J. Med. Chem. **1998,** *41,* 1124−1137

New Cyclooxygenase-2/5-Lipoxygenase Inhibitors. 2. 7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzofuran Derivatives as Gastrointestinal Safe Antiinflammatory and Analgesic Agents: Variations of the Dihydrobenzofuran Ring

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Received October 7, 1997

A series of 5-keto-substituted 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofurans (DHDMBFs) were found to be nonsteroidal antiinflammatory and analgesic agents. These compounds are inhibitors of 5-lipoxygenase (5-LOX) and cyclooxygenase (COX) with selectivity for the COX-2 isoform. A series of analogues were prepared to investigate the scope of this lead. Five ketone side chains from active DHDMBFs were used to investigate the effects of changes in the DHDMBF "core": the size and identity of the heterocycle and the substituent requirements of the heterocycle and phenyl ring. Biological testing showed that a variety of structural changes can be accommodated, but no structure was clearly superior to the DHDMBF structure.

Introduction

Di-*tert*-butylphenols are well-known antiinflammatory agents which are dual cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) inhibitors in vitro. The combination of COX/5-LOX inhibition and antioxidant properties has been proposed to account for the gastrointestinal (GI) safety of some members of this class, as discussed in the companion paper.[1]

The evolution of our work in the di-*tert*-butylphenol area began with tebufelone (**1**) (Chart 1) which was progressed to clinical testing. Among the metabolites of tebufelone was the 7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzofuran (DHDMBF) **2**, a nonphenolic compound. In the companion paper,[1] we disclosed that several 5-keto-substituted DHDMBFs were active antiinflammatory agents as well as COX/5-LOX inhibitors with selectivity for COX-2. Compound **3** was of particular interest as it showed excellent gastric safety in a variety of in vivo tests.

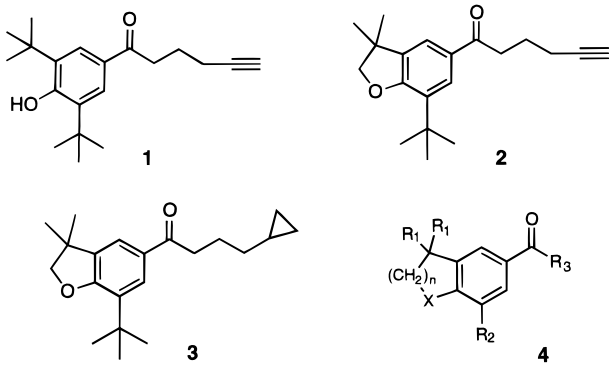
We now report our results on an exploration of the scope of the nonphenolic lead. Five different 5-keto substituents which provided active compounds in the DHDMBF series were appended to heterocyclic ring variants where ring size, substitution patterns, and heteroatom identity were changed as depicted in the generic structure **4** (Chart 1). Biological testing of the resulting analogues evaluated the effects of these structural changes on in vivo antiinflammatory and/or in vitro enzyme inhibition properties.

Chemistry

The syntheses of the requisite heterocyclic ring variants and substitution patterns are shown in Schemes 1−4. The preparation of compounds **8a**,**b**, in which the C-3 substituent varied, was accomplished by a route largely identical to that employed for the synthesis of the DHDMBF analogues.[1] Starting with the appropriate allyl bromides, *trans*-1-bromo-2-methyl-2-butene ($R_1 = R_2 =$ Me) or 1-(bromomethyl)cyclopentene ($R_1/R_2 = -(CH_2)_3-$), 2,4-dibromo-6-*tert*-butylphenol (**5**) was alkylated to give the corresponding ethers **6a**,**b**. These were cyclized to the dihydrobenzofurans via a hypophosphorus acid-induced 5-exo-trig radical ring closure as described in the companion paper. The cyclization was generally accompanied by partial dehalogenation at C-5, to provide a mixture of bromo and desbromo compounds **7** and **8**. Complete dehalogenation to either **8a** or **8b** was accomplished by lithium−halogen exchange of the respective mixture followed by an aqueous quench.

The preparation of compounds bearing hydrogen instead of methyl groups at the C-3 position of the DHDMBF (or C-4 of the dihydrobenzopyran analogues) was done using a variant of the Parham cyclialkylation[2] wherein the bromo ethers **9a**,**b** were ring-closed by lithium−halogen exchange to the dihydrobenzofuran

Chart 1



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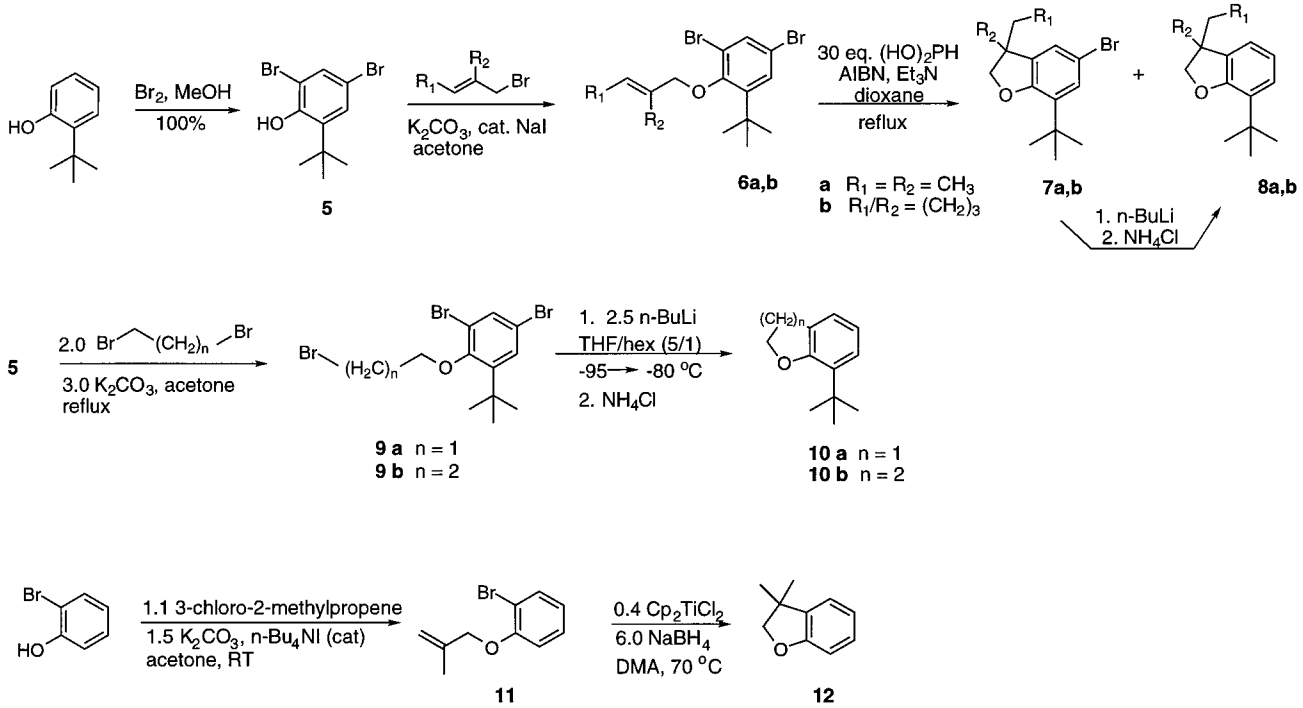
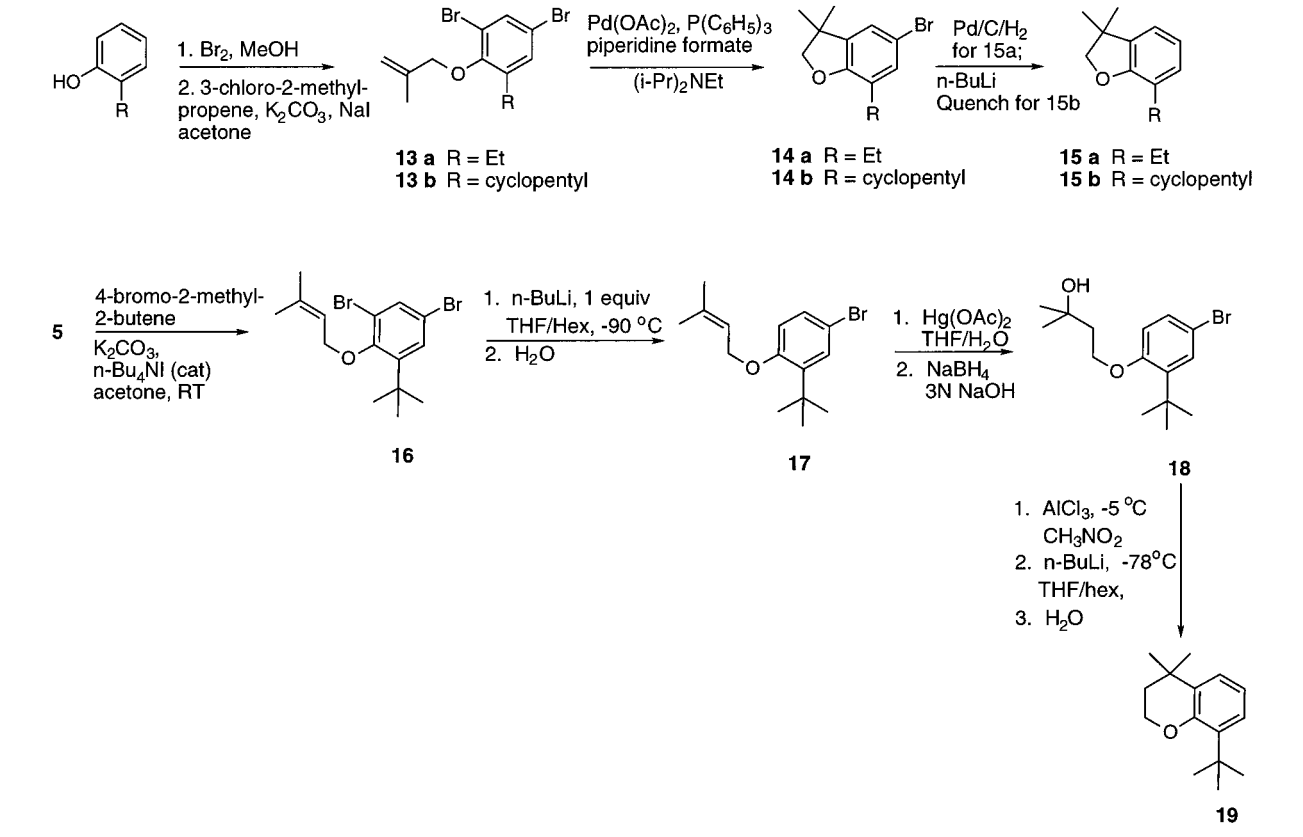
S0022-2623(97)00680-8 CCC: $15.00
Published on Web 03/10/1998

Scheme 1



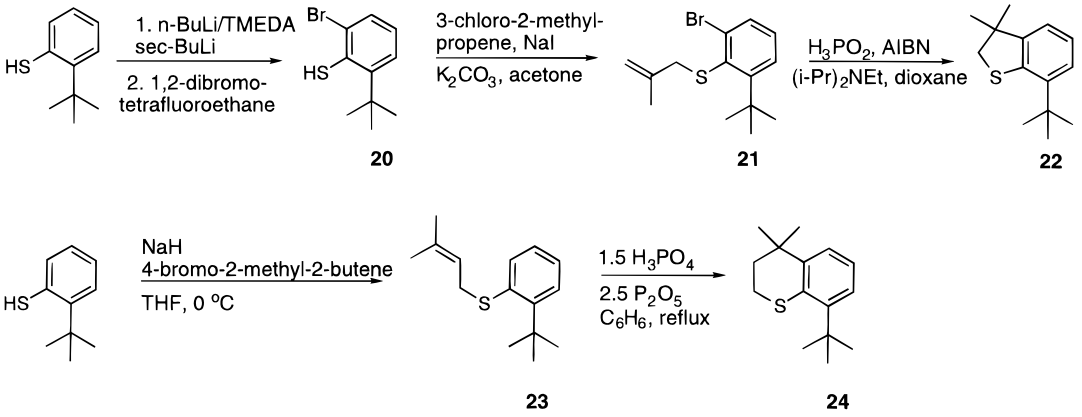
Scheme 2



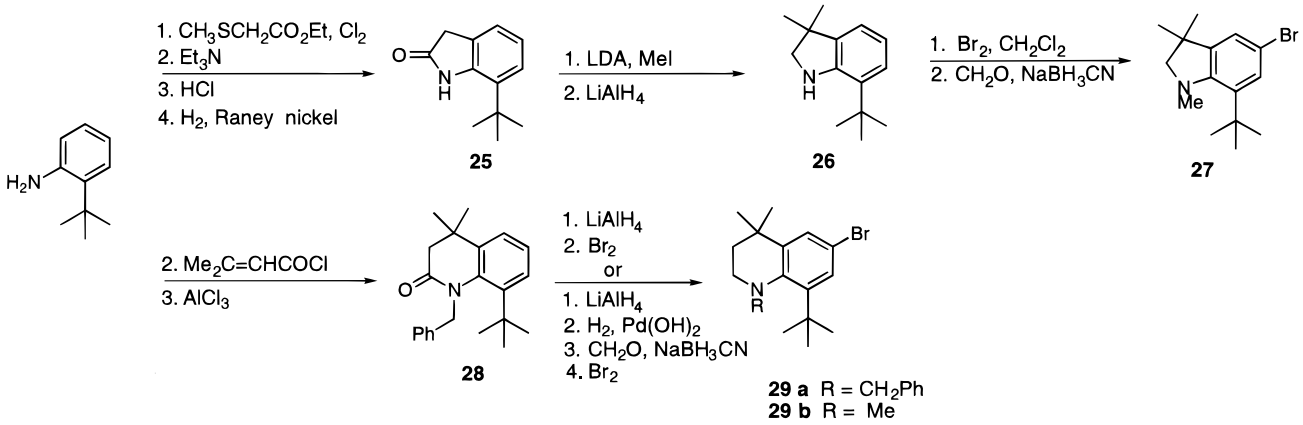
(DHBF) **10a** and the dihydrobenzopyran (DHBP) **10b** with simultaneous exchange of the remaining aromatic bromine. The des-*tert*-butyl DHDMBF **12** was prepared by a titanium-catalyzed radical cyclization[3] of the methallyl ether **11**.

Scheme 2 shows the preparation of compounds **15a**,**b** where the *tert*-butyl group has been replaced by other small alkyl groups. Replacement of the *tert*-butyl group with primary or secondary alkyl substituents precluded the use of the radical cyclization chemistry described above, possibly due to interference by the benzylic hydrogens. Instead, a palladium-catalyzed cyclization[4] of the methallyl ethers **13a**,**b** provided the bromo DHDMBFs **14a**,**b** which were converted to the respective desbromo compounds **15a**,**b** by hydrogenolysis and lithium−halogen exchange followed by an aqueous

Scheme 3



Scheme 4



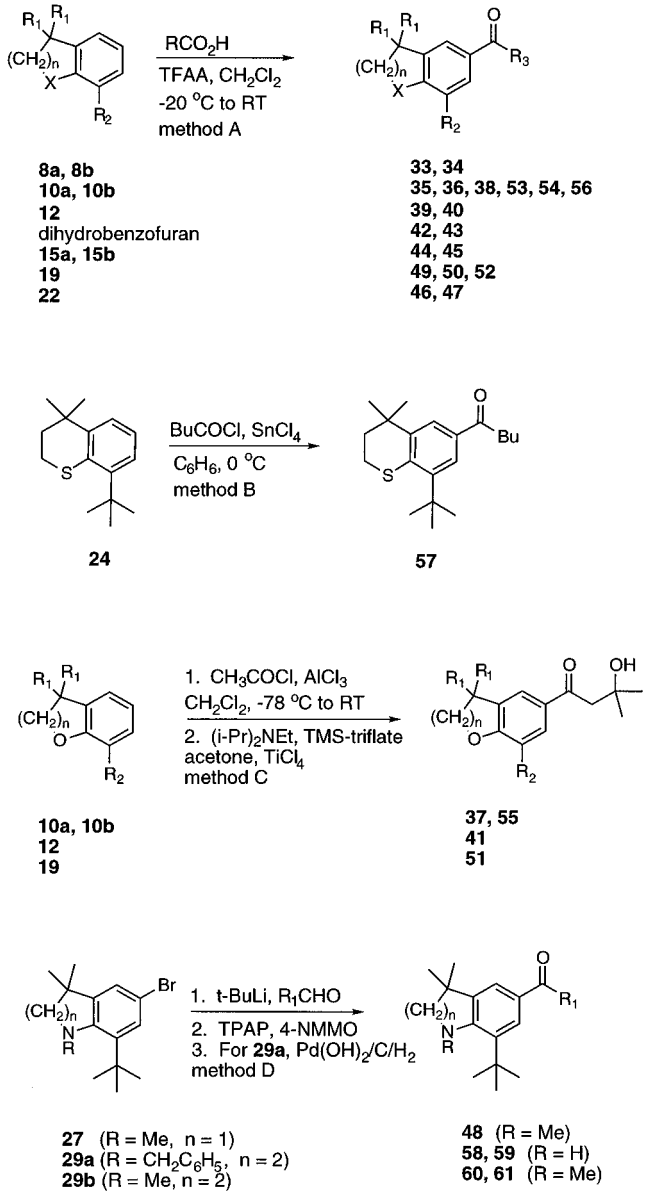
quench, respectively. The dihydrodimethylbenzopyran **19** was prepared by allylation of **5** to **16** followed by selective lithium−halogen exchange of the *o*-bromine to give the 4-bromo ether **17**. Oxymercuration/demercuration gave **18** which was cyclized to the dihydrobenzopyran with aluminum chloride. Lithium−halogen exchange followed by an aqueous quench gave the desired compound **19**.

The preparations of the sulfur isosteres of the dihydrobenzofurans and -pyrans are shown in Scheme 3. In a modification of a recently described methodology for ortho lithiation of thiophenols,[5,6] 2-*tert*-butylthiophenol was converted to its dianion which was brominated with 1,2-dibromotetrafluoroethane[7] to provide **20**. Allylation with 3-chloro-2-methylpropene provided compound **21** which was subjected to the hypophosphorus acid-induced 5-exo-trig radical cyclization to provide the dihyrodimethylbenzothiophene **22**. The dihydrothiopyran **24** was prepared from 2-*tert*-butylthiophenol by acid-induced ring closure via the 3-methyl-2-butenyl thioether **23**.

The syntheses of the requisite dihydroindole and tetrahydroquinoline ring systems are shown in Scheme 4. The preparation of the dihydroindole **27** involved, as a key step, a [2,3] rearrangement−cyclization reaction.[8] Reaction of chlorine and ethyl (methylthio)acetate followed by the addition of 2-*tert*-butylaniline formed the azasulfonium salt which, via ylid formation upon treatment with triethylamine, underwent a [2,3] rearrangement which linked the (methylthio)acetate group ortho to the aniline nitrogen. Acid-catalyzed ring closure and desulfurization with Raney nickel provided the oxindole **25**. Dimethylation of **25** with LDA/CH_3I and reduction with $LiAlH_4$ afforded the dihydroindole **26**. Bromination followed by N-methylation via a reductive amination gave the bromodihydroindole **27**. Synthesis of the tetrahydroquinoline compound **29b** centered around a 6-endo-trig cyclization reaction to provide the intermediate **28**.[9] Reductive amination of 2-*tert*-butylaniline with benzaldehyde and amide formation with dimethylacryloyl chloride followed by 6-endo-trig ring closure with $AlCl_3$ produced the dihydroquinolone **28**. In the absence of the *N*-benzyl group, cyclization was accompanied by loss of the *tert*-butyl group. A two-step procedure, reduction of **28** with $LiAlH_4$ followed by bromination, afforded the bromide **29a** (R = CH_2Ph). The *N*-Me tetrahydroquinoline **29b** was prepared via a similar procedure with the insertion of debenzylation and reductive amination steps in the preceding sequence.

Methods for the introduction of the keto substituent are given in Scheme 5. Friedel−Crafts reaction with trifluoroacetic anhydride activation of the desired carboxylic acid (method A) was used for many compounds.[10] The reaction was most commonly done in CH_2Cl_2 but could also be run in CH_3CN or done without solvent. In the case of the dihydrobenzothiopyran **57**, the acyl group was introduced by a $SnCl_4$-catalyzed Friedel−Crafts reaction (method B). The β-hydroxy ketone derivatives (**37**, **41**, **51**, **55**) were prepared via a Mukaiyama aldol reaction of the appropriate methyl ketone with acetone (method C). Introduction of the acyl group in the dihydroindole and tetrahydroquinoline series involved lithium−halogen exchange, followed by addition of the

Scheme 5



resulting aryllithium to the desired aldehyde. The resulting alcohol was oxidized without isolation with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (4-NMMO) (method D).[11]

Results and Discussion

In Vivo Activity. The carrageenan paw edema (CPE) assay was the primary screen used to assess in vivo antiinflammatory activity. Compounds were tested for their ability to inhibit paw swelling relative to tebufelone (positive control) after a single oral screening dose (50 mg/kg). The CPE data in Table 1 are given in terms of a CPE index which is the ratio of a compound's percent inhibition of paw edema versus control to tebufelone's percent inhibition of paw edema versus control.[12] At the 50 mg/kg screening dose, both naproxen, a marketed nonsteroidal antiinflammatory agent, and tebufelone exhibited about the same antiinflammatory activity. While uncertainties about bioavailability complicate the interpretation of the CPE results, the bioavailability of **30** was quite good (62%) in the rat.

Compounds bearing three types of ketone substituents, COR_3, were selected as targets (see Table 1): alkyl ketones (butanoyl, pentanoyl, or 4-cyclopropylbutanoyl), 3-hydroxy-3-methylbutanoyl, and hexynoyl. These substituents provided in vivo activity in the DHDMBF series (**2**, **3**, **30**−**32**)[1] and were used to probe the effect of changes in the heterocyclic core on biological activity.

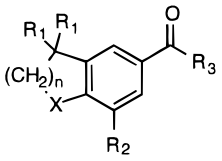
Some change of the C-3 geminal dimethyl group was tolerated. The 3-methyl-3-ethyl compound **33** was active, while the spirocyclopentyl analogue **34** was not. However, geminal dialkyl substitution was not required as all four compounds lacking the geminal dimethyl group were active (**35**−**38**). In contrast, the *tert*-butyl group appeared to be more important for activity: the butanoyl compound **39** was inactive, the cyclopropyl-containing analogue **40** was less active than the *tert*-butyl analogue **2**, and only the hydroxyl-containing **41** retaining activity equivalent to its *tert*-butyl analogue **32**. Compounds **42** and **43** lacking both the geminal dimethyl and the *tert*-butyl were inactive. Replacement of the *tert*-butyl group by secondary alkyl groups such as ethyl (**44**) and cyclopentyl (**45**) also eliminated activity.

Attempts at changing the nature of the heterocyclic ring system met with varied success. In the five-membered heterocyclic series, the replacement of sulfur for oxygen produced active derivatives (**46**, **47**), while the replacement with *N*-methyl (**48**) resulted in an inactive compound. Ring expansion to the 8-*tert*-butyl-2,3-dihydro-4,4-methylbenzopyrans **49**−**52** was a productive variation as all four compounds had significant activity. Variable activity was seen when the geminal dimethyl group was removed. The pentanoyl and 4-cyclopropylbutanoyl derivatives **53** and **54** were inactive, whereas the 3-hydroxy-3-methylbutanoyl and hexynoyl compounds **55** and **56** retained activity. Analogously to the dihydrobenzofuran series, the replacement of sulfur for oxygen (**57**) retained activity, whereas of the four nitrogen-containing analogues **58**−**61**, only the *N*-methyltetrahydroquinoline **61** retained some activity.

Most compounds which were active in the CPE assay were tested in an analgesia model, the phenylquinone abdominal constriction (PAC) assay. Many showed significant activity at the screening dose of 70 mg/kg. Notable exceptions were compounds **50** and **57** which were inactive at this dose demonstrating that compounds could be good antiinflammatory agents while having poor activity in the PAC assay. Dose−response studies with the most promising compounds from the high-dose screening resulted in a wide range of ED_{50} values. While ED_{50} values were generally in the 10−50 mg/kg range, compound **35** was significantly more potent with an ED_{50} of 0.6 mg/kg.

In Vitro Results. Selected compounds were tested in vitro for inhibition of cyclooxygenase and lipoxygenase (Table 2). Among the eight compounds which were active in the CPE assay, all were potent inhibitors of platelet-derived human COX-1 and/or recombinant human COX-2 with IC_{50} values < 1 μM except for compounds **36** and **50**. Among the compounds that were inactive (**44**, **45**, **60**) or less active than tebufelone (**40**) in the CPE assay, all were weak inhibitors of COX-1 and COX-2 with IC_{50} values > 1 μM except for compound **60**. Among all the compounds, only compound

Table 1. Structure, Synthetic Methods, and in Vivo Activity



compd	*n*	X	R_1	R_2	R_3	method	yield	mp, °C	formula	CPE index[a]	PAC assay[b]
1, tebufelone										**1.00**[c]	**26**
naproxen										**1.06**[c]	**1.3**
30	1	O	Me	*t*-Bu	Pr	*d*				**1.16**	**21**
31	1	O	Me	*t*-Bu	Bu	*d*				**0.92**	38%
2	1	O	Me	*t*-Bu	$(CH_2)_3$-*c*-Pr	*d*				**0.72**	**11**
32	1	O	Me	*t*-Bu	$CH_2C(OH)Me_2$	*d*				0.49[e]	NT[f]
3	1	O	Me	*t*-Bu	$(CH_2)_3CCH$	*d*				**0.94**	NT
33	1	O	Me, Et	*t*-Bu	Pr	A	78	oil	$C_{19}H_{28}O_2$	**0.68**	45%
34	1	O	*c*-C_5H_9[g]	*t*-Bu	Pr	A	22	oil	$C_{20}H_{28}O_2$	0.28	NT
35	1	O	H	*t*-Bu	Bu	A	79	oil	$C_{17}H_{24}O_2$	**0.69**	**0.6**
36	1	O	H	*t*-Bu	$(CH_2)_3$-*c*-Pr	A	84	oil	$C_{19}H_{26}O_2$	**0.50**	**6**
37	1	O	H	*t*-Bu	$CH_2C(OH)Me_2$	C	74	oil	$C_{17}H_{24}O_3$	**0.98**	**21**
38	1	O	H	*t*-Bu	$(CH_2)_3CCH$	A	79	oil	$C_{18}H_{22}O_2$	**0.84**	67%
39	1	O	Me	H	Pr	A	92	oil	$C_{14}H_{18}O_2$	0.31	NT
40	1	O	Me	H	$(CH_2)_3$-*c*-Pr	A	65	oil	$C_{17}H_{22}O_2$	0.50[e]	NT
41	1	O	Me	H	$CH_2C(OH)Me_2$	C	94	oil	$C_{15}H_{20}O_3$	0.39[e]	NT
42	1	O	H	H	Bu	A	21	56−57	$C_{13}H_{16}O_2$	0.00	NT
43	1	O	H	H	$(CH_2)_3$-*c*-Pr	A	22	41−42	$C_{15}H_{18}O_2$	0.13	NT
44	1	O	Me	Et	$(CH_2)_3$-*c*-Pr	A	44	oil	$C_{19}H_{26}O_2$	0.04	NT
45	1	O	Me	*c*-C_5H_9	$(CH_2)_3$-*c*-Pr	A	33	oil	$C_{22}H_{30}O_2$	0.27	NT
46	1	S	Me	*t*-Bu	Pr	A	22	oil	$C_{18}H_{26}OS$	**1.04**	**74**
47	1	S	Me	*t*-Bu	$(CH_2)_3$-c-Pr	A	17	oil	$C_{21}H_{30}OS$	**0.74**	NT
48	1	NMe	Me	*t*-Bu	$(CH_2)_3$-*c*-Pr	D	54	44−46	$C_{22}H_{33}NO$	0.36	NT
49	2	O	Me	*t*-Bu	Bu	A	79	oil	$C_{20}H_{30}O_2$	**0.69**	**53**
50	2	O	Me	*t*-Bu	$(CH_2)_3$-*c*-Pr	A	83	oil	$C_{22}H_{32}O_2$	**0.57**	10%
51	2	O	Me	*t*-Bu	$CH_2C(OH)Me_2$	C	70	92−93	$C_{20}H_{30}O_2$	0.48[e]	NT
52	2	O	Me	*t*-Bu	$(CH_2)_3CCH$	A	83	oil	$C_{21}H_{28}O_2$	**0.57**	46%
53	2	O	H	*t*-Bu	Bu	A	85	oil	$C_{18}H_{28}O_2$	0.21	NT
54	2	O	H	*t*-Bu	$(CH_2)_3$-*c*-Pr	A	66	oil	$C_{20}H_{28}O_2$	0.05	NT
55	2	O	H	*t*-Bu	$CH_2C(OH)Me_2$	C	72	oil	$C_{18}H_{26}O_3$	**0.70**	50%
56	2	O	H	*t*-Bu	$(CH_2)_3CCH$	A	79	52−53	$C_{19}H_{24}O_2$	**1.04**	79%
57	2	S	Me	*t*-Bu	Bu	B	37	oil	$C_{20}H_{30}O_S$	**0.86**	17%
58	2	NH	Me	*t*-Bu	Bu	D	45	109−110	$C_{20}H_{31}NO$	0.02	NT
59	2	NH	Me	*t*-Bu	$(CH_2)_3$-*c*-Pr	D	27	98−99	$C_{22}H_{33}NO$	0.00	NT
60	2	NMe	Me	*t*-Bu	Bu	D	41	oil	$C_{21}H_{33}NO$	0.42	NT
61	2	NMe	Me	*t*-Bu	$(CH_2)_3$-*c*-Pr	D	64	46−47	$C_{23}H_{35}NO$	0.37[e]	NT

[a] CPE index, carrageenan paw edema index, is defined as the ratio of the reduction in paw volume for test compounds relative to tebufelone; a value of >1 means more active than tebufelone, <1 means less active; dose = 50 mg/kg po. Bold faced values are statistically greater than vehicle control and not statistically different from tebufelone. See Experimental Section for complete details. [b] PAC, phenylquinone-induced abdominal constriction assay. Values are ED_{50}'s in bold or the percent reduction of constrictions at a po dose of 70 mg/kg. Maximal percent reduction is ~90%. See Experimental Section for complete details. [c] Percent inhibition of paw swelling for a 50 mg/kg po dose was 51.1 ± 10.0 for tebufelone (33−75%, $n = 65$) and 54% for naproxen (44−64%, $n = 2$). [d] See companion publication. [e] Activity is statistically greater than vehicle control but less than tebufelone. [f] NT, not tested. [g] The R_1 groups form a spirocyclopentyl ring.

36 was COX-1-selective, the others being nonselective (**30** and **57**) or moderately COX-2-selective with IC_{50} ratios from 2.5 to 50. The IC_{50} values for two benchmark compounds were determined for comparison. The marketed NSAID ibuprofen was a modestly selective COX-1 inhibitor,[13] while Searle's SC-57666[14] was a highly selective (>100-fold) COX-2 inhibitor, results consistent with literature reports. The inhibition of 5-LOX varies within a narrow range (3−12 μM) for those compounds tested.

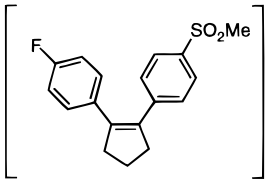
A few trends for changes in in vitro potency and selectivity with changes in structure are apparent. In the dihydrobenzofuran series, removal of the C-3 methyl groups results in a decrease in both COX-1 and COX-2 inhibition potency. The larger effect on COX-2 leads to a reversal in COX selectivity for **36** vs **2**. Likewise, replacement of the *tert*-butyl group with H, ethyl, or cyclopentyl has the greatest effect on COX-2, reducing inhibition potency and COX-2 selectivity (**2** vs **40**, **44**, **45**). The substitution of sulfur for oxygen reduces COX-1 potency most thereby increasing COX-2 selectivity (**30** vs **46**). For the ring-expanded compounds, the fully substituted dihydrobenzopyrans are less potent inhibitors of both COX-1 and COX-2 (**2** vs **50**), although the dihydrothiopyran **57** is a balanced moderately potent inhibitor.

Conclusions

The antiinflammatory and analgesic activity observed for the 5-substituted dihydrodimethylbenzofurans[1] extends to a variety of DMDHBF analogues. Changes in the degree of substitution, ring size, and heteroatom identity are all tolerated to varying degrees. Thus, the antiinflammatory/analgesic activity of the DMDHBF is not unique, and a variety of related nonphenolic structures are antiinflammatory in vivo and are COX-2-selective, dual COX/5-LOX inhibitors in vitro. However,

Table 2. In Vitro Activity of Dihydrodimethylbenzofurans and Analogues

compd	IC_{50}, μM[a] COX-1	COX-2	COX-1/COX-2	LOX[b] IC_{50}, μM
		Active in CPE		
30	0.095	0.095	1	8.5
31	2	0.04	50	12
2	7	0.22	32	8
3	0.060	0.015	4	6
36	5	15	0.33	12
46	1.5	~0.15	10	NT
50	20	3	6.6	8
57	0.4	0.4	1	NT
1, tebufelone	0.25	0.10	2.5	3
		Less Active in CPE[c]		
40	25	8	3.1	NT
		Inactive in CPE		
44	20	5	4	18
45	>100	20	>5	NT
60	2	~0.30	6.6	NT
		Benchmarks		
ibuprofen	3	30	0.1	
SC-57666	30	<0.3	>100	



[a] COX testing was done by testing duplicate samples in duplicate. [b] 5-LOX testing was done by testing single samples in triplicate. [c] Activity is statistically less than tebufelone but greater than vehicle.

no compounds were found which were more active or potent than the DHDMBFs.

Experimental Section

General Procedures. Reagents and solvents were generally used as received from the commercial supplier. Dry THF and dry Et_2O were obtained by distillation from sodium/benzophenone ketyl under a N_2 atmosphere. Dry hexanes, CH_2Cl_2, and DMF were obtained by distillation from CaH_2 under a N_2 atmosphere. Reactions were routinely performed under a N_2 atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless indicated otherwise, and chemical shifts are reported relative to tetramethylsilane ($\delta = 0.00$). Infrared spectra were recorded on a Perkin-Elmer instrument as a neat thin film on NaCl windows for oils or as KBr pellets for solids. Routine mass spectra were obtained using chemical ionization with NH_3 or CH_4 gas. Elemental microanalyses were performed by Oneida Laboratories, Inc. (Whitesboro, NY) or in-house at Procter & Gamble Pharmaceuticals in Norwich, NY. High-resolution mass spectral data were obtained using EI as the ionization method. HPLC was performed on a Spectra Physics system using a 300-mm C18 reverse-phase column and isocratic elution with 9:1 MeOH−H_2O and a flow rate of 1 mL/min. Low- and medium-pressure column chromatographies were performed using Merck silica gel 60 (270−400 mesh). TLC was performed on 250-μm precoated Merck silica gel 60 F_{254} glass-backed plates. Preparative TLC was performed using 20- × 20-cm 1500-μm precoated Analtech silica gel GF plates. Spots were visualized under 254-nm UV light or by staining with phosphomolybdate spray reagent.

1-(7-*tert*-Butyl-2,3-dihydro-3-ethyl-3-methyl-5-benzofuranyl)butan-1-one (33). 2,4-Dibromo-6-*tert*-butylphenyl *trans*-2-Methyl-2-butenyl Ether (6a). A solution of 2,4-dibromo-6-*tert*-butylphenol[1] (**5**) (13.9 g, 45.3 mmol), acetone (380 mL), *trans*-1-bromo-2-methyl-2-butene[15] (6.75 g, 45.6 mmol), K_2CO_3 (7.36 g, 54.4 mmol), and NaI (697 mg, 4.53 mmol) was refluxed for 3 h. The reaction mixture was cooled to 23 °C, the solids were removed by filtration, and the acetone was evaporated to give a dark oil. This oil was dissolved in hexanes (100 mL) and stirred in silica gel (10 g). The silica was removed by filtration, and the hexanes were evaporated to give a dark-yellow oil (13.1 g, 77%). ^1H NMR analysis indicated that this oil consisted of a 2:1 mixture of **6a** and the undesired enol ether resulting from double-bond migration. The mixture was carried forward without further purification: ^1H NMR δ 7.32 (d, $J = 1.5$ Hz, 1 H), 7.56 (d, $J = 1.5$ Hz, 1 H), 5.69 (q, $J = 6.8$ Hz, 1 H), 4.20 (s, 2 H), 1.82 (s, 3 H), 1.68 (d, $J = 6.8$ Hz, 3 H), 1.37 (s, 9 H).

5-Bromo-7-*tert*-butyl-2,3-dihydro-3-ethyl-3-methylbenzofuran (7a). A solution of **6a** (13.1 g, 35.2 mmol), 80% aqueous hypophosphorus acid (69 g, 1.06 mol), Et_3N (150 mL, 1.06 mol), and dioxane (650 mL) was deoxygenated by bubbling with nitrogen for 20 min. The reaction mixture was heated to reflux, and at 0.5-h intervals, 1.0 mL of a similarly deoxygenated AIBN solution (3.4 g dissolved in 30 mL of dioxane) was added. The reaction was monitored by TLC (CS_2) and after 4 h was cooled to 23 °C, and 1 N HCl (250 mL) and saturated brine (100 mL) were added. The H_2O/dioxane was extracted with Et_2O (4 × 250 mL), and the Et_2O/dioxane layers were dried ($MgSO_4$) and evaporated to a yellow oil (10.36 g). This oil was dissolved in EtOAc and shaken with 1 N NaOH (3 × 20 mL), and the organics were dried and evaporated to a dark oil (8.59 g). This oil was purified by medium-pressure chromatography (hexanes) to give the product (3.34 g, 34%) as a clear oil which was a 20:80 mixture of debrominated (**8a**) and brominated (**7a**) products: ^1H NMR δ 7.15 (d, $J = 1.8$ Hz, 1 H), 7.00 (d, $J = 1.8$ Hz, 1 H), 4.35 (d, $J = 9.7$ Hz, 1 H), 4.11 (d, $J = 9.7$ Hz, 1 H), 1.60 (q, $J = 7.7$ Hz, 2 H), 1.38 (s, 3 H), 1.30 (s, 9 H), 0.83 (t, $J = 7.7$, 3 H).

7-*tert*-Butyl-2,3-dihydro-3-ethyl-3-methylbenzofuran (8a). To a −78 °C solution of **7a** (2.34 g, 7.9 mmol) in dry Et_2O/hexanes (25 mL of 1:9) was added *n*-BuLi (1.59 M, 15.8 mmol, 9.9 mL) dropwise over 10 min. The reaction mixture was stirred at −70 °C for 40 min, and NH_4Cl (7.9 mmol, 422 mg) was added. This solution was stirred for 2 h at −10 °C, H_2O (20 mL) was added, and the organics were collected. The water was extracted with hexanes (3 × 10 mL), and the combined organics were dried ($MgSO_4$) and evaporated to provide **8a** as a yellow oil (1.63 g, 95%): ^1H NMR δ 7.08 (dd, $J = 7.0$, 1.8 Hz, 1 H), 6.90 (dd, $J = 7.0$, 1.8 Hz, 1 H), 6.80 (t, $J = 7.0$ Hz, 1 H), 4.32 (d, $J = 9.7$ Hz, 1 H), 4.10 (d, $J = 9.7$ Hz, 1 H), 1.60 (q, $J = 7.7$ Hz, 2 H), 1.36 (s, 9 H), 1.30 (s, 3 H), 0.82 (t, $J = 7.7$ Hz, 3 H).

1-(7-*tert*-Butyl-2,3-dihydro-3-ethyl-3-methyl-5-benzofuranyl)butan-1-one (33). Method A. In a three-neck flask equipped with magnetic stir bar, Ar inlet, and septum inlet were placed **8a** (700 mg, 3.2 mmol), butyric acid (0.29 mL, 3.2 mmol), and CH_2Cl_2 (5 mL). The solution was cooled to −20 °C, and then trifluoroacetic anhydride (freshly distilled, 0.55 mL, 3.9 mmol) was added. After 2 h at this temperature, the reaction mixture was allowed to warm to 23 °C and stirred for 6 h. The reaction was quenched with H_2O (15 mL), and the aqueous layer was extracted with fresh CH_2Cl_2 (3 × 10 mL) and discarded. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to a dark oil (1.08 g) which was purified by column chromatography using hexanes and then 1% EtOAc in hexanes as eluent, to provide 547 mg (78%) of **33** as a light-yellow oil: ^1H NMR δ 7.80 (d, $J = 1.8$ Hz, 1 H), 7.60 (d, $J = 1.8$ Hz, 1 H), 4.43 (d, $J = 8.7$ Hz, 1 H), 4.22 (d, $J = 8.8$ Hz, 1 H), 2.89 (t, $J = 7.2$ Hz, 2 H), 1.76 (q, $J = 7.4$ Hz, 2 H), 1.64 (q, $J = 7.3$ Hz, 2 H), 1.38 (s, 9 H), 1.35 (s, 3 H), 1.01 (t, $J = 7.25$ Hz, 3 H), 0.81 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR δ 199.3, 162.0, 136.0, 132.6, 130.6, 126.4, 121.1, 82.4, 44.7, 40.1, 34.1, 33.5, 29.1, 25.1, 18.1, 13.9, 8.7; IR 2981, 2874, 1674, 1596, 1453 cm^{-1}; MS 289 (MH^+). Anal. ($C_{19}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-3-spirocyclopentyl-5-benzofuranyl)butan-1-one (34). 2,4-Dibromo-6-*tert*-butylphenyl 1-Cyclopent-1-enylmethyl Ether (6b). A solution of 2,4-dibromo-6-*tert*-butylphenol (**5**) (3.63 g, 11.9 mmol), acetone (100 mL), 1-(bromomethyl)cyclopentene (1.9 g, 11.9 mmol, prepared from 1-cyclopentenecarboxylic acid by reduction[16] and bromination[17]), K_2CO_3 (1.93 g, 14.3 mmol), and NaI (183 mg, 1.19 mmol) was reacted as described for **6a** to provide 3.6 g (78%) of **6b** as a dark-yellow oil: ^{1}H NMR δ 7.55 (d, J = 1.8 Hz, 1 H), 7.40 (d, J = 1.8 Hz, 1 H), 5.85 (m, 1 H), 4.60 (s, 2 H), 2.45 (m, 4 H), 1.95 (quintet, J = 7.4 Hz, 2 H), 1.40 (s, 9 H); ^{13}C NMR δ 154.6, 147.2, 139.8, 134.1, 129.9, 128.0, 119.0, 116.5, 71.9, 33.1, 32.5, 30.7, 29.2, 23.3.

5-Bromo-7-*tert*-butyl-2,3-dihydro-3-spirocyclopentylbenzofuran (7b). A solution of **6b** (3.60 g, 9.33 mmol), 80% aqueous hypophosphorus acid (18.4 g, 280 mmol), Et_3N (40 mL, 280 mmol), and dioxane (175 mL) was reacted as described for **7a** to yield the desired product **7b** as a 3:1 mixture with 7-*tert*-butyl-2,3-dihydro-3-spirocyclopentylbenzofuran (**8b**) (3.42 g, 119%) of sufficient purity for the next reaction: ^{1}H NMR δ 7.15 (d, J = 1.8 Hz, 1 H), 7.08 (d, J = 1.8 Hz, 1 H), 4.28 (s, 2 H), 1.85 (m, 6 H), 1.70 (m, 2 H), 1.34 (s, 9 H).

7-*tert*-Butyl-2,3-dihydro-3-spirocyclopentylbenzofuran (8b). The 3:1 mixture from above containing primarily **7b** (1.62 g, 5.20 mmol) was reacted as described for **8a** to provide **8b** as an orange oil (1.37 g, 110%), of sufficient purity for the next reaction: ^{1}H NMR δ 7.09 (dd, J = 7.0, 1.8 Hz, 1 H), 7.00 (dd, J = 7.0, 1.8 Hz, 1 H), 6.84 (t, J = 7.0 Hz, 1 H), 4.28 (s, 2 H), 1.85 (bs, 6 H), 1.70 (m, 2 H), 1.36 (s, 9 H).

1-(7-*tert*-Butyl-2,3-dihydro-3-spirocyclopentyl-5-benzofuranyl)butan-1-one (34). Prepared by method A. Crude product was purified by column chromatography using hexanes and then 1% EtOAc in hexanes as eluent, to provide **34** (170 mg, 22%) as a clear oil: ^{1}H NMR δ 7.78 (d, J = 1.8 Hz, 1 H), 7.64 (d, J = 1.8 Hz, 1 H), 4.36 (s, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 1.89−1.73 (m, 10 H), 1.38 (s, 9 H), 1.01 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 199.3, 161.9, 136.4, 132.6, 130.6, 126.4, 120.9, 85.0, 52.0, 40.3, 40.2, 34.2, 29.2, 25.1, 18.2, 14.0; IR 2957, 2871, 1673, 1595 cm^{-1}; MS 301 (MH$^+$). Anal. ($C_{20}H_{28}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)pentan-1-one (35). 2,4-Dibromo-1-(2-bromoethoxy)-6-*tert*-butylbenzene (9a). To a pale-brown solution of 2,4-dibromo-6-*tert*-butylphenol (**5**) (5.00 g, 16.24 mmol) in acetone (70 mL) were added 1,2-dibromoethane (2.80 mL, 32.47 mmol) and K_2CO_3 (6.70 g, 48.72 mmol), and the mixture was allowed to reflux. After 14 h, the mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give an oil which was Kugelrohr distilled (210−213 °C, 0.1 mmHg) to give **9a** (5.97 g, 89%) as a pale-yellow oil: ^{1}H NMR δ 7.57 (d, J = 2.3 Hz, 1 H), 7.39 (d, J = 2.3 Hz, 1 H), 4.33 (t, J = 6.4 Hz, 2 H), 3.75 (t, J = 6.3 Hz, 2 H), 1.39 (s, 9 H); ^{13}C NMR δ 153.6, 147.1, 134.2, 130.1, 118.8, 117.1, 71.9, 35.8, 30.7, 29.2; IR 2963, 2914, 2873, 1546, 1428 cm^{-1}; MS (EI) 418 (M$^+$ + 3), 416 (M$^+$ + 1), 414, 412.

7-*tert*-Butyl-2,3-dihydrobenzofuran (10a). To a cold (−95 °C, MeOH/Et_2O, liquid N_2) solution of **9a** (5.00 g, 12.05 mmol) in THF/hexanes (100 mL/20 mL) was added *n*-BuLi (12.00 mL, 30.12 mmol) dropwise. The reaction mixture was stirred at −95 °C for 30 min and at −80 °C for 4 h. The reaction mixture was poured into saturated NH_4Cl, extracted with EtOAc, and washed with water and brine. The aqueous layers were extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash column chromatography on silica (hexanes) to give an off-white oil which was Kugelrohr distilled (87−90 °C, 0.25 mmHg) to give **10a** (1.52 g, 72%) as a low-melting white solid: ^{1}H NMR δ 7.07 (d, J = 7.5 Hz, 2 H), 6.80 (t, J = 7.2 Hz, 1 H), 4.56 (t, J = 8.7 Hz, 2 H), 3.18 (t, J = 8.7 Hz, 2 H), 1.37 (s, 9 H); ^{13}C NMR δ 158.7, 132.9, 127.3, 124.6, 122.6, 120.1, 70.31, 34.1, 29.7, 29.2; IR 2956, 2912, 2873, 1591, 1482 cm^{-1}; MS (EI) 176 (M$^+$), 161, 133.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)pentan-1-one (35). Method A was used. Purified by flash column chromatography (hexanes, hexanes/EtOAc, 25/1) to give a crude oil which was distilled (130−133 °C, 0.4 mmHg): ^{1}H NMR δ 7.77 (d, J = 1.5 Hz, 1 H), 7.71 (s, 1 H), 4.64 (t, J = 9.0 Hz, 2 H), 3.21 (t, J = 9.0 Hz, 2 H), 2.89 (t, J = 7.5 Hz, 2 H), 1.71 (m, 2 H), 1.42 (m, 2 H), 1.36 (s, 9 H), 0.95 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 199.5, 162.3, 132.6, 130.2, 127.8, 126.4, 123.3, 71.5, 38.0, 34.1, 29.1, 29.0, 27.0, 22.5, 13.9; IR 2957, 2934, 2871, 1674, 1596, 1414 cm^{-1}; MS 261 (MH$^+$). Anal. ($C_{17}H_{24}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)-4-cyclopropylbutan-1-one (36). Method A was used. Purified by flash column chromatography on silica (hexanes/EtOAc, 10/1 → 4/1): ^{1}H NMR δ 7.77 (d, J = 1.5 Hz, 1 H), 7.71 (d, J = 1.5 Hz, 1 H), 4.65 (t, J = 8.8 Hz, 2 H), 3.22 (t, J = 8.5 Hz, 2 H), 2.93 (t, J = 7.3 Hz, 2 H), 1.83 (quintet, J = 7.5 Hz, 2 H), 1.29 (q, J = 7.5 Hz, 2 H), (s, 9 H), 0.70 (m, 1 H), 0.42 (m, 2 H), 0.03 (m, 2 H); ^{13}C NMR δ 199.3, 162.1, 132.5, 130.0, 127.7, 126.2, 123.1, 71.4, 34.9, 34.2, 34.0, 29.0, 28.9, 24.8, 10.6, 4.3; IR 2995, 2956, 2868, 1673, 1596, 1414 cm^{-1}; MS 287 (MH$^+$). Anal. ($C_{19}H_{26}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)-3-hydroxy-3-methylbutan-1-one (37). Method C. 1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)ethanone. To a suspension of $AlCl_3$ (0.42 g, 3.12 mmol) in CH_2Cl_2 (20 mL) was added acetyl chloride (0.24 mL, 3.40 mmol). The resulting suspension was allowed to stir at −78 °C for 30 min, and a solution of 7-*tert*-butyl-2,3-dihydrobenzofuran (0.50 g, 2.84 mmol) in CH_2Cl_2 (5 mL) was added dropwise using an addition funnel. After the addition was completed, the reaction mixture (pale-yellow precipitate) was allowed to warm to room temperature over 4 h. The resulting suspension was cooled to 0 °C, the reaction was quenched with water, and the layers were separated. The organic phase was washed with water and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting off-white solid was recrystallized using hexanes to give the title compound (0.54 g, 87%) as white crystals: mp 96−97 °C; ^{1}H NMR δ 7.76 (d, J = 1.4 Hz, 1 H), 7.70 (d, J = 1.4 Hz, 1 H), 4.65 (t, J = 8.8 Hz, 2 H), 3.21 (t, J = 8.8 Hz, 2 H), 2.54 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR δ 197.1, 162.5, 132.6, 130.3, 127.9, 126.7, 123.5, 71.5, 34.1, 29.0, 28.9, 26.4; IR 3002, 2990, 2952, 2911, 1663, 1580 cm^{-1}; MS (EI) 218 (M$^+$), 204, 203. Anal. ($C_{14}H_{18}O_2$) C, H.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)-3-hydroxy-3-methylbutan-1-one (37). To a cold (−78 °C) solution of 1-(7-*tert*-butyl-2,3-dihydro-5-benzofuranyl)ethanone (0.45 g, 2.04 mmol) in CH_2Cl_2 (4.0 mL) were added TMSOTf (0.47 mL, 2.45 mmol) and *i*-Pr_2NEt (0.43 mL, 2.31 mmol) dropwise. The resulting mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature over 1 h. The resulting colorless solution was recooled to −78 °C, and acetone (0.18 mL, 2.45 mmol) and $TiCl_4$ (0.22 mL, 2.04 mmol) were added dropwise. The resulting deep-red solution was allowed to warm to room temperature over 2 h; 1 N HCl was added, and the mixture was stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with water and brine. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1, 8/1, 4/1) to give a crude oil which was distilled (139−142 °C, 0.4 mmHg) to give **37** (0.42, 74%) as a colorless oil: ^{1}H NMR δ 7.76 (s, 1 H), 7.70 (s, 1 H), 4.67 (t, J = 8.8 Hz, 2 H), 3.22 (t, J = 8.8 Hz, 2 H), 3.07 (s, 2 H), 1.37 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 200.6, 163.0, 132.9, 130.3, 128.1, 126.5, 123.4, 71.7, 69.9, 47.9, 34.2, 29.6, 29.2, 28.9; IR 3482, 2969, 2906, 2870, 1654, 1593 cm^{-1}; MS 277 (MH$^+$). Anal. ($C_{17}H_{24}O_3$) C, H; C: calcd, 73.88; found, 73.41.

1-(7-*tert*-Butyl-2,3-dihydro-5-benzofuranyl)-5-hexyn-1-one (38). Method A was used. Crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1) to give a yellow oil which was Kugelrohr distilled (175−177 °C, 0.2 mmHg) to give **38** (0.76 g, 85%): ^{1}H NMR δ 7.78 (s, 1 H), 7.72 (s, 1 H), 4.64 (t, J = 8.8 Hz, 2 H), 3.20 (t, J

= 8.7 Hz, 2 H), 3.05 (t, *J* = 7.3 Hz, 2 H), 2.33−2.28 (m, 2 H), 1.98−1.92 (m, 3 H), 1.36 (s, 9 H); ^{13}C NMR *δ* 198.3, 162.4, 132.6, 130.0, 127.8, 126.3, 123.2, 83.9, 71.4, 68.9, 36.6, 34.1, 29.0, 28.9, 23.2, 17.9; IR 3299, 2957, 2906, 2869, 2152, 1672, 1596 cm^{-1}; MS (EI) 270 (M^+), 255, 219, 218, 204, 203. Anal. ($C_{18}H_{22}O_2$) C, H.

2-Bromo-1-(2-methyl-2-propenoxy)benzene (11). To a solution of 2-bromophenol (5.00 g, 28.90 mmol) in acetone (50 mL) were added 3-chloro-2-methylpropene (3.14 mL, 31.79 mmol), *n*-Bu_4NI (catalytic amount), and K_2CO_3 (6.00 g, 43.35 mmol). The reaction mixture was stirred at room temperature in the dark. After 2 h, the mixture was filtered and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give **11** (2.89 g, 44%) as a colorless oil: ^{1}H NMR *δ* 7.55 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.24 (td, *J* = 8.0, 1.5 Hz, 1 H), 6.88 (dd, *J* = 8.2, 1.3 Hz, 1 H), 6.83 (td, *J* = 7.7, 1.5 Hz, 1 H), 5.17 (q, *J* = 1.0 Hz, 1 H), 5.02 (t, *J* = 1.5 Hz, 1 H), 4.50 (s, 2 H), 1.87 (d, *J* = 1.0 Hz, 3 H); ^{13}C NMR *δ* 155.0, 140.2, 133.3, 128.3, 121.9, 113.4, 112.8, 112.3, 72.4, 19.3.

2,3-Dihydro-3,3-dimethylbenzofuran (12). To a degassed solution of **11** (2.44 g, 10.75 mmol) in dimethylacetamide (20 mL) was added $NaBH_4$ (2.44 g, 64.52 mmol) followed by Cp_2TiCl_2 (1.07 g, 4.30 mmol) over 2 min. The resulting purple mixture was stirred at ∼75 °C. After 17 h, the mixture was cooled to room temperature, diluted with hexanes, and washed with 0.1 N HCl, water, and brine. The aqueous layers were extracted with hexanes, and the combined organic layer was dried over ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give **12** (0.44 g, 64%) as a colorless oil: ^{1}H NMR *δ* 7.12 (t, *J* = 7.2 Hz, 2 H), 6.90 (t, *J* = 7.2 Hz, 1 H), 6.81 (d, *J* = 8.7 Hz, 1 H), 4.24 (s, 2 H), 1.36 (s, 6 H); ^{13}C NMR *δ* 159.1, 136.5, 127.9, 122.2, 120.5, 109.6, 84.4, 41.9, 27.5.

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)butan-1-one (39). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give an oil which was distilled (84−87 °C, 0.5 mmHg) to give a solid: mp 47−48 °C; ^{1}H NMR *δ* 7.80 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.78 (d, *J* = 2.0 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 4.32 (s, 2 H), 2.89 (t, *J* = 7.2 Hz, 2 H), 1.75 (sextet, *J* = 7.5 Hz, 2 H), 1.37 (s, 6 H), 1.38 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR *δ* 199.0, 163.3, 137.3, 130.8, 130.0, 122.8, 109.8, 85.4, 41.5, 40.2, 27.6, 18.1, 14.0; IR 2950, 2873, 1676, 1605, 1488 cm^{-1}; MS 219 (MH^+). Anal. ($C_{14}H_{18}O_2$) C, H.

4-Cyclopropyl-1-(2,3-dihydro-3,3-dimethyl-5-benzofuranyl)butan-1-one (40). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give an oil which was distilled (95−99 °C, 0.4 mmHg): ^{1}H NMR *δ* 7.80 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.77 (d, *J* = 2.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 4.31 (s, 2 H), 2.93 (t, *J* = 7.3 Hz, 2 H), 1.83 (quintet, *J* = 7.5 Hz, 2 H), 1.36 (s, 6 H), 1.29 (q, *J* = 7.5 Hz, 2 H), 0.69 (m, 1 H), 0.40 (m, 2 H), 0.03 (m, 2 H); ^{13}C NMR *δ* 199.0, 163.3, 137.3, 130.8, 130.0, 122.7, 109.1, 85.4, 41.5, 38.0, 34.3, 27.6, 24.7, 10.6, 4.4; IR 3074, 2959, 2929, 1674, 1605, 1487 cm^{-1}. Anal. ($C_{17}H_{22}O_2$) C, H.

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-3-methylbutan-1-one (41). 1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)ethanone. Method C was used. The crude product was purified by flash column chromatography on silica (hexanes/EtOAc, 20/1) to give an oil which was distilled (72−74 °C, 0.5 mmHg) to afford a solid: yield 77%, mp 35−37 °C; ^{1}H NMR *δ* 7.80 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.77 (d, *J* = 1.5 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 4.31 (s, 2 H), 2.54 (s, 3 H), 1.36 (s, 6 H); ^{13}C NMR *δ* 196.7, 163.5, 137.3, 130.9, 130.5, 122.9, 109.2, 85.4, 41.3, 27.6, 26.4; IR 2960, 2884, 1673, 1606, 1487 cm^{-1}.

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-3-methylbutan-1-one (41). Method C was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1, 3/1) to give **41** (0.32 g, 94%, based on recovered starting material) as a colorless oil: ^{1}H NMR *δ* 7.78 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.75 (d, *J* = 2.0 Hz, 1 H), 6.79 (d, *J* = 8.5 Hz, 1 H), 4.32 (s, 2 H), 3.07 (s, 2 H), 1.36 (s, 6 H), 1.32 (s, 6 H); ^{13}C NMR *δ* 200.2, 164.0, 137.6, 130.9, 130.3, 122.8, 109.4, 85.5, 69.9, 48.0, 41.4, 29.6, 27.6; IR 3473, 2967, 2888, 1659, 1603, 1488 cm^{-1}; MS 249 (MH^+). Anal. ($C_{15}H_{20}O_3$) C, H; C: calcd, 72.55; found, 71.84.

1-(2,3-Dihydro-5-benzofuranyl)pentan-1-one (42). Method A was used. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes and then crystallized from 10% EtOAc/hexanes: mp 56−57 °C; ^{1}H NMR *δ* 7.84 (s, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 4.65 (t, *J* = 8.7 Hz, 2 H), 3.25 (t, *J* = 8.7 Hz, 2 H), 2.89 (t, *J* = 7.2 Hz, 2 H), 1.75 (m, 2 H), 1.39 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR *δ* 199.1, 164.1, 130.5, 130.0, 127.6, 125.3, 108.9, 72.1, 38.1, 29.0, 26.9, 22.6, 14.0; IR 3020, 2962, 2934, 2873, 1669, 1602, 1492 cm^{-1}; MS 205 (MH^+), 233 ($M + C_2H_5^+$), 245 ($M + C_3H_5^+$). Anal. ($C_{13}H_{16}O_2$) C, H.

1-(2,3-Dihydro-5-benzofuranyl)-4-cyclopropylbutan-1-one (43). Method A was used. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes and was then recrystallized from 5% EtOAc/hexanes: mp 41−42 °C; ^{1}H NMR *δ* 7.83 (d, *J* = 1.8 Hz, 1 H), 7.78 (dd, *J* = 9.0, 1.8 Hz, 1 H), 6.76 (d, *J* = 9.1 Hz, 1 H), 4.65 (t, *J* = 6.6 Hz, 2 H), 3.25 (t, *J* = 6.7 Hz, 2 H), 2.85 (t, *J* = 7.0 Hz, 2 H), 1.82 (m, 2 H), 1.23 (q, *J* = 7.0 Hz, 2 H), 0.65 (m, 1 H), 0.40 (m, 2 H), 0.12 (m, 2 H); ^{13}C NMR *δ* 200.1, 164.1, 130.5, 130.0, 127.6, 125.3, 108.9, 72.1, 38.0, 34.3, 29.0, 24.8, 10.7, 4.4; IR 3020, 1669, 1606 cm^{-1}; MS 231 (MH^+), 147. Anal. ($C_{15}H_{18}O_2$) C, H.

1-(2,3-Dihydro-3,3-dimethyl-7-ethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (44). 2,4-Dibromo-6-ethylphenol. To a solution of 2-ethylphenol (50 g, 0.41 mol) in MeOH (100 mL) at 0 °C was added Br_2 (42 mL, 0.86 mol) dropwise over 45 min. The reaction mixture was allowed to warm to 23 °C and stirred for 3 h. The reaction was quenched with H_2O (50 mL), the MeOH evaporated, and the water extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried ($MgSO_4$) and evaporated to a dark oil which was dissolved in hexanes (100 mL) and stirred with silica gel (70 g). The silica was removed by filtration, and the hexanes were evaporated to give the product as an orange oil (113 g, 99%), which was used without further purification: ^{1}H NMR *δ* 7.42 (d, *J* = 1.5 Hz, 1 H), 7.20 (d, *J* = 1.5 Hz, 1 H), 5.60 (s, 1 H), 2.69 (q, *J* = 8.7 Hz, 2 H), 1.25 (t, *J* = 8.7 Hz, 3 H).

2,4-Dibromo-6-ethylphenyl 2-Methallyl Ether (13a). A mixture of 2,4-dibromo-6-ethylphenol (25 g, 89 mmol), acetone (500 mL), 3-chloro-2-methylpropene (13.3 mL, 134 mmol), K_2CO_3 (14.8 g, 107 mmol), and NaI (1.33 g, 8.9 mmol) was refluxed 6 h. The reaction mixture was cooled to 23 °C, the solids were removed by filtration, and the acetone was evaporated to give **13a** as a yellow oil (28.64 g, 97%) which was used without further purification: ^{1}H NMR *δ* 7.57 (d, *J* = 1.5 Hz, 1 H), 7.29 (d, *j* = 1.5 Hz, 1 H0, 5.21 (s, 1 H), 5.03 (s, 1 H), 4.28 (s, 2 H), 2.70 (q, *J* = 8.7 Hz, 2 H), 1.93 (s, 3 H), 1.27 (t, *J* = 8.7 Hz, 3H).

5-Bromo-2,3-dihydro-3,3-dimethyl-7-ethylbenzofuran (14a). A solution of **13a** (26 g, 78 mmol), $Pd(OAc)_2$ (875 mg, 3.9 mmol), triphenylphosphine (1.02 g, 3.9 mmol), and anhydrous DMF (1200 mL) was degassed with N_2 for 15 min and then heated to 70 °C. To this solution was added a solution of piperidine (30 mL) and 98% formic acid (85 mL) in anhydrous DMF (800 mL) at a rate of 0.9 mL/min. After 200 mL was added, the addition was stopped and the reaction mixture stirred at 70 °C overnight. The reaction mixture was then cooled and the volume doubled with H_2O. The DMF/H_2O was extracted extensively with hexanes which were dried ($MgSO_4$) and evaporated to a dark oil (15.5 g). The oil was taken up in hexanes and extracted with 1 M NaOH (3 × 50 mL) and then H_2O (50 mL). The organic phase was dried ($MgSO_4$) and evaporated, and the resulting oil was chromatographed over SiO_2 by medium-pressure chromatography (1% EtOAc/hexanes). The desired product, **14a**, was obtained as a yellow oil (1.38 g, 7%). Also isolated were 2,3-dihydro-3,3-dimethyl-7-ethylbenzofuran (**15a**) (275 mg) and 2,4-dibromo-6-ethylphenyl 2-methyl-1-propenyl ether (3.66 g, 15%): ^{1}H NMR *δ* 7.08 (d, *J* = 1.8 Hz, 1 H), 7.02 (d, *J* = 1.8 Hz, 1 H),

4.21 (s, 2 H), 2.57 (q, J = 8.7 Hz, 2 H), 1.33 (s, 6 H), 1.19 (t, J = 8.7 Hz, 3 H).

2,3-Dihydro-3,3-dimethyl-7-ethylbenzofuran (15a). A solution of **14a** (840 mg) and 10% Pd/C (125 mg) in EtOH (10 mL) was shaken under 45 psi H_2 atmosphere for 18 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated to a thick orange oil (650 mg). This was taken up in hexanes, the insolubles were filtered, and the hexanes were evaporated to give **15a** as a light-orange oil (464 mg, 80%) which was used without further purification: ^{1}H NMR δ 7.08 (d, J = 7.8 Hz, 1 H), 6.97 (t, J = 7.8 Hz, 1 H), 6.84 (t, J = 7.8 Hz, 1 H), 4.22 (s, 2 H), 2.61 (q, J = 8.7 Hz, 2 H), 1.36 (s, 6 H), 1.24 (t, J = 8.7 Hz, 3 H).

1-(2,3-Dihydro-3,3-dimethyl-7-ethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (44). Method A was used. The crude product was purified by preparative TLC (1500 μm, 2% EtOAc/hexanes): ^{1}H NMR δ 7.68 (d, J = 1.5 Hz, 1 H), 7.62 (d, J = 1.5 Hz, 1 H), 4.34 (s, 2 H), 2.95 (t, J = 7.7 Hz, 2 H), 2.65 (q, J = 8.7 Hz, 2 H), 1.85 (quintet, J = 7.7 Hz, 2 H), 1.38 (s, 6 H), 1.30 (m, 2 H), 1.26 (t, J = 8.7 Hz, 3 H), 0.71 (m, 1 H), 0.42 (m, 2 H), 0.02 (m, 2 H); ^{13}C NMR δ 199.3, 162.0, 136.6, 130.9, 129.1, 125.8, 120.4, 85.2, 41.7, 38.0, 34.4, 27.7, 24.8, 22.8, 13.8, 10.7, 4.4; IR 2963, 1672, 1599, 1460 cm^{-1}; MS 287 (MH^+). Anal. ($C_{19}H_{26}O_2$) C, H.

1-(7-Cyclopentyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (45). 6-Cyclopentyl-2,4-dibromophenol. To a solution of 2-cyclopentylphenol (24 g, 148.8 mmol) in MeOH (50 mL) at 0 °C was added Br_2 (22.87 mL, 446 mmol) dropwise over 1 h. The reaction mixture was warmed to 23 °C and stirred for 64 h. The reaction mixture was quenched with H_2O (50 mL), the MeOH evaporated, and the aqueous mixture extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried ($MgSO_4$) and evaporated to a dark-red oil which was dissolved in hexanes (30 mL) and stirred in silica gel (5 g). The silica was removed by filtration, and the hexanes were evaporated to provide the product as an orange oil (43.33 g, 92%) which was used without further purification: ^{1}H NMR δ 7.41 (d, J = 1.5 Hz, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 5.58 (s, 1 H), 3.25 (quintet, J = 9.7 Hz, 1 H), 1.98−2.10 (m, 2 H), 1.60−1.90 (m, 4 H), 1.52−1.58 (m, 2 H).

6-Cyclopentyl-2,4-dibromophenyl 2-Methallyl Ether (13b). Prepared from 6-cyclopentyl-2,4-dibromophenol as described for **13a** to give a dark oil (28.6 g). This oil was dissolved in hexanes (100 mL) and stirred with silica gel (40 g). The silica was removed by filtration, and the hexanes were evaporated to give **13b** as a dark-yellow oil (38 g, 75%), suitable for the next reaction without further purification: ^{1}H NMR δ 7.50 (d, J = 1.5 Hz, 1 H), 7.31 (d, J = 1.5 Hz, 1 H), 5.19 (s, 1 H), 5.00 (s, 1 H), 4.28 (s, 2 H), 3.34 (quintet, J = 10.3 Hz, 1 H), 2.05 (m, 2 H), 1.90 (s, 3H), 1.65−1.90 (m, 4 H), 1.25−1.35 (m, 2 H).

5-Bromo-7-cyclopentyl-2,3-dihydro-3,3-dimethylbenzofuran (14b). Prepared from **13b** as described for **14a** to give a dark oil (21.2 g). This oil was dissolved in hexanes, washed with 1 M NaOH (3 × 50 mL), and then purified by medium-pressure chromatography (1% EtOAc/hexanes) to give **14b** as a yellow oil (4.21 g, 14%), suitable for the next reaction: ^{1}H NMR δ 7.10 (d, J = 1.8 Hz, 1 H), 6.99 (d, J = 1.8 Hz, 1 H), 4.20 (s, 2 H), 3.05 (quintet, J = 8.3 Hz, 1 H), 2.05 (m, 2 H), 1.50−1.80 (m, 6 H), 1.33 (s, 6 H); ^{13}C NMR δ 156.1, 138.2, 130.5, 128.4, 122.6, 112.4, 84.3, 42.2, 39.9, 32.8, 27.4, 25.4.

7-Cyclopentyl-2,3-dihydro-3,3-dimethyl-5-benzofuran (15b). This compound was isolated as a side product in the following carboxylation reaction. To a solution of **14b** (3.95 g, 13.4 mmol) in dry THF (15 mL) at −78 °C was added *n*-BuLi (10.7 mL, 26.8 mmol, 2.5 M solution in hexanes) dropwise over 10 min. The reaction mixture was slowly warmed to −20 °C and then cooled back to −50 °C. A large excess of freshly crushed dry ice was added and the milky-brown suspension warmed to 0 °C for 1 h. The THF was then evaporated, and the reaction mixture was dissolved in Et_2O and washed with 1 N NaOH (50 mL). The Et_2O was dried ($MgSO_4$) and evaporated to give **15b** (595 mg, 21%) as a yellow oil: ^{1}H NMR δ 7.29 (dd, J = 7.8, 1.8 Hz, 1 H), 7.15 (dd, J = 7.8, 1.8 Hz, 1 H), 6.75 (t, J = 7.8 Hz, 1 H), 4.20 (s, 2 H), 3.05 (m, 1 H), 2.05 (m, 2 H), 1.50−1.80 (m, 6 H), 1.30 (s, 6 H).

1-(7-Cyclopentyl-2,3-dihydro-3,3-dimethyl-5-benzofuranyl)-4-cyclopropylbutan-1-one (45). Method A was used. The crude product was purified by preparative TLC (1500 μm, hexanes/EtOAc, 99/1): ^{1}H NMR δ 7.73 (d, J = 1.5 Hz, 1 H), 7.61 (d, J = 1.5 Hz, 1 H), 4.32 (s, 2 H), 3.14 (m, 1 H), 2.96 (t, J = 8.7 Hz, 2 H), 2.05 (m, 2 H), 1.83 (m, 4 H), 1.68 (m, 4 H), 1.38 (s, 6 H), 1.30 (q, J = 8.7 Hz, 2 H), 0.70 (m, 1 H), 0.42 (m, 2 H), 0.05 (m, 2 H); ^{13}C NMR δ 199.2, 161.4, 136.6, 130.9, 128.1, 127.5, 120.2, 85.0, 41.6, 40.0, 38.0, 34.3, 32.7, 27.6, 25.4, 24.8, 10.7, 4.4; IR 2957, 1673, 1598 cm^{-1}; MS 327 (MH^+); HRMS calcd for $C_{22}H_{30}O_2$ (MH^+) 327.2324, found 327.2298; HPLC: 89.6%. Anal. ($C_{22}H_{30}O_2$) C, H; C: calcd, 80.94; found, 81.68.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzothienyl)-butan-1-one (46). 2-Bromo-6-*tert*-butylthiophenol (20). To a solution of tetramethylethylenediamine (198.4 mmol, 30 mL) in cyclohexanes (140 mL) was slowly added *n*-BuLi (99.2 mL, 198.4 mmol, 2 M solution in cyclohexanes) at 23 °C. The resulting solution was cooled to 0 °C. A solution of 2-*tert*-butylthiophenol (15.0 g, 90.2 mmol) in cyclohexanes (40 mL) was then added at a rate such that the temperature stayed below 10 °C. The reaction mixture was then stirred at 0 °C for 5 h and allowed to warm to 23 °C overnight. To the resulting yellow solution at 23 °C was added *sec*-BuLi (69.4 mL, 90.2 mmol, 1.3 M solution in cyclohexanes) over 0.5 h. The resulting solution gradually turned orange. After 1.5 h, the orange, cloudy reaction mixture was cannulated into a stirring solution of 1,2-dibromotetrafluoroethane (21.5 mL, 180.4 mmol) in THF (50 mL) over 1 h. After addition was complete, the resulting reaction was quenched with 1 N HCl (80 mL) and extracted with hexanes (3 × 100 mL). The hexanes were dried ($MgSO_4$) and evaporated to a dark oil (29.48 g). This oil was taken up in 1 N NaOH (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was discarded, and the aqueous phase was acidified with 12 N HCl and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried ($MgSO_4$) and evaporated to provide **20** as a yellow oil (12.4 g, 56%): ^{1}H NMR δ 7.46 (dd, J = 8.7, 1.4 Hz, 1 H), 7.30 (dd, J = 8.7, 1.4 Hz, 1 H), 6.90 (t, J = 8.7 Hz, 1 H), 4.85 (s, 1 H), 1.47 (s, 9 H); MS 244, 246 (MH^+).

2-Bromo-6-*tert*-butylphenyl 2-Methallyl Thioether (21). A solution of **20** (12.4 g, 50.6 mmol), K_2CO_3 (8.44 g, 61.1 mmol), NaI (766 mg, 50.6 mmol), and 3-chloro-2-methylpropene (5.17 mL, 50.6 mmol) in acetone (250 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to 23 °C, and the precipitated solids were filtered off. The filtrate was evaporated to a dark-yellow oil, which was taken up in hexanes (100 mL) and stirred with silica gel (10 g) for 20 min. The silica gel was filtered off and discarded, and the filtrate was evaporated to yield **21** as a light-yellow oil (9.01 g, 59.4%): ^{1}H NMR δ 7.58 (dd, J = 8.0, 0.9 Hz, 1 H), 7.42 (dd, J = 8.0, 0.9 Hz, 1 H), 7.08 (t, J = 8.0 Hz, 1 H), 4.98 (s, 1 H), 4.91 (s, 1 H), 3.53 (s, 2 H), 1.94 (s, 3 H), 1.58 (s, 9 H).

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzothiophene (22). A solution of **21** (9.00 g, 30.0 mmol), *i*-Pr_2NEt (160 mL, 0.90 mol), and 80% aqueous hypophosphorus acid (58 g, 0.90 mol) in dioxane (450 mL) was reacted as described for **7a** to yield the crude product as a yellow oil (5.61 g). Short-path vacuum distillation (85 °C, 40 mmHg) of this material provided **22** as a faint-yellow oil of approximately 80% purity by GC analysis, which was used without further purification: ^{1}H NMR δ 7.19 (d, J = 7.0 Hz, 1 H), 7.10 (t, J = 7.0 Hz, 1 H), 6.92 (d, J = 7.0 Hz, 1 H), 3.07 (s, 2 H), 1.41 (s, 9 H), 1.33 (s, 6 H); MS 221 (MH^+).

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzothienyl)-butan-1-one (46). Method A was used. The crude product was purified by medium-pressure chromatography (1% EtOAc/hexanes): ^{1}H NMR δ 7.84 (d, J = 1.7 Hz, 1 H), 7.54 (d, J = 1.7 Hz, 1 H), 3.19 (s, 2 H), 2.94 (t, J = 7.1 Hz, 2 H), 1.78 (m, J = 7.1 Hz, 2 H), 1.48 (s, 9 H), 1.43 (s, 6 H), 1.02 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 200.1, 150.0, 145.4, 144.7, 134.0, 125.1, 120.1, 47.3, 46.3, 40.6, 36.0, 29.2, 27.8, 18.2, 14.2; IR 2950,

2928, 2871, 1679 cm^{-1}; HRMS calcd for $C_{18}H_{26}OS$ (MH^+) 291.1783, found 291.1776; HPLC 95.2%. Anal. ($C_{18}H_{26}OS$) C, H, S; C: calcd, 74.43; found, 73.73.

1-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-5-benzothienyl)-4-cyclopropylbutan-1-one (47). Method A was used. The crude product was purified by medium-pressure chromatography (1% EtOAc/hexanes): ^1H NMR δ 7.80 (d, J = 1.7 Hz, 1 H), 7.70 (d, J = 1.7 Hz, 1 H), 3.15 (s, 2 H), 2.96 (t, J = 7.5 Hz, 2 H), 1.84 (m, 2 H), 1.42 (s, 9 H), 1.38 (s, 6 H), 1.30 (m, 2 H), 0.70 (m, 1 H), 0.41 (m, 2 H), 0.10 (m, 2 H); ^{13}C NMR δ 200.0, 149.7, 145.0, 144.4, 133.9, 124.9, 119.8, 47.0, 45.9, 38.1, 35.6, 34.2, 28.8, 27.4, 24.7, 10.6, 4.3; IR 2961, 1676, 1587 cm^{-1}; HRMS calcd for $C_{21}H_{30}OS$ (MH^+) 331.2096, found 331.2106; HPLC 96.4%.

7-*tert*-Butyl-5-(4-cyclopropylbutanoyl)-2,3-dihydro-1,3,3-trimethylindole (48). 7-*tert*-Butyl-2-indolinone (25). Ethyl (methylthio)acetate (13.0 mL, 0.1 mol) was added dropwise to a solution of chlorine (ca. 9.4 g, 0.13 mol) in 500 mL of CH_2Cl_2 at −78 °C. To the reaction mixture at −78 °C was added over 10 min 2-*tert*-butylaniline (15.6 mL, 0.1 mol) followed by Et_3N (25 mL, 0.18 mol) over 25 min. The resulting brown suspension was warmed to room temperature and the reaction quenched with 1 N HCl. This mixture was stirred for 1 h, and the organic layer was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to give 30.0 g of a brown solid. This solid residue was dissolved in 220 mL of EtOAc, and the resulting solution was hydrogenated for 24 h with Raney nickel (30 g). The reaction mixture was filtered through a short column of silica gel; the filtrate was placed at room temperature for 3 days to allow for slow evaporation of the solvent, thus affording 6.51 g (34%) of **25** as slightly amber transparent crystals: mp 162−163 °C; ^1H NMR δ 8.56 (bs, 1 H), 7.21 (d, J = 7.6 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 6.98 (t, J = 7.6 Hz, 1 H), 3.52 (s, 2 H), 1.39 (s, 9 H); MS 190 (MH^+), 207 (MNH_4^+).

7-*tert*-Butyl-3,3-dimethyl-2-indolinone. Lithium diisopropylamide (30.0 mL, 60.0 mmol, 2.0 M solution in heptane−THF−ethylbenzene) was added to a solution of **25** (3.0 g, 15.9 mmol) in 60 mL of anhydrous THF at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, and CH_3I (2.5 mL, 40.1 mmol) was added. The resulting mixture was kept at −78 °C for 0.5 h, warmed to 0 °C, stirred for 0.5 h, quenched with H_2O, and extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated to give a yellow solid residue. Recrystallization from acetone afforded 2.87 g (83%) of the title compound as a light-orange solid: mp 167−170 °C; ^1H NMR δ 8.55−8.25 (br, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.00 (m, 2 H), 1.35 (s, 15 H); ^{13}C NMR δ 183.8, 137.2, 136.9, 132.0, 124.7, 122.3, 120.3, 43.3, 34.0, 29.8, 24.4; IR 3206, 3083, 2965, 1709, 1601 cm^{-1}; MS 218 (MH^+).

7-*tert*-Butyl-2,3-dihydro-3,3-dimethylindole (26). A solution of 7-*tert*-butyl-3,3-dimethyl-2-indolinone (2.17 g, 10.0 mmol) in 50 mL of THF was added to a suspension of $LiAlH_4$ (2.20 g, 57.9 mmol) in 50 mL of ether. The reaction mixture was heated at reflux for 17 h, cooled to 0 °C, and quenched with H_2O until white solids precipitated out of solution. The organic phase was decanted out, and the solid residue was rinsed with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated to afford **26** (1.86 g, 91%) as an oil: ^1H NMR δ 7.07 (dd, J = 8.0, 1.8 Hz, 1 H), 6.94 (dd, J = 8.0, 1.8 Hz, 1 H), 6.74 (t, J = 8.0 Hz, 1 H), 3.32 (s, 2 H), 1.37 (s, 9 H), 1.28 (s, 6 H); ^{13}C NMR δ 147.5, 139.2, 131.6, 124.1, 119.8, 118.6, 61.3, 40.8, 34.1, 29.4, 27.5; IR 3427, 2957, 2865, 1591 cm^{-1}; MS 204 (MH^+).

5-Bromo-7-*tert*-butyl-2,3-dihydro-3,3-dimethylindole. A solution of bromine (1.0 mL, 18.5 mmol) in 5 mL of CH_2Cl_2 was added to a solution of **26** (3.75 g, 18.5 mmol) in 65 mL of CH_2Cl_2. The reaction mixture was stirred for 0.5 h and concentrated to afford 6.35 g of a solid residue, which was washed with hexane, suspended in 100 mL of MeOH, and reacted for 0.5 h with Et_3N (1.77 g, 17.5 mmol). This mixture was concentrated in vacuo, and the residue was partitioned between Et_2O and H_2O. The organic layer was dried ($MgSO_4$) and concentrated to furnish 4.57 g (87%) of the title compound as a yellowish oil, which solidified upon refrigeration: mp 64−65 °C; ^1H NMR δ 7.13 (d, J = 1.8 Hz, 1 H), 7.00 (d, J = 1.8 Hz, 1 H), 3.33 (s, 2 H), 1.31 (s, 9 H), 1.27 (s, 6 H); MS 283 (MH^+).

5-Bromo-7-*tert*-butyl-2,3-dihydro-1,3,3-trimethylindole (27). Formaldehyde (1.64 mL, 21.9 mmol, 37% aqueous solution) and $NaBH_3CN$ (0.50 g, 8.0 mmol) were added to a solution of 5-bromo-7-*tert*-butyl-2,3-dihydro-3,3-dimethylindole (2.07 g, 7.3 mmol) in 10 mL of of 1:9 HOAc−CH_3CN mixture. The reaction mixture was stirred for 0.5 h, poured into a 1:1 mixture of H_2O and 50% aqueous NaOH, and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (1% → 2% EtOAc/hexanes) yielded **27** (1.52 g, 70%) as a yellowish oil: ^1H NMR δ 7.15 (d, J = 1.8 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 3.36 (s, 2 H), 3.08 (s, 3 H), 1.34 (s, 9 H), 1.30 (s, 6 H); MS 296 (MH^+).

4-Cyclopropylbutanal. Pyridinium chlorochromate (12.33 g, 57.2 mmol) was added to a solution of 4-cyclopropylbutanol (3.78 g, 33.2 mmol) in 82 mL of CH_2Cl_2. The brown reaction mixture was vigorously stirred for 1.5 h; Et_2O was added to the mixture, and stirring was continued for 20 min. The resulting mixture was filtered through a short column of silica gel and concentrated in vacuo to give 3.17 g of the crude product. Purification by flash column chromatography on silica gel (5% Et_2O/hexanes) afforded 2.48 g (67%) of 4-cyclopropylbutanal as a yellowish oil: ^1H NMR δ 9.77 (d, J = 1.1 Hz, 1 H), 2.46 (dt, J = 7.4, 1.1 Hz, 2 H), 1.73 (m, 2 H), 1.24 (q, J = 7.4 Hz, 2 H), 0.66 (m, 1 H), 0.40 (m, 2 H), 0.03 (m, 2 H).

7-*tert*-Butyl-5-(4-cyclopropylbutanoyl)-2,3-dihydro-1,3,3-trimethylindole (48). Method D. *t*-BuLi (1.6 mL, 2.7 mmol, 1.7 M in pentane) was added dropwise to a solution of **27** (0.38 g, 1.3 mmol) in 7 mL of anhydrous Et_2O at −78 °C; the resulting yellow solution was stirred at −78 °C for 10 min, and 4-cyclopropylbutanal (0.21 g, 1.9 mmol) was introduced. The reaction mixture was kept at −78 °C for 15 min, warmed to −20 °C, quenched with H_2O, and warmed to room temperature. The ethereal layer was dried ($MgSO_4$) and concentrated to give a yellowish viscous oil, which was dissolved in 5 mL of CH_2Cl_2 and reacted for 3 h with 4-methylmorpholine *N*-oxide (0.09 g, 0.8 mmol) and tetrapropylammonium perruthenate (0.04 g, 0.1 mmol). The reaction mixture was filtered through a short column of silica gel and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% Et_2O/hexanes) gave **48** (0.23 g, 54%) as a light-yellow oil which solidified upon storage in a refrigerator: mp 44−46 °C; ^1H NMR δ 7.89 (d, J = 1.8 Hz, 1 H), 7.47 (d, J = 1.8 Hz, 1 H), 3.20 (s, 2 H), 3.05 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 1.79 (m, 2 H), 1.43 (s, 9 H), 1.27 (m, 2 H), 1.25 (s, 6 H), 0.66 (m, 1 H), 0.38 (m, 2 H), 0.02 (m, 2 H); ^{13}C NMR δ 199.2, 154.4, 143.2, 143.2, 133.9, 128.6, 119.5, 71.8, 44.4, 39.5, 37.8, 34.6, 34.4, 31.6, 28.6, 25.0, 10.6, 4.30; IR 2957, 2865, 1668, 1600, cm^{-1}; MS 328 (MH^+). Anal. ($C_{22}H_{33}NO$) C, H, N.

2,4-Dibromo-6-*tert*-butyl-1-((3-methyl-2-butenyl)oxy)-benzene (16). To a solution of 2,4-dibromo-6-*tert*-butylphenol (**5**) (10.00 g, 32.5 mmol) in EtOH (50 mL) were added K_2CO_3 (6.73 g, 48.7 mmol), a catalytic amount of *n*-Bu_4NI, and 4-bromo-2-methyl-2-butene (5.80 mL, 39.0 mmol). The resulting suspension was stirred at room temperature for 48 h, filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give **16** (12.40 g, 100%) as an oil: ^1H NMR δ 7.57 (d, J = 2.5 Hz, 1 H), 7.38 (d, J = 2.0 Hz, 1 H), 5.01 (t, J = 6.5 Hz, 1 H), 4.57 (d, J = 6.5 Hz, 2 H), 1.82 (s, 3 H), 1.76 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR δ 157.7, 147.1, 137.9, 134.0, 129.9, 128.3, 119.7, 116.5, 70.4, 35.9, 30.7, 25.9, 18.5; IR 2963, 2873, 1568 cm^{-1}.

4-Bromo-2-*tert*-butyl-1-((3-methyl-2-butenyl)oxy)benzene (17). To a cold (−78 °C) solution of **16** (12.47 g, 33.15 mmol) in THF/hexanes (100 mL/25 mL) was added *n*-BuLi (13.3 mL, 2.5 M/hexanes, 33.15 mmol) dropwise. The resulting pale-yellow solution was stirred at −78 °C for 15 min and the reaction quenched by slow addition of H_2O. The mixture was diluted with hexanes, and the layers were separated. The organic layer was washed with H_2O followed by brine. The

aqueous layers were extracted with hexanes; the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give **17** (9.35 g, 95%) as an oil: ^{1}H NMR δ 7.35 (d, J = 2.0 Hz, 1 H), 7.25 (dd, J = 8.7, 2.3 Hz, 1 H), 6.73 (d, J = 9.0 Hz, 1 H), 5.01 (t, J = 6.5 Hz, 1 H), 4.51 (d, J = 6.5 Hz, 2 H), 1.80 (s, 3 H), 1.73 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR δ 156.8, 140.7, 137.2, 129.7, 129.4, 119.8, 114.0, 112.6, 65.1, 35.0, 29.5, 25.7, 18.2; IR 2872, 1583 cm^{-1}.

4-Bromo-2-*tert*-butyl-1-((3-hydroxy-3-methylbutyl)-oxy)benzene (18). To a yellow suspension of $Hg(OAc)_2$ (6.36 g, 19.94 mmol) in THF/H_2O (25 mL/30 mL) was added **17** (5.93 g, 19.941 mmol) in THF (5 mL) dropwise, and the mixture stirred at room temperature for 4 h. To the resulting pale-yellow solution was added NaOH (15 mL, 3 M) followed by $NaBH_4$ (0.75 g, 19.94 mmol) in NaOH (5 mL, 3 M). The resulting ash-colored suspension was stirred at room temperature for 30 min, diluted with hexanes, and washed with water, saturated aqueous NH_4Cl, and brine. The aqueous layers were extracted with hexanes; the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes/EtOAc, 10/1 → 3/1) to give **18** (4.21 g, 67%) as an oil: ^{1}H NMR δ 7.35 (d, J = 2.0 Hz, 1 H), 7.26 (dd, J = 8.5, 2.5 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 4.15 (t, J = 7.5 Hz, 2 H), 2.07 (t, J = 7.5 Hz, 2 H), 1.67 (s, 1 H), 1.35 (s, 9 H), 1.34 (s, 6 H); ^{13}C NMR δ 156.8, 140.5, 129.7, 129.5, 114.1, 113.0, 70.1, 65.2, 42.3, 34.9, 29.8, 29.6; IR 2958, 1583, 1463 cm^{-1}.

6-Bromo-8-*tert*-butyl-2,3-dihydro-4,4-dimethylbenzopyran. To a cold (0 °C) suspension of $AlCl_3$ (1.67 g, 12.51 mmol) in CH_3NO_2 (20 mL) was added a solution of **18** (3.94 g, 12.51 mmol) in CH_3NO_2 (5 mL). The resulting red solution was stirred at 0 °C. After 1 h, the reaction was quenched by slow addition of H_2O. The mixture was diluted with hexanes, the layers were separated, and the organic layer was washed with H_2O and brine. The aqueous layers were extracted with hexanes; the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give the title compound (2.87 g, 77%) as a solid which was recrystallized from hexanes to give white crystals: mp 62−63 °C; ^{1}H NMR δ 7.23 (d, J = 2.5 Hz, 1 H), 7.16 (d, J = 2.0 Hz, 1 H), 4.15 (t, J = 5.5 Hz, 2 H), 1.81 (t, J = 5.5 Hz, 2 H), 1.33 (s, 9 H), 1.31 (s, 6 H); ^{13}C NMR δ 151.8, 140.2, 134.1, 127.7, 127.3, 112.2, 62.3, 37.3, 35.1, 31.5, 31.2, 29.6; IR 2960, 2872, 1436 cm^{-1}.

8-*tert*-Butyl-2,3-dihydro-4,4-dimethylbenzopyran (19). To a cold (−78 °C) solution of 6-bromo-8-*tert*-butyl-2,3-dihydro-4,4-dimethylbenzopyran (2.29 g, 7.72 mmol) in THF/hexanes (28 mL/7 mL) was added *n*-BuLi (3.70 mL, 2.5 M/hexanes, 9.26 mmol) dropwise. The resulting pale-yellow solution was stirred for 30 min at −78 °C and the reaction quenched by slow addition of H_2O. The mixture was diluted with hexanes, and the layers were separated. The organic layer was washed with 1 N HCl, H_2O, and brine. The aqueous layers were extracted with hexanes; the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography on silica (hexanes) to give **19** (1.60 g, 95%) as a solid which was recrystallized using hexanes to afford white crystals: mp 34−35 °C; ^{1}H NMR δ 7.20 (dd, J = 8.0, 2.0 Hz, 1 H), 7.15 (dd, J = 7.5, 1.5 Hz, 1 H), 6.87 (t, J = 7.7 Hz, 1 H), 4.22 (s, 2 H), 1.87 (m, 2 H), 1.42 (s, 9 H), 1.38 (s, 6 H); ^{13}C NMR δ 152.8, 137.7, 132.0, 125.1, 124.2, 119.5, 62.2, 37.8, 34.9, 31.7, 31.0, 29.8; IR 2958, 1583 cm^{-1}.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)pentan-1-one (49). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give an oil which was distilled (105−109 °C, 0.4 mmHg): ^{1}H NMR δ 7.85 (d, J = 2.0 Hz, 1 H), 7.75 (d, J = 2.0 Hz, 1 H), 4.26 (t, J = 5.5 Hz, 2 H), 2.91 (t, J = 7.5 Hz, 2 H), 1.86 (t, J = 5.5 Hz, 2 H), 1.72 (m, 2 H), 1.42 (m, 2 H), 1.39 (s, 9 H), 1.38 (s, 6 H), 0.96 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 199.8, 157.2, 137.7, 131.7, 128.7, 125.9, 124.8, 62.7, 37.8, 37.1, 35.0, 31.4, 31.0, 29.6, 26.9, 22.6, 14.0; IR 2958, 2872, 1674, 1595, 1465 cm^{-1}; MS 303 (MH^+). Anal. ($C_{20}H_{30}O_2$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)-4-cyclopropylbutan-1-one (50). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give an oil which was distilled (114−116 °C, 0.5 mmHg): ^{1}H NMR δ 7.85 (d, J = 2.5 Hz, 1 H), 7.76 (d, J = 2.5 Hz, 1 H), 4.26 (t, J = 5.5 Hz, 2 H), 2.95 (t, J = 7.5 Hz, 2 H), 1.87−1.81 (m, 4 H), 1.39 (s, 9 H), 1.37 (s, 6 H), 1.30 (q, J = 7.5 Hz, 2 H), 0.71 (m, 1 H), 0.42 (m, 2 H), 0.04 (m, 2 H); ^{13}C NMR δ 199.8, 157.0, 137.6, 131.7, 128.7, 125.9, 124.7, 62.7, 37.8, 37.0, 35.0, 34.4, 31.4, 31.0, 29.6, 24.9, 10.7, 4.4; IR 3074, 2998, 2959, 1673, 1595 cm^{-1}; MS 329 (MH^+). Anal. ($C_{22}H_{32}O_2$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)-3-hydroxy-3-methylbutan-1-one (51). 1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)ethanone. Method C was used. $AlCl_3$ (0.32 g, 2.39 mmol, 1.2 equiv), acetyl chloride (0.15 mL, 2.19 mmol, 1.1 equiv), and **19** were reacted as described for **37** except that the reaction was kept at −78 °C for 2 h and was then quenched. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give a solid which was recrystallized using hexanes to give the title compound (0.40 g, 76%) as a white solid: mp 118−119 °C; ^{1}H NMR δ 7.84 (d, J = 2.5 Hz, 1 H), 7.75 (d, J = 2.0 Hz, 1 H), 4.26 (t, J = 5.5 Hz, 2 H), 2.55 (s, 3 H), 1.85 (t, J = 5.5 Hz, 2 H), 1.39 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 197.4, 157.2, 137.7, 131.8, 128.9, 126.1, 125.0, 62.7, 37.0, 35.0, 31.3, 31.0, 29.6, 26.2; IR 2959, 1672, 1595 cm^{-1}.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)-3-hydroxy-3-methylbutan-1-one (51). Method C was used. 1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)ethanone was reacted as described for **37**. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1) to give **51** (0.30 g, 70%) as a pale-yellow solid which was recrystallized using pentane: mp 92−93 °C; ^{1}H NMR δ 7.82 (d, J = 2.0 Hz, 1 H), 7.73 (d, J = 2.0 Hz, 1 H), 4.51 (s, 1 H), 4.28 (t, J = 5.5 Hz, 2 H), 3.07 (s, 2 H), 1.86 (t, J = 5.5 Hz, 2 H), 1.38 (s, 9 H), 1.37 (s, 6 H), 1.34 (s, 6 H); ^{13}C NMR δ 201.0, 157.9, 138.0, 132.0, 128.9, 126.1, 122.8, 69.9, 62.8, 47.7, 36.9, 35.1, 31.4, 31.0, 29.7, 29.6; IR 3478, 2963, 1659, 1593 cm^{-1}; MS 319 (MH^+), 261 (MH^+ − acetone). Anal. ($C_{20}H_{30}O_3$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzopyranyl)-5-hexyn-1-one (52). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 20/1) to give an oil which was distilled (109−111 °C, 0.4 mmHg): ^{1}H NMR δ 7.87 (d, J = 2.0 Hz, 1 H), 7.77 (d, J = 2.0 Hz, 1 H), 4.26 (t, J = 5.5 Hz, 2 H), 3.07 (t, J = 7.5 Hz, 2 H), 2.33 (td, J = 7.0, 2.5 Hz, 2 H), 2.00 (s, 1 H), 1.97 (q, J = 7.0 Hz, 2 H), 1.80 (m, 2 H), 1.39 (s, 9 H), 1.37 (s, 6 H); ^{13}C NMR δ 198.8, 157.2, 137.7, 131.8, 128.76, 125.9, 124.7, 83.9, 68.9, 62.7, 37.0, 36.4, 35.0, 31.4, 31.0, 29.6, 23.3, 18.0; IR 3307, 2959, 1672, 1595 cm^{-1}; MS 313 (MH^+). Anal. ($C_{21}H_{28}O_2$) C, H.

1,5-Dibromo-2-((3-bromopropyl)oxy)-3-*tert*-butylbenzene (9b). Prepared as described for **9a** but with 1,3-dibromopropane. The crude product was purified by flash column chromatography on silica (hexanes) to give an off-white oil which was Kugelrohr distilled (220−222 °C, 0.1 mmHg) to give **9b** (6.13 g, 88%) as a pale-yellow oil: ^{1}H NMR δ 7.57 (s, 1 H), 7.39 (s, 1 H), 4.18 (t, J = 5.4 Hz, 2 H), 3.67 (t, J = 6.3 Hz, 2 H), 2.44 (m, 2 H), 1.36 (s, 9 H); ^{13}C NMR δ 154.3, 147.0, 134.1, 130, 119, 116.7, 70.7, 35.8, 33.2, 30.8, 29.6; IR 2964, 2912, 1545 cm^{-1}; MS (EI) 432 (M^+ + 3), 430 (M^+ + 1), 428, 310, 308, 306.

8-*tert*-Butyl-2,3-dihydrobenzopyran (10b). Prepared as described for **10a**. The crude product was purified by flash column chromatography on silica (hexanes) to give an off-white oil which was Kugelrohr distilled (100−103 °C, 0.3 mmHg) to give **10b** (1.92 g, 87%) as an off-white oil: ^{1}H NMR δ 7.11 (d, J = 7.2 Hz, 1 H), 6.92 (d, J = 7.2 Hz, 1 H), 6.79 (t, J = 7.3 Hz, 1 H), 4.20 (t, J = 5.2 Hz, 2 H), 2.83 (t, J = 6.6 Hz, 2 H), 2.01 (m, 2 H), 1.38 (s, 9 H); ^{13}C NMR δ 154.0, 137.7, 128.0, 124.3,

122.6, 119.4, 65.6, 34.8, 29.6, 25.4, 22.4; IR 2951, 2870, 1587 cm^{-1}; MS (EI) 190 (M^+), 176, 175, 147.

1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)pentan-1-one (53). Method A was used. The crude product was purified by flash column chromatography (hexanes, hexanes/EtOAc, 25/1) to give a crude oil which was distilled (135−139 °C, 0.5 mmHg) to give **53** (0.49 g, 85%) as a colorless oil: ^1H NMR δ 7.77 (d, J = 2.1 Hz, 1 H), 7.55 (d, J = 2.0 Hz, 1 H), 4.26 (t, J = 5.3 Hz, 2 H), 2.88 (t, J = 7.5 Hz, 2 H), 2.85 (t, J = 6.6 Hz, 2 H), 2.02 (m, 2 H), 1.70 (m, 2 H), 1.42 (m, 2 H), 1.38 (s, 9 H), 0.95 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 199.9, 158.1, 137.7, 128.8, 128.6, 124.9, 122.1, 66.2, 37.8, 34.8, 29.5, 26.9, 25.4, 22.5, 21.9, 13.9; IR 2956, 2933, 2872, 1675, 1582 cm^{-1}; MS 275 (MH^+). Anal. ($C_{18}H_{26}O_2$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)-4-cyclopropylbutan-1-one (54). Method A was used. The crude product was purified by flash column chromatography on silica (hexanes/EtOAc, 10/1−4/1): ^1H NMR δ 7.77 (d, J = 2.0 Hz, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 4.27 (t, J = 5.0 Hz, 2 H), 2.92 (t, J = 7.5 Hz, 2 H), 2.85 (t, J = 7.0 Hz, 2 H), 2.02 (m, 2 H), 1.83 (quintet, J = 7.5 Hz, 2 H), 1.38 (s, 9 H), 1.29 (q, J = 7.5 Hz, 2 H), 0.70 (m, 1 H), 0.42 (m, 2 H), 0.03 (m, 2 H); ^{13}C NMR δ 199.7, 158.0, 137.6, 128.7, 128.5, 124.8, 122.0, 66.2, 37.8, 34.8, 34.3, 29.5, 25.4, 24.8, 21.9, 10.6, 4.4; IR 2998, 2952, 2870, 1675, 1581 cm^{-1}; MS 261 (MH^+). Anal. ($C_{20}H_{28}O_2$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)-3-hydroxy-3-methylbutan-1-one (55). 1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)ethanone. Method C was used. Compound **10b** was reacted as described for **37**. The resulting off-white solid was recrystallized using hexanes to give the title compound (0.67 g, 79%) as white crystals: mp 74−75 °C; ^1H NMR δ 7.75 (d, J = 1.5 Hz, 1 H), 7.75 (d, J = 1.0 Hz, 1 H), 4.27 (t, J = 5.1 Hz, 2 H), 2.85 (t, J = 6.5 Hz, 2 H), 2.53 (s, 3 H), 2.02 (m, 2 H), 1.42 (s, 9 H); ^{13}C NMR δ 197.4, 158.3, 137.7, 129.2, 128.8, 125.1, 122.1, 66.4, 34.8, 29.5, 26.2, 25.4, 21.8; IR 2977, 2956, 2872, 1671, 1589 cm^{-1}; MS (EI) 232 (M^+), 218, 217, 189. Anal. ($C_{15}H_{20}O$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)-3-hydroxy-3-methylbutan-1-one (55). Method C was used. 1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)ethanone was reacted as described for **37**. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1, 8/1, 4/1) to give a crude oil which was distilled (138−141 °C, 0.5 mmHg) to give **55** (0.40, 72%) as a colorless oil: ^1H NMR δ 7.75 (d, J = 2.5 Hz, 1 H), 7.54 (d, J = 2.0 Hz, 1 H), 4.28 (t, J = 5.0 Hz, 2 H), 3.06 (s, 2 H), 2.85 (t, J = 6.5 Hz, 2 H), 2.02 (m, 2 H), 1.33 (s, 9 H), 1.33 (s, 6 H); ^{13}C NMR δ 201.0, 158.9, 138.0, 129.0, 128.8, 124.9, 122.2, 69.9, 66.4, 47.7, 34.9, 29.6, 29.5, 25.4, 21.0; IR 3482, 2987, 2874, 1655, 1579, 1558 cm^{-1}; MS 291 (MH^+). Anal. ($C_{18}H_{26}O_3$) C, H; C: calcd, 74.45; found, 73.94.

1-(8-*tert*-Butyl-2,3-dihydro-6-benzopyranyl)-5-hexyn-1-one (56). Method A was used except that the reaction was performed in CH_3CN at 40 °C. The crude product was purified by flash column chromatography on silica (hexanes, hexanes/EtOAc, 10/1) to give a yellow oil (0.75 g, 92%) which was recrystallized using hexanes to give **56** (0.64 g, 79%) as white crystals: mp 52−53 °C; ^1H NMR δ 7.77 (d, J = 1.9 Hz, 1 H), 7.55 (d, J = 1.9 Hz, 1 H), 4.27 (t, J = 5.1 Hz, 2 H), 3.05 (t, J = 7.2 Hz, 2 H), 2.85 (t, J = 6.6 Hz, 2 H), 2.30 (m, 2 H), 2.04−1.93 (m, 5 H), 1.42 (m, 2 H), 1.38 (s, 9 H); ^{13}C NMR δ 198.8, 158.3, 137.8, 128.8, 128.5, 124.8, 122.1, 83.9, 68.9, 66,3, 37.8, 36.5, 34.9, 29.5, 25.4, 23.2, 21.9, 18.0; IR 3306, 2954, 2873, 2128, 1672, 1581 cm^{-1}; MS (EI) 284 (M^+), 269, 233, 232. Anal. ($C_{19}H_{24}O_2$) C, H.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzothiopyranyl)pentan-1-one (57). 2-*tert*-Butylphenyl 1-(3-Methylbut-2-enyl) Sulfide (23). NaH as an 80% dispersion in mineral oil (2 g, 69 mmol) was washed twice with hexanes under argon atmosphere. To this was added 20 mL of anhydrous THF. The mixture was cooled to 0 °C. 2-*tert*-Butylthiophenol (10 g, 60 mmol) was dissolved in 60 mL of THF and added slowly to the NaH mixture. After 40 min at 0 °C, a solution of 4-bromo-2-methyl-2-butene (6.9 mL, 60 mmol) in 20 mL of anhydrous THF was added. The reaction mixture was stirred for 30 min at 0 °C and for 15 min at room temperature. The reaction mixture was diluted with 500 mL of Et_2O and washed with 1 M NaOH. The organics were dried over Na_2SO_4 and concentrated under reduced pressure to give 13.5 g (96% yield) of **23** as a tan liquid which was used without further purification: ^1H NMR δ 7.40 (m, 2 H), 7.18 (m, 2 H), 5.38 (m, 1 H), 3.59 (d, J = 7.8 Hz, 2 H), 1.72 (s, 3 H), 1.63 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR δ 149.7, 136.6, 136.0, 132.8, 126.3, 126.1, 126.0, 119.0, 36.5, 34.6, 30.4, 25.6, 17.66.

8-*tert*-Butyl-2,3-dihydro-4,4-dimethylbenzothiopyran (24). Compound **23** (11 g, 47 mmol) and 85% H_3PO_4 (8.25 g, 71.6 mmol) in 110 mL of benzene were refluxed for 16 h. Then, over an 8-h period, three 5.5-g (116 mmol) portions of P_2O_5 were added to the refluxing mixture. The reaction mixture was stirred at reflux for 16 h. The mixture was cooled to room temperature, and the solution was decanted off the resulting red residue into a separatory funnel containing a 10% solution of NaCl. The residue was washed with Et_2O and 10% NaCl, and both of these washings were added to the separatory funnel. The product was extracted into the benzene/Et_2O layer, and this was washed again with salt solution. The organics were dried over Na_2SO_4 and concentrated under reduced pressure to give **24** (6.5 g, 60% yield): ^1H NMR δ 7.38 (d, J = 8.7 Hz, 1 H), 7.27 (d, J = 8.7 Hz, 1 H), 7.04 (t, J = 8.7 Hz, 1 H), 2.99 (t, J = 6.8 Hz, 2 H), 2.00 (t, J = 6.8 Hz, 2 H), 1.57 (s, 9 H), 1.42 (s, 6 H); ^{13}C NMR δ 146.9, 143.5, 128.3, 124.7, 124.3, 123.4, 37.8, 36.7, 34.4, 31.1, 30.1, 23.98.

1-(8-*tert*-Butyl-2,3-dihydro-4,4-dimethyl-6-benzothiopyranyl)pentan-1-one (57). Method B. To compound **24** (500 mg, 2.1 mmol) and valeryl chloride (0.29 mL, 2.34 mmol) in 10 mL of benzene at 0 °C was added $SnCl_4$ (0.27 mL, 2.34 mmol). The reaction mixture was allowed to stir for 1 h at 0 °C and was then diluted with Et_2O and washed with H_2O and 10% NaCl. The product was purified by flash silica gel chromatography, eluting with 7/3 hexanes/EtOAc to give **57** (250 mg, 37% yield): ^1H NMR δ 7.90 (s, 1 H), 7.82 (s, 1 H), 3.03 (t, J = 8.0 Hz, 2 H), 2.92 (t, J = 8.0 Hz, 2 H), 1.98 (t, J = 7.8 Hz, 2 H), 1.73 (m, 2 H), 1.55 (s, 9 H), 1.42 (m, 2 H), 1.40 (s, 6 H), 0.98 (t, J = 8.2 Hz, 3 H); ^{13}C NMR δ 200.2, 146.0, 143.2, 138.9, 131.6, 124.0, 123.7, 37.7, 36.7, 34.2, 30.6, 29.8, 29.3, 26.6, 23.9, 22.3, 13.8; MS (MH^+) 319. Anal. ($C_{20}H_{30}OS$) C, H.

8-*tert*-Butyl-4,4-dimethyl-6-pentanoyl-1,2,3,4-tetrahydroquinoline (58). *N*-Benzyl-2-*tert*-butylaniline. Benzaldehyde (22.1 g, 0.21 mol) was added to a solution of 2-*tert*-butylaniline (31.0 g, 0.21 mol) in 500 mL of a 4:1 CH_3CN−HOAc mixture. The resulting yellow solution was stirred for 15 min, and $NaBH_3CN$ (13.3 g, 0.21 mol) was added. The reaction mixture was stirred for 3 h, concentrated to ca. 150 mL in volume, poured into a cold 25% aqueous NaOH solution, and extracted with Et_2O. The extract was washed with 10% aqueous NaOH solution and H_2O, dried ($MgSO_4$), and concentrated to afford 48.3 g (96%) of the title compound as a colorless oil: ^1H NMR δ 7.45−6.65 (m, 9 H), 4.42 (s, 2 H), 1.45 (s, 9 H); MS 240 (MH^+).

***N*-Benzyl-*N*-(2-*tert*-butylphenyl)-3,3-dimethylacrylamide.** A solution of 3,3-dimethylacryloyl chloride (24.5 mL, 0.22 mol) in 210 mL of benzene was added over 30 min to a solution of *N*-benzyl-2-*tert*-butylaniline (50.7 g, 0.21 mol) in 210 mL of benzene. The reaction mixture was stirred for 24 h, quenched with aqueous Na_2CO_3 solution, and diluted with Et_2O. The organic layer was washed with aqueous Na_2CO_3 solution and H_2O, dried ($MgSO_4$), and concentrated to afford 66.3 g (98%) of the title compound as a yellowish solid: mp 82−83 °C; ^1H NMR δ 7.54 (dd, J = 7.4, 2.2 Hz, 1 H), 7.28 (m, 6 H), 6.96 (dt, J = 7.4, 2.2 Hz, 1 H), 6.42 (dd, J = 7.4, 2.2 Hz, 1 H), 5.80 (d, J = 12.9 Hz, 1 H), 5.37 (bs, 1 H), 3.72 (d, J = 12.9 Hz, 1 H), 2.18 (s, 3 H), 1.64 (s, 3 H), 1.38 (s, 9 H).

1-Benzyl-8-*tert*-butyl-3,4-dihydro-4,4-dimethyl-2(1*H*)-quinolinone (28). $AlCl_3$ (29.3 g, 0.22 mol) was added in one portion to a solution of *N*-benzyl-*N*-(2-*tert*-butylphenyl)-3,3-dimethylacrylamide (66.3 g, 0.21 mol) in 520 mL of 1,2-dichloroethane. The reaction mixture was stirred for 2 h, quenched with cold H_2O, stirred for 0.5 h, and diluted with

CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (10% → 25% Et_2O/hexanes) gave 54.1 g (80%) of **28** as an off-white solid: mp 120−121 °C; ^{1}H NMR δ 7.42 (dd, J = 7.4, 2.2 Hz, 1 H), 7.07 (m, 4 H), 6.96 (dd, J = 7.4, 2.2 Hz, 1 H), 6.79 (m, 2 H), 5.50 (d, J = 12.9 Hz, 1 H), 4.32 (d, J = 12.9 Hz, 1 H), 2.38 (d, J = 14.2 Hz, 1 H), 2.15 (d, J = 14.2 Hz, 1 H), 1.47 (s, 9 H), 1.17 (s, 3 H), 0.23 (s, 3 H); MS 322 (MH^+).

1-Benzyl-8-*tert*-butyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline. To a suspension of $LiAlH_4$ (1.48 g, 39.0 mmol) in 10 mL of Et_2O at reflux was added a solution of **28** (10.0 g, 31.2 mmol) in 63 mL of 1:2 THF−Et_2O mixture. The reaction mixture was heated at reflux for 2.5 h and cooled to room temperature. To it was added 30 mL of H_2O followed by 30 mL of 10% aqueous NaOH solution. The organic layer was separated, and the aqueous layer was extracted with Et_2O; the combined organics were dried over $MgSO_4$ and concentrated to yield 9.20 g of a yellowish solid. Purification by flash column chromatography on silica gel (2% → 5% ether/hexanes) yielded 6.72 g (70%) of the title compound as a colorless solid: mp 101−103 °C; ^{1}H NMR δ 7.55 (d, J = 7.1 Hz, 2 H), 7.43 (d, J = 7.4 Hz, 2 H), 7.32 (m, 3 H), 7.12 (t, J = 7.4 Hz, 1 H), 4.06 (br, 2 H), 3.07 (br, 2 H), 1.61 (m, 2 H), 1.57 (s, 9 H), 1.40 (br, 6 H); MS 308 (MH^+).

1-Benzyl-6-bromo-8-*tert*-butyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (29a). A solution of bromine (3.04 g, 19.0 mmol) in 30 mL of CH_2Cl_2 was added dropwise over 0.5 h to a well-stirred solution of 1-benzyl-8-*tert*-butyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (5.80 g, 18.9 mmol) in 30 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature over 2.5 h, quenched with Et_3N, and concentrated in vacuo. The solid residue thus obtained was dissolved in Et_2O; the resulting solution was washed with 1 N aqueous NaOH solution and H_2O, dried ($MgSO_4$), and concentrated to produce 10.2 g of a yellow solid. Recrystallization from hexanes provided 7.12 g (97%) of **29a** as a colorless solid: mp 120−121 °C; ^{1}H NMR δ 7.45 (d, J = 7.1 Hz, 2 H), 7.40−7.25 (m, 5 H), 3.95 (bs, 2 H), 2.98 (m, 2 H), 1.54 (m, 2 H), 1.49 (s, 9 H), 1.32 (br, 6 H); MS 386 (MH^+).

1-Benzyl-8-*tert*-butyl-4,4-dimethyl-6-pentanoyl-1,2,3,4-tetrahydroquinoline. Method D. *t*-BuLi (9.6 mL, 16.4 mmol, 1.7 M in pentane) was added dropwise to a solution of **29a** (3.08 g, 8.0 mmol) in 40 mL of anhydrous THF at −78 °C. This solution was stirred at −78 °C for 10 min, and valeraldehyde (1.1 mL, 10.0 mmol) was introduced. The reaction mixture was warmed to room temperature, quenched with H_2O, and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give 4.02 g of a brownish oil. A solution of this crude oil (1.30 g) in 30 mL of CH_2Cl_2 was reacted for 1.5 h with 4-methylmorpholine *N*-oxide (0.72 g, 6.2 mmol) and tetrapropylammonium perruthenate (0.06 g, 0.2 mmol). The reaction mixture was washed with aqueous sodium bisulfite solution and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 10% EtOAc/hexanes) provided 0.86 g (28%) of the title compound as a yellow oil, which solidified upon storage in a refrigerator: mp 89−90 °C; ^{1}H NMR δ 7.90 (d, J = 1.8 Hz, 1 H), 7.88 (d, J = 1.8 Hz, 1 H), 7.42−7.25 (m, 5 H), 4.01 (s, 2 H), 3.04 (m, 2 H), 2.94 (t, J = 7.4 Hz, 2 H), 1.71 (m, 4 H), 1.53 (s, 9 H), 1.42 (m, 2 H), 1.33 (s, 6 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 200.4, 153.8, 144.8, 143.2, 137.8, 132.3, 128.4, 128.1, 126.9, 126.0, 125.3, 60.0, 42.0, 38.0, 36.7, 33.5, 33.1, 31.5, 30.7, 26.7, 22.5, 13.9; IR 3467, 2074, 2959, 1652, 1593 cm^{-1}; MS 392 (MH^+).

8-*tert*-Butyl-4,4-dimethyl-6-pentanoyl-1,2,3,4-tetrahydroquinoline (58). Method D. A mixture of 1-benzyl-8-*tert*-butyl-4,4-dimethyl-6-pentanoyl-1,2,3,4-tetrahydroquinoline (0.86 g, 2.2 mmol), palladium hydroxide on carbon (0.17 g), and 20 mL of EtOAc was hydrogenated at 50 psi for 2 h. The mixture was filtered through a short column of silica gel and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% → 10% EtOAc/hexanes) yielded 0.30 g (45%) of **58** as an off-white solid: mp 109−110 °C; ^{1}H NMR δ 7.81 (d, J = 1.8 Hz, 1 H), 7.77 (d, J = 1.8 Hz, 1 H), 4.72 (bs, −NH, 1 H), 3.46 (m, 2 H), 2.87 (t, J = 7.4 Hz, 2 H), 1.73 (m, 4 H), 1.40 (s, 9 H), 1.37 (m, 2 H), 1.31 (s, 6 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 199.1, 146.1, 130.6, 129.1, 125.3, 125.1, 124.5, 38.2, 37.4, 35.8, 33.9, 32.1, 30.7, 29.8, 27.3, 22.6, 13.9; IR 3468, 2958, 2871, 1657, 1593 cm^{-1}; MS 302 (MH^+). Anal. ($C_{20}H_{31}NO$) C, H, N.

8-*tert*-Butyl-6-(4-cyclopropylbutanoyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (59). Method D was used. The crude product was purified by flash column chromatography on silica gel (2% → 5% EtOAc/hexanes) and gave 0.35 g (27%) of **59** initially as a light-yellow syrup which upon storage and washing with hexanes became a light-yellow solid: mp 98−99 °C; ^{1}H NMR δ 7.81 (d, J = 1.8 Hz, 1 H), 7.78 (d, J = 1.8 Hz, 1 H), 4.70 (s, 1 H), 3.45 (m, 2 H), 2.87 (t, J = 7.4 Hz, 2 H), 1.87 (m, 2 H), 1.74 (m, 2 H), 1.41 (s, 9 H), 1.32 (s, 6 H), 1.28 (m, 2 H), 0.71 (m, 1 H), 0.42 (m, 2 H), 0.03 (m, 2 H); ^{13}C NMR δ 199.5, 146.4, 130.8, 129.4, 125.7, 125.5, 124.8, 38.5, 37.7, 36.0, 34.7, 34.3, 32.4, 31.0, 30.1, 25.5, 11.0, 4.61; IR 3467, 2074, 2959, 1652, 1593 cm^{-1}; MS 328 (MH^+). Anal. ($C_{22}H_{33}NO$) C, H, N.

8-*tert*-Butyl-6-pentanoyl-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline (60). 8-*tert*-Butyl-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline. A solution of 1-benzyl-8-*tert*-butyl-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (20.0 g, 65 mmol) in 100 mL of EtOAc was hydrogenated for 24 h with palladium hydroxide on carbon (1.0 g) as the catalyst. The reaction mixture was filtered through a short column of silica gel and concentrated to yield 7.8 g of a yellow oil, which was dissolved in 63 mL of a 1:20 HOAc−CH_3CN mixture; formaldehyde (14.8 mL, 0.18 mol, 37% aqueous solution) and $NaBH_3CN$ (3.5 g, 55.7 mmol) were added. The reaction mixture was stirred for 24 h, diluted with ether, washed with 1 N aqueous NaOH solution, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (2.5% Et_2O/hexanes) yielded 7.25 g (48%) of the title compound as a colorless oil: ^{1}H NMR δ 7.20 (d, J = 7.4 Hz, 2 H), 6.99 (t, J = 7.4 Hz, 1 H), 3.04 (m, 2 H), 2.59 (s, 3 H), 1.45 (m, 2 H), 1.45 (s, 9 H), 1.30 (s, 6 H); MS 232 (MH^+).

6-Bromo-8-*tert*-butyl-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline (29b). A solution of bromine (1.7 mL, 31.2 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 0.5 h to a solution of 8-*tert*-butyl-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline (7.2 g, 31.2 mmol) in 50 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, diluted with Et_2O, washed with 1 N aqueous NaOH solution and water, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5% ether/hexanes) provided 9.44 g (97%) of **29b** as a yellowish oil: ^{1}H NMR δ 7.28 (s, 2 H), 3.02 (m, 2 H), 2.55 (s, 3 H), 1.42 (m, 2 H), 1.41 (s, 9 H), 1.25 (s, 6 H); MS 310 (MH^+).

8-*tert*-Butyl-6-pentanoyl-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline (60). Method D was used. The crude product was purified by flash column chromatography on silica gel (5% ether/hexanes) and gave 0.51 g (41%) of **60** as a yellow oil: ^{1}H NMR δ 7.87 (d, J = 1.8 Hz, 1 H), 7.81 (d, J = 1.8 Hz, 1 H), 3.08 (m, 2 H), 2.91 (t, J = 7.4 Hz, 2 H), 2.66 (s, 3 H), 1.80 (m, 2 H), 1.72 (m, 2 H), 1.48 (s, 9 H), 1.43 (m, 2 H), 1.34 (s, 6 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 200.5, 153.5, 144.2, 141.8, 131.4, 126.8, 124.6, 47.7, 46.6, 37.9, 36.7, 33.6, 32.5, 32.3, 32.0, 26.9, 22.5, 13.9; IR 2934, 2865, 1677, 1591 cm^{-1}; MS 316 (MH^+). Anal. ($C_{21}H_{33}NO$) C, H, N.

8-*tert*-Butyl-6-(4-cyclopropylbutanoyl)-1,2,3,4-tetrahydro-1,4,4-trimethylquinoline (61). Method D was used. The crude product was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) and gave 0.66 g (64%) of **61** initially as a yellowish viscous oil which upon storage in a refrigerator became a yellowish solid: mp 46−47 °C; ^{1}H NMR δ 7.83 (d, J = 1.8 Hz, 1 H), 7.78 (d, J = 1.8 Hz, 1 H), 3.05 (m, 2 H), 2.91 (t, J = 7.4 Hz, 2 H), 2.62 (s, 3 H), 1.79 (m, 4 H), 1.42 (s, 9 H), 1.30 (s, 6 H), 1.27 (m, 2 H), 0.68 (m, 1 H), 0.39 (m, 2 H), 0.01 (m, 2 H); ^{13}C NMR δ 200.2, 153.7, 144.1, 141.7, 131.2, 126.7, 124.6, 47.5, 46.6, 37.9, 36.6, 34.3, 33.5, 32.5, 32.2, 31.7, 24.7, 10.6, 4.3; IR 2934, 2865, 1677, 1591 cm^{-1}; MS 342 (MH^+). Anal. ($C_{23}H_{35}NO$) C, H, N.

Biological Procedures. The procedures for the carrageenan-induced paw edema (CPE) assay, the phenylquinone-induced abdominal constriction (PAC) assay, the human COX-1/COX-2 isolated enzyme assays, and the RBL-2H3 intact cell assay for LTB_4 inhibition are given in the companion publication.[1]

Acknowledgment. We would like to thank Professor Daniel Tai of the University of Kentucky for the in vitro COX-1/COX-2 inhibition data.

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JM970680P