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Note

# Direct epoxidation of D-glucal and D-galactal derivatives with in situ generated DMDO

Pavel Cheshev, Alberto Marra and Alessandro Dondoni*

*Laboratorio di Chimica Organica, Dipartimento di Chimica, Università, di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy*

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**Abstract**—A multi-gram epoxidation of 3,4,6-tri-*O*-benzyl-D-glucal and D-galactal with dimethyldioxirane (DMDO) generated in situ from Oxone®/acetone in a biphasic system ($CH_2Cl_2$–aqueous $NaHCO_3$) resulted in the formation of the corresponding 1,2-anhydrosugars in a 99% yield and 100% selectivity. In a similar way, 3,4,6-tri-*O*-acetyl-D-glucal afforded a 7:1 mixture of the corresponding *gluco* and *manno* derivatives in an 87% overall yield.


*Keywords:* 1,2-Anhydro-D-glucopyranose; 1,2-Anhydro-D-galactopyranose; Dimethyldioxirane; DMDO; Epoxidation

1,2-Anhydrosugars display great synthetic potential as building blocks in oligosaccharide synthesis[1] and precursors of various sugar derivatives such as glycosyl sulfides and fluorides,[2] as well as C- or N-glycosides.[3] Moreover, liberation of the hydroxyl function at C-2, which accompanies the oxirane ring opening, provides additional synthetic perspectives. The extensive use of 1,2-anhydrosugars in oligosaccharide synthesis that commenced in the Danishefsky laboratory[4] in the 1990s relied on the discovery of the easy access to these oxiranes via epoxidation of glycals by dimethyldioxirane (DMDO).[5] The procedure employing a dilute solution of DMDO in acetone was first described by Murray and Ramasubbu.[6] This method provides substantial advantages over other procedures utilizing an MCPBA/KF complex,[7] perfluorodialkyloxaziridines,[8] $Ph_2SO/Tf_2O$/di-*t*-butylmethylpyridine/$CH_3OH$,[9] or $H_2O_2$ in the presence of metalloporphyrin catalyst.[10] Quite significantly, the use of DMDO results in a high yield and clean reaction and requires inexpensive commercially available reagents, while acetone is the sole co-product. However, the preparation and subsequent use of DMDO solutions have some serious drawbacks, such as (a) the solutions are typically obtained in concentrations that rarely exceed 0.1 M, this posing a substantial limit to the scaling-up of the synthesis; (b) the solutions have to be rigorously anhydrous and can be stored without loss of activity only for a short period of time, that is, from some days to few weeks; (c) DMDO is an organic peroxide that requires appropriate handling attention.

We required a multi-gram scale preparation of 1,2-anhydroglucose derivative **2** for the ongoing research in our laboratory dealing with the synthesis of unnatural oligosaccharides. Although the preparation of **2** via epoxidation of tri-*O*-benzyl-D-glucal **1** with DMDO solution was already described,[4] we were interested in the epoxidation of this and other glycals using in situ formed DMDO. Indeed, in the early report of Curci et al.,[11] the epoxidation of hydrophobic alkenes was carried out using in situ generated DMDO solutions under phase-transfer catalysis conditions. An example of a methodologically simpler procedure employing Oxone®/acetone system in biphasic conditions ($CH_2Cl_2$–aqueous $NaHCO_3$) was reported for the epoxidation of allenes.[12]

In our case, vigorous stirring of a solution of **1** (3.00 g, 7.21 mmol) in $CH_2Cl_2$ with Oxone® (2 equiv, 8.87 g),

* Corresponding author. Tel.: +39 0532 291176; fax: +39 0532 291167; e-mail: adn@unife.it

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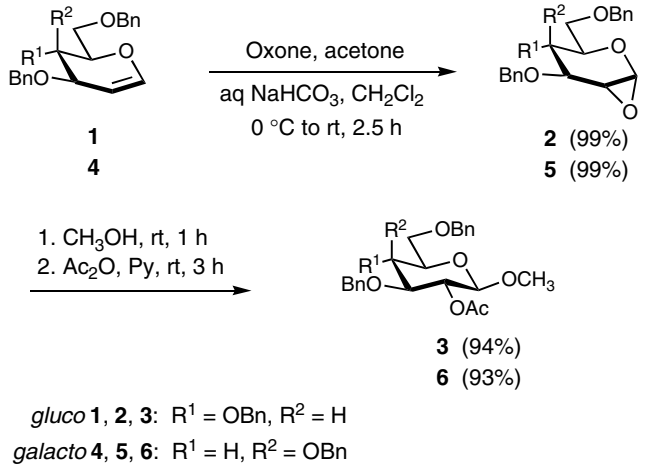
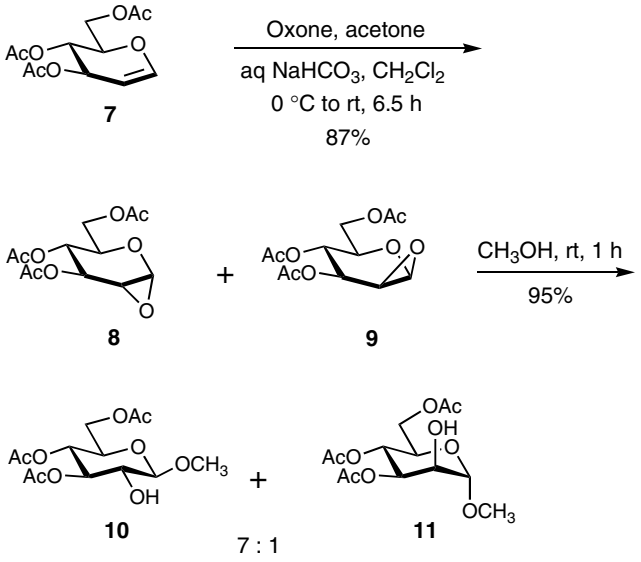
acetone and saturated aqueous $NaHCO_3$ to keep the pH of the reaction medium $\geqslant 8$, furnished epoxide **2** (Scheme 1) in almost quantitative yield (99%). The stereochemistry of **2** was confirmed by methanolysis and acetylation to give, after chromatography, β-glucoside **3** in a 94% yield. The $^1$H NMR data for both **2** and **3** were identical to those reported in the literature.[4] Likewise, the in situ epoxidation of tri-*O*-benzyl galactal **4** (3.00 g) gave α-epoxide **5**[13] again in an almost quantitative yield (Scheme 1). Then, product **5** was transformed into the methyl glycoside **6**[14] whose β-D-*galacto* configuration was unequivocally established by $^1$H NMR analysis.

Halcomb and Danishefsky reported[4] on the reaction of tri-*O*-acetyl glucal **7** with a DMDO solution to give a mixture of products whose composition was not further investigated. In our hands, the in situ epoxidation of **7** (3.00 g, 11.02 mmol) gave a mixture[8] of epoxides **8** and **9** in an 87% overall yield (Scheme 2). As expected,[4] glucal **7** was less reactive than its O-benzylated counterpart **1** and required a prolonged reaction time (ca. 6 h) to complete the epoxidation. This may explain the minor selectivity of this reaction. To prove the stereochemical outcome of the epoxidation of **7**, the mixture of **8** and **9** was subjected to methanolysis to give, after chromatography, a mixture of known methyl glycosides **10**[15] (β-D-*gluco*) and **11**[16] (α-D-*manno*) in a 95% total yield and a 7:1 ratio ($^1$H NMR analysis).

In conclusion, D-glucal and D-galactal derivatives were epoxidized with DMDO generated in situ. This procedure proved to be highly efficient and provided significant operating advantages over the epoxidation with earlier prepared DMDO solutions. This may serve as the basis for the large-scale preparation of 1,2-anhydro-D-glucose and D-galactose derivatives, which find numerous applications as building blocks and precursors in synthetic carbohydrate chemistry.




**Scheme 1.**




**Scheme 2.**

## 1. Experimental

### 1.1. General methods

All reactions were carried out in commercially available solvents of ACS reagent grade. Oxone® was purchased from Aldrich Chemical Company. The reactions were monitored by TLC on silica gel 60 $F_{254}$ with detection by charring with sulfuric acid. Flash column chromatography[17] was performed on Silica Gel 60 (230–400 mesh). The optical rotations were measured at $25 \pm 2$ °C in the stated solvent; $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. $^1$H (300 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature; chemical shifts are in ppm ($\delta$) from $Si(CH_3)_4$ (TMS) as internal standard; assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using 2,5-dihydroxybenzoic acid as the matrix.

### 1.2. 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (2)

To a vigorously stirred, cooled (ice bath) biphasic solution of tri-*O*-benzyl-glucal **1** (3.00 g, 7.21 mmol) in $CH_2Cl_2$ (30 mL), acetone (3 mL) and satd aq $NaHCO_3$ (50 mL), a solution of Oxone (8.87 g, 14.42 mmol) in $H_2O$ (35 mL) was added dropwise over 15 min. The mixture was vigorously stirred at 0 °C for 30 min and then at rt for an additional 2 h. The organic phase was separated and the aq phase extracted with $CH_2Cl_2$ ($2 \times 30$ mL). The combined organic phases were dried ($Na_2SO_3$) and concentrated to afford **2** (3.08 g, 99%) as a white solid. $[\alpha]_D$ +26.5 (*c* 1, $CHCl_3$), lit.[4] +29.2 (*c* 0.96, $CHCl_3$). The $^1$H NMR data were identical to those reported previously.[4] MALDI-TOF MS: 455.6 $[M+Na]^+$.

### 1.3. 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-galactopyranose (5)

Tri-*O*-benzyl-galactal **4** (3.00 g, 7.21 mmol) was oxidized as reported for the preparation of **2** to give **5** (3.08 g, 99%) as a syrup, which became solid upon standing in the freezer. $[\alpha]_D$ −18.9 (*c* 1, $CHCl_3$), lit.[13] −16.9 (*c* 0.62, $CHCl_3$). The $^1H$ NMR data were identical to those reported previously.[13] MALDI-TOF MS: 471.3 $[M+K]^+$.

### 1.4. 3,4,6-Tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose (8) and -β-D-mannopyranose (9)

To a vigorously stirred, cooled (ice bath) biphasic solution of tri-*O*-acetyl-glucal **7** (3.00 g, 11.02 mmol) in $CH_2Cl_2$ (50 mL), acetone (5 mL) and satd aq $NaHCO_3$ (100 mL), a solution of Oxone (13.6 g, 22.12 mmol) in $H_2O$ (60 mL) was added dropwise over 20 min. The mixture was vigorously stirred at 0 °C for 30 min and then at rt for an additional 6 h. The organic phase was separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were dried ($Na_2SO_3$) and concentrated to give a mixture of 1,2-anhydrosugars **8** and **9** (2.75 g, 87%). The selected $^1H$ NMR data for **8** (α-*gluco*) and **9** (β-*manno*): δ 5.38–5.28 (m, Man H-3 and H-4), 5.24 (dd, $J_{2,3} = 0.6$, $J_{3,4} = 8.5$ Hz, Glc H-3), 5.0–5.1 (m, Man H-1, Glc H-1 and H-4), 4.0 (ddd, $J = 10.5$, 4.0, 2.2 Hz, Glc H-5), 3.45 (t, $J = 2.6$ Hz, Man H-2), 3.03 (d, $J_{1,2} = 2.4$ Hz, Glc H-2).

### 1.5. Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (3)

To prove the configuration of 1,2-anhydrosugar **2**, a sample of the latter compound (100 mg, 0.23 mmol) was dissolved in anhydrous $CH_3OH$ (5 mL), kept at rt until TLC showed a complete consumption of the starting material (ca. 1 h), then concentrated and dried in vacuo. A solution of the crude methyl glycoside in pyridine (2 mL) and $Ac_2O$ (0.5 mL) was kept at room temperature for 3 h, then concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane–AcOEt to give **3** (110 mg, 94%) as a syrup. $[\alpha]_D$ +5.1 (*c* 1, $CHCl_3$), lit.[4] +4.90 (*c* 0.49, $CHCl_3$); The $^1H$ NMR data were identical to those reported previously.[4] MALDI-TOF MS: 529.6 $[M+Na]^+$.

### 1.6. Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranoside (6)

1,2-Anhydrosugar **5** (100 mg, 0.23 mmol) was treated with $CH_3OH$ and acetylated as described for the preparation of **3** to give **6** (109 mg, 93%) as a syrup. $[\alpha]_D$ +0.5 (*c* 1, $CHCl_3$), lit.[14] 0.0 (*c* 1, $CHCl_3$). The $^1H$ NMR data were identical to those reported previously.[14] MALDI-TOF MS: 529.2 $[M+Na]^+$.

### 1.7. Methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (10) and -α-D-mannopyranoside (11)

The mixture of 1,2-anhydrosugars **8** and **9** (100 mg, 0.35 mmol) was treated with anhydrous $CH_3OH$ as described for the preparation of **3** to give a ca. 7:1 mixture of **10** and **11** (153 mg, 95%). The selected $^1H$ NMR data for **10** (*gluco*) and **11** (*manno*): δ 5.34 (t, 0.12H, $J = 10.0$ Hz, Man H-4), 5.26 (dd, 0.12H, $J_{2,3} = 3.0$ Hz, Man H-3), 5.30 (t, 0.88H, $J = 9.0$ Hz, Glc H-4), 5.04 (t, 0.88H, $J = 9.6$ Hz, Glc H-3), 4.78 (d, 0.12H, $J_{1,2} = 1.6$ Hz, Man H-1), 4.30 (d, 0.88H, $J_{1,2} = 8.0$ Hz, Glc H-1), 3.58 (s, 3H, $OCH_3$).

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