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Note

Formation of 2,3-unsaturated pyranoid derivatives from a D-mannopyranose *p*-toluenesulfonate*

FANZUO KONG, BANGYING SU**,
Institute of Environmental Chemistry, Chinese Academy of Sciences, Beijing (People's Republic of China)

AND CONRAD SCHUERCH
Department of Chemistry, College of Environmental Science and Forestry, State University of New York, Syracuse, New York 13210 (U.S.A.)

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Two general methods, namely, rearrangement reactions of glycal esters, and elimination from such saturated precursors as vicinal disulfonates[1] and vicinal diol[2] or oxirane derivatives[3], have been reported for the synthesis of 2,3-unsaturated pyranoid sugar derivatives. For monosulfonic esters of deoxyglycopyranose derivatives, the elimination occurs readily under basic conditions[4]. However, elimination was only a side reaction, or did not occur, for monosulfonic esters of nondeoxyglycopyranose derivatives, even under forcing conditions[5,6]. We now report a new observation on an elimination reaction of 2,4,6-tri-*O*-benzyl- (**2**) and 1-*O*-acetyl-2,4,6-tri-*O*-benzyl-3-*O*-*p*-tolylsulfonyl-D-mannopyranose (**3**) with bases under mild conditions, to afford 2,4,6-tri-*O*-benzyl- (**4**) and 1-*O*-acetyl-2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enopyranose (**5**).

In the present research, 2,4,6-tri-*O*-benzyl-D-mannopyranose[7] (**1**) was used as the starting material. An initial attempt was made to prepare a 1,3-anhydro-α-D-altropyranose derivative by ring closure of **2** (which could be obtained from compound **1**) as a 1,4-anhydro-D-galactopyranose derivative had been prepared in this way[8]. It was, however, found that when compound **2** was treated with a base under conditions for ring closure[7,8], 2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enopyranose (**4**) was the sole product.

Different bases were used for the reaction, and the same product was obtained. Sodium hydride caused complete elimination under reflux conditions in 30 min, whereas potassium *tert*-butoxide and potassium hydroxide in oxolane

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**Present address: Photochemistry Institute, Chinese Academy of Sciences, Beijing, China.

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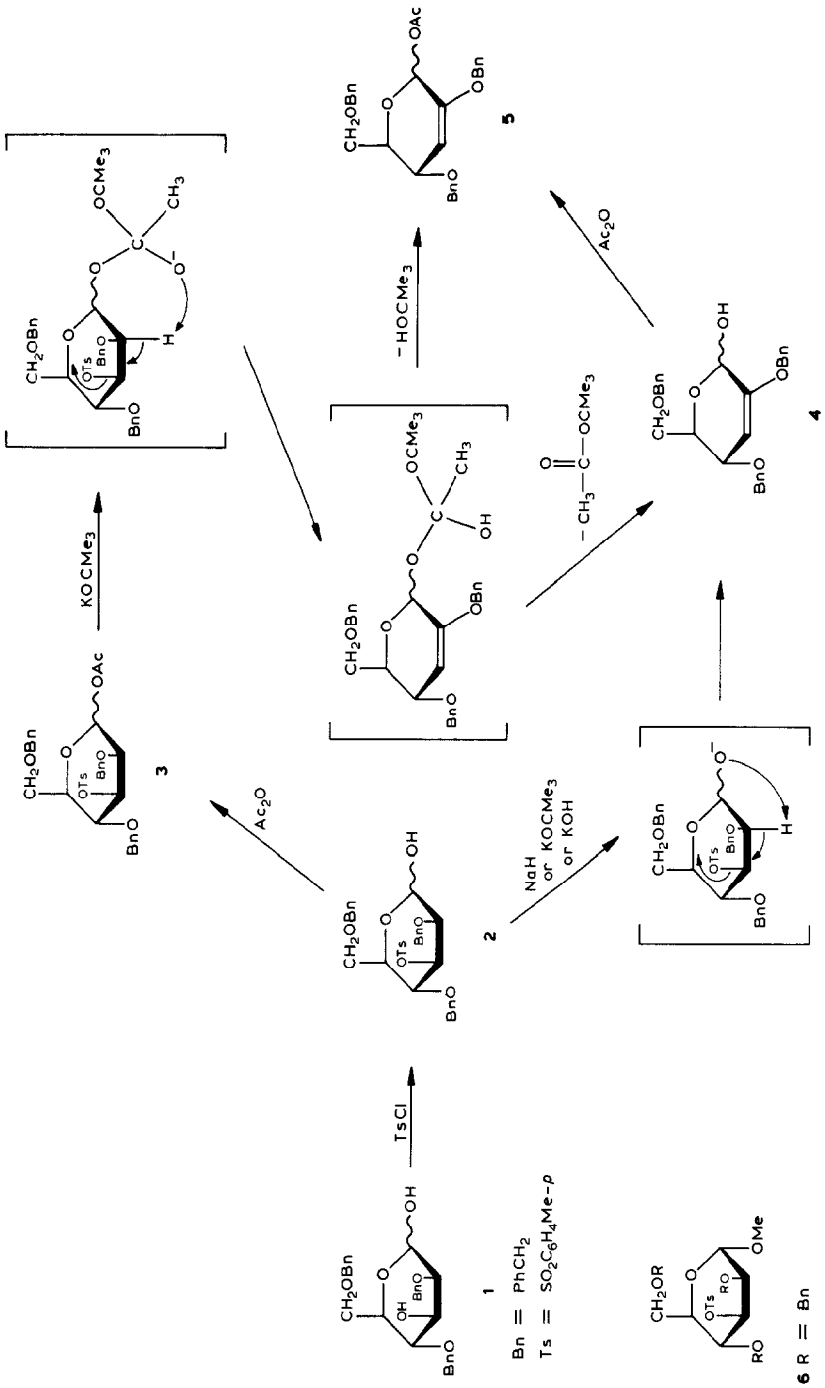
TsCl
Ac2O
KOCMe3
NaH
or KOCMe3
or KOH
Ac2O
-HOCMe3
-CH3—C(=O)—OCMe3
1
2
3
4
5
Bn = PhCH2
Ts = SO2C6H4Me-p
6 R = Bn
7 R = p-BrC6H4CH2-

Scheme 1

respectively required 1 h and 1 d at room temperature. Compound **4** was identified by mass spectrometry and i.r. and ^{1}H-n.m.r. spectroscopy, elemental analysis, and decolorization of a bromine solution. The mass spectrum showed a M^+ peak (432) and a retrodiene fragment peak (282) characteristic of a 2,3-unsaturated pyranoid enol. The i.r. spectrum showed strong absorption at 3390 and 1662 cm^{-1}, respectively characteristic of a hydroxyl group and a carbon–carbon double bond. The ^{1}H-n.m.r. spectrum contained a single peak for H-1, rather than a doublet or a quartet expected for a 1,3-anhydroaltropyranose derivative[9]. Acetylation of compound **4** afforded 1-*O*-acetyl-2,4,6-tri-*O*-benzyl-3-deoxy-D-*erythro*-hex-2-enopyranose (**5**), which was identified by elemental analysis, i.r. and ^{1}H-n.m.r. spectroscopy and mass spectrometry, and by decolorization of a bromine solution.

Acetylation of compound **2** afforded 1-*O*-acetyl-2,4,6-tri-*O*-benzyl-3-*O*-*p*-tolylsulfonyl-D-mannopyranose (**3**). Treatment of **3** with potassium *tert*-butoxide in oxolane at room temperature afforded compounds **4** (40%) and **5** (60%) in a short time, with no other products.

No elimination product was formed when methyl 2,4,6-tri-*O*-benzyl- (**6**) and methyl 2,4,6-tri-*O*-(*p*-bromobenzyl)-3-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside (**7**) were treated with bases under the same aforedescribed conditions. Compound **6** and **7** were completely recovered unchanged after processing the reaction mixtures.

Based on the experiments just described, an intramolecular elimination caused by the C-1 neighboring group, as shown in Scheme 1, is proposed.

None of the ring-closure product, namely, 1,3-anhydro-2,4,6-tri-*O*-benzyl-α-D-altropyranose, was formed by base treatment of compound **2** or **3**, perhaps because the transition state leading to the 1,3-anhydro sugar derivative would require a severely hindered $^5S_1$ conformation[9], wherein the bulky CH_2OBn group on C-5, being in an axial position, would have a strong, crowding interaction with OBn-2 and OTs-3, and, at the same time, O-1 and OBn-4 would be quite close to each other on the "bottom" side of the ring.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded with a Varian XL-100-15 spectrometer, with chloroform-*d* as the solvent and tetramethylsilane (Me_4Si) as the internal standard; chemical shifts are given in p.p.m. from the Me_4Si signal. Optical rotations were determined in a jacketed, 1-dm cell at 25°, with a Perkin–Elmer Model 241-MC polarimeter. Melting points were determined with a "Meltemp" apparatus and a 76-mm-immersion thermometer. Infrared spectra were recorded with a Perkin–Elmer 125 spectrometer. Mass spectra were recorded with a JMS-D 3005 mass spectrometer, using a direct-insertion technique to introduce the samples. Thin layer chromatography (t.l.c.) was performed on silica gel with detection by spraying with 30% sulfuric acid in methanol. Analytical l.c. was conducted by use of a pump (Model YSB-1, made in China), a stainless-steel column (10 × 150 mm, made in China) packed with silica gel, a differential refractometer (Model

1107L, made in the U.S.A.), a pressure of 10 MPa, and ethyl acetate–petroleum ether (b.p. 60–90°) as the eluant at a flow rate of 4.0 mL/min.

*2,4,6-Tri-*O*-benzyl-*D*-mannopyranose* (**1**). — Compound **1** was synthesized from methyl α-D-mannopyranoside according to the previously reported method[7]; m.p. 74°, $[\alpha]_D^{25}$ +3.1° (*c* 0.8, chloroform).

*2,4,6-Tri-*O*-benzyl-3-*O*-p-tolylsulfonyl-*D*-mannopyranose* (**2**). — To a stirred solution of compound **1** (500 mg, 1.1 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (475 mg, 2.5 mmol), and the mixture was kept for 3 d at room temperature. T.l.c. (1:1 ethyl acetate–petroleum ether) then indicated that the starting material had completely disappeared. The mixture was processed according to a standard procedure[6], the solvent evaporated at room temperature under diminished pressure, and the resulting syrupy mixture separated by analytical l.c. (1:1 ethyl acetate–petroleum ether). The main fraction was collected, and the solvent was evaporated. Crystalline compound **2** was obtained as needles from 2:1 ether–petroleum ether; yield 40%; m.p. 101°, $[\alpha]_D^{25}$ +32.4° (*c* 0.68, chloroform); ^{1}H-n.m.r.: δ 7.81–7.06 (m, 19 H, aromatic H), 5.09 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.93 (m, 1 H, $J_{3,4}$ 9, $J_{2,3}$3 Hz, H-3), 4.77–3.57 (m, 12 H, 3 C*H*$_2$Ph, H-2,4,5, 2 H-6, and OH-1), and 2.31 (s, 3 H, C*H*$_3$C$_6$H$_4$-SO$_2$).

Anal. Calc. for $C_{34}H_{36}O_8S$: C, 67.55; H, 5.96. Found: C, 67.57; H, 5.90.

*1-*O*-Acetyl-2,4,6-tri-*O*-benzyl-3-*O*-p-tolylsulfonyl-*D*-mannopyranose* (**3**). — Compound **2** (400 mg, 0.66 mmol) was acetylated by the standard method. After the usual processing, crystalline compound **3** was obtained as needles. The yield was quantitative; m.p. 62°, $[\alpha]_D^{25}$ +31.8° (*c* 0.82, chloroform); ^{1}H-n.m.r.: δ 7.77–7.09 (m, 19 H, aromatic H), 6.10 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.90 (m, 1 H, $J_{3,4}$ 9.5, $J_{2,3}$ 3.6 Hz, H-3), 4.68–3.69 (m, 11 H, 3 C*H*$_2$Ph, H-2,4,5, and 2 H-6), 2.35 (s, 3 H, C*H*$_3$C$_6$H$_4$-SO$_2$), and 2.08 (s, 3 H, C*H*$_3$-CO).

Anal. Calc. for $C_{36}H_{38}O_9S$: C, 66.87; H, 5.88. Found: C, 66.73; H, 5.83.

*2,4,6-Tri-*O*-benzyl-3-deoxy-*D*-erythro-hex-2-enopyranose* (**4**). — To a stirred solution of compound **2** (200 mg, 0.33 mmol) in anhydrous oxolane (30 mL) was added potassium *tert*-butoxide (74 mg, 0.66 mmol) at room temperature. A white precipitate of sulfonate appeared rapidly, and the reaction was complete in 1 h, as indicated by t.l.c. (1:1 ethyl acetate–petroleum ether). The solvent was evaporated and the excess of *tert*-butoxide was decomposed by adding ice–water. The product was extracted into dichloromethane, and the extract dried (anhydrous sodium sulfate) and evaporated to afford crude, crystalline compound **4**; yield 95%. Recrystallization from 1:2 dichloromethane–petroleum ether gave pure compound **4**; m.p. 117°, $[\alpha]_D^{25}$ +43.0° (*c* 0.6, chloroform); ^{1}H-n.m.r.: δ 7.36–7.25 (m, 15 H, aromatic H), 5.30 (s, 1 H, H-1), 4.90 (d, 1 H, $J_{3,4}$ 2 Hz, H-3), 4.82–3.68 (m, 11 H, 3 C*H*$_2$Ph, H-4,5, 2 H-6, and OH-1); i.r.: 3390 (OH) and 1662 cm^{-1} (C=C); *m/z* 432 (M^+), 414 ($M^+ - H_2O$), 282 (retrodiene fragment for the 2,3-unsaturated pyranoid), 107, 91, and 79 (benzyl group).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.97; H, 6.48. Found: C, 74.38; H, 6.54.

Compound **4** was stable under weakly basic conditions, but was sensitive to acid, and so it was difficult to get an accurate analysis.

Treatment of compound **2** with potassium hydroxide also gave compound **4**. However, the reaction was much slower than that caused by *tert*-butoxide under the same conditions. Instead of 1 h, 1 day was needed in order to complete the reaction (as indicated by t.l.c.). The elimination was quantitative, and the product had the same properties as that obtained with potassium *tert*-butoxide.

Sodium hydride was also used for the elimination reaction. Thus, to a stirred solution of compound **2** (100 mg, 0.16 mmol) in oxolane (25 mL) was added sodium hydride (in oil, 80%, 12 mg, 0.40 mmol), and the reaction was complete after boiling the mixture for 30 min, as indicated by t.l.c. (1:1 ethyl acetate–petroleum ether). The solid (excess sodium hydride and the sodium sulfonate) was filtered off, the filtrate evaporated to dryness, the mineral oil removed by analytical l.c. with 1:1 ethyl acetate–petroleum ether as the eluant, and the solvent evaporated, giving crystalline compound **4**; yield 90%.

1-O-Acetyl-2,4,6-tri-O-benzyl-3-deoxy-D-erythro-*hex-2-enopyranose* (**5**). — Compound **4** was quantitatively converted into compound **5** by standard acetylation; m.p. 101°, $[\alpha]_D^{25}$ +35.4° (*c* 0.65, chloroform); ^{1}H-n.m.r.: δ 7.42–7.20 (m, 15 H, aromatic H), 6.23 (s, 1 H, H-1), 5.04 (d, 1 H, $J_{3,4}$ 2 Hz, H-3), 4.78–3.70 (m, 10 H, 3 CH_2Ph, H-4,5, and 2 H-6), and 2.10 (s, 3 H, CH_3-CO); i.r.: 1730 (C=O) and 1670 cm^{-1} (C=C); *m/z* 474 (M^+), 431 ($M^+ - CH_3CO$), 414 ($M^+ - HOAc$), and 324 (retrodiene fragment for the 2,3-unsaturated pyranoid).

Anal. Calc. for $C_{29}H_{30}O_6$: C, 73.42; H, 6.33. Found: C, 73.33; H, 6.47.

Compound **5** was also obtained from compound **3**. Thus, to a stirred solution of compound **3** (400 mg, 0.619 mmol) in oxolane (15 mL) was added potassium *tert*-butoxide (138 mg, 1.24 mmol), and the reaction was conducted for 1 h at room temperature; the product was isolated as for the conversion of compound **2** into **4**. A white, solid mixture obtained on evaporation was separated by analytical l.c. with 2:3 ethyl acetate–petroleum ether as the eluant. Two fractions were collected, and each fraction afforded one crystalline compound after removal of the solvents. The crystalline compound obtained from the slow-moving fraction in analytical l.c. was identified as compound **4**. That obtained from the fast-moving fraction was identified as compound **5**. Recrystallization from 1:1 ether–petroleum ether gave pure compound **5**. The ratio of compound **4** to **5** was ~2:3, and both of them rapidly decolorized bromine solution. No byproduct or starting material was found.

Methyl 2,4,6-tri-O-benzyl-3-O-p-*tolylsulfonyl-α*-D-*mannopyranoside* (**6**). — To a stirred solution of methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside[7] (200 mg, 0.44 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (92 mg, 0.48 mmol), and the reaction was allowed to proceed for three days at room temperature. The mixture was processed by a standard procedure[4], and syrupy compound **6** was obtained after purification by analytical l.c. with 1:1 ethyl acetate–petroleum ether as the eluant; yield 95%; $[\alpha]_D^{25}$ +42.2° (*c* 1.4, chloroform); ^{1}H-n.m.r.: δ 7.80–7.02 (m, 19 H, aromatic H), 4.86 (m, 1 H, $J_{3,4}$ 9.5, $J_{2,3}$ 3.2 Hz, H-3), 4.70–3.67 (m, 12 H, 3 CH_2Ph, H-1,2,4,5, and 2 H-6), 3.30 (s, 3 H, OCH_3), and 2.34 (s, 3 H, C$H_3C_6H_4$-SO_2).

Anal. Calc. for $C_{35}H_{38}O_8S$: C, 67.96; H, 6.15. Found: C, 67.75; H, 6.23.

*Methyl 2,4,6-tri-*O-(p-*bromobenzyl)-3-*O-p-*tolylsulfonyl-α-*D-*mannopyranoside* (**7**). — Compound **7** was obtained as a crystalline compound from methyl 2,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-mannopyranoside[7] by the procedure described for compound **6**; yield 95%. Recrystallization from ether–petroleum ether afforded pure compound **7**; m.p. 95.5°, $[\alpha]_D^{25}$ +36.6° (*c* 0.88, chloroform); ^{1}H-n.m.r.: δ 7.78–6.82 (m, 16 H, aroamtic H), 4.87 (m, 1 H, $J_{3,4}$ 9, $J_{2,3}$ 3 Hz, H-3), 4.70–3.64 (m, 12 H, 3 CH_2Ph, H-1,2,4,5, and 2 H-6), 3.32 (s, 3 H, OCH_3), and 2.34 (s, 3 H, $CH_3C_6H_4$-SO_2).

Anal. Calc. for $C_{35}H_{35}Br_3O_8S$: C, 49.12; H, 4.09. Found: C, 49.19; H, 4.04.

No elimination reaction occurred when either compound **6** or **7** was treated with potassium *tert*-butoxide or potassium hydroxide in oxolane at room temperature.

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