

Synthesis of all-*cis*-1,2,4-cyclohexanetriol

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Dedicated to Professor Georges Hoornaert on the occasion of his 65th birthday

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Abstract

A one step synthesis of (±)-all-*cis*-1,2,4-cyclohexanetriol **1** by high pressure hydrogenation of the corresponding 1,2,4-benzenetriol in the presence of Raney-nickel or a catalytic amount of rhodium on aluminium oxide is disclosed.

Keywords: Cyclohexane-1,2,4-triol, high pressure hydrogenation, Raney-nickel, rhodium on aluminium oxide

Introduction

Polyhydroxycyclohexanes are of great interest as model compounds for studies in carbohydrate chemistry and stereochemistry, and are of importance because of their relationship to the biologically important cyclitol and *myo*-inositol.¹

In the literature,² an extensive study on the synthesis and conformational NMR-analysis of the series of nine isomeric cyclohexanetriols (there are 14 cyclohexanetriol isomers if the two enantiomers of each racemic pair are separately counted) was performed. For cyclohexanetriol, three structures are possible: cyclohexane-1,2,3-triol (vicinal); cyclohexane-1,3,5-triol (symmetric), and cyclohexane-1,2,4-triol (asymmetric). *cis*-1,2,4-Cyclohexanetriol **1** is a target molecule for the synthesis of the corresponding orthoester derivatives, which are the “core” of *resiniferatoxin 2* (Figure 1), isolated from *Euphorbia resinifera*.³ Resiniferatoxin acts as an ultrapotent analogue of capsaicin, the pungent constituent of hot peppers.⁴ Both of the latter substances possess the ability to excite and subsequently desensitize sensory nociceptor neurons, leading to analgesia.⁵

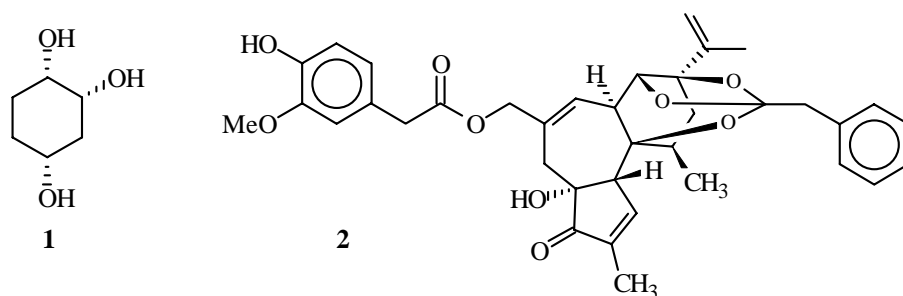


Figure 1

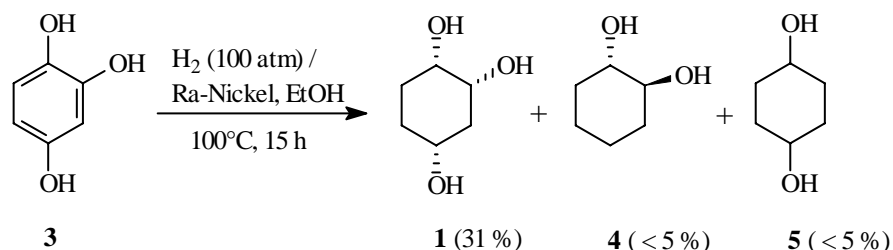
The asymmetric synthesis of (+)-all-*cis*-1,2,4-cyclohexanetriol was pointed out in the literature in the synthesis of aminocyclitols starting from (-)-quinic acid.⁶ The reaction sequence involved seven steps affording the optically active (+)-all-*cis*-1,2,4-cyclohexanetriol in reasonable yield (40%). Apparently, the preparation of the racemic all-*cis*-1,2,4-cyclohexanetriol **1** by hydrogenation or reduction of 1,2,4-trihydroxybenzene **3** has never been reported. On the other hand, the high pressure hydrogenation of the symmetric 1,3,5-trihydroxybenzene (pyrogallol) to all-*cis*-cyclohexane-1,3,5-triol was readily performed using Raney-nickel as catalyst (about 40 % yield).⁷ The only method reported in the literature for the synthesis of (±)-all-*cis*-1,2,4-cyclohexanetriol **1** used a *cis* dihydroxylation of 3-cyclohexen-1-ol² or its benzoate ester or benzyl ether. The two diastereomers with 1,2-*cis* configuration were separated by fractional crystallization affording the racemic mixture of (±)-all-*cis*-cyclohexane-1,2,4-triol **1** in very low yield (~ 8 %).

Because of the potential importance of a readily available source of racemic all-*cis*-cyclohexane-1,2,4-triol **1** as basic core of the daphnane diterpenes family, potent tumor promoters,⁸ and cage orthoesters, as present in resiniferatoxin (RTX) and various other esters of resiniferonol,⁹ a short synthesis of triol **1** was developed.

Results and Discussion

In the present communication a one step synthesis of (±)-all-*cis*-1,2,4-cyclohexanetriol **1**, based on the high pressure hydrogenation of 1,2,4-trihydroxybenzene **3** is described.

High pressure hydrogenation of 1,2,4-trihydroxybenzene **3** at 100 atmospheres was performed with Raney-nickel in ethanol at 100°C (Scheme 1). The workup of the reaction mixture obtained was not easy because of the high viscosity and the water solubility of the reaction products. After filtration, the viscous reaction mixture was preferably quickly distilled under high vacuum and, successively, the complex reaction mixture was separated by flash chromatography on silica gel affording the pure (±)-all-*cis*-cyclohexane-1,2,4-triol **1** in 31 % yield.



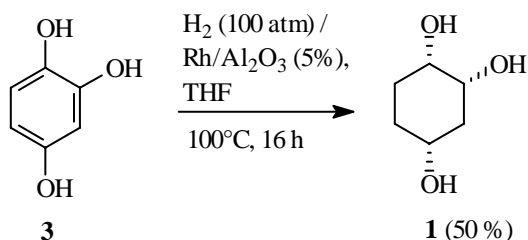
Scheme 1

The other compounds isolated by flash chromatography were *trans*-cyclohexane-1,2-diol **4**, and cyclohexane-1,4-diol **5**, both in a minor yield of 5 % (Scheme 1).

To avoid substantial loss of the triol **1** during the silica gel chromatography, the separation of the reaction mixture was performed also by centrifugal counter current chromatography (Centrifugal CCC). The yield of the triol **1** could not be improved higher than 30 %. This represents an alternative way for the isolation of the (±)-all-*cis*-cyclohexane-1,2,4-triol **1**.

(±)-*cis*-Cyclohexane-1,2,4-triol **1** is a white solid, readily soluble in water, in polar solvents such as methanol, dimethylsulfoxide and dimethylformamide. It also shows a moderate solubility in tetrahydrofuran. The melting point, and 60 MHz ¹H NMR spectral data obtained for (±)-all-*cis*-cyclohexane-1,2,4-triol **1** were identical with those reported in the literature.² Further spectrometric data (270 MHz ¹H NMR, 68 MHz ¹³C NMR, MS) of (±)-all-*cis*-1,2,4-cyclohexanetriol **1** are described in the experimental part.

To improve the results of the catalytic hydrogenation, other metals were used for this high pressure reaction. The hydrogenation reaction of trihydroxy-1,2,4-benzene **3** was performed with rhodium on aluminium oxide (5 %) as catalyst in tetrahydrofuran at 100 atmospheres of pressure (Scheme 2). The same complex mixture of isomers was obtained, but with the (±)-all-*cis*-1,2,4-cyclohexanetriol **1** as predominant compound. The high pressure was necessary for the completion of the reaction. In fact, the same reaction with Rh/Al₂O₃ performed at one atmosphere of pressure gave, after one week at 50°C, a reaction mixture in which the main compound was still the 1,2,4-trihydroxybenzene **3**.



Scheme 2

Using Rh/Al₂O₃ as catalyst, the high vacuum distillation of the reaction mixture was not necessary, and the mixture of reaction products was immediately separated by flash chromatography on silica gel, affording the desired all-*cis*-triol **1** in an improved yield of 50 %.

In conclusion, a convenient one step synthesis of (±)-all-*cis*-cyclohexane-1,2,4-triol **1**, a useful scaffold for natural products synthesis, is reported.

Experimental Section

General Procedures. NMR spectra were run on a JEOL JNM EX 270 spectrometer, using CD₃OD as the solvent. TLC was performed on Si gel plates Kieselgel 60F₂₅₄. Flash chromatography was carried out on Si gel (Merck; particle size 40-63 μm). Raney-nickel, Rh/Al₂O₃, and 1,2,4-trihydroxybenzene were of commercial grade (Aldrich or Acros) and used without further purification.

(±)-All-*cis*-cyclohexane-1,2,4-triol (1). The hydrogenation of trihydroxy-1,2,4-benzene **3** was performed in a Parr apparatus. To a solution of 1,2,4-trihydroxybenzene (10 g, 76 mmol) in 50 ml of absolute ethanol, 15 g of Raney-nickel (type W₄) was added, and the mixture was stirred for 15 hours at 100 atmospheres of pressure at 100°C. The cooled reaction mixture was filtered on celite and the solvent was evaporated in vacuo. The dark viscous reaction mixture was distilled at high vacuum to afford the crude triol **1**, b.p. 130°C at 0.01 mmHg, contaminated by other reaction products (NMR).

This mixture was further separated by flash chromatography. A mixture of CH₂Cl₂/MeOH (95:5) was used to eluate the first two compounds [compound **4** (R_f = 0.44, in CH₂Cl₂/MeOH 9:1) and **5** (R_f = 0.29, in CH₂Cl₂/MeOH 9:1), Scheme 1], then CH₂Cl₂/MeOH (9:1) was necessary to eluate the desired triol **1** (R_f = 0.16) in 31 % yield. Anal. Calcd. for C₆H₁₂O₃ (132): C, 54.53; H, 9.15. Found: C, 54.65; H, 9.54. ¹H NMR (270 MHz, CD₃OD) δ 1.30-1.95 (6 H, m, 3 × CH₂), 3.59 (2 H, m, 2 × CHOH), 3.77 (1 H, m, CHOH). ¹³C NMR (68 MHz, CD₃OD) δ 27.9 (CH₂), 29.5 (CH₂), 38.1 (CH₂), 69.1 (CHOH), 69.6 (CHOH), 71.5 (CHOH). Mass spectrum *m/z*, 70 eV (%): 132 (M⁺, 2), 114 (37), 96 (7), 88 (14), 86 (14), 83 (9), 75 (33), 74 (10), 73 (39), 71 (47), 70 (100), 69 (12), 68 (17), 67 (12), 60 (10), 58 (60), 57 (60), 55 (21), 45 (52), 44 (96), 43 (56), 42 (19), 41 (32), 39 (15).

The separation of the reaction products **1**, **4**, and **5**, obtained from the hydrogenation reaction, by centrifugal counter current chromatography was performed as follows. An amount of 100 mg of the reaction mixture was separated using the following solvent system: CHCl₃ / MeOH / *i*-PrOH / H₂O (5 : 6 : 1 : 4) affording 30 mg of (±)-all-*cis*-cyclohexane-1,2,4-triol **1**.

The high pressure hydrogenation reaction with Rh/Al₂O₃ was performed in an analogous way as the procedure described with Raney-nickel. The only difference was the amount of rhodium

on aluminium oxide used in a catalytic amount (0.5 g of Rh/Al₂O₃ for 10 g of 1,2,4-trihydroxybenzene). After filtration and evaporation of the solvent, the mixture of reaction products obtained was separated by flash chromatography on silica gel using a mixture of CH₂Cl₂/MeOH (4:1) to give compound **1** in 50 % yield.

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