quirements for the Doctor of Philosophy degree.
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11,12-Secoprostaglandins. 5. 8-Acetyl- or 8-(1-Hydroxyethyl)-12-hydroxy-13-aryloxytridecanoic Acids and Sulfonamide Isosteres as Inhibitors of Platelet Aggregation

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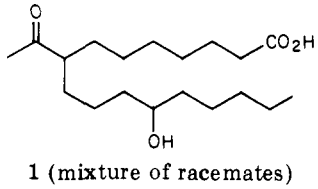
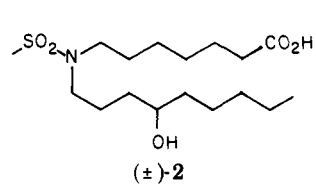
The synthesis of a series of 8-acetyl- (or 1-hydroxyethyl-) 12-hydroxy-13-aryloxytridecanoic acids and their sulfonamide isosteres is described. These compounds are formally derived from members of earlier reported series of modified secoprostaglandins by replacing the ω-butyl chain termini by substituted aryloxy groups. A number of these compounds are potent inhibitors of collagen-induced blood platelet aggregation in guinea pigs on oral administration.

The first paper[2] in this series described the chemistry and biological properties of a series of acylhydroxyalkanoic acids that represent simplified analogues of the secoprostaglandins formally derived from the natural substances by scission of the cyclopentane ring between carbon atoms 11 and 12. Certain members of this series that most closely resemble the prostaglandins in structure (e.g., 8-acetyl-12-hydroxyheptadecanoic acid, 1) have shown a



1 (mixture of racemates)



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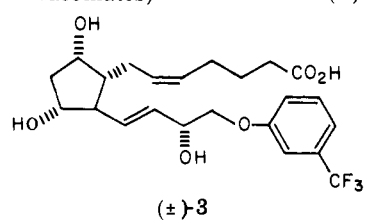

(±)-3

number of the characteristic in vitro and in vivo biological actions of the prostaglandins of the E series. Subsequently, we showed that acids in several series[3,4] isosteric with these acylhydroxyalkanoic acids display similar biological properties. The most thoroughly studied of these series is that of the sulfonamide isosteres[4] of which 7-[*N*-(4-hydroxynonyl)methanesulfonamido]heptanoic acid (**2**) is an active representative.

An important development in prostaglandin analogue research was reported in 1974 by Crossley and Walpole and co-workers of ICI Pharmaceuticals Division.[5] They found that some analogues of $PGF_{2\alpha}$ in which the terminal butyl group is replaced by an aryloxy group are markedly more selective in action than the natural substance. In particular, the potency of active compounds (e.g., **3**) in terminating pregnancy is markedly increased over that of $PGF_{2\alpha}$ while the potency in stimulating contraction of smooth muscle is diminished.

It was of obvious interest to determine the effect of a similar structural modification on the activity of our secoprostaglandins. The synthesis and biological examination of analogues of **1** and **2** that contain aryloxy groups are the subjects of this paper. An aryloxy-substituted member of the 8-methylsulfonyl-12-hydroxyalkanoic acid series [8-methylsulfonyl-12-hydroxy-13-(4-fluorophenoxy)tridecanoic acid] was described previously.[3b]

Chemistry. The method of preparation of the 8-acetyl-12-hydroxy-13-aryloxytridecanoic acids (**8a–f**) and their 8-(1-hydroxyethyl) reduction products (**9a–d**) is outlined in Scheme I. The key intermediate **6** was obtained by epoxidation with *m*-chloroperbenzoic acid of ethyl 8-acetyl-12-decenoate (**5**) prepared through a con-

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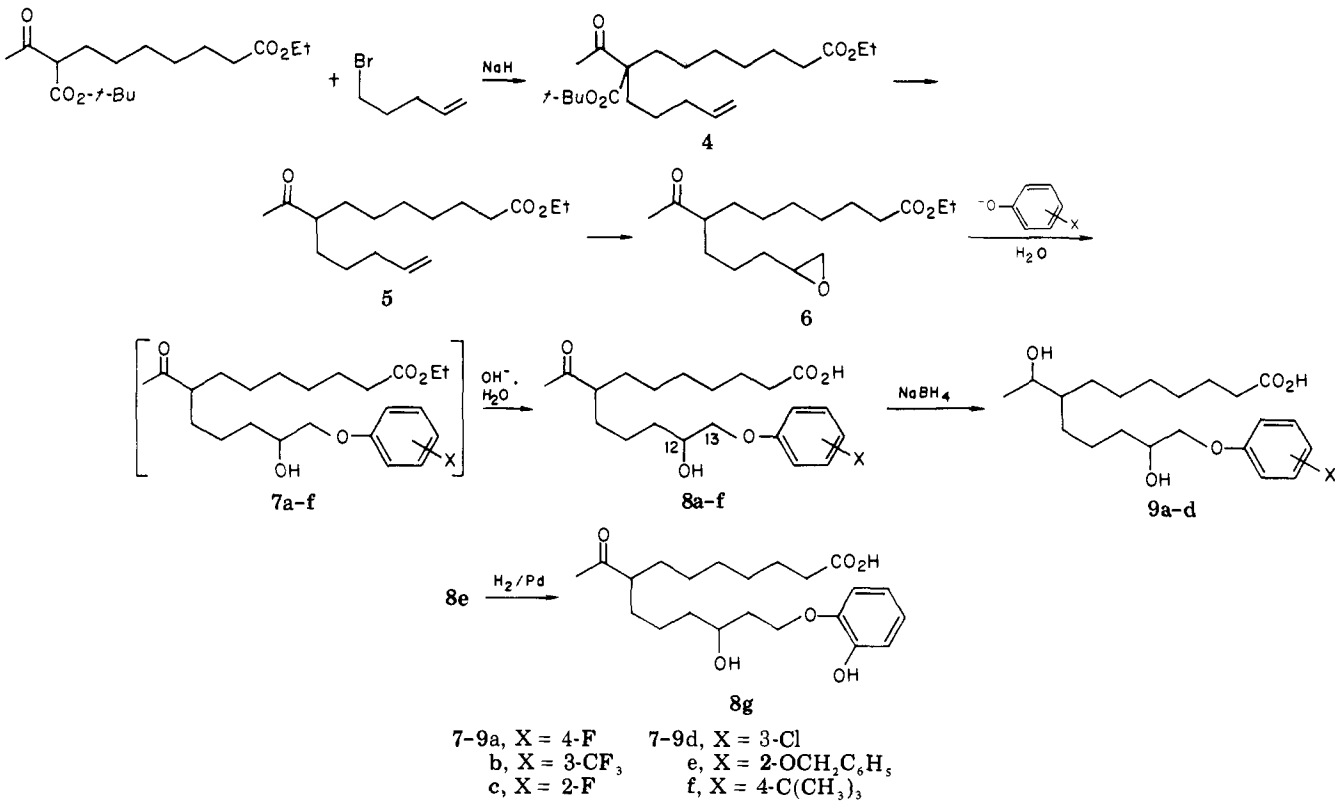
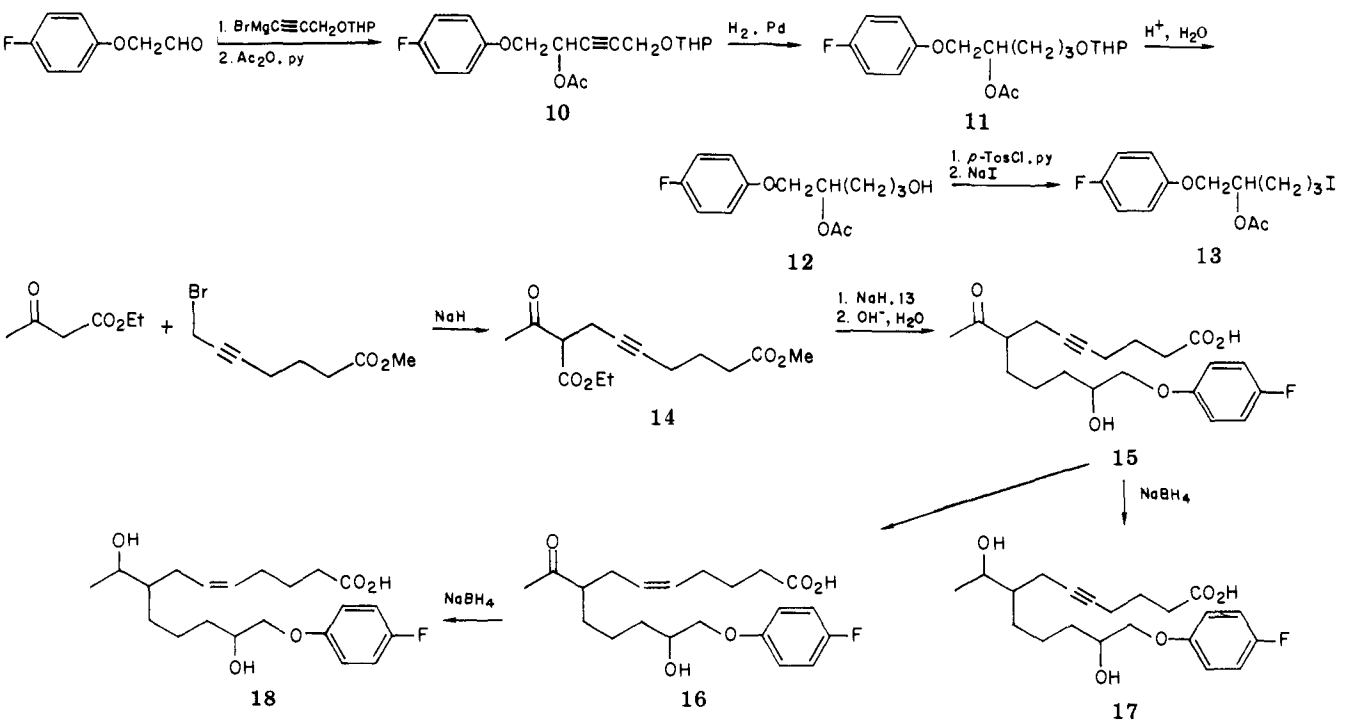
Scheme I



7-9a, X = 4-F
b, X = 3-CF_3
c, X = 2-F
7-9d, X = 3-Cl
e, X = 2-$OCH_2C_6H_5$
f, X = 4-$C(CH_3)_3$

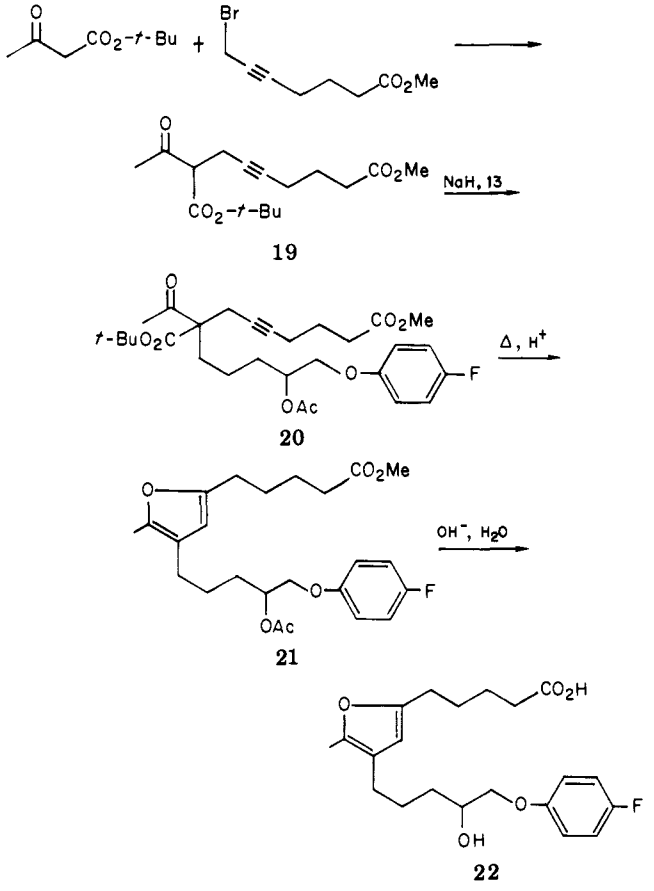
Scheme II



ventional acetoacetic ester synthesis. Epoxide **6** was treated with substituted phenoxide anions under a variety of conditions to yield the esters **7a–f** which were saponified to the target acids **8a–f**. Evidence that phenoxide anions attack epoxide **6** at the terminal carbon atom is found in the NMR spectra of hydroxy acids **8** and their 12-acetoxy analogues obtained by heating **8** with acetic anhydride. For example, the three protons on C-12 and C-13 of **8f** typically produce a multiplet centered at δ 3.90. The corresponding protons in the acetoxy analogue of **8f** produce a one-proton multiplet at δ 5.16 ($HCOCOCH_3$) and a two-proton doublet at δ 4.00 (H_2COAr). This pattern is compatible only with the indicated structure for hydroxy acids **8**.

In an approach to the introduction of the unsaturation found in the 2-series prostaglandins, the 5-*cis*-tridecenoic acids **16** and **18** were prepared as outlined in Scheme II. The cis olefinic bond was established when the intermediate 5-tridecynoic acid **15** was hydrogenated over a Lindlar catalyst. Compound **15** was prepared by a conventional synthesis involving the sequential alkylation of ethyl acetoacetate with methyl 7-bromo-5-heptynoate and

Scheme III



iodide **13**, followed by saponification and decarboxylation.

An attempt to use *tert*-butyl acetoacetate for the synthesis of **15** led to the rearrangement shown in Scheme III. The bis-alkylated acetoacetic ester **20** underwent the expected cleavage of the *tert*-butoxycarbonyl group when heated with acid but the furanpentanoic acid ester **21** was produced by a mechanism that must involve the acid-catalyzed attack of the acetyl oxygen atom on the acetylenic 6-carbon atom followed by aromatization of the five-membered ring so formed. Saponification of **21** gave the acid **22**. The structures of **21** and **22** are indicated by the ^1H and ^{13}C NMR spectra. The salient feature of the ^1H NMR spectrum of **22** is the lone proton singlet at δ 5.85 (furan 3H). The ^{13}C NMR spectrum indicates (1) the absence of a carbonyl carbon atom, (2) the absence of acetylenic carbon atoms, and (3) the presence of only ten aliphatic carbons rather than the 11 required by structure **15**.

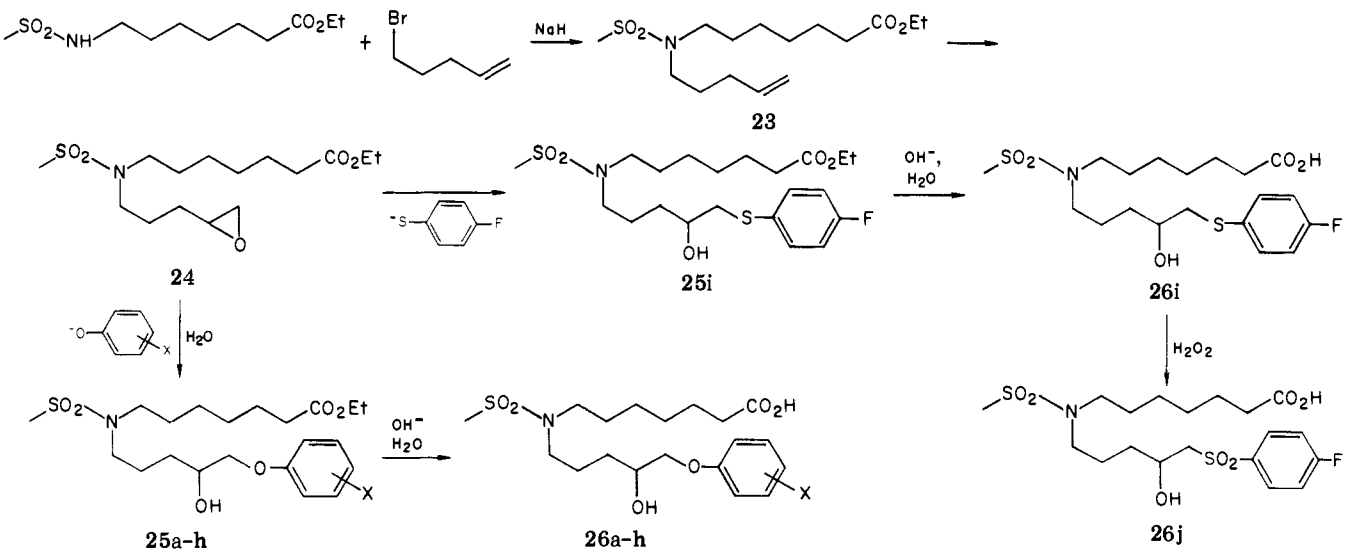
The sulfonamido acids **26** isosteric with the keto acids **8** were prepared by a reaction sequence analogous to that used for the preparation of **8** (Scheme IV) involving, in its key step, the attack of phenoxide and thiophenoxide anions on an intermediate epoxide **24**.

The previously described[4] *N*-(formylmethyl)sulfonamidoheptynoic acid ester **27** was used in the preparation of two sulfonamido acids (**29a,b**) with double bonds corresponding in position and configuration to those in the prostaglandins of the 2 series (Scheme V). The reaction of aldehyde **27** with the carbanions from the appropriate dimethyl 3-aryloxy-2-oxopropylphosphonates followed by borohydride reduction gave the intermediate esters **28a,b**. After ester hydrolysis, the cis double bonds in acids **29a,b** were established by partial hydrogenation of the triple bonds over a Lindlar catalyst.

The keto acids **8**, as obtained, must consist of four stereoisomers in equal parts; the hydroxy acids **9** probably consist of nearly equal amounts of the eight possible stereoisomers. Separation of isomers was not attempted in any case since our experience[2,4] with the separated isomers of **1** and **2** has been that biological activity is not strongly dependent on the configuration of the chiral centers in these molecules.

The product acids of these syntheses are viscous oils (except crystalline sulfone **26j**) that retain solvents tenaciously. Samples suitable for analysis and biological testing could be obtained only by being heated at 100 °C in high vacuum for long periods (4–8 h). It was not possible to obtain entirely satisfactory analyses on compounds that could not be subjected to these rigorous drying conditions. The most notable of these were the unsaturated sulfonamido acids **29a,b** which, as allylic alcohols, are subject to

Scheme IV



25,26a, X = 4-F **25,26e**, X = 4-Cl
b, X = 3-F **f**, X = 3-Cl
c, X = 2-F **g**, X = 4-CH_3
d, X = H **h**, X = 4-OCH_3

Table I. Biological Properties

compd	scheme	mouse ovary PG assay, fold increase in cAMP 10[a]	25[a]	100[a]	inhibn of platelet aggregation, guinea pig ex vivo, ED_{50}, mg/kg
8a	I		na[b]	4	0.5
8b	I		na	na	>10[c]
8e	I		na	na	>10
8f	I		na	na	10
8g	I		na	na	5.0
9a	I		na	3	1.0
9b	I		na	na	1.0
9c	I		na	na	7.5
9d	I		na	2	7.5
15	II		na	na	0.25
16	II		na	2	0.09
17	II		na	2	0.04
18	II		na	3	0.12
26a	IV	2	7	11	0.04
26b	IV		2	4	1.0
26c	IV		na	na	0.15
26d	IV		na	3	1.0
26e	IV	8	21	31	10
26f	IV		na	5	1.0
26g	IV	4	11	16	5.0
26h	IV	na	3	16	>10
26i	IV	6	14	18	6.0
26j	IV		na	3	>10
29a	V	2	4	11	0.01
29b	V		na	na	5.0
1		11	14	23	6.5
2		40	56	61	6.0
PGE_1		60[d]			0.02[e]
aspirin					4.5 (2.8–7.1)[f]

[a] Concentration in μg/mL. [b] Not significantly active. [c] The highest dose administered. [d] Complete concentration-response data have been published.[4] [e] Ip administration. PGE_1 is not active orally. [f] Values in parentheses are 95% confidence limits and indicate the variability of results in this assay.

facile dehydration. The structures of all products are supported by their NMR spectra.

Pharmacological Results and Discussion. The aryloxy secoprostaglandins were first submitted to our primary assay for the detection of prostaglandin-like activity in which the ability of test compounds to elevate cAMP levels in the mouse ovary is measured. This assay has been described earlier in detail.[2] PGE_1 produces roughly a 60-fold increase in cAMP level over baseline as a ceiling effect at a concentration of 10 μg/mL; a number of secoprostaglandins in earlier series (**1** and **2**, Table I) stimulate cAMP synthesis to a comparable degree at 10–100 times that concentration.

The aryloxy analogues show a generally diminished ability to stimulate cAMP synthesis in the mouse ovary (Table I). Among the analogues with all-carbon chains, **8**, **9**, and **15**–**18**, only the 4-fluorophenoxy-containing compounds are significantly active and then only at the highest concentration (100 μg/mL). The series of sulfonamide isosteres includes some compounds with substantial activity (**26a**,**e**,**g**–i and **29a**); all of these bear 4-position substituents, but of diverse types, on the phenoxy groups. Replacement of phenoxy by phenylthio enhances cAMP stimulatory activity (**26i** vs. **26a**); incorporation of the double bonds characteristic of the 2-series prostaglandins is without effect (**29a** vs. **26a**).

Since inactivity of a prostaglandin analogue in one assay may only be an indication of selectivity, the aryloxy secoprostaglandins were broadly screened in pharmacological assays. We have chosen to discuss in this paper the results of screening these compounds as inhibitors of collagen-induced aggregation of blood platelets in the guinea pig since this activity is the one most generally displayed by this series of compounds.

The ex vivo assay employed is described in the Experimental Section. Blood is withdrawn from guinea pigs 1 h after oral administration of the test compound. Platelet-rich plasma is prepared and treated with a collagen suspension. The rate of aggregation is measured as described and is compared with that of platelets in plasma from untreated animals. Data for the aryloxy analogues and reference compounds are collected in Table I and are expressed as doses in milligrams per kilogram of body weight required to produce a 50% decrease in rate of platelet aggregation (ED_{50}).

Collagen induces platelets in plasma to release ADP to the supernatant; the released ADP in the presence of Ca^{2+} causes aggregation.[6] Prostaglandin E_1 inhibits both the platelet-release reaction stimulated by collagen and the action of ADP. The mechanism of these effects is not known. The most widely held hypothesis is that PGE_1 mediates its influence on platelet aggregation by increasing levels of cAMP. It was not surprising, therefore, when it was discovered earlier[2,4] that the secoprostaglandins that strongly stimulate cAMP synthesis also inhibit collagen-induced platelet aggregation (**1** and **2**, Table I) with ED_{50} values in the range of 5–10 mg/kg.

A number of the aryloxy secoprostaglandins are markedly more potent than these representatives of our earlier series. Although structure–activity relationships must not be belabored in a limited series and with data from an essentially in vivo assay, a few patterns emerge. Where comparison is possible, the aryloxytridecanoic acid is less potent than its sulfonamide isostere (**8a** and **26a**). Inhibitory activity of a high order ($ED_{50} \leq 0.5$ mg/kg) is found only in compounds with a 4-fluoro substituent on the phenoxy group (with the exception of the 2-fluoro-substituted **26c**). Introduction of PG-like unsaturation increases potency significantly (compare **8a** and **16**, **26a**, and **29a**).

Structure–activity relationships of prostaglandin analogues derived from studies employing diverse cell types are notoriously inconsistent.[7] Here again, it is apparent that no correlation can be drawn between the ability of the aryloxy secoprostaglandins to inhibit platelet aggregation in the ex vivo assay and to elevate cAMP levels in the biochemical in vitro assay employed here.

The discovery that certain of the aryloxy secoprostaglandins are potent inhibitors of platelet aggregation suggests that further chemical and pharmacological study of this class of prostaglandin analogues can lead to the development of a clinically acceptable antithrombotic agent.

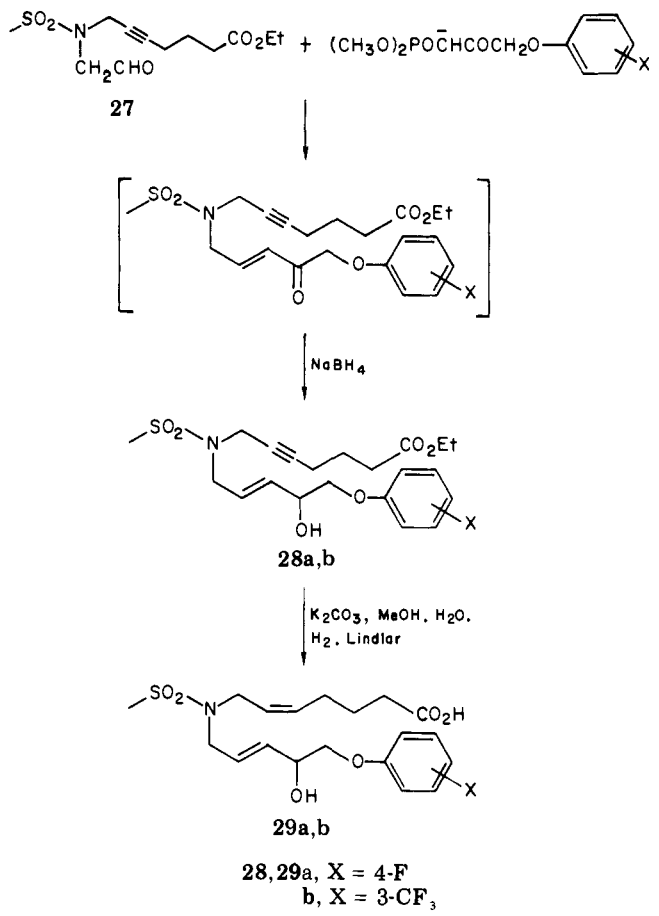
Experimental Section

Chemical. Melting and boiling points are uncorrected. ^1H NMR spectra were taken on a Varian T-60 spectrometer in $CDCl_3$. Chemical shifts are reported as parts per million relative to Me_4Si as an internal standard. ^{13}C NMR spectra were taken on a Varian XL-100 spectrometer. Mass spectra were obtained with an AEI MS 902 spectrometer.

Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.20 mm). Thin-layer chromatography (TLC) was used to monitor column fractions and to establish the purity of products. It was performed on Analtech silica gel GF plates (thickness 250 μm). Spots were located with iodine vapor. A standard solvent system was used for TLC of all acid products consisting of $CHCl_3$–CH_3OH–HOAc (95:4:1). Solvents and solvent mixtures used for TLC of esters are (A) $CHCl_3$, (B) $CHCl_3$–CH_3OH (19:1), and (C) EtOAc–hexane (3:2).

Compounds were prepared for analysis and biological testing

Scheme V



by being heated at 100 °C in oil pump vacuum for 4–6 h. 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-Acetyl-8-*tert*-butoxycarbonyl-12-tridecenoate (4). Ethyl 8-*tert*-butoxycarbonyl-9-oxodecanoate[2] (31.4 g, 0.1 mol) was added during 30 min to a stirred suspension of NaH (2.7 g, 0.11 mol) in benzene (50 mL) and DMF (50 mL). Stirring was continued for 30 min. 5-Bromo-1-pentene (16.4 g, 0.11 mol) was then added and the mixture was heated at 100 °C for 20 h. The mixture was cooled and treated with 200 mL of water. The organic layer was separated, diluted with ether, and dried over $MgSO_4$. Vacuum distillation of solvents left 39.4 g of crude product as an orange residual oil: NMR δ 1.47 [9 H, s, $(CH_3)_3C$], 2.10 (3 H, s, CH_3CO), 4.90–5.12 (2 H, m, CH_2=), 5.40–6.07 (1 H, m, CH=).

Ethyl 8-Acetyl-12-tridecenoate (5). A solution of 4 (39.4 g, 0.1 mol), *p*-toluenesulfonic acid (1.5 g), and Ac_2O (2 mL) in toluene (175 mL) was boiled under reflux for 23 h. The solution was cooled, washed with $NaHCO_3$ solution and brine, and dried over Na_2SO_4. Vacuum distillation gave 15.3 g (53%) of 5: colorless oil; bp 135–137 °C (0.1 mm). Anal. ($C_{17}H_{30}O_3$) C, H.

Ethyl 8-Acetyl-12,13-epoxytridecanoate (6). A solution of 5 (68.3 g, 0.24 mol) and *m*-chloroperbenzoic acid (45.9 g, 0.27 mol) in CH_2Cl_2 (500 mL) was kept at 26 °C for 7 h. The reaction mixture was treated with sufficient 5% aqueous NaOH solution to give a strongly alkaline aqueous phase. The organic layer was separated, washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent left 72.2 g of the crude oily product which was used in subsequent preparations. Column chromatography of 4.3 g on 70 g of silica gel with $CHCl_3$ elution gave 2.0 g of purified 6: colorless oil; R_f 0.69 on TLC (A). Anal. ($C_{17}H_{30}O_4$) C, H.

8-Acetyl-13-(4-fluorophenoxy)-12-hydroxytridecanoic Acid (8a). 4-Fluorophenol (6.5 g, 0.058 mol), followed by 6 (15.8 g, 0.053 mol), was added to a suspension of NaH (1.4 g, 0.058 mol) in benzene (30 mL) and DMF (30 mL). The mixture was stirred and heated at 90 °C for 19 h. The mixture was then cooled and treated with water (250 mL). The organic layer was taken up in ether, washed with $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The solvents were evaporated and the residual oil was chromatographed on 120 g of silica gel with 1% CH_3OH in $CHCl_3$ elution. **Ethyl 8-acetyl-13-(4-fluorophenoxy)-12-hydroxytridecanoate (7a)** was obtained in 4.6-g yield: colorless oil; R_f 0.66 on TLC (B). The ester was dissolved in a solution of NaOH (0.7 g, 0.17 mol) in water (6 mL) and CH_3OH (60 mL). The resulting solution was allowed to stand at 25 °C for 69 h. Most of the CH_3OH was removed by vacuum distillation. The residue was diluted with water and acidified with hydrochloric acid. The oily product was extracted with ether and chromatographed on 60 g of silica gel. Elution with 2% CH_3OH in $CHCl_3$ gave 2.2 g (11% overall from 6) of **8a**: yellowish viscous oil; R_f 0.40; NMR δ 2.10 (3 H, s, CH_3CO), 3.95 (3 H, m, CH_2O + CHO), 6.30 (2 H, br s, OH and COOH), 6.83 (4 H, m, aryl H). Anal. ($C_{21}H_{31}FO_5$) C, H.

8-Acetyl-12-hydroxy-13-(3-trifluoromethylphenoxy)tridecanoic Acid (8b). 3-Trifluoromethylphenol (14.6 g, 0.09 mol), followed by epoxide 6 (13.0 g, 0.0435 mol), was added to a solution of Na (1.15 g, 0.05 mol) in ethanol (60 mL). The resulting solution was held at 25 °C for 1 h and boiled under reflux for 1.5 h. Workup as in the preparation of **8a** ethyl ester gave 17.4 g of the crude ethyl ester of **8b** which was saponified as in the preparation of **8a** to yield 13.0 g of crude **8b**. Column chromatography on 260 g of silica gel with 2% CH_3OH in $CHCl_3$ elution gave 9.0 g (48% overall) of **8b**: yellow oil; R_f 0.48. Anal. ($C_{22}H_{31}F_3O_5$) C, H.

8-Acetyl-13-(2-benzyloxyphenoxy)-12-hydroxytridecanoic Acid (8e). This compound was prepared by the method described for **8b** in 52% yield: yellow oil; R_f 0.48; NMR δ 2.08 (3 H, s, CH_3CO), 5.12 (2 H, s, $PhCH_2O$). Anal. ($C_{28}H_{38}O_6$) C, H.

8-Acetyl-13-(4-*tert*-butylphenoxy)-12-hydroxytridecanoic Acid (8f). A solution of epoxide 6 (14.9 g, 0.05 mol), 4-*tert*-butylphenol (11.2 g, 0.075 mol), and NaOH (7.0 g, 0.175 mol) in water (30 mL) and THF (200 mL) was heated at 40 °C for 4 h and then boiled on the steam bath 1 h while the THF was allowed to distill. The residue was dissolved in water and extracted with ether. The aqueous layer was acidified with 5% hydrochloric acid. The oily acid that separated was taken up in ether, washed with water, and dried over $MgSO_4$. Evaporation of the ether left 10.2 g of crude **8f** which was chromatographed on 200 g of silica gel with 2% CH_3OH in $CHCl_3$ elution. There was obtained 5.1 g (24%) of **8f**: slightly yellowish oil; R_f 0.40; NMR δ 1.30 [9 H, s, $(CH_3)_3C$], 2.10 (3 H, s, CH_3CO), 3.90 (3 H, m, CH_2O + CHO). Anal. ($C_{25}H_{40}O_5$) C, H.

8-Acetyl-12-hydroxy-13-(2-hydroxyphenoxy)tridecanoic Acid (8g). A solution of **8e** (5.2 g, 0.011 mol) in EtOH (40 mL) with 1.4 g of a 5% Pd-on-charcoal catalyst was hydrogenated at atmospheric pressure and 27 °C. Uptake of H_2 ceased in 40 min with absorption of 0.012 mol. Conventional workup and column chromatography on 100 g of silica gel with 3% CH_3OH in $CHCl_3$ elution gave 2.7 g (65%) of **8g** as a colorless oil: R_f 0.37. Anal. ($C_{21}H_{32}O_6$) C, H.

13-(4-Fluorophenoxy)-12-hydroxy-8-(1-hydroxyethyl)-tridecanoic Acid (9a). Compound **8a** (15.4 g, 0.04 mol) and $NaBH_4$ (1.2 g, 0.03 mol) were dissolved in a solution of NaOH (2.0 g, 0.05 mol) in water (70 mL). The resulting solution was allowed to stand at 27 °C for 19 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 250 g of silica gel with 4% CH_3OH in $CHCl_3$ elution. There was obtained 2.6 g (17%) of **9a**: yellow oil; R_f 0.19; NMR δ 2.33 (2 H, t, CH_2CO_2H), 3.8–4.2 (4 H, m, CH_2O + CHO), 5.55 (3 H, br s, OH and CO_2H). Anal. ($C_{21}H_{33}FO_5$) C, H.

12-Hydroxy-8-(1-hydroxyethyl)-13-(4-trifluoromethylphenoxy)tridecanoic Acid (9b). This compound was prepared similarly in 45% yield by $NaBH_4$ reduction of 9a: colorless oil; R_f 0.38. Anal. ($C_{22}H_{33}F_3O_5$) C, H.

13-(2-Fluorophenoxy)-12-hydroxy-8-(1-hydroxyethyl)-tridecanoic Acid (9c). 2-Fluorophenol (8.9 g, 0.08 mol) and epoxide 6 (11.9 g, 0.04 mol) were added to a solution of Na (1.2 g, 0.052 mol) in EtOH (80 mL). The resulting solution was boiled under reflux for 1.5 h. Workup as in the preparation of **7a** gave 15.0 g of crude **ethyl 8-acetyl-13-(2-fluorophenoxy)-12-hydroxytridecanoate (7c)**: viscous orange oil. Crude **7c** was saponified as described in the preparation of **8a** to yield 13.2 g

of **8-acetyl-13-(2-fluorophenoxy)-12-hydroxytridecanoic acid (8c)**: viscous orange oil. Acid **8c** was reduced with $NaBH_4$ as described in the preparation of **9a** to yield 12.1 g of crude **9c**. Chromatography on 180 g of silica gel with 2% CH_3OH in $CHCl_3$ elution gave 5.1 g (33%) of **9c**: colorless oil; R_f 0.26. Anal. ($C_{21}H_{33}FO_5$) C, H.

13-(3-Chlorophenoxy)-12-hydroxy-8-(1-hydroxyethyl)-tridecanoic acid (9d) was prepared in 31% overall yield by the three-step process described for **9c** but beginning with the reaction of **6** with 3-chlorophenol: colorless, viscous oil; R_f 0.25. Anal. ($C_{21}H_{33}ClO_5$) H; C: calcd, 62.91; found, 63.33.

4-Acetoxy-5-(4-fluorophenoxy)-1-(2-tetrahydropyranyloxy)-2-pentyne (10). To the Grignard reagent prepared from Mg (11.7 g, 0.48 mol) and bromoethane (52.3 g, 0.48 mol) was added during 30 min a solution of 2-(2-propynyloxy)-3,4,5,6-tetrahydro-2*H*-pyran[8] (64.5 g, 0.46 mol) in THF (40 mL). The mixture was stirred at 25 °C for 1 h, then chilled in an ice bath, and treated with a solution of 4-fluorophenoxyacetaldehyde[3b] (61.9 g, 0.4 mol) in THF (60 mL). The mixture was heated on the steam bath for 1 h, then chilled in an ice bath, and treated, dropwise during 30 min, with a mixture of Ac_2O (48.9 g, 0.48 mol) and pyridine (75.0 g, 0.95 mol). The resulting mixture was then heated on the steam bath for 30 min. The mixture was poured into cold water (1200 mL). The organic layer was taken up in ether, washed with water, and dried over $MgSO_4$. The solvents were removed by vacuum distillation to leave the crude product as a yellow residual oil weighing 133 g: NMR δ 2.07 (3 H, s, CH_3COO), 4.17 (2 H, d, J = 6 Hz, CH_2OPh), 4.32 (2 H, d, J = 2 Hz, $CH_2C{\equiv}C$), 4.80 (1 H, br s, OCHO), 5.78 (1 H, m, CHOCO), 6.95 (4 H, m, aryl H).

4-Acetoxy-5-(4-fluorophenoxy)-1-(2-tetrahydropyranyloxy)pentane (11). Acetylene **10** (13.4 g, 0.04 mol) dissolved in AcOEt (100 mL) was hydrogenated at 25 °C over 0.5 g of a 5% Pd-on-charcoal catalyst in a Parr apparatus at an initial pressure of 41 lbs/in.^{2}. When 0.08 mol of hydrogen had been absorbed, the catalyst was removed by filtration and the solvent evaporated to leave 12.9 g of **11** as a light orange residual oil.

4-Acetoxy-5-(4-fluorophenoxy)-1-pentanol (12). A solution of **11** (143 g, 0.42 mol) and concentrated hydrochloric acid (3 mL) in CH_3OH (700 mL) and AcOEt (70 mL) was stirred at 25 °C for 1 h. The solution was poured into cold water (1500 mL). The organic layer was taken up in ether, washed with $NaHCO_3$ solution, water, and brine, and dried over $MgSO_4$. The solvents were evaporated and the residual oil was distilled to yield 72.6 g of **12** (63% overall from 4-fluorophenoxyacetaldehyde): light yellow oil; bp 158–160 °C (0.1 mm); NMR δ 2.08 (3 H, s, CH_3COO), 3.65 (2 H, t, $HOCH_2$), 4.00 (2 H, d, CH_2, OPh), 5.18 (1 H, m, CHOCO), 6.83 (4 H, m, aryl H). Anal. ($C_{13}H_{17}FO_4$) C, H.

4-Acetoxy-5-(4-fluorophenoxy)-1-iodopentane (13). To a solution of *p*-toluenesulfonyl chloride (42.0 g, 0.22 mol) in pyridine (100 mL) cooled in an ice bath was added **12** (49.7 g, 0.193 mol) during 40 min. The mixture was stirred at 20 °C for 2 h and then poured into 500 mL of water. The oily product was taken up in ether, washed with 2 N hydrochloric acid and water, and dried over Na_2SO_4. The solvent was distilled under vacuum to leave 73.5 g (93%) of the crude tosylate of **12** as a yellow oil. The tosylate (0.179 mol) and NaI (79.5 g, 0.53 mol) were dissolved in acetone (500 mL), and the mixture was stored at 25 °C for 18 h. The precipitated sodium tosylate was filtered off, the acetone evaporated, and the residual oil taken up in ether, washed with dilute $Na_2S_2O_3$ solution and water, and dried over Na_2SO_4. The solvent was evaporated to leave 66 g (quantitative) of **13** as a yellow oil: essentially one component on TLC, R_f 0.53 (A); NMR δ 2.07 (3 H, s, CH_3COO), 3.20 (2 H, t, CH_2I), 3.97 (2 H, d, CH_2OPh), 5.20 (1 H, m, CHO), 6.85 (4 H, m, aryl H).

Methyl 8-Ethoxycarbonyl-9-oxo-5-decynoate (14). Ethyl acetoacetate (21.5 g, 0.165 mol) was added during 30 min to a stirred suspension of NaH (4.4 g, 0.183 mol) in benzene (80 mL) and DMF (80 mL). Stirring was continued for 30 min. Methyl 7-bromo-5-heptynoate[9] (39.9 g, 0.183 mol) was added during 30 min, and the mixture was stirred at 25 °C for 1 h and at 70 °C for 1 h. The cooled mixture was treated with 400 mL of water. The organic layer was taken up in ether, washed with water, and dried over Na_2SO_4. The solvents were evaporated and the residual oil was distilled to yield 22 g (50%) of **14**: bp 140–142 °C (0.1 mm). Anal. ($C_{14}H_{20}O_5$) C, H.

Methyl 8-*tert*-butoxycarbonyl-9-oxo-5-decynoate (19) was prepared analogously from *tert*-butyl acetoacetate in 53% yield: oil; bp 145–147 °C (0.1 mm).

8-Acetyl-13-(4-fluorophenoxy)-12-hydroxy-5-tridecynoic Acid (15). Diester **14** (33.0 g, 0.123 mol) was added during 30 min to a stirred suspension of NaH (3.2 g, 0.13 mol) in benzene (60 mL) and DMF (60 mL). Iodide **13** (49.5 g, 0.135 mol) was then added and the reaction mixture was heated at 60 °C for 4 h. Workup as in the preparation of **4** gave 62.3 g of crude **methyl 12-acetoxy-8-acetyl-8-ethoxycarbonyl-13-(4-fluorophenoxy)-5-tridecynoate**. This ester was dissolved in a solution of NaOH (30.0 g, 0.75 mol) in water (200 mL) and CH_3OH (720 mL) and the resulting solution heated at 60 °C for 20 h. Standard workup gave 38.8 g of crude acid **15** which was chromatographed on 600 g of silica gel with 2% CH_3OH in $CHCl_3$ elution to yield 20.0 g (43% from **14**) of **15**: light yellow oil; R_f 0.36. Anal. ($C_{21}H_{27}FO_5$) C, H.

8-Acetyl-13-(4-fluorophenoxy)-12-hydroxy-5-*cis*-tridecenoic Acid (16). Compound **15** (10.8 g, 0.0285 mol) in EtOAc (90 mL) was hydrogenated at 1 atm and 27 °C over 1.5 g of Lindlar catalyst. Uptake of hydrogen had virtually ceased when 0.0285 mol had been absorbed in 70 min. The catalyst was removed by filtration and solvent was evaporated. The residual oil was chromatographed on 180 g of silica gel with 2% CH_3OH in $CHCl_3$ elution to obtain 8.8 g (82%) of **16**: slightly yellowish oil; R_f 0.39; NMR δ 2.12 (3 H, s, CH_3CO), 3.86 (3 H, m, CHO + CH_2O), 5.40 (2 H, m, cis-CH=CH). Anal. ($C_{21}H_{29}FO_5$) C, H.

13-(4-Fluorophenoxy)-12-hydroxy-8-(1-hydroxyethyl)-5-tridecynoic Acid (17). Compound **15** was reduced with $NaBH_4$ as described for **9a** to give **17** in 42% yield: colorless oil; R_f 0.25. Anal. ($C_{21}H_{29}FO_5$) H; C: calcd, 66.30; found, 65.81.

13-(4-Fluorophenoxy)-12-hydroxy-8-(1-hydroxyethyl)-5-*cis*-tridecenoic Acid (18). Compound **16** was similarly reduced with $NaBH_4$ to give **18** in 55% yield: colorless oil; R_f 0.32. Anal. ($C_{21}H_{31}FO_5$) C, H.

Methyl 12-Acetoxy-8-acetyl-8-*tert*-butoxycarbonyl-13-(4-fluorophenoxy)-5-tridecynoate (20). Diester **19** (14.8 g, 0.05 mol) was added during 30 min to a stirred suspension of NaH (1.4 g, 0.055 mol) in benzene (25 mL) and DMF (25 mL). Iodide **13** (22.0 g, 0.06 mol) was then added and the mixture was heated at 100 °C for 17 h. Workup as in the preparation of **4** gave 26.7 g of crude **20** as an orange residual oil.

Methyl 4-[4-Acetoxy-5-(4-fluorophenoxy)pentyl]-5-methyl-2-furanpentanoate (21). A solution of **20** (26.7 g, 0.05 mol), *p*-toluenesulfonic acid (1.0 g), and Ac_2O (1 mL) in toluene (85 mL) was boiled under reflux for 15 h. Workup as in the preparation of **5** and chromatography of the product on 330 g of silica gel with $CHCl_3$ elution gave 9.0 g of **21**: yellow oil; R_f 0.51 (A); NMR δ 2.05 (3 H, s, CH_3COO), 2.17 (3 H, s, CH_3 furan), 3.65 (3 H, s, CH_3OCO), 3.96 (2 H, d, CH_2OAr), 5.23 (1 H, m, $HCOCOCH_3$), 5.80 (1 H, s, furan 3H).

4-[5-(4-Fluorophenoxy)-4-hydroxypentyl]-5-methyl-2-furanpentanoic Acid (22). Ester **21** (9.0 g, 0.0207 mol) was saponified as described in the preparation of **8a**. The crude acid was chromatographed on 125 g of silica gel with 2% CH_3OH in $CHCl_3$ elution to yield 5.2 g (28% from **19**) of **22**: yellow oil; R_f 0.42; ^{1}H NMR δ 2.15 (3 H, s, CH_3 furan), 3.93 (3 H, m, HCO + H_2COAr), 5.85 (1 H, s, furan 3H); ^{13}C NMR 11–34 (8 aliphatic C), 70–73 (2C), 106–118 (6C), 145–164 (5C), 179 ppm (COOH). Anal. ($C_{21}H_{27}FO_5$) C, H.

Ethyl 7-[*N*-(4-Penten-1-yl)methanesulfonamido]heptanoate (23). Ethyl 7-(methanesulfonamido)heptanoate[4] (4.0 g, 0.16 mol) was added during 30 min to a stirred suspension of NaH (0.42 g, 0.0176 mol) in benzene (50 mL) and DMF (50 mL). The mixture was heated on the steam bath for 30 min, then 5-bromo-1-pentene (2.7 g, 0.018 mol) was added, and heating was continued for 20 h. Workup as in the preparation of **4** and distillation gave 3.2 g (60%) of **23**: colorless oil; bp 177–185 °C (0.1 mm). Anal. ($C_{15}H_{29}NO_4S$) H, N; C: calcd, 56.39; found, 57.01.

Ethyl 7-[*N*-(4,5-Epoxypentyl)methanesulfonamido]heptanoate (24). A solution of **23** (3.8 g, 0.012 mol) and *m*-chloroperbenzoic acid (2.2 g, 0.013 mol) in CH_2Cl_2 (50 mL) was heated at reflux for 1 h. Workup and chromatography as in the preparation of **6** gave 2.3 g (57%) of **24**: yellow oil; R_f 0.77 on TLC (B). Anal. ($C_{15}H_{29}NO_5S$) C, H, N.

Ethyl 7-[*N*-[4-Hydroxy-5-(4-fluorophenoxy)pentyl]-

methanesulfonamido]heptanoate (25a). 4-Fluorophenol (730 mg, 0.0065 mol) was added to a stirred suspension of NaH (156 mg, 0.0065 mol) in benzene (25 mL) and DMF (25 mL). After 30 min, **24** (2.2 g, 0.0065 mol) in benzene (10 mL) was added. The mixture was heated at 90 °C for 18 h and then poured into water (100 mL). The organic layer was separated, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residual oil was purified by chromatography on 50 g of silica gel with $CHCl_3$ elution. There was obtained 1.4 g (47%) of **25a**: viscous yellow oil; R_f 0.58 on TLC (B). Anal. ($C_{21}H_{34}FNO_6S$) C, H, N.

Ethyl 7-[*N*-[4-hydroxy-5-(3-fluorophenoxy)pentyl]-methanesulfonamido]heptanoate (25b) was prepared analogously from 3-fluorophenol and **24** in 25% yield: R_f 0.45 on TLC (A).

Ethyl 7-[*N*-[4-hydroxy-5-(2-fluorophenoxy)pentyl]-methanesulfonamido]heptanoate (25c) was prepared analogously from 2-fluorophenol and **24** in 54% yield: R_f 0.53 (B). Anal. ($C_{21}H_{34}FNO_6S$) H, N; C: calcd, 56.35; found, 56.80.

Ethyl 7-[*N*-(4-hydroxy-5-phenoxypentyl)methane-sulfonamido]heptanoate (25d) was prepared analogously from phenol and **24** in 28% yield: R_f 0.59 (B). Anal. ($C_{21}H_{35}NO_6S$) C, H, N.

Ethyl 7-[*N*-[4-hydroxy-5-(4-chlorophenoxy)pentyl]-methanesulfonamido]heptanoate (25e) was prepared analogously from 4-chlorophenol and **24** in 10% yield: R_f 0.49 (B).

Ethyl 7-[*N*-[4-hydroxy-5-(3-chlorophenoxy)pentyl]-methanesulfonamido]heptanoate (25f) was prepared analogously from 3-chlorophenol and **24** in 43% yield: R_f 0.59 (B). Anal. ($C_{21}H_{34}ClNO_6S$) C, H, N.

Ethyl 7-[*N*-[4-hydroxy-5-(4-fluorophenylthio)pentyl]-methanesulfonamido]heptanoate (25i) was prepared analogously from 4-fluorobenzenethiol and **24** in 54% yield: R_f 0.57 (B). Anal. ($C_{21}H_{34}FNO_5S_2$) C, H, N.

7-[*N*-[4-Hydroxy-5-(4-fluorophenoxy)pentyl]methane-sulfonamido]heptanoic Acid (26a). A solution of **25a** (4.9 g, 0.011 mol) and NaOH (1.0 g, 0.025 mol) in H_2O (13 mL) and EtOH (130 mL) was held at 26 °C for 20 h. Most of the solvent was removed by evaporation in vacuo, H_2O (150 mL) was added, and the solution was extracted with Et_2O. The aqueous layer was acidified with hydrochloric acid. The oily product was taken up in EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the solvent gave 3.7 g (84%) of **26a**: very viscous oil; R_f 0.41; NMR δ 2.37 (2 H, t, CH_2CO_2H), 2.80 (3 H, s, CH_3SO_2), 3.20 (4 H, m, CH_2N), 3.87 (3 H, m, CH_2O + CHO), 6.40 (2 H, br s, COOH + OH), 6.80 (4 H, m, aryl H). Anal. ($C_{19}H_{30}FNO_6S$) C, H, N.

7-[*N*-[4-Hydroxy-5-(3-fluorophenoxy)pentyl]methane-sulfonamido]heptanoic acid (26b) was prepared analogously from **25b** in 57% yield: R_f 0.39. Anal. ($C_{19}H_{30}FNO_6S$) H, N; C: calcd, 54.40; found, 53.93.

7-[*N*-[4-Hydroxy-5-(2-fluorophenoxy)pentyl]methane-sulfonamido]heptanoic acid (26c) was prepared analogously from **26b** in 65% yield: R_f 0.31. Anal. ($C_{19}H_{30}FNO_6S$) C, H, N.

7-[*N*-(4-Hydroxy-5-phenoxypentyl)methanesulfon-amido]heptanoic acid (26d) was prepared analogously from **25d** in 43% yield: R_f 0.42. Anal. ($C_{19}H_{31}NO_6S$) H, N; C: calcd, 56.83; found, 55.70.

7-[*N*-[4-Hydroxy-5-(4-chlorophenoxy)pentyl]methane-sulfonamido]heptanoic acid (26e) was prepared analogously from **25e** (61%): R_f 0.35. Anal. ($C_{19}H_{30}ClNO_6S$) C, N; H: calcd, 6.94; found, 7.50.

7-[*N*-[4-Hydroxy-5-(3-chlorophenoxy)pentyl]methane-sulfonamido]heptanoic acid (26f) was prepared analogously from **25f** (75%): R_f 0.26. Anal. ($C_{19}H_{30}ClNO_6S$) C, N; H: calcd, 6.94; found, 7.37.

7-[*N*-[4-Hydroxy-5-(4-fluorophenylthio)pentyl]methane-sulfonamido]heptanoic acid (26i) was prepared analogously from **25i** (94%): R_f 0.33. Anal. ($C_{19}H_{30}FNO_5S_2$) H, N; C: calcd, 52.39; found, 51.98.

7-[*N*-[4-Hydroxy-5-(4-methylphenoxy)pentyl]methane-sulfonamido]heptanoic Acid (26g). A solution of **24** (3.35 g, 0.01 mol), NaOH (1.2 g, 0.03 mol), and 4-methylphenol (2.16 g, 0.02 mol) in H_2O (10 mL) and THF (50 mL) was kept at 26 °C for 20 h. The solution was concentrated in vacuo, the residue treated with H_2O (100 mL), and the resulting mixture extracted with Et_2O. The aqueous layer was acidified with hydrochloric acid. The oily product was taken up in EtOAc, washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of solvent gave 1.2 g (29%) of **26g**: yellowish viscous oil; R_f 0.32. Anal. ($C_{20}H_{33}NO_6S$) C, N; H: calcd, 8.00; found, 7.53.

7-[*N*-[4-Hydroxy-5-(4-methoxyphenoxy)pentyl]methane-sulfonamido]heptanoic acid (26h) was prepared analogously from **24** and 4-methoxyphenol (32%): R_f 0.31. Anal. ($C_{20}H_{33}NO_7S$) C, H, N.

7-[*N*-[4-Hyroxy-5-(4-fluorophenylsulfonyl)pentyl]-methanesulfonamido]heptanoic Acid (26j). A solution of **26i** (1.9 g, 0.0044 mol), H_2O_2 (30%) (1.7 g, 0.015 mol), and $(NH_4)_2MoO_4$ (20 mg) in HOAc (10 mL) was stirred at 26 °C for 24 h. Water (100 mL) and $CHCl_3$ (100 mL) were added. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of solvent in vacuo gave a solid product. Recrystallization from EtOAc gave 0.9 g (44%) of **26j**: mp 121–122 °C. Anal. ($C_{19}H_{30}FNO_7S_2$) C, H, N.

Ethyl 7-[*N*-[4-Hydroxy-5-(4-fluorophenoxy)-*trans*-2-pentenyl]methanesulfonamido]-5-heptynoate (28a). Dimethyl [3-(4-fluorophenoxy)-2-oxopropyl]phosphonate[10] (2.0 g, 7.2 mmol) was added to a stirred suspension of NaH (240 mg, 10 mmol) in glyme (10 mL). After 30 min, ethyl 7-[*N*-(formylmethyl)-methanesulfonamido]-5-heptynoate[4] (**27**) (2.0 g, 6.9 mmol) in glyme (5 mL) was added. The solution was stirred at 26 °C for 20 h and then poured into H_2O (150 mL). The mixture was acidified with dilute H_2SO_4 and extracted with EtOAc. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was dissolved in EtOH (15 mL). The solution was cooled in an ice bath and treated with $NaBH_4$ (350 mg, excess). After 1.5 h, the solution was diluted with H_2O (150 mL), acidified with dilute H_2SO_4, and extracted with EtOAc. The organic solution was worked up as above. The residual oil was chromatographed on 45 g of silica gel with EtOAc–hexane (3:2) elution. There was obtained 1.85 g (60%) of **28a**: colorless oil; R_f 0.8 (C); NMR δ 1.1 (3 H, t, CH_3CH_2O), 2.90 (3 H, s, CH_3SO_2), 5.90 (2 H, m, CH=CH). Anal. ($C_{21}H_{28}FNO_6S$) H, N; C: calcd, 57.11; found, 55.62.

Ethyl 7-[*N*-[4-hydroxy-5-(3-trifluoromethylphenoxy)-*trans*-2-pentenyl]methanesulfonamido]-5-heptynoate (28b) was prepared analogously beginning with dimethyl [3-(3-trifluoromethylphenoxy)-2-oxopropyl]phosphonate[11] and **27** in 50% yield overall: yellow oil; R_f 0.65 (C). Anal. ($C_{22}H_{28}F_3NO_6S$) H, N; C: calcd, 53.72; found, 54.19.

7-[*N*-[4-Hydroxy-5-(4-fluorophenoxy)-*trans*-2-pente-nyl]methanesulfonamido]-*cis*-5-heptenoic Acid (29a). A mixture of **28a** (1.7 g, 3.8 mmol), K_2CO_3 (1.13 g, 8.2 mmol), MeOH (10 mL), and H_2O (0.1 mL) was stirred at 26 °C for 24 h. The mixture was poured into H_2O (100 mL). The solution was extracted with EtOAc, the aqueous layer acidified with dilute H_2SO_4, and the oily product taken up in EtOAc, washed with brine, and dried over Na_2SO_4. The solution was treated with Lindlar catalyst[12] (200 mg) and hydrogenated at 1 atm and 26 °C. H_2 (80 mL, 3.3 mmol) was absorbed before uptake ceased. The hydrogenation mixture was filtered and evaporated in vacuo to yield 1.4 g (84%) of **29a**: viscous yellow oil; NMR δ 2.80 (3 H, s, CH_3SO_2), 5.50 (2 H, m, cis-CH=CH), 5.80 (2 H, m, trans-CH=CH); mass spectrum m/e 415 (M^+), 336. Anal. ($C_{19}H_{26}FNO_6S$) N; C: calcd, 54.93; found, 53.01; H: calcd, 6.31; found, 5.60.

7-[*N*-[4-Hydroxy-5-(3-trifluoromethylphenoxy)-*trans*-2-pentenyl]methanesulfonamido]-*cis*-5-heptenoic acid (29b) was prepared similarly by hydrolysis and partial hydrogenation of **28b** in 40% yield: colorless viscous oil; NMR δ 2.85 (3 H, s, CH_3SO_2), 5.60 (2 H, m, cis-CH=CH), 5.90 (2 H, m, trans-CH=CH). Anal. ($C_{20}H_{26}FNO_6S$) H, N; C: calcd, 51.60; found, 50.28.

For mass spectral analysis, **29b** was converted to a methyl ester trifluoroacetyl derivative by treatment with CH_2N_2 and trifluoroacetic anhydride; its mass spectrum showed a weak molecular ion at m/e 575 and a prominent ion at m/e 496 corresponding to loss of CH_3SO_2.

Biological. Ex Vivo Platelet Aggregation Inhibition Assay. Male, Hartley strain guinea pigs weighing 0.6–1.1 kg were employed. Compounds were administered orally in suspension in 5 ml/kg of an EtOH–H_2O Emulphor mixture to three animals

at each of three doses; the suspending vehicle was administered to a control group of three animals. One hour after treatment, 9 mL of blood was withdrawn by cardiac puncture from each of the conscious animals. Blood samples from each drug-treated group and the control group were pooled and platelet-rich plasma (PRP) was prepared by centrifugation at 200g for 10 min. Platelet concentrations were matched among drug-treated and control PRP pools by diluting when necessary with platelet-poor plasma (prepared by centrifugation at 1400g for 10 min). Forty-five minutes after blood withdrawal, the minimal amount of bovine collagen (Worthington Biochemical, Freehold, N.J., employed as a suspension of 50 mg in 150 mL of physiological saline) required to produce a consistent aggregation of PRP from control animals was added to PRP from drug-treated animals. Aggregation was observed in a chronolog aggregometer at 37 °C and recorded as a curve that describes the rate of increase of light transmittance through PRP as aggregation proceeded. The percentage of inhibition was calculated from the formula $100 \times (\theta$ control PRP $- \theta$ drug PRP$)/\theta$ control PRP where θ stands for the rate of aggregation (curve slope).

Acknowledgment. We thank Mr. K. B. Streeter and his staff for elemental analyses, Mr. W. R. McGaughran and Dr. B. H. Arison for NMR spectra, Mr. R. E. Rhodes for mass spectra, and Miss M. Galavage for expert technical assistance with the in vitro assay.

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Synthesis and Biological Activity of Highly Active α-Aza Analogues of Luliberin

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Received May 1, 1978

Analogues of luliberin containing an α-azaamino acid in position 6, 9, or 10 (I–XIV) have been synthesized by the solution method of peptide synthesis. Two nonaza analogues, [D-Phe^6]- and [D-Ser(Bu^t)^6,des-Gly-NH$_2$^{10},Pro-ethylamide^9]luliberin, were also synthesized for comparison. The ovulation-inducing activity of the compounds was evaluated in androgen-sterilized constant-estrus rats. A combination of D-amino acid replacement in position 6 with an azaglycine residue at position 10 resulted in highly active compounds which were superior to the corresponding nonaza analogues. The most active compounds, [D-Phe^6,Azgly^{10}]-, [D-Tyr(Me)^6,Azgly^{10}]-, and [D-Ser(Bu^t)^6,-Azgly^{10}]luliberin, were about 100 times as potent as luliberin. *N*-Methylleucine substitution in position 7 in these compounds resulted in decreased activity; [D-Phe^6,MeLeu^7,Azgly^{10}]- and [D-Tyr(Me)^6,MeLeu^7,Azgly^{10}]luliberin were only 50 times as active as luliberin. The presence of either an azaproline residue in position 9, an azaphenylalanine or azaglycine residue in positions 6 and 10, or a *tert*-butyl ether protecting group on the hydroxyl group of the tyrosine residue in position 5 resulted in compounds with significantly reduced biological activity.

Following the discovery and synthesis of luliberin (luteinizing hormone-releasing hormone, <Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH$_2$) it was suggested that longer acting and more potent analogues could be useful for the treatment of infertility states in man and for the improvement of fertility in farm animals;[1,2] it was also concluded that an antagonist of luliberin might offer a new method of birth control.[3,4] Recently, additional information has indicated that luliberin agonists may also be of value as antifertility[5,6] and antitumor[7,8] agents. Thus, agonist and antagonist analogues of luliberin appear to have fairly wide therapeutic potential.

Structure–activity relationship studies on luliberin analogues have indicated that highly active analogues of luliberin can be obtained by replacing the glycine residue in position 6 with D-amino acids and the glycine amide residue in position 10 with various alkylamines.[9,10]

We reported previously the effects of replacing an amino acid residue in a biologically active molecule by an α-azaamino acid.[11] The presence of an α-aza residue in a peptide was expected to be beneficial for two reasons. Firstly, the change in the overall conformation of a molecule might lead to higher affinity for the receptor site. Secondly, the resulting compound might be more stable to enzymic degradation and, therefore, might have a longer duration of action. In addition, the absorption and transport properties of the analogues might also be altered favorably. In the case of luliberin, analogues marginally less active than the parent peptide were prepared by replacing the glycine residue in position 6 or 10 by an azaglycine residue.[11,12] When an azaglycine or azalanine change in position 6 was combined with an ethylamide substitution in position 10, the resulting compounds were two to four times as active as luliberin.[13] We have now

0022-2623/78/1821-1018$01.00/0