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Preparation of Activated Cyclopropanes by Phase Transfer Alkylation

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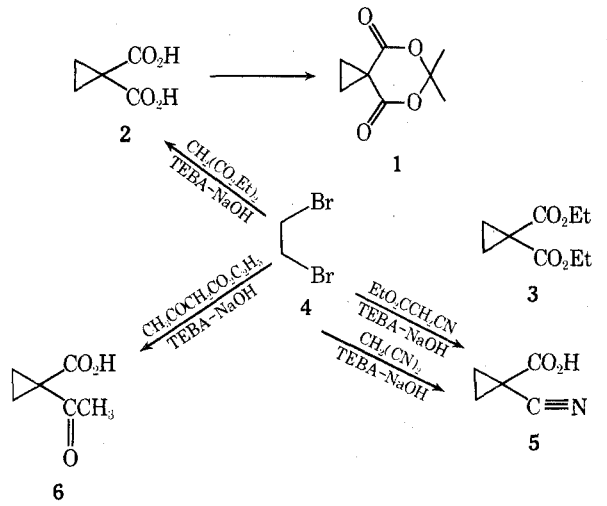
Recently we described the extreme vulnerability of the spiro acylal **1** to homoconjugate ring opening via nucleophilic attack.[2] Compound **1** has been demonstrated to be a useful synthetic equivalent of $^{+}CH_2CH_2CH(CO_2H)_2$ and $^{+}CH_2(CH_2)_2CO_2H$.

Our route to **1** involved reaction of cyclopropane-1,1-dicarboxylic acid (**2**) with isopropenyl acetate under the influence of concentrated H_2SO_4. This can be achieved in high (86%) yield. Compound **2** is obtained by saponification of the diester **3**. However, the preparation of **3** via the base-induced alkylation of diethyl malonate with 1,2-dibromoethane (**4**) has hitherto been accomplished in only poor yield.[3,4,5] Furthermore, the inefficiency of this double alkylation necessitates a complicated separation of **3** from diethyl malonate.[4]

In the light of some rather dramatic successes which have been recorded for the alkylation of carbonyl compounds by extractive alkylation through the action of quaternary ammonium hydroxides,[6] it seemed reasonable to study the application of this technology to the synthesis of 1,1-diactivated cyclopropanes.[7] Below we describe what we believe to be the most effective method for the preparation of these valuable synthetic reagents.

We find that reaction of diethyl malonate with 1,2-dibromoethane catalyzed by triethylbenzylammonium hydroxide [generated from the reaction of triethylbenzylammonium chloride (TEBA) and 50% sodium hydroxide] provides a 75% yield of the homogeneous crystalline diacid **2** without need for any purification. Apparently the reaction sequence starts with alkylation of the diester followed by saponification. We are unable to achieve this alkylation when malonic acid is the starting material, presumably because of the difficulties involved in generating synthetically usable concentrations of the required trianion. It is likely that saponification occurs most readily at the stage where enolization of the malonic ester is prevented by disubstitution, i.e., **3**. In any case, the phase transfer method has rendered compound **2** and, thus, **1**, readily available.



By a similar technology, ethyl cyanoacetate was transformed in 86% yield directly to the crystalline 1-cyanocyclopropanecarboxylic acid (**5**). Under these conditions, there is no indication for the formation of any diacid, **2**. Reaction of ethyl acetoacetate with **4** in the presence of aqueous sodium hydroxide–TEBA gives 1-acetylcyclopropane-1-carboxylic acid (**6**) in 69% yield after distillation. Unlike reported results in other cases,[6b] better yields were obtained using **4** rather than 1,2-dichloroethane as the alkylating agent.

It is interesting to note that alkylation of malononitrile under phase transfer conditions with **4** gives a 49% yield of the acid **5**. We find no indication either in this case or in that starting from ethyl cyanoacetate for the formation of **2**.

This methodology should now render diactivated cyclopropanes readily available compounds for organic synthesis.

Experimental Section[8]

Preparation of Cyclopropane-1,1-dicarboxylic Acid (2). To 30 ml of a stirred solution of 50% aqueous sodium hydroxide was added TEBA (3.54 g, 0.015 mol) followed by diethyl malonate (2.40 g, 0.015 mol) and dibromide **4** (4.23 g, 0.023 mol). The reaction mixture was stirred for 1 hr. After dilution with 75 ml of water, the system was extracted with ether. The aqueous layer was acidified with 40 ml of concentrated HCl and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 1.74 g (75%) of **2**, mp 134–136° (lit.[9] mp 139–141°), λ_{max} ($CHCl_3$) 5.69, 5.78 μ, whose NMR spectrum [δ $(CD_3)_2CO$ 1.70 (s, 2), 9.50 ppm (s, 1)] indicates it to be homogeneous.

Preparation of Spiro[2.5]-5,7-dioxa-6,6-dimethyloctane-4,8-dione (1). To a stirred suspension of compound **2** (1.30 g, 0.01 mol) and isopropenyl acetate (1.20 g, 0.012 mol) was added dropwise over 30 min 0.181 g of concentrated H_2SO_4. The resulting clear solution was stirred for an additional 30 min and maintained at 0° overnight. Upon dilution with 20 ml of cold water, a solid was obtained by filtration. The solid was twice washed with 5-ml portions of cold water and dried to afford pure **1**, 1.40 g (86%), mp 63.5–64.5°.

An analytical sample was obtained by recrystallization from acetone–water: λ_{max} ($CHCl_3$) 5.64, 5.70 μ; δ ($CDCl_3$) 1.82 (s, 3), 1.97 ppm (s, 2).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.46; H, 5.98.

Preparation of Cyanocyclopropane-1-carboxylic acid (5). A. From Ethyl Cyanoacetate. To a stirred solution of 40 ml of 50% aqueous sodium hydroxide was added TEBA (4.55 g, 0.02 mol) and a mixture of ethyl cyanoacetate (2.26 g, 0.02 mol) and 1,2-dibromoethane (7.52 g, 0.04 mol). Evolution of heat was noted and the ambient temperature was maintained by external cooling.[10] Stirring was continued for 1 hr. After dilution with 100 ml of water, the system was extracted with ether. The aqueous layer was acidified with 50 ml of concentrated HCl and extracted with ether.

The ether layer was washed with brine and dried over $MgSO_4$. Removal of the solvent at the water pump gave 1.91 g (86%) of **5**: mp 142–144° (lit.[11] mp 145–147°); λ_{max} ($CHCl_3$) 4.43, 5.60, 5.81 μ; δ $(CD_3)_2CO$ 1.65 (s, 4), 11.24 ppm (s, 1).

B. From Malononitrile. The reaction was carried out under conditions similar to those described above, except that the reaction time was reduced to 15 min. Thus 1.32 g (0.02 mol) of malononitrile gave 1.09 g (49%) of **5**, mp 142–144°.

Preparation of Acetylcyclopropane-1-carboxylic Acid (6). To 40 ml of a 50% solution of aqueous sodium hydroxide at 60° was added TEBA (2.27 g, 0.01 mol) following a solution of ethyl acetoacetate (2.60 g, 0.02 mol) and 1,2-dibromoethane (7.52 g, 0.04 mol). The resultant clear mixture was stirred for 1 hr, diluted with 100 ml of water, and extracted with ether. The aqueous layer was acidified with concentrated HCl and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent at the water pump left a residue which was evaporatively distilled (bp ca. 110°, 0.3 mm) to give **6**:[12] 1.77 g (69%); λ_{max} ($CHCl_3$) 5.71, 5.90 μ; δ ($CDCl_3$) 1.69–1.78 (m, 4), 2.28 (s, 3), 12.07 ppm (s, 1).

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Registry No.—**1**, 5617-70-9; **2**, 598-10-7; **4**, 106-93-4; **5**, 6914-79-0; **6**, 56172-71-5; diethyl malonate, 105-53-3; isopropenyl acetate, 108-22-5; ethyl cyanoacetate, 105-56-6; malononitrile, 109-77-3; ethyl acetoacetate, 141-97-9.

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Synthesis of δ-Lactones from Cyclohexenones. Preparation of a Vernolepin Analog

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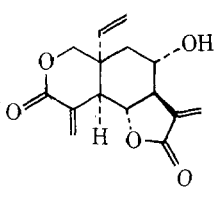
Lactone **2**, a prototype of the sesquiterpenoid antitumor agent vernolepin (**1**),[1] has been prepared by several workers[2] and has been found to show weak to moderate in vitro cytotoxicity in the CCNSC KB cell culture screen.[2f] The



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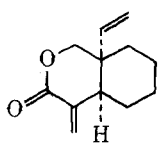

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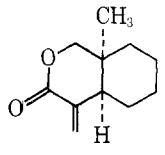
suggestion that the α-methylene δ-lactone moiety of vernolepin may contribute to this molecule's physiological activity is interesting and has prompted us to prepare other related α-methylene δ-lactones for evaluation. Since the angular vinyl group is apparently not crucial to activity (vernolepin and dihydrovernolepin have essentially the same activity),[3] lactones **3** and **4** have been selected for physio-



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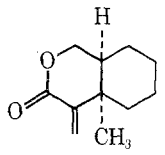

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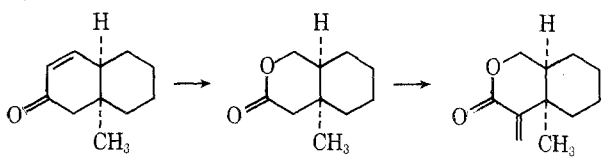
logical evaluation. Lactone **3** is available by a route involving ozonolytic cleavage of a silyloxyalkene.[2b] In this paper, we report the preparation of the isomeric lactone **4** by a route which shows some generality for the preparation of δ-lactones.

Ozonolysis of octalone **5**[4] in methanol solution at −60°, followed by the addition of excess sodium borohydride at 0°, afforded δ-lactone **6** in 45% yield. Introduction of the α-methylene unit by Grieco's two-step procedure[2a,5] (57% overall yield) afforded α-methylene δ-lactone **4**.



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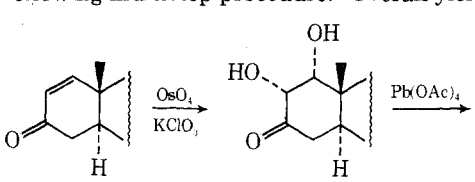
The conversion of **5** to **6** represents a convenient method for the synthesis of a δ-lactone when the corresponding cyclohexenone is available. While the yield in this case is only fair (although it has not been optimized), the conversion is a "one-flask" process, and may be generally useful in cases where the requisite cyclohexenone is not especially precious. Pappo has accomplished the same conversion by the following multistep procedure.[6] Overall yields in the Pappo



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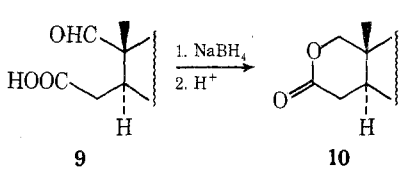

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procedure are 50–60%, and the process requires use of the toxic and expensive reagent osmium tetroxide.[7] Consequently, we have examined the generality of our ozonolytic procedure with several other cyclic enones. The results obtained are shown in Table I.

As can be seen in Table I, modest yields of δ-lactones may be obtained by this process in some cases. The single cyclopentenone tested (compound **15**) gave only an insignificant amount of γ-lactone **20**.

Experimental Section

Synthesis of 8aα-Octahydro-4aα-methyl-3*H*-2-benzopyran-3-one (6). A solution of octalone **5**[4] (1.074 g, 6.55 mmol) in methanol (15 ml) was ozonized at −60° with a Welsbach generator until 2 equiv of ozone had been added. After flushing with nitrogen, the solution was placed in an ice bath (0°) and sodium borohydride