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Stereospecific Synthesis of Functionalized Cyclopentane Derivatives

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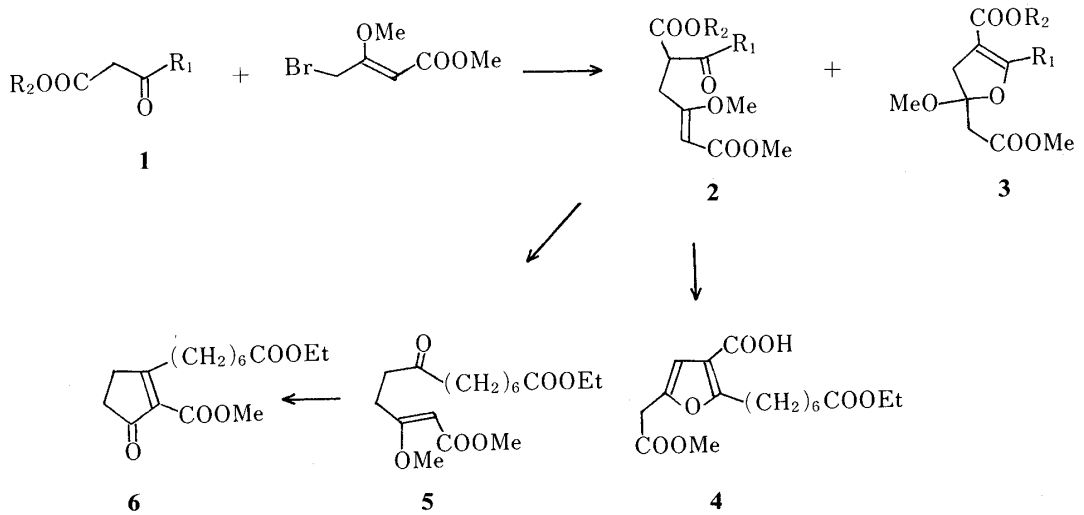
A general method for the stereospecific synthesis of 2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanones (**9**) is described. This synthetic method has the advantage that three functional groups can be stereospecifically introduced on a five-membered ring by the catalytic hydrogenation of 2,3,4-trisubstituted cyclopentenones. Furthermore, **9** could be stereospecifically converted to 1,2-*trans*-2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanols (**20**) and 3,4-*cis*-disubstituted cyclopentanones (**11**) by a simple procedure. These synthetic methods may be useful for the synthesis of natural products containing a five-membered ring.

Keywords——catalytic reduction; 2,3,4-trisubstituted cyclopentenone; stereospecific reduction; decarboxylation; 2,3-*trans*-3,4-*cis*-2,3,4-trisubstituted cyclopentanone; cyclopentane; cyclopentanone; cyclopentanol

One of the difficulties in the synthesis[1] of classical prostaglandins (PGs) and their derivatives is how to introduce the desired substituents on the five-membered ring in a stereocontrolled fashion. In connection with synthetic studies on natural products containing a five-membered ring, as well as PGs,[2] we have found a general method for the stereospecific synthesis of 2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanones. In this method,



a: $R_1=Me$, $R_2=CH_2Ph$
b: $R_1=C_8H_{17}$, $R_2=CH_2Ph$
c: $R_1=(CH_2)_3COOMe$, $R_2=CH_2Ph$
d: $R_1=(CH_2)_6COOEt$, $R_2=CH_2Ph$
e: $R_1=(CH_2)_7COOEt$, $R_2=CH_2Ph$
f: $R_1=Ph$, $R_2=Et$
g: $R_1=(CH_2)_3Ph$, $R_2=Me$
h: $R_1=$*tert*-Bu, $R_2=Me$

Chart 1

three asymmetric centers can be introduced by catalytic hydrogenation of a 2,3,4-trisubstituted cyclopentenone, and the resulting 2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanone can be stereospecifically transformed into the 1,2-*trans*-2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanol or the 3,4-*cis*-disubstituted cyclopentanone in one step. This synthetic method should be useful for the synthesis of natural products containing a five-membered ring, such as PGs.

Alkylation of β-keto esters (**1**)[3] with methyl β-methoxy-γ-bromocrotonate[4] and sodium sand in ether afforded a mixture of the normally alkylated products (**2**) and the dihydrofuran derivatives (**3**). By catalytic hydrogenation (5% Pd–C/H_2) followed by decarboxylation (quinoline–Cu), **2d** was converted into the keto diester (**5**). In a preliminary experiment, the cyclization of **5** with $SnCl_4$ in nitromethane[5] provided the desired cyclopentenone (**6**) in good yield. However, treatment of **2d** under similar reaction conditions resulted in the formation of the furan derivative (**4**) (Chart 1).

The difficulty of cyclization of **2** to the corresponding cyclopentenones was overcome in the following way. Treatment of a mixture of **2** and **3** with CF_3COOH in $CHCl_3$ at room temperature gave the 1,4-diketones (**7**), which are synthetically equivalent to the cyclopen-

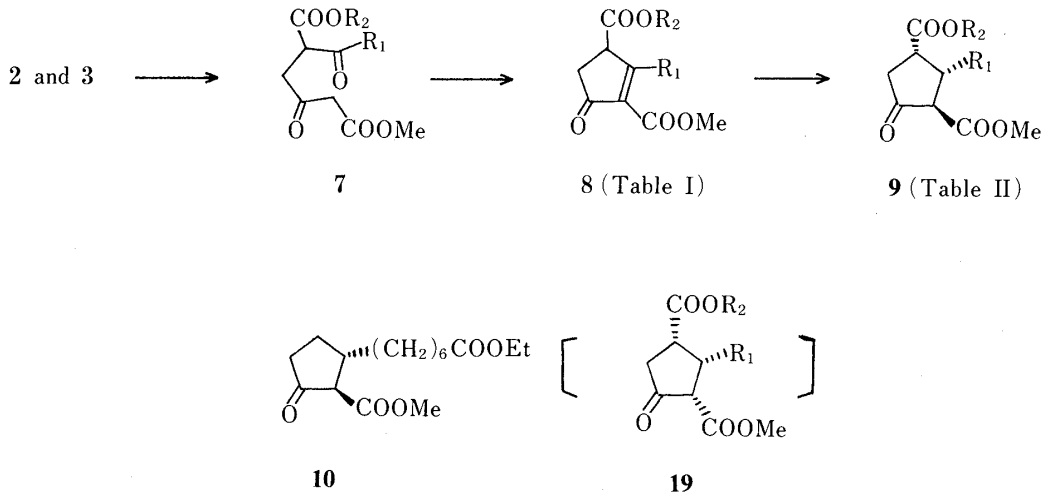
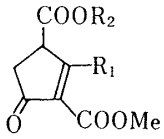


Chart 2

tenone. Treatment of **7** with $KHCO_3$ in methanol at room temperature to 40 °C afforded the expected cyclopentenones (**8**) in moderate yields[6] (Table I and Chart 2). Catalytic hydrogenation of **8** with 10% Pd–C/H_2 in methanol at 0 °C proceeded stereospecifically to afford the 2,3-*trans*-3,4-*cis*-cyclopentanones (**9**) as a sole product (Table II). Other possible stereoisomers could not be detected on thin-layer chromatography (TLC). In this catalytic hydrogenation, the reduction temperature seems to be important.[7] The catalytic hydrogenation of **8d** (R_2 = benzyl) at room temperature reduced the yield of **9d** and remarkably enhanced the yield of the decarboxylated product (**10**) as a by-product.

The configuration of **9** was determined in the following way. Decarboxylation of **9b** methyl ester (R_2 = Me) with NaI–AcOH in refluxing diglyme[8] yielded the corresponding 3,4-*cis*-cyclopentanone (**11b**) (Table III). The acetalization of **11b** with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene afforded the acetal (**12**) ($R_1 = C_8H_{17}$). By treatment with sodium methoxide followed by deprotection with 5% HCl, **11** ($R_1 = C_8H_{17}$) was isomerized to the thermodynamically more stable 3,4-*trans*-cyclopentanone (**13**)[9] ($R_1 = C_8H_{17}$) (Chart 3). Furthermore, the methyl ester at C_2 in **9** did not isomerize on treatment with K_2CO_3 in methanol. This finding suggests that the ester function at C_2 is *trans* relative to the substituent at the C_3 position.[10] On the basis of these data, the configuration of **9** was

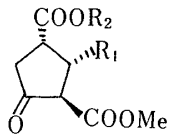
TABLE I.



Compd. No.	R_1	R_2	Formula	Analysis (%) Calcd (Found) C	H	Yield[6] (%)	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
8a	Me	CH_2Ph	$C_{16}H_{16}O_5$	66.66 (66.41	5.59 5.71)	59	1720, 1630	2.30 (3H, s, Me), 3.80 (3H, s, COOMe), 5.16 (2H, s, CH_2), 7.36 (5H, s, Ar-H)
8b	C_8H_{17}	CH_2Ph	$C_{23}H_{30}O_5$	71.48 (71.55	7.82 7.89)	68	1740, 1630	3.79 (3H, s, COOMe), 5.18 (2H, s, CH_2), 7.30 (5H, s, Ar-H)
8c	$(CH_2)_3COOMe$	CH_2Ph	$C_{20}H_{22}O_7$	64.16 (64.33	5.92 5.84)	60	1730, 1630	3.70 (3H, s, COOMe), 3.80 (3H, s, COOMe), 5.20 (2H, s, CH_2), 7.35 (5H, s, Ar-H)
8d	$(CH_2)_6COOEt$	CH_2Ph	$C_{24}H_{30}O_7$	66.96 (67.12	7.02 7.09)	63	1735, 1630	1.25 (3H, t, $J=7$ Hz, Me), 3.84 (3H, s, COOMe), 4.13 (2H, q, $J=7$ Hz, CH_2), 5.20 (2H, s, CH_2)
8e	$(CH_2)_7COOEt$	CH_2Ph	$C_{25}H_{32}O_7$	67.55 (67.49	7.26 7.21)	53	1735, 1630	3.83 (3H, s, COOMe), 4.13 (2H, q, $J=7$ Hz, CH_2), 5.20 (2H, s, CH_2), 7.33 (5H, s, Ar-H)
8f	Ph	Et	$C_{16}H_{16}O_5$	66.66 (66.80	5.59 5.65)	75	1735, 1620	0.97 (3H, t, $J=7$ Hz, Me), 3.82 (3H, s, COOMe), 4.02 (2H, q, $J=7$ Hz, CH_2), 7.35 (5H, s, Ar-H)
8g	$(CH_2)_3Ph$	Me	$C_{18}H_{20}O_5$	68.34 (68.50	6.37 6.41)	71	1730, 1630	3.72 (3H, s, COOMe), 3.80 (3H, s, COOMe), 7.35 (5H, s, Ar-H)
8h	*tert*-Bu	Me	$C_{13}H_{18}O_5$	61.40 (61.39	7.14 7.28)	69	1740, 1620	1.19 (9H, s, Me×3), 3.70 (3H, s, COOMe), 3.79 (3H, s, COOMe)

Compounds (**8a**—**8h**) were each obtained as a colorless oil.

TABLE II.



Compd. No.	R_1	R_2	Formula	Analysis (%) Calcd (Found) C	H	Yield (%)	Appearance	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
9a[a]	Me	H	$C_9H_{12}O_5$	53.99 (53.90)	6.04 6.09)	75	mp 96 °C	1754, 1690	1.21 (3H, d, J=6 Hz, Me), 3.75 (3H, s, COOMe), 3.15—3.40 (2H, m),[b] 2.65—3.05 (1H, m),[b] 2.50—2.60 (2H, m)[b]
9b	C_8H_{17}	H	$C_{16}H_{26}O_5$	64.40 (64.51	8.78 8.70)	70	mp 63 °C	1750, 1700	0.90 (3H, t, J=7 Hz, Me), 3.75 (3H, s, COOMe), 8.45 (1H, s, COOH)
9c	$(CH_2)_3COOMe$	H	$C_{13}H_{18}O_7$	54.54 (54.60	6.37 6.45)	69	Oil	1730 (broad)	3.63 (3H, s, COOMe), 3.72 (3H, s, COOMe), 7.95 (1H, br s, COOH)
9d	$(CH_2)_6COOEt$	H	$C_{17}H_{26}O_7$	59.63 (59.82	7.65 7.72)	68	Oil	1750, 1740	1.26 (3H, t, J=7 Hz, Me), 3.77 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2), 7.94 (1H, br s, COOH)
9e	$(CH_2)_7COOEt$	H	$C_{18}H_{28}O_7$	60.66 (60.73	7.92 8.05)	59	Oil	1750, 1740	1.26 (3H, 7, J=7 Hz, Me), 3.76 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2)
9f	Ph	Et	$C_{16}H_{18}O_5$	66.19 (66.38	6.25 6.19)	72	mp 91 °C	1760, 1730	1.12 (3H, t, J=7 Hz, Me), 3.80 (3H, s, COOMe), 7.35 (5H, s, Ar-H)
9g	$(CH_2)_3Ph$	Me	$C_{18}H_{22}O_5$	67.09 (67.25	6.62 6.69)	75	Oil	1765, 1730	3.56 (3H, s, COOMe), 3.76 (3H, s, COOMe), 7.30 (5H, s, Ar-H)
9h	*tert*-Bu	Me	$C_{13}H_{20}O_5$	60.92 (61.09	7.87 7.99)	69	mp 103 °C	1760, 1725	0.95 (9H, s, Me × 3), 3.63 (3H, s, COOMe), 3.72 (3H, s, COOMe)

a) Crystalline compounds were recrystallized from hexane and AcOEt, and IR spectra were taken in Nujol on a NaCl plate. *b*) Common signals due to five protons on the five-membered ring ketone.

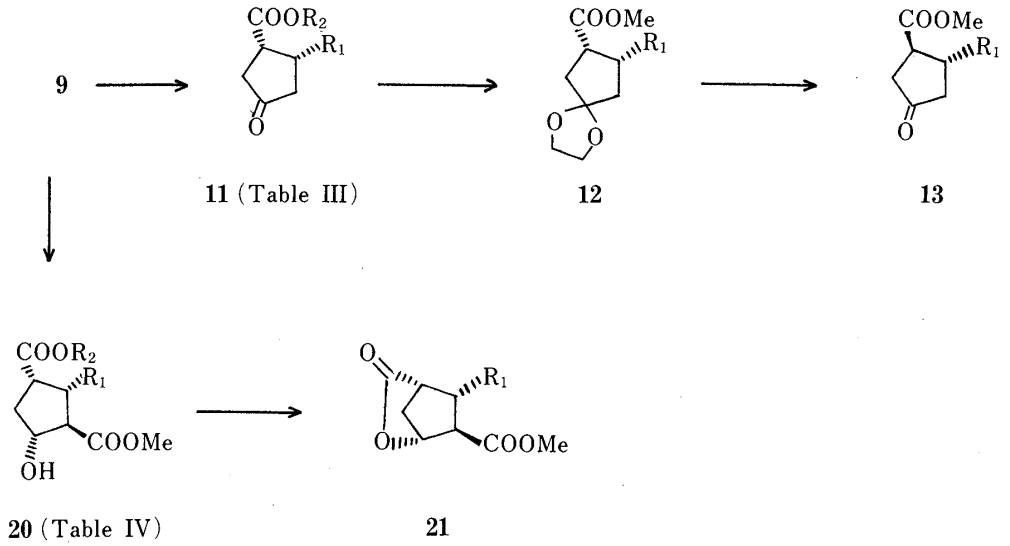


Chart 3

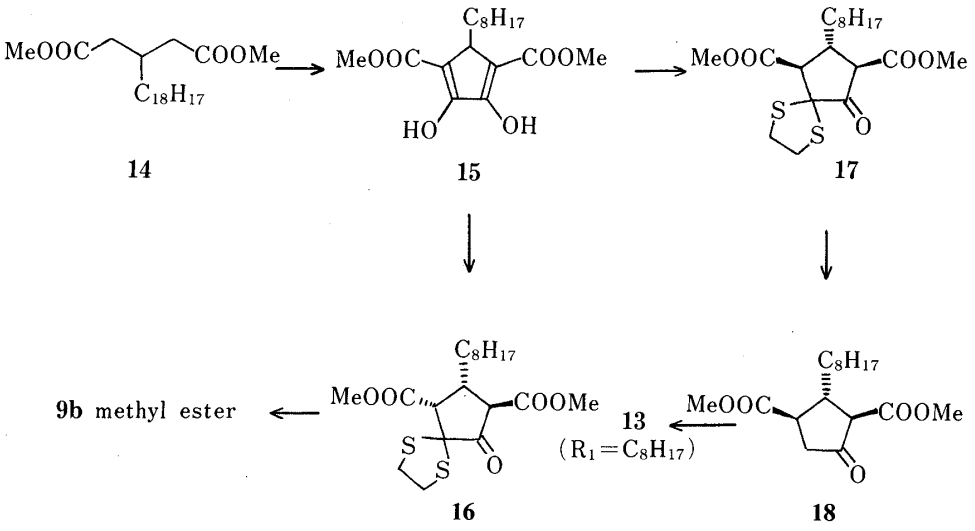
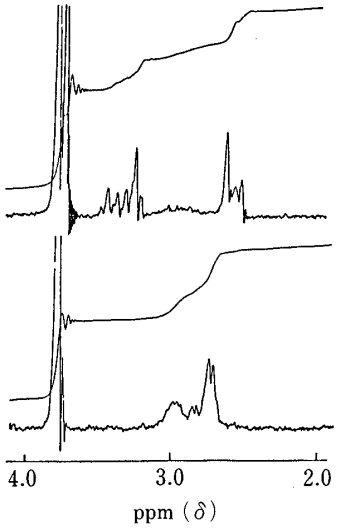


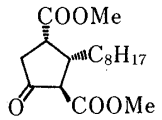
Chart 4

determined as 2,3-*trans*-3,4-*cis*.

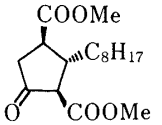
The *trans*,*cis*-cyclopentanone **9b** (R_2=Me) and its stereoisomer (**18**) could also be synthesized by an alternative route. Claisen condensation of the diester (**14**)[11] with dimethyl oxalate in the presence of sodium methoxide afforded the enol ester (**15**). Treatment of **15** with ethanedithiol and boron trifluoride etherate at room temperature gave a mixture of the oily monothioketal (**16**) and the crystalline monothioketal (**17**), which could be separated by crystallization from methanol. On desulfurization with Raney Ni, **16** and **17** afforded **9b** methyl ester and the *trans*,*trans*-cyclopentanone **18**, respectively. The stereochemistry of **18** was established by the findings that **18** could be converted into **13** ($R_1=C_8H_{17}$) by decarboxylation with NaI–AcOH in refluxing diglyme and the methyl ester at C_2 was not isomerized by treatment with K_2CO_3 in methanol (Chart 4).

It is noteworthy that the proton nuclear magnetic resonance (^{1}H-NMR) spectrum[12] of **9b** methyl ester (R_2=Me) was significantly different from that of **18** (Fig. 1 and Table II). Five protons on the five-membered ring in **9b** methyl ester were observed at δ 2.50—2.60 (2H, m), 2.65—3.05 (1H, m), and 3.15—3.40 (2H, m), while these protons in **18** were observed at δ 2.60—3.10 (5H, m). Furthermore, two methyl signals (C_2- and C_4-COOMe) in **9b** methyl





9b methylester



18

Fig. 1. ^{1}H-NMR Spectra of **9b** Methyl Ester and **18**

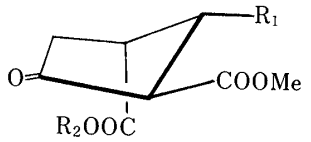


Fig. 2. Half Chair Conformation of **9**

ester appeared as separate peaks at δ 3.75 and 3.69, whereas those of **18** appeared as a single peak at δ 3.71. The **9** methyl esters (Table II, R_2=Me) obtained by treatment with CH_2N_2 showed essentially similar spectra to that of **9b** methyl ester. Such observations in the ^{1}H-NMR make it quite easy to distinguish the 2,3-*trans*-3,4-*cis* type **9** from the 2,3-*trans*-3,4-*trans* type **18**.

The formation of **9** may be rationalized as follows. In the catalytic hydrogenation of **8**, the attack of hydrogen from the less hindered side of the sterically hindered double bond is presumed to yield first the 2,3-*cis*-3,4-*cis* compounds (**19**) (Chart 2), and these unstable keto esters may be rapidly isomerized through the keto–enol equilibrium to the more stable keto esters **9**.

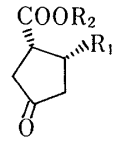
Reduction of **9** with $NaBH_4$ in methanol at 0 °C afforded exclusively the 1,2-*trans*-2,3-*trans*-3,4-*cis*-cyclopentanols (**20**), in which the configuration was favorable for the synthesis of PGF_α type[2] products (Table IV and Chart 3). The configuration of the C_1-alcohol in **20** was established by the facile transformation into the lactones (**21**) in refluxing benzene containing *p*-toluenesulfonic acid. This stereospecific reduction may be attributed to steric hindrance caused by the carboxyl function at C_4. A half-chair conformation of the cyclopentanone ring in **9** is considered to be the most stable when each substituent occupies the quasi equatorial configuration at C_2 and C_3, and the quasi axial configuration at C_4, as shown in Fig. 2. Consequently, the carboxyl function at C_4 seems to shield the α-site of the carbonyl function. It is likely that this shielding effect controls the steric approach of $NaBH_4$ to yield selectively the α-hydroxy function.

Thus, the present synthetic methods may be useful for the synthesis of natural products containing a five-membered ring, including PGs.

Experimental

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a JASCO IRA-2 spectrometer, and ^{1}H-NMR spectra on a Varian T-60; all chemical shifts are given in ppm downfield from tetramethylsilane. For column chromatography, Kanto Chemical Silica gel (60—100 mesh) or Merck Aluminium oxide 90 (neutral) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried on anhydrous sodium sulfate.

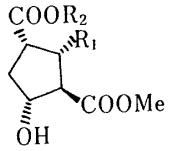
General Procedure for the Alkylation of the β-Keto Esters (1). A Typical Example: Methyl 4-Benzyloxycarbonyl-5-(6-ethoxycarbonylhexyl)-2-methoxy-2,3-dihydrofuran-2-yl-acetate (3d) and Methyl 5-Benzyloxycarbonyl-12-ethoxy-

TABLE III. 

Compd. No.	R_1	R_2	Formula	Analysis (%) Calcd (Found) C	H	Yield (%)	Appearance	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
11a	Me	Me	$C_8H_{12}O_3$	61.52 (61.77	7.75 7.89)	85	Oil	1750, 1200	1.04 (3H, d, J=7 Hz), 3.75 (3H, s, COOMe)
11b	C_8H_{17}	Me	$C_{15}H_{26}O_3$	70.83 (70.98	10.30 10.43)	79	Oil	1750, 1200	3.70 (3H, s, COOMe)
11c	$(CH_2)_3COOMe$	Me	$C_{12}H_{18}O_5$	59.49 (59.27	7.49 7.53)	88	Oil	1740, 1205	3.69 (3H, s, COOMe), 3.74 (3H, s, COOMe)
11d	$(CH_2)_6COOEt$	Me	$C_{16}H_{26}O_5$	64.40 (64.51	8.78 8.70)	75	Oil	1730, 1210	1.24 (3H, t, J=7 Hz, Me), 3.70 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2)
11e	$(CH_2)_7COOEt$	Me	$C_{17}H_{28}O_5$	65.36 (65.55	9.03 9.18)	89	Oil	1730, 1200	1.25 (3H, t, J=7 Hz, Me), 3.70 (3H, s, COOMe), 4.11 (2H, q, J=7 Hz, CH_2)
11f	Ph	Et	$C_{14}H_{16}O_3$	72.39 (72.51	6.94 6.74)	98	Oil	1755, 1605	0.95 (3H, t, J=7 Hz, Me), 4.05 (2H, q, J=7 Hz, CH_2), 7.41 (5H, s, Ar-H)
11g	$(CH_2)_3Ph$	Me	$C_{16}H_{20}O_3$	73.82 (73.99	7.74 7.82)	85	Oil	1740, 1600	3.75 (3H, s, COOMe), 7.31 (5H, s, Ar-H)
11h[a]	*tert*-Bu	Me	$C_{11}H_{18}O_3$	66.64 (66.79	9.15 9.35)	85	mp 101 °C	1745, 1200	0.98 (9H, s, Me×3), 3.66 (3H, s, COOMe)

a) Compounds (**11h**) was recrystallized from hexane and AcOEt, and the IR spectrum was taken in Nujol on a NaCl plate.

TABLE IV.



Compd. No.	R_1	R_2	Formula	Analysis (%) Calcd (Found) C	H	Yield (%)	Appearance	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
20a[a]	Me	H	$C_9H_{14}O_5$	53.46 (53.54	6.98 7.06)	79	mp 88 °C	3420, 1740	1.14 (3H, d, J=6 Hz, Me), 3.71 (3H, s, COOMe), 4.45 (1H, m, CHOH)
20b	C_8H_{17}	H	$C_{16}H_{28}O_5$	63.97 (64.16	9.40 9.51)	83	Oil	3450, 1740	0.90 (3H, t, J=7 Hz, Me), 3.75 (3H, s, COOMe), 4.40 (1H, m, CHOH)
20c	$(CH_2)_3COOMe$	H	$C_{13}H_{20}O_7$	54.16 (54.28	6.99 7.14)	88	Oil	3450, 1730	3.68 (3H, s, COOMe), 3.73 (3H, s, COOMe), 4.45 (1H, m, CHOH)
20d	$(CH_2)_6COOEt$	H	$C_{17}H_{28}O_7$	59.28 (59.41	8.19 8.08)	89	Oil	3480, 1740	1.28 (3H, t, J=7 Hz, Me), 3.76 (3H, s, COOMe), 4.14 (2H, q, J=7 Hz, CH_2); 4.42 (1H, m, CHOH)
20e	$(CH_2)_7COOEt$	H	$C_{18}H_{30}O_7$	60.31 (60.46	8.44 8.56)	80	Oil	3500, 1740	1.25 (3H, t, J=7 Hz, Me), 3.76 (3H, s, COOMe), 4.14 (2H, q, J=7 Hz, CH_2), 4.42 (1H, m, CHOH)
20f	Ph	Et	$C_{16}H_{20}O_5$	65.74 (65.88	6.90 6.98)	90	Oil	3450, 1730	1.00 (3H, t, J=7 Hz, Me), 3.80 (3H, s, COOMe), 4.15 (2H, q, J=7 Hz, CH_2), 4.45 (1H, m, CHOH)
20g	$(CH_2)_3Ph$	Me	$C_{18}H_{24}O_5$	67.48 (67.56	7.55 7.42)	85	Oil	3450, 1730	3.65 (6H, s, COOMe×2), 4.41 (1H, m, CHOH), 7.30 (5H, s, Ar-H)
20h	*tert*-Bu	Me	$C_{13}H_{22}O_5$	60.44 (60.61	8.59 8.63)	87	Oil	3500, 1735	0.99 (9H, s, Me×3), 3.71 (6H, s, COOMe×2), 4.35 (1H, m, CHOH)

a) Compound (**20a**) was recrystallized from hexane and AcOEt, and the IR spectrum was taken in Nujol on a NaCl plate.

carbonyl-3-methoxy-6-oxo-2-dodecenoate (2d)——A solution of **1d**[3] (16.166 g) in benzene (20 ml) was added dropwise with stirring to a suspension of sodium sand (1.10 g) in benzene (80 ml) at 10—15 °C. The mixture was stirred for 10 h at room temperature, then methyl β-methoxy-γ-bromocrotonate (10.10 g) was added dropwise, and the whole was heated under reflux for 5 h. The reaction mixture was poured into ice water (300 ml) and extracted with ether (200 ml × 3). The combined extracts were washed with 5% HCl and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on alumina (GIII, 200 g). The fraction eluted with 10% benzene in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **3d** (1.55 g, 7%) as a colorless oil. The fraction eluted with 10—12% benzene in hexane (v/v) afforded a mixture of **3d** and **2d** (1.62 g, 7%). Further elution with 12—20% benzene in hexane (v/v) afforded **2d** (13.60 g, 61%) as a colorless oil. **2d**; IR (neat): 1740, 1715, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H, s, OMe), 3.67 (3H, s, COOMe), 5.04 (1H, s, –CH=), 5.18 (2H, s, CH_2Ph), 7.33 (5H, s, Ar-H). *Anal.* Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 65.01; H, 7.35. **3d**; IR (neat): 1740, 1700, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, s, OMe), 3.68 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2Me), 5.17 (2H, s, CH_2Ph), 7.36 (5H, s, Ar-H). *Anal.* Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 65.10; H, 7.38.

In a similar manner, the other compounds were obtained as oily mixtures[13] of **2** and **3**, which were treated with CF_3COOH without further purification. Yields (mixture of **2** and **3**) were as follows. **a**; 65%, **b**; 73%, **c**; 59%, **d**; 75%, **e**; 78%, **f**; 70%, **g**; 80%, **h**; 75%.

Methyl 4-Carboxy-5-(6-ethoxycarbonylhexyl)-furan-2-yl-acetate (4)——Stannic chloride (10 ml) was added dropwise to a stirred solution of **2d** (4.114 g) in nitromethane (45 ml) under ice-water cooling. After 2 h, the reaction mixture was diluted with ether (100 ml) and water (50 ml). The organic layer was washed and dried. The solvent was removed *in vacuo* to yield crude **4** containing a trace of stannic chloride. To remove the stannic chloride,[14] the mixture was treated with $NaBH_4$ (600 mg) in a mixture of EtOH (30 ml), dioxane (35 ml), and water (12 ml) for 0.5 h under ice-water cooling. The reaction mixture was poured into ice-water (150 ml) and extracted with ether (100 ml × 3). The combined extracts were washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (50 g). The fraction eluted with 10—20% ether in benzene (v/v) was collected. The solvent was removed *in vacuo* to leave **4** (2.266 g, 75%) as a colorless oil. IR (neat); 1740, 1680, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, Me), 3.76 (3H, s, COOMe), 4.22 (2H, q, J=7 Hz, CH_2), 6.55 (1H, s, =CH), 9.25 (1H, s, COOH). *Anal.* Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 60.12; H, 7.25.

Methyl 12-Ethoxycarbonyl-3-methoxy-6-oxo-2-dodecenoate (5)——Compound **2d** (2.035 g) in methanol (30 ml) was hydrogenated in the presence of 5% Pd–C under an H_2 atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was heated in a mixture of quinoline (5 ml) and copper powder (80 mg) for 2 h at 130 °C. The reaction mixture was dissolved in AcOEt (50 ml), and the organic layer was successively washed with 5% HCl, 5% aq. $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* yielded an oily residue, which was purified by column chromatography on alumina (GIII, 15 g). The fraction eluted with 10—20% benzene in hexane (v/v) gave **5** (1.358 g, 94%) as a colorless oil. IR (neat); 1735, 1720, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, Me), 3.62 (3H, s, OMe), 4.13 (2H, q, J=7 Hz, CH_2), 5.02 (1H, s, =CH–). *Anal.* Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.34; H, 8.67.

3-(6-Ethoxycarbonylhexyl)-2-methoxycarbonyl-2-cyclopenten-1-one (6)——Stannic chloride (1.5 ml) was added dropwise to a stirred solution of **5** (615 mg) in nitromethane (6 ml) under ice-water cooling. The whole was stirred for 2 h at room temperature, diluted with water (50 ml) and extracted with ether (50 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on alumina (GIII, 10 g). The fraction eluted with 20—50% benzene in hexane (v/v) afforded **6** (331 mg, 60%) as a colorless oil. IR (neat): 1730, 1625, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, Me), 3.82 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.96; H, 8.28.

General Procedure for the Preparation of the 1,4-Diketones (7). A Typical Example: Methyl 5-Benzyloxycarbonyl-12-ethoxycarbonyl-3,6-dioxododecanoate (7d)——CF_3COOH (2 ml) was added dropwise to a stirred solution of a mixture (1.021 g) of **2d** and **3d** in $CHCl_3$ (30 ml) at room temperature. The whole was stirred for 7 h, diluted with water (50 ml), and extracted with ether (100 ml × 3). The combined extracts were washed and dried. The solvent was evaporated off *in vacuo* to give an oily residue (**7d**, 990 mg), which was subjected to the next cyclization reaction without further purification. IR (neat): 1745, 1730, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, Me), 3.50 (2H, s, CH_2), 3.70 (3H, s, COOMe), 4.11 (2H, q, J=7 Hz, CH_2), 5.15 (2H, s, CH_2Ph), 7.33 (5H, s, Ar-H).

In a similar manner, the other compounds were obtained from the mixtures of **2** and **3**, and characterized by ^{1}H-NMR spectroscopy ($CDCl_3$). **7a**; δ: 2.29 (3H, s, Me), 3.48 (2H, s, CH_2), 3.67 (3H, s, COOMe), 5.13 (2H, s, CH_2Ph). **7b**; δ: 3.50 (2H, s, CH_2), 3.70 (3H, s, COOMe), 5.11 (2H, s, CH_2Ph). **7c**; δ: 3.45 (2H, s, CH_2), 3.68 (6H, s, COOMe × 2), 5.15 (2H, s, CH_2Ph). **7e**; δ: 1.21 (3H, t, J=7 Hz, Me), 3.50 (2H, s, CH_2), 3.70 (3H, s, COOMe). 4.12 (2H, q, J=7 Hz, CH_2). 5.15 (2H, s, CH_2Ph). **7f**; δ: 1.15 (3H, t, J=7 Hz, Me), 3.58 (2H, s, CH_2), 3.75 (3H, s, COOMe), 4.12 (2H, q, J=7 Hz, CH_2). **7g**; δ: 3.41 (2H, s, CH_2), 3.71 (3H, s, COOMe), 7.22 (5H, s, Ar-H). **7h**; δ: 1.20

(9H, s, Me × 3), 3.40 (2H, s, CH_2), 3.68 (3H, s, COOMe), 3.71 (3H, s, COOMe).

General Procedure for the Preparation of the Trisubstituted Cyclopentenones (8). A Typical Example: 4-Benzyloxycarbonyl-3-(6-ethoxycarbonylhexyl)-2-methoxycarbonyl-2-cyclopentenone (8d)——$KHCO_3$ (400 mg) was added portionwise to a stirred solution of **7d** (500 mg) in methanol (20 ml) at room temperature. The mixture was stirred at 30—40 °C for 2 h, then neutralized with 5% aq. AcOH, and extracted with ether (100 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (5 g). The fraction eluted with 1—2% ether in benzene (v/v) afforded **8d** (302 mg, 63%) as a colorless oil.

The other compounds were prepared in essentially the same manner as described above (see Table I).

General Procedure for the Preparation of the 2,3-*trans*-3,4-*cis*-Cyclopentanones (9). A Typical Example: 4α-Carboxy-3α-(6-ethoxycarbonylhexyl)-2β-methoxycarbonylcyclopentanone (9d)——A solution of **8d** (249 mg) in methanol (40 ml) was hydrogenated in the presence of 10% Pd–C under an H_2 atmosphere at 0 °C. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 5—10% ether in benzene (v/v) was collected, and the solvent was removed *in vacuo* to yield **9d** (135 mg, 68%) as a colorless oil (see Table II).

The other compounds were prepared in a similar manner. Treatment of **9** (R_2 = H) with CH_2N_2 yielded the corresponding methyl esters **9** (R_2 = Me). In the ^{1}H-NMR ($CDCl_3$) of the esters **9** (R_2 = Me), two methyl signals due to the C_2-- and the C_4-COOMe were seen as follows. **9a**; oil, δ: 3.72, 3.76. **9b**; mp 37 °C, δ: 3.69, 3.75. **9c**; oil, δ: 3.65, 3.74 (Me × 2). **9d**; oil, δ: 3.74, 3.78. **9e**; oil, δ: 3.74, 3.78. Five protons on the five-membered ring showed a pattern similar to that of the corresponding acid.

Hydrogenation of **8d** (410 mg) at room temperature afforded a mixture of **9d** and **10**, which could be separated by column chromatography on silica gel (3 g). The fraction eluted with 1—2% ether in benzene (v/v) yielded **10** (105 mg) as a colorless oil, and the fraction eluted with 5—10% ether in benzene (v/v) afforded **9d** (190 mg). **10**; IR (neat): 1750, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7 Hz, Me), 3.77 (3H, s, COOMe), 4.12 (2H, q, J = 7 Hz, CH_2). *Anal.* Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.55; Hh, 8.86.

General Procedure for the Preparation of the 1,2-*trans*-2,3-*trans*-3,4-*cis*-Cyclopentanols (20). A Typical Example: 4α-Carboxy-3α-(6-ethoxycarbonylhexyl)-2β-methoxycarbonyl-1α-cyclopentanol (20d)——$NaBH_4$ (400 mg) was added portionwise to a stirred solution of **9d** (1.221 g) in a mixture of EtOH (30 ml), H_2O (7 ml), and $NaHCO_3$[15] (880 mg) at 0 °C. After 0.5 h, the reaction mixture was diluted with water (100 ml), made acidic with 5% HCl, and extracted with ether (100 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (12 g). The fraction eluted with 10—20% ether in benzene (v/v) afforded **20d** (1.095 g, 89%) as a colorless oil.

The other compounds were prepared in essentially the same manner as described above.

General Procedure for the Preparation of the Lactones (21). A Typical Example: *endo*-3-(6-Ethoxycarbonylhexyl)-*exo*-2-methoxycarbonyl-5-oxo-6-oxa-bicyclo[2.2.1]heptane (21d)——The hydroxy ester **20d** (160 mg) in benzene (30 ml) containing a catalytic amount of *p*-toluenesulfonic acid was heated under reflux with azeotropic removal of formed H_2O. After 2 h, the reaction mixture was successively washed with 5% aq. $NaHCO_3$ and water, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (2 g). The fraction eluted with 1% ether in benzene (v/v) was collected, and the solvent was removed *in vacuo* to yield **21d** (101 mg, 67%) as a colorless oil. IR (neat): 1795, 1740, 1195 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7 Hz. Me), 3.75 (3H, s, COOMe), 4.15 (2H, q, J = 7 Hz, CH_2), 4.91 (1H, br s, –CH–O). *Anal.* Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.68; H, 8.20.

The following compounds (**21b, f, g**) were prepared from the corresponding **20** in a similar way. **21b**; oil. IR (neat): 1790, 1735, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7 Hz, Me), 2.84 (1H, m, COCH–), 3.77 (3H, s, COOMe), 4.88 (1H, br s, –CH–O). *Anal.* Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.21; H, 9.34. **21f**; oil. IR (neat): 1790, 1735, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (1H, m, COCH–), 3.78 (3H, s, COOMe), 4.90 (1H, br s, –CH–O). *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.11; H, 6.75. **21g**; oil. IR (neat): 1795, 1730, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, COOMe), 4.90 (1H, br s, –CH–O), 7.35 (5H, s, Ar-H). *Anal.* Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.89; H, 7.08.

General Procedure for the Preparation of the 3,4-*cis*-Cyclopentanones (11). A Typical Example: 3α-Ethoxycarbonyl-4α-phenylcyclopentanone (11f)——Compound **9f** (1.585 g) in a mixture of diglyme (10 ml) and AcOH (1 ml) was heated under reflux in the presence of NaI (6 g) for 0.5 h. The reaction mixture was diluted with H_2O (50 ml) and extracted with AcOEt (50 ml × 3). The combined extracts were successively washed with brine, 5% aq. $Na_2S_2O_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (15 g). The fraction eluted with 30—50% benzene in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to leave **11f** (1.248 g, 98%) as a colorless oil.

In a similar manner, the other compounds were prepared from the corresponding **9** (or its methyl ester).

3α-Methoxycarbonyl-4α-octylcyclopentanone Ethylene Acetal (12, $R_1 = C_8H_{17}$)——BF_3-etherate (1 ml) was added dropwise to a stirred solution of **11b** (250 mg) in a mixture of CH_2Cl_2 (0.5 ml) and ethylene glycol (0.3 ml) at 0 °C. After 1 h, the reaction mixture was diluted with water (20 ml) and extracted with ether (30 ml × 3). The combined

extracts were successively washed with brine, 5% aq. $NaHCO_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 50% benzene in hexane (v/v) was collected, and the solvent was evaporated off *in vacuo* to afford **12** (230 mg, 78%) ($R_1=C_8H_{17}$) as a colorless oil. IR (neat): 1750, 1200, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s, COOMe), 3.88 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.53; H, 10.21.

By a similar technique, **12** ($R_1=Me$) was obtained as an oily compound. IR (neat): 1750, 1200, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, $J=7$ Hz, Me), 3.65 (3H, s, COOMe), 3.85 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.09; H, 8.01.

3β-Methoxycarbonyl-4α-octylcyclopentanone (13, $R_1=C_8H_{17}$)——NaOMe (200 mg) in methanol (4 ml) was added dropwise to a stirred solution of **12** ($R_1=C_8H_{17}$) (150 ml) in methanol (2 ml) at room temperature. The whole was stirred for 12 h at room temperature, diluted with 5% HCl (10 ml), and then stirred for a further 1 h at 40 °C. The reaction mixture was poured into ice water and extracted with ether (50 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (1 g). The fraction eluted with 50% AcOEt in hexane (v/v) gave **13** ($R_1=C_8H_{17}$) (82 mg, 64%) as a colorless oil. IR (neat): 1745, 1200, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, $J=7$ Hz, Me), 3.75 (3H, s, COOMe). *Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.92; H, 10.41.

In a similar manner, **12** ($R_1=Me$) was converted to **13** ($R_1=Me$) as a colorless oil. IR (neat): 1750, 1200, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, $J=7$ Hz, Me), 3.75 (3H, s, COOMe). *Anal.* Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.65; H, 7.69.

3,4-Dihydroxy-2,5-bis(methoxycarbonyl)-1-octyl-2,4-cyclopentadiene (15)——A mixture of the diester (**14**)[11] (54.4 g), dimethyl oxalate (23.6 g), and NaOMe (21.6 g) in ether (200 ml) was stirred for 0.5 h at room temperature, and then the reaction temperature was slowly raised to 105 °C over 3 h with removal of ether and formed methanol. The reaction mixture was diluted with 10% H_2SO_4 (100 ml) under ice-water cooling and extracted with $CHCl_3$ (100 ml × 3). The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was crystallized from EtOH. Recrystallization from EtOH gave **15** (21.5 g 33%) as colorless needles. mp 71 °C. IR (Nujol): 3350, 3300, 1675, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, $J=7$ Hz, Me), 3.82 (6H, s, COOMe × 2), 9.00 (2H, br, OH × 2). *Anal.* Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.72; H, 8.19.

3β-5α-Bis(methoxycarbonyl)-4α-octyl-2-oxo-cyclopentanone Ethylene Thioacetal (16) and 3β,5β-Bis(methoxycarbonyl)-4α-octyl-2-oxo-cyclopentanone Ethylene Thioacetal (17)——BF_3-etherate (25 ml) was added dropwise to a stirred solution of **15** (19.5 g) in a mixture of ethanedithiol (30 ml) and CH_2Cl_2 (10 ml) at room temperature. After 0.5 h, the reaction mixture was diluted with water (100 ml) and extracted with ether (100 ml × 3). The combined extracts were washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (200 g). The fraction eluted with 1—15% ether in benzene (v/v) was collected, and the solvent was evaporated off *in vacuo* to leave a mixture (26.5 g) of **16** and **17**. The mixture was dissolved in methanol (30 ml) and allowed to stand for 2 d at 0 °C. The crystalline precipitate **17** (4.4 g, 18%) was filtered off as colorless needles (mp 111 °C), and the filtrate was concentrated *in vacuo* to yield **16** (19.2 g, 80%) as a colorless oil. **16**; IR (neat): 1745, 1730, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, $J=7$ Hz, Me), 3.25—3.55 (7H, m, SCH_2CH_2S+3H on the five-membered ring), 3.75 (3H, s, COOMe), 3.80 (3H, s, COOMe). *Anal.* Calcd for $C_{19}H_{30}O_5S_2$: C, 56.70; H, 7.51. Found: C, 56.87; H, 7.69. **17**; IR (Nujol): 1745, 1730, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=7$ Hz, Me), 3.10 (3H, m, H on the five-membered ring), 3.30—3.50 (4H, m, SCH_2CH_2S), 3.70 (6H, s, COOMe × 2). *Anal.* Calcd for $C_{19}H_{30}O_5S_2$: C, 56.70; H, 7.51. Found: C, 56.82; H, 7.63.

2β,4β-Bis(methoxycarbonyl)-3α-octylcyclopentanone (18) and 9b Methyl Ester——Reney Ni (5 g) was added to a stirred solution of **17** (3.50 g) in methanol (30 ml) at room temperature, and the mixture was heated under reflux for 5 h. The Raney Ni was filtered off, and the filtrate was concentrated *in vacuo* to yield an oily residue, which was chromatographed on silica gel (40 g). The fraction eluted with 1—3% ether in benzene (v/v) was collected, and the solvent was removed *in vacuo*. The crystalline residue was recrystallized from hexane to yield **18** (2.12 g, 78%) as colorless needles, mp 39 °C. IR (Nujol): 1765, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (6H, s, COOMe × 2), 2.60—3.10 (5H, m) (see Fig. 1). *Anal.* Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.44; H, 9.09.

In a similar manner, **16** (15.3 g) afforded **9b** methyl ester (7.62 g, 88%) as colorless needles, mp 37 °C, recrystallized from hexane.

13 ($R_1=C_8H_{17}$) from 18——In a manner similar to that described for the preparation of **11b** from the **9b** methyl ester, **18** (245 mg) afforded **13** ($R_1=C_8H_{17}$) (175 mg, 88%).

References and Notes

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3) The β-keto esters (**1**) were prepared in a manner similar to the reported synthesis of diethyl β-ketopimelate ("Organic Syntheses" Coll. Vol. V, John Wiley & Sons, Inc., New York, 1973, p. 384). **1a**; oil. IR (neat): 1760,

1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s, Me), 3.48 (2H, s, CH_2). **1b**; oil. IR (neat): 1748, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (2H, s, CH_2), 5.12 (2H, s, CH_2). **1c**; oil. IR (neat): 1750, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, s, CH_2), 3.75 (3H, s, COOMe). **1d**; oil. IR (neat): 1740, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (2H, s, CH_2), 5.20 (2H, s, CH_2). **1e**; oil. IR (neat) 1740, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.43 (2H, s, CH_2), 5.17 (2H, s, CH_2). **1f**; commercially available. **1g**; oil. IR (neat): 1750, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (2H, s, CH_2), 3.72 (3H, s, COOMe). **1h**; oil. IR (neat): 1755, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (9H, s, Me × 3), 3.57 (2H, s, CH_2).

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6) Yields from a mixture of **2** and **3**.
7) The mechanism of decarboxylation is not clear.
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9) The 3,4-*trans* compounds ($R_1 = C_8H_{17}$ or Me) were observed as the less polar spot on TLC (AcOEt–hexane 1 : 1), while the corresponding *cis* compounds gave the more polar spot.
10) Unequivocal evidence for the 2,3-*trans* configuration was also obtained by the synthesis[2] of $PGF_{1\alpha}$ from **9d**.
11) The diester **14** was prepared by the Michael condensation of methyl 2-undecenoate and dimethyl malonate followed by decarboxylation with NaCl in DMSO.
12) The individual assignment of five protons on the five-membered ring ketone has not been achieved.
13) The IR and ^{1}H-NMR spectra of each compound (mixture of **2** and **3**) were not measured.
14) Although it was difficult to remove a trace of stannic chloride by column chromatography on silica gel, the reductive procedure with $NaBH_4$ facilitated the removal of stannic chloride.
15) In the reduction with $NaBH_4$ of the acidic compounds ($R_2 = H$ in **9**), $NaHCO_3$ was added to neutralize the solution.