Preparation of Butane-1,2-diaceatal-protected L-Glyceraldehyde from D-Mannitol

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Abstract: (2S, 5R, 6R)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carbaldehyde (5) represents an important stable alternative to glyceraldehyde acetonide. Its synthesis on a large scale from inexpensive D-mannitol is described together with other related building blocks.

Key words: 1,2-diaceatals, glyceraldehydes, glyceric esters, alkylation

The large scale preparation of stable and highly oxygenated three carbon building blocks in enantiomerically pure form has been a long-standing problem in many synthesis programmes. Thus far, 2,3-O-isopropylidene glyceraldehyde whose two enantiomers are accessible, are by far the most commonly used.1 However, these must always be freshly prepared owing to their propensity to polymerise, racemise, and form hydrates.2 Although, some new building blocks have been introduced to address these difficulties, they have failed to be adopted as general replacements.3 Here we describe a convenient preparation of butane-diacetal (BDA) protected glyceraldehyde4 and of 2-methyl methyl glycerate 6 as a new potential chiral three carbon building blocks.

Scope and Limitations

To be successful, the new unit must be obtained on a large scale from a cheap material and if possible without col-
umn chromatographic purification. Whereas (R)-glyceraldehyde acetonide is readily available from the inexpensive D-mannitol, the synthesis of the enantiomeric (S)-glyceraldehyde is longer and more difficult to accomplish. Interestingly, in our synthesis both enantiomers of BDA protected glyceraldehyde are available from D-mannitol (Scheme 2). 5

Firstly, D-mannitol was treated with butane-2,3-dione in the presence of anhydrous trimethyl orthoformate in MeOH, with a catalytic amount of BF₃·Et₂O 6 to give the diol 1 as the main product that could be isolated by recrystallisation from hexane. However, the crude diol 1 was usually obtained as an oil and was used without further purification in the next step. Oxidative cleavage with sodium metaperiodate in MeOH–water, followed by bromine oxidation 7 of the methyl hemiacetal gave the ester 3 in 45% yield on 70 g scale. The only purification necessary was distillation of the final product under vacuum (Scheme 1, Procedure 1).

In order to fully exploit the chirality incorporated into the diacetal backbone, an inversion protocol to obtain an ester in an axial position was investigated. It was expected that an axial position could improve chelation control and also give higher selectivities by shortening the distance to the chiral acetal centres.

Treatment of ester 3 with lithium diisopropylamide (LDA) at −78 °C followed by protic workup with t-BuOH at low temperature and subsequent quenching with aqueous NH₄Cl afforded the inverted ester 4. The concentration of the enolate should not be allowed to exceed 0.2 M to minimize β-elimination. Filtration through a short pad of silica gel, followed by recrystallisation from hexane gave one product as a highly crystalline and stable compound 4 whose structure was confirmed by X-ray crystallography (Scheme 1, Procedure 2).

Reduction with LiAlH₄ in THF was followed by oxidation with oxaly chloride and DMSO to give the axial aldehyde 5 as a white solid (95% overall yield on 25 g scale). The crude aldehyde was generally used without further purification but could be purified by flash chromatography or recrystallisation from hexane (Scheme 1, Procedure 3). This aldehyde 5 is stable and storable for long period of time (at least 3 months at r.t. under Ar or greater than 1 year at −50 °C).

The potential of 5 as a new building block is illustrated by the stereofacially selective addition of Grignard reagents via β-chelation control (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgX</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃MgCl</td>
<td>81</td>
<td>25:1</td>
</tr>
<tr>
<td>2</td>
<td>H≡C=CMgBr</td>
<td>95</td>
<td>15:1</td>
</tr>
<tr>
<td>3</td>
<td>CH₂C≡CMgBr</td>
<td>93</td>
<td>15:1</td>
</tr>
<tr>
<td>4</td>
<td>CH₂=CHCH₂MgBr</td>
<td>88</td>
<td>15:1</td>
</tr>
<tr>
<td>5</td>
<td>CH₂=CHMgBr</td>
<td>80</td>
<td>15:1</td>
</tr>
</tbody>
</table>

Although, 10% HMPA was required as a co-solvent, the lithium enolate of 3 could also be trapped by CH₃I to afford a new stereogenic center. 8 This reaction could be performed on a large scale to give 18 g of a white solid 6 in 70% yield. However, the crude ester 6 needs to be purified by flash chromatography prior to reaction (Scheme 1, Procedure 4).

In summary, the large scale and practical preparation of a stable BDA protected glyceraldehyde is described. This new building block should find application in a range of synthetic programmes.

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. CH₂Cl₂, MeOH and Et₃N were distilled from CaH₂. THF was distilled from CaH₂ and LiAlH₄. All other solvents were used as obtained from commercial source. Flash column chromatography was carried out using Merck silica gel 60 (0.040–0.063 mm). Analytical TLC was performed on precoated glass-backed plates (Merck silica gel 60 F254) and visualised by UV fluorescence or acidic ammonium molybdate(IV). Melting points were recorded on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 343 polarimeter with a path length of 100 mm; con-

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Table 1  Selective Addition of Grignard Reagents via β-Chelation Control

![Scheme 2](image-url)
centrations are quoted in g (100 mL) and [\(\delta\)] values are in units of 10\(^{-1}\) deg cm\(^{-1}\) g\(^{-1}\). IR spectra were recorded on a Perkin-Elmer ‘Spectrum-One’ spectrometer equipped with an Attenuated Total Reflection (ATR) sampling accessory. \(^1\)H NMR spectra were recorded at 400 MHz on a Bruker AM400 instrument. \(^{13}\)C NMR spectra were recorded at 100 MHz on a Bruker AM400 instrument. Chemical shifts are quoted in ppm and referenced to the appropriate CHCl\(_3\) peak (7.26 ppm for \(^1\)H, 77.0 ppm for \(^{13}\)C). HRMS were obtained on a Kratos Q-TOF or Bruker BIOAPEX 47 FTICR spectrometers using electrospray (+ESI) or electron impact (EI) techniques at the Department of Chemistry, University of Cambridge. Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, University of Cambridge.

\section*{(2R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxylic Acid Methyl Ester (3)}

BF\(_3\).Et\(_2\)O (10 mL, 81.3 mmol) was added to a stirred solution of trimannitol (61.9 g, 339.8 mmol), anhyd trimethyl orthoformate (150 mL, 1.37 mol) and butanedione (63 mL, 717.8 mmol) in MeOH (300 mL) at r.t., under an atmosphere of Ar. After 5 h, the reaction mixture was neutralized by the addition of Et\(_3\)N (10 mL, 71.74 mmol) and the solvent was removed in vacuo. The crude residue was used without further purification.

Sodium metaperiodate (95.4 g, 418.5 mmol) was added slowly to a stirred suspension of LiAlH\(_4\) (30.2 g, 129.05 mmol) solubilized in THF (30 mL) at –50 °C to –60 °C under Ar. The mixture was stirred overnight at r.t. Excess hydride was quenched by successive addition of water (3.5 mL), 15% aq NaOH (3.5 mL) and water (10.5 mL). The resulting suspension was filtered through Celite, rinsed with Et\(_2\)O, and the solvents were removed in vacuo. The crude residue was used without further purification.

DMSO (20 mL, 281.8 mmol) was added dropwise to a stirred solution of oxalyl chloride (12 mL, 137.5 mmol) in CH\(_2\)Cl\(_2\) (350 mL) at –50 °C to –60 °C under Ar. After 2 min, a solution of the crude alcohol in CH\(_2\)Cl\(_2\) (30 mL) was added. After stirring for 15 min, Et\(_3\)N (48 mL, 344.4 mmol) was added. The mixture was stirred for 5 min and then allowed to warm to r.t. Water (300 mL) was added and the aq layer was extracted with CH\(_2\)Cl\(_2\) (200 mL). The organic layers were combined, washed with brine (150 mL), 1 N HCl solution (300 mL), water (150 mL), sat. NaHCO\(_3\) (300 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo to give a white solid (25.0 g, 122.54 mmol, 95%). The crude aldehyde was used usually without further purification.

\section*{(2S,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2-carboxaldehyde (5)}

Ester 4 (30.2 g, 129.05 mmol) was added slowly to a stirred suspension of LiAlH\(_4\) (30.2 g, 95.27 mmol) in THF (30 mL) at 0 °C under Ar. The mixture was stirred overnight at r.t. Excess hydride was quenched by successive addition of water (3.5 mL), 15% aq NaOH (3.5 mL) and water (10.5 mL). The resulting suspension was filtered through Celite, rinsed with Et\(_2\)O, and the solvents were removed in vacuo. The crude residue was used without further purification.
purified by flash chromatography (hexane–EtOAc, 9:1) to give 6 as a white solid (18.43 g, 70%); mp 45–46 °C; [α]D25 −130.1 (c 0.9, CHCl3).

IR: 1731 cm−1.

1H NMR (400 MHz, CDCl3): δ = 3.96 (d, J = 11.5 Hz, 1 H, CHH), 3.62 (s, 3 H, CO2CH3), 3.41 (d, J = 11.5 Hz, 1 H, CHH), 3.11 (s, 3 H, OCH3), 3.07 (s, 3 H, OCH3), 1.16 (s, 3 H, CH3), 1.12 (s, 3 H, CH3), 1.11 (s, 3 H, CH3).

13C NMR (400 MHz, CDCl3): δ = 173.5, 99.2, 97.2, 70.9, 51.6, 49.9, 47.6, 22.9, 17.44, 17.42.


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References