Chemical Ligation

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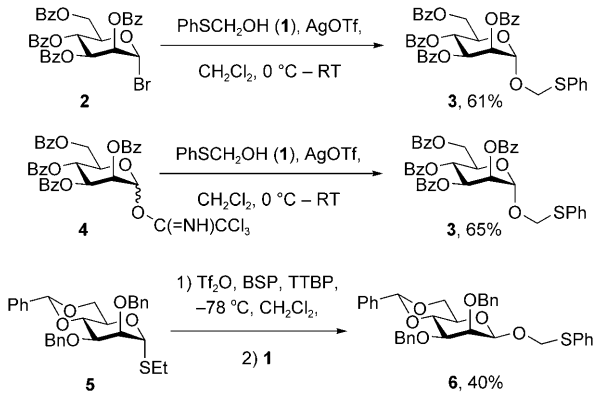
Phenylthiomethyl Glycosides: Convenient Synthons for the Formation of Azidomethyl and Glycosylmethyl Glycosides and Their Derivatives**

David Crich and Fan Yang*

Dedicated to Prof. Dr. Andrea Vasella

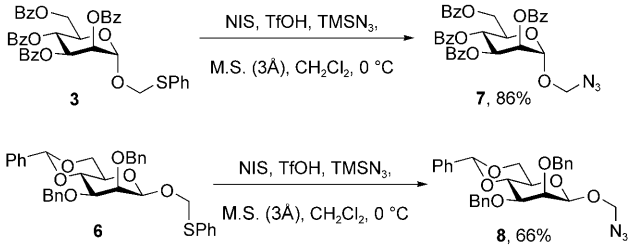
Click chemistry[1] has become one of the most important reactions in the field of glycoscience enabling the rapid assembly, under very mild conditions, of a vast array of glycoconjugates.[2] We were struck, however, by the absence of azidomethyl glycosides which necessarily excludes the whole class of triazolylmethyl glycosides from the arsenal of glycoconjugates accessible by Click chemistry.[3] Zhu and Schmidt addressed the problem indirectly through the synthesis of a series of azidomethyl thioglycosides,[4] but to date the more native *O*-glycosides have not been described.

Seeking to remedy this deficiency we prepared phenylthiomethanol **1**[5] and investigated its use as a glycosyl acceptor. Activation of tetrabenzoyl mannopyranosyl bromide **2** with silver triflate in the presence of **1** afforded the anticipated α-glycoside **3** in 61% yield (Scheme 1). When the corresponding trichloroacetimidate donor **4**[6,7] was activated with a catalytic amount of silver triflate in the presence of **1** it gave **3** in 65% yield. Interestingly, even thioglycoside donors could be applied provided that a preactivation protocol was employed. Thus, preactivation of a 4,6-*O*-benzylidene-protected β-mannopyranosyl donor **5** under our standard benzenesulfinyl piperidine (BSP)/trifluoromethanesulfonic anhydride (Tf_2O) conditions[8] resulted in the formation of a β-glycoside **6** (Scheme 1).[9]



Scheme 1. Synthesis of phenylthiomethyl glycosides Bn = benzyl, Bz = benzoyl, Tf = trifluoromethanesulfonyl, TTBP = 2,4,6-tri(*tert*-butyl)-pyrimidine.

Activation of **3** and **6** with *N*-iodosuccinimide (NIS) and trifluoromethansulfonic acid in the presence of azidotrimethylsilane resulted in conversion into the corresponding azidomethyl glycosides **7** and **8** in good yield (Scheme 2), thereby affording the first examples of this class of compound.



Scheme 2. Synthesis of azidomethyl glycosides. M.S. = molecular sieves, TMS = trimethylsilyl.

By employing the propargyl α-mannoside **9** as a reaction partner, the click reaction was investigated with the azidomethyl glycoside **7** under "classical" copper(I)-catalyzed conditions,[1,2] leading preferentially to the 1,4-disubstituted triazoles, and with a recent ruthenium-based system,[10] which afforded the 1,5-isomer (Scheme 3). The application of ruthenium catalysis in this manner, which, to our knowledge, has yet to be reported in glycoconjugate synthesis, provides a closer structural analogue to a branched trisaccharide motif than the more extended array obtained under the copper-catalyzed conditions.[11,12]

We next investigated the reaction of these novel azidomethyl glycosides with thioacids, with a view to forming amidomethyl glycosides. Perhaps not too surprisingly, in view of the relatively electron-rich nature of the azide,[13] the reaction of **7** with thioacetic acid required prolonged microwave heating and afforded the unusual amidomethyl glyco-

[*] Prof. Dr. D. Crich
Centre de Recherche de Gif
Institut de Chimie des Substances Naturelles
Centre Nationale de la Recherche Scientifique
Avenue de la Terrasse, 91198 Gif-sur-Yvette (France)
Fax: (+33) 1-6907-7752
E-mail: dcrich@icsn.cnrs-gif.fr
Prof. Dr. D. Crich, F. Yang
Department of Chemistry, Wayne State University
5101 Cass Avenue, Detroit, MI 48202 (USA)

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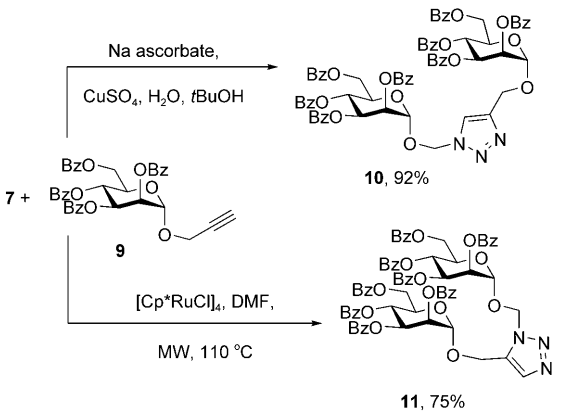
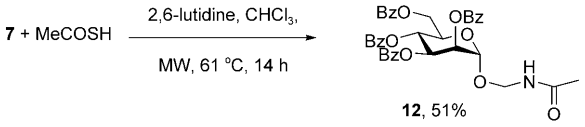


Scheme 3. Copper and ruthenium-catalyzed cycloaddition reactions with **7**. Cp* = pentamethylcyclopentadienyl, DMF = *N*,*N*-dimethylformamide, MW = microwave irradiation at 400 W.

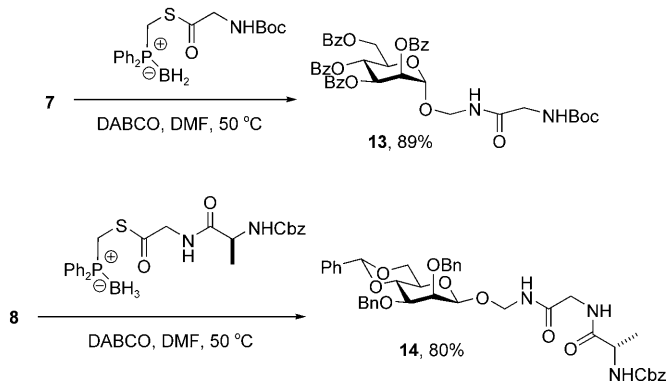
side **12** in 51% yield, together with 25% of unchanged **7** (Scheme 4).



Scheme 4. Reaction of **7** with thioacetic acid.

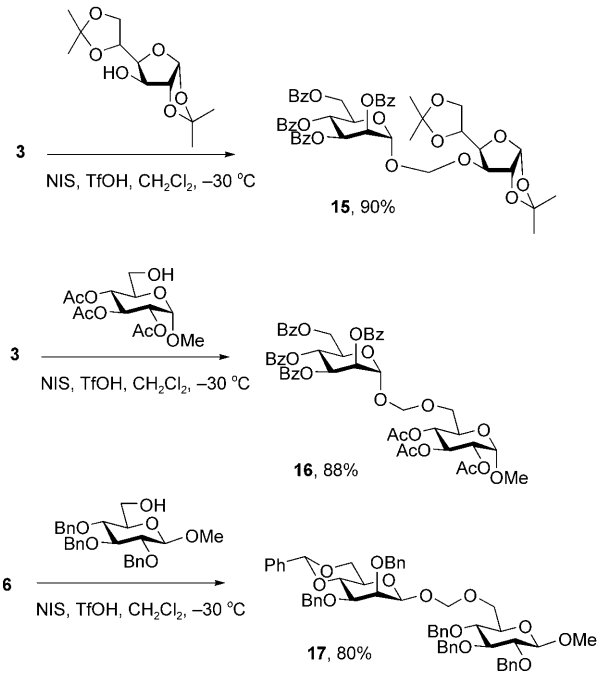
Better success in the formation of amidomethyl glycosides was obtained by the Raines variant[14] on the traceless Staudinger reaction.[15] Thus, a series of diphenylphosphinylmethyl thioesters were prepared in the form of their borane adducts. After transfer of the borane to diazabicyclooctane (DABCO) these substituted phosphines were treated with **7** and **8** and resulted in the formation of novel amidomethyl glycosides in high yield (Scheme 5).

Finally, in view of the successful conversion of **3** and **6** into the azidomethyl glycosides **7** and **8** we turned our attention to glycosidic bond formation. Simple "acetal glycosides" of this



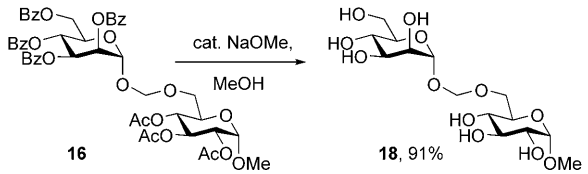
Scheme 5. Synthesis of azidomethyl glycosides by the traceless Staudinger reaction. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

type have been previously prepared by either the reaction of trimethylsilyl glycosides with formaldehyde acetals under catalysis by trimethylsilyl triflate, or by the reaction of anomeric hemiacetals with methylthiomethyl ethers in the presence of NIS, where the products were obtained as mixtures of stereoisomers.[16] Pleasingly, the reactions of both **3** and **6** with NIS and TfOH in the presence of a suitable acceptor alcohols provided the corresponding "acetal glycosides" **15**, **16**, and **17** in excellent yield and as single anomers (Scheme 6). Zemplen deacetylation of **16** gave the free



Scheme 6. Synthesis of alkoxymethyl glycosides.

"acetal glycoside" **18** in 91% yield (Scheme 7). The phenylthiomethyl glycosides therefore provide a new, convenient, and stereoselective means of entry into the "acetal glycosides", which are an unusual and somewhat limited class of compounds that were previously investigated for their potential as enzyme inhibitors.[17,18] We note that the syntheses of both the azidomethyl glycosides (Scheme 2) and the acetal glycosides (Scheme 6) likely proceed through a transient glycosyloxymethyl cation and that this intermediate is trapped by the incoming nucleophile substantially more rapidly than it undergoes decomposition to the glycosyl cation and formaldehyde. As has been previously recorded,[17a] the acetal glycosides are considerably less stable to



Scheme 7. Deprotection of a glycosyloxymethyl glycoside.

aqueous acid than simple glycosides, nevertheless we observed no difficulties in their purification by column chromatography on silica gel—either before or after removal of the protecting groups.

Overall, phenylthiomethyl glycosides may be obtained from thioglycosides and/or trichloroacetimidates by reaction with phenylthiomethanol under typical glycosylation conditions. They are stable compounds that upon activation of the phenylthiomethyl moiety provide direct access to the azidomethyl methyl glycosides and the "acetal glycosides". As the anomeric carbon atom is not implicated in these transformations the anomeric configuration of the phenylthiomethyl glycosides is completely retained. The azidomethyl glycosides take part in "click" reactions with alkynes under copper- or ruthenium-catalyzed conditions, thus providing access to new classes of 1,4- and 1,5-triazole derivatives. Finally, the azidomethyl glycosides readily take part in traceless Staudinger reactions enabling the formation of amidomethyl glycosides.

Experimental Section

Preparation of phenylthiomethyl tetra-*O*-benzoyl-α-D-mannopyranoside (**3**): 2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (2.24 g, 3.41 mmol), phenythiomethanol (1.91 g, 13.6 mmol), and activated 4 Å powdered molecular sieves (900 mg) were mixed in dichloromethane (17 mL) and stirred at room temperature for 10 min before AgOTf (964 mg, 3.75 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature until the donor was consumed (as evident by TLC; 2–4 h). Saturated aqueous $NaHCO_3$ then was added at 0 °C, and the mixture was filtered, and the filtrate was washed with brine. The organic layer was dried and concentrated under reduced pressure and the product was isolated by column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 20:1→10:1) and gave **3** (1.58 g, 61 %) as a white foam. $[\alpha]_D^{23} = +42.0^\circ$ ($c = 2.6\ g\,100\,cm^{-3}$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.15$–8.13 (m, 2H), 8.11–8.10 (m, 2H), 7.99–7.97 (m, 2H), 7.88–7.86 (m, 2H), 7.64–7.59 (m, 4H), 7.54–7.51 (m, 1H), 7.47–7.43 (m, 5H), 7.41–7.37 (m, 4H), 7.34–7.29 (m, 3H), 6.17 (t, $J = 10.0$ Hz, 1H), 5.96 (dd, $J = 3.5$, $J = 10.5$ Hz, 1H), 5.75 (m, 1H), 5.62 (d, $J = 1.5$ Hz, 1H), 5.27 (d, $J = 12.0$ Hz, 1H), 5.18 (d, $J = 12.0$ Hz, 1H), 4.72 (dd, $J = 2.5$, $J = 12.5$ Hz, 1H), 4.50 (dd, $J = 4.5$, $J = 12.0$ Hz, 1H), 4.41 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.4$, 165.74, 165.68, 165.6, 134.8, 133.81, 133.75, 133.5, 133.4, 131.3, 130.2, 130.1, 130.0, 129.5, 129.3, 129.2, 128.9, 128.8, 128.7, 128.6, 127.8, 94.9, 72.6, 70.6, 70.2, 69.9, 67.1, 63.0 ppm; HRMS (ESI): *m/z* calcd for $C_{41}H_{34}O_{10}S$ $[M+Na]^+$: 741.1770; found 741.1738.

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[1] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; c) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015.

[2] a) A. Dondoni, *Chem. Asian J.* **2007**, *2*, 700–708; b) S. Dedola, S. A. Nepogodiev, R. A. Field, *Org. Biomol. Chem.* **2007**, *5*, 1006–1017; c) F. Nicotra, L. Cipolla, F. Peri, B. La Ferta, C. Redaelli, *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 353–398; d) Z. Gyorgydeak, J. Thiem, *Adv. Carbohydr. Chem. Biochem.* **2006**, *60*, 103–182; e) F. Santoyo-Gonzalez, F. Hernandez-Mateo, *Top. Heterocycl. Chem.* **2007**, *7*, 133–177; f) R. J. Pieters, D. T. S. Rijkers, R. M. S. Liskamp, *QSAR Comb. Sci.* **2007**, *26*, 1181–1190; g) S. R. Hanson, W. A. Greenberg, C.-H. Wong, *QSAR Comb. Sci.* **2007**, *26*, 1243–1252; h) B. L. Wilkinson, L. F. Bornaghi, T. A. Houston, S.-A. Poulsen in *Drug Des. Res. Perspectives* (Ed.: S. P. Kaplan), Nova Science Publishers, Hauppauge, **2007**, pp. 57–102.

[3] Simple azidomethyl ethers have been prepared from methylthio ethers and chloromethyl ethers in the presence of azide anion, and have been used as protecting groups in nucleoside chemistry but the azidomethyl glycosides appear to be unknown; a) S. Zavgorodny, M. Polyanski, E. Besidsky, E. Kriukov, A. Sanin, M. Pokrovskaya, G. Gurskaya, H. Lönnberg, A. Azhayev, *Tetrahedron Lett.* **1991**, *32*, 7593–7596; b) S. G. Zavgorodny, A. E. Pechenov, V. I. Shvets, A. I. Miroshnikov, *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 1977–1991; c) J. Guo, N. Xu, Z. Li, S. Zhang, J. Wu, D. H. Kim, M. S. Marma, Q. Meng, H. Cao, X. Li, S. Shi, L. Yu, S. Kalachikov, J. J. Russo, N. J. Turro, J. Ju, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 9145–9150; d) B. Loubinoux, S. Tabbache, P. Gerardin, J. Mlazimbakana, *Tetrahedron* **1988**, *44*, 6055–6064; e) T. Young, L. L. Kiessling, *Angew. Chem.* **2002**, *114*, 3599–3601; *Angew. Chem. Int. Ed.* **2002**, *41*, 3449–3451.

[4] X. Zhu, R. R. Schmidt, *J. Org. Chem.* **2004**, *69*, 1081–1085.

[5] L. L. Gundersen, T. Benneche, *Acta Chem. Scand.* **1991**, *45*, 975–977.

[6] a) R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123; b) F. Bien, T. Ziegler, *Tetrahedron: Asymmetry* **1998**, *9*, 781–790.

[7] We note that the use of more than 1.1 equivalent of silver triflate resulted in lower yields of product **3** and over activation leading, for example, to the formation of phenylthiomethoxymethyl glycosides. The moderate yields for the formation of **3** and **6** are to some extent the result of the relative instability of phenylthiomethanol under the coupling conditions.

[8] a) D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020; b) D. Crich, L. B. L. Lim, *Org. React.* **2004**, *64*, 115–251.

[9] The moderate yield is most likely due to the persistence of thiophilic species in the reaction mixture after the preactivation step.

[10] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

[11] Zemplen de-*O*-benzoylation of **10** and **11** gave mimics of methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside, the binding motif for the mannose-binding lectin concanavalin A. These compounds were found—by isothermal titration calorimetry—to have binding constants of 80.0 and $13.7\ M^{-1} \times 10^3$, respectively, for binding to concanavalin A. In contrast, the binding constant exhibited by methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside itself was $390\ M^{-1} \times 10^3$. The significantly reduced binding affinity exhibited by the two triazoles is attributed in part to the absence of the hydroxyl groups at C2 and C4 of the "reducing sugar" in methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside, which are known to contribute substantially to binding. G. H. Veeneman, G. A. van der Marel, H. Vandenelst, J. H. van Boom, *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 449–451.

[12] a) E. E. Simanek, G. J. McGarvey, J. A. Jablonowski, C.-H. Wong, *Chem. Rev.* **1998**, *98*, 833–862; b) A. Bernardi, P. Cheshev, *Chem. Eur. J.* **2008**, *14*, 7434–7441.

[13] a) N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755; b) R. Merkx, A. R.

Brouwer, D. T. S. Rijkers, R. M. J. Liskamp, *Org. Lett.* **2005**, *7*, 1125 – 1128.

[14] a) M. B. Soellner, B. L. Nilsson, R. T. Raines, *J. Am. Chem. Soc.* **2006**, *128*, 8820 – 8828; b) C. Grandjean, A. Boutonnier, C. Guerreiro, J.-M. Fournier, L. A. Mulard, *J. Org. Chem.* **2005**, *70*, 7123 – 7132.

[15] a) B. L. Nilsson, L. L. Kiessling, R. T. Raines, *Org. Lett.* **2000**, *2*, 1939 – 1941; b) E. Saxon, J. I. Armstrong, C. R. Bertozzi, *Org. Lett.* **2000**, *2*, 2141 – 2143; c) C. P. R. Hackenberger, D. Schwarzer, *Angew. Chem. Int. Ed.* **2008**, *47*, 10030 – 10074; d) M. D. Best, *Biochemistry* **2009**, *48*, 6571 – 6584; e) A. Dirksen, P. E. Dawson, *Curr. Opin. Chem. Biol.* **2008**, *12*, 760 – 766.

[16] a) L. F. Tietze, R. Fischer, H. J. Guder, M. Neumann, *Liebigs Ann. Chem.* **1987**, 847 – 856; b) L. F. Tietze, R. Fischer, *Angew. Chem.* **1981**, *93*, 1002; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 969 – 970; c) L. F. Tietze, R. Fischer, *Tetrahedron Lett.* **1981**, *22*, 3239 – 3242.

[17] a) S. Jegge, J. Lehmann, *Carbohydr. Res.* **1985**, *142*, 47 – 59; b) L. F. Tietze, R. Seele, B. Leiting, T. Krach, *Carbohydr. Res.* **1988**, *180*, 253 – 262.

[18] The basic structural unit of the "acetal glycosides" occurs naturally in the 1,1′-disaccharides, in sucrose, in the iridoid glycosides, and in the *seco*-iridoid glycosides, albeit in a somewhat more complex form; a) L. F. Tietze, U. Niemeyer, P. Marx, K. H. Glusenkamp, L. Schwenen, *Tetrahedron* **1980**, *36*, 735 – 739; b) L. F. Tietze, U. Niemeyer, P. Marx, K. H. Glusenkamp, *Tetrahedron* **1980**, *36*, 1231 – 1236; c) L. F. Tietze, *Angew. Chem.* **1983**, *95*, 840 – 853; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 828 – 841; d) L. F. Tietze, R. Fischer, *Angew. Chem.* **1983**, *95*, 902; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 888; e) S. Oscarson, F. W. Sehgelmeble, *J. Am. Chem. Soc.* **2000**, *122*, 8869 – 8872.

