Michael Reactions of Benzylimines Derived from Morphinan-6-ones: Synthesis of Pyrrolo- and Pyridinomorphinans

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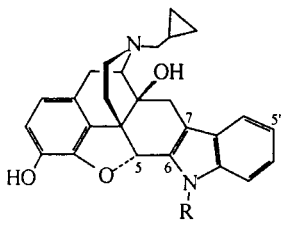
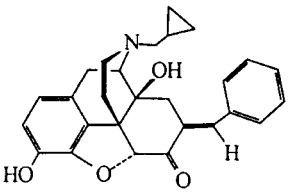
The benzylimines **15** derived from oxymorphones **14** and generated *in situ* reacted with *Michael* acceptors (methyl methacrylate, maleic anhydride, and α-methylene-γ-butyrolactone) to give opioid ligands **16**, **17**, and **19**–**21** having pyrrole- or pyridine-derived ring systems (see *Scheme 3*). The product of the reaction with maleic anhydride displayed a surprising preference for the 2-hydroxypyrrole form **19** rather than for the tautomeric 1,6-dihydro-2*H*-pyrrol-2-one form **24**, resulting from the stability of the C(6)=C(7) bond in oxymorphone and related structures.

Introduction. – The indolomorphinan structure has become a major focus of interest in opioid medicinal chemistry since the discovery of naltrindole (NTI; **1**), the first nonpeptide δ-opioid-receptor-selective antagonist [1]. It was hypothesised that the indole ring mimics the phenylalanine residue of [Met^5]- and [Leu^5]enkephalins, which are endogenous δ-opioid receptor ligands. *N*-Benzylnaltrindole (BNTI; **2**) is a potent δ antagonist with selectivity for the δ_2-subtype and long duration of action *in vivo* when administered intracerebroventricularly (icv) [2].

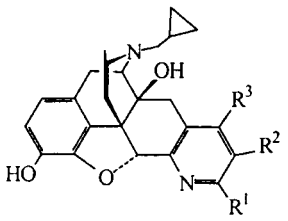


1 R = H, NTI

2 R = Bn, BNTI



3 BNTX



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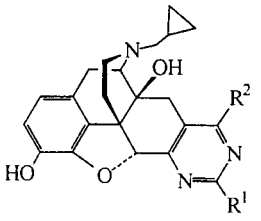

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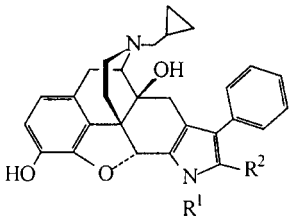
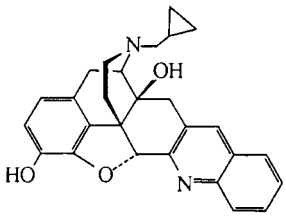


6a R = H
b R = Bn



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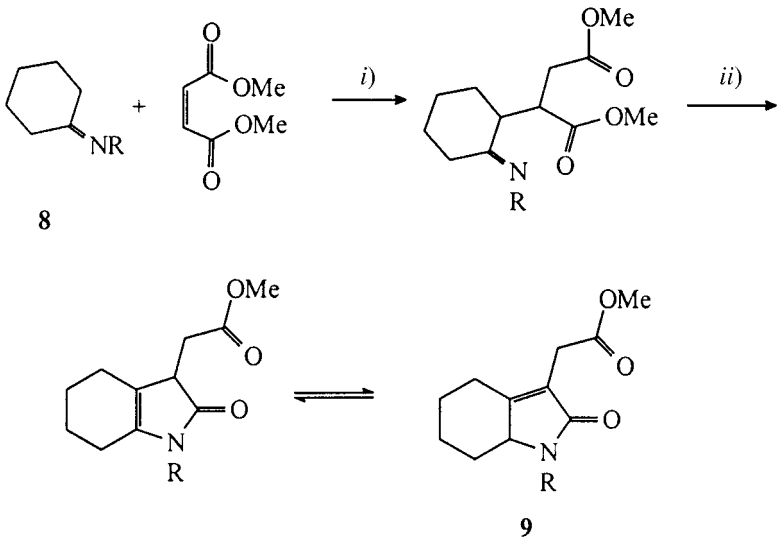
The indole moiety of naltrindole has been replaced by a number of structurally diverse heterocycles. These studies have tended to focus on the introduction of a phenyl ring into the morphinan structure in similar or slightly different positions compared to NTI or benzylidenenaltrexone (BNTX; **3**), a δ_1-selective antagonist [3]. Examples include **4**–**7** [4–7]. Compared to naltrindole, the new ligands typically have been of limited selectivity, in particular for δ/μ.

Our aim was to develop chemistry that would give access to a range of analogues of these ligands having pyrrole- or pyridine-derived rings to which potential opioid receptor binding groups could be attached. We were attracted to recent literature reports of the reactions of ketone-derived imines (as their secondary enamine tautomers) with *Michael* acceptors [8–10]. *Pfau* und *Ribiere* [11] had demonstrated that cyclohexanimines **8** reacted with dimethyl maleate and maleic anhydride to give 1,5-dihydro-2*H*-pyrrol-2-ones **9** related to indole-3-acetic acid (*Scheme 1*). In reactions with these reagents, *Pfau et al.* [9] showed that the *N*-benzylimine **10** derived from 2-methylcyclohexanone gave pyrrolone and pyridinone derivatives **11**–**13** (*Scheme 2*), in which the more substituted enamine tautomer was involved in the addition, and the products showed high diastereoselectivity.

Scheme 1



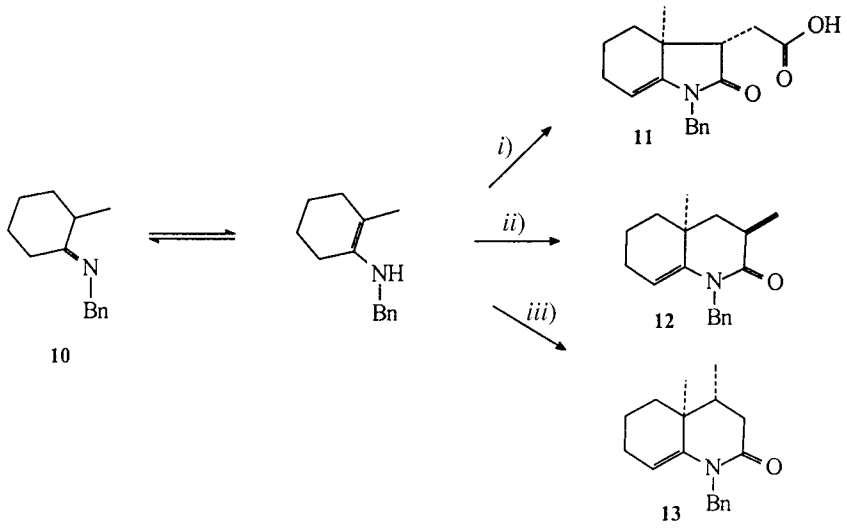
8 **9**

i) r.t. *ii*) 200°.

Our interest was heightened by the knowledge that the morphinan-6-ones and their imine counterparts react readily as their enol and enamine tautomers [7][12]. This suggested that the benzylimines derived from oxymorphone (**14a**) and naltrexone (**14b**) could react similarly with *Michael* acceptors, giving access to a range of pyrrolo- and pyridino-derived morphinans.

We here report the results of investigations of the reaction of the *N*-benzyl- and *N*-methylimines of oxymorphones generated *in situ* with several activated olefins.

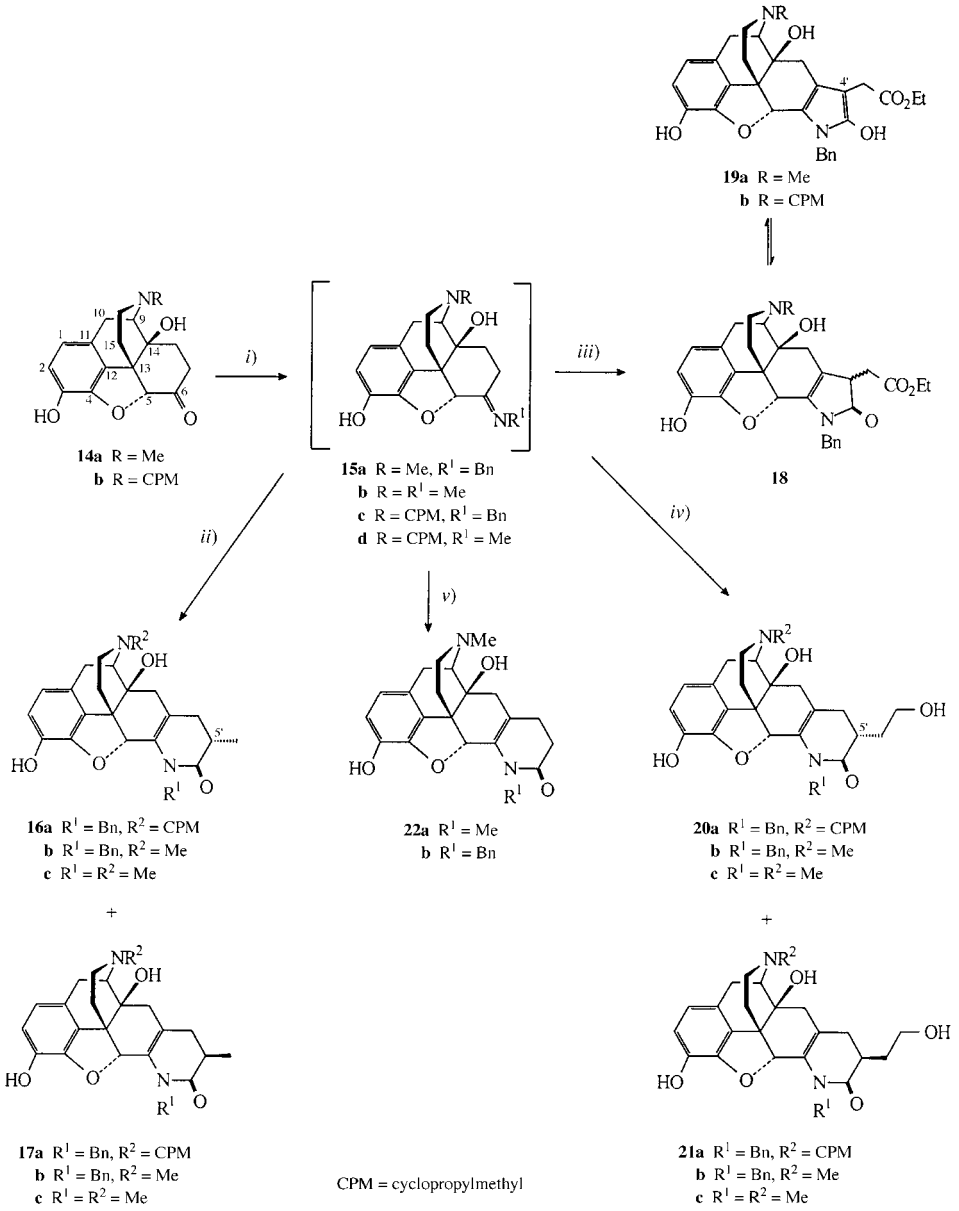
Scheme 2



i) Maleic anhydride, 0–20°, 10 min. *ii*) Methyl methacrylate, 100°, 3d. *iii*) Methyl crotonate, 120°, 5d.

Results. – Initially, the procedure of *Lim et al.* [8] with oxymorphone (=4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one; **14a**) was followed, but we were unable to purify the benzylimine **15a**, which decayed on silica-gel columns. However, it was found that, under one-pot conditions somewhat similar to those described by *Meyer* [13], but allowing the imine to form before introduction of the appropriate *Michael* acceptor and using powdered 4-Å molecular sieves to suppress reaction of the electrophile with amine [8], the desired cyclized *Michael* adducts were obtained in good yield. Thus, the reaction of the benzyl- and methylimines derived from oxymorphone (**14a**) and naltrexone ((=17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one; **14b**) with methyl methacrylate (=methyl 2-methylpropenoate) and maleic anhydride (=(2*Z*)-but-2-enedioic acid anhydride) gave **16**, **17**, and **19** (*via* **18**) in *ca.* 40% yields by means of the one-pot procedure (*Scheme 3*). In the latter case, the solvent EtOH reacted with the initially formed carboxylic acid to afford the ethyl ester. The only other material found in the reaction mixtures was unreacted ketone and imine, showing that addition of amine to the *Michael* acceptor reagents was effectively inhibited. The procedure was also used with α-methylene-γ-butyrolactone (=4,5-dihydro-3-methylenefuran-2(3*H*)-one) as *Michael* acceptor to give pyridinones **20** and **21**, analogous in structure to **16** and **17**, in 69% yield (combined). Methyl crotonate (=methyl (2*E*)-but-2-enoic acid) when used under identical conditions gave only a trace amount (<5%) of impure product, whereas reaction with ethyl acrylate (=ethyl propenoate) gave 60–70% of **22**. Thus, it appears that the addition is hindered by the presence of a substituent at C(β). The only other example where a β-substituent was present was in the reaction with maleic anhydride. Here the substituent is part of the ring system and thus held in the (*Z*)-configuration, whereas, in methyl crotonate, the β-methyl group is in the (*E*)-configuration. In each case where diastereoisomers

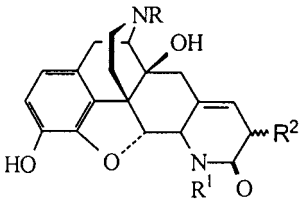
Scheme 3



i) R^1NH_2, EtOH, 4-Å molecular sieves, TsOH. *ii*) Methyl methacrylate, EtOH, 4-Å molecular sieves, TsOH. *iii*) Maleic anhydride, EtOH, 4-Å molecular sieves, TsOH. *iv*) α-Methylene-γ-butyrolactone, EtOH, 4-Å molecular sieves, TsOH. *v*): Ethyl acrylate, EtOH, 4-Å molecular sieves.

could be formed, they did so in approximately equivalent amounts. These could be separated by repeated, careful silica-gel column chromatography, except in the cases of **16b**, **16c**, and **17c**.

The structures of pyridinones **16**, **17**, **20**, and **21** were assigned from NMR and X-ray data. In no ^{1}H-NMR spectrum was there evidence for a vinyl proton, but, in each case, the C(5) proton was present and appeared as a *singlet*, indicating that no proton was present at C(6), thus ruling out products of type **23**. The configuration of the side chain in the pyridinone ring of **16**, **17**, **20**, and **21** was assigned from the X-ray crystal-structure analysis of **21a**, which showed that the hydroxyethyl group occupies the 5′β-position; a similar configuration for the 5′-methyl group of **17a** is assumed based on comparison of NMR spectra.



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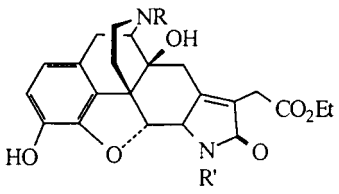


24

The structure of the dihydropyrrolone product of the maleic anhydride reaction was expected to be **24** on the basis of the normally preferred structure of dihydropyrrolones including that of the product **9** of the equivalent reaction with cyclohexanimines (see *Scheme 1*). Both the 1,6-dihydro-2*H*-pyrrol-2-one structure **24** (with C(7)=C(4′) and the 1,3-dihydro-2*H*-pyrrol-2-one structure **18** (with C(6)=C(7)) have a tertiary C-atom at C(4′) (**24**) or C(6) (**18**) that were not detected by DEPT NMR. Confirmation of this assignment was obtained from ^{1}H,^{1}H-COSY analysis of the side-chain CH_2 protons, establishing that these were not coupled to any others within the molecule.

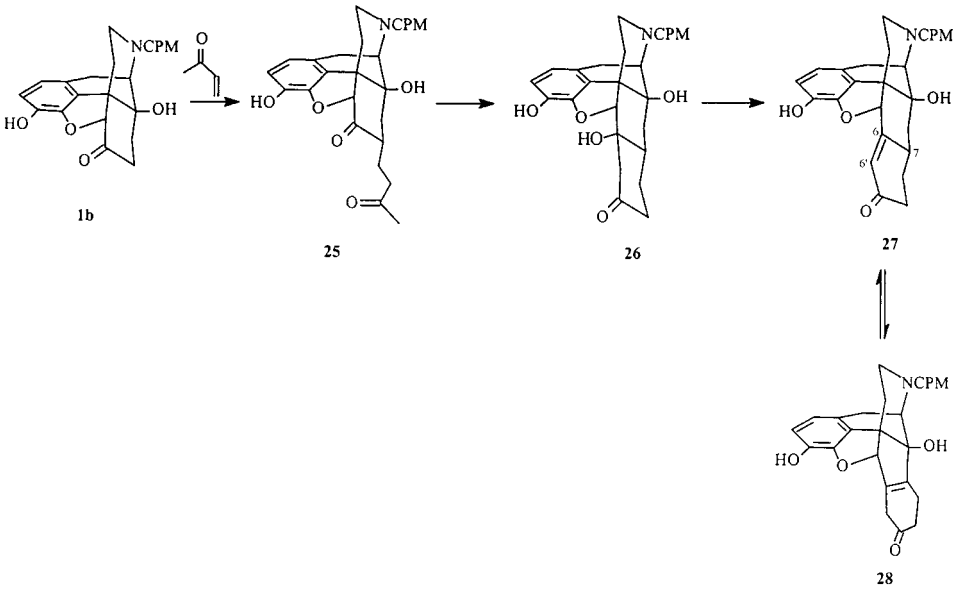
Discussion. – The imines derived from 4,5-epoxymorphinan-6-ones and generated *in situ* reacted smoothly with the *Michael* acceptors to give adducts that, as expected, cyclized under the reaction conditions. The structures of the products **16** and **17** from the reaction with methyl methacrylate differed from that reported from the reaction of *N*-benzyl-2-methylcyclohexanimine with methyl methacrylate (see **12** in *Scheme 2*) with respect to the position of the olefinic bond. In the latter case, the C=C bond is trisubstituted and exocyclic with respect to the pyridinone ring, whereas in **16**, **17** it is tetrasubstituted and endocyclic. The reasons for this difference are the steric strain that would be created by the presence of a C(5)=C(6) bond and the inherent stability of the C(6)=C(7) bond in derivatives of oxymorphones.

In the reactions with methyl methacrylate and α-methylene-γ-butyrolactone, both α- and β-epimers were formed. The lack of diastereoselectivity of the cyclizations was in contrast to the work of *Pfau et al.* [9], who constructed a model for *Michael* reactions of the *N*-benzyl-2-methylcyclohexanimine with maleic anhydride, methyl methacrylate, and methyl crotonate. The model involved a chair-like geometry for the reactant complex with concomitant C–C bond-formation and intramolecular H-transfer. The

lack of diastereoselectivity observed in the current work is likely to be related to the use of a protic solvent in the reaction. Thus, intramolecular proton transfer will be competing with proton transfer from the solvent, whereas *Pfau et al.* [9] were able to conduct their *Michael*-type addition in the absence of solvent. It is also possible that the extended reaction time may allow epimerization of the final product and/or uncyclized intermediate. This was investigated in part by refluxing **21a** in EtOH in the presence of TsOH (4-methylbenzenesulfonic acid) and molecular sieves. No epimerization was observed.

Reaction with maleic anhydride was predicted [7] to give **18** (*Scheme 3*). However, it was shown that, in the present case, the tautomeric 5′-hydroxypyrrole structure **19** is favored so that the chiral center at C(4′) is lost. As mentioned earlier, the unusual preference for the hydroxypyrrole structure most likely is due to the stability of the C(6)=C(7) bond in naltrexone-derived structures [12]. This was manifested in the acid-catalysed dehydration of the initial product **26** in the annulation of naltrexone (*Scheme 4*) [12]. The dehydration product at room temperature was the α,β-unsaturated ketone **27** (with C(6)=C(6′)), but this was converted to the C(6)=C(7) isomer **28** under reflux conditions. Thus, the C(6)=C(7) structure **18** would be preferred to the expected C(7)=C(4′) isomer **24** with aromatization to **19** giving added stability.

Scheme 4



In conclusion, imines derived from morphinan-6-ones were again shown to react readily as their enamine tautomers, confirming the stability of the C(6)=C(7) bond in the morphinan series. The isolation of the 5′-hydroxypyrrole derivative **19** provides further evidence for this stability. The one-pot-reaction conditions allowed rapid access to morphinans having pyrrole- and pyridine-derived ring systems. The functionalized side chains will allow ready elaboration and the generation of further series of opioid-receptor ligands.

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Experimental Part

General. Reagents and solvents were purchased from *Aldrich* or *Lancaster* and used as received. Org. solns. were dried (Na_2SO_4) and evaporated with a *Büchi* rotary evaporator at low pressure. Yields are of purified product and were not optimized. Compounds were converted to their hydrochloride salts by dissolving in MeOH and adding HCl/MeOH. M.p.: *Reichert* hot-stage apparatus; uncorrected. The compounds were routinely checked for their purity by TLC: aluminium sheets coated with silica gel *60 F_{254}* (*Merck*) 5% MeOH/CH_2Cl_2 with 1% NH_4OH; visualization by UV light and I_2 vapour. Column chromatography (CC): flash silica gel *60* (*Fluka*, mesh 220–240) and 2.5% MeOH/CH_2Cl_2 with 1% NH_4OH. ^{1}H- and ^{13}C-NMR Spectra: *Jeol JNM-GX-FT-300* spectrometer; at 300 (^{1}H) and 75 (^{13}C) MHz and r.t.; chemical shifts δ in ppm rel. to $SiMe_4$ (=0 ppm) as internal standard, *J* in Hz. EI-MS: *Fission-Auto* spectrometer with electron-impact ionization (70 eV); in *m*/*z* (% rel. int.). Elemental analyses: *Carlo-Erba EA-1108* analyser; results within ±0.4% of the theoretical values.

*1′-Benzyl-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′α,17-dimethylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**16b**) *and 1′-Benzyl-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′β,17-dimethylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**17b**). A soln. of oxymorphone (**14a**, 0.25 g, 0.84 mmol), benzylamine (0.1 ml, 0.88 mmol) and $TsOH \cdot H_2O$ (1 mg) in EtOH (3 ml) was refluxed in the presence of 4-Å molecular sieves under N_2 for 3 h. Methyl methacrylate (0.1 ml, 0.88 mmol) was added and reflux continued overnight. The mixture was then cooled, filtered, and evaporated, and the resultant solid washed with hexane to leave crude **16b** and **17b**, which were purified by CC: 0.15 g (41%) of **16b** and *ca*. 0.07 g of **17b** (isolated as a mixture with **16b**).

Data of **16b**: R_f 0.68. M.p. 227–229°. ^{1}H-NMR (CD_2Cl_2): 7.18 (*m*, *Ph*CH_2); 6.54 (*d*, *J* = 8.0, H–C(2)); 6.48 (*d*, *J* = 8.0, H–C(1)); 5.47 (*d*, *J* = 16.7, 1 H, PhCH_2); 4.85 (*s*, H–C(5)); 4.55 (*d*, *J* = 16.7, 1 H, PhCH_2); 3.05 (*d*, *J* = 18.7, 1 H–C(10)); 2.72 (*d*, *J* = 6.3, H–C(9)); 2.57 (*m*, 1 H); 2.08 (*m*, 11 H); 1.43 (*m*, 1 H); 1.05 (*d*, *J* = 6.4, Me). ^{13}C-NMR (CD_2Cl_2): 173.53, 142.93; 139.63; 139.15; 131.62; 128.91; 128.72; 128.35; 127.13; 126.43; 125.49; 119.34; 119.24; 117.27; 86.13; 70.36; 64.18; 46.24; 45.43; 44.53; 43.06; 36.82; 34.98; 34.27; 31.60; 22.39; 15.25. EI-MS: 458 (100, M^+, 91 (80). Anal. calc. for $C_{28}H_{30}N_2O_4 \cdot HCl \cdot 1.75\ H_2O$ (526.5): C 63.87, H 6.60, N 5.32; found: C 64.10, H 7.00, N 5.10.

Data of **17b** (mixture with **16b**): R_f 0.68. ^{1}H-NMR ($CDCl_3$): 7.17 (*m*, 10 H, *Ph*CH_2); 6.77–6.66 (*m*, 2 H, 2 H–C(2)); 6.63–6.51 (*m*, 2 H, 2 H–C(1)); 5.53–5.49 (*m*, 2 H, PhCH_2); 5.03 (*s*, 2 H, 2 H–C(5)); 4.76–4.72 (*m*, 2 H, PhCH_2); 1.12 (*d*, *J* = 6.8, 3 H, Me); 0.96 (*d*, *J* = 7.2, 3 H, Me). FAB-MS: 459 (82, $[M+1]^+$).

*1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′α-methylpyrido[2′,3′:6,7-]morphinan-6′(1′*H*)-one* (**16a**) *and 1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′β-methylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**17a**). As described for **16b**/**17b**, from naltrexone (**14b**; 0.50 g, 1.47 mmol), benzylamine (0.18 ml, 1.47 mmol) and methyl methacrylate (0.15 ml, 1.47 mmol): 0.06 g (20%) of **16a** and 0.05 g (17%) of **17a**.

Data of **16a**: R_f 0.78. M.p. 207–209°. ^{1}H-NMR (CD_2Cl_2): 7.30 (*m*, *Ph*CH_2); 6.59 (*d*, *J* = 8.1, H–C(2)); 6.51 (*d*, *J* = 8.1, H–C(1)); 5.44 (*d*, *J* = 16.6, 1 H, PhCH_2); 4.99 (*s*, H–C(5)); 4.76 (*d*, *J* = 16.6, 1 H, PhCH_2); 3.11 (*d*, *J* = 6.4, H–C(9)); 3.05 (*d*, *J* = 18.5, 1 H–C(10)); 2.62 (*m*, 2 H); 2.11 (*m*, 8 H); 1.50 (*m*, 2 H); 0.98 (*m*, H–C(19)); 0.81 (*d*, *J* = 6.0, Me); 0.49 (*m*, 2 H, H–C(20), H–C(21)); 0.11 (*m*, 2 H, H–C(20), H–C(21)). ^{13}C-NMR (CD_2Cl_2): 174.26; 142.89; 139.66; 139.38; 131.83; 128.92; 127.16; 125.45; 119.46; 118.25; 117.24; 86.56; 70.55; 62.55; 61.83; 59.75; 47.05; 44.64; 43.92; 43.81; 37.95; 35.36; 33.73; 31.93; 31.10; 22.95; 15.32; 9.72; 4.02; 3.94. EI-MS: 498 (100, M^+), 91 (80). Anal. calc. for $C_{31}H_{34}N_2O_4 \cdot HCl \cdot 2\ H_2O$ (571.11): C 65.20, H 6.88, N 4.91; found: C 65.12, H 6.77, N 4.61.

Data of **17a**: R_f 0.84. M.p. 215–220°. ^{1}H-NMR ($CDCl_3$): 7.40–7.2 (*m*, *Ph*CH_2); 6.65 (*d*, *J* = 8.0, H–C(2)); 6.51 (*d*, *J* = 7.6, H–C(1)); 5.51 (*d*, *J* = 16.4, 1 H, PhCH_2); 5.0 (*s*, H–C(5)); 4.77 (*d*, *J* = 16.4, 1 H, PhCH_2); 3.14 (*d*, *J* = 5.6, H–C(9)); 3.04 (*d*, *J* = 18.4, 1 H–C(10)); 2.8 (*m*, 1 H–C(10)); 2.41–1.4 (*m*, 13 H); 1.20 (*d*, 3 H, *J* = 6.8, Me); 0.83–0.80 (*m*, H–C(19)); 0.54–0.51 (*m*, 2 H, H–C(20), H–C(21)); 0.12–0.005 (*m*, 2 H, H–C(20), H–C(21)). ^{13}C-NMR ($CDCl_3$): 173.52; 142.63; 139.25; 138.78; 131.35; 128.80; 128.67; 127.01; 126.23; 119.21; 118.76; 117.08; 86.44; 70.34; 61.57; 59.72; 46.93; 44.86; 43.88; 37.13; 35.20; 34.40; 31.71; 23.29; 15.61; 9.78; 4.50; 4.17. FAB-MS: 499 (100, $[M+1]^+$), 91 (60). Anal. calc. for $C_{31}H_{34}N_2O_4 \cdot HCl \cdot 2\ H_2O$ (571.11): C 65.20, H 6.88, N 4.91; found: C 64.8, H 6.94, N 4.75.

*6,7-Didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-1′,5′α,17-trimethylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**16c**) *and 6,7-Didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-1′,5′β,17-trimethylpyri-*

*do[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**17c**). As described for **16b**/**17b**, from **14a** (0.5 g, 1.66 mmol), 2M $MeNH_2$ in MeOH (1.66 mmol, 1.0 ml), and methyl methacrylate (0.18 ml, 1.66 mmol): 0.2 g (32%) of **16c**/**17c**, which could not be separated by CC. R_f 0.4. ^{1}H-NMR ($CDCl_3$): 6.65–6.61 (*m*, 2 H, 2 H–C(2)); 6.52–6.48 (*m*, 2 H, 2 H–C(1)); 5.14 (*s*, 2 H, 2 H–C(5)); 3.21 (*s*, 6 H, 2 MeNC); 2.33 (*s*, 6 H, 2 MeN); 1.05 (*d*, *J* = 3.2, 3 H, Me); 0.66 (*d*, *J* = 3.6, 3 H, Me). EI-MS: 382 (100, M^+).

*1′-Benzyl-6,7-didehydro-4,5α-epoxy-3,5′,14-trihydroxy-17-methyl-1′*H*-pyrrolo[2′,3′:6,7]morphinan-4′-acetic Acid Ethyl Ester* (**19a**). As described for **16b**/**17b**, from **14a** (0.6 g, 1.99 mmol), benzylamine (0.24 ml, 2 mmol), and maleic anhydride (0.19 g, 2 mmol): 0.22 g (21%) of **19a**. R_f 0.56. M.p. 179–181°. ^{1}H-NMR (CD_2Cl_2): 7.17 (*m*, *Ph*CH_2); 6.54 (*d*, *J* = 8.0, H–C(2)); 6.34 (*d*, *J* = 8.0, H–C(1)); 6.06 (*s*, H–C(5)); 4.76 (*d*, *J* = 15.9, 1 H, PhC*H*$_2$); 4.55 (*d*, *J* = 15.9, 1 H, PhC*H*$_2$); 3.95 (*q*, *J* = 7.1, MeC*H*$_2$O); 3.16 (*m*, 3 H); 3.0 (*m*, 2 H); 2.5 (*m*, 10 H); 1.07 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR (CD_2Cl_2): 170.56; 143.10; 142.99; 141.28; 138.32; 135.95; 128.75; 127.73; 127.38; 122.04; 118.68; 72.98; 62.92; 61.39; 46.97; 43.34; 42.51; 42.47; 31.82; 31.51; 30.96; 29.39; 24.95; 14.24. EI-MS: 516 (50, M^+), 91 (100). Anal. calc. for $C_{30}H_{32}N_2O_6 \cdot HCl \cdot 1.75\ H_2O$ (584.57): C 61.63, H 6.28, N 4.78; found: C 61.69, H 5.88, N 4.90.

1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3,5′,14-trihydroxypyrrolo[2′,3′:6,7]morphinan-4′-acetic Acid Ethyl Ester (**19b**). As described for **16b**/**17b**, from **14b** (0.50 g, 1.47 mmol), benzylamine (0.16 ml, 1.5 mmol), and maleic anhydride (0.15 g, 1.5 mmol): 0.34 g (40%) of **19b**. R_f 0.65. M.p. 191–193°. ^{1}H-NMR (CD_2Cl_2): 7.24 (*m*, *Ph*CH_2); 6.61 (*d*, *J* = 8.2, H–C(2)); 6.43 (*d*, *J* = 8.2, H–C(1)); 6.16 (*s*, H–C(5)); 4.86 (*d*, *J* = 15.8, 1 H, PhCH_2); 4.59 (*d*, *J* = 15.8, 1 H, PhC*H*$_2$); 4.04 (*q*, *J* = 7.1, MeC*H*$_2$O); 3.27 (*d*, *J* = 16.9, 1 H, C*H*$_2$CO$_2$Et); 3.25 (*d*, *J* = 16.9, 1 H, C*H*$_2$CO$_2$Et); 3.08 (*d*, *J* = 5.9, H–C(9)); 3.03 (*d*, *J* = 18.7, 1 H, H–C(10)); 2.77 (*m*, 5 H); 2.36 (*m*, 2 H); 2.14 (*m*, 2 H); 1.65 (*m*, 1 H); 1.15 (*t*, *J* = 7.1, *Me*CH_2O); 0.80 (*m*, H–C(19)); 0.51 (*m*, 2 H, H–C(20), H–C(21)); 0.10 (*m*, 2 H, H–C(20), H–C(21)). ^{13}C-NMR (CD_2Cl_2): 170.60; 142.99; 142.69; 141.72; 138.35; 135.98; 128.80; 127.88; 127.74; 127.45; 121.86; 119.22; 118.69; 114.12; 73.10; 61.44; 60.50; 59.49; 45.07; 43.40; 32.49; 31.46; 29.48; 25.49; 14.28; 9.72; 4.02. EI-MS: 556 (50, M^+), 91 (100). Anal. calc. for $C_{33}H_{36}N_2O_6 \cdot HCl \cdot 1.25\ H_2O$ (615.64): C 64.38, H 6.47, N 4.55; found: C 64.13, H 6.52, N 4.32.

*1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′α-(2-hydroxyethyl)pyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**20a**) *and 1′-Benzyl-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′β-(2-hydroxyethyl)pyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**21a**): As described for **16b**/**17b**, from **14b** (0.5 g, 1.46 mmol), benzylamine (0.16 ml, 1.46 mmol), and α-methylene-γ-butyrolactone (0.13 ml, 1.46 mmol): 0.13 g (26%) of **20a** and 0.17 g (33%) of **21a**.

Data of **20a**: R_f 0.69. M.p. 200–202°. ^{1}H-NMR ($CDCl_3$): 7.19 (*m*, *Ph*CH_2); 6.59 (*d*, *J* = 8.0, H–C(2)); 6.47 (*d*, *J* = 8.0, H–C(1)); 5.42 (*d*, *J* = 16.5, 1 H, PhC*H*$_2$); 4.93 (*s*, H–C(5)); 4.75 (*d*, *J* = 16.5, 1 H, PhC*H*$_2$); 3.52 (*m*, 1 H); 3.07 (*d*, *J* = 6.4, H–C(9)); 2.97 (*d*, *J* = 18.8, 1 H, H–C(10)); 2.54 (*m*, 3 H); 2.15 (*m*, 8 H); 1.78 (*dd*, *J* = 6.0, 1 H); 1.55 (*m*, 1 H); 1.33 (*m*, 2 H); 0.75 (*m*, H–C(19)); 0.45 (*m*, 2 H, H–C(20), H–C(21)); 0.03 (*m*, 2 H, H–C(20), H–C(21)). ^{13}C-NMR ($CDCl_3$): 174.23; 143.08; 139.36; 138.32; 131.44; 128.81; 128.10; 127.11; 126.19; 126.07; 125.23; 119.53; 118.95; 117.96; 86.14; 69.94; 61.34; 60.98; 59.53; 46.73; 44.56; 43.59; 38.81; 37.72; 32.75; 31.95; 31.16; 23.02; 9.47; 4.11; 3.83. EI-MS: 528 (100, M^+), 91 (90). Anal. calc. for $C_{32}H_{36}N_2O_5 \cdot HCl \cdot 0.75\ H_2O$ (578.62): C 66.43, H 6.71, N 4.84; found: C 66.60, H 6.66, N 4.66.

Data of **21a**: R_f 0.75. M.p. 255–256°. ^{1}H-NMR ($CDCl_3$): 7.33–7.17 (*m*, *Ph*CH_2); 6.65 (*d*, *J* = 8.0, H–C(2)); 6.53 (*d*, *J* = 8.0, H–C(1)); 5.55 (*d*, *J* = 16.8, 1 H, PhC*H*$_2$); 4.98 (*s*, H–C(5)); 4.79 (*d*, *J* = 16.6, 1 H, PhC*H*$_2$); 3.8–3.7 (*m*, 1 H, CH_2C*H*$_2$OH); 3.67–3.57 (*m*, 1 H, CH_2C*H*$_2$OH); 3.13 (*d*, *J* = 6.3, H–C(9)); 3.04 (*d*, *J* = 18.6, 1 H–C(10)); 2.64–2.60 (*m*, 1 H–C(10)); 2.5–2.0 (*m*, 8 H, 1 H–C(8), CH_2(15), CH_2(16), CH_2(18), 1 H, C*H*$_2$CH$_2$OH); 1.7 (*m*, 1 H, C*H*$_2$CH$_2$OH); 1.55 (br. *d*, 1 H–C(8)); 0.80–0.79 (*m*, H–C(19)); 0.52–0.50 (*m*, 2 H, H–C(20), H–C(21)); 0.11–0.10 (*m*, 2 H, H–C(20), H–C(21)). ^{13}C-NMR ($CDCl_3$): 173.81; 142.56; 139.39; 138.23; 128.63; 126.87; 125.94; 119.06; 117.18; 85.71; 70.19; 61.29; 59.34; 46.55; 45.50; 43.0; 40.0; 36.5; 32.80; 32.47; 31.34; 30.90; 22.83; 9.32; 3.95; 3.65. EI-MS: 528 (100, M^+), 91 (80). Anal. calc. for $C_{32}H_{36}N_2O_5 \cdot HCl \cdot 1.5\ H_2O$ (592.05): C 64.91, H 6.80, N 4.72; found: C 65.12, H 6.46, N 4.59.

*1′-Benzyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-4′,5′-dihydro-5′α-(2-hydroxyethyl)-17-methylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**20b**) *and 1′-Benzyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxy-4′,5′-dihydro-5′β-(2-hydroxyethyl)-17-methylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**21b**). As described for **16b**/**17b**, from **14a** (0.5 g, 1.66 mmol), benzylamine (0.19 ml, 1.66 mmol), and α-methylene-γ-butyrolactone (0.14 ml, 1.66 mmol): 0.07 g (12%) of **20b** and 0.12 g (21%) of **21b**.

Data of **20b**: R_f 0.84. M.p. 200–205°. ^{1}H-NMR ($CDCl_3$): 7.30 (*m*, *Ph*CH_2); 6.59 (*d*, *J* = 8.0, H–C(2)); 6.56 (*d*, *J* = 8.0, H–C(1)); 5.47 (*d*, *J* = 16.6, 1 H, PhC*H*$_2$); 4.99 (*s*, H–C(5)); 4.81 (*d*, *J* = 16.4, 1 H, PhC*H*$_2$); 3.6–3.56 (*m*, CH_2C*H*$_2$OH); 3.14 (*d*, *J* = 18.6, 1 H–C(10)); 2.89 (*d*, *J* = 6.2, H–C(9)); 2.65 (*m*, 1 H–C(10)); 2.51–2.06 (*m*, 11 H); 1.58–1.5 (*m*, 2 H); 1.38–1.25 (*m*, C*H*$_2$CH$_2$OH). ^{13}C-NMR ($CDCl_3$): 174.14; 142.96; 139.38; 138.17;

131.06; 128.71; 127.93; 127.0; 126.08; 125.97; 119.49; 118.67; 117.97; 85.85; 70.01; 63.85; 61.35; 60.81; 45.88; 45.23; 44.46; 42.98; 38.64; 37.53; 32.60; 31.74; 30.95; 30.67; 22.27. EI-MS: 488 (100, M^+). Anal. calc. for $C_{29}H_{32}N_2O_5 \cdot HCl \cdot 1.25\,H_2O$ (547.56): C 63.6, H 6.52, N 5.11; found: C 63.5, H 6.21, N 5.24.

Data of **21b**: R_f 0.87. M.p. 280°. ^{1}H-NMR ($CDCl_3$): 7.30 (*m*, *Ph*CH_2); 6.65 (*d*, *J* = 8.0, H–C(2)); 6.55 (*d*, *J* = 8.0, H–C(1)); 5.54 (*d*, *J* = 16.8, 1 H, PhCH_2); 4.96 (*s*, H–C(5)); 4.77 (*d*, *J* = 16.8, 1 H, PhCH_2); 3.76–3.71 (*m*, 1 H, CH_2CH_2OH); 3.62–3.57 (*m*, 1 H, CH_2CH_2OH); 3.13 (*d*, *J* = 18.4, 1 H–C(10)); 2.81 (*d*, *J* = 6.0, H–C(9)); 2.60 (*dd*, *J* = 6.4, 18.8, 1 H–C(10)); 2.46–2.21 (*m*, 9 H); 2.20–2.0 (*m*, 3 H); 1.69–1.63 (*m*, 1 H, CH_2CH_2OH); 1.55–1.51 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 173.65; 142.37; 139.28; 138.05; 130.62; 128.53; 128.37; 126.73; 125.83; 124.34; 118.98; 118.91; 117.16; 85.56; 70.39; 63.78; 61.34; 45.96; 45.11; 44.75; 42.98; 39.19; 36.57; 32.87; 32.55; 31.22; 22.23. EI-MS: 488 (100, M^+), 91 (70). Anal. calc. for $C_{29}H_{32}N_2O_5 \cdot HCl \cdot H_2O$ (543.06): C 64.14, H 6.50, N 5.16; found: C 64.0, H 6.62, N 5.23.

*6,7-Didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′α-(2-hydroxyethyl)-1′,17-dimethylpyrido[2′,3′:6,7]-morphinan-6′(1′*H*)-one* (**20c**) *and 6,7-Didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-5′β-(2-hydroxyethyl)-1′,17-dimethylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**21c**). As described for **16b**/**17b**, from **14a** (0.6 g, 1.99 mmol), 2M $MeNH_2$ in MeOH (1.99 mmol, 1.26 ml), and α-methylene-γ-butyrolactone (0.17 ml, 1.99 mmol): 0.08 g (14%) of **20c** and 0.14 g (21%) of **21c**.

Data of **20c**: R_f 0.79. M.p. 255–260°. ^{1}H-NMR ($CDCl_3$): 7.25 (*m*, *Ph*CH_2); 6.68 (*d*, *J* = 8.0, H–C(2)); 6.56 (*d*, *J* = 8.0, H–C(1)); 5.29 (*d*, H–C(5)); 3.47–3.42 (*m*, CH_2CH_2OH); 3.28 (*s*, MeN); 3.16 (*d*, *J* = 18.8, 1 H–C(10)); 2.85 (*d*, *J* = 6.4, H–C(9)); 2.66–2.47 (*m*, 4 H); 2.38 (*s*, MeN); 2.29–2.27 (*m*, 2 H); 2.05 (br. *s*, 2 H); 1.65–1.45 (*m*, 2 H); 1.2–1.0 (*m*, CH_2CH_2OH). ^{13}C-NMR ($CDCl_3$): 174.09; 143.19; 139.79; 131.30; 128.32; 124.93; 119.77; 118.38; 117.82; 85.55; 70.26; 64.08; 60.71; 46.19; 45.56; 43.42; 38.43; 37.75; 32.79; 31.35; 29.24; 22.61. EI-MS: 412 (100). Anal. calc. for $C_{23}H_{28}N_2O_5 \cdot HCl \cdot 0.25\,H_2O \cdot 0.5\,CH_2Cl_2$ (496.84): C 56.8, H 6.18, N 5.63; found: C 57.2, H 5.84, N 5.78.

Data of **21c**: R_f 0.83. M.p. 265–267°. ^{1}H-NMR ($CDCl_3$): 7.25 (*m*, *Ph*CH_2); 6.67 (*d*, *J* = 8.0, H–C(2)); 6.56 (*d*, *J* = 8.0, H–C(1)); 5.19 (*s*, H–C(5)); 3.74–3.69 (*m*, 1 H, CH_2CH_2OH); 3.57–3.52 (*m*, 1 H, CH_2CH_2OH); 3.28 (*s*, MeN); 3.16 (*d*, *J* = 18.8, 1 H–C(10)); 2.84 (*d*, *J* = 6.4, H–C(9)); 2.65–2.59 (*dd*, *J* = 6.8, 18.8, 1 H–C(10)); 2.46 (*d*, *J* = 7.2, 1 H, CH_2N); 2.42 (*s*, MeN); 2.38–2.27 (*m*, 5 H); 2.25–2.19 (*m*, 1 H, CH_2CH_2OH); 1.99–1.83 (*m*, 2 H); 1.65 (*d*, *J* = 9.2, 1 H, CH_2N); 1.58–1.53 (*m*, 1 H, CH_2CH_2OH). ^{13}C-NMR ($CDCl_3$): 173.73; 142.74; 139.73; 130.85; 128.96; 124.52; 119.27; 118.54; 117.64; 85.54; 70.66; 64.08; 61.57; 46.24; 45.49; 43.32; 39.13; 36.61; 33.33; 32.71; 31.69; 29.52; 22.54. FAB-MS: 413 (100, $[M+1]^+$). Anal. calc. for $C_{23}H_{28}N_2O_5 \cdot HCl \cdot 0.5\,H_2O \cdot 0.5\,CH_2Cl_2$ (501.34): C 56.29, H 6.22, N 5.58; found: C 56.1, H 6.10, N 5.64.

*6,7-Didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-1′,17-dimethylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**22a**). As described for **16b**/**17b**, from **14a** (0.3 g, 0.99 mmol), 2M $MeNH_2$ in MeOH (0.49 ml, 0.99 mmol) and ethyl acrylate (0.11 ml, 0.99 mmol): 0.16 g (45%) of **22a**. R_f 0.5. M.p. 270–275°. ^{1}H-NMR ($CDCl_3$): 6.68 (*d*, *J* = 8.4, H–C(2)); 6.55 (*d*, *J* = 8.4, H–C(1)); 5.18 (*s*, H–C(5)); 3.28 (*s*, MeN); 3.15 (*d*, *J* = 18.8, 1 H–C(10)); 2.83 (*d*, *J* = 6.4, H–C(9)); 2.61 (*dd*, *J* = 18.8, 6.8, 1 H–C(10)); 2.50–2.11 (*m*, 10 H); 2.0–1.6 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 170.37; 142.54; 139.47; 130.64; 128.82; 124.25; 118.84; 117.68; 117.29; 85.49; 70.33; 63.77; 45.89; 45.16; 42.99; 36.44; 31.36; 30.42; 28.67; 25.58; 22.20. FAB-MS: 369.1 (100, $[M+1]$). Anal. calc. for $C_{21}H_{24}N_2O_4 \cdot HCl \cdot 1.5\,H_2O \cdot 0.5\,CH_2Cl_2$ (475.33): C 54.32, H 6.14, N 5.89; found: C 54.2, H 6.01, N 6.15.

*1′-Benzyl-6,7-didehydro-4,5α-epoxy-4′,5′-dihydro-3,14-dihydroxy-17-methylpyrido[2′,3′:6,7]morphinan-6′(1′*H*)-one* (**22b**). As described for **16b**/**17b**, from **14a** (0.5 g, 1.66 mmol), benzylamine (0.19 ml, 1.66 mmol), and ethyl acrylate (0.18 ml, 1.66 mmol): 0.4 g (60%) of **22b**. R_f 0.5. M.p. 185–186°. ^{1}H-NMR ($CDCl_3$): 7.35–7.18 (*m*, *Ph*CH_2); 6.63 (*d*, *J* = 8.0, H–C(2)); 6.54 (*d*, *J* = 8.0, H–C(1)); 5.43 (*d*, *J* = 16.8, 1 H, PhCH_2); 4.89 (*s*, H–C(5)); 4.86 (*d*, *J* = 16.8, 1 H, PhCH_2); 3.14 (*d*, *J* = 18.6, 1 H–C(10)); 2.81 (*d*, *J* = 6.3, H–C(9)); 2.63–2.55 (*m*, 2 H); 2.41–1.98 (*m*, 11 H); 1.56–1.51 (br. *d*, 1 H). ^{13}C-NMR ($CDCl_3$): 170.61; 142.52; 139.34; 138.59; 130.88; 128.76; 127.17; 126.82; 125.92; 124.64; 119.05; 118.74; 117.15; 86.11; 70.33; 63.82; 46.20; 45.07; 44.33; 42.95; 36.76; 31.13; 30.80; 26.08; 22.11. EI-MS: 444 (100, M^+), 91 (76). Anal. calc. for $C_{27}H_{28}N_2O_4 \cdot HCl \cdot 3.5\,H_2O$ (544.04): C 59.6, H 6.66, N 5.14; found: C 59.9, H 6.31, N 5.28.

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