SHORT PAPER

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A simple synthesis of 1,1,2-tris-(hydroxymethyl)-cyclopropane and its dihalo derivatives†

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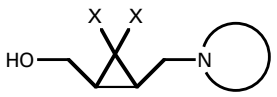
The phase transfer catalytic cyclopropanation of the malonic ester of allylic alcohol or its 3,3-dibromo and 3,3-dichloro derivatives yields bicyclic cyclopropane carboxylic acid lactones; reduction of these lactones with $LiAlH_4$ in boiling THF yields the appropriate 1,1,2-tris-(hydroxymethyl)cyclopropanes in satisfactory yield.

Keywords: cyclopropanes; cyclisation; reduction

Cyclopropyl nucleosides represented by structures **1** and **2** (X = H) can be regarded as potential candidates for biological evaluation for antiviral activity.[1] The same biological effect was suggested, for their difluoro analogues (**1** and **2**, X = F).[2,3] There are only few data in the literature about the synthesis of these compounds. A method was published for the preparation of the optically active derivatives of **1** (X = H),[1] and a 6- step procedure was presented yielding the difluoro derivative of **2**, starting from 1,3-dibenzyloxy-2-propanol.[3] Thus, the development of a rational method might have a synthetic importance.



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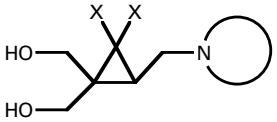

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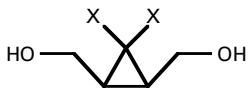
The 1,2-bis(hydroxymethyl)cyclopropane (**3**, X = H), the 1,1,2-tris(hydroxymethyl)cyclopropane (**4**, X = H) and their 3,3-difluoro derivatives (**3,4**, X = F) could be used as intermediates for a simple synthesis of **1** and **2**.



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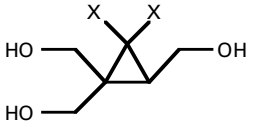

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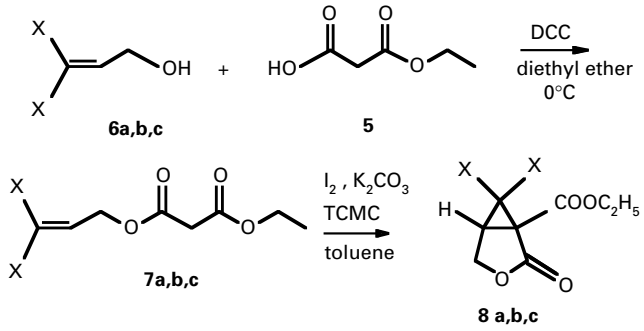
The phase transfer catalytic method producing bicyclic cyclopropane carboxylic lactones developed earlier[4] can offer a valuable precursor for the synthesis of **4**. The esterification of allylic alcohol **6a** with malonic acid monoethyl ester **5** (Scheme 1) in the presence of dicyclohexyl carbodiimide (DCC) yielded the desired mixed diester **7a** in excellent yield. This ester was subjected to cyclisation in the presence of either solid potassium carbonate (using a lipophilic quaternary ammonium salt: TCMC, tricaprylmethyl ammonium chloride as phase transfer catalyst) or Mg-Al 3:1 hydrotalcite[5] as base.

The lactone **8a** thus obtained was reduced with $LiAlH_4$ (Scheme 2). Using diethyl ether as solvent only the reduction of the lactone moiety occurred and the ester **9a** was obtained even after 6 h boiling. However, using THF as solvent and refluxing the reaction mixture for 8 h resulted in the formation of the desired triol **4a** in satisfactory yield.



Scheme 1 Synthesis of cyclopropane carboxylic acid lactones

To check the reactivity of the olefinic double bond having two geminal halogens the 2,2-dibromo- and 2,2-dichloro-derivatives **4b,c** of triol **4a** were prepared similarly. The appropriate 3,3-dihaloallylic alcohols **6b,c** were obtained by reacting ethyl or butyl vinyl ether **10a,b** with CCl_4[6] or CBr_4[7] respectively, according to the methods described (Scheme 3). Reduction of the aldehydes **11a,b** with sodium borohydride, esterification of the alcohols **6b,c** with malonic acid monoethyl ester and cyclisation of the esters yielded the dichloro- and dibromo-lactones **8b** and **8c** in satisfactory yield. Reduction of these lactones with $LiAlH_4$ gave similar results to the reduction of **8a**; in refluxing THF the triols **4b,c** were obtained while using diethyl ether as solvent only the lactone moiety could be reduced.

In the literature there are some characteristic examples of the reactivity difference of the cyclopropane ester and lactone moiety. Thus, the hydrolysis of the cyclopropane ester moiety is rather difficult, feasible only with special agents, *e.g.* with MgI_2.[8] Also, the lactone ring is more sensitive to the saponification and it can be performed with conventional reagents. This reactivity difference can be explained in our case if the temperature of boiling ether is adequate only for the reduction of the lactone group.

Experimental

IR spectra were recorded on Perkin Elmer Spectrum 1600 instrument. Data are given in cm^{-1}. ^1H NMR spectra were recorded on Bruker AW-250 (250 MHz) spectrometer, chemical shifts are given on the δ scale using TMS as internal standard. δ (TMS) = 0 ppm in $CDCl_3$. Coupling constants are given in Hz. The reagents were purchased from Merck, except TCMC which is the product of Fluka GmbH. Thin layer chromatography was carried out using Merck Kieselgel 60F plates with eluents hexane:acetone 4:1 or hexane:acetone 1:1. Column chromatography was carried out on Merck Kieselgel 60 to 200 mesh with the same eluents.

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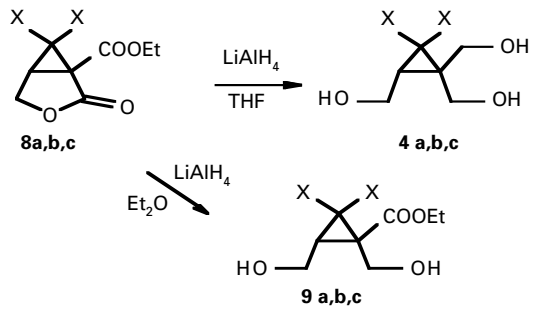
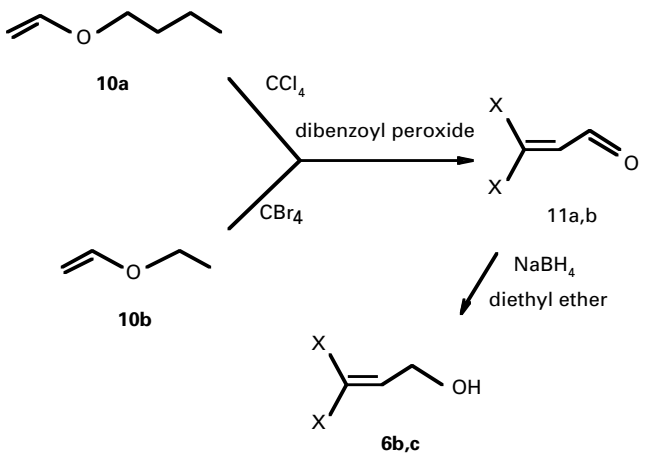
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 2 Reduction of the lactones.



Scheme 3 Synthesis of 3,3-dihaloallylic alcohols

3,3-Dichloroacrolein, **11a**, and *3,3-dibromoacrolein,* **12b** were synthesised according to the methods described in refs 6 and 7, respectively. All physical data of these compounds were identical with the described ones.

Reduction of **11a,b**: To the solution of **11a** or **11b** (15 mmol) in diethyl ether (15 ml) $NaBH_4$ (0.57 g, 15 mmol) was added under ice-bath cooling. The mixture was then stirred for 1.5 hour at room temperature, neutralised with 1 M $NaHSO_4$ and the layers were separated. The aqueous phase was extracted with diethyl ether (2×30 ml). The organic phase was dried over $MgSO_4$, and the solvent was evaporated.

3,3-Dichloro-2-propen-1-ol, **6b**: colourless liquid, yield: 90%, b.p.: 70ºC/18 Hgmm. IR (film): 3213, 2954, 2872, 1625. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.35 (s, 1H), 4.27 (d, 2H, *J* 6.49), 6.08 (t, 1H, *J* 6.49). Anal. Calcd. for $C_3H_4Cl_2O$: C, 28.35; H, 3.15; Found: C, 28.42; H, 3.11%.

3,3-Dibromo-2-propen-1-ol, **6c**: colourless liquid, yield: 92%. IR (film): 3350, 1671. ^{1}H-NMR (250 MHz, $CDCl_3$): 2.51 (s, 1H), 4.16 (d, 2H, *J* 6.33), 6.65 (t, 1H, *J* 6.33). Anal. Calcd. for $C_3H_4Br_2O$: C, 16.67; H, 1.85; Found: C, 16.31; H, 1.80%.

Esterification: The esterification of the alcohols **6a–c** with monoethyl malonate **5** was carried out using the procedure described.[9]

Ethyl 2-propen-1-yl malonate, **7a**: colourless liquid, yield: 96%, all physical and spectroscopic data were identical with the reported one.[4]

Ethyl 3,3-dichloro-2-propen-1-yl malonate, **7b**: colourless liquid, yield: 94%. IR (film): 2966, 1741, 1737, 1625. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.28 (t, 3H, *J* 7.89), 3.4 (s, 2H), 4.2 (q, 2H, *J* 7.89), 4.74 (d, 2H, *J* 6,83), 6.07 (t, 1H, *J* 6.83). Anal. Calcd. for $C_8H_{10}Cl_2O_4$: C, 39.83; H, 4.15; Found: C, 39.81; H, 4.10%.

Ethyl 3,3-dibromo-2-propen-1-yl) malonate, **7c**: colourless liquid, yield: 91%. IR (film): 1743, 1738, 1670. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.29 (t, 3H, *J* 5.32), 3.4 (s, 2H), 4.21 (q, 2H, *J* 5.32), 4.65 (d, 2H, *J* 8.08), 6.62 (t, 1H, *J* 8.08). Anal. Calcd. for $C_8H_{10}Br_2O_4$: C, 29.1; H, 3.03; Found: C, 29.15; H, 2.95%.

Cyclisation: The cyclisation of the esters **7a–c** under phase transfer catalytic conditions was carried out using the procedures described in refs 4 and 5, using solid potassium carbonate or hydrotalcite as base, respectively. There was no significant difference between the yields of the two procedures.

3-Oxa-bicyclo[3.1.0]hexane-2-one-1-carboxylic acid ethyl ester, **8a**: yellow oil, yield: 59%, all physical and spectroscopic data were identical with the reported ones[4].

6,6-Dichloro-3-oxa-bicyclo[3.1.0]hexane-2-one-1-car-boxylic acid ethyl ester, **8b**: colourless oil, yield: 47%. IR (film): 1788, 1738. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.38 (t, 3H, *J* 7.89), 3.27 (d, 1H, *J* 5.59), 4.42 (q, 2H, *J* 7.89), 4.58 (m, 2H). Anal. Calcd. for $C_8H_8Cl_2O_4$: C, 40.17; H, 3.35; Found: C, 40.19; H, 3.28%.

6,6-Dibromo-3-oxa-bicyclo[3.1.0]hexane-2-one-1-car-boxylic acid ethyl ester, **8c**: yellow oil, yield: 67%. IR (film): 1782, 1738. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.39 (t, 3H, *J* 5.42), 3.27 (d, 1H, *J* 5.44), 4.4 (m, 2H), 4.55 (m, 2H). Anal. Calcd. for $C_8H_8Br_2O_4$: C, 29.27; H, 2.44; Found: C, 29.23; H, 2.41%.

Reductions with LiAlH$_4$: (1) In THF: To the suspension of $LiAlH_4$ (0.07 g, 1.8 mmol) in abs. THF (10 ml) **8a–c** (0.6 mmol) was added in abs. THF (10 ml). The mixture was boiled for 8 h under stirring and then cooled, ethyl acetate (10 ml) and then water (1 ml) was added dropwise. The phases were separated and the aqueous was extracted with diethyl ether (2×10 ml). The organic phase was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane: acetone 1:1).

1,1,2-Tris(hydroxymethyl)cyclopropane, **4a**: yellow oil, yield: 65%. IR (film): 3411. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.36 (t, 1H *J* 6.3), 0.69 (m, 1H), 1.01 (m, 1H), 3.61 (s, 3H), 4.02-4.12 (m, 6H). Anal. Calcd. for $C_6H_{12}O_3$: C, 54.54; H, 9.09; Found: C, 54.50; H, 9.01%.

1,1-Dichloro-2,2,3-tris(hydroxymethyl) cyclopropane, **4b**: yellow oil, yield: 51%. IR (film): 3414. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.12 (s, 1H), 3.41 (s, 3H), 4.14–4.22 (m, 6H). Anal. Calcd. for $C_6H_{10}Cl_2O_3$: C, 35.82; H, 4.98; Found: C, 35.76; H, 4.96%.

1,1-Dibromo-2,2,3-tris(hydroxymethyl)cyclopropane, **4c**: yellow oil, yield: 55%. IR (film): 3413. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.10 (s, 1H), 3.41 (s, 3H), 4.14–4.22 (m, 6H). Anal. Calcd. for $C_6H_{10}Br_2O_3$: C, 24.8; H, 3.45; Found: C, 24.76; H, 3.4%.

(2) *In diethyl ether*: To the suspension of $LiAlH_4$ (0.07 g, 1.8 mmol) in abs. diethyl ether (20 ml), **8a–c** (0.6 mmol) was added in abs. diethyl ether (10 ml). The mixture was refluxed for 3 hours under stirring, then cooled. Ethyl acetate (10 ml) and then water (1 ml) was added dropwise. The phases were separated and the aqueous phase was extracted with diethyl ether (2×10 ml). The organic phase was dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (hexane: acetone 1:1).

cis-1,2-bis(hydroxymethyl)cyclopropane-1-carboxylic acid ethyl ester, **9a**: yellow oil, yield: 85%. IR (film): 3414, 1728. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.9 (m, 1H, *J* 6.3), 1.01 (m, 1H), 1.32 (t, 3H, *J* 3), 1.51 (m, 1H), 3.52 (s, 2H), 4.02–4.12 (m, 4H), 4.28 (m, 2H). Anal. Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 5.05; Found: C, 55.11; H, 4.98%.

cis-2,2-dichloro-1,3-bis(hydroxymethyl)cyclopropane-1-car-boxylic acid ethyl ester, **9b**: yellow oil, yield: 75%. IR (film): 3411, 1730. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.15 (s, 1H), 1.28 (t, 3H, *J* 5.40), 3.51 (s, 2H), 4.18-4.45 (m, 6H). Anal. Calcd. for $C_8H_{12}Cl_2O_4$: C, 39.52; H, 4.94; Found: C, 39.45; H, 4.86%.

*cis-1,1-Dibromo-2,3-bis(hydroxymethyl)cyclopropane-1-*carboxylic acid ethyl ester, **9c**: yellow oil, yield: 72%. IR (film): 3404, 1732. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.12 (s, 1H), 1.28 (t, 3H, *J* 5.40), 3.45 (s, 2H), 4.18–4.45 (m, 6H). Anal. Calcd. for $C_8H_{12}Br_2O_4$: C, 28.92; H, 3.61; Found: C, 28.83; H, 3.5%.

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