Pergamon

Tetrahedron Letters 42 (2001) 3901–3903

TETRAHEDRON LETTERS

Elaboration of a novel type of interglycosidic linkage: syntheses of disulfide disaccharides

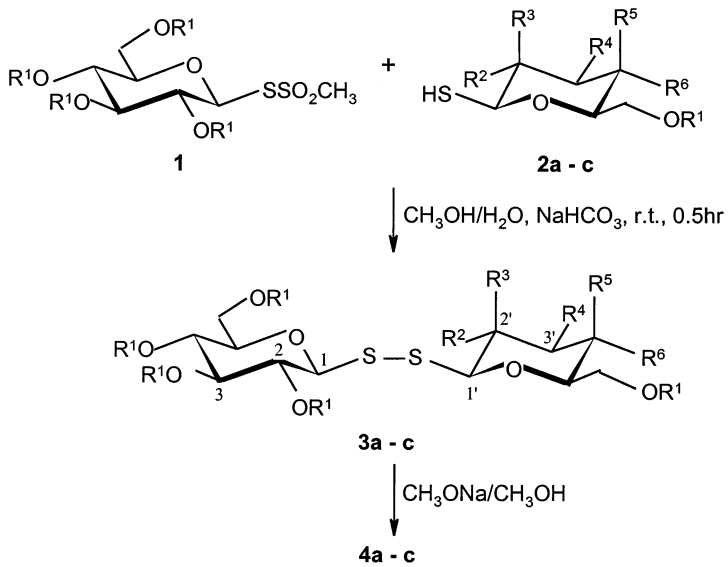
László Szilágyi,[a,*] Tünde-Zita Illyés[a] and Pál Herczegh[b]

[a]*Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, pf. 20., Hungary*
[b]*Antibiotics Research Group of the Hungarian Academy of Science, H-4010 Debrecen, pf. 20., Hungary*

Received 18 September 2000; revised 27 March 2001; accepted 6 April 2001

Abstract—Asymmetric non-reducing disaccharides containing an interglycosidic disulfide linkage were synthesised under mild conditions through reaction of tetraacetyl-β-D-glucopyranosyl methanethiolsulfonate with *O*-acetylated 1-thio-aldopyranoses. The preferred conformation around the –S–S– bond is close to that observed in unconstrained disulfides (–90°).

Analogues of oligosaccharides in which an N, S, Se or C atom replaces the glycosidic O-atom are well known and have been investigated in detail. On the other hand, few structures featuring a three-bond interglycosidic connection (–X–Y–, with X, Y = O, N, C, S), in place of the natural two-bond coupling between monosaccharide units, are known.[1,2] Some representatives of the latter also occur in nature as components of important antitumor antibiotics.[2] Disulfide linkages play an essential role in stabilising tertiary structures of proteins, in the formation of cyclopeptides and in many biologically relevant systems. This structural motif is, however, virtually non-existent within carbohydrates of either synthetic or natural origin. Obvious exceptions are symmetric disulfides formed through oxidation of 1-thioaldoses and some glycosyl-aryl/alkyl disulfides that have been known for a long time.[3] A few cyclic disulfide derivatives of mono-[4] and disaccharides[5] have also been described. Disaccharide mimics wherein two monosaccharide units are linked together by an



Scheme 1.

Keywords: disulfides; carbohydrates; conformation; NMR; thiosugars.

* Corresponding author. Fax: +36-52-453-836; e-mail: lszilagyi@tigris.klte.hu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00578-0

extended chain containing an S–S bond have recently been reported.[6] Some neoglycoproteins represent recent examples of interesting hybrid structures in which glycosyl units are attached to proteins through S–S linkages.[7]

We thought that the design of a novel type of *non-symmetric* oligosaccharide scaffold wherein a *disulfide bridge* replaces interglycosidic oxygen would be of interest for several reasons: (i) added flexibility within the resulting compounds with respect to the reference natural glycosides, (ii) increased distance between components in terms of the number of connecting bonds (3 versus 2), (iii) extension of the available conformational space as a result of (i) and (ii), and (iv) altered electronic and steric properties of the linker atoms. All these characteristics play a significant role in biological interactions involving carbohydrates[8] such as in cell recognition or proliferation or in carbohydrate metabolism.

S-S-Linked disaccharide model compounds were readily synthesised by adapting a general procedure[9] to prepare unsymmetrical disulfides (**III**) using alkylthiolsulfonate esters (**I**) for transferring RS groups to thiols (**II**):

$$\underset{\mathbf{I}}{\text{R-SSO}_2\text{CH}_3} + \underset{\mathbf{II}}{\text{R}'\text{-SH}} \rightarrow \underset{\mathbf{III}}{\text{R-S-S-R}'} + \text{CH}_3\text{SO}_2\text{H}$$

Thus, tetra-*O*-acetyl-β-D-glucopyranosyl methanethiolsulfonate (**1**), readily obtained[10] from acetobromoglucose by reaction with $NaSSO_2CH_3$, reacted smoothly with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-aldopyranoses (**2a–c**)[11] to furnish the protected β,β-(1,1′)-dithia-disaccharides **3a–c** in fair yields.[12] The anomeric configurations for both moieties in **3a** and **3c** are evident from the anomeric proton–proton couplings (Table 1); these data are, however, not relevant in the case of mannose derivatives. On the other hand, we could unequivocally confirm the β-configuration of the mannose unit in **3b** and **4b** by measuring the $^2J_{H1-C2}$ and $^3J_{H1-C3}$ values (Table 1)[13] (Scheme 1).

Products **3a–c** could be deacetylated smoothly under Zemplén's conditions and unprotected S–S disaccharides **4a–c** were obtained in near quantitative yields.[12]

The conformation around the glycosidic linkage is the single most important factor in determining the molecular shape of oligosaccharides influencing biological activity. Exploratory ^1H–^1H NOE measurements (1D and 2D) on **3b** disclosed significant interannular NOEs between H-2 of the mannose residue and various glucose ring protons as depicted in Fig. 1.

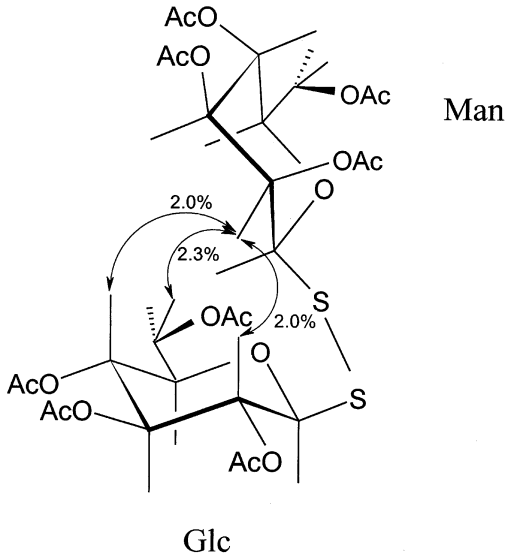


Figure 1. Structure of **3b** with key NOEs (Man-H2 to Glc-H2, -H4 and -H6a) indicated.

Inspection of molecular models indicated that in the conformation required by NOEs the C1–S–S–C1′ torsion angle is ca. −80° to −90°; this value is virtually identical with that observed in unconstrained disulfides.[14] It is known that the chemical reactivity of the S–S bond depends strongly on the CSSC dihedral angle[14] and this parameter should also play a role in biological interactions involving disulfides. It is of note in this respect that a peculiar conformation around the unusual three-bond (CNOC) interglycosidic linkage in calicheamicin was shown to be the key structural element that enables this molecule to bind in the minor groove of DNA to exert its biological action.[15]

Acknowledgements

This research was supported by grants from the Ministry of Education (FKFP 500/97 and 925/98) and the

Table 1. Thiol components and disulfide disaccharides

Compd	Config.	R^1	R^2	R^3	R^4	R^5	R^6	Relevant coupling constants (Hz)
2a, **3a**, **4a**	D-*gluco*	Ac	NHAc	H	OAc	H	OAc	**3a** $^3J_{H1-H2}=10.4$; $^3J_{H1'-H2'}=9.9$
		H	NHAc	H	OH	H	OH	**4a** $^3J_{H1-H2}=9.2$; $^3J_{H1'-H2'}=10.6$
2b, **3b**, **4b**	D-*manno*	Ac	H	OAc	OAc	H	OAc	**3b** $^3J_{H1-H2}=9.6$; $^3J_{H1'-H2'}=1.4$ $^2J_{H1'-C2'}=6.2$; $^3J_{H1'-C3'}\approx 0$
		H	H	OH	OH	H	OH	**4b** $^3J_{H1-H2}=9.2$; $^3J_{H1'-H2'}<1.5$ $^2J_{H1'-C2'}=4.0$; $^3J_{H1'-C3'}\approx 0$
2c, **3c**, **4c**	D-*galacto*	Ac	OAc	H	OAc	OAc	H	**3c** $^3J_{H1-H2}=10.1$; $^3J_{H1'-H2'}=10.1$
		H	OH	H	OH	OH	H	**4c** $^3J_{H1-H2}=9.3$; $^3J_{H1'-H2'}=9.5$

Hungarian National Science Fund (OTKA T34515 and T30138). The authors would like to express their gratitude to Drs. Z. Dinya, S. Kéki (Debrecen) and J. Jekő (Tiszavasvári) for the mass spectra and the microanalyses.

References

1. (a) X=C, Y=N: Andrews, J. S.; Weimar, T.; Frandsen, T. P.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1997**, *117*, 10799–10804; (b) X=Y=C: Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114–8124; X=Y=C, X=C, Y=S: Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939–2942.
2. (a) X=N, Y=O: *calicheamicins* and *esperamicins*, for a review see: Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103–2117; (b) X=C, Y=O: *namenamicin*: Weinstein, D. S.; Nicolaou, K. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 545–557.
3. (a) Staněk, J.; Šindlerova, M.; Černý, M. *Coll. Czech. Chem. Comm.* **1965**, *30*, 297–303; (b) Bell, R. H.; Horton, D.; Miller, M. J. *Carbohydr. Res.* **1969**, *9*, 201–214.
4. Wenzl, I.; Kähling, H.; Unger, F. M.; Schmid, W. *Monatsh. Chem.* **1999**, *130*, 1137–1145.
5. Hough, L.; Sinchareonkul, L. V.; Richardson, A. C.; Akhtar, F.; Drew, M. G. B. *Carbohydr. Res.* **1969**, *9*, 145–160.
6. Ramström, O.; Lehn, J.-M. *ChemBioChem* **2000**, *1*, 41–48.
7. (a) Davis, B. G.; Lloyd, R. C.; Jones, J. B. *J. Org. Chem.* **1998**, *63*, 9614–9615; (b) Macindoe, W. M.; van Oijen, A. H.; Boons, G.-J. *J. Chem. Soc., Chem. Commun.* **1998**, 847–848; (c) During the preparation of this manuscript, a synthesis of a partially deacetylated derivative of **3c** appeared in: Davis, B. G.; Ward, S. J.; Rendle, P. M. *J. Chem. Soc., Chem. Commun.* **2001**, 189–190.
8. Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
9. For reviews, see: (a) Keynon, G. L.; Bruice, T. W. *Methods Enzymol.* **1977**, *47*, 407–430; (b) Wynn, R.; Richards, F. M. *Methods Enzymol.* **1995**, *251*, 351–356.
10. Davis, B. G.; Maughan, M. A. T.; Green, M. P.; Ullman, A.; Jones, J. B. *Tetrahedron: Asymmetry* **2000**, *11*, 245–262.
11. (a) Compound **2a**: Akagi, M.; Haga, M. *Chem. Pharm. Bull.* **1961**, *9*, 360–366; (b) 2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-mannopyranose (Tejima, S.; Maki, T.; Akagi, M. *Chem. Pharm. Bull.* **1964**, *12*, 528–532) was selectively *S*-deacetylated using 2-aminoethanethiol (Defaye, J.; Guillot, J.-M. *Carbohydr. Res.* **1994**, *253*, 185–194) to give **2b**, which was identical to the product described by: Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881–2889; (c) Compound **2c**: Černý, M.; Staněk, J.; Pacák, J. *Monatsh. Chem.* **1963**, *94*, 267–290.
12. All new compounds were fully characterised by ^{1}H and ^{13}C NMR, elemental analyses and/or high resolution MS. In a typical procedure **1** (0.7 mmol) was dissolved in methanol–water (10 mL, 2:1 v/v) containing 1 equiv. of $NaHCO_3$ and 1 equiv. of the thiol component (**2a–c**) was added. The reaction mixture was stirred at room temperature for 0.5 h (TLC), evaporated to dryness and the residue purified by column chromatography on silica gel (toluene:EtOAc, 7:3).
Compound **3b**: white crystals (from EtOAc/hexane); mp 187–188°C; isolated yield 73.6%; $[\alpha]_D$ −118.4 (*c* 1.26, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 6.12 (d, 1H, Man-H2), 5.72 (t, 1H, Man-H4), 5.60 (dd, 1H, Glc-H2), 5.52 (dd, 1H, Man-H3), 5.40 (m, 2H, Glc-H3, Glc-H4), 5.10 (s, 1H, Man-H1), 4.56 (dd, 1H, Glc-H6a), 4.44 (dd, 1H, Man-H6a), 4.30 (dd, 1H, Glc-H6b), 4.23 (dd, 1H, Man-H6b), 3.92 (d, 1H, Glc-H1), 3.65 (ddd, 1H, Man-H5), 3.39 (m, 1H, Glc-H5); ^{13}C NMR (C_6D_6, 125 MHz): δ 90.92 (Man-C1), 84.43 (Glc-C1), 77.05 (Man-C5), 76.88 (Glc-C5), 73.74 (Glc-C3), 71.56 (Man-C3), 69.93 (Man-C2), 68.44 (Glc-C2), 68.05 (Glc-C4), 65.15 (Man-C4), 61.73 (Man-C6), 61.54 (Glc-C6).
Anal found: C, 46.35; H, 4.92; S, 8.96. Calcd for $C_{28}H_{38}O_{18}S_2$ (726.15): C, 46.27; H, 5.23; S, 8.81. High-resolution MS calcd for $C_{28}H_{38}O_{18}S_2$ [M+H$^+$]: 727.1578. Found: 727.1583.
Compounds **3a–c** could be smoothly deacetylated under Zemplén's conditions to give **4a–c**.
Compound **4b**: syrup; isolated yield 97%; $[\alpha]_D$ −115.42 (*c* 1.07, H_2O); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.17 (d, 1H, Glc-OH2), 5.02 (d, 1H, Glc-OH3), 4.97 (d, 1H, Glc-OH4), 4.91 (d, 1H, Man-OH2), 4.83–4.75 (m, 3H, Man-OH4, Man-OH3, Man-H1), 4.65 (t, 1H, Man-OH6), 4.59 (t, 1H, Glc-OH6), 4.23 (d, 1H, Glc-H1), 3.82 (d, 1H, Man-H2), 3.70 (dd, 1H, Man-H6a), 3.66 (dd, 1H, Glc-H6a), 3.45–3.30 (m, 3H, Man-H6b, Glc-H2, Glc-H6b), 3.28–3.25 (m, 2H, Man-H3, Man-H4), 3.23–3.14 (m, 2H, Glc-H3, Glc-H5), 3.08 (m, 1H, Man-H5), 3.01 (m, 1H, Glc-H4); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 92.39 (Man-C1), 87.98 (Glc-C1), 81.85 (Man-C5), 81.23 (Glc-C5), 77.84 (Glc-C3), 74.16 (Man-C3), 71.56 (Man-C2), 70.48 (Glc-C2), 69.94 (Glc-C4), 66.65 (Man-C4), 61.46 (Man-C6, Glc-C6). High-resolution MS calcd for $C_{12}H_{22}O_{10}S_2$ [M+H$^+$]: 391.0733. Found: 391.0739.
13. Podlasek, C. A.; Wu, J.; Stripe, W. A.; Bondo, P. B.; Serianni, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 8635–8644: large $^2J_{H1-C2}$ (ca. 7 Hz) and small (<2 Hz) $^3J_{H1-C3}$ values are characteristic for β-mannopyranosides; the opposite relationship was observed for the α-anomers.
14. Lees, W. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 1860–1869 and references cited therein.
15. Walker, S.; Gange, D.; Gupta, V.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 3197–3206.