Asymmetric Total Synthesis of (+)-Codeine via Intramolecular Carbenoid Insertion

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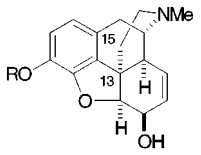
A strategy was devised for the synthesis of codeine that employed intramolecular insertion of a carbenoid into a benzylic methine CH bond for creation of the C13 quaternary center and construction of the pentacyclic skeleton of the alkaloid. The synthesis began from isovanillin, and asymmetry was introduced through catalytic hydrogenation of its Stobbe condensation product **7** over a chiral catalyst (**8**). The product (*S*)-**9** was advanced to tetralone **12**, which underwent Robinson annulation to give the phenanthrenone **33**. The latter was brominated and treated with base to afford the fused benzofuran **35**. Reduction with hydride followed by catalytic hydrogenation produced the tetracycle **44**, which was converted to diazoketone **48**. The latter was reacted in the presence of catalytic $Rh_2(OAc)_4$ to furnish the pentacyclic product **49**. Beckmann rearrangement of the derived oxime brosylate **59** gave lactam **57**, and the synthesis of (+)-**1** (the nonnatural enantiomer of codeine) was completed after oxidation to **63**, introduction of $\Delta^{7,8}$ unsaturation, and exhaustive reduction.

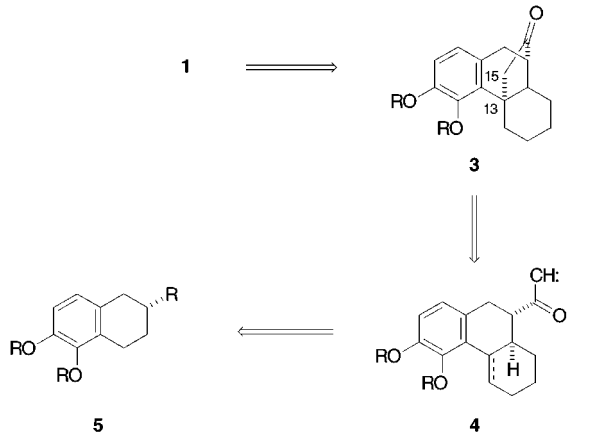
The unique position of codeine (**1**) and morphine (**2**) in contemporary medicine continues to inspire efforts toward an understanding of its analgesic and euphoriant properties.[1] Central to this endeavor is the development



1, R = Me, (+)-codeine
2, R = H, (+)-morphine

of new synthetic routes that not only lead to these alkaloids in enantiomerically pure form but also provide access to useful structural analogues.[2] Approaches to the synthesis of morphine began even before its structure was revealed by Robinson in 1925,[3] yet it was not until 1993 that the first asymmetric synthesis of the alkaloid was reported.[4] Our own preoccupation with codeine and morphine[5] has lately focused on a synthesis capable of delivering either enantiomer and which exploits a concept adopted by the pioneering efforts that envisioned a phenanthrene as an easily accessible platform for constructing the pentacyclic skeleton of morphine.[6] Although subsequent investigations abandoned this strategy, favoring biomimetic[7] and other approaches,[8] a revisitation of the classical phenanthrene route seemed appropriate in view of recent advances in methodology that could permit elaboration of the pentacyclic framework of **1** from this tricyclic nucleus.[9] For reasons associated with our interest in examining the pharmacological properties of the unnatural enantiomorph, we chose (+)-codeine (**1**) as the goal of this synthesis.[10]

The most important strategic decision made at the outset of this work was that the C13−C15 bond of **1** would be set in place after the phenanthrene nucleus was established. Of the many successful approaches to morphine, only that of Ginsburg has employed this design.[11] The means for achieving the pivotal C13−C15 bond of morphine was to be an intramolecular carbenoid reaction that would generate ketone **3** from a tricyclic precursor **4**. The piperidine ring of **1** would then be elaborated



through ring expansion of **3**. Acquisition of **4** was envisioned from tetralin **5** bearing a single stereogenic

(1) Lednicer, D. *Central Analgesics*; Wiley: New York, 1982; pp 137−213.

(2) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R. *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1996; pp 43−154.

(3) Gulland, J. M.; Robinson, R. *Mem. Proc. Manch. Lit. Soc.* **1925**, *69*, 79.

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(5) (a) White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron* **1983**, *39*, 2393. (b) White, J. D.; Butlin, R. J.; Hahn, H.-G.; Johnson, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 8595.

(6) (a) Pschorr, A. T. *Ber.* **1896**, *29*, 496. (b) Fieser, L. F.; Holmes, H. L. *J. Am. Chem. Soc.* **1936**, *58*, 2319. (c) Robinson, R.; Ghosh, R. J. *J. Chem. Soc.* **1944**, 506.

(7) Schwartz, M. A.; Pham, P. T. K. *J. Org. Chem.* **1988**, *53*, 2318 and references cited.

(8) (a) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, 23, 285. (b) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227. (c) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R.; Abboud, K. *Tetrahedron Lett.* **1996**, *37*, 8155. (d) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694. (e) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688. (f) Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959.

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Table 1. Effect of Catalyst−Substrate Ratio on the Asymmetric Hydrogenation of 7

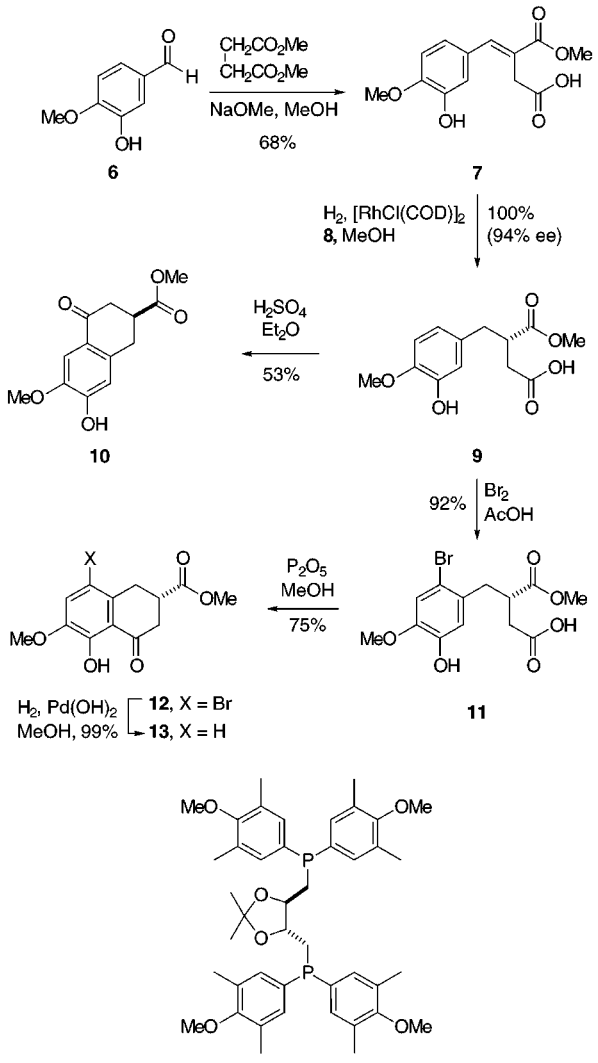
catalyst[a]−substrate[b] ratio	reaction time (h)	yield of **9** (%)	ee of **9**[c] (%)
2.0×10^{-3}	10	10	90
3.8×10^{-3}	10	50	92
5.6×10^{-3}	7	100	94

[a] Based on $[RhCl(COD)]_2$; (MOD-DIOP/Rh(I) ratio was 2:1). [b] Maintained at 0.6M in MeOH. [c] Determined by chiral HPLC analysis (Chiralpak AD, hexane−*i*-PrOH (90:10) containing 5% CF_3CO_2H, flow rate 0.9 mL/min).

center, and it is this center that directs all subsequent stereochemical events leading to **1**.

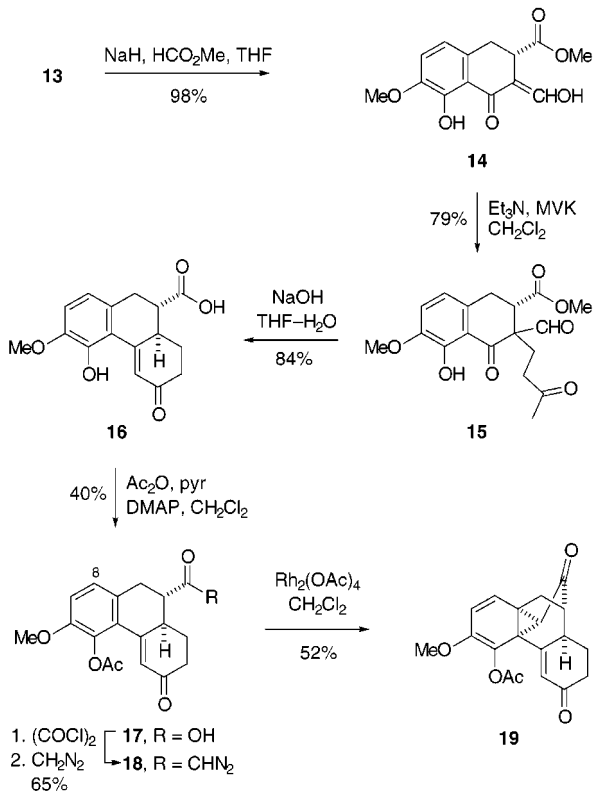
The route to **5** began with Stobbe condensation[12] of isovanillin (**6**) with dimethyl succinate. The resultant cinnamate half-acid **7** was subjected to asymmetric hydrogenation using a chiral rhodium catalyst based on the MOD-DIOP ligand **8** of Achiwa.[13] Although both the neutral [$(ClRhCOD)_2$-MOD-DIOP] and cationic [(RhCOD-MOD-DIOP)$^+$ BF_4^-] versions of this catalyst are reported to give good stereoselectivity in the asymmetric reduction of substituted benzylidenesuccinate half esters,[14] the neutral complex was found to be easier to prepare. Nevertheless, satisfactory asymmetric hydrogenation of **7** with the Rh complex of (4*R*,5*R*)-**8** required considerable optimization. Using a catalyst-to-substrate ratio of 2×10^{-3}, as suggested by Achiwa,[14] necessitated long reaction times and resulted in **9** of low optical purity. Chiral HPLC analysis of the reaction course revealed that enantiomeric purity of the product decreased over time, suggesting that the chiral catalyst was chemically transformed to a species that, while still catalytically active, possessed lower or no selectivity. This observation is consistent with results published by Glaser on asymmetric hydrogenation using a $(ClRhCOD)_2$-DIOP system.[15] For optimization, it was necessary to increase the catalyst-to-substrate ratio nearly 3-fold to obtain good enantioselectivity (see Table 1), and under these conditions, **7** was reduced in quantitative yield to (*S*)-**9** in 94% enantiomeric excess. However, for practical reasons, exploratory reactions with **9** were carried out on racemic material, prepared by hydrogenation of **7** over 10% Pd/C catalyst.

Not surprisingly, direct transformation of **9** to a tetralone led to the undesired isomer **10** in which intramolecular Friedel−Crafts acylation had occurred para to the free phenol. The simple expedient of bromination blocked this pathway,[16] and Friedel−Crafts cyclization[17] of brominated phenol **11** afforded tetralone **12** in good yield. The bromine substituent in **12**, having served its present purpose, was removed by hydrogenolysis over Pearlman's catalyst[18] to afford **13** in virtually quantitative yield. As subsequent events unfolded, however, this bromine substituent would be recalled for a different role.



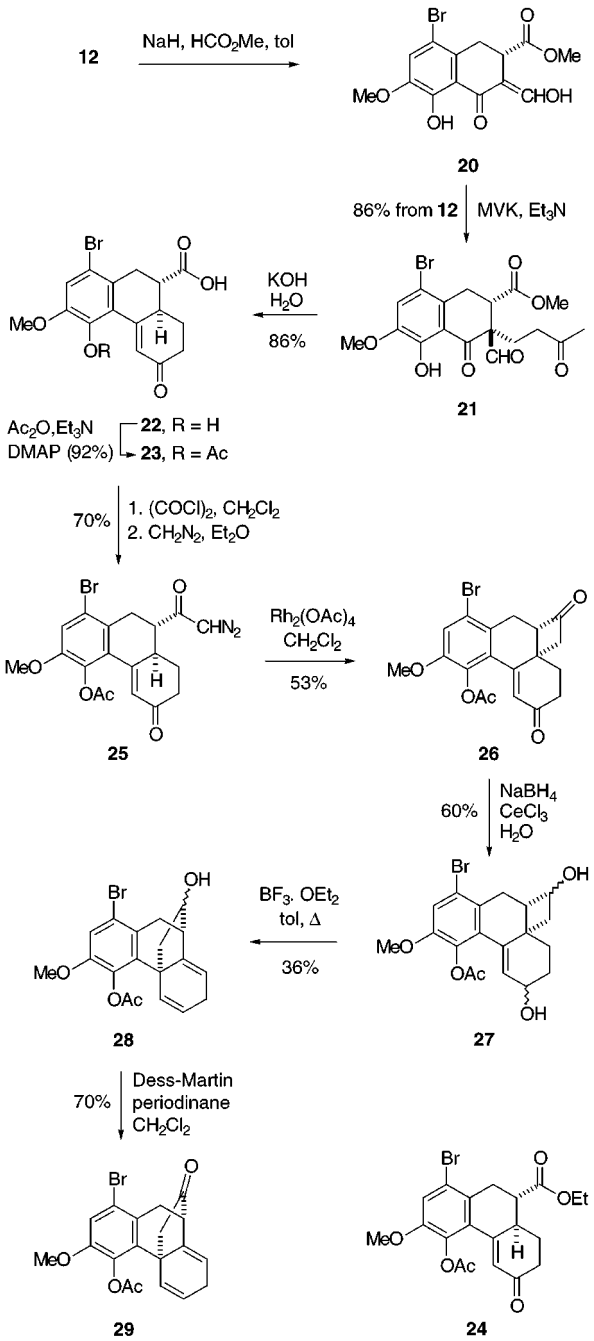
The next stage of the synthesis required conversion of keto ester **13** to a phenanthrenone derivative through Robinson annulation with methyl vinyl ketone. To effect this annulation, it was first necessary to convert **13** to its α-formyl derivative **14**, since this tactic facilitated Michael addition of the anion from **14** to MVK.[19] Intramolecular condensation, deformylation, and saponification of **15** occurred in a single step to yield carboxylic acid **16** as the sole stereoisomer. The relative configuration of **16** was confirmed in the course of a subsequent series of transformations (vide infra). This set the stage for constructing the tetracyclic core of morphine, for which the phenolic hydroxyl group of **16** was first blocked as its acetate **17** and the carboxylic acid was converted through its acyl chloride to diazoketone **18**. Unexpectedly, decomposition of **18** in the presence of $Rh_2(OAc)_4$ gave norcaradiene **19**,[20] indicating that the electron-rich aro-

(9) For a recent synthesis of morphine based on this strategy, see Mulzer, J.; Duerner, G.; Trauner, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2830.
(10) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250.
(11) (a) Ginsburg, D.; Pappo, R. *J. Chem. Soc.* **1953**, 1524. (b) Elad, D.; Ginsburg, D. *J. Chem. Soc.* **1954**, 3052.
(12) Johnson, W. S.; Daub, G. H. *Org. React.* **1951**, *6*, 1.
(13) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735.
(14) Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 1149
(15) Glaser, R.; Geresh, S.; Blumenfeld, J. *J. Organomet. Chem.* **1976**, *112*, 355.
(16) Stock, L. M.; Himoe, A. *J. Am. Chem. Soc.* **1961**, *83*, 4605.
(17) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.
(18) Prugh, J. D.; Rooney, C. S.; Deana, A. A.; Ramjit, H. G. *Tetrahedron Lett.* **1985**, *26*, 2947.
(19) Banwell, M. G.; Lambert, J. N.; Corbett, M.; Greenwood, R. J.; Gulbis, J. M.; Mackay, M. F. *J. Chem. Soc., Perkin Trans 1* **1992**, 1415.
(20) For an analogous example, see Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.



matic ring is more receptive than the enone moiety to attack by the keto carbenoid. The structure of **19** was readily apparent from the chemical shifts of the olefinic and cyclopropane carbons and protons in its NMR spectrum.

The formation of **19** from diazoketone **18** implied that a useful morphine precursor would only be accessible if carbene addition to the benzenoid ring could be suppressed. It was surmised that a bromine substituent at C8 could accomplish this, since on both steric and electronic grounds the aryl ring would become less reactive when it bears a bulky halogen. This conjecture led us back to **12**, which was taken through the same Robinson annulation sequence previously used on **13**. The α-formyl tetralone **20** was transformed via **21** to carboxylic acid **22**, which after acetylation produced **23**. The ethyl ester **24** of **23** was a highly crystalline compound, the structure of which was determined by X-ray analysis. This not only proved the relative configuration of **23** but also confirmed the same stereochemical relationship in **16**. Carboxylic acid **23** was converted to diazoketone **25**, but treatment of the latter with $Rh_2(OAc)_4$ produced another surprise, affording cyclobutanone **26**.[21] This substance was also highly crystalline, and its structure readily yielded to X-ray crystallographic analysis. Thus, although carbene attack had been diverted from the aryl ring by the bromine substituent, insertion into the γ C−H bond of the enone was now the preferred outcome. The optimistic conjecture that **26** did not represent a cul-de-sac was entertained briefly when it was found that diol **27**, obtained as a mixture of all four stereoisomers by Luche reduction[22] of **26**, underwent Wagner−Meerwein rearrangement in the presence of $BF_3{\cdot}OEt_2$ to give the bridged tetracycle **28**, albeit in low yield.[23] The latter was characterized as ketone **29**, obtained by oxidation of the pair of stereoisomeric alcohols with Dess−Martin periodinane.[24] Unfortunately, efficient chemical differentiation of the two olefins of the cyclohexadiene moiety of **29** proved insurmountable and effectively terminated this route.



A different strategy for fashioning the morphine C13−C15 bond from **22** is conceivable if the double bond of the enone is first reduced so that a hydrogen atom is installed at the 13α position. In this plan, carbene insertion into the resulting benzylic CH bond should lead

(21) Cyclobutanone formation via intramolecular decomposition of a α-diazoketone has been observed previously, albeit as a minor pathway (Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242).

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

(23) For a related example see White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376.

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

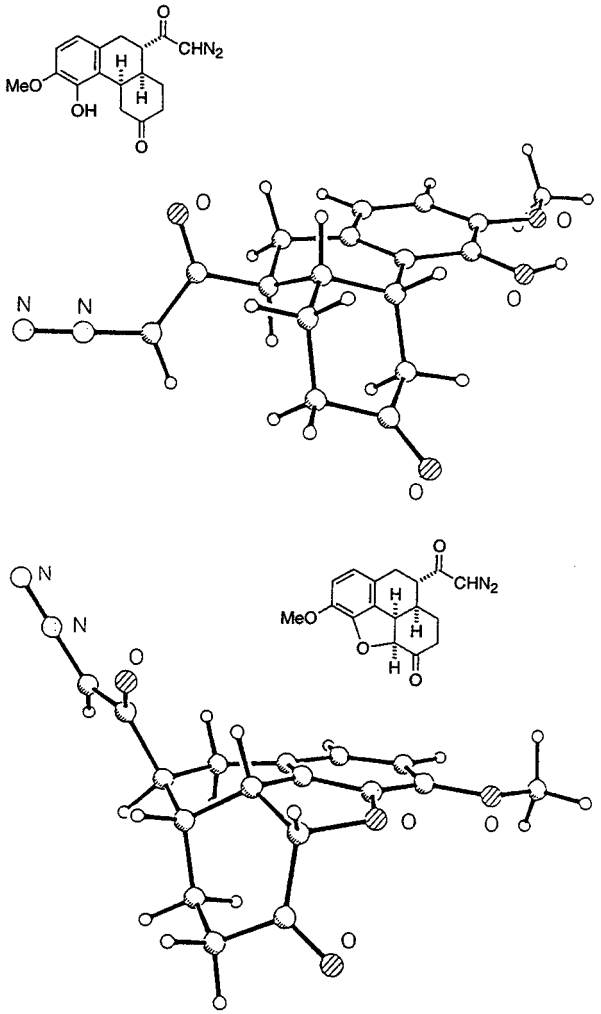
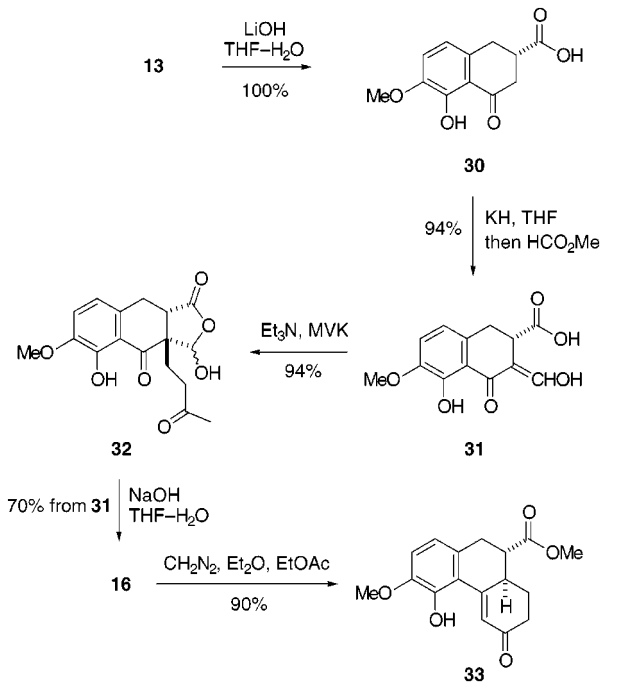


Figure 1. (a) AM1-optimized conformation of a tricyclic diazoketone showing pseudoequatorial orientation of diazo function and hydrogen atom. (b) AM1-optimized conformation of a tetracyclic diazoketone showing pseudoaxial orientation of diazo function and hydrogen atom.

directly to the desired configuration at the C13 quaternary center. There are, however, two important requirements for this approach to be productive. First, the enone must be reduced stereoselectively from the α face to afford a cis BC ring fusion, and second, the C13−H bond and diazoketone moiety must occupy a diaxial relationship. Even if the first of these requirements is met, the AM1-optimized geometry of the reduced structure reveals that the diazoketone moiety and the hydrogen atom it must target are both pseudoequatorial (Figure 1a). On the other hand, a structure in which the furanoid ring of morphine is closed enforces the necessary diaxial orientation of reacting partners (Figure 1b). This conformational analysis predicts that continuation of our original phenanthrene approach toward a tetracyclic diazoketone would lead to successful intramolecular CH insertion at C13 by the carbene generated from this species.

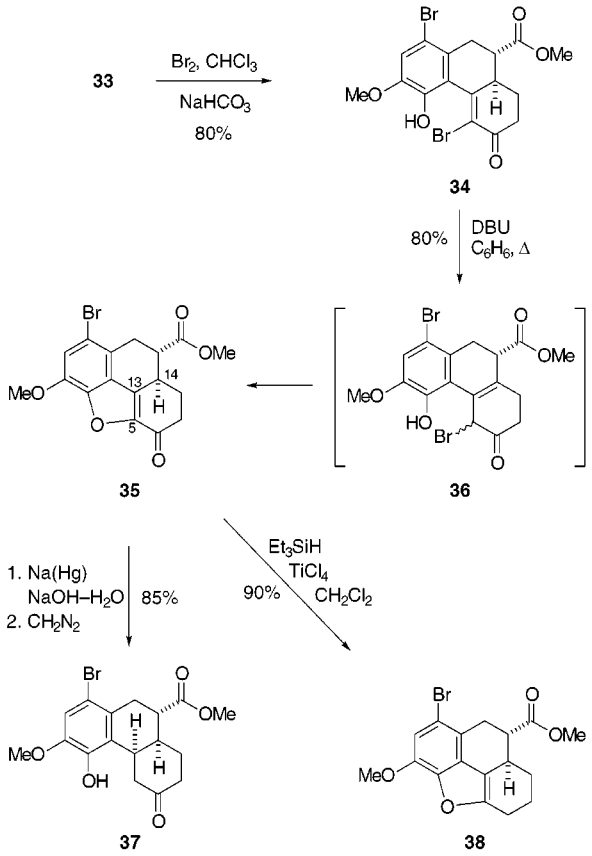
A return to **16** for the purpose of redirecting the synthesis along this line brought another unpleasant surprise; it was discovered that partial racemization of this compound had occurred en route from **13**! Fortunately, the problem was easily solved by a simple modification to the Robinson annulation sequence using carboxylic acid **30** rather than the corresponding methyl ester **13** as the substrate. Thus, after saponification of **13**, formylation of the trianion of **30** produced **31**. Annulation of the latter with MVK took a course different from that observed with **14** and afforded lactol **32** as an intermediate, but this substance underwent smooth intramolecular condensation in the presence of base to yield the crystalline keto acid **16**. Treatment of **16** with diazomethane in ethyl acetate then gave optically pure methyl ester **33**.



Closure of the furanoid ring of morphine from **33** required α bromination of the enone followed by intramolecular displacement of bromide by the phenoxide oxygen. However, before this displacement can occur, rehybridization of the α carbon of the enone toward sp^3 must take place. The mechanism proposed by Seshadri for this process in a conversion of 3-halocoumarins to benzo[*b*]furans is temporary, reversible conjugate addition of a nucleophile (hydroxide) to the α-bromoenone.[25] With this precedent in mind, **33** was treated with bromine in chloroform containing $NaHCO_3$. Addition followed by elimination of HBr occurred as expected, but it was not possible to suppress aromatic bromination under these conditions, and dibromo compound **34** therefore became the obligatory candidate for benzofuran formation. Several basic media were investigated for this purpose, but most led to epimerization at both stereogenic centers in **34**. In the event, DBU in hot benzene proved to be the most satisfactory method for the transformation of **34** to **35**. These conditions are not consonant with Seshadri's reversible 1,4-addition mechanism,[25] and we believe a more plausible scenario involves isomerization of **34** to the β,γ-enone **36** prior to cyclization. The return of C14 to its original *R* configuration in **35** is in accord with our observation that the trans stereoisomer of **16** and **24** is thermodynamically favored. In fact, analysis of **35** showed that <3% epimerization had occurred during its formation from **34**.

Our initial plan for saturation of the 5,13-double bond of **35** envisioned a thermodynamically controlled reduc-

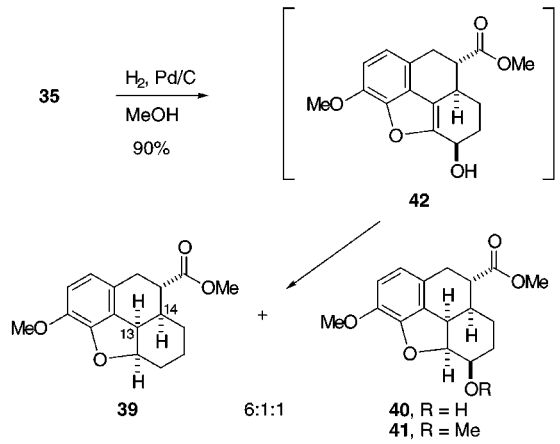
(25) Saroja, T.; Seshadri, T. R.; Muckerjee, S. K. *Indian J. Chem.* **1971**, *9*, 1316.



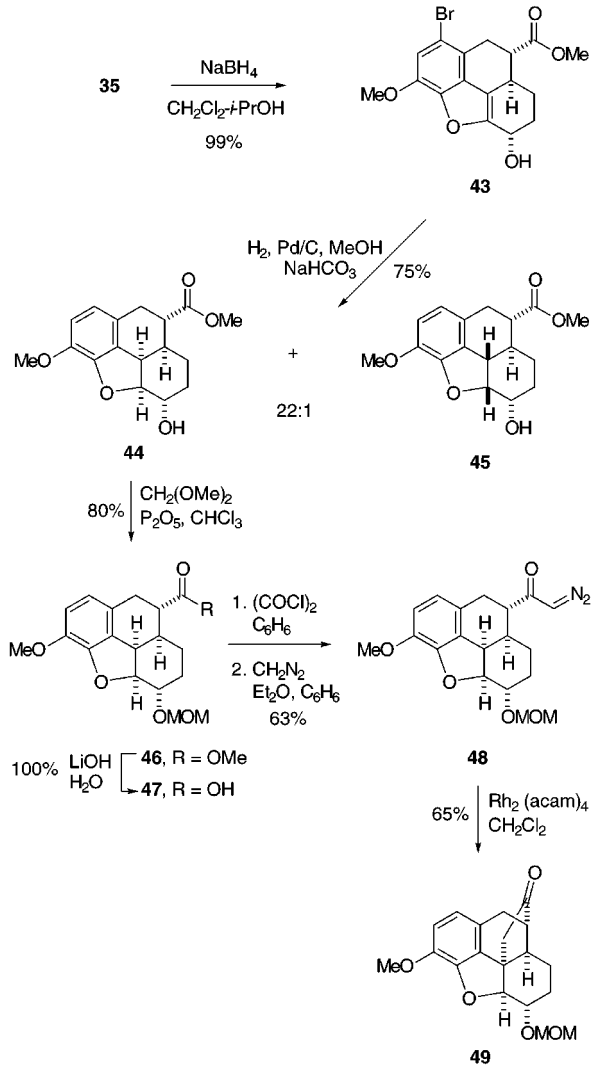
tion, since calculations had convinced us that the desired cis,syn isomer (5*S*,13*R*) was the most stable of the four possible stereoisomeric products. In fact, reduction of **35** with sodium amalgam did give a single product, but after esterification with diazomethane this was found to be **37**, in which reductive α cleavage as well as saturation of the double bond had taken place. The same keto ester was obtained upon exposure of **35** to lithium−ammonia. In an attempt to avoid α cleavage, **35** was treated with triethylsilane in the presence of $TiCl_4$ in the hope that only conjugate reduction would occur. In this case, the deoxygenated tetracycle **38** was the sole product. By contrast, hydrogenation of **35** over a palladium catalyst in MeOH afforded **39** accompanied by alcohol **40** and methyl ether (**39**:**40**:**41** = 6:1:1). The cis relationship between hydrogens at C13 and C14 in **39** was apparent from an NOE (7%) between these protons in its NMR spectrum. The major product **39** presumably arises from initial reduction of the keto group of **35**, leading to a pseudoaxial alcohol **42** that undergoes subsequent hydrogenolysis.[26] The perpendicular orientation of the alcohol of **42** with respect to the plane of the benzofuran would facilitate both hydrogenolysis and explain the solvolytic origin of **41**. Hydrogenation of the benzofuran is thus the terminal event in this scenario.

It became clear from the foregoing results that if both the tetracyclic framework of **35** and an oxygen substituent at C6 were to be preserved during hydrogenation of the benzofuran, a substrate bearing a pseudoequatorial alcohol at C6 would have better prospects. Although a 6α hydroxyl group would eventually require inversion to the natural β configuration of **1**, it was nevertheless

(26) Analogous reduction was observed by Gates in the course of his studies on thebaine (Gates, M.; Klein, D. A. *J. Med. Chem.* **1967**, *10*, 380).



decided to explore this option. Exposure of **35** to sodium borohydride gave the desired 6α alcohol **43** in quantitative yield and, as predicted, the parallel alignment of the alcohol substituent with the aromatic π system in this isomer resulted in complete suppression of hydrogenolysis. Thus, catalytic hydrogenation of **43** afforded mainly **44**, accompanied by a small amount of its stereoisomer **45** (**44**:**45** = 22:1).



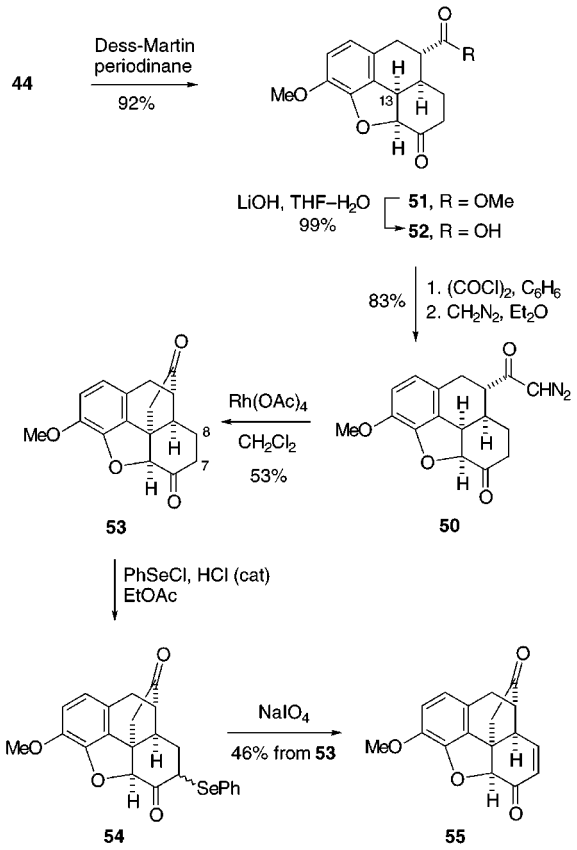
Acquisition of **44** brought us to the pivotal C9−C13 bond construction needed to secure the pentacyclic

framework of morphine. Ample precedent exists to suggest that a keto carbenoid derived from an ester such as **44** should undergo insertion into the CH bond of the benzylic methine to afford a bridged cyclopentanone,[27] and with the diversionary pathways seen with **18** and **25** now effectively blocked, preparation of a substrate for this key cyclization became our next objective. First, alcohol **44** was protected as its MOM ether **46**, after which saponification of the ester gave **47**. Conversion of this carboxylic acid to its acyl chloride, followed by treatment with diazomethane furnished diazoketone **48**.

Decomposition of **48** was carried out in the presence of several Rh(II) catalysts with varying success. The Doyle catalyst, dirhodium(II) tetrakisacetamide [Rh_2-(acam)$_4$],[28] is known to favor insertion by carbenes into electron-rich, methine CH bonds, and indeed this catalyst provided the highest yield (65%) of pentacyclic ketone **49**. A detailed discussion of the decomposition of **48** with various rhodium(II) catalysts will be presented elsewhere,[29] but it should be noted that the transformation **48** → **49** represents a unique method for setting configuration at the quaternary carbon of morphine and for creating its pentacyclic skeleton.

In a parallel study that examined intramolecular carbene insertion into the C13−H bond of ketone **50**, alcohol **44** was first oxidized to keto ester **51**. The latter was saponified, and keto acid **52** was converted to diazoketone **50** by the same protocol used for the preparation of **48**. Decomposition of **50** using $Rh_2(OAc)_4$ as catalyst furnished diketone **53** in 53% yield. Our hope was that this pathway could be continued from **53**, thereby avoiding protection of the C6 hydroxyl function and affording a more direct route to the 6*R* configuration required for **1**. The first objective in this plan was introduction of a $\Delta^{7,8}$ double bond, a task that was accomplished by acid-catalyzed phenylselenylation[30] of **53** followed by oxidation of α-selenyl ketone **54** with periodate. Unfortunately, the α,*β*-unsaturated ketone **55** proved to be a cul-de-sac, for although we had envisioned construction of the piperidine ring of **1** via Beckmann rearrangement of the cyclopentanone oxime derived from **55**, this diketone could not be induced to form the desired oxime without involvement of the enone moiety.

In contrast to **55**, however, ketone **49** yielded oxime **56** quite readily, and although the latter was produced as an inseparable 1.2:1 mixture of anti and syn isomers, respectively, progression to the *δ*-lactam **57** appeared to be straightforward. In practice, neither **56** nor the corresponding oxime tosylate[31] could be induced to undergo Beckmann rearrangement under a variety of conditions, including exposure to elevated temperatures.[32] The oxime derivative **58**, prepared in high yield by treatment of **56** with carbonyldiimidazole, did afford a low yield of **57** upon reaction with MeI in hot benzene,[33]



but it became clear from these studies that a successful transformation of **56** to **57** would necessitate careful examination of factors impeding this crucial Beckmann rearrangement. One of these is the poor alignment of the migrating bond with the breaking N−O linkage in either stereoisomer of this rigid framework. However, if the oxime carbon of **56** is rehybridized to sp^3, the stereoelectronic impediment to rearrangement is largely removed. It follows that conditions favoring addition across the C=N bond of the oxime prior to solvolysis and migration should facilitate Beckmann rearrangement.[34] This logic led us to examine the reactivity of brosylate **59** in glacial acetic acid, and to our delight, this resulted in smooth Beckmann rearrangement at room temperature. The desired *δ*-lactam **57** was accompanied by its isomer **60**, initially in the ratio 6.5:1, respectively, if **59** was prepared and used in situ. However, if brosylate **59** was warmed to 75 °C in toluene before exposure to acetic acid, the ratio **57**:**60** improved to 11:1, respectively. This temperature dependence reflects equilibration of the mixture of oxime brosylates toward the less sterically crowded anti stereoisomer and specifically sets the tetrahedral intermediate **61** in a configuration that favors migration of the bridgehead carbon. Lactam **57** was separated from the minor isomer **60** by chromatography on silica and was converted to its *N*-methyl derivative **62** in high yield with methyl iodide and sodium hydride.

To complete the synthesis of **1**, it was necessary to reverse the configuration of the C6 oxygen substitutent and introduce unsaturation into position C7−C8 of the C ring of **62**. Inspection of molecular models suggested that, whereas hydride reduction of **35** had given the 6α

(27) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.
(28) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.
(29) The product distribution from decomposition of **48** was found to depend markedly on the Rh(II) catalyst employed as well as on small structural variations in the substrate (Hrnciar, P. Ph.D. Thesis 1999, Oregon State University).
(30) Iijima, I.; Rice, K. C.; Silverton, J. V. *Heterocycles* **1977**, *6*, 1157.
(31) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48.
(32) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430.
(33) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1984**, *32*, 2560.
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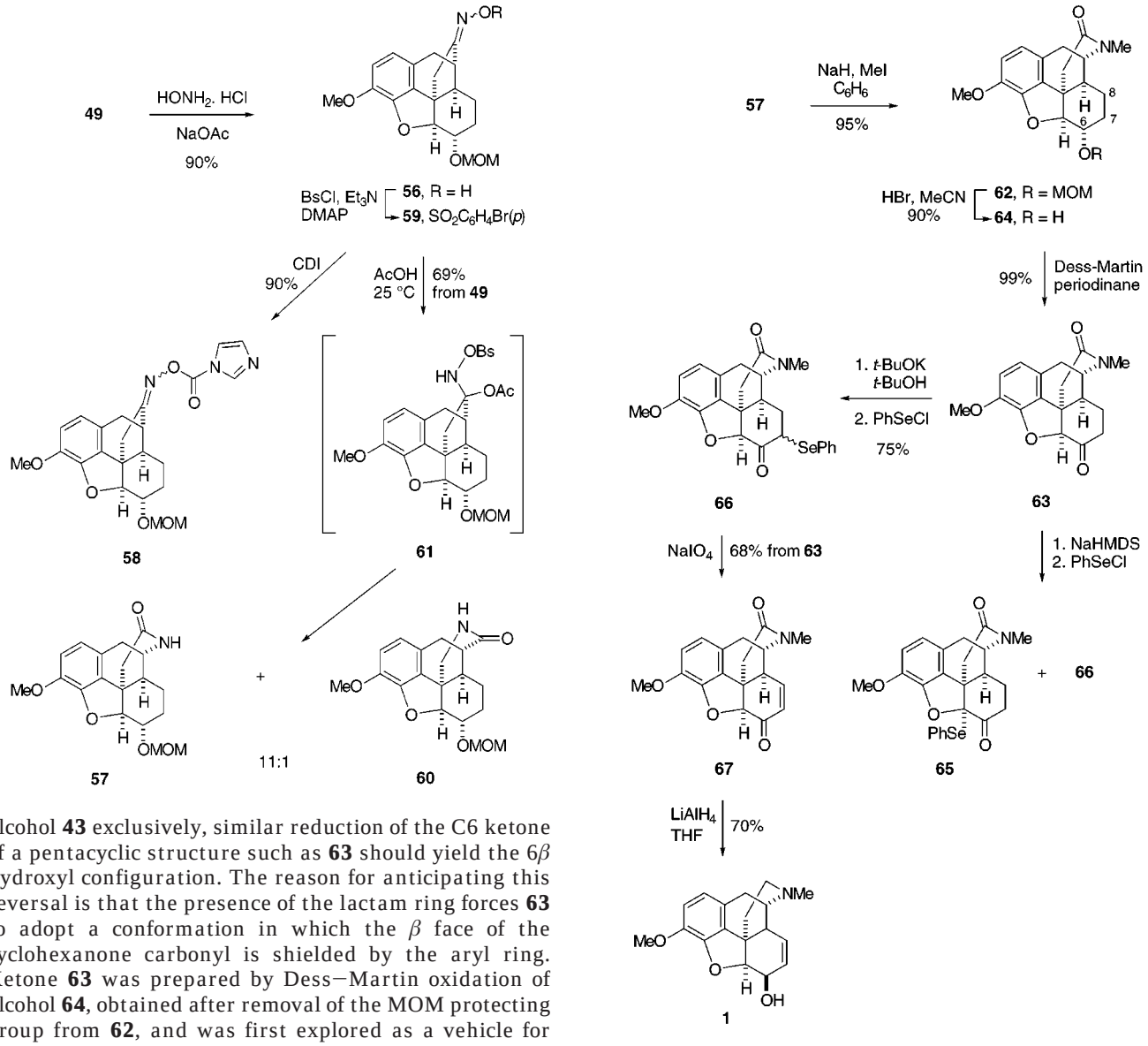

alcohol **43** exclusively, similar reduction of the C6 ketone of a pentacyclic structure such as **63** should yield the 6β hydroxyl configuration. The reason for anticipating this reversal is that the presence of the lactam ring forces **63** to adopt a conformation in which the β face of the cyclohexanone carbonyl is shielded by the aryl ring. Ketone **63** was prepared by Dess−Martin oxidation of alcohol **64**, obtained after removal of the MOM protecting group from **62**, and was first explored as a vehicle for introducing the $\Delta^{7,8}$ unsaturation required for **1**. Deprotonation of **63** with LDA or with NaHMDS, followed by reaction of the enolate with phenylselenyl chloride, produced a 1:1 mixture of **65** and **66**, but deprotonation under thermodynamic conditions with potassium *tert*-butoxide gave exclusively the desired enolate, resulting in the α-phenylselenyl ketone **66**. Elimination of the selenoxide derived from **66** led to α,β-unsaturated ketone **67** in good overall yield. As expected, exhaustive treatment of **67** with lithium aluminum hydride resulted in conversion of the δ-lactam to a piperidine as well as reduction of the keto group to the desired 6β alcohol. The product, (+)-codeine (**68**), was shown to be enantiomeric with natural (−)-codeine (**1**) by comparison of ^{1}H and ^{13}C NMR spectra and optical rotation. O-Demethylation of natural codeine is known,[35] and by extension exposure of **68** to boron tribromide would provide (+)-morphine (**2**).

It can be seen from the foregoing results that the complete stereogenicity of **1** arises from the single asymmetric center in (*S*)-**9**. Inversion of the latter reverses the absolute sense of the entire synthetic sequence and would therefore lead to natural (−)-codeine. Thus, either enantiomer of codeine and morphine is available in principle by selection of the appropriate enantiomer of the MOD-DIOP ligand[14] used for the asymmetric hydrogenation of **7**. A further attribute of the synthetic pathway disclosed here is that pentacyclic ketones **49** and **53** afford convenient entry points to certain analogues of the morphine structure that are not readily accessible by other routes. This aspect will be the subject of a future publication.

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Experimental Section

Melting points are uncorrected. Chemical ionization (CI) high- and low-resolution mass spectra (HRMS and MS) were obtained using a source temperature of 120 °C and CH_4 as the ionizing source. Perfluorokerosene was used as a reference. X-ray crystallographic structures were solved using the direct methods program contained in the SHELXTL software package.

(*E*)-4-(3-Hydroxy-4-methoxyphenyl)-3-methoxycarbonyl-3-butenoic Acid (7). To a solution of $NaOCH_3$, prepared from sodium metal (12.0 g, 0.52 mol) and MeOH (150 mL), were added isovanillin (20.0 g, 0.13 mol) and dimethyl succinate (25 g, 0.17 mol). The mixture was refluxed for 6 h, poured into stirred, aqueous HCl (5%, 250 mL) at 0 °C, and extracted with EtOAc. The extract was washed with water and was extracted with saturated aqueous $NaHCO_3$ (450 mL). The aqueous phase was separated, washed with EtOAc, and

acidified with aqueous HCl (10%). The aqueous solution was extracted with EtOAc, and the extract was washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from EtOAc−hexane (2:1) to afford 23.8 g (68%) of **7** as pale yellow prisms: mp 182−183 °C; IR (KBr) 3347, 2883, 2939, 1733, 1687, 1606, 1588, 1511, 1444, 1278, 1212, 1163, 1126, 1022, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (m, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 6.60−6.95 (m, 3H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5, 52.3, 55.9, 110.7, 115.3, 121.9, 123.4, 127.9, 142.4, 145.6, 147.5, 168.2, 177.0; MS (EI) *m*/*z* 266 (M^+), 222, 175, 167, 163, 162, 147, 131, 119, 103, 91; HRMS (EI) *m*/*z* 266.0790 (calcd for $C_{13}H_{14}O_6$ 266.0790). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.54; H, 5.27.

(3*S*)-4-(3-Hydroxy-4-methoxyphenyl)-3-methoxycarbonylbutanoic Acid (9). Chlororhodium(I) (4*R*,5*R*)-MOD-DIOP complex was prepared from chloro(1,5-cyclooctadiene)rhodium-(I) dimer (18 mg, 0.036 mmol) and (4*R*,5*R*)-MOD-DIOP (**8**, 54 mg, 0.074 mmol) in THF (4 mL). The complex was prehydrogenated for 10 min, and a solution of **7** (1.75 g, 6.57 mmol) in MeOH (8 mL) was added via syringe. The resulting mixture was stirred under an H_2 atmosphere at room temperature until TLC indicated complete consumption of **7** (ca. 10 h). The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica (EtOAc−hexane−HCOOH, 1:1:0.01) to afford 1.77 g (100%) of **9** as a colorless oil: $[\alpha]^{23}_D$ −27.2 (*c* 1.34, MeOH); IR (neat) 3447, 3234, 2980, 1724, 1715, 1513, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (dd, J = 5, 17 Hz, 1H), 2.63−2.73 (m, 2H), 2.98 (dd, J = 6, 13 Hz, 1H), 3.03−3.11 (m, 1H), 3.69 (s, 3H), 3.86 (s, 3H), 6.02 (dd, J = 2, 8 Hz, 1H), 6.70 (d, J = 2 Hz, 1H), 7.00 (d, J = 8 Hz, 1H) 7.21 (br, 2H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 32.3, 36.9, 42.8, 52.0, 55.9, 110.8, 115.2, 120.5, 131.1, 145.4, 145.5, 174.7, 177.0; MS *m*/*z* 268 (M^+), 208, 137, 131, 122, 103, 94, 77; HRMS *m*/*z* 268.0947 (calcd for $C_{13}H_{16}O_6$ 268.0947).

(3*S*)-4-(2-Bromo-5-hydroxy-4-methoxyphenyl)-3-methoxycarbonylbutanoic Acid (11). To a stirred solution of **9** (2.50 g, 9.3 mmol) in AcOH (50 mL) was added dropwise a solution of Br_2 (0.5 mL, 9.4 mmol) in AcOH (10 mL) during 30 min. The mixture was stirred at room temperature for 10 min, and 5 M aqueous $Na_2S_2O_3$ (5 mL) was added. The resulting mixture was poured onto ice, and the product was extracted with EtOAc. The extract was washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to yield 3.10 g (92%) of **11,** which was not further purified: $[\alpha]^{23}_D$ −32.7 (*c* 1.48, MeOH); IR (neat) 3315, 3238, 2983, 1715, 1502, 1441, 1277, 1230, 1183, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (dd, J = 4, 17 Hz, 1H), 2.71−2.85 (m, 2H), 3.09 (dd, J = 6, 13 Hz, 1H), 3.14−3.23 (m, 1H), 3.70 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 7.00 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 34.7, 37.0, 41.4, 52.1, 56.2, 113.5, 115.2, 116.7, 130.2, 145.0, 146.1, 174.4, 177.4; MS *m*/*z* 346 (M^+), 269, 267, 216, 191, 159, 127, 118; HRMS *m*/*z* 346.0054 (calcd for $C_{13}H_{15}BrO_6$ 346.0052).

Methyl (2*S*)-8-Bromo-5-hydroxy-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (12). To a solution of **11** (3.00 g, 8.61 mmol) in $MeSO_3H$ (50 mL) was added P_2O_5 (ca. 0.5 g), and the mixture was stirred for 10 h at ambient temperature. After addition of MeOH (30 mL), the mixture was poured onto ice, and the product was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ (3 × 70 mL) and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to give 2.10 g (75%) of pure **12** as a pale yellow solid: mp 95−96 °C; $[\alpha]^{23}_D$ +22.6 (*c* 1.68, $CHCl_3$); IR (neat) 2928, 1731, 1643, 1465, 1435, 1281, 1245, 1181 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz,) δ 2.85−3.30 (m, 5H), 3.74, (m, 3H), 3.87 (s, 3H), 7.20, (s, 1H), 12.7 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.8, 39.0, 39.9, 52.3, 56.3, 111.4, 116.9, 121.3, 131.3, 147.6, 152.7, 172.9, 202.9; MS *m*/*z* 328 (M^+), 298, 296, 271, 269, 253, 239, 191, 189, 175, 119; HRMS *m*/*z* 327.9946 (calcd for $C_{13}H_{13}BrO_5$ 327.9946). Anal. Calcd for $C_{13}H_{13}BrO_5$: C, 47.44; H, 3.98. Found: C, 47.52; H, 3.76.

Methyl (2*S*)-5-Hydroxy-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (13). A mixture of **12** (1.30 g, 3.40 mmol), $NaHCO_3$ (1.60 g), and $Pd(OH)_2$ catalyst (40 mg) in MeOH (100 mL) was stirred vigorously for 45 min under an H_2 atmosphere at ambient temperature and pressure. The mixture was filtered, and the filtrate was concentrated under reduced pressure. To the residue was added aqueous HCl (5%, 10 mL), and the product was extracted with EtOAc. The extract was washed with H_2O and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford 1.00 g (99%) of pure **13** as a yellow oil: $[\alpha]^{23}_D$ +42.5 (*c* 1.04, $CHCl_3$); IR (neat) 2960, 1733, 1645, 1422, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85−2.90 (m, 2H), 3.04−3.17 (m, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 6.65 (d, J = 8 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 12.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8, 40.2, 40.6, 52.4, 56.5, 116.5, 118.1, 118.3, 133.2, 147.3, 153.2, 173.6, 203.2; MS *m*/*z* 250 (M^+), 191, 159, 147, 131, 103, 91, 85, 83; HRMS *m*/*z* 250.0840 (calcd for $C_{13}H_{14}O_5$ 250.0841). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.07; H, 5.57.

(±)-3-Carbomethoxy-2-formyl-8-hydroxy-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (14). To a suspension of NaH (0.98 g, 40 mmol) in toluene (10 mL) was added methyl formate (6.13 g, 10.2 mmol) followed by a solution of **13** (2.55 g, 10.2 mmol) in toluene (20 mL). The mixture was stirred for 10 h at ambient temperature, poured into ice-cold aqueous HCl (10%), and extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to leave 2.76 g (98%) of pure **14** as a pale orange oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (dd, J = 10, 1 Hz, 1H), 3.20 (dd, J = 12, 3 Hz, 1H), 3.49 (m, 1H), 3.60 (s, 3H), 3.85 (s, 3H), 6.64 (d, J = 8 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 11.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.5, 40.5, 52.3, 56.1, 107.4, 115.7, 117.5, 118.0, 130.9, 147.1, 152.4, 167.2, 173.0, 193.9. This material was unstable and was used immediately for the next reaction.

(±)-3-Carbomethoxy-2-formyl-8-hydroxy-7-methoxy-1-oxo-2-[3-oxobutyl]-1,2,3,4-tetrahydronaphthalene (15). To a solution of **14** (2.70 g, 9.74 mmol) in CH_2Cl_2 (30 mL) was added methyl vinyl ketone (3.41 g, 42.5 mmol) followed by Et_3N (1 mL), and the mixture was stirred for 36 h at ambient temperature. The mixture was concentrated in vacuo, and the residue was taken up into EtOAc (100 mL). The solution was washed with dilute HCl (100 mL) and saturated aqueous NaCl and was dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica (hexanes−EtOAc, 2:1) afforded 2.67 g (79%) of **15** as a mixture of two stereoisomers (ca 1:1). This material was used immediately for the next reaction.

(±)-4-Acetoxy-3-methoxy-6-oxo-6,7,8,8a,9,10-hexahydro-9-phenanthrenecarboxylic Acid (17). To a stirred suspension of **16** (0.50 g, 1.36 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (1.9 mL), DMAP (9 mg), and Ac_2O (1.3 mL). The mixture was stirred under Ar for 10 h at ambient temperature, during which time the solution became dark. The mixture was poured into aqueous 10% HCl (70 mL) and was extracted with EtOAc. After removal of the solvent in vacuo, the residue was chromatographed on silica (hexane/EtOAc, 1:2) to give 0.22 g (40%) of **17** as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (dq, J = 10, 2 Hz, 1H), 2.10 (dq, J = 9, 1 Hz, 1H), 2.23 (dq, J = 10, 2 Hz, 1H), 2.27 (s, 3H), 2.40−2.53 (m, 2H), 2.71 (m, 1H), 2.95 (dd, J = 11, 2 Hz, 1H), 3.06 (m, 1H), 3.13 (dd, J = 11, 6 Hz, 1H), 3.82 (s, 3H), 6.70 (d, J = 1 Hz,1H), 6.93 (d, J = 7 Hz, 1H), 7.05 (d, J = 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 28.2. 31.7, 36.8, 38.0, 45.7, 56.2, 113.9, 126.2, 127.4, 129.7, 137.8, 139.9, 150.4, 153.0, 168.6, 174.8, 199.5.

(±)-5-Acetoxy-10-α-diazoacetyl-6-methoxy-3-oxo-1,2,9,-10-tetrahydrophenanthrene (18). To a solution of **17** (160 mg, 0.483 mmol) in dry benzene (25 mL) was added oxalyl chloride (0.21 mL, 4 equiv), and the mixture was stirred for 12 h at ambient temperature. The solvent was evaporated, and the residue was taken up into dry benzene (20 mL). To this solution was added an excess of ethereal CH_2N_2, and the yellow solution was stirred for 1 h at ambient temperature. The remaining CH_2N_2 was decomposed with AcOH, and the solution was concentrated to leave a yellow oil that was chromatographed on silica (hexane−EtOAc, 1:1). This yielded 79 mg (47%) of **18** as a pale yellow oil: IR (neat) 3089, 2931, 2106,

1778, 1667, 1638, 1504, 1381, 1194; ^{1}H NMR (300 MHz, $CDCl_3$) 1.09−1.85 (m, 1H), 2.20−2.31 (m, 1H), 2.32 (s, 3H), 2.39−2.64 (m, 3H), 2.96 (dd, J = 5, 6 Hz, 1H), 2.88−3.12 (m, 2H), 3.83 (s, 3H), 5.33 (s, 1H), 6.82 (d, J = 1 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 7.03 (d, J = 8 Hz, 1H).

(±)-Diketone 19. To a solution of **18** (70 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) was added $Rh_2(OAc)_4$ (1 mg), and the mixture was stirred under Ar for 0.5 h at ambient temperature. The solvent was evaporated in vacuo, and the residual oil was chromatographed on silica (hexane/EtOAc, 1:1) to give 33 mg (52%) of **19**: IR (neat) 3063, 2956, 1758, 1729, 1670, 1623, 1245, 1204, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, J = 1 Hz, 1H), 1.74−1.89 (m, 2H), 1.95 (d, J = 13 Hz, 1H), 2.16 (s, 3H), 2.24 (d, J = 5 Hz, 1H), 2.34−2.42 (m, 2H), 2.48−2.57 (m, 1H), 2.73−2.82 (m, 1H), 3.63 (s, 3H, 6.17 (s, 2H), 6.22 (d, J = 2 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 28.2, 28.4, 32.3, 37.5, 42.9, 46.0, 47.4, 48.6, 57.1, 121.3, 128.1, 129.2, 131.7, 144.0, 157.9, 168.8, 198.9, 212.0; MS (EI) m/z 326 (M^+), 284, 256, 241,228, 213, 128,115; HRMS m/z 326.1153 (calcd for $C_{19}H_{18}O_5$ 326.1154).

(±)-5-Bromo-3-carbomethoxy-2-formyl-8-hydroxy-1-oxo-7-methoxy-1,2,3,4-tetrahydronaphthalene (20). To a suspension of NaH in mineral oil (60 wt %, 38 mg, 1.0 mmol) in toluene (0.5 mL) was added methyl formate (1 mL, 12.4 mmol) followed by a solution of **12** (101 mg, 0.31 mmol) in toluene (3 mL). The suspension was stirred at room temperature for 18 h, after which time aqueous 0.1 N HCl (10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 110 mg of crude **20**. Due to its sensitivity to air, this material was used immediately without further purification: IR (neat) 2928, 1726, 1613, 1467, 1439, 1409, 1356, 1242, 1215, 1182 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (dd, J = 4.0, 1 Hz, 1H), 3.60 (m, 2H), 3.74 (s, 3H), 3.94 (s, 3H), 7.16 (s, 1H), 7.53 (d, J = 10 Hz, 1H), 12.18 (s, 1H).

(±)-5-Bromo-3-carbomethoxy-2-[1-(3-butanone)]-2-formyl-8-hydroxy-1-oxo-7-methoxy-1, 2, 3, 4-tetrahydronaphthalene (21). To a solution of crude **20** (110 mg, 0.28 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added freshly distilled methyl vinyl ketone (300 μL, 5 mmol) followed by Et_3N (10 μL, 0.14 mmol). The mixture was stirred at ambient temperature for 5 h, after which time the volatile components were evaporated in vacuo. Chromatography of the residue afforded 116 mg (86% from **12**) of **21** as a mixture of two stereoisomers: IR (neat) 2928, 1721, 1638, 1465, 1435, 1311, 1258, 1206, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 1H), 2.10 (s, 3H), 2.50 (m, 1H), 2.90 (m, 1H), 3.15 (m, 1H), 3.45 (m, 1H), 3.60 (s, 3H), 3.80 (m, 3H), 3.94 (s, 3H), 7.20 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 28.7, 30.0, 36.9, 45.6, 52.8, 56.4, 57.0, 60.4, 111.8, 121.8, 127.8, 148.2, 153.5, 171.1, 173.2, 200.0, 202.1; MS (CI) m/z 428, 426 (M^+), 383, 381, 368, 366, 343, 341, 283, 281; HRMS m/z 426.0313 (calcd for $C_{18}H_{19}$-Br $O_7$426.0314).

(±)-8-Bromo-10-carboxyl-5-hydroxy-6-methoxy-3-oxo-1,2,9,10-tetrahydrophenanthrene (22). A solution of **21** (2.00 g, 4.54 mmol) in aqueous 1.0 M KOH (100 mL) was stirred at ambient temperature for 7 h. The mixture was acidified with aqueous 10% HCl (50 mL), during which time the red color of the solution disappeared and a white precipitate was formed. Filtration of the mixture through a Büchner funnel provided 1.40 g (86%) of pure **22** as a colorless solid: mp 264 °C; IR (KBr) 2928, 1702, 1609, 1466, 1245, 1181, cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75 (m, 1H), 2.11 (m, 1H), 2.41 (m, 2H), 2.85 (m, 2H), 3.82 (s, 3H), 7,15 (s, 1H), 7.27 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.6, 32.8, 36.3, 37.8, 45.2, 56.5, 112.0, 116.5, 120.9, 127.5, 128.4, 145.9, 146.9, 153.2, 174.9, 199.2; MS (EI) m/z 368, 366 (M^+), 323, 321, 242, 240, 215, 214, 209, 199, 186, 185, 153, 152, 139, 119; HRMS m/z 366.0103 (calcd for $C_{16}H_{15}BrO_5$ 366.0103). Anal. Calcd for $C_{16}H_{15}Br$ O_5 C; 52.34; H; 4.12. Found: C; 52.74; H; 4.00.

(±)-5-Acetoxy-8-bromo-10-carboxyl-6-methoxy-3-oxo-1,2,9,10-tetrahydrophenanthrene (23). To a suspension of **22** (238 mg, 0.65 mmol) in CH_2Cl_2 (20 mL) were added Ac_2O (200 mL, 2.0 mmol), Et_3N (0.5 mL, 7 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred at ambient temperature for 12 h, after which time aqueous 0.1 N HCl (50 mL) was added and the mixture was extracted with Et_2O. The extract was washed with brine, dried (Na_2-SO_4), and concentrated in vacuo. Recrystallization of the residue from Et_2O afforded 250 mg (92%) of **23** as a colorless solid: mp 196 °C; IR (KBr) 2946, 1769, 1733, 1664, 1470, 1436, 1284, 1263, 1185, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (m, 1H), 2.18 (m, 1H), 2.50 (m, 2H), 2.28 (s, 3H), 3.05 (m, 2H), 2.78 (m, 1H), 3.20 (dd, J = 16, 7 Hz, 1H), 3.82 (s, 3H), 6.62 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 27.4, 32.0, 36.4, 39.9, 45.6, 56.4, 117.9, 121.3, 128.1, 128.4,129.0, 137.1, 150.6, 152.6, 168.3, 178.0, 199.4; MS (EI) m/z 410, 408 (M^+), 368, 366, 323, 321, 214, 212, 186, 185, 171, 169; HRMS m/z 408.0207 (calcd for $C_{18}H_{17}BrO_6$ 408.0208).

(±)-5-Acetoxy-8-bromo-10-carbethoxy-6-methoxy-3-oxo-1,2,9,10-tetrahydrophenanthrene (24): IR (KBr) 2942, 1770, 1730, 1670, 1601, 1558, 1472, 1287, 1262, 1124, 912, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J = 7 Hz, 3H), 1.85 (m, 1H), 2.18 (s, 1H), 2.26 (s, 3H), 2.50 (m, 2H), 2.71 (m, 1H), 2.98 (m, 2H), 3.20 (dd, J = 16, 10 Hz, 1H), 3.80 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 6.55 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.2, 20.7, 27.5, 31.9, 36.0, 37.3, 45.7, 56.4, 61.1, 117.6, 121.0, 128.0, 128.6, 129.3, 136.9, 150.5, 152.6, 168.2, 173.2, 199.0; MS (EI) m/z 438, 436 (M^+), 396, 394, 323, 321, 279, 277, 265, 263, 242, 240, 214, 213, 185, 128; HRMS m/z 436.0521 (calcd for $C_{20}H_{21}BrO_6$ 436.0521).

Compound **24** crystallized in the tetragonal space group $I4(1)/a$ with a = 26.878(4) Å, b = 26.878(4) Å, c = 10.870(3) Å, V = 7852.78 Å^3, Z = 16, D_{calc} = 1.479 g/cm^3. All 2187 nonequivalent reflections in the range of 3.5° < 2Θ < 95° were measured. The structure was solved by direct methods (SHELX-TL) using 1536 unique reflections with $F > 3\sigma(F)$. Full-matrix least-squares refinement with anisotropic temperature factors for all non-H atoms and calculated H atom positions led to the final discrepancy indices of R = 0.0749 and R_w = 0.0776.

(±)-5-Acetoxy-8-bromo-10-α-diazoacetyl-6-methoxy-3-oxo-1,2,9,10-tetrahydrophenanthrene (25). To a solution of **23** (85 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was added $(COCl)_2$ (50 μL, 0.60 mmol), and the mixture was stirred at ambient temperature for 18 h. The solvent and residual $(COCl)_2$ were evaporated in vacuo, and the residue was taken up into Et_2O (3 mL). A solution of CH_2N_2 in Et_2O (1 mL) was added, and the resulting yellow solution was stirred for 1 h at ambient temperature. The solvent was evaporated, and the residue was chromatographed on silica (hexanes−EtOAc, 1:1) to yield 63 mg (70%) of **25**: IR (neat) 2918, 2108, 1769, 1666, 1640, 1469, 1375, 1288, 1260, 1184, 1123, 1019, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (m, 1H), 2.20 (m, 1H), 2.28 (s, 3H), 2.49 (m, 2H), 2.61 (m, 1H), 3.05 (m, 3H), 3.81 (s, 3H), 5.39 (s, 1H), 6.66 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 27.1, 33.1, 35.9, 37.4, 50.7, 55.5, 56.4, 117.8, 121.3, 128.2, 128.6, 128.7, 137.3, 150.6, 152.8, 168.2, 194.3, 199.1. Anal. Calcd for $C_{19}H_{17}BrN_2O_5$ C; 52.77; H; 3.97; N; 6.48. Found: C; 52.59; H; 3.94; N; 5.78.

(±)-8-Acetoxy-11-bromo-2,3,4,5,6,7-hexadehydro-9-methoxy-4-oxo-15-oxotetracyclo[12.2.0^{1,6}.0^{7,12}.0^{1,14}]-5-hexadecene (26). To a suspension of rhodium(II) acetate dimer (10 mg, 0.02 mmol) in CH_2Cl_2 (20 mL) was added dropwise during 4 h a solution of **25** (340 mg, 0.78 mmol) in CH_2Cl_2 (60 mL). After addition was complete, the solvent was evaporated in vacuo. Column chromatography of the residue on silica (hexanes−EtOAc, 1:1) gave 170 mg (53%) of **26**: IR (neat) 2925, 1781, 1668, 1470, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.50 (m, 4H), 2.92 (dd, J = 18, 4 Hz, 1H), 3.20 (dd, J = 18, 4 Hz, 1H), 3.43 (m, 1H), 3.55 (m, 2H), 3.83 (s, 3H), 6.38 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 27.3, 34.1, 34.7, 35.3, 56.4, 56.6, 63.9, 118.0, 121.0, 127.9, 128.7, 129.3, 137.4, 150.9, 153.4, 168.5, 198.2, 206.9; MS (EI) m/z 406, 404 (M^+), 364, 362, 322, 320, 307, 305, 279, 277, 265, 263, 261, 242, 240, 213, 211, 198, 197, 169, 167, 116, 113; HRMS m/z 404.0259 (calcd for $C_{19}H_{17}BrO_5$ 404.0259).

Compound **26** crystallized in the triclinic space group P-1 with a = 9.489(2) Å, b = 11.102(2) Å, c = 16.969(3) Å, V =

1786.28 Å^3, $Z = 2$, $D_{calc} = 1.507$ g/cm^3. All 2340 nonequivalent reflections in the range of $3.5° < 2\Theta < 95°$ were measured. The structure was solved by direct methods (SHELXTL) using 2155 unique reflections with $F > 3\sigma(F)$. Full-matrix least-squares refinement with anisotropic temperature factors for all non-H atoms and calculated H atom positions led to the final discrepancy indices of $R = 0.1093$ and $R_w = 0.1051$.

(±)-8-Acetoxy-11-bromo-2,3,4,5,6,7-hexadehydro-4-hydroxy-15-hydroxy-9-methoxytetracyclo[12.2.0^{1,6}.0^{7,12}.0^{1,14}]-5-hexadecene (27). To a solution of **26** (95 mg, 0.23 mmol) in aqueous 0.4 M $CeCl_3$ (0.5 mL) was added $NaBH_4$ (20 mg, 0.54 mmol) in small portions. The mixture was stirred at ambient temperature for 15 min, treated with aqueous 0.1 N HCl (5 mL), and extracted with Et_2O. The extract was washed with brine, dried, and concentrated in vacuo. Column chromatography of the residue on silica (hexanes−EtOAc, 1:4) yielded 58 mg (60%) of **27** as a mixture of four stereoisomers: IR (neat) 3392, 2927, 1760, 1469, 1198 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.57 (m, 2H), 2.02 (m, 2H), 2.27 (m, 4H), 2.47 (m, 1H), 2.69 (m, 1H), 3.35 (m, 1H), 3.40 (m, 1H), 3·82 (s, 3H), 4.35 (m, 2H), 6.00 (s, 1H), 7.11 (s, 1H), 7.13 (s, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 20.6, 20.8, 26.6, 26.9, 29.4, 29.6, 32.5, 34.1, 34.7, 35.0, 43.0, 43.5, 46.5, 56.2, 64.7, 64.8, 66.0, 67.1, 115.2, 115.4, 119.9, 120.0, 129.1, 130.4, 130.5, 133.1, 135.5, 137.0, 150.4, 150.5, 168.9; MS (EI) *m*/*z* 410, 408 (M$^+$), 392, 390, 366, 364, 350, 287, 251, 226, 224, 193, 192, 181, 178, 153, 152, 115, 197, 169, 167, 116, 113; HRMS *m*/*z* 408.0572 (calcd for $C_{19}H_{21}BrO_5$ 408.0572).

(±)-3-Acetoxy-6-bromo-2,3,4,5,6,7-hexadehydro-15-hydroxy-4-methoxytetracyclo-[7.5.2.0^{2,7}.0^{1,10}]-10,13-hexadecadiene (28). To a solution of **27** (21 mg, 0.05 mmol) in toluene (2 mL) at reflux was added a 0.1 M solution of BF_3·OEt_2 (10 μL) in CH_2Cl_2. After 30 s, the mixture was poured into ice−water, the layers were separated, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried, and concentrated in vacuo, and the residue was chromatographed on silica (hexanes−EtOAc, 3:1) to give 7 mg (36%) of **28** as a mixture of stereoisomers: IR (neat) 3312, 2927, 1761, 1472, 1198, 1169, 1143, 1017 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.52−2.80 (m, 4H), 3.01 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 3.82 (m, 2H), 5.60 (s, 1H), 5.74 (m, 3H), 7.13 (s, 1H); MS (EI) *m*/*z* 392, 390 (M$^+$), 330, 304, 258, 207, 178, 165, 152, 139, 131, 120, 117, 107, 106, 105; HRMS *m*/*z* 390.0457 (calcd for $C_{19}H_{19}BrO_4$ 390.0467).

(±)-3-Acetoxy-6-bromo-2,3,4,5,6,7-hexadehydro-11-methoxy-15-oxotetracyclo[7.5.2.0^{2,7}.0^{1,10}]-10,13-hexadecadiene (29). To a solution of **28** (7 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (15 mg, 0.054 mmol), and the mixture was stirred at ambient temperature for 0.5 h. The solution was diluted with Et_2O (2 mL), and aqueous $Na_2S_2O_3$ (2 mL) was added. The organic layer was separated, the aqueous layer was extracted with Et_2O, and the extract was washed with brine, dried, and concentrated in vacuo. The residue was chromatographed on silica (hexanes−EtOAc, 3:1) to give 5 mg (70%) of **29**: IR (neat) 2971, 2933, 2929, 1768, 1752, 1477, 1195, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.70−3.25 (m, 5H), 3.75 (s, 3H), 3.80 (m, 1H), 5,71 (d, J = 8 Hz, 1H), 5.80 (m, 3H), 6.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 27.5, 34.7, 44.4, 57.8, 60.4, 60.7, 115.0, 115.7, 116.4, 120.0, 124.8, 126.4, 127.6, 135.4, 139.4, 151.6, 168.2, 216; MS (EI) *m*/*z* 390, 388 (M$^+$), 348, 346, 306, 304, 267, 225, 224, 223, 207, 165, 152, 139, 115, 91; HRMS *m*/*z* 388.0310 (calcd for $C_{19}H_{17}BrO_4$ (M$^+$) 388.0310).

(2*S*)-5-Hydroxy-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic Acid (30). To a solution of **13** (400 mg, 1.70 mmol) in THF−H_2O (1:1, 10 mL) was added LiOH (360 mg, 8.6 mmol), and the solution was stirred for 12 h at ambient temperature. The mixture was acidified with aqueous HCl (5%), and the product was extracted with EtOAc. The extract was washed with H_2O and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave 402 mg (100%) of pure **30** as a yellow crystalline solid: mp > 203 °C dec; $[\alpha]^{23}_D$ +38.4 (*c* 0.66, THF); IR (neat) 3047, 2969, 1728, 1611, 1445, 1347, 1259, 1195, 1039 cm^{-1}; ^{1}H NMR (300 MHz, THF-d_8) δ 2.81−2.85 (m, 2H), 3.01−3.18 (m, 3H), 3.78 (s, 3H), 6.65 (d, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 12.5 (s, 1H); ^{13}C NMR (75 MHz, THF-d_8) δ 35.1, 43.3, 44.0, 59.3, 120.0, 120.9, 122.4, 137.4, 150.8, 157.3, 177.1, 207.3; MS *m*/*z* 236 (M$^+$), 191, 159, 131, 80, 78, 69; HRMS *m*/*z* 236.0684 (calcd for $C_{12}H_{12}O_5$ 236.0685).

(2*S*)-5-Hydroxy-3-hydroxymethylidene-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic Acid (31). To a suspension of KH (35 wt % suspension in mineral oil, 540 mg, 4.6 mmol) in THF (15 mL) was added a solution of **30** (110 mg, 0.46 mmol) in dry THF (15 mL), and the mixture was stirred for 4 h at ambient temperature. Freshly distilled HCO_2Me (1 mL, 16 mmol) was added dropwise during 40 min. (The apparatus must be equipped with an outlet of sufficient size to accommodate the large volume of gas liberated during addition.) Stirring was continued for 3 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the solution was acidified with aqueous HCl (5%). The mixture was extracted with EtOAc, and the extract was washed with H_2O and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was washed with hexane to leave crude **31**, which was not further purified: IR (neat) 3218 (br), 2954, 1709, 1626, 1450, 1254, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (br, 1H), 3.09 (dd, J = 7, 15 Hz, 1H), 3.22 (dd, J = 3, 15 Hz, 1H), 3.52 (m, 1H), 3.87 (s, 3H), 6.65 (d, J = 8 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 7,49 (d, J = 3 Hz, 1H), 11.91 (s, 1H); MS *m*/*z* 264 (M$^+$), 220, 204, 191, 159, 131, 97, 71; HRMS *m*/*z* 264.0633 (calcd for $C_{13}H_{12}O_6$ 264.0634).

(3*R*,3a*R*,9a*S*)-3,5-Dihydroxy-6-methoxy-3a-(3-oxobutyl)-3,3a,9,9a-tetrahydronaphtho[2,3-*c*]furan-1,4-dione (32). A solution of **31** (130 mg, 0.49 mmol), methyl vinyl ketone (0.4 mL, 4.90 mmol), and Et_3N (0.15 mL, 1.0 mmol) in CH_2Cl_2 (30 mL) was stirred for 12 h at ambient temperature. The solution was concentrated under reduced pressure, and the residue was chromatographed on silica (40 g, EtOAc−hexane−HCO_2H, 1:1:0.005) to afford 161 mg (80%) of **32** as a pale yellow oil: IR (neat) 3418, 3022, 2944, 1782, 1718, 1635, 1435, 1254 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08−2.30 (m, 5H), 2.55−2.72 (m, 2H), 3.09−3.22 (m, 2H), 3.34 (d, J = 15 Hz, 1H), 3.85 (s, 3H), 6.04 (s, 1H), 6.70 (d, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 25.7, 30.1, 38.2, 42.1, 55.8, 56.6, 99.7, 116.0, 118.9, 120.0, 131.3, 147.3, 154.1, 176.1, 202.9, 208.6; MS *m*/*z* 334 (M$^+$), 316, 288, 260, 242, 203, 191, 175, 163, 159, 131, 98; HRMS *m*/*z* 334.1051 (calcd for $C_{17}H_{18}O_7$ 334.1053).

(8a*R*,9*S*)-4-Hydroxy-3-methoxy-6-oxo-6,7,8,8a,9,10-hexahydro-9-phenanthrenecarboxylic Acid (16). To a stirred solution of **32** (420 mg, 1.25 mmol) in THF−H_2O (1:1, 30 mL) was added NaOH (250 mg, 6.3 mmol). The mixture was stirred for 10 h at ambient temperature and then was acidified with aqueous HCl (5%). The precipitated solid was filtered off and was washed with MeOH to give 253 mg (70% from **31**) of pure **16** as a yellow crystalline solid: $[\alpha]^{23}_D$ +235.0 (*c* 0.31, DMSO); IR (neat) 3325, 2925, 1718, 1620, 1567, 1484, 1294 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.70−1.81 (m, 1H), 2.02−2.16 (m, 1H), 2.38−2.46 (m, 3H), 2.79−2.86 (m, 1H), 2.92 (d, J = 7 Hz, 2H), 3.80 (s, 3H), 6.67 (d, J = 8 Hz, 1H), 6.99 (d, J = 8 Hz, 1H), 7.35 (d, J = 2 Hz, 1H), 9.50 (s, 1H), 12.58 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 33.2, 38.2, 41.9, 50.9, 61.4, 118.3, 123.4, 123.7, 131.8, 135.7, 151.4, 151.9, 159.3, 191.8, 207; MS *m*/*z* 288 (M$^+$), 243, 215, 187, 183; HRMS *m*/*z* 288.0998 (calcd for $C_{16}H_{16}O_5$ 288.0998). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.61; H, 5.45. An additional 20−25% of **16** could be obtained by extraction of the filtrate with ether and chromatography of the residue after evaporation of the solvent.

Methyl (8a*R*,9*S*)-4-Hydroxy-3-methoxy-6-oxo-6,7,8,8a,9,-10-hexahydro-9-phenanthrenecarboxylate (33). To a suspension of **16** (1.00 g, 3.47 mmol) in EtOAc (30 mL) was added a 0.7 M solution of CH_2N_2 in Et_2O (10 mL), and the mixture was stirred at ambient temperature until a homogeneous solution was obtained. To this solution was added AcOH (0.5 mL), and stirring was continued for 10 min. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica (60 g, CH_2Cl_2−EtOAc−hexane, 1:2:

1) to give 0.94 g (90%) of **33** as a colorless crystalline solid: mp 178−179 °C; $[\alpha]^{23}_D$ +176.0 (*c* 1.27, $CHCl_3$); IR (neat) 2940, 2846, 1729, 1650, 1480, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80−1.90 (m, 1H), 2.04−2.16 (m, 1H), 2.42−2.65 (m, 3H), 2.87−3.00 (m, 2H), 3.10 (dd, J = 12, 15 Hz, 1H), 3.76 (s, 3H), 3.91 (s, 3H), 6.69 (d, J = 8 Hz, 1H), 6.79 (s, 1H), 6.84 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 34.0, 37.3, 39.9, 46.7, 52.2, 56.7, 112.2, 118.2, 119.4, 128.2, 131.0, 145.6, 146.7, 153.6, 175.0, 201.0; MS *m*/*z* 303 (M^+), 243, 193, 183, 113; HRMS *m*/*z* 303.1238 (calcd for $C_{17}H_{19}O_5$ 303.1233). Anal. Calcd for $C_{17}H_{19}O_5$: C, 67.54; H, 6.00. Found: C, 67.25; H, 5.57.

Methyl (8a*R*,9*S*)-1,5-Dibromo-4-hydroxy-3-methoxy-6-oxo-6,7,8,8a,9,10-hexahydro-9-phenanthrenecarboxylate (34). To a suspension of **33** (0.10 g, 0.31 mmol) and $NaHCO_3$ (0.29 g, 3.31 mmol) in $CHCl_3$ (30 mL) at 0 °C was added dropwise a solution of Br_2 in $CHCl_3$ (10%, 3.40 mL, 0.62 mmol) during 30 min. Stirring was continued for 1 h, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica (CH_2Cl_2−EtOAc−hexane, 1:2:1) afforded 0.11 g (70%) of **34** as a yellow crystalline solid: mp 129 °C dec; $[\alpha]^{23}_D$ +39.7 (*c* 0.35, $CHCl_3$); IR (neat) 3394, 3301, 2939, 1429, 1682, 1481, 1439, 1268, 1129 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91−2.05 (m, 1H), 2.25−2.34 (m, 1H), 2.54 (dd, J = 5, 15 Hz, 1H), 2.65−2.88 (m, 3H), 3.49−3.42 (m, 1H), 3.57 (dd, J = 3, 15 Hz, 1H), 3.61 (s, 3H), 3.91 (s, 3H), 6.13 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.9, 37.2, 41.0, 45.6, 56.2, 111.2, 115.2, 123.5, 124.3, 129.0, 141.1, 145.0, 153.0, 173.3, 190.8; MS (CI) *m*/*z* 461 (M^+ + 1), 383, 303, 229, 221, 213, 135 (100). Anal. Calcd for $C_{17}H_{16}Br_2O_5$: C, 44.37; H, 3.51. Found: C, 44.12; H, 3.43.

Methyl (7a*R*,8*S*)-1-Bromo-3-methoxy-6-oxo-5,6,7,7a,8,9-hexahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (35). A solution of **34** (235 mg, 0.51 mmol) and DBU (0.23 mL, 1.53 mmol) in benzene (50 mL) was stirred for 4 h at 68 °C. The mixture was cooled to room temperature and filtered through a short column of silica, which was subsequently rinsed with hexanes−EtOAc (2:1). The eluant was concentrated under reduced pressure to yield 174 mg (90%) of **35** as colorless crystals: mp 172 °C dec; $[\alpha]^{23}_D$ + 140.8 (*c* 0.70, CH_2Cl_2); IR (neat) 2949, 1728, 1674, 1503, 1269, 1171, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80−1.94 (dq, J = 12, 4 Hz, 1H), 2.50−2.88 (m, 5H), 3.03 (dd, J = 12, 17 Hz, 1H), 3.31 (dd, J = 4, 17 Hz, 1H), 3.45 (dt, J = 12, 4 Hz, 1H), 3.83 (s, 3H), 4.06 (s, 3H), 7.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 31.6, 32.6, 33.8, 39.9, 48.4, 52.5, 57.7, 115.1, 117.5, 123.6, 128.0, 137.7, 142.9, 145.5, 145.7, 173.6, 186.3; MS (CI) *m*/*z* 381 (100), 380 (M^+ + 1), 301, 243, 239, 95; HRMS (CI) *m*/*z* 379.0181 (calcd for $C_{17}H_{16}BrO_5$ 379.0181).

Methyl (2*S,8a*R**,9*S**)-1-Bromo-4-hydroxy-3-methoxy-6-oxo-2,5,6,7,8,8a,9,10-octahydro-9-phenanthrenecarboxylate (37).** A suspension of **35** (100 mg, 0.275 mmol) in 0.3 M NaOH (20 mL) was stirred at ambient temperature until a homogeneous solution was obtained. To the mixture was added Hg−(10%)Na, and stirring was continued for 1 h. The solution was acidified with aqueous HCl (5%) and was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and filtered. The filtrate was treated with CH_2N_2 (0.6 M in Et_2O), and the solution was concentrated under reduced pressure. Chromatography of the residue on silica (10 g, EtOAc−hexane, 2:1) afforded 88 mg (85%) of **37** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.95−2.07 (m, 2H), 2.13−2.39 (m, 3H), 2.47−2.62 (m, 1H), 2.81−2.95 (m, 2H), 3.04−3.27 (m, 2H), 3.50−3.63 (m, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 5.70 (s, 1H), 7.00 (s, 1H).

Methyl(7a*R,8*S**)-Bromo-3-methoxy-5,6,7,7a,8,9-hexahydrophenanthro[4,5-*bcd*-furan-8-carboxylate (38).** To a solution of **35** (50 mg, 0.110 mmol) in CH_2Cl_2 (5 mL) were added Et_3SiH (50 mL, 0.31 mmol) and 1 M $TiCl_4$ in CH_2Cl_2 (0.543 mL, 0.543 mmol). The mixture was stirred for 4 h at ambient temperature, poured onto ice, and extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (3 g, EtOAc−hexane, 1:3) gave 38 mg (90%) of **38** as a colorless oil: IR (neat) 2925, 2832, 1743, 1494, 1440, 1279, 1157, 1108, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01−1.17 (m, 1H), 1.68 (pent, J = 4 Hz, 1H), 1.88−2.08 (m, 1H), 2.14−2.26 (m, 1H), 2.32 (d t, J = 5, 9 Hz, 1H), 2.59−2.75 (m, 1H), 2.78−2.90 (m, 1H), 2.92−3.11 (m, 3H), 3.19 (dd, J = 5, 16 Hz, 1H), 3.80 (s, 3H), 4.01 (s, 3H), 6.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 23.5, 28.1, 31.4, 33.6, 48.9, 52.1, 57.1, 111.1, 113.8, 116.4, 121.1, 130.1, 141.1, 144.5, 154.2, 174.9; MS (CI) *m*/*z* 365 (M^+ + 1), 335, 314, 307, 285, 217, 205, 189, 159, 123, 115, 103; HRMS (CI) *m*/*z* 365.0373 (calcd for $C_{17}H_{18}BrO_4$ 365.0388).

Catalytic Hydrogenation of 35. Methyl (4a*S,7a*S**,8*S**,-9c*R**)-3-Methoxy-4a,5,6,7,7a,8,9,9c-octahydrophenanthro-[4,5-*bcd*]furan-8-carboxylate (39).** A suspension of **35** (12.8 mg, 0.0337 mmol) and 10% Pd/C (5 mg) in MeOH (5 mL) was stirred under H_2 at ambient temperature and pressure for 9 h. The mixture was filtered through a short column of silica, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica (5 g, EtOAc−hexane, 1:3) afforded 9.8 mg (68%) of **39** as a colorless oil: IR (neat) 2930, 2858, 1733, 1507, 1440, 1277, 1200, 1161, 1104, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92−1.05 (m, 1H), 1.06−1.24 (m, 2H), 1.50−1.68 (m, 2H), 1.93−2.03 (m, 1H), 2.64−2.73 (m, 2H), 2.85−2.91 (m, 1H), 3.20 (d, J = 17 Hz, 1H), 3.37 (t, J = 6 Hz, 1H), 3.68 (s, 3H), 3.86 (s, 3H), 4.96−5.04 (m, 1H), 6.66 (d, J = 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 23.5, 26.3, 27.9, 34.6, 37.8, 44.4, 52.2, 56.9, 85.9, 113.8, 119.9, 124.8, 127.0,143.6, 145.6, 175.4; MS (CI) *m*/*z* 288 (M^+), 257, 229, 197, 97, 84, 69; HRMS (CI) *m*/*z* 288.1363 (calcd for $C_{17}H_{20}O_4$ 288.1362);

There was also obtained 2.3 mg (18%) of methyl (4a*S**,5*R**,-7a*S**,8*S**,9c*R**)-3,5-dimethoxy-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (**41**) [IR (neat) 3366, 2923, 1724, 1508, 1445, 1281, 1152, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25−1.47 (m, 2H), 1.52−1.61 (m, 1H), 1.82−1.92 (m, 1H), 2.63−2.85 (m, 3H), 3.09 (d, J = 14 Hz, 1H), 3.28 (s, 3H), 3.50 (t br, J = 6 Hz, 1H), 3.58 (t br, J = 4 Hz, 1H), 3.69 (s, 3H), 3.87 (s, 3H), 5.02 (dd, J = 5, 9 Hz, 1H), 6.62 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.7, 26.4, 33.7, 37.0, 45.1, 52.2, 57.1, 59.1, 76.1, 86.4, 114.1, 119.4, 124.3, 127.7, 142.1, 148.1, 175.6; MS (CI) *m*/*z* 318 (M^+), 287, 259, 247, 227, 195, 187, 123, 97, 83; HRMS (CI) *m*/*z* 318.1471 (calcd for $C_{18}H_{22}O_5$ 318.1467)] and 2.0 mg (15%) of methyl (4a*S**,5*R**,7a*S**,8*S**,9c*R**)-5-hydroxy-3-methoxy-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (**40**): IR (neat) 3443, 2928,1 734, 1503, 1435, 1277, 1147, 1060, 940 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36−1.49 (m, 1H), 1.51−1.63 (m, 1H), 1.85−1.97 (m, 2H), 2.63−2.87 (m, 3H), 3.10 (dd, J = 1, 16 Hz, 1H), 3.51 (t, J = 8 Hz, 1H), 3.69 (s, 3H), 3.87 (s, 3H), 4.08−4.11 (m, 1H), 4.97 (dd, J = 5, 9 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.71 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.6, 28.2, 33.9, 36.6, 48.1, 52.3, 56.7, 66.2, 86.0, 113.5, 120.3, 124.4, 127.6, 141.7, 147.0, 175.5; MS (CI) *m*/*z* 304 (M^+), 287, 273, 245, 227, 215, 187; HRMS (CI) *m*/*z* 304.1306 (calcd for $C_{17}H_{20}O_5$ 304.1311).

Methyl (5*S*,7a*R*,8*S*)-1-Bromo-5-hydroxy-3-methoxy-5,6,7,7a,8,9-hexahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (43). To a solution of **35** (0.34 g, 0.90 mmol) in CH_2Cl_2−*i*-PrOH (3:1, 40 mL) was added sodium borohydride (0.34 g, 9.01 mmol), and the mixture was stirred for 12 h at ambient temperature. The reaction was quenched with aqueous HCl (5%), and the organic layer was separated, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure furnished 0.35 g (99%) of **43** as colorless crystals: mp 171 °C dec; $[\alpha]^{23}_D$ +105.8 (*c* 1.15, $CHCl_3$); IR (neat) 3400, 2947, 2834, 1729, 1493, 1432, 1272, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26−1.38 (m, 1H), 1.85−1.99 (m, 1H), 2.21−2.37 (m, 2H), 2.45−2.53 (m, 1H), 2.94 (dd, J = 12, 16 Hz, 1H), 3.10−3.21 (m, 1H), 3.18 (dd, J = 4, 16 Hz, 1H), 3.80 (s, 3H), 4.02 (s, 3H), 4.94−4.99 (m, 1H), 6.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 31.2, 33.7, 34.2, 48.7, 52.3, 57.2, 65.4, 112.4, 114.1, 120.0, 122.0, 129.2, 141.7, 144.7, 153.2, 174.5; MS *m*/*z* 381(M^+), 365, 303, 285, 278, 224, 149; HRMS *m*/*z* 380.0260 (calcd for $C_{17}H_{17}BrO_5$ 380.0259). Anal. Calcd for $C_{17}H_{17}BrO_5$: C, 53.56; H, 4.49. Found: C, 53.75; H, 4.62.

Methyl (4a*S*,5*S*,7a*S*,8*S*,9c*R*)-5-Hydroxy-3-methoxy-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (44). A suspension of **43** (0.35 g, 0.91 mmol), $NaHCO_3$ (75 mg, 091 mmol), and 10% Pd/C (30 mg) in MeOH (20 mL) was stirred under H_2 at ambient temperature and pressure for 24 h. The mixture was filtered through a short column of silica, and the filtrate was concentrated under reduced pressure. The residue was taken up into CH_2Cl_2 (20 mL), and the solution was washed with H_2O and saturated aqueous NaCl. The solvent was removed under reduced pressure, and the residue was chromatographed on silica (300 g, EtOAc−hexane, 1:1.5) to give 0.21 g (75%) of **44** as a colorless oil: $[\alpha]^{23}_D$ −4.1 (*c* 1.02, $CHCl_3$); IR (neat) 3428, 2939, 2861, 1729, 1503, 1440, 1279, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05−1.18 (m, 1H), 1.29−1.43 (m, 1H), 1.66−1.72 (m, 1H), 1.78−1.85 (m, 1H), 2.40 (br, 1H), 2.65−2.75 (m, 2H), 2.90−2.91 (m, 1H), 3.18 (d, J = 17 Hz, 1H), 3.37−3.49 (m, 2H), 3.68 (s, 3H), 3.86 (s, 3H), 4.67−4.72 (m, 1H), 6.65 (d, J = 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 25.1, 29.8, 34.2, 38.4, 43.7, 52.3, 56.8, 71.7, 93.2, 113.9, 120.3, 124.1, 127.2, 143.5, 145.4, 175.2; MS *m*/*z* 304 (M^+, 100), 287, 273, 245, 227, 187, 149, 119, 107, 102; HRMS *m*/*z* 304.1309 (calcd for $C_{17}H_{20}O_5$ 304.1307).

There was also obtained 9.5 mg (3%) of **45**: IR (neat) 3511, 2954, 1733, 1513, 1445, 1284, 1205, 1176, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37−1.47 (m, 2H), 1.88−2.00 (m, 2H), 2.66−2.85 (m, 3H), 3.07−3.13 (m, 1H), 3.51−3.60 (m, 1H), 3.70 (s, 3H), 3.87 (s, 3H), 4.10−4.14 (m, 1H), 4.95−5.00 (m, 1H), 6.66 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.5, 28.1, 33.8, 36.5, 45.1, 52.2, 56.7, 66.2, 86.0, 113.4, 120.2, 124.4, 127.6, 141.7, 147.0, 175.5; MS *m*/*z* 304 (M^+), 244, 227, 215, 201, 199, 195, 187, 121, 119, 115, 86, 84; HRMS *m*/*z* 304.1309 (calcd for $C_{17}H_{20}O_5$ 304.1311).

Methyl (4a*S*,7a*S*,8*S*,9c*R*)-3-Methoxy-5-(methox)-methoxy)-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (46). A mixture of **44** (130 mg, 0.43 mmol), $CH_2(OMe)_2$ (1.9 mL, 21.3 mmol), and P_2O_5 (30 mg) in dry $CHCl_3$ (30 mL) was stirred for 4 h at ambient temperature. The solid residue was filtered off, and the filtrate was neutralized with solid $NaHCO_3$ (200 mg). The neutral mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica (30 g, hexanes−EtOAc, 2:1) afforded 129 mg (86%) of **46** as a colorless oil: $[\alpha]^{23}_D$ −9.2 (*c* 0.78, $CHCl_3$); IR (neat) 2939, 1733, 1503, 1445, 1108, 1054 cm^{-1}; ^1HNMR (300 MHz, $CDCl_3$) δ 1.05−1.19 (m, 1H), 1.25−1.38 (m, 1H), 1.63−1.70 (m, 1H), 1.85−1.93 (m, 1H), 2.65−2.74 (m, 2H), 2.89−2.91 (m, 1H), 3.18 (d, J = 18 Hz, 1H), 3.34−3.42 (m, 1H), 3.37 (s, 3H), 3.48 (t, J = 7 Hz, 1H), 3.68 (s, 3H), 3.87 (s, 3H), 4.69 (d, J = 7 Hz, 1H), 4.75 (d, J = 7 Hz, 1H), 4.77 (t, J = 8 Hz, 1H), 6.64 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 24.9, 29.9, 34.2, 38.6, 43.7, 52.3, 55.4, 57.2, 76.1, 91.3, 95.6, 115.0, 120.2, 124.2, 127.2, 143.6, 145.7, 175.1; MS *m*/*z* 348 (M^+), 302, 243, 227, 215, 199, 183, 161, 115, 86, 84 69; HRMS *m*/*z* 348.1574 (calcd for $C_{19}H_{24}O_6$ 348.1573).

(4a*S*,5*S*,7a*S*,8*S*,9c*R*)-3-Methoxy-5-(methoxymethoxy)-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylic Acid (47). To a solution of **45** (100 mg, 0.29 mmol) in THF−H_2O (30 mL, 1:1) was added LiOH (50 mg, 1.2 mmol), and the mixture was stirred for 20 h at ambient temperature. The mixture was acidified with aqueous HCl (10%) and extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 100 mg (100%) of pure **46** as a colorless oil: $[\alpha]^{23}_D$ −8.5 (*c* 1.55 $CHCl_3$); IR (neat) 3174 (br), 2930, 1733, 1708, 1508, 1445, 1283, 1156, 1103, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05−1.18 (m, 1H), 1.25−1.38 (m, 1H), 1.62−1.71 (m, 1H), 1.87−1.92 (m, 1H), 2.64−2.75 (m, 2H), 2.91−2.96 (m, 1H), 3.16 (d, J = 17 Hz, 1H), 3.34−3.42 (m, 1H), 3.38 (s, 3H), 3.54 (t, J = 7 Hz, 1H), 3.86 (s, 3H), 4.69 (d, J = 7 Hz, 1H), 4.75 (d, J = 7 Hz, 1H), 4.78 (t, J = 8 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 24.9, 28.4, 34.0, 38.5, 43.5, 55.3, 57.2, 76.0, 91.2, 95.5, 115.0, 120.2, 123.9, 127.0, 143.7, 145.7, 180.7; MS *m*/*z* 334 (M^+), 304, 289, 271, 260, 243, 227, 215, 199, 183, 161, 115; HRMS *m*/*z* 334.1415 (calcd for $C_{18}H_{22}O_6$ 334.1417).

(4a*S*,5*S*,7a*S*,8*S*,9c*R*)-3-Methoxy-5-(methoxymethoxy)-4a,5,6,7,7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-yl]-2-diazo-1-ethanone (48). A solution of **47** (90 mg, 0.27 mmol) and oxalyl chloride (0.2 mL, 2.2 mmol) in dry benzene (30 mL) was stirred for 18 h at ambient temperature. The solvent and excess oxalyl chloride were removed under reduced pressure, and the residue was taken up into benzene (25 mL). The solution was added dropwise to CH_2N_2 (6 M in Et_2O, 30 mL), and the mixture was stirred at ambient temperature for 1 h. Excess CH_2N_2 was removed in a stream of N_2, and the solvent was removed under reduced pressure. The residue was chromatographed on silica (30 g, EtOAc−hexane, 1:1) to yield 61 mg (63%) of **48** as a yellow oil: $[\alpha]^{23}_D$ −36.7 (*c* 0.95, $CHCl_3$); IR (neat) 3091, 2930, 2099, 1630, 1503, 1445, 1362, 1152, 1112, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05−1.39 (m, 2H), 1.63−1.70 (m, 1H), 1.85−1.92 (m, 1H), 2.52−2.58 (m, 1H), 2.69−2.81 (m, 2H), 2.93 (d, J = 17, 1H), 3.35−3.41 (m,1H), 3.36 (s, 3H), 3.51 (t, J = 7 Hz, 1H), 3.87 (s, 3H), 4.67 (d, J = 7 Hz, 1H), 4.73 (d, J = 7 Hz, 1H), 4.76 (t, J = 8 Hz, 1H), 5.31 (s, 1H), 6.64 (d, J = 8 Hz, 1H), 6.73 (dd, J = 1, 8 Hz, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 23.5, 25.3, 28.5, 35.3, 38.4, 49.3, 54.3, 55.3, 57.2, 76.1, 91.3, 95.5, 115.1, 120.2, 123.6, 127.6, 143.8, 145.8, 197.2.

(1*R*,4*S*,12*S*,13*S*,16*R*)-9-Methoxy-13-(methoxymethoxy)-11-oxapentacyclo[8.6.1.0^{1,12}.0^{4,16}.0^{6,17}]heptadeca-6(17),7,9-trien-3-one (49). To a solution of **48** (47 mg, 0.13 mmol) in CH_2Cl_2 (50 mL) under argon was added $Rh_2(OAc)_4$ (1 mg), and the mixture was stirred for 1 h at ambient temperature. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica (10 g, EtOAc−hexane, 1:2) to afford 22 mg (51%) of **49** as a colorless oil: $[\alpha]^{23}_D$ +12.0 (*c* 0.44, $CHCl_3$); IR (neat) 2941, 1755, 1509, 1447, 1283, 1262, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21−1.31 (m, 1H), 1.34−1.57 (m, 1H), 1.73−1.83 (m, 1H), 1.86−1.95 (m, 1H), 2.47−2.55 (m, 1H), 2.49 (s, 2H), 2.72−2.76 (m, 1H), 2.85−2.93 (m, 2H), 3.40 (s, 3H), 3.57−3.64 (m, 1H), 3.87 (s, 3H), 4.72 (d, J = 7 Hz, 1H), 4.75 (d, J = 6 Hz, 1H), 4.79 (d, J = 7 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 27.5, 28.4, 42.2, 49.1, 50.1, 53.9, 55.5, 57.0, 77.9, 90.9, 95.9, 115.3, 120.7, 122.4, 133.1, 144.0, 144.2, 217.9; MS *m*/*z* 330 (M^+), 285, 257, 243, 199, 113, 83, 69, 55, 49, 45; HRMS *m*/*z* 330.1469 (calcd for $C_{19}H_{22}O_5$ 330.1467). Analogous decomposition of **48** using $Rh_2(acam)_4$ as the catalyst gave **49** in 65% yield.

(3a*S,9*R**,9a*S**,9b*R**)-9-(2-Diazoacetyl)-5-methoxy-1,-3a,8,9,9a,9b-hexahydrophenanthro[4,5-*bcd*]furan-3(2*H*)-one (50).** A solution of **52** (210 mg, 0.73 mmol) and oxalyl chloride (325 μL, 3.72 mmol) in dry benzene (20 mL) was stirred for 18 h at ambient temperature, after which time the solvent and excess oxalyl chloride were removed under reduced pressure. The residue was taken up into benzene (25 mL), and the solution was added dropwise to a 0.6 M solution of CH_2N_2 in Et_2O (100 mL). The mixture was stirred for 1 h, and N_2 was passed through the solution for 2 h to remove excess CH_2N_2. Most of the solvent was evaporated under reduced pressure, and the residual oil was chromatographed on silica (18 g, EtOAc−hexane, 1:1) to provide 190 mg (83%) of **50** as a yellow oil: IR (neat) 3086, 2930, 2109, 1728, 1636, 1504, 1440, 1362, 1284, 1157, 113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37−1.51 (m, 1H), 1.94−1.99 (m, 1H), 2.36−2.48 (m, 2H), 2.72 (dd, J = 6, 18 Hz, 1H), 2.84−2.88 (m, 1H), 2.96 (d, J = 18, 1H), 2.98−3.03 (m, 1H), 3.91 (s, 3H), 3.96 (t, J = 6 Hz, 1H), 5.05 (d, J = 9 Hz, 1H), 5.38 (s, 1H), 6.67 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8,27.4, 35.0, 39.6, 41.7, 48.8, 54.7, 57.1, 87.3, 115.3, 121.0, 123.3, 124.6, 143.2, 147.0, 196.7, 207.7.

Methyl (4a*S,7a*S**,8*S**,9c*R**)-3-Methoxy-5-oxo-4a,5,6,7,-7a,8,9,9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylate (51).** A mixture of **44** (30 mg, 0.099 mmol) and Dess−Martin periodinane (50 mg, 0.12 mmol) in $CHCl_3$ (5 mL) was stirred for 1 h at ambient temperature. A solution of $Na_2S_2O_3$−$NaHCO_3$ (5 mL, 50 g of $Na_2S_2O_3$ in 200 mL of saturated aqueous $NaHCO_3$) was added, and stirring was continued for

another 20 min. The $CHCl_3$ layer was separated, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (5 g, EtOAc−hexane, 1:2) gave 27 mg (92%) of **51** as a colorless oil: IR (neat) 2946, 1733, 1684, 1504, 1435, 1271, 1206, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37−1.50 (m, 1H), 1.92−1.99 (m, 1H), 2.38−2.43 (m, 2H), 2.67 (d, $J = 7$, 18 Hz, 1H), 2.94−2.98 (m, 1H), 3.17−3.10 (m, 1H), 3.22 (d, $J = 18$ Hz, 1H), 3.72 (s, 3H), 3.89 (s, 3H), 3.88−3.92 (m, 1H), 5.05 (d, $J = 9$ Hz, 1 H), 6.65 (d, $J = 8$ Hz, 1H), 6.71 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 26.9, 34.0, 39.5, 41.8, 43.3, 52.5, 57.1, 87.3, 115.0, 121.0, 123.8, 124.1, 142.9, 146.8, 174.7, 207.8; MS *m/z* 302 (M^+), 248, 231, 214, 187, 161, 119, 86, 84; HRMS *m/z* 302.1154 (calcd for $C_{17}H_{18}O_5$ 302.1154).

(4a*S,7a*S**,8*S**,9c*R**)-3-Methoxy-5-oxo-4a,5,6,7,7a,8,9,-9c-octahydrophenanthro[4,5-*bcd*]furan-8-carboxylic Acid (52).** To a solution of **51** (50 mg, 0.165 mmol) in THF−H_2O (1:1.3, 35 mL) was added LiOH (28 mg, 0.66 mmol), and the mixture was stirred for 18 h at ambient temperature. The mixture was acidified with aqueous HCl (10%) and was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 47 mg (99%) of **52** as a colorless oil: IR (neat) 3209, 2945, 1728, 1509, 1450, 1284, 1196, 1167, 1108, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38−1.48 (m, 1H), 1.95−1.99 (m, 1H), 2.37−2.46 (m, 2H), 2.86 (dd, $J = 7$, 18 Hz, 1H), 3.00 (d, $J = 8$ Hz, 1H), 3.11−3.18 (m, 1H), 3.22 (d, $J = 18$ Hz, 1H), 3.90 (s, 3H), 3.97 (t, $J = 7$ Hz, 1H), 5.06 (d, $J = 9$ Hz, 1H), 6.66 (d, $J = 8$ Hz, 1H), 6.72 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 26.9, 33.9, 39.5, 41.7, 43.2, 57.2, 87.2, 115.6, 121.0, 123.6, 124.2, 143.0, 146.9, 180.1, 207.7; MS *m/z* 288 (M^+), 260, 232, 215, 187, 183, 161, 115; HRMS *m/z* 288.0996 (calcd for $C_{16}H_{16}O_5$ 288.0998).

(1*R,12*S**,16*R**)-9-Methoxy-11-oxapentacyclo-[8.6.1.0^{1,12}.0^{4,14}.0^{6,17}]heptadeca-6(17),7,9-triene-3,13-dione (53).** To a stirred solution of **50** (0.19 g, 0.605 mmol) in dry CH_2Cl_2 (200 mL) under argon was added $Rh_2(OAc)_4$ (ca. 2 mg), and the mixture was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica (30 g, EtOAc−hexane, 1:2) to furnish 91 mg (53%) of **53** as a colorless oil: IR (neat) 2941, 2839, 1740, 1721, 1503, 1442, 1283, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48−1.63 (m, 1H), 2.03−2.11 (m, 1H), 2.39−2.50 (m, 1H), 2.55−2.64 (m, 2H), 2.72 (d, $J =$ 17 Hz, 1H), 2.84−2.92 (m, 4H), 3.90 (s, 3H), 4.92 (s, 1H), 6.62 (d, $J = 8$ Hz, 1H), 6.72 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.5, 40.7, 42.6, 49.9, 52.0, 53.3, 56.9, 88.2, 115.5, 121.7, 121.9, 129.9, 143.5, 145.1, 207.3, 216.6; MS *m/z* 284 (M^+), 256, 242, 227, 213, 199, 185, 181, 128, 121, 115; HRMS *m/z* 284.1047 (calcd for $C_{17}H_{16}O_4$ 284.1048).

(1*R,4*S**,12*S**,16*R**)-9-Methoxy-11-oxapentacyclo-[8.6.1.0^{1,12}.0^{4,16}.0^{6,17}]heptadeca-6(17),7,9,14-tetraene-3,13-dione (55).** To a stirred solution of **52** (48 mg, 0.17 mmol) in EtOAc (7 mL) was added PhSeCl (46 mg, 0.24 mmol), followed by aqueous HCl (36%, 5 drops), and the mixture was stirred for 5 h at ambient temperature. The mixture was neutralized with solid $NaHCO_3$ (30 mg) and was stirred for another 30 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up into THF−H_2O (1:1.5, 25 mL), $NaIO_4$ (150 mg, 0.70 mmol) was added, and the solution was stirred for 30 h at room temperature, after which time most of the THF was removed under reduced pressure. The residue was extracted with EtOAc, and the extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (5 g, EtOAc−hexane, 2:1) gave 19 mg (46%) **55** as a colorless oil: IR (neat) 2959, 2842, 1748, 1684, 1503, 1450, 1284, 1264, 1176, 1084, 927, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, $J =$ 5, 17 Hz, 1H), 3.02 (dd, $J = 2$, 17 Hz, 1H), 3.07−3.10 (m, 1H), 3.46−3.50 (m, 1H), 3.85 (s, 3H), 5.05 (s, 1H), 6.24 (d, $J =$ 2, 10 Hz, 1H), 6.70 (d, $J = 8$ Hz, 1H), 6.95 (dd, $J = 2$, 10 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 41.0, 49.5, 49.6, 52.1, 56.9, 86.3, 115.6, 121.3, 122.0, 132.3, 134.7, 143.1, 144.6, 145.3, 193.3, 215.3; MS *m/z* 282 (M^+), 254, 226, 211, 201, 185, 85, 83; HRMS *m/z* 282.0891 (calcd for $C_{17}H_{14}O_4$ 282.0892).

(1*R*,4*S*,12*S*,13*S*,16*R*)-9-Methoxy-13-(methoxymethoxy)-11-oxapentacyclo[8.6.1.0^{1,12}.0^{4,16}.0^{6,17}]heptadeca-6(17),7,9-trienone Oxime (56). A solution of **49** (20 mg, 0.062 mmol), $NH_2OH\cdot HCl$ (6.3 mg, 0.091 mmol), and NaOAc (16.5 mg, 0.12 mmol) in MeOH (10 mL) was stirred for 6 h at ambient temperature. The mixture was concentrated under reduced pressure, and the residue was taken up into $CHCl_3$ (15 mL). The resulting solution was washed with H_2O and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (20 g, EtOAc−hexane 1:1) afforded 18.8 mg (90%) of **56** as a colorless oil: IR (neat) 1073, 1284, 1440, 1507, 1606, 1640, 1552, 2935, 3374 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$) δ 1.16−1.24 (m, 1H), 1.39−1.51 (m, 1H), 1.66−1.75 (m, 1H), 1.73−1.91 (m, 1H), 1.87 (d, $J = 13$ Hz, 1H), 2.12−2.26 (m, 1H), 2.57 (m, 1H), 2.73−3.10 (m, 3H), 3.40 (s, 3H), 3.51−3.58 (m, 1H), 3.87 (s, 3H), 4.69−4.81 (m, 3H), 6.58 (d, $J = 8$ Hz, 1H), 6.71 (d, $J = 8$ Hz, 1H); MS (EI) *m/z* 345(M^+), 241, 199, 167, 149, 115; HRMS *m/z* 345.1575 (calcd for $C_{19}H_{23}NO_5$ 345.1576).

(1*R*,5*S*,13*S*,14*S*,17*S*)-10-Methoxy-14-(methoxymethoxy)-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-trien-3-one (57). A solution of **56** (25 mg, 0.072 mmol), *p*-bromobenzenesulfonyl chloride (28 mg, 0.11 mmol), Et_3N (16 μL, 0.12 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 mL) was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was taken up into AcOH (2 mL). The resulting solution was stirred for 1 h and was neutralized with saturated, aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (6 g, EtOAc−MeOH, 12:1) gave 17 mg (69%) of **57** as a colorless oil: $[\alpha]^{23}_D$ +114.2 (*c* 1.47, $CHCl_3$); IR (neat) 3271, 2932, 1673, 1509, 1437, 1288, 1119, 1037, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92−1.05 (m, 1H), 1.25−1.41 (m, 1H), 1.69−1.80 (m, 1H), 1.92−2.01 (m, 1H), 2.29 (dt, $J = 4$, 13 Hz, 1H), 2.52 (d, $J =$ 17 Hz, 1H), 2.68 (d, $J =$ 17 Hz, 1H), 2.75 (br s, 2H), 3.38 (s, 3H), 3.35−3.39 (m, 1H), 3.83 (br s, 1H), 3.88 (s, 3H), 4.41 (d, $J = 7$ Hz, 1H), 4.68 (d, $J = 7$ Hz, 1H), 4.75 (d, $J = 7$ Hz, 1H), 6.62 (d, $J = 8$ Hz, 1H), 6.76 (d, $J = 8$ Hz, 1H), 6.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 28.0, 28.3, 31.1, 38.2, 42.6, 43.8, 51.3, 55.4, 57.1, 76.4, 95.3, 95.6, 115.7, 121.5, 130.3, 144.6, 144.9, 170.9; MS (CI) *m/z* 346 (M^++1), 339, 323, 284, 246, 185, 169, 141, 125, 89, 86, 84, 78, 75, 73; HRMS *m/z* 345.1575 (calcd for $C_{19}H_{23}NO_5$ 345.1576).

(1*R*,5*S*,13*S*,14*S*,17*S*)-10-Methoxy-14-(methoxymethoxy)-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]-octadeca-7(18),8,10-trien-3-one (**62**). To a solution of **57** (24 mg, 0.069 mmol) in dry benzene (3 mL) were added NaH (55 wt % suspension in mineral oil, 12 mg, 0.28 mmol) and CH_3I (43 μL, 0.69 mmol), and the mixture was heated at reflux for 5 h. The mixture was diluted with EtOH (40 mL) and H_2O (2 mL), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (4 g, EtOAc−MeOH, 12:1) furnished 24 mg (95%) of **62** as a colorless oil: $[\alpha]^{23}_D$ +148.9 (*c* 0.092, $CHCl_3$); IR (neat) 2935, 1655, 1636, 1509, 1440, 1284, 1108, 1054, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98−1.26 (m, 1H), 1.28−1.38 (m, 1H), 1.68−1.78 (m, 1H), 1.91−1.97 (m, 1H), 2.34 (dt, $J = 4$, 13 Hz, 1H), 2.56 (d, $J = 17$ Hz, 1H), 2.95 (d, $J = 18$ Hz, 1H), 3.00 (s, 3H), 3.31−3.38 (m, 1H), 3.38 (s, 3H), 3.69−3.72 (m, 1H), 3.88 (s, 3H), 4.41 (d, $J =$ 7 Hz, 1H), 4.68 (d, $J = 7$ Hz, 1H), 4.75 (d, $J = 7$ Hz, 1H), 6.62 (d, $J = 8$ Hz, 1H), 6.75 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 26.8, 28.0, 34.2, 39.2, 43.1, 44.9, 55.4, 57.2, 59.0, 76.4, 95.1, 95.6, 115.7, 121.2, 121.5, 130.4, 144.6, 144.9, 168.4; MS *m/z* 359 (M^+), 329, 314, 298, 286, 256, 243, 225, 211, 199, 185; HRMS *m/z* 359.1733 (calcd for $C_{20}H_{25}NO_5$ 359.1733).

**(1*R*,5*S*,13*S*,14*S*,17*S*)-14-Hydroxy-10-methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-

7(18),8,10-trien-3-one (64). A solution of **62** (22 mg, 0.061 mmol) in MeCN (2 mL) and aqueous HBr (36%, 10 mL) was stirred for 2 h at ambient temperature. The mixture was neutralized with solid $NaHCO_3$ (30 mg) and filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica (3 g, EtOAc−MeOH, 9:1) gave 18 mg (95%) of **64** as a colorless oil: $[\alpha]^{23}_D$ +148.9 (*c* 0.092, $CHCl_3$); IR (neat) 3394, 2936, 1620, 1509, 1440, 1280, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00−1.10 (m, 1H), 1.28−1.48 (m, 1H), 1.73−1.80 (m, 2H), 1.84−1.90 (m, 1H), 2.36 (dt, J = 4, 13 Hz, 1H), 2.54 (m, 1H), 2.56 (d, J = 17 Hz, 1H), 2.65 (dd, J = 4, 18 Hz, 1H), 2.70 (d, J = 17 Hz, 1H), 2.95 (d, J = 18 Hz, 1H), 3.01 (s, 1H), 3.33−3.43 (m, 1H), 3.70−3.73 (m, 1H), 3.87 (s, 3H), 4.34 (d, J = 7 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 26.8, 29.4, 34.2, 39.2, 42.9, 44.9, 56.8, 59.0, 72.3, 97.0, 114.8, 121.3, 121.5, 130.5, 144.4, 144.7, 168.4; MS *m*/*z* 315 (M^+), 301, 286, 258, 243, 229, 213, 199, 185, 178; HRMS *m*/*z* 315.1472 (calcd for $C_{18}H_{21}NO_4$ 315.1471).

(1*R*,5*S*,13*S*,17*S*)-10-Methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10-triene-3,14-dione (63). A mixture of **64** (16 mg, 0.051 mmol) and Dess−Martin periodinane (26 mg, 0.061 mmol) in $CHCl_3$ (3 mL) was stirred for 1 h at ambient temperature. The suspension was treated with a $Na_2S_2O_3$−$NaHCO_3$ solution (4 mL, 50 g of $Na_2S_2O_3$ in 200 mL of saturated aqueous $NaHCO_3$), and the chloroform layer was separated, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (4 g, EtOAc−MeOH, 11:1) gave 15 mg (96%) of **63** as a colorless oil: $[\alpha]^{23}_D$ +181.3 (*c* 0.71, $CHCl_3$); IR (neat) 2935, 1738, 1636, 1504, 1440, 1284, 1101, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26−1.39 (m, 1H), 2.01−2.08 (m, 1H), 2.40−2.48 (m, 2H), 2.62 (dd, J = 4, 18 Hz, 1H), 2.76−2.80 (m, 3H), 2.98 (d, J = 18 Hz, 1H), 3.04 (s, 3H), 3.78−3.80 (m, 1H), 3.91 (s, 3H), 4.70 (s, 1H), 6.64 (d, J = 8 Hz, 1H), 6.75 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.9, 34.3, 39.1, 39.2, 44.5, 46.9, 57.2, 58.7, 91.6, 116.2, 121.2, 122.1, 127.3, 143.9, 146.2, 167.7, 206.0; MS *m*/*z* 313 (M^+), 256, 241, 231, 212, 198, 181, 131, 121, 97, 83, 71; HRMS *m*/*z* 313.1314 (calcd for $C_{18}H_{19}NO_4$ 313.1341).

(1*R*,5*S*,13*S*,17*S*)-10-Methoxy-4-methyl-12-oxa-4-azapentacyclo[9.6.1.0^{1,13}.0^{5,17}.0^{7,18}]octadeca-7(18),8,10,15-tetraene-3,14-dione (67). To a solution of **63** (35 mg, 0.11 mmol) in THF (5 mL) at 0 °C under argon was added a 1 M solution of KO-*t*-Bu in *t*-BuOH (130 mL, 0.13 mmol), and the mixture was stirred for 30 min at 0 °C. A solution of PhSeCl (28.7 mg, 0.15 mmol) in THF (0.4 mL) was added, and the mixture was allowed to warm to room temperature during 1 h. The mixture was diluted with saturated aqueous NH_4Cl (0.5 mL) and was extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was taken up into THF−H_2O (1:1, 4 mL), $NaIO_4$ (180 mg, 0.88 mmol) was added, and the mixture was stirred for 30 h at ambient temperature. The mixture was extracted with $CHCl_3$, and the extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (3 g, EtOAc−EtOH, 11:1) produced 22 mg (64%) of **67** as a colorless oil: $[\alpha]^{23}_D$ +168.4 (*c* 0.012, $CHCl_3$); IR (neat) 1159, 1287, 1449, 1505, 1634, 1681, 2859, 2929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (dd, J = 4, 18 Hz, 1H), 2.78 (d, J = 17 Hz, 1H), 2.89 (d, J = 17 Hz, 1H), 3.05 (s, 3H), 3.12 (m, 2H), 3.42 (br s, 1H), 3.87 (s, 3H), 4.05 (m, 1H), 4.71 (s, 1H), 6.19 (dd, J = 3, 10 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.69 (d, J = 10 Hz, 1H), 6.74 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9, 34.4, 38.4, 43.1, 43.2, 57.3, 58.5, 87.7, 118.2, 121.0, 122.3, 129.0, 134.1, 143.9, 144.2, 145.2, 167.6, 193.7; MS (CI) *m*/*z* 321 (M^+ + H), 201, 130, 121, 115, 111, 102, 97 86, 83, 69; HRMS (CI) *m*/*z* 312.1235 (calcd for $C_{18}H_{18}NO_4$ 312.1236).

(+)-Codeine (1). To a stirred suspension of $LiAlH_4$ (6.10 mg, 0.16 mmol) in dry THF (0.5 mL) was added a solution of **67** (5 mg, 0.0196 mmol) in THF (1 mL), and the mixture was refluxed for 6 h. After being cooled to ambient temperature, the mixture was treated with a saturated aqueous solution of Rochelle's salt (1 mL) and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (2 g, $CHCl_3$−Et_2NH, 20:1) yielded 4.1 mg (70%) of **1** as a colorless solid: mp 149−152 °C; $[\alpha]^{23}_D$ +137.5 (*c* 0.16, EtOH); ^{1}HNMR (400 MHz,$CDCl_3$) δ 1.90 (d, J = 12 Hz), 2.11−2.17 (m, 1H), 2.36 (dd, J = 6, 18 Hz, 1H), 2.44−2.47 (m, 1H), 2.49 (s, 3H), 2.65−2.68 (m, 1H), 2.78 (br s, 1H), 3.05 (d, J = 18 Hz, 1H), 3.41 (br s, 1H), 3.84 (s, 3H), 4.17−4.19 (m, 1H), 4.90 (d, J = 6 Hz, 1H), 5.26−5.30 (m, 1H), 5.72 (d, J = 10 Hz, 1H), 6.57 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 35.6, 40.6, 43.0, 43.1, 46.8, 56.6, 59.3, 66.5, 91.3, 113.3, 119.9, 128.0, 131.0, 133.9, 139.6, 142.6, 146.5. This material was spectroscopically identical with a sample of natural (−)-codeine.[5a]

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Supporting Information Available: Complete X-ray crystallographic data for **24** and **26** and NMR spectra (^1H and ^{13}C) of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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