

Design for Morphine Alkaloids by Intramolecular Heck Strategy: Chemoenzymatic Synthesis of 10-Hydroxy-14-*epi*-dihydrocodeinone via C–D–B Ring Construction

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Received 17 July 2007

Abstract: Enzymatic dihydroxylation of β -bromoethylbenzene provided a homochiral diene diol that served as starting material for the synthesis of the complete morphinan skeleton via an intramolecular Heck cyclization.

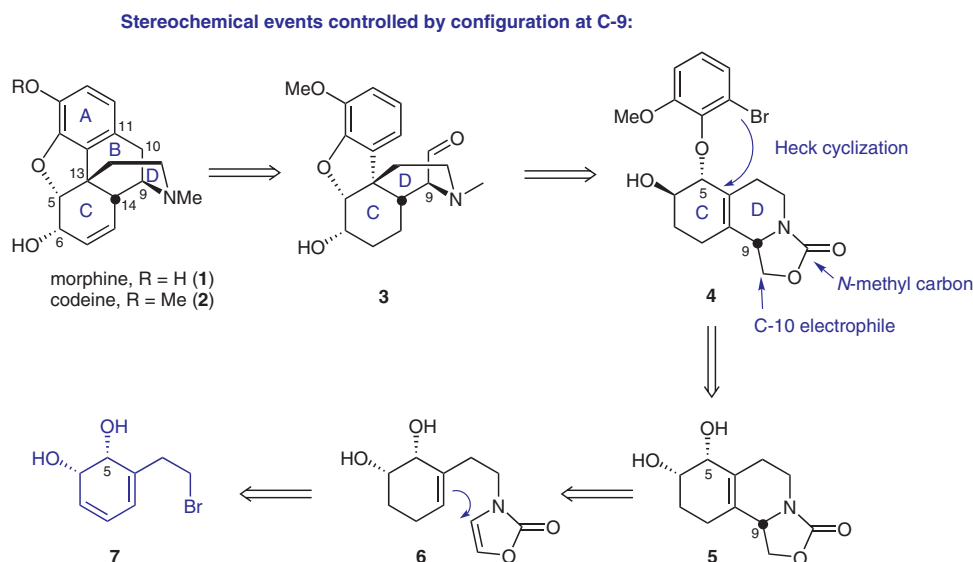
Key words: enzymatic dihydroxylation, Heck reaction, Mitsunobu reaction, Friedel–Crafts reaction, morphinans

Of the more than 20 total syntheses of morphine (**1**) or codeine (**2**) reported in the last 50 years, several used either radical or Heck cyclizations for the construction of the C-13 stereogenic center.¹ We have been pursuing Heck cyclization strategies toward morphinans for some time to address the construction of all contiguous stereogenic centers in an enantiodivergent fashion. One such strategy involves the construction of isoquinoline derivatives such as **5** so that the configuration of the C-9 center (morphine numbering) is set first with subsequent events defining either the natural or the antipodal enantiomeric series. The next center to be created is at C-13, whose configuration

depends on the stereochemistry of attachment of the aryl residue at C-5. The C-14 center is controlled by hydrogenation following the Heck reaction, and the C-6 configuration is adjustable by known oxidation–reduction protocols.²

The homochiral diene diol **7** is an ideal starting material because the configuration of each hydroxyl is easily manipulated by Mitsunobu or other processes. Here we report the implementation of the strategy described in Scheme 1 and the synthesis of a complete morphine skeleton via an intramolecular Heck cyclization and a C-10–C-11 closure.

In 1992 Parker reported a radical cascade to codeine³ initiated from an aryl halide to establish the C-13 stereogenic center. During our 1998 investigation of a similar approach, we prepared the enantiomer of the title compound from the C-9 diastereomer of the isoquinoline derivative **5**.⁴ The Heck cyclization has been successfully employed for the construction of the C-13 center by Overman,⁵ Trost,⁶ Cheng,⁷ and Hsin.⁸ We have reported⁹ model



Scheme 1 Intramolecular Heck cyclization and C-10–C-11 closure in the design of morphine synthesis

SYNLETT 2007, No. 18, pp 2863–2867

Advanced online publication: 15.10.2007

DOI: 10.1055/s-2007-990832; Art ID: S05107ST

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studies that utilized Heck cyclization with isoquinoline derivatives, such as **4**, containing the complete rings C and D of morphine as well as the C-9 stereogenic center. Thus the Heck cyclization strategy represents a viable and successful means toward the assembly of the morphine skeleton in cases where the C-13 center is set relatively early in the synthesis.

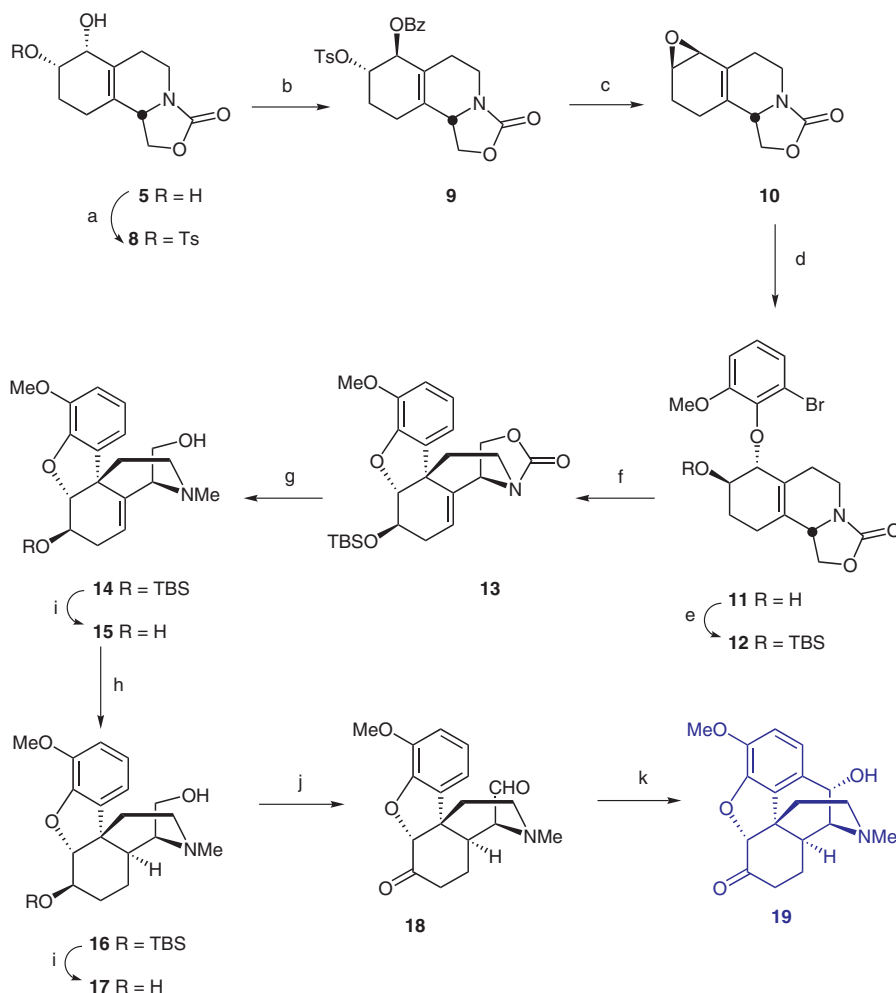
We have published an eight-step synthesis of isoquinoline **5**¹⁰ from the homochiral diol **7**, available from β -bromoethylbenzene by enzymatic oxidation.¹¹ The generation of **5** was accomplished either by the Lewis acid mediated closure of the bisbenzoate derived from **6** (ca. 4:1 mixture at C-9) or by electrochemical generation of the acyl iminium ion from the corresponding oxazolidinone.¹²

Attachment of the aryl residue to **5** destined for the natural enantiomeric series requires either a double Mitsunobu inversion or the generation of a β -epoxide. The second Mitsunobu reaction proved to be arduous because of the large protective group at the C-6 oxygen, therefore the epoxide route was chosen instead. To this end, diol **5** was converted to the allylic oxirane **10** by a three-step se-

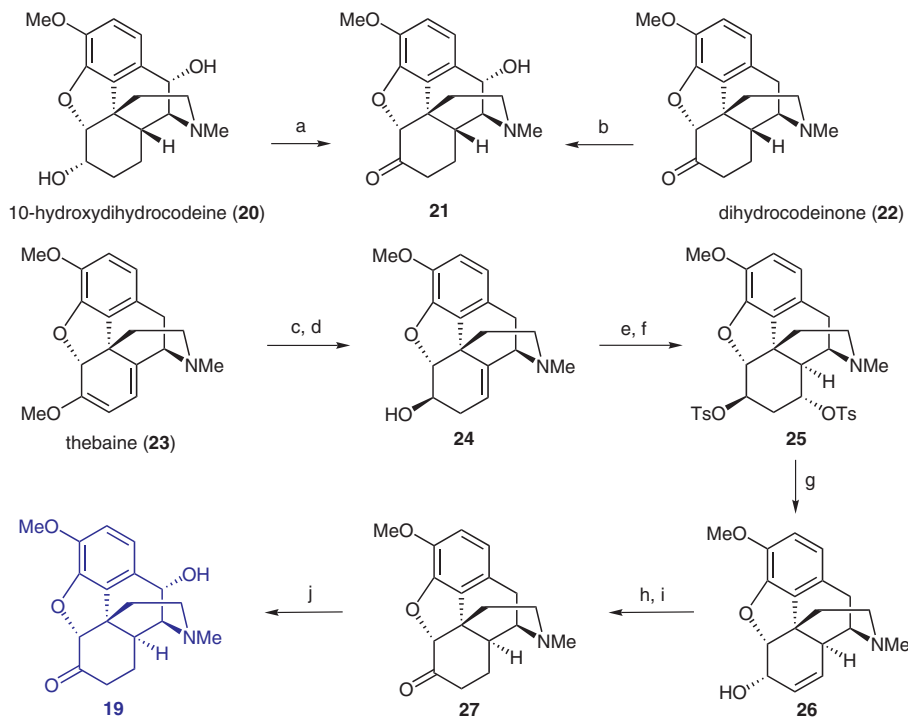
quence consisting of tosylation of the distal alcohol, Mitsunobu inversion of the allylic alcohol in **8**,¹³ and treatment of benzoate **9** with sodium methoxide in methanol, as shown in Scheme 2. The dry potassium salt of bromoguaiacol (7 equiv) in DME in the presence of 18-crown-6 was used for the opening of oxirane **10**, which set the C-5 stereogenic center in alcohol **11**. Protection of the C-6 hydroxyl as the silyl ether **12** provided the key intermediate for the Heck reaction leading to the pentacyclic carbamate **13** in 74% yield. A diastereomer of this compound was previously prepared by a similar cyclization.^{9a}

The intramolecular Heck cyclization required stoichiometric quantities of the palladium catalyst, otherwise low conversions were observed. These cyclizations should probably be conducted in the presence of Pd(dppf) catalyst and an equivalent amount of the free ligand as this combination has proven superior to other protocols in Suzuki and related coupling methods.¹⁴

The DIBAL-H reduction of the carbamate provided the *N*-methylamino alcohol **14**, which was subjected to hydrogenation over Adams catalyst to **16** under conditions



Scheme 2 Reaction conditions: (a) TsCl, pyridine, DMAP (45% based on recycled **5**); (b) BzOH, PPh₃, DEAD, THF (79%); (c) MeONa/MeOH, THF (68%); (d) Potassium 2-bromo-6-methoxyphenoxide, DME, 18-C-6, Δ (80%, or 63% over two steps); (e) TBSOTf, (*i*-Pr)₂NEt, CH₂Cl₂ (74%); (f) Pd(PPh₃)₄, Proton SpongeTM, PhMe, Δ (74%); (g) DIBAL-H, CH₂Cl₂ (69%); (h) H₂, PtO₂, AcOH (64%); (i) TBAF, THF-H₂O, (77–86%); (j) (COCl)₂, DMSO-Et₃N-CH₂Cl₂ (not isolated); (k) CF₃SO₃H (30% over two steps).



Scheme 3 Reaction conditions: (a) *t*-BuOK, PhCOPh, C₆H₆, reflux; (b) CrO₃, H₂SO₄; (c) Hg(OAc)₂, MeOH then 3 N AcOH, KBr (quant.); (d) NaBH₄, KOH, H₂O (88%); (e) B₂H₆, THF then NaOH, H₂O₂ (82%); (f) TsCl, pyridine; (g) KOAc, H₂O–DMF, reflux (52%); (h) H₂, PtO₂, EtOH; (i) (COCl)₂, DMSO–Et₃N; (j) CrO₃, H₂SO₄.

reported for the saturation of isoneopine-type compounds to the correct configuration of the C-14 center.¹⁵ Similarly, the free alcohol **15** obtained from **14** upon desilylation with TBAF was hydrogenated to **17**, identical to the material obtained by deprotection of silyl ether **16**. Contrary to the expected stereochemical outcome, both routes provided **16** with the α -configuration at C-14.

The final step requires the closure of the C-10–C-11 bond to complete the morphine skeleton and this strategy has not often been used. It was employed by Evans¹⁶ with a compound that did not contain the fully elaborated benzofuran subunit. The only three approaches to morphine via a C-10–C-11 closure late in the synthesis on intermediates possessing the benzofuran ring system are those reported by Schultz,¹⁷ Ogasawara,¹⁸ and by our group.¹⁹

A double Swern oxidation of **17** furnished the ketoaldehyde **18**, which was cyclized with trifluoromethanesulfonic acid to the complete morphinan skeleton **19**. To confirm the absolute stereochemistry as well as the outcome of the hydrogenation step, the known 10-hydroxydihydrocodeinone (**21**) was prepared according to literature methods either by oxidation of dihydrocodeinone (**22**) to 10-hydroxydihydrocodeinone or by oxidation of 10-hydroxydihydrocodeine (**20**), as shown in Scheme 3.²⁰ Comparison of spectral properties of **19** and **21** clearly indicated that the two compounds were isomeric. As we suspected that the two compounds differed only in the configuration at C-14, we prepared a standard of **19** from thebenaine **23**. (–)-Thebenaine was converted by known procedures to isoneopine (**24**),^{21,22} which was elaborated to the bistosylate **25** by a hydroboration and oxidation proce-

dures,²³ then tosylation. Elimination and displacement of the tosylates led to **26**, which was converted to the C-14 epimer of dihydrocodeinone (**27**).²⁴ The benzylic position was oxidized according to Rapoport's protocol²⁰ to **19**.

Comparison of spectral (¹H NMR and ¹³C NMR) and chromatographic properties of **19** and **21** confirmed that the hydrogenation of both **14** and **15** proceeded anti to the C-6 substituent.²⁵ This outcome is probably a function of the more conformationally flexible system relative to the fully elaborated phenanthrene skeleton present in neopine or neopinone.

To summarize, the synthesis of pentacyclic morphinan derivative **19** via the late-stage C-10–C-11 ring closure was accomplished in eight steps from the isoquinoline derivative **5** or 14 steps from the diene diol **7**.

Selected Experimental Procedures

7*R*-(2-Bromo-6-methoxy-phenoxy)-8*R*-hydroxy-1,5,6,7,8,9,10,10b-octahydro-oxazolo[4,3-*a*]isoquinolin-3-one (**11**)

A solution of epoxide **10** (0.036 g, 0.17 mmol) in anhyd DME (9 mL) was transferred into a flask containing anhyd potassium 2-bromo-6-methoxyphenoxide (0.220 g, 0.91 mmol, 5.4 equiv) under an argon atmosphere. After complete dissolution of phenoxide, 18-crown-6 ether (small spatula tip) was added and the reaction mixture was heated to reflux under argon atmosphere for 5 d, with one addition of extra phenoxide (0.1 g, 2.5 equiv) after 4 d of heating. The resulting purple reaction mixture was then cooled to r.t., and solvent was removed under reduced pressure. The residue was taken up in Et₂O (110 mL) and 5 wt% aq NaOH (5 mL). After separation of the phases, the organic phase was washed with 5 wt% aq NaOH (5 × 5 mL). The combined aqueous phases were back-

extracted with Et₂O (4 × 30 mL) then all organic layers were combined, washed with H₂O (5 mL), brine (5 mL), and dried over anhyd MgSO₄. The drying agent was then filtered, and solvents were removed under reduced pressure. The crude product was purified by column chromatography (silica; hexane–EtOAc, 2:8 then 1:9) to yield 0.057 g (80%) of an oil. Compound **11**: *R*_f = 0.34 (EtOAc); [*α*]_D²⁷ +20.21 (*c* 0.0100 g/mL, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 7.14 (dd, 1 H, *J*₁ = 7.5 Hz, *J*₂ = 1.8 Hz), 6.93 (t, 1 H, *J* = 8.4 Hz), 6.87 (dd, 1 H, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz), 4.68 (d, 1 H, *J* = 4.2 Hz), 4.53 (t, 1 H, *J* = 8.1 Hz), 4.30 (m, 1 H), 4.20 (m, 1 H), 4.05 (t, 1 H, *J* = 8.1 Hz), 3.97 (dd, 1 H, *J*₁ = 13.2 Hz, *J*₂ = 6.0 Hz), 3.86 (s, 3 H), 3.03 (ddd, 1 H, *J*₁ = 16.2 Hz, *J*₂ = 13.2 Hz, *J*₃ = 4.5 Hz), 2.62 (m, 1 H), 2.24 (m, 2 H), 2.02 (m, 2 H), 1.90 (m, 1 H), 1.80 (m, 1 H). ¹³C NMR (75 MHz, CDCl₃): δ = 157.3, 153.2, 145.0, 131.4, 127.9, 125.4, 125.0, 117.7, 111.9, 83.6, 69.6, 67.4, 55.9, 55.0, 38.1, 26.5, 26.4, 22.3. IR (neat): ν = 3430.6, 2928.4, 1738.5, 1732.6, 767.6, 731.5 cm⁻¹. HRMS: *m/z* calcd for C₁₈H₂₀NBrO₅ [M + H]⁺: 409.0525; found: 409.0596. Anal. Calcd: C, 52.70; H, 4.91. Found: C, 52.86; H, 5.10.

10-tert-Butyldimethylsilyloxy-6-methoxy-(1S,9R,10R,14S)-8,16,18-dioxazapentacyclo[11.7.0.0^{1,9}.0^{2,7}.0^{14,18}]jicosa-2(7),3,5,12-tetraene-17-one (13)

Aryl bromide **12** (0.068 g, 0.13 mmol) was dissolved in anhyd toluene (11 mL), to which was added Pd(PPh₃)₄ (0.180 g, 0.16 mmol, 1.2 equiv) and Proton SpongeTM (0.042 g, 0.19 mmol, 1.5 equiv). The solution was degassed with an argon stream for 30 min and then heated to reflux for 21 h (the originally bright yellow solution turned dark brown). Additional catalyst (0.018 g, 0.1 equiv) was added and reaction mixture was refluxed for 2 h. After the mixture was cooled to r.t., Et₂O (100 mL) was added, then the solution was filtered through a Celite bed and washed with 1 M HCl (5 × 5 mL), sat. NaHCO₃ (5 mL), H₂O (5 mL), brine (5 mL), and dried over anhyd MgSO₄. Filtration and evaporation with silica followed by column chromatography (silica; hexane–EtOAc, 70:30) gave compound **13** as a yellowish oil (0.042 g, 74%). *R*_f = 0.45 (hexane–EtOAc, 50:50); [*α*]_D²⁶ +15.65 (*c* = 0.0100 g/mL, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ = 6.85 (t, 1 H, *J* = 8.1 Hz), 6.78 (dd, 1 H, *J*₁ = 7.8 Hz, *J*₂ = 0.9 Hz), 6.66 (dd, 1 H, *J*₁ = 7.2 Hz, *J*₂ = 1.5 Hz), 5.49 (m, 1 H), 4.79 (br t, 1 H, *J* = 9.0 Hz), 4.61 (t, 1 H, *J* = 8.7 Hz), 4.39 (d, 1 H, *J* = 4.5 Hz), 4.25 (dd, 1 H, *J*₁ = 8.4 Hz, *J*₂ = 4.2 Hz), 4.00 (t, 1 H, *J* = 8.4 Hz), 3.87 (s, 3 H), 3.74 (ddd, 1 H, *J*₁ = 12.9 Hz, *J*₂ = 10.2 Hz, *J*₃ = 8.1 Hz), 3.38 (ddd, 1 H, *J*₁ = 12.6 Hz, *J*₂ = 10.1 Hz, *J*₃ = 7.5 Hz), 2.33–1.99 (m, 4 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.04 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): δ = 157.5, 146.9, 145.2, 136.4, 132.8, 122.2, 121.9, 117.0, 111.7, 91.3, 69.1, 67.2, 56.0, 54.6, 48.0, 36.8, 33.3, 29.9, 25.9, 18.2, –4.6, –4.9. IR (neat): ν = 3055.4, 2952.5, 1760.5, 836.6, 778.6, 735.1 cm⁻¹. HRMS: *m/z* calcd for C₂₄H₃₄NSiO₅ [M + H]⁺: 444.2206; found: 444.2226.

14-epi-10-Hydroxydihydrocodeinone (19)

Neat trifluoromethanesulfonic acid (400 μL) was added to a cooled crude keto aldehyde **18** (ca. 9 mg) in CHCl₃, and the resulting bright red solution was stirred at r.t. under argon for 30 min, diluted with CHCl₃ (6 mL), and then cooled to ca. –5 °C. Ice chips were added, and the red coloration changed to yellow. The two layers were vigorously mixed for a few minutes. After separation, the aqueous layer was cooled and the pH adjusted to 14 by the addition of 1 M KOH (ca. 5.5 mL). Extraction with CHCl₃ (7 × 4 mL), drying over Na₂SO₄, and evaporation gave a crude product purified by preparative TLC to give the morphinan **19** (3 mg, 30%). ¹H NMR (300 MHz, CDCl₃): δ = 6.95 (d, 1 H, *J* = 8.4 Hz), 6.80 (d, 1 H, 8.4 Hz), 5.03 (s, 1 H), 4.79 (s, 1 H), 3.91 (s, 3 H), 3.03 (br d, 1 H, *J* = 2.4 Hz), 2.81–2.67 (m, 1 H), 2.62–2.27 (5 H), 2.55 (s, 3 H), 1.94 (m, 1 H), 1.82 (br d, 1 H, *J* = 10.5 Hz). ¹³C NMR (75 MHz, CDCl₃): 207.4, 144.2, 133.6, 130.7, 127.3, 120.2, 114.6, 92.8, 67.9, 63.4, 56.7,

47.0, 45.6, 43.7, 39.3, 35.9, 32.1, 29.9. HRMS: *m/z* calcd for C₁₈H₂₂NO₄ [M – H]⁺: 316.1549; found: 316.1544.

Acknowledgment

The authors are grateful to the following agencies for support of this work: National Science Foundation (support of the PhD dissertation work of J.Z. at the University of Florida), Natural Sciences and Engineering Research Council (NSERC) of Canada, Brock University, Canada Foundation for Innovation (CFI), Research Corporation, TDC Research Foundation, and TDC Research, Inc. The support from the National Institutes of Health, DHHS (postdoctoral fellowship for J.Z.) is gratefully acknowledged. We also thank Dr. John D. Lloyd (NIDDK, NIH) for mass spectral measurements of compounds **14** through **19**.

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- (25) It is likely that the hydrogenation of neopine-type compounds only proceeds to the natural configuration at C-14 in systems containing the full phenanthrene core, which is not the case with **14** or **15**. The scarcity of material precluded us from performing the C-10–C-11 closure prior to hydrogenation.