Michael-Type Addition to 2-Nitrogalactal – A Simple Method to Access 1,1-Linked Oligosaccharides

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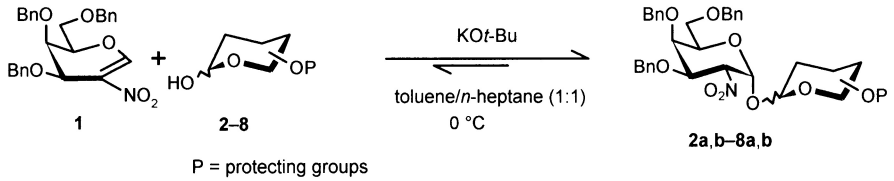
Abstract: Anomeric *O*-unprotected sugars add to 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal to accomplish nitro group-containing 1,1-linked oligosaccharides in respectable yields with good selectivities. A 1:1 mixture of toluene and *n*-heptane has been found as the appropriate solvent system for these Michael-type additions. The nitro group-containing 1,1-linked oligosaccharides are easily convertible into interesting trehalosamine analogues.

Key words: Michael-type addition, 2-nitrogalactal, 1,1-linked oligosaccharides, *O*-unprotected sugars, nitro group

1,1-Linked oligosaccharides occur as structural constituents in many organisms.[1] Trehalosamines, amino group containing 1,1-linked oligosaccharides, possess substantial antimicrobial activity, thus they serve as promising candidates for designing novel antibiotics and trehalase inhibitors.[2] Only a few reports have appeared in the literature on the synthesis of trehalosamines in general and their non-symmetrical analogues in particular. They mainly involve the glycosylation of anomeric *O*-unprotected sugars with 1-halo sugars,[3a–c] oxyamination of 1,1-linked pseudo glycals,[3d,e] selective displacement of hydroxyl functions in trehaloses with azide and subsequent reduction,[3f] and enzymatic processes.[3g] Hence, efficient methods are desirable to synthesize non-symmetrical analogues of trehalosamine.

Glycals are extensively employed in the synthesis of oligosaccharides and libraries thereof and of a variety of optically active products.[4] Nitroglycals, in particular, possess potential in the synthesis of glycoconjugates since D-glucosamine and D-galactosamine are frequently occurring glycoconjugate constituents.[5] Base assisted oxy-Michael addition of δ-lactols to acrylates has been reported.[6] Hence, it appeared that 2-nitroglycals could well serve as simple precursors for the synthesis of non-symmetrical analogues of trehalosamine. Herein we present our results on the Michael-type addition of anomeric *O*-unprotected sugars to 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal. The reaction is represented in Scheme 1 and the results are compiled in Table 1.

All reactions were carried out with easily accessible 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal **1**.[7f] Potassium *tert*-butoxide was the base of choice as it worked well in our hands for the Michael-type addition of various nucleophiles to 2-nitroglycals.[7] The required anomeric *O*-unprotected sugars can be easily prepared. In a preliminary experiment, **1** was treated with equimolar quantities of 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-D-galactose (**2**) and potassium *tert*-butoxide in toluene. The reaction yielded the desired 1,1-linked disaccharide **2** in 46% yield. Out of the four possible diastereomers, only two were obtained, namely **2a** and **2b**. Hence, in accordance with the previous reports,[7] exclusive α-addition of the anomeric oxide of **2** to nitrogalactal **1** occurred followed by protonation from the β-side, thus generating two new stereogenic centers with excellent stereocontrol. The anomeric carbon of the anomeric *O*-unprotected sugar part in the product was a 4:1 mixture of α- (**2a**) and β-products (**2b**). The configuration of the newly formed stereogenic centers were discerned from the corresponding coupling constant values of the anomeric protons of **2a**,**b**.[8] With other anomeric *O*-unprotected sugars such as **5** and **8**, the yields of the products **5a** and **8a**,**b** were also less than 40%. Reactions carried out in THF were found to be even worse. In order to find out the cause for the low yields, in a separate experiment a mixture of 1,1-disaccharides **2a** and **2b** was treated with potassium *tert*-butoxide in toluene. This reaction clearly revealed the reversible nature of the reaction under the reaction conditions. It in turn suggested reducing the polarity of the solvent so that the carbanion generated after the



Scheme 1 *t*-BuOK assisted synthesis of 1,1-linked oligosaccharides

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addition gets protonated quickly and the rate of the reverse reaction is decreased. In line with this suggestion, the reaction of **1** with **2** in a 1:1 mixture of toluene and *n*-heptane was found to be very clean and the yield of the product was improved dramatically to 85%;[8] the **2a/2b** ratio under these conditions was found to be 5:2. This result prompted a study with other anomeric *O*-unprotected sugars as well.

Different anomeric *O*-unprotected sugars **3**–**8** derived from glucose, mannose, glucosamine and two disaccharides were reacted with **1** under the new reaction conditions to furnish the corresponding 1,1-linked oligosaccharides in good yields (Table 1). Hence, this protocol can serve as a versatile method to synthesize 1,1-linked oligosaccharides with different sugar components. The configurations of the newly generated stereogenic centers were assigned using NMR methods. Like **2**, all the anomeric *O*-unprotected sugars gave a mixture of α- and β-anomers at the anomeric carbon of the anomeric O-unprotected sugar part. It is interesting to note that the α/β ratio in the anomeric *O*-unprotected sugars is not sustained in the product; rather, it is dependent on the nature of the substituent at its 2-position. For instance, when acetoxy and azido groups are in the equatorial position of carbon-2 (**2**, **3**, and **6**), the α-isomer is obtained predominantly even though, except **2**, both **3** and **6** were mostly β-anomers, whereas **4** behaved differently. Compounds **7** and **8** with equatorial 2-dimethylmaleimido (DMMN) groups resulted mostly in the β-isomer. However, tetra-*O*-acetylmannose (**5**) with an axial 2-acetoxy group at *C*-2 gave exclusively the α-anomer **5a**. These observations are not a surprise as the anomeric *O*-unprotected sugars are expected to undergo ring-opening and -closure under basic condition and vary their anomer ratio. Thus, the reaction of **1** with **6** and **7** can be advantageously exploited to synthesize either α- or β-isomers of trehalosamine.

Table 1 Michael-Type Additions of Anomeric *O*-Unprotected Sugars to 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal[a]

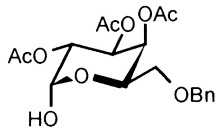
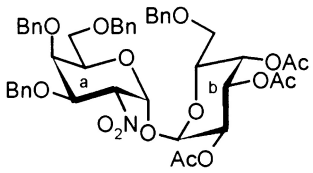
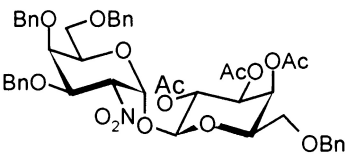
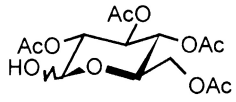
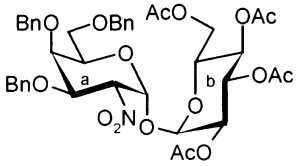
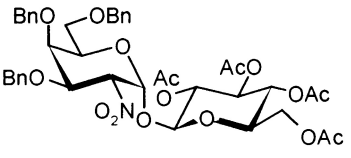
Sugar (α:β)	Time (h)	Products	Isolated yields (%) α:β
 **2** (α)	2	 **2a**  **2b**	85 (94)[b] 2.5:1
 **3** (1:6.3)	1	 **3a**  **3b**	57 (84)[b] 4.5:1

Table 1 Michael-Type Additions of Anomeric *O*-Unprotected Sugars to 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal[a] (continued)

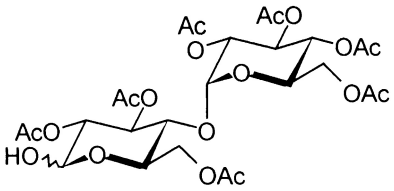
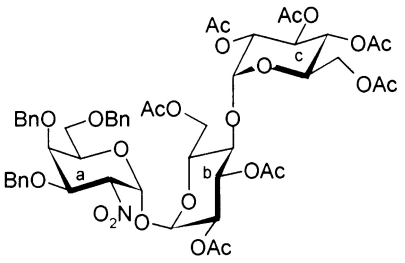
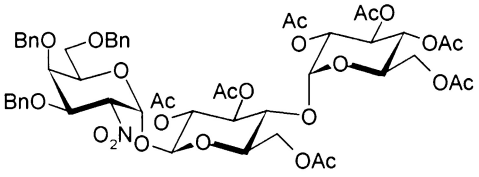
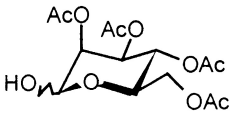
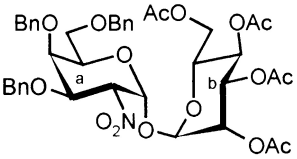
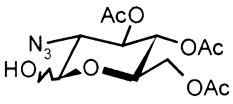
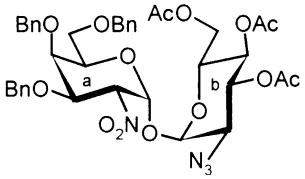
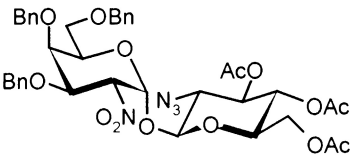
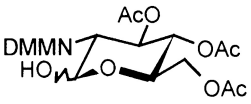
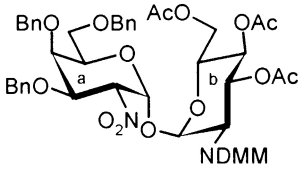
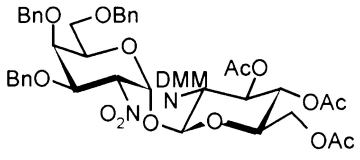
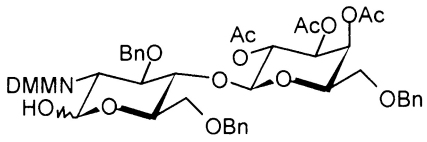
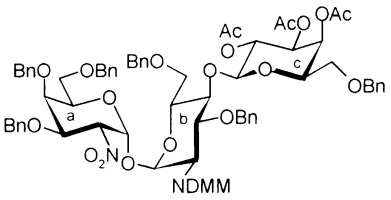
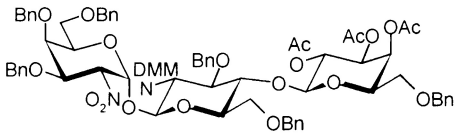
Sugar (α:β)	Time (h)	Products	Isolated yields (%) α:β
 **4** (1:1.2)	2	 **4a**  **4b**	61 (95)[b] 1:1.7
 **5** (6:1)	1	 **5a**	80 (95)[b] single isomer
 **6** (1:1.3)	1	 **6a**  **6b**	56 (72)[b] 3.2:1
 **7** (β)	2	 **7a**  **7b**	62 (84)[b] 1:3.9

Table 1 Michael-Type Additions of Anomeric *O*-Unprotected Sugars to 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal[a] (continued)

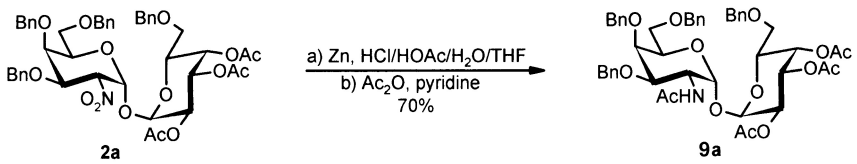
Sugar (α:β)	Time (h)	Products	Isolated yields (%) α:β
 **8** (1:5)	2	 **8a**  **8b**	68 (89)[b] 1:4.7

[a] For experimental details, see ref.[8,]
[b] Yields based on the consumed anomeric *O*-unprotected sugar.

Closely related anomeric *O*-alkylation of anomeric *O*-unprotected sugars has been studied as it constitutes a convenient and effective method to synthesize *O*-glycosides.[9] Several factors such as the nature of base, solvent, substituents, and temperature affect α/β selectivity. In this irreversible reaction, in a nonpolar solvent at room temperature, the equatorial β-oxide has been found to be more reactive than the axial α-oxide, thus furnishing mainly β-glycosides. On the other hand, polar solvents and low reaction temperatures led mainly to α-glycosides. In the present study, in a nonpolar solvent system at 0 °C and after 1–2 hours reaction time, independent of the anomeric configuration of the starting material, in most cases the thermodynamically more stable α-glycosides were obtained. Only for **7** and **8**, having a bulky dimethylmaleimido group at *C*-2, and for **4** mainly the β-anomers were received. Hence, these results are not in full agreement with those found for irreversible anomeric *O*-alkylations, which were mainly investigated with primary alkylating agents where also steric effects of the electrophile play a minor role. Rather the results obtained here resemble base-catalyzed trichloroacetonitrile addition to 1-*O*-unprotected sugars where α-trichloroacetimidate formation is thermodynamically favored.[9a] This view is also supported by the following investigations.

Due to the reversible nature of the anomeric ratio in the nucleophiles **2**–**8** and of their oxy-Michael addition to **1**, the time-dependency of the α/β product ratio was further investigated with substrate **3**. Aliquots taken from the reaction mixture after 15 minutes, 1 hour, 2 hours, and 20 hours were worked up and chromatographed; the α/β ratio of the product **3a**,**b** was found by ^{1}H NMR investigations to be 3:1, 5:1, 8:1, and 8.6:1, respectively. In another set of experiments, substrates **3** and **7** were treated with potassium *tert*-butoxide in the absence of **1** under otherwise identical conditions of the general procedure.[8] The α/β ratio of substrate **3** (α/β = 1:6.3) is reversed to 2.1:1 and 2.5:1, respectively, after 10 minutes in toluene and 1 hour in a 1:1 toluene–*n*-heptane mixture. With substrate **7**, from exclusive β-anomer, the α/β ratio is reduced to 1:11 and 1:9.3, respectively, after 10 minutes in toluene and 1 hour in a 1:1 toluene–*n*-heptane mixture. These experiments clearly show that α-glycoside formation (**2a**–**8a**) is favored for stereoelectronic reasons but it also requires (slow) equilibration of the β-anomers **2**–**8** to the corresponding α-anomers.

To show the usefulness of this method, the nitro group in the 1,1-linked oligosaccharide **2a** was reduced to the amino group using Zn, HCl/HOAc[7b] in a THF–H_2O mixture. Subsequent acetylation gave the corresponding acetylated trehalosamine derivative **9a** in 70% yield over two steps (Scheme 2).



2a **9a**

Scheme 2 Conversion of **2a** into trehalosamine analogue **9a**

In conclusion, potassium *tert*-butoxide assisted Michael addition of anomeric *O*-unprotected sugars to 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**1**) can be conveniently employed to prepare nitro group containing 1,1-linked oligosaccharides bearing different sugar units. Addition to 2-nitrogalactal as Michael acceptor was stereoselective leading only to α-galacto-configuration; anomerisation of the nucleophiles, the 1-*O*-unprotected sugars, furnished in most cases preferentially the α-anomer, hence α,α-1,1-linked products were predominantly obtained. Further, it has been demonstrated with an example that the nitro group of the 1,1-linked oligosaccharide can be easily converted into an amino group to access useful trehalosamine analogues.

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References

(1) (a) Haines, A. H. *Carbohydr. Res.* **2003**, *338*, 813. (b) Wang, W.; Kong, F. *Tetrahedron Lett.* **1990**, *40*, 1361. (c) Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, J. J.; Jin, Z.; Rodríguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057. (d) Hiruma, K.; Kajimoto, T.; Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 9265.

(2) (a) Dolak, L. A.; Castle, T. M.; Laborde, A. L. *J. Antibiot.* **1980**, *33*, 690. (b) Naganawa, H.; Usui, N.; Takita, T.; Hamada, M.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1974**, *27*, 145. (c) Hooper, I. R. *Aminoglycoside Antibiotics*; Springer-Verlag: New York, **1982**. (d) Haddad, J.; Kotra, L. P.; Mobashery, S. In *Glycochemistry Principles, Synthesis and Applications*; Wang, P. G.; Bertozzi, C. R., Eds.; Marcel Dekker: New York, **2001**, 307.

(3) (a) Karpiesiuk, W.; Banaszek, A. J. *Carbohydr. Chem.* **1990**, *9*, 909. (b) Paulsen, H.; Sumfleth, B. *Chem. Ber.* **1979**, *112*, 3203. (c) Koto, S.; Inada, S.; Zeu, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2728. (d) Baer, H. H.; Siemsen, L. *Carbohydr. Res.* **1986**, *146*, 63. (e) Hui, Y.; Chang, C.-W. T. *Org. Lett.* **2002**, *4*, 2245. (f) Bassily, R. W.; El-Sokkary, R. I.; Silwanis, B. A.; Nematalla, A. S.; Nahed, M. A. *Carbohydr. Res.* **1993**, *239*, 197. (g) Křen, V.; Rajnochová, E.; Huňková, Z.; Dvořáková, J.; Sedmera, P. *Tetrahedron Lett.* **1998**, *39*, 9777.

(4) (a) Collins, P. M.; Ferrier, F. J. *Monosaccharides, Their Chemistry and Their Roles in Natural Products*; John Wiley and Sons: Chichester, **1995**, 317. (b) Lichtenthaler, F. W. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: Weinheim, **1992**, 273. (c) Bols, M. *Carbohydrate Building Blocks*; Wiley: New York, **1996**, 49. (d) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (e) Izumi, M.; Ichikawa, Y. *Tetrahedron Lett.* **1998**, *39*, 2079.

(5) (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Garg, H. G.; von dem Bruch, K.; Kunz, H. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 277.

(6) (a) Schmidt, C. *Diploma Thesis*; University of Konstanz: Germany, **1994**. (b) Buchman, D. J.; Dixon, D. J.; Hernandez-Juan, F. A. *Org. Lett.* **2004**, *6*, 1357.

(7) (a) Barroca, N.; Schmidt, R. R. *Org. Lett.* **2004**, *6*, 1551. (b) Geiger, J.; Barroca, N.; Schmidt, R. R. *Synlett* **2004**, 836. (c) Khodair, A. I.; Pachamuthu, K.; Schmidt, R. R. *Synthesis* **2004**, 53. (d) Khodair, A. I.; Winterfeld, G. A.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, 1847. (e) Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2654; *Angew. Chem.* **2001**, *113*, 2718. (f) Das, J.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 1609; and references therein.

(8) **General Procedure for the Michael-Type Addition:** To a solution of anomeric *O*-unprotected sugar (0.16 mmol) in toluene (1 mL), *t*-BuOK (0.16 mmol) was added at 0 °C. After 10 min, a solution of **1** (0.19 mmol) in toluene–*n*-heptane mixture (1:2, 3 mL) was added to it. The reaction mixture was stirred at the same temperature for the specific period of time given in Table 1. Few drops of HOAc were added to quench the reaction. It was taken in EtOAc, washed with H_2O, and sat. brine, dried over anhyd $MgSO_4$, and concentrated. Purification of the crude residue by chromatography on silica gel afforded the 1,1-linked oligosaccharide. Selected ^1H NMR data (250 MHz, $CDCl_3$): Compound **2a**: δ = 5.58 ($J_{1,2}$ = 4.3 Hz, 1-H_a), 5.25 ($J_{1,2}$ = 3.7 Hz, 1-H_b). Compound **2b**: δ = 5.50 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 4.56 ($J_{1,2}$ = 8.3 Hz, 1-H_b). Compound **3a**: δ = 5.56 ($J_{1,2}$ = 4.2 Hz, 1-H_a), 5.25 ($J_{1,2}$ = 3.9 Hz, 1-H_b). Compound **3b**: δ = 5.49 ($J_{1,2}$ = 4.2 Hz, 1-H_a), 4.60 ($J_{1,2}$ = 8.1 Hz, 1-H_b). Compound **4a**: δ = 5.55 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 5.16 ($J_{1,2}$ = 3.8 Hz, 1-H_b), 5.36 ($J_{1,2}$ = 3.3 Hz, 1-H_c). Compound **4b**: δ = ($J_{1,2}$ = 4.0 Hz, 1-H_a), 4.63 ($J_{1,2}$ = 8.1 Hz, 1-H_b), 5.41 ($J_{1,2}$ = 3.8 Hz, 1-H_c). Compound **5a**: δ = 5.63 ($J_{1,2}$ = 4.2 Hz, 1-H_a), 5.11 ($J_{1,2}$ = 1.1 Hz, 1-H_b). Compound **6a**: δ = 5.60 ($J_{1,2}$ = 4.2 Hz, 1-H_a), 5.21 ($J_{1,2}$ = 3.9 Hz, 1-H_b). Compound **6b**: δ = 5.61 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 4.42 ($J_{1,2}$ = 8.2 Hz, 1-H_b). Compound **7a**: δ = 5.63 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 5.41 ($J_{1,2}$ = 4.1 Hz, 1-H_b). Compound **7b**: δ = 5.34 ($J_{1,2}$ = 4.0 Hz, 1-H_a), 5.35 ($J_{1,2}$ = 8.7 Hz, 1-H_b). Compound **8a**: δ = 5.50 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 5.01 ($J_{1,2}$ = 3.6 Hz, 1-H_b), 4.36 ($J_{1,2}$ = 8.3 Hz, 1-H_c). Compound **8b**: δ = 5.29 ($J_{1,2}$ = 4.1 Hz, 1-H_a), 5.08 ($J_{1,2}$ = 8.2, 1-H_b), 4.51 ($J_{1,2}$ = 8.0 Hz, 1-H_c). Compound **9a**: δ = 5.23 ($J_{1,2}$ = 3.0 Hz, 1-H_a), 5.32 ($J_{1,2}$ = 3.5 Hz, 1-H_b).

(9) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212; *Angew. Chem.* **1986**, *98*, 213. (b) Schmidt, R. R.; Klotz, W. *Synlett* **1991**, 168. (c) Lubineau, A.; Escher, S.; Alais, J.; Bonnaffé, D. *Tetrahedron Lett.* **1997**, *38*, 4087.