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Note

Ulose formation by selenoxide elimination

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Abstract

Ring opening of methyl 2,3-anhydro-(*R*)-4,6-*O*-benzylidene-α-D-mannopyranoside with phenyl selenide gives (*R*)-4,6-*O*-benzylidene-3-*Se*-phenyl-3-seleno-α-D-altropyranoside (**2**). Oxidation of (**2**) with H_2O_2 followed by thermolysis gives methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose via *syn*-elimination and ketoenol tautomerization.

Keywords: Selenoxide elimination; Enol formation; Epoxide ring opening; phenyl selenide; Methyl 2,3-anhydro-(*R*)-4,6-*O*-benzylidene-α-D-mannopyranoside

In connection with our interest in cyclomaltoheptaose, we sought an efficient method for converting a trans-vicinal diol to a methylene ketone without the necessity of protecting groups. Scheme 1 illustrates a possible sequence of reactions for this transformation. The related epoxide is a potentially useful intermediate because its formation and subsequent ring opening can be performed with selectivity and in the presence of hydroxyl groups. Nucleophilic ring opening of the epoxide creates a hydroxyl group that is antiperiplanar to the nucleophile. Syn-elimination of the nucleophile or derivative and an adjacent hydrogen atom gives an enol that tautomerizes to a ketone. Of the numerous potential nucleophiles, phenyl selenide seemed an ideal choice for this transformation.

Phenyl selenide anion is an extremely potent nucleophile. It reacts smoothly with epoxides even when complexed with borohydride [1]. With fused, six-membered rings a trans-diaxial β-hydroxyselenide is formed initially. The selenide can be converted to the corresponding selenoxide with a variety of oxidizing agents, most commonly H_2O_2. The thermal syn-elimination of phenyl selenenic acid to form an alkene is a useful synthetic method because elimination is so facile, often occurring at or below room temperature [2].

Sharpless and Lauer studied epoxide ring opening with phenyl selenide and found that the selenoxides generated from subsequent oxidation undergo regioselective elimination to form allylic alcohols and not enols [3]. Many other examples of the formation of allylic alcohols from β-hydroxyselenoxides have been reported [4]. The preference for allylic alcohol formation is supported by a theoretical study, but the magnitude of the observed specificity was not reproduced by the calculations [5].

In spite of overwhelming literature precedent, we felt that β-hydroxyselenoxides should react to form

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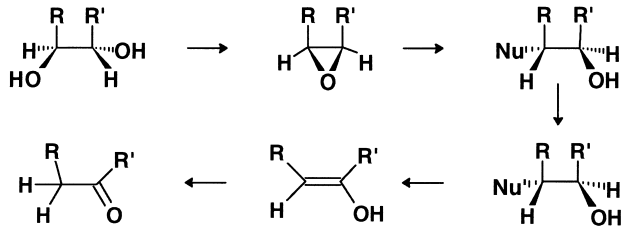


Scheme 1. Conversion of a vicinal *trans*-diol to a methylene ketone.

enols under appropriate conditions, such as when enol formation is the only option. We report here the use of a phenyl selenide ring opening of the manno epoxide of a protected glucopyranose and subsequent oxidation–elimination as a route into the 2-ulose derivative.

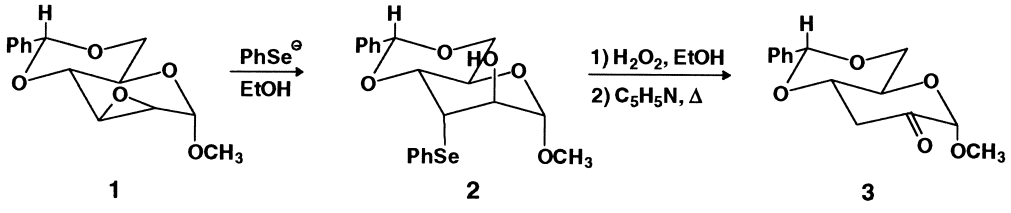
The manno epoxide **1** is available from the reaction of the benzylidene acetal of methyl– α-D-glucoside with tosylimidazole [6]. The epoxide reacts smoothly with phenyl selenide generated from diphenyl diselenide and $NaBH_4$. Addition is complete within several hours, and TLC conveniently monitors the progress of the reaction. The resulting β-hydroxy selenide **2** is assigned as the 3-seleno altro isomer shown in Scheme 2. The nucleophilic attack of the manno epoxide occurs at the C-3 position, and it results in trans diaxial ring opening according to the Fürst–Plattner rule [7]. The small coupling constants observed in the ^1H NMR spectrum indicate the equatorial orientations of H-1-H-3. The oxidation of **2** to the selenoxide with 30% aq H_2O_2 was allowed to run overnight to ensure complete reaction. Two equivalents of H_2O_2 were employed. The excess (second) equivalent helps minimize the production of diphenyl diselenide from the disproportionation of phenyl selenenic acid formed during thermolysis. The selenoxide is relatively stable in contrast to many other selenoxides that suffer elimination even at room temperature. Heating the reaction at reflux for several hours induces elimination. The addition of pyridine prevents decomposition of the benzylidene acetal. Ultimately, this procedure gave a 50% yield of the 2-ulose **3** after purification by silica gel chromatography (to remove remaining diphenyl diselenide) and sublimation. The identity of **3** was confirmed by independent synthesis from the reaction of **1** with $LiAlH_4$ followed by Cr(VI) oxidation [8]. We suggest that several factors may lead to the unusual reactivity of the selenoxide: the axial orientation of the selenoxide group (and the resulting strain), the conformational rigidity of the ring, and the fact that only H-2 is accessible to the selenoxide.

Since Martin et al. have shown that epoxide ring opening with phenyl selenide can be accomplished with unprotected carbohydrates, this synthetic sequence could have wider application [4]. Further study will define the limits of this unusual mode of selenoxide reactivity. We are hoping to apply this method to cyclomaltoheptaose chemistry.

1. Experimental

General methods.—Thin-layer chromatography was performed on Analtech silica gel HLF plates (250 μm, UV 254) using 1:3 v/v EtOAc–hexanes. NMR spectra were obtained using a GE QE-300 spectrometer. Combustion analysis was performed by Desert Analytics. Methyl 2,3-anhydro-(*R*)-4,6-*O*-benzylidene-α-D-mannopyranoside was prepared according to a literature method [6] and was purified by recrystallization, followed by sublimation (R_f 0.57).

*Methyl (*R*)-4,6-*O*-benzylidene-3-*Se*-phenyl-3-seleno-α-D-altropyranoside* (**2**).—Diphenyl diselenide (4.73 g, 15.1 mmol) was dissolved in absolute ethanol (100 mL), and $NaBH_4$ (1.64 g, 43.3 mmol) was added in several portions. After the solution became colorless, methyl 2,3-anhydro-(*R*)-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**, 2.00 g, 7.57 mmol) was added, and the mixture was heated at reflux for 2.5 h. The reaction was poured into cold aq NaCl. The resulting solid



Scheme 2. Formation of a 2-ulose by selenoxide elimination.

was collected with vacuum filtration and dried in vacuo. It was recrystallized from benzene (35 mL) and hexanes (350 mL) giving the selenide adduct (2.32 g. 5.50 mmol, 73%): mp 151–152 °C; $[\alpha]_D^{25}$ −49.7° (*c* 0.15, $CHCl_3$); R_f 0.20; ^{1}H NMR [$(CD_3)_2CO$–D_2O]: δ 7.65 (m, 2 H, PhSe), 7.34 (m, 5 H, PhSe, *Ph*CH), 7.22 (m, 3H, *Ph*CH), 5.76 (s, 1 H, PhC*H*), 4.66 (br d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 4.39 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.37 (br dd, 1 H, $J_{2,3}$ 2.6 Hz, H-2), 4.27 (dd, 1 H, $J_{6e,6a}$ −10.3 Hz, H-6e), 4.18 (ddd, 1 H, $J_{5,6e}$ 5.2 Hz, $J_{5,6a}$ 10.3 Hz, H-5), 3.89 (dd, 1 H, H-6a), 3.84 (dd, 1 H, $J_{3,4}$ 4.2 Hz, H-3), 3.42 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$): δ 137.5, 134.0, 132.6, 128.8, 128.2, 127.2, 126.4, 126.3, 101.7 (C-1), 100.8 (Ph*C*H), 75.5 (C-4), 72.9 (C-2), 69.1 (C-6), 61.1 (C-5), 55.1 (OMe), 47.3 (C-3); Anal. Calcd for $C_{20}H_{22}O_5Se$: C, 57.01; H, 5.26; O, 18.99. Found: C, 56.78; H, 5.22; O, 18.92.

*Methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-α-*D*-erythro-hexopyranosid-2-ulose* (**3**).—Methyl (*R*)-4,6-*O*-benzylidene-3-*Se*-phenyl-3-seleno-α-D-altropyranoside (**2**, 1.00 g, 2.78 mmol) was dissolved in absolute ethanol (24 mL). The solution was cooled in an ice bath, and H_2O_2 was added dropwise (30%, 0.19 g, 5.56 mmol). The solution was allowed to warm to room temperature and was stirred overnight. Pyridine (3.6 mL) was added, and the solution was heated to reflux for 3 h, after which time TLC indicated that the selenoxide (R_f 0.0) had been consumed. The reaction was cooled and diluted with H_2O (300 mL). The solution was extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were washed with H_2O (3×50 mL). The organic layers were dried over $CaCl_2$, concentrated in vacuo, and dried in vacuo overnight. The residue was chromatographed on silica gel eluting with hexanes (500 mL) and CH_2Cl_2 (500 mL). The fractions containing the 2-ulose were combined and concentrated in vacuo. The crude product was sublimed at 0.1 torr/150 °C giving 260 mg (1.12 mmol, 47%): R_f 0.32; ^{1}H NMR [$(CD_3)_2CO/D_2O$]: δ 7.50 (m, 2 H, *Ph*CH), 7.39 (m, 3 H, *Ph*CH), 5.68 (s, 1 H, PhC*H*), 4.60 (s, 1 H, H-1), 4.37 (dd, 1 H, $J_{6e,6a}$ −10.3 Hz, H-6e), 4.07 (ddd, 1 H, $J_{5,6e}$ 4.9 Hz, $J_{5,6a}$ 10.3 Hz, H-5), 3.96 (ddd, 1 H, $J_{3e,4}$ 5.1 Hz, $J_{3a,4}$ 12.1 Hz, H-4), 3.84 (dd, 1 H, H-6a), 3.50 (s, 3 H, OMe), 2.86 (dd, 1 H, $J_{3e,3a}$ −13.9 Hz, H-3a), 2.79 (dd, 1 H, H-3e); ^{13}C NMR ($CDCl_3$): δ 217.2 (CO), 137.1, 129.5, 128.6, 126.3, 101.7 (C-1), 100.7 (Ph*C*H), 77.4 (C-4), 69.3 (C-6), 64.3 (C-5), 55.9 (OMe), 42.9 (C-3).

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