Synthesis of 6-Amino Acid Substituted Derivatives of the Highly Potent Analgesic 14-*O*-Methyloxymorphone

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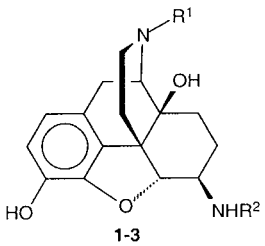
The novel morphinans **13**–**18**, which carry amino acid substituents at C(6), with potentially limited access to the central nervous system were prepared in two steps from 14-*O*-methyloxymorphone (**5**). Reductive amination with amino acid *tert*-butyl esters gave compounds **7**–**12**, which were hydrolyzed with tetrafluoroboric acid. Structure elucidation (including X-ray analysis), preliminary μ-opioid receptor binding studies, and calculations of pharmacokinetic parameters were carried out.

Introduction. – Currently, treatment of severe pain relies mostly on the use of centrally acting opioid analgesics. A significant drawback to the use of these opioids is the variety of adverse effects mediated predominantly *via* the central nervous system (CNS), such as sedation, nausea, confusion, respiratory depression, tolerance, and dependence. Recently, it has been described that a potentially successful strategy to reduce the adverse actions of opioids is to restrict the access of these compounds to the CNS. It was reported that usually centrally acting opioids are able to produce profound analgesia in animals by activating opioid receptors on peripheral nerve terminals when injected into the injured tissue [1–10]. In humans, very small doses of locally applied morphine produce considerable analgesia without serious central side effects [4][11–17]. A considerable drawback of current local opioid treatment is the requirement for repeated intra-articular injections, which carry risks such as bleeding, infection, or



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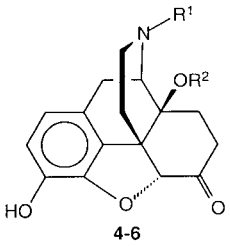

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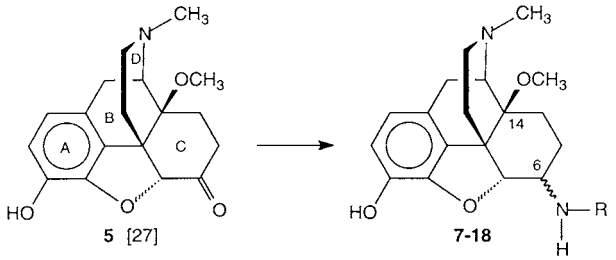
β-Oxymorphamine (**1**): R^1 = Me, R^2 = H; β-Naltrexamine (**2**): R^1 = cpm, R^2 = H; β-FNA (**3**): R^1 = cpm, R^2 = COCHCHCOOMe cpm: (cyclopropyl)methyl; NTX (**4**): R^1 = cpm, R^2 = H; 14-*O*-Methyloxymorphone (**5**): $R^1 = R^2$ = Me; Oxymorphone (**6**): R^1 = Me, R^2 = H.

possible cartilage breakdown [18]. Therefore, compounds with limited access to the CNS that are not able to pass the blood-brain barrier and that could be administered systemically or orally are of high interest.

Opioids with zwitterionic moieties show greatly reduced access to the CNS without substantially decreased opioid receptor activity [19–24]. Ionizable compounds with an amide function (except for the 6-glycine derivative of naltrexone) at C(6) of the morphinan skeleton were synthesized from β-oxymorphamine (**1**) and β-naltrexamine (**2**) [19], or from β-funaltrexamine (β-FNA; **3**) [22]. A recent study describes the synthesis of zwitterionic 6-sulfonamide compounds synthesized from naltrexone (NTX; **4**) [25].

Here, we report a novel synthetic approach for the synthesis of 6-amino acid derivatives in the morphinan series. These differ from the earlier published compounds, since the substituents at C(6) are amines instead of amides [19][22] or sulfonamides [25]. 14-*O*-Methyloxymorphone (**5**), a compound that is 40 times more potent in the hot-plate assay in mice than its 14-hydroxy analogue oxymorphone (**6**) [26], has been used as a starting material for the synthesis of the zwitterionic derivatives as outlined in the *Scheme*.

Scheme



14-*O*-Methyloxymorphone (**5**) [27]

7 R = $CH_2COO(t\text{-Bu})$, 6-H_β
8 R = $CH_2COO(t\text{-Bu})$, 6-H_α
9 R = (*S*)-CH(Me)COO(*t*-Bu), 6-H_β
10 R = (*S*)-CH(Me)COO(*t*-Bu), 6-H_α
11 R = (*S*)-$CH(CH_2Ph)COO(t\text{-Bu})$, 6-$H_\beta$
12 R = (*S*)-$CH(CH_2Ph)COO(t\text{-Bu})$, 6-$H_\alpha$
13 R = CH_2COOH, 6-H_β
14 R = CH_2COOH, 6-H_α
15 R = (*S*)-CH(Me)COOH, 6-H_β
16 R = (*S*)-CH(Me)COOH, 6-H_α
17 R = (*S*)-$CH(CH_2Ph)COOH$, 6-H_β
18 R = (*S*)-$CH(CH_2Ph)COOH$, 6-H_α

Results and Discussion. – Compounds **7** and **8**, **9** and **10**, and **11** and **12** were prepared from **5**·HBr [27] by reductive amination with glycine *tert*-butyl ester hydrochloride, alanine *tert*-butyl ester hydrochloride, and phenylalanine *tert*-butyl ester hydrochloride, respectively, and sodium cyanoborohydride in EtOH [28]. After separating the epimers by MPLC, hydrolysis of the esters **7** and **8** was first attempted with CF_3COOH in CH_2Cl_2 [29], which, surprisingly, did not yield the bis(trifluoroacetates) (**13**·2 CF_3COOH and **14**·2 CF_3COOH) but the sesqui(trifluoroacetates)

(**13** · 1.5 CF_3COOH and **14** · 1.5 CF_3COOH), which were confirmed by multiple elemental analyses. Thus, compounds **7**–**12** were treated with tetrafluoroboric acid in CH_2Cl_2 [30] to afford compounds **13**–**18** as bis(tetrafluoroborates).

Several studies have been published concerning the configuration at C(6) and the conformation of ring C of 6-amino- and 6-hydroxymorphinans [31–35]. Configurational assignments at C(6) were based on the coupling constants (J(5,6)) between H–C(5) and H–C(6). J(5,6) Values for 6α-amino epimers are smaller (3.2–4.0 Hz) than for 6β-amino compounds (6.5–7.8 Hz) [31][32]. The results for the title compounds agree with those findings: their J(5,6) values range from 2.8 to 3.8 Hz for 6α-amino derivatives and from 7.0 to 7.6 Hz for 6β-amino derivatives. The conformation of ring C of oxymorphamine epimers was resolved by two-dimensional high-field ^{1}H-NMR experiments [33]. Thus, the conformation of ring C of 6β derivatives is the expected chair, while that of 6α derivatives, however, is a twisted boat, as confirmed by X-ray analysis of 6α-oxymorphamine [34]. Different substituents at C(14) strongly influence the conformation of ring C of 6α-substituted morphinans [35]. While 14-OH-substituted compounds have C rings with the twisted boat conformation, compounds unsubstituted at C(14) have the chair conformation. Although we expected the 14-MeO substitution to have the same effect on ring-C conformation as the 14-OH substitution, we determined the crystal structure of 6α-amino derivative **9** by X-ray analysis (*Fig.*) to prove our assumption.

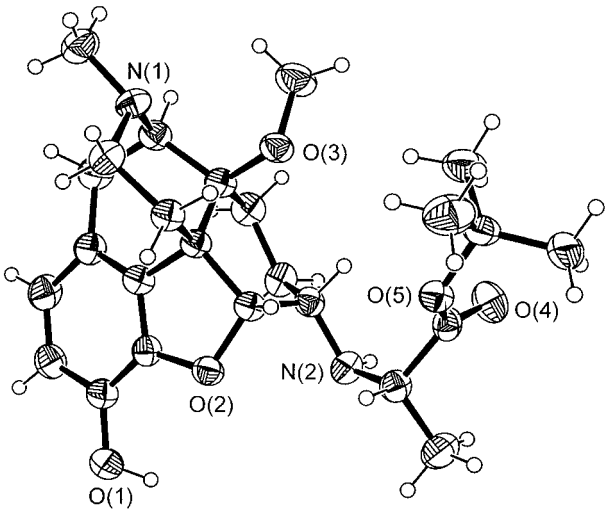


Figure. *ORTEP Plot of* **9** *drawn with 40% probability ellipsoids.* The boat conformation of ring C can be clearly seen.

The preliminary binding affinities of compounds **13**–**18** towards μ-opioid receptors were determined in rat brain homogenates by radioligand binding assays with [^{3}H]DAMGO [36][37], with morphine and 14-*O*-methyloxymorphone (**5**) as reference opioid compounds. The novel compounds show very high affinities for the μ receptor – the values of K_i (inhibition constant) for compounds **13**–**18** range from 0.77 to 2.58 nM

(morphine: 6.55 nM; **5**: 0.10 nM). Extended *in vitro* and *in vivo* studies are in progress and will be published elsewhere.

The blood–brain distributions of compounds **13**–**18** and of morphine were calculated with the Molecular Operating Environment (MOE) molecular-graphics program based on 2D descriptors [38][39]. All descriptors used include simple approximations of the *Van der Waals* surfaces of the compounds. The calculated log (*BB*) values (*BB* = (concentration in brain)/(concentration in blood)) are: −1.64 (compounds **13** and **14**), −1.65 (compounds **15** and **16**), −1.86 (compounds **17** and **18**), and −0.47 (morphine). From these values, we predict that compounds **13**–**18** will be *ca.* 98% distributed in peripheral tissue and *ca.* 2% in brain tissue (morphine: *ca.* 75% in the periphery and *ca.* 25% in brain).

Experimental Part

General. The required reagents and anh. solvents were purchased *via* www.sigma-aldrich.com (*Fluka*, *Aldrich*, and *Riedel de Haën*) in the highest purities available; other solvents were distilled before use. TLC: *POLYGRAM SIL G/UV$_{254}$* precoated plastic sheets (*Macherey-Nagel*, Germany); eluent: CH_2Cl_2/MeOH/conc. NH_4OH soln. 90:9:1. Column chromatography (CC): silica gel *60* (230–400 mesh ASTM, *Fluka*, Switzerland). M.p.: *Kofler* melting-point microscope; uncorrected. IR Spectra: *Mattson Galaxy Series FTIR 3000* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Varian Gemini 200* spectrometer (200 MHz); δ in ppm rel. to Me_4Si as internal standard; *J* in Hz. ^{13}C-NMR Spectra: *Varian Gemini 200* spectrometer (50.3 MHz); δ ($CDCl_3$) = 77.7; δ ($(D)_6DMSO$) = 39.5; for the measurements in D_2O, 3 drops of $(D)_6DMSO$ were added. MS: *Finnigan Mat SSQ 7000* apparatus. Elemental analyses were performed by Mag. *J. Theiner* at the Institute of Physical Chemistry at the University of Vienna, Austria (www.univie.ac.at/Mikrolabor/info.htm).

General Procedure for the Synthesis of Compounds **7**–**12**. A mixture of **5**·HBr (5 mmol) [27], the corresponding amino acid *tert*-butyl ester hydrochloride (6.5 mmol), $EtN(i\text{-}Pr)_2$ (12 mmol), 3-Å molecular sieves (3 g), and anh. EtOH (100 ml) was stirred under N_2 at r.t. for 3 h. $NaCNBH_3$ (6.5 mmol) was dissolved in anh. EtOH (20 ml) and added during 15 min. The mixture was stirred at r.t. for 2 d. After addition of H_2O (10 ml), the mixture was evaporated and then partitioned between H_2O (300 ml) and CH_2Cl_2 (1 × 100 ml, 3 × 50 ml). The combined org. layers were washed with brine (200 ml), dried (Na_2SO_4), and evaporated to give a yellow oil, which was separated and purified by MPLC (5 bar, silica gel; CH_2Cl_2/MeOH 10:1). Anal. amounts of compounds **9** and **10** were crystallized from MeOH and i-PrOH, respectively, while the other compounds failed to crystallize from a multitude of solvents (for the next step, all compounds were applied as foams).

tert-*Butyl 2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]acetate* (**7**). White foam (11% yield). IR (KBr): 3407 (OH), 1731 (C=O). ^{1}H-NMR ($CDCl_3$): 6.66 (*d*, *J* = 8.1, 1 arom. H); 6.47 (*d*, *J* = 8.1, 1 arom. H); 5.05 (br. *s*, OH, NH); 4.65 (*d*, *J* = 3.6, H–C(5)); 3.42 (*s*, NHCH_2); 3.21 (*s*, MeO); 2.36 (*s*, MeN); 1.43 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 171.9; 146.8; 138.9; 131.2; 126.1; 119.3; 118.9; 89.8; 82.1; 76.8; 59.2; 53.8; 49.6; 48.7; 47.7; 46.2; 43.7; 33.3; 28.7 (3C); 23.5; 23.0; 21.6. CI-MS: 431 ([*M* + 1]$^+$). Anal. calc. for $C_{24}H_{34}N_2O_5 \cdot 0.4\ H_2O$ (437.75): C 65.85, H 8.01, N 6.40; found: C 65.79, H 7.86, N 6.14.

tert-*Butyl 2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]acetate* (**8**). White foam (24% yield). IR (KBr): 3421 (OH), 1729 (C=O). ^{1}H-NMR ($CDCl_3$): 6.68 (*d*, *J* = 8.0, 1 arom. H); 6.53 (*d*, *J* = 8.0, 1 arom. H); 4.71 (br. *s*, OH, NH); 4.47 (*d*, *J* = 7.0, H–C(5)); 3.48 (*d*, *J* = 17.3, NHCH_2); 3.32 (*d*, *J* = 17.3, NHCH_2); 3.19 (*s*, MeO); 2.42 (*s*, MeN); 1.42 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 172.5; 143.1; 141.0; 132.6; 124.8; 119.5; 117.9; 95.5; 82.1; 76.3; 59.7; 58.8; 50.1; 48.3; 47.9; 47.3; 43.4; 29.1; 28.7 (3C); 24.5; 23.8; 23.6. CI-MS: 431 ([*M* + 1]$^+$). Anal. calc. for $C_{24}H_{34}N_2O_5 \cdot 0.6\ H_2O$ (441.36): C 65.31, H 8.04, N 6.35; found: C 65.38, H 7.81, N 6.13.

tert-*Butyl (2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]propanoate* (**9**). White crystals (11% yield). M.p. 196–200° (dec.). IR (KBr): 3203 (OH), 1729 (C=O). ^{1}H-NMR ($CDCl_3$): 6.69 (*d*, *J* = 8.2, 1 arom. H); 6.47 (*d*, *J* = 8.2, 1 arom. H); 4.71 (*d*, *J* = 3.2, H–C(5)); 3.55 (*q*, *J* = 6.8, NHC*H*); 3.19 (*s*, MeO); 2.35 (*s*, MeN); 1.47 (*s*, *t*-Bu); 1.26 (*d*, *J* = 6.8, NHCH*Me*). ^{13}C-NMR ($CDCl_3$): 175.6; 147.4; 138.4; 131.4; 126.8; 119.1 (2C); 89.2; 81.9; 76.8; 59.0; 54.7; 52.2; 48.4; 47.7; 46.1; 43.7; 33.6; 28.7 (3C); 23.3; 22.9; 22.2; 19.3. CI-MS: 445 ([*M* + 1]$^+$). Anal. calc. for $C_{25}H_{36}N_2O_5 \cdot 0.1\ H_2O$ (446.38): C 67.27, H 8.17, N 6.28; found: C 66.92, H 7.91, N 6.30.

tert-*Butyl (2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]propanoate* (**10**). White crystals (28% yield). M.p. 235–240° (dec.). IR (KBr): 3423 (OH), 1722 (C=O). ^{1}H-NMR ($CDCl_3$): 6.69 (*d*, *J* = 8.0, 1 arom. H); 6.54 (*d*, *J* = 8.0, 1 arom. H); 4.40 (*d*, *J* = 7.2, H–C(5)); 3.32 (*q*, *J* = 7.0, NHC*H*); 3.20 (*s*, MeO); 2.39 (*s*, MeN); 1.41 (*s*, *t*-Bu); 1.26 (*d*, *J* = 7.0, NHCH*Me*). ^{13}C-NMR ($CDCl_3$): 176.2; 143.2; 140.8; 133.0; 125.5; 119.5; 117.7; 96.2; 81.9; 76.3; 58.7; 58.6; 56.2; 48.1; 47.9; 47.2; 43.4; 29.0; 28.6 (3C); 24.6; 23.7; 23.3; 20.3. CI-MS: 445 ($[M+1]^+$). Anal. calc. for $C_{25}H_{36}N_2O_5 \cdot 0.5\ H_2O$ (453.58): C 66.20, H 8.22, N 6.18; found: C 66.08, H 8.35, N 6.00.

tert-*Butyl (2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-3-phenylpropanoate* (**11**). White foam (10% yield). IR (KBr): 3336 (OH), 1725 (C=O). ^{1}H-NMR ($CDCl_3$): 7.32–7.18 (*m*, 5 arom. H); 6.70 (*d*, *J* = 8.0, 1 arom. H); 6.48 (*d*, *J* = 8.0, 1 arom. H); 4.71 (*d*, *J* = 3.2, H–C(5)); 3.73 (*t*, *J* = 7.5, NHC*H*); 3.12 (*s*, MeO); 2.35 (*s*, MeN), 1.32 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 174.6; 147.2; 138.3; 138.1; 131.4; 130.2 (2C); 128.9 (2C); 127.2; 126.9; 119.3; 119.0; 89.1; 82.1; 76.7; 61.2; 59.1; 52.3; 48.4; 47.7; 46.1; 43.7; 40.4; 33.5; 28.5 (3C); 23.4; 23.0; 22.6. CI-MS: 521 ($[M+1]^+$). Anal. calc. for $C_{31}H_{40}N_2O_5 \cdot 0.3\ H_2O$ (526.08): C 70.78, H 7.78, N 5.32; found: C 70.39, H 7.67, N 5.62.

*(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-3-phenylpropanoate* (**12**). White foam (23% yield). IR (KBr): 3409 (OH), 1724 (C=O). ^{1}H-NMR ($CDCl_3$): 7.29–7.17 (*m*, 5 arom. H); 6.70 (*d*, *J* = 8.0, 1 arom. H); 6.54 (*d*, *J* = 8.0, 1 arom. H); 4.39 (*d*, *J* = 7.4, H–C(5)); 3.47 (*t*, *J* = 7.2, NHC*H*); 3.21 (*s*, MeO); 2.44 (*s*, MeN); 1.28 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 175.1; 143.2; 140.9; 138.2; 132.7; 130.0 (2C); 128.9 (2C); 127.2; 125.1; 119.6; 117.7; 96.2; 82.2; 76.3; 62.8; 59.1; 58.9; 48.3; 47.8; 47.3; 43.4; 40.8; 28.7; 28.6 (3C); 24.6; 23.6; 23.5. CI-MS: 521 ($[M+1]^+$). Anal. calc. for $C_{31}H_{40}N_2O_5 \cdot 0.6\ H_2O$ (531.48): C 70.06, H 7.81, N 5.27; found: C 69.66, H 7.78, N 5.18.

General Procedure for the Synthesis of Compounds **13**–**18**. A soln. of the corresponding *tert*-butyl esters **7**–**12** (1 mmol) in CH_2Cl_2 (7 ml) was treated with 54% HBF_4 in Et_2O (0.7 ml, 5 mmol), sonicated for 45 min, and then treated with Et_2O (1 ml). The precipitated compounds **13**–**16** were filtered off under N_2 and dried. Because compounds **17** and **18** failed to crystallize, the mixtures were evaporated, and the residues (orange oils) were dissolved in H_2O (300 ml) and freeze-dried.

2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]acetic Acid Bis(tetrafluoroborate) (**13** · 2 HBF_4). White crystals (78% yield). The compound was too hygroscopic for the measurement of the m.p. with a *Kofler* microscope. IR (KBr): 3403, 3219 (OH), 1740 (C=O). ^{1}H-NMR (D_2O): 6.90 (*d*, *J* = 8.4, 1 arom. H); 6.82 (*d*, *J* = 8.4, 1 arom. H); 5.05 (*d*, *J* = 3.8, H–C(5)); 4.03 (*m*, NHCH_2); 3.35 (*s*, MeO); 2.94 (*s*, MeN). ^{13}C-NMR (D_2O): 170.7; 146.4; 139.4; 129.9; 125.0; 122.7; 120.5; 85.9; 77.1; 61.7; 55.4; 51.1; 47.9; 47.8; 47.1; 42.7; 31.2; 25.5; 21.2; 17.8. ESI-MS: 375 ($[M+1]^+$). Anal. calc. for $C_{20}H_{26}N_2O_5 \cdot 2\ HBF_4 \cdot 2.0\ H_2O$ (586.10): C 40.99, H 5.50, N 4.78; found: C 40.97, H 5.37, N 4.68.

2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]acetic Acid Bis(tetrafluoroborate) (**14** · 2 HBF_4). White crystals (95% yield). M.p. >300° (dec.). IR (KBr): 3404 (OH), 1740 (C=O). ^{1}H-NMR (D_2O): 6.87 (*s*, 2 arom. H); 4.90 (*d*, *J* = 7.2, H–C(5)); 4.08 (*s*, NHCH_2); 3.33 (*s*, MeO); 2.92 (*s*, MeN). ^{13}C-NMR (D_2O): 170.2; 142.3; 141.4; 130.1; 123.1; 122.3; 119.9; 88.9; 76.3; 61.0; 60.1; 49.7; 48.7; 47.7; 47.1; 42.0; 27.7; 24.3; 23.4; 20.5. ESI-MS: 375 ($[M+1]^+$). Anal. calc. for $C_{20}H_{26}N_2O_5 \cdot 2\ HBF_4 \cdot 0.5\ H_2O$ (559.07): C 42.97, H 5.23, N 5.01; found: C 42.57, H 4.91, N 4.85.

*(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]propanoic Acid Bis(tetrafluoroborate)* (**15** · 2 HBF_4). White crystals (79% yield). M.p. >290° (dec.). IR (KBr): 3423 (OH), 1720 (C=O). ^{1}H-NMR (D_2O): 6.90 (*d*, *J* = 8.0, 1 arom. H); 6.81 (*d*, *J* = 8.0, 1 arom. H); 5.02 (*d*, *J* = 2.8, H–C(5)); 4.24 (*q*, *J* = 7.0, NHC*H*); 3.35 (*s*, MeO); 2.94 (*s*, MeN); 1.63 (*d*, *J* = 7.0, NH–CH*Me*). ^{13}C-NMR (D_2O): 174.3; 146.4; 139.4; 129.9; 125.0; 122.8; 120.5; 85.8; 77.1; 61.7; 55.3; 54.1; 51.2; 47.9; 42.8; 31.3; 25.5; 21.3; 18.1; 16.7. ESI-MS: 389 ($[M+1]^+$). Anal. calc. for $C_{21}H_{28}N_2O_5 \cdot 2\ HBF_4 \cdot 0.2\ Et_2O$ (578.92): C 45.23, H 5.57, N 4.84; found: C 45.29, H 5.33, N 4.83.

*(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]propanoic Acid Bis(tetrafluoroborate)* (**16** · 2 HBF_4). White crystals (89% yield). M.p. >290° (dec.). IR (KBr): 3423 (OH), 1741 (C=O). ^{1}H-NMR (D_2O): 6.90 (*s*, 2 arom. H); 4.86 (*d*, *J* = 7.6, H–C(5)); 4.31 (*q*, *J* = 7.0, NHC*H*); 3.33 (*s*, MeO); 2.92 (*s*, MeN); 1.58 (*d*, *J* = 7.0, NHCH*Me*). ^{13}C-NMR (D_2O): 173.8; 142.7; 141.8; 130.6; 123.5; 122.7; 120.4; 89.7; 76.6; 61.4; 58.9; 55.7; 50.2; 49.1; 48.1; 42.4; 28.0; 24.7; 23.9; 20.9; 16.1. ESI-MS: 389 ($[M+1]^+$). Anal. calc. for $C_{21}H_{28}N_2O_5 \cdot 2\ HBF_4 \cdot 1.2\ H_2O$ (585.71): C 43.06, H 5.58, N 4.78; found: C 42.73, H 5.16, N 4.47.

*(2*S*)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6α-yl)amino]-3-phenylpropanoic Acid Bis(tetrafluoroborate)* (**17** · 2 HBF_4). White lyophilisate (90% yield). IR (KBr): 3424 (OH), 1738 (C=O). ^{1}H-NMR (D_2O): 7.46–7.35 (*m*, 5 arom. H); 6.86 (*d*, *J* = 8.2, 1 arom. H); 6.77 (*d*, *J* = 8.2, 1 arom. H); 4.90 (*d*, *J* = 3.4, H–C(5)); 4.46 (*t*, *J* = 6.8, 1 H); 3.25 (*s*, MeO); 2.90 (*s*, MeN). ^{13}C-NMR (D_2O): 172.3; 146.3; 139.3; 135.6;

130.9 (2C); 130.8 (2C); 129.8; 129.7; 124.9; 122.7; 120.5; 85.6; 76.9; 61.6; 60.4; 54.6; 51.2; 47.9; 47.8; 42.7; 37.2; 31.2; 25.4; 21.2; 17.9. ESI-MS: 465 ($[M+1]^+$). Anal. calc. for $C_{27}H_{32}N_2O_5 \cdot 2\ HBF_4 \cdot 3.1\ H_2O$ (696.04): C 46.59, H 5.82, N 4.02; found: C 46.25, H 5.75, N 3.79.

(2S)-2-[(4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6β-yl)amino]-3-phenylpropanoic Acid Bis(tetrafluoroborate) (**18** · 2 HBF_4). White lyophilisate (92% yield). IR (KBr): 3432, 3184 (OH), 1742 (C=O). ^{1}H-NMR (D_2O): 7.28 (*s*, 5 arom. H); 6.88 (*d*, $J=8.4$, 1 arom. H); 6.81 (*d*, $J=8.4$, 1 arom. H); 4.83 (*d*, $J=7.6$, H–C(5)); 4.54 (*t*, $J=7.0$, NHC*H*); 3.25 (*s*, MeO), 2.86 (*s*, MeN). ^{13}C-NMR (D_2O): 172.1; 142.4; 142.0; 135.6; 130.7 (4C); 130.3; 129.4; 123.1; 122.6; 120.4; 89.6; 76.3; 61.7; 61.2; 59.9; 50.1; 48.9; 48.1; 42.3; 36.7; 28.0; 24.5; 23.9; 20.9. ESI-MS: 465 ($[M+1]^+$). Anal. calc. for $C_{27}H_{32}N_2O_5 \cdot 2\ HBF_4 \cdot 3.1\ H_2O$ (696.04): C 46.59, H 5.82, N 4.02; found: C 46.24, H 5.47, N 3.81.

Crystal-Structure Data of **9**. Single crystals were obtained by slow evaporation of a soln. of **9** in MeOH/CH_2Cl_2. $C_{25}H_{36}N_2O_5$, M_r 444.56; orthorhombic, $P2_12_12_1$, $a=12.2448(3)$, $b=15.7813(6)$, $c=25.485(1)$ Å; $\alpha=\beta=\gamma=90°$; $V=4924.7(3)$ Å^3 ($\lambda=0.71073$ Å); $Z=8$, $D_{calc.}=1.199$ g cm^{-3}, $F(000)=1920$; $\mu=0.083$ mm^{-1}, crystal size $0.4\times0.35\times0.25$ mm, colorless prism. Data were measured *via* θ and ω-scans with a *Nonius Kappa CCD* diffractometer. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on F^2 (SHELXL-97). All non-H-atoms were refined with anisotropic displacement parameters. All H-atoms were calculated and refined with isotropic displacement parameters 1.2 and 1.5 times higher than U_{eq} of the attached C-atoms. H-atoms on N- and O-atoms were located in difference-electron-density maps and refined with isotropic-displacement parameters. In the final least-squares-refinement cycles, the model converged at $R_1=0.0362$, $wR_2=0.0862$, and goodness-of-fit = 1.057 for 4995 reflections with $I>2\sigma(I)$ and 600 parameters. These data can be obtained, free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk) citing the deposition No. CCDC 199730.

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