

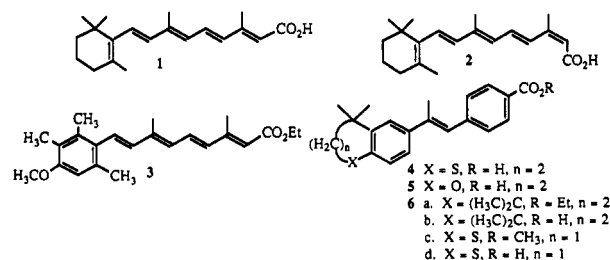
# Novel Heteroarotinoids: Synthesis and Biological Activity

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In this study, 13 heteroarotinoids were synthesized. The key step in each preparation was the condensation of the appropriate chroman-, thiochroman-, or benzothieryl-substituted phosphorus ylide, obtained from the independent synthesis of the corresponding phosphonium salts, with selected polyene-substituted aldehyde esters. Nine of these heterocycles contained a thiochroman group, two had a chroman group, and two others had a benzothieryl system. Screening of the compounds was with one of two assays. One assay measured the ability of a retinoid to inhibit the phorbol ester induced increase of mouse epidermal ornithine decarboxylase (ODC) activity. The other assay measured retinoid-induced differentiation of the human myeloid leukemia cell line HL-60. In the ODC assay, all thirteen compounds were screened. The most active heteroarotinoids were ester 10 [methyl (*E*)-4-[2-(2,2,4,4-tetramethylthiochroman-6-yl)-1-propenyl]benzoate] and acid 11 [(*E*)-4-[2-(2,2,4,4-tetramethyl-3,4-dihydro-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoic acid]. Both of these retinoids had ID<sub>50</sub> values (dose required for half-maximal inhibition of phorbol ester induced ODC activity) of about 0.3 nmol. In comparison, the ID<sub>50</sub> value for *trans*-retinoic acid (1) was 0.12 nmol while the ID<sub>50</sub> values for acids 7 and 9, namely (2*Z*,4*E*,6*E*)-3,7-dimethyl-7-(4,4-dimethylthiochroman-6-yl)-2,4,6-heptatrienoic acid and (2*E*,4*E*,6*E*)-3,7-dimethyl-7-(2,2,4,4-tetramethylthiochroman-6-yl)-2,4,6-heptatrienoic acid, respectively, were about 3.5 nmol. Heteroarotinoids 8 and 12-17 had ID<sub>50</sub> values of 35 nmol or greater. With a thiochroman unit, the most active acids in decreasing order of activity in the ODC assay were 7 > 9 > 8. Thus, simple replacement of the terminal propenyl system [C(16,17,18)] in 7 with a cyclopropyl group produced acid 8 [(2*E*,4*E*,6*E*)-7-methyl-7-(4,4-dimethylthiochroman-6-yl)-2,3-methylene-4,6-heptadienoic acid] with markedly reduced activity. With a benzoic acid group as part of the structure attached to the thiochroman unit, the ODC activity was enhanced as shown in 10 and 11. The combination of the 2,2,4,4-tetramethylthiochroman group and the benzoic acid (or ester) terminal group seemed to enhance the biological action which resembles that found with (*E*)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB, 6b), a well-known model system. Replacing the protons with fluorine in the C(12) methyl group in the side chain and altering the orientation of the aryl groups around the double bond from anti to syn lowered ODC activity in both the thiochroman- and chroman-containing systems. Esters 12 and 14 [methyl (*E*)-4-[2-(trifluoromethyl)-2-(2,2,4,4-tetramethylthiochroman-6-yl)ethenyl]benzoate and methyl (*E*)-4-[2-(trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoate, respectively] and acid 13 [(*E*)-4-[2-(trifluoromethyl)-2-(2,2,4,4-tetramethylthiochroman-6-yl)ethenyl]benzoic acid] were essentially inactive while acid 15 [(*E*)-4-[2-(trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoic acid] exhibited moderate activity in the ODC assay. In the chroman family, both ester 16 [methyl (*E*)-4-[2-(trifluoromethyl)-2-(4,4-dimethylchroman-6-yl)ethenyl]benzoate] and acid 17 [(*E*)-4-[2-(trifluoromethyl)-2-(4,4-dimethylchroman-6-yl)ethenyl]benzoic acid] had unfavorable ID<sub>50</sub> values. An observation is that since acid 13 differs only slightly from acid 15 [the latter is devoid of the geminal dimethyl group at C(2)] and acid 15 differs only slightly from acid 17 (the latter has an oxygen atom and the former a sulfur atom), possibly the nature of the heteroatom and the stereochemistry of the  $\alpha$  position may play important roles in regulating activity, but more examples are required to establish a trend. Changing the ring size from a fused six-six system to a five-six system led to ester 6c [methyl(*E*)-4-[2-(2,3-dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate] and acid 6d [(*E*)-4-[2-(2,3-dihydro-3,3-dimethylbenzo[*b*]thienyl-5-yl)-1-propenyl]benzoic acid], respectively. In separate experiments from those with 2-17, both 6c and 6d exhibited similar inhibition of ODC activity to that of *trans*-retinoic acid (1) at the 34 nmol level. The ID<sub>50</sub> values of topically administered 6c and 6d were, however, 10 and 200 times greater than that of 1, respectively. Of eight heteroarotinoids examined in the HL-60 assay system, only acid 7 [(2*Z*,4*E*,6*E*)-3,7-dimethyl-7-(4,4-dimethylthiochroman-6-yl)-2,4,6-heptatrienoic acid] displayed modest activity. This acid had an ED<sub>50</sub> value (dose required for half-maximal effect) of 500 nM. In comparison, the ED<sub>50</sub> for *trans*-retinoic acid (1) was 50 nM. All of the other heteroarotinoids had ED<sub>50</sub> values which were greater than 1000 nM.

Since the clinical use of natural retinoids (retinoic acid, retinol, and retinal) is handicapped by the toxic side effects (hypervitaminosis syndrome), there is considerable interest in synthetic retinoids which have usefulness in the fields of dermatology<sup>1</sup> and oncology.<sup>2</sup> Although a number of retinoids have been synthesized and screened for a range of biological activities, only a few have shown promise in pharmacological application. Currently three retinoids are used in the United States for the treatment of dermatological conditions but not for cancer. One retinoid is Tretinoin, the trade name for *all-trans*-retinoic acid (1), which is used to treat acne vulgaris.<sup>3</sup> Accutane, 13-*cis*-retinoic acid (2), is approved for treatment of severe cystic acne,<sup>4</sup> but it is teratogenic.<sup>5</sup> Etretinate (3) is the only synthetic retinoid



approved by the FDA, and it is used to treat hyperkeratotic conditions including psoriasis and Darier's disease.<sup>6</sup> These agents are principally reserved for dermatological conditions which have not responded to other protocols. A preliminary toxicity screen<sup>7</sup> was reported for "heteroarotinoid" acids 4 and 5 which suggested both compounds were less toxic than 1. Recently,<sup>8</sup> a rigorous toxicity study<sup>8</sup> revealed that 5 is less toxic than either 1 or 6b. Both carbocyclic systems 6a (ester) and 6b (acid)

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possesses a good therapeutic index,<sup>9</sup> but **6b**<sup>7</sup> is toxic. Very few assays<sup>7,10-12</sup> have been done on heteroarotinoids. Both **6c** and **6d** are recorded herein for the first time.

In view of undesirable toxicological traits associated with some natural retinoids and some synthetic arotinoids,<sup>1-3,7-9</sup> heteroarotinoids may offer a useful alternative in chemotherapy. Two possible chemical changes to alter undesirable qualities are (1) an increase in hydrophilicity and overall polarity of the retinoid and (2) modifications of selective sites to vary the metabolic oxidative pathway. Herein we report the syntheses and biological assays<sup>7,9,10</sup> of the new heteroarotinoids 7-17 shown in Table I and **6c** and **6d** in Table II. It should be recalled that certain arotinoids with a five-six fused ring system (as in **6c** and

Table I. Activity of Retinoids in the ODC and HL-60 Assays

retinoid	ODC ID <sub>50</sub> <sup>a</sup> nmol	HL-60 ED <sub>50</sub> nM
(1)	0.12	50
(7)	3.3	500
(8)	35.0	>1000
(9)	3.7	>1000
(10, R = CH <sub>3</sub> )	0.30	b
(11, R = H)	0.31	>1000
(12, R = CH <sub>3</sub> )	>50	b
(13, R = H)	>50	b
(14, X = S, R = CH <sub>3</sub> )	>50	b
(15, X = S, R = H)	35.0	>1000
(16, X = O, R = CH <sub>3</sub> )	>50	b
(17, X = O, R = H)	>50	>1000

<sup>a</sup> Dose administered topically inhibits TPA-induced mouse epidermal ODC activity by 50%. <sup>b</sup> Not tested.

Table II. Activity by Heteroarotinoids **6c** and **6d** in the ODC and HL-60 Assays

test system	ODC % inhibn <sup>a</sup>	ID <sub>50</sub> <sup>b</sup> nmols	compd for HL-60 test system	ED <sub>50</sub> nM
acetone + TPA	control			
acetone + TPA + retinoic acid (1)	87	0.12	2	100
<b>6c</b> + TPA	94	1.2	1a	>1000
<b>6d</b> + TPA	91	22.0	1b	>1000

<sup>a</sup> The percentage of inhibition of test retinoid as compared to the control was calculated as % inhibition = [(ODC activity from TPA) - (ODC activity from TPA + retinoid)] / (ODC activity from TPA) × 100. The concentration of members of 1 and **6c/6d** was 34 nmol.

<sup>b</sup> Inhibitory dose of retinoid that, when administered topically, inhibits 50% of TPA-induced mouse epidermal ODC activity.

**6d**) have exhibited lower toxicity compared to the six-six fused systems in terms of alleviating symptoms associated with hypervitaminosis in mice.<sup>9</sup>

## Results and Discussion

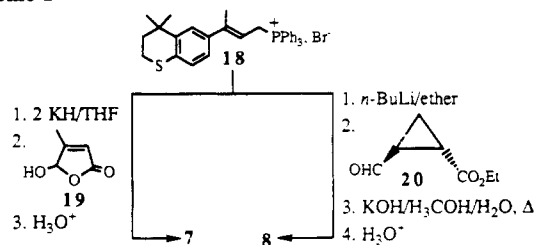
**Chemistry.** Reports have shown the potential pharmacological utility of several analogues of acid **4**.<sup>7,10</sup> Heteroarotinoids reported herein possess a modified side chain (**7**, **8**), a modified thiochromanyl ring (**9**-**11**), or both a modified side chain plus an altered heterocyclic ring (**6a**, **6b**, **12**-**17**). Acids **7** and **8** differ only in the substituents at C(16,18) attached to the terminal carboxyl group. Both analogues were obtained by a Wittig type reaction using phosphonium salt **18** (Scheme I).<sup>10</sup> Synthons **19**<sup>13</sup> and **20**<sup>14</sup>

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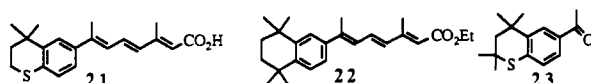
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## Scheme I



were obtained as previously described. The stereochemistry at the terminal double bond for acid **7** was established via  $^{13}\text{C}$  NMR analysis, which revealed the anticipated upfield shift for C(18) (e.g. the carbon  $\alpha$  to the carbonyl) at 115.9 ppm as compared to 118.3 ppm found for the all-trans analogue **21** reported earlier.<sup>10</sup> A similar shift phenomenon has been observed with acids **1** and **2**.<sup>15</sup>

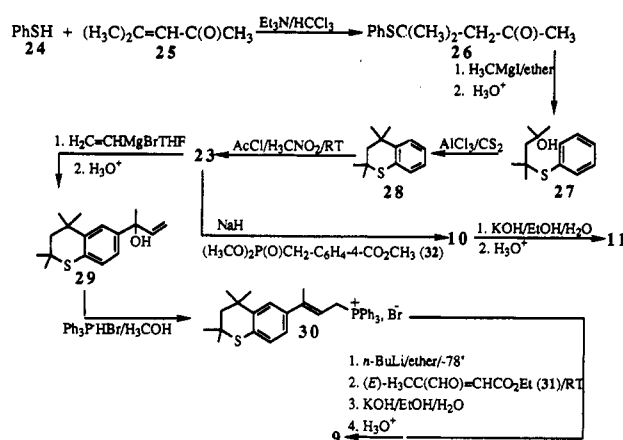
The stereochemistry of acid **8** was proven by evaluation of the  $^1\text{H}$  NMR coupling constants; the vinylic protons appeared at  $\delta$  6.34 ( $J = 12.0$  Hz) for H(13), at  $\delta$  6.61 ( $J = 12.0, 15.0$  Hz) for H(14), and at  $\delta$  5.34 ( $H = 9.0, 15.0$  Hz) for H(15). These characteristic coupling patterns were found also in the analogue all-trans-**21**.<sup>10</sup> From the coupling constants associated with these protons and with a HETCOR 2-D spectrum,<sup>16</sup> the  $^{13}\text{C}$  NMR signals were easily assigned for acid **8**.



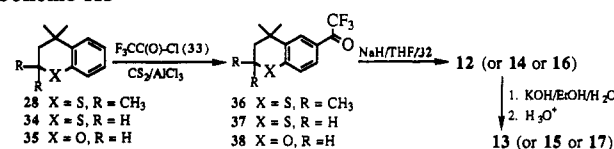
Analogues **9**–**11** were prepared by the routes shown in Scheme II. Although a relative of **9**, namely **22**,<sup>9</sup> was known, the starting ketone **23** needed to obtain acid **9** was unknown. The reaction sequence **24** + **25**  $\rightarrow$  **26**<sup>17</sup>  $\rightarrow$  **28**  $\rightarrow$  **23** gave ketone **23** in moderate yield as a light oil, and the latter was smoothly converted to alcohol **29** by the action of vinylmagnesium bromide. Treatment of alcohol **29** with triphenylphosphine hydrobromide in methanol produced phosphonium salt **30**, which had a  $\delta^{31}\text{P}$  NMR signal at 18.9 ppm (from 85%  $\text{H}_3\text{PO}_4$ ) as compared to 21.6 ppm for **18**<sup>10,18</sup> as a model. Generation of a Wittig reagent from **30** was achieved with *n*-butyllithium in ether/hexane at  $-78^\circ\text{C}$ , and the Wittig reagent was treated with ethyl (*E*)- $\beta$ -formylcrotonate (**31**).<sup>19</sup> A mixture of isomeric esters obtained was saponified (followed by neutralization) to give acid **9**.<sup>20</sup> Heteroarotinoids **10** and **11** could be prepared by allowing the anion of phosphonate **32**<sup>21</sup> to react with ketone **23** as also shown above. Methyl ester **10** was obtained initially and was then hydrolyzed to acid **11**. Both products are solids.

The synthetic pathway to the trifluoromethyl-substituted heteroarotinoids **12**–**17** is given in Scheme III. Trifluoroacetyl chloride (**33**)<sup>22</sup> could be condensed in a

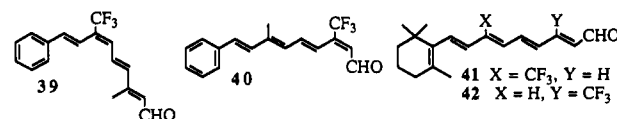
## Scheme II



## Scheme III



suspension of  $\text{AlCl}_3/\text{CS}_2$  with the appropriate ether (**28**, **34**, or **35**) to give the required ketones **36**–**38**, respectively. No other isomeric ketone was found from the acylation reaction. Condensation of the anion from phosphonate **32** with the required ketone (**36**, **37**, or **38**) led to esters **12**, **14**, or **16**, which in turn could be hydrolyzed to the respective acids **13**, **15**, or **17**. The stereochemistry assigned to the double bond in **12**–**17** is based partially upon comparison with data for stilbene derivatives with a trifluoromethyl group.<sup>23</sup> Although a few trifluoromethyl-substituted retinoids are reported,<sup>24</sup> no fluorine-containing heteroarotinoids could be found in a literature survey. Liu and co-workers reported upfield  $^{19}\text{F}$  shifts for (*E*)-(trifluoromethyl)retinal derivatives **39** ( $-64.3$  ppm) and **40**



( $-65.3$  ppm), as referenced to  $\text{FCCl}_3$  and compared to the corresponding *Z* isomers **41** ( $-59.3$  ppm) and **42** ( $-58.1$  ppm), respectively.<sup>25</sup> All  $^{19}\text{F}$  signals for trifluoromethyl-substituted retinoids **12**–**17** and ketones **36**–**38** are included in the Experimental Section and support the presence of the *E* isomer (note the  $\text{F}_3\text{C}$  group changes the stereochemical designation for naming) in all cases. Ester **12** has just been confirmed by X-ray diffraction analysis.<sup>26</sup>

Strategy for the synthesis of **6c** and **6d** began with esterification of acid **43** to give ester **44**. A small excess of methylmagnesium bromide and **44** gave alcohol **45**. Cyclization of **45** with  $\text{AlCl}_3/\text{CS}_2$  led to sulfide **46**, which, as a light oil, had not been previously well characterized.<sup>27</sup>

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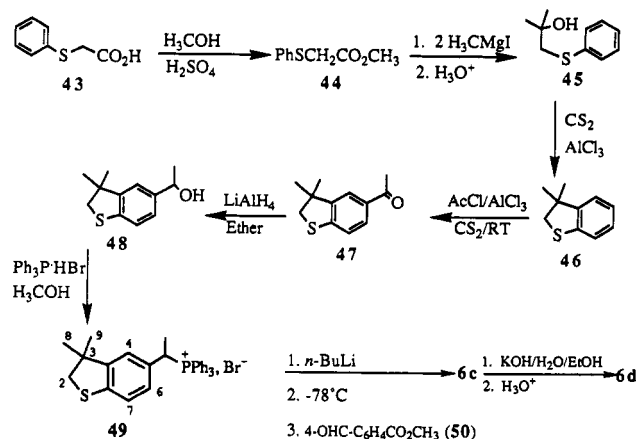
Acetylation of **46** at room temperature produced an oil which, when chilled, gave ketone **47** as a low-melting (20.1–21.4 °C), off-white solid (88.9%). The lone isomer isolated was reduced ( $\text{LiAlH}_4$ ) to solid alcohol **48** (91%) which was phosphorylated to yield salt **49** as a white powder. Conversion of **49** to the corresponding Wittig reagent was effected at room temperature with *n*-butyllithium. Treatment of this chilled (–78 °C) Wittig reagent with methyl 4-formylbenzoate (**50**)<sup>28</sup> gave, after workup, ester (*E*)-**6c** as a solid (mp 120.9–122 °C). Saponification of (*E*)-**6c** led to acid (*E*)-**6d** in the form of white needles (mp 204.0–204.7 °C) (Scheme IV).

The anti arrangement of the aryl groups in (*E*)-**6c** was established (X-ray analysis) and will be reported elsewhere.<sup>29</sup> The  $^1\text{H}$  chemical shifts for **6c/6d** for the vinyl proton ( $\delta$  6.81/6.84) and protons ortho ( $\delta$  8.04/8.14) to the carboxymethyl group and carboxyl group, respectively, are typical of arotinoids and heteroarotinoids with an anti arrangement or aryl groups attached to a double bond.<sup>7,9,10</sup> All protonated carbons in ester (*E*)-**6c** were assigned via correlation with the corresponding proton signals using a HETCOR 2-D plot.<sup>16</sup> These data served as a model for identifying  $^1\text{H}$  and  $^{13}\text{C}$  signals in acid (*E*)-**6d**.

**Biological Activity of Heteroarotinoids 7–17 and 6c,d.** All heteroarotinoids 7–17 (Table I) and **6c** and **6d** (Table II) were evaluated in the ODC and HL-60 assays. A few retinoids, including some arotinoids<sup>7</sup> and heteroarotinoids,<sup>7,10</sup> inhibit both the induction of epidermal ODC and tumor promotion by 12-*O*-tetradecanoylphorbol 13-acetate (TPA).<sup>30</sup> Potential antitumor promoting activity was therefore assessed by the ability of a test retinoid to inhibit TPA induction of ODC. The techniques employed in our experiments have been fully described.<sup>10,30</sup> It should be mentioned that certain heteroarotinoids are less toxic than *trans*-retinoic acid (**1**) in mice.<sup>7,8</sup> Three separate experiments were used in the present study to evaluate the heteroarotinoids and the results were normalized for comparison purposes between each compound.

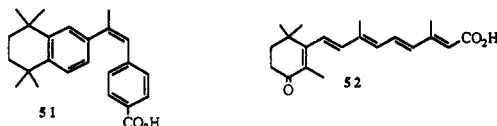
Due to the effect of the terminal double bond on toxicity and teratogenicity in early reported modified retinoids,<sup>31</sup> analogues **7** and **8** were designed to assess what structural modifications could be tolerated while good activity was maintained. Analogue **7** has a terminal double bond similar to that in 13-*cis*-retinoic acid (**2**), which, in the ODC assay, possesses good activity but is less than that of *trans*-retinoic acid (**1**).<sup>10</sup> However, altering the terminal double bond by incorporating a *trans*-substituted cyclopropyl group, as in acid **8**, resulted in an almost complete loss of activity as compared to acid **7** with the double bond present. Although the cyclopropyl carbon–carbon bond closely mimics an olefinic moiety (e.g. increased  $p$  character in the C–C bonds in cyclopropane),<sup>32</sup> the biological results suggest that planarity may be required to retain activity. Other workers have reported similar findings which sup-

Scheme IV



port this premise with the rat vaginal smear assay of cyclopropyl analogues of all-*trans* **1** and 13-*cis*-retinoic acid (**2**).<sup>33</sup> Of course it is conceivable that the conjugated olefinic system is needed for binding at the target site. The rigid cyclopropyl analogue **8** may be unable to accommodate this conformational requirement.

Compounds **9**–**13** possess a common tetramethylthiochroman group but vary in the nature of the polyene side chain. Acid **9** was much more active than acid **8**. In contrast, replacing the terminal diene group of **9** with an aryloxy group, as in **10** and **11**, resulted in a marked increase in activity. Ester **10** and acid **11** were about 10 times more potent than acid **7** in the ODC assay. It was encouraging that the combination of both the tetramethylthiochroman and the benzoyloxy groups (**10** and **11** versus **7** and **9**; **13** versus **15**) elicited a positive effect in activity. Ester **12** and acid **13** were inactive in the ODC assay compared to **10** and **11**. These results appear to be similar to those observed for TTNPB (**6b**) and *cis*-TTNPB (**51**).<sup>9,34</sup> Noteworthy is that positive or negative results



from any one particular assay do not necessarily eliminate or establish potential carcinostatic activity as illustrated by the report on Etreinate (**3**) and the free acid thereof (Etrein) which were ineffective in inducing differentiation in the HL-60 and U-937 lines.<sup>35</sup>

With the five–six fused systems (*E*)-**6c** and (*E*)-**6d**, it is clear that ester (*E*)-**6c** is considerably more active (Table II) than acid (*E*)-**6d**. Initial studies at the 34 nmol level suggested that both compounds had activity comparable to that of the standard **1**. However, the  $\text{ID}_{50}$  values (obtained from different experiments) indicated that acid **1** was more active in terms of the medium, effective dosage level. These results do confirm, however, that the smaller, fused, five-membered ring does not reduce the activity relative to the fused six-membered counterpart<sup>7,10</sup> and that such heteroarotinoids may possess useful specificity of action.

Some retinoids induce HL-60 cells to differentiate.<sup>36</sup> Thus, the retinoids reported herein were evaluated in the

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HL-60 assay, using *trans*-retinoic acid (1) as the standard. Because HL-60 cells<sup>10,12</sup> lack the necessary esterases, only the carboxylic acids were screened. However, we initially examined ester (E)-6c for activity in this screen for verification. Except for 7, the acids were essentially inactive in the HL-60 assay.

In summary, it has been shown that the presence of the polyene side chain on these heteroarotinoids diminishes the activity only slightly in terms of the ODC assay when compared with related compounds containing an aryl group in the chain. The introduction of methyl groups at C(2) (alpha to the heteroatom) also produced active analogues. In the case of the trifluoromethyl derivatives, marginal activity was exhibited by one compound. Thus, the presence of the fluorine atoms may negate activity or the configuration around the double bond may be important. The results suggest that the presence of sulfur atoms in certain heteroarotinoids (6a, 6b, 7, 9–11) conveys good activity as measured by the ODC assay. Thus, sulfur, rather than a CH<sub>2</sub> group at the 4-position of the basic retinoid structure, could be beneficial since this site in 1 undergoes oxidative metabolism.<sup>37</sup> In comparison, we had noted earlier that the ethyl ester of sulfide 4 was more active in the tracheal organ culture assay compared to the corresponding sulfoxide.<sup>10</sup> It should be pointed out that the ketone metabolite 52 was recently shown<sup>38</sup> to be teratogenic. With the fused five-membered systems containing sulfur, moderate activity was found compared to that of standard 1, but the latter is also known to be toxic.<sup>1</sup> In view of the reduced toxicity of 4,<sup>7</sup> 5,<sup>7,8</sup> and 21,<sup>8</sup> heteroarotinoids continue to show promise as potential chemotherapeutic agents.

## Experimental Section

All reactions were carried out under an inert nitrogen atmosphere with magnetic stirring. The NMR spectra were taken on a Varian XL-300 NMR spectrometer operating at 299.9485 MHz for <sup>1</sup>H, 75.429 MHz for <sup>13</sup>C, 121.421 MHz for <sup>31</sup>P, and at 282.203 MHz for <sup>19</sup>F. The <sup>1</sup>H and <sup>13</sup>C NMR signals are reported in  $\delta$  values or in ppm, respectively, downfield from tetramethylsilane (TMS) with DCCl<sub>3</sub> as the solvent. The <sup>31</sup>P NMR signal is reported in ppm downfield from the external reference of 85% H<sub>3</sub>PO<sub>4</sub> and with DCCl<sub>3</sub> as the solvent. For <sup>19</sup>F analysis, F<sub>3</sub>CCO<sub>2</sub>H was used as the external standard and then referenced to FCCl<sub>3</sub> (0 ppm). The <sup>19</sup>F NMR signals are reported in ppm upfield from FCCl<sub>3</sub> with DCCl<sub>3</sub> as the solvent. IR data were collected on a Perkin-Elmer 681 IR spectrophotometer. Melting points were obtained with a Thomas-Hoover melting point apparatus and were uncorrected as were all boiling points. Chromatography was accomplished with a Chromatotron Model 7924 (Harrison Research, 340 Moana Court, Palo Alto, CA 94306) as described in the Chromatotron operation manual with silica gel (unless otherwise specified). Certain starting materials were prepared by modified procedures from the literature: 18,<sup>10</sup> 19,<sup>13</sup> 20,<sup>14</sup> 32,<sup>22</sup> 33,<sup>22</sup> 34,<sup>7,10</sup> and 35.<sup>7,10</sup> Elemental analyses were obtained by Galbraith Laboratories, Knoxville, TN.

**(2Z,4E,6E)-3,7-Dimethyl-7-(4,4-dimethylthiochroman-6-yl)-2,4,6-heptatrienoic Acid (7).** To a stirred suspension of KH (0.214 g, 24% mineral oil dispersion, 5.35 mmol) in dry THF (6

mL) was added salt 18<sup>10</sup> (1.54 g, 2.68 mmol) at room temperature. After 20 min, the resulting dark red mixture was cooled in an ice bath (10 min) and 4-hydroxy-3-methylbut-2-enolide (19,<sup>13</sup> 0.45 g, 2.68 mmol) in 8.0 mL of dry THF was added dropwise (5 min). The reaction mixture was allowed to warm to room temperature overnight with stirring. The dark reaction mixture was poured into 50 mL of ice water, and the resulting solution was extracted with ether (2  $\times$  25 mL). The combined organics were extracted with H<sub>2</sub>O (2  $\times$  25 mL) and the aqueous layers were combined and acidified with 5% H<sub>2</sub>SO<sub>4</sub> to approximately pH 4.0. The resulting cloudy yellow solution was extracted with ether (3  $\times$  50 mL); the ether solutions were combined and washed with H<sub>2</sub>O (2  $\times$  25 mL). This new ether solution was treated with a small crystal of I<sub>2</sub> for 2 min, with stirring, followed by immediate quenching with 5% sodium thiosulfate (2  $\times$  25 mL). The resulting solution was washed with H<sub>2</sub>O (25 mL) and brine (25 mL) and then dried (Na<sub>2</sub>SO<sub>4</sub>). The mixture was concentrated and the yellow oil was crystallized twice (absolute ethanol) to give 0.31 g (35.2%) of acid 7 as a yellow solid: mp 172.5–173.0 °C dec; IR (KBr) 1675 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (DCCl<sub>3</sub>)  $\delta$  1.36 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.96 (m, 2 H, PhSCH<sub>2</sub>CH<sub>2</sub>), 2.14 (s, 3 H, CH<sub>3</sub>), 2.23 (s, 3 H, CH<sub>3</sub>), 3.03 (m, 2 H, PhSCH<sub>2</sub>CH<sub>2</sub>), 5.71 (br s, 1 H, CHCO<sub>2</sub>H), 6.69 [d, 1 H, *J* = 9 Hz, PhC(CH<sub>3</sub>)CHCH=CH], 7.07 [d, 1 H, *J* = 7 Hz, H(8)], 7.08 (dd, 1 H, *J* = 9.0 Hz, *J* = 15.0 Hz, CHCH=CH), 7.21 [dd, 1 H, *J* = 7.0 Hz, *J* = 2.0 Hz, H(7)], 7.51 [d, 1 H, *J* = 2.0 Hz, H(5)], 7.86 [d, 1 H, *J* = 15 Hz, CHC(CH<sub>3</sub>)CHCO<sub>2</sub>H]; <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 16.2 [PhC(CH<sub>3</sub>)], 21.3 [C(CH<sub>3</sub>)CHCO<sub>2</sub>H], 23.1 (PhSCH<sub>2</sub>CH<sub>2</sub>), 30.2 [(CH<sub>3</sub>)<sub>2</sub>C], 33.1 [(CH<sub>3</sub>)<sub>2</sub>C], 37.6 (PhSCH<sub>2</sub>CH<sub>2</sub>), 115.9 (CHCO<sub>2</sub>H), 123.5 [C(7)], 123.6 [C(5)], 126.0 [PhC(CH<sub>3</sub>)CH], 126.4 [C(8)], 129.2 [CHC(CH<sub>3</sub>)CHC(CH<sub>3</sub>)CH], 131.9 [C(8a)], 133.4 [CH=CHC(CH<sub>3</sub>)CHCO<sub>2</sub>H], 138.0 [C(6)], 140.9, 141.7, 153.7, [C(CH<sub>3</sub>)CHCO<sub>2</sub>H], 172.1 (CO<sub>2</sub>H). Anal. (C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>S) C, H, S.

**(2E,4E,6E)-7-Methyl-7-(4,4-dimethylthiochroman-6-yl)-2,3-methylene-6-heptadienoic Acid (8).** To a stirred suspension of 6.05 g (10.6 mmol) of phosphonium salt 18 in 60 mL of dry ether was added dropwise *n*-butyllithium (6.81 mL, 1.55 M, 10.6 mmol) in hexane (room temperature). The resulting, dark orange-red solution was cooled to -78 °C and 1.50 g (10.6 mmol) of ethyl *trans*-4-formylcyclopropanecarboxylate (20)<sup>14</sup> in 20 mL of ether was added dropwise in the dark. The mixture was allowed to warm at room temperature with stirring over 12 h. The almost colorless suspension was diluted with 50 mL of hexanes, filtered, and concentrated. The resulting oil was passed through a 15-cm column containing a slurry of silica gel using 1:1 ether/hexanes. Removal of the solvents gave 3.06 g of the crude esters as a thick oil. To 0.50 g (1.40 mmol) of this oil was added 10 mL of methanol, and this new solution was added to a mixture of KOH (0.28 g, 4.21 mmol) in H<sub>2</sub>O (2 mL). Heating this mixture to a gentle reflux followed for 30 min. The clear resultant solution was allowed to cool (30 min) to room temperature, was diluted with 50 mL of H<sub>2</sub>O containing 5.0 g of NaCl, and was finally extracted (ether, 100 mL). The ether layer was extracted with H<sub>2</sub>O (3  $\times$  25 mL), and the combined aqueous layers were acidified slowly with 5% H<sub>2</sub>SO<sub>4</sub> (pH  $\sim$  3). At the neutralization point, the solution became cloudy. The aqueous solution was extracted with ether (2  $\times$  50 mL); the organics were combined and then extracted with H<sub>2</sub>O (25 mL) and brine (50 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>), evaporation of the ether gave a lightly colored oil which was crystallized (ethanol/H<sub>2</sub>O) to give 0.130 g (28.2%) of acid 8 (recrystallized from ethanol/H<sub>2</sub>O) as a very light tan solid: mp 149.5–152.0 °C; <sup>1</sup>H NMR (DCCl<sub>3</sub>)  $\delta$  1.12 (m, 1 H), 1.33 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C] 1.51 (m, 1 H), 1.69 (m, 1 H), 1.95 (m, 2 H, PhSCH<sub>2</sub>CH<sub>2</sub>), 2.20 (m, 1 H), 2.12 [s, 3 H, PhC(CH<sub>3</sub>)], 3.02 (m, 2 H, PhSCH<sub>2</sub>), 5.34 [dd, 1 H, *J* = 9.0 Hz, *J* = 15.0 Hz, PhC(CH<sub>3</sub>)CHCH=CH], 6.34 [d, 1 H, *J* = 12.0 Hz, PhC(CH<sub>3</sub>)CH], 6.61 (dd, 1 H, *J* = 12.0 Hz, *J* = 15.0 Hz, CHCH=CH), 7.04 [d, 1 H, *J* = 8.0 Hz, H(8)], 7.12 [dd, 1 H, *J* = 8.0 Hz, *J* = 2.0 Hz, H(7)], 7.43 [d, 1 H, *J* = 2.0 Hz, H(5)]; <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 15.9, 16.9, 22.4, 23.1, 26.8, 30.2, 33.1, 37.1, 123.3, 123.6, 125.0, 126.4, 128.1, 130.7, 133.1, 135.2, 138.8, 141.6, 179.5. Anal. (C<sub>20</sub>H<sub>24</sub>SO<sub>2</sub>) C, H.

**4-Methyl-4-(phenylthio)-2-pentanone (26).** To a solution of 28.64 g (0.26 mol) of thiophenol (24), 24.54 g (0.25 mol) of mesityl oxide (25), and 100 mL of HCCl<sub>3</sub> at 0 °C (ice) was added 1.5 mL of triethylamine. The cold bath was removed (15 min) after the addition of triethylamine, and the solution was stirred at room temperature for 1 h. The resulting clear, colorless solution

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was heated at reflux for an additional 24 h. The new solution was allowed to cool to room temperature and then was washed with 10% NaOH (2 × 50 mL). The combined aqueous layers were extracted with ether (3 × 50 mL). The organics were then combined, washed with H<sub>2</sub>O (50 mL) and brine (50 mL), and then dried (Na<sub>2</sub>SO<sub>4</sub>). The dried solution was filtered and concentrated. Following vacuum distillation, 40.14 g (77.1%) of 4-methyl-4-(phenylthio)-2-pentanone (26) was obtained as a clear colorless liquid: bp 85–87 °C (0.01 mm) [lit.<sup>17</sup> bp 94–95 °C (0.01 mm)]; IR (neat) 1730 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.41 [s, 6 H, C(CH<sub>3</sub>)<sub>2</sub>], 2.15 [s, 3 H, O=CCH<sub>3</sub>], 2.69 [s, 2 H, CH<sub>2</sub>C(O)CH<sub>3</sub>], 7.34–7.42 (m, 3 H, Ph-H), 7.75 (dd, 2 H, *J* = 3.0 Hz, *J* = 8.0 Hz, Ph-H); <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 28.1 [q, (CH<sub>3</sub>)<sub>2</sub>C], 31.9 [q, O=CCH<sub>3</sub>], 46.9 [s, C(CH<sub>3</sub>)<sub>2</sub>], 54.2 [t, CH<sub>2</sub>C(O)CH<sub>3</sub>], 128.4 [d, C(2')], 128.8 [d, C(4')], 131.4 [s, C(1')], 137.4 [d, C(3')], 205.5 [s, C=O].

**2,4-Dimethyl-4-(phenylthio)-2-pentanol (27).** To a freshly prepared solution [from 24.06 g (0.24 mol) of methyl iodide and 5.83 g (0.24 g-atom) of magnesium in 100 mL of dry ether] of methylmagnesium iodide in 165 mL of ether was added dropwise 25.00 g (0.120 mol) of 2,4-dimethyl-4-(phenylthio)-2-pentanone (26) in ether (50 mL). The solution was stirred at room temperature (3 h) and poured slowly onto ice. The resulting mixture was neutralized with 5% H<sub>2</sub>SO<sub>4</sub> (pH ~6.5); the ether layer was separated, and the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave an oil which was vacuum distilled to give 20.24 g (75.2%) or 2,4-dimethyl-4-(phenylthio)-2-pentanol (27) as a clear, colorless liquid: bp 105–109 °C (0.075 mm). The oil was used without further purification. IR (neat) 3200–3600 (O-H) cm<sup>-1</sup>; <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.30 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.33 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.79 [s, 2 H, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 3.58 (br s, 1 H, OH), 7.26–7.34 (m, 3 H, Ph-H), 7.57 (dd, 2 H, *H* = 3.0 Hz, *H* = 8.0 Hz, Ph-H); <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 30.8 [q, (CH<sub>3</sub>)<sub>2</sub>C], 32.2 [q, (CH<sub>3</sub>)<sub>2</sub>C], 49.1 [s, PhSC(CH<sub>3</sub>)<sub>2</sub>], 52.4 [t, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 71.7 [s, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>C], 128.3 [d, C(2')], 128.6 [d, C(4')], 131.5 [s, C(1')], 137.1 [d, C(3')].

**2,2,4,4-Tetramethylthiochroman (28).** To standard equipment was added 42.8 g (0.32 mol) of AlCl<sub>3</sub> in dry CS<sub>2</sub> (150 mL). To the stirred suspension of AlCl<sub>3</sub> was added dropwise a solution of 18.0 g (80.2 mmol) of 2,4-dimethyl-4-(phenylthio)-2-pentanol (27) in CS<sub>2</sub> (50 mL) at room temperature over 15 min. The resulting suspension was heated at reflux (10 h) with stirring. After cooling to room temperature, the suspension was poured onto ice, and the mixture was stirred (5 min). This mixture was separated into two layers; the aqueous layer was extracted with ether (3–75 mL). The organic extracts were combined, extracted with H<sub>2</sub>O (50 mL) and brine (50 mL), and then dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave an oil which was flash chromatographed with hexane on silica gel. Removal of the hexane gave 14.78 g (89.3%) of 2,2,4,4-tetramethylthiochroman (28) as a clear, colorless oil, bp 66–68 °C (0.075 mm). The oil was suitable for use directly. <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.38 [s, 6 H, C(CH<sub>3</sub>)<sub>2</sub>], 1.40 [s, 6 H, C(CH<sub>3</sub>)<sub>2</sub>], 1.94 [s, 2 H, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 7.00–7.20 (m, 4 H, Ph-H); <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 30.4 [q, C(CH<sub>3</sub>)<sub>2</sub>], 31.3 [q, C(CH<sub>3</sub>)<sub>2</sub>], 34.2 [s, PhC(CH<sub>3</sub>)<sub>2</sub>], 40.7 [s, PhSC(CH<sub>3</sub>)<sub>2</sub>], 53.2 [t, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 123.6 (d), 124.5 (d), 125.3 (d), 126.6 (d), 131.3 (s), 141.2 (s).

**2,2,4,4-Tetramethyl-6-acetylthiochroman (23).** A solution of 5.0 g (0.024 mol) of 2,2,4,4-tetramethylthiochroman (28) and 1.91 g (0.924 mol) of acetyl chloride in nitromethane (30 mL) was added dropwise to a stirred solution of 6.46 g (0.048 mol) of AlCl<sub>3</sub> in nitromethane (30 mL) at 0 °C (ice bath). The ice bath was maintained for 0.5 h, and the resulting yellow solution was then allowed to warm to room temperature with stirring (12 h). The reaction mixture was slowly poured, with stirring, into a beaker half-filled with ice. The ether extracts (3 × 50 mL) were combined and washed with 50 mL of H<sub>2</sub>O and 50 mL of brine. After drying (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed, and the resulting oil was divided into four equal portions and separated individually with chromatography (silic gel/hexane; Chromatotron). The four purified solutions were combined and concentrated to give 4.10 g (68.1%) of 2,2,4,4-tetramethyl-6-acetylthiochroman (23) as a light yellow oil which was used without further purification. IR (neat) 1680 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.44 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.45 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.99 [s, 2 H, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 2.59 [s, 3 H, O=CCH<sub>3</sub>], 7.18 [d, 1 H, *J* = 8.0 Hz, H(8)], 7.63 [dd, 1 H, *J* = 2.0 Hz, *J* = 8.0 Hz, H(7)], 8.06 [d, 1 H, *J* = 2.0 Hz, *J* = 8.0 Hz, H(5)]; <sup>13</sup>C

NMR (DCCl<sub>3</sub>) ppm 26.1 [q, O=CCH<sub>3</sub>], 31.5 [q, (CH<sub>3</sub>)<sub>2</sub>C], 32.4 [(CH<sub>3</sub>)<sub>2</sub>C], 35.3 [s, PhC(CH<sub>3</sub>)<sub>2</sub>], 42.2 [s, PhSC(CH<sub>3</sub>)<sub>2</sub>], 53.7 [t, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 125.7 (d), 126.2 (d), 127.4 (d), 133.6 (s), 139.7 (s), 142.1 (s), 196.3 (C=O).

**[3-(2,2,4,4-Tetramethylthiochroman-6-yl)-2-butenyl]triphenylphosphonium Bromide (30).** To a freshly prepared solution of vinylmagnesium bromide [2.58 g (0.024 mol) of vinyl bromide and 0.59 g (0.024 g-atom) magnesium, in 50 mL of THF] was added dropwise 3.00 g (0.012 mol) of 2,2,4,4-tetramethyl-6-acetylthiochroman (23) in THF (30 mL) with stirring. The solution was heated at reflux (1 h) and then allowed to cool to room temperature. The resulting metallic-colored solution was poured into ice and neutralized carefully with 5% H<sub>2</sub>SO<sub>4</sub> (pH ~6.5). The aqueous layer was separated and extracted with ether (3 × 50 mL), and the organics were combined. The organic layer was washed with H<sub>2</sub>O (50 mL) and brine (50 mL) and was then dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent gave oil 29 which was dissolved in methanol (20 mL). The new solution was added dropwise to a cold (ice bath) suspension of 4.15 g (0.012 mol) of triphenylphosphine hydrobromide in 10 mL of methanol. This ice bath was removed after the addition, and the resulting lavender suspension was allowed to warm to room temperature over 4 h. Evaporation of the resulting dark purple reaction mixture under reduced pressure gave a thick purple oil which solidified upon trituration with ether (20 mL) and scratching. A dark orange solid formed which was filtered off and recrystallized (methanol and ether) to give 4.70 g (65.1%) of 30 as a light tan, powdery solid, suitable for further reactions without additional purification: mp 224–225 °C dec. A sample recrystallized (CH<sub>3</sub>OH/ether; mp 227.0–227.5 °C) well, but with a high material loss. The purified sample did not produce a higher yield of 9 in the next step. <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.36 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.42 [s, 6 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.67 [d, 3 H, *J* = 4.0 Hz, CH<sub>3</sub>C=CH (trans)], 1.94 [s, 2 H, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 4.85 (dd, 2 H, *J* = 8.0 Hz, *J*<sub>PH</sub> = 15.0 Hz, C=CHCH<sub>2</sub>PPh<sub>3</sub>), 5.64 (tq, 1 H, *J* = 4.0 Hz, *J* = 8.0 Hz, CH<sub>3</sub>C=CHCH<sub>2</sub>PPh<sub>3</sub>), 6.89 [dd, 1 H, *J* = 2.0 Hz, *J* = 8.0 Hz, H(7)], 7.02 [d, 1 H, *J* = 8.0 Hz, H(8)], 7.19 [d, 1 H, *J* = 2.0 Hz, H(5)], 7.70–7.99 [m, 15 H, P(Ph-H)<sub>3</sub>]; <sup>13</sup>C NMR (DCCl<sub>3</sub>) ppm 16.9 [CH<sub>3</sub>C=CH], 25.4 [d, *J*<sub>CP</sub> = 49.9 Hz, C=CHCH<sub>2</sub>], 31.6 [(CH<sub>3</sub>)<sub>2</sub>C], 32.4 [(CH<sub>3</sub>)<sub>2</sub>C], 35.5 [PhC(CH<sub>3</sub>)<sub>2</sub>], 42.1 [PhSC(CH<sub>3</sub>)<sub>2</sub>], 54.1 [PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 110.1, 110.5, 116.2, 119.6, 123.1, 123.9, 124.0, 127.6, 130.0, 130.4, 132.8, 132.9, 133.5, 133.9, 134.9, 135.0, 138.5, 138.7, 142.3, 144.9, 145.4; <sup>31</sup>P NMR (DCCl<sub>3</sub>) ppm 18.9.

**(2E,4E,6E)-3,7-Dimethyl-7-(2,2,4,4-tetramethylthiochroman-6-yl)-2,4,6-heptatrienoic Acid (9).** To a suspension of 1.50 g (2.5 mmol) of phosphonium salt 30 in dry ether (10 mL) was added dropwise at room temperature *n*-butyllithium (1.80 mL, 1.39 M, 2.5 mmol in hexane) in ether (5 mL). The resulting, dark orange-red solution was cooled to -78 °C (dry ice and acetone), and 0.39 g (2.75 mmol) of ethyl (E)-β-formylcrotonate (31)<sup>19</sup> in 15 mL of ether was added dropwise (~5 min) in the dark. The mixture was allowed to warm to room temperature with stirring over 10 h. The resulting yellow suspension was diluted with hexane (50 mL); this solution was filtered and passed through a plug of anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to give a yellow-orange thick oil. To this oil was added ethanol (20 mL), and the new solution was added all at once to a solution of KOH (2.70 g, 0.048 mol) in H<sub>2</sub>O (4 mL). The new mixture was heated at reflux (45 min). The final dark red solution was cooled to room temperature and then diluted with H<sub>2</sub>O (50 mL) containing 5.0 g of NaCl. This new mixture was extracted with ether (100 mL). The ether layer was extracted with H<sub>2</sub>O (3 × 25 mL), and the combined yellow aqueous layers were acidified (pH -3–4) slowly with 5% H<sub>2</sub>SO<sub>4</sub>. At the neutralization point, the solution became cloudy; the aqueous solution was then extracted with ether (2 × 50 mL). The combined organics were washed with H<sub>2</sub>O (25 mL) and brine (25 mL) and then dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the ether left a yellow solid which was fractionally recrystallized (absolute ethanol) to give 0.267 g (30.0% from the phosphonium salt 30) of acid 9 as a grainy yellow solid: mp 224.5–225 °C dec; IR (KBr) 1680 (C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR (DCCl<sub>3</sub>) δ 1.42 [s, 12 H, (CH<sub>3</sub>)<sub>2</sub>C], 1.97 [s, 2 H, PhSC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>], 2.25 [s, 3 H, CH<sub>3</sub>], 2.41 [s, 3 H, CH<sub>3</sub>], 5.86 (br s, 1 H, CHCO<sub>2</sub>H), 6.43 [d, 1 H, *H* = 15.0 Hz, CHC(CH<sub>3</sub>)], 6.58 [d, 1 H, *J* = 12.0 Hz, PhC(CH<sub>3</sub>)CH], 7.09 [d, 1 H, *J* = 8.0 Hz, H(8)], 7.10 [dd, 1 H, *J* = 12.0 Hz, *J* = 15.0 Hz, CHCH=CH], 7.21 [dd, 1 H, *J* = 2.0 Hz, *J* = 8.0 Hz, H(7)],



7.51 [d, 1 H,  $J = 2.0$  Hz, H(5)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 14.1 ( $\text{CH}_3$ ), 16.3 ( $\text{CH}_3$ ), 31.7 [ $(\text{CH}_3)_2\text{C}$ ], 32.6 [ $(\text{CH}_3)_2\text{C}$ ], 35.7 [ $(\text{CH}_3)_2\text{CPh}$ ], 42.2 [ $\text{PhSC}(\text{CH}_3)_2$ ], 54.4 [ $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 117.8 ( $\text{CHCO}_2\text{H}$ ), 123.5, 124.1, 125.7, 127.9, 132.0, 132.9, 135.4, 139.0, 140.7, 142.5, 155.1 [ $\text{C}(\text{CH}_3)\text{CHCO}_2\text{H}$ ], 170.8 ( $\text{CO}_2\text{H}$ ).

**Methyl (*E*)-4-[2-(2,2,4,4-tetramethylthiochroman-6-yl)-propenyl]benzoate (10).** To a suspension of dry THF (10 mL) and NaH (19 mg, 4.9 mmol, 60% as mineral dispersion) was added dropwise at room temperature a solution of 2,2,4,4-tetramethyl-6-acetylthiochroman (23, 1.10 g, 4.4 mmol), dimethyl (4-carbomethoxybenzyl)phosphonate (32, 1.25 g, 4.9 mmol), and 15-crown-5 ether (22 mg, 1.0 mmol, Aldrich) in 15 mL of THF. The mixture was stirred at room temperature (24 h) to give a dark red suspension. This reaction mixture was treated with glacial acetic acid (1.0 mL); the resulting light yellow solution was combined with 100 mL of brine solution and the two layers separated. The aqueous layer was extracted with ether ( $2 \times 50$  mL). The organics were combined, washed with  $\text{H}_2\text{O}$  ( $2 \times 50$  mL) and brine (50 mL), and finally dried ( $\text{Na}_2\text{SO}_4$ ). This solution was concentrated, and a resulting yellow oil was separated (Chromatotron) with hexanes and silica gel to give a new light yellow oil. This oil was crystallized three times with hexane to give 0.66 g (39.2%) of ester 10 as white flakes: mp 88.5–89.0 °C; IR (KBr) 1720 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.43 [s, 12 H,  $(\text{CH}_3)_2\text{C}$ ], 1.97 [s, 2 H,  $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 2.28 [d, 3 H,  $J = 1.0$  Hz,  $\text{CH}_3\text{C}=\text{CH}$  (trans)], 3.93 [s, 3 H,  $\text{CO}_2\text{CH}_3$ ], 6.82 [d, 1 H,  $J = 1.0$  Hz,  $\text{CH}_3\text{C}=\text{CH}$  (trans)], 7.13 [d, 1 H,  $J = 8.0$  Hz, H(8)], 7.23 [dd, 1 H,  $J = 2.0$  Hz,  $J = 8.0$  Hz, H(7)], 7.42 [d, 2 H,  $J = 8.0$  Hz, H(15,19)], 7.53 [d, 1 H,  $J = 2.0$  Hz, H(5)], 8.04 [d, 2 H,  $J = 8.0$  Hz, H(16,18)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 17.6 ( $\text{CH}_3\text{C}=\text{CH}$ ), 31.6 [ $(\text{CH}_3)_2\text{C}$ ], 32.6 [ $(\text{CH}_3)_2\text{C}$ ], 35.6 [ $(\text{CH}_3)_2\text{CPh}$ ], 42.1 [ $\text{PhSC}(\text{CH}_3)_2$ ], 52.1 ( $\text{CO}_2\text{CH}_3$ ), 54.4 [ $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 123.7 [C(7)], 124.4 [C(5)], 125.9 ( $\text{CH}_3\text{C}=\text{CH}$ ), 127.8, 127.9 [C(8)], 128.9 [C(15,19)], 129.1 [C(16,18)], 132.4, 139.5, 140.1, 142.5, 143.2, 167.0 ( $\text{CO}_2\text{CH}_3$ ). Anal. ( $\text{C}_{24}\text{H}_{28}\text{SO}_2$ ) C, H.

**(*E*)-4-[2-(3,4-Dihydro-2,2,4,4-tetramethyl-2H-1-benzopyran-6-yl)-1-propenyl]benzoic Acid (11).** Methyl (*E*)-4-[2-(2,2,4,4-tetramethylthiochroman-6-yl)propenyl]benzoate (10, 0.150 g, 0.394 mmol) was heated to reflux in an aqueous/ethanol (2.4 mL/10 mL) solution of KOH (0.105 g, 1.9 mmol) for 1 h. After cooling to room temperature (30 min), the resulting solution was diluted with ether (50 mL) and 50 mL of brine. The two layers were separated and the organic layer was washed with  $\text{H}_2\text{O}$  ( $2 \times 25$  mL). The combined aqueous layers were acidified with 5%  $\text{H}_2\text{SO}_4$  to give a cloudy solution which was extracted with ether ( $3 \times 50$  mL). The extracts were washed with  $\text{H}_2\text{O}$  (25 mL) and brine (50 mL) and then dried ( $\text{Na}_2\text{SO}_4$ ); concentration gave a white solid which, after recrystallization (95% ethanol), gave 0.112 g (78.1%) of acid 11 as white needles: mp 147–148 °C; IR (KBr) 1710 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.46 [s, 12 H,  $(\text{CH}_3)_2\text{C}$ ], 1.99 [s, 2 H,  $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 2.32 [d, 3 H,  $J = 1.0$  Hz,  $\text{CH}_3\text{C}=\text{CH}$  (trans)], 6.84 [d, 1 H,  $J = 1.0$  Hz,  $\text{CH}_3\text{C}=\text{CH}$  (trans)], 7.15 [d, 1 H,  $J = 8.0$  Hz, H(8)], 7.25 [dd, 1 H,  $J = 2.0$  Hz,  $J = 8.0$  Hz, H(7)], 7.48 [d, 2 H,  $J = 8.0$  Hz, H(15,19)], 7.57 [d, 1 H,  $J = 2.0$  Hz, H(5)], 8.14 [d, 2 H,  $J = 8.0$  Hz, H(16,18)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 17.7 ( $\text{CH}_3\text{C}=\text{CH}$ ), 31.7 [ $(\text{CH}_3)_2\text{C}$ ], 32.7 [ $(\text{CH}_3)_2\text{C}$ ], 35.7 [ $(\text{CH}_3)_2\text{CPh}$ ], 42.2 [ $\text{PhSC}(\text{CH}_3)_2$ ], 54.4 [ $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 123.7 [C(7)], 124.4 [C(5)], 125.8 ( $\text{CH}_3\text{C}=\text{CH}$ ), 126.9, 128.0 [C(8)], 129.2 [C(15,19)], 130.1 [C(16,18)], 132.5, 139.9, 140.1, 142.5, 144.1 171.7 ( $\text{CO}_2\text{H}$ ). Anal. ( $\text{C}_{23}\text{H}_{26}\text{SO}_2$ ) C, H.

**2,2,4,4-Tetramethylthiochroman-6-yl Trifluoromethyl Ketone (36).** To a suspension of 2,2,4,4-tetramethylthiochroman (28, 2.50 g, 0.012 mol),  $\text{AlCl}_3$  (3.28 g, 0.024 mol), and  $\text{CS}_2$  (30 mL) was added 1.5 mL of trifluoroacetyl chloride (32) over 30 min (stirred). After 1 h, an additional 1.5 mL of trifluoroacetyl chloride (32) was added to the dark orange suspension over 30 min. The resulting mixture was stirred for an additional 1 h and poured into ice; the two layers separated. The aqueous layer was extracted with ether ( $3 \times 50$  mL); the ether layers were combined, washed with brine, and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the ether gave a yellow oil which was separated (Chromatotron) with hexanes on silica gel to give 0.75 g (20.3%) of ketone 36 as a viscous yellow oil which was used without further purification. IR (neat) 1715 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.21 [br s, 12 H,  $(\text{CH}_3)_2\text{C}$ ], 1.98 [s, 2 H,  $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 7.21 [d, 1 H,  $J = 8.0$  Hz, H(8)], 7.69 [dd, 1 H,  $J = 8.0$  Hz,  $J = 1.0$  Hz, H(7)], 8.15 [d, 1 H,  $J = 1.0$  Hz,

H(5)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 31.6 [ $(\text{CH}_3)_2\text{C}$ ], 32.4 [ $(\text{CH}_3)_2\text{C}$ ], 35.4 [ $\text{PhC}(\text{CH}_3)_2$ ], 42.9 [ $\text{PhSC}(\text{CH}_3)_2$ ], 53.3 [ $\text{PhC}(\text{CH}_3)_2\text{CH}_2$ ], 116.9 (q,  $^1J_{\text{CF}} = 291.2$  Hz,  $\text{CF}_3$ ), 126.2, 126.9, 127.9, 128.5, 143.0, 144.4, 179.0 [q,  $^2J_{\text{CF}} = 34.0$  Hz,  $\text{C}(\text{O})\text{CH}_3$ ];  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm -71.74 ( $\text{CF}_3$ ).

**Methyl (*E*)-4-[2-(Trifluoromethyl)-2-(2,2,4,4-tetramethylthiochroman-6-yl)ethenyl]benzoate (12).** To a suspension of dry THF (10 mL) and NaH (0.0723 g, 60% dispersion in mineral oil, 1.81 mmol) was added dropwise at room temperature a solution of ketone 36 (0.50 g, 1.64 mmol), dimethyl (4-carbomethoxybenzyl)phosphonate (32, 0.456 g, 1.81 mmol) and 15-crown-5 ether (0.11 g, 0.5 mmol) in dry THF (15 mL). This suspension was stirred at room temperature (16 h) to give a new dark red suspension. Treatment of the mixture with 1.0 mL of glacial acetic acid gave a light yellow solution which was combined with 100 mL of brine; two layers separated. The aqueous layer was extracted (ether,  $2 \times 50$  mL) and dried ( $\text{Na}_2\text{SO}_4$ ). Concentration of the solution gave a yellow oil which was separated (Chromatotron) with hexanes and silica gel; a light yellow oil resulted. The oil was crystallized with hexanes and then recrystallized twice (hexanes) to give 0.339 g (47.7%) of ester 12 as clear, colorless prisms: mp 87.0–87.5 °C, IR (KBr) 1740 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.21 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.42 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.94 [s, 2 H,  $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 3.89 [s, 3 H,  $\text{CO}_2\text{CH}_3$ ], 6.98–7.30 (m, 6 H), 7.86 (d, 2 H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 31.4, 32.6, 35.3, 42.2, 52.2, 54.1, 126.7, 128.5, 128.9, 129.4, 129.9, 131.9, 132.0, 134.3, 138.4, 143.2, 166.4;  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm -66.59 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{24}\text{H}_{25}\text{SO}_2\text{F}_3$ ) C, H, F.

**(*E*)-4-[2-(Trifluoromethyl)-2-(2,2,4,4-tetramethylthiochroman-6-yl)ethenyl]benzoic Acid (13).** Methyl (*E*)-4-[2-(trifluoromethyl)-2-(2,2,4,4-tetramethylthiochroman-6-yl)ethenyl]benzoate (12, 0.150 g, 0.345 mmol) was heated to reflux with stirring in an aqueous/ethanol (2 mL/10 mL) solution of KOH (0.40 g, 7.13 mmol) for 1 h. After cooling to room temperature (30 min), the resulting solution was diluted with ether (50 mL) and brine (50 mL). The two layers were separated, and the organic layer was washed with  $\text{H}_2\text{O}$  ( $2 \times 25$  mL). The combined aqueous layers were acidified with 5%  $\text{H}_2\text{SO}_4$  to give a cloudy solution which was extracted with ether ( $3 \times 50$  mL). The extracts were washed with  $\text{H}_2\text{O}$  (25 mL) and brine (50 mL) and then dried ( $\text{Na}_2\text{SO}_4$ ); concentration gave a white solid which, after recrystallization (95% ethanol), gave 0.1135 g (78.2%) of acid 13: mp 169.0–170.0 °C. 1710 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.21 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.42 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.93 [s, 2 H,  $\text{PhSC}(\text{CH}_3)_2\text{CH}_2$ ], 6.97–7.30 (m, 6 H), 7.92 (d, 2 H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 31.7, 32.7, 35.7, 42.1, 54.5, 123.8, 124.5, 125.9, 127.0, 128.0, 129.2, 130.2, 132.6, 140.0, 140.1, 142.6, 144.1, 171.7;  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm -66.61 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{23}\text{H}_{23}\text{SO}_2\text{F}_3$ ) C, H, F.

**4,4-Dimethylthiochroman-6-yl Trifluoromethyl Ketone (37).** To a suspension of 4,4-dimethylthiochroman (34, 3.57 g, 0.020 mol),  $\text{AlCl}_3$  (5.33 g, 0.040 mol), and  $\text{CS}_2$  (35 mL) in a flask equipped with a dry ice condenser was added 1.5 mL of trifluoroacetyl chloride (33) over 30 min. After 1 h from the start of the reaction, an additional 1.5 mL of trifluoroacetyl chloride (33) was added to the orangish suspension over 30 min. The resulting mixture was treated in the same manner used to obtain 36 and gave a yellow oil which was separated (Chromatotron; hexanes/silica gel) to give 1.73 g (31.3%) of ketone 37 as a viscous yellow oil used without further purification: IR (neat) 1720 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.33 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.83 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 3.07 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 7.20 [d, 1 H,  $J = 8.0$  Hz, H(8)], 7.68 [dd, 1 H,  $J = 8.0$  Hz,  $J = 1.0$  Hz, H(7)], 8.14 [d, 1 H,  $J = 1.0$  Hz, H(5)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 23.2 ( $\text{PhSCH}_2\text{CH}_2$ ), 29.3 [ $(\text{CH}_3)_2\text{C}$ ], 32.8 [ $(\text{CH}_3)_2\text{C}$ ], 36.2 ( $\text{PhSCH}_2\text{CH}_2$ ), 116.7 (q,  $^1J_{\text{CF}} = 291.6$  Hz,  $\text{CF}_3$ ), 125.2, 126.5, 126.7, 127.5, 142.2, 143.8, 178.8 (q,  $^2J_{\text{CF}} = 34.5$  Hz,  $\text{C}=\text{O}$ );  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm -71.72 ( $\text{CF}_3$ ).

**Methyl (*E*)-4-[2-(Trifluoromethyl)-2-(4,4-dithiochroman-6-yl)ethenyl]benzoate (14).** To a suspension of dry THF (10 mL) and NaH (0.080 g, 60% as mineral dispersion, 2.01 mmol) was added dropwise at room temperature a solution of 4,4-dimethylthiochroman-6-yl trifluoromethyl ketone (37, 0.50 g, 1.82 mmol), dimethyl (4-carbomethoxybenzyl)phosphonate (32, 0.52 g, 2.01 mmol), and 15-crown-5 ether (0.11 g 0.50 mmol) in THF (15 mL). This suspension was stirred (room temperature) for 24 h to give a dark red suspension. The reaction mixture was treated as done with 12 to give a yellow oil which was separated (Chromatotron; hexanes/silica gel) to give a new, slightly yellow oil.

This oil was crystallized three times (hexanes) to give 0.45 g (61.2%) of ester 14 as a white powder: mp 83.5–84.5 °C; IR 1710 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.15 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.92 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 3.02 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 3.89 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 6.96–7.30 (m, 6 H, 7.86 (d, 2 H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR ppm 23.1 ( $\text{PhSCH}_2\text{CH}_2$ ), 30.1 [ $(\text{CH}_3)_2\text{C}$ ], 32.9 [ $(\text{CH}_3)_2\text{C}$ ], 37.4 ( $\text{PhSCH}_2\text{CH}_2$ ), 52.2 ( $\text{CO}_2\text{CH}_3$ ), 118.4, 126.7, 127.1, 127.4, 128.4, 129.4, 129.8, 131.9, 133.5, 138.4, 142.6, 166.4;  $^{19}\text{F}$  NMR ppm –66.60 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{22}\text{H}_{21}\text{O}_2\text{SF}_3$ ) C, H, F.

**(E)-4-[2-(Trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoic Acid (15).** Methyl (E)-4-[2-(trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoate (14, 0.2074 g, 0.510 mmol) was heated to reflux in an aqueous/ethanol (3 mL/12 mL) solution of KOH (0.844 g, 15.0 mmol) with stirring (1 h). After cooling to room temperature, the resulting solution was diluted with ether (50 mL) and brine (50 mL). The two layers separated, and the remaining workup was essentially the same as for 13. Concentration of the organic phase gave a white solid, which, after recrystallization (95% ethanol), gave 0.162 g (81.0%) of 15 as a white powder: mp 223.5–224.0 °C; IR (KBr) 1700 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.16 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 2.94 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 3.03 (m, 2 H,  $\text{PhSCH}_2\text{CH}_2$ ), 6.95–7.30 (m, 6 H), 7.95 (d, 2 H,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 23.1 ( $\text{PhSCH}_2\text{CH}_2$ ), 30.1 [ $(\text{CH}_3)_2\text{C}$ ], 32.9 [ $(\text{CH}_3)_2\text{C}$ ], 37.3 ( $\text{CHSCH}_2\text{CH}_2$ ), 126.6, 127.1, 128.3, 128.9, 129.9, 130.0, 131.6, 133.6, 139.3, 142.6, 170.7 ( $\text{CO}_2\text{H}$ );  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm –66.61 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{21}\text{H}_{19}\text{O}_2\text{SF}_3$ ) C, H, F.

**4,4-Dimethylchroman-6-yl Trifluoromethyl Ketone (38).** To a suspension of 4,4-dimethylchroman (35, 5.00 g, 0.02 mol),  $\text{AlCl}_3$  (10.66 g, 0.04 mol), and  $\text{CS}_2$  (60 mL) in a system equipped with a dry ice condenser was added with stirring 2.5 mL of trifluoroacetyl chloride (33) over 30 min. After 1.5 h, an additional 2.5 mL of trifluoroacetyl chloride (33) was added to the yellowish-orange suspension over 30 min. The resulting mixture was treated as was done for 36 and 38 to give an orange oil which was separated (Chromatotron; hexanes/silica gel) to give 2.74 g (53.1%) of 38 as a light orange solid: mp 41.5–42.5 °C. The compound was used without further purification: IR (KBr) 1720 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.33 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.82 (m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ), 4.26 (m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ), 6.83 [d, 1 H,  $J = 8.0$ , H(8)], 7.77 [dd, 1 H,  $J = 8.0$  Hz,  $J = 1.0$  Hz, H(7)], 8.06 [d, 1 H,  $J = 1.0$ , H(5)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 30.7 [ $(\text{CH}_3)_2\text{C}$ ], 30.9 [ $(\text{CH}_3)_2\text{C}$ ], 30.9 [ $(\text{CH}_3)_2\text{C}$ ], 36.9 ( $\text{PhOCH}_2\text{CH}_2$ ), 64.3 ( $\text{PhOCH}_2\text{CH}_2$ ), 118.0 (q,  $^1J_{\text{CF}} = 291.3$  Hz,  $\text{CF}_3$ ), 123.4, 130.8, 131.2, 133.5, 161.5, [C(8a)], 180.2 [q,  $^1J_{\text{CF}} = 34.0$  Hz, C(O)CF<sub>3</sub>];  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm –71.43 ( $\text{CF}_3$ ).

**Methyl (E)-4-[2-(Trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoate (16).** To a suspension of dry THF (10 mL) and NaH (0.16 g, 60% as mineral oil dispersion, 3.9 mmol) was added dropwise (room temperature) a solution of 4,4-dimethylthiochroman-6-yl trifluoromethyl ketone (38, 1.00 g, 3.87 mmol), dimethyl (4-carbomethoxybenzyl)phosphonate (32, 1.01 g, 3.9 mmol), and 15-crown-5 ether (0.22 g, 1.0 mmol) in dry THF (15 mL). The new suspension was stirred at room temperature for 16 h to give a red suspension. Treatment of this reaction mixture was essentially the same as for 12 and 14 to give a yellow oil which was separated (Chromatotron; hexanes/silica gel) and gave a new light yellow oil. After treatment with decolorizing carbon for 20 min in boiling ether, the resulting mixture was filtered, condensed, and, after crystallization (hexane), gave 0.52 g (34.4%) of ester 16 as a white, crystalline solid: mp 94.5–95.0 °C. IR (KBr) 1720 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.18 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.81 (m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ), 3.88 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 4.21 (m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ), 6.81 [d, 1 H,  $J = 8.0$  Hz, H(8)], 7.00 [dd, 1 H,  $J = 8.0$  Hz,  $J = 1.0$  Hz, H(7)], 7.11 [s, 1 H,  $\text{PhC}(\text{CF}_3)\text{CH}$ ], 7.12 [d, 1 H,  $J = 8.0$  Hz, H(16,18)], 7.20 [d, 1 H,  $J = 1.0$  Hz, H(5)], 7.86 [d, 2 H,  $J = 8.0$  Hz, H(15,19)];  $^{13}\text{C}$  NMR ppm ( $\text{DCCl}_3$ ) 30.5 [ $(\text{CH}_3)_2\text{C}$ ], 30.8 [ $(\text{CH}_3)_2\text{C}$ ], 37.3 ( $\text{PhOCH}_2\text{CH}_2$ ), 63.2 ( $\text{CO}_2\text{CH}_3$ ), 52.2 ( $\text{PhOCH}_2\text{CH}_2$ ), 117.6 [C(8)], 123.6, 128.1, [C(7)], 128.9 [ $\text{PhC}(\text{CF}_3)\text{CH}$ ], 129.4 [C(16,18)], 129.8 [C(15,19)], 131.5 [C(5)], 134.3, 138.6, 154.3, 166.5;  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm –66.80 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{22}\text{H}_{21}\text{O}_3\text{F}_3$ ) C, H, F.

**(E)-p-[2-(Trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoic Acid (17).** Methyl (E)-p-[2-(trifluoromethyl)-2-(4,4-dimethylthiochroman-6-yl)ethenyl]benzoate (16, 0.1645 g, 0.421 mmol) was heated to reflux in an aqueous/ethanol (1.0

mL/3.0 mL) solution of KOH (0.48 g, 8.5 mmol) for 1 h. After cooling to room temperature, the resulting solution was diluted with ether (50 mL) and brine (50 mL). The two layers were separated, and the workup was like that used for 13 and 15. Concentration of the organic layer gave a white solid, which after recrystallization (95% ethanol), gave 0.1276 g (80.5%) of 17 as a white, crystalline solid: mp 207.5–208.0 °C; IR 1710 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.18 [s, 6 H,  $(\text{CH}_3)_2\text{C}$ ], 1.82 [m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ], 4.22 (m, 2 H,  $\text{PhOCH}_2\text{CH}_2$ ), 6.81 (d, 1 H), 7.01 (dd, 1 H), 7.09 (d, 1 H), 7.15 (d, 2 H), 7.22 (d, 1 H), 7.92 (d, 2 H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 30.5 [ $(\text{CH}_3)_2\text{C}$ ], 30.8 [ $(\text{CH}_3)_2\text{C}$ ], 37.2 ( $\text{PhOCH}_2\text{CH}_2$ ), 63.2 ( $\text{PhOCH}_2\text{CH}_2$ ), 117.6, 123.5, 128.1, 128.89, 128.9, 129.9, 130.0, 131.4, 131.5, 132.4, 139.6, 154.3, 170.8 ( $\text{CO}_2\text{H}$ );  $^{19}\text{F}$  NMR ( $\text{DCCl}_3$ ) ppm –66.82 ( $\text{CF}_3$ ). Anal. ( $\text{C}_{21}\text{H}_{19}\text{O}_3\text{F}_3$ ) C, H, F.

**Methyl 2-(Phenylthio)acetate (44).** A solution of (phenylthio)acetic acid (43, 40.0 g, 0.238 mol), dry  $\text{H}_3\text{COH}$  (600 mL), and  $\text{H}_2\text{SO}_4$  (2.0 mL, 3.7 g, 38 mmol) in standard equipment [equipped with a Soxhlet extractor containing 3A molecular sieve (125 g)] was stirred at reflux (74 h). Upon cooling at room temperature for 20 min, the mixture was neutralized (pH 7) with a solution of  $\text{Na}_2\text{CO}_3$  (4.00 g, 37.7 mmol) in  $\text{H}_2\text{O}$  (16 mL). After concentration to approximately 50 mL, water (200 mL) and  $\text{H}_2\text{CCl}_2$  (200 mL) were added, and the two layers separated. The aqueous layer was extracted ( $\text{H}_2\text{CCl}_2$ , 4  $\times$  140 mL), and the combined organic extracts and original organic layer were washed with 5% aqueous  $\text{NaHCO}_3$  (2  $\times$  100 mL), water (100 mL), and saturated brine (100 mL). The organic solution was then dried ( $\text{MgSO}_4$ ), filtered and evaporated. Distillation of the residue gave 44 as a colorless oil (40.0 g, 92%), the major fraction distilling at 85.9–86.7 °C (0.23 mm) [lit.<sup>39</sup> bp 93–95 °C (0.6 mm)]: IR (film) 1742 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  3.62 (s, 2 H,  $\text{CH}_2$ ), 3.66 (s, 3 H,  $\text{OCH}_3$ ), 7.15–7.30 (m, 3 H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 36.3 (t,  $\text{SCH}_2$ ), 52.4 (q,  $\text{OCH}_3$ ), 126.8 (d, Ar-C), 129.0 (d, Ar-C), 129.7 (d, Ar-C), 135.0 (s, Ar-C), 170.0 (s,  $\text{CO}_2\text{CH}_3$ ).

**2-Methyl-1-(phenylthio)-2-propanol (45).** To a cooled (0 °C), freshly prepared solution of methylmagnesium iodide [from 25.0 g (0.176 mol) of  $\text{H}_3\text{Cl}$  and 4.0 g (0.165 mol) of magnesium in dry ether (100 mL)] was added a solution of ester 44 (10.0 g, 54.0 mmol) in dry ether (20 mL). The resulting mixture was stirred at 0–25 °C for 1 h and then at reflux (18 h). This new mixture was then diluted (ether, 75 mL), cooled (0 °C), and quenched (pH 7) with water (20 mL), 20%  $\text{NH}_4\text{Cl}$  (40 mL), and finally with 10%  $\text{H}_2\text{SO}_4$  (75 mL). The two layers separated and the aqueous layer was extracted (ether, 5  $\times$  50 mL). The combined organic extracts and original organic layer were washed with 5%  $\text{NaHCO}_3$  (100 mL) and then briefly dried ( $\text{Na}_2\text{SO}_4$ , 10 min). Evaporation of the solvent gave an oil which contained varying amounts (less than 10%) of 1-(phenylthio)-2-propane. It was necessary to eliminate this impurity which made the ensuing reaction mixtures difficult to manipulate. Removal of the impurity was effected by adding a solution of  $\text{I}_2$  (2.5 g) and NaI (5.0 g) in water (20 mL) in a dropwise manner to a stirred solution containing 4.8 g of the oil in 40 mL of 6% KOH/ $\text{H}_3\text{COH}$ . The resulting mixture was stirred for 10 min. The procedure was repeated for the remaining oil (about 4.8 g). The two mixtures were filtered separately and extracted separately (ether, 100 and 50 mL), and the extracts were dried ( $\text{Na}_2\text{SO}_4$ ). Filtration and evaporation of the solvent gave an oil which was vacuum distilled. The major fraction distilled at 80–85 °C (0.12 mm) [lit.<sup>40</sup> bp 136–137 °C (12 mm)]. Column chromatography over silica gel (3:1 hexanes/ether) gave alcohol 45 as a light yellow oil [5.6 g, 56%, pure by TLC (9:1 hexanes/ether)];  $n_D^{26.8} = 1.5582$  (lit.<sup>40</sup>  $n_D^{23} = 1.5609$ ); IR (film) 3650–3150 (O–H)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.29 [s, 6 H,  $\text{C}(\text{CH}_3)_2$ ], 2.31 (br s, 1 H, OH) 3.11 (s, 2 H,  $\text{CH}_2$ ), 7.13–7.21 (m, 1 H, Ar-H), 7.22–7.32 (m, 2 H, Ar-H), 7.41 (d, 2 H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 28.6 [C( $\text{CH}_3$ )<sub>2</sub>], 48.2 ( $\text{CH}_2$ ), 70.6 [C( $\text{CH}_3$ )<sub>2</sub>], 125.9, 128.7, 129.2, 136.8 (all Ar-C).

**2,3-Dihydro-3,3-dimethylbenzo[b]thiophene (46).** A solution of alcohol 45 (9.60 g, 52.7 mmol) in freshly distilled  $\text{CS}_2$  (55 mL) was added dropwise (ca. 35 min) to a stirred suspension of

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$\text{AlCl}_3$  (25.0 g, 0.187 mol) in  $\text{CS}_2$  (50 mL) with a dry ice condenser. A reddish-orange mixture resulted which was stirred at reflux (3 h). After cooling in a ice/water bath (0 °C) for 10 min, the new mixture was very cautiously quenched with 5% HCl (90 mL) and then diluted with  $\text{H}_2\text{CCl}_2$  (40 mL). The two layers separated and the aqueous layer was extracted ( $\text{H}_2\text{CCl}_2$ , 2 × 75 mL). The combined organic solutions were washed with 5%  $\text{NaHCO}_3$  (2 × 75 mL), water (75 mL), and saturated brine (75 mL). After drying ( $\text{MgSO}_4$ ) of the organic solution, it was filtered and evaporated. Vacuum distillation gave a pale yellow oil (6.97 g, 80.5%) boiling at 56.3–58.2 °C (0.37 mm) which was pure by TLC analysis (silica gel,  $R_f$  = 0.89 in hexanes). Pure, colorless 46 was obtained as an oil (6.30 g, 72.8%) via chromatography on silica gel (hexanes);  $n_D^{25}$  = 1.5757; IR (film) 1364, 1384 (*gem*-dimethyl C–H bend)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.35 [s, 6 H,  $\text{C}(\text{CH}_3)_2$ ], 3.16 (s, 2 H,  $\text{SCH}_2$ ), 7.02–7.22 (m, 4 H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 27.2 [ $\text{C}(\text{CH}_3)_2$ ], 46.9 ( $\text{SCH}_2$ ), 47.0 [ $\text{C}(\text{CH}_3)_2$ ], 122.0, 122.3, 124.1, 127.0, 140.1, 147.3 (all Ar-C). The sulfur-containing heterocycle, although previously<sup>27</sup> isolated from petroleum, was never adequately characterized by conventional methods. The derivative of 46, obtained by treatment with HI and trinitrobenzene, was characterized by IR and mass spectral analysis.<sup>27</sup> In our hands, 46 have a satisfactory elemental analysis in addition to the above data. Anal. ( $\text{C}_{10}\text{H}_{12}\text{S}$ ) C, H.

**1-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)ethanol (47).** A solution of thioether 46 (8.00 g, 48.7 mmol) and freshly distilled acetyl chloride (4.40 g, 56.1 mmol) in  $\text{CS}_2$  (65 mL) was added dropwise (ca. 40 min) to a stirred suspension of  $\text{AlCl}_3$  (9.8 g, 73 mmol) in  $\text{CS}_2$  (70 mL) in a system with a dry ice condenser. The resulting mixture was stirred vigorously at room temperature (2 h). After cooling of the mixture of 0 °C, it was quenched cautiously by dropwise addition of water (170 mL). The two layers separated and the aqueous layer was extracted (ether, 4 × 75 mL). The combined organic solutions were washed with 5%  $\text{NaHCO}_3$  (2 × 100 mL) and saturated brine (100 mL) and then dried ( $\text{Na}_2\text{SO}_4$ ). Filtration and evaporation led to an oil which was chromatographed with silica gel in hexanes. Elution with hexanes/ether gave a major band which was evaporated to a pale yellow oil. The oil was redissolved in hexanes (110 mL), and the solution was flushed with  $\text{N}_2$ , immersed in dry ice/acetone bath (–78 °C), and stoppered. A yellow precipitate formed but redissolved when the flask containing the solid was removed from the cooling bath and swirled. This process was repeated several times until small amounts of off-white crystals were visible in the flask. Formation of a total crystalline mass was achieved by intermittent immersion (ca. 30-s between immersions) in a cold bath (ca. –60 °C, 5–10 s/immersion period). Immediate decantation of the mother liquors gave crystals which were subjected at once to high vacuum drying (0.3 mm, ca. 15 min) at 0 °C. Using chilled glass plates with a Fisher-Johns melting point apparatus, the melting point of ketone 47 was determined to be 20.1–21.4 °C. At room temperature, the off-white crystals melted quickly to a pale yellow oil. Concentration of the mother liquors, followed by crystallization in hexanes in the above manner, afforded an additional 0.765 g (6.5%) of 47 to give a total yield of 8.93 g (88.9%). Properties of ketone 47:  $n_D^{25}$  = 1.6048; IR (film) 1683 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.39 [s,  $\text{C}(\text{CH}_3)_2$ ], 2.57 (s, 3 H,  $\text{CH}_3$ ), 3.24 (s, 2 H,  $\text{SCH}_2$ ), 7.25 (d, 1 H, Ar-H), 7.67 (d, 1 H, Ar-H), 7.73 (dd, 1 H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 26.4 ( $\text{CH}_3$ ), 27.6 [ $\text{C}(\text{CH}_3)_2$ ], 47.3 [ $\text{C}(\text{CH}_3)_2$ ], 47.7 ( $\text{SCH}_2$ ), 122.7, 122.9, 129.2, 134.9, 149.0, 149.5 (all Ar-C); 198.3 ( $\text{C}=\text{O}$ ). Anal.  $\text{C}_{12}\text{H}_{14}\text{OS}$  C, H.<sup>41</sup>

**1-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)ethanol (48).** A solution of ketone 47 (1.00 g, 4.85 mmol) in dry ether (7 mL) was added dropwise (ca. 20 min) to a stirred suspension of  $\text{LiAlH}_4$  (0.30 g, 7.9 mmol) in dry ether (18 mL). After being stirred at reflux (24 h), the mixture was carefully treated with ethyl

acetate (5 mL), then diluted (ether, 5 mL), and finally quenched with 5% HCl (15 mL). The mixture was transferred to a separatory funnel containing water (10 mL), and to this flask was added several rinses (1 × 7 mL of 5% HCl and 2 × 10 mL of ether) of the reaction flask. The aqueous layer was separated and extracted (ether, 3 × 40 mL). After washing [5%  $\text{NaHCO}_3$  (2 × 30 mL) and brine (2 × 30 mL)] of the combined organic solutions, the resulting solution was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated to an oil (1.02 g, qt) which crystallized via scratching with a glass rod under  $\text{N}_2$  at dry ice temperatures. Recrystallization (hot hexane, 5 mL) and using seed crystals gave, after filtration, washing (2 × 1 mL of cold hexanes), and high vacuum drying, white, crystalline alcohol 48: mp 60.5–61.5 °C; IR (KBr) 3650–3050 (O–H)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.373 (s, 3 H,  $\text{CH}_3$ ), 1.379 (s, 3 H,  $\text{CH}_3$ ), 1.47 (d, 3 H,  $\text{CHCH}_3$ ), 3.17 (s, 2 H,  $\text{SCH}_2$ ), 4.86 (q, 1 H,  $\text{CHCH}_3$ ), 7.07–7.16 (m, 3 H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 25.2 ( $\text{CHCH}_3$ ), 27.5 [ $\text{C}(\text{CH}_3)_2$ ], 47.5 [ $\text{C}(\text{CH}_3)_2$ ], 47.6 ( $\text{SCH}_2$ ), 70.6 [ $\text{CH}(\text{OH})\text{CH}_3$ ], 120.6, 122.9, 125.5, 140.3, 143.4, 149.1 (all Ar-C). Anal. ( $\text{C}_{12}\text{H}_{16}\text{OS}$ ) C, H, S.

**[1-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)ethyl]-triphenylphosphonium Bromide (49).** Alcohol 48 (0.800 g, 3.84 mmol) and  $\text{Ph}_3\text{P}\cdot\text{HBr}$  (1.30 g, 3.79 mmol) in dry  $\text{H}_3\text{COH}$  (30 mL) were stirred at room temperature (36 h). After concentration of the solution, the residual oil was dissolved in  $\text{H}_2\text{CCl}_2$  (150 mL), and this solution was dried ( $\text{MgSO}_4$ ), filtered, and evaporated to a foam which solidified. Dry ether (50 mL) was added, and the dried foam was pulverized. The resulting suspension was stirred under  $\text{N}_2$  for 8 h. Filtration and high vacuum drying at room temperature gave salt 49 as a white powder (1.44 g, 70.3%): mp 194.3–197.3 °C; IR (KBr) 1468 ( $\text{C}=\text{C}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.12 [s, 3 H,  $\text{C}(\text{CH}_3)_2$ ], 1.19 [s, 3 H,  $\text{C}(\text{CH}_3)_2$ ], 1.80 (d, 3 H,  $\text{CHCH}_3$ ), 3.09 [d,  $J$  = 11 Hz, 1 H,  $\text{SC}(\text{H})\text{H}$ ], 3.13 [d,  $J$  = 11 Hz, 1 H,  $\text{SCH}(\text{H})$ ], 6.59 (m, 1 H,  $\text{CHCH}_3$ ), 6.85–7.01 (m, 3 H, Ar-H), 7.61–7.88 [m, 15 H,  $\text{P}(\text{C}_6\text{H}_5)_3$ ];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 17.1 [ $\text{CH}(\text{CH}_3)$ ], 27.1 and 27.3 [ $\text{C}(8)$  and  $\text{C}(9)$ ], 35.5 (d,  $J_{\text{CP}}$  = 42.4 Hz,  $\text{CH}_3\text{CHP}$ ), 47.1 and 47.2 [ $\text{C}(2)$  and  $\text{C}(3)$ ], 117.5 [d,  $J_{\text{CP}}$  = 82.5 Hz, ortho C's of  $\text{P}(\text{C}_6\text{H}_5)_3$ ], 122.4 (d,  $J_{\text{CP}}$  = 2.2 Hz, Ar-C), 124.8 (d,  $J_{\text{CP}}$  = 5.4 Hz, Ar-C), 129.1 (d,  $J_{\text{CP}}$  = 5.8 Hz, Ar-C), 129.5 (d,  $J_{\text{CP}}$  = 6.5 Hz, Ar-C), 130.2 [d,  $J_{\text{CP}}$  = 12.2 Hz, meta C's of  $\text{P}(\text{C}_6\text{H}_5)_3$ ], 134.6 [d,  $J_{\text{CP}}$  = 9.4 Hz, ortho C's of  $\text{P}(\text{C}_6\text{H}_5)_3$ ], 134.9 [d,  $J_{\text{CP}}$  = 2.7 Hz, para C's of  $\text{P}(\text{C}_6\text{H}_5)_3$ ], 141.7 [d,  $J_{\text{CP}}$  = 3.4 Hz, Ar-C], 148.6 [ $\text{C}(3a)$ ]. Salt 10 was used without further purification.

**Methyl (E)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate (6c).** To a mixture of salt 49 (5.00 g, 9.37 mmol) in THF (100 mL) in a standard system was added (syringe, over 2 min) a solution of *n*-butyllithium (6.2 mL, 1.6 M, 9.9 mmol) in hexane. The resulting dark brown mixture was stirred at room temperature (1.5 h), and it was then cooled to –78 °C (dry ice/acetone bath). After 10 min, a solution of methyl 4-formylbenzoate (50,<sup>28</sup> 1.55 g, 9.44 mmol) in dry THF (50 mL) was added to the above Wittig reagent over 10 min, after which time the mixture became creamy yellow. This mixture was allowed to warm to room temperature with stirring (25 h). As dry ether (150 mL) was added dropwise, a white precipitate formed. Filtration separated the precipitate (this filtrate was set aside) which was dissolved in aqueous/acetone (5:3, 80 mL). Extraction of the resulting solution was done with hexanes (3–50 mL). Combining the extracts and the filtrate previously set aside gave, after evaporation, a crude solid (5.19 g) which was divided into four portions. Each portion was subjected to thin-layer chromatography using a Chromatotron with a 4-mm silica gel plate and hexanes/ether (9:1 and 4:1 ratios of solvents) for elution. Evaporation of solvent from fractions containing the major band gave a total of 3.0 g of product from the four portions. Recrystallization (hot 95% ethanol, 50 mL) gave ester 6c as white, crystalline flakes (1.87 g, 59.0%). A second recrystallization from 95% ethanol gave an analytical sample (1.62 g, 51.1%): mp 120.9–122.0 °C; IR (KBr) 1716 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DCCl}_3$ )  $\delta$  1.42 [s, 6 H, H(8,9)], 2.28 [d,  $J$  = 1.4 Hz, 1 H, H(11)], 3.21 [s, 1 H, H(2)], 3.93 [s, 3 H, H(20)], 6.81 [br s, 1 H, H(12)], 7.19 [d,  $J$  = 8 Hz, 1 H, H(7)], 7.20 [d,  $J$  = 2 Hz, 1 H, H(4)], 7.30 [dd,  $J$  = 8 Hz,  $J$  = 2 Hz, 1 H, H(6)], 7.42 [d,  $J$  = 8.3 Hz, 2 H, H(14, 18)], 8.04 [d,  $J$  = 8.3 Hz, 2 H, H(15, 17)];  $^{13}\text{C}$  NMR ( $\text{DCCl}_3$ ) ppm 17.8 [ $\text{C}(11)$ ], 27.4 [ $\text{C}(8,9)$ ], 47.3 [ $\text{C}(2)$ ], 47.5 [ $\text{C}(3)$ ], 52.1 [ $\text{C}(20)$ ], 120.3 [ $\text{C}(4)$ ], 122.2 [ $\text{C}(7)$ ], 125.4 [ $\text{C}(6)$ ], 125.9 [ $\text{C}(12)$ ], 127.8, 129.1 [ $\text{C}(14, 18)$ ], 129.5 [ $\text{C}(15, 17)$ ], 139.5, 140.2, 143.1, 148.2, 167.0 [ $\text{C}(19)$ ]. Anal. ( $\text{C}_{21}\text{H}_{22}\text{O}_2\text{S}$ ) C, H, S.

(41) A diacetylated product (53) was also obtained but in a low yield of 1% [mp 108.4–109.6 °C from hexanes/ethyl acetate (9:1)]. A pair of doublets ( $J$  = 1.6 Hz) at  $\delta$  7.75 and 8.34 indicated a meta orientation of the two acetyl groups across the aromatic ring. This is a somewhat rare example of a diacetylated product from one substrate, and the proton NMR spectrum [ $\delta$  2.64 and 2.68 for the  $\text{H}_3\text{CC}(\text{O})$ ] suggested it is the 5,7-diacetylated product. An analysis of this compound labeled 53 was obtained. Anal. ( $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}$ ) C, H.

(*E*)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoic Acid (**6d**). Heteroarotinoid **6c** (1.20 g, 3.55 mmol) in a degassed solution ( $N_2$ , 10 min) of dry KOH (0.62 g, 11 mmol) in absolute ethanol (9 mL) and  $H_2O$  (3 mL) was heated to reflux (10 min), after which time the mixture became a solution. This solution was heated at reflux (45 min) and then cooled to room temperature. Quenching was effected with acetic acid (15%, 10 mL) and saturated brine (10 mL). Ethyl acetate (100 mL) was added, and the two layers separated. Extraction of the aqueous layer was done with ethyl acetate (50 mL), and the original organic layer and extract were combined and washed (brine,  $2 \times 25$  mL; water, 25 mL). After drying ( $Na_2SO_4$ ), the solution was filtered and evaporated to a white solid. Two recrystallizations (absolute ethanol), followed by washes with cold, absolute ethanol and hexanes, gave white needles of acid **6d** (0.45 g, 56.4%); mp 203.7–204.8 °C. Another 61 mg (5.3%) of **6d** could be obtained via concentration of the mother liquors and repeated recrystallizations of the residual solid for a total weight of 0.71 g (61.7%); IR(KBr) 3250–2000 ( $CO_2H$ )  $cm^{-1}$ ;  $^1H$  NMR ( $DCCl_3$ )  $\delta$  1.42 [s, 6 H, H(8,9)], 2.31 [d, 3 H, H(11)], 3.23 [s, 2 H, H(2)], 6.84 [br s, 1 H, H(12)], 7.18–7.24 [m, 2 H, H(4) and H(7)], 7.32 [dd, 1 H, H(6)], 7.48 [d, 2 H, H(14, 18)], 8.14 [d, 2 H, H(15,17)];  $^{13}C$  NMR ( $DCCl_3$ ) ppm 17.9 [C(11)], 27.4 [C(8,9)], 47.3 [C(3)], 47.5 [C(2)], 120.3 [C(4)], 122.2 [C(7)], 125.4 [C(6)], 125.8 [C(12)], 129.2 and 130.2 [C(14,18) and C(15,17)], 171.8 [C(19)]; other quaternary carbons are at 126.9, 139.9, 140.1, 140.3, 144.1, and 148.2 ppm; mass spectral data for  $C_{20}H_{20}O_2S$   $m/z$  ( $M^+$ ) 324.1184, found 324.1184. Anal. ( $C_{20}H_{20}O_2S$ ) C, H.

**Biological Screening Procedures.** The procedures for determining the effect of a test retinoid on TPA-induced ODC activity in mouse epidermis have been described.<sup>10,30</sup> For  $ID_{50}$  determinations, various doses (0.1, 1.0, 5.0, 10, and 50 nmol) of

test retinoids 7–17 were applied 1 h before the application of 10 nmol of TPA to mouse skin. The ODC activity was determined 4.5 h after the TPA treatment. Three mice per group per compound were used. The  $ID_{50}$  values were obtained from dose-response curves. The experimental procedure for the HL-60 cell line has been reported in full.<sup>10,12,28</sup>

For standard 1 and systems **6c** and **6d**, 34 nmol were used and resulted in 0.13, 0.062, and 0.09 nmol of  $CO_2/30$  min per mg of protein, respectively. The control of TPA-induced ODC activity exhibited 1.02 nmol of  $CO_2/30$  min per mg of protein. Again, three groups of mice consisting of two mice/group were used in this assay. Various doses (0.1, 1.0, 5.0, 10, and 50 nmol) were applied 1 h before application of 10 nmol of TPA to mouse skin. The ODC activity was determined 4.5 h after TPA treatment.<sup>10,30</sup> The  $ID_{50}$  value for each compound was determined from dose-response curves. Known procedures to determine the HL-60 cell differentiation were applied to these retinoids.<sup>10,36</sup>

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## Design, Synthesis, and Physicochemical Properties of a Novel, Conformationally Restricted 2,3-Dihydro-1,3,4-thiadiazole-Containing Angiotensin Converting Enzyme Inhibitor Which Is Preferentially Eliminated by the Biliary Route in Rats

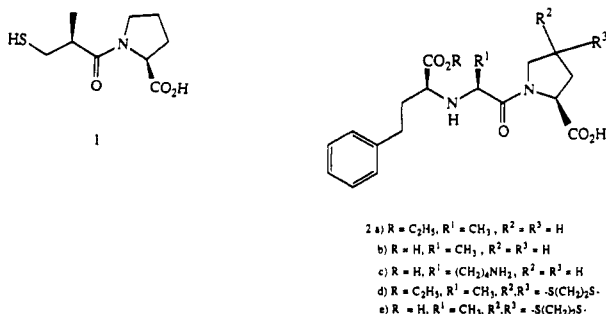
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Two novel series of dihydrothiadiazole ring containing inhibitors of angiotensin converting enzyme have been designed and synthesized. The compounds are highly potent enzyme inhibitors and, as a consequence of conformational restriction, chemically stable with respect to undesirable cyclization reactions. The most interesting compound from this series, **5a** (FPL 63547), is the monoethyl ester prodrug of the highly potent "aminocarboxy" inhibitor **5b** (FPL 63674). It produces an antihypertensive effect of long duration in animal models after oral dosing. Unlike other ACE inhibitors, **5b** is eliminated almost entirely by biliary clearance in the rat. The favorable pharmacological properties of **5a** and **5b** are rationalized in terms of their unique physicochemical profiles. The clear preference for biliary clearance seen with **5b** is consistent with its lipophilicity and its high degree of net ionization at physiological pH, which results from the very low  $pK_a$  of the C-terminus carboxylic acid function. FPL 63547 is presently undergoing clinical investigation in man.

### Introduction

The clinical success of the angiotensin converting enzyme inhibitors captopril (**1**)<sup>1</sup> and enalapril (**2a**)<sup>2</sup> in the



treatment of both hypertension and chronic heart failure is well-established.<sup>3</sup> Many clinicians now believe that drugs of this class may become the agents of choice for the

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