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Synthesis of thio-*C*-glycosides from 2′-carbonylalkyl *C*-glycosides by a tandem β-elimination and intramolecular hetero-Michael addition

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Abstract—2′-Carbonyl 5-*S*-acetyl-*C*-glycofuranosides and 2′-carbonyl 4-*S*-acetyl-*C*-glycopyranosides were converted in good yields to respective 5-thio-*C*-glycopyranosides and 4-thio-*C*-glycofuranosides under base treatment. The transformation was resulted from β-elimination on 2′-carbonyl *C*-glycoside to form α,β-conjugated aldehyde (or ketone) and following intramolecular hetero-Michael addition by the thiol group. Crown Copyright © 2003 Published by Elsevier Science Ltd. All rights reserved.

Thio-sugars, a class of sugar derivatives with sulfur in the ring, have been used as glycosidase inhibitors[1] and precursors for the thionucleotides[2] that have exhibited potential antiviral and anticancer activities.[3] In addition, thio-sugar have also been used to treat other diseases; e.g. 1,5-dithio-β-D-xylopyranosides are orally active against thrombosis by inhibition of glycosaminoglycan biosynthesis;[4] and natural products, Salacinol[5] and Kotalanol,[6] are potent α-glucosidase inhibitors and could be useful for the treatment of diabetes. The synthesis of thio-sugars has been reviewed by Fernandez-Bolanos et al.[7] However, few methods exist to synthesize thio-*C*-glycosides, which may even be superior inhibitors because of their chemical and metabolic stability. One synthesis reported by Praly et al. using thio-xylopyranosyl trichloroacetamide as a donor and heterocycles as receptors, afforded an anomeric mixture (α/β 2:3–2:1) of thio-*C*-glycosides in moderate yields.[8] Another was based on thio-glycosyl radical addition to an enone derivative.[9]

Recently, we found that 2′-carbonyl α-*C*-glycosides can be epimerized to their β-anomers by base treatment, the intermediate being an acyclic α,β-conjugated aldehyde or ketone formed by β-elimination.[10] An intramolecular hetero-Michael addition then led to the formation of stable β-*C*-glycopyranoside. Here, we describe a method based on the mechanism of this reaction, for the synthesis of thio-*C*-glycosides using respective 4-*S*-Ac and 5-*S*-Ac sugars as substrates. Under basic conditions de-*S*-acetylation generates a thiol group, which, in turn, reacts by an intramolecular 1,4-addition to an α,β-conjugated aldehyde (ketone) intermediate to form 2′-carbonyl 5-thio-*C*-glycopyranosides and 4-thio-*C*-glycofuranosides.

Acetolysis of allyl *C*-L-arabinofuranoside (**1**) with 0.05% H_2SO_4–Ac_2O selectively removed the 5-*O*-benzyl group to afford acetylated **2** in 70% yield. Removal of 5-*O*-Ac in 0.1% NaOMe followed by 5-*O*-mesylation (MsCl/Py), converted **2** into **3** in 77% yield. An S_N2 replacement by AcSK in DMF afforded allyl 5-*S*-acetyl-*C*-furanoside **4**, from which 2′-aldehyde **5** was then derived by ozonolysis (O_3 and Zn-HOAc) in good yield. Meanwhile, compound **2** was also subjected to ozonolysis and the resultant 2′-aldehyde was reacted to MeMgBr to furnish an alcohol **7** in 87%. Four diastereomers of **7** were formed which were inseparable. After protection of 5-OH with trityl group (Ph_3CCl/Py) the 2′-OH of **8** was oxidized to ketone by PCC and **9** was obtained in 31% yield. No attempt was made to optimize the reaction conditions. The trityl group was then removed by treatment of **9** with $ZnBr_2$ to give **10** (71%). The 5-OH was mesylated and substituted by AcS^- by a procedure similar to that described in the preparation of **4** to obtain 2′-ketone derivative **11** in 60%.

Keywords: synthesis; thio-glycoside; *C*-glycoside; β-elimination; cycloaddition.

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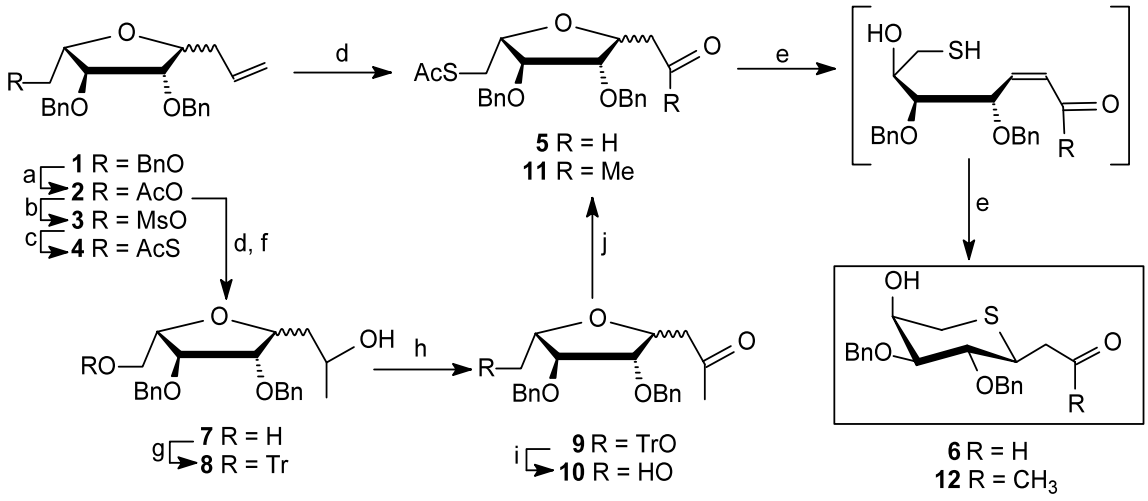
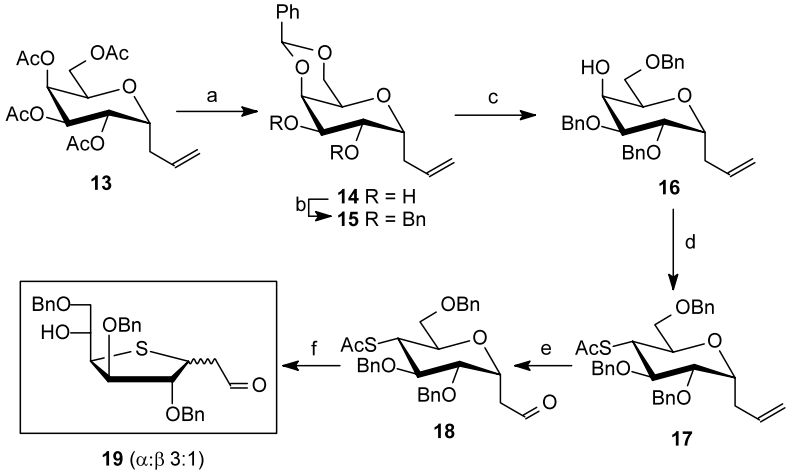
As a mixture of two anomers (α/β 1:1) compounds **5** and **11** were treated overnight with 4% NaOMe. Under basic conditions de-*S*-acetylation was quickly achieved releasing a thiol group as indicated by ^{1}H NMR analysis, while the enolation of the 2′-carbonyl group and subsequent β-elimination resulted in an acyclic α,β-conjugated aldehyde (from **5**) or ketone (from **11**) (see Scheme 1). Thus, there were two nucleophiles competing in the hetero-Michael cycloaddition, i.e. the 4-hydroxy group and 5-thiol group, but the complete conversion of *C*-furanosides (**5** and **11**) to 5-thio-*C*-α-L-arabinopyranosides (**6** and **12**, 60–80%) were achieved.[11] The same results were also obtained when the reactions were performed in the presence of $Zn(OAc)_2$, which indicates, on the contrary to our previous suggestion, that the additional Zn^{++} was not essential to the stereoselectivity. The absence of furanosides and the stereoselectivity in the product can be explained because it is known that 2′-carbonyl *C*-furanoside formed by *O*-1,4-addition can be reversibly opened by β-elimination to form more thermodynamically stable *C*-pyranosides.[10]

We further attempted to prepare thio-*C*-furanoside from respective *C*-pyranoside assuming that the C1–S bond in 2′-carbonyl thio-*C*-glycoside formed by cycloaddition, would be stable under these conditions. Thus, we prepared **18** from **13** in five steps (see Scheme 2). De-*O*-acetylation of **13** was followed by benzylidenation in acetonitrile to give compound **14**, which was readily crystallized from reaction mixture in excellent yield. Compound **15** obtained after benzylation of **14** was also crystallized (EtOAc–hexanes) without using column chromatography. Regioselective opening of benzylidene gave **16** ($NaCNBH_3/H^+$) in 81% yield, which was in turn treated with triflic anhydride. The



Scheme 1. *Reagents and conditions*: (a) 0.05% H_2SO_4–Ac_2O, rt, overnight, 70%; (b) i. 0.1% NaOMe, rt, 2 h; ii. $MeSO_2Cl$/Py, 0°C to rt, overnight, 77%; (c) AcSK/DMF, rt, overnight, 62%; (d) O_3/CH_2Cl_2, −78°C 1 h; Zn/HOAc, rt, overnight, 67%; (e) 4% NaOMe, rt, overnight, 76% for **6** and 70% for **12**; (f) $MeMgBr/Et_2O$, −78°C, 87%; (g) Ph_3CCl/Py, rt, overnight; 45%; (h) PCC/NaOAc/CH_2Cl_2, 31%; (i) $ZnBr_2/CH_2Cl_2$, 71%; (j) i. $MeSO_2Cl$/Py, 0°C to rt, overnight; ii. AcSK/DMF, rt, overnight, 60%.



Scheme 2. *Reagents and conditions*: (a) i. 0.1% NaOMe, rt, 2 h; ii. $PhCH(OMe)_2$/MeCN/TsOH, rt, overnight, 87%; (b) BnBr/NaH/DMF, rt, overnight, 73%; (c) $NaCNBH_3$/HCl/THF, 0°C to rt, 3 h, 81%; (d) i. Tf_2O/Py-CH_2Cl_2, 0°C to rt, 3 h; ii. AcSK/DMF, rt, overnight, 61%; (e) O_3/CH_2Cl_2, −78°C 1 h; Zn/HOAc, rt, overnight, 77%; (f) 4% NaOMe, rt, overnight, 70%.

introduction of 4-*S*-Ac by replacement of 4-*O*-triflate to **17** (61%) was accompanied by the inversion of configuration at C4. Ozonolysis of **17** afforded 2′-carbonyl *C*-glycopyranoside **18** in 60–80% yield. After base treatment of **18** we were able to obtain 4-thio-*C*-furanoside **19** in 70% yield.[12] The anomeric mixture of **19** was inseparable by silica gel chromatography and the α/β ratio was ca. 3:1 as determined by ^{1}H NMR analysis. Both anomers were characterized by various 2D NMR techniques and the stereochemistry of β-anomer in **19** was confirmed by the observation of an NOE between H-1 and H-3.

In conclusion we have described a new method for the preparation of 2′-carbonylalkyl thio-*C*-glycosides by a tandem β-elimination and intramolecular hetero-Michael addition. Both yield and stereoselectivity are excellent for pyranosides, but a mixture of anomers was obtained from thio-*C*-furanosides. Derivatization of the 2′-carbonyl group and further modification of the sugar moiety could lead to useful synthetic intermediates.

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11. Selected data for **6** and **12**. For **6**: ^{1}H NMR ($CDCl_3$) δ_H 2.50–2.53 (m, 2H, H-5e, C*H*HCHO), 2.66 (dd, 1H, C*H*HCHO, $J=7.6$, 17.6 Hz), 2.90 (dd, 1H, H-5a, $J=10.0$, 12.8 Hz), 3.64 (m, 2H, H-1, 2), 3.89 (m, 1H, H-3), 4.12 (m, 1H, H-4), 4.45–4.70 (m, 4H, 2×CH_2Ph), 9.51 (bs, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ_C 29.5 (C-5), 34.6 (C-1), 43.7 (CH_2CO), 67.5 (C-4), 73.1 (*C*H_2Ph), 73.4 (*C*H_2Ph), 75.7 (C-2), 76.9 (C-3), 199.5 (C=O); HRFABMS: Calcd for $C_{21}H_{25}O_4S$ (M+H): 373.1474. Found: 373.1522. For **12**: ^{1}H NMR ($CDCl_3$) δ_H 1.96 (s, 3H, CH_3), 2.33 (d, 1H, 4-OH, $J=10$ Hz), 2.45–2.51 (m, 2H, H-5ax, C*H*HCHO), 2.66 (dd, 1H, C*H*$_2$CHO, $J=8.4$, 17.6 Hz), 2.90 (dd, 1H, H-5eq, $J=10.0$, 13.2 Hz), 3.63–3.66 (m, 2H, H-1, 2), 3.97 (dd, 1H, H-3, $J=2.8$, 5.6 Hz), 4.11 (m, 1H, H-4), 4.43 and 4.62 (d and d, 1H each, C*H*$_2$Ph, $J=12.0$ Hz), 4.50 and 4.72 (d and d, 1H each, C*H*$_2$Ph, $J=12.0$ Hz), 7.28–7.39 (m, 10H, 2×*Ph*); ^{13}C NMR ($CDCl_3$) δ_C 29.3 (C-5), 30.2 (CH_3), 34.8 (C-1), 42.6 (*C*H_2CO), 67.3 (C-4), 72.7 (*C*H_2Ph), 72.8 (*C*H_2Ph), 74.9 (C-2), 76.4 (C-3), 205.7 (C=O); HRFABMS: calcd for $C_{22}H_{27}O_4S$ (M+H): 387.1630. Found: 387.1664.
12. Selected data for **19** (α/β 3:1): HRFABMS: calcd for $C_{29}H_{33}O_5S$ (M+H): 493.2049. Found: 493.1705. **19α**: ^{1}H NMR ($CDCl_3$) δ_H 2.62 (d, 1H, 5-OH, $J=4.8$ Hz), 2.79 (dd, 1H, C*H*$_2$CHO, $J=6.8$, 18.8 Hz), 2.87 (dd, 1H, C*H*$_2$CHO, $J=6.8$, 18.8 Hz), 3.43 (dd, 1H, H-6a, $J=6.4$, 9.6 Hz), 3.60 (d, 1H, H-6b, $J=2.8$, 9.6 Hz), 3.74 (dd, 1H, H-4, $J=4.0$, 10.0 Hz), 4.00 (m, 1H, H-2), 4.04 (m, 1H, H-1), 4.13 (m, 1H, H-5), 4.29 (m, 1H, H-3), 4.48–4.64 (m, 6H, 3×CH_2Ph), 7.19–3.38 (m, 15H, 3×Ph), 9.69 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ_C 43.5 (C-1), 44.8 (*C*H_2CHO), 51.4 (C-4), 70.0 (C-5), 73.8 (C-6), 82.5 (C-3), 83.4 (C-2), 200.5 (C=O). **19β**: δ_H 2.78 (d, 1H, 5-OH, $J=4.8$ Hz), 2.92 (dd, 1H, C*H*HCHO, $J=6.8$, 18.8 Hz), 2.98 (dd, 1H, C*H*HCHO, $J=6.8$, 18.8 Hz), 3.45 (dd, 1H, H-6a, $J=6.4$, 9.6 Hz), 3.60 (d, 1H, H-6b, $J=2.8$, 9.6 Hz), 3.74 (dd, 1H, H-4, $J=4.0$, 10.0 Hz), 3.77 (m, 1H, H-1), 3.89 (m, 1H, H-2), 4.14 (m, 1H, H-5), 4.25 (m, 1H, H-3), 4.48–4.64 (m, 6H, 3×CH_2Ph), 7.19–3.38 (m, 15H, 3×Ph), 9.64 (s, 1H, CHO); δ_C 45.0 (C-1), 50.2 (*C*H_2CHO), 51.7 (C-4), 70.4 (C-5), 73.8 (C-6), 84.9 (C-3), 86.1 (C-2), 200.5 (C=O).