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New and Facile Synthetic Routes to 5-Thioaldohexopyranosides *via* Aldose Monothioacetal Derivatives

Hironobu Hashimoto*, Masashi Kawanishi, and Hideya Yuasa

Department of Life Science

Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology,

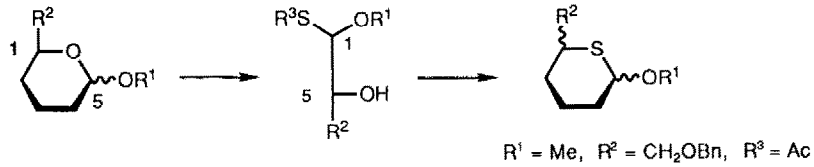
Nagatsuta, Midori-ku, Yokohama 227, Japan

Key Words: 5-thioaldopyranoside; acyclic monothioacetal; dimethylboron bromide

Abstract: *Two new synthetic routes of 5-thioaldohexopyranosides were developed via aldose S-acetyl O-methyl monothioacetals obtained by one-pot treatment of methyl hexopyranosides with dimethylboron bromide and then thiolacetic acid.*

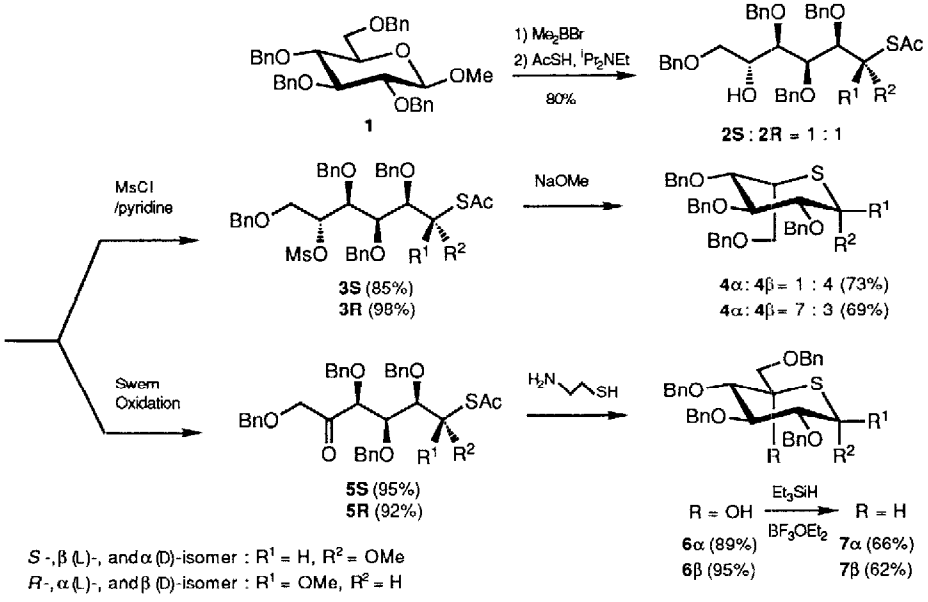
5-Thioaldose exists in a pyranose form having sulfur atom in the ring and can be classified as pseudosugar which was used originally for carbocyclic analog. Synthetic studies on 5-thioaldose started in early 1960s and several analogs of aldohexose such as D-glucose,[1] D-galactose,[2] *N*-acetyl-D-glucosamine,[3] L-rhamnose,[4] D-mannose[5] and L-fucose[6] were synthesized. However, their synthetic strategies are principally the same in terms of introducing sulfur atom at C-5 via furanose derivative except only one case[3b] and require many steps.

Recently 5-thio-D-mannnose[7] was isolated from marine sponge (*Clathria pyramida*) as the first natural 5-thioaldose and further 5-thio-L-fucose was found to have remarkable and specific inhibitory effects on bovine α-L-fucosidases.[6] Glycosidase inhibitor became one of the most attractive target compounds not only for the study of reaction mechanism of glycosidase[8] but also for manipulation of biologically multifuntional oligosaccharide chain of glycoconjugates.[9] These facts prompted us to develop new and facile synthetic routes according to the strategy outlined in Scheme 1.



Scheme 1

Acyclic monothioacetal derived from pyranoside by the method of Guindon and Anderson[10] was selected as a potential intermediate because the monothioacetal has two necessary functional groups for forming the 1,5-sulfide linkage, that is, a free hydroxyl at C-5 and sulfur atom at the acetalic carbon (C-1). To make attack of the sulfur atom at C-5 possible, acetylthio group[11] was introduced instead of phenylthio group. Methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (**1**) was treated with dimethylboron bromide at -78°C for 30 min and then with thiolacetic acid and diisopropylethylamine for further 1.5 h to give D-glucose *S*-acetyl *O*-methyl monothioacetal derivative (**2**)[12] in 80% yield as a 1:1 epimeric mixture. The monothioacetal **2** could be converted into two 5-thio-D-aldopyranoses, that is, 5-thio-L-idopyranoside and 5-thio-D-glucopyranoside derivatives (**4** and **7**), with inversion of the configuration at C-5 and retention of the configuration, respectively, as shown in Scheme 2.

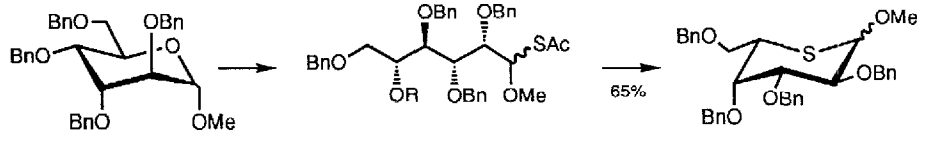


Scheme 2

In the first method, the 5-hydroxyl group was converted to the mesyloxy group (**3**), which was substituted with intramolecular sulfide anion formed by treatment of **3** with sodium methoxide to give methyl 5-thio-L-idopyranoside derivative **4** in 59% yield as a 1:1 anomeric mixture. In order to elucidate the configuration of the thioacetal carbon the pure epimers of **3**, *i.e.*, **3S** and **3R**, were derived from the chromatographically separated **2S** and **2R**, respectively. The cyclization of **3S** and **3R** gave unexpectedly the anomeric mixtures in 73% (**4**α:**4**β = 1:4) and 69% (**4**α:**4**β = 7:3), respectively. However, the distinct predominance of the β(L)-anomer from **3S** and that of the α(L)-anomer from **3R** could assign the configuration. Structures of **4**α and **4**β, that is, the configurations of the anomeric and C-5 carbons, were determined by the coupling constants of the ring protons,[12] indicating L-*ido* configurations and $^4C_1$ conformations. As an alternative and more efficient method, diethyl azodicarboxylate / triphenylphosphine reaction[13] was successfully applied to **2** using the intramolecular thiolacetate as nucleophilic carrier to give **4** in 64% yield again as a 1:1 anomeric mixture.

In the second cyclization method, to maintain the configuration of the original aldose, a spontaneous hemithioacetal formation was utilized. Swern oxidation of **2** gave the corresponding 5-ulose, which was converted to a cyclized hemithioacetal derivative **6** by de-*S*-acetylation with 2-aminoethylmercaptan. The configuration at C-5 was deduced from a thermodynamical point of view. When the pure epimers of **2**, *i.e.*, **2S** and **2R** was converted in the same manner via **5S** (95%) and **5R** (92%), only the α(D)-anomer **6α** for the former and the β(D)-anomer **6β** for the latter were obtained exclusively in 89% and 95% yields, respectively. The tertiary hydroxyl group of **6α** and 6β were deoxygenated with triethylsilane and trifluoroboron etherate to give per-*O*-benzylated methyl D-glucopyranoside **7α**[1d] and **7β** in 66% and 62% yields, respectively.

Furthermore, the first route was also proved to be applicable to the corresponding α-D-*altro* isomer **8**, giving per-*O*-benzylated methyl 5-thio-L-galactopyranoside **11** as shown in Scheme 3.



8 **9** R = H 67% (1:1) **10** R = Ms 86% **11** (α:β = 2 : 1)

Scheme 3

The above described new synthetic routes of 5-thioaldoses may contribute to their availability in the field of studies on the roll of carbohydrates in biological recognition.

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References and Notes

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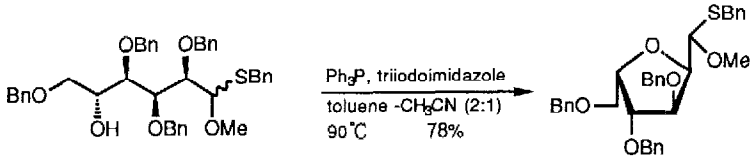
11. Benzylthio and ethylthio groups were also examinated to give 2,5-anhydro derivatives in good yields as shown in the following example and the related results will be published elsewhere.



12. All new compounds were characterized by spectroscopic data and elemental analysis. **2S**: $[\alpha]_D^{25}$ +24.7° ($CHCl_3$); ^{1}H NMR: 5.49(d, J=2.5Hz, H-1), 3.25(s, OMe), 2.96(broad s, OH), 2.33(s,SAc). **2R**: $[\alpha]_D^{25}$ -15.3° ($CHCl_3$); ^{1}H NMR($CDCl_3$, ppm): 5.62(d, J=2.5Hz, H-1), 3.30(s, OMe), 2.96(broad s, OH), 2.37(s, SAc). **3S**: ^{1}H NMR: 2.91(s, OMs). **3R**: ^{1}H NMR: 2.90(s, OMs). **4α**: $[\alpha]_D^{25}$ -67.2, ($CHCl_3$); ^{1}H NMR: 4.86(d, H-1), 3.93(dd, H-4), 3.86(dd, H-6a), 3.76(dd, H-3), 3.73(dd, H-6b), 3.68(t, H-2), 3.50(s, OMe), 3.13(m, H-5), $J_{1,2}$=8.2, $J_{2,3}$=8.2, $J_{3,4}$=8.6, $J_{4,5}$=5.2Hz; ^{13}C NMR ($CDCl_3$, ppm): 69.5(C-6), 58.7(OMe), 40.9(C-5). **4β**: $[\alpha]_D^{25}$ -23.2° ($CHCl_3$); ^{1}H NMR: 4.36(d, H-1), 4.01(dd, H-4), 3.92(dd, H-6a), 3.84(dd, H-3) 3.83(t, H-6b), 3.77(dd, H-2), 3.38(s, OMe), 3.21(m, H-5), $J_{1,2}$=3.2, $J_{2,3}$=9.5, $J_{3,4}$=9.5, $J_{4,5}$=4.3Hz; ^{13}C NMR: 69.8(C-6), 56.3(OMe), 43.2(C-5). **5S**: $[\alpha]_D^{18}$ +12.0° ($CHCl_3$); ^{1}H NMR: 5.35(d, H-1), 3.21(s, OMe), 2.33(s,SAc). **5R**: ^{1}H NMR: 5.53(d, H-1), 3.28(s, OMe), 2.38(s, SAc); ^{13}C NMR($CDCl_3$, ppm): 206.7(C=0). **6α**: $[\alpha]_D^{16}$ +28° ($CHCl_3$); ^{1}H NMR: 4.24(t, H-3), 4.23(s, OH), 4.00(d, H-4), 3.89(dd, H-2), 3.68 and 3.45(each d, H-6), 3.49(s, OMe), **6β**: ^{1}H NMR: 3.56 and 3.36(each d, H-6), 3.53(s, OMe). **7β**: ^{1}H NMR: 2.90(dt, H-5), $J_{4,5}$=9.8Hz; ^{13}C NMR: 68.9(C-6), 58.7(OMe), 43.8(C-5). **9**: ^{1}H NMR: 5.61 and 5.54(each d, H-1), 3.33(s, OMe), 2.74(s, OH), 2.37 and 2.35(each s, SAc). **10**: ^{1}H NMR: 5.59 and 5.54(each d, H-1), 3.31 and 3.29(each s, OMe), 2.96 and 2.94(each s, OMs), 2.36 and 2.32(each s, SAc). **11**: ^{1}HNMR: 4.45(d,H-1α), 3.88(dd, H-3α), 3.49 and 3.37(t and dd, H-6α), 3.42(s, α-OMe), 3.34(ddd, H-5), $J_{1,2}$=3.1, $J_{2,3}$=10.1, $J_{3,4}$= 2.5, $J_{4,5}$=1.2Hz; 4.49(d, H-1β), 4.17(t, H-4β), 4.10(t-H-2β), 3.59 and 3.54(t and dd, H-6β), 3.50(s, β-OMe), 3.39(dd, H-3β), 3.05(dt, H-5β), $J_{1,2}$=7.9, $J_{2,3}$=8.1, $J_{3,4}$=$J_{4,5}$=2.3Hz.

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