The Phenanthrenone Approach to Opium Alkaloids: Formal Total Synthesis of Morphine by Sigmatropic Rearrangement

Johann Mulzer,[a*] Jan W. Bats,[b] Benjamin List,[b] Till Opatz[b] and Dirk Trauner[a]

a) Institut für Organische Chemie der Universität Wien, Währingerstraße 38, A-1090 Vienna, Austria; Internet: mulzer@felix.orc.univie.ac.at

b) Institut für Organische Chemie der Johann Wolfgang Goethe-Universität, Marie-Curie-Straße 11, D-60439 Frankfurt, Germany

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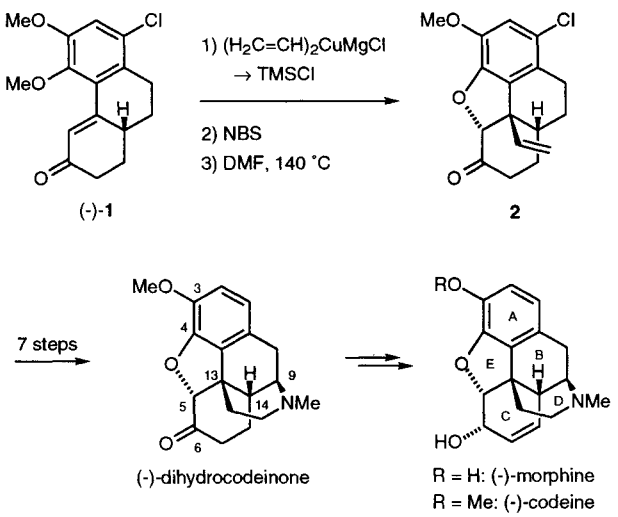
Dedicated to Professor E.J. Corey in recognition of his outstanding contributions to the art of chemical synthesis

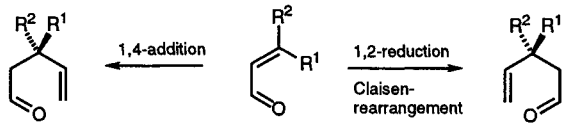
Abstract: The synthesis of morphine alkaloids involving sigmatropic rearrangements and novel ring closures of aromatic methyl pentenyl ethers is reported.

Recently, we described an asymmetric formal total synthesis of (-)-codeine and (-)-morphine, employing the conjugate addition of a vinyl cuprate to the optically pure enone **1** followed by α-bromination and S_N2 ring closure as the key sequence.[1] The resulting ketone **2** was then transformed into (-)-dihydrocodeinone, a standard synthetic precursor of the opium alkaloids.[2]



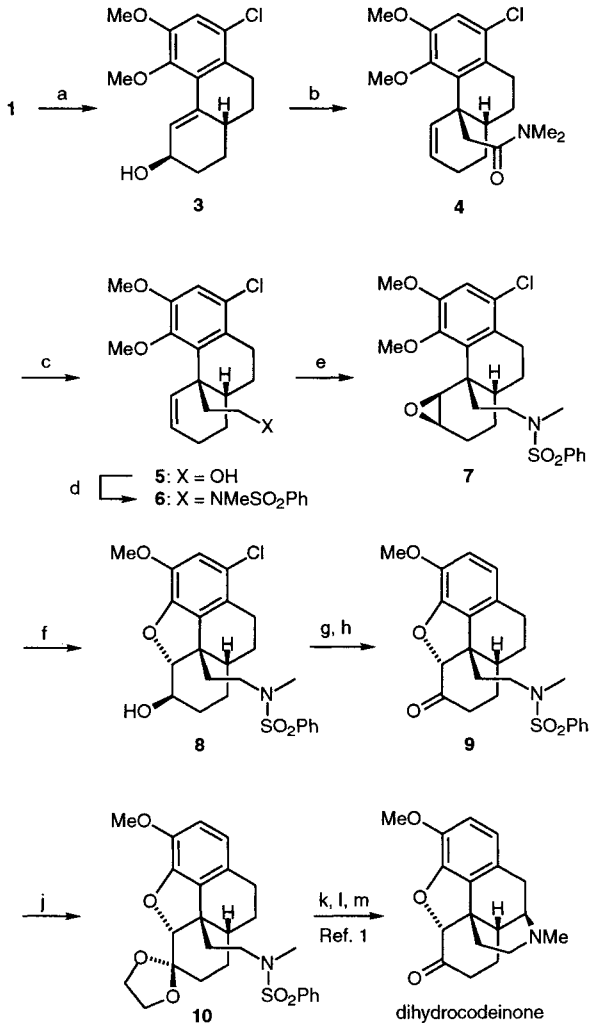
Scheme 1

We now report alternative strategies for the construction of the crucial benzylic quarternary stereogenic carbon (C-13) and the ring closure of the dihydrofurane E. We noticed that Claisen rearrangements[3] can be conveniently pursued in parallel with 1,4- additions of vinyl cuprates. Both synthetic strategies can be (directly or indirectly) applied to enones, and are suitable for the construction of quaternary stereogenic carbons bearing two functionalized C_2-residues:



In fact, sigmatropic rearrangements are well established methods for the construction of benzylic quaternary stereogenic centers.[4] They were successfully employed for the synthesis of sceletium[4a-c] and amaryllidaceae[4d] alkaloids and functioned as key reaction in Rapoport's[5] and Parson's[2b] formal total syntheses of morphine.

Our synthesis starts with the phenanthrenone **1**, which was prepared in 4 steps from commercially available 4-(3,4-dimethoxyphenyl)-butyric acid.[1] Compound **1** contains the entire carbocyclic framework of morphine and shows the correct substitution pattern of the aromatic ring A, the nucleophilicity of which is attenuated by the chlorine substituent. DIBAH-reduction of **1** afforded a 82:18 mixture of diasteromeric allylic alcohols in favor of **3** in 99 % combined yield



Scheme 2. (a) DIBAH, THF, -78 °C (80 %). (b) *N,N*-Dimethylacetamide dimethyl acetal, PhMe, reflux (64 %). (c) $LiBHEt_3$, THF, r.t. (96 %). (d) $PhSO_2NHMe$, ADDP, Bu_3P, r.t. (90 %). (e) Dimethyl dioxirane, CH_2Cl_2, 0 °C → r.t. (80 %). (f) TFA, THF, r.t. (83 %). (g) H_2, Pd/C, Et_3N, MeOH, r.t. (88 %). (h) Swern oxidation, -78 °C → r.t. (90 %). j) TMSCl, $(CH_2OH)_2$, CH_2Cl_2, r.t. (92 %). (k) NBS, $(PhCOO)_2$, CCl_4, reflux. (65 %). (l) Li, NH_3, THF, *t*-BuOH; (80 %). (m) 3 *N* HCl, 90 °C (95%)

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(Scheme 2). Other reducing agents (e.g. $NaBH_4$, $NaBH_4/CeCl_3$), as well as the change of solvent and temperature led to lower diastereomeric ratios in comparable yields. Strategically, the stereochemical outcome of this reduction is of little concern, since morphinanes with the unnatural configuration at C-14 can be epimerized by known procedures.[2f,6] In fact, this had to be done in the very first total synthesis of morphine by Gates and Tschudi.[6] Gratifyingly, the major isomer **3** proved to have the "correct" relative configuration. With ample amounts of allylic alcohol **3** at hand, we studied the [3,3]- and [2,3]-sigmatropic rearrangements of the molecule.

The Eschenmoser-Claisen rearrangement[7] of **3** afforded dimethyl amide **4**. This reaction creates the critical benzylic quaternary stereocenter (bearing a two carbon side chain) and places a $\Delta^{5,6}$ double bond into ring C. The relative stereochemistry of **4** was elucidated by single crystal structure analysis,[8] which also clarified the stereochemistry of precursor **3** (Figure 1). All attempts to perform the Johnson- or Ireland- variant of the Claisen rearrangement were unsuccessfull in our hands, probably due to the acid sensitivity of **3** and the considerable sterical hindrance at its reaction center.

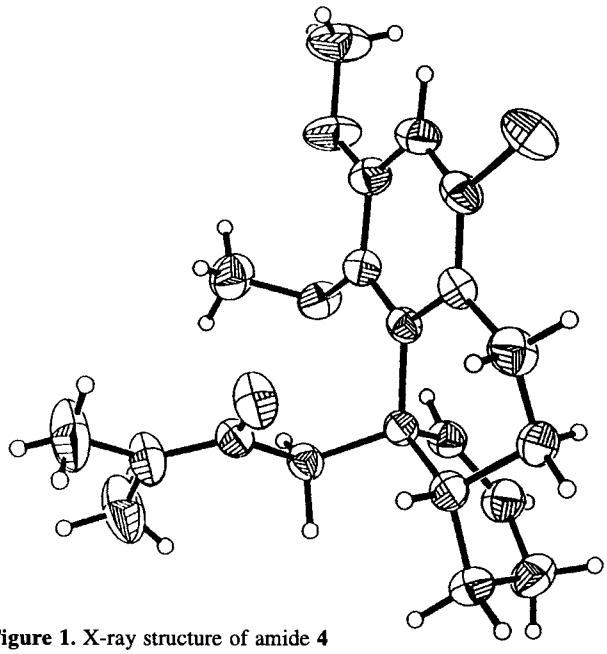
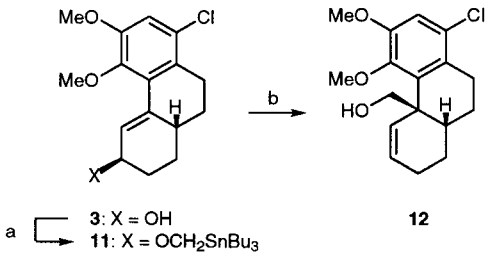


Figure 1. X-ray structure of amide **4**

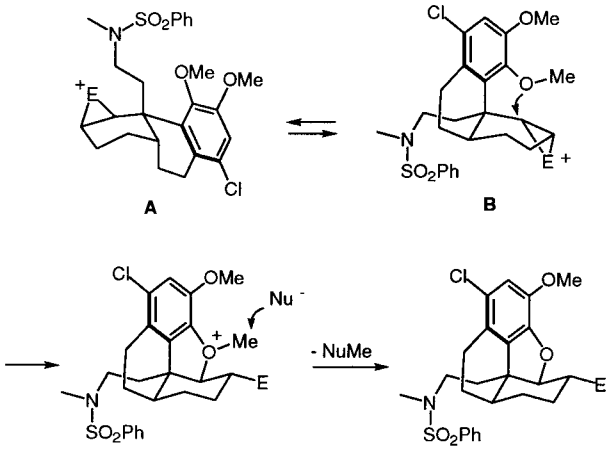
In order to test the [2,3]-Wittig-Still rearrangement,[9] allylic alcohol **3** was converted into the corresponding stannylmethyl ether **11** (Scheme 3). Tin-lithium exchange, followed by [2,3]-sigmatropic rearrangement furnished the homoallylic alcohol **12**.

We continued our synthesis with amide **4**, which was reduced with $LiBHEt_3$ to afford the primary alcohol **5** (Scheme 2). Mitsunobu reaction with *N*-methylbenzenesulfonamide, 1,1'-(azodicarbonyl)-dipiperidine (ADDP) and tributylphosphine[10] furnished sulfonamide **6**. In principle, amide **4** already contains the N-CH_3 moiety of the morphine alkaloids. Elaboration of this functional group, however, requires a difficult mono *N*-demethylation, and was therefore discarded.



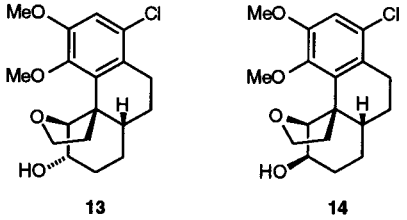
Scheme 3. (a) KH, Bu_3SnCH_2I (89 %). (b) *n*-BuLi, - 95 °C → -70 °C (54 %)

The stage was now set for the closure of the dihydrofuran ring E. We anticipated that electrophilic activation of the $\Delta^{5,6}$ double bond (E^+ = Br^+, OH^+) would lead to a methyl oxonium ion by participation of the 4-methoxy group, which would then be demethylated by the counter nucleophile Nu^- (Scheme 4). Thus, deprotection of the C-4 methoxy group and closure of ring E would be achieved in a single synthetic step.[11] It may be noted, that this sequence can only proceed *via* conformer **B** and not *via* **A** which corresponds to the conformation of **4** in the crystal (Figure 1).



Scheme 4. E^+ = Br^+, OH^+; Nu^- = Br^-, CF_3COO^-

Epoxidation of **6** with dimethyldioxirane afforded a 8.5:1 mixture of diastereomeric epoxides in favor of the desired isomer **7** which already contains all carbon-, oxygen- and nitrogen-atoms of codeine and morphine (89 % combined yield). By contrast, epoxidation with *m*CPBA was completely unselective. The reaction of primary alcohol **5** with *m*CPBA furnished tetrahydrofuranes **13** and **14** along with small amounts of the corresponding β-epoxide, whereas vanadyl acetyl-acetonate/*tert*-butyl hydroperoxide yielded **14** as the only isolable



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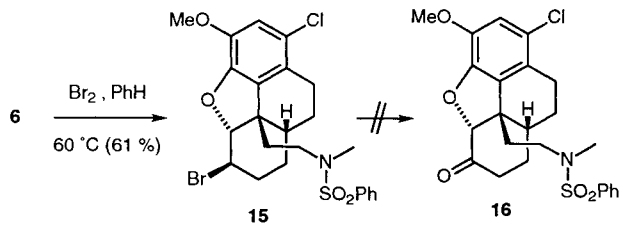
product. Compound **14** is most likely formed by way of a neighbouring group participation of the 4-methoxy group, which results in epoxide opening with net retention of configuration.

Treatment of the β-epoxide **7** with trifluoroacetic acid (TFA) in dry THF effected the desired E-ring closure with concomitant demethylation and provided secomorphinan **8**.[12] Dechlorination and Swern-oxidation furnished ketone **9**, which was protected as the ethylene ketal **10** using Chan's method.[13] Finally, **10** was transformed into dihydrocodeinone as previously described,[1] employing benzylic bromination / dehydro-bromination followed by Parker-Focas piperidine ring closure.[2e]

As an alternative to the epoxidation, we investigated the activation of the double bond with a reversibly attacking electrophile, such as bromine (Scheme 5). Indeed, treatment of **6** with 1.1 equivalents Br_2 afforded **15**. This dealkylating bromoetherification bears some resemblance to Fraser-Reid's elegant glycosylation method.[14] Unfortunately, the hindered secondary bromide **15** could not be converted to the desired ketone **16** as yet.



Scheme 5

In conclusion, we have presented a new variant of our phenanthrenone strategy for the synthesis of morphine alkaloids. Although the studies described herein were conducted in the racemic series, optically pure opiates could easily be prepared in this fashion, since **1** and **3** can be resolved by chromatography on cellulose triacetate[1] and porcine pancreatic lipase mediated kinetic resolution,[15] respectively. The applicability of the Eschenmoser-Claisen rearrangement to the synthesis of highly congested stereocenters was demonstrated, and novel ring closures of methyl pentenyl ethers were developed. Studies directed towards the total synthesis of hasubanane[16] and amaryllidaceae alkaloids based on our previous results are well underway in our laboratories.

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(12) Preparation of **8**: To a solution of the β-epoxide **7** (110mg, 0.224 mmol) in dry THF (5 ml) was added trifluoroacetic acid (2 ml) under argon. After stirring for 3 h at room temperature, the mixture was poured into saturated aqueous sodium bicarbonate (75 ml), and the product was extracted with ether (3 x 25 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (SiO_2; hexanes:EtOAc = 1:1; R_f = 0,2) to provide 89 mg (0.186 mmol, 83 %) of pure **8** as a colorless foam. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.78-7.73 (2H, m), 7.63-7.48 (3H, m), 6.76 (1H, s), 4.47 (1H, d, J = 7.0 Hz), 3.85 (3H, s), 3.38-3.26 (2H, m), 2.97-2.86 (1H, m), 2.76-2.66 (4H, m), 2.48-2.34 (1H, m), 2.23-1.99 (3H, m), 1.92-1.57 (5H, m), 1.40-1.24 (1H, m), 1.12-0.95 (1H, m). ^{13}C-NMR (63 MHz, $CDCl_3$): δ 143.59, 143.42, 137.40, 132.48, 132.26, 128.97, 127.17, 124.67, 123.20, 113.55, 96.30, 72.38, 56.42, 46.19, 46.06, 35.47, 34.47, 34.08, 29.41, 24.67, 23.12, 19.88.

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