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A Novel and Effective Procedure for the Preparation of Glucuronides

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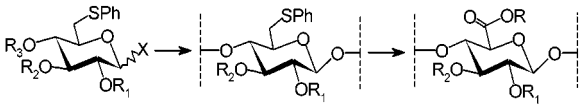
ABSTRACT



6-Phenylthio-6-deoxy-D-glucopyranosides were easily prepared from 6-hydroxy-D-glucopyranosides and employed as effective glycosyl donors or acceptors. And the resulting coupling products were then readily converted into the corresponding D-glucuronide-containing compounds.

Glucuronide is an integral component in proteoglycans which play essential roles in many cellular processes, including cell growth and cell−cell interactions.[1] Glucuronide exists also as an important structural unit in a number of bacterial capsular polysaccharides and plant glycosides which show promising biological activities.[2,3] Furthermore, glucuronide is frequently the final form of a drug or xenobiotic eliminated from the body, often performing a detoxification role.[4] As a consequence of these biological rationales, development of synthetic schemes for glucuronides has been targeted by many investigators.[4,5] Although most of the methods employed for glucuronide synthesis have their parallel in glucopyranoside synthesis, glucuronide donors or acceptors have been found to be more sluggish than the corresponding glucopyranoside counterparts. Schmidt and co-workers have in fact classified glycuronide donors as the type of glycosyl donor with the lowest reactivity.[6] The distinctive chemistry of glucuronides has been attributed to the electron-withdrawing 5-carboxyl group, which remarkably decreases the nucleophilicity of the hydroxy groups on glucuronide acceptors, or exerts a destabilizing effect on the incipient C-1 cation leading to the low reactivity of glucuronide donors. Consequently, coupling with glucuronide donors or acceptors usually gives low yields of the products.[4] Oscarson et al. therefore have recently developed ethyl thio-glucuronide donors with activating protective groups (benzyl or silyl) at O-3 and O-4 and a neighboring participating group at O-2.[7] Alternatively, glucuronides, glucuronide-containing oligosaccharides in particular, are often synthesized by introduction of the carboxyl group at a later oxidation step after coupling with a glucopyranoside moiety.[5] However, this approach requires extensive protective group manipulations for selectively generating a free 6-OH at a later stage.

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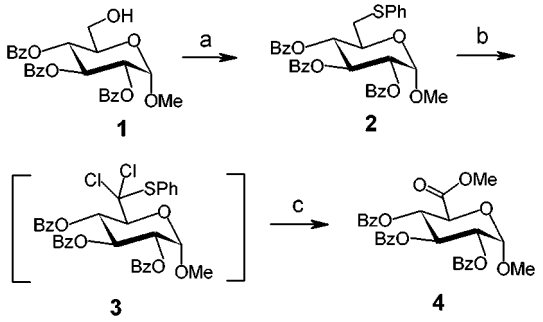
To circumvent the problems in glucuronide synthesis, we envisioned developing a glucuronide precursor, which could behave as a normal glycosyl donor or acceptor, while could be readily converted into the glucuronide residue after assembling of the whole molecule. This paper reports that 6-phenylthio-glucopyranosides serves nicely for these purposes.

To test the feasibility of using 6-phenylthio-glucopyranosides as glucuronide precursors, we first examined the substitution of 6-OH with phenylthio group and then the conversion of the resulting 6-SPh to carboxyl group on a simple glucopyranoside **1** (Scheme 1). Treatment of methyl

Scheme 1[a]



[a] (a) $(PhS)_2$, *n*-Bu_3P, pyridine, rt, 24 h, 94%; (b) SO_2Cl_2/pyridine (2.0 equiv), CCl_4, 0 °C; (c) $HgCl_2$ (10.0 equiv), pyridine (2 equiv), MeOH/H_2O/CH_2Cl_2 (2:1:1), rt, 90% (for two steps).

2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**1**) with phenyl disulfide and tri-*n*-butylphosphine in pyridine[8] at room temperature gave 6-phenyl sulfide **2** in 94% yield, which was then subjected to sulfuryl chloride and pyridine in carbon tetrachloride at 0 °C, the conditions developed by Fortes et al.,[9] to provide the α,α-dichloro-phenyl sulfide **3**. Compound **3** was found to be unstable upon silica gel column chromatography, and consequently was directly treated with mercury(II) chloride in methanol/water/dichloromethane at room temperature, affording the desired methyl ester **4** in 90% yield.

Encouraged by the ready transformation from glucopyranoside **1** to glucuronide **4** under mild conditions, we prepared 6-phenylthio-substituted ethylthio-glucopyranoside donor **6**, trichloroacetimidate donor **11**, and acceptor **8** with a free 4-OH from the corresponding 6-OH glucopyranosides (**5**, **7**, and **9**) (Scheme 2). It should be noted that the 6-phenylsulfenylation of glucopyranoside derivatives was achieved in excellent yields and in a regioselective manner (for diols **7** and **9**).

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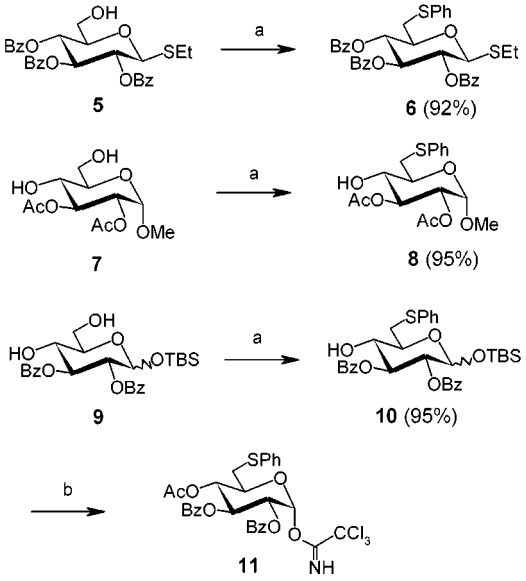
Scheme 2[a]



[a] (a) $(PhS)_2$, *n*-Bu_3P, pyridine, rt, 24 h; (b) (1) Ac_2O, pyridine, rt, overnight; (2) TBAF, HOAc, THF, rt, 10 h; (3) $CNCCl_3$, DBU, CH_2Cl_2, rt, 1 h, 81% (for three steps).

The use of 6-phenylthio-glucopyranose derivatives as glycosyl donors or acceptors for preparation of glycosides or disaccharides was examined. The results are listed in Figure 1 and Table 1. Glycosylation of sugar alcohol **1** and

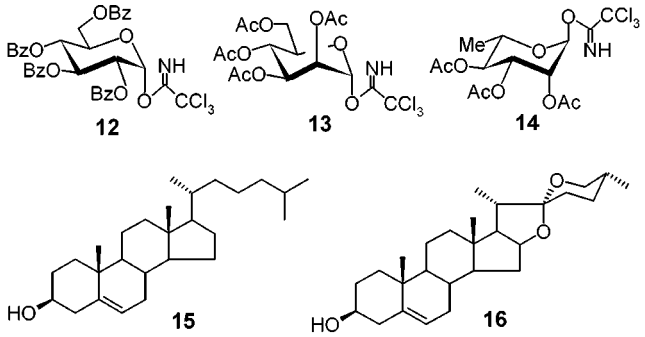


Figure 1. Selected donors and acceptors.

cholesterol (**15**) with ethyl 2,3,4-tri-*O*-benzoyl-6-phenylthio-6-deoxy-1-thio-β-D-glucopyranoside (**6**) under the promotion of MeOTf[10] provided the corresponding products (**17** and **18**) in 60% and 56% yields, respectively (entries 1 and 2). The moderate yields were conceivably resulted from the interference of the 6-phenylthio substitution on the activation of the anomeric ethylthio group of donor **6**. Stronger promotion conditions,[11] e.g., NIS/AgOTf as promoter, gave a complicated mixture of the products. Fortunately, using trichloroacetimidate **11** as donor, under the promotion of TMSOTf,[12] led to high yields of the coupling products (**19** and **20**, entries 3 and 4). Glycosylation of 6-phenylthio-

Table 1[a]

entry	donor	acceptor	conditions	product	yield,[b] %
1	**6**	**1**	A	**17**	60
2	**6**	**15**	A	**18**	56
3	**11**	**15**	B	**19**	82
4	**11**	**16**	B	**20**	85
5	**12**	**8**	C	**21**	70
6	**13**	**8**	C	**22**	81
7	**14**	**8**	C	**23**	92

[a] Conditions A: donor (2.0 equiv), acceptor (1.0 equiv), 4 Å MS, CH_2Cl_2, MeOTf (5.0 equiv). Conditions B: donor (1.0 equiv), acceptor (1.5−2.0 equiv), 4 Å MS, CH_2Cl_2, TMSOTf (0.2 equiv). Conditions C: donor (2.0 equiv), acceptor (1.0 equiv), 4 Å MS, CH_2Cl_2, TMSOTf (0.2 equiv). [b] Isolated yields.

substituted glucopyranoside **8** (as an acceptor) with trichloroacetimidate donors **12**−**14**, provided the corresponding coupling products in good to excellent yields (70−92%) (entries 5−7). All the glycosidic linkages produced were proved by ^{1}H NMR analysis to be 1,2-trans configurations due to the donors used possessing neighboring participating groups.

Glycosides and disaccharides which contained the 6-phenylthio-substituted glucopyranose residue were demonstrated to be ready precursors of the corresponding methyl glucuronates (Figure 2). The transformations were realized in two steps under the conditions developed by Fortes et al.[9] Thus, treatment of **17** or **19**−**23** with sulfuryl chloride in the presence of pyridine in carbon tetrachloride provided the corresponding α,α-dichloro-phenyl sulfides cleanly (on TLC), which after a usual workup, was directly subjected to hydrolysis ($HgCl_2$/MeOH/H_2O) to give the corresponding methyl glucuronates (**24**−**29**). Hydrolysis of disaccharide derivatives (**17**, **21**−**23**) was carried out in a mixture solvent of MeOH/H_2O/CH_2Cl_2, providing the corresponding methyl glucuronates (**24**, **27**−**29**) in high yields (85−89% for two steps). Because of the poor solubility in the above mixture solvent, steroidal glycosides **19** and **20** were subjected to hydrolysis in MeOH/H_2O/$CHCl_3$, generating methyl glucuronates **25** and **26** in lower yields (71% and 68%, respectively, for two steps). It should be noted that the acyl protective groups (acetyl and benzoyl groups), the glycosidic bonds, and the carbon−carbon double bonds containing in the substrates were unaffected under these transformation conditions.

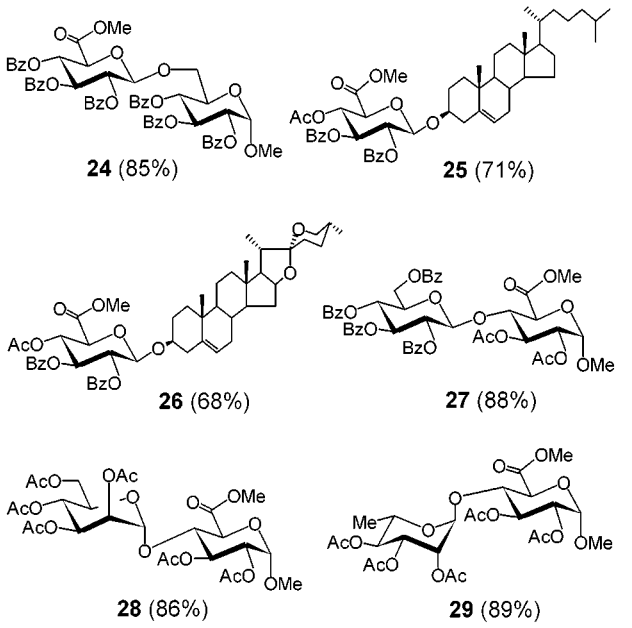


Figure 2. Methyl glucuronates prepared from 6-phenylthio substituted precursors. Experimental conditions are as follows: (1) SO_2Cl_2 (2.0 equiv), pyridine (2.0 equiv), CCl_4, 0 °C; (2) $HgCl_2$ (10.0 equiv), pyridine (2.0 equiv), MeOH/H_2O/CH_2Cl_2 (2:1:1), or MeOH/H_2O/$CHCl_3$ (2:1:1), rt. The numbers enclosed in parentheses are isolated yields for two steps.

In conclusion, we have developed an effective alternative to the preparation of glucuronides by using 6-phenylthio-substituted glucopyranosides as precursors. The present strategy should be applicable to the synthesis of other uronides as well. Application of this method to the synthesis of biologically active uronide-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 6-phenyl sulfides (**2**, **6**, **8 10 11**), coupling products (**17**−**23**), and final methyl glucuronates (**24**−**29**). This material is available free of charge via the Internet at http://pubs.acs.org.

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