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Total Synthesis of (±)-Morphine

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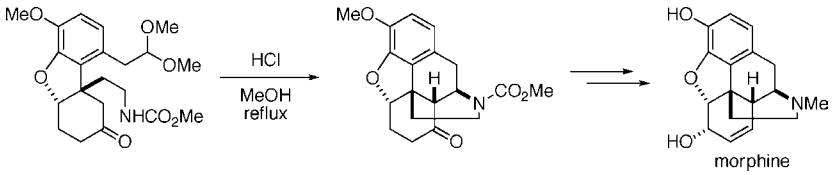
ABSTRACT

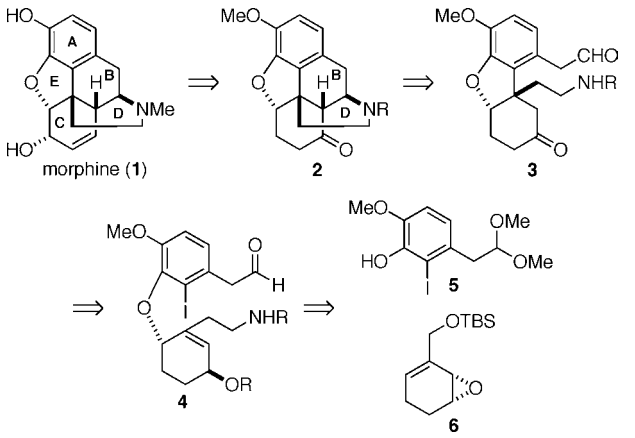


The morphinan skeleton was effectively synthesized by an intramolecular Mannich-type reaction. Further transformation led to total synthesis of morphine.

Morphine (**1**) is a fascinating compound that has been used as an efficient analgesic and is indispensable in treating pains associated with cancer. However, morphine is strictly controlled by authorities due to its addictive nature. On the other hand, the structure of morphine is quite attractive from a synthetic point of view. Its complicated pentacyclic skeleton, including a quaternary carbon center, has stimulated extensive synthetic efforts. Hence, a number of synthetic studies and the total syntheses of morphine have been reported to date.[1] Among them, the Pd-mediated total synthesis reported recently by Trost and co-workers seems quite versatile.[1b,c,2] In an effort to develop a novel morphine-type drug that is not addictive, we initiated our own studies of an efficient total synthesis of morphine. Herein, we disclose a total synthesis of (±)-morphine which involves a unique construction of the morphinan skeleton.

Our retrosynthetic analysis is shown in Scheme 1. Morphine could be derived from ketone intermediate **2**, which in turn would be prepared from ketoaldehyde **3** either by a successive aldol−Michael protocol or by a Mannich-type reaction (vide infra). Ketoaldehyde **3** would be obtained via

Scheme 1



an intramolecular Heck reaction[1b,c,2] of **4**, which could be prepared from phenol **5** and epoxide **6**[3] by means of Tsuji−Trost coupling.[4]

Our synthesis commenced with conversion of isovanillin (**7**) into iodide **8** according to a known procedure (Scheme

(1) (a) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449. (b) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785. (c) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542. (d) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416. (e) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. For a review and other syntheses, see: Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388.

(2) Similar strategies using the Heck reaction were employed to synthesize galanthamine: (a) Pilger, C.; Westermann, B.; Flörke, U.; Fels, G. *Synlett* **2000**, 1163. (b) Parsons, P. J.; Charles, M. D.; Harvey, D. M.; Sumoreeah, L. R.; Shell, A.; Spoors, G.; Gell, A. L.; Smith, S. *Tetrahedron Lett.* **2001**, *42*, 2209.

(3) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246. Although optically pure epoxide can be obtained in large quantities according to our procedure, a racemate was used for this preliminary study.

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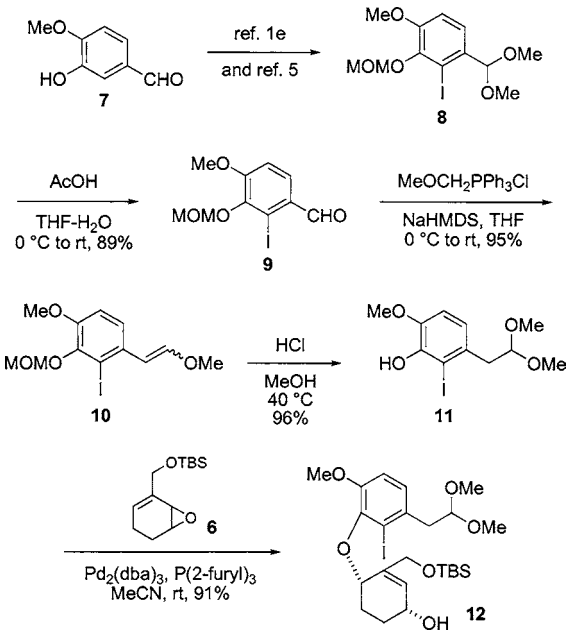
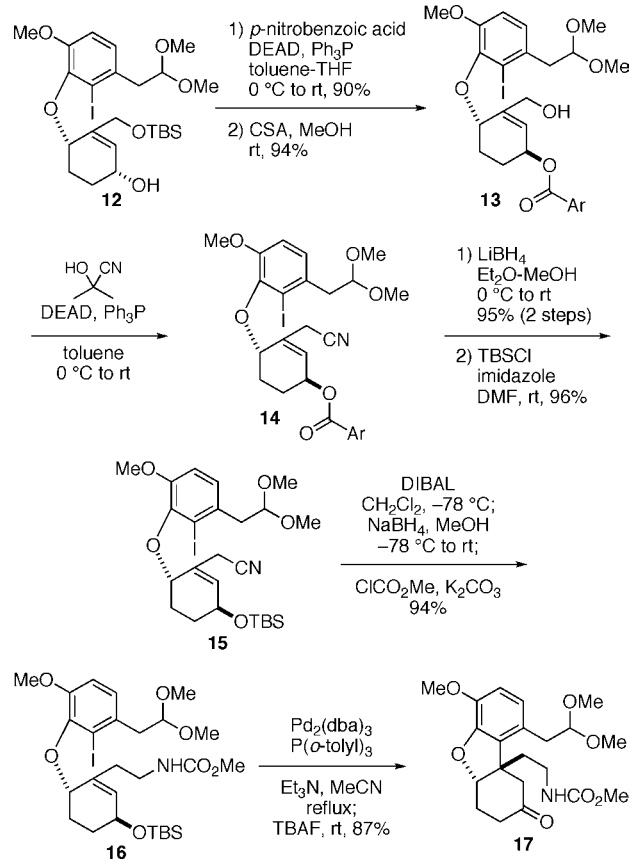
Scheme 2

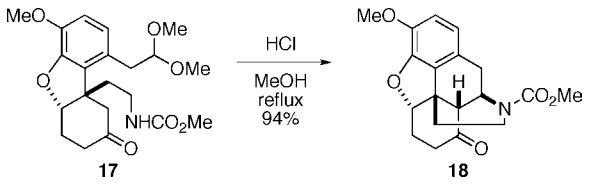


2).[1e,5] Acidic hydrolysis of the acetal and subsequent Wittig olefination gave the enol ether **10**, which, upon treatment with methanolic HCl, furnished phenol **11**. A palladium-mediated coupling reaction of phenol **11** and epoxide **6** proceeded smoothly to give **12** in 91% yield with complete regio- and stereoselectivity.[4]

Scheme 3

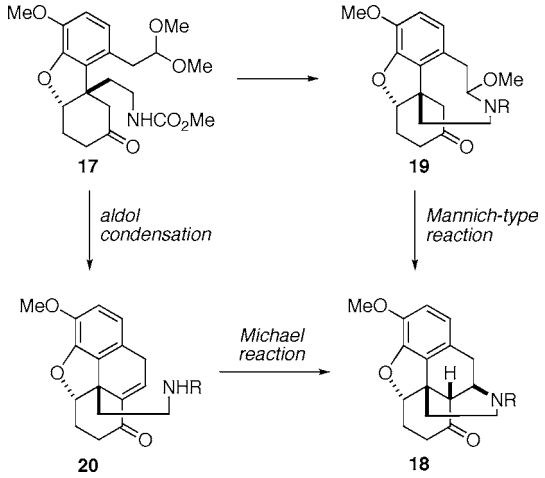


Scheme 4



We then focused our attention on the functionalities of the C ring (Scheme 3). After inversion of the hydroxy group of **12** under Mitsunobu conditions,[6] the *t*-butyldimethylsilyl (TBS) group was removed to give alcohol **13**. The alcohol was then converted to nitrile **14** by means of a Mitsunobu reaction.[7] To prevent the formation of an α,β-unsaturated nitrile, cleavage of the *p*-nitrobenzoate was effected by treatment with lithium borohydride. The resulting alcohol was protected as the TBS ether **15**. To suppress the reductive cleavage of the aromatic iodide, the nitrile was reduced first with diisobutylaluminum hydride (DIBAL) at −78 °C followed by addition of methanol and sodium hydride to give the desired amine, which was isolated as the corresponding methyl carbamate **16** in 94% yield. The crucial intramolecular Heck reaction of **16** proceeded smoothly in refluxing acetonitrile to give a silyl enol ether, which, upon treatment

Scheme 5



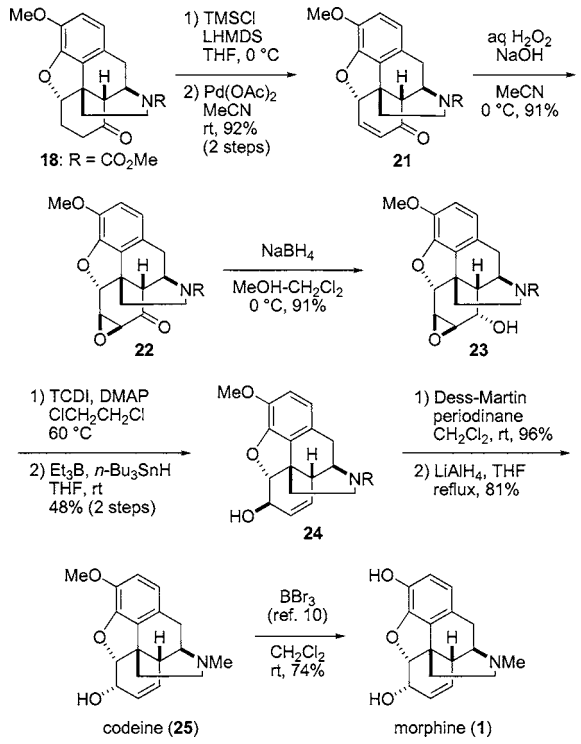
(4) (a) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (c) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940. (d) Review: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

(5) Plaumann, H. P.; Kaey, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921.

(6) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(7) Wilk, B. K. *Synth. Commun.* **1993**, *23*, 2481.

Scheme 6



with tetra-*n*-butylammonium fluoride (TBAF), furnished ketone **17** in 87% yield.

With the requisite ketone **17** in hand, we then focused on a one-step construction of the B and D rings. After extensive investigation, the double cyclization was accomplished by refluxing **17** in methanolic hydrogen chloride to afford **18** in 94% yield as a sole product (Scheme 4). When the reaction was stopped prematurely, eight-membered hemiaminal **19** could also be isolated, but enone **20** was not observed (Scheme 5). These findings strongly suggest that the reaction proceeded via an intramolecular Mannich-type reaction rather than an aldol condensation−Michael reaction.

What remained was to elaborate the C ring to complete the endgame (Scheme 6). Accordintg to Ito-Saegusa's method,[8] ketone **18** was converted into enone **21**. Both epoxidation and subsequent reduction of the ketone occurred from the less-hindered exo face to furnish epoxyalcohol **23** as the sole isomer. Conversion of the alcohol into thiocarbamate and subsequent exposure to radical conditions induced the epoxide opening to provide allylic alcohol **24**.[9] The resulting alcohol was inverted by a two-step oxidation−reduction sequence where the methyl carbamate was reduced with lithium aluminum hydride to afford codeine (**25**).[1d] Finally, the methyl ether was cleaved according to a literature procedure to furnish (±)-morphine (**1**).[10]

In summary, we have successfully synthesized morphine using an intramolecular Mannich-type reaction to construct the B and D rings. The substrate for this critical reaction was efficiently prepared by taking advantage of two types of palladium-catalyzed reactions. Further studies on a more efficient and enantioselective total synthesis of morphine are currently underway, and our results will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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