

## Direct synthesis of 2,5-polychloro-1,2-epoxycyclopentane-1-carboxylic acids and their alkyl esters

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This letter is dedicated to Professor J. A. Abad on occasion of his retirement

**Abstract**—The treatment of 3,3,6,6-tetrachloro-1,2-cyclohexanedione with sodium hydroxide gave 2,5,5-trichloro-1,2-epoxycyclopentane-1-carboxylic acid in almost quantitative yield. 3,6,6-Trichloro-2-hydroxy-2-cyclohexen-1-one was also found to be able to undergo a similar reaction providing *c*-2,*t*-5-dichloro-1,2-epoxy-*r*-1-cyclopentanecarboxylic acid, whose structure was confirmed by X-ray crystallographic analysis. The reactions with alkali metal alcoholates gave the corresponding esters in fair to good yields. In contrast to the properties described for further  $\alpha$ -chloroepoxides, the prepared compounds show remarkable stability.  
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3,3,6,6-Tetrachloro-1,2-cyclohexanedione **1** is an inexpensive and easily available compound whose reactivity remains little known and whose synthetic usefulness has scarcely been exploited.<sup>1–4</sup> It can be obtained in quantitative yield by direct treatment of commercial *trans*-cyclohexane-1,2-diol with chlorine. We recently reported effective, general new methods for preparing 1,4-dichloro- and 1-chlorophenazines starting from this interesting synthetic intermediate.<sup>2–4</sup> As a further result of our research project in the development of organic syntheses based on the chemistry of compound **1**, the first synthesis of the title compounds is reported here.

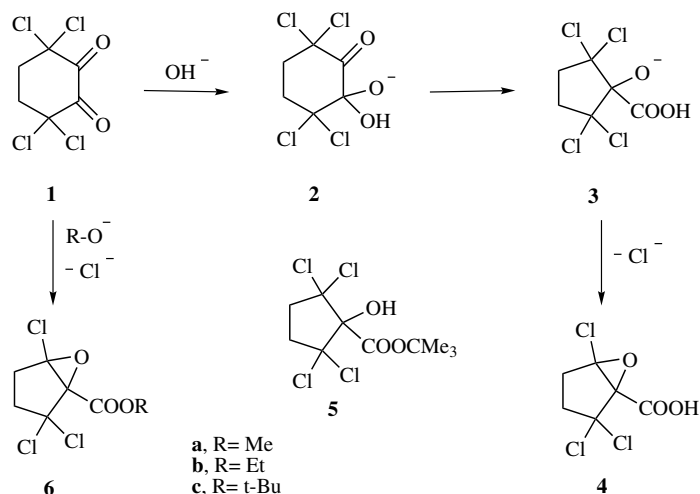
The low capacity of oxiranes to support a halogen atom linked to any of the oxygenated carbon atoms is well known. For example, 1-chloroepoxycyclohexane undergoes a rapid conversion to 2-chloro- and 2-hydroxycyclohexanone on exposure to moist air;<sup>5</sup> 2-chloro-2,3-epoxynorbornane is stable at dry-ice temperature, but on being left at room temperature undergoes a violent exothermic reaction with the evolution of hydro-

gen chloride.<sup>6</sup> The relatively low stability of this type of compound, in general, is due to a remarkable proclivity to undergo a rearrangement leading to  $\alpha$ -chlorocarbonyl derivatives. Sometimes such instability can provoke the failure of the usual epoxidation reactions, and the corresponding chloroepoxides seem to participate as reactive intermediates to yield different final reaction products.<sup>7</sup> On the other hand, the difficulty of achieving direct epoxidation of  $\alpha,\beta$ -unsaturated carboxylic acids should be noted. A  $\text{HOF}\cdot\text{CH}_3\text{CN}$  complex seems to be the most efficient epoxidizing agent for this transformation.<sup>8</sup> Given the above, and in order to broaden the synthetic methodology on this subject, we recognized an opportunity to attempt an approach to the title compounds by starting from **1** on the basis of an one-pot preparative process, which involves a benzylic acid rearrangement step followed by a spontaneous epoxidation of the generated chlorohydrin intermediates, as is shown in Schemes 1 and 2.

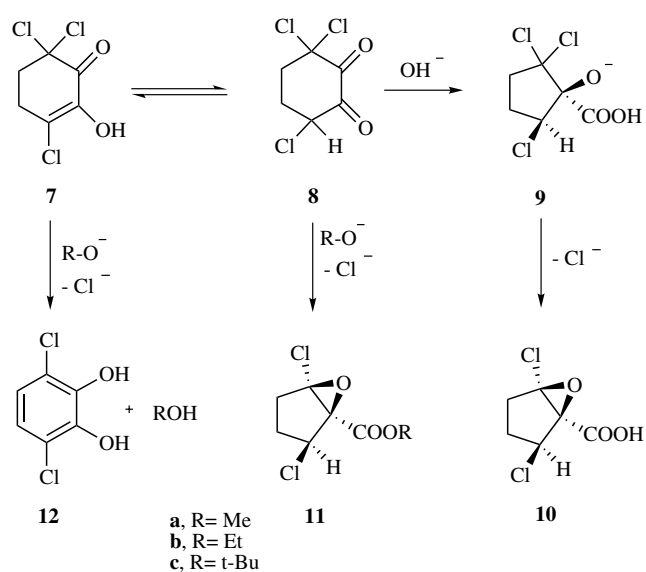
Treatment of **1** with sodium hydroxide at room temperature<sup>9</sup> gave a single product in almost quantitative yield that was characterized as 2,5,5-trichloro-1,2-epoxycyclopentane-1-carboxylic acid **4** (Scheme 1). This transformation can be explained by sequential participation of intermediates **2** and **3**. Compound **1** also reacted with alkali metal alcoholates, leading to the corresponding

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Scheme 1.



Scheme 2.

2,5,5-trichloro-1,2-epoxycyclopentane-1-carboxylic esters **6** in fair to high yields. On studying the course of these transformations, **1** was treated with potassium *t*-butoxide (ratio 1:1) at low temperature,<sup>9</sup> yielding 2,2,5,5-tetrachloro-1-hydroxycyclopentane-1-carboxylic acid *t*-butyl ester **5** in high yield. This compound was converted to the corresponding epoxyester **6c** by heating in the presence of potassium *t*-butoxide.

In an earlier work, we found that **1** can be selectively dechlorinated via electrochemical reduction to give 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **7** in near quantitative yield.<sup>3,4</sup> Given the possibility of tautomerism between **7** and **8** (Scheme 2), the extension of the discovered synthetic methodology was also investigated. A nearly quantitative formation of an acidic product was obtained by treatment of **7** with sodium hydroxide.<sup>9</sup> It was identified by X-ray crystallography<sup>10</sup> as *c*-2,5-dichloro-1,2-epoxy-*r*-1-cyclopentanecarboxylic acid **10** (Fig. 1) whose generation can be explained by participa-

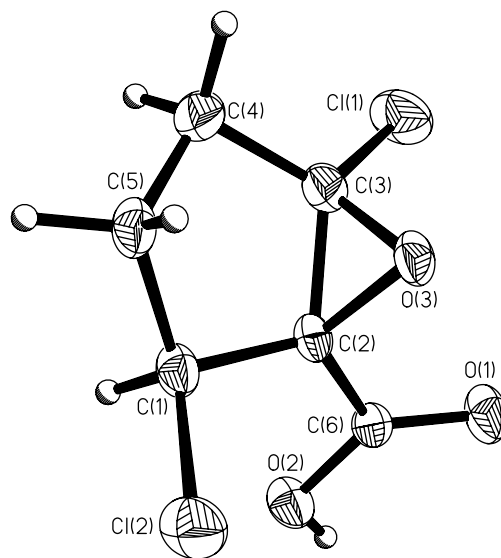


Figure 1. ORTEP of **10**, with thermal ellipsoids shown at 50% probability.

tion of intermediate **9**. The methyl and ethyl esters of **10** (**11a**, **11b**) were also obtained by efficient reactions with the respective sodium alcoholates.<sup>9</sup> These products were generated, accompanied by small amounts of 3,6-dichlorocatechol **12** which were removed easily by simple washing with dilute aqueous solution of sodium bicarbonate. However, the preparation of **11c** by treatment with potassium *t*-butoxide failed completely, **12** being the only product formed. This adverse result may be due to the relative higher basicity and lower nucleophilicity of this particular alcoholate anion.

It should be noted that all the above compounds (carboxylic acids as well as esters) were found to be stable enough to be handled and stored without any special care. It is worth taking into account that various lines of evidence indicate that the rearrangement of chloroepoxides with chlorine migration proceeds through the formation and subsequent collapse of an ion pair composed of a

chlorine anion and an  $\alpha$ -ketocarboxonium. <sup>6,7,11,12</sup> Therefore, the relative high stability of the compounds prepared here seems to be attributable to the electron withdrawing effect of carboxyl and alkoxy carbonyl groups preventing the formation of such ion pairs.

In conclusion, an effective new approach to remarkably stable  $\alpha$ -chloroepoxide derivatives is reported. Not only are these compounds of interest in themselves, but also their functional complexity suggests an attractive synthetic potential to be explored.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.08.079](https://doi.org/10.1016/j.tetlet.2006.08.079).

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- Starting materials **1** and **7** were prepared as described previously. 1–4.  
*Preparation of compounds 4 and 11*: An aqueous solution of sodium hydroxide 2 N (2 ml) was added to a stirred solution of the appropriate chlorinated diketone (5 mmol) in acetonitrile (20 ml). After stirring for 2 h at room temperature, the mixture was acidified with hydrochloric acid (5%) until pH = 3. Then, acetonitrile was removed in a rotary evaporator; water (150 ml) was added and the mixture was extracted with ether (3 × 60 ml). The combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure giving a highly pure white product that was crystallized from petroleum ether. Compound **4** (90%), selected properties: mp 228–229 °C; <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>, 300 MHz) 2.30–2.42 (m, 1H), 2.46–2.71 (m, 3H), 10.49 (br s, 1H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>, 75.4 MHz): 34.39, 43.90, 69.36, 82.11, 84.66, 166.02; IR (Nujol) 3150, 1726, 1350, 1269, 1166, 1097, 947, 933, 823, 764, 706 cm<sup>-1</sup>. (Found C, 31.05; H, 2.25; C<sub>6</sub>H<sub>5</sub>Cl<sub>3</sub>O<sub>3</sub> requires: C, 31.13; H, 2.18.) Compound **11** (93%), selected properties: mp 238–240 °C; <sup>1</sup>H NMR  $\delta$  (DMSO, 300 MHz): 1.39–1.56 (m, 1H), 2.26–2.38 (m, 2H), 2.56–2.65 (m, 1H), 4.99–5.06 (m, 1H), 10.35 (br s, 1H); <sup>13</sup>C NMR  $\delta$  (DMSO, 75.4 MHz): 30.71, 34.97, 57.31, 68.96, 82.15, 164.55; IR (Nujol) 3200, 1707, 1273, 1205, 1096, 953, 928, 794, 771, 746 cm<sup>-1</sup>. (Found C, 36.69; H, 3.13; C<sub>6</sub>H<sub>6</sub>Cl<sub>2</sub>O<sub>3</sub> requires: C, 36.58; H, 3.07.)  
*Preparation of compound 5*: A solution of potassium *t*-butoxide (2 mmol) in dry THF (2 ml) was added dropwise to a cooled solution (0 °C) of **1** (2 mmol) in dry THF (20 ml), and the mixture was stirred for 10 min. After acidification with hydrochloric acid (5%) until pH = 2, the reaction mixture was worked up as described above providing a solid compound that was crystallized from AcOEt-Hex, (82%) mp 76–78 °C. <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>, 200 MHz): 1.57 (s, 9H), 3.05–3.22 (m, 4H), 4.85 (s, 1H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>, 200 MHz): 27.61, 44.50, 87.68, 90.88, 92.19, 166.33; FAB<sup>+</sup>: 323 (M<sup>+</sup>+1); IR (Nujol): 3422, 1731, 1301, 1197, 1153, 1010, 855, 829, 685 cm<sup>-1</sup>. (Found C, 36.93; H, 4.29; C<sub>10</sub>H<sub>14</sub>Cl<sub>4</sub>O<sub>3</sub> requires: C, 37.07; H, 4.35.)  
*Preparation of compounds 6 and 12*: The appropriate starting material (**1** or **7**; 2 mmol) was added to a freshly generated solution of the corresponding sodium alcoholate (4 mmol) in dry alcohol (20 ml), and refluxed for 2 h. After acidification with hydrochloric acid (5%) until pH = 2, the reaction mixture was concentrated under reduced pressure; water (100 ml) was added and the suspension extracted with ether (3 × 60 ml). The combined extracts were washed with aqueous solution of sodium bicarbonate (5%; 2 × 60 ml), with water (60 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure giving highly pure compounds: **6a** (oil, 71%); **6b** (oil, 70%); **6c** (oil, 60%); **12a** (oil, 84%); **12b** (75%, crystallized from AcOEt-Hex, mp 53–54 °C). Selected properties of **6b**: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>, 400 MHz): 1.38 (t, 3H), 2.31–2.68 (m, 4H), 4.33–4.49 (m, 2H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>, 400 MHz): 14.12, 34.17, 43.74, 62.93, 69.25, 81.62, 85.09, 161.33; MS *m/z* (%): 225 (64), 223 (M<sup>+</sup>-Cl, 100), 166 (19), 149 (22), 89 (60), 61 (49); IR (neat) 1750, 1446, 1379, 1271, 1146, 1175, 1098, 1012, 821, 709 cm<sup>-1</sup>. (Found C, 36.89; H, 3.43; C<sub>8</sub>H<sub>9</sub>Cl<sub>3</sub>O<sub>3</sub> requires: C, 37.03; H, 3.50.) Selected properties of **12a**: <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>, 400 MHz): 1.60–1.85 (m, 1H), 2.18–2.43 (m, 2H), 2.58–2.73 (m, 1H), 3.91 (s, 3H), 4.81–4.89 (m, 1H); <sup>13</sup>C NMR  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 30.82, 35.38, 53.29, 56.01, 69.16, 81.93, 164.07; MS *m/z* (%): 177 (31), 175 (M<sup>+</sup>-Cl, 100), 111 (16), 87 (14), 59 (28); IR (neat) 1749, 1322, 1271, 1202, 1130, 1091, 1053, 992, 928, 802, 778, 735, 642 cm<sup>-1</sup>. (Found C, 39.91; H, 3.76; C<sub>7</sub>H<sub>8</sub>Cl<sub>2</sub>O<sub>3</sub> requires: C, 39.84; H, 3.82.)
- Selected X-ray crystallographic data of 11*: C<sub>6</sub>H<sub>6</sub>Cl<sub>2</sub>O<sub>3</sub>, triclinic, space group *P* - 1, *a* = 5.5394(6) Å, *b* = 6.7079(6) Å, *c* = 11.2773(11) Å,  $\alpha$  = 80.489(6)°,  $\beta$  = 89.482(7)°,  $\gamma$  = 74.357(6)°, *V* = 397.69(7) Å<sup>3</sup>, *Z* = 2. A colourless prism 0.26 × 0.20 × 0.15 mm was used to measure 1731 reflections at *T* = 173 K, of which 1380 were unique (*R*<sub>int</sub> = 0.0185). Refinement proceeded to *wR*<sub>2</sub> = *c* 0.0834 (all data), *R*<sub>1</sub> = 0.0337 and GOF = 1.059 [*I* > 2 $\sigma$ (*I*)]. Maximum residual electron density was 0.317 eÅ<sup>-3</sup>. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-609609.
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