Notes

Regiospecific Preparation of 2-(Carbomethoxy)-4-methylcyclohept-4-enone via the Divinylcyclopropane Rearrangement

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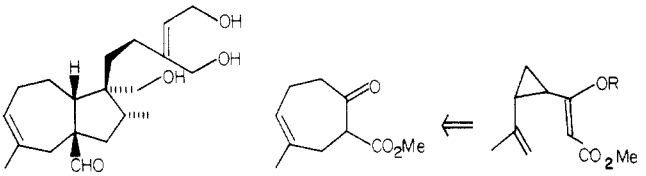
In connection with work in our laboratory concerning the synthesis of the diterpene plant-growth regulator portulal,[1] **1**, we required large quantities of the γ,δ-unsaturated enone **2**. Since enone **2** is an unsymmetrically substituted cycloheptenone, a regiospecific route was desired.[2] Our previous experience[3] in the use of divinylcyclopropane rearrangements prompted our consideration of the cyclopropane enol ether **3** as a precursor to **2**. In this note, we report a regiospecific synthetic route[4,5] to **2** via the divinylcyclopropane **3**. This synthetic scheme should be general for a number of substituted 2-(carbomethoxy)cyclohept-4-enones and could be conveniently carried out on a multigram scale.

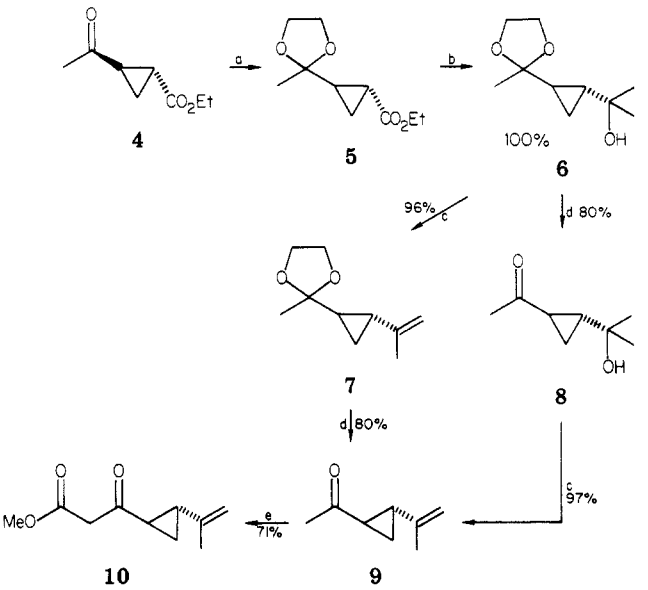


1 **2** **3**

Scheme I outlines the preparation of **10** from the readily available[6] ethyl *trans*-2-acetylcyclopropane carboxylate (**4**). Ketalization of ketone **4** under standard conditions and treatment of the resulting ketal **5** with 2 equiv of methyllithium in ether produced the tertiary alcohol **6** in quantitative yield.

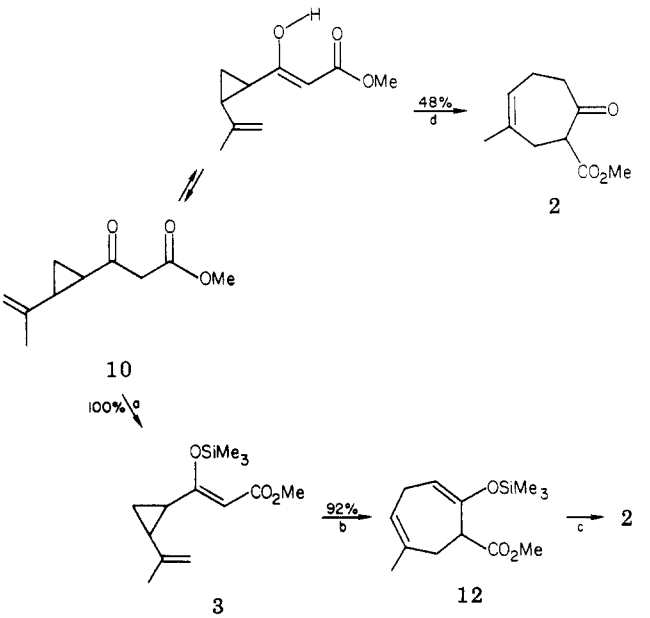
Dehydration of the tertiary alcohol **6** was not trivial. Attempted elimination reactions on **6** or **8** with thionyl chloride or phosphorous tribromide in pyridine failed or gave low yields of the desired alkenes. Only the use of Burgess' reagent,[7] [(carbomethoxy)sulfamoyl]triethylammonium hydroxide inner salt (**11**) resulted in clean dehydration of the cyclopropylcarbinyl alcohol system.

Scheme I[a]



[a] Reaction conditions: a, $(CH_2OH)_2$, *p*-TosH, PhH/Δ; b, 2.1 equiv of MeLI, Et_2O, 0 °C; c, $Et_3N^+SO_2NCO_2Me$ (**11**), PhH, Δ, 20 h; d, 3% aqueous HCl, THF, room temp; e, $(MeO)_2CO$, NaH, THF, room temp.

Scheme II[a]



[a] Reaction conditions: a, Me_3SiCl, Et_3N, Et_2O, room temp; b, 210 °C, 0.5 M PhH, 16 h; c, KF/MeOH, room temp; d, 240 °C, PhH, 20 h.

(1) (a) Yamazaki, S.; Tamura, S.; Marumo, F.; Saito, Y. *Tetrahedron Lett.* **1969**, 359. (b) Matsahashi, M.; Shibaoka, H. *Plant Cell Physiol. Jpn.* **1965**, *6*, 87. (c) Tokoroyama, T.; Matsuo, K.; Kanazawa, R.; Kotsuki, H.; Kubota, T. *Tetrahedron Lett.* **1974**, 3093. (d) Kanazawa, R.; Kotsuki, H.; Tokoroyama, T. *Ibid.* **1975**, 3651.

(2) The thermal rearrangement of alkylidenetetrahydrofurans is another regiospecific route to cyclohept-4-enones. For a review see: Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.

(3) (a) Marino, J. P.; Kaneko, T. *Tetrahedron Lett.* **1973**, 3971; *Ibid.* **1973**, 3975. (b) Marino, J. P.; Kaneko, T. *J. Org. Chem.* **1974**, *39*, 3175. (c) Marino, J. P.; Browne, L. J. *Ibid.* **1976**, *41*, 3245.

(4) Recently, Trost reported compound **2** from the thermal rearrangement of an alkylidenetetrahydrofuran: *J. Am. Chem. Soc.* **1980**, *102*, 2840.

(5) For recent applications of the divinylcyclopropane rearrangement to syntheses of cycloheptadienes see: (a) Wender, P. A.; Hilleman, C. C.; Symonifka, M. J. *Tetrahedron Lett.* **1980**, 2205; (b) Piers, E.; Nagakura, I. *Ibid.* **1976**, 3237; (c) Piers, E.; Ruediger, E. H. *J. Chem. Soc., Chem. Commun.* **1979**, 166; (d) Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490; (e) Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196; (f) Piers, E.; Reissig, H. U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 791; (g) Piers, E.; Nagakura, I.; Morton, H. E. *J. Org. Chem.* **1978**, *43*, 3630.

(6) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351.

(7) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *J. Org. Chem.* **1973**, *38*, 26.

0022-3263/81/1946-1912$01.25/0

Either the hydroxy ketal **6** or the deketalized alcohol **8** could be dehydrated with **11** in refluxing benzene. The conversion of **6** to **7** proceeded in 96% yield while the two-step (hydrolysis and dehydration) conversion of **6** → **8** → **9** proceeded in 77% yield. Carbomethoxylation[8] of the acetylcyclopropane proceeded regiospecifically to yield the keto ester **10**. The overall yield for the six steps from **4** to **10** averaged 55%.

It is possible to rearrange the β-keto ester **10** to the cycloheptenone **2** at 240 °C in a sealed tube (PhH, 20 h), but the reaction is slow and the yield is low (48%). The enolic character of **10** provides the structural prerequisites for the divinylcyclopropane rearrangement (Scheme II).

Silylation of the β-keto ester **10** with trimethylsilyl chloride in triethylamine/ether yields the trimethylsilyl enol **3** (R = Me_3Si) after a careful nonaqueous workup. The silyl enol ether **3** smoothly rearranges at 210 °C (0.5 M benzene) to the 1,4-cycloheptadiene **12** in 92% yield. Desilylation of **12** to the desired **2** could be effected in high yield by dilute acetic acid hydrolysis or with potassium fluoride in methanol.

The overall synthetic sequence in Schemes I and II illustrates the use of an enol ether of a β-keto ester in the divinylcyclopropane rearrangement and underlines the mild dehydration of a cyclopropylcarbinol with Burgess' reagent. The availability of substituted cyclopropylcarboxylates makes the synthetic route to **2** applicable to a variety of other unsymmetrical 2-(carbomethoxy)cyclohept-4-enones.

Experimental Section

Proton NMR spectra were recorded on Varian T-60A and JEOL MH-100 instruments. Infrared spectra were taken on a Perkin-Elmer 457 grating spectrophotometer. Carbon-13 NMR were taken on a JEOL FX-90Z instrument. High-resolution mass spectra were taken on a Finnegan 4021 GC–MS instrument. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI.

Ketalization of Ethyl *trans*-2-Acetylcyclopropanecarboxylate (4). A solution of 70.7 g (0.45 mol) of keto ester **4** in 500 mL of benzene containing 50 mL (0.90 mol) of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 10 h with the azeotropic removal of water by means of a Dean–Stark trap. The cooled solution was neutralized with a small quantity of solid potassium carbonate and washed twice with 200-mL portions of water and once with 100 mL of saturated brine solution. The benzene solution was dried over anhydrous sodium sulfate and filtered through a Celite pad with the aid of suction. The benzene was removed in vacuo to yield 90.7 g (100%) of a light yellow oil which was used without further purification: ^{1}H NMR (CCl_4) δ 4.0 (2 H, q, J = 7 Hz), 3.78 (4 H, s), 1.4–1.8 (2 H, m), 1.32 (3 H, s), 1.22 (3 H, t, J = 7 Hz), 0.7–1.1 (2 H, m); IR (CCl_4) 2980, 2875, 1735, 1320, 1175, 1055, 1040, 870 cm^{-1}; mass spectrum, m/e (no M$^+$) 185, 155, 113, 112, 111, 80 (100%), 55, 43.

Preparation of Hydroxy Ketal 6. A solution of 15.85 g (79.2 mmol) of ketal **5** in 300 mL of ether at −5 °C was treated with 111 mL of a pentane solution containing methyllithium (174 mmol) over 0.5 h. The temperature of the reaction was maintained between −5 and +5 °C during the addition. After the addition was completed, the reaction was stirred at ambient temperature for 8 h. The reaction mixture was again cooled to 0 °C and quenched by the careful addition of 10 mL of saturated sodium sulfate solution, followed by 300 mL of water. The layers were separated and the aqueous layer was saturated with solid sodium sulfate. The aqueous layer was extracted once with 150 mL of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The dried ether solution was filtered through a Celite pad with the aid of suction and concentrated in vacuo to yield 14.7 g (100%) of a colorless oil that was used without further purification: ^{1}H NMR (CCl_4) δ 3.83 (4 H, s), 2.2 (1 H, br s), 1.30 (3 H, s), 1.17 (3 H, s), 1.13 (3 H, s), 1.2–0.7 (2 H, m), 0.6–0.2 (2 H, m); IR (CCl_4) 3620, 3470, 2980, 1370, 1080 cm^{-1}; mass spectrum, m/e (no M$^+$) 171, 153, 109, 100, 99, 87, 43 (100%); high-resolution mass spectrum, calcd for $C_{10}H_{18}O_3$ 186.125 49, found 186.1258.

Preparation of Keto Alcohol 8. A 3.7% HCl solution (200 mL) was added to 81.8 g (0.44 mol) of alcohol **6** dissolved in 350 mL of THF. The homogeneous reaction mixture was left for 3 h at room temperature after which time the solution was cooled to 0 °C and quenched with excess solid potassium carbonate. The aqueous layer that separated was extracted once with 100 mL of ether, and the combined organic layers were concentrated in vacuo and taken up in 350 mL of ether. The ether solution was washed once with 100 mL of water and once with 100 mL of saturated brine and dried over anhydrous magnesium sulfate. The ether solution was filtered through a Celite pad with the aid of suction and concentrated in vacuo to 50 g (80%) of an oil. The crude product was distilled under reduced pressure through a short-path column and the fraction boiling at 70–71 °C (0.5 mm) (49 g, 80%) was collected: ^{1}H NMR (CCl_4) δ 2.95 (1 H, s), 2.18 (3 H, s), 2.1–1.8 (1 H, m), 1.6–0.8 (9 H, m); IR (CCl_4) 3620, 3490, 2970, 1690, 1350, 1170 cm^{-1}; mass spectrum, m/e 142 (M$^+$), 127, 109, 85, 84, 81, 72, 71, 69, 65, 63, 61, 42 (100%), 41. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.54; H, 9.85.

Preparation of Cyclopropyl Ketone 9 from 8. A solution of 11.24 g (79.1 mmol) of hydroxy ketone **8** and 200 mL of benzene was combined with 23.8 g (100 mmol) of (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester[7] and refluxed for 20 h. The benzene solution was decanted from the viscous gum which had formed and the gum was washed twice with 50-mL portions of benzene. The combined benzene layers were dried over anhydrous sodium sulfate and filtered through a pad of Celite with the aid of suction. The filtrate was concentrated in vacuo; the residue was distilled under reduced pressure through a short-path column and the fraction boiling at 38–40 °C (0.5 mm) (9.55 g, 97%) was collected: ^{1}H NMR (CCl_4) δ 4.67 (2 H, br s), 2.13 (3 H, s), 2.10–1.76 (3 H, m), 1.60 (3 H, br s), 0.8–1.4 (2 H, m); IR (CCl_4) 3085, 2975, 1700, 1650, 1170, 880 cm^{-1}; mass spectrum, m/e 124 (M$^+$), 109, 81, 43 (100%); high-resolution mass spectrum, calcd for $C_8H_{12}O$ 124.088 75, found 124.0888.

Preparation of β-Keto Ester 10. A 14.4-g portion of 50% sodium hydride (300 mmol) and oil was washed three times with 30 mL of ether and suspended in 500 mL of dry THF. The reaction flask was cooled to 0 °C and 29.12 g (234 mmol) of cyclopropyl ketone **9** was introduced. After the mixture was stirred at 0 °C for 10 min, 25.3 mL (300 mmol) of dimethyl carbonate was added. The reaction was stirred for 3 days at room temperature and then was cooled to 0 °C and cautiously quenched with 10% hydrochloric acid to pH 3. The organic layer was quickly separated and the aqueous layer was extracted once with 150 mL of ether. The combined organic layers were washed once with 100 mL of saturated brine, dried over anhydrous magnesium sulfate, and filtered through a Celite pad with the aid of suction. The filtrate was concentrated in vacuo to 37.8 g of a red oil which was distilled under reduced pressure through a short-path column. The fraction boiling at 85–88 °C (1 mm) (30.3 g, 71%) was collected: ^{1}H NMR (CCl_4) δ 4.73 (2 H, br s), 3.67 (3 H, s), 3.47 (2 H, s), 1.8–2.3 (2 H, m), 1.67 (3 H, br s), 0.8–1.0 (2 H, m); ^{13}C NMR ($CDCl_3$) 200.9, 167.4, 142.6, 110.9, 52.1, 49.7, 32.2, 28.6, 20.2, 16.7 ppm; IR (CCl_4) 2960, 1750, 1705, 1650, 1625, 890 cm^{-1}; mass spectrum, m/e 182 (M$^+$), 164, 109, 108, 101, 81 (100%), 80, 59. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.77; H, 7.60.

2-(Carbomethoxy)-4-methylcyclohept-4-en-1-one (2) from 10. A solution comprised of 17 mL of benzene and 1.50 g (8.24 mmol) of β-keto ester **10** (0.5 M) was degassed and sealed under reduced pressure. The tube, surrounded by benzene, was placed in a stainless-steel bomb and heated for 20 h at 240 °C. The reaction mixture was concentrated to a dark viscous oil and was distilled under reduced pressure through a short-path column. The fraction boiling at 72–77 °C (0.2 mm) (0.72 g, 48%) was collected: ^{1}H NMR (CCl_4) δ 5.55 (1 H, br t, $w_{1/2}$ = 14 Hz), 3.9–3.5 (1 H, m), 3.68 (3 H, s), 2.7–2.0 (6 H, m), 1.78 (3 H, br s); ^{13}C NMR ($CDCl_3$) 206.9, 169.9, 135.3, 123.6, 56.2, 51.7, 42.0, 31.7, 25.6, 22.8

(8) Brady, S. F.; Ilton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882.

ppm; IR (CCl_4) 2970, 1755, 1720, 1655, 1440 cm^{-1}; mass spectrum, m/e 182 (M^+), 150, 129, 105 (100%), 87, 81, 57, 55, 44, 41. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.87; H, 7.65.

Silyl Enol Ether 3. To a solution containing 24.9 g (137 mmol) of β-keto ester **10** and 60 mL (430 mmol) of triethylamine in 900 mL of ether was added 27.5 mL (217 mmol) of chlorotrimethylsilane at room temperature over 5 min. The reaction mixture was stirred for 3.5 h at room temperature and was filtered through a Celite pad with the aid of suction. The filtrate was concentrated in vacuo and taken up in 200 mL of ether. The ether solution was filtered as before and concentrated to 34.8 g (100%) of a very light yellow oil which was used without further purification: ^1H NMR (CCl_4) δ 5.00 (1 H, s), 4.73 (2 H, br s, $w_{1/2}$ = 8 Hz), 3.57 (3 H, s), 3.6–3.1 (1 H, m), 1.67 (3 H, br s), 1.3–0.7 (3 H, m), 0.25 (9 H, s); IR (CCl_4) 3090, 2960, 1715, 1610, 1145 cm^{-1}; mass spectrum, m/e 254 (M^+), 239, 186 (100%), 105, 89, 75, 73, 59, 45.

Cycloheptadiene 12. A 0.5 M solution prepared by combining 5.36 g (21.1 mmol) of silyl enol ether **3** and 40 mL of benzene was degassed and sealed under reduced pressure in a glass tube for reaction. The glass tube was placed in a stainless-steel bomb, surrounded with benzene and heated to 210 °C for 16 h. The crude reaction product was concentrated to 5.15 g (96%) and was used without further purification: ^1H NMR (CCl_4) δ 5.50 (1 H, m), 4.80 (1 H, t, J = 5 Hz), 3.62 (3 H, s), 3.3 (1 H, m), 2.9–2.2 (4 H, m), 1.70 (3 H, br s), 0.20 (9 H, s); IR (CCl_4) 2960, 1745, 1665, 1440, 1250, 1160, 880, 845 cm^{-1}; mass spectrum, m/e 254 (M^+), 157, 129, 89, 89, 82, 75, 73 (100%).

2-(Carbomethoxy)-4-methylcyclohept-4-en-1-one (2) from 12. A solution of 5.15 g (20.2 mmol) of cycloheptadiene **12** in 75 mL of methanol was combined with 1.74 g (30 mmol) of potassium fluoride and stirred for 3 h at room temperature. The crude reaction mixture was concentrated in vacuo and partitioned between 50 mL each of water and ether. The aqueous layer was extracted twice more with 40-mL portions of ether and the combined ether extracts were dried over anhydrous sodium sulfate. The dried ether solution was filtered through a pad of Celite and concentrated in vacuo to yield 3.60 g (98%) of an orange oil. The crude material was chromatographed on 100 g of silica. Elution with ether yielded 3.50 g (95%) of pure material that was identical spectroscopically with purified arising from thermal rearrangement of **10**.

Registry No. 2, 76757-71-6; **3**, 76833-06-2; **4**, 13949-95-6; **5**, 74857-26-4; **6**, 76833-07-3; **7**, 76833-08-4; **8**, 33383-61-8; **9**, 33383-66-3; **10**, 76833-09-5; **11**, 29684-56-8; **12**, 76833-10-8.

Preparation of Macrocyclic Lactones from Cyclohexane-1,3-diones[1]

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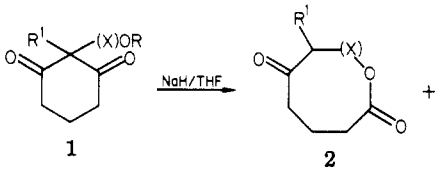
The dearth of general synthetic methods for the construction of macrocyclic lactones places severe restrictions on routes to the macrolide antibiotics.[2] Recent syntheses[3] have relied on the cyclization of hydroxy acids in the final stages. It would be of interest to have methods available by which the lactone function could be constructed at an early stage. Mahajan[4] has reported a novel synthesis of lactones **2** through a base-induced intramolecular rearrangement of 2,2-dialkylcyclohexane-1,3-diones (**1**, R = H).



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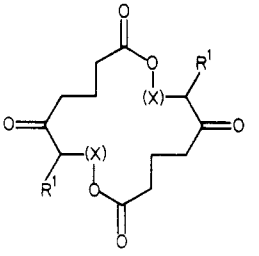

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This internal version of the retro-Dieckmann reaction was described for a limited number of precursors with short cyclizing side chains (X)OR. We show how a slight modification to the reaction conditions, the use of THF or THF–toluene as solvent in place of the benzene specified, broadens the scope of the Mahajan lactone synthesis, allowing yields greater than 50% to be obtained for 16-membered rings, the ring size of the leucomycin antibiotics.

The syntheses of the precursor 2,2-dialkylated cyclohexane-1,3-diones (**1a–d**, Table I) were accomplished by the consecutive alkylation of cyclohexane-1,3-dione.[5] Thus, **1c** was prepared by initial alkylation with 9-iodononanol followed by alkylation with allyl bromide. Since C-alkylation proceeds in poor yield with other than allylic halides, this step presently limits the utility of the lactone synthesis.

The cyclization of diketones **1a–d**, using catalytic amounts of sodium hydride in THF or THF–toluene, gave useful yields (Table I) of lactones **2a–d** which were easily separated by chromatography from the dimeric lactones

Table I. Synthesis of Cyclohexane-1,3-diones and 5-Oxo Lactones (R = H; R^1 = $CH_2CH{=}CH_2$)

compd[a]	X	lactone ring size	mp, °C	yield,[b] %
1a	$(CH_2)_4$		oil	20
1b	$(CH_2)_6$		oil	20
1c	$(CH_2)_9$		oil	19
1d	$(CH_2)_{20}$		66-67[c]	15
2a	$(CH_2)_4$	11	oil	49
2b	$(CH_2)_6$	13	20-21[d]	28
2c	$(CH_2)_9$	16	oil	56
2d	$(CH_2)_{20}$	27	oil	11
3a	$(CH_2)_4$	22	oil	15
3b	$(CH_2)_6$	26	77-78[c]	37
3c	$(CH_2)_9$	32	52[c]	12

[a] All new compounds were adequately characterized by proton NMR, IR, and mass spectroscopy and by elemental analysis (±0.4% for C and H). [b] Yields of **1a–d** from cyclohexane-1,3-dione. Yields of **2a–d** and **3a–c** for lactone formation. [c] From ethyl acetate–hexane. [d] From hexane at −20 °C.

(1) Contribution No. 556 from the Syntex Institute of Organic Chemistry.

(2) For recent reviews, see: Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683; Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585; Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(3) Corey, E. J.; Hopkins, P. B.; Yoo, S. K. S.; Nambiar, P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837.

(4) (a) Mahajan, J. R. *Synthesis* **1976**, 110. (b) Mahajan, J. R.; de Carvalho, H. *Ibid.* **1979**, 518. (c) Mahajan, J. R.; Monteiro, M. B. *J. Chem. Res. (S)* **1980**, 264.

(5) Stetter, H. In "Newer Methods of Preparative Organic Chemistry"; Foerst, W., Ed.; Academic Press: New York, 1963; Vol. 2, pp 51–99.

0022-3263/81/1946-1914$01.25/0