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Protecting group directed stereoselective reduction of an *epi*-inosose: efficient synthesis of *epi*-inositol

Madhuri T. Patil [a], Shobhana Krishnaswamy [b], Manash P. Sarmah [a,†], Mysore S. Shashidhar [a,*]

[a] Division of Organic Chemistry, National Chemical Laboratory (Council of Scientific and Industrial Research-CSIR), Pune 411 008, India
[b] Center for Materials Characterization, National Chemical Laboratory (Council of Scientific and Industrial Research-CSIR), Pune 411 008, India

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ABSTRACT

A facile and high yielding synthesis of *epi*-inositol *via* stereoselective reduction of a pentaprotected *epi*-inosose is reported. Extent of stereoselectivity during the hydride reduction appears to depend on the ability of the substrate to complex with metal ions in the reducing agent.

Selective reactions of organic compounds are of interest to a large cross section of chemists due to their synthetic as well as mechanistic implications in wide areas of research. Organic chemists strive to identify and develop selective reactions of small molecules containing several functional groups, especially of the same kind (polyols, polyamines, poly acids, etc.). Chemistry of cyclohexane polyols (inositols, cyclitols) has been the subject of intense investigations in the recent past due to the ubiquitous presence of their derivatives in living cells and implication in biological phenomena such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation, intracellular trafficking of vesicles and anchoring of certain proteins to cell membranes.[1] Polyols are also interesting because of their structure and reactivity in the solid state[2] and they have been used as starting materials for natural product synthesis.[3] As expected, reactivity and selectivity in reactions of small molecules containing several functional groups can to some extent be tuned by varying the protecting groups utilized during a synthetic sequence. We herein report hydride reduction of the *epi*-inososes **10** and **14**, wherein, the reduction of **10** was highly stereoselective to provide the *epi*-inositol derivative with excellent yield, while that of **14**, devoid of any protecting group, resulted in the formation of relatively more *myo*-inositol (**1**) due to loss of stereoselectivity. The method of conversion of *myo*-inositol to *epi*-inositol (**13**) presented here (Scheme 1) gives a single product with high yield in each step, while most of the previous reports involved separation of isomeric cyclitol derivatives.[4] This work also illustrates the versatility of *myo*-inositol orthobenzoate **2**[5] as an intermediate for the preparation of cyclitols and their derivatives. *epi*-Inositol is biologically active in its ability to affect regulation of the *myo*-inositol biosynthetic pathway[6] and it has been evaluated as a potential antidepressant drug that could interact with Li^+ ion and *myo*-inositol receptors in brain.[6,7]

The synthetic route for the conversion of *myo*-inositol to *epi*-inositol is shown in Scheme 1. The racemic PMB ether[4k] **3** on benzylation with NaH and excess benzyl bromide afforded the corresponding dibenzyl ether **4**. The orthobenzoate moiety in **4** was reduced with DIBAL-H to obtain a mixture of diols **5** and **6**. Benzylation of this mixture of diols afforded the pentabenzyl ether **7**. The PMB ether in **7** was cleaved using HCl to afford the alcohol **8**; oxidation of **8** with IBX gave the protected *epi*-inosose **10**. Reduction of the *epi*-inosose **10** with sodium borohydride was stereoselective to yield the corresponding *epi*-alcohol **11** with about 98% selectivity (or more, see below). The pentabenzyl ether **11** was isolated by column chromatography; global deprotection of **11** by hydrogenolysis afforded *epi*-inositol as a colorless solid (yield over 9 steps, 52%). Yield of *epi*-inositol in the methods reported previously[4] was not more than 40%.

We also attempted to prepare *epi*-inositol by the hydride reduction of the *epi*-inosose **14** (Scheme 2). However, unlike the reduction of the protected inosose **10**, reduction of **14** was not that selective and yielded a mixture of *epi*-inositol and *myo*-inositol.

* Corresponding author. Tel.: +91 20 2590 2055; fax: +91 20 2590 2629.
E-mail address: ms.shashidhar@ncl.res.in (M.S. Shashidhar).
† Present address: Jubilant Chemsys Ltd, B-34, Sec-58, Noida 201 301, UP, India.

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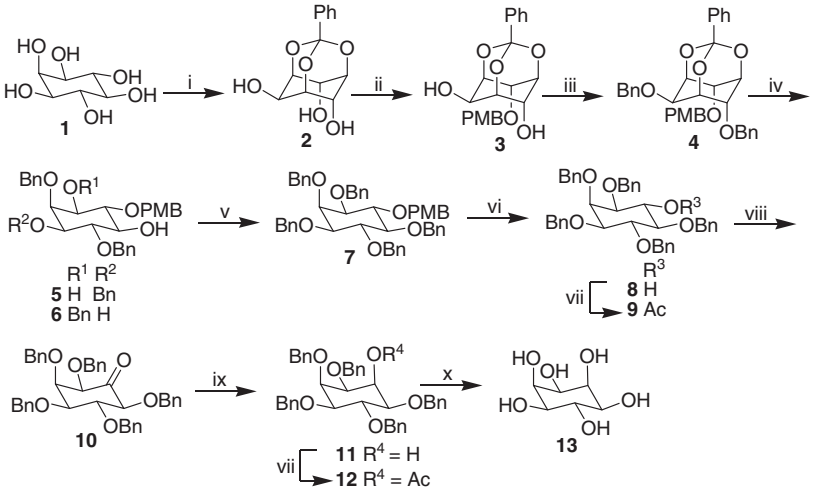
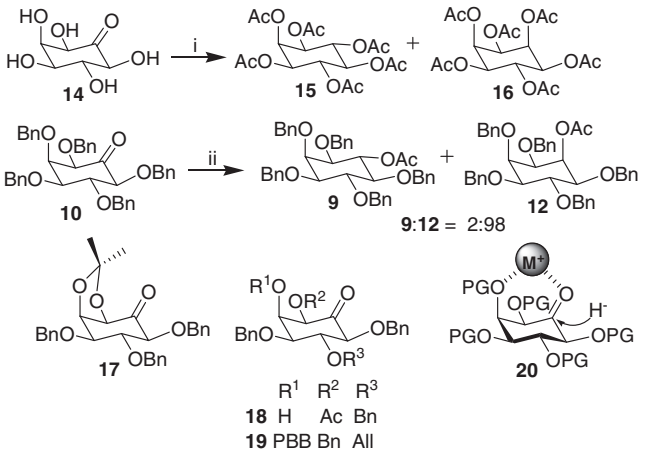


Scheme 1. Reagents and conditions: (i) as in Ref. 5; (ii) as in Ref. 4k; (iii) DMF, NaH, BnBr, 16 h, 96%; (iv) DCM, 1 M DIBAL-H in toluene, 20 h; (v) DMF, NaH, BnBr, 16 h, 81% over two steps; (vi) DCM–MeOH, concd HCl, reflux, 6 h, 93%; (vii) pyridine, DMAP, Ac_2O, reflux, 18 h, 92–95%; (viii) IBX, EtOAc, reflux, 6 h, 94%; (ix) $NaBH_4$, DCM–MeOH (4:1), 30 min, 94%; (x) 20% $Pd(OH)_2/C$, THF, H_2O, TFA, H_2, 60 psi, rt, 20 h, 96%.



Scheme 2. Reagents and conditions: (i) (a) borohydride, H_2O; (b) pyridine, DMAP, Ac_2O, reflux, 18 h; (ii) (a) $NaBH_4$, DCM–MeOH (4:1), 30 min; (b) pyridine, DMAP, Ac_2O, reflux, 18 h, 88%.

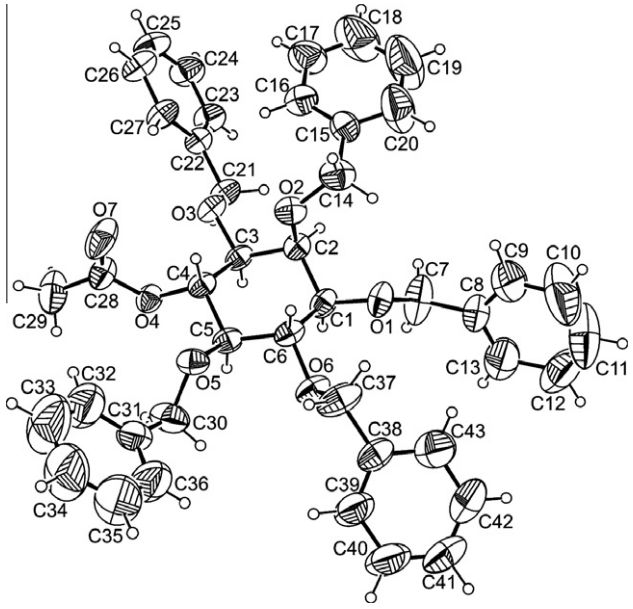


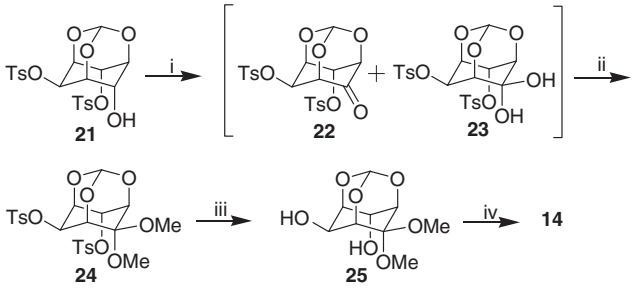
Figure 1. ORTEP diagram of **9**; thermal ellipsoids are shown at 30% probability and hydrogen atoms are depicted as small spheres of arbitrary radii.

The *epi:myo* ratio (at 55 °C) were 89:11, 82:18, 50:50 and 43:57 (90 °C) on reduction, respectively, with borohydrides of sodium, potassium, lithium and sodium cyanoborohydride. These ratios were estimated by ^{1}H NMR spectroscopy of the mixture of hexaacetates **15** and **16** since the *epi*-hexaacetate and the *myo*-hexaacetate show distinct peaks at 2.17 δ (6H) and 2.21 δ (3H), respectively, in their ^{1}H NMR spectra.[4d,8]

Selective reduction of the protected *epi*-inosose **10** to the *epi*-alcohol **11** with >98% selectivity was also confirmed by conversion of the crude product obtained by reduction of the protected *epi*-inosose **10** to the corresponding acetate and its scrutiny by ^{1}H NMR spectroscopy (the acetate methyl peak for the *epi*-isomer **12** appears at δ 2.09 while the corresponding peak for the *myo*-isomer **9** appears at δ 1.92). The structure of the racemic *myo*-acetate **9** was established by single crystal X-ray diffraction analysis (Fig. 1).[9]

Perusal of the earlier reports[4d,e,k] on the synthesis of *epi*-inositol revealed that the hydride reduction of the protected inososes **17**, **18** and **19** were also selective to yield the corresponding *epi*-isomer. We are of the opinion that higher selectivity in hydride reduction of the fully protected *epi*-inososes (in contrast to the reduction of **14**) arises due to their ability to complex the metal ions which offers steric hindrance for the approach of the reducing agent on one face of the inositol ring and forces the hydride to approach the carbonyl group as shown in **20** (Scheme 2) to yield the axial alcohol. This line of thought is supported by the fact that reduction of the ketone **18** with a hydride reducing agent devoid of metal ions yields the corresponding equatorial alcohol predominantly.[4e] Also, the *epi*-inosose **14** gives a mixture of products since its chelation with metal ions is not expected to be strong enough in water to facilitate the approach of the hydride from one face of the carbocyclic ring. The synthetic sequence for the preparation of the *epi*-inosose **14** used in the present work is shown in Scheme 3.

Swern oxidation of **21**[10] gave a mixture of the ketone **22** and the *gem*-diol **23**. Methylation of a mixture of **22** and **23** gave the ketal **24** exclusively; it is interesting to note that the ketal **24** was obtained from the ketone **22** under basic conditions. Conversion of a carbonyl compound to the corresponding acetal under basic



Scheme 3. Reagents and conditions: (i) DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C, 82%; (ii) DMF, Ag_2O, MeI, rt, 24 h, 92%; (iii) NaOMe, MeOH, reflux, 12 h, 75%; (iv) TFA–H_2O, rt, 24 h, 99%.

conditions is seldom encountered in the literature. The ease of formation of the *gem*-diol **23** (and the acetal **24**) is perhaps due to the rigid trioxaadamantane frame-work in which presence of a sp^2 carbon induces strain. The rigid trioxaadamantane frame-work also facilitates the removal of the tosylates by S–O bond cleavage, since nucleophilic substitution on the corresponding carbon (which is a part of the rigid frame-work) is not possible.

In conclusion we have reported a method for the facile synthesis of *epi*-inositol **13** involving the following novel features: highly stereoselective reduction of the protected *epi*-inosose **10**; use of reaction sequence in which each step gives a single product with excellent yields; delineation of the role of the protecting group in the selective reduction of a ketone; and the use of tosylate as a hydroxyl protecting group.

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Supplementary data

Supplementary data (experimental procedures for compounds **4**, **7**–**12**, **14**, **24**, and **25**, along with all data for all new compounds and crystallographic data for compound **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.051.

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