

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; Me₃N, 75-50-3; Cl(CH₂)₃Br, 109-70-6; Br(C₂H₅)₂Br, 629-03-8; MeSO₃Me, 66-27-3; Et₂NH, 109-89-7; CH₂=C-H(CH₂)₂Br, 5162-44-7; MeSO₃(CH₂)₂Cl, 3570-58-9; CH₃CO₂H, 64-19-7; pyridine, 110-86-1; 2-picoyl chloride hydrochloride, 6959-47-3; 2-picoyl 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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Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, and IIT Research Institute, Life Sciences Division, Chicago, Illinois 60616. Received February 13, 1984

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-dimethylthiochroman-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-dimethylthiochroman-6-yl)propenyl]benzoic acid (**1e**). IR, ¹H NMR and ¹³C 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*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 unit 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 activity³ and exert a preventive activity in models of chemical carcinogenesis.^{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 toxicity⁶ has been associated with high dosages of natural retinoids. This "hypervitaminosis A" limits clinical use

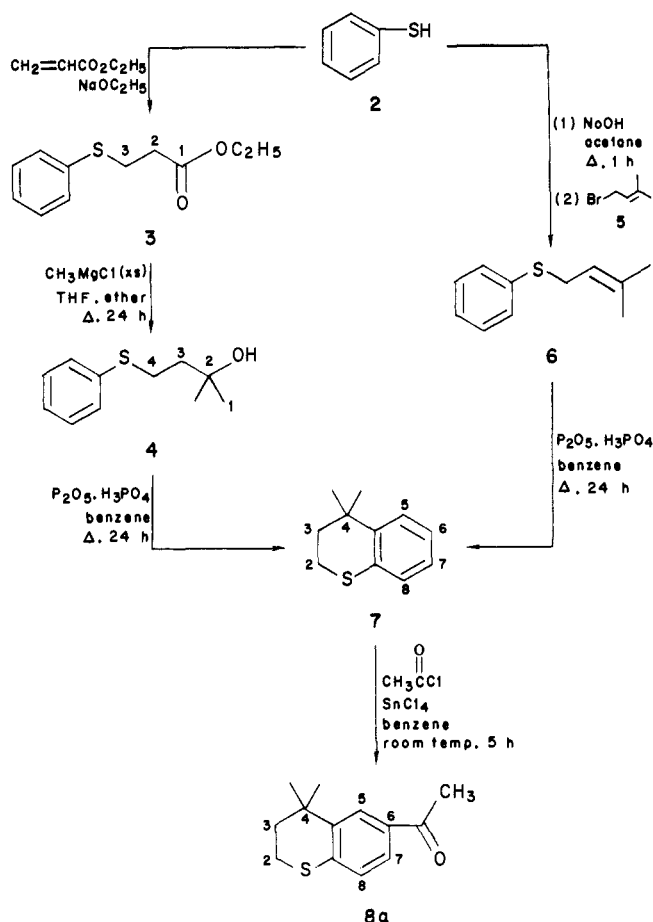
of such compounds. Modifications of the basic retinoid structure have been the subject of intensive effort recently.⁷

- (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.; Ehmman, 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.

[†]Oklahoma State University.

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Scheme I



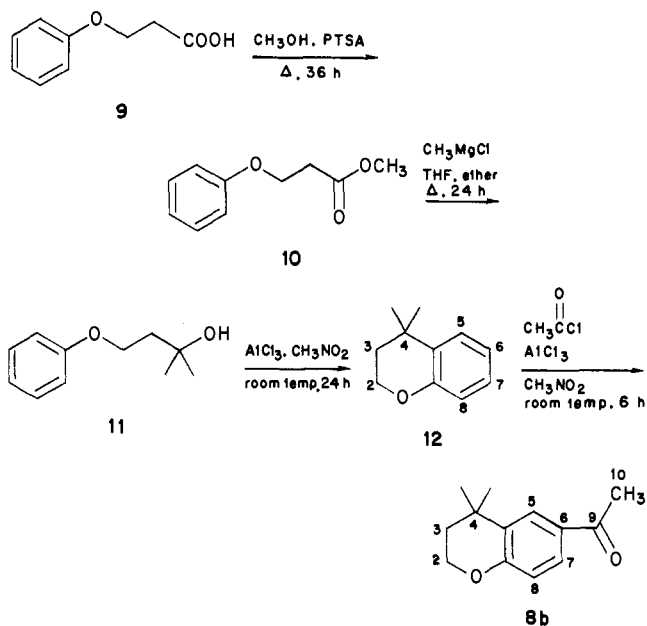
Systems with fused aryl rings (as in 1a^{5n,8a} and related molecules⁸) have good potency^{9,10} (in a tracheal assay⁵ⁿ the

- (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.

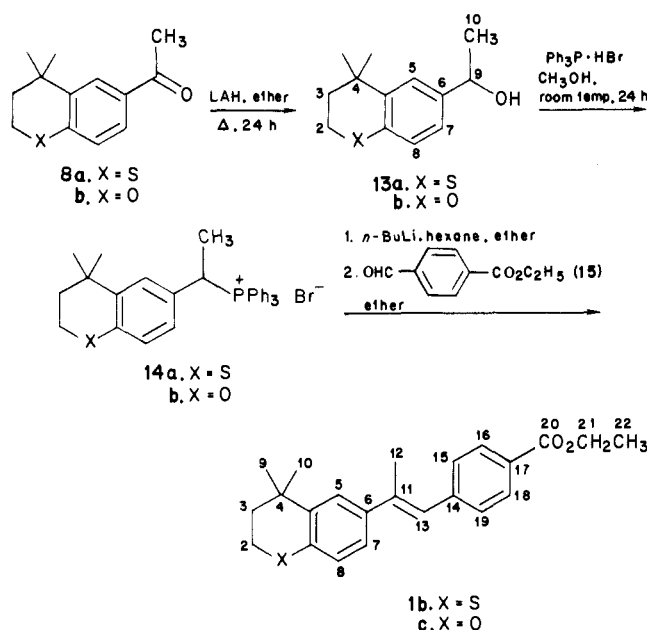
For references to show that retinoids can effect the regression of epithelial papillomas induced by carcinogens in animals, see: (f) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M.; Wenk, M. L.; Springer, S. *Science* 1977, 195, 487. (g) Becci, P. J.; Thompson, H. J.; Grubbs, C. J.; Squire, R. 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.

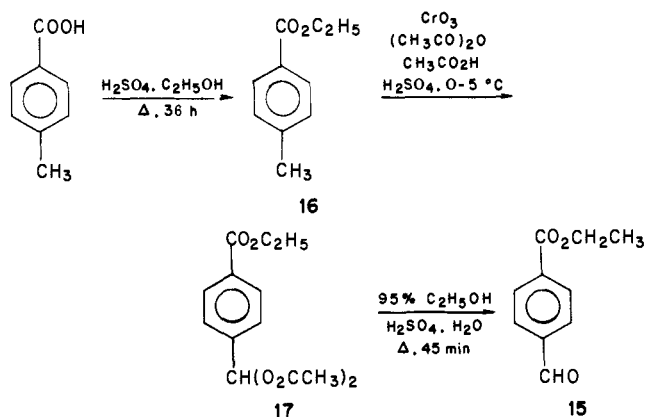
Scheme II



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

Table I. Crystal Data for 18

formula	C ₁₃ H ₁₆ O ₃ S	γ	79.60 (4)
mol wt	252.3	volume	631.5 (5) Å ³
Mo K α	0.71069 Å	μ (Mo K α)	2.38 cm ⁻¹
<i>a</i>	9.292 (5)	independent obs	5373
<i>b</i>	9.219 (5)	<i>R</i>	6.4%
<i>c</i>	7.951 (3)	space group	P1
α	102.16 (3)°	<i>Z</i>	2
β	77.49 (3)	<i>D</i> _{calcd}	1.327 g cm ⁻³

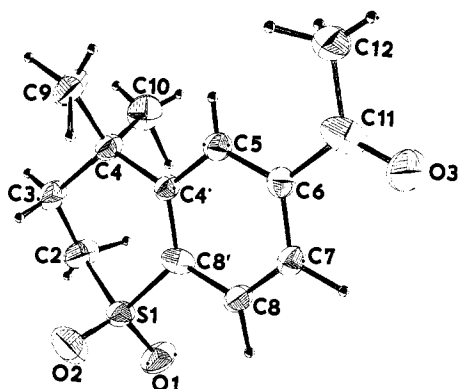
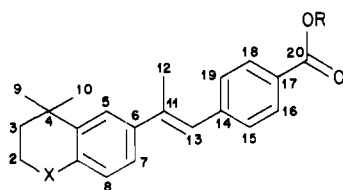


Figure 1. ORTEP drawing for sulfone 18.

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(CH₃)₂; R = C₂H₅
 b. X = S; R = C₂H₅
 c. X = O; R = C₂H₅
 d. X = S(O); R = C₂H₅
 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 NaIO₄ in methanol-water

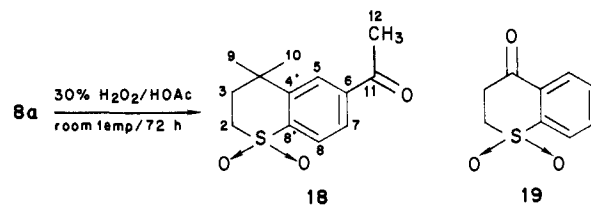
Table II. Bond Angles and Distances of 18

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)		

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

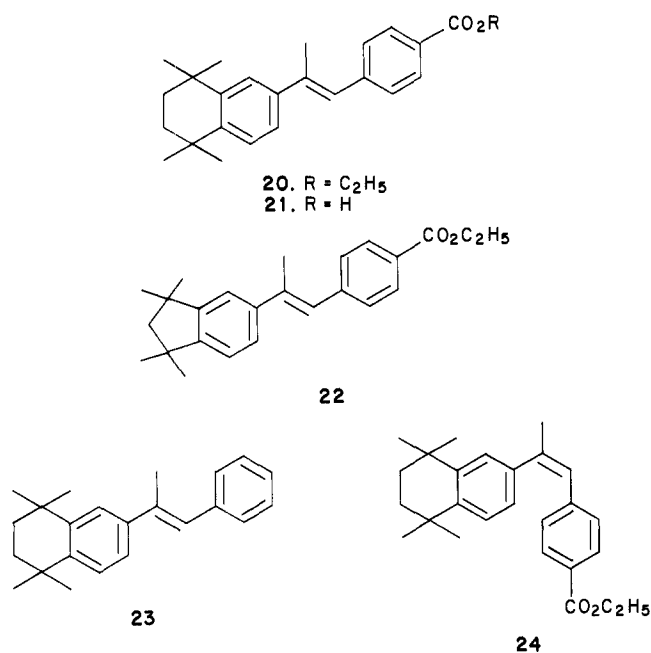


crystallizes in a centrosymmetric cell with one molecule per asymmetric unit. The hetero ring adopts a C2/C3 half-chair conformation unlike that observed in 19.¹² The C-S bond lengths (Table II) involving C(8') [sp² hybridized] and C(2) [sp³ hybridized] are nearly equal in 18 [S-C(8'), 1.767 (3) Å and S-C(2), 1.761 (4) Å] as in 19¹² [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,

- (6) Orfanos, 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.



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**,^{9a} 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 ¹³C 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 experiments¹³ permits correlation of an ¹H chemical shift for a particular proton with the ¹³C NMR chemical shift of the corresponding carbon provided the ¹H or ¹³C spectrum can be assigned unequivocally. Using INEPT¹⁴ experiments, the assignments could be made for the ¹³C 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 proton signals with those from the appropriately substituted carbon as shown in the contour plot¹³ 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 bond¹¹ [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

Table III. ¹³C NMR Data for the Heteroarotinoids

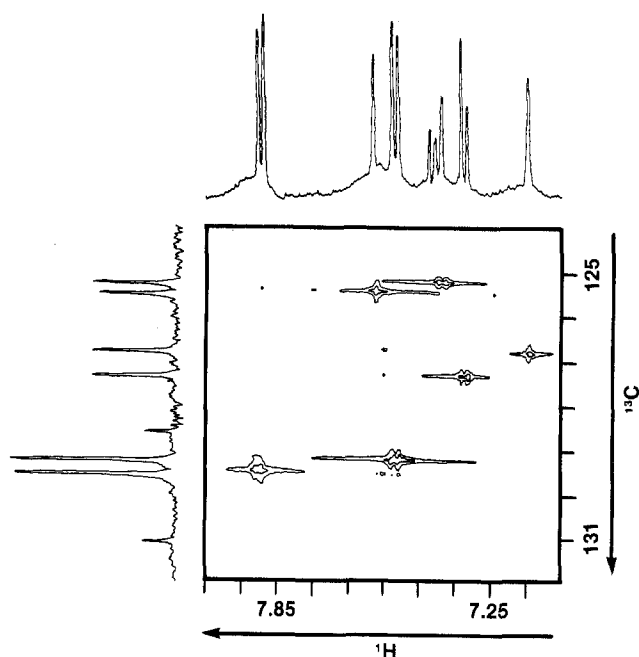
1b. X = S
1c. X = O
1d. X = O; R = H
1e. X = SO

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	143.0	153.4	153.5	147.1
aromatic and	141.7	143.3	144.3	144.6
vinyllic carbons	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 Me₄Si.

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

formula	C ₂₃ H ₂₆ O ₂ S	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
<i>a</i>	20.568 (6)	independent obs	3463
<i>b</i>	14.760 (3)	<i>R</i>	5.8%
<i>c</i>	7.679 (2)	space group	P1
α	113.33 (2) ^o	<i>Z</i>	4
β	79.45 (2)	<i>D</i> _{calcd}	1.202 g cm ⁻³

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

(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 V. Bond Angles (deg) and Distances (Å) for C₂₃H₂₆O₂S (1b)

Bond Distances								
	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)			

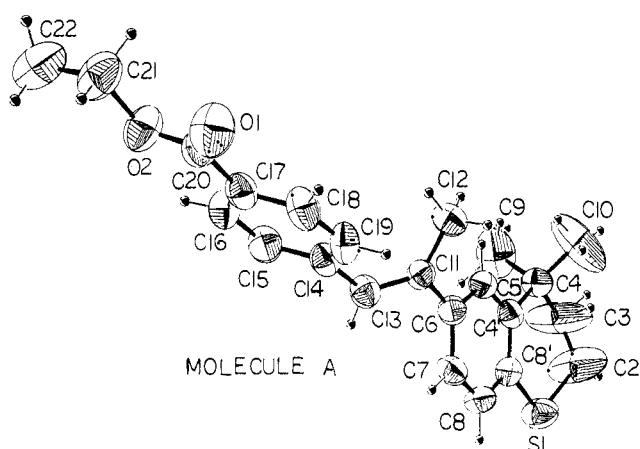
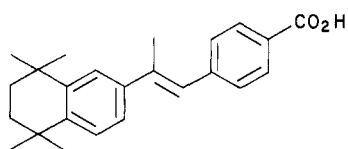


Figure 3. ORTEP drawing of molecule A in the unit cell of 1b.

(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



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which the two aryl rings show a displacement angle of 71° between the two planes. The sulfur-containing ring in 1b

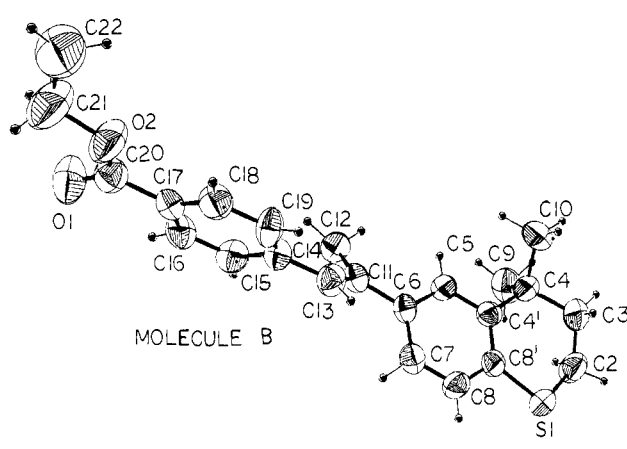


Figure 4. ORTEP drawing of molecule B in the unit cell of 1b.

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 Assay⁵ⁿ

retinoid	concn, M	% active	ED ₅₀ ^a , M
<i>trans</i> -retinoic acid	10 ⁻¹⁰	76.9	2 × 10 ⁻¹¹
	10 ⁻¹¹	41.7	
	10 ⁻¹²	23.1	
	10 ⁻⁹	100	
	10 ⁻¹⁰	53.8	
1b	10 ⁻¹¹	28.6	6 × 10 ⁻¹¹
	10 ⁻¹²	33.7	
	10 ⁻¹⁰	100	
	10 ⁻¹¹	53.8	
	12 ⁻¹²	23.1	
<i>trans</i> -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	
<i>trans</i> -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	
	10 ⁻¹⁰	83.7	
<i>trans</i> -retinoic acid	11 ⁻¹¹	50.0	1 × 10 ⁻¹¹
	10 ⁻¹²	33.3	
	10 ⁻⁸	100	
	10 ⁻⁹	100	
1e	10 ⁻¹⁰	57.1	1 × 10 ⁻¹⁰
	10 ⁻¹¹	11.1	
	10 ⁻¹¹	11.1	

^a ED₅₀ (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 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 Me₄Si 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 F₂₅₄ (EM, 0.20-mm layer).

Ethyl 3-(Phenylthio)propionate (3). Freshly distilled ethyl acrylate (75 mL) was added dropwise under N₂ 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 (DCCl₃) δ 1.22 (t, 3 H, OCH₂CH₃), 2.58 (t, 2 H, CH₂CO₂C₂H₅), 3.14 (t, 2 H, SCH₂), 4.1 (q, 2 H, OCH₂CH₃), 7.07–7.37 (m, 5 H, Ar H); ¹³C NMR (DCCl₃) 14.2 (OCH₂CH₃), 29.0 (SCH₂), 34.4 (CH₂CO₂), 60.5 (OCH₂CH₃), 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 N₂ 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 NH₄Cl. The supernatant liquid was decanted, and the residue was washed with dry ether (3 × 50 mL). The combined organics were dried (Na₂SO₄), 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 (DCCl₃) δ 1.17 (s, 6 H, (CH₃)₂), 1.66–1.84 (m, 2 H, Ar SCH₂CH₂), 2.38–2.47 (br s, 1 H, OH), 2.88–3.05 (m, 2 H, Ar SCH₂), 7.04–7.34 (m, 5 H, Ar H); ¹³C NMR (DCCl₃) 28.2 (SCH₂), 28.9 (CH₃), 42.4 (SCH₂CH₂), 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 N₂ 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 H₂O (75 mL), and extracted with ether (2 × 50 mL). The organic layers were combined and washed with 5% aqueous NaOH (3 × 30 mL), H₂O (50 mL), and brine (50 mL). After the solution was dried (Na₂SO₄), 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 (DCCl₃) δ 1.55 (s, 3 H, CH₃), 1.68 (s, 3 H, CH₃), 3.52 (d, 2 H, PhSCH₂), 5.24–5.34 (m, 1 H, (CH₃)₂C=CH), 7.1–7.36 (m, 5 H, Ar H); ¹³C NMR (DCCl₃) 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), H₃PO₄ (85%, 5 mL), and benzene (50 mL) was heated to reflux under N₂ with vigorous stirring for 20 h. During this period, P₂O₅ (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 (Na₂SO₄), 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 (DCCl₃) δ 1.29 (s, 6 H, (CH₃)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); ¹³C NMR (DCCl₃) 23.1 (SCH₂), 30.2 (CH₃), 32.9 ((CH₃)₂C), 37.7 (SCH₂CH₂), 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), H₃PO₄ (85%, 15 mL), and P₂O₅ (17.2 g, 0.121 mol) in benzene (220 mL) was heated at reflux under N₂ 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% NaHCO₃ (2 × 75 mL), H₂O (75 mL), and brine (2 × 75 mL). After the solution was dried (Na₂SO₄), 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 ¹³C 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 N₂ 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 Na₂CO₃ (2 × 40 mL), H₂O (50 mL), and brine (60 mL). After the solution was dried (Na₂SO₄), 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 (DCCl₃) δ 1.32 (s, 6 H, (CH₃)₂), 1.84–1.97 (m, 2 H, H(3)), 2.51 (s, 3 H, CH₃C=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)); ¹³C NMR (DCCl₃) 23.1 (SCH₂), 26.2 (H₃CC=O), 29.7 (C-(CH₃)₂), 32.9 (C(CH₃)₂C), 36.8 (CSCH₂CH₂), Ar C (125.7, 126.1, 132.8, 139.3, 141.6), 196.7 ppm (C=O); MS (C₁₃H₁₆OS) 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% H₂O₂ (13 mL) was added dropwise under N₂ 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 (SO₂), 1130–1150 cm⁻¹ (SO₂); ¹H NMR (DCCl₃) δ 1.46 (s, 6 H, (CH₃)₂), 2.36–2.48 (m, 2 H, H(3)), 2.63 (s, 3 H, H₃CC=O), 3.37–3.50 (m, 2 H, H(2)), 7.91–8.04 (m, 3 H, Ar H); ¹³C NMR (DCCl₃) 26.8 (H₃CC=O), 30.6 ((H₃C)₂C), 34.5 ((H₃C)₂C), 35.4 (SCH₂CH₂), 47.0 (SCH₂), Ar C (124.2, 126.9, 127.2, 139.8, 140.9, 145.1), 196.6 (C=O); MS (C₁₃H₁₆O₃S) 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 N₂ to a stirred suspension of LiAlH₄ (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 LiAlH₄. 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 Na₂CO₃ (2 × 50 mL) and brine (2 × 50 mL). After the solution was dried (Na₂SO₄), 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 (DCCl₃) 1.3 (s, 6 H, (CH₃)₂), 1.39 (d, 3 H, H₃CHOH), 1.84–2.0 (m, 2 H, SCH₂CH₂), 2.74–2.86 (br s, 1 H, OH), 2.9–3.06 (m, 2 H, SCH₂), 4.71 (q, 1 H, CH₃CHOH), 6.94–7.02 (m, 2 H, Ar H), 7.30–7.36 (m, 1 H, Ar H); ¹³C NMR (DCCl₃) 23.0 (H₃CCOH), 30.2 ((H₃C)₂C), 33.1 (C(H₃C)₂C), 37.7 (SCH₂CH₂), 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 CH₃OH (20 mL) was stirred at room temperature under N₂ 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 (DCCl₃) δ 1.07 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃), 1.75 (d, 3 H, CHCH₃), 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⁺PPh₃), 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(C₆H₅)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 N₂ 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 (DCCl₃) δ 1.938 (3, 6 H, (CH₃)₂), 1.41 (t, 3 H, OCH₂CH₃), 1.96–2.02 (m, 2 H, SCH₂CH₂), 2.28 (s, 3 H, CH=CCH₃), 3.04–3.09 (m, 2 H, SCH₂), 4.4 q, 2 H, OCH₂), 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 (C₂₃H₂₆O₂S) 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 (C₆H₆), 0.604 (HCCl₃), 0.729 (dioxane).

Ethyl (*E*)-*p*-[2-(4,4-Dimethyl-1-oxothiochroman-6-yl)-propenyl]benzoate (1d). A solution of NaIO₄ (0.14 g, 0.654 mmol) in H₂O (1 mL) was added in one portion under N₂ 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 HCCl₃ (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 (DCCl₃) δ 1.37 (s, 3 H, CH₃), 1.41 (t, 3 H, OCH₂CH₃), 1.51 (s, 3 H, CH₃), 1.84–1.94 (m, 1 H, H(3)), 2.30 (s, 3 H, CH=C(CH₃)), 2.48–2.60 (m, 1 H, H(3)), 3.08–3.23 (m, 2 H, H(2)), 4.41 (q, 2 H, OCH₂CH₃), 6.8 (s, 1 H, CH=C(CH₃)), (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 (C₂₃H₂₆O₃S) 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 N₂ 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 NaHCO₃ (75 mL), H₂O (75 mL), and brine (75 mL). After the solution was dried (Na₂SO₄), 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 (DCCl₃) δ 2.78 (t, 2 H, CH₂CO₂CH₃), 3.70 (s, 3 H, OCH₃), 4.23 ns, 2 H, OCH), 6.84–7.02 and 7.18–7.35 (m, 5 H, Ar H); ¹³C NMR (DCCl₃) 34.3 (H₂CCO₂), 51.7 (CH₃), 63.2 (COCH₂), Ar C (114.5, 120.8, 129.2, 158.3, 171.1 ppm).

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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 (s, 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.

$\alpha,4,4$ -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 ($C_{13}H_{16}O_2$) 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 \times 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 **1e** 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

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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 additional 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 Na₂CO₃ (2 × 200 mL), and brine (200 mL). After the solution was dried (Na₂SO₄), the solvent was removed, leaving the diacetate 17 as a pale yellow liquid. A mixture of the diacetate 17, concentrated H₂SO₄ (2 mL), water (200 mL), and 95% ethanol (20 mL) was heated at reflux under N₂ 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 NaHCO₃ (2 × 50 mL) and water (50 mL). After the solution was dried (Na₂SO₄), 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 (DCCl₃) δ 1.42 (5, 3 H, OCH₂CH₃), 4.41 (q, 2 H, OCH₂CH₃), 7.87–8.22 (pseudo q, 4 H, Ar H), 10.08 (br s, 1 H, CHO); ¹³C NMR (DCCl₃) 14.2 (OCH₂CH₃), 61.4 (OCH₂CH₃), Ar C (129.2, 135.2, 138.9), 169.2 (CO₂C₂H₅), 191.2 ppm (CHO).

Experimental Data for Crystal Structures of 18 and 1b. Crystals [triclinic 95% alcohol, C₁₃H₁₁O₃S (18) and C₂₃H₂₆O₂S (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 (2θ > 15°) during normal alignment procedures using molybdenum radiation (λ = 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 Kα₁ and 1.2° above Kα₂ 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 (1a) and 3463 (1b) reflections were considered observed [*I* > 3.0σ(*I*)]. The structures were solved by direct methods by using MULTAN⁸⁰.²³ 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 Σ(|*F*_o| – |*F*_c|)²] led to a final agreement factor of *R* = 6.5% (18) and 5.8% (1b) [*R* = (Σ||*F*_o| – |*F*_c||/*F*_o) × 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.^{5b}

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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; CH₂=CH-CO₂C₂H₅, 140-88-5; CH₃Cl, 74-87-3; Ph₃P, 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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