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A concise route to (−)-morphine

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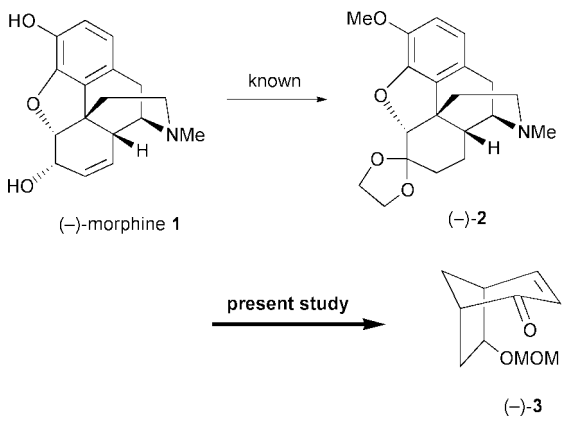
A concise enantio- and diastereocontrolled route to (−)-morphine has been developed starting from a bicyclo[3.2.1]octenone chiral building block through an acid-catalyzed tandem retro-aldol-oxonium ion-mediated hydrophenanthrene formation reaction as the key step.

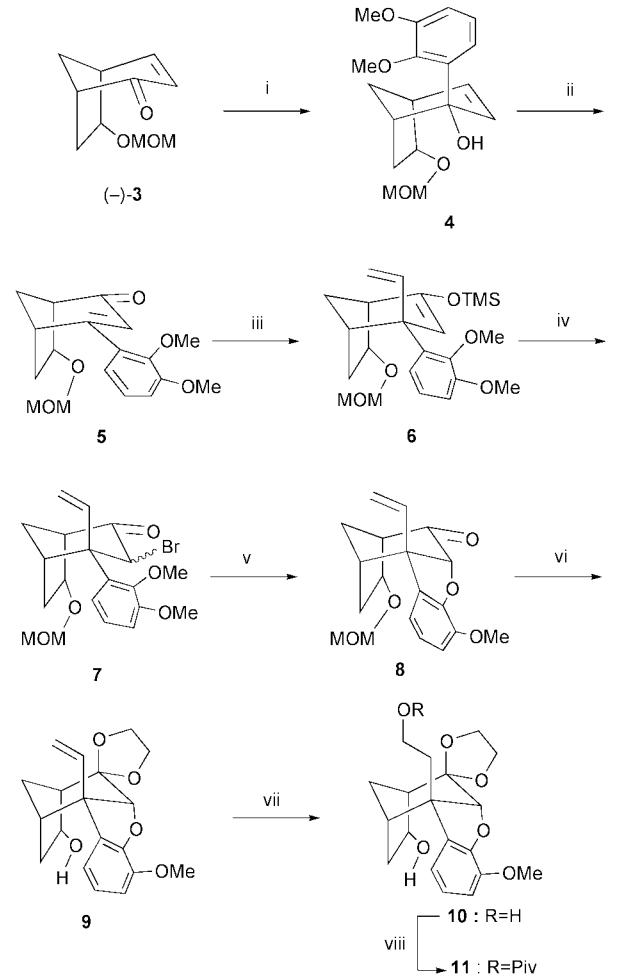
The total synthesis of (−)-morphine **1**, the main alkaloid of the opium poppy, has been a challenging target for organic chemists for many decades.[1,2] Although a number of successful syntheses have been developed to date since the first accomplishment by Gates[3] in 1952, only a few could produce the alkaloid in an enantio- and diastereocontrolled manner. We report here a concise diastereocontrolled synthesis of the key intermediate[4] dihydrocodeinone ethylene ketal (−)-**2** of (−)-morphine **1** and the related opium alkaloids starting from the bicyclo[3.2.1]octenone chiral building block[5] (−)-**3** by employing a tandem retro-aldol cleavage and oxonium ion-mediated cyclization[6] as the key step (Scheme 1).

Enantiopure enone **3**, $[\alpha]_D^{26}$ −438.6 (*c* 1.6, $CHCl_3$)], was reacted with 3-lithioveratrole generated *in situ* by reaction of veratrole with butyllithium,[7] to give diastereoselectively tertiary alcohol† **4**, mp 82–84 °C, $[\alpha]_D^{26}$ −151.6 (*c* 1.5, $CHCl_3$)], which on oxidation with pyridinium chlorochromate (PCC) afforded β-aryl-enone **5**, $[\alpha]_D^{26}$ +173.5 (*c* 3.0, $CHCl_3$)], in 81% yield. Construction of the dihydrobenzofuran moiety of the target molecule was carried out at this point by employing the procedure developed by Mulzer and coworkers[4] in their synthesis of **1**. Thus, reaction of **5** with vinylmagnesium chloride in THF containing HMPA in the presence of copper(I) bromide and trimethylsilyl chloride furnished silyl enol ether **6** in 75% yield by concurrent diastereoselective 1,4-addition and *O*-silylation. Exposure of **6** to *N*-bromosuccinimide (NBS) gave α-bromoketone **7** in excellent yield as an inseparable mixture of two epimers (5:1). When the mixture was refluxed in DMF,[4e] intramolecular etherification took place to give rise to dihydrobenzofuran **8**, mp 80–82 °C, $[\alpha]_D^{23}$ −109.7 (*c* 0.5, $CHCl_3$)], in 81% yield as a single diastereomer. Since terminal hydroxylation of the vinyl functionality of **8** under hydroboration–oxidation conditions[8] brought about formation of a mixture by concomitant reduction of the carbonyl functionality in the molecule, the ketone was first protected under mild conditions[9] using 1,2-bis(trimethylsiloxy)ethane in the presence of trimethylsilyl triflate. Under these conditions, **8** furnished hydroxyketal **9** in 71% yield with concurrent removal of the MOM-protecting group. Primary hydroxylation carried out at this stage under standard hydroboration–oxidation conditions[8] afforded diol **10** whose primary hydroxy functionality was selectively acylated with pivaloyl chloride to give hydroxypivalate **11**, the substrate of the key acid-catalyzed hydrophenanthrene formation reaction, in 72% yield. Overall yield of **11** from (−)-**3** was 22% in eight steps (Scheme 2).

Conversion of **11** into the key hydrophenanthrene intermediate **16** could be accomplished in one step just by refluxing with ethylene glycol in benzene with removal of generating water. Thus, **11**, on reflux with ethylene glycol in benzene using a Dean–Stark apparatus in the presence of a catalytic amount of toluene-*p*-sulfonic acid,[2c] furnished the hydrophenanthrene **16**,



Scheme 1



Scheme 2 *Reagents and conditions*: i) 3-Li-veratrole, THF, −78 °C. ii) PCC, CH_2Cl_2 (81% in 2 steps). iii) vinyl-MgCl, CuBr-Me_2S, TMS-Cl, HMPA, THF (75%). iv) NBS, CH_2Cl_2, rt (99%). v) DMF, reflux, 30 min (82%). vi) $(CH_2OTMS)_2$, TfOTMS(cat.), CH_2Cl_2 (71%). vii) BH_3-Me_2S then 30% H_2O_2, NaOH (72%). viii) Piv-Cl, pyridine (87%).

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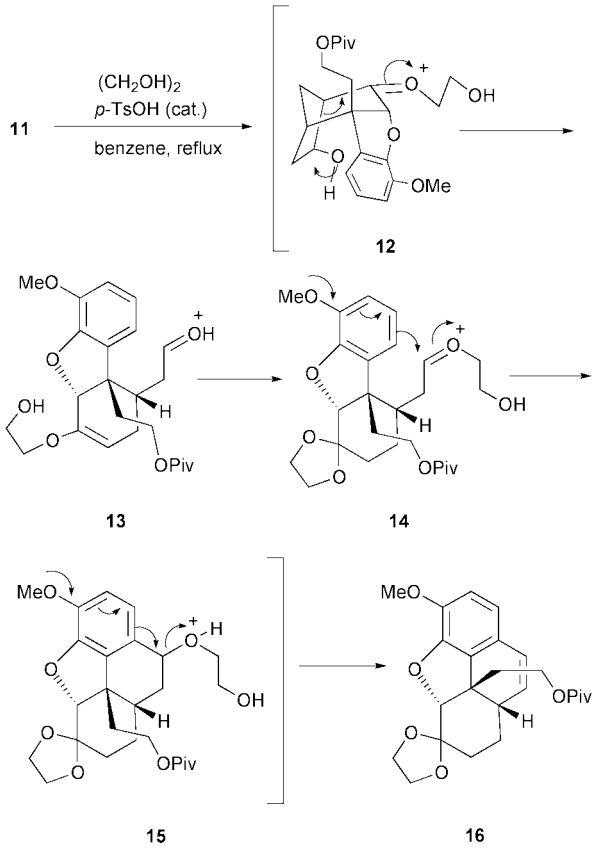
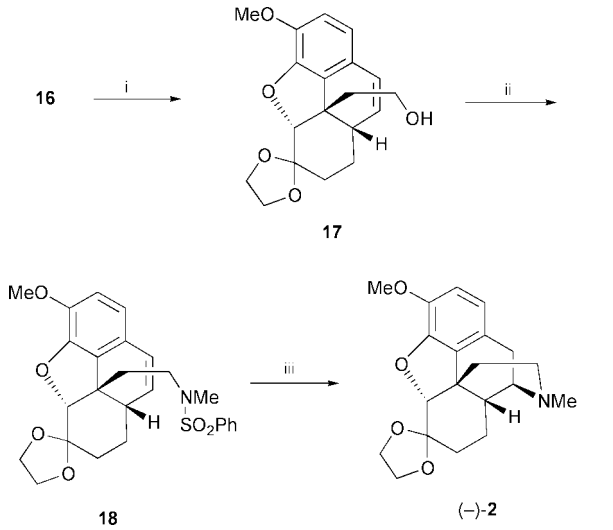


Scheme 3



Scheme 4 *Reagents and conditions*: i) $LiAlH_4$, THF, rt (100%). ii) $PhSO_2NHMe$, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF (78%). iii) Li, NH_3, *t*-BuOH, THF (70%).

$[\alpha]_D^{25}$ +20.6 (*c* 0.7, $CHCl_3$), in 50% yield as a single product after 15 h. The reaction may be explained by initial formation of oxonium ion **12** which underwent retro-aldol cleavage leading to another oxonium ion **14** *via* protonated aldehyde **13** after reaction with an ethylene glycol in the reaction medium.[2c] The reaction proceeded further under the conditions to bring about cyclization to give hydrophenanthrene **16** through a transient **15**. Although we did not examine this point extensively, the addition of ethylene glycol seemed to be essential to accelerate this cyclization reaction[2c] (Scheme 3).

Transformation of **16** into the penultimate intermediate **18** of the target molecule (−)-**2** could be carried out in a straightforward manner. The pivaloyl group from **16** was first removed by reduction and the resulting primary alcohol **17**, mp 92–94 °C, $[\alpha]_D^{28}$ +31.4 (*c* 0.7, $CHCl_3$), was then transformed into the tertiary sulfonamide **18** by employing the modified Mitsunobu reaction.[4,10] Thus, the reaction of **17** with *N*-methylbenzenesulfonamide in the presence of 1,1′-(azodicarbonyl)dipiperidine[10] and tributylphosphine gave **18**, mp 113–115 °C, $[\alpha]_D^{26}$ −28.5 (*c* 0.1, $CHCl_3$)]{ref. [4d]: mp 115–117 °C, $[\alpha]_D^{20}$ −24.1 (*c* 1.0, $CHCl_3$)}, in 78% yield, whose spectroscopic data were identical with those reported.[4d] Since this compound has been transformed into (−)-morphine **1** and the related opium alkaloids *via* the key intermediate **(**−)-2,[4] the present synthesis constitutes a formal synthesis at this point. Actually, our product (−)-**18** furnished the key morphinan (−)-**2**, mp 170–172 °C, $[\alpha]_D^{27}$ −167.1 (*c* 0.1, $CHCl_3$)]{ref.[4d]: mp 173–175 °C, $[\alpha]_D^{20}$ −173.3 (*c* 1.0, $CHCl_3$)}, in 70% yield on treatment with lithium in liquid ammonia containing *tert*-butanol.[4d,11] Overall yield of (−)-**2** from **11** was 27% in four steps, thus, 6% in twelve steps from the chiral building block (−)-**3** (Scheme 4).

The present methodology for the synthesis of the key intermediate of (−)-morphine may be utilized widely not only for the construction of the alkaloids having a *cis*-fused tetrahydrophenanthrene framework but also for the synthesis of the *trans*-fused congeners as the bicyclo[3.2.1]octenone chiral building block allows diastereocontrolled construction of the pivotal stereogenic center owing to its inherent convex-face selectivity.

Notes and references

† Satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, 1H NMR, and MS) data were obtained for new compounds.

1 For pertinent reviews, see: T. Hudlicky, G. Butora, S. P. Fearnley, A. G. Gum and M. R. Stabile, *Studies in Natural Products Chemistry*, Atta-ur-Rahman ed., Elsevier, Amsterdam, 1996, Vol. 18, pp. 43–154; B. H. Novak, T. Hudlicky, J. W. Reed, J. Mulzer and D. Trauner, *Curr. Org. Chem.*, 2000, **4**, 343; K. W. Bentley, *Nat. Prod. Rep.*, 2000, **17**, 247 and previous reports.

2 For the synthesis of morphine alkaloids after ref. 1, see: (*a*) J. D. White and P. Hrncier, *J. Org. Chem.*, 1999, **64**, 7271; (*b*) J. D. White, P. Hrncier and F. Stappenbeck, *J. Org. Chem.*, 1999, **64**, 7871; (*c*) O. Yamada and K. Ogasawara, *Org. Lett.*, 2000, **2**, 2785.

3 M. Gates and G. Tschudi, *J. Am Chem. Soc.*, 1952, **72**, 1109.

4 (*a*) J. Mulzer, G. Durner and D. Trauner, *Angew. Chem., Int. Ed. Engl.*,1996, **35**, 2836; (*b*) J. Mulzer, J. W. Bats, B. List, T. Opatz and D. Trauner, *Synlett*, 1997, 441; (*c*) D. Trauner, S. Porth, T. Opatz, J. W. Bats, G. Giester and J. Mulzer, *Synthesis*, 1998, 653; (*d*) D. Trauner, J. W. Bats, A. Werner and J. Mulzer, *J. Org. Chem.*, 1998, **63**, 5908; (*e*) J. Mulzer and D. Trauner, *Chirality*, 1999, **11**, 475.

5 H. Nagata, M. Kawamura and K. Ogasawara, *Synthesis*, 2000, 1825; H. Nagata, N. Miyazawa and K. Ogasawara, *Synthesis*, 2000, 2013.

6 H. Nagata, N. Miyazawa and K. Ogasawara, *Org. Lett.*, 2001, in press.

7 E. D. Bergmann, P. Pappo and D. Ginsburg, *J. Chem. Soc.*, 1950, 1369.

8 C. F. Lane, *J. Org. Chem.*, 1974, **39**, 1437.

9 T. Tsunoda, M. Suzuki and R. Noyori, *Tetrahedron Lett.*,198, **21**, 1357.

10 T. Tsunoda, Y. Yamamiya and S. Ito, *Tetrahedron Lett.*, 1993, **34**, 1639.

11 K. A. Parker and D. Fokas, *J. Am. Chem. Soc.*, 1992, **114**, 9688.