Asymmetric Synthesis of Either Enantiomer of Opium Alkaloids and Morphinans. Total Synthesis of (–)- and (+)-Dihydrocodeinone and (–)- and (+)-Morphine

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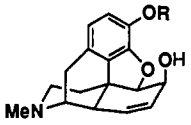
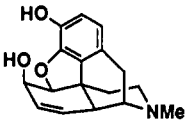
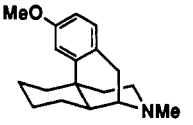
The natural opium alkaloids (–)-morphine (**1**) and (–)-codeine (**2**)[2] and simpler morphinan[3] and benzomorphan structural analogs are indispensable analgesics in the practice of medicine.[4] Pharmacological activity in these series, not surprisingly, is dramatically dependent on absolute configuration. For example, unnatural (+)-morphine (**3**) has extremely weak affinity for opiate receptors,[2,5] while dextromethorphan (**4**), a morphinan with the unnatural opiate stereochemistry, is not an analgesic, but rather a powerful antitussive.[3] Herein we disclose a versatile approach for the asymmetric synthesis of either enantiomer of opiates and morphinans.[6,7]



R = H (-)-morphine (**1**)
R = Me (-)-codeine (**2**)



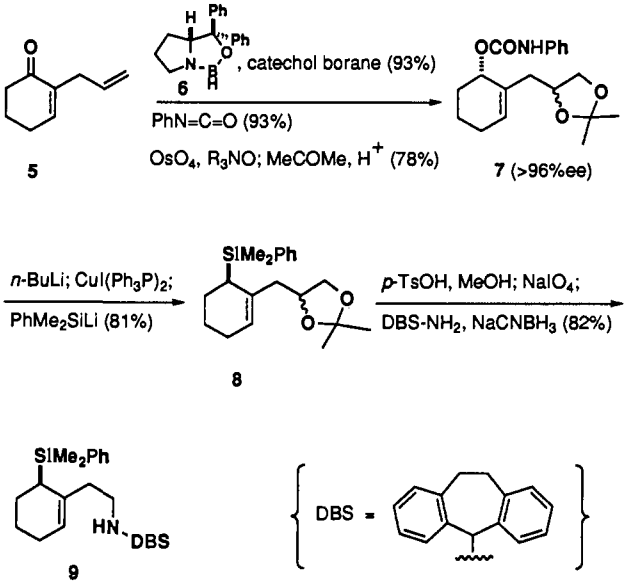
(+)-morphine (**3**)



dextromethorphan (**4**)

Our strategy was to first form an enantioenriched octahydroisoquinoline[8] and then employ an intramolecular Heck reaction to forge the critical quaternary center of the morphinan skeleton.[9,10] The synthesis of the (*R*)-allylsilane amine **9**, the precursor of natural morphine, is summarized in Scheme I. Enantioselective reduction[11] of 2-allylcyclohex-2-en-1-one (**5**)[12] with catecholborane in the presence of the (*R*)-oxazaborolidine catalyst **6**[13] provided the corresponding (*S*)-cyclohexenol in 93% yield and >96% ee.[14] Condensation of this intermediate with phenyl isocyanate, followed by selective catalytic dihydroxylation of the terminal double bond[15] and protection of the resulting diol, provided **7** in 68% overall yield from **5**. Suprafacial S_N2' displacement of this allylic carbamate could be accomplished with minimal stereochemical leakage to an achiral (η^3-alkyl)-copper intermediate[16,17] by sequential treatment of **7** in THF with *n*-BuLi (1.1 equiv, –30 °C), $CuI(Ph_3P)_2$ (1.0 equiv, 0 °C), and $PhMe_2SiLi$ (2.0 equiv, 0 °C) to provide allylsilane **8** in 81% yield. Cleavage of the acetonide of **8** at room temperature in MeOH with catalytic *p*-toluenesulfonic acid followed by periodate cleavage of the resulting diol gave the corresponding β,γ-unsaturated aldehyde, which was immediately treated with dibenzosuberylamine (DBS-NH_2)[18] and $NaCNBH_3$ to provide the homoallylic amine **9** as a colorless oil ($[\alpha]^{25}_D$ +36.7°; *c* = 1.0, $CHCl_3$).[19] Alternatively, reduction of **5** using the enantiomeric (*S*)-oxazaborolidine catalyst[11] and subsequent processing of the derived (*R*)-cyclohexenol by the sequence described in Scheme I readily provided *ent*-**9** in similar overall yield.[19]

Scheme I



The second component of the iminium ion–allylsilane cyclization, arylacetaldehyde **12**, was prepared efficiently from isovanillin as summarized in Scheme II. Lithiation–iodination of acetal **10** (available in two steps and 96% yield from isovanillin),[20] followed by hydrolysis and protection of the resulting phenolic aldehyde, yielded **11**. Reaction of this intermediate with dimethylsulfonium methylide,[21] and then BF_3·OEt_2-catalyzed rearrangement of the resulting epoxide at room temperature in THF, gave **12** in 84% yield. The desired condensation of the allylsilane **9** and aryl acetaldehyde **12** (1.1 equiv) was accomplished cleanly at 60 °C in EtOH in the presence of 5 mol % of ZnI_2 to give the crystalline

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(19) The enantiomeric purity of **9** was estimated to be ~90% (HPLC analysis Chiralcel OJ, 9:1 hexane–EtOH, non-base-line separation); accurate assessment of enantiopurity could be accomplished after conversion to **14** (see text). The absolute stereochemistry assigned to **8** is consistent with precedent[16] and the stereochemical outcome of the iminium ion–allylsilane cyclization to form **14**.

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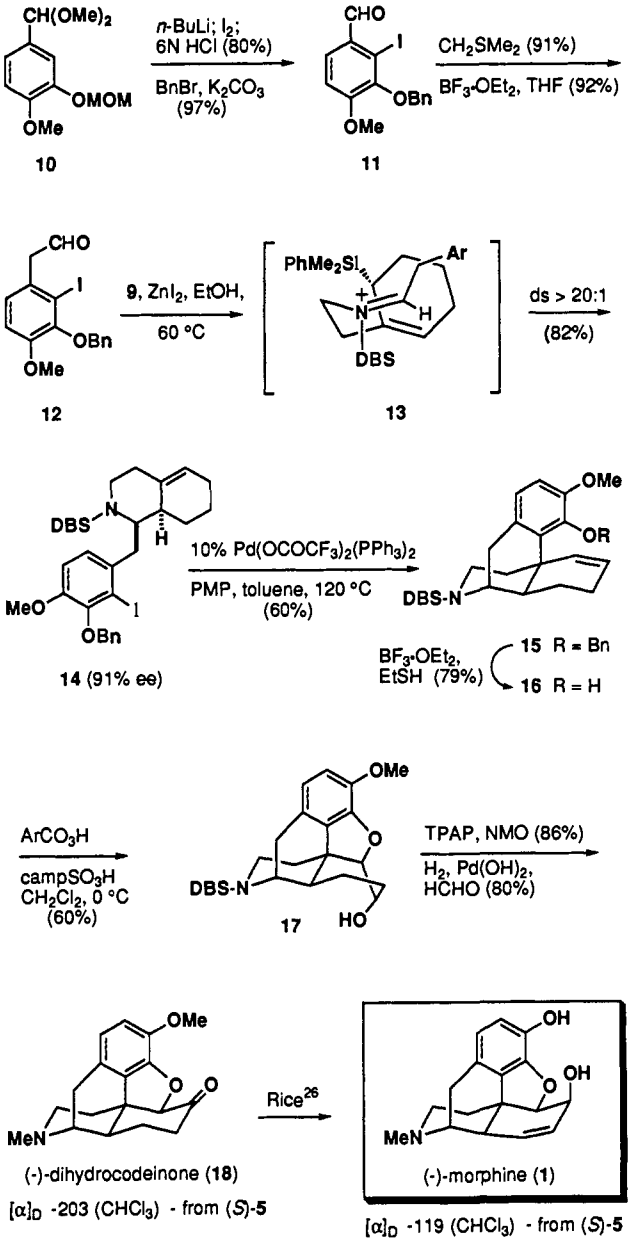
Scheme II



octahydroisoquinoline **14** (mp 167–169 °C) in 82% yield. The enantiomeric purity of this intermediate (91% ee) could be accurately established by HPLC analysis (Chiralcel OD, 9:1 hexane–2-propanol), confirming that the key silylcuprate displacement and iminium ion–allylsilane cyclization steps took place with high stereochemical fidelity. As depicted in **13**, preferential approach of an (*E*)-iminium ion intermediate[8] to the cyclohexenylsilane from the face opposite the silyl residue[22] accounts for the high diastereoselection (>20:1) and transfer of absolute chirality observed in this transformation.

Heck cyclization of **14** was best accomplished using 10 mol % of a reactive catalyst formed from $Pd(OCOCF_3)_2(Ph_3P)_2$ in refluxing toluene (in the presence of 4 equiv of 1,2,2,6,6-pentamethylpiperidine) to give the unsaturated morphinan **15**, $[\alpha]^{25}_D$ −46.6° (*c* = 1.0, $CHCl_3$) in 60% yield. After cleavage of the benzyl ether of **15**,[23] the final ring of the opioid skeleton was formed by reaction of the camphorsulfonate salt of **16** with 3 equiv of 3,5-dinitroperoxybenzoic acid[24,25] in CH_2Cl_2 at 0 °C to provide **17** in 60% yield. Oxidation of **17**, followed by hydrogenolysis of the DBS group in the presence of formaldehyde, provided (−)-dihydrocodeinone (**18**) in 72% overall yield. One recrystallization from Et_2O–$CHCl_3$ (3:1) provided an enantiopure sample of (−)-dihydrocodeinone: mp 193.5–194.5 °C; $[\alpha]^{25}_D$ −203° (*c* = 0.41, $CHCl_3$), lit.[26] $[\alpha]^{25}_D$ −207° ($CHCl_3$). Synthetic dihydrocodeinone (91% ee) was transformed, using a five-step sequence optimized by Rice,[7,27] to (−)-morphine: $[\alpha]^{25}_D$ −119° (*c* = 0.14, $CHCl_3$), corresponding to 91% ee. In identical fashion, *ent*-**9** was converted to enantiopure (+)-dihydrocodeinone, $[\alpha]^{25}_D$ +201° (*c* = 0.21, $CHCl_3$), and enantioenriched (+)-morphine, $[\alpha]^{25}_D$ +118° (*c* = 0.25, $CHCl_3$).

The asymmetric syntheses of natural and unnatural dihydrocodeinone and morphine disclosed herein are the first total syntheses of these opiates that do not entail resolution of an intermediate, although a number of formal asymmetric syntheses are known.[28,29] Significantly, sequential iminium ion–allylsilane cyclization and intramolecular Heck insertion will allow a wide variety of enantioenriched natural and unnatural morphinans, including ones not available by conventional Grewe cyclizations, to be assembled from allylsilanes **9** and *ent*-**9**.[30]

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Supplementary Material Available: Listings of spectroscopic and analytical data for new compounds (6 pages). This material is contained in many libraries on micofiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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