A NEW METHOD FOR THE CONVERSION OF HEXOSE DERIVATIVES INTO SUBSTITUTED PYRROLIDINES

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Abstract - The consecutive reduction and cyclisation of O-benzoyl protected 5-O-mesylhexose O-(tert-butyldiphenylsilyl)oximes to afford chiral N-hydroxypyrrolidines is discussed. The mechanism involves a cascade of neighboring group participation steps involving the O-benzoyl protecting groups. This protocol gave rise to new chiral N-hydroxypyrrolidines in good overall yield.

Polyhydroxylated piperidine and pyrrolidine alkaloids, often referred to as azasugars, continue to attract considerable attention due to their well-established function as glycosidase inhibitors and as inhibitors of glycoprotein processing\(^1\). The development of general synthetic methods, which embody considerable flexibility for the construction of other stereoisomers and analogues, continues to be important in probing structure activity correlations. Numerous synthetic routes to azasugars such as (+)-deoxynojirimycin\(^2\) and 1,4-dideoxy-1,4-imino-D-mannitol\(^3\) have been published, usually starting from sugars as chiral precursors.\(^4\)

An important element in our strategy\(^5\) for the synthesis of this type of heterocycles involves the use of oximes of appropriate hexopyranoses as key intermediates. The use of oximes in related heterocyclic syntheses has been extensively developed in the past.\(^6\) Tronchet \textit{et al.}\(^7\) reported the synthesis of N-hydroxypyrrolidine and N-hydroxypiperidine analogs of sugars \textit{via} cyanoborohydride reduction of appropriate \(\gamma\)- and \(\delta\)-keto-oximes, respectively. A novel method for the generation of cyclic nitrones by intramolecular addition of oximes to proximate activated alkenes (1,3-azaprotio cyclotransfer reaction) was employed by Grigg \textit{et al.}\(^8\) in their synthesis of complex polyhydroxylated indolizidines. In this communication we report a novel and facile synthesis of chiral N-hydroxypyrrolidines involving the reductive cyclisation of the oxime derivatives of suitably protected hexopyranoses.
The \(O\)-benzoyl protected hemiacetals of D-glucose (1a), D-mannose (1b), D-galactose (1c) and L-rhamnose (1d) were synthesized according to known literature procedures.\(^9\) These were reacted with \(N\)-benzylhydroxylamine hydrochloride to furnish the desired oximes as mixtures of their \(E\)- and \(Z\)-isomers (Scheme 1). The acyclic derivatives (2a-d) were treated with mesyl chloride/DMAP in pyridine to afford the corresponding mesylates (3a-d) in good yield.

The next step required the reduction of the oximes to the corresponding benzyloxyamines. The acid-catalysed reduction of ketones employing hydrosilanes\(^10\) was successfully modified by Fujita \textit{et al.}\(^11\) for the reduction of oximes to hydroxylamines. We obtained consistently good results on treatment of the oximes with 2.3 equivalents of dimethylphenylsilane in trifluoroacetic acid. Under these conditions, the reduction of mesylates (3a-d) was successfully carried out at room temperature. The reduced intermediates were immediately dissolved in THF and heated under reflux to afford cyclisation products. Unexpectedly, the 5-(1-mesyl) derivatives of the hexose intermediates (4a-c) furnished \(N\)-benzyloxypyrrolidine ring systems (Scheme 2).\(^12\) Conversely, the 6-deoxyhexose analogue (4d) furnished the expected piperidine ring system (Scheme 2).\(^13\)
The cyclisation reaction leading to the pyrrolidine ring system is an extremely efficient and simple procedure. Application of this reaction to the synthesis of the corresponding N-hydroxypyrrolidines required the use of a labile O-protecting group for the oxime, which could be removed under relatively mild conditions after cyclisation. We previously reported on the application of the tert-butyldiphenylsilyl oxime protecting group in the synthesis of chiral cyclic nitrones starting from D-ribose.\textsuperscript{14} The oximes of 1a and 1b were therefore reacted with 1 mole equivalent of tert-butyldiphenylsilyl chloride in pyridine at room temperature. This resulted in selective O-silylation of the oxime groups (Scheme 3).
We found that the reaction of 1a and 1b with O-(tert-butyldiphenylsilyl)hydroxylamine to furnish 8a and 8b, respectively, was less efficient (slow and incomplete). The free C-5 hydroxyl groups of the products were mesylated using standard conditions to furnish compounds (8a) and (8b).

Treatment of 8a and 8b with 2.3 equivalents of dimethylphenylsilane in trifluoroacetic acid at 60°C afforded the N-hydroxypyrrolidine ring systems (9a) and (9b) in satisfactory yields (Scheme 4).

The structures and stereochemistry of the ring carbons of the pyrrolidines described above were deduced on the basis of 1H- and 13C-NMR spectra, nOe-effects established by means of ROESY spectra (e.g. strong nOe effects between H-3 and the side chain protons as well as a moderate nOe effect between H-2 and H-4 in compound 9a), and the calculation of consistent sets of dihedral angles derived from coupling constants. The stereochemistry of the products indicates that cyclisation occurred with inversion of stereochemistry at C-4 (carbohydrate numbering). The stereochemistry at C-1' (C-5 carbohydrate numbering) which at this stage can only be assigned tentatively on the basis of coupling constants and conformational analysis is the subject of an independent study of our group. The formation of pyrrolidines requires the presence of a good leaving group at C-4, while the structures of the cyclisation products may be explained in terms of a cascade of neighboring group participation steps. The tendency of benzoate esters to take part in neighboring group participation reactions is well documented. It is suggested that the cyclisation occurs via the formation of an intermediate of type (10) (Scheme 5) which is attacked by the nitrogen lone pair to afford a five-membered rather than a six-membered ring (cyclisation under kinetic control). Formation of the intermediate is initiated by neighbouring group participation of the C-6 benzoate
group. The absence of this group in 4d may therefore allow for its conversion into the piperidine (5d), rather than the corresponding pyrrolidine.

\[ \text{Scheme 5} \]

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REFERENCES


12. 5a: mp 198-199°C (ethyl acetate/hexane); [α]_D^25 +102.77° (c=1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 8.13 (2H, m), 7.96 (6H, m), 7.37 (17H, m), 6.06 (1H, t, J=6.4 Hz), 5.50 (1H, m), 4.83 (2H, s), 4.71 (1H, dd, J=4.8 Hz, 11.7 Hz), 4.69 (1H, dd, J=3.9 Hz, 11.7 Hz), 3.75 (1H, dd, J=4.1 Hz, 5.8 Hz), 3.45 (1H, dd, J=5.7 Hz, 11.9 Hz), 3.41 (1H, dd, J=2.4 Hz, 11.9 Hz); ¹³C NMR (75 MHz, CDCl₃): 165.9, 165.6 (2C), 165.2, 136.8, 133.3, 133.1 (2C), 133.0, 129.8, 129.7 (2C), 129.6, 129.5 (2C), 129.1, 129.0, 128.5 (3C), 128.4 (10C), 128.3 (2C), 128.2, 128.1, 77.6, 77.0, 76.6, 76.3, 76.2, 71.7, 69.2, 63.8, 60.3; MS: m/z 685 (M⁺, 14%), 563 (9%), 105 (100%).

13. 5d: colourless oil; [α]_D^25 +54.8° (c=1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 7.99 (6H, m), 7.34 (14H, m), 6.08 (1H, dd, J=4.1 Hz, 4.8 Hz), 5.76 (1H, dd, J=7.0 Hz, 4.0 Hz), 5.69 (1H, m), 4.63 (2H, s), 4.31 (1H, m), 4.18 (1H, dd, J=3.9 Hz, 14.2 Hz), 3.90 (1H, dd, J=7.4 Hz, 14.2 Hz); ¹³C NMR (75 MHz, CDCl₃): 165.8, 165.5 (2C), 137.5, 133.3, 133.1, 133.0, 129.3 (3C), 129.1, 129.0, 128.9, 128.6 (8C), 128.5, 128.4, 128.1, 128.0, 127.9 (2C), 76.1, 74.1, 71.3, 70.2, 54.3, 51.6, 20.4; MS: m/z 565 (M⁺, 2%), 443 (1%), 105 (100%).


15. 9a: colourless oil; [α]_D^25 +28.8° (c=1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 7.98 (8H, m), 7.51 (12H, m), 6.07 (1H, m), 5.86 (1H, dd, J=9.8 Hz, 1.7 Hz), 5.52 (1H, m), 4.66 (1H, dd, J=1.8 Hz, 12.0 Hz), 4.62 (1H, dd, J=8.0 Hz, 12.0 Hz), 3.75.

16. 1H, dd, J=3.9 Hz, 9.8 Hz), 3.58 (2H, d, J=6.3 Hz); ¹³C NMR (75 MHz, CDCl₃): 166.1, 165.9, 165.4, 165.0, 133.8, 133.5, 133.3 (2C), 130.0, 129.8 (6C), 129.6 (2C), 128.5 (8C), 128.4 (2C), 128.3, 128.2, 75.0, 74.9, 72.7, 68.0, 63.1, 60.6; FAB-MS: m/z 596 (M+1)⁺, 56%.


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