in pyloric ligated rats. Male, albino rats weighing approximately 140–150 g were housed in individual cages and fasted for 48 h but allowed water ad libitum. The test compounds were administered either po stomach tube or sc as a suspension in 1% gum tragacanth in a volume of 1.0 ml/100 g of body weight. Drugs were administered as a single dose either 24 or 1 h prior to pyloric ligation or immediately following ligation. Five hours after pyloric ligation, the rats were sacrificed. Acidity of the stomach contents was determined by titration with 0.1 N NaOH to a phenolphthalein end point (pH 7.8). Gastric pH was determined on a Beckman zeromatic pH meter.

Anticholinergic activity was assessed by means of the mouse mydriasis test. Test compounds were administered po in 1% gum tragacanth. Pupillary diameter was measured 1, 3, 5, and 24 h after medication with a microscope. Atropine at a dose 10 mg/kg sc was used as a positive control. Compounds **2**, **18**, and **23** were tested at 100 mg/kg and were found to be inactive.[12]

The effect of test compounds on the rate of beating of guinea pig right atria which had been stimulated with histamine was measured in vitro in an oxygenated Krebs–Henseleit solution at 35 °C. Compounds **2**, **18**, and **23** were dissolved in Me_2SO–H_2O and evaluated at concentrations of 10^{-5} and 5×10^{-5} M. The tissue was exposed to the drugs for 5 min. They were found to be without effect on the histamine dose–response curve. Metiamide[13] was used as a positive control. At concentrations of 10^{-5} and 5×10^{-5} M this drug caused an 11-fold and 38-fold shift in the histamine dose–response curve.[14]

Evaluation of the gastric antisecretory inhibitory activity in the dog was carried out in the following manner. Nonanesthetized beagle dogs weighing 9–13 kg with intact stomachs containing chronic gastric fistulas (Thomas cannula) and trained to Pavlov stands were used. The dogs were medicated via the cannula at a dose of 50 mg/kg in 1% gt. Two hours later, they were placed in the Pavlov stands and their stomach contents removed under slight vacuum for 10–15 min. The dogs then received 0.04 mg of base/kg of histamine dihydrochloride im in a volume of 0.05 mL of H_2O/kg. Aspiration of the stomach contents continued under slight vacuum and total secretions were collected at 15-min intervals. Analyses of secretions were carried out as described in the Shay rat preparation.

References and Notes

(1) H. Shay, S. A. Komarov, S. S. Fels, D. Meranze, M. Gruenstein, and H. Siplet, *Gastroenterology*, **5**, 43 (1945).
(2) J. H. Thompson, "Search for New Drugs", Vol. 6, Allan A. Rubin, Ed., Marcel Dekker, New York, N.Y., 1972.
(3) P. Bass, *Adv. Drug Res.*, **8**, 205 (1974).
(4) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).
(5) We are indebted to Dr. Noel F. Albertson for this suggestion.
(6) R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, and M. E. Parsons, *J. Int. Med. Res.*, **3**, 86 (1975).
(7) S. Swaminathan and S. Ranganathan, *J. Org. Chem.*, **22**, 70 (1957).
(8) C. Y. Almond and F. G. Mann, *J. Chem. Soc.*, 1870 (1964).
(9) A. H. Jackson and A. E. Smith, *J. Chem. Soc.*, 5510 (1964).
(10) M. Julia and J. Lenzi, *Bull. Soc. Chim. Fr.*, 2267 (1962).
(11) A. Wolf, German Patent 876 237 (1953).
(12) We thank Drs. Bertram A. Spilker and Jack Pearl for these results.
(13) J. W. Blade, W. A. M. Duncan, J. C. Emmett, C. R. Ganellin, T. Hesselbo, M. E. Parsons, and J. H. Wyllie, *Agents Actions*, **3**, 133 (1973).
(14) Personal communication from Dr. Bertram A. Spilker.

11,12-Secoprostaglandins. 3. 8-Alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic Acids and Related Compounds

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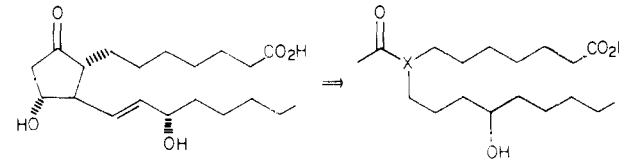
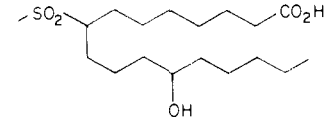
A series of 8-alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic acids which embody structural features of 11,12-secoprostaglandins was synthesized and evaluated for their ability to mimic the E series prostaglandins in stimulating cAMP formation in the mouse ovary and in binding to the rat lipocyte prostaglandin receptor. A key member of the series, 8-methylsulfonyl-12-hydroxyheptadecanoic acid, markedly stimulates cAMP formation at reasonable pharmacological concentrations, shows significant affinity for a prostaglandin receptor, and effectively inhibits antigen-induced lymphocyte transformation. In contrast, this compound is not a substrate for 15-hydroxyprostaglandin dehydrogenase, the major prostaglandin-metabolizing enzyme.

Recent publications from these laboratories have described our approach to the design of structurally unique compounds displaying desirable prostaglandin-like activity, satisfactory metabolic stability, oral efficacy, and selective tissue specificity involving 11,12-secoprostaglandins typified by Ia and Ib.[1,2] The interesting in vitro and in vivo prostaglandin-like activity of certain compounds (e.g., Ia and Ib) prompted the synthesis and biological examination of a series of 8-alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic acids (e.g., **3b**) which constitute the subject of this manuscript. Furthermore, application of the concept of carbonyl surrogation via isosteric substitution of carbon by sulfur appeared to be especially attractive to investigate at this point in our studies.[3]



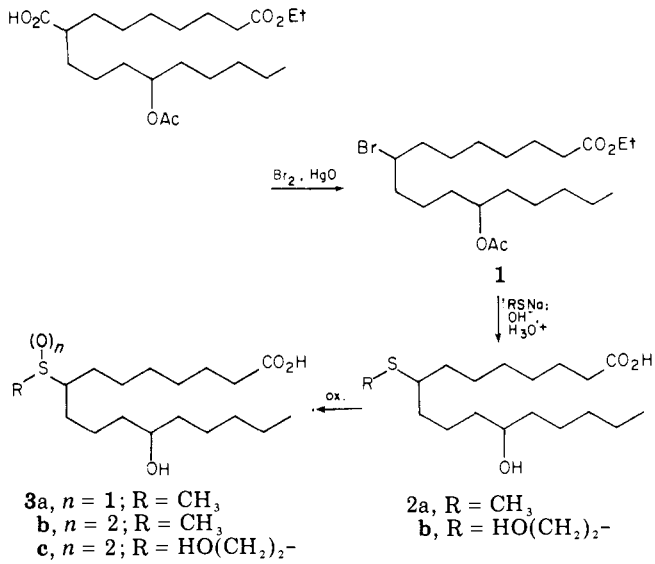
PGE_1 Ia, X = CH; b, X = N



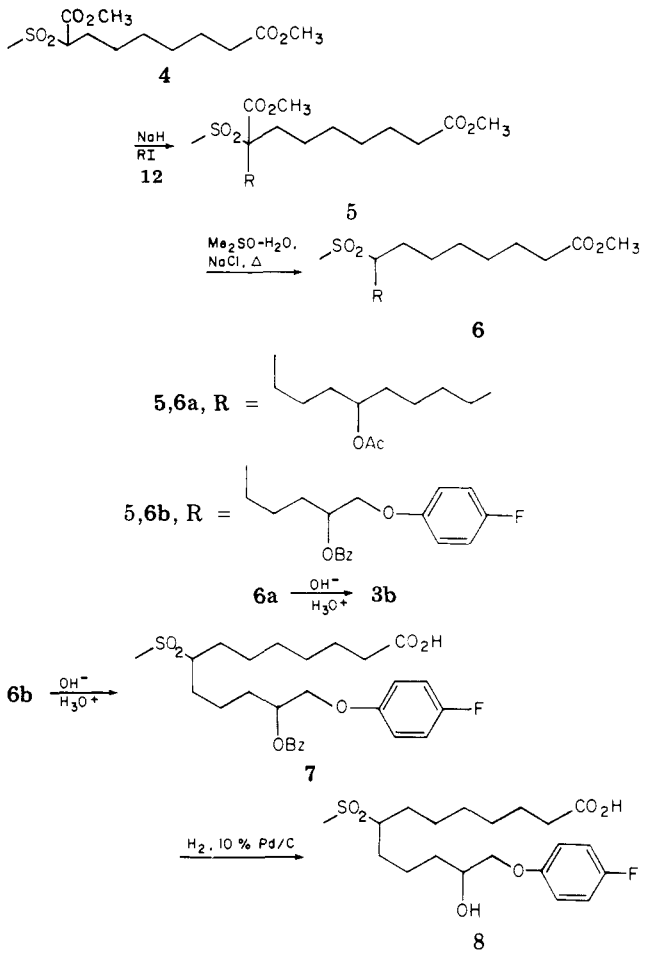
3b

Chemistry. The sulfur-containing hydroxyalkanoic acids that were prepared are tabulated in Table I. Compounds **2a,b** and **3a–c** are diastereomeric mixtures and were synthesized as shown in Scheme I. Ethyl 8-carboxy-12-acetoxyheptadecanoate[1] was converted to the bromo derivative **1** with bromine-red mercuric oxide. The latter reacted smoothly with the appropriate mercaptide to give, after saponification, thioethers **2a,b**. Oxidation of **2a** with sodium metaperiodate provided sulfoxide **3a** whereas treatment of **2a** with 30% hydrogen peroxide in the presence of ammonium molybdate afforded sulfone **3b**. Likewise, oxidation of **2b** with the latter reagent gave sulfone **3c**.

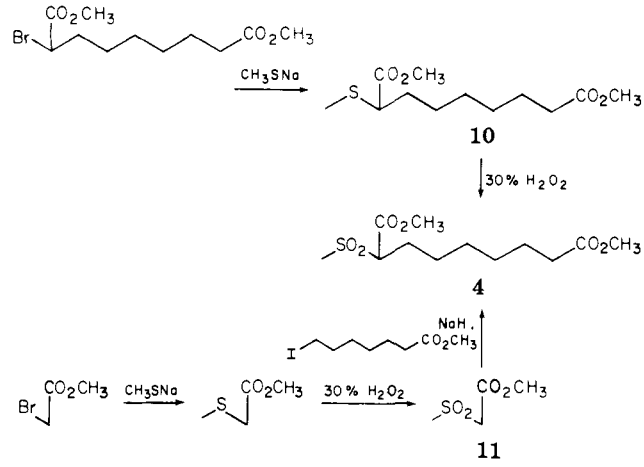
Scheme I



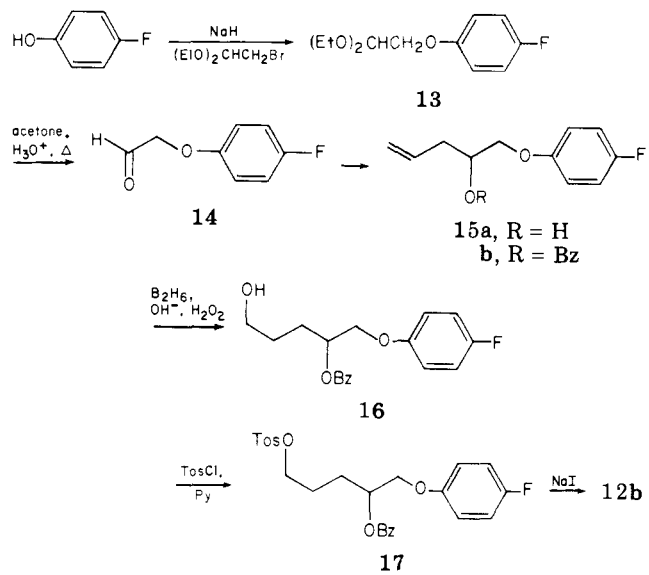
Scheme II



Scheme III



Scheme IV



Scheme II was used to prepare 4-fluorophenyl ether 8 as well as large quantities of sulfone **3b**. Diester 4, the key intermediate in Scheme II, was synthesized by the two routes indicated in Scheme III. In the first and principal route, dimethyl 2-bromoazelate[4] was treated with sodium methylmercaptide to give thioether 10 which was subsequently oxidized to 4 as shown. Alternatively, methyl (methylthio)acetate, readily prepared from methyl bromoacetate in the usual manner, was oxidized with 30% hydrogen peroxide to give β-sulfoester 11. Alkylation of the latter with methyl 7-iodoheptanoate[5] afforded diester 4. The latter route to 4 proved useful for the preparation of 8-^{14}C-labeled **3b**.

Alkylation of diester 4 with iodide **12a** (Scheme II) provided **5a** which underwent facile decarbomethoxylation using the Krapcho[6,7] procedure to give sulfone **6a**. It should be noted that **5a**, as well as the corresponding β-sulfo acid, was completely inert to acid-catalyzed decarbomethoxylation conditions as would be anticipated on mechanistic grounds. Saponification of diester **6a** gave **3b**. The synthetic utility of this route to **3b** was demonstrated by the preparation of [8-^{14}C]-**3b**[8] beginning with methyl [2-^{14}C]bromoacetate. The entire sequence was accomplished in greater than 50% yield and required no chromatographic purification other than preparative TLC of the final product.

Elaboration of ether 8 required the synthesis of iodide **12b** which was accomplished as indicated in Scheme IV. Alkylation of sodium 4-fluorophenoxide with bromoacetaldehyde diethyl acetal gave acetal **13** which underwent acid-catalyzed hydrolysis in aqueous acetone to yield aldehyde **14**. The latter proved to be relatively unstable and, accordingly, was immediately converted to alcohol **15a** with allylmagnesium bromide. Alkylation of the alkoxide derived from **15a** afforded benzyl ether **15b**. Hydroboration of **15b** employing an alkaline hydrogen peroxide work-up led to primary alcohol **16**. Treatment of the latter with *p*-toluenesulfonyl chloride in pyridine gave tosylate **17** which reacted smoothly with sodium iodide in acetone to yield **12b**.

Table I

Compd	Yield, %	R_f[a]	Formula[b]	Mouse ovary PG assay, fold increase in cAMP, concn in μg/ml: 1	25	100	Lipocyte receptor binding, μg equiv to 1 ng of PGE_1
2a	22[c]	0.40 (A)	$C_{18}H_{36}O_3S$	2.5	35	24	0.77
3a	32[d]	0.14 (B)	$C_{18}H_{36}O_4S$	4	40	57	7.14
3b	56,[e] 31[e]	0.42 (C)	$C_{18}H_{36}O_5S$[f]	14	27	38	0.67
2b	34[g]	0.22 (B)	$C_{19}H_{38}O_4S$	1.5	4	14	
3c	37[h]	0.18 (C)	$C_{19}H_{38}O_6S$[f,i]	0.7	2	10	
8	54[e]	0.33 (C)	$C_{20}H_{31}FO_6S$	1	23	27	1.11
23	48[j]	0.51 (D)	$C_{19}H_{38}O_5S$[f]		0.5	1	

[a] Determined on SiO_2 plates using the eluent designated in parentheses: A, $CHCl_3$-CH_3OH-HOAc (97:2:1); B, $CHCl_3$-CH_3OH-HOAc (96:3:1); C, $CHCl_3$-CH_3OH-HOAc (95:4:1); D, $CHCl_3$-CH_3OH-HOAc (8:1:1); [b] All compounds were analyzed for C and H. Analytical results are within 0.4% of the theoretical values except where noted. [c] Overall yield from ethyl 8-carboxy-12-acetoxyheptadecanoate (Scheme I). [d] Yield from thioether 2a (Scheme I). [e] Overall yield from diester 4 (Scheme II). [f] Analyzed for C, H, and S. [g] Overall yield from diester 1. [h] Yield from thioether 2b. [i] C: calcd, 57.84; found, 58.29. [j] Overall yield from diester 21 (Scheme V).

Table II

Compd	Mouse ovary PG assay, fold increase in cAMP, concn in μg/ml: 0.01	0.05	0.1	1.0	10	25	50	100	200	Lipocyte receptor binding, ng equiv to 1 ng of PGE_1
PGE_1	8	29	25	54						1
Tetrahydro-PGA_1				10	25	26	19			10
Ia				2	11	14	16	23	16	1700
3b			2	14	24	27		38		670
23						0.5		1		

The sequence **4** → **5b** → **6b** → **7** was effected as described above for preparation of **3b**. Hydrogenolytic O-debenzylation of **7** completed the synthesis of ether **8**.

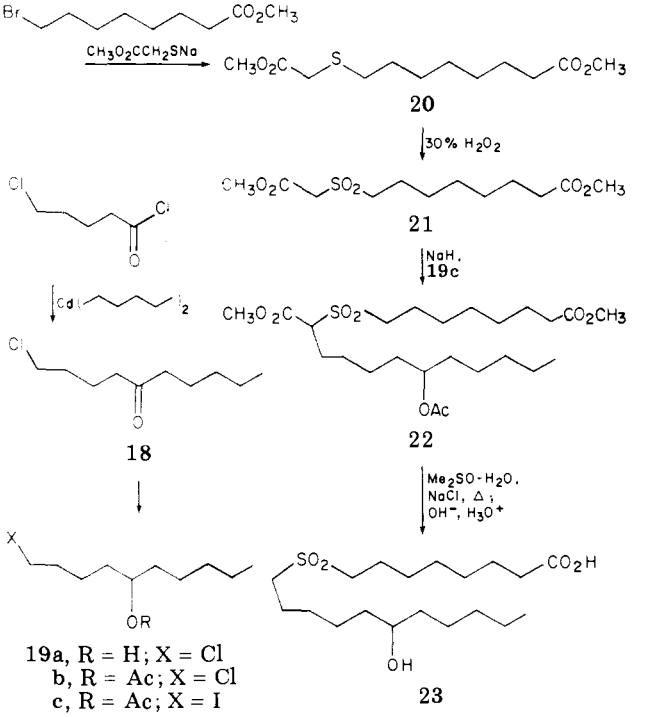
Racemic 8,12-secoprostaglandin analogue **23** was prepared by the route delineated in Scheme V. The four-step synthesis of iodide **19c** from 5-chlorovaleryl chloride was accomplished as shown in excellent overall yield (69%). The success of the key step, preparation[9] of ketone **18** via reaction of the starting acyl chloride with (di-*n*-pentyl)-cadmium, proved to be predicated upon the use of pulverized cadmium chloride rigorously dried over P_2O_5 at or above 180 °C for 10–12 h in vacuo (0.05 mm) immediately prior to use. Reduction of ketone **18** with sodium borohydride gave alcohol **19a** which was converted to acetate **19b** and thence to iodide **19c** with acetic anhydride and sodium iodide, respectively.

Conversion of methyl 7-bromoheptanoate to acid product **23** was effected via the five-step sequence, **20** → **21** → **22** → → **23**, using the reagents indicated in Scheme V.

With exception of **23**, the final products and intermediate esters are viscous oils, many of which are not amenable to purification by distillation. These compounds, generally purified by column chromatography on silica gel when required to achieve TLC homogeneity, retain solvents tenaciously. Hence, samples suitable for analysis and biological evaluation were desolvated at elevated temperatures (e.g., 100 °C) in high vacuum for extended periods. For this reason and with few exceptions, analytical data were obtained only for the final products. Structural assignments for the intermediates were confirmed by NMR and IR spectroscopy. Further evidence of their purity was provided by TLC analysis.

Biological Activity. Elevation of cAMP levels in many types of cells by the prostaglandins of the E series has been demonstrated.[10] The dose-related stimulation of cAMP formation by PGE_1 in the mouse ovary is the basis for the primary assay used in these laboratories for the detection

Scheme V



and measurement of prostaglandin-like activity.[11] In this assay, described in detail in the Experimental Section, mouse ovaries are initially incubated with [8-^{14}C]adenine to allow formation of intracellular [^{14}C]-ATP. Then, the test compound, along with the phosphodiesterase inhibitor theophylline, is added and incubation is continued. Reactions are ultimately terminated by addition of trichloroacetic acid and, subsequently, [^{14}C]-cAMP is isolated from the ovaries and measured. In this paper, results are expressed as fold increases in cAMP formation obtained

by dividing the cAMP levels in treated ovaries by those levels in untreated ovaries.

Table II records the effectiveness of 8-methylsulfonyl-12-hydroxyheptadecanoic acid (**3b**) in stimulating cAMP formation which is compared with that of PGE_1, tetrahydro-PGA_1, and 8-acetyl-12-hydroxyheptadecanoic acid (Ia), a representative compound from the first paper[1] of this series. These data indicate that sulfone **3b** raises cAMP levels markedly at reasonable pharmacological concentrations and, although less active than PGE_1 in this assay, **3b** compares favorably with tetrahydro-PGA_1 and is more active than Ia. It should be noted that 8,12-seco analogue **23** is essentially devoid of activity even at high concentrations; this result is in accord with the observed lack of activity of ricinoleic acid in this assay.[1]

Demonstration that 11,12-secoprostaglandin analogues not only express a characteristic action of the prostaglandins but are capable of interacting with prostaglandin receptors is imperative if these compounds are to be properly termed prostaglandin analogues in any biological sense. A prostaglandin receptor binding assay employing a binding fraction prepared from rat lipocytes has been devised in these laboratories.[12] In this assay, the test compound is allowed to compete with [^{3}H]-PGE_1 for binding to the receptors. Results are expressed herein as nanograms of test compound equivalent to 1 ng of cold PGE_1 in displacing [^{3}H]-PGE_1 from receptor binding sites. These data, also recorded in Table II, reveal that **3b** appears to have demonstrably greater affinity for the lipocyte PG receptor than 1a. The decreased receptor affinity in going from PGE_1 to **3b** parallels the decreased potency of **3b** toward cAMP stimulation in the mouse ovary. Likewise, no lipocyte PG receptor binding can be determined for **23**.

Having established a relationship between the activity, first of Ia and then of **3b** in comparison to the PGE series of prostaglandins, evaluation of the entire series of sulfur-containing alkanoic acids for their ability to stimulate cAMP formation and to bind to the lipocyte PG receptor was appropriate. These data are tabulated in Table I. Structure–activity relationships (SAR's) for this series will be discussed, noting those changes in activity resulting from structural manipulation of **3b**. In addition, it should be mentioned that the composition and scope of this series were rationally determined on the basis of SAR's previously described for other analogue series.[1,2] Since no meaningful correlation between stereochemistry and biological activity was observed in the acylhydroxyalkanoic acid series,[1] no attempt was made either to separate or stereospecifically elaborate the various possible diastereomers in the present series. Hence, compounds **2a,b** and **3a–c** are diastereomeric mixtures and **23** is racemic.

The oxidation state of the 8-substituent sulfur atom appears to be an important determinant of activity in both assay systems as reflected by the diminished activities of thioether 2a and sulfoxide 3a. Perhaps the increased stereochemical complexities imposed by the presence of an additional asymmetric center, i.e., inherent in the –SO– moiety, explain the greatly reduced affinity of **3a** for the lipocyte PG receptor site relative to that of 2a.

Substitution of the methylthio and methylsulfonyl moieties with the hydroxymethyl group to form *S*-(2-hydroxyethyl) derivatives **2b** and **3c**, respectively, leads to a substantial loss of activity. A possible explanation for this result involves diminution of the steric availability of the sulfur-containing group for interaction with the appropriate receptor site due to intramolecular hydrogen bonding between the hydroxyl group and the given sulfur moiety. We have previously observed this same phenomenon in the acylhydroxyalkanoic acid series (e.g., 11,12-secotetrahydro-PGA_1 is essentially devoid of activity in these assays).[13]

Table III

Compd	Human psoriatic epidermis assay, fold increase in cAMP, concn in μg/ml				
	10	25	50	100	200
PGE_1	10				
3b		2.5	3.4	3.5	2.7

Replacement of the terminal butyl group of **3b** by the 4-fluorophenoxy group, a modification that markedly increases the luteolytic potency and specificity of $PGF_{2\alpha}$,[14] proved to be detrimental to cAMP stimulant activity as reflected by ether 8. The ablation of activity resulting from preparation of **23**, the 8,12-seco analogue of **3b**, was noted earlier.

As is obvious from the preceding discussion, sulfone **3b** emerged as the key member of this series and, accordingly, has been evaluated in a variety of in vitro and in vivo assays including the human psoriatic epidermis assay developed in these laboratories and described in detail in the Experimental Section. In this assay, skin sections are removed by biopsy from human volunteers afflicted with psoriasis who have been instructed not to use medication 48 h prior to tissue acquisition. Following 1–2% lidocaine hydrochloride injection (sc), tissue sections are removed and then preincubated with [^{14}C]adenine to allow intracellular [^{14}C]-ATP to accumulate. Subsequently the test compound is added and incubation continued. Termination of reactions by addition of trichloroacetic acid is followed by work-up. Accumulated tissue [^{14}C]-cAMP levels are determined using a minor modification of published methods.[15,16] The results of this assay, tabulated in Table III, are expressed as fold increases in cAMP formation obtained by dividing the cAMP concentrations in treated psoriatic tissue slices with those levels in unmedicated tissue slices. These data (average of four experiments) demonstrate that **3b** increases cAMP formation 2.5–3.5-fold at concentrations of 25–200 μg/ml, whereas PGE_1 effects a tenfold stimulation of cAMP formation at 10 μg/ml concentration. These results are rendered more attractive when coupled with the observation (in vitro) that **3b** is not a substrate for 15-hydroxyprostaglandin dehydrogenase and, hence, is more metabolically stable than PGE_1. In view of the pronounced cAMP formation activity enumerated in the above assays, it should be noted that **3b** is not a phosphodiesterase inhibitor.

The pharmacological specificity apparently incorporated into **3b** is reflected by its lack of activity in several in vivo assays. For example, **3b** is inactive as a gastric acid antisecretory agent when administered orally to dogs at a dose of 12.3 mg/kg. Likewise, **3b** was devoid of antihypertensive activity in the spontaneously hypertensive rat when given po at doses up to 40 mg/kg.

Perhaps the most noteworthy activity displayed by **3b** is the ability to inhibit lymphocytes in vitro. For example, **3b** inhibits antigen-induced lymphocyte transformation to the extent of 88–100 and 30% at concentrations of 10 and 1 μg/ml, respectively. By comparison, PGE_1 inhibits 82% at 10 μg/ml and 60% at 5 μg/ml. Pronounced activity in this and other autoimmune related assay systems prompted selection of **3b** for evaluation in renal allograft rejection studies in rats.[17]

In conclusion, these results serve (a) to further validate our approach to the design of structurally unique compounds displaying prostaglandin-like activity, satisfactory

metabolic stability, oral efficacy, and tissue specificity and (b) to establish the applicability of the concept of carbonyl surrogation via isosteric substitution of carbon by sulfur as typified by 11,12-secoprostaglandin analogue **3b**.

Experimental Section

Chemical. Melting points were determined in open capillary tubes and are uncorrected as are boiling points. ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian A-60A spectrometer. Chemical shifts are expressed as δ values relative to Me_4Si as internal standard. IR spectra were taken on a Perkin-Elmer Infracord spectrophotometer and are reported in reciprocal centimeters.

Column chromatography was carried out on silica gel (E. Merck, 0.063–0.20 mm mesh). Thin-layer chromatography (TLC) on Analtech silica gel GF plates (250-μ thickness) was used to monitor column fractions and to establish product purity. Spots were visualized with both iodine vapor and Mineral-Light exposure.

All final products were homogeneous on TLC using the designated $CHCl_3$–CH_3OH–HOAc system (see Table I) as eluent. Satisfactory elemental analyses (within 0.4% of the theoretical analyses) were obtained for those compounds whose analyses are indicated only by the symbols of the elements. Solvents were removed in vacuo (water aspirator) using a rotary evaporator. Oily products were dried at 100 °C in vacuo (0.1–0.05 mm) for 6–12 h to remove the last traces of solvents prior to analysis and biological evaluation.

8-Methylthio-12-hydroxyheptadecanoic Acid (2a). (a) Ethyl 8-Bromo-12-acetoxyheptadecanoate (1). Br_2 (12.6 g, 0.079 mol) was added dropwise during 1 h to a stirred mixture of ethyl 8-carboxy-12-acetoxyheptadecanoate[1] (31.5 g, 0.079 mol) and red HgO (12.8 g, 0.059 mol) in CCl_4 (200 mL). After being heated at reflux for 1 h, the reaction mixture was cooled and filtered. The filtrate was washed successively with dilute HCl, water, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to a residual oil (24.5 g). Chromatography on silica gel (250 g) with $CHCl_3$ elution gave 14.4 g (42%) of **1** as a yellow oil: R_f 0.49 (homogeneous) on TLC ($CHCl_3$); NMR 0.90 (3 H, t, 17-CH_3), 2.03 (3 H, s, CH_3CO_2), 4.07 (H, m, CHBr), 4.13 (2 H, q, $CO_2CH_2CH_3$), 4.92 (H, m, CHOAc).

(b) **8-Methylthio-12-hydroxyheptadecanoic Acid (2a).** Bromide **1** (17.8 g, 0.041 mol) was added to a freshly prepared solution of sodium methylmercaptide (11.2 g, 0.16 mol) in dry CH_3OH (150 mL) maintained under N_2. The resulting solution was heated at reflux for 4 h, 10% NaOH (50 mL) was added, and reflux was continued for an additional 1 h. The cooled reaction mixture was partitioned between water and ether. Acidification of the aqueous extract with concentrated HCl provided an oil which was taken up in ether, washed with water, and dried over Na_2SO_4. Evaporation of the solvent left an oily residue (12.5 g) which was eluted from a silica gel column (250 g) with $CHCl_3$–CH_3OH (98:2) to afford **2a** as a viscous, pale yellow oil (7 g, 51%): NMR 0.90 (3 H, t, 17-CH_3), 2.07 (3 H, s, CH_3S), 3.64 (H, m, CHOH). Anal. ($C_{18}H_{36}O_3S$) C, H.

8-[(2-Hydroxyethyl)thio]-12-hydroxyheptadecanoic Acid (2b). This compound was prepared analogously to thioether **2a** beginning with bromide **1** and 2-mercaptoethanol. Chromatography on silica gel with $CHCl_3$–CH_3OH (97:3) elution gave **2b** in 34% yield as a viscous, colorless oil: NMR 0.90 (3 H, t, CH_3), 2.34 (2 H, t, CH_2CO_2H), 2.72 (2 H, t, CH_2S), 3.74 (3 H, distorted t, CH_2OH and CHOH), 5.40 (3 H, s, CO_2H and OH). Anal. ($C_{19}H_{38}O_4S$) C, H.

8-Methylsulfinyl-12-hydroxyheptadecanoic Acid (3a). A mixture of thioether **2a** (6.7 g, 0.02 mol), $NaIO_4$ (4.7 g, 0.022 mol), and NaOH (1 g, 0.025 mol) in water (80 mL) was stirred at 20 °C for 17 h and filtered. The oil which separated upon acidification of the filtrate with dilute HCl was extracted with ether. The ethereal extract was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give crude **3a** (5.8 g). Elution from silica gel (125 g) with $CHCl_3$–CH_3OH (96:4) afforded 2.2 g (32%) of **3a** as a viscous, colorless oil: NMR 2.50 (3 H, s, CH_3SO). Anal. ($C_{18}H_{36}O_4S$) C, H.

8-(2-Hydroxyethylsulfonyl)-12-hydroxyheptadecanoic Acid (3c). Oxidation of thioether **2b** as described for the preparation of sulfone **3b** (see method A below) followed by chromatography on silica gel with $CHCl_3$–CH_3OH (97:3) elution provided **3c** in 37% yield as a viscous, colorless oil: NMR 3.21 (2 H, t, J = 5 Hz, CH_2SO_2), 3.66 (H, m, CHOH), 4.14 (2 H, t, J = 5 Hz, CH_2OH), 5.52 (3 H, s, CO_2H and OH). Anal. ($C_{19}H_{38}O_6S$) H, S; C: calcd, 57.84; found, 58.29.

8-Methylsulfonyl-12-hydroxyheptadecanoic Acid (3b). Method A (Scheme I). To a stirred mixture of thioether **2a** (3 g, 9 mmol) and ammonium molybdate (0.1 g, catalyst) in *i*-PrOH (10 mL) maintained below 20 °C (ice bath cooling) was added *cautiously* 30% H_2O_2 (5 mL, 44 mmol). Stirring at 20 °C was continued for 16 h; then the reaction mixture was diluted with ice water (75 mL) and extracted with $CHCl_3$. The organic extract was washed with saturated brine (until peroxide free as determined by KI–starch paper) and dried over Na_2SO_4. Removal of the solvent left an oily residue which was applied to silica gel (50 g). Elution with benzene–dioxane–HOAc (90:30:1) provided **3b** as a viscous oil (1.85 g, 56%): NMR 2.82 (3 H, s, CH_2SO_2). Anal. ($C_{18}H_{36}O_5S$) H, S; C: calcd, 59.30; found, 58.95.

Method B (Scheme II). Dimethyl 2-(Methylthio)azelate (10). This compound was prepared analogously to thioether **2a** (without the saponification step) beginning with sodium methylmercaptide and dimethyl 2-bromoazelate;[4] **10** was obtained in 58% yield as a colorless liquid, bp 128–138 °C (0.2 mm). Anal. ($C_{12}H_{22}O_4S$) C, H.

Dimethyl 2-Methylsulfonylazelate (4). Thioether **10** was converted to sulfone **4** in 89% yield essentially by the procedure described for **3b**; crystallization of crude product, mp 47–48 °C, from ether gave an analytical sample of **4** as colorless needles, mp 50–50.5 °C. Anal. ($C_{12}H_{22}O_6S$) C, H.

Alternatively, diester **4** was prepared from methyl bromoacetate as described below.

Methyl (Methylsulfonyl)acetate (11). Methyl mercaptan(g) was passed into a stirred solution of $NaOCH_3$ (73 mg, 1.34 mmol) in dry CH_3OH (4.7 mL) for 2 min with ice bath cooling, methyl bromoacetate (205 mg, 1.34 mmol) was added, and the reaction solution was heated at reflux for 5 min. The cooled mixture was diluted with cold, half-saturated brine (15 mL) and extracted with freshly distilled pentane (7 × 15 mL). The organic extract was washed with saturated brine, dried over Na_2SO_4, and evaporated in vacuo leaving methyl (methylthio)acetate as a colorless oil.

The oil was oxidized with 30% H_2O_2 in the presence of ammonium molybdate as described for the preparation of sulfone **3b**. The reaction mixture was worked up in the usual manner to give **11** as a colorless oil (113 mg, 53%) which crystallized upon standing at room temperature: mp 60.5–61.5 °C. Recrystallization from CH_3OH afforded colorless needles: mp 61–62 °C; NMR 3.23 (3 H, s, CH_3SO_2), 3.90 (3 H, s, CO_2CH_3), 4.18 (2 H, s, CH_2). Anal. ($C_4H_8O_4S$) C, H.

Dimethyl 2-Methylsulfonylazelate (4). A mixture of β-sulfoester **11** (420 mg, 2.76 mmol) and NaH (66 mg, 2.76 mmol) in dry DMF (5 mL) was swirled and warmed (steam bath) until a homogeneous solution (H_2 evolution ceased) was obtained, methyl 7-iodoheptanoate[5] (784 mg, 2.76 mmol) was added, and the reaction mixture was stirred at 20 °C for 2 h. After heating on the steam bath for 5 min, the mixture was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo leaving **4** as a crystalline solid, mp 48–49 °C, in 91% yield which proved to be identical with an authentic sample of **4**, mmp 48–50 °C.

1-Iodo-4-acetoxynonane (12a). A mixture of 1-chloro-4-acetoxynonane[1] (35.3 g, 0.16 mol) and NaI (120 g, 0.8 mol) in acetone (350 mL) was stirred and heated at reflux in the dark for 10 h, cooled, and filtered. Collected inorganic solids were washed with acetone. Concentration of the combined filtrate and washings gave a slurry which was partitioned between ether and water. The organic layer was washed with 2% aqueous $Na_2S_2O_3$ and water, dried over Na_2SO_4, and evaporated in vacuo to give 48.7 g (98%) of **12a** as a colorless liquid: NMR 2.0 (3 H, s, CH_3CO_2), 3.18 (2 H, t, CH_2I), 4.98 (H, m, CHOAc).

(a) Methyl 8-Methoxycarbonyl-8-methylsulfonyl-12-acetoxyheptadecanoate (5a). To a stirred suspension of NaH (2.19 g, 0.091 mol) in dry DMF (100 mL) was added dropwise a solution of diester **4** (23.5 g, 0.08 mol) in DMF (60 mL). After 1 h at 20 °C, the reaction solution was cooled to 10 °C and iodide **12a** (30 g, 0.096 mol) added at such a rate so as to prevent the internal reaction temperature from exceeding 35 °C. The resulting mixture was stirred at ambient temperature for 19 h and filtered.

Collected inorganic solids were washed with ether. The combined filtrate and washings were concentrated to an oily residue which was partitioned between ether and dilute HCl. After washing with water and saturated brine, the ethereal layer was dried over $MgSO_4$. Removal of the solvent in vacuo left **5a** as a viscous oil (37.7 g, 98%): NMR 0.90 (3 H, t, 17-CH_3), 2.0 (3 H, s, CH_3CO_2), 3.0 (3 H, s, CH_3SO_2), 3.65 (3 H, s, 1-CO_2CH_3), 3.81 (3 H, s, 8-CO_2CH_3), 4.90 (H, m, CHOAc).

(b) Methyl 8-Methylsulfonyl-12-acetoxyheptadecanoate (6a). A stirred mixture of triester **5a** (36.7 g, 0.077 mol) and NaCl (4.68 g, 0.08 mol) in a solution of Me_2SO containing 1.6% H_2O (60 mL) was heated under a N_2 atmosphere in an oil bath (185 °C) for 5 h. Concentration in vacuo at 100 °C gave an oily mixture which was diluted with water. The resulting dispersion was acidified with 6 N HCl and extracted with ether. The organic layer was washed with water, dried over Na_2SO_4, and evaporated in vacuo leaving 31 g (95%) of **6a** as a viscous oil: NMR 2.82 (3 H, s, CH_3SO_2).

(c) 8-Methylsulfonyl-12-hydroxyheptadecanoic Acid (3b). A solution of diester **6a** (29.4 g, 0.07 mol) and 20% NaOH (70 mL) in CH_3OH (70 mL) was stored at 20 °C for 17 h and then concentrated in vacuo to an oily residue which was partitioned between ether and water. After an additional extraction with ether, the aqueous phase was acidified with 6 N HCl. The liberated oily acid was taken up in ether, washed with water, and dried over Na_2SO_4. Removal of the solvent left crude **3b** as a viscous oil (23.6 g, 93%) which was applied to silica gel (700 g). Elution with benzene–dioxane–HOAc (90:15:1) gave 16.5 g (65%) of **3b** as a viscous oil shown to be identical with an authentic sample (method A above) via TLC and NMR. Anal. ($C_{18}H_{36}O_5S$) C, H, S.

1-Iodo-4-benzyloxy-5-(4-fluorophenoxy)pentane (12b). (a) (4-Fluorophenoxy)acetaldehyde Diethyl Acetal (13). A solution of 4-fluorophenol (28.1 g, 0.25 mol) in dry DMF (30 mL) was added dropwise to a vigorously stirred suspension of NaH (6.24 g, 0.26 mol) in dry DMF (120 mL). After 10 min at 20 °C, bromoacetaldehyde diethyl acetal (49.3 g, 0.25 mol) was added and the resulting mixture was heated (steam bath) for 4 h. The cooled suspension was filtered and the filtrate concentrated in vacuo to provide an oily residue. Trituration of the latter with acetone (100 mL) caused additional solid to precipitate. Filtration of the resulting suspension followed by distillation of the filtrate afforded 46.7 g (82%) of **13** as a colorless liquid: bp 87 °C (0.05 mm); NMR (CCl_4) 1.17 (6 H, t, CH_3), 3.57 (2 H, q, CH_2CH_3), 3.61 (2 H, q, CH_2CH_3), 3.85 (2 H, d, J = 5 Hz, OCH_2CH), 4.68 (H, t, J = 5 Hz, CH), 6.6–7.1 (4 H, m, 4-F-C_6H_4).

(b) (4-Fluorophenoxy)acetaldehyde (14). A solution of **13** (30 g, 0.131 mol) and concentrated H_2SO_4 (0.8 mL) in 50% aqueous acetone (300 mL) was heated at reflux for 16 h, cooled, and extracted with CH_2Cl_2. The organic extract was washed with 5% $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave **14** as a colorless oil (19 g, 94%): IR (neat) 1740 cm^{-1} (CH=O); NMR (CCl_4) 4.37 (2 H, d, CH_2), 9.68 (H, t, CHO).

(c) 5-(4-Fluorophenoxy)-1-penten-4-ol (15a). To a vigorously stirred mixture of Mg turnings (4.49 g, 0.185 mol) in dry ether (50 mL) was added a solution of allyl bromide (24.2 g, 0.2 mol) and aldehyde **14** (19 g, 0.123 mol) in ether (110 mL) at such a rate as to maintain gentle reflux. After an additional 1 h at reflux, the reaction mixture was cooled in an ice bath and treated with cold 3.2 N H_2SO_4 (70 mL) with vigorous stirring and the phases were allowed to separate. The aqueous phase was extracted with ether. The combined organic extract was washed with 5% $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent left an oily residue which was distilled to give 18.6 g (77%) of **15a** as a colorless oil: bp 73 °C (0.03 mm); IR (neat) 3400 cm^{-1} (OH); NMR (CCl_4) 2.32 (2 H, m, $CHOHCH_2CH$), 2.54 (H, s, OH), 3.6–4.1 (3 H, m, OCH_2CHOH), 4.80–5.05 (H, m, $CH=CH_2$), 5.05–5.25 (H, m, $CH=CH_2$), 5.40–6.30 (H, m, $CH=CH_2$), 6.7–7.1 (4 H, m, 4-F-C_6H_4).

(d) 4-Benzyloxy-5-(4-fluorophenoxy)-1-pentene (15b). Ether **15b** was prepared in 92% yield from **15a** using essentially the same procedure described for **13**. **15b** was obtained as a colorless oil: bp 112–116 °C (0.025 mm); NMR (CCl_4) 4.57 (2 H, s, $OCH_2C_6H_5$). Anal. ($C_{18}H_{19}FO_2$) C, H.

(e) 4-Benzyloxy-5-(4-fluorophenoxy)-1-pentanol (16). A solution of boron trifluoride etherate (2.1 mL, 17 mmol) in dry THF (5 mL) was added slowly to a stirred solution of **15b** (2.86 g, 10 mmol) and $NaBH_4$ (0.47 g, 12.5 mmol) in dry THF (25 mL) cooled in an ice bath. The resulting mixture was kept at 20 °C for 15 h, then cooled to 0–5 °C, and cautiously treated with successive additions of water (2 mL), 5 N NaOH (4 mL), and 30% H_2O_2 (8 mL). The reaction mixture was stirred 30 min at 20 °C, diluted with water, and extracted with $CHCl_3$. After being dried over $MgSO_4$, the extract was evaporated in vacuo to afford 3 g (100%) of **16** as a viscous oil: IR (neat) 3400 cm^{-1} (OH); NMR (CCl_4) 1.4–1.9 (4 H, m, CH_2CH_2), 3.2–4.2 (6 H, m, CH_2OH, CHO, and CH_2O-4-F-C_6H_4), 4.58 (2 H, s, $OCH_2C_6H_5$), 6.6–7.1 (4 H, m, 4-F-C_6H_4), 7.20 (5 H, s, C_6H_5).

(f) 4-Benzyloxy-5-(4-fluorophenoxy)-1-pentanol *p*-Toluenesulfonate (17). A stirred mixture of **16** (3 g, 10 mmol) and *p*-TosCl (2.28 g, 12 mmol) in dry Py (10 mL) was kept at 10 °C for 16 h. Upon pouring the reaction mixture into ice–water, the oil which separated was taken up in ether, washed with 2 N HCl and 5% $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent in vacuo left **17** as a viscous oil (3.8 g, 83%): NMR (CCl_4) 2.35 (3 H, s, $CH_3C_6H_4$).

(g) 1-Iodo-4-benzyloxy-5-(4-fluorophenoxy)pentane (12b). Tosylate **17** was converted to **12b** in 79% yield using NaI as described for preparation of **12a**. Chromatography of the crude product on silica gel using $CHCl_3$ as eluent gave **12b** as a colorless oil: NMR (CCl_4) 3.08 (2 H, t, CH_2I).

8-Methylsulfonyl-12-hydroxy-13-(4-fluorophenoxy)tridecanoic Acid (8). (a) Methyl 8-Methylsulfonyl-8-methoxycarbonyl-12-benzyloxy-13-(4-fluorophenoxy)tridecanoate (5b). This compound, prepared analogously to triester **5a** beginning with diester **4** and iodide **12b**, was obtained in quantitative yield as a pale yellow, viscous oil: NMR (CCl_4) 2.83 (3 H, s, CH_3SO_2), 3.55 (3 H, s, 1-CO_2CH_3), 3.71 (3 H, s, 8-CO_2CH_3), 4.47 (H, d, J = 12 Hz, $OCH_2C_6H_5$), 4.70 (H, d, J = 12 Hz, $OCH_2C_6H_5$), 6.6–7.1 (4 H, m, 4-F-C_6H_4), 7.20 (5 H, s, C_6H_5).

(b) Methyl 8-Methylsulfonyl-12-benzyloxy-13-(4-fluorophenoxy)tridecanoate (6b). Decarbomethoxylation of **5b** using the procedure described for **6a** gave **6b** in 98% yield as a viscous oil: NMR (CCl_4) 3.54 (3 H, s, 1-CO_2CH_3).

(c) 8-Methylsulfonyl-12-benzyloxy-13-(4-fluorophenoxy)tridecanoic Acid (7). Ester **6b**, after saponification as described for **6a** and chromatographic purification of the crude product on silica gel with $CHCl_3$–CH_3OH (98:2) elution, afforded **7** in 61% yield as a viscous, colorless oil: NMR 10.68 (H, s, CO_2H).

(d) 8-Methylsulfonyl-12-hydroxy-13-(4-fluorophenoxy)tridecanoic Acid (8). A magnetically stirred solution of ether **7** (1.24 g, 2.43 mmol) in EtOH (100 mL) was hydrogenated at 25 °C and atmospheric pressure in the presence of 10% Pd/C (0.2 g) until H_2 uptake ceased. The catalyst was collected and washed with EtOH (2 × 25 mL). Evaporation of the combined filtrate and washings in vacuo provided 0.93 g (91%) of **8** as a colorless, viscous oil: NMR 2.82 (3 H, s, CH_3SO_2), 6.7–7.2 (4 H, m, 4-F-C_6H_4). Anal. ($C_{20}H_{31}FO_6S$) C, H.

1-Iodo-5-acetoxydecane (19c). (a) 1-Chloro-5-decanone (18). To a chilled solution (ice bath) of *n*-pentylmagnesium bromide in ether (200 mL), generated in the usual manner from 1-bromopentane (60.4 g, 0.4 mol) and Mg(0) turnings (97.3 g, 0.4 mol), was added $CdCl_2$ (39.2 g, 0.214 mol, dried in vacuo over P_2O_5 at 180 °C for 10 h *immediately prior to use*) portionwise over 5 min. The resulting flocculent slurry was heated at reflux for 45 min, benzene (140 mL) was added, ether was removed by distillation, and additional benzene (140 mL) was added. Upon removal of the last traces of ether by distillation, a solution of 5-chlorovaleryl chloride (50 g, 0.323 mol) in benzene (60 mL) was added to the warm, vigorously stirred reaction mixture over 10 min. After the ensuing exothermic reaction had subsided, the thick reaction mixture was heated at reflux for 1 h, cooled to 0–5 °C, and cautiously treated with ice water (240 mL) followed by 20% H_2SO_4 (10 mL). The phases were separated and the aqueous phase was extracted with benzene (200 mL). The combined organic extract was washed in the usual manner and dried over Na_2SO_4. Distillation of the dried extract gave 47.1 g (77%) of **18** as a colorless liquid: bp 135–138 °C (13 mm); IR (neat) 1710 cm^{-1}; NMR 0.90 (3 H, t, CH_3), 2.40 (4 H, m, CH_2COCH_2), 3.52 (2 H, t, CH_2Cl).

(b) 1-Chloro-4-decanol (19a). A solution of ketone **18** (47.1 g, 0.247 mol) in EtOH (30 mL) was added dropwise to a solution

of $NaBH_4$ (5.15 g, 0.136 mol) and NaOH (1 g, 0.025 mol) in EtOH (150 mL) cooled to 12–15 °C. After being stirred at ambient temperature for 1 h, the turbid solution was cooled to 0–5 °C, acidified with concentrated HCl (15 mL), and concentrated to a thick slurry which was partitioned between water (200 mL) and ether (200 mL). The aqueous layer was extracted with ether (4 × 100 mL). The combined organic extract was washed with water, 5% $NaHCO_3$, and saturated brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded **19a** as a colorless liquid (46.3 g, 98%): IR (neat) 3350 cm^{-1} (OH); NMR 0.90 (3 H, s, CH_3), 1.52 (H, s, OH), 3.52 (3 H, t, CH_2Cl and $CHOH$).

(c) **1-Chloro-5-acetoxydecane (19b).** A neat mixture of **19a** (46.3 g, 0.24 mol) and Ac_2O (49 g, 0.48 mol) was heated (steam bath) for 2 h. Distillation gave 52 g (93%) of **19b** as a colorless liquid: bp 143–146 °C (13 mm); IR (neat) 1745 cm^{-1} (C=O); NMR 0.90 (3 H, s, CH_3), 2.0 (3 H, s, CH_3CO_2), 3.52 (2 H, t, CH_2Cl), 4.88 (H, m, CHOAc).

(d) **1-Iodo-5-acetoxydecane (19c).** Chloride **19b** was converted to **19c** in quantitative yield using NaI as described for preparation of **12a**: NMR 3.18 (2 H, t, CH_2I).

9,9-Dioxo-9-thia-12-hydroxyeicosanoic Acid (23). (a) **Methyl 8-[(Methoxycarbonylmethyl)thio]octanoate (20).** This compound was prepared analogously to thioether **2a** (without the saponification step) beginning with sodium methoxycarbonylmethyl mercaptide and 7-bromooctanoate. **20** was obtained in 96% yield as a colorless liquid: IR (neat) 1750 cm^{-1} (C=O); NMR 2.34 (2 H, t, $CH_2CO_2CH_3$), 2.67 (2 H, t, CH_2CH_2S), 3.22 (2 H, s, $SCH_2CO_2CH_3$), 3.64 (3 H, s, $1\text{-}CO_2CH_3$), 3.73 (3 H, s, $SCH_2CO_2CH_3$).

(b) **Methyl 8-(Methoxycarbonylmethylsulfonyl)octanoate (21).** Oxidation of **20** with 30% H_2O_2 as described for the preparation of **3b** gave sulfone **21** in 36% yield as a colorless oil: bp 185–193 °C (0.05–0.075 mm); NMR 3.24 (2 H, t, $CH_2CH_2SO_2$), 3.64 (3 H, s, $1\text{-}CO_2CH_3$), 3.80 (3 H, s, $SO_2CH_2CO_2CH_3$), 3.95 (2 H, s, $SO_2CH_2CO_2CH_3$).

(c) **Methyl 9,9-Dioxo-10-methoxycarbonyl-15-acetoxyeicosanate (22).** This compound was prepared essentially by the procedure described for **5a** starting with diester **21** and iodide **19c**. Triester **22** was obtained in quantitative yield as a pale yellow oil: NMR 0.90 (3 H, t, $20\text{-}CH_3$), 2.0 (3 H, s, CH_3CO_2CH), 2.34 (2 H, t, $CH_2CH_2CO_2CH_3$), 3.64 (3 H, s, $1\text{-}CO_2CH_3$), 3.80 (3 H, s, $8\text{-}CO_2CH_3$), 4.88 (H, s, CHOAc).

(d) **9,9-Dioxo-9-thia-15-hydroxyeicosanoic Acid (23).** Triester **22** (18 g, 34.4 mmol) was decarbomethoxylated using the procedure described for **5a** to give a pale yellow oil (15.8 g) devoid of the ^1H NMR singlet at δ 3.80. The latter was saponified with KOH (7.85 g, 0.14 mol) in 90% CH_3OH (150 mL) for 22 h at 20 °C. Evaporation of the reaction solution left a residual solid which was dissolved in H_2O (100 mL). The white solid which precipitated upon acidification to the cold aqueous solution with concentrated HCl (15 mL) was collected, washed with water, and partitioned between $CHCl_3$ and 3 N HCl. The organic extract was washed with saturated brine and dried over Na_2SO_4. Removal of the solvent in vacuo afforded a solid which crystallized from ether as colorless needles (6.2 g, 48%), mp 99.5–101 °C. Recrystallization from $CHCl_3$–hexane (1:1) provided an analytical sample of **23**: mp 100–101 °C (sharp); NMR 0.90 (3 H, s, CH_3), 2.37 (2 H, t, CH_2CO_2H), 3.04 (4 H, m, $CH_2SO_2CH_2$), 3.65 (H, s, $CHOH$), 6.48 (2 H, s, OH and CO_2H). Anal. ($C_{19}H_{38}O_5S$) C, H, S.

Biological. Mouse Ovary Prostaglandin Assay.[11] 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 [8-^{14}C]adenine. The tissues were incubated 1 h at 37 °C with moderate shaking to cause a pool of intracellular [^{14}C]-ATP 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[12] 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 at 1000g for 5 min and the [^{14}C]-cAMP 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.[12] Appropriate concentrations of the test compound were incubated with 0.4 ng of [^3H]-PGE_1 and 125 μg of the rat lipocyte binding preparation for 60 min at 37 °C. The amount of [^3H]-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.

Human Psoriatic Epidermis Assay. The effects of PGE_1 and **3b** on cAMP formation in psoriatic skin slices incubated in vitro were evaluated as follows. The patients were instructed not to use medication for at least 48 h. The area selected for biopsy was washed and 3–10 cm^{-1} of 1–2% lidocaine hydrochloride was injected sc; 50–350 mg of tissue was taken with a Davol-Simon dermatome, rinsed in saline, and cut into 10–30-mg sections. The preincubation period with the [^{14}C]adenine was approximately 60 min at 22 °C and then 45 min at 37 °C; during this time intracellular [^{14}C]-ATP was accumulating. The incubation period with the test compounds was 30 min at 37 °C. Reactions were terminated by addition of TCA to 2.5%. A mixture (0.05 mL) of adenine, adenosine, AMP, ADP, ATP, and cAMP (10 mM each) was added, and the skin slices were removed and pulverized at −70 °C. The powdered tissue was returned to the acidified medium and homogenized. The homogenates were centrifuged and the supernatant fraction was analyzed for [^{14}C]-cAMP by minor modification of published methods.[15,16]

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References and Notes

(1) J. B. Bicking, C. M. Robb, R. L. Smith, E. J. Cragoe, Jr., F. A. Kuehl, Jr., and L. R. Mandel, *J. Med. Chem.*, **20**, 35 (1977).
(2) J. H. Jones, W. J. Holtz, J. B. Bicking, E. J. Cragoe, Jr., L. R. Mandel, and F. A. Kuehl, Jr., *J. Med. Chem.*, **20**, 44 (1977).
(3) During the course of this investigation, syntheses of 9-thia- and 9-dioxothiaprostaglandin E_1 were described by I. Vlattas and L. Dellanecchia, *Tetrahedron Lett.*, 4267 (1974).
(4) W. Triebs and G. Leichssenring, *Chem. Ber.*, **84**, 52 (1951).
(5) A. A. Kraerskii, I. K. Sarycheva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **32**, 3541 (1962).
(6) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).
(7) A. P. Krapcho, E. G. E. Jahngen, Jr., and A. J. Lovey, *Tetrahedron Lett.*, 1091 (1974).
(8) N. P. Gould, unpublished results.
(9) Recently, 1-chloro-4-nonanone, bp 112–113 °C (13 mm), was prepared from 4-chlorobutyryl chloride and (di-*n*-pentyl)cadmium in 56% yield using the procedure described for ketone **18** (see Experimental Section): R. L. Smith, unpublished results. This represents a considerable improvement over the Grignard procedure based on 4-chlorobutyronitrile described in ref 1.
(10) R. W. Butcher and C. E. Baird, *J. Biol. Chem.*, **243**, 1713 (1968).
(11) F. A. Kuehl, Jr., J. L. Humes, J. Tarnoff, V. J. Cirillo, and E. A. Haw, *Science*, **169**, 883 (1970).
(12) F. A. Kuehl, Jr., and J. L. Humes, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 480 (1972).
(13) R. L. Smith, J. B. Bicking, and E. J. Cragoe, Jr., unpublished observations.
(14) D. Binder, J. Bowler, E. D. Brown, N. S. Crossley, J. Hutton, M. Senior, L. Slater, P. Wilkinson, and N. C. A. Wright, *Prostaglandins*, **6** (1), 87 (1976).

(15) J. L. Humes, M. Rounbehler, and F. A. Kuehl, Jr., *Anal. Biochem.*, **32**, 210 (1969).
(16) F. A. Kuehl, Jr., J. T. Patanelli, J. Tarnoff, and J. L. Humes, *Biol. Reprod.*, **2**, 154 (1970).
(17) Preliminary results of these studies were presented by T. B. Strom, S. Washington, and C. B. Carpenter at The Sixth International Transplantation Society Congress, New York, N.Y., August 22–28, 1976.

Synthesis, Antifertility Activity, and Protein Binding Affinity of 7(8→11α)*abeo* Steroids

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A series of 7(8→11α)*abeo* steroids was synthesized by a modification of the previously described total synthesis of this class of compounds and evaluated for biological activity. In general, there was a marked reduction in the relative binding affinities of these compounds for the rabbit uterus estrogen and progestin receptor proteins. None of the compounds which were subjected to uterotropic, antiuterotropic, postcoital, progestational, antiprogestational, or antiandrogenic assays showed any significant activity.

We have previously described the synthesis of a number of 7(8→11α)*abeo*-estranes.[1] The D and L forms of this ring system differ from the natural estranes only by displacement of rings B and D, respectively; other stereochemical relationships are retained (Chart I). As such, 7(8→11α)*abeo* steroids provide an interesting probe of hydrophobic interactions in receptor binding. Here we report the synthesis, antifertility activity, and receptor binding affinity of new 7(8→11α)*abeo*-estranes and -pregnanes.

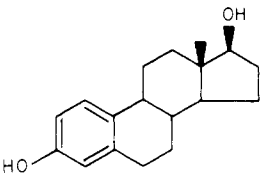
Chemistry. The synthesis of the 7(8→11α)*abeo*-estrane ring system is shown in Scheme I. Several improvements in the original procedure have been made. **2** was obtained in 78% yield, in one step rather than four, by treatment of the acid from **1** with dimethylamine hydrochloride and aqueous formaldehyde in Me_2SO.[2] Cyclization of **4** to **5** was better accomplished using anhydrous hydrogen fluoride in place of polyphosphoric acid.

Demethylation of **6** with boron tribromide in methylene chloride, followed by saponification of the 17-acetate function, gave the diol **7**. Conversion of **6** to the 17β-alcohol and oxidation with Jones reagent gave the ketone **8a**. Demethylation of the latter gave the free phenol **8b** (85%, GC), which was converted to the 17α-ethynyl derivative **9** by treatment with lithium acetylide–ethylenediamine in dioxane.

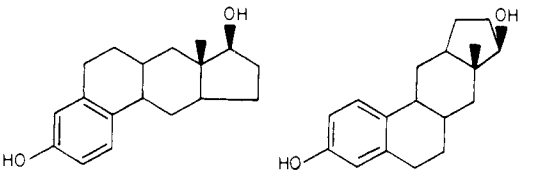
Birch reduction of **6** with lithium in ammonia and *tert*-butyl alcohol proceeded smoothly to give the 3-methoxy-$\Delta^{2,5(10)}$-diene **10** [^{1}H NMR δ 6.45 (1, t, J = 3 Hz, C-2)]. Hydrolysis of **10** with aqueous oxalic acid gave the $\Delta^{5(10)}$-3-ketone **11** (IR 1705 cm^{-1}) in 55% overall yield, while hydrolysis with dilute hydrochloric acid gave the Δ^4-3-ketone **12** (IR 1660 cm^{-1}) in 69% overall yield. Treatment of **10** with ethylene glycol and *p*-toluenesulfonic acid gave the ketal **13**. Oxidation of **13** with pyridine–chromium trioxide gave the ketone **14**. Ethynylation of **14** with freshly prepared[3] lithium acetylide in THF at −78 °C gave **15** which, upon hydrolysis with dilute hydrochloric acid, gave **16** in 42% overall yield from **6**.

The 7(8→11α)*abeo*-estrane skeleton was converted to the 19-nor-7(8→11α)*abeo*-pregnane skeleton by a standard two-step procedure.[4] The reaction of **8a** with excess ethylidenetriphenylphosphorane in Me_2SO[5] yielded **17** as a mixture of cis and trans isomers (71%). Hydroboration of **17** with borane in THF proceeded smoothly to give **18**. Birch reduction of **18** with lithium in ammonia and *tert*-butyl alcohol gave the 3-methoxy-$\Delta^{2,5(10)}$-diene **19**, which was hydrolyzed to the Δ^4-3-ketone **20** with dilute hydrochloric acid. Oxidation of **20** with chromium trioxide and sulfuric acid in DMF[5] gave the Δ^4-3,20-dione **21** in

Chart I. Stereochemical Relationships between D-Estradiol and D- and L-7(8→11α)*abeo*-Estra-1,3,5(10)-triene-3,17β-diol



D-estradiol



D- and L-7(8→11α)*abeo*-estra-1,3,5(10)-triene-3,17β-diol

Scheme I