# Practical Synthesis of 1,6-Anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose from Levoglucosan

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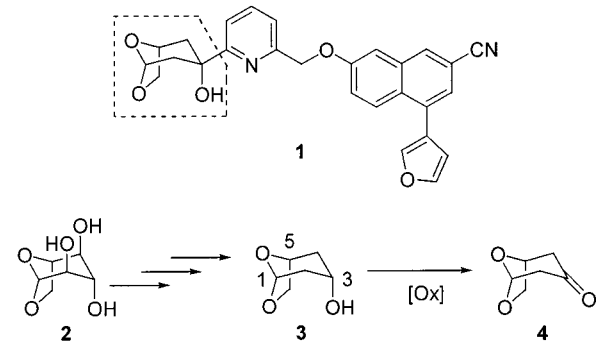
The potential utility of 1,6-anhydro-2,4-dideoxyhexopyranoses (e.g., **3** and **4**, Scheme 1) as chirons in the synthesis of important biologically active compounds has increased interest in developing methods for their preparation. In particular, a number of methods have been described in accounts of the synthesis of precursors to the lactonic portion of mevinic acids, which are potent inhibitors of the enzyme HMG-CoA reductase.[1] The 1,6-anhydro-2,4-dideoxyhexopyranoses have also been employed in the synthesis of a wide variety of other biologically important compounds including indanomycin,[2] and the spiroacetal portions of the avermectins and milbemycins.[3] Moreover, the 1,6-anhydro-2,4-dideoxyhexopyanose ring system is found in pheromones such as the brevicomins[4] and the multistriatins,[5] as well as the aroma constituents of beer.[6]

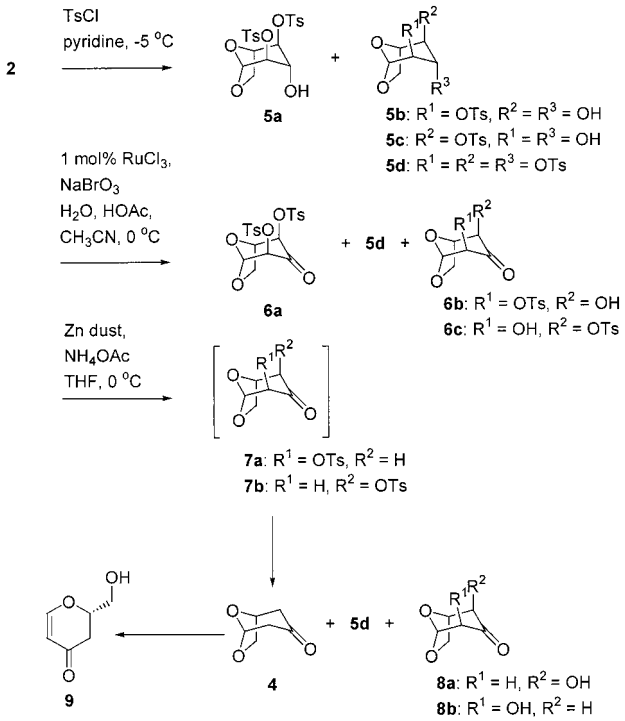
We required enantiomerically pure **4** as a key fragment in the synthesis of the potent 5-lipoxygenase inhibitor **1** (Scheme 1).[7]

Despite the wide-spread reports of their use, few efficient methods exist for the large-scale preparation of 1,6-anhydro-2,4-dideoxyhexopyranoses.[8] Černý and coworkers described the first synthesis of ketone **4**.[9] Preparation entailed tosylation of levoglucosan (**2**) at C-2 and C-4 to give **5a** followed by oxidation at C-3 to give ketone **6a** (cf., Scheme 2). Reduction of the tosylate groups with Raney nickel afforded **4** in low overall yield from **2** (ca. 24%). Kelly and Roberts later reported an improved preparation of **4** whereby the oxidation and reduction steps of the original synthesis were reversed.[10]

**Scheme 1**




**Scheme 2**




However, the reduction of **5a** with $LiBHEt_3$ resulted in a 5:1 mixture of **3** and its 3,4-dideoxy isomer that required chromatographic separation after selective oxidation of **3** to ketone **4**. Subsequently, David and coworkers demonstrated that complete regioselectivity for the reduction of **5a** could be obtained by nucleophilic displacement of the tosylate groups with thiophenol followed by reductive cleavage of the phenylsulfide groups with a large excess of Raney Ni.[11] In our hands, however, we found that the Raney Ni reduction of the intermediate bis(phenyl sulfide) was not reproducible and gave low yields despite a wide variety of conditions and types of Raney Ni. Only when an excess of $Bu_3SnH$ or $((CH_3)_3Si)_3SiH$ was used in the phenyl sulfide reduction could acceptable yields be obtained. Other groups have also reported radical chain dideoxygenation of derivatives of **2** to prepare **3**,[12] which can readily be oxidized to give

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the desired ketone **4**.[13] In general, the use of undesirable reagents and the need for chromatographic purification of **3** made the use of radical reduction routes unattractive.

The three-step approach via the deoxygenation of the derivatized ketone **6a** proved to be most amenable to large-scale preparation after several major improvements were made. Most notable of these were the use of $NaBrO_3$ with $RuCl_3$ for the alcohol oxidation at C-3 and the reductive cleavage of the α,α′-ditosylate ketone using Zn/$NH_4OAc$. To the best of our knowledge, this is the first example of a one-pot α,α′-substituted dideoxygenation of a ketone by a metal or metal salt other than Raney Ni. Herein we report an efficient three-step process for the preparation of ketone **4** in 75% yield from commercially available[14] levoglucosan (**2**). The process is amenable to multi-kilogram scale.

## Results and Discussion

The synthesis of 1,6-anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (**4**) is illustrated in Scheme 1. The original procedure[15] for tosylation of levoglucosan (**2**) was modified to produce at least a 50% higher yield of **5a** and to simplify the purification of ketone **4**. Use of only a slight excess of TsCl (220 mol %) in dry pyridine at a low temperature (−5 °C) afforded the ditosylate **5a** in excellent yield (85% by HPLC wt % vs std) after extractive workup with EtOAc, aq citric acid, and water. Under the optimized conditions, the tritosylate **5d** was obtained as the major impurity (ca. 14%) which was easily removed by crystallization in the final step, while only minor amounts of the monotosylates **5b** and **5c** were present (ca. 0.5%). The desired selectivity for the C-2 and C-4 positions is most likely due to steric hindrance at C-3 from the acetal bridge. Purification of **5a** was not necessary before proceeding.

The next step in the synthesis called for oxidation of **5a** to ketone **6a**. Oxidation with $RuCl_3$/NaOCl in $CH_3CN$ and AcOH[16] gave **6a** in only 15% yield. The low yield under these conditions was attributed to incomplete conversion. Complete oxidation of **5a** was obtained only in the presence of a large excess of NaOCl or $NaIO_4$; however, epimerization at C-2 and C-4 was observed under these conditions. The best conditions were found with the substitution of $NaBrO_3$ as oxidant. This finding has previously been observed for $RuCl_3$-catalyzed oxidations of alcohols, yet there are few examples in the literature which utilize $NaBrO_3$ despite its advantages as an efficient, inexpensive oxidant.[17] We found that complete conversion of **5a** to ketone **6a** could be accomplished in a solvent system of $CH_3CN$/AcOH/$H_2O$ using $NaBrO_3$ (65 mol %) in the presence of 1 mol % $RuCl_3$. After extractive workup, the ditosyl ketone **6a** was obtained in high yield (95%).[18] Compared to the original chromic anhydride oxidation of **5a**,[9c] this oxidation method provides **6a** in at least 40% higher yield without need for further purification. The ketone was isolated as a mixture of the free ketone and its hydrate;[19] however, this mixture was directly employed in the last step.

The final step required reductive cleavage of the tosylate groups to give ketone **4**. We found that reduction of the carbonyl activated tosylate groups could be accomplished in the presence of zinc and a proton source. Initial studies using acetic acid as the proton source produced small amounts of desired ketone **4**, along with intermediate monotosylates **7a/7b**, and the secondary product enone **9**.[20] Conversion of **6a** to **4** was improved by use of aq $NH_4Cl$ as the proton source; however, secondary formation of **9** was rapid.[21] Substitution of solid $NH_4OAc$ as the proton source reduced enone formation to <1%, but incomplete reduction was observed. The use of zinc, previously activated by an aq HCl wash, proved to be the important factor in obtaining complete conversion. Thus, reduction of **6a** was accomplished with activated zinc in THF using solid $NH_4OAc$ as the proton source.

Upon completion, the reaction mixture was filtered and the filtrate containing **4** was neutralized with solid $K_2CO_3$. Removal of the solids by filtration provided **4** as a solution in THF. Concentration of this solution and dilution with MTBE/hexanes resulted in crystallization of the unreduced tritosylate **5d**. Concentration of the mother liquors afforded **4** in excellent yield (93%) and purity (96 area % by GC).[22]

In summary, we have developed a practical synthesis of 1,6-anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (**4**) from commercially available 1,6-anhydro-D-glucose (**2**). This chromatography-free process has been successfully demonstrated on a 23 g product scale in 75% yield.

## Experimental Section

**General Methods**. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ at a frequency of 250.1 and 62.9 MHz, respectively. Removal of residual solvents was monitored by $^1H$ NMR. Gas chromatography was conducted on an HP-5 column (30 m × 0.32 mm). HPLC analysis was carried out on a Zorbax Rx-C8 column (4.6 × 25 mm) with detection at 220 nm using $CH_3CN$ and $H_2O$ as eluents. Reactions can be monitored by silica gel TLC using 4:1 EtOAc/hexanes. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Zinc activation for the preparation of **4** was accomplished by the following procedure:[23] Zinc dust (400 g, 325 mesh) was mechanically stirred for 1 h at 20 °C with 1.5 L 1.5% aq HCl. The aqueous layer was decanted, and the solids were washed with 2 × 1.5 L of THF. After filtration the solid was dried at 145 °C under vacuum overnight prior to use.

**1,6-Anhydro-2,4-di-*O*-*p*-tolylsufonyl-β-D-glucopyranose (5a)**. Over a 2 h period, TsCl (129 g, 678 mmol) was added to a

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(14) Levoglucosan (1,6-anhydro-β-D-glucose) is commercially available from Aldrich, P.O. Box 2060, Milwaukee, WI 53201 or Schweizerhall, Inc., 3001 Hadley Rd, South Plainfield, NJ 07080. For lab-scale preparations of 1,6-anhydro-D-glucose, see Zottola, M.; Alonso, R.; Vite, G.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 6123 and references therein.

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(16) These conditions were reported for the oxidation of **3**. See ref 13.

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(18) Monotosylate byproducts **5b** and **5c** from the tosylation step were also oxidized to give **6b** and **6c**. As expected, tritosylate **5d** was not affected under the reaction conditions.

(19) Typically 60% hydrate exists. The hydrate can be converted to the ketone by azeotropic or molecular sieve drying.

(20) Černý et al. observed reductive cleavage of at least one of the tosylate groups using zinc and acetic acid (see footnote 9c), but they apparently did not develop this approach.

(21) See Experimental Section for the preparation of enone **9**.

(22) Ketone **4** contained monodeoxy reduction adducts **8a** and **8b** arising from **6b** and **6c** (ca. 1% by GC) and tritosylate **5d** (ca. 2% by GC).

(23) In situ activation of zinc with 1,2-dibromoethane lead to increased amounts of enone **9**.

solution of levoglucosan (**2**) (50 g, 308 mmol) in anhydrous pyridine (250 mL) at −10 °C in four portions, keeping the temperature below −5 °C. The reaction was aged for 12.5 h at −5 °C. Water (10 mL) was added to the white suspension, and the reaction was aged 0.5 h. Ethyl acetate (1 L) was added, and the mixture was washed with 23 wt % aq citric acid (4 × 375 mL) and water (375 mL). The organic layer was concentrated and flushed with $CH_3CN$ to remove EtOAc. The ditosylate **5a** was obtained in 85% isolated yield (123 g) along with tritosylate **5d** in 14% isolated yield (26 g) as a solution in $CH_3CN$. Separation of **5a** and **5d** was not required before proceeding.[24] Ditosylate **5a**: $^1$H NMR spectrum was in agreement with published data.[25] $^{13}$C NMR $\delta$ 21.64 (2C), 65.93, 69.34, 74.61, 77.40, 78.68, 99.67, 127.81, 127.87, 130.02 (2C), 132.68, 132.89, 145.41, 145.46. Tritosylate **5d**: $^1$H NMR $\delta$ 2.46 (3H, s), 2.47 (6H, s), 3.69 (1H, dd, $J$ = 8.2, 5.7 Hz), 4.04 (1H, d, $J$ = 8.4 Hz), 4.15 (1H, br d, $J$ = 1.2 Hz), 4.51 (1H, br s), 4.57−4.62 (2H, om), 5.25 (1H, br s), 7.35 (6H, m), 7.68 (4H, m), 7.78 (2H, m). $^{13}$C NMR $\delta$ 21.63, 21.66, 21.69, 64.81, 71.93, 73.60, 73.73, 73.80, 98.51, 127.87, 127.92, 128.11, 129.98, 130.01, 130.05, 131.77, 132.36, 132.67, 145.44, 145.50, 145.81.

**1,6-Anhydro-2,4-di-*O*-*p*-tolylsufonyl-β-D-ribo-hexopyranos-3-ulose (6a).** To a solution of **5a** (100 g, 213 mmol) in $CH_3CN$ (300 mL) were added glacial acetic acid (62 mL) and $RuCl_3 \cdot 3H_2O$ (440 mg, 2.1 mmol) at 0 °C. To the resulting dark brown mixture was added $NaBrO_3$ (21 g, 138 mmol) as a solution in water (98 mL) over 2.5 h, keeping the temperature below 8 °C. The resulting black mixture was aged 1.5 h at 0 °C. 2-Propanol (1.0 mL) was added at 0 °C and aged 15 min. The reaction was poured into a mixture of isopropyl acetate (850 mL) and 15% aq $Na_2S_2O_3$ (100 mL). The resulting mixture was stirred for 15 min, and the layers were separated. The organic layer was washed with water (200 mL), sat. sodium bicarbonate (2 × 540 mL), and water (200 mL). The organic layer was concentrated and flushed with THF. Ditosyl ketone **6a** was obtained in 95% yield (90 g) as a solution in THF and required no further purification. $^1$H NMR $\delta$ 2.46 (6H, s), 3.83 (1H, dd, $J$ = 8.5, 5.0 Hz), 3.90 (1H, dd, $J$ = 8.5, 1.2 Hz), 4.48 (1H, d, $J$ = 1.0 Hz), 4.60 (1H, d, $J$ = 1.0 Hz), 4.94 (1H, ddd, $J$ = 5.0, ∼1.2, ∼1.2 Hz), 5.65 (1H, d, $J$ = 1.4 Hz), 7.34 (4H, m), 7.76 (4H, m). $^{13}$C NMR $\delta$ 21.65 (2C), 66.55, 76.43, 77.15, 79.08, 101.17, 128.01, 128.04, 129.93 (2C), 132.27 (2C), 145.61, 145.67, 190.49.

**1,6-Anhydro-2,4-dideoxy-β-D-glycero-hexopyranos-3-ulose (4).** Crushed $NH_4OAc$ (370 g, 4.80 mol) was added to a suspension of activated zinc (314 g, 4.80 mol) in THF (1.3 L) with mechanical stirring at 20 °C. The suspension was aged for 45 min and then cooled to 0 °C. The crude ditosyl ketone **6a** (90 g, 0.19 mol) in THF (400 mL) was added over 2.5 h with stirring, keeping the temperature below 5 °C. The reaction was warmed to 20 °C and aged for 16 h. The suspension was filtered, and the salts were washed with THF (1.0 L). Powdered (325 mesh) potassium carbonate (93 g, 0.67 mol) was added to the combined organic filtrates with stirring and aged at 20 °C for 22 h. The salts were filtered and washed with THF (300 mL). The combined filtrates were concentrated, and **4** was obtained as a solution in THF. The unreduced tritosylate **5d** was removed from **4** by precipitation from 1:2:7 MTBE:THF:hexanes. Filtration of **5d** and concentration of the mother liquors afforded ketone **4** in 93% isolated yield (23 g, 96 area % pure by GC) as a yellow oil: bp 90 °C/3 mmHg; $[\alpha]^{20}_D$ −103° (*c* 0.7, $CHCl_3$) [lit.[9a] $[\alpha]_D$ −103° (*c* 0.8, $CHCl_3$)]; $^1$H NMR $\delta$ 2.41 (1H, d, $J$ = 16.8 Hz), 2.52 (2H, om), 2.74 (1H, ddd, $J$ = 16.8, 4.8, 1.4 Hz), 3.77 (1H, m), 3.82 (1H, m), 4.80 (1H, dd, $J$ = ∼4.8, ∼4.8 Hz), 5.74 (1H, br s); $^{13}$C NMR $\delta$ 46.80, 48.51, 69.49, 72.11, 100.43, 204.35. Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.23; H, 6.43.

**Enone (9).** Ketone (**4**) is added to TFA at room temperature and aged 5 h. The enone is then isolated as an unstable light brown oil by prep TLC (4:1) EtOAc:hexanes.$^1$H NMR $\delta$ 2.38 (1H, br s), 2.40 (1H, ddd, $J$ = 16.8, 3.6, 1.3 Hz), 2.78 (1H, dd, $J$ = 16.8, 14.3 Hz), 3.80 (1H, dd, $J$ = 12.3, 5.4 Hz), 3.93 (1H, dd, $J$ = 12.3, 3.1 Hz), 4.54 (1H, dddd, $J$ = 14.3, 5.4, 3.3, 3.3 Hz), 5.45 (1H, dd, $J$ = 6.0, 1.3 Hz), 7.40 (1H, d, $J$ = 6.0 Hz).

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(24) If desired, the ditosylate **5a** can be separated from the tritosylate **5d** by chromatography on RP-C18 adsorbent (Delta-Pak C18, 15 μm 100 Å). The ditosylate **5a** is isolated by elution with 1: 1 $CH_3CN$/water.

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