Regioselective Lewis Acid-Directed Reactions of 2-Alkoxy-5-alkyl-1,4-benzoquinones with Styrenes: Synthesis of Burchellin and Guianin Neolignans

Thomas A. Engler,* Dong (Donna) Wei, Michael A. Letavic, Keith D. Combrink, and Jayachandra P. Reddy

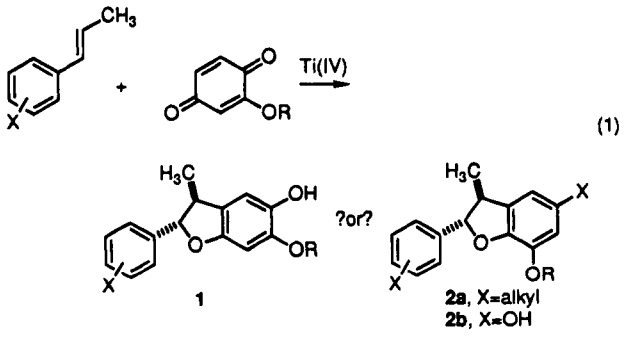
Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received May 31, 1994®

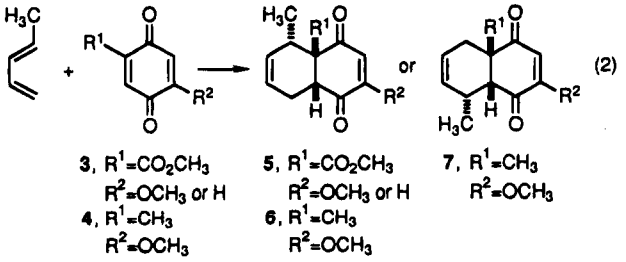
Reactions of 2-carbomethoxy-5-methoxy-1,4-benzoquinone with (*E*)-propenylbenzenes promoted by Ti(IV) regio- and stereoselectively yield trans 2-aryl-4-carbomethoxy-7-methoxy-3-methyl-2,3-dihydro-5-benzofuranols. However, the products found in Lewis acid-promoted reactions of 2-alkoxy-5-alkyl-1,4-benzoquinones with (*E*)-propenylbenzenes depend on the nature of the Lewis acid. Low-temperature reactions with $SnCl_4$ produce *rel*-(1*R*,6*S*,7*S*,8*R*)-4-alkoxy-1-alkyl-7-aryl-8-methylbicyclo[4.2.0]oct-3-ene-2,5-diones **21**–**23** and products derived from them. Allowing the reactions to warm to room temperature results in *rel*-(2*S*,3*S*,3a*R*)-3a-alkyl-2-aryl-5-hydroxy-3-methyl-2,3,3a,6-tetrahydro-6-oxobenzofurans as mixtures of keto–enol tautomers **26/27** and **28/29**. With Ti(IV) as promoter, the reactions can be made to produce either **21**–**23** or the regioisomeric *rel*-(1*S*,6*R*,7*R*,8*S*)-4-alkoxy-1-alkyl-8-aryl-7-methylbicyclo[4.2.0]oct-3-ene-2,5-diones **18**–**20**. The ratio of the two depends upon the makeup of the Ti(IV) promoter and the substituents on the propenylbenzene. A mechanistic rationale is presented involving regioselective coordination of the different Lewis acids to the quinone. Thus, $SnCl_4$ binds to the C-1 carbonyl and C-2 alkoxy oxygens, forming a complex possessing a 2-alkoxy-5-alkyl-4-oxo-2,5-cyclohexadienyl carbocation moiety (e.g. **30**) which undergoes a thermally allowed $4\pi + 2\pi$ (5 + 2) cycloaddition with propenylbenzene to give a bicyclo[3.2.1]octenyl carbocation **31**; this cation then rearranges to the observed products. On the other hand, the Ti(IV)-promoted reactions give either bicyclo[3.2.1]octenyl carbocation **31** or **34**, depending upon reaction conditions, followed by rearrangement. Cyclobutanes **18**–**20** undergo protic acid rearrangement to give trans 7-alkoxy-4-alkyl-2-aryl-3-methyl-2,3-dihydro-5-benzofuranols **15**–**17**, whereas cyclobutanes **21**–**23** yield 5-alkyl-7-aryl-3-hydroxy-6-methylbicyclo[3.2.1]oct-3-ene-2,8-diones **24/25**. The reactions provide an efficient and stereoselective route to neolignans of the guianin and burchellin classes.

Introduction

Previous reports from these laboratories have established that Lewis acid-promoted reactions of various 1-propenylbenzenes with 2-alkoxy-1,4-benzoquinones represent an efficient and stereo-/regioselective route to 6-alkoxy-2-aryl-3-methyl-2,3-dihydrobenzofuran-5-ols **1** (eq 1).[1] Because the isomeric 7-alkoxy-2-aryl-3-methyl-



2,3-dihydrobenzofuran substructure **2a** is found in a number of biologically active natural products,[2] we sought to develop methods to reverse the regioselectivity of these reactions and provide a route to dihydrobenzofuran **2b**. Regioselective control of quinone Diels–Alder reactions is commonly achieved by one of two strategies: (a) incorporation of substituents on the quinone that strongly activate one of the carbon–carbon double bonds or (b) use of a Lewis acid that selectively binds to one of the carbonyl groups of a substituted quinone.[3] For example, Diels–Alder reactions of 2-carbomethoxy-1,4-benzoquinone **3** occur exclusively at C-2/C-3 to give **5** (eq 2).[4] On



the other hand, BF_3-promoted Diels–Alder reactions of 2-methoxy-1,4-benzoquinone **4** with piperylene afford mainly regioisomer **6** whereas reactions promoted by $SnCl_4$ produce **7**.[5] An explanation for the latter results involves selective coordination of the bidentate Lewis acid $SnCl_4$ to both of the C-1 carbonyl and C-2 methoxy oxygen resulting in C-1 controlling of the regioselectivity of the

® Abstract published in *Advance ACS Abstracts*, September 15, 1994.

(1) (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.*, preceding paper in this issue. (b) For a preliminary report, see: Engler, T. A.; Wei, D.; Letavic, M. A. *Tetrahedron Lett.* **1993**, *34*, 1429. (c) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (d) The letter designations for the substituents on **8**, **10**, **11**, **15**–**29**, and **38**–**41** were chosen as **a**, **c**, **f**, and **h** to be consistent with the preceding paper.

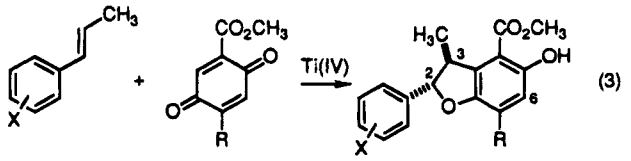
(2) (a) For a number of reports, see references cited in Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1 and earlier chapters in this series. (b) See also Hirano, T.; Wakasugi, A.; Oohara, M.; Oka, K.; Sashida, Y. *Planta Med.* **1991**, *57*, 331.

0022-3263/94/1959-6588$04.50/0

reaction. However, the monodentate Lewis acid BF_3 binds to the more basic ester-like C-4 carbonyl group, and it is this group that then controls the regioselectivity. Herein, we report that either of these strategies can be effectively used to control the regioselectivity of reactions of 2-alkoxy-5-substituted-1,4-benzoquinones with propenylbenzenes which results in stereo- and regioselective methods to prepare 7-alkoxy-2-aryl-2,3-dihydro-5-benzofuranols **2b** and/or neolignans from the guianin and burchellin classes.[2a]

Results and Discussion

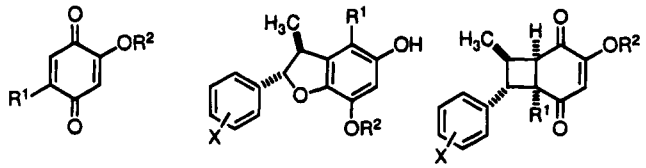
Based on the mechanistic rationale presented in the previous paper,[1a] reactions of 2-carbomethoxy-5-methoxy-1,4-benzoquinone (**9a**) offered one possibility to reverse the regioselectivity of reactions of alkoxy-1,4-benzoquinones. It was expected that the carbomethoxy group would render C-3 the most electrophilic site and also provide basic sites for bidentate binding to a Lewis acid which would further increase the electrophilicity of C-3. Thus, Ti(IV)-promoted reactions of propenylbenzenes **8c/f**[1d] with **9a**, prepared and used immediately from silver oxide oxidation of methyl 2,4,5-trimethoxybenzoate,[6] were explored and found to give dihydrobenzofurans **10c/f**[1d] stereo- and regioselectively in 71% and 32% yields, respectively (eq 3). In a similar manner, reactions of 2-carbomethoxy-1,4-benzoquinone (**9b**)[7] gave dihydrobenzofurans **11c/f** in 79% and 22% yields, respectively. In **10**, assignment of the positions of the methoxy and carbomethoxy groups at C-7 and C-4, respectively, was made from the upfield chemical shift of the H-6 singlet at ~6.4–6.5 ppm in their ^1H NMR spectra due the two ortho oxygens. In the other possible dihydrobenzofuran from **9a**, this signal would be β to the CO_2Me moiety and would be expected to be further downfield. In dihydrobenzofurans **11**, a $J_{H\text{-}6/H\text{-}7}$ = 8–9 Hz was observed, confirming the C-4 position of the CO_2Me group. The stereochemistry at C-2 and C-3 in **10/11** was assigned as discussed previously.[1]



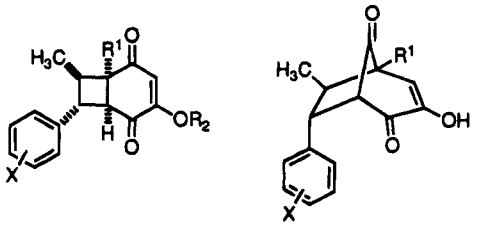
8a, X=4-OCH_3 **8c**, X=3,4-$(OCH_3)_2$ **8f**, X=H **8h**, X=3,4-(OCH_2O) **9a**, R=OCH_3 **9b**, R=H **10c**, R=OCH_3, X=3,4-$(OCH_3)_2$ **10f**, R=OCH_3, X=H **11c**, R=H, X=3,4-$(OCH_3)_2$ **11f**, R=H, X=H

Surprisingly, reactions of 2-alkoxy-5-alkyl-1,4-benzoquinones **12–14** with propenylbenzenes provided efficient routes not only to dihydrobenzofurans **15–17** and the cyclobutanes **18–20**[1] but also to the cyclobutanes **21–23**, the bicyclo[3.2.1]adducts **24/25**, and the benzofuranoid systems **26–29** (Chart 1). Compounds **15–20** and **21–29** can be viewed as regioisomers in that the former all result from bond formation between the β-carbon of the propenylbenzene and C-6 of the quinone whereas the latter result from bond formation between C-β of the propenylbenzene and C-5 of the quinone. The regioselectivity of the reactions was dependent on the nature of the Lewis acid employed. Initial experiments involving reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**12**) promoted by $TiCl_4$ or mixtures of $TiCl_4$:$Ti(OiPr)_4$ were found to produce up to four different products: **15**, **18**, **21**, and/or **26/27** depending upon conditions (Table 1). The ratio of these products varied greatly with (a) substituents on the propenylbenzene, (b) the ratio of $TiCl_4$:$Ti(OiPr)_4$ and equiv of Ti(IV), with respect to quinone, used as promoter, and (c) reaction temperature. For example, reaction of anethole with **12** promoted by 0.8–1.3 equiv of a 1:1 to 3:1 mixture of $TiCl_4$:$Ti(OiPr)_4$ at −78 °C gave small amounts of dihydrobenzofuran **15a**, as a 10:1 mixture of trans:cis isomers, identified as discussed previously,[1] and major quantities of cyclobutanes **18a** and **21a**. Surprisingly, the ratio of the cyclobutanes was >4:1. Thus, the regioselectivity observed in reactions of quinone **12** were opposite to that of 2-methoxy- or 2-methoxy-6-methyl-1,4-benzoquinones.[1] Utilization of 2 equiv of Ti(IV) with respect to quinone as a promoter gave trans:cis mixtures of dihydrobenzofurans **15a** in 64–80% yields, presumably from in situ rearrangement of **18a** (vide infra). Similarly, reactions of 3,4-dimethoxy-1-propenylbenzene (**8c**) with **12** pro-

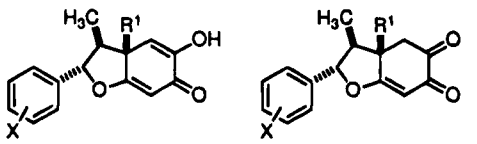
Chart 1



12, R^1=CH_3, R^2=CH_3 **13**, R^1=allyl, R^2=CH_3 **14**, R^1=allyl, R^2=CH_2Ph **15**, R^1=CH_3, R^2=CH_3 **16**, R^1=allyl, R^2=CH_3 **17**, R^1=allyl, R^2=CH_2Ph **18**, R^1=CH_3, R^2=CH_3 **19**, R^1=allyl, R^2=CH_3 **20**, R^1=allyl, R^2=CH_2Ph



21, R^1=CH_3, R^2=CH_3 **22**, R^1=allyl, R^2=CH_3 **23**, R^1=allyl, R^2=CH_2Ph **24**, R^1=CH_3 **25**, R^1=allyl



26, R^1=CH_3 **28**, R^1=allyl **27**, R^1=CH_3 **29**, R^1=allyl

For **15-29**: **a**, X=4-OCH_3; **c**, X=3,4-$(OCH_3)_2$; **f**, X=H; **h**, X=3,4-(OCH_2O).

(3) For reviews and summaries of many examples, see (a) Desimoni, G.; Tacconi, G.; Barco, A.; Piero-Pollini *Natural Product Synthesis Through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, DC, 1983. (b) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*, Vol. 2, Part 2, Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1988; p 537. (c) Onishchenko, A. S. In *Diene Synthesis*, Israel Program for Scientific Translations; Daniel Davey & Co.: 1964. (d) Bruce, J. M. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S.; Ed.; Elsevier: Amsterdam, 1974; Vol. III, Part B, pp 67–70.

(4) For examples, see (a) Ansell, M. F.; Nash, B. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3012. (b) Ansell, M. F.; Lown, J. W.; Turner, D. W.; Wilson, D. A. *Ibid.* **1963**, 3036. (c) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174. (d) Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308 and citations in ref 3.

(5) (a) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5012. See also: (b) Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1972**, *50*, 2377. (c) Stojanac, Z.; Dickinson, R. A.; Stojanac, N.; Woznow, R. J.; Valenta, Z. *Ibid.* **1975**, *53*, 616.

(6) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183 and ref 4b.

(7) Cassis, R.; Valderrama, J. A. *Synth. Commun.* **1983**, *13*, 347.

Table 1. Lewis Acid-Promoted Reactions of 2-Methoxy-5-methyl-1,4-benzoquinone with Propenylbenzenes

entry	propenylbenzene, X	Lewis acid (equiv)	temp (°C)	time (h)	% yields: **18/21** (ratio)	**15**	**26/27**
1	**8a**, 4-OCH_3	1:1 $TiCl_4$:$Ti(OiPr)_4$ (1.3)	−78	1	61 (4.4:1)		
2	**8a**, 4-OCH_3	1.8:1 $TiCl_4$:$Ti(OiPr)_4$ (1.25)	−78	1.5−6	60−65 (3.8−4.2:1)		
3	**8a**, 4-OCH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (1.0)	−78	30	83 (7:1)	13[a]	
4	**8a**, 4-OCH_3	3:1 $TiCl_4$:$Ti(OiPr)_4$ (1.0)	−78	6	55−86 (37−100:1)	8	
5	**8a**, 4-OCH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (2.0)	−78	6		64[b]	
6	**8a**, 4-OCH_3	3:1 $TiCl_4$:$Ti(OiPr)_4$ (2.0)	−78	6		80[c]	
7	**8c**, 3,4-$(OCH_3)_2$	1.5:1 $TiCl_4$:$Ti(OiPr)_4$ (3.0)	−78	18	92 (2:1)	6	
8	**8c**, 3,4-$(OCH_3)_2$	3:1 $TiCl_4$:$Ti(OiPr)_4$ (1.5)	−78	18	93 (4.2:1)		
9	**8c**, 3,4-$(OCH_3)_2$	4:1 $TiCl_4$:$Ti(OiPr)_4$ (1.0)	−78	10	78 (7.7:1)	4	
10	**8c**, 3,4-$(OCH_3)_2$	Ti(IV)-solid[d] (5.2)	−78	22	83 (4.7:1)		
11	**8c**, 3,4-$(OCH_3)_2$	3:1 $TiCl_4$:$Ti(OiPr)_4$ (2)	−78 → −20	8		56[e]	
12	**8c**, 3,4-$(OCH_3)_2$	$SnCl_4$ (1.0)	−78	16	57 (0:1)		
13	**8c**, 3,4-$(OCH_3)_2$	$SnCl_4$ (2.0)	−78	15			72
14	**8h**, 3,4-(OCH_2O)	Ti(IV)-solid[d] (2.7)	−78	4	99 (5:1)		
15	**8h**, 3,4-(OCH_2O)	$SnCl_4$ (1.0)	−78	12	68 (0:1)		21
16	**8h**, 3,4-(OCH_2O)	$SnCl_4$ (2.0)	−78 → −30	6			72
17	**8f**, H	1.5−2.0:1 $TiCl_4$:$Ti(OiPr)_4$ (2.6−4.0:1)	−78	3−30	47−57 (1:5−35)		
18	**8f**, H	3−4:1 $TiCl_4$:$Ti(OiPr)_4$ (1.0)	−78	3−24	25−34 (13−29:1)		

[a] As a 10:1 mixture of trans:cis isomers. [b] As a 7:1 mixture of trans:cis isomers. [c] As a 4:1 mixture of trans:cis isomers. [d] See text. [e] As an 8:1 mixture of trans:cis isomers.

moted by 2 equiv of a 3:1 mixture of $TiCl_4$:$Ti(OiPr)_4$ at −78 °C followed by warming to −20 °C gave an 8:1 mixture of trans:cis dihydrobenzofurans **15c** (entry 11). With 1−1.5 equiv of Ti(IV), as 2−4:1 mixtures of $TiCl_4$:$Ti(OiPr)_4$ at −78 °C, cyclobutanes **18c** and **21c** were produced in ratios varying from 2:1 to 7:1. The regioselectivity of Ti(IV)-promoted reactions of (*E*)-propenylbenzene (**8f**) with quinone **12** was also dependent upon the amount of Ti(IV) used as promoter. In general, reactions of **8f** were slower and gave poorer yields than reactions of styrenes **8a/c**, probably due to its lower nucleophilicity. With 1 equiv of Ti(IV), as a 3 or 4:1 mixture of $TiCl_4$:$Ti(OiPr)_4$, 13−28:1 mixtures of cyclobutanes **18f** and **21f** were found in 25−34% yields. However, with 2.5 to 4 equiv of Ti(IV), as 1.5−2.0:1 mixtures of $TiCl_4$:$Ti(OiPr)_4$, **18f/21f** were produced with the latter as the major product (1:5−35). The cyclobutanes **18/21** were generally obtained as a mixture following flash chromatography on silica gel. Pure compounds were obtained by fractional recrystallization of mixtures that were enriched in either isomer.

In these experiments, the yields and ratios of cyclobutanes **18/21** were erratic and difficult to reproduce accurately. The mixtures of $TiCl_4$ and $Ti(OiPr)_4$ used as promoter were mixed at 0−5 °C or 20 °C in CH_2Cl_2 just prior to the reactions, and it is likely that an equilibrium mixture of a number of different Ti(IV) species is formed. The number and reactivity of these various species in promoting the quinone−styrene reactions may be dependent upon several factors including the initial ratio of $TiCl_4$:$Ti(OiPr)_4$, mixing times, temperature, etc. The lack of control over the formation of the various probable Ti(IV) species may be responsible for our inability to accurately reproduce the experiments. However, during the course of these studies it was observed that a 5:1 mixture of $TiCl_4$ and $Ti(OiPr)_4$ stirred at room temperature in CH_2Cl_2 produced an off-white precipitate. This precipitate, which we have dubbed as "Ti(IV)-solid", was isolated by removal of solvent via cannula, washing quickly with CH_2Cl_2 and drying under vacuum. All subsequent manipulations of the "Ti(IV)-solid" were done in a glovebag under nitrogen. Although attempts to identify the structure of the "Ti(IV)-solid" have failed thus far, it does effectively and reproducibly promote the quinone−styrene reactions. Utilizing the "Ti(IV)-solid" as a 5.2:1 by weight ratio with respect to quinone as promoter, reaction of **12** with **8c** gave a 4.7:1 ratio of cyclobutanes **18c** and **21c** in 83% yield. In a similar manner, reaction with isosafrole (**8h**) gave a 5:1 ratio of **18h** and **21h** in quantitative yield.

In a remarkable development, reactions of 3,4-dimethoxy-1-propenylbenzene (**8c**) and isosafrole (**8h**) with quinone **12** promoted by 1 equiv of $SnCl_4$ gave cyclobutanes **21c/21h** in 68 and 57% yields, respectively; in the latter reaction, a mixture of benzofuranoid products **26h/27h** was also found in 21% yield. Cyclobutanes **18c/h** were not found. With 2 equiv of $SnCl_4$ as promoter, mixtures of keto−enol tautomers **26c/27c** and **26h/27h** resulted, each in 72% yield, apparently from rearrangement of **21c/h** (vide infra). Reactions of (*E*)-propenylbenzene with **12** were not studied with the "Ti(IV)-solid" or $SnCl_4$ as promoters.

These limited data show that the regioselectivity of reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**12**) is dependent upon the nucleophilicity of the styrene and the strength and number of equivalents of Lewis acid used as promoter. The data suggest the following trends: (1) nucleophilic propenylbenzenes **8a,c,h** produce cyclobutanes **18**, or products derived from it, as the major products with Ti(IV) as promoter; (2) the stronger the Ti(IV)-Lewis acid used, i.e., the higher the ratio of $TiCl_4$:$Ti(OiPr)_4$, the higher the ratio of **18:21**; (3) the less nucleophilic propenylbenzene **8f** also gives **18f** as the major product with $TiCl_4$ or 3−4:1 mixtures of $TiCl_4$:$Ti(OiPr)_4$ as promoter; however, with excess amounts of the milder 1.5−2:1 $TiCl_4$:$Ti(OiPr)_4$ promoter, cyclobutane **21f** is the major product; and (4) reactions of either **8c** or **8f** with $SnCl_4$ as promoter produce cyclobutanes **21c/f** or products derived from them. Thus, in general it appears that cyclobutane **18** is favored with strong Lewis acids, i.e. those enriched in $TiCl_4$, whereas more of **21** is found with milder Lewis acids, i.e. $SnCl_4$ or low ratios of $TiCl_4$:$Ti(OiPr)_4$.

With these trends as a working model, attention was directed to reactions of 2-alkoxy-5-allyl-1,4-benzoquinones **13/14** which were of greater significance as a potential route to the neolignan natural products.[2a] These quinones were prepared by $TiCl_4$-mediated allylation of 2-methoxy- and 2-(benzyloxy)-1,4-benzoquinones, respectively, with allyltrimethylsilane.[8] Two equivalents of the quinone−$TiCl_4$ complexes, with respect to the allylsilane, were required to obtain high yields. The second equiva-

Table 2. Lewis Acid-Promoted Reactions of 5-Alkoxy-2-allyl-1,4-benzoquinone with Propenylbenzenes

						% yields		
entry	propenylbenzene, X	quinone, R^2	Lewis acid (equiv)	temp (°C)	time (h)	**22** or **23**	**25**	**28–29**
1	**8f**, H	**13**, CH_3	$SnCl_4$ (2–3)	−78 to 10	26	29–34		
2	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	$SnCl_4$ (1)	−78	10–20	61–75		
3	**8h**, 3,4-(OCH_2O)	**13**, CH_3	$SnCl_4$ (1)	−78	10	87–94		
4	**8f**, H	**14**, CH_2Ph	$SnCl_4$ (1.5)	−78 to −60	13		75	
5	**8c**, 3,4-$(OCH_3)_2$	**14**, CH_2Ph	$SnCl_4$ (2)	−78	15	80		16
6	**8h**, 3,4-(OCH_2O)	**14**, CH_2Ph	$SnCl_4$ (2)	−78	6	86		
7	**8c**, 3,4-$(OCH_3)_2$	**14**, CH_2Ph	$SnCl_4$ (1–2)	−78 to rt	4	8		75–78
8	**8h**, 3,4-(OCH_2O)	**14**, CH_2Ph	$SnCl_4$ (1)	−78 to −30	3			69
						19/22 (ratio)	**25**	**28–29**
9	**8f**, H	**13**, CH_3	$TiCl_4$ (4)	−78	1	66–70 (1:0)		
10	**8f**, H	**13**, CH_3	$TiCl_4$ (2)	−78[a]	1.5	97 (1:0)		
11	**8f**, H	**13**, CH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (3.5)	−78	44	67 (1:3.3–5.2)	17–19	
12	**8f**, H	**13**, CH_3	Ti(IV)-solid (9)	−78	16–20	82–97 (>1:10)		
13	**8f**, H	**14**, CH_2Ph	Ti(IV)-solid (2.5)[b]	−78 to −10	24		20	
14	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	$TiCl_4$ (2)	−78	3	37 (4.8:1)		
15	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	Ti(IV)-solid (4.5)	−78	26	92–97 (>10:1)		
16	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	5:1 $TiCl_4$:$Ti(OiPr)_4$ (4)	−78	18	87 (1:0)		
17	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	3:1 $TiCl_4$:$Ti(OiPr)_4$ (3)	−78	24	68 (2.8:1)		
18	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (5)	−78	24	85 (2.3:1)		
19	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	$TiCl_4$ (1)	−78	8	52–55 (1:3.5–5.9)		
20	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	Ti(IV)-solid (2.3)	−78	26	48–65 (1:7–10)		
21	**8c**, 3,4-$(OCH_3)_2$	**13**, CH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (2)	−78	24	34–58 (1:3.5–8.5)		
22	**8h**, 3,4-(OCH_2O)	**13**, CH_3	3:1 $TiCl_4$:$Ti(OiPr)_4$ (2)	−78	4	83 (>10:1)		
23	**8h**, 3,4-(OCH_2O)	**13**, CH_3	2:1 $TiCl_4$:$Ti(OiPr)_4$ (2–3)	−78	8	61–96 (>10:1)		
24	**8h**, 3,4-(OCH_2O)	**13**, CH_3	Ti(IV)-solid (2.3)	−78[c]	0.5–6	89–94 (>5.4:1)		
						20–23 (ratio)		
25	**8c**, 3,4-$(OCH_3)_2$	**14**, CH_2Ph	Ti(IV)-solid (2.3)	−78	14	93 (3.9:1)		
26	**8h**, 3,4-(OCH_2O)	**14**, CH_2Ph	Tl(IV)-solid (1.5)	−78	7	91 (2.5:1)		

[a] Quinone and $TiCl_4$ were mixed at −30 °C. [b] The quinone degraded with larger amounts of Ti(IV)-solid or with mixtures of $TiCl_4$:$Ti(OiPr)_4$. [c] Quinone and Ti(IV)-solid were pre-equilibrated −30 °C.

lent of the quinone−$TiCl_4$ complex is necessary presumably to effect in situ oxidation of the initially formed titanium 2-alkoxy-5-allyl-4-hydroxyphenolate to the quinones (*vide supra*). The regioselectivity of the allylation was established by HMBC NMR experiments.[9]

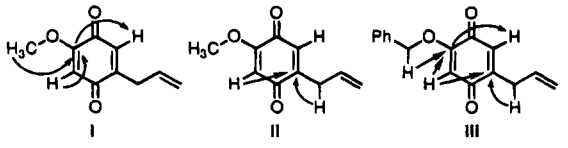
Reactions of quinones **13/14** with the propenylbenzenes were studied in more detail than reactions of 2-methyoxy-5-methyl-1,4-benzoquinone (**12**). With a few interesting differences, the results summarized in Table 2 were similar to those found with **12**. Thus, reactions of quinone **13** with propenylbenzenes **8c,f,h** promoted by $SnCl_4$ at −78 °C gave cyclobutanes **22**. Similarly, reactions of the 2-benzyloxy quinone **14** with propenylbenzenes **8c** and **8h** gave cyclobutanes **23**; however, with (*E*)-propenylbenzene (**8f**), the bicyclo[3.2.1] adduct **25** was produced. Warming reactions of **8c/h** with **14** from −78 to −30 °C resulted in mixtures of keto−enol tautomers **28/29** in 69−78% yields.[10]

The interesting differences observed between reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**12**) and those of 2-alkoxy-5-allyl-1,4-benzoquinones **13/14** were found in the Ti(IV)-promoted processes. As expected on the basis of reactions of **12**, reactions of **13** utilizing excess amounts of the more reactive $TiCl_4$ or mixtures of $TiCl_4$:$Ti(OiPr)_4$ enriched in $TiCl_4$ as promoter gave mainly cyclobutanes **19** accompanied by lesser quantities of cyclobutanes **22** (Table 2, entries 10, 14, 16, and 22). On the other hand, reactions promoted by limited amounts of Ti(IV), particularly as the less reactive 2:1 mixtures of $TiCl_4$:$Ti(OiPr)_4$, gave more of cyclobutanes **22** and in some cases it was the major product (entries 11, 19, and 21). The preferences for cyclobutanes **22** were particularly noticeable in reactions of (*E*)-propenylbenzene promoted by the weaker $TiCl_4$:$Ti(OiPr)_4$ Lewis acids.

As in reactions of **12**, reactions of **13** and **14** with mixtures of $TiCl_4$:$Ti(OiPr)_4$ as promoter could be erratic and difficult to reproduce accurately. However, utilization of the "Ti(IV)-solid" prepared as described above were more reproducible. The Lewis acidity of the Ti(IV)-solid apparently lies somewhere between $SnCl_4$ and $TiCl_4$, or mixtures of $TiCl_4$:$Ti(OiPr)_4$ prepared in situ, and the regioselectivy of reactions employing the Ti(IV)-solid is determined by the reactivity of the propenylbenzene. Utilization of the Ti(IV)-solid in reactions of **13/14** with the more reactive isosafrole (**8h**) results in mainly cyclobutanes **19/20** (entries 24/25) whereas in reactions with the less nucleophilic propenylbenzene **8f**, cyclobutane **22f** is found (entry 12). The propenylbenzene of intermediate reactivity, i.e., **8c**, gives cyclobutane **19c** with excess amounts of the Ti(IV)-solid (entry 15);

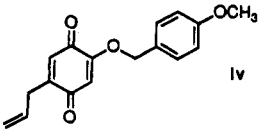
(8) For a review, see (a) Fleming, I.; Donoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57−575. See also: (b) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, *18*, 4041. (c) Ipaktschi, J.; Heydari, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 313. (d) Naruta, Y.; Uno, H.; Maruyama, K. *Tetrahedron Lett.* **1981**, *22*, 5221. (e) Takuwa, A.; Soga, O.; Mishima, T.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 1261.

(9) Important correlations observed are summarized in **i**−**iii**.



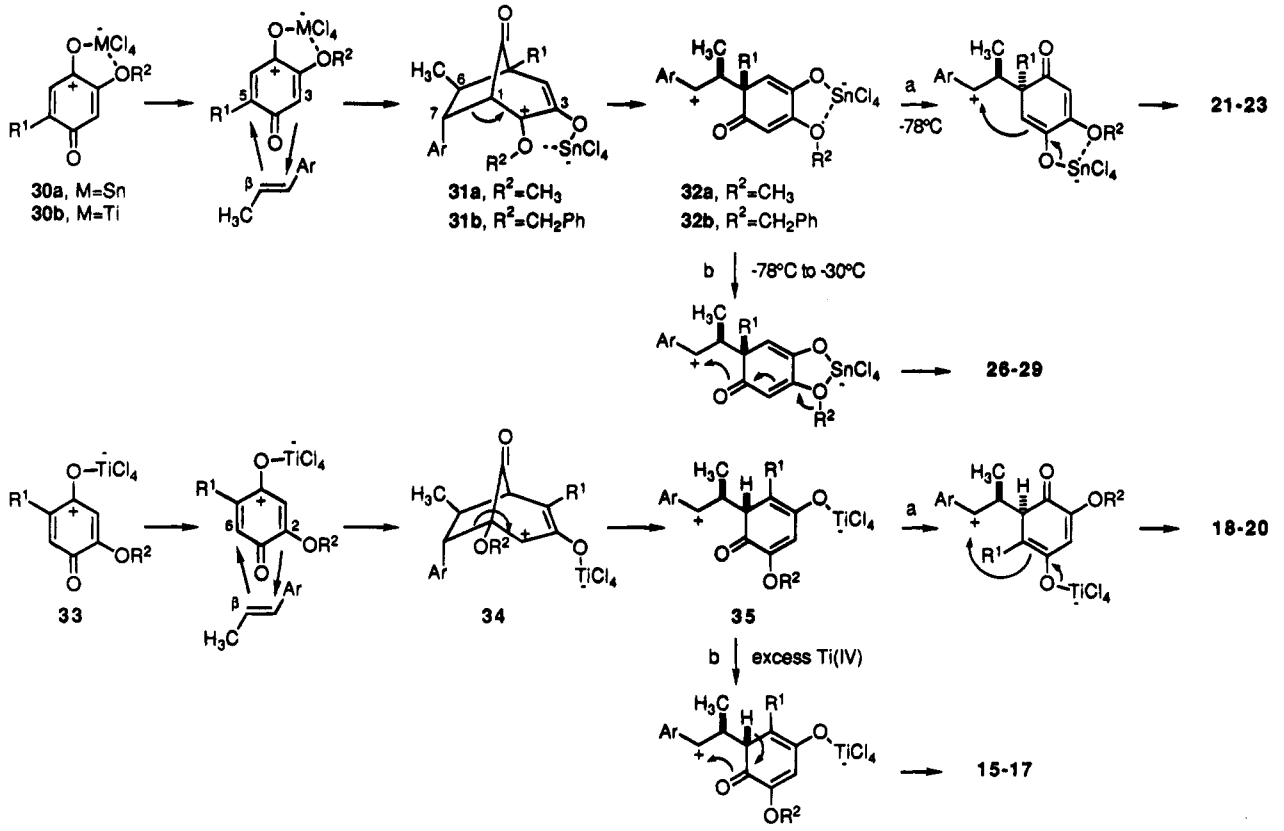
I II III

(10) Reactions of quinone iv were also examined in an attempt to access bicyclo[3.2.1] adducts from all of the styrenes (see: Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* **1990**, *55*, 5810). Unfortunately, no identifiable products were found. The *p*-methoxybenzyl moiety was apparently not robust enough to tolerate the reaction conditions and the quinone decomposed before cycloaddition could occur.



iv

Scheme 1



however, with smaller amounts, **22c** is found (entry 20). Again, the cyclobutanes **19/22** and **20/23** were not separable by flash chromatography; however, recrystallization of mixtures enriched in one or the other provided pure samples of all of the cyclobutanes.

These results suggest two competing cycloaddition processes in reactions of **12**–**14** (Scheme 1). Using the mechanistic rationale discussed in the preceding paper,[1] the first involves complexation of the Lewis acid to the C-1 carbonyl and the C-2 alkoxy group to give pentadienyl carbocation **30** and $4\pi + 2\pi$ cycloaddition with the propenylbenzene, with the aryl group in an endo orientation with respect to the carbocation, to produce bicyclic carbocation **31**. Alternatively, coordination of the Lewis acid to the C-4 carbonyl group gives pentadienyl cation **33** and cycloaddition of this species with the propenylbenzene results in bicyclic cation **34**. Complex **30** may be favored due to chelation effects; however, the C-4 oxygen is more basic due to reasonance electron donation by the C-2 alkoxy group favoring **33**. In fact, there may be an equilibrium between the two modes of complexation and, in the cycloaddition step, the C-5 alkyl group may be expected to sterically inhibit C-β/C-5 bond formation and slow the process leading to **31** compared to that leading to **34**.[11] On the other hand, the oxygen-stabilized carbocation intermediate **31** would be expected to be more stable than **34**. Thus, the product of kinetic control may be **34** whereas **31** may be the product of thermodynamic control.

We reason that with the mild Lewis acid $SnCl_4$ as promoter, intermediates **31** are produced in a thermodynamically controlled process. At low temperature, these intermediates rearrange to cyclobutanes **21**–**23** via **32** and then path a, or in the case of **31b** (Ar = Ph), undergo debenzylation to give bicyclo[3.2.1] adduct **25**. However, upon warming the reactions involving **31a/b**, keto–enol tautomers **26**–**29** are found apparently through the sequence **31** → **32** and then path b.

Promotion of the reactions of **12**–**14** with the powerful Lewis acid $TiCl_4$ and/or excess Ti(IV) at −78 °C produced mainly cyclobutanes **18**–**20**, via **34** and **35** and then path a, in a kinetically controlled process. Warming reactions of **12** gave the dihydrobenzofuran **15**, apparently via ring opening of cyclobutane **18** followed by C–O bond formation and loss of H^+. In addition to those mentioned above, there are several other possible reasons for the preference to give **34** in the cycloadditions, particularly with the nucleophilic styrenes **8a,c,h**. The C-4 carbonyl complex **33** may include a pentacoordinate Ti(IV) which would be expected to be a stronger Lewis acid than a hexacoordinate Ti(IV) such as may be found in complex **30b**. As a result, the former may be more reactive to cycloaddition than the latter and give products of kinetic control. It is also possible that a quinone–$[Ti(IV)]_2$ complex[12] may be involved in reactions utilizing larger amounts of Ti(IV).

(11) Indeed, reactions of quinones **12**–**14** are much slower than those of 2-methoxy- or 2-methoxy-6-methyl-1,4-benzoquinone requiring stronger Lewis acids, longer reaction times, and/or higher temperatures; for comparison, see preceding paper in this issue.

(12) For discussions and references to 2:1 complexes of Lewis acids with carbonyl compounds, see (a) Shambayati, S.; Schreiber, S. In *Comprehensive Organic Synthesis*, Vol. 1; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; p 283. (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. (c) Schultz, A. G.; Lee, H. *Tetrahedron Lett.* **1992**, *33*, 4397. (d) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (e) Kiyooka, S.; Nakano, M.; Shiota, F.; Fujiyama, R. *ibid.* **1989**, *54*, 5409. (f) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. *Ibid.* **1991**, *56*, 3958. (g) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872. (h) Simard, M.; Vaugeois, J.; Wuest, J. D. *Ibid.* **1993**, *115*, 370. (i) Sharma, V.; Simard, M.; Wuest, J. D. *Ibid.* **1992**, *114*, 7931 and references cited therein. (j)For detailed studies of $(carbonyl)_2$·Lewis acid complexes, see: Denmark, S. E.; Almstead, N. G. *Tetrahedron* **1992**, *48*, 5565 and ref 13f. For a theoretical study, see: (k) Branchadell, V.; Oliva, A. *Ibid.* **1992**, *114*, 4357.

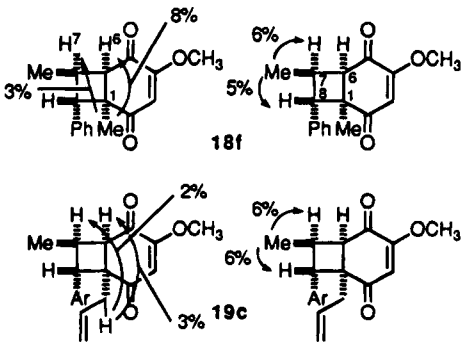


Figure 1. Summary of $^1H-^1H$ NOE data accumulated on **18f** and **19c**.

Such a complex would be expected to be highly reactive and the products of kinetic control again result. Evidence that quinone–$[Ti(IV)]_2$ complexes may be involved comes from the following experiments. In reactions of **13** with **8c** employing limited amounts of Ti(IV), the products of thermodynamic control (**22**) are major. However, with excess Ti(IV), the kinetic product **19** is predominant, if not exclusive. For example, reaction of propenylbenzene **8c** with quinone **13** utilizing 4 equiv, with respect to the quinone, of a 5:1 mixture of $TiCl_4$:$Ti(OiPr)_4$ as promoter gave **19c** exclusively in 87% yield. The need for the large amount of Ti(IV) in this experiment may be due to the basic ether oxygens on the propenylbenzene competing with the quinone for binding to the Ti(IV). Styrene **8f** lacks basic oxygens and the regioselectivy of its reactions is controlled by the strength of the Lewis acid; the powerful $TiCl_4$ Lewis acid gives the product of kinetic control whereas mixtures of the weaker Lewis acid $TiCl_4$:$Ti(OiPr)_4$ gave none of the product of thermodynamic control. Yet another possibility is that the Ti(IV) binds to the π-face of the quinone[13] activating both C-2/C-6 and C-3/C-5 to cycloaddition and the latter is slower due to steric factors imposed by the C-5 alkyl group. With $TiCl_4$ and/or excess Ti(IV), the faster cycloaddition to give **34** is found. However, with the milder Ti(IV) Lewis acids made from mixtures of $TiCl_4$:$Ti(OiPr)_4$ and/or limited amounts of Ti(IV) with respect to quinone, thermodynamic control starts to take over, particularly with the nonnucleophilic propenylbenzene and more of cyclobutanes **21**–**23** are formed.

Structural assignments of the cyclobutanes **18**–**23** are based on spectral data, their subsequent rearrangement reactions, and comparison of the rearrangement products to known natural or previously synthesized compounds. In the ^1H NMR spectra of **18**–**20**, the methine hydrogens are observed as two doublets and a doublet of doublet of a quartet. Irradiation of the C-1 methyl signal in **18f** resulted in large NOE enhancements of both the H-6 doublet and the H-7 multiplet (Figure 1).[1c] Similar NOE enhancements were observed upon irradiation of the allylic signals in **19c**. Irradiation of the C-7 methyl doublet in both resulted in enhancements of the H-7 and H-8 signals. Upon treatment with protic acid at room temperature or above, cyclobutanes **18**–**20** gave dihydrobenzofurans **15**–**17** (eq 4, Table 3) as mixtures of trans:cis isomers in which the former predominate (8–12:1); benzylic cation **36** is a likely intermediate. Small amounts of quinones **12**–**14** were also found resulting from fragmentation of **36**. The structures of the dihydrobenzofurans **15**–**17** were assigned by the appearance of H-6 as a singlet at ~6.4 ppm and the C-3 methyl doublet at ~1.40–1.45 ppm.[1]

Table 3. Protic Acid-Promoted Rearrangement of Cyclobutanes 18–20 to Dihydrobenzofurans 15–17

			% yields[b]		
entry	cyclobutane, X	conditions[a]	**15**	(t:c ratio)[c]	**12**
1	**18a**, 4-OCH_3	[TFA]/CH_2Cl_2, rt, 2 h	57	(7:1)	43
2	**18c**, 3,4-$(OCH_3)_2$	10% TFA/TFE, rt, 12 h	69	(11:1)	20
3	**18h**, 3,4-(OCH_2O)	10% TFA/THF, 40 °C, 12 h	58	(11:1)	27
4	**18f**, H	10% TFA/TFE, reflux, 16 h	73	(14:1)	
			16		**13**
5	**19c**, 3,4-$(OCH_3)_2$	10% TFA/TFE, reflux, 20 h	63	(12:1)	21
6	**19h**, 3,4-(OCH_2O)	10% TFA/THF, rt, 6 h	45	(11:1)	32
7	**19f**, H	10% TFA/THF, reflux, 12 h	67	(12:1)	10
			17		**14**
8	**20c**, 3,4-$(OCH_3)_2$	20% TFA/TFE, rt, 10 h	68	(10:1)	9
9	**20h**, 3,4-(OCH_2O)	10% TFA/TFE, rt, 5 h	65	(8:1)	13

[a] TFA = trifluoroacetic acid; TFE = 2,2,2-trifluoroethanol; THF = tetrahydrofuran. [b] Isolated yields. [c] By ^1H NMR.

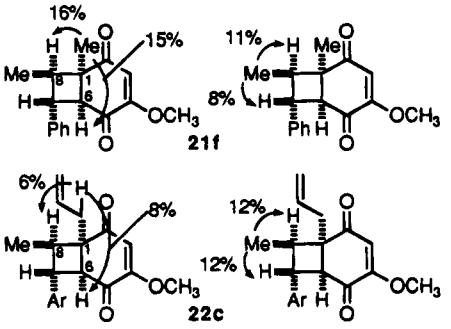
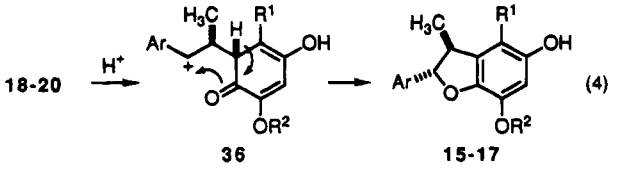


Figure 2. Summary of $^1H-^1H$ NOE data accumulated on **21f** and **22c**.



In cyclobutanes **21**–**23**, the H-8, H-7, and H-6 methine signals were observed as a doublet of quartets, a doublet of doublets, and a doublet, respectively. In **21f** and **22c**, $^1H-^1H$ NOE enhancements of both H-6 and H-8 were observed upon irradiation of the signals from the methyl or allylic groups, respectively, attached to C-1 (Figure 2).[1c] In addition, irradiation of the C-8 methyl group gave enhancements of the H-7 and H-8 signals. Cyclobutanes **21**–**23** gave bicyclic adducts **24**/**25** (eq 5, Table 4) upon treatment with H^+ at room temperature or above, and only the diastereomers with an endo Ar group were found;[14,16] some of the quinones **12**–**14** were again produced. Intermediates **37** are probably involved in these rearrangements, and it is noteworthy that they collapse via attack of the carbocation on the enol ether

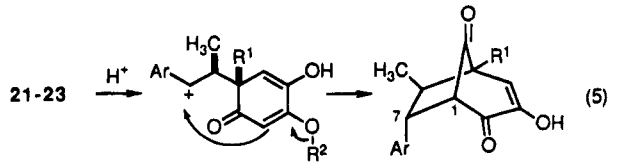
(13) π-Complexes of transition metals with quinones have been suggested: (a) Sternberg, H. W.; Markby, R.; Wender, I. *J. Am. Chem. Soc.* **1958**, *80*, 1009. (b) Hendrickson, J. B.; Singh, V. *J. Chem. Soc., Chem. Commun.* **1983**, 837. (c) Bohle, D. S.; Goodson, P. A. *Ibid.* **1992**, 1205. See also: (d) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 8973. (e) Méndez, N. Q.; Seyler, J. W.; Arif, A. M.; Gladysz, J. A. *Ibid.* **1993**, *115*, 2323. (f) Denmark, S. E.; Almstead, N. G. *ibid.* **1993**, *115*, 3133, ref 12a and references cited therein. Similarly, arene–Ti(IV) π-complexes have been reported; (g) Gillis, D. J.; Tudoret, M.-J.; Baird, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 2543. (h) Solari, E.; Floriani, C.; Chiesi-Villa, A.; Guastini,C. *J. Chem. Soc., Chem. Commun.* **1989**, 1747.

Table 4. Protic Acid-Promoted Rearrangement of Cyclobutanes 21–23 to Bicyclo[3.2.1]octenediones 24/25

entry	cyclobutane, X	conditions[a]	% yields[b] 24	12
1	**21c**, 3,4-$(OCH_3)_2$	30% TFA/THF, reflux, 14 h	65	26
2	**21h**, 3,4-(OCH_2O)	30% TFA/THF, 40 °C, 15 h	69	21
3	**21f**, H	10% TFA/TFE, reflux, 13 h	54	40
			25	**13**
4	**22c**, 3,4-$(OCH_3)_2$	30% TFA/THF, reflux, 17 h	48	20
5	**22h**, 3,4-(OCH_2O)	30% TFA/THF, reflux, 24 h	48	32
6	**22h**, H	30% TFA/TFE, reflux, 24 h	21	*c*
			25	**14**
7	**23c**, 3,4-$(OCH_3)_2$	30% TFA/THF, reflux, 17 h	75	22
8	**23h**, 3,4-(OCH_2O)	30% TFA/THF, reflux, 17 h	67	18

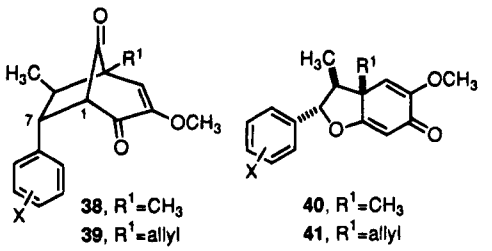
[a] TFA = trifluoroacetic acid; TFE = 2,2,2-trifluoroethanol; THF = tetrahydrofuran. [b] Isolated yields. [c] 46% starting **22f** was recovered.

moiety with dealkylation. In contrast, benzylic cation intermediates **32**, which are likely involved in the $SnCl_4$-promoted reactions of **13** and **14** at −30 °C, yield the keto–enol tautomers **26–29** through C–O bond formation and dealkylation. In the latter case, coordination of the Sn(IV) to the enol ether oxygen apparently lowers the nucleophilicity of the carbon–carbon double bond and attack of the carbocation on the carbonyl oxygen results.



37 24 25

Methylation of the bicyclic adducts **24/25** with methyl iodide and potassium carbonate in acetone gave **38/39** in 75–89% yields. Compounds **25h**, **38c/h**, and **39h** have been reported previously,[15] and the structures of their analogs were determined by spectral comparison. Particularly noteworthy in the spectral data from these compounds is the ~7 Hz coupling between H-1 and H-7 which establishes the endo orientation of the Ar moiety.[16] Similarly, methylation of the mixtures of keto–enol tautomers **26/27** and **28/29** gave **40/41**, respectively, in



For **38-41**: **a**, X=4-OCH_3; **c**, X=3,4-$(OCH_3)_2$; **f**, X=H; **h**, X=3,4-(OCH_2O).

64–82% yields. Again, compounds **41c/h**[14] are known natural products (burchellin) and structures related to them were determined by comparison of spectra. Results of $^1H-^1H$ NOE experiments provide further support for structures **40/41** (Figure 3).[16b]

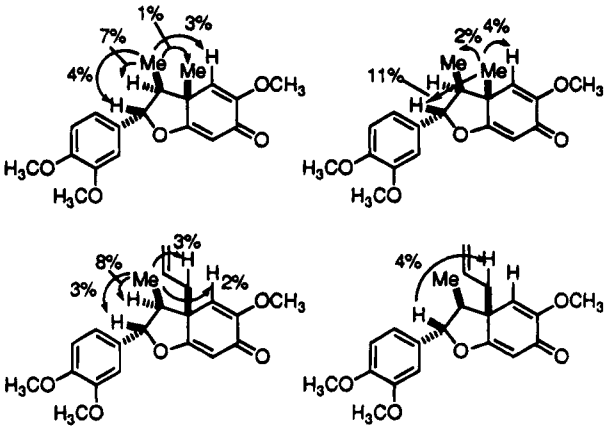
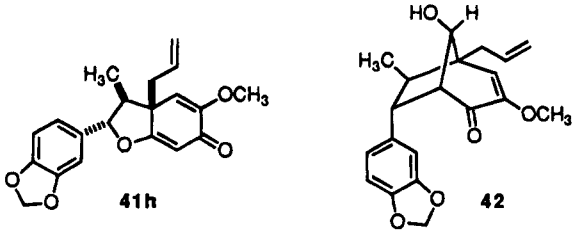


Figure 3. Summary of $^1H-^1H$ NOE data accumulated on **40c** and **41c**.

Conclusions

Burchellin (**41h**) and guianin (**42**) are representatives of two structural types of neolignans, a large family of biologically active natural products. As detailed above,



Lewis acid-promoted reactions of 2-(benzyloxy)-5-allyl-1,4-benzoquinone with various propenylbenzenes provide stereoselective routes to both types of neolignans. In addition, with proper choice of reaction conditions, these reactions also provide a route to biologically active natural products possessing the 7-alkoxy-2-aryl-3-methyl-2,3-dihydrobenzofuran structure. These methods, and those described in the previous paper, hold considerable promise in synthesis of natural products and biologically important compounds. We are presently working on the development of enantioselective variants.[1]

Experimental Section

General. 2-Methoxy-5-methyl-1,4-benzoquinone was prepared by Fremy's salt oxidation of 2-methoxy-5-methylphe-

(14) For an example of a rearrangement involving a related intermediate, see: (a) Iida, T.; Ito, K. *Phytochemistry* **1983**, *22*, 763. Rearragements involving analogs of **37** (R^1 = allyl) with the OH and OR^2 groups reversed are known to give benzofuranoid systems **41**, although these reactions are solvent and temperature dependent. See: (b) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (c) De Alvarenga, M. A.; Brocksom, U.; Gottlieb, O. R.; Yoshida, M.; Filho, R. B.; Figliuolo, R. *J. Chem. Soc., Chem. Commun.* **1978**, 831. (d) Filho, R. B.; Figliuola, R.; Gottlieb, O. R. *Phytochemistry* **1980**, *19*, 659. (e) Castro, C. O.; Gottlieb, O. R. *Ing. Cienc Quim.* **1981**, *5*, 67; *Chem. Abstr.* 96, 181040. (f) Turnbull, K. D. Ph.D. Dissertation, University of California, Riverside, 1991 (we thank Professor S. Angle for providing us with this information). (g) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717.

(15) (a) **25h**: see ref 14b. (b) **38c**: Shizuri, Y.; Suyama, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 63. (c) **38h**: Shizuri, Y.; Nakamura, K.; Yamamura, S. *Ibid.* **1985**, 530. (d) **39h**: see ref 14b. Fernandes, J. B.; Gottlieb, O. R.; Maia, J. G. S. *Phytochemistry* **1976**, *15*, 1033. Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011. (e) **41c**: see refs 14c,d. (f) **41h**: see ref 14b. Aiba, C. J.; Fernandes, J. B.; Gottlieb, O. R.; Maia, J. G. S. *Ibid.* **1975**, *14*, 1597. See spectral data in above and in (g) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1 and ref 16 in the previous paper in this issue.

(16) (a) For NMR data of analogs with exo-Ar groups, see refs 14a,f and Martinez, V. J. C.; Maia, J. G. S.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1980**, *19*, 474. Khan, M. R.; Gray, A. I.; Waterman, P. G. *Ibid.* **1987**, *26*, 1155. (b) For results of other NOE studies, see Angle, S. R.; Turnbull, K. D. *J. Org. Chem.* **1993**, *58*, 5360.

nol.[17] Carbomethoxy-1,4-benzoquinone and 2-carbomethoxy-5-methoxy-1,4-benzoquinone were prepared by methods reported by Valderrama[7] and Parker[6] and were used without purification. 2-Allyl-5-(benzyloxy)-1,4-benzoquinone and 2-allyl-5-methoxy-1,4-benzoquinone were prepared by $TiCl_4$-mediated allylation of 2-(benzyloxy)- and 2-methoxy-1,4-benzoquinone, respectively, with allyltrimethylsilane.[8] Full experimental details for the synthesis of the quinones are provided in the supplementary material.

General Methods for Reactions of the 2-Alkoxy-5-substituted-1,4-benzoquinones with Propenylbenzenes. Methods A, C, D, and E are described in the previous paper.[1]

General Method F. $SnCl_4$ was added to a solution of the quinone in CH_2Cl_2 cooled to −78 °C followed, after 15 min, by the propenylbenzene. The mixture was stirred for the times and temperatures indicated in Tables 1 and 2. Solid $NaHCO_3$ (1−2 g) and *i*-PrOH (5−10 mL) were added, and the mixture was diluted with water, filtered through Celite, and then extracted with CH_2Cl_2 (3×). The extracts were combined, dried (Na_2SO_4), and concentrated and the residue purified by flash chromatography on silica gel with EtOAc/hexanes as eluent and/or by recrystallization.

Reaction of 9a with 8c. According to method C, a solution of $TiCl_4$ (0.055 mL, 0.50 mmol) and $Ti(OiPr)_4$ (0.15 mL, 0.50 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of quinone **9a**, prepared from methyl 2,3,5-trimethoxybenzoate (256 mg, 1.13 mmol) in CH_2Cl_2 (5 mL) followed by propenylbenzene **8c** (0.25 mL, 1.48 mmol). The reaction was complete in 1 h and gave dihydrobenzofuran **10c** (300 mg, 71%) as an oil: R_f 0.27 (EtOAc/hexanes); ^{1}H NMR (500 MHz) 1.43 (d, J =7, 3H), 3.76 (dq, J = 7, 3, 1H), 3.826 (s, 3H), 3.834 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 5.28 (d, J = 3, 1H), 6.42 (s, 1H), 6.78−6.84 (m, 3H); ^{13}C NMR (125 MHz) 21.5, 47.6, 51.6, 55.65, 55.66, 55.74, 91.0, 99.5, 101.0, 108.6, 110.9, 117.3, 131.5, 134.2, 140.5, 148.6, 148.8, 150.3, 159.2, 170.2; HRMS m/z 374.1361 (calcd for $C_{20}H_{22}O_6$ 374.1366).

Reaction of 9a with 8f. According to method D, a solution of $TiCl_4$ (0.04 mL, 0.36 mmol) and $Ti(OiPr)_4$ (0.06 mL, 0.20 mmol) in CH_2Cl_2 (1 mL) was added to a solution of quinone **9a** (113 mg, 0.576 mmol) in CH_2Cl_2 (4 mL) followed by propenylbenzene **8f** (0.09 mL, 0.69 mmol). The mixture was stirred 1 h at −78 °C and 3 h at 0 °C. Workup and chromatography gave dihydrobenzofuran **10f** (58 mg, 32%) as an oil which was crystallized from EtOAc/hexanes, mp 93.0−94.5 °C: R_f (25% EtOAc/hexanes) 0.50; ^{1}H NMR (500 MHz) 1.45 (d, J = 7, 3H), 3.75 (dq, J = 7, 2, 1H), 3.88 (s, 3H), 3.93 (s, 3H), 5.36 (d, J = 2, 1H), 6.44 (s, 1H), 7.26−7.32 (m, 5H); ^{13}C NMR (125 MHz) 21.9, 48.2, 51.8, 56.0, 91.1, 99.8, 101.3, 125.0, 127.9, 128.6, 131.5, 140.8, 142.0, 150.5, 159.5, 170.4. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.70; H, 6.00.

Reaction of 9b with 8c. According to method E, a solution of quinone **9b**, prepared from methyl 2,5-dihydroxybenzoate (510 mg, 3.03 mmol) in CH_2Cl_2 (15 mL), was added to a solution of $TiCl_4$ (0.17 mL, 1.6 mmol) and $Ti(OiPr)_4$ (0.45 mL, 1.5 mmol) in CH_2Cl_2 (4 mL) followed by propenylbenzene **8c** (0.55 mL, 3.3 mmol). The reaction was complete in 3 h and gave dihydrobenzofuran **11c** (828 mg, 79%): R_f (50% EtOAc/hexanes) 0.5; ^{1}H NMR (500 MHz) 1.44 (d, J = 7, 3H), 3.75 (dq, J = 3, 7, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 5.26 (d, J = 3, 1H), 6.79−6.85 (m, 4H), 7.05 (d, J = 8, 1H), 10.5−10.6 (s, 1H); ^{13}C NMR (126 MHz) 170.3, 156.5, 151.9, 148.9, 148.6, 134.6, 131.6, 117.22, 117.17, 117.0, 111.0, 109.2, 108.4, 90.8, 55.77, 55.75, 52.0, 47.5, 21.7; HRMS m/z 344.1248 (calcd for $C_{19}H_{20}O_6$ − 344.1260).

Reaction of 9b with 8f. In a manner exactly as described for the reaction of **9b** with **8c**, reaction of **9b** (3.04 mmol) with **8f** gave dihydrobenzofuran **11f** (193 mg, 22%) as white needles from hexanes, mp 99−99.5 °C: R_f (50% EtOAc/hexanes) 0.72; ^{1}H NMR (500 MHz) 1.46 (d, J = 7, 3H), 3.74 (dq, J = 3, 7, 1H), 3.91 (s, 3H), 5.31 (d, J = 3, 1H), 6.85 (d, J = 9, 1H), 7.07 (d, J = 9, 1H), 7.25−7.34 (m, 5H), 10.54 (s, 1H); ^{13}C NMR (126 MHz) 170.4, 156.7, 152.1, 142.2, 131.5, 128.6, 127.9, 124.9, 117.4, 117.2, 109.3, 90.8, 52.1, 47.8, 22.0; HRMS m/z 284.1058 (calcd for $C_{17}H_{16}O_4$ 284.1049).

Reaction of 12 with 8a. According to method A, an aliquot [2.5 mL, 1.0 mmol Ti(IV)] of a solution of $TiCl_4$ (0.165 mL, 1.50 mmol) and $Ti(OiPr)_4$ (0.149 mL, 0.50 mmol) in CH_2Cl_2 (5 mL) was added to a solution of quinone **12** (152 mg, 1.00 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8a** (0.30 mL, 2.07 mmol). The reaction was complete in 6 h and gave dihydrobenzofuran **15a** (24 mg, 8%) and cyclobutane **18a** (257 mg, 86%).

Data for **15a**: an oil, R_f (30% EtOAc/hexanes) 0.32; ^{1}H NMR (300 MHz) 1.41 (d, J = 7, 3H), 2.10 (s, 3H), 3.42 (dq, J = 7, 7, 1H), 3.78 (s, 6H), 5.19 (d, J = 7, 2H), 6.35 (s, 1H), 6.85 (d, J = 8, 2H), 7.25 (d, J = 8, 2H) (phenolic signal missing); ^{13}C NMR (75 MHz) 11.3, 19.7, 45.8, 55.2, 56.0, 91.6, 100.3, 113.3, 113.8, 126.9, 127.5, 133.9, 140.9, 141.8, 148.1, 159.2; HRMS m/z 300.1359 (calcd for $C_{18}H_{20}O_4$, 300.1361).

Data for **18a**: a colorless solid, mp 141−141.5 °C (EtOAc/hexanes); R_f (50% EtOAc/hexanes) 0.49; HPLC (2% *i*-PrOH/hexanes, 2 mL/min) t_R 13.63 min; ^{1}H NMR (300 MHz) 1.03 (s, 3H), 1.15 (d, J = 7, 3H), 3.05 (d, J = 11, 1H), 3.30 (ddq, J = 11, 11, 7, 1H), 3.42 (d, J = 10, 1H), 3.80 (s, 3H), 6.11 (s, 1H), 6.88 (d, J = 7, 2H), 7.07 (d, J = 7, 2H); ^{13}C NMR (75 MHz) 17.1, 17.8, 33.5, 48.4, 50.5, 54.0, 55.3, 56.4, 112.5, 113.9, 128.6, 129.4, 158.7, 162.4, 193.5, 200.8. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.91; H, 6.94.

Another experiment carried out exactly as described above, except that 2 equiv of Ti(IV) was used, afforded a 4:1 mixture of dihydrobenzofuran **15a** and its cis isomer (241 mg, 80%) as an oil. Spectral data consistent with the minor isomer; ^{1}H NMR (300 MHz) 0.75 (d, J = 7, 3H), 5.69 (d, J = 7, 1H).

In other reactions (see Table 1), cyclobutanes **18a** and **21a** were found in ratios varying from 3.8:1 to 100:1. A pure sample of **21a** was obtained by HPLC: R_f (50% EtOAc/hexanes) 0.49; HPLC (2% *i*-PrOH/hexanes, 2 mL/min) t_R 12.18 min; ^{1}H NMR (300 MHz) 1.05 (d, J = 7, 3H), 1.43 (s, 3H), 2.46 (dq, J = 7, 10, 1H), 3.10 (dd, J = 9, 10, 1H), 3.18 (d, J = 9, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 6.10 (s, 1H), 6.86 (d, J = 8, 2H), 7.14 (d, J = 8, 2H); ^{13}C NMR (75 MHz) 16.6, 25.9, 46.6, 49.3, 50.0, 55.3, 56.2, 56.3, 113.7, 114.1, 127.5, 133.0, 158.7, 161.7, 192.4, 200.0; HRMS m/z 300.1350 (calcd for $C_{18}H_{20}O_4$, 300.1360).

Reaction of 12 with 8c. According to method A, an aliquot [3 mL, 1.01 mmol Ti(IV)] of a solution of $TiCl_4$ (0.173 mL, 1.58 mmol) and $Ti(OiPr)_4$ (0.119 mL, 0.40 mmol) in CH_2Cl_2 (6 mL) was added to a solution of quinone **12** (152 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) followed by propenylbenzene **8c** (0.337 mL, 2.0 mmol). The reaction was complete in 10 h and the residue obtained on workup was recrystallized from 35% EtOAc/hexanes to give pure cyclobutane **18c** (175 mg, 53%). The mother liquor was concentrated and the residue was chromatographed with 35% and then 50% EtOAc/hexanes as eluents to give dihydrobenzofuran **15c** (12 mg, 4%) and a 1.9:1 mixture of cyclobutane **18c** and its regioisomer **21c** (82 mg, 25%).

Data for **18c**: mp 135−136 °C; R_f (50% EtOAc/hexanes) 0.17; ^{1}H NMR (500 MHz) 1.06 (s, 3H), 1.16 (d, J = 7.0, 3H), 3.06 (d, J = 11.0, 1H), 3.29 (ddq, J = 11.0, 10.1, 7.0, 1H), 3.40 (d, J = 10.1, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.10 (s, 1H), 6.65 (d, J = 1.7, 1H), 6.69 (dd, J = 8.3, 1.7, 1H), 6.84 (d, J = 8.3, 1H); ^{13}C NMR (126 MHz) 17.1, 17.9, 33.4, 48.4, 50.5, 54.2, 55.86, 55.90, 56.4, 110.9, 111.0, 112.4, 119.1, 130.2, 148.1, 148.9, 162.4, 193.4, 200.9. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 69.01; H, 6.79.

In another experiment carried out according to method A, an aliquot [4 mL, 2.03 mmol Ti(IV)] of a solution of $TiCl_4$ (0.329 mL, 3.00 mmol) and $Ti(OiPr)_4$ (0.298 moL, 1.01 mmol) was added to a solution of quinone **12** (152 mg, 1.0 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8c** (0.337 mL, 2.0 mmol). The reaction was stirred 8 h at −78 °C and then allowed to warm to −20 °C. Workup and chromatography gave an 8:1 mixture of compound **15c** and its cis isomer (185 mg, 56%) as an oil: R_f (50% EtOAc/hexanes) 0.30; ^{1}H NMR (500 MHz) 1.43 (d, J = 6.8, 3H), 2.12 (s, 3H), 3.45 (dq, J = 5.4, 6.8, 1H), 3.84 (s, 3H), 3.86 (s, 6H), 4.65 (s, 1H), 5.18 (d, J = 5.4, 1H), 6.36 (s, 1H), 6.81 (d, J = 8.7, 1H), 6.89 (d, J = 1.9, 1H), 6.89 (dd, J = 8.7, 1.9, 1H); ^{13}C NMR (126 MHz) 11.4, 19.6,

(17) Hayakawa, K.; Ueyama, K.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 1963.

45.9, 55.85, 55.87, 56.1, 91.9, 100.3, 109.0, 110.7, 110.9, 118.2, 118.7, 131.5, 134.2, 141.1, 148.1, 148.8, 149.0; HRMS m/z 330.1464 (calcd for $C_{19}H_{22}O_5$, 330.1467).

In an experiment carried out according to method F, $SnCl_4$ (0.10 mL, 0.86 mmol) was added to a solution of quinone **12** (131 mg, 0.86 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8c** (0.20 mL, 1.20 mmol). The reaction was complete in 16 h and workup and chromatography afforded cyclobutane **21c** (154 mg, 57%) as a white solid, mp 123.0–123.5 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.17; ^{1}H NMR (500 MHz) 1.17 (d, J = 7.0 , 3H), 1.44 (s, 3H), 2.50 (dq, J = 9.8, 7.0, 1H), 3.12 (dd, J = 9.8, 9.9, 1H), 3.20 (d, J = 9.9, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 6.11 (s, 1H), 6.74 (d, J = 1.8 , 1H), 6.77 (dd, J = 8.2, 1.8, 1H), 6.83 (d, J = 8.2, 1H); ^{13}C NMR (126 MHz) 16.7, 25.9, 46.2, 49.2, 50.0, 55.81, 55.88, 56.1, 56.3, 109.8, 111.2, 113.8, 118.0, 133.7, 148.1, 149.0, 161.5, 192.6, 199.9. Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.81; H, 6.66.

In another experiment according to method F, $SnCl_4$ (0.30 mL, 2.56 mmol) was added to a solution of quinone **12** (195 mg, 1.28 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8c** (0.302 mL, 1.79 mmol). The reaction was stirred for 15 h and workup and chromatography gave a mixture of **26c** and **27c** (305 mg, 72%) as a semisolid. A solution of this semisolid (415 mg, 13.1 mmol) and K_2CO_3 (1.81g, 13.1 mmol) in acetone (30 mL) was treated with CH_3I (1.63 mL, 26.2 mmol) and the mixture stirred 20 h at room temperature. The mixture was filtered, concentrated and the residue chromatographed to give **40c** (295 mg, 65%) as a white solid, mp 127–128 °C: R_f (50% EtOAc/hexanes) 0.09; ^{1}H NMR (300 MHz) 1.11 (d, J = 6.8, 3H), 1.38 (s, 3H), 2.22 (dq, J = 10.1, 6.8, 1H), 3.70 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 5.12 (d, J = 10.1, 1H), 5.60 (s, 1H), 5.74 (s, 1H), 6.77 (s, 1H), 6.87 (s, 2H); ^{13}C NMR (75 MHz) 8.6, 22.3, 47.4, 48.6, 55.2, 55.9, 91.3, 99.9, 109.2, 110.6, 110.9, 119.5, 128.3, 129.7, 149.3, 149.7, 152.1, 182.5, 185.1; HRMS m/z 330.1474 (calcd for $C_{19}H_{22}O_5$, 330.1467).

Reaction of 12 with 8f. This experiment was carried out exactly as described for the reaction of **12** with **8a** employing 1 equiv of Ti(IV). The reaction was complete in 24 h and gave a 29:1 mixture of cyclobutane **18f** and its regioisomer **21f** (91 mg, 34%). Pure **18f** was obtained by recrystallization from EtOAc/hexanes, mp 133.5–134 °C: R_f (30% EtOAc/hexanes) 0.22; ^{1}H NMR (300 MHz) 1.04 (s, 3H), 1.17 (d, J = 6.8, 3H), 3.08 (d, J = 10.8, 1H), 3.36 (ddq, J = 10.8, 10.0, 6.8, 1H), 3.47 (d, J = 10.0, 1H), 3.87 (s, 3H), 6.12 (s, 1H), 7.15 (d, J = 7.3, 2H), 7.26 (m, 1H), 7.35 (m, 2H); ^{13}C NMR (75 MHz) 17.1, 18.0, 33.2, 48.2, 50.5, 54.4, 56.4, 112.5, 127.0, 127.5, 128.4, 137.4, 162.4, 193.0, 200.7. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.43; H, 6.76.

Another experiment was carried out exactly as described above except that 2.6 equiv of Ti(IV) [as $Ti(OiPr)_4$ (0.31 mL, 1.05 mmol) and $Ti(Cl_4$ (0.17 mL, 1.55 mmol) in CH_2Cl_2 (4 mL)] was used. The reaction was complete in 3 h and chromatography afforded a 1:7.6 mixture of **18f** and **21f** (154 mg, 57%). Pure **21f** was obtained by recrystallization from EtOAc/hexanes, mp 122–123 °C: R_f (30% EtOAc/hexanes) 0.22; ^{1}H NMR (300 MHz) 1.16 (d, J = 7.0, 3H), 1.44 (s, 3H), 2.51 (dq, J = 7.0, 9.8, 1H), 3.17 (dd, J = 9.8, 9.0, 2H), 3.25 (d, J = 9.0, 1H), 3.85 (s, 3H), 6.11 (s, 1H), 7.22–7.36 (m, 5H); ^{13}C NMR (75 MHz) 16.8, 25.9, 46.4, 49.4, 50.3, 55.7, 56.4, 113.8, 126.4, 127.1, 128.7, 140.9, 161.7, 192.5, 199.9. Anal. Calcd for $C_{17}H_{18}O_3$: 75.53; H, 6.71. Found: C, 75.21; H, 6.88.

Reaction of 12 with 8h. $TiCl_4$ (0.92 mL, 8.4 mmol) was added quickly with slow stirring to a solution of $Ti(OiPr)_4$ (0.5 mL, 1.7 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 1 h, the precipitate that formed was separated by decanting the liquid via cannula, washed with dichloromethane (1.0 mL), and dried under vacuum to yield a light yellow Ti(IV) solid. A solution of the Ti(IV) solid (176 mg) in CH_2Cl_2 (2.0 mL) was added slowly to a solution of quinone **12** (65 mg, 0.43 mmol) in dichloromethane (5 mL) maintained at −78 °C. The solution was stirred at −78 °C for 30 min, and (*E*)-isosafrole (0.085 mL, 0.59 mmol) was then added. The reaction mixture was stirred at −78 °C for 4 h and worked up as described in method C. Chromatography afforded a 5.0:1 mixture of cyclobutane **18h** and its regioisomer **21h** (133.7 mg, 99%) as a white solid. Pure **18h** was obtained by recrystallization from EtOAc/hexanes, mp 171–172 °C: R_f (30% EtOAc/hexanes) 0.16; ^{1}H NMR (500 MHz) 1.06 (s, 3H), 1.13 (d, J = 7.0, 3H), 3.05 (d, J = 11.0, 1H), 3.25 (ddq, J = 11.0, 10.2, 7.0, 1H), 3.36 (d, J = 10.2, 1H), 3.86 (s, 3H), 5.95 (br s, 2H), 6.10 (s, 1H), 6.59 (dd, J = 8.0, 1.6, 1H), 6.64 (d, J = 1.6, 1H), 6.78 (d, J = 8.0, 1H); ^{13}C NMR (126 MHz) 17.0, 17.7, 33.6, 48.4, 50.3, 54.3, 56.3, 101.0, 108.0, 108.1, 112.4, 120.5, 131.2, 146.4, 147.8, 162.4, 193.3, 200.6. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.56; H, 5.90.

In an experiment carried out according to method F, $SnCl_4$ (0.10 mL, 0.86 mmol) was added to a solution of quinone **12** (130 mg, 0.86 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8h** (0.17 mL, 1.2 mmol). The reaction was complete in 12 h and gave a 1:3.2 mixture of keto–enol tautomers **26h/27h** and cyclobutane **21h** (238 mg, 89%). Recrystallization from EtOAc/hexanes gave pure **21h**, mp 123–124 °C: R_f (30% EtOAc/hexanes) 0.16; ^{1}H NMR (500 MHz) 1.12 (d, J = 7.0 3H), 1.43 (s, 3H), 2.44 (dq, J = 9.8, 7.0, 1H), 3.06 (dd, J = 9.8, 9.3, 1H), 3.15 (d, J = 9.3, 1H), 3.84 (s, 3H), 5.94 (s, 2H), 6.10 (s, 1H), 6.66 (dd, J = 7.8, 1.4, 1H), 6.72 (d, J = 1.4, 1H), 6.75 (d, J = 7.8, 1H); ^{13}C NMR (126 MHz) 16.5, 25.9, 46.6, 49.2, 50.4, 56.2, 56.3, 101.0, 106.9, 108.3, 113.7, 119.7, 134.7, 146.7, 147.9, 161.6, 192.3, 199.8. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.22; H, 5.98.

In another experiment carried out according to method F, $SnCl_4$ (0.20 mL, 1.71 mmol) was added to a solution of quinone **12** (130 mg, 0.86 mmol) in CH_2Cl_2 (15 mL) followed by propenylbenzene **8h** (0.173 mL, 1.20 mmol). This mixture was stirred for 5 h at −78 °C and then warmed to −30 °C over 1 h. Workup and chromatography gave a mixture of **26h** and **27h** (305 mg, 72%) as a semisolid. A portion of this mixture (196 mg, 0.65 mmol) was dissolved in acetone (30 mL), and K_2CO_3 (829 mg, 6.0 mmol) and CH_3I (0.747 mL, 12.0 mmol) were added. The reaction mixture was stirred at room temperature for 20 h, filtered, and concentrated. Chromatography of the residue gave **40h** (168 mg, 82%) as a white solid, mp 125–126 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.13; ^{1}H NMR (500 MHz) 1.11 (d, J = 6.8, 3H), 1.36 (s, 3H), 2.17 (dq, J = 9.9, 6.8, 1H), 3.69 (s, 3H), 5.07 (d, J = 9.9, 1H), 5.57 (s, 1H), 5.73 (s, 1H), 5.98 (s, 2H), 6.76 (d, J = 1.6, 1H), 6.78 (dd, J = 7.9, 1.6, 1H), 6.81 (dd, J = 7.9, 1.6, 1H); ^{13}C NMR (126 MHz) 8.5, 22.4, 47.3, 48.8, 55.2, 91.2, 100.0, 101.4, 106.7, 108.2, 110.5, 120.7, 131.3, 148.2, 148.3, 152.2, 182.4, 184.9; HRMS m/z 314.1148 (calcd for $C_{18}H_{18}O_5$, 314.1154).

$SnCl_4$-Promoted Reactions of 13 with 8c, 8f, and 8h. All reactions were conducted in exactly the same way. Thus, $SnCl_4$ (0.100–0.22 mL, 0.855–1.72 mmol, see Table 2) was added to a solution of quinone **13** (152 mg, 0.855 mmol) in CH_2Cl_2 (15 mL) cooled to −78 °C followed by the propenylbenzenes (1.2 mmol). The mixtures were stirred at the temperatures and for the times indicated in Table 2, and the reactions were quenched by the addition of $NaHCO_3$ (1.5–2 g) and *i*-PrOH (10–15 mL) or by pouring into saturated aqueous $NaHCO_3$. Workup and chromatography afforded cyclobutanes **22.**

Data for **22c**: white solid (227 mg 75%), mp 117.5–118.5 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.26; ^{1}H NMR (500 MHz) 1.12 (d, J = 7.0, 3H), 2.20 (dd, J = 13.3, 8.0, 1H), 2.52 (dq, J = 10.0, 7.0, 1H), 2.85 (dd, J = 13.3, 6.8, 1H), 3.10 (dd, J = 10.0, 9.8, 1H), 3.21 (d, J = 9.8, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 5.00 (dd, J = 10.2, 1.7, 1H), 5.05 (dd, J = 17.0, 1.7, 1H), 5.53 (m, 1H), 6.10 (s, 1H), 6.69 (d, J = 1.9, 1H), 6.72 (dd, J = 8.2, 1.9, 1H), 6.78 (d, J = 8.2, 1H); ^{13}C NMR (126 MHz) 16.9, 44.1, 44.5, 49.7, 53.1, 54.0, 55.8, 55.9, 56.3, 109.8, 111.1, 114.7, 118.0, 119.4, 131.6, 133.6, 148.1, 149.0, 161.7, 192.4, 199.1. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.61; H, 6.79.

Data for **22f**: white solid (86 mg, 34%), mp 97.5–98 °C (EtOAc/hexanes); R_f (50% EtOAc/hexanes) 0.43; ^{1}H NMR (500 MHz) 1.16 (d, J = 7.0, 3H), 2.24 (dd, J = 13.4, 8.1, 1H), 2.57 (dq, J = 9.9, 7.0, 1H), 2.90 (dd, J = 13.4, 6.8, 1H), 3.19 (dd, J = 9.9, 9.7, 1H), 3.31 (d, J = 9.7, 1H), 3.83 (s, 3H), 5.03 (dd, J = 9.7, 1.1, 1H), 5.09 (dd, J = 17.0, 1.1, 1H), 5.58 (m, 1H), 6.14 (s, 1H), 7.22 (d, J = 7.3, 2H), 7.25 (d, J = 7.3, 1H), 7.32 (dd, J = 7.3, 7.3, 2H); ^{13}C NMR (126 MHz) 16.9, 44.1, 44.7, 50.0, 53.3, 53.5, 56.3, 114.7, 119.4, 126.3, 127.1, 128.6, 131.6, 140.8, 161.8,

192.3, 199.1. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.02; H, 6.80. Found: C, 76.96; H, 6.89.

Data for **22h**: white solid (273 mg, 94%), mp 109–110 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.39; ^{1}H NMR (500 MHz) 1.13 (d, J = 6.9, 3H), 2.25 (dd, J = 13.4, 8.1, 1H), 2.50 (dq, J = 10.0, 6.9, 1H), 2.88 (dd, J = 13.4, 6.8, 1H), 3.08 (dd, J = 10.0, 9.7, 1H), 3.22 (d, J = 9.7, 1H), 3.83 (s, 3H), 5.04 (dd, J = 10.1, 2.2, 1H), 5.09 (dd, J = 17.0, 2.2, 1H), 5.56 (m, 1H), 5.94 (s, 2H), 6.13 (s, 1H), 6.66 (dd, J = 7.8, 0.5, 1H), 6.72 (br s, 1H), 6.75 (d, J = 7.8, 1H); ^{13}C NMR (75 MHz) 16.6, 44.0, 44.9, 50.1, 53.1, 54.0, 56.3, 101.0, 106.8, 108.2, 114.7, 119.4, 119.7, 131.6, 134.6, 146.6, 147.9, 161.7, 192.1, 199.0. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.52; H, 6.01.

$SnCl_4$-Promoted Reactions of 14 with 8c, 8f, and 8h. The low-temperature (−78 °C) reactions were conducted utilizing 0.43 mmol of quinone **14** (109 mg) in a manner exactly analogous to reactions described above for quinone **13**.

Reaction with **8c** gave a mixture of keto–enol tautomers **28c/29c** (23 mg, 16%) and cyclobutane **23c** (148 mg, 80%), both as semisolids. Data for **23c**: R_f (50% EtOAc/hexanes) 0.23; ^{1}H NMR (500 MHz) 1.15 (d, J = 7.0, 3H), 2.24 (dd, J = 8.0, 13.4, 1H), 2.55 (dq, J = 9.7, 7.0, 1H), 2.87 (dd, J = 13.4, 6.8, 1H), 3.15 (dd, J = 9.7, 9.1, 1H), 3.27 (d, J = 9.1, 1H), 3.86 (s, 3H), 3.89 (s, 3H), 5.03 (s, 2H), 5.04 (dd, J = 8.1, 1.3, 1H), 5.09 (dd, J = 17.0, 1.3, 1H), 5.56 (m, 1H), 6.20 (s, 1H), 6.75 (d, J = 1.9, 1H), 6.77 (dd, J = 8.1, 1.9, 1H), 6.83 (d, J = 8.1, 1H), 7.38 (m, 5H); ^{13}C NMR (126 MHz) 16.9, 44.1, 44.6, 49.6, 53.1, 53.9, 55.85, 55.90, 71.1, 109.8, 111.2, 116.0, 118.1, 119.4, 127.6, 128.7 128.8, 131.7, 133.8, 133.9, 148.1, 149.0, 160.8, 192.3, 199.2; HRMS m/z 432.2934 (calcd for $C_{27}H_{28}O_5$, 432.1937).

Reaction with **8f** gave bicyclic adduct **25f** (86 mg, 75%) as a white solid, mp 105.0–105.5 °C (EtOAc/hexanes): R_f (30% EtOAc/hexanes) 0.45; ^{1}H NMR (500 MHz) 1.16 (d, J = 7.0, 3H), 2.43 (dd, J = 14.7, 7.1, 1H), 2.61 (dd, J = 14.7, 7.1, 1H), 2.63 (dq, J = 7.0, 6.0, 1H), 3.23 (dd, J = 6.0, 7.6, 1H), 3.84 (d, J = 7.6, 1H), 5.26 (br d, J = 9.6, 1H), 5.29 (dd, J = 16.2, 1.0, 1H), 5.81 (s, 1H), 5.93 (m, 1H), 6.62 (s, 1H), 7.07 (d, J = 7.4, 2H), 7.24 (t, J = 7.0, 1H), 7.29 (dd, J = 7.4, 7.0, 2H); ^{13}C NMR (126 MHz) 18.0, 32.3, 44.0, 49.7, 55.5, 67.2, 119.8, 123.8, 127.7, 128.2, 128.8, 132.8, 137.7, 149.1, 191.5, 200.9. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.21; H, 6.57.

Reaction with **8h** gave cyclobutane **23h** (154 mg, 86%) as a semisolid: R_f (50% EtOAc/hexanes) 0.39; ^{1}H HMR (500 MHz) 1.11 (d, J = 7.0, 3H), 2.23 (dd, J = 13.4, 8.0, 1H), 2.49 (dq, J = 9.8, 7.0, 1H), 2.86 (dd, J = 13.4, 6.8, 1H), 3.09 (dd, J = 9.8, 9.4, 1H), 3.23 (d, J = 9.4, 1H), 5.02 (s, 2H), 5.03 (dd, J = 11.7, 1.4, 1H), 5.08 (dd, J = 17.1, 1.4, 1H), 5.55 (m, 1H), 5.93 (s, 2H), 6.19 (s, 1H), 6.66 (d, J = 7.9, 1.4, 1H), 6.72 (d, J = 1.4, 1H), 6.74 (d, J = 7.9, 1H), 7.36 (m, 3H), 7.39 (br d, J = 4.5, 2H); ^{13}C NMR (126 MHz) 16.7, 44.0, 44.9, 50.1, 53.0, 54.0, 71.1, 101.0, 106.9, 108.3, 115.9, 119.5, 119.7, 127.6, 128.7, 128.8, 131.6, 133.9, 134.8, 146.6, 147.9, 160.8, 192.0, 199.2; HRMS m/z 416.1619 (calcd for $C_{26}H_{24}O_5$, 416.1624).

In another experiment, a reaction of **14** (109 mg, 0.42 mmol) with **8c** (0.101 mL, 0.60 mmol) promoted by $SnCl_4$ (0.10 mL, 0.86 mmol) according to the protocol described above was stirred at −78 °C for 3 h and then allowed to warm to room temperature over 4 h. Workup and chromatography with 30% EtOAc/hexanes as eluent gave a mixture of keto–enol tautomers **28c/29c** (111 mg, 75%) and cyclobutane **23c** (12 mg, 8%), both as semisolids. Compounds **28c/29c** were characterized by conversion to **41c**. Thus, a solution of **28c/29c** (234 mg, 0.684 mmol) in acetone (20 mL) was treated with K_2CO_3 (940 mg, 6.8 mmol) and CH_3I (0.847 mL, 13.6 mmol) and the mixture stirred 15 h at room temperature. Filtration and concentration of the mixture and chromatography of the residue afforded **41c** (155 mg, 64%) as a white solid, mp 115–116 °C, and recovered **28c/29c** (40 mg, 17%). Data for **41c**: R_f (50% EtOAc/hexanes) 0.10; ^{1}H NMR (500 MHz)[14d,f] 1.16 (d, J = 6.9, 3H), 2.31 (dq, J = 10.0, 6.9, 1H), 2.35 (dd, J = 13.2, 7.5, 1H), 2.57 (dd, J = 13.2, 7.5, 1H), 3.69 (s, 3H), 3.887 (s, 3H), 3.894 (s, 3H), 5.1 (dd, J = 16.9, 13, 1H), 5.09 (dd, J = 10.2, 1.3, 1H), 5.21 (d, J = 10.0, 1H), 5.43 (s, 1H), 5.56 (m, 1H), 5.81 (s, 1H), 6.77 (s, 1H), 6.87 (s, 2H); ^{13}C NMR (126 MHz)[18] 8.4, 36.7, 49.4, 51.0, 55.3, 55.96, 55.99, 91.2, 102.1, 107.9, 109.3, 111.0, 119.5, 120.0, 130.0, 130.9, 149.4, 149.8, 153.5, 181.5, 182.9.

In a similar manner, a reaction of **14** (109 mg, 0.43 mmol) with **8h** (0.087 mL, 0.60 mmol) promoted by $SnCl_4$ (0.05 mL, 0.43 mmol) was stirred at −78 °C for 12 h and then gradually warmed to −30 °C over 3 h and stirred at that temperature for an additional 1 h. Workup and chromatography gave a mixture of keto–enol tautomers **28h/29h** (101 mg, 69%) as a light yellow semisolid. This mixture was characterized by conversion to compound **41h**. Thus, a solution of **28h/29h** (166 mg, 0.51 mmol) in acetone (20 mL) was treated with K_2CO_3 (705 mg, 5.0 mmol) and CH_3I (0.62 mL, 10.0 mmol). The mixture was stirred at room temperature for 15 h. Filtration and concentration of the mixture and chromatography of the residue gave **41h** (138 mg, 80%) as a white solid, mp 136–137 °C (EtOAc/hexanes) (lit.[14b] mp 135 °C): R_f (50% EtOAc/hexanes) 0.11; ^{1}H NMR (500 MHz)[14d,g] 1.15 (d, J = 6.9, 3H), 2.28 (dq, J = 9.9, 6.9, 1H), 2.33 (dd, J = 13.4, 7.5, 1H), 2.54 (dd, J = 13.4, 7.5, 1H), 3.68 (s, 3H), 5.00 (dd, J = 16.9, 1.4, 1H), 5.08 (dd, J = 10.2, 1.4, 1H), 5.17 (d, J = 9.9, 1H), 5.42 (s, 1H), 5.54 (m, 1H), 5.79 (s, 1H), 5.98 (s, 2H), 6.76 (d, J = 1.4, 1H), 6.77 (dd, J = 8.1, 1.4, 1H), 6.81 (d, J = 8.1, 1H); ^{13}C NMR (126 MHz)[18] 8.3, 36.7, 49.5, 50.9, 55.3, 91.0 101.3, 102.1, 106.6, 107.8, 108.2, 120.0, 120.6, 130.9, 131.5, 148.2, 148.3, 153.5, 181.3, 182.8.

Ti(IV)-Promoted Reactions of 13/14 with 8c, 8f, and 8h: Reaction of 13 with 8c. According to method B, Ti(OiPr)$_4$ (0.10 mL, 0.34 mmol) and $TiCl_4$ (0.18 mL, 1.64 mmol) were added to a solution of quinone **13** (90 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) followed by propenylbenzene **8c** (0.12 mL, 0.71 mmol). The reaction was complete in 18 h, worked up as described in method C, and gave **19c** (155 mg, 87%) as a white solid, mp 122–124 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.26; ^{1}H NMR (500 MHz) 1.13 (d, J = 6.8, 3H), 1.77 (dd, J = 14.0, 8.6, 1H), 2.46 (dd, J = 14.0, 5.7 1H), 3.18 (d, J = 11.3, 1H), 3.24 (ddq, J = 11.3, 9.6, 6.8, 1H), 3.38 (d, J = 9.6, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.93 (d, J = 16.4, 1H), 4.94 (d, J = 11.0, 1H), 5.39–5.47 (m, 1H), 6.08 (s, 1H), 6.66 (d, J = 1.6, 1H), 6.68 (dd, J = 9.1, 1.6, 1H), 6.80 (d, J = 9.1, 1H); ^{13}C NMR (126 MHz) 17.1, 33.2, 36.2, 47.2, 51.4, 54.0, 55.79, 55.84, 56.3, 110.8, 111.1, 113.2, 118.8, 118.9, 129.4, 132.6. 148.1, 148.8, 162.6, 193.4, 200.2. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.62; H, 6.82.

In another experiment, $TiCl_4$ (0.92 mL, 8.4 mmol) was added quickly with slow stirring to a solution of Ti(OiPr)$_4$ (0.5 mL, 1.7 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 1 h, the precipitate that formed was separated by decanting the liquid via cannula, washed with CH_2Cl_2 (1.5 mL), and dried under vacuum to yield a light yellow solid. A solution of this solid (548 mg) in CH_2Cl_2 (3 mL) was added to a solution of quinone **13** (122 mg, 0.684 mmol) in CH_2Cl_2 (6 mL) maintained at −78 °C. The solution was stirred at −78 °C for 15 min, and propenylbenzene **8c** (0.162 mL, 0.958 mmol) then added. The reaction mixture was stirred at −78 °C for 26 h and then worked up as described above to give cyclobutane **19c** (233 mg, 97%).

Reaction of 13 with 8f. According to method C, $TiCl_4$ (0.12 mL, 1.1 mmol) was added to a solution of quinone **13** (100 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) at −30 °C. The mixture was stirred for 10 min and cooled to −78 °C and propenylbenzene **8f** (0.145 mL, 1.12 mmol) added. The reaction was complete in 1.5 h and gave cyclobutane **19f** (161 mg, 97%) as a light yellow solid. Recrystallization from EtOAc/hexanes gave white plates, mp 127.0–127.5 °C: R_f (50% EtOAc/hexanes) 0.43; ^{1}H NMR (500 MHz) 1.17 (d, J = 6.9, 3H), 1.82 (dd, J = 14.0, 8.5, 1H), 2.48 (dd, J = 14.0, 5.7, 1H), 3.24 (d, J = 11.3, 1H), 3.35 (ddq, J = 11.3, 9.9, 6.9, 1H), 3.48 (d, J = 9.9, 1H), 3.85 (s, 3H), 4.97 (dd, J = 16.3, 1.25, 1H), 4.98 (d, J = 11.0, 1H), 5.42–5.51 (m, 1H), 6.14 (s, 1H), 7.19 (d, J = 7.6, 2H), 7.26 (ddd, J = 7.6, 7.6, 1.6, 1H), 7.35 (ddd, J = 7.6, 7.6, 1.6, 2H); ^{13}C NMR (126 MHz) 17.1, 33.0, 36.3, 47.2, 51.3, 54.2, 56.3, 113.2, 118.8, 127.0,

(18) (a) Wenkert, E.; Gottlieb, H. E.; Gottlieb, O. R.; Pereira, M. O. da S.; Formiga, M. D. *Phytochemistry* **1976**, *15*, 1547. For review of ^{13}C NMR data for related compounds, see: (b) Agrawal, P. K.; Thakur, R. S. *Magn. Reson. Chem.* **1985**, *23*, 389.

127.5, 128.3, 132.6, 136.8, 162.6, 193.3, 200.0. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.86: H, 6.97.

In another experiment, $TiCl_4$ (0.92 mL, 8.4 mmol) was added to a solution of $Ti(OiPr)_4$ (0.50 mL, 1.7 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 1 h, a precipitate had formed. The liquid was decanted via cannula and the precipitate was washed with CH_2Cl_2 (1.5 mL) and dried under vacuum to yield a light yellow solid. A solution of this solid (0.60 g) in CH_2Cl_2 (2 mL) was added to a solution of quinone **13** (67 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The solution was stirred at −78 °C for 15 min and propenylbenzene **8f** (0.068 mL, 0.52 mmol) then added. The reaction mixture was stirred at −78 °C for 16 h and worked up as described in method C. Chromatography afforded cyclobutane **22f** (108 mg, 97%) as a white solid.

Reaction of 13b with 8h. According to method C, an aliquot [2 mL, 1.99 mmol of Ti(IV)] of a solution of $TiCl_4$ (0.82 mL, 7.48 mmol) and $Ti(OiPr)_4$ (0.74 mmol, 2.50 mmol) in (10 mL) was added to a solution of quinone **13** (179 mg, 1.01 mmol) in CH_2Cl_2 (10 mL) followed by propenylbenzene **8h** (0.20 mL, 1.39 mmol). The reaction was complete in 4 h and gave cyclobutane **19h** (284 mg, 83%) as a white solid, mp 114−115 °C (EtOAc/hexanes): R_f (50% EtOAc/hexanes) 0.39; ^{1}H NMR (500 MHz) 1.12 (d, J = 6.4, 3H), 1.81 (dd, J = 14.0, 8.6, 1H), 2.49 (dd, J = 14.0, 5.7, 1H), 3.18 (d, J = 11.2, 1H) 3.21 (ddq, J = 11.2, 9.0, 6.4, 1H), 3.36 (d, J = 9.0, 1H), 3.82 (s, 3H), 4.96 (dd, J = 13.2, 2.9, 2H), 5.45 (m, 1H), 5.93 (s, 2H), 6.09 (s, 1H), 6.61 (d, J = 8.0, 1H), 6.67 (d, J = 1.3, 1H), 6.76 (br d, J = 8.0, 1H); ^{13}C NMR (126 MHz) 17.0, 33.4, 36.1, 47.1, 51.4, 54.1, 56.3, 101.0, 108.1 (2C), 113.1, 118.8, 120.5, 130.6, 132.6, 146.6, 147.7, 162.5, 193.3, 199.9. Anal. Calcd for $C_{20}H_{20}O_5$: C, 76.58; H, 5.92. Found: C, 76.67; H, 6.01.

Reaction of 14 with 8c. $TiCl_4$ (0.92 mL, 8.4 mmol) was added quickly with slow stirring to a solution of $Ti(OiPr)_4$ (0.5 mL, 1.7 mmol) in dichloromethane (2 mL) at room temperature. After 1 h, the precipitate that formed was separated by decanting the liquid via cannula, washed with CH_2Cl_2 (1.5 mL), and dried under vacuum to yield a light yellow solid. A solution of this solid (735 mg) in CH_2Cl_2 (3 mL) was added to a solution of quinone **14** (320 mg, 1.26 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C. The solution was stirred at −78 °C for 15 min and propenylbenzene **8c** (0.276 mL, 1.64 mmol) then added. The reaction mixture was stirred at −78 °C for 14 h and then worked up as described in method C. Chromatography with 20% and then 30% EtOAc/hexanes as eluents gave a 3.9:1 mixture of cyclobutanes **20c/23c** (500 mg, 93%) as a light yellow semisolid. Recrystallization from EtOAc/hexanes gave pure **20c** (308 mg, 61%), mp 125−126 °C: R_f (30% EtOAc/hexanes) 0.23; ^{1}H NMR (500 MHz) 1.17 (d, J = 6.6, 3H), 1.81 (dd, J = 14.1, 8.2, 1H), 2.49 (dd, J = 14.1, 5.7, 1H), 3.23 (d, J = 11.2, 1H), 3.27 (ddq, J = 11.2, 9.2, 6.6, 1H), 3.41 (d, J = 9.2, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 4.97 (d, J = 16.4, 1H), 4.97 (d, J = 10.9, 1H), 5.06 (s, 2H), 5.46 (m, 1H), 6.18 (s, 1H), 6.70 (d, J = 1.6, 1H), 6.71 (d, J = 8.1, 1H), 6.84 (d, J = 8.1, 1H), 7.35−7.42 (m, 5H); ^{13}C NMR (126 MHz) 17.2, 33.3, 36.3, 47.2, 51.4, 54.0, 55.8, 55.9, 71.0, 110.8, 111.2, 114.4, 118.7, 119.0, 127.5, 128.7, 128.8, 129.5, 132.7, 134.0, 148.1, 148.8, 161.6, 193.1, 200.3. Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.52. Found: C, 74.78; H, 6.62.

Reaction of 14 with 8h. The Ti(IV)-solid was prepared exactly as described in the reaction of **14** with **8c.** A solution of the Ti(IV)-solid (550 mg) in CH_2Cl_2 (3 mL) was added to a solution of quinone **14** (367 mg, 1.44 mmol) in CH_2Cl_2 (20 mL) maintained at −78 °C. The solution was stirred at −78 °C for 15 min and propenylbenzene **8h** (0.292 mL, 2.02 mmol) then added. The reaction mixture was stirred at −78 °C for 7 h and worked up as described in method C. Chromatography with 20% and then 30% ethyl acetate/hexanes as eluents gave a 2.5:1 mixture of cyclobutanes **20h/23h** (545 mg, 91%) as a light yellow semisolid. Recrystallization from EtOAc/hexanes gave pure **20h** (207 mg, 38%), mp 150−151 °C (EtOAc/hexanes): R_f (30% EtOAc/hexanes) 0.39; ^{1}H NMR (500 MHz) 1.15 (d, J = 6.3, 3H), 1.82 (dd, J = 14.0, 8.6, 1H), 2.49 (dd, J = 14.0, 5.8, 1H), 3.22 (d, J = 8.0, 1H), 3.23 (ddq, J = 8.6, 8.0, 6.3, 1H), 3.37 (d, J = 8.6, 1H), 4.98 (m, H), 5.05 (s, 2H), 5.46 (m, 1H), 5.95 (s, 2H), 6.61 (s, 1H), 6.62 (br d, J = 8.0, 1H), 6.68 (d, J = 1.3, 1H), 6.78 (d, J = 8.0, 1H), 7.37 (m, 3H), 7.41 (br d, J = 4.5, 2H); ^{13}C NMR (126 MHz) 17.2, 33.5, 36.2, 47.1, 51.4, 54.2, 71.1, 101.1, 108.1 (2C), 114.4, 118.9, 120.6, 127.6, 128.8, 128.9, 130.7, 132.7, 134.0, 146.7, 147.8, 161.6, 193.2, 200.1. Anal. Calcd for $C_{26}H_{24}O_5$: C, 74.97; H, 5.81, Found: C 74.54; H, 6.00.

Rearrangements of Cyclobutanes 18−20 and 21−23. All reactions were conducted in a similar manner. Three representative procedures are given.

Trifluoroacetic acid (0.5 mL) was added to a solution of cyclobutane **18f** (99 mg, 0.37 mmol) in trifluoroethanol (5 mL) and the mixture refluxed for 16 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL), washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography of the residue with 20% EtOAc/hexanes as eluent gave a 14:1 mixture of dihydrobenzofuran **15f** and its cis isomer (72 mg, 73%). Pure **15f** was obtained by recrystallization from EtOAc/hexanes; mp 129−131 °C: R_f (50% EtOAc/hexanes) 0.49; ^{1}H NMR (500 MHz) 1.45 (d, J = 6.9, 3H), 2.10 (s, 3H), 3.43 (dq, J = 4.8, 6.9, 1H), 3.84 (s, 3H), 4.43 (s, 1H), 5.27 (d, J = 4.8, 1H), 6.37 (s, 1H), 7.26−7.33 (m, 5H); ^{13}C NMR (126 MHz) 11.4, 20.1, 46.2, 56.2, 91.7, 100.3, 111.7, 125.4, 127.8, 128.5, 131.4, 141.2, 142.0, 142.1, 148.1; HRMS m/z 270.1259 (calcd for $C_{17}H_{18}O_3$, 270.1256).

Data for **15h** (30 mg, 58% from 52 mg of **18h**), colorless semisolid: R_f (30% EtOAc/hexanes) 0.24; ^{1}H NMR (500 MHz) 1.42 (d, J = 6.9, 3H), 2.10 (s, 3H), 3.39 (dq, J = 5.0, 6.9, 1H), 3.82 (s, 3H), 4.46 (s, 1H), 5.16 (d, J = 5.0, 1H), 5.92 (s, 2H), 6.35 (s, 1H), 6.74 (d, J = 7.9, 1H), 6.81 (d, J = 1.6, 1H), 6.80 (dd, J = 7.9, 1.6, 1H); ^{13}C NMR (126 MHz) 11.4, 19.9, 46.1, 56.2, 91.8, 101.0, 106.1, 108.1, 111.7, 119.2, 131.4, 131.5, 135.9, 141.1, 142.1, 147.3, 147.8, 148.1; HRMS m/z 314.1151 (calcd for $C_{18}H_{18}O_5$, 314.1154).

Trifluoroacetic acid (0.5 mL) was added to a solution of cyclobutane **19h** (101 mg, 0.30 mmol) in THF (5 mL). The mixture was stirred at 0 °C for 3 h and at room temperature for 3 h and then worked up as described in the reaction of **18f**. Chromatography of the residue with 5%, 10%, and then 20% EtOAc/hexanes as eluents gave a 11:1 mixture of dihydrobenzofuran **16h** and its cis isomer (44 mg, 45%) as an oil and quinone **13** (17 mg, 32%) as a yellow solid. Data for **16h**: R_f (50% EtOAc/hexanes) 0.46; ^{1}H NMR (500 MHz) 1.39 (d, J = 6.9, 3H), 3.31 (d, J = 5.6, 2H), 3.40 (dq, J = 6.9, 4.7, 1H), 3.83 (s, 3H), 4.73 (s, 1H), 5.10 (dd, J = 17.2, 1.6, 1H), 5.14 (dd, J = 9.3, 1.6, 1H), 5.15 (d, J = 4.7, 1H), 5.92 (s, 2H) 5.94−6.02 (m, 1H), 6.40 (s, 1H), 6.74 (d, J = 7.8, 1H), 6.79 (dd, J = 7.8, 1.7, 1H), 6.81 (br s, 1H); ^{13}C NMR (126 MHz) 20.6, 31.0, 45.8, 56.0, 91.8, 100.9, 101.0, 106.1, 108.0, 112.9, 116.2, 119.2, 131.3, 135.7, 135.9, 141.2, 142.9, 147.3, 147.8, 149.0; HRMS m/z 340.1312 (calcd for $C_{21}H_{24}O_5$, 340.1311).

Data for **16c** (34 mg, 63% from 53 mg of **19c**), an oil: R_f (50% EtOAc/hexanes) 0.32; ^{1}H NMR (500 MHz) 1.41 (d, J = 6.9, 3H), 3.33 (d, J = 4.5, 2H), 3.46 (dq, J = 6.9, 5.4, 1H), 3.84 (s, 3H), 3.86 (s, 6H), 4.73 (s, 1H), 5.11 (dd, J = 17.2, 1.8, 1H), 5.14 (dd, J = 11.0, 1.8, 1H), 5.17 (d, J = 5.4, 1H), 5.95−6.03 (m, 1H), 6.41 (s, 1H), 6.81 (d, J = 7.9, 1H), 6.88 (d, J = 1.9, 1H), 6.89 (dd, J = 7.9, 1.9, 1H); ^{13}C NMR (126 MHz) 20.4, 30.9, 45.6, 55.84, 55.86, 56.0, 92.0, 100.8, 108.9, 110.9, 112.9, 116.1, 118.3, 131.4, 134.0, 136.0, 141.3, 143.0, 148.8, 148.9, 149.0; HRMS m/z 356.1624 (calcd for $C_{21}H_{24}O_5$, 356.1624).

Data for **16f** (80 mg, 67% from 120 mg of **19f**), semisolid: R_f (30% EtOAc/hexanes) 0.34; ^{1}H NMR (500 MHz) 1.42 (d, J = 6.9, 3H), 3.26 (d, J = 5.6, 2H), 3.43 (dq, J = 6.9, 4.8, 1H), 3.83 (s, 3H), 4.82 (s, 1H), 5.08 (dd, J = 17.3, 1.7, 1H), 5.12 (dd, J = 11.8, 1.7, 1H), 5.25 (d, J = 4.8, 1H), 5.93−6.03 (m, 1H), 6.41 (s, 1H), 7.26−7.32 (m, 5H); ^{13}C NMR (126 MHz) 20.7, 31.0, 45.9, 56.0, 91.8, 100.9, 113.0, 116.1, 125.4, 127.8, 128.4, 131.3, 135.9, 141.3, 141.8, 142.9, 149.0; HRMS m/z 296.1419 (calcd for $C_{19}H_{20}O_3$, 296.1412).

Trifluoroacetic acid (1.6 mL) was added to a solution of cyclobutane **20c** (105 mg, 0.24 mmol) in trifluoroethanol (8 mL). The mixture was stirred at room temperature for 10 h and then worked up as described for the reaction of **19h.** Chromatography with 20% EtOAc/hexanes as eluent gave a 9:1 ratio of dihydrobenzofuran **17c** and its cis isomer (71.4 mg, 68%) as an oil and quinone **14** (9.3 mg, 9%) as a yellow solid. Data for **17c**: R_f (30% EtOAc/hexanes) 0.24; ^{1}H NMR (500

MHz) 1.41 (d, J = 6.9, 3H), 3.30 (br d, J = 5.2, 2H), 3.43 (dq, J = 6.9, 5.1, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 4.57 (s, 1H), 5.09 (dd, J = 17.2, 1.7, 1H), 5.12 (dd, J = 11.8, 1.7, 1H), 5.15 (s, 2H), 5.20 (d, J = 5.1, 1H), 5.97 (m, 1H), 6.41 (s, 1H), 6.81 (d, J = 7.8, 1H), 6.88 (br s, 1H), 6.89 (dd, J = 7.8, 1.9, 1H), 7.34 (m, 5H); ^{13}C NMR (126 MHz) 20.5, 31.0, 45.6, 55.8, 55.9, 71.2, 91.8, 103.4, 108.9, 111.0, 113.8, 116.2, 118.1, 127.4 (2C), 127.8, 128.5 (2C), 131.9, 134.3, 136.0, 137.2, 148.7, 148.8, 149.0; HRMS m/z 432.1938 (calcd for $C_{27}H_{28}O_5$, 432.1937).

Data for **17h** (54 mg, 65% from 83 mg of **20h**), an oil: R_f (30% EtOAc/hexanes) 0.36; ^{1}H NMR (500 MHz) 1.39 (d, J = 6.9, 3H), 3.28 (br d, J = 5.7, 2H), 3.38 (dq, J = 6.9, 4.7, 1H), 4.64 (br s, 1H), 5.08 (dd, J = 17.3, 1.6, 1H), 5.11 (dd, J = 10.6, 1.6, 1H), 5.12 (s, 2H), 5.17 (d, J = 4.7, 1H), 5.92 (s, 2H), 5.95 (m, 1H), 6.40 (s, 1H), 6.74 (d, J = 7.9, 1H), 6.79 (dd, J = 7.9, 1.5, 1H), 6.81 (d, J = 1.5, 1H), 7.28 (t, J = 7.7, 1H), 7.33 (t, J = 7.7, 2H), 7.32 (d, J = 7.7, 2H); ^{13}C NMR (126 MHz) 20.7, 31.0, 45.8, 71.2, 91.7, 101.0, 103.4, 106.0, 108.1, 113.8, 116.2, 119.1, 127.5, 127.8, 128.4, 131.7, 135.89, 135.94, 137.1, 141.8, 141.9, 147.3, 147.8, 148.8; HRMS m/z 416.1615 (calcd for $C_{26}H_{24}O_5$, 416.1624).

Data for **24c** (31 mg, 65% from 50 mg of **21c**), a white solid, mp 134–135 °C: R_f (30% EtOAc/hexanes) 0.16; ^{1}H NMR (500 MHz) 1.09 (d, J = 7.0, 3H), 1.34 (s, 3H), 2.54 (dq, J = 6.4, 7.0, 1H), 3.12 (dd, J = 7.4, 6.4, 1H), 3.81 (d, J = 7.4, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 6.43 (s, 1H), 6.56 (d, J = 2.1, 1H), 6.63 (dd, J = 8.3, 2.1, 1H), 6.77 (d, J = 8.3, 1H) (the OH signal is not observed); ^{13}C NMR (126 MHz) 14.1, 17.9, 45.5, 49.4, 52.9, 55.7, 55.8, 67.6, 111.2, 111.4, 120.3, 126.9, 130.4, 148.4, 148.98, 149.04, 191.7, 201.6; HRMS m/z 316.1302 (calcd for $C_{18}H_{20}O_5$, 316.1311).

Data for **24f** (15 mg, 54% from 30 mg of **21f**), an oil: R_f (30% EtOAc/hexanes) 0.53; ^{1}H NMR (300 MHz) 1.11 (d, J = 7, 3H), 1.35 (s, 3H), 2.60 (dq, J = 6, 7, 1H), 3.18 (dd, J = 7, 7, 1H), 3.84 (d, J = 7, 1H), 5.85 (s, 1H), 6.43 (s, 1H), 7.07 (d, J = 7, 2H), 7.2–7.3 (m, 3H); ^{13}C NMR (75 MHZ) (APT) 14.5 (q), 18.3 (q), 45.5 (q), 50.1 (q), 53.2 (s), 67.8 (d), 127.4 (d), 128.0 (d), 128.6 (d), 129.2 (d), 138.2 (s), 149.4 (s), 192.0 (s), 201.9 (s); HRMS m/z 256.1101 (calcd for $C_{16}H_{16}O_3$, 256.1098).

Data for **24h** (61 mg, 69% from 92 mg **21h**), a semisolid: R_f (30% EtOAc/hexanes) 0.32; ^{1}H NMR (500 MHz) 1.07 (d, J = 7.0, 3H), 1.32 (s, 3H), 2.49 (dq, J = 6.7, 7.0, 1H), 3.09 (dd, J = 7.3, 6.7, 1H), 3.78 (d, J = 7.3, 1H), 5.91 (s, 2H), 5.96 (br s, 1H), 6.41 (s, 1H), 6.53 (d, J = 1.6, 1H), 6.54 (dd, J = 7.9, 1.6, 1H), 6.70 (d, J = 7.9, 1H); ^{13}C NMR (126 MHz) 14.0, 17.8, 45.5, 49.4, 52.8, 67.6, 101.2, 108.36, 108.45, 121.5, 127.2, 131.6, 147.0, 148.0, 149.0, 191.6, 201.5; HRMS m/z 300.0999 (calcd for $C_{17}H_{16}O_5$, 300.0998).

Data for **25c** (74 mg, 75% from 102 mg of **23c**), white solid, mp 130–130.5 °C (EtOAc/hexanes): R_f (30% EtOAc/hexanes) 0.20; ^{1}H NMR (500 MHz) 1.16 (d, J = 7.0, 3H), 2.43 (dd, J = 14.7, 7.2, 1H), 2.57 (dq, J = 5.6, 7.0, 1H), 2.61 (dd, J = 14.7, 7.0, 1H), 3.16 (dd, J = 5.6, 7.6, 1H), 3.81 (d, J = 7.6, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 5.26 (br d, J = 9.0, 1H), 5.28 (dd, J = 17.0, 1.6, 1H), 5.82 (s, 1H), 5.92 (m, 1H), 6.55 (d, J = 2.1, 1H), 6.61 (s, 1H), 6.63 (dd, J = 8.3, 2.1, 1H), 6.76 (d, J = 8.3, 1H); ^{13}C NMR (126 MHz) 18.0, 32.4, 44.6, 49.6, 55.6, 55.76, 55.81, 67.4, 111.1, 111.3, 119.8, 120.4, 123.6, 130.3, 132.9, 148.5, 149.0, 149.1, 191.6, 200.9. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48, Found: C, 69.91; H, 6.64.

Data for **25h** (61 mg, 67% from 116 mg of **23h**), white solid, mp 141–142 °C (EtOAc/hexanes) (lit.[14b] mp 147–148 °C): R_f (30% EtOAc/hexanes) 0.38; ^{1}H NMR (500 MHz) 1.14 (d, J = 7.0, 3H), 2.41 (dd, J = 14.7, 7.1, 1H), 2.53 (dq, J = 6.0, 7.0, 1H), 2.59 (dd, J = 14.7, 7.0, 1H), 3.13 (dd, J = 6.0, 7.5, 1H), 3.78 (d, J = 7.5, 1H), 5.26 (br d, J = 8.4, 1H), 5.28 (dd, J = 16.0, 1.4, 1H), 5.80 (s, 1H), 5.91 (m, 1H), 5.93 (s, 2H), 6.53 (d, J = 1.6, 1H), 6.54 (dd, J = 8.0, 1.6, 1H), 6.61 (s, 1H), 6.70 (d, J = 8.0, 1H); ^{13}C NMR (126 MHz) 17.9, 32.3, 44.6, 49.6, 55.6, 67.4, 101.2, 108.4, 108.5, 119.8, 121.6, 123.8, 131.5, 132.8, 147.1, 148.1, 149.1, 191.5, 200.8; HRMS m/z 326.1155 (calcd for $C_{19}H_{18}O_5$, 326.1154).

Methylation of 24c and 25c,f,h: Representative Procedure. Methyl iodide (0.5 mL, 8.0 mmol) was added to a mixture of **25h** (98 mg, 0.30 mmol) and K_2CO_3 (166 mg, 1.20 mmol) in acetone (20 mL), and the mixture was stirred at room temperature for 14 h. The inorganic salts were removed by filtration, and the filtrate was concentrated. Chromatography of the residue with 20% EtOAc/hexanes as eluent gave **39h** (82 mg, 80%) as white solid, mp 109–110 °C (EtOAc/hexanes) (lit.[14b] mp 117–118 °C): R_f (30% EtOAc/hexanes) 0.20; ^{1}H NMR (500 MHz)[14d] 1.14 (d, J = 7.0, 3H), 2.44 (dd, J = 14.8, 7.0, 1H), 2.53 (dq, J = 5.8, 7.0, 1H), 2.61 (dd, J = 14.8, 7.2, 1H), 3.12 (dd, J = 5.8, 7.6, 1H), 3.68 (s, 3H), 3.74 (d, J = 7.6, 1H), 5.27 (dd, J = 10.2, 1.7, 1H), 5.30 (dd, J = 17.0, 1.7, 1H), 5.91 (s, 2H), 5.90–5.98 (m, 1H), 6.26 (s, 1H), 6.52 (d, J = 1.8, 1H), 6.54 (dd, J = 8.0, 1.8, 1H), 6.70 (d, J = 8.0, 1H); ^{13}C NMR (126 MHz) 18.0, 32.5, 44.7, 49.4, 54.9, 55.6, 68.9, 101.1, 108.4, 108.5, 119.6, 121.6, 121.7, 131.5, 133.2, 146.9, 148.0, 153.5, 189.8, 201.4; HRMS m/z 340.1308 (calcd for $C_{20}H_{20}O_5$, 340.1311).

Data for **38c** (15 mg, 75% from 19 mg of **87c**), a white solid: mp 124–125 °C (EtOAc/hexanes) (lit.[14c] mp 104–105 °C): R_f (50% EtOAc/hexanes) 0.20; ^{1}H NMR (500 MHz) 1.10 (d, J = 7.0, 3H), 1.36 (s, 3H), 2.52 (dq, J = 6.7, 7.0, 1H), 3.09 (dd, J = 7.2, 6.7, 1H), 3.70 (s, 3H), 3.77 (d, J = 7.2, 1H), 3.829 (s, 3H), 3.830 (s, 3H), 6.10 (s, 1H), 6.58 (d, J = 2.1, 1H), 6.61 (dd, J = 8.3, 2.1, 1H), 6.77 (d, J = 8.3, 1H); ^{13}C NMR (126 MHz) 14.4, 18.0, 46.1, 49.4, 52.4, 55.6, 55.7, 55.8, 69.2, 111.3, 111.7, 120.2, 125.2, 130.5, 148.4, 148.9, 153.5, 190.1, 202.2; HRMS m/z 330.1467 (calcd for $C_{19}H_{22}O_5$, 330.1467).

Data for **39c** (27 mg, 75% from 35 mg of **25c**), a semisolid: R_f (30% EtOAc/hexanes) 0.10; ^{1}H NMR (500 MHz) 1.16 (d, J = 7.0, 3H), 2.45 (dd, J = 14.8, 7.1, 1H), 2.55 (dq, J = 6.0, 7.0, 1H), 2.63 (dd, J = 14.8, 7.1, 1H), 3.13 (dd, J = 7.6, 6.0, 1H), 3.68 (s, 3H), 3.78 (d, J = 7.6, 1H), 3.83 (s, 6H), 5.27 (d, J = 9.9, 1H), 5.30 (d, J = 16.9, 1H), 5.91–5.99 (m, 1H), 6.27 (s, 1H), 6.57 (d, J = 2.0, 1H), 6.60 (dd, J = 8.3, 2.0, 1H), 6.76 (d, J = 8.3, 1H); ^{13}C NMR (75 MHz) 18.1, 32.5, 45.1, 49.4, 54.9, 55.6, 55.7, 55.8, 69.0, 111.2, 111.7, 119.6, 120.2, 121.7, 130.4, 133.3, 148.4, 148.9, 153.6, 190.0, 201.4; HRMS m/z 356.1621 (calcd for $C_{21}H_{24}O_5$, 356.1624).

Data for **39f** (25 mg, 89% from 27 mg of **25f**), a semisolid: R_f (30% EtOAc/hexanes) 0.34; ^{1}H NMR (300 MHz) 1.15 (d, J = 7.1, 3H), 2.46 (dd, J = 14.8, 7.0, 1H), 2.60–2.67 (m, 2H), 3.19 (dd, J = 7.5, 5.9, 1H), 3.68 (s, 3H), 3.80 (d, J = 7.5, 1H), 5.27 (br d, J = 10.2, 1H), 5.30 (dd, J = 17.0, 1.5, 1H), 5.95 (m, 1H), 6.28 (s, 1H), 7.06 (d, J = 6.8, 2H), 7.20–7.30 (m, 3H); ^{13}C NMR (75 MHz) 18.1, 32.5, 44.5, 49.6, 54.9, 55.6, 68.8, 119.6, 121.8, 127.5, 128.2, 128.7, 133.3, 137.8, 153.5, 189.9, 201.5; HRMS m/z 296.1417 (calcd for $C_{19}H_{20}O_3$, 296.1412).

Acknowledgment. Financial support for this research was provided by the National Institutes of Health [GM 39820 and GM 07775 (as a predoctoral fellowship to M.A.L.)], the National Science Foundation (CHE-9116576), and the University of Kansas General Research Fund. We thank Professor Steven R. Angle (University of California, Riverside) for sharing results of his experiments prior to publication and for spectral data. T.A.E. acknowledges a Fellowship from the Alfred P. Sloan Foundation and a Granteeship from Eli Lilly and Co.

Supplementary Material Available: Experimental details for the preparation of quinones **12–14** and **iv**; IR, mass, and selected UV spectral data for new compounds; ^{1}H and ^{13}C NMR spectra of all new compounds for which C,H,N elemental analyses were not obtained (60 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.