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Asymmetric synthesis of an isoxazolidine nucleoside analog of Thymine Polyoxin C

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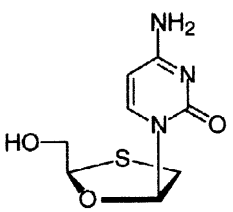
Abstract

The first synthesis of an isoxazolidine amino acid nucleoside analog is reported. The key step of the synthesis is the stereoselective nucleophilic addition of a silyl ketene acetal to the N-benzyl nitrone derived from N,O-isopropylidene-L-serinal. The overall yield from the starting nitrone was 16.4% (10 steps).

Keywords: Nitrones; nucleosides, amino acids and derivatives; isoxazolidines

In recent years much attention has been given to the development of efficient methodologies for the synthesis of novel nucleoside analogs because such compounds have many interesting potential biological applications [1-6]. Among the structural modifications that can be introduced in the nucleoside framework [7,8], the replacement of the furanose ring by a different heterocyclic ring has emerged as a promising alternative [9-12]. Lamivudine **1** [13,14] and Dioxolane-T **2** [15] are nucleoside analogs with antiviral activity in which the furanose moiety has been replaced by 1,3-oxathiolane and 1,3-dioxolane rings, respectively. Isoxazolidinyl nucleosides have also attracted particular attention [16-18]; in this context, we have reported the stereoselective synthesis of isoxazolidinyl thymine **3** [19].



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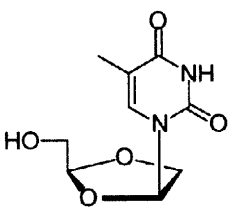

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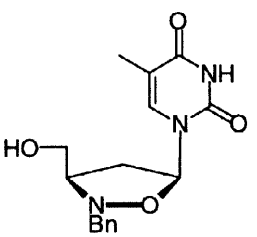

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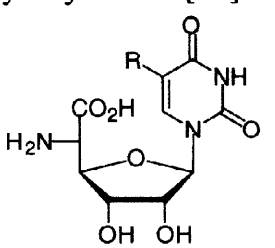

4 R = H Uracil polyoxin C
5 R = Me Thymine Polyoxin C
6 R = CH_2OH Polyoxin C

Having recently described the total synthesis of Polyoxin J [20], a peptidyl nucleoside

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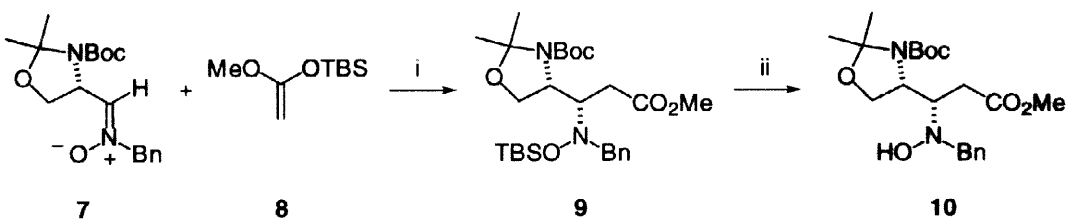
antibiotic, we decide to explore new strategies for the preparation of peptidyl nucleosides analogs with modified backbones. The amino acid nucleosides **4-6** constitute the key components common to most of polyoxins and nikkomycins [21], an important class of peptidyl nucleosides which exhibit a marked activity against phytopathogenic fungi [20].

Although several analogs of polyoxins have been described with variations in the substituents of the furanose ring and/or changes in the nucleobase moiety [20], to our knowledge, derivatives in which the carbohydrate ring has been replaced by another saturated (hetero)cycle have not been reported except for the synthesis of a carbocyclic analog of uracil polyoxin C **4** [11]. In the present communication we describe the stereoselective synthesis of an analog of thymine polyoxin C **5** in which the furanose ring has been replaced by an isoxazolidine ring.

The easily available [23] N-benzyl-N,O-isopropylidene-L-serine nitrone **7** was reacted with 3 equiv of O-methyl-O-tert-butyldimethylsilyl ketene acetal[1] **8** at -80°C in dichloromethane as a solvent and in the presence of a stoichiometric amount of tert-butyldimethylsilyl triflate to afford a 86:14 mixture of the adduct **9** and its C-3 epimer that was easily separable by column chromatography. Deprotection of the hydroxyamino group using hydrogen fluoride-pyridine provided hydroxylamine **10** in quantitative yield (Scheme 1).

Scheme 1

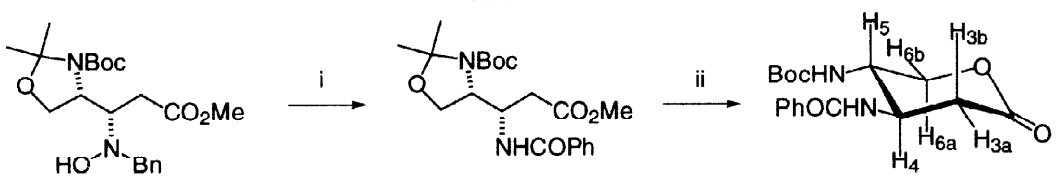


7 **8** **9** **10**

Reagents and conditions: i) TBSOTf, CH_2Cl_2, -60°C, 2 h, 92%, ds=86%. ii) HF-pyridine, THF, 0°C, 1 h, 100%

The relative configuration of the newly created center was determined by converting **10** into the cyclic compound **12** as outlined in Scheme 2.

Scheme 2



10 **11** **12**

Reagents and conditions: i) Zn, $Cu(OAc)_2$, AcOH, 70°C, 1h; then H_2, $Pd(OH)_2$-C, MeOH, 70 psi., r.t., 1 h; then PhCOCl, Py, CH_2Cl_2, 0°C, 16 h, 76% ii) 70% AcOH (aq.), 50°C, 15 h, 70%.

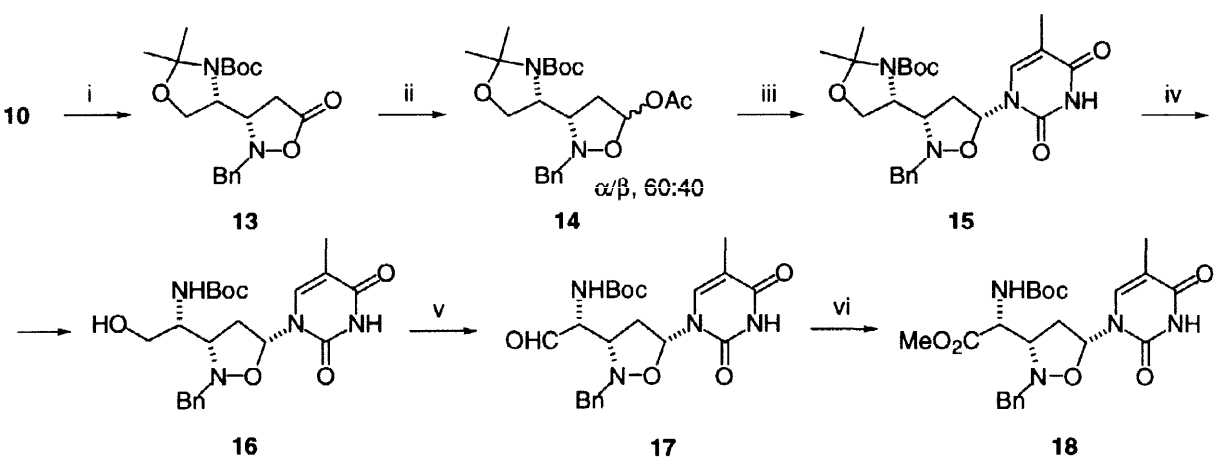
Two-step reduction of the N-benzyl hydroxylamine moiety followed by benzoylation (PhCOCl, Py, 0°C, 16 h) provided the methyl ester **11** (oil, $[\alpha]_D = 27.3$ (c 0.53, $CHCl_3$)) in 76% overall yield. Removal of the isopropylidene protecting group in **12** with 70% acetic acid in water afforded the 4,5-diamino lactone **12** (65%, sticky foam, $[\alpha]_D = -33.3$ (c 0.13,

[1] The silyl ketene acetal **8** (b.p. 76-77°C, 24 mm Hg) was prepared by treating methyl acetate with LDA and $^tBuMe_2SiCl$ as described: Ainsworth C, Chen F, Kuo, Y-N. J. Organomet. Chem. 1972;46:59-71

$CHCl_3$)) whose structure followed from the ^1H NMR spectrum.[2] Specifically, the trans diequatorial orientation of the NHBoc and NHCOPh groups is substantiated by the large value of the vicinal coupling constant between H_4 and H_5 ($^3J_{4,5}$ = 9.9 Hz) corresponding to trans diaxial protons. Also, the substantial NOE between H-4 and H-6a supported the cis structure of **12**. Consequently, a syn configuration of **9** was confirmed. This result was consistent with our previous results on nucleophilic additions to **7** [23,24] and with those observed by Kita and co-workers [25] for the addition of silyl ketene acetals to α,β-dialkoxy nitrones.

A solution of sodium methoxide in methanol was employed to induce cyclization of hydroxylamine **10** to the corresponding isoxazolidin-5-one **13** (98%, oil, $[\alpha]_D$ = -128.0 (c 1.40, $CHCl_3$)). Subsequent reduction and acylation provided **14** as a 60:40 mixture of anomers (Scheme 3). This mixture was subjected to Vorbrüggen condensation [26] with 5-methyl-2,4-bis(trimethylsiloxy) pyrimidine to provide nucleoside **15** as a 60:40 mixture of α/β anomers. Both anomers could be easily separated by column chromatography (toluene:EtOAc, 70:30, R_f α-isomer = 0.15, R_f β-isomer = 0.21, visualized with UV at 254 nm), the anomeric configurations being confirmed by ^1H NMR (300 MHz) and NOE experiments.

Scheme 3



Reagents and conditions: i) MeONa, MeOH, 5 min, r.t., 98%. ii) DIBAH, CH_2Cl_2, -80°C, 1 h; then Ac_2O, Py, r.t., 12 h, 78%. iii) 2,4-bis(trimethylsiloxy)pyrimidine, TMSOTf, CH_3CN, r.t., 6 h, 59%. iv) 70% AcOH (aq.), 50°C, 15 h, 66%. v) DMSO, $(COCl)_2$, CH_2Cl_2, -80°C, 2h; then Et_3N, -80°C to r.t., 1 h, 85%. vi) $NaClO_2$, NaH_2PO_4 (aq), r.t., 15 min; then CH_2N_2, Et_2O, 0°C, 5 min, 82%.

To complete the synthesis the major anomer **15** (m.p. 53-54°C, $[\alpha]_D$ = -64.8 (c 0.31, $CHCl_3$)), depicted in Scheme 3, was treated with 70% aqueous acetic acid to remove the acetonide moiety. The resulting primary alcohol **16** (66%, m.p. 157-158°C, $[\alpha]_D$ = -11.7 (c 0.89, $CHCl_3$)) was then oxidized under Swern conditions [27] to furnish aminoaldehyde **17** which was used immediately without further purification.

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[2] ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H, ^{t}Bu), 2.62 (dd, 1H, H-3a), 3.23 (dd, 1H, H-3b), 4.05 (dd, 1H, H-6a), 4.06 (dddd, 1H, H-5), 4.40 (dddd, 1H, H-4), 4.50 (dd, 1H, H-6b), 4.91 (d, 1H, N*H*Boc), 6.73 (d, 1H, N*H*COPh), 7.31-7.39 (m, 3H, Ar*H*), 7.72-7.80 (m, 2H, Ar*H*). $J_{3a,3b}$ = -17.6 Hz; $J_{3a,4}$ = 6.5 Hz; $J_{3b,4}$ = 10.0 Hz; $J_{4,5}$ = 9.9 Hz; $J_{4,NH}$ = 7.2 Hz; $J_{5,6a}$ = 9.7 Hz; $J_{5,6b}$ = 5.3 Hz; $J_{5,NH}$ = 7.4 Hz; $J_{6a,6b}$ = -11.5 Hz. Assignments were aided by homodecoupling 2D experiments and simulation techniques.

Finally, oxidation of **17** with sodium chlorite as described [28] afforded the corresponding carboxylic acid which was treated with an ethereal solution of diazomethane to give the isoxazolidinyl nucleoside amino ester[3] **18** in 82% yield from **16**.

In summary, the first synthesis of an isoxazolidine nucleoside amino acid analog has been achieved using the readily available nitrone **7** as a chiral starting material. Our current efforts involve application of this methodology to the synthesis of other nucleoside analogs for their incorporation into more complex structures.

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References and Notes

[1] Duheholm KL, Pedersen EB. Synthesis 1992:1-21.
[2] Perigaud C, Gosselin G, Imbach J-L Nucleosides & nucleotides 1992;11:903-945.
[3] Agrofoglio L, Suhas E, Farese A, Condom R, Challand SR, Earl RA, Guedj R. Tetrahedron 1994;50:10611-10670.
[4] Huryn DM, Okabe M. Chem. Rev. 1992;92:1745-1768.
[5] Fedorov II, Kazmina EM, Gurskaya GV, Jasko MV, Zavodnic VE, Balzarini J, De Clercq E, Faraj A, Sommadossi J-P, Imbach J-L, Gosselin G. J. Med. Chem. 1997;40:486-494 and references therein.
[6] Kato K, Suzuki H, Tanaka H, Miyasaka T. Tetrahedron: Asymmetry 1998;9:911-914 and references cited therein.
[7] Matteuci M. Perspectives in Drug Discovery and Design 1996;4:1-16
[8] Nair V, Jahnke TS. Antimicrob. Agents Chemother. 1995;39:1017-1029.
[9] Mellor BJ, Murray PE, Thomas EJ. Tetrahedron 1998;54:243-256.
[10] Rassu G, Zanardi F, Cornia M, Casiraghi G. Nucleosides & Nucleotides 1996;15:1113-1120.
[11] Faury P, Camplo M, Mourier N, Trabaud C, Niddam V, Kraus J-L. Bull. Soc. Chim. Fr. 1996;133:553-561.
[12] Branalt J, Kvarnstrom I, Classon B, Samuelsson B. J. Org. Chem. 1996;61:3599-3603 and 3604-3610.
[13] Perry CM, Faulds D. Drugs 1997;53:657-680.
[14] Harris RK, Yeung RR, Lamont BR, Lancaster RW, Lynn SM, Staniforth SE. J. Chem. Soc. Perkin Trans. 2 1997:2653-2659 and references cited therein.
[15] Norbeck DW, Spanton S, Broder S, Mitsuya H. Tetrahedron Lett. 1989;30:6263-6266.
[16] Tronchet JMJ, Iznaden M, Barbalat-Rey F, Dhimane H, Ricca A, Balzarini J, De Clercq E. Eur. J. Med. Chem. 1992;27:555-560.
[17] Chiacchio U, Gumina G, Rescifina A, Romeo R, Uccella C, Casuscelli F, Piperno A, Romeo G. Tetrahedron 1996;52:8889-8898.
[18] Xiang Y, Gi H-J, Niu D, Schinazi RF, Zhao K. J. Org. Chem. 1997;62:7430-7434.
[19] Merino P, Franco S, Garces N, Merchan FL, Tejero T. Chem. Commun. 1998:493-494.
[20] Dondoni A, Junquera F, Franco S, Merchan FL, Merino P, Tejero T. J. Org. Chem. 1997;62:5497-5507.
[21] Knapp S. Chem. Rev. 1995;95:1859-1876.
[22] Zhang D, Miller MJ. J. Org. Chem. 1998;63:755-759.
[23] Merino P, Lanaspa A, Merchan FL, Tejero T. Tetrahedron: Asymmetry 1998;9:629-646.
[24] Merino P, Lanaspa A, Merchan FL, Tejero T. J. Org. Chem. 1996;61:9028-9032.
[25] Kita Y, Tamura O, Ito F, Kishino H, Miki T, Kohno M, Tamura Y. Chem. Commun. 1988:761.763.
[26] Vorbrüggen H, Krolikiewicz K, Bennua B Chem. Ber. 1981;114:1234-1255.
[27] Omura K, Swern D. Tetrahedron 1978:1651-1660
[28] Dalcanale E, Montanari F. J. Org. Chem. 1986;51:567-569.

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[3] Data for **18**: sticky foam; $[\alpha]_D$ +13.6 (c, 0.30, $CHCl_3$); ^1H NMR δ 1.45 (s, 9H, ^tBu), 1.74 (d, 3H, J = 1.5 Hz, CH_3C), 2.39 (ddd, 1H, J = 3.3, 8.5, 14.0 Hz, H-4b), 2.89 (ddd, 1H, J = 7.3, 8.5, 14.0 Hz, H-4a), 3.35 (dt, 1H, J = 3.3, 8.5 Hz, H-3), 3.76 (s, 3H, CH_3O), 3.78 and 4.45 (2d, 2H, J = 13.6 Hz, $PhCH_2$), 4.67 (dd, 1H, J = 3.3, 8.1 Hz, *CH*NHBoc), 5.25 (d, 1H, J = 8.1 Hz, N*H*Boc), 5.90 (dd, 1H, J = 3.3, 7.3 Hz, H-5), 7.20 (q, 1H, J = 1.5 Hz, *H*C=C), 7.26-7.40 (m, 5H), 7.81 (bs, 1H, OCN*H*CO). Labelling of protons has been made according to the isoxazolidine ring numbering.