acid with 2,2,2-trifluoroethyl iodide.[5] The acid chloride was formed by stirring the acid overnight in excess thionyl chloride. Excess reagent was removed under vacuum and the residue distilled to give 90–100% of acid chloride **14a** as a pale yellow liquid, bp 46–48 °C (10 mm).

7-[[2-(2,2,2-Trifluoroethyl)sulfinyl]acetamido]cephalosporins (19, 22, 25). Triethylamine was added dropwise to a stirred suspension of 10 mmol of the appropriate 7-amino-3-cephem-4-carboxylic acid in 50 ml of dry DMF until solution was complete. The activated ester (10 mmol) was added in one portion and the resulting solution was stirred at room temperature for 1.5 h. The DMF was evaporated and the residue partitioned between 150 ml of EtOAc and 150 ml of H_2O. The pH was adjusted to 6.8 and the organic extract separated and discarded. The aqueous phase was layered with fresh EtOAc and adjusted to pH 2.0 with 3 N HCl. An emulsion usually formed which was broken by filtration through a pad of Celite. The filtrate layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined extracts were dried and evaporated to give the cephalosporin. If the cephalosporin was not solid, it was dissolved in CH_3OH and titrated to pH 7.0 with 5% $NaOCH_3$ in CH_3OH. Et_2O was added dropwise with rapid stirring to precipitate the sodium salt of the cephalosporin which was collected and dried under vacuum.

7-[[2-(2,2,2-Trifluoroethyl)sulfonyl]acetamido]cephalosporins (20, 23, 26). A solution of 10 mmol of the *tert*-butyl 7-amino-3-cephem-4-carboxylate, 10 mmol of 2-[(2,2,2-trifluoroethyl)sulfonyl]acetic acid, and 10 mmol of DCC in 150 ml of dry THF was stirred at room temperature overnight. The precipitated urea was removed by filtration and the filtrate evaporated to a gum. This was dissolved in a solution of 20 ml of TFA and 20 ml of *m*-dimethoxybenzene and stirred at room temperature for 2 h. It was added dropwise to 300 ml of rapidly stirred ether and the resulting precipitate collected, washed with ether, and dried. The cephalosporin was converted to its sodium salt by dissolving it in 20 ml of MeOH and adjusting the pH to 7.0 with 5% $NaOCH_3$ in CH_3OH. The product was precipitated by the dropwise addition of Et_2O.

Note Added in Proof. Several other laboratories have recently reported studies on some of the chemical and biological properties of compound 11.[9,10]

Acknowledgment. We wish to thank Mr. John Zarembo and his staff in the Analytical & Physical Chemistry Department of Smith Kline & French Laboratories for the elemental analyses. We are also grateful to Mr. William M. Bryan for the synthesis of compounds **18** and **23**.

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(4) 7-ACA *tert*-butyl ester was prepared according to R. J. Stedman, *J. Med. Chem.*, **9**, 444 (1966). The 3-heterocyclic thiomethyl-3-cephem-4-carboxylic acid esters were prepared by treating a suspension of the corresponding acid in CH_2Cl_2 with a threefold molar excess of O-*tert*-butyl diisopropylpseudourea: B. M. Bain and E. P. Tiley, Belgian Patent 755505 (1970).
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11,12-Secoprostaglandins. 1. Acylhydroxyalkanoic Acids and Related Compounds

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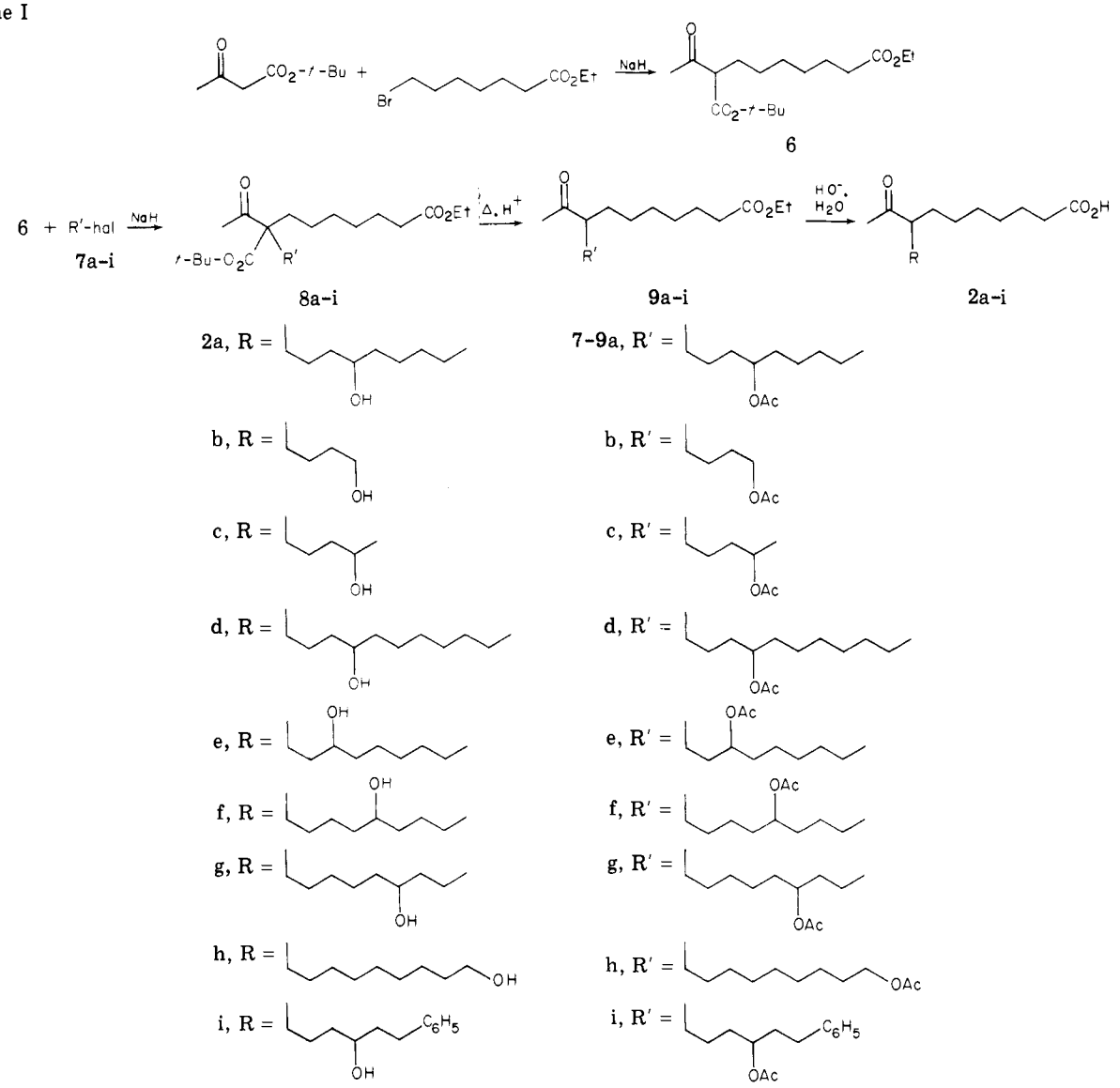
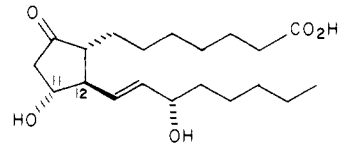
The synthesis is described of a series of acylhydroxyalkanoic acids which embody structural modifications of that class of secoprostaglandins which are formally derived from the natural substances by scission of the cyclopentane ring between carbon atoms 11 and 12. These analogues have been tested for their ability to stimulate cAMP formation in the mouse ovary, a characteristic action of the (*E*)-prostaglandins, and for their ability to bind to the rat lipocyte prostaglandin receptor. Certain members of the series that most closely resemble the prostaglandins in structure (e.g., 8-acetyl-12-hydroxyheptadecanoic acid) markedly stimulate cAMP formation at concentrations in the pharmacological range and show a significant affinity for the prostaglandin receptor. Conversely, these compounds are not substrates for prostaglandin 15-hydroxydehydrogenase which catalyzes a major reaction in the biological deactivation of the prostaglandins.

A practical objective of prostaglandin analogue research is the development of a group of compounds with adequate metabolic stability and differing tissue specificities so that the numerous biological actions of the prostaglandins[1] can, in effect, be separated and applied in the treatment of various diseases. Our work in this field has centered on compounds that may be termed 11,12-secoprostaglandins since they are formally derived from the prostaglandins by cleavage of the C-11 to C-12 bond of the cyclopentane ring. Ring opening of prostaglandin E_1 in this manner gives, for example, a branched chain alkanoic acid 8-(*R*)-(3-hydroxypropionyl)-12(*S*)-hydroxy-10-*trans*-heptadecenoic acid (**1**).

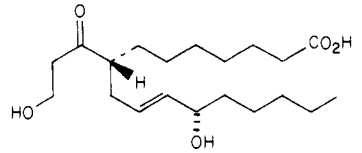
During studies on the synthesis of 11,12-secoprostaglandins such as **1**, it was discovered that the simpler analogue, 8-acetyl-12-hydroxyheptadecanoic acid (**2a**), possesses a number of the biological actions of the natural prostaglandins. The synthesis and biological examination

Scheme I



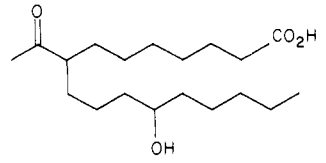


PGE_1



1

of acylhydroxyalkanoic acids related to **2a** are the subject of this first paper of a series on the 11,12-secoprostaglandins.[2]



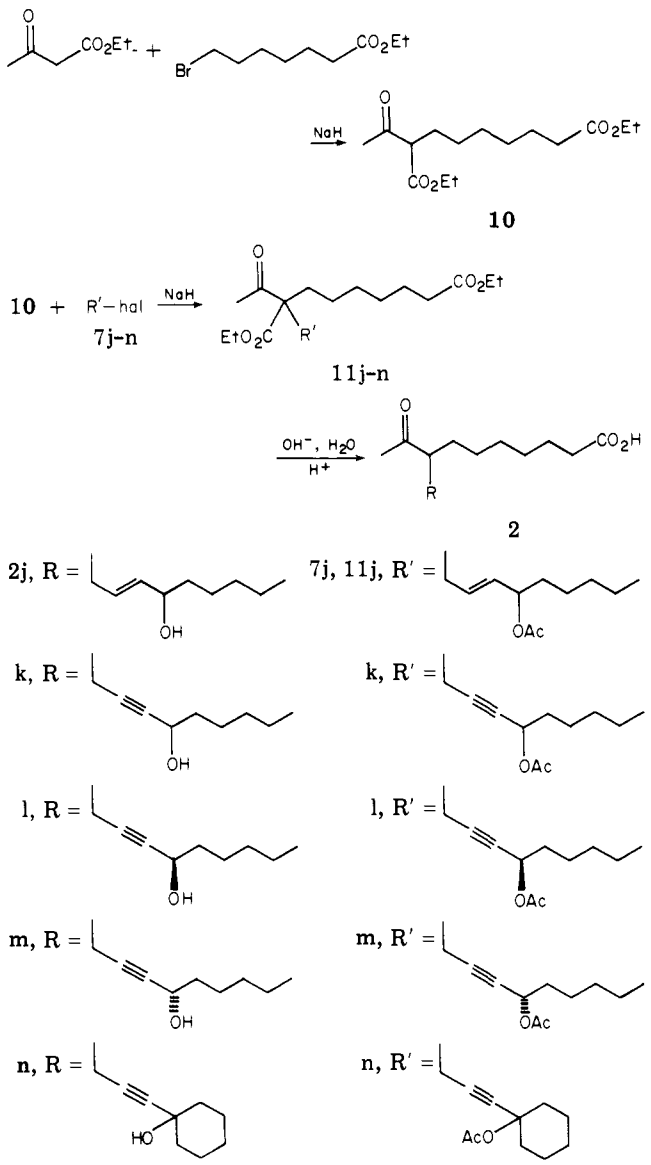
2a

Chemistry. Acylhydroxyalkanoic acids and derived compounds are listed in Table I. Compounds **2a–i** were prepared as shown in Scheme I. *tert*-Butyl acetoacetate was alkylated with ethyl 7-bromoheptanoate to give dicarboxylic ester **6**. This ester was alkylated with the array of acetoxy-substituted alkyl halides R'-hal (**7a–i**) and the resulting esters were heated with acid to effect elimination and decarboxylation and yield esters **9**. Saponification of **9** yielded products **2a–i**.

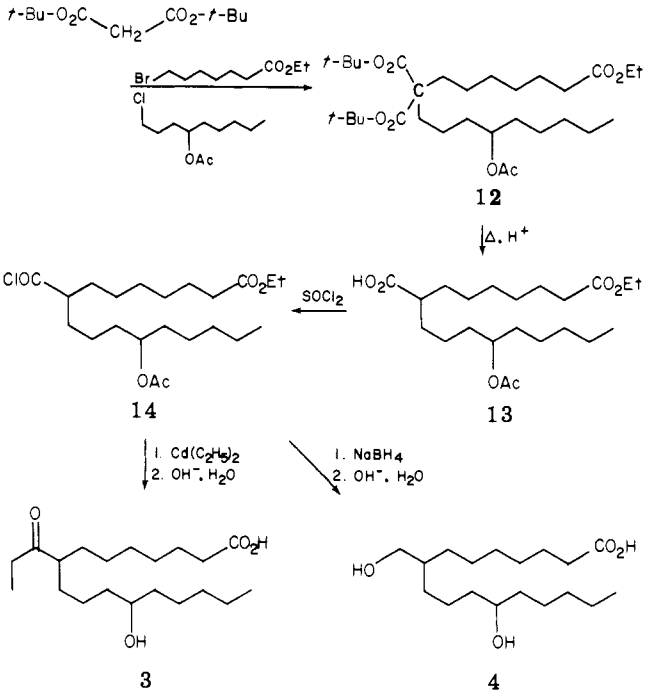
The slightly modified Scheme II was used for the preparation of acylhydroxy acids **2j–n** which contain allylic and proparglyic hydroxy groups and thus readily undergo acid-induced dehydration. In Scheme II, ethyl acetoacetate was alkylated sequentially with ethyl 7-bromoheptanoate and the unsaturated acetoxyalkyl halides **7j–n** to give dicarboxylic esters **11** which were saponified and decarboxylated to yield **2j–n**.

The preparation of 8-propionyl-12-hydroxyheptadecanoic acid (**3**) is outlined in Scheme III. Sequential alkylation of di-*tert*-butyl malonate with ethyl 7-bromoheptanoate and 1-chloro-4-acetoxynonane (**7a**) gave the tricarboxylic ester **12** which was heated with acid to effect elimination and decarboxylation and yield nonanedioic acid half-ester **13**. Reaction of **13** with thionyl chloride gave the acid chloride **14**. This compound reacted smoothly with diethylcadmium. The resulting acetoxy keto ester was saponified to yield **3**.

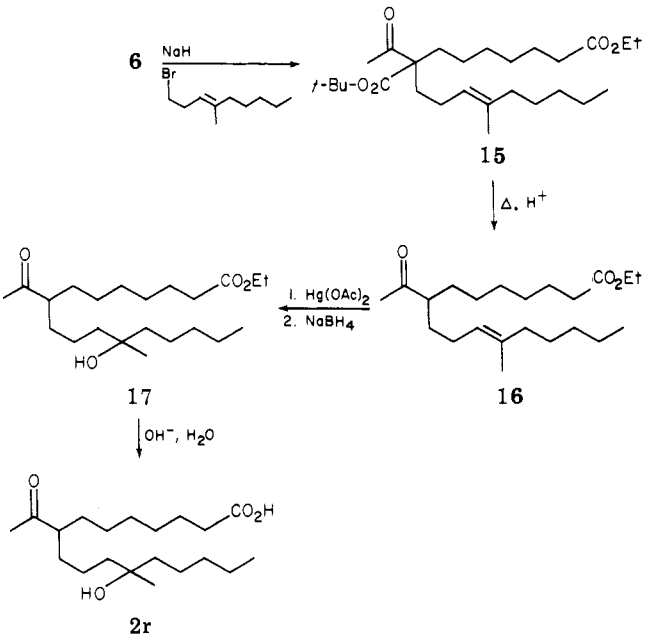
Scheme II



Scheme III



Scheme IV



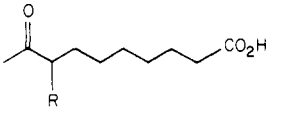
Futher compounds were prepared by reactions on these primary products. The acetylenic compounds **2l–n** were hydrogenated to yield saturated chain acids **2o–q**, respectively. Sodium borohydride reduction of **2a** gave the 8-(1-hydroxyethyl) derivative **5**; chromic acid oxidation of **2a** gave the 12-keto derivative **2s**. 8-Hydroxymethyl-12-hydroxyheptadecanoic acid (**4**) was obtained by $NaBH_4$ reduction of the acid chloride **14** (Scheme III).

The oxymercuration–demercuration reaction[3] sequence was used in the preparation of 8-acetyl-12-methyl-12-hydroxyheptadecanoic acid (**2r**) (Scheme IV). Addition of mercuric acetate to the double bond of the olefinic keto ester **16** followed by demercuration with $NaBH_4$ gave the tertiary alcohol **17** which was saponified to yield **2r**.

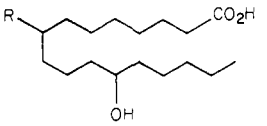
The final products and intermediate esters **8**, **9**, **11**, **12**, **16**, and **17** are viscous oils that cannot be purified by distillation. The products and esters **9** and **17** were purified by column chromatography on silica gel. These substances retain solvents tenaciously and samples suitable for analysis and biological testing can be obtained only by being heated in high vacuum for long periods. For this reason, analytical data have been obtained, with few exceptions, only on the final product acids. The structures of the enumerated intermediates are supported by their NMR and ir spectra and the purity of chromatographed intermediates by thin-layer chromatographic evidence.

Where racemic alkylating agents R′-hal are used, the products **2** must consist of four stereoisomers in equal parts. Separation of isomers was not attempted except in the case of **2a**. This one compound of the group, after long standing, deposited about half its weight of crystalline material, mp 53–55.5 °C, which could be efficiently separated. That this crystalline material is one of the two racemic forms of **2a** can be seen by examination of the ^1H NMR spectra ($CDCl_3$) with and without the shift reagent $Eu(fod)_3$.[4] The acetylmethyl protons of the total stereomixture **2a** resonate as a sharp singlet at δ 2.12. Addition of $Eu(fod)_3$ shifts this signal downfield and splits it into two well-separated singlets of equal area. The corresponding signal of the crystalline fraction of **2a**, originally also at δ 2.12, is shifted downfield by $Eu(fod)_3$ but remains one singlet with a chemical shift at the position of the

Table I. Acylhydroxyalkanoic Acids



2



3-5

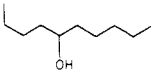
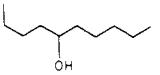
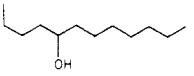
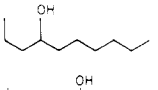
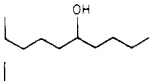
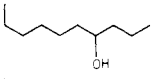
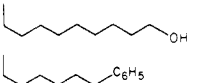
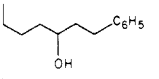
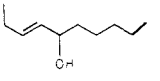
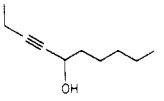
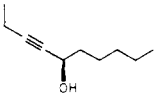
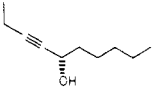
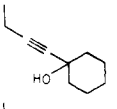
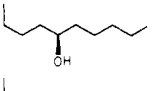
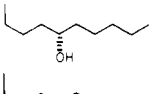
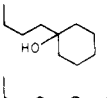
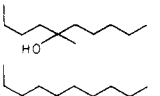
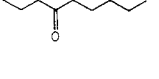
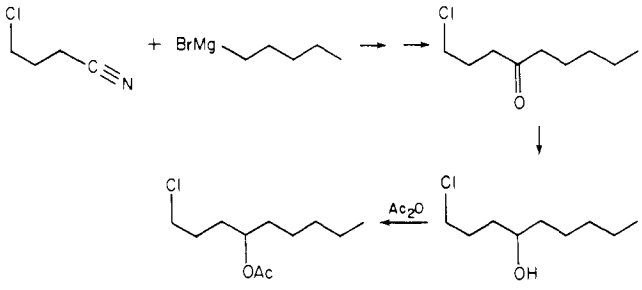
No.	R	Yield, %	R_f[a]	Formula[b]	Mouse ovary PG assay, fold increase in cAMP			Lipocyte receptor binding, μg equiv to 1 ng of PGE_1
					10^{l}	25^{l}	100^{l}	
2a		26[c]	0.44	$C_{19}H_{36}O_4$	11	14	23	1.7
α-2a[d]		*e*	0.44	$C_{19}H_{36}O_4$	7	19	23	
2b		17[c]	0.46	$C_{14}H_{26}O_4$		1	1	450
2c		22[c]	0.46	$C_{15}H_{28}O_4$		1	1	>100
2d		22[c]	0.56	$C_{21}H_{40}O_4$	19	37	39	6.6
2e		18[c]	0.47	$C_{19}H_{36}O_4$	5		11	41
2f		41[c]	0.51	$C_{19}H_{36}O_4$	9	9	20	2.1
2g		37[c]	0.58	$C_{19}H_{36}O_4$	4	4	8	65
2h		14[c]	0.64	$C_{19}H_{36}O_4$	1	1	1	>125
2i		30[c]	0.49	$C_{22}H_{34}O_4$	1	1	2	
2j		31[f]	0.53	$C_{19}H_{34}O_4$	2	8	14	3.2
2k		36[f]	0.47	$C_{19}H_{32}O_4$	2	4	7	
21[g]		40[f]	0.47	$C_{19}H_{32}O_4$	2	3	3	
2m[h]		49[f]	0.47	$C_{19}H_{32}O_4$	3	7		
2n		49[f]	0.44	$C_{19}H_{30}O_4$		1	1	
2o		*e*	0.44	$C_{19}H_{36}O_4$	5	12	19	2.1
2p		*e*	0.44	$C_{19}H_{36}O_4$	19	25	29	3.2
2q		*e*	0.46	$C_{19}H_{34}O_4$	1	3	4	>125
2r		*e*	0.47	$C_{20}H_{38}O_4$	4	9	11	0.4
2s		*e*	0.64	$C_{19}H_{34}O_4$	2	4	9	7

Table I (*Continued*)

No.	R	Yield, %	R_f[a]	Formula[b]	Mouse ovary PG assay, fold increase in cAMP 10[l]	25[l]	100[l]	Lipocyte receptor binding, μg equiv to 1 ng of PGE_1
3		*e*	0.58	$C_{20}H_{38}O_4$[i]	6	17	26	2.4
4		*e*	0.30	$C_{18}H_{36}O_4$[j]	8	9	18	4.6
5		*e*	0.30	$C_{19}H_{38}O_4$[k]	15	25	33	2.5

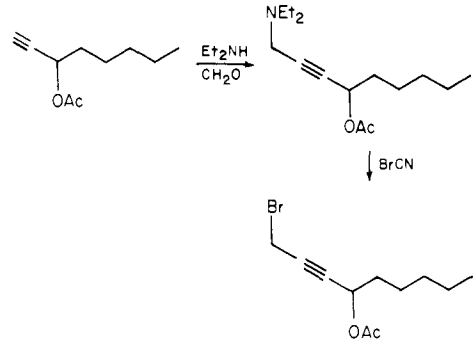
[a] Determined on SiO_2 plates with $CHCl_3$-CH_3OH-AcOH (95:4:1). [b] All compounds were analyzed for C and H. Analytical results were within 0.4% of the theoretical values except where noted. [c] Overall yield from diester **6** (Scheme I). [d] Racemate, mp 53–55.5 °C. [e] See Experimental Section. [f] Overall yield from diester **10** (Scheme II). [g] $[\alpha]^{26}D$ +2.18° (c 3.85, $CHCl_3$). [h] $[\alpha]^{26}D$ −1.94° (c 3.45, $CHCl_3$). [i] H: calcd, 11.18; found, 11.69. [j] C: calcd, 68.31; found, 68.72. [k] H: calcd, 11.59; found, 12.03. [l] Concentration in μg/ml.

Scheme V



7a

Scheme VI



7k

upfield singlet of **2a**. The fraction of **2a** that remains an oil shows two singlets with the shift reagent, the downfield one predominating (~4:1). The crystalline racemate is designated α-**2a** in Table I.

Another separation of isomer pairs of **2a** was achieved when 8-acetyl-12(*R*)-hydroxyheptadecanoic acid (**2o**) and 8-acetyl-12(*S*)-hydroxyheptadecanoic acid (**2p**) were synthesized. Scheme II was employed. The alkylating agents R′-hal were the *R* and *S* enantiomers of 1-bromo-4-acetoxy-2-nonyne. The acetylenic epimer pairs **2l** and **2m** were obtained. Hydrogenation of these gave **2o** and **2p**.

Further separation into single stereoisomers was not attempted since the C-8 chiral center is configurationally labile (through enolization), making the configurational integrity of individual stereoisomers and racemic pairs uncertain. At any rate, with a racemate and the two epimeric pairs available, an estimate could be made of the dependence of biological activity on configuration in this key compound.

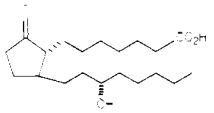
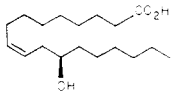
The various preparations of alkylating agents **7** are described in the Experimental Section. Two of the more broadly applied processes are shown in Schemes V and VI. The synthesis of 1-chloro-4-acetoxynonane (**7a**, Scheme V) exemplifies the process used to prepare **7a,d–g,i**. The initial step, a Grignard reaction on chloronitriles, gave the intermediate chloro ketones in only modest yields (20–30%). The synthesis of 1-bromo-4-acetoxy-2-nonyne (**7k**, Scheme VI) exemplifies the process used to prepare propargylic bromides **7k–n**. The final step was an efficient cyanogen bromide cleavage of an acetylenic Mannich amine.

Biological Activity. The prostaglandins of the *E* series have been shown to raise cAMP levels in cells of many types.[5] The dose-related stimulation by PGE_1 of cAMP formation in the mouse ovary is the basis for the primary assay used in these laboratories for the detection and measurement of prostaglandin-like activity.[6] In this assay, described in detail in the Experimental Section, mouse ovaries are first incubated with adenine-8-^{14}C to allow formation of intracellular ATP-^{14}C. Then, the test compound along with the phosphodiesterase inhibitor theophylline is added and incubation is continued. Reactions are finally terminated by the addition of trichloroacetic acid, and cAMP-^{14}C is isolated from the ovaries and measured. Results are expressed in this paper as fold increases in cAMP formation obtained by dividing the cAMP levels in treated ovaries by those levels found in untreated ovaries.

The effectiveness of 8-acetyl-12-hydroxyheptadecanoic acid (**2a**) in stimulating cAMP formation is compared with that of PGE_1, PGE_2, and tetrahydro-PGA_1 in Table II. Analogue **2a** is seen to raise cAMP levels markedly at pharmacologically attainable concentrations, although these concentrations are about 1000 times the concentrations of PGE_1 required for similar effects. The related ricinoleic acid is without effect except at the highest concentrations.

It is important to demonstrate that the secoprostaglandins not only possess a characteristic action of the natural prostaglandins but that they can interact with prostaglandin receptors. Without the ability to so interact, these substances can hardly be described as prostaglandin analogues in any biological sense. A prostaglandin receptor binding assay has been devised in these laboratories that employs a binding fraction prepared from rat lipocytes.[7] In this assay, the test compound is allowed to compete with tritiated PGE_1 for binding to the receptors. Results are here expressed as nanograms of test compound equivalent to 1 ng of cold PGE_1 in displacing tritiated PGE_1 from

Table II

	Mouse ovary PG assay, fold increase in cAMP									Lipocyte receptor binding, ng equiv to 1 ng of PGE_1
	0.01[a]	0.05[a]	0.1[a]	1.0[a]	10[a]	25[a]	50[a]	100[a]	200[a]	
PGE_1	8	29	25	54						1
PGE_2	14	35	57	75	80					1.4
				10	25	26	19			10
2a				2	11	14	16	23	16	1700
 ricinoleic acid							2	2	1	

[a] Concentration in μg/ml.

binding sites. These data, also presented in Table II, show that **2a** appears to have weak but real affinity for the lipocyte PG receptor. The roughly 1000-fold loss in receptor affinity in going from PGE_1 to **2a** parallels the 1000-fold loss of potency of **2a** toward cAMP stimulation in the mouse ovary.

With a relationship established between the activity of our key analogue **2a** and those of the natural (*E*)-prostaglandins, we may turn to the data obtained by evaluating the entire series of acylhydroxyalkanoic acids for their ability to stimulate cAMP formation and to bind to the lipocyte prostaglandin receptor. These data are presented in Table I. The relation between structure and activity in this series will be discussed by noting the changes in activity caused by structural modification of **2a**.

The length and character of the hydrocarbon terminus are important determinants of activity. Activity is abolished by removal of the terminal 5- or 4-carbon atoms (to give **2c** and **2b**, respectively) and by replacement of the terminal 3-carbon atoms by phenyl (**2i**). Attachment of C-17 to the hydroxy-bearing C-12 to form a cyclohexane ring (**2q**) reduces activity to a low level. Addition of a 12-methyl group to give tertiary alcohol **2r** significantly reduces activity.

At this point, it should be noted that the acylhydroxyalkanoic acids are not substrates for the enzyme prostaglandin 15-hydroxydehydrogenase which catalyzes the metabolic deactivation of the natural prostaglandins. Thus, addition of a 12-methyl group in this series is without the significance of the analogous addition of a 15-methyl group in the prostaglandin series which blocks the enzymatic dehydrogenation of the 15-position secondary alcohol function.

Activity is also highly dependent on the position of the hydroxy group. Activity is diminished when the hydroxy group is placed on the 11-carbon atom (**2e**). Activity is largely retained in the 13-OH isomer of **2a** (**2f**) but is strongly reduced in the 14-OH isomer **2g** and lost in the 17-OH isomer **2h**.

Introduction of a trans-10,11 double bond which corresponds to the prostaglandin 13,14 double bond markedly reduces activity (**2j**). Introduction of an acetylenic bond in the same position (**2k**) reduces activity further.

Reduction of the ketone function in **2a** to give the 8-(1-hydroxyethyl) derivative **5** significantly increases activity. Oxidation of **2a** to give the 12-oxo analogue **2s** markedly reduces activity—consistent with the effect of the similar oxidation (metabolic dehydrogenation) in the prostaglandin series. Lengthening the acetyl group of **2a** to propionyl (**3**) did not affect activity.

The compounds compared thus far have been total mixtures of stereoisomers. The dependence of activity on configuration of the chiral centers of 8-acetyl-12-hydroxyheptadecanoic acid can be assessed by comparing the cAMP stimulatory activities of the total stereomixture **2a**, the crystalline racemate, and the 12(*R*) and 12(*S*) epimeric pairs. The activity of the crystalline racemate (and, inferentially, of the uncrystallized racemate) does not differ significantly from that of **2a**. Both epimeric pairs are active; however, the 12(*S*) pair in which the configuration of the hydroxy-bearing C-12 is the same as that of C-15 in the prostaglandins gives cAMP levels that are roughly double those produced by the 12(*R*) pair. The stereoselectivity of this action is nevertheless slight relative to the high order of stereoselectivity associated with many of the actions of the prostaglandins. This loss of stereoselectivity undoubtedly is connected with the loss of structural rigidity that attends the cutting of the cyclopentane ring of the natural substances.

The receptor binding data for this series correlate well with the cAMP stimulatory data. The values for relative receptor affinity of all active compounds cluster closely around that of **2a**; inactive compounds show negligible affinity for the lipocyte receptor (e.g., **2b,c,h**).

The evaluation of the acylhydroxyalkanoic acids in vivo is in progress in these laboratories. Complete results will be published elsewhere. It may suffice to state here that a number of these analogues which have shown prostaglandin-like activity in vitro and affinity for the prostaglandin receptor have also shown some, but not all, of the characteristic actions of the prostaglandins in whole animals.

For example, **2a** possesses renal vasodilatory activity which can be demonstrated when renal blood flow is measured electromagnetically. Intravenous infusion of 0.5 mg/kg/min of **2a** in anesthetized dogs gives a maximum increase in renal blood flow of 92 ml/min above the control value of 206 ml/min (measurements in single kidney). PGE_1 produces renal vasodilation but only on infusion into the renal artery when its metabolic inactivation is minimized.

Compound **2a** inhibits collagen-induced platelet aggregation when administered orally to guinea pigs, ED_{50} 6.5 mg/kg. The ED_{50} of PGE_1 (not active by oral administration) is 0.02 mg/kg ip.

Experimental Section

Chemical. Melting points were taken in open capillary tubes

and are uncorrected as are boiling points. ^{1}H NMR spectra were obtained in $CDCl_3$ on a Varian A-60A spectrometer. Chemical shifts are reported as parts per million relative to Me_4Si as an internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Column chromatography was carried out on E. Merck's silica gel 60, particle size 0.063–0.20 mm. Thin-layer chromatography (TLC) was used to monitor column fractions and to establish purity of products. It was performed on Analtech silica gel GF plates (thickness 250 μ). Spots were located with iodine vapor. A standard solvent system was used for TLC of all acid products (Table I) consisting of $CHCl_3$–CH_3OH–HOAc (95:4:1).

Chromatographed compounds were prepared for analysis and biological testing by being heated at 100 °C in oil pump vacuum for 4–6 h in order to remove the last traces of solvents. When analyses are indicated only by the symbols of the elements, the analytical results obtained for these elements are within 0.4% of the theoretical values.

Ethyl 8-*tert*-Butoxycarbonyl-9-oxodecanoate (6). *tert*-Butyl acetoacetate (126 g, 0.80 mol) was added during 80 min to a stirred suspension of NaH (21.1 g, 0.88 mol) in benzene (400 ml) and DMF (400 ml). The mixture was stirred for an additional 30 min. Ethyl 7-bromoheptanoate (208 g, 0.88 mol) was then added during 30 min and the mixture heated at 100 °C for 3.5 h. The mixture was cooled and treated with 1600 ml of water. The organic layer was separated, diluted with ether, and dried over $MgSO_4$. Vacuum distillation gave 158 g (63%) of **6**: yellow oil; bp 175–177 °C (0.5 mm). Anal. ($C_{17}H_{30}O_5$) C; H: calcd, 9.62; found, 10.17.

Diethyl 2-Acetylnonanedioate (10). This compound was prepared analogously from ethyl acetoacetate and ethyl 7-bromoheptanoate in 70% yield: bp 155–157 °C (0.5 mm). Anal. ($C_{15}H_{26}O_5$) C, H.

1-Chloro-4-acetoxybutane (**7b**)[8] and 1-chloro-4-acetoxypentane (**7c**)[9] were prepared by published procedures. The preparation of **1-bromo-9-acetoxynonane (7h)** was described recently;[10] **7h** has bp 126–127 °C (0.4 mm). Anal. ($C_{11}H_{21}BrO_3$) C, H.

1-Chloro-4-acetoxynonane (7a). (a) 1-Chloro-4-nonanone. 4-Chlorobutyronitrile (155 g, 1.5 mol) was added during 1 h to the Grignard reagent prepared from 1-bromopentane (227 g, 1.5 mol) and Mg (36.5 g, 1.5 g-atoms) in ether (1 l.). After an additional hour of stirring, the mixture was poured into finely crushed ice (1 kg) and concentrated hydrochloric acid (750 ml). The ether layer was separated and discarded. The aqueous solution was heated 1 h on a steam bath. The ketone which separated as an oil was taken up in ether, dried over $MgSO_4$, and distilled to yield 69.0 g (26%) of 1-chloro-4-nonanone: colorless oil; bp 115–117 °C (14 mm). Anal. ($C_9H_{17}ClO$) C, H.

(b) 1-Chloro-4-nonanol. 1-Chloro-4-nonanone (61.4 g, 0.35 mol) was added during 1 h to a suspension of $NaBH_4$ (6.5 g, 0.17 mol) in ethanol (310 ml) in which 1.3 g of NaOH had been dissolved. The temperature was kept at 45–50 °C. After an additional hour of stirring, the mixture was acidified with concentrated hydrochloric acid and the ethanol distilled at reduced pressure. The residue was treated with water and the oily product taken up in ether and dried over $MgSO_4$. Evaporation of ether left the product as a yellow residual oil which weighed 58.8 g: ir 3400 cm^{-1} (OH).

(c) 1-Chloro-4-acetoxynonane (7a). A mixture of crude 1-chloro-4-nonanol (58.8 g, 0.33 mol) and Ac_2O (67.3 g, 0.66 mol) was heated at 95 °C for 1.5 h and then distilled at reduced pressure to yield 46.5 g (64%) (14% overall from 1-bromopentane) of **7a**: bp 130–133 °C (14 mm); NMR δ 0.89 (3 H, t, CH_3), 2.02 (3 H, s, CH_3COO), 3.53 (2 H, t, CH_2Cl), 4.89 (1 H, m, HCOAc). Anal. ($C_{11}H_{21}ClO_2$) C, H.

1-Chloro-5-acetoxynonane (7f). This compound was prepared by a three-step process analogous to that used for **7a** beginning with 1-bromobutane and 5-chlorovaleronitrile: overall yield 22%; bp (**7f**) 130–134 °C (13 mm). Anal. ($C_{11}H_{21}ClO_2$) C, H.

1-Bromo-6-acetoxynonane (7g). This compound was prepared analogously to **7a** beginning with 1-bromopropane and 6-bromohexanenitrile: overall yield 14%; bp (**7g**) 142–145 °C (13 mm); ^{1}H NMR δ 3.45 (2 H, t, CH_2Br). Anal. ($C_{11}H_{21}BrO_2$) H; C: calcd, 49.82; found, 50.33.

1-Chloro-4-acetoxyundecane (7d). This compound was prepared analogously to **7a** beginning with 1-bromoheptane and 4-chlorobutyronitrile: overall yield 9%; bp 155–158 °C (15 mm). Anal. ($C_{13}H_{25}ClO_2$) C, H.

1-Chloro-4-acetoxy-6-phenylhexane (7i). This compound was prepared analogously to **7a** beginning with phenethyl bromide and 4-chlorobutyronitrile: overall yield 24%; bp 185–193 °C (15 mm). Anal. ($C_{14}H_{19}ClO_2$) C, H.

1-Chloro-3-acetoxynonane (7e). 3-Chloropropanal (37.4 g, 0.40 mol) was added during 1 h to the Grignard reagent prepared from 1-bromohexane (73.9 g, 0.46 mol) and Mg (11.0 g, 0.46 mol) in Et_2O (200 ml). After 1 h additional reaction time, the mixture was worked up in the standard manner and the product distilled to yield 25.0 g (35%) of **1-chloro-3-nonanol**, bp 123–126 °C (14 mm). A mixture of this alcohol (25 g, 0.14 mol) and Ac_2O (28.6 g, 0.28 mol) was heated at 95 °C for 15 h and then distilled to yield 26.8 g (87%) of **7e**, bp 133–135 °C (14 mm). Anal. ($C_{11}H_{21}ClO_2$) C, H.

(*E*)-1-Bromo-4-acetoxy-2-nonene (7j). A mixture of (*E*)-4-acetoxy-2-nonene[11] (73.5 g, 0.4 mol), *N*-bromosuccinimide (80.0 g, 0.45 mol), and CCl_4 (500 ml) was boiled under reflux for 3 h. The mixture was cooled and succinimide filtered off. The solution was washed with dilute $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated and the residual oil distilled to yield 62 g (59%) of crude **7j**, bp 110–112 °C (0.1 mm). For further purification, 20 g of this product was chromatographed in benzene on a column containing 275 g of silica gel. **7j** (11 g) was obtained as a colorless oil: homogeneous on TLC (benzene) R_f 0.47; NMR δ 2.03 (3 H, s, CH_3COO), 3.87 (2 H, d, J = 6 Hz, CH_2Br), 5.20 (1 H, m, *H*CO), 5.6–5.9 (2 H, m, vinyl H). Anal. ($C_{11}H_{19}BrO_2$) H; C: calcd, 50.20; found, 49.69.

1-Bromo-4-acetoxy-2-nonyne (7k). (a) 3-Acetoxy-1-octyne. Acetic anhydride was added dropwise with stirring to a solution of 1-octyn-3-ol (100 g, 0.794 mol) in pyridine (79 g, 1.0 mol) during 1 h. The temperature rose to 45 °C. The solution was heated at 55 °C for 1 h and then cooled and poured into 300 ml of ice-cold 5% hydrochloric acid. The separated oil was taken up in ether, washed with water, dried over Na_2SO_4, and distilled to yield 106 g (80%) of product, bp 91–92 °C (15 mm). Anal. ($C_{10}H_{16}O_2$) H; C: calcd, 71.39; found, 71.89.

(b) 1-Diethylamino-4-acetoxy-2-nonyne. A mixture of 3-acetoxy-1-octyne (58.5 g, 0.35 mol), diethylamine (28.5 g, 0.39 mol), paraformaldehyde (13.8 g, 0.46 mol), and *p*-dioxane (60 ml) was heated at 95 °C under a reflux condenser for 17 h. The resulting solution was cooled, diluted with ether, and extracted with 300 ml of 5% hydrochloric acid. The acidic aqueous solution was made basic with 10% NaOH solution. The liberated amine was taken up in ether, washed with water, dried over Na_2SO_4, and distilled to yield 73.1 g (89%) of product, bp 103–109 °C (0.3 mm). Anal. ($C_{15}H_{27}NO_2$) C, H, N.

(c) 1-Bromo-4-acetoxy-2-nonyne (7k). A solution of 1-diethylamino-4-acetoxy-2-nonyne (50.6 g, 0.20 mol) and BrCN (21.2 g, 0.20 mol) in ether (250 ml) was let stand at 27 °C for 18 h. The solution was washed with 5% hydrochloric acid and water and dried over Na_2SO_4. The ether was evaporated and the residual oil distilled. After a forerun of diethylcyanamide, there was collected 34.1 g (65%) of **7k**, bp 97–105 °C (0.2 mm). Anal. ($C_{11}H_{17}BrO_2$) C, H.

(4*R*)-1-Bromo-4-acetoxy-2-nonyne (7l) was prepared analogously to **7k** from (3*R*)-1-octyn-3-ol:[11] $[\alpha]^{26}_D$ +6.10° (c 3.05, $CHCl_3$). Bromide **7l** was obtained in 73% yield: bp 113–115 °C (0.4 mm); $[\alpha]^{26}_D$ +75.4° (c 3.2, $CHCl_3$). The intermediates obtained were (a) **(3*R*)-3-acetoxy-1-octyne** [86%; bp 86–88 °C (13 mm); $[\alpha]^{26}_D$ +70.0° (c 3.10, $CHCl_3$)] and (b) **(4*R*)-1-diethylamino-4-acetoxy-2-nonyne** [80%; bp 114–117 °C (1 mm); $[\alpha]^{26}_D$ +74.0° (c 3.16, $CHCl_3$)].

(4*S*)-1-Bromo-4-acetoxy-2-nonyne (7m) was prepared analogously to **7k** from (3*S*)-1-octyn-3-ol:[12,13] $[\alpha]^{26}_D$ −6.61° (c 3.3, $CHCl_3$), −20.2° (c 3.3, Et_2O). Bromide **7m** was obtained in 60% yield: bp 103–109 °C (0.4 mm); $[\alpha]^{26}_D$ −83.1° (c 3.7, $CHCl_3$). The intermediates obtained were (a) **(3*S*)-3-acetoxy-1-octyne** [88%; bp 90–91 °C (15 mm); $[\alpha]^{26}_D$ −79.1° (c 3.0, $CHCl_3$)] and (b) **(4*S*)-1-diethylamino-4-acetoxy-2-nonyne** [84%; bp 119–121 °C (1 mm); $[\alpha]^{26}_D$ −80.5° (c 3.3, $CHCl_3$)].

1-Acetoxy-1-(3-bromo-1-propynyl)cyclohexane (7n). (a) 1-Acetoxy-1-(3-diethylamino-1-propynyl)cyclohexane. A mixture of 1-acetoxy-1-ethynylcyclohexane (64.0 g, 0.385 mol), diethylamine (30.9 g, 0.42 mol), paraformaldehyde (15.0 g, 0.5 mol),

CuCl (1.5 g), and dioxane (60 ml) was stirred while an initial exothermic reaction took place and subsided. The mixture was then heated at 95 °C for 1.5 h. The mixture was cooled, diluted with ether, and extracted with cold 5% hydrochloric acid. The acidic aqueous solution was made basic with 10% NaOH solution. The liberated amine was taken up in ether, dried over Na_2SO_4, and distilled to yield 72.7 g (75%) of nearly colorless oily product: bp 113–115 °C (0.15 mm); NMR δ 1.07 (6 H, t, CH_3CH_2), 2.02 (3 H, s, CH_3COO), 2.60 (4 H, q, CH_3CH_2), 3.52 (2 H, s, $CH_2C{\equiv}$). Anal. ($C_{15}H_{25}NO_2$) C, H; N: calcd, 5.57; found, 5.13.

(b) 1-Acetoxy-1-(3-bromo-1-propynyl)cyclohexane (7n). A solution of 1-acetoxy-1-(3-diethylamino-1-propynyl)cyclohexane (61 g, 0.24 mol) and BrCN (31.8 g, 0.30 mol) in ether (350 ml) was let stand at 25 °C for 18 h. The solution was washed with 5% hydrochloric acid and water, dried over Na_2SO_4, and distilled to yield 34.8 g (55%) of **7n**, bp 114–120 °C (0.2 mm). Anal. ($C_{11}H_{15}BrO_2$) C, H.

Physical, analytical, and yield data for the following acylhydroxyalkanoic acids and congeners **2–5** are listed in Table I. The method used for the preparation of **2a–i** (Scheme I) is exemplified by the preparation of **8-acetyl-12-hydroxyheptadecanoic acid (2a).**

(a) **Ethyl 8-Acetyl-8-*tert*-butoxycarbonyl-12-acetoxyheptadecanoate (8a).** Ester **6** (20.4 g, 0.065 mol) was added during 30 min to a stirred suspension of NaH (1.7 g, 0.071 mol) in benzene (40 ml) and DMF (40 ml). After an additional hour, **7a** (15.8 g, 0.072 mol) and KI (100 mg) were added and the mixture was heated at 100 °C for 66 h. The mixture was cooled and treated with 200 ml of water. The organic layer was separated, diluted with Et_2O, washed with water, and dried over $MgSO_4$. Vacuum distillation of solvents left 32.0 g of crude **8a** as an orange residual oil: NMR δ 0.90 (3 H, t, 17-CH_3), 1.45 [9 H, s, $(CH_3)_3C$], 2.02 (3 H, s, CH_3COO), 2,12 (3 H, s, CH_3CO), 4.13 (2 H, q), 4.84 (1 H, m, HCOAc).

(b) Ethyl 8-Acetyl-12-acetoxyheptadecanoate (9a). A solution of **8a** (32 g, 0.064 mol) and *p*-toluenesulfonic acid (1.0 g) in toluene (110 ml) was boiled under reflux for 22 h. The solution was cooled, washed with saturated $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvent was distilled leaving 26.7 g of residual oil. Ester **9a** was isolated by chromatography on 400 g of silica gel. There was obtained 9.6 g (38%) of **9a** as a colorless oil showing one spot on TLC (1% CH_3OH in $CHCl_3$), R_f 0.38. Anal. ($C_{23}H_{42}O_5$) C, H.

(c) 8-Acetyl-12-hydroxyheptadecanoic Acid (2a). A solution of ester **9a** (9.6 g, 0.024 mol) and NaOH (3.7 g, 0.092 mol) in water (17 ml) and CH_3OH (150 ml) was let stand at 25 °C for 72 h. Most of the MeOH was distilled and the residual solution was diluted with water and extracted with ether. The aqueous solution was acidified with concentrated hydrochloric acid. The precipitated product was taken up in ether and dried over $MgSO_4$. Evaporation of the solvent left 7.6 g of crude **2a** which was chromatographed on 125 g of SiO_2 with 2% CH_3OH in $CHCl_3$ elution to yield 5.4 g (69%) of **2a**, a colorless viscous oil, showing one spot on standard TLC: NMR δ 0.90 (3 H, t, 17-CH_3), 2.12 (3 H, s, CH_3CO), 3.64 (1 H, m, *CH*OH), 6.65 (2 H, s, OH and COOH).

Compound **2a** deposited a crop of small crystals on standing at room temperature for 8 weeks. A 6.2-g sample was stirred with 5 ml of CH_3CN. The undissolved crystalline material was collected on a filter and washed with 2 ml of CH_3CN. There was obtained 1.4 g of colorless crystals, mp 53–55.5 °C, identical with stereomixture **2a** in NMR spectrum and R_f (TLC).

The method used for the preparation of acylhydroxyalkanoic acids **2j–n** (Scheme II) is exemplified by the preparation of **8-acetyl-12-hydroxy-10-heptadecynoic acid (2k).**

(a) **Diethyl 2-Acetyl-2-(4-acetoxy-2-nonyn-1-yl)nonanedioate (11k).** Ester **10** (36.7 g, 0.128 mol) was added during 30 min to a stirred suspension of NaH (3.4 g, 0.14 mol) in benzene (65 ml) and DMF (65 ml). After 1 h of additional stirring, bromide **7k** (36.7 g, 0.14 mol) was added and the mixture was heated at 100 °C for 1 h. The mixture was cooled and treated with 300 ml of water. The organic layer was separated, washed with water, and dried over Na_2SO_4. The solvent was evaporated to leave 59.8 g of crude **11k**.

(b) 8-Acetyl-12-hydroxy-10-heptadecynoic Acid (2k). A solution of ester **11k** (59.7 g, 0.128 mol) and NaOH (30 g, 0.75 mol) in water (200 ml) and CH_3OH (800 ml) was heated at 60 °C for 16 h. Most of the MeOH was then distilled at reduced pressure. The residue was dissolved in water and the solution acidified to congo red with concentrated hydrochloric acid. The separated acid was taken up in ether and dried over Na_2SO_4. Evaporation of the ether left 41.1 g of crude **2k** as a red viscous oil. It was purified by chromatography on 650 g of silica gel with 2% MeOH in $CHCl_3$ as eluent. There was obtained 15.0 g (36%) of **2k**, a yellow viscous oil, showing one spot on standard TLC: NMR δ 0.90 (3 H, t, 17-CH_3), 2.20 (3 H, s, CH_3CO), 4.37 (1 H, t, *CH*OH).

(12*R*)-8-Acetyl-12-hydroxyheptadecanoic Acid (2o). (12*R*)-8-Acetyl-12-hydroxy-10-heptadecynoic acid (**2l**) (25.8 g, 0.079 mol) was dissolved in a mixture of EtOAc (80 ml) and cyclohexane (160 ml) and hydrogenated over a 5% Pt on charcoal catalyst (3.5 g) in a Parr apparatus with an initial hydrogen pressure of 45 lb/in.^{2}. The uptake of the required 0.158 mol of hydrogen required 10 min. The catalyst was removed by filtration and the solvents were evaporated. The residual oily product was chromatographed on 400 g of silica gel with 2% CH_3OH in $CHCl_3$ elution. There was obtained 11.7 g (45%) of **2l**: nearly colorless viscous oil; $[\alpha]^{26}D$ −0.79° (c 3.8, $CHCl_3$).

(12*S*)-8-Acetyl-12-hydroxyheptadecanoic Acid (2p). This compound was prepared analogously in 60% yield by hydrogenation of **2m**: $[\alpha]^{26}D$ +1.0° (c 3.9, $CHCl_3$).

8-Acetyl-11-(1-hydroxycyclohexyl)-10-undecynoic Acid (2q). This compound was prepared analogously in 85% yield by hydrogenation of **2n**.

8-(1-Hydroxyethyl)-12-hydroxyheptadecanoic Acid (5). Compound **2a** (7.2 g, 0.022 mol) and $NaBH_4$ (0.76 g, 0.02 mol) were dissolved in a solution of NaOH (1.2 g, 0.03 mol) in water (80 ml). The resulting solution was allowed to stand at 27 °C for 20 h. It was then acidified with concentrated hydrochloric acid. The oily acid that separated was taken up in ether, dried over Na_2SO_4, and chromatographed on 120 g of silica gel with 4% CH_3OH in $CHCl_3$ elution. There was obtained 4.0 g (55%) of **5**.

8-Acetyl-12-oxoheptadecanoic Acid (2s). A solution of **2a** (9.8 g, 0.03 mol) in acetone (30 ml) was cooled to 5 °C and treated dropwise during 2 h with a solution prepared from CrO_3 (2.6 g, 0.026 mol), concentrated H_2SO_4 (2.1 ml), and water (7.5 ml). The solution was then diluted with water (250 ml). The oily layer was taken up in ether, washed with water, and dried over Na_2SO_4. Evaporation of ether left 9.1 g (93%) of **2s**: yellowish oil; NMR δ 0.88 (3 H, t, 17-CH_3), 2.12 (3 H, s, CH_3CO), 2.38 (7 H, m, CHCO and various CH_2CO), 11.18 (1 H, s, COOH).

8-Propionyl-12-hydroxyheptadecanoic Acid (3) (Scheme III). (a) Di-*tert*-butyl (6-Ethoxycarbonylhexyl)malonate. Di-*tert*-butyl malonate (41.1 g, 0.19 mol) was added to a stirred suspension of NaH (5.0 g, 0.21 mol) in benzene (95 ml) and DMF (95 ml). Then ethyl 7-bromoheptanoate (49.8 g, 0.21 mol) was added during 30 min and the mixture was heated at 100 °C for 4.5 h. The mixture was cooled and treated with 500 ml of water. The organic layer was separated, diluted with ether, and dried over $MgSO_4$. The solvents were evaporated leaving 69.7 g of crude tricarboxylic ester.

(b) Di-*tert*-butyl 2-(4-Acetoxynonyl)-2-(6-ethoxycarbonylhexyl)malonate (12). The above ester (69.7 g, 0.187 mol) was alkylated in the same manner with NaH (5.0 g, 0.21 mol) and **7a** (46.3 g, 0.21 mol). The mixture was heated at 100 °C for 42 h. Work-up gave 104.1 g of crude **12** as a residual oil.

(c) Ethyl 8-Carboxy-12-acetoxyheptadecanoate (13). A solution of **12** (104.1 g, 0.187 mol) and *p*-toluenesulfonic acid (3.3 g) in toluene (330 ml) was boiled under reflux for 9.5 h. The solution was worked up as in the preparation of **9a** to yield 74.9 g of crude **13**, a viscous red oil, which was chromatographed on 700 g of silica gel with 2% CH_3OH in $CHCl_3$ elution. There was obtained 46 g (62%) of **13** showing one spot, R_f 0.42, on TLC [$CHCl_3$–CH_3OH–AcOH (98:1:1)]. Anal. ($C_{22}H_{40}O_6$) C, H.

(d) Ethyl 8-Chlorocarbonyl-12-acetoxyheptadecanoate (14). A solution of **13** (12.0 g, 0.03 mol) and $SOCl_2$ (7.2 g, 0.06 mol) in benzene (50 ml) was boiled under reflux for 2.5 h. Volatile materials were removed on a rotary evaporator. The residual crude **14** weighed 12.5 g (100%): ir (neat) 1790 (COCl), 1730 cm^{-1} (ester CO).

(e) Ethyl 8-Propionyl-12-acetoxyheptadecanoate. A solution of EtMgBr in ether (100 ml) was prepared from EtBr (5.5

g, 0.05 mol) and Mg (1.2 g, 0.05 mol). The solution was chilled to 0 °C and $CdCl_2$ (5.5 g, 0.03 mol) was added. The mixture was stirred 10 min without cooling and 30 min at reflux. Most of the ether was then allowed to distill off and benzene (100 ml) was added and then acid chloride 14 (12.5 g, 0.03 mol) during 20 min. The mixture was boiled under reflux for 2 h, then cooled, and treated with a 10% solution of H_2SO_4. The benzene layer was separated, dried over Na_2SO_4, and evaporated leaving the product as a residual oil which was chromatographed on 200 g of silica gel with $CHCl_3$ elution. There was obtained 6.2 g (50%) of the title ester showing one spot, R_f 0.23, on TLC ($CHCl_3$). Anal. ($C_{24}H_{44}O_5$) C, H.

(f) 8-Propionyl-12-hydroxyheptadecanoic Acid (3). A solution of the above ester (6.0 g, 0.146 mol) and NaOH (1.0 g, 0.025 mol) in water (10 ml) and MeOH (70 ml) was let stand at 27 °C for 24 h. Work-up as in the preparation of **2a** gave 4.5 g of oily product which was chromatographed on 60 g of silica gel with 2% CH_3OH in $CHCl_3$ elution to yield 2.4 g (48%) of **3**.

8-Hydroxymethyl-12-hydroxyheptadecanoic Acid (4). Acid chloride 14 (14.0 g. 0.335 mol) was added to a solution of $NaBH_4$ (2.7 g, 0.07 mol) in diglyme (75 ml). The exothermic reaction caused the temperature to rise to 55 °C. After 2 h, the solution was cooled in an ice bath and acidified with 10% hydrochloric acid. Water (250 ml) was then added and the oily product taken up in ether, washed with water, and dried over Na_2SO_4. The ether was evaporated to leave 12.2 g of crude **ethyl 8-hydroxymethyl-12-hydroxyheptadecanoate**. The ester was dissolved in a solution of NaOH (4.0 g, 0.1 mol) in water (20 ml) and MeOH (100 ml). The solution was allowed to stand for 64 h at 25 °C and then worked up as in the preparation of **2a** to obtain 6.6 g of crude 4. Column chromatography on 110 g of silica gel with 4% CH_3OH in $CHCl_3$ elution gave 3.7 g (35%) of purified 4: colorless viscous oil; NMR δ 0.90 (3 H, t, 17-CH_3), 2.32 (2 H, t, CH_2COOH), 3.55 (3 H, m, $CHOH$ and CH_2OH), 5.1 (3 H, br s, OH and COOH).

8-Acetyl-12-hydroxy-12-methylheptadecanoic Acid (2r) (Scheme IV). (a) Ethyl 8-Acetyl-8-*tert*-butoxycarbonyl-12-methyl-11-heptadecenoate (15). Ester **6** (81.4 g, 0.259 mol) was added during 30 min to a stirred suspension of NaH (6.8 g, 0.284 mol) in benzene (130 ml) and DMF (130 ml). After an additional hour, 1-bromo-4-methyl-3-nonene[14] (62.2 g, 0.284 mol) was added and the mixture was heated at 100 °C for 20 h. Work-up as in the preparation of **8a** gave 124.4 g of crude **15** as a red residual oil.

(b) Ethyl 8-Acetyl-12-methyl-11-heptadecenoate (16). A solution of **15** (124.4 g, 0.259 mol assumed) and *p*-toluenesulfonic acid in toluene (450 ml) was boiled under reflux for 21 h. Work-up as in the preparation of **9a** gave 94.8 g of crude **16**.

(c) Ethyl 8-Acetyl-12-hydroxy-12-methylheptadecanoate (17). Mercuric acetate (3.8 g, 0.012 mol) was dissolved in water (12 ml) and THF (20 ml) was added to give a suspension of a yellow solid. Ester **16** (4.2 g, 0.012 mol) in THF (20 ml) was added and the mixture was stirred at 27 °C for 24 h. After 6 h, the yellow solid had disappeared and a cloudy solution resulted. To this solution, a 3 M NaOH solution (12 ml) and then a 0.5 M solution of $NaBH_4$ in 3 M NaOH (12 ml) were added. Liquids were decanted from the precipitated mercury. The organic layer was taken up in ether, washed with water, and dried over Na_2SO_4. Evaporation of the ether left 4.4 g of **17** as a yellow oil. Column chromatography on 70 g of silica gel with $CHCl_3$ elution gave 2.9 g (65%) of **17** showing one spot, R_f 0.27, on TLC (1% CH_3OH in $CHCl_3$). Anal. ($C_{22}H_{42}O_4$) C, H.

(d) 8-Acetyl-12-hydroxy-12-methylheptadecanoic Acid (2r). Ester **17** (4.6 g, 0.0124 mol) and NaOH (1.0 g, 0.025 mol) were dissolved in a mixture of water (10 ml) and CH_3OH (50 ml) and the solution was let stand at 27 °C for 64 h. Work-up as in the preparation of **2a** gave 3.5 g of oily product which was chromatographed on 60 g of silica gel with 2% CH_3OH in $CHCl_3$ elution. There was obtained 1.5 g (36%) of **2r**: colorless viscous oil; NMR δ 0.90 (3 H, t, 17-CH_3), 1.13 (3 H, s, CH_3COH), 2.10 (3 H, s, CH_3CO), 6.80 (2 H, br s, OH and COOH).

Biological. Mouse Ovary Prostaglandin Assay.[6] Virgin female mice over 70 days old (Charles River CD-1) were killed and the ovaries dissected and denuded of adhering fatty tissue. Three ovaries were weighed (15–25 mg) and placed in 2 ml of aerated Krebs–Ringer phosphate buffer, pH 7.2, containing 1 μCi of adenine-8-^{14}C. The tissues were incubated 1 h at 37 °C with moderate shaking to cause a pool of intracellular ATP-^{14}C to accumulate.

The following additions were then made: 0.2 ml of 0.05 M theophylline in 0.15 M NaCl and the test compound in 0.1 ml of Me_2SO. The ovaries were again incubated at 37 °C for 30 min. The reactions were terminated by the addition of 0.4 ml of 10% trichloroacetic acid, and 50 μl of a nucleotide mixture solution[15] was added to facilitate recovery of the labeled nucleotides. The incubation mixture was transferred to a glass homogenizer and the ovarian tissue was homogenized into the acidified incubation solution. The homogenate was centrifuged 1000g for 5 min and the cAMP-^{14}C was isolated from the supernatant fluid as described by Humes and co-workers[14] including the final paper chromatography step.

Prostaglandin Receptor Binding Assay. Details of this assay have been published.[7] Appropriate concentrations of the test compound were incubated with 0.4 ng of [^{3}H]-PGE_1 and 125 μg of the rat lipocyte binding preparation for 60 min at 37 °C. The amount of [^{3}H]-PGE_1 associated with the binding preparation was determined as described in the reference. Duplicate experiments were run on each test compound at each of three concentrations.

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