Malonate Anion Induced Favorskii-Type Rearrangement. 3. Reaction of Methyl-Substituted α-Chlorocyclohexanones with Sodiomalonates

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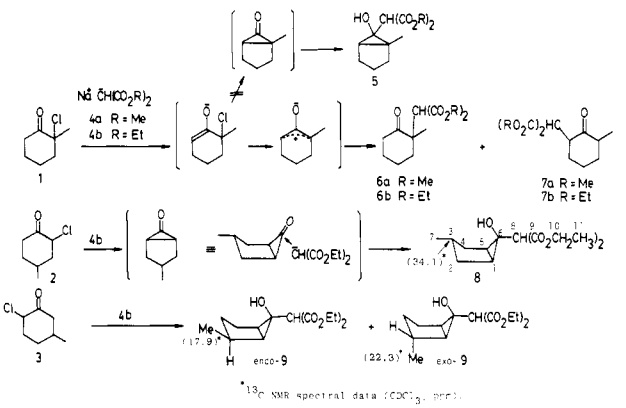
The regioselectivity and the stereoselectivity of the ring-opening reaction of bicyclic cyclopropanols such as 6-[bis(ethoxycarbonyl)methyl]-3-methylbicyclo[3.1.0]hexan-6-ol (**8**) and 6-[bis(ethoxycarbonyl)methyl]-*endo*-2-methylbicyclo[3.1.0]hexan-6-ol (*endo*-**9**) and its *exo*-2-methyl isomer (*exo*-**9**) have been studied. Reaction of 2-chloro-4-methylcyclohexanone (**2**) with diethyl sodiomalonate (**4b**) gave **8** in 59% yield. The similar reaction of 2-chloro-5-methylcyclohexanone (**3**) with **4b** afforded a 44:56 mixture of *endo*-**9** and *exo*-**9** in 49% yield. This mixture was separated to each component by means of HPLC. Reaction of 2-chloro-2-methylcyclohexanone (**1**) with **4b** afforded only the substitution products. The alkaline hydrolysis (2 N NaOH) of **8** followed by pyrolysis gave *trans*-1-(3-methylcyclopentyl)ethanone (*trans*-**11**) selectively, while the acidic (6 N HCl) hydrolysis of **8** afforded a 1:1 mixture of *cis*- and *trans*-**11** as a result of decarboxylation. The alkaline hydrolysis of *endo*-**9** followed by pyrolysis gave a 50:34 mixture of *cis*- and *trans*-**11** predominantly, whereas the acidic (35% HCl) hydrolysis of *endo*-**9** afforded *trans*-**13** regio- and stereoselectively. The similar treatment of *exo*-**9** never displayed such regioselectivity in the ring-opening reaction.

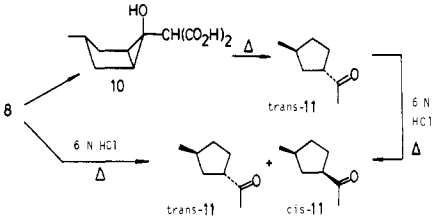
In the previous papers of this series,[1,2] we reported the isolation of cyclopropanol derivatives, the Favorskii-type intermediates in the reaction of cyclic[1] and acyclic[2] α-halo ketones with the enolate of malonic ester. The cyclopropanols were then successfully converted into a variety of ketones, β-keto esters, and related compounds, which are products of skeletal rearrangement in a Favorskii fashion. To expand the synthetic utility of this reaction, it is worthwhile to investigate the regioselectivity and the stereoselectivity of the ring-opening reaction of the cyclopropanol intermediates such as 3- and 2-methyl-substituted bicyclo[3.1.0]hexan-6-ols **8** and **9**, which may lead to useful starting materials, i.e., 1-(3-methylcyclopentyl)-ethanone (**11**) and 1-(2-methylcyclopentyl)ethanone (**13**). Compounds **8** and **9** were prepared by the reaction of the appropriate methyl-α-chlorocyclohexanone (**2** or **3**) with diethyl sodiomalonate (**4b**) (Scheme I). These bicyclic compounds were then transformed to *cis*- and *trans*-**11** and/or *cis*- and *trans*-**13** by basic or acidic hydrolysis followed by thermal treatment[3] (Schemes II and III). It has been found that the 2-methyl group of *endo*-**9** had a great influence on determining the direction of the ring-cleavage, whereas the 2-methyl group of *exo*-**9** displayed little effect.

The reaction of 2-chloro-2-methylcyclohexanone (**1**) with dimethyl sodiomalonate (**4a**) carried out at ice-bath temperature did not give the bicyclic compound but afforded only the substitution product[4] as a 52:48 mixture of methyl α-(methoxycarbonyl)-1-methyl-2-oxocyclohexaneacetate (**6a**) and methyl α-(methoxycarbonyl)-3-methyl-2-oxocyclohexaneacetate (**7a**)[5] in 50% yield. The reaction of **1** with **4b** likewise afforded a 27:73 mixture[6] of the esters **6b** and **7b** in 43% yield. These results may be explained by the zwitter ion mechanism[7] as indicated in Scheme I.

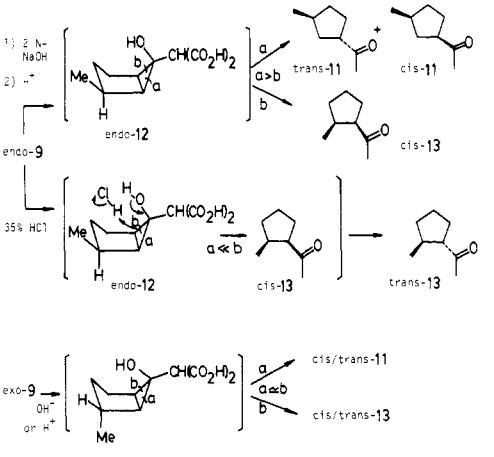
Scheme I



Scheme II



Scheme III



(1) Sakai, T.; Amano, E.; Kawabata, A.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 2039.
(2) Sakai, T.; Katayama, T.; Takeda, A. *J. Org. Chem.* **1981**, *46*, 2924.
(3) Base- or acid-catalyzed ring-opening reactions of other cyclopropanol systems: Dupuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347.
(4) The results bear a parallel resemblance to the fact that the reaction of **1** with aqueous NaOH yielded only substitution product: (a) Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307. (b) Mousseron, M.; Winternitz, F.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1947**, *14*, 83.
(5) Methyl α-(methoxycarbonyl)-2-methyl-3-oxocyclohexaneacetate was ruled out from the possible structures of the products on the basis of the spectral data of its authentic sample: Rabid, U.; Ikan, R.; Sachs, R. M. *J. Agric. Food. Chem.* **1975**, *23*, 835.
(6) Attempts to separate **6b** and **7b** by preparative TLC and HPLC were unsuccessful. Structural assignment was done by the comparison of the spectral data of the mixture with those of **6a** and **7a**.

0022-3263/83/1948-4618$01.50/0

Table I. Hydrolysis of Bicyclo[3.1.0]hexan-6-ols

compd	reaction condition	yield,[a] %	product ratio (%)			
			cis-11[b]	*trans*-11[b]	*cis*-13[b]	*trans*-13[c]
8	2 N NaOH	53[d]		100		
8	6 N HCl	59	50	50		
endo-9	2 N NaOH	68	50	34	11	5
endo-9	6 N HCl	62	21	26		53
endo-9	35% HCl	64	4	5		91
exo-9	2 N NaOH	67	20	32	2	46
exo-9	6 N HCl	60	24	26	2	48
exo-9	35% HCl	60	20	23	4	53

[a] Based on the starting material. [b] Based on ^{1}H NMR spectrum (see ref 17). [c] Based on GLC analysis. [d] Based on compound 10.

On the contrary, a similar reaction of 2-chloro-4-methylcyclohexanone (2) with **4b** gave 6-[bis(ethoxycarbonyl)methyl]-3-methylbicyclo[3.1.0]hexan-6-ol (8) in 59% yield. Compound 8 was tentatively assigned to a more preferable[8] boatlike conformation, which makes the bulky ester moiety take the more stable equatorial conformation. In the ^{13}C NMR spectra of the compound 8, the doublet at 34.1 ppm can be safely assigned to C_4, which gives support to the boat conformation, since this signal should appear at 55–60 ppm in the chair form due to anti effect.[8c] In the similar way, a 44:56 mixture of *endo*-2-methyl and *exo*-2-methyl isomers of 6-[bis(ethoxycarbonyl)methyl]-2-methylbicyclo[3.1.0]hexan-6-ol (9) was obtained from the reaction of 2-chloro-5-methylcyclohexanone (3)[9] and **4b** in 49% yield. These diastereomers (*endo*-9 and *exo*-9) were separated by means of HPLC. The ^{13}C NMR signal of the *endo*-2-methyl group (17.9 ppm) appeared at higher field than that of the *exo*-2-methyl group (22.3 ppm).

Hydrolysis of the compound 8 with 2 N NaOH gave the corresponding dicarboxylic acid (10) in 82% yield (Scheme II). Pyrolysis of the acid 10 afforded the trans isomer of the ketone 11 (*trans*-11),[10] reflecting the stereochemistry of the starting material. On the other hand, the treatment of 8 with 6 N HCl at reflux temperature gave a 1:1 mixture of *cis*-11 and *trans*-11. It is thought that *trans*-11, which is produced initially, may undergo partial epimerization to give a cis/trans mixture. In practice, *trans*-11 was epimerized by heating it with 6 N HCl to give the cis/trans mixture.

The alkaline hydrolysis (2 N NaOH) of *endo*-9 analogously afforded the corresponding dicarboxylic acid (*endo*-12)[11] (Scheme III). Pyrolysis of *endo*-12 gave a 50:34 mixture of *cis*-11 and *trans*-11 along with lesser amounts of *cis*-13 and *trans*-13, indicating that the fission of bond a has occurred predominantly. On the other hand, the acidic hydrolysis (35% HCl, reflux temperature) of *endo*-9 gave *trans*-13[12,13] principally. Under these conditions, as illustrated in Scheme III, the sterically hindered 2-methyl group of *endo*-12 appears to display some effect on the selective fission of bond b to give *cis*-13 as the initial product, which was then epimerized to *trans*-13. When a similar reaction was carried out under less strongly acidic (6 N HCl) conditions, such a selectivity was not observed. On the contrary, the less hindered 2-methyl group of *exo*-9 exhibited little effect on determining the direction of ring cleavage. The results of these experiments are summarized in Table I.

Experimental Section

Melting points were determined on a Yamato Model MP-21 melting point apparatus and are uncorrected. The evaporative bulb-to-bulb distillations were done by using a Büchi Kugelrohrofen at the pressure and oven temperature indicated. Elemental analyses were carried out by Eiichiro Amano of our laboratory. IR spectra were taken on a Hitachi Model EPI-S2 or a JASCO Model A-102 spectrometer. ^{1}H NMR spectra (60 MHz) were measured with a Hitachi Model R-24 spectrometer. Both ^{1}H NMR spectra (100 MHz) and ^{13}C NMR spectra (25 MHz) were taken on a JEOL Model FX-100 spectrometer equipped with FT facilities and with Me_4Si as an internal standard. The analytical determinations by GLC were performed on a Hitachi Model K-53 gas chromatograph (N_2, 42 mL/min; oven temperature 130 °C) by using a column (5 mm o.d. × 2 m) packed with SE-30. The preparative isolations by GLC were done with a Yanagimoto Model G-80 gas chromatograph under the same conditions as those employed in the analytical determination. Preparative isolations by high-performance liquid chromatography (HPLC) were carried out with a Yanagimoto Model L-2000 apparatus. Column chromatography was performed through silica gel (Wakogel C-200, Wakojunyaku, Tokyo). TLCs were done on silica gel (Kieselgel 60 PF_{254}, Merck A. G., Darmstadt).

The reaction of methyl-substituted 2-chlorocyclohexanones with malonate anion was carried out by a modification of the procedure described in the previous paper,[1] as is exemplified by the following experiment with 1.

Reaction of 2-Chloro-2-methylcyclohexanone (1) with Dimethyl Sodiomalonate (4a). Methyl α-(Methoxycarbonyl)-1-methyl-2-oxocyclohexaneacetate (6a) and Methyl α-(Methoxycarbonyl)-3-methyl-2-oxocyclohexaneacetate (7a). A solution of 1.46 g (0.01 mol) of 1[14] in 5 mL of THF was added dropwise to a suspension of 0.011 mol of **4a** [dimethyl malonate (1.32 g, 0.011 mol), NaH (0.26 g, 0.011 mol), and THF (20 mL)] at 0 °C. After being stirred for 2 h at 0 °C and for additional 12 h at room temperature, the resulting mixture was acidified with 10% HCl. The organic layer was extracted

(7) House, H. O.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 164.

(8) (a) Smith, H. E.; Brand, J. C. D.; Massey, E. H. *J. Org. Chem.* **1966**, *31*, 690. (b) ^{13}C NMR spectrum of bicyclo[3.1.0]hexane: Christl, M. *Chem. Ber.* **1975**, *108*, 2781. (c) Christl, M.; Leininger, H.; Brunn, E. *J. Org. Chem.* **1982**, *47*, 661.

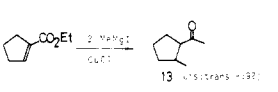
(9) Contains 31% (based on ^{1}H NMR spectrum) of 2-chloro-3-methylcyclohexanone: (a) Tsuboi, S.; Shimozuma, K.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 1517. (b) McDonald, R. N.; Tabor, T. E. *J. Am. Chem. Soc.* **1967**, *89*, 6573.

(10) Granger, R.; Boussinesq, J.; Girard, J. P.; Rossi, J. C.; Vidal, J. P. *Bull. Soc. Chim. Fr.* **1969**, 2806.

(11) Compound *endo*-12 was too labile to get acceptable spectral data: IR (neat) 3600–2300, 1710 cm^{-1}.

(12) ^{1}H NMR spectra of *cis*-13 and *trans*-13: Jorgenson, M. J.; Brattesani, A. J.; Thacher, A. F. *J. Org. Chem.* **1969**, *34*, 1103.

(13) Identical with the sample which was prepared alternatively as follows:



(14) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 162.

with several portions of ether, washed with water, dried over $MgSO_4$, and concentrated under vacuum. The residual oil was distilled to give 1.22 g of a 52:48 mixture of **6a** and **7a**: bp 125–130 °C (0.4 mmHg); yield 50%. This product partially crystallized on standing, and filtration afforded 0.44 g of white crystals of the ester **7a**. The filtrate was concentrated under vacuum to give 0.77 g of a 82:18 mixture (^1H NMR) of the esters **6a** and **7a**.

Compound **6a**:[15] IR (neat) 1760, 1740, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3, CH_3), 1.4–2.75 (m, 8, ring protons), 3.72 (s, 6, ester 2 CH_3), 3.97 (s, 1 α-H); ^{13}C NMR ($CDCl_3$) 21.1 (t), 22.5 (q), 25.4 (t), 34.6 (t), 38.2 (t), 49.6 (s), 52.2 (q), 57.4 (d), 168.9 (s), 212.7 ppm (s). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.23; H, 7.47.

Compound **7a**: mp 83–84 °C [after two recrystallizations from hexane–ether (2:1)]; IR (KBr) 1765, 1712, 1705 cm^{-1}; ^1H NMR δ 1.00 (d, 3, J = 6 Hz, CH_3), 1.2–2.9 (m, 7, ring protons), 2.9–3.4 (m, 1, C_1 H), 3.65 (d, 1, J = 10 Hz, α-H), 3.69 (s, 6, ester 2 CH_3); ^{13}C NMR ($CDCl_3$) 14.3 (q), 25.0 (t), 32.0 (t), 37.0 (t), 45.3 (d), 50.4 (d), 52.1 (d), 52.6 (q), 168.8 (s), 169.0 (s), 211.1 ppm (s). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.35; H, 7.45.

Ethyl α-(Ethoxycarbonyl)-1-methyl-2-oxocyclohexaneacetate (6b) and Ethyl α-(Ethoxycarbonyl)-3-methyl-2-oxocyclohexaneacetate (7b). Reaction of 1.46 g (0.01 mol) of **1** with **4b** (0.011 mol) in 25 mL of THF was carried out in the usual manner. Distillation of the residual oil under vacuum gave 1.08 g of a 27:73 mixture[6] of **6b** and **7b**: bp 115–135 °C (1 mmHg); yield 43%; IR (neat) 1755, 1731, 1712 cm^{-1}; ^1H NMR (CCl_4) δ 0.96 (d, 2.2, J = 6 Hz, CH_3 of **7b**), 1.23 (s, 0.8, CH_3 of **6b**), 1.23 (t, 6, J = 7 Hz, ester 2 CH_3), 1.2–3.3 (m, 8, ring protons), 3.46 (d, 0.73, J = 10 Hz, α-H of **7b**), 3.73 (s, 0.27, α-H of **6b**), 4.07 (q, 4, J = 7 Hz, ester 2 CH_2); ^{13}C NMR ($CDCl_3$) of **6b** 14.0 (q), 21.2 (t), 22.7 (q), 25.4 (t), 34.5 (t), 38.2 (t), 49.4 (s), 57.7 (s), 61.5 (t), 168.5 (s), 212.6 ppm (s); ^{13}C NMR ($CDCl_3$) of **7b** 14.0 (q), 14.4 (q), 25.1 (t), 32.0 (t), 37.0 (t), 45.4 (d), 50.4 (d), 52.4 (d), 61.5 (t), 168.3 (s), 211.0 ppm (s). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.56; H, 8.40.

6-[Bis(ethoxycarbonyl)methyl]-3-methylbicyclo[3.1.0]hexan-6-ol (8). Reaction of 8.33 g (0.0569 mol) of **2**[9b] with **4b** (0.0569 mol) in 80 mL of THF was carried out in the usual manner. Distillation of the residual oil in vacuo [bp 126–146 °C (2 mmHg)] followed by purification by column chromatography (silica gel; hexane–acetone, 10:1) gave **8**: 9.1 g (yield 59%); bp 130–146 °C (2 mmHg); IR (neat) 3500, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3, J = 6 Hz, CH_3), 1.28 (t, 6, J = 8 Hz, ester 2 CH_3), 1.0–2.6 (m, 7 H, ring protons), 2.75 [s, 1, $CH(CO_2Et)_2$], 3.43 (br s, 1, OH), 4.20 (q, 4, J = 8 Hz, ester 2 CH_2). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.16; H, 8.16.

6-[Bis(ethoxycarbonyl)methyl]-2-methylbicyclo[3.1.0]hexan-6-ol (9). Reaction of 2.69 g (0.0184 mol) of **3**[9b] with **4b** (0.0184 mol) in 40 mL of THF was carried out in the usual manner. Distillation of the residual oil in vacuo [bp 100–140 °C (4 mmHg)] followed by purification by column chromatography (silica gel; hexane–ether, 20:1) gave 2.43 g of a mixture of *endo*-**9** and *exo*-**9**, yields 49%. HPLC analysis [Yanapak SA-II, 6 mm × 250 mm column, hexane–ether (10:1)] of this mixture showed two peaks with the retention times (integrated percentage) of 14 (*endo*-**9**, 44%) and 22 min (*exo*-**9**, 56%). These components were separated by HPLC under the same conditions as above.

***endo*-9**: bp 110–145 °C (3 mmHg); IR (neat) 3500, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7 Hz, CH_3), 1.20 (t, 6, J = 8 Hz, ester 2 CH_3), 1.0–2.6 (m, 7, ring protons), 2.73 [s, 1, $CH(CO_2Et)_2$], 3.32 (br s, 1, OH), 4.23 (q, 4, J = 8 Hz, ester 2 CH_2). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.25; H, 8.32.

***exo*-9**: bp 115–140 °C (3 mmHg); IR (neat) 3500, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3, J = 7 Hz, CH_3), 1.30 (t, 6, J = 8 Hz, ester 2 CH_3), 0.9–2.6 (m, 7 Hz, ring protons), 2.76 [s, 1, $CH(CO_2Et)_2$] 3.44 (br s, 1, OH), 4.22 (q, 4, J = 8 Hz, ester 2 CH_2). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.14; H, 8.17.

Alkaline Hydrolysis of 8. 6-(Dicarboxymethyl)-3-methylbicyclo[3.1.0]hexan-6-ol (10). A suspension of 3.5 g (0.013 mol) of compound **8** in 50 mL of 2 N NaOH was stirred for 24 h at room temperature. A workup in the usual manner[1] gave **10** as white crystals: 2.88 g (yield 82%); mp 120–121 °C (CCl_4); IR (KBr) 3600–2500, 1710 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 1.1–2.4 (m, 7, ring protons), 3.12 [s, 1, $CH(CO_2Et)_2$], 9.0–11.0 (br s, 3, 3 CO_2H). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.82; H, 6.59.

Pyrolysis of 10. *trans*-1-(3-Methylcyclopentyl)ethanone (*trans*-11).[10,16] Bulb-to-bulb distillation of 1.30 g (6.07 mmol) of the acid **10** under diminished pressure caused decarboxylation to give *trans*-**11**: 0.40 g (yield 53%); bp 120–130 °C (88 mmHg); IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3, J = 6 Hz, CH_3), 1.1–2.2 (m, 7, ring protons), 2.14 [s, 3, $C(O)CH_3$], 2.8–3.2 (m, 1, C_1 H).

Acidic Hydrolysis of 8. A suspension of 2.0 g (0.0074 mol) of **8** in 40 mL of 6 N HCl was stirred for 24 h under reflux. A workup in the usual manner[1] gave 0.55 g (yield 59%) of a 1:1 mixture (^1H NMR) of *cis*-**11**[10,16] and *trans*-**11**.[10,16] GLC analysis of this product showed a single peak at the retention time of 9.0 min. The constituent ratio was based on the ^1H NMR spectrum.

Ketone **11** (1:1 cis/trans): IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 1.5, J = 6 Hz, CH_3 of *cis*-**11**), 1.00 (d, 1.5, J = 6 Hz, CH_3 of *trans*-**11**), 0.95–2.65 (m, 7, ring protons), 2.13 [s, 3, $C(O)CH_3$], 2.65–3.05 (m, 1, C_1 H).

Acidic hydrolyses (6 N HCl or 35% HCl) of *endo*-9 and *exo*-9 were done in a similar way. The resulting products were analyzed by GLC and ^1H NMR spectra (see Table I).

Acidic Treatment of *trans*-11. A suspension of 83 mg (0.659 mmol) of *trans*-**11** in 2 mL of 6 N HCl was heated under reflux for 2 h. The workup carried out as usual gave 72 mg of a 1:1 mixture (^1H NMR) of *cis*-**11** and *trans*-**11**.

Alkaline Hydrolysis of *endo*-9. A suspension of 205 mg (0.759 mmol) of *endo*-**9** in 5 mL of 2 N NaOH was stirred for 24 h at room temperature. The usual workup afforded the acid *endo*-**12**[11] as a viscous oil. The crude acid was subjected to vacuum distillation to give 65 mg of a ketonic fraction: bp 125–140 °C (88 mmHg); 65 mg (yield 68%). GLC analysis of this product showed two peaks with retention times (integrated percentage based on GLC and/or ^1H NMR signal) of 8.2 (*trans*-**13**, 5%)[12] and 9.0 min [*cis*-**11** (50%), *trans*-**11** (34%), *cis*-**13**[12] (11%)].[17] Separation of the two fractions was carried out by GLC.

trans-**13**:[12] IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (d, 3, J = 6 Hz, CH_3), 1.45–2.55 (m, 8, ring protons), 2.15 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) 20.1 (q), 24.7 (t), 29.1 (q), 29.6 (t), 34.9 (d), 37.7 (d), 60.5 (d), 211.9 ppm (s).

Alkaline hydrolysis of *exo*-9 was done in the similar way (see Table I).

***trans*-1-(2-Methylcyclopentyl)ethanone (*trans*-13).** To a suspension of 0.288 g (0.012 mol) of magnesium turnings in 20 mL of ether was added with stirring a solution of 1.70 g (0.012 mol) of methyl iodide in 10 mL of ether at a rate at which gentle reflux occurred spontaneously. To this mixture was added 0.118 g (0.0012 mol) of cupper(I) chloride at room temperature, and then the mixture was stirred for 30 min. To the resulting mixture cooled on an ice–salt bath was slowly added a solution of 1.48 g (0.01 mol) of ethyl 1-cyclopentenecarboxylate[18] in 10 mL of ether. After being stirred for 2 h at 0 °C, the mixture was poured into aqueous NH_4Cl and acidified with 10% HCl. The organic layer was extracted with ether, washed with water, dried over $MgSO_4$, and evaporated under vacuum. The residual oil was subjected to vacuum distillation [bp 110–125 °C (90 mmHg)] to give 0.70 g (yield 55%) of a 8:92 mixture (^1H NMR) of *cis*- and *trans*-**13**. The mixture was separated by preparative GLC to each component.

Acknowledgment. This research was supported in part by a Grant-in-Aid for Special Project Research from the

(15) Further attempts to separate **6a** and **7a** by preparative TLC and HPLC were unsuccessful. The product still contained 18% of **7a**.

(16) ^{13}C NMR spectral data are identical with those reported: Belikova, N. A.; Ordubadi, M. D.; Bobyleva, A. A.; Dubitskaya, N. F.; Loshkareva L. N.; Pekhk, T. I.; Lippmaa, E. T.; Platé, A. F. *Zh. Org. Khim.* **1979**, *15*, 320.

(17) Separation of this fraction to each component (*cis*-**11**, *trans*-**11**, and *cis*-**13**) was unsuccessful. The constituent ratio was based on ^1H NMR spectrum.

(18) Büchi, G.; Hochstrasser, U.; Pawlak, W. *J. Org. Chem.* **1973**, *38*, 4348.

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Registry No. 1, 10409-46-8; 2, 39512-00-0; 3, 38043-89-9; 4a, 18424-76-5; 4b, 996-82-7; 6a, 87451-62-5; 6b, 87451-63-6; 7a, 87451-64-7; 7b, 87451-65-8; 8, 87451-66-9; *endo*-9, 87451-67-0; *exo*-9, 87451-68-1; 10, 87451-69-2; *cis*-11, 70430-75-0; *trans*-11, 70430-70-5; *endo*-12, 87451-70-5; *cis*-13, 3664-69-5; *trans*-13, 3664-70-8; dimethyl malonate, 108-59-8; diethyl malonate, 105-53-3; ethyl 1-cyclopentenecarboxylate, 10267-94-4.

Supplementary Material Available: ^{13}C NMR spectral data of compounds 8, *endo*-9, *exo*-9, and 10 (1 page). Ordering information is given on any current masthead page.

Chemistry of Substituted (α-Carbethoxyvinyl)cuprates. 2. Stereospecific Olefin Synthesis

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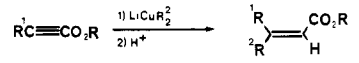
The reactivity of substituted (α-carbethoxyvinyl)cuprate reagents with various electrophiles has been studied systematically. The reaction of this type of cuprate reagent with ketones and epoxides leads to high yields of isomerically pure olefinic esters, while its condensation reaction with aldehydes produced mixtures of isomers. The stereochemistry of the condensation reaction with carbonyl compounds is explained by a steric control mechanism involving an allenoate intermediate.

Introduction

The stereospecific synthesis of substituted alkenes is a challenging problem in synthetic organic chemistry. Within the array of olefinic natural products are the insect pheromones.[1] Such compounds as the codling moth pheromone,[2] and Cecropia juvenile hormone,[3] have stimulated much of the development in the methodology for olefin synthesis. The high sensitivity of physiological activity in relation to olefin geometry mandates strict control of stereochemistry.

While many methods for the synthesis of substituted olefins are known,[4] the carbometalation of alkynes by organometallic reagents has become a highly regarded and widely used method.[5] The stereospecific cis addition of organocuprates to acetylenes has provided a versatile method for the synthesis of trisubstituted olefins.[4,5]

The regiospecific, copper-catalyzed conjugate addition of butylmagnesium bromide to esters of propiolic, tetrolic, and acetylenedicarboxylic acids was first described in 1960.[6] In the absence of a catalyst, the addition of Grignard reagents to activated acetylenes led exclusively to tertiary acetylenic alcohol products. The pioneering works of Corey and Katzenellenbogen,[7] Siddall et al.,[8] and Klein and Turkel[9] on the addition of organocuprates and copper(I) species to acetylenic esters have provided the groundwork for what has now become a general method for the preparation of β-disubstituted olefinic esters. The extension of this methodology to α,β-substituted olefinic esters has not been effectively carried out.



The addition of lithium dialkylcuprates to substituted acetylenic esters has found frequent application.[10] Vinylcuprate species also add to acetylenic esters in good yield.[11] Other functionalized cuprate reagents have been added to substituted acetylenic esters and amides, as well as to ethyl propiolate.[12] Many of these examples are not stereospecific; mixtures of cis and trans isomers are obtained upon protonolysis.

Although the organocuprate addition reaction to activated acetylenes appears to have enjoyed wide application, little attention has been given to the reactivity of the cuprate intermediate with electrophilic species. Carlson[13] has synthesized 5,6-dihydro-2*H*-pyran-2-ones by reaction of the copper intermediate with very reactive electrophiles in the presence of excess hexamethylphosphorous triamide (HMPA). All of the alkylated products were obtained as

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