



Pergamon

Tetrahedron Letters 41 (2000) 2569–2572

TETRAHEDRON
LETTERS

The expeditious preparation and reactivity of some protected forms of gluconolactones

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Received 13 September 1999; revised 14 December 1999; accepted 28 January 2000

Abstract

2,3-Bis-*O*-(*tert*-butyldimethylsilyl)-5,6-*O*-isopropylidene-D-glucono-1,4-lactone has been easily prepared from commercially available starting material and its activity investigated. Based on the lactone functionality, this compound can proceed via nucleophilic addition, reduction, and hydrolysis to generate various highly functionalized molecules. © 2000 Elsevier Science Ltd. All rights reserved.

Aldonolactones are sugar lactones formed from aldoses by oxidation of the C-1 aldehyde to carboxylic acid and further intramolecular esterification with one hydroxyl group (normally at the C-4 or C-5 position). Although they are usually commercially available and can be purchased at costs as low as common aldose sugars such as glucose and galactose, their synthetic usage as a starting material has not been generally recognized.^{1,2} Lundt has studied aldonolactones for the synthesis of pyrrolidines, piperidines, carbocyclic compounds (carbasugars), and tetrahydrofurans;³ however, most of this work was involved in the preparation of selectively functionalized aldonolactones with little exploration into protection group chemistry. In the past, methods for making protected sugar lactones always utilized corresponding aldose sugars as starting materials, which required tedious protection and deprotection steps at anomeric positions and provided only one protecting group for all hydroxyl groups.^{4–7} As our synthetic interest is to develop different and distinguishable protecting groups in aldonolactone chemistry, here we would like to demonstrate that 2,3-bis-*O*-(*tert*-butyldimethylsilyl)-5,6-*O*-isopropylidene-D-glucono-1,4-lactone (**2**) can be synthesized in a concise way to serve as a versatile chiral synthon leading to the preparation of various carbohydrate derivatives.

Compound **2** was prepared in two steps from D-glucono-1,5-lactone, i.e., the formation of 5,6-*O*-isopropylidene and the protection at the C-2 and C-3 positions using the *tert*-butyldimethylsilyl (TBDMS) group, as shown in Fig. 1.⁸ Although the starting material exists as a δ -lactone, compound **1** was characterized as the γ -lactone of a five-membered ring, which was consistent with the results of Chittenden.⁹

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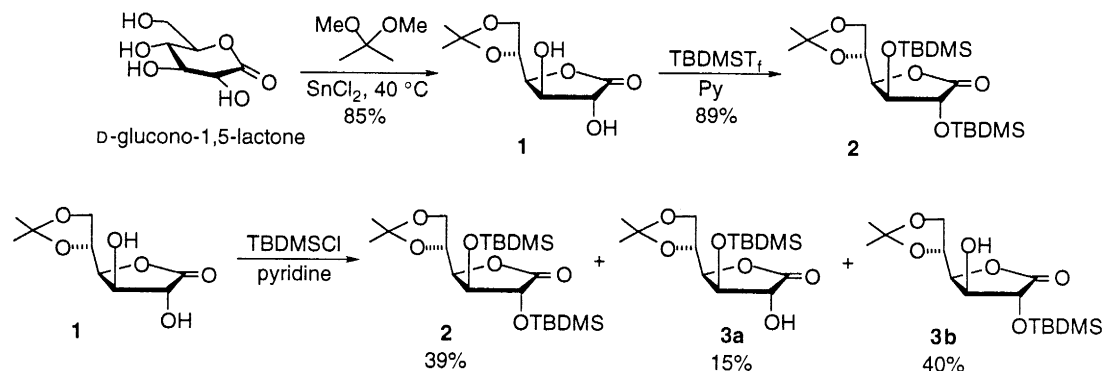


Fig. 1.

Furthermore, when using two equivalents of *tert*-butyldimethylsilyl chloride as the silylation reagent, partially protected products (compounds **3a** and **3b**) were obtained in the company of the desired compound **2** with purified yields of 15, 40 and 39%, respectively. The reason for the excessive amount of **3b** relative to **3a** can be explained based on the understanding that the hydroxyl group at C-2 is sterically less hindered than that at C-3.

To investigate the nucleophilic addition of the lactone functionality, compound **2** reacted with allylmagnesium chloride to give *C*-glycoside **4** (Fig. 2) as the inseparable mixture of the α - and β -anomers (ratio 3:1). In order to simplify the characterization of the reaction product, further acetylation gave compound **5** as the exclusive β -anomer.¹⁰ The β configuration was determined based on the NOESY spectra and supported by the MM2 calculations.¹¹ Such a result is concordant with the understanding that the β -anomer is more reactive than the α -anomer due to less steric hindrance. Compound **5** was subject to ozonolysis and epoxidation to give the aldehyde **7** and epoxide **8**, respectively.¹² The elimination reaction of the former product is currently being investigated since the conjugated aldehyde can be generated for further synthetic exploration; such as Michael addition to introduce an extra substituent in the anomeric position, and a Diels–Alder reaction to build up a spiro moiety.

For the purpose of reduction, compound **2** was treated with sodium borohydride in THF/H₂O to give a mixture with a complicated ¹H NMR spectrum, which implied the migration of the TBDMS group(s) under the strongly basic conditions. Therefore, further silylation with *tert*-butyldimethylsilyl-trifluoromethanesulfonate (TBDMSTf) generated the fully protected compound **9** to facilitate the product characterization.¹³ The result provides an approach to prepare biologically interesting carbohydrates with discernible protecting groups. For example, compound **9** was selectively removed from the isopropylidene group in the presence of BCl₃. Subsequent treatment with the pyridinium dichromate oxidation and final acidic deprotection generated L-gulose,¹⁴ a sugar component of the glycopeptide antibiotic bleomycin A₂.

As for the lactone hydrolysis to generate an acid/ester and a hydroxyl group, compound **2** was tried under several different conditions (e.g., EtOH/H₂O and various temperatures) and found to be resistant to the nucleophilic attack of water or alcohol. The problem was overcome by replacing TBDMS with acetyl group. The acetate analog **10** can easily proceed the methanolysis, as shown in Fig. 3. The methyl ester **11** was produced after further protection with Ac₂O/pyridine.¹⁵ It is interesting that different protecting groups can influence the reactivity of the lactone moiety. Whether an electron-withdrawing group (such as the acetyl group) activates the lactone, or the steric hindrance of TBDMS plays a major role, requires further investigation. Moreover, since the migration of the acetyl and TBDMS groups was observed in this study, additional protection was required for result analysis and product characterization.

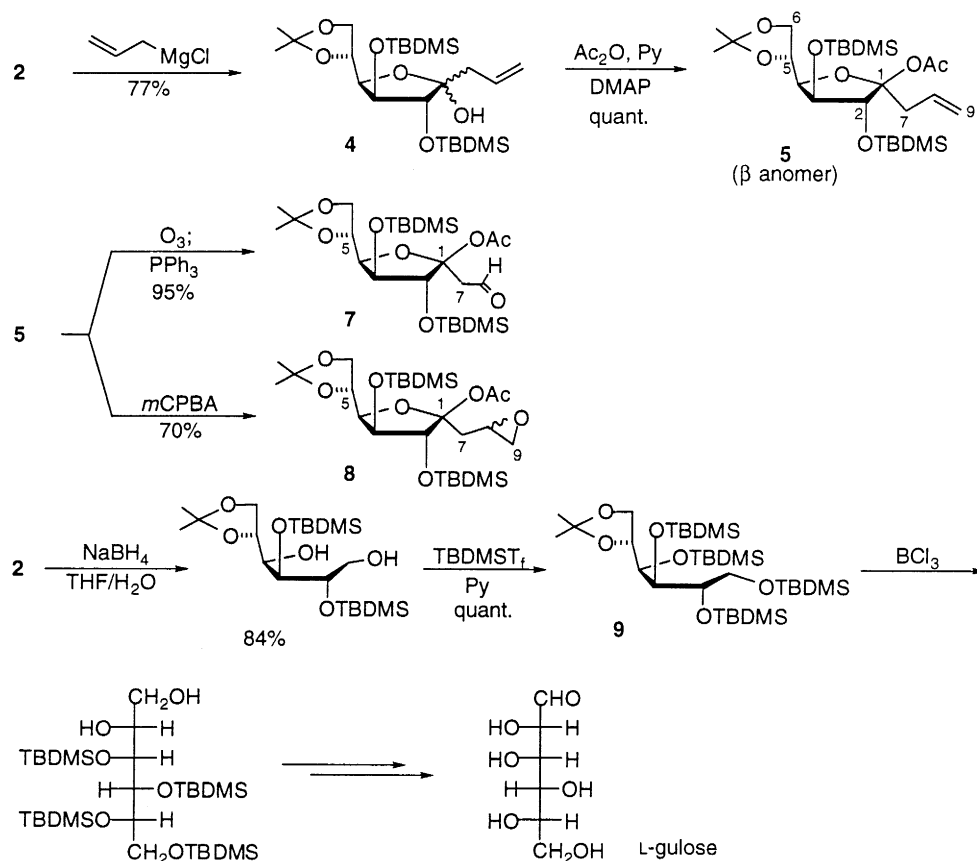


Fig. 2.

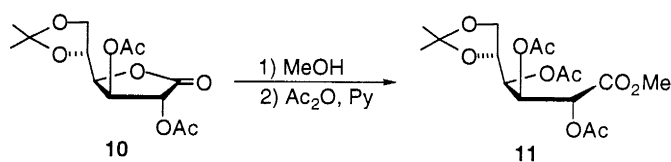


Fig. 3.

In conclusion, 2,3-bis-*O*-(*tert*-butyldimethylsilyl)-5,6-*O*-isopropylidene-D-glucono-1,4-lactone (2) and its analog have been examined on the reactivity of the lactone functionality and applied to prepare various highly functionalized molecules, such as *C*-glycosides and polyhydroxyl compounds. The strategy developed here is useful for other sugar lactones. Further investigations based on this concept are currently in progress.

Acknowledgements

This work was supported by the National Science Council (NSC-88-2113-M-0010-028) and Lee Foundation. C.-H. Tsai thanks the NSC for an undergraduate scholarship.

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- Compound **2**: ^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H, $-\text{SiCH}_3$), 0.10 (s, 3H, $-\text{SiCH}_3$), 0.13 (s, 3H, $-\text{SiCH}_3$), 0.14 (s, 3H, $-\text{SiCH}_3$), 0.72 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 0.87 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 1.32 (s, 3H, $-\text{CH}_3$), 1.41 (s, 3H, $-\text{CH}_3$), 3.94 (d, 1H, $J=1.4$ Hz, H-2), 3.96 (dd, 1H, $J=8.8$, 5.9 Hz, H-6), 4.11 (dd, 1H, $J=8.8$, 5.5 Hz, H-6), 4.12 (dd, 1H, $J=1.4$, 3.2 Hz, H-3), 4.31 (ddd, 1H, $J=8.2$, 5.9, 5.5 Hz, H-5), 4.46 (dd, 1H, $J=8.2$, 3.2 Hz, H-4); ^{13}C NMR (100 MHz, CDCl_3) δ -5.54, -5.16, -4.89, -4.81, 18.05, 25.10, 25.54, 25.56, 25.61, 26.76, 67.13, 71.67, 74.40, 75.28, 82.93, 109.44, 174.03.
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- Compound **5**: ^1H NMR (400 MHz, CDCl_3) δ 0.07 (s, 3H, $-\text{SiCH}_3$), 0.08 (s, 3H, $-\text{SiCH}_3$), 0.09 (s, 3H, $-\text{SiCH}_3$), 0.11 (s, 3H, $-\text{SiCH}_3$), 0.84 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 0.89 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 1.31 (s, 3H, $-\text{CH}_3$), 1.38 (s, 3H, $-\text{CH}_3$), 2.05 (s, 3H, $-\text{COCH}_3$), 2.54 (d, 2H, $J=7.0$ Hz, H-7), 3.87 (dd, 1H, $J=8.3$, 6.4 Hz, H-6), 4.03 (dd, 1H, $J=7.2$, 3.6 Hz, H-4), 4.06 (dd, 1H, $J=8.3$, 6.4 Hz, H-6), 4.18 (dd, 1H, $J=3.6$, 1.5 Hz, H-3), 4.17–4.21 (m, 1H, H-5), 4.90 (d, 1H, $J=1.5$ Hz, H-2), 5.05 (s, 1H, H-9), 5.09 (d, 1H, $J=7.0$ Hz, H-9), 5.67–5.87 (m, 1H, H-8). For the numbering of each carbon, please see compound **5** in Fig. 2. ^{13}C NMR (100 MHz, CDCl_3) δ -5.47, -4.90, -3.09, -2.86, 18.01, 18.09, 20.99, 25.43, 25.79, 26.68, 45.34, 67.29, 72.85, 76.50, 79.96, 81.33, 106.08, 108.92, 117.95, 133.58, 169.20.
- The NOESY experiment of compound **5** was carried out at -50°C . The NOESY connection was observed among H-3, H-4, and H-9. The two methyl groups of isopropylidene were also found to be spatially close to H-2 and the acetyl group. These observations indicate that the β -anomer is the reaction product. Also, the MM2 calculation suggests that the β -anomer is 1.0 kcal/mol more stable than the α -anomer.
- Compound **7**: ^1H NMR (400 MHz, CDCl_3) δ 0.11 (s, 3H, $-\text{SiCH}_3$), 0.11 (s, 3H, $-\text{SiCH}_3$), 0.12 (s, 3H, $-\text{SiCH}_3$), 0.15 (s, 3H, $-\text{SiCH}_3$), 0.84 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 0.89 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 1.32 (s, 3H, $-\text{CH}_3$), 1.40 (s, 3H, $-\text{CH}_3$), 2.14 (s, 3H, $-\text{COCH}_3$), 2.84 (dd, 2H, $J=2.8$, 1.1 Hz, H-7), 3.87 (dd, 1H, $J=8.4$, 6.1 Hz, H-6), 4.06 (dd, 1H, $J=7.8$, 3.1 Hz, H-4), 4.09 (dd, 1H, $J=8.4$, 6.2 Hz, H-6), 4.18–4.23 (m, 1H, H-5), 4.25 (dd, 1H, $J=3.1$, 1.1 Hz, H-3), 4.96 (d, 1H, $J=1.1$ Hz, H-2), 9.77 (t, 1H, $J=2.8$ Hz, H-8). Compound **8** (as a mixture of two isomers in the ratio of 1.2:1): ^1H NMR (400 MHz, CDCl_3) δ 0.08 (s, 3H, $-\text{SiCH}_3$), 0.08 (s, 3H, $-\text{SiCH}_3$), 0.09 (s, 3H, $-\text{SiCH}_3$), 0.10 (s, 3H, $-\text{SiCH}_3$), 0.10 (s, 3H, $-\text{SiCH}_3$), 0.12 (s, 3H, $-\text{SiCH}_3$), 0.12 (s, 3H, $-\text{SiCH}_3$), 0.14 (s, 3H, $-\text{SiCH}_3$), 0.85 (s, 18H, $-\text{C}(\text{CH}_3)_3$), 0.87 (s, 18H, $-\text{C}(\text{CH}_3)_3$), 1.78 (dd, 1H, $J=14.1$, 7.1 Hz, H-7'), 1.93 (dd, 1H, $J=14.3$, 6.9 Hz, H-7), 2.03 (dd, 1H, $J=14.3$, 4.5 Hz, H-7), 2.29 (dd, 1H, $J=14.1$, 4.3 Hz, H-7'), 2.42 (dd, 1H, $J=4.8$, 2.5 Hz, H-9), 2.50 (dd, 1H, $J=4.8$, 2.5 Hz, H-9'), 2.73 (t, 1H, $J=4.8$ Hz, H-9), 2.77 (t, 1H, $J=4.8$ Hz, H-9'), 3.04–3.09 (m, 2H, H-8, H-8'), 3.83–3.89 (m, 2H, H-6, H-6'), 4.02–4.09 (m, 4H, H-6, H-4, H-6', H-4'), 4.15–4.22 (m, 4H, H-5, H-3, H-5', H-3'), 4.96 (s, 1H, H-2'), 5.16 (s, 1H, H-2).
- Compound **9**: ^1H NMR (400 MHz, CDCl_3) δ 0.02 (s, 6H, $-\text{SiCH}_3$), 0.03 (s, 3H, $-\text{SiCH}_3$), 0.06 (s, 3H, $-\text{SiCH}_3$), 0.07 (s, 6H, $-\text{SiCH}_3$), 0.09 (s, 3H, $-\text{SiCH}_3$), 0.10 (s, 3H, $-\text{SiCH}_3$), 0.87 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 0.88 (s, 18H, $-\text{C}(\text{CH}_3)_3$), 0.90 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 1.27 (s, 3H, $-\text{CH}_3$), 1.34 (s, 3H, $-\text{CH}_3$), 3.56 (dd, 1H, $J=9.9$, 6.4 Hz, H-6), 3.73 (dd, 1H, $J=9.9$, 4.6 Hz, H-6), 3.80 (dd, 1H, $J=7.5$, 2.5 Hz, H-2), 3.81 (t, 1H, $J=7.5$ Hz, H-1), 3.83–3.86 (m, 1H, H-5), 3.99 (t, 1H, $J=7.5$ Hz, H-1), 4.00 (dd, 1H, $J=4.9$, 3.6 Hz, H-4), 4.30 (m, 1H, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ -5.29, -5.17, -4.46, -4.32, -3.90, -3.70, -3.30, -3.18, 18.19, 18.29, 18.40, 25.73, 25.87, 26.02, 26.06, 26.12, 26.13, 26.47, 64.19, 66.47, 72.68, 73.08, 74.89, 75.42, 107.84.
- The total synthesis of L-gulose has been accomplished starting from gluconolactone with the overall yield of 46%: Yang, W.-B.; Lin, C.-H. *Chem. Commun.* submitted.
- Compound **11**: ^1H NMR (400 MHz, CDCl_3) δ 1.29 (s, 3H, $-\text{CH}_3$), 1.32 (s, 3H, $-\text{CH}_3$), 2.02 (s, 3H, $-\text{COCH}_3$), 2.03 (s, 3H, $-\text{COCH}_3$), 2.13 (s, 3H, $-\text{COCH}_3$), 3.70 (s, 3H, $-\text{C}(\text{O})\text{OCH}_3$), 3.75 (dd, 1H, $J=8.6$, 6.1 Hz, H-6), 3.97 (dd, 1H, $J=8.6$, 6.3 Hz, H-6), 4.12 (ddd, 1H, $J=7.5$, 6.3, 6.1 Hz, H-5), 5.23 (dd, 1H, $J=7.5$, 5.9 Hz, H-4), 5.32 (d, 1H, $J=3.5$ Hz, H-2), 5.52 (dd, 1H, $J=5.9$, 3.5 Hz, H-3); ^{13}C NMR (100 MHz, CDCl_3) δ 20.42, 25.10, 25.19, 26.23, 26.32, 52.64, 66.46, 70.39, 70.82, 71.02, 74.18, 110.14, 167.41, 169.41, 169.46, 169.62.