Natural Product Synthesis

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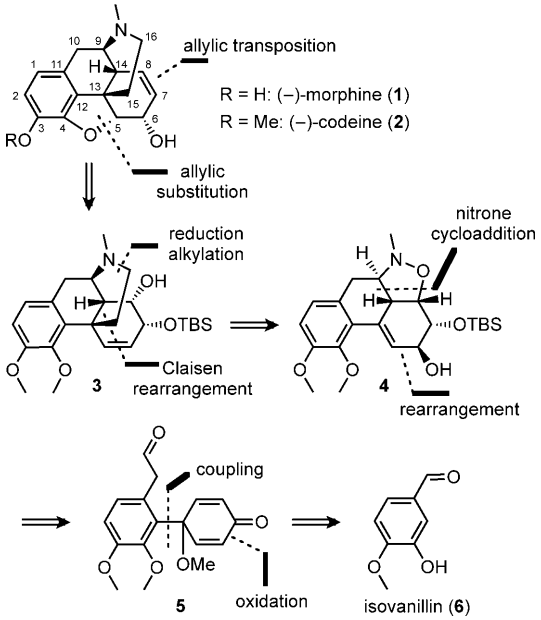
A Total Synthesis of (±)-Codeine by 1,3-Dipolar Cycloaddition**

*Thomas Erhard, Gunnar Ehrlich, and Peter Metz**

Not only due to its potent analgesic effect but also because of its complex molecular architecture, (−)-morphine (**1**) is one of the most interesting and most thoroughly investigated alkaloids. Since millennia humans have used opium, which contains morphine, to alleviate pain. In the search for morphine derivatives with reduced side effects, total synthesis offers an attractive opportunity although an economical route competitive to isolation is currently not within reach.[1,2] Several efforts in the recent past, for example, the elegant synthesis by Magnus,[3] the improved strategy of Fukuyama,[4] the chemoenzymatic approach of Hudlicky,[5] and the innovative route of Stork,[6] express the permanent interest of the scientific community. Among the numerous strategies for construction of the phenanthrene skeleton, an approach based on intramolecular nitrone cycloaddition starting from a suitably substituted aldehyde seems powerful enough for this challenging task.[7] Initial investigations in our group focused on prochiral *p*-quinol ether **5** as an appropriate dipolarophile also offering the option for an enantioselective modification (Scheme 1). Key intermediate **4** already bears the correct relative configuration at C9 and C14. Completion of the carbocyclic framework should be accomplished by Claisen rearrangement[8] which would also install the quaternary center. After correction of the oxidation state in the side chain, morphinane core **3** would be completed by transannular alkylation of the secondary amine liberated by reductive N–O bond cleavage.[9] Allylic substitution[10] could yield allopseudocodeine and another allylic transposition in which the hydroxy group is shifted from C8 to C6 would finally yield codeine (**2**). With allopseudocodeine in hand, a formal synthesis is already completed.[11] In addition, a second formal synthesis is possible by preparation of a carbamate previously used by Fukuyama.[4a,b]

Our synthesis started from commercially available isovanillin (**6**, Scheme 2). Hydroxy-directed bromination[12] followed by blocking of the phenol as a methyl ether[13] afforded 2-bromoveratrylaldehyde. After chain extension with the methoxymethyl chloride (MOMCl)-derived Wittig



Scheme 1. Pentacyclic morphine (**1**) and retrosynthetic analysis of the applied phenanthrene route.

ylide and methanolysis of the intermediate enol ethers, dimethyl acetal **7** was readily available on a large scale.[4a,b] A commutable strategy in terms of ordering the coupling and oxidation events might be attractive for the construction of the necessary dienone moiety. Suzuki coupling with **A**[3] following the Magnus protocol provided biaryl **8** in excellent yield after basic hydrolysis of the TBS ether.[14] Phenolic oxidation[15] with $PhI(OAc)_2$ (PIDA) by inverse addition (**8** was added slowly to PIDA in methanol) afforded the *p*-quinol ether in good overall yield along with a 2,2-dimethoxy-3,5-cyclohexadienone[16a] as a byproduct. Alternatively, bromine–lithium exchange, reaction with *p*-benzoquinone (*p*BQ) monoketal **B**,[17] and Williamson ether synthesis with bisacetal **9** furnished the corresponding methyl ether. After extensive experimentation, we succeeded in merging the two pathways by single and double acetal cleavage; the highly acid-labile substrates were treated with a catalytic amount of CAN in a buffered MeCN–water mixture at 60 °C to give **5** in virtually quantitative yields.[18] The crystal structure[16b] of **5** unambiguously proved the isolation of this crucial intermediate. Intramolecular nitrone cycloaddition, reduction with L-selectride, and silylation under standard conditions yielded the protected alcohol **10** with complete diastereoselectivity in excellent yield over three steps. Boron trichloride induced allylic rearrangement and subsequent solvolysis of allylic chloride **11**[16c] delivered secondary alcohol **4**, which set the stage for installation of the benzylic quaternary center by thermal Eschenmoser–Claisen rearrangement.

[*] T. Erhard, Dr. G. Ehrlich, Prof. Dr. P. Metz
Fachrichtung Chemie und Lebensmittelchemie
Professur für Organische Chemie I, Technische Universität Dresden
Bergstrasse 66, 01069 Dresden (Germany)
Fax: (+49) 351-463-33162
E-mail: peter.metz@chemie.tu-dresden.de
Homepage: http://www.chm.tu-dresden.de/oc1/

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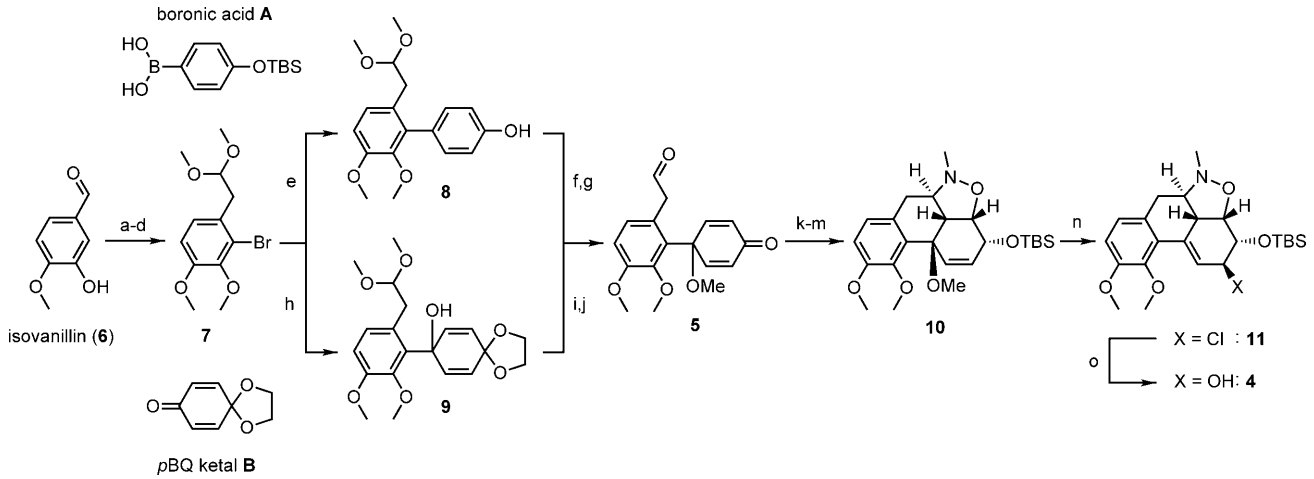
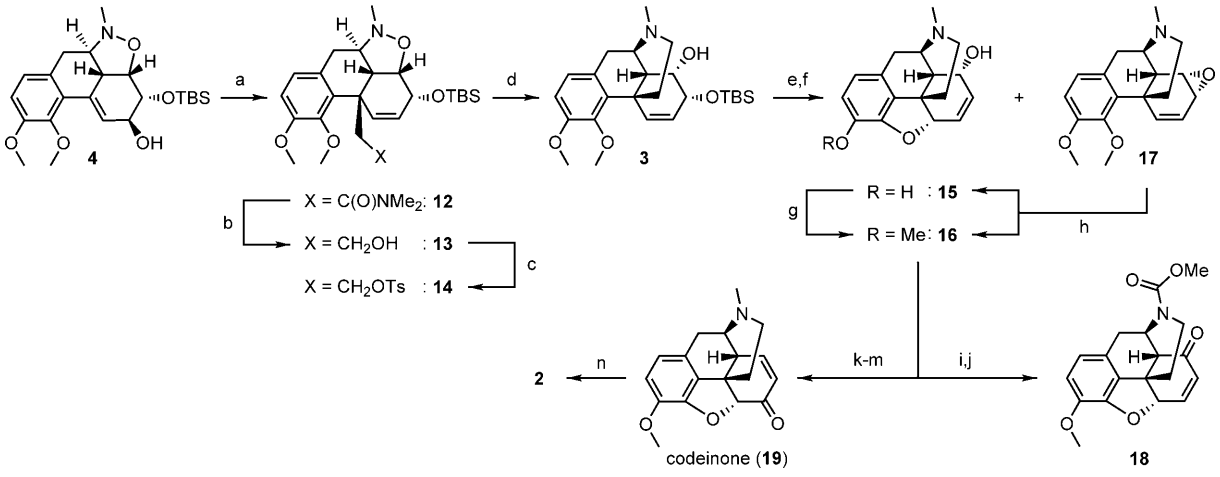


Scheme 2. Facile preparation of the highly functionalized phenanthrene **4**. a) Br_2, cat. Fe powder, NaOAc, HOAc, RT, 92%; b) aq. KOH, Me_2SO_4, 50°C, 95%; c) Ph_3PCH_2OMeCl, KO*t*Bu, THF, 0°C; d) cat. *p*TsOH·H_2O, MeOH, $HC(OMe)_3$, reflux, 95% (2 steps); e) 1. boronic acid **A**, K_2CO_3, 1,4-dioxane/water (7:3), cat. BHT, 2.6 mol% $[Pd_2(dba)_3]$, 5.2 mol% PCy_3, 80°C, 2. aq. NaOH, 50°C, 95% (2 steps); f) PIDA, MeOH, $HC(OMe)_3$, RT, 66% + 24% *o*-quinone dimethylacetal; g) cat. CAN, MeCN/borate buffer (1:1), pH 5–6, 60°C, 97% crude; h) 1. BuLi, THF, −78°C, 2. *p*BQ ketal **B**, −78°C→−70°C, 70%; i) NaH, MeI, THF, 30°C, 94%; j) cat. CAN, MeCN/borate buffer (1:1), pH 5–6, 60°C, 104% crude; k) MeNHOH·HCl, $NaHCO_3$, $MgSO_4$, MeCN, 0°C; l) 1. L-selectride, THF, −78°C, 2. MeOH, −78°C→RT, 3. aq. NaOH, H_2O_2, RT; m) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, RT, 80% (3 steps); n) 1. BCl_3, CH_2Cl_2, −78°C, 2. Et_3N, MeOH, −78°C→RT; o) ZnO, acetone/water (4:1), 80°C, 76% (2 steps). BHT = 2,6-di-*tert*-butyl-4-methylphenol, CAN = ceric ammonium nitrate, Cy = cyclohexyl, dba = dibenzylideneacetone, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, L-selectride = lithium tri-*sec*-butylborohydride, TBS = *tert*-butyldimethylsilyl, *p*Ts = *p*-toluenesulfonyl.

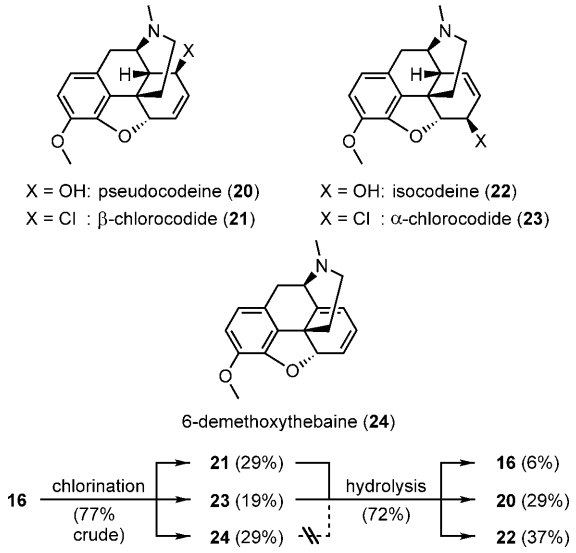
Alcohol **4** was converted to amide **12** in very good yield (Scheme 3). Amide reduction by $LiH_2N{\cdot}BH_3$ furnished primary alcohol **13** nearly quantitatively.[19] The more commonly used superhydride[20] failed, probably because of concomitant reduction of the isoxazolidine moiety. Tosylation of the resulting alcohol and hydrogenolysis of the isoxazolidine with Raney nickel[9] induced spontaneous intramolecular alkylation affording the properly bridged isoquinoline **3**.[16d] Desilylation with TBAF and cleavage of the aryl methyl ether by boron tribromide caused, after alkaline workup, cyclization to a mixture of allopseudocodeine (**16**) and allopseudomorphine (**15**) along with some not demethylated epoxide **17**.[10] Allylic substitution could be performed by BBr_3 starting from **17** too, allowing the recycling of this material. Chemoselective methylation of phenol **15** succeeded by a reported procedure with sodium ethoxide and Me_3NPhCl as the methylating agent.[21] At this point, the first formal synthesis had been successfully achieved. Oxidation of **16** with DMP to



Scheme 3. Completion of both formal and total syntheses of (±)-codeine. a) $MeC(OMe)_2NMe_2$, toluene, Dean–Stark trap, reflux, 87%; b) LDA, $BH_3{\cdot}NH_3$, 0°C→RT, 97%; c) *p*TsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0°C→RT; d) EtOH/EtOAc (3:1), Et_3N, Raney Ni, 1 atm H_2, RT, 86% (2 steps); e) TBAF, THF, 0°C, 100% crude; f) 1. BBr_3, CH_2Cl_2, −65°C, 2. aq. $NaHCO_3$, RT, 15% **16** + 19% **15** + 16% **17** (2 steps); g) Me_3NPhCl, NaOEt, toluene, reflux, 80%; h) 1. BBr_3, CH_2Cl_2, −65°C, 2. aq. $NaHCO_3$, RT, 37% **16** + 16% **15**; i) DMP, $NaHCO_3$, CH_2Cl_2, RT, 91%; j) ClC(O)OMe, $NaHCO_3$, $CHCl_3$, reflux, 93%; k) $SOCl_2$, 0°C→RT, 77% crude; l) 1,4-dioxane/water (1:1), 100°C, microwave irradiation, 72%; m) DMP, $NaHCO_3$, CH_2Cl_2, RT, 29% **19** + 30% pseudocodeinone; n) $NaBH_4$, MeOH, RT, 99%. DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride.

give pseudocodeinone and N-demethylation with methyl chloroformate[22] afforded the known codeine precursor **18**,[4a,b] the spectral data of which were identical to that reported by Fukuyama et al.

For the critical allylic transposition required for the conversion of **16** to **2**, hydrolysis of β-chlorocodide (**21**, Scheme 4) was envisioned.[11a,b] In contrast to the literature



Scheme 4. A closer look at the allylic transposition.

report,[11a] treatment of **16** with thionyl chloride did not afford pure **21** but led to a mixture of the isomeric chlorocodides **21**/**23** along with 6-demethoxythebaine (**24**)[23] as an elimination product. Hydrolysis of this crude mixture under microwave irradiation in dioxane–water yielded a chromatographically inseparable mixture of isocodeine (**22**) along with pseudocodeine (**20**) and **16**. However, after oxidation of this mixture with DMP, codeinone (**19**) could be readily separated from pseudocodeinone and was finally reduced by treatment with sodium borohydride[11d] in methanol following Gates' procedure. The synthetic (±)-codeine (**2**) obtained in this way showed spectral data identical to that of an authentic sample.

In conclusion, we have developed a straightforward route from isovanillin (**6**) to allopseudocodeine (**16**) as part of one total and two formal syntheses of the target alkaloid **2**. Several crucial steps such as the challenging acetal cleavage, intramolecular nitrone cycloaddition, and Claisen rearrangement allowed the facile construction of the morphine core. Further optimization of the final allylic transposition is the subject of ongoing work.

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