ORGANIC LETTERS

2003
Vol. 5, No. 23
4457−4459

Transformation of D-Glucose into 1*D*-3-Deoxy-3-hydroxymethyl-*myo*-inositol by Stereocontrolled Intramolecular Henry Reaction

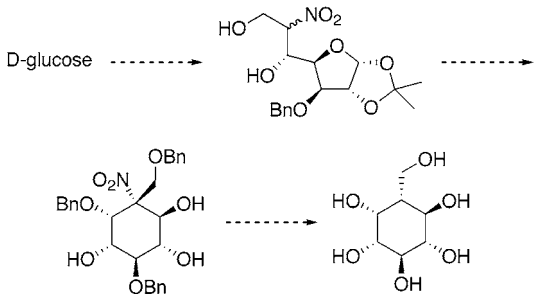
Raquel G. Soengas, Juan C. Estévez, and Ramón J. Estévez*

Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain

qorjec@usc.es

Received September 13, 2003

ABSTRACT



An intramolecular Henry cyclization provides a promising new strategy for the transformation of nitroheptofuranoses into deoxyhydroxymethylinositols. This method has allowed a stereospecific transformation of D-glucose into 1*D*-3-deoxy-3-hydroxymethyl-*myo*-inositol.

The nitroaldol condensation, or Henry reaction, couples a carbonyl compound to a nitroalkane bearing an α hydrogen atom, thereby creating an α-nitroalkanol. It is one of the classical methods for carbon−carbon bond formation and can result in the formation of one or two chiral centers.[1] Following the condensation reaction, the nitro group can be subjected to a range of chemical transformations,[2] including its removal.[3]

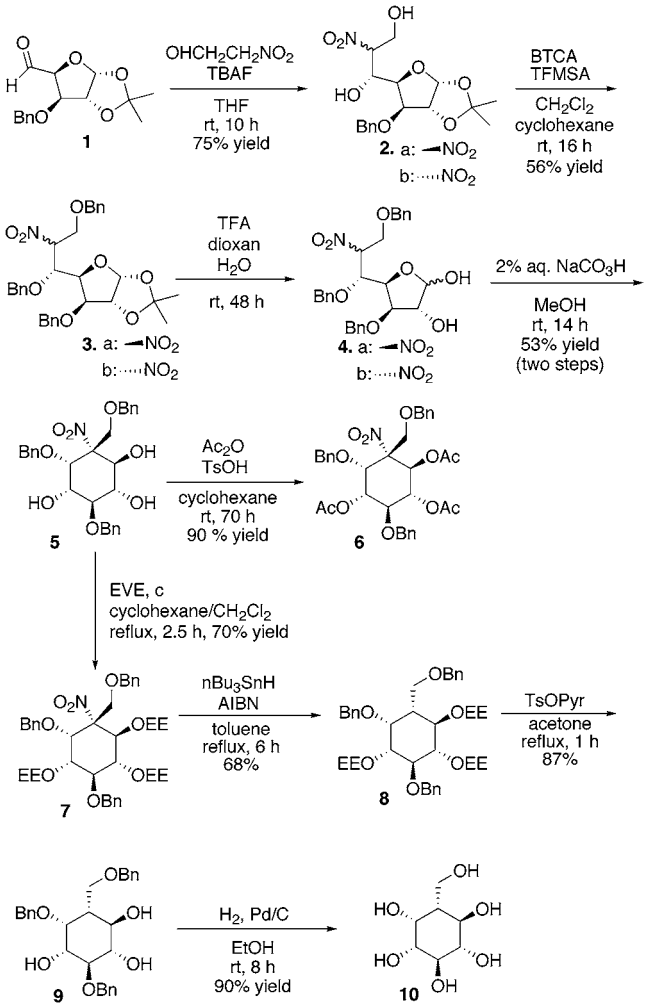
Nitroethanol has been used as the nitroalkane of the Henry reaction[4] in several total syntheses of natural products (sphinganine analogues,[5] cerebroside B1b,[6] etc.) and, more recently, in studies on the asymmetric synthesis of nitroalkanols, in which dendritic,[7] lanthanum−lithium−binaphthol,[8] La−Li-6,6′-disubstituted BINOL,[9] and zirconium phosphate[10] catalysts have been used to achieve enantioselectivity. Nevertheless, to the best of our knowledge, nitroethanol has been used in only one intramolecular Henry reaction[11] and in only one Henry reaction in which the substrate has been a sugar (D-glyceraldehyde).[12]

(1) (a) Henry, C. R. *Acad. Sci. Paris* **1985**, *120*, 1265. (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
(2) (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (b) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259. (c) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367. (d) Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44. (e) Crosslay, M. J.; Crumbie, R. L.; Fung, Y. M.; Potter, J. J.; Pegler, M. A. *Tetrahedron Lett.* **1987**, *28*, 2883.
(3) Baumberg, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.
(4) For the first reported example of a Henry reaction involving nitroethanol, see: Grob, C. A.; Gadient, F. *Helv. Chim. Acta* **1957**, *40*, 1145.
(5) (a) Kolter, T.; van Echten-Deckert, G.; Sandhoff, K. *Tetrahedron* **1994**, *50*, 13425. (b) Mori, K.; Funaki, Y. *Tetrahedron* **1985**, *41*, 2369.
(6) (a) Kodato, S.; Nakagawa, M.; Nakayama, K.; Hino, T. *Tetrahedron* **1989**, *45*, 7247. (b) Nakagawa, M.; Kodato, S.; Nakayama, K.; Hino, T. *Tetrahedron Lett.* **1987**, *28*, 6281.
(7) Morao, I.; Cossio, F. P. *Tetrahedron Lett.* **1997**, *38*, 6461.
(8) Sasai, H.; Watanabe, S.; Shibasaki, M. *Enantiomer* **1997**, *2*, 267.
(9) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.
(10) Costantino, U.; Curini, M.; Marmottini, F.; Rosati, O.; Pisani, E. *Chem. Lett.* **1994**, 2215.
(11) Lichtenthaler, F. W.; Leinert, H. *Chem. Ber.* **1968**, *101*, 1815.
(12) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783.

10.1021/ol035771x CCC: $25.00 © 2003 American Chemical Society
Published on Web 10/14/2003

In the course of our work on nitrosugars,[13] and more specifically in relation to the synthesis of inositols from sugars, we have prepared deoxyhydroxymethylinositol **10** (Scheme 1) by a synthetic sequence involving two Henry

Scheme 1. Synthesis of Deoxyhydroxymethylinositols



reactions. The first couple nitroethanol and D-glucose derivative **1** and the second use the coupled nitroalkane in an intramolecular reaction converting the furanose into a cyclohexane.

Condensation of D-glucose derivative **1**[14] with nitroethanol under typical Henry reaction conditions gave a 3:2 mixture of epimers **2** in 75% yield (Scheme 1). To protect hydroxy groups at C_5 and C_7, **2** was then treated with benzyl trichloroacetimidate and triflic acid, giving the epimeric mixture **3**, from which the acetonide protecting group was removed by treatment with a 1:1:1 mixture of trifluoroacetic acid, dioxane, and water. Surprisingly, immediate treatment of the resulting unstable mixture of compounds **4** with 2% aqueous sodium bicarbonate solution gave the enantiomerically pure compound **5**.

The stereochemistry of compound **5** was easily established from that of its derivative **6**, which was obtained by treatment of **5** with acetic anhydride and *p*-toluenesulfonic acid. ^{1}H NMR experiments on compound **6** showed NOEs between the methylene group on the CH_2OBn substituent and H_2 (2.6%) and H_4 (1.9%) and between H_1 and H_3 (5.5%). Accordingly, the favored chair conformation for this compound (Figure 1) is that in which the CH_2OBn and NO_2

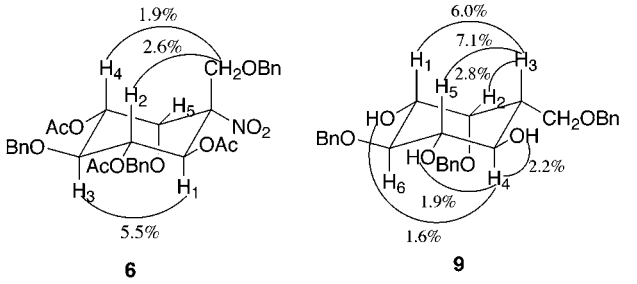
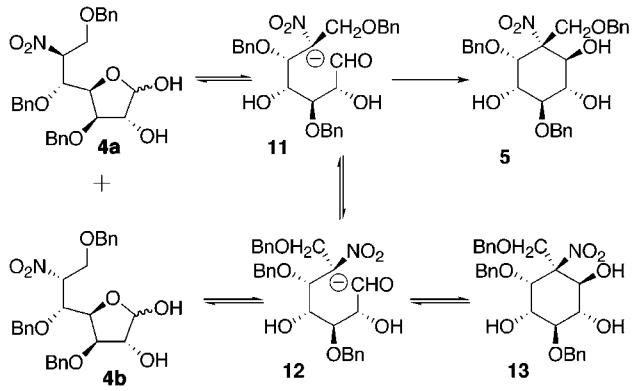


Figure 1. NOESY diagrams of compounds **6** and **9**.

substituents at C_6 are axial and equatorial, respectively, the OBn groups at C_3 and C_5 are equatorial and axial, respectively, and the OAc groups at C_1, C_2, and C_4 are all equatorial. The coupling constants between H_4 and H_5 (J = 2.2 Hz, typical of an axial−equatorial interaction) and between H_2 and H_3 (J = 9.6 Hz, typical of a diaxial interaction) provide further evidence of the axial orientation of the protons H_1, H_2, H_3, and H_4 and the equatorial disposition of H_5.

The fact that reaction of the isomeric mixture **4** afforded **5** but not its diastereomer **13** may be attributed to the former, in which the bulky groups at C_5 and C_6 are trans to each other, presumably being significantly more stable than the latter, in which they are cis (Scheme 2). Because of this, whereas carbanion **11**, the reaction intermediate derived from

Scheme 2. Mechanism of the Transformation of Compounds **4** into Cyclohexane **5**



(13) (a) Soengas, R. G.; Estévez, J. C.; Estévez, R. J.; Maestro, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1653. (b) Soengas, R. G.; Estévez, J. C.; Estévez, R. J. *Org. Lett.* **2003**, *9*, 1425.

(14) Paulsen, H.; Brieden, M.; Sinwell, V. *Liebigs Ann. Chem.* **1985**, 113.

nitrosugar **4a**, proceeds easily to **5**, its epimer **12** (the intemediate derivative of **4b**) finds isomerization to **11** and subsequent conversion to **5** to be more favored than conversion to **13**.

Nitrocyclohexane **5** was transformed into inositol **10** as follows (Scheme 1). After protection of the OH groups of **5** as OEE by reaction with ethyl vynyl ether, the nitro group was removed by treating the product, compound **7**, with *n*-Bu_3SnH and AIBN,[15] a process that brought about inversion of the configuration at C_6. The OEE protecting groups were then removed with PPTS, and the benzyloxy groups were removed by catalytic hydrogenation.

The absolute stereochemistry of deoxyhydroxymethylinositol **10** was deduced from the ^{1}H NMR spectrum of its precursor **9**, which shows NOEs between H_1 and H_3 (6.0%), H_3 and H_5 (7.1%), and between H_4 and the OH groups at C_1 (1.6%), C_4 (2.2%), and C_5 (1.9%). These NOEs show that, in the cyclohexane chair conformation favored in **9** (Figure 1), the three OH groups are equatorial, the OBn groups at C_2 and C_6 are axial and equatorial, respectively, and the CH_2-OBn group is equatorial. This stereochemistry was confirmed by the presence in the ^{1}H NMR spectrum of a triplet at $\delta = 3.46$ ppm due to proton H_5 ($J_{5,4} = J_{5,6} = 9.0$ Hz) and a doublet of doublets at $\delta = 3.73$ ppm due to H_4 ($J_{4,3} = 10.7$ Hz, $J_{4,5} = 9.0$ Hz), which clearly indicate the axial orientation of protons H_3, H_4, H_5, and H_6.

In conclusion, we have developed a promising novel strategy for the transformation of nitrosugars into deoxyhydroxymethylinositols. This process has allowed the first total synthesis of deoxyhydroxymethylinositol **10** with total stereochemical control. The new route to these targets constitutes a simpler and more efficient approach than the few previously described routes[16] and has the additional advantage of offering the possibility of orthogonal protection of the OH groups at C_1, C_2, and C_4 with respect to those borne by C_3, C_5, and the methylene group at C_6. This possibility is of significant interest for phosphorylation of specific OH groups for biological studies.

We are currently applying the new strategy systematically to sugars other than D-glucose in order to prepare all the possible deoxyhydroxymethylinositol derivatives of D-hexoses with the aim of studying their chemical and biological properties. The interest of these studies is supported by the recent observation that deoxyhydroxymethyl-*scillo*-inositol, which should be possible to obtain from D-mannose by our approach, is a potent agonist of the receptor of the classical inositol known as Ins(1,4,5)P3, which influences the transport of Ca^{2+} in several types of cells.[17,18] This finding suggests that replacement of the C_6 hydroxy group of inositols with a hydroxymethyl group can result in an increase in biological activity.

Acknowledgment. We thank the Spanish Ministry of Science and Technology for financial support and for an FPI grant to Raquel G. Soengas, as well as Prof. George W. J. Fleet for useful suggestions and discussions.

Supporting Information Available: General experimental procedure, ^{1}H and ^{13}C NMR spectra for compounds **5**, **7**, **8**, **10**, **11**, **13**, **15**, **17**, and **18**, and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035771X

(15) See ref 3.

(16) (a) Paulsen, H., Röben, W. *Liebigs Ann. Chem.* **1983**, 1073. (b) Riley, A. M.; Guedat, P.; Schlewer, G.; Spiess, B.; Potter, B. V. L. *J. Org. Chem.* **1998**, *63*, 295.

(17) Riley, A. M., Murphy, C. T., Lindley, C. J.; Westwick, J.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2197.

(18) Berridge, M. J. *Nature* **1993**, *361*, 315.