Synthesis of Racemic Frenolicin via Organochromium and Organopalladium Intermediates

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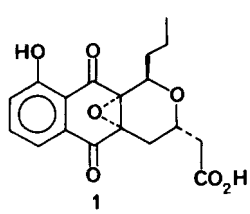
Abstract: A synthesis of the natural quinone antibiotic frenolicin has been completed. Crucial steps include nucleophilic addition/oxidation with an arene–chromium complex to produce a 2,3-disubstituted anisole derivative and intramolecular alkoxy-carbonylation of an alkene to form the substituted pyran ring. The palladium-catalyzed alkoxy-carbonylation procedure is shown in models to be effective with disubstituted double bonds, giving stereochemical control in formation of adjacent chiral centers. While the pyran synthesis in this case produces the unnatural cis arrangement of substituents, a deprotection and equilibration procedure with boron tribromide generates the natural trans configuration.

Frenolicin (**1**) was isolated as pale yellow needles from



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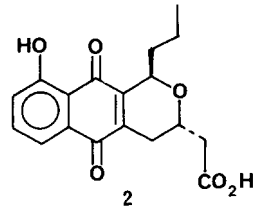

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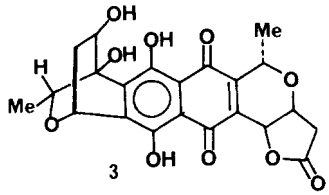

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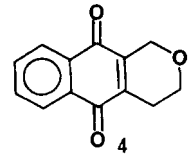

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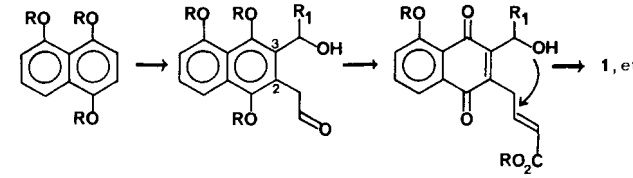
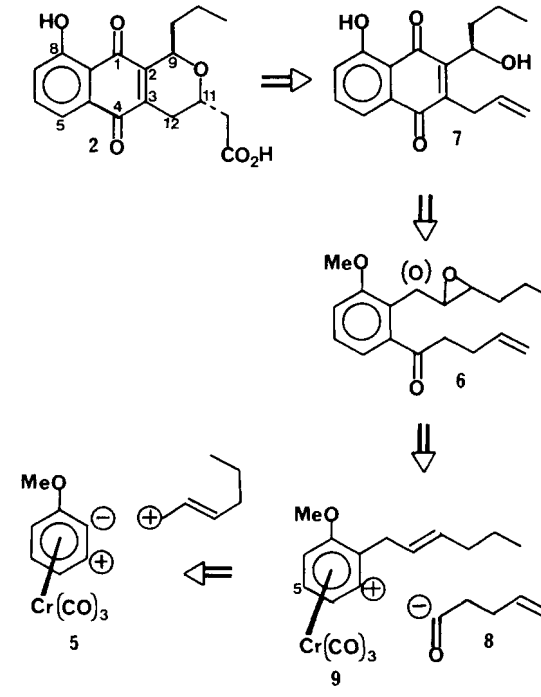
Streptomyces fradiae in 1960.[1] The structure and relative stereochemistry were determined by Ellestad and co-workers.[2] Deoxyfrenolicin (**2**), the chemical reduction product of frenolicin, was isolated from *Streptomyces roseofulvus*.[3] Optical rotatory dispersion studies on deoxyfrenolicin established the absolute configuration as 9*R*,11*S*.[3] Both quinones exhibit moderate antibiotic activity and antifungal activity.[1-3] A number of natural products such as the nanaomycins,[4] kalafugin,[5] and more complex analogues such as granaticin (**3**)[6] also show biological activity and have in common the isochromanquinone skeleton (**4**). This basic structural type can lead to reactive alkylating agents by in vivo reduction, a process suggested to be responsible for the antitumor activity of certain members of the series.[7]

This interesting biological activity may be responsible for substantial recent synthesis activity, including the total synthesis of frenolicin,[8] nanaomycin A[8-10] and kalafugin.[10] In the case of frenolicin, the initial target was deoxyfrenolicin, and then the epoxy oxygen was added with basic *tert*-butyl hydroperoxide.[8a] A

Scheme I. General Approach to Isochromanquinones



Scheme II. Synthesis Strategy



common feature of the existing syntheses is the use of 1,4-naphthoquinone derivatives as initial precursors and various techniques for adding side chains in the 2- and 3-position. Horner–Wittig olefination is often used to convert the side chain at C-2 into an acrylate unit which undergoes conjugate addition by the hydroxyl on the C-3 side chain to complete the pyran ring (see Scheme I). With one exception, **8a**, the stereochemistry of the two substituents on the pyran ring has not been controlled in the existing syntheses; this is not a serious limitation since equilibration of the side chains occurs in strong sulfuric acid and leads to a mixture rich in the natural trans arrangement, by a factor of 3:1 or better.[8-10] While the use of naphthoquinone precursors is reasonably efficient for the synthesis of frenolicin and nanaomycin A, they are less attractive in plans to synthesize the structurally more complex isochromanquinones such as gra-

(1) Van Meter, J. C.; Dann, M.; Bohonos, N. "Antimicrobial Agents Annual 1960"; Plenum Press: New York, 1961; p 77.
(2) Ellestad, G. A.; Kunstman, M. P.; Whaley, H. A.; Patterson, E. L. *J. Am. Chem. Soc.* **1968**, *90*, 1325.
(3) Iwai, Y.; Kōra, A.; Takahashi, Y.; Hayashi, T.; Awaya, J.; Masuma, R.; Ōiwa, R.; Ōmura, S. *J. Antibiot.* **1978**, *31*, 959.
(4) Tanaka, H.; Koyama, Y.; Nagain, T.; Marumo, H.; Omura, S. *J. Antibiot.* **1975**, *28*, 868.
(5) Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704.
(6) Snipes, C. E.; Chang, C.; Floss, H. G. *J. Am. Chem. Soc.* **1979**, *101*, 701.
(7) Zeeck, A.; Zähner, H.; Mardin, M. *Liebigs Ann. Chem.* **1974**, 1100.
(8) (a) Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, 4463. (b) Naruta, Y.; Uño, H.; Maruyama, K. *Chem. Lett.* **1982**, 609–612.
(9) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.
(10) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263.

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naticin (**3**) and others.[11] In these cases, alicyclic rings would have to be added to both rings of the naphthoquinones. We envisage a more general procedure, starting from a simple monocyclic aromatic ring to which the appropriate substituents could be added. The plan is based on observations that substitutions in anisole derivatives can be achieved with high efficiency and selectivity by the addition/oxidation method for coupling of carbon nucleophiles with η^6-(anisole)tricarbonylchromium complexes.[12] In addition, more direct techniques for the construction of the required pyran rings with acetic acid side chains seemed possible by using palladium-promoted reactions of simple alkenes. In this paper, we describe the development of a successful approach to frenolicin based on these two central ideas.

Strategy. The general strategy is presented in Scheme II. We imagine that anisole–$Cr(CO)_3$ (**5**) can be elaborated into a 2,3-disubstituted derivative such as **6**. Ring closure by conventional addition to an epoxide would provide the naphthalene ring system, and then intramolecular alkoxy-carbonylation of the allyl side chain (in **7**) promoted by palladium in the presence of CO would give the proper skeleton.

The η^6-arene–$Cr(CO)_3$ complexes are well suited for the preparation of multiply substituted aromatic derivatives. They are easily accessible, stable under a variety of common reaction conditions, and they undergo several general carbon-coupling reactions.[13] Relevant to the present problem are the ease of metalation adjacent to a methoxyl substituent[14] and the ability to add carbon nucleophiles directly to a position meta to a methoxyl group.[12] These reactivity parameters are the basis for the polarity suggested in structure **5** (Scheme II). Metalation and coupling with a carbon electrophile (an equivalent of the 2-hexenyl cation) is the plan for attachment of the side chain at C-2, maintaining the activating $Cr(CO)_3$ group. Then nucleophilic addition with an equivalent of acyl anion **8** should be controlled to attack at a position meta to the methoxyl group. However, in intermediate **9**, the two positions meta to methoxy are nonequivalent. Consistent with the substantial steric effects on regioselectivity seen in addition to substituted arene–$Cr(CO)_3$ complexes, nucleophilic addition to species such as **9** occurs predominantly from the (undesired) less hindered position (at C-5).[14c] Therefore, new control features must be built into the arene complex.

Many examples of the addition of oxygen nucleophiles to alkenes promoted by Pd(II) have been presented.[15] However, trapping of the intermediate σ-alkyl–Pd(II) complex is usually not efficient; products from β-hydride elimination and from positional isomerization of the Pd tend to predominate. Intramolecular addition of amines to alkenes followed by CO trapping under Pd(II) catalysis has been successful in a limited series,[16] but no general and efficient process with oxygen nucleophiles has been recorded.[17] There is little information on which to base predictions of the stereochemical outcome of the proposed ring closure, **7** → **2** in Scheme II.

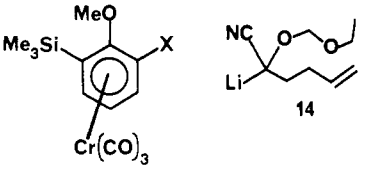
Table I. Synthesis of *Z* and *E* Silyl Enol Ethers, **21** and **22**

entry	base	solvent	*T*, °C	*Z*:*E*[g]	yield,[f] %
1	LTMP[a]	THF/HMPA	0	92:8[d]	74
2	LDEA[b]	THF	−78	77:23[d]	
3	LDEA[b]	THF	25	77:23[d]	79
4	LDA[c]	THF	−78	71:29[d]	
5	LDA[c]	Et_2O	−78	69:31[d]	
6	LTMP[a]	THF	−78	57:43[d]	76
7	LTMP[a]	THF	−78	57:43[e]	

[a] Lithium tetramethylpiperidide. [b] Lithium diethylamide. [c] Lithium diisopropylamide. [d] *tert*-Butyldimethylsilyl ether. [e] Trimethylsilyl ether. [f] Isolated yield. [g] Determined by ^1H NMR integration.

Results and Discussion

The key to altering the selectivity in nucleophile addition to 2-substituted anisole–$Cr(CO)_3$ complexes is the use of a trialkylsilyl group as a directing substituent. It is easily introduced and removed[14] and is a strong para director.[18] Starting from *o*-trimethylsilylanisole,[19] the chromium tricarbonyl complex **10** was prepared in 94% yield by heating at reflux a solution of the arene and chromium hexacarbonyl in dioxane. Metalation using *n*-butyllithium in ether according to the general procedure[14] proceeded smoothly, but the resulting *o*-lithio compound (**11**) could not be coupled with 2-hexenyl bromide directly. Instead, it was converted to the copper derivative (**12**) by reaction with cuprous iodide; reaction with (*E*)-2-hexenyl bromide then gave **13** in 96% yield (from **10**).



10: X = H
11: X = Li
12: X = Cu
13: X = E-2-hexenyl

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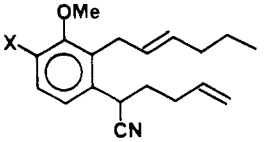

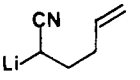

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16: X = $SiMe_3$
17: X = H

The substituent at C-3 would be introduced by addition of a carbonyl anion equivalent, as shown in Scheme II. With simple arene–$Cr(CO)_3$ complexes, carbonyl anion equivalents such as the 2-alkyl-1,3-dithianyl anions and the anions from cyanohydrin acetals are very effective nucleophiles, leading to high yields of substitution for hydrogen after addition/oxidation.[12,13] However, in heavily substituted arene ligands, addition of tertiary carbanions can become inefficient; addition of anion **14** to complex **13** led to less than 60% conversion even with excess anion and vigorous reaction conditions. However, the simple secondary cyano-stabilized anion **15** was much more successful. Addition of **15** to complex **13** followed by oxidation with excess iodine gave the free substituted arene, **16**, and then protodesilylation in aqueous acid[20]

(11) Multiring analogues include actinorhodin [Brockmann, H.; Zeeck, A.; van der Merwe, D.; Müller, W. *Liebigs Ann. Chem.* **1966**, *698*, 209] and the naphthocyclinones [Zeeck, A.; Zähner, H.; Mardin, M. *Ibid.* **1974**, 1100].

(12) (a) Semmelhack, M. F.; Clark, G. *J. Am. Chem. Soc.* **1977**, *99*, 1695. (b) Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, *44*, 3275–3277.

(13) (a) Semmelhack, M. F.; Clark, G.; Farina, R.; Saeman, M. *J. Am. Chem. Soc.* **1979**, *101*, 217. (b) For a recent discussion, see: Semmelhack, M. F.; Clark, G. R.; Garcia, J. L.; Harrison, J. J.; Thebtaranonth, Y.; Wulff, W.; Yamashita, A. *Tetrahedron* **1981**, *37*, 3957.

(14) (a) Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2555–2559. (b) Nesmeyanov, A. N.; Kolobova, N. E.; Anisimov, K. N.; Makarov, Yu. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 2665. (c) Semmelhack, M. F.; Bisaha, J.; Czarny, M. *J. Am. Chem. Soc.* **1979**, *101*, 768. (d) Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2560–2566.

(15) For discussions, see: (a) Stille, J. K.; Hines, L. F.; Fries, R. W.; Wong, P. K.; James, D. E.; Lau, K. *Adv. Chem. Ser.* **1974**, *No. 132*, 90. (b) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980; pp 585, 604. (c) For a theoretical analysis, see: Eisenstein, O.; Hoffman, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308.

(16) The problems associated with palladium-promoted addition of nucleophiles to alkenes followed by carbonylation have been discussed recently. The same work describes examples of intramolecular addition of amine nucleophiles with CO trapping which are efficient in a limited number of examples. See: Hegedus, L. S.; Allen, G.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583. Hegedus, L. S.; McKearin, J. *Ibid.* **1982**, *104*, 2444–2453.

(17) For examples, see: James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.

(18) Semmelhack, M. F.; Clark, G. R.; Farina, R.; Saeman, M. *J. Am. Chem. Soc.* **1979**, *101*, 217–218.

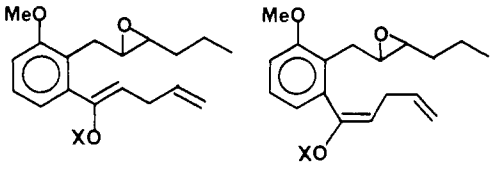
(19) Gilman, H.; Nobis, J. F. *J. Am. Chem. Soc.* **1950**, *72*, 2629.

(20) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.

gave a mixture of the desired substitution product (**17**, 61% yield) and the desilylated starting arene, *o*-(hex-2-en-1-yl)anisole (14%).

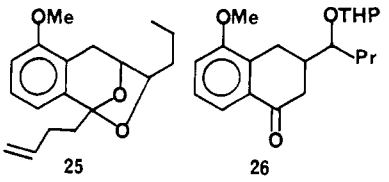
With the method of Watt,[21] oxidative decyanation converted **17** to the ketone **18**, in 85% yield. This procedure, although it requires four discrete reactions, can be carried out without isolation of intermediates and makes anions such as **15** effective as acyl anion equivalents. Intermediate **18** is activated for ring closure by selective epoxidation of the disubstituted double bond, using *m*-chloroperoxybenzoic acid in the presence of 5% aqueous sodium bicarbonate.[22] After chromatography, the yield of pure **19** was 75%.

The enolate anion **20**, generated with a small excess of lithium diisopropylamide, failed to undergo ring closure by attack on the epoxide; this result is unsurprising considering related ring closure studies.[23] Instead, the enol silyl ethers (**21**, **22**) were formed from



20: X = Li
21a: X = $SiMe_3$
b: X = $SiMe_2tBu$

22a: $SiMe_3$
b: $SiMe_2tBu$



25 **26**

20 by reaction with trimethylsilyl chloride or *tert*-butyldimethylsilyl chloride. Depending on the reaction conditions, varying ratios of the *E* and *Z* enol silyl ethers were produced (Table I). The assignment of geometry is based on the chemical shift of the vinyl proton in the enol silyl ether unit. In closely related examples, this proton in the *Z* isomers (**21a**, **21b**) is observed upfield by 0.3 ppm compared to the same proton in the *E* isomers (**22a**, **22b**).[24] The *Z* isomer was favored in all cases, presumably due to the steric bulk of the arene.[24c] A greater proportion of the *E* isomer was formed as the size of the substituents on the amide base was increased, but not higher than 43%. As expected, a mixture rich (92:8) in the *Z* isomer was obtained with HMPA as cosolvent.[24a,b] The geometry of the enol ether double bond is important only in that the relative proportion of stereoisomers (**23**, **24**) from the next step depends on this factor, but the relevant stereocenters become achiral in subsequent intermediates.

Treatment of the enol silyl ether mixtures with boron trifluoride etherate[25] in dichloromethane at 25 °C led to rapid formation of three products, the cis (**23**) and trans (**24**) ring-closed products, and the internal ketal, **25**.[26] The byproduct ketal **25** was formed in yields of 18–24% but it was easily removed by chromatography. The desired products (**23**, **24**) were obtained together in 51–66% yield, after chromatography. Table II displays the results of cyclization of different mixtures of enol ether isomers; from these

Table II. Cyclization of Silyl Enol Ethers (**21**, **22**) with Boron Trifluoride

entry	reactant *Z*:*E*	silane	yield, % (**23** + **24**)	ratio **23**:**24**	yield of **25**
1	92:8	TBDMS[a]	*c*	48:52	*c*
2	77:23	TBDMS[a]	61	57:43	18
3	57:43	TBDMS[a]	63	68:32	24
4	57:43	TMS[b]	66[d]	81:18	*c*
5	57:43	TMS[b]	51[d]	82:18	25

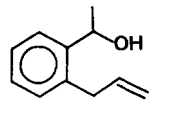
[a] *tert*-Butyldimethylsilyl enol ethers, **21b**, **22b**. [b] Trimethylsilyl enol ethers, **21a**, **22a**. [c] Not determined. [d] Yield overall from **18**.

data, it is clear that the *Z* isomer tends to produce nearly a 1:1 mixture of **23**:**24**, while the *E* isomer leads to mainly the cis product, **23**. From the experiment reported in Table II, entry 4, the cis product was obtained analytically pure as a colorless solid, mp 130.5–131.5 °C. The primary evidence for the stereochemistry of **23** and **24** arrives from parallel work on **26** which is not reported in detail here.[27] Reaction of **26** with lithium diisopropylamide followed by addition of allyl bromide gave primarily (>95%) a product with the same chromatographic and spectroscopic properties as **24**. Since the trans product is strongly preferred from alkylation of 3-substituted cyclohexanone enolates,[28] this product is assigned the trans geometry. The next steps in the synthesis were developed by using the pure cis isomer, **23**, and later shown to proceed with equal efficiency with a mixture containing **23**:**24** in the ratio 82:18.

Pyran ring formation was first studied with a series of model compounds, **27**–**29**. A simple model for the desired ring closure is *o*-allyl-α-methylbenzyl alcohol, **27**. Treatment of **27** with a mixture containing 0.05 mol equiv of palladium chloride, 2.0 mol equiv of cupric chloride, and carbon monoxide at about 1.1 atm in methyl alcohol gave complete conversion in 2 h and a mixture of pyrans (**30a**, **30b**) in 82% yield. Analytical HPLC indicated a ratio of 2.8:1 favoring **30a**. The stereochemistry of each isomer was determined by analogy with closely related isochroman derivatives.[29,37] The pyran ring prefers a pseudochair conformation with the C-3 carboxymethyl group equatorial. In the cis isomer, the benzylic methine hydrogen (H_a at C-1) is pseudoaxial and shows long-range (homobenzylic) coupling constants of about 2.0 Hz (to pseudoaxial H at C-4) and 1.0 Hz (to pseudoequatorial H). The corresponding trans isomers show long-range coupling of <0.5 Hz for the benzylic methine hydrogen.[29] By multiple irradiation, the benzylic methine hydrogen (H_a) of the major isomer (**30a**) was shown to have long-range coupling constants of 1.5 and 1.3 Hz, while the minor isomer (**30b**) showed no observable long-range coupling (less than 0.5 Hz) and is assigned the trans structure. The intramolecular alkoxy-carbonylation was also efficient with *tert*-butyl alcohol to trap the acylpalladium intermediate. In this case, a similar mixture of isomers was obtained (**31a**, **31b**), as the *tert*-butyl esters, in 87% yield.

Intramolecular alkoxy-carbonylation was equally effective when disubstituted alkenes were employed, although longer reaction times were required, about 24 h. Reaction of **28** was stereospecific, giving >98% of one diastereoisomer in 84% yield. It is assigned structure **32a** on the basis of the usual anti addition of alkoxy to olefin–Pd(II) complexes and retention of configuration during alkyl migration from metal to carbon monoxide.[30] The corresponding cis alkene (**29**) led to a different diastereoisomer with similar selectivity (80% yield) which is assigned structure **32b** on the basis

(21) Selikson, S. S.; Watt, D. S. *J. Org. Chem.* **1975**, *40*, 267.
(22) (a) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267. (b) Semmelhack, M. F.; Yamashita, A. *J. Am. Chem. Soc.* **1980**, *102*, 5924.
(23) For discussion, see: Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268 and references therein.
(24) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *Ibid.* **1980**, *102*, 3959. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. A.; Sahn, J. A.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (d) Nakamara, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.
(25) For related Lewis acid promoted displacement of epoxides, see: Boeckmann, R. D.; Bruza, K. J.; Heinrich, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 7101.
(26) Ketal **25** was formed from the ketone **19** or from the silyl enol ethers (**21**, **22**) under mild acidic conditions. For related examples, see: Gaoni, Y. *J. Chem. Soc. C* **1968**, 2925.
(27) Zask, A. Ph.D. Thesis, Princeton University, 1982.
(28) (a) Coates, R. M.; Sandetur, L. D. *J. Org. Chem.* **1974**, *39*, 275. (b) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, N. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (c) Boeckman, R. K. *J. Org. Chem.* **1973**, *38*, 4450.
(29) Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191.
(30) (a) Stille, J. K.; Divakaruni, R. *J. Am. Chem. Soc.* **1978**, *100*, 1304. (b) Stille, J. K.; James, D. E.; Hines, L. F. *Ibid.* **1973**, *95*, 5062. (c) Backvall, J. E.; Åkermark, B.; Livnggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264; *J. Am. Chem. Soc.* **1979**, *101*, 2411. (d) Hines, L. F.; Stille, J. K. *Ibid.* **1972**, *94*, 485.



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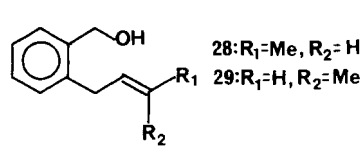
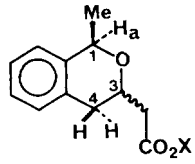
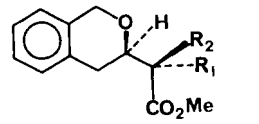


28: R_1=Me, R_2=H
29: R_1=H, R_2=Me



30 X=Me
a: cis
b: trans

31 X=tBu
a: cis
b: trans

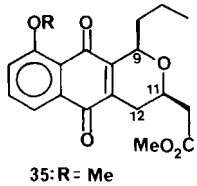


32 a: R_1 = Me, R_2 = H
b: R_1 = H, R_2 = Me

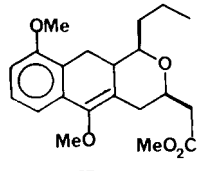
of the expected mechanism, as above.

Under similar conditions, the key intermediate **23** gave the expected pyran, **33**, as a single diastereoisomer (mp 87.5–88.5 °C) in 81% yield. Slow addition of solid **23** was important in achieving good efficiency, apparently to maintain the proper concentration of CO and assure effective trapping of the alkyl–Pd intermediate before β-elimination can occur. A mixture of **23** and **24** (82:18) under the same conditions gave two products (87% yield, ratio 81:19), where the major isomer was identical on HPLC with **33**; the minor isomer is assumed to be epimeric at C-3, **34**. This relationship is confirmed by aromatization of a mixture of **33** and **34** to give a single product (see below).

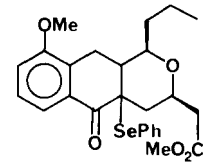
The addition of an oxygen unit and aromatization of the middle ring of **33/34** was expected at the outset to be a straightforward procedure, allowing us to use simplified intermediates up to this point. However, an extensive series of experiments designed to introduce the benzylic oxygen (e.g., in **35**) failed to provide a useful procedure. Among the reagents tested to introduce a benzylic heteroatom were *N*-bromosuccinimide,[31] benzeneseleninic anhydride,[32] and selenium dioxide.[33] Low reactivity of the desired benzylic position and eventual side reactions at other positions were the general features of the failures. Similarly, direct aromatization of **33/34** to a naphthol such as **36** were not successful. For example, heating **33** with selenium metal[34] in 1-methylnaphthalene at reflux for 112 h led to recovery of **33** (81%). Instead, a multistep procedure was employed beginning with the enol methyl ether **37**, obtained from **33** by reaction with tri-



35: R = Me
39: R = H



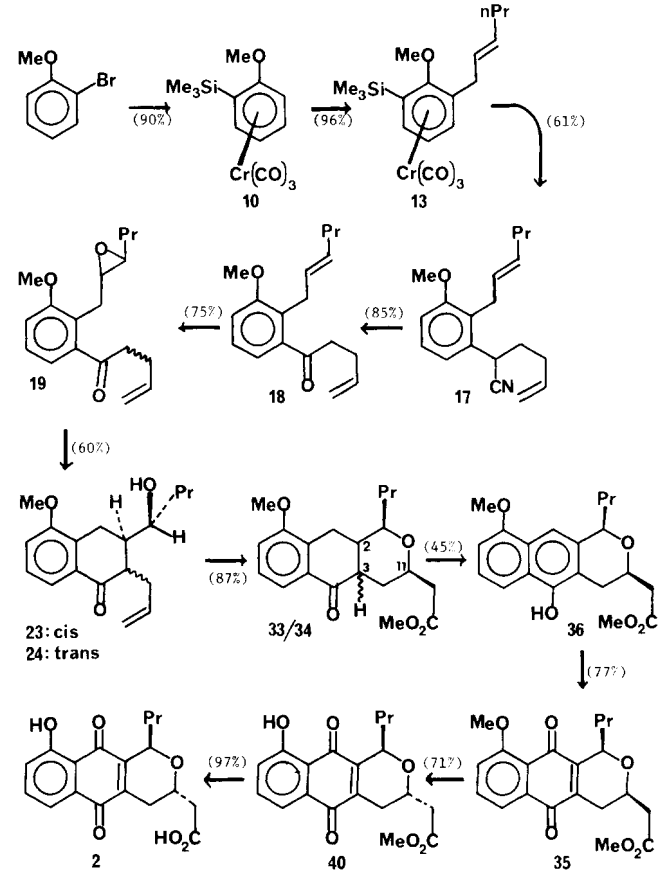
37



38

methylorthoformate in the presence of *p*-toluenesulfonic acid, followed by acid-catalyzed elimination of methyl alcohol in hot benzene (92% yield). Reaction of **37** with phenylselenyl bromide in the presence of silver trifluoroacetate,[35] followed by addition of aqueous base produced α-(phenylselenyl) ketone **38**. Oxidation of **38** gave the selenoxide which underwent fragmentation below

Scheme III. Synthesis of Frenolicin



25 °C, giving primarily the naphthol **36** (62% yield). Finally, Jones oxidation conditions converted the naphthol **36** to naphthoquinone **35**. Column chromatography gave the pure product as an orange solid with mp 146–147 °C, in 77% yield. Both HPLC and ^{13}C NMR spectral analysis indicated that a single diastereoisomer was present. In the ^1H NMR spectrum, the C-12 pseudoequatorial hydrogen appeared as a doublet of doublet of doublets centered at δ 2.84 with J = 18.0, 2.6, and 2.6 Hz, and the C-12 pseudoaxial hydrogen appeared as a doublet of doublet of doublets centered at δ 2.21 with J = 18.0, 10.4, and 3.9 Hz. The chemical shift assignments are made on the basis of observed vicinal coupling constants with the pseudoaxial methine hydrogen at C-11 (10.4 and 2.6 Hz).[36] The homoallylic coupling constants are therefore 3.9 Hz (C-9/C-12, axial/axial) and 2.6 Hz (C-9/C-12, axial/equatorial) consistent with a cis pyran configuration.[37] Starting from a mixture of enol silyl ethers **21/22** and carrying the product diastereoisomer mixture through the entire sequence gave naphthoquinone **35** in essentially the same yield as obtained in the more systematic series of experiments from pure **33**. In addition, the product **35** was a single diastereoisomer, confirming that the products **33** and **34** differ from one another in the configuration at C-2 and not C-11.

Following literature precedent,[8-10] treatment of **35** with aluminum chloride in dichloromethane produced the free phenol, with the cis relationship of the propyl and acetic acid side chains, **39**. Equilibration of the side chains was achieved with concentrated sulfuric acid[8-10] to provide a 6:1 mixture of the trans:cis products, **40**:**39**. A more efficient process was discovered in which excess boron tribromide brings about both demethylation of the phenolic

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(32) Barton, D. H. R.; Hui, R. A. H.; Lester, D. J.; Ley, S. U. *Tetrahedron Lett.* **1979**, 3331.
(33) Rabjohn, N. *Org. React.* **1976**, *24*, 261.
(34) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.
(35) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (b) Clive, D. L. J. *Tetrahedron* **1978**, 1049. (c) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 428. (d) Addition of phenylselenyl chloride has also been reported. Nicolaou, K. C.; Magnolda, R. L.; Sipio, W. J. *Synthesis* **1979**, 982.

(36) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2871 and references therein.
(37) The stereochemistry of each isomer was determined by analogy with the eleutherin–isoeleutherin system: Cameron, D. W.; Kingston, D. G. I.; Sheppard, N.; Lord, T. *J. Chem. Soc.* **1964**, 98. The pseudochair arrangement with the C-11 alkyl group equatorial is preferred. In the ^1H NMR spectra, the homoallylic coupling between H at C-12 and H at C-9 is greater when the C-9 H is pseudoaxial (eleutherin, C-9 shows J = 3.5 and 2.9 Hz for coupling to the H_a' and H_e' at C-12).

hydroxyl group and equilibration to the pure trans compound **40**, which could be isolated in 71% yield after chromatography. Saponification of **40** according to a literature procedure[8a] gave deoxyfrenolicin (**2**) in 97% yield as a yellow orange powder with mp 214–214.5 °C. It was shown to be identical in spectral and chromatographic properties with a sample of (+)-deoxyfrenolicin (mp 177–179 °C) prepared from (+)-frenolicin.[2] The melting point of an equimolar mixture of synthetic (±)-deoxyfrenolicin with (+)-deoxyfrenolicin is 182–183 °C. Since deoxyfrenolicin (**1**) has been converted to frenolicin,[8a] a formal synthesis of the natural product (racemic) is complete.

Scheme III summarizes the successful synthesis of deoxyfrenolicin from *o*-bromoanisole, identifying all intermediates which need to be isolated during the procedure. The overall yield for ca. 15 steps is 4%.

Experimental Section

Spectra. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Perkin-Elmer R 24B spectrometer operating at 60 MHz, or a JEOL FX-90Q Fourier transform spectrometer operating at 90 MHz. Peak positions are reported in parts per million relative to tetramethylsilane internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a JEOL FX-90Q Fourier transform spectrometer operating at 22.5 MHz. Peak positions are reported in parts per million relative to deuterochloroform (δ 77.00). Spectra which were recorded with off-resonance decoupling have peaks reported as singlets (s), doublets (d), triplets (t) or quartets (q). Infrared (IR) spectra were recorded on a Perkin-Elmer Model 299 spectrometer. Peak intensities were recorded as strong (s), medium (m), or weak (w). The 1601-cm^{-1} signal of polystyrene was used for calibration. Mass spectra were recorded on an AEI MS-902 instrument or a Finnigan Model 3300 GC–MS.

Chromatography. Medium-pressure liquid chromatography (MPLC) was done by using Lobar prepacked silica gel columns at pressures up to 50 psi applied by a Fluid Metering Inc. Model RP lab pump. UV-active fractions were detected with an ISCO Model UA-5 Absorbance monitor. Column chromatography was done with E. Merck silica gel 60 (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was done with E. Merck Reagents silica gel 60 F-254 aluminum-backed plates with a 0.2-mm thickness. Developed plates were visualized under UV light and by charring with 25% aqueous sulfuric acid. Analytical high-performance liquid chromatography (HPLC) was performed with a Waters Associates system equipped with: Radial-PAK B silica gel cartridges in a Model RCM-100 module, Model 6000A solvent delivery system, Model U6K universal liquid chromatograph injector, Model 4400 UV absorbance detector, Model R401 differential refractometer, and a dual pen data module.

Reagents and Solvents. Diethyl ether (ether), tetrahydrofuran (THF), and *p*-dioxane were distilled under argon from benzophenone ketyl immediately before use. Benzene, chlorotrimethylsilane, dimethylformamide, propionitrile, hexamethylphosphoramide (HMPA), diisopropylamine, diethylamine, and 2,2,6,6-tetramethylpiperidine were distilled from calcium hydride (under reduced pressure as necessary) and stored under argon. *tert*-Butyl alcohol was distilled from calcium oxide, under argon. Dichloromethane was distilled from phosphorus pentoxide, under argon. Methanol was distilled from magnesium under argon. Cuprous iodide was further purified according to a literature procedure.[38] Anhydrous cupric chloride was heated at 100 °C under vacuum (0.01 mm) for 15 h and then stored under argon. Triethylamine was filtered through a short plug of alumina immediately before use. *n*-Butyllithium and methyllithium were used as solutions in hexane and their concentrations were determined by using a literature procedure.[39] Ozone was generated with an OREC Model 03V5-0 ozonator.

General Information. "Rotary evaporation" refers to removal of solvent at water aspirator pressure with a Büchi Rotovapor-R. The term "concentrated" refers to removal of solvent by rotary evaporation followed by removal of residual solvent at oil pump pressure (~0.01 mm) until constant weight is achieved. The term "under argon" implies that the apparatus was evacuated to 0.01 mm and then filled with argon 3 times. Melting points were determined on an Electrothermal solid block apparatus. Melting points and boiling points were uncorrected. Elemental analyses were carried out by Scandinavia Microanalytical Labs, Herlev, Denmark. Lithium diisopropylamide, lithium diethylamide, and lithium 2,2,6,6-tetramethylpiperidide were prepared by treating a solution of the amine (1.1 mol equiv) in THF or ether at −78 °C, under argon, with *n*-butyllithium (1.0 mol equiv). The solution was then warmed to 0 °C for 15 min and then cooled to −78 °C.

Preparation of (η^6-*o*-(Trimethylsilyl)anisole)tricarbonylchromium (10). A mixture of *o*-trimethylsilylanisole[19] (15.00 g, 83 mmol), chromium hexacarbonyl (25.00 g, 113 mmol), and 150 mL of dioxane was heated at reflux under argon in a 300-mL round-bottom flask equipped with an air condenser[40] for 4 days. The yellow solution was allowed to cool and the excess chromium hexacarbonyl was filtered and washed with ether. Rotary evaporation of the filtrate gave a yellow semisolid which was dissolved in ether and applied to a column of Florisil. Elution with ether gave a yellow band which was collected and diluted with 100 mL of *n*-hexane. The volume of the solution was reduced to ca. 70 mL, resulting in precipitation of a yellow solid. It was collected and dried to give 24.68 g (94%) of **10** as fine yellow crystals: mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 9), 3.71 (s, 3 H), 4.90 (m, 2 H, aryl-H), 5.65 (m, 2 H, aryl-H); IR ($CHCl_3$) 1960 (s, C=O) and 1880 (s, C=O); mass spectrum, *m/e* 268 (M^+).

Preparation of (η^6-2-(2(*E*)-Hexenyl)-6-(trimethylsilyl)anisole)tricarbonylchromium(0) (13). To yellow crystalline **10** (6.33 g, 20.0 mmol), in a 250-mL three-neck round-bottom flask equipped with magnetic stir bar, vacuum adapter, serum stopper, and a solid addition funnel charged with cuprous iodide (4.19 g, 22 mmol) under argon was added THF (100 mL). The resulting yellow solution was cooled to −30 °C and *n*-butyllithium (9.24 mL, 22 mmol, 2.38 M) was added dropwise over 2 min. After 3 h, the dark reaction mixture was warmed to 0 °C for 5 min and then cooled to −30 °C. The cuprous iodide in the solid addition funnel was added all at once. The reaction mixture was warmed to 0 °C. After 1 h, the resulting dark green mixture was cooled to −30 °C and 1-bromo-2(*E*)-hexene[41] (3.59 g, 22 mmol) was added all at once. The reaction mixture was then warmed to 25 °C. After 3 h, analysis by analytical TLC (1:1 hexane:ether) showed the disappearance of **10** (R_f 0.52) and the appearance of an orange spot (R_f 0.64). The reaction mixture was diluted with ether and washed with saturated aqueous potassium iodide (3×). The aqueous layers were combined and washed with ether (3×). The organic layers were combined and washed sequentially with water and saturated aqueous sodium chloride, dried over potassium carbonate, filtered through a plug of Florisil, and rotary evaporated. The resulting clear orange oil (8.15 g) was column chromatographed (100 g of Florisil, ether) to give **13** as an orange oil (7.69 g, 96%): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.17 (s, $Si(CH_3)_3$, 9 H), 0.71 (t, CH_3, 3 H, J = 7 Hz), 0.92–1.44 (m, CH_2CH_3, 2 H), 1.64–1.98 (m, $CH_2CH_2CH_3$, 2 H), 2.99 (br d, $ArCH_2$, 2 H, J = 4.7 Hz), 3.53 (s, CH_3, 3 H), 4.65 (dd, Ar*H*, 1 H, J = 6.2, 6.2 Hz), 5.08–5.26 (m, Ar*H*, C*H*=C*H*, 4 H); ^{13}C NMR ($CDCl_3$) δ 0.08 (q), 13.66 (q), 22.38 (t), 32.17 (t), 34.44 (t), 62.74 (q), 87.70 (d), 92.63 (s), 97.03 (d), 99.45 (d), 103.78 (s), 126.69 (c), 134.43 (d), 146.56 (s), 233.43 (s); IR (neat) 1960 (s, br, C=O), 1886 (s, br, C=O), 1660 (w, C=C), 1340 (m), 1250 (m), 1003 (m), 843 (s), 766 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (rel intensity) 398 (23), 312 (79), 309 (61), 286 (24), 262 (68), 247 (24), 217 (61), 89 (100), 73 (58), 59 (56), 52 (58); mass spectral M_r calcd for $C_{19}H_{26}O_4SiCr$, 398.1005; found, 398.0984.

Preparation of 2-(2-(2(*E*)-Hexenyl)-3-methoxyphenyl)-5-hexenenitrile (17). To a solution of lithium diisopropylamide (3.3 mmol) in THF (30 mL) in a 100-mL round bottom flask under argon at −78 °C was added 5-hexenenitrile[42] (0.314 g, 3.3 mmol). After 1 h, HMPA (10.4 mL, 60 mmol) was added over 2 min, followed by a solution of **12** (1.19 g, 3.0 mmol) in THF (4 mL). After 30 min, the reaction mixture was warmed to 0 °C for 30 min and then cooled to −78 °C. A solution of iodine (3 g) in THF (10 mL) was then added all at once. The resulting black mixture was warmed to 25 °C for 6 h. The reaction mixture was diluted with ether and washed with saturated aqueous sodium bisulfite (2×) and water (1×). Rotary evaporation gave an oil to which *p*-dioxane (50 mL) and 12 M aqueous hydrochloric acid (5 mL) were added. The resulting mixture was heated at reflux for 3 h and then cooled to 25 °C and rotary evaporated. The residue was partitioned between ether and water, and the ether layer was washed with water (2×) and saturated aqueous sodium chloride (1×), dried over potassium carbonate, and rotary evaporated to give a dark oil (924 mg). MPLC (10:1 hexane:ether) gave *o*-(hex-2-en-1-yl)anisole (78 mg, 14%), followed by **17** (511 mg, 60%). The ^{1}H NMR spectrum of **17** showed that it was >95% pure. A portion of **17** was rechromatographed and distilled (short path, 25–170 °C (0.1 mm)) to give a clear colorless oil for full characterization: ^{1}H NMR

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(39) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
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(41) Prepared from commerically available (*E*)-hex-2-en-1-ol as described by Truscheit and Eiter (Truscheit, E.; Eiter, K. *Liebigs Ann. Chem.* **1962**, *658*, 65.
(42) LaForge, F. B.; Green, N.; Gersdorff, A. *J. Am. Chem. Soc.* **1948**, *70*, 3707.

($CDCl_3$, 90 MHz) δ 0.85 (t, CH_3, 2.4 H, J = 7.2 Hz), 1.12–1.56 (m, CH_2CH_3, 2.0 H), 1.71–2.24 (m, $CH_2CH_2CH_3$, CH_2CH_2, 5.5 H), 3.20 (dd, ArC*H*, 1.0 Hz, J = 3.8, 14.4 Hz), 3.48 (dd, 1.0 Hz, J = 4.3, 14.4 Hz), 3.80 (s, OCH_3, 2.7 H), 4.03 (dd, ArC*H*, 0.9 H, J = 5.6, 8.6 Hz), 4.96–6.02 (m, $CH{=}CH_2$, $CH{=}CH$, 4.7 H), 6.74–7.36 (m, Ar*H*, 2.8 H); ^{13}C NMR ($CDCl_3$) 13.5, 22.4, 28.4, 31.3, 32.6, 34.4, 34.4, 55.6, 110.1, 116.4, 119.7, 121.0, 126.3, 127.4, 127.6, 131.0, 135.8, 136.0, 157.5; IR (neat) 2246 (w, CN), 1653 (w, C=C), 1637 (w, C=C), 1585 (s), 1467 (s), 1265 (s), 1064 (m), 789 (m), 748 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (rel intensity) 283 (100), 254 (18), 242 (21), 229 (56), 212 (26), 186 (27), 173 (53), 160 (38), 147 (54), 115 (30).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.48; H, 8.89; N, 4.97.

Oxidative Decyanation of 17 To Give 18. To a solution of lithium diisopropylamide (1.71 mmol) in THF (20 mL) in a 50-mL round-bottom flask at −78 °C under argon was added a solution of **17** (0.242 g, 0.854 mmol) in THF (2 mL). After 1 h, oxygen which had been passed through a 50-cm × 2-cm calcium chloride drying tube was bubbled into the reaction mixture for 1 h at −78 °C. Dimethyl sulfide (4.4 mL) was then added all at once. The reaction mixture was warmed to 25 °C for 6 h. The clear brown reaction mixture was diluted with ether, washed sequentially with 5% aqueous sodium hydroxide and saturated aqueous sodium chloride, dried over magnesium sulfate, and rotary evaporated. A dark oil (230 mg) was obtained which was column chromatographed (10 g of silica gel; 10:1 hexane:ether) to give ketone **18** as a pale yellow oil (179 mg, 77%). This material was homogeneous by analytical TLC and ^1H NMR spectroscopy. In a separate run, treatment of nitrile **17** (0.051 g, 0.176 mmol) under the above conditions gave, after column chromatography, ketone **18** (0.041 mg, 85%) as a pale yellow oil. These samples were sufficiently pure to be carried on in the synthesis. A portion of the material obtained from the above reaction was further purified by MPLC (10:1 = hexane:ether) and short-path distillation (25–150 °C (0.1 mm)) to give a clear, colorless oil for full characterization: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.83 (t, CH_3, 2.7 H, J = 7.0 Hz), 1.08–1.54 (m, CH_2CH_3, 2.2 H), 1.72–2.08 (m, $CH_2CH_2CH_3$, 2.0 H), 2.20–2.56 (m, $CH_2CH{=}CH_2$, 2.0 H), 2.88 (br t, $COCH_2$, 2.0 H, J = 6.8 Hz), 3.47 (br d, $ArCH_2$, 1.9 H, J = 4.4 Hz), 4.84–6.12 (m, CH=CH, $CH{=}CH_2$, 5.1 H), 6.80–7.32 (m, Ar*H*, 3.0 H); ^{13}C NMR ($CDCl_3$) 13.24 (q), 22.29 (t), 27.81 (t), 28.68 (t), 34.26 (t), 41.57 (t), 55.22 (q), 112.27 (d), 114.76 (t), 118.82 (d), 126.41 (d), 127.33 (s), 157.56 (s), 204.20 (s); IR (neat) 1693 (s, C=O), 1641 (w, C=C), 1578 (m), 1455 (s), 1438 (s), 1265 (s), 973 (m) cm^{-1}; mass spectrum (70 eV), *m/e* (rel intensity) 272 (36), 218 (24), 217 (100), 215 (76), 175 (51), 174 (21), 161 (36), 115 (19), 91 (25), 55 (50).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.28; H, 8.87.

Preparation of (2*RS*,3*RS*)-1-(2-(2,3-Epoxyhexyl)-3-methoxyphenyl)-4-penten-1-one (19). To a solution of **18** (1.0 g, 3.67 mmol) in dichloromethane (50 mL) in a 250-mL round-bottom flask equipped with a magnetic stir bar was added 0.5 M aqueous sodium bicarbonate (11 mL). The resulting mixture was cooled to 0 °C. A solution of *m*-chloroperoxybenzoic acid (0.89 g, 4.40 mmol, 85%), in dichloromethane (17 mL) was added dropwise over 20 min. The reaction mixture was stirred for 21 h, whereupon the organic phase was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate (2×) and saturated aqueous sodium chloride (1×), dried over potassium carbonate, and rotary evaporated. The resulting yellow oil was purified by MPLC (3:1 hexane:ether containing 5% triethylamine). Compound **19** was obtained as a clear colorless oil, homogeneous by analytical TLC (0.796 g, 75%). A portion of this material was rechromatographed and short-path distilled (25–150 °C (0.1 mm)) for full characterization: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.87 (t, CH_3, 2.86 H, J = 6.1 Hz), 1.13–2.63 (m, $CH_2CH_2CH_3$, 4.1 H), 2.25–2.61 (m, 2.1 H), 2.63–3.30 (m, $ArCH_2CHCH$, $ArCOCH_2$, 6.0 H), 3.83 (s, OCH_3, 3.0 H), 4.89–5.25 (m, $CH{=}CH_2$, 2.0 H), 5.65–6.15 (m, $CH{=}CH_2$, 1.1 H), 6.88–7.43 (m, Ar*H*, 3.1 H); ^{13}C NMR ($CDCl_3$) 13.5, 18.98, 27.92, 28.08, 33.82, 41.52, 55.44, 57.82, 58.53, 112.38, 114.98, 119.09, 124.02, 127.16, 137.02, 141.57, 158.15, 204.31; IR (neat) 1692 (s, C=O), 1642 (w, C=C), 1580 (m), 1458 (s), 1440 (s), 12.69 (s), 778 (m), 7444 (w) cm^{-1}; mass spectrum (70 eV), *m/e* (rel intensity) 288 (64), 246 (42), 245 (100), 216 (75), 215 (95), 175 (51), 161 (92), 91 (40), 83 (47), 55 (86).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.73; H, 8.40.

General Procedure for Preparation of *tert*-Butyldimethylsilyl Enol Ethers 21b and 22b. To a solution of lithium dialkylamide (0.382 mmol) in THF (2.5–5 mL) in a 10–25-mL round-bottom flask, under argon, was added a solution of **19** (100 mg, 0.347 mmol) in THF (2 mL) all at once. After 2 h, a solution of *tert*-butyldimethylsilyl chloride (63.3 mg, 0.420 mmol) in THF was added all at once, followed immediately by the addition of HMPA (0.603 mL, 3.47 mmol). The reaction mixture was then brought to 25 °C. After 3–6 h, the reaction mixture was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate (4×) and saturated aqueous sodium chloride (1×), dried over potassium carbonate, and rotary evaporated to give an oil. Eluted first from column chromatography (10:1 hexane:ether containing 5% triethylamine) was a mixture of **21b** and **22b**, followed by **19**.

Characterization of a Typical Mixture of 21b/22b. The product listed in Table I, entry 3 was isolated by column chromatography as a clear colorless oil (0.110 g, 79%): ^1H NMR ($CDCl_3$, 90 HMz) δ −0.18, −0.11 (s, $Si(CH_3)_2$, 4.63 H), 0.07 (br s, $Si(CH_3)_2$, 1.37 H), 0.90–0.93 (s, $SiC(CH_3)_3$, 9 H), 0.70–0.98 (CH_3, 3 H), 0.24–1.54 (m, CH_2CH_2, 4 H), 2.41–3.45 (m, $ArCH_2CHCH$, $CH_2CH{=}CH_2$, 6 H), 3.86 (s, OCH_3, 3 H), 4.80 (t, C=C*H*, 0.85 H, J = 7.2 Hz), 4.89–5.26 (m, $C{=}CHCH_2CH{=}CH_2$, 2.15 H), 5.68–6.08 (m, $CH_2{=}CH$, 1 H), 6.80–7.31 (m, Ar*H*, 3 H); IR (neat) 1655 (w, C=C), 1640 (w, C=C), 1580 (m), 1462 (m), 1260 (s), 843 (s), 786 (s) cm^{-1}.

Preparation of Trimethylsilyl Enol Ethers 21a and 22a. To a solution of 2,2,6,6-tetramethylpiperidide (5.34 mmol) in THF (50 mL) in a 100-mL round-bottom flask, at −78 °C, under argon, was added a solution of **19** (1.03 g, 3.56 mmol) in THF (10 mL) all at once. After 2 h at −78 °C, chlorotrimethylsilane (0.745 mL, 5.87 mmol) was added to the solution all at once. The reaction mixture was then warmed to 25 °C for 5 h. After dilution with ether, the solution was washed sequentially with 5% aqueous sodium bicarbonate (2×) and aqueous sodium chloride, dried over potassium carbonate, and rotary evaporated to give a mixture of **21a/22a** as a yellow oil (1.48 g): ^1H NMR ($CDCl_3$, 60 MHz) δ 0.10 (s, $Si(CH_3)_3$, 3.91 H), 0.26 (s, $Si(CH_3)_3$, 5.09 H), 0.78–1.88 (m, $CH_2CH_2CH_3$, 7 H), 2.48–3.60 (m, $ArCH_2CHCH$, $CH_2CH{=}CH_2$, 6 H), 3.94 (s, OCH_3, 3 H), 4.70–5.40 (m, $CH{=}CH_2$, $C{=}CH$, 3 H), 5.60–6.20 (m, $CH{=}CH_2$, 1 H), 6.72–7.33 (m, Ar*H*, 3 H); IR (neat) 1653 (m, C=C), 1637 (m, C=C), 1578 (m), 1253 (s), 1146 (m), 847 (s) cm^{-1}.

General Procedure for Cyclization of Silyl Enol Ethers 21 and 22. To a solution of an *Z*/*E* mixture of silyl enol ethers (**21a/22a** or **21b/22b**) (1.0 mmol) in dichloromethane (14 mL) at 25 °C under argon was added freshly distilled boron trifluoride etherate (0.12 mL, 1.0 mmol) all at once. After 5 min, 5% aqueous sodium bicarbonate was added. Dilution with ether, followed by sequential washing of the organic layer with 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride gave a solution which was dried over potassium carbonate and rotary evaporated. Analytical TLC (hexane:ether = 2:1) showed two major spots at R_f 0.42 and R_f 0.20. Column chromatography (hexane:ether = 2:1) gave as a first eluent spectroscopically pure 5-(3-butenyl)-7,8-dihydro-1-methoxy-5,8-epoxy-9*H*-6-oxabenzocycloheptane, **25**, as a colorless oil. The analytical sample was obtained by MPLC (hexane:ether = 10:1) followed by short-path distillation (25–170 °C (0.1 mm)): ^1H NMR ($CDCl_3$, 90 MHz) δ 0.88 (br t, CH_3, 3 H, J = 6 Hz), 1.20–1.61 (m, CH_2CH_2, 4 H), 2.18–2.41 (m, $H_2C{=}CHCH_2CH_2$, 4 H), 2.72 (d, ArC*H*H, 1 H, J = 18.0 Hz), 3.12 (dd, ArCH*H*, 1 H, J = 18.0, 5.0 Hz), 3.82 (s, OCH_3, 3 H), 3.96–4.27 (m, OC*H*, 1 H), 4.76 (dd, OC*H*, 1 H, J = 5.0 Hz), 4.85–5.22 (m, $CH{=}CH_2$, 2 H), 5.72–6.20 (m, $CH{=}CH_2$, 1 H), 6.67–7.28 (m, Ar*H*, 3 H); ^{13}C NMR ($CDCl_3$) 14.00, 20.17, 24.89, 27.49, 32.96, 33.44, 55.28, 75.65, 80.25, 104.95, 109.29, 114.22, 114.54, 120.28, 126.51, 138.60, 141.29, 157.01; IR (neat) 1641 (w, C=C), 1590 (m), 1477 (s), 1263 (s), 1079 (s), 1024 (s), 792 (m) cm^{-1}; mass spectrum, *m/e* 288 (M^+, 38), 245 (100), 216 (51), 215 (39), 175 (35), 161 (60), 131 (15), 103 (16), 86 (31), 84 (48).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.94; H, 8.39.

The second eluent gave a spectroscopically pure mixture of **23** and **24**. The ratio of these diastereomers was determined by analytical HPLC (hexane:ethyl acetate = 10:1); see Table II. Typical retention times for **23** were 13.5 min, for **24** 11.1 min. The cis diastereomer, **23**, was obtained analytically pure as white plates (mp 130.5–131.5 °C) by recrystallization (ether:chloroform = 10:1): ^1H NMR ($CDCl_3$, 90 MHz) δ 0.94 (br t, CH_3, 3 H, J = 7 Hz), 1.30–1.80 (m, CH_2CH_2, 4 H), 2.10–3.32 (m, $ArCH_2CHCHCH_2$, 6 H), 3.70–4.00 (m, OC*H*, 1 H), 3.86 (s, OCH_3, 3 H), 4.86–5.14 (m, $CH{=}CH_2$, 2 H), 5.57–6.08 (m, $CH{=}CH_2$, 1 H), 6.98 (dd, Ar*H*, 1 H, J = 8.1, 1.3 Hz), 7.24 (dd, Ar*H*, 1 H, J = 8.1, 8.1 Hz), 7.57 (dd, Ar*H*, 1 H, J = 7.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.94, 18.76, 22.39, 29.98, 37.40, 42.17, 49.59, 55.55, 71.80, 114.00, 116.44, 118.61, 126.79, 131.34, 133.39, 136.16, 156.74, 199.76. IR ($CHCl_3$) 3475 (br w, OH), 1685 (s, C=O), 1642 (w, C=C), 1600 (m), 1588 (m), 1473 (m), 1262 (s), 922 (m) cm^{-1}; mass spectrum, *m/e* 288 (M^+, 32), 270 ($M^+ - H_2O$, 6), 227 (9), 215 (51), 187 (31), 175 (83), 115 (20), 95 (100), 68 (76), 55 (91).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.45.

Oxypalladation–Carbonylation of 27 To Give Methyl *cis*- and *trans*-(1-Methylisochroman-3-yl)acetate (30a, 30b). Cupric chloride (168 mg,

1.23 mmol), palladous chloride (10.9 mg, 0.0616 mmol), and **27** (100 mg, 0.616 mmol) were placed in a 10-mL round-bottom flask. The flask was placed under vacuum (0.1 mm) and then filled with carbon monoxide via a filled rubber balloon. Anhydrous methanol (2 mL) was then added via syringe. After 30 min at 25 °C, the initially green-brown suspension was a bright yellow solution. After a total reaction time of 2 h, analytical TLC (hexane:ether = 1:1) showed disappearance of **27** (R_f 0.36) and the appearance of a new spot (R_f 0.40). The methanol was removed in vacuo and the residue was triturated with ether (5×). Filtration of the combined ether extracts through a plug of silica gel followed by rotary evaporation gave a mixture of **30a/30b** as a yellow oil (112 mg, 82%). Analytical HPLC (hexane:ethyl acetate = 100:2) showed two peaks in the ratio 2.8:1 of retention times 8.54 and 12.16 min. MPLC (hexane:ether = 2:1) gave a first eluent containing a clear colorless oil, **30a** (60 mg): ^{1}H NMR δ 1.52 (d, CH_3, 3.0 H, J = 6.6 Hz), 2.54–2.92 (m, ArCH_2, $CH_2CO_2CH_3$, 4.0 H), 3.72 (s, CO_2CH_3, 3.0 H), 3.96–4.33 (m, O$CH$$CH_2CO_2CH_3$, 1.1 H), 4.87 (br q, Ar$CH$O, 1.1 H, J = 6.8 Hz), 6.94–7.32 (m, ArH, 4.3 H); irradiation at δ 7.19 collapsed the broad quartet at δ 4.87 to a quartet of doublets of doublets (J = 6.8, 1.5, 1.3 Hz); ^{13}C NMR ($CDCl_3$) 21.74, 34.58, 41.08, 51.65, 70.99, 73.42, 124.40, 126.35, 128.68, 133.02, 139.25, 171.53; IR (neat) 1739 (s, C=O), 1492 (w), 1438 (m), 1219 (m), 1160 (m), 1101 (m) cm^{-1}; mass spectrum, m/e 220 (M^+, 15), 205 (63), 202 (93), 147 (85), 146 (100), 145 (86), 118 (68), 117 (98), 91 (59), 83 (61); mass spectral M_r calcd for $C_{13}H_{16}O_3$, 220.1099; found, 220.1098.

The second eluent gave **30b** as a clear colorless oil (23 mg): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.52 (d, CH_3, 3 H, J = 6.8 Hz), 2.52–2.84 (m, benzylic ArCH_2, $CH_2CO_2CH_3$, 4 H), 3.72 (s, CO_2CH_3, 3 H), 4.20–4.53 (m, O$CH$$CH_2CO_2CH_3$, 1 H), 5.01 (q, Ar$CH$O, 1 H, J = 6.8 Hz), 6.91–7.26 (m, ArH, 4 H); irradiation at δ 7.11 produced no significant change in the quartet at δ 5.01; ^{13}C NMR ($CDCl_3$) 21.85, 33.88, 40.49, 51.59, 64.81, 70.99, 125.21, 126.14, 126.30, 128.79, 132.31, 138.92, 171.48; IR ($CHCl_3$) 1739 (s, C=O), 1493 (w), 1439 (m), 1302 (m), 1159 (m), 1099 (s) cm^{-1}; mass spectrum, m/e 220 (M^+, 11), 205 (65), 202 (100), 147 (65), 146 (64), 145 (89), 131 (40), 119 (44), 118 (44), 117 (89), 91 (37).

Oxypalladation–Carbonylation of 27 in *tert*-Butyl Alcohol To Give Isomeric *tert*-Butyl (1-Methylisochroman-3-yl)acetates (31a/31b). Cupric chloride (0.134 g, 1.00 mmol), palladous chloride (0.005 g, 0.028 mmol), and **27** (81.1 mg, 0.500 mmol) were placed in a 10-mL round-bottom flask. The flask was placed under vacuum (0.1 mm) and then filled with carbon monoxide via a filled rubber balloon. Anhydrous *tert*-butyl alcohol (1.5 mL) was then added via syringe. After 24 h, the resulting tan suspension was analyzed by analytical TLC (hexane:ether = 1:1). The starting material, **27** (R_f 0.33), was absent and a new spot was present (R_f 0.61). Removal of *tert*-butyl alcohol in vacuo gave a dark residue which was triturated with ether (5×). The combined ether extracts were filtered through a plug of silica gel and concentrated to give a yellow oil (0.114 g, 87%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.47 (s, $C(CH_3)_3$, 9 H), 2.43–2.89 (m, ArCH_2, $CH_2CO_2CH_3$, 4 H), 3.91–4.45 (m, O$CH$$CH_2CO_2CH_3$, 1 H), 4.66–5.27 (m, Ar$CH$O, 1 H), 7.01 (br s, Ar$H$, 4 H); IR ($CHCl_3$) 1729 (s, C=O), 1492 (m), 1447 (m), 1367 (s), 1152 (s), 1103 (s), 1040 (s) cm^{-1}.

Oxypalladation–Carbonylation of 28 To Give Methyl (2*RS*,3*SR*)-2-(isochroman-3-yl)propanoate (32a). Cupric chloride (0.402 g, 3.0 mmol), palladous chloride (17.7 mg, 0.10 mmol), and **28** (0.162 g, 1.0 mmol) were placed in a 10-mL round-bottom flask. The flask was placed under vacuum (0.1 mm) and then filled with carbon monoxide via a filled rubber balloon. Anhydrous methanol (3 mL) was then added. After 24 h, the dark reaction was checked by analytical TLC (hexane:ether = 1:1). Starting material, **28** (R_f 0.32) was almost absent and a new spot was present (R_f 0.51). Removal of methanol in vacuo gave a dark residue which was triturated with ether (5×). The ether extracts were combined, filtered through a plug of silica gel, and rotary evaporated to give a pale yellow oil (0.204 g). Column chromatography of this material (6.5 silica gel, hexane:ether = 3:2) gave a small amount (8 mg) of recovered **28**, followed by **32a** as a clear colorless oil (0.185 g, 84%): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.31 (d, CH_3, 3 H, J = 6.8 Hz), 2.48–2.92 (m, $CHCO_2CH_3$, ArCH_2, 3 H), 3.70 (s, CO_2CH_3, 3 H), 3.67–3.99 (m, OCH, 1 H), 4.82 (br s, ArCH_2O, 2 H), 6.87–7.28 (m, ArH, 4 H); ^{13}C NMR ($CDCl_3$) δ 12.86, 31.39, 44.71, 5.48, 68.29, 75.59, 123.92, 125.87, 126.24, 128.74, 132.75, 134.26, 174.46; IR (neat) 1738 (s, C=O), 1589 (w), 1493 (w), 1456 (m), 1435 (m), 1088 (s), 750 (s) cm^{-1}; mass spectrum, m/e 220 (M^+, 15), 202 (36), 189 (14), 143 (24), 133 (81), 132 (95), 105 (88), 104 (100), 91 (17), 88 (35).

Oxypalladation–Carbonylation of 29 To Give Methyl (2*RS*,3*RS*)-2-(Isochroman-3-yl)propanoate (32b). Cupric chloride (0.154 g, 1.15 mmol), palladous chloride (6.8 mg, 0.038 mmol), and **29** (62 mg, 0.38 mmol) were placed in a 10-mL round-bottom flask. The flask was placed under vacuum (0.1 mm) and then filled with carbon monoxide via a filled rubber balloon. Anhydrous methanol (1.2 mL) was then added. After 25 h, the methyl alcohol was removed in vacuo to give a dark residue which was triturated with ether (5×). The ether extracts were combined, filtered through a plug of silica gel, and rotary evaporated to give a yellow oil. Column chromatography (4 g of silica gel, hexane:ether = 2:1) gave a clear colorless oil (67.3 mg, 80%). Analytical TLC (hexane:ether = 3:2) indicated a major component (**32b**) of R_f 0.32 and a faint spot of R_f 0.40 assigned to diastereoisomer **32a**. The minor isomer was shown to be present in less than 5% by analysis of the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.21 (d, CH_3, 3.0 H, J = 7.3 Hz), 2.52–2.89 (m, ArCH_2, $CHCO_2Me$, 3.1 H), 3.72 (s, CO_2CH_3, 3.0 H), 3.68–4.05 (m, OCH, 1.0 H), 4.79 (br s, ArCH_2O, 2.0 H), 6.90–7.29 (m, ArH, 4.2 H); ^{13}C NMR ($CDCl_3$) 12.80 (q, CH_3), 30.90 (t, ArCH_2), 45.20 (d, $CHCO_2Me$), 51.59 (q, CO_2CH_3), 68.28 (t, ArCH_2O), 76.19 (d, OCH), 124.02 (d), 125.97 (d), 126.30 (d), 128.79 (d), 132.53 (s), 134.48 (s), 175.05 (s, CO_2CH_3); IR (neat) 1736 (s, C=O), 1494 (w), 1457 (m), 1165 (s), 1100 (m), 751 (m) cm^{-1}; mass spectrum, m/e 220 (M^+, 15), 202 (37), 189 (15), 143 (27), 133 (82), 132 (80), 105 (91), 104 (100), 91 (17), 88 (33); mass spectral M_r calcd for $C_{13}H_{16}O_3$, 220.1099; found, 220.1111.

Preparation of 2-Allylbenzaldehyde. To a 100-mL round-bottom flask equipped with a reflux condenser and containing magnesium turnings (0.892 g, 36.7 mmol) in THF (4 mL) under argon at 25 °C was added a solution of the tetrahydropyranyl ether of *o*-bromobenzyl alcohol (9.04 g, 33.4 mmol) in THF (11 mL) portionwise over 20 min. After the addition was complete, the mixture was heated at reflux for 1.5 h and then cooled to 25 °C. A solution of allyl bromide (3.76 mL, 43.4 mL) in THF (7 mL) was added dropwise over 20 min. After the addition was complete, the reaction mixture was heated at reflux for 30 min and then cooled to 25 °C. After 12 h, saturated aqueous ammonium chloride (20 mL) was added portionwise over 20 min. Filtration through a plug of Celite to remove the salts and rotary evaporation gave an oil which was combined with a 1 M aqueous hydrochloric acid:methanol (1:1) solution. After 24 h, the reaction mixture was diluted with ether and washed with water (3×); the ether solution was dried over magnesium sulfate and rotary evaporated to give 2-allylbenzyl alcohol as an oil (3.09 g, 63%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.27 (br s, OH, 1 H), 3.41 (br dd, ArCH_2, 2 H, J = 6, 1 Hz), 4.55 (br s, ArCH_2O, 2 H), 4.65–5.15 (m, CH=CH_2, 2 H), 5.45–6.29 (m, CH=CH_2, 1 H), 7.15 (br s, ArH, 4 H).

By use of the procedure of Corey and Suggs,[43] 2-allylbenzyl alcohol (3.09 g, 20.9 mmol) and pyridinium chlorochromate (6.76 g, 31.4 mmol) in dichloromethane (63 mL) at 25 °C for 30 min gave 2-allylbenzaldehyde as a clear colorless oil (2.65 g, 85%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.80 (br d, ArCH_2, 2 H, J = 6 Hz), 4.6–5.2 (m, CH=CH_2, 2 H), 5.65–6.35 (m, CH=CH_2, 1 H), 7.0–7.9 (m, ArH, 4 H), 10.1 (s, CHO, 1 H). We are unaware of characterization data published for this compound. It was used directly without further characterization.

Preparation of 2-Allyl-α-methylbenzyl Alcohol (27). To a solution of *o*-allylbenzaldehyde (2.65 g, 18.2 mmol) in THF (30 mL) in a 100-mL round-bottom flask under argon at −78 °C was added methyllithium (20 mmol, 13.9 mL of a 1.44 M ether solution) dropwise over 15 min via a syringe pump. After an additional 15 min, saturated aqueous ammonium chloride was added. The resulting mixture was warmed to 25 °C, diluted with ether, washed with water (2×), dried over magnesium sulfate, and rotary evaporated. The resulting slightly yellow oil (2.7 g) was purified by MPLC (hexane:ether = 2:1) followed by short-path distillation (24–120 °C (0.1 mm)) to give **27** as a clear colorless oil (1.65 g, 56%): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.32 (d, CH_3, 3.0 H, J = 6.4 Hz), 3.33 (br d, ArCH_2, OH, 3.1 H, J = 6.2 Hz), 4.78–5.15 (m, CH=CH_2, ArCH, 3.2 H), 5.68–6.17 (m, CH=CH_2, 1.2 H), 6.96–7.32 (m, ArH, 3.1 H), 7.34–7.57 (m, ArH, 1.2 H); ^{13}C NMR ($CDCl_3$) 24.18, 36.32, 65.73, 115.52, 125.05, 126.51, 127.00, 129.43, 135.67, 137.29, 143.58; IR (neat) 3340 (br s, OH), 1638 (w, C=C), 1485 (w), 1448 (m), 1070 (s), 1000 (m), 912 (s), 716 (s) cm^{-1}; mass spectrum, m/e 147 ($M^+ - CH_3$, 22), 145 (12), 144 ($M^+ - H_2O$, 48), 130 (16), 129 (100), 128 (28), 117 (15), 115 (24), 91 (25), 77 (10).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.22; H, 8.72.

Preparation of 2-((*E*)-But-2-en-1-yl)benzyl Alcohol (28). A solution of the tetrahydropyranyl ether of *o*-bromobenzyl alcohol (5.0 g, 18.4 mmol) in THF (15 mL) was added dropwise over 10 min to magnesium turnings (0.49 g, 20.2 mL) in THF (5 mL) in a 50-mL round-bottom flask equipped with a reflux condenser and under argon. After the addition was complete, the brown suspension was heated at reflux for 1 min and then cooled to 25 °C. After 30 min, (*E*)-1-bromo-2-butene[41] (3.23 g, 23.9 mmol) was added all at once. A vigorous exothermic reaction took place, and after 10 min, a white precipitate appeared. After 3 h, the reaction mixture was treated with saturated aqueous ammonium

(43) Corey, E. J.; Suggs, W. *Tetrahedron Lett.* **1975**, 2647.

chloride, diluted with ether, and washed with water. Rotary evaporation gave a yellow oil which was treated with a 1 M aqueous hydrochloric acid:methanol (1:1) solution (20 mL) for 2 h at 25 °C to hydrolyze the tetrahydropyranyl ether. The methanol was then removed by rotary evaporation and the residual material was diluted with ether. The organic layer was washed sequentially with 5% aqueous sodium bicarbonate (2×), water (1×), and saturated aqueous sodium chloride (1×) and then dried over magnesium sulfate. Rotary evaporation gave a yellow oil (3.9 g) which showed only one UV-active spot (R_f 0.42) by analytical TLC (hexane:ether = 1:1). Purification by MPLC (hexane:ether = 2:1), followed by short-path distillation (25–150 °C (0.1 mm)), gave **28** as a clear, colorless oil (1.96 g, 66%): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.62 (br d, CH_3, 2.7 H, J = 4.0 Hz), 3.27 (br d, $ArCH_2$, OH, 2.8 H, J = 4.3 Hz), 4.52 (br d, $ArCH_2OH$, 2.0 H, J = 5.0 Hz), 5.10–5.80 (m, CH=CH, 2.0 H), 6.98–7.28 (m, ArH, 3.9 H); ^{13}C NMR ($CDCl_3$) 17.63 (q, CH_3), 35.29 (t, $ArCH_2$), 62.37 (t, $ArCH_2OH$), 126.08 (d), 127.49 (d), 127.76 (d), 127.76 (d), 129.28 (d), 129.66 (d), 138.38 (s); IR (neat) 3320 (br s, OH), 1603 (w), 1450 (s), 1005 (s), 970 (s), 755 (s) cm^{-1}; mass spectrum, m/e 162 (M^+, 2), 145 (13), 144 (51), 143 (13), 130 (16), 129 (100), 128 (26), 119 (19), 115 (20), 91 (25).

Preparation of 2-((*Z*)-But-2-en-1-yl)benzyl Alcohol (29). A solution of the tetrapyranyl ether of *o*-bromobenzyl alcohol (5.0 g, 18.4 mmol) in THF (15 mL) was added dropwise over 5 min to magnesium turnings (0.49 g, 20.2 mmol) in THF (5 mL) in a 40-mL round-bottom flask equipped with a reflux condenser and under argon. The reaction mixture was briefly heated at reflux (5 min) and then cooled to 25 °C. Propargyl bromide (2.35 mL, 21 mmol) was then added dropwise over 5 min. After 6 h at 25 °C, the resulting suspension was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate (2×) and water (1×), dried over potassium carbonate, and rotary evaporated. The residual dark red oil (3.97 g) showed a single UV-active spot by TLC (hexane:ether = 5:1), expected to be the tetrahydropyranyl ether of 2-(2-propyn-1-yl)benzyl alcohol.

A solution of the product of the above reaction in THF (20 mL) was added all at once to a solution of lithium diisopropylamide (20 mmol) in THF (50 mL) at −78 °C in a 200-mL round-bottom flask under argon. The reaction mixture immediately turned black. After 45 min at −78 °C, iodomethane (1.25 mL, 20 mmol) was added all at once. The reaction mixture was allowed to warm to 25 °C. After 4 h, dilution with ether, sequential washing with 5% aqueous sodium bicarbonate (2×) and water, and rotary evaporation gave an oil. Hydrolysis of the tetrahydropyranyl ether by treatment with a methanol:THF:1 M aqueous hydrochloric acid solution (5:2:1, 160 mL) gave, after aqueous extraction procedures, a dark orange oil. Purification by MPLC (hexane:ether = 1:1) afforded an orange oil (0.9 g) whose ^{1}H NMR spectrum showed a small amount of residual benzyl alcohol. Short-path distillation (80–150 °C (0.1 mm)) gave 2-(but-2-yn-1-yl)benzyl alcohol as a white semisolid (311 mg, 11%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.75 (t, CH_3, 3.0 H, J = 1.8 Hz), 2.55 (br s, OH, 1.1 H), 3.48 (q, $ArCH_2$, 2.0 H, J = 1.8 Hz), 4.50 (s, $ArCH_2OH$, 2.1 H), 7.13 (br s, ArH, 4.3 H).

Lindlar catalyst[44] (5% palladium on calcium carbonate, poisoned with lead, 20 mg) was added to a solution of the 2-(but-2-yn-1-yl)benzyl alcohol (108 mg, 0.675 mmol) in methanol (2 mL). Hydrogen gas was then bubbled into the dark suspension for 30 min. Filtration through Celite and rotary evaporation gave a yellow oil (130 mg). Column chromatography (6 g silica gel, hexane:ether = 3:1) gave pure **29** as a clear, colorless oil (71 mg, 65%): ^{1}H NMR ($CDCl_3$, 90 MHz) 1.71 (br d, CH_3, 3.1 H, J = 5.1 Hz), 2.16 (br s, OH, 1.1 H), 3.42 (br d, $ArCH_2$, 2.0 H, J = 4.7 Hz), 4.64 (br s, $ArCH_2OH$, 1.8 H), 5.29–5.79 (m, CH=CH, 2.1 H), 7.04–7.43 (m, ArH, 4.5 H); ^{13}C NMR ($CDCl_3$) δ 12.80, 30.03, 63.02, 124.89, 126.30, 127.92, 128.09, 128.84, 129.22, 138.54, 139.08; IR (neat) 3320 (br s, OH), 1660 (w, C=C), 1603 (w), 1453 (m), 1211 (m), 1006 (s), 756 (s), 696 (m) cm^{-1}; mass spectrum, m/e 162 (M^+, 2), 144 (53), 143 (10), 130 (15), 129 (100), 128 (22), 120 (11), 119 (17), 115 (18), 91 (26); mass spectral M_r calcd for $C_{11}H_{14}O$, 162.1045; found, 162.1041.

Oxypalladation–Carbonylation of 23 To Give Methyl (1*RS*,3*RS*,4a*RS*,9a*RS*)-(1,3,4,4a,9,9a-Hexahydro-8-methoxy-10-oxo-1-propyl-2-oxa-3-anthryl)acetate (33). A 50-mL round-bottom flask under vacuum (0.01 mm) containing palladous chloride (62 mg, 0.347 mmol) and cupric chloride (1.39 g, 10.41 mmol), and equipped with a solid addition funnel charged with **23** (1.0 g, 3.47 mmol), was filled with carbon monoxide by attachment of a filled rubber balloon. Anhydrous methanol (10 mL) was then added at 25 °C. To the resulting green suspension, **23** was added portionwise over 2 h (after 5–10 min the reaction mixture turned dark brown). After the addition was complete, the reaction mixture was stirred for 1 h. The methanol was then removed in vacuo and the residual dark solid was triturated with ether (5×). The ether extracts were combined and filtered through a plug of silica gel. Rotary evaporation gave a solid (1.02 g). Column chromatography (20 g of silica gel, hexane:ether = 1:1) yielded a yellow oil, 0.908 g, 97% (analysis by analytical HPLC showed a single peak). Repeated crystallization of this material from hexane:ether = 10:1 gave fine white needles (mp 87.5–88.5 °C) in 81% yield (0.756 g): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.95 (t, CH_3, 3 H, J = 5.9 Hz), 1.14–1.84 (m, CH_2CH_2, $ArCOCHCH_2$, 6 H), 1.98–2.35 (m, $ArCH_2CH$, 1 H), 2.40–2.60 (m, $CH_2CO_2CH_3$, 2 H), 2.40–3.00 (m, $ArCH_2$, $ArCOCH$, 3 H), 3.3–3.6 (m, OCH, 1 H), 3.68 (s, CO_2CH_3, 3 H), 3.7–4.0 (m, OCH, 1 H), 3.88 (s, OCH_3, 3 H), 7.07 (dd, *o*-methoxy ArH, J = 1.3, 7.9 Hz), 7.30 (dd, *m*-methoxy ArH, J = 7.7, 7.7 Hz), 7.71 (dd, *p*-methoxy ArH, J = 1.3, 7.9 Hz); ^{13}C NMR ($CDCl_3$) 13.89, 17.73, 19.09, 29.06, 34.15, 35.34, 41.03, 47.58, 51.43, 55.55, 73.64, 79.00, 114.33, 118.98, 126.73, 131.77, 132.09, 157.18, 171.10, 199.49; IR ($CHCl_3$) 1737 (s, CO), 1680 (s, CO), 1600 (m), 1584 (m), 1300 (s), 1255 (s) cm^{-1}; mass spectrum, m/e 346 (M^+, 57), 272 (50), 240 (13), 201 (73), 200 (33), 175 (43), 174 (100), 159 (21), 115 (21), 103 (17).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.35; H, 7.66.

A mixture of **23** and **24** in a ratio of 82:18, respectively (0.496 g, 1.72 mmol), was treated as above. An orange oil (0.569 g) was obtained. Column chromatography (10 g of silica gel, hexane:ether = 1:1) gave a yellow oil (0.516 g, 87%). The ^{1}H NMR spectrum of this material was similar to that of **23** obtained above. Analytical HPLC (hexane:ethyl acetate = 10:1, 4 mL/min) showed peaks at 7.79 min and 8.62 min whose areas were in a ratio of 81:19, respectively. The major product had the same retention time as **33**; the minor product is assumed to be a diastereoisomer, but was not obtained pure (see Discussion section).

Attempted Bromination of 33 with *N*-Bromosuccinimide. To a solution of **33** (22 mg, 0.0635 mmol) in carbon tetrachloride (0.5 mL) was added *N*-bromosuccinimide (NBS, 11.3 mg, 0.0635 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.4 mg). The NBS was insoluble and remained at the bottom of the reaction vessel. A reflux condenser was attached and the system was flushed with argon. The reaction mixture was irradiated with a sunlamp (General Electric, 275 W), causing it to reflux. After 30 min, a bright yellow-orange solution with a white solid (succinimide) floating on top resulted. The sunlamp was removed and the reaction mixture cooled to 25 °C. Filtration and rotary evaporation gave a clear bright orange oil (26 mg). Analysis by TLC (hexane:ether = 2:1) showed a single spot corresponding to **33** at R_f 0.39, plus smearing from the baseline to R_f 0.5. The ^{1}H NMR spectrum ($CDCl_3$, 90 MHz) contained predominantly signals assigned to **33**. No peaks were present in the region δ 4.0–5.0.

Attempted Oxidation of 33 with Benzene Seleninic Anhydride. A solution of **33** (5 mg, 0.0144 mmol) and benzene seleninic anhydride[32] (20 mg, 0.056 mmol) in chlorobenzene (0.5 mL) was heated at reflux for 2 h. Analytical TLC (hexane:ether = 1:1) showed **33** (R_f 0.27) and a minor yellow spot (R_f 0.14). Heating at reflux for an additional 17 h gave a red solution. Analytical TLC showed mostly **33** (R_f 0.27) and more than five polar products appearing from the origin to R_f 0.14.

Attempted Oxidation of 33 with Selenium Dioxide. To a solution of **33** (7.1 mg, 0.021 mmol) in dioxane (0.1 mL) was added selenium dioxide (7.4 mg, 0.067 mmol). The resulting pale yellow suspension was heated at reflux for 28 h. Analytical TLC (hexane:ether = 1:1) showed mainly **33** (R_f 0.35) plus a minor spot of R_f 0.24. Rotary evaporation, dilution with ether, and washing with water gave a solution which was dried over magnesium sulfate. Concentration gave an oil (8.8 mg). The ^{1}H NMR spectrum ($CDCl_3$, 90 MHz) showed signals assigned to **33** and no significant additional signals.

Attempted Aromatization of 33 with 10% Palladium on Carbon. To a solution of **33** (50 mg, 0.145 mmol) in *p*-cymene (0.3 mL) was added 10% palladium on carbon (50 mg). The black suspension was heated at reflux for 68 h and then cooled to 25 °C, filtered through a plug of Celite, and rotary evaporated. Analytical TLC (hexane:ether = 1:1) showed a single discrete spot corresponding to **33**; the ^{1}H NMR spectrum ($CDCl_3$, 60 MHz) confirmed essentially complete recovery of **33**.

Attempted Aromatization of 33 with Selenium. To a solution of **33** (100 mg, 0.289 mmol) in 1-methylnaphthalene (1 mL) was added selenium powder (100 mg, 1.27 mmol). The suspension was heated at reflux under argon for 115 h and then cooled to 25 °C. A clear orange-brown solution with a black precipitate resulted. Filtration through a plug of Celite and rotary evaporation gave an oil which showed a spot at R_f 0.33 corresponding to **33**, a minor spot at R_f 0.18, and a spot at the base line. Column chromatography (8 g of silica gel, hexane:ether = 2:1) gave **33** (80.6 mg) and a small amount of material (1.6 mg) which corresponded to R_f 0.18 and which was not identified.

Preparation of Methyl (1*RS*,3*RS*,9a*RS*)-(1,3,9,9a-Tetrahydro-8,10-dimethoxy-1-propyl-4*H*-2-oxa-3-anthryl)acetate (37). A solution of **33** (1.22 mmol, 421 mg), trimethyl orthoformate (12.2 mmol, 1.33 mL),

(44) Available from Aldrich Chemical Co.

methanol (2.5 mL), and *p*-toluenesulfonic acid monohydrate (0.12 mmol, 23 mg) was stirred at 25 °C for 20 h. Additional trimethyl orthoformate (4.6 mmol, 0.5 mL) and *p*-toluenesulfonic acid monohydrate (0.05 mmol, 9 mg) were added, and the reaction mixture was stirred an additional 10 h. Triethylamine (1 mL) was added, and the reaction was diluted with ether and washed with 5% aqueous sodium bicarbonate (3×). The organic layer was dried over potassium carbonate and concentrated to give the acetal as a viscous yellow oil (516 mg). The ^{1}H NMR spectrum ($CDCl_3$, 60 MHz) showed four singlets of equal intensity at δ 2.98 (acetal OCH_3), 3.34 (acetal OCH_3), 3.63 (CO_2CH_3), 3.82 ($ArOCH_3$). It was not further characterized.

A solution of the oil obtained from the above reaction was dissolved in anhydrous benzene (100 mL) in a 250-mL one-necked round-bottom flask to which a simple distillation apparatus was attached. A rubber septum was placed over the thermometer opening. The apparatus was flushed with argon and the benzene solution was heated until distillation began. After approximately 10 mL of benzene had distilled, a solution of *p*-toluenesulfonic acid (0.122 mmol, 21 mg) in anhydrous benzene was added portionwise via syringe through the septum over 45 min. The rate of distillation was maintained so that after the addition was complete, approximately 10 mL of solution remained. The reaction mixture was then cooled to 25 °C, and triethylamine (2 mL) was added. The solution was diluted with ether, washed with 5% aqueous sodium bicarbonate (3×), dried over potassium carbonate, and concentrated to give a cloudy yellow oil (491 mg). Column chromatography (20 g of silica gel, hexane:ether = 2:1 containing 5% triethylamine) gave **37** as a clear colorless oil which slowly solidified to a white solid (404 mg, 92%). The ^{1}H NMR spectrum showed this material to be >95% pure. Two recrystallizations (hexane:ether = 50:1) gave fine white needles (mp 81–82 °C, 167 mg) for characterization: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.96 (br t, CH_3, 2.6 H, J = 6.2 Hz), 1.16–1.76 (m, CH_2CH_2, 3.9 H), 2.19–3.10 (m, CH_2C-O_2CH_3, $ArCH_2CHCCH_2$, 6.9 H), 3.52–3.98 (m, OCH, 1 H), 3.60 (s, $COCH_3$, 3 H), 3.69 (s, CO_2CH_3, 3 H), 3.83 (s, $ArOCH_3$, 3 H), 4.32–4.64 (m, OCH, 1.0 H), 6.70–7.32 (m, ArH, 3.0 H); ^{13}C NMR ($CDCl_3$) 14.05 (q, CH_3), 19.63 (t), 19.90 (t), 24.46 (t), 33.61 (t), 37.78 (d), 41.08 (t), 51.38 (q, OCH_3), 55.44 (q, OCH_3), 59.77 (q, OCH_3), 70.12 (d, OCH), 74.07 (d, OCH), 109.83 (d), 114.49 (d), 120.23 (s), 124.29 (s), 126.51 (d), 132.15 (s), 149.97 (s), 156.42 (s), 171.42 (s, CO_2CH_3); IR ($CHCl_3$) 1730 (s, C=O), 1578 (m), 1458 (m), 1439 (m), 1310 (s), 1070 (s) cm^{-1}; mass spectrum, m/e 360 (M^+, 27), 329 (7), 288 (87), 287 (34), 273 (29), 241 (12), 214 (23), 200 (25), 188 (100), 173 (16).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.97; H, 7.78.

Treatment of the mixture of diastereomers obtained from oxypalladation–carbonylation of a mixture of **33**/**34** (82:18) as described above gave the dimethyl acetal as a yellow oil (670 mg). This was treated as above to give an orange oil (569 mg). Column chromatography (125 g of silica gel, hexane:ether = 2:1) gave the methyl enol ether as a pale yellow oil (410 mg, 76%). The ^{1}H NMR spectrum of this material was nearly superimposable on the spectrum obtained above. The starting ketone was also isolated (85 mg, 16%). This material was homogeneous by analytical TLC.

Phenylselenation of 37 To Give 38. To a solution of **37** (640 mg, 1.78 mmol) and silver trifluoroacetate[45] (562 mg, 2.54 mmol) in anhydrous benzene (40 mL) in a 100-mL round-bottom flask equipped with a magnetic stirbar, at 25 °C under argon, was added phenylselenenyl bromide[46] (2.54 mmol, 4.48 mL of a 0.568 M solution in benzene) all at once. After 2 min, the yellow heterogeneous reaction mixture was treated with saturated aqueous sodium chloride (2 mL) and aqueous potassium carbonate (414 mg, 3.0 mmol in 3 mL of water). After 5 min, the mixture was filtered through a plug of Celite and magnesium sulfate. The clear yellow eluent was rotary evaporated to give an orange oil. Analytical TLC (benzene:ether = 10:1) showed three components: R_f 0.65 (yellow), 0.43, and 0.36. MPLC (hexane:ether = 2:1) gave the major product, **38** (R_f 0.36), 655 mg, 74%, as a yellow foam: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.96 (br t, CH_3, 2.75 H, J = 5 Hz), 1.13–2.02 (m, CH_2CH_2, $ArCH_2CHCCH_2$, 7.5 H), 2.20–2.82 (m, ArCHH, CH_2CO_2C-H_3, 3.5 H), 3.08 (dd, ArCHH, 1.2 H, J = 4.3, 17.3 Hz), 3.67 (s, CO_2-CH_3, 3.2 H), 3.81 (s, OCH_3, 3.0 H), 4.20–4.62 (m, CHOCH, 2.0 H), 6.86–7.77 (m, ArH, 8.0 H); ^{13}C NMR ($CDCl_3$) 13.94, 18.71, 19.20, 33.61, 34.42, 40.00, 40.81, 51.48, 55.55, 58.69, 70.72, 75.81, 114.27, 119.85, 126.68, 127.06, 128.74, 130.96, 132.91, 137.62, 156.20, 170.88, 196.94; IR ($CHCl_3$) 1740 (s, C=O), 1679 (m, C=O), 1605 (m), 1593 (m), 1446 (s), 1270 (s), 1029 (m) cm^{-1}.

The methyl enol ether (386 mg, 1.07 mmol) derived from a mixture of **33**/**34** (82:18) was converted as above to give a bright yellow oil (625 mg). Column chromatography (21 g of silica gel, hexane:ether = 2:1) of this material gave a yellow oil (406 mg, 79%). The ^{1}H NMR spectrum of this material was superimposable to that listed above for **38**.

Preparation of Methyl (1*RS*,3*RS*)-(3,4-Dihydro-10-hydroxy-8-methoxy-1-propyl-1*H*-2-oxa-3-anthryl)acetate (36). Ozone was bubbled into a solution of **38** (324 mg, 0.648 mmol) in methylene chloride (25 mL) in a 50-mL pear-shaped flask at −78 °C. After 3 min, the initially yellow solution turned blue, indicating that excess ozone was present. Introduction of ozone into the reaction mixture was terminated. After 1 min, argon was bubbled into the blue solution until the blue color was gone (5 min). The resulting pale yellow solution was removed from the cooling bath and allowed to warm to 25 °C for 15 min. The bright yellow solution was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate (3×) and saturated aqueous sodium chloride (1×), dried over magnesium sulfate, and rotary evaporated to give a yellow oil (310 mg). Analytical TLC (hexane:ether = 1:1) showed a yellow spot at R_f 0.61 and spots at R_f 0.32, 0.24 (major), 0.19 and 0.07. Isolation of the material corresponding to R_f 0.24 by MPLC (hexane:ether = 2:1) gave **36** as a white powder (138 mg, 62%). This material was homogeneous by analytical TLC and its ^{1}H NMR spectrum showed it to be >95% pure. Recrystallization (hexane:ether = 5:1) gave a white powder (mp 127–128 °C; 124 mg): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.94 (t, CH_3, 2.8 H, J = 6.4 Hz), 1.23–2.23 (m, CH_2CH_2, 4.0 H), 2.36–3.05 (m, $ArCH_2$, $CH_2CO_2CH_3$, 3.9 H), 3.72 (s, CO_2CH_3, 3.0 H), 3.95 (s, OCH_3, 3 H), 3.90–4.27 (m, OCH, 1 H), 4.71–4.91 (m, ArCH, 1.0 H), 5.63 (br s, O-H, 1.0 H, disappears upon addition of deuterium oxide), 6.73 (d, ArH, 1.0 H, J = 7.47 Hz), 7.29 (dd, ArH, 1.0 H, J = 7.65, 7.56 Hz), 7.58 (d, ArH, 1 H, J = 7.2 Hz), 7.62 (br s, ArH, 1 H); ^{13}C NMR ($CDCl_3$) 13.94 (q, -CH_3), 18.38 (t), 29.00 (t), 37.89 (t), 41.30 (t), 51.76 (q, OCH_3), 55.44 (q, OCH_3), 70.88 (d, OCH-), 77.33 (d, OCH), 103.65 (d), 109.34 (d), 112.70 (d), 115.84 (s), 123.75 (s), 124.89 (d), 136.48 (s), 147.70 (s), 155.33 (s), 171.86 (s, C=O); IR ($CHCl_3$) 3600 (m, OH), 1732 (s, C=O), 1601 (m), 1502 (m), 1400 (s), 1261 (s), 1048 (m) cm^{-1}; mass spectrum, m/e 344 (M^+, 72), 326 (5), 302 (19), 301 (100), 283 (30), 242 (18), 241 (67), 227 (16), 213 (14), 201 (5).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.74; H, 7.03.

Treatment of the selenide (406 mg) derived from a mixture of **33**/**34** (82:18) as above gave a red oil (365 mg). MPLC (hexane:ether = 2:1) of this material gave an off-white solid (159 mg, 57%). The ^{1}H NMR and ^{13}C NMR spectra of this material were superimposable on the spectra obtained above for **36**.

Preparation of Methyl (1*RS*,3*RS*)-(3,4-Dihydro-8-methoxy-9,10-dioxo-1-propyl-1*H*-2-oxa-3-anthryl)acetate (35). To a stirring solution of **36** (149 mg, 0.433 mmol) in acetone (15 mL) at 25 °C was added Jones reagent[47] (0.97 mL, 2.60 mmol chromium trioxide). After 15 min, 2-propanol (1 mL) was added. The resulting greenish reaction mixture was diluted with ether, washed with 5% aqueous sodium bicarbonate (3×), dried over potassium carbonate, and concentrated to give a red oil (160 mg). Column chromatography (10 g of silica gel, hexane:ether = 1:1), gave **35** as a red oil which slowly crystallized (120 mg, 77%). Analysis by analytical HPLC (hexane:ethyl acetate = 45:1, 4 mL/min) showed a single peak (RT 33 min). The ^{1}H NMR spectrum of this material showed it to be >95% pure. Recrystallization (hexane:ether = 2:1) gave small red-brown diamond-shaped crystals (mp 146–147 °C): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (t, CH_3, 3 H, J = 6.6 Hz), 1.08–2.08 (m, CH_2-CH_2, 4 H), 2.21 (ddd, C-12a′ H, 1 H, J = 3.9, 10.4, 18 Hz), 2.56–2.76 (m, $CH_2CO_2CH_3$, 2 H), 2.84 (ddd, C-12e′ H, 1 H, J = 2.6, 2.6, 18 Hz), 3.72 (s, CO_2CH_3, 3 H), 3.99 (s, OCH_3, 3 H), 3.64–4.04 (m, CH_2CHCH_2, 1 H), 4.68–4.93 (m, C-9a′ H, 1 H), 7.28 (dd, ArH, J = 6.84, 2.64 Hz), 7.52–7.81 (m, ArH, 2 H); ^{13}C NMR ($CDCl_3$) 13.67 (q, CH_3), 18.33 (t), 27.81 (t), 35.94 (t), 40.32 (t), 51.54 (q, OCH_3), 56.31 (q, OCH_3), 68.93 (d, OCH), 73.64 (d, OCH), 117.68 (d), 118.82 (d), 133.83 (s), 134.42 (d), 139.79 (s), 147.80 (s), 159.34 (s), 170.99 (s, CO_2CH_3), 183.23 (s, C=O), 183.34 (s, C=O); IR ($CHCl_3$) 1731 (s, CO_2Me), 1658 (s, quinone C=O), 1599 (s), 1440 (m), 1274 (s), 1228 (m), 950 (w) cm^{-1}; mass spectrum, m/e 358 (M^+, 100), 328 (58), 307 (30), 305 (61), 285 (49), 256 (41), 255 (68), 241 (57), 239 (23), 227 (32).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.93; H, 6.17.

Preparation of *cis*-Deoxyfrenolicin Methyl Ester (39). Treatment of **36** (98.4 mg, 0.286 mmol) with Jones reagent (1.38 mmol) in acetone

(45) Purified by extraction from a Soxhlet with ether as described by Janssen and Wilson (Janssen, D. E.; Wilson, C. V. "Organic Syntheses"; Wiley: New York, 1968; Collect. Vol. IV, p 547).

(46) Prepared by reaction of diphenyl diselenide and bromine as described by Reich et al. (Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5441).

(47) Prepared as described by Djerassi et al. (Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.

(10 mL) for 20 min as described previously gave 89 mg of an orange oil. This material was not purified. A solution of this material in dichloromethane (18 mL) at 25 °C under argon was treated with aluminum trichloride (0.367 g, 2.75 mmol). After 15 min, 5% aqueous sodium bicarbonate was added. The aqueous phase was extracted with ether (10×). The organic extracts were combined and dried over magnesium sulfate. Rotary evaporation gave 76 mg of a dark red oil. Column chromatography (0.5 × 20 cm, hexane:ether = 2:1) gave **39** as a yellow-orange solid (30 mg, 29%): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (t, CH_3, 3 H, J = 6.8 Hz), 1.10–2.07 (m, CH_2CH_2, 4 H), 2.26 (ddd, C-12a′ *H*, 1 H, J = 10.0, 8.0, 4.0 Hz), 2.55–2.72 (m, $CH_2CO_2CH_3$, 2 H), 2.87 (ddd, C-12e′ H, 1 H, J = 18.5, 2.9, 2.9 Hz), 3.73 (s, OCH_3, 3 H), 3.74–4.05 (m, CH_2CHCH_2, 1 H), 4.71–4.94 (m, C-9a′ *H*, 1 H), 7.12–7.70 (m, Ar*H*, 3 H).

Isomerization of 39 To Give 40. Concentrated sulfuric acid (5 mL) was stirred with **39** (27.7 mg) in a 10-mL round-bottom flask at 25 °C for 30 min. The resulting dark solution was poured into saturated aqueous sodium chloride. Extraction with dichloromethane and concentration of the combined organic extracts gave **40** as a yellow solid (24.8 mg). Analytical HPLC (hexane:ether = 40:1, 5 mL/min) showed peaks at 25.14 min (**39**) and 27.94 min (**40**) in the area ratio 1:6.5. Recrystallization from hexane:ether (1:1) gave **40** as yellow-orange needles (11.4 mg, mp 138–138.5 °C): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.99 (t, CH_3, 3 H, J = 6.8 Hz), 1.52–1.90 (m, CH_2CH_2, 4 H), 2.28 (ddd, C-12a′ *H*, 1 H, J = 10.1, 9.0, 2.5 Hz), 2.64 (d, CH_2CO_2Me, 2 H, J = 6.8 Hz), 2.83 (dd, C-12e′ *H*, 1 H, J = 19.1, 3.6 Hz), 3.74 (s, CO_2CH_3, 3 H), 4.06–4.52 (m, CH_2CHCH_2, 1 H), 4.83 (br t, C-9e′ *H*, 1 H, J = 6.3 Hz), 7.16–7.71 (m, Ar*H*, 3 H); IR ($CHCl_3$) 1735 (s, CO_2CH_3), 1642 (s, C=O), 1618 (s, C=O), 1456 (m), 1276 (s), 1245 (m), 1155 (m), 839 (w) cm^{-1}.

Preparation of 40 by Treatment of 35 with Boron Tribromide. To a yellow solution of **35** (75 mg, 0.209 mmol) in dichloromethane (15 mL) in a 100-mL round-bottom flask at −78 °C under argon was added a solution of boron tribromide (2.09 mmol) in dichloromethane (12 mL) dropwise over 5 min. The resulting dark red solution was kept at −78 °C for 5 min and then warmed to 0 °C. After 10 min at 0 °C, the orange solution was treated with 5% aqueous sodium bicarbonate. The yellow aqueous phase was extracted with chloroform (15×) until the aqueous phase was nearly colorless. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and rotary evaporated to give a black semisolid. Column chromatography (5 g of silica gel, hexane:ether = 3:2) gave **40** as a yellow-orange solid (51.5 mg, 71%). The ^{1}H NMR spectrum of this material showed none of the cis diastereomer, **39**, as evidenced by the lack of signals in the region δ 3.74–4.05 for the C-11 hydrogen. The analytical HPLC (hexane:ethyl acetate = 36:1, 5 mL/min) trace showed a single peak at 25.35 min.

Saponification of 40 To Give (±)-Deoxyfrenolicin (2). To a dark purple suspension of **40** (30.1 mg, 0.0874 mmol) in methanol (6 mL) in a 25-mL round-bottom flask at 25 °C was added aqueous potassium hydroxide (4.2 mL, 0.16 M) all at once. After 3 h, analytical TLC (ether) showed a single yellow spot at R_f 0.49. Aqueous hydrochloric acid (1 M) was then added dropwise to the purple solution until the reaction mixture turned yellow and a fine solid had formed. This suspension was extracted with chloroform (15×) until the aqueous phase was nearly colorless. The organic extracts were combined and washed with saturated aqueous sodium chloride (1×), dried over magnesium sulfate and concentrated to give an orange powder (27.9 mg, 97%, mp 200–204 °C): ^{1}H NMR ($CHCl_3$, 90 MHz) δ 0.97 (t, CH_3, J = 7.0 Hz), 1.31–1.95 (m, CH_2CH_2, 4 H), 2.30 (ddd, C12a′ *H*, 1 H, J = 19.8, 9.7, 2.2 Hz), 2.68 (d, CH_2CO_2H, 2 H, J = 6.2 Hz), 2.85 (dd, C-12e′ *H*, 1 H, J = 19.1, 3.6 Hz), 4.08–4.44 (m, CH_2CHCH_2, 1 H), 4.83 (br t, C-9e′ *H*, 1 H, J = 5.4 Hz), 7.10–7.92 (m, Ar*H*, 3 H); IR ($CHCl_3$) 3080 (br w, CO_2H), 17.19 (m, CO_2H), 1664 (m), 1647 (s, C=O), 1622 (s, C=O), 1463 (m), 1428 (m), 1280 (s), 1170 (w), 879 (w) cm^{-1}.

Recrystallization of this material from benzene:chloroform (3:1) gave a yellow-orange powder (mp 214–214.5 °C). A 1:1 mixture of this material and (+)-deoxyfrenolicin (see next experiment) melted at 182–183 °C. Analysis of this mixture by analytical TLC using dichloromethane:methanol = 10:1 gave a single spot at R_f 0.44. Similarly, analytical TLC using hexane:ether:acetone:methanol = 10:10:4:1 gave a single spot at R_f 0.38.

Preparation of (+)-Deoxyfrenolicin from (−)-Frenolicin. By the procedure of Ellestad and co-workers,[2] a solution of (−)-frenolicin (16.5 mg) in acetic acid (0.66 mL) was treated with 30% hydrobromic acid in acetic acid (0.13 mL) for 14 h. (+)-Deoxyfrenolicin was obtained as an orange solid (14.9 mg). Recrystallization from benzene gave 6.4 mg of a yellow solid (mp 177–179 °C): ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.96 (t, CH_3, 3 H, J = 7.0 Hz), 1.30–1.93 (m, CH_2CH_2, 4 H), 2.28 (ddd, C-12a′ *H*, 1 H, J = 19.1, 9.4, 2.2 Hz), 2.69 (d, $CH_2CO_2CH_3$, 2 H, J = 6.4 Hz), 2.83 (dd, C-12e′ *H*, 1 H, J = 19.1, 3.6 Hz), 4.06–4.43 (m, CH_2CHCH_2, 1 H), 4.82 (br t, C-9e′ *H*, 1 H, J = 5.2 Hz), 7.08–7.92 (m, Ar*H*, 3 H); IR ($CHCl_3$) 3044 (br w, CO_2H), 1720 (m, CO_2H), 1667 (m), 1646 (s, C=O), 1622 (s, C=O), 1463 (m), 1430 (m), 1282 (s), 1172 (w), 880 (w) 845 (w) cm^{-1}.

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Registry No. (±)-**2**, 73804-49-6; (+)-**2**, 10023-11-7; **10**, 69786-79-4; **13**, 82328-22-1; (*E*)-(±)-**17**, 84800-91-9; (*E*)-**18**, 82316-02-7; (±)-**19**, 84800-92-0; (±)-**21a**, 84800-93-1; (±)-**21b**, 84800-94-2; (±)-**22a**, 84823-41-6; (±)-**22b**, 84823-42-7; (±)-**23**, 84823-43-8; (±)-**24**, 84823-44-9; **25**, 84800-95-3; (±)-**27**, 84800-96-4; **28**, 82316-08-3; **28** tetrahydropyranyl ether, 84800-97-5; **29**, 82316-07-2; (±)-**30a**, 84800-98-6; (±)-**30b**, 84800-99-7; (±)-**31a**, 84801-00-3; (±)-**31b**, 84801-01-4; (±)-**32a**, 84801-02-5; (±)-**32b**, 84801-03-6; (±)-**33**, 84847-58-5; (±)-**33** dimethyl acetal, 84801-04-7; (±)-**35**, 81702-90-1; (±)-**36**, 82316-06-1; (±)-**37**, 84801-05-8; **38**, 84801-06-9; (±)-**39**, 82690-99-1; (±)-**40**, 73804-48-5; $Cr(CO)_6$, 13007-92-6; 2-trimethylsilylanisole, 704-43-8; 1-bromo-2-(*E*)-hexene, 73881-10-4; 5-hexenenitrile, 5048-19-1; *o*-bromobenzyl alcohol tetrahydropyranyl ether, 17100-66-2; allyl bromide, 106-95-6; 2-allylbenzyl alcohol, 84801-07-0; 2-allylbenzaldehyde, 62708-42-3; (*E*)-1-bromo-2-butene, 29576-14-5; propargyl bromide, 106-96-7; 2-(2-propyn-1-yl)benzyl alcohol tetrahydropyranyl ether, 84801-08-1; 2-(but-2-yn-1-yl)benzyl alcohol tetrahydropyranyl ether, 84809-57-4; 2-(but-2-yn-1-yl)benzyl alcohol, 84801-09-2; trimethyl orthoformate, 149-73-5; phenylselenyl bromide, 34837-55-3; (−)-frenolicin, 10023-11-7.