Pergamon

Tetrahedron Letters 42 (2001) 6487–6489

TETRAHEDRON LETTERS

A facile synthesis of Cerny epoxides and selectively blocked derivatives of 2-azido-2-deoxy-β-D-glucopyranose

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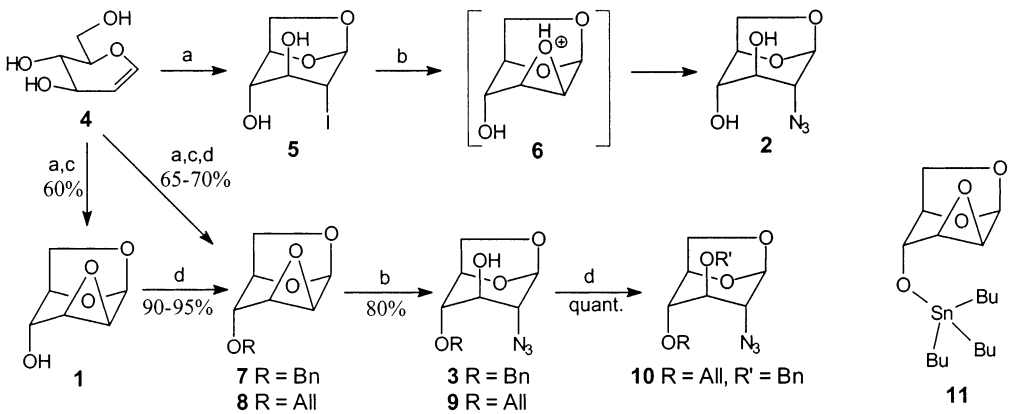
Received 18 June 2001; accepted 19 July 2001

Abstract—1,6:2,3-Dianhydro-β-D-glucopyranose and its 3-alkylated derivatives were prepared from D-glucal in one pot with overall isolated yields of 60–70%, and these Cerny epoxides were further conveniently converted to selectively blocked 2-azido-2-deoxy-β-D-glucopyranose derivatives by azido opening of the epoxide ring. © 2001 Elsevier Science Ltd. All rights reserved.

1,6:2,3-Dianhydro-β-D-glucopyranose (**1**, one of the Cerny epoxides) and 2-azido-2-deoxy-β-D-glucopyranose (**2**) are useful precursors for complex oligosaccharide synthesis.[1–3] Consequently, the preparation of **1** and **2**, as well as their derivatives, is a significant research focus in carbohydrate chemistry. However, all the reported synthetic methods[4–24] for them are laborious, multistep processes that result in unsatisfactory yields. For example, the most efficient synthesis for Cerny epoxides, which was illustrated in the preparation of 4-*O*-benzyl-1,6:2,3-dianhydro-β-D-glucopyranose (**3**) from D-glucal (**4**), involved five separate steps that offered an overall yield of only 13.5%.[13] Furthermore, the synthesis is incompatible with other protecting groups, such as allyl. For **2**, an efficient synthesis also started from D-glucal (Scheme 1), and the two-step transformation gave an overall yield of 68%.[12] However, it involves time-consuming and costly separations, e.g. longtime continuous extractions, and our study indicated that ordinary work-up procedures could only produce very low yields (20–30%), though the reactions were quite clean. In addition, the differentiation of 3- and 4-hydroxyls in **2** requires multiple protection and deprotection operations.[12]

We report herein a one-pot synthesis of **1** and its derivatives from readily available D-glucal (**4**), as well as a two-step, efficient route to selectively blocked derivatives of **2** (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) i. $(Bu_3Sn)_2O$, MS 3 Å, MeCN, refl., 3 h; ii. I_2, MeCN, rt, 1.5 h; (b) NaN_3, DMF, 120°C, overnight; (c) $NaHCO_3$, DMF, 120°C, 4 h; (d) BnBr or AllBr, NaH, DMF, rt, 2 h.

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PII: S0040-4039(01)01354-5

Previous studies[12,14] indicated that D-glucal (**4**) could be stereospecifically transformed to **2** following tin-mediated 1,6-iodocyclization and azido substitution (Scheme 1). The latter involved a double-inversion process through an epoxide intermediate **6**, which was supported by the isolation of epoxide **1** under certain strict conditions.[12] Based on these results, we anticipate that if the nucleophile N_3^- is eliminated from the reaction, the transformations may terminate at the stage of intramolecular cyclization to afford Cerny epoxide **1**, which may be developed into a convenient synthetic method for these useful compounds. For this purpose, we studied the reactions of **5** under neutral conditions. TLC showed that heating **5** in DMF and water (9:1) at 120°C gave a new product, but the reaction was very slow, and after 4 hours of treatment, only less than 10% conversion was observed. Nevertheless, the product was proved to be the expected **1**.[25] To improve the reaction rate, we then investigated the influence of mild bases on this reaction. Thus, the solutions of **5** in DMF and water (9:1) containing 10% pyridine, 1.2 M sodium acetate or 1.2 M sodium bicarbonate were respectively heated at 120°C. It was disclosed that pyridine had little influence on the reaction rate, but sodium acetate and sodium bicarbonate could significantly accelerate the reaction, and under these conditions, the cyclization could finish within 4 hours. After usual work-up and column chromatography, **1** was obtained in 60% yield. Thereafter, **1** was readily converted to its benzyl and allyl derivatives **7** and **8**[25] by conventional alkylations in excellent yields.

We further investigated the transformations of **7** and **8** to the selectively blocked derivatives of **2**. The ring opening of **7** and **8** by sodium azide was readily achieved in DMF and water (9:1) at 120°C to give **3** and **9**[25] in excellent isolated yields (80%). The reactions were very clean, but slower than the azido substitution of **5** under the same conditions, which may result from the steric hindrance in **7** and **8**. Compared to **2**, these products could be much more conveniently isolated via ordinary extraction and column chromatography. Finally, modification of the 3-positions of **3** and **9** by other protecting groups can be easily achieved by conventional methods to afford corresponding derivatives, e.g. **10**, that have 3-, 4- and 6-hydroxyls differentiated and can be used in the preparation of various complex oligosaccharides.

After the reaction conditions for effective conversion of **4** to **1** and its alkyl derivatives were established, we further examined the possibility of achieving these transformations in one pot. A one-pot procedure should be very useful for the synthesis of Cerny epoxide, as the intermediates **5** and **1** are soluble in water, and thus, their extractions are very difficult. Therefore, after D-glucal **4** was refluxed with 0.8 equiv. of bis(tributylstannyl)oxide in acetonitrile for 3 h, the reaction mixture was treated with 1.2 equiv. of iodine at room temperature. Then, acetonitrile was removed under vacuum, and the resulting residue was directly treated with DMF and water (9:1) containing 1.2 M sodium bicarbonate at 120°C for 4 h. After the reaction mixture was again condensed under vacuum, the residue was dissolved in anhydrous DMF, and the solution was stirred with benzyl or allyl bromide and sodium hydride at room temperature for 2 h. All these steps were monitored with TLC. Finally, routine workup, which include extraction with ethyl acetate, washing of the extracts with acidic, basic aqueous solutions and brine, drying over sodium sulfate and condensation followed by silica gel column chromatography, afforded **7** and **8** in excellent overall yield (65–70%).

We further examined the possibility to transform D-glucal (**4**) to **2** in one pot. Thus, after D-glucal (**4**) was sequentially treated with bis(tributylstannyl)oxide and iodine, and then removal of the solvent under vacuum, the resulting residue was heated at 120°C with excess (5 equiv.) sodium azide in DMF and water. To our surprise, however, no azido compound **2** was formed from this reaction. Instead, the product turned out to be **1**. The result suggests that the nucleophilic attack of azide on the epoxide of **1** was somehow prohibited in the one-pot procedure, even though purified **1** could be readily converted to **2** under the same condition. Two possible mechanisms are proposed to explain this experimental outcome. One is that the azide was deactivated through complexation with the stannyl compounds used and/or formed in the 1,6-iodocyclization of D-glucal (**4**). A more plausible explanation is that the stannyl compounds could form a chelating structure (**11**) with the epoxide **1** and its steric hindrance inhibited the approach of azide to the epoxide ring. In either way, the sodium azide was only acting as a weak base to assist the formation of epoxide.

In conclusion, this work presents a new, one-pot and highly efficient synthetic method for **1** and its derivatives, as well as a facile route to selectively blocked derivatives of **2**, from commercially available D-glucal (**4**). Thus, 2-azido-2-deoxy-β-D-glucopyranose derivatives with differentiated 3- and 4-positions, such as **3** and **9**, can be prepared from D-glucal (**4**) in two separate steps and more than 50% yields. Compounds **3** and **9** can be directly used as glycosyl acceptors in the synthesis of oligosaccharides containing 1,3-linked glucosamine residues. They can also be very easily converted to other derivatives of 2-azido-2-deoxy-β-D-glucopyranose and D-glucosamine which are of wide applications in carbohydrate chemistry.

Acknowledgements

We are grateful for the financial support from a Research Innovation Award (RI 0663) of the Research Corporation.

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25. All products are known compounds. Their NMR spectra were identical to those of the reported.[4–24] For example: **1** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 5.68 (d, 1H, $J_{1,2}$ 3.0 Hz, 1-H), 4.40 (bd, 1H, $J_{5,6'}$ 5.4 Hz, 5-H), 3.89 (bd, 1H, $J_{6,6'}$ 7.4 Hz, 6-H), 3.73 (m, 2H, 6′-H, 3-H), 3.43 (m, 1H, 4-H), 3.13 (d, 1H, $J_{1,2}$ 3.0 Hz, 2-H), 2.86 (bs, 1H, -OH). **2** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 5.52 (s, 1H, 1-H), 4.59 (bd, 1H, $J_{5,6'}$ 5.4 Hz, 5-H), 4.22 (d, 1H, $J_{6,6'}$ 7.4 Hz, 6-H), 3.90 (m, 1H, 4-H), 3.81 (dd, 1H, $J_{6,6'}$ 7.4 Hz, $J_{5,6'}$ 5.4 Hz, 6′-H), 3.67 (d, 1H, $J_{3,OH}$ 9.6 Hz, 3-H), 3.52 (br, 1H, 2-H), 2.62 (d, 1H, $J_{3,OH}$ 9.6 Hz, OH), 2.46 (d, 1H, $J_{4,OH}$ 6.9 Hz, OH). **7** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 7.38 (m, 5H, Ph), 5.71 (d, 1H, $J_{1,2}$ 3.1 Hz, 1-H), 4.74 (s, 2H, Bn), 4.52 (m, 1H, 5-H), 3.70 (m, 2H, 6-H, 6′-H), 3.66 (bs, 1H, 4-H), 3.46 (dd, 1H, $J_{1,2}$ 3.1 Hz, $J_{2,3}$ 3.1 Hz, 2-H), 3.19 (m, 1H, 3-H). **8** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 5.96 (m, 1H, All), 5.70 (d, 1H, $J_{1,2}$ 3.1 Hz, 1-H), 5.34 (ddd, *J* 17.3 Hz, 3.1 Hz, 1.6 Hz, 1H, All), 5.25 (ddd, *J* 10.4 Hz, 2.6 Hz, 1.2 Hz, 1H, All), 4.48 (m, 1H, 5-H), 4.20 (m, 2H, All), 3.70 (m, 2H, 6-H, 6′-H), 3.62 (bs, 1H, 4-H), 3.44 (m, 1H, 2-H), 3.17 (m, 1H, 3-H). **3** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 7.38 (m, 5H, Ph), 5.48 (s, 1H, 1-H), 4.70 (s, 2H, Bn), 4.62 (bd, 1H, $J_{5,6'}$ 5.4 Hz, 5-H), 3.95 (d, 1H, $J_{6,6'}$ 7.4 Hz, 6-H), 3.91 (m, 1H, 4-H), 3.70 (dd, 1H, $J_{6,6'}$ 7.4 Hz, $J_{5,6'}$ 5.4 Hz, 6′-H), 3.38 (m, 1H, 3-H), 3.24 (d, 1H, $J_{1,2}$ 3.1 Hz, 2-H), 2.48 (d, 1H, $J_{3,OH}$ 6.1 Hz, OH). **9** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 5.94 (m, 1H, All), 5.47 (s, 1H, 1-H), 5.34 (ddd, *J* 16.6 Hz, 3.0 Hz, 1.5 Hz, 1H, All), 5.24 (ddd, *J* 10.5 Hz, 2.5 Hz, 1.0 Hz, 1H, All), 4.64 (d, 1H, $J_{5,6'}$ 5.3 Hz, 5-H), 4.15 (d, 2H, *J* 5.7 Hz, All), 4.01 (d, 1H, $J_{6,6'}$ 7.5 Hz, 6-H), 3.88 (bs, 1H, 4-H), 3.75 (dd, 1H, $J_{6,6'}$ 7.5 Hz, $J_{5,6'}$ 5.3 Hz, 6′-H), 3.36 (m, 1H, 3-H), 3.23 (m, 1H, 2-H), 2.62 (bs, 1H, OH). **10** (^{1}H NMR, 300 MHz, $CDCl_3$) δ 7.36 (m, 1H, Ph), 5.90 (m, 1H, All), 5.49 (s, 1H, 1-H), 5.29 (bdd, *J* 17.3 Hz, 1.6 Hz, 1H, All), 5.22 (bdd, *J* 10.3 Hz, 1.6 Hz, 1H, All), 4.68 (d, 1H, *J* 11.9 Hz, Bn), 4.64 (bd, 1H, $J_{5,6'}$ 6.0 Hz, 5-H), 4.59 (d, 1H, *J* 11.9 Hz, Bn), 4.06 (m, 3H, All, H-6), 3.76 (dd, 1H, $J_{6,6'}$ 7.1 Hz, 6′-H), 3.66 (m, 1H, 4-H), 3.38 (bs, 1H, 3-H), 3.27 (bs, 1H, 2-H); **10** (^{13}C NMR, 50 MHz, $CDCl_3$) δ 137.4, 134.2, 128.6, 128.1, 127.9, 117.9, 100.7, 76.4, 76.2, 74.5, 72.5, 70.5, 65.4, 59.9.