Synthesis of Neolignans via a Proposed Biosynthetic Intermediate. Total Synthesis of (±)-Futoenone

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The attempted spectroscopic observation of a quinone methide proposed to be an intermediate in the biosynthesis of neolignans is reported. The results afforded substantial indirect evidence for the formation of quinone methide **3**. The synthesis of racemic bicyclo[3.2.1]octenedione **22**, a natural product, is proposed to occur through a similar quinone methide intermediate. The synthesis of (±)-futoenone via a benzylic cation intermediate related to quinone methide **3** is reported. The results provide support for Gottlieb's proposal that several different neolignans arise from a common biosynthetic precursor. The efficient synthesis of (±)-futoenone and related spiro[5.5]undecanoids using a Büchi quinone ketal cycloaddition is also described.

Introduction

The lignans and neolignans comprise a group of natural products characterized by carbon skeletons which are dimers of phenylpropanoids derived from shikimic acid. The two groups are generally differentiated based on the carbons through which dimerization occurs. The term lignan originated for the designation of dimers which were coupled at the C(8)-C(8′) positions of the phenylpropanoids (**A**, Figure 1).[1] Neolignan was later introduced to designate those natural products linked through any position other than the C(8)-C(8′) position.[2] Three major neolignan subgroups are represented by the skeletons **B**, **C**, and **D** (Figure 1).

Neolignans exhibit a broad range of biological activity including: stimulant, sedative, muscle relaxant, cytotoxic, antileukemic, antitumor, antioxidant, antifungal, antimicrobial, insect antifeedant, and other diverse activity.[3] This range of biological activity has led to intensive synthetic efforts being focused on these compounds.[3-5] Recently, futoenone (**6**, Scheme I) and related neolignans isolated from the Chinese herbal plant *Piper futokadsura*, were found to be potent and competitive receptor antagonists of platelet activating factor (PAF).[6,7] PAF is a highly potent lipid mediator of acute inflammation, allergy, and anaphylaxis. Shen and co-workers have demonstrated that

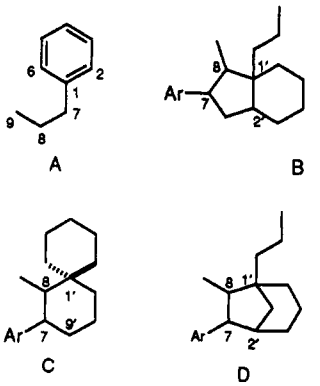

Figure 1. Representative neolignans derived from arylpropanoids.

futoenone acts as a dual PAF receptor antagonist and 5-lipoxygenase inhibitor which enhances its potential role as a therapeutic agent for asthma and various cardiovascular and inflammatory disorders.[6a,b]

Gottlieb has proposed that the three different types of neolignans, **B**, **C**, and **D**, shown in Figure 1 arise via a common biosynthetic pathway (Scheme I).[2,8] His proposal calls for the enzymatically directed radical coupling of appropriately oxidized and *O*-methylated propenyl- and allylphenols (**1** and **2**) to afford quinone methide **3**, a postulated intermediate (Scheme I).[2,8] Quinone methide **3** might react by one of three different pathways: (a) C-alkylation of the β-diketone would afford the bicyclo[3.2.1]octene skeleton found in *epi*-guianin (**4**), (b) *O*-alkylation of the β-diketone would afford the hydrobenzofuran skeleton found in *epi*-burchellin (**5**), or (c) attack of the alkene followed by capture of the resulting cation by the β-diketone oxygen would afford the spiro[5.5]undecane skeleton found in futoenone **6**. The proposed bifurcation of quinone methide **3** might be directed enzymatically or chemically. Pathways a and b both involve the enolized β-diketone acting as a nucleophile, a

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(1) (a) Hawthorn, R. D. *J. Chem. Soc.* **1942**, 448. (b) Hawthorn, R. D. *Nature* **1941**, *147*, 225.

(2) (a) Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. For an alternative definition of the terms lignan and neolignan see: (b) Barbosa-Filho, J. M.; Yoshida, M.; Gottlieb, O. R. *An. Acad. Bras. Ci.* **1987**, *59*, 335. (c) Gottlieb, O. R. *Prog. Chem. Org. Nat. Prod.* **1978**, *35*, 1.

(3) For reviews on the biological activity, structure, and synthesis of lignans and neolignans see: (a) Gottlieb, O. R. In *New Natural Products and Plant Drugs with Phamacological, Biological, or Therapeutic Activity*; Proceedings of the First International Congress on Medicinal Plant Research, Sec. A, 1976; Wagner, H.; Wolff, P. M., Eds.; Springer-Verlag: Berlin, 1977, pp 227-248. (b) Gottlieb, O. R.; Yoshida, M. *Quim. Nova* **1984**, *7*, 250.

(4) For an excellent series of reviews on lignans, neolignans, and related compounds see: Whiting, D. A. *Nat. Prod. Rep.* **1993**, *10*, 1. *Ibid.* **1990**, *7*, 349. *Ibid.* **1987**, *4*, 499. *Ibid.* **1985**, *2*, 191.

(5) For a review on the synthesis of lignans and neolignans see: Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.

(6) (a) Shen, T. Y. *Lipids* **1991**, *26*, 1154. (b) Gingrich, D. E.; Hussaini, I.; Shen, T. Y. 199th National Meeting of the American Chemical Society, Boston, MA; April 22–27, 1990; Abstr. MEDI 08. (c) Shen, T. Y.; Hussaini, I.; Hwang, S. B.; Chang, M. N. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1989**, *19*, 359. (d) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brokker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309.

(7) For the isolation, structure, and relay synthesis of futoenone see: (a) Ogiso, A.; Kurabayashi, M.; Mishima, H.; Woods, M. C. *Tetrahedron Lett.* **1968**, *9*, 2003. (b) Woods, M. C.; Miura, I.; Ogiso, A.; Kurabayashi, M.; Mishima, H. *Tetrahedron Lett.* **1968**, *9*, 2009. (c) Ogiso, A.; Kurabayashi, M.; Takahashi, S.; Mishima, H.; Woods, M. C. *Chem. Pharm. Bull.* **1970**, *18*, 105.

(8) (a) Gottlieb, O. R. *Phytochemistry* **1989**, *28*, 2545. (b) Pelter, A. In *Recent Advances in Phytochemistry*; Conn, E. E., Ed.; Plenum Press: New York, 1985; Vol 20, pp 201–240.

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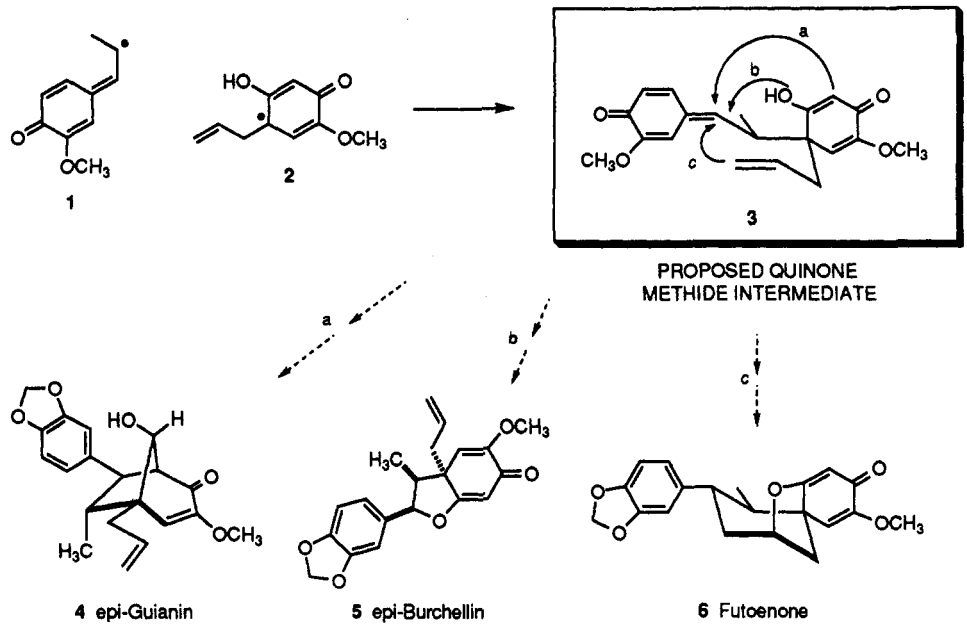
Scheme I. Gottlieb's Proposed Neolignan Biosynthesis[8]



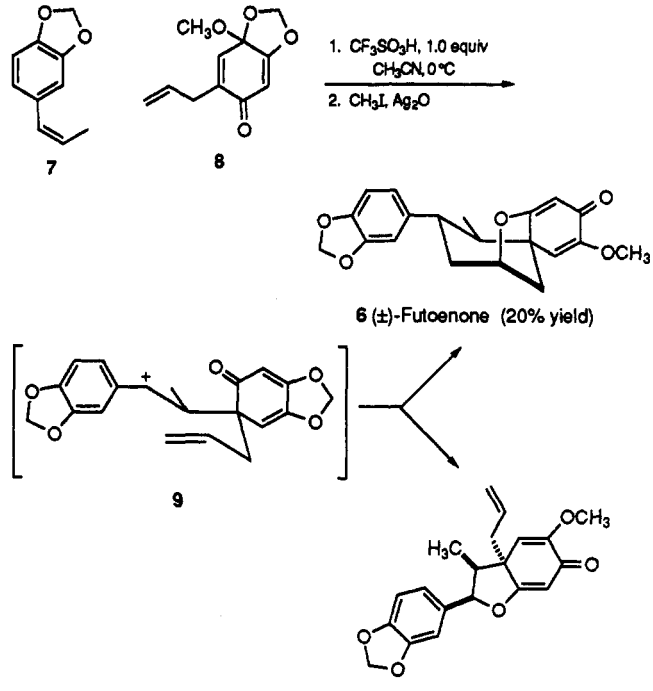
reasonable proposal with literature precedent.[9] However, pathway c appears somewhat less reasonable than pathways a and b requiring the alkene, a relatively poor nucleophile, to participate in an intramolecular cyclization to the exclusion of the enolized β-diketone.

Chemical precedent for Gottlieb's proposal can be found in the Büchi–Mak synthesis of (±)-futoenone via a quinone-ketal cycloaddition reaction (Scheme II).[10,11] Benzylic cation **9**, a proposed intermediate, corresponds to Gottlieb's quinone methide intermediate **3**.[12,13]

Despite the abundance of literature related to the isolation, characterization, synthesis, and biological activity of the neolignans, the chemistry of quinone methide **3** has not been studied. Our previous work with quinone methides[9] led us to believe that such an investigation would provide results that impact both synthetic approaches toward neolignans, as well as provide chemical evidence to support the possible intermediacy of quinone methides in biosynthesis.

Gottlieb and co-workers have shown that natural products possessing the hydrobenzofuran skeleton such as *epi*-burchellin (**5**) undergo acid-mediated rearrangement to the bicyclo[3.2.1]octane skeleton of *epi*-guanin (**4**).[14] On the basis of these results, and suggestions by Büchi,[10]

Scheme II. Büchi–Mak Synthesis of (±)-Futoenone[10]



it seemed reasonable that an *O*-protected *epi*-burchellin derivative might serve as a potential precursor to quinone methide **3**. We thought it should be possible to trigger the opening of the hydrobenzofuran in **10a** (Scheme III) under mild conditions by treatment with fluoride ion to afford phenol anion/siliconate complex **11** which might facilitate opening of the hydrobenzofuran ring to afford quinone methide **3**$^-$ (the anion of **3**). In accordance with Gottlieb's proposal, quinone methide **3**$^-$ might then be expected to undergo three different intramolecular reactions affording hydrobenzofuran **12**, bicyclo[3.2.1]octene **13**, and/or spiro-

(9) (a) For a preliminary report of this work see: Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1990**, *112*, 3698. (b) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (c) Angle, S. R.; Louie, M. L.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193. (d) For background on quinone methide-initiated cyclization reactions and a detailed account of this work described here see: Turnbull, K. D., Ph.D. Dissertation, University of California, Riverside, 1991.

(10) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073.

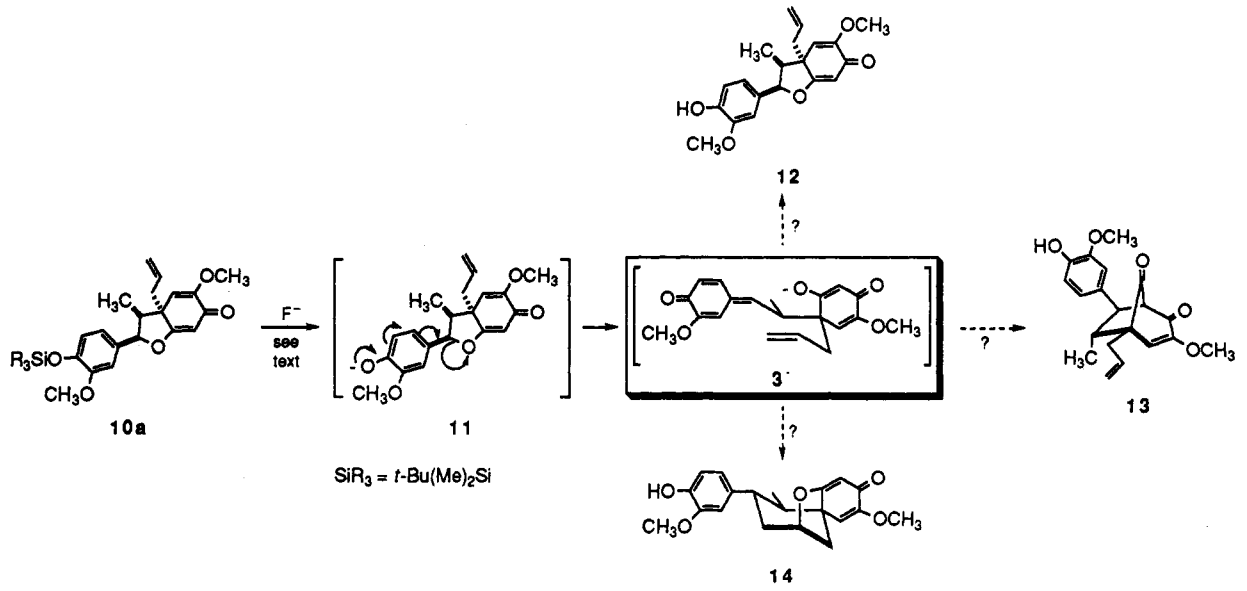
(11) For leading references to other work from the Büchi group using quinone ketal/styrene cycloadditions see: (a) Büchi, G.; Chu, P. S. *J. Am. Chem. Soc.* **1981**, *103*, 2718. (b) Büchi, G.; Chu, P. S. *J. Org. Chem.* **1978**, *43*, 3717.

(12) For another synthesis of futoenone via a similar cycloaddition see: Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 5011.

(13) For related types of cycloadditions with quinone ketals and quinones see: (a) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979. (b) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *52*, 2135. (c) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (d) Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* **1990**, *55*, 5810. (e) Mortlock, S. V.; Seckington, J. K.; Thomas, E. J. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2305. (f) Shizuri, Y.; Sayama, K.; Yamamura, S. *J. Chem. Soc. Chem. Commun.* **1986**, 63.

(14) (a) De Alavarenga, M. A., Brocksom, U.; Gottlieb, O. R.; Yoshida, M. *J. Chem. Soc. Chem. Commun.* **1978**, 831. (b) De Alavarenga, M. A.; Castro, C. O.; Giesbrecht, A. M.; Gottlieb, O. R. *Phytochemistry* **1977**, *16*, 1801. (c) Castro, C. O.; Gottlieb, O. R. *Ing. Cienc. Quim.* **1981**, *5*, 67.

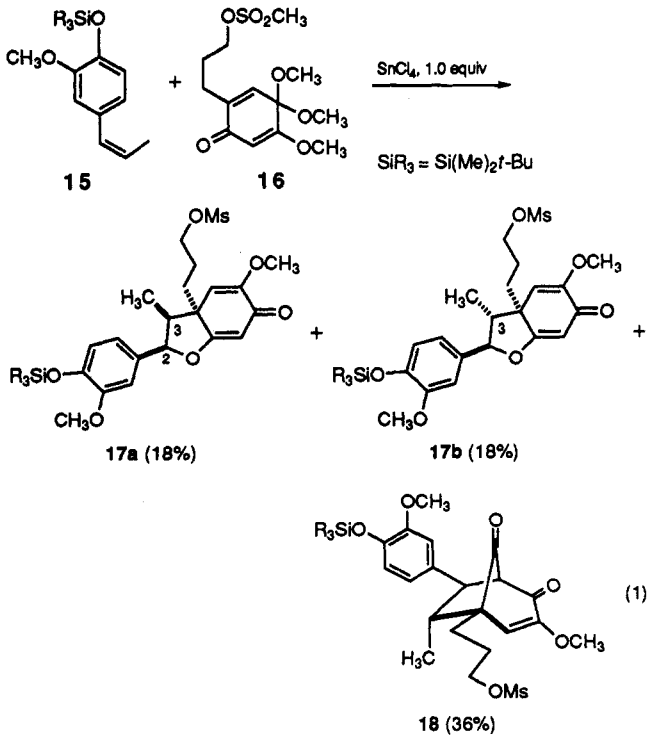
Scheme III. Proposed Route to Quinone Methide 3⁻



[5.5]undecane **14** (Scheme III). At this stage it was unclear if the desired fragmentation would occur under such mild conditions; it seemed plausible that **11** might simply undergo protonation upon workup to afford **12** directly. A survey of the literature revealed there were no hydrobenzofuran neolignan natural products that have a free phenol *para* to the linkage with the hydrobenzofuran. This suggested the possible instability of these compounds and provided hope that the desired fragmentation might occur.

Results and Discussion

Benzofuranone **10a** was prepared using the quinone ketal cycloaddition chemistry pioneered in the Büchi laboratory.[10,11] Treatment of the known quinone ketal **16**[11a] with $SnCl_4$ in the presence of styrene **15** afforded benzofuranones **17** as a 1:1 mixture of diastereomers at C(3) in approximately 40% yield and **18** in 36% yield (eq 1).



Preparative HPLC and recrystallization afforded **17a** and **17b** in identical 18% yields.

2,3-*cis*-Benzofuranone **17a** was readily differentiated from **17b** by the upfield resonance for the shielded C(3)-methyl (*cis* to the C(2)-aryl ring) at δ 0.49 (doublet, J = 7.2 Hz) in the ^{1}H NMR spectrum for **17a**. In contrast, the ^{1}H NMR spectrum of 2,3-*trans*-benzofuranone **17b** showed a resonance for the C(3)-methyl at δ 1.13 (doublet, J = 6.9 Hz). The signal for the C(2)-benzylic hydrogen of **17a** was a distinctive doublet at δ 5.97 (J = 4.7 Hz). This relatively small coupling constant is consistent with the *cis*-stereochemistry of the C(2)-aryl and C(3)-methyl substituents. The coupling constant was confirmed through decoupling studies by irradiation of the doublet at δ 0.49 [C(3)-methyl] which resulted in the collapse of the multiplet for the C(3)-hydrogen geminal to the methyl at δ 2.58–2.66 into a doublet (J = 4.9 Hz). These assignments are in agreement with spectral data for similar compounds reported by Büchi and Chu.[11a]

As part of an attempt to optimize the formation of **17a**, the stability of **17a**, **17b**, and **18** to the reaction conditions was examined. Treatment of **17a** under the condensation reaction conditions ($SnCl_4$, −30 °C, 30 min) afforded a 2:3 ratio (^{1}H NMR) of **17a** to **18**. Treatment of **18** under the same conditions resulted in no detectable change in **18** by ^{1}H NMR. It was not until the reaction was conducted at 23 °C for 30 min that a minor amount (≤5%) of **17a** was detected. There was no observable reaction when diasteromeric benzofuranone **17b** was treated under the reaction conditions; thus, there is no sign of an equilibrium between **17a** and **17b**. These results show that at low temperature, in the presence of $SnCl_4$, an equilibrium does exist between benzofuranone **17a** and bicyclo[3.2.1]-octenone **18**, which favors **18**. This agrees with reports by Büchi and Mak,[10] as well as Gottlieb and co-workers,[14] on the stability of hydrobenzofuran relative to the corresponding bicyclo[3.2.1]octenes. Attempts to maximize the yield of **17a** by taking advantage of this information (e.g. varying Lewis acid, reaction time, temperature, equiv of styrene) were not productive.[9d]

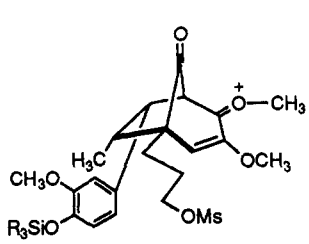
Quinone ketal cycloadditions are thought to be concerted cycloadditions between a pentadienyl cation, formed upon loss of one of the ketal alkoxy groups, and a styrene.[10,15a]

Table I. Attempted Observation of the Quinone Methide Intermediate

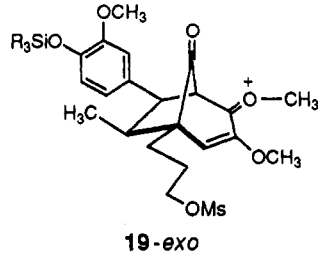
		reaction conditions						
entry	SM[a]	reagent	solvent	equiv	temp, °C	time	monitor	result[b]
1	**10a**	*n*-Bu_4NF	$CDCl_3$	1.0	25	5 min	NMR/UV	**13**
2	**10a**	KF	CD_3CN	1.0	25	5.5 h	NMR	no reaction
3	**10a/b**	KF, 18-c-6	CD_3CN	1.0	25	4.5 h	NMR	**13/22**
4	**17**	*n*-Bu_4NF	CD_2Cl_2	1.0	25	5 min	NMR	**20/21**
5	**17**	*n*-Bu_4NF	CD_2Cl_2	1.0	−40	2 min	NMR	**20/21**
6	**17**	*n*-Bu_4NF	CD_2Cl_2	0.1–1.0 (10 addns)	−40	30 min/0.1 equiv	NMR	**20/21**
7	**17**	*n*-Bu_4NF	THF	0.2	−78	1.5 h	–	**17** (80%) **20/21** (20%)
8	**10a**	*n*-Bu_4NF	THF	1.1	−96	2 min	IR	**13**
9	**17**	*n*-Bu_4NF	THF	0.2	25	5 min	–	**20/21**
10	**17**	KF/18-c-6	CD_3CN	14/2.4	25	2 h	UV	**20/21**
11	**17**	KF/18-c-6	CD_3CN	14/2.4	25	2 h	NMR	**20/21**
12	**17**	40% HF/H_2O	CD_3CN		25	6 h	–	**20/21**
13	**17**	2 N NaOH	THF/EtOH	2.5	25	24 h	–	intractable mixture
14	**17**	AcOH	THF/H_2O		25	6 h	–	no reaction
15	**10a**	none	DMSO-d_6	–	100	2 h	NMR	no reaction

[a] Starting material **17** was a 1:1 mixture of **17a/17b**. [b] In cases where no yield is given complete conversion to the indicated products was observed by ^1H NMR spectroscopic analysis of the crude reaction mixture.

Products **17a** and **18** likely arise from a common adduct, **19-*endo***, whereas **17b** must arise from adduct **19-*exo***. The *trans*-relative stereochemistry of the aryl to the adjacent methyl that is observed in the final products presumably arises via equilibration of the initially formed sterically disfavored *cis*-isomers.[15b,c] The product ratios are indicative of a 3:1 endo/exo selectivity in the cycloaddition.

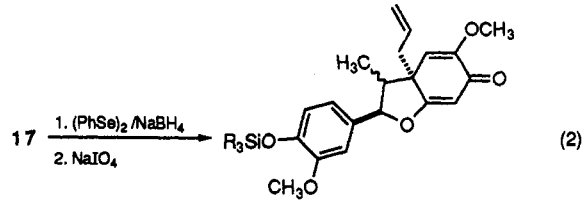


19-*endo*



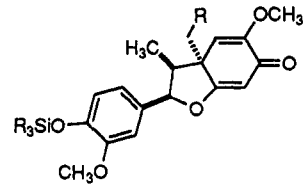
19-*exo*

Diastereomers **17a** and **17b** were separately treated with phenylselenide ion and oxidized to afford **10a** in 70% yield and **10b** in 79% yield, respectively (eq 2). The relative stereochemistry of the three stereogenic centers in **10a** and **10b** was confirmed by difference NOE experiments[16] and comparison of spectral data to similar compounds of known stereochemistry.[9d]



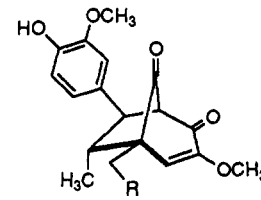
17 → 1. $(PhSe)_2/NaBH_4$, 2. $NaIO_4$ → **10a** β CH_3 (70%), **10b** α CH_3 (79%) (2)

With **10a** in hand, the key fragmentation reaction to the quinone methide was examined. Treatment of **10a** with (*n*-Bu)$_4$NF (1.2 equiv, THF) at room temperature afforded phenol **13**, with the bicyclo[3.2.1]octene skeleton, in 91% isolated yield (eq 3). Monitoring the reaction by ^1H NMR at ambient temperature failed to provide evidence for the intermediacy of quinone methide **3**. The propenyl substituent in **10a** is not involved in the reaction, and benzofuranones **17a/b** should react via the same mechanism as **10a** to afford bicyclo[3.2.1]octenes. The readily available mixture of benzofuranones **17a/b** was treated with (*n*-Bu)$_4$NF to afford phenols **20** and **21** as a 1:1 mixture. It is important to note that products **13** and **20/21** are free phenols; none of the corresponding silyl ethers were observed.



n-Bu_4NF

10a R = CH=CH_2
17a R = CH_2CH_2OMs



(3)

13 R = CH=CH_2
20 R = CH_2CH_2OMs

These initial results are consistent with a mechanism involving quinone methide **3** as an intermediate in the conversion of **10a** to **13**. In an attempt to observe the quinone methide and to learn more about this transformation, a series of experiments (monitored by ^1H NMR, IR, and/or UV) were carried out on **10a** and **17a/b** (Table I).

At low temperatures the reaction is clearly stoichiometric in fluoride ion. One key experiment that illustrates this fact was the conversion of **17** to **20/21** at −40 °C by the sequential addition of 0.1 equiv of (*n*-Bu)$_4$NF (0.1–1.0 equiv; 30 min between each addition; ^1H NMR monitoring; Table I, entry 6). For each 0.1 equiv of fluoride ion added, only an equivalent amount of **20/21** was formed. Addition of 0.2 equiv of fluoride at −78 °C for 1.5 h, followed by workup, produced **20** and **21** in 20% yield and **17** was

(15) (a) Joseph-Nathan, P.; Mendoza, V.; Garcia, E. *Tetrahedron*, **1977**, *33*, 1473; see also refs 10–13. (b) There are a limited number of reports of *cis*-styrenes participating in the cycloaddition, see refs. 10, 12, and 13b. The spectral data for structure **15** in ref 12 does not agree with the assigned cis-exo stereochemistry. (c) See refs 10 and 14 for examples of equilibrium between benzofuranoids and bicyclo[3.2.1]octanoids due to steric constraints.

(16) See supplementary material for details.

recovered in 80% yield (entry 7). This is in contrast to the complete conversion of **17** to **20/21** with catalytic (n-Bu)$_4$NF at room temperature (Table I, entry 9). IR monitoring of the reaction with **10a** [(n-Bu)$_4$NF, 1.1 equiv; 0.02 M] at −96 °C showed the reaction to be complete *within 2 min* (entry 8). Subtraction of the spectra for starting material **10a** and product **13** from the spectra acquired during the reaction (in hopes of obtaining spectroscopic evidence for the presence of the quinone methide) gave flat base lines. This result implies that if the quinone methide is an intermediate it is present in extremely low steady state concentrations.

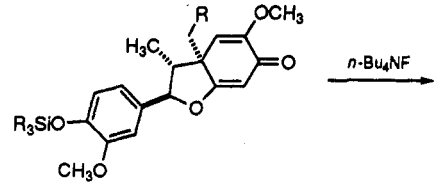
Slower reaction rates were observed when using KF·18-crown-6 in CD_3CN (Table I, entries 2, 3, 10, 11); however, even though the rate of silyl cleavage decreased, experiments at variouis temperatures monitored by ^{1}H NMR and UV failed to provide evidence for the intermediacy of quinone methide **3**. The rate-determining step of the process appears to be silyl cleavage; once the silyl group on **10a** or **17** is lost, the formation of bicyclooctanoid products is extremely rapid. This is consistent with the thermal stability of **10a**. Benzofuranone **10a** was unchanged after heating at 100 °C for 2 h in DMSO-d_6 (^{1}H NMR monitoring, entry 15). This result stands in stark contrast to the fluoride ion-mediated conversion of **10a** to **13** at −96 °C in 2 min.

Treatment of **10a** and **17** with electrophilic reagents (e.g. $(CH_3)_3OBF_4$, p-TsOH, Ac_2O, $(CH_3)_3SiBr$, TBDMS-OTf) provided no evidence for the intermediacy of quinone methide **3**.[9d] For example, treatment of **10a** with (n-Bu)$_4$-NF in acetic anhydride (solvent) afforded the acetates corresponding to **10a** and **13** (^{1}H NMR monitoring).[9d]

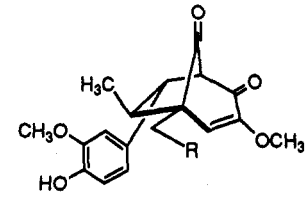
With the failure to observe quinone methide **3** as an intermediate, we questioned the mechanism for the conversion of **10a** to **13** and **17** to **20/21**. Our results show the bond reorganization (hydrobenzofuran to bicyclo[3.2.1]-octene) is driven by cleavage of the silyl protecting group on the phenol, consistent with quinone methide **3** being an intermediate. Possible mechanisms that do not invoke **3** as an intermediate were considered. Simplistically, the **10a** to **13** conversion entails removal of the silyl group on the phenol (which initiates the subsequent bond reorganization), breaking of the benzylic C–O bond, and formation of a C–C bond. The timing of these bonding changes becomes a crucial question in determining the mechanism for the transformation. If bond formation/breakage are synchronous, the **10a** to **13** transformation is a [1,3]-sigmatropic shift. If C–O bond cleavage occurs prior to C–C bond formation, quinone methide **3** is an intermediate.

To rationalize our results, which require cleavage of the silyl group to effect the transformation, one might invoke an anion (p-phenoxide)-accelerated [1,3]-shift. The **10a** to **13** conversion is a net inversion of configuration from C(2) in **10a** to C(7) in **13**; the methyl and aryl groups are *cis* in **10a** and *trans* in **13**. A thermally allowed [1,3]-shift might be expected to occur with an inversion in one of the partners,[17] as observed. While this seemed an unlikely possibility due to the poor orbital alignment (analysis of Dreiding models), we elected to examine the viability of this process. The similar orientation of the aryl group in **10b** suggests that if it undergoes the same reaction that **10a** does, the transformation should also occur with net inversion of configuration at C(7).

To test this notion, **10b** was treaetd with (n-Bu)$_4$NF to afford **22** in 91% yield (eq 4). The **10b** to **22** transformation thus occurs with net retention of configuration. At this



10b R = CH=CH$_2$
17b R = CH$_2$CH$_2$OMs



(4)

22 R = CH=CH$_2$
21 R = CH$_2$CH$_2$OMs

stage the **17** to **20/21** transformation, which had been carried out on 1:1 mixtures of **17a/b** (Table I), was studied with each pure diastereomer. Treatment of mesylate **17a** with (n-Bu)$_4$NF afforded **20** with net inversion of configuration (eq 3), and **17b** afforded **21** with net retention of configuration. These results suggest a nonconcerted reaction pathway.

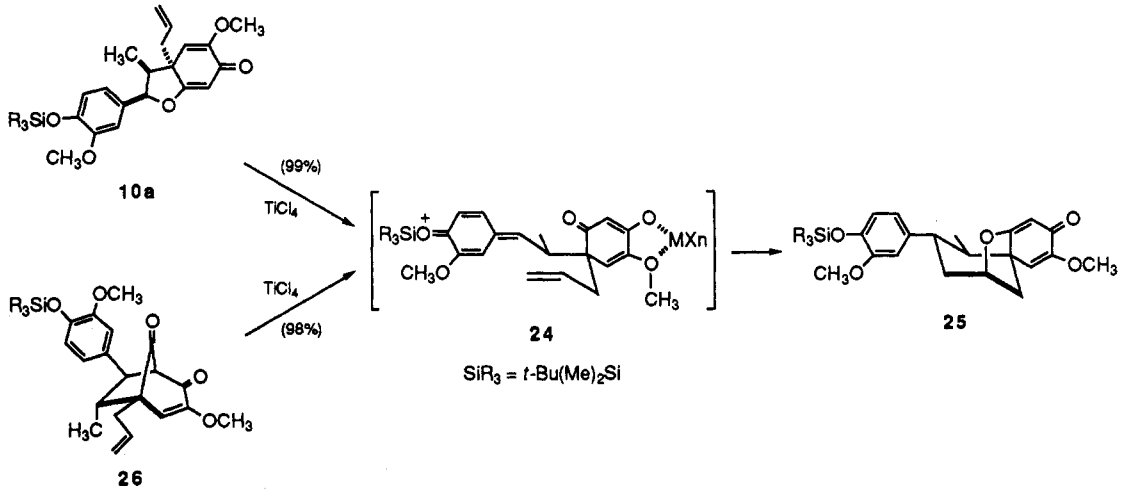
The previously mentioned poor orbital overlap makes a concerted process unlikely. If the reaction is not synchronous, bond breakage precedes bond formation and quinone methide **3** must be an intermediate. Indeed, we believe that the cleavage of the silyl group triggers a fragmentation which results in the cleavage of the C(2)–O bond of **10a** to afford quinone methide **3**$^-$. The quinone methide then suffers intramolecular carbon alkylation by the β-diketone enolate that was formed in the fragmentation step. Not surprisingly, formation of a quinone methide with a β-diketone enolate five centers away results in low steady state concentrations of the quinone methide. This scenario is consistent with all of our results and previous experience with the intramolecular reaction of quinone methides and β-keto esters.[9b,d] Spectroscopic observation of 2,6-disubstituted quinone methides possessing a β-keto ester moiety proved to be challenging due to the rapid intramolecular reaction of the quinone methide with the β-keto ester.[9b,d] Quinone methide **3**$^-$, with a single substituent adjacent to the carbonyl, is expected to be more reactive than the 2,6-disubstituted quinone methides in the previous study and thus more difficult to observe spectroscopically.[9b,d]

It should be mentioned that bicyclo[3.2.1]octanoid **22** has the same structure as a natural product isolated by Gottlieb and co-workers.[18] The spectral data for **22** are identical to those reported by Gottlieb for the (−)-enantiomer of **22**. Gottlieb assigned the relative stereochemistry on the basis of ^{1}H NMR data. We have carried out difference NOE experiments[16] and compared our

(17) [1,3]-Sigmatropic shifts have been reported with both retention and inversion of configuration. In this case if **10a** and **10b** react via the same mechanism, the net stereochemical result (inversion or retention) should be the same. (a) Forman, M. A.; Leber, P. A. *Tetrahedron Lett.* **1986**, *27*, 4107. (b) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406.

(18) De Alavarenga, M. A.; Brocksom, U.; Castro, O. C.; Gottlieb, O. R.; Magalhaès, M. T. *Phytochemistry* **1977**, *16*, 1797.

Scheme IV



spectral data to that reported by Engler and co-workers for similar bicyclo[3.2.1]octanoids with *endo*- and *exo*-aryl groups.[19] All of the data is consistent with the structure assigned by Gottlieb.

It seemed possible that the quinone methide intermediate might be accessed from one of the bicyclo[3.2.1]-octenes (e.g. **13** or **22**). All attempts to effect this conversion and observe or trap the quinone methide intermediate under a variety of conditions were unsuccessful.[9d]

With the development of a selective route to the bicyclo-[3.2.1]octene skeleton, we sought conditions to divert the cyclization toward formation of products with the spiro-[5.5]undecane skeleton. We reasoned that alkene participation in the cyclization would require the nucleophilicity of the β-diketone to be decreased and the electrophilicity of the quinone methide to be increased. Accordingly, **10a** was treated with $TiCl_4$ (−78 °C to room temperature) to afford a 99% isolated yield of *tert*-butyldimethylsilyl ether **25** possessing the spiro[5.5]-undecane skeleton (Scheme IV). Since the silyl group was retained, the intermediate was not the quinone methide; rather, it must have been benzylic cation **24**. Thus, the complete diversion of the reaction pathway toward spiro-[5.5]undecane **25** can be attributed to two reinforcing factors that cannot be examined separately in our experiments: (1) the benzylic cation provides a highly electrophilic intermediate for reaction with the terminal alkene, and (2) complexation of the β-diketone with Ti-(IV) may moderate its nucleophilicity.

To test for the possible formation of the bicyclo[3.2.1]-octene in the Lewis acid-mediated reaction, *tert*-butyldimethylsilyl ether **26** was treated with $TiCl_4$ (1.8 equiv, −78 °C to 25 °C, 10 min, CD_2Cl_2) to afford a 98% yield of spiro[5.5]undecane **25**. Thus, bicyclo[3.2.1]octene **26** is a possible initial kinetic product in the **10a** to **25** transformation, which reversibly opens to benzylic cation **24** and irreversibly affords **25**. The isomerization was sensitive to choice of Lewis acid; treatment of **26** with $SnCl_4$ (1.8 equiv, 24 h, 25 °C, CD_2Cl_2) afforded a 45% yield of **25**. To examine the effect of an unprotected phenol on the isomerization process, phenol **13** (Scheme III) was treated with $SnCl_4$ (1.0 equiv, −78 °C to 25 °C, 30 min, CD_2Cl_2) to afford a 60:40 mixture of **13** to **14** by analysis of the ^1H NMR spectrum of the crude reaction mixture. Treatment of **13** with $TiCl_4$ (1.0 equiv) under the same conditions afforded unreacted starting materials.[9d]

We realized the similarity of this cationic process to the key step of the Büchi–Mak synthesis of (±)-futoenone. A survey of quinone ketal and similar quinone cycloaddition chemistry shows that this type of cycloaddition affords spiro[5.5]undecanoids in poor yields at best.[10–13] Examination of our results shows that similar intermediates are involved, and we might have the ability to directly prepare spiro[5.5]undecanoids in high yield. Due to the recent interest in futoene and related spiro[5.5]undecanoids as PAF receptor antagonists,[6,7] the synthesis of these compounds via a Büchi quinone ketal styrene cycloaddition was examined.[10–13]

On the basis of literature reports[11a] and our results in these studies, we expected the yields of spiro[5.5]-undecanoids to be highest when Lewis acids are used to promote the cycloaddition of dimethoxyquinone ketals. This indeed proved to be the case. The synthesis of racemic futoenone was accomplished by the addition of stannic chloride to a solution of isosafrole **7** (2.0 equiv, 85:15 mixture *Z*/*E*, capillary GC) and quinone ketal **27** in dichloromethane at −78 °C (Scheme V). Workup and recrystallization afforded analytically pure (±)-futoenone **6** in 64% yield.[7,10,12] It is likely that the yield could be further optimized by using isomerically pure (*Z*)-isosafrole.

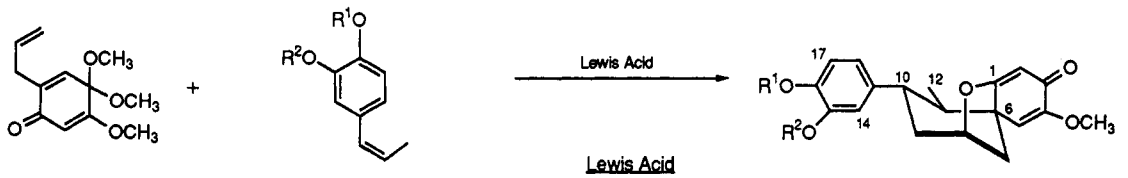
Analogs of futoenone with different substituents on the aryl ring were also made *via* this methodology. The phenol analog **14** was obtained from quinone ketal **27** and hydroxystyrene **28** (11:1 mixture *Z*/*E*, capillary GC) with $SnCl_4$ (Scheme V). HPLC purification afforded **14** in 67% isolated yield. The *tert*-butyldimethylsiloxy analog **25** was obtained in 85% yield upon treatment of quinone ketal **27** and silyl-protected styrene **15** (1.5 equiv) with $TiCl_4$. The use of titanium(IV) isopropoxide under these conditions led to recovered starting materials. As proof of the similarity in structure, **25** was converted to **14** upon treatment with $(n\text{-Bu})_4NF$. Compounds prepared by both routes showed identical spectral and chromatographic properties.

Conclusion

The work described here has provided chemical support for Gottlieb's proposal that several different neolignans arise via a common biosynthetic precursor. It is indeed

(19) Engler, T. A.; Wei, D.; Letavic, M. A. *Tetrahedron Lett.* **1993**, *34*, 1429.

Scheme V[20]



27

7 $R^1 = R^2 = CH_2$
28 R^1 = H, $R^2 = CH_3$
15 R^1 = t-Bu(Me)$_2$Si, $R^2 = CH_3$

Lewis Acid	
$SnCl_4$	6 $R^1 = R^2 = CH_2$, (64%)
$SnCl_4$	14 R^1 = H, $R^2 = CH_3$, (67%)
$TiCl_4$	25 R^1 = t-Bu(Me)$_2$Si, $R^2 = CH_3$, (85%)

quite reasonable to imagine a quinone methide reacting with an internal alkene if it is sufficiently activated. The results of research on quinone methide **3** led to insight into the Büchi quinone ketal cycloaddition and the synthesis of bicyclooctanoid natural product **22** and allowed the efficient preparation of spiro[5.5]undecanes in high yield for the first time.

Experimental Section[21a]

General Information. The low-temperature IR work was accomplished using a variable-temperature vacuum-jacketed cell with a vacuum-tight liquid cell (CaF_2 windows, 0.05-mm path length) and an automatic temperature controller. HPLC was carried out with an RI detector using a 25-cm column (4.6 mm or 1.0 cm i.d.) packed with 8-μm silica gel. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[21b] In cases where products were isolated by "aqueous workup (solvent, drying agent)" the procedure was to dilute the reaction mixture with water, extract the aqueous layer several times with the indicated organic solvent, wash the combined organic layers with brine, dry over the indicated drying agent, and concentrate the reaction mixture. "Concentration" in the experimental procedures refers to isolation of product(s) from a solvent/product mixture by removal of the solvent under reduced pressure (water aspirator) with a rotavapor. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen or argon in flame dried glassware.

(±)-Futoenone (6). Neat $SnCl_4$ (100 μL, 0.855 mmol) was added via syringe to a stirred solution of quinone ketal **27** (194 mg, 0.866 mmol), isosafrole **7**[22] (258 mg, 176 mmol, 85:15 Z/E, GC), and CH_2Cl_2 (10 mL) at −78 °C. The resulting solution was stirred for 10 min and the cooling bath was removed. After an additional 20 min, the reaction mixture was added via cannula to a solution of saturated aqueous $NaHCO_3$ (25 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) followed by recrystallization (ethyl acetate, three crops) afforded 189 mg (64%) of analytically pure (±)-futoenone **6** as white crystals: mp 225.0–226.5 °C (lit.[7c] 197 °C; lit.[10] 242–246 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H, H-17), 6.67 (s, 1H, H-14), 6.63 (d, J = 7.9 Hz, 1H, H-18), 5.93 (s, 2H, CH_2-19), 5.78 (s, 2H, H-2), 5.46 (s, 1H, H-5), 5.03 (apparent t, J = 5.5 Hz, 1H, H-8), 3.66 (s, 3H, =C(OCH$_3$)), 2.55 (apparent dt, J = 6.2, 11.4 Hz, 1H, H-10), 2.39–2.24 (m, 2H, H-7β and H-9β), 2.18 (apparent d, J = 11.3 Hz, 1H, H-7α), 2.02 (dq, J = 11.3, 6.4 Hz, 1H, H-11), 1.71 (apparent t, J = 12.9 Hz, 1H, H-9α), 0.58 (d, J = 6.5 Hz, 3H, CH_3-12); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 182.9, 180.3, 153.6, 148.2, 146.6, 137.9, 121.5, 109.6, 108.5, 108.0, 101.5, 101.3, 82.4, 55.4, 50.6, 46.5, 45.7, 43.9, 38.3, 14.5; IR (CH_2Cl_2) cm^{-1} 1654, 1613, 1506, 1489, 1251; MS (El, 70 eV) m/z 340 (M$^+$, 100), 163 (76), 135 (67); HRMS for $C_{20}H_{20}O_5$ calcd 340.1311; found 340.1308. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.56; H, 5.93. Found: C, 70.33; H, 5.91.

(±)-(2β,3β,3aα)-2-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-3,3a-dihydro-5-methoxy-3-methyl-3a-(2-propenyl)-6(2*H*)-benzofuranone (10a). $NaBH_4$ (34.3 mg, 0.907 mmol) was slowly added to a stirred, room temperature solution of $(PhSe)_2$ (141 mg, 0.453 mmol) and ethanol (4.5 mL) until the color of the reaction mixture changed from yellow to colorless. The resulting solution was then cooled to 0 °C and stirred for 20 min, and a solution of mesylate **17a** (250 mg, 0.453 mmol) and THF (2.5 mL) was added *via* cannula. The flask and cannula were rinsed with an additional 2 mL of THF. The cooling bath was removed and the reaction mixture was stirred for 6 h. Concentration followed by aqueous workup (ether, Na_2SO_4) afforded the phenyl selenide which was used without further purification. A solution of $NaIO_4$ (962 mg, 4.03 mmol) and 1:1 THF/H_2O (14.0 mL) was added via cannula to a stirred solution of the above phenyl selenide and THF (4.5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 80 min, at room temperature for 60 min, at 70 °C for 4 h, and then allowed to cool to room temperature. Aqueous workup [ether (combined organic layers were washed with $NaHCO_3$), $MgSO_4$] afforded crude **10a** as a yellow solid. Recrystallization (hexane/ethyl acetate, two crops) afforded 165 mg (80%) of benzofuranone **10a** as a white solid: mp 143.0–144.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.0 Hz, 1H, ArH), 6.70–6.66 (m, 2H, 2 × ArH), 5.94 (d, J = 4.8 Hz, 1H, ArCH), 5.87 (s, 1H, C*H*=C(OCH$_3$)C=O), 5.83–5.69 (m, 1H, CH_2CH=CH_2), 5.50 (s, 1H, =CHC=O), 5.21 (d, J = 10.2 Hz, 1H, CH_2CH=C*H*H), 5.14 (d, J = 17.0 Hz, 1H, CH_2-CH=CH*H*), 3.81 (s, 3H, ArOCH$_3$), 3.68 (s, 3H, OCH$_3$), 2.76–2.64 (m, 2H, C*H*HCH=CH_2 and C*H*CH$_3$), 2.54 (dd, J = 13.5, 6.8 Hz, 1H, CH*H*CH=CH_2), 0.99 (s, 9H, SiC(CH$_3$)$_3$), 0.49 (d, J = 7.2 Hz, 3H, CH_3), 0.15 (s, 6H, Si(CH$_3$)$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 182.5, 181.5, 152.7, 150.9, 144.6, 131.6, 129.8, 120.7, 120.0, 117.9, 109.3, 109.1, 101.7, 87.3, 55.4, 55.1, 53.9, 44.5, 43.7, 25.5, 18.2, 11.9, −4.8; IR (CH_2Cl_2) 1657, 1615, 1471 cm^{-1}; UV (CH_3CN) λ_{max} (log ϵ), 238 (sh, 4.12), 258 (4.24), 284 (sh, 3.91); MS (El, 70 eV) m/z 456 (M$^+$, 29), 400 (34), 399 (100); HRMS for $C_{26}H_{36}O_5Si$ calcd 456.2332, found 456.2349.

(±)-2β,3β,3aα)-2-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-3,3a-dihydro-5-methoxy-3-methyl-3a-(2-propenyl)-6(2*H*)-benzofuranone (10b). The same procedure employed for the synthesis of **10a** from **17a** was carried out with mesylate **17b** (120 mg, 0.217 mmol). Flash chromatography (1:1 hexane/ethyl acetate) followed by HPLC (1 cm i.d. column, 1:1 hexane/ethyl acetate) afforded 69.5 mg (70%) of analytically pure **10b** as a white viscous oil that crystallized upon standing: mp 53.5-55.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8.3 Hz, 1H, ArH), 6.76–6.73 (m, 2H, 2 × ArH), 5.80 (s, 1H, C*H*=C-(OCH$_3$)C=O), 5.54 (m, 1H, CH_2CH=CH_2), 5.43 (s, 1H, =CHC=O), 5.19 (d, J = 9.9 Hz, 1H, ArCH), 5.08 (d, J = 9.7 Hz, 1H, CH_2CH]=C*H*H), 5.00 (d, J = 16.9 Hz, 1H, CH_2CH=CH*H*), 3.80 (s, 3H, ArOCH$_3$), 3.68 (s, 3H, OCH$_3$), 2.56 (dd, J = 13.2, 7.0 Hz, 1H, C*H*HCH=CH_2), 2.37–2.25 (m, 2H, CH*H*CH=CH_2 and C*H*CH$_3$), 1.14 (d, J = 6.9 Hz, 3H, CH_3), 0.98 (s, 9H, SiC(CH$_3$)$_3$), 0.15 (s, 6H, Si(CH$_3$)$_2$); ^{13}C (75 MHz, $CDCl_3$) δ 182.8, 181.6, 153.4, 151.2, 145.9, 130.9, 130.8, 120.7, 119.9, 119.4, 110.0, 107.9, 101.9, 91.2, 55.5, 55.2, 51.0, 49.4, 36.6, 25.6, 18.3, 8.4, −4.7; IR (CH_2Cl_2) 1658, 1616, 1514, 1471 cm^{-1}; MS (EI, 70 eV) m/z 456 (M$^+$, 53), 400 (32), 399 (100); HRMS for $C_{26}H_{36}O_5Si$ calcd 456.2332, found 456.2345. Anal. Calcd for $C_{26}H_{36}O_5Si$: C, 68.39; H, 7.95. Found: C, 68.58; H, 7.96.

(20) The numbering system used for **6**, **14**, and **25** in Scheme V and ^{1}H NMR assignments follows the futoenone numbering system, see ref 7.

(21) (a) General experimental protocols have recently been described: Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937. (b) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. J. Chem. Soc. Chem. Commun.* **1980**, 87.

(22) The Z-styrenes were prepared using the procedure in ref 23. (Z)-Isosafrole (**7**) was prepared from piperonal in 96% yield as an 85:15 Z/E mixture, 99% pure (capillary GC). For a detailed experimental see ref 9d.

(±)-(6-*endo*,7-*exo*)-7-(4-Hydroxy-3-methoxyphenyl)-3-methoxy-6-methyl-5-(2-propenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (13). A solution of $(n\text{-Bu})_4NF$ (0.087 mL, 1 M in THF, 0.087 mmol) was added via syringe to a stirred solution of **10a** (33.1 mg, 0.0726 mmol) in THF (1 mL) at room temperature. Upon addition, the reaction mixture immediately changed to an orange color. After the mixture was stirred for 30 min, aqueous workup (CH_2Cl_2, $MgSO_4$) afforded crude **13**. Flash chromatography (2:1 hexane/ethyl acetate) afforded 22.1 mg (89%) of analytically pure **13** as a viscous oil that crystallized upon standing. Recrystallization (hexane/ethyl acetate) afforded an analytical sample: mp 52.0-53.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 8.1 Hz, 1H, ArH), 6.59 (dd, J = 8.1, 1.7 Hz, 1H, ArH), 6.53 (d, J = 1.4 Hz, 1H, ArH), 6.04–5.90 (m, 1H, C*H*=CH_2), 5.80 (s, 1H, C*H*C(OCH_3)C=O), 5.59 (br s, 1H, OH), 5.22 (d, J = 16.6 Hz, 1H, =C*H*H), 5.17 (d, J = 9.4 Hz, 1H, =CH*H*), 3.87 (s, 3H, $ArOCH_3$), 3.74 (s, 3H, OCH_3), 3.57 (s, 1H, bridgehead-H), 2.59–2.53 (m, 2H, CH_2CH=CH_2), 2.54 (d, J = 8.0 Hz, 1H, ArCH), 2.16 (dq, J = 7.0, 6.8 Hz, 1H, C*H*CH_3), 1.07 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 202.8, 190.3, 152.4, 146.8, 144.8, 133.3, 133.1, 120.0, 119.1, 117.9, 114.7, 109.5, 70.3, 57.4, 55.7, 50.0, 46.9, 35.4, 14.1; IR (CH_2Cl_2) 3536, 1764, 1696, 1606, 1518 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 232 (3.99), 270 (3.92), 286 (sh, 3.79); MS (EI, 70 eV) m/z 342 (M^+, 100), 163 (40); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1475.

(±)-(2α,4α,5β,5aα)-4-(4-Hydroxy-3-methoxyphenyl)-2,5a-methano-7-methoxy-5-methyl-8*H*-2,3,4,5-tetrahydro-1-benzoxepin-8-one (14). From Quinone Ketal 27 and Hydroxy Styrene 28. Neat $SnCl_4$ (92 μL, 0.79 mmol) was added to a stirred solution of crude quinone ketal **27** (176 mg, 0.784 mmol), hydroxystyrene **28**[20] (257 mg, 1.57 mmol, 11:1 Z/E-mixture, capillary GC), and CH_2Cl_2 (10 mL) at −78 °C. After 15 min, the cooling bath was removed and stirring continued an additional 15 min. The reaction mixture was then poured into a solution of saturated aqueous $NaHCO_3$ (25 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, Na_2SO_4) afforded crude **14** as a viscous yellow oil. HPLC (1 cm i.d. column, 1:9 hexane/ethyl acetate, 8 mL/min, t_R = 27.3 min) afforded 179.6 mg (67%) of analytically pure **14** as a clear viscous oil.

From 13 (by NMR). Neat $SnCl_4$ (0.6 μL, 0.005 mmol) was added to a stirred solution of **13** (1.6 mg, 0.0047 mmol) in CH_2Cl_2 (60 μL) at −78 °C. After being stirred for 15 min, the cold bath was removed and stirring continued for an additional 15 min. The reaction mixture was then poured into a solution of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, Na_2SO_4) afforded crude **14** as a viscous yellow oil. ^{1}H NMR analysis of the crude reaction mixture showed the formation of a *ca.* 60:40 mixture of starting bicyclooctenoid **13** and spiro-[5.5]undecanoid **14**, respectively (integration of the C_{12}-methyl resonances; products were not purified in this experiment).

From 25. $(n\text{-Bu})_4NF$ (50 μL, 1 M in THF) was added to a stirred solution of **25** (21.6 mg, 0.0473 mmol) and $CDCl_3$ (0.6 mL) at room temperature. The reaction mixture changed from a clear to a yellow solution upon addition. After the mixture was stirred 10 min, aqueous workup (CH_2Cl_2, Na_2SO_4) afforded crude **14**. HPLC purification as above afforded 15.1 mg (93%) of analytically pure **14** as a white solid: mp 198.0–199.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.1 Hz, 1H, H-17), 6.69 (dd, J = 8.1, 1.5 Hz, 1H, H-18), 6.65 (s, 1H, H-14), 5.79 (s, 1H, H-2), 5.64 (s, 1H, ArOH), 5.48 (s, 1H, H-5), 5.04 (apparent t, J = 5.5 Hz, 1H, H-8), 3.87 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, =C(OCH_3)), 2.53 (apparent dt, J = 6.1, 11.5 Hz, 1H, H-10), 2.40–2.26 (m, 2H, H-7β and H-9β), 2.20 (apparent d, J = 11.3 Hz, 1H, H-7α), 2.05 (dq, J = 11.4, 6.4 Hz, 1H, H-11), 1.74 (apparent t, J = 12.9 Hz, 1H, H-9α), 0.58 (d, J = 6.5 Hz, 3H, CH_3-12); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 180.2, 153.2, 146.4, 144.3, 135.3, 119.8, 114.6, 110.6, 109.1, 101.3, 81.9, 55.9, 55.2, 50.3, 46.1, 45.5, 43.6, 37.9, 14.4; IR (CH_2Cl_2) 3538, 1655, 1614, 1516 cm^{-1}; MS (EI, 70 eV) m/z 342 (M^+, 100), 178 (72), 164 (68); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1456.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-methoxy-4-(1-propenyl)benzene (15). According to the general procedure of Sreekumar, Darst, and Still,[23] hexamethyldisilazane (13.3 mL, 63.0 mmol) was added *via* syringe to a stirred suspension of KH (7.22 g, 63.0 mmol) in THF (65 mL) at room temperature and allowed to stir for 1 h. The resulting solution was then added via cannula to a stirred solution of (ethyl)triphenylphosphonium bromide (25.7 g, 69.3 mmol) and hexamethylphosphoric triamide (24.8 mL, 143 mmol) in THF (230 mL) at room temperature. The resulting orange solution was stirred for 10 min and then cooled to −78 °C. After 20 min, a solution of 4-[(*tert*-butyldimethylsilyl)-oxy]-3-methoxybenzaldehyde (4.19 g, 15.7 mmol)[24] in THF (15 mL) was added *via* cannula, and the resulting solution was allowed to warm to room temperature over 1 h and stirred for an additional 1 h. H_2O (125 mL) was slowly added, resulting in the formation of a white precipitate. Aqueous workup (ether, $MgSO_4$) followed by flash chromatography (10:1 hexane/ethyl acetate) afforded 4.02 g (92% yield, 99% pure by GC, 92.4:7.6 Z/E mixture) of styrene **15** as a clear oil: ((*Z*)-isomer) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–6.82 (m, 3H, 3 × ArH), 6.41 (d, J = 11.5 Hz, 1H, =C*H*Ar), 5.81–5.70 (m, 1H, =C*H*CH_3), 3.85 (s, 3H, OCH_3), 1.97 (d, J = 7.2 Hz, 3H, CH_3), 1.07 (s, 9H, Si$C(CH_3)_3$), 0.23 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 143.7, 131.5, 129.7, 125.1, 120.5, 112.9, 55.4, 25.7, 18.4, 14.6, −4.7; IR (neat) 1513, 1472, 923 cm^{-1}; MS (EI, 20 eV) m/z 278 (M^+, 7), 221 (61), 206 (100); HRMS calcd for $C_{16}H_{26}O_2Si$ 278.1702, found 278.1690. Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.05; H, 9.70.

2-[3-[(Methylsulfonyl)oxy]propyl]-4,4,5-trimethoxycyclohexa-2,5-dienone (16).[11a] According to the procedure of Büchi and Chu,[11a] DDQ (0.949 g, 4.18 mmol) was added to a stirred solution of 4,5-dimethoxy-2-[3-[(methylsulfonyl)oxy]-propyl]phenol[11a] (1.01 g, 3.48 mmol) in CH_3OH (38 mL, freshly distilled from Mg) at room temperature. After 45 min, the solution was poured into saturated aqueous $NaHCO_3$ (20 mL) and stirred for 10 min. Aqueous workup [CH_2Cl_2 (combined organic layers washed with $NaHCO_3$), Na_2SO_4] afforded **16**[11a] (1.07 g) as a light yellow oil. The crude quinone ketal **16** was used immediately without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H, ArH), 5.63 (s, 1H, ArH), 4.26 (t, J = 6.2 Hz, 2H, CH_2OMs), 3.82 (s, 3H, =C(OCH_3)), 3.33 (s, 6H, 2 × OCH_3), 3.03 (s, 3H, SCH_3), 2.47–2.52 (m, 2H, =CCH_2), 2.01–1.92 (m, 2H, CH_2).

(±)-(2β,3β,3aα)- and (2β,3α,3aα)-2[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-3,3a-dihydro-5-methoxy-3-methyl-3a-[3-[(methylsulfonyl)oxy]propyl]-6(2*H*)-benzofuranone [17a (2β,3β,3aα) and 17b (2β,3α,3aα)]. According to the general procedure of Büchi and Chu,[11a] $SnCl_4$ (390 μL, 3.35 mmol) was added dropwise to a stirred solution of crude quinone ketal **16** (1.07 g, 3.35 mmol), styrene **15** (1.89 g, 6.75 mmol), and CH_2Cl_2 (35 mL) at −30 °C. After 30 min the reaction mixture was added (via cannula) to 5% HCl (50 mL) and rapidly stirred for 5 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded 2.82 g of crude products. Flash chromatography (sequential elution with hexane/ethyl acetate mixtures 1:1, 1:2, and 1:5) afforded **18** (1.30 g; R_f = 0.32, 1:2 hexane/ethyl acetate) and **17a**/**17b** (1.07 g; R_f = 0.16, 1:2 hexane/ethyl acetate) as a 1:1 mixture (^{1}H NMR). The fraction containing the benzofuranones was further purified by HPLC (1 cm i.d. column; 1:3 hexane/ethyl acetate; 5.0 mL/min; 900 μL per injection; 215 mg/mL) to afford **17b** (t_R = 78.7 min) and **17a** (t_R = 89.2 min) in equal amounts. Recrystallization of **17a** (hexane/ethyl acetate) afforded 336 mg (two crops, 18% yield) of analytically pure **17a** as white crystals: mp 150.0–150.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 7.8 Hz, 1H, ArH), 6.68–6.65 (m, 2H, 2 × ArH), 5.97 (d, J = 4.7 Hz, 1H, CHAr), 5.87 (s, 1H, =CH), 5.42 (s, 1H, =CHC=O), 4.28–4.17 (m, 2H, CH_2-OMs), 3.79 (s, 3H, $ArOCH_3$), 3.67 (s, 3H, =C(OCH_3)), 2.99 (s, 3H, SCH_3), 2.66–2.58 (m, 1H, C*H*CH_3), 2.21–2.10 (m, 1H, CC*H*HCH_2), 2.05–1.94 (m, 1H, CCH*H*CH_2), 1.81–1.64 (m, 2H, CH_2), 0.98 (s, 9H, Si$C(CH_3)_3$), 0.49 (d, J = 7.2 Hz, 3H, CHCH_3), 0.14 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 180.9, 153.3, 151.0, 144.8, 129.8, 120.8, 117.9, 109.3, 108.5, 102.6, 87.7, 69.4, 55.5, 55.3, 53.7, 46.3, 37.3, 34.2, 25.6, 24.1, 18.3, 12.0, −4.8; IR (CH_2Cl_2) 1656, 1616, 1516, 1465 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ε) 244 (sh, 4.09), 256 (4.19), 2.82 (sh, 3.93); MS (EI, 70 eV) m/z 552 (M^+, 1), 399 (28), 179 (100); HRMS calcd for $C_{27}H_{40}O_8SiS$ 552.2213; found 552.2210. Anal. Calcd for $C_{27}H_{40}O_8SiS$: C, 58.67;

(23) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(24) Prepared by silylation of vanillin in 98% yield (>99% pure by capillary GC).

H, 7.29. Found: C, 58.80; H, 7.33. Diastereomer **17b** was collected off the HPLC and recrystallized from hexane/ethyl acetate to afford 335 mg (three crops, 18% yield) of analytically pure **17b** as white crystals: mp 142.0–143.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H, ArH), 6.74 (m, 2H, 2 × ArH), 5.83 (s, 1H, =CH), 5.42 (s, 1H, =CHC=O), 5.19 (d, J = 10.0 Hz, 1H, CHAr), 4.22–4.18 (m, 2H, CH_2OMs), 3.80 (s, 3H, $ArOCH_3$), 3.70 (s, 3H, =C(OCH_3)), 3.00 (s, 3H, SCH_3), 2.36–2.24 (m, 1H, C*H*CH_3), 2.04–1.91 (m, 1H, CC*H*HCH_2), 1.78–1.68 (m, 1H, CC*H*HCH_2), 1.64–1.55 (m, 2H, CH_2), 1.13 (d, J = 6.9 Hz, 3H, CH_3), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 181.6, 153.5, 151.2, 145.9, 130.6, 120.8, 119.4, 110.0, 107.7, 102.4, 91.3, 69.6, 55.5, 55.3, 50.4, 49.7, 37.3, 27.5, 25.6, 23.2, 18.4, 8.2, –4.7; IR (CH_2Cl_2) 1655, 1615, 1515, 1465 cm^{-1}; MS (EI, 70 eV) m/z 552 (M^+, 1), 495 (86), 399 (100), 221 (41); HRMS calcd for $C_{27}H_{40}O_8SiS$ 552.2213; found 552.2230. Anal. Calcd for $C_{27}H_{40}O_8SiS$: C, 58.67; H, 7.29. Found: C, 58.39; H, 7.46.

(±)-(6-*endo*,7-*exo*)-7-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-methoxy-6-methyl-5-[3-[(methylsulfonyl)oxy]propyl]bicyclo[3.2.1]oct-3-ene-2,8-dione (18). According to the experimental for **17a**/**17b**, bicyclo[3.2.1]octenedione **18** was collected after flash chromatography and further purified by HPLC (1 cm i.d. column; 1:2 hexane/ethyl acetate; 5 mL/min) to afford 658 mg (36%) of analytically pure **18** as white crystals: mp 88.5–90.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (m, 1H, ArH), 6.51 (m, 2H, 2 × ArH), 5.77 (s, 1H, =CH), 4.39–4.27 (m, 2H, CH_2OMs), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.57 (s, 1H, $CH(C{=}O)_2$), 3.05 (s, 3H, SCH_3), 2.54 (apparent d, J = 7.7 Hz, 1H, ArCH), 2.28–2.03 (m, 2H, C*H*CH_3 and C*H*HCH_2OMs), 2.03–1.92 (m, 1H, CH*H*CH_2OMs), 1.92–1.79 (m, 2H, CCH_2), 1.07 (d, J = 6.7 Hz, 3H, CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 190.0, 152.6, 151.0, 144.2, 134.4, 121.0, 119.1, 117.4, 110.9, 70.2, 70.1, 57.1, 55.7, 55.4, 49.6, 47.0, 37.2, 26.8, 25.5, 24.0, 18.2, 13.8, –4.8; IR (CH_2Cl_2) 1763, 1698, 1606, 1516, 1472 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 234 (4.22), 272 (4.19); MS (EI, 70 eV) m/z 552 (M^+, 1), 206 (23), 180 (23), 179 (100); HRMS calcd for $C_{27}H_{40}O_8SiS$ 552.2213, found 552.2191. Anal. Calcd for $C_{27}H_{40}O_8SiS$: C, 58.67; H, 7.29. Found: C, 58.97; H, 7.50.

(±)-(6-*endo*,7-*exo*)-7-(4-Hydroxy-3-methoxyphenyl)-5-[3-[(methylsulfonyl)oxy]propyl]-3-methoxy-6-methylbicyclo[3.2.1]oct-3-ene-2,8-dione (20). The same procedure used for the preparation of **13** from **10a** was carried out with **17a** (4.7 mg, 0.0085 mmol). Preparative TLC (1:5 hexane/ethyl acetate, R_f = 0.51) of the crude product afforded 2.2 mg (59%) of analytically pure **20** as a white solid: mp 145–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 8.1 Hz, 1H, ArH), 6.57 (dd, J = 2.0, 8.1 Hz, 1H, ArH), 6.52 (d, J = 2.0 Hz, 1H, ArH), 5.77 (s, 1H, C*H*=C(OCH_3)C=O), 5.55 (s, 1H, OH), 4.39–4.27 (m, 2H, CH_2OMs), 3.86 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, =C(OCH_3)), 3.56 (d, J = 1.0 Hz, 1H, bridgehead-H), 3.05 (s, 3H, SCH_3), 2.55 (dd, J = 1.0, 7.9 Hz, 1H, ArCH), 2.18–1.82 (m, 5H, $CH_2CH_2CH_2OMs$, C*H*CH_3), 1.07 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 190.0, 150.3, 146.2, 144.9, 133.0, 119.9, 117.3, 114.8, 109.5, 70.4, 70.1, 57.3, 56.0, 55.9, 49.9, 47.3, 37.5, 27.1, 24.2, 13.9; IR (CH_2Cl_2) 3460, 1760, 1683, 1605, 1520, 1455, 1267, 1202 cm^{-1}; MS (EI, 70 eV) m/z 438 (M^+, 100), 342 (34), 164 (54); HRMS calcd for $C_{21}H_{26}O_8S$ 438.1348, found 438.1328.

(±)-(6-*exo*,7-*endo*)-7-(4-Hydroxy-3-methoxyphenyl)-5-[3-[(methylsulfonyl)oxy]propyl]-3-methoxy-6-methylbicyclo[3.2.1]oct-3-ene-2,8-dione (21). The same procedure used for the preparation of **13** from **10a** was carried out with **17b** (24.6 mg, 0.0445 mmol). Flash chromatography (2:1 hexane/ethyl acetate) of the crude product afforded 15.2 mg (78%) of analytically pure **21** as a white solid: mp 162.0–163.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 7.8 Hz, 1H, ArH), 6.55 (m, 2H, 2 × ArH), 6.18 (s, 1H, C*H*=C(OCH_3)C=O), 5.52 (s, 1H, OH), 4.28–4.44 (m, 2H, CH_2OMs), 3.84 (s, 3H, $ArOCH_3$), 3.77 (d, J = 7.5 Hz, 1H, bridgehead-H), 3.72 (s, 3H, =C(OCH_3)), 3.13–3.08 (m, 1H, ArCH), 3.07 (s, 3H, SCH_3), 2.55 (dq, J = 6.4, 6.7 Hz, 1H, C*H*CH_3), 2.24–2.12 (m, 1H, CH_2CHHCH_2OMs), 2.02–1.73 (m, 3H, $CH_2CH_2CH_2$-OMs and CH_2CHHCH_2OMs), 1.12 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 189.7, 154.1, 146.6, 145.1, 129.6, 121.5, 120.8, 114.5, 110.9, 70.2, 69.2, 55.8, 55.7, 55.1, 49.4, 45.7, 37.5, 24.7, 24.6, 17.9, IR (CH_2Cl_2) 3536, 1761, 1694, 1609, 1465 cm^{-1}; MS (EI, 70 eV) m/z 438 (M^+, 28), 342 (100), 165 (55); HRMS calcd for $C_{21}H_{26}O_8S$ 436.1348, found 438.1357.

(±)-(6-*exo*,7-*endo*)-7-(4-Hydroxy-3-methoxyphenyl)-3-methoxy-6-methyl-5-(2-propenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (22). The same procedure used to prepare **13** from **10a** was carried out with **10b** (24.5 mg, 0.0537 mmol). HPLC purification (4.6 mm i.d. column, 2:1 hexane/ethyl acetate) of the crude product afforded 16.7 mg (91%) of analytically pure **22** as white crystals (lit. (–)-enantiomer[18] viscous oil): mp 145.0–145.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 8.7 Hz, 1H, ArH), 6.57 (m, 2H, 2 × ArH), 6.28 (s, 1H, C*H*=C(OCH_3)C=O), 6.04–5.90 (m, 1H, CH_2CH=CH_2), 5.55 (s, 1H, OH), 5.31 (d, J = 17.2 Hz, 1H, =C*H*H), 5.27 (d, J = 9.8 Hz, 1H, =CH*H*), 3.84 (s, 3H, $ArOCH_3$), 3.79 (d, J = 7.5 Hz, 1H, bridgehead-H), 3.69 (s, 3H, =C(OCH_3)), 3.12 (m, 1H, ArCH), 2.64 (dd, J = 14.7, 7.1 Hz, 1H, C*H*HCH=CH_2), 2.62–2.50 (m, 1H, C*H*CH_3), 2.47 (dd, J = 14.7, 7.0 Hz, 1H, CH*H*CH=CH_2), 1.17 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 190.0, 153.6, 146.5, 145.0, 133.3, 129.8, 121.7, 120.8, 119.6, 114.5, 111.0, 69.0, 55.8, 55.6, 55.0, 49.5, 45.1, 32.6, 18.1; IR ($CHCl_2$) 3537, 1760, 1693, 1608, 1518 cm^{-1}; MS (EI, 70 eV) m/z 342 (M^+, 100), 163 (31); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1450.

(±)-(2α,4α,5β,5aα)-4-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-2,5a-methano-7-methoxy-5-methyl-8*H*-2,3,4,5-tetrahydro-1-benzoxepin-8-one (25). From Quinone Ketal 27 and Styrene 15: Neat $TiCl_4$ (21 μL, 0.19 mmol) was added dropwise to a stirred solution of crude quinone ketal **27** (40.3 mg, 0.180 mmol) and styrene **15** (73.0 mg, 0.262 mmol) in CH_2Cl_2 (1.8 mL) at –78 °C. The resulting solution was stirred 5 min and then the cooling bath removed. After 10 min, the reaction mixture was transferred *via* cannula to a stirred solution of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) and recrystallization (hexane/ethyl acetate) afforded 69.4 mg (three crops, 85% overall yield) of analytically pure **25**.

From 10a. Neat $TiCl_4$ (2.0 μL, 0.018 mmol) was added to a stirred solution of **10a** (7.4 mg, 0.016 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C. After stirring for 5 min, the cooling bath was removed and stirring continued an additional 15 min. The reaction mixture was then added to saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded 7.3 mg (99%) of analytically pure **25**.

From 26. Neat $TiCl_4$ (2.0 μL, 0.018 mmol) was added to a solution of bicyclooctane **26** (4.7 mg, 0.010 mmol) in CD_2Cl_2 (0.6 mL) in a 5-mm NMR tube at –78 °C. After stirring for 5 min at –78 °C the solution was allowed to warm to room temperature over 5 min. The reaction mixture was then added to saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) followed by HPLC (1:5 hexane/ethyl acetate) purification afforded 4.6 mg (98%) of analytically pure **25** as white crystals: mp 208.0–208.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J = 8.4 Hz, 1H, H-17), 6.64 (apparent s, 2H, H-14 and H-18), 5.80 (s, 1H, H-2), 5.47 (s, 1H, H-5), 5.04 (apparent t, J = 5.2 Hz, 1H, H-8), 3.79 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, OCH_3), 2.54 (ddd, J = 11.22, 11.23, 6.14 Hz, 1H, H-10), 2.37 (dd, J = 11.4, 6.4 Hz, 1H, H-7β), 2.35–2.25 (m, 1H, H-9β), 2.20 (apparent d, J = 11.3 Hz, 1H, H-7α), 2.04 (dq, J = 11.3, 6.3 Hz, 1H, H-11), 1.75 (apparent t, J = 12.9 Hz, 1H, H-9α), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.58 (d, J = 6.3 Hz, 3H, CH_3-12), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C (75 MHz, $CDCl_3$) δ 183.1, 180.2, 153.2, 150.8, 143.7, 136.7, 120.9, 119.5, 112.0, 109.1, 101.2, 81.9, 55.5, 55.2, 50.3, 46.1, 45.5, 43.6, 37.8, 25.6, 18.3, 14.4, –4.7; IR (CH_2Cl_2) 1656, 1614, 1515 cm^{-1}; MS (EI, 70 eV) m/z 456 (M^+, 1), 400 (29), 399 (100), 207 (15); HRMS calcd for $C_{26}H_{36}O_5Si$ 456.2332, found 456.2331. Anal. Calcd for $C_{26}H_{36}O_5Si$: C, 68.39; H, 7.95. Found: C, 68.56; H, 8.05.

(±)-(6-*endo*,7-*exo*)-7-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-methoxy-6-methyl-5-(2-propenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (26). The same procedure employed for the synthesis of **10a** from **17a** was carried out with mesylate **18** (155 mg, 0.281 mmol). HPLC (1 cm i.d. column, 2:1 hexane/ethyl acetate) purification afforded 101 mg (79%) of analytically pure **26** as a white solid: mp 108.0–109.0 °C; ^{1}H NMR (300 MHz $CDCl_3$) δ 6.76 (d, J = 8.5 Hz, 1H, ArH), 6.51–6.53 (m, 2H, 2 × ArH), 6.05–5.91 (m, 1H, CH_2CH=CH_2), 5.80 (s, 1H, C*H*=C(OCH_3)C=O), 5.20 (d, J = 16.8 Hz, 1H, C*H*H), 5.17 (d, J = 9.2 Hz, 1H, =CH*H*), 3.76 (s, 3H, $ArOCH_3$), 3.73 (s, 3H, =$COCH_3$),

3.57 (s, 1H, bridgehead-H), 2.56 (d, J = 7.4 Hz, 2H, $CH_2CH{=}CH_2$), 2.53 (apparent d, J = 8.3 Hz, 1H, ArCH), 2.20–2.12 (m, 1H, CHH_3), 1.06 (d, J = 6.6 Hz, 3H, CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 190.4, 152.4, 151.1, 144.3, 134.8, 133.1, 121.1, 119.4, 119.0, 118.0, 111.1, 70.3, 57.4, 55.7, 55.5, 50.0, 46.8, 35.4, 25.6, 18.4, 14.2, −4.7; IR (CH_2Cl_2) 1763, 1696, 1604, 1516 cm^{-1}; MS (EI, 70 eV) m/z 456 (M^+, 1), 400 (31), 399 (100); HRMS calcd for $C_{26}H_{36}O_5Si$ 456.2332, found 456.2313. Anal. Calcd for $C_{26}H_{36}O_5Si$: C, 68.39; H, 7.95. Found: C, 68.20; H, 7.98.

2-(2-Propenyl)-4,4,5-trimethoxycyclohexa-2-5-dienone (27). The experimental procedure used for the preparation of **16** from the corresponding phenol was carried out with 3,5-dimethoxy-6-(2-propenyl)phenol (200 mg) to afford 176 mg of **27** (76%) as a clear oil (>95% pure by ^1H NMR analysis). The crude quinone ketal **27** was used immediately without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H, $=CHC{=}O$), 5.80–5.95 (m, 1H, $=CH$), 5.67 (s, 1H, $=CHC(OCH_3)_2$), 5.16–5.11 (m, 2H, $=CH_2$), 3.83 (s, 3H, OCH_3), 3.32 (s, 6H, geminal OCH_3's), 3.12 (d, J = 6.6 Hz, 2H, CH_2).

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Supplementary Material Available: Summary of key NOE experiments for **10a**, **10b**, **22**, and **26**, and copies of ^1H NMR and ^{13}C NMR spectra for new compounds lacking combustion analysis (18 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.