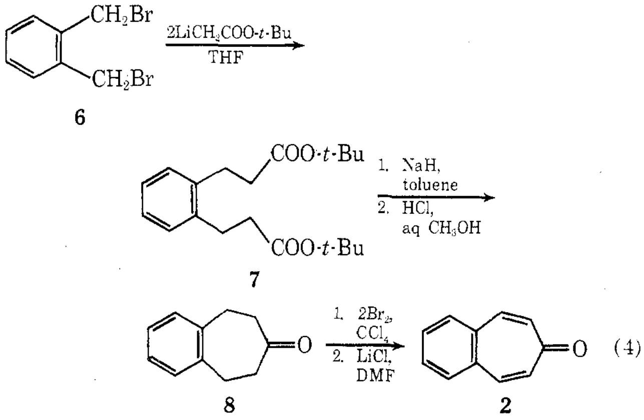
In the present approach, we have focused on the fact that **2** is a bisdehydro derivative of 4,5-benzocycloheptenone (**8**), and have gained simple access to **8** in 51% overall yield by bisalkylation of the readily available *o*-xylylene dibromide (**6**)[7] with lithio *tert*-butyl acetate[8] and subsequent Dieckmann cyclization[9] (eq 4). Addition of **6** to a cold (−78°) solution of the lithium enolate in anhydrous tetrahydrofuran followed by gradual warming to room temperature during 3 hr routinely afforded >90% yield of di-*tert*-butyl ester **7** of purity adequate for direct cyclization. A comparable attempt to employ lithio ethyl acetate[10] was unsuccessful. Bromination of **8** with molecular bromine in carbon tetrachloride solution can be conveniently arrested at the α,α'-dibromo ketone stage, since this dibromide precipitates from solution when formed. Direct dehydrobromination of this solid with lithium chloride in dimethylformamide solvent[11] provides **2** in 85% isolated yield. Benzylic bromination with *N*-bromosuccinimide is not equally successful because the ready elimination of hydrogen bromide which ensues has an appreciable deleterious effect. Acid scavengers are seemingly of little value.



In summary, the scheme illustrated by eq 4 has proven to be an especially reliable route to quantities of the title ketone.

Experimental Section

4,5-Benzocycloheptenone (8). To a cold (−78°) solution of 206.4 g (1.10 mol) of *N*-isopropylcyclohexylamine in 700 ml of dry tetrahydrofuran was added 1 mol of *n*-butyllithium in hexane (Alfa Inorganics) via cannula. After being stirred for 20 min at this temperature, the solution was treated dropwise with 127.8 g (1.1 mol) of *tert*-butyl acetate[12] at such a rate that the temperature did not exceed −68°. Some solid which had precipitated earlier was now totally redissolved. After an additional 20 min at −78°, a solution of 110.0 g (0.416 mol) of **6**[7] in 500 ml of the same solvent was added below −68°. When all had been introduced, the mixture was allowed to warm to −23° and stirred for 2.5 hr at this temperature. The cooling bath was removed and when 25° was attained, 1 l. of cold hydrochloric acid (100 ml of concentrated HCl diluted to volume) was added and the mixture was poured into 1 l. of brine. The organic layer was separated and combined with the ethereal extracts (3 × 500 ml) of the aqueous phase before washing with 1 *M* hydrochloric acid, drying, and evaporation. There was obtained 130 g (93.5%) of **7** as a light orange oil which was utilized directly; ^{1}H NMR (CDCl$_3$) δ 7.13 (s, 4), 2.75–3.15 (m, 4), 2.3–2.7 (m, 4), and 1.43 (s, 18).

A 5-l., three-necked Morton flask was fitted with a mechanical stirrer, high-dilution adapter to which a condenser was attached,[13] constant addition funnel, and nitrogen inlet tube. Sodium hydride (48.0 g of 50% mineral oil dispersion freed of oil by washing with toluene, 1 mol) was introduced, followed by 1.4 l. of dry toluene and 5 ml of dry *tert*-butyl alcohol. After being blanketed by nitrogen, this slurry was brought to reflux with rapid stirring. A solution of the unpurified **7** in 1.5 l. of dry toluene was added slowly during 3–4 days; subsequently, heating was maintained for an additional 3–4 hr. After cooling, glacial acetic acid (90.0 g, 1.5 mol) was introduced dropwise (some thickening occurs), followed by rapid addition of 1 l. of ice water. The layers were separated and the organic phase was washed with brine, dried, and evaporated.

To the residue was added 400 ml of methanol and 200 ml of 6 *N* hydrochloric acid and this mixture was refluxed for 3 hr, poured onto ice, and extracted with ether. After washing with saturated sodium bicarbonate solution, the organic phase was dried and evaporated. Distillation of the residue afforded 34 g (51% overall from **6**) of 4,5-benzocycloheptenone, bp 88° (0.3 mm), mp 41–42° (lit.[14,15] mp 41–42°, 42–43°).

4,5-Benzotropone (2). A magnetically stirred solution of **8** (17.3 g, 0.108 mol) in 325 ml of carbon tetrachloride was treated dropwise with 34.5 g (0.216 mol) of bromine dissolved in 195 ml of the same solvent. Upon completion of the addition, the mixture was brought briefly to reflux. The solvent was removed in vacuo and the off-white solid residue was added to 975 ml of dry dimethylformamide containing 13.05 g (0.308 mol) of lithium chloride. After 1 hr at the reflux temperature under nitrogen, the dimethylformamide was removed in vacuo and the residue was partitioned between ether (400 ml) and water (200 ml). The organic layer was washed with water (3 × 250 ml), dried, and evaporated. Trituration of the residue with boiling pentane afforded 14.3 g (85%) of 4,5-benzotropone as yellow flakes, mp 68–69° (lit.[3,4,6] mp 66–67°, 67.5–68.5°, 69°).

Acknowledgment. The authors thank the National Science Foundation for their support of this investigation.

Registry No.—**2**, 4443-91-8; **6**, 91-13-4; **8**, 37949-03-4; *N*-isopropylcyclohexylamine, 1195-42-2; *tert*-butyl acetate, 540-88-5.

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Reactions of Glycyrrhetic Acid Derivatives with Trifluoromethyl Hypofluorite. Preparation of a New Triterpenoid System

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Trifluoromethyl hypofluorite, CF$_3$OF, is known to give with some types of double bonds addition products which, after a brief treatment with bases, produce monofluoro compounds.[1] We have investigated the reaction of this reagent with a conjugated enone and with an enol acetate derived from glycyrrhetic acid (**1**). This is the first attempt to

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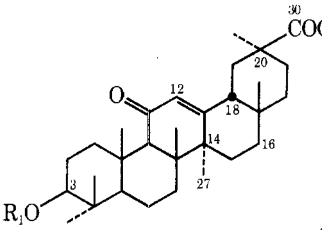
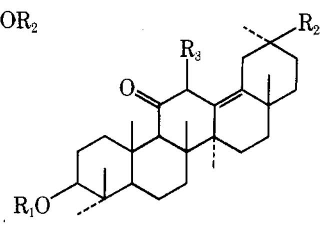
use this reagent in the triterpenoid field. The action of an excess of CF_3OF on methyl 3-*O*-acetylglycyrrhetate (**2**) at room temperature is violent and brings about a far-reaching destruction of the molecule. However, at −70° and with an excess of only 4 equiv of CF_3OF, a single fluorinated compound is obtained in high yield. From the carbonyl absorption ($\tilde{\nu}$ 1715 cm^{-1}) it is clear that the enone double bond has been saturated. The uv spectrum shows a maximum at 290 nm (ϵ 800), which compares well with that of olean-13(18)-en-11-one (**3**) [λ_{max} 286–290 nm (ϵ 600)[2]]. The NMR spectrum shows a hydrogen atom at δ 4.52 ppm (d, J = 49 Hz) while in the ^{19}F NMR spectrum the fluorine atom resonates at relatively low field (117 ppm) as a doublet (J = 49 Hz). These data suggest the presence of a secondary allylic fluorine atom which is also in the α position to a carbonyl. This, and other facts, make it clear that methyl 12-fluoroolean-13(18)-en-11-on-30-oat-3β-yl acetate (**4**) has been formed.



1, $R_1 = H; R_2 = H$

2, $R_1 = Ac; R_2 = \overset{31}{Me}$



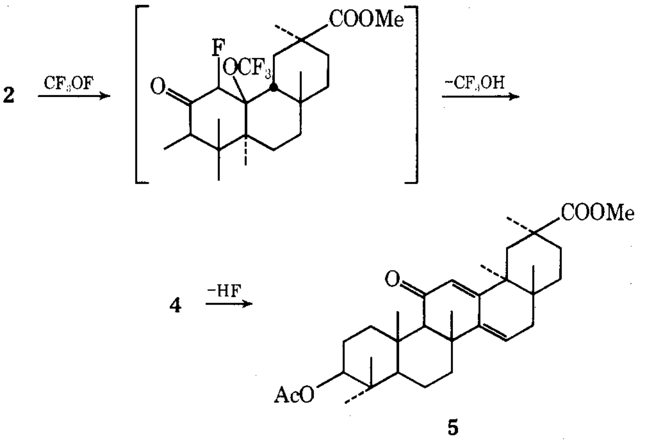
3, $R_1 = R_3 = H; R_2 = CH_3$

4, $R_1 = Ac; R_2 = COOCH_3; R_3 = F$

The β configuration for the fluorine atom is deduced mainly from the ir spectrum. Barton[2] reported for **3** $\tilde{\nu}_{max}$ 1700 cm^{-1}; the fluorine atom thus causes a shift of +15 cm^{-1} and must thus be in the equatorial position.[3] The negative optical rotation ($[\alpha]D$ −37.8°) and the strongly negative background in the ORD spectrum, already apparent at 420 nm, are characteristic of a 13(18) double bond.[4,5] The CD spectrum shows relatively small amplitudes [$\Delta\epsilon_{max}(355)$ −0.54, $\Delta\epsilon_{max}(282)$ −0.93] in agreement with the geometry of **4**, which does not permit an interaction between the n electrons of the carbonyl and the π electrons of the double bond.[6] Thus the negative Cotton effects could be predicted by application of the ordinary octant rule to the 11-keto group.

It seems that **4** was formed by addition of CF_3OF to the 12 double bond, followed by extrusion of CF_3OH.

In the solid state, **4** is a fairly stable compound, but in polar solvents or when absorbed on silica gel, it decomposes with the loss of the elements of HF to give **5** quantitatively.



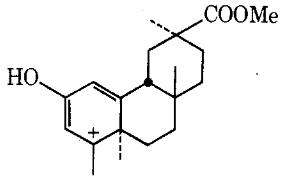
5

This reaction is hindered by traces of base; otherwise it appears to depend on the polarity of the solvent. In boiling methanol, for example, the transformation requires 30 min as against 2–3 days in chloroform, methylene chloride, or acetone at room temperature. On the other hand, nonpolar solvents such as benzene do not affect **4** at all.

For the reasons detailed below we conclude that **5** is a new triterpenoidal system: methyl 27-nor-18α-methylolean-12,14(15)-dien-11-on-30-oat-3β-yl acetate.

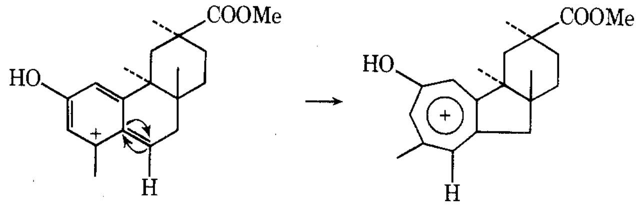
The uv spectrum has a maximum at 293–295 nm (ϵ 0.6 × 10^4), which fits well with the presence of a dienone system. The NMR of **5** shows two vinylic protons of which one, at 5.70 ppm (singlet), is obviously the C-12 hydrogen, while the second at 5.24 ppm is a triplet (J = 7 Hz) and corresponds to the C-15 hydrogen atom. An allylic methylene group is also observed. These two C-16 protons appear as doublets (J = 7 Hz) at 3.04 (H_{eq}) and 2.90 ppm (H_{ax}). Double irradiation of the vinylic hydrogen at 5.24 ppm changes these doublets to singlets. Proton 9α can be observed as a singlet in the region 2.35–2.45 ppm in all glycyrrhetic acid derivatives which possess the enone system at ring C. In compound **5** this proton is shifted to lower field, 2.75 ppm. In the methyl area of the NMR spectrum a methyl is found that resonates at 0.72 ppm, which is the highest recorded value for a methyl in any known glycyrrhetic acid derivative. As can be seen from Dreiding models, C-18 is the only carbon in rings C, D, E that is not affected by the enone system; thus a methyl at C-18 would not suffer any deshielding effects. On the other hand, the C-28 methyl is shifted to lower field (from its usual position of 0.82 ppm to 0.90 ppm), a shift due to the deshielding effect of the dienone system.[7]

The suggested structure is further supported by the mass spectrum. One of the typical ions of the methyl olean-12-en-11-one system is of type a, *m/e* 317.[8]



a, *m/e* 317

In the tens of glycyrrhetic acid derivatives which we have studied, this ion has never been found to be the most intense fragment. Only in the mass spectrum of **5** the ion of type a′ is found (at *m/e* 315) as the most intense one. This

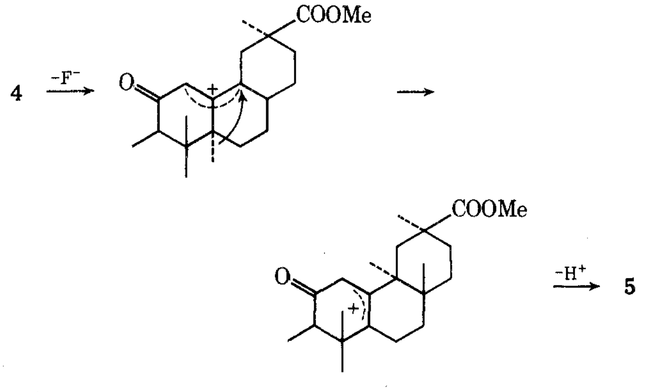


a′, *m/e* 315

can be explained by the high stability this ion should have; perhaps its formation is followed by isomerization to the corresponding tropylium ion.

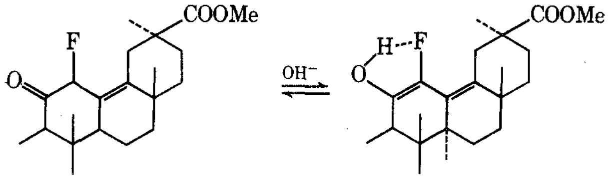
The CD of **5** supports the presence of a conjugated dienone system. The outstanding features of the spectrum are the large bathochromic shift of the Cotton effects and their very large amplitudes:[9] $\Delta\epsilon_{347.5}$ −2.17, $\Delta\epsilon_{283}$ −33.40. The negative sign of the n $\rightarrow \pi^*$ region at 347.5 nm is in agreement with Snatzke's "inverse octane rule".[10] We cannot decide what is the source of the second Cotton effect ($\pi \rightarrow \pi^*$) beyond stating that it may be associated either with the second double bond, at 14(15)[9] or with the transoid junction of the D/E rings.

Some thought should be devoted to the curious migration of the 27 methyl group to C-18. As we cannot explain it by two consecutive [1,2] rearrangements we assume that the whole process is concerted, and [1,3] sigmatropic rearrangement of the methyl group takes place according to the following scheme.



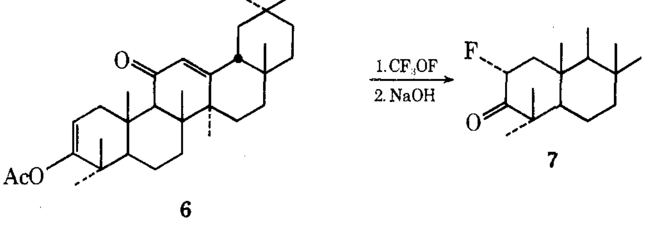
As such rearrangements in small or medium rings can only be suprafacial, it is obvious that the moving methyl would adopt the 18α configuration. As far as we know, this is the first case of a methyl undergoing a [1,3] sigmatropic shift.

We have mentioned that alkali has a retarding effect on the dehydrofluorination of 4. It seems that this is due to the alkali causing enolization, so that a hydrogen bond to the fluorine atom can be formed. The latter is thus stabilized.



4

Trifluoromethyl hypofluorite was also applied to methyl olean-2,12(13)-dien-11-on-30-oat-3β-yl acetate (**6**). Under sufficiently mild conditions, only the enol acetate system reacts, while the double bond at the 12(13) position remains unaffected. After treatment of the crude product with base, methyl 2α-fluoroolean-12-ene-3,11-dion-30-oate (**7**) was obtained in good yield.



6

7

The NMR spectrum of **7** shows a proton split into a doublet (J = 48 Hz), each half of which is split further into four lines of equal intensity. It is easily found that $J_{H_2H_{1eq}}$ = 6, $J_{H_2H_{1ax}}$ = 12 Hz and thus it is clear that the hydrogen at C-2 is axial. The ^{19}F NMR spectrum shows double triplets (J_1 = 48, J_2 = 10 Hz) centered at 187 ppm. This splitting can be explained if $J_{F,H\text{-}1ax} = J_{F,H\text{-}1eq}$. Such an equality is only possible for an equatorial fluorine atom.

Experimental Section

General. 18β-Glycyrrhetic acid was kindly supplied to us by D. Grediger of Chemicals and Phosphates Ltd., Haifa, Israel. NMR spectra were measured with a Varian HA-100 instrument, $CDCl_3$ serving as solvent, Me_4Si as internal standard, and $CHCl_3$ as lock signal. Fluorine NMR spectra were determined on the same instrument in $CDCl_3$ solutions at 94.1 MHz using $CFCl_3$ as an external standard. Chemical shifts are reported in parts per million upfield from this standard. Optical rotations were determined in chloroform (c 1.0) with a Perkin-Elmer 141 polarimeter, ir spectra in Nujol mulls, ORD and CD spectra with a Cary 60 spectropolarimeter, and melting points on a Thomas-Hoover capillary apparatus.

The term "treated in the usual way" refers to the treatment of extracts and indicates that they were washed with water till neutral, dried over magnesium sulfate, and evaporated to dryness in vacuo. Solutions of CF_3OF in $CFCl_3$ were prepared as indicated in ref 12.

Methyl 12-Fluoroolean-13(18)-en-11-on-30-oat-3β-yl Acetate (4). To a solution of 4 molar equiv of CF_3OF in 150 ml of $CFCl_3$, cooled at −75°, a solution of 2 g of 2[11] in 50 ml of chloroform was added slowly and the mixture was stirred for 2 hr at that temperature. The excess of the fluorinating reagent was removed with argon and the solvent was evaporated. Trituration of the residue with hexane containing a small amount of benzene gave 1.9 g (92%) of **4**: mp 205°; $[\alpha]^{25}D$ −37.8°; ir $\tilde{\nu}_{max}$ 1730, 1715, 1625, and 1250 cm^{-1}; NMR 4.52 (d, 1 H, H-12, J = 49 Hz), 4.47 (q-like, 1 H, H-3α), 3.67 (s, 3 H, methyl ester group), 2.03 (s, 3 H, acetyl protons), 1.26, 1.17, 1.14, 1.14, 0.86, 0.86, 0.86 ppm for methyls 26, 27, 25, 29, 24, 23, and 28, respectively; CD (c 0.21, dioxane) 25° θ_{400} 0, θ_{355} −1790, θ_{330} +52, $\theta_{282.5}$ −3061, θ_{240} −104, θ_{230} −311, θ_{225} −156, $\theta_{217.5}$ −415. For other spectral data see the discussion.

Anal. Calcd for $C_{33}H_{49}FO_5$: C, 72.8; H, 9.0; F, 3.5; mol wt, 544. Found: C, 72.5; H, 8.9; F, 3.8; mol wt, 544 (mass spectrum).

Methyl 27-Nor-18α-methylolean-14(15),12-dien-11-on-30-oat-3β-yl Acetate (5). Treating **4** with boiling methanol for 0.5 hr or dissolving it in methanol, acetone, chloroform, or methylene chloride for a period not longer than 4 days gave a quantitative yield of **5**. The same transformation takes place on silica gel: mp 200°; ir $\tilde{\nu}_{max}$ 1725, 1640 (shoulder), 1630, 1250 cm^{-1}; $[\alpha]D$ −358.9°; NMR 3.68 (s, 3 H, methyl ester group), 2.04 (s, 3 H, acetyl protons), 1.43. 1.26, 1.13, 0.86, 0.86, 0.90, and 0.72 ppm for methyls 26, 25, 29, 24, 23, 28, and the 18α methyl, respectively; ORD (c 0.204, dioxane) 25° Φ_{420} −6870, Φ_{305} −57,425, $\Phi_{257.5}$ +89,211, Φ_{240} +70,750; CD (c 0.204, dioxane) 25° θ_{410} 0, $\theta_{347.5}$ −7178, θ_{330} −5845, θ_{283} = −110,235, θ_{240} 0. For other spectral data see the discussion.

Anal. Calcd for $C_{33}H_{48}O_5$: C, 75.4; H, 9.0; mol wt, 524. Found: C, 75.6; H, 9.1; mol wt, 524 (mass spectrum).

Methyl Olean-2(3),12-dien-11-on-30-oat-3β-yl Acetate (6).[13] Methyl 3-deoxy-3-oxoglycyrrhetate[14] (3 g), 60 ml of isopropenyl acetate, and a few drops of concentrated H_2SO_4 were stirred at 70° for 15 hr. About 20 ml of this mixture were distilled off and the residue was poured into water, extracted with chloroform, and treated as usual: yield 2.4 g (74%); mp 249° (from methanol and methylene chloride); ir $\tilde{\nu}_{max}$ 1750, 1735, 1690, 1660, 1620, and 1220 cm^{-1}; $[\alpha]D$ +211°.

Anal. Calcd for $C_{33}H_{48}O_5$: C, 75.6; H, 9.2. Found: C, 75.9, H, 9.3.

Methyl 2α-Fluoroolean-12-ene-3,11-dion-30-oate (7). To a solution of 4 mmol of CF_3OF in 150 ml of $CFCl_3$ at −75°, 1.4 g (2.7 mmol) of **6** in 40 ml of chloroform was added. After 12 min, the excess of the reagent was removed with argon and the solvent was evaporated. The crude product was dissolved in 120 ml of methanol, which contained 6 g of NaOH and 20 ml of water. Dioxane and chloroform were added until the reaction mixture became homogeneous. After stirring for 12 hr, the mixture was poured into dilute hydrochloric acid, extracted with $CHCl_3$, and treated as usual.

Crystallization from methanol gave 1.1 g (82%) of **7**: mp 265°; $[\alpha]^{25}D$ = +163.3°; ir $\tilde{\nu}$ 1735 (shoulder), 1725, and 1655 cm^{-1}; NMR 5.71 (s, 1 H, H-12), 5.24 (d, q-like, 1 H, H-2, J_1 = 6, J_2 = 12 Hz), 3.70 ppm (s, 3 H, methyl ester group). For other spectral data see the discussion.

Anal. Calcd for $C_{31}H_{45}FO_4$: C, 74.4; H, 9.0; F, 3.8; mol wt, 500. Found: C, 74.3; H, 9.0; F, 4.0; mol wt, 500 (mass spectrum).

Registry No.—**2**, 10301-74-3; **4**, 56114-28-4; **5**, 56114-29-5; **6**, 38736-92-4; **7**, 56114-30-8; trifluoromethyl hypofluorite, 373-91-1; methyl 3-deoxy-3-oxoglycyrrhetate, 5195-71-1.

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Preparation of Activated Cyclopropanes by Phase Transfer Alkylation

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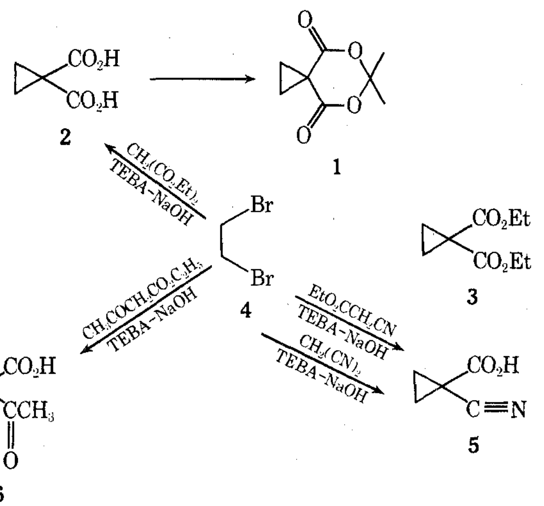
Recently we described the extreme vulnerability of the spiro acylal 1 to homoconjugate ring opening via nucleophilic attack.[2] Compound 1 has been demonstrated to be a useful synthetic equivalent of $^{+}CH_2CH_2CH(CO_2H)_2$ and $^{+}CH_2(CH_2)_2CO_2H$.

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.