A Novel Method for the Introduction of a 5β-Methyl Group into 4,5α-Epoxymorphinan-6-ones *via* the Enol Ether

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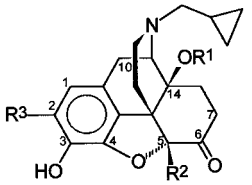
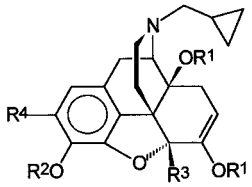
The introduction of a 5β-methyl group into 14-alkoxy substituted naltrexone derivatives was accomplished *via* the enol ethers **2a** and **2b** by means of the 'LICKOR' (*t*-BuLi/*t*-BuOK) base system. According to this new method, the highly selective δ-opioid antagonist HS 378 (**7b**) and its 14-methoxy analog **7a**, both originally prepared in nine steps from thebaine, are now available in only four steps.

1. Introduction. – The 5β-methyl-substituted 14β-alkoxy-4,5α-epoxymorphinan-6-ones [1] [2] are usually prepared from 5-methylthebaine, which is available from thebaine [3] [4]. As this method is restricted to the 5-methylation of thebaine, 4,5α-epoxymorphinans containing a 5β-methyl group have to be prepared from this alkaloid. Thus we sought for a new method of introducing such a group in 4,5α-epoxymorphinans. Here we describe a method of preparing 14β-alkoxy-17-(cyclopropylmethyl)-5β-methylmorphinan-6-ones starting from naltrexone (**1**). Thus 5β,14-*O*-dimethylnaltrexone (**5a**) as well as the more potent 14-*O*-ethyl-5β-methylnaltrexone (**5b**), which are opioid antagonists with unusual properties [5] [6] and from which the highly selective δ-opioid antagonists **7a** and **7b** (HS 378) [7] [8] are synthesized, were prepared in only three steps instead of eight [1–4].

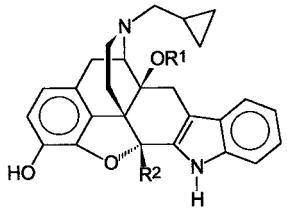
2. Chemistry. – The 3,14β-di-*O*-alkyl-substituted enol ethers **2a** and **2b** were prepared from naltrexone (**1**) by alkylation with dimethyl and diethyl sulfate, respectively, in DMF with NaH as base. Since BuLi, which was used to form the thebaine anion [3], was too weak a base to deprotonate the allyl-ether system of **2a**,**b** without a conjugated double bond, we decided to employ the 'LICKOR' (*t*-BuLi/*t*-BuOK) superbase [9] in THF at $-90°$. The following methylation was accomplished with dimethyl sulfate ($\rightarrow$ **3a**,**b**). The optimal quantity of the complex base proved to be 1.7–2.0 mol-equiv. (1:1 mixture). At lower quantities, the reaction rate was not acceptable, at higher quantities, the formation of the 2,5-dimethylated by-products **4a** and **4b**, respectively, was too marked, especially the formation of the former, as demonstrated by means of ^{1}H-NMR. X-Ray crystal-structure determination of compound **6** (see below) established methylation at position 2 in the by-products. Since no difference between the R_f values of the 5β-methylated products **3a** and **3b**, and



1 $R^1 = R^2 = R^3 = H$
5a $R^1 = R^2 = CH_3$, $R^3 = H$
b $R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 = H$
6 $R^1 = R^2 = R^3 = CH_3$



2a $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
b $R^1 = R^2 = C_2H_5$, $R^3 = R^4 = H$
3a $R^1 = R^2 = R^3 = CH_3$, $R^4 = H$
b $R^1 = R^2 = C_2H_5$, $R^3 = CH_3$, $R^4 = H$
4a $R^1 = R^2 = R^3 = R^4 = CH_3$
b $R^1 = R^2 = C_2H_5$, $R^3 = R^4 = CH_3$



7a $R^1 = R^2 = CH_3$
b $R^1 = C_2H_5$, $R^2 = CH_3$

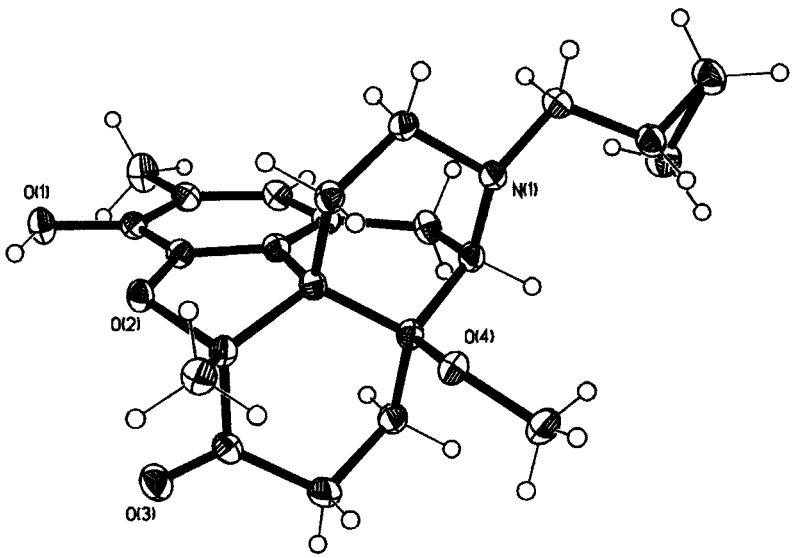


Figure. *ORTEP Plot of the molecular structure of* **6** (with 40% probability ellipsoids)

the 2,5-dimethylated by-products **4a** and **4b**, respectively, was observed on TLC with several different solvent systems, a separation of these compounds by CC was not feasible. Therefore, in the case of compound **3a**, which could not be purified by crystallization in an acceptable yield, we prepared the 3-hydroxy-6-oxo compounds **5a** and **6** by treatment of the unpurified oily mixture **3a**/**4a** with refluxing 48%

HBr solution, whereafter the R_f values were different and a separation by CC could ensue.

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Experimental Part

General. Naltrexone · HCl was purchased from *Mallinckrodt Speciality Chemicals Company*, St. Louis, MO 63147, USA. M.p.: *Kofler* melting-point microscope; uncorrected. IR Spectra: in cm^{-1}; *Mattson-FTIR-3000* spectrometer. ^{1}H-NMR Spectra: *Varian Gemini-200* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, J in Hz. Elemental analyses were performed by Mag. *J. Theiner* at the Institute of Physical Chemistry, University of Vienna.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14β-trimethoxymorphinan (**2a**). A mixture of **1** · HCl (3.0 g, 7.94 mmol), NaH (1.5 g, 62.50 mmol; obtained from 2.5 g of 60% NaH dispersion in oil by washings with petroleum ether), and anh. DMF (50 ml) was stirred under N_2 at 0–5° (bath temp.) for 20 min. Dimethyl sulfate (2.7 ml, 28.58 mmol) was added, and the resulting mixture was stirred for 45 min at 0–5° (bath temp.). Excess NaH was destroyed carefully by addition of small pieces of ice. The mixture was poured onto H_2O (150 ml) and extracted with CH_2Cl_2 (1 × 75 ml, 2 × 25 ml). The combined org. layers were washed with H_2O (3 × 200 ml), dried (Na_2SO_4), and evaporated. The crystalline residue (2.85 g) was treated with boiling MeOH: 2.33 g (77%) of **2a**. An anal. sample was prepared by recrystallization from MeOH. M.p. 150–152°. ^{1}H-NMR ((D$_6$)DMSO): 6.71 (*d*, *J* = 8.3, 1 arom. H); 6.59 (*d*, *J* = 8.3, 1 arom. H); 4.67 (*s*, H–C(5)); 4.59 (*m*, H–C(7)); 3.72 (*s*, MeO–C(3)); 3.41 (*s*, MeO–C(6)); 3.19 (*s*, MeO–C(14)). Anal. calc. for $C_{23}H_{29}NO_4 \cdot 0.2$ MeOH (389.90): C 71.47, H 7.70, N 3.59; found: C 71.45, H 7.60, N 3.59.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14β-trimethoxy-5β-methylmorphinan (**3a**) *and 17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14β-trimethoxy-2,5β-dimethylmorphinan* (**4a**). To a stirred soln. of **2a** (1.0 g, 2.61 mmol) in anh. THF (70 ml) under N_2, *t*-BuOK (553 mg, 4.93 mmol) and then 1.7M *t*-BuLi (2.9 ml, 4.93 mmol) were added at −90° (bath temp.). After 15 min, dimethyl sulfate (467 µl, 4.93 mmol) was added. The originally orange mixture turned yellow and was then allowed to come to r.t. while stirring was continued. The mixture was evaporated and the oily residue partitioned between CH_2Cl_2 and H_2O. The org. layer was washed with brine, dried, and evaporated to give a yellow oil (1.02 g). ^{1}H-NMR: **3a**/**4a**. The main product **3a** could be crystallized from MeOH to some extent (m.p. 63–72°), whereas the by-product **4a** was impossible to isolate (TLC: identical R_f for **3a** and **4a**). An anal. sample of **3a** was prepared by recrystallization from MeOH.

Data of **3a**: M.p. 94–96°. ^{1}H-NMR ($CDCl_3$): 6.67 (*d*, *J* = 8.2, 1 arom. H); 6.55 (*d*, *J* = 8.2, 1 arom. H); 4.48 (*dd*, *J* = 6.2, 1.8, H–C(7)); 3.81 (*s*, MeO–C(3)); 3.47 (*s*, MeO–C(6)); 3.31 (*s*, MeO–C(14)); 1.69 (*s*, Me–C(5)). Anal. calc. for $C_{24}H_{31}NO_4 \cdot 0.9$ MeOH (426.36): C 70.15, H 8.18, N 3.29; found: C 70.17, H 7.88, N 3.41.

Data of **4a** (unpurified oil, containing **3a** as main component): ^{1}H-NMR ($CDCl_3$): 6.41 (*s*, H–C(1)); 4.48 (*dd*, *J* = 6.2, 1.8, H–C(7)); 3.86 (*s*, MeO–C(3)); 3.47 (MeO–C(6)); 3.31 (*s*, MeO–C(14)); 2.17 (*s*, Me–C(2)).

17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-14β-methoxy-5β-methylmorphinan-6-one (**5a**) *and 17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-14β-methoxy-2,5β-dimethylmorphinan-6-one* (**6**). A soln. of the unpurified oil **3a**/**4a** (1.0 g) in 48% HBr soln. (10 ml) was refluxed for 15 min. After addition of ice, the soln. was alkalinized with conc. NH_4OH soln. and extracted with CH_2Cl_2 (3 × 20 ml) and the combined org. layer dried and evaporated. The resulting brownish foam (760 mg, 78%), which could not be purified by crystallization, was chromatographed (silica gel *60*; CH_2Cl_2/MeOH/NH_4OH soln. 250 : 2 : 0.5): 42 mg (4% rel. to **2a**) of **6** and 173 mg (18% rel. to **2a**) of **5a**. Both compounds were recrystallized from MeOH: 33 mg (3% rel. to **2a**) of pure **6** and 134 mg (14% rel. to **2a**) of pure **5a**.

Data of **5a**: M.p. 85–88° and 165–168° ([5]: 177–179°). IR (KBr): 3397 (OH), 1723 (CO). ^{1}H-NMR ($CDCl_3$): 6.67 (*d*, *J* = 8.2, 1 arom. H); 6.53 (*d*, *J* = 8.2, 1 arom. H); 5.57 (br. *s*, OH); 3.38 (*s*, MeO); 1.61 (*s*, Me–C(5)). NMR Data identical with those of authentic **5a**.

Data of **6**: M.p. 93–96°. IR (KBr): 3420 (OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.43 (*s*, 1 arom. H); 3.38 (*s*, MeO); 2.19 (*s*, Me–Ar); 1.60 (*s*, Me–C(5)). Anal. calc. for $C_{23}H_{29}NO_4 \cdot 2.2$ MeOH (453.98): C 66.67, H 8.39, N 3.09; found: C 66.74, H 8.14, N 3.09.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14β-triethoxymorphinan (**2b**). As described for **2a**, with **1** · HCl (4.0 g, 10.59 mmol), NaH (1.5 g, 62.50 mmol) anh. DMF (90 ml), and diethyl sulfate (8.0 ml, 60.81 mmol) (12 h at 0–5°). Excess NaH was destroyed by addition of small pieces of ice, excess diethyl sulfate

by addition of NH_4OH soln. (10 ml), after which the mixture was stirred for 1 h at r.t. Then it was poured onto H_2O (300 ml) and extracted with Et_2O (1×150 ml, 2×50 ml). The combined org. layers were washed with H_2O (6×300 ml), dried (Na_2SO_4), and evaporated: slightly impure **2b** (4.24 g, 94%). Yellowish oil. ^{1}H-NMR ($CDCl_3$): 6.67 (*d*, *J* = 8.0, 1 arom. H); 6.52 (*d*, *J* = 8.0, 1 arom. H); 4.83 (*s*, H–C(5)); 4.52 (*m*, H–C(7)); 1.34 (*t*, *J* = 7.0, *Me*CH_2O); 1.29 (*t*, *J* = 7.0, *Me*CH_2O); 1.17 (*t*, *J* = 7.0, *Me*CH_2O).

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,6,14β-trimethoxy-5β-methylmorphinan (**3b**). As described for **3a**/**4**, with **2b** (3.07 g, 7.21 mmol), anh. THF (170 ml), *t*-BuOK (1.52 g, 13.37 mmol), 1.7M *t*-BuLi (8.0 ml, 13.60 mmol), and dimethyl sulfate (1.28 ml, 13.52 mmol) (red → pale mixture). The yellow oil (3.37 g) was crystallized from MeOH: 1.59 g (50%) of **3b** with m.p. 134–143°. An anal. sample was prepared by recrystallization from MeOH. M.p. 147–148°. ^{1}H-NMR ($CDCl_3$): 6.65 (*d*, *J* = 8.2, 1 arom. H); 6.50 (*d*, *J* = 8.2, 1 arom. H); 4.46 (*m*, H–C(7)); 1.69 (*s*, Me–C(5)); 1.32 (*t*, *J* = 7.0, *Me*CH_2O); 1.26 (*t*, *J* = 7.0, *Me*CH_2O); 1.16 (*t*, *J* = 7.0, *Me*CH_2O). Anal. calc. for $C_{27}H_{37}NO_4 \cdot 0.3$ MeOH (449.21): C 73.00, H 8.57, N 3.12; found: C 72.91, H 8.51, N 3.18.

17-(Cyclopropylmethyl)-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methylmorphinan-6-one (**5b**). As described for **5a**/**6**, with **3b** (500 mg, 1.14 mmol) and 48% HBr soln. (5 ml) (extraction with CH_2Cl_2 (3×10 ml)). The yellow foam (429 mg, 98%) was crystallized from MeOH: 232 mg (53%) of yellow **5b**. Recrystallization from MeOH afforded 175 mg (40%) of pure **5b**. M.p. 181–185° (dec.) ([6]: 172–174°). IR (KBr): 3384 (OH), 1725 (CO). ^{1}H-NMR ((D$_6$)DMSO): 9.05 (*s*, OH); 6.51 (*d*, *J* = 8.2, 1 arom. H); 6.46 (*d*, *J* = 8.2, 1 arom. H); 1.47 (*s*, Me–C(5)); 1.21 (*t*, *J* = 7.0, *Me*CH_2O). NMR Data identical with those of authentic **5b**.

Crystal Structure Data of **6**. $C_{23}H_{29}NO_4 \cdot 2$ MeOH, *M* 447.56; monoclinic, $P2_1$, $a = 9.073(2)$, $b = 12.300(5)$, $c = 11.097(3)$ Å, $\beta = 103.31(2)°$; $V = 1205.1(6)$ Å^3 (λ 0.71073), $Z = 2$, $D_{calc} = 1.233$ g/cm^3, $F(000) = 484$; $\mu = 0.087$ mm^{-1}, crystal size $0.7 \times 0.65 \times 0.15$ mm. Data were collected at 218(2) K in the θ range 2.5–24.5° on a *Bruker-P4* diffractometer. Data were measured *via* ω scans and corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods (SHELXS-86) and refined by full-matrix least-squares against F^2 (SHELXL-93). All non-H-atoms were refined with anisotropic displacement parameters. All H-atoms were located by difference *Fourier* methods and refined at the OH group and the cyclopropane ring, the others were generated geometrically and refined with isotropic displacement parameters 1.2 times higher than *U*(eq) of the attached C-atoms. In the final least-squares refinement cycles, the model converged at $R_1 = 0.0272$, $wR_2 = 0.0669$, and g.o.f. = 1.031 for 2582 reflections with $F_o \geq 4\sigma$ (F_o) and 327 parameters. Copies of the crystallographic data are available on application to the *Cambridge Crystallographic Data Centre,* 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk) citing the deposition No. CCDC-134616.

REFERENCES

[1] H. Schmidhammer, J. B. Deeter, N. D. Jones, J. D. Leander, D. D. Schoepp, J. K. Swartzendruber, *Helv. Chim. Acta* **1988**, *71*, 1801.

[2] H. Schmidhammer, A. Schratz, J. Mitterdorfer, *Helv. Chim. Acta* **1990**, *73*, 1784.

[3] R. M. Boden, M. Gates, S. Ho Peng, P. Sundararaman, *J. Org. Chem.* **1982**, *47*, 1347.

[4] H. Schmidhammer, F. Fritsch, W. P. Burkard, L. Eggstein-Aeppli, M. I. Holck, *Helv. Chim. Acta* **1988**, *71*, 642.

[5] H. Schmidhammer, C. Nussbaumer, D. Patel, J. R. Traynor, *Helv. Chim. Acta* **1994**, *77*, 1585.

[6] H. Schmidhammer, A. Schratz, C. Schmidt, D. Patel, J. R. Traynor, *Helv. Chim. Acta* **1993**, *76*, 476.

[7] H. Schmidhammer, R. Krassnig, E. Greiner, J. Schütz, A. White, I. P. Berzetei-Gurske, *Helv. Chim. Acta* **1998**, *81*, 1064.

[8] H. Schmidhammer, D. Daurer, M. Wieser, K. Monory, A. Borsodi, J. Elliot, J. R. Traynor, *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 151.

[9] M. Schlosser, *Pure Appl. Chem.* **1988**, *60*, 1627.

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