VOLUME 71, NUMBER 2

JOC Articles

JANUARY 20, 2006

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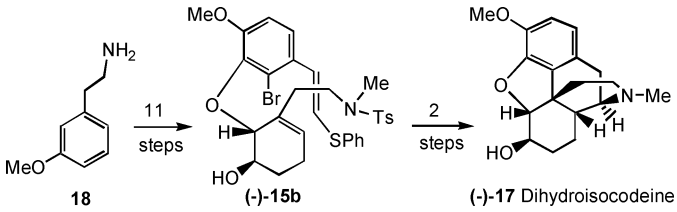
Enantioselective Synthesis of (−)-Dihydrocodeinone: A Short Formal Synthesis of (−)-Morphine[1,†]

Kathlyn A. Parker*,‡ and Demosthenes Fokas§

Department of Chemistry, Brown University, Providence, Rhode Island 02912

kparker@notes.cc.sunysb.edu

Received June 24, 2005



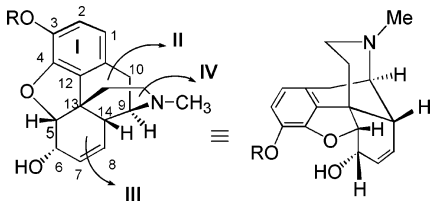
The radical cyclization approach to the morphine alkaloids has been applied in an asymmetric synthesis of (−)-dihydrocodeinone. A chiral cyclohexenol (*R*-**32**), from the CBS reduction of the enone, is the source of chirality. The first key step, tandem closure in which stereochemistry is controlled by geometric constraints, (−)-**15b** → (+)-**16**, was followed by an unprecedented reductive hydroamination, completing the synthesis of (−)-dihydroisocodeine ((−)-**17**) in 13 steps from commercially available materials.

Introduction

Morphine Alkaloids as Targets for Total Synthesis. Morphine (**1a**)[2] is the principal active component of opium, the extract of the immature seed capsule of the opium poppy. Morphine and related opioids are analgesics.

Morphine itself is a potent compound. Despite serious side effects, including physical addiction, it continues to be one of the most widely used drugs for the treatment of severe pain. Codeine (**1b**), a weak analgesic, is also an antitussive and commonly used in cough medicines. Research focused on the discovery of morphine derivatives or analogues which maintain desirable activity but exhibit reduced side effects continues at a steady pace.[3]

The compact, functional-group-rich structures of this class continue to provoke the interest and effort of synthetic chemists. Among many imaginative approaches which have been explored, a number have led to total syntheses or formal total syntheses.[4]



1a R = H morphine
1b R = Me codeine

Our own synthesis of (±)-dihydrocodeinone[1] employed a tandem radical cyclization of an easily obtained aryl cyclohexenyl ether and introduced an unprecedented intramolecular hydroamination reaction carried out under reductive conditions. This key step, which may involve a nitrogen radical, completed the construction of the morphine ring system.

† This paper is dedicated to the memory of Arthur G. Schultz.

‡ Current address: Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400.

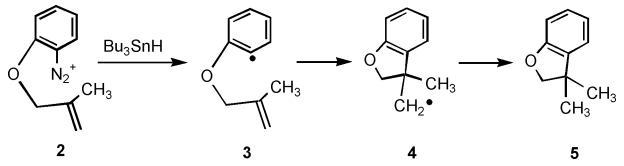
§ Current address: Department of Chemistry, ArQule Inc., 19 Presidential Way, Woburn, MA 01801. E-mail: dfokas@arqule.com.

(1) A preliminary report of part of this work has appeared: Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688.

(2) In their 1925 paper in which they deduce the structures of codeine and thebaine, Gulland and Robinson designated the carbocyclic rings of the morphine skeleton as I, II, and III. In our 1992 communication we extended this convention by labeling the nitrogen-containing bridge as ring IV. Although other systems have been introduced in recent years, we continue to use the original Robinson nomenclature in the discussion in this paper, see: Gulland, J. M.; Robinson, R. *Mem. Proc. Manchester Lit. Philos. Soc.* **1925**, *69*, 79.

10.1021/jo0513008 CCC: $33.50 © 2006 American Chemical Society
Published on Web 11/04/2005

SCHEME 1

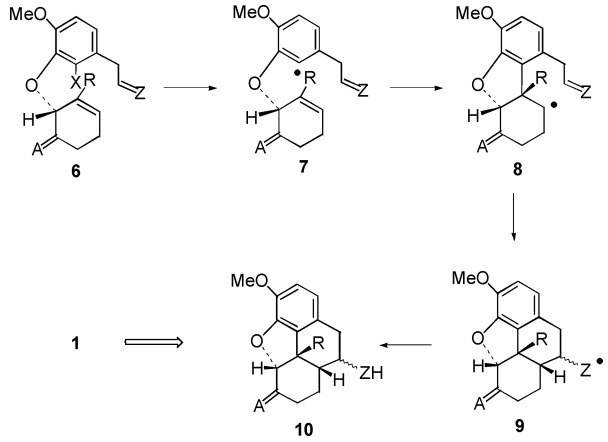


In light of continuing interest in morphine as a synthetic target and given the recurring use of the reductive hydroamination protocol in the context of the synthesis of morphinoids,[5,6] we disclose the full history and experimental procedures for this work. In addition, we describe herein the application of our tandem radical cyclization/reductive hydroamination approach to the asymmetric synthesis of (−)-dihydrocodeinone. (−)-Dihydrocodeinone has been converted to codeine, and codeine has been demethylated to morphine. Therefore, this paper constitutes a report of a formal asymmetric synthesis of morphine.

Background of the Tandem Radical Cyclization Strategy. Our strategy for the synthesis of the morphine alkaloids is based on the cyclization of an allyloxy aryl radical to produce a 3,3-disubstituted dihydrobenzofuran, a key structural component of the target molecules. In studies focused on the kinetics of radical cyclization (Scheme 1), Beckwith reported that the diazonium salt **2**, when treated with tributyltin hydride, affords a 71% yield of the 3,3-disubstituted dihydrobenzofuran **5**, presumably via the intermediate radicals **3** and **4**.[7] Thus, it appeared that a key structural feature of our target molecules might be generated in one step from a readily available precursor.

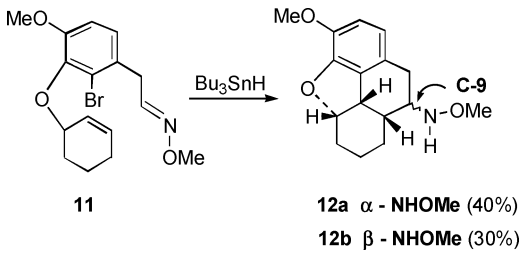
Furthermore, it seemed likely that the tandem radical cyclization strategy might be extended to cascades triggered by the formation of aryl radicals. For example (Scheme 2), cyclization of aryl radical **7** (from halo arene **6**) to cyclohexyl radical **8** might be followed by a second cyclization event to

SCHEME 2

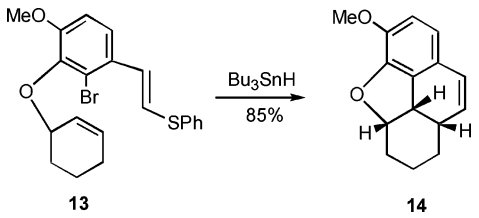


afford the tetracyclic radical **9**. Hydride trapping would then complete the conversion of an aryl allyl ether to an advanced morphine intermediate **10**.

A preliminary study showed that the tandem radical closure of substrates of this type, specifically **11**, provide efficient preparations of the desired *cis*,*cis*-tetracycles (**12a** and **12b**).[8] However, this and a related study[9] suggested that a reaction of this general type is unlikely to generate products in which the C-9 center is formed with stereocontrol.



Therefore, we modified our approach to one in which the cyclization would produce a functionalized but not tetrahedral C-9, as in the closure of **13** to **14**. The C-9 center might then be introduced in a subsequent step.



The remaining challenges for application of this methodology in the total synthesis of morphine were to (1) include additional required functionality in the cyclization substrate, (2) devise a practical method of closing the final ring IV of the target structure, (3) complete the morphine molecule, at least in a formal sense, and (4) demonstrate that the synthesis could be applied to an enantiomerically enriched intermediate in order to ultimately afford an enantiomerically enriched product. In this paper we are pleased to report having achieved all of these goals.

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(6) See also the nonreductive method of Trost: (a) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542. (b) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744.

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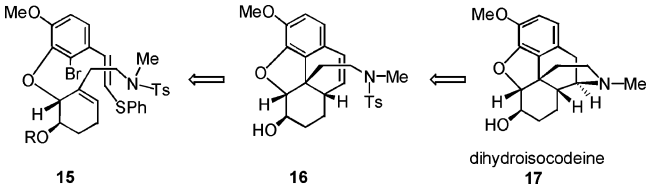
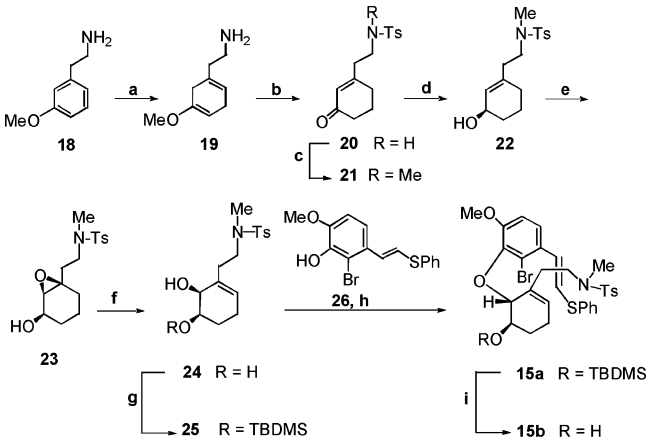
SCHEME 3



SCHEME 4



[a] Li/NH_3, *t*-BuOH, -68 °C, 97%; [b] TsCl, NEt_3, THF, then 1 N HCl, 81%; [c] MeI, K_2CO_3, acetone, 96%; [d] $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 97%; [e] *m*-CPBA, CH_2Cl_2, 0 °C, 92%; [f] $Ti(OiPr)_4$, C_6H_6, 70 °C, 85%; [g] TBDMSOTf, *i*-Pr_2NEt, -78 °C, 82%; [h] PBu_3, DEAD, THF, 0 °C, 83%; [i] 10% HF, CH_3CN, 98%.

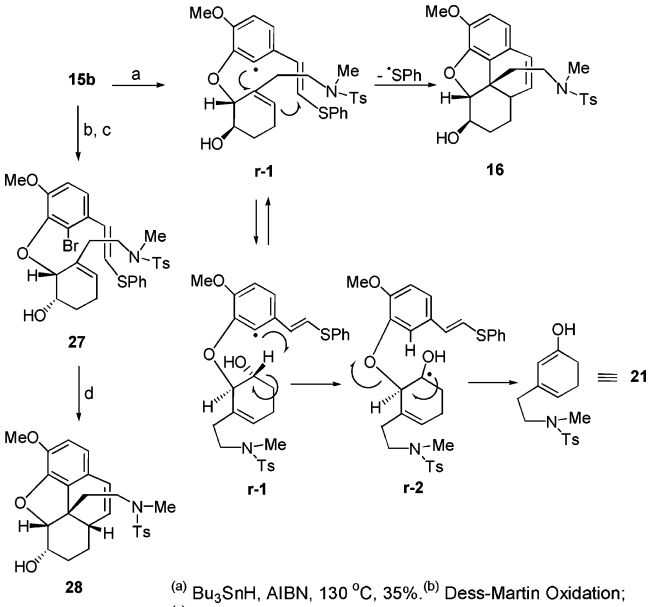
Results and Discussion

Preparation and Tandem Cyclization of Fully Functionalized Substrates. To generate a tandem closure product, which would exhibit maximum correspondence of functionality with that of the target structures, we needed a cyclization substrate in which the latent C-6 would bear a hydroxyl or keto group and in which the latent C-13 would bear an aminoethyl side chain. Furthermore, to optimize the overall efficiency of the final scheme, we sought routes in which the nitrogen functionality would be in place from the beginning of the synthesis. We chose, therefore, to base our synthesis on the key intermediate **15**. Scheme 3 shows the retrosynthetic analysis which drove our experiments. We anticipated that the tandem closure of the aryl radical derived from bromoarene **15** would give tetracycle **16**. Conversion of this product to the known morphine intermediate, dihydroisocodeine (**17**), would require only deprotection and formation of the C9−N bond.

On the basis of our model studies[9,10] we expected to be able to prepare substrate **15** (Scheme 4) by Mitsunobu coupling of phenol **26** and cyclohexenol **25** and both coupling partners to be readily available. These assumptions proved to be correct.

Preparation of alcohol **25** required seven steps and was achieved in a straightforward fashion. Birch reduction of *m*-methoxyphenethylamine afforded the nonconjugated dienol ether **19**. Tosylation of the amino group followed by hydrolysis of the enol ether afforded enone **20**. N-Alkylation[11] gave enonesulfonamide **21**, and Luche reduction[12] afforded allylic alcohol **22**. Peracid epoxidation of cyclohexenol **22** yielded the *cis*-epoxy alcohol **23**. Cyclohexenediol **24** was prepared by regioselective isomerization[13] of epoxy alcohol **23** with $Ti(OiPr)_4$ according to the Sharpless protocol. Silylation of the less hindered hydroxyl group of *cis*-diol **24** afforded the target monoprotected diol **25**.

SCHEME 5



[a] Bu_3SnH, AIBN, 130 °C, 35%. [b] Dess-Martin Oxidation; [c] $NaBH_4$, MeOH-THF, 0 °C, 51% (for **15b** to **27**); [d] Bu_3SnH, AIBN, 130 °C, 20-30%.

Preparation of the cyclization substrate required coupling of alcohol **25** with phenol **26**, which was obtained in one step from condensation of bromoisovanillin with diethyl phenylthiomethylphosphonate. The key step was accomplished by Mitsunobu coupling, affording aryl ether **15a**. Removal of the silyl protecting group generated alcohol **15b** (R = H), which proved to be a suitable substrate for the proposed radical-initiated reaction. When heated with Bu_3SnH (0.035 M) and AIBN in benzene in a sealed tube (130 °C), bromoaryl ether **15b** underwent the projected tandem cyclization/elimination sequence (Scheme 5) to afford the tetracyclic styrene **16** in a modest but serviceable 35% yield. Chatgilialoglu's reagent, tris(trimethylsilyl)silane,[14] effected the same transformation, affording the desired styrene **16** in 20−30% yield.

A byproduct in the tributyltin hydride-initiated reaction, isolated in 11% yield, proved to be ketone **21**. Formation of ketone **21** may be the result of intramolecular hydrogen abstraction from the homoallylic position which bears the hydroxyl group in radical **r-1** (Scheme 5). The α-hydroxy radical **r-2** could then expel the adjacent phenoxide radical to produce the conjugated dienol corresponding to enone **21**.

We reasoned that we might improve the yield of the cyclization step by using a modified substrate. We assumed that the aryl radical derived from the *cis*-hydroxy ether **27**, the epimer of **15b**, would undergo the tandem closure but be unable to abstract a hydrogen from the homoallylic carbinol carbon (as in **r-1**) because of geometric constraints. Attempts to prepare alcohol **27** from alcohol **15b**, under the standard Mitsunobu conditions,[15] led only to the recovery of starting material.

(10) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933.
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(15) Mitsunobu, O. *Synthesis* **1981**, 1.

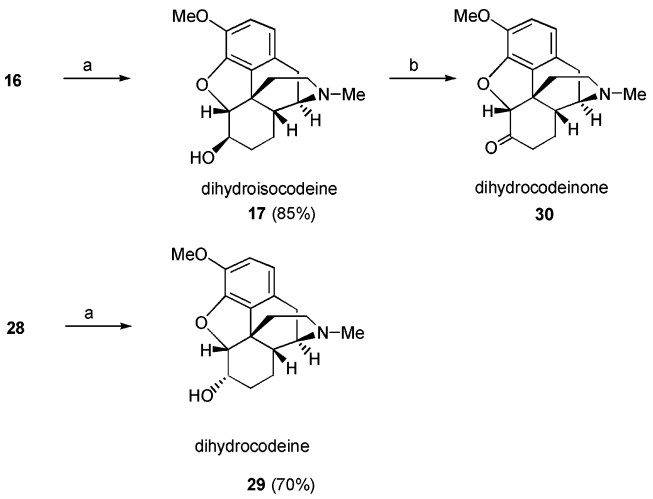
However, Dess−Martin oxidation[16] of **15b** followed by immediate sodium borohydride reduction of the intermediate β,γ-enone (Scheme 5) allowed the formation of the desired stereoisomeric alcohol **27**. The tributyltin hydride cyclization of this substrate afforded a 20−30% yield of styrene **28** with no detectable byproduct **21**. Although the cyclization reaction of substrate **27** did not produce the fragmentation byproduct, the yield of tetracyclic material was not improved.

Closure of Ring IV. With ready access to tosylamides **16** and **28**, we were now in a position to consider the completion of the morphine skeleton by closure of the final ring. We postulated that the C9−N bond connection would result from the intramolecular addition of an electrophilic aminyl radical to the electron-rich styrene via the stable benzylic radical. N-Centered radicals are available from N-functionalized amines.[17] Therefore, we reviewed the standard methods for desulfonation of sulfonamides, focusing first and foremost on the dissolving metal reduction which we viewed as particularly intriguing in the present context. It seemed possible that the nitrogen radical (or anion), generated by reductive detosylation of intermediate **16**, might add to the β-carbon of the styrene moiety, affording dihydroisocodeine (**17**) directly.

Although the reductive desulfonation of olefinic sulfonamides had not previously resulted in a cyclization event,[18] treatment of tosylamide **16** with Li/NH_3 in the presence of *t*-BuOH (−78 °C) afforded (±)-dihydroisocodeine (**17**) in 85% yield (see Scheme 6). Likewise, treatment of sulfonamide **28** (Scheme 6) with Li/NH_3 at −78 °C afforded (±)-dihydrocodeine (**29**)[19] in 70% yield. This type of closure provides an efficient means of connecting the C9−N17 bond of the morphine ring system. Others have used it in the elaboration of morphinan intermediates.[5,6,20] However, it is not representative of a general transformation for the closure of piperidine rings.[21]

Formal Syntheses of (±)-Morphine. The cyclizations of tosylamides **16** and **28** constitute formal total syntheses of morphine. Both dihydroisocodeine (**17**)[22] and dihydrocodeine (**29**)[23] have been oxidized to dihydrocodeinone (**30**, Scheme 6), which has been converted to codeine (**1b**).[24] Facile O-demethylation of codeine provides morphine (**1a**).[25] Of the two variations in this approach, the former, proceeding through intermediate **16** and dihydroisocodeine (**17**), is shorter and allows for a higher overall yield. Therefore, we applied this synthesis in the chiral series.

SCHEME 6



[(a)] Li, NH_3, *t*-BuOH, -78 °C, THF, 10 min; [(b)] Swern Oxidation, 83%.

Chiral Synthesis of (−)-Morphine Alkaloids. The asymmetric synthesis of morphine alkaloids by the approach described above requires chiral alcohol (*R*)-**22**. In principle, this chiral starting material would be available by either a chiral reduction[26] of enone **21** or a Sharpless kinetic resolution[27] of the racemic allylic alcohol **22**. Although chiral reduction of 3-substituted-2-cyclohexenones generally does not proceed with good enantiomeric excess, Terashima's reagent had been reported to reduce 3-methyl-2-cyclohexenone with 90% ee.[28] In our studies, however, Terashima's reagent reduced unsaturated ketone **21** to afford allylic alcohol **22** with only 5% enantiomeric excess. We obtained better results with the Corey−Bakshi−Shibata (CBS) (*S*)-oxazaborolidine-catechol borane reagent,[29] which produced the desired (*R*)-enantiomer of alcohol **22** with a 35−40% enantiomeric excess from reduction of ketone **21**. An attempt to use this procedure in conjunction with a Sharpless kinetic resolution[30] yielded material in which the enantiomeric excess was improved to 44%.

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(19) The NMR spectrum of (±)-dihydrocodeine was identical to that of an authentic sample of (−)-dihydrocodeine, prepared by the hydrogenation of codeine (Rapoport, H.; Payne, G. B. *J. Org. Chem*. **1950**, *15*, 1093).

(20) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Org. Lett*. **2002**, *4*, 4515.

(21) The factors required for "trapping" of a reactive N-centered species, during the reductive detosylation, are the subject of current study in our laboratories.

(22) In our studies Swern oxidation of dihydroisocodeine **17** afforded (±)-dihydrocodeinone (**30**) in 83% yield. When applied in the chiral series Swern oxidation of (−)-**17** produced 80% of (−)-**30**.

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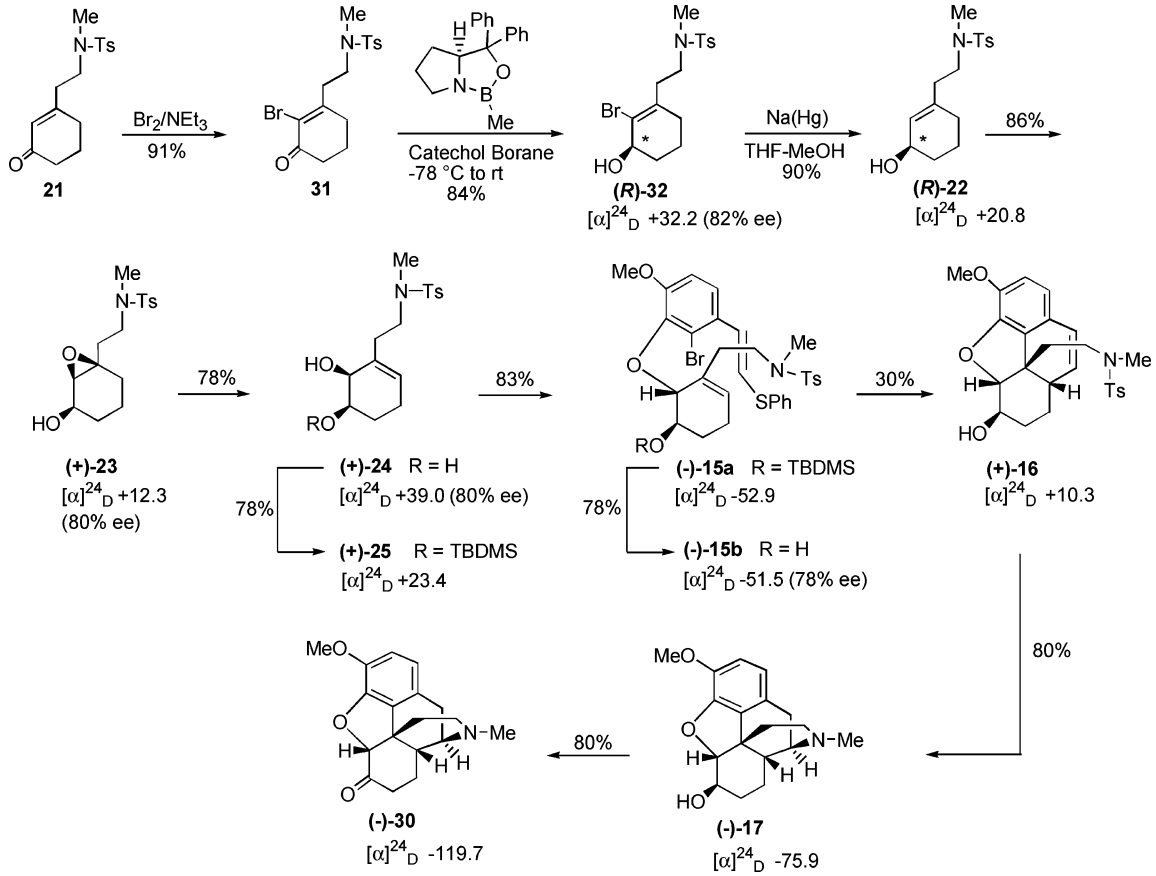
SCHEME 7



In the absence of an efficient direct method for producing alcohol **22** in high ee we resorted to an indirect strategy (see Scheme 7) based on the asymmetric reduction of a 2-bromocyclohexenone. Although 2-unsubstituted cyclohexenones give relatively low enantiomeric excesses when subjected to the CBS reducing system, 2-bromocyclohexenone is reported to be reduced in a 91% ee under these conditions.[29b] Thus, bromination of enone **21**, followed by treatment with triethylamine, afforded bromoenone **31** in 91% yield. Reduction of **31** with (*S*)-oxazaborolidine (2.4 equiv) and catechol borane afforded alcohol (*R*)-**32** with enantiomeric excesses ranging from 82% to 96%.[31] When reduction was performed on a 1 g scale, bromo alcohol (*R*)-**32** was obtained in 84% yield with an 82% enantiomeric excess as indicated by Mosher ester analysis. (It is important to note that reaction of **31** with a catalytic amount (0.1 equiv) of oxazaborolidine was extremely slow; starting material was recovered even after stirring at room temperature for 24 h with excess catechol borane.) Attempted removal of bromine from (*R*)-**32** by metal halogen exchange was not successful. When bromo alcohol (*R*)-**32** was treated with *t*-BuLi or *n*-BuLi at various temperatures, a mixture of starting material and unidentified products was obtained. However, reduction by sodium amalgam in MeOH−THF proved to be a suitable method for debromination. Thus, bromo alcohol (*R*)-**32** (82% ee) was converted to allylic alcohol (*R*)-**22** in 90% yield (Scheme 7); this material was shown to have an 80% ee by Mosher ester analysis. Having established access to chiral alcohol **22** we were poised to complete an asymmetric synthesis of (−)-morphine alkaloids.

As we had determined that there was no practical advantage in a scheme based on the α-alcohol **27**, we chose the more direct route in which the *β*-alcohol **15b** is the substrate for tandem cyclization. In fact, allylic alcohol (*R*)-**22** was converted to (−)-dihydroisocodeine [(−)-**17**] by application of Schemes 4 (**22** → **15b**), 5 (**15b** → **16**), and 6 (**16** → **17**, **17** → **30**) as described above for the racemic synthesis. Yields, optical rotations, and enantiomeric excesses as calculated by Mosher ester analysis or comparison with optical rotation values for authentic materials are reported in Scheme 7 as well as in the Experimental Section. Synthetic (−)-dihydroisocodeine [(−)-**17**], prepared according to Scheme 7, had an $[\alpha]^{24}_D$ −75.9 in $CHCl_3$. A negative specific rotation ($[\alpha]^{28}_D$ −136 in $CHCl_3$)[32b,c] has been reported for dihydroisocodeine derived from natural materials.[32]

Swern oxidation of (−)-dihydroisocodeine (**17**) afforded (−)-dihydrocodeinone (**30**) in 80% yield (Scheme 7). Our synthetic (−)-dihydrocodeinone ($[\alpha]^{24}_D$ −119.7 in $CHCl_3$) was produced with approximately 75% ee, as calculated from the specific rotation of an authentic sample prepared from natural codeine

(30) For an example of a double kinetic resolution and references to procedures which couple a kinetic resolution with an enantioselective reaction, see: Brown, S. M.; Davies, S. G.; de Sousa, J. A. A. *Tetrahedron: Asymmetry* **1991**, *2*, 511.

(31) Reduction of **31** with $LiAlH_4$/Darvon Alcohol (Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. Reich, C. J.; Sullivan, G. R.; Mosher, H. S. *Tetrahedron Lett.* **1973**, 1505) afforded bromoallylic alcohol (*R*)-**32** in 70% yield with 84% ee.

(32) For the synthesis of (−)-dihydroisocodeine from natural codeine, see: (a) Baizer, M. M.; Loter, A.; Ellner, K. S.; Satriana, D. R. *J. Org. Chem.* **1951**, *16*, 543. (b) Ginsburg, P.; Elad, D. *J. Am. Chem. Soc.* **1956**, *78*, 3691. (c) Okuda, S.; Tsuda, K.; Yamaguchi, S. *J. Org. Chem.* **1962**, *27*, 4121. (d) Chatterjie, N.; Umans, J. G.; Inturrisi, C. E. *J. Org. Chem.* **1976**, *41*, 3624. (e) Brine, G. A.; Boldt, K. G.; Coleman, M. L.; Bradley, D. J.; Carroll, F. I. *J. Org. Chem.* **1978**, *43*, 1555. (f) Fuska, J.; Proska, B.; Fuskova, A.; Khandlova, A. *Acta Biotechnol.* **1988**, *8*, 291.

([α]$^{24}_D$ −159.1 in $CHCl_3$).[33,34] The synthesis of (−)-dihydrocodeinone completes a formal total synthesis of (−)-codeine (**1b**) and (−)-morphine (**1a**).

Conclusions

This convergent synthesis of the morphine alkaloids by radical cyclization illustrates the versatility of these processes for construction of multifunctional polycyclic compounds. In particular, it demonstrates the power of this methodology for "stitching" rings together to build convex ring systems. This synthesis is completely stereospecific. A single stereocenter, the first to be introduced in the synthetic scheme, controls the remaining four stereocenters in the target structure.

The key steps in this synthetic scheme come in sequence at the end of the synthesis. They are (1) the convergent step, the efficient Mitsunobu coupling of a readily available cyclohexene *cis*-diol derivative with a phenol to form the cyclization substrate, (2) the tandem radical cyclization of an aryl cyclohexenyl ether to produce a suitably functionalized tetracyclic styrene, and (3) completion of the morphine ring system by the reductive deprotection/hydroamination reaction.

The radical cyclization approach to morphine has proven amenable to asymmetric synthesis, affording (−)-dihydroisocodeine with 75% ee in a total of 13 steps and in an overall yield of 4.2% from the commercially available *m*-methoxyphenethylamine.

Experimental Section

(±)-Aryl Ether 15a. A solution of 0.25 mL (1.61 mmol) of diethyl azodicarboxylate in 5 mL of THF at 0 °C was treated dropwise with 0.4 mL (1.61 mmol) of tri-*n*-butylphosphine. The resulting solution was stirred at 0 °C for 10 min and then added dropwise at 0 °C to a THF solution (50 mL) containing 589 mg (1.34 mmol) of alcohol (±)-**25** and 495 mg (1.47 mmol) of phenol **26**. The reaction mixture was stirred in an ice bath for 4 h and then concentrated to give a yellow residue. Flash chromatography with EtOAc−Hex (1:4) afforded 842 mg (83%) of a colorless oil. IR ($CDCl_3$) 3040, 1596, 1585, 1474, 1333, 1286, 1204, 1086, 1033, 1004 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2 H, J = 8.2 Hz), 7.43 (dd, 2 H, J = 7.5, 1.5 Hz), 7.35 (t, 2 H, J = 7.6 Hz), 7.28 (d, 3 H, J = 8.2 Hz), 7.21 (d, 1 H, J = 8.7 Hz), 7.05 (d, 1 H, J = 15.3 Hz), 6.84 (d, 1 H, J = 8.7 Hz), 6.72 (d, 1 H, J = 15.3 Hz), 5.81 (d, 1 H, J = 4.8 Hz), 4.52 (s, 1 H), 3.95 (s, 1 H), 3.87 (s, 3 H), 3.35 (m, 1 H), 2.97 (m, 1 H), 2.72 (s, 3 H), 2.54 (m, 1 H), 2.44 (s, 4 H), 2.20 (d, 2 H, J = 10.0 Hz), 2.00 (m, 1 H), 1.67 (br s, 1 H), 0.76 (s, 9 H), −0.14 (s, 3 H), −0.19 (s, 3 H). 100.6 MHz ^{13}C NMR ($CDCl_3$) δ, 152.4, 144.3, 143.0, 135.1, 134.7, 130.6, 130.4, 130.3, 129.9, 129.5, 129.1, 127.4, 127.0, 124.6, 121.4, 119.4, 111.3, 79.2, 67.3, 55.8, 50.0, 35.1, 33.4, 25.8, 25.7, 25.1, 21.5, 20.8, 18.0, −5.1, −5.2. HRMS (FAB/NBA) for $C_{37}H_{48}O_5N^{79}BrS_2Si$: calcd, 757.1925; found, 757.1984.

(−)-Aryl Ether (15a). The above procedure was applied to (+)-**25** to afford a colorless oil, [α]$^{24}_D$ −52.9 (c = 0.07 in $CHCl_3$), in 83% yield.

Cyclization Substrate (±)-15b. A solution of 605 mg (0.8 mmol) of the silyl ether (±)-**15a** in 10 mL of CH_3CN was treated with 2 mL of 10% HF. The reaction mixture was stirred at room temperature for 24 h, quenched with water, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated to produce the crude product. Flash chromatography with EtOAc−Hex−acetone (1:3:1) yielded 503 mg (98%) of a foamy solid, mp 56−59 °C. IR ($CDCl_3$) 3515, 3044, 1580, 1474, 1330, 1285, 1156, 1026 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2 H, J = 8.2 Hz), 7.42 (dd, 2 H, J = 7.5, 1.4 Hz), 7.35 (t, 2 H, J = 7.6 Hz), 7.28 (m, 3 H), 7.20 (d, 1 H, J = 8.7 Hz), 7.02 (d, 1 H, J = 15.4 Hz), 6.85 (d, 1 H, J = 8.7 Hz), 6.71 (d, 1 H, J = 15.3 Hz), 5.82 (s, 1 H), 4.74 (d, 1 H, J = 3.6 Hz), 4.08 (br s, 1 H), 3.86 (s, 3 H), 3.32 (m, 1 H), 3.06 (m, 1 H), 2.73 (s, 3 H), 2.61 (m, 1 H), 2.41 (s, 4 H), 2.24−2.14 (m, 3 H), 1.97 (d, 1 H, J = 4.5 Hz), 1.77 (m, 1 H). 100.6 MHz ^{13}C NMR ($CDCl_3$) δ 152.1, 144.7, 143.1, 134.92, 134.90, 131.2, 130.3, 130.2, 130.1, 129.9, 129.5, 129.1, 127.2, 127.0, 124.7, 121.4, 118.9, 111.4, 80.2, 68.5, 55.8, 49.4, 34.7, 32.2, 25.4, 21.4. HRMS (FAB/NBA) for $C_{31}H_{34}O_5{}^{79}BrNS_2$: calcd, 643.1061; found, 643.1054.

(−)-15b. The above procedure was applied to aryl ether (−)-**15a** to afford a white solid, mp 52−54 °C, in 95% yield. This material had [α]$^{24}_D$ −51.5 (c = 0.08 in $CHCl_3$), corresponding to a 78% ee by Mosher ester analysis.

Cyclization of Alcohol (±)-15b. Tetracyclic Sulfonamide (±)-16 and Enone 21. A solution of 120 mg (0.187 mmol) of the alcohol (±)-**15b**, 75 μL (0.280 mmol) of Bu_3SnH, and a catalytic amount of AIBN (0.1−0.2 equiv) in 8 mL of benzene was heated in a sealed tube at 130 °C. A small amount of AIBN was added every 8 h in order to maintain the radical chain. After 35 h the reaction mixture was concentrated, and the residue was dissolved in Et_2O and then stirred vigorously with 10% KF for 2 h. The ether phase was separated, washed with brine, dried over Na_2SO_4, and concentrated to produce a yellow residue. Preparative TLC on silica gel with EtOAc−Hex−acetone (1:3:1) afforded 30 mg (35%) of sulfonamide (±)-**16** as a yellow oil. IR ($CDCl_3$) 3500, 3057, 1498, 1446, 1333, 1153, 1086 cm^{-1}. 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 2 H, J = 8.2 Hz), 7.28 (d, 2 H, J = 8.4 Hz), 6.70 (d, 1 H, J = 8.1 Hz), 6.64 (d, 1 H, J = 8.1 Hz), 6.37 (d, 1 H, J = 9.5 Hz), 5.83 (dd, 1 H, J = 9.5, 5.7 Hz), 4.54 (d, 1 H, J = 7.2 Hz), 3.89 (s, 3 H), 3.46 (m, 1 H), 3.13 (m, 1 H), 2.84 (m, 1 H), 2.61 (s, 3 H), 2.48 (m, 1 H), 2.42 (s, 5 H), 1.88−1.65 (m, 2 H), 1.35 (m, 1 H), 0.93 (m, 1 H). HRMS (EI) for $C_{25}H_{29}O_5NS$: calcd, 455.1766; found, 455.1756. Also recovered from the preparative TLC plate was 7 mg (11%) of enone **21**.

(+)-Tetracyclic Sulfonamide 16. Application of the above procedure to alcohol (−)-**15b** afforded a yellow oil, [α]$^{24}_D$ +10.3 (c = 0.007 in $CHCl_3$), in 30% yield.

(±)-Dihydroisocodeine (17). A 10 mg (1.44 mmol) amount of lithium metal was added to a solution of THF−anhydrous ammonia (10 mL) containing 20 μL (0.21 mmol) of *t*-BuOH at −78 °C. The resulting dark blue solution was stirred at −78 °C for 5 min, and 10 mg (0.022 mmol) of tetracyclic styrene (±)-**16** in THF (0.5 mL) was then added dropwise. The initial blue color was discharged after the addition of (±)-**16**, and an additional 5 mg (0.72 mmol) of lithium metal was added until the blue color became persistent. After stirring at −78 °C for 10 min the reaction was quenched with a MeOH−aqueous NH_4Cl solution, and the resulting mixture was extracted with CH_2Cl_2 (20 mL). After the aqueous phase was washed with CH_2Cl_2 (3 × 15 mL) the combined organic solution was dried over Na_2SO_4 and concentrated. Purification by standard acid−base extraction afforded 5.6 mg (85%) of a white solid, mp 134−136 °C. IR (CH_2Cl_2) 3590 (s), 3370 (br), 3051, 1633, 1603, 1504, 1443, 1087, 1057 cm^{-1}. 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.73 (d, 1 H, J = 8.2 Hz), 6.64 (d, 1 H, J = 8.2 Hz), 4.36 (d, 1 H, J = 6.6 Hz), 3.87 (s, 3 H), 3.44 (m, 1 H), 3.14 (br s, 1 H), 3.01 (d, 1 H, J = 18.4 Hz), 2.54 (d, 1 H, J = 12.0 Hz), 2.43 (s, 3 H), 2.38 (dd, 1 H, J = 17.9, 4.6 Hz), 2.26−2.17 (m, 2 H), 1.91−1.80 (m, 2 H), 1.71 (dd, 1 H, J = 12.5, 2.1 Hz), 1.59 (m, 1 H), 1.37 (q, 1 H, J = 12.7 Hz), 0.98 (q, 1 H, J = 13.0 Hz). 100.6 MHz ^{13}C NMR

(33) We prepared (−)-dihydrocodeinone in two steps from natural codeine. Codeine was first hydrogenated to (−)-dihydrocodeine (Rapoport, H.; Payne, G. B. *J. Org. Chem.* **1950**, *15*, 1093), followed by a Swern oxidation (DMSO/$(COCl)_2$) to yield dihydrocodeinone.

(34) Recrystallized (−)-dihydroisocodeine has an [α]$^{24}_D$ −136, see refs 32b,c. Enantiopure (−)-dihydrocodeinone is crystalline, mp 193.5−194.5 °C, and has an [α]$^{24}_D$ −203, see: Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.

($CDCl_3$) δ 144.1, 143.6, 130.3, 126.2, 119.0, 113.4, 97.1, 73.2, 59.5, 56.4, 47.0, 43.0, 42.7, 42.6, 35.3, 30.0, 23.6, 20.2. HRMS (CI) for $C_{18}H_{23}O_3N$ (M^+): calcd, 301.1677; found, 301.1690.

(−)-Dihydroisocodeine (17). The above procedure was applied to sulfonamide (+)-**16** to afford a 70−80% yield of (−)-dihydroisocodeine as a yellow oil, $[\alpha]^{24}_D$ −75.9 (c = 0.003 in $CHCl_3$).

Alcohol (*R*)-32. A 0.70 g (1.82 mmol) amount of bromoenone **31** in toluene (5 mL) was added to a solution of 4.36 mmol of freshly prepared (*S*)-oxazaborolidine[29c] in 35 mL of toluene at −78 °C. The resulting mixture was stirred at −78 °C for 10 min, and 4.40 mL (4.40 mmol) of catechol borane 1.0 M in THF was then added. The reaction mixture was warmed gradually to room temperature overnight, under stirring. Water was added to quench the hydride excess, and the organic phase was separated. The organic phase was first washed with 10% HCl and then 10% NaOH, dried over Na_2SO_4, and concentrated to produce the crude alcohol. Purification by flash chromatography on silica gel with EtOAc−Hex−acetone (1:3:1) afforded 590 mg (84%) of a colorless viscous oil (82% ee by Mosher ester analysis), $[\alpha]^{24}_D$ +32.2 (c = 0.03 in $CHCl_3$). IR (CH_2Cl_2) 3589, 1649 (w), 1596, 1091 cm^{-1}. 250 MHz ^1H NMR ($CDCl_3$) δ 7.68 (d, 2 H, J = 8.3 Hz), 7.33 (d, 2 H, J = 8.0 Hz), 4.25 (d, 1 H, J = 4.2 Hz), 3.25−2.98 (m, 2 H), 2.78 (s, 3 H), 2.45 (s, 5 H), 2.30 (d, 1 H, J = 4.5 Hz), 2.18 (m, 2 H), 1.92−1.60 (m, 4 H). 100.6 MHz ^{13}C NMR ($CDCl_3$) δ 143.4, 137.4, 134.8, 129.7, 127.3, 125.0, 71.0, 47.6, 35.6, 35.0, 32.0, 31.9, 21.5, 18.1. MS (CI, NH_3) *m*/*e*: 386 [M^+ − H] for ^{79}Br.

Acknowledgment. This research was supported by the National Science Foundation and the National Institutes of Health. NMR spectra were acquired with a spectrometer purchased with funds from the National Science Foundation. Mass spectra were acquired with a spectrometer purchased with funds from the Division of Research Resources of the National Institutes of Health. For part of the period during which this work was carried out, K.A.P. held an NSF Career Advancement Award.

Supporting Information Available: General methods, experimental details for compounds **19**−**31**, and a general procedure for the preparation of MTPA esters; copies of ^1H and ^{13}C NMR spectra (PDF) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0513008