Natural Products

DOI: 10.1002/anie.201400286

Short Chemoenzymatic Total Synthesis of *ent*-Hydromorphone: An Oxidative Dearomatization/Intramolecular [4+2] Cycloaddition/Amination Sequence**

*Vimal Varghese and Tomas Hudlicky**

Abstract: *A short synthesis of ent-hydromorphone has been achieved in twelve steps from β-bromoethylbenzene. The key transformations involved the enzymatic dihydroxylation of the arene to the corresponding cis-dihydrodiol, Mitsunobu coupling with the ring A fragment, oxidative dearomatization of the C3 phenol, and the subsequent [4+2] cycloaddition to form ring B of the morphinan. The synthesis was completed by intramolecular amination at C9.*

A truly practical synthesis of morphine and its congeners has not yet appeared in spite of focused efforts and many creative approaches having been published.[1] We have been involved in the design and synthesis of morphinans for many years and published several total syntheses of codeine and congeners, the shortest, at 12 steps, still far removed from reaching the realm of practicality.

We recently designed an advanced strategy to construct the morphine skeleton by an intramolecular [4+2] cycloaddition of dienone **2** produced by oxidative dearomatization of a phenol such as **1** (Figure 1). The homochiral portion of **1**, prepared by toluene-dioxygenase-mediated dihydroxylation of an appropriate arene, is coupled with the phenolic fragment by a Mitsunobu reaction. The functionalities at C16 and C9 are appropriate for the incipient closure of the ethylamino bridge in **3** (or its aromatized equivalent). Deprotection and oxidation will lead directly to *ent*-hydromorphone (**4**).

To test the feasibility of the cycloaddition of a species such as **2**, we pursued a model study of the cycloaddition of **5** (without the nucleophilic group Y) to **6** followed by the known hydroamination methodology[2] to set C9 late in the synthesis, at the stage of phenol **7** (Figure 1). This approach to *ent*-hydromorphone (**4**) is enantiodivergent and is also applicable to the natural enantiomer. In several previous approaches to morphinans we have demonstrated that the configuration at C5 in intermediates of type **1** controls all subsequent stereochemical events in either enantiomeric series and that the natural configuration in **1** is attainable by double Mitsunobu inversion.[2a] Herein we report a short synthesis of **4** by a new design employing an oxidative dearomatization/intramolecular [4+2] cycloaddition/amination strategy.

The Diels–Alder reaction has been used only once in a direct construction of ring B of the morphine skeleton, namely in an intermolecular [4+2] approach by Kerr and Tius.[3] Two model studies utilizing an intramolecular Diels–Alder reaction to construct ring B, leading to morphinan substructures, have been reported by us[4,5] and by Rodrigo and co-workers.[6] Thus our current report constitutes the first use of the intramolecular Diels–Alder strategy for ring B closure in a total synthesis of a morphinan and also the first total synthesis of *ent*-hydromorphone (**4**).

In 1992[4] and 1998[5] we published two simple model studies on the intramolecular Diels–Alder cycloadditions of homochiral dienes with unsaturated tethers to furnish tricyclic systems with five contiguous stereogenic centers, representing rings B, C, and E of morphine. The dienes were derived in three steps from toluene[4] or β-bromoethylbenzene[5] by enzymatic dihydroxylation. In 1998, a Diels–Alder/Cope sequence, similar in concept to our model studies, was published by Rodrigo and co-workers.[6e] The oxidative dearomatization of phenols[7] and subsequent cycloaddition was exploited by Rodrigo and co-workers on structurally different substrates in their approaches to various natural products, including the synthesis of a partial morphine skeleton, that is, rings A, B, C, and E.[6a,e,f]

The above precedents bode well for a successful approach, which we began with the synthesis of the two subunits to be joined to the precursor required for a compound such as **5**. The syntheses of the homochiral subunits **13** and **14** were accomplished as shown in Scheme 1 and as previously described.[2a,8] Dihydroxylation of **8** by whole-cell fermentation with E. *coli* JM 109 (pDTG601A)[9] yielded **9**, which was immediately subjected to a selective reduction with potassium azodicarboxylate and subsequent protection of the diol to give **10**. The displacement of bromine in **10** with methylamine produced **11** (the tosylation of this compound could be used in the future to provide **14** and hence **19b**, in a more direct way; see Scheme 3). Hydrolysis of the acetonide with HCl and subsequent protection of the secondary amine as a Boc

[*] V. Varghese, Prof. T. Hudlicky
Department of Chemistry and Centre for Biotechnology
Brock University, St. Catharines, ON L2S 3A1 (Canada)
E-mail: thudlicky@brocku.ca

[**] We thank the following agencies for financial support of this work: Natural Sciences and Engineering Research Council of Canada (NSERC) (Idea to Innovation and Discovery Grants), Canada Research Chair Program, Canada Foundation for Innovation (CFI), TDC Research, Inc., TDC Research Foundation, the Ontario Partnership for Innovation and Commercialization (OPIC), and The Advanced Biomanufacturing Centre (Brock University). We also appreciate the skillful assistance of Jef de Brabander, Jr. and Stuart Williamson for the preparation of several starting materials. We thank Razvan Simionescu and Tim Jones for their help with NMR and mass spectrometry analyses. Last but not least we are indeed very grateful to Christie and Eric Boros, Gabor Butora, Andrew Gum, and Khalil Abboud for their efforts in the model studies some two decades ago.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400286.

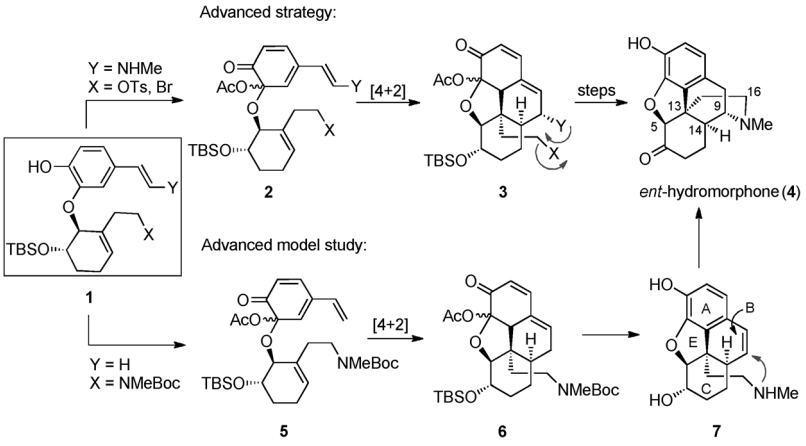
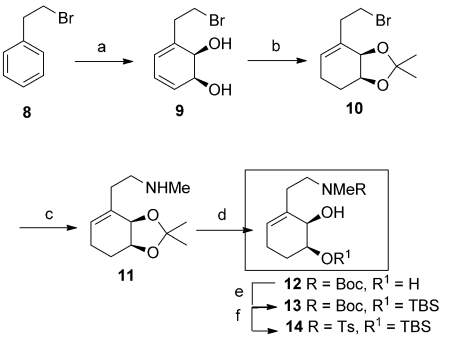


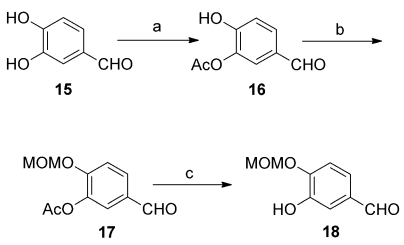
Figure 1. Advanced strategy to access morphinans by cycloaddition to construct ring B.



Scheme 1. a) *E. coli* JM 109 (pDTG601A), 10–15 g L^{-1}; b) 1. potassium azodicarboxylate, AcOH, MeOH, 0 °C, 83 %; 2. 2,2-dimethoxypropane, acetone, *p*TsOH, 80 %; c) $MeNH_2$, K_2CO_3, THF, sealed tube, 93 %; d) 1. 3 M HCl, EtOH; 2. Boc_2O, $NaHCO_3$, EtOH, 74 % (2 steps); e) TBSCl, imidazole, CH_2Cl_2, −78 °C to RT, 92 %; f) 1. TFA, CH_2Cl_2, 0 °C; 2. TsCl, Et_3N, CH_2Cl_2, RT, 86 % over two steps. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.

carbamate provided **12** in a one-pot operation. Regioselective silylation of the distal hydroxy group then provided alcohol **13**, and subsequent deprotection and tosylation gave **14**.

The arene coupling partner **18** was synthesized from 3,4-dihydroxybenzaldehyde by adjustment of a known protocol,[10] as shown in Scheme 2. The synthesis of **18** started with the regioselective acetylation of 3,4-dihydroxybenzaldehyde (**15**) to the monoacetylated derivative **16**. Protection of the



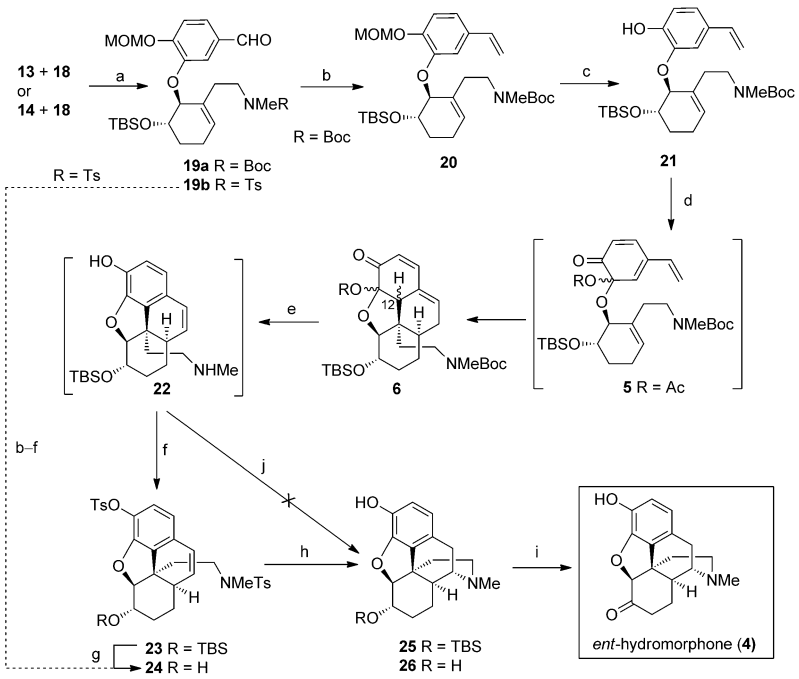
Scheme 2. a) Ac_2O, NaOH, THF, 0 °C, 82–85 %; b) MOMCl, K_2CO_3, DMF, 0 °C to RT, 76–80 %; c) K_2CO_3, MeOH, RT, 88–90 %. DMF = *N*,*N*-dimethylformamide.

phenol with MOMCl under mild basic conditions afforded aldehyde **17**, and the hydrolysis of the acetyl group completed the synthesis of the required phenol **18**.

The two units were coupled, by a Mitsunobu protocol, to give either **19a** (R = Boc) or **19b** (R = Ts, obtained from **14**), as shown in Scheme 3. After the aldehyde was converted into a vinyl group by a Wittig reaction, the MOM group in **20** was removed under mild reaction conditions[11] to produce the free phenol **21**. Exposure of this material to lead tetraacetate in refluxing dichloroethane provided, via dienone **5**, the [4+2] adduct **6** in 50 % yield upon isolation. It is possible that only one diastereomer of **5** underwent the cycloaddition, thus further optimization of this step will be required.

Dienone **5** underwent the cycloaddition exclusively at the site of the exocyclic diene, and no other cycloaddition products or dimerizations were observed in this reaction (only once, about 3–4 % of the product of the endocyclic cycloaddition was detected). Even though the endocyclic diene is quite reactive, the exclusive formation of **6** can be attributed to steric reasons, which deny the dienophile the proximity of the endocyclic diene. The ^{13}C NMR spectrum of **6** exhibited three carbonyl signals, a signal at $\delta = 188.2$ ppm corresponding to the enone, a signal at $\delta = 170.9$ ppm corresponding to the ester carbonyl group of the acetyl group, and a signal at $\delta = 155.4$ ppm corresponding to the amide carbonyl group. The assignment of the stereochemistry at C4/C12 in **6**, obtained as a single stereoisomer, was complicated by the presence of rotamers and was not made (H12 should be β, assuming the *exo* transition state). Rodrigo and co-workers showed in their synthesis of indolinocodeine that the quinoid portion acts as both diene and dienophile, thus leading to mixtures of different products.[6a,e]

Dienone **6** was treated with trifluoroacetic acid to afford phenol **22** by re-aromatization and the concomitant hydrolysis of the Boc carbamate. We then turned our attention to the construction of the D ring by hydroamination of **22**. However, all our attempts failed to install the ethylamino bridge through either an aminomercuration used previously by us[2a] or through a photostimulated addition of lithium amide reported Trost and Tang.[2c] Analysis of the crude reaction mixture suggested some evidence of hydroamination under the aforementioned conditions but the isolation of pure products from these reactions was not possible. The failure of the aminomercuartion was likely due to the instability of **22**. This compound (**22**) was therefore taken to the next step without purification to provide the tosyl amide **23** upon treatment with excess tosyl chloride (with concomitant tosylation of the phenolic hydroxyl) in 45 % yield, over the two steps. Treatment of **6** with trifluoroacetic acid for longer period of time resulted in the formation of **7**, which was converted into the corresponding amide **24** by treatment with excess tosyl chloride. The establishment of the ethylamino bridge in **25** was accomplished by a nitrogen-centered radical cyclization enabled by a dissolved-metal reduction of the tosyl



Scheme 3. a) TMAD, PBu_3, 81–85%; b) CH_3PPh_3Br, *n*BuLi, THF, −78°C to 0°C then reflux for 4 h, 82–88%; c) $ZnBr_2$, $CH_3(CH_2)_{10}CH_2SH$, CH_2Cl_2, RT, 10 min, 92%; d) $Pb(OAc)_4$, DCE, reflux, 4 h, 50%; e) TFA, CH_2Cl_2, 0°C, 15 min; f) TsCl, Et_3N, CH_2Cl_2, 0°C to RT, 45% over two steps; g) TBAF, THF, RT, 86%; h) Li, *t*BuOH, $NH_{3(liq)}$, THF, −78°C, 10 min [82–86% for **23** to **25**; 93% for **24** to **26**]; i) *t*BuOK, PhCOPh, $PhCH_3$/DME, 85°C, 8 h, 44%; j) 1. $Hg(OCOCF_3)_2$, CH_3CN RT; 2. $NaBH_4$, THF, −78°C to RT. DCE = 1,2-dichloroethane, DME = dimethoxyethane, TBAF = *tert*-*n*-butylammonium fluoride, TMAD = *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide.

amide according to conditions adapted from the work of Parker and Fokas[12] and Chida and co-workers,[13] and similar in concept to Trost's lithium amide cyclization[2c,d] noted above. The reductive cyclization of **23** to **25** was superior to the hydroamination conditions [$Hg(OAc)_2$, followed by $LiAlH_4$] we have used previously,[2a,b] and gave **25** in 82–86% yield. In addition, the reductive cyclization was also performed with the free alcohol **24** to give **26** in 93% yield.

Oxidation of **26** to *ent*-hydromorphone (**4**) was accomplished with benzophenone and *t*BuOK in 44% yield (83% based on recovered starting material) using a modified procedure from Woodward and co-workers and Rapoport and co-workers.[14–16] Because of poor solubility of **26** in most of the solvents, the reaction did not proceed to completion, and the starting material (53%) was recovered from the reaction. Another explanation for the low yield is the *trans* relationship between the C5 and C6 positions in the *ent*-dihydroisomorphine **26.** Rapoport has provided a reasonable explanation based on the pseudo-six-membered ring conformation involved in such oxidations.[15]

In summary, the most effective route to the first total synthesis of *ent*-hydromorphone (**4**) (NMR matched with an authentic sample prepared from oripavine)[17] described in this paper was accomplished in just seven steps (five operations) from **19a** (it can be also attained from **19b** through six steps or 12 steps from β-bromoethylbenzene), thus making it one of the shortest synthesis of a morphinan. The successful oxidative dearomatization and cycloaddition strategy presented here bodes well for the pursuit of the next generation of this approach and further improvements in the synthesis of other morphinans in either or both enantiomeric series.

Received: January 10, 2014
Published online: ■■ ■■, ■■■■

Keywords: alkaloids · cycloaddition · natural products · oxidation · total synthesis

[1] For reviews of morphine alkaloid syntheses and discussion of strategies, see: a) U. Rinner, T. Hudlicky, *Top. Curr. Chem.* **2012**, *309*, 33–66; b) J. Zezula, T. Hudlicky, *Synlett* **2005**, 388–405; c) D. F. Taber, T. D. Neubert, M. F. Schlecht in *Strategies and Tactics in Organic Synthesis*, *Vol. 5* (Ed.: H. Michael), Elsevier, London, **2004**, pp. 353–389; d) T. Hudlicky, *J. Heterocycl. Chem.* **2000**, *37*, 535–539; e) B. H. Novak, T. Hudlicky, J. W. Reed, J. Mulzer, D. Trauner, *Curr. Org. Chem.* **2000**, *4*, 343–362; f) T. Hudlicky, G. Butora, S. P. Fearnley, A. G. Gum, M. R. Stabile in *Studies in Natural Products Chemistry*, *Vol. 18*, *Part K* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 43–154; g) M. Maier in *Organic Synthesis Highlights II* (Ed.: H. Waldmann), VCH, Weinheim, **1995**, pp. 357–369.

[2] See for example: a) H. Leisch, A. T. Omori, K. J. Finn, J. Gilmet, T. Bissett, D. Ilceski, T. Hudlicky, *Tetrahedron* **2009**, *65*, 9862–9875; b) A. T. Omori, K. J. Finn, H. Leisch, R. J. Carroll, T. Hudlicky, *Synlett* **2007**, 2859–2862; c) B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543; d) B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803.

[3] M. A. Tius, M. A. Kerr, *J. Am. Chem. Soc.* **1992**, *114*, 5959–5966.

[4] T. Hudlicky, C. H. Boros, E. E. Boros, *Synthesis* **1992**, 174–178.

[5] G. Butora, A. G. Gum, T. Hudlicky, K. A. Abboud, *Synthesis* **1998**, 275–278.

[6] a) J. Gao, J. Orso Simon, R. Rodrigo, A. Assoud, *J. Org. Chem.* **2013**, *78*, 48–58; b) Y. Lang, F. E. S. Souza, X. Xu, N. J. Taylor, A. Assoud, R. Rodrigo, *J. Org. Chem.* **2009**, *74*, 5429–5439; c) H. S. Sutherland, K. C. Higgs, N. J. Taylor, R. Rodrigo, *Tetrahedron* **2001**, *57*, 309–317; d) F. E. S. Souza, R. Rodrigo, *Chem. Commun.* **1999**, 1947–1948; e) R. Carlini, K. Higgs, R. Rodrigo, N. Taylor, *Chem. Commun.* **1998**, 65–66; f) R. Carlini, K. Higgs, C. Older, S. Randhawa, R. Rodrigo, *J. Org. Chem.* **1997**, *62*, 2330–2331; g) R. Carlini, K. Higgs, N. Taylor, R. Rodrigo, *Can. J. Chem.* **1997**, *75*, 805–816.

[7] a) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, 1–16; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem.* **2012**, *124*, 12834–12858; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686; c) S. P. Roche, J. A. Porco, Jr., *Angew. Chem.* **2011**, *123*, 4154–4179; *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093; d) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261; e) S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467–495; f) F. López Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar Sánchez, G. Ruiz Gómez, *Chem. Rev.* **2007**, *107*, 1580–1691; g) J. M. Keane, W. D. Harman, *Organometallics* **2005**, *24*, 1786–1798; h) C.-C. Liao, *Pure Appl. Chem.* **2005**, *77*, 1221–1234; i) D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004**, *104*, 1383–1429; j) C.-C. Liao, R. K. Peddinti, *Acc. Chem. Res.* **2002**,

35, 856 – 866; k) P. L. Smith, M. D. Chordia, W. Dean Harman, *Tetrahedron* **2001**, *57*, 8203 – 8225; l) A. R. Pape, K. P. Kaliappan, E. P. Kunding, *Chem. Rev.* **2000**, *100*, 2917 – 2940; m) S. Quideau, L. Pouysegu, *Org. Prep. Proced. Int.* **1999**, *31*, 617 – 680; n) V. Singh, *Acc. Chem. Res.* **1999**, *32*, 324 – 333; o) T. Bach, *Angew. Chem.* **1996**, *108*, 795 – 796; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 729 – 730; p) L. N. Mander, *Synlett* **1991**, 134 – 144.

[8] J. Duchek, T. G. Piercy, J. Gilmet, T. Hudlicky, *Can. J. Chem.* **2011**, *89*, 709 – 729.

[9] G. J. Zylstra, D. T. Gibson, *J. Biol. Chem.* **1989**, *264*, 14940 – 14946.

[10] A. M. Sawayama, H. Tanaka, T. J. Wandless, *J. Org. Chem.* **2004**, *69*, 8810 – 8820.

[11] a) J.-H. Sohn, N. Waizumi, H. M. Zhong, V. H. Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 7290 – 7291; b) J. H. Han, Y. E. Kwon, J.-H. Sohn, D. H. Ryu, *Tetrahedron* **2010**, *66*, 1673 – 1677.

[12] a) K. A. Parker, D. Fokas, *J. Am. Chem. Soc.* **1992**, *114*, 9688 – 9689; b) K. A. Parker, D. Fokas, *J. Org. Chem.* **2006**, *71*, 449 – 455.

[13] M. Ichiki, H. Tanimoto, S. Miwa, R. Saito, T. Sato, N. Chida, *Chem. Eur. J.* **2013**, *19*, 264 – 269.

[14] R. B. Woodward, N. L. Wendler, F. J. Brutschy, *J. Am. Chem. Soc.* **1945**, *67*, 1425 – 1429.

[15] H. Rapoport, R. Naumann, E. R. Bissell, R. M. Bonner, *J. Org. Chem.* **1950**, *15*, 1103 – 1107.

[16] R. Csuk, G. Vasileva, A. Barthel, *Synthesis* **2012**, 2840 – 2842.

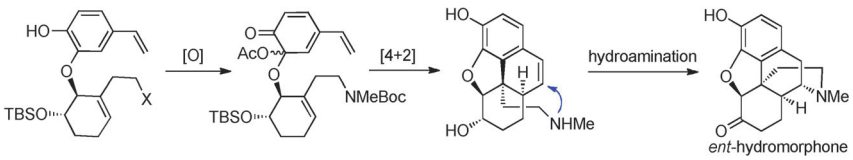
[17] M. A. E. Arias, T. Hudlicky, unpublished observations, United States Provisional Patent Application No. 61/937,126, Methods for the preparation of Hydromorphone. Filed: February 7, **2014**.

Communications

Natural Products

V. Varghese, T. Hudlicky* ____

Short Chemoenzymatic Total Synthesis of *ent*-Hydromorphone: An Oxidative Dearomatization/Intramolecular [4+2] Cycloaddition/Amination Sequence



A short synthesis of *ent*-hydromorphone has been achieved in twelve steps from β-bromoethylbenzene. The key transformations involved the enzymatic dihydroxylation of the arene to the corresponding *cis*-dihydrodiol, oxidative dearomatization, subsequent [4+2] cycloaddition to form ring B of the morphinan, and intramolecular amination at C9. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.