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Ring-closing double reductive amination route to aza-heteroannulated sugars

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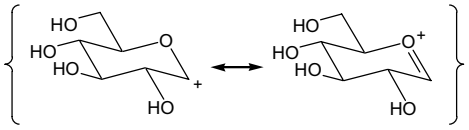
Abstract—1,4-Dicarbonyl derivatives of glycosides are produced by ozonolysis or Wacker oxidation. A stable ozonide is isolated and a carbonyl group reduced whilst maintaining the ozonide functionality. The 1,4-dicarbonyl compounds are converted to various *N*-substituted pyrrolidines by diastereoselective double reductive amination The resulting aza-heteroannulated sugars no significant inhibition of any glycosidase, with the exception of compound **12g**, which is a weak inhibitor of β-galactosidase.

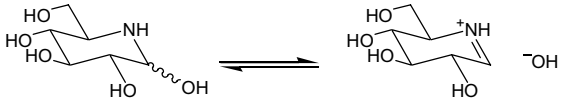
Polyhydroxylated aza-heterocycles and aminosugars are of interest because they evince a wide range of biological activity.[1–3] Particular attention has been paid to their ability to inhibit glycoside-processing enzymes, with resulting potential therapeutic applications in treatment of cancer, HIV and diabetes.[4,5]

The mechanism of glycosidases has been extensively studied, and is now thought to proceed via protonation of the *exo*-cyclic oxygen, which after bond cleavage gives rise to an oxo-carbonium ion intermediate such as **1**.[1]



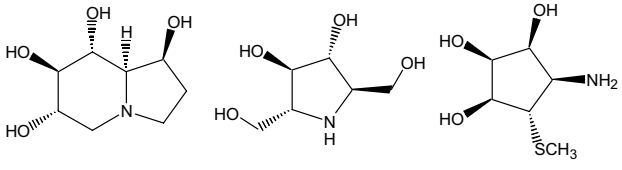
1

Design of inhibitors has subsequently focused upon mimicking the shape and charge of the transition state that leads to intermediate **1**. Potent naturally-occurring inhibitors such as nojirimycin (**2**) are thought to work via formation of an iminium ion (**3**), which is an aza-analogue of oxonium ion **1**.



2 **3**

Other potent inhibitors, such as castanospermine (**4**) and (2*R*,5*R*,3*R*,4*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (**5**), lack an hydroxyl group adjacent to the *endo*-cyclic heteroatom, and therefore cannot form an iminium ion analogous to **3**.[6] In these compounds the presence of a nitrogen that can be protonated is sufficient to give high glycosidase inhibitory activity.[1] Mannostatin A (**6**) is a potent inhibitor without obvious resemblance to the proposed transition state. This illustrates the importance of a basic amino group being present.[7a] Acetylation of this amino group has been found to destroy inhibitory activity.[7b]



4 **5** **6**

Keywords: Pyrrolidines; Carbohydrate annulation; Amino sugars; Stable ozonide decomposition; Glycosidase inhibitors.
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The synthesis of such compounds has therefore attracted considerable interest, with routes to enantiopure materials of special importance.

Previous work within this group has focused on the use of carbohydrates as scaffolds for stereoselective construction of various cyclic compounds.[8,9] Extension of this approach to include aza-heterocycles was expected to provide a facile route to substituted pyrrolidines. Production of the desired compounds by double reductive amination of a 1,4-dicarbonyl precursor was envisaged. Several examples of highly stereoselective double reductive amination ring-closures indicated the broad applicability of the intended approach.[10,11] The potential to create a diverse range of derivatives by altering the substituent on the nitrogen of the resulting pyrrolidine was also attractive, as it allows for possible optimisation of any biological activity, which is found.

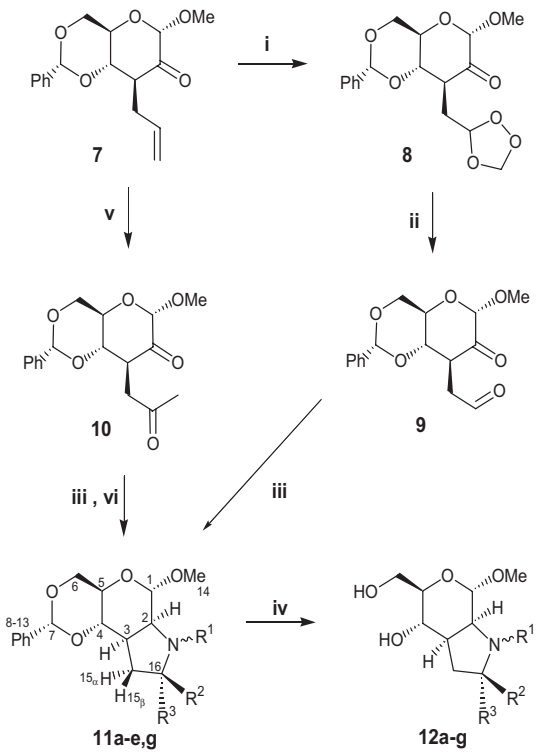
The transformation of the known alkene **7**[8] to a 1,4 dicarbonyl compound can be achieved by various methods in which oxidation of the alkene bond is a common feature. The simplest route was expected to be the ozonolysis of the double bond.

Formation of ozonide **8** in 85% yield was achieved by bubbling O_3 through a solution of alkene **7** in DCM at −78 °C.[12,13] Decomposition of ozonide **8** was initially attempted by treatment with excess DMS at rt overnight.[12] Removal of the DMS and DCM resulted in a clear syrup that was identified as a mixture of two diastereoisomers of ozonide **8** by ^{1}H NMR (Scheme 1).[13] Further attempts at reduction of the ozonide were made using thiourea, which also failed. Reduction using powdered zinc in acetic acid, which has been reported in the literature as reducing ozonides impervious to reduction with DMS[14] gave a complex mixture of products that did not have the Ph or OMe ^{1}H NMR signals of the starting material, indicating loss of the protecting groups. Direct conversion of the ozonide to an amine was also attempted without success.[15] Reaction of ozonide **8** with $NaCNBH_3$ in 2:1 THF–DCM at rt resulted in the reduction of the ketone functional group without decomposition of the ozonide moiety to afford ozonide **13** (Scheme 2); indicating an unusually stable ozonide.[16]

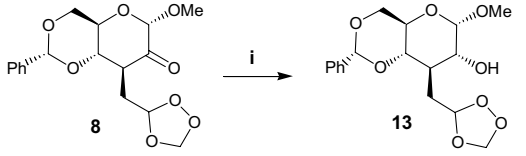
Decomposition of ozonide **8** was eventually achieved by treatment with 1 equiv of PPh_3 in DCM at rt to afford the dicarbonyl compound **9** in 62% yield.[17,18] Difficulties in removal of the Ph_3PO from **9** were overcome by use of a polymer-bound reagent (Scheme 1).[19]

An alternative approach for the conversion of ketone **7** to a 1,4-dicarbonyl compound makes use of the Wacker oxidation. This involves the oxidation of a terminal alkene to a methyl ketone using $PdCl_2$.[20] The desired diketone **10** was produced according to the literature procedure in 85% yield as a colourless syrup and identified by ^{1}H and ^{13}C NMR.[8]

Ring closure of the dicarbonyl compound **9** was achieved by treatment with an excess of amine with a catalytic amount of AcOH in THF at rt, followed by addition of $NaCNBH_3$ (Scheme 1). We were encouraged by the initial success with aliphatic amines, in which only one diastereoisomer was formed, in moderate yields (Table 1).[21] The configuration and stereochemistry of the ring junction was confirmed by single-crystal X-ray crystallography (Fig. 1)[22] and ^{1}H NMR NOESY experiments. For example, NOE interactions were observed between H-3 and H-5 for **11d**, and between H-4, H-15$_\beta$ and H-16$_\beta$ and H-2, H-15$_\alpha$ and H-16$_\alpha$ for **12a**.



Scheme 1. Reagents and conditions: (i) O_3, DCM, rt, 1 h, 85%; (ii) polymer-bound PPh_3, PhMe, 90 °C, 1 h, 62%; (iii) R^1NH^2, AcOH, THF, then $NaCNBH_3$, rt, 2 h (Table 1); (iv) 80% AcOH aq, reflux, 4 h or 80% AcOH in EtOH, reflux, 30 h (Table 1); (v) $PdCl_2$, $CuCl_2$, O_2, 1:1 DMF–H_2O, rt, 4 h, 85%; (vi) chromatographic separation.



Scheme 2. Reagents and conditions: (i) $NaCNBH_3$, THF–DCM, rt, 1 h, 83%.

Table 1. Structures and yields of compounds **11a–e**, **g** and **12a–g**

	R^1	R^2	R^3	% Yield of **11**	% Yield of **12**
11a, **12a**	Pr^i	H	H	49	78
11b, **12b**	Pr^i	Me	H	29	83
11c, **12c**	Pr^i	H	Me	15	67
11d, **12d**	$CH_2CH_2CH_2OH$	H	H	45	94
11e, **12e**	CH_2CO_2Et	H	H	42	65
12f	CH_2CO_2H	H	H	—	80
11g, **12g**	OH	H	H	57	77

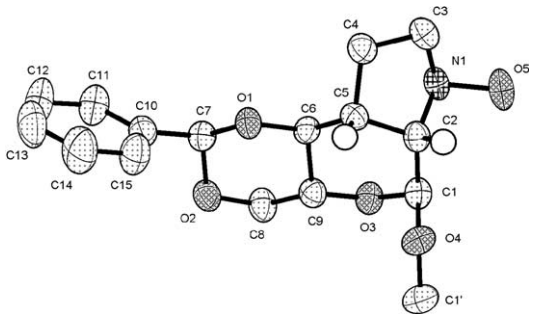


Figure 1. X-ray crystal structure of **12g**. One of the unique molecules of the asymmetric unit with atom label scheme and 50% displacement ellipsoids. The unique molecules have different orientations of the phenyl group. H atoms except those on C2 and C5 are omitted for clarity.[22]

The stereochemistry at the C-2 ring junction is thought to arise due to an initial reaction at C-16, followed by ring closure, resulting in the less strained *cis* ring junction. Nonring-closing reductive amination at C-2 of analogous compounds was found to give the opposite stereochemistry (i.e., α-amines) due to the preference of the hydride to attack from the opposite direction to the C-1 substituent.

The applicability of this reaction to a number of amines containing functional groups was studied, including aromatic rings, alcohols and esters (Table 1). In all cases the reaction was stereoselective, with yields in the range 40–55% after purification by column chromatography.

Diketone **10** was found to react under the same conditions. It was hoped that high diastereoselectivity would be observed due to the preference for a *cis* ring junction and for reduction at C-16 from the less hindered face. However, it was found that diastereomers **11b** and **11c** were produced in a 2:1 ratio when diketone **10** was reacted with *iso*-propylamine (Table 1). Separation by flash chromatography allowed assignment of stereochemistry by ^{1}H NMR and NOESY experiments, confirming that the products differed in configuration at the centre bearing the methyl group. For example, NOE interactions were observed between H-3 and H-5 for both **11b** and **11c**. However interactions between H-3, H-15$_{\alpha}$ and H-16 and between H-15$_{\beta}$ and the methyl attached at C-16 were found for **11b** and not **11c**, whereas for **11c** interactions between H-4, H-15$_{\beta}$ and H-16, and between H-15$_{\alpha}$ and the methyl attached at C-16 were seen.

Removal of the benzylidene protecting group was achieved in good yields by heating in 80% aq AcOH for 4 h (Table 1).[23] Pyrrolidine **11e** was also heated to reflux for 30 h in 80% ethanolic AcOH to afford deprotection of the diol whilst maintaining the ester functionality of **12e** (Scheme 1).

Measurement of the inhibitory activity of compounds **12a–g** against various glycoside processing enzymes was undertaken. The results indicate that these compounds are not significant inhibitors of a range of glycosidases. Compound **12g** was found to be a weak inhibitor of β-D-galactosidase (Table 2).

In conclusion, we have developed a versatile and efficient method for the construction of pyrrolidine rings on carbohydrates. Work is in progress to synthesise further analogues of **12**, and to alter the regio- and stereochemistry of the ring junction. Further evaluation of the glycosidase inhibitory activity of these compounds will also be undertaken.

Acknowledgements

We would like to acknowledge the ESPRC and the University of Leicester for financial support of this research.

References and notes

1. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.
2. Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750.
3. Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodriguez-Garcia, E.; Asenjo, A. T. C.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489.

Table 2. % Inhibition of **12a–g** (0.14 mg/mL solutions) against various glycoside-processing enzymes

Enzyme	12a	12b	12c	12d	12e	12f	12g
α-D-Glucosidase (yeast)	NI	NI	NI	NI	1.3	NI	NI
α-D-Glucosidase (bacillus)	NI	NI	NI	NI	NI	9.1	NI
α-D-Glucosidase (rice)	2.1	6.9	NI	2.8	NI	NI	NI
β-D-Glucosidase	6.8	NI	NI	NI	4.7	NI	NI
α-D-Galactosidase	12.4	2.9	NI	NI	NI	NI	NI
β-D-Galactosidase	—	5.9	14.7	—	—	—	**41.3**
α-L-Fucosidase	NI	NI	NI	14.2	7.9	7.7	NI
α-D-Mannosidase	NI	5.3	2.6	12.4	NI	10.1	NI
Naringinase	3.7	NI	NI	NI	NI	NI	NI
N-Acetyl-β-D-glucosaminidase (bovine kidney)	3.2	5.7	8.6	7.3	NI	3.0	NI
N-Acetyl-β-D-glucosaminidase (jack bean)	NI	15.4	3.9	NI	NI	NI	NI
N-Acetyl-β-D-hexosaminidase	3.3	NI	NI	NI	NI	NI	NI
Amyloglucosidase	NI	1.3	4.9	NI	NI	NI	NI

NI indicates no inhibition was observed.

4. Asano, N. *Glycobiology* **2003**, *13*, 93R.
5. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
6. Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546.
7. (a) Winkler, D. A. *J. Med. Chem.* **1996**, *39*, 4332; (b) Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchel, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062.
8. Wood, A. J.; Holt, D. J.; Dominguez, M.; Jenkins, P. R. *J. Org. Chem.* **1998**, *63*, 8522.
9. Holt, D. J.; Barker, W. D.; Jenkins, P. R. *J. Org. Chem.* **2000**, *65*, 482.
10. Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175.
11. Cheng, X.; Kumaran, G.; Mootoo, D. R. *Chem. Commun.* **2001**, *9*, 811.
12. Meyers, A. I.; Bienz, S.; Kwon, H.; Wallace, R. H. *Helv. Chim. Acta* **1996**, *79*, 1026.
13. For **8**, two diastereoisomers, white solid; δ_H (300 MHz, $CDCl_3$) 1.92–1.98 (1H, overlapping AB systems, dt, J = 14.3, 5.0 and dt, J = 14.1, 4.6, H-15_a), 2.17–2.25 (1H, overlapping AB systems, ddd, J = 15.2, 7.2, 5.6 and ddd, J = 14.4, 7.0, 5.4, H-15_b), 3.18–3.22 (1H, overlapping AB systems, dt, 11.7, 4.5 and dt, J = 11.6, 4.6, H-3), 3.42 (3H, s, OMe), 3.48 (1H, dd, J = 11.5, 9.4, H-4), 3.69 (1H, t, J = 10.3, H-6_{ax}), 4.27 (1H, td, J = 9.6, 5.1, H-5), 4.31 (1H, dd, J = 10.4, 4.9, H-6_{eq}), 4.58 (1H, s, H-1), 5.01 (2H, m, H-$17_{a,b}$), 5.39–5.47 (2H, m, H-16, H-7), 7.28–7.44 (5H, m, Ph). δ_C (75.5 MHz, $CDCl_3$), 27.0/27.2 (CH_2, C-15), 47.0/47.1 (CH, C-3), 55.7 (CH_3, C-14), 64.4 (CH, C-5), 69.0 (CH_2, C-6), 81.3/81.4 (CH, C-4), 93.9 (CH, C-17), 100.8 (CH, C-1), 101.5 (CH, C-7), 101.7 (CH, C-16), 126.1 (CH, *o*-Ph), 128.3 (CH, *m*-Ph), 129.2 (CH, *p*-Ph), 136.8 (C, Ph), 199.0 (C, C-2). ESI MS found for $C_{17}H_{24}O_8$ $(M+H)^+$ 353, $(M-OMe)^+$ 321. Mp = 118–121 °C.
14. Chen, L.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 7561.
15. Hon, Y.; Lu, L. *Tetrahedron Lett.* **1993**, *34*, 5309.
16. For **13**, major diastereoisomer, white solid; δ_H (300 MHz, $CDCl_3$) 1.52 (1H, br s, 2-OH), 2.01 (2H, dd, J = 11.2, 5.9, H-$15_{a,b}$), 2.14 (1H, tt, J = 16.4, 5.5, H-3), 3.24 (1H, dd, J = 10.6, 9.1, H-4), 3.40 (3H, s, H-14), 3.42 (1H, d, J = 4.9, H-2), 3.62 (1H, t, J = 10.1, H-6_{ax}), 3.71 (1H, td, J = 10.0, 4.7. H-5), 4.20 (1H, dd, J = 9.8, 4.4, H-6_{eq}), 4.63 (1H, d, J = 3.7, H-1), 5.05 (2H, m, H-$17_{a,b}$), 5.42 (1H, s, H-7), 5.49 (1H, dd, J = 11.9, 6.6, H-16), 7.27–7.43 (5H, m, Ph). δ_C (75.5 MHz, $CDCl_3$) 29.1 (CH_2, C-15), 39.1 (CH, C-3), 55.4 (CH_3, C-14), 63.7 (CH, C-5), 69.2 (CH_2, C-6), 71.6 (CH, C-2), 80.2 (CH, C-4), 93.9 (CH_2, C-17), 99.0 (CH, C-1), 101.6 (CH, C-7), 102.6 (CH, C-16), 126.1 (CH, *o*-Ph), 128.3 (CH, *m*-Ph), 129.0 (CH, *p*-Ph), 137.3 (C, Ph). ESI MS found for $C_{17}H_{22}O_8$ $(M+H)^+$ 355, $(M-OMe)^+$ 323.
17. Hon, Y.; Yan, J. *Tetrahedron Lett.* **1993**, *41*, 6591.
18. For **9**, colourless oil; δ_H (400 MHz, $CDCl_3$) 2.79 (1H, ddd, J = 18.0, 4.3, 1.1, H-15_a), 2.92 (1H, ddd, J = 18.0, 6.8, 0.9, H-15_b), 3.54 (3H, s, OMe), 3.59 (1H, ddd, J = 11.2, 6.8, 4.3, H-3), 3.67 (1H, dd, J = 11.7, 9.0, H-4), 3.80 (1H, t, J = 10.4, H-6_{ax}), 4.27 (1H, ddd, J = 9.7, 9.2, 4.8, H-5), 4.42 (1H, dd, J = 10.5 5.0, H-6_{eq}), 4.70 (1H, s, H-1), 5.52 (1H, s, H-7), 7.35-7.52 (5H, m, Ph), 9.82 (1H, t, J = 1.0, H-16). δ_C (75.5 MHz, $CDCl_3$) 38.0 (CH_2, C-15), 46.6 (CH, C-3), 55.8 (CH_3, C-14), 64.4 (CH, C-5), 68.9 (CH_2, C-6), 80.2 (CH, C-4), 100.6 (CH, C-1), 101.5 (CH, C-7), 126.1 (CH, *o*-Ph), 128.4 (CH, *m*-Ph), 129.3 (CH, *p*-Ph), 136.7 (C, Ph), 198.4 (C, C-2), 199.3 (CH, C-16). FAB HRMS calcd for $C_{16}H_{19}O_6$ $(M+H)^+$ 307.11816, found 307.11814.
19. Ferraboschi, P.; Gambero, C.; Azadani, M. N.; Santaniello, E. *Synth. Commun.* **1986**, *16*, 667.
20. Mereyala, B.; Lingannagaru, S. R. *Tetrahedron* **1997**, *53*, 17501.
21. For **11a** δ_H (300 MHz, $CDCl_3$) 0.86 (3H, d, J = 6.4, H-18_a), 1.05 (3H, d, J = 6.7, H-18_b), 1.56 (1H, dddd, J = 12.9, 10.1, 9.0, 6.7, H-15_α), 1.84 (1H, ddd, J = 12.9, 7.4, 2.8, H-15_β), 2.38 (1H, dt, J = 10.2, 6.1, H-3), 2.70 (1H, td, J = 10.2, 3.0, H-16_α), 2.90 (1H, d, J = 5.8, H-2), 2.95 (1H, obs. m, H-16_β), 2.96 (1H, sept, J = 6.6, H-17), 3.31 (3H, s, H-14), 3.54 (1H, ddd, J = 9.9, 7.2, 1.3, H-4), 3.70 (1H, obs. m, H-5), 3.70 (1H, ddd, J = 17.3, 10.6, 1.5, H-6_{ax}) , 4.18 (1H, dd, J = 16.2, 10.8, H-6_{eq}), 4.57 (1H, s, H-1), 5.48 (1H, s, H-7), 7.22–7.32 (3H, m, *m*-Ph, *p*-Ph), 7.38-7.45 (2H, m, *o*-Ph). δ_C (75.5 MHz, $CDCl_3$) 13.3 (CH_3, C-18_a), 22.4 (CH_3, C-18_b), 26.1 (CH_2, C-15), 39.9 (CH, C-3), 43.2 (CH, C-16), 49.1 (CH_3, C-17), 54.9 (CH_3, C-14), 62.5 (CH, C-5), 63.5 (CH, C-2), 69.3 (CH_2, C-6), 77.8 (CH, C-4), 98.9 (CH, C-1), 102.0 (CH, C-7), 126.2 (CH, *o*-Ph), 128.3 (CH, *m*-Ph), 128.9 (CH, *p*-Ph), 137.9 (C, Ph). FAB HRMS calcd. for $C_{19}H_{27}O_4N$ $(M+H)^+$ 334.20183, found 334.20184.

    For **12a**, colourless oil; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, J = 6.3, H-11_a), 1.03 (3H, d, J = 6.7, H-11_b), 1.71 (1H, dtd, J = 12.7, 9.4, 6.7, H-8_β), 1.90 (1H, m, H-8_α), 2.25 (1H, dt, J = 8.8, 5.9, H-3), 2.75 (1H, td, J = 10.1, 3.0, H-9_α), 2.90 (1H, d, J = 5.9, H-2), 2.94 (1H, obscured m, H-9_β), 2.99 (1H, sept, J = 6.5, H-10), 3.23 (2H, br s, 4-OH, 6-OH), 3.38 (3H, s, H-7), 3.57 (2H, overlapping m, H-4, H-5), 3.84 (1H, dd, J = 11.6, 3.3, H-6_a), 4.18 (1H, dd, J = 11.6, 3.9, H-6_b), 4.64 (1H, s, H-1). δ_C (75.5 MHz, $CDCl_3$) 14.1 (CH_3, C-11_a), 22.1 (CH_3, C-11_b), 27.2 (CH_2, C-8), 43.0 (CH, C-3), 43.9 (CH, C-9), 49.7 (CH_3, C-10), 54.9 (CH_3, C-7), 63.0 (CH, C-2), 63.1 (CH_2, C-6), 67.1 (CH, C-5), 70.9 (CH, C-4), 98.8 (CH, C-1). FAB HRMS calcd. for $C_{12}H_{23}O_4N$ $(M+H)^+$ 246.17053, found 246.17047.
22. Crystal data for $C_{16}H_{21}NO_5$ (**12g**), M = 307.34, monoclinic, space group $P2_1$, a = 11.8679(15), b = 8.1933(13), c = 16.417(2) Å, β = 96.296(11)°, V = 1586.74(4) Å^3, T = 210(2) K, Z = 4, D_c = 1.287 g cm^{-3}, μ (Mo-Kα) = 0.096 mm^{-1}. Final, R_1 = 0.0336 (for 2624 reflections with $I > 2\sigma(I)$) and wR_2 = 0.0911 for all data. Crystallographic data for **12g** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 252127. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
23. Sakakibara, T.; Shindo, T.; Hirai, H. *Carbohydr. Res.* **2002**, *337*, 2061.