Fluorinated Retinoic Acids and Their Analogues. 3. Synthesis and Biological Activity of Aromatic 6-Fluoro Analogues[1,2]

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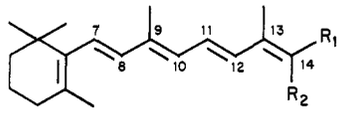
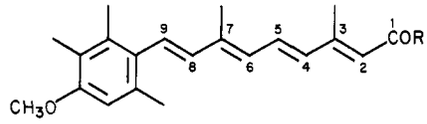
Several analogues (**15a–e**) of methyl (*E,E,Z,E*)-3,7-dimethyl-6-fluoro-9-(4-methoxy-2,3,6-trimethylphenyl)nonatetraenoate (**15f**), which had been found to cause a marked regression of chemically induced skin papillomas in mice, were prepared. Two synthetically versatile methods leading to these derivatives are described. The key intermediate, ethyl (*Z*)-2-fluoro-3-methyl-4,4-dimethoxy-2-butenoate (**8**), was elaborated to the C_{10} aldehyde ester, methyl (2*E*,4*E*,6*Z*)-3-methyl-6-fluoro-7-formyl-2,4,6-octatrienoate (**14a**), which upon Wittig condensation with the arylphosphonium salts **13a–e** gave the (2*E*,4*E*,6*Z*,8*E*)-3,7-dimethyl-6-fluoro-9-aryl-2,4,6,8-nonatetraenoates **15a–e**. Alternatively, Wittig reaction of **8** and [(4-methoxy-2,3,6-trimethylphenyl)methyl]triphenylphosphonium chloride (**13f**) gave a mixture of (*E/Z,E*)-2-fluoro-3-methyl-5-(2,3,6-trimethyl-4-methoxyphenyl)-2,4-pentadienoates **17** and **18**, which was converted to **15f**. The biological activity of these analogues and the ^1H and ^{19}F NMR spectral properties of the intermediates and final products are discussed.

Recent interest in retinoids[3] [e.g., retinoic acid (**1**) and its analogues **2–5**] as cancer chemopreventive and chemotherapeutic agents[4,5] has generated considerable effort on the chemistry of this class of compounds. In an earlier paper in this series,[6] the syntheses of analogues of **4** with fluorine substitution on the side chain were reported. In that work, substitution of a fluorine atom at C-4 or C-6 of **4** was shown to have a positive effect on the biological activity. The effect of varying the substitution pattern on the aromatic ring in these 4- and 6-fluorinated derivatives was explored next.[7] This paper describes the preparation of the 6-fluorinated aromatic retinoids **15a–e** via two synthetically versatile routes. The biological activity of these derivatives, and the ^1H and ^{19}F NMR spectral properties of the intermediates and final products are discussed.



1, R_1 = COOH; R_2 = H
2, R_1 = H; R_2 = COOH (13-*cis*-retinoic acid)



3, R = OH
4, R = OC_2H_5
5, R = NHC_2H_5

Chemistry. Wittig and Wadsworth–Emmons (Horner) reactions are principal methods which have long been used in effecting efficient and stereoselective syntheses of polyenes and vitamin A analogues.[8] Utilizing this methodology, we synthesized the C_{10} aldehyde ester **14a** via the fluorinated intermediates shown in Scheme I. This was treated with the ylides of the phosphonium salts **13a–e**[9,10] to form the desired aromatic 6-fluororetinoids **15a–e** (Scheme II).

Scheme I. Synthesis of Fluorinated Intermediates

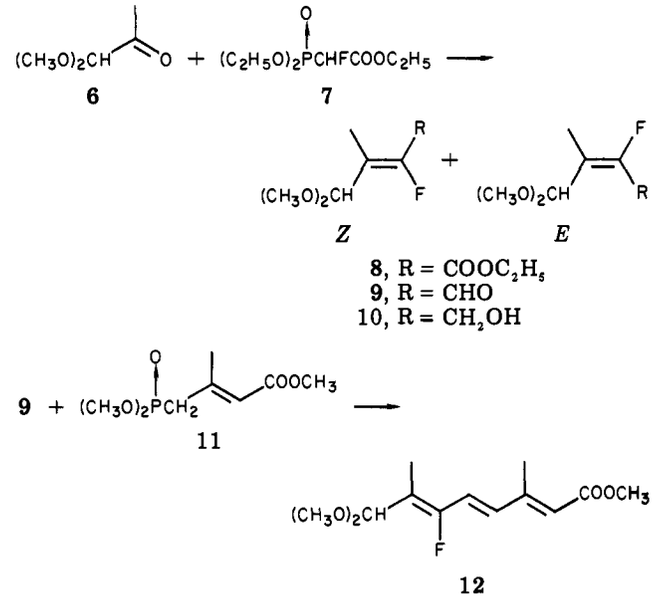


Table I. Chemical Shifts and ^1H–^{19}F Coupling Constants of C-3 Methyl Protons

compd	δ	$^4J_{H-F}$	^{19}F, [a] δ
(*E*)-**8**	1.73	4.5	
(*Z*)-**8**	1.94	3.0	
(*E*)-**9**	1.82	6.5	
(*Z*)-**9**	1.95	4.0	
(*E*)-**10**	1.56	*b*	
(*Z*)-**10**	1.56	*b*	
(*Z*)-**16**	2.03	3.2	−124.1
(*E*)-**16**	1.89	4.1	−124.1
17	2.35	2.8	−128.1
18	2.13	*b*	−123.6
19	1.90	2.9	−117.9
20	1.94	4.0	−113.9
21	2.31	3.0	−133.5

[a] Upfield from CCl_3F. [b] Obscured by overlapping peaks.

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(2) Part 2: Chan, K.-K.; Specian, A. S.; Pawson, B. A. *J. Med. Chem.* **1981**, *24*, 101–104.
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Table II. ^1H and ^{19}F NMR Signals and ^1H-^{19}F Coupling Constants for the 6-Fluoro-Substituted Compounds 14a,b and 15a-f[a]

	^1H NMR chemical shifts, δ								coupling constants, Hz				
compd[b]	C-2 H	C-3 CH_3	C-4 H	C-5 H	C-7 CH_3	C-8 H	C-9 H	aromatic H	$J_{4,5}$	$J_{8,9}$	$^4J_{H-F}$	$^3J_{H-F}$	^{19}F, δ
14a	6.02	2.35	6.93	6.69	1.82				16		2.5	24	−122.3
14b	5.97	2.35	6.85	7.19	1.87				16		3.8	26	−99.6
15a	5.91	2.35	6.57	6.77	2.04	7.35	6.68	6.84	16	16	2.5	26	−122
15b	5.90	2.34	6.55	6.75	2.03	6.88	6.61	6.63	15	16	2.5	24	−122
15c	5.88	2.33	6.60	6.78	2.04	6.95	6.70	6.62	16	16	2.5	26	−123
15d	5.93	2.36	6.59	6.79	2.05	7.40	6.61	6.95	16	16	3.0	30	−125.3
15e	5.90	2.36	6.61	6.80	2.05	6.99	6.76	6.63	15	16	2.5	26	−123.1
15f	5.93	2.36	*c*	*c*	2.04	*c*	*c*	*c*	*c*	*c*	3.0	23	−123.8

[a] NMR spectra were measured on Varian HA-100 or XL-100 spectrometers, with $CDCl_3$ as solvent and tetramethylsilane and CCl_3F as internal references for the proton and fluorine spectra, respectively. For 15d, the solvent was a mixture of $CDCl_3$ and Me_2SO-d_6. ^1H and ^{19}F NMR chemical shifts are reported as downfield from Me_4Si and upfield from CCl_3F, respectively. [b] All methoxy groups appear at δ ~3.85, and all aromatic methyl groups appear between δ 2.10 and 2.40. [c] Obscured by overlapping peaks.

Wadsworth–Emmons reaction[11] of triethyl fluorophosphonoacetate[12] (7) and pyruvaldehyde dimethyl acetal (6) afforded 8 as an *E*/*Z* mixture (65:35), which could be separated into its isomers by fractional distillation. Compound 8 proved to be a key intermediate, which was also utilized in a second route to the retinoid **15f** (see below).

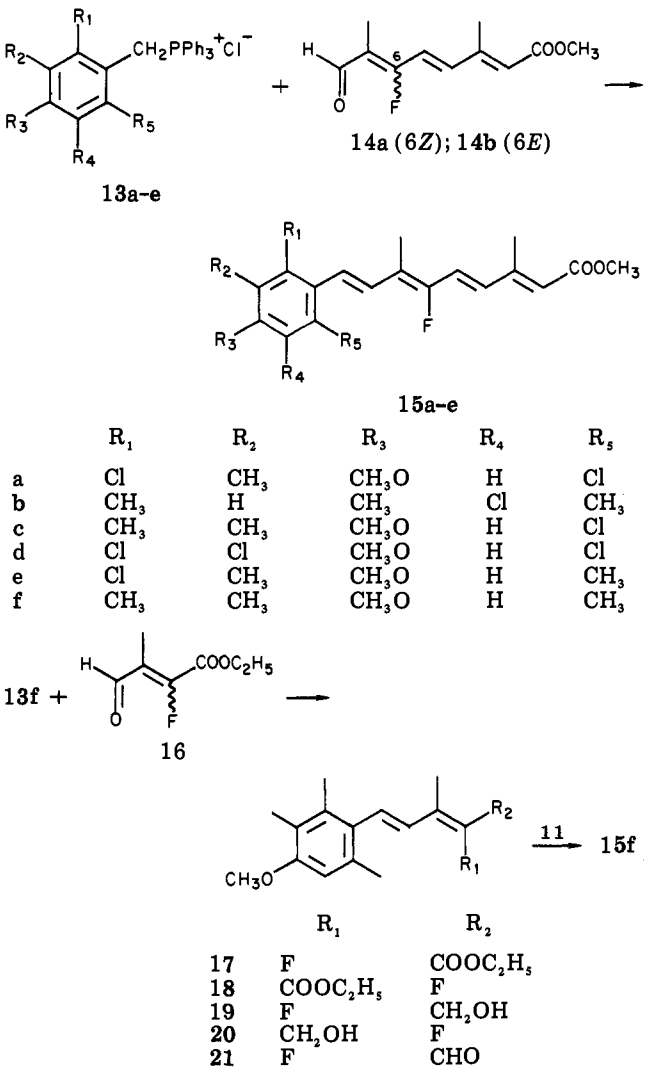
The (*Z*)-ester 8 was reduced with diisobutylaluminum hydride (*i*-Bu_2AlH) at −75 °C to obtain the (*Z*)-aldehyde **9**. At higher reaction temperatures or with different reducing agents, mixtures containing varying amounts of (*Z*)-allylic alcohol **10** were obtained. In these cases, manganese dioxide oxidation converted the mixture to (*Z*)-**9**. All attempts to reduce the *E*-isomer 8 or the mixture led to some alcohol formation and required reoxidation.

Before proceeding further, we sought to establish our assignment of stereochemistry about the double bond from the chemical shifts and coupling constants of intermediates (Table I), thereby assisting in the assignments of stereochemistry to the final retinoids. In the esters 8 and the aldehydes **9**, the methyl group at C-3 for the *Z* isomers is deshielded, as expected, by more than 0.13 ppm.[13] We also found that the four-bond coupling constants ($^4J_{^1H-^{19}F}$) (Table I) between the C-2 fluorine and C-3 methyl protons in 8 and **9** follow a pattern of $^4J_{^1H-^{19}F}$ (*E* isomer) > $^4J_{^1H-^{19}F}$ (*Z* isomer).[14]

The aldehyde (*Z*)-**9**, containing 5% (*E*)-**9**, was condensed with **11**[15] to give the acetal ester **12**, which after hydrolysis gave **14**. Purification by silica gel chromatography afforded the desired 2*E*,4*E*,6*Z*-isomer **14a** as the major component; the 2*E*,4*E*,6*E* stereochemistry was assigned to the minor isomer **14b**. These assignments were based on the large (16 Hz) trans coupling constant between the C-4 and C-5 protons observed in both compounds and the slightly greater coupling constant between the C-7 methyl protons and the C-6 fluorine atom for the 6*E* isomer **14b** (3.8 vs. 2.5 Hz).

Wittig reaction of **14a** with the ylides derived from **13a–e** afforded the 6-fluororetinoids **15a–e**, in which the major isomer had the 2*E*,4*E*,6*Z*,8*E* stereochemistry. This assignment was based largely on the ^1H NMR data (Table II). These assignments closely followed generalizations made in the 6-fluororetinal series[16] and retinal itself.[17] We also found that the coupling constant between the C-7

Scheme II. Synthesis of 6-Fluorinated Aromatic Retinoids



	R_1	R_2	R_3	R_4	R_5
a	Cl	CH_3	CH_3O	H	Cl
b	CH_3	H	CH_3	Cl	CH_3
c	CH_3	CH_3	CH_3O	H	Cl
d	Cl	Cl	CH_3O	H	Cl
e	Cl	CH_3	CH_3O	H	CH_3
f	CH_3	CH_3	CH_3O	H	CH_3

	R_1	R_2
17	F	$COOC_2H_5$
18	$COOC_2H_5$	F
19	F	CH_2OH
20	CH_2OH	F
21	F	CHO

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(12) Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *674*, 1.
(13) Pattenden, G. L.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1984. In comparison, the 3-methyl group in methyl (*E*)-3-formylcrotonate dimethyl acetal is deshielded by 0.22 ppm relative to the *Z* isomer.
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Table III. Effects of Aromatic Substitution on Toxicity and Antipapilloma Activity of Aromatic 6-Fluororetinoids

compd	hypervitaminosis A: [a] dose, (mg/kg)/day	antipapilloma act. [b] dose, (mg/kg)/day	antipapilloma act. [b] effect, %
15a	200	80	−64
15b	200	80	−48
15c	200	40	−41
15d	>200	80	−58
15e	50	20	−56
15f [c]	50	40	−79
		20	−60
		10	−35
		5	−28

[a] Retinoids were suspended in water containing 0.1% carboxymethylcellulose and 0.01% Triton X-100 and administered ip daily Monday through Friday the first week and Monday through Thursday the second week. One day after the last injection; the hypervitaminosis A symptoms, which are manifested as weight loss, redness and scaling of the skin, hair loss, changes in the mucosa of the nose and mouth, and bone fractures, were evaluated. The hypervitaminosis dose is defined as the lowest daily dose for which 2 out of 3 mice tested have one or more symptoms of hypervitaminosis A. [b] Compounds were suspended in a 0.1% aqueous solution of carboxymethylcellulose and administered ip daily five times per week for 2 weeks to groups of eight mice. [c] Reference 6.

methyl protons and the C-6 fluorine atom had a value of ≃2.5 Hz for the whole series, thus indicating the *Z* stereochemistry at the 6,7 double bond.[6] Further evidence for this assignment was obtained from the close agreement of the ^{19}F NMR chemical shifts for **15a–e** (Table II). ^{19}F NMR signals for compounds with the *E* configuration at C-6 are shifted downfield by ≃4.0 ppm.[1,6]

An alternate synthetic route to **15f** utilized the (*E*/*Z*)-aldehyde ester **16** (Scheme II). Condensation of **16** with the ylide of **13f**[9] gave mainly two isomeric esters (**17** and **18**), which were used to prepare **15f** by the method described previously.[6] Reduction of the esters **17** and **18** gave the allylic alcohols **19** and **20**, which were separated by chromatography. Pure alcohol **19** was oxidized to the aldehyde **21**. Condensation with **11** afforded the desired **15f**.[6]

Assignments of stereochemistry for **16–20** were again based on ^1H NMR (Table I). A downfield shift of the methyl protons in (*Z*)-**16** and **17** relative to (*E*)-**16** and **18** is again observed, and the four-bond coupling constants between the methyl protons and the fluorine atom remained *E* > *Z* in both (*E*)-**16** and **20** with respect to (*Z*)-**16** and **19**. An upfield shift of ~4.0 ppm was also observed in the ^{19}F NMR chemical shifts when the methyl group at C-3 was trans to the fluorine atom as in the case of **17** and **19**.

Biological Results

In Vivo Studies. Each compound described in this study was tested for its therapeutic effect on chemically induced skin papillomas in mice as described previously.[18,19] The hypervitaminosis dose, a measure of toxicity, was determined as described by Bollag.[20]

Table III lists the results obtained for **15a–e** and for **15f**, which had been reported earlier[6] to cause a marked regression of chemically induced skin papillomas in mice. Of the compounds reported, all but **15e** were found to be less toxic than **15f**. Compound **15e**, in which one of the methyl groups of **15f** was replaced by chlorine, had toxicity and antipapilloma activity comparable to **15f**, based on the limited data. The other analogues **15a–d** also appeared to have antipapilloma activities similar to **15f**, when tested at comparable fractions of the hypervitaminosis A dose.

Experimental Section

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were obtained on a Beckman IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. ^1H and ^{19}F NMR spectra were obtained on a Varian HA-100 or XL-100 spectrometer, except where noted, using tetramethylsilane and CCl_3F as internal references for proton and fluorine spectra, respectively. Mass spectra were recorded on a CEC 21-110B mass spectrometer. Thin-layer chromatography and column chromatography were conducted on silica gels F-254 and 60, respectively, from E. M. Laboratories, Elmsford, NY. A Waters 244 HPLC with two 30-cm columns of Microporsil was used to analyze the isomeric purity of products. Each of the retinoids was obtained finally as >98% of one isomer.

All glassware was washed in 1 N NH_4OH and dried before use. Tetrahydrofuran (THF) and dimethylformamide (DMF) were dried by storage over Davidson 4A molecular sieves and filtered before use.

Reducing agents, diisobutylaluminum hydride, and Vitride [sodium bis(2-methoxyethoxy)aluminum hydride] were purchased from Ethyl Corporation and Fisher Scientific, respectively. Sodium hydride (56% in oil) was washed with pentane before use.

All fluorinated retinoids and their synthetic intermediates are unstable to varying degrees with respect to air, moisture, and light. All reactions were performed under an argon atmosphere, and all synthetic products were stored at −20 °C, under argon, and protected from light.

General workup procedures involved washing all organic extracts with water and saturated sodium chloride solution, drying with magnesium sulfate ($MgSO_4$), and filtration. Workup for the *i*-Bu_2AlH reductions consisted of hydrolysis with saturated aqueous $MgSO_4$ at 30 °C for 1 h. Celite was added, and the solutions were filtered under argon.

Ethyl (*E*)- and (*Z*)-2-Fluoro-3-methyl-4,4-dimethoxy-2-butenoate (8). A solution of 30 g (0.124 mol) of **7**[12] in 50 mL of DMF was added with stirring to a cold (5 °C) suspension of 5.4 g (0.13 mol) of NaH in 75 mL of DMF. After 1 h, 16.5 g (0.14 mol) of **6** was added. The reaction was stirred at 5 °C for 2 h, poured into ice–water, and extracted with hexane. Workup and evaporation gave an oil, which was distilled to give 18.0 g (84%) of **8** containing an *E*/*Z* ratio of 35:65.

The two isomers could be separated by distillation through a Goodloe column (1 ft × 1 in.) to give (*Z*)-**8**: bp 68 °C (3 mm); IR (neat) 1730 (s, COOEt), 1667 (s, C=C), 1313 (s, C–F) cm^{-1}; UV max (EtOH) 217 nm (ε 13 480); MS, *m*/*e* 206 (M^+) 191, 186, 175, 161; NMR (CCl_4) δ 5.08 (d, J_{H-F} = 2 Hz, 1 H, C-4 H), 4.22 (q, 2 H, CH_3CH_2O), 3.31 (s, 6 H, CH_3O), 1.94 (d, J_{H-F} = 3 Hz, 3 H, C-3 CH_3), 1.33 (t, 3 H, CH_3CH_2O); ^{19}F NMR −128.2 ppm. Anal. ($C_9H_{15}FO_4$) C, H, F.

(*E*)-**8**: bp 65 °C (3 mm); IR (neat) 1730 (s, COOEt), 1675 (s, C=C), 1305 (s, C–F) cm^{-1}; UV max (EtOH) 217 nm (ε 11 170); MS, *m*/*e* 206 (M^+) 191, 177, 175, 159; NMR (CCl_4) δ 5.72 (d, J_{H-F} = 2 Hz, 1 H, C-4 H), 4.20 (q, 2 H, CH_3CH_2O), 3.28 (s, 6 H, CH_3O), 1.73 (d, J_{H-F} = 4.5 Hz, 3 H, C-3 CH_3), 1.31 (t, 3 H, CH_3CH_2O). Anal. ($C_9H_{15}FO_4$) C, H, F.

(*Z*)-4,4-Dimethoxy-2-fluoro-3-methyl-2-buten-1-al (9). A. By Direct Reduction. A solution of 15.8 g (0.077 mol) of (*Z*)-**8** in 500 mL of hexane was stirred at −75 °C while 63 mL (~0.11 mol) of *i*-Bu_2AlH was added over 30 min. Stirring was maintained at −75 °C for 0.5 h, and then the mixture was hydrolyzed in the usual manner, filtered through Celite, and evaporated to a volume of 100 mL. An analytical sample was obtained by short-path distillation [bath 60 °C (0.2 mm)]; the remainder was carried to

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the next step immediately: IR (neat) 2830 (aldehyde CH), 1693 (aldehyde C=O), 1180 (C–F) cm^{-1}; UV max (EtOH) 240 nm (ϵ 7850), 330 (25); MS, *m/e* 162 (M^+), 133, 87, 75; NMR (CCl_4, 60 MHz) δ 8.41 (d, J_{H-F} = 22 Hz, 1 H, C*H*O), 5.12 (d, $J_{H-F} \simeq$ 2 Hz, 1 H, C-4 H), 3.40 (s, 6 H, CH_3O), 1.95 (d, J_{H-F} = 4 Hz, 3 H, C-3 CH_3). Anal. ($C_7H_{11}FO_3$) C, H, F.

B. By **Oxidation of (*Z*)-10.** (*Z*)-Aldehyde **9** was also obtained by oxidation of 19.7 g (0.12 mol) of the unstable (*Z*)-alcohol **10** (see below) in 500 mL of ether and 500 mL of hexane with 100 g of MnO_2 for 14 h. Workup gave (*Z*)-**9**, which was identical in all respects with that described above.

(*Z*)-4,4-Dimethoxy-2-fluoro-3-methyl-2-buten-1-ol (10). A solution of 25 g (0.12 mol) of (*Z*)-**8** in 350 mL of ether at –70 °C was treated with 40 mL (>2 equiv) of Vitride. The mixture was warmed to –20 °C for 1 h and poured into a 5% Na_2CO_3 solution. Extraction with ether, drying ($MgSO_4$), and filtration gave a solution, which was concentrated to a volume of 100 mL and taken immediately to the next step.

An analytical sample was prepared by short-path distillation [bath 70 °C (0.2 mm)] to give pure (*Z*)-**10**: IR (neat) 3420 (OH), 1155 (C–F) cm^{-1}; MS, *m/e* 164 (M^+), 133, 101, 75; NMR (CCl_4) δ 5.03 (d, *J* = 1.5 Hz, 1 H, C-4 H), 4.11 (dd, J_{H-H} = 5, J_{H-F} = 22 Hz, 2 H, CH_2OH), 3.79 (t, *J* = 5 Hz, 1 H, OH), 3.28 (s, 6 H, 2 CH_3O), 1.56 (d, J_{H-F} = 3 Hz, 3 H, C-3 CH_3); ^{19}F NMR –119 ppm (t, J_{H-F} = 22 Hz). Anal. ($C_7H_{13}FO_3$) C, H, F.

(*E*/*Z*)-4,4-Dimethoxy-2-fluoro-3-methyl-2-buten-1-ol (10). In the same manner as described above for (*Z*)-**10**, 14.5 g (70 mmol) of (*E*/*Z*)-**8** was treated with 25 mL of Vitride (~0.18 mol) at 0 °C for 1 h. Workup as above gave an unstable oil. A pure sample was obtained by short-path distillation [bath 70 °C (0.2 mm)] to give (*E*/*Z*)-**10**. The NMR of the mixture had chemical shifts corresponding to (*Z*)-**10** (see above) and the remaining chemical shifts could be assigned to (*E*)-**10**: NMR (CCl_4, 60 MHz) δ 5.00 (d, J_{H-F} = 1.5 Hz, 1 H, C-4 H), 4.11 (d, J_{H-F} = 22 Hz, 2 H, CH_2OH), 3.30 (s, 6 H, 2 CH_3O), 2.98 (br, 1 H, OH), 1.56 (d, J_{H-F} = 4.0 Hz, 3 H, C-3 CH_3).

Methyl (2*E*,4*E*,6*Z*)-3-Methyl-6-fluoro-7-formyl-2,4,6-octatrienoate (14a). A suspension of 9.6 g (225 mmol) of NaH in 500 mL of DMF was cooled to 5 °C and 50 g (225 mmol) of **11**[15] in 100 mL of DMF was added. This was stirred at 5 °C for 2 h. A solution of 17 g (105 mmol) of (*Z*)-**9** containing 5% *E* isomer in 50 mL of DMF was added and the mixture was stirred for 2 h at 5 °C. The reaction was poured into cold water and extracted with ether. After workup, the extracts were concentrated to 600 mL. This solution was stirred at 23 °C with 200 mL of 3 N HCl for 2 h. The ether layer was separated, washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to give a yellow solid. Recrystallization (1:1 ether–hexane) gave 10 g (45%) of **14a**: mp 124–127 °C; IR (KBr) 2790 (aldehyde CH), 1662 (aldehyde C=O), 1175 (C–F) cm^{-1}; UV max (EtOH) 318 nm (ϵ 45 500); MS, *m/e* 212 (M^+), 197, 181, 153, 125. Anal. ($C_{11}H_{13}FO_3$) C, H, F.

A second component, isolated from the mother liquor by silica gel chromatography, was the 2*E*,4*E*,6*E* isomer **14b**: mp 113.5–115 °C; IR (KBr) 2795 (aldehyde CH), 1665 (aldehyde C=O), 1175 (C–F) cm^{-1}; UV max (EtOH) 312 nm (ϵ 40 700); MS, *m/e* 212 (M^+) 197, 181, 153, 125. Anal. ($C_{11}H_{13}FO_3$) C, H, F.

Methyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-6-fluoro-9-(2,6-dichloro-3-methyl-4-methoxyphenyl)-2,4,6,8-nonatetraenoate (15a). [(2,6-Dichloro-3-methyl-4-methoxyphenyl)methyl]triphenylphosphonium chloride (**13a**;[10] 3.86 g, 7.7 mmol) was suspended in 50 mL of THF. *n*-Butyllithium (2.3 M, 3.6 mL, 8.3 mmol) was added slowly at –70 °C and warmed to –30 °C for 15 min. A solution of 1.7 g (8.0 mmol) of **14a** in 5 mL of THF was added at –70 °C and then stirred at 0 °C for 30 min. The reaction was poured into water and extracted with ether–ethyl acetate (1:1). After workup, the solvent was evaporated and the yellow residue was filtered through a plug of silica gel with methylene chloride as elutant. After evaporation of the solvent, the residue was recrystallized twice from ethyl acetate–isopropyl ether (1:1) to give 1.32 g (47%) of **15a**: mp 179–181 °C; IR (KBr) 1706 (COOMe), 1170 (C–F), 955 (trans HC=CH) cm^{-1}; UV max (EtOH) 230 nm (ϵ 10 000), 360 (44 750); MS, *m/e* 398 (M^+), 378, 366, 351, 339, 331, 319, 303, 268. Anal. ($C_{20}H_{21}Cl_2FO_3$) C, H, Cl, F.

Methyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-6-fluoro-9-(2,4,6-trimethyl-5-chlorophenyl)-2,4,6,8-nonatetraenoate (15b). [(2,4,6-Trimethyl-5-chlorophenyl)methyl]triphenylphosphonium chloride (**13b**;[9] 7.5 g, 16.1 mmol) was suspended in 50 mL of THF. *n*-Butyllithium (2.3 M, 10 mL, 23 mmol) was added slowly at –30 °C and the mixture was stirred for 15 min. A solution of 3.2 g (15.1 mmol) of **14a** in 10 mL of THF was added and the mixture was stirred at 0 °C for 30 min. Workup was identical with that of **15a** (see above). The yellow solid obtained was dissolved in 150 mL of benzene, treated with 0.1 g of iodine, and allowed to stand for 5 days. After washing with 5% $Na_2S_2O_3$, drying ($MgSO_4$), and evaporation, the residue was purified by silica gel chromatography. Two recrystallizations from isopropyl ether gave 1.28 g (23%) of **15b**: mp 100–101 °C; IR (KBr) 1716 ($COOCH_3$), 1160 (C–F), 967 and 943 (trans HC=CH) cm^{-1}; UV max (EtOH) 225 nm (ϵ 12 500), 263 (6600), 352 (49 400); MS, *m/e* 362 (M^+), 347, 342, 331, 315, 253. Anal. ($C_{21}H_{24}ClFO_2$) C, H, Cl, F.

Methyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-6-fluoro-9-(2,3-dimethyl-4-methoxy-6-chlorophenyl)-2,4,6,8-nonatetraenoate (15c). [(2,3-Dimethyl-4-methoxy-6-chlorophenyl)methyl]triphenylphosphonium chloride (**13e**;[10] 4.2 g, 8.75 mmol), 1.6 g (7.5 mmol) of **14a**, 120 mL of 1,2-epoxybutane, and 80 mL of toluene were combined and heated at 110 °C for 4 h. The solvent was evaporated; the crude material was dissolved in 500 mL of hexane, washed twice with 300 mL of 60% aqueous methanol and once with 200 mL of saturated sodium chloride solution, filtered, and evaporated.

Two crystallizations from isopropyl ether gave 1.45 g (51%) of **15c**: mp 138–139 °C; IR (KBr) 1713 ($COOCH_3$), 1160 (C–F), 960 and 948 (trans HC=CH) cm^{-1}; UV max (EtOH) 361 nm (ϵ 44 700); MS, *m/e* 378 (M^+), 363, 358, 347, 331, 311. Anal. ($C_{21}H_{24}ClFO_3$) C, H, Cl, F.

Methyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-6-fluoro-9-(2,3,6-trichloro-4-methoxyphenyl)-2,4,6,8-nonatetraenoate (15d). [(2,3,6-Trichloro-4-methoxyphenyl)methyl]triphenylphosphonium chloride (**13d**;[10] 4.5 g, 8.7 mmol), 1.8 g (8.6 mmol) of **14a**, 150 mL of 1,2-epoxybutane, and 200 mL of toluene were mixed together and heated at 90–100 °C for 5.5 h. Solvent was evaporated and the crude material was passed through a short column of silica gel with methylene chloride as elutant. The solvent was evaporated and the residue was recrystallized from isopropyl ether–ethyl acetate (4:1) to give 1.4 g (40%) of **15d**: mp 186–187 °C; IR (KBr) 1703 ($COOCH_3$), 1150 (C–F), 958 (trans HC=CH) cm^{-1}; UV max (EtOH) 209 nm (ϵ 29 800), 359 (47 300); MS, *m/e* 418 (M^+), 398, 359, 223, 195. Anal. ($C_{19}H_{18}Cl_3FO_3$) C, H, Cl, F.

Methyl (2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-6-fluoro-9-(2,5-dimethyl-4-methoxy-6-chlorophenyl)-2,4,6,8-nonatetraenoate (15e). [(2,5-Dimethyl-4-methoxy-6-chlorophenyl)methyl]triphenylphosphonium chloride (**13e**;[10] 4.1 g, 8.54 mmol), 1.8 g (8.5 mmol) of **14a**, 75 mL of toluene, and 75 mL of 1,2-epoxybutane were mixed together and heated to 80–90 °C for 15 h. The solvent was evaporated and the residue was filtered through a short column of silica gel with methylene chloride as elutant. The resulting product was recrystallized from isopropyl ether to give 1.25 g (80%) of **15e**: mp 138–139 °C; IR (KBr) 1710 (s, $COOCH_3$), 1120 (s, C–F), 970 (s) and 960 (m) (trans HC=CH) cm^{-1}; UV max (EtOH), 363 nm (ϵ 43 500); MS, *m/e* 378 (M^+), 359, 332, 320, 284. Anal. ($C_{21}H_{24}ClFO_3$) C, H, Cl, F.

Ethyl (*E*/*Z*)-2-Fluoro-3-formyl-2-butenoate (16). A solution of 15 g (73 mmol) of (*E*/*Z*)-**8** in 200 mL of hexane was stirred with 100 mL of 3 N HCl at 23 °C for 0.5 h. The organic phase was separated, washed twice, dried, and evaporated. The residue was distilled to give 10 g (85%) of (*E*/*Z*)-**16**: bp 70–75 °C (0.1 mm); NMR (CCl_4) for (*E*)-**16** δ 10.29 (s, 1 H, C*H*O), 4.37 (q, 2 H, COOCH_2CH$_3$), 1.89 (d, J_{H-F} = 4.1 Hz, 3 H, C-3 CH_3), 1.39 (t, 3 H, COOCH$_2$CH_3); NMR (CCl_4) for (*Z*)-**16** δ 10.53 (d, J_{H-F} = 1 Hz, 1 H, C*H*O), 2.03 (d, J_{H-F} = 3.2 Hz, 3 H, C-3 CH_3); ^{19}F NMR –124.1 ppm for both isomers. A semicarbazone derivative was prepared for analysis. Anal. ($C_8H_{12}FN_3O_3$) C, H, N, F.

(*E*/*Z*,*E*)-2-Fluoro-3-methyl-5-(2,3,6-trimethyl-4-methoxyphenyl)-2,4-pentadienoate (17 and 18). A suspension of 23.4 g (50 mmol) of [(2,3,6-trimethyl-4-methoxyphenyl)-methyl]triphenylphosphonium chloride (**13f**)[9] in 100 mL of THF was cooled to –70 °C and treated with 22 mL (2.5 M, 55 mmol) of *n*-butyllithium in hexane. The temperature was raised to –30 °C for 0.5 h. At –70 °C, a solution of 8 g (50 mmol) of **16** in 25 mL of THF was added and the reaction was stirred at 0 °C for 1 h. The reaction was poured into water and extracted with ether, and the ether layer was washed twice with water, dried, and

evaporated to give a crude solid. This was chromatographed on silica gel to give 12 g (78%) of 17 and 18.

NMR indicated two major isomers, (2Z,4E)-17 and (2E,4E)-18, in a 4:1 ratio, respectively: ^{1}H NMR ($CDCl_3$) for 17 δ 6.95 (d, J = 15 Hz, 1 H, C-5 H), 6.72 (dd, J_{H-F} = 1 Hz, J_{H-H} = 15 Hz, 1 H, C-4 H), 6.58 (s, 1 H, aromatic H), 4.29 (q, 2 H, $COOCH_2CH_3$), 3.78 (s, 3 H, OCH_3), 2.35 (d, J_{H-F} = 2.8 Hz, 3 H, C-3 CH_3), 2.28, 2.23, and 2.13 (singlets, 9 H, 3 CH_3), 1.35 (t, 3 H, $COOCH_2CH_3$); ^{19}F NMR −128.1; ^{1}H NMR ($CDCl_3$) for 18 δ 7.46 (dd, J_{H-F} = 1.5 Hz, J_{H-H} = 18 Hz, 1 H, C-4 H), 6.92 (d, J = 18 Hz, 1 H, C-5 H), 6.55 (s, 1 H, aromatic), 4.29 (q, 2 H, $COOCH_2CH_3$), 2.28, 2.23, and 2.13 (singlets, 9 H, 3 CH_3), 2.13 (3 H, C-3 CH_3); ^{19}F NMR −123.6 ppm. Anal. ($C_{18}H_{23}FO_3$) C, H, F.

(2Z,4E)- and (2E,4E)-2-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadien-1-ol (19 and 20). The ester mixture 17 and 18 (8 g, 26 mmol) was dissolved in 150 mL of ether and reduced with i-Bu_2AlH (see procedure above for **9**). The resulting mixture of isomers was separated by silica gel chromatography. The major component proved to be (2Z,4E)-**19**: mp 65–68 °C; ^{1}H NMR ($CDCl_3$) δ 6.71 (dd, J_{H-F} = 1 Hz, J_{H-H} = 16 Hz, 1 H, C-4 H), 6.54 (d, J = 16 Hz, 1 H, C-5 H), 4.36 (d, J_{H-F} = 22 Hz, 2 H, CH_2OH), 3.78 (s, 3 H, CH_3O), 2.27, 2.21, and 2.13 (singlets, 9 H, 3 CH_3), 1.90 (d, J_{H-F} = 2.9 Hz, 3 H, C-3 CH_3); ^{19}F NMR −117.9 ppm (t, J_{H-F} = 22 Hz). Anal. ($C_{16}H_{21}FO_2$) C, H, F.

The minor compound, (2E,4E)-**20**: ^{1}H NMR ($CDCl_3$) δ 6.63 (d, J = 16 Hz, C-5 H), 6.56 (s, 1 H, aromatic), 6.25 (dd, J_{H-H} = 16 Hz, J_{H-F} = 2 Hz, 1 H, C-4 H), 4.33 (d, J_{H-F} = 23 Hz, 2 H, CH_2OH), 3.76 (s, 3 H, OCH_3), 2.24, 2.18, and 2.11 (singlets, 9 H, 3 CH_3), 1.94 (d, J_{H-F} = 4 Hz, 3 H, C-3 CH_3). This is in agreement with that previously reported for **20**.[6]

(2Z,4E)-2-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadien-1-al (21). A solution of 5 g (16 mmol) of **19** in 50 mL of ether was added to a suspension of 30 g of manganese dioxide in 400 mL of hexane. After 14 h, the mixture was filtered and the filtrate was evaporated to give a yellow solid. Recrystallization (ether) gave 4.1 g (82%) of **21**: NMR ($CDCl_3$) δ 9.83 (d, J_{H-F} = 16.5 Hz, 1 H, CHO), 7.13 (d, J = 16 Hz, 1 H, C-5 H), 6.79 (dd, J_{H-F} = 1.5 Hz, J_{H-H} = 16 Hz, 1 H, C-4 H), 6.58 (s, 1 H, aromatic), 3.78 (s, 3 H, CH_3O), 2.31 (d, 3 H, C-3 CH_3), 2.30, 2.23, and 2.13 (singlets, 9 H, 3 CH_3); ^{19}F NMR −133.5 ppm (d, J_{H-F} = 16.5 Hz). Anal. ($C_{16}H_{19}FO_2$) C, H, F.

Methyl (2E,4E,6Z,8E)-3,7-Dimethyl-6-fluoro-9-(2,3,6-trimethyl-4-methoxyphenyl)-2,4,6,8-nonatetraenoate (15f). A solution of 3 g (11 mmol) of **21** in 10 mL of dry DMF was added to the anion prepared from 3.5 g (13 mmol) of **11**[15] and 500 mg (12 mmol) of NaH in 15 mL of DMF at 0 °C. Workup as described[6] and silica gel chromatography provided 2 g (50%) of **15f**, which was identical in all respects with that previously reported.[6]

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1-(Alkylamino)isochromans: Hypotensives with Peripheral and Central Activities

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A series of 1-[1-(3,4-dihydro-6,7-dimethoxy-1*H*-2-benzopyran-1-yl)alkyl]-4-arylpiperazines that shows hypotensive activity in the conscious rat has been investigated. Structure–activity relationships are described. A typical example that was investigated in greater detail is 1-[2-(3,4-dihydro-6,7-dimethoxy-1*H*-2-benzopyran-1-yl)ethyl]-4-(4-fluorophenyl)piperazine. This compound decreases sympathetic nerve activity recorded from the external carotid and splanchnic nerves of baroreceptor-denervated cats and, therefore, has a central component to its mechanism of action. It also blocks pressor effects of norepinephrine and phenylephrine and is thus an α-adrenergic antagonist. Binding data characterize this as α_1-adrenergic receptor blockade.

Humber has reported the synthesis of 1-(haloalkyl)-6,7-dimethoxyisochromans and the reaction of these halides with simple alphatic amines.[1] Recently, a patent issued to Takeda named as hypotensives the adducts of various arylpiperazines and 1-(1-bromomethyl)- and 1-(2-chloroethyl)-6,7-dimethoxyisochromans.[2] This prompted us to report our own work in this area. We now report as hypotensives a variety of 6,7-dimethoxyisochromans which are substituted at C-1 via a one- to three-carbon chain with arylpiperazines (compounds **12–18**, Scheme I). In addition, C-1 has been optionally substituted by *p*-fluorophenyl or methyl, and C-3 and C-4 are optionally substituted by methyls. Most of these piperazines are novel, although a few which are referenced are described in the Takeda patent of ref 2. These isochromans are hypotensives which lower blood pressure presumably by both peripheral and central α-adrenoreceptor blockade. Structure–activity relationships (SAR) have been developed. The mechanism of action of these isochromans has been investigated by both in vitro receptor binding analysis and whole animal pharmacology. In addition, receptor binding information is reported for 1-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]-4-(4-fluorophenyl)piperazine, a compound which we have already described.[3]

Chemistry. Our synthetic strategy is outlined in Scheme I. The isochroman ring was formed by the method of Humber.[1,4] Compounds **5** and **6** are literature compounds,[1] while the analogues **7–11** are novel although well precedented. During the synthesis of **7** and **8**, methyl substitution at isochroman position C-3 and C-4 was established in the 2-(3,4-dimethoxyphenyl)ethanol intermediates **4** and **3b**. These methyl-substituted phenylethanols were then cyclized to the corresponding 3,3- and 4,4-dimethylisochromans **8** and **7**. Methyl and *p*-fluorophenyl substitutions at isochroman C-1 were made by reacting alcohol **3a** with 4-chloro-*p*-fluorobutyrophenone, 5-chloro-2-pentanone, or ethyl acetoacetate.[1,4] 4-Arylpiperazines reacted readily with the 1-(haloalkyl)-6,7-dimethoxyisochromans **5–11** to yield compounds of generic structures **12–18**. These adducts were evaluated for hy-

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