Articles

Heteroarotinoids: Analytical Criteria for the Rapid Identification of *E* and *Z* Isomers of These Novel Retinoids via NMR, UV, and X-ray Analyses of Selected Examples

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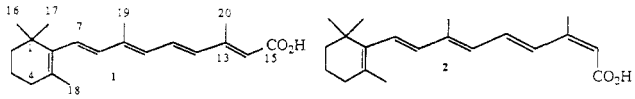
A series of derivatives of *E* and *Z* isomers of 4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoic acid and 4-[2-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoic acid and sulfur-containing counterparts have been examined in terms of ^{1}H, ^{13}C, and ultraviolet (UV) analyses for the purpose of establishing which parameters are diagnostic for identifying E and Z isomers in this family of heteroarotinoids. Several members of the latter have previously exhibited potentially useful anticancer properties. In addition, X-ray diffraction analyses for methyl (*E*)-[2-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoate [(*E*)-**3b**], methyl (*E*)-4-[2-(2,3-dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate [(*E*)-**3d**], and methyl (*Z*)-4-[2-(2,3-dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate [(*Z*)-**3d**] were performed to confirm the arrangment around the central double bond in the solid state in these rare examples containing a fused, five-six-membered ring system. The proton NMR analyses of solutions of the *E* versus the *Z* isomers, particularly the enhanced shielding of the vinylic proton and protons at "ortho" positions on the aryl groups attached to the double bond, provide markers to identify the *Z* isomers in these heteroarotinoids. In the ^{13}C spectra, the methyl carbon attached to the double bond was usually about 10 ppm *downfield* in the *Z* isomer compared to the counterpart in the *E* isomer. These data, taken on the whole, suggest that in solution the two aryl rings in the *Z* isomers [and possibly the *E* isomers] are turned out of plane of the double bond, and, due to the closer proximity of the rings, induced shielding of nearby protons occurs to a greater extent in the *Z* isomers compared to the *E* isomers. This evaluation is supported by UV spectral data which show maxima in two ranges, namely at 210–270 and 280–350 nm. The "conjugation band" at the longer wavelength is always more intense, relative to the band at the shorter wavelength, in the *E* isomers. This is taken to imply improved overlap of p orbitals in the double bond with those in the aryl rings in the *E* isomers. In contrast, the band at shorter wavelength is more intense than the band at long wavelength in the *Z* isomers. These two features are clearly distinguishing for the two isomeric forms in solution and are reminiscent to some degree of the situation found in stilbenes. Characterization of (*E*)-**3b**, (*E*)-**3d**, and (*Z*)-**3d** via X-ray diffraction analysis of single crystals is confirmatory in that the rings in both isomeric alkenes lack coplanarity with the central double bond in the solid state. The deviation from overall planarity is greatest for the *Z* isomers with the internal torsional angle being 10.7° in (*Z*)-**3d** rather than the "ideal" value of 0°. Moreover, the aryl rings are not far from being nearly perpendicular to each other in (*Z*)-**3d**. Molecular mechanics calculations, using the MMP2 program, indicate the deviation from planarity is less than that found from X-ray analysis on solid (*Z*)-**3d**. These data provide a foundation for rapid identification of certain groups of heteroarotinoids. A comparison of crystal data of (*E*)-**3b** and (*E*)-**3d** with that of *trans*-retinoic acid (1) was also made. The least-squares "fit" is quite satisfactory in spite of differences in conformational angles, and an RMS value of 0.90 Å is calculated. It appears that placing the ester group of (*E*)-**3b** or (*E*)-**3d** in a "meta" position would improve the fit considerably. Consequently, the work has ramifications for aiding in the design of potential medicinal agents in this family of heterocycles.

Introduction

An increasing interest in the structure and functionality of relatives of *trans*-retinoic acid (1) and 13-*cis*-retinoic acid (2) is evident from the voluminous literature in this decade.[1-9] Certain heteroarotinoids (retinoids containing an aryl ring and a heteroatom incorporated in one ring) have shown carinostatic properties,[5,10-13] and some have shown reduced toxicity compared to 1.[10,14] Arotinoids



(retinoids with an aryl ring but without a heteroatom in a ring) have exhibited anticancer activity in several assays but have been toxic.[15,16] Preparative methods for both

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Table I. Spectral Data for Members of 3 and Model Systems

	selected NMR signals (δ and ppm for ^1H and ^{13}C, respectively) [in $DCCl_3$]						UV bands (in C_2H_5OH)			
							210–270 nm		280–350 nm	
compd	H(8)[a]	H(9)[a]	H(11)[a]	H(12)[a]	H(15,17)[a]	C(11)[a]	λ_{max}, nm	ϵ ($\times 10^4$)	λ_{max}, nm	ϵ ($\times 10^4$)
(*E*)-**3a**	1.39	1.39	2.31	6.79	8.12	18.0	230	1.2	311	2.2
(*E*)-**3b**	1.38	1.38	2.29	6.77	8.03	17.9	237	1.2	319	2.2
(*Z*)-**3b**	1.22	1.22	2.22	6.43	7.78	27.1	242	2.1	310	1.7
(*E*)-**3c**	1.42	1.42	2.31	6.84	8.14	17.9	238	1.3	316	1.8
(*E*)-**3d**	1.42	1.42	2.28	6.81	8.04	17.8	244	1.2	326	2.4
(*Z*)-**3d**	1.21	1.21	2.21	6.46	7.78	26.9	269	2.0	317	1.2
(*E*)-**3e**	3.63[b] 3.72	1.42	2.28	6.77	8.03	17.9	240	1.2	315	1.5
(*E*)-**3f**	3.64[b] 3.77	1.45	2.28	6.80	8.04	17.8	245	1.1	317	1.3
(*E*)-**3g**[c]	1.23	1.23	4.49	6.68	7.79	68.1	242	1.5	287	1.3
(*E*)-**3h**	1.40	1.40	2.31	6.80	8.14	17.8 16.4[d]	231	1.3	307	2.5
(*E*)-**3i**	1.38	1.38	2.28	6.78	8.08	18.0	236	1.4	316	2.4[10]
(*Z*)-**3i**	1.12	1.12	2.20	6.45	7.85		244	1.7	306	1.2[10]
(*E*)-**3j**	1.39	1.39	2.29	6.80	8.06	17.8	237	1.5	318	2.5
(*Z*)-**3j**	1.12	1.12	2.20	6.43	7.78	26.8	245	2.2	310	1.6
(*E*)-**3k**	1.38	1.38	2.29	6.80	8.11	16.5[d]	233	1.1	319	2.5[10]
(*E*)-**3l**	1.38	1.38	2.27	6.79	8.04	17.6	244	1.2	326	2.6[10]
(*E*)-**3m**[c]	1.18	1.18	4.43	6.64	7.79	66.8	247	2.0	285	1.7
(*E*)-**4a**	1.42[e] 1.38	1.42[e] 1.38	2.37	6.88	8.08				304	2.26[15]
(*E*)-**4b**	1.31[e] 1.35	1.31[e] 1.35	2.30	6.85	8.08				306	2.62[15]
(*Z*)-**4b**	1.28[e] 1.36	1.28[e] 1.36	2.23	6.46	7.77				297	1.43[15]

[a] For the six-membered analogues **3b–m** and **4a–b**, H(8,9,11,12,15,17) become H(9,10,12,13,16,18), respectively [likewise C(11) becomes C(12)]. [b] The chiral center causes the two hydrogen at H(8) to be nonequivalent. [c] These compounds, although all are *E* isomers, have *cis*-aryl groups. [d] Taken in $DCCl_3$/DMSO-d_6;[9] all NMR data were taken in $DCCl_3$. [e] There are two sets of geminal methyl pairs.

arotinoids and heteroarotinoids have commonly employed a condensation of a traditional Wittig reagent involving derivatives of triphenylphosphonium salts[11,12] or the Wadsworth–Emmons reagent[10,17] with a carbonyl compound. Frequently, this produces both the *E* and Z isomeric alkenes. Methodology to rapidly differentiate these isomers, even in crude mixtures, has not been fully addressed. Indeed, it has not been possible in many instances to isolate both isomeric alkenes. Thus the need exists for a diagnostic tool to identify the isomer formed since the heteroatom influences most spectral properties of the product. Herein we report the ^1H NMR, the ^{13}C NMR, and ultraviolet (UV) spectra of several members in the family of heteroarotinoids along with X-ray diffraction analyses of three selected members. The data clearly permit the immediate identification of the isomer present and will be valuable for future work in this field. Not all members of **3a–m** have been obtained in terms of both *E* and Z isomers for each alkene, but the data in Table I are for *pure* samples. Table I also contains data for reported[15] arotinoids (*E*)-**4a**, (*E*)-**4b**, and (*Z*)-**4b** for the sake of completeness and for comparison purposes.

Results and Discussion

Since members of **3a–m** have configurations related to that in *cis*-stilbene (**5**) and *trans*-stilbene (**6**), it seems reasonable that some spectral features of heteroarotinoids would mimic those of the stilbenes although the heteroatom should shift the absorption maxima and enhance the absorptivity. It is known that both the aromatic and vinyl protons in *cis*-stilbenes are shielded with respect to those in *trans*-stilbenes in general.[18] Apparently both aromatic rings are turned so that the aromatic protons of one ring are located in the *shielding* cone of the other ring, the effect on the chemical shifts falling off with distance from the opposite ring. Thus upfield shifts (δ_{trans}-δ_{cis}>0) for ortho protons are greater than for meta and para protons. Likewise, the vinyl protons are more *deshielded* in *trans*-stilbenes due to the greater coplanarity of most atoms in this system compared to that found in *cis*-stilbenes. An overall examination of the ^1H NMR data for **3a–m** [signals for the protons are in Table I or in the Experimental Section] shows that a clear parallelism exists in the

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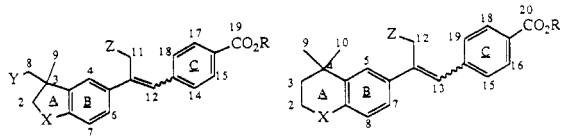
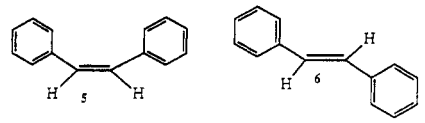


3a: X = O, Y = Z = R = H
3b: X = O, Y = Z = H, R = CH_3
3c: X = S, Y = Z = R = H
3d: X = S, Y = Z = H, R = CH_3
3e: X = O, Y = OH, Z = H, R = CH_3
3f: X = S, Y = OH, Z = H, R = CH_3
3g X = O, Y = H, Z = OH, R = CH_3

3h: X = O, Z = R = H
3i: X = O, Z = H, R = Et
3j: X = O, Z = H, R = CH_3
3k: X = S, Z = R = H
3l: X = S, Z = H, R = Et
3m: X = O, Z = OH, R = CH_3
4a: X = $C(CH_3)_2$, Z = R = H
4b: X = $C(CH_3)_2$, Z = H, R = Et



heteroarotinoids. In our discussion, cis and trans isomers shall refer to isomers with the respective arrangement of the aryl groups around the central double bond. All proton shifts for the cis isomers are *upfield* compared to those for the trans isomers, including those shifts from protons three or four bonds removed from an aromatic carbon. Considering members of **3a–g**, the largest chemical shift differences ($\Delta\delta = \delta_{trans} - \delta_{cis}$) were observed for protons ortho to the central carbon–carbon double bond [H(4,6,14,18), $\Delta\delta$ = 0.31–0.46]. Upfield shifts of similar magnitude were found for the vinyl protons H(12) [generally $\Delta\delta$ = 0.31–0.36]. Among the aliphatic protons, the most pronounced shielding was noted for the protons of the geminal methyl groups [H(8,9), $\Delta\delta$ = 0.18 to 0.28]. The *smallest* shifts occurred for protons the most distant from the double bond, namely, those protons α to the heteroatoms [H(2), $\Delta\delta$ = 0.03–0.08] and protons in the methyl [H(20), $\Delta\delta$ = 0.07–0.08] group of the ester function. The latter suggests the absence of a nearby shielding group such as might be expected by an aryl ring in a juxtaposition. Similar arguments hold for **3h–m** (note the different numbering of atoms). Both the *E* and *Z* isomers of **3b,d,j** were isolated in pure form, and a complete assignment was possible for each proton, including certain aryl protons H(4,6,7). Chemical shift differences ($\Delta\delta = \delta_{trans} - \delta_{cis}$) for ortho proton H(4) [$\Delta\delta$ = 0.42–0.46] in **3b,d,j** [H(5) in this isomer] are greater than those observed for the other ortho proton H(6) [$\Delta\delta$ = 0.33–0.36] [this is H(7) in **3j**]. Since the resolution of the spectrometer is much greater than these differences, we suggest the data are defensible with the general interpretation being applicable to those other systems in which it was not possible to isolate both E and *Z* isomers or in which complete proton assignment could not be made (i.e., **3i**, **4a**, **4b**). Considering **3a–g**, the data above also suggest that H(4) in ring B of the *cis*-aryl isomers (*Z* isomers) is *shielded* by ring C to a greater extent than is H(6). Consequently, a major conformation in solution ($DCCl_3$) for the cis isomers may have ring B out of plane with the central double bond and twisted in such a manner that H(4) is closer to ring C (and its shielding cone) than is H(6) [such as is implied for the isomeric system (*Z*)-**3d** herein]. In this arrangement, H(7) would seemingly be more distant from ring C (and its shielding cone) than perhaps H(15,17) are from ring B. This appears to be supported by the *smaller* chemical shift differences observed for meta proton H(7) [$\Delta\delta$ = 0.07–0.11] in ring B compared to those of meta protons H(15,17) [$\Delta\delta$ = 0.23–0.28] in ring C. In the major conformation in solution, it is likely that ring C of the cis isomers is also turned out of plane with the middle double bond, which could explain the large shielding of H(4,6) in the cis isomers relative to that found in the trans isomers. The same situation exists for **3h–m**.

For rapid identification of a cis or trans isomer in this family of heteroarotinoids, the following distinguishing features can be gleaned from data in Table I. In the ^1H NMR spectra of trans isomers bearing a carboxyl or carboxyalkyl terminus, there is usually a signal at δ 8.0–8.2 for H(15,17). This signal is the most downfield of the aromatic protons in both isomers, but the counterpart in the cis isomer occurs from δ 7.7 to 7.9. Another readily distinguishable signal in **3a–g** is for the vinyl proton H(12) [H(13) in **3h–m**] which appears at δ 6.75–6.90 for the trans isomers and at δ 6.4–6.5 for the cis isomers [an exception is seen for (*E*)-**3g** and (*E*)-**3m**, both cis isomers showing the signal for H(12) at δ 6.68 and δ 6.64, respectively, which is likely the result of the proximate hydroxyl group]. In addition, the methyl group [H(11), Z = H in **3a–g**] shows signals at δ 2.25–2.40 for the trans isomers and at δ 2.20–2.23 for the cis isomers. Finally, the proton signals for the geminal methyl groups [H(8,9)] occur at or very near δ 1.4 for the trans isomers and at δ 1.1–1.2 for the cis isomers. The same results were seen with **3h–m**.

In general, the ^{13}C NMR spectra were less informative concerning the configuration around the central double bond. Nevertheless, trans isomers displayed a signal in **3a–m** for the methyl carbon [C(11), Z = H] at 17–18 ppm [this is C(12) in **3h–m**; (*E*)-**1h** and (*E*)-**1k** had the signal reported at 16.5 ppm[10]] while the cis isomers had the signal at ~27 ppm. A single explanation for the deshielding of C(11) in **3a–g** [or C(12) in **3h–m**] in the cis isomers, relative to the trans isomers, is not intuitively obvious.

Analysis of conjugation differences in the cis and trans isomers of the heteroarotinoids via UV spectroscopic analysis revealed quite distinguishing features, somewhat like those found with *cis*- and *trans*-stilbenes.[18-20] Two maxima are common in the UV spectra of the heteroarotinoids and appear in the ranges of 210–270 and 280–350 nm. Both bands for each system contain much fine structure, but the most intense peak is at the center of the ranges specified. The region of 280–350 nm in stilbenes has been designated the "conjugation band",[19] presumably because of its dependence upon conjugation and is always more intense in the trans isomers.[20] From Table I it can be seen that the *differences* in *relative* intensities between the "conjugation band" and the band at shorter wavelength (210–270 nm) provide a diagnostic tool for identifying the specific isomer. The trans heteroarotinoids (*E* isomers) exhibit a much more intense "conjugation band", relative to the band at shorter wavelength. In contrast, the cis heteroarotinoids (*Z* isomers) display a band at shorter wavelength which has larger extinction coefficients than the "conjugation band". This appears to be a characteristic feature for these heteroarotinoids. Furthermore, the maxima of the "conjugation band" of the trans isomer (aryl groups being anti) appears at a longer wavelength ($\Delta\lambda_{max}$ ~ 8–10 nm) than that observed for the cis-isomers.

To date, very few X-ray diffraction analyses have been recorded on heteroarotinoids [only (*E*)-**3l** with a six-membered ring heterocycle has been so examined[11a]]. Therefore, to evaluate stereochemistry as function of spectral data and to establish a basis for rapid structure identification of new, five-membered heterocycles in this family, as well as assess conjugative effects, we have determined the single crystal structures for (*E*)-**3b**, (*E*)-**3d**, and (*Z*)-**3d**. Moreover, systems (*E*)-**3b** and (*E*)-**3d** differ only in the nature of the heteroatom and presented an opportunity

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Table II. Data Collection Parameters and Crystal Data

	(*E*)-**3d**	(*Z*)-**3d**	(*E*)-**3b**
molecule	E-$C_{21}H_{22}O_2S$	Z-$C_{21}H_{22}O_2S$	E-$C_{21}H_{22}O_3$
scan width	(0.80 + 0.20 tan θ)	(0.90 + 0.15 tan θ)	(0.95 + 0.20 tan θ)
aperature	(3.00 + 0.86 tan θ)	(2.00 + 0.86 tan θ)	(2.00 + 0.86 tan θ)
unique reflections	3574	3472	3477
observed reflections[a]	2966	3449	3121
MW	338.47	338.47	322.41
μ	16.06	15.64	5.77
$F(000)$	720	360	688
temperature, K	135	150	150
space group	$P2_1/a$	$P\bar{1}$	$P2_1/n$
a, Å	10.039 (3)	10.577 (3)	10.034 (1)
b, Å	26.378 (8)	12.254 (8)	26.601 (7)
c, Å	7.029 (2)	7.680 (2)	6.788 (1)
α, deg	90	97.66	90
β, deg	109.94 (2)	107.45 (2)	108.81 (1)
γ, deg	90	103.96 (2)	90
V, Å^3	1749.8	898.5	1715.0
Z	4	2	4
D_c	1.285	1.252	1.249
R	0.036	0.046	0.043
R_w	0.044	0.076	0.063
maximum shift/sd	0.034	0.076	0.083

[a] $I > 2\sigma(I)$.

to assess structural aberrations which the larger sulfur atom might impose. Thus, the arrangements of the two *C*-aryl bonds attached to the double bond [suggested by NMR and UV analyses as anti for (*E*)-**3b** and (*E*)-**3d** and syn for (*Z*)-**3d**] were confirmed by the X-ray data (see crystal data in Table II). Although (*E*)-**3b** and (*E*)-**3d** have similar cell dimensions, they are not isomorphous. The C=C bond distances range from 1.344 (2) Å to 1.348 (2) Å. The C(5)–C(10) bond, which is on the same side of the double bond as the methyl group [C(11)H_3], ranges from 1.482 (1) Å to 1.490 (2) Å, while C(12)—C(13), on the other side of the double bond, is observed at 1.474 (1) Å to 1.477 (1) Å. Small differences for bond angles C(5)—C(10)=C-(12) [120.4° in (*E*)-**3b**, 120.1° in (*E*)-**3d**, and 124.4° for (*Z*)-**3d**] and for C(10)=C(12)—C(13) [127.2° for (*E*)-**3b**, 126.5° for (*E*)-**3d**, and 128.0° for (*Z*)-**3d**] were found. These facts seem to suggest steric interactions between the methyl group and the adjacent aryl ring C in the E isomers and between the two aryl rings in the *Z* isomer. In all three molecules, the five-membered ring has an envelope conformation with C(2) as the out-of-plane atom. The asymmetry parameter ΔC_s, which is zero for an ideal envelop conformation,[21] is 8.6, 7.9, and 3.6° for (*E*)-**3d**, (*Z*)-**3d**, and (*E*)-**3b**, respectively.

A knowledge of ring orientation is important for assessing differing degrees of conjugation in the cis and trans isomers of the solid heteroarotinoids **3**. The torsion angles about the double bonds C(5)—C(10)=C(12)—C(13) in (*E*)-**3b** and (*E*)-**3d** are, respectively, −179.5° and 177.8°. Thus, in the *E* isomers the atoms attached to the double bond are nearly coplanar with the latter bond in the solid state. This supports the observation of greater conjugation in the UV spectra for the *E* isomers than for the *Z* isomers. In contrast, the above torsion angle in cis isomer (*Z*)-**3d** is 10.7° which differs significantly from the ideal "cis" conformation angle (0°) and suggests steric interactions between the two aryl rings. The two aromatic phenyl rings make an angle of 82.5° in (*E*)-**3b** and 81.6° in (*E*)-**3d**.

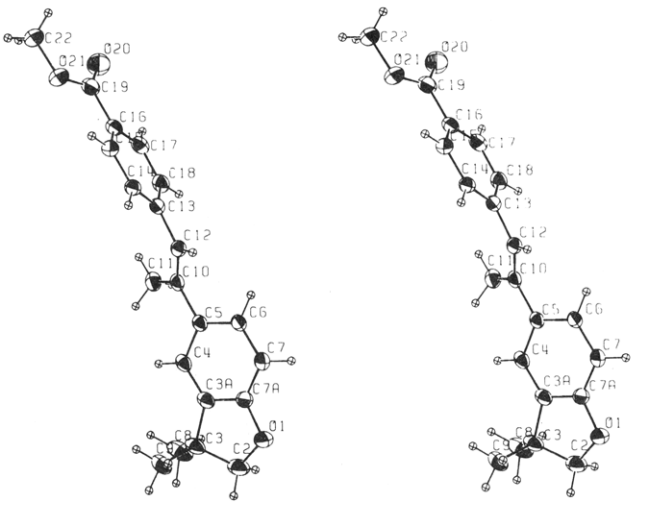


Figure 1. The stereoview numbering for (*E*)-**3b** (E-$C_{21}H_{22}O_3$).

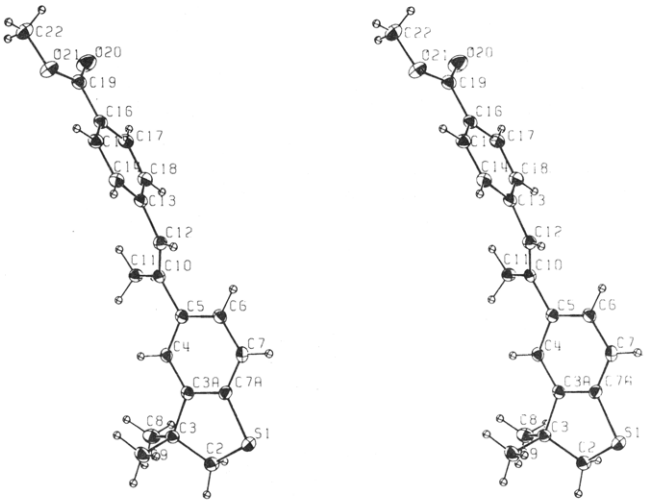


Figure 2. The stereoview numbering for (*E*)-**3d** (E-$C_{21}H_{22}O_2S$).

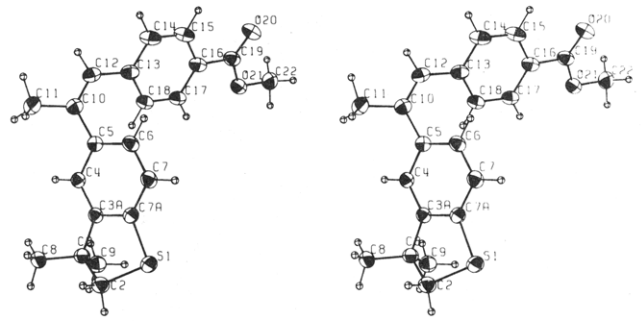


Figure 3. The stereoview numbering for (*Z*)-**3d** (Z-$C_{21}H_{22}O_2S$).

Interestingly, the X-ray data indicate that ring C is turned out of the plane of the double bond [−48.4° and −46.2° for (*E*)-**3b** and (*E*)-**3d**, respectively], whereas molecular mechanics calculations (MMP2 program[22]) had slightly smaller values (−45.6° and −44.5°, respectively), suggesting slightly improved conjugation of ring C with the double bond. Similarly, the X-ray data indicate that in the crystal, ring B is turned out of the plane of the double bond [−34.0° and −34.3° for (*E*)-**3b** and (*E*)-**3d**, respectively], whereas the energy minimization calculations (MMP2[22]) gave larger

(21) Duax, W. L.; Norton, D. A. *Atlas of Steroid Structure, Vol. 1*; Duax, W. L., Norton, D. A., Eds.; IFI/Plenum Data Company: New York, 1975; pp 16–22.

(22) (a) Allinger, N. L. *Molecular Mechanics* (Operating instructions for MM2 and MMP2 programs), QCPE, Indiana University, 1985. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

Table III. The Conformational Angles Around and Next to the Central Double Bond and Selected Bond Angles Before and After the Energy Minimization of the Crystal Structure by MMP[22]

	(*E*)-**3d** (*E*-$C_{21}H_{22}O_2S$)		(*Z*)-**3d** (*Z*-$C_{21}H_{22}O_2S$)		(*E*)-**3b** (*E*-$C_{21}H_{22}O_3$)	
	crystal	MMP2	crystal	MMP2	crystal	MMP2
C(6)—C(5)—C(10)=C(12)	-34.3	-46.3	48.1	42.7	-34.0	-48.0
C(5)—C(10)=C(12)—C(13)	177.8	179.7	10.7	8.3	-179.5	-178.9
C(10)=C(12)—C(13)—C(18)	-46.2	-44.5	37.8	37.2	-48.4	-45.6
C(4)—C(5)—C(10)=C(12)	147.1	131.7	-137.2	-137.5	146.1	132.4
C(10)=C(12)—C(13)—C(14)	134.1	142.0	-146.9	-149.1	131.8	140.3
C(5)—C(10)=C(12)	120.1	118.9	124.4	123.8	120.4	118.7
C(10)=C(12)—C(13)	126.5	126.7	128.0	127.2	127.2	126.4

negative values [-48.0° and -46.3°, respectively]. This suggests a slight decrease in conjugation of ring B with the double bond in the energy minimized structure of these *E* isomers. Complete conjugation of the π-system, in which the two aryl rings are coplanar with the central double bond, is clearly *not* observed in any of the structures subjected to X-ray analyses (see Figures 1–3). Many nonbonded distances are too small for a totally planar, conjugated unit. For example, in (*Z*)-**3d** a total planarity of the aryl rings attached to the central double bond would require an H(6)···H(18) distance of 0.17 Å. Some torsional angles observed between the double bond and bonds adjacent to the double bond are found in Table III. In (*Z*)-**3d** both aryl rings deviate from planarity with the central double bond by 48.1° (ring B) and 37.8° (ring C). The MMP2 energy refinements also show nonplanar arrangements [42.7° for ring B and 37.2° for ring C]. As cited earlier, the double bond in (*Z*)-**3d** deviates from planarity in the crystal since the C(5)—C(10)=C(12)—C(13) angle is 10.7° and a value of 8.3° is found after energy refinement. The angles [C(5)—C(10)—C(12) and C(10)—C(12)—C(13)] between the aryl rings and the double bond in *cis*-(*Z*)-**3d** have increased, relative to those in *trans*-(*E*)-**3d** and (*E*)-**3b** (Table III). Moreover, it appears that the aryl rings in (*Z*)-**3d** are slightly "bent back" with respect to bonds C(5)—C(10) and C(12)—C(13) {|∠C(6)—C(5)—C(10)=C(12)| + |∠C(4)—C(5)—C(10)=C(12)| = 185.3° > 180° < 184.7° = |∠C(10)=C(12)—C(13)—C(14)| + |∠C(10)=C(12)—C(13)—C(18)|} (Table III). However, the two corresponding angles in (*E*)-**3d** [181.4° (|-34.3°| + 147.1°) and 180.3° (134.1° + |-46.2°|)] (in Table III) suggest a minimal electronic repulsion between the rings. Both the ^{1}H NMR and X-ray analyses imply the rings are twisted in the cis isomer (*Z*)-**3d**, but the direction of the twist appears to differ for each data set. As mentioned earlier, the ^{1}H NMR spectrum of (*Z*)-**3d** [and also for (*Z*)-**3b** and (*Z*)-**3j**] suggested that H(4) was closer to ring C than was H(6). This is not the case in solid (*Z*)-**3d** [as also indicated by the MMP2 data] where C(6) is closer to ring C than is C(4); C(6)···C(13) = 3.236 Å and C(4)···C(13) = 4.276 Å]. A conformational search around the C(5)—C(10) bond for (*Z*)-**3d**, using MMP2, shows that the crystal conformation has a much larger dipole moment (7.6 Debye) and a slightly higher energy (1.0 kcal/mol) than the NMR analysis suggested for the solution conformation which has a smaller dipole (3.6 Debye). Packing in the crystal structure may prefer the conformation with the high dipole moment at the cost of the slightly higher energy for a single molecule. In solution in a nonpolar solvent ($DCCl_3$), a conformation with a low dipole moment would likely be preferred (it would also have a lower energy than that calculated for the molecules in the crystal). Of course, solvation effects are not considered in the X-ray or MMP2 calculations and undoubtedly contribute to the major conformation preferred in solution.

The energy minimization work indicates the bond distances and bond angles do not differ significantly between

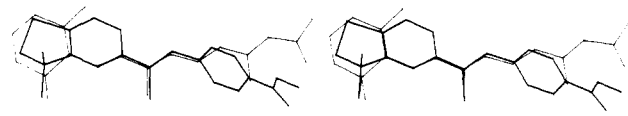


Figure 4. A stereoview shows the least-squares fitting between the (*E*)-**3d** (*E*-$C_{21}H_{22}O_2S$) (thick lines, present work) and the triclinic vitamin A acid (thin lines, Stam, 1972).[23]

the minimized and observed structures. In (*E*)-**3d**, for example, the average difference is 0.008 Å for bond distances and 1.2° for bond angles. The conformational angles for the bonds adjacent to the double bond, after minimization, differ by relatively small amounts from those in the crystal structures of the three compounds [the differences are between 1° and 14° (Table III)]. The results indicate that the molecules in the crystal are close to their minimum energy conformation. One major difference, however, between the minimum energy and crystal structure data is the orientation of the CH_3 [C(11)] group attached to the central double bond. In all three compounds, this group, after minimization, is rotated by about 30° to optimize the nonbonded H–H distances between the CH_3 group and the rest of the molecule. For (*E*)-**3b** and (*E*)-**3d**, the shortest H–H contacts are between H(4) and the methyl hydrogen H(11') [2.1 Å] and H(18) and the methyl hydrogen H(11) [2.3–2.4 Å]. These two distances are 2.3 and 2.7 Å, respectively, in the energy-minimized crystal structures. For (*Z*)-**3d**, the shortest H–H contact observed between H(12) and the methyl hydrogen H(11) is 2.3 Å. This distance is 2.4 Å in the energy-minimized crystal structure. Restricting the CH_3 group to the crystal structure conformation in the energy minimization of (*E*)-**3b** and (*E*)-**3d** results in conformational angles which are closer by 2° to the observed angles in the crystal structures. Decreasing the effective van der Waals radius of the H atoms from 1.50 to 1.45 Å allows the whole π-system to be more planar and thus to improve the agreement for the C(5)—C(10) bond but to *decrease* the agreement for the C(12)—C(13) bond. None of these experiments, unfortunately, explain the apparent unfavorable conformation of the vinyl-substituted CH_3 group observed in the three crystal structures. Bond distances from X-ray analyses are in Table IV.

It is interesting to compare the conformation of the (*E*)-**3b** and (*E*)-**3d** with the crystal structure of *trans*-retinoic acid (**1**).[23] A least-squares fit was done for atoms C(8), C(3), C(3a), C(4), C(5), C(10), C(11), C(12), C(13), and C(14) with the corresponding atoms of the triclinic form of retinoic acid (Figure 4). The "fit" is satisfactory, despite differences in conformational angles, and an RMS value of 0.90 Å is calculated. The two most obvious failures of the superposition are the orientation of the geminal dimethyl group and the location of the acid group of retinoic acid, relative to the ester group in structures **3**. Placing the ester group in the meta, rather than para

(23) Stam, C. H. *Acta Crystallogr.* **1972**, *B28*, 2936–2945.

Table IV. Bond Lengths (Å) with esd's in Parentheses

bond	(*E*)-**3d** (E-$C_{21}H_{22}O_2S$)	(*Z*)-**3d** (Z-$C_{21}H_{22}O_2S$)	(*E*)-**3b** (E-$C_{21}H_{22}O_3$)
S(1)–C(2)	1.830 (2)	1.833 (1)	
S(1)–C(7a)	1.761 (1)	1.754 (1)	
O(1)–C(2)			1.463 (2)
O(1)–C(7a)			1.368 (1)
C(2)–C(3)	1.538 (2)	1.540 (2)	1.533 (2)
C(3)–C(3a)	1.522 (2)	1.523 (1)	1.516 (2)
C(3)–C(8)	1.524 (2)	1.527 (1)	1.528 (2)
C(3)–C(9)	1.537 (2)	1.534 (2)	1.535 (2)
C(3a)–C(7a)	1.397 (2)	1.399 (1)	1.386 (2)
C(3a)–C(4)	1.386 (2)	1.379 (1)	1.380 (1)
C(4)–C(5)	1.406 (2)	1.408 (1)	1.409 (2)
C(5)–C(6)	1.402 (2)	1.400 (1)	1.401 (1)
C(5)–C(10)	1.490 (2)	1.482 (1)	1.488 (1)
C(6)–C(7)	1.392 (2)	1.383 (2)	1.397 (1)
C(7)–C(7a)	1.390 (2)	1.401 (2)	1.383 (2)
C(10)–C(11)	1.508 (2)	1.504 (1)	1.514 (2)
C(10)–C(12)	1.348 (2)	1.344 (2)	1.344 (2)
C(12)–C(13)	1.475 (2)	1.477 (1)	1.474 (1)
C(13)–C(14)	1.406 (2)	1.400 (2)	1.399 (2)
C(13)–C(18)	1.403 (2)	1.404 (2)	1.402 (2)
C(14)–C(15)	1.386 (2)	1.384 (2)	1.387 (1)
C(15)–C(16)	1.402 (2)	1.394 (2)	1.398 (2)
C(16)–C(17)	1.396 (2)	1.400 (2)	1.397 (2)
C(16)–C(19)	1.486 (2)	1.477 (2)	1.487 (2)
C(17)–C(18)	1.383 (2)	1.379 (1)	1.389 (2)
C(19)–O(20)	1.207 (2)	1.211 (1)	1.206 (2)
C(19)–O(21)	1.377 (2)	1.346 (2)	1.340 (2)
O(21)–C(22)	1.446 (2)	1.446 (1)	1.442 (2)

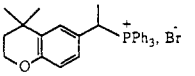
position of the terminal aryl ring, would seem to improve the fit considerably.[24]

In summary, we have established that NMR and UV analyses can be instructive for the rapid identification of isomeric heteroarotinoids which have a stilbene type structure. Both systems have the aryl groups out of the plane of the double bond to which they are attached. Both X-ray characterization of and MMP2 calculations on three members of the family are in reasonably close agreement in terms of the stereochemistry in the molecular system. A comparison of the structures for both *E* isomers with that of *trans*-retinoic acid (**1**) shows a good "fit" for most of the molecule. Consequently, such heteroarotinoids may have potential for mimetic action of that observed with *trans*-retinoic acid (**1**) in biological systems. The work reported herein is the first example of a rigorous study, in terms of physical and structural properties, of *related* heteroarotinoids with *E* and Z isomeric structures. This should provide a basis to compare similar systems.

Experimental Section

The NMR spectra for **3a–h**, **3j**, and **3m** were obtained using a variety of spectrometers. All ^{13}C NMR spectra were recorded either at 25.2, 75.43, or 100.6 MHz. All ^1H NMR spectra were taken at 299.94 or 399.95 MHz. All NMR signals were reported in ppm or δ values downfield from TMS using $DCCl_3$. The atom numbering of the NMR data for the six-membered heteroarotinoids **3j** and **3m** differs by one atom from that used for the five-membered ring heteroarotinoids. Thus, positions 4,6,...,19 (see structures in Results and Discussion) are 5,7,...,20 for the six-membered heteroarotinoids. NMR data for **3i**, **3k**, and **3l** (and ^{13}C NMR data for **3h** and **3k** in $DCCl_3$/DMSO-d_6) have been included as reported.[10,11] The NMR data for **4a,b** has also been reported earlier.[15] All UV data for **3a–h**, **3j**, and **3m** were recorded on solutions which were prepared by dissolving 0.04–2.0 mg of the heteroarotinoid in 50–100 mL of absolute alcohol. Maxima and intensities for **3h**, **3i**, **3k**, and **3l**[10] and for **4a,b**[15] have been reported. The syntheses of (*E*)-**3a**, **-3b**, **-3h**, **-3i**, **-3j**, **-3k**, and **-3l** have been recorded[10,11] as have those for **4a,b**.[15] Heteroarotinoids (*Z*)-**3b**, **-3d**, and **-3j** were obtained from the mother liquors in the preparation of (*E*)-**3b**,[11] **-3d**,[13] and **-3j**,[11] respectively, described below. The syntheses of (*E*)-**3g** and (*E*)-**3m** are also outlined below, while the preparation of (*Z*)-**3i** has been reported previously.[10,11] The syntheses of **3c,e–g** are being reported elsewhere.[13,25]

Methyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate [(*E*)-3j]:[11] Isolation Also of the (*Z*)-3j Isomer. A solution of *n*-butyllithium in hexane (1.39 M, 9.98 mL, 13.80 mmol) was added dropwise under N_2 to a stirred suspension of phosphonium salt[11a] (4.89 g, 9.20 mmol; structure given) in dry ether (90 mL). The resulting dark red-



dish-brown mixture was cooled to −78 °C, and a solution of methyl 4-formylbenzoate (1.51 g, 9.2 mmol; Aldrich) was added over a period of 3 min. The solution was stirred for a few min at −78 °C and then at room temperature for 48 h. The mixture changed from a reddish-brown to an off-white color. After 48 h, the reaction mixture was filtered. The resulting solid was washed with 250 mL of ether (anhydrous); the filtrate was concentrated to a yellow oil. This yellow oil was refrigerated for 8 h and became a yellow solid. This yellow solid was passed through 30 g of silica gel. The product was eluted with 300 mL of hexane–ethyl acetate (4:1). Concentration of the eluent gave a viscous oil which slowly crystallized at room temperature. The white solid was dissolved in a minimum amount of boiling 95% ethanol and filtered hot. After the filtrate was concentrated, cooling this solution to room temperature gave 1.29 g (40.3%) of white crystals of (*E*)-**3j**: mp 90–90.5 °C; IR (KBr) 1710–1725 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, H(9), H(10)], 1.9 [m, 2 H, H(3)], 2.29 [s, 3 H, H(12)], 3.9 [s, 3 H, H(21)], 4.2 [m, 2 H, H(2)], 6.80 [s, 1 H, H(13)], 6.84 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.4 [d, J = 3 Hz, 1 H, H(5)], 7.5 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.06 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 17.8 [C(12)], 30.7 [C(4)], 31.1 [C(9), C(10)], 37.6 [C(3)], 52.1 [C(21)], 63.1 [C(2)], 116.8 [C(8)], 124.5 [C(5)], 124.9 [C(7)], 125.9 [C(13)], 129.0 [C(15), C(19)], 129.5 [C(16), C(18)], 153.4 [C(8a)], 167.0 [H_3C(20)], nonprotonated and vinylic carbons (127.6, 131.3, 135.7, 139.5, 143.4); mass spectral data for $C_{22}H_{24}O_3$ m/e (M^+) 336.1725, found 336.1728. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.59; H, 7.18. Found: C, 78.39; H, 7.10.

The mother liquor from the above crystallization of (*E*)-**3j** contained predominantly the (*Z*)-**3j** (50 mg, 1.6%) as white needles: mp 80–80.5 °C; ^1H NMR ($DCCl_3$) δ 1.12 [s, 6 H, H(9), H(10)], 1.78 [m, 2 H, H(3)], 2.20 [s, 3 H, H(12)], 3.86 [s, 3 H, H(21)], 4.17 [m, 2 H, H(2)], 6.43 [s, 1 H, H(13)], 6.73 [d, J = 9 Hz, H(8)], 6.95 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.03 [d, J = 3 Hz, 1 H, H(5)], 7.51 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.78 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 26.79 [C(12)], 30.42 [C(4)], 30.78 [C(9), C(10)], 37.48 [C(3)], 51.91 [C-(21)], 63.08 [C(2)], 116.9 [C(8)], 125.0 [C(13)], 126.5 [C(7)], 126.5 [C(5)], 128.8 [C(15), C(19)], 129.1 [C(16), C(18)], 143.1 [C(8a)], 167.0 [C(20)], nonprotonated and vinylic carbons (127.5, 128.8, 128.97, 132.9, 141.4); mass spectral data for $C_{22}H_{24}O_3$ m/e (M^+) 336.17254, found 336.1729. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.59; H, 7.18. Found: C, 78.24; H, 7.38.

Methyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoate [(*E*)-3m]. Ester (*E*)-**3j** (1.29 g, 3.84 mmol) and selenium dioxide (1.28 g, 11.52 mmol) were mixed in 75 mL of 95% ethanol. The reaction mixture

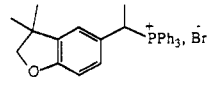
(24) The "fit" is likely important for maximum activity by an agent since human, protein receptors with apparent retinoic acid and DNA binding sites have been discovered. See: (a) Petkovich, M.; Brand, N. J.; Krust, A.; Chambon, P. *Nature (London)* **1987**, *330*, 444–450. (b) Giguere, V.; Ong, E. S.; Sequi, P.; Evans, R. M. *Nature (London)* **1987**, *330*, 624–629. (c) Brand, N.; Petkovich, M.; Krust, A.; Chambon, P.; The, H. d.; Marchio, H.; Tiollaio, P.; Dejean, A. *Nature (London)* **1988**, *332*, 850–853. (d) Benbrook, D.; Lernhardt, E.; Pfahl, M. *Nature (London)* **1988**, *333*, 669–672. (e) Nervi, C.; Grippo, J. F.; Sherman, M. I.; George, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 5854–5858. Although the cellular retinoic acid binding protein (CRABP) may be involved in the overall scheme of retinoic acid transport in certain cell lines, the nature of its interaction with chromatin is uncertain; see: Sherman, M. I. In *Retinoids and Cell Differentiation*; Sherman, M. I., Ed.; CRC: Boca Raton, 1986; pp 161–186.

(25) Gale, J. B.; Berlin, K. D.; Schoolery, J. N. Unpublished results.

was stirred at reflux for 24 h, and then the solution was allowed to cool to room temperature. Filtering the solution through a cotton plug removed elemental selenium which had formed during the course of the reaction. This solution was concentrated under reduced pressure to a volume of 15 mL, and the new solution was diluted with 75 mL of ether. This solution was washed with saturated $NaHCO_3$ solution (2 × 50 mL), H_2O (50 mL), and saturated NaCl solution (50 mL). After drying ($MgSO_4$, 2 h), the resultant organic solution was evaporated, leaving a yellow oil. Chromatography of the oil was performed using silica gel (15 grams) through a column. Elution was effected with hexane–ethyl acetate (4:1, 200 mL). Concentration of the eluent gave a viscous oil which solidified upon refrigeration for 5 days. The off-white solid obtained was recrystallized (absolute ethanol) to give 0.202 g (15%) of (*E*)-**3m** (aryl groups are syn to each other) as pale yellow crystals: mp 85–86 °C; IR (KBr) 3150–3600 (O—H), 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, H(9), H(10)], 1.62 [t, 1 H, O*H*], 1.81 [m, 2 H, H(3)], 3.9 [s, 1 H, H(21)], 4.2 [m, 2 H, H(2)], 4.43 [d, 2 H, H(12)], 6.64 [s, 1 H, H(13)], 6.79 [d, J = 9 Hz, 1 H, H(8)], 6.96 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.06 [d, J = 3 Hz, 1 H, H(5)], 7.1 [d, J = 9 Hz, 2 H, H(15), H(19)], 7.79 [d, J = 9 Hz, 2 H, H(16), H(18)]; ^{13}C NMR ($DCCl_3$) ppm 29.33 [C(4)], 29.68 [C(9), C(10)], 36.27 [C(3)], 50.83 [C(21)], 61.98 [C-(12)], 66.77 [C(2)], 116.24 [C(8)], 123.46 [C(5)], 125.69 [C(7)], 126.73 [C(13)], 127.91 [C(15), C(19)], 128.08 [C(16), C(18)], 152.32 [C(8a)], 165.81 [H_3C(20)], nonprotonated and vinylic carbons [126.91, 127.99, 130.95, 140.77, 142.86]; mass spectral data for $C_{22}H_{24}O_4$ m/e (M^+) 352.16745, found 352.1673. Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.03; H, 6.87. Found: C, 74.84; H, 7.00.

The presence of the (*Z*)-**3m** as a slightly impure (estimated impurity <1%) oil from the chromatography was indicated by the following ^1H NMR and UV signals: ^1H NMR ($DCCl_3$) δ 1.38 [2, 6 H, H(9), H(10)], 1.62 [t, 1 H, O*H*], 1.86 [m, 2 H, H(3)], 3.9 [s, 1 H, H(21)], 4.2 [m, 2 H, H(2)], 4.7 [d, 2 H, H(12)], 6.8 [s, 1 H, H(13)], 6.9 [d, J = 9 Hz, 1 H, H(8)], 7.3 [dd, J = 9 Hz, J = 3 Hz, 1 H, H(7)], 7.5 [d, J = 3 Hz, 1 H, H(5)], 7.5 [d, J = 9 Hz, 2 H, H(15), H(19)], 8.0 [d, J = 9 Hz, 1 H, H(16), H(18)]; UV (EtOH) λ_{max} 241 nm (ϵ 1.7 × 10^4), 314 (2.4 × 10^4).

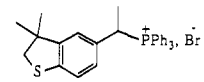
Methyl (*E*)-4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoate [(*E*)-3b]: Isolation Also of (*Z*)-3b. Although (*E*)-**3b** has been reported,[11a] the procedure below gives more consistent yields and, just as importantly, allowed (*Z*)-**3b** to be isolated. A solution of *n*-butyllithium (1.6 M, 3.0 mL, 4.8 mmol) in hexane was added (via syringe, ca. 2 min) to the salt[11a] (2.50 g, 4.83 mmol; structure is given) in dry THF (15 mL) in a standard system under N_2 [all glassware were dried (oven, 100 °C, 0.5 h) and assembled hot]. After stirring at room tem-



perature for 15 min, the black-red Wittig reagent was cooled (dry ice–acetone bath, −78 °C, 5 min), followed by the addition (continued cooling at −78 °C) of a solution of methyl 4-formylbenzoate (0.80 g, 4.9 mmol) in dry THF (10 mL) over a period of about 2 min. The cold bath (−78 °C) was removed, and the mixture was stirred (room temperature) for 12 h. Dry ether (40 mL) was added which induced great amounts of a white precipitate (presumably Ph_3P=O) to form. After filtering the mixture, the precipitate was washed (20 mL of dry ether); the wash was collected as a filtrate. The combined filtrates were concentrated to about 5 mL, and this concentrate was applied to a column of silica gel (20 g) packed in hexanes. Elution was effected using hexanes–EtOAc (9:1, 200 mL). A large fraction [ca. 80 mL, principal component R_f = 0.80 (9:1 hexanes–EtOAc)] was collected and evaporated to a thick oil which crystallized upon standing (crystallization was initiated by cooling the flask over dry ice). Two recrystallizations (boiling 95% ethanol), followed by drying (P_2O_5, ≤0.5 mm, 77 °C, 30 min), gave (*E*)-**3a** as white flakes (0.51 g, 33%). Another 61 mg (3.9%) of (*E*)-**3b** was obtained by concentrating the mother liquors from the first recrystallization, adjusting the volume to about 8 mL (added 95% ethanol), boiling the resulting solution, and allowing the solution to stand which permitted crystallization to occur. After filtration and washing (5 mL of chilled 95% ethanol), the crystals were recrystallized twice (95% ethanol); the total yield of (*E*)-**3b** was 0.57 g (37%): mp 96.8–97.8 °C; IR (KBr) 1717 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, H(8,9)], 2.29 [d, J = 1.2 Hz, 3 H, H(11)], 3.93 [s, 3 H, H(20)], 4.28 [s, 2 H, H(2)], 6.77 [br s, 1 H, H(12)], 6.80 [d, J = 8.3 Hz, 1 H, H(7)], 7.28 [d, J = 2 Hz, 1 H, H(4)], 7.31 [dd, J = 8.3 Hz, J = 2 Hz, 1 H, H(6)], 7.41 [d, 2 H, H(14,18)], 8.03 [d, 2 H, H (15,17)]; ^{13}C NMR ($DCCl_3$) ppm 17.9 [q, C(11)], 27.6 [q, C(8, 9)], 41.9 [s, C(3)], 52.0 [q, C(20)], 109.3 [d, C(7)], 120.0 [d, C(4)], 125.1 [d, C(12)], 126.1 [d, C(6)], 129.0 [d, C(14,18)], 129.5 [d, C(15,17)], 159.0 [s, C(7a)], 167.0 [s, C(19)]; other nonprotonated carbons [127.6, 136.4, 136.8, 139.6, 143.4]; mass spectral data for $C_{21}H_{22}O_3$ m/e (M^+) 322.1569, found 322.1572. Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 77.88; H, 6.98.

Slow evaporation of the mother liquors (which had been reduced to 8 mL) from the recrystallization mixture over a period of 4.5 days gave a mixture of flakes and needles. The needles were isolated manually, recrystallized (minimum amount of boiling, 95% ethanol), washed with chilled 95% ethanol, and dried (P_2O_5, ≤0.5 mm, room temperature, 30 min) to give (*Z*)-(**3b**) as white needles (12 mg, 0.8%): mp 100.0–101.0 °C; IR (KBr) 1718 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.22 [s, 6 H, H(8,9)], 2.22 [d, J = 1.4 Hz, 3 H, H(11)], 3.87 [s, 3 H, H(20)], 4.24 [s, 2 H, H(2)], 6.43 [br s, 1 H, H(12)], 6.71 [d, J = 8.1 Hz, 1 H, H(7)], 6.84 [d, J = 2 Hz, 1 H, H(4)], 6.96 [dd, J = 8.1 Hz, J = 2 Hz, 1 H, H(6)], 7.01 [d, J = 8 Hz, 2 H, H(14,18)], 7.78 [d, J = 8 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 27.1 [C(11)], 27.5 [C(8,9)], 41.8 [C(3)], 51.9 [C(20)], 84.7 [C(2)], 109.6 [C(7)], 128.8 and 129.1 [C(14,18) and C(15,17)], 158.6 [C(7a)], 167.0 [C(19)]; other nonprotonated carbons [122.6, 125.1, 127.3, 127.7, 133.6, 136.8, 141.6, 142.9]. Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.28; H, 6.84.

Methyl (*E*)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate [(*E*)-3d]: Isolation Also of (*Z*)-3d. To a stirred mixture of salt[13] (5.00 g, 9.37 mmol; the structure is shown) in THF (100 mL) in standard apparatus under



N_2 was added (via syringe, ca. 2 min) a solution of *n*-butyllithium (6.2 mL, 1.6 M, 9.9 mmol) in hexane. The resulting black-brown mixture was stirred at room temperature for 1.5 h. After the Wittig reagent was cooled in a dry ice–acetone bath (−78 °C) for 10 min, a solution of methyl 4-formylbenzoate (1.55 g, 9.44 mmol) in dry THF (50 mL) was added to the Wittig reagent over a period of 10 min, after which time the color of the mixture had turned to a creamy yellow. The cold bath (−78 °C) was removed, and the mixture was allowed to stir at ambient temperature for 25 h. To the mixture was added dry ether (150 mL) dropwise. A creamy white precipitate formed and was removed by filtration (the filtrate was set aside) and then dissolved in an aqueous acetone solution 5:3 H_2O–acetone, 80 mL). The resulting solution was extracted with hexanes (3 × 50 mL). Evaporation of the combined filtrate and hexanes extracts gave a total weight of 5.19 g of a crude solid which was divided in four portions. Each portion was subjected to centrifugal thin-layer chromatography (Chromatotron) using a silica gel plate (4 mm). Elution of the first portion was effected with hexanes–ether [9:1 (200 mL), 4:1 (50 mL), and 150 mL of ether to strip the plate]. Immediate use of the same plate to separate the components of the other three portions required slightly increased amounts of hexanes [ratio of hexanes–ether was 14:1] due to increased amounts of residual ether in the silica gel plate. Evaporation of the fractions from the principle band gave 3 g of solid. Recrystallization from boiling 95% ethanol (50 mL) gave the heteroarotinoid ester (*E*)-**3d** as white crystalline flakes (1.87 g, 59.0%) which was essentially pure (mother liquors set aside, see isolation of (*Z*)-**3d** below). A second recrystallization (95% EtOH, 50 mL) gave pure (*E*)-**3d** (1.62 g, 51.1%) as assessed by TLC (silica gel, 9:1 hexane–ether): mp 120.9–122.0 °C; IR (KBr) 1716 (C=O cm^{-1}); ^1H NMR ($DCCl_3$) δ 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)], 7.20 [d, J = 2 Hz, 1 H, H(4)], 7.19 [d, J = 8 Hz, 1 H, H(7)], 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}C NMR ($DCCl_3$) ppm 17.8 [C(11)], 27.4 [C(8,9)], 47.3 [C(2)], 47.5 [C(3)], 52.1 [C(20)], 120.3 [C(4)], 122.2 [C(7)], 125.4 [C(6)], 125.9 [C(12)], 127.8, 129.1 [C-(14,18)], 129.5 [C(15,17)], 139.5, 140.2, 143.1, 148.2, 167.0 [C(19)].

Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.47. Found: C, 74.70; H, 6.70; S, 9.33.

Slow evaporation of the mother liquors from the first recrystallization gave rod-shaped crystals which were recrystallized twice (boiling 95% ethanol) to give the (*Z*)-**3d** as pale yellow crystals (36 mg, 1.1%): mp 84.0–84.5 °C; IR (KBr) 1725 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.21 [s, 6 H, H(8,9)], 2.21 [d, J = 1.4 Hz, 3 H, H(11)], 3.15 [s, 2 H, H(2)], 3.86 [s, 3 H, H(20)], 6.46 [br s, 1 H, H(12)], 6.78 [d, J = 1.6 Hz, 1 H, H(4)], 6.97 [dd, J = 7.9 Hz, J = 1.6 Hz, 1 H, H(6)], 7.02 [d, J = 8.4 Hz, 2 H, H(14,18)], 7.12 [d, J = 7.9 Hz, 1 H, H(7)], 7.78 [d, J = 8.4 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 26.9 [C(11)], 27.3 [C(8,9], 47.1 [C(3)], 47.3 [C(2)], 51.9 [C(20)], 122.4 [C(4)], 123.0 [C(7)], 125.6 [C(12)], 127.0 [C(6)], 128.8 and 129.2 [C(14,18) and C(15,17)], 167.0 [C(19)]; other quaternary carbons [127.4, 137.5, 139.7, 141.2, 142.7, 148.2]. Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55. Found: C, 74.71; H, 6.47.

Crystal Data. Data for the crystal structures were collected on an Enraf-Nonius CAD4 diffractometer using Cu Kα. All data were collected using a θ–2θ scan technique at low temperature maintained by a liquid nitrogen cooling system. The following parameters were the same for each data set: 2θ (max) = 150°; the maximum scan time was 90 s; three intensity control monitors were checked every 7200 s of X-ray exposure time; three orientation control monitors were checked every 200 measurements. The crystals used for the X-ray work were no less than 0.2 mm in any dimension, except for (*E*)-**3d** which was a platelike crystal 0.04 mm thick. Absorption correction was done only for (*E*)-**3d**. Lorentz-polarization corrections were applied. Other information pertinent to data collection and crystal properties are listed in Table II. Cell parameters were determined by a least-squares fit of no less than 48 reflections. Space groups were determined from systematic extinctions.

The heavy atom method was used to locate the sulfur atom in (*E*)-**3d** [$C_{21}H_{22}O_2S$] with the program SHELX76.[26] Direct methods with SHELX76 gave a partial structure of (*Z*)-**3d**. A partial structure of (*E*)-**3b** [$C_{21}H_{22}O_3$] was obtained by using MULTAN80.[27]

(26) Sheldrick, G. M. *SHELX76, Program for crystal structure determination*; University of Cambridge; London, England, 1976.

(27) Main, P. *MULTAN80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data*; University of York: York, England, 1980.

All structures were completed from successive difference Fourier syntheses with SHELX76. All three structures were refined using SHELX76 with the minimization of $\Sigma w(F_o - F_c)^2$, $w = 1/\sigma^2(F_o)$. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms which were located from successive difference Fourier syntheses were refined isotropically. The maximum and minimum peaks in the final Fourier map were within the range of 0.29 to –0.23 e/Å^3 for the three compounds. Final coordinates and isotropic equivalent temperature factors of the non-hydrogen atoms for all three structures can be obtained upon request.

Molecular Mechanics Calculation. Molecular mechanics calculations were carried out by using the program MMP2.[22] The strain energy of (*E*)-**3b**, (*E*)-**3d**, and (*Z*)-**3d** was minimized while using the crystal coordinates as the starting structure. An iterative variable-electronegativity self-consistent field (VESCF)[22] was utilized to reduce bond-stretch force constants and V2 torsional parameters for the bonds in which the 16 π atoms were involved [C(3a), C(4), C(5), C(6), C(7), C(7a), C(10), C(12), C(13)8 C(14), C(15), C(16), C(17), C(18), C(19), and O(20)]. Rotation around C(5)–C(10) in (*Z*)-**3d** was carried out by driving the angle in 10° increments while relaxing all other angles.

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Supplementary Material Available: Anisotropic thermal parameters, hydrogen parameters, bond angles, and final coordinates and isotropic equivalent temperature factors for non-hydrogen atoms for (*E*)-**3d**, (*Z*)-**3d**, and (*E*)-**3b** (11 pages). Ordering information is given on any current masthead page.