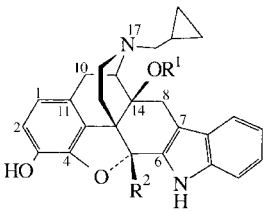
The 14-Alkyl- and 14-Alkenyl-5β-methylindolomorphinan Series Provide δ-Selective Partial Opioid Agonists

by **Peter Grundt**[a]), **Fernando Martinez-Bermejo**[b]), **John W. Lewis**[a]), **Stephen M. Husbands***[a])

[a]) Department of Pharmacy and Pharmacology, University of Bath, Bath BA27AY, UK
[b]) School of Chemistry, University of Bristol, Bristol, BS81TS, UK

A series of 14β-alkyl- and 14β-alkenyl-5β-methylindolomorphinans was synthesized and evaluated in opioid binding and functional assays. While being relatively nonselective in binding assays, the 14-cinnamyl and 14-isopentyl members showed selective opioid δ-receptor partial agonist activity in [^{35}S]GTPγS assays.

Introduction. – The δ-opioid receptor (DOR) is one of three types of opioid receptors. Agonists for this receptor have analgesic properties but have much lower propensity than traditional μ-opiates, *e.g.*, morphine, to induce physical dependence and to be abused [1][2]; they also have immunostimulant properties [3][4]. The indolomorphinan structure (*e.g.*, **1** and **2**) is a major source of selective DOR ligands; the 17-(cyclopropylmethyl) (CPM) derivatives (*e.g.*, naltrindole (NTI; **1a**)) generally are δ-selective antagonists, and the 17-methyl derivatives (*e.g.*, oxymorphindole (OMI; **2a**)) are δ-agonists or partial agonists [5].



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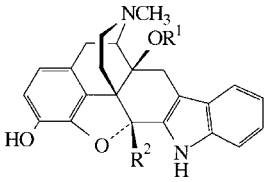

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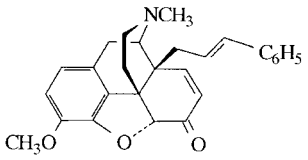

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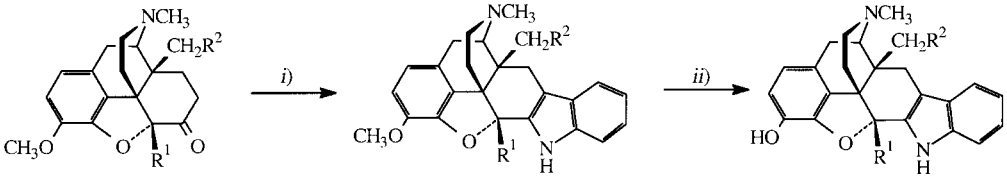
a $R^1 = R^2 = H$ **d** $R^1 = Ph(CH_2)_3$, $R^2 = Me$
b $R^1 = Et$, $R^2 = H$ **e** $R^1 = Me_2CH(CH_2)_3$, $R^2 = Me$
c $R^1 = Et$, $R^2 = Me$

Ethylation of the 14-hydroxy group of NTI to give **1b** reduced δ-affinity but not δ-selectivity, whereas introduction of a 5β-methyl group (as in **1c**) had little effect on δ-affinity but reduced μ- and κ-affinity so that δ-selectivity was substantially increased [6]. In our search for ligands selective for DOR, particularly δ-agonists related to OMI, we have investigated 14-substituted indolomorphinans [7], and, herein, we report the extension of our studies to a series of 14β-alkyl- and 14β-alkenylindolomorphinans, only one example of which (**6f**) has previously been reported [8].

Chemistry. – The 7,8-dihydro-14β-(3-phenylpropyl)codeinone (**4a**) was prepared by hydrogenation of 14β-cinnamylcodeinone (**3**) [9] and converted to **6a** by *Fischer* indolization ($\rightarrow$ **5a**) followed by 3-*O*-demethylation with BBr_3 (*Scheme*). The 14β-alkenyl-7,8-dihydro-5β-methylcodeinones **4c** and **4d** [10] were similarly converted to the indole derivatives **5c** and **5d**, respectively, which, with sodium propanethiolate, gave the target indolomorphinans **6c** and **6d**, respectively; these were hydrogenated to give the corresponding alkyl analogues **6b** and **6e** (*Scheme*).

Scheme



4 5 6

a R^1 = H, R^2 = $PhCH_2CH_2$ **b** R^1 = Me, R^2 = $PhCH_2CH_2$ **c** R^1 = Me, R^2 = (*E*)-PhCH=CH

d R^1 = Me, R^2 = (*E*)-Me_2C=CH **e** R^1 = Me, R^2 = Me_2CHCH_2 **f** R^1 = H, R^2 = Me_2CHCH_2

i) $PhNHNH_2$, AcOH, HCl. *ii*) PrSNa, HMPA or BBr_3, CH_2Cl_2, MeOH.

Results and Discussion. – Receptor binding affinities for the test compounds were determined in recombinant human opioid receptors (HOR) transfected into chinese hamster ovary (CHO) cells [11]. The displaced type-selective opioid radioligands were [^{3}H]Cl-DPDPE (δ), [^{3}H]U69,593 (κ), and [^{3}H]DAMGO (μ). In these assays (*Table 1*), the new ligands **6a**–**e** have moderate to high δ-affinity but little δ-selectivity. The exception is **6e**, which has 30-fold selectivity for δ as a result of its very low κ- and μ-affinity. Comparison of **6a** with its 5-methyl congener **6b** shows that the latter has fivefold lower μ-affinity but higher δ-affinity, with the result that modest μ-selectivity in **6a** is transformed into similar δ-selectivity in the 5-methyl analogue. Comparison of the previously reported **6f** [8] with **6e** shows that, in this case, the 5-methyl group is primarily associated with a ninefold loss of δ-affinity giving lower δ-selectivity. Since the published data for **6f** refers to different assay conditions, the comparison with **6e** is only approximate. It is interesting that in the 5-methyl series, insertion of an O-atom as the linkage to C(14) as in **2d** and **2e** [12], when compared to **6b** and **6e**, has very little effect on δ-affinity. This suggests that the O-atom in the alkoxy derivatives **2** is unlikely to be involved in binding to the DOR as a H-bond acceptor. Introduction of unsaturation into the side-chain of the indolomorphinans, as in **6c** and **6d** (*cf.* **6b** and **6e**) has very little effect on opioid receptor binding affinity (*Table 1*).

The opioid receptor functional activity of the new ligands was determined in assays involving stimulation of [^{35}S]GTPγS in recombinant human opioid receptors transfected into CHO cells [11][13]. In addition to potency values (EC_{50}), maximum

Table 1. *Binding of 14-Alkyl- and 14-Alkenylindolomorphinans to Recombinant HOR*[9]

	K_i [nM]			κ/δ	μ/δ
	δ	κ	μ		
6a	23.6 ± 2.6	63.3 ± 16.4	4.91 ± 0.47	2.7	0.21
6b	9.6 ± 2.3	36.4 ± 0.16	24.3 ± 6.9	4.0	2.5
6c	12.5 ± 2.5	94.2 ± 0.49	43.8 ± 1.6	7.5	3.5
6d	51.4 ± 2.7	440 ± 119	254 ± 4.9	8.6	4.9
6e	13.1 ± 1.0	457 ± 110	422 ± 83.5	35	32
6f[a])	1.4	204	186	146	133

[a]) Data from [8].

efficacy was determined as % of the effect of standard agonists, DPDPE (δ), U69593 (κ), and DAMGO (μ) (*Table 2*). In these assays, the indolomorphinans are moderately potent δ-partial agonists with varying levels of selectivity for δ over μ. Though introduction of unsaturation into the side chain of **6b** results in some loss of δ-potency, there is a higher loss of κ- and particularly μ-potency (180-fold) so that **6c** is an opioid partial agonist with δ-potency 94-times higher than κ- and 37-times higher than μ-potency. The 14-isopentyl ligand **6e** has even higher selectivity as a δ-partial agonist (147-fold over κ, 53-fold over μ) but its efficacy for all three opioid receptor types is substantially lower than that of **6c**. These δ-selectivity values in the functional assays are substantially higher than those recorded in the binding assays. Such discrepancies are not unusual in series of selective opioid ligands [14]. In the current series, the main reason is lower than expected κ- and μ-agonist potencies. The effect of introducing side-chain unsaturation into **6e**, to give **6d**, is to reduce δ-potency to a greater extent than μ- and κ-potency resulting in only modest δ-selectivity.

Table 2. *Stimulation of [*^{35}*S]GTPγS Binding in Recombinant HOR*[9]

	δ		κ		μ	
	EC_{50} [nM]	% stim	EC_{50} [nM]	% stim	EC_{50} [nM]	% stim
6a	7.53 ± 0.58	65	96.5 ± 0.9	67	21.5 ± 7.7	91
6b	4.02 ± 0.32	59	175 ± 9.2	33	4.46 ± 0.98	83
6c	21.8 ± 5.3	79	2046 ± 60	60	804 ± 41	85
6d	90.1 ± 30	43	945 ± 191	31	1201 ± 92	72
6e	13.2 ± 1.7	45	1936 ± 488	20	703 ± 150	28

In summary, new 5β-methylindolomorphinan ligands substituted at C(14) with phenylpropyl, cinnamyl, or isopentenyl groups (see **6a**–**d**) were shown to have moderate affinity for DOR. The 5β-methyl-14-isopentyl derivative **6e** was the only ligand to show appreciable δ-selectivity in opioid receptor binding assays, but both **6e** and the 14-cinnamyl analogue **6c** were substantially selective as δ-partial agonists in the [^{35}S]GTPγS assay.

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Experimental Part

General. M.p.: *Gallenkamp MFB-595* melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer 881* instrument; in cm^{-1}. NMR Spectra: *Jeol Lambda-300-MHz* instrument: ^1H at 300 MHz, ^{13}C at 75 MHz; δ in ppm with $SiMe_4$ as a standard. High- and low-resolution MS: *V.G.-Autospec* instrument equipped with a *Fisons* autosampler; EI at 70 eV; *m/z* (rel.%). Microanalysis: *Perkin-Elmer 240C* analyzer.

4,5α-Epoxy-3-methoxy-17-methyl-14β-(3-phenylpropyl)morphinan-6-one (**4a**). A mixture of **3** (0.46 g, 1.11 mmol) and anh. K_2CO_3 (0.29 g, 2.10 mmol) in AcOH (10 ml) and EtOH (1 ml) was added to a slurry of 10% Pd/C (0.29 g) and hydrogenated at 30 psi for 4 h at r.t. The mixture was then filtered through *Celite* and washed with CH_2Cl_2 and the solvents were evaporated. H_2O/Ammonia was added to the solid, and the free base was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and evaporated. Trituration with EtOH yielded **4a** (0.36 g, 78%). White foam. R_f ($MeOH/CH_2Cl_2$ 10:90) 0.66. IR ($CHCl_3$): 1722*s* (C=O). ^1H-NMR ($CDCl_3$); 2.31 (*s*, MeN); 3.07 (*d*, $J = 18.5$, H_β–C(10)); 3.87 (*s*, MeO–C(3)); 4.45 (*s*, H–C(5)); 6.62 (*d*, $J = 8.3$, H–C(1)); 6.68 (*d*, $J = 8.3$, H–C(2)); 7.25 (*m*, Ph). ^{13}C-NMR ($CDCl_3$): 20.0; 25.2; 25.6; 28.8; 29.3; 36.3; 36.4; 39.1; 43.2; 46.0; 49.2; 56.7; 59.3; 89.7; 114.1; 119.4; 125.9; 126.5; 128.3; 128.5; 130.1; 142.3; 142.7; 144.8; 208.9. EI-MS: 417 (100, M^+). HR-MS: 417.2301 ($C_{27}H_{31}N_1O_3^+$; calc. 417.2303).

6,7-Didehydro-4,5α-epoxy-3-methoxy-17-metyl-14β-(3-phenylpropyl)-indolo[2′,3′:6,7]morphinan (**5a**). A soln. of **4a** (0.1 g, 0.24 mmol) and phenylhydrazine hydrochloride (0.05 g, 0.33 mmol) in conc. HCl soln./AcOH 1:4 (20 ml) was stirred to reflux for 7 h. The mixture was then allowed to cool and poured into ice/ammonia. The aq. layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. extract washed with brine, dried ($NaSO_4$), and evaporated, and the residue purified by column chromatography (CH_2Cl_2/CH_3OH 98:2): **5a** (0.08 g, 73%). Solid. R_f (CH_2Cl_2/CH_3OH 95:5) 0.48. IR ($CHCl_3$): 3465. ^1H-NMR ($CDCl_3$, selected signals): 2.35 (*s*, MeN); 3.14 (*d*, $J = 18.5$, H_α–C(10)); 3.72 (*s*, MeO–C(3)); 5.60 (*s*, H–C(5)); 6.60 (*s*, H–C(1), H–C(2)); 7.1 (*m*, 9 arom. H (ind, Ph)); 8.30 (*s*, NH(ind)). ^{13}C-NMR ($CDCl_3$): 20.5; 24.1; 25.8; 29.9; 30.2; 36.3; 42.4; 43.4; 46.0; 46.9; 55.9; 60.0; 84.9; 111.2; 112.3; 113.0; 118.5; 118.8; 119.1; 122.5; 125.4; 126.9; 127.2; 128.1; 128.2; 128.4; 128.6; 129.7; 131.5; 136.9; 142.7; 143.0; 143.5. EI-MS: 490 (80, M^+). HR-MS: 490.2610 ($C_{33}H_{34}N_2O_2^+$; calc. 490.2620).

6,7-Didehydro-4,5α-epoxy-17-methyl-14β-(3-phenylpropyl)indolo[2′,3′:6,7]morphinan-3-ol (**6a**). A 1M BBr_3 soln. in CH_2Cl_2 (1.2 ml, 1.12 mmol) was added dropwise to a soln. of **5a** (85 mg, 0.17 mmol) in anh. CH_2Cl_2 and the mixture was stirred at r.t. for 15 min. After that time, it was added carefully to MeOH at 0° and refluxed in the open-mouthed flask for 30 min. The mixture was then quenched with ice/ammonia 1:1, stirred for 30 min, and then extracted (3×) with $MeOH/CHCl_3$ 1:3. The extract was washed with brine, dried ($MgSO_4$), and evaporated and the residue purified by column chromatography. Further purification by prep. TLC ($MeOH/CH_2Cl_2$ 5:95) yielded **6a** (47 mg, 57%). Solid. R_f (CH_2Cl_2/MeOH 10:90) 0.41. M.p. (hydrochloride) >250°. IR ($CHCl_3$): 3467. ^1H-NMR ($CDCl_3$, selected signals): 2.33 (*s*, MeN); 5.55 (*s*, H–C(5)); 6.56 (*d*, $J = 8.2$, H–C(1)); 6.65 (*d*, $J = 8.2$, H–C(2)); 7.1 (*m*, 9 arom. H (ind, Ph)); 8.48 (*s*, NH(ind)). ^{13}C-NMR ($CDCl_3$): 20.8; 24.1; 25.9; 29.8; 30.1; 36.3; 42.7; 43.4; 46.1; 47.0; 60.1; 85.8; 111.4; 113.4; 116.7; 118.9; 119.3; 119.5; 122.7; 125.6; 126.9; 128.2; 128.4; 129.1; 131.5; 137.0; 138.8; 142.0; 142.7. EI-MS: 476 (100, M^+). HR-EI-MS. 476.2463 ($C_{32}H_{32}N_2O_2^+$; calc. 476.2457). Anal. calc. for $C_{32}H_{32}N_2O_2 \cdot 2\,HCl \cdot 0.1\,CH_2Cl_2$: C 69.09, H 6.17, N 5.01; found: C 69.41, H 6.26, N 4.61.

*6,7-Didehydro-4,5α-epoxy-3-methoxy-5,17-dimethyl-14β-[(2*E*)-3-methylbut-2-enyl]indolo[2′,3′:6,7]morphinan* (**5d**). A soln. of **4d** (0.63 g, 1.65 mmol) and phenylhydrazine hydrochloride (0.30 g, 2.1 mmol) in AcOH (5 ml) was refluxed for 4 h. Then most of the solvent was evaporated, the residue basified (NH_4OH) and extracted with $CHCl_3$ (3 × 10 ml), the extract dried ($MgSO_4$) and evaporated, and the crude product purified by flash chromatography (CH_2Cl_2/CH_3OH 30:1 → 20:1): **5d** (0.52 g, 69%). Foam. R_f (CH_2Cl_2/CH_3OH 20:1) 0.46. IR (film): 3582*s*, 3406. ^1H-NMR ($CDCl_3$): 1.36 (*s*, 3 H); 1.47 (*m*, 1 H); 1.73 (*s*, 3 H); 1.90 (*s*, 3 H); 2.03–2.42 (*m*, 4 H); 2.36 (*s*, 3 H); 2.53–2.67 (*m*, 3 H); 2.87–3.14 (*m*, 3 H); 3.71 (*s*, 3 H); 5.23 (*m*, 1 H); 6.56 (*s*, 2 H); 7.00 (1 H); 7.12 (*td*, $J = 7.6$, 1.2, 1 H); 7.27 (*d*, $J = 8.3$, 1 H); 7.33 (*d*, $J = 7.9$, 1 H); 8.18 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 18.10; 20.55; 21.15; 23.95; 26.25; 27.27; 27.34; 43.33; 43.95; 46.02; 47.31; 55.76; 59.99; 89.98; 111.07; 111.71; 111.83; 118.25; 118.80; 119.07; 120.57; 122.38; 127.19; 127.45; 132.87; 133.63; 134.58; 136.66; 142.52; 143.10. EI-MS: 454 (100, M^+). HR-EI-MS: 454.2626 ($C_{30}H_{34}N_2O_2^+$; calc. 454.2620).

*6,7-Didehydro-4,5α-epoxy-3-methoxy-5,17-dimethyl-14β-[(2*E*)-3-phenylprop-2-enyl]indolo[2′,3′:6,7]morphinan* (**5c**). Prepared from **4c** (0.28 g, 0.65 mmol) and phenylhydrazine hydrochloride (0.14 g, 1.0 mmol) as described for **5d**: **5c** (0.13 g, 25%). Foam. R_f (CH_2Cl_2/CH_3OH 20:1) 0.48. IR (film): 3408. ^1H-NMR ($CDCl_3$): 1.51 (*dd*, $J = 2.2$, 12.5, 1 H); 1.91 (*s*, 3 H); 2.15–2.32 (*m*, 3 H); 3.38–2.46 (*m*, 1 H); 2.41 (*s*, 3 H); 2.55–2.66 (*m*, 2 H); 2.78 (*d*, $J = 15.6$, 1 H); 3.07–3.14 (*m*, 2 H); 3.28 (*ddd*, $J = 13.2$, 5.4, 1.5, 1 H); 3.73 (*s*, 3 H); 6.29–6.28 (*m*, 2 H); 6.55–6.60 (*m*, 2 H); 7.05 (*m*, 1 H); 7.13–7.23 (*m*, 2 H); 7.27–7.34 (*m*, 5 H); 7.38 (*d*, $J = 7.8$, 1 H); 8.18

(*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.59; 21.09; 23.96; 27.29; 32.60; 43.33; 43.78; 46.02; 47.31; 55.74; 60.25; 89.85; 111.16; 111.49; 111.73; 118.35; 118.8; 119.23; 122.59; 125.97; 126.96; 127.08; 127.13; 127.25; 128.53; 132.62; 133.48; 133.57; 136.63; 137.92; 142.57; 143.09. EI-MS: 502 (100, M^+). HR-EI-MS: 502.2613 ($C_{34}H_{34}N_2O_2^+$; calc. 502.2620).

*6,7-Didehydro-4,5α-epoxy-5,17-dimethyl-14β-[(2*E*)-3-methylbut-2-enyl]indolo[2′,3′:6,7]morphinan-3-ol* (**6d**). A sample of **5d** (0.20 g, 0.44 mmol) and NaH (0.12 g, 3.0 mmol; 60%) were suspended in HMPA (1 ml), and under N_2, propane-1-thiol (0.32 ml, 3.5 mmol) was added. After the effervescence had subsided, the mixture was heated at 120° for 4 h. Then the mixture was diluted with sat. NH_4Cl soln. (10 ml), and, after stirring overnight, it was extracted with AcOEt (3 × 10 ml). The combined extract was dried ($MgSO_4$) and evaporated and the residue purified by flash chromatography (gradient AcOEt/CH_2Cl_2): **6d** (0.14 g, 72%). Solid. R_f (AcOEt) 0.71. M.p. (oxalate) 193–195°. IR (film, oxalate): 3205. ^{1}H-NMR ($CDCl_3$, selected signals): 1.34 (*s*, 3 H); 1.72 (*s*, 3 H); 1.80 (*s*, 3 H); 2.35 (*s*, 3 H); 2.89 (*dd*, *J* = 12.7, 6.1, 1 H); 2.97–3.18 (*m*, 2 H); 5.21 (*m*, 1 H); 6.49 (*d*, *J* = 8.2, 1 H); 6.59 (*d*, *J* = 7.9, 1 H); 6.96 (*m*, 1 H); 7.06 (*m*, 1 H); 7.20 (*d*, *J* = 8.3, 1 H); 7.29 (*d*, *J* = 7.6, 1 H); 8.55 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 18.06; 20.73; 21.02; 23.97; 26.20; 27.20; 27.37; 43.28; 44.06; 46.07; 47.47; 60.08; 90.72; 111.11; 111.85; 116.39; 118.67; 118.77; 118.97; 120.62; 122.31; 126.92; 127.14; 132.86; 133.43; 134.45; 136.81; 138.41; 142.01. EI-MS: 440 (100), 369 (39). HR-EI-MS: 440.2461 ($C_{29}H_{32}N_2O_2^+$; calc. 440.2464). Anal. calc. for $C_{29}H_{32}N_2O_2 \cdot (COOH)_2 \cdot 1.5\ H_2O$: C 66.77, H 6.69, N 5.02; found: C 66.38, H 6.76, N 4.82.

*6,7-Didehydro-4,5α-epoxy-5,17-dimethyl-14β-[(2*E*)-3-phenylprop-2-enyl]indolo[2′,3′:6,7]morphinan-3-ol* (**6c**). From **5c** (0.28 g, 0.56 mmol) as described for **6d**: **6c** (0.21 g, 77%). Solid. M.p. >230°. R_f (AcOEt) 0.82. IR (film): 3434. ^{1}H-NMR ($CDCl_3$): 1.48 (*m*, 1 H); 1.87 (*s*, 3 H); 2.09–2.34 (*m*, 3 H); 2.38 (*m*, 1 H); 2.40 (*s*, 3 H); 2.57 (*dd*, *J* = 18.8, 6.1, 1 H); 2.63 (*dd*, *J* = 11.2, 1 H); 2.75 (*d*, *J* = 15.6, 1 H); 3.06–3.12 (*m*, 2 H); 3.24 ('*d*', *J* = 12.4, 1 H); 6.26–6.34 (*m*, 2 H); 6.54 (*d*, *J* = 8.3, 1 H); 6.60 (*d*, *J* = 8.3, 1 H); 7.02 (*m*, 1 H); 7.13 (*m*, 1 H); 7.18–7.35 (*m*, 7 H); 8.33 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.72; 21.07; 23.91; 27.24; 32.53; 43.29; 43.93; 46.02; 47.48; 60.22; 91.10; 111.20; 111.76; 116.36; 118.86; 119.01; 119.26; 122.69; 125.99; 126.95; 126.99; 127.02; 127.18; 128.53; 132.64; 133.02; 133.52; 136.67; 137.88; 138.01; 141.72. FAB-MS: 489 (100, $[M+1]^+$). Anal. calc. for $C_{33}H_{32}N_2O_2 \cdot (COOH)_2 \cdot C_2H_5OH$: C 71.14, H 6.45, N 4.48; found: C 71.23, H 6.63, N 4.69.

6,7-Didehydro-4,5α-epoxy-5,17-dimethyl-14β-(3-methylbutyl)-indolo[2′,3′:6,7]morphinan-3-ol (**6e**). A suspension of **6d** (0.29 g, 0.66 mmol) and 10% Pd/C (0.13 g) in AcOEt (50 ml) was stirred under H_2 for 24 h. The catalyst was filtered off over *Celite*, and the crude mixture was purified by flash chromatography (silica gel, AcOEt/CH_2Cl_2 gradient): **6e** (0.24 g, 82%). Solid. M.p. 199–201°. R_f (AcOEt): 0.81. IR (film): 3381. ^{1}H-NMR ($CDCl_3$): 0.72 (*d*, *J* = 6.4, 3 H); 0.83 (*d*, *J* = 6.3, 3 H); 1.17 (*m*, 1 H); 1.21–1.42 (*m*, 4 H); 1.81 (*s*, 3 H); 2.11–2.38 (*m*, 4 H); 2.33 (*s*, 3 H); 2.52–2.66 (*m*, 3 H); 3.02–3.09 (*m*, 2 H); 5.24 (*s*, 1 H); 6.51 (*d*, *J* = 7.8, 1 H); 6.57 (*d*, *J* = 8.3, 1 H); 6.99 (*m*, 1 H); 7.08 (*td*, *J* = 7.6, 1.5, 1 H); 7.19 (*d*, *J* = 8.3, 1 H); 7.34 (*d*, *J* = 8.3, 1 H); 8.46 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.71; 21.1; 22.76; 22.88; 23.77; 26.52; 27.13; 28.59; 32.9; 42.54; 43.32; 45.86; 47.63; 59.67; 91.20; 111.14; 111.95; 116.21; 118.78; 118.85; 119.03; 122.47; 127.08; 127.12; 133.00; 133.06; 136.67; 138.01; 141.64. EI-MS: 442 (100), 371 (42), 314 (31). HR-EI-MS: 442.2619 ($C_{29}H_{34}N_2O_2^+$; calc. 442.2620). Anal. calc. for $C_{29}H_{34}N_2O_2 \cdot (COOH)_2 \cdot 1.75H_2O$: C 66.24, H 6.72, N 4.98; found: C 66.12, H 6.93, N 4.83.

6,7-Didehydro-4,5α-epoxy-5,17-dimethyl-14β-(3-phenylpropyl)-indolo[2′,3′:6,7]morphinan-3-ol (**6b**). As described for **6e**, from **6c** (0.21 g, 0.43 mmol) and 10% Pd/C (0.15 g) in AcOEt (50 ml): **6b** (0.19 g, 90%). Solid. M.p. 196–198. R_f (AcOEt): 0.80. IR (film): 3404. ^{1}H-NMR ($CDCl_3$): 1.32 (*dd*, *J* = 12.5, 3.2, 1 H); 1.40 (*m*, 1 H); 1.55 (*m*, 1 H); 1.81 (*s*, 3 H); 2.34 (*s*, 3 H); 3.02–3.11 (*m*, 2 H); 6.52 (*d*, *J* = 8.1, 1 H); 6.58 (*d*, *J* = 8.1, 1 H); 7.01 (*m*, 1 H); 7.08–7.13 (*m*, 4 H); 7.17–7.22 (*m*, 3 H); 7.33 (*d*, *J* = 7.7, 1 H); 8.38 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 20.73; 20.97; 23.99; 25.93; 27.07; 28.95; 36.43; 42.57; 43.33; 45.88; 47.51; 59.86; 91.02; 111.18; 111.77; 116.31; 118.82; 118.87; 119.08; 122.54; 125.53; 126.90; 126.99; 128.15; 128.23; 128.39; 132.85; 133.05; 136.63; 138.10; 141.70; 142.88. EI-MS: 490 (100, M^+). HR-EI-MS: 490.2618 ($C_{33}H_{34}N_2O_2^+$; calc. 490.2620). Anal. calc. for $C_{33}H_{34}N_2O_2 \cdot (COOH)_2 \cdot 2.25\ H_2O$: C 67.67, H 6.57, N 4.51; found: C 67.53, H 6.16, N 4.41.

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