An Efficient and Highly Stereoselective Synthesis of *gala*-Quercitol from 1,4-Cyclohexadiene

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Abstract: *gala*-Quercitol was synthesized from 1,4-cyclohexadiene in seven steps and overall yield of 68%. Reaction of 5,6-dibromo-2,2-dimethylhexahydro-1,3-benzodioxole, synthesized from 1,4-cyclohexadiene in three steps, with excess NaOMe gave (3aα,5α,7aα)-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole. *cis*-Hydroxylation of the benzodioxole followed by acetylation with AcCl gave 5-*O*-methyl-*gala*-quercitol tetraacetate from which *gala*-quercitol was obtained by hydrolysis and demethylation with aq HBr (47%).

Key words: alcohols, quercitol, cyclohexol, cyclitol, hydroxylation, eliminations, stereoselective synthesis

In our ongoing research of cyclitol syntheses,[1] we have successfully used cyclohexadienes to prepare many natural cyclitols and some of their synthetic derivatives. For this purpose, readily available 1,4-cyclohexadiene was used as the starting material to prepare conduritol-A,[2] conduritol-F,[3] *proto*-quercitol,[4a–c] *vibo*-quercitol,[4b,5] *talo*-quercitol,[5] and 1,4/2,5-cyclohexanetetrol.[6] Again, 1,3-cyclohexadiene was used for the preparation of toxocarol,[7] a natural cyclohexanetetrol, and some other cyclohexanetetrols.[8] In our previous research,[4c] photooxygenation of 1,4-cyclohexadiene gave a mixture of *anti*- and *syn*-2,3-dioxabicyclo[2.2.2]oct-7-en-5-ylhydroperoxide from which the corresponding triols **1** and **2**[9] were readily obtained by reduction with thiourea or $LiAlH_4$. Acetylation of **1** followed by *cis*-hydroxylation gave *proto*-quercitol **3**, while the same proceeding for **2** gave *gala*-quercitol **4** (Figure 1).

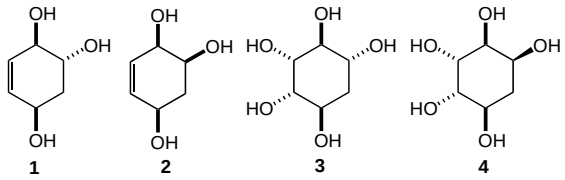
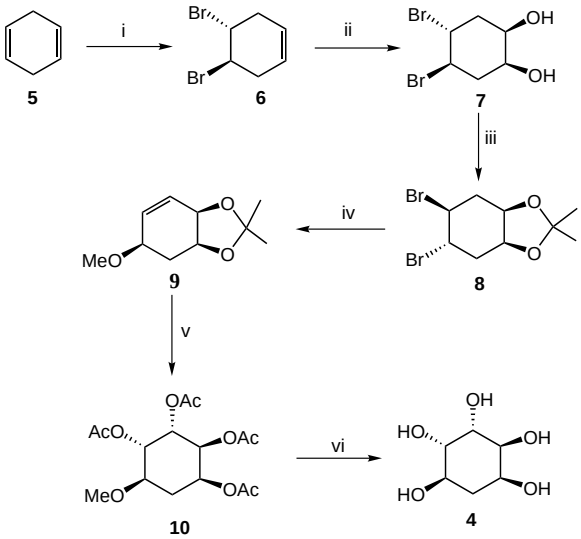


Figure 1

So far, many synthetic procedures for *gala*-quercitol **4** have been described in the literature. For this purpose, conduritol-A epoxide,[10] L-bromoquercitol,[11] pinitol,[12] silyl-2,5-cyclohexadiene,[13] D-galactose,[14] 6-(benzyloxy)-3-cyclohexen-1-ol,[15] which required a multi-step synthesis, were used as the starting material. In particular, over the last number of years, we have been developing a general strategy for the synthesis of polyhydroxylated cyclohexanes. In this work, we present a convenient and stereospecific synthesis of *gala*-quercitol starting from 1,4-cyclohexadiene in high yield.



Scheme 1 *Reagents and conditions*: (i) Br_2, hexane, –45 °C, 95%; (ii) OsO_4, NMO, acetone–H_2O, 90%; (iii) 2,2-Dimethoxypropane, TsOH, 97%; (iv) NaOMe, MeOH, r.t., 96%; (v) OsO_4, NMO, acetone–H_2O; then AcCl, 95%; (vi) 47% HBr, r.t., 97%.

Our synthesis is outlined in Scheme 1. Bromo ketal **8**, the key compound of the synthesis, was prepared by slight modification of the procedure described by Yang et al.[16] Bromination of 1,4-cyclohexadiene (**5**) at –45 °C followed by OsO_4-catalyzed *cis*-hydroxylation with *N*-methylmorpholine oxide (NMO) gave dibromo diol **7** from which the corresponding dibromo ketal **8** was obtained by ketalisation with 2,2-dimethoxypropane. The reaction of the ketal **8** with excess of NaOMe gave the methoxy compound **9** as the sole product. All ^1H- and ^{13}C NMR data of **9** were in agreement with the proposed structure. OsO_4-catalyzed *cis*-hydroxylation of **9** with NMO followed by acetylation with acetyl chloride gave methoxytetraacetate **10**. Hydrolysis and demethylation of methoxytetraacetate **10** with aq HBr (47%) afforded *gala*-quercitol **4** in 95%

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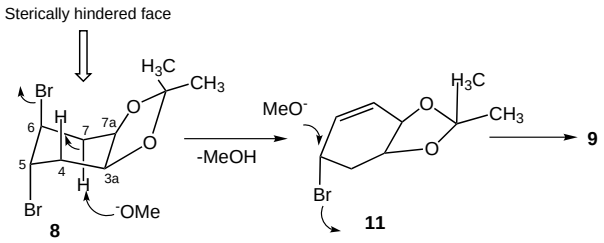
yield (Scheme 1). We especially point out that all steps proceed with yields over 90%.

The formation of **9** as the sole product may be questioned. A similar elimination reaction was previously observed by treatment of 1,2-dibromocyclohexane with NaOMe to give 3-methoxycyclohexene[17] as the major product in a yield of 60%.

The first step in the formation of **9** is the HBr elimination. As seen from Scheme 2, two bromine atoms at C5 and C6 are suitable for the elimination reaction. However, the top face of the molecule is sterically hindered for the abstraction of axial protons $H4_{axial}$ by the *syn*-methyl group of the ketal functionality. Therefore, the base attacks exclusively the proton $H7_{axial}$ to give the allylic bromide **11** with an *anti*-configuration of the bromine atom. An S_N2 attack of methoxide at C5 results in the formation of the key compound **9**, where the methoxyl and ketal group have the desired configuration for the synthesis of *gala*-quercitol.



Scheme 2

In summary, with relatively little synthetic effort we have achieved the stereoselective synthesis of DL-*gala*-quercitol in seven steps starting from commercially available 1,4-cyclohexadiene (overall yield of 68%) and introduced the complex stereochemistry in a very simple way. We suppose that **9** may be used as a versatile precursor for preparation of different cyclitol derivatives.

Mps are uncorrected. IR spectra were obtained from KBr pellets on a Mattson 1000 FT-IR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian 200 MHz spectrometer. Apparent splittings are given in all cases. Column chromatography was performed on silica gel (60–200 mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates.

4,5-Dibromocyclohexene (6)[16,18]

To a stirred solution of 1,4-cyclohexadiene (35.0 g, 0.44 mol) in hexane (600 mL) was added dropwise a solution of bromine (70.0 g, 0.44 mol) in hexane (200 mL) at –45 °C over 4 h. After bromine addition was completed, the mixture was warmed to r.t. The precipitate was filtered off and discarded. Evaporation of the solvent under reduced pressure gave 4,5-dibromocyclohexene.

Yield: 100.3 g (95% isolated yield); white crystals; mp 34–36 °C (lit.[16] 34–37 °C).

^1H NMR (200 MHz, $CDCl_3$): δ = 5.65 (m, 2 H), 4.58 (m, 2 H), 3.17 (dm, A part of AB system, *J* = 20 Hz), 2.60 (dm, B part of AB system, 2 H, *J* = 20 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.0, 50.5, 33.0.

[1*R*(*S*),2*S*(*R*),4*S*(*R*),5*S*(*R*)]-4,5-Dibromocyclohexane-1,2-diol (7)[16]

A 50 mL three-necked, round-bottomed flask equipped with a magnetic stirrer and a nitrogen inlet, was charged with NMO (0.91 g, 7.78 mmol), H_2O (10 mL), and acetone (5.0 mL). To this solution were added OsO4 (ca. 20 mg) and 4,5-dibromocyclohexene (**6**) (1.61 g, 6.7 mmol). The resulting mixture was stirred vigorously under nitrogen at r.t. During the overnight stirring, the reaction mixture became homogeneous. After 24 h, the reaction was complete. Sodium hydrosulfite (1.0 g) and Florisil (5 g) slurried in H_2O (2 mL) were added, the slurry was stirred for 10 min, and the mixture was filtered through Celite (10 g). The pH of the filtrate was adjusted to 3 using aq HCl (0.5 M). Acetone was removed under reduced pressure (25 mmHg, 30 °C). The organic phase was extracted with EtOAc (3 × 50 mL) and dried (Na_2SO_4). Removal of the solvent gave *trans*-4,5-dibromocyclohexane-*cis*-1,2-diol (**7**).

Yield: 1.65 g (90%); mp 103–104 °C (recrystallized from CH_2Cl_2) (lit. mp 103–105 °C[14]).

^1H NMR (200 MHz, $CDCl_3$): δ = 4.40–3.80 (m, 4 H), 3.70 (br s, 1 H), 3.13 (br s 1 H), 2.60–1.99 (m, 4 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 72.3, 72.1, 56.9, 56.1, 44.3, 42.1.

[3a*R*(*S*),5*S*(*R*),6*S*(*R*),7a*S*(*R*)]-5,6-Dibromo-2,2-dimethylhexahydro-1,3-benzodioxole (8)[16]

To a solution of *trans*-4,5-dibromocyclohexane-*cis*-1,2-diol (**7**) (2.57 g, 9.38 mmol) in CH_2Cl_2 (50 mL) was added 2,2-dimethoxypropane (1.30 g, 12.5 mmol) and TsOH (100 mg). The mixture was stirred at r.t. for 3 h. The solution was filtered over basic Al_2O_3 (10 g). Evaporation of the solvent gave ketal **8**.

Yield: 2.85 g (97%); colorless oil.

^1H NMR (200 MHz): δ = 4.39 (dt, 1 H, *J* = 7.5, 4.0 Hz), 4.29–4.09 (m, 3 H), 2.70 (dt, 2 H, *J* = 15.0, 4.0 Hz), 2.32 (ddd, 1 H, *J* = 15.0, 7.9, 6.2 Hz), 2.18 (ddd, 1 H, *J* = 14.9, 8.3, 5.0 Hz), 1.49 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (50 MHz): δ = 110.9, 74.6, 74.1, 53.2, 51.0, 38.3, 36.8, 30.2, 28.5.

(3aα,5α,7aα)-5-Methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydro-1,3-benzodioxole (9)

To magnetically stirred MeOH (50 mL) was added sodium (0.50 g, 21.7 mmol) and then a solution of **8** (2.00 g, 6.37 mmol) in MeOH (5 mL) at r.t.. The reaction mixture was stirred at r.t. for 6 h. After removal of MeOH at reduced pressure the residue was dissolved in CCl_4 and the solution filtered over an Al_2O_3 (basic, 10 g) column. Removal of the solvent gave **9**.

Yield: 1.13 g (96%); colorless oil.

IR: 3037, 2987, 2933, 2825, 1381, 1316, 1247, 1216, 1170, 1143, 1112, 1062, 1008, 958 cm^{-1}.

^1H NMR (200 MHz) δ = 5.93–5.96 (dm, A part of AB system, 1 H, *J* = 11.0 Hz), 5.81 (ddd, B part of AB system, 1 H, *J* = 11.0, 3.5, 2.0 Hz), 4.35–4.37 (m, 1 H), 4.17 (dt, 1 H, *J* = 10.9, 5.4 Hz), 3.67–3.71 (m, 1 H), 3.31 (s, 3 H), 2.23–2.14 (m, 1 H), 1.50–1.39 (m, 1 H), 1.38 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR (200 MHz): δ = 136.4, 126.3, 111.5, 76.2, 74.3, 72.7, 57.7, 34.2, 30.3, 28.0.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.88; H, 8.56.

5-*O*-Methyl-*gala*-quercitol Tetraacetate (10)

To a solution of NMO (1.39 g, 11.9 mmol) in H_2O (5 mL) was added methoxy ketal **9** (2.00 g, 10.9 mmol). Under N_2 atmosphere, OsO_4 (19 mg) was added and the resulting mixture was stirred for

24 h. The solvent was removed under reduced pressure (25 mmHg; 70 °C). Without further purification, the crude product was submitted to acetylation. For this purpose, acetyl chloride (5 mL) was added to the residue. The reaction mixture was stirred for 24 h. The excess of unreacted acetyl chloride was evaporated (25 mmHg, 40 °C). The residue was dissolved in CCl_4 and filtered over basic Al_2O_3. Evaporation of solvent gave **10**.

Yield: 3.57 g (95%); mp 96–98 °C (colorless crystals from EtOAc).

IR (CH_2Cl_2): 3029, 3004, 2953, 2902, 2851, 1779, 1676, 1472, 1395, 1242, 1165, 1140, 1089, 987 cm^{-1}.

^1H NMR (200 MHz): δ = 5.33 (dd, 1 H, *J* = 5.9, 3.3 Hz), 5.20–5.10 (m, 3 H), 3.51 (dt, 1 H, *J* = 8.4, 4.4), 3.34 (s, 3 H, *O*-methyl), 2.18–1.81 (m, 2 H), 2.05 (s, 3 H, methyl), 2.04 (s, 3 H, methyl), 2.00 (s, 3 H, methyl), 1.98 (s, 3 H, methyl).

^{13}C NMR (50 MHz): δ = 172.1, 171.8, 171.4, 171.2, 77.0, 73.2, 70.5, 69.4, 59.3, 30.6, 22.8 (2 C), 22.6 (2 C).

Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 51.86; H, 6.37.

***gala*-Quercitol (4)**

To a aq HBr (47%; 5 mL) was added the tetraacetate **10** (0.50 g, 1.45 mmol). The mixture was stirred at r.t. for 72 h. Removal of the excess H_2O and HBr under reduced pressure (25 mmHg, 70 °C) gave *gala*-quercitol (**4**).

Yield: 0.23 g (97%); mp 256–258 °C (colorless crystals from abs. EtOH).

^1H and ^{13}C NMR data of **4** are in agreement with data reported previously by us.[4c]

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