Efficient Syntheses of Thiochromans via Cationic Cycloadditions

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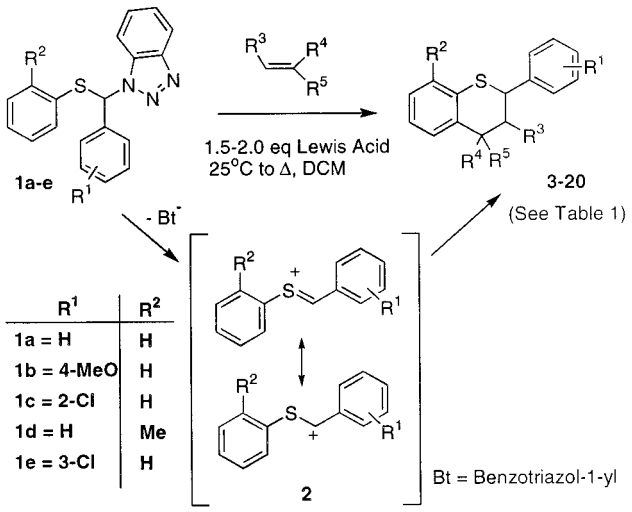
α-(Benzotriazolyl)methyl thioethers **1a**−**e** reacted with styrenes under Lewis acid catalysis to give novel polysubstituted thiochromans (3,4-dihydro-2*H*-1-benzothiopyrans) **3**−**14** and **16**−**20** in generally high yields. Most thiochromans were isolated as one diastereomer following recrystallization. The configuration and conformation of the products are predicted on the basis of their NMR data. A stepwise reaction, proceeding via a [4$^+$ + 2] cationic polar cycloaddition mechanism, is proposed.

Introduction

The chemistry of sulfur based six-membered rings, thiopyrans, has, to date, been less extensively studied than that of the analogous pyrans.[1] Although not particularly common throughout nature, this class of sulfur-containing heterocycles is of synthetic and biological interest. 3,4-Dihydro-2*H*-1-benzothiopyrans, more commonly known as thiochromans, exhibit antiinflammatory, antipyretic, antidepressant, and analgesic activity.[1a] Thiochromans have previously been synthesized from the corresponding 2*H*-1-benzothiopyrans (thiochromens),[2] benzothiopyranones,[3] and by Claisen rearrangement of phenyl allyl sulfides.[4] Another approach to the synthesis of thiochromans utilizes cycloadditions of stabilized sulfur carbocations.[5] While other cationic polar cycloadditions have become well-known,[6] relatively few examples of sulfur stabilized cationic cycloadditions have been reported.[5,7] However, in our application of benzotriazole methodology to organic synthesis,[8] we have used α-(benzotriazolyl)alkyl thioethers as precursors to thionium ions.[9] Such thioethers are simple to prepare and easily structurally modified.[9c,f] We now report the Lewis acid generation of α-thionium ion dienes, precursors of substituted thiochromans, from α-(benzotriazolyl)methyl thioethers **1a**−**e**. These thionium ions undergo efficient cationic cycloadditions to afford thiochromans **3**−**14** and **16**−**20** in generally high yields.

Scheme 1



R^1	R^2
1a = H	H
1b = 4-MeO	H
1c = 2-Cl	H
1d = H	Me
1e = 3-Cl	H

Results and Discussion

α-(Benzotriazolyl)methyl thioether starting materials **1a**−**c** were easily prepared by the condensation of benzotriazole, thiophenol, and benzaldehyde derivatives as previously reported.[9c,f] Novel compounds **1d**,**e** were obtained in 51% and 60% yields, respectively, using the same method as for **1a**−**c**. Reactions of substrates **1a**−**e** with styrenes, under Lewis acid conditions, afforded thiochroman derivatives **3**−**14** and **16**−**20** in yields ranging from 40 to 99% (Scheme 1, Table 1). The reactions were either carried out in dichloromethane at room temperature for 14 to 18 h, or at reflux for ca. 4 h. The reaction temperature had negligible effect on yield or diastereoselectivity. The workup, following the reac-

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Table 1. Yields and Diastereomeric Ratios for Thiochromans 3−20

1	R^1	R^2	R^3	R^4	R^5	prod.	dr[a]	yield[b] (%)	yield[c] (%)
a	H	H	H	H	Ph	**3**	12:1	95	84
a	H	H	H	H	4-MeC_6H_4	**4**	exclusive	96	96
c	2-Cl	H	H	H	Ph	**5**	23:1	94	92
e	3-Cl	H	H	H	Ph	**6**	20:1	92	84
d	H	Me	H	H	4-MeC_6H_4	**7**	20:1	96	90
b	4-MeO	H	H	H	Ph	**8**	1.9:1	94	72 (1.2:1)[d]
b	4-MeO	H	H	H	4-MeC_6H_4	**9**	1.3:1	97	76 (2.5:1)[d]
a	H	H	H	H	4-$MeOC_6H_4$	**10**	exclusive	40	20[e,h]
a	H	H	H	Me	Ph	**11**	5.5:1	85	65
e	3-Cl	H	H	Me	Ph	**12**	8:1	95	75 (7:1)[e,g]
c	2-Cl	H	H	Me	Ph	**13**	7:1	96	79
d	H	Me	H	Me	Ph	**14**	7:1	99	81
a	H	H	H	Ph	Ph	**15**	N/A	0	0
a	H	H	Me	H	Ph	**16**	6:4:2:1	84	38
a	H	H	Me	H	4-$MeOC_6H_4$	**17**	1.4:1	99	54
e	3-Cl	H	Me	H	4-$MeOC_6H_4$	**18**	1.3:1	98	36[f]
d	H	Me	Me	H	4-$MeOC_6H_4$	**19**	1:1	91	80 (10:1)[d]
a	H	H	Ph	Ph	H	**20**	6:1	41	30[e,h,i]
a	H	H	Ph	H	Ph	**20**	4:1	40	24[e,h,i]

[a] Ratio determined by GC and NMR. [b] Yield of isolated mixture. [c] Yield of pure diastereomer, isolated by recrystallization (unless stated). [d] Purified by recrystallization to give two isomers, ratio in parentheses. [e] Could not be separated by recrystallization. [f] Recrystallized to give minor diastereomer only. [g] Crude product was an oil, column chromatography afforded pure product as a mixture of diastereomers. [h] As *g* but as one pure diastereomer. [i] The same 2,3-*trans*-3,4-*trans* isomer of **20** was produced from both *cis*- and *trans*-stilbene.

tion of **1a**−**e** with $ZnBr_2$ and a suitable alkene, consisted of simple filtration and solvent removal to afford the desired crude thiochromans **3**−**14** and **16**−**20**, either as pure isomers, or as mixtures of up to four diastereomers. Interestingly, in all cases apart from **16**, only one or two isomers were detected (Table 1). Most crude products were ≥90% pure, and frequently the major isomer was isolated in good yield following recrystallization, but column chromatography was occasionally necessary. Variation of the functionality of the starting materials allowed the syntheses of three different major classes of thiochromans: (i) 2,4- (**3**−**6**, **8**−**10**) and 2,4,8- (**7**); (ii) 2,4,4- (**11**−**13**) and 2,4,4,8- (**14**), and; (iii) 2,3,4- (**16**−**18**, **20**) and 2,3,4,8- (**19**) substituted thiochromans (Table 1). Each of the classes (i) to (iii) are discussed in more detail below.

(i) 2,4-Diaryl-Substituted Thiochromans. Compounds **3**−**7** were each obtained as single diastereomers following recrystallization. The large $J_{2,3a}$ and $J_{3a,4}$ coupling constants for compounds **3**−**7** (ca. 10−12 Hz, see Table 2) suggest that the C-2 and C-4 substituents are both equatorial and therefore *cis* to each other.[5a] The overlap of signals and complex splitting patterns in some cases precluded measurement of accurate coupling constants (as demonstrated for **3** and **4**). However, we could determine the product stereochemistry by considering the overall coupling constants for $J_{2,3a} + J_{2,3e}$ and $J_{3e,4} + J_{3a,4}$[10] (where a and e represent axial and equatorial orientations, respectively). The total sums for $J_{2,3a} + J_{2,3e}$ and $J_{3e,4} + J_{3a,4}$ were obtained by taking the values of the outermost lines for the H-2 and H-4 multiplets. The sum of these coupling constants was 16.8 Hz ($J_{3e,4} + J_{3a,4}$) for **3** and 15.0 Hz ($J_{2,3a} + J_{2,3e}$) for **4**, thus supporting the *cis*-diequatorial relationship between the substituents at C-2 and C-4 in thiochromans **3** and **4**. However, the coupling constants for H-4 in compound **3** and H-2 in compound **4** were found to be easier to define using $(CD_3)_2CO$ as the NMR solvent (Table 2). Moreover, chroman skeletons are known to exist preferentially in a half-chair or "sofa" conformation.[11,12] Large values, ca. 16.0 Hz, for the overall coupling constants for both the H-2 and H-4 resonances, are consistent with *trans*-diaxial proton orientations and corresponding interactions with the C-2 and C-4 substituents both pseudoequatorial.[13,14] This predicted stereochemistry is highlighted in Figure 1, where the *cis*-configuration of the 2,4-diarylthiochroman is shown in both half chair (I) and "sofa" (II) conformations.[11,12,13b] Unfortunately, despite many attempts, only imperfect crystals of **3** could be obtained: however, partial X-ray results support the *cis* stereochemistry.

The coupling constants for compound **7** were $J_{3a,4}$ = 9.3 Hz and $J_{2,3a}$ = 8.7 Hz, compared with values of between 10.0 and 12.0 Hz for **3**−**6**. The slightly lower vicinal coupling constants for **7** may be a result of conformation averaging; however, the values are still large enough to support the presence of a single predominant conformation, i.e., the protons are pseudoaxial for a majority of the time. From the observed coupling constants, it was not possible to confirm whether the thiochromans exist predominantly in the half chair (I) or the "sofa" (II) form, or as a mixture of both. In the cases of **3** and **5**−**7**, i.e., whenever a mixture of two diastereomers were present, the minor *trans*-isomers, which were not isolated, could be unambiguously identified by their characteristic 1:2:1 triplet for the H-4 protons which resonate at approximately 4.37−4.43 ppm ($J \cong 4$ Hz). This NMR pattern is typical for that observed in reported *trans*-4-substituted thioflavans.[2,13a]

Using 4-methoxyphenyl-α-(benzotriazolyl) methylthio ether (**1b**), 2,4-diaryl substituted thiochromans **8** and **9** were each obtained as a mixture of two diastereomers after recrystallization (Table 1). The configurations for

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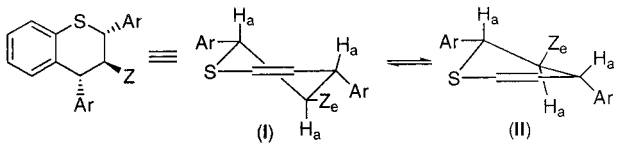
Table 2. Selected NMR Data for Thiochromans 3−14, 16−20

compd	δ ($CDCl_3$) $H_2 + H_4$ and multiplicity	J/Hz[a,b]
3	H-4 4.20−4.28 (m)	$J_{3a,4} + J_{3e,4} = 16.8$
	[H-4 4.36 (dd)][c]	[$J_{3e,4} = 5.7$, $J_{3a,4} = 11.1$][c]
	H-2 4.62 (dd)	$J_{2,3e} = 4.5$, $J_{2,3a} = 10.2$
4	H-4 4.21 (dd)	$J_{3e,4} = 6.6$, $J_{3a,4} = 9.9$
	H-2 4.61−4.66 (m)	$J_{2,3a} + J_{2,3e} = 15$
	[H-2 4.73 (dd)][c]	[$J_{2,3e} = 3.9$, $J_{2,3a} = 10.8$][c]
5	H-4 4.27 (dd)	$J_{3e,4} = 4.5$, $J_{3a,4} = 12$
	H-2 5.18 (dd)	$J_{2,3e} = 3.0$, $J_{2,3a} = 11.4$
6	H-4 4.22 (dd)	$J_{3e,4} = 4.8$, $J_{3a,4} = 11.4$
	H-2 4.58 (dd)	$J_{2,3e} = 3.9$, $J_{2,3a} = 11.1$
7	H-4 4.26 (dd)	$J_{3e,4} = 7.2$, $J_{3a,4} = 9.3$
	H-2 4.59 (dd)	$J_{2,3e} = 6.3$, $J_{2,3a} = 8.7$
8	H-4 4.10−4.27 (m)	—[d]
	H-2 4.56−4.65 (m)	—[d]
9	H-4 4.15−4.24 (m)	—[d]
	[H-4, 4.29 (dd)][e]	[$J_{3e,4} = 5.1$, $J_{3a,4} = 12.0$][e]
	H-2 4.55−4.63 (m)	—[d]
	[H-2 4.70 (dd)][e]	[$J_{2,3e} = 3.6$, $J_{2,3a} = 11.1$][e]
10	H-4 4.20 (dd)	$J_{3e,4} = 6.0$, $J_{3a,4} = 10.5$
	H-2 4.63 (dd)	$J_{2,3e} = 4.5$, $J_{2,3a} = 10.2$
11	H-3_e 2.21 (dd)	$J_{2,3e} = 2.7$, $J_{3e,3a} = 13.8$
	H-3_a 2.66 (dd)	$J_{2,3a} = 12.6$, $J_{3a,3e} = 13.8$
	H-2 4.64 (dd)	$J_{2,3e} = 2.7$, $J_{2,3a} = 12.6$
12	H-3_e 2.18 (dd)	$J_{2,3e} = 2.4$, $J_{3e,3a} = 13.5$
	H-3_a 2.60 (dd)	$J_{2,3a} = 12.6$, $J_{3a,3e} = 13.5$
	H-2 4.58 (dd)	$J_{2,3e} = 2.4$, $J_{2,3a} = 12.6$
13	H-3_e 2.22 (dd)	$J_{2,3e} = 2.4$, $J_{3e,3a} = 13.8$
	H-3_a 2.52 (dd)	$J_{2,3a} = 12.3$, $J_{3a,3e} = 13.8$
	H-2 5.22 (dd)	$J_{2,3e} = 2.4$, $J_{2,3a} = 12.3$
14	H-3_e 2.21 (dd)	$J_{2,3e} = 2.4$, $J_{3e,3a} = 13.8$
	H-3_a 2.66 (dd)	$J_{2,3a} = 12.6$, $J_{3a,3e} = 13.8$
	H-2 4.58 (dd)	$J_{2,3e} = 2.4$, $J_{2,3a} = 12.6$
16	H-4 3.83 (d)	$J_{3a,4} = 10.2$
	H-2 4.15 (d)	$J_{2,3a} = 10.5$
17	H-4 3.68−3.85 (m)	—[f]
	H-2 4.14 (d)	$J_{2,3a} = 10.5$
18	H-4 3.76 (d)	$J_{3a,4} = 10.5$
	H-2 4.10 (d)	$J_{2,3a} = 10.5$
19	H-4 3.98 (d)	$J_{3a,4} = 10.8$
	H-2 4.27 (d)	$J_{2,3a} = 10.5$
20[c]	H-3 3.84 (dd)	$J_{3a,4} = 10.8$, $J_{2,3a} = 11.1$
	H-4 4.55 (d)	$J_{3a,4} = 10.8$
	H-2 4.92 (d)	$J_{2,3a} = 11.1$

[a] Total coupling constants for $J_{2,3a} + J_{2,3e}$ or $J_{3a,4} + J_{3e,4}$ quoted when the signal is not a clear doublet of doublets.[10] [b] Abbreviations: a = axial and e = equatorial. [c] Carried out in $(CD_3)_2CO$. [d] Overlap of signals for diastereomers. [e] Carried out in $(CD_3)_2CO$ to separate signals for two diastereomers [slight overlap of isomers still observed]. [f] Overlap of signals.



cis-2,4-diarylthiochromans (Z = H)

2,3-*trans*-3,4-*trans*-thiochromans (Z ≠ H)

Figure 1. Conformation of *cis*-2,4-diarylthiochromans.

8 and **9** were difficult to determine by ^{1}H NMR since the signals for the H-2 and H-4 protons of both diastereomers overlapped. However, the signals for **9**, present in a ratio of 2.5:1.0, were resolved significantly using $(CD_3)_2CO$ as the NMR solvent to reveal a doublet of doublets for the major diastereomer with coupling constants of ca. J = 3.6, 11.1 Hz (4.70 ppm) for H-2 and J = 5.1, 12.0 Hz (4.29 ppm) for H-4 (Table 2). The major diastereomer was therefore assigned to be the *cis*-isomer. However, it was not possible to get good separation of the signals for either the *cis*- or the *trans*-isomers of compound **8**, present in a ratio of 1.2:1.0. Attempts to improve signal separation using high-temperature NMR (up to 60 °C) were not successful.

Reaction of 4-methoxystyrene with **1a** gave the *cis*-2,4-diarylthiochroman **10**, but only in a low yield (20%) following column chromatography, together with bis-(phenylthio)methyl benzene[15] (**24**) as a major byproduct (Table 1, Table 2). The *cis*-stereochemistry was once again assigned on the basis of the high coupling constants for $J_{2,3a}$ and $J_{3a,4}$ which were 10.2 and 10.5 Hz, respectively. Interestingly, in contrast to the previous 2,4-diarylthiochromans, no other isomer was observed.

(ii) 2-Aryl-4-methyl-4-phenylthiochromans. Compounds **11**−**14**, from α-methylstyrene, were all obtained as mixtures of 2 diastereomers in 5.5−8:1 ratios (Table 1). For compounds **11**, **13**, and **14**, the major isomer was obtained pure after recrystallization. Thiochroman **12** was isolated as an oil, and attempts to remove the last traces of minor isomer failed by both crystallization or chromatography. In both major and minor diastereomers of **11**−**14**, the 2-aryl substituent was again assigned to occupy the pseudoequatorial orientation on the basis of the H-2 coupling constants of ca. 2.5 and 12.5 Hz, the latter representing the *trans*-diaxial $J_{2,3a}$ proton interactions (Table 2). This observation is analogous to the results observed for similar 2,4,4-substituted chromans.[16] From the crude ^{1}H NMR spectra, it appears that the C-2 aryl substituents of the minor isomers in **11**−**14** were also pseudoequatorial since the $J_{2,3a}$ coupling constants varied over the range of 9.6−12.3 Hz; the minor isomer signals were present as doublet of doublets at higher field than those for the major products. The major diastereomers for compounds **11**−**14** were predicted to be *cis* with respect to the 2- and 4-aryl groups. This was based on the assumption that the more bulky C-2 aryl and C-4 phenyl groups would preferentially occupy the equatorial position, with the less bulky C-4 methyl axial. Spectral evidence supports this conclusion, the ^{1}H NMR chemical shifts for the C-2 protons of the major diastereomers in 2-aryl-4-methyl-4-phenylthiochromans **11**−**14** are exactly identical to those observed for the C-2 protons of the *cis*-2,4-diarylthiochromans **3**−**6**. This compares with the significant upfield shift of >0.6 ppm observed for the chemical shift of the minor diastereomers. Moreover, further conclusive evidence was obtained by carrying out NOE experiments on compound **11**. When the axial H-2 proton at 4.64 ppm was irradiated, a significant NOE was observed at the 4-methyl substituent as well as at the H-3 equatorial proton and at the ortho protons on the C-2 phenyl ring (Figure 2, **A**). Similarly, irradiation of the C-4 methyl protons at 1.81 ppm led to an NOE with the C-2 proton as well as the geminal equatorial C-3 proton and the ortho protons on the C-4 phenyl ring (Figure 2, **B**). These strong NOE enhancements, observed between H-2 and the C-4 methyl substituent, verify that the methyl group is axial and are caused by the 1,3-diaxial type interaction as highlighted in Figure 2.

When 1,1-diphenylethylene was employed as an alkene, the desired thiochroman **15** was not obtained; only

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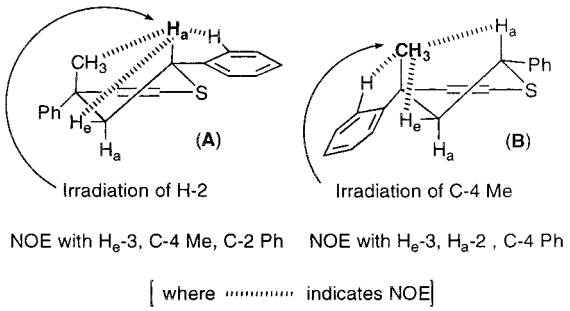


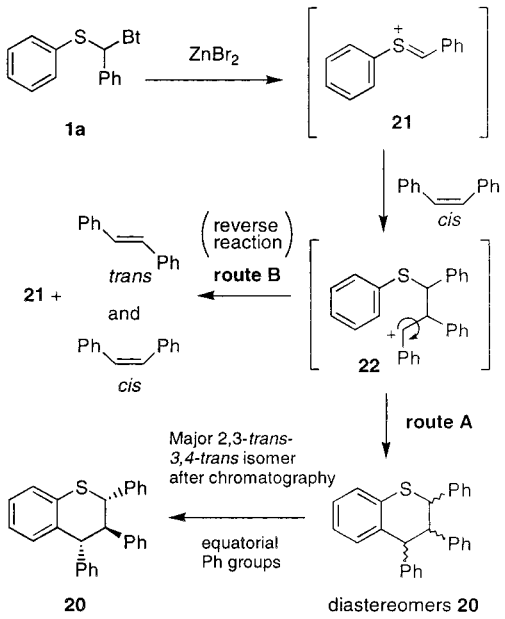
Figure 2. Diagnostic NOEs for major isomer of **11**.

decomposition of the starting material and formation of byproducts, such as bis(phenylthio)methylbenzene (**23**),[15] was observed.

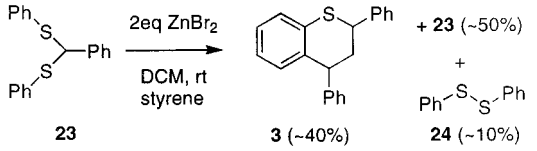
(iii) 2,3,4-Substituted Thiochromans. Thiochroman **16** was produced as a mixture of four diastereomers, while **17**, **18**, and **20** were each obtained as mixtures of two diastereomers. However, single isomers for each of them were isolated after recrystallization of **16**−**18** and column chromatography of **20**. Compound **19**, produced as a 1:1 mixture of isomers, was obtained as a 10:1 mixture of diastereomers following recrystallization. Coupling constants of between 10.2 and 11.1 Hz for both the H-2 and H-4 protons were observed for compounds **16**−**20** (Table 2), consistent with those previously reported for 2,3,4-substituted thiochromans,[17] thus confirming the all *trans*-triaxial conformation for the H-2, H-3, and H-4 protons. Consequently, all the substituents must be pseudoequatorially arranged in the major isomers of thiochromans **16**−**20**. The minor isomers were not isolated, and their stereochemistry could not be confirmed since the axial−equatorial and equatorial−equatorial coupling constants are very similar.

The major products from the reactions of **1a** with both *trans*- and *cis*-stilbene were identical, each composed of a mixture of diastereomers as indicated by the NMR spectra and GC-MS analyses (Table 1). Purification of the major *trans*-isomer of **20** was achieved by column chromatography. The lack of stereochemical retention during the reaction of **1a** with both stilbene isomers indicates that the reaction mechanism is not completely concerted. Further evidence to support a stepwise mechanism includes the regiospecificity resulting from the use of unsymmetrical styrene derivatives with α-(benzotriazolyl)methyl thioethers **1a**−**e**. The electrophilic attack of the thionium ion **21** on unsymmetrical alkenes led to the most stable benzylic carbocation prior to cyclization. The resulting diastereoselectivity also supports the stepwise mechanism: when using both *cis*- and *trans*-stilbene, the intermediate **22** cyclized to give the most stable and favorable thiochroman diastereomer (route A, Scheme 2). The stereochemistry of the alkene is not retained during this reaction. When recrystallization was used in an attempt to purify the crude reaction mixture obtained from the reaction of **1a** with *trans*-stilbene, only *trans*-stilbene was recovered. Moreover, the reaction mixture resulting from the reaction of **1a** with *cis*-stilbene, which is not crystalline, also afforded pure *trans*-stilbene after

Scheme 2



Scheme 3



crystallization, presumably by a reversal of the reaction from **22** back to **21** (route B, Scheme 2). A control experiment was carried out by refluxing *cis*-stilbene with $ZnBr_2$ in DCM without inclusion of substrate **1a-e**; after the workup, only *cis*-stilbene was recovered. This result again suggests that this reaction proceeds in a stepwise manner as highlighted in Scheme 2.

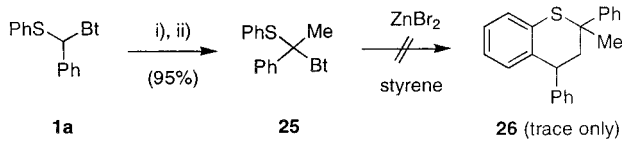
The use of other Lewis acids, such as $BF_3{\cdot}Et_2O$, $ZnCl_2$ and $SnCl_4$ also afforded the desired products **3** and **4** after reaction with **1a**, although attempts with $AlCl_3$ or $TiCl_4$ did not. With $BF_3{\cdot}Et_2O$, the diastereoselectivities were comparable to those observed using $ZnBr_2$. However, the yields were lower, and significant amounts of byproducts, such as bis(phenylthio)methylbenzene (**23**)[15] and phenyl disulfide (**24**),[18] were obtained. Compound **23** was also used instead of α-(benzotriazolyl)methyl thioethers **1a**−**e** as a precursor for this cycloaddition type reaction (Scheme 3). Although we obtained the desired thiochroman **3**, the yield was only ca. 40%, considerably less than the yields obtained using benzotriazole substrates **1a**−**e**, and with significant amounts of unreacted **23** (ca. 50%) and byproduct **24** (ca. 10%), thus making the purification more difficult.

α-(Benzotriazolyl)alkyl thioether (**1a**) was alkylated with methyl iodide to give 1-[(phenyl)(methyl)phenylthiomethyl]-1*H*-benzotriazole (**25**) in 95% yield (Scheme 4). However, no significant amount of the desired thiochroman **26** was observed using the cycloaddition reaction conditions previously discussed. This lack of reactivity may be a consequence of steric hindrance resulting from the α-methyl substituent on the thionium ion intermediate (Scheme 4).

(17) (a) Baruah, P. D.; Mukherjee, S.; Mahajan, M. P. *Tetrahedron* **1990**, *46*, 1951. (b) Takahashi, H.; Kubota, Y.; Miyazaki, H.; Onda, M. *Heterocycles* **1984**, *22*, 1147. (c) Funicello, M.; Spagnolo, P.; Zanirato, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2971.

(18) Barton, D. H. R.; Chen, C.; Wall, G. M. *Tetrahedron* **1991**, *47*, 6127.

Scheme 4



1a **25** **26** (trace only)

i) *n*-BuLi, 1.05 eq, THF, -78°C, 1 h: ii) MeI, -78°C-25°C, 16 h, 95%.

Conclusion

A new and efficient synthesis of novel thiochromans is described which utilizes α-benzotriazolyl sulfides **1d**−**e** in place of the α-chloro sulfides as previously employed by Ishibashi.[5a] Compounds **1d**−**e** are easier to prepare and undergo the cycloadditions with a less toxic catalyst and in significantly high yields. A majority of the present reactions proceeded with high diastereoselectivity. Most of the thiochromans could be purified by recrystallization, often affording the major diastereoisomer. A stepwise, rather than concerted, [$4^+ + 2$] cationic cycloaddition mechanism is proposed.

Experimental Section

General Comments. Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using tetramethylsilane as the internal standard. The ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent $CDCl_3$ or $(CD_3)_2CO$ peak as internal reference. The GC-MS instrument used was Hewlett-Packard 5890 series II gas chromatograph coupled to a 5972 mass selective detector. Elemental analyses (C, H, N) were carried out on a Carlo Erba-1106 instrument. Column chromatography was carried out on silica gel (200−425 mesh). Dichloromethane was distilled over calcium hydride prior to use. THF was dried by distillation in the presence of Na and benzophenone under a nitrogen atmosphere.

Preparation of α-(Benzotriazolyl)methyl Thioethers 1d, 1e, and 25. The starting thioethers **1a**−**e** were prepared in good yields using previously reported condensations of benzotriazole, thiophenol, and benzaldehydes in the presence of catalytic PTSA in refluxing toluene with azeotropic water removal.[9f] Compounds **1a**−**c** were previously reported, but **1d**−**e** are novel and satisfactory analytical data are given below.

1-[(Phenyl)-2-methylphenylthiomethyl]-1*H*-benzotriazole (1d). Compound **1d** was obtained following recrystallization from ether to afford white plates (51%), mp 82−83 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 6.84−6.92 (m, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.07−7.14 (m, 2H), 7.29−7.42 (m, 6H), 7.46−7.53 (m, 2H), 7.62 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.4, 69.6, 111.8, 120.2, 124.0, 126.6, 126.9, 127.2, 128.9, 129.0, 129.1, 130.5, 130.6, 131.7, 134.1, 135.6, 141.0, 146.7. Anal. Calcd for $C_{20}H_{17}N_3$: C, 72.48; H, 5.17; N, 12.68. Found: C, 72.36; H, 5.25; N, 12.59.

1-[(3-Chlorophenyl)phenylthiomethyl]-1*H*-benzotriazole (1e). Compound **1e** was obtained following recrystallization from ether to afford white plates (60%), mp 106−107 °C; ^{1}H NMR ($CDCl_3$) δ 7.13−7.47 (m, 11H), 7.54 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 69.8, 111.6, 120.4, 124.2, 125.1, 127.3, 127.5, 129.2, 129.29, 129.31, 130.2, 130.9, 131.6, 133.6, 134.9, 137.5, 146.7. Anal. Calcd for $C_{19}H_{14}N_3$: C, 64.91; H, 4.01; N, 11.95. Found: C, 64.90; H, 4.01; N, 11.95.

1-[(Phenyl)(methyl)phenylthiomethyl]-1*H*-benzotriazole (25). To a solution of thioether **1a** (9.46 mmol) in dry THF (20 mL) was added *n*-BuLi (10 mmol) at −78 °C. The reaction mixture was left stirring for 1 h at −78 °C before addition of methyl iodide (10.4 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to 25 °C and left for 16 h before quenching with saturated ammonium chloride solution. The solution was worked up by extracting the product into ethyl acetate (3 × 20 mL), washing with water and brine, and drying over $MgSO_4$. Following removal of the desiccant by filtration and solvent under reduced pressure, a yellow oil was obtained. Crystallization from methanol afforded **25** as white macroprisms (95%), mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 6.73 (d, J = 7.8 Hz, 2H), 7.09 (t, J = 6.9 Hz, 2H), 7.22−7.40 (m, 9H), 8.10 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 32.4, 76.0, 114.5, 119.9, 124.0, 125.6, 126.6, 128.4, 128.8, 128.9, 129.9, 130.0, 132.2, 136.6, 141.8, 146.9. Anal. Calcd for $C_{20}H_{17}N_3$: C, 72.48; H, 5.17; N, 12.68. Found: C, 72.44; H, 5.16; N, 12.75.

General Procedure for the Preparation of Thiochromans (3−14, 16−20). To a solution of $ZnBr_2$ (4 mmol) in dry DCM (10 mL) at room temperature under nitrogen atmosphere was added a suitable alkene (2.1 mmol) in DCM (5 mL), followed by 1-[(aryl)arylthiomethyl]-1*H*-benzotriazoles (**1a**−**e**) (2 mmol). This reaction mixture was either heated at reflux for 4 h or left at room temperature for 14−18 h. A precipitate formed and was removed by filtration followed by solvent removal under vacuum to afford the desired crystalline products. Further purification was achieved by recrystallization using ethyl acetate/hexanes, or occasionally by column chromatography. In some cases, where a mixture of diastereomers was obtained, the NMR data for the minor diastereomers are bracketed.

***cis*-2,4-Diphenylthiochroman (3):** pale yellow plates, mp 127 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 2.47−2.61 (m, 2H), 4.20−4.28 (m, $J_{3a,4} + J_{3e,4}$ = 16.8 Hz, 1H), 4.62 (dd, J = 4.5, 10.2 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.88 (dt, J = 1.5, 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.14 (dd, J = 1.2, 7.8 Hz, 1H), 7.20−7.44 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 41.5, 46.1, 47.7, 124.2, 126.1, 126.6, 126.7, 127.5, 127.8, 128.7, 130.0, 134.6, 136.8, 141.1, 145.0. Anal. Calcd for $C_{21}H_{18}S$: C, 83.40; H, 6.00. Found: C, 83.09; H, 6.03.

***cis*-4-(4-Methylphenyl)-2-phenylthiochroman (4):** white needles, mp 148 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.46−2.60 (m, 2H), 4.21 (dd, J = 6.6, 9.9 Hz, 1H), 4.61−4.66 (m, $J_{2,3a} + J_{2,3e}$ = 15 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.88 (dt, J = 1.5, 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.08−7.43 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 21.1, 41.5, 46.1, 47.3, 124.2, 126.0, 126.5, 127.5, 127.8, 128.6, 128.7, 129.4, 130.0, 134.6, 136.3, 137.0, 141.2, 142.0. Anal. Calcd for $C_{22}H_{20}S$: C, 83.50; H, 6.37. Found: C, 83.28; H, 6.51.

***cis*-2-(2-Chlorophenyl)-4-phenylthiochroman (5):** pale yellow plates, mp 103−104 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 2.39−2.63 (m, 2H), 4.27 (dd, J = 4.5, 12 Hz, 1H), 5.18 (dd, J = 3, 11.4 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.91 (dt, J = 1.5, 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.15−7.38 (m, 9H), 7.60 (dd, J = 1.8, 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 40.6, 41.9, 47.6, 124.4, 126.4, 126.6, 126.8, 127.4, 128.6, 128.7, 129.7, 129.9, 133.5, 134.2, 137.1, 138.7, 144.7. Anal. Calcd for $C_{21}H_{17}ClS$: C, 74.87; H, 5.09. Found: C, 74.53; H, 5.16.

***cis*-2-(3-Chlorophenyl)-4-phenylthiochroman (6):** white plates, mp 133−134 °C from EtOAc/hexanes. ^{1}H NMR ($CDCl_3$) δ 2.42−2.59 (m, 2H), 4.22 (dd, J = 4.8, 11.4 Hz, 1H), 4.58 (dd, J = 3.9, 11.1 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.89 (dt, J = 1.5, 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.13 (dd, J = 1.5, 7.8 Hz, 1H), 7.20−7.37 (m, 8H), 7.41 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 41.4, 45.6, 47.5, 124.4, 125.8, 126.1, 126.7, 126.8, 127.7, 128.0, 128.7, 128.8, 130.0, 134.1, 134.5, 136.8, 143.3, 144.7. Anal. Calcd for $C_{21}H_{17}ClS$: C, 74.87; H, 5.09. Found: C, 74.68: H, 5.05.

8-Methyl-*cis*-4-(4-methylphenyl)-2-phenylthiochroman (7): pale yellow plates, mp 158−159 °C from EtOAc/hexanes. ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.35 (s, 3H), 2.52−2.58 (m, 2H), 4.26 (dd, J = 7.2, 9.3 Hz, 1H), 4.59 (dd, J = 6.3, 8.7 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 7.09−7.17 (m, 4H), 7.24−7.37 (m, 3H), 7.41−7.46 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 20.1, 21.1, 41.1, 45.9, 47.7, 123.3, 127.6, 127.7, 127.8, 127.8, 128.5, 128.7, 129.3, 133.9, 134.1, 136.2, 136.8, 141.3, 142.5. Anal. Calcd for $C_{23}H_{22}S$: C, 83.59; H, 6.71. Found: C, 83.61; H, 7.02.

2-(4-Methoxyphenyl)-4-phenylthiochroman (8): pale orange plates, mp 134−135 °C from EtOAc/hexanes; all signals for mixture of both diastereomers (1.2:1.0) unless stated; ^{1}H NMR ($CDCl_3$) δ 2.45−2.59 (m, 2H), [3.78 (s, 3H, minor diastereomer)], 3.79 (s, 3H, major diastereomer), 4.10−4.27 (m, 1H), 4.56−4.65 (m, 1H), 6.73 (t, J = 8.0 Hz, 1H), 6.83−6.92 (m, 3H), 7.05 (t, J = 7.4 Hz, 1H), 7.10−7.16 (m, 2H), 7.20−7.44 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 41.6, 41.7 45.4, 46.1, 46.8, 47.8, 55.2, 55.3, 114.1, 124.2, 124.1, 126.0, 126.5, 126.7, 127.5, 127.8, 128.6, 128.7, 129.6, 129.9, 130.0, 133.1, 134.6, 134.8, 136.7, 137.0, 137.2, 141.1, 145.1, 158.3, 159.1. Anal. Calcd for $C_{22}H_{20}OS$: C, 79.48; H, 6.06. Found: C, 79.18; H, 6.38.

4-(4-Methylphenyl)-2-(4-methoxyphenyl)thiochroman (9): pale orange plates, mp 152−153 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ (all signals for both diastereomers (2.5:1.0) unless stated) 2.32 (s, 3H, major diastereomer), [2.34 (s, 3H, minor diastereomer)], 2.47−2.56 (m, 2H), [3.78 (s, 3H, minor diastereomer)], 3.80 (s, 3H, major diastereomer), 4.15−4.24 (m, 1H), 4.55−4.63 (m, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.83−6.92 (m, 3H), 7.04 (t, J = 7.7 Hz, 1H), 7.09−7.17 (m, 5H), 7.28−7.35 (m, 2H). Figures in {parentheses} are unassigned to either diastereomer. ^{13}C NMR ($CDCl_3$) δ [21.0], 21.1, 41.6, [41.7], [45.5], 45.8, 46.9, [47.4], {55.2, 114.0, 124.1, 126.0, 126.4, 127.4, 128.5, 128.6, 129.4, 129.6, 129.9, 130.0}, [133.2], 134.7, [134.8], [136.2], [136.9], 137.1, 137.2, [137.4], 138.2, [142.1], 158.3, [159.1]. Anal. Calcd for $C_{23}H_{22}OS$: C, 79.73; H, 6.40. Found: C, 80.51; H, 6.38.

***cis*-4-(4-Methoxyphenyl)-2-phenylthiochroman (10):** white plates, mp 158−159 °C following column chromatographic separation using EtOAc/hexanes as an eluent. ^{1}H NMR ($CDCl_3$) δ 2.44−2.60 (m, 2H), 3.81 (s, 3H), 4.20 (dd, J = 6.0, 10.5 Hz, 1H), 4.63 (dd, J = 4.5, 10.2 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.84−6.93 (m, 3H), 7.06 (t, J = 7.5 Hz, 1H), 7.05−7.18 (m, 3H), 7.22−7.36 (m, 3H), 7.42 (d, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 41.6, 46.1, 46.9, 55.3, 114.1, 124.2, 126.0, 126.5, 127.5, 127.8, 128.7, 129.6, 129.9, 134.6, 137.0, 137.2, 141.2, 158.4. Anal. Calcd for $C_{22}H_{20}OS$: C, 79.48; H, 6.06. Found: C, 79.12; H, 6.46.

4-Methyl-2,4-diphenylthiochroman (11): white plates, mp 151−152 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 2.21 (dd, J = 2.7, 13.8 Hz, 1H), 2.66 (dd, J = 12.6, 13.8 Hz, 1H), 4.64 (dd, J = 2.7, 12.6 Hz, 1H), 6.76 (dd, J = 1.5, 8.1 Hz, 1H), 6.89 (dt, J = 1.2, 7.5 Hz, 1H), 7.05 (dt, J = 1.2, 7.5 Hz, 1H), 7.14 (dd, J = 1.2, 7.8 Hz, 1H), 7.18−7.36 (m, 8H), 7.43 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 28.5, 42.2, 44.6, 49.0, 124.2, 126.0, 126.1, 126.2, 127.3, 127.7, 127.8, 128.1, 128.7, 130.5, 133.6, 140.8, 141.2, 150.1. Anal. Calcd for $C_{22}H_{20}S$: C, 83.50; H, 6.37. Found: C, 83.37; H, 6.66.

2-(3-Chlorophenyl)-4-methyl-4-phenylthiochroman (12): colorless oil, purified by column chromatography using EtOAC/hexanes 20:1 as eluent to give the product as a 7:1 mixture of isomers; ^{1}H NMR ($CDCl_3$) δ (major isomer), 1.78 (s, 3H), 2.18 (dd, J = 2.4, 13.5 Hz, 1H), 2.60 (dd, J = 12.6, 13.5 Hz, 1H), 4.58 (dd, J = 2.4, 12.6 Hz, 1H), 6.75 (dd, J = 1.5, 8.1 Hz, 1H), 6.87 (dt, J = 1.5, 8.1 Hz, 1H), 7.03 (dt, J = 1.5, 7.5 Hz, 1H), 7.12 (dd, J = 1.5, 8.1 Hz, 1H), 7.12−7.32 (m, 8H), 7.43 (s, 1H); (minor isomer, selected signals) [1.82 (s, 3H)], [3.94 (dd, J = 3.6, 12.3 Hz, 1H)], [2.39 (dd, J = 12, 13.5 Hz, 1H)], [2.50 (dd, J = 3.3, 13.5 Hz, 1H)]. ^{13}C NMR ($CDCl_3$) δ 28.4, 41.8, 44.5, 48.8, 124.3, 125.9, 126.0, 126.2, 126.8, 127.2, 127.9, 128.0, 128.2, 129.9, 130.5, 133.1, 134.4, 141.0, 142.9, 149.7. Anal. Calcd for $C_{22}H_{19}ClS$: C, 75.30; H, 5.46. Found: C, 75.27; H, 5.35.

2-(2-Chlorophenyl)-4-methyl-4-phenylthiochroman (13): white plates, mp 154 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.22 (dd, J = 2.4, 13.8 Hz, 1H), 2.52 (dd, J = 12.3, 13.8 Hz, 1H), 5.22 (dd, J = 2.4, 12.3 Hz, 1H), 6.77 (dd, J = 1.5, 7.8 Hz, 1H), 6.90 (dt, J = 1.5, 7.5 Hz, 1H), 7.05 (dt, J = 1.5, 7.5 Hz, 1H), 7.13−7.38 (m, 9H), 7.65 (dd, J = 1.8, 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 28.3, 38.3, 44.9, 48.5, 124.3, 126.18, 126.24, 126.3, 127.26, 127.32, 128.1, 128.7, 128.8, 129.7, 130.6, 133.1, 133.5, 138.2, 141.3, 149.9. Anal. Calcd for $C_{22}H_{19}ClS$: C, 75.30; H, 5.46. Found: C, 75.31; H, 5.82.

4,8-Dimethyl-2,4-diphenylthiochroman (14): white plates, mp 150−151 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 2.21 (dd, J = 2.4, 13.8 Hz, 1H), 2.29 (s, 3H), 2.66 (dd, J = 12.6, 13.8 Hz, 1H), 4.58 (dd, J = 2.4, 12.6 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.80 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.16−7.37 (m, 8H), 7.43−7.47 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 20.3, 28 0.8, 42.0, 44.9, 48.5, 123.2, 126.0, 127.2, 127.5, 127.8, 127.9, 128.1, 128.2, 128.7, 133.2, 133.7, 141.0, 141.1, 150.6. Anal. Calcd for $C_{23}H_{22}S$: C, 83.59; H, 6.71. Found: C, 83.85; H, 7.04.

2,3-*trans*-3,4-*trans*-3-Methyl-2,4-diphenylthiochroman (16): white plates, mp 164−165 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 6.3 Hz, 3H), 2.55−2.69 (m, 1H), 3.83 (d, J = 10.2 Hz, 1H), 4.15 (d, J = 10.5 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.88 (dt, J = 1.5, 7.5 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 7.12 (dd, J = 1.5, 7.8 Hz, 1H), 7.19−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 18.6, 42.9, 52.2, 55.0, 124.4, 126.0, 126.1, 126.5, 127.7, 128.3, 128.6, 128.7, 129.5, 131.2, 134.4, 137.7, 140.1, 145.1. Anal. Calcd for $C_{22}H_{20}S$: C, 83.50; H, 6.37. Found: C, 83.28; H, 6.71.

2,3-*trans*-3,4-*trans*-4-(4-Methoxyphenyl)-3-methyl-2-phenylthiochroman (17): pale yellow plates, mp 155−200 °C (decomp) from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 6.3 Hz, 3H), 2.48−2.64 (m, 1H), 3.68−3.85 (m, 1H), 3.81 (s, 3H), 4.14 (d, J = 10.5 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.84−6.92 (m, 3H), 7.03 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 3H), 7.24−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.6, 42.9, 52.2, 54.2, 55.2, 114.0, 124.4, 125.9, 126.1, 127.7, 128.3, 128.7, 130.3, 131.1, 134.4, 137.1, 138.0, 140.3, 158.2. HRMS (EI) Calcd for $C_{23}H_{22}OS$: 346.1391. Found: 346.1420. Anal. Calcd for $C_{23}H_{22}OS$: C, 79.73; H, 6.40. Found: C, 79.33; H, 6.56.

2,3-*trans*-3,4-*trans*-(4-Methoxyphenyl)-3-methyl-2-(2-chlorophenyl)thiochroman (18): white plates, mp 144−146 °C from EtOAc/hexanes; ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J = 6.6 Hz, 3H), 2.46−2.59 (m, 1H), 3.76 (d, J = 10.5 Hz, 1H), 3.81 (s, 3H), 4.10 (d, J = 10.5 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.84−6.93 (m, 3H), 7.04 (t, J = 7.4 Hz, 1H), 7.08−7.14 (m, 3H), 7.25 (d, J = 1.5 Hz, 3H), 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.7, 42.9, 51.8, 54.0, 55.2, 114.0, 124.6, 126.0, 126.2, 126.5, 127.9, 128.4, 130.0, 130.3, 131.0, 133.8, 134.5, 136.7, 137.9, 142.5, 158.3. HRMS (EI) Calcd for $C_{23}H_{21}ClOS$: 380.1002. Found: 380.0971.

8-Methyl-2,3-*trans*-3,4-*trans*-4-(4-methoxyphenyl)-3-methyl-2-phenylthiochroman (19): white plates, mp 140−142 °C from EtOAc/hexanes; all signals for major diastereomer unless stated; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.6 Hz, 3H), 2.45 (s, 3H), 2.58−2.82 (m, 1H), 3.98 (s, 3H), 3.98 (d, J = 10.8 Hz, 1H), 4.27 (d, J = 10.5 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.96−7.14 (m, 4H), 7.29 (d, J = 8.7 Hz, 2H), 7.42−7.60 (m, 5H). The only signals identifiable for minor diastereomer (<10%) are [1.14 (d, J = 6.6 Hz, 3H)], [2.57 (s, 3H)], [4.60 (d, J = 3.0 Hz, 1H)]. ^{13}C NMR ($CDCl_3$) δ 18.7, 20.7, 42.6, 52.1, 54.6, 55.2, 113.9, 123.6, 127.4, 127.7, 128.3, 128.7, 128.8, 130.3, 133.7, 134.0, 137.6, 137.9, 140.4, 158.1. Anal. Calcd for $C_{24}H_{24}OS$: C, 79.96; H, 6.71. Found: C, 79.56; H, 7.09.

2,3-*trans*-3,4-*trans*-2,3,4-Triphenylthiochroman (20): white plates, mp 145−146 °C following column chromatography using EtOAc/hexanes (20:1) as an eluent followed by washing resultant colorless oil with hexanes; ^{1}H NMR $(CD_3)_2CO$ δ 3.84 (dd, J = 11.1, 10.8 Hz, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.92 (d, J = 11.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.80−7.34 (m, 18H). ^{13}C NMR ($CDCl_3$) δ 51.1, 55.3, 56.3, 125.1, 126.6, 126.7, 126.9, 127.1, 128.0, 128.5, 128.9, 129.0, 129.6, 130.3, 132.1, 135.3, 139.3, 140.5, 142.8, 145.5. Anal. Calcd for $C_{27}H_{22}S$: C, 85.67; H, 5.86. Found: C, 85.98: H, 6.67.

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