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Note

One-pot synthesis from 1,4-cyclohexadiene of (±)-1,4/2,5-cyclohexanetetrol, a naturally occurring cyclitol derivative

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Abstract

SeO_2-catalyzed direct hydroxylation of 1,4-cyclohexadiene with two molar equivalents of 30% H_2O_2 afforded (±)-1,4/2,5-cyclohexanetetrol, a naturally occurring cyclitol derivative, as the sole product in a good yield (88%).

Keywords: (±)-1,4/2,5-Cyclohexanetetrol; 1,4-Cyclohexadiene; Selenium dioxide

For many years the cyclitols [1,2] have been recognized as a small group of natural products, but nowadays their status has changed as a result of extensive chemical and biochemical investigations. In this context, cyclohexanetetrols, a class of cyclitols, are worthy of attention. So far, only three naturally occurring cyclohexanetetrol isomers have been reported: Betitol [3], D-(+)-1,4/2,5-cyclohexanetetrol [4,5] (**2a**), and toxocarol [6]. Betitol was reported to be present in very small amounts in sugarbeet molasses. The proposed structure of betitol (mp 224 °C) is mainly based on elemental analyses, a negative response to Fehling's reagent, and its conversion to quinone by oxidation with $KMnO_4$ and H_2SO_4. However, the occurrence of betitol has never been confirmed and the structure remains uncertain [2]. Craigie and collaborators [4] isolated tetrol **2a** from the marine alga *Monochrysis lutheri* and described most of the physical data. Subsequently, they isolated tetrol **2a** from an alga of the genus *Porphyridium* [5]. Toxocarol isolated from a plant source (*Toxocarpus himalensis* Falc. Ex Hook. f.) was reported to be 1,4/2,3-cyclohexanetetrol [6]. One of the stereospecific syntheses for toxocarol started from 1,3-cyclohexadiene, and was reported in our previous study [7].

The first synthesis of tetrol **2a** presumably was performed by Zelinsky and Titowa [8]. They converted 1,4-cyclohexadiene (**1**) into a dioxide (mp 110 °C) which was hydrolyzed to a tetrol (monohydrate, mp 195 °C). This product probably corresponds to tetrol **2a**. Tetrol **2a** was also prepared by hydrogenolytic reduction of inositol dibromohydrins by McCasland and Horswill [9]. McCasland et al. [10,11] also synthesized tetrol **2a** beside a small proportion of *meso*-1,5/2,4-cyclohexanetetrol (**3**) by trans-hydroxylation of 1,4-cyclohexadiene (**1**), or of *trans*-cyclohexene-4,5-diol dibenzoate using the Prevost method. Craig et al. [12] also synthesized tetrol **2a** as a sole product by acidic

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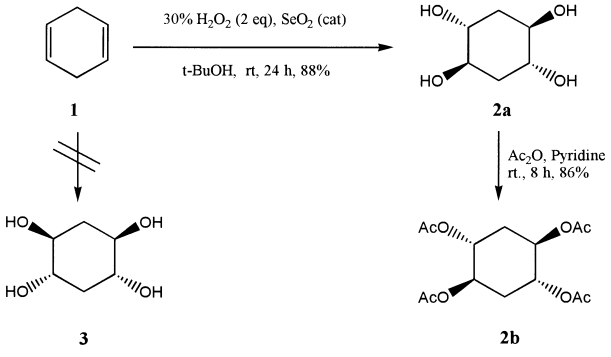
hydrolysis of *cis*- and *trans*-1,4-cyclohexadiene dioxide similar to Zelinsky's method. We now present a new and more efficient method to give tetrol **2a** by direct hydroxylation of 1,4-cyclohexadiene (**1**).

In our approach we focused on the hydroxylation of 1,4-cyclohexadiene (**1**) with H_2O_2 in the presence of SeO_2 (Scheme 1). By this method, the formation of a *trans*-diol was directly accomplished [13] presumably via a perselenious acid species. Recently, we reported on the synthesis of *proto*-quercitol and *vibo*-quercitol by hydroxylation of cyclohex-5-ene-1,4/2-triol [14] without anchimeric assistance using this method.

According to studies of Craig et al. [12], both *cis*- and *trans*-1,4-cyclohexadiene dioxide give only tetrol **2a**. We assumed that the SeO_2-catalyzed hydoxylation method also proceeded by an in situ epoxidation followed by acidic hydrolysis, generating tetrol **2a** directly by this method.

Indeed, hydroxylation of 1,4-cyclohexadiene (**1**) with two molar equivalents of 30% H_2O_2 in the presence of SeO_2 gave tetrol **2a** in a good yield (88%) as a sole product. Although compound **3** is also a possibly expected product as a result of the reaction, NMR analysis of the crude product did not show any signal that belongs to meso-1,5/2,4-cyclohexanetetrol (**3**). The structural assignment of **2a** was easily made by comparison of the ^1H NMR [11] and physical data with those previously published. Tetrol **2a** was converted to its tetraacetate **2b** for further structural proof; the NMR and physical data of **2b** were also in agreement with published values.

In conclusion, even though the SeO_2-catalyzed hydroxylation method with H_2O_2 has very restricted examples in the literature, in our present study, a new and very versatile application has been shown by synthesis of the racemic form of natural tetrol **2a** in only one step.



Scheme 1.

1. Experimental

(±)-1,4/2,5-Cyclohexanetetrol (**2a**).—To a stirred solution of selenium dioxide (5.6 mg, 0.63 mmol) in t-BuOH (7.5 mL) was added 1,4-cyclohexadiene (**1**) (2.00 g, 25 mmol). To the resulting mixture 30% H_2O_2 (5.60 g, 50 mmol) was added dropwise over 20 min at room temperature. Additionally, the mixture was stirred for 24 h at room temperature, then $NaHSO_3$ (500 mg) was added to reduce possibly unreacted H_2O_2. The solid precipitate was filtered, then washed with EtOH. The filtrates were combined and concentrated under reduced pressure to give a syrup. Hot EtOH (50 mL) was added to the syrup, and after filtration EtOH was evaporated to give 1,4/2,5-cyclohexanetetrol (**2a**) (3.26 g, 88%). Compound **2a** was recrystalized from absolute EtOH to afford a colorless crystalline product (mp 194–196 °C; lit. [4] [(+)-isomer] mp 205–207 °C (with decomp.), lit. [5] [(+)-isomer] mp 202–204.5 °C, lit. [9] mp 207.5–208 °C, lit. [10] mp 208 °C, lit. [12] mp from 191–193 to 196–197 °C). ^1H NMR (200 MHz, CD_3OD): δ 3.73 (m, 4 H), 1.84 (m, 4 H); ^{13}C NMR (50 MHz, CD_3OD): δ 73.47, 37.53. ^1H NMR (200 MHz, D_2O): δ 3.71 (m, 4 H), 1.78 (m, 4 H); ^{13}C NMR (50 MHz, D_2O): δ 74.42, 38.30. IR (KBr): ν 3285, 3004, 2953, 2927, 2493, 2417, 1497, 1370, 1217, 1063, 910 cm^{-1}.

(±)-1,4/2,5-Cyclohexanetetrol tetraacetate (**2b**).—Tetrol **2a** was acetylated with Ac_2O-pyridine as described in our published procedure for the synthesis of conduritol-E tetraacetate [15] to give **2b**; Yield: 86%; colorless syrup; mp 144–145 °C, recrystallized from CH_2Cl_2–hexane, lit. [10,11] mp 148 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 5.03 (m, 4 H), 2.03 (m, 4 H; s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.65, 71.09, 32.15, 22.90. IR (KBr): ν 2978, 1753, 1446, 1395, 1248, 1191, 1038, 936, 910 cm^{-1}.

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