ORGANIC LETTERS

2004
Vol. 6, No. 13
2165−2168

# Thioglycuronides: Synthesis and Application in the Assembly of Acidic Oligosaccharides

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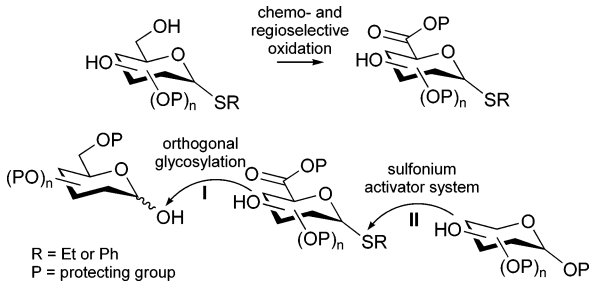
**Received April 6, 2004**

## ABSTRACT




**Partially protected thioglycuronic acids are prepared efficiently by chemo- and regioselective oxidation of the corresponding thioglycosides using the TEMPO/BAIB reagent combination. After esterification, the thioglycuronic acids proved to be useful as both donor and acceptor in sulfonium-mediated condensations toward acidic di- and trisaccharides.**

Uronic acids are present in a wide array of biologically relevant oligosaccharides, polysaccharides, and glycoconjugates.[1] Hence, flexible and straightforward synthesis routes toward these important molecules should have a major impact on research in glycobiology. Although it is well established that thioglycosides are versatile synthons en route toward such carbohydrate targets,[2] approaches in which thioglycuronic acids are employed are scarce. This can be explained by the lack of efficient synthetic protocols for the preparation of suitably protected thioglycuronides.[3] In addition, thioglycuronic acids have been shown to be rather poor glycosyl donors, generally requiring the presence of activating protecting groups.[3d] In our program directed toward the development of efficient methodologies for the preparation of biologically relevant oligosaccharides,[4] we recently reported a novel sequential glycosylation strategy (Figure 1, route A).[5] Our method is based on $Ph_2SO/Tf_2O$-mediated condensation[6] (**I**) of 1-hydroxyl donor **1** and

(1) (a) *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. P., Eds.; Marcel Dekker: New York, 2001; pp 425−492. (b) For a recent review on the synthesis of glycosaminoglycans, see: Yeung, B. K. S.; Chong, P. Y. C.; Petillo, P. A. *J. Carbohydr. Chem.* **2002**, *21*, 799−865.

(2) (a) For a review on the use of thioglycosides as glycosyl donors, see: Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179−205. (b) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, *14*, 2137−2160.

(3) The few methods known in the literature are mainly based on the use of chromium-based oxidants: (a) Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 1597−1600. (b) Nilsson, M.; Svahn, C.-M.; Westman, J. *Carbohydr. Res.* **1993**, *246*, 161−172. (c) Goto, F.; Ogawa, T. *Tetrahedron Lett.* **1993**, *33*, 5099−5102. (d) Garegg, P. J., Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200−2204. (e) Magaud, D.; Grandjean, C.; Doutheau, A.; Anker, D.; Shevchik, V.; Cotte-Pattat, N.; Robert-Baudouy, J. *Tetrahedron Lett.* **1997**, *38*, 241−244. (f) Allanson, N. M.; Liu, D.; Chi, F.; Jain, R. K.; Chen, A.; Ghosh, M.; Hong, L.; Sofia, M. J. *Tetrahedron Lett.* **1998**, *39*, 1889−1892.

(4) Codée, J. D. C.; Van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. *Eur. J. Org. Chem.* **2002**, *23*, 3954−3965.

(5) (a) Codée, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947−1950. (b) Codée, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *Tetrahedron* **2003**, *60*, 1057−1064.

10.1021/ol049380+ CCC: $27.50 
**Published on Web 05/22/2004**

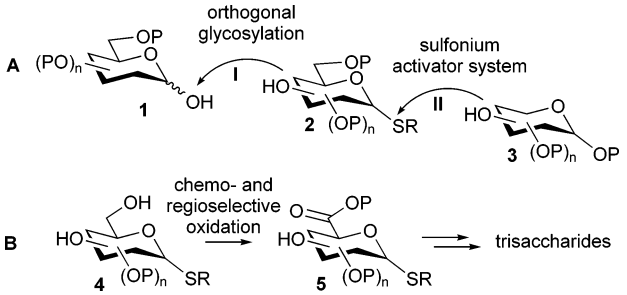



**Figure 1.** Glycosylation strategy toward acidic trisaccharides.

partially protected thioglycoside **2** to afford the corresponding thiodisaccharide. In the next glycosylation event (**II**), successive treatment of the intermediate thio function with sulfonium triflate species **7a** or **7b**, generated in situ from BSP/$Tf_2O$[7] or $Ph_2SO/Tf_2O$,[8] respectively (see Figure 2), and

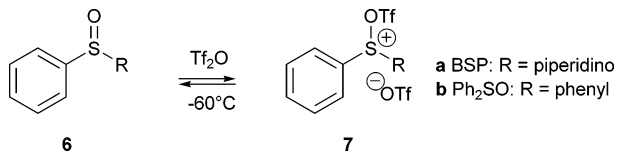
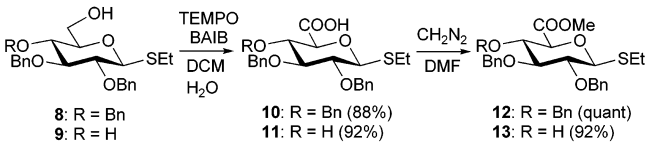



**Figure 2.** Recently developed sulfonium triflate activator systems.

subsequent addition of a suitably protected nucleophile **3** afforded the desired trisaccharide. The potency of the novel activator systems **7a** and **7b** in these syntheses encouraged us to evaluate the highly unreactive thioglycuronides in the aforementioned glycosylation sequence. This evidently called for an efficient mode of synthesis to access a wide variety of thioglycuronic acid synthons. We here disclose the 2,2,6,6-tetramethyl-1-piperidinyloxyl, free radical (TEMPO)/[bis-(acetoxy)-iodo]benzene (BAIB)-mediated chemo- and regioselective oxidation of readily available partially protected thioglycosides as a powerful means to obtain the corresponding thioglycuronic acids (Figure 1, route B).[9] After esterification of the carboxylate functions, these partially protected thioglycuronides **5** can, in the same way as key building block **2**, be incorporated in our strategy to furnish acidic oligosaccharides.

Piancatelli and co-workers[9] recently reported the oxidation of primary alcohols into their corresponding aldehydes[10] using TEMPO and an equimolar amount of BAIB as a co-oxidant. Interestingly, this oxidation protocol could also be applied to alcohols containing sulfo- and selenoethers. We set out to establish whether this reagent combination could be employed for the selective oxidation of suitably protected thioglycosides to provide the corresponding thioglycuronic acids. As the initial research objective, we evaluated the compatibility of the TEMPO/BAIB system with thiogluco-pyranosides **8** and **9** (Scheme 1). Treatment of ethyl 2,3,4-

**Scheme 1**




tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside **8** with a catalytic amount of TEMPO and excess BAIB in a mixture of dichloromethane and water (2:1), followed by methylation of the thus-formed carboxylate **10** with freshly prepared diazomethane afforded thioglucuronide **12** in a rewarding 88% yield over the two steps. It should be noted that careful monitoring of the reaction mixture by TLC and timely quenching, with an aqueous thiosulfate solution, could adequately prevent unwanted sulfoxide and/or sulfone formation. Following the same sequence of reactions, ethyl 2,3-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside **9** was converted into methyl ester **13** in 85% (based on **9**), demonstrating the excellent chemo- and regioselective nature of this method.

The results of the TEMPO/BAIB oxidation of a variety of thio- and selenoglycosides are summarized in Table 1. Phenyl 2,3,4-tri-*O*-benzoyl-1-seleno-α-D-galactopyranoside **14** was also readily transformed, via acid **15**, into galacturonic ester **16** (entry 1). In the same way, subjection of phenyl 2,3-*O*-isopropylidene-4-*O*-benzyl-1-thio-α-D-mannopyranoside **17** to the two-step procedure produced ester **19** (entry 2). The selectivity of our strategy in the oxidation of a primary alcohol in the presence of both a thioglycosidic linkage and a secondary alcohol is revealed in entries 3−8. Both *S*-phenyl- and *S*-ethylthioglycosides can be employed in our strategy, as is illustrated by the equally efficient transformation of **20** and **21** into **24** and **25**, respectively. Furthermore, both the starting glycoside (glucose, glucosamine, galactose, and idose) and the nature of the protective groups (benzyl, benzoyl, isopropylidene, *tert*-butyldimethylsilyl, azide, and phthalimide) can be readily varied without having major implications on the outcome of the oxidation step (all yields are within the range of 70−90%).

As the next research objective, we set out to establish the reactivity of the obtained thioglycuronates in sulfonium triflate-mediated glycosylation reactions. The reactivity of these thioglycuronic acids toward various activating systems is considerably reduced compared to the corresponding thioglycosides due to the electron-withdrawing effect of the carboxyl function. Illustrative examples of this phenomenon

(6) (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269−4279.

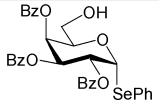
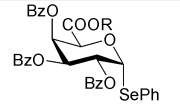
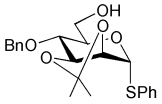
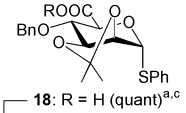
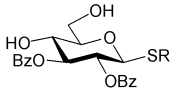
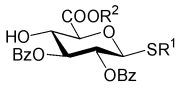
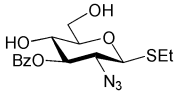
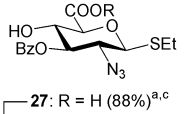
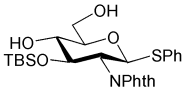
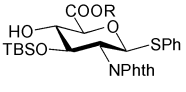
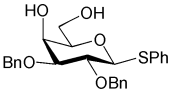
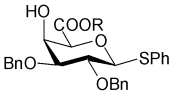
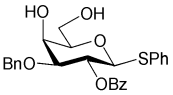
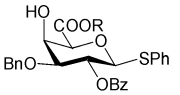
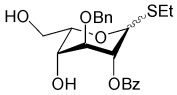
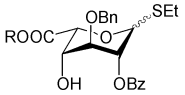
(7) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020.

(8) Codée, J. D. C.; Litjens, R. E. J. N.; Den Heeten, R.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.

(9) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.

(10) Use of high concentrations of water and 2 equiv of BAIB facilitates the conversion of the aldehyde into the respective carboxylic acid: Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293−295. See also ref 9.

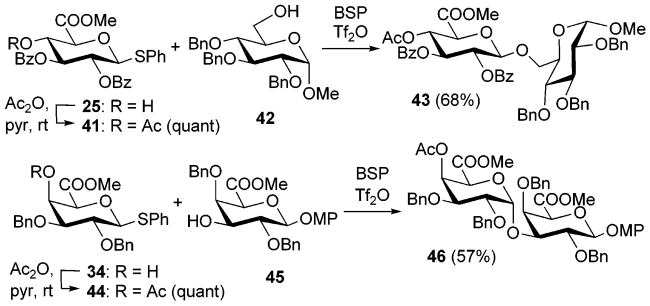
**Table 1.** Regio- and Chemoselective Oxidation of Thioglycosides

| entry | substrate | product |
|---|---|---|
| 1 |  **14** |  **15**: R = H (61%)[a,c] → **16**: R = Me (83%)[b,c] |
| 2 |  **17** |  **18**: R = H (quant)[a,c] → **19**: R = Me (81%)[b,c] |
| 3 |  **20**: R = Et, **21**: R = Ph |  **22**: $R^1$ = Et, $R^2$ = H (76%)[a,c] → **24**: $R^1$ = Et, $R^2$ = Me (83%)[b,c]; **23**: $R^1$ = Et, $R^2$ = H (81%)[a,c] → **25**: $R^1$ = Et, $R^2$ = Me (86%)[b,c] |
| 4 |  **26** |  **27**: R = H (88%)[a,c] → **28**: R = Me (80%)[b,c] |
| 5 |  **29** |  **30**: R = H (67%)[a,c] → **31**: R = Me (80%)[b,c] |
| 6 |  **32** |  **33**: R = H (85%)[a,c] → **34**: R = Me (93%)[b,c] |
| 7 |  **35** |  **36**: R = H (85%)[a,c] → **37**: R = Me (93%)[b,c] |
| 8 |  **38** |  **39**: R = H (84%)[a,c] → **40**: R = Me (96%)[b,c] |

[a] Conditions: 0.2 equiv TEMPO, 2.5 equiv BAIB, $DCM/H_2O$ (2:1), rt. [b] Conditions: $CH_2N_2$, DMF, rt. [c] Isolated yields.

were published by the groups of Garegg and Oscarson who had to install at least two activating benzyl functions or a 3,4-tetraisopropyldisiloxyl group in the thioglucuronate donors to obtain sufficient activation with dimethyl(methylthio)sulfonium triflate (DMTST).[3d,11] We reasoned that the reactive benzenesulfinylpiperidino bistriflate **7a**[7] would be sufficiently electrophilic for reaction with the highly "disarmed", acylated donor **41** and the benzylated donor **44**. Indeed, preactivation of **41** occurred smoothly and subsequent addition of acceptor **42** afforded the corresponding disaccharide **43** in good yield. Compared to the standard

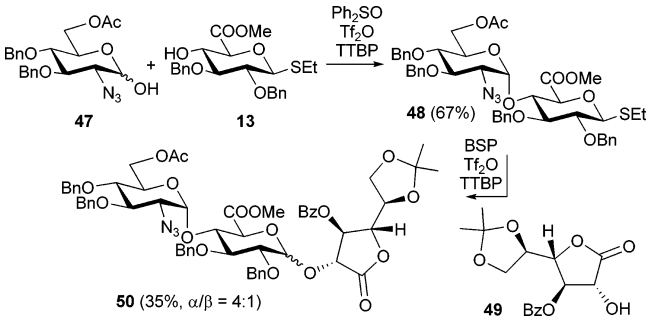
**Scheme 2**




conditions prescribed by the Crich laboratory, higher activation temperatures and longer activation times were needed.[12] Analogous results were obtained in the glycosylation of the more reactive thiogalactoside donor **44** with acceptor **45** delivering diuronate **46**.

Having established that thioglycuronates could be readily applied as donors in the sulfonium activator-mediated disaccharide synthesis, we turned our attention to their implementation in the sequential chemoselective synthesis of trisaccharide **50**. This protected carbohydrate motive corresponds to the (Glc*p*NAcα(1→4)-Glc*p*Aα(1→2)Gal*f*) trisaccharide present in the capsular polysaccharide of the Fungus *Fusarium* sp. M7-1.[13] Activation of hemiacetal donor **47** with diphenylsulfonium bistriflate **7b** in the presence of tri-*tert*-butylpyrimidine (TTBP)[14] (Scheme 3) as a base and

**Scheme 3**




subsequent treatment with uronic acid acceptor **13** gave the α-linked thiodisaccharide **48** as the sole product in a gratifying 67% yield. In the second glycosylation event, **48** was smoothly activated under the agency of BSP/$Tf_2O$ and

(11) Krog-Jensen, C.; Oscarson, S. *Carbohydr. Res.* **1998**, *308*, 287−296.

(12) Activation of the donor for 5 min at −60 °C revealed incomplete activation of the donor glycoside. We therefore started the activation at −60 °C and gradually warmed the reaction mixture to −40 °C within 15 min (see also ref 7).

(13) (a) Iwahara, S.; Suemori, N.; Ramli, N.; Takegawa, K. *Biosci. Biotech. Biochem.* **1995**, *59*, 1082−1085. (b) Jikibara, T.; Takegawa, K.; Iwahara, S. *J. Biochem.* **1992**, *111*, 225−229.

(14) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.

condensed with partially protected galactono-1,4-lactone **49**[15] to give the desired trisaccharide **50** as an anomeric mixture ($\alpha/\beta$ = 4:1) in 35% yield.

In conclusion, we have presented a novel and efficient strategy for the regio- and chemoselective oxidation of thioglycosides to give the corresponding thioglycuronides. In turn, these thioglycuronides proved to be useful as both acceptors and donors in the synthesis of acidic oligosaccharides as exemplified by the assembly of trisaccharide **50**. Further, the efficient BSP/$Tf_2O$ activator system proved to be capable of activating even the highly deactivated donor **41**. Our strategy nicely complements contemporary synthetic efforts toward uronic acid-containing oligosaccharides, which are often based on the introduction of the carboxylate functions after oligosaccharide assembly. The efficiency of oligosaccharide synthesis using these thioglycuronic acid donors is somewhat compromised by the reduced reactivity of the anomeric center compared to the parent thioglycosides. The yields observed in the presented examples are in the range of 35−68%. However, we feel that the partial loss in glycosylation efficiency is more than compensated by the reduced number of protecting group manipulations required. Current research efforts are aimed at the optimization of our glycosylation procedure and its application in the synthesis of more complex uronic acid-containing oligosaccharides.

(15) For preparation of compound **49**, galactono-1,4-lactone was subsequently treated with (1) $Me_2C(OMe)_2$, *p*-TsOH, acetone; (2) TBDMSCl, imidazole, DCM, 0°C; (3) BzCl, pyridine, 0 °C; and (4) TBAF, AcOH in THF (62% over four steps).

**Acknowledgment.** The authors thank Kees Erkelens en Fons Lefeber for recording NMR spectra and Bertil Hofte for measuring accurate mass spectra. This work was supported by The Netherlands Technology Foundation (STW) and the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO).

**Supporting Information Available:** General procedures and characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049380+