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Carbohydrate Research 304 (1997) 39–42

CARBOHYDRATE RESEARCH

A practical multigram-scale synthesis of *allo*-inositol

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Received 12 May 1997; accepted 1 June 1997

Abstract

allo-Inositol was prepared on a multigram scale starting with bromobenzene in seven steps by three different *cis*-dihydroxylations (enzymatic, OsO_4 and RuO_4 catalyzed) employed in tandem. © 1997 Elsevier Science Ltd.

Keywords: *allo*-Inositol; Multigram synthesis; Biooxidation; *cis*-Dihydroxylation

1. Introduction

Inositols or hexahydroxycyclohexanes have been of particular interest in the carbohydrate field [1–3]. The biological activities of these compounds and their phosphate derivatives, especially their role in intracellular communication, have been studied [4–8] and their syntheses have been summarized [9–11]. Of the nine stereoisomers of inositol, only three are commercially available; [1] it, therefore, seemed appropriate to develop a convenient synthetic route to this and other members of the inositol class of compounds.

allo-Inositol (**8**), a non-natural cyclitol, was synthesized for the first time by Dangschat and Fischer in 1939 [12,13]. Other syntheses have since been reported [14–19]; unfortunately, most of the approaches are not amenable to a multigram-scale synthesis. We have previously reported a three-step synthesis of *allo*-inositol in which the key step was the $KMnO_4$ oxidation of diol **2** or its chloro derivative. However, the synthesis produced extremely carcinogenic materials, was not amenable to scaleup, and resulted in a lower overall yield of 26% [18]. Herein we report a seven-step stereoselective synthesis of *allo*-inositol in an overall yield of 45%, suitable for a multigram scale, using the versatile synthon, (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**2**), that has been featured in many syntheses of natural products and compounds of biological interest [20–28].

2. Results and discussion

Microbial oxidation of bromobenzene (**1**) with toluene dioxygenase expressed in *Escherichia coli* JM109 (pDTG601) furnished the bromodienediol **2** in a yield of 10 g/L. This reaction is performed easily on large scale [29] [2], and diol **2** is also commercially available. [3] Protection of **2** as its acetonide using 2,2-dimethoxypropane (2,2-DMP), acetone and a cat-

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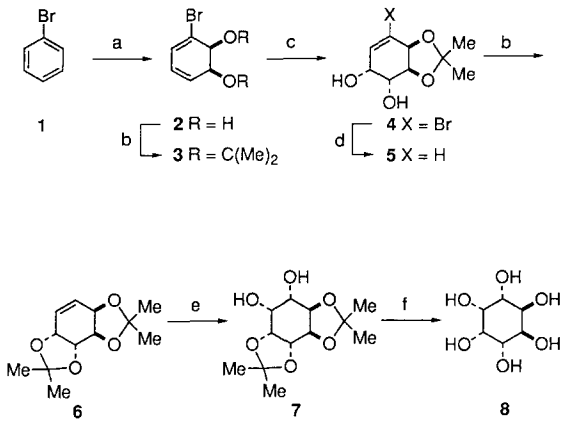
[1] Sigma Chemical Co. prices (1997): *epi*-inositol, 100 mg/$160.35; *myo*-inositol, 1 kg/$135.15; *scyllo*-inositol, 100 mg/$188.15.

[2] Preprints of this reference are available from the corresponding author.

[3] Available from Genecor International, Inc.

PII S0008-6215(97)00186-9

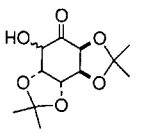


Scheme 1. Reagents: (a) *Escherichia coli* JM109 (pDTG601); (b) 2,2-DMP, *p*-TsOH, acetone; (c) OsO_4, NMO, acetone, water; (d) Bu_3SnH, AIBN, THF, reflux; (e) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, 0 °C; (f) HCl, EtOH.

alytic amount of *p*-toluenesulfonic acid [4] gave acetonide **3** in excellent yield (> 90%), which was used without any further purification. Osmylation of the unsubstituted double bond using a catalytic amount of osmium tetroxide in presence of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant gave the diol **4** whose configuration has already been established [30,31]. Dehalogenation of diol **4** with tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) in tetrahydrofuran at reflux gave 1L-1,2-*O*-isopropylidenecyclohex-5-ene-1,2/3,4-tetrol (**5**), a derivative of conduritol E, in 90% yield as a white solid [31]. All of these reactions have been carried out on a 30–40 gram scale (Scheme 1).

Attempts at the *cis*-dihydroxylation of **5** using osmium tetroxide as oxidant failed. The use of a catalytic amount of OsO_4 with NMO as co-oxidant in a mixture of acetone and water afforded a small amount of the desired tetrol, but only after 5 days. Increasing the amount of catalyst to 0.6 equivalents gave the tetrol in 24 h. Because of the high cost of OsO_4 and its toxicity, and the difficult recovery of the tetrol that is soluble in water, this methodology was rejected for a multigram-scale synthesis. Protection of the diol as its diacetate or its acetonide, followed by osmylation, also failed to furnish the dihydroxylated compound presumably because of the double deactivation of the olefin.

Recently, a fast and convenient procedure for *cis*-hydroxylation of alkenes with ruthenium oxide as catalyst has been published [32,33] based on the previous work from Sharpless and Akashi [34]. Because of the use of sodium periodate in that reaction, the diol was first protected as its acetonide as described earlier to give **6** [15,35] in 97% yield. On a one-gram scale, oxidation of **6** using $RuCl_3$ and $NaIO_4$ in a mixture of ethyl acetate, acetonitrile and water furnished diol **7** in 71% yield with the reaction complete within 3 minutes. Longer reaction times led to products of oxidative fission and lower yields. A byproduct of the reaction isolated during preliminary small-scale experiments, was assigned as inosose **9** (8–10% as evaluated by ^1H NMR spectroscopy).



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On a larger scale, the reaction was performed in acetonitrile in which the workup procedure is more convenient. The diol was purified by recrystallization and was obtained in 70% yield. Deprotection with aqueous hydrochloric acid in ethanol gave crystalline *allo*-inositol (**8**).

In summary, a simple synthesis of *allo*-inositol amenable to a multigram scale has been accomplished using readily available reagents in an overall yield of 45% (from bromocyclohexadiene *cis*-diol). Further developments of this technology aimed at the synthesis of protected (i.e., 'chiral') versions of the *meso*-inositols, including their phosphate derivatives, are in progress and will be reported in due course.

3. Experimental

General methods.—All nonhydrolytic reactions were conducted in an argon atmosphere with standard techniques for exclusion of air and moisture. Flash column chromatography was performed on Fisher silica gel (grade 60, 200–425 mesh). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. NMR spectra were recorded with a Varian (Gemini-300) instrument in $CHCl_3$ at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

1L-1,2:3,4-di-O-isopropylidenecyclohex-5-ene-1,2/3,4-tetrol (**6**).—To a stirred solution of diol **5**

[4] The use of too large an amount of *p*-TsOH gives rise to the formation of phenols by acid-catalyzed elimination of water.

[31] (10.4 g, 56.0 mmol) in a mixture of acetone and 2,2-dimethoxypropane (7:3, 100 mL) was added *p*-TsOH (64 mg, 0.33 mmol). Stirring was continued at rt for 2 h. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc and washed with aq $NaHCO_3$, followed by brine. The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo to afford **6** (12.4 g, 97.9%). Compound **6** was recrystallized in a mixture of MeOH and water. ^{1}H NMR: δ 5.71 (br s, 2 H, 2 × =C*H*), 4.55 (m, 4 H, 4 × C*H*–O), 1.37 (s, 12 H, 2 × CMe_2); ^{13}C NMR: δ 126.9 (2 × =*C*H), 109.0 (2 × *C*Me_2), 73.3 (2 × *C*HO), 70.2 (2 × *C*HO), 27.8 (2 × Me), 26.4 (2 × Me).

*1*D *- 1, 2:5, 6 - di* - O - *isopropylidene* - allo - *inositol* (**7**).—*Method A (small scale).* To a stirred solution of **6** (1.03 g, 4.56 mmol) in EtOAc–acetonitrile (20 mL/20 mL) at 0 °C was added a solution of $RuCl_3 \cdot H_2O$ (70 mg, 0.34 mmol) and $NaIO_4$ (1.27 g, 5.95 mmol) in distilled water (8 mL). The mixture was stirred vigorously for 2.5 min and quenched with a 20% solution of $Na_2S_2O_3$. The solution was filtered through a pad of silica gel, which was then washed with EtOAc. The organic layer was separated, and the water phase was extracted three times with EtOAc. The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil that was purified by flash chromatography (55:45 EtOAc–hexanes) to yield **7** as a white solid (0.84 g, 71%).

Method B (large scale). To a stirred solution of **6** (21.9 g, 96.7 mmol) in acetonitrile (440 mL) at 0 °C was added a solution of $RuCl_3 \cdot H_2O$ (1.45 g, 6.99 mmol) and $NaIO_4$ (26.9 g, 126 mmol) in distilled water (90 mL). The mixture was stirred vigorously for 3 min and quenched with a saturated solution of $Na_2S_2O_3$ (15 mL). The suspension was filtered through a pad of silica gel, which was then washed with EtOAc. The solvents were evaporated under reduced pressure, and the residue was dissolved in EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. Purification by recrystallization (CH_2Cl_2–hexanes) afforded **7** as a white solid (17.6 g, 69.9%) along with 8–10% of protected inosose **9**.

Data for **7**: mp 81–82°C; $[\alpha]_D^{25}$ +8.9° (*c* 1.12, $CHCl_3$); IR (KBr): ν 3447, 2990, 2940, 2882, 1432, 1383, 1264, 1210, 1159, 1056, 860 cm^{-1}; ^{1}H NMR: δ 4.47 (m, 2 H), 4.38 (m, 2 H), 4.11 (br s, 1 H), 3.72 (br s, 1 H), 3.13 (br s, 1 H, OH), 2.81 (br s, 1 H, OH), 1.52 (s, 3 H, Me), 1.46 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.34 (s, 3 H, Me); ^{13}C NMR: δ 109.5 (*C*Me_2), 108.6 (*C*Me_2), 78.1, 76.4, 75.7, 74.4, 72.7, 68.1, 27.0 (Me), 26.3 (Me), 24.2 (Me), 23.7 (Me). HRMS: Calcd for ($C_{12}H_{20}O_6$ + H): 261.1338. Found: 261.1308. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.31; H, 7.79.

Data for inosose **9**: mp 90–91 °C; IR (KBr): ν 3482, 2991, 2924, 1752, 1462, 1386, 1261, 1212, 1159, 1062, 901, 862, 783 cm^{-1}; ^{1}H NMR: δ 4.90 (m, 1 H), 4.81 (m, 1 H), 4.74 (m, 2 H), 4.37 (d, *J* 6.3 Hz, 1 H), 3.20 (br s, 1 H, OH), 1.52 (s, 3 H, Me), 1.39 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.32 (s, 3 H, Me); ^{13}C NMR: δ 203.6 (C=O), 111.5 (*C*Me_2), 109.7 (*C*Me_2), 78.7, 76.7, 75.7, 72.4, 69.3, 26.4 (Me), 26.0 (Me), 24.1 (Me), 23.9 (Me). HRMS: Calcd for ($C_{12}H_{18}O_6$ + H): 259.1182. Found: 259.1184. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.98; H, 7.22.

allo-*Inositol* (**8**).—Hydrochloric acid (5 mL) was added to a solution of **7** (17.3 g; 66.4 mmol) in EtOH (220 mL), and the mixture was left at room temperature for 16 h, whereupon the inositol crystallized out of the solution. The white solid was filtered off and washed with EtOH to give crystalline *allo*-inositol (11.5 g, 95.8%) whose spectral data matched with the previously published data [18]: mp 270–280 °C dec., lit. 270–275 °C [12]. Anal. Calcd for $C_6H_{12}O_6$: C, 40.00; H, 6.71. Found: C, 40.09; H, 6.65.

Acknowledgements

The authors are grateful to NSF (CHE-9615112), TDC Research, Inc. and the University of Florida for the financial support of this work. M.D. thanks FCAR (Fonds pour la Formation de Chercheurs et l'Aide à la Recherche, Québec) for a postdoctoral fellowship.

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