Synthesis of Enantiomerically Pure Morphine Alkaloids: The Hydrophenanthrene Route

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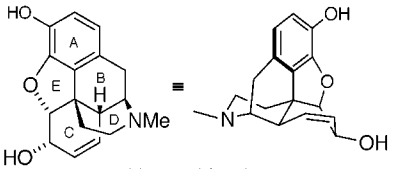
A concise, linear, total synthesis of (−)-dihydrocodeinone—a close synthetic precursor of (−)-codeine and (−)-morphine—has been achieved. The carbocyclic core of the alkaloid was provided in the form of a phenanthrenone, which was resolved by chromatography on cellulose triacetate. A cuprate conjugate addition was used to establish the crucial benzylic quaternary stereocenter and to introduce the C_2-side chain. Dimeric byproducts provide evidence for a single electron transfer (SET) mechanism. Unusual S_N2 and radical cyclizations were employed for the formation of the dihydrobenzofuran and the piperidine ring, respectively.

Introduction

The morphine alkaloids represent a family of structurally related natural products of eminent importance in medicine.[1] Total syntheses of the parent compound, (−)-morphine (**1**), and derivatives thereof have attracted the

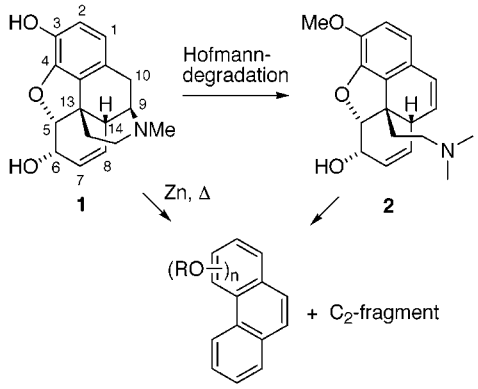


(-)-morphine (**1**)

interest of organic chemists for many decades.[2] These efforts have resulted in numerous successful routes, which, however, mostly led to racemic material and were too long to be of practical use. Our approach is unusually direct and is based on considerations which are derived from the early degradation studies of morphine.[3]

Zinc-dust distillation of **1** was observed to afford phenanthrene as early as 1881. Subsequently, milder methods allowed the isolation of intermediates which provided more insight into the substitution pattern of the phenanthrene core (Scheme 1). Hofmann-type degradations, for instance, led to cleavage of the C9-N bond and introduction of a $\Delta^{9,10}$-double bond to yield so-called morphimethines (**2**). Further degradation under more drastic conditions usually resulted in elimination of the C_2-chain and full aromatization of the tricyclic nucleus. Accordingly, the carbon skeleton has been conceptually disconnected into an oxygenated hydrophenanthrene core

Scheme 1



and a two carbon "side chain" linked with the nitrogen, whose other point of attachment was under debate for many years until Robinson established the C13-linkage in 1926.[4]

Hence, many attempts to synthesize morphine were based on the idea to provide a suitably substituted hydrophenanthrenone and to mount the ethanamine bridge onto this platform subsequently. This deceptively simple concept, however, requires a reaction which is powerful enough to introduce the crucial benzylic quaternary carbon (C13) against considerable steric hindrance—an issue that has been solved by an intramolecular strategy in approaches by Ginsburg[5] and White.[6] In contrast, our approach is characterized by an *intermolecular* addition to create the quaternary C13 center. We report now full details of our synthesis, which is essentially a reversal of the degradation shown above, and give an account of its gradual evolution.[7]

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(1) Iversen, L. *Nature* **1996**, *383*, 759, and references cited therein.

(2) For reviews on the total synthesis of morphine alkaloids, see: (a) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1996; pp 43 ff. (b) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, Germany, 1995; p 357 ff. (c) Szántay, G.; Dörnyei, G. In *The Alkaloids*; Cordell, G.A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, pp 127 ff.

(3) Fieser, L.; Fieser, M. *Natural Products Related to Phenanthrene*, 3rd ed.; Reinhold: New York, 1949.

(4) Gulland, J. M; Robinson, R. *Mem. Proc. Manchester Lit. Phil. Soc.* **1925**, *69*, 79.

(5) Ginsburg, D.; Elad, D. *J. Am. Chem. Soc.* **1954**, *76*, 312; *J. Chem. Soc.* **1954**, 3052.

(6) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1997**, *62*, 5250.

(7) For preliminary accounts of this work, see: (a) Mulzer, J.; Dürner, G.; Trauner, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2830 [*Angew. Chem.* **1996**, *108*, 3046]. (b) Mulzer, J.; Bats, J. W.; List, B.; Opatz, T.; Trauner, D. *Synlett* **1997**, 441.

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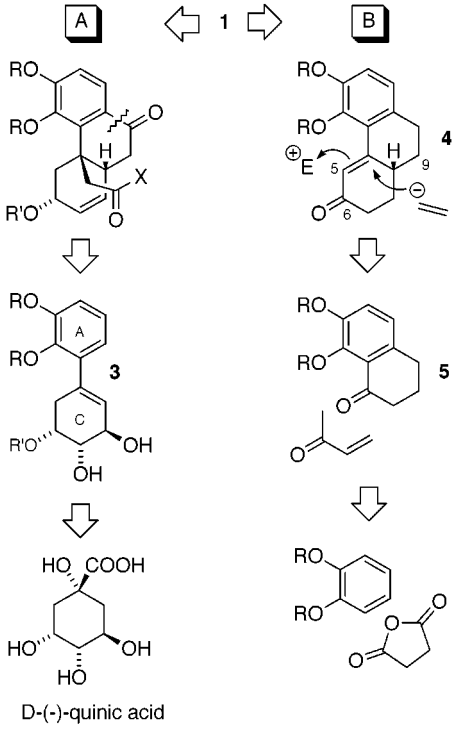
Scheme 2



Initial Studies: Development of the Phenanthrenone Approach

Initially, our approach was based on a completely different strategy, which is shown in Scheme 2 (path A). It was planned to establish the benzylic quaternary and the adjacent tertiary stereocenter by consecutive Claisen rearrangements of an allylic diol **3** (Scheme 1, path A), which was retrosynthetically derived from D-(−)-quinic acid.

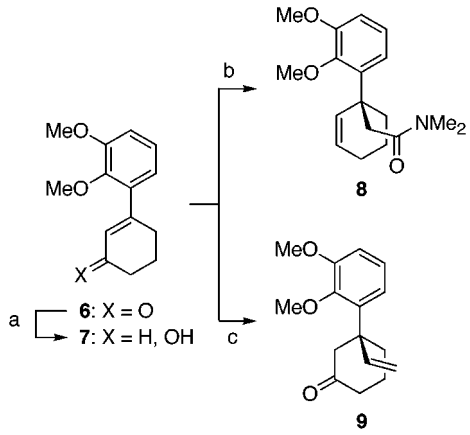
However, in model studies with simple racemic allylic alcohols, the envisioned [3,3]-sigmatropic rearrangements proceeded with unacceptably low yields. For instance, the Claisen−Eschenmoser rearrangement of **7**, which is readily available by reduction of the known enone **6**,[8] afforded amide **8** in only 25% yield (Scheme 3). The Ireland and Johnson variation of the Claisen reaction failed completely.

A more elaborate substrate, **13**, was prepared in three steps from the vinylogous ester **10** by addition of ortho lithiated veratrole followed by hydrolysis and dehydration to afford enone **12** (Scheme 4). Alternatively, **12** was obtained from the addition of veratrole−lithium to 2-allyl-2-cyclohexen-1-one (**11**),[9] followed by oxidation of the resulting tertiary alcohol with concomitant allylic transposition. 1,2-Reduction of **12** then furnished **13**.

Although allylic alcohol **13** did afford the desired rearrangement product **14** upon treatment with several equivalents of *N*,*N*-dimethylacetamide dimethyl acetal, the yields obtained were, again, unacceptable. Notwithstanding, the resulting amide **14** was selectively cleaved at the terminal double bond to afford aldehyde **15**. Unfortunately, **15** failed to undergo the desired B-ring closure upon treatment with various Lewis acids.

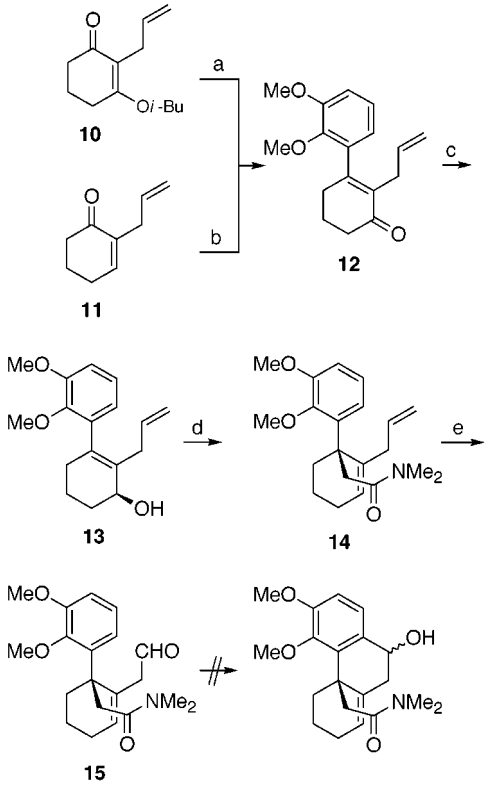
(8) McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers. D. R.; Shenvi, A. *J. Org. Chem.* **1984**, *49*, 3803.
(9) Taber, D. F.: Gunn, B. P.; Chiu, I. C. *Org. Syntheses Collect. Vol. VII*; Wiley: New York, 1990; p 249.

Scheme 3



[a] (a) $NaBH_4$, MeOH (98%). (b) $MeC(OMe)_2NMe_2$, xylenes, Δ (maximum 25%). (c) (i) $H_2C{=}CHMgCl$, 5% $CuBr{-}SMe_2$, (TMS)Cl; (ii) 2 N HCl (87% from **6**).

Scheme 4[a]

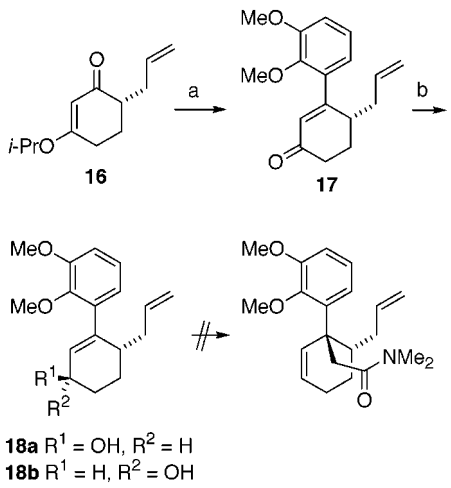


[a] (a) (i) (2,3-Dimethoxyphenyl)lithium, Et_2O, 0 °C; (ii) saturated aqueous NH_4Cl (56%). (b) (i) (2,3-Dimethoxyphenyl)lithium, Et_2O, 0 °C; (ii) PCC, CH_2Cl_2 (44%). (c) $NaBH_4$, MeOH (94%). (d) $MeC(OMe)_2NMe_2$, xylenes, Δ (maximum 24%). (e) (i) OsO_4, NMO, acetone, H_2O; (ii) $NaIO_4$, EtOH (87%).

Our third model compound, **18a**, prepared from enone **16** as shown in Scheme 5 did not undergo [3,3]-sigmatropic rearrangements at all.

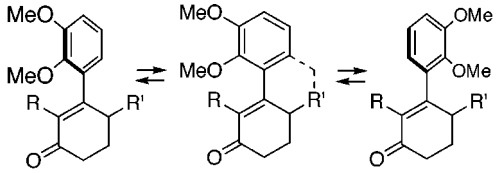
Being aware that Claisen rearrangements and 1,4-additions of vinyl cuprates complement one another, we also explored the conjugate addition of organocuprates to enones **6**, **12**, and **17.** Indeed, the copper(I) catalyzed reaction of vinyl magnesium chloride in the presence of (TMS)Cl with **6** followed by acidic hydrolysis of the intermediary silyl enol ether gave ketone **9** in good overall yield (Scheme 3). Unfortunately, the application

Scheme 5[a]



[a] (a) (i) (2,3-Dimethoxyphenyl)lithium, Et_2O, 0 °C; (ii) 0.5 N H_2SO_4 (72%). (b) $NaBH_4$, MeOH (82%), separation of diastereomers.

Scheme 6

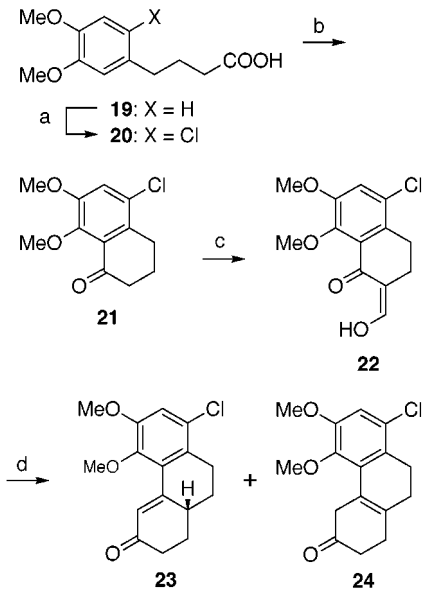


of this reaction to the more advanced intermediates **12** and **17** was unsuccessful. Despite many attempts to perform the conjugate addition under various conditions, only products of 1,2-addition were isolated.

The discouraging results of these model studies may be explained by repulsive interactions between the *o*-methoxy group on the one hand and the corresponding substituents R and R′ on the other hand which twist the aromatic ring out of conjugation with the double bond (Scheme 6). This assumption was based on the ^{1}H-NMR spectra of allylic alcohol **13**, which clearly demonstrate the existence of two rotamers. The whole situation bears some resemblance to the well-known atropisomerism of biphenyls. With the aromatic residue more or less perpendicular to the double bond, any attack on the benzylic sp^2-hybridized carbon is obviously highly unfavorable for steric reasons. The intramolecular hydroxyalkylation of **15** probably failed for similar reasons.

An obvious solution to this problem was to restrict the conformational flexibility of the aromatic ring by means of a tether which would also provide for the missing two carbon B-ring fragment. This idea led to a phenanthrenone of type **4**. A conjugate addition/enolate trapping sequence would then not only establish the quaternary center but also activate C5 toward dihydrofuran ring formation (Scheme 2). Furthermore, the valuable carbonyl function at C6 would be be retained with this strategy. The exact scenario for the functionalization of C9 and closure of the piperidine ring was left undefined at this stage of our planning. Phenanthrenones of type **4** can be prepared in a straigtforward manner via tetralones of type **5**, as shown in Scheme 2.

Scheme 7[a]



[a] (a) Cl_2, AcOH (99%). (b) (i) $(COCl)_2$, PhH, Δ; (ii) $SnCl_4$, PhH, 0 °C (71%). (c) HCOOMe, NaOMe, PhH (95%). (d) (i) MVK, Et_3N, MeOH; (ii) KOH, dioxane, H_2O (81% **23**; 8% **24**).

Total Synthesis of (−)-Dihydrocodeinone, Formal Synthesis of (−)-Morphine

Our synthesis starts with the known tetralone **21**,[10] which was prepared from **19** as described (Scheme 7). The introduction of the chlorine (**19** → **20**) serves to direct the Friedel−Crafts cyclization into the less reactive aromatic position. Activation of **21** as its formyl derivative **22** followed by Robinson annulation and retro-Claisen cleavage provided the crystalline key phenanthrenone **23** in good overall yield. The achiral ketone **24**, a double bond isomer of **23**, was isolated as a byproduct (∼10% with respect to **23**). This ketone **24** was recycled by prolonged treatment under the Robinson annulation conditions to afford the 10:1 equilibrium mixture of **23** and **24**.

Compound **23** was resolved by chromatography on cellulose triacetate (CTA, either on a 1 g scale by flash chromatography (eluent: MeOH) or on a 10 g scale by MPLC (eluent: EtOH:H_2O = 96:4).[11] Under basic conditions the undesired enantiomer **(+)-23** underwent rapid racemization and partial deconjugation to afford the usual mixture of *rac*-**23** and **24**.

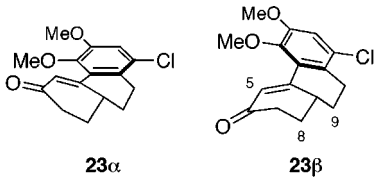
Single crystal X-ray diffraction[12] gave some insight into the ground-state conformation of **(−)-23** and allowed the assignment of its absolute configuration. The four crystallographically independent, homochiral molecules in the unit cell fall into two classes of atropisomers, **23**α and **23**β (Figure 1).

In both cases the 4-methoxy group tends to avoid the vinylic hydrogen at C5 for steric reasons. As these atropisomers, however, are not visible in the NMR spectra at room temperature, the rotational barrier

(10) Robinson, R.; Gosh, R. *J. Chem. Soc.* **1944**, 506.

(11) For an excellent review on the chromatographic resolution on polysaccharide derivatives, see: Okamoto, Y.; Yashima, E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1020 [*Angew. Chem.* **1998**, *110*, 1072].

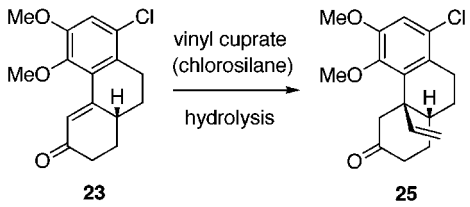
(12) Details of the crystal structure determinations of compounds **23**, **26**, **27**, **31**, **37**, **38a**, **43**, **44**, and **45** may be obtained from: The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1 EZ, U.K.



23α **23β**

Figure 1.

Scheme 8



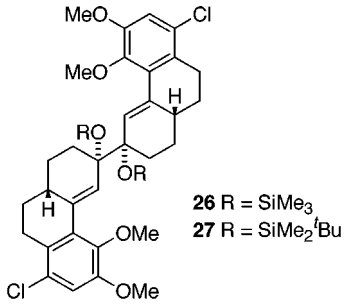
23 **25**

appears to be rather small. Due to the W-shaped arrangement of the saturated C7−C10 periphery, the diastereoface opposite to the angular hydrogen (*re*-face) is sterically more hindered than the *si*-face in both conformers. In particular, the *pseudo*-axial hydrogens at C8 and C9 exert a stereocontrolling effect and direct any attack at C13 to the *si*-face to provide the natural cis linkage of the B- and C-ring. Apart from its primary purpose of blocking the C1 position, the chlorine substituent deactivates the electron-rich aromatic A-ring toward electrophiles and oxidants. Furthermore, it allows the determination of the absolute configuration of enantiomerically pure **(−)-23** by anomalous X-ray dispersion.

With gram quantities of racemic and enantiomerically pure phenanthrenone **23** at hand, the conjugate addition of functionalized organocuprates was explored. Considering the results with compounds **6**, **12**, and **17** (see above), we felt that only a sophisticated reagent would undergo the reaction and that some kind of activation would be mandatory. Indeed, the "(TMS)Cl-accelerated" vinyl cuprates described by Kuwajima and Nakamura (H_2C=CHMgCl, 5−10% $CuBrMe_2S$, (TMS)Cl did provide the desired 1,4-adduct **25**, which represents the entire carbon skeleton of morphine, after hydrolysis of the intermediary silyl enol ether with strong acid (Scheme 8, Table 1). The average yields obtained, however, were low, and the experiments proved difficult to reproduce and scale up. Other vinyl cuprates [e.g. $(H_2C$=$CH)_2CuLi$/(TMS)Cl and $(H_2C$=$CH)_2Cu(CN)Li$/(TMS)Cl] also gave erratic results. Unpolar byproducts were consistently observed which were partially destroyed during acidic workup. The nature of these compounds became apparent when the hydrolysis was conducted under milder conditions. Brief treatment of the crude material with tetrabutylammonium fluoride ((TBA)F) in tetrahydrofuran (THF) gave low yields of **25** along with ca. 20% of the C_2 symmetrical dimer **26**. Similar results were obtained with other vinyl cuprates (Table 1, entries 2−4) and (TBS)Cl (entry 5).

Since our relevant experiments were carried out with racemic **23**, the pinacols **26** and **27** represent one out of 6 possible diastereomeric dimers in each case. Highly C_2 selective electrochemical pinacol dimerizations of similar racemic phenanthrenones have been previously observed by Dana and Esktra.[13] Single crystal X-ray

(13) Dana, G.; Estera, T. *J. Org. Chem.* **1979**, *44*, 1397.



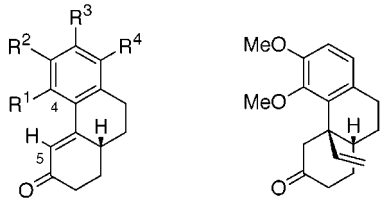
26 R = $SiMe_3$
27 R = $SiMe_2{}^tBu$

diffraction confirmed the C_2 symmetry of **26** and **27** (Figure 2).[12] The central bond of **27** is very crowded, and its homolytic cleavage would generate two stabilized radicals. Nevertheless, it is not much longer than a "normal" C,C-bond (1.573 ± 0.002 Å).

The formation of **26** and **27** under these aprotic conditions can be rationalized by single electron transfer (SET) from the organocuprate to the enone **23**, which generates the stable radical anion **28** and a labile copper(II) species (Scheme 9).[14] Radical anion **28** reacts with the chlorosilane ((TMS)Cl, (TBS)Cl) to the neutral radical **29**, which either dimerizes (see **26**) or combines with the copper(II) species to form the copper(III) intermediate **30**, commonly postulated in the conjugate addition of cuprates. Reductive elimination of vinyl copper(I) then generates the silyl enol ether **31**, which is hydrolyzed in a separate step. The formation of the sterically congested copper(III) intermediate may be so slow that the destruction of the copper(II) species via reductive elimination can compete. The remaining silylated radical then dimerize despite extreme steric hindrance.

Due to Coulombic repulsion, radical anion **28** should be much less prone to dimerization than its neutral counterpart **29**. In the absence of (TMS)Cl the dimerization should, therefore, not be observed. Indeed, under these conditions, **25** was formed as a single diastereomer in excellent yields without any dimeric byproducts (Table 1, entries 6 and 7). As a final optimization, the simple magnesiocuprate $(H_2C$=$CH)_2CuMgCl$ was introduced (entry 7). Despite its convenient preparation from a commercially available Grignard compound and copper(I) iodide, this reagent has not found many applications in chemical synthesis so far.[15]

The success of the conjugate addition to the phenanthrenone was found to be critically dependent on the substitution pattern of the aromatic ring. Whereas the "correctly" substituted phenanthrenones **25** and **32**[16]



23 $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = Cl$ **37**
32 $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H$
33 $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
34 $R^1 = R^2 = R^3 = R^4 = H$
35 $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
36 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$

underwent clean conjugate addition of our standard vinyl cuprate $(H_2C$=$CH)_2CuMgCl$ (91 and 85% yields, respectively) to afford **25** and **37**,[17] respectively, the simpler

Table 1

entry	vinyl cuprate	chlorosilane	workup	yield of **25** (%)
1	$H_2C{=}CHMgCl$, 5−20% $CuBr{-}Me_2S$	(TMS)Cl	2 N HCl	5−21
2	$H_2C{=}CHMgCl$, 10% $CuBr{-}Me_2S$	(TMS)Cl	(TBA)F, THF	23
3	$(H_2C{=}CH)_2CuLi$	(TMS)Cl	(TBA)F, THF	11
4	$(H_2C{=}CH)_2Cu(CN)Li$	(TMS)Cl	(TBA)F, THF	21
5	$(H_2C{=}CH)_2Cu(CN)Li$	(TBS)Cl	(TBA)F, THF	24
6	$(H_2C{=}CH)_2Cu(CN)Li$	none	H_2O/NH_4Cl	73
7	$(H_2C{=}CH)_2CuMgCl$	none	H_2O/NH_4Cl	91

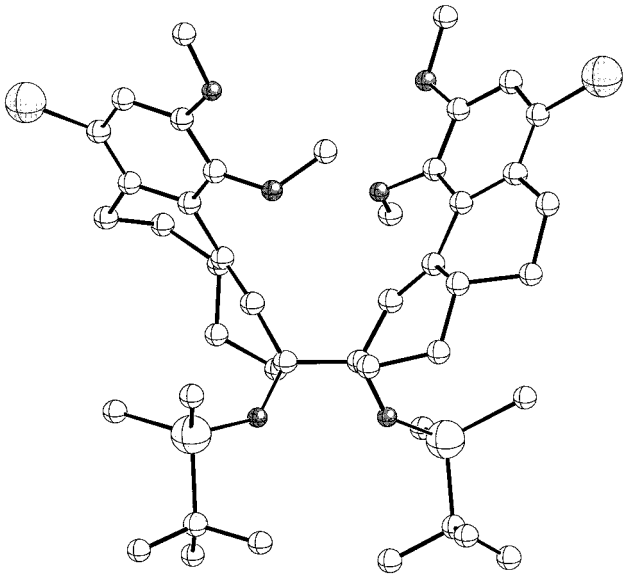
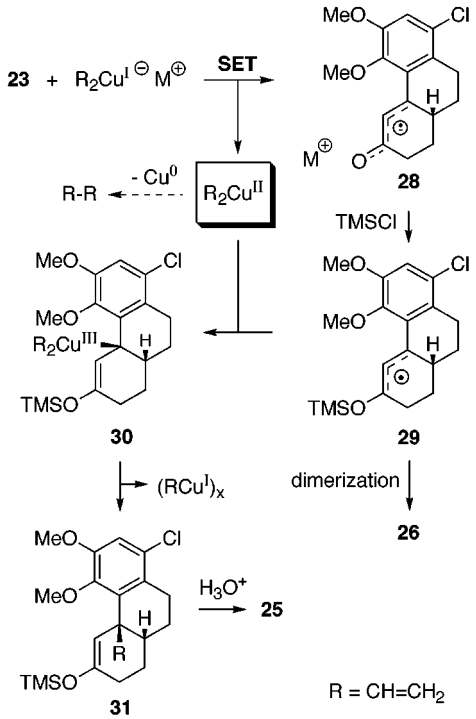


Figure 2. Crystal structure of dimer **27**. Hydrogens are omitted for clarity.

Scheme 9



model compounds **33**, **34**, **35**, and **36** which lack the 4-methoxy substituent failed to produce significant amounts of 1,4-adducts under identical conditions. Compounds **34**, **36**, and, most notably, enone **33**, which is electronically very similar to **25** and **32**, underwent 1,2-addition exclusively. In the case of **35**, the corresponding 1,4-adduct was formed in low yield (14%).

These results can be explained in terms of the above-mentioned 1,4-strain between the vinylic hydrogen at C5 and the 4-methoxy substituent of **23** and **32**, which is apparent in the X-ray structure of **23** (Figure 1). This strain, which does not exist in **33**−**36**, is relieved as the benzylic carbon is pyramidalized in the transition state of the reaction. Additionally, the crucial *o*-methoxy group might stabilize the hypothetical copper(III) intermediate (cf. **30**) by coordination to the metal.

Once the problem of the quaternary stereocenter had been overcome, the synthesis progressed quickly. The conjugate addition not only provided the key quaternary center but also functionalized the neopentylic position (C5), which is otherwise difficult to access, as an enolate or enol ether. In order to achieve the E-ring closure by nucleophilic attack of the proximate oxygen, some kind of "umpolung", transforming the nucleophilic enolate into an electrophilic species, had to be achieved. This could be done by trapping it as an α-bromoketone. Attempted direct bromination of the enolate gave unsatisfactory results in terms of yield and diastereoselectivity. It was therefore necessary to use silyl enol ether **31**, which was now prepared by *subsequent* addition of (TMS)Cl to the enolate resulting from conjugate addition (Scheme 10). Racemic **31**[12] was purified by twofold recrystallization from *n*-pentane (84% yield). Bromination of **31** with NBS in THF at low temperature afforded a 3:1 mixture of the isomeric α-bromoketones **38a** and **38b**. This ratio could not be improved by variation of the reagent, the solvent, or the temperature. Attempted direct epimerizaton of **38b** was unsuccessful as well. However, the undesired isomer **38b** could be recycled by reductive removal of bromide with zinc and concomitant silylation of the resultant enolate (Scheme 10).[18]

Interestingly, the two epimeric α-bromoktones **38a** and **38b** adopt two completely different overall conformations, as shown in Scheme 10.[19] These conformations, which were elucidated by detailed NMR analysis and a single crystal X-ray structure analysis[12] of **38a**, can be inter-

(14) For lead references on the mechanism of organocuprate conjugate additions, see: (a) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (c) *Organocopper Reagents, A Practical Approach*; Taylor, R. K., Ed.; Oxford University Press: Oxford, 1994. For a recent example of a (TMS)Br mediated cuprate addition to form a quaternary center, see: (d) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590.

(15) (a) Harding, K. E.; Clement, B. A.; Moreno, L.; Peter-Katalinic, J. *J. Org. Chem.* **1981**, *46*, 940. (b) Wege, P. M.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144.

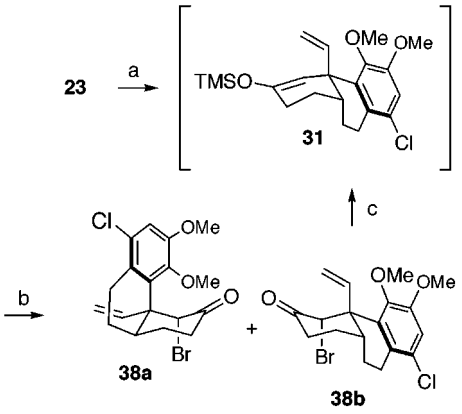
(16) Compound **32** was prepared along similar lines starting from the corresponding chlorine-free tetralone (Bruce, B. H.; Thomson, R. F. *J. Chem. Soc.* **1955**, 1089).

(17) Interestingly, **37**, underwent spontaneous resolution upon crystallization.[12] Bats, J. W.; Trauner, D. Unpublished results.

(18) (a) Rubottom, G. M.; Mott, R. C.; Krueger, D. S. *Synth. Commun.* **1977**, *7*, 333. (b) Joshi, G. C.; Pande, L. M. *Synthesis* **1975**, 451.

(19) Trauner, D.; Opatz, T.; Porth, S.; Bats. J. W.; Giester, G.; Mulzer, J. *Synthesis* **1998**, 653.

Scheme 10[a]



[a] (a) (i) $(H_2C{=}CH)_2CuMgCl$, THF, −78 °C → 0 °C; (ii) (TMS)Cl, Et_3N, 0 °C → 25 °C. (b) NBS, THF (60% **38a**, 21% **38b**; two steps). (c) Zn, (TMS)Cl, TMEDA, Et_2O (71%).

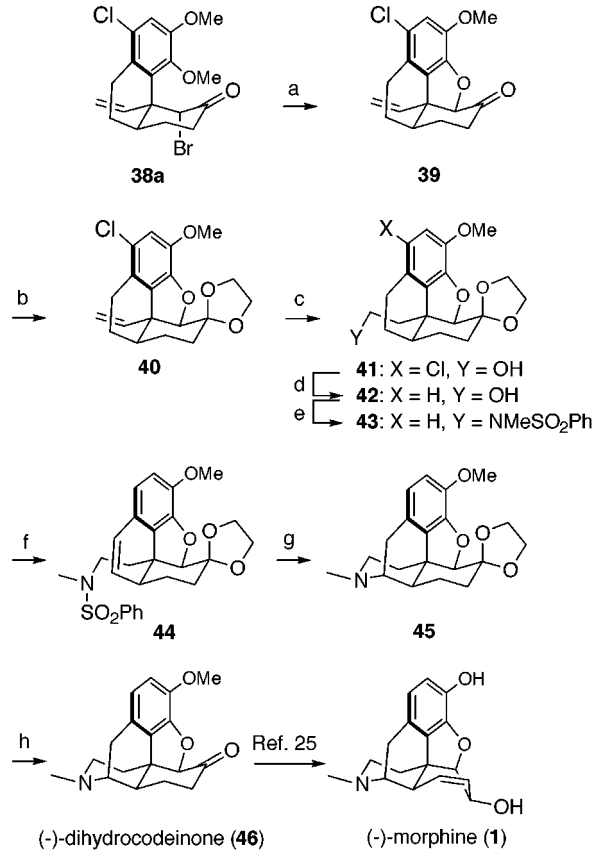
preted in terms of the α-haloketone effect.[20] In **38a**, the bromine and the aromatic A-ring are axial with respect to the cyclohexanone chair (C-ring). The other two substituents adopt equatorial positions. Epimerization of the bromine triggers inversion of the C-ring chair and leads to **38b** wherein the aromatic substituent is equatorial and all other ring substituents axial.

The α-bromoketone in **38a** not only provides the required functionality for the subsequent ring closure but also forces the carbon skeleton of the molecule into a morphine-like, L-shaped conformation which ensures a suitable S_N2 trajectory for the intramolecular nucleophilic attack of the proximate methoxy group. In fact, when heated in dimethylformamide (DMF) at 140 °C, bromoketone **38a** afforded the dihydrobenzofuran derivative **39** *within 20 min in virtually quantitative yield* (Scheme 11)! This clean intramolecular transetherification most likely proceeds through a methoxonium ion.[19,21] Bromination and ring closure could also be performed in one flask. Thus, treatment of **31** with NBS in DMF at low temperature followed by brief heating of the solution to 140 °C produced an easily separable 1:2 mixture of **39** and **38b** in excellent overall yield (91%).

The next stage of our synthesis involved the introduction of the nitrogen and the functionalization of C9. Ketone **39** was protected as ethylene ketal **40** under Chan's conditions.[22] Hydroboration of the vinyl group with $BH_3{\cdot}SMe_2$ followed by oxidation then gave the primary alcohol **41**. At this point, it was time to get rid of the "dummy" chlorine substituent by catalytic hydrogenation. The resultant alcohol **42** was directly converted to the benzenesulfonamide **43** using a novel variant of the Mitsunobu reaction [*N*-methylbenzenesulfonamide, 1,1′-azodicarbonyldipiperidine (ADDP), Bu_3P].[23]

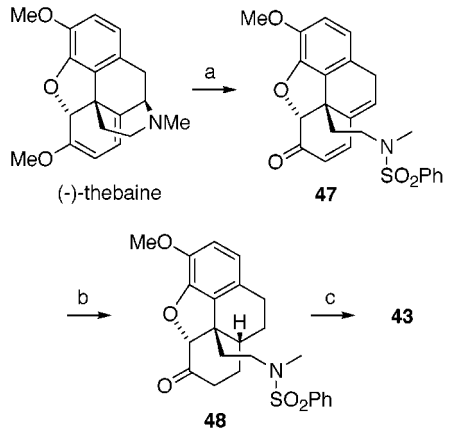
Alternatively, the sulfonamide **43** was prepared in only three steps from (−)-thebaine (Scheme 12). Quaternization of the tertiary nitrogen with benzenesulfonyl bromide in aqueous potassium carbonate induced cleavage

Scheme 11[a]



[a] (a) DMF, 140 °C (99%). (b) (TMS)Cl, $(CH_2OH)_2$, CH_2Cl_2 (92%). (c) (i) $BH_3.SMe_2$, THF; (ii) H_2O_2, OH^- (70%). (d) RaNi, MeOH, KOH (98%). (e) $PhSO_2NHMe$, ADDP, Bu_3P (81%). (f) NBS, $(PhCOO)_2$, CCl_4, reflux, Et_3N (67%). (g) Li, NH_3, THF, *t*-BuOH, −78 °C (79%). (h) 3 N HCl, 90 °C (95%).

Scheme 12[a]



[a] (a) $PhSO_2Br$, H_2O, K_2CO_3 (91%). (b) H_2, Pd−$CaCO_3$ (97%). (c) (TMS)Cl, $(CH_2OH)_2$, CH_2Cl_2 (91%).

of the C9−N bond to afford a good yield of dienone **47**.[24] Hydrogenation of **47** in the presence of palladium on calcium carbonate occurred with remarkable stereoselectivity, furnishing ketone **48** as a single diastereomer in excellent yield. Finally, **48** was protected as the ethylene ketal to give relay compound **43**. A third route to **43** involved a Claisen−Eschenmoser rearrangement

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(23) Tsuda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639.
(24) (a) Bertgen, C.; Fleischhacker, W.; Vieböck, F. *Chem. Ber.* **1967**, *100*, 3002. (b) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 2594.

of an allylic alcohol derived from **23** and Lewis-acid promoted opening of a 5,6-epoxide by the 4-methoxy group.[7b]

With ready access to **43**, we investigated the introduction of a $\Delta^{9,10}$ double bond by benzylic radical bromination and ensuing dehydrobromination. Exposure of **43** to 1 equiv of NBS and a catalytic amount of dibenzoyl peroxide in refluxing carbon tetrachloride, afforded the "morphimethine" **44** in 67% yield (Scheme 11). On the basis of recovered starting material, the overall yield was 81%. Although the dehydrobromination occurred spontaneously on prolonged heating, the yields were usually better if triethylamine was added after 10−15 min.

The stage was now set for the final heterocyclization and the completion of the synthesis. Treatment of styrene **44** under the conditions of Parker and Focas (Li, THF/NH_3) cleanly effected the desired heterocyclization and afforded dihydrocodeinone ethyleneketal (**45**)[12] in good yield. Hydrolysis of **45** with aqueous hydrogen chloride at 90 °C afforded an excellent yield of (−)-dihydrocodeinone (**46**), which was identical with an authentic sample according to the ^{1}H-, ^{13}C-NMR, IR, MS spectra, DC, $[\alpha]_D^{20}$, and mp.

Dihydrocodeinone is a well-known precursor of codeine and morphine and has served as a relay in several previous formal syntheses of morphine and other opium alkaloids. Its conversion to codeine and morphine, first reported by Gates, has been reinvestigated and optimized by Rice and Rapoport.[25] Unfortunately, all our attempts to perform this transformation independently via Pd(0) mediated Saegusa oxidation of the known dihydrocodeinone silyl enol ether[26] were unsuccessful. The failure of this reaction may be attributed to the well-known competing oxidation of the tertiary amine followed by polymerization.[27]

Conclusion

Our synthesis requires only 13 isolated intermediates—all of which are crystalline—from commercially available 4-(3,4-dimethoxyphenyl)butyric acid (**19**) to (−)-dihydrocodeinone, (**46**; total yield, 11.5%). The stereochemical course of all additions is efficiently controlled by the growing ring template in the sequence of ring closures A → AB → ABC → ABCE → ABCDE. The reagents and building blocks employed are inexpensive and readily available. In the end, the carbons and heteroatoms of morphine are derived from veratrol, succinic anhydride, vinyl magnesium chloride, methyl vinyl ketone, and methylamine. The use of protecting groups is confined to the ethylene ketal. Undesired isomers [**(+)-23**, **24**, **38b**] are recycled. Therefore, the synthesis shows a high degree of atom economy and efficiency. As the resolution is performed at the earliest stage possible and the undesired enantiomer can be racemized, it shows chiral economy as well. Both enantiomers and the racemate are accessible equally well.

Experimental Section

General Methods. See Supporting Information.

4-(2-Chloro-3,4-dimethoxyphenyl)butyric Acid (20). To a vigorously stirred solution of 4-(3,4-dimethoxyphenyl)butyric acid (50.0 g, 224 mmol) in glacial acetic acid (150 mL) at 10 °C was added dropwise chlorine (19.0 g, 268 mmol) in acetic acid (200 mL) within 1 h. After being stirred 1 h further, the solution was heated to reflux for 10 min, cooled, diluted with ice water (300 mL), and extracted with methylene chloride (7 × 100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo to afford the chloro acid **20** (58.3 g, 224 mmol, >99%) as colorless crystals (mp 112 °C).

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.95 (m, 2H), 2.45 (t, 2H, J = 7.1 Hz), 2.72 (t, 2H, J = 7.0 Hz), 3.83 (s, 3H), 3.86 (s, 3H), 6.67 (s, 1H), 6.85 (s, 1H 11.10 (s br, 1H). 13C-NMR (63 MHz, $CDCl_3$): δ 24.9, 32.3, 33.2, 56.1 (2C), 112.7, 113.1, 124.7, 130.6, 147.8, 147.9, 179.5. MS (EI, 70 eV, 200 °C): m/z 260 ($M^{\bullet+}$, 22), 260 (70), 198 (23), 187 (34), 185 (100). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2966, 1703, 1507, 1382, 1278, 1164. Anal. Calcd for $C_{12}H_{15}ClO_4$ (M_r = 258.701 g·mol^{-1}): C, 55.71; H, 5.84. Found: C, 55.58; H, 5.87.

5-Chloro-7,8-dimethoxy-3,4-dihydronaphthalin-1(*2H*)-one (21). Oxalyl chloride (36.5 mL, 425 mmol) was added to a solution of **20** (50 g, 193 mmol) in refluxing anhydrous benzene (500 mL). After the vigorous evolution of gases ceased, the solution was stirred for 2 h at 50 °C and then cooled to 0 °C. Stannic chloride (80 mL, 680 mmol) was added, and the mixture was stirred at 0 °C for another 36 h. The reaction was quenched by careful addition of concentrated hydrochloric acid (100 mL), followed by ether (250 mL) and ice water (100 mL). The organic phase was washed with diluted hydrochloric acid (2 N, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, hexanes:EtOAc = 7:1) afforded **21** (33.0 g, 137 mmol, 71%) as yellow crystals (mp 77−78 °C).

R_f = 0.30 (hexanes:EtOAc = 4:1). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.04 (mc, 2H), 2.58 (mc, 2H), 2.82 (t, 2H, J = 7.5 Hz), 3.78 (2s, 6H) 7.08 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 22.1, 27.0, 40.1, 56.2, 61.3, 117.6, 127.9, 128.3, 133.6, 148.5, 152.2, 196.8. MS (EI, 70 eV, 120 °C): m/z 242 (61), 241 (61), 240 ($M^{\bullet+}$, 100), 211 (41), 169 (32), 155 (24). IR (KBr; cm^{-1}): $\tilde{\nu}$ 2943, 2862, 1694, 1582, 1480, 1426, 1349, 1266, 1029. Anal. Calcd for $C_{12}H_{13}ClO_3$ (M_r = 240.69 g·mol^{-1}): C, 59.88; H, 5.44. Found: C, 59.82; H, 5.35.

5-Chloro-7,8-dimethoxy-2-(hydroxymethylene)-3,4-dihydronaphthalin-1(*2H*)-one (22). Methyl formate (10.3 mL, 165 mmol) in anhydrous ether (40 mL) was added to a suspension of sodium methoxide (6.70 g, 123 mmol) in anhydrous benzene (125 mL). After stirring for 30 min, tetralone **21** (19.8 g, 82.3 mmol) was added in one portion. The mixture was heated to reflux for 3 h, cooled, and stirred for another 12 h at room temperature. Ice cold water was added to the mixture to dissolve the precipitated sodium salt. The organic phase was separated and extracted with aqueous 5% KOH (3 × 100 mL). The combined alkaline phases were washed with ether (100 mL) and acidified (pH 3) with cold 2 M HCl. The resulting mixture was extracted with methylene chloride (5 × 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford pure **22** (21.5 g, 80.0 mmol, 97%) as light brown solid (mp 100−102 °C).

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(26) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276.

(27) For a successful Saegusa oxidation in the presence of a bridgehead tertiary amine, see: Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050.

R_f = 0.57 (hexanes:EtOAc = 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 2.42−2.47 (m, 2H), 2.83−2.88 (m, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 7.05 (s, 1H), 8.60 (s br, 1H), 13.89 (s br, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 15.14, 20.9 (br), 25.6, 56.2, 70.3, 110.7, 116.3, 125.8, 127.5, 130.9, 146.5, 152.0, 180.3 (br). MS (EI, 70 eV, 200 °C): *m*/*z* 271 (16), 270 (34), 269 ($M^{\bullet+}$, 55), 268 (100), 89 (33). IR (KBr; cm^{-1}): $\tilde{\nu}$ = 3198, 2967, 1628, 1445, 1316, 1262, 1195, 1083. Anal. Calcd for $C_{13}H_{13}ClO_4$ (M_r = 268.696 g·mol^{-1}): C, 58.11; H, 4.88. Found: C, 58.06; H, 4.85.

10a(*R*)-8-Chloro-5,6-dimethoxy-1,9,10,10a-tetrahydrophenanthren-3(*2H*)-one (23) and 8-Chloro-5,6-dimethoxy-1,4,9,10-tetrahydro-3(*2H*)-phenanthrenone (24). To a vigorously stirred solution of **22** (49 g, 182 mmol) in anhydrous methanol (700 mL) was added dropwise at 0 °C anhydrous Et_3N (50 mL, 364 mmol), followed by MVK (17.9 mL, 218 mmol). After stirring at room temperature for 2 days, additional MVK (1.5 mL, 18 mmol) was added. After 3 days the solution was neutralized with acetic acid (21 mL, 370 mmol). The solvent was evaporated in vacuo, and the resulting solid was dissolved in methylene chloride (1000 mL) and washed with H_2O (5 × 100 mL). The organic phase was evaporated in vacuo, and the resulting material was redissolved in a mixture of dioxane (400 mL) and a solution of KOH (33.6 g, 728 mmol) in H_2O (400 mL). After 3 h stirring at room temperature, the resulting suspension was diluted with H_2O (1000 mL), saturated with NaCl, and extracted with CH_2Cl_2 (7 × 200 mL). The organic layer was dried ($MgSO_4$) and concentrated to give the crude mixture of products. Purification by chromatography (silica gel, hexanes:EtOAc = 10:1 → 5:1) afforded **24** (4.47 g, 15.3 mmol; 8.3%) and racemic **23** (43.3 g, 148 mmol; 81.2%) as colorless crystals.

MPLC Resolution. A 1 g amount of racemic **23** was dissolved in EtOH:$H_2$0 (96:4, 40 mL) and separated on swollen microcrystalline cellulose triacetate (Merck). Separation was effected by a single run through a 63 × 660 mm column thermostated at 40 °C, eluting with EtOH:$H_2$0 (96:4). Fraction 1: $k_1' = 0.77$; ee > 99%. Fraction 2: $k_2' = 1.29$; ee > 96 %. Enantioselectivity α = 1.68. Resolution R_s = 1.15 was calculated using the tangent method. Throughput was 2 g per day with 95% recovery.

Compound 23. Mp: 101−103 °C (racemic); 113−115 °C (enantiomerically pure). R_f = 0.10 (hexanes:EtOAc = 10:1). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.73 (mc, 1H), 1.83 (dddd, 1H, *J* = 5.9 Hz, 10.0 Hz, 11.9 Hz, 13.2 Hz), 2.03 (mc, 1H), 2.24 (mc, 1H), 2.40−2.62 (m, 3H), 2.72−2.84 (m, 1H), 2.92 (ddd, 1H, *J* = 4.3 Hz, 5.5 Hz, 17.1 Hz), 3.74 (s, 3H), 3.86 (s, 3H), 6.99 (s, 1H), 7.16 (d, 1H, *J* = 2.1 Hz). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 27.0, 29.5, 29.7, 36.1, 36.5, 56.2, 60.1, 114.8, 127.6, 128.4, 128.5, 129.7, 147.8, 151.7, 154.5, 200.7. MS (EI, 70 eV, 120 °C): *m*/*z* 292 ($M^{\bullet+}$, 100), 264 (51), 249 (43), 233 (19), 115 (28). IR (KBr; cm^{-1}): $\tilde{\nu}$ = 2938, 1656, 1471, 1450, 1423, 1296, 1255. $[\alpha]_D^{20}$ = −245.1° (*c* = 2, $CHCl_3$). Anal. Calcd for $C_{16}H_{17}ClO$ (M_r = 292.762 g·mol^{-1}): C, 65.64; H, 5.85. Found: C, 65.44; H, 5.69.

Compound 24. Mp: 107−109 °C. R_f = 0.11 (hexanes:EtOAc = 10:1). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.16 (t, 2H, *J* = 5.0 Hz), 2.56−2.78 (m, 6H), 3.53 (s, 2H), 3.75 (s, 3H), 3.86 (s, 3H), 6.81 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 25.2, 28.1, 31.2, 37.9, 42.8, 55.8, 60.7, 111.4, 124.5, 126.7, 127.3, 129.8, 136.1, 144.8, 151.9, 210.6. MS (EI, 70 eV, 120 °C): *m*/*z* 292 ($M^{\bullet+}$, 100), 277 (5), 250 (7), 235 (23). IR (KBr; cm^{-1}): $\tilde{\nu}$ = 2913, 2829, 1702, 1584, 1467, 1426, 1248, 1117, 1093. Anal. Calcd $C_{16}H_{17}ClO_3$ (M_r = 292.762 g·mol^{-1}): C, 65.64; H, 5.85. Found: C, 65.61; H, 5.82.

4a(*R*),10a(*R*)-8-Chloro-5,6-dimethoxy-4a-ethenyl-1,4,4a,9,10,10a-hexahydrophenanthren-3(*2H*)-one (25). Vinylmagnesium chloride (1.6 M in THF, 25 mL, 40 mmol) was added to a suspension of CuI (3.81 g, 20 mmol) in THF (100 mL) at −78 °C. The mixture was briefly warmed to −10 °C until it became almost homogeneous and became brown in color. It was then rapidly cooled to −78 °C. Enone **23** (2.93 g, 10 mmol) in THF (50 mL) was added dropwise at −78 °C. The mixture was warmed to room temperature within 1 h, diluted with hexanes (100 mL), and then quenched with saturated aqueous NH_4Cl/25% aqueous NH_3 (9:1, 10 mL). After filtration through a pad of Celite, the organic layer was washed with saturated aqueous NH_4Cl/25% aqueous NH_3 (9:1, 2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The crude, crystalline product was purified by column chromatography (silica gel, hexanes:EtOAc = 10:1) to afford ketone **25** (2.91 g, 9.1 mmol, 91%) as colorless crystals (mp: 140−142 °C (racemic); 142 °C (enantiomerically pure).

R_f = 0.22 (hexanes:EtOAc = 10:1). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.74−2.04 (m, 4H), 2.16−2.31 (m, 2H), 2.39 (mc, 1H), 2.53 (d, 1H, *J* = 15.2 Hz), 2.70 (mc, 1H), 3.02 (ddd, 1H, *J* = 3.1 Hz, 5.1 Hz, 17.2 Hz), 3.22 (d, 1H, *J* = 15.2 Hz), 3.71 (s, 3H), 3.79 (s, 3H), 4.94 (d, 1H, *J* = 17.6 Hz), 5.15 (d, 1H, *J* = 10.8 Hz), 5.91 (dd, 1H, *J* = 10.8 Hz. 17.6 Hz), 6.88 (s, 1H). 13C-NMR (63 MHz, $CDCl_3$): δ 24.0, 27.2, 27.9, 37.3, 39.3, 46.5, 48.3, 55.8, 60.2, 112.5, 113.3, 126.5, 128.1, 137.2, 146.2, 146.8, 151.4, 211.1. MS (EI, 70 eV, 120 °C): *m*/*z* 321 (22), 320 ($M^{+\bullet}$, 100), 237 (23), 55 (42). IR (KBr; cm^{-1}): $\tilde{\nu}$ 2937, 1710, 1585, 1471, 1426, 1294. $[\alpha]_D^{20}$ = + 37.7° (*c* = 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{21}ClO_3$ (M_r = 320.816 g·mol^{-1}) C, 67.39; H, 6.60. Found: C, 67.47; H, 6.58.

4a(*R*),10a(*R*)-8-Chloro-5,6-dimethoxy-4a-ethenyl-3-(trimethylsilyloxy)-1,2,4a,9,10,10a-hexahydrophenanthrene (31). Vinylmagnesium chloride (1.6 M in THF, 25 mL, 40 mmol) was added to a suspension of CuI (3.81 g, 20 mmol) in THF (100 mL) at −78 °C. The mixture was briefly warmed to −10 °C until it became almost homogenous and became dark brown in color. It was then rapidly cooled to −78 °C. Enone **23** (2.93 g, 10 mmol) in THF (50 mL) was added dropwise at −78 °C, and the reaction mixture was allowed to warm to 0 °C within 3 h. (TMS)Cl (50 mmol, 6.34 mL) was added, followed by Et_3N (60 mmol, 8.36 mL). The mixture was warmed to room temperature, stirred for 1 additional hour, diluted with hexanes (100 mL), and then quenched with saturated aqueous NH_4Cl/25% aqueous NH_3 (9:1, 10 mL). After filtration through a pad of Celite, the organic layer was washed with saturated aqueous NH_4Cl/25% aqueous NH_3 (9:1, 2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo. The crystalline crude product (4.58 g) was recrystallized from *n*-pentane (100 mL) to yield pure **31** as large colorless crystals (3.033 g, 77.2 mmol, 77%). A second recrystallization afforded additional 269 mg of **31** (total yield: 8.42 mmol, 84 %). The enantiomerically pure material remained an oil and could neither be purified by recrystallization nor by chromatography (mp 99−100 °C (racemic)).

R_f = 0.10 (hexanes). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.45−2.13 (m, 7H), 2.57 (ddd, 1H, J = 3.0, 9.1, 17.0 Hz), 2.84 (dt, 1H, J = 5.5, 17.0 Hz), 3.71 (s, 3H), 3.79 (s, 3H), 4.92 (dd, 1H, J = 1.4, 17.1 Hz), 5.10 (dd, 1H, J = 1.4, 10.2 Hz), 5.14 (s, 1H), 5.80 (dd, 1H, J = 10.2, 17.1 Hz), 6.85 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ −4.9, 18.5, 18.6, 21.6, 21.7, 32.6, 41.8, 50.7, 55.0, 104.2, 107.0, 107.5, 122.2, 122.7, 132.3, 142.5, 142.7, 144.8, 146.1. MS (EI, 70 eV, 30 °C): m/z 394 (18), 392 ($M^{+\bullet}$, 54), 377 (60), 365 (61), 363 (72), 361 (100), 73 (80). IR (KBr; cm^{-1}): $\tilde{\nu}$ 2931, 2864, 1652, 1631, 1591, 1468, 1251, 1206. HRMS. Calcd for $C_{21}H_{29}ClO_3Si$ (M_r = 392.997 g·mol^{-1}): 392.1575. Found: 392.1575 ± 0.002.

4(*S*),4a(*S*),10a(*S*)-4-Bromo-5,6-dimethoxy-10a-ethenyl-1,4,4a,9,10,10a-hexahydrophenanthren-3(*2H*)-one (38a) and 4(*R*),4a(*S*),10a(*S*)-4-Bromo-5,6-dimethoxy-10a-ethenyl-1,4,4a,9,10,10a-hexahydrophenanthren-3(*2H*)-one (38b). NBS (2.14 g, 12 mmol) was added in one portion at −78 °C to a solution of crude enantiomerically pure silyl enol ether **31** (4.9 g), which was prepared from **23** (2.93 g, 10 mmol) as described above, in anhydrous THF (100 mL). The mixture was allowed to warm to room temperature within 4 h. After addition of saturated $NaHCO_3$ solution (50 mL), the resulting mixture was thoroughly extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated in vacuo. Purification of the residue by silica gel chromatography, eluting with hexanes/ethyl acetate (10:1) followed by HPLC [*Macherey-Nagel* Nucleosil 50-10 (250 × 20), *n*-hexane:MeOAc = 10:0.5, 2 mL·min^{-1}] provided enantiomerically pure bromoketones **38a** (2.36 g, 6.0 mmol, 60%) and **38b** (0.84 g, 2.1 mmol, 21%) as pale brown crystals and colorless oil, respectively.

Major Isomer 38a. Mp: 102−104 °C (racemic); 102−104 °C (enantiomerically pure). R_f = 0.65 (hexanes:EtOAc = 10:1). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.64−1.82 (m, 2H), 1.94−2.16 (m, 3H), 2.61−2.75 (m, 3H), 3.14 (ddd, 1H, J = 6.6 Hz, 10.7 Hz, 10.8 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.47 (dd, 1H, J = 1.1 Hz, 17.2 Hz), 5.21 (dd, 1H, J = 1.1 Hz, 10.5 Hz), 5.87 (s, 1H), 6.34 (dd, 1H, J = 10.5 Hz, 17.2 Hz), 6.93 (s, 1H). ^{13}C-NMR (68 MHz, $CDCl_3$): δ 22.6, 23.8, 24.9, 32.2, 34.6, 50.9, 55.9, 57.8, 60.3, 113.8, 116.8, 127.8, 128.7, 128.8, 142.2, 147.9, 151.3, 203.5. MS (EI, 70 eV, 60 °C): m/z 400 ($M^{\bullet+}$, 100), 398 (73), 320 (46), 319 (46), 304 (47), 228 (30), 165 (26), 149 (23), 115 (36). IR (Si; cm^{-1}): $\tilde{\nu}$ 2941, 1718, 1587, 1465, 1424, 1292, 1214, 1063, 912. $[\alpha]_D^{20}$ = −1.2° (c = 2, $CHCl_3$), $[\alpha]_{436}^{20}$ +33.7° (c = 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}BrClO_3$ (M_r = 399.712 g·mol^{-1}): C, 54.09; H, 5.04. Found: C, 54.11; H, 5.01.

Minor Isomer 38b. Mp: 63−68 °C (racemic, oil if enantiomerically pure). R_f = 0.58 (hexanes:EtOAc = 10:1). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.72−1.99 (m, 3H), 2.17−2.33 (m, 2H), 2.62−2.88 (m, 2H), 3.05−3.315 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.92 (d, 1H, J = 17.8 Hz), 5.16 (d, 1H, J = 11.0 Hz), 5.24 (s, 1H), 5.96 (dd, 1H, J = 11.0, 17.8 Hz), 6.95 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 24.1, 27.3, 27.7, 32.1, 39.9, 50.5, 54.6, 55.8, 60.2, 113.2, 113.5, 127.6, 128.0, 135.0, 144.8, 146.4, 150.7, 205.0. MS (EI, 80 eV, 60 °C): m/z 400 ($M^{\bullet+}$, 100), 398 (77), 320 (38), 263 (65), 228 (30), 165 (27), 149 (29), 115 (31). IR (Si; cm^{-1}): $\tilde{\nu}$ 2941, 1718, 1587, 1465, 1424, 1292, 1214, 1063, 1044. $[\alpha]_D^{20}$ = −93.9° (c = 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}BrClO_3$ (M_r = 399.712 g·mol^{-1}): C, 54.09; H, 5.04. Found: C, 54.30; H, 5.19.

1,3a(*R*),8,9,9a(*R*),9b(*S*)-Hexahydro-9b-ethenyl-5-methoxy[4,4a,4b,5-*bcd*]furan-3(*2H*)-one (39). A solution of **38a** (3.99 g, 10 mmol) in anhydrous DMF (50 ml) was heated to 140 °C for 20 min. After cooling to room temperature, the solvent was removed in vacuo. The crystalline crude product was purified by chromatography on silica gel, eluting with hexanes/ethyl acetate (1:1), to afford dihydrofuran **39** (2.99 g, 9.8 mmol, 98%) as colorless crystals. (Mp: 147−148 °C (racemic); 178−179 °C (enantiomerically pure)).

R_f = 0.25 (hexanes:EtOAc = 3:1). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.29 (dq, 1H, J = 4.9 Hz, 12.6 Hz), 1.70−2.20 (m, 3H), 2.23−2.45 (m, 4H), 2.61 (ddd, 1H, J = 0.9 Hz, 7.3 Hz, 18.0 Hz), 3.82 (s, 3H), 4.52 (dd, 1H, J = 0.7 Hz, 17.0 Hz), 4.71 (s, 1H), 5.14 (dd, 1H, J = 0.7 Hz, 10.2 Hz), 5.97 (dd, 1H, J =10.2 Hz, 17.0 Hz), 6.71 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 19.9, 22.9, 26.5, 36.1, 39.4, 55.2, 56.6, 91.7, 114.7, 117.1, 123.9, 125.0, 126.8, 141.8, 142.9, 145.6, 206.5. MS (EI, 70 eV, 30 °C): m/z 306 (57), 304 ($M^{+\bullet}$, 99), 244 (87), 174 (76), 69 (100). IR (Si; cm^{-1}): $\tilde{\nu}$ 2938, 1729, 1631, 1491, 1436, 1186, 1147, 1096, 1037. $[\alpha]_D^{20}$ = −35.7° (c = 2, $CHCl_3$). Anal. Calcd for $C_{17}H_{17}ClO_3$ (M_r = 304.773 g·mol^{-1}): C, 67.00; H, 5.62. Found: C, 66.92; H, 5.55.

1,2,3,3a(*R*),8,9,9a(*S*),9b(*S*)-Octahydro-7-chloro-9b-ethenyl-5-methoxy-3-(ethylenedioxy)phenanthro-[4,4a,4b,5-*bcd*]furan (40). To a vigorously stirred biphasic mixture of anhydrous CH_2Cl_2 (20 mL) and ethylene glycol (20 mL) was added **39** (790 mg, 2.59 mmol) and (TMS)Cl (1.5 mL, 12 mmol). After stirring for 18 h at room temperature, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was thoroughly extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the resulting residue by chromatography (silica gel, hexanes:EtOAc = 10:1) gave dioxolane **40** (831 mg, 2.4 mmol, 92%) as colorless crystals (mp: 121−123 °C (racemic); 94−95 °C (enantiomerically pure)). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.30 (mc, 1H), 1.49−1.78 (m, 4H), 1.95−2.10 (m, 2H), 2.38 (mc, 1H), 2.66 (mc, 1H), 3.55−3.99 (m, 3H), 3.85 (s, 3H), 4.17 (mc, 1H), 4.53 (dd, 1H, J = 1.0, 17.0 Hz), 4.57 (s, 1H), 5.13 (dd, 1H, J = 0.9, 10.2 Hz), 5.88 (dd, 1H, J = 10.2, 17.0 Hz), 6.80 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 20.2, 22.8, 23.3, 33.1, 35.8, 51.3, 56.6, 64.8, 66.3, 94.7, 107.9, 113.9, 116.2, 123.7, 124.2, 128.83 142.2, 143.8, 146.8. MS (EI, 70 eV, 40 °C): m/z 350 (33), 348 ($M^{+\bullet}$, 72), 112 (38), 99 (100). IR (Si; cm^{-1}): $\tilde{\nu}$ 2936, 1630, 1489, 1436, 1286, 1190, 1070. $[\alpha]_D^{20}$ = −44.2° (c = 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}ClO_4$ (M_r = 348.826 g·mol^{-1}): C, 65.42; H, 6.07. Found: C, 65.44; H, 6.20.

1,2,3,3a(*R*),8,9,9a(*R*),9b(*S*)-Octahydro-7-chloro-5-methoxy-9b-(2-hydroxyethyl)-3-(ethylenedioxy)-phenanthro[4,4a,4b,5-*bcd*]furan (41). BH_3·SMe_2 (2 M THF, 6.25 mL, 12.5 mmol) was added dropwise to a solution of **40** (888 mg, 2.5 mmol) in anhydrous THF (20 mL) at −15 °C. The mixture was warmed to room temperature within 3 h and stirred at this temperature for a further 18 h. Water (3 mL), NaOH (3 N, 6 mL) and 30% aqueous H_2O_2 H_2O_2 (6 mL) were carefully added, and the mixture was stirred at room temperature for 20 h. Subsequently, 10% aqueous $Na_2S_2O_3$ (20 mL) was added, and the mixture was stirred for 30 min. The

organic phase was separated, and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The combined organic phases were washed with brine (2 × 25 mL), dried, and evaporated in vacuo. Purification of the residue by chromatography (silica gel, hexanes:EtOAc = 5:1 → 3:1) afforded **41** (714 mg, 78%) as colorless crystals (mp: 149−150 °C (racemic); 103 °C (enantiomerically pure)). R_f = 0.14 (hexanes:EtOAc = 5:1). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.18−1.34 (m, 1H), 1.44− 1.68 (m, 3H), 1.75−1.98 (m, 4H), 2.04−2.22 (m, 2H), 2.42 (mc, 1H), 2.70 (mc, 1H), 3.61−3.96 (m, 5H), 3.84 (s, 3H), 4.15 (mc, 1H), 4.78 (s, 1H), 6.77 (s, 1H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 20.0, 23.4 (2C), 32.9, 34.8, 42.1, 46.5, 56.5, 59.3, 64.7, 66.23, 94.5, 108.1, 113.6, 123.3, 124.1, 131.4, 142.2, 146.1. MS (EI, 70 eV, 110 °C): *m*/*z* 368 (14), 366 ($M^{+\bullet}$, 48), 321 (34), 112 (22), 99 (100). IR (Si; cm^{-1}) 3460, 2939, 1631, 1489, 1437, 1287, 1190, 1150, 1065. $[\alpha]_D^{20} = -62.5°$ (*c* = 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}ClO_5$ (M_r = 366.841 g·mol^{-1}): C 62.21; H, 6.32. Found: C, 62.41; H, 6.35.

1,2,3,3a(*R*),8,9,9a(*R*),9b(*S*)-Octahydro-5-methoxy-9b-(2-hydroxyethyl)-3-(ethylenedioxy)phenanthro-[4,4a,4b,5-*bcd*]furan (42). A suspension of Raney nickel (1 g) in methanol (25 mL) was thoroughly saturated with H_2. Potassium hydroxide (164 mg, 3 mmol) was added, followed by **41** (125 mg, 0.34 mmol). The mixture was stirred under a hydrogen atmosphere at room temperature for 5 h. Ammonium chloride (500 mg) was added, and the resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was taken up in H_2O/CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to produce the alcohol **42** (111 mg, 33 mmol, 98%) as colorless crystals (mp: 115 °C (racemic); 113−114 °C (enantiomerically pure)). R_f = 0.14 (hexanes:EtOAc = 5:1). ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.21−2.24 (m, 10H), 2.47−2.74 (m, 2H), 3.56−3.99 (m, 5H), 3.85 (s, 3H), 4.17 (mc, 1H), 4.74 (s, 1H), 6.61 (d, 1H, *J* = 8.2 Hz), 6.74 (d, 1H, *J* = 8.2 Hz). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 21.0, 23.5, 23.8, 32.9, 35.2, 42.5, 46.1, 56.5, 59.5, 64.7, 66.2, 94.3, 108.3, 113.6, 120.2, 125.3, 130.1, 141.8, 147.2. MS (EI, 70 eV, 120 °C): *m*/*z* 332 ($M^{+\bullet}$, 80), 287 (76), 260 (61), 199 (62), 99 (100), 55 (97). IR (KBr; cm^{-1}): 3440, 2941, 1607, 1503, 1440, 1275, 1189, 1059. $[\alpha]_D^{20} = -60.8°$ (*c* = 1, $CHCl_3$). Anal. Calcd for $C_{19}H_{24}O_5$ (M_r = 332.396 g·mol^{-1}): C, 68.66; H, 7.28. Found: C, 68.81; H, 7.11.

1,2,3,3a(*R*),8,9,9a(*R*),9b(*S*)-Octahydro-5-methoxy-9b-[2-[*N*-methyl-*N*-(phenylsulfonyl)amino]ethyl]-3-(ethylenedioxy)phenanthro[4,4a,4b,5-*bcd*]furan (43). To a solution of **42** (332 mg, 1 mmol), tributylphosphane (370 μl, 303 mg, 1.5 mmol) and *N*-methylbenzenesulfonamide (257 mg, 1.5 mmol) in anhydrous benzene (10 mL) at 0 °C was added 1,1′-(azodicarbonyl)dipiperidine (ADDP, 378 mg, 1.5 mmol). After stirring for 10 min, at 0 °C and 24 h at room temperature, *n*-hexane (20 mL) was added to the reaction mixture. The dihydro-ADDP separated out was filtered off, and the clear solution was concentrated in vacuo. Purification of the residue by chromatography (silica gel, hexanes:EtOAc = 5:1) afforded a mixture of *N*-methylbenzenesulfonamide and **43**. Further purification by HPLC [*Macherey-Nagel* Nucleosil 50-10 (250 × 20), *n*-hexane:EtOAc = 10:6.7, 2 mL × min^{-1}] provided **43** (428 mg, 88 mmol, 88 %) as colorless crystals (mp: 174−175 °C (racemic); 175 °C (enantiomerically pure)). R_f = 0.15 (hexanes:EtOAc = 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (mc, 1H), 1.46−1.53 (m, 2H), 1.61 (mc, 1H), 1.70−1.82 (m, 2H), 1.90 (ddd, 1H, *J* = 5.2, 10.3, 15.1 Hz), 2.03−2.16 (m, 2H), 2.54 (mc, 1H), 2.68 (mc, 1H), 2.70 (s, 3H), 2.88 (ddd, 1H, *J* = 5.2, 10.5, 15.7 Hz), 3.34 (ddd, 1H, *J* = 5.6, 10.5, 16.1 Hz), 3.75 (mc, 1H), 3.84 (mc, 1H), 3.85 (s, 3H), 3.94 (mc, 1H), 4.17 (mc, 1H), 4.59 (s, 1H), 6.60 (d, 1H, *J* = 8.2 Hz), 6.74 (d, 1H, *J* = 8.2 Hz), 7.48−7.58 (m, 3H), 7.72−7.74 (m, 2H). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 21.1, 23.6, 23.9, 32.9, 34.5, 34.9, 37.0, 46.2, 46.5, 56.7, 64.9, 66.4, 93.4, 108.3, 113.9, 120.3, 125.4, 127.3, 129.0, 129.9, 132.5, 137.7, 141.9, 147.1. MS (EI, 80 eV, 120 °C): *m*/*z* 485 ($M^{+\bullet}$, 53), 287 (100), 99 (99), 84 (30). IR (Si; cm^{-1}): $\tilde{\nu}$ 2946, 1503, 1445, 1337, 1274, 1190, 1162, 1092, 1057. $[\alpha]_D^{20} = -15.0°$ (*c* = 1, $CHCl_3$). Anal. Calcd for $C_{26}H_{31}NO_6S$ (M_r = 485.601 g·mol^{-1}): C, 64.31; H, 6.43; N, 2.88. Found: C, 64.33; H, 6.48; N, 3.01.

1,2,3,3a(*R*),9a(*R*),9b(*S*)-Hexahydro-5-methoxy-9b-[2-[*N*-methyl-*N*-(phenylsulfonyl)amino]ethyl]-3-(ethylenedioxy)phenanthro[4,4a,4b,5-*bcd*]furan (44). A solution of **43** (486 mg, 1 mmol), NBS (187 mg, 1.05 mmol) and a catalytic amount of benzoyl peroxide (5 mg, 0.02 mmol, recrystallized from chloroform/methanol) in anhydrous CCl_4 (150 mL) was kept at reflux for 30 min. Subsequently, Et_3N (10 mL) was added, and the mixture was refluxed for 10 more minutes. After cooling to room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and saturated aqueous $Na_2S_2O_3$ (50 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by HPLC [*Macherey-Nagel* Nucleosil 50-10 (250 × 20), *n*-hexane:MeOAc = 10:4, 10 mL·min^{-1}; *Merck* Si-60, *n*-hexane:MeOAc = 10:4, 2 mL·min^{-1}] to afford the starting sulfonamide **43** (102 mg, 0.21 mmol, 21%) and styrene **44** (324 mg, 0.67 mmol, 67%, 85% based on recovered starting material) as colorless crystals (mp: 115−117 °C (enantiomerically pure)). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (dq, 1H, *J* = 2.7, 12.8 Hz), 1.38−1.62 (m, 2H), 1.66−1.93 (m, 3H), 2.43 (mc, 1H), 2.62 (s, 3H), 2.86 (ddd, 1H, *J* = 5.4, 10.7, 16.0 Hz), 3.18 (ddd, 1H, *J* = 5.4, 10.7, 16.0 Hz), 3.66−3.90 (m, 2H), 3.87 (s, 3H), 4.00 (mc, 1H), 4.20 (mc, 1H), 4.69 (s, 1H), 5.79 (dd, 1H, *J* = 5.7, 9.6 Hz), 6.36 (dd, 1H, *J* = 0.8, 9.6 Hz), 6.63 (d, 1H, *J* = 8.1 Hz), 6.71 (d, 1H, *J* = 8.1 Hz), 7.44−7.58 (m, 3H), 7.67−7.72 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.2, 31.3, 34.7, 36.5, 38.8, 45.3, 46.1, 56.3, 64.8, 66.4, 94.1, 108.0, 112.9, 117.6, 123.0, 123.1, 127.1, 128.9, 129.6, 132.3, 137.6, 143.8, 146.1. MS (EI, 70 eV, 80 °C): *m*/*z* = 483 ($M^{+\bullet}$, 44), 342 (79), 286 (74), 285 (53), 199 (67), 99 (100), 77 (58). IR (KBr; cm^{-1}): $\tilde{\nu}$ 2948, 1636, 1622, 1505, 1446, 1338, 1278, 1163, 1092. $[\alpha]_D^{20}$ = −24.1° (*c* = 1, $CHCl_3$); $[\alpha]_D^{20} = -23.8°$ (*c* = 0.5, $CHCl_3$). Anal. Calcd for $C_{26}H_{29}NO_6S$ (M_r = 483.578 g·mol^{-1}): C, 64.58; H, 6.04; N, 2.90. Found: C, 64.61; H, 6.08; N, 2.75.

(−)-Dihydrocodeinone Ethyleneketal (45). To a mixture of liquid ammonia (20 mL) and anhydrous THF (20 mL) at −78 °C was added *tert*-butanol (400 μL, 4.2 mmol) followed by lithium metal (200 mg, 28.8 mmol). The resulting dark blue solution was stirred for 10 min, and then styrene **44** (200 mg, 0.41 mmol) in THF (10 mL) was added dropwise. The blue color was rapidly discharged, and additional lithium (200 mg, 28.8 mmol) was added. After 30 min, the reaction was quenched with a mixture of saturated aqueous ammonium chloride (25 mL) and methanol (25 mL). After dilution with ethyl

acetate (50 mL) and separation of the basic aqueous phase, the organic phase was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography (silica gel, $CHCl_3$:MeOH = 5:1) to give morphinane **45** (111 mg, 0.32 mmol, 79%) as colorless crystals (mp: 173−175 °C (enantiomerically pure)). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.16 (dq, 1H, J = 2.3, 12.8 Hz), 1.50−1.56 (m, 2H), 1.64−1.71 (m, 2H), 1.88 (td, 1H, J = 4.9, 12.3 Hz), 2.19−2.24 (m, 2H), 2.36 (dd, 1H, J = 5.4, 18.3 Hz), 2.41 (s, 3H), 2.53 (dd, 1H, J = 3.8, 12.2 Hz), 3.00 (d, 1H, J = 18.3 Hz), 3.11 (dd, 1H, J = 2.6, 5.4 Hz), 3.79 (mc, 1H), 3.87 (s, 3H), 3.88 (mc, 1H), 4.11 (mc, 1H), 4.18 (mc, 1H), 4.48 (s, 1H), 6.62 (d, 1H, J = 8.2 Hz), 6.74 (d, 1H, J = 8.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.0, 22.2, 33.2, 36.3, 42.4, 42.7, 43.5, 47.0, 56.4, 59.5, 64.8, 66.3, 94.2, 108.4, 113.4, 118.5, 126.2, 129.0, 142.1, 146.4. MS (EI, 70 eV, 120 °C): m/z 343 ($M^{+\bullet}$, 100), 286 (23), 244 (18), 168 (17), 115 (16), 99 (40). IR (Si; cm^{-1}): $\tilde{\nu}$ 2924, 1638, 1614, 1503, 1446, 1276, 1246, 1194, 1058. $[\alpha]_D^{20}$ = −173.3° (c = 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NO_4$ (M_r = 343.422 g·mol^{-1}): C, 69.95; H, 7.34; N, 4.08. Found: C, 69.82; H, 7.21; N, 3.83.

(−)-Dihydrocodeinone. A solution of dihydrocodeinone ethyleneketal **45** (100 mg, 0.29 mmol) in dilute aqueous hydrochloric acid (3 *N*, 2 mL) was kept at 90 °C for 1 h. The reaction mixture was cooled, diluted with ice water (5 mL), neutralized carefully with sodium carbonate, and extracted with chloroform (5 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Filtration through a pad of silica, eluting with chloroform, and concentration of the filtrate afforded synthetic (−)-dihydrocodeinone (83 mg, 0.28 mmol, 95%) as colorless crystals (mp: 194−197 °C (enantiomerically pure)). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.17 (dq, 1H, J = 5.9, 13.0 Hz), 1.70−1.80 (m, 2H), 1.96−2.33 (m, 5H), 2.35 (s, 3H), 2.46−2.54 (m, 2H), 2.95 (d, 1H, J = 18.5 Hz), 3.11 (dd, 1H, J = 2.7, 5.2 Hz), 3.82 (s, 3H), 4.59 (s, 1H), 6.55 (d, 1H, J = 8.2), 6.62 (d, 1H, J = 8.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.8, 25.4, 35.3, 40.0, 42.4, 42.7, 46.6, 46.7, 56.6, 59.0, 91.2, 114.5, 119.6, 126.1, 127.1, 142.6, 145.2, 207.6. MS (EI, 80 eV, 80 °C): m/z 299 ($M^{\bullet+}$, 100), 243 (27), 242 (42), 215 (15), 185 (14), 115 (8), 96 (12), 83 (10), 71 (9). IR (Si; cm^{-1}): $\tilde{\nu}$ 2935, 2790, 1718, 1501, 1444, 1318, 1271, 1058. $[\alpha]_D^{20}$ = −206.8° (c = 1, $CHCl_3$). HRMS. Calcd for 299.1521. Found: 299.1521 ± 0.0015.

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Supporting Information Available: Tables of full experimental details and spectra for **9**, **26**, **27**, **47**, and **48**; details of the chromatographic resolution of **23**, and X-ray crystallographic data for **27** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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