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Total Synthesis of Thymine Polyoxin C

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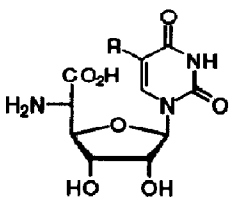
Abstract: *An expeditious synthesis of thymine polyoxin C in 6 steps (7.2% overall yield) based on the stereocontrolled addition of 2-lithiofuran, a masked carboxylate group, to the N-benzyl nitrone derived from methyl 2,3-O-isopropylidene-dialdo-D-ribofuranoside, is described.*

Polyoxins form an important class of peptidyl nucleosides identified in the culture broths of *Streptomyces cacaoi* var. *asoensis*,[1] which are potent competitive inhibitors of *Candida albicans* chitin synthetase. Since chitin is a major component of the cell walls of many fungi, inhibitors of chitin synthetase hinder fungal growth. Quite interestingly, all members of the polyoxin family[1] and related classes of compounds such as nikkomycins,[2] feature the 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)pyrimidine **1** as a common structural unit. Hence, the development of a general synthetic route to *N*-glycosides **1a-c** is an issue of considerable importance.[3]

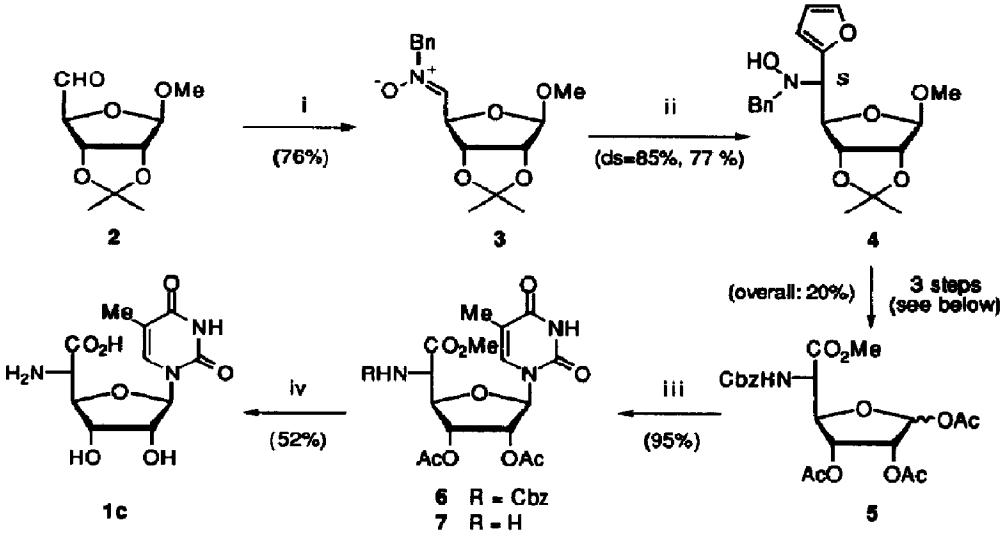


1a R = CH_2OH Polyoxin C
1b R = H Uracil Polyoxin C
1c R = CH_3 Thymine Polyoxin C

We recently described a route to chiral α-amino acids based on the stereocontrolled addition of 2-lithiothiazole to nitrones derived from polyalkoxy aldehydes.[4] In this methodology the *N*-oxide moiety of the nitrone is the precursor of the amino group while the furan ring furnishes the carboxylic acid. In a related nitrone-based synthesis of α-amino aldehydes,[5] the thiazole ring served as a masked formyl group equivalent. Hence, we report here the total synthesis of thymine polyoxin C **1c** using the nitrone-furan strategy. The starting material for the synthesis, the *N*-benzyl nitrone **3** (mp 54 °C; $[\alpha]_D$ = -85.9° (c 0.9, $CHCl_3$) (Scheme 1),[6] was prepared (76 %) by condensation of benzylhydroxylamine with the readily available methyl 2,3-*O*-

isopropylidene-dialdo-D-ribofuranoside[7] **2** as described.[8] Crucial to a successful synthesis was the stereocontrolled installation of the furan ring at the carbon atom of the nitrone **3**. Following previous observation on the effect of Lewis acids on this reaction,[4] 2-lithiofuran was reacted with **3** in the presence of 1.0 equiv. of Et_2AlCl. This reaction proceeded with good diastereoselectivity (ds = 85%) to give the *N*-benzyl hydroxylamine[9] **4** as the major adduct in 77% isolated yield by chromatography (90:10, hexane-diethyl ether). That the adduct **4** was the stereoisomer with the correct *S*-configuration at C-5 required for the continuation of the synthesis was demonstrated by comparative n.O.e. experiments carried out on both this compound and its epimer obtained by stereoselective addition (ds ≥95%) of 2-lithiofuran to **3** in the absence of Et_2AlCl.

Scheme 1



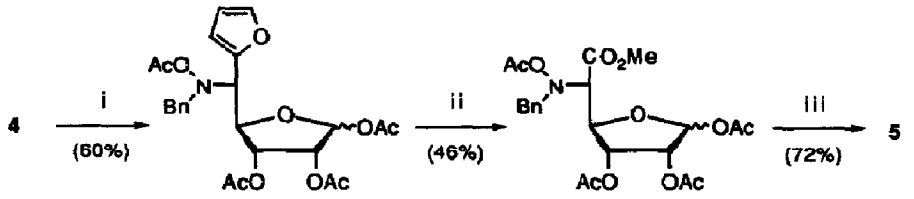
Reagents and conditions: (i) $PhCH_2NHOH$, CH_2Cl_2, $MgSO_4$. (ii) Et_2AlCl, Et_2O, r.t., 5 min; then 2-lithiofuran, THF, -80°C, 1h. (iii) 2,4-bis(trimethylsiloxy)-5-methyl-pyrimidine, TMSOTf, CH_2Cl_2, reflux. (iv) LiOH, THF, 0°C, 1h; then H_2, 10% Pd-C, MeOH, 1 atm., r.t., 4h.

The hydroxylamine **4** was transformed (see below) into the key intermediate glycosyl α-amino ester[3] **5** that was isolated (20 %) as a mixture of α- and β-anomers in 40 : 60 ratio.[10] Although the conversion of anomeric mixtures of **5** into **1c** has been described,[3a,c] the synthesis was continued with our own material to prove its efficiency. First, the trimethylsilyl triflate (TMSOTf, 6 equiv.) promoted coupling of **5** with the bis-silylated thymine (3.5 equiv.) afforded the β-nucleoside α-amino ester **6** in 75% isolated yield.[11] Then, deprotection of **6** by hydrolysis with lithium hydroxyde in THF and catalytic hydrogenation in methanol, gave thymine polyoxin C **1c** in 7.2% overall yield from the nitrone **3**. The characteristics of our synthetic **1c** were in agreement with the literature values,[12] thus confirming all stereochemical assignments in this series.

The elaboration of the hydroxylamine **4** to the α-amino ester **5** required three operations : a) the glycosyl activation; b) the conversion of hydroxylamino into amino group; c) the oxidative cleavage of furyl to carboxyl group. After several unsuccessful attempts caused mainly by endocyclic mode of glycosyl cleavage in step a) by acetolysis,[3a] a suitable reaction sequence[6] is presented in Scheme 2. After deacetonization of **4** by acid hydrolysis, treatment of the resultant product with acetic anhydride in pyridine led to the peracetylated glycosyl

acetate **8** (60 % yield) as a mixture (40 : 60) of α- and β-anomers. Athough these anomers were separated by colum chromatography (60:40, hexane-diethyl ether) and characterized,[13] the synthesis was continued with the mixture of these compounds. Thus, the carboxylic acid was liberated from **8** by cleavage of the furan ring with catalytic RuO_2 in the presence of 4.0 equiv. of $NaIO_4$ as a reoxidant. Then, treatment of this crude reaction product with diazomethane gave the ester **9** (45 % yield) as a mixture (40 : 60) of α- and β-anomers.[14] The exposure of this mixture to the action of molecular hydrogen (r.t., 7 atm) using 10% Pd-C as a catalyst, induced the removal of the *N*-acetoxy and *N*-benzyl group leading to a primary amine which was protected as the *N*-benzyloxycarbonyl (Cbz). The resultant *C*-glycosyl amino ester **5** was isolated in 20 % overall yield from **4**.

Scheme 2



8 **9**

Reagents and conditions: (i) AcOH-H_2O-HCl (80:19:1), 60°C, 4h; then Ac_2O, Py, DMAP. (ii) RuO_2, $NaIO_4$, CH_3CN-CCl_4-H_2O (3:2:2); then CH_2N_2, Et_2O, 0°C, 5 min. (iii) H_2, 10% Pd-C, AcOH, 7 atm., r.t., 48h; then BnOCOCl, $NaHCO_3$, dioxane, 0°C, 15 min.

The route described above provides an expeditious total synthesis of thymine polyoxin C **1c** based on a new approach to the key intermediate **5**. Since this C-glycosyl amino ester and differentially *N*-protected analogs have been shown[15] to be advanced intermediates in the synthesis of various polyoxins, the extension of this chemistry now becomes quite interesting

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6. All compounds showed consitent NMR and IR data with the assigned structure and gave satisfactory elemental analyses.
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9. **4**: oil; $[\alpha]_D$ = -12.2° (c 2.3 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.46 (s, 3H), 3.04 (s, 3H), 3.64 (d, 1H, J = 13.0 Hz), 3.72 (d, 1H, J = 13.0 Hz), 3.93 (d, 1H, J = 11.0 Hz), 4.58 (d, 1H, J = 6.1 Hz), 4.75 (dd, 1H, J = 11.0, 1.0 Hz), 4.88 (s, 1H), 4.97 (bs, 1H, ex. D_2O), 5.16 (dd, 1H, J = 6.1, 1.0 Hz), 6.39 (dd, 1H, J = 3.3, 0.7 Hz), 6.43 (dd, 1H, J = 3.3, 1.8 Hz), 7.22-7.34 (m, 5H), 7.47 (dd, 1H, J = 1.8, 0.7 Hz).
10. The ^1H and ^{13}C NMR spectra of this compound were identical to those reported in ref. 3a.
11. The crude reaction product which contained 15-20 % of **7** was used to continue the synthesis . A pure sample of **6** was isolated by chromatography (silica gel, chloroform-metanol 30:1) : white solid; mp 81-82 °C ; $[\alpha]_D$ = +20.1° (c 0.16, $CHCl_3$) [Lit.[3a] mp 80-82 °C, $[\alpha]_D$ = +19.8° (c 0.56, $CHCl_3$).
12. **1c**: slightly colored solid; mp 180-190 °C (shr 150 °C); $[\alpha]_D$ = +7.2° (c 0.10, H_2O) [Lit.[3a] mp 182-185 °C and 190-194 °C (authentic **1c**); $[\alpha]_D$ = +8.0° (c 0.37, H_2O)]; identical ^1H and ^{13}C NMR spectra to those reported in ref. 3a.
13. **α-8**: oil; $[\alpha]_D$ = +73.5° (c 0.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 3.80 (d, 1H, J = 12.9 Hz), 3.88 (d, 1H, J = 12.9 Hz), 4.29 (d, 1H, J = 4.8 Hz), 4.75 (t, 1H, J = 4.6 Hz), 4.81 (dd, 1H, J = 7.3, 4.6 Hz), 5.18 (dd, 1H, J = 7.3, 4.2 Hz), 6.29 (d, 1H, J = 4.8 Hz), 6.44 (dd, 1H, J = 3.3, 1.2 Hz), 6.49 (dd, 1H, J = 3.3, 0.9 Hz), 7.25-7.40 (m, 5H), 7.48 (dd, 1H, J = 1.2, 0.9 Hz). **β-8**: oil; $[\alpha]_D$ = -25.0° (c 0.18, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.15 (s, 3H), 3.72 (d, 1H, J = 12.5 Hz), 3.99 (d, 1H, J = 7.2 Hz), 4.04 (d, 1H, J = 12.5 Hz), 4.67 (t, 1H, J = 7.0 Hz), 5.19 (d, 1H, J = 4.9 Hz), 5.32 (dd, 1H, J = 6.8, 4.9 Hz), 5.98 (s, 1H), 6.40 (dd, 1H, J = 3.4, 0.9 Hz), 6.43 (dd, 1H, J = 3.4, 1.9 Hz), 7.24-7.40 (m, 5H), 7.47 (dd, 1H, J = 1.9, 0.9 Hz).
14. **α-9**: (impure by 10 % of β-9) : ^1H NMR (300 MHz, $CDCl_3$) (selected) δ 1.87 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 2.15 (s, 3H), 3.48 (d, 1H, J = 6.8 Hz), 3.83 (s, 3H), 4.17 (d, 1H, J = 12.7 Hz), 4.30 (d, 1H, J = 12.7 Hz), 4.63 (dd, 1H, J = 6.8, 3.2 Hz), 5.07 (dd, 1H, J = 6.8, 4.4 Hz), 5.54 (dd, 1H, J = 6.8, 3.2 Hz), 6.29 (d, 1H, J = 4.4 Hz), 7.25-7.50 (m, 5H). **β-9**: oil; $[\alpha]_D$ = -43.1° (c 0.17, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.73 (s, 3H), 1.95 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 3.43 (d, 1H, J = 9.3 Hz), 3.85 (s, 3H), 4.14 (d, 1H, J = 11.7 Hz), 4.32 (d, 1H, J = 11.7 Hz), 4.60 (dd, 1H, J = 9.3, 6.4 Hz), 5.18 (d, 1H, J = 4.9 Hz), 5.40 (t, 1H, J = 5.1 Hz), 6.03 (s, 1H), 7.25-7.45 (m, 5H).
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