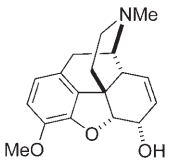
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800744

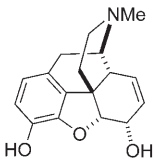
# Diastereoselective Total Synthesis of (±)-Codeine

**Marie Varin, Elvina Barré, Bogdan Iorga,* and Catherine Guillou*[a]**

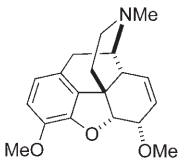
Codeine **1** and morphine **2**, the principal constituents of opium, continue to attract the attention of organic chemists thanks to both their biological activities and their unique structure.[1] Their complex pentacyclic skeleton, which includes a quaternary carbon center, has stimulated extensive efforts. To date there have been more than 20 total syntheses of codeine (**1**), morphine (**2**), and thebaine (**3**).[2] We were interested in the synthesis of codeine for two reasons: first, codeine was found to be an allosteric potentiating ligand of nicotinic receptors,[3] and second we have a general program underway in the laboratory in which we have shown that tricyclic spirocyclohexadienones are valuable intermediates for the synthesis of natural products in the *Amaryllidacea* galanthamine-type, maritidine-type, and *Aspidosperma* alkaloids.[4]




**1** (-)-Codeine



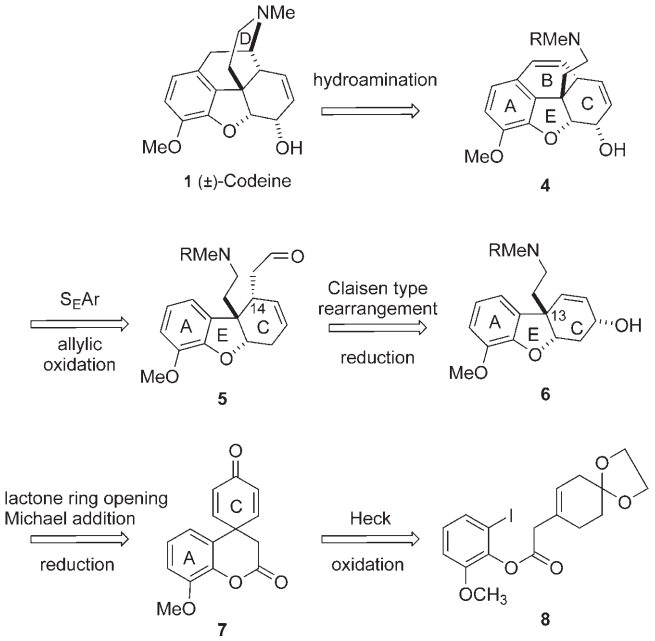

**2** (-)-Morphine




**3** (-)-Thebaine

In an effort to develop new allosteric potentiating ligands of nicotinic receptors with a codeine-type scaffold, we initiated our own studies of a total synthesis of codeine. Herein we disclose a total diastereoselective synthesis of (±)-codeine (**1**), which involves a new construction of the morphinan skeleton. The present study provides an efficient method for the elaboration of the quaternary carbon at C-13 and for the highly diastereoselective introduction of the C-14 stereogenic center of the morphinan system.

Our retrosynthetic analysis of (±)-codeine (**1**) is shown in Scheme 1. Codeine could be obtained from amine intermediate **4** by using an intramolecular hydroamination reaction to form the D ring. Compound **4** could in turn be prepared from aldehyde **5**. In our synthetic pathway, we planned to use for the first time a Claisen-type rearrangement to introduce the C-14 substituent. This type of rearrangement applied to compound **6** would provide a precursor of the aldehyde **5** and control the stereochemistry of the substituent at C-14 of **5**. The tricyclic amine **6** would be obtained from the spirocyclohexadienone **7** by a lactone ring opening with an amine followed by a spontaneous intramolecular Michael



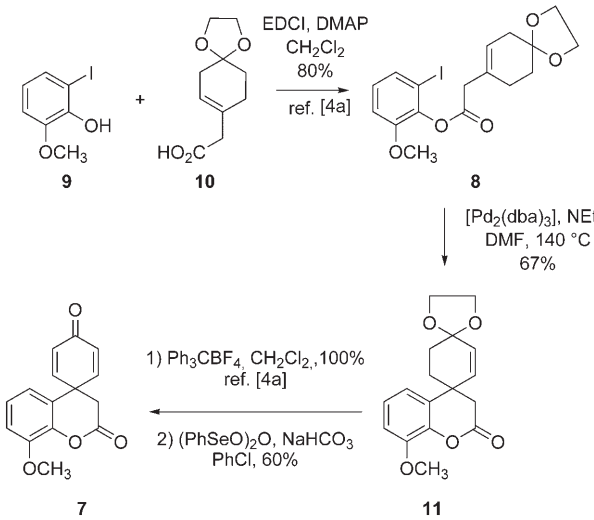

Scheme 1. Retrosynthesis of (±)-codeine **1**.

[a] M. Varin, E. Barré, Dr. B. Iorga, Dr. C. Guillou
Institut de Chimie des Substances Naturelles
CNRS
Avenue de la Terrasse, 91190 Gif-sur-Yvette (France)
Fax: (+33) (0) 69 07 72 47
E-mail: guillou@icsn.cnrs-gif.fr
iorga@icsn.cnrs-gif.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800744.

addition of the resulting phenol to cyclohexadienone. Compound **7** could be prepared in two steps from the ester **8** by an intramolecular Heck reaction followed by an oxidation.

Our synthesis started with esterification of 2-iodo-6-methoxyphenol (**9**)[5] with acid **10**[6] according to a known procedure.[4a] Heck cyclization of **8** was accomplished in 67% yield under new conditions. Indeed, in the absence of phosphine ligands, the reaction time for the cyclization of **8** to **11** was greatly reduced from three days[4a] to 5 h.[7] After hydrolysis of the dioxolane group of **11** with triphenylcarbenium tetrafluoroborate,[4a] oxidation of the α,β-unsaturated ketone function of the resulting product to the corresponding dienone **7**[4a] was realized in the presence of $(PhSeO)_2O$ and $NaHCO_3$ (Scheme 2).

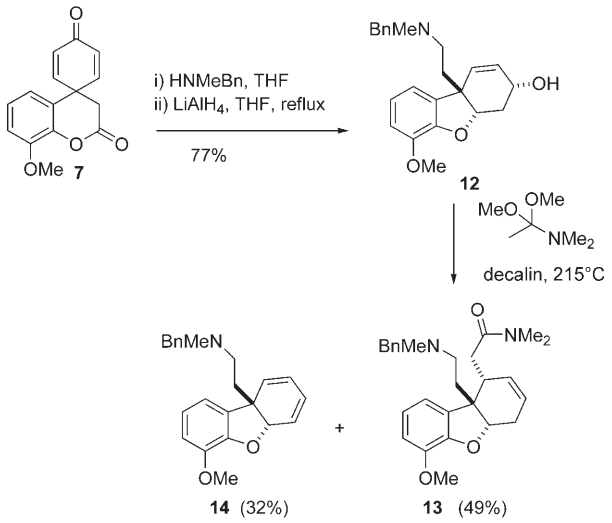



Scheme 2. Synthesis of tricyclic spirocyclohexadienone **7**. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-dimethylaminopyridine, dba = dibenzylideneacetone.

The reaction of lactone **7** with *N*-methylbenzylamine with concurrent amide formation and lactone ring opening afforded the corresponding enone, which was then reduced with $LiAlH_4$ to give the allylic alcohol **12** in 77% yield (Scheme 3). With a ready access to the key tricyclic allylic alcohol **12**, we then turned our attention to the introduction of the crucial substituent at C-14.

Several approaches have been developed to introduce this substituent based on the intramolecular Heck reaction,[2a,e,8] the tandem radical cyclization,[9] 1,4-addition of vinyl magnesium bromide (in the presence of copper(I) bromide) to α,β-enone,[10] CpCO-mediated [2+2+2] cyclization of functionalized 4-(3-butynyl)benzofurans,[11] or by aldol condensation.[2c]

In our study, introduction of the C-14 substituent starting from allylic alcohol **12** proved difficult. Attempts to achieve a Claisen rearrangement on **12** under Kazmaier's,[12] Ireland's,[13] or Johnson's[14] conditions failed.



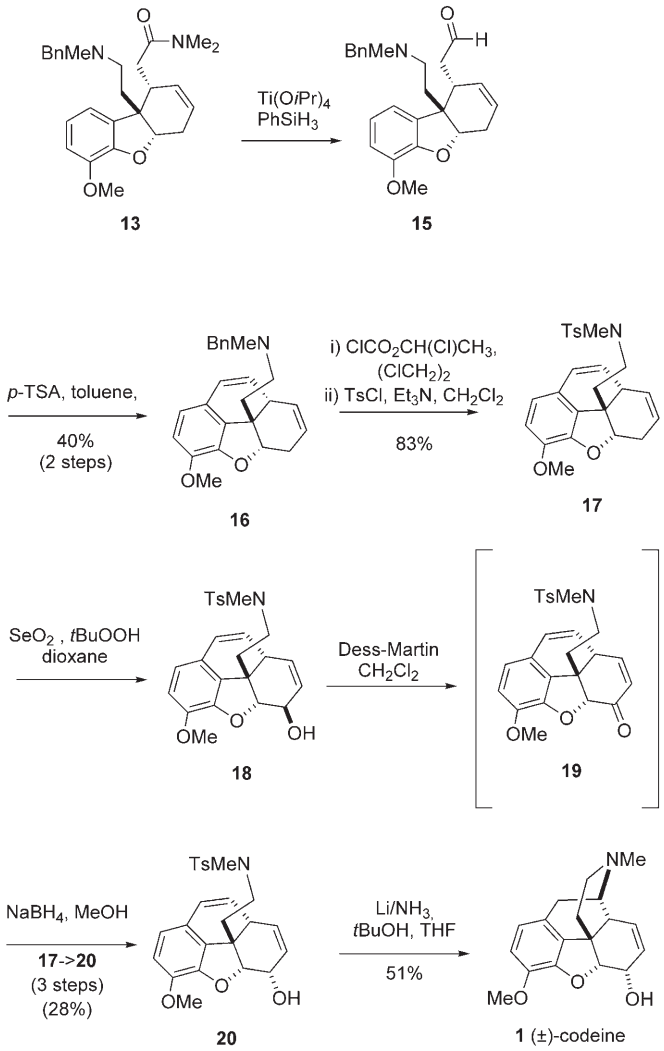

Scheme 3. Synthesis of amide **13**.

However, we found that, under Eschenmoser's[15] conditions, the C-14 substituent could be diastereoselectively introduced. Heating **12** in the presence of dimethylacetamide dimethylacetal in decalin at 215 °C afforded the expected amide **13** (49%) and diene **14** (32%) as a by-product (Scheme 3). In spite of numerous attemps,[16] it was not possible to reduce the amount of **14** produced.

Reduction of the amide **13** with $PhSiH_3$ in the presence of $Ti(OiPr)_4$[17] yielded the aldehyde **15**, which upon treatment with *p*-TSA in toluene furnished the amine **16** (Scheme 4). The next step was the introduction of the allylic alcohol function. To prevent oxidation of the nitrogen atom, the *N*-benzyl group was first removed in the presence of 1-chloroethyl chloroformate to give the corresponding secondary amine, which was then protected with TsCl to give the sulfonamide **17**. Oxidation of **17** with $SeO_2$ in presence of *t*BuOOH in dioxane furnished the allylic alcohol **18** with incorrect stereochemistry. The latter was thus oxidized into the corresponding ketone **19** by reaction with Dess–Martin periodinane. Reduction of ketone **19** proceeded stereoselectively using $NaBH_4$ in methanol to give the required alcohol **20** now having the correct stereochemistry. The final step required to construct the D ring of codeine involves a hydroamination reaction. This type of cyclization was recently applied to a precursor of codeine (using $Hg(OAc)_2$ and then $LiAlH_4$) to give (+)-codeine in 17.6% yield.[2d] In our case, we found that exposure of the sulfonamide **20** to lithium in liquid ammonia[18] resulted in reductive cyclization to furnish codeine (**1**) in satisfactory yield (51%).

In conclusion, we have achieved a diastereocontrolled synthesis of (±)-codeine (**1**) from the tricyclic spirocyclohexadienone **7** in 10 steps. An intramolecular Heck reaction followed by a Claisen–Eschenmoser rearrangement, a reductive deprotection, and an intramolecular hydroamination reaction constitute the key steps of this new total synthesis of codeine.




Scheme 4. Synthesis of (±)-codeine **1**. *p*-TSA = *p*-toluenesulfonic acid.

## Acknowledgements

The authors thank the CNRS for financial support, Prof. J. Y. Lallemand for his interest in this work, and Dr. R. H. Dodd, ICSN-CNRS, Gif-sur-Yvette, France for carefully reading the manuscript and for helpful comments.

**Keywords:** alkaloids · diastereoselectivity · Heck reaction · hydroamination · rearrangement · total synthesis

[1] For pertinent reviews on the synthesis of morphine, see: a) T. Hudlicky, G. Butora, S. P. Fearnley, A. G. Gum, M. R. Stabile, *Studies in Natural Products Chemistry* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1996**, pp. 43–154; b) P. R Blakemore, J. D. White, *Chem. Commun.* **2002**, 1159–1168; c) J. Zezula, T. Hudlicky, *Synlett* **2005**, 388–405.

[2] For the syntheses of morphine and codeine after ref. [1c] see : a) B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803; b) K. A. Parker, D. Fokas, *J. Org. Chem.* **2006**, *71*, 449–455; c) K. Uchida, S. Yokoshima, T. Kan, T. Fukuyama, *Org. Lett.* **2006**, *8*, 5311–5313; d) A. T. Omori, K. J. Finn, H. Leish, R. J. Carroll, T. Hudlicky, *Synlett* **2007**, 2859–2862; e) J. Zezula, K. C. Rice, T. Hudlicky, *Synlett* **2007**, 2863–2867.

[3] a) A. Maelicke, A. Schrattenholz, M. Samochocki, M. Radina, E. X. Albuquerque, *Behav. Brain Res.* **2000**, *113*, 199–206; b) A. Maelicke, M. Samochocki, R. Jostock, A. Fehrenbacher, J. Ludwig, E. X. Albuquerque, M. Zelin, *Biol. Psychiatry* **2001**, *49*, 279–288; c) J. T. Coyle, H. Geerts, K. Sorra, J. Amatniek, *J. Alzheimer's Dis.* **2007**, *11*, 491–507.

[4] a) C. Guillou, J. L. Beunard, E. Gras, C. Thal, *Angew. Chem.* **2001**, *113*, 4881–4882; *Angew. Chem. Int. Ed.* **2001**, *40*, 4745–4746; b) C. Bru, C. Thal, C. Guillou, *Org. Lett.* **2003**, *5*, 1845–1846; c) C. Bru, C. Guillou, *Tetrahedron* **2006**, *62*, 9043–9048; d) J. Pereira, M. Barlier, C. Guillou, *Org. Lett.* **2007**, *9*, 3101–3103.

[5] C. Y. Chen, J. P. Liou, M. J. Lee, *Tetrahedron Lett.* **1997**, *38,* 4571–4574.

[6] Acid **10** was obtained by Birch reduction of *p*-methoxyphenyl acetic acid followed by protection with ethylene glycol (See Supporting Information).

[7] For an example of reduction of the reaction time (19.5 h to 5 h) of a Heck arylation reaction under ligand-free conditions see: M. Qadir, T. Möchel, K. K. Hii, *Tetrahedron* **2000**, *56*, 7975–7979.

[8] B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543.

[9] K. A. Parker, D. Fokas, *J. Org. Chem.* **2006**, *71*, 449–455.

[10] H. Nagata, N. Miyazawa, K. Ogasawara, *Chem. Commun.* **2001**, 1094–1095.

[11] D. Pérez, B. A. Siesel, M. J. Malaskaa, E. David, K. P. C. Vollhardt, *Synlett* **2000**, 306–311.

[12] U. Kazmaier, *Angew. Chem.* **1994**, *106*, 1046–1047; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 998–999.

[13] R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

[14] W. S. Johnson, L. Werthermann, W. R. Barlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

[15] A. E. Wick, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425.

[16] Variations of reaction time, temperature, or use of microwaves did not modify the amount of diene produced.

[17] S. Bower, K. A. Kreutzer, S. L. Buchwald, *Angew. Chem.* **1996**, *108*, 1662–1664; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515–1516.

[18] These conditions were used for the synthesis of (−)-O-methylpallidinine (K. Hanada, N. Miyazawa, K. Ogasawara, *Org. Lett.* **2002**, *4*, 4515–4517) and for the synthesis of (−)-dihydrocodeinone.[2b]

Received: April 18, 2008
Published online: June 18, 2008