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Tetrahedron Letters 49 (2008) 910–913
Tetrahedron Letters

Iminosugar thioglycosides as glycosyl donors: a route to disaccharides with an iminosugar moiety

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Received 27 September 2007; revised 14 November 2007; accepted 26 November 2007
Available online 3 December 2007

Dedicated to Professor M. Ángeles Pradera on the occasion of her retirement

Abstract

The iminosugar thioglycosides are used as glycosyl donors in glycosidation reactions. Thereby, iminosugar glycosides and disaccharide analogues with an iminosugar moiety are prepared. The yields are high and the method is stereoselective.

Keywords: Iminosugars; Thioglycosides; Glycosidations; Iminosugar–disaccharides

The iminocyclitols, also known as iminosugars, are a type of natural and synthetic sugar analog in which the endocyclic oxygen atom has been substituted by a nitrogen atom. These compounds are glycosidase and glycosyltransferase inhibitors, and consequently they can be useful in the treatment of metabolic disorders and inflammatory processes.[1] In the last 15 years, much effort has been directed at the synthesis of five-, six- and seven-membered iminocyclitols, that is, 'monosaccharide–iminosugars'.[2,3] However, data on disaccharide derivatives containing one or two iminosugar moieties are scarce. Several C-linked imino-disaccharide derivatives with an iminosugar moiety have been prepared,[4] and related compounds with an amino group[5,6] or sulfur atom as inter-glycosidic group have also been described.[5] The synthesis of 1,6-imino-di- and imino-tri-saccharide derivatives, through glycosidation of nojirimycin derivatives with catalytic amounts of TMSOTf, has also been reported.[7]

The thioglycosides, a type of glycoside in which the anomeric carbon atom has been substituted by a sulfur atom, have been widely used as glycosyl donors in glycosidation reactions, to prepare oligosaccharides.[8] The thioglycosides have also been used as chiral inductors in enzymatic synthesis[9] and have been tested as antithrombotic agents.[10] Recently, we have reported the stereoselective preparation of iminosugar thioglycosides[11] starting from anhydroiminosugar derivatives.

In this Letter, we report on the use of the iminosugar ethyl thioglycoside **3** (Scheme 1) as glycosyl donor in glycosidation reactions. The glycosyl acceptors were simple alcohols and partially protected sugar derivatives with a free hydroxyl group at position 6 or position 3.

In an earlier paper,[12] we have reported the glycosidation of methanol using an imino-anhydroglucose derivative, related to **1**, as glycosyl donor, but the yield was low and no other alcohol was used. We have also carried out the reaction of the anhydroiminoribose[11] derivative **1** with different alcohols to obtain compounds **2**; however, the reaction was not possible when benzyl and cyclohexyl alcohols were used as glycosyl acceptors.[13]

Compound **1** was transformed[11] into the ethyl thioglycoside **3**, which by reaction with benzyl bromide produced the 5-*O*-benzyl derivative **4**, suitable for use as glycosyl donor in glycosidation reactions.

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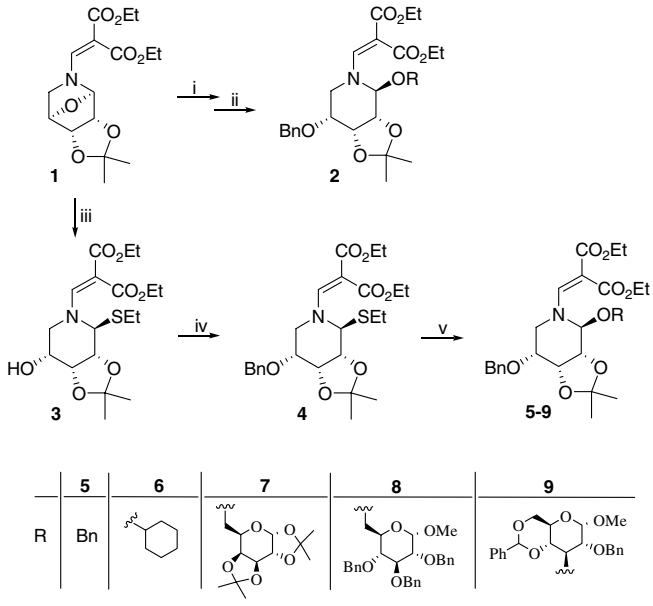
doi:10.1016/j.tetlet.2007.11.160



Scheme 1. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$; (ii) ROH, 0 °C, 45 min; (iii) PTSA/DMF, EtSH, 0 °C, 45 min; (iv) DMF/NaH, BnBr; (v) DMTST, MeCN, ROH, −20 °C.

The reaction of **4** with benzyl and cyclohexyl alcohol in acetonitrile using dimethyl(methylthio)sulfonium triflate (DMTST) as promoter, at −20 °C for 2 h, produced the iminosugar glycosides **5** and **6**[14] in 88% and 87% yield, respectively, and as a single diastereoisomer each. The pseudoanomeric configuration (configuration of C-2, using the number of piperidine ring) was established through NOE experiments and molecular modelling calculations. Thus, a NOESY experiment performed on **6** showed the results indicated in Figure 1. The molecular model of **6** obtained by energy minimization using a force field based approach[15] yielded theoretical $^3J_{H,H}$ couplings ($J_{2,3} = 1.2$, $J_{3,4} = 8.5$, $J_{4,5} = 2.7$, $J_{5,6a} = 4.9$, $J_{5,6b} = 10.1$) in very good agreement with the experimental data,[14] and proton–proton distances that were in very good agreement with the whole set of NOE experimental observations. Particularly important was the detection of a weak NOE between H-2 and the *endo* methyl group (Me_a) (4.5 A) and between H-5 and a CH_2 of the cyclohexyl group (3.7 A) which are exclusive NOEs crucial to demonstrate the proposed *S* configuration for C-2.

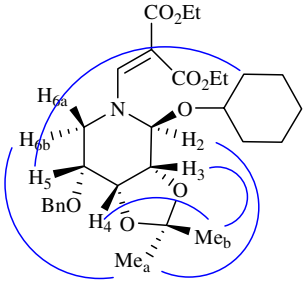
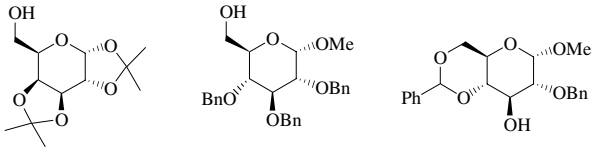


Fig. 1. NOE experiments on **6**.

To study the use of **4** as glycosyl donor, the acceptor being a sugar derivative, the partially protected monosaccharide derivatives with the CH_2OH group free, **10** and **11**, and the derivative with the 3-OH group free, **12**, were chosen.[16]



The glycosidation reactions between the iminoglycosyl donor **4** and acceptors **10**–**12** were carried out (Table 1) in different solvents, under different conditions, and using methyl triflate,[17] DMTST[18] and methyl benzene selenyl triflate[19] (PhSeTfOMe) as promoter. In every case, the corresponding disaccharide derivative with iminosugar moieties **7**–**9** (Scheme 1) was obtained only as the β-anomer.[20] The yields were higher for the glycosidations on primary positions (**10**, **11**) than for the glycosidation on a secondary

Table 1
Glycosidations of **10**–**12** with **4**

Acceptor	Product	Solvent	Promotor (equiv)	Temperature (°C)	Reaction time (h)	Yield (%)
10	**7**	DMF	TFOMe (5.0)	rt	48.0	23
		Ether	TfOMe (5.0)	rt	24.0	30
		Ether	DMTST (3.0)	−40	3.0	65
		Dichloromethane	DMTST (3.0)	−40	3.0	30
		Acetonitrile	**DMTST (2.0)**	**−20**	**2.0**	**80**
		Acetonitrile	PhSeTfOMe (2.0)	−10	2.0	45
11	**8**	Acetonitrile	**DMTST (2.0)**	**−20**	**2.0**	**60**
		Dichloromethane	DMTST (3.0)	−20	1.0	50
		Acetonitrile	PhSeTfOMe (1.5)	−30	24.0	32
		Toluene	PhSeTfOMe (1.5)	0	2.0	42
12	**9**	Acetonitrile	**DMTST (2.0)**	**0**	**2.0**	**45**
		1,2-Dichloroethane	PhSeTfOMe (2.0)	0	3.0	Decompose
		Acetonitrile	PhSeTfOMe (2.0)	0	2.0	44

position (**12**). The best yields were obtained using acetonitrile as solvent, DMTST as promoter, reaction time of 2 h and a temperature of −20 °C (0 °C for **12**).

The vicinal coupling constants for the iminosugar ring of the iminodisaccharides **7**–**9** had similar values to that for **6**, which is indicative of β-configuration for the pseudoanomeric carbon (C-2 in the piperidine numbering).

In conclusion, glycosidation using iminosugar thioglycosides as glycosyl donors is a highly stereoselective method to prepare disaccharide analogs with an iminosugar moiety. The method has been used with partially protected sugars with one free hydroxyl group at position 6 or 3, and with simple alcohols as glycosyl acceptors. The scope and limitations of this method are currently under study in our laboratory.

Acknowledgements

We thank the Dirección General de Investigación of Spain and the Junta de Andalucía (grant numbers CTQ 2005-01830/BQU and FQM 134) and the AECI of the Ministerio de Asuntos Exteriores of Spain for the award of a fellowship to NRAB. We also thank Dr. M. A. Pradera for some starting materials and Dr. J. Angulo for the help in the molecular modelling study.

References and notes

1. See as examples: (a) Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *12*, 1239–1287; (b) Lillelund, V. H.; Jensen, H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553; (c) Stutz, A. E. *Iminosugars as Glycosidase Inhibitors*; Wiley-VCH: Weinheim, 1999; (d) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202; (e) Winchester, B.; Fleet, G. W. G. *Glycobiology* **1992**, *2*, 199–210; (f) Giannis, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 178–180.
2. For a review, see: Casiragui, G.; Zanardi, F.; Rassu, G.; Spann, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
3. See as examples: (a) Blanco, M. J.; Sardina, F. J. *J. Org. Chem.* **1998**, *63*, 3411–3416; (b) Sayago, F. J.; Fuentes, J.; Angulo, M.; Gasch, C.; Pradera, M. A. *Tetrahedron* **2007**, *63*, 4695–4702; (c) Fuentes, J.; Gasch, C.; Olano, D.; Pradera, M. A.; Repetto, G.; Sayago, F. J. *Tetrahedron: Asymmetry* **2002**, *13*, 1743–1753; (d) Chabeand, L.; Landais, Y.; Reneaud, P. *Org. Lett.* **2005**, *7*, 2587–2590; (e) Li, H.; Bleriot, Y.; Chantereau, C.; Mallet, J. M.; Sollogoub, M.; Zhang, Y.; Rodríguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinay, P. *Org. Biomol. Chem.* **2004**, *2*, 1492–1499.
4. See as examples: (a) García-Aparicio, V.; Fernández-Alonso, M. C.; Angulo, J.; Asencio, J. L.; Cañada, F. J.; Jiménez-Barbero, J.; Mootoo, D. R.; Cheng, X. *Tetrahedron: Asymmetry* **2005**, *16*, 519–527; (b) Aslam, T.; Fuchs, M. G. G.; Le Formal, A.; Wightman, R. H. *Tetrahedron Lett.* **2005**, *46*, 3249–3252; (c) Sharma, G. V. M.; Pendem, N.; Reddy, K. R.; Krishna, P. R.; Narsimulo, K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8807–8810; (d) Agryropoulos, N. G.; Sarli, V. C. *Tetrahedron Lett.* **2004**, *45*, 4237–4240; (e) Dondoni, A.; Giovanni, P. P.; Marra, A. *Tetrahedron Lett.* **2000**, *41*, 6195–6199.
5. (a) Campanini, L.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 5095–5098; (b) Barbaud, C.; Bols, M.; Lundt, I.; Sierks, M. R. *Tetrahedron* **1995**, *51*, 9063–9078.
6. (a) Gravier-Pelletier, C.; Maton, W.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 8285–8288; (b) Gravier-Pelletier, C.; Maton, W.; Lecourt, T.; Le Merrer, Y. *Tetrahedron Lett.* **2001**, *42*, 4475–4478.
7. Sawada, D.; Takahashi, H.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **2005**, *46*, 2399–2403.
8. For a review, see: (a) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205. See also:(b) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072; (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435–436; (d) López, J. C.; Gómez, A. M.; Uriel, C.; Fraser-Reid, B. *Tetrahedron Lett.* **2003**, *44*, 1417–1420.
9. Defaye, J.; Gelas, J. In *Studies Natural Products Chemistry*; Altaur-Rahman, Ed.; Elsevier Science: Amsterdam, 1991; Vol. 8.
10. See as examples: (a) Witczak, Z. J.; Boryczewski, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3265–3268; (b) Fitz, W.; Rosenthal, P.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 1349–1353.
11. (a) Fuentes, J.; Sayago, F. J.; Illangua, J. M.; Gasch, C.; Angulo, M.; Pradera, M. A. *Tetrahedron: Asymmetry* **2004**, *15*, 603–615. and **2004**, *15*, 3783–3789; (b) Pradera, M. A.; Sayago, F. J.; Illangua, J. M.; Gasch, C.; Fuentes, J. *Tetrahedron Lett.* **2003**, *44*, 6605–6608.
12. Fuentes, J.; Olano, D.; Pradera, M. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3443–3456.
13. Fuentes, J.; Al Bujuq, N. R.; Pradera, M. A.; Gasch, C. Unpublished results communicated to the 'Eighth Tetrahedron Symposium' Berlin, Germany, June 2007, Communication P343.
14. Selected structural data for (2*S*,3*R*,4*R*,5*R*)-5-benzyloxy-2-cyclohexyloxy-1-diethoxycarbonylvinyl-3,4-*O*-isopropylidenepiperidine (**6**). Yield: 87%; $[\alpha]_D^{25}$ −94.2 (*c* 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H, =CHN), 7.35–7.28 (m, 5H, Ar), 4.61 (s, 2H, PhCH_2), 4.54 (dd, 1H, $J_{4,3} = 7.7$, $J_{4,5} = 2.3$, H-4), 4.47 (d, 1H, $J_{2,3} = 1.6$, H-2), 4.33 (ddd, 1H, $J_{5,6a} = 6.1$, $J_{5,6b} = 10.3$, H-5), 4.24 (m, 3H, COOCH_2CH$_3$ and H-3), 4.15 (q, 2H, COOCH_2CH$_3$), 3.36 (dd, 1H, $J_{6a,6b} = 11.4$, H-6a), 3.33 (m, 1H, C_6H_{11}), 3.18 (t, 1H, H-6b), 1.73–1.44 (m, 6H, C_6H_{11}), 1.41, 1.32 (each s, each 3H, C(CH_3)$_2$), 1.32, 1.24 (each t, each 3H, 2COOCH$_2$CH_3), 1.20–1.10 (m, 4H, C_6H_{11}); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.6, 167.1 (2C=O), 149.9 (=CHN), 137.6, 128.6, 128.2, 128.1 (Ph), 110.8 (*C*(CH$_3$)$_2$), 95.9 (=C), 90.7 (C-2), 75.8 (C-3), 72.2 (C-4), 71.9 (Ph*C*H$_2$), 68.9 (C-5), 61.1, 60.2 (2COO*C*H$_2$CH$_3$), 43.6 (C-6), 74.5, 32.8, 31.0, 25.5, 23.7, 23.4 (C_6H_{11}), 26.3, 24.5 [C(CH_3)$_2$], 14.4, 14.2 (2COOCH$_2$*C*H$_3$). HRCIMS *m*/*z* obsd 532.2887; calcd for $C_{24}H_{42}NO_8$, 532.2910.
15. For the molecular modelling calculations the force field TRIPOS was used as implemented in Sybyl 7.3 (Tripos Inc.). The starting structure was built with a ring puckering corresponding to a skewed boat conformation, as it was the only ring conformation in qualitative agreement with the experimental *J*-couplings, and, at the same time, showing the largest number of bulky exocyclic groups in the most stable equatorial or isoclinal orientations. The exocyclic torsions were optimized by determining the energy minimum in torsional energy maps with 60° increments (gridsearch module in Sybyl). Gasteiger–Hückel atomic partial charges were used and the energy minimization steps in all the calculations consisted in 1000 conjugated-gradients maximum iterations, an energy gradient limit of 0.01 Kcal/mol A, using a distance-dependent dielectric constant of 1·*r*, and a non-bonded cutoff of 8 A. Energy minimization led to significantly improved agreement between experimental and theoretical *J*-couplings. Theoretical distances were measured on the energy minimum, and the *J*-couplings were obtained using the Haasnoot–Altona empirical equation (Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792). Any molecular model with an inverted configuration at C-2 was unable to predict the set of exclusive NOEs described in the discussion of results.
16. Compound **10** was a commercial product. For the preparation of **11**, see: Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305–311; and for the preparation of **12**, see: Roën, A.; Padrón, J. I.; Vázquez, J. T. *J. Org. Chem.* **2003**, *68*, 4615–4630.
17. Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301–306.
18. Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234–1238.
19. Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1990**, *202*, 165–175.
20. Selected structural data for the iminodisaccharide **7**. Yield: 77%; $[\alpha]_D^{25}$ −65.5 (*c* 1.9, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H,

=CHN), 7.34-7.25 (m, 5H, Ph), 5.50 (d, 1H, $J_{1',2'} = 5.1$, H-1′), 4.60 (s, 2H, PhCH_2), 4.58–4.54 (m, 2H, H-4, H-3′), 4.49 (d, 1H, $J_{2,3} = 1.3$, H-2), 4.34 (dd, 1H, $J_{3,4} = 7.7$, H-3), 4.31 (dd, 1H, $J_{2',3'} = 2.5$, H-2′), 4.28 (m, 1H, H-5), 4.25, 4.15 (each q, each 2H, 2COOCH_2CH$_3$), 4.04 (dd, 1H, $J_{3',4'} = 2.0$, $J_{4',5'} = 7.8$, H-4′), 3.84 (m, 1H, H-5′), 3.64 (dd, 1H, $J_{5',6'a} = 5.6$, $J_{6'a,6'b} = 10.0$, H-6′a), 3.49 (m, 2H, H-6′b, H-6a), 3.25 (t, 1H, $J_{5,6b} = 10.7$, $J_{6a,6b} = 10.7$, H-6b), 1.56, 1.49, 1.44, 1.43 (each s, each 3H, 2C(CH_3)$_2$), 1.32, 1.23 (each t, each 3H, 2COOCH$_2$CH_3), 1.23 (s, 6H, C(CH_3)$_2$). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ 167.6, 167.0 (2C=O), 149.6 (=CHN), 137.0, 128.6, 128.0, 127.8 (Ph), 110.9, 109.9, 108,7 (3 C(CH$_3$)$_2$), 96.5 (=C), 96.3 (C-1′), 93.0 (C-2), 75.1 (C-3), 71.9, 71.8 (C-4 and CH$_2$Ph), 71.2 (C-4′), 70.8, 70.5 (C-5 and C-3′), 70.0 (C-2′), 67.1 (C-5′), 66.2 (C-6′), 61.1, 60.2 (2COOCH$_2$CH$_3$), 43.1 (C-6), 26.3, 26.2, 26.1, 25.0, 24.9, 24.6 (3 C(CH$_3$)$_2$), 14.5, 14.3 (2COOCH$_2$$CH_3$). HRFABMS m/z obsd 714.3107; calcd for $C_{35}H_{49}NO_{13}Na$, 714.3102.