Acknowledgment. These studies were supported by the National Science Foundation (CHE-9011593). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Funds for the purchase of the X-ray diffraction equipment were made available from NSF Grant CHE-85-14495. F.J.F. gratefully acknowledges financial support from an Alfred P. Sloan Foundation Research Fellowship. The early creative input of Dr. Theodore A. Budzichowski is gratefully acknowledged.

Supplementary Material Available: Listings of experimental procedures and characterization data for **3**, **5**, and **6** and X-ray crystal data for **6** including experimental procedures, tables of crystal data, atomic coordinates, thermal parameters, bond lengths, and bond angles, and ORTEP figures (25 pages); table of calculated and observed structure factors for **6** (30 pages). Ordering information is given on any current masthead page.

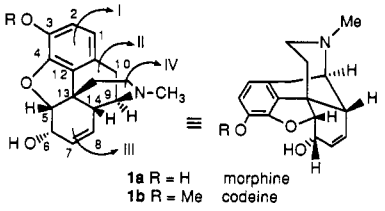
Convergent Synthesis of (±)-Dihydroisocodeine in 11 Steps by the Tandem Radical Cyclization Strategy. A Formal Total Synthesis of (±)-Morphine†,‡

Kathlyn A. Parker* and Demosthenes Fokas

Department of Chemistry, Brown University
Providence, Rhode Island 02912

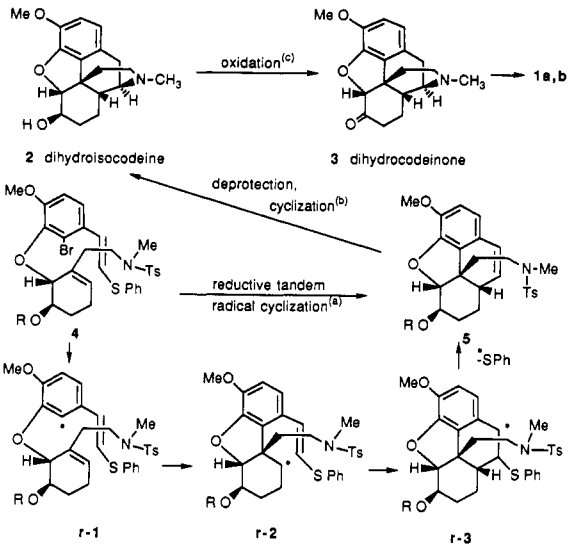
Received August 13, 1992

Morphine (**1a**) and its derivatives and analogs continue to hold the fascination of chemists and neuroscientists.[1] For the synthetic chemist, this small molecule offers an interesting challenge.[2] Its intrinsic complexity arises from the presence of five contiguous chiral centers, four of which define the ring junctions. The problem of establishing these chiral centers is especially difficult because the C-13 center is quaternary and bears an aryl substituent.[3,4]



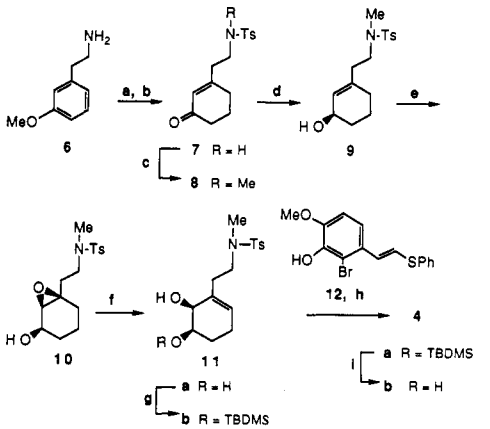
Our approach to the construction of the morphine ring system is based on a tandem cyclization of an ortho allyloxy aryl radical.[5] We are now pleased to report the short (11 steps from commercial materials), convergent, and stereospecific synthesis of (±)-dihydroisocodeine (**2**).[6] Oxidation to dihydrocodeinone (**3**) completes the formal total synthesis of (±)-morphine (Scheme I).

Scheme I. Strategy for the Synthesis of the Morphine Alkaloids[a]



[a] (a) Bu_3SnH, AIBN, C_6H_6, 130 °C, 35 h, 35% of **5** (R = H) from **4b** (R = H). (b) Li, *t*-BuOH, NH_3, THF, −78 °C, 10 min, 85%. (c) $(COCl)_2$, DMSO, 0 °C to room temperature, 2.5 h, 83%.

Scheme II[a]



[a] (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%.

By analogy to transformations in our model studies,[5b,c] we predicted that aryl ether **4** would undergo tandem closure to tetracyclic styrene **5** via an intramolecular tandem cyclization. We expected the C-12 aryl radical (**r-1**), derived from substrate **4**, to attack the nearer but more substituted end of the cyclohexene double bond, generating the 5-membered dihydrofuran ring and establishing the desired cis fusion between this ring and ring III. Radical **r-2** was expected to add to the β-carbon of the styrene double bond to give radical **r-3**, a resonance-stabilized radical which is not especially strained. This second closure would form the 6-membered ring II, completing the desired tetracyclic carbon skeleton and establishing the cis fusion between rings II and III. Finally, elimination of the phenylthio group from the styryl radical would give the key intermediate **5**.

In order to achieve the morphine ring system, the final critical bond connection, that from C-9 to the nitrogen, would have to

† Dedicated to Professor Gilbert Stork.

‡ This work was described at the 204th National Meeting of the American Chemical Society, Washington, DC, August 1992.

(1) A review entitled "Medicinal Chemistry of Central Analgetics" by D. Lednicer includes a concise history of morphine and a discussion of the development of structural analogs; see: Lednicer, D. *Central Analgetics*; John Wiley & Sons, Inc.: New York, 1982; pp 137-213.

(2) For a recent formal total synthesis and many references to much of the previous work on this problem, see: Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959. In addition, see: Magnus, P.; Coldham, I. *J. Am. Chem. Soc.* **1991**, *113*, 672.

(3) (a) Rieke, R. D.; Schulte, L. D.; Dawson, B. T.; Yang, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 8388. (b) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260 and references therein.

(4) (a) The intramolecular Heck reaction has been shown to be an efficient method for the generation of a quaternary center which bears an aryl group; see: Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) The use of this methodology for the preparation of dihydrothebainone was recently reported by Overman at the 9th International Conference on Organic Synthesis, Montreal, Quebec, Canada, July 1992.

(5) (a) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833. (b) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. (c) Parker, K. A.; Fokas, D. Submitted for publication.

(6) For (−)-dihydroisocodeine, see: Makleit, S.; Bognár, R. *Acta Chim. Acad. Sci. Hung.* **1969**, *59*, 387 and references therein.

0002-7863/92/1514-9688$03.00/0

be made. The literature contains some approaches to this linkage[7,8] and others can be imagined.[9] Therefore, we decided to test the cyclization of aryl ether **4**, which we expected to be available from the coupling of the appropriate phenol and cyclohexenediol derivative (see Scheme II).

Allylic alcohol **11b** was prepared in seven steps from commercially available *m*-methoxyphenethylamine (**6**). Birch reduction of phenethylamine **6**, tosylation of the amino group of the resulting nonconjugated dienol ether, and hydrolysis afforded enone **7**. N-Alkylation[10] followed by reduction of the keto group according to Luche's procedure[11] gave allylic alcohol **9**. Cyclohexenediol **11a** was prepared by epoxidation and regioselective isomerization[12] of the resulting epoxy alcohol **10** with $Ti(OiPr)_4$, according to the Sharpless protocol. Silylation of the less hindered hydroxyl group of *cis*-diol **11a** afforded the target monoprotected diol **11b**.

Alcohol **4b** was obtained by Mitsunobu coupling[13] of alcohol **11b** with phenol **12**[14] followed by removal of the silyl protecting group. This compound proved to be a suitable substrate for radical-initiated cyclization.

When heated with Bu_3SnH (0.035 M) and AIBN in benzene in a sealed tube (130 °C), bromoaryl ether **4b** underwent tandem cyclization followed by elimination of the *S*-phenyl radical to afford the tetracyclic styrene **5** (R = H) in 35% yield.[15,16]

With ready access to tosylamide **5**, we were now ready to consider the completion of the morphine skeleton by closure of ring IV. Of the methods available for the cleavage of sulfonamides, those which employ dissolving metal reducing conditions[17] seemed especially attractive for the task at hand. One could imagine that the nitrogen radical (or anion) generated by reductive detosylation of intermediate **5** might add to the β-carbon of the styrene moiety, affording dihydroisocodeine directly. *In fact, treatment of tosylamide 5 with Li/NH_3 in the presence of t-BuOH (−78 °C) did afford* (±)*-dihydroisocodeine* (**2**) *in 85% yield* (refer to Scheme I). This unprecedented closure[18] provides a remarkably simple solution to the final bond connection required for the morphine ring system.

Swern oxidation of dihydroisocodeine afforded (±)-dihydrocodeinone (**3**)[19] in 83% yield. When combined with the efficient procedures for the conversion of dihydrocodeinone to codeine (**1b**)[20] and the facile O-demethylation of codeine to morphine (**1a**),[21] Scheme I represents the formal total synthesis of (±)-codeine and (±)-morphine.

This synthesis illustrates the versatility of radical cyclization processes for the construction of multifunctional polycyclic compounds. In particular, it demonstrates the power of this methodology for "stitching" rings together to build convex ring systems. In addition, it introduces a new and convenient method for the joining of certain carbon–nitrogen bonds. It is potentially amenable to chiral synthesis, a modification which is currently being pursued in our laboratories.

Acknowledgment. This research was supported by the National Science Foundation and the National Institutes of Health. NMR spectra were acquired with a Bruker AM400WB spectrometer, purchased with funds from the National Science Foundation. The Kratos MS-80 mass spectrometer was purchased with funds from the Division of Research Resources of the National Institutes of Health.

Supplementary Material Available: Listings of experimental procedures and IR and ^1H NMR spectra for **2-5** and **7-12** (7 pages). Ordering information is given on any current masthead page.

(7) For previously reported methods of making this connection, see: (a) Gates, M.; Woodward, R. B.; Newhall, W. F.; Künzli, R. *J. Am. Chem. Soc.* **1950**, *72*, 1141. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109. (b) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694.

(8) For closures in model systems, see: (a) Broka, C. A.; Gerlits, J. F. *J. Org. Chem.* **1988**, *53*, 2144. (b) Sdassi, H.; Revial, G.; Pfau, M.; d'Angelo, J. *Tetrahedron Lett.* **1990**, *31*, 875. (c) Monkovic, I.; Wong, H. *Can. J. Chem.* **1976**, *54*, 883. Also see: Chandler, M.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1984**, 322.

(9) See, for example: Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275 and references therein.

(10) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 3839.

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

(12) Morgans, D. J., Jr.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.

(13) Mitsunobu, O. *Synthesis* **1981**, 1.

(14) Phenol **12** was prepared in two steps by bromination[22] of commercially available isovanillin and reaction of the resulting bromoisovanillin with diethyl [(phenylthio)methyl]phosphonate.[23]

(15) A byproduct in the tributyltin hydride-initiated reaction, isolated in 11% yield, proved to be ketone **8**. The formation of ketone **8** may be the result of intramolecular hydrogen abstraction from the homoallylic position which bears the hydroxyl group in radical **r-1**. The α-hydroxy radical could then expel the adjacent phenoxide radical to give the conjugated dienol corresponding to enone **8**.

(16) Tris(trimethylsilyl)silane also converted bicyclic **4b** to tetracyclic **5**; however, the yield of isolated product was only 20–30%. See: Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1989**, *54*, 2492.

(17) (a) Heathcock, C. H.; Smith, K. M.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 5022. (b) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.

(18) Reductive desulfonation of olefinic tosylamides does not generally result in cyclization (see: Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650). The Li/NH_3/*t*-BuOH-induced detosylation of *N*-(5-phenyl-4-pentenyl)-*p*-toluenesulfonamide affords 5-phenylpentan-1-amine (K. A. Parker, D. Fokas, D. Lee, unpublished results); also note the example in ref 17a. It is likely that the "trapping" of a reactive N-centered species during the reductive detosylation of tetracycle **5** is rapid because of entropic factors. (For the fate of δ,ε-unsaturated aminyl radicals under various reaction conditions, see: Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317.) A study of the mechanism and scope of this reaction is currently underway in our laboratories.

(19) This product had spectra which were identical to those of (−)-dihydrocodeinone obtained by hydrogenation and Swern oxidation of natural codeine.

(20) (a) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171. (b) Iijima, I.; Rice, K. C.; Silverton, J. V. *Heterocycles* **1977**, *6*, 1157.

(21) (a) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164. (b) Lawson, J. A.; DeGraw, J. I. *J. Med. Chem.* **1977**, *20*, 165.

(22) Hazlet, S. E.; Brotherton, R. J. *J. Org. Chem.* **1962**, *27*, 3253.

(23) (a) Green, M. *J. Chem. Soc.* **1963**, 1324. (b) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777.

An Allyl Radical–Dioxygen Caged Pair Mechanism for *cis*-Allylperoxyl Rearrangements

Karen A. Mills, Sarah E. Caldwell, George R. Dubay, and Ned A. Porter*

Department of Chemistry
Duke University
Durham, North Carolina 27706
Received August 10, 1992

Rearrangements of allylperoxyl radicals have been known since the late 1950s,[1] yet the mechanism for this reaction is still open to debate.[2-6] Previous work has demonstrated that optically pure *trans*-allylperoxyl radicals derived from methyl oleate rearrange in a highly stereoselective process with minimal atmospheric oxygen incorporation, suggesting a concerted 2,3 free-radical pathway.[7,8] However, recent theoretical investigations on allylperoxyl radicals have failed to find a concerted transition state for the rearrangement, but rather support a dissociative process involving an allyl radical intermediate.[9] A mechanism consistent

(1) Schenck, G. D.; Neumuller, O. A.; Eisfeld, K. C. *Angew. Chem.* **1958**, *70*, 595.

(2) Porter, N. A.; Kaplan, J. K.; Dussault, P. H. *J. Am. Chem. Soc.* **1990**, *112*, 1266.

(3) Brill, W. F. *J. Chem. Soc., Perkin Trans. 2* **1984**, 621.

(4) Brill, W. F. *J. Am. Chem. Soc.* **1965**, *87*, 3286.

(5) Porter, N.; Zuraw, P. *J. Chem. Soc., Chem. Commun.* **1985**, 1472.

(6) (a) Beckwith, A. L.; Davies, A. G.; Davison, I. G. E.; Maccoll, A.; Mruzek, M. H. *J. Chem. Soc., Chem. Commun.* **1988**, 475. (b) Avila, D. V.; Davies, A. G.; Davison, I. G. E. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1847. (c) Davies, A. G.; Kinart, W. J. *J. Chem. Res.* **1989**, 22. (d) Dang, H.; Davies, A. G.; Davison, I. G. E.; Schiesser, C. H. *J. Org. Chem.* **1990**, *55*, 1432.

(7) Porter, N. A.; Sullivan Wujek, J. *J. Org. Chem.* **1987**, *52*, 5085.

(8) Dussault, P. H.; Porter, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 6276.

(9) Boyd, S. L.; Boyd, R. J.; Shi, Z.; Barclay, R. C.; Porter, N. A. Submitted for publication.

0002-7863/92/1514-9689$03.00/0