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Alkaloids

Total Synthesis of Codeine

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Abstract: In this paper, a new strategy towards the synthesis of codeine and morphine is reported. This new approach features a cascade cyclization to construct the dihydrofuran ring, and an intramolecular palladium catalyzed C–H olefination of unactivated aliphatic alkene to install the morphinan ring system.

The opium alkaloids constitute a class of structurally related natural products isolated from opium poppy, *Papaver somniferum*.[1] Among them, morphine, one of the most effective analgesic and anesthetic drugs with a serious addictive side effect, and its derivatives (Figure 1) are especially attractive due to

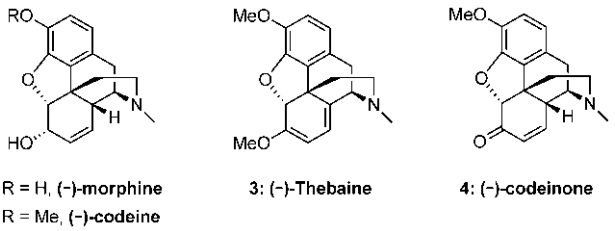
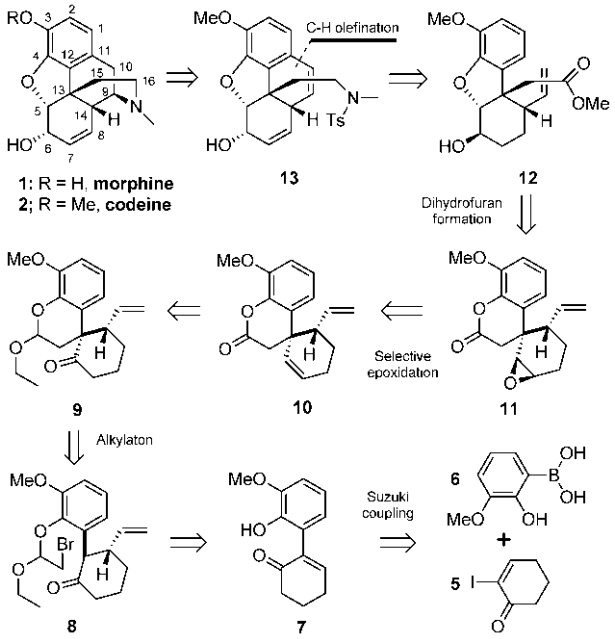


Figure 1. Natural opium alkaloids.

their highly challenging molecular architecture and biological activities.[1d] The structure of morphine contains a strained pentacyclic core with five contiguous chiral centers including a benzylic quaternary carbon (morphinan[1b,d] skeleton). Morphine is considered to be one of the most interesting molecules for testing contemporary synthetic methodologies.[2] Since Gates published the first total synthesis of morphine,[3a,b] the synthesis of morphinans has attracted the attention of many generations of synthetic chemists. To date, there are more than 30 reported routes for the total synthesis or formal synthesis of codeine, morphine and its analogues.[3]

Over the past decade, direct C–H functionalization has emerged as a powerful and straightforward method in organic synthesis.[4] Carbon–carbon and carbon–heteroatom bond formation through C–H activation enables novel disconnections for retrosynthetic analysis, and improve the overall efficiency in the total synthesis of natural products.[5] Although significant advances have been made in method development, the application of C–H bond activation to the synthesis of structurally complex natural products is still a challenge.[5a,c] Herein we report a new approach towards the synthesis of (±)-codeine and morphine. Our new strategy features a cascade cyclization to construct the dihydrofuran ring and a palladium-catalyzed C–H olefination to furnish the morphinan ring system. The retrosynthetic analysis is outlined in Scheme 1. The opium alkaloids (**1** and **2**) shown in Figure 1 could be synthesized from intermediate **13** (Parker–Guillou procedure[3s,ak]) by a reductive hydroamination to form the C9–N bond. A transition-metal-mediated C–H olefination of compound **12** to connect the C10–C11 bond followed by functional-group transformation might lead to intermediate **13**. Lactone ring opening and dihydrofuran ring closing sequential reaction of epoxide **11** would afford **12**. The key all-carbon quaternary centers required for the synthesis of opium alkaloids could be constructed by an intramolecular alkylation of ketone **8**. The enone (**7**) could be obtained by a Suzuki coupling of commercially available starting materials (**6** and **5**).



Scheme 1. Retrosynthetic analysis of codeine.

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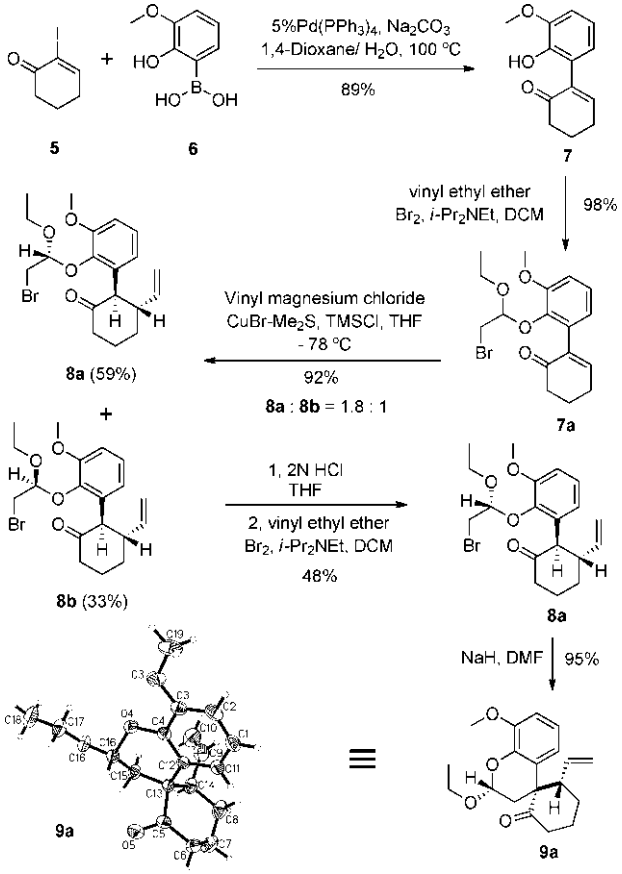
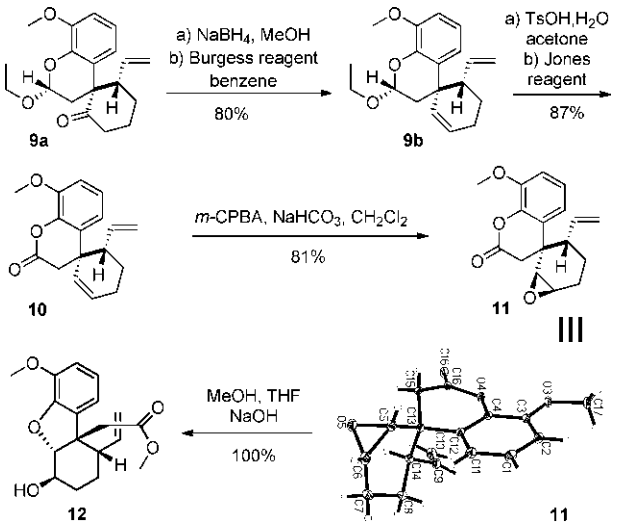
Our synthesis commenced with arylboronic acid **6** and 2-iodocyclohexenone (**5**), and the Suzuki coupling provided phenol **7** in 89% yield. Treatment of **7** with ethyl vinyl ether and bromine in dichloromethane (DCM)[3an] afforded **7a** (99%). Michael addition with vinyl magnesium bromide towards **7a** in the presence of copper(I) bromide resulted in a pair of diastereoisomers (only *anti*-form relative stereochemistry for C13 and C14 was observed, diastereoisomers were formed at the ketal center, **8a** and **8b**, d.r. = 1.8:1, Scheme 2) in 92% overall yield.



Scheme 2. Synthesis of intermediate **9a** containing a benzylic all-carbon quaternary center.

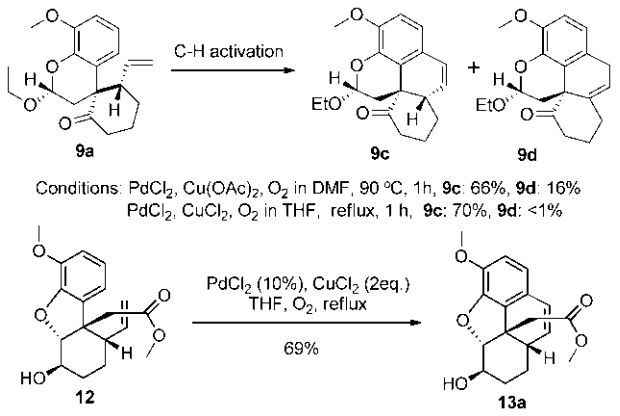
Compound **8b** could be converted to **8a** in a 48% yield (see Supporting Information). Treatment of **8a** with sodium hydride in DMF afforded spiro-compound **9a** in excellent yield (95%) as a single diastereomer, and the relative stereochemistry was confirmed by X-ray crystallography analysis (Scheme 2).

With **9a** in hand, refunctionalization of the cyclohexane ring was initiated. Reduction of ketone **9a** with sodium borohydride in methanol followed by dehydration with Burgess reagent[6] afforded olefin **9b**. Treatment of **9b** with *p*-toluenesulfonic acid (TsOH) in acetone followed by Jones reagent provided lactone **10** in a 63% yield. Chemoselective and diastereoselective epoxidation of olefin **10** with 3-chloroperbenzoic acid (*m*-CPBA) in dichloromethane afforded epoxide **11** (the relative stereochemistry was confirmed by X-ray crystallography) in an 81% yield. The key cascade cyclization was achieved in quantitative yield by treatment of epoxide **11** with methanol in the presence of sodium hydroxide (see Scheme 3).



Scheme 3. Synthesis of intermediate **12**.

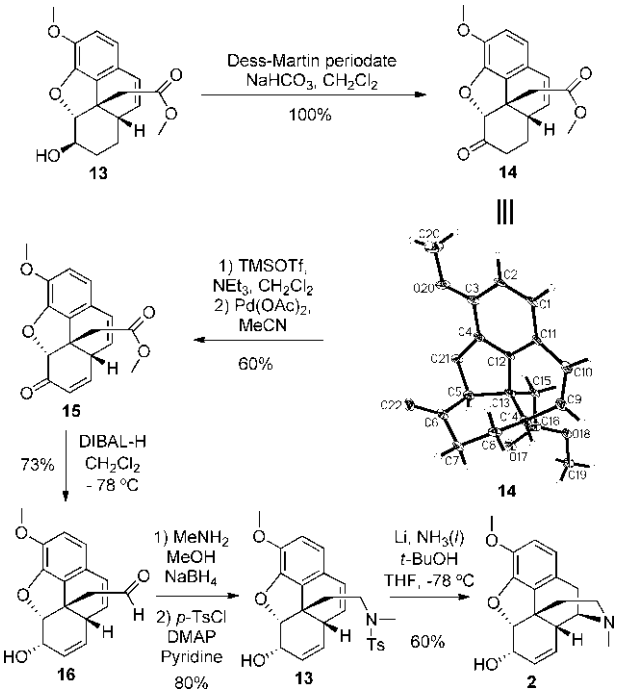
Next, we came to the key stage of our research, the palladium mediated C–H activation to connect the C10–C11 bond. Although the Fujiwara–Moritani reaction (or oxidative Heck reaction) has been intensively studied for many years, trends are directed towards introduction of new directing groups and other transition metals to improve regioselectivity and reactivity.[7] The electrophiles are mainly olefins containing an electron-withdrawing group or styrene derivatives. To the best of our knowledge, unactivated aliphatic terminal vinyl olefin has rarely been used in Fujiwara–Moritani reaction and a preinstalled coordinating group is necessary to achieve C–H olefination.[8] Utilization of intramolecular Fujiwara–Moritani-type coupling as the key step in the total synthesis of natural products was first reported in 1978 by Trost's group.[9] After this pioneering work, a number of elegant works have been accomplished using intramolecular arene–alkene coupling as the key step, including Williams's synthesis of paraherquamide B and notoamide B,[10] Corey's synthesis of okaramine N,[11] Stoltz's synthesis of dragmacidin F,[12] Gaunt's synthesis of rhazinicine,[13] and Trauner's synthesis of rhazinal.[14] To date, intramolecular Fujiwara–Moritani-type couplings of arene moiety with an alkene unit are limited to indole or pyrrole derivatives[9–14] and, except in protocols developed by Gaunt and Trauner, a stoichiometric amount of palladium was required for the desired transformation.[9–12] The initial model reaction was then conducted with spiro-ketal **9a**. After some experiments, we finally found that the desired product could be formed in the presence of $PdCl_2$ and $CuCl_2$ in THF under a dry oxygen atmosphere (Scheme 4), a multifunctional-group-tolerated reaction condition. With the optimized reaction condition in hand, we next carried out the intramolecular Fujiwara–Moritani-type coupling with substrate **12** and the desired intermediate **12a** was obtained in a 69% yield. This is an intramolecular palladium-catalyzed oxidative coupling of terminal unactivated vinylic C–H bond without using pre-installed coordinating groups, and with high regiose-



Scheme 4. Pd-catalyzed intramolecular Fujiwara–Moritani-type olefinations.

lectivity. Although this process might be a C–H activation process, we can't rule out the possibility of olefin activation and then an anti-Markovnikov carbo-palladation of the alkene, followed by *beta*-hydride elimination.

Having established the palladium-mediated procedure to connect the C10–C11 bond, we next came to the final stage of synthesis of codeine and morphine (see Scheme 5). Treatment



Scheme 5. Synthesis of codeine and morphine.

of **13a** with Dess–Martin periodinane in dichloromethane afforded ketone **14** in quantitative yield.[15] Saegusa oxidation of **14** provided enone **15** in a 60% yield.[16] Selective reduction of the ketone and ester moieties presented in **15** with DIBAL-H afforded aldehyde **16** in 73% yield. Reductive amination of **16** with $MeNH_2$ and sodium borohydride followed by treatment with *p*-toluene sulfonyl chloride in pyridine-furnished amide **13**. Finally, amide **13** was converted to codeine in 60% yield by following Guillou's procedure.[3ak] The NMR spectra of our synthetic sample were in complete agreement with the reported data.[3]

In conclusion, we have developed a new strategy towards the total synthesis of codeine and morphine (formal synthesis) with a palladium-catalyzed C–H olefination as the key step. Based on this new disconnection, a general and flexible synthetic strategy has been successfully established. This palladium-catalyzed intramolecular Fujiwara–Moritani olefination, with additional-directing-group-free C–H olefination and multifunctional group tolerance, should find further application in the synthesis of morphine alkaloids as well as its medicinally interesting analogues.

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Keywords: alkaloids · C–H olefination · codeine · palladium · total synthesis

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