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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). © 1998 Elsevier Science Ltd. All rights reserved.

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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1 [13,14] and Dioxolane-T 2 [15] are nucleoside analogs with antiviral activity in which the furanose moiety has been replaced by 1,3-oxathiolane and 1,3-dioxolane rings, respectively.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].





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ring and/or changes in the nucleobase moiety [20], to our knowledge, derivatives in which the carbohydrate ring has been replaced by another saturated (hetero)cycle have not been reported except for the synthesis of a carbocyclic analog of uracil polyoxin C 4 [11].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we describe the stereoselective synthesis of an analog of thymine polyoxin C 5 in which the furanose ring has been replaced by an isoxazolidine ring.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 acetal¹ 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).



Reagents and conditions: i) TBSOTf, CH2Cl2, -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.



Reagents and conditions: i) Zn, Cu(OAc)₂, AcOH, 70°C, 1h; then H₂, Pd(OH)₂)-C, MeOH, 70 psi., r.t., 1 h; then PhCOCl, Py, CH₂Cl₂, 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, CHCl₃)) 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 ^tBuMe₂SiCl as described: Ainsworth C, Chen F, Kuo, Y-N. J. Organomet. Chem. 1972;46:59-71

CHCl₃)) 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 H₄ and H₅ (${}^{3}J_{4,5} = 9.9$ 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, CHCl₃)). 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.



Reagents and conditions: i) MeONa, MeOH, 5 min, r.t., 98%. ii) DIBAH, CH₂Cl₂, -80°C, 1 h; then Ac₂O, Py, r.t., 12 h, 78%. iii) 2,4-bis(trimethylsiloxy)pyrimidine, TMSOTf, CH₃CN, r.t., 6 h, 59%. iv) 70% AcOH (aq.), 50°C, 15 h, 66%. v) DMSO, (COCl)₂, CH₂Cl₂ -80°C, 2h; then Et₃N, -80°C to r.t., 1 h, 85%. vi) NaClO₂, NaH₂PO₄ (aq), r.t., 15 min; then CH₂N₂, Et₂O, 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, CHCl₃)), 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, CHCl₃)) was then oxidized under Swern conditions [27] to furnish aminoaldehyde **17** which was used immediately without further purification.

^{2 1}H NMR (CDCl₃) δ 1.35 (s, 9H, ¹Bu), 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, NHBoc), 6.73 (d, 1H, NHCOPh), 7.31-7.39 (m, 3H, ArH), 7.72-7.80 (m, 2H, ArH). $J_{3a,3b} = -17.6$ 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 ester³ 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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³ Data for 18: sticky foam; [α]_D +13.6 (c, 0.30, CHCl₃); ¹H NMR δ 1.45 (s, 9H, ¹Bu), 1.74 (d, 3H, J = 1.5 Hz, CH₃C), 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, CH₃O), 3.78 and 4.45 (2d, 2H, J = 13.6 Hz, PhCH₂), 4.67 (dd, 1H, J = 3.3, 8.1 Hz, CHNHBoc), 5.25 (d, 1H, J = 8.1 Hz, NHBoc), 5.90 (dd, 1H, J = 3.3, 7.3 Hz, H-5), 7.20 (q, 1H, J = 1.5 Hz, HC=C), 7.26-7.40 (m, 5H), 7.81 (bs, 1H, OCNHCO). Labelling of protons has been made according to the isoxazolidine ring numbering.