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General synthesis of sugar-pendant 1,3-propanediamines containing a *C*-glycoside linkage

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Abstract—A straightforward route to *C*-glycoside linked sugar-pendant 1,3-propanediamines is described. The three-step preparation procedure involves (1) *C*-glycosylation of an OH-protected α-glycosyl halide with malononitrile, (2) catalytic hydrogenation of the nitriles to amines, and (3) deprotection of acetyl groups via acid-catalyzed hydrolysis. In the case of the galactose derivative, excess sodiomalononitrile promotes the second addition of a carbanion in the first step. The β-anomeric configuration was confirmed by X-ray crystallography of the glycosylated intermediates. This method demonstrates a general method to access a new class of carbohydrate-pendant *C*-glycoside chelators.

Carbohydrates are essential materials in biological systems. These important biological building blocks exist in various forms including polysaccharides, nucleic acids, glycoproteins, and glycolipids. Molecular recognition events promoted by carbohydrates are also of importance, for example, cell–cell interactions are based on carbohydrate–protein recognition events.[1–3] Metal ion–carbohydrate interactions are also of significant interest in bioinorganic chemistry,[4] and metal complexes containing carbohydrates have been exploited as molecular targets to study structural coordination[5] and asymmetric catalysis.[6] Considering the above constraints, we developed novel carbohydrate-pendant ligands exhibiting *O*-glycoside linkages[7–9] and have studied the bioactivity of the associated metal complexes.[10,11] It is well known that the *O*-glycoside is susceptible for enzymatic degradation, whereas the *C*-glycoside is not. The *C*-glycoside analog may exhibit improved activity compared to the corresponding *O*-glycosides.[12] In the present study, we report a convenient synthesis of a new family of sugar-pendant 1,3-propanediamines exhibiting a *C*-glycoside link between the glycoside and the chelating moiety. This three-step synthesis serves as a general method to access carbohydrate–diamine conjugates and their associated metal complexes with a more robust, nonbiodegradable feature.

Literature methods for the construction of *C*-alkyl glycosides[13–17] include nucleophilic and electrophilic substitution, as well as intermolecular free radical coupling. Malononitrile was selected as the carbanion source in this study as nucleophilic *C*-glycoside formation utilizing dialkyl malonate has been studied extensively.[18,19] The two nitrile functions of malononitrile stabilize the carbanion, allowing the substitution reaction to proceed smoothly in a controlled manner. Another benefit of utilizing malononitrile is that, upon reduction of the nitrile moieties, it affords a 1,3-propanediamine skeleton, that can exhibit a stable six-membered chelate ring after complexation with metal ions. Thus, we carried out the synthesis of 2-(β-D-glucopyranosyl)-1,3-diaminopropane (**3**) and 2-(β-D-galactopyranosyl)-1,3-diaminopropane (**6**) starting from the corresponding α-acetobromopyranoses as shown in Scheme 1.

Three equivalents of sodiomalononitrile, prepared from malononitrile and sodium hydride, were reacted with α-acetobromoglucose in dry DMF at 0 °C and the reaction was warmed to room temperature. After stirring for 1 h aqueous acetic acid (10%) was added to the reaction mixture from which the *C*-glycosylated product (**1**) was obtained as a white precipitate in 60% yield.[20] No

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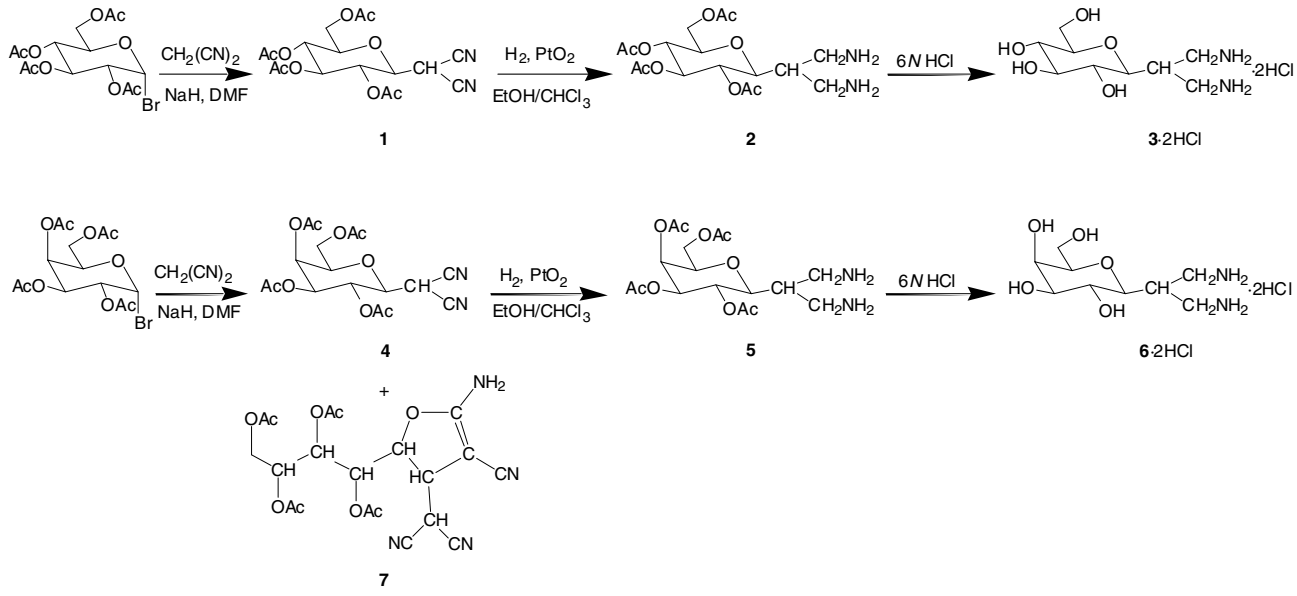

Scheme 1.

further compound **1** was obtained from the organic extract of the filtrate.

In the corresponding reaction using α-acetobromogalactose, no precipitate was isolated after the addition of acetic acid. Silica gel column chromatography (ethyl acetate–hexane = 1:1) of the residue from the organic extract of the aqueous solution afforded two major products. The first band ($R_f = 0.35$) was determined to be compound **4** (60% yield).[20] The second, more polar product ($R_f = 0.29$), was characterized as the 2:1 adduct **7** (14% yield),[20] in which additional malononitrile was attached and no more pyranose ring was present as judged from MS and ^{1}H NMR spectra.

The structure of compound **7** was determined by X-ray crystallography (Fig. 1).[21] As seen in Figure 1, the chirality of carbons C2–5 are retained. The C5 oxygen atom derived from pyranose ring oxygen (O4 in Fig. 1) is acetylated, whereas the C2 oxygen (O1 in Fig. 1) is deacetylated. To account for the mechanism of formation for compound **7**, the following control experiments were conducted: (1) the reaction of compound **4** with sodiomalononitrile (5 equiv) affords compound **7** in 40% yield with 36% recovery of the starting material, (2) the reaction of compound **4** with NaH affords no appreciable product (83% recovery of the starting material). These results suggest that the formation of compound **7** is initiated by nucleophilic attack of excess carbanion at the anomeric carbon of compound **4** to

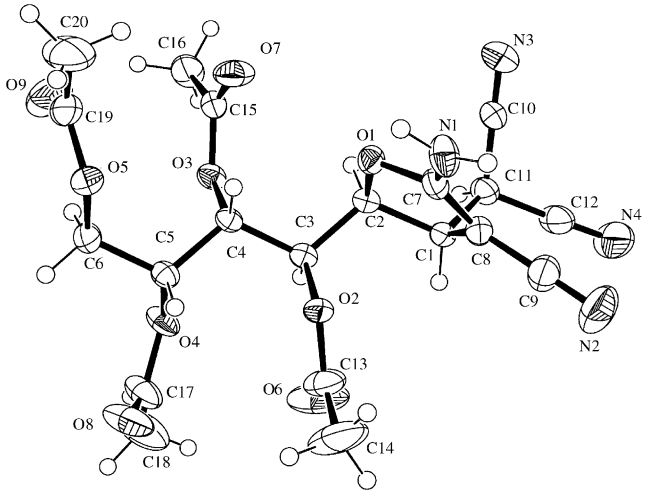

Figure 1. ORTEP plot for compound **7** with 50% probability thermal ellipsoids.

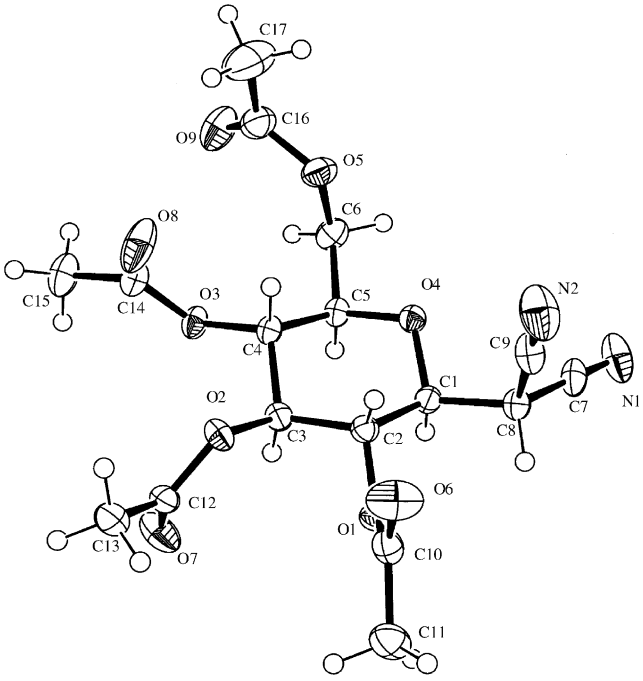

Figure 2. ORTEP plot for compound **1** with 50% probability thermal ellipsoids.

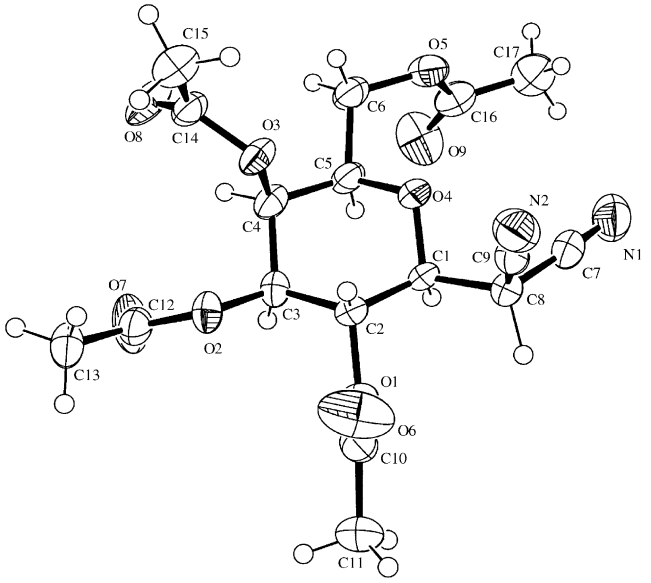

Figure 3. ORTEP plot for compound **4** with 50% probability thermal ellipsoids.

give the C5 (O4) alkoxide. In the second step, acetyl group transfer occurs from C2 (O1) acetate to C5 (O4) alkoxide in a direct or indirect manner. The C2 (O1) alkoxide then attacks the adjacent nitrile carbon (C7 in Fig. 1) to form the dihydrofuran ring of compound **7**. Although excess carbanion reacts with compound **4**, decreasing the amount of sodiomalononitrile did not improve the yield of compound **4**.

The structures of the *C*-glycosides **1** and **4** were also determined by X-ray crystallography (Figs. 2 and 3).[21] Both structures adopt the $^4C_1$ pyranose ring conformation and exhibit the β-*C*-glycoside configuration in the solid state. These crystal structure studies are useful predictors of the final structures of diamines (**3**, **6**) as the hydrogenation and deacetylation steps are not expected to cause sugar conformational changes. The sugar conformation of **1** and **4** in solution ($CDCl_3$), determined via ^1H–^1H coupling, correlated well with the crystal structure data.[20]

Nitrile reduction was carried out quantitatively by catalytic hydrogenation (PtO_2) in chloroform–ethanol.[22] The isolated diamines **2** and **5** were then deprotected by refluxing in 6 N HCl to give **3** and **6** as the hydrochloride salts (~90%).[23] Conventional deacetylation of **2** by sodium methoxide in methanol afforded monoamide derivative **8** (Scheme 2).[24] Treatment of **1** by sodium methoxide was also unsuccessful due to deprotonation of the acidic dicyanomethane methine proton, leading to decomposition of the compound.

In summary, two sugar-pendant 1,3-propanediamines exhibiting a β-*C*-glycoside linkage were prepared conveniently in a three-step synthesis from α-acetobromosugars in high yield. This method offers a general pathway for access to *C*-glycoside linked diamines. The intermediate dinitriles (**1** and **4**) afforded suitable crystals for X-ray crystallography. Preparation of corresponding α-*C*-glycosides and metal ion complexation studies of these sugar-pendant diamines are now under investigation.

Acknowledgements

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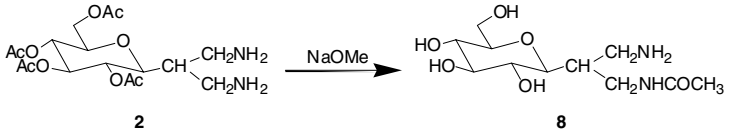
References and notes

1. Qasba, P. K. *Carbohydr. Polym.* **2000**, *41*, 293–309.
2. Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637–674.
3. Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–327.
4. Gyurcsik, B.; Nagy, L. *Coord. Chem. Rev.* **2000**, *203*, 81–149.
5. Whitfield, D. M.; Stojkovski, S.; Sarkar, B. *Coord. Chem. Rev.* **1993**, *122*, 171–225.
6. Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215.
7. Mikata, Y.; Yoneda, K.; Tanase, T.; Kinoshita, I.; Doe, M.; Nishida, F.; Mochida, K.; Yano, S. *Carbohydr. Res.* **1998**, *313*, 175–179.
8. Yano, S.; Shinohara, Y.; Mogami, K.; Yokoyama, M.; Tanase, T.; Sakakibara, T.; Nishida, F.; Mochida, K.; Kinoshita, I.; Doe, M.; Ichihara, K.; Naruta, Y.; Mehrkhodavandi, P.; Bugló, P.; Song, B.; Orvig, C.; Mikata, Y. *Chem. Lett.* **1999**, 255–256.
9. Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Esaki, K.; Tanahashi, M.; Brudziñska, I.; Hirohara, S.; Yokoyama, M.; Mogami, K.; Tanase, T.; Kitayama, T.; Takashiba, K.; Nabeshima, K.; Takagi, R.; Takatani, M.; Okamoto, T.; Kinoshita, I.; Doe, M.; Hamazawa, A.; Morita, M.; Nishida, F.; Sakakibara, T.; Orvig, C.; Yano, S. *J. Org. Chem.* **2001**, *66*, 3783–3789.
10. Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Brudziñska, I.; Tanase, T.; Kitayama, T.; Takagi, R.; Okamoto, T.; Kinoshita, I.; Doe, M.; Orvig, C.; Yano, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3045–3047.
11. Brudziñska, I.; Mikata, Y.; Obata, M.; Ohtsuki, C.; Yano, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2533–2536.



2 **8**

Scheme 2.

12. Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 3818–3822.
13. Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913–9959.
14. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700–717.
15. Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54.
16. Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55–83.
17. Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599.
18. Hanessian, S.; Pernet, A. G. *Can. J. Chem.* **1974**, *52*, 1266–1279.
19. Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961–6967.
20. Selected data for **1**: ^{1}H NMR ($CDCl_3$, 300.07 MHz): δ (ppm) 5.29 (t, J = 9.5, 9.2 Hz, H-3), 5.17 (dd, J = 9.5, 9.2 Hz, H-4), 5.13 (dd, J = 9.5, 9.2 Hz, H-2), 4.28 (dd, J = 4.9, 12.5 Hz, H-6a), 4.19 (dd, J = 2.4, 12.5 Hz, H-6b), 4.05 (d, J = 4.3 Hz, H-α), 3.99 (dd, J = 9.8, 4.3 Hz, H-1), 3.84 (ddd, J = 10.1, 4.9, 2.4 Hz, H-5), 2.113 (s, acetyl), 2.106 (s, acetyl), 2.06 (s, acetyl), 2.04 (s, acetyl). ^{13}C NMR ($CDCl_3$, 300.07 MHz): δ (ppm) 170.72, 170.24, 169.80, 169.36, 109.11, 76.43, 74.43, 72.86, 69.78, 67.46, 61.31, 26.59, 20.51, 20.36. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_9$ $(M-H)^-$: 395.1096. Found: 395.1095. Anal. Calcd for $C_{17}H_{20}N_2O_9$: H, 5.09; C, 51.52; N, 7.07. Found: H, 4.94; C, 51.37; N, 6.99. IR (KBr): 1732 (C=O) cm^{-1}. For **4**: ^{1}H NMR ($CDCl_3$, 800.303 MHz): δ (ppm) 5.46 (dd, J = 3.3, 1.0 Hz, H-4), 5.35 (dd, J = 11.5, 9.8 Hz, H-2), 5.12 (dd, J = 10.0, 3.3 Hz, H-3), 4.21 (dd, J = 11.5, 6.9 Hz, H-6a), 4.13 (dd, J = 11.5, 6.1 Hz, H-6b), 4.07 (m, H5), 4.05 (d, J = 4.3 Hz, H-α), 3.96 (dd, J = 9.7, 4.3 Hz, H-1), 2.19 (s, acetyl), 2.13 (s, acetyl), 2.07 (s, acetyl), 2.01 (s, acetyl). ^{13}C NMR ($CDCl_3$, 300.07 MHz): δ (ppm) 170.53, 170.20, 170.11, 170.04, 110.05, 109.24, 74.96, 74.78, 70.97, 67.10, 66.68, 61.00, 26.86, 20.59, 20.47, 20.41, 20.34. HRMS (ESI) calcd for $C_{17}H_{21}N_2O_9$ $(M+H)^+$: 397.1242, Found: 397.1238. Anal. Calcd for $C_{17}H_{20}N_2O_9$: H, 5.09; C, 51.52; N, 7.07. Found: H, 4.97; C, 51.42; N, 7.07. For **7**: ^{1}H NMR ($CDCl_3$, 300.07 MHz): δ (ppm) 5.49 (dd, J = 9.3, 2.1 Hz, H-4), 5.43 (br s, NH2), 5.35 (m, H-5), 5.23 (dd, J = 9.0, 1.4 Hz, H-3), 4.67 (dd, J = 3.8, 1.4 Hz, H-2), 4.32 (dd, J = 11.7, 5.1 Hz, H-6a), 3.97 (d, J = 4.5 Hz, H-α), 3.87 (dd, J = 11.6, 7.4 Hz, H-6b), 3.62 (t, J = 3.9 Hz, H-1). ^{13}C NMR ($CDCl_3$, 300.07 MHz): δ (ppm) 170.69, 170.38, 169.99, 168.99, 115.84, 110.76, 110.42, 82.21, 81.89, 69.93, 69.56, 68.17, 67.97, 67.63, 67.31, 61.84, 50.95, 46.80, 46.50, 27.96, 27.77, 20.68, 20.38, 20.18. HRMS (ESI) calcd for $C_{20}H_{23}N_4O_9$ $(M+H)^+$: 463.1460, Found: 463.1452. Anal. Calcd for $C_{20}H_{22}N_4O_9$: H, 4.80; C, 51.95; N, 12.12. Found: H, 4.58; C, 51.71; N, 11.91.
21. Crystal data for **1**: orthorhombic, space group $P2_12_12_1$, a = 6.9805(4), b = 15.6792(9), c = 17.6943(10) Å, V = 1936.6(2) Å^3, Z = 4, T = −100 °C, 14,932 data collected, 3993 data with $I > 2\sigma(I)$. The structure was solved by direct method (SIR-97) and refined by full-matrix least-squares methods on F^2. R = 0.041, R_w^2 (all data) = 0.096, GOF = 1.052. For **4**: orthorhombic, space group $P2_12_12_1$, a = 9.217(5), b = 14.397(8), c = 14.626(8) Å, V = 1940.9(19) Å^3, Z = 4, T = −100 °C, 16,007 data collected, 3270 data with $I > 2\sigma(I)$. The structure was solved by direct method (SIR-97) and refined by full-matrix least-squares methods on F^2. R = 0.052, R_w^2 (all data) = 0.095, GOF = 0.991. For **7**: orthorhombic, space group $P2_12_12_1$, a = 10.1915(7), b = 11.2191(8), c = 21.001(2) Å, V = 2401.3(3) Å^3, Z = 4, T = −100 °C, 14,142 data collected, 4224 data with $I > 2\sigma(I)$. The structure was solved by direct method (SIR-97) and refined by full-matrix least-squares methods on F^2. R = 0.043, R_w^2 (all data) = 0.070, GOF = 0.961. These crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-243033 (**4**), 243042 (**1**), and 243053 (**7**). 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].
22. Selected data for **2**: ^{1}H NMR (CD_3OD, 300.07 MHz): δ (ppm) 5.31 (t, J = 9.3, H-3), 5.20–5.07 (m, H-2, H-4), 4.30 (dd, J = 12.6, 5.4 Hz, H-6a), 4.19 (dd, J = 12.6, 2.4 Hz, H-6b), 3.96–3.89 (m, H-1, H-5), 3.38–3.17 (m, H-β), 2.36 (br s, H-α), 2.11 (s, acetyl), 2.07 (s, acetyl), 2.03 (s, acetyl), 2.00 (s, acetyl). ^{13}C NMR (CD_3OD, 300.07 MHz): δ (ppm) 173.27, 172.76, 172.28, 171.45, 77.52, 77.39, 75.11, 69.84, 69.47, 63.27, 39.57, 37.71, 36.35, 20.69, 20.46. HRMS (ESI) calcd for $C_{17}H_{29}N_2O_9$ $(M+H)^+$: 405.1868. Found: 405.1865. IR (KBr): 1751 (C=O) cm^{-1}. For **5**: ^{1}H NMR (D_2O, 300.07 MHz): δ (ppm) 5.47 (s, H-4), 5.21–5.19 (m, H-2, H-3), 4.20–4.09 (m, H-5, H-6), 3.97 (1H, br s, H-1), 3.39–3.16 (m, H-β), 2.41 (br s, H-α), 2.15 (s, acetyl), 2.14 (s, acetyl), 2.05 (s, acetyl), 1.96 (s, acetyl). ^{13}C NMR (CD_3OD, 300.07 MHz): δ (ppm) 172.39, 171.68, 171.31, 77.18, 75.71, 72.81, 68.75, 66.91, 62.41, 39.16, 37.27, 36.11, 20.53, 20.35, 20.14. HRMS (ESI) calcd for $C_{17}H_{29}N_2O_9$ $(M+H)^+$: 405.1868. Found: 405.1860.
23. Selected data for **3**: ^{1}H NMR (D_2O, 300.07 MHz): δ (ppm) 3.82 (dd, J = 12.6, 1.8 Hz, H-6), 3.73–3.61 (m, H-6b, H-2), 3.52–3.24 (m, H-3, H-4, H-5, H-β), 2.62 (m, H-α). ^{13}C NMR (D_2O, 300.07 MHz): δ (ppm) 81.08, 79.12, 78.36, 71.14, 70.40, 61.86, 39.64, 38.22, 36.26. HRMS (ESI) calcd for $C_9H_{21}N_2O_5$ $(M+H)^+$: 237.1445. Found: 237.1452. For **6**: ^{1}H NMR (D_2O, 300.07 MHz): δ (ppm) 3.99 (1H, dd), 3.75–3.64 (5H, m), 3.57 (1H, dd, J = 9.0, 3.0 Hz), 3.45–3.27 (m, H-β), 2.64 (m, H-α). ^{13}C NMR (D_2O, 300.07 MHz): δ (ppm) 80.37, 79.77, 75.03, 70.01, 68.56, 62.36, 39.77, 38.46, 36.26. HRMS (ESI) calcd for $C_9H_{21}N_2O_5$ $(M+H)^+$: 237.1445. Found: 237.1470.
24. Selected data for **8**: ^{1}H NMR (D_2O, 300.07 MHz): δ (ppm) 3.88 (d, J = 12.3 Hz, H-6a), 3.68 (dd, J = 12.0, 5.1 Hz, H-6b), 3.47–3.32(6H, m), 3.03–2.92 (2H, m), 2.20 (m, H-α), 2.00 (s, acetyl). HRMS (ESI) calcd for $C_{11}H_{23}N_2O_6$ $(M+H)^+$: 279.1551. Found: 279.1559. IR (KBr): 1632 (C=O) cm^{-1}.