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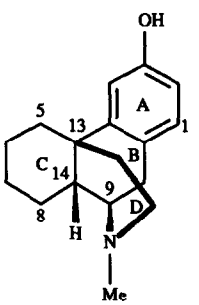
# ENANTIOSELECTIVE APPROACH TO MORPHINANS

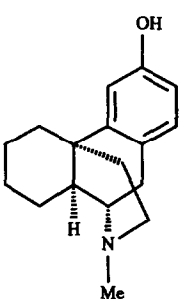
Hamid Sdassi, Gilbert Revial, Michel Pfau, and Jean d'Angelo,
Unité de Chimie Organique Associée au CNRS
ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05 (France).

***Summary** : Enantioselective synthesis of morphinan derivative* **20** *from 2,7-dimethoxynaphthalene has been achieved in twelve steps (11 % overall yield).*

The morphine-like tetracyclic derivatives morphinans are widely used pharmaceutical agents[1]. The development of efficient enantioselective approaches to these alkaloids is essential since, in general, their chemotherapeutic properties strongly depend on their *absolute configurations* [2]. Thus, for example, levorphanol **1** is a powerful analgesic (about *five times* as active as morphine in humans, both on parenteral *and oral* [3] administrations) while dextrorphan **2**, which possesses the opposite absolute configuration, is a cough suppressant drug [4], free from the undesirable opiate psychomimetic side-effects [1].



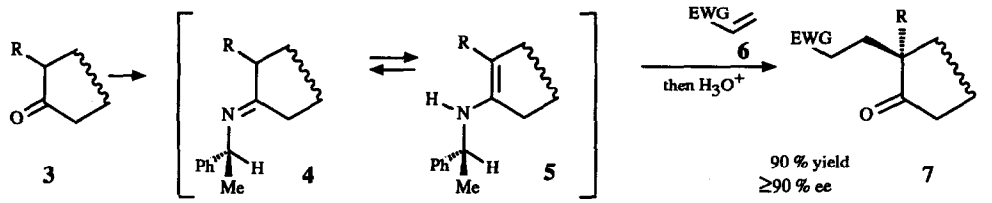

**1**



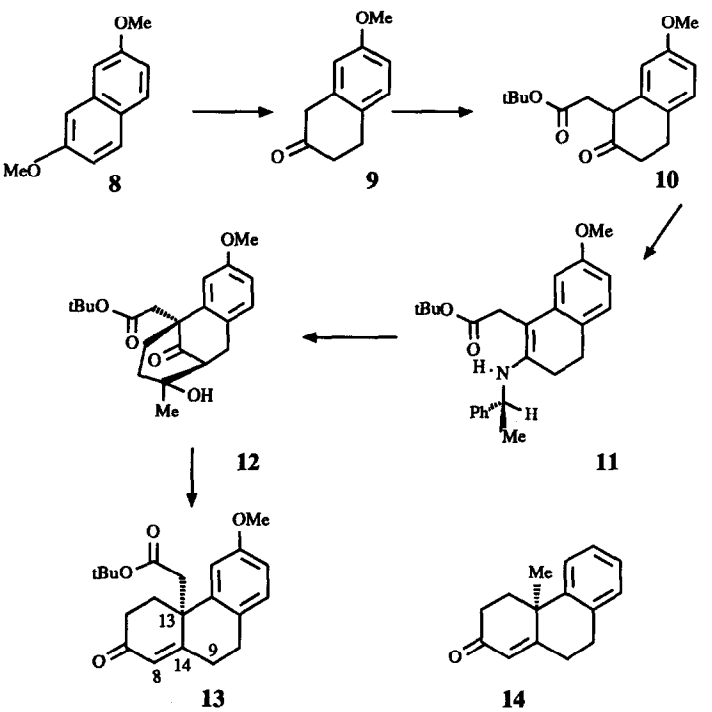

**2**

In this paper we show that optically active phenanthrenone **13**, which carries an acetate side-chain at the BC ring junction (morphinan numbering), is a particularly well-suited [ABC]-type tricyclic intermediate in the synthesis of morphinans. We have actually achieved the construction of the fourth bridging ring D by the intramolecular cyclization of this acetate appendage, after the requisite functional group adjustments [**18** → **20**].

Subunit phenanthrenone **13**, which contains a *single asymmetric center* (future C-13 center in morphinans) was readily built by using an [AB → ABC] asymmetric annulation sequence [**10** → **13**] involving as the key-step the highly potent enantioselective Michael process which we have disclosed [5], summarized by the conversion [**3** → **7**]. Thus, imines **4**, derived from α-substituted cyclanones **3** and optically active 1-phenylethylamine add to electron-deficient alkenes **6** (the reactive nucleophilic species being tautomeric secondary enamines **5**) to lead, after hydrolytic work-up, to α-disubstituted cyclanones **7**, with a high degree of regio- and stereoselectivity.

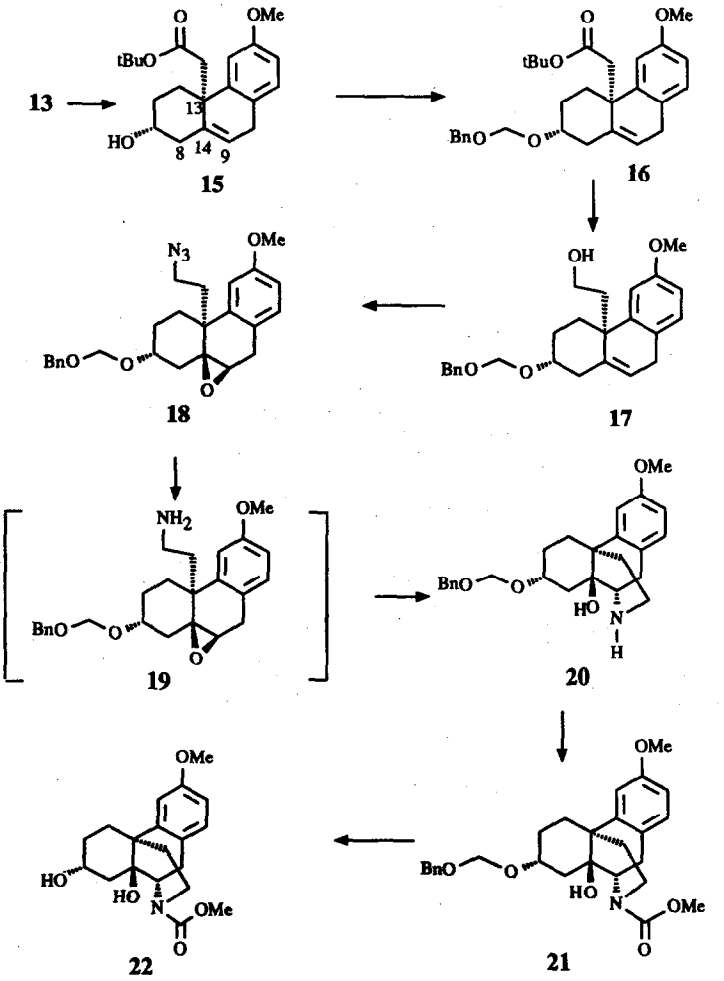



The requisite phenanthrenone **13** was prepared in four steps, from 2,7-dimethoxynaphthalene **8**, with an overall yield of 50 %, according to the following reaction sequence. Birch reduction of this naphthalene[6] ($Na/NH_3/EtOH/Et_2O/THF$ at -78 °C, followed by dilute hydrochloric acid treatment) led to tetralone **9** (80 % yield). This tetralone was alkylated by using Stork's enamine procedure [7] (*i* : pyrrolidine, refluxing benzene with azeotropic removal of water, *ii* : $BrCH_2COOtBu$, tBuOH, 20 °C, 24 h, *iii* : $AcOH/AcONa/H_2O$) to give keto-ester **10** (92 % yield). The latter compound was then transformed into bridged ketol **12**, via enamine **11** [*i* : (*S*)-1-phenylethylamine, refluxing benzene, 2 h, with azeotropic removal of water, *ii* : methylvinylketone, 20 °C, 24 h, *iii* : $AcONa/AcOH/H_2O$] with an overall yield of 80 %. This ketol was next converted into target (*S*)-phenanthrenone **13** [8] (*i* : pyrrolidinium acetate, refluxing benzene, 30 h, with azeotropic removal of water, *ii* : $AcONa/AcOH/H_2O$, 24 h at reflux, 85 % yield). The optical purity of the latter derivative was found to be ≥ 95 % (by $^1H$ NMR, using a chiral complexing reagent) and its absolute configuration was determined by circular dichroism, by comparison with known phenanthrenone **14** [9] [**13** : $\lambda_{max}$ 342 nm ($\Delta\epsilon$ –2.26), **14** : $\lambda_{max}$ 340 nm ($\Delta\epsilon$ –0.88)].




The achievement of the morphinan skeleton from phenanthrenone **13** requires the construction of an ethylamino bridge between the C-13 and C-9 centers by using the pendent angular acetate moiety at C-13, and

therefore implies "the activation" of the C-9 center. This was efficiently performed by migrating the double bond from the C8-C14 position in the ring C to the C14-C9 position in the ring B. For this purpose, the thermodynamically generated enolate anion [10] of enone **13** (tBuOK/tBuOH, 20 °C, 2 h) was protonated under kinetic conditions (AcOH) and the resulting crude unstable β-γ ethylenic ketone reduced into the *equatorial* alcohol **15** [11] ($NaBH_4$, iPrOH, 20 °C, 2 h, 60 % overall yield). Compound **15** was then converted quantitatively into acetal-ester **16** [12] ($iPr_2NEt$, $BnOCH_2Cl$, 20 °C, 3 h) which was reduced into alcohol **17** [13] (DIBAH, −78 °C then 20 °C, 15 mn, quantitative yield). Azido-epoxide **18** [14] was prepared in three steps [15] from this alcohol with an overall yield of 58 % (*i* : $MsCl/Et_3N$, *ii* : MCPBA, 0 °C, 1 h, *iii* : $NaN_3$/DMF, 50 °C, 5 h)[16]. Staudinger reduction of the azide function in compound **18** led to the intermediary amino-epoxide **19**, which cyclized [15] into 14-hydroxyisomorphinan **20** [17] ($Ph_3P$, THF, 20 °C, 3 h, then $H_2O$, 65 % yield). Protection of the nitrogen atom of compound **20** gave carbamate **21** [18] (methyl chloroformate, 1 N NaOH, 0 °C, 1 h, 90 % yield) which was next converted into diol **22** [19] [$Pd(OH)_2$, 2 bars of hydrogen, EtOH, 20 °C, 95 % yield]. Structures of morphinan derivatives **20** and **22** were unambiguously confirmed by extensive spectroscopic studies including 2D NMR experiments.



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3 In contrast to morphinans, morphine exerts its analgesic action orally only in relatively high doses [1].

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8 **13** : oil. $[\alpha]_D^{22}$ −160 ° (c = 1.85, EtOH). **CD** $\lambda_{max}$ 342 nm ($\Delta\epsilon$ −2.26, c = 0.5 mg/mL EtOH). **MS** (CI, $NH_3$) m/e 343 $(M+H)^+$. **IR** (neat) 1725, 1670, 1610 $cm^{-1}$. **$^1$H NMR** (250 MHz, $CDCl_3$) δ 1.22 (s, 9H) 2.05 (m, 2H) 2.4-3.0 (m, 8H) 3.73 (s, 3H) 5.91 (s, 1H) 6.69 (dd, J = 8.4, 2.6 Hz, 1H) 6.79 (d, J = 2.6 Hz, 1H) 6.98 (d, J = 8.4 Hz, 1H). **$^{13}$C NMR** (63 MHz, $CDCl_3$) δ 198.2 (s) 169.6 (s) 167.4 (s) 158.5 (s) 141.8 (s) 129.5 (d) 127.4 (s) 125.5 (d) 112.4 (d) 112.3 (d) 80.9 (s) 55.3 (q) 41.6 (s) 46.2 (t) 35.6 (t) 34.5 (t) 31.5 (t) 29.6 (t) 27.7 (q).

9 T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.*, **28**, 236 (1987).

10 H.J. Ringold, S.K. Malhotra, *Tetrahedron Lett.*, 669 (1962).

11 **15** : oil, $[\alpha]_D^{22}$ + 52 ° (c = 6.6, EtOH).

12 **16** : oil, $[\alpha]_D^{22}$ + 23 ° (c = 2.4, EtOH).

13 **17** : oil, $[\alpha]_D^{22}$ − 20 ° (c = 1.5, EtOH).

14 **18** : oil, $[\alpha]_D^{22}$ + 53 ° (c = 4.5, EtOH), **IR** (neat) 2095, 1610 $cm^{-1}$, **$^1$H NMR** (200 MHz, $CDCl_3$) δ 1.4-2.4 (m, 8H) 2.9-3.3 (m, 5H) 3.76 (s, 3H) 3.95 (m, 1H) 4.63 (s, 2H) 4.83 (s, 2H) 6.72 (m, 2H) 6.9 (d, J = 9 Hz, 1H) 7.33 (m, 5H). **$^{13}$C NMR** (63 MHz, $CDCl_3$) δ 158.6 (s) 140.6 (s) 138.0 (s) 130.2 (d) 128.4 (2C, d) 127.8 (2C, d) 127.6 (d) 123.2 (s) 112.3 (d) 111.7 (d) 93.3 (t) 73.8 (d) 69.5 (t) 62.0 (s) 58.5 (d) 55.2 (q) 47.3 (t) 40.8 (s) 37.0 (t) 35.3 (t) 30.8 (t) 30.2 (t) 28.4 (t).

15 This epoxidation-intramolecular oxirane opening sequence has been previously applied to an analogue to compound **17** : G. Lim, J.W. Hooper, US Patent 4,017,497 (Apr. 12, 1977) ; *Chem. Abstr.*, **87**, 102507j (1977).

16 The azido-olefin which results from the application of reactions *i* and *iii* to compound **17** is a thermally unstable compound, which undergoes an unexpected rearrangement : H. Sdassi, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.*, **30**, 3427 (1989).

17 **20** : oil, **IR** (neat) : 3350, 1610 $cm^{-1}$.

18 **21** : oil, **IR** ($CDCl_3$) : 3615, 3370, 1670, 1610 $cm^{-1}$.

19 **22** : solid (no definite m.p). $[\alpha]_D^{22}$ + 135 ° (c = 1.3, EtOH), **MS** (CI, $NH_3$) m/e 348 $(M+H)^+$. **IR** ($CCl_4$) 3590, 3440, 1680, 1610 $cm^{-1}$. **$^1$H NMR** (250 MHz, $CDCl_3/CD_3OD$) δ 1.56 (m, 2H) 1.9-2.15 (m, 4H) 2.25 (m, 2H) 2.7 (dd J = 16, 8 Hz, 1H) 2.92 (dd J = 16, 5 Hz, 1H) 3.16 (m, 1H) 3.55 (m, 1H) 3.61 (s, 3H) 3.73 (s, 3H) 4.04 (m, 1H) 4.46 (dd, J = 7.8, 5.0 Hz, 1H) 6.69 (dd, J = 8.36, 2.52 Hz, 1H) 6.79 (d, J = 2.52 Hz, 1H) 6.98 (d, J = 8.36 Hz, 1H). **$^{13}$C NMR** (63 MHz, $CDCl_3/CD_3OD$) δ 158.5 (s) 157.1 (s) 141.6 (s) 130.4 (d) 125.2 (s) 112.0 (d) 111.8 (d) 72.3 (d) 66.9 (s) 65.6 (d) 55.2 (q) 52.3 (q) 48.9 (s) 45.0 (t) 36.2 (t) 34.6 (t) 34.2 (t) 30.3 (t) 29.0 (t).


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