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Stereoselective Synthesis of 2-*S*-Phenyl-2-deoxy-β-glycosides Using Phenyl 2,3-*O*-Thionocarbonyl-1-thioglycoside Donors via 1,2-Migration and Concurrent Glycosidation

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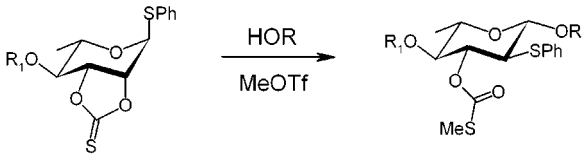
ABSTRACT



1,2-Migration and concurrent glycosidation of phenyl 2,3-*O*-thionocarbonyl-1-thio-α-L-rhamnopyranosides under the action of methyl trifluoromethanesulfonate (MeOTf) afforded in high yields the 3-*O*-(methylthio)carbonyl-2-*S*-phenyl-2,6-dideoxy-β-L-glucopyranosides, ready precursors to the corresponding 2-deoxy-β-glycosides.

2-Deoxyglycosides exist as important structural components in many antibiotics (e.g., macrolides, anthracyclins, aureolic acids, and enediynes),[1] cardiac glycosides,[2] and pregnane glycosides.[3] Consequently, considerable efforts have been given to the synthesis of 2-deoxyglycosides.[4] In comparison to the synthesis of other glycosides, stereocontrolled construction of the 2-deoxyglycosidic linkages is particularly challenging, because the absence of a functionality at C-2 excludes neighboring group assistance during glycosylation and furthermore enhances the lability of the resulting 2-deoxyglycosidic linkages. Direct glycosylation with 2-deoxyglycosyl donors provides the α-glycosides dominantly as controlled by the anomeric effect.[5] 2-Deoxy-β-glycosides have mostly been synthesized by using donors with equatorial C-2 heteroatom substituents (e.g., Br,[6] I,[7] SR,[8−14] SeR,[15] NHCHO,[16] OAc,[16] and OC(S)Ph[17]), which act as directing groups and are removed after the glycosylation event. The

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(4) For reviews, see: (a) Boons, G.-J. *Contemp. Org. Synth.* **1996**, 173. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (c) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, 154, 285.

(5) Schene, H.; Waldmann, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2759 and references therein.

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(7) (a) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1*, 891. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (c) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990.

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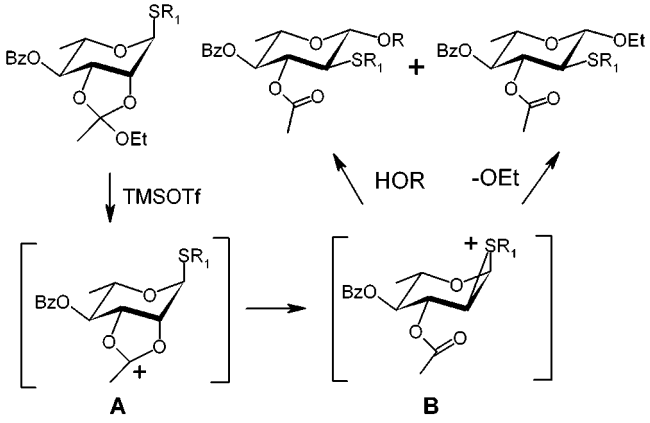
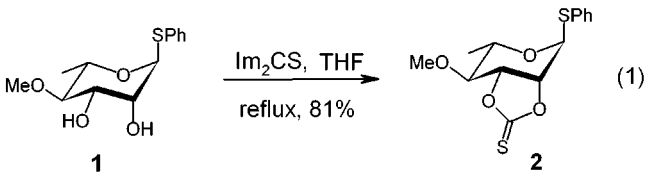
preparation of these donors often requires specialized methods. 1,2-Migration and concurrent glycosidation of 1-thioglycosides provides a facile stereocontrolled approach to the synthesis of 2-thioglycosides.[9−14] The migration is facilitated by a "pull" from the C-2 initiated by the departure of a leaving group and a "push" from the ring oxygen lone pair of electrons, providing the groups involved are in *trans*-configuration. A 1,2-episulfonium is believed to be involved, resulting in the stereoselective formation of the 1,2-*trans* glycosides.[18] The "pull" has been installed by a mesyl,[9] hydroxyl (under the action of the Mitsunobu conditions[10] or DAST[8a]), a phenoxythiocarbonyl group[11] (upon subjection to NIS/TfOH), or incidentally, a 2,3-*O*-ortho ester,[12] or even a remote 3,4-*O*-benzyldioxonium cation.[13] We recently reported that ethyl(phenyl) 2,3-*O*-ethoxyethylidene-1-thio-α-mannopyranosides were easily accessible donors for the expeditious preparation of 2-*S*-ethyl(phenyl)-2-deoxy-*β*-glucopyranosides via 1,2-migration and concurrent glycosidation; however, an inherent competing glycosidation by the ethoxy group resulting from the 2,3-ortho ester donors diminished the utility of this protocol[14] (Scheme 1). To

Scheme 1

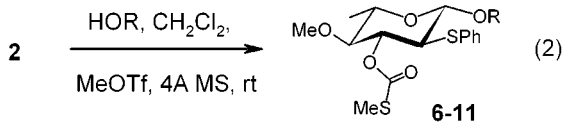


circumvent this drawback, we developed phenyl 2,3-*O*-thionocarbonyl-1-thio-α-mannopyranosides as donors instead. Some preliminary results are herewith reported.

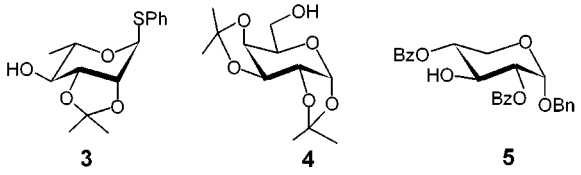
Phenyl 4-*O*-methyl-2,3-*O*-thionocarbonyl-1-thio-α-L-rhamnopyranoside (**2**) was readily prepared from 2,3-diol **1** in the presence of 1,1′-thiocarbonyldiimidazole in refluxing THF (2 h, 81%) (eq 1). It was known that the sulfur of the



thionocarbonyl moiety was prone to be methylated with methyl iodide,[19] and on the other hand activation of the anomeric alkylthio group of a thioglycoside with MeOTf was also viable.[20] We anticipated that the former process would prevail upon treatment of 2,3-*O*-thionocarbonate **2** with MeOTf to generate the 2,3-*O*-methylthiodioxonium cation, which would then lead to the 1,2-episulfonium intermediate and finally the 1,2-migration glycosidation product in the presence of an alcohol acceptor. Indeed, when benzyl alcohol, cyclohexanol, cholesterol, and sugar alcohols **3**, **4**, and **5**[21] were employed as acceptors, the expected 3-*O*-(methylthio)-carbonyl-2-*S*-phenyl-2,6-dideoxy-*β*-L-glucopyranosides **6**−**11** were readily obtained in satisfactory yields (eq 2 and Table



HOR = Benzyl alcohol, cyclohexanol, cholesterol, and



1). No α-anomers were detected.[22] A typical reaction involved the addition of MeOTf (1.2 equiv) to a mixture of the donor (1.0 equiv), acceptor (1.5 equiv), and 4Å molecular sieves in methylene chloride at room temperature, leading

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(17) Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501.

(18) Calculations using both MNDO semiempirical and high-level ab initio methods argued that the glycosyl oxacarbenium ions were likely to be of the lower energy; see: (a) Jones, D. K.; Liotta, D. C. *Tetrahedron Lett.* **1993**, *34*, 7209. (b) Dudley, T. J.; Smoliakova, I. P.; Hoffmann, M. R. *J. Org. Chem.* **1999**, *64*, 1247. And indeed, experimental results of producing the anomeric isomers have also been reported.[9a]

(19) (a) Patroni, J. J.; Stick, R. V. *Aust. J. Chem.* **1987**, *40*, 795. (b) Patroni, J. J.; Stick, R. V.; Tilbrook, D. M. G.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1989**, *42*, 2127.

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(22) The ^{1}H NMR signals for the corresponding 3-*O*-(methylthio)-carbonyl-2-*S*-phenyl-2,6-dideoxy-*β*-L-glucopyranosyl residue are very diagnostic. In compound **6** (for an example): δ 5.06 (dd, 1 H, J = 11.4, 9.0, H-3), 4.35 (d, 1 H, J = 8.9, H-1), 3.46 (s, 3 H, OCH_3), 3.31 (m, 1 H, H-5), 3.08 (dd, 1 H, J = 11.4, 8.8, H-4), 2.94 (t, 1 H, J = 9.1, H-2), 2.41 (s, 3 H, SCH_3), 1.34 (d, 3 H, J = 7.5, H-6).

Table 1. Glycosidation with 2,3-*O*-Thionocarbonate **2**

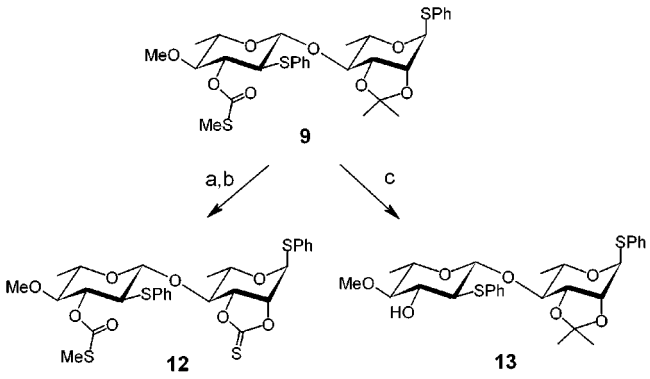
entry	acceptor	product	yield (%)
1	BnOH	**6**	79[a]; 86[b]
2	$C_6H_{11}OH$	**7**	78[a]
3	cholesterol	**8**	72[a]
4	**3**	**9**	56[a]; 83[c]; 90[d]
5	**4**	**10**	80[b]
6	**5**	**11**	64[b]

[a] **2**:acceptor = 1:1.5. [b] **2**:acceptor = 1.2:1. [c] **2**:acceptor = 1:1.2; 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv) was added in the reaction. [d] **2**:acceptor = 1.2:1; 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv) was added in the reaction.

to the desired products (**6**−**8**) in 72−79% yields. (Entries 1−3) The yields could be reasonably improved (79% → 86%, entry 1) by using a little excess amount of the donor (1.2 equiv) in the reaction. For the glycosylation of phenyl 2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (**3**), the desired product **9** was isolated in a lower yield (56%). Polar products were observed on TLC, which were conceivably derived from the cleavage of the isopropylidene group and the anomeric phenylthio group. Therefore, a hindered base (2,6-di-*tert*-butyl-4-methylpyridine, 1.5 equiv) was added to scavenge the resulting acid in the reaction. Evidently, the yield for **9** was hence greatly improved (83%, entry 4).

Obviously, the resulting product **9** (as an example) was a versatile intermediate for the further elaboration of complex oligosaccharides containing 2-deoxy-β-glycosidic linkages. As shown in Scheme 2, treatment of **9** with 80% acetic acid (50 °C, overnight) gave in 99% yield the corresponding 2,3-diol, which was then subjected to 1,1′-thiocarbonyldiimidazole in DMF in the presence of an excess amount of 4-(dimethylamino)pyridine (DMAP, 2.2 equiv) to afford the phenyl 1-thiodisaccharide 2,3-*O*-thionocarbonate **12**, a new donor, in 69% yield. Alternatively, treatment of **9** with sodium methoxide in methanol (60 °C, 3 days) provided the 3′-OH disaccharide **13**, a new acceptor, in 93% yield.

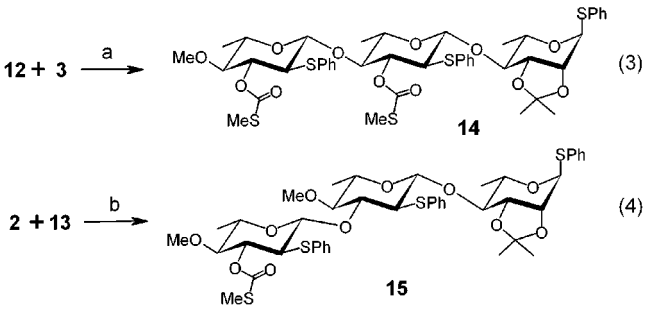
Scheme 2[a]



[a] (a) 80% HOAc, 50 °C, overnight, 99%; (b) $Im_2C{=}S$, DMAP (2.2 equiv), DMF, 55 °C, 69%; (c) NaOMe (2.0 equiv), HOMe, 60 °C, 3 days, 93%.

The successful reaction of disaccharide donor **12** with **3** (eq 3, Scheme 3) and donor **2** with disaccharide acceptor **13**

Scheme 3[a]



[a] (a) **12** (1.0 equiv), **3** (1.5 equiv), MeOTf (1.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH_2Cl_2, 4Å MS, rt, 69% (based on **12**). (b) **2** (2.0 equiv), **13** (1.0 equiv), MeOTf (1.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv), CH_2Cl_2, 4Å MS, rt, 5 h, 75% (based on **13**).

(eq 4) strongly demonstrated the usefulness of the present protocol. The resulting trisaccharides **14** and **15** were obtained in 69% and 75% yields, respectively.[22] Analogous transformations from **14** and **15** to synthesize more complex oligosaccharides would by no means be unsuccessful.[23]

In conclusion, here we have demonstrated that phenyl 2,3-*O*-thionocarbonyl-1-thio-α-L-rhamnopyranosides were effective donors for the preparation of the corresponding 3-*O*-(methylthio)carbonyl-2-*S*-phenyl-2,6-dideoxy-β-L-glucopyranosides, ready precursors to 2-deoxy-β-glycosides, via 1,2-migration and concurrent glycosidation. Application of this protocol to the synthesis of biologically active 2-deoxy-β-glycoside containing compounds is our current interest and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (**2**, **6**−**15**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Raney nickel mediated desulfurization of 2-SPh to elaborate the final 2-deoxyglycosides has been shown to be a facile process.[8a,11]