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Note

A short, stereoselective synthesis of *neo*-inositol

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Abstract

A practical synthesis of *neo*-inositol is described in which the target is prepared on a multigram scale in six operations from bromobenzene. © 2000 Elsevier Science Ltd. All rights reserved.

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The inositols (collectively known as cyclitols) and their derivatives figure prominently in numerous biological processes. For example, inositol phosphates are involved in cellular signaling and regulation of cellular calcium with implications in such processes as sensory perception and fertilization [1]. The study of inositol-containing compounds and their effects is one of the most active fields in biology today, and there is considerable interest among chemists in the synthesis of analogues [2]. It can be argued that development of synthetic routes to even the most abundant of the nine isomers would facilitate research on the inositols — the study of structure–activity relationships and mechanisms through radiolabeled compounds, for instance. We have provided synthetic routes to five of these isomers [3–5]. All but one of the nine inositols (*cis*) are commercially available[1], some as a direct result of our endeavors.

neo-Inositol **1** was first described and named by Angyal and Matheson in 1955, when it was prepared, along with L-*chiro*-inositol, in two steps from 1,2:5,6-di-*O*-isopropylidine-L-*chiro*-inositol [6]. It was first identified in nature in soil samples as its hexaphosphate [7]. Since then, it has been isolated from *Croton celtidifolius*, a plant used in Brazilian folklore medicine [8], and from animal tissues [9]. The crystal structure of *neo*-inositol has been examined in relation to its unusual stability [10], and molecular modeling studies have been reported [11,12].

We have already prepared *neo*-inositol on a small scale [13,14] and have reported the isola-

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[1] *allo*-Inositol, $80/100 mg (Aldrich); D-(+)-*chiro*-inositol, $195/100 mg (Aldrich); L-(−)-*chiro*-inositol, $195/100 mg (Aldrich); *epi*-inositol, $174/100 mg (Sigma); *muco*-inositol, $134/100 mg (Aldrich); *myo*-inositol, $75/500 g (Aldrich); *neo*-inositol, $199/100 mg, *scyllo*-inositol, $204/100 mg (Sigma).

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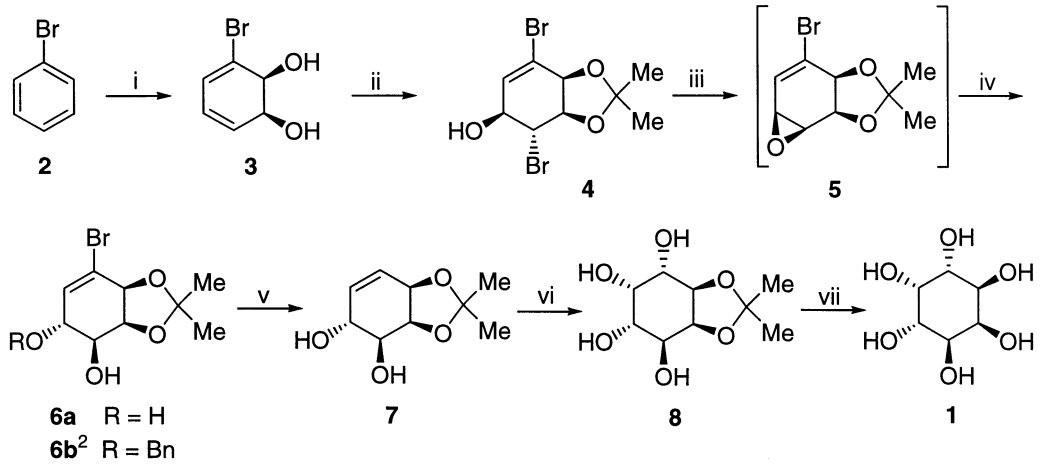

Scheme 1. (i) Toluene dioxygenase; (ii) dimethoxypropane, *p*-TsOH, acetone; then DBH, H_2O, acetone; (iii) 10% aq KOH, DME, 5 h, rt; (iv) rt → reflux; (v) Bu_3SnH, AlBN, benzene, reflux, 18 h; (vi) OsO_4, NMO, ^tBuOH, acetone–water; (vii) concd HCl, MeOH, 48 h.

tion of *neo*-inositol as a side-product in the synthesis of D-*chiro*-inositol [5]. Chung and Kwon have synthesized *neo*-inositol and other inositols from *myo*-inositol [15]. Recently, as the work described in this paper was in progress, a practical multigram synthesis of *neo*-inositol from *myo*-inositol was reported by Riley and co-workers [16]. Herein, we report a practical synthesis of *neo*-inositol from bromobenzene.

neo-Inositol was prepared as shown in Scheme 1. The major thrust of the strategy arose from our synthesis of deoxyfluoro inositols [17] and from our efforts in the synthesis of the sphingosines [18]. The present synthesis represents a substantial scale-up of those procedures already reported.

We have used the biooxidation of aromatic compounds as a technique to prepare diverse chiral starting materials for many of the syntheses we have undertaken in our laboratories over the past few years [3]. In this case, bromobenzene **2** was enzymatically hydroxylated to the corresponding cyclohexadiene-*cis*-diol **3** [19] in >99% ee by treatment with *Escherichia coli* JM109 (pDTG601). The diol was subsequently protected as its acetonide and converted to bromohydrin **4** by means of 1,3-dibromo-5,5-dimethylhydantoin (DBH) in acetone–water [17,18].

Treatment of **4** with excess aqueous KOH at room temperature generated the epoxide **5** [17], which was not isolated; heating the reaction mixture to reflux effected the hydrolysis[2]. The regioselectivity of the oxirane opening can be attributed in part to the atomic charge distribution being more positive at C-3 than C-4 [20,21], in part to the steric requirements for pseudo trans-diaxial opening and the bulk of the acetonide group. Radical debromination of **6a** to **7**, followed by dihydroxylation with osmium tetroxide and 4-methylmorpholine *N*-oxide (NMO) yielded tetrol **8**. Deprotection in methanolic HCl or water containing a catalytic amount of sodium benzoate readily provided *neo*-inositol **1** in 77% yield.

This efficacious, high-yielding route provided *neo*-inositol selectively in only six operations from bromobenzene, without the need for column chromatography. We have prepared 3.8 g of analytically pure *neo*-inositol[3] from approximately 20 g of the bromocyclohexadiene-*cis*-diol **3** in a 17% overall yield.

1. Experimental

(3R,4S,5S,6S)-1-Bromo-5,6-O-isopropylidene-1-cyclohexene-3,4,5,6-tetrol (**6a**).—Bromohydrin **4** [17,18] (40 g, 0.10 mol) was dis-

[2] Lewis acid-catalyzed cleavage (BF_3) of epoxide **5** with benzyl alcohol yields **6b**, prepared in conjunction with a project on the synthesis of oligo inositols and used here only to check purity by HPLC.

[3] The 6.3 g batch of *neo*-inositol obtained in the final step is of a purity suitable for further transformations. The overall yield in this instance is 28%.

solved in 1,2-dimethoxyethane (DME, 350 mL), then aq KOH (10%, 176 mL) was slowly added. The reaction mixture was stirred at ambient temperature until thin-layer chromatography (TLC) analysis (19:1 CH_2Cl_2–EtOAc) showed no remaining bromohydrin (5 h). The flask was fitted with a reflux condenser and the mixture was heated at reflux overnight. When the reaction mixture had cooled to room temperature (rt), NH_4Cl was added and the solvent was removed in vacuo. The crude product was dissolved in EtOAc, washed with water, and dried over $MgSO_4$. Removal of the solvent yielded 22 g of material of sufficient purity to use directly in the next step.

*(3*R,*4*S,*5*S,*6*R*) - 5,6* - O - *Isopropylidene - 1-cyclohexene-3,4,5,6-tetrol* (**7**).—To diol **6a** [17] (22 g, 0.08 mol) dissolved in benzene (125 mL) and MeOH (65 mL) was added a spatula-tip of AlBN and *n*-$BuSn_3H$ (56 mL, 0.2 mol). After stirring at reflux overnight, the reaction mixture was concentrated in vacuo and the residue was dissolved in MeCN. The mixture was washed with hexanes; as the hexane phase contained some of the diol it was extracted with another portion of MeCN. The combined MeCN extracts were evaporated to dryness to yield 15 g of material of sufficient purity to use in the next step.

neo-*Inositol* **1**.—To compound **7** (5.0 g, 0.027 mol) in acetone (70 mL) and water (20 mL) were added 4-methylmorpholine *N*-oxide (3.6 g, 1.1 equiv) and osmium tetroxide in *t*-BuOH (75 mL, 0.05 M). The reaction mixture was stirred at rt for 72 h, at which time TLC analysis indicated complete conversion. The solvent was removed in vacuo and the residue was dissolved in 1:1 CH_2Cl_2–MeOH and filtered through a short plug of silica gel. Removal of the solvent in vacuo yielded 5.4 g (90% yield) of protected *neo*-inositol (**8**), of sufficient purity to use directly in the next step.

To crude **8** (8.9 g) dissolved in MeOH (125 mL) and water (12.5 mL) was added 100 drops of concd HCl. After stirring for 16 h, the solvent was removed under reduced pressure to give a white solid (6.3 g). Recrystallization from boiling water gave 3.8 g of analytically pure white crystals after drying for 12 h at 100 °C under reduced pressure: mp 313 °C (dec), lit. 315 °C (dec) [6]; $[\alpha]_D^{27}$ 0° (*c* 0.01, H_2O); IR (KBr): *v* 3250–2910, 1392, 1283, 1258, 1131, 1058, 1037 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6): δ 4.34 (d, 2 H, OH), 4.21 (bs, 4 H, OH), 3.71 (bs, 2 H), 3.43 (bs, 4 H); MS: $C_6H_{13}O_6$ requires 181.07121; found [M + H] 181.07121; *m/z* (CI): 181 $[M+H]^+$, 361 $[2M+H]^+$, 554 $[3M+4H]^+$, 163 $[(M+H)-OH]^+$, 127 $[(M+H)-3\ OH]^+$. Anal. Calcd for $C_{24}H_{48}O_{24}\cdot H_2O$ [4:1 hydrate]: C, 39.02; H, 6.50. Found: C, 39.16; H, 6.69.

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