Novel Heteroanalogues of Methyl Maltoside Containing Sulfur and Selenium as Potential Glycosidase Inhibitors

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In recent years, much attention has focused on the synthesis of heteroanalogues of sugars as glycosidase inhibitors.[1] Several reports have investigated the use of oligosaccharides with sulfur in the glycosidic linkage as potential inhibitors.[2] Recently, the enzymatic syntheses of disaccharides containing sulfur in the ring of the reducing[3] and nonreducing[4] monosaccharide units were reported, and we have reported the chemical synthesis of 5′-thio analogues of methyl kojibioside and methyl α- and β-isomaltosides.[5] Although the first seleno sugar, selenoisotrehalose, was reported as early as 1917,[6] no general synthesis of oligosaccharides containing selenium is available and selenoglycoside analogues of a reducing disaccharide are hitherto unknown. Moreover, there are no reports to date of disaccharides of 5-thioglucose with sulfur or selenium in the interglycosidic linkage. We report herein the synthesis of three novel heteroanalogues of α-methyl maltoside with sulfur in the ring of the nonreducing sugar and either oxygen, sulfur, or selenium in the interglycosidic linkage for evaluation as glycosidase inhibitors.

We chose the 5-thioglucopyranosyl trichloroacetimidate donor **1**,[5] and the method of Schmidt,[7] for glycosylation of the 4-OH, 4-SH, and 4-SeH glucopyranoside acceptors. Thus, the glycosylation of acceptor **2**[8] with donor **1** in the presence of 0.1 equiv of triethylsilyl triflate as catalyst afforded exclusively the α-disaccharide **3** in 87% yield (Table 1, entry 1).[9,10] The temperature at which this reaction is quenched is of great significance in controlling its outcome. The ortho ester **4** was isolated in 88% yield when compounds **1** and **2** were reacted at a temperature lower than −50 °C (Table 1, entry 2). When the ortho ester was reintroduced into the same reaction conditions but the reaction mixture was warmed to room temperature, only the α-disaccharide **3** was formed.[12] This result therefore suggests that the stereoselective α-disaccharide formation is preceded by ortho ester formation.[13] Glycosylation of the more reactive benzylated acceptor **5**[14] with glycosyl donor **1** was also examined. In this case, loss of stereoselectivity was observed, as expected with the more reactive acceptor, and a 1:1 mixture of the α- and β-disaccharides **6** and **7** was isolated (Table 1, entry 3).

Table 1. Results of Glycosylation Reactions

entry	donor	acceptor	molar ratio[a]	reactn condtns[b]	product	yield, %
1	**1**	**2**[8]	1:2:0.1	−78 °C for 1 h, rt[c] for 1 h	**3**	87
2	**1**	**2**	2:1:0.2	−78 °C for 1 h, −50 °C for 1.5 h	**4**	88
3	**1**	**5**[14]	1:2:0.1	−78 °C for 1 h, rt for 1 h	**6**	45
					7	45
4	**1**	**8**[18]	1:2:0.25	−78 to −50 °C in 1 h	**9**	53
					10	1.5
5	**1**	**11**	1:2:0.2	−78 °C for 10 min, rt for 1 h	**12**	46
					13	11

[a] Donor:acceptor:triethylsilyl triflate. [b] All reactions were cooled to −78 °C prior to quenching with collidine. [c] Room temperature.

The synthesis of the dithiomaltose derivative in which the interglycosidic oxygen atom and the ring oxygen atom of the nonreducing sugar have been replaced by sulfur was examined next. Disaccharides with sulfur in the glycosidic linkage have been synthesized previously by a variety of methods including S_N2-type reactions involving the action of a thiolate anion on a glycosyl halide,[15] the displacement of a leaving group by a 1-thioglycopyranose,[16] and more recently, by the condensation of benzylated 1,6-anhydroglucopyranose with a suitably protected 4-thioglucopyranoside to give predominantly an α-linked disaccharide.[17] In our synthesis, glycosylation of the selectively protected 4-thioglucopyranoside **8**[18] with glycosyl donor **1** in the presence of triethylsilyl triflate afforded predominantly the α-disaccharide **9** in 53% yield and a minor amount of the β-isomer **10** (1.5%) (Table 1, entry 4).

A similar approach was followed for the synthesis of the 4-seleno-5′-thiomaltoside. The selectively protected 4-selenoglucopyranoside acceptor **11** was first required. This was synthesized by the initial displacement of the 4-trifluoromethane-

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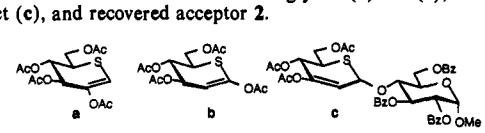
(9) Despite the presence of a participating acetate group at the 2-position of the glycosyl donor, no β-isomer was detected in the reaction. This exceptional behavior of 5-thiohexopyranosyl donors is in accord with our earlier observations[5] as well as those of Hashimoto and Isumi[11] and may be accounted for by the thermodynamic stability of the axially oriented aglycon.

(10) Initial glycosylations were attempted with a 2:1 ratio of the donor **1** and alcohol **2**. These afforded only 50% of the disaccharide **3**. Other compounds isolated in this case were the glycals (**a**) and (**b**), the elimination product (**c**), and recovered acceptor **2**.



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(12) Other compounds isolated were the glycals (**a**) and (**b**), the elimination product (**c**), and recovered acceptor **2**.

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(20) Compound **11** is isolated as a stable solid and can be stored under nitrogen. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.07 (1H, d, $^1J_{Se,H}$ = 23 Hz, $^3J_{SeH,4}$ = 7.9 Hz, Se*H*), 3.62 (1H, dt, $J_{3,4+4,5}$ = 22.0 Hz, $^2J_{4,Se}$ = 7.9 Hz, H-4), 3.94 (3H, s, OCH_3), 4.24 (1H, ddd, $J_{4,5}$ = 11.0 Hz, $J_{5,6a}$ = 4.4 Hz, $J_{5,6b}$ = 2.7 Hz, H-5), 4.80 (1H, dd, $J_{5,6a}$ = 4.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.83 (1H, dd, $J_{5,6b}$ = 2.7 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 5.18 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 5.22 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 5.89 (1H, dd, $J_{2,3}$ = 9.8 Hz, $J_{3,4}$ = 11.0 Hz, H-3), 7.30–8.15 (15H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): 36.2 (C-4), 55.6 (OCH_3), 65.0 (C-6), 71.8 (C-5), 72.7 (C-3), 73.2 (C-2), 97.5 (C-1) ppm.

(21) It is noteworthy that direct displacement of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide with the selenol **11** afforded exclusively the β-disaccharide in 56% yield. Johnston, B. D.; Pinto, B. M. Unpublished results.

(22) All compounds were characterized by high-field ^{1}H and ^{13}C NMR spectroscopy and by microanalysis or electrospray mass spectrometry.

(23) **14**: ^{1}H NMR (400 MHz, D_2O) δ 4.77 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 5.30 (1H, d, $J_{1',2'}$ = 3.3 Hz, H-1′); ^{13}C NMR (100 MHz, D_2O) 85.5 [$^1J(^{13}C,^1H)$ = 163 Hz, (C-1′)], 101.8 ppm [$^1J(^{13}C,^1H)$ = 167 Hz, (C-1)]. **15**: ^{1}H NMR (400 MHz, D_2O) δ 4.56 (1H, d, $J_{1,2}$ = 4.5 Hz, H-1′), 4.82 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1); ^{13}C NMR (100 MHz, D_2O) 56.0 [$^1J(^{13}C,^1H)$ = 154 Hz, (C-1′)], 102.1 ppm (C-1). **16**: ^{1}H NMR (400 MHz, D_2O) δ 4.68 (1H, d, $J_{1',2'}$ = 4.3 Hz, H-1′), 4.84 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1); ^{13}C NMR (100 MHz, D_2O) 41.9 (C-1′), 102.1 ppm (C-1).

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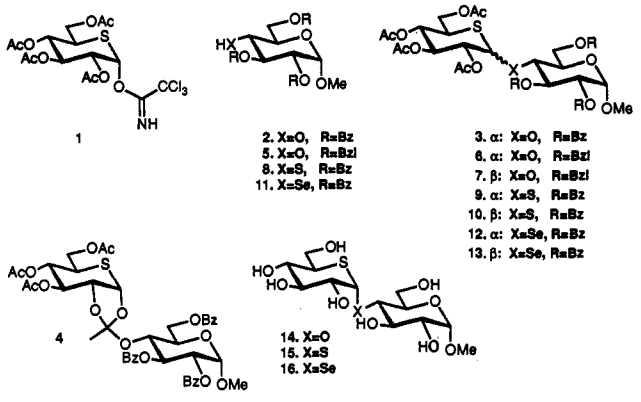

sulfonate of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[18] by potassium selenocyanate, followed by reduction of the selenocyanate with sodium borohydride.[19,20] Glycosylation of **11** with **1** under triethylsilyl triflate catalysis yielded a mixture of the α- and β-disaccharides **12** and **13** in yields of 46% and 11%, respectively.[21] Disaccharides **3**, **9**, and **12** were deprotected by treatment with 2 N sodium methoxide in methanol to afford the disaccharides **14**, **15**, and **16**, respectively, in 75–90% yields.[22,23]

In conclusion, the 5-thioglucopyranosyl trichloroacetimidate **1** has proved to be an effective glycosyl donor for the synthesis of novel disaccharides with sulfur in the ring of the nonreducing sugar and a chalcogen atom in the interglycosidic linkage. The synthesis of 4,5′-dithiomaltoside and the heavier congener, 4-seleno-5′-thiomaltoside, provides entry to a new class of compounds for evaluation as glycosidase inhibitors.

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