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Polyhydroxylated *N*-(thio)carbamoyl piperidines: nojirimycin-type glycomimetics with controlled anomeric configuration

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Abstract

N-(Thio)carbamoyl D-*xylo*-nojirimycin derivatives have been prepared by intramolecular rearrangement of sugar thiourea precursors under basic conditions. The stereochemistry at the aminoketal stereocentre is under stereoelectronic control, with the diastereomer having the pseudoanomeric group in axial orientation being obtained in all cases.

Nitrogen-in-the-ring carbohydrate mimics with glycosyl hydrolase inhibitory properties (iminosugars, 'azasugars') have been attracting much attention due to their great chemotherapeutic potential.[1–10] However, the majority of the naturally occurring azasugars and the plethora of synthetic analogues reported so far simultaneously inhibit several α- as well as β-glycosidases, which seriously hampers clinical applications.[11] Since many glycosidases that recognise the same glycon configuration differ only in the type of *O*-glycosidic linkage (α or β), introduction of an *O*-anomeric group with a precise spatial orientation in azasugars might provide greater selectivity in recognition by a targeted enzyme.

The development of aza-*O*-glycoside glycomimetics has been limited by the lability of the *O*/*N* acetal function under hydrolytic conditions.[12] Reducing derivatives of the nojirimycin type **1** likewise suffer from low stability and, moreover, rapid epimerisation at the aminoketal centre occurs in water solution.[13] We reasoned that replacement of the sp^3 *N*-atom by a thiourea or urea nitrogen, with substantial sp^2 character, should significantly increase the hyperconjugative contribution to the anomeric effect due to the favourable π symmetry of the lone-pair orbital of *N*-(thio)carbamoyl functionalities.[14,15] Recently, this principle was applied to the synthesis of the first reducing castanospermine analogue with a stereoelectronically controlled anomeric configuration **2**.[16] Validation of this concept in the nojirimycin series was, however, prevented by the strong tendency of the transient D-glucose mimic **3** to undergo intramolecular glycosylation involving the primary OH group to give **4**.[17] We describe here the synthesis of several pentose-mimic homologues, i.e. *N*-(thio)carbamoyl D-*xylo*-nojirimycin derivatives, in which

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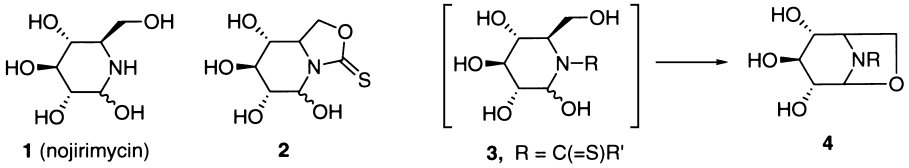
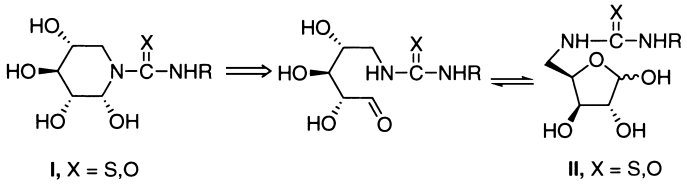
the anomeric OH or *O*-glycosylic group is anchored in the axial disposition as the aglycons of the putative substrates of α-glycosidases.



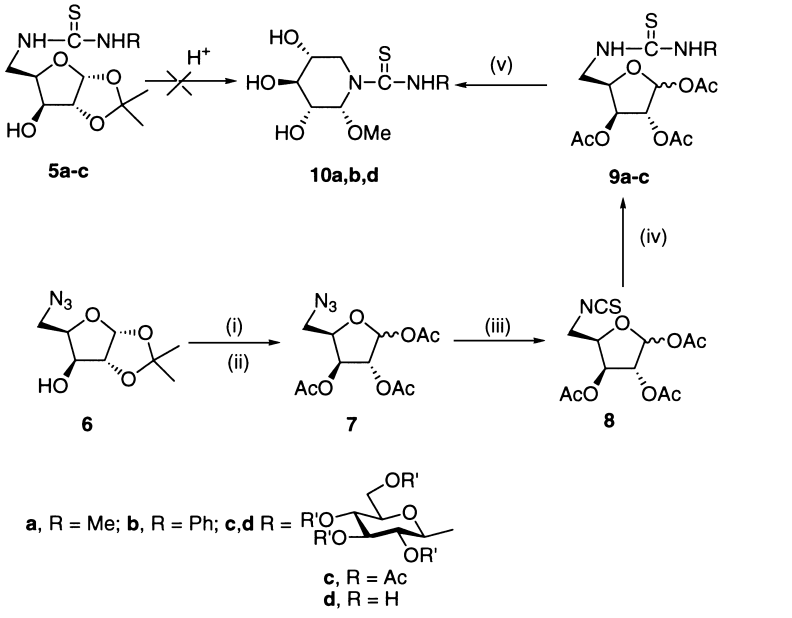
A retrosynthetic analysis revealed that the polyhydroxylated *N*-(thio)carbamoyl piperidine skeleton **I** can be constructed by intramolecular nucleophilic addition of the sugar-*N*-atom of 5-deoxy-5-(thio)ureido substituents to the masked aldehydo group of D-xylose derivatives **II**, with simultaneous generation of the aminoketal stereocentre (Scheme 1). The possibility of introducing a virtually unrestricted variety of substituents at the *N′*-atom is of further interest since this may provide additional interactions with enzymes. In a first approach, the 1,2-*O*-isopropylidene-α-D-xylofuranose thioureas **5a**–**c** were considered as suitable precursors.[18] However, acidic hydrolysis of the acetal protecting group resulted in extensive dehydration reactions, probably through acid-catalysed formation of an anomeric azacarbenium cation. To avoid this undesired side-reaction, an alternative route was devised using acetyl protecting groups. The aza-Wittig type reaction of azide **7**, obtained from the known 1,2-*O*-isopropylidene derivative **6**,[18] with CS_2 provided isothiocyanate **8**, which upon coupling with amines afforded the corresponding thioureas **9a**–**c**.[19] Deacetylation of **9a**–**c** with methanolic sodium methoxide proceeded with concomitant glycosylation yielding the methyl *N*-thiocarbonyl-D-*xylo*-nojirimycin glycosides **10a**,**b**,**d** as single diastereomers having the *R* (α) configuration at the aminoketal centre ($J_{1,2}$=3.3–3.6 Hz),[20] with the piperidine ring in a conformation close to $^4C_1$, as seen from the vicinal $^3J_{H,H}$ coupling constant values (Scheme 2).[21]



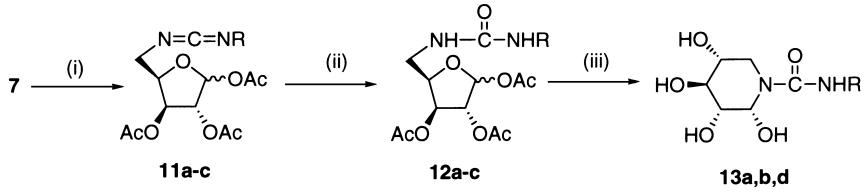
Scheme 1. Retrosynthetic scheme for *N*-(thio)carbamoyl D-*xylo*-nojirimycin derivatives

For the preparation of the *N*-carbamoyl analogues, a different synthetic strategy which avoids the use of hazardous isocyanate reagents was devised. Condensation of azide **7** with triphenylphosphine and further in situ aza-Wittig type reactions with isothiocyanates gave the carbodiimide adducts **11a**–**c**,[22] which readily underwent acid-catalysed nucleophilic addition of water to afford the 5-deoxy-5-ureido-D-xylofuranoses **12a**–**c**.[23] Sodium methoxide promoted deacetylation resulted in intramolecular rearrangement to give the tetrahydroxypiperidine heterocycles **13a**,**b**,**d** (Scheme 3) as the major reaction products.[24,25] Exclusively, the diastereomer 2*R*, having the aminoketal hydroxy group in axial disposition, was detected in D_2O solution by NMR spectroscopy ($J_{1,2}$=3.8 Hz),[20] in spite of the expected abatement of the sp^2 character of the urea nitrogen atom as compared with thioureas.

The propensity of *N*-thiocarbonyl azasugars to undergo acid-catalysed glycosylation reactions has been previously ascribed to the stabilisation of a transient azacarbenium species by the neighbouring thiocarbonyl group.[15,17] Remarkably, formation of the methyl glycosides **10a**–**c** occurred under basic conditions. The fact that the axial glycosides were obtained as the single reaction products suggests a similar cationic intermediate, further addition of methoxide anion proceeding under strict stereoelectronic



Scheme 2. (i) TFA:water, 9:1; (ii) Ac_2O–pyridine (50% overall); (iii) TPP, CS_2 (95%); (iv) methylamine, aniline or 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (lit.),[26] pyridine (60–98%); (v) NaMeO/MeOH (50–90%)



Scheme 3. See Scheme 2 for the identity of the *R* substituent in the **a**–**d** series. (i) Methyl, phenyl or 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (lit.),[26] toluene (50–82%); (ii) acetone:water, TFA (90–95%); (iii) NaMeO/ MeOH (55–93%)

control. This reactivity is lessened in the oxo analogues, in agreement with the decreased capability of the carbonyl group to stabilise a vicinal positive charge as compared to the thiocarbonyl group.

In conclusion, the present results validate a concise and efficient approach to polyhydroxylated piperidine glycomimetics bearing an axially disposed pseudoanomeric hydroxyl or *O*-glycosylic group. The control of the anomeric configuration relies on a very efficient overlapping between the π-type lone-pair orbital of the nitrogen atom in the ground-state of (thio)carbamic functionalities and the σ* antibonding orbital of the contiguous C–O bond, fully operative in polar solvents. It is noteworthy that the *N*-(thio)carbamoyl substituent imparts configurational and conformational integrity at the piperidine ring even in the case of reducing derivatives. Thus, no equilibration to the β anomers was observed for compounds **13a**,**b**,**d** after a week in D_2O solution. The enhanced anomeric effect also provides additional stabilisation as compared with classical aminoketal azasugars. Extensions of the methodology to other sugar configurations and evaluation of the inhibitory properties of the new structures as glycosidase inhibitors are currently in progress.

Acknowledgements

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21. All new compounds gave satisfactory microanalytical, MS and spectroscopic data. Data for **10a**: $[\alpha]_D^{22}$=+61.0 (*c* 1.0, H_2O); δ_H (D_2O, 300 MHz) 3.08 (1H, dd, $J_{4,5b}$=11.0, $J_{5a,5b}$=13.0, H-5b), 3.07 (3H, s, OMe), 3.31 (3H, s, NMe), 3.50 (1H, ddd, $J_{4,5a}$=5.3, $J_{3,4}$=9.3, H-4), 3.54 (1H, dd, $J_{1,2}$=3.3, $J_{2,3}$=9.3, H-2), 3.69 (1H, t, H-3), 4.15 (1H, dd, H-5a), 6.22 (1H, d, H-1); δ_C (D_2O, 75.5 MHz) 34.7, 46.8, 57.5, 71.3, 73.4, 6.2, 90.5, 184.6. Data for **10b**: $[\alpha]_D^{22}$=+54.0 (*c* 1.0, MeOH); δ_H (D_2O, 500 MHz, 313K) 3.27 (1H, dd, $J_{4,5b}$=11.0, $J_{5a,5b}$=13.0, H-5b), 3.45 (3H, s, OMe), 3.66 (1H, ddd, $J_{4,5a}$=5.5, $J_{3,4}$=9.3, H-4), 3.67 (1H, dd, $J_{1,2}$=3.5, $J_{2,3}$=9.3, H-2), 3.79 (1H, t, H-3), 4.44 (1H, dd, H-5a), 6.27 (1H, d, H-1), 7.30–7.50 (5H, m, Ph); δ_C (D_2O, 125.5 MHz, 313K) 45.9, 55.7, 69.2, 70.8, 74.0, 88.8, 126.9, 127.3, 129.4, 139.3, 183.7. Data for **10d**: $[\alpha]_D^{22}$=+25.4 (*c* 1.0, H_2O); δ_H (D_2O, 500 MHz, 313K) 3.06 (1H, dd, $J_{4,5b}$=11.3, $J_{5a,5b}$=13.5, H-5b), 3.25 (3H, s, OMe), 3.36 (1H, dd, $J_{4',5'}$=8.5, $J_{3',4'}$=9.5, H-4′), 3.45 (1H, ddd, $J_{5',6'a}$=2.0, $J_{5',6'b}$=5.0, H-5′), 3.45 (1H, m, H-4), 3.46 (1H, dd, $J_{1,2}$=3.6, $J_{2,3}$=9.5, H-2), 3.50 (1H, t, $J_{1',2'}$=$J'_{2',3'}$=9.5, H-2′), 3.53 (1H, t, H-3′), 3.60 (1H, t, $J_{3,4}$=9.5, H-3), 3.66 (1H, dd, $J_{6a,6b}$=12.5, H-6′b), 3.79 (1H, dd, H-6′a), 4.21 (1H, bs, H-5a), 5.70 (1H, d, H-1′), 6.25 (1H, d, H-1); δ_C (D_2O, 125.5 MHz) 44.9, 55.5, 60.7, 68.7, 69.4, 70.5, 71.8, 73.9, 76.7, 77.6, 85.1, 88.8, 184.3.
22. The converse strategy using isothiocyanate **8** in reaction with azides–triphenylphosphine proved less convenient. The reaction probably involves a sugar phosphazide instead of an iminophosphorane intermediate, as previously observed for related transformations. See: García Fernández, J. M.; Ortiz Mellet, C.; Díaz Pérez, V. M.; Fuentes, J.; Kovács, J.; Pintér, J. *Carbohydr. Res*. **1997**, *304*, 261–270.
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24. Minor amounts of the corresponding methyl glycosides were detected in the ^{1}H NMR spectra of the crude reaction mixtures.
25. Data for **13a**: $[\alpha]_D^{22}$=−2 (*c* 1, H_2O); δ_H (D_2O, 500 MHz) 3.13 (3H, s, MeN), 3.42 (1H, dd, $J_{4,5b}$=10.9, $J_{5a,5b}$=12.6, H-5b), 3.89 (1H, dd, $J_{1,2}$ 3.8, $J_{2,3}$=9.4, H-2), 3.95 (1H, ddd, $J_{4,5a}$=5.6, H-4), 4.07 (1H, t, H-3), 4.14 (1H, dd, H-5b), 6.03 (1H, d, H-1); δ_C (D_2O, 125.5 MHz, 318K) 23.0, 38.6, 65.6, 67.8, 69.5, 72.9, 159.6. Data for **13b**: $[\alpha]_D^{22}$=−6.0 (*c* 0.5, MeOH); δ_H (D_2O, 500 MHz) 3.20 (1H, dd, $J_{4,5b}$=11.0, $J_{5a,5b}$=12.7, H-5b), 3.61 (1H, dd, $J_{1,2}$=3.8, $J_{2,3}$=9.7, H-2), 3.67 (1H, ddd, $J_{4,5a}$=5.6, $J_{3,4}$=9.7, H-4), 3.76 (1H, t, H-3), 4.00 (1H, dd, H-5a), 5.82 (1H, d, H-1), 7.47–7.31 (m, 5 H, Ph); δ_C (D_2O, 75.5 MHz) 43.1, 69.8, 71.9, 73.7, 77.2, 123.3, 125.2, 129.5, 138.1, 157.8. Data for **13d**: $[\alpha]_D^{22}$=+6.0 (*c* 1.0, H_2O); δ_H (D_2O, 500 MHz) 3.19 (1H, dd, $J_{4,5b}$=11.0, $J_{5a,5b}$=13.0, H-5b), 3.54 (1H, t, $J_{3',4'}$=$J_{4',5'}$=9.2, H-4′), 3.59 (1H, t, $J_{1',2'}$=$J_{2',3'}$=9.2, H-2′), 3.63 (1H, dd, $J_{1,2}$=3.8, $J_{2,3}$=9.4, H-2), 3.64 (1H, ddd, $J_{5',6'a}$=5.7, $J_{6'a,6'b}$=12.4, H-5′a), 3.67 (1H, t, H-3′), 3.70 (1H, dd, $J_{4,5a}$=5.3, $J_{3,4}$=9.4, H-4), 3.79 (1H, t, H-3), 3.84 (1H, dd, $J_{5',6'b}$=5.4, H-6′b), 3.99 (1H, dd, H-6′a), 5.03 (1H, d, H-1′), 5.8 (1H, d, H-1); δ_C (D_2O, 125.5 MHz) 42.4, 60.6, 69.3, 69.4, 71.5, 71.6, 73.3, 76.6, 76.7, 77.3, 81.6, 158.1.
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