Novel Synthesis of α-Methylene Carbonyl Compounds

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Abstract: The reaction of enol acetates or silyl enol ethers with α-chloromethyl methyl ether in the presence of active zinc compounds followed by an acid-catalyzed elimination of methanol from the resulting α-methoxymethyl ketones led to regioselective synthesis of α-methylene ketones in satisfactory overall yields. Furthermore, this novel reaction was applicable to the introduction of a methylene group to the γ position of α,β-unsaturated ketones and the α position of carboxylic esters including γ-butyrolactone.

Extensive studies[2,3] have been carried out in synthesis of α-methylene carbonyl compounds in recent years, since they are not only useful as synthetic intermediates but also the structure is often found in biologically active natural compounds. The introduction of a methylene group to the α position of a carbonyl group by hitherto known methods,[2-7] however, may encounter a certain difficulty owing to limited regioselectivity, low yields, low relative stability of products, or troublesome procedure.

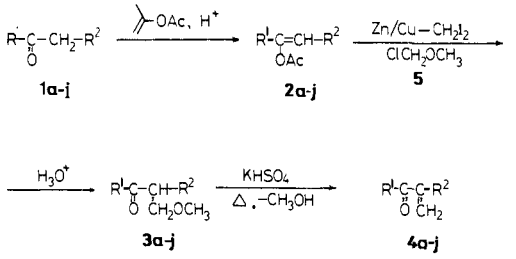
Recently, we have found that active zinc compounds prepared by the treatment of pure zinc or Simmons-Smith zinc-copper couple with alkyl iodides or methylene iodide promote several new carbon-carbon bond formation reactions between olefinic systems and electrophiles.[8]

We describe herein a new reaction of enol acetates or silyl enol ethers with chloromethyl ethers in the presence of the active zinc compounds showing novel methods of regioselective synthesis of α-methylene carbonyl compounds.

Results and Discussion

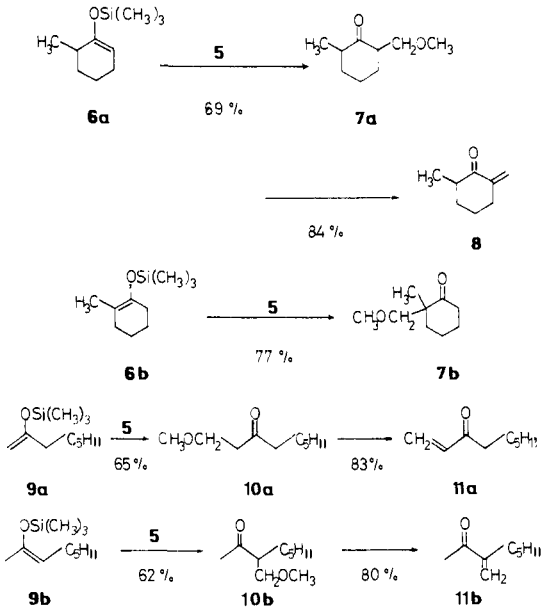
Synthesis of α-Methylene Ketones. Introduction of a methylene group to the α position of ketones was accomplished according to Scheme I.

Scheme I



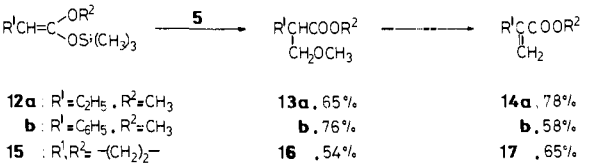
Dropwise addition of α-chloromethyl methyl ether (**5**) to enol acetates **2a–j**,[9] easily prepared from ketones **1a–j**, in the presence of the active zinc compounds[10] in methylene chloride gave the corresponding α-methoxymethylated ketones **3a–j** as the sole product in good yields. Subsequent treatment of **3a–j** with potassium hydrogen sulfate at 160–180 °C resulted in smooth elimination of methanol yielding α-methylene ketones **4a–j** in 79–89% yields. No rearrangement of the α-*exo*-methylene cycloalkanones **4a–d** to 2-methylcycloalk-2-enones took place under the reaction conditions. Yields of **3a–j** and **4a–j** are summarized in Table I.

Silyl enol ethers instead of enol acetates also brought about the formation of the same products in comparable yields (footnote *b*, Table I). Thus, α-methylene ketones **8** and **11a,b** were regioselectively obtained in reasonable yields starting from isomeric silyl enol ethers **6a** and **9a,b** respectively, which were readily prepared from the corresponding ketones according to the reported procedure.[11]



Substitution of the active zinc compounds by the usual Lewis acids such as aluminum chloride, zinc iodide, or zinc chloride[12] brought about the formation of only a small amount (20–25%) of a complex mixture of products containing the expected α-methoxymethyl ketone as one minor component.

Synthesis of α-Methylenecarboxylic Esters. In a similar manner, α-methylenecarboxylic esters **14a,b** were readily



prepared in satisfactory yields from silyl ketene acetals **12a,b**[13] prepared from the corresponding carboxylic esters. Introduction of a methylene group to the α position of γ-butyrolactone was also successfully attained.[14]

Regioselective Introduction of a Methylene Group to the γ Position of α,β-Unsaturated Ketones. This novel reaction was applied to the regioselective introduction of a methylene group to the γ position of α,β-unsaturated ketones. The reaction of acetoxybutadienes **19a,b**,[15] derived from α,β-unsaturated ketones **18a,b**, with **5** under similar conditions afforded γ-methoxymethylated enones **20a,b** regioselectively, which gave conjugate dienone **21a,b** in moderate yields upon subsequent treatment with potassium hydrogen sulfate.

Reactions of Enol Acetates with α-Chloro Ethers Other Than 5. The similar reaction of enol acetates **2** with α-chloro ethers **22**[16] or **23**[17] in the presence of the active zinc compounds successfully gave the expected products **24–26.**

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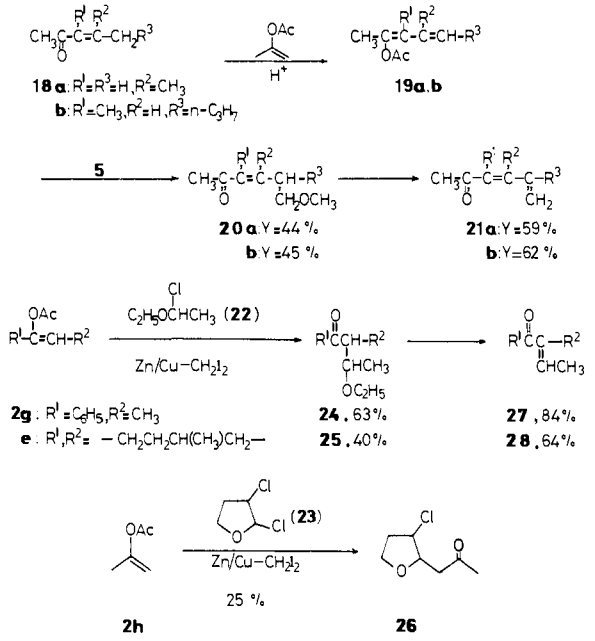
Table I. Reaction of Enol Acetates **2a–j** with **5** in the Presence of the Activated Zinc Catalyst

	enol acetates **2** R^1	R^2	α-methoxymethyl ketones **3** yield, %[a]	α-methylene ketones **4** yield, %[a]
a	$-(CH_2)_3-$		65	83
b	$-(CH_2)_4-$		72 (70)[b]	80
c	$-(CH_2)_5-$		89	84
d	$-(CH_2)_{10}-$		77	83
e	$-CH_2CH_2CH(CH_3)CH_2-$		69	81
f	C_6H_5	H	56	79
g	C_6H_5	CH_3	69 (68)[b]	82
h	CH_3	H	69	82
i	C_2H_5	CH_3	68	87
j	CH_3	i-C_4H_9	67	89

[a] Isolated. [b] The yield from the corresponding silyl enol ethers.



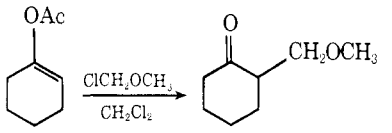
Reaction Pathway. The methoxymethylation of enol acetates or silyl enol ethers with α-chloro ethers proceeds evidently through the electrophilic attack of the α-chloro ethers to the double bond, while the detail of the role of the active zinc compounds is not always clear, since the zinc compounds did not react with enol acetates or silyl enol ethers before the addition of α-chloro ethers, and also common Lewis acids such as aluminum chloride, zinc chloride, zinc iodide, or titanium tetrachloride[18] did not give good results (Table II). Simmons-Smith type reagent, that is, $Zn/Cu-CH_2I_2$, gave the best result, whereas cyclopropanation was not observed under the reaction conditions, and furthermore methyl iodide, iodoform, or iodine instead of methylene iodide gave similar results, though the yields were lower (Table II). Although some species derived in situ from the active zinc compounds is supposed to behave as the catalyst which promotes the electrophilic attack of the α-chloro ethers to the enol compounds, the structure of the species is not clear yet.

In view of its high regioselectivity, wide generality, reasonable yield, and simple procedure, the present reaction is undoubtedly reliable for synthesis of α-methylene carbonyl compounds and conjugate dienones.

Experimental Section

Preparation of Enol Acetates 2a–j and 19a,b and Trimethylsilyl Enol Ethers 6a,b, 9a,b, 12a,b, and 15. The starting enol acetates, **1-acetoxycyclopentene (2a),[19] 1-acetoxycyclohexene (2b),[19] α-acetoxystyrene (2f),[9a] α-acetoxy-β-methylstyrene (2g),[9b] and 3-acetoxypent-2-ene (2i)[19]** were obtained by the reported methods. The other enol acetates **2c–e, 2j,** and **19a,b** were prepared from the corresponding ketones or α,β-unsaturated enones according to the procedure similar to the method of Hagemeyer[9a] or Bedoukian.[9b] The reported procedure[11,13,14] was applied to prepare trimethylsilyl enol ethers **6a,b, 9a,b, 12a,b,** and **15.**

Table II. Reaction of **2b** with **5**



2b **3b**

reagent	yield of **3b**, %
$Zn/Cu-CH_2I_2$	72
$Zn/Cu-CH_3I$	56
$Zn/Cu-CHI_3$	45
$Zn/Cu-I_2$	41
$Zn-CHI_3$	trace
$Zn-CH_2I_2$	19
$Zn-CH_3I$	trace
$Zn-I_2$	trace

General Procedure for Methoxymethylation of Enol Acetates 2a–j and 19a,b and Trimethylsilyl Enol Ethers 6a,b, 9a,b, 12a,b, and 15 with α-Chloro Ethers 5, 22, and 23 in the Presence of the Active Zinc Compounds. A mixture of zinc dust (6.54 g, 0.1 mol) and cuprous chloride (1.0 g, 0.01 mol) in 30 mL of methylene chloride was stirred and heated to reflux under a nitrogen atmosphere for 30 min. After the mixture was cooled to room temperature, methylene iodide (13.4 g, 0.05 mol) was added into the mixture, which was then refluxed for an additional 1 h. Into the solution of the freshly prepared active zinc compound was added during several minutes a solution of an enol acetate or a trimethylsilyl enol ether (0.05 mol) in methylene chloride (10 mL) at 0–5 °C with stirring under a nitrogen atmosphere. After a short while,[20] a solution of an α-chloro ether (0.055 mol) in methylene chloride (10 mL) was added dropwise into the mixture during 15 min at 5–15 °C with external cooling. An exothermic reaction took place and the mixture gradually turned red-brown. The reaction mixture was stirred at room temperature for 2 h, and then was refluxed for another 2 h. Cooled with an ice-water bath, 30 mL of ether and 30 mL of 10% aqueous sulfuric acid were added carefully and the mixture was filtered. The filtrate was extracted with three 50-mL portions of ether and the combined ethereal solution was washed with saturated aqueous sodium bicarbonate. After drying over anhydrous magnesium sulfate and evaporation of the solvent, the residue was distilled under reduced pressure to give a methoxymethyl carbonyl compound. All the products were identified by spectroscopic and elemental analyses as shown below.

2-Methoxymethylcyclopentanone (3a): bp 76–78 °C (25 mm); IR (neat) 1720, 1110 cm^{-1}; NMR (CCl_4) δ 1.47–2.48 (m, 7 H), 3.20 (s, 3 H), 3.43 (d, J = 3 Hz, 2 H). Anal. ($C_7H_{12}O_2$) C, H.

2-Methoxymethylcyclohexanone (3b): bp 78–79 °C (25 mm); IR (neat) 1705, 1110 cm^{-1}; NMR (CCl_4) δ 1.20–2.60 (m, 9 H), 3.20 (s, 3 H), 3.42 (d, J = 4 Hz, 2 H). Anal. ($C_8H_{14}O_2$) C, H.

2-Methoxymethylcycloheptanone (3c): bp 105–106 °C (25 mm); IR (neat) 1700, 1110 cm^{-1}; NMR (CCl_4) δ 1.22–2.18 (m, 8 H), 2.46–2.80 (m, 3 H), 3.20 (s, 3 H), 3.31 (d, J = 5 Hz, 2 H). Anal. ($C_9H_{16}O_2$) C, H.

2-Methoxymethylcyclododecanone (3d): bp 95–96 °C (3 mm); IR (neat) 1700, 1115 cm^{-1}; NMR (CCl_4) δ 1.03–1.85 (m, 18 H), 2.20–2.54 (m, 3 H), 3.22 (s, 3 H), 3.38 (d, J = 5 Hz, 2 H). Anal. ($C_{14}H_{26}O_2$) C, H.

2-Methoxymethyl-4-methylcyclohexanone (3e): bp 68–72 °C (15 mm): IR (neat) 1705, 1110 cm^{-1}; NMR (CCl_4) δ 1.00 (d, J = 5 Hz, 3 H), 1.75–2.50 (m, 8 H), 3.21 (s, 3 H), 3.48 (d, J = 4 Hz, 2 H). Anal. ($C_9H_{16}O_2$) C, H.

1-Methoxy-2-benzoylethane (3f): bp 95–96 °C (5 mm): IR (neat) 1680, 1110 cm^{-1}; NMR (CCl_4) δ 3.08 (t, J = 6 Hz, 2 H), 3.22 (s, 3 H), 3.67 (t, J = 6 Hz, 2 H), 7.08–7.95 (m, 5 H). Anal. ($C_{10}H_{12}O_2$) C, H.

1-Methoxy-2-benzoylpropane (3g): bp 80–81 °C (3 mm); IR (neat) 1680, 1110 cm^{-1}; NMR (CCl_4) δ 1.05 (d, J = 5 Hz, 3 H), 3.09–3.40 (m, 1 H), 3.18 (s, 3 H), 3.51 (d, J = 6 Hz, 2 H), 7.08–8.04 (m, 5 H). Anal. ($C_{11}H_{14}O_2$) C, H.

1-Methoxybutan-3-one (3h): bp 104–105 °C; IR (neat) 1720, 1110 cm^{-1}; NMR (CCl_4) δ 2.06 (s, 3 H), 2.52 (t, J = 6 Hz, 2 H), 3.22 (s, 3 H), 3.50 (t, J = 6 Hz, 2 H). Anal. ($C_5H_{10}O_2$) C, H.

1-Methoxy-2-methylpentan-3-one (3i): bp 57–58 °C (25 mm); IR (neat) 1710, 1110 cm^{-1}; NMR (CCl_4) δ 0.98 (t, J = 7 Hz, 3 H), 1.00 (d, J = 7 Hz, 3 H), 2.38 (q, J = 7 Hz, 2 H), 2.33–2.92 (m, 1 H), 3.20 (s, 3 H), 3.26 (d, J = 5 Hz, 2 H). Anal. ($C_7H_{14}O_2$) C, H.

3-Methoxymethyl-5-methylhexan-2-one (3j): bp 60–61 °C (15 mm); IR (neat) 1710, 1110 cm^{-1}; NMR (CCl_4) δ 0.89 (d, J = 5 Hz, 6 H), 1.05–1.60 (m, 3 H), 2.09 (s, 3 H), 2.74 (m, 1 H), 3.25 (s, 3 H), 3.45 (d, J = 5 Hz, 2 H). Anal. ($C_9H_{18}O_2$) C, H.

2-Methoxymethyl-6-methylcyclohexanone (7a): bp 80–81 °C (15 mm); IR (neat) 1695, 1110 cm^{-1}; NMR (CCl_4) δ 1.08 (d, J = 6 Hz, 3 H), 1.58–1.98 (m, 5 H), 2.00–2 62 (m, 3 H), 3.24 (s, 3 H), 3.34–3.57 (m, 2 H). Anal. ($C_9H_{16}O_2$) C, H.

2-Methoxymethyl-2-methylcyclohexanone (7b): bp 55–56 °C (2 mm); IR (neat) 1700, 1110 cm^{-1}; NMR (CCl_4) δ 1.05 (s, 3 H), 1.29–2.41 (m, 8 H), 3.22 (s, 3 H), 3.28 (s, 2 H). Anal. ($C_9H_{16}O_2$) C, H.

1-Methoxynonan-3-one (10a): bp 82–83 °C (12 mm); IR (neat) 1700, 1110 cm^{-1}; NMR (CCl_4) δ 0.84 (t, J = 5 Hz, 3 H), 1.08–1.72 (m, 8 H), 2.32 (t, J = 6 Hz, 2 H), 2.41 (t, J = 6 Hz, 2 H), 3.23 (s, 3 H), 3.38 (t, J = 6 Hz, 2 H). Anal. ($C_{10}H_{20}O_2$) C, H.

3-Methoxymethyloctan-2-one (10b): bp 95–96 °C (20 mm); IR (neat) 1700, 1110 cm^{-1}; NMR (CCl_4) δ 0.89 (t, J = 5 Hz, 3 H), 1.07–1.56 (br s, 8 H), 2.05 (s, 3 H), 2.28–2.80 (m, 1 H), 3.24 (s, 3 H), 3.29 (d, J = 3 Hz, 2 H). Anal. ($C_{10}H_{20}O_2$) C, H.

Methyl 2-Methoxymethylbutyrate (13a): bp 96–97 °C (5 mm); IR (neat) 1735, 1110 cm^{-1}; NMR (CCl_4) δ 0.85 (t, J = 7 Hz, 3 H), 1.57 (m, 2 H), 2.45 (m, 1 H), 3.20 (s, 3 H), 3.47 (d, J = 4 Hz, 2 H), 3.58 (s, 3 H). Anal. ($C_7H_{14}O_3$) C, H.

Methyl 2-Phenyl-3-methoxyproplonate (13b): bp 103–104 °C (6 mm); IR (neat) 1720, 1110 cm^{-1}; NMR (CCl_4) δ 3.20 (s, 3 H), 3.50 (s, 3 H), 3.61 (d, J = 4 Hz, 2 H), 3.69 (t, J = 6 Hz, 1 H), 7.11 (br s, 5 H). Anal. ($C_{11}H_{14}O_3$) C, H.

2-Methoxymethyl-γ-butyrolactone (16): bp 92–93 °C (5 mm); IR (neat) 1770, 1110 cm^{-1}; NMR (CCl_4) δ 2.01–1.80 (m, 3 H), 3.28 (s, 3 H), 3.50 (d, J = 3 Hz, 2 H), 4.02–4.38 (m, 2 H). Anal. ($C_6H_{10}O_3$) C, H.

4-Methyl-6-methoxyhex-3-en-2-one (20a): bp 55–56 °C (3 mm); IR (neat) 1670, 1610, 1110 cm^{-1}; NMR (CCl_4) δ 1.80 (s, 3 H), 2.07 (s, 3 H), 2.73 (t, J = 6 Hz, 2 H), 3.25 (s, 3 H), 3.45 (t, J = 6 Hz, 2 H), 6.00 (br s, 1 H). Anal. ($C_8H_{14}O$) C, H.

3-Methyl-5-methoxymethyloct-3-en-2-one (20b): bp 60–62 °C (5 mm); IR (neat) 1660, 1640, 1110 cm^{-1}; NMR (CCl_4) δ 0.88 (t, J = 7 Hz, 3 H), 1.42–1.65 (m, 4 H), 1.72 (s, 3 H), 2.21 (s, 3 H), 2.50–2.81 (m, 1 H), 3.24 (s, 3 H), 3.26 (d, J = 5 Hz, 2 H), 6.27 (d, J = 10 Hz, 1 H). Anal. ($C_{11}H_{20}O_2$) C, H.

2-Benzoyl-3-ethoxybutane (24): bp 95–96 °C (3 mm); IR (neat) 1680, 1110 cm^{-1}; NMR (CCl_4) δ 0.95–1.31 (m, 9 H), 3.14–3.89 (m, 4 H), 7.08–8.04 (m, 5 H). Anal. ($C_{13}H_{18}O_2$) C, H.

2-(1-Ethoxyethyl)-4-methylcyclohexanone (25): bp 96–97 °C (4 mm); IR (neat) 1720, 1110 cm^{-1}; NMR (CCl_4) δ 0.95–1.21 (m, 9 H), 1.61–2.44 (m, 8 H), 3.21–3.85 (m, 3 H). Anal. ($C_{11}H_{20}O_2$) C, H.

2-Acetonyl-3-chlorotetrahydrofuran (26): bp 90–91 °C (3 mm); IR (neat) 1700, 1110 cm^{-1}; NMR (CCl_4) δ 1.55–1.89 (m, 2 H), 1.91 (s, 3 H), 3.32–3.61 (m, 3 H), 3.85–4.15 (m, 3 H). Anal. ($C_7H_{11}O_2Cl$) C, H. Cl.

General Procedure for $KHSO_4$-Catalyzed Elimination of Methanol from 3a–j, 7a, 10a,b, 13a,b, 16, 20a,b, 24, and 25. To a catalytic amount (0.40 g) of anhydrous potassium hydrogen sulfate being heated at 160–180 °C was added dropwise an α-methoxymethyl carbonyl compound or a γ-methoxymethyl α,β-unsaturated ketone under reduced pressure, so that an α-methylene carbonyl compound or a conjugate dienone was distilled out at 100–120 °C. The product was generally almost pure without further purification. α-Methylene ketones **4a–j**,[21-28] α-methylene esters **14a,b**,[29,30] and α-methylene-γ-butyrolactone **17**[31] were characterized by comparison of their gas chromatographic and spectroscopic behaviors with those of authentic samples. The other products **8, 11a,b, 21a,b, 27,** and **28** gave satisfactory spectroscopic and elemental analyses as shown below.

2-Methylene-6-methylcyclohexanone (8): bp 70–71 °C (10 mm); IR (neat) 1660, 1640 cm^{-1}; NMR (CCl_4) δ 1.05 (d, J = 5 Hz, 3 H), 1.56–1.78 (m, 4 H), 1.95–2.52 (m, 3 H), 5.05 (s, 1 H), 5.70 (s, 1 H). Anal. ($C_8H_{12}O$) C, H.

Non-1-en-3-one (11a): bp 85–87 °C (35 mm); IR (neat) 1690, 1630 cm^{-1}; NMR (CCl_4) δ 0.85 (t, J = 7 Hz, 3 H), 1.05–1.80 (m, 8 H), 2.34 (t, J = 6 Hz, 2 H), 5.62 (d of d, J = 9 and 2 Hz, 1 H), 5.74 (d of d, J = 16 and 2 Hz, 1 H), 6.81 (d of d, J = 16 and 9 Hz, 1 H). Anal. ($C_9H_{16}O$) C, H.

3-Methyleneoctan-2-one (11b): bp 90–92 °C (40 mm); IR (neat) 1695, 1630 cm^{-1}; NMR (CCl_4) δ 0.80 (t, J = 6 Hz, 3 H), 1.10–1.55 (m, 6 H), 2.00 (t, J = 6 Hz, 2 H), 2.24 (s, 3 H), 5.63 (s, 1 H), 5.78 (s, 1 H). Anal. ($C_9H_{16}O$) C, H.

3-Methylhexa-1,3-dien-5-one (21a): bp 81–82 °C (50 mm); IR (neat) 1670, 1660 cm^{-1}; NMR (CCl_4) δ 2.09 (s, 3 H), 2.17 (s, 3 H), 5.20 (s, 1 H), 5.46 (s, 1 H), 5.71–6.01 (m, 1 H), 6.69–7.10 (m, 1 H). Anal. ($C_7H_{10}O$) C, H.

3-Methyl-5-methyleneoct-3-en-2-one (21b): bp 91–92 °C (30 mm); IR (neat) 1675, 1660 cm^{-1}; NMR (CCl_4) δ 0.90 (t, J = 7 Hz, 3 H), 1.53–1.62 (m, 2 H), 1.74 (s, 3 H), 2.20 (s, 3 H), 2.15–2.30 (m, 2 H), 5.68–5.84 (m, 2 H), 6.80–6.92 (m, 1 H). Anal. ($C_{10}H_{16}O$) C, H.

2-Benzoylbut-2-ene (27): bp 110–112 °C (70 mm); IR (neat) 1650, 1630 cm^{-1}; NMR (CCl_4) δ 1.87 (br s, 6 H), 6.20–6.31 (m, 1 H), 7.02–8.90 (m, 5 H). Anal. ($C_{11}H_{12}O$) C, H.

2-Ethylidene-4-methylcyclohexanone (28): bp 105–107 °C (25 mm); IR (neat) 1690, 1620 cm^{-1}; NMR (CCl_4) δ 1.06 (d, J = 4 Hz, 3 H), 1.60–2.32 (m, 7 H), 1.98 (d, J = 6 Hz, 3 H), 6.32–6.75 (m, 1 H). Anal. ($C_9H_{14}O$) C, H.

Activity of Various Zinc Compounds in the Reaction of 2b with 5. The method of preparation of the active zinc compounds shown in Table II was similar to that described above. The reaction of **2b** with **5** was carried out under the reaction conditions mentioned above.

Reaction of 2b with 5 in the Presence of Some Lewis Acids. Into a dispersion of a Lewis acid (0.02 mol) such as aluminum chloride, zinc iodide, or zinc chloride in methylene chloride (30 mL) was added **2b** (0.02 mol) at 0–5 °C under a nitrogen atmosphere. Then a solution of **5** (0.022 mol) dissolved in methylene chloride (10 mL) was added dropwise with stirring at 0 °C, and the mixture was stirred for 3 h at 0–5 °C. The reaction mixture was poured into 50 mL of ice-water and extracted with ether. The combined ethereal solution was washed with saturated sodium bicarbonate solution. After drying over anhydrous magnesium sulfate and evaporation of the solvent, the residue was distilled under reduced pressure to give a small amount (20–25%) of a complex mixture containing cyclohexanone as a main component. The reaction of **2b** with **5** in the presence of titanium chloride[18] gave only a tarry material at 0 °C, or resulted in a complete recovery of **2b** at −78 °C.

References and Notes

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A Total Synthesis of *dl*-Cerulenin

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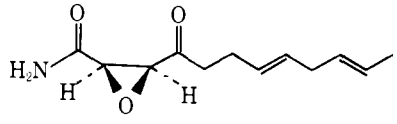
Abstract: A general route to endocyclic α,β-epoxy-γ-butyrolactones is described. The α,β-epoxylactones are potential protein cross-linking agents based upon the spectrum of reactivity displayed with amines and thiolate anion. The epoxylactone **8** is prepared from 1-bromo-2-butyne and serves as the key intermediate in a total synthesis of cerulenin (**1**), an important substance for the study of the enzyme systems involved in fatty acid biosynthesis.

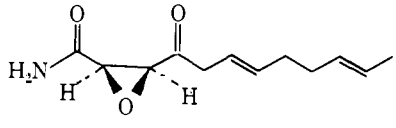
The fungus *Cephalosporium caerulens* has proven to be a rich source of novel terpenoid metabolites, some of which possess antibiotic activity.[2] Among the nonterpenoid metabolites, a relatively minor component was isolated by Hata in 1960.[3,4] This substance, called cerulenin (**1**), possessed an



1

extremely interesting spectrum of biological activity. Cerulenin (**1**) was shown to have both antibiotic and antifungal activity, but the mechanism by which these effects were manifested has proven to be the most significant finding. It has been shown to be a potent inhibitor of fatty acid synthesis in a number of organisms,[5-8] and in *E. coli*, at least, the inhibition has been traced to reversible inactivation of the enzyme, β-keto-acyl-carrier-protein-synthetase.[9]

Originally, on the basis of spectroscopic and mass spectral studies, the novel fatty acid derived structure **2** was proposed



2

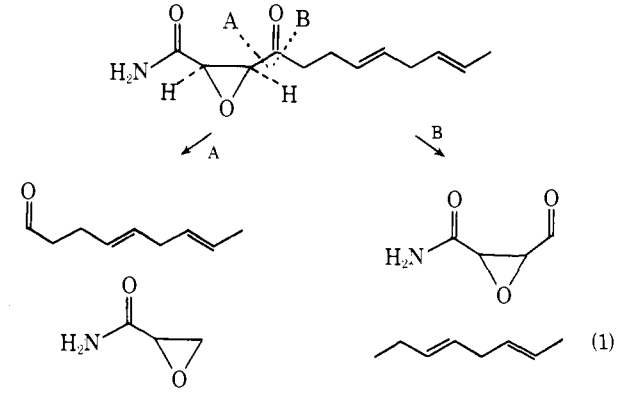
by Omura.[10] This initial assignment was subsequently revised to the double bond isomer **1** on the basis of high-resolution NMR measurements.[11] Recently the correct absolute configuration of (+)-cerulenin has been established by two groups as that shown.[12] This double bond arrangement is analogous to some naturally occurring fatty acids such as linelaidic acid (**3**),[13] but the cis epoxy amide grouping is unique among naturally occurring systems.

$$HOOC(CH_2)_7CH{=}CHCH_2CH{=}CHC_5H_{11}$$

3

In view of biosynthetic studies which established that cerulenin (**1**) was acetate derived,[14] and the value of this substance as a biochemical tool for study of the enzyme systems involved in fatty acid biosynthesis, especially the nature of substrate bonding at the active site, it was decided to undertake the total synthesis of **1**. Particular attention was paid to the feasibility of preparation of specifically labeled **1** for biochemical studies.

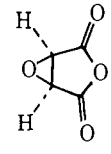
A number of plausible routes can be envisioned for the construction of cerulenin (**1**). Our efforts were focused on two convergent routes involving the retrosynthetic cleavage of the α carbonyl bonds illustrated in eq 1. In each case, the con-



(1)

struction of the olefinic side chain with labels in a variety of positions seems possible. Furthermore, labels could be incorporated in the synthon leading to the epoxy amide. The degree of flexibility inherent in these schemes also makes them particularly attractive by permitting the preparation of analogues with a variety of side-chain structures.

Acylation of Epoxymaleic Anhydride 4. Our initial approach utilized scheme B (eq 1) above in which the precursor of the epoxy amide was the known epoxymaleic anhydride **4**.[15] This



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