A Convenient Synthesis of *N*-substituted Trihydroxypiperidines from *Bis*-Epoxides: Nucleophilic Opening of 1,2:4,5-Dianhydropentitols

Rachel D. Smith, Neil R. Thomas*

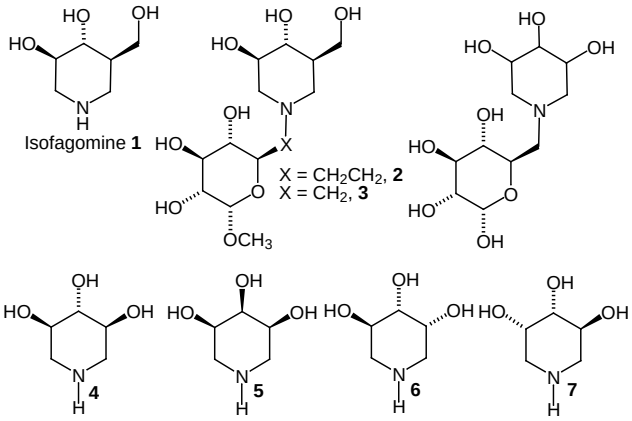
School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK

E-mail: Neil.Thomas@Nottingham.ac.uk

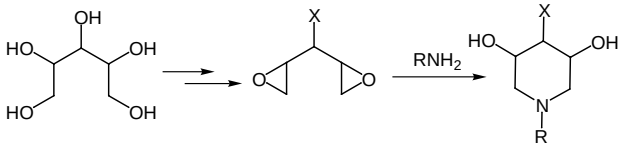
Received 12 November 1999

Abstract: Synthesis of a number of *N*-substituted trihydroxypiperidine and trihydroxypyrrolidines is described via the nucleophilic opening and cyclisation of suitable *bis*-epoxides. Reaction conditions to maximise the yield of the trihydroxypiperidine products formed by a *6-endo-tet* cyclisation process are provided.

Key words: aza-sugar, imino sugar, *bis*-epoxide, glycosidase inhibitor, isofagomine



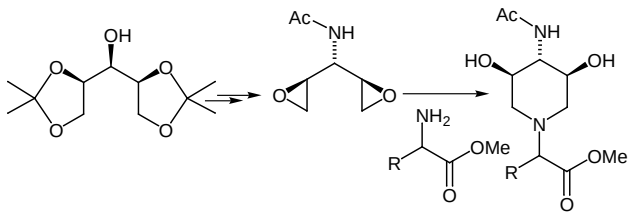
The synthesis and biological evaluation of 'aza-sugars' has been an area of intense research over the past decade, as the importance of glycosidase-mediated processes in disease states such as viral or bacterial infections, diabetes and cancer metastasis has become apparent.[1] One important recent discovery has been the fact that monosaccharide analogues with a nitrogen introduced into the anomeric carbon position, rather than the more usual ring oxygen position gives potent glycosidase inhibitors *i.e* isofagomine (**1**, $K_i = 0.11$ μM, β-D-glucosidase from sweet almonds).[2,3] However, a significant deterrent to the use of azasugars as therapeutics is the fact that they often inhibit a broad range of glycosidases leading to detrimental side effects. Recent research has shown that the affinity of an aza-sugar can be dramatically increased by inclusion of an appropriate aglycon moiety.[4-6] This is seen in the case of methyl-6,7-dideoxy-7-[(3R,3R,5R)-3,4-dihydroxy-5-hydroxymethyl-piperidinyl]-α-D-glucoheptopyranoside (**2**) which has a much higher affinity for glucoamylase from *Aspergillus awamori* ($K_i = 0.063$ μM), than its parent azasugar, isofagomine (**1**, $K_i = 3.7$ μM),[4] and the Merrell Dow compound MDL 73945 (**3**) which is a potent inhibitor of sucrase, maltase, glucomaltase and isomaltase.[6] In an effort to produce a 'second generation' of inhibitors with increased specificity for selected glycosidases we wished to explore the preferences of the aglycon binding site within a range of glycosidases as this is currently very poorly defined.[7] To achieve this a synthetic route which would allow the rapid preparation of a considerable number of *N*-substituted aza sugars was required. To observe any positive contributions made by the aglycon of an *N*-substituted aza sugar to binding, we targeted the 1,5-dideoxy-1,5-imino-D-pentitols **4-7** which are known to have moderate binding affinity for a broad range of glycosidases (1,5-dideoxy-1,5-imino-D-xylitol (**4**), $K_i = 430$ μM, β-D-glucosidase from sweet almonds[8]; 1,5-dideoxy-1,5-imino-adonitol $K_i = 40$ mM (**5**) α-D-galactosidase from green coffee beans;[9] and 1,5-dideoxy-1,5-imino-D-arabitol (**6**), $K_i = 2.2$ μM α-L-fucosidase from human placenta[10]). Simple affinity measurements would allow us to identify any increased selectivity caused by the inclusion of an aglycon substituent. A number of routes to 3,4,5-trihydroxy piperidines have been reported in the literature.[11-13] However, these routes either required a large number of steps, or the early introduction of the amine which could significantly restrict the nitrogen substituent that could be incorporated. We have designed an alternative synthesis based on the use of 1,2:4,5-dianhydropentitols **8a-d** as key intermediates (Scheme 1). These have previously been used in the preparation of pentitol derivatives from divinyl methanol;[14] as potential DNA crosslinking agents;[15] for the synthesis of a 3,4,5-trihydroxy-tetrahydrothiopyran;[16] in the preparation of a C_2-symmetric HIV protease inhibitor;[17] and in the synthesis of the immunosuppressant FK506,[18] their use in the preparation of polysubstituted piperidines has yet to be reported.



Scheme 1

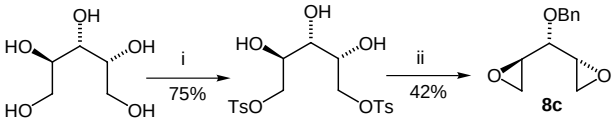
Literature precedence for the nucleophilic opening/aminocyclisation of *bis*-epoxides to give heterocyclic amines has been established by Depezay and coworkers,[19] who have prepared 7-membered ring polyhydroxyazepanes from the appropriate *bis*-epoxide.

The overall strategy for our synthesis is shown in Scheme 1. This route allows the incorporation of any suitable primary amine in the penultimate step in the synthesis permitting the rapid generation of a library of potential inhibitors.[20] The route also allows functional group interconversion of the C-4 hydroxyl of the trihydroxypiperidine which complements the substitution of the C-3 and C-5 hydroxyl positions which is possible using a route described by Kim et al.[21]. Conversion of the C-4 hydroxyl to its epimeric amine has been performed to give rapid access to the sialidase inhibitors, *trans,trans*-3,5-dihydroxy-4-acetamido-piperidines originally reported by Parr and Horenstein (Scheme 2).[22]



Scheme 2

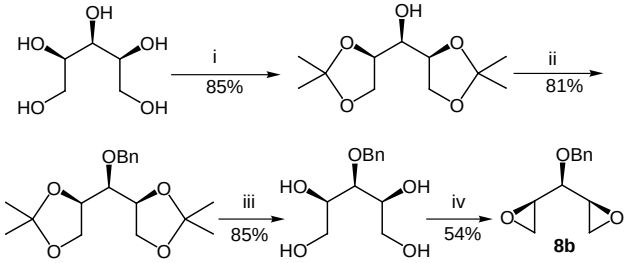
Several syntheses of 1,2:4,5-dianhydropentitols have appeared in the literature.[14-18] The most reproducible route to 3-benzyl-1,2:4,5-dianhydroarabitol was found to be that reported by Dreyer et al.[17] in which D-arabitol was treated with two equivalents of *p*-toluenesulfonyl chloride in pyridine to give the ditosylate in 75% yield. The ditosylate was then taken up in THF at 0 °C and treated with three equivalents of sodium hydride followed by benzyl bromide to give 3-benzyl-1,2:4,5-dianhydro-D-arabitol (**8c**) in 42% yield (31% over 2 steps) (Scheme 3). Repeating this approach we obtained similar yields of 3-benzyl-1,2:4,5-dianhydropentitols from L-arabitol (**8d**) and xylitol (**8a**). However this approach failed to yield the ditosylated compound in the case of adonitol even when the 3-hydroxyl functionality of this pentitol was protected as its benzyl ether. In this case a slightly longer route (Scheme 4) was used in which the 1,2 and 4,5 hydroxyls were first protected as their acetonides using dimethoxypropane, acetone and a catalytic amount of tosyl chloride in anhydrous DMF. Following alkylation of the 3-hydroxyl with benzyl bromide and removal of the isopropylidene protecting groups using 75% acetic acid, the diepoxides were generated via a Mitsunobu reaction on the two terminal hydroxyl groups to yield 3-benzyl-1,2:4,5-dianhydroadonitol (**8b**) in 32% yield over 4 steps from adonitol.



(i) TsCl (2 eq.), pyr., 0 °C, 30 min. (ii) NaH (3.3 eq.), THF, 0 °C; BnBr (1.1 eq.), 0 °C to RT, 16 h.

Scheme 3

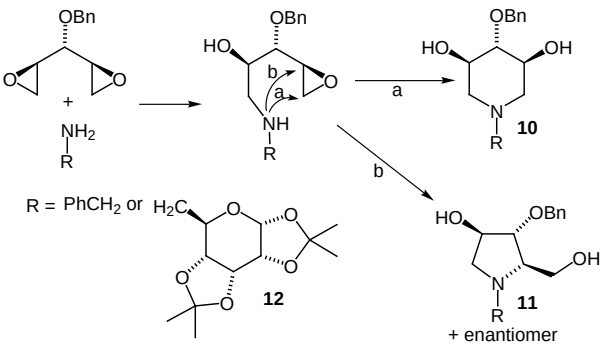
Altenbach and Merhof[16] have shown that 3-acetyl-1,2:4,5-dianhydro-D-arabitol generated in situ from 2,3,4-tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabitol can be cyclised in the presence of sodium sulfide in methanol to form a 3,4,5-trihydroxy-tetrahydrothiopyran in 35% yield together with 10% of a mixture of two thiofuranoses. This is the only report in the literature on the preparation of heterocycles from a 1,2:4,5-dianhydropentitol.



(i) Dimethoxypropane, acetone, TsOH, DMF, RT, 16 h. (ii) NaH (1.1 eq.), BnBr (1.2 eq.), THF, 0 °C to RT, 16 h. (iii) 75% AcOH, 50 °C, 2 h. (iv) DIAD (2.3 eq.), PPh_3 (2.3 eq.), $PhCH_3$, 130 °C, 4 h.

Scheme 4

A number of reaction conditions were investigated in the nucleophilic opening and aminocyclisation of the *bis*-epoxides to maximise the yield of the piperidine (Scheme 5, route a), in preference to the pyrrolidine products (route b). Depezay has reported a number of examples of regiospecific ring opening/aminocyclisation of *bis*-epoxides derived from D-mannitol[19] leading to polyhydroxy-piperidines and/or azepanes via *6-exo-tet* or *7-*



Scheme 5

endo-tet processes. He found that reactions conducted with benzylamine in an aprotic medium such as chloroform favoured the *6-exo-tet* ring closure, whereas use of a protic medium (water/$HClO_4$), or a Lewis acid in an aprotic medium favoured the formation of the polyhydroxyazepane via a *7-endo-tet* ring closure. We have investigated a number of different reaction conditions (refluxing the diepoxide and amine in methanol; stirring with $AlCl_3$ in DCM; stirring with silica in chloroform) and found that for small amines such as benzylamine, the slow addition of 6 eq. of perchloric acid and 12 eq. of the amine followed by stirring for 2 hours at 0 °C, and for 16 hrs at room temperature favoured the *6-endo-tet* cyclisation to the trihydroxypiperidine **10a-d**, in preference to a *5-exo-tet* cyclisation to the related pyrrolidines **11a-d.** The piperidine:pyrrolidine ratio was approximately 3:1 under these conditions, although only the piperidine product could be isolated from the cyclisation of 3-aminobenzyl-3-deoxy-1,2:4,5-dianhydroxylitol **8e** with benzylamine (Table). For sterically hindered amines such as 6-amino-6-deoxy-1,2-3,4-*bis*-*O*-isopropylidene-D-galactose **12**,[24] these conditions led to the formation of tetrahydrofurans via an intramolecular cyclisation. This is in agreement with the observations of Capon and Barrow on stepped epoxides.[23] The reaction conditions which led to the best yield of trihydroxypiperidines from 1,2:4,5-dianhydropentitols with bulky amines such as **12** was found to be simply to heat the compounds together in water at 50 °C for 24 h. This again gave an approximate 3:1 ratio of piperidine to pyrrolidine products. Repeating the reaction under aprotic conditions, such as DMF (120 °C, 24 h) gave only 25% yield of the *N*-substituted trihydroxypiperidine. The results for these transformations are summarised in the Table. The benzyl protecting groups were removed by hydrogenation, and the acetonides by treatment with aqueous hydrochloric acid. The deprotected aza-disaccharide products were then purified using ion exchange column chromatography. Spectroscopic data on the xylitol family of compounds is given below. Biological testing of the trihydroxypiperidine and pyrrolidine compounds reported in this paper is currently underway.

Table 1

Bis-epoxide	Amine	Reaction conditions	% Piperidine	% Pyrrolidine
8a	$BnNH_2$	A	56	21
8b	$BnNH_2$	A	56	31
8c	$BnNH_2$	A	63	24
8e	$BnNH_2$	A	68	0
8a	RNH_2	B	64	26
8b	RNH_2	B	51	26
8c	RNH_2	B	53	22
8e	RNH_2	B	85	0

Reaction conditions
A) 6 eq. 60% $HClO_4$, 12 eq. amine, 2 h at 0 °C, then 16 h at RT.
B) 0.9 eq. amine, H_2O, 50 °C, 24 h (at 0.1 mM concentration).
RNH_2 = 6-amino-6-deoxy-1,2-3,4-*bis*-*O*-isopropylidene-D-galactose

Acknowledgement

We thank the EPSRC for a studentship to RDS, and The Royal Society for a University Research Fellowship to NRT.

References and Notes

(1) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A.E., Ed.; Wiley-VCH: Weinheim, 1999.
(2) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; Legler, G. in Ref. 1 p 41.
(3) Ishikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, 120, 3007.
(4) Dong, W.; Jesperson, T.; Bols, M.; Skrydstrup, T.; Sierks, M.R. *Biochemistry* **1996**, *35*, 2788.
(5) Sun, L.; Li, P.; Amankulor, N.; Tang, W.; Landry, D.W.; Zhao, K. *J. Org.Chem.* **1998**, *63*, 6472.
(6) Robinson, K.M.; Begovic, M.E.; Rhinehart, B.L.; Heinke, E.W.; Ducep, J.-B.; Kastner, P.R.; Marshall, F.N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
(7) G. Legler in Ref. 1. p 56-59.
(8) Lehman, J.; Rob, B. *Carbohydrate Res.* **1995**, *272*, C11.
(9) Igarashi, Y.; Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 553.
(10) Legler, G.; Stütz, A. E.; Immrich, H. *Carbohydrate Res.* **1995**, *272*, 17.
(11) Paulsen, H.; Steinert, G. *Chem. Ber.* **1967**, *100*, 2467.
(12) Bernotas, R.C.; Papandreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 3393.
(13) Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857.
(14) Holland, D.; Stoddart, J.F. *Carbohydrate Res.* **1982**, *100*, 207.
(15) Vidra, I.; Institóris, L.; Simon, K.; Czugler, M.; Csöregh, I. *Carbohydrate Res.* **1983**, *111*, 215.
(16) Altenbach, H.J.; Merhof, G.F. *Tetrahedron: Asymmetry* **1996** *7*, 3087.
(17) Chenera, B.; Boehm, J.C.; Dreyer, G.B. *Bioorg. Med. Chem. Lett* **1991**, *1*, 219.
(18) Schreiber, S.L.; Sammakia, T.; Uehling, D.E. *J. Org. Chem.* **1989**, *54*, 15.
(19) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293; Depezay, J.-C. In *Carbohydrate Mimics: Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim 1998; chap. 16.
(20) A first combinatorial library of azasugar glycosidase inhibitors based on 1-azafagomine has recently been reported; Lohse, A.; Jensen, K.B.; Bols, M. *Tetrahedron Lett.* **1999**, *40*, 3033.
(21) Kim, D.-K.; Kim, G.; Kim, Y.-W. *J. Chem. Soc., Perkin Trans. 1*. **1996**, 803.
(22) Parr, I.B.; Horenstein, B.A. *J. Org. Chem.* **1997**, *62*, 7489.
(23) Capon R.J.; Barrow, R.A. *J. Org. Chem.* **1998**, *63*, 75.
(24) For the synthesis of 6-amino-6-deoxy-1,2-3,4-bis-O-isopropylidene-D-galactose see J.M. Garcia Fernandez, C.O. Mellet, J. Fuentes *J. Org. Chem.* **1993**, *58*, 5192.
(25) Selected spectroscopic data:
N-Benzyl-3-benzyl-3,4,5-*trans*,*trans*-trihydroxypiperidine (**9a**)
^{1}H NMR (400 MHz/$CDCl_3$) 2.28 (dd, 2H, H1b, H5b), 2.87 (dd, 2 H, *J*=11.4 and 3.4 Hz, H1b, H5b), 3.28 (t, 1H, *J*=7.2 Hz, H3), 3.58 (s, 2H, NCH_2Ph), 3.79 (dt, 2H, *J*=11.4 and 7.2 Hz, H2, H4), 4.79 (s, 2H, OCH_2Ph), 7.38-7.25 (m, 10H, Ar).
^{13}C NMR (100 MHz/$CDCl_3$) 57.0 (CH_2, C1, C5), 62.0 (CH_2, NCH_2Ph), 69.8 (CH, C2, C4), 73.8 (CH_2, OCH_2Ph), 84.3 (CH, C3), 127.2, 127.7, 127.9, 128.3, 128.6, 129.0 (all CH, Ar), 137.7, 138.6 (C, Ar).

3,4,5-*trans*,*trans*-Trihydroxypiperidine (4)
^{1}H NMR (400 MHz/D_2O) 2.26 (dd, 2H, *J*=10.5 and 12.6 Hz, H1b, H5b), 2.94 (dd, 2H, *J*=4.9, 12.6 Hz, H1a,H5a), 3.11 (t, *J*=9.1 Hz, H3), 3.31 (ddd, 2H, *J*=4.9, 9.1 and 10.5 Hz, H2, H4). ^{13}C NMR (67.80 MHz/D_2O) 49.6 (CH_2, C1, C5), 71.1 (CH, C2, C4), 78. 6 (CH, C3).

***N*-(6'-Deoxy-1',2'-3',4'-bis-*O*-isopropylidene-D-galactosyl)-3-benzyl-3,4,5-*trans*,*trans*-trihydroxypiperidine (10a)**
^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (s, 6H, $C(CH_3)_2$), 1.45 (s, 3H, $C9CH_3)_2$), 1.54 (s, 3H, $C(CH_3)_2$), 2.39-2.49 (m, 2H, H2b, H6b), 2.61-2.78 (m, 2H, H6'), 2.96 (m, 2H, H2a, H6a), 3.31 (t, 1H, *J*=6.5 Hz, H4), 3.80 (m, 2H, H3, H5), 3.94, (m, 1H, H5'), 4.20 (dd, 1H, *J*=2 and 8 Hz, H4'), 4.30 (dd, 1H, *J*=2 and 5 Hz, H2'), 4.59 (dd, 1H, *J*=2 and 8 Hz, H3'), 4.76 (s, 2H, CH_2Ph), 5.54, (d, 1H, *J*=5 Hz, H1'), 7.36 (m, 5H, Ar). ^{13}C NMR (67.80 MHz/$CDCl_3$) 25.3 (CH_3, $C(CH_3)_2$), 26.4 (CH_3, $C(CH_3)_2$), 26.5 (CH_3, $C(CH_3)_2$), 57.5 (CH_2, C2, C6), 57.6 (CH_2, C6'), 66.0 (CH, C5'), 69.9, (CH, C3, C5), 70.9 (CH, C2'), 71.3 (CH, C3'), 73.0 (CH, C4'), 74.2 (CH_2, CH_2Ph), 83.1 (CH, C4), 97.0 (CH, C1'), 109.0 (C, $C(CH_3)_2$), 110.0, (C, $C(CH_3)_2$), 128.1, 128.3, 129.0 (all CH, Ar), 138.0 (C, Ar). HRMS (EI): m/z found: 465.2343; $C_{24}H_{35}NO_8$ requires 465.2363.

***N*-(6'-Deoxy-1',2'-3',4'-bis-*O*-isopropylidene-D-galactosyl)-3,4,5-*trans*,*trans*-trihydroxypiperidine**
^{1}H NMR (400 MHz, $CDCl_3$) 1.32 (s, 6H, $C(CH_3)_2$), 1.44 (s, 3H, $C9CH_3)_2$), 1.55 (s, 3H, $C(CH_3)_2$), 2.09 (m, 2H, H2b, H6b), 2.56-2.7 (m, 2H, H6'), 3.03 (m, 2H, H2a, H6a), 3.24 (t, 1H, *J*=8.6 Hz, H4), 3.64 (m, 2H, H3, H5), 3.92, (m, 1H, H5'), 4.16 (app. d, 1H, H4'), 4.29 (dd, 1H, *J*=2.3 and 5.0 Hz, H2'), 4.5 (dd, 1H, *J*=2.3 and 7.9 Hz, H3'), 5.54 (d, 1H, *J*=5 Hz, H1'). ^{13}C NMR (67.80 MHz/$CDCl_3$) 25.3 (CH_3, $C(CH_3)_2$), 24.4 (CH_3, $C(CH_3)_2$), 24.9 (CH_3, $C(CH_3)_2$), 26.0 (CH_3, $C(CH_3)_2$), 26.1 (CH_3, $C(CH_3)_2$), 57.2 (CH_2, C2, C6), 57.9 (CH_2, C6'), 65.1 (CH, C5'), 69.9, (CH, C4), 70.0 (CH, C3, C5), 70.4 (CH, C2'), 70.8 (CH, C3'), 72.3 (CH, C4'), 96.4 (CH, C1'), 108.7 (C, $C(CH_3)_2$), 109.3, (C, $C(CH_3)_2$).

Article Identifier:
1437-2096,E;2000,0,02,0193,0196,ftx,en;L21699ST.pdf