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Preparation of Opium Alkaloids by Palladium Catalyzed Bis-Cyclizations. Formal Total Synthesis of Morphine.

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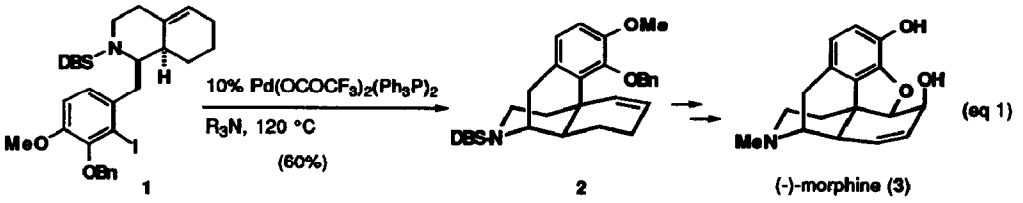
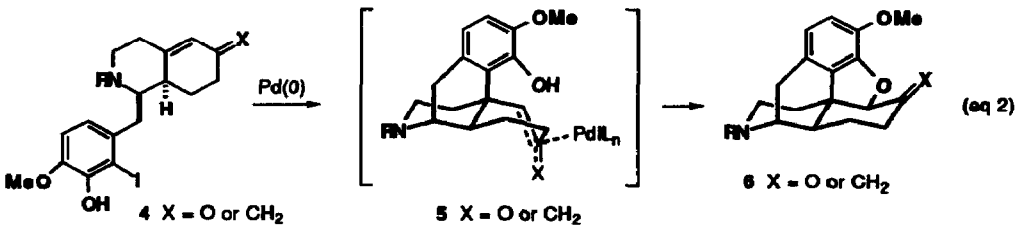
Abstract. Palladium catalyzed cyclization of hydroisoquinoline diene **10** to afford the pentacyclic opiate **11** is the central step in a new synthesis of opium alkaloids.

We recently described a new asymmetric synthesis of opium alkaloids in which an intramolecular Heck arylation was a central step (e.g., eq 1).[2,3] This palladium catalyzed conversion forges the key quaternary center of the morphinan and opium alkaloid skeleta and is notably flexible with regard to the electronic character of the aromatic ring.[2] However, this approach to opium alkaloids has the shortcoming that the dihydrobenzofuran ring must be fabricated subsequently to the Heck cyclization step (e.g., **2** → **3**).

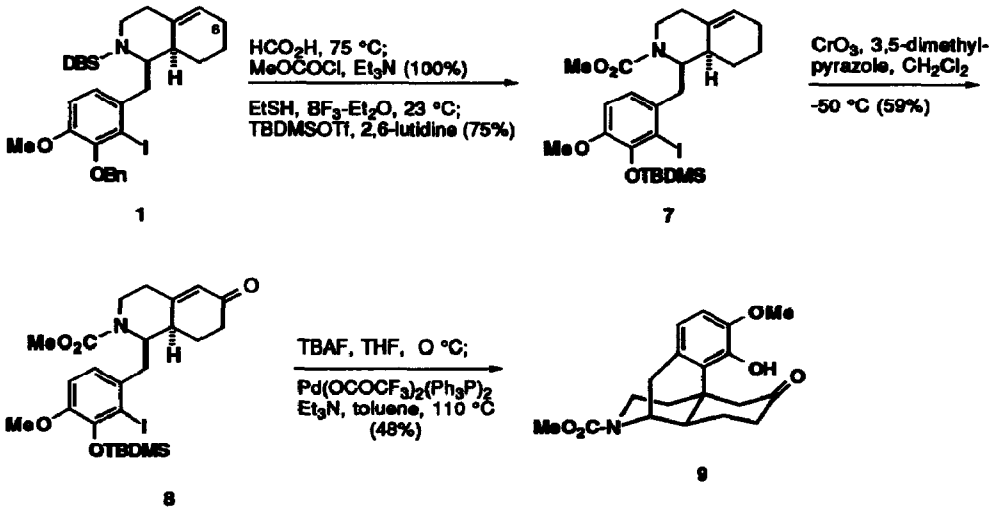


A more attractive construction of the opiate skeleton by a palladium catalyzed bis-cyclization is suggested in eq 2. In the case of the hydroisoquinoline 1,3-diene substrate **4** (X = CH_2), this conversion has precedent in the known preparation of dihydrobenzofurans from the palladium catalyzed reaction of 1,3-dienes and 2-iodophenols.[4] Herein we report the successful use of a palladium catalyzed bis-cyclization to assemble the opiate alkaloid skeleton.



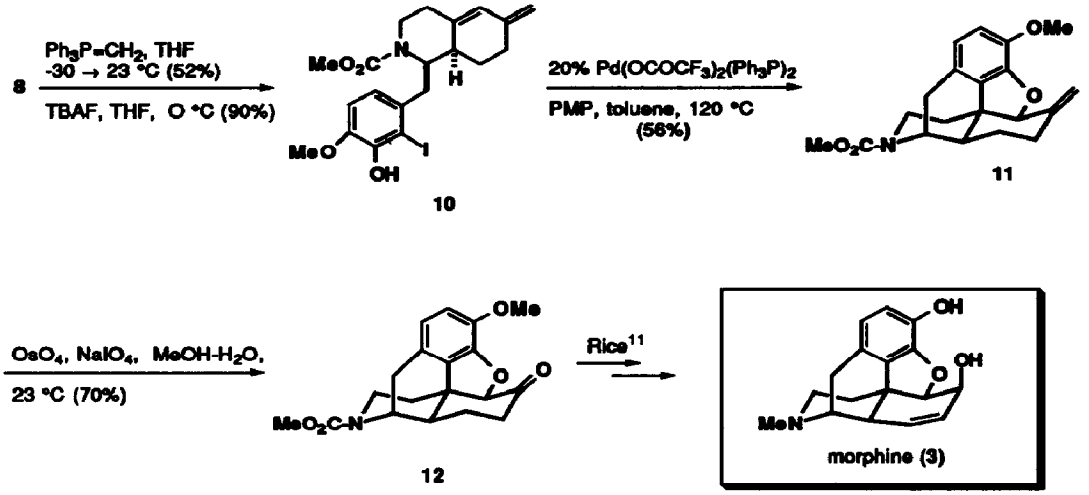
Octahydroisoquinoline **1**, which is available from an allylsilane-iminium ion cyclization,[2,5] served as the starting point for our studies (Scheme 1). In preparation for allylic oxidation to introduce functionality at C(6), the nitrogen and phenol protecting groups of **1** were modified using standard procedures to provide **7**.[6] Selective oxidation of this intermediate with CrO_3-3,5-dimethylpyrazole[7] could be achieved at low temperature to provide enone **8** in 59% yield. Treatment of this hydroisoquinolone with a wide variety of palladium(0) catalysts did not bring about *bis*-cyclization, but rather provided the keto morphinan **9** as the predominant product of cyclization . This result is not surprising, since reductive elimination of an alkoxy oxa-π-allylpalladium intermediates is not expected to be facile.[8]

Scheme 1



We next examined cyclization of the hydroisoquinoline diene **10**, which was directly available from enone **8** by Wittig methylenation followed by desilylation (Scheme 2). Treatment of diene **10** with 0.2 equiv of Pd(OCOCF$_3$)$_2$(Ph$_3$P)$_2$ and 5 equiv of 1,2,2,6,6-pentamethylpiperidine (PMP) in

Scheme 2



refluxing toluene provided the desired pentacyclic opiate **11** in 56% yield.[9] To our knowledge, this is the first example of tandem intramolecular Heck insertion / heterocyclization of a tri-substituted 1,3-diene. The structure of **11** was rigorously secured by cleavage of the exomethylene group[10] to provide the known dihydrocodeinone analog **12**, which completed a formal total synthesis of (±)-morphine.[11]

The formation of **11** from palladium catalyzed cyclization of the hydroisoquinoline diene **10** constitutes a convenient new method for preparing opium alkaloids.[12] Although the studies reported here were conducted in the racemic series, enantioenriched opiates could easily be prepared in this fashion, since either enantiomer of octahydroisoquinoline **1** is available in only seven steps from 2-allylcyclohex-2-en-1-one.[2]

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References and Notes

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(6) All intermediates were fully characterized by ^{1}H, ^{13}C, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Yields refer to isolated, purified products.

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(9) A solution of **10** (17 mg, 36 μmol), $Pd(OCOCF_3)_2(Ph_3P)_2$ (6.2 mg, 7.2 μmol) and 1,2,2,6,6-pentamethylpiperidine (33 μL, 0.18 mmol) was heated at reflux in 10 mL of toluene. After 10h, the reaction mixture was concentrated *in vacuo* and the residue was directly purified by column chromatography (silica gel, 5:1 hexanes-EtOAc) to give 6.9 mg (56%) of **11** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (1H, d, J = 8.4 Hz), 6.61 (1H, d, J = 7.3 Hz), 5.28 (1H, s), 4.90 (1H, s), 4.84 (1H, s), 4.65 (1H, m), 4.05 (1H, m), 3.90 (3H, s), 3.70 (3H, s), 2.60-2.90 (3H), 2.29 (1H, d, J = 12.8 Hz), 2.16 (1H, d, J = 12.1 Hz), 1.60-2.05 (4H, m), 0.90 (1H, dq, J = 2.0 Hz, 12.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 28.6, 28.9, 32.2, 34.9, 38.6, 42.2, 44.6, 51.2, 52.6, 56.7, 89.8, 111.3, 114.2, 119.4, 125.7, 135.2, 143.3, 144.9, 156.0; IR (film) 2931, 1695, 1506, 1443, 1275, 1125, 1038 cm^{-1}; MS (EI) m/z 341.1613 (341.1627 calcd. for $C_{20}H_{23}NO_4$, M, 80%), 282 (10%), 239 (100%), 143 (15%).

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