Syntheses of 1-Cyclopentene-1,2-dicarboxaldehyde and 1-Cyclobutene-1,2-dicarboxaldehyde

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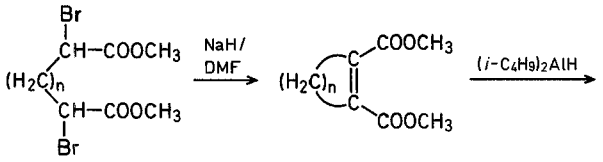
A method has recently been developed in these laboratories whereby *o*-phthalaldehyde can be converted conveniently to benzannelated bisdehydroannulenes, often in satisfactory yield[2]. This method has been extended to the synthesis of other bisdehydroannulenes annulated to a cyclic π-system, by starting with the appropriate 1,2-dialdehyde (naphthalene-2,3-dicarboxaldehyde[3], naphthalene-1,2-dicarboxaldehyde[3], furan-3,4-dicarboxaldehyde[4,5], furan-2,3-dicarboxaldehyde[6], thiophene-2,3-dicarboxaldehyde[6], etc.).

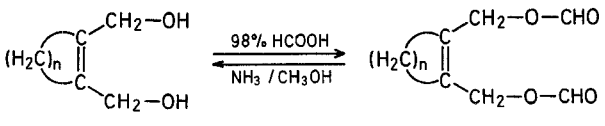
In order to prepare bisdehydroannulenes not annelated to another cyclic π-system, we required, as starting materials, 1-cycloalkene-1,2-dicarboxaldehydes of type **5**. The unsubstituted malealdehyde[7] appeared to be less desirable, in view of its intractable nature, tendency to polymerization, and ease of isomerization to fumaraldehyde[7]. The first attempts to prepare 1-cyclohexene-1,2-dicarboxaldehyde, made by us and others[8] over 12 years ago, were uniformly unsuccessful for reasons described subsequently. We now describe successful syntheses of the lower homologues, 1-cyclopentene-1,2-dicarboxaldehyde (**5b**) and 1-cyclobutene-1,2-dicarboxaldehyde (**5c**).

The cyclization of dimethyl α,α'-dibromo-α,ω-alkanedioates **1**[9] to dimethyl 1-cycloalkene-1,2-dicarboxylates **2** with sodium hydride in dimethylformamide has been described previously[9]. In the case of the cyclization of dimethyl α,α'-dibromopimelate (**1b**), it was observed that an appreciable amount of unchanged **1b** remained. Recyclization of this material then raised the total yield of **2b** from **1b** to 77%.

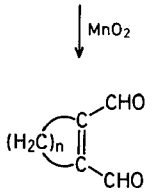


1a n = 4
b n = 3
c n = 2

2a-c



3a-c **4a-c**



5b,c

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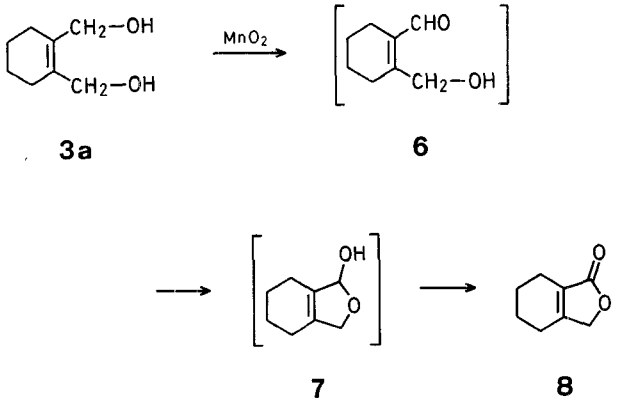
The reduction of the diesters **2a**, **2b**, and **2c** to the corresponding diols **3a**, **3b**, and **3c**, respectively, was best carried out with diisobutylaluminium hydride in pentane. The resulting diols were found to be quite impure, as determined by ^{1}H-N.M.R. spectral analysis, and were difficult to purify. Treatment with 98% formic acid converted them to the corresponding diformates **4a**, **4b**, and **4c**, which could be purified easily and then smoothly hydrolyzed to the pure diols **3a**[10], **3b**[11], and **3c** with methanol and ammonia.

Finally, oxidation of the diols **3b** and **3c** with manganese dioxide in dichloromethane led to the required dialdehydes **5b** and **5c**, respectively, in ~95% yield each. These dialdehydes were rather unstable, and gradually decomposed on standing in light at room temperature, but could be kept with little change for several days in ether solution in a refrigerator.

The maxima in the U.V. spectra of **5b** and **5c** are at 261 and 255.5 nm respectively ($\varepsilon = \sim 7000$) in ether solution, and at 264.5 and 261 nm, respectively in dichloromethane solution. This bathochromic shift of ~4 nm caused by changing from ether to a halogenated solvent (like dichloromethane) is quite usual. However, changing from ether to methanol results in unusual hypsochromic shifts, of ~14 nm, in the U.V. spectra of **5b** [$\lambda_{max}(CH_3OH) = 248.5$ nm] and **5c** [$\lambda_{max}(CH_3OH) = 241$ nm]. The most likely explanation for these hypsochromic shifts is that methanol results in hemiacetal formation of one of the aldehyde groupings in **5b** and **5c**. The annelated malealdehyde derivatives **5b** and **5c** should not only be of use for the preparation of annelated annulene derivatives, but appear to be valuable starting materials for other interesting substances.

In contrast to the smooth oxidation of the diols **3b** and **3c** to the corresponding dialdehydes **5b** and **5c**, oxidation of the six-membered ring diol **3a** with manganese dioxide (as well as with other oxidizing agents)[8] gave no detectable amounts of the corresponding dialdehyde. The only product, obtained in 66% yield, proved to be the lactone **8**. Evidently, oxidation of one of the primary hydroxy groups of **3a** leads to the monoaldehyde **6**, which undergoes cyclization to the five-membered lactol **7**, and subsequent oxidation to the lactone **8**.



3a **6** **7** **8**

It was this failure to effect the oxidation of the diol **3a** to the corresponding dialdehyde, which led us to investigate the oxidation of the lower analogues **3b** and **3c**. It was considered that formation of the lactol corresponding to **7** was less likely to occur on oxidation of these compounds, since fusion of a five-membered ring onto a five- or four-membered ring is a less favoured process than fusion onto a six-membered ring. This indeed proved to be the case.

Dimethyl 1-Cyclopentene-1,2-dicarboxylate (2b):
Dimethyl α,α'-dibromopimelate[9] (**1b**; 184 g, 0.532 mol) is added to a suspension of sodium hydride (32 g, 1.327 mol, in mineral oil) in dry dimethylformamide (2.2 l), and the mixture is stirred at room temperature for 5 h. Ether (3 l) is then added, the solid is removed by filtration, and washed with ether. The combined ether extracts are washed with brine (2.2 l), and the aqueous layer is reextracted with ether (2 l). The combined ether layers are dried with magnesium sulphate, the solvent is evaporated, and the remaining dimethylformamide is then removed by distillation at 50 °C (water bath)/0.1 torr through a 20 cm column. Distillation of the residue at 100 °C (water bath)/0.15 torr through a short path still then yields 64.1 g (66%) of pure **2b**, b.p. 75–78 °C/0.15 torr. The residue (32.2 g, 0.0931 mol, 17.5%), essentially unchanged **1b**, on repeated treatment with sodium hydride in dimethylformamide as before, gives a further 10.8 g (11%) of pure **2b**; total yield: 74.9 g (77%).

^{1}H-N.M.R. ($CDCl_3$, cf. Ref.[9]): $\delta = 3.75$ (s, 6H, OCH_3); 2.70 (t, 4H, allylic H); 1.95 ppm (q, 2H, nonallylic H).

I.R. (NaCl; cf. Ref.[9]): $\nu = 1725$ ($COOCH_3$), 1645 cm^{-1} (C=C).

1,2-Bis[hydroxymethyl]-1-cyclopentene Diformate (4b):
A solution of dimethyl 1-cyclopentene-1,2-dicarboxylate (**2b**; 18.4 g, 0.1 mol) in dry tetrahydrofuran (20 ml) is added dropwise to a stirred solution of diisobutylaluminium hydride (0.44 mol) in dry pentane (1 l) at 5 °C, with ice cooling. The excess reagent is decomposed by careful addition of methanol, the mixture is poured on to ice and 2 normal hydrochloric acid, and the mixture is stirred for 1 h. The aqueous layer is separated, saturated with sodium chloride, and extracted with ethyl acetate. The combined organic layers are dried with magnesium sulphate, and the solvent is removed under reduced pressure (water bath at 25–30 °C). The resulting diol **3b** (11.5 g, 90%) is quite impure, as determined by ^{1}H-N.M.R. spectrometry. Attempted distillation at 111.5–113 °C/0.15 torr, as described by Perrotti et al.[11], results in considerable decomposition of **3b**.

A solution of the crude diol **3b** (11.5 g) in 98% formic acid (115 ml) is allowed to stand at room temperature for 2 h, when no diol remains (T.L.C.: silica gel, 3:1 toluene/ethyl acetate). Formic acid is evaporated at 20 °C/0.15 torr, and the residue is purified by column chromatography [silica; petroleum ether (b.p. 40–60 °C)/ethyl acetate, 19:1]. Crystallization from petroleum ether (b.p. 40–60 °C)/chloroform gives **4b**; yield: 5.51 g (30% based on **2b**); m.p. 39–40 °C.

$C_9H_{12}O_4$	calc.	C 58.69	H 6.57
(184.2)	found	58.39	6.58

M.S.: $m/e = 184$ (M^+), 139 ($M^+ - OCHO$).

I.R. (CCl_4): $\nu = 1715$ cm^{-1} (ester).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.10$ (s, 2H, —CHO); 4.80 (s, 4H, —CH_2O—); 2.50 (t, 4H, allylic H); 1.88 ppm (q, 2H, nonallylic H).

1,2-Bis[hydroxymethyl]-1-cyclopentene (3b):
A solution of 1,2-bis[hydroxymethyl]-1-cyclopentene diformate (**4b**; 0.55 g, 3.0 mmol) in methanol (6 ml) is added with stirring to methanol (5 ml) saturated with ammonia gas at 5 °C. After 10 min, the solvent is evaporated under reduced pressure in a water bath kept at room temperature. Dichloromethane (20 ml) is added to the residue, the mixture is filtered through celite, and the solvent is evaporated as before to give an oil (homogeneous by T.L.C.: silica gel, 3:1 toluene/ethyl acetate); yield: 0.375 g (98%); Lit.[11] m.p. 46–48 °C.

^{1}H-N.M.R. ($CDCl_3$; cf. Ref.[11]): $\delta = 4.20$ (s, 4H, CH_2O). 3.64 (bs, 2H, OH); 2.47 (t, 4H, allylic H); 1.85 ppm (q, 2H, nonallylic H).

I.R. (NaCl; cf. Ref.[11]): $\nu = 3300$ (OH), 1645 cm^{-1} (C=C).

1-Cyclopentene-1,2-dicarboxaldehyde (5b):
A solution of pure diol **3b** (0.256 g, 2 mmol) in dichloromethane (25 ml) is stirred with manganese dioxide (3.5 g, Merck, activated, kept at 100 °C) for 3 h. Filtration through celite and evaporation under reduced pressure gives **5b** as an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 0.238 g (96%).

High resolution M.S. ($C_7H_8O_2$): M^+, *m/e:* calc. 124.0524; found 124.0525.

I.R. (CCl_4): ν=2865 (—CO—H), 1720 (C=O), 1640 cm^{-1} (C=C).

U.V. (ether): λ_{max}=261 nm (ε=7100).

^{1}H-N.M.R. ($CDCl_3$): δ=10.41 (s, 2H, —CHO); 2.78 (t, 4H, allylic H); 1.92 ppm (q, 2H, nonallylic H).

1,2-Bis[hydroxymethyl]-1-cyclobutene Diformate (4c):
The reduction of dimethyl 1-cyclobutene-1,2-dicarboxylate[9] (**2c**; 1.7 g, 10 mmol) in dry tetrahydrofuran (20 ml) with diisobutylaluminium hydride (44 mmol) in dry pentane (200 ml) at 5 °C is carried out as described for the reduction of **2b**. The resulting diol **3c** (1.03 g, 90%) proves to be quite impure, as determined by ^{1}H-N.M.R. spectrometry. Treatment of this crude diol with 98% formic acid, as described for the formation of **4b**, leads to **4c** as an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 0.46 g (27% based on **2c**).

$C_8H_{10}O_4$	calc.	C 56.47	H 5.88
(170.2)	found	56.25	5.94

I.R. (CCl_4): ν=1715 cm^{-1} (ester).

^{1}H-N.M.R. ($CDCl_3$): δ=8.05 (s, 2H, —CHO); 4.70 (s, 4H, —CH_2O—); 2.41 ppm (s, 4H, ring CH_2).

1,2-Bis[hydroxymethyl]-1-cyclobutene (3c):
The hydrolysis of **4c** (0.46 g) with methanol and ammonia is carried out as described for the hydrolysis of **4b**. The resulting **3c** is an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 0.293 g (95%).

Microanalysis: the diol **3c** decomposed on drying for microanalysis, and no satisfactory microanalysis could be obtained.

^{1}H-N.M.R. ($CDCl_3$): δ=4.60 (bs, 2H, —OH); 4.04 (s, 4H, —CH_2O—); 2.37 ppm (s, 4H, ring CH_2).

1-Cyclobutene-1,2-dicarboxaldehyde (5c):
The oxidation of **3c** (110 mg) with manganese dioxide (1.7 g) in dichloromethane (25 ml) is carried out as for the oxidation of **3b**. The resulting **5c** (101 mg, 95%) is an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 101 mg (95%).

High resolution M.S. ($C_6H_6O_2$): M^+, *m/e:* calc. 110.0368; found 110.0368.

I.R. (CCl_4): ν=2865 (—CO—H), 1720, 1670 (C=O), 1640 cm^{-1} (C=C).

U.V. (ether): λ_{max}=255.5 nm (ε=7000).

^{1}H-N.M.R. ($CDCl_3$): δ=10.10 (s, 2H, —CHO); 2.80 ppm (s, 4H, CH_2).

1,2-Bis[hydroxymethyl]-1-cyclohexene Diformate (4a):
The reduction of dimethyl 1-cyclohexene-1,2-dicarboxylate[9] (**2a**; 1.98 g, 10 mmol) in dry tetrahydrofuran (20 ml) with diisobutylaluminium hydride (44 mol) in dry pentane (200 ml) at 5 °C is carried out as described for the reduction of **2b**. The resulting diol **3a**[10] (1.25 g, 88%) is quite impure, as determined by ^{1}H-N.M.R. spectrometry. Treatment of this crude diol with 98% formic acid, as described for the formation of **4b**, gives as an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 0.39 g (20% based on **2a**).

$C_{10}H_{14}O_4$	calc.	C 60.59	H 7.12
(198.2)	found	60.39	7.03

I.R. (CCl_4): ν=1715 cm^{-1} (ester).

^{1}H-N.M.R. ($CDCl_3$): δ=8.07 (s, 2H, —CHO); 4.75 (s, 4H, —CH_2O—); 2.15 (m, 4H, allylic H); 1.65 ppm (m, 4H, nonallylic H).

1,2-Bis[hydroxymethyl]-1-cyclohexene (3a):
The hydrolysis of **4a** (390 mg) with methanol and ammonia is carried out as described for the hydrolysis of **4b**. The resulting **3a** is an oil, homogeneous by T.L.C. (silicia gel, 3:1 toluene/ethyl acetate); yield: 266 mg (96%).

Microanalysis: the diol **3a** decomposed on drying for microanalysis, and no satisfactory microanalysis could be obtained.

^{1}H-N.M.R. ($CDCl_3$): δ=4.10 (s, 4H, —CH_2O—); 3.45 (bs, 2H, —OH); 2.15 (m, 4H, allylic H); 1.60 ppm (m, 4H, nonallylic H).

1-Hydroxymethyl-1-cyclohexene-2-carboxylic Acid Lactone (8):
The oxidation of the diol **3a** (142 mg) with manganese dioxide (2.2 g) in dichloromethane (25 ml) is carried out as described for the oxidation of **3b**. The resulting product is purified by column chromatography [silica; petroleum ether (b.p. 40–60 °C)/ethyl acetate, 19:1]. Crystallization from petroleum ether (b.p. 40–60 °C)/chloroform gives **8**; yield: 91 mg (66%); m.p. 53–54 °C.

$C_8H_{10}O_2$	calc.	C 69.54	H 7.30
(138.2)	found	69.58	7.43

M.S.: *m/e*=138 (M^+), 137 (M^+-1).

I.R. (CCl_4): ν=1750 (γ-lactone), 1690 cm^{-1} (C=C).

^{1}H-N.M.R. ($CDCl_3$): δ=4.75 (s, 2H, —CH_2O—); 2.33 (m, 4H, allylic H); 1.78 ppm (m, 4H, nonallylic H).

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