Department of Energy, under Grant DE-ACO2-78ERO5006.

Supplementary Material Available: Table of crystal and experimental data for X-ray structural studies (Table V), tables of positional and thermal parameters of the atoms of $11 \cdot H_2O$, methylsubstituted 11, [benzylamine complex of 11]$\cdot 2.6CH_2Cl_2$, and [benzylammonium complex of 11] + ClO_4^- (Tables VI, VII, VIII, and IX, respectively), and tables of selected bond lengths and angles of those compounds (Tables X, XI, XII, and XIII, respectively) (13 pages). Ordering information is given on any current masthead page.

(*E*)-1-Bromo-3,3-diethoxy-1-propene (Diethyl Acetal of 3-Bromoacrolein). A Versatile Synthon for the Synthesis of Furans, Butenolides, and (*Z*)-Allyl Alcohols

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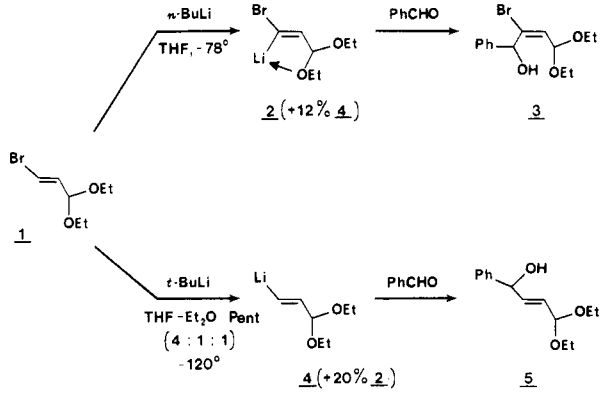
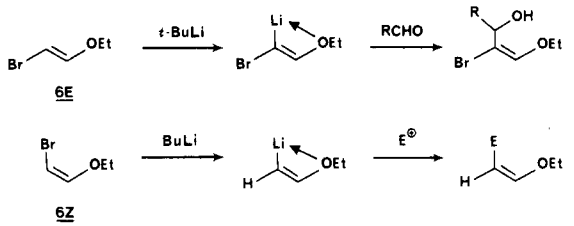
A convenient preparation of the title compound allowed a study in which the α-lithio-α-bromovinyl acetal **2** could be evaluated as a precursor to furans, butenolides, and (*Z*)-allyl alcohols. Reaction of the lithio derivative with aldehydes, ketones, and alkyl halides took place in a convenient manner. The bromine was either transformed at a later stage to an alkyl group or reduced to hydrogen with tin hydrides. The carbonyl adducts of **2** could be transformed, on mild hydrolysis, to butenolides or 2,3-disubstituted furans. An interesting solvent system (1:1:1 THF–Et_2O–pentane) allowed vinyl proton abstraction and halogen–metal exchange to take place in one pot.

During the course of our synthetic work on the total synthesis of (±)-maytansine and (–)-maysine,[1] we utilized an interesting version of 3-bromoacrolein, namely the diethyl acetal **1**, which, although prepared earlier,[2] was difficult to reproduce on multigram scale. We were successful in preparing this compound on 20-g scale[1] and now report our findings wherein **1** can serve as a useful precursor to furans, butenolides, and (*Z*)-allyl alcohols. These compounds have attracted considerable attention[3] in recent years due to their presence in a number of naturally occurring materials.



When the bromo acetal **1** was treated with *n*-butyllithium in THF (–78 °C), followed by the addition of benzaldehyde after 5 min, the bromoallylic alcohol **3** was obtained accompanied by 12% of the debromoallylic alcohol **5**. The bromo alcohol **3** was isolated in 60–65% yield after chromatography. On the other hand, when **1** was treated with 2.3 equiv of *tert*-butyllithium[4] in Trapps solvent[5] at –120 °C and benzaldehyde added, the debromoallylic alcohol **5** was isolated (61%) accompanied by 20% of the bromo alcohol **3**. Thus, at lower temperatures halogen–metal exchange was the predominant process, whereas with the less encumbered base (*n*-BuLi) at higher temperature, proton abstraction became the major event.[4] Halogen–metal exchange (**1** → **4**) has been observed on numerous occasions[6] while deprotonation of α-halovinyl compounds (**1** → **2**) affording α-lithio-α-halovinyl derivatives has been examined less frequently. Schlosser has shown[7] that the (*E*)-bromovinyl ether **6E** is deprotonated with strong base affording the bromovinyl adducts on addition to carbonyls. On the other hand, the (*Z*)-



bromovinyl ether **6Z** undergoes the expected halogen–lithium exchange with high stereoselectivity. More recently, Smithers[8] reported the behavior of the 1,1-dibromovinyl ether **7** and showed that the α-lithio-α-bromo derivative **8** could be formed and induced to react with

(1) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

(2) Protopova, T. V.; Skoldinov, A. P. *Zh. Obschch. Khim.* **1959**, *29*, 963; *Chem. Abstr.* **1960**, *54*, 1288*d*.

(3) Katsumura, S.; Ohsuka, A.; Katake, M. *Heterocycles* **1978**, *10*, 87. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1980**, *21*, 731. Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131. Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, 5191. Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2891. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615. Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819. Sato, F.; Hiroshi, K.; Youichi, T. *Tetrahedron Lett.* **1984**, *25*, 5063. Tanis, S. P.; Head, D. B. *Tetrahedron Letters* **1984**, *25*, 4451. Schmidt, R. R.; Miyata, O. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 637. Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835 and references cited therein.

(4) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(5) Kobrich, G.; Trapp, H. *Chem. Ber.* **1966**, *99*, 680.

(6) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N. Y.)* **1979**, *26*, 1. McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, *25*, 5977 and references cited therein.

(7) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.

(8) Smithers, R. H. *J. Org. Chem.* **1933**, *88*, 2095 and references cited therein.

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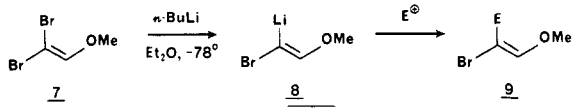
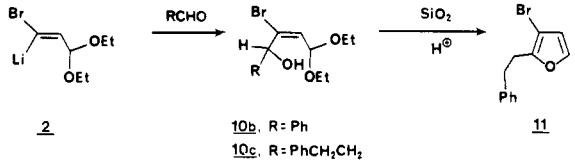
various carbonyl compounds to give **9**. Thus, it can be

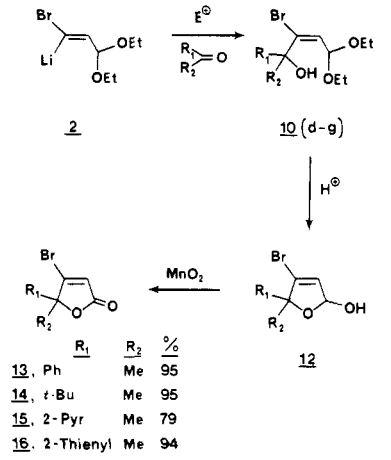


concluded that the proton cis to a chelating group is more prone to abstraction (or halogen–metal exchange) due to the stability imparted by chelation.

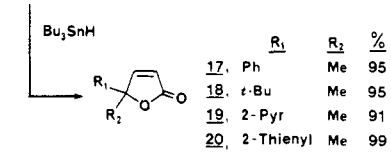
The synthetic utility of the lithiobromovinyl acetal **2** was demonstrated by addition of a number of electrophiles and gave generally good yields of the alkylated acetal **10** (Table I). In most instances, complete characterization was not carried out, although the product appeared to be >95% pure by TLC and NMR spectroscopy. When the electrophile was an aldehyde the resulting allylic alcohol **10** could be smoothly transformed into furans (e.g., **11**) by treatment with silica gel–oxalic acid mixtures. In this



fashion, a route to 2-substituted 3-bromofurans was achieved. If the electrophiles added to **2** were ketones, **10** was obtained, which on aqueous acid treatment gave the unsaturated bromolactols **12**, and subsequent treatment with manganese dioxide gave the bromobutenolides **13–16** in excellent yields. Thus, the addition of **2** to various



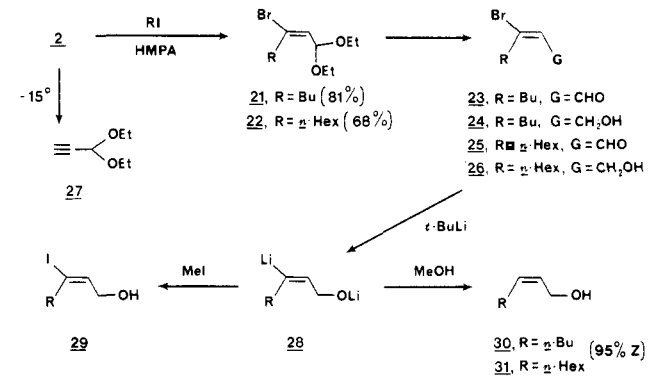
	R_1	R_2	%
13,	Ph	Me	95
14,	*t*-Bu	Me	95
15,	2-Pyr	Me	79
16,	2-Thienyl	Me	94



	R_1	R_2	%
17,	Ph	Me	95
18,	*t*-Bu	Me	95
19,	2-Pyr	Me	91
20,	2-Thienyl	Me	99

ketones gave rise to a series of 5,5-disubstituted 4-bromobutenolides which were readily transformed with tri-*n*-butyltin hydride to the 5,5-disubstituted butenolides **17–20**.

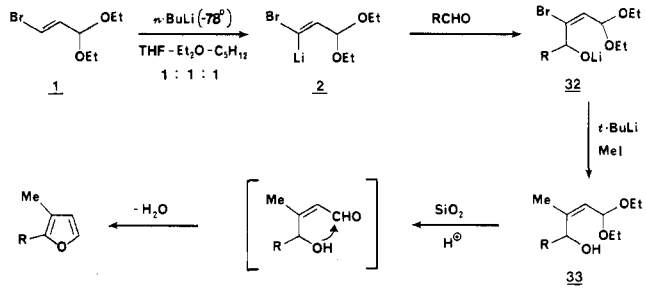
The lithiobromovinyl acetal **2** was also found to react with alkyl iodides to give the 3-alkyl-3-bromo acetals **21** and **22** in fair yields. In order to preserve the stability of the lithio derivative **2** at temperatures required for the alkylation (ca. −15 °C), 3.0 equiv of HMPA were introduced prior to addition of the alkyl halide. In its absence, the lithiobromovinyl acetal, on warming to −15 °C, decomposed, giving ca. 20% of the acetylene **27** as the only isolable product. The acetals **21** and **22** were hydrolyzed (silica gel–oxalic acid) to the α,β-unsaturated aldehydes **23** and **25** and immediately reduced with diisobutyl-



21, R = Bu (81%)
22, R = *n*-Hex (68%)
23, R = Bu, G = CHO
24, R = Bu, G = CH_2OH
25, R = *n*-Hex, G = CHO
26, R = *n*-Hex, G = CH_2OH
30, R = *n*-Bu (95% Z)
31, R = *n*-Hex

aluminum hydride to the corresponding allylic alcohols **24** and **26**. The bromine was replaced by hydrogen by treatment with *tert*-butyllithium in ether at −78 °C followed by methanol quench to give the (*Z*)-allylic alcohols **30** and **31**. NMR, VPC, and HPLC analyses indicated that these allyl alcohols were 95 ± 1% *Z* isomers. Interestingly, when the dilithiovinyl compound **28** was treated with methyl iodide, no methylation occurred and a 50% yield of the vinyl iodide **29** was the only product isolated. This reaction has been discussed and observed by Seebach.[4] That this iodination process can be circumvented by appropriate choice of solvent (to minimize radical processes) is shown in the following discussion leading to disubstituted furans.

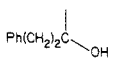
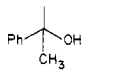
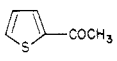
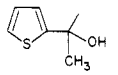
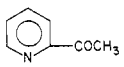
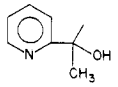
A convenient synthesis of 2-substituted 3-methylfurans **34–37** was also achieved by slight modification of the preceding methodology. The route involved the use of a three-component solvent system comprised of equal ratios of THF, ether, and pentane. This solvent system was found to allow metalation of **1** to **2** and further allow halogen–metal exchange of **32** followed by methylation to



34, R = 1-naphthyl (68%)
35, R = Ph (61%)
36, R = $PhCH_2CH_2$ (41%)
37, R = *t*-Bu (59%)

33. Acidic hydrolysis gave the furans in 40–70% overall yields. The synthesis of **33** from **1** was accomplished in "one-pot", while the acidic cleavage to the furans required that the entire reaction mixture containing **33** be poured into the silica gel–oxalic acid–methylene chloride mixture. The decision to use the ternary solvent was the result of a study shown in Table II wherein conditions were sought for metalation–alkylation of **1** → **32** (R = Ph). Since the halogen–metal exchange of **32** was found to be most efficient in ether–pentane mixtures, it was important to effect efficient initial metalation of **1**, which is poor in ether–pentane mixtures, and best in THF. Thus, the reaction of **1** with *n*-BuLi and treatment with benzaldehyde **32** (R = Ph) was examined in various solvent mixtures. Although metalation to the lithiobromovinyl acetal **2** was satisfactory in THF, THF–DME, and THF–TMEDA, these solvents were poor in promoting halogen–metal exchange for the bromovinyl derivative **32** and subsequent methylation to

Table I. Metalation and Alkylation of (*E*)-1-Bromo-3,3-diethoxy-1-propene (1)

		10			
	electrophile	R	mp, °C	% yield[a]	^{1}H NMR
a	D_2O	D		62	1.20 (t, 6 H), 3.56 (d of q, 4 H), 4.87 (d, 1 H), 6.19 (m, 1 H)
b	PhCHO			60	1.22 (d of t, 6 H), 3.10 (s, 1 H), 3.60 (m, 4 H), 5.32 (d, 1 H), 5.70 (s, 1 H), 6.15 (d, 1 H), 7.30 (m, 5 H)
c	$Ph(CH_2)_2CHO$			65	1.20 (d of t, 6 H), 1.67-2.17 (m, 2 H), 2.5-2.9 (m, 3 H), 3.48 (d of q, 4 H), 4.42 (t, 1 H), 5.02 (d, 1 H), 6.02 (d, 1 H), 7.11 (s, 5 H)
d				69[b]	1.20 (t, 6 H), 1.4-2.5 (m, 7 H), 3.57 (m, 4 H), 5.4-6.2 (m, 4 H)
e	$PhCOCH_3$		78-79	51[c]	1.05 (t, 3 H), 1.20 (t, 3 H), 2.81 (s, 3 H), 3.42 (m, 4 H), 4.32 (s, 1), 5.32 (d, 1 H), 6.15 (d, 1 H), 7.1-7.6 (m, 5)
f				42	1.18 (d of t, 6 H), 1.97 (s, 3 H), 3.57 (m, 4 H), 4.74 (s, 1), 5.50 (d, 1 H), 6.12 (d, 1 H), 6.80-7.3 (m, 3 H)
g				80	1.24 (d of t, 6 H), 1.94 (s, 3), 3.60 (d of q, 4 H), 5.70 (d, 1 H), 5.77 (s, 1 H), 6.11 (d, 1 H), 6.9-7.9 (m, 3 H), 8.3-9.60 (m, 1 H)
h	*n*-BuI	*n*-Bu		81	0.65-1.85 (m, 7 H), 1.18 (t, 6 H), 2.50 (m, 2 H), 3.50 (d of q, 4 H), 5.01 (d, 1 H), 5.90 (d, 1 H)

[a] Isolated yields purified on flash or radial chromatography using 2-3% triethylamine in ether-hexane (1:10 to 1:1). If the Et_3N was omitted, some hydrolysis of the acetal results. [b] Anal. Calcd for $C_{13}H_{21}O_3Br$: C, 51.16; H, 6.97. Found: C, 51.01, H, 6.78. [c] Recrystallized from hexane.

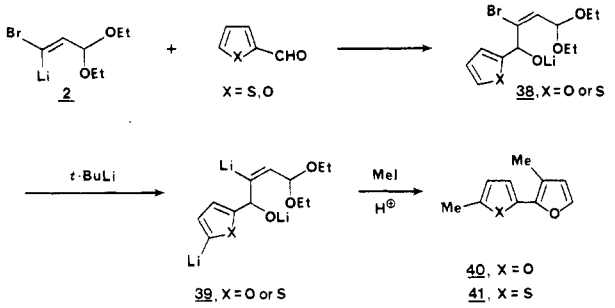
Table II. Solvent Effects on Metalation-Alkylation of 1 to 32 (R = Ph)

solvent	*T*, °C	% 32[a]	% 1[a]
THF	-100	60	15
THF	-78	60	15
pentane	-120	0	80
pentane	-78	0	80
pentane	-78	0	80[b]
Et_2O	-78	20	60
DME	-60	35	20[c]
DME-THF (1:1)	-78	60	15
DME-hexane (1:1)	-60	30	20[c]
THF-HMPA (4:1)	-78	0	80
THF-TMEDA (8:1)	-78	60	15[d]
THF-pentane-Et_2O (1:1:1)	-78	63	15

[a] Isolated yields of products and starting material. [b] *tert*-Butyllithium used as the base. [c] Contains 30% of 5 as a result of halogen-metal exchange on 1. [d] Yield determined by NMR analysis.

33. However, the ternary mixture of THF-ether-pentane allowed both metalation processes to proceed in a satisfactory manner.

Two examples of furan syntheses involving 2-thiophenecarboxaldehdye and furfural gave, on introduction of the lithiobromovinyl acetal 2, the adducts 38.



When either of these were treated with *tert*-butyllithium, not only did halogen-metal exchange take place but deprotonation of the heterocyclic ring also occurred (39). Methyl iodide addition to the latter gave the dimethyl derivatives 40 and 41 in 53% and 57% yields, respectively. The metalation of furans[9] and thiophenes[10] are well-known to occur with *n*-butyllithium at the 2-position in high yields, thus metalation of 38 to 39 was not unexpected.

In summary, bromoacrolein diethyl acetal, now readily available, has shown useful synthetic properties as a viable entity for various three-carbon homologations and may be considered the synthetic equivalent of $^-$C=CHCHO.

Experimental Section[11]

(*E*)-1-Bromo-3,3-diethoxy-1-propene (1). The procedure reported previously[1] is unchanged, and only ^{13}C NMR data, not reported earlier, is given: ^{13}C NMR ($CDCl_3$), 25 MHz) δ 15.17, 60.94, 99.71, 110.46, 134.86.

(*E*)-4-Hydroxy-4-phenyl-1,1-diethoxy-2-butene (5). To 7 mL of Trapp solvent [THF-pentane-Et_2O (4:1:1)] was added 0.095 g (0.45 mmol) of vinyl bromide 1. This was cooled to ca. -120 °C (95% EtOH/N_2) for 15 min and 0.289 mL (1.11 equiv, 0.50 mmol) of *tert*-butyllithium was added. The solution began to freeze and was allowed to melt, returned to -120 °C, and stirred for 45 min without further freezing. Benzaldehyde, 0.061 mL (0.60 mmol, 1.33 equiv) was slowly added neat. Each drop of benzaldehyde made the solution more orange from the initial yellow color. This was warmed until all color was gone and quenched with excess methanol, which produced a return of the initial yellow color. The solution was warmed, added to 10 mL of Et_2O, washed with brine (2 × 10 mL), dried (K_2CO_3), filtered, and concentrated (in vacuo) to 0.100 g (93%). PLC purification (50% Et_2O/pentane; R_f 0.3) on 0.078 g afforded 0.051 g (61% overall): NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 6), 2.66 (br s, 1), 3.54 (d of q, J = 2.7, 7 Hz, 4), 4.89 (d, J = 4.7 Hz, 1), 5.18 (d, J = 4.7 Hz, 1), 5.86 (ABX, J = 4.5, 16 Hz, 2), 7.15-7.0 (m, 5).

1-Substituted (*E*)-1-Bromo-3,3-diethoxy-1-propene 3 and 10a-h. General Procedure for Table I. To 8 mL of THF was added 0.100 mL (1.0-1.05 equiv, 0.57 mmol) of the bromovinyl acetal 1 and the mixture cooled to -78 °C. *n*-Butyllithium (0.60

(9) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216.
(10) Gilman, H.; Shirley, D. A. *J. Am. Chem. Soc.* **1949**, *71*, 1870.
(11) Combustion Analyses were performed by Micro-Tech Labs, Skokie, IL, or MicAnal, Tuscon, AZ. NMR spectra were taken at 100 MHz on a JEOL FX-100 instrument.

mmol, 1.05 equiv in hexane) was added and the solution stirred for 5 min, after which the carbonyl compound, alkyl halide, or deuterium oxide (1.05 equiv) was introduced. Stirring was continued at −78 °C for 10 min and the solution allowed to warm to room temperature. If an alkyl halide was to be introduced, 3 equiv of HMPA in THF (33% v/v) was slowly added. If the solution color increased significantly (yellow to orange), this was an indication of significant acetylene (**27**) formation and the HMPA should be added even slower. To the yellow solution was added 1.05 equiv of alkyl halide, stirring was continued for 2 h at −78 °C, and then the solution was allowed to warm between −25 and −15 °C and stirred at this temperature for 2 h. After the solution reached room temperature (12–15 h), excess methanol was added, and the THF was removed under vacuum and the residue taken up in hexane, washed with brine (3 × 20 mL), dried (K_2CO_3), and concentrated to give crude product. Purification was accomplished with either preparative thin-layer chromatography or flash chromatography with ether–pentane containing 2–3% triethylamine. This solvent system also performed well by using a Chromatotron (radial chroamtography, Harrison Assoc., Palo Alto, CA).

2,5-Dihydro-2-hydroxy-4-bromo-5-methyl-5-(2-pyridyl)-2,5-dihydrofuran (12, R_1 = 2-pyridyl; R_2 = Me). To 125 mL of THF were added 1.55 g of the hydroxy acetal **10g** and 25 mL of 5% HCl and the mixture stirred at ambient temperature overnight. The solution was washed once with hexanes (50 mL). The aqueous layer was neutralized with 15% KOH and made basic with K_2CO_3 to a pH of 8.0–9. Extraction with hexanes (3 × 50 mL) followed by a brine wash (2 × 50 mL), drying (K_2CO_3), and concentration in vacuo gave 0.937 g (79%) of a solid. Recrystallization from diethyl ether gave rectangular crystals: mp 108–108.5 °C; NMR ($CDCl_3$) δ 1.96 (s, 3), 5.77–6.15 (m, 2), 6.45–6.80 (m, 1), 7.0–7.85 (m, 3), 8.4–8.6 (m, 1).

Anal. Calcd for $C_{10}H_{10}O_2NBr$; C, 46.90; H, 3.94. Found: c, 46.86; H, 3.80.

The remaining lactols **12** were not isolated or characterized but were oxidized to the furanones **13–16** directly. Reduction was also done on crude bromofuranones **13–16** and only the furanones **17–20** were characterized.

4-Bromo-4-methyl-5-(2-pyridyl)-2(5*H*)-furanone (15). The lactols **12** above were oxidized by using 6 times the weight of MnO_2 on carbon[12] and 10 mL dichloromethane for every gram of lactol. The mixture was stirred at room temperature overnight and then filtered through Celite which was washed twice with dichloromethane. Concentration gave a residue, which was purified by radial chromatography (65% ether in hexane). From 144 mg of **12** (R_1 = 2-pyridiyl; R_2 = Me) and with 850 mg of MnO_2 on carbon, there was obtained 144 mg (ca. 100%) of the furanone: mp 76–77 °C; NMR ($CDCl_3$) δ 2.06 (s, 3), 6.32 (s, 1), 7.0–7.85 (m, 3), 8.48–8.70 (m, 1).

Anal. Calcd for $C_{10}H_8O_2BrN$: C, 47.24; H, 3.17. Found: C, 47.33; H, 2.82.

The remaining furanones **13**, **14**, and **16** were not isolated in pure form but were reduced directly to the furanones **17**, **18**, and **20**.

5-Methyl-5-(2-pyridyl)-2(5*H*)-furanone (19). A THF solution containing 130 mg of the bromofuranone **15**, 1.1 equiv of tri-*n*-butyltin hydride, and 5–10 mol % of azoisobutyronitrile was heated to reflux overnight and then the THF removed in vacuo. The residue was dissolved in a mixture of 10 mL of ethyl acetate and 20 mL of saturated ethanolic potassium fluoride. After the mixture was stirred at ambient temperature overnight, the colorless precipitate was removed by filtration through Celite and the solution concentrated in vacuo. Purification of the crude residue was performed with radial chromatography (silica gel) and gradually eluting with hexanes to 65% ether–hexane. The pure product **19**, 81 mg (91%), was obtained in 58% overall yield from **1**: NMR ($CDCl_3$) δ 1.89 (s, 3), 6.03 (d, J = 6 Hz, 1), 7.05–7.75 (m, 3), 7.82 (d, J = 6 Hz, 1), 8.42–8.60 (m, 1).

Anal. Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.43; H, 5.41.

The following 5,5-disubstituted furannes were all prepared with the typical procedure described for **19**.

(12) Carpino, L. A. *J. Org. Chem.* **1970**, *35*, 3971.

5-Methyl-5-phenyl-2(5*H*)-furanone (17). Following the general procedure, 0.76 mL (1.05 equiv, 6.00 mmol) of acetophenone was used. Reductive removal of the bromine was performed on 0.200 g (0.80 mmol), and 0.155 g (95%) of **17** as an oil was obtained after purification (RPLC; gradient, hexanes, 40% Et_2O/hexanes). The overall yield based on the starting vinyl bromide *17* was 46%, isolated and purified: NMR ($CDCl_3$) δ 1.85 (s, 3), 6.00 (d, J = 6 Hz, 1), 7.33 (s, 5), 7.62 (d, J = 6 Hz, 1).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.33; H, 5.93.

5-Methyl-5-*tert*-butyl-2(5*H*)-furanone (18). In the usual manner 0.76 mL (1.05 equiv, 6.00 mmol) of pinacolone was used. The hydroxy acetal was purified by flash chromatography (5% Et_2O/2% Et_3N/93% hexanes) and gave 0.830 g of **18** as an oil (51%). The reduction of the bromide was performed on 0.080 g, and after purification (PTLC; 50% Et_2O/hexanes (R_f 0.25)) gave 0.065 g (overall yield, 44%) of **18**: IR 1750, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 9), 1.50 (s, 3), 5.97 (d, J = 6 Hz, 1), 7.42 (d, J = 6 Hz, 1).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 68.77; H, 9.63. This material was air sensitive and a satisfactory combustion analysis could not be obtained.

5-Methyl-5-(2-thienyl)-2(5*H*)-furanone (20). In the usual manner, 0.65 mL (1.05 equiv, 6.00 mmol) of 2-acetylthiophene was used in the reaction sequence. The tin hydride reduction was performed on 0.165 g of bromobutenolide and after purification (RPLC, graident elution, first hexanes up to 70% ether–hexanes) gave 0.113 g of furanone (overall yield, 39%): NMR ($CDCl_3$) δ 1.90 (s, 3), 6.05 (d, J = 6 Hz, 1), 7.0 (m, 2), 7.24 (m, 1), 7.54 (d, J = Hz, 1).

Anal. Calcd for $C_8H_5O_2S$: C, 58.17; H, 3.05. Found: C, 59.62; H, 4.36. This material was air sensitive precluding a satisfactory combustion analysis.

General Procedure for the Synthesis of (*E*)-3-Alkyl-3-bromo-1,1-diethoxy-2-propenes 21 and 22. To a two-necked 10-mL flask, fitted with septa and stir bar, were added 7 mL of THF and 0.100 mL of (*E*)-1-bromo-3,3-diethoxy-1-propene **1**, and the mixture was cooled to −78 °C. Addition of 1.05 equiv of *n*-BuLi generated a faint yellow solution. The *slow* addition of 3 equiv of hexamethylphosphoric triamide in THF (a 33% v/v solution) should produce only a slight increase in the intensity of the yellow color of the solution. The color of the solution is a qualitative determination of the amount of acetylene formation and decomposition of the anion. The more intense the color became (i.e., orange to deep orange), the more undesired compounds were formed. The alkyl iodide (1.05 equiv) was introduced neat and stirred at −78 °C for 2 h, warmed to between −25 and −15 °C, and stirred for an additional 2 h. Finally, after allowing the solution to warm to ambient temperature overnight, the THF was removed in vacuo. The residue was dissolved in hexanes (25 mL), and the HMPA was removed by washing with brine (3–5 × 20 mL). The organic layer was dried (K_2CO_3) filtered, and concentrated in vacuo to give an oil.

Purification was achieved with either flash chromatography or preparative thin-layer chromatography and a solvent system containing 2% triethylamine. The desired material was visualized with a 6% w/v solution of ceric ammonium nitrate in 2 N nitric acid.

General Procedure for the Hydrolysis of (*E*)-Alkyl-1-bromo-3,3-diethoxy-1-propene to α,β-Unsaturated Aldehydes 23 and 25. In a 25-mL Erlenmeyer flask were placed 10 mL of methylene chloride, 2 g of column grade silica gel, and 1 mL of saturated aqueous oxalic acid. This was vigorously stirred until the silica gel was evenly coated with the aqueous solution. The purified acetal was then added and stirred at 0 °C for 30 min. The solution was filtered through Celite and concentrated in vacuo to an oil. The stability of these compounds was not determined. Because they may decompose or isomerize upon standing, they were immediately reduced.

General Synthesis of (*E*)-Alkyl-3-bromoallyl Alcohols 24 and 26. To a solution of the crude aldehyde dissolved into ether (0.1 g/5 mL) and cooled to 0 °C was added 1.1 equiv of diisobutylaluminum hydride (1 M in Et_2O), and this solution was stirred for 15 min. Excess reagent methanol was added, and the reaction was stirred for 1 h with warming to room temperature. The solution was filtered through Florisil on top of Celite and

concentrated in vacuo to give an oil.

General Synthesis of (*Z*)-Allyl Alcohols 30 and 31. To a solution of 0.10 g of bromide dissolved in 5 mL of Et_2O at −78 °C was added 3.3 equiv of *tert*-butyllithium and warmed to −15 °C and stirred for 15 min. Methanol was then added to the solution. It was poured into brine (10 mL), extracted (2 × 10 mL) with hexanes, dried (K_2CO_3), and concentrated at 160 torr to an oil.

(*E*)-1,1-Diethoxy-3-bromo-2-heptene (21). Following the general procedure, 0.068 mL (1.05 equiv) of 1-iodobutane was used and afforded 0.123 g (81%) of crude product. Purification using 17% EtOAc/hexanes/3% Et_3N afforded 0.092 g (61%) of purified product as an oil: NMR ($CDCl_3$) δ 0.65–1.85 (m, 7 H), 1.18 (t, J = 7 Hz, 6) 2.50 (m, 2), 3.50 (d of q, J = 2, 7 Hz, 4) 5.01 (d, J = 6 Hz, 1), 5.90 (d, J = 6 Hz, 1).

(*E*)-3-Bromo-2-heptenal (23). Following the general procedure as above, 0.140 g of acetal **21** was hydrolyzed to 0.115 g(ca. 100%). NMR of the crude compound shows about 20% acetylene compound. **23**: NMR ($CDCl_3$) δ 0.7–1.9 (m, 7), 2.98 (t, J = 7 Hz, 2), 6.45 (d, J = 7 Hz, I), 9.72 (d, J = 7 Hz, I); IR (film) 2935 (w), 1675 (s), 1600 (m) cm^{-1}. This compound was immediately reduced. This spectrum was consistent with that of the natural product.[13]

(*E*)-3-Bromo-2-heptenol (24). The aldehyde (0.105 g) was reduced following the general procedure and gave after PTLC purification (17% EtOAc/hexanes) 0.067 g (64%) of **24**. The alcohol has a boiling point of about 200 °C and must be Kugelrohr distilled to remove the solvents: NMR ($CDCl_3$) δ 0.7–1.9 (m, 7); 2.45 (br t, J = 6 Hz, 2), 3.20 (s, 1), 4.11 (d, J = 7.5 Hz, 2), 6.08 (br t, J = 7.5 Hz, 1). This spectrum was consistent with that of the natural product.[13]

(*Z*)-2-Heptenol (30). To 0.428 g of purified bromo alcohol **24**, on treatment with *t*-BuLi, gave after a methanol quench the cis alcohol, 0.280 g. PTLC (40% Et_2O/hexane) gave 0.101 g of purified alcohol (36%). GC (20% Carbowax 20 m on Chromosorb W, 60–80 mesh, 100 °C) analysis indicated that the isomer ratio was 94% *Z* and 6% *E*: NMR ($CDCl_3$) δ 0.6–1.8 (m, 7), 2.10 (m, 2), 2.50 (s, 1), 4.20 (br d, 2), 5.55 (m, 2). Some compound was lost upon isolation due to the low boiling point and high vapor pressure. The spectrum was consistent with that of the known compound.[14]

(*E*)-3-Bromo-1,1-diethoxy-2-nonene (22). Following the general procedure, 0.100 mL (1.25 equiv) of *n*-hexyl iodide afforded without purification 0.117 g (68%) of **22**: NMR ($CDCl_3$) δ 0.68–1.82 (m, 17), 2.48 (m, 2), 3.51 (d of q, J = 2, 7 Hz, 4), 5.00 (d, J = 6.5 Hz, 1), 5.90 (d, J = 6.5 Hz, 1).

(*E*)-3-Bromo-2-nonenal (25). Following the general procedure above, 0.376 g of the acetal **22** were hydrolyzed to 0.282 g (100%) of **25** and carried on to the next step without purification: NMR ($CDCl_3$) δ 0.5–1.90 (m, 11), 2.98 (t, J = 6.5 Hz, 2), 6.43 (d, J = 6.5 Hz, 1), 9.71 (d, J = 6.5 Hz, 1).

(*E*)-3-Bromo-2-nonenol (26). Following the above procedure, 0.282 g of aldehyde was reduced by using the DIBAL procedure and afforded, after purification (PLC; 20% EtOAc/hexanes), 0.143 g of the alcohol (51%): NMR ($CDCl_3$) δ 0.67–2.00 (m, 11), 2.50 (m, 2), 4.11 (d, J = 8 Hz, 2), 6.11 (t, J = 8 Hz, 1).

(*Z*)-2-Nonenol (31). Following the general procedure above, 0.134 g of bromo alcohol **26** afforded, after purification (PLC, 20% EtOAc/hexanes), 0.091 g (70%) of **31**: NMR ($CDCl_3$) δ 0.57–1.68 (m, 11), 2.04 (m, 2), 4.13 (m, 2), 5.50 (m, 2). The spectra was consistent with that of the known compound.[15]

General Procedure for the Synthesis of 2-Substituted 3-Methylfurans 34–37. To a 25-mL two-necked flask, fitted with septa and stir bar, containing a dry, oxgyen-free argon atmosphere and 15 mL of a solution of 1:1:1 dry distilled THF–Et_2O–pentane was added 0.300 mL (1.707 mmol, 1.0 equiv) of (*E*)-1-bromo-3,3-diethoxy-1-propene (**1**), and the mixture was cooled to −78 °C (dry ice/acetone). The vinyl anion was formed by the addition of 1.05 equiv of *n*-butyllithium and stirring for 5 min. The aldehyde (1.05 equiv) was then added and stirred for 5 min. The dianion (and in some cases a trianion for **40**, **41**) was formed by the addition of 2.3 equiv of *tert*-butyllithium and stirring for 30 min at −78 °C. The solution was warmed to −15 °C, and excess methyl iodide was added and stirred for 5 min at −15 °C followed by warming to ambient temperature. The reaction was quenched with methanol. The hydrolysis solution was then prepared as follows: In a 125-mL Erlenmeyer flask were placed 3 g of a silica gel (column grade), 20 mL of methylene chloride, and 1.5 mL of saturated aqueous oxalic acid.[16] This was vigorously stirred to evenly coat the silica gel with the aqueous acid. The entire reaction mixture was then added to the hydrolyzing solution and stirred for 15 min at ambient temperature. The mixture was then filtered through Celite and concentrated to the crude furan. Purification was achieved with radial preparative chromatography with 0–2% ether–hexane solutions on silica gel.

2-Phenyl-3-methylfuran (35). Following the general procedure, 1.05 equiv (0.182 mL, 1.79 mmol) of benzaldehyde as the first electrophile and excess (10 equiv) methyl iodide as the second electrophile afforded, after purification (RPLC; 0.5% Et_2O/hexanes), 0.165 g (61% overall) of the furan as an oil: NMR ($CDCl_3$) δ 2.23 (s, 3), 6.20 (d, J = 1.5 Hz, 1), 7.10–7.70 (m, 6).

Anal. Calcd for $C_{11}H_{10}O$; C, 83.51; H, 6.37. Found: C, 83.38; H, 6.28.

2-(1-Naphthyl)-2-methylfuran (34). In the usual manner, 0.245 mg (1.05 equiv, 1.79 mmol) of 1-naphthaldehyde and excess (10 equiv) methyl iodide were used as the electrophile(s) in the sequence. Purification, achieved with preparative thin-layer chromatography (PTLC) (20% Et_2O/hexane) gave 0.243 g (68%) of **34**: NMR ($CDCl_3$) δ 1.98 (s, 3), 6.26 (d, J = 1.5 Hz, 1), 7.10–8.10 (m, 8).

Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.54; H, 6.18.

1-(2-Phenylethyl)-3-methylfuran (36). Following the above conditions, 0.239 mL (1.05 equiv, 1.79 mmol) of 3-phenylpropanal and excess (10 equiv) methyl iodide gave after PTLC (20% Et_2O/hexane) 0.130 g (41%) of **36**: NMR ($CDCl_3$) δ 1.76 (s, 3), 2.83 (s, 4), 6.03 (d, J = 1.5 Hz), 7.10 (s, 6); mass spectrum (EI) for $C_{13}H_{14}O$, m/e 186 (M^+), 95 (M^+ − 91, base peak), 91.

2-*tert*-Butyl-3-methylfuran (37). The reaction sequence was performed with 1.00 mL (5.69 mmol, 1.0 equiv) of (*E*)-1-bromo-3,3-diethoxy-1-propene (**1**), 0.652 mL (1.05 equiv, 6.0 mmol) of trimethylacetaldehyde, and excess methyl iodide. The reaction solvents were distilled at atmospheric pressure (product boiling point is ca. 120 °C) to give 0.806 g (81%) of furan. Purification on 0.421 g of crude product by RPLC (hexanes) gave 0.308 g (overall yield 59%) of **37**: NMR ($CDCl_3$) δ 1.33 (s, 9), 2.07 (s, 3), 6.00 (d, J = 1.5 Hz, 1), 7.05 (d, J = 1.5 Hz, 1); mass spectrum, m/e 138 (M^+, 91%), 123 (M^+ − 15, base peak).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.40; H, 10.17.

1-(2-Phenylethyl)-3-bromofuran (11). This compound was prepared by following the general furan synthesis but omitting the *tert*-butyllithium step on a 0.57–mmol scale and affored 0.048 g (55% overall) of the furan. The hydroxy acetal **10c** was purified (62%) before cyclization (88%) to the furan: IR (film) 3130 (w), 3100 (w), 3070 (w), 3045 (w), 3010 (m), 1600 (m), 1500 (m), 1490 (s), 1450 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.90 (s, 4), 6.30 (d, J = 1 Hz, 1), 7.17 (s, 5), 7.21 (d, J = 1 Hz, 1); mass spectrum (EI) for $C_{12}H_{11}BrO$, m/e 252, 250 (M^+), 161, 159, 91 (base peak).

2-(5-Methyl-2-thienyl)-3-methylfuran (41). Following the usual procedure, 0.168 mL (1.05 equiv, 1.79 mmol) of thiophene-2-carboxaldehyde gave a trianion upon addition of 3.3 equiv of *t*-BuLi (i.e., the O–Li derivative, the anion from halogen–metal exchange, and deprotonation at C-5 of the thiophene). Addition of excess methyl iodide (10 equiv) followed by purification (PTLC, hexanes) gave 0.173 g (57%) of **41** as an oil: NMR ($CDCl_3$) δ 2.16 (s, 3), 2.44 (s, 3), 6.19 (d, J = 1.5 Hz, 1), 6.72 (m, 1), 6.93 (d, J = 3 Hz, 1), 7.20 (d, J = 1.5 Hz, 1); mass spectrum (EI) m/e 178 (M^+ base peak), 149 (M^+ − 29, 50%).

Anal. Calcd for $C_{10}H_{10}SO$: C, 67.38; H, 5.66. Found: C, 71.01; H, 7.53. The compound was not sufficiently stable for combustion analysis.

2-(5-Methyl-2-furyl)-3-methylfuran (40). In the same manner as described for **41**, 0.150 mL (1.05 equiv, 1.79 mmol) of furfural and excess (10 equiv) methyl iodide gave after purification (PTLC, hexanes) 0.145 g (53%) of **40** as an oil: NMR ($CDCl_3$)

(13) McConnell, O. J.; Fenical, W. *Phytochemistry* **1980**, *19*, 233.
(14) Crandall, J. K.; Collonges, F. *J. Org. Chem.* **1976**, *41*, 4089.
(15) Rossi, R.; Carpita, A.; Vita, G. *Gazz. Chim. Ital.* **1978**, *108*, 709.
(16) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

δ 2.19 (s, 3), 2.30 (s, 3), 5.95 (m, 1), 6.20 (m, 2), 7.2 (d, J = 1.5 Hz, 1). The compound was air sensitive, and a satisfactory combustion analysis could not be obtained.

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Registry No. 1, 86046-93-7; **5**, 98761-33-2; **10a**, 98761-34-3; **10b**, 98761-35-4; **10c**, 98761-36-5; **10d**, 98761-37-6; **10e**, 98761-38-7; **10f**, 98761-39-8; **10g**, 98761-40-1; **10h**, 98761-41-2; **10i**, 98777-27-6; **11**, 98761-42-3; **12g**, 98761-43-4; **13**, 98761-44-5; **14**, 98761-45-6; **15**, 98761-46-7; **16**, 98761-47-8; **17**, 53774-21-3; **18**, 98761-48-9; **19**, 98761-49-0; **20**, 98761-50-3; **22**, 98777-28-7; **23**, 74055-95-1; **24**, 66002-49-1; **25**, 98761-51-4; **26**, 98761-52-5; **27**, 10160-87-9; **30**, 55454-22-3; **31**, 41453-56-9; **32** (R = Ph), 98761-58-1; **34**, 98761-53-6; **35**, 30078-92-3; **36**, 98761-54-7; **37**, 98761-55-8; **40**, 98761-56-9; **41**, 98761-57-0; $Me(CH_2)_5I$, 21369-64-2; D_2O, 7789-20-0; PhCHO, 100-52-7; $Ph(CH_2)_2CHO$, 104-53-0; $PhCOCH_3$, 98-86-2; Me_3CCOMe, 75-97-8; methyl iodide, 74-88-4; 1-naphthaldehyde, 66-77-3; trimethylacetaldehyde, 630-19-3; furfural, 98-01-1; 2-cyclohexen-1-one, 930-68-7; 2-acetylthiophene, 88-15-3; 2-acetylpyridine, 1122-62-9; 1-iodobutane, 542-69-8.

Carboxylation of Ketones Using Triethylamine and Magnesium Halides

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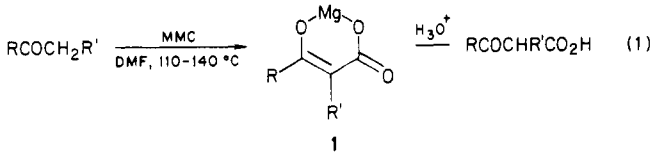
Procedures for the carboxylation of ketones with carbon dioxide at atmospheric pressure in the presence of magnesium halides and triethylamine are described. A variety of ketones are converted to the corresponding β-keto acids in satisfactory yields by using magnesium chloride–sodium iodide mixtures in acetonitrile. This carboxylation reaction exhibits little regioselectivity with 2-butanone.

A variety of procedures have been reported for the conversion of ketones to the corresponding β-keto acids.[1] Perhaps the most widely used procedure is that developed by Stiles and Finkbeiner using the reagent magnesium methyl carbonate (MMC), eq 1.[2] This method often gives



(1)

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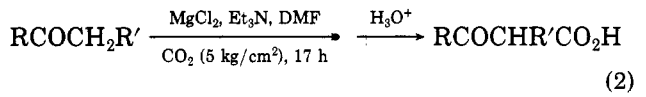
good yields of β-keto acids but has a number of disadvantages including the high reaction temperature, the inconvenient preparation of MMC (usually taken in 4–10× excess), and the difficulty of isolating the product from a large volume of dimethylformamide (DMF) solvent. The formation of the magnesium chelate **1** is probably an essential feature of the reaction. Thus, the reaction has never been reported for ketones possessing only one α hydrogen and fails in a similar situation[3] where a chelate structure analogous to **1** cannot be formed.

More recently, Matsumura has described a direct reaction of ketones with carbon dioxide at elevated pressure which is promoted by a mixture of triethylamine and magnesium chloride in DMF solution (eq 2).[4] We have examined this carboxylation reaction at atmospheric pressure using a variety of solvents and magnesium halides with the results reported here.



(2)

(1) For leading references, see: Haruki, E. In "Organic and Bio-organic Chemistry of Carbon Dioxide"; Inoue, S., Yamayaki, N.; Eds.; Wiley: New York, 1982; pp 5–78.

(2) (a) Stiles, M.; Finkbeiner, H. L. *J. Am. Chem. Soc.* **1959**, *81*, 505. (b) Stiles, M. *Ibid.* **1959**, *81*, 2598.

(3) For example, MMC reacts readily with 3-phenylhydantoin but not with 3-phenyl-5-methylhydantoin: Finkbeiner, H. *J. Am. Chem. Soc.* **1964**, *86*, 961.

(4) Matsumura, N.; Yagyu, T.; Imoto E. *Nippon Kaguku Kaishi* **1977**, *1344*.

Table I. Carboxylation of Cyclohexanone with $MgCl_2$ in a Variety of Solvents[a]

solvent	$T_{50\%}$[b]	$T_{90\%}$[c]
acetonitrile	7 min	45 min
THF	12 min	80 min
methylene chloride	30 min	160 min
dimethoxyethane	2 h	10 h
DMF	3 h	12 h

[a] Reaction at 25 °C; 0.5 M in ketone in each solvent; cyclohexanone/$MgCl_2$/Et_3N (1:1:2). [b] Time for absorption of 0.5 mol of CO_2/mol of cyclohexanone. [c] Time for absorption of 0.9 mol of CO_2/mol of cyclohexanone.

Table II. Carboxylation of Cyclohexanone with a Variety of Magnesium Halides[a]

MgX_2	$T_{50\%}$,[b] min	$T_{90\%}$,[c] min
$MgCl_2$	7	45
$MgBr_2$	3	17
"MgI_2"	1	6

[a] Cyclohexanone/MgX_2/Et_3N (1:1:2); 0.5 M in acetonitrile at 25 °C. [b] Time for absorption of 0.5 mol of CO_2/mol of cyclohexanone. [c] Time for absorption of 0.9 mol of CO_2/mol of cyclohexanone.

Results and Discussion

Our initial experiments were aimed at achieving maximum rates of carbon dioxide absorption. To this end, the carboxylation of cyclohexanone was examined in a variety of solvents in the presence of 2 equiv of triethylamine and 1 equiv of $MgCl_2$. The rate of absorption of CO_2 at atmospheric pressure was followed by using a gas buret. Reaction mixtures were heterogeneous in all cases and the absorption of carbon dioxide was accompanied by formation of additional insoluble material. In general, initial concentrations 0.5 M or less in ketone were necessary to maintain magnetic stirring. As shown in Table I, the fastest rates are obtained in acetonitrile, and the reaction is exceptionally slow in DMF. Presumably, DMF neutralizes the Lewis acidity of Mg^{+2}, accounting for the slow rate in this solvent.

Using acetonitrile solvent, the carboxylation of cyclohexanone was examined in the presence of 2 equiv of

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