Diarylspiro[2.4]heptenes as Orally Active, Highly Selective Cyclooxygenase-2 Inhibitors: Synthesis and Structure−Activity Relationships

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A novel series of 5,6-diarylspiro[2.4]hept-5-enes was shown to provide highly potent and selective cyclooxygenase-2 (COX-2) inhibitors. A study of structure−activity relationships in this series suggests that 3,4-disubstituted phenyl analogs are generally more selective than 4-substituted phenyl analogs and that replacement of the methyl sulfone group on the 6-phenyl ring with a sulfonamide moiety results in compounds with superior *in vivo* pharmacological properties, although with lower COX-2 selectivity. Several compounds have been shown to possess promising pharmacological properties in adjuvant-induced arthritis and edema analgesia models. The absence of gastrointestinal (GI) toxicity at 200 mpk of several selected compounds in rats and mice corresponds well with the weak potency for inhibition of COX-1 observed in the enzyme assay. Methyl sulfone **55** and sulfonamide **24** were shown to have superior *in vivo* pharmacological profiles, low GI toxicity, and good oral bioavailability and duration of action.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin possess antiinflammatory, analgesic, and antipyretic activities and have been widely used to treat chronic inflammatory conditions such as arthritis.[1] The most common side effects associated with all currently available NSAIDs are sometimes life-threatening gastrointestinal (GI) hemorrhage and ulceration.[1,2] Decreased renal function in some patients has also been observed.[3,4] Because of these problems, the pharmaceutical industry has been pursuing opportunities to develop drugs that possess antiinflammatory activity without the toxic side effects associated with known NSAIDs.

In the early 1970s, it was reported that NSAIDs prevent the production of prostaglandins (PGs) by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid to prostaglandin H_2 (PGH_2).[5,6] For many years it was believed that COX was a single enzyme (COX-1) constitutively expressed in tissues such as gut and kidney. Recently, a previously unknown, inducible isozyme associated with inflammation was also identified (COX-2).[7−10]

Two structurally distinct experimental compounds have been reported to inhibit PG production in inflammatory cells (DuP 697 and NS-398; see Figure 1).[11,12] In contrast to other NSAIDs, these compounds do not cause ulcers in the stomach or intestines of experimental animals at doses that exhibit antiinflammatory and analgesic activities. It has since been reported that both compounds are also selective COX-2 inhibitors.[13−17] These observations support the hypothesis that the constitutive COX-1 isozyme protects the GI tract, whereas the inducible COX-2 isoform mediates inflammatory prostaglandin production.[13−18] Selective inhibition of COX-2 thus offers an attractive target for the design of antiinflammatory agents that avoid the GI toxicity seen with current nonselective NSAIDs.

Our laboratories have reported the discovery of several novel classes of potent and selective COX-2 inhibitors, e.g., the methyl sulfones **1** (SC-57666) and **2** (SC-58231) (Figure 1).[19−21] Recently we communicated our preliminary findings on 5,6-diarylspiro[2.4]hept-5-enes.[22] In this paper we report in detail on our study of this series of orally active, potent, and selective COX-2 inhibitors.

Chemistry

Our initial goal in this study was to prepare the spiro[2.4]hept-5-ene **3** (Scheme 1), whose structure was suggested by the good activity observed previously with 4,4-dimethylcyclopentene **2**.[19] As shown in Scheme 1, one possible retrosynthetic disconnection of the cyclopropyl ring moiety in **3** leads to a diarylcyclopentenyl diester (**4**). Further disconnection of the cyclopentene ring (route A) gives a diaryldichlorobutene (**5**), which in turn may be derived from the corresponding lactone. Alternatively, disconnection of the double bond in the cyclopentene ring of **4** (route B) leads to **6**, a diketomalonate which is readily accessible from the corresponding bromoacetophenones and dimethyl malonate.

Since both synthetic routes required appropriately substituted bromoacetophenones as starting materials, several traditional methods (as illustrated in Scheme 2) were utilized to prepare the required bromoacetophenones. The initial synthesis of diarylspiro[2.4]cycloheptenes was accomplished according to route A of Scheme 1, and is shown in Scheme 3. The preparation of an early intermediate, the diaryl lactone **15**, was conveniently accomplished by the alkylation of 4-fluorophenylacetic acid with bromide **10** and subsequent ring closure of the resulting ester.[23] DIBAL reduction

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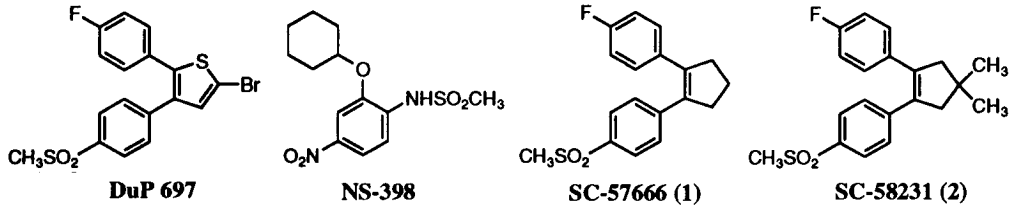
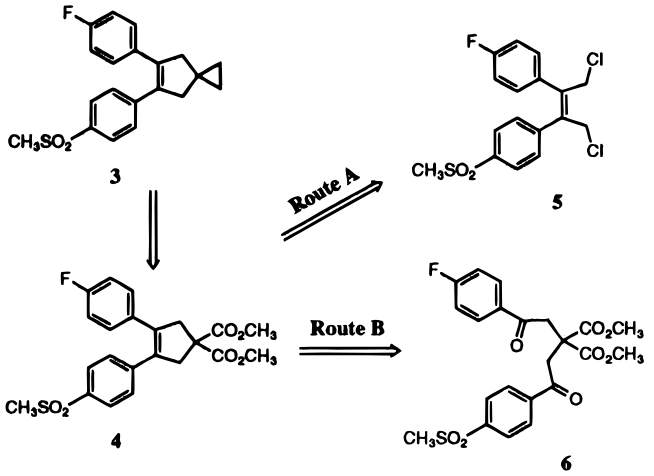
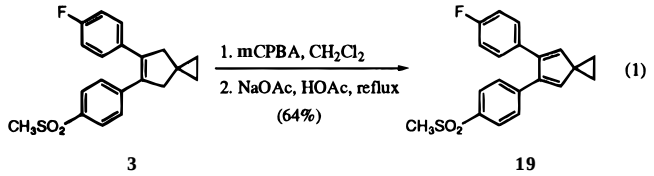


Figure 1. Structures of some selective COX-2 inhibitors.

Scheme 1

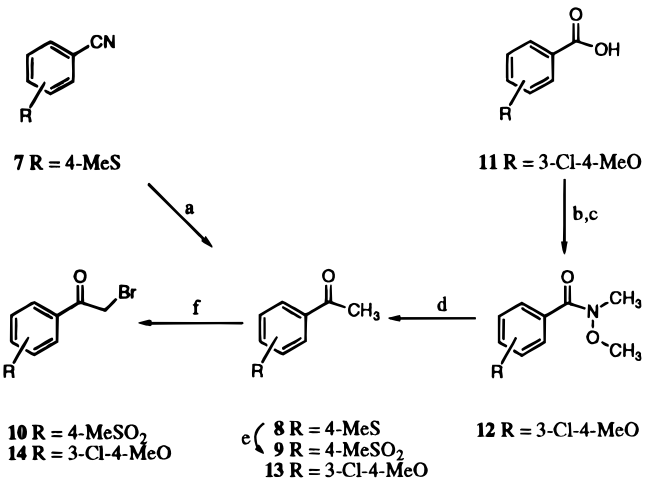


of lactone **15** in THF yielded diol **16**, which was converted to the corresponding dichloride **5** with thionyl chloride in DMF. Cyclopentene ring formation was achieved via double alkylation of dimethyl malonate with dichloride **5** to give the key intermediate **4**.[24] Reduction of diester **4** with DIBAL yielded diol **17**, which was converted to ditosylate **18** and reductively cyclized to give the target compound **3**. Cyclopentadiene analogs were also prepared by epoxidation of cyclopentene **3** with mCPBA followed by AcOH-catalyzed epoxide ring opening and subsequent dehydration to give cyclopentadiene **19** (eq 1).



This initial synthesis of diarylspiro[2.4]cycloheptene **3** was lengthy and involved reduction of lactone **15** with a large excess of DIBAL, which created serious problems during aqueous workup of large-scale reactions. Furthermore, our structure−activity relationship (SAR) study was restricted by the limited commercial availability of substituted phenylacetic acids, one of the starting materials in Scheme 3. An alternative synthetic route (Scheme 1, route B) was therefore developed,[20,22] which was utilized to prepare most of the spiro[2.4]cycloheptene analogs reported in this paper. The general procedure for the preparation of compounds via this route is exemplified in Scheme 4 for the synthesis of the 3-chloro-4-methoxyphenyl compound **20**. The substituted bromoacetophenones needed for this sequence were prepared according to Scheme 2. Bromoacetophenone **10** was treated with dimethyl malonate and powdered K_2CO_3 in THF to give the ketomalonate **21**. Under similar conditions the treatment of

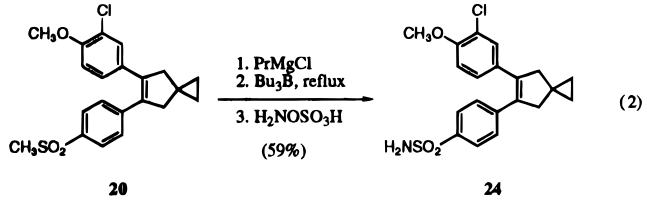
Scheme 2[a]



[a] Reagents: (a) CH_3Li and then aqueous HCl (98%); (b) thionyl chloride, reflux; (c) HN(OMe)Me (HCl salt), Et_3N, CH_2Cl_2 (quantitative, steps b and c); (d) CH_3MgBr (99%); (e) mCPBA (91%); (f) Br_2, HOAc (80−85%).

malonate **21** with an appropriate bromoacetophenone (2-bromo-3′-chloro-4′-methoxyacetophenone (**14**) from Scheme 2) gave the diketomalonate **22**. McMurry reductive cyclization ($TiCl_3$ and Zn)[25] of the diketone **22** yielded the key intermediate **23**, which was carried through a synthetic sequence similar to that shown in Scheme 3 to give the spiro[2.4]cycloheptene **20**.

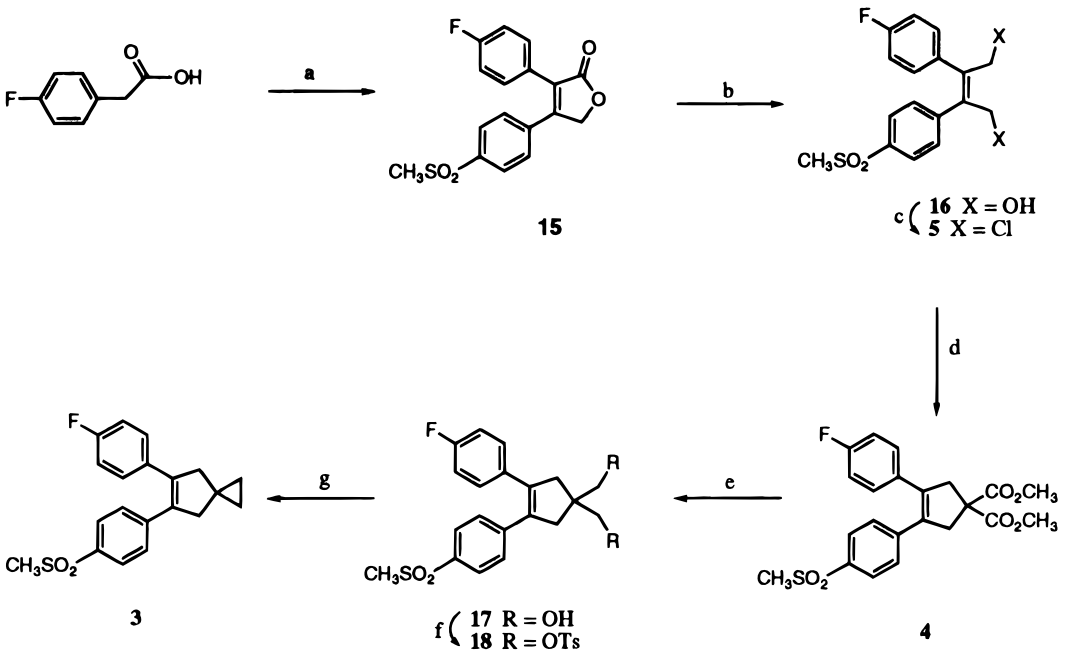
Synthetic routes described above are not suitable for the preparation of spiro[2.4]cycloheptene sulfonamides. Thus, it appeared to us that the most effective access to such compounds would be the direct conversion of the existing methyl sulfones to the corresponding sulfonamides via a one-pot procedure recently developed (eq 2).[26] All of the sulfonamides reported in this paper



were prepared from the corresponding methyl sulfones via this novel conversion. The general procedure for this conversion is exemplified in eq 2 for the synthesis of the 3-chloro-4-methoxyphenyl compound **24**.

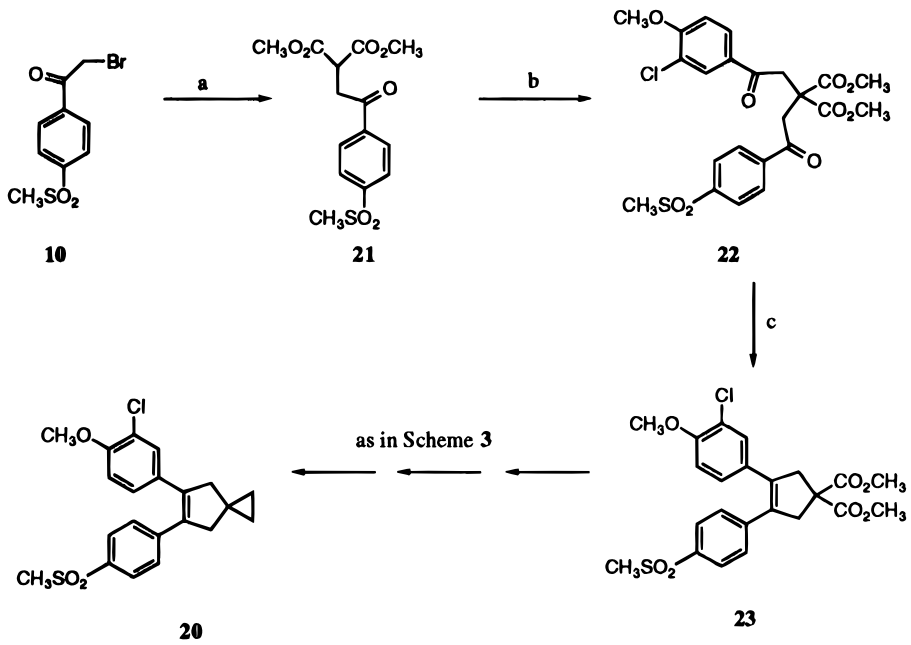
The construction of the cyclopentene ring of spiro[3.4]-cyclooctene, spiro[4.4]cyclononene, and spiro[5.4]cyclodecene was again accomplished by McMurry coupling of the corresponding diketo intermediates, as illustrated in the synthesis of the spiro[2.4]cycloheptene analog **25** (Scheme 5). The starting exo-enone **26** was prepared according to a published method by the condensation of silyl enol ether **27** with the appropriate cyclic ketone

Scheme 3[a]



[a] Reagents: (a) **10**, Et_3N, CH_3CN (68%) and then TsOH, Et_3N, molecular sieves, CH_3CN, reflux (94%); (b) DIBAL, THF (quantitative); (c) thionyl chloride, DMF; (d) dimethyl malonate, LiH, DMF (34% for steps c and d); (e) DIBAL, THF; (f) TsCl, pyridine (66% for steps e and f); (g) NaI, Zn, DMF, 150 °C (85%).

Scheme 4[a]



[a] Reagents: (a) dimethyl malonate, K_2CO_3, KI, THF (63%); (b) **14**, K_2CO_3, KI, THF (73%); (c) $TiCl_3$, Zn, DME, reflux (50%).

(cyclobutanone in this example).[27] The enone **26** was then treated with titanium chloride and the silyl enol ether of (4-methylthio)acetophenone (**8**) to give a diketone methyl sulfide, which was oxidized to the sulfone **28**.[28] McMurry coupling of the diketone **28** gave the desired spirocyclobutyl cyclopentene **25**.

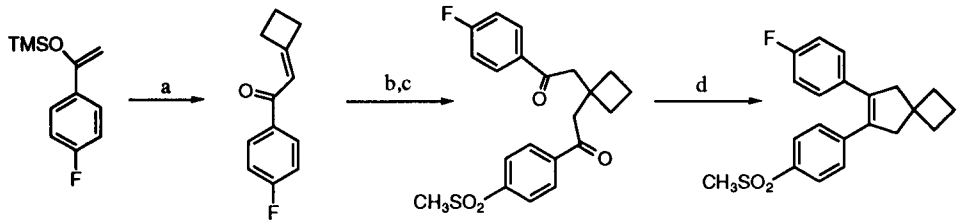
Biology

All compounds were screened by assessing the selectivity of the inhibitors toward human COX-2 and COX-1.[29,30] Compounds with sufficient potency and selectivity for COX-2 were advanced for assessment of oral activity in the rat carrageenan-induced foot-pad edema model.[31,32] Compounds that expressed good oral anti-inflammatory activity in this acute model were then tested more extensively *in vivo* using the chronic adjuvant-induced arthritis model and carrageenan-induced hyperalgesia assay. Compounds showing the most favorable *in vivo* pharmacological properties were referred to more extensive GI toxicity assays and pharmacokinetic studies.

Results and Discussion

***In Vitro* and Primary *in Vivo* Screening Assays.** We theorized that the limited bioavailability (11%) and relatively short duration of action (1.6 h in rats) of

Scheme 5[a]



[a] Reagents: (a) cyclobutanone, $TiCl_4$, CH_2Cl_2 (98%) and then $(CF_3CO)_2O$, 4-DMAP, Et_3N, CH_2Cl_2 (65%); (b) silyl enol ether of **8**, $TiCl_4$, CH_2Cl_2 (81%); (c) mCPBA (97%); (d) $TiCl_3$, Zn, DME, reflux (76%).

Table 1. Comparison of Spiro[2.4]hept-5-ene **3** and Cyclopentene **1**

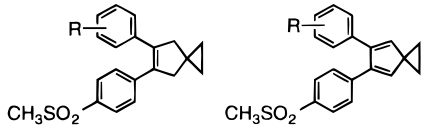
	IC_{50}, μM			
no.[a]	COX-2	COX-1	oral bioavailability,[b] (po, 10 mpk, 24 h)	half-life,[b] h (iv, 10 mpk)
1	0.026	>1000	11	1.6 h
3	0.008	5.4	58	2.3 h

[a] All new compounds were identified by spectroscopic data and confirmed by elemental analysis. [b] For details, see the Experimental Section.

cyclopentene **1** may be due to the metabolic oxidation of the potentially labile allylic methylene groups in the cyclopentene ring (Table 1). It occurred to us that substituents introduced at the 4-position of the cyclopentene ring might exert sufficient steric hindrance to shield the allylic methylene position from enzymatic oxidation and thus slow down potential metabolic degradation of the cyclopentene ring. Hence, 4,4-dimethylcyclopentene **2** (Figure 1) and spiro[2.4]cycloheptene **3** (Table 1) were chosen as our initial targets. Although dimethylcyclopentene **2** was a potent and selective COX-2 inhibitor (IC_{50} = 15 nM and 18.3 μM against COX-2 and COX-1, respectivley),[19] it was less active than cyclopentene **1** in adjuvant-induced arthritis model (51% inhibtion and 75% inhibition at 10 mpk, respectively). We therefore turned our attention to the spiro[2.4]cycloheptene **3**. As compared to **1**, the potency of spiro[2.4]cycloheptene **3** for inhibition of COX-2 was enhanced 3-fold (IC_{50} = 8 nM), while the potency for inhibition of COX-1 was increased almost 200-fold (IC_{50} = 5.4 μM). This compound is nevertheless a very selective COX-2 inhibitor with a selectivity ratio (IC_{50}(COX-1/COX-2)) of 760. More importantly, as shown in Table 1, inhibitor **3** has dramatically improved oral bioavailability (58%) and a somewhat longer duration of action (2.3 h in rats). Notwithstanding these improvements, it was essential for us to explore in depth the structural changes leading to the observed enhancement of COX-1 activity.

We hypothesized that the introduction of a spirocyclopropyl moiety into the cyclopentene ring had rigidified the central ring and restricted its conformational mobility sufficiently to cause a dramatic enhancement in COX-1 activity. On the basis of this assumption, one might expect the spiral cyclopentadiene analogs to be even less selective enzymatically than the corresponding spiral cyclopentenes, due to still greater ring strain and reduced flexibility. On the other hand, increasing the size of the spiro ring should relieve ring strain in the central cyclopentene ring and thus allow for greater conformational mobility, consequently yielding a more selective compound. These expectations were in fact borne out by further experimentation. As shown in

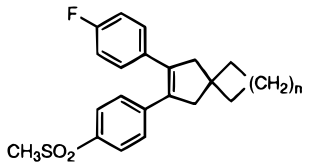
Table 2. Comparison of Spiro[2.4]hept-5-enes A and Spiro[2.4]hepta-4,6-dienes B



			IC_{50},[b] μM		
no.[a]	class	R	COX-2	COX-1	selectivity[c] ratio
3	A	4-fluoro	0.0075	5.4	720
19	B	4-fluoro	0.026	1.32	51
20	A	3-chloro-4-methoxy	0.017	>100	5880
29	B	3-chloro-4-methoxy	0.027	3.38	125

[a] All new compounds were identified by spectroscopic data and confirmed by elemental analysis. [b] For details, see the Experimental Section. [c] Selectivity ratio = IC_{50}(COX-1)/IC_{50}(COX-2).

Table 3. Ring Size Effect of the Spiro[2.4]hept-5-ene

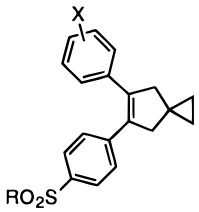


		IC_{50},[b] μM		carrageenan edema[b,c]
no.[a]	*n*	COX-2	COX-1	(po, 30 mpk, % inhibitn)
3	0	0.008	5.4	49
25	1	0.004	>100	23
30	2	0.062	>100	10
31	3	>100	>100	

[a] All new compounds were identified by spectroscopic data and confirmed by elemental analysis. [b] For details, see the Experimental Section. [c] Rat carrageenan foot-pad edema test, oral dosing.

Table 2, cyclopentadiene **19** was less active toward the COX-2 enzyme than **3** and also less selective, with IC_{50} values of 26 nM against COX-2 and 1.32 μM against COX-1. This trend was even more pronounced in the 3-chloro-4-methoxy analogs **20** and **29**. The introduction of the additional double bond decreased the selectivity ratio of cyclopentene **20** from 6000 to 125 for cyclopentadiene **29**. *In vitro* data of inhibitors with increased ring sizes also supported our hypothesis (Table 3). The spirocyclobutyl cyclopentene **25** showed greater COX-2 activity and was more selective for COX-2 than the three-membered ring analog **3**, displaying IC_{50} values of 3.5 nM and >100 μM against COX-2 and COX-1, respectively (Table 3). However, as the ring size was increased further, the COX-2 activity diminished rapidly (62 nM for spirocyclopentyl **30** and >100 μM for spirocyclohexyl **31**). Unfortunately, *in vivo* inhibition of carrageenan-induced edema by the cyclobutyl compound

Table 4. Biological Properties of Some Selected Spiro[2.4]hept-5-enes



no.[a]	X	R	IC50,[b] μM COX-2	IC50,[b] μM COX-1	carrageenan edema,[b,c] (30 mpk, % inhibitn)
3	4-fluoro	CH_3	0.008	5.4	49
32	4-fluoro	NH_2	0.003	0.33	60
33	4-chloro	CH_3	0.001	3.1	
34	4-chloro	NH_2	0.001	0.14	
35	4-methyl	CH_3	0.0015	4.04	
36	4-methoxy	CH_3	0.005	0.57	0
37	4-methoxy	NH_2	0.001	0.005	
38	4-trifluoromethoxy	CH_3	0.135	>100	20
39	4-trifluoromethoxy	NH_2	0.130	1.8	
40	4-trifluoromethyl	CH_3	0.002	>100	35
41	4-trifluoromethyl	NH_2	0.001	0.5	46
42	3-fluoro-4-methoxy	CH_3	0.010	>100	30
43	3-fluoro-4-methoxy	NH_2	0.002	0.48	40
20	3-chloro-4-methoxy	CH_3	0.017	>100	42
24	3-chloro-4-methoxy	NH_2	0.002	2.8	47
44	3-bromo-4-methoxy	CH_3	0.013	>100	21
45	3-bromo-4-methoxy	NH_2	0.002	0.4	
46	3,4-methylenedioxy	CH_3	0.0025	1.4	41
47	3,4-difluoro	CH_3	0.0033	>100	23
48	3,4-difluoro	NH_2	0.003	0.92	18
49	3,4-dichloro	CH_3	0.003	>100	23
50	3,4-dichloro	NH_2	0.001	0.38	47
51	3-chloro-4-fluoro	CH_3	0.007	6.01	38
52	3-chloro-4-fluoro	NH_2	0.0015	0.31	
53	2,4-difluoro	CH_3	0.022	0.74	
54	2,4-dichloro	CH_3	0.033	>100	
55	3,5-dichloro-4-methoxy	CH_3	0.006	>100	44
56	3,5-dichloro-4-methoxy	NH_2	0.004	16.4	

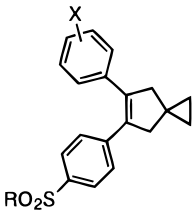
[a] All new compounds were identified by spectroscopic data and confirmed by elemental analysis. [b] For details, see the Experimental Section. [c] Rat carrageenan foot-pad edema test, oral dosing.

25 was not as favorable as for the cyclopropyl compound **3** (23% and 49% inhibition at 30 mpk, respectively). We therefore decided to retain the spiro[2.4]cycloheptene moiety in all further compounds and focused our attention on the preparation of sulfonamide analogs.

In contrast to our previous observations,[19] the sulfonamides in this series generally showed superior *in vivo* pharmacological properties as compared with the corresponding methyl sulfones. However, sulfonamides also showed less selectivity for inhibition of the COX-2 enzyme (Table 4). For example, after the replacement of the sulfone group in **3** with a sulfonamide moiety, the COX-1 activity of **32** was increased 16-fold (IC_{50} = 0.33 μM), whereas the COX-2 activity was increased only 3-fold (IC_{50} = 3 nM). The selectivity ratio (IC_{50}-(COX-1/COX-2)) thus decreased from about 700 for **3** to only 100 for **32**. In the acute carrageenan-induced edema model, the sulfonamide **32** demonstrated better oral antiinflammatory activity than did the methyl sulfone **3** (60% inhibition vs 49% inhibition at 30 mpk, respectively). Since *in vivo* activity depends on highly complex physiological interactions, such activity is often difficult to alter by rational synthesis. Selectivity, on the other hand, is more likely to depend on well-defined structural features amenable to optimization via a SAR study. We therefore decided to retain the benzenesulfonamide moiety to improve *in vivo* pharmacological properties and instead varied the 4′-fluorophenyl group in order to obtain a higher degree of selectivity. We have in fact conducted an extensive SAR using various substituents to replace the 4′-fluoro group on the 5-phenyl ring, which has allowed us to identify compounds with improved *in vivo* properties and greater selectivity (Table 4).

We initially focused our attention on the 4′-monosubstituted phenyl analogs. Replacing the 4′-fluoro substituent in compound **3** (IC_{50}(COX-2/COX-1) = 8 nM/5.4 μM) with 4′-chloro, 4′-methyl, or 4′-methoxy groups afforded inhibitors (**33**, **35**, and **36**) with greater potency for inhibition of COX-2 (IC_{50} = 1, 2, and 5 nM, respectively). While the COX-1 activity did not change significantly for the 4′-chloro and 4′-methyl compounds (IC_{50} = 3.1 and 4.04 μM for **33** and **35**, respectively), the COX-1 activity of the 4′-methoxy analog **36** was enhanced quite dramatically (IC_{50} = 0.57 μM). However, replacement of the 4′-methoxy substituent by a 4′-trifluoromethoxy group provided a selective inhibitor (**38**) with weaker COX-2 potency (135 nM/>100 μM for COX-2/COX-1). It was postulated that the electron-donating character of a methoxy group might have enhanced the COX-1 activity in the case of the 4′-methoxy analog **36**. Such electron-donating potential should be reduced in compound **38** by the electron-withdrawing character of the trifluoromethyl group. To test this hypothesis, we prepared an analog with a strongly electron-withdrawing substituent but without a resonance-donating moiety. The 4′-trifluoromethyl compound **40**, which displayed IC_{50} values of 2 nM for

Table 5. *In Vivo* Pharmacological Properties of Selected Spirocyclopropyl Cyclopentenes



			IC_{50}, μM		AA[b,c]		analg[b,d]	
no.[a]	X	R	COX-2	COX-1	ED_{50}, mpk	% inhib/mpk	ED_{50}, mpk	% inhib/mpk
55	3,5-dichloro-4-methoxy	CH_3	0.006	>100	0.52	57/1	32.7	50/30
42	3-fluoro-4-methoxy	CH_3	0.010	>100		63/2		19/30
20	3-chloro-4-methoxy	CH_3	0.017	>100		12/2	27.7	45/30
24	3-chloro-4-methoxy	NH_2	0.002	2.8	0.21	79/1	35.4	47/30
3	4-fluoro	CH_3	0.008	5.4	0.3	68/1		31/30
41	4-trifluoromethyl	NH_2	0.001	0.45	0.04	92/2	46.7	40/30
50	3,4-dichloro	NH_2	0.001	0.38		72/0.3	31.3	47/30
43	3-fluoro-4-methoxy	NH_2	0.002	0.48	0.08	89/1	40.8	38/30
32	4-fluoro	NH_2	0.003	0.33	0.24	85/1	17.6	34/10

[a] All new compounds were identified by spectroscopic data and confirmed by elemental analysis. [b] Oral dosing. [c] Rat adjuvant arthritis test. For details, see the Experimental Section. [d] Rat carrageenan-induced analgesia test. For details, see the Experimental Section.

COX-2 and >100 μM for COX-1, was indeed a very selective and active COX-2 inhibitor. Unfortunately, it was a weak inhibitor of carrageenan-induced edema (35% inhibition at 30 mpk). Some of the 4′-substituted 5-phenyl compounds in this series were converted to sulfonamides. The increase in COX-1 activity of these compounds ranged from 20-fold (4′-chloro analog **34**) to 200-fold (4′-trifluoromethyl analog **41**). The least selective 4′-methoxy-5-phenyl compound **37** showed high potencies for both COX-1 and COX-2 (1 and 5 nM, respectively). The most selective sulfonamide in this series was the trifluoromethyl compound **41**, displaying a selectivity ratio (IC_{50}(COX-1/COX-2)) of 500. This compound also showed improved *in vivo* activity over the corresponding sulfone **40** (46% inhibition in the edema assay). Of the compounds prepared in this study, the highly active compounds **3**, **32**, and **41** were selected for further pharmacological studies (*vide infra*).

We next directed our attention to the preparation of disubstituted phenyl analogs. While the 4′-methoxy-5-phenyl compound **36** (the methyl sulfone) has high potency for COX-1(IC_{50} = 0.57 μM), the 3′-halo-4′-methoxyphenyl sulfone compounds **42**, **20**, and **44** were surprisingly selective for COX-2 (with IC_{50} values of 10, 17, and 13 nM for COX-2 and >100 μM for COX-1, respectively). As previously suggested in rationalizing the selectivity of the (trifluoromethoxy)phenyl analog **38**, the electron-withdrawing 3′-halo moieties in these compounds are likely to have balanced the electron-donating potential of the methoxy group, thus yielding selective COX-2 inhibitors. On the other hand, replacement of the 3′-halo moiety with another oxygen should not improve selectivity. The dioxymethylene analog **46** thus showed an IC_{50} value of 1.2 μM for COX-1. However, the unique selectivity[33] of the 3′-chloro-4′-methoxyphenyl analog sulfonamide **24** (*vide infra*), when compared with the corresponding 3′-fluoro and 3′-bromo compounds **43** and **45**, respectively, suggests that the selectivity for COX-2 cannot be attributed solely to the electronic effect of various substituents. The 3′-bromo-4′-methoxyphenyl compound **44** demonstrated poor *in vivo* activity (21% inhibition of acute edema at 30 mpk), and this compound was not pursued any further. Both 3-fluoro-4-methoxyphenyl and 3′-chloro-4′-methoxyphenyl analogs **42** and **20** displayed acceptable inhibition in carrageenan edema assay (30% and 42%, respectively). The sulfonamides of these compounds were also prepared to improve their *in vivo* properties. However, COX-1 activities of the sulfonamides were again lowered to the sub-micromolar range for fluoro and bromo analogs **43** and **45** (IC_{50} = 0.48 and 0.4 μM, respectively). The 3′-chloro-4′-methoxy compound **24** was still quite selective (selectivity ratio = 1400), even though it had an IC_{50} of 2.8 μM against COX-1. On the basis of this study, compounds **42**, **43**, **20**, and **24** were chosen for further biological evaluation (*vide infra*).

Several 3′,4′-dihalophenyl analogs (**47**−**52**) were also prepared as both the methyl sulfones and the corresponding sulfonamides. All the 3,4-dihalo compounds (methyl sulfones **47**, **49**, and **51**) were potent inhibitors of COX-2 and either inactive or weakly active toward COX-1. As with other analogs, the methyl sulfones displayed weak *in vivo* activity, while the corresponding sulfonamides showed high COX-1 activity. The 2′,4′-dihalophenyl compounds **53** and **54** did not possess favorable properties either. Among these, only the dichlorophenyl analog **50** was chosen for further evaluation. As an extension of this study, 3′,4′,5′-trisubstituted 5-phenyl compounds were also prepared. Among these, the 3′,5′-dichloro-4′-methoxyphenyl compound **55** (COX-2 IC_{50} = 6 nM, COX-1 IC_{50} > 100 μM) demonstrated good oral activity in the edema assay (44% at 30 mpk). The corresponding sulfonamide **55** was also very selective (4 nM and 16 μM for COX-2 and COX-1, respectively). The sulfone **55** was selected for further study on the basis of its significantly higher selectivity ratio.

Secondary *in Vivo* Pharmacological Studies. A number of COX-2 inhibitors prepared in this study were advanced to secondary *in vivo* pharmacological studies (Table 5). All of these analogs were potent and selective COX-2 inhibitors that displayed good oral antiinflammatory activity in the acute edema assay. Table 5 summarizes the properties of these compounds, listed in order of their selectivity toward COX-2. As expected, the most selective inhibitors were the methyl sulfones. The dichloromethoxyphenyl analog **55** was the most

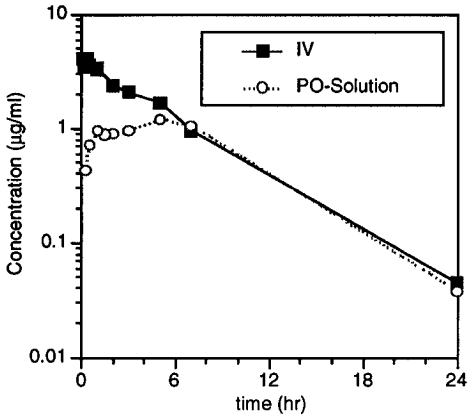


Figure 2. Plasma concentration of **24** after iv and oral administration to the male rat. Compound **24** was administered at 10 mpk in PEG-400:H_2O, 2:1. The plasma half-life was 4 h, and oral bioavailability was 56%.

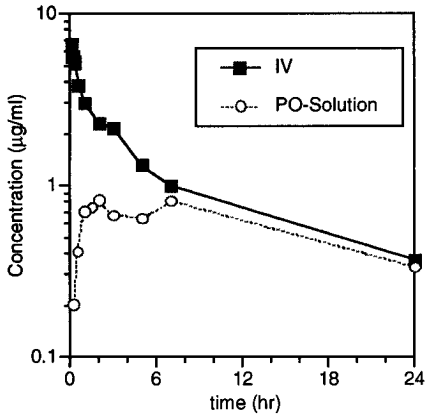


Figure 3. Plasma concentration of **55** after iv and oral administration to the male rat. Compound **55** was administered at 10 mpk in PEG-400:H_2O, 2:1. The plasma half-life was 9.2 h, and oral bioavailability was 58%.

selective compound, with acceptable antiinflammatory activity in the adjuvant-induced arthritis assay (ED_{50} = 0.52 mpk), and **55** was also more active than the 4-fluorophenyl analog **3** in the hyperalgesia assay. The 3′-fluoro- and 3′-chloro-4′-methoxyphenyl compounds **42** and **20** were potent and selective COX-2 inhibitors, although each had shortcomings when assayed *in vivo*. While the 3′-fluoro-4′-methoxyphenyl compound **42** showed weak analgesic activity (19% inhibition at 30 mpk), the 3′-chloro-4′-methoxyphenyl compound **20** was only weakly active in the arthritis assay (12% inhibtion at 2 mpk).

With these observations in hand, we turned to the sulfonamides in a search for improved *in vivo* properties. The only sulfonamide having excellent COX-2 selectivity (1400-fold) was the 3′-chloro-4′-methoxyphenyl analog **24**. This compound was very potent in the adjuvant-induced arthritis assay with an ED_{50} of 0.21 mpk, and it also possessed good analgesic activity (ED_{50} = 35.4 mpk). The 4′-(trifluoromethyl)phenyl analog **41** was the most potent sulfonamide compound in the adjuvant-induced arthritis assay (ED_{50} = 0.04 mpk), although it was only weakly active in the hyperalgesia assay, with an ED_{50} of 46.7 mpk. The 3′-fluoro-4′-methoxyphenyl analog **43** was another compound that was very potent in the arthritis model (ED_{50} = 0.08 mpk) but weakly active in the hyperalgesia assay (ED_{50} = 40.8 mpk). The 4-fluorophenyl compound **32** displayed good potency in the adjuvant-induced arthritis assay (ED_{50} = 0.24 mpk) and also had the best analgesic activity (ED_{50} = 17.6 mpk) from among all synthesized compounds in this series; however, this compound displayed some acute GI toxicity in mice at high doses (200 mpk).

Pharmacokinetics and Gastrointestinal Toxicity Studies. Because of their high selectivity for COX-2, and superior *in vivo* pharmacological properties in the secondary *in vivo* screening assays, compounds **55** and **24** were advanced further to the pharmacokinetics and GI toxicity studies. As shown in Figures 2 and 3, the peak plasma concentrations (C_{max}) following a 10 mpk oral solution dose to the rat were 1.0 μg/mL for **24** and 0.81 μg/mL for **55** and were reached at 1.0 and 2.0 h (T_{max}), respectively. Systemic availability of **24** and **55** following oral solution dose to the rat (10 mpk) was 56% and 58%, respectively. Plasma elimination half-lives of **24** and **55** in the rat were 4.0 and 9.2 h, respectively. With these promising pharmacokinetic data in hand, we turned our attention to establishing a safety profile. The compounds were evaluated in the acute gastric and intestinal toxicity studies (Table 6). Both compounds caused no lesions in the rat gastric study and no significant damage in the mouse gastric toxicity assay at oral doses up to 200 mpk. Compound **24** also caused no intestinal damage in rats at a dose of 200 mpk. Our studies have thus succeeded in identifying two compounds which possess excellent antiinflammatory activity without the toxic effects associated with current NSAIDs.

Table 6. Gastric and Intestinal Toxicity Studies of Compounds **24** and **55**

		gastric[b]		
no.	dose,[a] mpk (ig)	mouse	rat	intestinal[b] (rat)
24	20	1/10[c]	0/6	0/6
24	200	2/10[c]	0/6	0/6
55	20	0/10	0/6	not done
55	200	1/10[c]	0/6	not done

[a] For experimental details, see ref 20. [b] Number of animals with damage/number of animals treated. [c] Not signicant, compared with the control group of animals.

Conclusion

We have designed and synthesized novel, highly potent 5,6-diarylspiro[2.4]hept-5-enes as selective COX-2 inhibitors. Our SAR studies in this series suggest that 3′,4′-disubstituted phenyl analogs are generally more selective than 4′-monosubstituted phenyl analogs. Furthermore, replacement of the methyl sulfone group with a sulfonamide moiety affords compounds with improved *in vivo* pharmacological properties, although with lower COX-2 selectivity. Several compounds have been shown to possess promising pharmacological properties in adjuvant-induced arthritis and edema analgesia models. The absence of GI toxicity at 200 mpk of several selected compounds in rats and mice corresponds well with the weak potency for inhibition of COX-1 observed in the enzyme assay. Methyl sulfone **55** and sulfonamide **24**[34] were shown to have superior *in vivo* pharmacological profiles, low GI toxicity, and good oral bioavailability and duration of action.

Experimental Section

Unless otherwise stated, reactions were carried out under nitrogen and in commercial grade solvents. Solvents were

evaporated on a Büchi rotary evaporator at reduced pressure, unless stated otherwise. Silica gel chromatography was performed on either medium pressure liquid chromatography (MPLC) or preparative high-performance liquid chromatography (Waters Associates, Prep-500A or LC-2000), eluted with EtOAc and hexane. All new compounds were fully characterized, and structures were assigned spectrally and confirmed by elemental analysis. Purity of final products were checked by elemental analyses, and the data are within ±0.4% of the theoretical values. Melting points were determined without correction on a Thomas Hoover Unimelt apparatus. NMR spectra were obtained on a Varian VXR-300 spectrometer at 300 MHz. Abbreviations used in NMR analyses are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets. High-resolution mass spectra (HRMS) were obtained on a Finnigan MAT 90 or VG model 250T spectrometer with FAB or EI ionization. Elemental analyses were obtained from Galbraith Laboratories, Inc.

Biology. Preparation of COX-1 and COX-2 Enzymes and Binding Assay (IC_{50}). Experimental details have been published earlier.[29,30]

Rat Carrageenan Foot-Pad Edema Test.[1,31] The carrageenan foot edema test was performed with materials, reagents, and procedures essentially as described by Winter.[32] Male Sprague−Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over 16 h prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle (0.5% methyl cellulose and 0.025% Tween-20) or with vehicle alone. One hour later a subplantar injection of 0.1 mL of a 1% solution of carrageenan/sterile 0.9% saline was administered. The volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals, and the percent inhibition of edema was determined.

Rat Adjuvant Arthritis Assay.[35] Arthritis was induced in male Lewis rats (125−150 g; Harlan Sprague−Dawley, Indianapolis, IN) by injection of 1 mg of *Mycobacterium butyricum* (Difco Laboratories, Detroit, MI) in 50 uL of mineral oil (Mallinkrodt, Paris, KY) into the right hind foot pad. Fourteen days after injection of adjuvant, the contralateral left foot-pad volume was measured with a water displacement plethysmometer. Animals with paw volumes 0.37 mL greater than normal paws were then randomized into treatment groups. Compounds were prepared as a suspension in 0.5% methyl cellulose (Sigma) and 0.025% Tween-20 (Sigma). Drug administration was begun on day 15 postadjuvant injection and continued until final assessment on day 25. Animals were dosed twice daily by gavage at the indicated dosages in a volume of 1.0 mL/day. During this period contralateral paw volume measurements were taken intermittently. The typical increase in contralateral paw volume measured on day 25 ranged from 1.4 to 1.9 mL.

Rat Carrageenan-Induced Analgesia Test.[31] Male Sprague−Dawley rats were treated as previously described for the Rat Carrageenan Foot-Pad Edema Test. Three hours after the injection of carrageenan, the rats were placed in a special Plexiglass container with a transparent floor having a high-intensity lamp as a radiant heat source, positionable under the floor. After an initial 20 min period, thermal stimulation was begun on either the injected foot or the contralateral uninjected foot. A photoelectric cell turned off the lamp and timer when light was interrupted by paw withdrawal. The time to withdrawal of the injected paw was then measured. The withdrawal latency in seconds was determined for the control and drug-treated groups, and percent inhibition of the stimulus-induced decrease in withdrawal latency was determined.

Gastric and Intestinal Damage Study. The experimental details have been disclosed previously.[31]

Pharmacokinetics and Metabolism Study. Compounds were administered to male Sprague−Dawley rats by tail vein injection or gavage, with 4 animals/group. Multiple blood samples were collected from each rat by retroorbital bleeding into heparinized tubes. Bond Elut C-18 solid phase extraction columns (Varian, 100 mg/1 mL) were activated with CH_3CN, methanol, and water. Columns were loaded with samples, rinsed with water, rinsed with CH_3CN:water (35:65), and eluted with CH_3CN. Acetonitrile extracts were concentrated under nitrogen and resuspended in mobile phase. Acetonitrile extracts were analyzed on a Beckman System Gold HPLC system which included UV and radioisotope detectors. C-18 columns (Waters Novapak, 3.9 × 150 mm) were eluted isocratically with 55:45 CH_3CN:8.3 mM phosphate buffer, pH 7.2 (Sigma P-3288), at 1.0 mL/min, with UV monitoring at 232 nm. Terminal phase elimination half-life was calculated from plasma concentration versus time data using the CSTRIP computer program.[36]

Chemistry. Most of the compounds were prepared using one of the three general procedure sequences described below.

General Procedure I (Route B). Preparation of diarylspiro[2.4]cycloheptenes is illustrated below in the synthesis of 5-(3′-chloro-4′-methoxyphenyl)-6-[4′-(methylsulfonyl)phenyl]-spiro[2.4]hept-5-ene (**20**).

Step 1: 4-(Methylthio)acetophenone (8). To a stirred solution of 98.93 g (0.63 mol) of 4-(methylthio)benzonitrile in 1.2 L of THF under nitrogen at −78 °C was added 568 mL (0.795 mol) of methyllithium (1.4 M in ethyl ether). The resulting dark red solution was warmed to room temperature and stirred for another 2.5 h. The reaction was slowly quenched with 400 mL of 3 N HCl, and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated to about 500 mL, diluted with EtOAc, and washed with saturated Na_2CO_3 and brine. The extract was dried ($MgSO_4$) and concentrated to give 108.5 g (98.5%) of desired acetophenone as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 2.56 (s, 3H), 7.28 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H).

Step 2: 4-(Methylsulfonyl)acetophenone (9). To a solution of 108.5 g (0.653 mol) of acetophenone **8** in 3 L of CH_2Cl_2 at 0 °C was added in portions 414 g (68%, 1.63 mol) of mCPBA over a period of 1 h. The mixture was stirred at room temperature overnight. To the cooled, white suspension was added a solution of 124 g (0.653 mol) of sodium *m*-bisulfite in 300 mL of water, and the mixture was stirred at room temperature for 1 h and then filtered. The filtrate was concentrated to about 1 L and repeatedly washed carefully with saturated $NaHCO_3$ to remove 3-chlorobenzoic acid. The extract was dried ($MgSO_4$) and concentrated to give 117.33 g (91%) of the desired product as a bright yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.67 (s, 3H), 3.08 (s, 3H), 8.05 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H).

Step 3: 2-Bromo-4′-(methylsulfonyl)acetophenone (10). To a stirred solution of 11.91 g (60.5 mmol) of 4-(methylsulfonyl)acetophenone (**9**) in 133 mL of glacial AcOH and 0.11 mL of hydrochloric acid at ambient temperature was added a solution of 8.22 g (51.4 mmol) of bromine in 9.3 mL of glacial AcOH over a period of 3 h. The reaction mixture was diluted with 500 mL of water and extracted with chloroform. The combined extracts were dried ($MgSO_4$) and concentrated to give 15.7 g of crude bromoacetophenone **10** as a solid: ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H), 4.45 (s, 2H), 8.08 (d, J = 9.0 Hz, 2H), 8.17 (d, J = 9.0 Hz, 2H).

Step 4: 3′-Chloro-4′-methoxyacetophenone (13). To a solution of 132.5 g (0.71 mol) of 3-chloro-4-methoxybenzoic acid in 514 mL (7.05 mol) of thionyl chloride was added in portions 2.5 mL of DMF, and the resulting solution was stirred under reflux for 4 h. The mixture was concentrated and dissolved in 600 mL of CH_2Cl_2. To the resulting solution was added 83.1 g (0.85 mol) of *N*,*O*-dimethylhydroxyamine (HCl salt), and the mixture was cooled to 0 °C. To the suspension was added slowly 198 mL (1.4 mL) of triethylamine, and the mixture was stirred at room temperature overnight. The resulting solution was washed twice with 1 N $KHSO_4$, $NaHCO_3$, and brine. The extract was dried ($MgSO_4$) and concentrated to give 163.2 g (quantitative) of desired benzamide **12** as a light brown oil:

^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.56 (s, 3H), 3.94 (s, 3H), 6.93 (d, J = 8.7 Hz, 1H), 7.68 (dd, J = 2.2, 8.7 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H).

To a stirred solution of 64.7 g (0.28 mol) of the resulting benzamide **12** in 1 L of THF under nitrogen at −78 °C was added 110 mL (3 M in ethyl ether, 0.3 mol) of methylmagnesium bromide. The resulting solution was warmed to room temperature and stirred for another 3 h. The reaction was slowly quenched with 3 N HCl and the mixture diluted with EtOAc and washed with saturated $NaHCO_3$ and brine. The extract was dried ($MgSO_4$) and concentrated to give 51.7 g (99%) of the desired product **13** as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 3.97 (s, 3H), 6.96 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 2.2, 8.7 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H).

Step 5: 2-Bromo-3′-chloro-4′-methoxyacetophenone (14). To a solution of 51.7 g (0.28 mol) of acetophenone **13** in 103 mL of glacial AcOH was added 1 mL of concentrated HCl. To the resulting solution was added dropwise a solution of 14.5 mL (0.28 mol) of bromine in 20 mL of glacial AcOH over a period of about 1.5 h, and the resulting dark solution was stirred at room temperature for 2 h. The precipitate was collected by filtration and washed with water. More solid was collected from the filtrate. The combined solid was dried to give 65 g (88%) of the desired product as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 4.37 (s, 2H), 6.99 (d, J = 8.7 Hz, 1H), 7.91 (dd, J = 2.4, 8.7 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H).

Step 6: Dimethyl 2-[2-[4-(Methylsulfonyl)phenyl]-2-oxoethyl]propanedioate (21). Under nitrogen, 161.8 g (87% pure, 0.508 mol) of 2-bromoacetophenone **10** was added to a suspension of 133.44 g (1.01 mol) of dimethyl malonate, 350.5 g (2.54 mol) of K_2CO_3 (powder; Aldrich), and 38.1 g (0.254 mol) of KI in 450 mL of THF, and the resulting suspension was stirred at room temperature for 6 h (exothermic, temperature reached 40 °C in 30 min). The mixture was filtered and concentrated, and the residue was recrystallized from EtOAc. The mother liquor was concentrated and purified by silica gel chromatography (Prep-500, Waters), eluting with 15% of EtOAc in CH_2Cl_2, to give a total of 100 g (63.3%) of dimethyl ketomalonate **21** as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.64 (d, J = 7.05 Hz, 2H), 3.78 (s, 6H), 4.09 (t, J = 7.04 Hz, 1H), 8.05 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H).

Step 7: Dimethyl 2-[2-(3-Chloro-4-methoxyphenyl)-2-oxoethyl]-2-[2-[4-(methylsulfonyl)phenyl]-2-oxoethyl]propanedioate (22). Under nitrogen, to a stirred suspension of 24 g (0.077 mol) of dimethyl ketomalonate **21**, 42 g (0.3 mol) of K_2CO_3 (powder; Aldrich), and 6 g (0.04 mol) of potassium iodide in 85 mL of THF was added 30 g (0.114 mol) of 2-bromoacetophenone **14** in three portions over a 24 h period. The mixture was filtered through a silica gel plug, eluted with 50% of EtOAc in hexane, and concentrated. The residue was purified by silica gel chromatography (Prep-500, Waters), eluting with 33% of EtOAc in hexane, to give 27.8 g (73%) of dimethyl diketomalonate as a white solid. The material was used directly in step 8 without further characterization.

Step 8: 1-[2-(3-Chloro-4-methoxyphenyl)-4,4-dicarbomethoxycyclopenten-1-yl]-4-(methylsulfonyl)benzene (23). To a vigorously stirred suspension of 38.4 g (0.249 mol) of titanium(III) chloride in 400 mL of DME under nitrogen was added 14 g (0.214 mol) of zinc dust (Aldrich), and the resulting mixture was stirred under reflux for 1 h. To the dark solution at reflux was added 27.8 g (0.054 mol) of dimethyl diketomalonate **22**, and the resulting mixture was stirred under reflux for 1 h. The mixture was filtered, concentrated, diluted with EtOAc, washed with water, saturated $NaHCO_3$, and brine, and then dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography to give 13 g (50%) of diarylcyclopentenyl diester as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 3.5−3.6 (m, 4H), 3.80 (s, 6H), 3.88 (s, 3H), 6.77 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 2.2, 8.7 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 1.8, 6.9 Hz, 2H), 7.79 (dd, J = 1.8, 6.8 Hz, 2H).

Step 9: 5-(3-Chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (20). To a solution of 13 g (27.2 mmol) of cyclopentenyl diester **23** in 200 mL of THF under nitrogen at −78 °C was added 100 mL (150 mmol) of DIBAL (1.5 M in toluene) over a period of 30 min. The resulting solution was stirred at −78 °C for 15 min and then at room temperature overnight. The reaction was carefully quenched sequentially with 15 mL of acetone, 30 mL of water (caution: exothermic), and 90 mL of 10% NaOH. The aqueous layer was extracted with EtOAc, and the combined extracts were washed with saturated $NaHCO_3$, 1 N HCl, water, and brine. The extract was dried ($MgSO_4$) and concentrated to give 11.8 g (quantitative) of crude diol as a colorless oil which was used directly in next step: ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 2H), 2.78 (d, J = 10.5 Hz, 4H), 3.04 (s, 3H), 3.83 (s, 4H), 3.87 (s, 3H), 6.76 (d, J = 8.7 Hz, 1H), 6.95 (dd, J = 2.2, 8.7 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 1.8, 6.8 Hz, 2H), 7.77 (dd, J = 1.8, 6.6 Hz, 2H).

To a solution of 11.8 g (26.8 mmol) of crude diarylcyclopentenyl diol (obtained from above) in 92 mL of pyridine under nitrogen at 0 °C was added 23 g (120 mmol) of *p*-toluenesulfonyl chloride in portions (exothermic), and the resulting dark solution was stirred at room temperature overnight. The mixture was concentrated to remove the pyridine, and the residue was dissolved in EtOAc. The solution was washed with water, 1 N HCl, $NaHCO_3$, and brine. The extract was dried ($MgSO_4$), concentrated, and chromatographed to give 11.6 g (59% from diester) of ditosylate as a tan solid: ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 6H), 2.70 (d, J = 15.1 Hz, 4H), 3.04 (s, 3H), 3.88 (s, 3H), 4.03 (s, 4H), 6.74 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 2.2, 8.7 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 7.19 −7.25 (m, 2H), 7.35 (d, J = 8.1 Hz, 4H), 7.7−7.82 (m, 6H). The ditosylate was used in the next step to prepare the final product **20**.

Under nitrogen, a solution of 11.6 g (15.9 mmol) of diarylcyclopentenyl ditosylate in 260 mL of DMF was treated with 34.7 g (231 mmol) of NaI and 17.2 g (263 mmol) of zinc dust. The resulting mixture was stirred at 150 °C for 3 h and concentrated. The residue was dissolved in EtOAc, and the solid was filtered off. The filtrate was washed with sodium sulfite, water, and brine and then dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel to give 5.32 g (86%) of pale yellow solid, which was recrystallized to give 2.32 g of the desired product **20** as a white solid: mp 140.0−140.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.84−2.95 (m, 4H), 3.04 (s, 3H), 3.88 (s, 3H), 6.76 (d, J = 8.5 Hz, 1H), 6.95 (dd, J = 2.0, 8.5 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 1.6, 6.7 Hz, 2H), 7.77 (dd, J = 1.8, 6.6 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{21}ClO_3S$ 388.0900, found 388.0909. Anal. ($C_{21}H_{21}ClO_3S$) C, H, S.

The mother liquor from the recrystallization described above was concentrated to give 3.0 g of pale yellow solid which was used directly in the preparation of compound **24** using general procedure II.

General Procedure II. Using a published procedure[26] the methylsulfonyl group in most of the compounds was converted to a sulfonamidyl group as illustrated in the synthesis of benzenesulfonamide **24**.

4-[6-(3-Chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (24). Under nitrogen, a solution of 3.6 g (9.26 mmol) of **20** in 10 mL of THF at 0 °C was treated with 6.3 mL (10.08 mmol) of propylmagnesium chloride (1.6 M in ether). The reaction mixture was stirred at ambient temperature for 25 min, cooled to 0 °C, and treated with 16.5 mL (1.0 M in THF, 16.5 mmol) of tributylborane (or triethylborane). The resulting solution was stirred at ambient temperature for 15 min and then at reflux for 18 h prior to the addition of 7 g (85 mmol) of NaOAc, 18 mL of water, and 4 g (35 mmol) of hydroxylamine-*O*-sulfonic acid at 0 °C. The resulting light orange mixture was stirred at ambient temperature for 3.5 h, and the resulting aqueous phase was extracted with EtOAc. The combined extracts were washed with water and brine and then dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel to give 2.5 g (59%) of the desired product **24** as a white solid: mp 191.0−192.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 4H), 2.84 (s, 4H), 3.83 (s, 3H), 5.74 (br s, 2H), 6.72 (d, J = 8.5 Hz, 1H), 6.92 (dd, J = 2.0, 8.5 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 2.0, 6.9 Hz, 2H), 7.72 (dd, J = 1.8, 6.7 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{20}ClNO_3S$ 389.0852, found 389.0869. Anal. ($C_{20}H_{20}ClNO_3S \cdot 0.05CH_2Cl_2$) C, H, N, S.

General Procedure III. Preparation of other spirocycloalkyl diarylcyclopentenes (**25**, **30**, and **31**) is illustrated below in the synthesis of diaryl spirocyclobutyl cyclopentene **25**.

Step 1: 1-(4-Fluorophenyl)-2-(cyclobut-1-ylidene)ethan-1-one (26). Under nitrogen, 17.7 g (128 mmol) of 4-fluoroacetophenone (Aldrich) and 20.7 mL (192 mmol) of triethylamine at ambient temperature were treated with 24.4 mL (192.3 mmol) of chlorotrimethylsilane and allowed to stir for 20 min prior to the slow addition of a suspension of 30 g (200 mmol) of NaI in 200 mL of CH_3CN. The reaction mixture was stirred for 3 h, poured into ice/water, and extracted with hexane. The extracts were combined, dried (K_2CO_3), and concentrated to give 27 g of the crude enol ether as an oil: ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 9H), 4.41 (d, J = 2.0 Hz, 1H), 4.84 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 7.53−7.60 (m, 2H).

Under nitrogen, 11.0 g (100 mmol) of $TiCl_4$ in 140 mL of CH_2Cl_2 at 0 °C was slowly treated with a solution of 8.2 mL (110 mmol) of cyclobutanone in 30 mL of CH_2Cl_2 prior to the dropwise addition of a solution of 21.1 g (100 mmol) of the enol ether obtained from above in 15 mL of CH_2Cl_2. The reaction mixture was stirred for 15 min and then poured into 200 mL of ice/water; the phases were separated. The aqueous phase was extracted twice with 30 mL of CH_2Cl_2 and combined with the original CH_2Cl_2 phase. The combined extracts were washed three times with 120 mL of aqueous Na_2CO_3 and once with brine. The extract was dried ($MgSO_4$) and concentrated to give 20.4 g (98%) of the crude alcohol as an oil: ^{1}H NMR ($CDCl_3$) δ 1.53−1.70 (m, 1H), 1.80−1.94 (m, 1H), 1.99−2.10 (m, 2H), 2.17−2.31 (m, 2H), 3.31 (s, 2H), 7.10−7.19 (m, 2H), 7.95−8.03 (m, 2H).

Under nitrogen, 20.3 g (98 mmol) of the alcohol obtained from above, 37 mL (260 mmol) of triethylamine, and 50 mg of 4-(dimethylamino)pyridine (DMAP) in 80 mL of CH_2Cl_2 at 0 °C was slowly treated with a solution of 16.6 mL (118 mmol) of trifluoroacetic anhydride (TFAA) in 40 mL of CH_2Cl_2. The reaction mixture was allowed to stir for 3 h at 0 °C and then allowed to warm to ambient temperature to stir for an additional 3 h prior to the addition of 200 mL of saturated $NaHCO_3$:water (1:1) and 300 mL of ether. The phases were separated, and the aqueous phase was extracted twice with 100 mL of ether. The ether extracts were combined with the original ether/CH_2Cl_2 phase, washed with brine, dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography (Waters Prep-500A) with EtOAc:hexane (2:98) gave 12.1 g (65%) of the desired enone **26** as an oil: ^{1}H NMR ($CDCl_3$) δ 2.11−2.24 (m, 2H), 2.95 (t, J = 8.0 Hz, 2H), 3.19−3.29 (m, 2H), 2.68−2.74 (m, 1H), 7.05−7.16 (m, 2H), 7.84−7.97 (m, 2H).

Step 2: 1-(4-Fluorophenyl)-2-[1-[2-[4-(methylthio)phenyl]-2-oxoethyl]cyclobut-1-yl]ethan-1-one (28). Under nitrogen, 11.0 g (66.2 mmol) of 4-(methylthio)acetophenone (**8**) (from general procedure I, step 1) and 13.8 mL (99 mmol) of triethylamine in 50 mL of CH_3CN were treated with 12.6 mL (99.3 mmol) of chlorotrimethylsilane at ambient temperature and allowed to stir for 20 min prior to the slow addition of a suspension of 14.9 g (99.4 mmol) of NaI in 60 mL of CH_3CN. The reaction mixture was stirred for 3 h, poured into ice/water, and extracted with hexane. The extracts were combined, dried (K_2CO_3), and concentrated to give 16 g of the crude enol ether as an oil: ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 2.48 (s, 3H), 4.39 (d, J = 2.0 Hz, 1H), 4.87 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H).

Under nitrogen, 7.2 mL (70.2 mmol) of $TiCl_4$ in 100 mL of CH_2Cl_2 at −78 °C was slowly treated with a solution of 12.1 g (63.8 mmol) of enone **26** in 30 mL of CH_2Cl_2 followed by the addition of a solution of silyl enol ether obtained from above in 40 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 1 h, poured into a solution of 22 g of $NaHCO_3$ in 160 mL of water, and filtered through Celite. The phases were separated, and the aqueous phase was extracted twice with 40 mL of CH_2Cl_2. The extracts were combined with the original CH_2Cl_2 phase, washed with brine, dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography (Waters Prep-500A) with EtOAc:hexane (10:90) gave the desired product **28** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.91−2.04 (m, 2H), 2.11 (t, J = 8.0 Hz, 4H), 2.49 (s, 3H), 3.48 (s, 2H), 3.49 (s, 2H), 7.08 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 8.0 Hz, 2H), 7.84 (d, J = 9.0 Hz, 2H), 7.91−7.99 (m, 2H).

Step 3: 6-(4-Fluorophenyl)-7-[4-(methylsulfonyl)phenyl]-spiro[3.4]oct-6-ene (25). A solution of 18.3 g (51.4 mmol) of methyl sulfide **28** in 200 mL of chloroform at 10 °C was slowly treated with 35.6 g (ca. 103 mmol) of solid mCPBA (50−60%). The reaction mixture was allowed to stir for 30 min and treated with aqueous sodium bisulfite. The chloroform was removed and the residue partitioned between EtOAc and water. The EtOAc extract was washed three times with saturated Na_2CO_3 and once with brine, dried ($MgSO_4$), and concentrated to give 19.27 g (97%) of the crude diketone product as an oil: ^{1}H NMR ($CDCl_3$) δ 1.95−2.06 (m, 2H), 2.11 (t, J = 7.0 Hz, 4H), 3.05 (s, 3H), 3.52 (s, 2H), 3.59 (s, 2H), 7.09 (t, J = 9.0 Hz, 2H), 7.92−8.04 (m, 4H), 8.19 (d, J = 9.0 Hz, 2H).

Under nitrogen, 16.3 mL (149 mmol) of $TiCl_4$ was slowly added to a suspension of 19.5 g (298 mmol) of zinc dust in 500 mL of anhydrous THF at −78 °C. The resulting mixture was allowed to warm to ambient temperature and then to stir at reflux for 45 min. The reaction mixture was cooled to ambient temperature prior to the addition of 19.27 g (49.6 mmol) of neat diketone (obtained from above) by syringe. The reaction mixture was allowed to stir at ambient temperature overnight, filtered through Celite, and concentrated. The residue was partitioned between EtOAc and water; the EtOAc phase was washed with brine, dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography (Waters Prep-500A) with EtOAc:hexane (20:80) gave 13.5 g (76%) of the desired product **25** as a colorless solid: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 1.85−1.98 (m, 2H), 2.08 (t, J = 7.0 Hz, 4H), 2.98 (s, 4H), 3.04 (s, 3H), 6.92 (t, J = 9.0 Hz), 7.05−7.13 (m, 2H), 7.30 (t, J = 8 Hz, 2H), 7.75 (t, J = 8.0 Hz, 2H); MS (FAB) *m/e* 357 (M + H). Anal. ($C_{21}H_{21}FO_2S$) C, H, F, S.

Preparation of 5-(4-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (3) (Route A). Step 1: 3-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-5*H*-furan-2-one (15). To a stirred solution of 4.45 g (28.9 mmol) of 4-fluorophenylacetic acid (Aldrich) in 3.26 g (31.8 mmol) of triethylamine and 275 mL of CH_3CN was added 8.9 g (28.9 mmol) of 2-bromo-4′-(methylsulfonyl)acetophenone (**10**) (from general procedure I, step 3) at ambient temperature. The reaction mixture was stirred for 30 min, concentrated, and partitioned between EtOAc and water. The organic phase was dried ($MgSO_4$) and concentrated. Purification by silica gel chromatography with EtOAc:hexane (1:1) gave 6.87 g (68%) of the desired ester as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.79 (s, 2H), 5.35 (s, 2H), 7.06 (s, t, J = 9.0 Hz, 2H), 7.32 (dd, J = 6.0, 9.0 Hz, 2H), 8.06 (s, 4H).

Under nitrogen, 4.10 g (11.7 mmol) of the ester obtained from above, 6.52 mL (46.8 mmol) of triethylamine, 4.89 g (25.7 mmol) of *p*-toluenesulfonic acid, and 12 g of 4 Å molecular sieves were added to 117 mL of CH_3CN and stirred at reflux for 16 h. The reaction mixture was concentrated and the residue partitioned between dichloromethane and water. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated. Recrystallization from hexane:EtOAc (2:1) gave 3.65 g (94%) of the desired product **15** as a solid: mp 166−167 °C; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 5.19 (s, 2H), 7.10 (t, J = 9.0 Hz, 2H), 7.42 (dd, J = 6, 9.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H); HRMS calcd for $C_{17}H_{13}FO_4S$ 332.0519, found 332.0501. Anal. ($C_{17}H_{13}FO_4S$) C, H, O.

Step 2: 2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1,4-dihydroxy-2-butene (16). To a solution of 3.08 g (9.28 mmol) of furanone **15** in 93 mL of THF at −78 °C under an atmosphere of nitrogen was added 20 mL (30 mmol) of diisobutylaluminum hydride (DIBAL) (1.5 M in THF) over 10 min. The solution was stirred at −78 °C for 20 min, allowed to warm to ambient temperature, and stirred overnight. An additional 15 mL (22 mmol) aliquot of DIBAL was added, and stirring was continued for 2 h. The reaction mixture was cooled to −78 °C, treated dropwise with 25 mL of acetone, warmed to room temperature, and slowly treated with 25 mL of water. The mixture was stirred for 30 min prior to the careful addition of 35 mL of 1.2 N NaOH. The mixture was extracted with EtOAc, washed with 1 N HCl followed by brine,

dried ($MgSO_4$), and concentrated to give 3.8 g of the crude desired diol **16** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.98 (s, 3H), 4.60 (d, J = 6.0 Hz, 4H), 6.80 (t, J = 9.0 Hz, 2H), 6.94−7.02 (m, 2H), 7.22 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H).

Step 3: 2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1,4-dichloro-2-butene (5). To a solution of 3.5 g (7.62 mmol) of crude **16** in 58 mL of DMF at 5 °C under an atmosphere of nitrogen was added dropwise 1.52 mL (20.84 mmol) of thionyl chloride. The reaction mixture was stirred at 5 °C for 22 h and at ambient temperature for an additional 8 h and then concentrated. The residue was partitioned between EtOAc and water; the EtOAc phase was dried ($MgSO_4$) and concentrated to give the crude desired product as a solid: ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 3H), 4.55 (d, J = 3.4 Hz, 4H), 6.86 (t, J = 9.0 Hz, 2H), 6.75 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 9.0 Hz, 2H).

Step 4: 1-[2-(4-Fluorophenyl)-4,4-dicarbomethoxycyclopenten-1-yl]-4-(methylsulfonyl)benzene (4). To a solution of 1.2 mL (10.5 mmol) of dimethyl malonate in 10 mL of DMF under an atmosphere of nitrogen was added 215 mg (26.9 mmol) of lithium hydride in portions. The resulting suspension was stirred at ambient temperature for 20 min prior to the addition of a solution of crude dichloride **5** in 10 mL of DMF. The reaction mixture was stirred at ambient temperature for 15 h, treated with another 150 mg (18.8 mmol) of lithium hydride, and stirred for another 4 h. The mixture was concentrated and partitioned between EtOAc and water; the organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel to give 1.1 g (34%) of the desired diester **4** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 3H), 3.55 (s, 4H), 3.79 (s, 6H), 6.93 (t, J = 9.0 Hz, 2H), 7.11 (dd, J = 6, 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H).

Step 5: 1-[2-(4-Fluorophenyl)-4,4-bis(hydroxymethyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (17). Following a procedure similar to step 9 of general procedure I, diester **4** was reduced to alcohol **17** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.82 (d, J = 5.0 Hz, 4H), 3.04 (s, 3H), 3.86 (d, J = 5.0 Hz, 4H), 6.94 (t, J = 9.0 Hz, 2H), 7.11 (dd, J = 5, 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H).

Step 6: 1-[2-(4-Fluorophenyl)-4,4-bis(tosylmethyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (18). Following a procedure similar to step 9 of general procedure I, diol **17** was converted to ditosylate **18** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 6H), 2.73 (s, 3H), 3.04 (s, 3H), 4.05 (s, 4H), 6.85−7.0 (m, 4H), 7.20 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 4H), 7.75 (d, J = 8.0 Hz, 6H).

Step 7: 5-(4-Fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (2). Following a procedure similar to step 9 of general procedure I, ditosylate **18** was reductively cyclized to **3** as a colorless solid: mp 140.5−142.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.92 (s, 4H), 3.04 (s, 3H), 6.93 (t, J = 9.0 Hz, 2H), 7.10 (dd, J = 5, 9.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H); HRMS calcd for $C_{20}H_{19}FO_2S$ 342.1090, found 342.1126. Anal. ($C_{20}H_{19}FO_2S$) C, H, F, S.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]spiro[4.4]non-2-ene (30). Following a procedure similar to the one described in general procedure III, with the substitution of cyclopentanone for cyclobutanone, the desired product was obtained as a colorless solid: mp 142−143 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 8H), 2.83 (s, 4H), 3.04 (s, 3H), 6.93 (t, J = 9.0 Hz, 2H), 7.10 (dd, J = 5, 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H); HRMS calcd for $C_{22}H_{23}FO_2S$ 370.1403, found 370.1411. Anal. ($C_{22}H_{23}FO_2S$) C, H, F, S.

2-(4-Fluorophenyl)-3-[4-(methylsulfonyl)phenyl]spiro[4.5]dec-2-ene (31). Following a procedure similar to the one described in general procedure III, with the substitution of cyclohexanone for cyclobutanone, the desired product was obtained as a colorless glass: ^{1}H NMR ($CDCl_3$) δ 1.41−1.63 (m, 10H), 2.72 (s, 4H), 3.03 (s, 3H), 6.92 (t, J = 8.7 Hz, 2H), 7.05−7.12 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H); HRMS calcd for $C_{23}H_{25}FO_2S$·Li 391.1719, found 391.1690. Anal. ($C_{23}H_{25}FO_2S$·0.08C_6H_8) C, H, F, S.

4-[6-(4-Fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (32). Following general procedure II, **3** was converted to **32** as a colorless solid: mp 131.0−133.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.90 (s, 3H), 4.81 (s, 2H), 6.92 (t, J = 9.0 Hz, 2H), 7.11 (dd, J = 6, 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H); HRMS calcd for $C_{19}H_{18}FNO_2S$ 344.1121, found 344.1122. Anal. ($C_{19}H_{18}FNO_2S$·0.1$CH_3CO_2CH_2CH_3$) C, H, N, S.

5-(4-Chlorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (33). Following a procedure similar to the one described in general procedure I, with the substitution of 2-bromo-4′-chloroacetophenone (Aldrich) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 143.0−145.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.92 (s, 4H), 3.05 (s, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.77 (dd, J = 8.7 Hz, 2H); MS (FAB) *m/e* 365 (100, M + Li). Anal. ($C_{20}H_{19}ClO_2S$) C, H, Cl, S.

4-[6-(4-Chlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (34). Following a procedure similar to the one described in general procedure II, 7.5 g (20.9 mmol) of **33** was converted to crude sulfonamide. Purification by silica gel chromatography gave 2.82 g (37%) of the desired product as a white solid: mp 152.5−153.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.91 (s, 4H), 4.85−5.05 (br s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); HRMS (EI) calcd for $C_{19}H_{18}ClNO_2S$ 359.0747, found 359.0747. Anal. ($C_{19}H_{18}ClNO_2S$) C, H, Cl, N, S.

5-(4-Methylphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (35). Following a procedure similar to the one described in general procedure I, with the substitution of 2-bromo-4′-methylacetophenone (Aldrich) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 4H), 2.32 (s, 3H), 2.91 (s, 4H), 3.03 (s, 3H), 7.04 (s, 4H), 7.34 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{22}O_2S$ 338.1341, found 338.1323. Anal. ($C_{21}H_{22}O_2S$) C, H, S.

5-(4-Methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (36). Following a procedure similar to the one described in general procedure I, with the substitution of 2-bromo-4′-methoxyacetophenone (Aldrich) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 170.2−173.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 4H), 2.91 (s, 4H), 3.04 (s, 3H), 3.79 (s, 3H), 6.77 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{22}O_3S$ 354.1290, found 354.1317. Anal. ($C_{21}H_{22}O_3S$) C, H, S.

4-[6-(4-Methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (37). Following a procedure similar to the one described in general procedure II, 200 mg (0.564 mmol) of **36** was converted to crude sulfonamide. Purification by silica gel chromatography gave 96 mg (48%) of the desired product as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 4H), 2.90 (s, 4H), 3.78 (s, 3H), 4.86 (br s, 2H), 6.76 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H). HRMS (EI) calcd for $C_{20}H_{21}NO_3S$ 355.1242, found 355.1250. Anal. ($C_{20}H_{21}NO_3S$·0.6H_2O) C, H, N.

5-[4-(Trifluoromethoxy)phenyl]-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (38). Following a procedure similar to the one described in general procedure I, with the substitution of 4′-(trifluoromethoxy)acetophenone (Aldrich) for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 126.0−127.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.93 (s, 4H), 3.05 (s, 3H), 7.08 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{19}F_3O_3S$ 408.1007, found 408.1017. Anal. ($C_{21}H_{19}F_3O_3S$·0.12H_2O) C, H, F, S.

4-[6-[4-(Trifluoromethoxy)phenyl]spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (39). Following a procedure similar to the one described in general procedure II, 1.80 g (4.4 mmol) of **38** was converted to crude sulfonamide. Purification by silica gel chromatography gave 0.73 g (40%) of the desired product as a white solid: mp 144.0−145.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.92 (s, 4H), 4.78 (br s, 2H), 7.08 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.76 (d,

J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}F_3NO_3S$ 409.0960, found 409.0974. Anal. ($C_{20}H_{18}F_3NO_3S \cdot 0.29C_3H_6O_2$) C, H, N, F, S.

5-[4-(Trifluoromethyl)phenyl]-6-[4-(methylsulfonyl)-phenyl]spiro[2.4]hept-5-ene (40). Following a procedure similar to the one described in general procedure I, with the substitution of 4-(trifluoromethyl)acetophenone [prepared by the addition of methyllithium to α,α,α-trifluoro-*p*-tolunitrile (Aldrich), see general procedure I, step 1] for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 170.0−170.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 4H), 2.95 (s, 4H), 3.05 (s, 3H), 7.24 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{19}F_3O_2S$ 392.1058, found 392.1080. Anal. ($C_{21}H_{19}F_3O_2S$) C, H, F, S.

4-[6-[4-(Trifluoromethyl)phenyl]spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (41). Following a procedure similar to the one described in general procedure II, 1.81 g (4.6 mmol) of **40** was converted to crude sulfonamide. Purification by silica gel chromatography gave 1.20 g (66%) of the desired product as a white solid: mp 157.2−188.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 4H), 2.94 (s, 4H), 4.80 (s, 2H), 7.21−7.30 (m, 4H), 7.48 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}F_3NO_2S$ 393.1010, found 393.1045. Anal. ($C_{20}H_{18}F_3NO_2S \cdot 0.07CH_2Cl_2$) C, H, N, S.

5-(3-Fluoro-4-methoxyphenyl)-6-[4-(methylsulfonyl)-phenyl]spiro[2.4]hept-5-ene (42). Following a procedure similar to the one described in general procedure I, with the substitution of 3′-fluoro-4′-methoxyacetophenone (Aldrich) for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 110.5−111.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.85−2.95 (m, 4H), 3.05 (s, 3H), 3.87 (s, 3H), 6.77−6.94 (m, 3H), 7.35 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{21}FO_3S$ 372.1192, found 372.1187. Anal. ($C_{21}H_{21}FO_3S$) C, H, F, S.

4-[6-(3-Fluoro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (43). Following a procedure similar to the one described in general procedure II, 1.40 g (3.76 mmol) of **42** was converted to crude sulfonamide. Purification by silica gel chromatography gave 0.88 g (63%) of the desired product as a white solid: mp 153.0−154.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.89 (s, 4H), 3.87 (s, 3H), 4.79 (s, 2H), 6.75−6.93 (m, 3H), 7.31 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{20}FNO_3S$ 373.1148, found 373.1172. Anal. ($C_{20}H_{20}FNO_3S$) C, H, F, N.

5-(3-Bromo-4-methoxyphenyl)-6-[4-(methylsulfonyl)-phenyl]spiro[2.4]hept-5-ene (44). Following a procedure similar to the one described in general procedure I, with the substitution of 3′-bromo-4′-methoxyacetophenone [prepared by the addition of methylmagnesium bromide to 3-bromo-4-methoxybenzaldehyde (Aldrich) followed by MnO_2 oxidation of the resulting alcohol] for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 89.5−91.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.85−2.93 (m, 4H), 3.04 (s, 3H), 3.87 (s, 3H), 6.73 (d, J = 8.7 Hz, 1H), 6.97 (dd, J = 2.5, 7.5 Hz, 1H), 7.3−7.4 (m, 3H), 7.78 (d, J = 8.5 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{21}BrO_3S$ 432.0395, found 432.0375. Anal. ($C_{21}H_{21}BrO_3S \cdot 0.64CH_2Cl_2$) C, H, Br.

4-[6-(3-Bromo-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (45). Following a procedure similar to the one described in general procedure II, 3 g (6.92 mmol) of **44** was converted to crude sulfonamide. Purification by silica gel chromatography gave 1.32 g (44%) of the desired product as a white solid: mp 187.5−189.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 4H), 2.89 (s, 4H), 3.87 (s, 3H), 4.76 (br s, 2H), 6.73 (d, J = 8.5 Hz, 1H), 7.0 (dd, J = 2.1, 8.5 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.37 (dd, J = 2.1 Hz, 1H), 7.76 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{20}BrNO_3S$ 433.0347, found 433.0310. Anal. ($C_{20}H_{20}BrNO_3S$) C, H, N.

5-[6-[4-(Methylsulfonyl)phenyl]spiro[2.4]hept-5-en-5-yl]-1,3-benzodioxole (46). Following a procedure similar to the one described in general procedure I, with the substitution of 3′,4′-(methylenedioxy)acetophenone [prepared by the addition of methyllithium to piperonylonitrile (Aldrich), see general procedure I, Step 1] for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 110.5−111.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 4H), 2.89 (br d, J = 2.4 Hz, 4H), 3.05 (s, 3H), 5.94 (s, 2H), 6.55−6.67 (m, 2H), 6.70 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{20}O_4S$ 368.1082, found 368.1077. Anal. ($C_{21}H_{20}O_4S$) C, H, S.

5-(3,4-Difluorophenyl)-6-[4-(methylsulfonyl)phenyl]-spiro[2.4]hept-5-ene (47). Following a procedure similar to the one described in general procedure I with the substitution of 3′,4′-difluoroacetophenone (Aldrich) for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was obtained as a white solid: mp 113−114 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.90 (s, 2H), 2.92 (s, 2H), 3.06 (s, 3H), 6.80−6.87 (m, 1H), 6.91−7.07 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H); HRMS calcd for $C_{20}H_{18}F_2O_2S$ 360.0996, found 360.1014. Anal. ($C_{20}H_{18}F_2O_2S$) C, H, N, F, S.

4-[6-(3,4-Difluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (48). Following a procedure similar to the one described in general procedure II, 880 mg (2.44 mmol) of **47** was converted to crude sulfonamide. Purification by silica gel chromatography (MPLC) with EtOAc:hexane (1:5) as the eluent followed by recrystallization from CH_2Cl_2/hexane gave 370 mg (42%) of the desired product as a white solid: mp 136−137 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.89 (s, 2H), 2.90 (s, 2H), 4.79 (s, 2H), 6.81−6.87 (m, 1H), 6.91−7.06 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H); MS (FAB) m/z 362 (M + H); HRMS calcd for $C_{19}H_{17}F_2NO_2S$ 361.0948, found 361.0952. Anal. ($C_{19}H_{17}F_2NO_2S \cdot 0.29CH_2Cl_2$) C, H, N, F, S.

5-(3,4-Dichlorophenyl)-6-[4-(methylsulfonyl)phenyl]-spiro[2.4]hept-5-ene (49). Following a procedure similar to the one described in general procedure I, with the substitution of 2-bromo-3′,4′-dichloroacetophenone (Lancaster) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 107.5−108.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.91 (d, J = 3.0 Hz, 4H), 3.05 (s, 3H), 6.90 (dd, J = 1.9, 8.7 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H); MS (FAB) m/z 399 (100, M + Li). Anal. ($C_{20}H_{18}Cl_2O_2S \cdot 0.08C_6H_{14}$) C, H, Cl, S.

4-[6-(3,4-Dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (50). Following a procedure similar to the one described in general procedure II, 5.20 g (13.2 mmol) of **49** was converted to crude sulfonamide. Purification by silica gel chromatography gave 1.40 g (27%) of the desired product as a white solid: mp 162.0−163.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.90 (d, J = 2.1 Hz, 4H), 4.77 (s, 2H), 6.92 (dd, J = 2.1, 8.4 Hz, 1H), 7.23−7.32 (m, 4H), 7.78 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{19}H_{17}Cl_2NO_2S$ 393.0357, found 393.0354. Anal. ($C_{19}H_{17}Cl_2NO_2S \cdot 0.035C_6H_{14}$]) C, H, N, Cl, S.

5-(3-Chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (51). Following a procedure similar to the one described in general procedure I, with the substitution of 3′-chloro-4′-fluoroacetophenone (Lancaster) for 3′-chloro-4′-methoxyacetophenone (general procedure I, step 5), the desired product was prepared as a white solid: mp 128.0−130.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.91 (d, J = 3.6 Hz, 4H), 3.05 (s, 3H), 6.9−7.02 (m, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}ClFO_2S$ 376.0700, found 376.0710. Anal. ($C_{20}H_{18}ClFO_2S$) C, H, F, Cl, S.

4-[6-(3-Chloro-4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]-benzenesulfonamide (52). Following a procedure similar to the one described in general procedure II, 1.0 g (2.65 mmol) of **51** was converted to crude sulfonamide. Purification by silica gel chromatography gave 0.19 g (19%) of the desired product as a white solid: mp 163.0−165.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.90 (d, J = 2.7 Hz, 4H), 4.75 (br s, 2H), 6.70−7.05 (m, 2H), 7.18−7.24 (m, 1H), 7.24−7.32 (m, 3H), 7.78 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{19}H_{17}ClFNO_2S$ 377.0652, found 377.0639. Anal. ($C_{19}H_{17}ClFNO_2S \cdot 0.018CH_2Cl_2$) C, H, N, F, Cl, S

5-(2,4-Difluorophenyl)-6-[4-(methylsulfonyl)phenyl]-spiro[2.4]hept-5-ene (53). Following a procedure similar to the one described in general procedure I, with the substitution of 2-chloro-2′,4′-difluoroacetophenone (Aldrich) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 116.0−117.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.89 (s, 2H), 2.94 (s, 2H), 3.03 (s, 3H), 6.78 (t, J = 8.4 Hz, 2H), 7.05 (q, J = 6.6 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.74 (dd, J = 1.8, 6.9 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}F_2O_2S$ 360.0996, found 360.1010. Anal. ($C_{20}H_{18}F_2O_2S\cdot0.22H_2O$) C, H, S.

5-(2,4-Dichlorophenyl)-6-[4-(methylsulfonyl)phenyl]-spiro[2.4]hept-5-ene (54). Following a procedure similar to the one described in general procedure I, with the substitution of 2,2′,4′-trichloroacetophenone (Aldrich) for 2-bromo-3′-chloro-4′-methoxyacetophenone (general procedure I, step 7), the desired product was prepared as a white solid: mp 90.0−91.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.85 (s, 2H), 2.95 (s, 2H), 3.01 (s, 3H), 7.02 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 2.1 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}Cl_2O_2S$ 392.0405, found 392.0423. Anal. ($C_{20}H_{18}Cl_2O_2S\cdot0.36H_2O\cdot0.05C_6H_{14}$) C, H, Cl, S.

5-(3,5-Dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)-phenyl]spiro[2.4]hept-5-ene (55). Under nitrogen, a mixture of 41.4 g (0.200 mol) of 3-chloro-4-hydroxybenzoic acid, 75 mL (1.2 mol) of iodomethane, and 81.5 g (0.25 mol) of K_2CO_3 in 250 mL of DMF was stirred at 55 °C for 18 h. The reaction mixture was filtered and concentrated. The residue was dissolved in EtOAc, washed with water and brine, and then dried ($MgSO_4$) and concentrated. The residue was dissolved in 84 mL of methanol and 84 mL of 2.5 N NaOH, and the resulting mixture was stirred at reflux for 4 h. The reaction mixture was concentrated. The residue was dissolved in 600 mL of water, and the pH was adjusted to 2 with concentrated HCl. The solution was extracted with EtOAc, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 38.12 g (89%) of 3,5-dichloro-4-methoxybenzoic acid as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.98 (s, 2H).

Following a procedure similar to the one described in general procedure I, with the substitution of 3,5-dichloro-4-methoxybenzoic acid (obtained from above) for 3-chloro-4-methoxybenzoic acid (general procedure I, step 4), an unexpected demethylated phenol product was isolated instead of the expected product **55**. The phenol product was recrystallized as a white solid: mp 163.5−164.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.88 (br d, J = 12.5 Hz, 4H), 3.05 (s, 3H), 5.83 (s, 2H), 7.02 (s, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{18}Cl_2O_3S$ 408.0354, found 408.0349. Anal. ($C_{20}H_{18}Cl_2O_3S$) C, H, Cl, S.

Under nitrogen, a mixture of 0.2 g (0.49 mmol) of the phenol obtained from above, 91 mL (1.5 mmol) of iodomethane, and 0.32 g (1 mmol) of cesium carbonate in 6 mL of DMF was stirred at 25 °C for 16 h. The reaction mixture was diluted in EtOAc, washed with water and brine, and then dried ($MgSO_4$) and concentrated. The residue was recrystallized to give 0.18 g (90%) of the desired product **55** as a white solid: mp 107.0−108.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 4H), 2.89 (d, J = 14 Hz, 4H), 3.05 (s, 3H), 3.89 (s, 3H), 7.04 (s, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H); HRMS (EI) calcd for $C_{21}H_{20}Cl_2O_3S$ 422.0510, found 422.0513. Anal. ($C_{21}H_{20}Cl_2O_3S\cdot0.67H_2O$) C, H, Cl, S.

4-[6-(3,5-Dichloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (56). Following a procedure similar to the one described in general procedure II, with the substitution of butyllithium instead of propylmagnesium chloride, 423 mg (1 mmol) of **55** was converted to crude sulfonamide. Purification by silica gel chromatography gave 87 mg (15%) of the desired product as a white solid: mp 94.5−97.0 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 4H), 2.83−2.95 (m, 4H), 3.89 (s, 3H), 4.81 (br s, 2H), 7.05 (s, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H); HRMS (EI) calcd for $C_{20}H_{19}Cl_2NO_3S$ 423.0463, found 423.0455.

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