Synthesis and Epoxidation of Methyl *trans*-5,6-Diacetoxy-1,3-cyclohexadiene-1-carboxylate

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Synopsis. The (±)-methyl 1,3-cyclohexadiene-1-carboxylate, a useful intermediate for synthesis of derivatives of shikimic acid, was prepared by bromination of (±)-methyl (1,3/2)-2,3-diacetoxy-4-cyclohexene-1-carboxylate, followed by debromination of the major dibromide obtained with zinc dust. Epoxidation of the diene with peracid gave selectively two 3,4-monoepoxides.

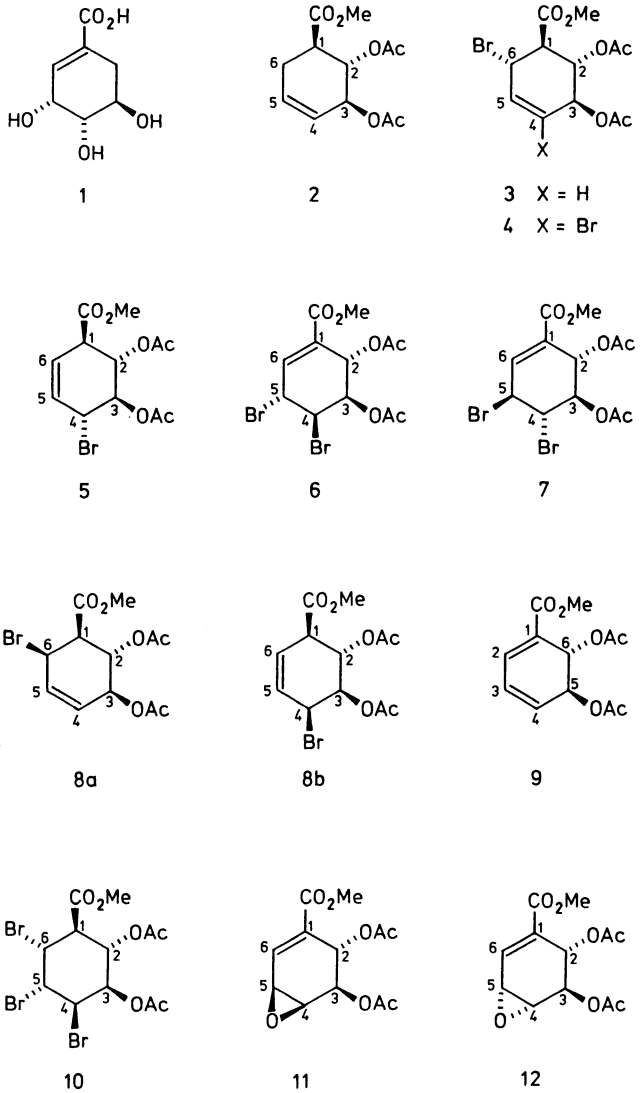
Shikimic acid (**1**) occupies an important position in biosynthesis (shikimate pathway) of aromatic amino acids in nature.[1,2] On the other hand, some related compounds derived from **1**, viz. glyoxalase I inhibitor,[3] rancinamycins,[4] dioxolamycin,[5] etc., have been known to possess an interesting biological activity. We now describe a synthesis of the title compound, substituted (±)-methyl 1,3-cyclohexadiene-1-carboxylate, a versatile precursor for preparation of derivatives[2,6] of shikimic acid and analogs of naturally occurring cyclohexene oxides.[7]

Bromination of (±)-methyl (1,3/2)-2,3-diacetoxy-4-cyclohexene-1-carboxylate[8] (**2**) with 2 molar equiv of *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of a trace amount of α,α'-azobisisobutyronitrile (AIBN) at reflux temperature for 2 h produced one major and four minor components. The products were separated by chromatography on silica gel to give two monobromides **3** (5%) and **5** (4%), and three dibromides **4**[9] (2%), **6** (50%), and **7**[10] (7%). Their structures were deduced on the basis of the previous results[11] on the reaction of the corresponding benzoyloxy and bromomethyl derivatives[12] with NBS, and finally confirmed by the ^{1}H NMR spectra (data in Experimental).

Mechanistically, four monobromides **3**, **5**, **8a**, and **8b** are considered to be formed initially by allylic bromination. The highly unstable isomer **8a**, in which the bromo group exists in quasi-axial position and cis to the 1-methoxycarbonyl group, readily undergoes elimination of hydrogen bromide to yield a diene **9**, which rapidly reacts with bromine generated in situ to give the dibromides **6** and **7**. The formation of the dibromide **4** might be deduced that the monobromide **3** possibly reacts with bromine to give a tribromide **10** which is convertible to **4** by elimination of hydrogen bromide under these reaction conditions or during chromatography on a silica-gel column.

Debromination of **6** was effected by treatment with zinc dust in acetic acid to give 83% yield of the diene **9**[13] as crystals. When ethanol was used as a solvent, partial *O*-deacetylation occurred to produce a mixture of two monoacetates and dihydroxy compound, together with a low yield of **9**. Since racemic **2** can readily be optically resolved,[14] and the absolute configurations of both enantiomers have already been established, it may be possible to provide optically active **9**.

In order to demonstrate the reactivity of the diene system, oxidation of **9** with equimolar *m*-chloroperbenzoic acid (MCPBA) was carried out in dichloromethane in the presence of phosphate buffer (pH 8) at room temperature. Two monoepoxides **11** (13%) and **12** (45%) were obtained selectively, and the structures were confirmed on the basis of the ^{1}H NMR spectra. The favored conformation of **11**, deduced by consideration of $J_{2,3}$ (7.5 Hz), would adopt the twist form with the 2- and 3-OAc groups being oriented in diequatorial positions. On the other hand, two acetoxyl groups of **12** seems to situate in diaxial positions ($J_{2,3}$=2.3 Hz). Each conformation is compatible with that of the corresponding benzoyloxymethyl derivatives.[11]



Experimental

Melting points were determined in an open capillary tube in a MEL-TEMP melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in chloroform-*d* solution with tetramethylsilane as an internal standard. The peak positions are given in δ values. TLC was performed on precoated silica gel 60 F-254 (E. Merck, Darmstadt; 0.2 mm thickness). The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka; 300 mesh). Organic solutions were concentrated below 30 °C under reduced pressure.

Bromination of (±)-Methyl (1,3/2)-2,3-Diacetoxy-4-cyclohexene-1-carboxylate (2) with NBS. A mixture of **2**[8] (0.50 g, 2.0 mmol), NBS (0.71 g, 4.0 mmol), AIBN (5 mg), and carbon tetrachloride (10 ml) was refluxed under nitrogen atmosphere for 2 h. TLC (2-butanone-toluene 1 : 5) showed a disappearance of **2** (R_f 0.46), and a formation of one major (R_f 0.56) and several minor components (R_f 0.67, 0.63, 0.50, and 0.46). Succinimide formed was removed by filtration and the filtrate was concentrated. The residue (0.98 g) was chromatographed on silica gel (50 g) with 2-butanone-toluene (1 : 20) as eluent to give as the first fraction (±)-methyl (1,3/2,6)-2,3-diacetoxy-4,6-dibromo-4-cyclohexene-1-carboxylate (**4**) (22 mg, 2%) as crude crystals (from ethanol): Mp 112—113 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s) and 2.07 (3H, s) (OAc), 3.44 (1H, dd, $J_{1,2}$=9 Hz, $J_{1,6}$=7.2 Hz, H-1), 3.75 (3H, s, CO_2Me), 5.00 (1H, ddd, $J_{3,6}$=2.3 Hz, $J_{5,6}$=3.3 Hz, H-6), 5.36 (1H, dd, $J_{2,3}$=6 Hz, H-2), 5.66 (1H, ddd, $J_{3,5}$=1.3 Hz, H-3), 6.49 (1H, dd, H-5).

The above mother liquid of **4** was concentrated and the residue was rechromatographed on silica gel (8 g) with acetone-hexane (1 : 15) as eluent to give (±)-methyl (2,4/3,5)-2,3-diacetoxy-4,5-dibromo-6-cyclohexene-1-carboxylate (**7**) (57 mg, 7%) as a syrup contaminated with an unidentified compounds. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s) and 2.10 (3H, s) (OAc), 3.81 (3H, s, CO_2Me), 4.54 (1H, dd, $J_{3,4}$=7.5 Hz, $J_{4,5}$=5.3 Hz, H-4), 5.01 (1H, br dd, $J_{5,6}$=3 Hz, H-5), 5.32 (1H, dd, $J_{2,3}$=4.5 Hz, H-3), 5.87 (1H, br dd, $J_{2,6}$=1.5 Hz, H-2), 7.13 (1H, br dd, H-6).

The second fraction (R_f 0.56) gave a syrup which crystallized from ethanol to give (±)-methyl (2,5/3,4)-2,3-diacetoxy-4,5-dibromo-6-cyclohexene-1-carboxylate (**6**) (0.40 g, 50%) as prisms: Mp 115—116 °C. ^{1}H NMR ($CDCl_3$) δ=2.07 (3H, s) and 2.12 (3H, s) (OAc), 3.80 (3H, s, CO_2Me), 4.57 (1H, dd, $J_{3,4}$=2.7 Hz, $J_{4,5}$=4 Hz, H-4), 4.97 (1H, t, $J_{5,6}$=4 Hz, H-5), 5.49 (1H, dd, $J_{2,3}$=6.5 Hz, H-3), 6.03 (1H, d, H-2), 7.10 (1H, d, H-6).

Found: C, 34.97; H, 3.45; Br, 38.83%. Calcd for $C_{12}H_{14}Br_2O_6$: C, 34.81; H, 3.41; Br, 38.60%.

The third fraction (R_f 0.50) gave a syrup which crystallized from ethanol to give (±)-methyl (1,3/2,4)-2,3-diacetoxy-4-bromo-5-cyclohexene-1-carboxylate (**5**) (27 mg, 4%) as needles: Mp 91.5—93 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (3H, s) and 2.08 (3H, s) (OAc), 3.53 (1H, ddd, $J_{1,2}$=8.8 Hz, $J_{1,5}$=2.5, $J_{1,6}$=1.8 Hz, H-1), 3.74 (3H, s, CO_2Me), 4.06 (1H, ddd, $J_{3,4}$=7 Hz, $J_{4,5}$=2.5 Hz, $J_{4,6}$=1.8 Hz, H-4), 5.38—5.47 (2H, m, H-2 and H-3), 5.72 (1H, dt, $J_{5,6}$=10 Hz, H-6), 5.99 (1H, dt, H-5).

Found: C, 43.13; H, 4.59; Br, 23.97%. Calcd for $C_{12}H_{15}BrO_6$: C, 43.01; H, 4.51; Br, 23.84%.

The last fraction was concentrated to give a syrup (0.22 g) which was rechromatographed on silica gel (13 g) with acetone-hexane (1 : 5) as eluent to give as a major component (±)-methyl (1,3/2,6)-2,3-diacetoxy-6-bromo-4-cyclohexene-1-carboxylate (**3**) (32 mg, 5%) as needles (from benzene-hexane): Mp 78—79 °C. ^{1}H NMR ($CDCl_3$) δ=2.03 (6H, s, 2 OAc), 3.29 (1H, dd, $J_{1,2}$=10.5 Hz, $J_{1,6}$=9 Hz, H-1), 3.75 (3H, s, CO_2Me), 5.01 (1H, ddd, $J_{4,6}$=1.5 Hz, $J_{5,6}$=2.7 Hz, H-6), 5.24 (1H, dd, $J_{2,3}$=7.2 Hz, H-2), 5.47—5.66 (2H, m, H-3 and H-4), 6.03 (1H, dt, $J_{3,5}$=2.7 Hz, $J_{4,5}$=10 Hz, H-5).

Found: C, 43.22; H, 4.57; Br, 23.90%. Calcd for $C_{12}H_{15}BrO_6$: C, 43.01; H, 4.51; Br, 23.84%.

(±)-Methyl *trans*-5,6-Diacetoxy-1,3-cyclohexadiene-1-carboxylate (9). To a stirred solution of **6** (100 mg, 0.24 mmol) in acetic acid (1.0 mL) was added portionwise zinc dust (63 mg, 0.96 matom) at room temperature. After 10 min, TLC (2-butanone-toluene 1 : 5) showed a disappearance of **6** and formation of a single component (R_f 0.41). An insoluble material was removed by filtration and washed with ether (15 ml). The filtrate and washing were combined and washed successively with water, saturated sodium hydrogen carbonate, and aqueous sodium chloride, dried, and concentrated. The residual syrup (80 mg) was crystallized from aqueous ethanol to give **9** (52 mg, 83%) as prisms: Mp 80—81 °C. ^{1}H NMR ($CDCl_3$) δ=2.04 (6H, s, 2 OAc), 3.80 (3H, s, CO_2Me), 5.27 (1H, dd, $J_{4,5}$=4.5 Hz, $J_{5,6}$=1.7 Hz, H-5), 5.92 (1H, d, H-6), 6.33 (2H, m, H-3 and H-4), 7.28 (1H, dd, $J_{2,3}$=4.5, $J_{2,4}$=1.5 Hz, H-2).

Found: C, 56.46; H, 5.53%. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55%.

Epoxidation of 9 with MCPBA. A mixture of **9** (110 mg, 0.43 mmol), MCPBA (0.13 g, ca. 0.43 mmol), dichloromethane (3 ml), and phosphate buffer (pH 8, 3 ml) was stirred vigorously at room temperature for 3 d. TLC (ethyl acetate-hexane 1 : 3) showed a formation of one major (R_f 0.20) and one minor component (R_f 0.23). The mixture was diluted with dichloromethane (20 ml) and the solution was washed with aqueous 10% sodium thiosulfate, saturated sodium hydrogencarbonate, and water, and dried and concentrated. The residual syrup (0.11 g) was chromatographed on silica gel (5 g) with ethyl acetate-hexane (1 : 4) as eluent to give as a first fraction (±)-methyl 2,3-di-*O*-acetyl-4,5-anhydro-(2/3,4,5)-2,3,4,5-tetrahydroxy-6-cyclohexene-1-carboxylate (**11**) (15 mg, 13%) as prisms: Mp 82—84 °C (from ethanol). ^{1}H NMR ($CDCl_3$) δ=2.00 (3H, s) and 2.13 (3H, s) (OAc), 3.53 (1H, t, $J_{4,5}$= $J_{5,6}$=3.3 Hz, H-5), 3.64 (1H, dd, $J_{3,4}$=1.5 Hz, H-4), 3.74 (3H, s, CO_2Me), 5.33 (1H, dd, $J_{2,3}$=7.5 Hz, H-3), 5.88 (1H, dd, $J_{2,6}$=2.3 Hz, H-2), 7.05 (1H, dd, H-6).

Found: C, 53.36; H, 5.24%. Calcd for $C_{12}H_{14}O_7$: C, 53.34; H, 5.22%.

The second fraction gave (±)-methyl 2,3-di-*O*-acetyl-4,5-anhydro-(2,4,5/3)-2,3,4,5-tetrahydroxy-6-cyclohexene-1-carboxylate (**12**) (53 mg, 45%) as needles (from ethanol): Mp 104—105.5 °C. ^{1}H NMR ($CDCl_3$) δ=2.07 (6H, s, 2 OAc), 3.51 (1H, t, $J_{4,5}$= $J_{5,6}$=3.8 Hz, H-5), 3.72 (1H, dt, $J_{2,4}$= $J_{3,4}$=2.3 Hz, H-4), 3.80 (3H, s, CO_2Me), 5.46 (1H, t, $J_{2,3}$=2.3 Hz, H-3), 5.82 (1H, t, H-2), 7.50 (1H, d, H-6).

Found: C, 53.62; H, 5.30%.

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