Stereoselective Deoxygenation of *myo*-Inositol Monotosylates with Lithium Triethylborohydride

Jinquan Yu and Jonathan B. Spencer*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Received February 29, 1996

myo-Inositol 1,4,5-triphosphate has been identified as an important secondary messenger which is involved in many intracellular signaling events.[1] In particular, it has been demonstrated to have a profound effect on neurotransmitter release mechanisms.[2] Selective inhibition of some of the enzymes involved in formation and breakdown of *myo*-inositol 1,4,5-triphosphate is of potential therapeutic value in conditions such as manic depression.[3] A number of deoxy derivatives of *myo*-inositol 1-phosphate have been demonstrated to be strong inhibitors of *myo*-inositol monophosphatase, a key enzyme in recycling *myo*-inositol, which hydrolyzes both *myo*-inositol 1-phosphate and *myo*-inositol 4-phosphate[4] and of *myo*-inositol 1-phosphate synthase that catalyzes the *de novo* biosythesis of *myo*-inositol 1-phosphate from glucose 6-phosphate.[5] We now report a high yield stereoselective deoxygenation of *myo*-inositol that allows convenient entry into this series of compounds.

Existing methods for the selective deoxygenation of *myo*-inositol have, at best, been achieved in four steps with a overall yield of 30%.[6] In an attempt to find a more convenient route we initially investigated the possibility of utilizing Barton's methodology[7] for the reduction of the phenoxythiocarbonyl derivative of **1** with tributyltin hydride; however, this proved unsucessful because of the formation of a stable cyclic thiocarbonate that could not be reduced even under harsh conditions.[8]

Lithium triethylborohydride (LTBH) has been used for the deoxygenation of primary alcohols by reduction of their *p*-toluenesulfonyl esters.[9] It has only found limited application with secondary tosylates owing to the reaction being sluggish or not occurring at all if the alcohol is hindered. The mechanism in these cases has been demonstrated to occur by S_N2 displacement of the tosylate with the hydride from LTBH, but, if there is a hydroxyl group next to the tosylate an alternative mechanism is preferred which involves an interesting rearrangement.[10] The hydrogen on the carbon with the hydroxyl group undergoes a [1,2] shift to displace the tosylate group with the probable formation of a ketone intermediate that is quickly reduced by LTBH back to a hydroxyl. This mechanism is less sensitive to steric hinderance and it has been utilised to deoxygenate the 2′ position of adenosine[10] and some hexose sugars.[11]

We wanted to explore whether this reactivity could be utilized for the selective deoxygenation of *myo*-inositol and other suitably substituted cyclohexanes. Racemic 3,4,5,6-tetra-*O*-benzyl *myo*-inositol[12] **1** (1 mmol) was selectively tosylated under solid/liquid phase-transfer conditions[13] at room temperature in CH_3CN using dibutyltin oxide (2 mmol), tosyl chloride (1 mmol), and benzyltriethylammonium chloride (0.2 mmol) for 24 h to give **2a** in 92% yield. Reaction of **2a** with LTBH in anhydrous THF under argon at room temperature for 24 h, gave 2-deoxy-3,4,5,6-tetra-*O*-benzyl *myo*-inositol **3a** in 79% yield. To investigate whether the tosylate group is directly displaced or a more complicated mechanism occurs, the reaction was carried out with lithium triethylborodeuteride (LTBD). The reaction proceeds smoothly under the same conditions as before to give **3a** with a deuterium at the 1 position (Scheme 1). This eliminates a simple S_N2 displacement and implicates either a [1,2] hydride shift as has been demonstrated in the deoxygenation of 2′-*O*-tosyladenosine with LTBH[10] or elimination of the tosylate followed by protonation of the resulting enolate; in either case the final step would be stereoselective reduction of the derived ketone. To distinguish between these two possible mechanisms, the deuterated alcohol **2b** (scheme 1) was prepared by oxidizing **2a** using pyridinium chlorochromate (PCC) to give the ketone **7**, which was then reduced with $NaBD_4$.[14] **2b** was reacted with LTBH at room temperature, which gave **3b** with the deuterium located solely in the axial position at C-2, thus confirming a stereoselective [1,2] hydride shift.

A likely sequence for the conversion of **2a** into **3a** would involve a conformational change of the alkoxide triethylboron complex towards a boat conformation **4** (Scheme 2) to allow antiperiplanar migration of the hydride and the expulsion of the tosylate. The resulting 2-deoxy 1-ketone **5** could then be stereoselectively reduced by LTBH to give **3a**. An interesting difference in the deoxygenation of 2′-*O*-tosyladenosine[10] is that in that case the hydroxyl group suffers an inversion of configuration, whereas in the case of **2a** complete retention of configuration of the hydroxyl group is observed. To investigate whether the stereoselectivity arises from the reduction of the ketone **5** or whether a more "concerted" sequence occurs as suggested in the deoxygenation of 2′-*O*-tosyladenosine, **5** was made by oxidation of **3a** with PCC. Reduction of **5** with LTBH under identical conditions to those used for the conversions of **2a** into **3a**, yielded exclusively **3a**. Using **5** as a standard, it was possible to isolate a small quantity of this compound in the reaction mixture when **2a** was converted into **3a** at low temper-

(1) (a) Berridge, M. J.; Irvine, R. F. *Nature* **1982**, *312*, 315. (b) Nishizukay, Y. *Nature* **1984**, *308*, 693. (c) Altman, J. *Nature* **1988**, *331*, 119.

(2) (a) Rhee, S. G.; Suh, P. G.; Ryu, S. H.; Lee, S. Y. *Science* **1989**, *244*, 546. (b) Meldrum, E.; Parker, P. J.; Catozzi, A. *Biochem. Biophys. Acta* **1991**, *1092*, 49. (c) Schoepp, D.; Bockaert, J.; Sladescsek, F. *Trends Pharmacol. Sci.* **1990**, *11*, 508.

(3) (a) Agranoff, B. W.; Fisher, S. K. In *Inositol Phosphates and Derivatives: Synthesis Biochemistry and Therapeutic Potenial;* Reitz, A. B., Ed.; ACS Symposium Series 463; American Chemical Society: Washington, DC, 1991; p 20. (b) Billington, D. C. *The Inositol Phosphates: Chemical Synthesis and Biological Significance*; VCH: New York, 1993.

(4) Gani, D.; Downes, C. P.; Bramham. *J. Biochim. Biophys. Acta* **1993**, *1177*, 253.

(5) Migaud, M. E.; Frost, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 495.

(6) Baker, R.; Kulagowski, J. J.; Billington, D. C.; Leeson, P. D.; Lennon, I. C.; Liverton, N. *J. Chem. Soc., Chem. Commun.* **1989**, 1383.

(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.

(8) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(9) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669. (b) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc*, **1973**, *93*, 8486. (c) Krishnamurthy, S.; Brown H. C. *J. Org. Chem.* **1976**, *41*, 3064.

(10) Hansske, F.; Robins, M. J. *J. Am. Chem Soc.* **1983**, *105*, 6736.

(11) Baer, H. H.; Hanna, H. R. *Carbohydr. Res.* **1982**, *110*, 19.

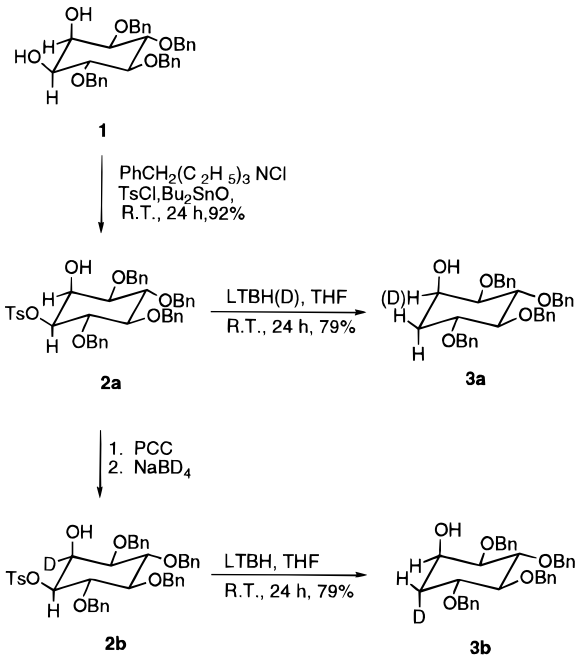
(12) Grigg, J.; Grigg, R.; Paynes, S.; Conant, R. *Carbohydr. Res.* **1985**, *142*, 132.

(13) Grouiller, A.; Buet, V.; Utezav, V.; Descotes, G. *Synlett* **1993**, 221.

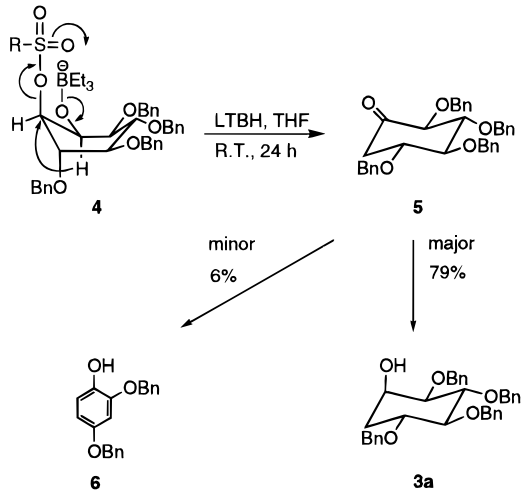
(14) Reduction of **7** with NaB^2H_4 gives a mixture (1:3) of **2b** and its epimer, which were separated by preparative TLC with chloroform hexane (12:1) as the eluent.

S0022-3263(96)00413-6 CCC: $12.00

Scheme 1



Scheme 2

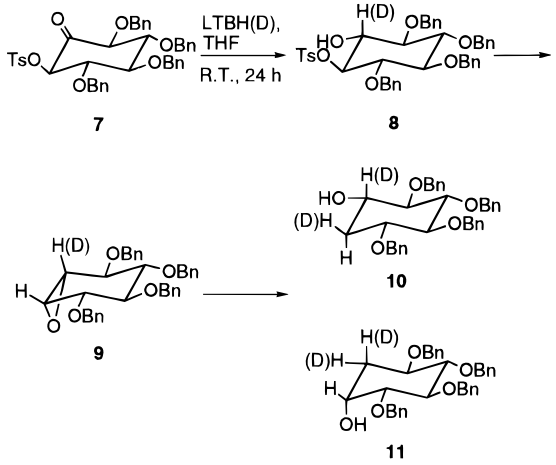


ature.[15] The existence of **5** as a free intermediate also explains the formation of the phenolic compound **6**, a minor product in the conversion of **2a** into **3a**, as the keto group would facilitate elimination of the benzyloxy groups under the basic conditions.

The necessity of the free hydroxyl group next to the tosylate prompted us to explore whether the deoxygenation could be achieved if these two groups were *trans*

(15) To isolate the ketone **5**, the reaction was carried out at 10 °C for 3 h. A weak upper running spot on TLC (ethyl acetate−petroleum ether 2:3) had the same R_f as the standard **5**. Careful quenching with H_2O, followed by purification using preparative TLC gave a small quantity of **5** identified by ^1H NMR and high resolution mass spectrometry.

Scheme 3



to one another. Reduction of ketone **7** with LTBH gave exclusively **8**, and this reacted further in the presence of LTBH to give two deoxygenated products, **10** in 60% yield and **11** in 30% yield, which could be separated by chromatography (Scheme 3). When this one-pot synthesis was carried out using LTBD, the deuterium distribution in the products **10** and **11** was as outlined in Scheme 3. The labeling pattern is not consistent with a [1,2] hydride shift, which would be unlikely to occur for stereoelectronic reasons, but is consistent with formation of an epoxide intermediate. Careful chromatography of the reaction mixture resulted in isolation of the epoxide **9** (Scheme 3), thus confirming it as an intermediate in the reaction. This deoxygenation, like that involving the [1,2] hydride shift, proceeds in high overall yield.

This paper reports for the first time conclusive evidence for the formation of a ketone intermediate (e.g. **5**) during the deoxygenation of *cis*-diol monotosylates using LTBH. The observed stereoselectivity arises from the reduction of the free ketone, which explains why opposite results (complete retention of configuration during the formation of 2-deoxy-*myo*-inositol and inversion of configuration of the 3′-hydroxyl group in the attempted formation of 2′-deoxyadenosine) were achieved with these two classes of compounds.

The methodology described here involves a simple two-step deoxygenation of tetra-*O*-benzyl-*myo*-inositol in high overall yield (70%) which provides convenient access into a range of compounds that are difficult to obtain by conventional methods.

Acknowledgment. The Royal Society for the award of a Royal Society University Research Fellowship (J.B.S.) and British Council for the award of Sino-British Friendship Scholarship (J.Y.). We thank Drs. F. Leeper and I. Paterson for carefully reading the manuscript.

Supporting Information Available: Experimental details, spectroscopic and analytical data for compounds **2a**,**b**, **3a**,**b**, and **5**−**11** (4 pages).

JO960413B