Asymmetric Synthesis of (+)-Morphine. The Phenanthrene Route Revisited

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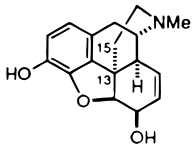
Morphine (**1**) continues to occupy a position of unique clinical importance in medicine, its wide prescription for the treatment of severe pain and for relief of suffering in the terminally ill placing it foremost among analgesic agents.[1] Synthesis of morphine engaged the interest of organic chemists even before its complete structure was revealed,[2] and many optimistic schemes were devised in the hope that a route could be found from a hydrophenanthrene precursor.[3] Subsequent efforts brought numerous syntheses of (±)-morphine,[4] but asymmetric approaches have encountered difficulties that have made this aspect of morphine synthesis a significant challenge.[5] In fact, it was not until Overman's publication in 1993 that a synthesis of natural (−)-morphine was achieved by a route which did not involve resolution.[6] We now report an asymmetric synthesis of morphine having its origins in those early studies[7] that viewed the phenanthrene nucleus as an appropriate platform upon which to construct the morphine framework. Because our interest is primarily in pharmacological properties of the unnatural enantiomorph, particularly its binding to



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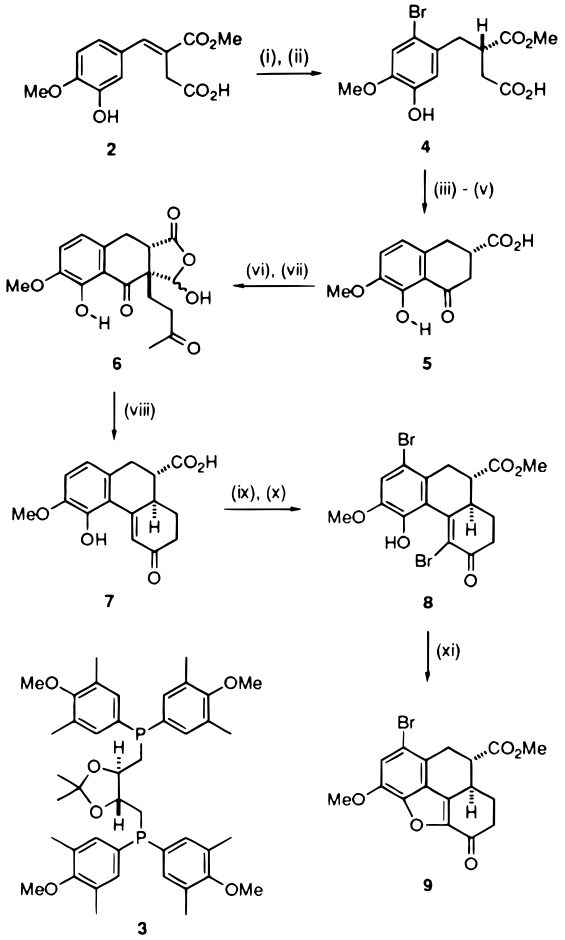
opioid receptors, the focus of our synthetic work has been (+)-morphine (**1**).[8] Our approach to **1** departs from all previous schemes by invoking as the key step a carbenoid C−H insertion to establish the C13−C15 bond.[9] This reaction is used to fashion a pentacyclic skeleton from which the piperidine ring of **1** evolves at a final stage.

Scheme 1[a]



[a] (i) H_2, $[Rh(COD)Cl]_2$, (4*R*,5*R*)-(−)-MOD-DIOP, 100%, (94% ee); (ii) Br_2, HOAc, 93%; (iii) MsOH, P_2O_5, 75%; (iv) H_2, Pd/C, $NaHCO_3$, 100%; (v) LiOH, THF−H_2O, 100%; (vi) KH, HCO_2Me, DME, 0 °C, 85%; (vii) MVK, Et_3N, CH_2Cl_2, 95%; (viii) NaOH, H_2O, THF, 95%; (ix) CH_2N_2, Et_2O−CH_2Cl_2, 99%; (x) Br_2, $NaHCO_3$, CH_2Cl_2, 80%; (xi) DBU, C_6H_6, 50 °C, 90%.

Asymmetric hydrogenation[10] of the Stobbe condensation product **2**[11] of isovanillin and dimethyl succinate using a chiral rhodium catalyst prepared from the bisphosphine **3** [(4*R*,5*R*)-MOD-DIOP][12] gave the succinate derivative **4** in quantitative yield and 94% enantiomeric excess (Scheme 1).[13] The resulting (2*S*) configuration of **4** controls all subsequent stereochemical events throughout the synthesis. Intramolecular Friedel−Crafts reaction of **4** yielded exclusively the undesired tetralone from cyclization *para* to the free phenol, but this was easily corrected by prior bromination. This aryl blocking group conveniently steers Friedel−Crafts acylation toward tetralone **5**.[14] Condensation of the carboxylic acid **5** with methyl formate,[15] followed by treatment of the resultant α-formyl tetralone with methyl vinyl ketone (MVK),

(1) For a concise history of morphine and its development as an analgesic, see Lednicer, D. *Central Analgesics*; Wiley: New York, 1982; pp 137−213.

(2) (a) Gulland, J. M.; Robinson, R. *Mem. Proc. Manch. Lit. Soc.* **1925**, *69*, 79. (b) Robinson, R.; Sugasawa, S. *J. Chem. Soc.* **1933**, 1079.

(3) These early endeavors were heavily influenced by degradative experiments with morphine which yielded a phenanthrene system after exhaustive dehydrogenation. For a recent successful approach to morphine along these lines, see Mulzer, J.; Durner, G.; Trauner, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2830.

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

(5) For example, see Schwartz, M. A.; Pham, P. T. K. *J. Org. Chem.* **1988**, *53*, 2318.

(6) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993,** *115*, 11028.

(7) (a) Pschorr, A. T. *Ber.* **1896**, *29*, 296. (b) Fieser, L. F.; Holmes, H. L. *J. Am. Chem. Soc.* **1936**, *58*, 2319. (c) Robinson, R.; Gosh, R. J. *J. Chem. Soc.* **1944**, 506.

(8) For a recent approach to the unnatural enantiomer of morphine, see Butora, G.; Hudlicky, T.; Fearnley, S. P.; Gunn, A. G.; Stabile, M. R.; Abboud, K. *Tetrahedron Lett.* **1996**, *37*, 8155.

(9) Of the 16 completed morphine syntheses only one, that of Ginsburg, attacks the morphine problem from this direction (a) Ginsburg, D.; Pappo, R. *J. Chem. Soc.* **1953**, 1524. (b) Ginsburg, D.; Elad, D. *J. Chem. Soc.* **1954**, 3052.

(10) Harada, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5, p 345.

(11) Johnson, W. S.; Daub, G. *Org. React.* **1951**, *6*, 1.

(12) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 735.

(13) Enantiomeric excess of **4** was determined by chiral HPLC using a Chiralpak AD column and 9:1 hexane-2-propanol (containing 5% trifluoroacetic acid) as eluent.

(14) For a previous application of this tactic, see White, J. D.; Caravatti, G.; Kline, T. B.; Edstrom, E.; Rice, K. C.; Brossi, A. *Tetrahedron* **1983**, *39*, 2393.

(15) Banwell, M. G.; Lambert, J. N.; Corbett, M; Greenwood, R. J.; Gulbis, J. M.; Mackay, M. F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1415. Saponification of the methyl ester of **5** is necessary in order to avoid racemization in this step.

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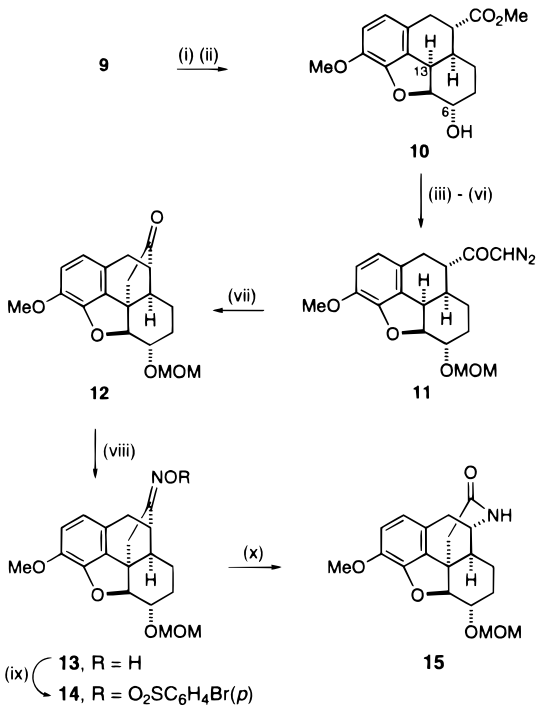
Scheme 2[a]

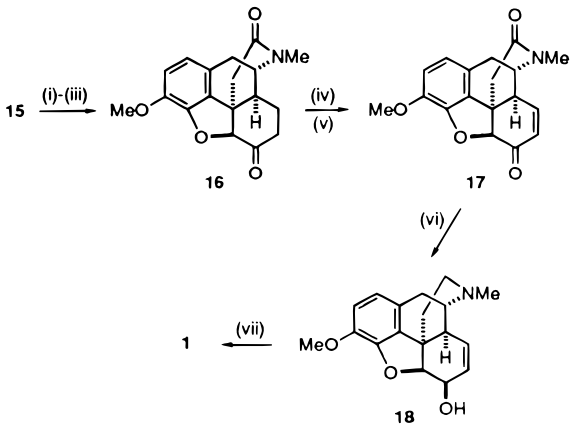


[a] (i) $NaBH_4$, *i*-PrOH−CH_2Cl_2, 99%; (ii) H_2, Pd/C, MeOH, 78%; (iii) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$ 80%; (iv) LiOH, THF−H_2O, 99%; (v) $(COCl)_2$, C_6H_6; (vi) CH_2N_2, 63%; (vii) $Rh_2(OAc)_4$, CH_2Cl_2, 50%; (viii) H_2NOH·HCl, NaOAc, MeOH, 90%; (ix) *p*-$BrC_6H_4SO_2Cl$, Et_3N; (x) AcOH, rt, 62% from **13**.

produced the tricyclic lactol **6**. Exposure of **6** to base furnished the product **7** of Robinson annulation, whose relative configuration was established by X-ray crystallographic analysis of the corresponding ethyl ester. Careful methylation of the acid and subsequent bromination of the enone gave the dibromophenanthrenone derivative **8**, and exposure of this α-bromo enone to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the tetracycle **9**.[16]

Hydrogenation of the benzofuran nucleus of **9** unexpectedly reduced the ketone and left no oxygen substituent at C6. Hence, **9** was first treated with sodium borohydride to yield exclusively the 6α alcohol in which the C−O bond is aligned nearly coplanar with the furan (Scheme 2). This orientation not only ensures proper placement of the crucial 13α hydrogen during the catalytic hydrogenation which follows, but also denies the reduced product **10** opportunity for hydrogenolysis. Straightforward transformation of **10** to diazo ketone **11** set the stage for the pivotal, rhodium(II)-catalyzed carbenoid C−H insertion[17] which creates the pentacyclic nucleus of **12**. In the event, decomposition of **11** afforded principally **12** accompanied by two minor products, one of which arose from intramolecular hydrogen transfer and the other from fragmentation of the diazo ketone.[18]

Scheme 3[a]



[a] (i) NaH, MeI, C_6H_6, Δ, 95%; (ii) HBr, MeCN, 96%; (iii) Dess−Martin periodinane, $CHCl_3$, 99%; (iv) PhSeCl, MsOH, CH_2Cl_2; (v) $NaIO_4$, 65% from **16**; (vi) $LiAlH_4$, THF, Δ, 90%; (vii) ref 17.

Attempts to effect expansion of the bridged cyclopentanone of **12** through Beckmann rearrangement to a δ-lactam were initially unsuccessful. Although oxime **13** was produced (as a 1.2:1 mixture of *syn* and *anti* isomers) in good yield, it failed to yield any trace of a δ-lactam under acidic conditions.[19] Fortunately, the brosylate **14** derived from **13** was more compliant, affording **15** and the regioisomeric δ-lactam in the ratio 11:1, respectively, upon exposure to acetic acid. N-Methylation of **15**, followed by removal of the MOM protecting group and oxidation of the resultant alcohol, gave keto lactam **16** (Scheme 3). Introduction of the conjugated olefin into **16** was effected by α-phenylselenylation of the ketone under acidic conditions[20] and subsequent oxidation of the selenide with periodate. As expected, treatment of **17** with lithium aluminum hydride reduced the enone from the α face[21] and also reduced the lactam to furnish (+)-codeine (**18**). The latter was identical with the natural substance in all respects, except for its optical rotation. Final demethylation of **18** to (+)-morphine (**1**) followed the protocol previously published by Rice.[22]

In summary, a new asymmetric route to (+)-morphine has been demonstrated that takes isovanillin in 28 steps and *ca*. 3% overall yield to the unnatural enantiomer. The synthesis, which can be easily adapted to natural (−)-morphine by hydrogenation of **2** using catalyst prepared from the bisphosphine enantiomeric with **3**, affords good opportunities for the preparation of analogues en route.

Acknowledgment. We are indebted to Professor John H. Block, College of Pharmacy, Oregon State University, for a sample of (−)-codeine and to Professor P. Shing Ho, Department of Biochemistry and Biophysics, Oregon State University, for assistance with the X-ray structure determination of a derivative of **7**. Financial support was provided by the National Science Foundation.

Supporting Information Available: Experimental procedures and characterization data for **2**, **4**−**13**, and **15**−**18** (13 pages).

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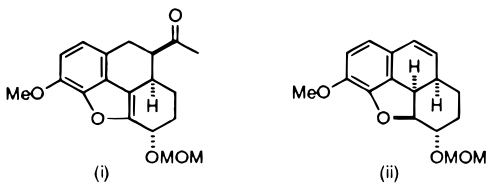
(16) Cyclization probably occurs via the isomeric β,γ-unsaturated ketone.

(17) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon, Oxford, U.K., 1991; Vol. 3, p 1045.

(18) The two byproducts (*ca*. 15% each) have been identified as **i** and **ii**, respectively:



(19) Gawley, R. E. *Org. React.* **1988**, *35*, 1. The principal reaction pathway is believed to involve Beckmann fragmentation.

(20) Iijima, I.; Rice, K. C. *Heterocycles* **1977**, *6*, 1157.

(21) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171.

(22) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.