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Glycosyl Transfer to Nitrogen via Cycloaddition

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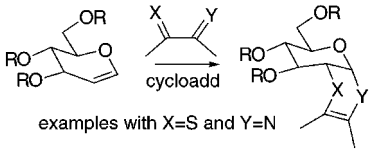
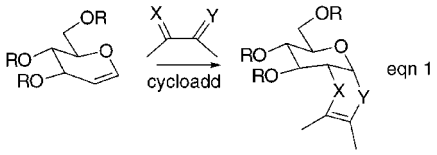
ABSTRACT



This letter describes the reduction to practice of a novel concept for functionalization of the anomeric carbon of carbohydrates with a nitrogen substituent. Thus, bisheterodienes with a thiono sulfur terminus and a sulfonylimine terminus are shown to undergo cycloaddition smoothly and stereoselectively to three different glycals.

Glycoproteins are a class of molecules under intense study by glycobiologists.[1,2] As a consequence of this interest, the organic chemistry required for the synthesis of glycosylated amino acids and peptides has been a rapidly developing area of research. The synthesis of N-linked glycoside derivatives is almost universally accomplished by derivatizing a glycosyl-NH_2 species.[3] Two recent examples of "the state-of-the-art" from the Danishefsky lab and the Meldal/Bock/Paulsen team describe polymer-bound methods. The former uses a resin-attached trisaccharide-NH_2 coupling to tri- and pentapeptides in solution.[4] The latter uses solution-phase glycosyl donors reacting with peptides attached to a PEG-based resin.[5] The one exception to this generalization is the modfied Ritter reaction described by Fraser-Reid.[6] We wish to describe a second exception: our cycloaddition approach depicted in eq 1 where X = S and Y= N which delivers functionalized N to C-1 of glycals.



Our earlier work, where X = S and Y = O, used the computed gap between the LUMO of the heterodiene and the HOMO of the glycal as a predictor of successful cycloaddition.[7] After completing a computational survey of potential substitutents for imine nitrogens, we settled on the sulfonylimine function as being suitable for production of a low-lying LUMO for our heterodiene. As the model case, we chose methyl acetoacetate *N*-phenylsulfonylimine **1** (shown as the predominant enamine tautomer), easily

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(1) Varki, A. *Glycobiology* **1993**, *3*, 97−130.
(2) (a) Bill, R. M.; Flitsch, S. L. *Chem. Biol.* **1996,** 145. (b) Paulsen, H.; Peters, S.; Bielfeldt, T. *Glycoproteins*; Montreuil, J., Schacter, H., Vliegenthart, J. F. G., Eds.; Elsevier: New York, 1995; Chapter 4, p 87.
(3) Glycoconjugates resembling glycopeptides, but with "unnatural" linkers, are also an important area of research, for example: Rodriguez, E. Z.; Marcaurelle, L. A.; Bertozzi, C. R. *J. Org. Chem.* **1998**, *63*, 7134−7135.
(4) Roberge, J. Y.; Beebe, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 3915−3927.
(5) Schleyer, A.; Meldal, M.; Manat, R.; Paulsen, H.; Bock, K. *Angew. Chem., Int. Ed. Engl.* **1997,** *36*, 1976.
(6) Ratcliffe, A. J.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1990** *112*, 5665.
(7) Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem.* **1996**, *108*, 805−807; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777−779. (b) Dios, A.; Geer, A.; Marzabadi, C.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 6673.

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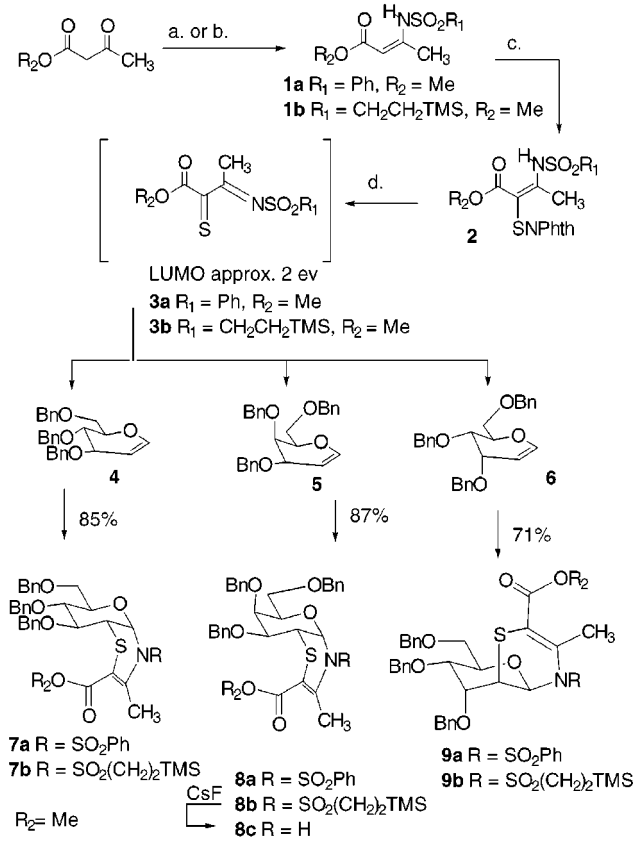
prepared from methyl acetoacetate by heating with benzenesulfonamide. Phthalimidosulfenylation of **1** smoothly afforded derivative **2**, the key precursor to the transient thiono sulfonylimine **3**. When **2** was treated with pyridine in the presence of tribenzyl glucal **4**, tribenzyl galactal **5**, and tribenzyl allal **6,** the cycloadducts **7**, **8**, and **9** were produced in very good yield (Scheme 1).

Scheme 1. Iminothione for N-Linkage to Carbohydrate C-1

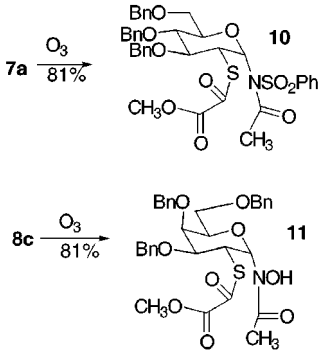


[a] $PhSO_2NH_2$, TsOH, benzene, 95%. [b] $TMSCH_2CH_2SO_2NH_2$, TsOH, benzene, 93%. [c] PhthNSCl, **2a** >95%, **2b** 95%. [d] Pyridine, CH_2Cl_2.

The experiments were also repeated with the TMS-ethylsulfonyl N-protecting group developed by Weinreb,[8] with similar results. The TMS-ethyl group can be cleanly removed with CsF to afford the NH species **8c**. Preliminary ozonolysis experiments with adducts **7a** and **8c** showed that the bicyclic species could be cleaved to produce the glycosylamide function illustrated in compounds **10** and **11** (Scheme 2).

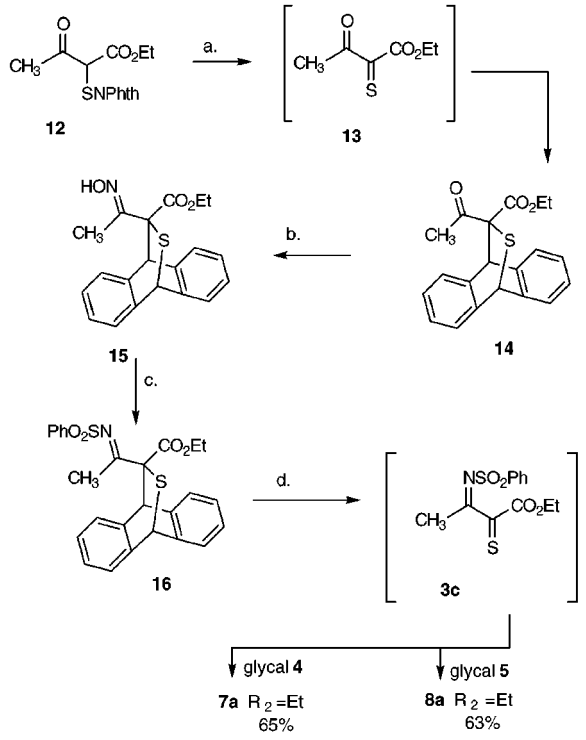
As an alternate route to the key sulfonylimino thione **3**, we took advantage of the reversibility of the anthracene adduct **14** of thiono keto ester **13**.[9] Adduct **14** was converted to its oxime **15**. The oxime, when treated with toluenesulfinyl chloride, undergoes sulfinylation followed by rearrangement

Scheme 2. Cleavage of Cycloadducts



to the sulfonylimine **16**.[10] Then, mild thermolysis of this modified anthracene adduct in the presence of glycals **4** and **5** liberates the transient thiono species **3c** (R_2 = Et) which is smoothly trapped in cycloaddition to afford **7a** and **8a** (R_2 = Et) (Scheme 3).

Scheme 3. Retrocycloaddition Route to N-Transfer Reagent



[a] Pyridine (1 equiv), anthracene, 90%. [b] NH_2OH, 85%. [c] PhSOCl, Et_3N, Et_2O/CH_2Cl_2 (1:1), −10 °C to rt. 20 h, 40%. [d] Lutidine (0.2 equiv), $CHCl_3$ 60 °C.

To develop our cycloaddition for a direct transfer to a model peptide, we modified aspartic acid as shown in

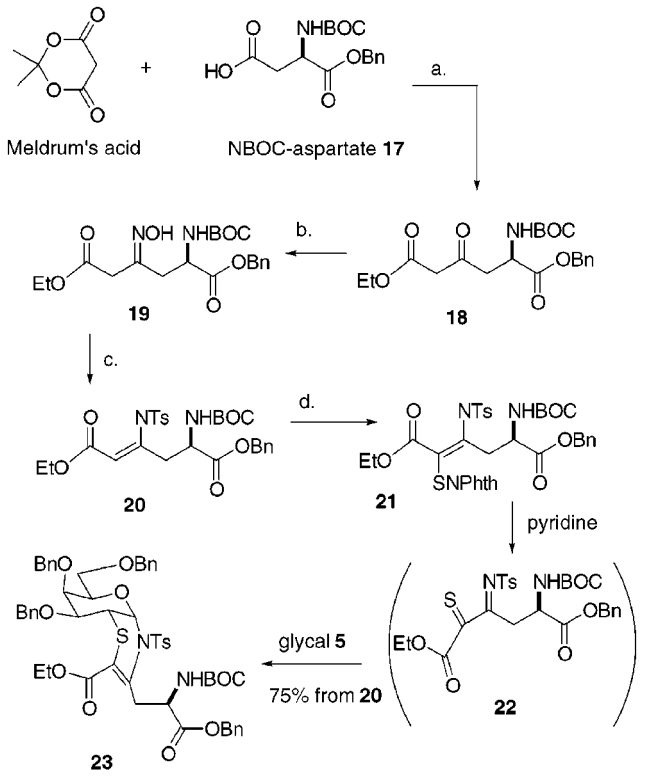
(8) Weinreb, S. M.; Ralbovsky, J. L. Trimethylsilyl ethanesulfonyl chloride. In *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; Vol. 7, pp 5255−5256.

(9) Capozzi, G.; Menichetti, S.; Nativi, C.; Vergamini, C. *Synthesis* **1998**, 915−918. Cycloadditions to simple dienophiles of an NOAc heterodiene related to **3c**, and also prepared via retrocycloaddition.

(10) Brown, C.; Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, 822−826.

Scheme 4. Blocked aspartic acid derivative **17** was converted to keto ester **18** using Meldrum's acid as a nucleophilic

Scheme 4. Transfer of Aspartate



[a] (i) Isopropenyl chloroformate, DMAP, Et_3N; (ii) EtOH, heat, 92% for two steps. [b] NH_2OH. [c]TsCN, Et_3N, CCl_4, 65% for two steps. [d]PhthNSCl.

C-donor in a peptide coupling protocol following the work of Shiori.[11] The ketone was then converted to its sulfonyl oxime **19** according to a sulfinylation−rearrangement procedure reported by Boger.[12] Phthalimidosulfenylation of **20** followed by cycloaddition led smoothly to glycopeptide analogue **23**, thus validating our concept. In conclusion, we have described a unique method for introducing functionalized nitrogen to the anomeric carbon of carbohydrates.[13,14]

Acknowledgment. (a) In Memoriam, Gertrude Elion, 1918−1999. (b) This research was presented at the ACS Meeting, Boston August 23−27, 1998, ORG 744. (c) The research in Firenze was carried out within the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell'Università e ella Ricerca Scientifica e Tecnologica, Rome, and by the University of Firenze.. At Hunter funding came from NIH grants GM 51216 and RR 03037 and PSC/CUNY awards. The NMR laboratory has received support from the NY State GRI and HEAT initiatives. The mass spectrometry facility has also received funding from GRI and NSF grant CHE-9708881.

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(11) Hamada, Y.; Kondo, Y.; Shibata, M.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *101*, 669−673

(12) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1992**, *57*, 4777.

(13) All cycloadducts had molecular ions (either ESMS or CI/MS) and proton and carbon NMR data consistent with their structures. Adducts **7a**, **8b**, **10,** and **11** have confirming combustion analyses and the structure of **7a** has been confirmed by X-ray crystallography.

(14) **Representative Procedures. Phthalimidosulfenylation of methyl 3-benzenesulfonylamino-2-butenoate.** To a solution of sulfonyl imine **1a** (prepared via refluxing a solution of methyl acetoacetate (1.2 equiv) and benzenesulfonylamide (1 equiv) in a convenient amount of benzene with a catalytic amount of *p*-toluenesulfonic acid followed by conventional workup) was added PhthN-S-Cl (1.2 equiv) in portions at 0 °C during a period of 15 min. The reaction mixture was stirred at such temperature for an additional 20 min and allowed to warm to room temperature in 30 min. Cold *n*-pentane was added. A lot of white precipitate formed which was filtered and then washed with cold *n*-pentane to afford the desired **2a**. Yield of crude suitable for the following step: >99%; ^{1}HNMR ($CDCl_3$) δ 12.53 (s, 1H), 7.95−7.57 (m, 9H), 3.80 (s, 3H), 2.89 (s, 3H). **Cycloaddition of methyl 2-phthalimidosulfenyl-3-benzenesulfonylamino-2-butenoate 2a with tri-*O*-benzyl-D-glucal (4).** To a solution of the phthalimidosulfenyl imine **2a** (1.2 equiv) and tri-*O*-benzyl-D-glucal **(4)** in $CHCl_3$ was added a catalytic amount of 2,6-lutidine (2 mol %). The resulting solution was stirred at room temperature until the reaction was complete as monitored by TLC. The solution was dissolved in dichloromethane and washed with saturated ammonium chloride and brine and dried over Na_2SO_4. The organic solvent was removed under reduced pressure. The crude materials were purified by a silica gel column (ethyl acetate/petroleum ether) to give the desired product **7a**. When phthalimide residues are not cleanly separated, a 20% NaOH wash was used to extract the phthalimide after flash chromatography. Yield of **7a**: 82% (140 mg, 0.35 mmol); FTIR (neat) 1715.3, 1585.4, 1448.2, 1357.6, 1251.5, 1169.1; ^{1}HNMR ($CDCl_3$) δ 7.96 (d, 2H), 7.52 (t, 2H), 7.40−7.16 (m,), 6.33 (d, J = 7.2, 1H), 4.82−4.57 (m,), 3.71 (s, 3H), 3.52−3.3 (m, 4H), 2.52 (s, 3H); ^{13}CNMR ($CDCl_3$) δ 165.2, 148.1, 139.2, 137.9, 137.6, 133.1, 128.6, 128.2, 128.0, 127.7, 127.6, 127.5, 117.4, 87.9, 79.0, 77.9, 76.1, 74.9, 73.3, 72.0, 67.5, 52.1, 47.9, 21.4. Anal. Calcd for $C_{38}H_{39}O_8NS_2$: C, 65.03; H, 5.56; N, 2.00. Found: C, 64.67; H, 5.93; N, 2.12.