

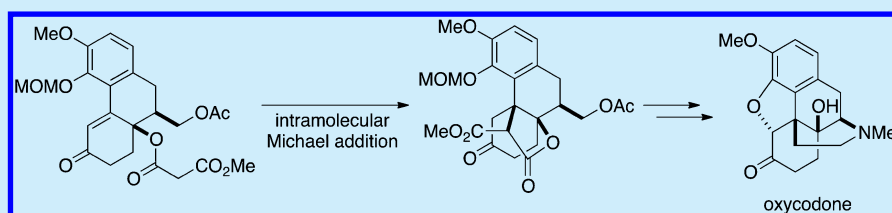
Synthesis of (–)-Oxycodone

Atsushi Kimishima,^{†,§} Hirotatsu Umihara,^{†,‡} Akihiro Mizoguchi,[†] Satoshi Yokoshima,[‡] and Tohru Fukuyama^{*,‡}

[†]Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

S 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 analgesic¹ 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.

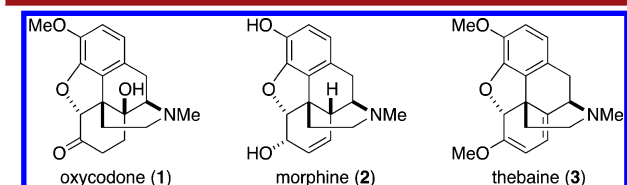
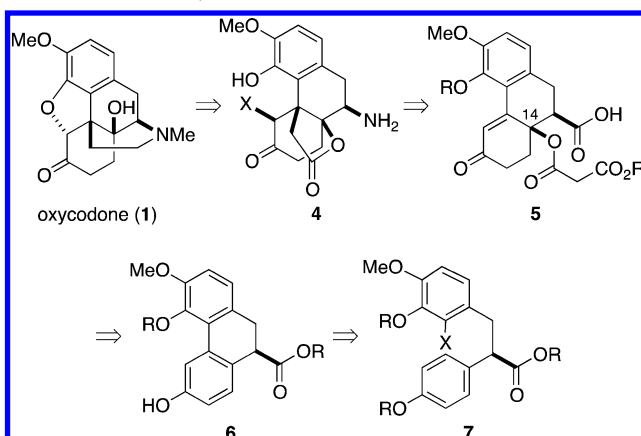


Figure 1. Structures of oxycodone, morphine, and thebaine.

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 dihydrophe-

Scheme 1. Retrosynthesis

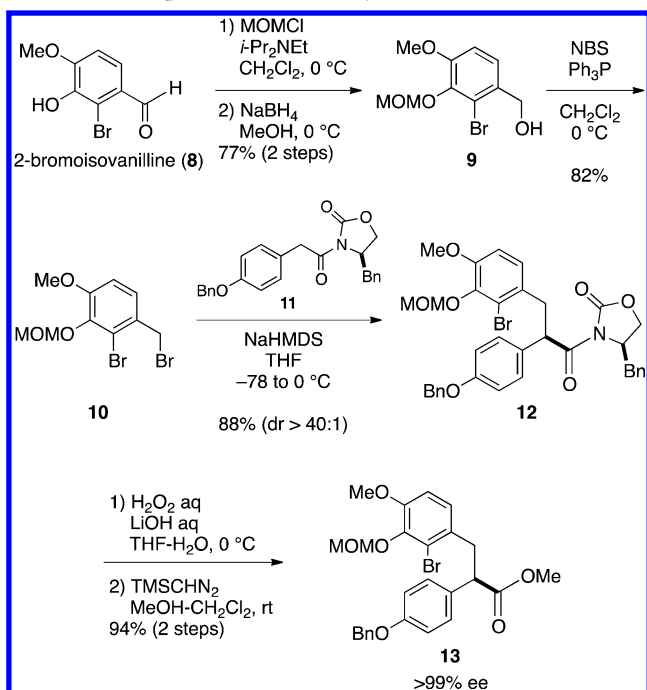


nanthrenol **6**, which in turn would be prepared by a direct intramolecular arylation of aryl halide **7**.

Our synthesis commenced with the preparation of aryl bromide **13**, a substrate for the direct intramolecular arylation (Scheme 2). Protection of 2-bromoisoavanillin (**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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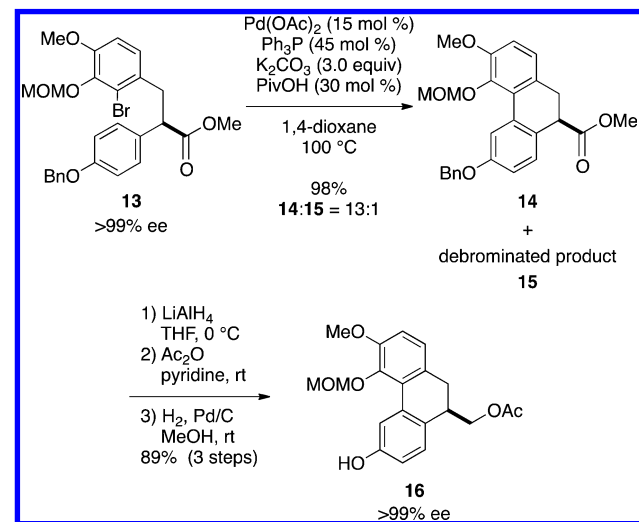
Scheme 2. Preparation of the Aryl Bromide



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

The crucial direct arylation was conducted according to Fagnou's conditions⁸ with some modifications (Scheme 3).⁹

Scheme 3. Direct Intramolecular Arylation

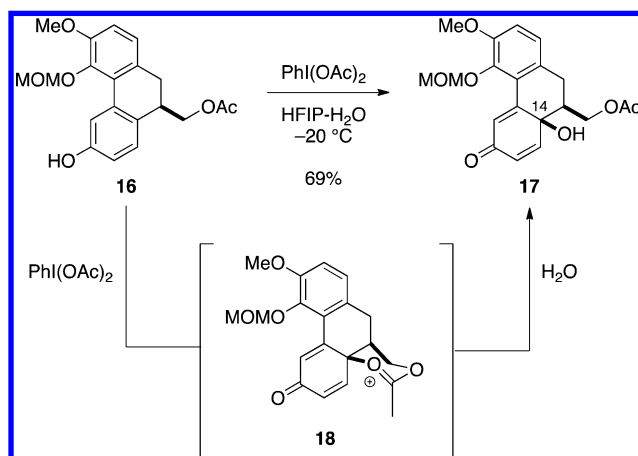


Thus, **13** was treated with palladium acetate (15 mol %) and triphenylphosphine (45 mol %) in the presence of potassium carbonate (3.0 equiv) and pivalic acid (30 mol %) in 1,4-dioxane at 100°C to provide **14** in good yield. A small amount of the undesired debrominated product **15** was formed as 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 oxygen¹⁰ produced a 2:5 diastereomeric mixture of

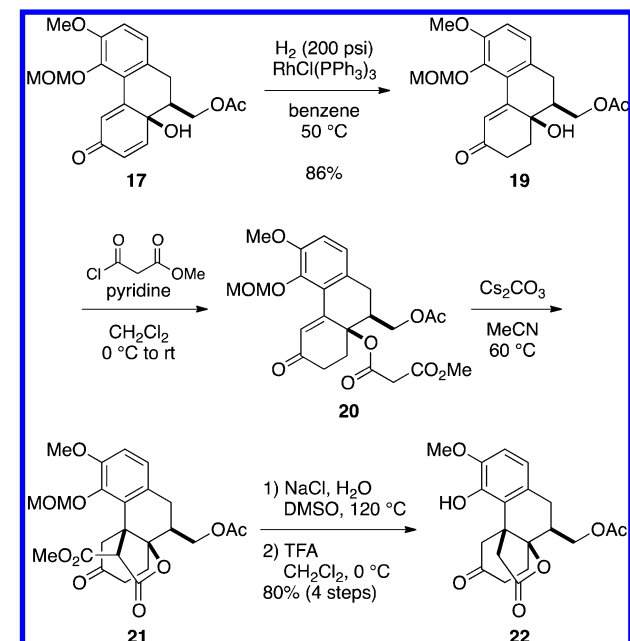
Scheme 4. Oxidative Dearomatization



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

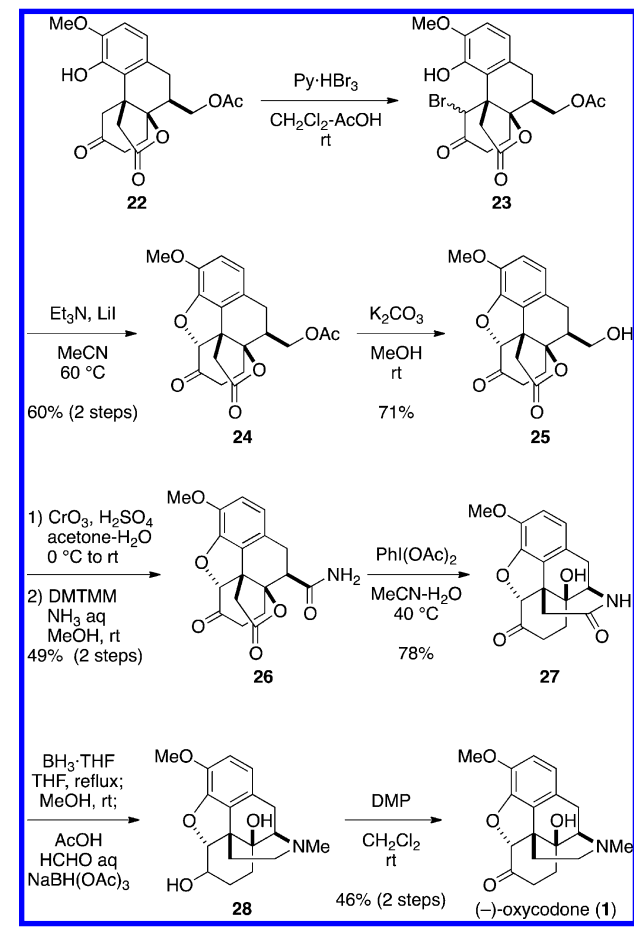
Scheme 5. Construction of the Benzylic Quaternary Carbon



rhodium-catalyzed site-selective hydrogenation¹³ 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.

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 tribromide¹⁴ 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 rearrangement¹⁷ 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 periodinane¹⁸ 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/lactamiza-

tion 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>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fukuyama@ps.nagoya-u.ac.jp.

Present Address

[§]Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA.

Notes

The authors declare no competing financial interest.

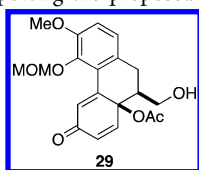
■ ACKNOWLEDGMENTS

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(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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