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Carbohydrate Research 339 (2004) 1773–1778
Carbohydrate RESEARCH

Concise chemoenzymatic synthesis of *epi*-inositol

Cecilia Vitelio, Ana Bellomo, Margarita Brovetto, Gustavo Seoane and David Gonzalez*

Departamento de Química Orgánica, Facultad de Química, Universidad de la República, C.C. 1157, Montevideo, Uruguay

Received 12 December 2003; accepted 15 April 2004

Abstract—*epi*-Inositol was synthesized in six steps in 40% overall yield from a bacterial bromobenzene metabolite. The chemoenzymatic route involved toluene dioxygenase oxidation, substrate-directed catalytic osmylation, *m*-CPBA epoxidation, radical debromination, and Amberlite-catalized hydrolysis. The route described is amenable to scaleup and could allow access to *cis*-inositol, and deoxy derivatives of *epi*-inositol.

Keywords: Dioxygenase; Chemoenzymatic; *epi*-Inositol; *cis*-Inositol; Haloepoxide

1. Introduction

Inositols are important bioactive molecules involved in cellular communication. Particularly *myo*-inositol plays a role in signal transduction, and its importance as second messenger has been thoroughly studied.[1–6] Aside from *myo*-inositol, the other isomers are scarce (*neo*-, D-*chiro*-, L-*chiro*-, and *scyllo*-inositol) or nonexistent (*cis*-, *epi*-, *allo*-, and *muco*-inositol) in nature, and their chemical and biological properties have been target of continued studies. D- and L-*chiro*-inositol are potential antidiabetic compounds.[7–11] *neo*-Inositol phosphates have been isolated from both mammalian tissue[12] and parasitic amoebas.[13] *scyllo*-Inositol has been isolated from human brain,[14–17] as well as from plants,[18] and its function is under discussion. Finally, *epi*-inositol has recently been evaluated as a potential antidepressant drug that could interact with lithium and *myo*-inositol receptors in the brain.[15,19–27] Unfortunately, the lack of availability of most isomers has limited the extension of the research. In addition, many deoxygenated derivatives such as inosamines, conduramines, and deoxyfluoroinositols are on demand for studies as glycosidase inhibitors[28,29] and for metabolic pathway research.[30–33]

The chemoenzymatic approach to diverse cyclitols and cyclitol analogs via whole-cell oxidation of aromatics by toluene dioxygenase has been extensively explored by Hudlicky,[34–41] Carless,[42–45] and Nicolosi.[46–50] (Fig. 1). As a result, syntheses of five of the nine possible inositol isomers, as well as aminofluorodeoxy derivatives have been disclosed.[28,51–54] The three remaining rare

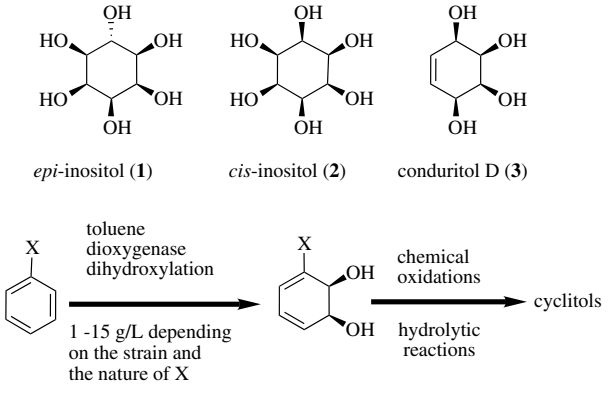

Figure 1. Chemoenzymatic strategy towards diverse sterically congested cyclitols.

* Corresponding author. Fax: +598-2-924-1906; e-mail: davidg@fq.edu.uy

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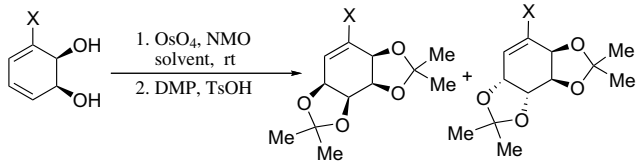
doi:10.1016/j.carres.2004.04.011

isomers, *epi*-, *cis*-, and *scyllo*-inositol, have not yet lended themselves to total synthesis by this type of chemoenzymatic strategy. The completely *trans* stereochemistry of the later isomer is not structurally suited for this approach. On the other hand, *cis*- and *epi*-inositol, although sterically congested, appear as attainable targets for the direct preparation from a *cis*-diol. In this report, we present our results in the development of a short, chemoenzymatic route to *epi*- and *cis*-inositol and some deoxygenated congeners as shown in Figure 1.

2. Results and discussion

Our first approach to the sterically congested cyclitols **1**, **2**, and **3** explored the directed osmylation of the known toluene dioxygenase metabolites **4** and **5**. Osmylation is generally considered to be sterically controlled, and the diol is formed almost exclusively on the less hindered face of the molecule. Nevertheless, research has been done on reversing the stereoselectivity and particularly on the directing effect of an hydroxyl group attached to the allylic position. Donohoe et al. have extensively investigated the topic[55–59] and have applied the results to the synthesis of conduritol D.[60] These findings indicate that the use of an aprotic solvent instead of the classical conditions for stoichiometric or catalytic osmylation favors the electronic directing effect of a neighboring Lewis base over the steric control. Brovetto et al. have studied a series of chiral *cis*-cyclohexadienediols and found that both regio- and stereoselectivity of the osmylation were influenced by the nature of the protective groups.[61] In our hands, the technique rendered a mixture of diasteromeric tetrols favoring the *syn*-dihydroxylation in variable ratios (Table 1). The reaction proceeded well in aprotic solvents of intermediate polarity such as dichloromethane, although the rate was considerably slower than the comparable reaction in water, *t*-BuOH or their mixtures. Attempts to run the reaction in solvents of very low polarity such as toluene slowed down the reaction to unacceptable values and decreased the overall yield without improving the diastereoselectivity (Table 1).

Table 1. Results obtained in the chemical dihydroxylation of diene diols with OsO_4/NMO



4 X = Cl
5 X = Br

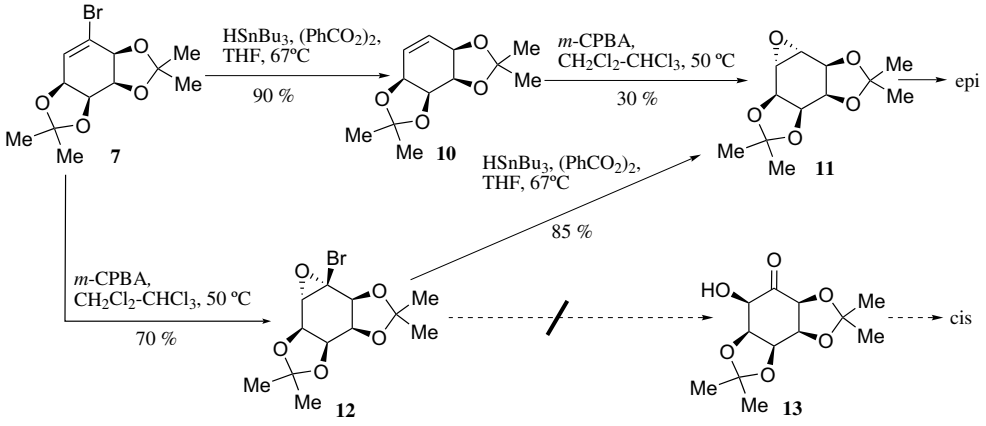
6 X = Cl
7 X = Br

8 X = Cl
9 X = Br

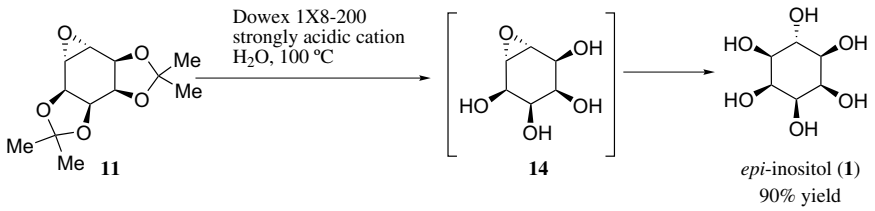
Solvent	Yield (%)	*cis*:*trans* ratio
Polar (acetone–water)	85	50:50
Nonpolar (toluene)	40	80:20
Intermediate polarity (CH_2Cl_2)	75	80:20

With the bromoconduritol derivative **7**[45] in hand, we explored the oxidation of the remaining double bond to target *cis*- and *epi*-inositol. We reasoned that we should be able to achieve the desired diasterodivergence by either epoxidizing compound **7** or the conduritol D derivative **10** (Scheme 1). The meso epoxide **11** should be attainable either from **10** or bromoepoxide **12**. Surprisingly, **7** was epoxidized faster than **10**, and the route via the bromoepoxide was finally chosen. Finally, compound **12** was subjected to radical dehalogenation conditions by means of $SnBu_3H/(PhCO_2)_2$ to furnish the epoxide **11**.[62]

Several conditions were tested for the epoxide ring opening of **11** without concomitant acetonide hydrolysis, but the compound proved to be systematically unreactive. The epoxide did not react with 20% KOH in various water–methanol mixtures either at room temperature or at reflux. This fact could be explained by a very effective blocking of the β face of the molecule by

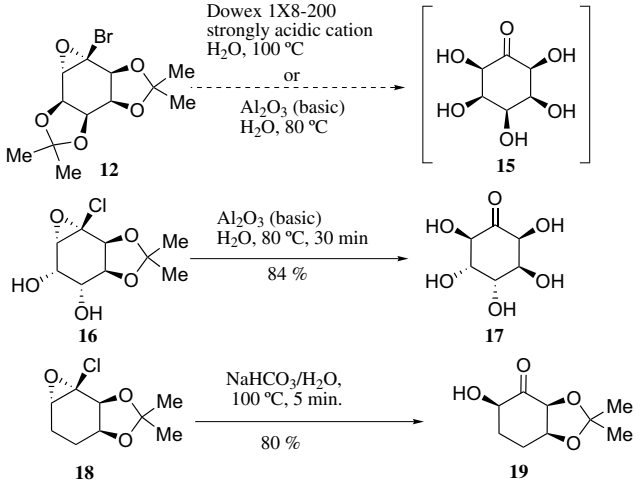


Scheme 1. Diasterodivergent strategy towards *cis*- and *epi*-inositol.



Scheme 2. Acetonide deprotection and attendant epoxide ring opening in H_2O.

the acetonide groups. On the other hand, when **11** was boiled in water containing either an acidic or basic resin, it readily deprotected, and the resulting epoxitetrol **14** was smoothly opened to render *epi*-inositol (**1**) that remained in solution. Filtration of the resin and evaporation of the water rendered crystalline *epi*-inositol in 90% yield with identical ^1H NMR and ^{13}C NMR spectra to those previously reported (Scheme 2).[63–66] The order of the events in this one-pot reaction was confirmed by performing the experiment in D_2O and analyzing aliquots by NMR at different times. Under all the conditions tested, the epoxide ring-opening was effected prior to the acetonide group deprotection.



Scheme 3. Hydrolytic ring opening of conduritol haloepoxides.

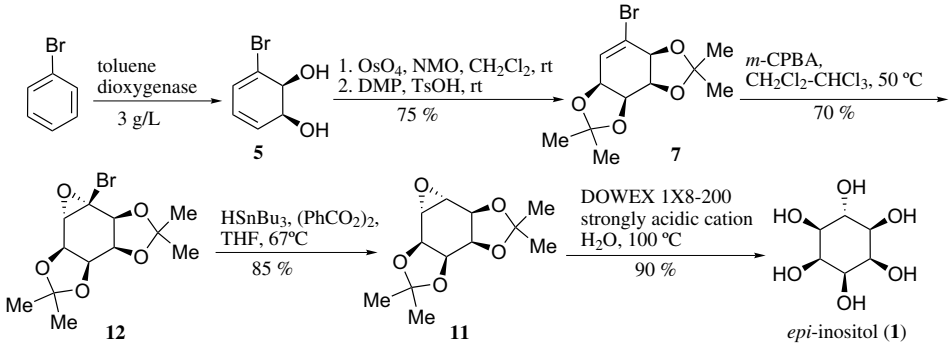
A similar strategy was followed in an attempt to synthesize *cis*-inositol. We reasoned that bromoepoxide **12** would react in a similar way to that of the analogous epoxide **11** to furnish the inosose **15**. In addition, related inosose **17** was reported previously by Mandel and Hudlicky for the opening of chloroepoxide **16** with alumina and water.[67] Unfortunately, **15** turned out to be unstable under the reaction conditions and could only be obtained in minute amounts, since it degraded promptly to render aromatic derivatives. Conversely, deoxygenated derivatives of type **18** can be smoothly converted into ketone **19** without observed degradation (Seoane, G., and Fonseca, G., unpublished data) (Scheme 3).

We have completed a chemoenzymatic synthesis of *epi*-inositol in six steps (five synthetic operations) from bromobenzene in an overall yield of 40% from metabolite **5** (Scheme 4). The preparation is amenable to scaleup and also potentially stereodivergent to the synthesis of *cis*-inositol and inosamines. Research on the syntheses of these compounds is in progress and will be disclosed in forthcoming reports.

3. Experimental

3.1. General methods

All nonhydrolytic reactions were carried out under a nitrogen atmosphere with standard techniques for the exclusion of moisture. All solvents were distilled prior to use. Melting points were determined on a Leitz Wetzlar



Scheme 4. Total chemoenzymatic synthesis of *epi*-inositol from bromobenzene.

Microscope Heating Stage apparatus model 350. Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a 7-mL cell. Infrared spectra were recorded on a Matheson Excalibur spectrometer. Mass spectra were performed on a Shimadzu GS-MS QP 1100 EX instrument using the electron-impact mode. Nuclear magnetic resonance spectra were recorded on Bruker Avance DPX-400 instrument with Me_4Si as the internal standard and chloroform-*d* as solvent unless otherwise indicated in the experimental section. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia 30091). Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or anisaldehyde–H_2SO_4–AcOH as the detecting agent. Flash column chromatography was performed using silica gel (Kieselgel 60, EM Reagents, 230–400 mesh).

3.1.1. Preparation of (2*R*,3*R*,4*S*,5*S*)-1-bromo-2,3,4,5-di-*O*-isopropylidene-6-cyclohexene (7).[45] To a solution of 1-bromo-4,6-cyclohexadiene-2,3-diol (**5**, 500 mg, 2.62 mmol) in CH_2Cl_2 (10 mL) was added *N*-methylmorpholine *N*-oxide (465 mg, 3.97 mmol) and a catalytic amount of OsO_4 (0.1 mL of a 10% solution in *tert*-butyl alcohol). The mixture was stirred overnight at room temperature, protected from light. After removal of CH_2Cl_2, the crude product from the osmylation was treated with DMP (3 mL, 22.26 mmol) in acetone (3.0 mL) and *p*-TsOH (689 mg, 4.00 mmol). Stirring was continued during 45 min at rt. At the end of that time the acetone was evaporated, and the residue was dissolved in CH_2Cl_2 (15 mL). The resulting solution was washed with aq Na_2CO_3 (10 mL) and brine, dried over $MgSO_4$, and filtered. The solvent was evaporated to give the crude mixture, which was chromatographed (silica gel, 1:9 EtOAc–hexanes) to furnish **7** (1.2 g, 75%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.22 (d, 1H, $J_{6,5}$ 3.8 Hz, H-6), 4.56 (m, 2H, H-3, and H-5), 4.45 (m, 1H, H-4), 4.41 (m, 1H, H-2), 1.53 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.8, 124.7, 111.5 (di), 75.9, 74.3, 73.1, 72.3, 27.2 (di), 26.8 (di).

3.1.2. (1*R*,2*S*,3*S*,4*S*,5*R*,6*R*)-1-Bromo-1,2-epoxy-3,4,5,6-di-*O*-isopropylidenecyclohexane (12). *cis*-Diacetonide **7** (300 mg, 0.98 mmol) was dissolved in 1:1 CH_2Cl_2–$CHCl_3$ (10 mL). 3-Chloroperoxybenzoic acid (485 mg, 1.96 mmol) was added to the stirred solution, and the system was allowed to react at reflux temperature for 6 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL) and poured onto aq Na_2CO_3 (10 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. Concentration and purification by flash chromatography (silica gel, 1:9 EtOAc–hexanes) rendered **12** (220 mg, 70%) as a white crystalline solid: mp 100–120 °C (d); $[\alpha]_D^{20}$ +42 (*c* 0.36, CH_2Cl_2); IR (KBr): *v* 2993, 2944, 2891, 1378, 1243, 1220 (C–O–C), 1107, 1055, 884, 797, 788 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 (bd, 1H, $J_{3,4}$ 5.3 Hz, H-3), 4.40 (m, 1H, H-6), 4.24 (m, 2H, H-4, and H-5), 3.66 (s, 1H, H-2), 1.61 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.4, 110.8, 74.8, 72.7, 72.4, 69.5, 63.0, 27.7 (di), 26.4 (di); MS *m*/*z* (relative intensity): 305 (M^+-CH_3, 23%), 247 (2), 187 (2), 159 (4), 97 (9), 85 (6), 69 (6), 59 (14), 43 (100). Anal. Calcd for $C_{12}H_{17}BrO_5$: C, 44.88; H, 5.34. Found: C, 45.02; H, 5.23.

3.1.3. Preparation of (1*R*,2*S*,3*S*,4*R*,5*S*,6*R*)-2,3-epoxy-3,4,5,6-di-*O*-isopropylidenecyclohexane (11).[62] Tributyltin hydride (146 mg, 0.50 mmol) was added to a mixture of benzoyl peroxide (25 mg, 0.10 mmol) and the epoxide bromide **12** (120 mg, 0.37 mmol) in dry THF (6 mL). The reaction mixture was refluxed for 4 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 1:9 EtOAc–hexanes) to afford the pure product as a white solid (76 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (d, 2H, $J_{3,4} = J_{6,5}$ 4.7 Hz, H-3, and H-6), 4.23 (d, 2H, H-4, and H-5), 3.40 (s, 2H, H-1, and H-2), 1.52 (s, 6H), 1.40 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.4, 72.3, 71.2, 54.2, 27.2 (di), 26.3 (di).

3.1.4. Preparation of cyclohexane-1,2,3,4,5,6-hexaol (epi-inositol) (1).[63] A mixture of epoxide **11** (76 mg, 0.31 mmol), Dowex 1X8-200 resin (75 mg) and H_2O was stirred at reflux for 24 h. After completion of the reaction, the resin was filtered off, and the solvent was removed under reduced pressure to give *epi*-inositol (**1**) (50 mg, 90%) as a white solid: mp 270 °C (d); ^{1}H NMR (400 MHz, D_2O): δ 4.03 (d, 2H, $J_{2,1} = J_{4,5}$ 2.6 Hz, H-2, and H-4), 3.80 (t, 1H, $J_{6,1}$ 9.9 Hz, H-6), 3.69 (t, 1H, $J_{3,2}$ 2.9 Hz, H-3), 3.45 (dd, 2H, H-1, and H-5), ^{13}C NMR (100 MHz, D_2O): δ 74.9, 72.2, 70.5, 67.3.

Acknowledgements

The authors acknowledge Mr. Horacio Pezzaroglo and Mr. Eleuterio Umpierrez for recording spectra and Prof. Stephen Angyal for reading the manuscript.

The following organizations contributed to support this work: OPCW/IFS partnership programme (Research Grant F/3078-1 and F/3078-2), CONICYT-BID (project FCE5065) and PEDECIBA (URU 97/016).

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