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Reversible Generation of Glycosyl Radicals from Telluroglycosides under Photochemical and Thermal Conditions

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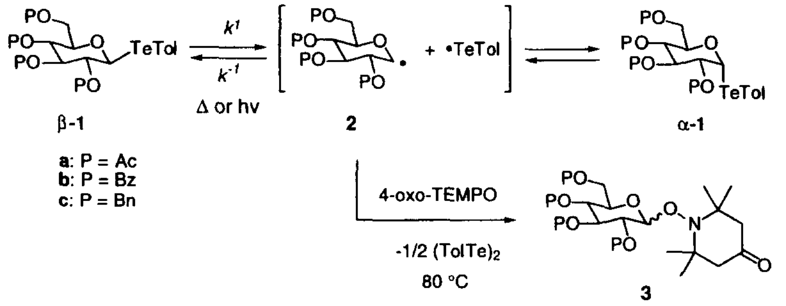
Abstract: 1-β-Telluroglycosides isomerize to α-isomers upon photolysis and thermolysis. The isomerization follows first-order reaction kinetics and proceeds through a glycosyl radical intermediate by homolytic C-Te bond cleavage. The radicals so generated are trapped intermolecularly by TEMPO free radical, indicating that the glycosyl radicals are efficiently generated by a non-chain mechanism.

As radicals are a neutral species and thus compatible with a wide range of functional groups, glycos-1-yl radicals have been a topic for *C*-glycoside synthesis.[1] The glycosyl radicals are commonly generated in a radical chain reaction by, for example, the tin hydride reduction of 1-halo-[2] and 1-selenoglycosides,[3] and they react with a variety of electron-deficient olefins to give *C*-glycosides. However, since chain-carrying radicals are subject to several competing pathways, e.g., reduction of the glycosyl radical by tin hydride, or termination of the chain by radical coupling reactions, only a certain combination of substrates can be used for the chain reaction. In this respect, new methods for the generation of the glycosyl radicals by a non-chain mechanism are strongly needed. While a variety of new methods for the generation has been developed so far,[2-5] only few examples are based on a non-chain reaction.[6] We report here that telluroglycoside **1** generates glycosyl radical **2** under photolysis and thermolysis by homolytic C–Te bond cleavage without the need of chain-carrying reagents.[7] While the glycosyl radical so generated predominantly returned to the starting telluroglycoside without trapping agents, it reacts intermolecularly with various radical scavengers, e.g., 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) free radical (Eq. 1).[8] Though the glycosyl radical generation from telluroglycoside has been already reported,[5] both the radical initiator and mediator play important roles in such cases.



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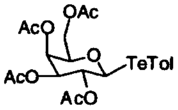
The initial information of the generation of the glycosyl radical was obtained by the photochemical isomerization of **1a** (P = Ac). When a C_6D_6 solution of β-**1a** (stereochemical purity >99%, λ_{max} = 324 nm) in a Pyrex NMR tube was irradiated with a UV lamp [Rayonet RMR-600 photo-reactor equipped with RMR-3000Å lamp (3.9 W x 8)] at 40 °C, rapid growth of α-**1a** was observed. After 2h irradiation, the reaction mixture consisted of an 84:16 mixture of the α- and β-isomers (Table 1, entry 1). Stereochemically pure α-**1a** (λ_{max} = 326 nm) also isomerized to an 83:17 mixture of the α- and β-isomers upon UV irradiation at 40 °C for 0.5 h, and the isomeric ratio remained unchanged even after 10 h (entry 2). These results clearly revealed that the isomerization took place under thermodynamic control. The rate of the isomerization followed *first-order reaction kinetics* and was virtually insensitive to the concentration of **1** (0.10 M and 0.20 M C_6D_6 solution) as well as the solvent polarity (C_6D_6 and CD_3CN). The first-order rate constant (k) from β-**1a** to α-**1a** and that of the reverse reaction (k^{-1}) were obtained as 22 x 10^{-5} s^{-1} and 9.6 x 10^{-5} s^{-1} (40 ± 3 °C in CD_3CN), respectively. These results are consistent with the assumption that the isomerization proceeds by an unimolecular radical mechanism[9] which involves reversible generation of the glycosyl radical **2** by homolytic C–Te bond cleavage. During the isomerization, slow decomposition of **1a** was observed, but ca. 80% of **1a** still remained intact after 2 h in C_6D_6. Since no homo-coupling product of **2** was observed, the generated radical pair selectively recombined to **1** under these conditions. It is interesting to note that the equilibrium composition was slightly altered by the reaction conditions, and that the isomeric ratio varied from 84:16 to 69:31 depending on the solvent polarity and the light sources (RMR-3500Å UV lamp and Xe lamp).[10]



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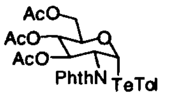

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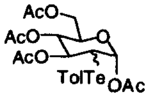

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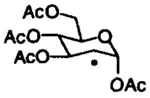

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A variety of telluroglycosides with various protecting groups and substitution patterns were found to generate the corresponding glycos-1-yl radicals under UV irradiation as judged by the stereochemical isomerization (entries 3-8). The α-isomers were found to be more thermodynamically stable than the β-isomers in all cases except for **6**. As in the case of glycosyl cation formation,[11] the glycosyl radical formation from alkyl protected glycosides took place faster than that from acyl protected ones. Thus, while acyl protected **1a** and **1b** required 2 h to reach complete equilibrium, alkyl protected **1c** completely isomerized within 1 h (entries 1-5). The galactose derivative β-**4** also isomerized, and the first-order rate constants k and k^{-1} were obtained as 38 x 10^{-5} s^{-1} and 4.6 x 10^{-5} s^{-1}, respectively (40 ± 3 °C in C_6D_6, entry 6). The C-2 substituent was found to have pronounced effects. Isomerization of the 2-deoxyglucose derivative **5** completed within 2 h (α:β = 83:17), but a significant amount of side products, e.g., 3,4,6-tri-*O*-acetyl-glycal, was formed (entry 7). The rate of isomerization of the phthaloyl protected 2-deoxy-2-aminoglucose **6** was slow, and a 27:73 mixture of the α- and β-isomers was obtained after 40 h (entry 8).

We next examined the trapping of the radical **2** by external radical scavengers. Photolysis of **1a** with 4-oxo-TEMPO free radical (2.2 equiv.) in toluene at room temperature to 80 °C afforded **3a** (P = Ac) in 93%

Table 1. Photochemical and Thermal Isomerization of Telluroglycosides.

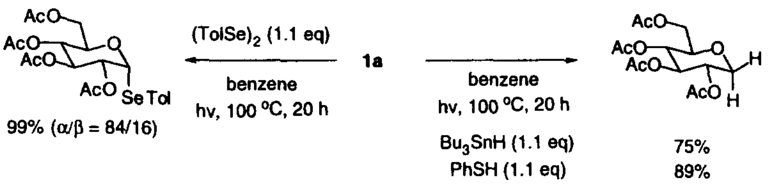
Entry	Telluroglycoside	λmax (nm)[a]	hv[b]	Time (h)[c]	α:β[d]	% Recovery[d]
1	**β-1a**	324	**A**	2	84:16	76
			A[e]	2	70:30	100
			B	2	81:19	79
			C	5	69:31	90
			D	8	69:31	28
2	**α-1a**	326	**A**	0.5	83:17	100
3	**β-1b**	324	**A**	2	86:14	91
4	**α-1b**	325	**A**	0.6	87:13	87
5	**β-1c**	327	**A**	1	88:12	83
			D	10	89:11	92
6	**β-4**	324	**A**	2	89:11	99
7	**β-5**	324	**A**	2	83:17	32
8	**α-6**	(302)[f]	**A**	40	27:73	77

[a] UV absorption corresponding to the tellurium moiety. [b] Photochemical reaction was carried out in C_6D_6 at 40 °C with irradiation by various light sources. **A**: Rayonet RMR-3000Å (3.9 W x 8) was used. **B**: Rayonet RMR-3500Å (4.5 W x 8) was used. **C**: Xe lamp (5.4 W) was used. **D**: The reaction under the dark at 140 °C. [c] The time required for the complete equilibration as monitored by ^1H NMR. [d] Determined by ^1H NMR. [e] The reaction was carried out in CD_3CN. [f] No characteristic UV absorption corresponding to the tellurium moiety was observed.

yield as a 35:65 mixture of the α- and β-anomers (eq. 1). The tolyltelluro group was quantitatively recovered as the corresponding ditelluride. The reaction of **1b** and **1c** with 4-oxo-TEMPO also afforded **3b** (P = Bz) and **3c** (P = Bn) in 93% (α:β = 36:64) and 43% (α:β = 32:68) yield, respectively.[12] Since the trapping of TEMPO does not proceed via a chain reaction, the present results clearly show that a stoicheometric amount of the glycosyl radical is generated by a non-chain reaction. It is worth noting that, while the isomerization proceeded at room temperature, the external trapping reaction required an elevated temperature.

The glycosyl radicals were also trapped with several radicophilic molecules under photo-thermal conditions (Scheme 1). The reaction of **1a** and diaryl diselenide afforded the corresponding selenoglycoside as an 84:16 mixture of α- and β-anomers in quantitative yield. Bu_3SnH-mediated reduction of **1a** gave the corresponding reduced glycoside in 75% yield. Benzenthiol was also found to be effective for the reduction, and the product was obtained in 89% yield.

Scheme 1



While telluroglycosides are stable without photo-irradiation at room temperature, they underwent stereochemical isomerization upon thermolysis above 140 °C. Thus, β-**1a** slowly isomerized to α-**1a** at 140 °C in the dark, and the isomeric ratio became constant after 10 h (α:β = 7:3). Under these conditions, however, **1a** was mainly converted to 2-telluroglycoside **7**, which seemed to be formed by 1,2-acetyl migration from the glycos-1-yl radical **2a** to the glycos-2-yl radical **8** followed by the coupling with the tolyltellurium radical.[13] While the isomerization of the benzoyl-protected **1b** also competed with the 1,2-benzoyl migration, that of benzyl protected **1c**, which does not have a migrating group, proceeded smoothly to give an 89:11 mixture of the α- and β-isomers after 10 h with 92% recovery of **1b**. These results are also consistent with the reversible generation of the glycos-1-yl radical **2** from the telluroglycoside **1** under thermal conditions.

In conclusion, we have developed a new method for the generation of the glycosyl radicals via a non-chain mechanism. A virtue of this method is demonstrated by the intermolecualr addition of the glycosyl radical with various carbon radicophiles.[14] Elucidation of the detailed mechanism of the isomerization as well as the synthetic applications are currently underway.

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