Total Synthesis of (±)-Myrocin C

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Abstract: A stereoselective total synthesis of racemic myrocin C (**1**) has been achieved. Initial investigations produced cyclopropane-containing AB sector **22** via intramolecular ester-tethered Diels–Alder reaction of quinone **14** followed by internal alkylation of bromide **19**. Although the natural product was not to be obtained through this route, the information garnered from this impetus provided the basis for a strategically improved and ultimately successful synthesis of **1**. Thus, intermolecular Diels–Alder reaction of *p*-benzoquinone with cyclic diene **39** gave endo cycloadduct **41** which could be elaborated to cyclopropane precursors **52** and **99**. While a plethora of intramolecular alkylation reactions of derivatives of **52** failed to afford cyclopropane-containing products, a novel organolithium-induced cyclization reaction of **99** did indeed provide key compound **96** via postulated intermediate **100**. The resultant functionality in **96** paved the way for a directed intramolecular Diels–Alder annulation of the C-ring and concomitant introduction of the remote quaternary C13 stereocenter (cf. **96** → **107** → **108**). The tertiary hydroxyl group at C9 was then introduced via epoxidation of **119** followed by overall eliminative ring-opening (**123** → **125** → **5**). The incorporation of the C6 tertiary hydroxyl group was accomplished via oxidation of the enolate derived from 6-desoxymyrocin C (**5**), yielding racemic **1**. Studies on the bioactivation process of **5** and **1** led to support for a hypothesis which emphasized the importance of the C6 hydroxyl group in facilitating cyclopropane-ring-opening possibly through the intermediacy of quinone homomethide **134**.

Introduction

Myrocin C (**1**) was isolated in 1989 from the culture filtrate of a soil fungus, *Myrothecium verrucaria* strain no. 55, during the course of a screening program directed toward the identification of antitumor antibiotic agents (Figure 1).[1a] From 30 L of fermentation broth, 40 mg of the natural product was obtained as colorless needles. The structural assignment of myrocin C was accomplished through recourse to standard spectroscopic methods and was rendered more secure through single-crystal X-ray analysis of the C6 derived acetate, **2**.[1b] The latter was obtained by treatment of the natural product with excess acetic anhydride in pyridine. Myrocin C is thus revealed to be a pentacyclic pimarane diterpene which is structurally related to myrocin B (**3**),[2] and LL-S491β (**4**).[3]

Myrocin C possesses a broad spectrum of antimicrobial activity mainly against Gram-positive bacteria. Some activity against fungi and yeasts was also detected. Antitumor activity was evidenced in mice which had been infected with Ehrlich ascites carcinoma and assayed by mean survival time (test/control (T/C)). Myrocin C (T/C = 130%) was evaluated against the very potent agent mitomycin C (T/C = 247%). Although myrocin C clearly did prolong the lives of the tumor-bearing mice, its activity is modest in comparison to that of mitomycin C.

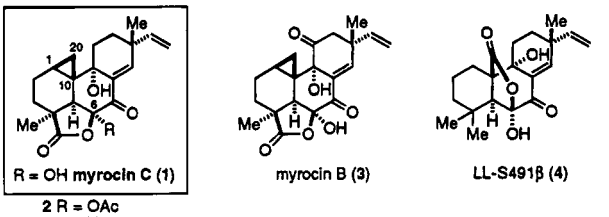

Figure 1.

At first glance, myrocin C does not appear to be endowed with the structural markers commonly associated with DNA-damaging agents. However, in light of our past involvements in the field of activated cyclopropanes,[4] we were drawn to the C1–C10–C20 triad as a potential locus of electrophilicity with appropriate bionucleophiles. Our guiding hypothesis by which myrocin C might function as a powerful bioelectrophile carries with it the prediction that deletion of the C6 hydroxyl group could diminish the bioelectrophilicity of the system.[5] Accordingly, 6-desoxymyrocin C (**5**) emerged as a desirable goal structure *en route* to myrocin C.[6]

Results and Discussion

Early Synthetic Planning. Our first approach contemplated Diels–Alder reaction between a system of type **6** (various R groups are unspecified) and *p*-benzoquinone (Scheme 1). At a stage which would be difficult to define in advance, a leaving group would be fashioned from R″O appearing in structure **7**. Intramolecular alkylation of an enolate derived from **8** was expected to produce cyclopropane **9**. The future C4 methyl group could be incorporated in the diene (R′ = Me in structure **6**), or if R′ in **6** were hydrogen, the methyl group might be

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⊥ Yale Instrumentation Center.
⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1994.
(1) (a) Nakagawa, M.; Hsu, Y.-H.; Hirota, A.; Shima, S.; Nakayama, M. *J. Antibiot.* **1989**, *42*, 218–222. (b) Hsu, Y.-H.; Hirota, A.; Shima, S.; Nakagawa, M.; Adachi, T.; Nozaki, H.; Nakayama, M. *J. Antibiot.* **1989**, *42*, 223–229.
(2) Hsu, Y.-H.; Nakagawa, M.; Hirota, A.; Shima, S.; Nakayama, M. *Agric. Biol. Chem.* **1988**, *52*, 1305–1307.
(3) Ellestad, G. A.; Kunstmann, M. P.; Mirando, P.; Morton, G. O. *J. Am. Chem. Soc.* **1972**, *94*, 6206–6208.
(4) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72.
(5) Chu-Moyer, M. Y.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 3025–3028.
(6) Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 8333–8334.

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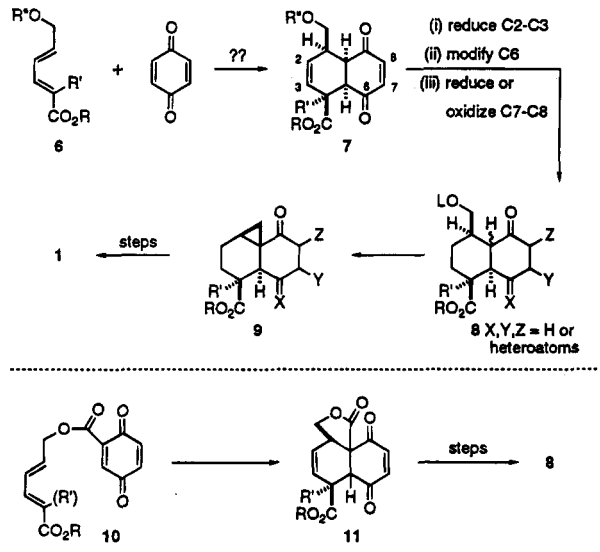
Scheme 1

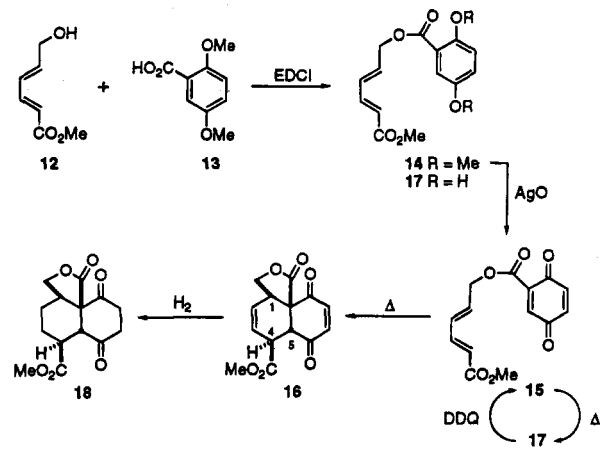


introduced via ester enolate alkylation of a suitably modified version of structure **7**.

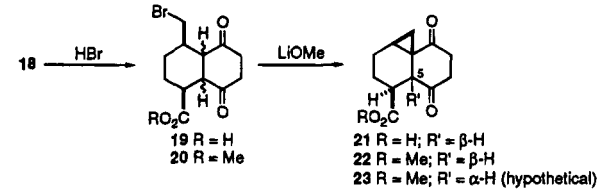
While *p*-benzoquinones are widely used dienophiles in Diels–Alder cycloadditions,[7] precedents as to the quality of such reactions with electron-deficient dienes were not particularly encouraging.[8] Under forcing thermal conditions needed to overcome sluggish reactivity, primary adducts of type **7** often undergo aromatization. The only promising solution to this problem was reported by Dauben and involved the use of high pressure (15 kbar).[9] Under these conditions, reactions occur at room temperature and satisfactory yields of adducts related to **7** are obtained. Our approach focused on intramolecular cycloaddition of a substrate such as **10**. It was anticipated that cycloadduct **11** could be manipulated to afford a product which would be functionally equivalent to compound **8**.

Diels–Alder Reaction: Initial Studies. Dienol **12** was prepared by known chemistry[10] and coupled[11] to commercially available 2,5-dimethoxybenzoic acid (**13**), providing benzoate ester **14** (Scheme 2). Oxidation[12] of **14** with argentic oxide[13] gave rise to quinone **15** as a reasonably stable entity. However, even with the advantage of intramolecularity, cycloaddition was rather slow, producing after 5 h in refluxing toluene the cycloadduct **16**, accompanied by hydroquinone **17**. The chromatographic separation of these compounds was further complicated by the instability of the former.[14] Eventually, a protocol was developed where the thermolysis mixture was directly

Scheme 2



Scheme 3



hydrogenated to afford fully saturated compound **18**. Another improvement was realized when the product mixture from the cycloaddition of **15** was directly oxidized with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) with a view toward returning hydroquinone **17** to the reaction stream. The crude cycloadduct was hydrogenated as above to afford a 46% overall yield of intermediate **18** from Diels–Alder precursor **14**.

The stereochemical assignment advanced for cycloadduct **16** corresponds to that in which the quinone moiety was presented to the diene in an exo topography. This outcome is apparently opposite to that asserted by Auerbach and Weinreb[15] in a related ester-tethered intramolecular Diels–Alder cycloaddition. Our proposal of the relative stereochemistry at the stage of **16** is consistent with the coupling constant observed between the protons at C4 and C5 (J = 10.8 Hz).[16] Furthermore, the C1–C5 relationship in structure **16** was subsequently established in the derived cyclopropane **22** (*vide infra*) by crystallographic means.

Cyclopropane Installation: Intramolecular Alkylation. Following literature precedents,[17] lactone **18** was converted to a mixture of bromides **19** through the action of HBr (Scheme 3). Subsequent esterification with diazomethane afforded ester **20**. Attempted intramolecular cyclopropanation of **20** using potassium *tert*-butoxide was unsuccessful. However, when bromo acid **19** was treated with lithium methoxide in methanol, cyclopropane acid **21** was obtained. Esterification with diazomethane gave rise to cyclopropane methyl ester **22** (59% from lactone **18**). The cis-junction stereochemistry assigned to compound **22** was in accord with its ^{1}H NMR spectrum and was further confirmed by an X-ray crystallographic structure determination.

It appeared that cis-fused isomer **22** was the preferred product relative to desired trans-fused isomer **23**, even under the

(7) (a) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Avon, Great Britain, 1988; Vol. 2, pp 614–635. (b) Butz, L. W.; Rytina, A. W. *Org. React.* **1949**, *5*, 136–192.

(8) See, for example: (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1–57. (b) Bohlmann, F.; Mathar, W.; Schwarz, H. *Chem. Ber.* **1977**, *110*, 2028–2045. (c) Hayakawa, K.; Ueyama, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1984**, 71–72.

(9) Dauben, W. G.; Baker, W. R. *Tetrahedron Lett.* **1982**, *23*, 2611–2614.

(10) From a slight modification of the literature procedure: Dekönig, H.; Subramanian-Erhart, K. E. C.; Huisman, H. O. *Synth. Commun.* **1973**, *3*, 25–28. A representative experimental procedure for dienol **12** can be found in the supplementary material.

(11) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.

(12) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1174–1175.

(13) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231.

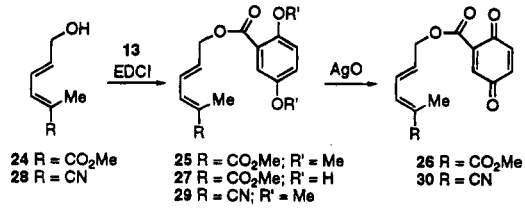
(14) Upon silica gel chromatography, the majority of cycloadduct **16** isomerizes via migration of the C2–C3 double bond to provide the derived C3–C4 enoate.

(15) Auerbach, J.; Weinreb, S. M. *J. Org. Chem.* **1975**, *40*, 3311–3312.

(16) While it is theoretically possible that the course of events allowed for endo cycloaddition followed by C5 epimerization (thus justifying the large observed $J_{4,5}$ value), we note that this epimerization would produce an isomer of highly strained nature and most likely would not occur.

(17) Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 597–600.

Scheme 4



equilibrating conditions used in the cyclopropane-forming reaction. This preference can be explained by inspecting the three-dimensional representations of these structures. In isomer **23** there would be a significant steric interaction between the cyclopropane and the axial carbomethoxy group. Such a 1,3-diaxial abutment is not present in the observed product **22**.

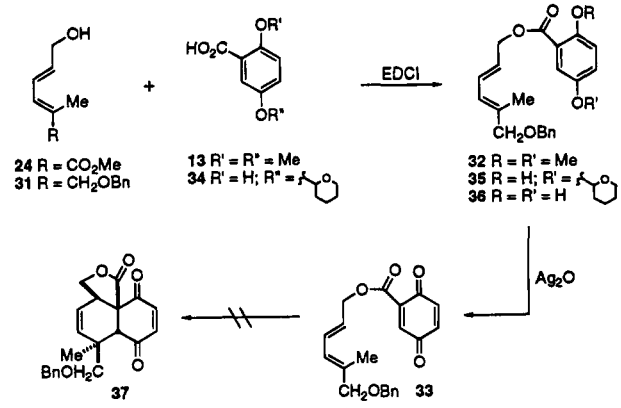
The prospect of introducing the C4 methyl group in compound **22** via ester enolate alkylation in the presence of two enolizable methylene groups (α to the two ketones) was daunting. Because precedents dealing with formation of a carbon–carbon bond at C4 in related systems, via an ester enolate[18] or through nucleophilic addition (on a Δ^4-6-keto system),[19] pointed to preferential attack syn to the angular C10 substituent, we elected to pursue the rather more inviting possibility of early incorporation of the future C4 methyl group in the Diels–Alder diene.

Diels–Alder Reaction: Attempted Incorporation of the C4 Methyl Group. Hydroxy methyl dienoate **24** was prepared by literature methods,[10] and coupled to acid **13**, as described earlier, to afford benzoate ester **25** which after argentic oxide oxidation provided quinone **26** (Scheme 4). Unfortunately, a variety of attempts to realize intramolecular cycloaddition of **26** were unsuccessful. For instance, thermolysis of this compound in toluene in a sealed tube at 165 °C resulted in no reaction. Thermolysis under more forcing conditions afforded hydroquinone **27**. Many other conditions including solvent variation (1,2-dichlorobenzene, acetonitrile,[20] DMSO,[20] and 1,2-propanediol[21]), high pressures (12 kbar),[9,22] and additives ($LiClO_4$)[23] either failed to promote any reaction or provided varying amounts of **27**.

In the hope that a C1 nitrile group might sterically outperform the carbomethoxy function in promoting Diels–Alder reaction, we set about to synthesize quinone **30**. Cyano alcohol **28** was prepared by modification of the method used to prepare **24** (i.e., in the Horner–Emmons olefination, diethyl (1-cyanoethyl)-phosphonate[24] was used in place of the corresponding methyl ester). Coupling of **28** with acid **13** proceeded smoothly to give benzoate ester **29** which was oxidized to give desired quinone **30**. Again, a variety of attempts to achieve internal cycloaddition were to no avail.

Our last effort directed toward the incorporation of the C4 methyl in the diene moiety was predicated on the hope that cycloaddition would be improved if the electron-withdrawing power of the C1 substituent were downgraded. Accordingly, we returned to ester **24** (Scheme 5). Protection of the primary hydroxyl moiety as its *tert*-butyldimethylsilyl ether was followed

Scheme 5



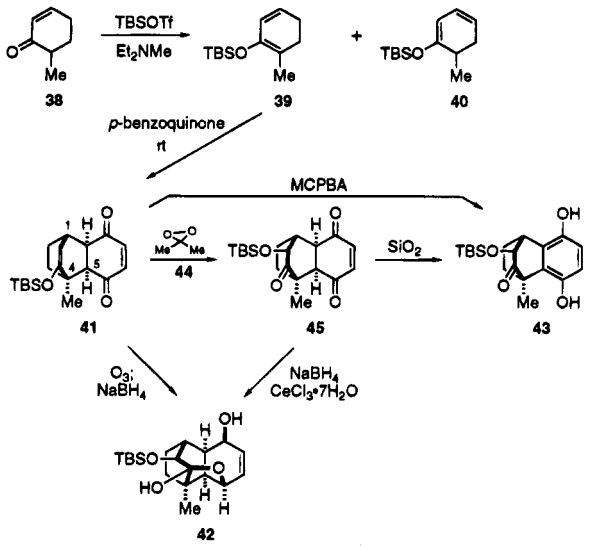
by reduction of the ester with diisobutylaluminum hydride (DIBAL-H), benzylation of the free primary hydroxyl function, and subsequent release of the C6 primary alcohol. This sequence led to diene **31** which upon esterification with acid **13** gave rise to benzoate ester **32**. However, attempted oxidative demethylation of **32** (through either argentic oxide or ceric ammonium nitrate) failed to afford desired quinone **33**. The use of these reagents led to gross destruction of the system. Apparently replacement of the terminal carbomethoxy group by the less electron-deficient (benzyloxy)methyl group rendered the side chain more vulnerable to the action of such oxidizing agents. This problem was solved by the coupling of diene **31** with 5-[(2′-tetrahydropyranyl)oxy]salicylic acid (**34**)[25] to afford benzoate ester **35**. Cleavage of the THP group under mild conditions (PPTS, MeOH) produced hydroquinone **36** which was smoothly oxidized (silver(I) oxide)[12] to desired quinone **33**. Unfortunately, this success in generating **33** was to no avail. Under a variety of conditions, this compound failed to undergo intramolecular cycloaddition to afford desired adduct **37** or any other obvious product.

A Revised Diels–Alder Strategy. A Diels–Alder route which would directly introduce the C4 quaternary carbon of myrocin C, even with the advantage of intramolecularity, appeared improbable. If the general concept of a Diels–Alder route to **1** were to survive, a more astute selection of the diene component would be required. The key departure at the perception level was the use of a surrogate diene (cyclic siloxy diene **39**) in the cycloaddition reaction with *p*-benzoquinone (Scheme 6).[26] The electronic nature of **39**, as well as its obligatory s-cis conformation, should favor the cycloondensation reaction with *p*-benzoquinone. After generation of cycloadduct **41**, the one-carbon fragments projecting from the eventual C1 and C4 positions of myrocin C would be unveiled through oxidative cleavage. In this way, the desired substitution pattern might be fashioned (cf. compound **47**, *vide infra*).

In our hands, the enol silylation[26] of 6-methyl-2-cyclohexen-1-one (**38**)[27] to produce diene **39** proved to be no trivial matter. Various methods of enol silylation of **38** produced not only **39** but undesired isomer **40**.[28] Eventually a protocol which optimized among overall yield, isomer ratio, and ease of workup

(18) Burke, S. D.; Powner, T. H.; Kageyama, M. *Tetrahedron Lett.* **1983**, *24*, 4529–4532.
(19) Van Hijte, L. V.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 1149–1158.
(20) Jung, M. E. *Synth. Lett.* **1990**, *4*, 186–190.
(21) Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3745–3748.
(22) Ferroud, C.; Revial, G.; d'Angelo, J. *Tetrahedron Lett.* **1985**, *26*, 3981–3984.
(23) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595–4596.
(24) D'Incan, E.; Seyden-Penne, J. *Synthesis* **1975**, 516–517.
(25) This compound was prepared in 52% yield via treatment of gentisic acid methyl ester with dihydropyran/PPTS in CH_2Cl_2 followed by LiOH hydrolysis of the methyl ester. See: Duthaler, R. O.; Lyle, P. A.; Heuberger, C. *Helv. Chim. Acta* **1984**, *67*, 1406–1426. Alternatively, direct monotetrahydropyranylation of the non-hydrogen-bonded hydroxyl group of gentisic acid could be effected to give **35** directly in 58% yield.
(26) Diels–Alder reaction of **39** with maleic anhydride has been shown. See: Ihara, M.; Ishida, Y.; Fukumoto, K.; Kametani, T. *Chem. Pharm. Bull.* **1985**, *33*, 4102–4105.
(27) Schuda, P. F.; Potlock, S. J. *Tetrahedron* **1987**, *43*, 463–468.

Scheme 6



was developed. Thus, diene **39** could be isolated as a single compound after chromatographic separation from **40** (see Experimental Section). When diene **39** was reacted with *p*-benzoquinone in THF at room temperature for 5 d, endo cycloadduct **41** was isolated after silica gel purification in 94% yield as a single diastereomer. *The relative stereochemistry at C1, C4, and C5 generated in this single cycloaddition step was conducive toward an advance toward myrocin C.*

Formation of a Competent AB Ring System. We now began the process of retrieving a workable facsimile of the AB sector of myrocin C from adduct **41**. Ozonolysis under several sets of conditions[29,30] generated extremely polar and complicated reaction mixtures. In one case, an interesting product, hemiketal **42**, was isolated, albeit in low yield, after reductive workup with sodium borohydride ($NaBH_4$). This result could be understood by recalling the work of Clark and Heathcock[31] wherein the ozonolysis of hindered *tert*-butyldimethylsilyl enol ethers was shown to give rise to α-(silyloxy) ketones.

Attempts to achieve a Rubottom oxidation[32] of **41** with either *m*-chloroperbenzoic acid (MCPBA) or peracetic acid under buffered conditions led only to the isolation of aromatized silyloxy ketone **43**. Fortunately, undesired aromatization could be avoided by the use of 3,3-dimethyldioxirane (**44**) to yield desired silyloxy ketone **45**.[33,34] The very mild, neutral conditions, the nondemanding workup (evaporation), and the production of an innocuous byproduct (acetone) make this a superior method for generating otherwise labile oxidation products.

Attempted purification of **45** by silica gel chromatography led to the previously encountered aromatized compound **43**. However, compound **45**, in crude form, could be immediately reduced under Luche conditions[35] to give desired hemiketal **42** in 62% overall yield for the two steps. As expected, reduction

(28) Silyl enol ether formation (TBSOTf, Et_3N) of 2-methylcyclohexanone provided a 2:1 ratio of thermodynamic to kinetic product. See: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953–5956.

(29) Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

(30) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.

(31) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396–1403.

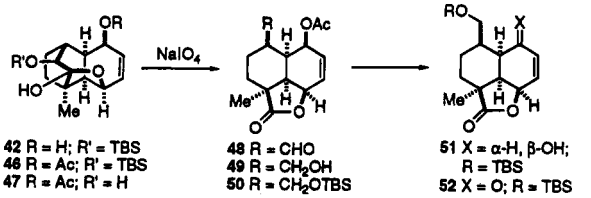
(32) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319–4322.

(33) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800–2803.

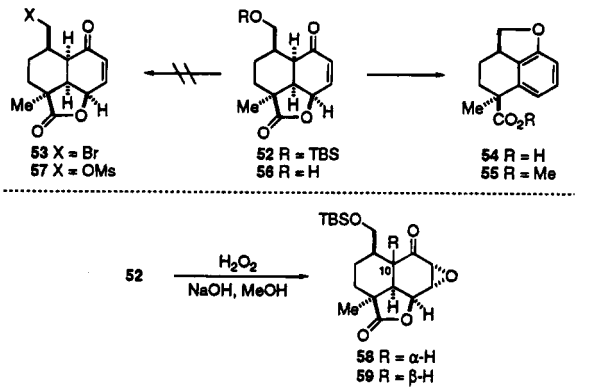
(34) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249–4250.

(35) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

Scheme 7



Scheme 8



of the two ketone functions had occurred through hydride addition to the convex face of the bicyclic system. Subsequent trapping of the ketone by the proximal alcohol took place faster than reduction of that ketone by the borohydride reductant. *Thus, simple reduction had provided access to an intermediate, 42, in which the four oxygens containing the functional groups needed to reach myrocin C were all differentiated.*

Selective acetylation of the allylic alcohol in hemiketal **42** proceeded without incident to provide acetate **46** (Scheme 7). Treatment of **46** with tetrabutylammonium fluoride (TBAF) gave pseudodiol **47** containing a vicinal hydroxy hemiacetal. Treatment of diol **47** with sodium metaperiodate ($NaIO_4$) produced aldehydolactone **48**. Reduction of this compound with $NaBH_4$ gave primary alcohol **49** which was protected as its silyl ether **50**. The acetate in **50** was cleaved under basic conditions, and the resulting allylic alcohol **51** was oxidized with pyridinium dichlorochromate (PDC)[36] to give enone **52**. This substrate and its derivatives were to be used in the subsequent studies to introduce the cyclopropane ring (*vide infra*).

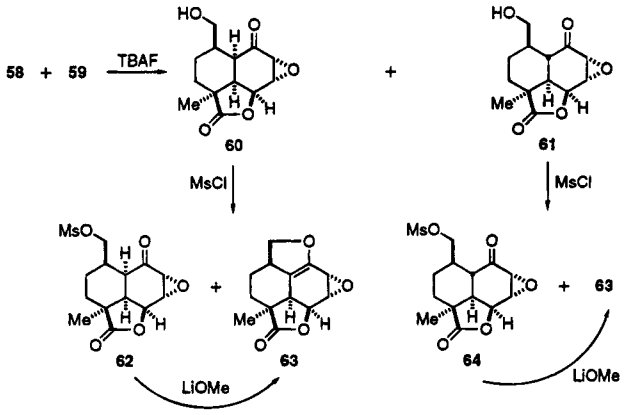
Cyclopropane Installation: An Intramolecular Alkylation Approach. Given the initial indication of feasibility in establishing a cyclopropane sector by intramolecular alkylation (see **19** → **21**), it seemed reasonable to attempt to advance compound **52** to a substrate which bears a potential leaving group at C20 (myrocin numbering). Some indications of future difficulties began to surface upon attempted reaction of **52** with dibromotriphenylphosphorane (Ph_3PBr_2)[37] (Scheme 8). Instead of desired bromide **53**, we obtained dihydrobenzofuran derivative **54**, best characterized as methyl ester **55**. Furthermore, attempted generation of mesylate **57** (via primary alcohol **56**) at low temperature led only to dihydrobenzofuran **54**.

Although our data do not speak directly to the order of events governing this overall transformation, an obvious sequence could be O-alkylation followed by trans-diaxial elimination of the carboxylate and concomitant aromatization. We hoped that either possibility could be countered by removal of the double bond. Accordingly, enone **52** was treated with hydrogen peroxide in alkaline methanol. There was thus isolated an 86%

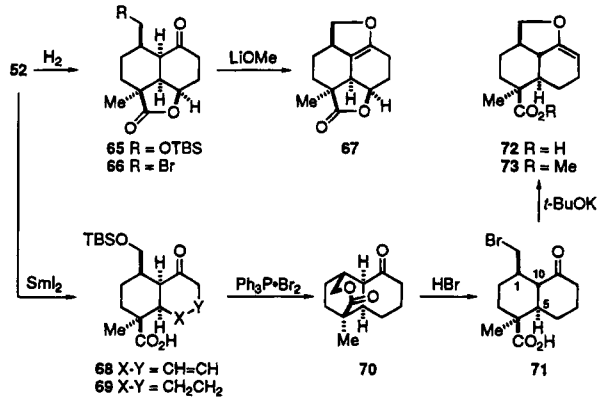
(36) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–403.

(37) Aizpurua, J. M.; Cossío, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.

Scheme 9



Scheme 10

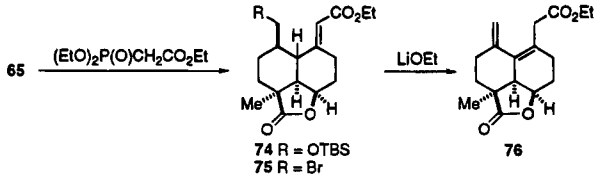


yield of a mixture of epoxy ketones **58** and **59**. Since the compounds were equilibrated upon treatment with sodium methoxide, we surmise that they are epimeric at the junction carbon (C10). When the reaction was conducted from −78 to −48 °C, the major product was cis-fused system **58** with only minor amounts (10:1) of epimeric trans-fused compound **59**. When the reaction was carried out at room temperature, the ratio of **58** to **59** was ca. 1.4:1. The epoxidation process, per se, appears to be stereospecific, with attachment of the hydroperoxide nucleophile having occurred from the α-face.

While installation of the epoxide did serve to close off the aromatization pathway, it did not solve the problem of realizing cyclopropane formation by intramolecular alkylation. Thus, desilylation of the mixture of epoxy ketones **58** and **59** provided the corresponding mixture of alcohols **60** and **61** which were separated and subsequently subjected to the action of mesyl chloride in methylene chloride containing Et_3N and DMAP (Scheme 9). With cis compound **60**, a 2:1 mixture of pure *cis*-mesylate **62** and the O-alkylated enol ether **63** was obtained. When **62** was subjected to the action of lithium methoxide−methanol, it was converted, via O-alkylation, to enol ether **63**. The same sequence applied to *trans*-alcohol **59** led to a 1:3 mixture of mesylate **64** and previously encountered O-alkylation product **63**. Again, as above, treatment of **64** with lithium methoxide−methanol produced **63**.

The possibility of using a simple dihydro version of bromo enone **53** (cf. **66**) as a substrate for internal alkylation was also explored (Scheme 10). Hydrogenation of **52** (5% Rh/Al_2O_3) occurred quite smoothly to afford **65** which was converted to the corresponding bromide through the agency of Ph_3PBr_2 (see **65** → **66**). When bromide **66** was subjected to the action of lithium methoxide, O-alkylation again occurred, producing cyclic enol ether **67** in 75% yield.

Scheme 11



The possibility that the rigid lactone ring was undermining intramolecular cyclopropanation was also briefly examined. Reductive cleavage of the γ-lactonic oxygen of **52** was achieved with samarium(II) iodide, giving rise to carboxylic acid **68** in 66% yield.[38] Compound **69** was obtained by hydrogenation of **68** (10% Pd/C). Interestingly, attempted halogenation of the silyloxy function in **69** gave rise to bridged lactone **70** instead of the expected bromide.[39] Treatment of the latter with concentrated HBr gave rise to bromo acid **71** wherein the ring junction hydrogen at C10 had undergone epimerization.

Compound **71** shares many common features with compound **19**, which was a successful substrate for cyclopropanation. A difference, however, can be found in the resulting anti relationship of the C1 bromomethyl group with the C5 hydrogen in **71** versus an achievable syn relationship in **19**. Attempted intramolecular alkylation reaction of **71** with potassium *tert*-butoxide gave rise to acid **72**, and then, after esterification with diazomethane, ester **73**. Again, intramolecular O-alkylation appeared to be preferred over C-alkylation.

Our last initiative to achieve cyclopropanation through enolate alkylation was via an extended enolate of an α,β-unsaturated ester (Scheme 11). Dihydro compound **65** was subjected to carbethoxymethylenation under standard Horner−Emmons conditions[40] to afford α,β-unsaturated ester **74** which upon treatment with Ph_3PBr_2 afforded bromide **75**. Exposure of this compound to lithium ethoxide−ethanol under reflux afforded a complex mixture which, upon spectroscopic examination, showed no indications of the presence of a cyclopropane. The only properly characterized product was diene **76** arising from double-bond tautomerization and elimination.

Cyclopropane Formation: A Novel Approach. Following this litany of failures to effect cyclopropanation came the development of a new strategy to achieve this end. The unifying concept was that cyclization in the desired sense might be favored if a C9−C10 double bond and a group of significant size at C9 were already in place (Figure 2). The strategy would involve one of two possible closure types not related to enolates with their attendant O-alkylation problems. Aside from providing the relevant functional groups to promote the cyclization possibilities (*vide infra*), the presence of a group attached to C9 of a C9−C10 olefin would also tend, by allylic ($A^{1,3}$) strain,[41] to favor an axial disposition of the CH_2OL fragment (OL = leaving group) mounted at C1.

Such a conformation (cf. **77**) would allow for a useful interaction between the "backside" of C20 and the π-orbitals of the C9−C10 olefin. The repeated failures of many of the cyclopropanation reactions could have reflected a common problem at the stereoelectronic level. Thus, in the cases of substrates which failed to undergo cyclopropanation (**53**, **57**, **62**, **64**, **66**, **71**, and **75**), C20 with its potential leaving group

(38) Molander, G. A.; Hahn, H. *J. Org. Chem.* **1986**, *51*, 1135−1138.
(39) Dibromotriphenylphosphorane is known to convert carboxylic acids to their corresponding acid bromides.[37] Thus, a likely reaction pathway for acid **69** would be lactonization via the activated acid followed by silyl ether cleavage.
(40) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87−99.
(41) (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.

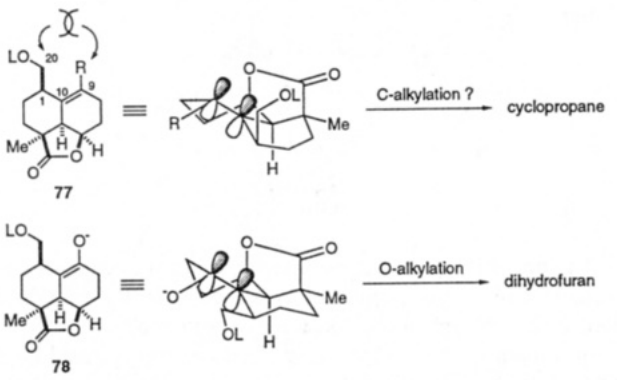
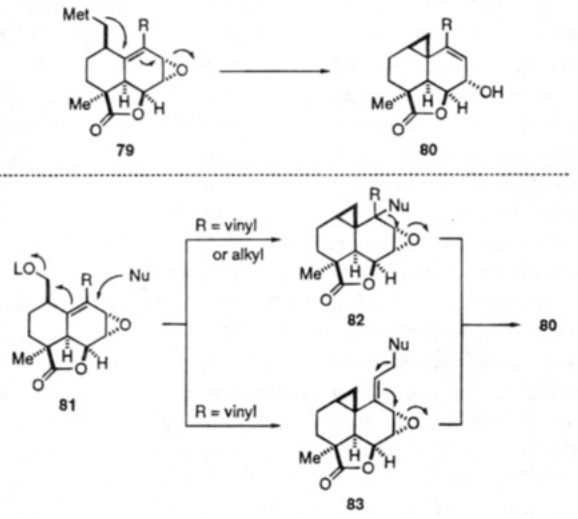


Figure 2.

Scheme 12



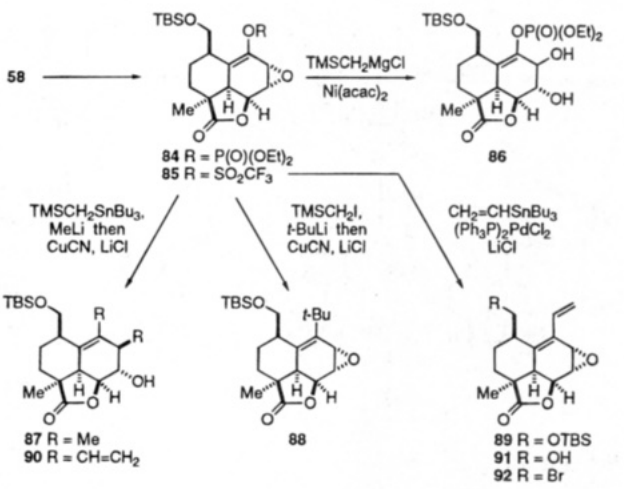
may have been substantially equatorial (cf. **78**). In that case, it is poorly juxtaposed to interact with the π-system of a C9–C10 enolate. In conformer **78**, the limiting case, the emerging backside orbital at C20, in a projected cyclopropanation, overlaps the nodal plane of the C9–C10 double bond.

Two alternate and less traditional cyclization modalities are summarized in constructs **79** and **81** (Scheme 12). In model **79**, a nucleophile is generated at C20. This nucleophile interacts with the C9–C10 double bond with concurrent expulsion of the C8–oxido bond (see arrows **79** → **80**). This perception envisioned, in essence, an intramolecular S_N2' displacement of the C8–oxygen bond with an anti relationship of nucleophile and "leaving group". Although the conventional S_N2' reaction tends to occur with a syn relationship between attacking heteroatom and hetero leaving group, there are certainly many organometallic S_N2' variations, which occur in an anti relationship.[42]

In the alternative scenario, C20 is equipped with a leaving group which is homoallylic to the C9–C10 double bond. The transformation of **81** → **82** is viewed as a homoallyl → cyclopropylcarbinyl rearrangement. If a vinyl-type group is positioned at C9 in **81**, solvolysis at C12 could, alternatively, lead to **83**. Displacement products **82** or **83** might at some stage serve as substrates for reductive elimination (1,2- or 1,4-, respectively) of the allylic oxirane to afford a product of type **80** (R is unspecified).

In order to test our "second generation" propositions, cis-fused epoxy ketone **58** was converted to enol phosphate **84**[43]

Scheme 13



and to vinyl triflate **85**[44] (Scheme 13). The goal with **84** was its conversion to an allylsilane via nickel-mediated cross-coupling with [(trimethylsilyl)methyl]magnesium chloride.[45] However, only diol **86** was isolated (48% yield). Apparently, nickel-mediated opening of the allylic epoxide occurs faster than oxidative insertion into the enol phosphate linkage.

Several other endeavors were made to introduce a (trimethylsilyl)methyl group via triflate **85**. One of these probes involved projected cross-coupling with tris[(trimethylsilyl)-methyl]aluminum mediated by tetrakis(triphenylphosphine)-palladium.[46] This attempt resulted in the formation of a complex mixture. Next, two protocols were followed to generate a higher-order cuprate from [(trimethylsilyl)methyl]lithium.[47] In one instance, tributyl[(trimethylsilyl)methyl]stannane was treated with methyllithium and then with cuprous cyanide and lithium chloride followed by triflate **85**. The only product isolated (20%) was compound **87** apparently arising from cuprate cross-coupling with the triflate as well as cuprate-opening of the epoxide. Another effort started with reaction of *tert*-butyllithium with (trimethylsilyl)methyl iodide. The species thus produced was exposed to the action of cuprous cyanide followed again by triflate **85**. The only product isolated (17%) in this case was *tert*-butyl cross-coupled product **88**.

Though the yields of **87** and **88** were far from impressive, the results had a learning benefit. First, they did demonstrate that cross-coupling of the congested vinyl triflate would be possible. Furthermore, ^{1}H NMR examination of the resonance of the proton at C1 (H-1) over the compounds **85** → **87** → **88** revealed a downfield "drift", possibly suggesting greater equatorial character of H-1 (and thus, greater axial character of the C1 substituent) as the size of the substituent at C9 increased.[48]

With these considerations in mind, we turned to the possibility of introducing a vinyl function at C9. Thus, diene **89** was obtained in 54% yield via Stille-like coupling[49] of triflate **85** with vinyltributyltin under mediation of palladium(II) in the presence of excess LiCl. Under these conditions, less than 10%

(42) For a recent review on the intramolecular S_N' reaction, see: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383–7423.

(43) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198–2208.

(44) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.

(45) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129–8133.

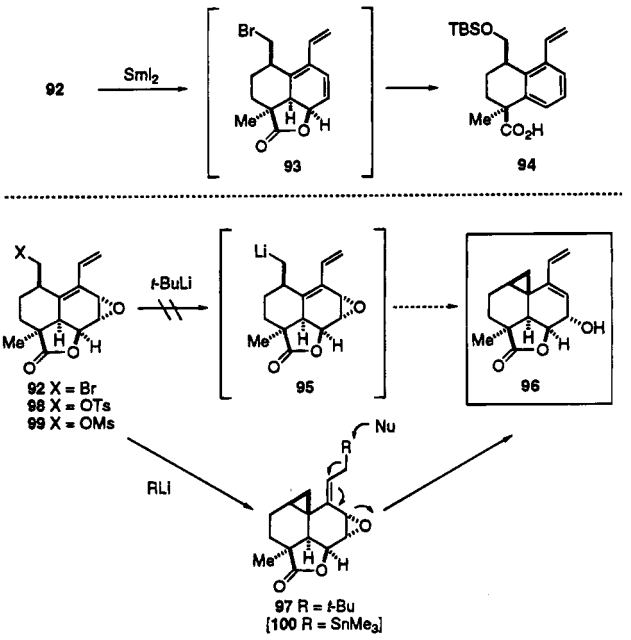
(46) Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320–8321.

(47) Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695–1696.

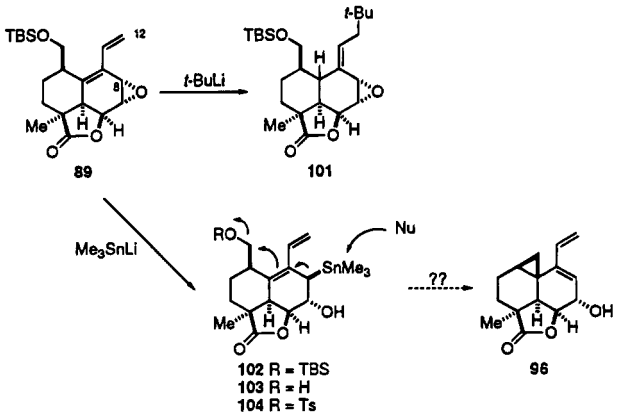
(48) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; p 175.

(49) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

Scheme 14



Scheme 15



of products derived from opening of the epoxide was observed (see compound **90**). The liberation of the C20 hydroxyl group from its TBS derivative under standard conditions[50] was also complicated by the lability of the C8−oxido bond, this time to fluoride-induced cleavage. However, this side reaction could be completely suppressed by conducting the reaction under buffered (acetic acid) TBAF conditions, affording alcohol **91** in 96% yield. The latter could then be converted to bromide **92** through the action of triphenylphosphine−carbon tetrabromide.[51]

An initial attempt at reductive ring closure with samarium(II) iodide[52] gave a 59% yield of **94** possibly via deoxygenated intermediate **93** (Scheme 14).[53] We then attempted to achieve cyclization by lithiation of the C20 carbon−bromine bond. The reagent selected for this purpose was *tert*-butyllithium. We hoped to generate lithio derivative **95** which might undergo conversion of **96**. This transformation was not realized. However, a most interesting reaction did occur. *Bromide **92**, upon treatment with t-BuLi at −78 °C for 5 min afforded vinylcyclopropane **97** in 35% yield.* While it would be difficult to chart a pathway to myrocin C in which **97** itself would be a useful intermediate, the capacity to produce a fused cyclopropane in the context of this ring system was most welcome. Vinylcyclopropane **97** could also be produced from tosylate **98** in 74% yield. It seems likely that **97** is elaborated by addition of *tert*-butyllithium to the terminal position of the diene system (possibly following electron transfer) and displacement of the C20 leaving group.[54]

We then turned to the possibility of accessing a nucleophile which might eventually serve as a substrate for reductive elimination of the epoxide. With this in mind, the reaction of (trimethylstannyl)lithium[55] in THF with derived mesylate **99** was studied. *Remarkably, this reaction afforded a 66% yield of **96** which was the original intermediate goal system projected via **92** and **95**.* Cyclopropane formation and reductive elimination of the C8−oxido bond had occurred concurrently.[56] In assuming that the stannyllithium acted in analogous fashion to the alkyllithium, an intermediate such as **100** could be contemplated. System **100** would then be a prime candidate for nucleophile-induced elimination of the 1,4-allylically related stannyl and oxido bonds.

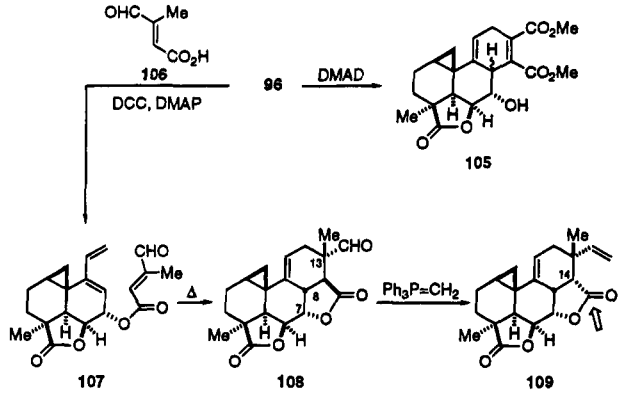
Since it was not plausible to support this hypothesis by the isolation, or even detection, of **100**, we sought to challenge the proposal by probing the credibility of alternative possibilities. For instance, it was of interest to examine the consequences of decoupling of the expulsion of a leaving group at C20 from the nucleophilic event (at C8 or C12). For this purpose we returned to compound **89** (Scheme 15). Interestingly, this compound did react with *tert*-butyllithium to afford C12 addition product **101** in 66% yield without cyclization to C20. Thus, the conjugated diene appears to be sufficiently electrophilic to accept a *t*-BuLi-derived nucleophile at C12 even in the absence of leaving group capacity at C20.

Of perhaps greater importance was the finding that **89** did react with (trimethylstannyl)lithium to afford a 66% yield, not of the related C12 addition product but of the C8 addition product, epoxide-opened compound **102**. Treatment of **102** with tetrabutylammonium fluoride provided **103** and then, by tosylation, **104**. This foray was of interest to us since **104** could well have been a plausible alternative intermediate to hypothesized allylstannane **100** in going from diene **98** to desired cyclopropane **96**. Thus, **104** which could have arisen by direct displacement of the allylic oxido bond of **98** might, in principle, have gone on to **96** by nucleophilic attack at the tin center (see arrows **104** → **96**). In an attempt to simulate a scenario for such a process, tosylate **104** was treated with (trimethylstannyl)lithium. However, this reaction failed to provide detectable quantities of **96**. Starting material **104** was substantially recovered, accompanied by small amounts of decomposition product. We emphasize that a negative result on an alternative to our proposed sequence can hardly be construed as proving the correctness of the **98/99** → **[100]** → **96** pathway. Thus far, however, we have found no evidence running counter to the proposal.

Annulation of the C-Ring. A preliminary exploration of Diels−Alder annulation of the C-ring with eiene **96** and

(50) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 80−83.
(51) Castro, B. *Org. React.* **1983**, *29*, 1−162.
(52) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171−6176.
(53) This transformation with SmI_2 is known, although an additive such as (*N,N*-dimethylamino)ethanol is usually necessary to promote the reaction. See: (a) Matsukawa, M.; Tabuchi, T.; Inaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2101−2102. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.
(54) This reaction can be viewed as a homologue of the addition of organometallic reagents to allylic dienol derivatives. See, for example, with RLi: (a) Ishii, T.; Kawamura, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Hitomi, T. *J. Org. Chem.* **1987**, *52*, 4416−4418. With RMgBr: (b) Nakanishi, M.; Matsubara, S.; Utimoto, K.; Kozima, S.; Yamaguchi, R. *J. Org. Chem.* **1991**, *56*, 3278−3283.
(55) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836−4838.
(56) Tosylate **98** also provides **96** under the same reaction conditions.

Scheme 16



dimethyl acetylenedicarboxylate (DMAD) as a dienophile demonstrated that this idea was indeed feasible (Scheme 16). This reaction was conducted in refluxing benzene to provide a 1:1 mixture of Diels–Alder adducts (see structure **105**), showing that, unfortunately, little facial discrimination was achievable.

Given the work which had been carried out in the total synthesis of forskolin by Ziegler and associates,[57] an interesting solution to the problem of facial selectivity presented itself. The idea involved coupling of the dienophile to the C7 α-hydroxyl group through a suitable tether. In the event, the selected tether for presentation of a methacrolein dienophile was an ester bond. The known[57,58] acylating agent **106** was reacted with dienol **96** in the presence of dicyclohexylcarbodiimide (DCC) and stoichiometric DMAP to produce, in excellent yield, ester **107**. Thermolysis of **107** in benzene for 13 h provided intramolecular Diels–Alder adduct dilactone **108** as a single stereoisomer. *Thus, the remote C13 quaternary stereocenter had been introduced in a completely stereoselective manner through the agency of the transient C7 stereocenter.*

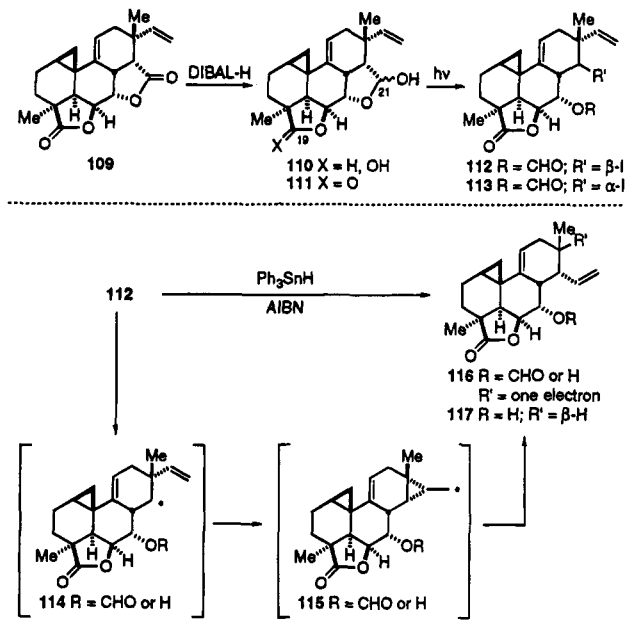
Given the facial selectivity imposed by the nature of the tether, and the likely predominance of endo control by the aldehyde, it was expected that the intramolecular Diels–Alder reaction would, in fact, produce adduct **108**. Operating on this assumption, **108** was subjected to Wittig olefination. This reaction proceeded smoothly, with concomitant epimerization at C14, to provide a 79% yield (from Diels–Alder precursor **107**) of the compound formulated as **109**. This structural assignment was amply supported by physical measurements including two-dimensional nuclear Overhauser effect experiments (NOESY) and was corroborated most convincingly by single-crystal X-ray analysis.

Synthesis of Myrocin C. While much progress had, indeed, been accomplished through the use of the acyl tether in the intramolecular Diels–Alder reaction, it would now be necessary to remove the extraneous carbon (structure **109**, see arrow) which had served the useful purpose of orchestrating the stereochemistry of cycloaddition. Toward this end, dilactone **109** was reduced with DIBAL-H in methylene chloride to give a mixture of dilactols **110** (Scheme 17). Treatment of this mixture with PDC in the presence of Celite resulted in selective oxidation of the E-ring (C19) hemiacetal, providing monolactal **111**. Although the origins of the regioselectivity of this oxidation are far from clear, it would appear that, in relation to the C19 hemiacetal hydroxyl group, the C21 hydroxyl group

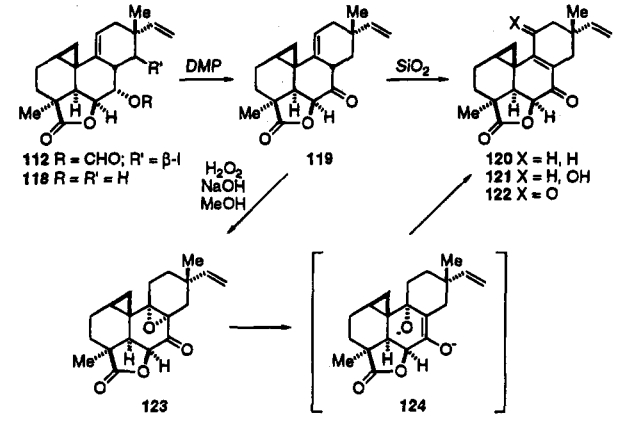
(57) (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115–8116. (b) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307–3310.

(58) (a) Jaynes, B. H. Ph.D. Dissertation, Yale University, 1988. (b) Curley, R. W.; Ticoras, C. J. *Synth. Commun.* **1986**, *16*, 627–631. (c) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

Scheme 17



Scheme 18



situated in the concavity of the 6,6,5-tricyclic array is extremely hindered and, therefore, less susceptible to oxidation via the large chromium-based oxidant.

Photolysis of lactol **111** in the presence of iodine and iodobenzene diacetate ($PhI(OAc)_2$) gave rise to a 96% yield of iodo formates **112** and **113** in a 7:1 ratio.[59] Naively, we presumed that it would be a relatively straightforward matter to remove the iodine function at C14. In practice, treatment of **112** with triphenyltin hydride in the presence of catalytic 2,2′-azobis(2-methylpropionitrile) (AIBN) gave rise to compound **117** in which the vinyl group had migrated from C13 to C14. A reasonable explanation for this transformation contemplates reduction of the iodine function at C14 to give rise to homoallyl radical **114** which cyclizes into the vinyl group to generate cyclopropylcarbinyl radical **115**. The latter, upon electronic reorganization, gives rise to a more stable tertiary homoallyl radical, **116**, which serves as the locus for hydrogen atom abstraction. This process also appears to be stereospecific in that ^1H NMR analysis suggests that the product is that shown in structure **117** with the C13 methyl group occupying an equatorial position.

This rearrangement could be overcome by utilization of neat tributyltin hydride (Bu_3SnH) (Scheme 18). Under these condi-

(59) Freire, R.; Marrero, J. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1986**, 383–386.

tions a 5:1 ratio of desired compound **118** to undesired compound **117** was obtained from iodo formate **112**. Apparently, use of the stronger hydrogen atom donor in massive excess[60] serves to interdict radical **114** before it rearranges. The formate ester had undergone cleavage presumably through the agency of adventitious tin alkoxides.[61]

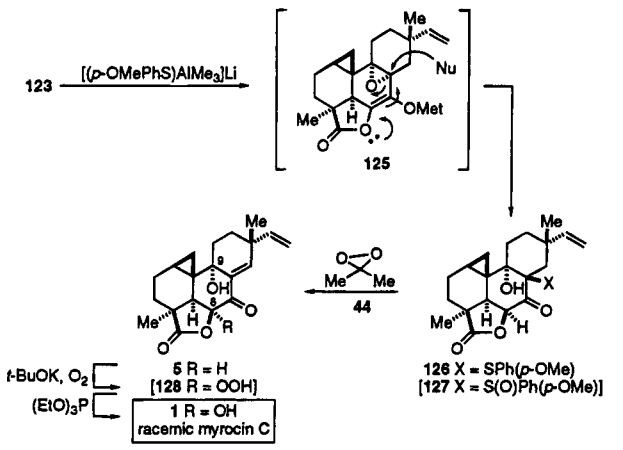
Dess-Martin periodinane (DMP)-mediated oxidation of **118** smoothly gave rise to β,γ-unsaturated ketone **119**.[62] Our plan of attack involved isomerization of the double bond in **119** in hopes of obtaining isomer **120** which would be used to introduce additional functionality required to reach myrocin C. While treatment of **119** with basic reagents (*t*-BuOK or NaOMe) led to decomposition of starting material, attempted chromatography (silica gel) led to a mixture of desired compound **120** and autooxidation product **121** (2.8:1).

If the oxidation of alcohol **118** was conducted with Jones reagent instead of DMP, the only isolable product was enedione **122**. Such an oxidation may very well be involved in the biosynthesis of myrocin B (**3**). Indeed, the possibility that myrocin B is not a natural product but is an artifact in the isolation of other intermediates containing the $\Delta^{8,9}$ linkage cannot be ruled out. Fortunately, subjection of β,γ-unsaturated ketone **119** to alkaline hydrogen peroxide in deoxygenated MeOH directly produced the desired epoxide **123** via nucleophilic epoxidation of intermediate enone **120**. Overall, this compound could be obtained in 50% yield from hemiacetal lactone **111**.

With compound **123** in hand, a variety of attempts were directed toward generation of a site-specific enolate, **124**, in the hope that it could be used to introduce the C8−C14 double bond. Surprisingly, a range of such attempts were unsuccessful. For instance, reaction of epoxy ketone **123** with SmI_2,[63] conducted in anticipation of generating a usable metalloenolate (cf. **124**), gave rise instead to enone **120**. Similar outcomes were encountered when epoxy ketone **123** was subjected to the action of lithium ammonia[64] or lithium naphthalenide.[65] In each case, spectroscopic examination pointed to the rapid formation of the formal dehydration product, i.e., the previously encountered enone **120**.

Fortunately, an implementable solution was discovered. Reaction of epoxy ketone **123** with a Nozaki reagent ([(*p*-OMePhS)$AlMe_3$]Li)[66] gave rise to thiolate addition product **126** (Scheme 19). At first glance the success of this transformation is somewhat surprising given the tertiary nature of the leaving group at C8. However, in the enolized version of **123** (see **125**) the C8 bond is now allylic to the C6−C7 double bond, and is likely rendered even more labile by possible electronic assistance from the C6 oxygen (see arrows in **125**).[67] Oxidation of sulfide **126** through the agency of 3,3-dimethyldioxirane[68] did not produce the sought after intermediate sulfoxide **127**. Rather, in its place 6-desoxymyrocin (**5**) was directly produced in 55% overall yield from **123**.

Scheme 19



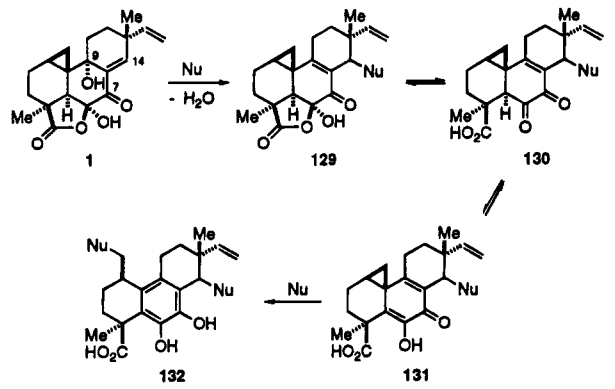
The installation of the C6 hydroxyl group of myrocin C turned out to be fairly straightforward. Treatment of racemic 6-desoxymyrocin (**5**) with potassium *tert*-butoxide in *tert*-butyl alcohol/THF at low temperature in the presence of oxygen[69] gave rise, upon workup, to a new product as indicated by TLC analysis. This product, presumably hydroperoxide **128**, proved to be unstable. Treatment of the reaction mixture at this stage with triethyl phosphite afforded a new product, racemic myrocin C (**1**), in 68% yield from **5**.

Unfortunately, an authentic sample of naturally derived myrocin C was not available to us. Small differences in the ^1H and ^{13}C NMR spectra of our presumed racemic material with those published for the natural product[1b] occasioned considerable concern as to whether the object had been achieved. Suffice it to say that all doubt was subsequently removed when it was possible to crystallize (EtOAc/hexane) fully synthetic material (racemate). *A single-crystal X-ray determination showed that we had indeed achieved the synthesis of racemic myrocin C.* The minor discrepancies in the spectroscopic data with published material may reflect the consequence of differences in the measurement protocols, or might even conceivably reflect real differences arising from measurements on a homochiral material versus a racemate. The total synthesis of racemic myrocin C had thus been achieved.

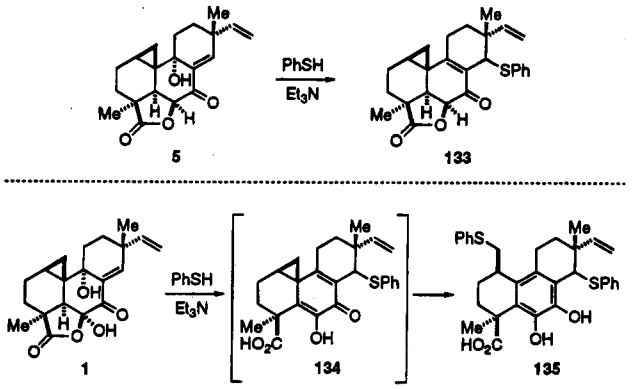
Investigation of a Proposal for Bioactivation of Myrocin C. With myrocin C (**1**) now in hand, we were ready to test our bioactivation hypothesis. The cyclopropane would appear to derive its bioelectrophilic properties from its cyclopropylcarbinyl relationship to the C9 tertiary hydroxyl group (Scheme 20). However, closer inspection reveals that the juxtaposition of functional groups allows for a more intriguing mechanism by which the cyclopropane would be better poised for nucleophilic attack. To realize this possibility, priming would be necessary. For instance, addition of a nucleophile to C14, followed by loss of hydroxide, would produce an intermediate, **129**, still containing the γ-hydroxy lactone. Ring-chain tautomerization of the latter would provide diketone **130** whose diosphenol isomer is represented as **131**. This intermediate allows activation of the cyclopropane through two distinct enone networks, and is formally related, at the conceptual level, to the CC-1065 family of antibiotic agents.[70] Additional driving force for such an alkylation would be provided by aromatization of the B-ring.

(60) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529−4532.
(61) Hydrolysis of esters with bis(tributyltin) oxide has been studied. See: Mata, E. G.; Mascaretti, D. A. *Tetrahedron Lett.* **1988**, *29*, 6893−6896.
(62) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(63) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596−2599.
(64) McChesney, J. D.; Thompson, T. N. *J. Org. Chem.* **1985**, *50*, 3473−3481.
(65) Bartmann, E. *Angew. Chem., Int. Ed. Eng.* **1986**, *25*, 653−654.
(66) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361−364.
(67) Curiously, if the same reaction is conducted using the Nozaki reagent derived from thiophenol ([PhS$AlMe_3$]Li), a 2.4:1 mixture of compounds is obtained. The major product is derived from addition of the ate complex to C8 to give the thiophenol congener of **126**. The minor product, interestingly, is that due to addition at C6 (via what could be viewed as an S_N2'-like opening of the vinyl epoxide in **125**) followed by elimination of the newly formed C9 hydroxyl group by the metalloenolate.
(68) Murray, R. W.; Jeyaraman, R.; Krishna Pillay, M. *J. Org. Chem.* **1987**, *52*, 746−748.
(69) Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695−3699.

Scheme 20



Scheme 21



This bisalkylation hypothesis clearly relies on the presence of the C6 hydroxyl group (see **129** → **130**). Thus, 6-desoxymyrocin C (**5**) could not be expected to suffer comparable cyclopropane-ring rupture. It was at this point of departure that we began our studies.

In the event, treatment of **5** with thiophenol in the presence of triethylamine afforded monoadduct **133** (18:1 β/α at C14) in 74% yield (Scheme 21). The nucleophilic addition could be perceived as a direct addition in the S_N2' sense through the C9 allylic alcohol system or as a Michael addition followed by C9 alcohol dehydration. Exposure of compound **133** to thiophenol and triethylamine over a prolonged period of time gave no further detectable reaction.

Application of the same conditions to myrocin C (**1**) resulted in the rapid formation of a new compound in 63% yield. Conventional analysis revealed that catechol **135** had indeed been produced. Although the exact mechanistic pathway cannot be rigorously established, it is reasonable that an intermediate such as **134** could be involved.

Many electrophilic cyclopropanes are known bioalkylators (e.g., CC-1065,[70] ptaquiloside,[71] and the illudins[72]). While it is possible that a structure such as **133** could undergo cyclopropane opening, the activation barrier for such a process would be significantly higher than that for the postulated quinone homomethide **134**. To our knowledge, this appears to be a most interesting circumstance in which alkylation capacity follows from the accessibility of a doubly activated cyclopropane.

Conclusion

In summary, the stereoselective total synthesis of racemic myrocin C (**1**) has been achieved in 1.1% overall yield and 29 chemical steps. The key stereochemical issues were addressed via application of [4 + 2] cycloaddition strategy and from the anticipation that the rigid decalinoid framework would provide exploitable diastereofacial biases for ensuing reactions. Thus, the initial advance in the synthesis proved to be the accessibility of a suitably substituted AB sector (cf. **41**) in which three of seven asymmetric centers, including one of the stereogenic quaternary centers, were established and in which sufficient functionality was present for elaboration into the final product. Subsequently, in a critical step, the cyclopropane was installed via a novel organolithium-initiated reaction (see **99** → **96**) which also liberated the requisite diene and C7 α-hydroxyl group for C-ring annulation and concomitant introduction of the remote C13 quaternary stereocenter (cf. **108**). Finally, stereoselective oxygenation of C6 and C9 provided the target structure. Following from these studies, a mechanistic hypothesis for the bioactivation process of myrocin C (**1**) was advanced.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl under nitrogen (N_2) atmosphere, benzene (PhH), toluene (PhMe), and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under N_2 atmosphere, and methanol (MeOH) was stored over 3 Å molecular sieves at least 24 h prior to use.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording spectrophotometer. ^1H NMR spectra were obtained on a Bruker WM-250 or a Bruker WM-500 and are reported in parts per million (δ) relative to residual $CHCl_3$ (7.24 ppm) as an internal reference with coupling constants (J) reported in hertz (Hz). Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker WM-250 or a Bruker WM-500 and are reported in parts per million (δ) relative to $CDCl_3$ (77 ppm) as an internal reference.

Low-resolution electron-impact (EI) or chemical-ionization (CI) mass spectra were obtained on a Hewlett-Packard 5989A or a Kratos MS08RFA mass spectrometer at 20 eV. Low-resolution fast-atom bombardment (FAB) mass spectra and all high-resolution mass spectra were obtained on a Kratos MS08RFA mass spectrometer. Analytical fused silica capillary GC spectra were obtained on a Hewlett-Packard 5890 Series II gas chromatograph (Supelco SPB-5 column; 30 m × 0.25 mm) with flame-ionization detection. Elemental analyses were determined by Robertson Laboratories, Inc., Madison, NJ 07940.

Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds which did not absorb UV light were visualized by dipping in a ceric sulfate/ammonium molybdate solution[73] or in an anisaldehyde solution[74] followed by heating. Liquid column chromatography was performed using forced flow[75] (flash chromatography) of the indicated solvent on EM Science silica gel 60 (230–400 mesh).

***tert*-Butyldimethyl[(2-methyl-1,5-cyclohexadien-1-yl)oxy]silane(39) and *tert*-Butyldimethyl[(2-methyl-4,6-cyclohexadien-1-yl)oxy]silane (40).** To a colorless solution of 6-methyl-2-cyclohexen-1-one[27] (**38**; 8.32 g, 75.6 mmol) in CH_2Cl_2 (190 mL) at 0 °C with stirring under N_2 was added Et_2NMe (14.5 mL, 121 mmol) followed by TBSOTf (22.5 mL, 98.1 mmol). This mixture was warmed to room temperature,

(70) (a) Reynolds, V. L.; McGovern, J. P.; Hurley, L. H. *J. Antibiot.* **1986**, *39*, 319–334. (b) Hurley, L. H.; Needham-VanDervanter, D. R. *Acc. Chem. Res.* **1986**, *19*, 230–237. (c) Boger, D. L. *Heterocycl. Bio-Org. Chem.* [*Proc. Fed. Eur. Chem Soc. FECHEM Conf.*], *6th, 1990*, **1991**, 103–129.

(71) (a) Ojika, M.; Wakamatsu, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1987**, *43*, 5261–5274. (b) Kogoshi, H.; Tanaka, H.; Hirokawa, J.; Mizuta, K.; Yanada, K. *Tetrahedron Lett.* **1992**, *33*, 6647–6650.

(72) McMorris, T. C.; Kelner, M. J.; Wang, W.; Estes, L. A.; Montoya, M. A.; Taetle, R. *J. Org. Chem.* **1992**, *57*, 6876–6883.

(73) $Ce(SO_4)_3$ (4 g), $(NH_4)_2MoO_4$ (10 g), and concentrated H_2SO_4 (40 mL) in distilled H_2O (360 mL).

(74) Anisaldehyde (10 mL), concentrated H_2SO_4 (10 mL), and glacial AcOH (1 mL) in absolute EtOH (380 mL).

(75) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

stirred for 15 min, and then poured into ice-cold saturated aqueous $NaHCO_3$ (190 mL)/1% Et_2NMe in pentane (190 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 200 mL), dried (K_2CO_3), filtered, evaporated, and purified by flash column chromatography (0.01% Et_2NMe in pentane, 2×) to give 6.85 g (40%) of silyloxy diene **39** as a colorless liquid: TLC R_f 0.41 (pentane); GC (T_{init} = 100 °C, rate 10 °C/min, T_{max} = 200 °C) t_r = 8.52 min; IR (neat) 3030, 2960, 2950, 2850, 1820, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.67 (br s, 2 H), 2.09 (br s, 4 H), 1.66 (s 3 H), 0.94 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 142.0, 126.4, 125.2, 112.4, 28.6, 25.8, 23.0, 18.1, 16.2, −4.2 (2); MS (FAB, thioglycerol + 1% *p*-TsOH) *m/z* 225 (M + H^+); HRMS (FAB, thioglycerol + 1% *p*-TsOH) exact mass calcd for $C_{13}H_{25}OSi$ (M + H^+) 225.1675, found 255.1682.

A portion of undesired isomer **40** was isolated for analytical data: TLC R_f 0.55 (pentane); GC (T_{init} = 100 °C, rate 10 °C/min, T_{max} = 200 °C) t_r = 8.08 min; IR (neat) 3030, 2950, 2930, 2860, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.76 (ddd, *J* = 9.4, 5.8, 1.4 Hz, 1 H), 5.33 (dt, *J* = 9.3, 4.6 Hz, 1 H), 5.01 (d, *J* = 5.8 Hz, 1 H), 2.44 (ddq, *J* = 8.4, 3.9, 2.3 Hz, 1 H), 2.24 (dt, *J* = 7.3, 5.2 Hz, 1 H), 1.97 (m, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 158.2, 124.0, 117.0, 100.6, 33.2, 32.2, 25.7, 18.1, 16.8, −4.4, −4.7; MS (FAB, thioglycerol + 1% *p*-TsOH) *m/z* 225 (M + H^+); HRMS (FAB, thioglycerol + 1% *p*-TsOH) exact mass calcd for $C_{13}H_{25}OSi$ (M + H^+) 225.1675, found 255.1687.

(1α,4aα,4aα,8aα)-(±)-2-[(*tert*-Butyldimethylsilyl)oxy]-1,4,4a,8a-tetrahydro-1-methyl-1,4-ethanonaphthalene-5,8-dione (41). To a colorless solution of silyloxy diene **39** (11.3 g, 50.4 mmol) in THF (25 mL) at room temperature with stirring under N_2 was added *p*-benzoquinone[76] (5.17 g, 47.8 mmol) in one portion. The resulting dark red mixture was stirred for 5 d to give a bright yellow solution that was concentrated to a dark green solid and purified by flash column chromatography (1:9 EtOAc/hexane) to give 15.0 g (94%) of endo cycloadduct **41** as a yellow solid: mp 96−98 °C; TLC R_f 0.17 (1:9 EtOAc/hexane); IR ($CDCl_3$) 2950, 2850, 1665, 1625, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.59 (d, *J* = 10.5 Hz, 1 H), 6.54 (d, *J* = 10.5 Hz, 1 H), 4.90 (d, *J* = 7.0 Hz, 1 H), 3.03 (m, 1 H), 2.91 (dd, *J* = 8.4, 3.0 Hz, 1 H), 2.69 (d, *J* = 8.4 Hz, 1 H), 1.74−1.57 (c, 2 H), 1.52−1.35 (c, 2 H), 1.08 (s, 3 H), 0.84 (s, 9 H), 0.09 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.7, 198.2, 155.8, 142.2 (2), 100.5, 54.9, 51.4, 41.3, 36.7, 36.6, 25.5, 25.4, 19.0, 17.9, −4.8, −5.0; MS (CI, methane) *m/z* 333 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{19}H_{29}O_3Si$ (M + H^+) 333.1887, found 333.1905. Anal. Calcd for $C_{19}H_{28}O_3Si$: C, 68.63; H, 8.49. Found: C, 68.70; H, 8.65.

(2α,2aα,5β,5aα,6β,8aα,8bα,9*R)-(±)-9-[(*tert*-Butyldimethylsilyl)oxy]-2a,3,4,5,5a,6,8a,8b-octahydro-2a-methyl-2,5-methano-2*H*-naphtho[1,8-*bc*]furan-2,6-diol (42).** To a yellow heterogeneous mixture of silyl enol ether **41** (16.1 g, 48.4 mmol) in CH_2Cl_2 (24 mL) at −78 °C with stirring under N_2 was rapidly added 3,3-dimethyldioxirane[77] (**44**; 690 mL, 0.07 M in acetone, 48.4 mmol). After 30 min, this mixture was warmed to 0 °C, whereupon a homogeneous solution resulted. After another 30 min, a second portion of dimethyldioxirane (475 mL, 0.07 M in acetone, 33.2 mmol) was added, and this mixture was stirred at 0 °C for 1 h, warmed slowly to room temperature over 30 min, and then concentrated to give unstable silyloxy ketone **45** as a yellow solid: TLC R_f 0.24 (1:3 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1735, 1680, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.78 (d, *J* = 10.4 Hz, 1 H), 6.64 (d, *J* = 10.4 Hz, 1 H), 3.23 (d, *J* = 4.9 Hz, 1 H), 3.02 (dd, *J* = 9.1, 2.6 Hz, 1 H), 2.78 (m, 1 H), 2.74 (d, *J* = 9.2 Hz, 1 H), 1.85−1.75 (c, 2 H), 1.43−1.21 (c, 2 H), 1.12 (s, 3 H), 0.80 (s, 9 H), 0.10 (s, 3 H), −0.04 (s, 3 H); MS (CI, methane) *m/z* 349 (M + H^+).

To a pale yellow solution of crude silyloxy ketone **45** in MeOH (325 mL) at room temperature with stirring under N_2 was added $CeCl_3 \cdot 7H_2O$ (90.0 g, 242 mmol). After 5 min, the pale yellow homogeneous mixture was cooled to −78 °C (mixture becomes heterogeneous), and $NaBH_4$ (3.66 g, 96.8 mmol) was added in several portions over 1 min. This mixture was stirred for 1.5 h, quenched by addition of saturated aqueous NH_4Cl (100 mL), warmed to room temperature, concentrated, and diluted with H_2O (200 mL)/CH_2Cl_2 (250 mL). The resulting emulsion was removed by addition of cold 1 N HCl (100 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phases were washed with brine (1 × 150 mL), and the aqueous wash was back-extracted with CH_2Cl_2 (1 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:3 EtOAc/hexane) to give 11.5 g (67%) of hemiketal **42** as a white solid: mp 121−123 °C; TLC R_f 0.20 (1:3 EtOAc/hexane); IR ($CDCl_3$) 3590 (s), 3420 (br), 2950, 2930, 2860, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.88−5.73 (c, 2 H), 4.46 (s, 1 H), 4.38 (dd, *J* = 6.8, 1.2 Hz, 1 H), 4.23 (m, 1 H), 4.00 (dd, *J* = 3.7, 1.3 Hz, 1 H), 2.25−2.12 (c, 2 H), 2.09 (m, 1 H), 1.90 (m, 1 H), 1.67 (br s, 1 H), 1.62−1.41 (c, 2 H), 1.16 (m, 1 H), 1.00 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 133.1, 128.7, 103.3, 78.0, 66.2, 65.1, 44.0, 42.2, 39.1, 30.6, 26.3, 23.9, 20.6, 19.3, 18.5, −4.1, −4.7; MS (CI, methane) *m/z* 353 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{19}H_{33}O_4Si$ (M + H^+) 353.2149, found 353.2150. Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 64.48; H, 8.87.

(2α,2aα,5β,5aα,6β,8aα,8bα,9*R)-(±)-9-[(*tert*-Butyldimethylsilyl)oxy]-2a,3,4,5,5a,6,8a,8b-octahydro-2a-methyl-2,5-methano-2*H*-naphtho[1,8-*bc*]furan-2,6-diol 6-Acetate (46).** To a colorless solution of hemiketal **42** (17.7 g, 50.4 mmol) and DMAP (307 mg, 2.52 mmol) in CH_2Cl_2 (250 mL) at 0 °C with stirring under N_2 was added Et_3N (10.5 mL, 75.6 mmol) followed by Ac_2O (6.2 mL, 65.5 mmol). This pale yellow solution was stirred for 30 min at 0 °C, diluted with Et_2O (500 mL), washed sequentially with 1 N H_3PO_4 (2 × 125 mL), saturated aqueous $NaHCO_3$ (2 × 125 mL), and brine (1 × 125 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:7 → 1:5 EtOAc/hexane) to give 19.2 g (97%) of acetate **46** as a pale yellow oil: TLC R_f 0.15 (1:7 EtOAc/hexane); IR ($CDCl_3$) 3440 (br), 2950, 2930, 2860, 1725, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.92 (ddd, *J* = 10.3, 4.2, 2.6 Hz, 1 H), 5.69 (dt, *J* = 10.3, 0.8 Hz, 1 H), 5.38 (ddd, *J* = 7.8, 4.2, 1.9 Hz, 1 H), 4.43 (s, 1 H), 4.26 (m, 1 H), 4.00 (dd, *J* = 3.4, 1.3 Hz, 1 H), 2.43 (t, *J* = 7.8 Hz, 1 H), 2.20 (dd, *J* = 7.8, 6.5 Hz, 1 H), 2.07 (s, 3 H), 1.93−1.77 (c, 2 H), 1.61−1.36 (c, 2 H), 1.12 (m, 1 H), 1.01 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.1, 129.6, 128.5, 102.8, 76.0, 68.9, 64.3, 43.6, 41.4, 35.0, 31.3, 25.8, 23.2, 21.0, 19.8, 18.7, 18.1, −4.7, −5.2; MS (CI, methane) *m/z* 395 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{21}H_{35}O_5Si$ (M + H^+) 395.2254, found 395.2268. Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.68. Found: C, 63.75; H, 8.51.

(2α,2aα,5β,5aα,6β,8aα,8bα,9*R)-(±)-2a,3,4,5,5a,6,8a,8b-Octahydro-2a-methyl-2,5-methano-2*H*-naphtho[1,8-*bc*]furan-2,6,9-triol 6-Acetate (47).** To a pale yellow solution of silyl ether **46** (19.2 g, 48.7 mmol) in THF (270 mL) at 0 °C with stirring under N_2 was added glacial AcOH (3.1 mL, 53.5 mmol) followed by TBAF (53.5 mL, 1.0 M in THF, 53.5 mmol). After 30 min, this mixture was concentrated to a bright yellow oil that was purified by flash column chromatography (1:1 → 2:1 EtOAc/hexane) to give 12.5 g (91%) of diol **47** as a white solid: mp 169−170 °C; TLC R_f 0.31 (2:1 EtOAc/hexane); IR ($CDCl_3$) 3600 (s), 3400 (br), 2930, 1725, 1370 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.86 (ddd, *J* = 10.3, 3.9, 2.7 Hz, 1 H), 5.72 (d, *J* = 10.3 Hz, 1 H), 5.37 (dd, *J* = 7.6, 2.0 Hz, 1 H), 4.43 (br s, 1 H), 4.28 (m, 1 H), 4.03 (d, *J* = 3.0 Hz, 1 H), 3.62 (br s, 1 H), 2.42 (t, *J* = 7.6 Hz, 1 H), 2.24 (t, *J* = 7.6 Hz, 1 H), 2.09 (s, 3 H), 1.97−1.83 (c, 2 H), 1.65−1.38 (c, 2 H), 1.20 (m, 1 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.4, 129.4, 128.5, 103.5, 73.3, 68.9, 64.6, 43.4, 41.6, 35.2, 30.7, 23.1, 21.0, 19.9, 18.6; MS (CI, methane) *m/z* 281 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{15}H_{21}O_5$ (M + H^+) 281.1389, found 281.1404. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.99; H, 7.18.

(2aα,5β,5aα,6β,8aα,8bα)-(±)-6-(Acetyloxy)-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2a,3,4,5,5a,6,8a,8b-octahydro-2a-methyl-2*H*-naphtho[1,8-*bc*]furan-2-one (50). To a colorless solution of diol **47** (12.5 g, 44.5 mmol) in THF (200 mL)/H_2O (100 mL) at room temperature with stirring was added $NaIO_4$ (14.3 g, 66.8 mmol) in one portion. After a few minutes, a white flocculent solid appeared. This mixture was stirred well for 1 h and then diluted with H_2O (100 mL)/

(76) Recrystallized from hot benzene.

(77) Freshly prepared and stored over 3 Å sieves overnight prior to use. See also ref 33.

Et_2O (400 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give aldehyde lactone **48** as a white solid: mp 100−102 °C; TLC R_f 0.24 (2:1 EtOAc/hexane); IR ($CDCl_3$) 2930, 1760, 1730, 1720, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.62 (d, J = 1.7 Hz, 1 H), 6.28 (dd, J = 9.9, 3.8 Hz, 1 H), 6.13 (ddd, J = 9.9, 4.7, 0.8 Hz, 1 H), 5.30 (t, J = 4.1 Hz, 1 H), 4.95 (ddd, J = 6.7, 4.8, 1.4 Hz, 1 H), 2.66 (m, 1 H), 2.59−2.47 (c, 2 H), 2.21 (ddd, J = 13.8, 5.2, 2.1 Hz, 1 H), 2.04 (s, 3 H), 1.94 (m, 1 H), 1.77 (m, 1 H), 1.49 (dt, J = 13.6, 5.7 Hz, 1 H), 1.34 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 202.0, 179.4, 170.0, 135.3, 126.2, 69.8, 68.0, 45.9, 43.7, 41.0, 32.5, 29.3, 26.3, 21.0, 17.2; MS (CI, methane) m/z 279 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{15}H_{19}O_5$ (M + H^+) 279.1233, found 279.1235.

To a colorless solution of crude aldehyde lactone **48** in MeOH (300 mL) at 0 °C with stirring under N_2 was added $NaBH_4$ (1.68 g, 44.5 mmol). This mixture was stirred at 0 °C for 30 min, quenched by addition of saturated aqueous NH_4Cl (50 mL), concentrated, diluted with half-saturated brine (100 mL), and extracted with CH_2Cl_2 (8 × 125 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give primary alcohol **49** as a white solid. A portion was removed and purified by flash column chromatography (2:1 EtOAc/hexane) for analytical data: mp 129−131 °C; TLC R_f 0.17 (2:1 EtOAc/hexane); IR ($CDCl_3$) 3600 (s), 3490 (br), 2960, 2920, 2870, 1760, 1730, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.58 (dd, J = 9.4, 6.0 Hz, 1 H), 6.24 (dd, J = 9.4, 6.1 Hz, 1 H), 5.20 (dd, J = 6.0, 3.1 Hz, 1 H), 5.12 (t, J = 6.3 Hz, 1 H), 3.56 (d, J = 7.4 Hz, 2 H), 2.41 (dd, J = 9.4, 6.5 Hz, 1 H), 2.34 (m, 1 H), 2.19 (ddd, J = 9.3, 6.0, 3.3 Hz, 1 H), 1.96 (s, 3 H), 1.83 (m, 1 H), 1.59 (br s, 1 H), 1.48−1.40 (c, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 180.1, 170.3, 136.6, 127.9, 70.6, 66.2, 64.6, 43.5, 41.4, 39.3, 33.3, 31.7, 27.5, 21.5, 21.2; MS (CI, methane) m/z 281 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{15}H_{21}O_5$ (M + H^+) 281.1389, found 281.1399. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.20.

To a colorless solution of crude alcohol **49** in CH_2Cl_2 (220 mL) at 0 °C with stirring under N_2 was added Et_3N (7.9 mL, 57.2 mmol) followed by TBSOTf (11.1 mL, 48.4 mmol). This pale yellow solution was stirred at 0 °C for 30 min and then poured into cold saturated aqueous $NaHCO_3$ (100 mL)/Et_2O (400 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:6 → 1:4 EtOAc/hexane) to give 17.4 g (99%) of silyl ether **50** as a pale yellow oil that solidifies slowly upon standing: mp 67−68 °C; TLC R_f 0.19 (1:4 EtOAc/hexane); IR ($CDCl_3$) 2950, 2920, 2850, 1760, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.61 (dd, J = 9.4, 6.3 Hz, 1 H), 6.24 (dd, J = 9.4, 6.2 Hz, 1 H), 5.16 (dd, J = 6.0, 3.0 Hz, 1 H), 5.13 (t, J = 6.3 Hz, 1 H), 3.58−3.42 (c, 2 H), 2.39 (dd, J = 9.7, 6.5 Hz, 1 H), 2.35 (m, 1 H), 2.14 (m, 1 H), 1.95 (s, 3 H), 1.78 (m, 1 H), 1.52−1.30 (c, 3 H), 1.32 (s, 3 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 180.0, 170.1, 136.8, 128.1, 70.6, 66.1, 64.8, 43.5, 41.6, 40.0, 33.5, 32.0, 27.7, 25.8, 21.5, 21.2, 18.1, −5.5, −5.6; MS (CI, methane) m/z 395 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{21}H_{35}O_5Si$ (M + H^+) 395.2254, found 395.2260. Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.68. Found: C, 63.79; H, 8.82.

(2aα,5β,5aα,8aα,8bα)-(±)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3,4,5,5a,8a,8b-hexahydro-2a-methyl-2*H*-naphtho[1,8-*bc*]furan-2,6-(2a*H*)-dione (52). To a colorless solution of acetate **50** (17.4 g, 44.1 mmol) in MeOH (220 mL) at room temperature with stirring under N_2 was added NaOMe (1.9 mL, 25 wt% in MeOH, 8.83 mmol). This mixture was stirred for 24 h and then quenched by addition of saturated aqueous NH_4Cl (50 mL). After stirring for an additional 15 min, this heterogeneous mixture was concentrated, diluted with brine (100 mL), and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL), and the aqueous wash was back-extracted with CH_2Cl_2 (1 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give allylic alcohol **51** as a colorless oil. A portion was removed and purified by flash column chromatography (1:2 → 1:1 EtOAc/hexane) to provide a white solid for analytical data: mp 90−92 °C; TLC R_f 0.26 (1:2 EtOAc/hexane); IR ($CDCl_3$) 3370 (br), 2950, 2930, 2860, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.24 (dd, J = 10.0, 2.8 Hz, 1 H), 5.93 (ddd, J = 10.0, 4.1, 1.7 Hz, 1 H), 4.83 (br t, J = 5.3 Hz, 1 H), 4.29 (m, 1 H), 3.99 (d, J = 10.2 Hz, 1 H), 3.63 (t, J = 10.1 Hz, 1 H), 3.23 (dd, J = 10.3, 3.5 Hz, 1 H), 2.40 (t, J = 7.2 Hz, 1 H), 2.26 (dd, J = 7.4, 5.4 Hz, 1 H), 2.18 (m, 1 H), 1.96−1.73 (c, 2 H), 1.49 (dt, J = 13.7, 4.9 Hz, 1 H), 1.30 (s, 3 H), 1.17 (m, 1 H), 0.86 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 180.7, 140.4, 122.7, 70.9, 66.7, 65.7, 44.4, 42.2, 34.0, 34.0 (2), 29.3, 25.8, 25.5, 22.1, 18.1, −5.4, −5.7; MS (CI, methane) m/z 353 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{19}H_{33}O_4Si$ (M + H^+) 353.2149, found 353.2141. Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 64.56; H, 9.14.

To a colorless solution of crude allylic alcohol **51** in CH_2Cl_2 (285 mL) at room temperature with stirring under N_2 was added Celite followed by PDC[36] (48.2 g, 128 mmol). This dark brown heterogeneous mixture was stirred at room temperature for 20 h and then filtered through a pad of Celite, washing thoroughly with CH_2Cl_2. The filtrate was concentrated and purified by flash column chromatography (1:4 → 1:3 EtOAc/hexane) to give 12.9 g (84%) of enone **52** as a white solid: mp 87−88 °C; TLC R_f 0.18 (1:4 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1765, 1680, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.72 (dd, J = 10.3, 3.2 Hz, 1 H), 6.06 (dd, J = 10.3, 1.3 Hz, 1 H), 5.28 (ddd, J = 9.2, 3.4, 1.4 Hz, 1 H), 4.16 (dd, J = 9.7, 8.2 Hz, 1 H), 3.77 (dd, J = 9.7, 6.0 Hz, 1 H), 3.00 (t, J = 9.1 Hz, 1 H), 2.86 (dd, J = 8.9, 3.1 Hz, 1 H), 1.97−1.60 (c, 3 H), 1.50−1.22 (c, 2 H), 1.37 (s, 3 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 197.8, 180.4, 141.4, 131.4, 71.8, 65.7, 45.4, 41.6, 40.2, 38.2, 27.0, 26.4, 25.9, 18.5, 18.3, −5.4 (2); MS (CI, methane) m/z 351 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{19}H_{31}O_4Si$ (M + H^+) 351.1992, found 351.1975. Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.62. Found: C, 64.82; H, 8.42.

(2aα,5β,5aα,6aβ,7aβ,7bα,7cα)-(±)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3,4,5,5a,6a,7a,7b,7c-octahydro-2a-methyl-2*H*-oxireno-[2,3]naphtho[1,8-*bc*]furan-2,6(2a*H*)-dione (58) and (2aα,5β,5aβ,-6aβ,7aβ,7bα,7cα)-(±)-5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3,4,5,5a,6a,7a,7b,7c-octahydro-2a-methyl-2*H*-oxireno[2,3]naphtho[1,8-*bc*]furan-2,6(2a*H*)-dione (59). To a white heterogeneous mixture of enone **52** (8.48 g, 24.2 mmol) in MeOH (180 mL) at −78 °C with stirring under N_2 was added a premixed solution of H_2O_2 (7.4 mL, 30 wt % in H_2O, 72.7 mmol) and 3 N NaOH (4.0 mL, 12.1 mmol) in MeOH (60 mL) dropwise slowly over 20 min. This mixture was stirred at −78 °C for 30 min and at −48 °C for 5 h, quenched by addition of glacial AcOH (832 μL, 14.2 mmol), warmed to room temperature, and diluted with saturated aqueous NH_4Cl (90 mL). Upon concentration, the residue was resuspended with H_2O (100 mL) and extracted with Et_2O (6 × 100 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (2 × 150 mL) and brine (1 × 150 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:7 EtOAc/hexane) to give 7.25 g (82%) of *cis*-epoxy ketone **58** and 0.70 g (8%) of *trans*-epoxy ketone **59**, both as white solids. Data for **58**: mp 118−119 °C; TLC R_f 0.34 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1775, 1720, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.13 (dd, J = 6.5, 3.1 Hz, 1 H), 3.92 (dd, J = 4.4, 3.3 Hz, 1 H), 3.75 (dd, J = 9.7, 8.3 Hz, 1 H), 3.63 (dd, J = 9.7, 6.2 Hz, 1 H), 3.44 (dd, J = 10.5, 3.8 Hz, 1 H), 3.37 (d, J = 4.4 Hz, 1 H), 2.92 (dd, J = 10.5, 6.5 Hz, 1 H), 2.07 (m, 1 H), 1.55−1.28 (c, 4 H), 1.26 (s, 3 H), 0.83 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 205.6, 178.4, 72.5, 63.8, 59.2, 55.0, 47.9, 43.3, 38.8, 37.5, 32.2, 26.5, 25.8, 20.3, 18.1, −5.5 (2); MS (CI, methane) m/z 367 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{19}H_{31}O_5Si$ (M + H^+) 367.1941, found 367.1945. Anal. Calcd for $C_{19}H_{30}O_5Si$: C, 62.32; H, 8.26. Found: C, 62.08; H, 7.99.

Data for **59**: mp 131−132 °C; TLC R_f 0.44 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1775, 1725, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.00 (d, J = 3.5 Hz, 1 H), 3.77 (dd, J = 9.7, 5.4 Hz, 1 H), 3.73 (d, J = 2.7 Hz, 1 H), 3.61 (dd, J = 9.7, 2.5 Hz, 1 H), 3.36 (d, J = 2.8 Hz, 1 H), 2.18 (dd, J = 12.8, 10.2 Hz, 1 H), 2.08 (m, 1 H), 2.00 (dd, J = 12.8, 4.0 Hz, 1 H), 1.82 (m, 1 H), 1.63−1.35 (c, 3 H), 1.28 (s, 3 H), 0.82 (s, 9 H), −0.02 (s, 3 H), −0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 200.1, 178.6, 72.2, 64.2, 54.2, 51.1, 45.4, 44.9, 43.1, 34.7, 30.1, 25.8, 24.3, 22.3, 18.2, −5.6 (2); MS (CI, methane) m/z 367 (M + H^+); HRMS (CI, isobutane) exact mass calcd for

$C_{19}H_{31}O_5Si$ ($M + H^+$) 367.1941, found 367.1948. Anal. Calcd for $C_{19}H_{30}O_5Si$: C, 62.32; H, 8.26. Found: C, 62.06; H, 8.33.

(2aα,5β,6aβ,7aβ,7bα,7cα)-(±)-5-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-2a,3,4,5,6a,7a,7b,7c-octahydro-2a-methyl-2-oxo-2*H*-oxireno-[2,3]naphtho[1,8-*bc*]furan-6-yl Trifluoromethanesulfonate (85). To a tan-yellow heterogeneous mixture of *cis*-epoxy ketone **58** (6.57 g, 17.9 mmol) and $PhNTf_2$ (8.34 g, 23.3 mmol) in THF (93 mL) at −78 °C with stirring under N_2 was added NaHMDS (26.9 mL, 1.0 M in THF, 26.9 mmol). The resulting brown-orange homogeneous solution was stirred at −78 °C for 30 min, quenched by addition of saturated aqueous NH_4Cl (100 mL), warmed to room temperature, diluted with H_2O (50 mL), and extracted with Et_2O (5 × 125 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:10 → 1:8 EtOAc/hexane) to give 7.28 g (81%) of vinyl triflate **85** as a white solid: mp 140−141 °C; TLC R_f 0.27 (1:3 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1780, 1420, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.08 (dd, J = 6.0, 2.2 Hz, 1 H), 3.96 (dd, J = 10.0, 4.2 Hz, 1 H), 3.88 (dd, J = 4.0, 2.4 Hz, 1 H), 3.56 (t, J = 9.9 Hz, 1 H), 3.53 (d, J = 4.0 Hz, 1 H), 2.75 (d, J = 6.1 Hz, 1 H), 2.53 (m, 1 H), 2.18 (m, 1 H), 1.82 (m, 1 H), 1.65−1.45 (c, 2 H), 1.41 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 178.2, 137.7, 129.3, 118.3 (q, J = 320 Hz), 71.0, 61.6, 52.9, 49.3, 45.4, 45.2, 41.0, 29.8, 25.8, 25.0, 23.2, 18.1, −5.6 (2); MS (CI, methane) m/z 499 ($M + H^+$); HRMS (CI, isobutane) exact mass calcd for $C_{20}H_{30}F_3O_7SSi$ ($M + H^+$) 499.1434, found 499.1425. Anal. Calcd for $C_{20}H_{29}F_3O_7SSi$: C, 48.18; H, 5.86. Found: C, 48.17; H, 5.74.

(2aα,5β,6aβ,7aβ,7bα,7cα)-(±)-5-[[(*tert*-Butyldimethylsilyl)oxy]-methyl]-6-ethenyl-2a,3,4,5,6a,7a,7b,7c-octahydro-2a-methyl-2*H*-oxireno[2,3]naphtho[1,8-*bc*]furan-2-one (89). To a colorless mixture of vinyl triflate **85** (3.91 g, 7.85 mmol), vinyltributyltin (4.59 mL, 15.7 mmol), and LiCl (999 mg, 23.6 mmol, dried at 160 °C under high vacuum for 24 h) in THF (78 mL) with stirring under N_2 was added $(Ph_3P)_2PdCl_2$ (550 mg, 785 μmol). The resulting yellow solution was stirred at reflux for 3.5 h, cooled to room temperature, diluted with H_2O (20 mL), and extracted with Et_2O (4 × 50 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:10 → 1:8 EtOAc/hexane, 2x) to give 1.59 g (54%) of diene **89** as a white solid: mp 108−109 °C; TLC R_f 0.34 (1:3 EtOAc/hexane); IR ($CDCl_3$) 2950, 2930, 2850, 1770, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.72 (dd, J = 17.6, 11.3 Hz, 1 H), 5.48 (d, J = 17.6 Hz, 1 H), 5.27 (d, J = 11.3 Hz, 1 H), 5.10 (dd, J = 5.9, 2.2 Hz, 1 H), 3.76 (d, J = 3.8 Hz, 1 H), 3.72 (dd, J = 3.9, 2.3 Hz, 1 H), 3.60 (dd, J = 10.5, 4.9 Hz, 1 H), 3.24 (t, J = 10.5 Hz, 1 H), 2.80 (m, 1 H), 2.58 (d, J = 5.8 Hz, 1 H), 2.07 (m, 1 H), 1.89 (ddd, J = 13.3, 7.8, 3.9 Hz, 1 H), 1.58−1.39 (c, 2 H), 1.40 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) 180.1, 133.9 (2), 127.1, 114.8, 72.5, 62.4, 50.6, 48.7, 44.2, 43.7, 39.2, 27.0, 25.8, 25.2, 20.6, 18.1, −5.4, −5.5; MS (CI, methane) m/z 377 ($M + H^+$); HRMS (CI, isobutane) exact mass calcd for $C_{21}H_{33}O_4Si$ ($M + H^+$) 377.2149, found 377.2136. Anal. Calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.56. Found: C, 66.70; H, 8.48.

(2aα,5β,6aβ,7aβ,7bα,7cα)-(±)-6-Ethenyl-2a,3,4,5,6a,7a,7b,7c-octahydro-5-(hydroxymethyl)-2a-methyl-2*H*-oxireno[2,3]naphtho[1,8-*bc*]furan-2-one (91). To a pale yellow solution of silyl ether **89** (1.59 g, 4.23 mmol) in THF (42 mL) with stirring under N_2 at 0 °C was added glacial AcOH (290 μL, 5.08 mmol) followed by TBAF (10.6 mL, 1.0 M in THF, 10.6 mmol). The resulting yellow solution was stirred with slow warming to room temperature over 1 h and then at room temperature for an additional 3 h, concentrated, and purified by flash column chromatography (2:3 → 3:2 EtOAc/hexane) to give 1.06 g (96%) of dienyl alcohol **91** as a white foam: mp 124−126 °C; TLC R_f 0.18 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3600 (s), 3490 (br), 2920, 2880, 1770, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.72 (dd, J = 17.6, 11.2 Hz, 1 H), 5.49 (d, J = 17.5 Hz, 1 H), 5.30 (d, J = 11.3 Hz, 1 H), 5.11 (d, J = 6.2 Hz, 1 H), 3.73 (s, 2 H), 3.71 (dd, J = 10.5, 4.7 Hz, 1 H), 3.40 (t, J = 10.5 Hz, 1 H), 2.81 (m, 1 H), 2.60 (d, J = 5.9 Hz, 1 H), 2.15 (m, 1 H), 1.83 (m, 1 H), 1.67−1.53 (c, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 180.1, 133.7, 133.5, 127.2, 115.4, 72.5, 62.5, 50.8, 48.9, 44.4, 44.0, 39.6, 27.5, 25.2, 21.2; MS (CI, methane) m/z 263 ($M + H^+$); HRMS (CI, isobutane) exact mass calcd for $C_{15}H_{19}O_4$ ($M + H^+$) 263.1284, found 263.1283. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.78; H, 6.85.

(2aα,5β,6aβ,7aβ,7bα,7cα)-(±)-6-Ethenyl-2a,3,4,5,6a,7a,7b,7c-octahydro-5-[[(methylsulfonyl)oxy]methyl]-2a-methyl-2*H*-oxireno[2,3]-naphtho[1,8-*bc*]furan-2-one (99). To a pale yellow solution of dienyl alcohol **91** (1.06 g, 4.05 mmol) and DMAP (49.3 mg, 405 μmol) in CH_2Cl_2 (27 mL) at 0 °C with stirring under N_2 was added Et_3N (1.1 mL, 9.16 mmol) followed by MsCl (467 μL, 6.07 mmol). This mixture was stirred at 0 °C for 15 min, poured into saturated aqueous $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:1 → 3:2 EtOAc/hexane) to give 1.32 g (96%) of dienyl mesylate **99** as a white foam/oil: TLC R_f 0.28 (1:1 EtOAc/hexane); IR ($CDCl_3$) 2960, 2930, 1770, 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.70 (ddd, J = 17.5, 11.2, 1.1 Hz, 1 H), 5.56 (d, J = 17.4 Hz, 1 H), 5.42 (d, J = 11.2 Hz, 1 H), 5.13 (dt, J = 5.9, 1.6 Hz, 1 H), 4.30 (dd, J = 10.7, 4.4 Hz, 1 H), 3.86 (t, J = 10.8 Hz, 1 H), 3.75 (s, 1 H), 3.74 (d, J = 1.7 Hz, 1 H), 3.10 (m, 1 H), 2.99 (s, 3 H), 2.62 (d, J = 5.9 Hz, 1 H), 2.11 (m, 1 H), 1.83 (m, 1 H), 1.73−1.57 (c, 2 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 179.6, 132.9, 130.6, 128.8, 117.0, 72.2, 68.1, 50.4, 48.4, 44.0, 43.3, 37.3, 36.5, 26.7, 24.9, 20.8; MS (CI, isobutane) m/z 341 ($M + H^+$); HRMS (CI, isobutane) exact mass calcd for $C_{16}H_{21}O_6S$ ($M + H^+$) 341.1060, found 341.1054.

(2aα,4aα,5a*R,8α,8aα,8bα)-(±)-6-Ethenyl-2a,3,4,4a,5,8,8a,8b-octahydro-8-hydroxy-2a-methyl-2*H*-cyclopropa[4a,5]naphtho[1,8-*bc*]-furan-2-one (96).** To a colorless solution of dienyl mesylate **99** (1.32 g, 3.88 mmol) in THF (26 mL) at 0 °C with stirring under N_2 was added Me_3SnLi[55] (8.54 mL, 0.5 M in Et_2O/THF, 4.27 mmol). After 5 min, a second aliquot of Me_3SnLi (8.54 mL, 0.5 M in Et_2O/THF, 4.27 mmol) was added. This pale yellow homogeneous solution was stirred for another 5 min, quenched by addition of saturated aqueous NH_4Cl (10 mL), warmed to room temperature, and extracted with EtOAc (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:3 → 1:2 EtOAc/hexane) to give 635 mg (66%) of cyclopropyl dienol **96** as a white solid: mp 101−103 °C; TLC R_f 0.42 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3590 (s), 3450 (br), 2960, 2930, 2860, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.01 (dd, J = 17.4, 10.8 Hz, 1 H), 5.84 (d, J = 2.0 Hz, 1 H), 5.34 (d, J = 17.3 Hz, 1 H), 5.02 (d, J = 10.8 Hz, 1 H), 4.63 (dd, J = 6.9, 4.6 Hz, 1 H), 4.59 (m, 1 H), 2.84 (d, J = 4.4 Hz, 1 H), 2.28 (d, J = 6.8 Hz, 1 H), 1.90−1.78 (c, 3 H), 1.72 (m, 1 H), 1.49 (m, 1 H), 1.26 (s, 3 H), 0.81 (t, J = 5.0 Hz, 1 H), 0.07 (dd, J = 8.4, 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 183.0, 143.3, 132.5, 127.4, 115.9, 86.7, 72.0, 44.4, 40.1, 26.5, 26.4, 20.4, 18.6, 14.4, 8.3; MS (EI) m/z 246 (M^+); HRMS (EI) exact mass calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1252. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.96; H, 7.37.

(2aα,4aα,5a*R,8α,8aα,8bα)-(±)-6-Ethenyl-2a,3,4,4a,5,8,8a,8b-octahydro-2a-methyl-2-oxo-2*H*-cyclopropa[4a,5]naphtho[1,8-*bc*]furan-8-yl (*E*)-3-Methyl-4-oxo-2-butenoate (107).** To a colorless solution of dienol **96** (635 mg, 2.58 mmol), (*E*)-3-methyl-4-oxo-2-butenoic acid[57b,58] (**106**; 441 mg, 3.87 mmol), and DMAP (315 mg, 2.58 mmol) in CH_2Cl_2 (12.9 mL) at 0 °C with stirring under N_2 was added DCC (3.35 mL, 1.0 M in CH_2Cl_2, 3.35 mmol). This turbid mixture was immediately warmed to room temperature, and after 35 min, additional DMAP (105 mg, 861 μmol), butenoic acid **106** (147 mg, 1.29 mmol), and DCC (1.11 mL, 1.0 M in CH_2Cl_2, 1.11 mmol) were added. The resulting brown mixture was stirred for 25 min, diluted with EtOAc (15 mL), and filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (1:5 EtOAc/hexane) to give 821 mg (93%) of dienyl ester **107** as a pale yellow oil: TLC R_f 0.26 (1:3 EtOAc/hexane); IR ($CDCl_3$) 2910, 2840, 1765, 1715, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.55 (s, 1 H), 6.54 (d, J = 1.5 Hz, 1 H), 6.01 (dd, J = 17.3, 10.8 Hz, 1 H), 5.71 (d, J = 2.2 Hz, 1 H), 5.62 (m, 1 H), 5.36 (d, J = 17.3 Hz, 1 H), 5.07 (d, J = 10.8 Hz, 1 H), 4.80 (dd, J = 7.1, 4.6 Hz, 1 H), 2.34 (d, J = 7.1 Hz, 1 H), 1.85 (s, 3 H), 1.92−1.79 (c, 3 H), 1.74 (m, 1 H), 1.50 (m, 1 H), 1.28 (s, 3 H), 0.88 (t, J = 5.1 Hz, 1 H), 0.21 (dd, J = 8.4, 5.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 193.9, 181.7, 164.3, 151.2, 144.9, 134.2, 131.9, 122.5, 117.0, 82.3, 74.6, 43.8, 39.9, 26.3, 26.2, 20.3, 18.5, 14.4,

10.8, 8.4; MS (EI) *m/z* 342 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{22}O_5$ (M^+) 342.1468, found 342.1470.

(1aα,3aα,5aα,5bβ,7aβ,7bβ,8α,10b*R,10cα)-(±)-8-Ethenyl-1,1a,2,3,-3a,5a,5b,7a,7b,8,9,10c-dodecahydro-3a,8-dimethylcyclopropa[4,4a]-phenanthro[9,8-*bc*:10,1-*b'c'*]difuran-4,7-dione (109).** A solution of dienyl ester **107** (821 mg, 2.40 mmol) in PhH (48 mL) was heated at reflux with stirring under N_2 for 13 h, cooled to room temperature, and concentrated to give Diels–Alder adduct **108** as a white solid. A portion was removed and purified by flash column chromatography (2.5 → 5% Et_2O/CH_2Cl_2) for analytical data: mp 245–258 °C dec; TLC R_f 0.20 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2980, 2920, 1775, 1765, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.57 (s, 1 H), 5.34 (dt, *J* = 6.4, 3.0 Hz, 1 H), 4.99 (dd, *J* = 8.7, 3.8 Hz, 1 H), 4.82 (dd, *J* = 7.1, 3.8 Hz, 1 H), 3.10 (dd, *J* = 14.6, 8.7 Hz, 1 H), 2.60 (dd, *J* = 17.6, 6.4 Hz, 1 H), 2.50 (d, *J* = 14.7 Hz, 1 H), 2.48 (d, *J* = 7.0 Hz, 1 H), 1.92–1.73 (c, 4 H), 1.61–1.48 (c, 2 H), 1.36 (s, 3 H), 1.28 (s, 3 H), 0.72 (t, *J* = 4.8 Hz, 1 H), 0.26 (dd, *J* = 8.3, 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.2, 181.4, 172.2, 143.7, 117.2, 80.0, 79.8, 46.6, 46.3, 45.5, 40.8, 37.4, 33.4, 26.5, 26.4, 18.5, 17.0, 13.5, 9.8; MS (EI) *m/z* 342 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{22}O_5$ (M^+) 342.1468, found 342.1457.

To a white heterogeneous mixture of crude Diels–Alder adduct **108** in THF (12 mL) at −78 °C with stirring under N_2 was added $Ph_3P{=}CH_2$ (12.0 mL, 0.5 M in THF, 6.00 mmol; prepared by addition of NaHMDS to Ph_3PCH_3Br at room temperature, 15 min). The resulting green mixture was stirred at −78 °C for 10 min and at 0 °C for 10 min, quenched by addition of saturated aqueous NH_4Cl (5 mL), concentrated, diluted with half-saturated brine (10 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:5 EtOAc/hexane) to give 697 mg (85%) of dilactone **109** as a white solid: mp 216–217 °C (recrystallized from 3:2 EtOAc/hexane); TLC R_f 0.33 (1:3 EtOAc/hexane); IR ($CDCl_3$) 2960, 2920, 1770 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.38 (dd, *J* = 17.5, 10.9 Hz, 1 H), 5.59 (m, 1 H), 5.11 (d, *J* = 10.9 Hz, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 4.88 (d, *J* = 4.7 Hz, 1 H), 4.75 (d, *J* = 4.3 Hz, 1 H), 3.14 (m, 1 H), 2.68 (dd, *J* = 6.3, 1.1 Hz, 1 H), 2.48 (d, *J* = 4.5 Hz, 1 H), 2.39 (dt, *J* = 18.2, 2.4 Hz, 1 H), 1.96 (dd, *J* = 13.9, 5.7 Hz, 1 H), 1.89–1.68 (c, 3 H), 1.55–1.37 (c, 2 H), 1.23 (s, 3 H), 1.00 (s, 3 H), 0.78 (dd, *J* = 5.5, 4.0 Hz, 1 H), 0.03 (dd, *J* = 8.3, 5.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 181.5, 174.2, 144.8, 133.1, 122.4, 112.3, 77.1, 74.5, 49.7, 44.8, 43.0, 37.6, 35.0, 32.8, 27.4, 24.3, 23.6, 21.6, 19.1, 14.5, 10.2; MS (EI) *m/z* 340 (M^+); HRMS (EI) exact mass calcd for $C_{21}H_{24}O_4$ (M^+) 340.1675, found 340.1661.

(1aα,3aα,5aα,5bβ,7β,7aβ,7bβ,8a,10b*R,10cα)-8-Ethenyl-1a,2,3,-3a,5a,5b,7,7a,7b,8,9,10c-dodecahydro-7-hydroxy-3a,8-dimethylcy-clopropa[4,4a]phenanthro[9,8-*bc*:10,1-*b'c'*]furan-4(1*H*)-one (111).** To a colorless solution of dilactone **109** (697 mg, 2.05 mmol) in CH_2Cl_2 (13.7 mL) at −48 °C with stirring under N_2 was added DIBAL-H (5.20 mL, 1.0 M in PhMe, 5.20 mmol). After 10 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), warmed to room temperature, and diluted with 1 N HCl (15 mL)/CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give an inseparable mixture (4:1 at C19) of dilactols **110** as a white solid. A portion was removed and purified by flash column chromatography (2% → 5% MeOH in 1:2 EtOAc/hexane) for analytical data: TLC R_f 0.29 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3580 (s), 3380 (s), 2970, 2920 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.90 (dd, *J* = 17.7, 10.7 Hz, 1 H), 5.37 (m, 1 H), 5.17 (d, *J* = 4.0 Hz, 0.8 H), 5.08–4.95 (c, 3 H), 4.88 (d, *J* = 4.1 Hz, 0.2 H), 4.58 (d, *J* = 4.0 Hz, 0.2 H), 4.54 (d, *J* = 4.0 Hz, 0.8 H), 4.36 (d, *J* = 3.7 Hz, 0.8 H), 4.02 (d, *J* = 4.1 Hz, 0.2 H), 3.45 (d, *J* = 4.0 Hz, 0.2 H), 3.14 (d, *J* = 4.9 Hz, 0.8 H), 3.05 (d, *J* = 3.7 Hz, 0.8 H), 2.94 (d, *J* = 4.0 Hz, 0.2 H), 2.84 (m, 1 H), 2.22 (br d, *J* = 18.0 Hz, 1 H), 2.15–2.07 (c, 1.8 H), 1.98 (d, *J* = 4.7 Hz, 0.2 H), 1.85–1.72 (c, 3 H), 1.66–1.22 (c, 3 H), 1.03 (s, 2.4 H), 1.01 (s, 0.6 H), 0.95 (s, 3 H), 0.81 (t, *J* = 4.3 Hz, 1 H), 0.00 (dd, *J* = 8.3, 5.2 Hz, 0.8 H), −0.09 (dd, *J* = 9.3, 6.2 Hz, 0.2 H); MS (EI) *m/z* 344 (M^+).

To a white heterogeneous mixture of crude dilactols **110** in CH_2Cl_2 (102 mL) at room temperature with stirring under N_2 was added Celite followed by PDC[36] (1.16 g, 3.08 mmol). This dark brown mixture was stirred for 5 h and then filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (1:4 → 1:2 EtOAc/hexane) to give 521 mg (74%) of desired monolactol **111** and 100 mg (14%) of starting dilactone **109**, both as white solids. Data for **111**: mp 188–189 °C; TLC R_f 0.41 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3570 (s), 3400 (br), 2960, 2920, 1760, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.90 (dd, *J* = 17.7, 10.6 Hz, 1 H), 5.46 (m, 1 H), 5.07–4.98 (c, 3H), 4.71 (d, *J* = 4.1 Hz, 1 H), 4.62 (d, *J* = 4.2 Hz, 1 H), 2.87 (m, 1 H), 2.62 (d, *J* = 4.0 Hz, 1 H), 2.41 (d, *J* = 4.3 Hz, 1 H), 2.24 (d, *J* = 17.9 Hz, 1 H), 2.15 (dd, *J* = 6.1, 5.1 Hz, 1 H), 1.96 (dd, *J* = 13.9, 5.0 Hz, 1 H), 1.89–1.68 (c, 3 H), 1.51–1.36 (c, 2 H), 1.22 (s, 3 H), 0.96 (s, 3 H), 0.75 (dd, *J* = 5.5, 4.9 Hz, 1 H), −0.01 (dd, *J* = 8.0, 5.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 182.3, 146.4, 134.9, 119.1, 111.3, 98.5, 76.9, 76.0, 56.5, 45.0, 43.1, 39.6, 35.0, 31.4, 27.6, 26.0, 23.7, 22.3, 19.3, 14.3, 10.3; MS (EI) *m/z* 342 (M^+); HRMS (EI) exact mass calcd for $C_{21}H_{26}O_4$ (M^+) 342.1832, found 342.1826.

(2aα,4aα,5α,5aβ,6β,7α,9b*R,9cα,10aα)-(±)-7-Ethenyl-5-(formyl-oxy)-1,2,2a,4a,5,5a,6,7,8,9c,10,10a-dodecahydro-6-iodo-2a,7-dimethyl-3*H*-cyclopropa[4,4a]phenanthro[10,1-*bc*]furan-3-one (112) and (2aα,-4aα,5α,5aβ,6α,7α,9b*R**,9cα,10aα)-(±)-7-Ethenyl-5-(formyloxy)-1,2,2a,4a,5,5a,6,7,8,9c,10,10a-dodecahydro-6-iodo-2a,7-dimethyl-3*H*-cyclopropa[4,4a]phenanthro[10,1-*bc*]furan-3-one (113).** A heterogeneous purple mixture of monolactol **111** (521 mg, 1.52 mmol), iodobenzene diacetate (506 mg, 1.57 mmol), and iodine (425 mg, 1.68 mmol) in cyclohexane (152 mL) was stirred at room temperature under N_2 in the presence of a 150-W white flood light (3 in. away) for 30 min. The dark purple homogeneous solution was cooled to room temperature, diluted with brine (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (2 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:6 → 1:5 EtOAc/hexane) to give 601 mg (84%) of β-iodo formate **112** as a white solid and 89.3 mg (12%) of α-iodo formate **113** as a pale yellow solid. Data for **112**: mp 187–189 °C dec; TLC R_f 0.36 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2960, 2920, 2850, 1770, 1725, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.14 (s, 1 H), 5.97 (t, *J* = 2.7 Hz, 1 H), 5.69 (dd, *J* = 17.3, 10.7 Hz, 1 H), 5.42 (dt, *J* = 6.3, 1.8 Hz, 1 H), 5.06 (d, *J* = 10.7 Hz, 1 H), 5.00 (d, *J* = 17.3 Hz, 1 H), 4.51 (dd, *J* = 3.5, 2.9 Hz, 1 H), 4.15 (d, *J* = 10.4 Hz, 1 H), 2.95 (br d, *J* = 8.5 Hz, 1 H), 2.42 (d, *J* = 3.8 Hz, 1 H), 2.30 (d, *J* = 17.5 Hz, 1 H), 2.04 (dd, *J* = 17.3, 6.2 Hz, 1 H), 1.92 (dd, *J* = 14.4, 5.6 Hz, 1 H), 1.86–1.65 (c, 3 H), 1.42 (m, 1 H), 1.21 (s, 3 H), 0.99 (s, 3 H), 0.88 (dd, *J* = 5.4, 3.8 Hz, 1 H), −0.08 (dd, *J* = 8.3, 5.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 181.6, 159.5, 148.2, 136.5, 117.7, 112.8, 75.9, 71.3, 46.3, 43.8, 43.7, 43.0, 41.1, 35.4, 27.9, 23.4, 22.5, 19.5, 18.5, 14.6, 13.6; MS (CI, isobutane) *m/z* 469 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{21}H_{26}IO_4$ (M + H^+) 469.0877, found 469.0870. Anal. Calcd for $C_{21}H_{25}IO_4$: C, 53.86; H, 5.38. Found: C, 54.09; H, 5.43. Data for **113**: mp 160–162 °C dec; TLC R_f 0.48 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2960, 2920, 1775, 1720, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.20 (s, 1 H), 5.81 (dd, *J* = 17.3, 10.8 Hz, 1 H), 5.60 (t, *J* = 8.4 Hz, 1 H), 5.50 (dt, *J* = 3.4, 3.2 Hz, 1 H), 5.44 (t, *J* = 7.7 Hz, 1 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 4.96 (d, *J* = 17.4 Hz, 1 H), 3.86 (d, *J* = 3.0 Hz, 1 H), 3.80 (m, 1 H), 2.64 (d, *J* = 7.7 Hz, 1 H), 2.42 (dt, *J* = 18.5, 3.6 Hz, 1 H), 2.00 (dt, *J* = 18.5, 3.2 Hz, 1 H), 1.93–1.67 (c, 3 H), 1.61–1.48 (c, 2 H), 1.28 (s, 3 H), 1.12 (s, 3 H), 0.71 (t, *J* = 4.8 Hz, 1 H), 0.31 (dd, *J* = 8.3, 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 182.0, 160.0, 148.1, 135.6, 118.8, 112.5, 77.5, 75.9, 45.2, 41.8, 40.4, 40.0, 39.4, 35.0, 27.3, 26.5, 23.0, 21.7, 19.0, 13.9, 10.1; MS (CI, isobutane) *m/z* 469 (M + H^+); HRMS (CI, isobutane) exact mass calcd for $C_{21}H_{26}IO_4$ (M + H^+) 469.0877, found 469.0862.

(2aα,4aα,5α,5aβ,7α,9b*R,9cα,10aα)-(±)-7-Ethenyl-1,2,2a,4a,5,-5a,6,7,8,9c,10,10a-dodecahydro-5-hydroxy-2a,7-dimethyl-3*H*-cyclo-propa[4,4a]phenanthro[10,1-*bc*]furan-3-one (118) and (2aα,4aα,5α,-5aβ,6α,7α,9b*R**,9cα,10aα)-(±)-6-Ethenyl-1,2,2a,4a,5,5a,6,7,8,9c,10,10a-dodecahydro-5-hydroxy-2a,7-dimethyl-3*H*-cyclopropa[4,4a]-phenanthro[10,1-*bc*]furan-3-one (117). From β-Iodo Formate 112.** To a cloudy solution of β-iodo formate **112** (251 mg, 536 μmol) in aged[78] Bu_3SnH (26.8 mL, 0.02 M) at 80 °C with stirring under N_2 was added AIBN (17.6 mg, 107 μmol). After 20 min, the resulting

homogeneous solution was cooled to room temperature and purified by flash column chromatography (1:3 EtOAc/hexane, 2×) to give 132 mg (78%) of desired β,γ-unsaturated alcohol **118** as a white foam and 26.1 mg (15%) of rearrangement product **117** as a white solid.

From α-Iodo Formate 113. To a cloudy solution of α-iodo formate **113** (78.6 mg, 168 μmol) in aged Bu_3SnH (8.4 mL, 0.02 M) at 110 °C with stirring under N_2 was added AIBN (5.6 mg, 33.6 μmol). After 10 min, the resulting homogeneous solution was cooled to room temperature and purified by flash column chromatography (1:3 EtOAc/hexane, 2×) to give 32.0 mg (61%) of desired β,γ-unsaturated alcohol **118** as a white foam and 14.3 mg (27%) of rearrangement product **117** as a white solid.

Data for **118**: mp 131−133 °C; TLC R_f 0.29 (1:2 EtOAc/hexane); IR ($CDCl_3$) 3600 (s), 3520 (s), 3490 (br), 2960, 2920, 2850, 1760, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.82 (dd, J = 17.5, 10.7 Hz, 1 H), 5.43 (dt, J = 6.3, 1.8 Hz, 1 H), 4.94 (dd, J = 17.5, 1.0 Hz, 1 H), 4.90 (dd, J = 10.6, 1.0 Hz, 1 H), 4.58 (t, J = 3.3 Hz, 1 H), 4.20 (t, J = 3.1 Hz, 1 H), 2.65 (m, 1 H), 2.46 (d, J = 3.8 Hz, 1 H), 2.04 (d, J = 16.6 Hz, 1 H), 1.91 (dd, J = 14.3, 5.7 Hz, 1 H), 1.83−1.52 (c, 5 H), 1.48−1.35 (c, 2 H), 1.23 (s, 3 H), 0.86 (m, 1 H, buried), 0.84 (s, 3 H), −0.10 (dd, J = 8.1, 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 183.0, 149.2, 137.0, 118.4, 109.9, 79.3, 69.5, 43.7, 42.6, 36.1, 35.9, 35.4, 34.5, 27.8, 23.5, 22.9, 22.0, 19.3, 14.1, 13.5; MS (EI) m/z 314 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{26}O_3$ (M^+) 314.1883, found 314.1874. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.28; H, 8.37.

Data for **117**: mp 195−220 °C dec; TLC R_f 0.34 (1:2 EtOAc/hexane); IR ($CDCl_3$) 3590 (s), 3480 (br), 2980, 2930, 2900, 1755, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.65 (dt, J = 17.2, 10.1 Hz, 1 H), 5.36 (m, 1 H, buried), 5.31 (dd, J = 17.3, 2.4 Hz, 1 H), 5.18 (dd, J = 10.0, 2.4 Hz, 1 H), 4.64 (t, J = 7.8 Hz, 1 H), 4.51 (m, 1 H), 3.05 (m, 1 H), 2.66 (dt, J = 10.2, 3.4 Hz, 1 H), 2.26 (d, J = 7.8 Hz, 1 H), 2.21−2.04 (c, 2 H), 1.95−1.55 (c, 5 H), 1.53−1.32 (c, 2 H), 1.23 (s, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.62 (t, J = 4.5 Hz, 1 H), 0.26 (dd, J = 8.2, 5.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 182.8, 137.1, 135.1, 119.6, 119.3, 82.4, 73.8, 46.1, 44.3, 43.2, 40.6, 32.7, 31.2, 27.6, 26.4, 22.0, 19.9, 19.0, 13.3, 10.1; MS (EI) m/z 314 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{26}O_3$ (M^+) 314.1883, found 314.1896.

(2aα,4aα,5a*R,7α,9a*R**,9b*R**,9cα,10aα)-(±)-7-Ethenyldecahydro-2a,7-dimethyl-5a,9a-epoxy-3*H*-cyclopropa[4,4a]phenanthro[10,1-*bc*]-furan-3,5(1*H*)-dione (123).** To a colorless solution of β,γ-unsaturated alcohol **118** (132 mg, 419 μmol) in CH_2Cl_2 (4.2 mL) at room temperature with stirring under N_2 was added Dess-Martin periodinane[62] (895 mg, 2.10 mmol). This white heterogeneous mixture was stirred for 10 min and then rapidly filtered through a plug of silica gel (10 g), washing with CH_2Cl_2 (250 mL). The filtrate was evaporated to approximately 40 mL, PhMe (40 mL) was added, and this mixture was concentrated to give β,γ-unsaturated ketone **119** as a pale yellow solid: mp 112−115 °C; TLC R_f 0.45 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2950, 2920, 2850, 1770, 1710, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.72 (dd, J = 17.2, 10.5 Hz, 1 H), 5.50 (m, 1 H), 4.91 (dd, J = 17.2, 0.8 Hz, 1 H), 4.90 (dd, J = 10.5, 1.1 Hz, 1 H), 4.59 (d, J = 5.4 Hz, 1 H), 3.17 (m, 1 H), 2.54 (d, J = 5.4 Hz, 1 H), 2.02 (dt, J = 17.8, 3.2 Hz, 1 H), 1.94−1.71 (c, 6 H), 1.67 (m, 1 H), 1.49 (m, 1 H), 1.24 (s, 3 H), 0.91 (s, 3 H), 0.84 (dd, J = 5.4, 4.0 Hz, 1 H), 0.16 (dd, J = 8.2, 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 204.1, 181.4, 147.5, 135.6, 120.0, 110.8, 78.5, 47.7, 46.1, 42.2, 35.4, 35.2, 34.3, 27.3, 24.4, 23.8, 23.2, 19.2, 15.0, 10.9; MS (EI) m/z 312 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{24}O_3$ (M^+) 312.1726, found 312.1728.

Argon gas was bubbled directly into a pale yellow solution of crude β,γ-unsaturated ketone **119** in MeOH (4.2 mL) with stirring at room temperature for 20 min when a premixed, deoxygenated solution of H_2O_2 (260 μL, 2.55 mmol) and 3 N NaOH (140 μL, 420 μmol) in MeOH (300 μL) was added rapidly. The solution yellowed and then turned colorless after 10 min. This mixture was stirred for an additional 5 min, quenched by addition of saturated aqueous NH_4Cl (10 mL), concentrated, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (1 × 20 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:4 EtOAc/hexane) to give 91.5 mg (67%) of epoxy ketone **123** as a white solid: mp 200−201 °C; TLC R_f 0.36 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2950, 2920, 2850, 1770, 1720, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.73 (dd, J = 17.5, 10.7 Hz, 1 H), 4.95 (d, J = 17.9 Hz, 1 H), 4.94 (d, J = 7.5 Hz, 1 H), 4.91 (d, J = 10.7 Hz, 1 H), 3.16 (d, J = 7.4 Hz, 1 H), 2.68 (dd, J = 15.0, 2.4 Hz, 1 H), 1.90−1.66 (c, 4 H), 1.54−1.37 (c, 5 H), 1.30 (s, 3 H), 1.21 (m, 1 H), 0.85 (s, 3 H), 0.54 (dd, J = 6.6, 4.6 Hz, 1 H), 0.34 (ddd, J = 8.1, 6.6, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.2, 180.5, 147.6, 110.8, 79.2, 68.3, 64.7, 42.0, 40.3, 32.8, 31.4, 28.8, 27.0, 26.2, 22.4, 19.8, 18.6 (2), 13.8, 5.0; MS (EI) m/z 328 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{24}O_4$ (M^+) 328.1675, found 328.1669. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.36. Found: C, 72.90; H, 7.49.

(2aα,4aα,5aβ,7α,9aα,9b*R,9cα,10aα)-(±)-7-Ethenyldodecahydro-9a-hydroxy-5a-[(4-methoxyphenyl)thio]-2a,7-dimethyl-3*H*-cyclopropa-[4,4a]phenanthro[10,1-*bc*]furan-3,5(1*H*)-dione (126).** To a colorless solution of 4-methoxythiophenol (405 μL, 3.30 mmol) in THF (2.4 mL) at 0 °C with stirring under N_2 was added n-BuLi (1.94 mL, 1.55 M in hexanes, 3.00 mmol) followed by Me_3Al (1.50 mL, 2.0 M in hexanes, 3.00 mmol). The resulting biphasic mixture was diluted with THF (2.7 mL) whereupon a homogeneous colorless solution (0.35 M) of the ate complex [4-MeOPhSAlMe$_3$]Li was obtained.[66]

To a pale yellow solution of epoxy ketone **123** (91.5 mg, 279 μmol) in THF (930 μL) at −20 °C with stirring under N_2 was added [4-MeOPhSAlMe$_3$]Li (4.0 mL, 0.35 M in THF/hexanes, 1.39 mmol). The resulting yellow solution was warmed to 0 °C, stirred for 1 h, diluted with EtOAc (5 mL), quenched by addition of 1 N HCl (5 mL), and warmed to room temperature over 10 min. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:9 → 1:1 EtOAc/hexane) to give 129 mg (99%) of β-hydroxy sulfide **126** as a white solid: mp 247−250 °C dec; TLC R_f 0.35 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3560 (s), 3450 (br), 2930, 2850, 1765, 1695, 1590, 1490, 1250, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.47 (d, J = 8.8 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 5.73 (dd, J = 17.5, 10.7 Hz, 1 H), 4.90 (dd, J = 17.6, 0.8 Hz, 1 H), 4.85 (dd, J = 10.7, 0.9 Hz, 1 H), 4.73 (d, J = 5.5 Hz, 1 H), 3.77 (s, 3 H), 3.19 (d, J = 5.5 Hz, 1 H), 2.07−1.89 (c, 2 H), 1.86−1.67 (c, 4 H), 1.57 (m, 1 H), 1.56 (s, 3 H), 1.51−1.37 (c, 3 H), 1.29 (s, 3 H), 1.23 (m, 1 H), 1.08 (dd, J = 7.6, 4.2 Hz, 1 H), 0.90 (t, J = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 194.8, 181.7, 160.8, 150.4, 139.2, 120.2, 114.3, 109.6, 79.5, 76.8, 65.3, 55.2, 43.5, 42.3, 35.3, 32.6, 31.3, 27.0, 26.4, 24.4, 23.6, 22.8, 19.4, 12.0, 9.9; MS (EI) m/z 468 (M^+); HRMS (EI) exact mass calcd for $C_{27}H_{32}O_5S$ (M^+) 468.1972, found 468.1996.

(±)-6-Desoxymyrocin C (5). To a white heterogeneous mixture of β-hydroxy sulfide **126** (129 mg, 276 μmol) in CH_2Cl_2 (2.0 mL) at 0 °C with stirring under N_2 was added 3,3-dimethyldioxirane[33] (**44**; 6.9 mL, 0.1 M in acetone, 691 μmol). The resulting homogeneous solution was stirred for 30 min, diluted with CH_2Cl_2 (10 mL), and quenched by addition of saturated aqueous $Na_2S_2O_3$ (6 mL)/saturated aqueous $NaHCO_3$ (3 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:3 → 2:3 EtOAc/hexane) to give 51.0 mg (56%) of 6-desoxymyrocin C (**5**) as a white solid: mp 177−179 °C; TLC R_f 0.24 (1:1 EtOAc/hexane); IR ($CDCl_3$) 3580 (s), 3470 (br), 2950, 2920, 2850, 1760, 1690, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.90 (d, J = 1.6 Hz, 1 H), 5.81 (dd, J = 17.5, 10.7 Hz, 1 H), 5.04 (d, J = 17.4 Hz, 1 H), 5.03 (d, J = 10.7 Hz, 1 H), 4.83 (d, J = 6.8 Hz, 1 H), 3.51 (d, J = 6.8 Hz, 1 H), 1.95−1.78 (c, 5 H), 1.64−1.44 (c, 3 H), 1.40 (m, 1 H), 1.33 (s, 3 H), 1.32 (m, 1 H), 1.06 (s, 3 H), 0.48 (dd, J = 6.8, 4.6 Hz, 1 H), 0.20 (td, J = 7.2, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 192.2, 181.9, 147.6, 144.9, 134.2, 112.8, 77.5, 69.9, 41.1, 39.9, 39.2, 29.1, 27.1, 26.3, 26.2, 24.0, 23.9, 18.8, 13.5, 5.9; MS (EI) m/z 328 (M^+); HRMS (EI) exact mass calcd for $C_{20}H_{24}O_4$ (M^+) 328.1675, found 328.1677.

(±)-Myrocin C (1). Oxygen was bubbled through a colorless solution of 6-desoxymyrocin C (**5**; 26.1 mg, 79.6 μmol) in THF (1.6 mL)/t-BuOH (0.8 mL) at −78 °C with stirring for 5 min, and then t-BuOK (26.7 mg, 239 μmol) was added in one portion. This bright

(78) It was necessary to utilize aged Bu_3SnH (presumably containing tin oxides; see ref 61) in order for formate cleavage to occur.

yellow mixture was stirred for an additional 3 h, quenched by addition of saturated aqueous NH_4Cl (5 mL), warmed to room temperature, and extracted with $CHCl_3$ (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, redissolved in THF (1.6 mL), and cooled to 0 °C. To this pale yellow solution with stirring under N_2 was added triethyl phosphite (20 μL, 119 μmol). After 10 min, this mixture was diluted with saturated aqueous NH_4Cl (5 mL), and extracted with $CHCl_3$ (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by flash column chromatography (1:2 EtOAc/hexane) to give 18.5 mg (68%) of myrocin C (**1**) as a white solid: mp >214 °C dec (recrystallized from EtOAc in a hexane atmosphere); TLC R_f 0.36 (1:1 EtOAc/hexane); IR (KBr) 3430 (s), 3290 (br), 2950, 2920, 2840, 1740, 1695, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.96 (d, J = 1.5 Hz, 1 H), 5.82 (dd, J = 17.5, 10.6 Hz, 1 H), 5.09 (d, J = 17.4 Hz, 1 H), 5.09 (d, J = 10.7 Hz, 1 H), 4.44 (s, 1 H), 3.35 (s, 1 H), 1.92−1.83 (c, 4 H), 1.65−1.54 (c, 4 H), 1.55 (s, 3 H), 1.47 (dt, J = 14.0, 3.7 Hz, 1 H), 1.42 (td, J = 13.9, 3.6 Hz, 1 H), 1.07 (s, 3 H), 0.47 (dd, J = 6.9, 4.7 Hz, 1 H), 0.19 (dd, J = 8.1, 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.8, 181.9, 149.0, 144.5, 134.2, 112.9, 99.0, 70.0, 44.8, 41.7, 39.3, 29.2, 28.8 (2), 26.5, 23.9, 23.7, 18.8, 14.0, 6.3; MS (CI, isobutane) m/z 345 ($M + H^+$); HRMS (CI, isobutane) exact mass calcd for $C_{20}H_{25}O_5$ ($M + H^+$) 345.1702, found 345.1717.

(2aα,4aα,7α,9b*R*,9cα,10aα)-(±)-7-Ethenyl-2,2a,4a,6,7,8,9,9c,10,-10a-decahydro-2a,7-dimethyl-6-(phenylthio)-3*H*-cyclopropa[4,4a]-phenanthro[10,1-*bc*]furan-3,5(1*H*)-dione (133).** To a colorless solution of 6-desoxymyrocin C (**5**; 2.0 mg, 6.10 μmol) in CH_2Cl_2 (200 μL) at room temperature with stirring under N_2 was added thiophenol (3.1 μL, 30.5 μmol) followed by Et_3N (4.2 μL, 30.5 μmol). This mixture was stirred for 15 min and then purified by pipet column chromatography (1:9 → 1:3 EtOAc/hexane) to give 1.9 mg (74%) of thiophenol monoadduct **133** (18:1 β/α mixture at C14) as a white solid: TLC R_f 0.37 (1:2 EtOAc/hexane); IR ($CDCl_3$) 2960, 2920, 2860, 1775, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, major isomer) δ 7.51−7.42 (c, 2 H), 7.22 (br s, 3 H), 5.85 (dd, J = 17.6, 10.8 Hz, 1 H), 5.01 (d, J = 17.3 Hz, 1 H), 4.97 (d, J = 10.8 Hz, 1 H), 4.31 (s, 1 H), 4.30 (d, J = 5.8 Hz, 1 H), 2.58 (d, J = 5.9 Hz, 1 H), 2.22 (m, 1 H), 2.16 (m, 1 H), 1.94−1.78 (c, 4 H), 1.73 (m, 1 H), 1.57−1.46 (c, 2 H), 1.24 (3 H), 0.94 (dd, J = 6.2, 4.9 Hz, 1 H), 0.83 (s, 3 H), 0.37 (dd, J = 8.3, 6.6 Hz, 1 H); MS (EI) m/z 420 (M^+); HRMS (EI) exact mass calcd for $C_{26}H_{28}O_3S$ (M^+) 420.1760, found 420.1750.

[1S*-(1β,4β,7α,8β)]-(±)-7-Ethenyl-1,2,3,4,5,6,7,8-octahydro-9,10-dihydroxy-1,7-dimethyl-8-(phenylthio)-4-[(phenylthio)methyl]phenanthrene-1-carboxylic acid (135). To a colorless solution of myrocin C (**1**; 3.5 mg, 10.2 μmol) in CH_2Cl_2 (200 μL) at room temperature with stirring under N_2 was added thiophenol (10.4 μL, 102 μmol) followed by Et_3N (14.1 μL, 102 μmol). This mixture was stirred for 14 h, quenched by addition of saturated aqueous NH_4Cl (1 mL), and extracted with $CHCl_3$ (4 × 1 mL). The combined organic extracts were dried ($MgSO_4$), filtered, evaporated, and purified by pipet column chromatography (1:9 → 1:1 EtOAc/hexane then 10% MeOH/$CHCl_3$) to give 3.5 mg (63%) of catechol **135** as a bright yellow oil: TLC R_f 0.38 (10% MeOH/$CHCl_3$); IR ($CDCl_3$) 3510 (s), 3310 (br), 2920, 2960, 1700, 1440, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.45−7.14 (c, 10 H), 5.82 (dd, J = 17.4, 10.7 Hz, 1 H), 4.98 (d, J = 17.3 Hz, 1 H), 4.83 (d, J = 10.8 Hz, 1 H), 4.21 (s, 1 H), 3.16−2.85 (c, 3 H), 2.45 (dd, J = 17.8, 5.2 Hz, 1 H), 2.38−2.18 (c, 3 H), 1.97 (m, 1 H), 1.83−1.67 (c, 2 H), 1.48 (s, 3 H), 1.46 (buried, 1 H), 0.96 (s, 3 H); MS (FAB, NOBA−NaI) m/z 569 ($M + Na^+$); HRMS (FAB, NOBA−NaI) exact mass calcd for $C_{32}H_{34}NaO_4S_2$ ($M + Na^+$) 569.1798, found 569.1821.

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Supplementary Material Available: Figures showing the PLUTO representations and tables giving the X-ray diffraction data for **22**, **109**, and synthetic (±)-**1** and text describing the experimental procedures for **12**, **14**, **18**, and **22** (36 pages). This material is contained in many 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.