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From Chiral *ortho*-Benzoquinone Monoketals to Nonracemic Indolinocodeines through Diels–Alder and Cope Reactions

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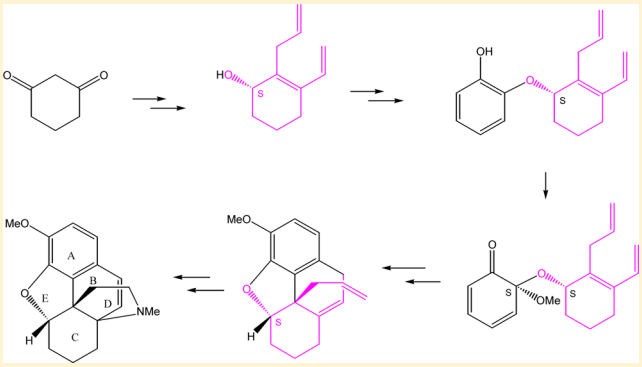
Supporting Information

ABSTRACT: The *S*-dienol (−)-**4** containing 10 carbons and one oxygen of the final product was prepared in 98.6% ee and 39% yield from cyclohexan-1,3-dione. It was attached to the aromatic ring as a monoether of catechol *S*-(−)-**6** and subsequently subjected to oxidative ketalization in methanol. The allylated phenanthrofuran obtained was selectively oxidized at the terminal double bond. The fifth ring was completed by a "one-pot" amidation–cyclization process promoted by palladium acetate. The final homochiral indolinocodeine (−)-**31** was obtained in 16 steps and 3.6% overall yield from cyclohexan-1,3-dione.



INTRODUCTION

The prolific Diels–Alder chemistry of transient *ortho*-benzoquinonoid monoketals has captured the attention of many research groups.[1] The presence of an *s-cis* diene unit constrained in the six-membered ring together with a conjugated carbonyl group at C-1 confers remarkable diene and dienophilic reactivity on these structures and results in facile dimerization[2] during their preparation. The diene reactivity[3] is well-known and has been exploited imaginatively by incorporating a dienophilic unit in one of the pendant alkoxy groups of the ketal, resulting in intramolecular cycloadditions that generate bicyclo[2,2,2]octenone adducts[4] in good yields.

In seeking to solve a difficult problem in our research program in natural product synthesis, we extended the scope of the intramolecular cycloaddition by incorporating a diene unit in the ketal. This was easily accomplished by merely oxidizing a guaiacol in the presence of a dienol, used in excess to retard dimerization of the quinone ketal. The resulting ketals **1** reacted in situ by Diels–Alder cycloadditions to form *endo* adducts **2** (quinone as diene) and **3** (quinone as dienophile). The relative yields of each varied with the nature of the substituent at C-4 of the guaiacol in the expected manner, but the bridged adducts **2** always predominated (Scheme 1).

The excess dienol was recovered by vacuum distillation, but this becomes experimentally troublesome when larger, more complex dienols like **4** are used. The synthetic value of the reaction was much enhanced when we discovered that the predominant bridged adducts **2** were smoothly transformed into naphthofuranones **3** with the *endo* stereochemistry, by thermally induced [3,3] sigmatropic rearrangements.[5] In addition, the two-step sequence was found to be tolerant of major structural variations in both the guaiacol and dienol segments of the *o*-benzoquinone ketal. The pentacyclic quinones of *Xestospongia* species[5,6] as well as the furanosteroid ring systems of viridin and wortmannolone[7] were synthesized by application of these methods. In a concurrent effort, a complex homochiral dienol **4** was prepared and subjected to the same synthetic protocol with methyl vanillate to produce a chiral phenanthrofuran.[8] Several theoretical uncertainties and practical shortcomings were left unaddressed, but the work did constitute the first example of the successful use of a homochiral reactant in the three-step oxidative ketalization, intramolecular cycloaddition, and Cope rearrangement sequence. In this paper, we modify the structures of the substrates to improve overall yields substantially and overcome some serious experimental difficulties that plagued the existing process. We are also able to gain some insights into the stereochemical options chosen by the reaction and to complete a synthesis of the fifth ring of a morphine-like system.

RESULTS AND DISCUSSION

Synthesis of a New Substrate for the Three-Step Process. Our initial attempts to increase yields were directed at optimizing the intramolecular Diels–Alder reaction of the *o*-benzoquinone monoketals. We therefore made several structural adjustments to the dienol component to improve its electron-donating character. It was extremely disappointing to find that incorporating an ethoxy group in the dienol reactant as in **5** was of little value in the reaction with methyl vanillate (Scheme 2).

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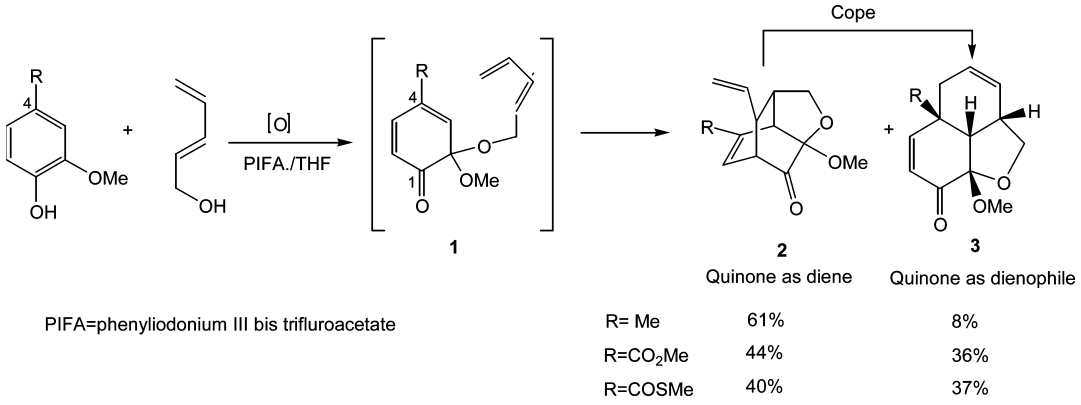
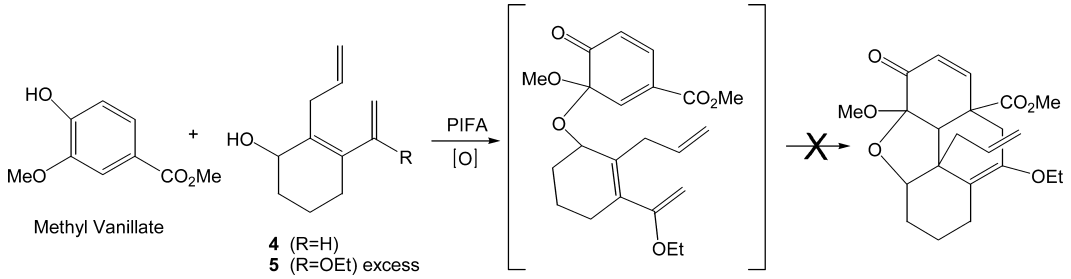
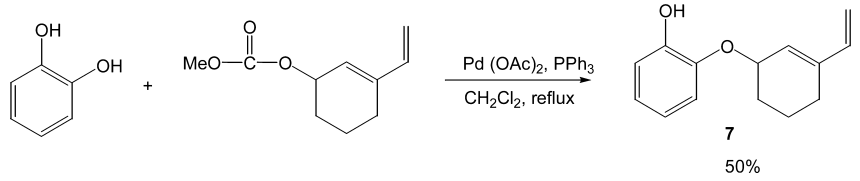
Scheme 1. Diels–Alder Reactions of *o*-Benzoquinone Monoketals



Scheme 2. Unsuccessful Attempts To Employ an Electron-Rich Dienol in the Reaction



Scheme 3. Pd(II)-Catalyzed Coupling of Catechol with a Dienyl Carbonate



Every variation of solvent, temperature, time, and ratio of reactants that we tested did not help and nor did the presence of sodium bicarbonate in the mixture. Similar failure attended our modifications of the position and number of ester groups on the guaiacol. Although frustrating, these results seemed to indicate that the problem resided with *formation* of the ketal and not its subsequent reaction. We therefore set out to explore the feasibility of attaching the dienol to the aromatic reactant as a phenyl ether and then conducting the oxidative dearomatization in methanol, now acting as both a solvent and nucleophile. There are ancillary advantages to this strategy. The methanol, a less hindered nucleophile, is in vast excess, but the dienol, a bulky secondary alcohol, was not. The methanol is easily removed after the reaction, unlike the high boiling dienol. However, there is an obvious hazard associated with this plan. The configurational integrity at C-1 of the dienol had to be assured in any preparation of such a catechol monoether. In order to avoid difficult regiochemical obstacles, we decided to exclude the ester substituent and settled on the simpler catechol monoethers *S*-(−)-**6** as our initial synthetic objective. Our starting material, 1,3-cyclohexanedione, was allylated at C-2,[9] O-methylated,[10] and reacted with freshly prepared vinyl magnesium bromide. The C-1 keto group of the resultant 3-ethenyl-2-(2-propenyl)-2-cyclohexen-1-one was reduced with catecholborane in the presence of 20 mol % of the CBS reagent *R*-oxazaborolidine, at −78 °C for 18 h to form *S*-(−)-**4** in 89% yield[11] with 98.6% ee and $[\alpha]_D = -272$. This was established by chromatography on an OD-H column (see Supporting Information). The use of catecholborane at −78 °C compared to our earlier reduction[8] with borane at 35 °C largely avoids hydroboration of the double bonds, improving the yield and ee of the product considerably. Having established a reliable, reproducible four-step synthetic route to *S*-(−)-**4** in 39% yield from 1,3-cyclohexanedione, we turned our attention to the next objective, the homochiral catechol monoether *S*-(−)-**6**. This was not a trivial undertaking because any method contemplated for construction of the ether link could not risk disturbing the absolute configuration at C-1 of the dienol *S*-(−)-**4**. Although some examples were available in the literature of Mitsunobu coupling of phenols with secondary allyl alcohols,[12] the reaction between *S*-(−)4 and catechol failed under every set of conditions we tried and, indeed, we could not find Mitsunobu conditions that made cyclohexanol react with catechol in good yield. Another published protocol that was attempted was the Larock Pd-catalyzed coupling of phenols with allylic carbonates.[13] This did produce an ether **7** in 50% yield (Scheme 3), and even though the reaction mechanism implied that some racemization at C-1 was likely, we were encouraged enough to attempt the coupling with *S*-(−)-**4** in order to access an ether that could be tested in the oxidative dearomatization sequence. However, our enthusiasm was premature because the reaction failed under five different sets of experimental conditions.

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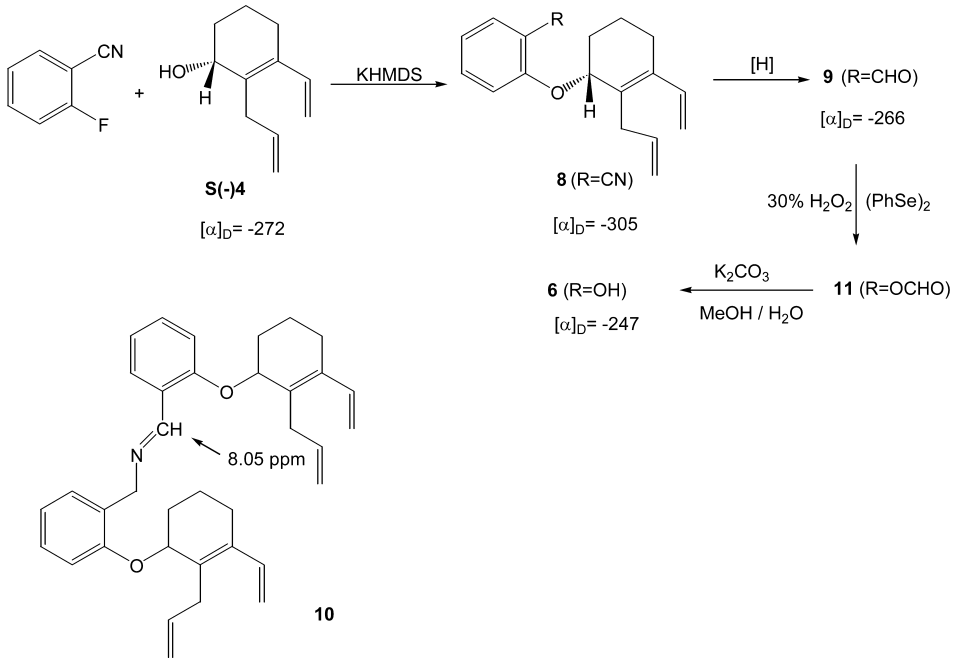
Scheme 4. Preparation of Aromatic Ether *S*-(−)-6



The one remaining option, the reliable nucleophilic aromatic substitution, was well-known and well-tested. The best prospects of success are with fluoroaromatic substrates bearing an electron-withdrawing group (EWG) *ortho* or *para* to the fluorine. Again, success was elusive because our initial choices and combinations of EWG (CHO, CO_2Me) and base (NaH) were ineffective. However, *o*-fluorobenzonitrile, in THF at 0–25 °C, with KHMDS as the base[14] did provide a substitution product **8**, $[\alpha]_D$ −304.8, in 89% yield. Although the reduction of an aromatic nitrile to an aldehyde is a well-known process, this one was tricky. A modified hydride reagent, preformed from *N*,*N*′-dimethylethylenediamine and LAH[15] was used at 0 °C, and the precooled nitrile dissolved in THF was added also at 0 °C and stirred for 1.5 h to produce the aldehyde **9** in 84% yield ($[\alpha]_D$ = −266). If the temperature is not carefully controlled in this manner, over-reduction to the benzylamine is followed upon acidic workup by condensation with the aldehyde to form an imine **10** whose presence was revealed by a ^{1}H NMR signal at 8.05 ppm, instead of the usual 10.46 ppm for the desired aldehyde (Scheme 4)

The next step, the Baeyer–Villiger oxidation of (−)-**9**, was best accomplished with 30% aqueous H_2O_2 and 20 mol % of diphenyl diselenide,[16] which is converted to phenylseleninic acid, the actual oxidizing agent. The formate **11** is obtained in 94% yield and hydrolyzed with aqueous methanolic potassium carbonate to furnish the catechol monoether (−)-**6** in 78% yield. Thus, the much desired attachment of the dienol (−)-**4** to the aromatic segment was achieved with the C-1 stereochemistry preserved in four steps, without the need for chromatographic purification of any of the intermediates **8**, **9**, or **11**. The crucial ether (−)-**6** was produced in 55% yield from *S*-(−)-**4**, which in turn is available in 39% overall yield from commercial 1,3-cyclohexanedione.

Oxidative Ketalization of (−)-6. The catechol monoether **6** contains all of the atoms correctly arranged for initiating and completing the benzoquinone monoketal sequence by oxidative dearomatization. In Scheme 5, we outline and compare the pathways followed by two very similar reactants and attempt to discuss and interpret the differences observed in products and yields. The oxidative ketalization of *S*-**6** in methanol (solvent and nucleophile) produced diastereomeric ketals **12** (*SS*) and **13** (*RS*). Similar ketals, **14** (*SS*) and **15** (*RS*) are formed[8] from methyl vanillate and *S*-(−)-**4** in THF. These transient intermediates react in intramolecular cycloadditions to form *endo* adducts with the quinonoid segment acting as a diene (**17** and **19**) and as a dienophile (**16** and **18**). Adducts **16** and **17** arise from *SS*-**12** (R = H) in a combined yield[17] of 64%, while those from *SS*-**14** (R = CO_2Me) were produced in much lower yields (11% for **18** and 17% for **19**). Our new strategy produces useful adducts in more than double the previous yields and amply rewards the effort involved in the four-step attachment of *S*-(−)-**4** to the aromatic segment. Furthermore, this increase occurs in spite of the greater dienophilicity of the C_4–C_5 double bond in **14** (R = CO_2Me) over **12** (R = H). The failure of dienol **5** (Scheme 2) to react with methyl vanillate can thus be understood in terms of the lesser nucleophilicity of **5** in the oxidative ketalization step and the intervention of deleterious side reactions instead. Methanol, a nucleophile superior to the bulky secondary allylic alcohols **4** and **5** is also employed as the solvent in the new procedure.

An interesting divergence is evident in the reaction of *RS* ketals **13** and **15**. For steric reasons, neither intermediate is able to assume a conformation that assures *endo* cycloaddition. *Exo* addition aided by the presence of the C-4 ester in **15** is favored, and the adduct **20** was isolated in 13% yield.[8] The ketal **13** (R = H), however, is much more prone to dimerization and converts to the expected[18a] dimer **21** in 28% yield by an intermolecular Diels–Alder reaction. We have secured an X-ray of (±)-**21** to confirm its structure and relative stereochemistry and note that both monomer units of the compound possess the *RS* configuration of the ketal **13** (Figure 1). The combined yield of three products **16**, **17**, and **21** isolated from the oxidative ketalization of *S*-(−)-**6** was 92%. Unlike our earlier work,[8] where the dienol *S*-(−)-**4** had to be used in at least a 5-fold excess, the present procedure did not involve a tedious separation of a surplus reactant. The solvent/nucleophile

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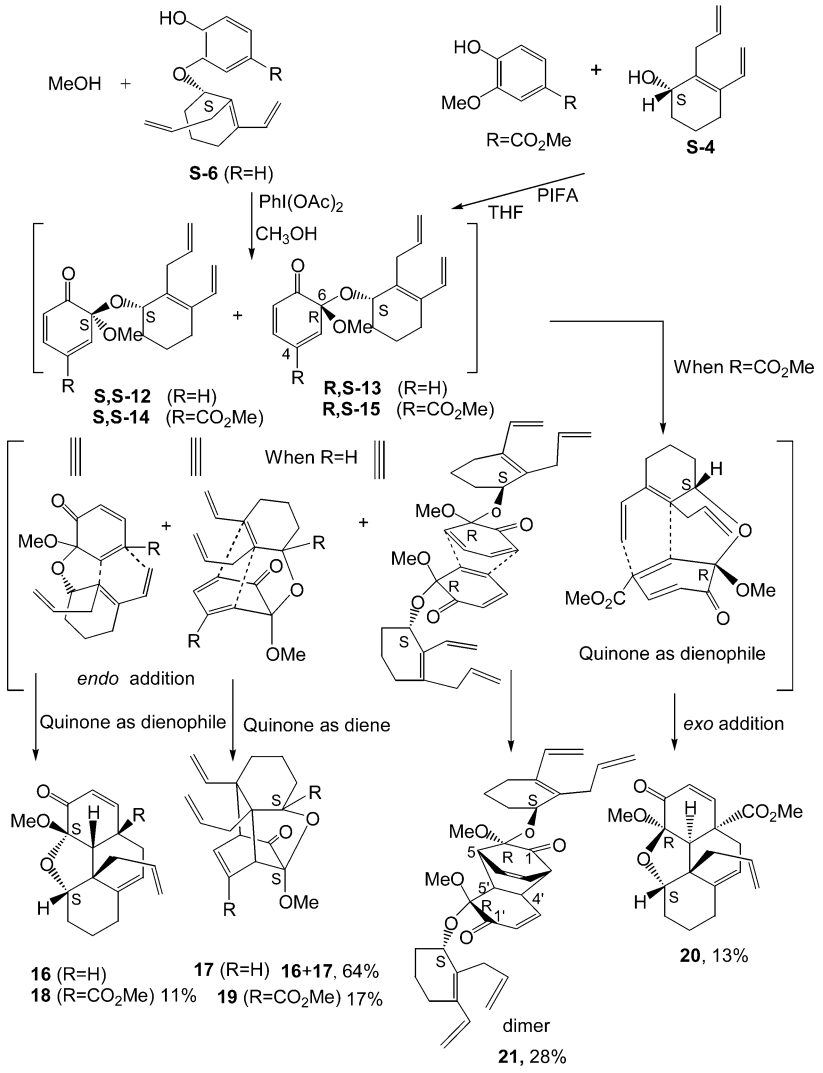
Scheme 5. Oxidative Ketalizations of Catechol Monoethers



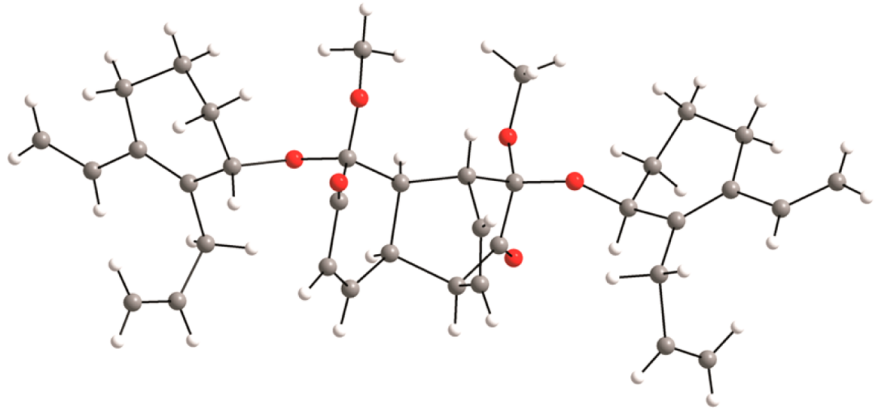


Figure 1. X-ray structure of (±)-**21**.[18b]

methanol was simply removed in vacuo. Since the isolated product yield is almost 100%, and each individual product can be traced to its ketal precursor, it can be reasonably argued that the ratio (yield of **16** + **17**):(yield of **21**) is approximately equal to the relative abundance of the *SS* and *RS* ketals formed in the oxidative dearomatization step.[19] This implies that a modest diastereoselectivity (64:28 or 2.3:1) exists in favor of **12** (*SS*) over **13** (*RS*) during their formation.

Control of stereochemistry in the formation of *o*-benzoquinone monoketals has attracted some attention recently.[20] In one study, a chiral ethanol unit was preattached to the *ortho*-position of a phenol and subsequent intramolecular ketalization conducted with a hypervalent iodine reagent to

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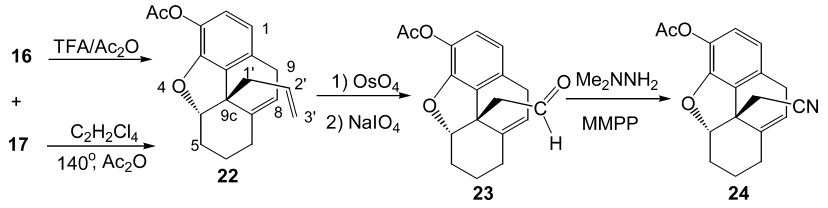
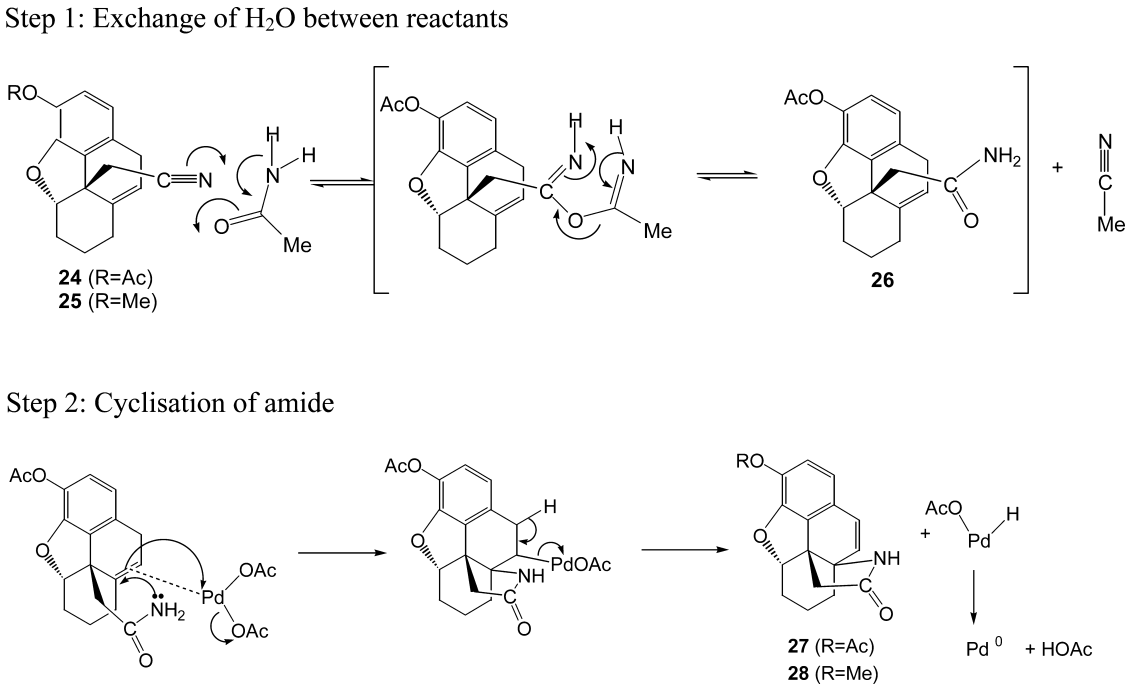
Scheme 6. Oxidative Processing of Allyl Phenanthrofurans



Scheme 7. Hydration and Cyclization of Nitriles 24 and 25



generate *RR* and *RS* (or *SS* and *SR*) diastereomers of spiroketals. Excellent diastereoselection (95:5) in favor of the *SS* and the *RR* diastereomers was achieved in some instances. The chiral auxiliary (the ketal) was then used to induce asymmetry in a reaction of the neighboring carbonyl group. It was removed by hydrolysis and, unlike our chiral dienol, not involved in subsequent synthetic manipulations.

Further Synthetic Elaboration of Adducts 16 and 17. The availability of advanced homochiral intermediates **16** and **17** in good yields persuaded us to attempt the incorporation of a nitrogen atom and closure of the fifth ring. Success in this initiative would afford access to a morphine-like system. The inseparable mixture of **16** and **17** was treated briefly with TFA and acetic anhydride to aromatize and acetylate **16** to phenanthrofuran **22**, leaving bridged adduct **17** unaffected. Separation of **17** from **22** was now possible by column chromatography. The pure bridged adduct was heated in tetrachloroethane at 140 °C for 4 days to effect the desired Cope rearrangement, which proceeded directly to the phenol this time. Again, a small amount of acetic anhydride was added for in situ acetylation of the phenol to reduce its decomposition during the reaction. Another practical advantage of our current strategy became apparent in this step. The absence of the ester substituent in **17** (unlike **19**) meant that an aromatic product was formed directly in the rearrangement. Thus the separation of the starting material **17** from an equilibrium mixture that was necessary earlier[8] was avoided. In this manner, the mixture of **16** and **17** was converted to the acetoxy phenanthrofuran **22** in 70% yield, with $[\alpha]_D = -208$.

The oxidative modification of the allyl substituent in **22** was achieved by selective hydroxylation of $C_{2'}-C_{3'}$ double bond with OsO_4/DMAP. The selectivity of this reaction may be attributed to better steric accessibility of the reagent to this bond rather than to $C_{7a}-C_8$ or to better π-stacking[21] of the osmate/DMAP complex with the aromatic ring of the substrate. The diastereomeric mixture of $C_{2'}-C_{3'}$ diols was then cleaved with sodium periodate to produce the desired aldehyde **23** ($[\alpha]_D = -51.8$). This two-step oxidative degradation was completed in 85.5% yield.

The nitrogen atom was introduced by conversion of the aldehyde to the nitrile **24**. Many methods are known for this transformation, but the most convenient for our substrate was a one-pot, two-step process through a dimethyl hydrazone intermediate[22] with magnesium monoperoxyphthalate (MMPP) in methanol. It involved mild conditions and a simple workup, yielding the desired nitrile (Scheme 6) after column chromatography (77%, $[\alpha]_D = -89.8$).

A Cope elimination of *N*,*N*-dimethylhydroxylamine from the hydrazone-*N*-oxide is probably responsible for formation of the product. To reach our next objective, to connect the nitrogen to either terminus of the $C_{7a}-C_8$ double bond, we envisaged the intermediacy of a primary amide in place of the nitrile. In selecting a method for hydrating the nitrile, we were careful to avoid methods that may cause hydrolysis of the phenyl acetate.

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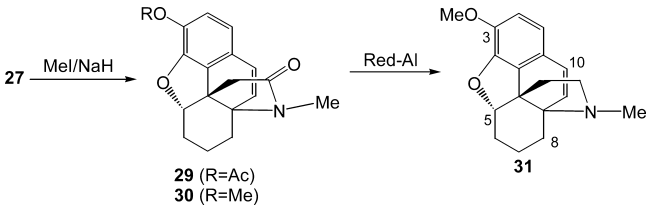
After evaluating the options, we settled on a recently published[23a] Pd-catalyzed hydration of nitriles in aqueous THF with acetamide. The latter reagent used in a 4-fold excess exchanges the elements of water with the substrate, and in spite of this source of water for hydration of the nitrile, the additional water in the solvent is absolutely necessary. Without it, no reaction occurs, but its actual role has not been assigned. In our studies of the hydration, we found that the use of catalytic amounts of Pd(II) resulted in incomplete reaction, and stoichiometric quantities of $Pd(OA_C)_2$ took the reaction to completion only after 3 days. The product was not the amide **26** that we had anticipated, but a lactam **27** (93% yield, $[\alpha]_D$ = −158.5). It was presumably formed from the initial product **26** by the intervention of Pd(II) and the $C_{2'}-C_{3'}$ double bond. A mechanistic proposal[23] reflecting these features is outlined in Scheme 7. It has been suggested[23b] that bimetallic species are intermediates in the hydration step. The second step is more recognizable and similar to the cyclization of carboxamides and sulforamide with allylic double bonds.[24]

The structure of **27** was supported by the presence of two doublets at δ 5.59 (1H, J = 9.6 Hz) and δ 6.39 (1H, J = 9.6 Hz) in its ^{1}H NMR spectrum. The HRMS showed the molecular ion at m/z 311.1157 corresponding to a formula of $C_{18}H_{17}NO_4$. The acetyl group in **24** was replaced with methyl (**25**) ($[\alpha]_D$ = −108.3) by hydrolysis (NaOH, aqueous MeOH) and methylation (Me_2SO_4/K_2CO_3/acetone). Chiral HPLC of a sample of **25** on an OD-H column in 1% isopropyl alcohol/hexane indicated an ee of 98.6% (see Supporting Information). The C-3 methoxylated pentacyclic lactam was produced in the same way in comparable yield (91%, $[\alpha]$ = −172). Both **27** and **28** were N-methylated with NaH/MeI to form **29** and **30** ($[\alpha]_D$ = −167, 89%), respectively. Reduction of the amide in **29** was complicated by sensitivity of the 3-acetyl group to hydride reducing agents, but **30** was converted to the amine **31** in good yield (77%, $[\alpha]_D$ = −179) with Red-Al in benzene. This completes the synthesis of a pentacycle with an absolute configuration similar to that of (−)-codeine and a pyrrolidine ring similar to that of (+)-cepharamine **33**. Ring systems such as **31** have been named indolinocodeine.[25] Our example was synthesized in 3.6% overall yield from cyclohexan-1,3-dione in 16 steps (Scheme 8).

Scheme 8. Final Steps in the Synthesis of (−)-Indolinocodeine 31



In the mid to late 1960s and early 1970s, the rearrangement of the morphine ring system to the indolinocodeine via bromo- and iodocodeines was studied by two groups of Japanese[26] and British[27] researchers. One of the products isolated in the course of their work was assigned a structure and stereochemistry identical to that of synthetic product **31**. Only fragmentary ^{1}H NMR data at 60 MHz were provided,[26] and some differences were apparent between the spectra (Table 1).

It does appear from the data in the table that the chemical shift of H-5 in compound VII has been incorrectly recorded. In addition, the coupling constant of H-5β is significantly different from our data, which are the same in all of the indolinocodeines **27**−**31** that we synthesized in this work. The NMR data recorded for compound **32**, V in the same 1969 paper, are much closer to our's, however. The MS of **32** has also been reported[28] and is similar to the fragmentation pattern we observe for **31** (SI), which contains one double bond less. It therefore displays each ion at 2 mass units more than the corresponding ion in **32**.

Our synthetic indolinocodeine **31** ($[\alpha]_D$ = −169) has structural and stereochemical similarities to (+)-cepharamine **33** (the unnatural enantiomer) synthesized[29] by Schultz in 1998 to test his hypothesis that valuable analgesic activity may reside in such compounds. Both **31** and **33** combine the C-13 stereochemistry of the morphine alkaloids with the pyrrolidine ring structure of the hasubanan alkaloids. The unnatural enantiomers of the morphine alkaloids, like the natural Hasubanans and Isohasubanans,[30] show no pain relieving activity. Unfortunately, no pain relief data have been published for (+)-cepharamine or for any indolinocodeine as yet.

EXPERIMENTAL SECTION

2-Allyl-1,3-cyclohexanedione.[9] To a 5% aqueous KOH solution (250 mL, 0.223 mol) were added cyclohexanedione (25 g, 0.223 mol) and copper powder (14.2 g, 0.223 mol). While stirring, allyl bromide (26 mL, 0.307 mol) was added dropwise within 1 h, and the reaction mixture was stirred at room temperature for 2 h more. After filtration, the residue was stirred in CH_2Cl_2 (250 mL). The mixture was filtered again, and the filtrate was dried over Na_2SO_4 and evaporated to afford the solid. Washing with ether (2 × 50 mL) gave a white solid product (19.3 g, 57%) which was used without further purification in the next step: ^{1}H NMR (300 MHz) δ 1.95 (2H, m), 2.43 (2H, t, J = 6.4 Hz), 2.55 (2H, t, J = 6.4 Hz), 3.05 (2H, d, J = 6.4 Hz), 5.01 (1H, d, J = 10.2 Hz), 5.10 (1H, d, J = 17.3 Hz), 5.82 (1H, m, J = 17.3, 10.2, 7.2 Hz).

2-Allyl-3-methoxy-2-cyclohexenone.[10] 2-Allyl-1,3-cyclohexanedione (20 g, 0.13 mol) was refluxed with Me_2SO_4 (11.3 mL, 0.14 mol) and K_2CO_3 (20.7 g, 0.15 mol) in acetone (300 mL) at 80 °C. After 3 h, acetone was removed in vacuo, and the residue was washed with water (250 mL) and extracted with EtOAc (2 × 300 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by distillation (0.01 mm, 82 °C) gave the product (18.7 g, 87%) as a pale yellow liquid: ^{1}H NMR (300 MHz) δ 1.96 (2H, m), 2.32 (2H, t, J = 6.2 Hz), 2.55 (2H, t, J = 6.2 Hz), 3.0 (2H, d, J = 6.2 Hz), 3.78 (3H, s), 4.85 (1H, dd, J = 10.2, 1.8 Hz), 4.95 (1H, dd, J = 17.3, 1.8 Hz), 5.75 (1H, m, J = 17.3, 10.2, 6.2 Hz).

3-Ethenyl-2-(2-propenyl)-2-cyclohexen-1-one. Vinylmagnesium bromide (1.0 M in THF, 80 mL, 79.5 mmol) was added dropwise over 1 h to a solution of 2-allyl-3-methoxy-2-cyclohexenone (8.8 g, 53 mmol) in dry THF (120 mL) at 0 °C. The mixture was stirred for 5 h. A 3 N aqueous HCl solution was added until pH 2−3 was reached, and the resulting solution was stirred for 2 h more at room temperature. The reaction was extracted with ether (2 × 150 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on a silica column (EtOAc/hexanes 1:1) to give the product (7 g, 81%) as yellow oil: ^{1}H NMR (300 MHz) δ 2.00 (2H, m), 2.43 (2H, t, J = 6.6 Hz), 2.51 (2H, t, J = 6.6 Hz), 3.19 (2H, d, J = 6.0 Hz), 4.93 (2H, m), 5.45 (1H, d, J = 11.0 Hz), 5.67 (1H, d, J = 17.5 Hz,), 5.78 (1H, m, J = 17.8, 9.5, 6.0 Hz), 6.87 (1H, dd, J = 17.5, 11.0 Hz). Anal. Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.57; H, 8.80.

(*S*)-3-Ethenyl-2-(2-propenyl)-2-cyclohexen-1-ol 4.[11] To a solution of 3-ethenyl-2-(2-propenyl)-2-cyclohexen-1-one (8 g, 0.049 mol) in dry toluene (200 mL) and methyl oxazaborolidine (1.0 M in toluene, 7.4 mL, 0.0074 mol) at −78 °C was added a solution of catecholborane (9.5 mL, 0.089 mol) in toluene (80 mL) via syringe pump over 1 h. After stirring for 18 h at −78 °C, NaOH solution (1 N, 600 mL) was added; the resulting solution was stirred at room temperature for an additional 30 min. The organic phase was

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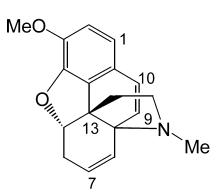
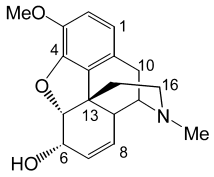
Table 1. Comparison of Selected ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz) for Indolinocodeines 31 and 32[26]

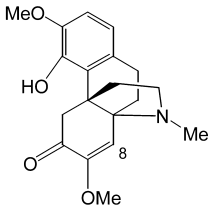
	NMe	OMe	H-5β	H-9, H-10	H-1, H-2
(1) **31**, 300 MHz, $CDCl_3$, current work	2.37 (s)	3.86 (s)	4.73, 4.86 (dd, J = 10.3, 7.0)	5.79, 6.40 (dd, J = 9.6)	6.62, 6.66 (dd, J = 8)
(2) **31** (VII in ref 26) 60 MHz, $CDCl_3$	2.42 (s)	3.90 (s)	4.72 (dd, J = 6.6, 3.0)	5.78, 6.70 (dd, J = 10)	6.68 (s)
(3) **32** (V in ref 26) 60 MHz, $CDCl_3$	2.47 (s)	3.88 (s)	4.89 (t, J = 7.2)	5.72, 6.42 (dd, J = 10)	6.6 (s)



32



(-) Codeine



(+) Cepharamine , **33**

separated, and the aqueous phase was extracted with diethyl ether (2 × 300 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was purified by flash chromatography (hexane/EtOAc = 3:1) to give the product (7.2 g, 89%) as light yellow oil: ^{1}H NMR (300 MHz) δ 1.56 (1H, d, J = 6.9 Hz), 1.65−1.85 (4H, m), 2.10−2.35 (2H, m), 3.10 (2H, d, J = 6.0 Hz), 4.15 (1H,br), 5.00−5.20 (3H, m), 5.30 (1H, d, J = 17.2 Hz), 5.84 (1H, m, J = 17.2, 11.0, 6.0 Hz), 6.76 (1H, dd, J = 17.2, 11.0 Hz); ^{13}C NMR (75 MHz) δ 17.5, 25.0, 31.8, 34.3, 68.2, 114.0, 115.4, 132.9, 134.6, 135.0, 136.7; LRMS(EI) 164 (6), 123 (100); HRMS(EI) m/z calcd for $C_{11}H_{16}O$ M^+ 164.1201, found 164.1200; $[\alpha]_D$ = −271.5 (c = 0.73, $CHCl_3$); ee = 98.66% (see Supporting Information).

3-(1-Ethoxyethenyl)-2-allyl-2-cyclohexen-1-one. *tert*-Butyllithium (38 mL, 64 mmol, 1.7 M in hexane) was added dropwise to a solution of freshly distilled ethyl vinyl ether (8.5 mL, 84 mmol) in anhydrous THP (30 mL) at −78 °C under N_2. The solution turned yellow, and it was stirred for 10 min at −78 °C and for 40 min at 3−5 °C (at this temperature, the yellow precipitate redissolved). After the reaction was recooled to −78 °C, the solution was diluted with 50 mL of dry THF, and 2-allyl-3-methoxy-2-cyclohexenone (7 g, 42 mmol) in 30 mL of dry THF was added. Stirring was continued for 15 min and the mixture warmed to 0 °C for 50 more minutes. The solution was diluted with ether and brine, extracted with ether (3 × 50 mL), washed once with water and brine, dried, and concentrated. Flash chromatography (2:1 EtOAc/hexane) gave 6.30 g of a mixture of alcohols. To this mixture were added 40 g of silica gel and 100 mL of dry CH_2Cl_2 and stirred for approximately 2 h (monitoring by TLC) at rt. The suspension was filtered, concentrated, and purified by silica gel chromatography (1:3 EtOAc/hexane) to give 3-(1-ethoxyethenyl)-2-allyl-2-cyclohexen-1-one (6 g, 70%) as a yellow oil: IR (neat) 2977, 1674, 1636, 1610, 1273 cm$^{-1;}$ ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (3H, t, J = 7.0 Hz), 2.01 (2H, m), 2.40 (2H, t, J = 6.5 Hz), 2.52 (2H, t, J = 6.5 Hz) 3.15 (2H, d, J = 6.0 Hz), 3.75 (2H, q, J = 6.5 Hz), 4.15 (1H, d, J = 2.3 Hz), 4.21 (1H, d, J = 2.3 Hz), 4.90 (2H, m), 5.82 (1H, ddt, J = 15.0, 9.6, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 22.4, 29.9, 31.2, 38.1, 63.1, 85.5, 114.8, 134.3, 136.7, 152.8, 159.7, 199.2; HRMS(EI) m/z calcd for $C_{13}H_{18}O_2$ M^+ 206.1279, found 206.1307.

3-(1-Ethoxyethenyl)-2-allyl-2-cyclohexen-1-ol 5. Compound 3-(1-ethoxyethenyl)-2-allyl-2-cyclohexen-1-one (5.7 g, 27.7 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.1 g, 30.5 mmol) in 100 mL of dry ether at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction was quenched with two spatulas of $Na_2SO_4 \cdot 10\ H_2O$, 10 mL of 1 N NaOH, and 20 mL of H_2O. The suspension was then filtered through a Celite pad to remove the lithium salts and the filtrate extracted with ether (3 × 100 mL). The organic layer was washed with water and brine, dried, and concentrated to give product **5** (4.3 g, 75%) as a colorless oil: IR (neat) 3368, 2977, 1635, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (3H, t, J = 7.0 Hz), 1.64 (4H, m), 2.15 (2H, m), 3.04 (2H, d, J = 6.0 Hz), 3.75 (2H, q, J = 7.0 Hz), 3.95 (1H, d, J = 1.9 Hz), 4.05 (1H, d, J = 1.9 Hz), 4.14 (1H, br), 5.02 (1H, d, J = 10.3 Hz), 5.06 (1H, dd, J = 17.2, 1.7 Hz), 5.85 (1H, ddt, J = 17.2, 10.3, 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 17.8, 29.6, 31.4, 36.1, 62.9, 66.5, 83.6, 115.8, 134.5, 134.5, 137.7, 161.6; HRMS(EI) m/z calcd for $C_{13}H_{20}O_2$ M^+ 208.1463, found 208.1461. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.40.

3-Vinylcyclohex-2-en-1-yl Methyl Carbonate. Dimethyl pyrocarbonate (40 mmol) was added dropwise to a stirred solution of allylic alcohol (20 mmol) and DMAP (2.5 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C (some bubbling was observed). The ice bath was removed and the reaction stirred for 1 h at rt. The solvent was evaporated, and the residue was taken up in CH_2Cl_2 (50 mL) and treated with dimethyl pyrocarbonate (40 mmol). This evaporation/retreatment with dimethyl pyrocarbonate sequence was repeated until no starting material remained by TLC. Purification by silica gel chromatography using 1:1 hexane/ether afforded the 3-vinylcyclohex-2-en-1-yl methyl carbonate in 73% yield as a yellow oil: IR (neat) 2943, 1744, 1607, 1442, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65−2.30 (6H, m), 3.75 (3H, s, OCH_3), 5.10 (2H, m), 5.20 (1H, d, J = 17.5 Hz), 5.75 (1H, br), 6.34 (1H, dd, J = 17.5, 10.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.2, 23.3, 28.0, 54.2, 72.3, 113.5, 125.2, 138.6, 140.8, 155.2.

2-[(3-Vinylcyclohex-2-en-1-yl)oxy]phenol 7. To a flask were added 3-vinylcyclohex-2-en-1-yl methyl carbonate (120 mg, 0.66 mmol), catechol (145 mg, 1.32 mmol), PPh_3 (28 mg, 0.10 mmol), $Pd(OAc)_2$ (6 mg, 0.026 mmol), and 10 mL of CH_2Cl_2. The resulting mixture was stirred under reflux for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography using ether/hexane (1:1) as eluent to give **7** (70 mg, 50%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69−2.41 (6H, m), 4.93 (1H, br), 5.07 (1H, d, J = 10.7 Hz), 5.26 (1H, d, J = 17.5 Hz), 5.69 (1H, s, OH), 5.85 (1H, br), 6.34 (1H, dd, J = 17.5, 10.7 Hz), 6.85 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 23.7, 28.4, 74.7, 113.4, 113.6, 114.5, 121.6, 123.2, 128.4, 138.8, 140.3, 144.5, 146.6; HRMS(EI) m/z calcd for $C_{14}H_{16}O_2$ M^+ 216.1150, found 216.1138.

(*S*)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]benzonitrile 8. The general method of Wandless and co-workers[14] was employed. NaHMDS (1.0 M in THF, 60 mL, 60 mmol) was added dropwise over 1 h to a solution of (*S*)-**4** (7.5 g, 46 mmol) and 2-fluorobenzonitrile (7.2 g, 60 mmol) in dry THF (180 mL) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 3 h. CH_2Cl_2 (400 mL) was added and washed once with saturated aqueous NH_4Cl (300 mL). The aqueous layer was back-extracted once with CH_2Cl_2 (300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica column (EtOAc/hexanes 1:4) to give the product (10.8 g, 89%) as a yellow oil: ^{1}H NMR (300 MHz) δ 1.63−1.71 (2H, m), 1.85−2.17 (3H, m), 2.37−2.44 (1H, m), 2.87−2.95 (1H, dd, J = 15.7, 7.6 Hz), 3.19−3.25 (1H, dd, J = 15.7, 4.8 Hz), 4.82 (1H, br), 4.90−5.00 (2H, m), 5.16 (1H, d, J = 11.0 Hz), 5.34 (1H, d, J = 17.4 Hz), 5.79 (1H, m), 6.78 (1H, dd, J = 17.4, 11.0 Hz), 6.93−7.03 (2H, m), 7.45−7.56 (2H, m); ^{13}C NMR (75 MHz) δ 17.5, 25.0, 27.5, 34.2, 75.1, 103.4, 113.8, 114.9, 115.7, 116.6, 120.7, 130.9, 134.0, 134.1, 134.3, 135.4, 136.0, 160.4; LRMS(EI) 265(2.2), 147(100), 105(35), 91(35); HRMS(EI) m/z calcd for $C_{18}H_{19}ON$ M^+ 265.1467, found 265.1465. Anal. Calcd for

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$C_{18}H_{19}ON$: C, 81.51; H, 7.17. Found: C, 81.91; H, 6.72; $[\alpha]_D$ = −304.8 (c = 1.3, $CHCl_3$).

(*S*)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]benzaldehyde 9.[15] Ice cold *N*,*N*′-dimethylethylenediamine (1.5 mL, 0.0139 mol) was added via cannula to a suspension of LAH (0.53 g, 0.0139 mol) in dry THF (30 mL) at −78 °C under argon. The suspension was stirred for 1 h, and hydrogen was released through a bubbler. Then the mixture was diluted with dry THF (24 mL) and allowed to warm to 0 °C.

To the above mixture was added a cooled solution of benzonitrile **8** (2.45 g, 0.0093 mol) in THF (20 mL), and the mixture was stirred at 0 °C for 1.5 h. Cold 3 N HCl (30 mL) was added until the pH reached 2−3 and stirring continued for 10 min. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried, and concentrated to give the product used directly without purification for the next step. For the purpose of accurate rotation measurement, the residue was purified on a silica column (EtOAc/hexanes = 1:2) to give the product (2.1 g, 84%) as a yellow oil: ^{1}H NMR (300 MHz) δ 1.72−1.82 (3H, m), 2.08−2.21 (2H, m), 2.42 (1H, m), 2.87−2.95 (1H, dd, J = 15.7, 7.0 Hz), 3.19−3.25 (1H, dd, J = 15.7, 4.8 Hz), 4.91 (1H, br), 4.94−5.06 (2H, m), 5.22 (1H, d, J = 11.0 Hz), 5.39 (1H, d, J = 17.4 Hz), 5.81 (1H, m), 6.83 (1H, dd, J = 17.4, 11.0 Hz), 6.96−7.24 (2H, m), 7.49 (1H, m), 7.82 (1H,m), 10.50 (1H, s); ^{13}C NMR (75 MHz) δ 17.7, 25.0, 27.5, 34.3, 74.3, 113.7, 114.9, 115.7, 120.5, 125.9, 128.3, 131.2, 134.2, 135.2, 135.8, 135.9, 161.1, 190.1; LRMS(EI) 268(2), 147(100), 105(35), 91(35); HRMS(EI) m/z calcd for $C_{18}H_{20}O_2$ M^+ 268.1463, found 268.1465; $[\alpha]_D$ = −265.7 (c = 1.8, $CHCl_3$).

(*S*)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenylformate 11. To a solution of PhSeSePh (230 mg, 0.74 mmol) in CH_2Cl_2 (50 mL) was added H_2O_2 (1.7 g, 15 mmol, 30% w/w).[16] The yellow solution was stirred until colorless, and a solution of benzaldehyde **9** (1 g, 3.7 mmol) in CH_2Cl_2 (30 mL) was added. The reaction was stirred vigorously at rt overnight. Water (50 mL) was added, and the reaction mixture was separated. The organic layer was washed successively with 10% aqueous $NaHSO_3$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (30 mL), dried, and concentrated. The resulting yellow oil (1.0 g, 94%) was directly used for the next step without further purification: ^{1}H NMR (300 MHz) δ 1.57−1.69 (3H, m), 1.98−2.04 (2H, m), 2.34 (1H, m), 2.89−2.93 (1H, dd, J = 15.7, 7.2 Hz), 3.14−3.17 (1H, dd, J = 15.7, 4.6 Hz), 4.74 (1H, br), 4.92−5.01 (2H, m), 5.15 (1H, d, J = 11.0 Hz), 5.33 (1H, d, J = 17.4 Hz), 5.78 (1H, m), 6.78 (1H, dd, J = 17.4, 11.0 Hz), 6.91−6.97 (1H, m), 7.03−7.11 (2H, m), 7.17−7.20 (1H, m), 8.23 (1H,s); ^{13}C NMR (75 MHz) δ 17.5, 25.0, 27.3, 34.0, 74.4, 114.5, 115.0, 115.5, 120.9, 122.9, 127.2, 131.6, 134.4, 135.0, 135.8, 136.1, 149.6, 159.3; LRMS(CI) $[M + NH_4]^+$ 302.2.

(*S*)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenol 6. Ice cold aqueous K_2CO_3 solution (12.2 mL, 3.52 mmol, 4% v/v) was added dropwise over 30 min to the solution of phenyl formate **11** (1 g, 3.52 mmol) in methanol (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After methanol was evaporated, the mixture was neutralized with dry ice to pH 7, then extracted with EtOAc (2 × 30 mL). The combined organic layer was dried and concentrated. The residue was purified on a silica column (EtOAc/hexanes = 1:4) to give the product (0.7 g, 78%) as a yellow oil: ^{1}H NMR (300 MHz) δ 1.56−1.75 (3H, m), 2.01−2.07 (2H, m), 2.37 (1H, m), 2.97−3.00 (1H, dd, J = 15.7, 7.0 Hz), 3.08−3.10 (1H, dd, J = 15.7, 5.0 Hz), 4.75 (1H, br), 4.96−5.05 (2H, m), 5.18 (1H, d, J = 11.0 Hz), 5.35 (1H, d, J = 17.2 Hz), 5.75−5.95 (2H, m), 6.78−6.94 (5H, m); ^{13}C NMR (75 MHz) δ 17.7, 24.9, 27.5, 34.3, 75.2, 112.8, 114.7, 114.8, 115.6, 120.0, 121.4, 131.5, 134.3, 135.2, 136.3, 145.1, 146.7; LRMS(EI) 256 (2), 147 (100), 105(40), 91(35); HRMS(EI) m/z calcd for $C_{17}H_{20}O_2$ M^+ 256.1461, found 256.1463; $[\alpha]_D$ = −247 (c = 1.2, $CHCl_3$).

Oxidation and Intramolecular Diels−Alder Reaction of (−)-2-[(2-Allyl-3-vinylcyclohex-2-en-1-yl)oxy]phenol 6. To a solution of phenol **6** (1 g, 3.9 mmol) in methanol (50 mL) was added a solution of DAIB (1.50 g, 4.66 mmol) in methanol (70 mL) via syringe pump over 1 h. The reaction mixture was stirred overnight; $NaHCO_3$ (1.25 g) was added and the mixture stirred for 20 min. After the methanol was removed in vacuo, the residue was extracted with EtOAc (2 × 40 mL), washed with water (50 mL) and brine (40 mL), dried, and evaporated. The residue was purified on a silica column (CH_2Cl_2/hexane/CH_3OH = 5:1:0.1) to give the *endo*-**16** and bridged compound **17** mixture (714 mg, 64%, *endo*/bridged = 1.2:1) as a yellow oil and the dimer **21** (312 mg, 28%) as a yellow solid. The dimer **21** was crystallized from the mixture using CH_2Cl_2/pentane as small prisms, and X-ray was obtained. The *endo*-**16** and bridged compound **17** mixture could not be separated in any solvent system; therefore, it was used directly for the next reaction.

Dimer Compound 21: ^{1}H NMR (300 MHz) δ 1.15−1.75 (4H, m), 1.85−2.15 (5H, m), 2.16−2.30 (2H, m), 2.65−2.85 (2H, m), 2.86−3.05 (2H, m), 3.15−3.25 (3H, m), 3.30 (1H, s), 3.42 (4H, br), 3.49 (3H, s), 3.79 (1H, br), 4.24 (1H, br), 4.87−4.97 (4H, m), 5.02−5.09 (2H, m), 5.21−5.27 (2H, dd, J = 17.3, 10.0 Hz), 5.50−5.72 (2H, m), 5.75−5.82 (1H, t, J = 7 Hz), 6.05−6.13 (1H, d, J = 10 Hz), 6.27−6.35 (1H, t, J = 7 Hz), 6.45−6.55 (1H, dd, J = 10 Hz, J = 4 Hz), 6.58−6.75 (2H, m); ^{13}C NMR (75 MHz) δ 17.5, 17.7, 24.9, 24.9, 28.4, 29.3, 30.8, 31.8, 32.9, 40.0, 41.1, 42.4, 49.7, 50.6, 53.0, 72.1, 72.3, 96.9, 100.2, 114.4, 114.8, 115.3, 115.5, 127.3, 129.4, 133.1, 133.4, 134.4, 134.4, 134.4, 134.6, 135.2, 136.1, 146.8, 193.8, 202.5; $[\alpha]_D$ = −118.6 (c = 0.57, $CHCl_3$); mp 52−54 °C.

3-Acetoxy-9c-(2′-propenyl)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan 22. TFA (3.0 mL) and acetic anhydride (3.0 mL) were added to a solution of a mixture of *endo*-**16** and bridged compound **17** (500 mg, 1.75 mmol) in CH_2Cl_2 (80 mL) and stirred at rt for 15 min. $NaHCO_3$ was added in small portions until the pH reached 7, then washed with water (2 × 30 mL). The layers were partitioned, and the organic layer was dried and concentrated to give an oil that was further purified by column chromatography (hexane/ether = 6:1) to give the product (214 mg, 76%) as a light yellow oil (R_f = 0.33) and the unchanged bridged adduct (225 mg) as a light yellow oil (R_f = 0.2).

To a solution of bridged compound **17** (225 mg, 0.79 mmol) in tetrachloroethane (20 mL) was added acetic anhydride (3 mL). The reaction mixture was stirred at 140 °C for 4 days. After the tetrachloroethane was removed by vacuum distillation, the residue was extracted with EtOAc (50 mL) and washed with water (2 × 20 mL). The organic layer was dried and concentrated. The residue was purified by column chromatography (hexane/ether = 6:1) to give the product (147 mg, 63%) as a light yellow oil: ^{1}H NMR (500 MHz) δ 1.10−1.24 (1H, m), 1.45−1.60 (1H, m), 1.70−1.78 (2H, m), 2.29−2.37 (7H, m), 3.11−3.17 (1H, dd, J = 19.2, 6.0 Hz), 3.29−3.30 (1H, dd, J = 19.2, 3.5 Hz), 4.74−4.78 (1H, dd, J = 12.2, 4.2 Hz), 5.05−5.09 (2H, m), 5.72−5.80 (2H, m), 6.70 (1H, d, J = 8.0 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 17.5, 20.8, 25.3, 25.7, 29.7, 42.0, 50.1, 90.2, 118.4, 118.9, 121.1, 123.3, 132.5, 133.7, 134.0, 134.2, 140.5, 147.0, 168.7; LRMS(EI) 296(6), 255(87), 213(75), 195(100), 167(45); HRMS(EI) m/z calcd for $C_{19}H_{20}O_3$ M^+ 296.1412, found 296.1411; $[\alpha]_D$ = −208 (c = 0.19, $CHCl_3$).

Bridged Compound 17: ^{1}H NMR (500 MHz) δ 1.45 (1H, m), 1.57−1.60 (2H, m), 1.75−1.95 (3H, m), 2.10 (1H, dd, J = 14.3, 7.0 Hz), 2.17 (1H, dd, J = 14.3, 7.8 Hz), 2.88−2.90 (1H, dd, J = 6.5, 1.1 Hz), 3.20−3.22 (1H, dd, J = 6.4, 1.7 Hz), 3.49 (3H, s), 4.28 (1H, t), 5.04−5.12 (4H, m), 5.75−5.85 (1H, m), 5.97−6.03 (1H, dd, J = 17.5, 11.1 Hz), 6.18−6.28 (2H, m); ^{13}C NMR (75 MHz) δ 16.0, 25.6, 32.2, 38.3, 44.3, 48.4, 48.5, 48.9, 60.0, 80.0, 99.5, 113.4, 118.7, 128.3, 131.8, 134.2, 141.7, 201.8; LRMS(EI) 258(50), 217(100), 157(45), 131(52); LRMS(CI) $[M + NH_4]^+$ 304.2 (100); HRMS(EI) m/z calcd for $C_{17}H_{22}O_2$ $[M - CO]^+$ 258.1620, found 258.1621; $[\alpha]_D$ = +299 (c = 0.34, $CHCl_3$).

3-Acetoxy-9c-(2′,3′-dihydroxy)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan. To a solution of DMAP (644 mg, 5.28 mmol) and phenanthrofuran **22** (650 mg, 2.20 mmol) in THF (150 mL) was added OsO_4 (676 mg, 2.64 mmol) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 12 h, then 10% $NaHSO_3$ solution (30 mL) was added and stirring continued for another hour. The mixture was extracted with EtOAc (2 × 40 mL), and the organic layer was separated washed with brine (80 mL), then dried and concentrated to give the product (661 mg, 91%), a colorless

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oil, as a diastereomeric mixture which was used directly without further purification for the next step: ^{1}H NMR (500 MHz, mixture of diastereomers) δ 1.10−1.75 (4H, m), 1.85−1.95 (1H, m), 2.17 (1H, m), 2.30−2.50 (7H, m), 3.19−3.55 (4H, m), 3.65 (0.55H, m), 4.00 (0.45H, m), 4.86−4.88 (0.45H, dd, J = 12.5, 4.5 Hz), 5.00−5.04 (0.55H, dd, J = 12.5, 4.5 Hz), 5.79−5.81 (0.45H, m), 5.73−5.75 (0.55H, m), 6.73−6.82 (2H, m); ^{13}C NMR (75 MHz) δ 19.0, 19.1 (1C), 20.7, 24.9, 25.5, 29.3, 29.4 (1C), 39.9, 40.1 (1C), 48.6, 48.8 (1C), 67.1, 67.2 (1C), 69.6, 69.9 (1C), 90.9, 91.0(1C), 119.2, 119.3 (1C), 120.7, 122.4, 123.4 (2C), 132.2, 133.3, 133.8, 134.3, (2C), 141.4, 141.6 (1C), 146.7, 147.1 (1C), 168.8, 169.1 (1C); LRMS(EI) 330 (25), 288(40), 255(55), 213(100), 195(60); HRMS(EI) m/z calcd for $C_{19}H_{22}O_5$ M^+ 330.1467, found 330.1462; $[\alpha]_D$ = −29.2 (c = 0.76, $CHCl_3$).

3-Acetoxy-9c-(2′-oxoethyl)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan 23. $NaIO_4$ (1.52 g, 7.1 mmol) was added to a solution of 3-acetoxy-9c-(2′,3′-hydroxy)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan (650 mg, 1.97 mmol) in water and *t*-BuOH (25 mL/25 mL) and stirred at rt for 1.5 h. The reaction mixture was extracted with EtOAc (80 mL), and the organic layer was washed with water (2 × 30 mL), dried, and concentrated to give a colorless oil (552 mg, 94%) directly used for the next reaction without further purification: ^{1}H NMR (500 MHz) δ 1.17−1.79 (3H, m), 2.29−2.50 (6H, m), 2.59−2.65 (1H, dd, J = 14.9, 3.0 Hz), 2.68−2.73 (1H, dd, J = 14.9, 2.6 Hz), 3.23−3.26 (2H, m), 4.82−4.86 (1H, dd, J = 12.2, 4.6 Hz), 5.83−5.86 (1H, m), 6.75−6.77 (1H, d, J = 8.0), 6.83−6.86 (1H, d, J = 8.0), 9.65 (1H, t, J = 2.8 Hz); ^{13}C NMR (75 MHz) δ 17.5, 20.7, 25.0, 25.4, 29.6, 47.5, 50.2, 90.7, 119.5, 121.9, 124.5, 132.7, 132.8, 133.9, 139.7, 147.1, 168.5, 200.9; LRMS(EI) 298(20), 256(65), 212(100), 195(35); HRMS(EI) m/z calcd for $C_{18}H_{18}O_4$ M^+ 298.1211, found 298.1205; $[\alpha]_D$ = −51.8 (c = 0.95, $CHCl_3$).

3-Acetoxy-9c-(2′-oxoethyl-*N*,*N*-dimethylhydrazone)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan. *N*,*N*-Dimethylhydrazine (0.12 mL, 1.57 mmol) was added to a solution of aldehyde **23** (334 mg, 1.12 mmol) in methanol (60 mL). The mixture was stirred for 2 h at rt, and methanol was removed in vacuo. The residue was extracted with EtOAc (70 mL), washed with water (50 mL), and separated. The organic layer was dried and concentrated to give a colorless oil (339 mg, 89%) used directly for the next reaction without further purification: ^{1}H NMR (300 MHz, mixture of diastereomers) δ 1.11−1.72 (4H, m), 2.25−2.39 (6H, m), 2.48−2.52 (1H, m), 2.68−2.71 (6H, m), 3.08−3.35 (2H, dd, J = 19.1, 5.7 Hz), 4.78−4.84 (1H, m), 5.73−5.76 (1H, m), 6.35−6.40 (1H, m), 6.60−6.79 (2H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 17.4, 17.6 (1C), 20.7, 25.1, 25.4 (1C), 29.3, 29.5, 29.7 (2C), 39.9, 40.1 (1C), 43.0, 43.2, 49.7, 49.9 (1C), 89.4, 89.9 (1C), 115.5, 119.0, 119.2 (1C), 121.2, 123.0, 132.4, 133.5, 133.9, 140.4, 140.6 (1C), 147.5, 168.5; LRMS(EI) 340(30), 255(80), 213(100), 195(90), 86(45); HRMS(EI) m/z calcd for $C_{20}H_{24}N_2O_3$ M^+ 340.1787, found 340.1794.

3-Acetoxy-9c-(2′-cyanoethyl)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan 24. To a solution of MMPP·$6H_2O$ (890 mg, 1.8 mmol) in methanol (10 mL) was added a solution of 3-acetoxy-9c-(2′-oxoethyl-*N*,*N*-dimethylhydrazone)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan (259 mg, 0.76 mmol) in methanol (30 mL) at 0 °C. The mixture was allowed to stir for 5 min, and H_2O (180 mL) was added. The mixture was extracted with CH_2Cl_2 (60 mL), and the aqueous layer was extracted again with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried and concentrated. The residue was purified by column chromatography (CH_2Cl_2) to give a white solid product (173 mg, 77%): ^{1}H NMR (300 MHz) δ 1.18−1.86 (4H, m), 2.31−2.50 (4H, m), 2.54−2.73 (3H, m), 3.20−3.28 (1H, dd, J = 19.8, 6.0 Hz), 3.43−3.55 (1H, dd, J = 19.8 Hz, 3.5 Hz), 4.80−4.87 (1H, dd, J = 12.1, 4.4 Hz), 5.99−6.01 (1H, m), 6.77−6.84 (1H, d, J = 8.1 Hz), 6.87−6.91 (1H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz) δ 17.2, 20.7, 25.0, 25.3, 25.6, 29.7, 47.5, 90.5, 117.5, 119.7, 122.5, 126.3, 131.3, 132.9, 134.3, 137.9, 147.0, 168.5; LRMS(EI) 295(25), 253(85), 213(100), 195(57), 167(25); HRMS(EI) m/z calcd for $C_{18}H_{17}N$ O_3 M^+ 295.1208, found 295.1214; $[\alpha]_D$ = −89.8 (c = 1.1, $CHCl_3$).

3-Methoxy-9c-(2′-cyanoethyl)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan 25. NaOH (5 mL, 1 N) was added to a solution of acetoxy nitrile **24** (50 mg, 0.17 mmol) in MeOH (15 mL). The reaction mixture was stirred at rt overnight. Methanol was removed in vacuo, and dry ice was added to reach a pH of 6−7. The resulting mixture was extracted with EtOAc (2 × 10 mL). The organic layer was dried and concentrated to obtain crude 3-hydroxy-9c-(2′-cyanoethyl)-4a,5,6,7,9,9c-pentahydrophenanthro[4,5-*bcd*]furan. To the solution of above product and dimethylsulfate (74.8 mg, 0.68 mmol) in acetone (10 mL) was added K_2CO_3 (234.6 mg, 1.7 mmol). The mixture was stirred at rt for 16 h, and acetone removed in vacuo. The residue was extracted with CH_2Cl_2 (20 mL) and washed with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried, concentrated, and purified by column chromatography (CH_2Cl_2) to give a white solid (41 mg, 91%): ^{1}H NMR (300 MHz) δ 1.13−1.86 (4H, m), 2.38−2.65 (4H, m), 3.11−3.20 (1H, dd, J = 19.8, 6.0 Hz), 3.36−3.51 (1H, dd, J = 19.8, 3.5 Hz), 3.85 (3H, s), 4.76−4.82 (1H, dd, J = 12.1, 4.4 Hz), 5.94−5.97 (1H, m), 6.71 (2H, s); ^{13}C NMR (75 MHz) δ 17.3, 25.1, 25,4, 25.6, 29.3, 47.5, 56.5, 89.7, 113.2, 117.6, 119.5, 126.6, 128.5, 130.3, 137.9, 143.3, 145.3; LRMS(EI) 267(85), 227(58), 195(100); HRMS(EI) m/z calcd for $C_{17}H_{17}NO_2$ M^+ 267.1257, found 267.1259; $[\alpha]_D$ = −108.3 (c = 0.45, $CHCl_3$); ee = 98.62%.

Palladium-Catalyzed Cyclization of Tetracyclic Nitriles. *3-Acetoxy-7a,9c-(amidoethano)-4a,5,6,7,9c-pentahydrophenanthro-[4,5-bcd]furan **27** and 3-Methoxy-7a,9c-(amidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan **28**.* The nitrile **24** or **25** (0.15 mmol) was dissolved in a mixture of H_2O/THF = 1:3 (12 mL). Acetamide (0.60 mmol) and $Pd(OAc)_2$ (0.16 mmol) were added, and the mixture was stirred at rt for 3 days. THF was removed in vacuo, and the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (20 mL), dried, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH = 99:1) to give the product.

*3-Acetoxy-7a,9c-(amidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan **27**:* obtained in 93% yield as a light yellow solid by the above procedure; ^{1}H NMR (300 MHz) δ 1.20−1.59 (4H, m), 1.78−1.83 (1H, m), 2.05−2.15 (1H, m), 2.29 (3H, s), 2.52−2.59 (1H, d, J = 16.9 Hz), 2.61−2.67 (1H, d, J = 16.9 Hz), 4.74−4.81 (1H, dd, J = 10.3, 7.0 Hz), 5.59 (1H, d, J = 9.6 Hz), 5.91 (1H, br) 6.39 (1H, d, J = 9.6 Hz), 6.78−6.81 (1H, d, J = 8.0 Hz), 6.85−6.88 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 15.2, 20.7, 28.1, 31.8, 42.8, 47.7, 62.9, 92.3, 118.4, 122.6, 123.2, 126.8, 127.3, 133.7, 134.7, 147.7, 168.4, 176.6; LRMS(EI) 311(19), 269(100); HRMS(EI) m/z calcd for $C_{18}H_{17}NO_4$ M^+ 311.1158, found 311.1157; $[\alpha]_D$ = −158.5 (c = 1.1, $CHCl_3$).

*3-Methoxy-7a,9c-(amidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan **28**:* . obtained in 91% yield as a light yellow solid by the above procedure; ^{1}H NMR (300 MHz) δ 1.19−1.52 (4H, m), 1.80−1.85 (1H, m), 2.05−2.15 (1H, m), 2.50−2.56(1H, d, J = 16.8 Hz), 2.57−2.64 (1H, d, J = 16.8 Hz), 3.86 (3H, s), 4.73−4.80 (1H, dd, J = 10.3, 7.0 Hz), 5.59 (1H, d, J = 9.6 Hz), 6.34 (1H, d, J = 9.6 Hz), 6.57 (1H, br), 6.65−6.68 (1H, d, J = 8.0 Hz), 6.69−6.72 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 14.1, 28.3, 31.9, 43.0, 48.1, 56.3, 62.8, 91.4, 113.1, 118.6, 121.9, 122.8, 126.4, 131.8, 144.8, 145.3, 176.6; LRMS(EI) 283(100), 240(10); HRMS(EI) m/z calcd for $C_{17}H_{17}NO_3$ M^+ 283.1206, found 283.1208; $[\alpha]_D$ = −172.3 (c = 1.3, $CHCl_3$).

N-Methylation of Pentacyclic Lactams. *3-Acetoxy-7a,9c-(methylamidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan **29** and 3-Methoxy-7a,9c-(methylamidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan **30**.* NaH (0.14 mmol, 60% in mineral oil) was added to a solution of amide **27** or **28** (0.096 mmol) and MeI (6.6 mL) in THF (20 mL) at 0 °C. The reaction mixture was continued to stir at 0 °C for 3 h and warmed to rt. After adding saturated NH_4Cl (15 mL), the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with brine (10 mL), separated, and dried. The residue was purified by column chromatography (CH_2Cl_2/CH_3OH = 99:1) to give the product.

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3-Acetoxy-7a,9c-(methylamidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan ***29:*** obtained in 87% yield as a light yellow solid; ^{1}H NMR (300 MHz) δ 0.99−1.29 (4H, m), 1.99−2.23 (2H, m), 2.29 (3H, s), 2.58 (2H, s), 2.84 (3H, s), 4.68−4.75 (1H, dd, J = 10.3, 7.0 Hz), 5.67 (1H, d, J = 9.6 Hz), 6.41 (1H, d, J = 9.6 Hz), 6.69−6.72 (1H, d, J = 8.0 Hz), 6.86−6.89 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 16.0, 20.3, 28.1, 30.2, 31.8, 40.8, 44.7, 62.9, 92.3, 118.4, 122.8, 123.6, 127.1, 127.3, 133.7, 134.7, 147.7, 168.4, 174.8; LRMS(EI) 325(25), 283(100); HRMS(EI) m/z calcd for $C_{19}H_{19}NO_4$ M^+ 325.1314, found 325.1315; $[\alpha]_D$ = −153.1 (c = 0.89, $CHCl_3$).

3-Methoxy-7a,9c-(methylamidoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan ***30:*** obtained (89%) as a light yellow solid; ^{1}H NMR (300 MHz) δ 1.03−1.33 (2H, m), 1.44−1.56 (2H, m), 1.99−2.17 (2H, m), 2.49−2.54(1H, d, J = 16.5 Hz), 2.56−2.63 (1H, d, J = 16.5 Hz), 2.83 (3H, s), 3.87 (3H, s), 4.67−4.74 (1H, dd, J = 10.3, 7.0 Hz), 5.56 (1H, d, J = 9.6 Hz), 6.38 (1H, d, J = 9.6 Hz), 6.65−6.68(1H, d, J = 8.0 Hz), 6.69−6.73 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 15.1, 24.6, 28.2, 29.9, 42.5, 46.7, 56.3, 66.1, 91.4, 113.1, 118.6, 122.1, 123.3, 126.8, 126.9, 144.8, 145.3, 174.3; LRMS(EI) 297(100), 283(10); HRMS(EI) m/z calcd for $C_{18}H_{19}NO_3$ M^+ 297.1360, found 297.1365; $[\alpha]_D$ = −166.7 (c = 0.67, $CHCl_3$).

3-Methoxy-7a,9c-(methyliminoethano)-4a,5,6,7,9c-pentahydrophenanthro[4,5-bcd]furan ***31.*** Compound **30** (10 mg, 0.034 mmol) in benzene (3 mL) was added to a solution of Red-Al (15 μL, 0.051 mmol, 65% w/w) in benzene (0.5 mL). The reaction mixture heated spontaneously, and the apparatus was connected with a condenser. The mixture was stirred at rt for 1.5 h. Water (6 mL) was added until precipitation occurred, and the mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried, concentrated, and purified by column chromatography (CH_2Cl_2/CH_3OH = 95:5) to give a white solid (7.4 mg, 77%): ^{1}H NMR (300 MHz) δ 1.03−1.87 (6H, m), 2.11−2.25 (2H, m), 2.37 (3H, s), 2.40−2.44 (1H, m), 3.17−3.20 (1H, m), 3.86 (3H, s), 4.73−4.80 (1H, dd, J = 10.3, 7.0 Hz), 5.79 (1H, d, J = 9.6 Hz), 6.40 (1H, d, J = 9.6 Hz), 6.61−6.64 (1H, d, J = 8.0 Hz), 6.65−6.68 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz) δ 15.1, 20.4, 24.6, 28.2, 42.5, 46.7, 48.0, 56.7, 66.1, 92.4, 112.3, 117.4, 122.1, 123.3, 125.8, 126.1, 144.5, 145.1; LRMS(EI) 283 (100), 268(50), 149(50), 57(48); HRMS(EI) m/z calcd for $C_{18}H_{21}NO_2$ M^+ 283.1568, found 283.1572; $[\alpha]_D$ = −169.1 (c = 0.15, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **4**, **5**, **6**, **7**, **8**, **9**, **11**, **17**, and **21**−**31**, LRMS of **31**, general experimental methods, and details of columns, solvent, and flow rates for chiral HPLC determination of ee. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Robert E. Ireland.

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