

Highly Efficient Inversion of the C-3 Configuration in 1,2-*O*-Isopropylidenefuranose Derivatives by an Adapted Swern Oxidation/Sodium Borohydride Reduction Protocol in One Pot

Silvano Cruz-Gregorio, Luis Hernández, Mónica Vargas, Leticia Quintero,* and Fernando Sartillo-Piscil.*

Centro de Investigación de la Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, 14 Sur Esq. San Claudio, San Manuel 72570, Puebla, México, Tel.: +52-2222-295500-7387; fax: +52-2222-454293
e-mail: fsarpis@siu.buap.mx

Received February 8, 2005; accepted March 29, 2005

Abstract. One pot Swern oxidation-sodium borohydride reduction of 1,2-*O*-isopropylidenefuranose derivatives having the *D*-*gluco* or *D*-*xylo* configurations led to the corresponding stereoisomers resulting from the stereoselective inversion of C-3. This method is a simple adaptation to the traditional procedure that consists in quenching the Swern oxidation at -60 °C with a mixture of H₂O/EtOH (1:4), in which NaBH₄ is dissolved. Thus, the inversion of the configuration at C-3 of 1,2-*O*-isopropylidenefuranose derivatives is accomplished in yields up to 98%.

Keywords: Inversion of the configuration, Swern oxidation-sodium borohydride reduction in one pot.

Resumen. La reacción de oxidación de Swern-reducción con borohidruro de sodio en un solo paso de los derivados de 1,2-*O*-isopropilidenefuranosa con configuración *D*-*gluco* o *D*-*xilo*, producen sus estereoisómeros correspondientes, los cuales provienen de la inversión estereoselectiva del C-3. Este método es una adaptación al procedimiento tradicional de oxidación de Swern, en donde al término de la reacción se adiciona una mezcla de H₂O/EtOH (1:4) a -60 °C, en la cual se disuelve NaBH₄. Así, la inversión de la configuración del C-3 en los derivados de 1,2-*O*-isopropilidenefuranosa se logra en rendimientos hasta del 98%.

Palabras clave: Inversión de configuración, Oxidación de Swern-reducción borohidruro de sodio, un solo paso.

Introduction

The 1,2:5,6-di-*O*-isopropylidene- α -*D*-glucofuranose **1** and the 1,2:5,6-di-*O*-isopropylidene- α -*D*-allofuranose **2** (and its respective sugar derivatives), are diastereomerically different only at C-3. The excessive price of **2** compared to **1** is not justifiable [1]. Obviously this concerns to organic chemists, and motivates them to develop efficient protocols to synthesize the compound **2** from the compound **1**.

Classic Mitsunobu procedure [2], may represent a convenient alternative, due to the use of strong carboxylic acids, which is favorable for the effective inversion of the configuration of sterically congested alcohols, including carbohydrates and nucleosides [3]. Unfortunately, Mitsunobu method requires two separate steps, and due to the formation of at least two by products, a rigorous purification by column chromatography is needed, and sometimes the yields are low.

Another convenient strategy for the inversion of the configuration at C-3 consists also in two separate steps: oxidation and reduction by a stereoselective manner [4]. The first step is generally achieved by the use of oxidative systems like DMSO/Ac₂O [5], RuCl₃.xH₂O/NaIO₄ [6], DMSO/P₂O₅ [7], PDC/Ac₂O [8] and PCC [9]. The stereoselective reduction is performed with NaBH₄ in either water or alcoholic solution [4,6,9d].

Although both procedures above mentioned have been widely applied, and good yields are observed; the simplification of this two protocols in one-stage with only one final

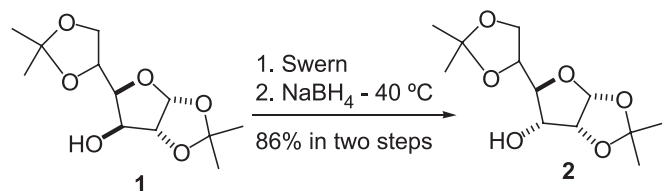
extraction, with or without purification by column chromatography could represent an important advantage over the traditional procedures [9,10].

In this regard, this work describes an efficient and an easy method for the inversion of the configuration at C-3 of chiral alcohols derived from 1,2-*O*-isopropylidenefuranoses by using an adapted Swern oxidation-sodium borohydride reduction in just one pot. It is important to mention that similar records have been reported, however, in all of them, an extraction process between the oxidation and reduction steps is required; besides, purification by column chromatographic is also required [9,10].

Results and Discussion

It is well-known that the classic Swern procedure [11] is carried out at low temperature and anhydrous conditions. Then, the only possibility to perform this reaction in one pot fashion is during the quenching stage. Thus, with the addition of sodium borohydride dissolved in a mixture of ethanol/water at low temperatures, the quenching of the reaction followed by the respective ketone reduction should proceed nicely.

Recently, it has been reported that the yields of the Swern oxidation is considerably improved if the quenching step is performed at temperatures below to -50 °C [12]. Thus, in accordance with this report, and considering the stereoselective reduction of the C-3 ketone derived from 1,2:5,6-di-*O*-



Scheme 1. Classic Swern oxidation-sodium borohydride reduction in two steps procedure.

isopropylidene- α -D-glucofuranose **1** with sodium borohydride under polar protic solvents [4,13], we add such a reagent ethanol/water to the reaction mixture in order to carry out the quenching of the Swern reaction, as well as the stereoselective reduction of the respective ketone in just one pot. So that, the inversion of configuration at C-3 of 1,2-*O*-isopropylidene-furanose derivatives is accomplished.

The 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose **1** was selected to carry out our preliminary assays. Following the classic Swern oxidation protocol [11], and subsequent treatment of the corresponding ketone with NaBH₄ in ethanol at -40 °C; the 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose **2** was obtained in 86% (after purification by column chromatography), see Scheme 1.

By means of our modified one pot Swern oxidation-sodium borohydride reduction, which basically consists in quenching the Swern oxidation by the slow addition of NaBH₄ dissolved in a mixture of Ethanol/H₂O, 4:1 at -60 ~ -40 °C; then, extraction with CH₂Cl₂ and evaporation of the solvent under reduced pressure, the desired product **2** is obtained in 98% [mp 74-76 °C; [α]_D +34.3 (c 1, CHCl₃); lit [14]. mp 75-77 °C, [α]_D +35.1 (c 1, CHCl₃)].

Therefore, we proceeded to apply this adapted protocol to various 1,2-*O*-isopropylidene-furanose derivatives (**3** [15], **5** [16], **7** [18], **9**, [20] **11** and **13**, Table 1). As is evident from Table 1, all the inversion products (**2** [1], **4** [15], **6** [17], **8**

Table 1. One stage and two-steps Swern oxidation-sodium borohydride reduction.

Alcohol	Product	Yield in one-pot	Yield in two steps
		98 ^a	86 ^b
		95 ^a	80 ^b
		96 ^a	85 ^b
		96 ^a	86 ^b
		94 ^a	65 ^b
		91	76 ^b
		95 ^a	79 ^b

^aWithout purification by column chromatography; ^bafter purification by column chromatography.

[19], **10**, **12** and **14**) were obtained in excellent yields when the one pot procedure is used. On the contrary, by using the traditional Swern oxidation [11] and the residue submitted to a sodium borohydride reduction at $-40\text{ }^{\circ}\text{C}$, the inversion of the C=O group at C-3 was achieved in lower yields (about 80%). However, in all these cases purification by column chromatography was needed. In the transformation of **9**, **11** and **13** into **10**, **12** and **14** respectively, yields were low due to the formation of some unidentified by products. The results shown presented in Table 1 indicate that employing this novel adapted one pot Swern oxidation-sodium borohydride reduction, yields were very satisfactory in every instance, even in compounds bearing sensitive functional groups. It is not so if the traditional method is used.

Conclusion

We have developed an efficient and easy one pot Swern oxidation-sodium borohydride procedure for the inversion of the C-3 configuration of the 1:2,5:6-*O*-isopropylidene- α -D-glucofuranose and various 1:2-*O*-isopropylidene- α -D-xylofuranoses derivatives. Additionally, this modified procedure might be applied in green chemistry if is combined with the recently developed Fluorous Swern Reaction [16].

Experimental

General

Instrumental. NMR studies were carried out with Varian Mercury 400 and 300 instruments. Internal reference (TMS) for ^1H and ^{13}C . Chemical shifts are stated in parts per million. COSY and HSQC experiments have been carried out in order to assign the ^1H and ^{13}C spectra in full. High resolution Mass spectra (EI ion mode) were realized on a Jeol JMS-SX102A 10 Kvolts, and Elemental Analysis at Service de Microanalyse I.C.S.N.-C.N.R.S.-France. IR were carried out with a SHI-MADZU FTIR-8400 instrument.

1,2-*O*-Isopropylidene-(5-*O*-mesyl)- α -D-xylofuranose (**11**).

To a stirred solution of 1,2-*O*-Isopropylidene-D-xylofuranose (0.5 g, 2.6 mmol) and triethylamine (0.55 mL, 3.9 mmol) in dry CH_2Cl_2 (20 mL) at $0\text{ }^{\circ}\text{C}$ was added MsCl (0.36 g, 3.1 mmol), dissolved in dry CH_2Cl_2 (10 mL). The reaction mixture was allowed to react for 4 h before to add water (15 mL). Extraction with ethyl acetate (3 x 60 mL), dried over Na_2SO_4 and concentrated *in vacuo* gave **11** as colorless oil. Purification by Flash chromatography yielded **11** as white crystals, mp $130\text{--}131\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}} - 14.2$ (*c* 1, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.32 (s, 3H), 1.51 (s, 3H), 3.08 (s, 3H), 4.32 (s, 1H), 4.39 (m, 1H), 4.52 (m, 1H), 4.54 (d, 1H, $J = 3.2$ Hz), 5.95 (d, 1H, $J = 3.6$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.3, 26.9, 37.6, 66.4, 74.5, 77.8, 85.1, 104.9, 112.2; HRMS (EI) calcd for $\text{C}_9\text{H}_{16}\text{O}_7\text{S}$ (M+), 268.0617. Found 268.0621.

1,2-*O*-Isopropylidene-(5-*N*-phthalimidoxy)- α -D-xylofuranose (13**).** To a solution of 1,2-*O*-Isopropylidene-D-xylofuranose (2.3 g, 0.012 mol), *N*-hydroxy-phthalimide (2.9 g, 0.017 mol) and triphenyl phosphine (3.17 g, 0.012 mol) in dry THF (150 mL) at $0\text{ }^{\circ}\text{C}$, was added DTAD (3.6 g, 0.015 mol) dropwise. The reaction mixture was stirred for 8 h, at room temperature before to add 100 mL of water. Extraction with ethyl acetate (3 x 60 mL), dried over Na_2SO_4 and concentrated *in vacuo* gave **13** as colorless oil. Purification by Flash chromatography yielded **13** as white crystals, mp $98\text{--}100\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}} - 42.1$ (*c* 1, EtOH); ^1H NMR (CDCl_3 , 300 MHz) δ 1.37 (s, 3H), 1.49 (s, 3H), 1.8 (b, 1H), 4.32 (m, 1H), 4.49 (m, 2H), 4.61 (d, 1H, $J = 3.6$ Hz), 4.64 (m, 1H), 5.92 (d, 1H, $J = 3.6$ Hz), 7.75-7.86 (m, 4H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 26.3, 26.9, 62.3, 74.8, 75.0, 76.6, 84.9, 105.0, 111.8, 123.3, 128.4, 134.1, 163.4. Anal calcd for: C, 57.31%; H, 5.11%. Found: 57.45%; H, 5.02%.

Swern-reduction in one-stage. To a stirred solution of oxalyl chloride (5.027 mL, 57.17 mmol) in dry CH_2Cl_2 (70 mL) at $-80\text{ }^{\circ}\text{C}$ was added methyl sulfoxide (8.17 mL, 115.25 mmol) dissolved in dry CH_2Cl_2 (20 mL) dropwise. The reaction mixture was stirred for additional 15 min, and 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose **1** (5 g, 19.2 mmol) dissolved in dry CH_2Cl_2 (150 mL) was also added dropwise. The mixture was allowed to react for 90 min at $-80\text{ }^{\circ}\text{C}$ and then triethylamine (20.2 mL, 144.6 mmol) was added dropwise maintaining the temperature at $-70\text{ }^{\circ}\text{C}$. Finally, the reaction was quenched by adding NaBH_4 (1.45 g, 38.75 mmol) dissolved in a mixture of EtOH/ H_2O , 4:1 (100 mL). The temperature of the reaction mixture should keep within -60 to $-40\text{ }^{\circ}\text{C}$. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 4.9 g of a white solid **2** (98%, without purification), [mp $74\text{--}76\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}} +34.3$ (*c* 1, CHCl_3); lit [1], mp $75\text{--}77\text{ }^{\circ}\text{C}$ [14], $[\alpha]_{\text{D}} +35.1$ (*c* 1, CHCl_3)].

1,2-*O*-Isopropylidene-(5-iodo-5-deoxy)- α -D-ribofuranose (**10**).

White crystals, mp $76\text{--}77\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}} +32.4$ (*c* 1, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.38 (3H, s), 1.57 (s, 3H), 2.40 (d, 1H, $J = 10.8$ Hz), 3.32-3.38 (m, 1H), 3.52-3.59 (m, 2H), 3.75 (m, 1H), 4.60 (dd, 1H, $J = 3.9, 5.1$ Hz), 5.80 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 5.7, 26.4, 26.5, 75.8, 78.8, 103.7, 112.8.; HRMS (EI) calcd for $\text{C}_8\text{H}_{13}\text{IO}_4$ (M+) 299.9859. Found 299.9842.

1,2-*O*-Isopropylidene-(5-*O*-mesyl)- α -D-ribofuranose (**12**).

Colorless oil, $[\alpha]_{\text{D}} + 56.9$ (*c* 1, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 1.38 (s, 3H), 1.58 (s, 3H), 3.07 (s, 3H), 3.95 (m, 2H), 4.30 (d, 1H, $J = 4.5$ Hz), 4.54 (dd, 1H, $J = 12.0, 2.1$ Hz), 4.61 (t, 1H, $J = 4.2$ Hz), 5.8 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 26.4, 26.5, 37.5, 67.9, 71.2, 78.0, 78.2, 100.0, 103.9, 113.1; HRMS (EI) calcd for $\text{C}_9\text{H}_{16}\text{O}_7\text{S}$ (M+) 268.0617. Found 268.0611.

1,2-*O*-Isopropylidene-(5-*N*-phthalimidoxy)- α -D-ribofuranose (14**).** White crystals, mp $26\text{--}28\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}} +19.6$ (*c* 1,

CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 1.36 (s, 3H), 1.56 (s, 3H), 2.51 (d, 1H, J = 6.2 Hz), 4.10 (m, 2H), 4.38 (dd, 1H, J = 12.0, 4.6 Hz), 4.56 (dd, 1H, J = 12.0, 2.1 Hz), 4.63 (t, 1H, J = 4.5 Hz), 7.71-7.91 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 26.5, 26.6, 71.3, 75.7, 78.4, 79.5, 104.2, 112.8, 123.4, 128.9, 134.4, 163.3. Anal calcd for: C, 57.31%; H, 5.11%. Found: 57.62%; H, 5.34%.

Acknowledgements

We thank CONACyT for financial support, Project No. 35102 and scholarships numbers: 171952 and 171990; also thanks to Benemérita Universidad Autónoma de Puebla for a PROMEP professorship.

References and Notes

1. Sigma-Aldrich Co. 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (25 g 37.7 dollar) and 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose (1 g 53.1 dollar).
2. Mitsunobu, O. *Synthesis* **1981**, 1-28.
3. (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, 32, 3017-3021, and references cited therein; (b) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, 59, 234-236, and references cited therein; (c) Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, 33, 4317-4320; (d) Bessodes, M.; Saïah, M.; Antonakis, K. *J. Org. Chem.* **1992**, 57, 4441-4444.
4. Bols, M. *Carbohydrate Bulding Block*; Wiley & Sons: New York 1996, pp 22.
5. (a) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, 89, 2416-2423; (b) Stevens, J. D. *Methods Carbohydr. Chem.* **1972**, 6, 123-128.
6. Mio, S., Kumagawa, Y., Sungai, S. *Tetrahedron* **1991**, 47, 2133-2144.
7. Onodera, K.; Hirano, S.; Kashimura, N. *J. Am. Chem. Soc.* **1965**, 87, 4651-4652.
8. Hung, S.-C.; Wang, C.-C.; Thopate, S.R. *Tetrahedron Lett.* **2000**, 41, 3119-3122.
9. (a) Estevez, J. C.; Fairbanks A. J.; Fleet, G.W. J. *Tetrahedron* **1998**, 54, 13591-13620; (b) Wood, W. W.; Watson, G. M. *J. Chem. Soc. Perkin Trans. I*, **1987**, 2681-2688. (c) Suwa, W.; Thomas, G. H. S. *Can. J. Chem.* **1966**, 44, 836; (d) Chen, H.; Guo, Z.; Liu, H-W. *J. Am. Chem. Soc.* **1998**, 120, 9951-9952.
10. (a) Austin, G. N.; Baird, P. D.; Feet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, 43, 3095-3108; (b) Barton, D. H. R.; Jaszberenyi, J. Cs.; Theodorakis. E. A. *J. Am. Chem. Soc.* **1992**, 114, 5904-5905; (c) Chiu, M. I.; Madrazo, A. O.; Verez, B. V. *J. Carbohydr. Chem.* **1994**, 13, 465-469; (d) Han S. Y.; Liddell, P. A.; Joullie, M. M. *Synth. Commun.* **1988**, 18, 275-284; (e) Martin, P. *Helv. Chim. Acta* **2003**, 86, 204-209.
11. (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480-2482; (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165-185.
12. Fang, X.; Bandarage, U. K.; Wang, T.; Schroeder, J. D.; Garvey, D. S. *J. Org. Chem.* **2001**, 66, 4019-4021.
13. Smith. M. B. *Organic Synthesis*; McGraw-Hill, New York, **2001**, pp 368-371.
14. Sigma-Aldrich Co. **2003-2004**, pag. 694, product number: 29,637-6.
15. Parr, I. B.; Horenstein, B. A. *J. Org. Chem.* **1997**, 62, 7489-7494.
16. Snyder, J. R.; Serianni, A. S. *Carbohydr. Res.* **1991**, 210, 21-38.
17. Snyder, J. R.; Serianni, A. S. *Carbohydr. Res.* **1987**, 163, 169-188.
18. Kuzuhara, H.; Emoto, S. *Agric. Biol. Chem.* **1964**, 28, 900-907.
19. Faul, M. M.; Grutsch, J. L.; Kobierski, M. E.; Kopach, M. E.; Kumrich, C. A.; Staszak, M. A.; Udodong, U.; Vicenzi, J. T.; Sullivan, K. A. *Tetrahedron* **2003**, 59, 7215-7229.
20. Enholm, E. J.; Schulte II, J. P. *Org. Lett.* **1999**, 1, 1275-1277.
21. (a) Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.* **2001**, 123, 7449-7450; (b) Crich, D.; Neelamkavil, S. *Tetrahedron* **2002**, 58, 3865-3870.