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Synthesis of (−)-Oxycodone

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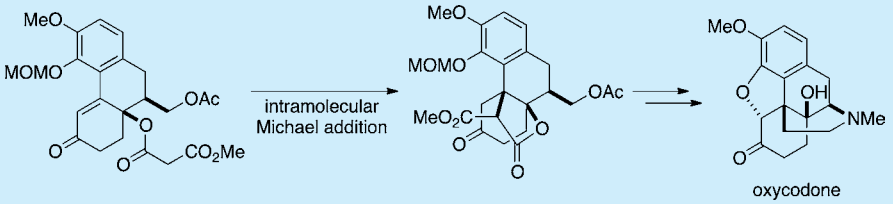
Supporting Information



ABSTRACT: Our novel synthetic route to (−)-oxycodone, a semisynthetic opioid analgesic, features a palladium-catalyzed direct intramolecular arylation of an aryl bromide, oxidative dearomatization of a dihydrophenanthrenol, formation of a benzylic quaternary carbon by an intramolecular Michael addition of a malonate moiety, and construction of the morphinan skeleton via a Hofmann rearrangement/lactamization cascade.

Oxycodone (**1**) is a semisynthetic analgesic[1] that is clinically prescribed as a primary opioid for cancer pain management (Figure 1). Although the structure of oxycodone is similar to morphine (**2**), oxycodone has a much better oral bioavailability, making it superior for pain management in some clinical studies.[2] Because of these advantages, it is hoped that more efficient analogues of oxycodone will be developed. While a variety of its analogues have been prepared to date, extensive modifications of oxycodone are hampered by the fact that it is derived from thebaine (**3**),[3] a minor constituent of opium. In order to synthesize a range of analogues that are not accessible from thebaine, we initiated our studies on the first synthesis of (−)-oxycodone starting from readily available, simple substrates.

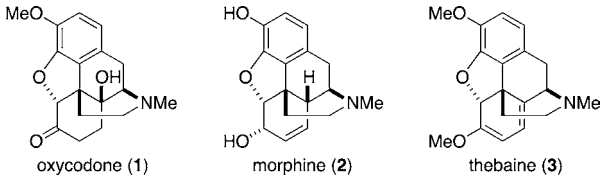
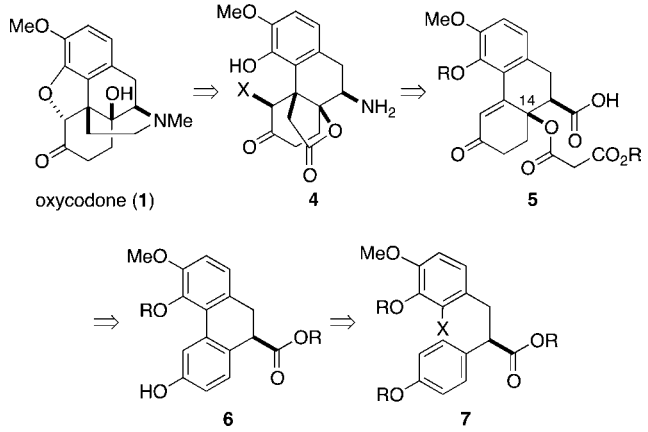


Figure 1. Structures of oxycodone, morphine, and thebaine.

Scheme 1 outlines our retrosynthesis of (−)-oxycodone. Cleavage of the two heterocycles in **1** would lead to lactone **4**. The amine moiety in **4** could be derived from the carboxylic acid of **5** via either a Curtius or a Hofmann rearrangement. Stereoselective construction of the benzylic quaternary carbon in **4** could be performed via an intramolecular Michael addition of the malonate moiety of **5** by taking advantage of the stereochemistry at C-14. Requisite **5** could be synthesized via stereoselective oxidative dearomatization of dihydrophenanthrenol **6**, which in turn would be prepared by a direct intramolecular arylation of aryl halide **7**.

Scheme 1. Retrosynthesis



Our synthesis commenced with the preparation of aryl bromide **13**, a substrate for the direct intramolecular arylation (Scheme 2). Protection of 2-bromoisovanillin (**8**)[4] with a MOM group,[5] followed by reduction of the aldehyde moiety, afforded alcohol **9**, which was converted into benzyl bromide **10**. Alkylation of the enolate derived from imide **11**[6] with **10** proceeded diastereoselectively to furnish **12**.[7] Cleavage of the oxazolidinone auxiliary with hydrogen peroxide and lithium hydroxide, and subsequent methylation of the resulting carboxylic acid with (trimethylsilyl)diazomethane provided

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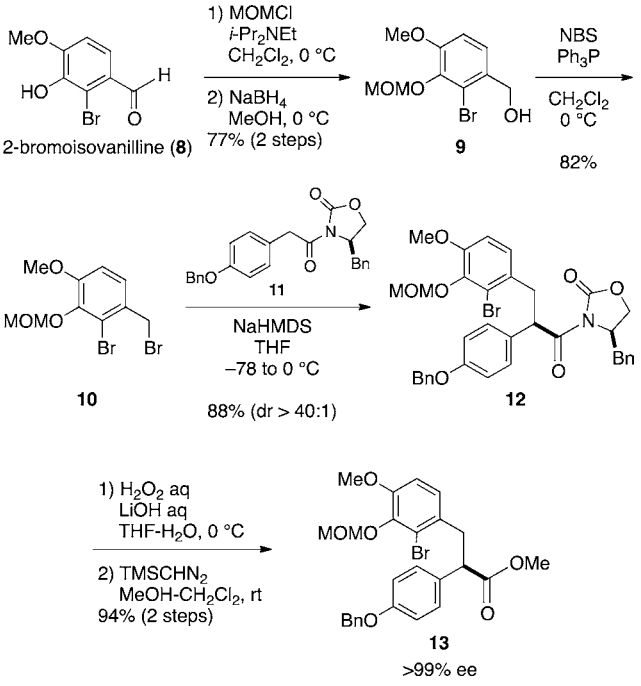
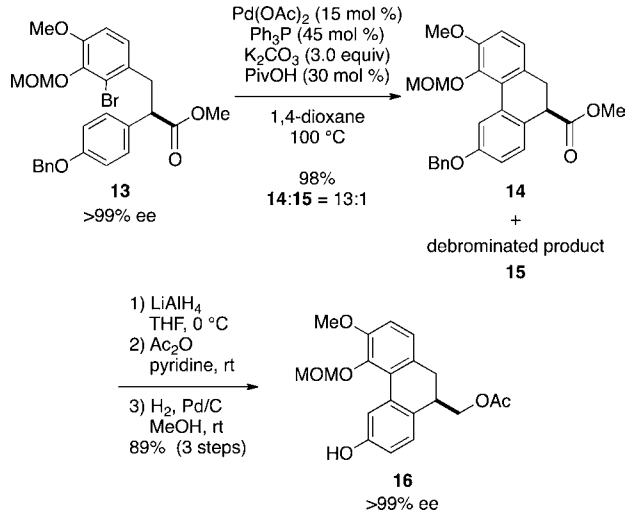
Scheme 2. Preparation of the Aryl Bromide



the desired aryl bromide **13** in good yield and in high enantiomeric purity.

The crucial direct arylation was conducted according to Fagnou's conditions[8] with some modifications (Scheme 3).[9]

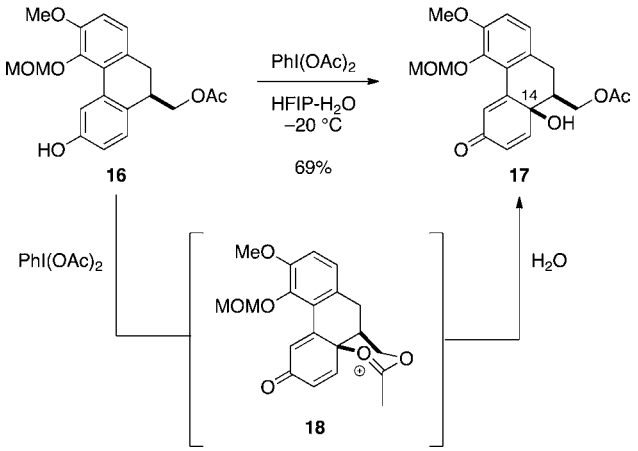
Scheme 3. Direct Intramolecular Arylation



Thus, **13** was treated with palladium acetate (15 mol %) and triphenylphosphine (45 mol %) in the presence of potassium carbonate (3.0 equiv) and pivalic acid (30 mol %) in 1,4-dioxane at 100 °C to provide **14** in good yield. A small amount of the undesired debrominated product **15** was formed as an inseparable mixture. However, a three-step conversion involving reduction of the ester moiety, acetylation of the resulting primary alcohol, and reductive cleavage of the benzyl ether afforded pure dihydrophenanthrenol **16** in good yield with preservation of the optical purity.

With the requisite substrate in hand, we next attempted to introduce the C-14 hydroxy group via an oxidative dearomatization (Scheme 4). An attempted reaction of **16** with singlet oxygen[10] produced a 2:5 diastereomeric mixture of

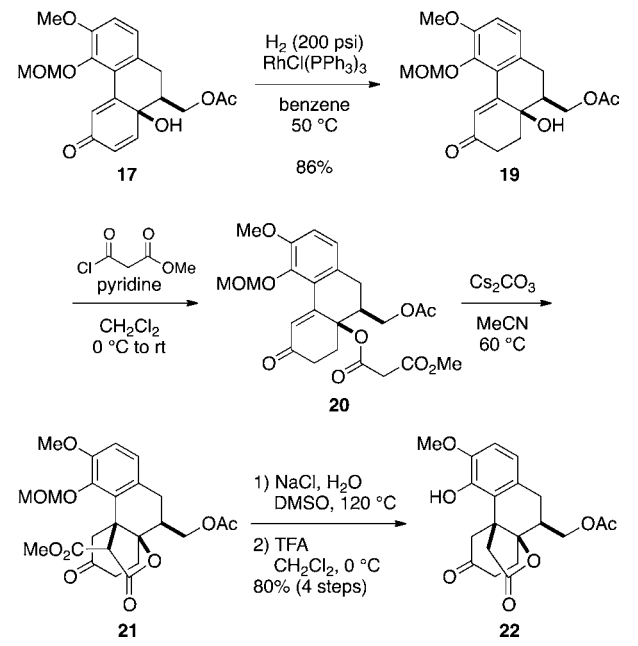
Scheme 4. Oxidative Dearomatization



17, the desired isomer, and its epimer at C-14. Oxidation of **16** with (diacetoxyiodo)benzene in aqueous 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),[11] on the other hand, afforded the desired isomer **17** in 69% yield as the sole isomer. The drastic change in the selectivity might be attributed to the participation of the neighboring acetoxy group to form **18** as an intermediate.[12]

Having successfully installed the C-14 hydroxy group, we turned our attention to the formation of the benzylic quaternary carbon (Scheme 5). Dienone **17** was subjected to

Scheme 5. Construction of the Benzylic Quaternary Carbon



rhodium-catalyzed site-selective hydrogenation[13] to give enone **19**. Acylation of the tertiary alcohol of **19** with methyl malonyl chloride afforded enone **20**. Upon treatment of **20** with cesium carbonate in acetonitrile, an intramolecular Michael addition proceeded smoothly to yield the desired lactone **21** with a benzylic quaternary carbon. Dealkoxycarbonylation of **21** and subsequent cleavage of the methoxymethyl ether gave ketone **22** in high yield.

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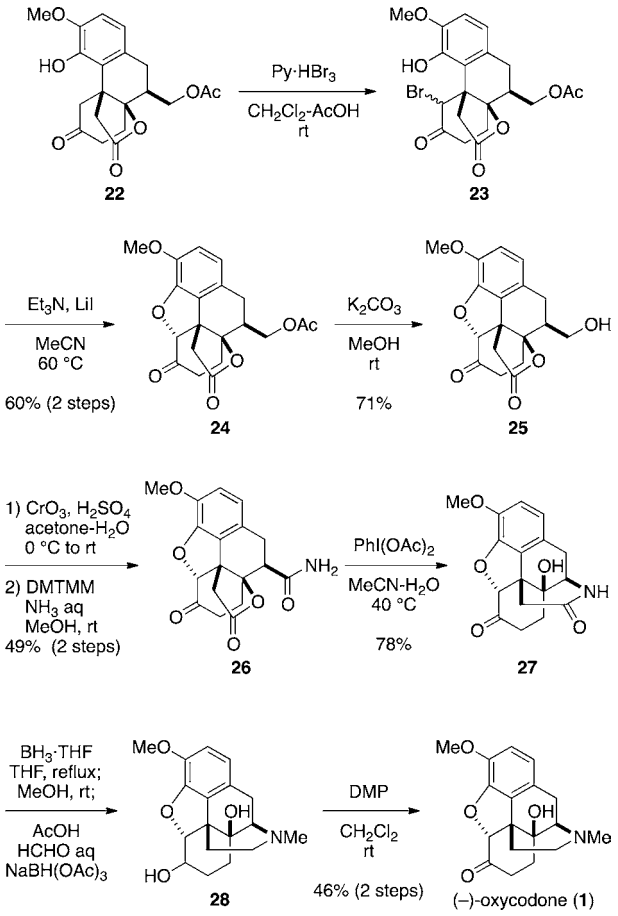
With **22** in hand, the remaining tasks involved construction of the dihydrobenzofuran and the piperidine (Scheme 6). Site-

Scheme 6. Completion of the Synthesis



selective α-bromination of **22** was conducted by means of pyridinium tribromide[14] to afford α-bromoketone **23** as a diastereomeric mixture. Upon treatment with lithium iodide and triethylamine, both diastereomers were converted into the desired product **24**.[15] After methanolysis of the acetyl group in **24**, the resulting primary alcohol **25** was oxidized into a carboxylic acid, which was subsequently condensed with ammonia using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[16] to give amide **26**. A (diacetoxyiodo)benzene-mediated Hofmann rearrangement[17] followed by hydrolysis of the resulting isocyanate afforded a primary amine, which spontaneously attacked the lactone to form the desired lactam **27** in good yield. Reduction of the lactam in **27** and subsequent methylation of the resulting amine gave diol **28**. Finally, oxidation of the secondary alcohol to the ketone with Dess−Martin periodinane[18] furnished (−)-oxycodone. The spectroscopic data of (−)-oxycodone thus prepared are consistent with those reported in the literature.[19]

In conclusion, we have completed the first synthesis of (−)-oxycodone. The key features of our synthesis include a palladium-catalyzed direct arylation, oxidative dearomatization, formation of the benzylic quaternary carbon by an intramolecular Michael addition, and construction of the morphinan skeleton via a Hofmann rearrangement/lactamization cascade. Further improvement in the synthesis of morphinan alkaloids is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Freund, M.; Speyer, E. DE 286431, 1914. (b) Freund, M.; Speyer, E. DE 296916, 1916. (c) Freund, M.; Speyer, E. *J. Prakt. Chem.* **1916**, *94*, 135.

(2) (a) Heiskanen, T.; Kalso, E. *Pain* **1997**, *73*, 37. (b) Mercadante, S.; Arcuri, E. *Cancer Treat. Rev.* **1998**, *24*, 425. (c) Watson, C. P.; Babul, N. *Neurology* **1998**, *50*, 1837. (d) Silvestri, B.; Bandieri, E.; Del Prete, S.; Ianniello, G. P.; Micheletto, G.; Dambrosio, M.; Sabbatini, G.; Endrizzi, L.; Marra, A.; Aitini, E.; Calorio, A.; Garetto, F.; Nastasi, G.; Piantedosi, F.; Sidoti, V.; Spanu, P. *Clin. Drug Investig.* **2008**, *28*, 399.

(3) (a) Sándor, B.; Csaba, C.; Attila, S. *Curr. Med. Chem.* **2009**, *16*, 3215. (b) Halvorsen, H.; Lovli, T. WO 2009004491, 2009. (c) Weber, B.; Sahli, S. WO 2011117172, 2011. (d) Keskeny, E. M.; Mencel, J. J.; Dung, J.-S. WO 2012003468, 2012.

(4) Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1998**, *53*, 4694.

(5) Duchek, J.; Piercy, T. G.; Gilmet, J.; Hudlicky, T. *Can. J. Chem.* **2011**, *89*, 709.

(6) For preparation of imide **11**, see the Supporting Information: Arvanitis, E.; Ernst, H.; Ludwig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521.

(7) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Heemstra, J. M.; Kerrigan, S. A.; Doerge, D. R.; Helferich, W. G.; Boulanger, W. A. *Org. Lett.* **2006**, *8*, 5441.

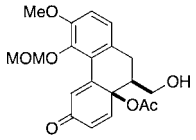
(8) (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

(9) The reaction using *N*,*N*-dimethylacetamide (DMA), a common solvent for palladium-catalyzed direct arylation, gave **14** in low yield with an unacceptable amount of **15**.

(10) (a) Saito, I.; Chujo, Y.; Shimazu, H.; Yamane, M.; Matsuura, T.; Cahnmann, H. J. *J. Am. Chem. Soc.* **1975**, *97*, 5272. (b) Breton, J. L.; Llera, L. D.; Navarro, E.; Trujillo, J. *Tetrahedron* **1987**, *43*, 4447. (c) Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737.

(11) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(12) Under the (diacetoxyiodo)benzene-mediated oxidative dearomatization reaction conditions, a trace amount of acetate **29** was also produced, strongly supporting the proposed reaction pathway.



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(13) Fang, L.; Chen, Y.; Huang, J.; Liu, L.; Quan, J.; Li, C.-C.; Yang, Z. *J. Org. Chem.* **2011**, *76*, 2479.

(14) Pyridinium tribromide was recrystallized twice from ethanol prior to use. Use of commercial pyridinium tribromide without recrystallization caused overbromination at the less hindered α-position.

(15) (a) Mulzer, J.; Dürner, G.; Trauner, D. *Angew. Chem., Int. Ed.* **1996**, *35*, 2830. (b) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun.* **2001**, 1094. (c) Wang, P. X.; Jiang, T.; Cantrell, G. L.; Berberich, D. W.; Moser, F. W.; Bao, J. US 20090221825, 2009.

(16) Kunishima, M.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. *Tetrahedron Lett.* **1990**, *40*, 5327.

(17) Moriarty, R. M.; Chany, C. J., II; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478.

(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(19) ^{1}H NMR: Dung, J.-S.; Mudryk, B.; Sapino, C.; Sebastian, A. EP0889045, 1998. ^{13}C NMR: Tavakol, H.; Esfandyari, M.; Taheri, S.; Heydari, A. *Spectrochim. Acta, Part A* **2011**, *79*, 574. Optical rotation: Currie, A. C.; Gillon, J.; Newbold, G. T.; Spring, F. S. *J. Chem. Soc.* **1960**, 773.

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