by TLC in two solvent systems, ethyl acetate–cyclohexane (4:1) and ethyl acetate–2-propanol–water (85:10:5). Molecular formulas were determined by high-resolution mass spectroscopy. In cases where high-resolution spectra were not obtained, the molecular composition of the low-resolution molecular ion was obvious from either the composition of the starting material or from a subsequent transformation product.

Fluorinated Retinoic Acids and Their Analogues. 1. Synthesis and Biological Activity of (4-Methoxy-2,3,6-trimethylphenyl)nonatetraenoic Acid Analogues

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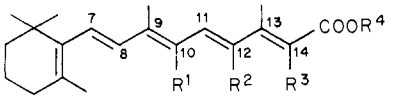
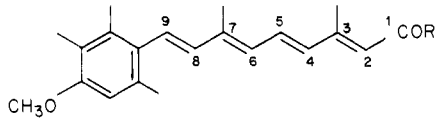
(4-Methoxy-2,3,6-trimethylphenyl)nonatetraenoic acids, esters, and amides (analogues of retinoic acid) bearing a fluorine atom(s) or a trifluoromethyl group on the polyene side chain were synthesized. The biological activities of these compounds and of 10-, 12-, and 14-fluororetinoic acid esters were evaluated in vivo in a chemically induced mouse papilloma test; the toxicities were assessed in an in vivo mouse hypervitaminosis A test. Antipapilloma activity greater than the parent nonfluorinated ester was found for **1c** (ethyl 12-fluororetinoate) and **23** and **39** (aromatic 4- and 6-fluororetinoid esters, respectively). A similar increase in antipapilloma activity was observed for **71** and **72**, the aromatic 4- and 6-fluororetinoic acids, respectively, relative to **2** and for **73** (aromatic 4-fluororetinoid amide) relative to **4**.

Recent studies[1-3] have demonstrated that retinoic acid (**1a**) and the aromatic analogues **2**–**4** (retinoids) can inhibit



	R^1	R^2	R^3	R^4
1a	-H	-H	-H	-H
b	-F	-H	-H	$-C_2H_5$
c	-H	-F	-H	$-C_2H_5$
d	-H	-H	-F	$-C_2H_5$
e	-H	-H	-H	$-C_2H_5$



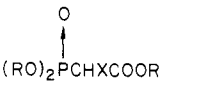
2, R = -OH
3, R = $-OC_2H_5$
4, R = $-NHC_2H_5$

the growth of and cause marked regression of chemically induced papillomas and carcinomas in mice. Retinoids have also been shown to inhibit the growth of and cause the regression of a transplantable chondrosarcoma.[4] Furthermore, topical or systemic administration of retinoic acid (**1a**) was found to have some effect on precancerous conditions in humans.[5] Numerous reports concerning the effectiveness of natural and synthetic retinoids for the prevention or reversal of a number of precancerous conditions in animals have also appeared.[1,6]

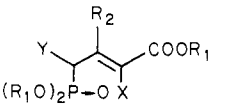
Although these findings are encouraging, experimental and clinical results have also demonstrated that systemic application of large doses of natural and synthetic retinoids can induce a series of toxic side effects, known as hypervitaminosis A.[1-3] While the synthetic retinoids **3** and **4** were shown to be more potent and less toxic[2,3] than retinoic acid, they still have toxic effects. As a result, the research described below was undertaken to synthesize new retinoids which might be more effective and less toxic for the prophylaxis and therapy of precancerous conditions.

Since many fluorine-containing compounds are known to be useful therapeutic agents,[7] it was of interest to introduce a fluorine atom or a trifluoromethyl group at different positions on the side chain of the aromatic retinoids. Recently, 10- and 14-fluororetinal were synthesized and shown to form fluorinated rhodopsin analogues.[8] Although the 10-, 12- and 14-fluororetinoic acid derivatives **1b–d**, respectively, were synthesized in 1964[9b,c]

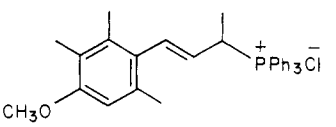
Chart I. Synthons for Fluorinated Retinoids



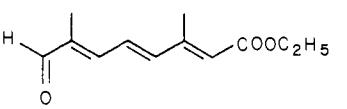
	R	X	ref
5	$-CH_3$	-H	11
6	$-C_2H_5$	-H	11
7	$-C_2H_5$	-F	9a



	R_1	R_2	X	Y	ref
8	$-C_2H_5$	$-CH_3$	-F	-H	9b
9	$-C_2H_5$	$-CH_3$	-H	-F	9c
10	$-CH_3$	$-CH_3$	-H	-H	12
11	$-C_2H_5$	$-CF_3$	-H	-H	13



32, ref 10



55, ref 10

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and were claimed to have hypocholesteremic activity,[9d] the use of compounds of this type as cancer prophylactic agents was not investigated. This paper describes the synthesis and biological properties of several fluorinated retinoids.

Chemistry. Fluorinated Retinoic Acid Analogues. The fluorinated retinoic acid derivatives **1b** ($R^4 = CH_3$), **1c**, and **1d** were prepared according to the methods described previously.[6a-c] Experimental details and spectral data for these compounds are reported in the Supplementary Material (see paragraph at the end of the Experimental Section concerning Supplementary Material). The biological properties of **1b–d** are discussed below.

Fluorinated Aromatic Retinoids. The syntheses of the fluorinated aromatic retinoids utilized to a large extent the known synthons **5–11**, shown in Chart I.

2-Fluoro Analogues. The unsaturated ketone **12**[10] served as starting material for the synthesis of the 2-fluorinated derivatives **17–19** (Scheme I, eq 1). Condensation of **12** with the anion of trimethyl phosphonoacetate[11] (**5**) gave a 3:7 (*Z*/*E*) mixture of esters **13**, which, upon reduction with diisobutylaluminum hydride followed by manganese dioxide oxidation, furnished the isomeric aldehydes **15** and **16**. The *E*-isomer **15** was separated from the less polar *Z*-isomer **16** by chromatography on silica gel. Reaction of **15** with the anion of the C_5 fluorophosphonate[9b] **8** then gave a 1:1 mixture of the 2-fluoro analogues **17** and **18**. The 2*Z*-isomer **17** was isolated by crystallization.

Similarly, the 2*Z*,6*Z*-isomer **19** was prepared from the 2*Z*-aldehyde **16**.

4-Fluoro Analogues. The 4-fluoro analogues **23** and **24** were prepared as shown in Scheme I, eq 2. Treatment of **15** with the anion of triethyl fluorophosphonacetate[9a] (**7**) gave a 3:2 (*E*/*Z*) mixture of fluoro esters, which on isomerization with iodine afforded **20**. Reaction of the acid **21** with methyllithium[14] gave the methyl ketone **22**, which on condensation with the anion of **6** afforded **23**.

The 4*E*-isomer **24** was also obtained, together with **23**, by condensation of **15** with the C_5 phosphonate **9**.[9c]

5-Fluoro Analogue. γ-Acetoxytiglic aldehyde (**25**),[15] starting material for the synthesis of the 5-fluororetinoid **34**, was condensed with the anion of **7** to form the ester **26**, as a mixture of isomers (2*Z*/2*E* ≃ 3:7) (Scheme I, eq 3). Selective hydrolysis gave the alcohol **27**, which was oxidized with manganese dioxide to the unstable aldehyde **28**. Aldehyde **28** was converted to the more stable dimethyl acetal **29** with methanol–ammonium chloride. Diisobutylaluminum hydride reduction of **29** gave the unstable hexadienal **30** containing ~10–20% of the alcohol **31**. Wittig reaction of this mixture with the phosphonium chloride **32**[10] (Chart I) gave the isomeric aldehydes **33** (6*E*/6*Z* ≃ 3:2) after acidic workup. Conversion of **33** to the corresponding methyl esters **34** was accomplished with sodium cyanide, acetic acid, and manganese dioxide.[16]

6-Fluoro Analogues. Ketone **12** also served as starting material for the 6-fluoro analogues **39–41** (Scheme I, eq 1). Reaction of **12** with the anion of **7** afforded the mixture of 2-fluoro esters **35** (2*E*/2*Z* ≃ 3:2). Reduction and oxidation as described above yielded the isomeric aldehydes **37** and **38**. Separation of this mixture was easily achieved by column chromatography on silica gel and gave first the less polar 2*E*-isomer **38**, followed by the 2*Z*-isomer **37**. Assignment of stereochemistry was made on the basis of the ^1H NMR spectra (see Experimental Section).

Reaction of **37** with the phosphonate **10**[12] gave a mixture of 6-fluoro isomers **39** and **40**, which were separated by fractional crystallization. Similarly, aldehyde **38** was converted into the isomeric (6*E*)-fluoro analogue **41**.

8-Fluoro Analogues. The aldehyde **42**[10] served as starting material for the synthesis of the 8-fluoro analogue **50** (Scheme I, eq 4). Condensation with **7** afforded a mixture of fluoro esters **43** (*Z*/*E* ≃ 2:1). The acid **44**, when treated as described above for **21**, gave **45** as a major product.

Condensation of **45** with **6** afforded the ester **47**, which was converted to the aldehyde **49** in the manner previously described. The 2*E*,4*Z* stereochemistry of **49** was assigned based on NMR[17] [$J_{(E)\text{-}HF}$ = 37 Hz; δ 2.42 (C_3-CH_3)]. Treatment of aldehyde **49** with the anion of **10** gave the desired (8*Z*)-fluoro analogue **50**.

9-Fluoro Analogues. The synthesis of the 9-fluoro analogues commenced with the phosphonate **53** (Scheme I, eq 5). Fluorination of the anion of **53**, obtained from the alcohol **51**[7] via the bromide **52**, with perchloryl fluoride[18] gave the unisolated intermediate **54**. Reaction of **54** with the aldehyde **55**[10] (Chart I) and lithium diisopropylamide (LDA) afforded the (8*Z*)- and (8*E*)-9-fluoro analogues **56** and **57**.

3- and 7-(Trifluoromethyl) Analogues. The 3-(trifluoromethyl) analogue **58** was prepared via reaction of the aldehyde **15** and the phosphonate **11** (Scheme I, eq 1).

For the synthesis of the 7-(trifluoromethyl) analogue, the carbinol **59**, obtained by treatment of the aldehyde **42** with the Grignard derivative of trifluoropropyne, was subjected to Meyer–Shuster rearrangment[19] to give the trifluoromethyl ketone **60** (Scheme I, eq 6). Condensation of **60** with **5** afforded the 2-carbon homologous product **61**, which after the usual reduction–oxidation sequence was reacted with the C_5 phosphonate **10** to give the desired 7-(trifluoromethyl) derivative **64**. (An attempt to convert **59** directly to **61**, via Claisen rearrangement of the propargyl vinyl ether formed from **59** and triethyl orthoacetate, was not successful.)

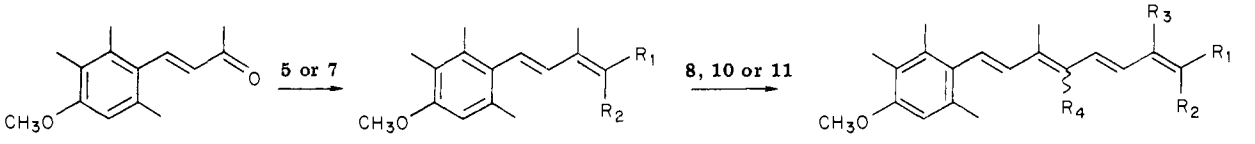
2,4-, 2,6-, and 4,6-Difluoro Analogues. The 2,4-difluoro analogue **65** was obtained by reaction of ketone **22** with the anion of the fluorinated phosphonate **7** (Scheme I, eq 2).

The 2,6-difluoro analogue **66** was synthesized from the aldehyde **37** and the C_5-fluorinated phosphonate **8** (Scheme I, eq 1).

Aldehyde **37** also served as the starting material for the synthesis of the 4,6-difluoro analogue **70**. Reaction of **37** and triethyl fluorophosphonacetate (**7**) afforded the difluoro ester **67** (Scheme I, eq 2). Hydrolysis of the ester and treatment of the resulting acid with methyllithium, as described above for **21**, gave the methyl ketone **69**. Reaction with **6** gave the desired 4,6-difluoro derivative **70**.

Biological Results. In Vivo Studies. The compounds described in this study were tested for their therapeutic effect on chemically induced skin papillomas in mice as described previously.[20] In addition, the dose of selected compounds was titrated and the ED_{50} (the effective dose causing a 50% decrease in papilloma diameter) was obtained from a plot of percent decrease in papilloma diameter vs. log dose. At least four doses were used in the determinations and the ED_{50} values, and correlation coefficients were determined by the method of least squares. The variability of the percent change in papilloma diameter for a given dose of retinoid has been determined for a few compounds and has generally been less than 10% (coefficient of variation). For example, for compound **4** at 40 mg/kg the percent change was 73.8 ± 3.96 (mean of five determinations plus or minus standard deviation), and for compound **3** at 80 mg/kg it was 47.0 ± 4.06 for five

Scheme I. Syntheses of Fluorinated Aromatic Retinoids

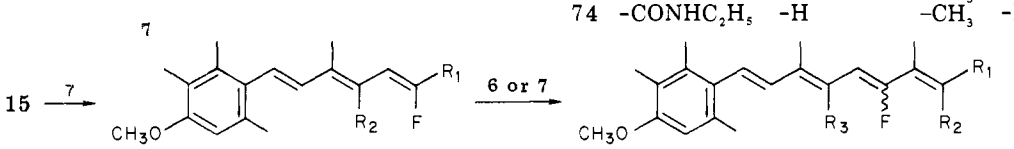


(1)

12

	R_1	R_2	Config
13	$-COOCH_3$	-H	2*E*/*Z*
14	$-CH_2OH$	-H	2*E*/*Z*
15	-CHO	-H	
16	-H	-CHO	
35	$-COOC_2H_5$	-F	2*E*/*Z*
36	$-CH_2OH$	-F	2*E*/*Z*
37	-CHO	-F	
38	-F	-CHO	

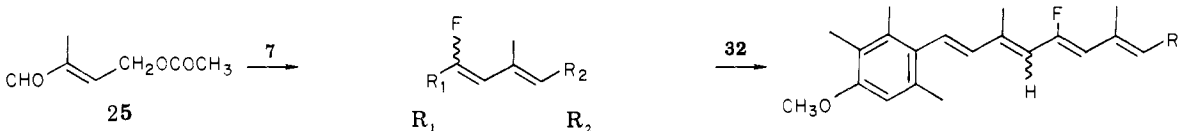
	R_1	R_2	R_3	R_4	Config
17	$-COOC_2H_5$	-F	$-CH_3$	-H	6*E*
18	-F	$-COOC_2H_5$	$-CH_3$	-H	6*E*
19	$-COOC_2H_5$	-F	$-CH_3$	-H	6*Z*
39	$-COOCH_3$	-H	$-CH_3$	-F	6*Z*
40	-H	$-COOCH_3$	$-CH_3$	-F	6*Z*
41	$-COOCH_3$	-H	$-CH_3$	-F	6*E*
58	-H	$-COOC_2H_5$	$-CF_3$	-H	
66	$-COOC_2H_5$	-F	$-CH_3$	-F	
72	-COOH	-H	$-CH_3$	-F	6*Z*
74	$-CONHC_2H_5$	-H	$-CH_3$	-F	6*Z*



(2)

	R_1	R_2
20	$-COOC_2H_5$	-H
21	-COOH	-H
22	$-COCH_3$	-H
67	$-COOC_2H_5$	-F
68	-COOH	-F
69	$-COCH_3$	-F

	R_1	R_2	R_3	Config
23	$-COOC_2H_5$	-H	-H	4*Z*
24	$-COOC_2H_5$	-H	-H	4*E*
65	$-COOC_2H_5$	-F	-H	
70	$-COOC_2H_5$	-H	-F	
71	-COOH	-H	-H	4*Z*
73	$-COONHC_2H_5$	-H	-H	4*Z*

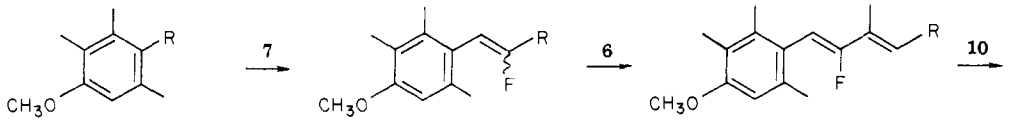


(3)

25

	R_1	R_2
26	$-COOC_2H_5$	$-CH_2OCOCH_3$
27	$-COOC_2H_5$	$-CH_2OH$
28	$-COOC_2H_5$	-CHO
29	$-COOC_2H_5$	$-CH(OCH_3)_2$
30	-CHO	$-CH(OCH_3)_2$
31	$-CH_2OH$	$-CH(OCH_3)_2$

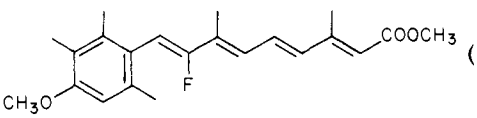
	R
33	-CHO
34	$-COOCH_3$



	R
42	-CHO
51	$-CH_2OH$
52	$-CH_2Br$
53	$-CH_2P(\rightarrow O)(OC_2H_5)_2$

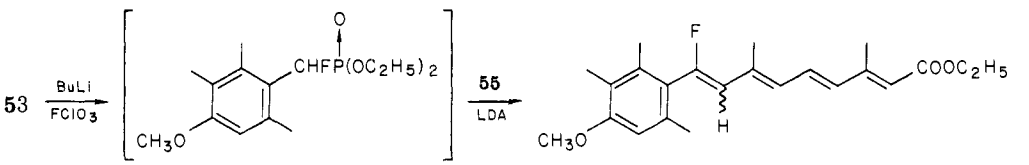
	R	Config
43	$-COOC_2H_5$	
44	-COOH	
45	$-COCH_3$	2*Z*
46	$-COCH_3$	2*E*

	R
47	$-COOC_2H_5$
48	$-CH_2OH$
49	-CHO



(4)

50

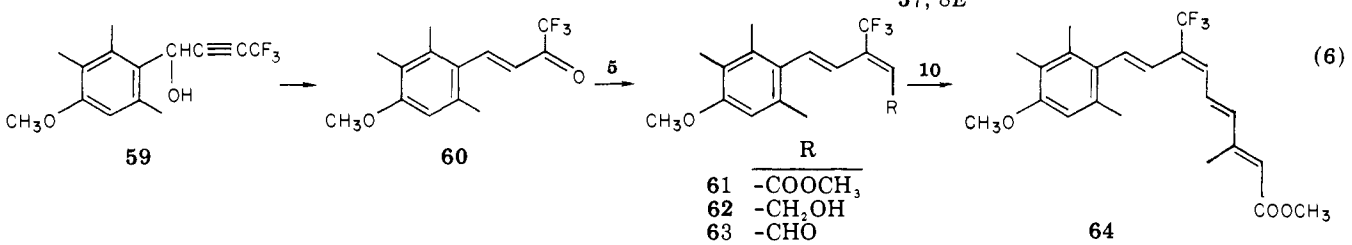


(5)

53

54

56, 8*Z*
57, 8*E*



(6)

59

60

	R
61	$-COOCH_3$
62	$-CH_2OH$
63	-CHO

64

Table I. Effects of Fluorine Substitution on Toxicity and Antipapilloma Activity of 1 (R = C_2H_5)

		Antipapilloma act.		
no.	hypervitaminosis dose, (mg/kg)/day[a]	dose, (mg/kg)/day[b]	effect, %	ED_{50}, (mg/kg)/day[b]
1e	50	200	-85[c]	
		120	-76[c]	
		80	-47[c]	48 (r = 0.878)[d]
		40	-36[c]	
1d	100	20	-40	>20
1c	100	80	-83	
		40	-67	
		20	-33	24.3 (r = 0.946)[d]
		10	-33	
1b[e]	200	80	-60	<80

[a] Retinoids were suspended in water containing 0.1% carboxymethylcellulose and 0.01% Triton X-100 and administered intraperitoneally daily Monday through Friday the first week and Monday through Thursday the second week. Evaluation for hypervitaminosis was made 1 day after the last injection. [b] Compounds were suspended in a 0.1% aqueous solution of carboxymethylcellulose and administered intraperitoneally daily five times per week for 2 weeks. [c] Data obtained by Dr. W. Bollag. Five times the indicated daily dose was given once weekly for 2 weeks. [d] r = correlation coefficient. [e] R = CH_3.

Table II. Effects of Fluorine Substitution on Toxicity and Antipapilloma Activity of 3

		Antipapilloma act.		
no.	hypervitaminosis dose, (mg/kg)/day[a]	dose, (mg/kg)/day[b]	effect, %	ED_{50}, (mg/kg)/day[b]
3	100	80	-47	
		40	-33	80
		20	-29	
		10	-9	
17	12.5	10	-37	>10
23	50	80	-82	
		40	-69	
		20	-62	4.0 (r = 0.733)[c]
		10	-76	
		5	-43	
24	200	80	-56	~80
39	50	40	-79	
		20	-60	13.8 (r = 0.980)[c]
		10	-35	
		5	-28	
41	200	80	-17	>80
50	>200	80	-3	>80
34	>200	80	-25	>80
56		40	-40	>40
57		40	-26	>40
65	>200	80	-17	>80
70	>200	80	-33	>80
66	>200	80	-35	>80
58	>200	80	-8,+2	>80
64	>200	80	-25	>80

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] r = correlation coefficient.

determinations. The hypervitaminosis dose, a measure of toxicity, was determined as described by Bollag.[2]

The effects of substitution of fluorine for hydrogen at C-14, C-12, and C-10 on the toxicity and antipapilloma activities of retinoic acid ethyl ester are shown in Table I. Although **1c**, **1d**, and the parent compound **1e** were ethyl esters whereas **1b** (R^4 = CH_3) was a methyl ester, no significant differences in biological activity between methyl and ethyl ester derivatives have been observed for compounds in the retinoid class (unpublished data).

Substitution of fluorine at C-14 (**1d**) resulted in a compound with possibly decreased toxicity relative to the parent compound. Papilloma-bearing mice, however, appeared to have an increased sensitivity to **1d**, since 20 (mg/kg)/day was the maximum tolerated dose in such mice whereas the hypervitaminosis dose in normal mice was 100 (mg/kg)/day. Substitution of fluorine at C-12 (**1c**), which may also have slightly reduced the toxicity, resulted in a twofold increase in activity relative to **1e**. Compound **1b** (R^4 = CH_3) is definitely less toxic than **1e** and, on the basis of the limited data obtained, may be slightly more active than it.

The effects on toxicity and antipapilloma activity of **3** by substitution of fluorine for hydrogen at one or more positions on the side chain are shown in Table II. Compound **17** (F at C-2) was fourfold more toxic and more active against mouse skin papillomas than **3**. It was not possible to obtain an ED_{50} for **17** because of toxicity. Compounds **23** and **39**, with substitution of fluorine at C-4 and C-6, respectively, were 2-fold more toxic and approximately 20- and 6-fold more active, respectively, than **3**. Compounds **34** and **50**, with substitution of fluorine at C-5 and C-8, respectively, were at least twofold less toxic, but also less active than **3**. Substitution at C-9 resulted in a compound with activity similar to that of the parent substance; however, the toxicity of this agent was not determined. Substitution of fluorine at both C-2 and C-4, C-4 and C-6, or C-2 and C-6 (**65**, **70**, and **66**, respectively) resulted in agents that were less toxic but also less active than **3**. A similar result was also obtained for the sub-

Table III. Effects of Fluorine Substitution on Toxicity and Antipapilloma Activities of 2 and 4

no.	hypervitaminosis dose, (mg/kg)/day[a]	Antipapilloma act. dose, (mg/kg)/day[a]	effect, %	ED_{50}, (mg/kg)/day[b]
2	100	40	−90	
		20	−66	12.5 (r = 0.999)[c]
		10	−43	
		5	−18	
71	25	10	−80	
		5	−63	2.7 (r = 0.999)[c]
		2.5	−48	
		1.25	−34	
72	50	20	−87	
		10	−54	7.1 (r = 0.944)[c]
		5	−30	
		2.5	−28	
4	50	40	−74	
		20	−54	19.2 (r = 0.988)[c]
		10	−23	
		5	−11	
73	50	20	−67	<10
		10	−73	
74	200	80	−53	~80

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] r = correlation coefficient.

stitution of trifluoromethyl for methyl at C-3 and C-7 (**58** and **64**, respectively).

The fluorinated derivatives of **3** discussed above all possess the all-trans configuration of the double bonds. To study the effect of the cis configuration at the point of fluorination on activity, **24** [(*E*)-4-fluoro], **41** [(*E*)-6-fluoro], and **57** [(*E*)-9-fluoro] were prepared. In the case of the 4- and 6-fluoro derivatives, the cis (*E*) isomers were less toxic and less active than their corresponding trans (*Z*) isomers. Although the toxicities of the 9-fluoro compounds were not measured, the antipapilloma activity of the 8-cis isomer **57** was lower than that of the trans isomer **56**.

The 4- and 6-fluoro derivatives of the acid **2** and the amide **4** were also prepared. As shown in Table III, the effects of substitution of fluorine at these positions in **2** were similar to those observed for the same substitutions in **3**. Thus, **71** and **72** were four- and twofold more toxic and about five- and twofold more active, respectively, than **2**.

Similar effects were not observed for 4- and 6-fluoro derivatives of **4**. The 4-fluoro analogue **73** had the same toxicity as **4** but, on the basis of limited data, appeared to be more active. However, the 6-fluoro derivative **74** was fourfold less toxic but also about fourfold less active than **4**.

In general, substitution of fluorine for hydrogen at C-4 or C-6 in the aromatic series had the greatest positive effect on antipapilloma activity. This effect was observed with the free acids (**71** and **72**), esters (**23** and **39**) and ethyl amides (**73** and **74**).

Experimental Section

General. Spectra and analyses were made by the Physical Chemistry Department of Hoffmann-La Roche Inc., Nutley, N.J. High-pressure liquid chromatography (LC) was carried out with two 4.6 mm × 50 cm Partisil 10 (Whatman) columns in series. THF–heptane (1%) at a flow rate at 3 mL/min was the mobile phase; a 350-nm UV detector was used. Microanalyses are within ±0.4% of theory, except where otherwise noted. Melting points were taken on a Kofler hot stage and are uncorrected.

Reagents. All solvents were ACS grade and were not further purified unless otherwise noted. Dry tetrahydrofuran (THF) and dimethoxyethane (DME) were prepared by distillation from sodium bis(2-methoxyethoxy)aluminum hydride.[21] The mineral oil in sodium hydride was removed by washing three times with petroleum ether (35–60 °C) or pentane; the residual solvent was removed in vacuo prior to suspension of NaH in the reaction solvent. Ethyl bromofluoroacetate was purchased from PCR Inc., Gainesville, Fla. Unless otherwise indicated, reaction mixtures were partitioned between water and the organic solvent, and the aqueous layer was washed twice with the organic solvent. The organic extracts were combined, washed with water, dried with anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure (20–40 mmHg) at 35–40 °C on a rotary evaporator. For reactions carried out in an argon atmosphere, the apparatus was evacuated and filled with argon at least three times. Column chromatography was performed using E. Merck (Darmstadt) silica gel, 0.063–0.2 mm. Reactions were monitored for completion by thin-layer chromatography (TLC) on silica gel in an ethyl acetate–hexane (3:7) solvent system unless otherwise indicated.

Methyl (*Z*/*E*,*E*)-3-Methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienoate (13). A solution of 182.1 g (1.0 mol) of **5** in 300 mL of DME was added dropwise, under argon, over a 45-min period to a stirred suspension of 48 g (1.0 mol) of 50% sodium hydride in 2.5 L of DME. After the addition was complete, the mixture was stirred at 23 °C for 2 h until no more hydrogen evolved. A solution of 200 g (0.918 mol) of **12** in 700 mL of DME was added dropwise. The reaction mixture was refluxed for 3.5 h, then cooled to 20 °C, and approximately 3 L of crushed ice–water was added. Neutralization (pH 6–7, 2 N HCl) and extraction (CH_2Cl_2) afforded 259 g of yellow-orange crude product. A rapid filtration (3 kg of silica gel, 5% ether–petroleum ether) gave 218 g (79.5%) of **13** as a colorless oil. Anal. ($C_{17}H_{22}O_3$) H; C: calcd, 74.70; found, 75.29.

(*Z*/*E*,*E*)-3-Methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienol (14). A solution of 112 g (0.41 mol) of **13** in 1.3 L of ether was cooled to −73 °C in an argon atmosphere. Diisobutylaluminum hydride (*i*-Bu_2AlH; 271 mL, 1.5 M in hexane, 0.41 mol) was added dropwise with stirring over a period of 1 h. The reaction mixture was stirred at −73 °C and monitored by TLC. Two successive additions of *i*-Bu_2AlH (100 mL, 0.15 mol each) were added dropwise at −73 °C over 10 min with a 15-min interval between additions. The reaction mixture was allowed to warm slowly to −25 °C and 500 mL of methanol–water (1:1) was added slowly. The mixture was stirred at 23 °C for 1 h, filtered through a coarse sintered-glass funnel, and washed with ether. The filtrate was worked up to give 109.6 g of orange-colored oily product. Chromatography (900 g of silica gel, 20% ether–petroleum ether) gave 79.0 g (71%) of **14** as a light yellow oil. Anal. ($C_{16}H_{22}O_2$) C, H.

(*E*,*E*)-3-Methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienal (15) and (*Z*,*E*)-3-Methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienal (16). The mixture of alcohols **14** (185 g, 0.75 mol) and MnO_2 (695 g, 8.0 mol) were stirred in 4.0 L of CH_2Cl_2 at 23 °C, under argon for 40 h. Filtration and evaporation of the filtrate gave 198 g of crude product. Chromatography (4.3 kg of silica gel, 1:5 ether–petroleum ether) gave

32.8 g of the less polar isomer **16** (TLC R_f 0.73) and 2.1 g of a mixture of **15** and **16**. Further elution (1:4 to 1:2 ether–petroleum ether) gave 113.7 g of the more polar isomer **15** (TLC R_f 0.42). Final elution (3:1 ether–petroleum ether) yielded 20.4 g of starting alcohol **14** containing mostly the 2*Z* isomer.

Crystallization of **16** (32.8 g; 50 mL of boiling ether, 300 mL of 30–60 °C petroleum ether) at −10 °C overnight gave 28.0 g (15%) as yellow needles, mp 83–85 °C. Anal. ($C_{16}H_{20}O_2$) C, H.

The more polar 2*E*-isomer **15** (113.7 g) was crystallized (120 mL of boiling ether, 600 mL of 30–60 °C petroleum ether) at −10 °C to give 98.1 g (53.5%) as yellow prisms, mp 62–65 °C. Anal. ($C_{16}H_{20}O_2$) C, H.

Ethyl (*Z,E,E,E*)-2-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (17). The anion of **8** (5.05 g, 0.018 mol) was prepared from NaH (50%, 0.83 g, 0.017 mol) in 60 mL of DME at 5 °C under argon. A solution of 4.35 g (0.018 mol) of **15** in 20 mL of DME was added dropwise, and the reaction mixture was stirred at 23 °C for 2 h. Workup (CH_2Cl_2) and chromatography (250 g of silica gel, 1:19 ether–petroleum ether) gave 4 g (60.4%) of crystalline substance. Recrystallization (CH_2Cl_2–petroleum ether) afforded 1.6 g of pure **17**: yellow crystals; mp 140–143 °C. Anal. ($C_{23}H_{29}FO_3$) C, H, F.

The mother liquor from above was shown by high-pressure LC to be mainly the 2*E*-isomer **18**. (See Supplementary Material for spectral data.)

Ethyl (*Z,E,Z,E*)-2-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (19). This compound was prepared by the procedure described above from 0.98 g (0.02 mol) of 50% sodium hydride, 5.5 g (0.020 mol) of **8**, and 4.8 g (0.020 mol) of the 2*Z*-aldehyde **16**. The crude product (9 g) was chromatographed as above to give 5.7 g (78%). Five recrystallizations (petroleum ether) afforded 1.46 g of **19** as yellow crystals, mp 103–113 °C. Anal. ($C_{23}H_{29}FO_3$) C, H, F.

Ethyl (*Z,E,E*)-2-Fluoro-5-methyl-7-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6-heptatrienoate (20). The anion prepared at 23 °C from 79.9 g (0.33 mol) of **7**, 20.2 g (0.42 mol) of 50% NaH, and 250 mL of dry DME was stirred at 40 °C for 1 h under argon and then cooled to 23 °C. Aldehyde **15** (75 g, 0.31 mol) in 500 mL of DME was added dropwise with stirring. The reaction mixture was heated at 40 °C for 2 h, cooled to 20 °C, and worked up to give 138.1 g of crude product. Filtration (2.2 kg of silica gel, 10–20% ether–petroleum ether) afforded 59.3 g (58% yield) of **20** as a mixture of isomers [2*E*/2*Z* ≃ 3:2 by TLC, EtOAc–hexane (15:85)]. Further elution (2:3 ether–petroleum ether) gave 11.6 g of aldehyde **15**.

The isomeric esters **20** (66.1 g, 0.20 mol, from two similar preparations) in 600 mL of absolute ether were treated with 1.4 g of iodine crystals and stirred at 23 °C for 48 h under argon. It was then washed (5% $Na_2S_2O_3$, H_2O), dried ($MgSO_4$), and concentrated. Filtration (100 g of Fluorisil, ether) and crystallization (700 mL, 1:6 ether–petroleum ether) gave 26.2 g of the 2*Z*-ester **20**: yellow crystals, mp 106–110 °C. Anal. ($C_{20}H_{25}FO_3$) C, H, F.

Repetition of the iodine treatment gave an additional 6 g of **20** from the above mother liquor (37.1 g).

(*Z,E,E*)-2-Fluoro-5-methyl-7-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6-heptatrienoic Acid (21). The ester **20** (41.5 g, 0.125 mol) was hydrolyzed with 6 N NaOH (40 mL) in 450 mL of THF and 150 mL of MeOH. Water (650 mL) was added and the organic solvents were removed at 50 °C under reduced pressure. The aqueous alkaline phase was extracted (ether), cooled, and acidified to pH 3–4 (concentrated HCl). Ether extraction gave 37.8 g (99%) of **21**, yellow crystals [dried (P_2O_5), 23 °C (0.5 mm), 20 h]. An analytical sample was recrystallized from ether–hexane (1:2), mp 203–210 °C. Anal. ($C_{18}H_{21}FO_3$) C, H, F.

(*Z,E,E*)-3-Fluoro-6-methyl-8-(4-methoxy-2,3,6-trimethylphenyl)-3,5,7-octatrien-2-one (22). The acid **21** (37.8 g, 0.124 mol) in 400 mL of dry THF was cooled to −70 °C, and CH_3Li (1.6 M in ether, 154 mL, 0.25 mol) was added dropwise with stirring under argon. After the addition was complete, the mixture was stirred at −70 °C for 15 min. TLC indicated some acid was still present; 15.4 mL (0.025 mol) of CH_3Li was added and stirring was maintained at −70 °C for 1 h. The cold bath was removed and 150 mL of water was added carefully. Concentration [50 °C (30-50 mm)] and extraction gave 28.8 g of crude product, which was allowed to crystallize (50 mL of CH_2Cl_2, 300 mL of hexane) overnight to give 24.2 g (64.5%) of **22**: orange crystals; mp 108–110 °C. Anal. ($C_{19}H_{23}FO_2$) C, H, F.

Ethyl (*E,Z,E,E*)-4-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (23). (A) From Ketone 22. To the anion prepared from 11.1 g (0.049 mol) of **6**, 2.37 g (0.049 mol) of 50% NaH, and 40 mL of DME at 23 °C under argon, a solution of **22** (10 g, 0.033 mol) in 75 mL of DME was added dropwise. The reaction mixture was heated at 50 °C for 2 h, cooled, and worked up as described above. The crude product was chromatographed (200 g of Florisil, 1:9 ether–petroleum ether) and further purified by treatment with activated charcoal (10 g, 300 mL of CH_2Cl_2) to give 8 g (65.2%) of **23**. Recrystallization (1:2 ether–petroleum ether) afforded 6 g of **23**: yellow crystals; mp 94–97 °C. Anal. ($C_{23}H_{29}FO_3$) C, H, F.

(B) From Aldehyde 15 and Phosphonate 9. The anion prepared from 4.88 g (0.017 mol) of **9** (*E*/*Z* ≃ 7:2), 1.25 g (0.026 mol) of 50% NaH, and 80 mL of DME at 23 °C under argon was refluxed for 1.25 h and cooled to 40 °C, and a solution of 4.23 g (0.017 mol) of **15** in 20 mL of DME was added dropwise over a period of 0.5 h. The reaction mixture was refluxed for 45 min, cooled, and worked up (CH_2Cl_2) to give 6.20 g of oily product. Chromatography (700 g of silica gel, 1:19 ether–petroleum ether) gave 1.84 g (28.6%) of **24** as the less polar material. Recrystallization (petroleum ether) afforded 1.41 g of pure **24**, mp 78–84 °C. Anal. ($C_{23}H_{29}FO_3$) C, H, F.

Further elution (5–10% ether in petroleum ether) gave 1.59 g (24.7%) of the more polar isomer **23**. Recrystallization (ether) yielded 1.24 g: yellow crystals; mp 92.5–96.5 °C; IR, UV, and NMR identical with the material prepared in A.

Ethyl (*Z/E,E*)-2-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienoate (35). The anion, prepared from 72.7 g (0.30 mol) of **7**, 14.4 g (0.3 mol) of 50% NaH, and 330 mL of DME at 23 °C under argon was treated with a solution of 65.4 g (0.30 mol) of **12** in 200 mL of DME over a 40-min period. The reaction was stirred at 50 °C for 4 h, cooled, and crushed ice–water (1 L) was added. The pH was adjusted to 4 (1 N HCl); workup (CH_2Cl_2) gave 89 g of crude product. Chromatography [800 g of silica gel, 5:95 ether–petroleum ether (30–60 °C)] gave 59.9 g (72.3%) of **35** as a yellow oil. Anal. ($C_{18}H_{23}FO_3$) C, H, F.

(*Z/E,E*)-2-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienol (36). The isomeric esters **35** (57.5 g, 0.19 mol) in 1.2 L of absolute ether at −70 °C under argon were treated with a total of 375 mL (0.57 mol) of *i*-Bu_2AlH (1.5 M in hexane) in two portions as described above for the preparation of **14**. Workup as described above gave 49.5 g of crude **36** as a mixture of isomers (*E*/*Z* ≃ 3:2 by TLC).

An analytical sample, yellow crystals, obtained by crystallization (petroleum ether–ether) had mp 48–80 °C. Anal. ($C_{16}H_{21}FO_2$) C, H, F.

(*Z,E*)- and (*E,E*)-2-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienal (37 and 38). The alcohol mixture **36** (53.5 g, 0.20 mol), 200 g of MnO_2 and 1.1 L of CH_2Cl_2 were stirred for 3 days under argon. More MnO_2 (100 g) was added and stirring was continued for 4 more days. Workup (CH_2Cl_2), as described previously for **15** and **16**, and chromatography (1.4 kg of silica gel, 1:9 ether–hexane) gave 18.7 g (35%) of the less polar **38**. One recrystallization (1:1 ether–petroleum ether) yielded 14 g of pure **38**: light yellow crystals, mp 79–84 °C. Anal. ($C_{16}H_{19}FO_2$) C, H, F.

Further elution (1:4 ether–hexane) gave 16.6 g (31%) of the more polar isomer **37**: light yellow crystals; mp 89–93 °C (two recrystallizations, ether). Anal. ($C_{16}H_{19}FO_2$) C, H, F.

Further elution (2:3 ether–hexane) gave 6.8 g (13%) of **36**, shown by TLC to be mostly the 2*E* isomer.

Methyl (*E,E,Z,E*)-6-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (39) and Methyl (*Z,E,Z,E*)-6-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (40). To the anion prepared from 5.3 g (0.024 mol) of **10**, 1.2 g (0.024 mol) of 50% NaH, and 50 mL of DME at 23 °C under argon, a solution of 6.3 g (0.024 mol) of **37** in 55 mL of DME was added dropwise over a 35-min period. The reaction mixture was stirred at 23 °C for 2.5 h, cooled, and quenched with ice–water. The pH was adjusted to 5–6 (1 N HCl); workup (CH_2Cl_2) gave 9.3 g of crude

product. Chromatography [300 g of silica gel, 1:9 ether–petroleum ether (30–60 °C)] gave 7.2 g (83.7%); fractional crystallization (1:4 CH_2Cl_2–petroleum ether) at 4 °C gave 2.7 g of the 2*E*-isomer **39**: yellow-orange crystals; mp 119–121.5 °C. Anal. ($C_{22}H_{27}FO_3$) C, H, F.

Crystallization of the mother liquor from above (ether–petroleum ether) gave 0.9 g (10.5%) of the 2*Z*-ester **40**: yellow crystals; mp 134–139.5 °C. Anal. ($C_{22}H_{27}FO_3$) C, H, F.

By repetition of the above described crystallization procedure, a total of 4.07 g (47.4%) of **39** and 1 g of **40** was obtained.

Methyl (*E,E,E,E*)-6-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (41). This compound was prepared by the procedure described above from 6.29 g (0.024 mol) of **38**, 5.32 g (0.024 mol) of **10**, and 1.15 g (0.024 mol) of 50% NaH in 100 mL of DME. The reaction mixture was stirred at 25 °C for 17 h and refluxed for 1 h. Workup (CH_2Cl_2) gave 9.7 g of crude crystalline substance, which was purified by chromatography (200 g of silica gel, 5–10% ether–petroleum ether) to give 7.3 g (85%) of yellow crystals. Two recrystallizations (1:4 CH_2Cl_2–petroleum ether) afforded 2.40 g of **41**: yellow needles; mp 133–141 °C. An analytical sample, obtained by one more recrystallization, had mp 139–143 °C. Anal. ($C_{22}H_{27}FO_3$) C, H, F.

Ethyl (*Z*/*E*)-2-Fluoro-3-(4-methoxy-2,3,6-trimethylphenyl)-2-propenoate (43). To the anion prepared from 80 g (0.33 mol) of **7**, 17.8 g (0.37 mol) of 50% NaH, and 200 mL of DME at 23 °C under argon, a solution of 44 g (0.25 mol) of **42** in 50 mL of DME was added dropwise over 15 min. The reaction mixture was stirred at 23 °C for 20 h and then was refluxed for 1.5 h, cooled, and poured into 1 L of ice–water. The solution was adjusted to pH 3 (150 mL of 1 N HCl) and worked up (CH_2Cl_2) to yield 80.1 g of an oil. This and 47.3 g from another preparation were combined and chromatographed [1.5 kg of silica gel, 1:19 to 1:9 ether–petroleum ether (30–60 °C)] to give 79.1 g (62%) of esters **43** (*Z*:*E* ≃ 7:3) as a light yellow oil. A small sample was distilled (Kugelrohr) at 160 °C (bath) (0.25 mm) for analysis. Anal. ($C_{15}H_{19}FO_3$) H, F; C: calcd, 67.65; found, 68.13.

(*Z*/*E*)-2-Fluoro-3-(4-methoxy-2,3,6-trimethylphenyl)-2-propenoic Acid (44). The ester **43** (78.1 g, 0.29 mol) in 150 mL of methanol was stirred with 6 N NaOH (97.7 mL, 0.59 mol) at 23 °C for 0.5 h. Ice–water (1 L) was added and the solution was acidified to pH 1 (~50 mL of concentrated HCl). Ether extraction gave 65.4 g (84%) of **44**: colorless solid [dried (P_2O_5), 23 °C (0.5 mm), several days]; mp 163–181 °C.

(*E*)- and (*Z*)-3-Fluoro-4-(4-methoxy-2,3,6-trimethylphenyl)-3-buten-2-one (46 and 45). A solution of 25 g (0.11 mol) of the isomeric acids **44** in 35 mL of THF and 215 mL of anhydrous ether was cooled to −70 °C under argon and CH_3Li (100 mL total, 2.23 M in ether) was added slowly via syringe in three portions at 1-h intervals, with stirring at −70 °C. Stirring was continued for 10 min, and the reaction mixture was then poured onto 500 mL of ice–water, acidified to pH 1 (concentrated HCl), and extracted (ether). Separation of the neutral and acidic fractions gave 18.6 g (75%) of the crude **45** and **46** as a light yellow oil and 5.8 g (23%) of unchanged acids **44**. The crude ketonic fraction (45.6 g from several preparations) was purified by chromatography (1.6 kg of silica gel, 1:9 ether–petroleum ether) to give 7.8 g of 2,3,6-trimethyl-4-methoxyphenylacetylene as the least polar material (TLC R_f 0.57), followed by 3.8 g of crystalline **46** (R_f 0.42), mp 56–59 °C. Anal. ($C_{14}H_{17}FO_2$) C, H, F.

In later fractions, the same eluent afforded 27.6 g of the desired *Z*-ketone **45** as the more polar substance (R_f 0.38). Crystallization (30–60 °C petroleum ether) gave 23.7 g of **45**: colorless crystals; mp 34–43.5 °C. Anal. ($C_{14}H_{17}FO_2$) C, H, F.

Ethyl (*E,Z*)-4-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienoate (47). Phosphonate **6** (26.8 g, 0.12 mol) was converted to its anion with 5.75 g (0.12 mol) of 50% NaH in 200 mL of DME and treated with a solution of 23.5 g (0.10 mol) of **45** in 100 mL of DME as described above for **23**. The reaction mixture was stirred at 23 °C under argon for 1.25 h and worked up as previously described to give 31.2 g. Chromatography (600 g of silica gel, 1:19 to 1:9 ether–petroleum ether) gave 21.5 g (70.5%) of **47** as colorless crystals. An analytical sample (one recrystallization, petroleum ether, −70 °C) had mp 50–51 °C. Anal. ($C_{18}H_{23}FO_3$) C, H, F.

(*E,Z*)-4-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadien-1-ol (48). A solution of 19.5 g (0.065 mol) of **47** in 400 mL of anhydrous ether was treated with *i*-Bu_2AlH (a total of 103.5 mL, 0.156 mol, 1.5 M in hexane) in three portions at −65 °C as described above for **14**. The reaction was quenched (85 mL of 1:1 methanol–water) at −30 °C. Water (100 mL) was then added and the mixture was stirred at 10 °C for approximately 40 min. Workup as described previously for 14 gave 16.5 g of crude product, which was crystallized (215 mL of ether, 60 mL of 30–60 °C petroleum ether, −10 °C) to give 13.4 g (78%) of **48**: pale yellow crystals; mp 71–73.5 °C. Anal. ($C_{16}H_{21}FO_2$) C, H, F.

(*E,Z*)-4-Fluoro-3-methyl-5-(4-methoxy-2,3,6-trimethylphenyl)-2,4-pentadienal (49). A mixture of 13.8 g (0.052 mol) of **48**, 54.7 g (0.63 mol) of MnO_2, and 115 mL of CH_2Cl_2 was stirred at 23 °C under argon for 65 h and worked up as usual. Recrystallization (1:4 CH_2Cl_2–petroleum ether) gave 13.2 g (96%) of aldehyde **49**: yellow crystals; mp 86–88.5 °C. Anal. ($C_{16}H_{19}FO_2$) C, H, F.

Methyl (*E,E,E,Z*)-8-Fluoro-3,7-Dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (50). To the anion prepared from 6.1 g (0.027 mol) of **10** and 1.31 g (0.027 mol) of 50% NaH in 90 mL of DME at 23 °C under argon, a solution of 6 g (0.023 mol) of **49** in 30 mL of DME was added, and the reaction was carried out and worked up as described above for **39** and **40**. Chromatography (500 g of silica gel, 1:9 ether–petroleum ether) gave 7.5 g (92%) of yellow crystalline substance containing mainly two isomers. Recrystallization (1:3 CH_2Cl_2–ether) gave 3.85 g (47%) of **50** as yellow crystals, mp 121.5–130 °C. An analytical sample, recrystallized from CH_2Cl_2–ether (1:6), had mp 127–130 °C. Anal. ($C_{22}H_{27}FO_3$) C, H, F.

(*E,Z*/*E,E*)-5-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraen-1-al (33). To the anion of **7**, prepared as described above from 14.3 g (0.30 mol) of 50% NaH, 70 g (0.30 mol) of **7**, and 100 mL of DME, 39.8 g (0.28 mol) of **25** in 60 mL of DME was added dropwise over a period of 25 min. The reaction mixture was stirred at 23 °C for 17 h under argon and then worked up as described. Distillation at 0.4–0.5 mm gave 7.42 g of **25**, bp 60 °C, and 36.5 g (56.6%) of fluoro ester **26** as a light yellow oil, bp 110–115 °C. A redistilled sample [Kugelrohr, 124 °C (bath) (0.6 mm)] had MS (*m*/*e*) 230 (M^+).

A cold (4 °C) solution of 34.5 g (0.15 mol) of **26** in 100 mL of ethanol was treated with 70 mL of NaOEt (3.7 g of Na/100 mL of EtOH), stirred at 4 °C for 40 min, and neutralized to pH 6 with glacial acetic acid. Filtration, evaporation of the filtrate, and chromatography (200 g of silica gel, 1:1 ether–petroleum ether) gave 21.5 g (76%) of **27** as a light yellow oil, which was used directly in the next step. A distilled sample [Kugelrohr, 126–130 °C (bath) (0.15 mm)] had IR (neat) 3400, 1738 cm^{-1}; MS (*m*/*e*) 188 (M^+), 168, 157, 129.

A mixture of 24.8 g of **27** and 150 g of manganese dioxide in 500 mL of CH_2Cl_2 was stirred at 23 °C under argon for 3 days. Workup gave 19 g of **28** as a light yellow liquid: IR (neat) 2770, 1737, 1675 cm^{-1}; MS (*m*/*e*) 186 (M^+). This unstable material was dissolved in 100 mL of methanol containing 0.1 g of NH_4Cl and stirred at 23 °C under argon for 18 h. The solution was adjusted to pH 8 with solid $NaHCO_3$ and filtered, and the methanol was evaporated at 35 °C (25–35 mm) to give 19 g of **29** as a light yellow liquid, which was used immediately in the next step.

A solution of 16 g of **29** in 450 mL of ether was treated with 105 mL of *i*-Bu_2AlH (1.5 M in hexane) at −70 °C as described above for **14**. After quenching and workup, evaporation of the ether under nitrogen gave 11 g of **30** containing approximately 10–20% of the alcohol **31** (TLC, ether–petroleum ether, 2:3). This mixture was dissolved in 150 mL of CH_2Cl_2; 10 g of activated MnO_2 was added and the mixture was stirred at 23 °C for 4 h under argon. After filtration, the CH_2Cl_2 filtrate containing the unstable isomeric mixture of aldehydes **30** was kept under argon and used immediately for the reaction described below. A small aliquot was evaporated in a stream of argon to give a light yellow oil: IR (neat) 3440, 1695, 1675, 1665 (sh) cm^{-1}; NMR (CCl_4) δ 9.2 (d, *J* = 8 Hz, 20%), 9.7 (d, *J* = 8.5 Hz, ~80% major isomer).

The aldehyde mixture **30** (11 g) in 300 mL of CH_2Cl_2 was cooled to 4 °C with stirring under argon, and a suspension of 30 g of **32** in 200 mL of water was added in several portions. Aqueous 6 N NaOH (11 mL) was added dropwise over a period of 5 min. The resulting mixture was stirred vigorously at 4 °C under argon for

40 min and then poured onto 500 mL of cold water. The combined CH_2Cl_2 extracts were washed twice with aqueous 2 N HCl and once with water and then dried ($MgSO_4$). The residue (36.8 g) was chromatographed (850 g of silica gel, 3:7 ether–petroleum ether) to give 4.2 g (21% based on **32**) of isomeric aldehydes **33** (6*E*/6*Z* = 62:38): orange crystals; mp 85–115 °C. Anal. ($C_{21}H_{25}FO_2$) C, H; F: calcd, 5.78; found, 5.20.

Methyl (*E,Z,Z*/*E,E*)-5-Fluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (34). A mixture of 2.44 g (7.4 mmol) of **33**, 1.47 g (29.8 mmol) of NaCN, 7.8 g (89 mmol) of activated MnO_2, and 650 mg (10.8 mmol) of glacial acetic acid in 20 mL of CH_2Cl_2 and 150 mL of methanol was stirred at 23 °C for 18 h under argon. The mixture was filtered and concentrated. The residue was treated with 500 mL of water and extracted (CH_2Cl_2). The crude product (2.64 g) was chromatographed (150 g of silica gel, 1:4 petroleum ether) to give 2.24 g (92%) of **34** as yellow crystals. Two recrystallizations (petroleum ether) gave 1.30 g, mp 57–83 °C. Anal. ($C_{22}H_{27}FO_3$) C, H, F.

4-Methoxy-2,3,6-trimethylbenzyl Alcohol (51). A solution of 40 mL (0.14 mol) of sodium bis(2-methoxyethoxy)aluminum hydride (70% in benzene) in 200 mL of ether was cooled to 0 °C, and a suspension of 35.6 g (0.2 mol) of **42** in 200 mL of ether was added dropwise at 0–10 °C. Stirring at 0 °C was continued for 15 min and then the mixture was allowed to warm to room temperature. Workup after the addition of 200 mL of 20% aqueous NaOH gave 31.4 g (87%) of **51** as off-white crystals, mp 108–110 °C. Anal. ($C_{11}H_{16}O_2$) C, H.

Diethyl 4-Methoxy-2,3,6-trimethylbenzylphosphonate (53). The alcohol **51** (31.4 g, 0.17 mol) in 350 mL of ether containing 2.6 mL (0.03 mol) of pyridine was cooled to −5 °C. Phosphorus tribromide (6.1 mL, 17.3 g, 0.06 mol) in 100 mL of ether was added dropwise over a 1-h period. The mixture was stirred at 0–5 °C for 20 min, then allowed to warm to room temperature, and poured into a mixture of ice and saturated NaCl solution. The usual workup gave 40.0 g (95%) of **52**, mp 70–80 °C. The material was used directly in the next step.

A mixture of 18 g (0.074 mol) of **52** and 15.8 g (0.095 mol) of triethyl phosphite was heated carefully to 40–50 °C, at which point the reaction started vigorously. *Heating should be discontinued, if necessary*. After the vigorous reaction subsided, the mixture was heated again slowly to 150 °C and held at that temperature for 2 h. The low-boiling bromoethane was collected in a Dean–Stark trap during the heating period. Distillation at 0.15 mm gave 21.5 g (97%) of **53**, bp 140–144 °C (0.15 mm). Anal. ($C_{15}H_{25}O_4P$) C, H, P.

Ethyl (*E,E,E,Z*)- and Ethyl (*E,E,E,E*)-3,7-Dimethyl-9-fluoro-9-(4-methoxy-2,3,6-trimethylphenyl)nonatetraenoate (56 and 57). To a cold (−70 °C) solution of 2.16 g (7.2 mmol) of **53** in 26 mL of THF, 3 mL (6.5 mmol) of *n*-butyllithium (2.1 M in hexane) was added. The resulting pale-yellow solution was allowed to warm to −27 °C, and a mixture of argon and perchloryl fluoride was bubbled through the solution for 3–5 min. Then the perchloryl fluoride stream was discontinued and argon was continued for 15–20 min longer. A solution of 1.5 g (7.2 mmol) of **55** in 6 mL of THF and the fluorinated phosphonate were mixed well and then added dropwise over a 45-min period to a cold (−70 °C) solution of lithium diisopropylamide, prepared by adding 3 mL (6.5 mmol) of *n*-butyllithium (2.1 M in hexane) to a cold (−65 °C) solution of 1.2 mL (8.5 mmol) of diisopropylamine in 2 mL of THF. After the addition was complete, the resulting solution was stirred at −70 °C for 10 min longer and then poured into a mixture of saturated NaCl solution and ether. The organic layer was washed with saturated NaCl solution until neutral and dried. Evaporation of the solvent gave 4 g of a yellow oil.

The product from the five reactions carried out as described above was combined (20 g) and chromatographed (silica gel, 5% ether–hexane) to give 350 mg of a yellow solid, which was treated with 2–3 mL of pentane and filtered to give **56**: pale yellow crystals; mp 120–130 °C. Anal. ($C_{23}H_{29}FO_3$) C, H.

The mother liquor was cooled to −78 °C and filtered to give **57**: yellow crystals; mp 74–87 °C. Anal. ($C_{23}H_{29}FO_3$) C, H.

Ethyl (*E*/*Z*)-4-(Diethoxyphosphinyl)-3-(trifluoromethyl)-2-butenoate (11). *N*-Bromosuccinimide (4.87 g, 27.4 mmol) and 55 mg of 2,2′-azobis(isobutyronitrile) (AIBN) in 30 mL of CCl_4 were heated to 70 °C, with stirring and 5.0 g (27.4 mmol) of 3-(trifluoromethyl)-2-butenoic acid ethyl ester[22,23] in 10 mL of CCl_4 was added. The reaction mixture was refluxed for 3 h, cooled, and filtered. The filtrate was evaporated and the residue was distilled to give 4.81 g (60.5%) of ethyl 3-(trifluoromethyl)-4-bromo-(*E*/*Z*)-2-butenoate as a colorless liquid, bp 75–80 °C (20 mm). Anal. ($C_7H_8BrF_3O_2$) C, H, Br.

The bromo ester (18.5 g, 70.7 mmol) and 13.0 g (78 mmol) of triethyl phosphite were heated at 140 °C for 3 h with removal of the bromoethane formed during the reaction. The crude product was distilled (Vigreux column) to give 17.2 g of **11**, bp 105–113 °C (1 mm), as a mixture of isomers. Anal. ($C_{11}H_{18}F_3O_5P$) C, H, F, P.

Ethyl (*E,E,E,E*)-3-(Trifluoromethyl)-7-methyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (58). To the anion, prepared from 9.44 g (29.7 mmol) of 11, 1.42 g (29.7 mmol) of 50% NaH, and 75 mL of DME at 23 °C under argon, 6.6 g (27 mmol) of **15** in 50 mL of DME was added slowly. The reaction was carried out and worked up (ether) as described above for **39**. The crude product (14.4 g) was purified by chromatography (300 g of silica gel, 1:19 ether–petroleum ether) to give 4.6 g (42%) of crystalline **58**, which after recrystallization (petroleum ether) gave 2.9 g (26%) of bright-yellow crystals, mp 72–75 °C. Anal. ($C_{23}H_{27}F_3O_3$) C, H, F.

4-(4-Methoxy-2,3,6-trimethylphenyl)-1,1,1-trifluoro-2-butyn-4-ol (59). Ethylmagnesium bromide was prepared from 10.6 g (0.44 mol) of magnesium metal and 43.4 g (0.40 mol) of ethyl bromide in ether in the usual manner. Trifluoropropyne (41 g, 0.44 mol) was then added through a gas dispersion tube. The reaction mixture was mechanically stirred at 23 °C under argon while the trifluoropropyne was recycled three times. Aldehyde **42** (a total of 60 g, 0.34 mol) in 100 mL of ether was added slowly in two portions at 23 °C with a 2-h interval between additions. The reaction was stirred for 1 h and cooled, and saturated aqueous NH_4Cl solution was added slowly with stirring. Workup (ether) gave 105 g of crude product, which was recrystallized twice (chloroform–hexane) to yield 61.5 g (67%) of **59**: white crystals; mp 126–130 °C. Anal. ($C_{14}H_{15}F_3O_2$) C, H, F.

(*E*)-4-(4-Methoxy-2,3,6-trimethylphenyl)-1,1,1-trifluoro-3-buten-2-one (60). A solution of 60 g (0.22 mol) of **59**, 300 mL of glacial acetic acid, 18.7 g (0.07 mol) of mercuric sulfate, and 12 mL of concentrated sulfuric acid was refluxed with stirring for 2 h, diluted with 4 L of ice–water, and extracted (ether). The crude product (65 g) was chromatographed (500 g of silica gel, 10% ether–petroleum ether), and the product was recrystallized (petroleum ether) to give 27 g (45%) of **60**: yellow crystals; mp 79–81 °C. Anal. ($C_{14}H_{15}F_3O_2$) C, H, F.

Methyl (*E,E*)-5-(4-Methoxy-2,3,6-trimethylphenyl)-3-(trifluoromethyl)-2,4-pentadienoate (61). In the usual manner, 4.92 g (0.103 mol) of 50% NaH, 20.1 g (0.111 mol) of **5**, and 250 mL of DME were reacted at 0 °C under argon, and 26 g (0.10 mol) of **60** in 200 mL of DME was added at 23 °C. The reaction mixture was refluxed for 2 h, cooled, and worked up (CH_2Cl_2) as previously described. The crude product (34.3 g) was purified by chromatography (700 g of silica gel, 3% ether in petroleum ether) to give 20.6 g (65.5%) of **61**, which upon crystallization (pentane, −70 °C) gave 10.3 g of yellow crystals, mp 42–48 °C. Anal. ($C_{17}H_{19}F_3O_3$) C, H, F.

(*E,E*)-5-(4-Methoxy-2,3,6-trimethylphenyl)-3-(trifluoromethyl)pentadien-1-ol (62). Ester **61** (17.4 g, 0.053 mol) in 500 mL of dry ether was reduced with 94.5 mL (0.144 mol) of *i*-Bu_2AlH (1.53 M in hexane) at −70 °C, quenched, and worked up in the usual manner. The crude crystalline product (15.7 g) was recrystallized (petroleum ether) to give 13 g (81%) of **62**, mp 69–71 °C. Anal. ($C_{16}H_{19}F_3O_2$) C, H, F.

(*E,E*)-4-(Methoxy-2,3,6-trimethylphenyl)-3-(trifluoromethyl)pentadien-1-al (63). A mixture of MnO_2 (78 g, 0.90 mol) and 13 g (0.043 mol) of **62** in 750 mL of methylene chloride was stirred at 23 °C under argon for 15 h. The usual workup gave 13.4 g of crude product, which was chromatographed (600 g of silica gel, 5% ether in petroleum ether) to give 10.1 g (78.5%) of **63** as yellow crystals. An analytical sample, recrystallized (pentane, −70 °C), had mp 55–58 °C. Anal. ($C_{16}H_{17}F_3O_2$) C, H, F.

Methyl (*E,E,E,E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3-methyl-7-(trifluoromethyl)-2,4,6,8-nonatetraenoate (64). The anion, prepared from 745 mg (3.35 mmol) of **10**, 116 mg (3.35 mmol) of 50% NaH, and 10 mL of DME at 0 °C, was

treated with aldehyde **63** (1 g, 3.35 mmol) in 5 mL of DME. The reaction was carried through and worked up (CH_2Cl_2) as previously described. The crude product (1.6 g) was purified by chromatography (25 g of silica gel, 5% ether in petroleum ether) to give 402 mg of starting material **63** and then 680 mg (51.5%) of **64**, yellow crystals; mp 112–113.5 °C, after recrystallization (petroleum ether). Anal. ($C_{22}H_{25}F_3O_3$) C, H, F.

Ethyl (*Z,Z,E,E*)-2,4-Difluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (65). The anion, prepared from 2.39 g (9.9 mmol) of **7**, 470 mg (9.8 mmol) of 50% NaH, and 12 mL of DME at 23 °C under argon, was reacted with 1 g (3.31 mmol) of **22** in 10 mL of DME at 23 °C under argon for 15 min as described above for **35**. After workup, 3.31 g of a yellow oil was obtained. Filtration (40 g of Fluorisil, CH_2Cl_2) yielded 2.64 g, which on crystallization (hexane) gave 2.19 g of **65**, a mixture of 2*E*,*Z* isomers, as yellow crystals, mp 59–64 °C.

A 500-mg sample in 40 mL of ether was stirred with 15 mg of iodine for 16 h at 23 °C and treated as described for **20**. The residue was crystallized (hexane) to give 154 mg of yellow crystals, mp 85–86 °C. Anal. ($C_{23}H_{28}F_2O_3$) C, H, F.

Ethyl (*Z,E,Z,E*)-2,6-Difluoro-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (66). The anion, prepared from 12.4 g (0.044 mol) of **8**, 2.1 g (0.044 mol) of 50% NaH, and 40 mL of DME, was treated with 7 g (0.027 mol) of **37** in 25 mL of DME and stirred at 23 °C under argon for 18 h. Workup (CH_2Cl_2) and filtration (silica gel, CH_2Cl_2) yielded 5.6 g (53%) of **66** as a mixture of 2*Z*,*E* isomers. Two recrystallizations (1:9 ether–petroleum ether) afforded 1.7 g of pure **66**: yellow crystals; mp 134–136 °C. Anal. ($C_{23}H_{28}F_2O_3$) C, H, F.

Ethyl (*Z,Z,E*)-2,4-Difluoro-5-methyl-7-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6-heptatrienoate (67). Sodium hydride (2.35 g, 0.049 mol, 50%), 15.4 g (0.063 mol) of **7**, and 70 mL of DME were reacted at 0 °C under argon in the usual manner. A solution of 12.8 g (0.049 mol) of **37** in 60 mL of DME was then added and the reaction was carried through as described above. The crude product (26 g) was filtered (Florisil, CH_2Cl_2) to give 18 g of **67** as a mixture of 2*Z*,*E* isomers. Crystallization (1:4 ether–petroleum ether) afforded 2.7 g of **67**: yellow crystals; mp 122–125 °C. The mother liquor was isomerized (235 mg of iodine, ether) in the dark at 23 °C for 30 min. A second crop (9.7 g) of pure **67** was obtained (72% total yield). Anal. ($C_{20}H_{24}F_2O_3$) C, H, F.

(*Z,Z,E*)-2,4-Difluoro-5-methyl-7-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6-heptatrienoic Acid (68). Hydrolysis of **67** (7 g, 0.02 mmol) was carried out as described above for **21**. Workup (CH_2Cl_2) gave 6.3 g of **68**: yellow crystals; mp 209–214 °C. Anal. ($C_{18}H_{20}F_2O_3$) C, H, F.

(*Z,Z,E*)-3,5-Difluoro-6-methyl-8-(4-methoxy-2,3,6-trimethylphenyl)-3,5,7-octatrien-2-one (69). The acid **68** (3.32 g, 0.01 mol) in 50 mL of THF–ether (2:3) was treated with CH_3Li (10 mL, 1.85 M in ether) in four portions as described for **22**. Workup gave 0.46 g of a neutral fraction containing mainly **69**. The aqueous phase was acidified (concentrated HCl) and extracted (CH_2Cl_2) to give 2.9 g of **68**.

The crude **69** (3.3 g from several preparations) was chromatographed (250 g of silica gel, 1:9 ether–petroleum ether) to give 1.8 g of **69**: yellow crystals; mp 85–100 °C.

Ethyl (*E,Z,Z,E*)-3,7-Dimethyl-4,6-difluoro-9-(4-methoxy-2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenoate (70). Phosphonate **6** (2.02 g, 9.02 mmol), 384 mg (8.04 mmol) of 50% NaH, and 9 mL of DME were reacted in the usual manner. A solution of 1.8 g (5.63 mmol) of **69** in 10 mL of DME was added at 23 °C. The reaction mixture was stirred at 23 °C overnight, worked up, and purified by chromatography (200 g of silica gel, 2:3 CH_2Cl_2–petroleum ether) to give 0.90 g, which was recrystallized (1:9 ether–petroleum ether) to give 0.66 g of **70**: yellow crystals; mp 110–118 °C. Anal. ($C_{23}H_{28}F_2O_3$) C, H; F: calcd, 9.73; found, 9.16.

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Supplementary Material Available: Spectral data for all compounds reported and experimental procedures for **71–74** are included (16 pages). Ordering information is given on any current masthead page.

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