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Synthesis of Differentially Protected Phenyl D-Thioglucopyranosides and 1-Phenyl D-Thioglucopyranosiduronic Acids

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Abstract: : Convergent syntheses of differentially protected phenyl D-thioglucopyranosides and 1-phenyl D-thioglucopyranosiduronic acids were achieved by employing the Hanessian reaction method.

Thioglycosides are used extensively in synthetic carbohydrate chemistry. They are most often used as glycosyl donors[1] and as key intermediates in the preparation of anomeric sulfoxides. Glycosyl sulfoxides are known to be excellent glycosyl donors in both solution and solid phase glycosylation reactions.[2] In addition, the anomeric alkyl/aryl thio group can be used as a temporary protecting group for the sugar anomeric center. As a protecting group, it is stable under many reaction conditions and can be easily removed.[3]

Thioglycosides have been prepared from the precursor lactol sugar and from 1-halo, 1-O-acyl and 1-O-alkyl derivatives of carbohydrates.[4] Direct conversion of alkyl glycosides to their corresponding thioglycosides was first reported by Hanessian and Guindon.[5] The conditions used for the conversion of alkyl glycosides to thioglycosides have also been used for the cleavage of benzyl ether protecting groups (see Fig. 1).[6] However, the dual capability of these reaction conditions has not been utilized in any concerted fashion in carbohydrate synthesis.

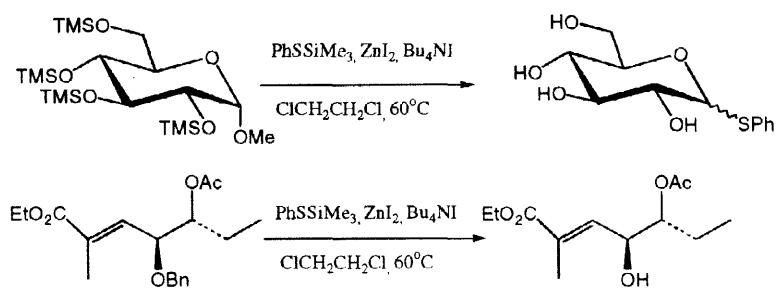

Figure 1

In an effort to construct carbohydrate-based combinatorial libraries to identify new therapeutic agents, we wanted to synthesize a series of thioglucoside and thioglucosiduronic acid building blocks **1** and **2**. It

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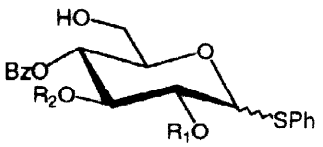
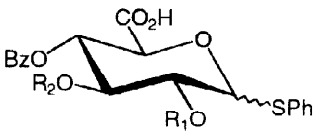
was necessary that these building blocks be differentially protected with orthogonal or modulated protecting groups[7] to allow selective derivatization in a combinatorial format.

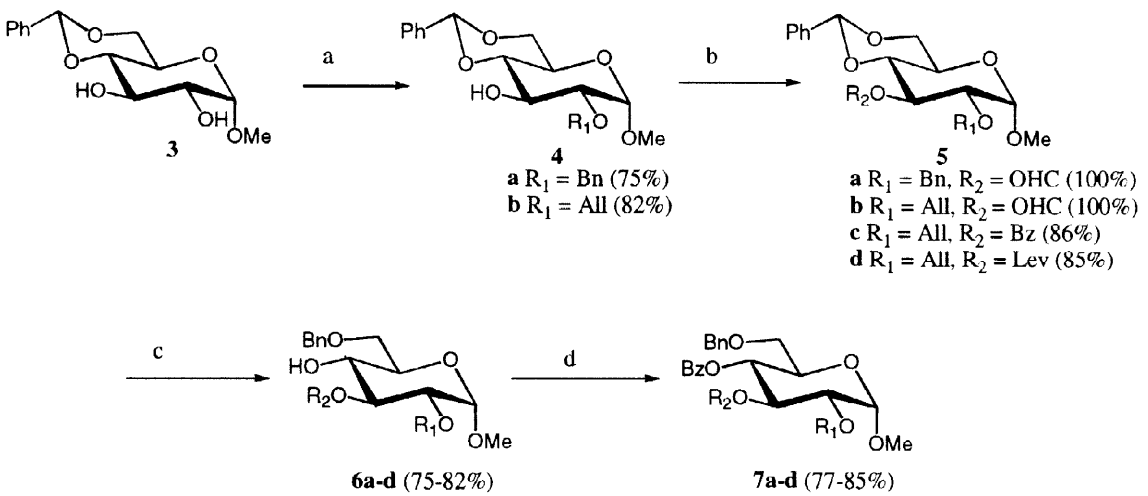


1 a R_1 = Bn, R_2 = OHC
b R_1 = All, R_2 = OHC
c R_1 = All, R_2 = Bz
d R_1 = All, R_2 = Lev



2 a R_1 = Bn, R_2 = OHC
b R_1 = All, R_2 = OHC
c R_1 = All, R_2 = Bz
d R_1 = All, R_2 = Lev
e R_1 = H, R_2 = Lev

Although the synthesis of compounds **1** and **2** could be achieved using published procedures requiring multiple protection/deprotection steps and a non-regioselective phase transfer catalyzed reaction,[8] we envisioned utilizing the dual capability of the Hanessian reaction to efficiently synthesize these building blocks. We were particularly encouraged by a preliminary experimental result indicating that under the conditions of the Hanessian reaction, the benzyl ether of a primary hydroxyl group was preferentially cleaved over the benzyl ether of a secondary hydroxyl group.[9] Scheme 1 outlines the synthesis of intermediates **7a-d** required for the preparation of compounds **1** and **2** via this strategy.



3

4
a R_1 = Bn (75%)
b R_1 = All (82%)

5
a R_1 = Bn, R_2 = OHC (100%)
b R_1 = All, R_2 = OHC (100%)
c R_1 = All, R_2 = Bz (86%)
d R_1 = All, R_2 = Lev (85%)

6a-d (75-82%)

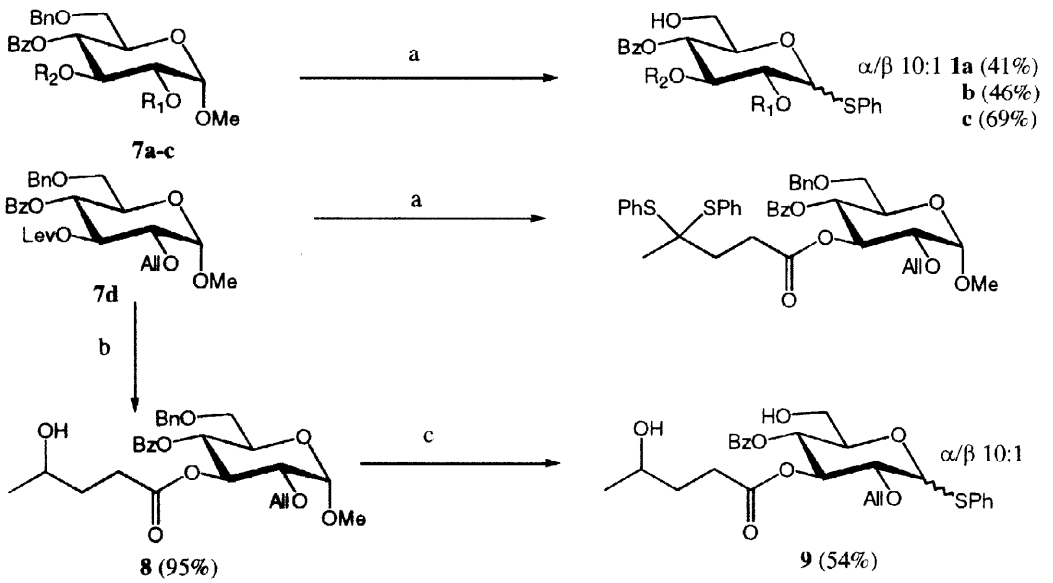
7a-d (77-85%)

Reagents and conditions: a) 1. Bu_2SnO, toluene; 2. BnBr for **4a** or AllBr for **4b**;[10] b) HCO_2H, Ac_2O, TEA, DMAP DCM for **5a** and **5b**; BzCl, DMAP, Py. for **5c**; LevOH, DCC, DMAP, DCM for **5d**; c) TES, TFA, DCM;[11] d) BzCl, DMAP, Py.

Scheme 1

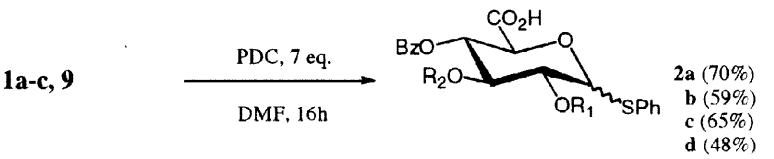
As hoped, when **7a-c** were subjected to the Hanessian conditions, the desired debenzylated thioglucosides **1a-c** were obtained. However, when **7d** was treated under the same condition, the ketone carbonyl functionality of the levulinoyl protecting group was transformed to a thioketal. To circumvent this problem, we carefully reduced the carbonyl group with $NaBH_4$. With a masked Lev group, **8** was now successfully converted to the thioglucoside **9** (Scheme 2).[12,13] Compounds **1a-c** and **9** were subsequently oxidized to the corresponding glucosiduronic acids **2a-d** with PDC in DMF (Scheme 3). Contrary to an

early report,[14] no sulfoxide or sulfone by-products were detected even when excess PDC was used. We also showed that a sonicated Jones oxidation afforded the same selectivity.[15]



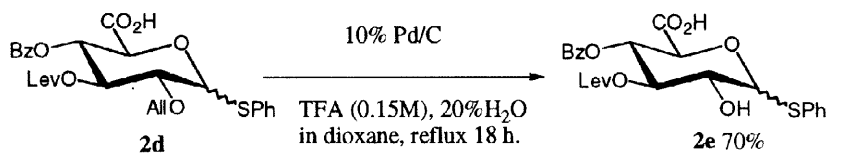
Reagents and conditions: a) $PhSSiMe_3$ (5 eq.), ZnI_2 (3 eq), Bu_4NI (1.5 eq), $ClCH_2CH_2Cl$, 60°C, 3h; b) $NaBH_4$, EtOH; c) $PhSSiMe_3$ (8 eq.), ZnI_2 (6 eq), Bu_4NI (3 eq), $ClCH_2CH_2Cl$, 60°C, 6h.

Scheme 2



Scheme 3

To obtain a carbohydrate building block with a free C-2 hydroxyl group, we investigated deallylation of **2d**. After several unsuccessful or unsatisfactory attempts using reagents $PdCl_2$/MeOH, $PdCl_2$/NaOAc/AcOH/H_2O, $(Ph_3P)_3RhCl$/DABCO/EtOH/Hg(II), Pd-C/PTSA/MeOH/H_2O[16] and Pd-C/PTSA/dioxane/H_2O,[17] we found that **2e** was obtained in 70% yield by treatment of **2d** with 10%Pd-C in refluxing dioxane/water containing TFA (Scheme 4).



Scheme 4

In summary, we have demonstrated that differentially protected phenyl thioglucopyranosides and 1-phenyl thioglucopyranosiduronic acids can be efficiently synthesized from readily available methyl glucopyranoside using the Hanessian reaction conditions to effect simultaneous thiolation and

debenzylation. We are currently using these building blocks in the generation of carbohydrate-based combinatorial libraries.

References and Notes

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12. General procedure: ZnI_2 and Bu_4NI was dried at 60°C over vacuum for 2h in a reaction flask. A solution of methyl glucoside (**7a-c** or **8**) in 1,2-dichloroethane was added followed by $PhSSiMe_3$. The mixture was stirred at 60°C for 3 to 6 h until no starting material remained by TLC analysis. The reaction mixture was cooled and diluted with DCM, washed with H_2O and dried. The crude product was purified by flash column chromatography (ethyl acetate-hexane, 50-80%) to give the desired product. All new compounds gave satisfactory NMR and MS analytical results. For preparation of **8**: to **7d** (20g, 38 mmol) in MeOH (100ml) was added $NaBH_4$ (1.3g, 34 mmol) portionwise at 0°C. After stirring at r.t. for 30 min., ethyl acetate (220ml) was added. The reaction mixture was washed with H_2O and brine, dried over anhydr. $MgSO_4$.. **8** (19g, 95%) was obtained after solvent removal and used in the next reaction without purification.
13. Thioglycoside formation is probably occurred before debenzylation since the former reaction normally proceeds relatively fast as reported in ref. 5 d). The modest yields of 1a, b are likely due to cleavage of the formyl protecting group.
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