temp., 2 h; iv, $RuCl_3$, $NaIO_4$, MeCN–CCl_4–H_2O (2 : 2 : 3), room temp., 15 min. then CH_2N_2, Et_2O, 0 °C, 1 h; v, 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, $Me_3SiOSO_2CF_3$, CH_2Cl_2, reflux, 2 h; vi, H_2, $Pd(OH)_2$–C 20%, MeOH, room temp., 6 h; vii, LiOH, THF–H_2O (6 : 1), 0 °C, 1 h



Scheme 3 *Reagents and conditions*: i, *N*-hydroxysuccinimide, DCC, EtOAc, 0 °C, room temp., 8 h; ii, thymine polyoxin C **3**, Pr^i_2EtN, Me_2SO, room temp., 24 h; iii, TFA–MeOH–H_2O (1 : 1 : 2), 0 °C, 2 h

N,*N*-diisopropylethylamine as base[13] (Scheme 3). Thus, the polyoxamic acid derivative **12** obtained as described earlier (21.7% from a protected derivative of L-threose),[9] by treatment with DCC–HOSu was converted into the active ester **13** which was then condensed with **3** to give the dipeptide **14** (58%).‡ Removal of the *N*-Boc and *O*-isopropylidene protecting groups from **14** upon acid hydrolysis afforded polyoxin J **1** in 80% yield (46.4% overall from **3** and **12**). The physical properties of compound **1** were in good agreement with the literature values of both synthetic and natural polyoxin J.‡ The efficient coupling of unprotected **3** with the relatively hindered α-amino acid **12** is noteworthy since a similar reaction employed for the assemblage of the components of nikkomycin Z gave very poor results.[14]

This new synthesis of polyoxin J **1** from protected derivatives of L-threose and dialdo-D-ribofuranose§ provides an illustration of the synthetic utility of the aminohomologation strategy and indicates a viable route for the synthesis of other components of the polyoxin[1] and nikkomycin[14] families.

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Footnotes

† All new compounds as well as the synthetic polyoxin J **1** and thymine polyoxin C **3** exhibited consistent ^1H and ^{13}C NMR spectra.

‡ *Physical and spectroscopic data* for compound **3**: mp 170 (soft), 192 °C, $[\alpha]_D$ +8.8 (*c* 0.09, H_2O), HRMS (FAB, H_2O–glycerol): Calc. for $C_{11}H_{15}N_3O_7$ (M + H$^+$): 302.0988, Found: 302.0987. Lit.,[11] mp 182–185 and 190–194 °C, $[\alpha]_D$ +8.0 (*c* 0.37, H_2O). For compound **14**: mp 110° (soft), 172 °C, $[\alpha]_D$ −17.2 (*c* 0.34, MeOH), LRMS (FAB, MeOH–glycerol): 632 (M + H$^+$). For compound **1**: mp 200 °C (dec), $[\alpha]_D$ +30.3 (*c* 0.10, H_2O), LRMS (FAB, MeOH–NBA): 492 (M + H$^+$). For synthetic **1**: Lit.,[5] mp 200–210 °C (dec), $[\alpha]_D$ +35.0 (*c* 0.8, H_2O), lit.,[4] $[\alpha]_D$ +33 (*c* 0.75, H_2O); for authentic **1**: lit.,[5] mp 198–208 °C (dec), lit.,[4] $[\alpha]_D$ +31 (solvent not given).

§ 4-*O*-Benzyl-2,3-*O*-isopropylidene-L-threose (T. Mukaiyama, K. Suzuki, T. Yamada and F. Tabusa, *Tetrahedron*, 1990, **46**, 265) is the starting material for the synthesis of **12** while methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside (A. M. Sepulchre, G. Vass and S. D. Gero, *Tetrahedron Lett.*, 1973, 3619) is used for the synthesis of **3**.

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