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A novel and short synthesis of (1,4/2)-cyclohex-5-ene-triol and its conversion to (±)-*proto*-quercitol

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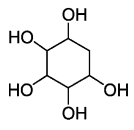
Abstract

(1,4/2)-Cyclohex-5-ene-triol was synthesized starting from cyclohexa-1,4-diene with two different approaches. Photooxygenation of cyclohexa-1,4-diene and epoxy-cyclohexene afforded *anti*-2,3-dioxabicyclo[2.2.2]oct-7-en-5-yl hydroperoxide and *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-yl hydroperoxide, respectively. Hydroperoxy endoperoxide was reduced with aqueous sodium bisulfite; hydroperoxy-epoxide with dimethylsulfide-titanium tetraisopropoxide to give 7-oxabicyclo[4.1.0]hept-4-en-3-ol. Acidic hydrolysis of the epoxy-alcohol gave the (1,4/2)-cyclohex-3-ene-triol. Oxidation of the double bond with $KMnO_4$ resulted in the formation of (±)-*proto*-quercitol.

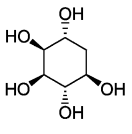
Keywords: Quercitol; Singlet oxygen; Ene-reaction; Endoperoxide; Hydroperoxide

1. Introduction

Highly oxygenated cyclohexene derivatives occur widely in the nature and usually possess a wide of interesting biological activities. Typical examples are conduritols,[1,2] quercitols[2,3] and inositols.[2,4] 'Quercitol' has been used as a generic term for cyclohexanepentols. Only three optically active forms of 16 stereoisomeric quercitols have been found in plants, namely (+)-*proto*-quercitol, (−)-*proto*-quercitol, and (−)-*vibo*-quercitol.[5]



Quercitol



DL-proto-Quercitol
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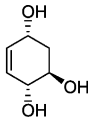

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The synthesis of *proto*-quercitol was accomplished by McCasland and coworkers[3b] using (−)-*chiro*-inositol, by Suami and coworkers[6] using (±)-1,2-anhydro-5,6-*O*-cyclohexylidene-*chiro*-inositol, and by Cambie and coworkers[7] using conduritol-A. In all previously reported syntheses, starting materials have been natural products or compounds which required many steps. Recently, we developed new, concise and convenient synthesis of *proto*-,[8a8b,8c,8d] *gala*-,[8b] *vibo*-,[8c] and *talo*-quercitols[8e] starting from 1,4-cyclohexadiene. In this paper, we describe two new syntheses for the cyclohexenetriol **2**,[9] which is a key compound for the synthesis of quercitols and their derivatives. The cyclohexenetriol **2** was prepared starting from cyclohexadiene and cyclohexene epoxide **4**[10] using photooxygenation as the key reaction.

2. Results and discussions

Cyclohexa-1,4-diene was used as the starting material for the synthesis of triol **2**. *m*-Chloroperbenzoic acid oxidation of **3** afforded epoxide **4**.[10] Tetraphenylporphyrin-sensitized photooxygenation[11] of cyclohexene epoxide **4** in methylene chloride at room temperature gave the epoxy-hydroperoxide **5** in 90% yield, via ene

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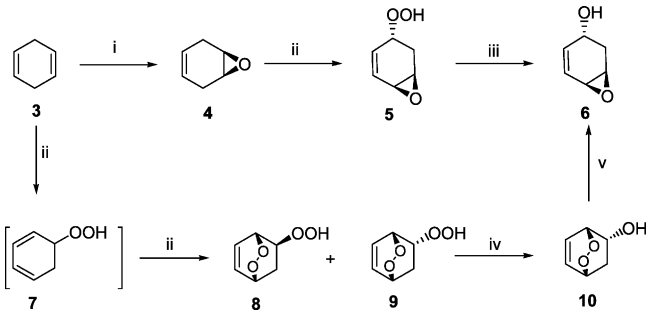


Scheme 1. (i) *m*-CPBA, CH_2Cl_2, $NaHCO_3$; (ii) TPP, *hv*, O_2, CH_2Cl_2, 90%; (iii) Dimethylsulfite, $Ti(Oi\text{-}Pr)_4$, $CHCl_3$, room temperature, 10 min, (93%) or $NaBH_4$, THF, 0 °C, 30 min, (75%) or $P(OEt)_3$; (iv) $P(OEt)_3$ (1.0 equiv), $CHCl_3$, −15 °C 1.5 h, 25 °C 2 h or Na_2SO_3, $CHCl_3$, −5 °C, 30 min; (v) $P(OEt)_3$ (2.5 equiv), $CHCl_3$, 0 °C 2 h, 25 °C, 18 h or Na_2SO_3, $CHCl_3$, −15 °C, 1 h, 25 °C, 19 h.

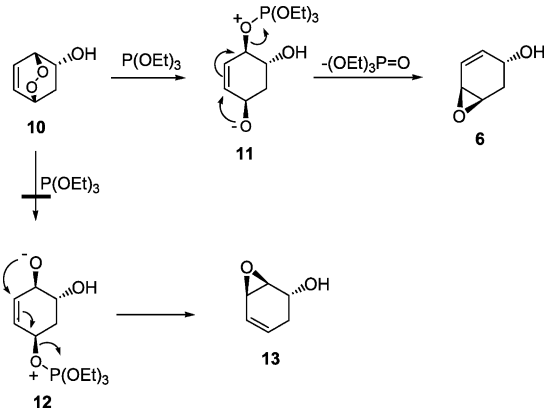
reaction of singlet oxygen, as the sole product (Scheme 1).

Structural assignment of hydroperoxy-epoxide **5** was made on the basis of 200 MHz ^1H and ^{13}C NMR spectral data. The most conspicuous feature in the ^1H NMR spectrum of the adduct **5** were three distinct AB systems which correspond to two olefinic protons, oxirane ring protons and methylenic protons. The ^{13}C NMR spectrum consisting of two sp^2 and four sp^3 carbon atoms supported also the proposed structure. In the next step, the hydroperoxy-epoxide **5** was reduced to the epoxy-alcohol **6** using dimethylsulfide-titanium tetraisopropoxide[12] (Scheme 1).

Without exception, allylic hydroperoxidation reaction has been found to proceed dependence on steric factors.[13] The allylic hydrogen's at the axial position are more reactive, because the orbital overlap between oxygen and allylic hydrogen's is optimum in such a conformation.[14] In the photooxidation reaction of **4**, singlet oxygen is quite sensitive to steric considerations and approaches the epoxide **4** exclusively, from the less congested side.

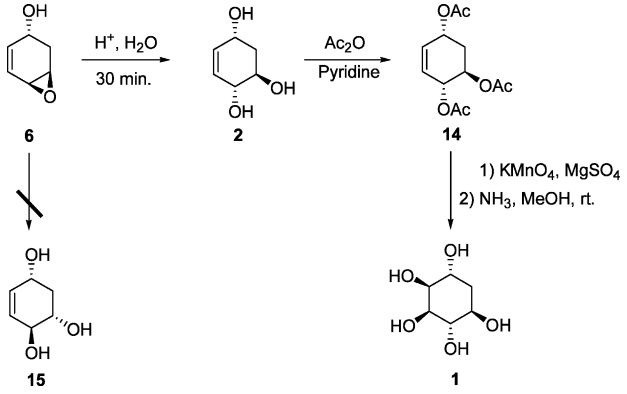
On the other hand, tetraphenylporphyrin sensitized photooxygenation of cyclohexa-1,4-diene in methylene chloride at room temperature resulted in the formation of the bicyclic endoperoxides **8** and **9** in a ratio of 12:88.[8b] The reaction mixture was chromatographed on silica gel column with 1:1 ether–petroleum ether as eluant and product mixture was separated (Scheme 1). Reductive extrusion of one oxygen atom with trivalent phosphorus compounds provides a convenient entry to the unsaturated epoxides.[11,13] Furthermore, it has been demonstrated that this reaction is stereospecific. The reduction of **9** was achieved by using triethyl phosphite. Two isomeric epoxy alcohols **6** and **13** were expected from this reduction reaction as depicted in Scheme 2.

For the formation of this epoxy-alcohol **6**, we propose the following mechanism. Since the hydroxy-endoperoxide **10** has no plane of symmetry, triethyl phosphite can attack both oxygen atoms in the peroxide linkage to form the intermediates **11** and **12**. The epoxy-alcohol **6** can be formed only from the intermediate **11**, whereas the other expected epoxy-alcohol **13** can be formed from **12**. However, the isomer **13** was not found. This indicates clearly that triethyl phosphite approaches the peroxide unit in **10** exclusively from the sterically more crowded face of the molecule. It is likely that the alcohol functionality in **10** plays an important role in the directing of triethyl phosphite by approach, probably by the formation of hydrogen bondings. Furthermore, the hydroperoxide and peroxide functionalities in **9** have been reduced successfully to hydroxyl endoperoxide **10** and to epoxy-alcohol **6** by Na_2SO_3 which shows also regioselectivity. Since only the oxygen–oxygen bond breaks in reduction of endoperoxide linkage in **9** as well as in **10**, it preserves the configuration at hydroxy carbon atoms.



Scheme 2.

After successful isolation and characterization of the epoxy-alcohol **6**, it was submitted to acid-catalyzed ring-opening reaction in acidified water (Scheme 3). Analysis of the reaction mixture has revealed that the triol **2**[8b] was formed as the sole product in quantitative yield. The isomeric triol **14** was not formed by this ring-opening reaction because water attacks the epoxide-ring only at



Scheme 3.

the allylic position. Acetylation of the hydroxyl group in **2** followed by $KMnO_4$ oxidation of the double bond and ammonolysis of acetate groups resulted in the formation of *proto*-quercitol **1** (Scheme 3).[8b]

In conclusion, two short and convenient methods for the synthesis of the epoxyalcohol **6** has been developed starting from cyclohexa-1,4-diene which has been converted to triol **2** and quercitol **1**. The presence of an epoxide ring in **6** provided an entry for the formation of amino alcohols which can be transformed to various aminoquercitol derivatives.

3. Experimental

3.1. General methods

Melting points were determined on a Thomas–Hoover Capillary melting point apparatus. Solvents were concentrated at reduced pressure. IR spectra were recorded on a Mattson 1000 FTIR. ^{1}H NMR spectra were recorded on 60 MHz (EM 360) and 200 MHz Varian-Gemini spectrometer and are reported in δ units with $SiMe_4$ as an internal standard. All column chromatography was performed on Silica Gel (60 Mesh, Merck) and alumina (neutral, activity-III, basic, activity-III).

3.2. Epoxidation of 1,4-cyclohexadiene with *m*-CPBA[9]

To a magnetically stirred solution of *m*-CPBA (10.78 g, 62.50 mmol) in 200 mL of CH_2Cl_2 at 0 °C, was added 1,4-cyclohexadiene (5 g, 62.50 mmol) and $NaHCO_3$ (7.5 g, 90 mmol). The reaction mixture was rapidly stirred for 1 h at 0 °C. The mixture was allowed to warm up to room temperature (rt) and then filtered. The solvent was rotovaparated (25 °C, 20 mmHg) and epoxy-cyclohexene **4** was distilled at 119–122 °C (colourless liquid, 3.6 g, 60%). 7-Oxabicyclo[4.1.0]hept-3-ene (**4**); ^{1}H NMR (200 MHz): δ 5.21 (s, 2 H), 2.97 (s, 2 H), 2.29 (AA′ BB′ system, 4 H). ^{13}C NMR (50 MHz): δ 123.3, 52.2, 26.9.

3.3. Photooxygenation of epoxy-cyclohexene 4

To a magnetically stirred solution of epoxy-cyclohexene **4** (3.0 g, 31.25 mmol) in 150 mL of $CHCl_3$ was added 30 mg tetraphenylporphyrin (TPP) as a sensitizer. The solution was irradiated with a projection lamp (500 W) at rt while continuously passing a slow stream of dry oxygen gas. The progress of the photooxygenation was monitored by thin layer chromatography (TLC) until total consumption of the starting material. After 36 h the reaction was completed. The solvent was evaporated (25 °C, 20 mmHg) and the residue was chromatographed on neutral alumina (10 g, Al_2O_3, activity-III) eluting with $CHCl_3$ to give *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-yl hydroperoxide (**5**); light yellow oil, 3.6 g, 90%; IR (neat): 3336, 3029, 2978, 1600, 1446, 1395, 1344, 1268, 1089, 1038, 1012, 910 cm^{-1}. ^{1}H NMR (200 MHz): δ 6.13 (ddd, 1 H, *J* 10.2, 5.2, 1.8 Hz), 6.03 (dd, *J* 10.2, 1.9 Hz), 4.58 (m, 1 H), 3.53 (ddd, 1 H, *J* 7.6, 2.4, 1.2 Hz), 3.28 (ddd, 1 H, *J* 7.6, 3.4, 1.8 Hz), 2.58 (ddd, 1 H, *J* 14.1, 7.8, 2.4 Hz) 1.43 (ddd, 1 H, *J* 14.2, 10.2, 1.4 Hz), 8.30 (s, 1 H). ^{13}C NMR (50 MHz): δ 135.5, 126.5, 78.6, 53.6, 49.1, 27.3.

3.4. Deoxygenation of the hydroxy-epoxide 5 with titanium tetraisopropoxide (Ti(O*i*-Pr)$_4$)-dimethyl sulfite

To a magnetically stirred solution of the hydroperoxy-epoxide **5** (1 g, 7.8 mmol) in 150 mL of $CHCl_3$ at −5 °C was added dimethyl sulfide (0.96 g, 15.6 mmol) and titanium tetraisopropoxide (19.0 mg, 0.065 mmol). The reaction mixture was stirred for 10 min and 30 μL water was added to reaction mixture. Evaporation of solvents (40 °C, 20 mmHg) and chromatography of residue on neutral alumina (50 g, Al_2O_3, activity-III) eluting with 80:20 hexane–Et_2O gave as only product *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-ol (**6**). IR (neat): 3412, 3055, 3029, 2953, 2851, 1446, 1421, 1344, 1268, 1089, 1012, 961 cm^{-1}; colourless liquid, 0.81 g, 93%. ^{1}H NMR (200 MHz): δ 5.90 (ddd, 1 H, *J* 10.0, 3.7, 2.2 Hz), 5.83 (d, 1 H *J* 10.0 Hz), 4.24 (m, 1 H), 3.24 (m, 1 H), 3.44 (m, 1 H), 2.68 (ddd, *J* 1 H 14.0, 7.8, 2.6 Hz), 1.48 (dd, 1 H, *J* 14.0, 10.0 Hz); ^{13}C NMR (50 MHz): δ 140.3, 125.1, 65.6, 53.3, 48.7, 32.6. Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.03.

3.5. Deoxygenation of the hydroxy-epoxide 5 with triethyl phosphite

To a magnetically stirred solution of the hydroperoxy-epoxide **5** (1 g, 7.8 mmol) in 150 mL of $CHCl_3$ at 0 °C was added drop wise a solution of triethyl phosphite (1.55 g, 9.3 mmol) in 30 mL of $CHCl_3$ over 1 h. After the addition was complete, the reaction mixture was stirred for additional 1 h at rt. Evaporation of the solvent (30 °C, 20 mmHg) and chromatography of residue on a neutral alumina (100 g, Al_2O_3, activity-III) eluting with 85:15 hexane–EtOAc gave the *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-ol (**6**) (0.34 g, 40%).

3.6. Deoxygenation of the hydroxy-epoxide 5 with $NaBH_4$

To a magnetically stirred solution of the hydroperoxy-epoxide **5** (1 g, 7.8 mmol) in 150 mL of dry THF at 0 °C was added powder $NaBH_4$ (0.6 g, 15.6 mmol). The reaction mixture was stirred for additional 30 min and water (3 mL) was added slowly drop wise at 0 °C. The reaction mixture was filtered and 100 mL of water was added. The aqueous solution was extracted with EtOAc (3 × 50 mL) and the extracts were dried (Na_2SO_4).

Evaporation of the solvent gave *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-ol (**6**) (0.63 g, 75%).

3.7. Deoxygenation of hydroperoxy-endoperoxide 9[8b] with triethyl phosphite

a) To a stirred solution of hydroperoxy-endoperoxide **9** (380 mg, 2.64 mmol) in $CHCl_3$ (30 mL) at 0 °C was added drop wise triethyl phosphite (1096 mg, 6.60 mmol) during 2 h. After the addition was complete, the reaction mixture was stirred for additional 18 h at rt. The ^1H NMR spectrum of the mixture showed that the ratio of **6**:**10** was 3:2. Evaporation of the solvent (30 °C, 20 mmHg) and chromatography of the residue on a basic alumina column (100 g, Al_2O_3, activity-III) eluting with 95:5 hexane–EtOAc gave the epoxy-alcohol **6** as the first fraction (89 mg, 30%) and hydroxy-endoperoxide **10** as the second fraction (30 mg, 9%).

b) To a stirred solution of the hydroperoxy-endoperoxide **9** (300 mg, 2.08 mmol) in $CHCl_3$ (20 mL) at −15 °C was added drop wise triethyl phosphite (346 mg, 2.08 mmol) for 1.5 h. After the addition was complete, the reaction mixture was stirred for additional 2 h at rt. The ^1H NMR spectrum of the mixture showed that the presence of only *anti*-2,3-dioxabicyclo[2.2.2]oct-7-en-5-ol (**10**)[12]: colourless solid; mp 104–105 °C from ether (45%).

3.8. Reduction of the hydroperoxy-endoperoxide 9 with aqueous sodium bisulfite

a) To a stirred solution of the hydroperoxy-endoperoxide **9** (1.0 g, 6.94 mmol) in $CHCl_3$ (30 mL) at −5 °C was added drop wise 1 M Na_2SO_3 (6.9 mL, 6.94 mmol) within approx. 5 min. The reaction was completed in 30 min 5 mL of satd NaCl solution was added to the mixture and extracted with $CHCl_3$ (4×20 mL). The combined organic extracts were dried (Na_2SO_4). Removing of the solvent under reduced pressure and recrystallization of product from ether gave **10** (450 mg, 51%).

b) To a magnetically stirred $CHCl_3$ solution (30 mL) of hydroperoxy-endoperoxide **9** (1.0 g, 6.94 mmol) was added drop wise a solution of 1 M Na_2SO_3 (8.0 mL, 8.0 mmol) at 15 °C. The reaction mixture was stirred at 15 °C for 1 h and then for additional 19 h at rt. The reaction mixture was worked up as described above and the residue was purified by column chromatography on neutral alumina (20 g, Al_2O_3, activity-III), eluting with $CHCl_3$, affording pure *anti*-7-oxabicyclo[4.1.0]hept-4-en-3-ol (**6**) (310 mg, 40%).

3.9. (1,4/2)-Cyclohex-5-ene-triol (2)

The epoxy-alcohol **6** (200 mg, 1.78 mmol) was added to 20 mL of 1.0 N H_2SO_4 solution. The reaction mixture was stirred for 30 min at rt and 8.0 g $BaCO_3$ added and then stirred for additional 30 min at the given temperature. The residue was filtered. Evaporation of the solvent under reduced pressure and then recrystallization of product from abs CH_3OH gave **2** (220 mg, 95%, colourless solid, mp[8b] 76–78 °C). ^1H NMR (200 MHz, D_2O): δ 5.75 (bd, 1 H, J 10.5 Hz); 5.66 (dd, 1 H, J 10.5, 1.8 Hz), 4.28 (bq, 1 H, J 3.8 Hz), 3.91 (ddd, 1 H, J 7.2, 1.7, 1.4 Hz), 3.73 (ddd, J 1 H 11.9, 7.2, 4.7 Hz), 1.82 (m, 1 H); ^{13}C NMR (50 MHz, D_2O): δ 133.8, 132.3, 74.3, 71.4, 67.1, 38.7.

3.10. (1,4/2)-Triacetoxy-5-cyclohexene (14)

The triacetate **14** was prepared as in Ref. 8b. The synthesis of (±)-*proto*-quercitol **1** was accomplished as described in Lit. 8b.

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