Prostaglandins. III.[1] Synthesis of Methyl Esters of 15-Dehydro-PGB$_1$, 15-Dehydro-PGE 237, and DL-PGE 237

MASATERU MIYANO

Chemical Research Division, G. D. Searle & Co., Chicago, Illinois 60680

Received November 19, 1969

The stereochemistry of bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylic acid (**1**) was elucidated and the chloro ketone (**12**) was prepared. The methyl ester of 15-dehydro-PGB$_1$ (**23**) was synthesized in 10% overall yield from the chloro ketone (**12**) as described in Scheme I. Also presented are the unequivocal proof of structure **23** and evidence for the erroneous structural assignment to the free acid of **23** in the literature. Compound **23** was converted into the methyl esters of 15-dehydro-PGE 237 (**25**) and racemic PGE 237 (**26**).

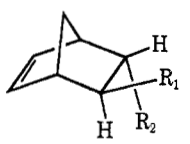
Methyl bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylate and the corresponding free acid have been described in the literature,[2] although the stereochemistry remained unknown. The free acid, prepared easily from the readily available 5-norbornene-2,3-*endo*-dicarboxylic anhydride, seemed to be a good starting material for the chloro ketone (**12**), the key intermediate for the synthesis of the prostaglandins.[3]

The objectives of this work were to elucidate the stereochemistry of these bicycloheptenes and to convert them into the properly functionalized prostanoic acid[3a] derivatives.

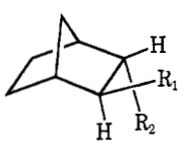
Fraser[4] described a method for determining the configuration of 2- and 3-substituted bicyclo[2.2.1]hept-5-enes. Upon hydrogenation of the double bond, the 2- or 3-*exo* hydrogen exhibited an upfield shift, whereas the *endo*-hydrogen resonance exhibited a downfield shift. This behavior was attributed to the magnetic anisotropy of the double bond. It is also known[4,5] that the 2- and 3-*endo* hydrogens of bicyclo[2.2.1]hept-5-enes are generally found 0.47–0.67 ppm upfield from the *exo*-proton resonances. To simplify our presentation we have used the correct configurations throughout the following discussion.

Bicyclo[2.2.1]hept-5-ene-3-*n*-hexanoyl-2-carboxylic acid (**1**) prepared by Walton's procedure,[2] was hydrogenated to **8** and subsequently both **1** and **8** were esterified to give **3** and **9**, respectively. The pmr data (summarized in Table I) indicated that **1** and **3** must have one *exo* and one *endo* hydrogen at C-2 and C-3; that is **1** and **3** must be the *trans* isomers. However, the pmr data presented in Table I fit equally well for the alternative *trans* configuration (**2** for the acid, **4** for the ester). To determine which *trans* structure is correct, the corresponding hydroxy acid (**5**), prepared by borohydride reduction of **1**, was esterified with diazomethane to give **6**. The pmr spectra (see Table I) of **6** and the hydrogenation product (**10**) were compatible only with **6** and **10**, but not with the alternative *trans* structures.

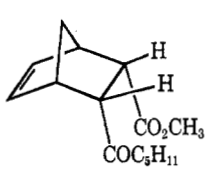
The methyl ester **7**, from which **1** was prepared[2] by saponification, was different from the methyl ester **3** prepared from **1** with diazomethane. Taking into account the method of preparation, **7** must be the *cis*,-



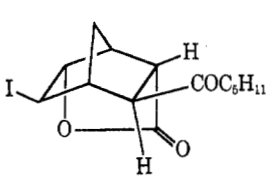
1, $R_1 = COC_5H_{11}$; $R_2 = CO_2H$
2, $R_1 = CO_2H$; $R_2 = COC_5H_{11}$
3, $R_1 = COC_5H_{11}$; $R_2 = CO_2CH_3$
4, $R_1 = CO_2CH_3$; $R_2 = COC_5H_{11}$
5, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2H$
6, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2CH_3$



8, $R_1 = COC_5H_{11}$; $R_2 = CO_2H$
9, $R_1 = COC_5H_{11}$; $R_2 = CO_2CH_3$
10, $R_1 = CHOHC_5H_{11}$; $R_2 = CO_2CH_3$



7



11

TABLE I
NMR SIGNALS[a] OF C-2 AND C-3 HYDROGENS

	2-*exo* H chemical shift[b] (multiplicity, *J* in Hz)	3-*endo* H chemical shift[b] (multiplicity, *J* in Hz)
1	6.62 (t, 4.5)	7.22 (d, 4.5)
↓ H_2		
8	6.62 (t, 4.5)	7.15[c] (d, 5.5)
3	6.62 (t, 4.5)	7.22 (d, 4.5)
↓ H_2		
9	6.72[d] (t, 4.5)	7.12[c] (d, 5)
6	7.46 (t, 4)	In envelope region
↓ H_2		
10	7.60[d] (t, 4)	In envelope region

[a] Reference 16a. [b] Given in τ. [c] A typical downfield shift for *endo* H. [d] A typical upfield shift for *exo* H.

(1) For a preliminary communication of some of these results, see M. Miyano, *Tetrahedron Lett.*, 2771 (1969).

(2) H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(3) (a) P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. F. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, **9** (2), 231 (1968); (b) S. Bergström, *Science*, **157**, 382 (1967); (c) S. Bergström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); (d) S. Bergström and B. Samuelsson, Editors, Nobel Symposium, 2, Prostaglandins, Almqvist and Wiksell, Stockholm, and Interscience Publishers, Inc., New York, N. Y., 1967; (e) U. S. von Euler and E. Eliasson, "Medicinal Chemistry Monographs," Vol. 8, Academic Press Inc., New York, N. Y., 1967; (f) V. R. Pickles, *Nature*, **224**, 221 (1969).

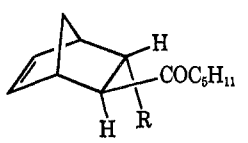
(4) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(5) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).

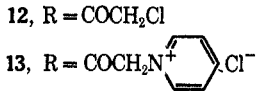
endo isomer. It was not possible to confirm the expected upfield shifting of the *exo* hydrogen of **7** upon hydrogenation of the double bond, because isomerization to a *trans* isomer took place during the hydrogenation (see Experimental Section).

Chemical evidence supported the pmr data; that is the keto acid **1** was converted into the iodo lactone **11** by the well-known iodolactonization procedure.[6]

It was reported[2] that the pyrolysis of **7** (without regard to stereochemistry) gave methyl 4-oxo-2-nonenoate (**18**, without statement of the geometry), mp 48.5°, in about 75% yield. A reverse Diels–Alder

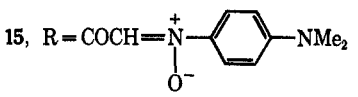


12, R = $COCH_2Cl$

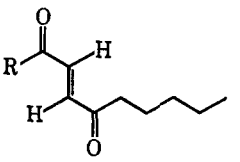


13, R = $COCH_2N^+$ Cl^-

14, R = $COCH_2OAc$



15, R = $COCH{=}N^+(O^-)$–NMe_2



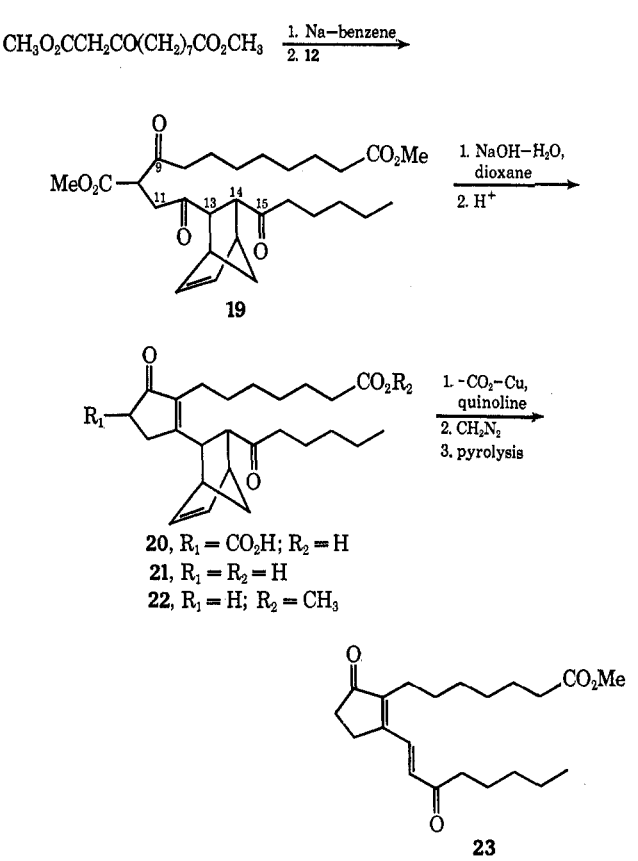
16, R = CH_2Cl
17, R = CH_2OAc
18, R = OCH_3

mechanism suggests that the nonenoate is probably *cis* if the starting material is *endo,cis*. Repetition of Walton's procedure[2] gave only one crystalline product, mp 49°, in only 19.7% yield. The pmr spectrum (typical AB-type olefinic protons, J = 16 Hz) demonstrated, however, that this was the *trans* olefin. The noncrystalline portion was found to be the *cis* olefin (major component, J = 12 Hz) contaminated by the *trans* olefin, suggesting that the *cis* alkene, the primary pyrolysis product, was partially isomerized to the more stable geometric isomer.

Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic acid (**1**) was converted into the chloro ketone (**12**) by successive treatment with oxalyl chloride, excess diazomethane, and finally with hydrogen chloride. The chloro ketone (**12**) was a poorly characterized, low melting compound slightly contaminated by **16** (see Experimental Section). However, crude **12** gave good yields of pyridinium chloride (**13**, further characterized as the crystalline nitrone **15**) and the acetoxy ketone (**14**). The latter was pyrolyzed to the *trans*-enedione (**17**) *via* a reverse Diels–Alder mechanism.

The chloro ketone (**12**) was condensed with the sodium derivative of dimethyl 3-oxoundecane-1,11-dioate[7] to afford the triketo diester (**19**) which was cyclized to the diketo diacid (**20**) (Scheme I). It must be emphasized that the cyclopentenyl-protecting group possesses many unique advantages. The bicyclo system makes only one mode of condensation (**19** → **20**) possible, although **19** contains three ketonic groups and several active methylenes or methines in the same molecule. More specifically, the rigid system in **19** holds the C-13-*endo* and C-14-*exo* substituents far enough apart to eliminate certain undesirable condensations (for example, between C-11 and C-15). The bicyclo

SCHEME I



system makes the C-13 and C-14 carbons tertiary ones, thus preventing undesirable condensations, for example, between C-9 and C-14 (no dehydration can take place). The keto acid **20** was decarboxylated smoothly in quinoline to **21**, which was then esterified with diazomethane to **22**, and the ester was finally pyrolyzed to afford methyl 9,15-dioxoprosta-8(12),13-*trans*-dienoate (**23**, 15-dehydro-PGB_1 methyl ester) in 10–15% overall yield from crude **12**. The geometry of the 13,14 double bond in **23** can be predicted to be *trans* provided that the C-13 and C-14 substituents in **22** are *trans*. The structure of **23** was well supported by the spectral data. The expected uv maximum[8] was 202 (five-membered enone) + 30 (γ,δ double bond) + 10 (α substituent) + 12 (β substituent) + 18 (δ substituent) + x. Since the increment (x) of the fully transoid ketone[9] is about 26, the expected value for **23** should be about 298 mμ. The actual uv (methanol) of 296 mμ (ϵ 22,800) was in good agreement with the calculated value. In addition, the two olefinic protons formed a typical AB pattern (J = 15.5 Hz, suggesting *trans*) and **23** was further characterized as the crystalline dioxime (**24**).

The free acid of structure **23** was incorrectly assigned to another compound by Änggård and Samuelsson.[10] The Swedish workers treated **27** [uv in ethanol 230 mμ (ϵ 8450)] with 0.5 N sodium hydroxide in 50% ethanol and observed the shift of the uv absorption to a longer wavelength (280 mμ, no extinction coefficient or any

(6) E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, **76**, 2315 (1954).

(7) K. E. Arosenius, G. Ställberg, E. Stenhagen and B. Tägtström-Eketorp, *Ark. Kemi, Mineral., Geol.*, **26A**, No. 19, 20 (1948).

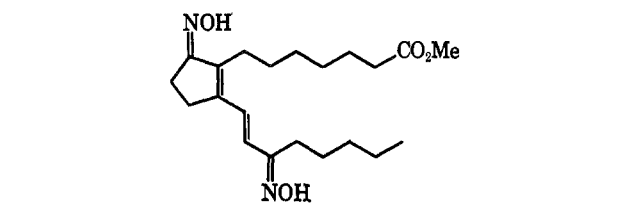
(8) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," a Pergamon Press Book, The Macmillan Co., New York, N. Y., 1964, pp 58, 61, and 69.

(9) Taking into account the dipole repulsion between C-9 and C-15 carbonyl groups, the full transoid conformation (**23**) is a good one.

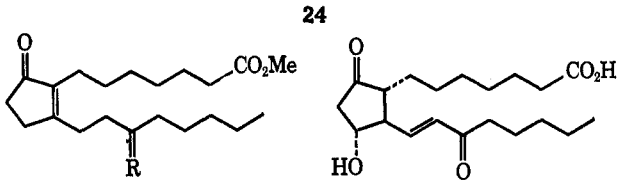
(10) (a) E. Änggård and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964); (b) B. Samuelsson, *Angew. Chem.*, **77**, 445 (1965).

other physical data were given). They stated that the shift was probably due to the formation of **23** (the free acid instead of methyl ester). However, the uv maximum is different from **23** (uv in methanol 296 mμ) and it seems unlikely to ascribe the shift of 16 mμ to the difference of the free carboxylic acid and its ester, because the carboxyl function is far removed from the chromophore. Saponification of **23** with methanolic alkali at room temperature resulted in total destruction of the chromophore demonstrating that **23** is very unstable to alkali while Samuelsson's compound was supposedly formed by an alkaline treatment. More careful saponification of **23** with 0.1 *N* methanolic sodium hydroxide at room temperature indicated that the disappearance of the chromophore was about 3 to 10 times as fast as saponification of the ester group. The half-life of the chromophore in 0.1 *M* potassium carbonate solution in 50% aqueous dioxane at 25° was 8 hr. We next tried pyrolysis of **21** in an attempt to prepare the free acid directly. The pyrolysis product, which was not purified completely, showed a uv maximum at 296–297 mμ (not at 280 mμ), and could be converted to **23** by treatment with diazomethane.

Additional chemical and spectral evidence supporting structure **23** are presented below. The formation of **25** by zinc reduction is excellent evidence that the two



24



25, R = O
26, R = H, OH

27

double bonds in **23** are located between two carbonyl groups.[11] The structure **25** was substantiated by the spectral evidence. The uv (methanol) of 238 mμ (ε 13,400) was in agreement with the calculated value (236 mμ)[8] and the extinction coefficient was also in accordance with the known examples.[12] The pmr spectrum showed no olefinic proton, but a "sharp" singlet at τ 7.32 representing the four protons of C-13 and C-14 which happen to exhibit equal chemical shifts. Catalytic hydrogenation of **23**, on the other hand, gave rise to two products **25** and **26** in almost equal amount. The spectral data of the more polar substance (**26**) were in good agreement with authentic[13] optically active PGE 237 as summarized in Table II.

An additional proof of structure **23** was obtained later by comparison of the spectral data with **28** and **29** (prepared by another totally independent synthesis[14]) as summarized in Table III.

(11) See among others (a) P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **32**, 1934 (1949); (b) D. H. R. Barton, *J. Chem. Soc.*, 3830 (1963).

(12) B. Samuelsson and G. Ställberg, *Acta Chem. Scand.*, **17**, 810 (1963).

(13) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *J. Biol. Chem.*, **238**, 3555 (1963).

(14) To be published elsewhere.

TABLE II

UV AND IR SPECTRA OF AUTHENTIC AND SYNTHETIC **26**

PGE 237[a]	PGE 237 methyl ester[a]	Synthetic **26**
237 mμ (ε 14,200)[b]	5.75 μ	237.5 mμ (ε 15,600)[c]
	5.90 μ	5.76 μ (ester)
	6.11 μ	5.90 μ (ketone)
		6.105 μ (olefin)

[a] Reference 13. [b] In ethanol. [c] In methanol.

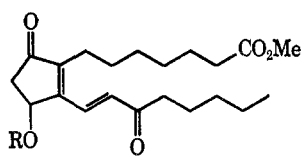
TABLE III

UV (IN METHANOL) AND NMR SPECTRA[a] OF **23**, **28** AND **29**

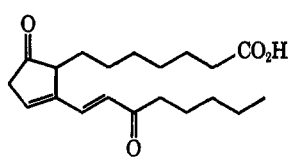
	Uv, mμ (ε)	C-11 H	C-13 H	C-14	$J_{13,14}$, Hz
23	296 (22,800)	None	2.22[b]	3.32[c]	15.5
		downfield	2.48	3.58	
28	291.5[d] (24,600)	4.84[f]	2.30[b]	2.92[c]	16.0
			2.56	3.19	
29	288[g] (27,200)	3.94[f]	2.35[b]	3.35[c]	16.0
			2.62	3.62	

[a] Reference 16a. [b] A little broadened doublet owing to coupling either with the C-11 or more likely with the C-7 H. [c] Doublet. [d] A hypsochromic shift of about 4–5 mμ by the 11-OH is expected.[e] [e] For example, uv values (methanol) for **31** and **32** are 231.5 mμ (ε 12,000) and 229.5 mμ (ε 13,900), respectively, while the calculated value[8] for **33** is 236 mμ. For the preparation of **31** and **32** see Experimental Section. [f] A doublet of multiplets. [g] A hypsochromic shift of about 6–7 mμ by the 11-OAc is expected.[e]

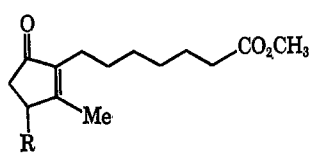
After this work had been completed, the methyl ester of **30** was synthesized by another group of investigators[15] and the identity of **30** with Samuelsson's compound was suggested.



28, R = H
29, R = Ac



30



31, R = OH
32, R = OAc
33, R = H

Experimental Section[16]

Methyl Bicyclo[2.2.1]hept-5-ene-3-*endo*-*n*-hexanoyl-2-*endo*-carboxylate (7).—This material was prepared by a known procedure[2] and the stereochemistry was determined by the pmr spectral evidence as well as the chemical transformations (see text).

Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic Acid (1).—This material was prepared by Walton's procedure[2] and recrystallized from hexane and the stereochemistry was elucidated by means of the pmr spectrum and the chemical evi-

(15) R. B. Morin, D. O. Spry, K. L. Hauser, and R. A. Mueller, *Tetrahedron Lett.*, 6023 (1968).

(16) (a) All pmr spectra were determined in deuteriochloroform on Varian A-60 using tetramethylsilane as an internal reference. (b) Melting points given in the Experimental Section represent the highest value obtained after successive recrystallizations unless otherwise stated and were obtained on Thomas–Hoover apparatus (uncorrected).

dence (see text): mp 90.5–92° (lit.[2] 85°); nmr ($CDCl_3$) τ 6.54 (t, J = 4.5 Hz, C-2-*exo* H), 7.22 (d, J = 4–4.5 Hz, C-3-*endo* H), 6.72 and 6.98 (bridgeheads).

Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylic Acid (8).—The unsaturated acid **1** was hydrogenated in the presence of palladium on carbon in ethanol. The distilled product, bp 148° (0.08 mm), crystallized spontaneously: mp 53.5–55°; nmr ($CDCl_3$) τ 6.62 (t, J = 5 Hz, C-2-*exo* H), 7.15 (d, J = 5.5 Hz, C-3-*endo* H). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.30; H, 9.33.

Methyl Bicyclo[2.2.1]hept-5-ene-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylate (3).—The free acid **1** was esterified with diazomethane in the usual manner (94.5%): bp 108° (0.3 mm); nmr ($CDCl_3$) τ 6.62 (t, J = 4.5 Hz, C-2-*exo* H), 7.22 (d, J = 4.5 Hz, C-3-*endo* H), 6.75 and 7.02 (s, bridgeheads). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.68; H, 8.76.

Methyl Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-2-*endo*-carboxylate (9).—The free acid **8** was esterified with diazomethane in the usual manner: bp 110° (0.3 mm); nmr ($CDCl_3$) τ 6.72 (t, J = 4.5 Hz, C-2-*exo* H), 7.12 (d, J = 5 Hz, C-3-*endo* H). *Anal.* Calcd or $C_{15}H_{24}O_3$: C, 71.39; H, 9.95. Found: C, 71.48; H, 9.33.

Attempted Synthesis of Methyl Bicyclo[2.2.1]heptane-3-*endo*-*n*-hexanoyl-2-*endo*-carboxylate.—The unsaturated ester **7** was hydrogenated in ethanol in the presence of 5% palladium on carbon (4 hr at room temperature). The product, bp 124° (0.4 mm), was found to have partially isomerized during the hydrogenation to 3-*exo*-*n*-hexanoyl compound **9**. Judging from the height of the methoxy signals (3-*exo* at τ 6.31, 3-*endo* at 6.37), the *exo*/*endo* ratio was about 3/4.

Bicyclo[2.2.1]hept-5-ene-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylic Acid (5).—The keto acid **1** was suspended in 150 ml of 33% methanol and neutralized with sodium hydroxide. To the clear solution was added 3 g of sodium borohydride, and the mixture was kept in a refrigerator overnight and then at room temperature for 6 hr, acidified with hydrochloric acid, filled with water to 400 ml, and again refrigerated overnight. The crystals were collected, dried, and recrystallized first from benzene and then from ethyl acetate, mp 164–165°. *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.60; H, 9.24.

Methyl Bicyclo[2.2.1]hept-5-ene-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylate (6).—The free acid **5**, dissolved in a minimum amount of ethyl acetate, was esterified with ethereal diazomethane and distilled: bp 131° (0.3 mm); nmr ($CDCl_3$) τ 7.46 (t, J = 4 Hz, C-2-*exo* H), 6.86 and 6.99 (2, bridgeheads), 6.57 (C-1′ H). *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.53.

Methyl Bicyclo[2.2.1]heptane-3-*exo*-(1-hydroxy-*n*-hexyl)-2-*endo*-carboxylate (10).—The unsaturated hydroxy ester **6** was hydrogenated in ethanol in the presence of 5% palladium on charcoal and the product was recrystallized from cyclohexane–pentane: mp 62–63°; nmr ($CDCl_3$) τ 7.60 (t, J = 4 Hz, C-2-*exo* H overlapped with others), 6.70 (C-1′ H). *Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.08; H, 10.22.

Bicyclo[2.2.1]heptane-3-*exo*-*n*-hexanoyl-5-*exo*-iodo-6-*endo*-hydroxy-2-*endo*-carboxylic Acid Lactone (11).—To a solution of 23.6 g (0.1 mol) of **1** in 200 ml (0.2 mol) of 10% potassium bicarbonate solution was added dropwise under ice cooling potassium iodide–iodine solution, which had been prepared from 63.5 g (0.4 g-atom) of iodine, 166 g (1.0 mol) of potassium iodide, and 500 ml of water. Soon the oily iodo lactone started to separate. About 100 ml of ether was added to the reaction mixture. After 180 ml of the iodine solution had been consumed, decoloration of the iodine on addition of the reagent slowed remarkably. More ether was added and the organic layer was washed successively with water, with thiosulfate solution, and again with water, dried over sodium sulfate, concentrated, and dried at 60° (0.1 mm): 35.6 g (0.98 mol, 98%); ir ($CHCl_3$) 5.58 (lactone), 5.81 μ (ketone); nmr ($CDCl_3$) τ 4.86 (d, of m, J = 4.5 and 1.0 Hz, C-6-*exo* H), 6.05 (d, J = 2.5 Hz, C-5-*endo* H). *Anal.* Calcd for $C_{14}H_{19}IO_3$: C, 46.42; H, 5.29; I, 35.04. Found: C, 46.66; H, 5.35; I, 35.29.

Methyl 4-Oxo-2-nonenoate (18).—Compound **18** was prepared by Walton's procedure:[2] mp 49° (lit.[2] 48.5°); yield 19.7%; nmr ($CDCl_3$) τ 2.88 (d, 1, J = 16 Hz), 3.37 (d, 1, J = 16 Hz). The noncrystalline portion of the pyrolysis product was a mixture of two compounds. One (about 45% deduced from the methoxy signal at τ 6.18) was the *trans*-nonenoate (**18**) and the other (about 55%, the methoxy at 6.25) was the *cis*-nonenoate as shown by the AB-type olefinic protons at τ 3.49 (d, J = 12 Hz) and 4.00 (d, J = 12 Hz).

2-*endo*-Chloroacetyl-3-*exo*-*n*-hexanoylbicyclo[2.2.1]hept-5-ene (12).—To a solution of 27 g (0.114 mol) of **1** in 100 ml of benzene was added 30 g (0.236 mol) of oxalyl chloride. The mixture was refluxed for 10 min, concentrated, dissolved in benzene, and added gradually to 1 l. of cold ethereal diazomethane, prepared from 28 g (0.30 mol) of nitrosomethylurea and dried over potassium hydroxide. After 2 hr, the reaction mixture was treated with dry hydrogen chloride gas, set aside for 1.5 hr, and then washed twice with water, with bicarbonate solution, and with water, dried over sodium sulfate, and distilled giving 22.8 g of crude **12**: bp 146–147° (0.2 mm); ir ($CHCl_3$) 5.76 ($COCH_2Cl$), 5.83 (ketone); nmr ($CDCl_3$) τ 5.84 (s, 2, $COCH_2Cl$), 6.29 (t, J = 4 Hz, C-2-*exo* H), 2.91 (s, impurity **16**), 5.72 (s, impurity **16**). *Anal.* Calcd for $C_{15}H_{21}O_2Cl$: C, 67.03; H, 7.82; Cl, 13.19. Found: C, 65.89; H, 7.73; Cl, 10.77.

Pyridinium Chloride (13).—The chloro ketone **12** prepared from 40 g (0.169 mol) of acid was dissolved in 100 ml of anhydrous pyridine. After 48 hr, the crystals were collected, washed with dioxane, and recrystallized from ethanol–dioxane giving 35.3 g (0.101 mol, 60%) of **13**: mp 186°; nmr ($CDCl_3$) τ 6.11 (t, J = 4 Hz, C-2 *exo* H), 6.95 (C-3-*endo* H overlapped with a bridgehead), 6.35 (another bridgehead), 3.19 (s, $NCH_2C{=}O$). *Anal.* Calcd for $C_{20}H_{26}O_2NCl$: C, 69.05; H, 7.53; N, 4.03; Cl, 10.19. Found: C, 68.99; H, 7.60; N, 3.79; Cl, 10.33.

Nitrone 15.—To a solution of 24.6 g (70.8 mmol) of **13** in 50 ml of ethanol was added a solution of 10.6 g (70.7 mmol) of *p*-dimethylaminonitrosobenzene in 200 ml of ethanol. The stirred mixture was cooled in an ice bath and treated with 70 ml of 1 *N* sodium hydroxide solution. The greenish solution turned to deep red brown and crystals soon separated. The flask was stored in a refrigerator overnight. The crystals were collected, washed with cold aqueous ethanol, dried (15 g), and dissolved in acetone. Sodium chloride was removed by filtration and the filtrate was concentrated. Crystallization was accomplished by addition of aqueous ethanol: mp 125°; nmr ($CDCl_3$) τ 0.47 (s, N=CHCO), 7.10 (s, NMe). *Anal.* Calcd for $C_{28}H_{30}O_3N_2$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.29; H, 8.06; N, 7.49.

2-*endo*-Acetoxyacetyl-3-*exo*-*n*-hexanoylbicyclo[2.2.1]hept-5-ene (14).—A solution of 24.8 g (92 mmol) of **12** and 32 g (326 mmol) of potassium acetate in 240 ml of ethanol was refluxed for 1.5 hr, concentrated, diluted with water, and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, concentrated, and distilled, giving 18.1 g (62 mmol, 67.3%) of oil: bp 158° (0.35 mm); nmr ($CDCl_3$) τ 3.75 (m, 1, olefinic), 4.00 (t, of d, 1, olefinic), 5.28 (broad s, 2, $AcOCH_2CO$), 6.68 and 7.0 (bridgeheads), 7.85 (s, 3, acetoxy); ir ($CHCl_3$) 5.70 ($-CO-CH_2OAc$), 5.76 (OAc), 5.83 μ (hexanoyl). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.78; H, 8.28.

1-Acetoxy-2,5-dioxo-3-*trans*-decene (17).—Pyrolysis of **14** (12.0 g, 41.3 mmol) at a bath temperature of 230–240° under reduced pressure (12 mm) gave 7.0 g of distillate which was recrystallized from hexane giving 2.9 g (12.8 mmol, 31%) of pure substance: mp 79.5°; ir ($CHCl_3$) 5.69, 5.87–5.90 μ; uv (in methanol) 229.5 mμ (ϵ 12,600); nmr ($CDCl_3$) τ 3.04 (s, 2, olefinic), 5.11 (s, 2, $AcOCH_2CO$), 7.82 (s, 3, acetoxy), 7.35 (t, 2, J = 7 Hz, $BuCH_2CO$).

Methyl 9,15-Dioxoprosta-8(12),13-dienoate (23).—To 8 g (0.348 g-atom) of sodium sand in 400 ml of benzene was added 93 g (0.36 mol) of dimethyl 3-oxoundecane-1,11-dioate[7] in several portions. To the clear solution of the soldio derivative was added 48.7 g (0.181 mol) of the chloro ketone (**12**, about 75% pure) dissolved in 50 ml of benzene. The mixture was stirred at room temperature for 0.5 hr and refluxed for 3.5 hr. After cooling, the reaction mixture was treated with iced hydrochloric acid, washed with dilute sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was dissolved in 3.8 l. of 50% aqueous dioxane containing 127 g of sodium hydroxide, stirred under nitrogen for 2 hr, set aside overnight, stirred at 65° for 3 hr, cooled, poured onto ice and 350 ml of concentrated hydrochloric acid, and extracted with ether and the ether extract was washed twice with sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was dissolved in 500 ml of quinoline containing 0.8 g of copper powder, heated to 120–126° for 5 hr under nitrogen stream, cooled, poured into iced hydrochloric acid, and extracted with ether. The extract was washed with sodium chloride solution and esterified in the usual manner with excess diazomethane prepared from 100 g

of nitrosomethylurea. The solvent was removed *in vacuo* (15 mm) at 100° and the residue (126.4 g) was further concentrated at 200° (0.5–1.0 mm[17]). About 45 g of mobile liquid, bp 130° (0.5–1.0 mm), was distilled with decomposition (strong odor of cyclopentadiene). The residue (78.0 g) was pyrolyzed in eight portions as mentioned below. About one-fourth (22.8 g) of the total residue was further concentrated in a short-pass flask to remove 1.161 g of mobile liquid, bp 160° (0.05 mm), no uv maximum at ~296 mμ. The residue was divided into two equal portions, each one thus corresponding to about one-eighth of the total product. This material was transferred to a short-pass (3 cm) still equipped with a magnetic stirrer and distilled slowly with concomitant liberation of cyclopentadiene. The first batch gave 3.622 g of pale yellow distillate, bp 155–172° (0.03 mm), uv (in methanol) 296 mμ (ε 8050), purity about 35%, followed by 0.614 g of amber oil, bp 172–185° (0.04 mm), uv (in methanol) 296 mμ (ε 2900), purity about 13%), during 8 hr. The second batch gave 4.083 g of pale yellow oil, bp 160–175° (0.04 mm), uv (in methanol) 296.5 mμ (ε 7600), purity about 33%, followed by 0.953 g of brown distillate, bp 175–185° (0.04 mm), uv (in methanol) 295 mμ (ε 3000), purity about 13%. The pyrolysis product of the two batches amounted to 10.4 g which corresponded to 2.85 g of the pure material (15.4% of the calculated amount based upon the chloro ketone[18]). The whole pyrolysis product, amounting to 33.5 g, was purified by dry column chromatography using silica gel containing 8% water as adsorbent and benzene containing ethyl acetate (5:1, v/v) as a solvent. The desired material was recovered by elution with ethyl acetate containing methanol as a pale yellow oil (6.4 g, 18.4 mmol, or 10.1% of the calculated amount based upon **12**): uv (in methanol) 296 mμ (ε 22,800); nmr (see Table II). *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.20; H, 9.22.

Beside the pure material mentioned above, an additional 1.8 g of slightly impure product was recovered from the dry column chromatogram.

Methyl 9,15-Dioximinoprosta-8(12),13-*trans*-dienoate (24).—The hydroxylamine solution used in this experiment was prepared as follows: a solution of 16.4 g of sodium acetate and 6.95 g of hydroxylamine hydrochloride were diluted with 40 ml of methanol, set aside, and decanted from the precipitate (NaCl). A solution of 271 mg of **23**, 5 ml of the hydroxylamine solution, and 3 ml of ethanol was heated on a steam bath for 1 hr. Most of the solvent was removed and the residue was taken up in ether. The ethereal extract was washed with bicarbonate, dried over sodium sulfate, concentrated, and refrigerated overnight. The crystals were triturated with benzene, filtered, washed with benzene, and recrystallized from benzene giving 140 mg of **24**: mp 120.5°; uv (in methanol) 308 mμ (ε 38,400), 317 (38,300); nmr (warm $CDCl_3$) 2.99 (d, 1, J = 16 Hz), 3.63 (d, 1, J = 16 Hz), 6.34 (s, 3), 7.28 (broad s, 4, C-9 and C-10 protons). *Anal.* Calcd for $C_{21}H_{34}O_4N_2$: C, 66.63; H, 9.05; N, 7.40. Found: C, 66.60; H, 9.04; N, 7.39.

Methyl 9,15-Dioxoprost-8(12)-enoate (25).—A solution of 1.4 g of **23** in 50 ml of acetic acid was stirred with 2 g of zinc powder for 2 hr at room temperature. The reaction mixture was filtered to remove inorganic material, diluted with ether, washed twice with water, washed with bicarbonate solution, dried over potassium carbonate, concentrated, and purified by dry column chromatography on silica gel containing 8% water and 2% acetic acid as adsorbent and 20% ethyl acetate in benzene as solvent. The major fraction (894 mg, 59%, colorless oil) was **25**: ir ($CHCl_3$) 5.76–5.87 (carbonyls), 6.09 μ (C=C); uv (in methanol) 238 mμ (ε 13,400); nmr ($CDCl_3$) τ 7.32 (s, 4, C-13 and C-14 protons). *Anal.* Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.14; H, 9.66.

Methyl DL-15-Hydroxy-9-oxoprost-8(12)-enoate (26, PGE 237 Methyl Ester).—Compound **23** (417 mg) was hydrogenated in 50 ml of 95% ethanol in the presence of 0.1 g of 5% palladium on carbon and 32 ml of hydrogen was taken up in 15 min. The catalyst was removed and the filtrate was concentrated *in vacuo* giving 371 mg of residue which was separated into two components (**25** and **26**) by preparative tlc on silica gel using 25% ethyl acetate in benzene. The less polar product (75 mg) was **25** and the more polar product (83 mg) was identified as **26** based upon the spectral data: ir ($CHCl_3$); uv (in methanol), see Table I; nmr ($CDCl_3$) τ 6.32 (s, 3, OMe), 6.44 (m, 1, C-15 H). *Anal.* Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.40; H, 10.10.

Methyl 2-Methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoate (31).[19]—Dimethyl 3-oxoundecan-1,11-dioate[7] (76.4 g, 92% pure) was dissolved in 400 ml of cold 10% potassium hydroxide solution, refrigerated for 4 days, and neutralized to pH 8 with solid carbon dioxide. An aqueous solution (132 ml, pH was adjusted to 8 just before use) containing 0.296 mol of pyruvaldehyde was added and the mixture was set aside under nitrogen for 53 hr. The reaction mixture was washed with ether, acidified with hydrochloric acid, satuated with sodium chloride, and extracted with ether. The ethereal extract was washed twice with saturated salt solution, concentrated, dissolved in 560 ml of cold 5% sodium hydroxide solution, kept under nitrogen at room temperature for 4 hr, made acidic with 70 ml of concentrated hydrochloric acid, saturated with salt, and extracted with ether. The ethereal extract was washed with saturated salt solution, esterified with diazomethane in the usual manner, and distilled giving 35.9 g (52%) of the crude ester **31** (estimated to be 85–96% pure by gas chromatography), bp 180–205° (0.5 mm). The purification was carried out by redistillation, bp 175–185° (0.025 mm), or better by chromatography on silica gel using chloroform containing increasing amounts (up to 5%) of ethyl acetate: ir ($CHCl_3$) 2.71 (OH), 2.83 (broad, OH), 5.73 (ester), 5.82 (ketone), 6.02 (C=C); uv (in methanol) 231.5 mμ (ε 12,000); nmr ($CDCl_3$) τ 5.27 (broad d, J = 5.5 Hz, C-3 H), 6.33 (s, 3, OMe), 7.90 (s, CMe). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.26; H, 8.90.

2-Methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid.—The methyl ester (**31**, 2.5 g) was saponified with 0.5 g of sodium hydroxide in 50 ml of 90% methanol at room temperature overnight. The reaction mixture was diluted with water, washed with ether, made acidic with hydrochloric acid, and extracted with ether, and the ethereal extract was washed twice with salt solution, dried over sodium sulfate, and concentrated (1.2 g): ir ($CHCl_3$) 5.82 (broad, carboxyl and ketone), 6.05 μ (C=C); uv (in methanol) 231.5 mμ (ε 11,700); nmr ($CDCl_3$) τ 5.27 (broad d, 1, J = 5.5 Hz), 7.91 (s, CMe). *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.04; H, 8.33.

Methyl 2-Methyl-3-acetoxy-1-cyclopentene-5-one-1-heptanoate (31).—The hydroxy ester (**31**, 16.1 g) was dissolved in 14 g of acetic anhydride and 30 g of pyridine and set aside for 2 days. The reaction mixture was decomposed with ice and taken up with ether. The ethereal extract was washed successively with dilute hydrochloric acid, water, and potassium carbonate solution, dried over sodium sulfate, and distilled giving 8.1 g of **32**: bp 157–159° (0.04 mm); ir ($CHCl_3$) 5.76 (broad, carbonyls), 6.02 (C=C); uv (MeOH) 229.5 mμ (ε 13,900); nmr ($CDCl_3$) τ 4.31 (broad d, J = 6 Hz, C-3 H), 6.41 (s, 3, OMe), 7.89 (s, 3, acetoxy), 7.99 (s, 3, CMe). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.10. Found: C, 64.65; H, 8.10.

Registry No.—**3**, 24694-56-2; **5**, 24694-57-3; **6**, 24694-58-4; **8**, 24694-59-5; **9**, 24694-60-8; **10**, 24694-61-9; **11**, 24694-62-0; **12**, 24692-63-1; **13**, 24728-15-2; **14**, 24694-64-2; **15**, 24710-84-7; **17**, 24704-23-2; **23**, 24710-85-8; **24**, 24710-86-9; **25**, 24716-17-4; **26**, 20106-43-8; **28**, 24716-18-5; **29**, 24716-19-6; **31**, 24716-20-9; **32**, 24716-21-0; 2-methyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic acid, 24716-22-1.

Acknowledgment.—The author thanks Mr. C. R. Dorn for his helpful discussion and revision of English. Thanks are due to Dr. Frank B. Colton for many helpful discussions. The author thanks Mr. G. Plume, Mr. C. H. Yen, Mr. T. Bonnie, Mr. H. Erisman, and Mr. T. Belletire for preparation of the starting materials. Hydrogenation was carried out by Mr. M. G. Scaros of these laboratories.

(17) All boiling points shown in this paragraph are bath temperatures.

(18) Taking into account the purity (75%) of the chloro ketone, this yield (15.4%) can be evaluated as 20.5%.

(19) Similar condensations of pyruvic aldehyde and various β-keto acids are very well known: M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, **71**, 3165 (1949).