lowed to acclimate to their environment for at least 7 days prior to use. Rats were housed individually in a temperature-controlled animal room maintained on a 12-h light–dark cycle. Laboratory rat chow and water were available at all times. Following decapitation with a guillotine, blood was collected in a beaker containing 0.5 mL of 0.25 M EDTA. Whole brains were immediately excised from the skull and dropped into liquid nitrogen within 1 min after decapitation. Frozen brains were homogenized by pulverization under liquid nitrogen with use of a ceramic mortar and pestle. Samples for the AChE assay were taken after weighed aliquots of the pulverized brain were placed in 10 mM sodium phosphate buffer (pH 7.4) at 4 °C and dispersed with a Polytron homogenizer (Brinkmann Instruments).

Registry No. 1, 6712-43-2; 2, 62884-14-4; 3, 93185-37-6; 4, 93185-38-7; 5, 93185-39-8; 6, 93185-40-1; 7, 6893-34-1; 8, 7279-54-1; 9, 93185-41-2; 10, 93185-43-4; 11, 93185-44-5; 2-PAM, 94-63-3; AChE, 9000-81-1; Me_3N, 75-50-3; $Cl(CH_2)_3Br$, 109-70-6; $Br(CH_2)_6Br$, 629-03-8; $MeSO_3Me$, 66-27-3; Et_2NH, 109-89-7; $CH_2{=}CH(CH_2)_2Br$, 5162-44-7; $MeSO_3(CH_2)_2Cl$, 3570-58-9; CH_3CO_2H, 64-19-7; pyridine, 110-86-1; 2-picolyl chloride hydrochloride, 6959-47-3; 2-picolyl chloride, 4377-33-7; succinimide, 123-56-8; 4-vinylpyridine, 100-43-6; 4-(2-succinimidoethyl)pyridine, 93185-45-6; 2-vinylpyridine, 100-69-6; 2-(2-succinimidoethyl)-pyridine, 74274-11-6; 4-[2-(diethylamino)ethyl]pyridine, 67580-61-4; 2-[2-(diethylamino)ethyl]pyridine, 25877-30-9; 2-[2-(diethylamino)ethyl]-1-methylpyridinium iodide, 93185-46-7; 2-picoline, 109-06-8; epichlorohydrin, 106-89-8; 1-(2-pyridyl)-4-chloro-3-butanol, 93185-47-8; *N*-(3-buten-1-yl)succinimide, 58805-10-0; *N*-(3,4-epoxybutyl)succinimide, 93185-48-9; *N*-[4-(diethylamino)-3-hydroxybutyl]succinimide, 93185-49-0; *N*-[4-(diethylamino)-3-oxobutyl]succinimide, 93222-21-0; (−)-eserine, 57-47-6; (−)-eseroline, 469-22-7; *O*-(chloroethyl)eseroline, 93185-42-3.

Synthesis and Characterization of Selected Heteroarotinoids. Pharmacological Activity as Assessed in Vitamin A Deficient Hamster Tracheal Organ Cultures. Single-Crystal X-ray Diffraction Analysis of 4,4-Dimethylthiochroman-6-yl Methyl Ketone 1,1-Dioxide and Ethyl (*E*)-*p*-[2-(4,4-Dimethylthiochroman-6-yl)propenyl]benzoate

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There is reported the first four members of heteroarotinoids, the names of which are ethyl (*E*)-*p*-[2-(4,4-dimethylthiochroman-6-yl)propenyl]benzoate (**1b**), ethyl (*E*)-*p*-[2-(4,4-dimethylchroman-6-yl)propenyl]benzoate (**1c**), ethyl (*E*)-*p*-[2-(4,4-dimethyl-1-oxothiochroman-6-yl)propenyl]benzoate (**1d**), and (*E*)-*p*-[2-(4,4-dimethylchroman-6-yl)propenyl]benzoic acid (**1e**). IR, ^1H NMR and ^{13}C NMR data have been recorded for each compound and support the structural assignments. To provide a firm basis for comparison purposes of future analogues, an X-ray analysis was performed on a single crystal of ethyl (*E*)-*p*-[2-(4,4-dimethylthiochroman-6-yl)propenyl]benzoate (**1b**) and a precursor 4,4-dimethylthiochroman-6-yl methyl ketone 1,1-dioxide (**18**). These data for the heteroarotinoid **1b** revealed that the two aryl ring systems were nearly perpendicular in each of the two molecules present in the unit cell (86.37° and 84.17°, respectively). The space group for both molecules was $P\bar{1}$ in triclinic systems. Unit cell dimensions (at 15 °C) are as follows: for **1b**, a = 20.568 (6) Å, b = 14.760 (3) Å, c = 7.679 (2) Å, α = 113.33 (2)°, β = 79.45 (2)°, γ = 79.98 (2)°, Z = 4; for **18**, a = 9.292 (5) Å, b = 9.291 (5) Å, c = 7.951 (3) Å, α = 102.16 (3)°, β = 77.49 (3)°, γ = 79.60 (4)°, Z = 2. The sulfur-containing ring is in a distorted half-chair in **1b** and the methyl carbon C(12) is shown to be trans to H(13) at the C(11)–C(13) bond. The biological activity of these arotinoids was determined in the tracheal organ culture assay and compared with *trans*-retinoic acid for ability to reverse keratinization in vitamin A deficient hamsters. The ester **1b** displayed activity about one-half log unit less than that of the reference while **1c** and **1e** had activity nearly one log until less than *trans*-retinoic acid. The sulfoxide was the least active of the heteroretinoids.

Retinoids (vitamin A and derivatives thereof) constitute a group of compounds of enormous current interest.[2] The stimulus for this interest arises from observations that these compounds exhibit some antitumor activity[3] and exert a preventive activity in models of chemical carcinogensis.[2c,3-5] Unfortunately, the use of natural retinoids in cancer chemotherapy has some disadvantages. With the exception of *trans*-retinoic acid, natural and retinoids are stored in the liver, and blood levels of the materials do not increase proportionately even after massive doses.[6] Thus, it is difficult to achieve a good distribution and to deliver a retinoid to specific target sites. In addition, acute toxicity[6] has been associated with high dosages of natural retinoids. This "hypervitaminosis A" limits clinical use of such compounds. Modifications of the basic retinoid structure have been the subject of intensive effort recently.[7]

† Oklahoma State University.
‡ IIT Research Institute.

(1) Taken in part from the Ph.D. Dissertation, Oklahoma State University, May, 1983. Phillips Petroleum Fellow, Summer, 1982; Skinner Fellow, 1982–1983.

(2) (a). Wolf, G. *Nutr. Rev.* **1982**, *40*, 257. (b) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *25*, 1269. (c) Peto, R.; Doll, R.; Buckley, J. D.; Sporn, M. B. *Nature (London)* **1981**, *290*, 201. (d) Peck, G. L. *Gynecol. Oncol.* **1981**, *12*, S331. (e) Sporn, M. B.; Newton, D. L. In "Inhibition of Tumor Induction and Development"; Zedeck, M.; Lipkin, M., Ed.; Plenum Press: New York, 1981; pp 71–100. (f) Newton, D. L.; Henderson, W. R.; Sporn, M. B. "Structure–Activity Relationships of Retinoids"; National Cancer Institute, Revised Edition, February 26, 1980. (g) Sporn, M. B.; Newton, D. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2528. (h) Lasnitzki, J. *Brit. J. Cancer* **1976**, *34*, 239.

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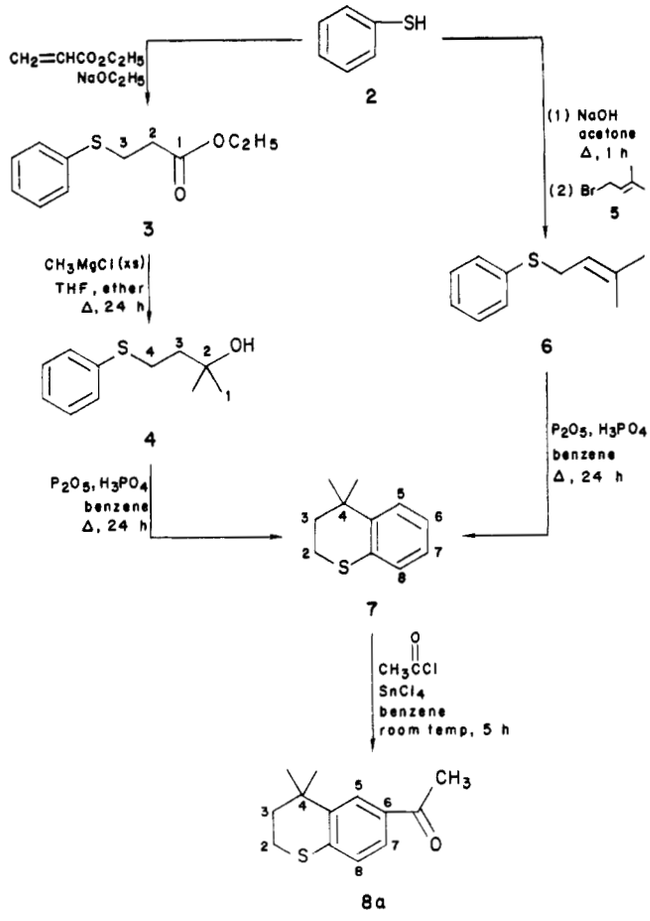
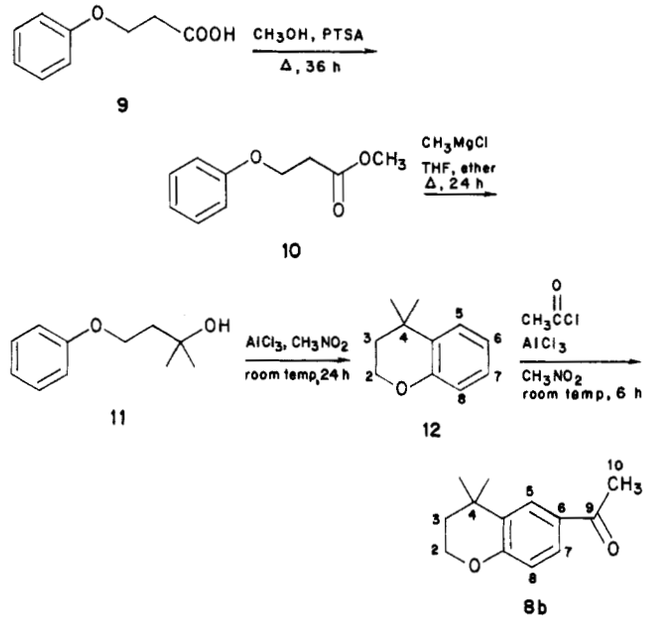
Scheme I

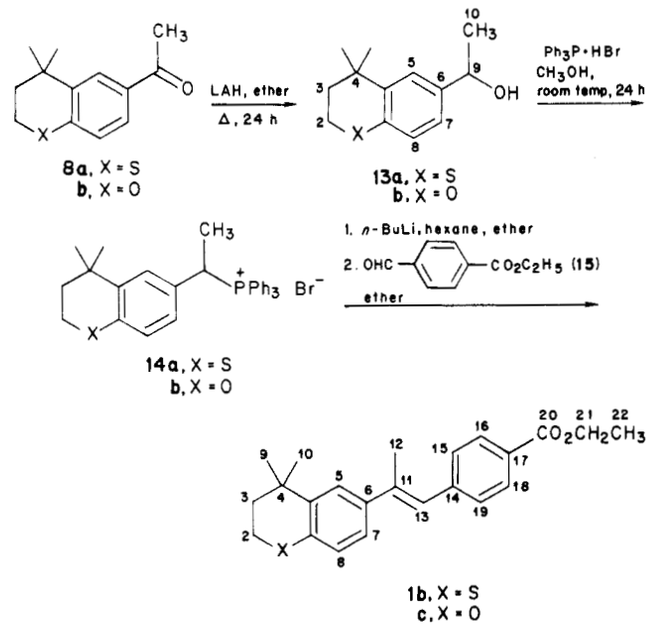


Systems with fused aryl rings (as in **1a**[5n,8a] and related molecules[8]) have good potency[9,10] (in a tracheal assay[5n] the

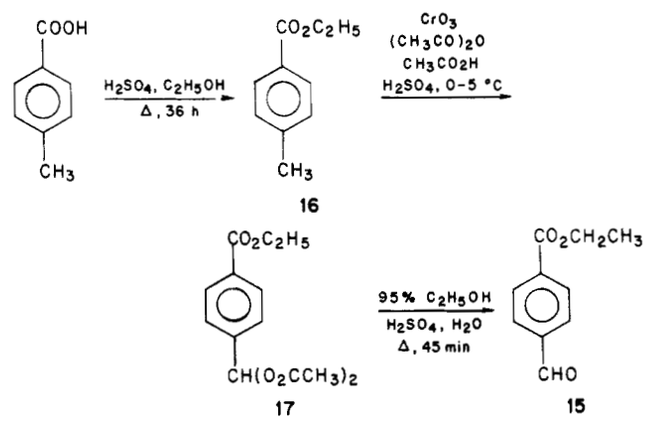
Scheme II



Scheme III



Scheme IV



ED_{50} for **1a** was reported to be 1×10^{-11} M compared to an ED_{50} of 3×10^{-11} M for the standard *trans*-retinoic

(3) (a) Davies, R. E. *Cancer Res.* **1967**, *27*, 237. (b) Chytil, F.; Ong, D. E. *Nature (London)* **1972**, *260*, 1976. (c) Moon, R. C.; Grubbs, C. J.; Sporn, M. B.; Goodman, D. G. *Nature (London)* **1977**, *267*, 620. (d) Verma, A. K.; Boutwell, R. K. *Cancer Res.* **1977** *37*, 2196. (e) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Smith, J. M. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1976**, *35*, 1332.

(4) Seifter, E.; Zisblatt, M.; Levine, N. *Life Sci.* **1973**, *13*, 145.

(5) For references on the effectiveness of retinoids to suppress or reverse the transformation of premalignant cells to a malignant state, see: (a) Sporn, M. B.; Newton, D. L.; Smith, J. M.; Acton, N.; Jacobson, A. E.; Brossi, A. In "Carcinogens; Identification and Mechanisms of Actions"; Griffin, A. C., Shaw, C. R., Eds.; Raven Press: New York, 1979; pp 441–453. (b) Reference 3c. (c) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Henderson, W. R. *Nature (London)* **1976**, *263*, 100. (d) Sporn, M. B.; Newton, D. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2528. (e) Todaro, G. J.; DeLarco, J. E.; Sporn, M. B. *Nature (London)* **1978**, *276*, 272.

For references to show that retinoids can effect the regression of epithelial papillomas induced by carcinogens in animals, see: (f) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L.; Springer, S. *Science* **1977**, *195*, 487. (g) Becci, P. J.; Thompson, H. J.; Grubbs, C. J.; Squire, R. A.; Brown, C. C.; Sporn, M. B.; Moon, R. C. *Cancer Res.* **1978**, *38*, 4663. (h) Bollag, W. *Cancer Chemother. Rep.* **1971**, *55*, 53. (i) Reference 3c.

For references that show the inhibitory prowess of retinoids against the tumor-promoting action of phorbol esters, see: (j) Verma, A. K.; Shapas, B. G.; Rice, H. M.; Boutwell, R. K. *Cancer Res.* **1979**, *39*, 419. (k) Verma, A. K.; Rice, H. M.; Shapas, B. G.; Boutwell, R. K. *Cancer Res.* **1978**, *38*, 793. (l) Verma, A. K.; Boutwell, R. K. *Cancer Res.* **1977**, *37*, 2196. (m) Verma, A. K.; Slage, T. J.; Wertz, T. W.; Mueller, G. C.; Boutwell, R. K. *Cancer Res.* **1980**, *40*, 2367. (n) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413.

Table I. Crystal Data for 18

formula	$C_{13}H_{16}O_3S$	γ	79.60 (4)
mol wt	252.3	volume	631.5 (5) Å
Mo K_α	0.71069 Å	μ(Mo K_α)	2.38 cm^{-1}
a	9.292 (5)	independent obs	5373
b	9.219 (5)	R	6.4%
c	7.951 (3)	space group	$P\bar{1}$
α	102.16 (3)°	Z	2
β	77.49 (3)	D_{calcd}	1.327 g cm^{-3}

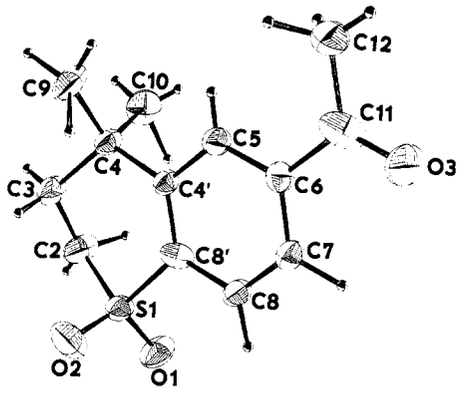
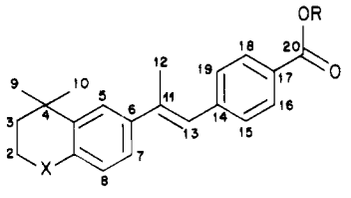


Figure 1. ORTEP drawing for sulfone 18.

acid), but frequently these "arotinoids" have shown undesirable toxic properties.[8] One objective of our work was to obtain heteroarotinoids which had increased hydrophilicity and lower lipophilicity with, hopefully, concomitant lower toxicity. Reported herein are the syntheses and selected pharmacological properties of heteroarotinoids **1b–e**. These structures also possess the 12-s-cis topology, which is a structural feature that appears to convey high activity in the chemoprophylaxis of epithelial cancer.[5n,11]

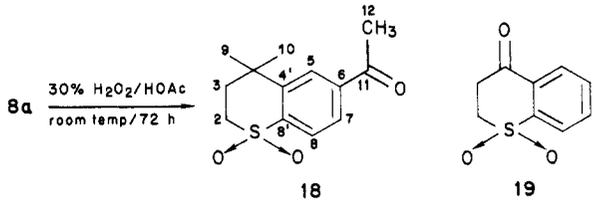


1a, X = $C(CH_3)_2$; R = C_2H_5
b, X = S; R = C_2H_5
c, X = O; R = C_2H_5
d, X = S(O); R = C_2H_5
e, X = O; R = H

Synthesis. Synthetic methodologies to prepare **1b** and **1c** are shown in Schemes I–III. Although our initial entry to obtain **7** utilized the left pathway of Scheme I, the pathway on the right gave comparable yields in less time and also served as an independent synthesis to confirm the structure. Oxidation of **1b** with $NaIO_4$ in methanol–water gave sulfoxide **1d**. Saponification of ester **1c**, followed by neutralization, gave acid **1e**.

Since ethyl 4-formylbenzoate (**15**) was not available, a synthesis was effected as shown in Scheme IV (**16** → **17** → **15**). Crude acetate **17** could be stored (only some darkening and hydrolysis occurred) prior to conversion to **15**. It was found convenient to hydrolyze the crude **17** to **15** without isolation of the former.

The structural configuration of **8a** was determined via a single-crystal X-ray diffraction analysis of the corresponding crystalline sulfone **18** (crystal data in Table I), confirming the position of the acetyl group. Sulfone **18** crystallizes in a centrosymmetric cell with one molecule per asymmetric unit. The hetero ring adopts a C2/C3 half-chair conformation unlike that observed in **19**.[12] The C–S bond lengths (Table II) involving C(8′) [sp^2 hybridized] and C(2) [sp^3 hybridized] are nearly equal in **18** [S–C(8′), 1.767 (3) Å and S–C(2), 1.761 (4) Å] as in **19**[12] [1.766 (2) Å and 1.763 (2) Å, respectively]. The S–O bonds in **18** are essentially equal in contrast to those in **19**,[12] where a difference of 0.01 Å was observed. Figure 1 is an ORTEP drawing of **18**.

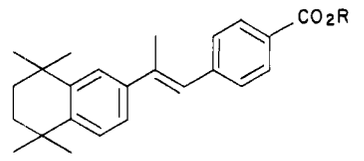


The ^1H NMR spectral data for **1b,c** are given in the Experimental Section. Certain common characteristics deserve mention. Signals for the vinyl proton in **1b–e** occurred as singlets at δ 6.82, 6.77, 6.80, and 6.86, respectively. In model *E*-arotinoids **20–23**[8a] the corresponding signal was observed at δ 6.85, 6.88, 6.72, and 6.82,

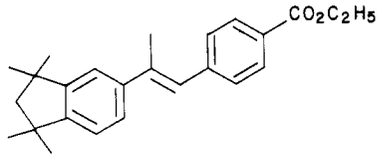
Table II. Bond Angles and Distances of 18

angle	angle, deg	bond	bond distance, Å
O1–S1–O2	117.4 (2)	S1–O1	1.443 (3)
O1–S1–C2	109.3 (2)	S1–O2	1.447 (4)
O1–S1–C8′	109.3 (2)	S1–C2	1.761 (4)
O2–S1–C2	110.1 (2)	S1–C8′	1.767 (3)
O2–S1–C8′	107.3 (2)	C2–C3	1.539 (5)
C2–S1–C8′	102.2 (2)	C3–C4	1.535 (5)
S1–C2–C3	107.7 (2)	C4–C9	1.548 (5)
C2–C3–C4	113.5 (4)	C4–C10	1.546 (6)
C3–C4–C9	106.3 (3)	C4–C4′	1.537 (4)
C3–C4–C10	110.3 (3)	C4′–C5	1.397 (4)
C3–C4–C4′	112.3 (3)	C4′–C8′	1.397 (4)
C9–C4–C10	110.1 (3)	C5–C6	1.394 (5)
C3–C4–C4′	112.3 (3)	C6–C11	1.501 (4)
C9–C4–C4′	110.4 (2)	C6–C7	1.399 (5)
C10–C4–C4′	107.4 (3)	C7–C8	1.374 (4)
C4–C4′–C5	118.9 (3)	C8–C8′	1.409 (5)
C4–C4′–C8′	124.4 (2)	C11–C12	1.505 (6)
C5–C4′–C8′	116.7 (3)	C11–O3	1.227 (5)
C6–C5–C4′	121.8 (3)		
C5–C6–C7	120.1 (3)		
C5–C6–C11	121.7 (3)		
C7–C6–C11	118.2 (3)		
C6–C7–C8	119.6 (3)		
C7–C8–C8′	119.6 (3)		
S1–C8′–C8	114.9 (2)		
S1–C8′–C4′	122.8 (2)		
C8–C8′–C4′	122.2 (2)		
O3–C11–C12	121.5 (3)		
O3–C11–C6	119.5 (3)		
C6–C11–C12	119.0 (4)		

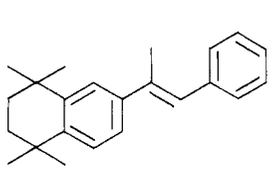
(6) Orfanes, C. E.; Brown-Falcoz, O.; Farber, E. M.; Grupper, C.; Polano, M. K.; Schuppli, R. "Retinoids: Advances in Basic Research and Therapy"; Springer-Verlag: New York, 1981.
(7) See ref 2c and Waugh, K. M., Ph.D. Dissertation, Oklahoma State University, May, 1983, for reviews in the area.
(8) (a) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.–Chim. Therap.* **1980**, *15*, 9. (b) Lovey, A. J.; Pawson, B. A. *J. Med. Chem.* **1982**, *25*, 71. Dawson, M. I.; Chen, R. L.-S.; Derzinski, K.; Hobbs, P.; Chao, W.-R. *J. Med. Chem.* **1983**, *26*, 1653.
(9) The assays that are commonly used involved cultures of the tracheal organ taken from vitamin A deficient hamsters. The basic procedure is given in ref 5n.
(10) A second assay involves the assessment of retinoids on chemically induced multiple papillomas; see ref 8a.
(11) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583.
(12) Ealick, S. E.; van der Helm, D.; Baker, J. K.; Berlin, K. D. *Acta Crystallogr., Sect. B* **1979**, *B35*, 495.



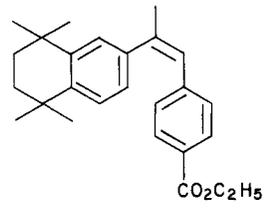
20, R = C_2H_5
21, R = H



22



23



24

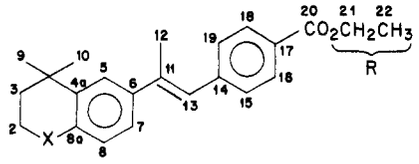
respectively, while in *Z*-arotinoid **24** a singlet occurred at δ 6.46. Also, the signal for the vinyl-substituted methyl group in **1b–e** was a singlet at δ 2.28, 2.27, 2.31, and 2.30, respectively. In **20–23**, this corresponding signal appeared at δ 2.30, 2.37, 2.27, and 2.28, respectively, while in *Z*-arotinoid **24**,[8a] a signal was observed at δ 2.23. These data suggest an *E* configuration for **1b–e** although X-ray diffraction data for members of **20–23** are not available to confirm the models.

The ^{13}C NMR data for **1b–e** are given in Table III, and assignments were based, in part, upon comparisons with precursors **7**, **8a,b**, **12**, **13a,b**, **14a,b** and **15**. The development of heteronuclear correlated two-dimensional (HETCOR 2-D) NMR experiments[13] permits correlation of an ^1H chemical shift for a particular proton with the ^{13}C NMR chemical shift of the corresponding carbon provided the ^1H or ^{13}C spectrum can be assigned unequivocally. Using INEPT[14] experiments, the assignments could be made for the ^{13}C NMR signals in the aliphatic region for **1d**. Aromatic protons H(5), H(7), and H(8) gave expected splitting patterns at δ 7.58 (d, $J_{5,7}$ = 3 Hz), 7.51 (dd, $J_{5,7}$ = 3 Hz, $J_{7,8}$ = 9 Hz), and δ 7.77 (d, $J_{7,8}$ = 9 Hz). Similar patterns and coupling values were found in **1b,c,e**. With use of HETCOR 2-D experiments,[13] it was possible to correlate these protons signals with those from the appropriately substituted carbon as shown in the contour plot[13] for **1e** (Figure 2). Similar assignments were possible for **1b,c** for the corresponding aromatic protons H(5,7,8) as well as for H(2,3). These data should serve as standards for related systems.

In view of the relationship of activity with the geometric arrangement at the C(11)–C(13) double bond[11] [corresponds to the C(9)–C(10) double bond in retinoic acid], the stereochemistry at this bond was confirmed by a single-crystal X-ray analysis of **1b** (crystal data in Table IV). Two molecules (A and B) are present in the unit cell (Figures 3 and 4). Although many structural details are in close agreement in the two molecules, disorder is evident at C(2) and C(3) in molecule A and at C(22) in molecule B as reflected in the anisotropic thermal parameters for these atoms and in the related bond angles and distances

(13) Gray, G. A. *Varian Instrum. Appl.* **1982**, *16*, 11. Gray, G. A. Org. *Magn. Reson.* **1983**, *21*, 111 and references therein.
(14) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760.

Table III. ^{13}C NMR Data for the Heteroarotinoids



1b, X = S
1c, X = O
1d, X = O; R = H
1e, X = SO

carbon no.	chemical shifts 1b	1c	1d	1e
2	23.0	63.1	63.1	42.9
3	37.6	37.6	37.6	29.4
4	33.1	30.7	30.7	34.4
9	30.2	31.1	31.1	31.3
10	30.2	31.1	31.1	31.1
12	17.6	17.7	17.8	17.7
21	60.8	60.8		60.9
22	14.3	14.4		14.3
5	124.0	124.5	124.6	125.5
7	123.7	124.9	124.9	124.8
8	126.4	116.8	116.8	130.5
13	125.7	125.1	125.0	128.4
15 (19)	128.9[a]	129.0[a]	129.1[a]	129.0[a]
16 (18)	129.4[a]	129.4[a]	130.1[a]	129.5[a]
20	166.5	166.1	172.1	166.3
nonprotonated aromatic and vinylic carbons	143.0	153.4	153.5	147.1
	141.7	143.3	144.3	144.6
	139.3	139.4	139.9	142.2
	139.2	135.7	135.6	138.6
	131.4	131.3	131.3	136.9
	128.0		126.8	128.7

[a] May be interchanged. All values are in ppm referenced from Me_4Si.

Table IV. Crystal Data for **1b**

formula	$C_{23}H_{26}O_2S$	γ	79.98 (2)
mol wt	366.5	volume	2024.3 (10) Å^3
Mo K_α	0.71069 Å	μ(Mo K_α)	1.65 cm^{-1}
a	20.568 (6)	independent obs	3463
b	14.760 (3)	*R*	5.8%
c	7.679 (2)	space group	$P\bar{1}$
α	113.33 (2)°	*Z*	4
β	79.45 (2)	D_{calcd}	1.202 g cm^{-3}

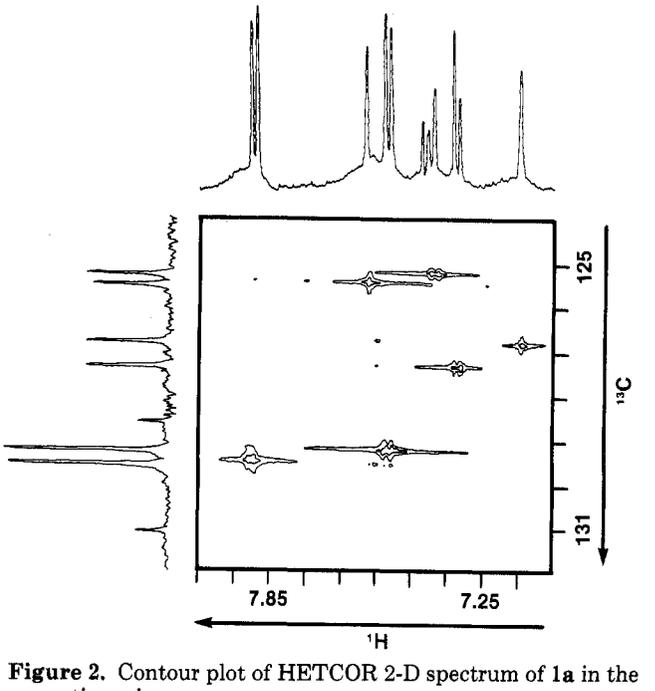


Figure 2. Contour plot of HETCOR 2-D spectrum of **1a** in the aromatic region.

Table V. Bond Angles (deg) and Distances (Å) for $C_{23}H_{26}O_2S$ (**1b**)

Bond Distances

	molecule A	molecule B		molecule A	molecule B		molecule A	molecule B
S1–C2	1.778 (15)	1.786 (8)	C6–C7	1.396 (10)	1.390 (9)	C16–C17	1.380 (10)	1.369 (12)
S1–C8′	1.761 (9)	1.759 (9)	C7–C8	1.370 (12)	1.373 (12)	C17–C18	1.373 (9)	1.371 (12)
C2–C3	1.324 (18)	1.489 (13)	C8–C8′	1.403 (10)	1.393 (11)	C18–C19	1.386 (13)	1.386 (14)
C3–C4	1.519 (18)	1.556 (13)	C6–C11	1.484 (11)	1.494 (12)	C19–C14	1.399 (10)	1.393 (11)
C4–C4′	1.521 (9)	1.533 (10)	C11–C12	1.482 (11)	1.500 (8)	C17–C20	1.481 (13)	1.480 (14)
C4–C9	1.537 (11)	1.512 (10)	C11–C13	1.358 (11)	1.341 (10)	C20–O1	1.201 (10)	1.203 (12)
C4–C10	1.501 (16)	1.548 (13)	C13–C14	1.471 (12)	1.471 (13)	C20–O2	1.344 (10)	1.332 (12)
C4′–C8′	1.403 (10)	1.396 (9)	C14–C15	1.398 (10)	1.387 (10)	O2–C21	1.479 (13)	1.448 (17)
C4′–C5	1.401 (12)	1.426 (12)	C15–C16	1.387 (13)	1.380 (14)	C21–C22	1.478 (13)	1.370 (21)
C5–C6	1.393 (10)	1.387 (10)						

Bond Angles

	molecule A	molecule B		molecule A	molecule B
C2–S1–C8′	100.0 (6)	102.0 (4)	C7–C6–C11	122.2 (6)	121.8 (6)
S1–C2–C3	119.5 (12)	112.4 (6)	C6–C11–C12	116.7 (7)	117.0 (6)
C2–C3–C4	122.4 (9)	114.9 (8)	C6–C11–C13	119.8 (7)	119.7 (5)
C3–C4–C4′	113.8 (8)	111.4 (5)	C12–C11–C13	123.6 (7)	123.3 (7)
C3–C4–C9	99.3 (7)	110.4 (7)	C11–C13–C14	125.5 (7)	128.0 (6)
C3–C4–C10	111.3 (10)	104.5 (7)	C13–C14–C15	122.2 (6)	122.2 (7)
C9–C4–C10	106.6 (8)	110.2 (6)	C13–C14–C19	120.6 (6)	120.8 (6)
C4′–C4–C9	110.8 (7)	110.8 (7)	C15–C14–C19	117.3 (8)	117.0 (8)
C4′–C4–C10	111.4 (6)	109.2 (7)	C14–C15–C16	120.6 (7)	121.0 (7)
C4–C4′–C8′	124.1 (7)	124.2 (7)	C15–C16–C17	121.0 (6)	121.9 (7)
C4–C4′–C5	119.7 (6)	119.2 (5)	C16–C17–C18	119.2 (8)	117.8 (8)
C5–C4′–C8′	116.1 (6)	116.6 (6)	C17–C18–C19	120.3 (7)	121.4 (8)
C4′–C5–C6	124.5 (6)	123.4 (5)	C18–C19–C14	121.4 (6)	121.0 (7)
C5–C6–C7	116.5 (7)	117.7 (7)	C16–C17–C20	116.9 (6)	119.1 (7)
C6–C7–C8	121.7 (6)	120.3 (7)	C18–C17–C20	123.7 (7)	123.1 (8)
C7–C8–C8′	120.3 (7)	122.1 (6)	C17–C20–O1	125.3 (8)	124.8 (9)
C8–C8′–C4′	120.8 (7)	119.9 (8)	C17–C20–O2	112.5 (7)	111.8 (8)
C8–C8′–S1	114.7 (6)	114.7 (5)	O1–C20–O2	122.2 (9)	123.4 (9)
C4′–C8′–S1	124.6 (6)	125.4 (6)	C20–O2–C21	114.6 (6)	116.5 (7)
C5–C6–C11	121.3 (6)	120.4 (5)	O2–C21–C22	105.9 (7)	110.7 (12)

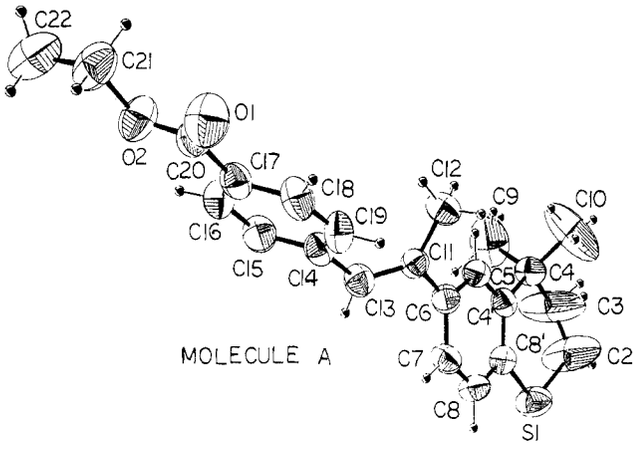


Figure 3. ORTEP drawing of molecule A in the unit cell of **1b**.

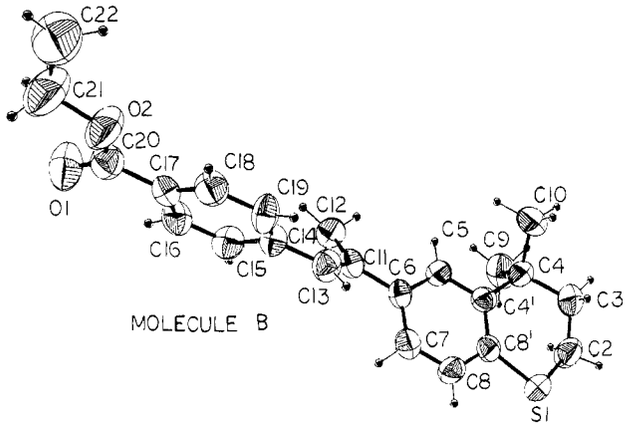
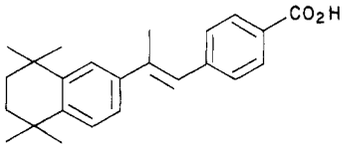


Figure 4. ORTEP drawing of molecule B in the unit cell of **1b**.

(Table IV). These data reveal clearly that the methyl carbon C(12) is trans to H(13) at the C(11)–C(13) double bond. The two aromatic rings [carbons C(14) through C(19) and C(4′), C(5), C(6), C(7), C(8) and C(8′)] subtend angles in the range of 39.42–52.72° (see Table V) with the plane of C(6), C(11), C(12), and C(13). Consequently, the aryl rings appear nearly perpendicular to each other [86.37° in molecule A and 84.17° in molecule B]. It is interesting to compare these angles with that of **25**[8a] in



25

which the two aryl rings show a displacement angle of 71° between the two planes. The sulfur-containing ring in **1b** exists in a distorted half-chair form with C(2) and C(3) displaced by approximately equal distances [−0.28 Å for C(2) and +0.47 Å for C(3) from the plane: C(4), C(4′), and S(1)] in molecule B where no disorder is evident in the hetero ring. In view of the activity found for **1b**, the lack of planarity for the aryl groups attached to C(11)–C(13) suggests that total planarity of structure may not be required for maximum chemoprophylaxis of epithelial cancer.

Pharmacological Activity of 1b–e. The pharmacological action of heteroarotinoids **1b–e** was assessed by using the standard hamster tracheal organ culture bioassay developed by Newton and co-workers.[2f,5n] The assay involves the ability of a test compound in vitro to reverse keratinization in tracheal organ cultures obtained from vitamin A deficient hamsters. A compound is considered active if neither keratin or keratohyaline granules are observed or if only keratohyaline granules were absent. If both were observed, the test compound was considered

Table VI. Activity of **1b–e** in the Hamster Tracheal Organ Culture Assay[5n]

retinoid	concn, M	% active	ED_{50},[a] M
trans-retinoic acid	10^{-10}	76.9	2×10^{-11}
	10^{-11}	41.7	
	10^{-12}	23.1	
1b	10^{-9}	100	6×10^{-11}
	10^{-10}	53.8	
	10^{-11}	28.6	
	10^{-12}	33.7	
trans-retinoic acid	10^{-10}	100	9×10^{-12}
	10^{-11}	53.8	
	12^{-12}	23.1	
1c	10^{-9}	100	1×10^{-10}
	10^{-10}	50.0	
	10^{-11}	28.2	
trans-retinoic acid	10^{-10}	83.3	1×10^{-11}
	10^{-11}	50.0	
	10^{-12}	16.7	
1d	10^{-8}	71.4	6×10^{-10}
	10^{-9}	71.4	
	10^{-10}	18.6	
trans-retinoic acid	10^{-10}	83.7	1×10^{-11}
	11^{-11}	50.0	
	10^{-12}	33.3	
1e	10^{-8}	100	1×10^{-10}
	10^{-9}	100	
	10^{-10}	57.1	
	10^{-11}	11.1	

[a] ED_{50} (M) is the dose for reversal of keratinization in epithelium of 50% of retinoid-deficient hamster tracheas in organ culture.

inactive. Also the standard *trans*-retinoic acid was examined simultaneously as a control with each compound in separate experiments.

It is clear that **1b** showed good activity (Table VI) and approximately one-half log unit less than that of all *trans*-retinoic acid. Heteroarotinoids **1c** and **1e** displayed activity of about one log unit unit less than that of the standard. The sulfoxide analogue **1d** was the least active of the four systems examined. Work is continuing in this general area since it is clear that the nature of the heteroatom does have a significant influence on the activity of the arotinoid.

Experimental Section

All reactions carried out at room temperature were at or near 25 °C. All reactions were stirred with a magnetic stirrer unless otherwise specified. During workup, solvents were removed with a rotary evaporator unless otherwise stated. A Varian XL-100 NMR spectrometer equipped with a Nicolet TT-100 PFT accessory or a Varian XL-300 NMR spectrometer was used. All NMR data were reported in ppm or δ values downfield from Me_4Si as an internal reference. IR spectral data were obtained with a Perkin-Elmer 681 IR spectrophotometer. Melting points were determined with a Thomas-Hoover melting point apparatus and were uncorrected.

The following starting materials and special reagents were purchased from the source listed and were used without further purification unless otherwise indicated: thiophenol (Aldrich), ethyl acrylate (Aldrich), 1-bromo-3-methyl-2-butene (Columbia), acetyl chloride (Fisher), methylmagnesium chloride/THF (2.9 M, Aldrich), *p*-toluic acid (Aldrich), α-bromo-*p*-toluic acid (Aldrich), stannic chloride (Baker), aluminum chloride (Fisher), and 3-phenoxypropionic acid (Columbia). Ether and thiophene-free benzene were distilled from sodium prior to use. All other solvents were used without purification. All solids were recrystallized to a constant melting point in each example. All TLC work was done with silica G 60 F_{254} (EM, 0.20-mm layer).

Ethyl 3-(Phenylthio)propionate (3). Freshly distilled ethyl acrylate (75 mL) was added dropwise under N_2 to a stirred, ice-cold mixture of thiophenol (**2**; 31.5 g, 0.286 mol) and sodium ethoxide (1.0 g). The ice bath was removed, and the mixture was stirred at room temperature for 24 h. The mixture was diluted with ether (30 mL) and filtered. The ether and excess ethyl acrylate were removed (vacuum). Vacuum distillation gave 49.6 g (82.5%) of **3** as a colorless liquid: bp 115–118 °C (0.2 mm) [lit.[15] bp 117 °C (2.5 mm)]; IR (neat) 1730–1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.22 (t, 3 H, OCH_2CH_3), 2.58 (t, 2 H, $CH_2CO_2C_2H_5$), 3.14 (t, 2 H, SCH_2), 4.1 (q, 2 H, OCH_2CH_3), 7.07–7.37 (m, 5 H, Ar H); ^{13}C NMR ($DCCl_3$) 14.2 (OCH_2CH_3), 29.0 (SCH_2), 34.4 (CH_2CO_2), 60.5 (OCH_2CH_3), Ar C (126.3, 128.8, 129.8, 135.2), 171.3 ppm (C=O).

2-Methyl-4-(phenylthio)-2-butanol (4). A solution of ethyl 3-(phenylthio)propionate (**3**; 20.0 g, 0.095 mol) in dry ether (5 mL) was added under N_2 to a stirred solution of methylmagnesium chloride in THF (2.9 M, 105 mL, 0.304 mol) at a rate such that the solution boiled. The solution was then heated at reflux for an addition 36 h. The mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl. The supernatant liquid was decanted, and the residue was washed with dry ether (3 × 50 mL). The combined organics were dried (Na_2SO_4), and the ether was removed (vacuum). Vacuum distillation of the crude oil gave 14.95 g (80.1%) of **4** as a colorless liquid: bp 93–98 °C (0.01 mm) [lit.[16] bp 110–113 °C (0.7 mm)]; IR (neat) 3200–3600 cm^{-1} (OH); ^1H NMR ($DCCl_3$) δ 1.17 (s, 6 H, $(CH_3)_2$), 1.66–1.84 (m, 2 H, Ar SCH_2CH_2), 2.38–2.47 (br s, 1 H, OH), 2.88–3.05 (m, 2 H, Ar SCH_2, 7.04–7.34 (m, 5 H, Ar H); ^{13}C NMR ($DCCl_3$) 28.2 (SCH_2), 28.9 (CH_3), 42.4 (SCH_2CH_2), 70.2 (COH), Ar C (125.3, 128.1, 128.4 ppm).

3-Methyl-1-(phenylthio)-2-butene (6).[17,18] A mixture of thiophenol (**2**; 16.3 g, 0.148 mol) and NaOH (6.0 g, 0.150 mol) in acetone (100 mL) was heated at reflux under N_2 with vigorous stirring for 1 h. A solution of 1-bromo-3-methyl-2-butene (**5**; 22.3 g, 0.149 mol) in acetone (20 mL) was then added dropwise. The resulting mixture was maintained at reflux for 24 h. The mixture was concentrated to 30 mL, diluted with H_2O (75 mL), and extracted with ether (2 × 50 mL). The organic layers were combined and washed with 5% aqueous NaOH (3 × 30 mL), H_2O (50 mL), and brine (50 mL). After the solution was dried (Na_2SO_4), the solvent was removed to leave a pale yellow liquid. Vacuum distillation gave 22.9 g (83.4%) of **6** as a pale yellow liquid: bp 76–78 °C (0.14 mm); ^1H NMR ($DCCl_3$) δ 1.55 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 3.52 (d, 2 H, $PhSCH_2$), 5.24–5.34 (m, 1 H, $(CH_3)_2C=CH$), 7.1–7.36 (m, 5 H, Ar H), ^{13}C NMR ($DCCl_3$) 17.6, 29.6, 32.1, 119.2, Ar C (136.7, 136.0, 129.4, 128.4, 125.7 ppm). The liquid was used without further purification.

4,4-Dimethylthiochroman (17).[18] **Method I.** A mixture of 2-methyl-4-(phenylthio)-2-butanol (**4**; 10.0 g, 0.051 mol), H_3PO_4 (85%, 5 mL), and benzene (50 mL) was heated to reflux under N_2 with vigorous stirring for 20 h. During this period, P_2O_5 (3 × 60 g, 0.126 mol) was added in three equal portions at 6–8-h intervals. After cooling, the solution was decanted from the reddish-purple residue, and the residue was washed with ether (2 × 50 mL) and saturated aqueous NaCl (3 × 50 mL). After the solution was dried (Na_2SO_4), the solvent was removed, and the residual oil was vacuum distilled to give 7.4 g (81.5%) of **7** as a colorless liquid: bp 80–85 °C (0.01 mm); ^1H NMR ($DCCl_3$) δ 1.29 (s, 6 H, $(CH_3)_2$), 1.84–1.97 (m, 2 H, H(3)), 2.91–3.03 (m, 2 H, H(2)), 6.9–7.35 (m, 4 H, Ar H); ^{13}C NMR ($DCCl_3$) 23.1 (SCH_2), 30.2 (CH_3), 32.9 ($(CH_3)_2C$), 37.7 (SCH_2CH_2), Ar C [123.8, 125.8, 126.26, 126.3, 131.5 (C(4a)), 141.7 ppm (C(8a)]. The material was used without further purification.

Method II. A mixture of 3-methyl-1-(phenylthio)-2-butene (**6**; 21.5 g, 0.120 mol), H_3PO_4 (85%, 15 mL), and P_2O_5 (17.2 g, 0.121 mol) in benzene (220 mL) was heated at reflux under N_2 with vigorous stirring for 20 h. After cooling, the supernatant liquid was decanted from the phosphorus-containing residue, and the residue was washed with ether (3 × 50 mL). The organics were

(15) Iwai, K.; Kosugi, H.; Miyazaki, A.; Uda, H. *Synth. Commun.* **1976**, *6*, 357.
(16) Montanari, F.; Danieli, R.; Hogeveen, H.; Maccagnani, G. *Tetrahedron Lett.* **1964**, 2685.
(17) Fleming, I.; Paterson, I.; Pearce, A. *J. Chem. Soc., Perkins Trans. 1* **1981**, 256. The preparation of allyl sulfides is discussed herein.
(18) Brownbridge, P.; Warren, S. *J. Chem. Soc., Perkins Trans. 1* **1977**, 2272. This reference discusses synthetic routes to allyl sulfides.

combined and washed with 5% $NaHCO_3$ (2 × 75 mL), H_2O (75 mL), and brine (2 × 75 mL). After the solution was dried (Na_2SO_4), the solvent was evaporated, leaving a yellow oil. Vacuum distillation gave 16.3 g (75.8%) of **7** as a pale liquid: bp 80–85 °C (0.01 mm). The spectral data obtained (^1H and ^{13}C NMR) were identical with those obtained for **7** prepared by method I.

4,4-Dimethylthiochroman-6-yl Methyl Ketone (8a). Stannic chloride (4.7 mL, 0.050 mol) was added dropwise under N_2 to a stirred solution of 4,4-dimethylthiochroman (**7**; 6.6 g, 0.037 mol) and acetyl chloride (3.1 g, 0.039 mol) in dry, thiophene-free benzene (30 mL). The resulting dark green solution was stirred at room temperature for 5 h and then diluted with water (30 mL) and concentrated HCl (15 mL). The resulting mixture was heated to just below the boiling point for 15 min. The mixture was allowed to cool to room temperature, and the two layers were separated. The aqueous layer was extracted with benzene (5 × 20 mL), 5% aqueous Na_2CO_3 (2 × 40 mL), H_2O (50 mL), and brine (60 mL). After the solution was dried (Na_2SO_4), the solvent was removed (vacuum), leaving a viscous brown oil. Vacuum distillation gave 4.92 g (60.3%) of **8a** as a pale yellow oil: bp 126–130 °C (0.02 mm); IR (neat) 1675–1685 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.32 (s, 6 H, $(CH_3)_2$), 1.84–1.97 (m, 2 H, H(3)), 2.51 (s, 3 H, CH_3C=O), 2.95–3.07 (m, 2 H, H(2)), 7.07 (d, 1 H, J = 8 Hz, H(8)), 7.53 (dd, 1 H, J = 2 Hz, J = 8 Hz, H(7)), 7.95 (d, 1 H, J = 2 Hz, H(5)); ^{13}C NMR ($DCCl_3$) 23.1 (SCH_2), 26.2 (H_3CC=O), 29.7 ($C(CH_3)_2$), 32.9 ($C(CH_3)_2C$), 36.8 ($CSCH_2CH_2$), Ar C (125.7, 126.1, 132.8, 139.3, 141.6), 196.7 ppm (C=O); MS ($C_{13}H_{16}OS$) calcd 220.0922, found 220.0922. The compound was used without further purification.

4,4-Dimethylthiochroman-6-yl Methyl Ketone 1,1-Dioxide (18). A solution of 30% H_2O_2 (13 mL) was added dropwise under N_2 to a stirred solution of the sulfide **8a** (0.50 g, 2.29 mmol) in glacial acetic acid (10 mL). The mixture was stirred at room temperature for 72 h during which time a white solid precipitated. The mixture was poured into ice water (25 mL). The resulting white solid was filtered, washed with water (10 mL), an air-dried. Recrystallization (95% ethanol) gave 0.30 g (52.3%) of **18** as white crystals: mp 197–197.5 °C; IR (KBr) 1680–1690 (C=O), 1280–1295 (SO_2), 1130–1150 cm^{-1} (SO_2); ^1H NMR ($DCCl_3$) δ 1.46 (s, 6 H, $(CH_3)_2$), 2.36–2.48 (m, 2 H, H(3)), 2.63 (s, 3 H, H_3CC=O), 3.37–3.50 (m, 2 H, H(2)), 7.91–8.04 (m, 3 H, Ar H); ^{13}C NMR ($DCCl_3$) 26.8 (H_3CC=O), 30.6 ($(H_3C)_2C$), 34.5 ($(H_3C)_2C$), 35.4 (SCH_2CH_2), 47.0 (SCH_2), Ar C (124.2, 126.9, 127.2, 139.8, 140.9, 145.1), 196.6 (C=O); MS ($C_{13}H_{16}O_3S$) calcd 252.0820; found 252.0817. The melting point did not change upon repeated recrystallization. A single crystal of the material was subjected to X-ray diffraction analysis.

α,4,4-Trimethylthiochroman-6-methanol (13a). A solution of 4,4-dimethylthiochroman-6-yl methyl ketone (**8a**; 4.0 g, 0.018 mol) in dry ether (20 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (1.0 g, 0.026 mol) in ether (75 mL). The resulting mixture was heated at reflux for 24 h. Ethyl acetate was then added dropwise to destroy the excess $LiAlH_4$. A solution of 5% HCl (50 mL) was added, and the mixture was stirred for 10 min. The layers were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined organic layers were washed with 5% aqueous Na_2CO_3 (2 × 50 mL) and brine (2 × 50 mL). After the solution was dried (Na_2SO_4), the solvent was removed, leaving 3.8 g (94%) of **13a** as a colorless oil. Crystallization (hexane) with cooling to 0 °C gave a white granular powder: IR (melt) 3120–3640 cm^{-1} (OH); ^1H NMR ($DCCl_3$) 1.3 (s, 6 H, $(CH_3)_2$), 1.39 (d, 3 H, H_3CHOH), 1.84–2.0 (m, 2 H, SCH_2CH_2), 2.74–2.86 (br s, 1 H, OH), 2.9–3.06 (m, 2 H, SCH_2), 4.71 (q, 1 H, CH_3CHOH), 6.94–7.02 (m, 2 H, Ar H), 7.30–7.36 (m, 1 H, Ar H); ^{13}C NMR ($DCCl_3$) 23.0 (H_3CCOH), 30.2 ($(H_3C)_2C$), 33.1 ($C(H_3C)_2C$), 37.7 (SCH_2CH_2), 70.2 (C(9)), 123.1, 123.6, 126.6, 130.7, 141.6, 142.9 ppm. The alcohol was used without further purification.

[1-(4,4-Dimethylthiochroman-6-yl)ethyl]triphenylphosphonium Bromide (14a). A solution of the alcohol **13a** (0.5 g, 25.25 mmol) and triphenylphosphine hydrobromide (0.78 g, 2.27 mmol) in CH_3OH (20 mL) was stirred at room temperature under N_2 for 26 h. Removal of the solvent left a yellow oil which solidified after repeated trituration with dry ether. The resulting powder was stirred in dry ether (30 mL) for 8 h, filtered, and dried [110 °C (2 mm)] to give 0.9 g (73.1%) of **14a** as a tan powder: mp 139–145 °C dec; ^1H NMR ($DCCl_3$) δ 1.07 (s, 3 H, CH_3, 1.15 (s, 3 H, CH_3), 1.75 (d, 3 H, $CHCH_3$), 1.80–1.88 (m, 2 H, H(3)), 2.96–3.02 (m, 2 H, H(2)), 6.40–6.55 (m, 1 H, CH^+PPh_3), 6.58 (dd, 1 H, H(7)), 6.86 (d, 1 H, H(8)), 7.45 (br s, 1 H, H(5)), 7.62–7.90 (m, 15 H, $^+P(C_6H_5)_3$). The salt was used without further purification.

Ethyl (*E*)-*p*-[2-(4,4-Dimethylthiochroman-6-yl)propenyl]benzoate (1b). A solution of *n*-butyllithium in hexane (1.55 M, 1.3 mL, 2.01 mmol) was added dropwise under N_2 to a stirred suspension of the phosphonium salt **14a** (1.1 g, 2.01 mmol) in dry ether (30 mL). The resulting dark red mixture was stirred for 5 min. A solution of the freshly distilled aldehyde **15** (0.40 g, 2.24 mmol) in dry ether (15 mL) was then added all at once. The mixture became creamy yellow and then cream colored, and a large amount of off-white solid precipitated. After stirring at room temperature for 36 h, the mixture was filtered. The solid was washed with ether (50 mL). The combined filtrates were concentrated to give a yellow oil which was dissolved in warm 95% ethanol (50 mL). The resulting solution was filtered and then concentrated to 10 mL. After cooling slowly to room temperature, the resulting solid was filtered and washed with cold 95% ethanol. After drying in the air, 0.30 g (40.7%) of **1b** was obtained as a white solid: mp 92–93 °C; IR (KBr) 1710–1725 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1938 (3, 6 H, $(CH_3)_2$), 1.41 (t, 3 H, OCH_2CH_3), 1.96–2.02 (m, 2 H, SCH_2CH_2), 2.28 (s, 3 H, CH=CCH_3), 3.04–3.09 (m, 2 H, SCH_2), 4.4 q, 2 H, OCH_2), 6.82 (s, 1 H, C=CH), 7.11 (d, 1 H, J = 9 Hz, H(8)), 7.21–7.28 (m, 1 H, H(7)), 7.44 (d, 2 H, Ar H), 7.54 (s, 1 H, H(5)), 8.07 (d, 2 H, Ar H); MS ($C_{23}H_{26}O_2S$) calcd 366.1653, found 366.1650.[19] Repeated washings with alcohol did not change the melting point of the solid material. The TLC of the product **1b** gave one spot: R_f (solvent) 0.377 (C_6H_6), 0.604 ($HCCl_3$), 0.729 (dioxane).

Ethyl (*E*)-*p*-[2-(4,4-Dimethyl-1-oxothiochroman-6-yl)propenyl]benzoate (1d). A solution of $NaIO_4$ (0.14 g, 0.654 mmol) in H_2O (1 mL) was added in one portion under N_2 to a stirred suspension of **1b** (0.118 g, 0.322 mmol) in methanol (10 mL). The mixture was stirred at room temperature for an additional 36 h. A large amount of white solid precipitated during this time. The mixture was concentrated. The residue was dissolved in $HCCl_3$ (20 mL) and then filtered and concentrated. The resulting oil was triturated with cold hexane to induce crystallization. Recrystallization (hexane) gave 55 mg (44.7%) of **1d** as a white powder: mp 91–93 °C; IR (KBr) 1700–1715 (C=O), 1030–1040 cm^{-1} (S→O); ^1H NMR ($DCCl_3$) δ 1.37 (s, 3 H, CH_3), 1.41 (t, 3 H, OCH_2CH_3), 1.51 (s, 3 H, CH_3), 1.84–1.94 (m, 1 H, H(3)), 2.30 (s, 3 H, CH=$C(CH_3)$), 2.48–2.60 (m, 1 H, H(3)), 3.08–3.23 (m, 2 H, H(2)), 4.41 (q, 2 H, OCH_2CH_3), 6.8 (s, 1 H, CH=$C(CH_3)$), (d, 2 H, Ar H), 7.51 (dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)), 7.58 (d, J = 3 Hz, 1 H, H(5)), 7.77 (d, J = 9 Hz, 1 H, H(8)), 8.09 (d, 2 H, Ar H); MS ($C_{23}H_{26}O_3S$) calcd 382.1603, found 382.1595. Repeated recrystallizations did not change the melting point.

Methyl 3-Phenoxypropionate (10). A solution of 3-phenoxypropionic acid (**9**; 10.0 g, 0.060 mol) and *p*-toluenesulfonic acid (0.6 g) in methanol (250 mL) was heated at reflux through 3-Å molecular sieves for 36 h under N_2 in a flask equipped with a Soxhlet extractor and a condenser. The solution was allowed to cool to room temperature and then was concentrated to a volume of 50 mL, diluted with water (50 mL), and extracted with ether (2 × 75 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (75 mL), H_2O (75 mL), and brine (75 mL). After the solution was dried (Na_2SO_4), the solvent was removed (vacuum). Vacuum distillation gave 9.45 g (87.1%) of **10** as a colorless liquid: bp 85–87 °C (0.1 mm) [lit.[20] bp 85 °C (0.4 mm)]; IR (neat) 1740–1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 2.78 (t, 2 H, $CH_2CO_2CH_3$), 3.70 (s, 3 H, OCH_3), 4.23 ns, 2 H, OCH), 6.84–7.02 and 7.18–7.35 (m, 5 H, Ar H); ^{13}C NMR ($DCCl_3$) 34.3 (H_2CCO_2), 51.7 (CH_3), 63.2 ($COCH_2$), Ar C (114.5, 120.8, 129.2, 158.3, 171.1 ppm).

(19) Compounds **1b–d** have just been reported in the literature, but no properties were included in the abstract; see: Klaus, M.; Loelinger, P. (Hoffmann-La Roche, F. and Co., A.-G.), Ger. Offen. DE 3 316 932, 1983; Appl. 12 May, 1982; *Chem. Abstr.* **1984**, *100*, 51468z.

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2-Methyl-4-phenoxy-2-butanol (11). A solution of methyl 3-phenoxypropionate (**10**; 7.9 g, 0.038 mol) in dry ether (20 mL) was added dropwise under N_2 to a stirred solution of CH_3MgCl in THF (2.9 M, 40.2 mL, 0.11 mol). The mixture was heated at reflux for 24 h, allowed to cool to room temperature, and quenched with saturated aqueous NH_4Cl. The supernatant liquid was decanted, and the residue was washed with dry ether (3 × 50 mL). The combined organic solutions were dried (Na_2SO_4), and the solvent was removed. Vacuum distillation gave 5.35 g (76.4%) of **11** as a colorless liquid: bp 81–84 °C (0.07 mm); IR (neat) 3140–3620 cm^{-1} (OH); ^1H NMR ($DCCl_3$) δ 1.26 (s, 6 H, $(CH_3)_2$), 1.95 (t, 2 H, Ar OCH_2CH_2), 2.8–3.0 (br s, 1 H, OH), 4.12 (t, 2 H, Ar OCH_2), 6.82–6.96 (m, 3 H, Ar H), 7.16–7.3 (m, 2 H, Ar H); ^{13}C NMR ($DCCl_3$) 29.5 (CH_3), 41.6 (OCH_2CH_2), 64.9 (OCH_2), 64.9 (OCH_2), 70.3 ($(H_3C)_2C$), Ar C (114.3, 120.8, 129.3, 158.3 ppm). The alcohol was used without further purification.

4,4-Dimethylchroman (12). A solution of 2-methyl-4-phenoxy-2-butanol (**11**; 7.8 g, 0.043 mol) in nitromethane (50 mL) was added dropwise under N_2 to a stirred suspension of anhydrous $AlCl_3$ (7.8 g, 0.058 mol) in nitromethane (30 mL). After stirring at room temperature for an additional 24 h, a solution of 6 M HCl (80 mL) was added slowly. The resulting mixture was stirred for 10 min and diluted with ether (50 mL). The layers were separated, and the organic layer was washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (4 × 50 mL), H_2O (50 mL), and brine (4 × 50 mL). After the solution was dried (Na_2SO_4), the solvent was removed. Vacuum distillation of the resulting dark brown oil gave 4.35 g (62%) of **12** as a colorless liquid: bp 74–80 °C (0.7 mm) [lit.[21] bp 93 °C (10 mm)]; ^1H NMR ($DCCl_3$) δ 1.31 (3, 6 H, $(CH_3)_2$), 1.80–1.84 (m, 3 H, H(3)), 4.16–4.20 (m, 2 H, H(2)), 6.78–7.29 (m, 4 H, Ar H); ^{13}C NMR ($DCCl_3$) 30.5 ($(H_3C)_2C$), 31.1 (CH_3), 37.7 (OCH_2CH_2), 63.0 (OCH_2), Ar C (116.9, 120.4, 126.9, 127.0, 131.6, 153.5 ppm).

4,4-Dimethylchroman-6-yl Methyl Ketone (8b). Anhydrous $AlCl_3$ (3.4 g, 0.025 mol) was added in small portions to a solution of 4,4-dimethylchroman (**12**; 4.0 g, 0.024 mol) and acetyl chloride (2.0 g, 0.025 mol) in nitromethane (35 mL) under N_2. After the mixture was stirred at room temperature for 6 h, 6 M HCl (35 mL) was added slowly, and the resulting mixture was stirred for 10 min. The mixture was diluted with ether (40 mL), and the layers were separated. The organic layer was washed with H_2O (40 mL), saturated aqueous $NaHCO_3$ (4 × 30 mL), H_2O (40 mL), and brine (2 × 40 mL). After the solution was dried (Na_2SO_4), the solvent was removed, leaving a dark reddish-brown oil. Vacuum distillation gave 3.4 g (76.5%) of **8b** as a pale yellow liquid: bp 108–112 °C (0.01 mm); IR (neat) 1675–1685 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.36 (s, 6 H, $(CH_3)_2$), 1.83–1.87 (m, 2 H, H(3)), 2.55 (s, 3 H, H_3CC=O), 4.24–4.28 (m, 2 H, H(2)), 6.83 (d, J = 9 Hz, 1 H, H(8)), 7.71 (dd, J = 9 Hz, J = Hz, 1 H, H(7)), 7.98 (d, J = 3 Hz, H(5)); ^{13}C NMR ($DCCl_3$) 26.3 (CH_3), 30.6 ($(H_3C)_2C$), 30.7 ($(H_3C)_2C$), 37.0 (OCH_2CH_2), 116.9 (C(8)), 127.8, 128.16 (C(5), C(7)), 130.0, 131.6 (C(4a), C(6)), 158.0 ppm (C(8a)); MS ($C_{13}H_{16}O_2$) calcd 204.1150, found 204.1153. The ketone was used without further purification.

α,4,4-Trimethylchroman-6-methanol (13b). A solution of the ketone **8b** (3.80 g, 0.014 mol) in anhydrous ether (15 mL) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (0.8 g, 0.0211 mol) in dry ether (50 mL). The mixture was heated at reflux for 24 h. After the mixture cooled to room temperature, ethyl acetate was added dropwise to destroy the excess $LiAlH_4$. A solution of 5% HCl (50 mL) was then added, and the resulting mixture was stirred for 5 min. The layers were separated, and the aqueous layer was washed with ether (2 × 50 mL). The combined organic layers were washed with 5% aqueous Na_2CO_3 (2 × 50 mL) and brine (2 × 50 mL). After the solution was dried (Na_2SO_4), the solvent was removed, leaving a yellow oil which solidified after scratching. Recrystallization (hexane) gave 1.80 g (59.4%) of **13b** as a white solid: mp 70–71 °C; IR (KBr) 3140–3640 cm^{-1} (OH); ^1H NMR ($DCCl_3$) δ 1.31 (s, 6 H, $(CH_3)_2C$), 1.43 (d, 3 H, H_3CHOH), 1.74–1.83 (m, 2 H, H(3)), 2.4–2.44 (s, 1 H, OH), 4.10–4.18 (m, 2 H, H(2)), 4.76 (q, 1 H, CHOH), 6.76 (d, J = 9 Hz, 1 H, H(8)), 7.07 (dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)), 7.28 (d, J = 3 Hz, 1 H, H(5)); ^{13}C NMR ($DCCl_3$) 25.0 (H_3CC=O), 30.6 (C(4)), 31.0 ($(H_3C)_2C$), 37.6 (C(3)), 63.0 (C(2)), 70.2 (C(9)), 116.9 (C(8)), 124.0, 124.3 (C(5), C(7)), 131.4, 137.7 (C(4a), C(6)), 152.9 ppm (C(8a)); MS ($C_{13}H_{10}O_2$) calcd 206.1307, found 206.1308. Repeated recrystallizations did not change the melting point of the solid. It was used without further purification.

[1-(4,4-Dimethylchroman-6-yl)ethyl]triphenylphosphonium Bromide (14b). A solution of the alcohol **13b** (0.70 g, 3.4 mmol) and triphenylphosphine hydrobromide (1.2 g, 3.5 mmol) in methanol (30 mL) was stirred under N_2 at room temperature for 24 h. The solvent was removed (vacuum), and the resulting oil was triturated repeatedly with dry ether until it solidified. The white solid was stirred in dry ether (30 mL) at room temperature under N_2 for 4 h, filtered, and dried [110 °C (~2 mm)] to give 1.45 g (80.3%) of **14b** as a white powder: mp 149–155 °C dec; ^1H NMR ($DCCl_3$) δ 1.08 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.72–1.78 (m, 2 H, H(3)), 1.83 (d, 3 H, $CHCH_3$), 4.12–4.18 (m, 2 H, H(2)), 6.2–6.32 (m, 1 H, $CHPPh_3^+Br^-$), 6.57 (d, 1 H, H(8)), 6.67 [d, 1 H, H(7)], 7.24 [brs, 1 H, H(5)], 7.63–7.84 [m, 15 H, $P^+(C_6H_5)_3$]. The salt was used without further purification.

Ethyl (*E*)-*p*-[2-(4,4-Dimethylchroman-6-yl)propenyl]benzoate (1c). A solution of *n*-butyllithium in hexane (1.55 M, 2.13 mL, 3.30 mmol) was added dropwise under N_2 to a stirred suspension of the phosphonium salt **14b** (1.75 g, 3.29 mmol) in dry ether (30 mL). The resulting dark reddish-brown mixture was stirred at room temperature for 5 min. A solution of the aldehyde **15** (0.60 g, 3.37 mmol) in dry ether (15 mL) was then added. The mixture changed from reddish brown to creamy yellow, and a large amount of off-white solid precipitated. After stirring at room temperature for 36 h, the mixture was filtered. The resulting solid was washed with ether (75 mL), and the combined filtrates were concentrated to give a yellow oil. The oil was chromatographed through a column (8 × 200 mm) packed with neutral alumina (about 10 g). The product was eluted with 5% ether/hexane (250 mL). Concentration of the eluent gave a viscous oil which was dissolved in a minimum amount of boiling 95% ethanol. Cooling the solution to 0 °C and scratching of the flask with a glass rod gave 0.30 g (26.0%) of **1c** as a white granular solid: mp 72.5–73.5 °C; IR (KBr) 1710–1725 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.37 (s, 6 H, $(CH_3)_2C$), 1.39 (t, 3 H, OCH_2CH_3), 1.81–1.87 (m, 2 H, H(3)), 2.27 (s, 3 H, CH=$C(CH_3)$), 4.17–4.24 (m, 2 H, H(2)), 4.38 (q, 2 H, OCH_2CH_3), 6.77 (s, 1 H, CH=$C(CH_3)$), 6.81 (d, J = 9 Hz, 1 H, H(8)), 7.26 (dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)), 7.41 (d, 2 H, Ar H), 7.44 (d, J = 3 Hz, 1 H, H(5)), 8.06 (d, 2 H, Ar H); MS ($C_{23}H_{26}O_3$) calcd 350.1881, found 350.1884. The presence of the *Z* isomer in an oil obtained from the chromatography was indicated by the following ^1H NMR signals: δ 2.76–2.81 (m, H(3)), 2.20 (s, 3 H, *Z* CH=$C(CH_3)$), 4.16–4.20 (m, H(2)), 6.44 (br s, 1 H *Z* CH=$C(CH_3)$). Repeated washing with cold 95% ethanol did not raise the melting point of the white solid. The TLC of the product **1c** gave one spot: R_f (solvent) 0.305 (C_6H_6), 0.537 ($HCCl_3$), 0.712 (dioxane).

(*E*)-*p*-[2-(4,4-Dimethylchroman-6-yl)propenyl]benzoic Acid (1e). The heteroarotinoid **1c** (0.20 g, 0.57 mmol) was heated at reflux under N_2 for 4 h in a solution of NaOH (0.1 g, 2.50 mmol) in 95% C_2H_5OH (2 mL) and H_2O (5 mL). After cooling slowly to room temperature, the solution was acidified (litmus) with concentrated HCl. The resulting white solid was filtered, washed with water, and air-dried. Recrystallization (95% ethanol) gave 0.135 g (73.4%) of **1c** as a white solid: mp 183–183.5 °C; IR KBr) 2390–3320 (OH, CH), 1670–1695 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.38 (s, 6 H, $(CH_3)_2C$), 1.84–1.9 (m, 2 H, H(3)), 2.30 (s, 3 H, CH=$C(CH_3)$), 4.21–4.26 (m, 2 H, H(2)), 6.80 (s, 1 H, CH=$C(CH_3)$), 6.83 (d, J = 9 Hz, 1 H, H(8)), 7.29 (dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)), 7.46 (d, J = 3 Hz, 1 H, H(5)), 7.48 (d, 2 H, Ar H), 8.15 (d, 2 H, Ar H); MS ($C_{21}H_{22}O_3$) calcd 322.1569, found 322.1570. Repeated recrystallizations did not change the melting point of the solid. The TLC of the product **1e** gave one spot: R_f (solvent) 0.456 (EtOAc), 0.613 (dioxane), 0.523 (2-propanol).

Ethyl 4-Formylbenzoate (15). A solution of ethyl *p*-toluate (**16**; 6.0 g, 0.036 mol; prepared from *p*-toluic acid and ethanol by conventional techniques), glacial acetic acid (57 mL), and acetic anhydride (57 mL) in a flask equipped with a thermometer and a mechanical stirrer was cooled to 0.5 °C in an ice–salt bath. Concentrated H_2SO_4 (8.5 mL) was added slowly to the stirred

(21) Colonge, J.; LeSech, E.; Marey, R. *Bull. Soc. Chim. Fr.* **1957**, 776.

solution. Chromium trioxide (10.0 g, 0.10 mol) was added in small portions over a period of 25 min. The temperature of the mixture was maintained below 5 °C at all times. After stirring at 0–5 °C for an addition 20 min, the mixture was poured into a beaker (two-thirds full) with ice. Cold water was then added to bring the total volume to 600 mL. The resulting dark green-brown mixture was extracted with ether (3 × 250 mL), and the organic layers were combined. The organic layer was washed with water (3 × 200 mL), 5% aqueous Na_2CO_3 (2 × 200 mL), and brine (200 mL). After the solution was dried (Na_2SO_4), the solvent was removed, leaving the diacetate **17** as a pale yellow liquid. A mixture of the diacetate **17**, concentrated H_2SO_4 (2 mL), water (200 mL), and 95% ethanol (20 mL) was heated at reflux under N_2 for 45 min. The solution was allowed to cool to room temperature. After the solution was diluted with water (40 mL), the resulting mixture was extracted with ether (3 × 40 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 × 50 mL) and water (50 mL). After the solution was dried (Na_2SO_4), the solvent was removed, leaving a yellow liquid. Vacuum distillation gave 3.1 g (47.6%) of **15** as a colorless liquid: bp 80–84 °C (0.05 mm) [lit.[22] bp 142 °C (13 mm)]; IR (neat) 1705–1735 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.42 (5, 3 H, OCH_2CH_3), 4.41 (q, 2 H, OCH_2CH_3), 7.87–8.22 (pseudo q, 4 H, Ar H), 10.08 (br s, 1 H, CHO); ^{13}C NMR ($DCCl_3$) 14.2 (OCH_2CH_3), 61.4 (OCH_2CH_3), Ar C (129.2, 135.2, 138.9), 169.2 ($CO_2C_2H_5$), 191.2 ppm (CHO).

Experimental Data for Crystal Structures of 18 and 1b. Crystals [triclinic 95% alcohol, $C_{13}H_{10}O_3S$ (**18**) and $C_{23}H_{26}O_2S$ (**1b**)] were mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (Tables I and IV) were determined by least-squares refinement of the best angular positions for 15 independent reflections ($2\theta > 15°$) during normal alignment procedures using molybdenum radiation ($\lambda = 0.71069$ Å). Data [8703 (**18**) and 7630 (**1b**) points] were collected at room temperature with use of a variable scan rate, a θ–2θ scan mode, and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 116°. Background was measured at each end of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were measured after every 97 reflections and the intensities of these reflections showed less than 8% variation. Corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, and background effects. After removal of redundant data, 5373 (**1**,) and 3463 (**1b**) reflections were considered observed [$I > 3.0\sigma(I)$]. The structures were solved by direct methods by using MULTAN 80.[23] Refinement of scale factor and positional and anisotropic thermal parameters for all non-hydrogen atoms was carried out to convergence.[24] Hydrogen positional parameters were determined from a difference Fourier synthesis. For **18**, these positional parameters and the associated isotropic thermal parameters were refined along with non-hydrogen parameters in the final cycles of refinement. For **1b**, the hydrogen atoms were included in the final cycles of refinement with assigned isotropic thermal parameters of $U = 0.03$, but all parameters associated with hydrogen atoms were held invariant. The final cycle of refinement [function minimized $\sum(|F_o| - |F_c|)^2$] led to a final agreement factor of $R = 6.5\%$ (**18**) and 5.8% (**1b**) [$R = (\sum||F_o| - |F_c||/|F_o|) \times 100$]. Scattering factors were taken from Cromer and Mann.[25] Unit weights were used throughout.

Bioassay Procedure. The entire procedure for the assay for keratinization with and without retinoids has been clearly delineated.[5n]

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Registry No. **1b**, 88579-35-5; **1c**, 88579-28-6; **1d**, 88579-37-7; **1e**, 88579-29-7; **2**, 108-98-5; **3**, 60805-64-3; **4**, 91967-95-2; **5**, 870-63-3; **6**, 10276-04-7; **7**, 66165-06-8; **8a**, 88579-23-1; **8b**, 88579-19-5; **9**, 7170-38-9; **10**, 7497-89-4; **11**, 87077-92-7; **12**, 40614-27-5; **13a**, 92788-06-2; **13b**, 88579-20-8; **14a**, 92788-07-3; **14b**, 88579-22-0; **15**, 6287-86-1; **16**, 94-08-6; **17**, 92788-08-4; **18**, 92788-09-5; CH_2=CH-$CO_2C_2H_5$, 140-88-5; CH_3Cl, 74-87-3; Ph_3P, 603-35-0.

Supplementary Material Available: Listings of positional parameters, anisotropic, and isotropic thermal parameters, F_o and F_c, for single-crystal X-ray analysis of **1b** and **18** (88 pages). Ordering information is given on any current masthead page.

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