R_f 0.33); IR (neat) 3030, 1735, 970, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, 3 H), 1.3-2.7 (m, 10 H), 4.33 (m, 1 H), 5.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.5 (t), 20.7 (t), 27.2 (t), 29.5 (t), 33.3 (t), 80.2 (t), 122.4 (d), 135.1 (d), 171.8 (s).

The ^{13}C NMR spectrum exhibited two minor peaks at 122.8 and 136.3 ppm with the relative intensity of 13/87 to the major peaks (122.4 and 135.1 ppm). The minor peaks are due to the *E* isomer **1b** which arises from 1-bromo-(*E*)-2-pentene present in the used 1-bromo-2-pentene.

3-(2-Pentynyl)-5-pentanolide (1d): yield 57% (purified by preparative TLC); bp 100 °C (2 torr); IR (neat) 2230 (weak), 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3 H), 1.4-2.3 (m, 6 H), 2.3-2.7 (m, 4 H), 4.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.4 (t), 14.1 (q), 18.3 (t), 26.0 (t), 29.5 (t), 73.7 (s), 78.7 (d), 84.8 (s), 171.2 (s). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.35; H, 8.25. Found: C, 72.26; H, 8.49

5-[(*Z*)-2-Pentenyl]-5-pentanolide (1c) from 1d. The pentanolide **1d** (107 mg) was hydrogenated using Lindlar catalyst[12] (5% Pd-$BaSO_4$, 25 mg; quinoline, 25 mg) in benzene (3 mL) to afford **1c** in 90% yield as a colorless oil. The ^1H NMR spectrum was essentially identical with that for **1c** from **4c**. The ^{13}C NMR spectrum exhibited no peak for *E* isomer. The IR and ^1H NMR spectra were identical with those reported.[2,4]

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Efficient Preparation of Polyfunctional α-Diketones from Carboxylic Acids

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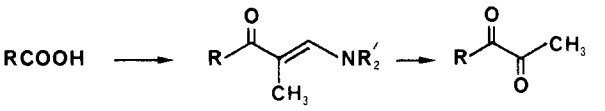
Many enzymes contain an essential arginyl residue at the active site. Butanedione and other simple α-diketones characteristically inactivate these enzymes by bonding covalently to arginine.[1] In an effort to confer specificity to this interaction, we have sought methods for incorporating an α-diketone moiety into polyfunctional inhibitors of such enzymes.[2] The ideal synthetic method for our purpose would involve the conversion of an existing carboxylic acid function into an α-diketone under mild conditions. Here we report on studies directed to developing such a route.

Results and Discussion

Since substrates, inhibitors, or cofactors that contain carboxylate or phosphate groups are usually involved in ion-pair formation with the guanidinium moiety of an arginyl residue at an enzyme active site, our intent was to develop a synthetic route that would transform a carboxyl group in an inhibitor molecule into an α-diketone without disturbing the integrity of other functionality. The target compounds **1** and **2** are derivatives of carboxylic acids with known inhibitory activity toward carboxypeptidase,[3,4] and **3** is an analogue of proline, an amino acid which is a component of a number of peptidase inhibitors.[5]

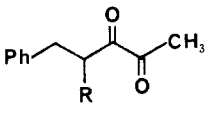
The synthetic approach that ultimately afforded the best results involved the conversion of a carboxylic acid to an

Scheme I

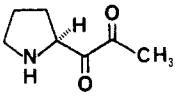


α-enamino ketone which was photooxygenated[6] to yield the desired α-diketone (Scheme I). The route to the α-enamino ketone depended on whether or not the carboxylic acid is branched at the α′-position.

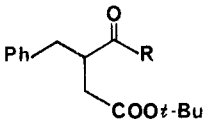
Diketone **1** was synthesized from carboxylic acid **5** which was obtained by treatment of the lithium enolate of ethyl 3-phenylpropanoate with *tert*-butyl iodoacetate followed by saponification of the resultant diester **4**. The acid **5**

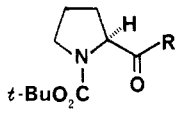


1 R=CH_2COOH
2 R=H

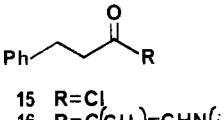


3

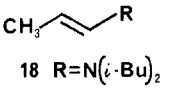




	R	
4	OEt	
5	OH	**10**
6	S-Pyr	**11**
7	CH_2CH_3	**12**
8	$C(CH_3)=CHNMe_2$	**13**
9	$COCH_3$	**14**



15 R=Cl
16 R=$C(CH_3)=CHN(i\text{-}Bu)_2$
17 R=N O



18 R=$N(i\text{-}Bu)_2$
19 R=N O

was converted to the 2-pyridyl thio ester[7] **6** which reacted cleanly with ethylmagnesium bromide to afford ethyl ketone **7**. Conversion of **7** to enamino ketone **8** was effected with 2.5 equiv of Bredereck's reagent,[8] $(Me_2N)_2CHO$-*t*-Bu. The crude product was photooxygenated at once to produce the diketo ester **9**, which, upon formolysis, afforded the diketo acid **1**. This compound displays broadened ^1H NMR resonances (particularly CH_3, δ 2.2) and a displaced carboxylic absorption (1800 cm^{-1}) in the IR spectrum, suggesting the predominance of cyclic hemiacylal tautomers.

Prolylmethyl diketone **3** was prepared by a similar sequence starting with Boc-proline **10**. This involved the intermediacy of the corresponding thio ester **11**, ethyl ketone **12**, enamino ketone **13**, and BOC-diketone **14**. Intermediate **14** was cleaved with periodate to give Boc-proline **10** with an optical purity of 82%. The unprotected diketone **3** was isolated as the hydrochloride salt. This compound appeared to be stable at 0 °C but decomposed upon attempted crystallization from chloroform.

Since one of the α-positions in the ethyl ketones **7** and **12** is branched, condensation with Bredereck's reagent afforded a single enamino ketone (**8** and **13**, respectively). However, if an identical route were employed for synthesis

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of **2**, the requisite intermediate, 1-phenylpentan-3-one, would likely give rise to an undesirable mixture of regioisomers in the condensation step with Bredereck's reagent. Therefore, we have developed a complementary sequence suitable for preparation of unbranched α-diketones. Enamino ketone **16** was prepared from acid chloride **15** by treatment with the diisobutyl enamine **18** and diisopropylethylamine. Photooxygenation of **16** gave the desired diketone **2**. Use of the hindered enamine **18** was crucial,[9] since the morpholine-derived enamine **19** reacted with acid chloride **15** to produce the amide **17** as the major product. This curious reaction is precedented,[10] but its mechanism remains unclear. Amide formation also predominated with branched acid chlorides such as that derived from acid **5**, even when enamine **18** was used.

We are actively pursuing the synthesis of other functionalized α-diketones by using the procedures outlined above. Details of these investigations and of the biochemical properties of these compounds will be reported in due course.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer Model 281 infrared spectrometer. NMR spectra were taken at ambient temperature in $CDCl_3$ with tetramethylsilane as internal standard on a JEOL FX90Q instrument. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Flash chromatography employed E. Merck silica gel (230–400 mesh) adsorbent. All reactions except photooxygenations were performed under a nitrogen atmosphere.

2-Benzylbutanedioic Acid, 1-Ethyl, 4-*tert*-Butyl Diester (4). To a stirred, cooled (0 °C) solution of 1.75 mL (12.5 mmol) of diisopropylamine in 20 mL of dry tetrahydrofuran (THF) was added 8.6 mL (11.4 mmol) of 1.33 M *n*-butyllithium in hexane. The solution was cooled (−78 °C) and 1.90 mL (10.5 mmol) of ethyl 3-phenylpropanoate was added. After 7 min of stirring, a solution of 3.0 g (12.4 mmol) of *tert*-butyl iodoacetate in 3 mL of dry THF was added. The mixture was allowed to warm to 0 °C (a precipitate forms) and was stirred for 15 min. Aqueous tartaric acid (3.6 mL of 4 M) was added and the crude product was isolated with ether to give 3.36 g of an oil. This material was purified by flash chromatography (10% ethyl acetate–hexane) to afford 2.43 g (79%) of diester **4** as an oil: IR (film) ν 2970, 1725 (vs), 1365, 1140 (vs), 690 cm^{-1}; ^1H NMR δ 1.2 (t, J = 7 Hz, CH_3CH_2O), 1.4 (s, *t*-Bu), 2.2–3.2 (m), 4.1 (q, J = 7 Hz, CH_3CH_2O), 7.2 (Ph). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.79; H, 8.22.

2-Benzylbutanedioic Acid, 4-*tert*-Butyl Ester (5). To a stirred solution of 446 mg (1.53 mmol) of diester **4** in 10 mL of ethanol and 5 mL of water was added 490 mg (8.7 mmol) of KOH. The solution was stirred for 4.2 h. Ether was added and the solution was extracted twice with water. The combined aqueous extracts were washed once with ether and then acidified with 3 mL of 4 M aqueous tartaric acid (a precipitate forms). The crude product was isolated by extraction with ethyl acetate to afford 355 mg (88%) of the monoester **5** as a solid: IR (film ν 3600–2500 (br), 2975, 1725, 1710, 1375, 1150 cm^{-1}; ^1H NMR δ 1.4 (s, *t*-Bu), 2.3–3.3 (m), 7.2 (Ph), 10.6 (br s, COOH). The analytical sample, mp 92–94 °C, was secured by two recrystallizations from hexane. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.18; H, 7.81.

2-Benzylbutanedioic Acid, 1-(2-Thiopyridyl), 4-*tert*-Butyl Diester (6). The procedure of Lloyd and Young[11] was used. To a stirred, cooled (−5 °C) solution of 1.50 g (5.68 mmol) of ester–acid **5** and 660 mg (5.95 mmol) of 2-pyridinethiol in 15 mL of ethyl acetate was added dropwise a filtered solution of 1.30 g (6.25 mmol) of *N,N*-dicyclohexylcarbodiimide (DCC) in 13 mL of ethyl acetate. The stirred solution was allowed to attain room temperature overnight. Filtration and evaporation gave 2.51 g of an oil that was purified by flash chromatography (25% EtOAc–hexane) to afford 1.51 g (74%) of thio ester **6** as an oil: IR (film) ν 2975, 1725, 1705 (sh), 1420, 1145, 930 cm^{-1}; ^1H NMR δ 1.4 (s, *t*-Bu), 2.2–3.6 (m), 7.3 (br s, Ph), 7.6 (m) and 8.6 (d, J = 4 Hz), Py.

3-Benzyl-4-oxohexanoic Acid, *tert*-Butyl Ester (7). The procedure of Araki et al.[7] was used. To a stirred, cooled (0 °C) solution of 1.44 g (4.03 mmol) of thio ester **6** in 25 mL of dry THF was added 4.05 mL (4.4 mmol) of a 1.09 M solution of ethylmagnesium bromide in THF dropwise over 2 min. After 30 min the mixture was quenched with excess 10% aqueous ammonium chloride. Ether was added and the organic solution was extracted with 1 M aqueous NaOH to remove 2-pyridinethiol, then twice with water, and once with brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.09 g (98%) of keto ester **2** as an oil: IR (film) ν 2970, 1725, 1365, 1150 cm^{-1}; ^1H NMR δ 0.95 (t, J = 7 Hz, CH_3), 1.4 (s, *t*-Bu), 2.0–3.2 (m), 7.2 (m, Ph). The analytical sample was secured by flash chromatography (ether–hexane). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.89; H, 8.75. Found: C, 73.86; H, 8.73.

3-Benzyl-4,5-dioxohexanoic Acid, *tert*-Butyl Ester (9). A solution of 150 mg (0.54 mmol) of keto ester **7** and 0.28 mL (1.35 mmol) of *tert*-butoxybis(dimethylamino)methane was heated at 75 °C for 12 h. The volatiles were removed by rotary evaporation under vacuum to give crude enamino ketone **8**. (^1H NMR δ 1.9 (s, vinyl CH_3)).

The photooxygenation procedure of Wasserman and Ives[6] was modified. A solution of enamino ketone **8** from above in 50 mL of dry dichloroethane was transferred to a 100-mL, two-necked flask equipped with a fritted gas bubbler inlet and a condenser. Bisacenaphthenethiophene (5 mg) was added, the flask was cooled (ca. −78 °C; dry ice–acetone bath), and the solution was irradiated in a Rayonet photoreactor (equipped with 16 G.E. F8T5-CW fluorescent tubes) for 1.8 h while a continuous stream of oxygen was maintained. Activated charcoal was added to remove the sensitizer dye and the suspension was filtered and concentrated. The crude product was purified by flash chromatography (10% ethyl acetate–hexane) to afford 102 mg (64%) of diketo ester **9** as an oil: IR (film) ν 2970, 1725, 1715, 1370, 1160, 910, 730 cm^{-1}; ^1H NMR (300 MHz) δ 1.36 (s, *t*-Bu), 2.29 (s, CH_3), 2.6 (m) and 2.95 (dd, J = 6 Hz, 13.5 Hz) (CH_2), 3.9 (m, CH), 7.2 (m, Ph). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.05; H, 7.51.

3-Benzyl-4,5-dioxohexanoic Acid (1). Diketo ester **9** (243 mg, 0.84 mmol) was dissolved in 4 mL of distilled formic acid (95–97%). After 16 h at room temperature, water was added and the solution was extracted with ether to give 184 mg of a crude product which was purified by flash chromatography (ether) to afford 169 mg (86%) of diketo acid **1** as an oil: IR (film) ν 3600–2500 (br), 1800 (m), 1725, 1715, 1190 cm^{-1}; ^1H NMR δ 2.2 (br s, CH_3), 2.4–3.1 (br m), 7.2 (m, Ph). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.89; H, 6.21.

***tert*-Butyl (*S*)-2-Propionyl-1-pyrrolidinecarboxylate (12).** The procedure of Araki et al.[7] was modified. To a stirred, cooled (0 °C) solution of 1.085 g (3.52 mmol) of Boc-proline 2-thiopyridyl ester (**11**)[11] in 15 mL of dry THF was added 3.25 mL (3.8 mmol) of 1.17 M ethylmagnesium bromide in THF dropwise over 2 min. After 30 min the mixture was quenched with excess 10% aqueous NH_4Cl. Ether workup gave 1.05 g of a yellow oil. Flash chromatography (25% ethyl acetate–hexane) afforded 504 mg (63%) of ketone **12** as a volatile oil: IR (film) ν 2980, 1730 (m), 1710, 1695, 1405, 1390, 1370, 1165, 1115 cm^{-1}; ^1H NMR δ 1.1 (t, J = 7 Hz, CH_3), 1.4 and 1.45 (s, *t*-Bu, rotamers), 1.6–2.0 (m, ring H-3s, H-4s), 2.5 (br q, J = 7 Hz, CH_2CO), 3.5 (q, J = 7 Hz, ring H-5s), 4.3 (m, ring H-2); $[\alpha]^{24}_D$ −62.7° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.19; H, 9.09; N, 6.14.

***tert*-Butyl (*S*)-2-Pyruvoyl-1-pyrrolidinecarboxylate (14).** A solution of 450 mg (1.95 mmol) of ketone **12** and *tert*-butoxybis(dimethylamino)methane (0.52 mL, 2.47 mmol) was heated at 60 °C for 24 h. The excess volatiles were removed by rotary evaporation under vacuum. The crude enamino ketone **13** thus obtained was dissolved in 50 mL of dry CH_2Cl_2, and 5 mg of bisacenaphthenethiophene was added. The solution was pho-

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tooxygenated for 4 h, as described above for compound **8**. Activated charcoal was added and the suspension was filtered and concentrated. The crude product was purified by flash chromatography (25% ethyl acetate–hexane) to afford 370 mg (77.5%) of diketone **14** as an oil: IR (film) ν 2980, 1710 (vs, br), 1400, 1370, 1165 cm^{-1}; ^1H NMR δ 1.4 and 1.45 (s, *t*-Bu, rotamers), 1.6–2.2 (m, ring H-3s, H-4s), 2.36 (s, CH_3), 3.5 (br q, J = 6 Hz, ring H-5s), 4.8 (br m, ring H-2); $[\alpha]^{24}_D$ −42.0° (*c* 0.85, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.60; H, 7.80; N, 5.64.

Cleavage of Diketone 14. To a solution of 21 mg (0.087 mmol) of diketone **14** in 1 mL of 50% aqueous methanol was added 37 mg (0.16 mmol) of periodic acid. After 4 h the product was isolated with ethyl acetate, affording 15 mg (80%) of Boc-proline **10** (IR, ^1H NMR, TLC). This material showed $[\alpha]^{24}_D$ −72.7° (*c* 1.4, $CHCl_3$) and −77.0° (*c* 0.75, $CHCl_3$) vs. −89.2° (*c* 1.4, $CHCl_3$) and −94.5° (*c* 0.75, $CHCl_3$) for starting **10**. The optical purity of **10** derived from diketone **14** is therefore 81.5%.

(*S*)-1-(2-Pyrrolidinyl)-1,2-propanedione Hydrochloride (3·HCl). Boc-diketone **14** (46 mg, 0.19 mmol) was dissolved in 1 mL of 4 M hydrogen chloride in dioxane. After 1.2 h the solution was concentrated and the resulting oil was triturated with two portions of ether. The diketone **3** (33 mg, 98%) was thus obtained as a yellow solid, mp 128–130 °C dec; $[\alpha]^{24}_D$ −18° (*c* 0.45, $CHCl_3$); IR (film) ν 3650–3100 (br, vs) 3000 (br), 1725, 1355 cm^{-1}; ^1H NMR δ 2.45 (s, CH_3), 2.0 (br s, 4 H) and 3.5 (br s, 2 H) (ring CH_2), 5.1 (br s, H-2), 8.9, 10.2 (br s, NH_2^+). Anal. Calcd for $C_7H_{12}NO_2Cl$: C, 47.33, H, 6.81; N, 7.89. Found: C, 47.12; H, 7.06; N, 7.66.

5-Phenyl-2,3-pentanedione (2). To a stirred solution of 345 mg (2.0 mmol) of 3-phenylpropanoyl chloride (**15**) in 10 mL of THF was added 0.35 mL (2.0 mmol) of diisopropylethylamine followed at once by 0.43 mL (2.0 mmol) of enamine **18**. A precipitate formed after several minutes. The mixture was stirred overnight. Filtration and concentration gave crude enamino ketone **16**. This material was dissolved in 50 mL of CH_2Cl_2, 5 mg of bisacenaphthenethiophene was added, and the solution was photooxygenated for 2.2 h as described above for compound **8**. The crude product was purified by flash chromatography (10% ethyl acetate–hexane) to afford 184 mg (52%) of diketone **3** as a volatile yellow oil: IR (film) ν 2920 (w), 1720, 1710, 1350 cm^{-1}; ^1H NMR δ 2.3 (s, CH_3), 3.0 (m, CH_2s), 7.25 (s, Ph). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 75.06; H, 6.88.

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Registry No. 1, 100334-72-3; 2, 52017-06-8; 3, 100334-73-4; 4, 100334-74-5; 5, 100334-75-6; 6, 100334-76-7; 7, 100334-77-8; 8, 100334-78-9; 9, 100334-79-0; 10, 15761-39-4; 11, 33857-76-0; 12, 100334-80-3; 13, 100350-06-9; 14, 100350-07-0; 15, 645-45-4; 16, 100334-81-4; 17, 17077-46-2; 18, 100334-82-5; 19, 20521-59-9; 2-pyridinethiol, 2637-34-5; ethyl 3-phenylpropanoate, 2021-28-5; *tert*-butyl iodoacetate, 49827-15-8; *tert*-butoxybis(dimethylamino)methane, 5815-08-7.

Lithiation of 2-Bromoketene Dithioacetals

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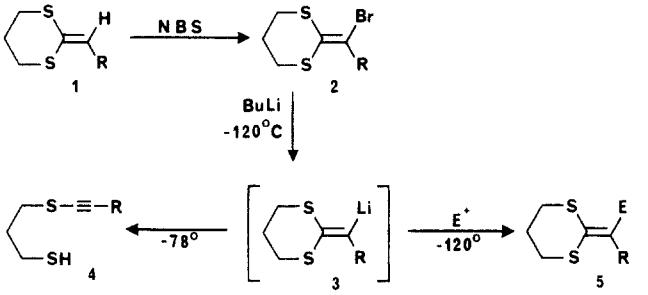
The preparation of tetrasubstituted ketene dithioacetals such as **5** can be carried out by using a number of standard methods.[1] Because several of those procedures either failed or were too lengthy for a particular derivative of interest to us, we sought a new route that would complement the others by converting a simple ketene dithioacetal (e.g., **1**) into a more highly functionalized one (**5**).

Table I. Reactions of Vinyllithium 3 with Electrophiles

entry	electrophile, E^+	product (5), E	yield, %
a	CH_3OD	−D	81[a]
b	$(CH_3)_3SiCl$	$-Si(CH_3)_3$	93[b]
c	CH_3I	$-CH_3$	84
d	$CH_3(CH_2)_2I$	$-(CH_2)_2CH_3$	74[c]
e	$CH_3(CH_2)_4CHO$	$-CH(OH)(CH_2)_4CH_3$	64
f	$HCON(CH_3)_2$	−CHO	71
g	$TolSO_2$ menthyl[7]		47

[a] MS and ^1H NMR indicate 94% deuterium incorporation. [b] Crude yield; decomposes during silica gel chromatography; homogenous by TLC. [c] Requires HMPA as cosolvent.



One possible approach would be to treat an electrophile with a vinyllithium derivative such as **3**. The successful utilization of this intermediate poses several challenges, however. First, trisubstituted ketene dithioacetals **1** undergo direct metalation (deprotonation) either in the allylic position or in the dithiane ring but not at the desired vinylic position.[2] Furthermore, even if **3** could be generated by some other means, it might be prone to undergo β-elimination of the trans heteroatom, by analogy with the well-known instability of *trans*-1-lithio-2-methoxyethene,[3] to give the alkyne **4** after workup. Bearing these potential problems in mind, we chose to attempt regioselective generation of the vinyllithium derivative via halogen–metal exchange. The required vinyl bromide precursor **2** is easily prepared by treating **1** with NBS in the presence of Et_3N for 5 min at 20 °C.[4] Standard aqueous workup followed by flash chromatography gives **2**, an oil that is reasonably stable in the dark at −20 °C, in 86% yield.

When **2** is metallated at −78 °C (2*t*-BuLi, −78 °C in THF), the major product isolated after quenching with MeOH is the elimination product **4**. At a lower temperature, however, the vinyllithium intermediate is stable. Thus, treatment of **2** in THF/ether/pentane (4:1:1)[5] with 2 equiv of *t*-BuLi at −120 °C cleanly generates **3** within 20 min. The addition of any of a variety of electrophiles gives the products derived from **3**, as shown in Table I, after reaction at −120 °C for 30 min, slow warming to room temperature, aqueous workup, and purification by flash chromatography.[6] Less reactive electrophiles such as

(1) Kolb, M. In "The Chemistry of Ketenes, Allenes, and Related Compounds"; Patai, S., Ed.; John Wiley: New York, 1980; Part 2, Chapter 16.

(2) Seebach, D.; Kolb, M. *Liebigs Ann. Chem.* **1977**, 811.

(3) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. Vinyllithium reagents similar to **3** have been generated and shown to undergo this elimination, but efficient trapping of electrophiles by the vinyl anion was not reported. Andersen, N. H.; Duffy, P. F.; Denniston, A. D.; Grothjahn, D. B. *Tetrahedron Lett.* **1978**, 4315.

(4) Vinyl bromides such as **2** are intermediates in the "oxidative solvolysis" of ketene dithioacetals to give α-halo esters: see ref 1, p 690.

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

(6) All products gave satisfactory spectral data (see above). In addition, products **5c** and **5d** were identical spectrally (^1H NMR, IR, and MS) and chromatographically (TLC) with material prepared independently by procedures described in ref 2.

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