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Pummerer rearrangement of 1-deoxy-5-thioglucopyranose oxides; novel synthesis of 5-thioglucopyranose derivatives

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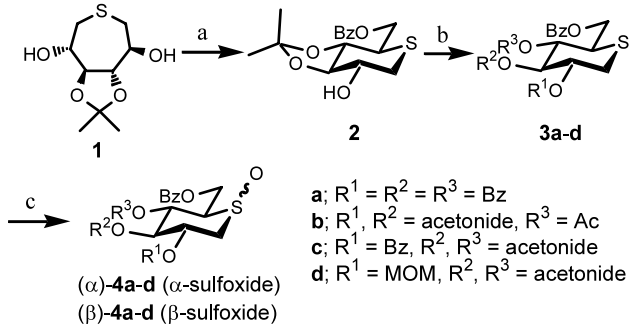
Abstract—The Pummerer rearrangement of 3,4-*O*-isopropylidene-1-deoxy-5-thiopyranose oxide derivatives took place at the C1 position regioselectively to give the corresponding 5-thiopyranoses. The reaction mechanism of this reaction is also discussed.

Since Pummerer rearrangement provides a synthetic equivalent of carbonyl compounds from sulfoxides, an equivalent for alcohols under non-oxidative conditions, it has been utilized in the total syntheses of natural products as an alternative protocol for oxidation of the alcohols.[1,2] This reaction might be desirable for introduction of the C1 hemithioacetal group of thiosugars if we can perform the reaction of 1-deoxy-5-thiopyranose oxides (or thiofuranose oxides[3]) at the C1 position regioselectively. In the course of our synthetic studies on oligothiosaccharides,[4] we revealed that the Pummerer rearrangement of 1-deoxy-5-thioglucopyranose with an acetonide protective group at the C3-, C4-alcohols proceeds at the C1 position regioselectively, providing 5-thioglucose derivatives in good yields. The mechanism of this selectivity is also discussed in this paper.

In spite of extensive studies by Oae[5] and Crucianelli[6] on Pummerer rearrangements, the regioselectivity for asymmetric sulfoxides has not been discussed well. Recently, Naka et al. investigated regio- and stereoselective formation of thionucleosides via Pummerer-type glycosidation.[3] However, their studies did not provide enough information to predict the regioselectivity for our substrates. Thus, 1-deoxy-5-thioglucopyranose oxides (α)-**4** and (β)-**4** carrying various protective groups were prepared as the substrates in order to study the reactivity and regioselectivity in the Pummerer rearrangement. Based on the information by Merrer et al.,[7,8] thiepane **1** was subjected to a ring contraction under the Mitsunobu conditions to give 1-deoxy-5-thioglucopyranose **2** in 80% yield (Scheme 1). This was first converted to tetrabenzoate **3a** by acidic removal of the acetonide group of **2** and subsequent treatment with BzCl in pyridine. Since acidic treatment of **2** in acetone resulted in partial migration of the acetonide, the 2,3-*O*-acetonide thus obtained was also converted into acetate **3b**. The recovered 3,4-*O*-acetonide was transformed to dibenzoate **3c** and MOM ether **3d** under the usual conditions. Oxidation of **3a–d**



Scheme 1. *Reagents and conditions*: (a) PPh_3, DEAD, PhCOOH, THF, rt (80%); (b) for **3a**; (i) *cat*. HCl, MeOH, rt (84%), (ii) BzCl, pyridine, rt (100%); for **3b–d**; (i) *cat*. *p*-TsOH, rt, acetone, then separations, (ii) →**3b**, Ac_2O, pyridine, rt (100%); →**3c**, BzCl, pyridine, rt (95%); →**3d**, MOMCl, $(iPr)_2NEt$, CH_2Cl_2, 0°C (60%); (c) *m*CPBA, CH_2Cl_2, –20°C (**4a**, 96%, **4b**, 92%, **4c**, 91%, **4d**, 88%, isomeric ratios (α:β) **4a**, 50:50, **4b**, 60:40, **4c**, 60:40, **4d**, 50:50).

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Table 1. The characteristic ^1H and ^{13}C NMR chemical shifts of sulfoxides (α)- and (β)-**4a**–**d**, and their differences $\Delta\delta(=\delta(\alpha)-\delta(\beta)$, *italic*)

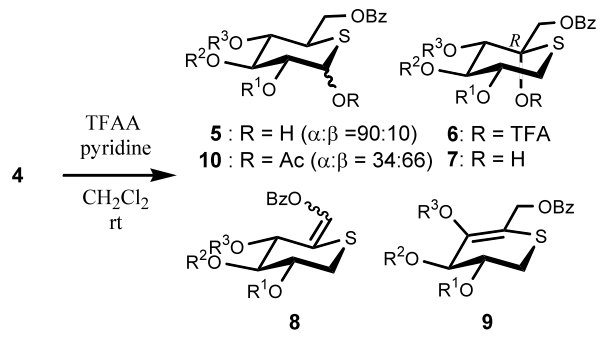
Signals	**4a**[a]		**4b**[b]		**4c**[b]		**4d**	
	α	β	α	β	α	β	α	β
C1Hax	3.22	2.72	2.57	1.63	2.66	1.58	3.01[a]	2.41[a]
	+0.50		*+0.94*		*+1.08*		*+0.60*	
C1Heq	4.02	3.85	3.33	3.03	3.24	3.33	3.79[a]	3.72[a]
	+0.17		*+0.30*		*−0.09*		*+0.07*	
C2H	5.45	6.11	3.10	4.61	5.32	6.13	4.03[a]	4.52[a]
	−0.70		*−1.51*		*−0.81*		*−0.49*	
C4H	5.79	6.23	5.52	6.00	3.25	4.39	3.50[a]	4.13[a]
	−0.44		*−0.48*		*−1.14*		*−0.63*	
C5H	3.49	3.38	2.73	2.53	2.82	2.65	3.23[a]	3.11[a]
	+0.11		*+0.20*		*+0.17*		*+0.12*	
C1	52.6	47.4	52.3	48.1	53.4	49.2	55.1[b]	50.6[b]
	+5.2		*+4.2*		*+4.2*		*+4.5*	
C2	65.3	67.3	67.1	68.9	67.8	69.3	68.9[b]	71.1[b]
	−2.0		*−1.8*		*−1.5*		*−2.2*	
C4	64.8	67.9	69.2	71.5	71.4	72.9	70.7[b]	72.7[b]
	−3.1		*−2.3*		*−1.5*		*−2.0*	
C5	65.7	59.0	65.1	60.6	64.8	59.2	63.9[b]	58.8[b]
	+6.7		*+4.5*		*+5.6*		*+5.1*	

[a] Observed in $CDCl_3$.
[b] Observed in C_6D_6.

by *m*CPBA gave diastereomeric mixtures of α-sulfoxides (α)-**4a**–**d** and β-sulfoxides (β)-**4a**–**d**, respectively, in high yields. These isomers were readily separated by column chromatography. Their stereochemistry was estimated by comparison of their ^1H and ^{13}C NMR spectra.[8–11] The characteristic signals are shown in Table 1. Except for C1Heq, signs of the $\Delta\delta$ value $[=\delta(\alpha\text{-isomer}-\delta(\beta\text{-isomer})]$ are consistent with the literature. There were no significant differences in the chemical shifts in the C1Heq, probably due to both *gauche* relationship of sulfoxide-C1Hax and sulfoxide-C1Heq.

With these sulfoxides **4** in hand, their Pummerer rearrangement reactions were examined. Our preliminary experiments disclosed that the rearrangement did not proceed at room temperature when Ac_2O was employed. The heating conditions gave complex mixtures in the cases that **4a** and **4c** were employed as the substrates. The conditions using trifluoroacetic anhydride (TFAA) in place of Ac_2O,[2] the modified protocol developed by one of the authors, was found to proceed at room temperature. Thus, treatment of (α)-**4a** with TFAA (5.0 equiv.) in the presence of pyridine (12 equiv.) in CH_2Cl_2 at room temperature for 3 h gave 5-thioglucopyranose derivative **5a** in low yield (5.7%). 5-Trifluoroacetoxy derivative **6a** (8.9%), the corresponding alcohol **7a** (50%), *exo*-olefin **8a** (4.0%), and *endo*-olefin **9a** (9.5%) were also afforded by the reaction as shown in Table 2. The product **5a** was isolated as an alcohol but not the corresponding TFA ester, which will be discussed later. The products **6a**, **7a**, and **8a** were observed as single isomers, respectively, on their ^1H NMR spectra. The stereochemistries of **6a** and **7a**

Table 2. Pummerer rearrangement employing some sulfoxides



a; $R^1=R^2=R^3$ = Bz: **b**; R^1, R^2 = acetonide, R^3 = Ac:
c; R^1 = Bz, R^2, R^3 = acetonide: **d**; R^1 = MOM, R^2, R^3 = acetonide

Run	Substrates	Products (%)				
		5	**6**	**7**	**8**	**9**
1	(α)-**4a**	5.7	8.9	50	4.0	9.5
2	(β)-**4a**	2.7	5.6	41	0.3	8.1
3	(α)-**4b**	N.d.[b]	40	1.7	14	1.7
4	(β)-**4b**	N.d.	45	1.2	9.4	1.2
5	(α)-**4c**	55	Trace	Trace	Trace	N.d.
6	(β)-**4c**	61	Trace	Trace	Trace	N.d.
7[a]	(α)-**4c**	66	N.d.	N.d.	N.d.	N.d.
8[a]	(β)-**4c**	65	N.d.	N.d.	N.d.	N.d.
9	(α)-**4d**	66[c]	N.d.	N.d.	Trace	N.d.
10	(β)-**4d**	84[c]	N.d.	N.d.	N.d.	N.d.

[a] Pyridine was employed as the solvent.
[b] N.d. = not detected.
[c] Yields of **10c** obtained after acetylation employing Ac_2O in pyridine.

were both tentatively assigned as 5*R* (*carbohydrate numbering*) by considering the anomeric effect. However, conclusive evidence for their stereochemistry was not provided by NOE studies. It can be supposed that **7a**, **8a**, and **9a** are generated by degradation of TFA ester **6a** under the reaction conditions and/or purification process.[12] Accordingly, the rearrangement for **4a** proceeded at the C5 position regioselectively.

When 2,3-*O*-acetonide (α)-**4b** was employed, the rearrangement proceeded with higher regioselectivity at the C5 position (*carbohydrate numbering*) to give a mixture of **6b**, **7b**, **8b**, and **9b**. Thioglucopyranose **5b**, obtainable through the rearrangement at the C1 position, was not observed under those conditions.

In contrast, similar treatment of 3,4-*O*-acetonide (α)-**4c** effected the rearrangement at the C1 position in a highly regioselective manner to give 5-thioglucopyranose derivative **5c**[13] along with trace amounts of **6c**–**9c**, caused by the rearrangement at the C5 position (runs 5 and 6). The reactions gave **5c** in slightly higher yields without production of **6c**–**9c** when pyridine was employed as the solvents (runs 7 and 8). The existence of the OH group in **5c** was confirmed by observing strong absorption at 3440 cm^{-1} (broad) in the IR spectrum. Probably, the corresponding TFA ester of **5c**

is not stable enough, so that the ester moiety might be hydrolyzed during the work-up. The ^{1}H NMR spectrum indicated that **5c** consists of the two anomers (α:β = 90:10).

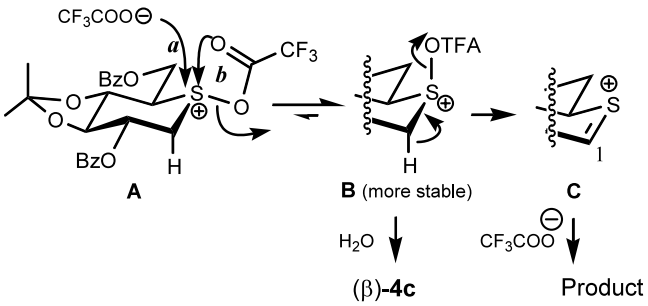
Since **5d** appeared as a broad spot on the TLC, the crude mixture was acetylated prior to purification, giving an anomeric mixture of **10d** in 66% yield in two steps. Preparative silica gel TLC could separate the isomers.[13]

When a series of β-sulfoxides (β)-**4a**–**d** were subjected to the Pummerer conditions, the same products as those obtained from the corresponding α-sulfoxides were afforded in slightly different yields. Noteworthy, (β)-**4d** gave **10d** in 84% yield after acetylation. It seems the stereochemistry about the sulfoxide moiety is not important for the regioselectivity in the rearrangements according to these observations. This is inconsistent with Naka's report, disclosing the stereochemistry of sulfoxides contributes significantly to the regioselectivity, although they used TMSOTf as the activator.[3] By performing at 0°C for 20 min, the reaction transformed (α)-**4c** into (β)-**4c** in 60% yield along with the rearranged product **5c** (27%). This observation suggests that the rearrangements may proceed through the common intermediates in our cases. The isomerization of sulfonium ion **A** may occur through intermolecular path ***a*** or intramolecular path ***b*** as shown in Scheme 2, although we can not figure out at this time which pathway contributes predominantly. The sulfonium **B** seemed to be hydrolyzed to sulfoxides during work-up, giving sulfoxide (β)-**4c**. Inversion by a hydroxy anion can be ignored because of excess TFAA which must consume H_2O quickly. Since Oae et al. have disclosed that the Pummerer rearrangement of cyclic sulfoxides proceeds through E2 1,2-elimination,[5] carbenium ion **C** might be formed from sulfonium **B**. A trifluoroacetate ion attacks the C1 to terminate the reaction. Subsequent hydrolysis of the ester moiety during work-up afforded **5c**. Isomerizations to α-sulfoxides (α)-**4a**–**d** were not observed by those TLC analyses in the cases of the reaction for the corresponding β-sulfoxides.

The regioselectivities are discussed next. Acetonides **4c** and **4d** carry an electron-withdrawing benzoate ester and an electron-donating MOM ether, respectively, at their C2 positions (*carbohydrate numbering*). However, these provided similar results. Accordingly, an electrostatic factor might not contribute to the regioselectivity. On the other hand, the position of the acetonide group dramatically influenced the selectivity as mentioned above. Thus, a relationship between the selectivity and conformations of the ring moiety of **4** was investigated using molecular modeling calculations. Model compounds **X**, **Y**, and **Z** were chosen in order to save the time required for the calculations. The results are summarized in Table 3.[14]

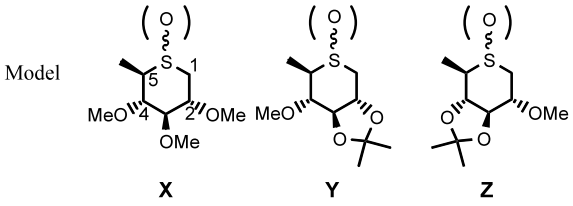
In the cases of bicyclic **Y** and **Z**, the annular bond angles of the carbons, where the rearrangement occurred mainly in the experiments (∠S–C5–C4 for **Y**, ∠S–C1–C2 for **Z**), were suggested to be around 115°, which approximates that for sp^2 carbons. Thus, these carbons can be easily transformed to the planar carbocation by losing the proton attached. In contrast, the angles for other sites (∠S–C1–C2 for **Y**, ∠S–C5–C4 for **Z**) were estimated to be around 105°, which is rather narrower than that of standard sp^3. So, these carbons might stay during the reactions. While there was no remarkable difference between the angles ∠S–C1–C2 and ∠S–C5–C4 for monocyclic **X** according to similar calculations, the Pummerer rearrangement of **4a** proceeded selectively at C5. It can still be explained by taking the Saytzeff rule into account.[15]

As described, the Pummerer rearrangement of 1-deoxy-5-thioglucopyranoses with an acetonide group at the C3-, C4-hydroxy groups were found to provide 5-thioglucose derivatives efficiently. Since the products **5c** and **5d** carry nonidentical hydroxyl protective groups which can be distinguished in the deprotecting steps, those can be utilized for our synthetic studies on oligothiosaccharides.



Scheme 2.

Table 3. Bond angles ∠S–C1–C2 and ∠S–C5–C4 of sulfoxides suggested by molecular modeling calculations (6-31G*)



∠S–C1–C2			
Sulfide (°)	112.2	107.3	115.3
α-Sulfoxide (°)	112.1	106.5	116.3
β-Sulfoxide (°)	112.6	107.7	116.2
∠S–C5–C4			
Sulfide (°)	110.9	113.9	106.3
α-Sulfoxide (°)	110.6	114.6	105.4
β-Sulfoxide (°)	111.1	114.3	106.5

Acknowledgements

We would like to thank Professor Jun Kawabata and Dr. Eri Fukushi of Hokkaido University for measurements of mass spectra and Emeritus Professor Haruhisa Shirahama of Hokkaido University for fruitful discussions.

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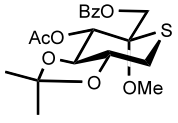
12. Actually, treatment of **6b** with triethylamine in MeOH gave **8b** (8.0%), **9b** (17%), recovered **6b** (25%), and methyl ether **11** (12%).



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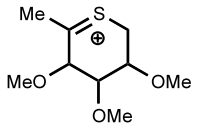
13. Typical reaction conditions are as follows:
A mixture of (α)-**4c** (40.5 mg, 91.2 mmol) and TFAA (30 mL, 212 mmol) in pyridine (1.5 mL, 594 mmol) was stirred at room temperature for 2 h. After MeOH (1.0 mL) was added, the mixture was concentrated in vacuo to give the crude **6d** as an oil, which was treated with Ac_2O (300 mL, excess) in pyridine (600 mL) for 2 h. After concentration in vacuo, silica gel column chromatography of the residue (AcOEt:hexane = 10:90) gave a diastereomeric mixture of **6c** (26.5 mg, 66%) as an oil. IR (film) 3440, 2985, 2930, 1720, 1270, 1110, 1070, 710 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two anomers (α:β = 90:10). Assignments of signals for the main α-anomer and some for the minor β-isomer are described. ^1H NMR (400 MHz, C_6D_6, α:β = 90:10) 1.24, 1.26 (each 3H′b, s, $C(CH_3)_2$ (β-anomer)), 1.27, 1.30 (each 3H′a, s, $C(CH_3)_2$ (α-anomer)), 3.66 (1H′a, dt, J = 3.9, 11.2 Hz, C5*H* (α-anomer)), 3.82 (1H′a, dd, J = 11.2, 11.7 Hz, C4*H* (α-anomer)), 4.25 (1H′a, t, J = 11.7 Hz, C3*H* (α-anomer)), 4.39 (1H′a, dd, J = 3.9, 11.2 Hz, C6*H* (α-anomer)), 4.48 (1H′b, t, J = 10.3 Hz, C3*H* (β-anomer)), 4.71 (1H′b, dd, J = 6.8, 11.2 Hz, C6*H* (β-anomer)), 4.78 (1H′a, dd, J = 3.9, 11.2 Hz, C6*H* (α-anomer)), 5.08 (1H, brs, C1*H*), 5.54 (1H′a, dd, J = 3.4, 11.7 Hz, C2*H* (α-anomer)), 5.65 (1H′b, dd, J = 7.8, 10.3 Hz, C2*H* (β-anomer)), 6.94–7.20 (6H, *aromatic protons*), 8.08–8.20 (4H, *aromatic protons*). FDMS m/z = 445 ([M+H]$^+$), EIMS (rel. int.) m/z = 429 (1.8, [M−CH_3]$^+$), 322 (4.5, [M−PhCOOH]$^+$), 105 (100, [PhCO]$^+$), EIHRMS calcd for $C_{22}H_{21}O_7S$ ([M−CH_3]$^+$): 429.1008, found m/z = 429.1012.
As described in the text, **5d** appeared as a broad spot on the TLC. So, the crude residue including **5d** was acetylated under the usual conditions, providing acetate **10d** in 66% in two steps. Product **10d** consisted of a 34:66 anomeric mixture. These were separated by preparative silica gel TLC (AcOEt:benzene = 3:97).
Spectral data for **10d** are as follows: (α-anomer) $[\alpha]_D^{23}$ +92° (*c* 9.5, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6) δ 1.28, 1.29 (each 3H, s, $C(CH_3)_2$), 1.64 (3H, s, CH_3CO-), 3.20 (3H, s, CH_3OCH_2O-), 3.60–3.68 (2H, C4*H*, C5*H*), 4.01 (1H, dd, J = 8.3, 10.8 Hz, C3*H*), 4.10 (1H, dd, J = 3.9, 10.8 Hz, C2*H*), 4.32 (1H, dd, J = 7.9, 11.8 Hz, C6*H*), 4.57, 4.72 (each 1H, d, J = 6.8 Hz, CH_3OCH_2O-), 4.81 (1H, dd, J = 3.4, 11.8 Hz, C6*H*), 6.41 (1H, d, J = 3.9 Hz, C1*H*), 6.97–8.14 (5H, *aromatic protons*). FDMS m/z = 426 (M$^+$), EIMS (rel. int.) m/z = 411 (4.1, [M−CH_3]$^+$), 304 (8.0, [M−PhCOOH]$^+$), 105 (100, [PhCO]$^+$), EIHRMS calcd for $C_{19}H_{23}O_8S$ ([M−CH_3]$^+$): 411.1114, found m/z = 411.1121.
(β-isomer): $[\alpha]_D^{23}$ −43° (*c* 14.5, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6) δ 1.15, 1.17 (each 3H, s, $C(CH_3)_2$), 1.41 (3H, s, CH_3CO-), 3.00 (1H, ddd, J = 5.3, 7.3, 9.3 Hz, C5*H*), 3.11 (3H, s, CH_3OCH_2O-), 3.48 (1H, t, J = 9.3 Hz, C3*H*), 3.78 (1H, t, J = 9.3 Hz, C4*H*), 4.13 (1H, dd, J = 4.9, 9.3 Hz, C2*H*), 4.20 (1H, dd, J = 7.3, 11.7 Hz, C6*H*), 4.57, 4.73 (each 1H, d, J = 6.8 Hz, CH_3OCH_2O-), 4.60 (1H, dd, J = 5.3, 11.7 Hz, C6*H*), 6.10 (1H, d, J = 4.9 Hz, C1*H*), 6.85–8.08 (5H, *aromatic protons*). FDMS m/z = 426 (M$^+$), EIMS (rel. int.) m/z = 411 (7.3, [M−CH_3]$^+$), 304 (39, [M−PhCOOH]$^+$), 105 (100, [PhCO]$^+$), EIHRMS calcd for $C_{19}H_{23}O_8S$ ([M−CH_3]$^+$): 411.1114, found m/z = 411.1137.
14. PC Spartan Pro version 1.08 by Wavefunction Inc. was used for the calculations. Since some model compounds employed for the calculations involved a sulfoxide function, ab initio method based on the 6-31G* basis set was employed by taking the accuracy into account. When 6-31G* was employed, optimization for these model compounds required 20–60 h by our systems (Athron XP 1800+, 256 Mb RAM). Since conformation search by AM1 for sulfide **X** gave many stable conformations (15 conformations), only the conformation found as the most stable by the above calculations was re-optimized by 6-31G* for sulfide and sulfoxides **X**. Conformation searches for model sulfides **Y** and **Z** could be performed directly with 6-31G*, providing three and five stable conformations, respectively. The conformations with

minimum energies found by the above calculations were employed as the initial geometries for optimization of the corresponding sulfoxides.

15. Our preliminary calculations for carbenium ions **12** and **13** based on 6-31G* suggested that **12** is 9 kcal/mol more stable than that of **13**. This result may explain the selectivity of the rearrangement. However, that energy difference obtained is too large to explain the ratio in the experiment. The existence of the counter anion (TFA^-) also might be important for this kind of consideration.



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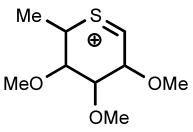

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