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Preparation of 1-Thio Uronic Acid Lactones and Their Use in Oligosaccharide Synthesis

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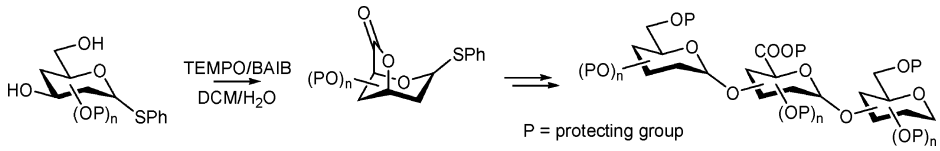
ABSTRACT



The chemo- and regioselective TEMPO/BAIB-mediated oxidation of 2,6- and 3,6-dihydroxy 1-thio glycopyranosides to the corresponding 1-thio uronic acid lactones is described. These locked 1-thio glycuronides can directly be used as donors in glycosidation reactions using the Ph_2SO/Tf_2O reagent system. Alternatively, selective opening of the lactone bridge liberates a hydroxyl function for ensuing glycosylations.

The 2,2,6,6-tetramethylpiperidinyloxy free radical **1** (TEMPO, Figure 1A) is a versatile and often applied reagent for the selective oxidation of primary hydroxyl functions. The active species in this reaction is believed to be the *N*-oxoammonium salt **2**, generated in situ from reaction between TEMPO (**1**) and any of a number of co-oxidants. Many co-oxidants have been used, for instance, *m*-chloroperoxybenzoic acid,[1] calcium or sodium hypochlorite,[2] and several hypervalent iodine(III) species.[3] Piancatelli and co-workers revealed that

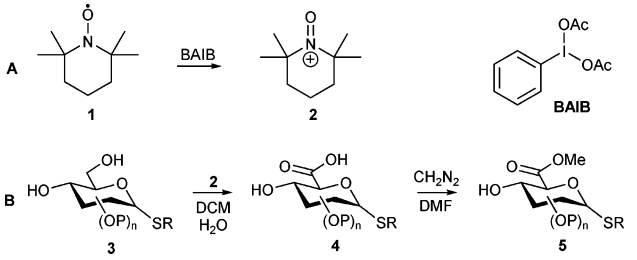


Figure 1. TEMPO/BAIB-mediated chemo- and regioselective oxidation.

the combination of TEMPO and [bis(acetoxy)iodo]benzene (BAIB) enabled the chemo- and regioselective oxidation of primary alcohols into the corresponding aldehydes.[4,5] The Forsyth group used the same reagent combination for the synthesis of δ-lactones from the corresponding 1,5-diol systems having a primary and secondary hydroxyl function.[6]

(1) (a) Cella, J. A.; Kelley, J. A.; Kenhan, E. F. *J. Org. Chem.* **1975**, *40*, 1860−1862. (b) Ganem, B. *J. Org. Chem.* **1975**, *40*, 1998−2000. (c) Cella, J. A.; McGrath, J. P.; Kelley, J. A.; El Soukkary, O.; Hilpert, L. *J. Org. Chem.* **1977**, *42*, 2077−2080.

(2) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972. (c) Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177−2180. (d) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181−1184. (e) De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Carbohydr. Res.* **1995**, *269*, 89−98. (f) Haller, M.; Boons, G.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 814−822. (g) Litjens, R. E. J. N.; Den Heeten, R.; Timmer, M. S. M.; Overkleeft, H. S.; Van der Marel, G. A. *Chem. Eur. J.* **2005**, *11*, 1010−1016.

(3) (a) Spyroudis, S.; Varvoglis, A. *Synthesis* **1975**, 445−447. (b) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773−2776. (c) Muller, P.; Godoy, J. *Tetrahedron Lett.* **1981**, *22*, 2361−2364. (d) Muller, P.; Godoy, J. *Helv. Chim. Acta* **1983**, *66*, 1790−1795. (e) Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2417−2427. (f) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406−3418.

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

(5) Oxidation toward the carboxylic acid, see: Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293−295.

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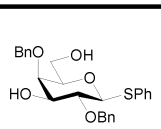
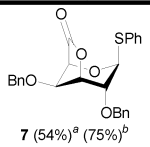
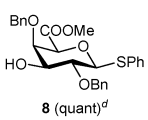
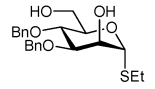
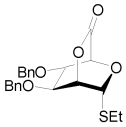
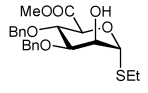
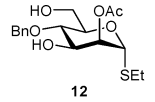
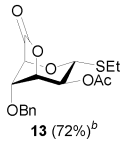
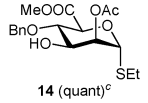
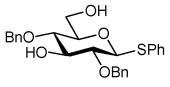
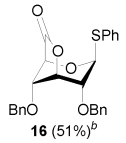
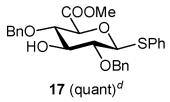
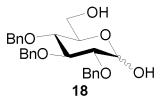
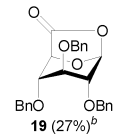
Studies on the latter process revealed the occurrence of a lactol intermediate formed by selective oxidation of the primary hydroxyl function and ensuing nucleophilic attack of the secondary alcohol on the resulting aldehyde. In the next oxidation cycle, the lactol is oxidized to the lactone.[7]

We recently demonstrated the efficacy of the TEMPO/BAIB reagent system in the chemo- and regioselective oxidation of a variety of 4,6-dihydroxy 1-thioglycosides (**3**, Figure 1B).[8] The 1-thio uronic esters (**5**), obtained by treatment of **4** with diazomethane, proved to be valuable building blocks in oligosaccharide synthesis.[9]

In an extension of the above-described method for the selective oxidation of 4,6-dihydroxy 1-thioglycosides, we here report on a tandem oxidation−lactonization process of a variety of 2,6- and 3,6-dihydroxy 1-thioglycosides and application of the resulting 6,2- and 6,3-lactones in oligosaccharide synthesis.

In a first attempt to induce lactone formation (Table 1, entry 1), phenyl 2,3-di-*O*-benzyl-1-thio-*β*-D-galactopyranoside **6** was treated with 0.2 equiv of TEMPO and 2.5 equiv of BAIB in anhydrous dichloromethane. The expected 6,3-lactone[10] **7** was obtained in 54% yield along with a considerable amount of sulfoxide and sulfone byproducts.

Table 1.

entry	substrate	lactone (yield)[e]	ester (yield)[e]
1	 **6**	 **7** (54%)[a] (75%)[b]	 **8** (quant)[d]
2	 **9**	 **10** (77%)[b]	 **11** (quant)[c]
3	 **12**	 **13** (72%)[b]	 **14** (quant)[c]
4	 **15**	 **16** (51%)[b]	 **17** (quant)[d]
5	 **18**	 **19** (27%)[b]	---

[a] Conditions: 0.2 equiv of TEMPO, 2.5 equiv of BAIB, DCM, rt. [b] Conditions: 0.2 equiv of TEMPO, 2.5 equiv of BAIB, DCM/H_2O (2:1), rt. [c] Conditions: MeOH, reflux. [d] Conditions: catalytic H^+, MeOH, rt. [e] Isolated yields.

Changing the reaction medium to the biphasic dichloromethane/water system led to the rapid and efficient transformation of diol **6** to lactone **7** (75% yield) with only trace amounts of side-products formed. Subjection of ethyl 3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside **9**, having a 2,6-*cis*-diol configuration, to the latter oxidation conditions afforded lactone product **10** in 77% yield. Similarly, glycopyranosides **12** and **15** were converted into lactones **13** and **16** (entries 3 and 4). The relatively poor yield in transforming glucopyranoside **15** into lactone **16** is likely due to the change from the "all-equatorial" $^4C_1$ conformation into the $^1C_4$ conformation having all substituents in an axial orientation. As a final example, compound **18** containing an anomeric hydroxyl group was converted into the corresponding 6,1-lactone **19**, albeit in moderate yield (27%).

Our next objective was to identify suitable conditions for selective opening of the lactone bridge, liberating a hydroxyl function for potential functionalization in ensuing glycosylation events. Stirring compounds **10** and **13** in anhydrous methanol under a gentle reflux furnished the corresponding transesterified products **11** and **14** (entries 2 and 3) in a quantitative yield. As exemplified in entry 3, the relatively labile acetyl group is stable with respect to the cleavage conditions of the lactone bridge.[11] The lactone function in compounds **7** and **16** (entries 1 and 4) could not be opened under these conditions, most likely due to steric hindrance of the bulky benzyl and thiophenyl groups. However, stirring **7** and **16** in methanol and a catalytic amount of *p*-toluenesulfonic acid at ambient temperature delivered the desired esters **8** and **17**, respectively, in a quantitative yield.

The conformationally locked lactones (**7**, **10**, **13**, **16**) bear promising properties in stereoselective glycosylation.[12] It is now well established that the conformation of donor glycosides can play a pivotal role in governing both reactivity and anomeric selectivity in glycosidations. For example, Fraser-Reid and co-workers reported that benzylidene-protected glycosides are less reactive than their benzylated counterparts.[13] This difference in reactivity stems from "torsional disarmament" and has been exploited to increase anomeric selectivities.[14] It has been stated that, in a glycosylation event, torsional effects are, in general, overruled by

(6) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J. H.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57−59.

(7) For a comprehensive review on the mechanism of TEMPO oxidations, see: De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153−1174.

(8) Van den Bos, L. J.; Codée, J. D. C.; Van der Toorn, J. C.; Boltje, T. J.; Van Boom, J. H.; Overkleeft, H. S.; Van der Marel, G. A. *Org. Lett.* **2004**, *6*, 2165−2168.

(9) For a review on the oxidation of carbohydrates using TEMPO, see: Bragd, P. L.; Van Bekkum, H.; Besemer A. C. *Top. Catal.* **2004**, *27*, 49−66.

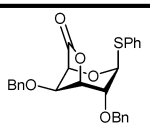
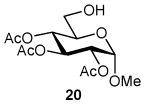
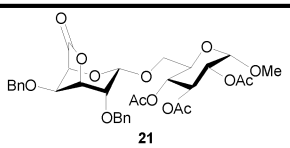
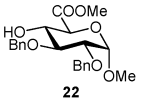
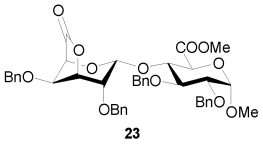
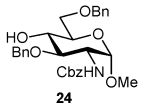
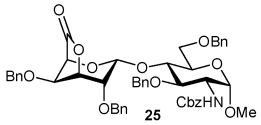
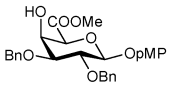
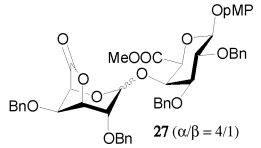
(10) Formation of the lactone ring was confirmed by the change in coupling constant between H-1 and H-2. The doublet in compound **6** ($^3J_{1,2}$ = 7.1 Hz) was transposed into a singlet after the oxidation−lactonization process.

(11) (a) Chernyak, A. Y.; Kononov, L. O.; Kochetkov, N. K. *Carbohydr. Res.* **1992**, *216*, 381−398. (b) Kornilov, A. V.; Sherman, A. A.; Kononov, L. O.; Shashkov, A. S.; Nifant'ev, N. E. *Carbohydr. Res.* **2000**, *329*, 717−730.

(12) For a related study on the use of 6,1-lactones, see: Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem., Int. Ed.* **2004**, *116*, 2572−2575.

(13) Fraser-Reid, B.; Wu, Z. F.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435.

Table 2.

entry	donor	acceptor	activator/yield[a]	disaccharide
1	 **7**	 **20**	Ph_2SO, Tf_2O[b] 98%	 **21**
2	**7**	 **22**	Ph_2SO, Tf_2O[b] 91%	 **23**
3	**7**	 **24**	Ph_2SO, Tf_2O[c] 69%	 **25**
4	**7**	 **26**	Ph_2SO, Tf_2O[b] 50%	 **27** ($\alpha/\beta = 4/1$)

[a] Isolated yields. [b] Performed with 2.5 equiv of TTBP. [c] Performed with 1 equiv of TTBP.

the electronic effects exerted by the ring substituents.[15] At the same time, Bols and co-workers demonstrated that, in the case of $^1C_4$-locked methyl 3,6-anhydro-β-D-glycosides, the reactivity of the anomeric function is influenced by electronic effects originating from the orientation of the remaining hydroxy substituents.[16] In this respect, we previously found that the remotely attached carboxylic ester on the 6-position decreases the nucleophilicity of the sulfur atom at the anomeric center.[8] The intrinsic low reactivity of these 1-thio methyl uronates could be overcome by activation with the highly electrophilic Ph_2SO/Tf_2O reagent combination at slightly elevated temperature (−40 °C) compared to the standard activation temperature (−60 °C).[17] Galactosyl donor **7** was chosen as a model compound to determine the influence of the bridged lactone function in glycosidation reactions (Table 2). Treatment of lactone **7** with 1.3 equiv of Ph_2SO, 1.3 equiv of Tf_2O, and 2.5 equiv of TTBP at −50 °C gave full activation within 15 min. Addition of acceptor **20**, bearing a primary hydroxyl group, afforded disaccharide **21** in a near quantitative yield. Spectroscopic analysis revealed the presence of an α-interglycosidic linkage. This anomeric outcome is in accord with earlier studies showing that the coupling of "disarmed" gluco- and galactopyranosyl donors with disarmed acceptors proceeds in an α-selective fashion.[8,18] Analogously, methyl uronate **22** was applied as an acceptor species in the Ph_2SO/Tf_2O-mediated glycosidation involving donor **7**, resulting in α-selective formation of disaccharide **23** in 91% yield (entry 2). Changing the acceptor toward *N*-(benzyloxycarbonyl)-protected glucosamine **24** also delivered, fully α-selectively, the corresponding disaccharide **25**. This reaction proceeded slower compared to the other glycosidations, probably due to reduced reactivity of the acceptor alcohol via intramolecular H-bonding.[19] The amount of base (TTBP) used in this condensation was reduced to 1 equiv with respect to the amount of Tf_2O to circumvent possible side-reactions involving the nucleophilic N-atom.[20] Performing the reaction in the absence of base gave no significant rise in yield. Upon addition of galactopyranose **26** to the activated mixture of donor **7**, Ph_2SO, and Tf_2O, a 4:1 mixture of α- and β-disaccharides **27** was formed (entry 4). The reduced stereoselectivity may be related to the axial orientation of OH-4 in acceptor **26**, hampering the formation of the α-product.[21]

(14) (a) Grice, P.; Ley, S. V.; Pietruszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, *3*, 431−440. (b) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−66. (c) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53−80. (d) Litjens, R. E. J. N.; Leeuwenburgh, M. A.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8693−8696. (e) Crich, D.; De la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142−8148. (f) Jensen, H. H.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.

(15) Dean, K. E. S.; Kirby, A. J.; Komarov, I. V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 337−341.

(16) Bols and co-workers found that $^1C_4$-locked methyl 3,6-anhydro-β-D-glucoside hydrolyzes much faster than the corresponding nonlocked $^4C_1$ methyl β-D-glucoside: McDonnell, C.; López, O.; Murphy, P.; Fernández Bolaños, J. G.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374−12385.

(17) (a) 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. (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.

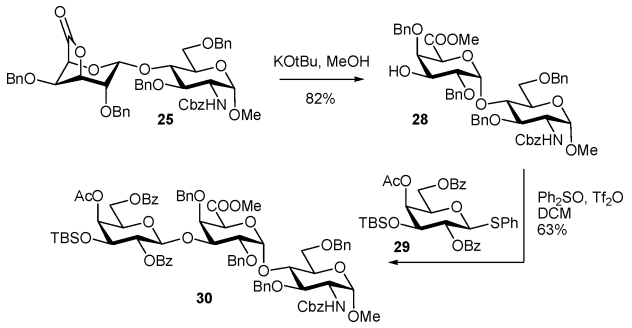
(18) (a) Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297−1300 and references therein. (b) Codée, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947−1950. (c) Codée, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; Van Boeckel, C. A. A.; Van Boom, J. H.; Van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767−3773.

(19) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819−6825.

(20) Van den Bos, L. J.; Codée, J. D. C.; Van Boom, J. H.; Overkleeft, H. S.; Van der Marel, G. A. *Org. Biomol. Chem.* **2003**, 4160−4165.

Having established that locked 1-thio uronic acid lactones can be used as donors in glycosylation reactions, we set out to explore their acceptor properties after opening of the lactone bridge. Disaccharide **25** was taken as a model compound toward the synthesis of nonnatural trisaccharide **30** (Scheme 1). Treatment of benzylated lactone **25** with

Scheme 1



potassium *tert*-butoxide in MeOH, under strictly anhydrous conditions, afforded in 82% the desired acceptor **28**. Preactivation of 2-O-acylated donor **29** using diphenylsulfonium bistrifluoromethanesulfonate at −60 °C in dichloromethane followed by addition of acceptor **28** afforded trisaccharide **30** in 63% yield. The regular acid scavenger TTBP was excluded from the reaction mixture to prevent putative ortho ester formation.

In summary, we have developed an efficient route for the synthesis of locked 1-thio 6,2- and 6,3-lactones and their implementation as both donor and acceptor in Ph_2SO/Tf_2O-mediated coupling reactions. Further research is being devoted to comparing the open 1-thio uronic acids with their corresponding locked forms and the implementation of these 1-thio uronates in the synthesis of complex oligosaccharides.

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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.

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(21) Spijker, N. M.; Van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180−183.