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Synthesis of novel amidoxime-linked pseudodisaccharides

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ABSTRACT

Disaccharide analogues containing amidoxime interglycosidic linkages have been synthesised by nucleophilic addition of aminomethylene pyranoses to pyranosyl nitrile oxides, generated by dehydrochlorination of the corresponding hydroximoyl chlorides. The structure of the *C*-xylopyranosyl-*N*-galactopyranosyl amidoxime **1** was established by X-ray crystallography.

There has been considerable interest in the chemistry of disaccharide analogues (pseudodisaccharides) in which the glycosidic oxygen is replaced by other groups that are more resistant to enzymatic and chemical hydrolysis.[1–12] *C*-Disaccharides in which the sugar units are joined by a methylene group have been the subject of detailed study.[1] Other bridging units that have been incorporated include amide,[2] urea,[3] thiourea,[3b,4] carbamate,[3c,5] thiocarbamate,[6] guanidine,[3b,6] sulfonamide,[7] thiohydroximate,[8] methoxyimino[9] and triazole.[10] Carbasugar-containing non-glycosidically-linked disaccharides have also been reported,[11] as have dinucleotides with nitrone, hydroxylamine and amidoxime links.[12] We have previously established a route to carbon-linked pseudodisaccharides based on nitrile oxide cycloaddition reactions[13] and now describe a short route to (1 → 6) and (1 → 1) amidoxime-linked disaccharides that is also based on nitrile oxide chemistry. The key step (Scheme 1) involves nucleophilic addition of an aminomethylene monosaccharide to a pyranose-1-carbonitrile oxide.

The approach is illustrated in Scheme 2 for the amidoxime-bridged disaccharide **1** derived from D-xylose and D-galactose. We have previously shown[14] that pyranosyl nitrile oxides react readily with primary aliphatic amines (e.g., benzylamine, butylamine) to afford *N*-alkyl-pyranosylamidoximes, and the same methodology was used in the present work. In order to avoid unwanted dimerisation by-products,[15] the xylopyranosyl nitrile oxide **2** was generated in situ by base-induced dehydrochlorination of the corresponding hydroximoyl chloride **3**, which in turn was prepared by the established literature route[15,16] from the readily-accessible nitromethyl compound **4**. The amino-D-galactose component **5** was prepared from di-*O*-isopropylidene-D-galactose (**6**) via the azide derivative **7**, as described by Reitz et al.;[17] the product was isolated (57% overall yield from **6**) as its hydrochloride salt, which was then used in the final step. In a typical coupling experiment a solution of the xylose-derived hydroximoyl chloride **3** (0.40 mmol) in dry chloroform was added dropwise to a cooled (0 °C) and vigorously stirred solution of the galactose amine **5** (1.30 mmol) and triethylamine (7.2 mmol) in dry chloroform (3 ml). After stirring for 1 h the mixture was diluted with dichloromethane, washed with 0.1 M aq HCl, and the combined organic layers dried ($MgSO_4$). Removal of the solvent in vacuo and chromatography (silica, hexane/Et_2O gradient elution) of the residue afforded a white solid (81%), which was identified by its spectroscopic properties[18] as the target amidoxime **1** (Table 1, entry 1). In the ^1H and ^{13}C NMR spectra there are, in addition to the expected signals for the xylopyranosyl and galactopyranosyl moieties, characteristic signals[14] for the amidoxime unit [δ_H 7.76 (OH), 5.24 ppm (NH); δ_C 149.0 ppm]. The furoxan dimer **8**[15] was not detected. Under similar conditions, addition of the amino-D-galactose **5** to the D-glucopyranosyl nitrile oxide **9**, generated from the hydroximoyl chloride **10**, afforded the D-Glc-D-Gal amidoxime **11** in 75% yield (Table 1, entry 2).

The structure of D-Xyl-D-Gal amidoxime **1** was established by X-ray crystallography (Fig. 1).[19] Noteworthy features include the *Z*-configuration of the oxime and the *s-trans* conformation about the amidic nitrogen with the H of the NH group facing the oxime OH. The near planarity of the NH–C=N–O unit [torsion angle 2.14°] and the short non-bonded distance [2.531 Å] between the amidic N and the oxime O are consistent with an intramolecular H-bond between these atoms. These results also support the previously proposed mechanism in which the amine adds to the nitrile oxide in a concerted but non-synchronous manner.[14,20]

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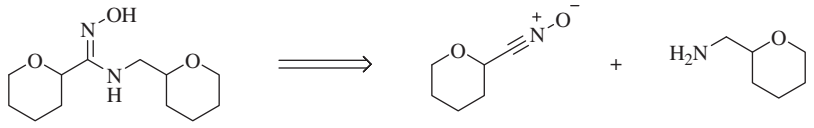
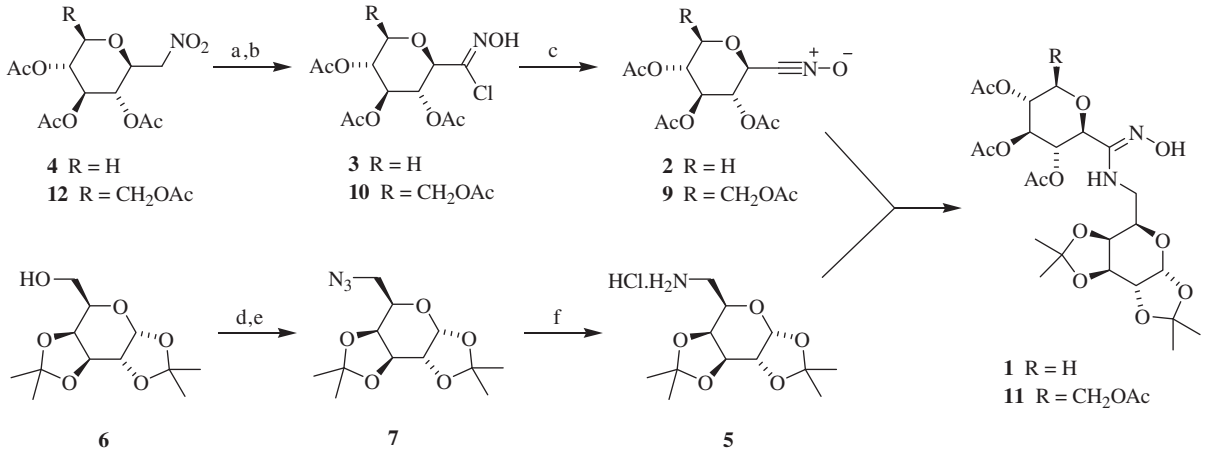


Scheme 1.



Scheme 2. Reagents and conditions: (a) PhSH, Et_3N, $SnCl_2$, THF, 0 °C; (b) Cl_2, CH_2Cl_2, −78 °C; (c) Et_3N; (d) TsCl, pyridine–MeCN; (e) NaN_3, DMSO, 115 °C; (f) H_2, 10% Pd/C, EtOH–5% $CHCl_3$.

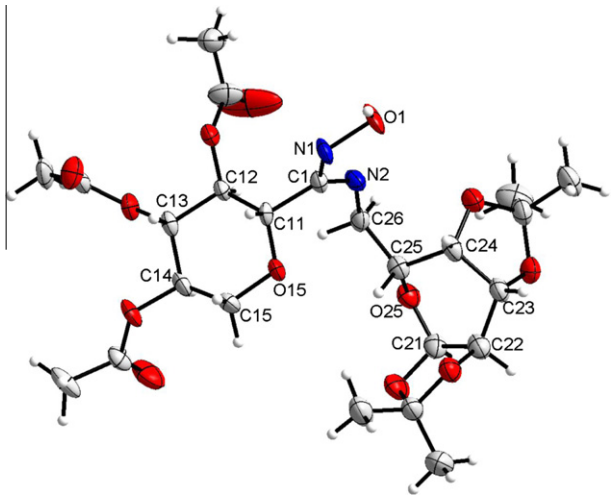
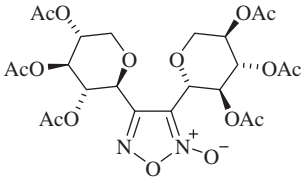


Figure 1. X-ray crystal structure of compound **1** showing *Z-s-trans* arrangement of the amidoxime.

Table 1
Formation of amidoxime-linked disaccharides **1**, **11**, and **15**–**18**



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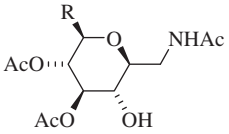
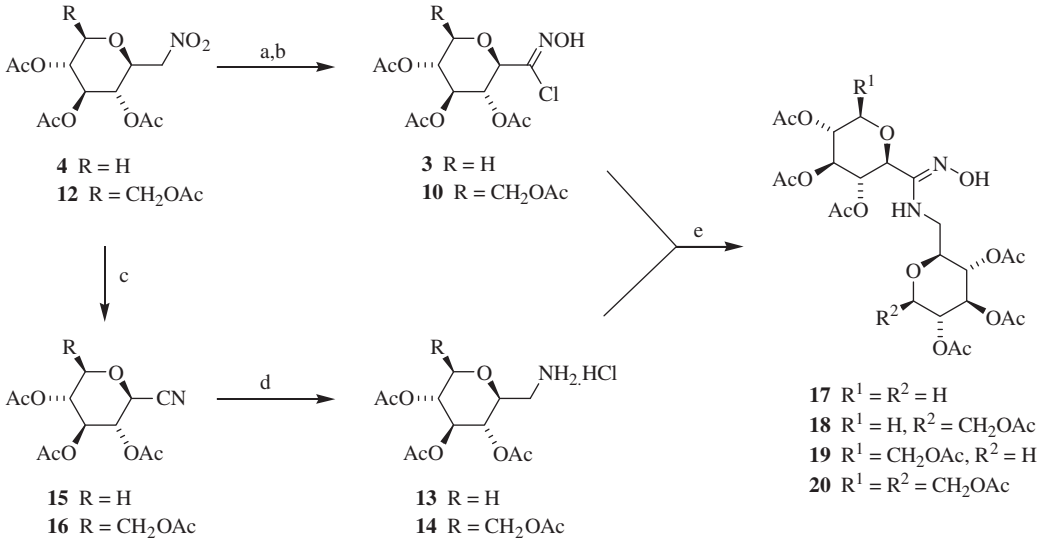


21 R = H
22 R = CH_2OAc

Entry	RCCl=NOH	Amine	Amidoxime (yield)
1	D-Xyl (**3**)	D-Gal (**5**)	**1** (81%)
2	D-Glc (**10**)	D-Gal (**5**)	**11** (75%)
3	D-Xyl (**3**)	D-Xyl (**13**)	**17** (44%)
4	D-Xyl (**3**)	D-Glc (**14**)	**18** (40%)
5	D-Glc (**10**)	D-Xyl (**13**)	**19** (31%)
6	D-Glc (**10**)	D-Glc (**14**)	**20** (49%)

The strategy for the synthesis of the (1 → 1) amidoxime-linked pseudodisaccharides involved a dual role for the pyranosyl nitromethanes as sources of both the nitrile oxide and the amino components of the coupling reactions, as illustrated in Scheme 3. Thus the nitromethyl pyranoses **4** and **12** were converted, not only into the hydroximoyl chlorides **3** and **10**, as described above, but also into the corresponding aminomethyl pyranoses **13** and **14**. Attempts to prepare the amines **13** and **14** by direct reduction of the nitromethyl compounds proved to be unreliable, and a two-step approach was therefore adopted. Initial treatment with PCl_3/pyridine afforded the nitriles **15** and **16**,[21] which were then reduced to the amino compounds by catalytic hydrogenation, with overall yields of 75% and 74%, respectively. The amines **13** and **14** were each reacted with the in situ formed D-xylose and D-glucose nitrile oxides **2** and **9**, as outlined above for the (1 → 6)-linked compounds **1** and **11** (Table 1, entries 3–6). The structures of the resulting (1 → 1)-linked compounds **17**–**20** were established from their spectroscopic properties.[22] The yields were consistently lower than those for the (1 → 6)-linked analogues described above. A likely explanation is the formation, as by-products, of the acetaminomethyl compounds **21** and **22**, resulting from O → N acetyl migration; this was shown in the case of compound **21** by comparison (NMR, TLC) with an authentic sample prepared via catalytic hydrogenation of nitromethyl compound **4**.[23]

In conclusion, a route to (1 → 6) and (1 → 1) amidoxime-linked disaccharides has been established based on 1,3-nucleophilic addition of amino sugars to pyranosyl nitrile oxides. In view of the ready availability of the starting materials this approach should provide easy access to a wide range of such pseudodisaccharides.



Scheme 3. Reagents and conditions: (a) PhSH, Et_3N, $SnCl_2$, THF, 0 °C; (b) Cl_2, CH_2Cl_2, −78 °C; (c) PCl_3, pyridine; (d) H_2, 10% PtO_2, EtOH–5% $CHCl_3$; (e) Et_3N.

References and notes

1. For examples of *C*-disaccharide synthesis, see: (a) Witzcak, Z. J.; Chhabra, R.; Chojnacki, J. *Tetrahedron Lett.* **1997**, *38*, 2215–2218; (b) Vogel, P.; Ferritto, R.; Kraehenbuehl, K.; Baudat, A. *Carbohydr. Mimics* **1998**, 19–48; (c) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133–1167; (d) Dondoni, A.; Marra, A.; Mizuno, M.; Giovannini, P. P. *J. Org. Chem.* **2002**, *67*, 4186–4199; (e) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron* **2005**, *61*, 7184–7192; (f) Li, X. L.; Xu, X.-M.; Tian, J.; Li, Y.-X. *Chin. J. Chem.* **2005**, *23*, 1564–1568; (g) Awad, L.; Demange, R.; Zhu, Y.-H.; Vogel, P. *Carohydr. Res.* **2006**, *341*, 1235–1252; (h) Zeitouni, J.; Norsikian, S.; Merlet, D.; Lubineau, A. *Adv. Synth. Catal.* **2006**, *348*, 1662–1670; (i) Denton, R. W.; Cheng, X.; Tony, K. A.; Dilhas, A.; Hernandez, J. J.; Caneles, A.; Jiminez-Barbero, J.; Mootoo, D. R. *Eur. J. Org. Chem.* **2007**, 645–654; (j) Werner, L.; Kniezo, L.; Dvorakova, H. *Tetrahedron Lett.* **2007**, *48*, 609–612; (k) Wan, Q.; Lubineau, A.; Guillot, R.; Scherrmann, M.-C. *Carbohydr. Res.* **2008**, *343*, 1754–1765.
2. (a) Sabesan, S. *Tetrahedron Lett.* **1997**, *38*, 3127–3130; (b) Gremyachinskiy, D. E.; Samoshin, V. V.; Gross, P. H. *Tetrahedron Lett.* **2003**, *44*, 6587–6590.
3. (a) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Palacios, J. C.; Perez, E. M. S. *Eur. J. Org. Chem.* **2006**, 657–671; (b) Blanco, J. L. J.; Bootello, P.; Benito, J. M.; Mellet, C. O.; Fernandez, J. M. G. *J. Org. Chem.* **2006**, *71*, 5136–5143; (c) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219–7223.
4. (a) Avalos, M.; Babiano, R.; Cintas, P.; Jiminez, J. L.; Light, M. E.; Palacios, J. C.; Fuentes, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 495–501; (b) Benito, J. M.; Mellet, C. O.; Sadalapure, K.; Lindhorst, T. K.; Defaye, J.; Fernandez, J. M. C. *Carbohydr. Res.* **1999**, *320*, 37–48.
5. Laupichler, L.; Thiem, J. *Synlett* **1992**, 159–160.
6. Osawa, T. *J. Org. Chem.* **1966**, *31*, 3839–3840.
7. Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549–2551.
8. Joseph, B.; Rollin, P. *Carbohydr. Res.* **1995**, *266*, 321–325.
9. (a) Peri, F.; Deutman, A.; La Ferla, B.; Nicotra, F. *Chem. Commun.* **2002**, 1504–1505; (b) Peri, F.; Jimenez-Barbaro, J.; Garcia-Aparacio, V.; Tvaroska, I.; Nicotra, F. *Chem. Eur. J.* **2004**, *10*, 1433–1444.
10. (a) Cheshev, P.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2006**, *4*, 3225–3227; (b) Marra, A.; Vecchi, A.; Chiappe, C.; Melai, B.; Dondoni, A. *J. Org. Chem.* **2008**, *73*, 2458–2461.
11. Cumpstey, I. *Carbohydr. Res.* **2009**, *344*, 2285–2310.
12. Gallos, J. K.; Dellios, C. C. *Tetrahedron Lett.* **2003**, *44*, 5679–5681.
13. (a) Dawson, I. M.; Johnson, T.; Paton, R. M.; Rennie, R. A. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1339–1340; (b) Paton, R. M.; Penman, K. J. *Tetrahedron Lett.* **1994**, *35*, 3163–3166.
14. Baker, K. W. J.; Horner, K. S.; Moggach, S. A.; Paton, R. M.; Smellie, I. A. S. *Tetrahedron Lett.* **2004**, *45*, 8913–8916.
15. (a) Baker, K. W. J.; Gibb, A.; March, A.; Paton, R. M. *Tetrahedron Lett.* **2001**, *42*, 4065–4068; (b) Baker, K. W. J.; March, A. R.; Parsons, S.; Paton, R. M.; Stewart, G. W. *Tetrahedron* **2002**, *58*, 8505–8513.
16. Baker, K. W. J.; Gibb, A.; March, A. R.; Parsons, S.; Paton, R. M.; Stewart, G. W. *Synth. Commun.* **2003**, *33*, 1707–1715.
17. Reitz, A. B.; Tuman, R. W.; Marchione, C. S.; Jordan, A. D.; Bowden, C. R.; Maryanoff, B. E. *J. Med. Chem.* **1989**, *32*, 2110–2116.
18. (*Z*)-*N*-(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)-*C*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)formamide oxime (**1**); white solid (81%); mp 167–168 °C; $[\alpha]_D^{20}$ −74 (*c* = 1.0, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 1.33, 1.38, 1.49, 1.53 (12H, 4 × s, CH_3), 1.97, 2.04, 2.05 (9H, 3s, $COCH_3$), 3.33 (1H, dd, 5a-H), 3.34–3.59 (2H, m, 6a′-H, 6b′-H), 3.84–3.89 (1H, m, 5′-H), 4.00 (1H, d, 1-H), 4.15 (1H, dd, 5e-H), 4.29–4.34 (2H, m, 2′-H, 4′-H), 4.63 (1H, dd, 3′-H), 5.04 (1H, ddd, 4-H), 5.20 (1H, dd, 3-H), 5.24 (1H, m, NH), 5.40 (1H, dd, 2-H), 5.53 (1H, d, 1′-H), 7.76 (1H, br s, OH); *J*(*x*–*y*)/Hz 1–2 10.1, 2–3 9.4, 3–4 9.4, 4–5a 9.0, 4–5e 5.4, 5a–5e 11.2, 1′–2′ 5.0, 2′–3′ 2.5, 3′–4′ 7.9; δ_C (93 MHz, $CDCl_3$) 20.6 ($COCH_3$), 24.3, 24.8, 25.8, 25.9 (ketal CH_3), 42.6 (C-6′), 66.7 (C-5), 67.4, 68.6, 68.7, 70.4, 70.6, 70.9, 73.7, 76.2 (C-1, C-2, C-3, C-4, C-2′, C-3′, C-4′, C-5′), 96.1 (C-1′), 108.6, 109.3 (ketal C), 149.0 (C=N), 169.3, 169.7, 170.2 ($COCH_3$); FAB-HRMS $[M+H]^+$ calculated for $C_{24}H_{37}N_2O_{13}$: 561.2292; found: 561.2282.
19. CCDC no. 782624.
20. Nguyen, M. T.; Malone, S.; Hegarty, A. F.; Williams, I. I. *J. Org. Chem.* **1991**, *56*, 3683–3687.
21. Köll, P.; Fortsch, A. *Carbohydr. Res.* **1987**, *171*, 301–315.
22. For example: (*Z*)-*N*-(3,4,5-tri-*O*-acetyl-β-D-xylopyranosylmethyl)-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)formamide oxime (**18**, R^1 = H, R^2 = CH_2OAc); white solid (40%); mp 141–143 °C; $[\alpha]_D^{20}$ −36 (*c* = 1.0, $CHCl_3$); δ_H (600 MHz, $CDCl_3$) 1.93, 1.95, 1.98, 1.99, 2.00, 2.03, 2.04 (21H, 7 × s, $COCH_3$), 3.17 (1H, ddd, 1a′-H), 3.26 (1H, dd, 6a′-H), 3.43 (1H, ddd, 2′-H), 3.54 (1H, ddd, 1b′-H), 3.64 (1H, ddd, 5-H), 4.03 (1H, d, 1-H), 4.04–4.07 (1H, m, 6a-H), 4.09 (1H, m, 6e′-H), 4.14 (1H, dd, 6b-H), 4.85 (1H, dd, 3′-H), 4.89–4.93 (1H, m, 5′-H), 4.95 (1H, dd, 4-H), 5.14–5.19 (2H, m, 4′-H, 3-H), 5.25 (1H, dd, 2-H), 5.34 (1H, dd, NH); *J*(*x*–*y*)/Hz 1–2 10.2, 2–3 9.6, 3–4 9.7, 4–5 9.9, 5–6a 2.2, 5–6b 5.8, 6a–6e 12.4, 1a′–2′ 6.6, 1b′–2′ 2.6, 1a′–1b′ 11.1, 2′–3′ 9.6, 3′–4′ 9.6, 4′–5′ 9.9, 5′–6a′ 10.9, 5′–6e′ 5.8, 6a′–6e′ 11.2; δ_C (93 MHz, $CDCl_3$) 20.4, 20.5, 20.6 ($COCH_3$), 43.2 (C-1′), 62.2 (C-6), 65.2 (C-6′), 68.0, 68.2, 68.9, 70.0, 73.1, 73.8, 75.1, 75.9, 77.5 (C-1, C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 147.8 (C=N), 169.3, 169.7, 170.1, 170.4 ($COCH_3$); FAB-HRMS: $[M+H]^+$ calculated for $C_{27}H_{39}N_2O_{17}$: 663.2249; found: 663.2250.
23. Simo, O.; Lee, V. P.; Davis, A. S.; Kreutz, C.; Gross, P. H.; Jones, P. R.; Michael, K. *Carbohydr. Res.* **2005**, *340*, 557–566.