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.

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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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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)

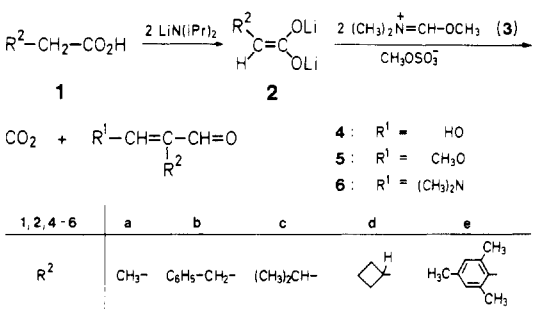

Table I. Preparation of Malonaldehyde Derivatives 4–6 from 1

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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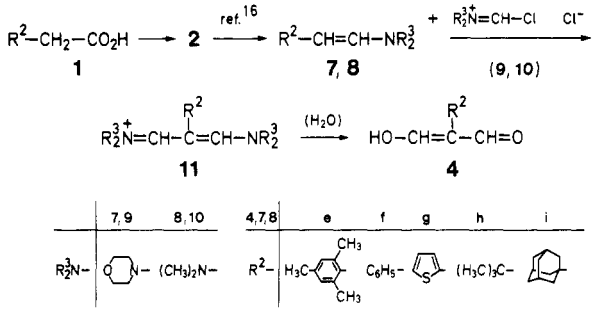
Table II. Formylation of Enamines 7/8 with Vilsmeier Reagents 9/10

product	enamine	reagent	% yield	mp,[a] °C	lit. mp or bp, °C
4e	7e	9	66	181-183.5[b]	c
4e	8e	9	63		
4f	7f	9	47	92-93[d]	92-93,[e] 95[f]
4g	7g	9	45	134-135.5[g]	c
4g	8g	9	52		
4h	7h	9	56	h	52-53/12[h]
4h	7h	10	24	h	
4i	7i	9	42	102-104[c,i]	101.5-102.5[j]
4i	7i	10	16		

[a] Purified. [b] Diethyl ether digestion. [c] Reference 22. [d] From water. [e] Reference 24. [f] Reference 26. [g] From cyclohexane. [h] Decomposes on distillation, ref 12. [i] From methanol. [j] Reference 10.

Scheme II (Substituents e-i)



our recent solution[16] to this problem now opens the enamine route as exemplified below.

One-Step Synthesis (Scheme I)

Our approach starts with the easily available substituted acetic acids 1. The propensity of 1 toward electrophilic α-substitution may be increased by double deprotonation to give the dilithium alkene-1,1-diolates 2.[17-20] We have found *N,N*-dimethylmethoxymethaniminium methyl sulfate (3)[21] to be a reagent of choice for decarboxylative double-formylation of 2 in Scheme I, yielding the desired malonaldehyde derivatives[22] in Table I.[23,24]

Best and reproducible yields of 30–35% were obtained by using 6 (rather than the theoretical 2) equiv of the formylating reagent 3 and by choosing different reaction conditions for the "dianions" 2 with primary (**2a, 2b**) and secondary alkyl (**2c, 2d**) substituents (see Experimental Section). Up to 20% of starting compounds were usually recovered (even with higher reactant ratios), along with decomposed material and small amounts of defined by-products. A rationalization for all of these observations must await supplementary mechanistic studies.

Two-Step Synthesis (Scheme II)

As one step, the procedure presented above appears to be limited to acetic acids 1 with nonaromatic substituents smaller than tertiary. If subjected to similar reaction conditions, mesityl, phenyl, 2-thienyl, *tert*-butyl, and 1-adamantyl acetic acids are only monoformylated[16] to yield the enamines **7e–i** and **8e–g** (Scheme II). Therefore, a further step is required for the synthesis of malonaldehydes **4e–i** in these cases.

The current optimum procedure consists of adding 0.8–0.95 equiv of the enamines 7 or 8 to suspensions of the chloromethaniminium chlorides 9 or 10[25] in dichloromethane at 0 °C. The more soluble vinamidinium chlorides 11 (Scheme II) may be obtained as primary products. However, the most convenient workup prescription aims at isolating the malonaldehydes 4 via alkali extraction, rendering further purification normally unnecessary. The yields in Table II[22,26] are distinctly better with the more reactive 4-(chloromethylene)morpholinium chloride (9) than with the conventional Vilsmeier reagent 10. Enamines and their hydrolysis products R^2CH_2CHO are often recovered from the nonacidic fractions, although preliminary mechanistic studies suggest complete vinamidinium (11) formation prior to workup.

The present synthesis in one or two steps can be recommended as a short approach to malonaldehydes if their preparations by conventional methods meet problems.

Experimental Section

All operations before workup were carried out under dry nitrogen gas. THF had been distilled from potassium benzophenone ketyl. ^1H NMR spectra were obtained with Varian spectrometers A-60 or HA-60-IL at 60 MHz.

***N,N*-Dimethylmethoxymethaniminium Methyl Sulfate[21] (3).** The preparation requires heating of dimethylformamide (9.24 mL, 120 mmol) and dimethyl sulfate (11.36 mL, 120 mmol) at 60–70 °C for 2 h; 3 is used without purification.

2-(2-Propyl)-3-(dimethylamino)propenal (6c). General Procedure A for *sec*-Alkylmalonaldehyde Derivatives, Scheme I. 3-Methylbutanoic acid (20 mmol of 1c in 20 mL of THF) is added to lithium diisopropylamide (40 mmol in 20 mL of THF and 28 mL of hexane) below 9 °C. After stirring 1 h at room temperature, all volatile components are removed at 0.3 torr and 25 °C, the distillation apparatus is opened to a reservoir of dry nitrogen gas, and the residue is dissolved in 20 mL of THF. The crude formylating reagent 3 (120 mmol, prepared above) is added at −70 °C and remains frozen out until the mixture is warmed with stirring to ca. −40 °C, whereupon an exothermic reaction sets in and the precipitate dissolves to give a yellow two-phase system. Stirring is continued for 30 min at 0 °C and then for 2 h at 50–60 °C. After cooling and addition of ice (10 g) and saturated aqueous K_2CO_3 (20 mL), the hydrolyzing mixture is stirred for 15 min at room temperature and then distilled from a steam bath for 1 h.[24] The cooled residue is extracted with ether or better with benzene/ethanol[24] (2:1, 3 × 25 mL) and the dried extract is distilled (Tables I and III). 3-(Dimethylamino)-2-(2,4,6-trimethylphenyl)propenal (**6e**) can similarly be obtained from **1e** and **3** if the mixture before workup is treated with 5 equiv of *N,N*-dimethylchloromethaniminium chloride (**10**).

Benzylmalonaldehyde Derivatives 4b, 5b, or 6b. General Procedure B for Propanoic Acids 1a and 1b, Scheme I. The

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Table III. Spectral Characterization

product	^{1}H NMR ($CDCl_3/Me_4Si$), δ
4b	8.27 (s, 2 CHO), 7.23 (s, C_6H_5), 3.52 (s, CH_2)
4e	8.10 (s, 2 CHO), 6.87 (s, 2 H), 2.25 (s, p-CH_3), 2.09 (s, 2 o-CH_3)
4f	8.60 (s, 2 CHO), 7.32 (s, C_6H_5)
4g[a]	9.20 (very br s, OH), 8.53 (s, 2 CHO), 7.87 (dd, J = 3.7 and 1.3 Hz, 1 H), 7.37 (dd, J = 5.0 and 1.3 Hz, 1 H), 7.05 (dd, J = 5.0 and 3.7 Hz, 4′-H)
4h	14.0 (very br s, OH), 8.48 (br d, 2 CHO), 1.20 (s, 3 CH_3)
4i	14.13 (t, J = 5.8 Hz, OH), 8.38 (d, J = 5.8 Hz, 2 CHO), 2.03 (br, 3 H), 1.77 (pseudo d, 6 CH_2)
5b[b]	9.01 (s, 1-H), 7.03 (s, C_6H_5), 6.65 (s, 3-H), 3.82 (s, OCH_3), 3.40 (s, CH_2)
6b	9.01 (s, CHO), 7.12 (s, C_6H_5), 6.69 (s, CHN), 3.79 (s, CH_2), 2.92 (s, NMe_2)
6c	8.80 (d, J = 2 Hz, CHO), 6.35 (s, CHN), 3.03 (s, NMe_2), 1.26 (d, J = 7 Hz, 2 CH_3)
6d[b]	8.77 (d, J = 1.7 Hz, CHO), 6.27 (s, CHN), 3.03 (s, NMe_2), 1.83 (br m, C_4H_7)
6e	8.88 (s, CHO), 6.72 (s, 3 H), 2.67 (s, NMe_2), 2.23 (s, p-CH_3), 2.03 (s, 2 o-CH_3)

[a] In CD_3COCD_3. [b] In CCl_4.

preparation[17] of the "dianions" **2a** and **2b** containing the unbranched propionic acid moiety is carried out as in procedure A, but the vacuum distillation must be omitted. The formylating reagent **3** (120 mmol, prepared in 40 mL of DMF as *solvent*) is added dropwise at −70 °C, and the mixture is stirred at −28 °C for 90 min and poured into the aqueous workup solution. If hydrolysis is carried out by stirring with iced 2 N hydrochloric chloric acid for 1 h, benzylmalonaldehyde (**4b**, 33%) can be isolated from the acidic product fraction. Working up at pH ca. 7.7 with aqueous phosphate buffer rather than with HCl yields 30% of the methyl ether **5b** by distillation of the neutral product fraction. 2-Benzyl-3-(dimethylamino)propenal (**6b**) is obtained if the reaction mixture is quenched with K_2CO_3 as in procedure A. After heating to 50 °C prior to workup, the resulting **6b** is produced in similar yield (33%) but is heavily contaminated by diisopropylformamide (from **3** and diisopropylamine).

Methylmalonaldehyde[24] (**4a**) is amphoteric[7,23] and hence difficult to isolate; the yield of its sodium salt was therefore determined by conversion to a vinamidinium perchlorate with 2 equiv of *p*-toluidine.

4-(Chloromethylene)morpholinium Chloride (9). Oxalyl chloride (0.86 mL, 10.0 mmol) is added dropwise at 0 °C to a solution of 4-formylmorpholine (1.00 mL, 10.0 mmol) in 10 mL of methylene chloride. Evolution of gases starts slowly, becomes vigorous, and ceases after a few minutes at room temperature; continued stirring for 30 min yields a colorless suspension.

N,N-Dimethylchloromethaniminium chloride[25] (**10**) is prepared from oxalyl chloride and DMF in the same manner.

2-(2,4,6-Trimethylphenyl)propanedial (4e). General Procedure C for Arylmalonaldehydes 4e–g from Enamines 7 and 8, Scheme II. A mixture of crude 4-[2-(2,4,6-trimethylphenyl)-1-ethenyl]morpholine[16] (**7e**, 5.2 mmol) and 4-(chloromethylene)morpholinium chloride (**9**, 6.0 mmol) in 20 mL of dichloromethane is kept in a refrigerator at 4 °C for 13–20 h. (Prolonged treatment at higher temperatures results in decomposition.) The dark red, clear solution is freed from the solvent by vacuum distillation, dissolved in 5 mL of 50% aqueous NaOH plus 10 mL of 1,2-dihydroxyethane, and heated at 65–100 °C for 9–24 h. The alkaline solution is diluted with 50 mL of water, extracted to remove impurities, and then acidified and extracted into methylene chloride. The residue recovered from the dried extracts crystallyzes on digestion with hot CCl_4 (5 mL) to give spectroscopically pure **4e** (Table III) with mp 166–175 °C. Repeated extraction with boiling diethyl ether leaves the analytically pure material (Table II) at the expense of great losses.

***tert*-Alkyl-Substituted Malonaldehydes 4h and 4i from Enamines, Scheme II.** Procedure (C) is followed but, omitting vacuum distillation, the reaction mixtures are stirred with ice for 8 h (**4h**) or 2 h (**4i**). The resulting acidic two-phase systems are treated with excess 2 N sodium hydroxide solution; after separation from nonacidic byproducts, **4h** and **4i** are obtained by acidification.[10,12] The crude (1-adamantyl)malonaldehyde (**4i**) is sufficiently pure to show ^{1}H NMR triplet splitting of its OH signal at room temperature.

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Registry No. **1a**, 79-09-4; **1b**, 501-52-0; **1c**, 503-74-2; **1d**, 6540-33-6; **1e**, 4408-60-0; **1f**, 103-82-2; **1g**, 1918-77-0; **1h**, 1070-83-3; **1i**, 4942-47-6; **3**, 21511-55-7; **4a**, 57325-58-3; **4b**, 88905-12-8; **4e**, 88905-13-9; **4f**, 4432-64-8; **4g**, 88905-14-0; **4h**, 88905-15-1; **4i**, 88905-16-2; **5b**, 88905-17-3; **6b**, 17773-58-9; **6c**, 87234-38-6; **6d**, 51007-69-3; **6e**, 88905-18-4; **7e**, 58047-49-7; **9**, 59611-75-5; **10**, 3724-43-4; dimethylformamide, 68-12-2; dimethyl sulfate, 77-78-1; oxalyl chloride, 79-37-8; 4-formylmorpholine, 4394-85-8.

Synthesis of Chiral Acetic Acid by Chirality Transfer from D-Glucose

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Although a number of approaches have been described,[1] there is still a need for more efficient methods for the synthesis of compounds containing chiral methyl groups of high configurational purity for studies on the cryptic stereochemistry of bioorganic reactions. One of us recently described[2] a new synthesis of chiral [2-^{2}H]glycine using D-glucose as chiral template. The key intermediates in the synthesis, (1′*S*,2′*R*)-**1** and (1′*R*,2′*S*)-**2**, were prepared from the readily available[3,4] 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-3-hexulofuranose (**3**) in four steps by stereoselective addition of acetylene, deuteration of the acetylenic hydrogen, stereospecific reduction to a deuterated (*E*)-ethenylcarbinol and epoxidation.[5] It was suggested[2] that the same intermediates could also be converted to chiral acetic acid. We now report the implementation of this suggestion.

Treatment of **1** or **2** with [^{3}H]$LiAlH_4$ in tetrahydrofuran (THF) gave the corresponding methylcarbinols **4** or **5** carrying a chiral methyl group, which were oxidized with permanganate/periodate[6] to acetic acid (Scheme I). Chirality analysis of the acetic acid by the method of Cornforth et al.[7] and Arigoni and co-workers[8] under the conditions described[9] gave F values[10] of 22.5 ± 0.3 for the material from the *S* epoxide **2**, indicating 95% ee of (*S*)-[2-^{2}H,^{3}H]acetate. The material from the *R* epoxide **1** had F = 79 ± 1.7, corresponding to 100% ee (*R*)-[2-^{2}H,^{3}H]acetate. Although the radiochemical yield is only modest (0.4–1% based on [^{3}H]$LiAlH_4$), owing undoubtedly to extensive decomposition of the tritiated metal hydride

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