Electrophilic Azidation of 2-Deoxy-aldono-1,5-lactones: an Alternative Route to 2-Azido-2-deoxy-aldopyranoses

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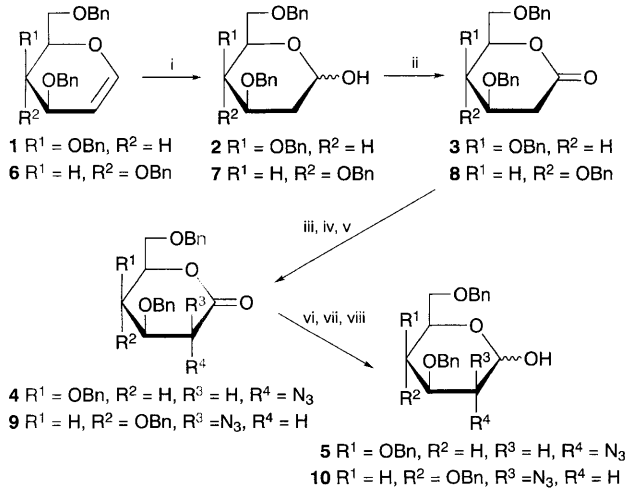
Electrophilic azidation of tri-*O*-benzyl-2-deoxy-D-galactono-1,5-lactone **3** with triisopropylphenylsulfonyl azide, followed by selective reduction with diisobutylaluminium hydride, yielded tri-*O*-benzyl-2-azido-2-deoxy-D-galactopyranose **5** as the sole product in 80% yield, while the same sequence of reactions with the 2-deoxy-glucono-1,5-lactone derivative **8** afforded only tri-*O*-benzyl-2-azido-2-deoxy-D-mannopyranose **10** in 65% yield.

Over the past decade the carbohydrate units of glycoconjugates (glycans) have received increasing attention in both academic and industrial sectors.[1] Particularly, the recent discovery of carbohydrate-mediated cell–cell interactions associated with inflammation and cancer metastasis has initiated intensive research focused on the development of carbohydrate-based therapeutics.[2] Glycans often contain 2-amino-2-deoxy-aldopyranosides as their building blocks. For glycan synthesis the 2-azido-2-deoxy derivatives of mono- and di-saccharides are versatile intermediates.[3] These azido sugars have been prepared by (*a*) azidonitration,[4] azidohalogenation[5] or azidophenylselenylation[6] of *O*-protected glycals, (*b*) azidolysis of the 2,3-epoxide ring in 1,6-anhydro-sugars,[7] (*c*) azide displacement of 2-*O*-sulfonate derivatives,[8] or (*d*) the direct[9] or stepwise[10] transformation from 2-amino-2-deoxy-sugars.

Electrophilic azide transfer to enolates using arylsulfonyl azides has been studied extensively and proven to be a general approach to the asymmetric synthesis of α-amino acids.[11] Herein, we report our preliminary findings that electrophilic azidation is highly stereoselective for the preparation of 2-azido-2-deoxy-aldopyranoses.

The 2-deoxy-aldono-1,5-lactones **3**[12] and **8**[13] were prepared in two steps from readily available tri-*O*-benzyl-D-glycals **1**[5] and **6**,[14] respectively (Scheme 1). Treatment of **1** and **6** in an acidic aqueous medium gave the corresponding 2-deoxy-aldopyranoses **2**‡,§ and **7** without allylic rearrangement (the Ferrier reaction).[15] The subsequent oxidation was effected by portionwise addition of pyridinium chlorochromate (PCC), whereas the use of Me_2SO with P_2O_5, Ac_2O or $(CF_3CO)_2O$ was not satisfactory. In contrast to the previous report,[12] the direct oxidation of glycals to lactones was accompanied by β-elimination leading to the formation of α,β-unsaturated lactones. Based on the ^1H NMR data ($J_{2ax,3} = J_{2eq,3} = J_{3,4} = 4.5$ Hz and NOE between H-2ax and H-5), the lactone **8**§ seems to adopt a $B_{2,5}$ conformation rather than $^4C_1$ as in the case for **3** (Scheme 2).



1 R^1 = OBn, R^2 = H
6 R^1 = H, R^2 = OBn
2 R^1 = OBn, R^2 = H
7 R^1 = H, R^2 = OBn
3 R^1 = OBn, R^2 = H
8 R^1 = H, R^2 = OBn
4 R^1 = OBn, R^2 = H, R^3 = H, R^4 = N_3
9 R^1 = H, R^2 = OBn, R^3 = N_3, R^4 = H
5 R^1 = OBn, R^2 = H, R^3 = H, R^4 = N_3
10 R^1 = H, R^2 = OBn, R^3 = N_3, R^4 = H

Scheme 1 *Reagents and conditions*: i, THF–H_2O–conc. HCl (5 : 1 : 0.1), room temp. overnight, 85% **2** and 88% **7**; ii, PCC (3 × 1 equiv. at 2 h intervals), 4 Å molecular sieves CH_2Cl_2, room temp. 5 h, 85% **3** and 90% **8**; iii, KHMDS (1.1 equiv.), THF, −90 °C, 15 min; iv, trisyl azide (1.2 equiv.), 2 min; v, AcOH (1.2 equiv.), −90 °C → room temp.; vi, DIBAL-H (2 equiv.), THF, −70 °C, 30 min; vii, H_2O, −70 °C → room temp. viii, 6 mol dm^{-3} HCl (a few drops), 15 min, 80% **5** from **3** and 65% **10** from **8**.

Electrophilic azidation of **3**/**8** was carried out according to the procedure reported by Evans and Britton,[11] *i.e.* enolization with potassium bis(trimethylsilyl)amide (KHMDS), triazine formation with triisopropylphenylsulfonyl azide (trisyl azide)[16] and quenching the reaction with AcOH. Since the azidolactones **4**§ and **9**§ decomposed slowly during work-up, the azidation was followed by selective reduction of lactone to lactol with diisobutylaluminium hydride (DIBAL-H) in the same pot, furnishing 2-azido-2-deoxy-aldopyranoses **5** and **10**§ in 80 and 65% overall yields, respectively. For the analysis, small amounts of **4** and **9** could be isolated by flash column chromatography on silica gel (6 : 1 hexane–EtOAc).

A general procedure for the one-pot reaction (**3** → **4** → **5** and **8** → **9** → **10**) is as follows: a solution of **3**/**8** in anhydrous THF was cooled to −90 °C and a 0.5 mol dm^{-3} solution of KHMDS (1.1 equiv.) was added dropwise with vigorous stirring. After 15 min, a precooled 0.2 mol dm^{-3} solution of trisyl azide in THF (1.2 equiv., −90 °C) was added dropwise. After another 2 min, AcOH (1.2 equiv.) was added and the mixture was warmed gradually to room temp. and stirred for 15 min. The mixture was again cooled to −70 °C and precooled DIBAL-H (2 equiv.) was added. After 30 min, H_2O was added and the mixture was warmed to room temp. The mixture was then acidified by a few drops of 6 mol dm^{-3} HCl and stirred for 15 min. The product was extracted with CH_2Cl_2 and purified by flash column chromatography on silica gel (20 : 1 toluene–acetone).

The high stereochemistry of this azidation reaction, is comparable to (for the *lyxo*-series, *i.e.* **3**) or better than (for the *arabino*-series, *i.e.* **8**) those observed in the known azide additions to glycals[4–6] mentioned above. For the azidation of **8**, the production of another diastereoisomer, the 2-azido-2-deoxy-glucopyranose derivative, was not detected. It seems that the azidation yields preferentially an equatorial azido group.¶ Therefore, the electrophilic azidation to 2-deoxy-aldono-1,5-lactones provides a highly stereoselective alternative to the existing methods for preparing 2-azido-2-deoxy-aldopyranoses.

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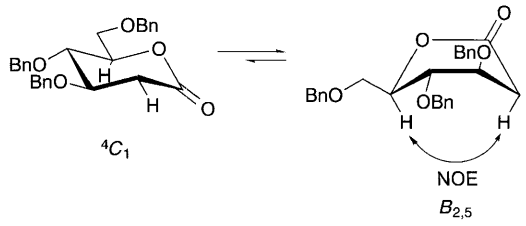

$^4C_1$ $B_{2,5}$

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Footnotes

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‡ All new compounds exhibited satisfactory spectral and high-resolution MS data.

§ *Selected physical properties of compounds.* **2**: colourless oil, 3.5 : 1 (α : β); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (br d, 1 H, *J* 4.0 Hz, H-1α), 4.13 (ddd, 1H, *J* 5.5, 5.5, *ca.* 0 Hz, H-5α), 3.98 (ddd, 1 H, *J* 11.0, 4.5, 3.0 Hz, H-3α), 3.87 (br s, 1 H, H-4α), 3.81 (br s, 1 H, H-4β), 3.63 (dd, 1 H, *J* 9.5, 6.0 Hz, H-6β), 3.58 (dd, 1 H, *J* 9.5, 5.5 Hz) and 3.50 (dd, 1 H, *J* 9.5, 5.5 Hz) (2 × H-6α), 2.21 (ddd, 1 H, *J* 12.0, 11.0, 4.0 Hz, H-2axα), 2.15 (br d, 1 H, *J* 12 Hz, H-2eqβ) and 2.01 (ddd, 1 H, *J* 12.0, 4.5, *ca.* 0 Hz, H-2eqα). HRFABMS: 457.2001 ($C_{27}H_{30}NaO_5$ [M + Na]$^+$, calc. 457.1991). **4**: colourless oil, $[\alpha]_D$ +63 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (d, 1 H, *J* 10.5 Hz, H-2), 4.31 (ddd, 1 H, *J* 9.0, 6.0, 2.0 Hz, H-5), 4.15 (br s, 1 H, H-4), 3.70 (dd, 1 H, *J* 10.0, 9.0 Hz) and 3.65 (dd, 1 H, *J* 10.0, 6.0 Hz) (2 × H-6) and 3.67 (dd, 1 H, *J* 10.5, 2.0 Hz, H-3). HRFABMS: 496.1839 ($C_{27}H_{27}N_3NaO_5$ [M + Na]$^+$, calc. 496.1848). **8**: colourless crystals, mp 79 °C, $[\alpha]_D$ +37 (*c* 0.6, $CHCl_3$) {lit.[13] mp 83 °C, $[\alpha]_D$ +48 (*c* 1.0, EtOH)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (ddd, 1 H, *J* 7.5, 4.0, 4.0 Hz, H-5), 3.94 (ddd, 1 H, *J* 4.5, 4.5, 4.5 Hz, H-3), 3.89 (dd, 1 H, *J* 7.5, 4.5 Hz, H-4), 3.73 (dd, 1 H, *J* 10.5, 4.0 Hz) and 3.70 (dd, 1 H, *J* 10.5, 4.0 Hz) (2 × H-6), 2.84 (dd, 1 H, *J* 15.0, 4.5 Hz, H-2ax) and 2.74 (dd, 1 H, *J* 15.0, 4.5 Hz, H-2eq). **9**: colourless oil, $[\alpha]_D$ +6 (*c* 0.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (m, 1 H, H-5), 4.14 (d, 1 H, *J* 3.5 Hz, H-2), 4.05 (dd, 1 H, *J* 3.5, 1.5 Hz, H-3), 3.90 (dd, 1 H, *J* 6.0, 1.5 Hz, H-4) and 3.66 (d, 2 H, *J* 4.5 Hz, 2 × H-6). HRFABMS: 496.1848 ($C_{27}H_{27}N_3NaO_5$ [M + Na]$^+$ calc. 496.1848). **10**: colourless oil, 3.5 : 1 (α : β); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (br s, 1 H, H-1α), 4.69 (br s, 1 H, H-1β), 4.10 (dd, 1 H, *J* 9.0, 4.0 Hz, H-3α), 3.99 (ddd, 1 H, *J* 9.5, 5.0, 2.5 Hz, H-5α), 3.93 (m, 1 H, H-2β), 3.92 (dd, 1 H, *J* 4.0, 2.5 Hz, H-2α), 3.82 (dd, 1 H, *J* 9.5, 9.5 Hz, H-4β), 3.78 (dd, 1 H, *J* 9.0, 9.0 Hz, H-4α), 3.71 (dd, 1 H, *J* 9.0, 3.5 Hz, H-3β), 3.69 (m, 2 H, 2 × H-6β) and 3.65 (m, 2 H, 2 × H-6α). HRFABMS: 498.2010 ($C_{27}H_{29}N_3NaO_5$ [M + Na]$^+$ calc. 498.2005).

¶ On the basis of the ^{1}H NMR data, the azidolactones **4** and **9** seem to exist similarly to **3** and **8** as $^4C_1$ and $B_{2,5}$ conformations, respectively. NOE between H-2 and H-5 observed in **9** implies the $B_{2,5}$ conformation.

References

1 Some reviews: T. M. Carlos and J. M. Harlan, *Blood*, 1994, **84**, 2068; A. Varki, *Proc. Natl. Acad. Sci. USA*, 1994, **91**, 7390; A. Varki, *Glycobiology*, 1993, **3**, 97; H. Lis and N. Sharon, *Eur. J. Biochem.*, 1993, **218**, 1.

2 For example, see: S. Hakomori, *Cancer Cells*, 1991, **3**, 461; K.-A. Karlsson, *TiPS*, 1991, **12**, 265; J. Hodgson, *Bio/Technology*, 1991, **9**, 609; J. L. Winkelhake, *Glycoconjugate J.*, 1991, **8**, 381; B. N. N. Rao, M. Moreland and B. K. Brandley, *Med. Chem. Res.*, 1991, **1**, 1.

3 For example, see: H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 823; R. R. Schmidt, *Pure Appl. Chem.*, 1989, **61**, 1257.

4 R. U. Lemieux and R. M. Ratcliffe, *Can. J. Chem.*, 1979, **57**, 1244.

5 N. V. Bovin, S. É. Zurabyan and A. Ya. Khorlin, *Carbohydr. Res.*, 1981, **98**, 25.

6 S. Czernecki, E. Ayadi and D. Randriamandimby, *J. Chem. Soc., Chem. Commun.*, 1994, 35; F. Santoyo-González, F. G. Calvo-Flores, P. García-Mendoza, F. Hernández-Mateo, J. Isac-García and R. Robles-Díaz, *J. Org. Chem.*, 1993, **58**, 6122.

7 (*a*) D. Tailler, J.-C. Jacquinet, A.-M. Noirot and J.-M. Beau, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3163; (*b*) T. Takamura, T. Chiba and S. Tejima, *Chem. Pharm. Bull.*, 1979, **27**, 721; (*c*) H. Paulsen and W. Stenzel, *Chem. Ber.*, 1978, **111**, 2334.

8 V. Pavliak and P. Kováč, *Carbohydr. Res.*, 1991, **210**, 333; F. Dasgupta and P. J. Garegg, *Synthesis*, 1988, 626; J. N. Vos, J. H. van Boeckel and T. Beetz, *J. Carbohydr. Chem.*, 1984, **3**, 117.

9 A. Vasella, C. Witzig, J.-L. Chiara and M. Martin-Lomas, *Helv. Chim. Acta*, 1991, **74**, 2073.

10 F. Dasgupta and P. J. Garegg, *J. Chem. Soc., Chem. Commun.*, 1989, 1640.

11 D. A. Evans and T. C. Britton, *J. Am. Chem. Soc.*, 1987, **109** 6681.

12 P. Rollin and P. Sinaÿ, *Carbohydr. Res.*, 1981, **98**, 139.

13 C. Bernasconi, L. Cottier, G. Descotes and G. Rémy, *Bull. Soc. Chim. Fr.*, 1979, **5–6**, II-332.

14 M. Chmielewski, I. Fokt, J. Grodner, G. Grynkiewicz and W. Szeja, *J. Carbohydr. Chem.*, 1989, **8**, 735.

15 R. J. Ferrier and N. Prasad, *J. Chem. Soc. C*, 1969, 570.

16 R. E. Harmon, G. Wellman and S. K. Gupta, *J. Org. Chem.*, 1973, **38**, 11.