exponential multiplication factor. The $H_2{}^{18}O$ (99%) was obtained from Stohler.

Preparation of Furans 1-3 and Their ^{18}O Analogues. The synthesis for each of these compounds has already been reported in ref 4-6.

Oxidation of ^{18}O-Labeled 3-Methyl-4,5,6,7-tetrahydrobenzofuran (2-^{18}O). To a stirred solution of **2** (0.144 g, 1.1 mmol) in 20 mL of methylene chloride was added $NaHCO_3$ (0.2 g). The mixture was cooled to 0 °C and then mCPBA (0.456 g, 2.2 mmol, technical grade) was added in one portion. Stirring was continued 10 min at 0 °C. The reaction mixture was washed with 10% $Na_2S_2O_3$, 5% NaOH, and brine and dried over $MgSO_4$. Removal of solvent afforded 0.152 g of **5** (85%) as a clear oil. High-resolution ^{13}C NMR analysis of the resonances at 189.8, 164.8, and 123.9 ppm showed them all to be single lines in the proton-decoupled spectrum. However, the resonance at 170.7 ppm was resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.040 ppm (41% ^{18}O). IR (neat) 1755 ($C^{16}O$), 1715 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 42% isotope incorporation.

Oxidation of ^{18}O-Labeled Perhydrodibenzofuran (3-^{18}O). To a stirred solution of mCPBA (0.76 g, 4.4 mmol) in 20 mL of methylene chloride at 0 °C was added a solution of **3** (0.38 g, 2.2 mmol) in methylene chloride (10 mL). After being stirred for an additional 10 min, the reaction mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH, and brine and dried over $MgSO_4$. Removal of solvent gave 0.37 g of **6** (82%) as a white solid. The resonance at 201.5 ppm was resolved into two lines with the upfield resonance shifted by 0.050 ppm. Comparison of the intensities of these lines showed 20% ^{18}O incorporation at this point. In a similar manner the resonance at 172.3 ppm was resolved with the upfield resonance shifted by 0.040 ppm. Analysis showed 20% ^{18}O incorporation at this site also. Mass spectral analysis showed 39% ^{18}O incorporation.

Preparation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran (7). Following the procedure of Cohen,[8] a solution of *n*-butyllithium (7.3 mL, 12 mmol, 1.6 M in hexane, Aldrich) was added to a stirred solution of 3-methyl-4,5,6,7-tetrahydrobenzofuran (**2**) (1.58 g, 12 mmol) in 50 mL of tetrahydrofuran at -20 °C (ice-$CaCl_2$ slush) under a nitrogen atmosphere in one portion. To this yellow solution was added methyl iodide (1.80 g, 13 mmol, Baker). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. At this point, 25 mL of water was added and the mixture extracted three times with pentane-ether (1:1). The combined extracts were washed with 5% $NaHSO_3$, three times with water, and brine and dried over K_2CO_3. Removal of solvent gave a yellow liquid which was chromatographed on silica gel. Elution with pentane afforded 1.67 g of a clear oil. Analysis by gas chromatography (SE-30 column) and ^1H NMR spectroscopy showed this material to contain 10% unreacted 3-methyl-4,5,6,7-tetrahydrobenzofuran (**2**) as well as the dimethylfuran **7**: ^1H NMR 2.59-2.47 (2 H, m), 2.37-2.25 (2 H, m), 2.17 (3 H, s), 1.83 (3 H, s), 1.86-1.65 (4 H, m) ppm; ^{13}C NMR 147.8 (s), 144.8 (s), 118.3 (s), 113.7 (s), 23.3 (t), 23.3 (t), 23.2 (t), 20.8 (t), 11.3 (q), 8.0 (q) ppm; IR (neat) 1605, 1450, 1390, 1370, 1270, 1255, 1230, 1165, 1150, 1100, 905 cm^{-1}; mass spectrum, *m/e* (relative intensity) 150 (M^+), 122 (100).

Oxidation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran (7). To a stirred solution of **7** (0.78 g, 5.2 mmol) in 50 mL of methylene chloride at 0 °C was added dropwise a solution of mCPBA (1.78 g, 10.4 mmol) in methylene chloride (50 mL). This addition required 15 min and the reaction mixture was then stirred for 2 min. The mixture was washed with 10% $Na_2S_2O_3$ twice and with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded 0.87 g of a clear oil. Analysis by NMR spectroscopy showed this material to be 50% enol acetate **9** and 50% ϵ-lactone **8**. This material was chromatographed on silica gel. Elution with hexane afforded **9** as a clear oil: ^1H NMR 2.40-2.25 (4 H, m), 2.27 (3 H, s), 2.21 (3 H, s), 1.80-1.58 (4 H, m) ppm; ^{13}C NMR 198.4 (s), 168.5 (s), 155.0 (s), 126.1 (s), 30.5 (q), 28.8 (t), 25.0 (t), 22.3 (t), 21.8 (t), 21.3 (q) ppm; IR (neat) 1760, 1695, 1600, 1430, 1370, 1285, 1260, 1215, 1160, 1110, 1075, 920, 735 cm^{-1}; mass spectrum, *m/e* (relative intensity) 182 (M^+), 140, 125, 43 (100); TLC on silica gel, R_f 0.29 [hexane-ether (1:1)]. A sample for elemental analysis was prepared by preparative gas chromatography (SE-30 column). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.69. Elution with 10% ethyl acetate in hexane afforded **8** as a clear liquid: ^1H NMR 2.65-2.58 (2 H, m), 2.58-2.51 (2 H, m), 2.37 (3 H, s), 1.86 (3 H, s), 2.00-1.77 (4 H, m) ppm; ^{13}C NMR 200.2 (s), 171.2 (s), 154.5 (s), 124.5 (s), 33.7 (t), 31.8 (q), 31.1 (t), 26.0 (t), 23.3 (t), 13.3 (q) ppm; IR (neat) 1755, 1670, 1580, 1450, 1365, 1300, 1225, 1175, 1130, 1105, 1000, 915, 735 cm^{-1}; mass spectrum, *m/e* (relative intensity) 182 (M^+), 140, 99 (100), 43; TLC on silica gel, R_f 0.15 [hexane-ether (1:1)]. A sample for elemental analysis was prepared by chromatography on silica gel. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.76; H, 7.78.

Oxidation of 7-^{18}O. To a stirred solution of **7**-^{18}O (0.39 g, 2.6 mmol) in 20 mL of methylene chloride at 0 °C was added dropwise a solution of mCPBA (1.20 g, 5.9 mmol, technical grade) in methylene chloride (30 mL). The addition was complete in 30 min. The reaction mixture was then washed with 10% $Na_2S_2O_3$, and twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave a clear oil, which was shown by NMR spectroscopic analysis to be 50% **8**-^{18}O and 50% **9**-^{18}O. This material was then chromatographed on silica gel. Elution with hexane afforded 0.14 g of **9**-^{18}O as a clear oil. The resonance at 168.5 ppm was resolved into three lines with one resonance shifted upfield of the main resonance by 0.010 ppm and the third resonance shifted upfield by 0.037 ppm. Comparison of the intensities of these lines showed 26% of the material to be associated with the resonance shifted by 0.010 ppm and 16% with the resonance shifted by 0.037 ppm: IR (neat) 1760 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}.

Mass spectral analysis showed 41% incorporation of ^{18}O. Elution with 10% ethyl acetate in hexane afforded 0.13 g of **8**-^{18}O as a clear oil. The resonance at 200.2 ppm was resolved into two lines with the upfield resonance shifted by 0.049 ppm (15% ^{18}O). Similarly the resonance at 171.2 ppm was resolved into two lines with the upfield resonance shifted by 0.040 ppm (26% ^{18}O): IR (neat) 1755 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 40% incorporation of ^{18}O.

Registry No. **2**, 1919-00-2; **3**, 1010-77-1; **5**, 88888-86-2; **6**, 88888-87-3; **7**, 67722-28-5; **8**, 88888-88-4; **9**, 88888-89-5; *m*-chloroperoxybenzoic acid, 937-14-4.

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A Convenient and Simple Method for the α'-Chlorination of α,β and Conjugated Ketones

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Received March 11, 1983

A wide variety of synthetic reagents and methods are available for the synthesis of α-halo ketones, which are versatile synthetic intermediates.[1] These reagents and methods are however confined to the halogenation of saturated ketones or unsaturated ketones having the unsaturation remote from the carbonyl group. The specific α'-halogenation of α,β and higher unsaturated ketones has, by comparison, received very little attention.[2,3]

The α-halomethyl ketone function has found wide use in the design of site-specific reagents for affinity labeling of proteins.[4,5] To incorporate the α'-chloromethyl radical in α,β and higher unsaturated ketones as affinity probes for the visual pigment rhodopsin,[12] we have developed a

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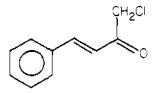
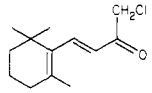
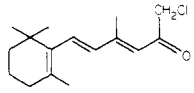
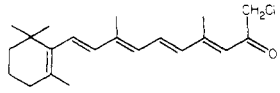
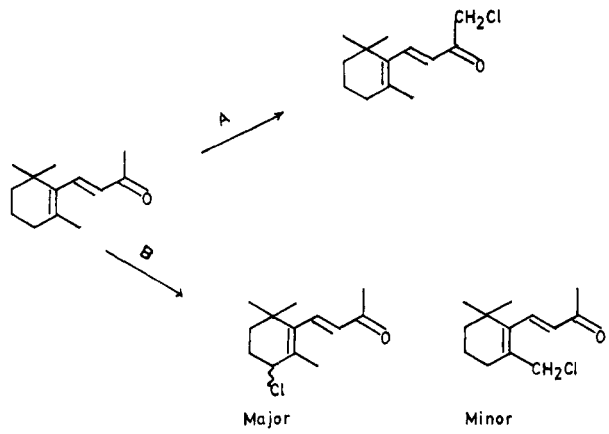
Table I. Relevant Structural Data of α′-Chloromethyl Ketones Obtained by Direct Chlorination of Kinetically Derived α′-Lithium Enolates

compound	NMR, δ	IR (C=O stretch), cm^{-1}	yield, %	mp/bp, °C
	4.27 (s, 2 H), 7.0 (d, 1 H, J_{AB} = 17 Hz), 7.75 (d, 1 H, J_{AB} = 17 Hz)	1685	72[a]	170 (ref 2)
	4.17 (s, 2 H), 6.33 (d, 2 H, J_{AB} = 16.5 Hz), 7.48 (d, J_{AB} = 16.5 Hz)	1680	65[a]	oil dec
	4.1 (s, 2 H), 6.18 (d, 1 H, J_{AB} = 16.5 Hz), 6.83 (d, 1 H, J_{AB} = 16.5 Hz), 6.33 (s, 1 H)	1675	68[b]	oil dec
	4.14 (s, 2 H)	1675	20[b]	51–56 dec

[a] Purified in solvent system diethyl ether/petroleum ether (v/v, 10:90). [b] Purified in solvent system diethyl ether/petroleum ether (v/v, 4:96).

Scheme I



A: [(CH3)2CH]2N Li, 0°C, 1hr; NCS, -70°C.
B: [(CH3)2CH]2N Li, 20°C, 5hrs; NCS, -70°C.

relatively simple and direct method of α′-chlorination using kinetically derived lithium enolates[6] from methyl ketone precursors (Scheme IA). Accordingly, lithium enolates were generated by slow addition of the methyl ketone to a slight excess of lithium diisopropylamide at 0 °C. The enolate thus derived was quenched by *N*-chlorosuccinimide at −70 °C (dry ice/acetone mixtures). After aqueous workup of the reaction mixture the α′-chloromethyl ketones were purified by preparative silica gel thin-layer chromatography.

Lithium α′-enolates thus derived are unstable. β-Ionone α′-lithium enolate was found to rearrange at room temperature after 5 h to the thermodynamically more stable allylic form as shown by the formation of the allylic chlorinated product on quenching with *N*-chlorosuccinimide (Scheme IB). It is interesting to note that the reaction of β-ionone with *N*-chlorosuccinimide in acetic acid resulted in a similar product (data not presented). Structural evidence for α′-chlorination of the ketones was obtained from proton NMR (90 MHz) and infrared spectra. The α′-chloromethyl protons appear at 4.17–4.20 ppm. Similar chemical shifts are observed for this function in saturated systems.[7] The carbonyl group shows a shift of 20–25 cm^{-1} to higher frequencies relative to the parent ketone. This is consistent with α′-substitution.[8] The α′-chloromethyl ketones of β-ionolydeneacetone and retinyl methyl ketone are extremely sensitive to hydrolytically generated traces of hydrochloric acid and undergo considerable decomposition on storage even at −70 °C. Elemental analysis of these compounds gave variable results. Examination of unused portions of these compounds sent for microanalysis showed extensive decomposition during shipment. β-Ionone α′-chloromethyl ketone, which is considerably more stable, gave carbon, hydrogen, and chlorine compositions that were in good agreement with their calculated values. The α′-chloromethyl ketones of β-ionolydeneacetone and retinyl methyl ketone could be stored at −70 °C as dilute solutions in anhydrous diethyl ether, over anhydrous magnesium sulfate containing 1% anhydrous sodium carbonate, for periods greater than 2 months without significant decomposition. Purification of all the α′-chloromethyl ketones was done by preparative thin-layer chromatography since attempts at high vacuum distillation of β-ionone α′-chloromethyl ketone resulted in complete decomposition to uncharacterized products. Table I lists some unsaturated ketones chlorinated by this method. In general good yields were obtained after purification, however, retinyl α′-chloromethyl ketone was consistently recovered in low yields. This may be due to decomposition during the extended exposure to air during chromatography on silica gel plates.

The method herein reported is fairly general and does not require the conversion of the unsaturated ketone to the appropriate enol silane.[3] Although we report only the chlorination of conjugated unsaturated methyl ketones by this method, we have successfully used it for bromination of β-ionone and β-ionolydeneacetone. This method may thus be extended to the halogenation of other conjugated unsaturated ketones possessing functional groups appropriately proctected against the strong base lithium diisopropylamide. It thus provides a simple method for preparing valuable α′-halo ketones of conjugated unsaturated ketones as synthetic intermediates.

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Experimental Section

β-Ionolydeneacrylic acid was synthesized as described.[9] Retinyl methyl ketone and β-ionolydeneacetone were synthesized from the corresponding acids by direct alkylation with methyl lithium.[10] Proton nuclear magnetic resonance spectra were obtained on a Varian EM 390 (90 MHz) instrument at room temperature in deuteriochloroform with 1% tetramethylsilane as reference. IR spectra were recorded on a Beckman IR-10 spectrometer in KBr pellets. Elemental analyses were done by Galbraith Laboratories Inc., Knoxville, TN.

Typical Procedure. β-Ionone α′-Chloromethyl Ketone. Tetrahydrofuran (10 mL) freshly distilled over calcium hydride is purged with dry nitrogen and maintained at 0 °C under an atmosphere of nitrogen. To this is added 1.5 mmol (209 μL) of diisopropylamine (freshly distilled over calcium hydride) followed by 1.2 mmol of methyllithium. Prior to use the methyllithium solution was titrated as described.[11] β-Ionone, 1 mmol (203 μL) dissolved in dry tetrahydrofuran (5 mL) is added dropwise with stirring to the lithium diisopropylamide solution over a period of 20–30 min. The reaction is allowed to stand another 30 min at 0 °C and then cooled to −70 °C in a dry ice/acetone bath. Rapidly 1.3 mmol (174 mg) of *N*-chlorosuccinimide in dry tetrahydrofuran (10 mL) is added to the reaction mixture. The quenched reaction mixture is stirred for 1–2 min at −70 °C, and then aqueous, saturated sodium bicarbonate/sodium chloride solution (20 mL) is added and the temperature is allowed to rise to 0 °C. After thorough mixing of the aqueous and organic phases, the organic layer is separated and the aqueous layer is extracted twice with 10-mL portions of diethyl ether. The combined organic phases are dried over anhydrous sodium sulfate, and then the solvent is removed under reduced pressure. The residue is taken up in a minimum volume of petroleum ether (boiling range 30–60 °C) and applied to preparative thin-layer plates (0.5-mm thick, made from silica gel GF, a product of Merck A.G.) and chromatographed in petroleum ether/diethyl ether (v/v, 90:10). β-Ionone α′-chloromethyl ketone was recovered from the silica gel by eluting with diethyl ether.

Acknowledgment. This work was supported by a grant from the National Eye Institute (EY03350). The authors thank the Department of Chemistry, Tulane University, for use of the nuclear magnetic resonance facilities and Dr. K. Agrawal, Department of Pharmacology, Tulane University Medical Center, for the use of the Beckman IR-10 spectrometer.

Registry No. (*E*)-1-chloro-4-phenyl-3-buten-2-one, 88981-42-4; α′-chloro-β-ionone, 88981-43-5; 1-(β-ionolydene)-3-chloroacetone, 88981-44-6; retinyl α′-chloromethyl ketone, 88981-45-7; (*E*)-4-phenyl-3-buten-2-one, 1896-62-4; β-ionone, 79-77-6; β-ionolydeneacetone, 56013-14-0; retinyl methyl ketone, 67517-37-7.

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Malonaldehyde Derivatives: A General One- or Two-Step Synthesis from Substituted Acetic Acids

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Received August 31, 1983

We wish to contribute a novel method to the synthetic arsenal[1,2] for preparation of malonaldehyde derivatives (**4–6** in Scheme I), which are important in heterocyclic,[2-5] carbocyclic,[5,6] and physiological[7] chemistry. Vilsmeier–Haack–Arnold formylation[1] by chloromethaniminium salts (**9** or **10** in Scheme II) to give malonaldehydes **4** is the most important of the known methods and may be applied to malonic acids, but mesityl and *tert*-alkyl malonic acids are merely decarboxylated under these conditions.[8] The method is also applicable to carboxylic acids **1** sufficiently activated for α-substitution, mainly arylacetic acids;[1,2] however, mesitylacetic acid (**1e** in Scheme I) and alkanoic acids (e.g., **1a–d**) will fail to react, and (2-thienyl)acetic acid is ring-formylated.[9] On the other hand, 1-adamantyl[10] (**4i**), *tert*-butyl,[11,12] and cyclobutyl[13] (**4d**) malonaldehyde derivatives have been obtained by Vilsmeier formylation of acetals or the corresponding enol ethers. Enamines **7** or **8** might be used in these or similar[14] formylations according to Scheme II to give **4**, but probably due to some inconveniences in preparing their parent acetaldehydes (or acetals), such enamines have very rarely been formylated;[15]

Scheme I (Substituents a–e)

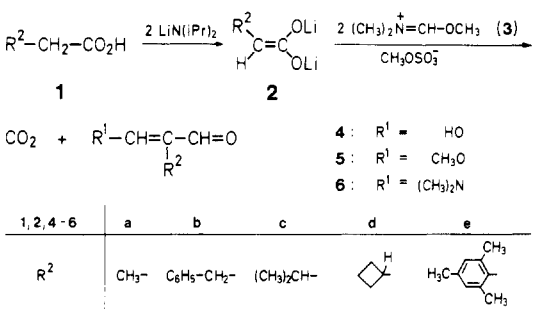

Table I. Preparation of Malonaldehyde Derivatives 4–6 from 1

product	procedure[a]	% yield	mp or bp,[b] °C	lit. mp or bp, °C
4a	B	>16[a]	*a*	*a,c*
4b	B	33	135-137	136-137[d]
5b	B	30	110-115/0.3	*e*
6b	B	35	104-107[f]	108.5-109[d]
6c	A	30	110-130/0.4	90/0.3[d]
6d	A	31	130-135/0.1	110-112/0.05[g]
6e	A[a,h]	33	93-96[f]	*e*

[a] See Experimental Section. [b] °C (bath temp)/torr. [c] References 7, 23, and 24. [d] Reference 24. [e] Reference 22. [f] From cyclohexane. [g] Reference 13. [h] After treatment with **10**.

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