# Structural Determinants of Opioid Activity in the Orvinols and Related Structures. Ethers of 7,8-Cyclopenta-Fused Analogs of Buprenorphine

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A series of ethers of 7,8-cyclopenta-fused analogs of the orvinols related to buprenorphine were prepared and evaluated in opioid-binding and functional assays. Comparison of the ethyl ethers **4b** and **5b** with the parent alcohols **4a** and **5a**, respectively, in both the (5′*R*) (= 5′$\beta$) and (5′*S*) (= 5′$\alpha$) series, shows that the 20-OH group in the orvinols (corresponding to 5′-OH of **4** and **5**) is not crucial for opioid activity, although in the [$^{35}$S]GTP$\gamma$S assay, the 5′$\beta$-ethyl ether **4b** had 80-fold greater $\kappa$-agonist potency than its epimer **5b**. Increasing the size of the 5′$\beta$-OR group has a major effect on $\mu$-agonist efficacy and potency, a more modest effect on $\delta$-efficacy, and no effect on $\kappa$-activity. These data show that $\mu$- and $\delta$-agonist efficacy is favoured by lipophilic binding in the area occupied by the $^t$Bu in the lowest-energy conformation of buprenorphine, and that $\kappa$-agonist binding may involve interaction with an H-bond-donor group in that region.

**Introduction.** – Buprenorphine (**1a**) is a potent opioid analgesic that has been developed as a pharmacotherapy for opiate abuse [1], partly due to its profile of $\mu$ partial agonism and $\kappa/\delta$-antagonism. We have explored the active conformation of buprenorphine and related orvinols by synthesizing ring-constrained analogs including furomorphides **2** [2] and 7,8-cycloalka-fused analogs **3** [3]. The 7,8-cyclopentanol derivatives **4a** and **5a** both showed $\kappa$-agonist effects in the guinea pig *ileum* assay (GPI) and $\delta$-agonist activity in the mouse *vas deferens* assay (MVD). However, in mouse antinociceptive assays, only the $\beta$-OH derivative **4a** showed an agonist response which was $\kappa$-receptor-mediated [3][4]. Both epimers showed morphine($\mu$)-antagonist effects in the mouse tail-flick test and in morphine-dependent rhesus monkeys [4]. To throw light on the significance of the 5′-OH group[1]) in **4a** and **5a**, we prepared a series of ethers, *i.e.* **4b**–**d** and **5b**, and evaluated them in opioid-receptor binding and functional assays.

**Chemistry.** – The cyclopentanols **6** and **7** [3] were treated with NaH to give the alkoxides which were alkylated with the appropriate electrophiles (EtI, BnBr, $^i$BuI) in refluxing THF in the presence of [18]crown-6 (*Scheme*). Alkylation of the $\beta$-epimer **6** with $^i$BuI gave only a low yield of the ether, which was more conveniently prepared by alkylation of **6** with methallyl chloride followed by hydrogenation (Pd/C, atmospheric pressure). Alkylation of the hindered $\alpha$-OH epimer **7** was more difficult, and only the ethyl ether could be obtained. *O*-Demethylation to the oripavine derivatives **4b**–**d** and **5b** was performed with NaSPr in hexamethylphosphoric triamide (HMPA).

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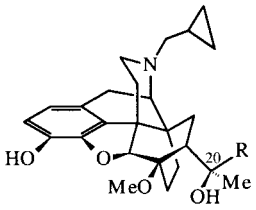
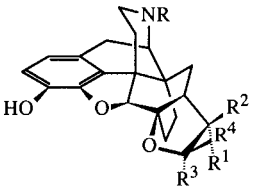
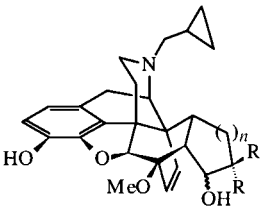
[1]) C(5′) of the parent structure of the 7,8-cyclopenta-fused **4** and **5** corresponds to C(20) of the orvinols.



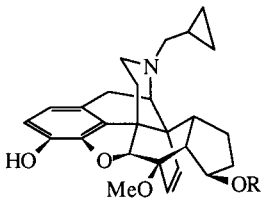
**1a** R = $^t$Bu



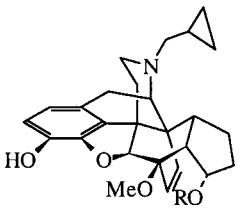
**2**



**3**

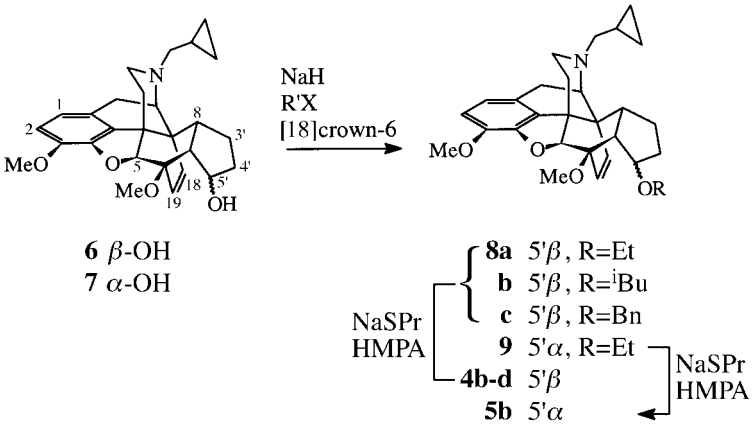


**4a** R = H
**b** R = Et
**c** R = $^i$Bu
**d** R = Bn



**5a** R = H
**b** R = Et

*Scheme*




**6** $\beta$-OH
**7** $\alpha$-OH

**8a** 5'$\beta$, R=Et
**b** 5'$\beta$, R=$^i$Bu
**c** 5'$\beta$, R=Bn
**9** 5'$\alpha$, R=Et
**4b-d** 5'$\beta$
**5b** 5'$\alpha$

**Pharmacological Results and Discussion**. – In displacement binding assays in guinea pig brain membranes [5], the ethers **4b**–**d** and **5b** showed high affinity for all opioid receptor types; this is typical of the orvinols including **4a** and **5a** (*Table 1*). The effect of the larger ether substituents in **4c** and **4d** was to reduce $\delta$-affinity, and in the case of **4c** also $\kappa$-affinity. *In vitro* functional activity of the ethers was measured as stimulation of [$^{35}$S]GTP$\gamma$S binding in membranes from Chinese hamster ovary (CHO) cells transfected with cloned human $\mu$-, $\delta$- and $\kappa$-opioid receptors [5][6]. These assays provide data on both potency in stimulating [$^{35}$S]GTP$\gamma$S and efficacy in comparison to

the maximum stimulation produced by the standard agonists for each opioid receptor type (DAMGO $\mu$; Cl-DPDPE $\delta$; U69593 $\kappa$). In the $\mu$-assay, the $\beta$-ethoxy derivative **4b** had no agonist activity and was a potent antagonist of DAMGO (*Table 2*). The epimeric ether **5b** also had low $\mu$-efficacy and potency. In the $\beta$-series (**4b**–**d**) $\mu$-efficacy increased regularly as the ether alkyl group increased in size with the benzyl ether **4d** showing potent high-efficacy agonist activity. In the GTP$\gamma$S assay for $\delta$-opioid receptors, efficacy also increased with size of ether group in the $\beta$-series, and the epimeric ethyl ethers **4b** and **5b** had similar partial agonist effects (*Table 2*). The $\kappa$-effects of all the $\beta$-ethers **4b**–**d** were very similar – high agonist efficacy and subnanomolar potency – but the $\alpha$-ethoxy derivative **5b** was eighty-fold less potent than its epimer.

Table 1. *Opioid-Receptor Binding Affinities of Ethers* **4b**–**d** *and* **5b** *in Guinea Pig Brain Membrane Radioligand-Displacement Assays and Comparison with Those of the Corresponding Alcohols* **4a** *and* **5a**, *Respectively*

| | $K_i$ [nM] | | |
|---|---|---|---|
| Ligand | [$^3$H]DAMGO ($\mu$) | [$^3$H]Cl-DPDPE ($\delta$) | [$^3$H]U69593 ($\kappa$) |
| **4b** | 0.3 ± 0.0 | 0.7 ± 0.2 | 0.3 ± 0.0 |
| **4c** | 1.7 ± 0.5 | 9.9 ± 2.9 | 11.8 ± 5.9 |
| **4d** | 0.5 ± 0.05 | 8.1 ± 3.7 | 1.2 ± 0.25 |
| **5b** | 1.1 ± 0.2 | 0.4 ± 0.05 | 2.5 ± 0.35 |
| **4a**[a]) | 0.6 ± 0.05 | 0.9 ± 0.08[b]) | 1.02 ± 0.1[c]) |
| **5a**[a]) | 0.9 ± 0.2 | 1.4 ± 0.2[b]) | 2.7 ± 0.1[c]) |

[a]) Data from mouse-brain homogenates reported in [3]. [b]) Displacement of [$^3$H]DPDPE. [c]) Displacement of [$^3$H]CI977.

Table 2. *Effects of Ethers* **4b**–**d** *and* **5b** *in [$^{35}$S]GTP$\gamma$S Assays in Cloned Human Opioid Receptors Transfected into CHO Cells and Comparison with Those of the Corresponding Alcohols* **4a** *and* **5a**, *Respectively*

| | $\mu$ | | $\delta$ | | $\kappa$ | |
|---|---|---|---|---|---|---|
| Ligand | $EC_{50}$ [nM] | % stim[a]) | $EC_{50}$ [nM] | % stim[a]) | $EC_{50}$ [nM] | % stim[a]) |
| **4b** | > 10[4 b])[c]) | – | 3.2 ± 0.93 | 50 ± 1.1 | 0.52 ± 0.17 | 92 ± 8.7 |
| **4c** | 1.93 ± 0.04 | 49 ± 6.6 | 6.6 ± 1.7 | 66 ± 12 | 1.0 ± 0.2 | 93 ± 8.3 |
| **4d** | 0.67 ± 0.21 | 87 ± 0.9 | 2.6 ± 0.25 | 83 ± 15 | 0.58 ± 0.17 | 87 ± 7.8 |
| **5b** | 371 ± 110 | 31 ± 6 | 1.6 ± 0.26 | 52 ± 6.4 | 41.1 ± 12.9 | 80 ± 12 |
| **4a** | n.d. | 11 ± 2.5[d])[e]) | 2.2 ± 1.6d | 23 ± 1.3[d])[f]) | 0.18 ± 0.04[g]) | 78 ± 6.5 |
| **5a** | n.d. | 2.4 ± 0.8[d])[e]) | 3.8 ± 1.3d | 21 ± 1.0[d])[f]) | 2.0 ± 0.52[g]) | 54 ± 3.3 |

[a]) % of maximum effect achieved by standard agonists DAMGO ($\mu$), Cl-DPDPE ($\delta$), and U69593 ($\kappa$). [b]) No agonist activity. [c]) $K_e$ (*vs.* DAMGO) 0.32 ± 0.09 nM. [d]) In cloned rat receptors expressed in C6-glioma cells. [e]) *vs.* Fentanyl. [f]) *vs.* SNC 80. [g]) Data from [3].

Further investigation of the agonist effects of the ethers was undertaken in GPI. In this preparation, the agonist effects of the epimeric ethoxy derivatives **4b** and **5b** were reversed by norBNI but not by CTAP, indicating that they were $\kappa$-receptor-mediated (*Table 3*). Surprisingly, the $\beta$-epimer **4b** was only a partial agonist, as was the $\beta$-isobutyl ether **4c** (*ca.* 60% of maximum possible effect). The benzyl ether **4d** was a full agonist, but this response, and that of **4c**, could not be attributed to $\kappa$-agonism since it was only

reversed by norBNI at very high concentrations. The $\beta$-ethers **4b** – **d**, but not the $\alpha$-ether **5b**, were extremely difficult to remove from the tissue even after repeated washing.

The $\kappa$-agonist data from the [$^{35}$S]GTP$\gamma$S and GPI assays, particularly for **4b** and **4c**, are in poor agreement. The ethers **4b** and **4c** were partial agonists in GPI but full agonists in GTP$\gamma$S with 6- to 7-fold greater potency. Though the parent cyclopentanols **4a** and **5a** were not evaluated alongside the ethers, comparable data are available for these from similar receptor binding, [$^{35}$S]GTP$\gamma$S, and GPI assays [3] to allow assessment of the effects of masking the 5′-OH groups[1]). The data for **4a** and **5a** are included in *Tables 1 – 3*. In the binding assay, the ethyl ethers **4b** and **5b** had profiles quite similar to those of the parent alcohols **4a** and **5a**, respectively, showing that etherification of the 5′-OH group does not inhibit binding to any opioid-receptor type. The effect of etherification of the 5′-OH group in the functional assays is not so clear. However, this can be attributed partly to procedural differences in the [$^{35}$S]GTP$\gamma$S assays in the participating laboratories (University of Michigan (UM) for **4a** and **5a**, Stanford Research Institute (SRI) for **4b** and **5b**). In the $\mu$- and $\delta$-assays, both the cell lines and the standard agonists were different (see *Footnotes* to *Table 2*). This particularly applies to the standard $\delta$-agonist since in the UM assay which uses SNC80, DPDPE has a maximum effect only 50% of the standard. Thus the 23 and 21% $\delta$-effects of **4a** and **5a**, respectively, against SNC80, and the 50 and 52% for the ethyl ethers **4b** and **5b**, respectively, against Cl-DPDPE may be approximately equivalent. With these provisos, the functional data do not provide any evidence for a major effect of masking the 5′-OH group[1]) in **4a** and **5a** on $\mu$- and $\delta$-potency and -efficacy.

Table 3. *Effects of Ethers* **4b** – **d** *and* **5b** *and Alcohols* **4a** *and* **5a** *on the Guinea Pig* Ileum *Preparation*

| Ligand | $IC_{50}$ [nM] | Inhibition of twitch [%] | norBNI $K_e$ [nM] |
|---|---|---|---|
| **4b** | 3.60 ± 1.9 | 59 ± 6.4 | 0.61 ± 0.06 |
| **4c** | 5.66 ± 1.9 | 57 ± 6.9 | n.d.[b]) |
| **4d** | 0.53 ± 0.55 | > 80 | n.d.[b]) |
| **5b** | 12.1 ± 2.4 | > 80 | 0.10 ± 0.01 |
| **4a**[a]) | 0.3 ± 0.2 | 82 ± 0.6 | 0.03 ± 0.03 |
| **5a**[a]) | 3.6 ± 1.3 | 83 ± 3.7 | 0.04 ± 0.01 |

[a]) Data from [3]. [b]) Could not be determined.

The procedure for the GTP$\gamma$S assay for $\kappa$-receptors was sufficiently consistent between the two laboratories that comparisons between the data for the alcohols **4a** and **5a** from UM and the ethyl ethers **4b** and **5b** from SRI can be made with some confidence. In these assays, **4a** and **4b** had quite similar $\kappa$-agonist profiles, but there was a 20-fold loss of potency between **5a** and **5b**. It would thus appear that etherification of the OH group has a greater effect on $\kappa$-activity in the $\alpha$-series than in the $\beta$-series. However, the evidence from GPI, in which the agonist activity of both alcohols **4a** and **5a** and ethers **4b** and **5b** was $\kappa$-receptor-mediated, does not confirm this finding. In fact, the GPI data suggest that the effect of etherification of the 5′-OH group[1]) on $\kappa$-agonist potency and efficacy is greater in the $\beta$-series than in the $\alpha$-series. Similar lack of agreement between the results of the *in vitro* assays has been previously reported for nalorphine [5] and suggests that the $\kappa$-receptors expressed in the CHO cells and GPI

*myenteric plexus* are different. It does not invalidate the conclusion that the 5′-OH group[1]) in **4a** and **5a** is not crucial for $\kappa$-agonist activity.

The higher $\kappa$-potency and efficacy of the 5′$\beta$-OH derivative **4a** over the 5′$\alpha$ epimer **5a**[1]) shown in the [$^{35}$S]GTP$\gamma$S assay parallels the results from mouse antinociceptive tests [3]. It was suggested that the 5′$\beta$-OH group in **4a** can interact with a suitably located H-bond donor or acceptor on the $\kappa$-receptor that is not available to the 5′$\alpha$-OH in **5a** [3]. The present data indicate that this site is more likely to be a H-bond donor than a H-bond acceptor.

The effects in the 5′$\beta$-series of ethers of increasing the size of the OR group (**4b**–**d**) in the [$^{35}$S]GTP$\gamma$S assays allows conclusions to be drawn about the significance of lipophilic binding in the position occupied by the $^t$Bu group in the lowest-energy conformation of buprenorphine (**1a**). $\delta$-Agonist efficacy and particularly $\mu$-agonist efficacy and potency increased with the size of the 5′$\beta$-OR group[1]) showing that these receptor interactions benefit from lipophilic binding in this position. In contrast, $\kappa$-agonist efficacy and potency remained remarkably constant in the $\beta$-ether series. This shows that lipophilic binding in the area occupied by the $^t$Bu group in buprenorphine is not important for $\kappa$-agonist activity. Further evidence for the significance of the receptor binding of the 5′$\beta$-OR group in **4b**–**d** is provided by the difficulty of removing these ligands from the GPI preparation even after extensive washing. This phenomenon is shared by buprenorphine (**1a**) and related orvinols and has been attributed to powerful lipophilic binding to the $\mu$-opioid receptor [7].

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## Experimental Part

*General.* All reagents were used as supplied by *Aldrich*. Compounds for pharmacological analysis were converted to their HCl salts by dissolving in THF and making acidic with methanolic HCl. M.p. *Reichert* hot-stage microscope; uncorrected. IR Spectra: *Perkin-Elmer-881* spectrophotometer; $\tilde{\nu}$ in cm$^{-1}$. $^1$H- and $^{13}$C-NMR Spectra: *Jeol-JNM-GX-270* (67.5) spectrometer at 20° in $CDCl_3$, unless otherwise stated; $\delta$ in ppm rel. to $SiMe_4$ (= 0 ppm) as internal standard, *J* in Hz. MS: *Fisons-Autosampler* instrument with electron ionization (70 eV); *m*/*z* (rel. %). Elemental analyses were obtained on a *Perkin-Elmer-240C* analyzer. CC = Column chromatography.

*General Procedure A (G.P. A): Alkylation*. NaH (2 equiv.) was added to a soln. of the alcohol (1 equiv.) in dry THF under $N_2$. The alkyl halide (5 equiv.) was then added, followed by [18]crown-6 (0.1 equiv.). The soln. was heated to reflux for the required time, before cooling and quenching with aq. $NH_4Cl$ soln. The THF was evaporated and the mixture extracted wtih $CH_2Cl_2$ (3 × 30 ml). The org. extracts were combined, washed with brine, dried ($Na_2SO_4$) and evaporated: crude product.

*General Procedure B (G.P. B): 3*-O-*Demethylation.* Propanethiol (5.5 equiv.) was added to a stirred mixture of the 3-methyl ether (1 equiv.), NaH (5 equiv.), and HMPA (1 ml/mmol) under $N_2$. After effervescence had subsided, the mixture was stirred at 110° for 3 h and then cooled to r.t. The reaction was quenched by the addition of aq. $NH_4Cl$ soln. (30 ml) and the mixture stirred overnight, then diluted with $H_2O$ (15 ml), and extracted with $Et_2O$ (5 × 40 ml). The combined org. layers were washed with aq. $NH_4Cl$ (2 × 100 ml) and NaCl soln. (40 ml), dried ($Na_2SO_4$), and evaporated: crude product.

*(5α,5′β,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-5′-ethoxy-4′,5′,7,8-tetrahydro-3,6-dimethoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphinane* (**8a**). Alcohol **6** (500 mg, 1.2 mmol) was treated with EtI for 48 h according to *G.P. A*. CC (silica gel, AcOEt/$CH_2Cl_2$ 1:1) yielded **8a** (490 mg, 92%). $R_f$ 0.72 (AcOEt/$CH_2Cl_2$ 1:1). $^1$H-NMR: 0.14–0.21 (*m*, $NCH_2CH(CH_2CH_2)$); 0.43–0.61 (*m*, $NCH_2CH(CH_2CH_2)$); 0.78–0.92 (*m*, $NCH_2CH(CH_2CH_2)$); 1.18 (*t*, *J* = 7.1, *Me*$CH_2$–C(5′)); 3.09 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.56 (*s*, MeO–C(6)); 3.81 (*s*, MeO–C(3)); 4.64 (*d*, *J* = 1.5, H–C(5)); 5.32 (*d*, *J* = 8.6, H–C(19)); 5.72 (*d*, *J* = 8.6, H–C(18)); 6.50 (*d*, *J* = 8.2, H–C(1)); 6.61 (*d*, *J* = 8.2, H–C(2)). EI-MS: 463 (67, $M^+$), 448 (10, $[M^+ - CH_3]^+$).

*(5β,5′α,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-5′-ethoxy-4′,5′,7,8-tetrahydro-3,6-dimethoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphinane* (**9**). Alcohol **7** (500 mg, 1.2 mmol) was treated with EtI for 72 h according to *G.P. A*. CC (silica gel, AcOEt/$CH_2Cl_2$ 1:1) yielded **9** (260 mg, 49%). $R_f$ 0.64 (AcOEt/$CH_2Cl_2$ 1:1). $^1$H-NMR: 0.14–0.21 (*m*, $NCH_2CH(CH_2CH_2)$); 0.42–0.61 (*m*, $NCH_2CH(CH_2CH_2)$); 0.79–0.92 (*m*, $NCH_2CH(CH_2CH_2)$); 1.10 (*t*, *J* = 7.0, *Me*$CH_2O$–C(5′)); 3.08 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.42–3.53 (*m*, Me$CH_2O$–C(5′)); 3.63 (*s*, MeO–C(6)); 3.82 (*s*, MeO–C(3)); 4.52 (*d*, *J* = 1.5, H–C(5)); 5.09 (*d*, *J* = 8.9, H–C(19)); 6.02 (*d*, *J* = 8.9, H–C(18)); 6.50 (*d*, *J* = 8.2, H–C(1)); 6.61 (*d*, *J* = 8.2, H–C(2)). EI-MS: 463 (61, $M^+$), 448 (11, $[M - CH_3]^+$).

*(5α,5′β,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-5′-ethoxy-4′,5′,7,8-tetrahydro-6-methoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphinan-3-ol* (**4b**). Ether **8a** (490 mg, 1.06 mmol) was treated according to *G.P. B:* **4b** (360 mg, 76%). $R_f$ 0.32 (AcOEt/$CH_2Cl_2$ 1:1). IR ($CHBr_3$): 3392 (phenolic OH). $^1$H-NMR: 0.14–0.21 (*m*, $NCH_2CH(CH_2CH_2)$); 0.43–0.60 (*m*, $NCH_2CH(CH_2CH_2)$); 0.79–0.91 (*m*, $NCH_2CH(CH_2CH_2)$); 1.19 (*t*, *J* = 7.1, *Me*$CH_2O$–C(5′)); 3.08 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.57 (*s*, MeO–C(6)); 4.65 (*d*, *J* = 1.3, H–C(5)); 5.30 (*d*, *J* = 8.7, H–C(19)); 5.68 (*d*, *J* = 8.7, H–C(18)); 6.45 (*d*, *J* = 8.1, H–C(1)); 6.60 (*d*, *J* = 8.1, H–C(2)). EI-MS: 449 (65, $M^+$); 434 (10, $M - CH_3]^+$). Anal. calc. for $C_{28}H_{35}NO_4 \cdot HCl$: C 69.19, H 7.47, Cl 7.29, N 2.88; found: C 68.87, H 7.62, Cl 7.43, N 2.79.

*(5α,5′α,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-5′-ethoxy-4′,5′,7,8-tetrahydro-6-methoxy-4,5-epoxy-6,14-etheno-3′*-H-*cyclopenta[7,8]morphinan-3-ol* (**5b**). Ether **9** (250 mg, 0.54 mmol) was treated according to *G.P. B:* **5b** (175 mg, 72%). $R_f$ 0.16 (AcOEt/$CH_2Cl_2$ 1:1). IR ($CHBr_3$): 3387 (phenolic OH). $^1$H-NMR: 0.15–0.22 (*m*, $NCH_2CH(CH_2CH_2)$); 0.43–0.62 (*m*, $NCH_2CH(CH_2CH_2)$); 0.79–0.94 (*m*, $NCH_2CH(CH_2CH_2)$); 1.10 (*t*, *J* = 7.0, *Me*$CH_2$–C(5′)); 3.06 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.41–3.54 (*m*, Me$CH_2O$–C(5′)); 3.61 (*s*, MeO–C(6)); 4.54 (*d*, *J* = 1.3, H–C(5)); 5.06 (*d*, *J* = 8.5, H–C(19)); 5.94 (*d*, *J* = 8.5, H–C(18)); 6.45 (*d*, *J* = 8.1, H–C(1)); 6.60 (*d*, *J* = 8.1, H–C(2)). EI-MS: 449 (62, $M^+$), 434 (5, $[M - CH_3]^+$). Anal. calc. for $C_{28}H_{35}NO_4 \cdot HCl$: C 69.19, H 7.47, Cl 7.29, N 2.88; found: C 68.98, H 7.72, Cl 7.40, N 2.83.

*(5α,5′β,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-4′,5′,7,8-tetrahydro-5′-isobutoxy-3,6-dimethoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]monphinane* (**8b**). Alcohol **6** (400 mg, 0.92 mmol) was treated with 3-chloro-2-methylpropene for 30 h according to the *G.P. A*. CC (AcOEt with 0.5% aq. $NH_3$ soln.) followed by a second CC (AcOEt/$CH_2Cl_2$ 1:1) yielded a gum (230 mg). This was dissolved in EtOH (20 ml) containing $PtO_2$ (20 mg) and treated with $H_2$ (1 atm) for 0.5 h. The catalyst was removed by filtration through *Celite* and the solvent evaporated: **8b** (210 mg, 47%). $R_f$ 0.83 (AcOEt/$CH_2Cl_2$ 1:1). $^1$H-NMR: 0.15–0.22 (*m*, $NCH_2CH(CH_2CH_2)$); 0.44–0.62 (*m*, $NCH_2CH(CH_2CH_2)$); 0.83–1.00 (*m*, $NCH_2CH(CH_2CH_2)$, $Me_2CHCH_2O$); 3.07 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.13–3.29 (*m*, $Me_2CHCH_2O$–C(5′)); 3.58 (*s*, MeO–C(6)); 3.60–3.68 (*m*, $H_\alpha$–C(5′)); 3.82 (*s*, MeO–C(3)); 4.62 (*d*, *J* = 1.3, H–C(5)); 5.31 (*d*, *J* = 8.7, H–C(19)); 5.72 (*d*, *J* = 8.7, H–C(18)); 6.47 (*d*, *J* = 8.1, H–C(1)); 6.61 (*d*, *J* = 8.1, H–C(2)). EI-MS: 491 (100, $M^+$), 476 (12, $M - CH_3]^+$).

*(5α,5′β,6*R*,7*R*,8*R*,14α)-17-(Cyclopropylmethyl)-4′,5′-7,8-tetrahydro-5′-isobutoxy-6-methoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphinan-3-ol* (**4c**). Ether **8b** (219 mg, 0.43 mmol) was treated according to *G.P. B:* **4c** (170 mg, 83%). $R_f$ 0.55 (AcOEt/$CH_2Cl_2$ 1:1). IR: 3379 (phenolic OH). $^1$H-NMR: 0.14–0.21 (*m*, $NCH_2CH(CH_2CH_2)$); 0.44–0.62 (*m*, $NCH_2CH(CH_2CH_2)$); 0.83–1.01 (*m*, $NCH_2CH(CH_2CH_2)$, $Me_2CHCH_2O$–C(5′)); 3.08 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.13–3.28 (2*m*, $Me_2CHCH_2O$–C(5′)); 3.58 (*s*, MeO–C(6)); 3.60–3.64 (*m*, $H_\alpha$–C(5′)); 4.63 (*d*, *J* = 1.3, H–C(5)); 5.27 (*d*, *J* = 8.7, H–C(19)); 5.64 (*d*, *J* = 8.7, H–C(18)); 6.42 (*d*, *J* = 8.1, H–C(1)); 6.61 (*d*, *J* = 8.1, H–C(2)). $^{13}$C-NMR: 146.7, 137.7, 135.4, 134.5, 129.8, 127.4, 119.6, 116.3, 92.1, 83.1, 81.7, 56.7, 54.6, 50.7, 49.0, 47.8, 45.4, 44.4, 41.2, 33.1, 32.5, 28.7, 25.6, 22.9, 19.5, 9.4, 4.6, 2.8. EI-MS: 477 (58, $M^+$), 462 (5, $[M - CH_3]^+$). HR-MS: 477.2866 ($C_{30}H_{39}NO_4^+$; calc. 477.2879). Anal. calc. for $C_{30}H_{39}NO_4 \cdot HCl \cdot 2\,H_2O$: C 65.50, H 8.06, Cl 6.46, N 2.55; found: C 65.21, H 7.62, Cl 6.62, N 2.60.

*(5α,5′β,6*R*,7*R*,8*R*,14α)-5′-(Benzyloxy)-17-(Cyclopropylmethyl)-4′,5′,7,8-tetrahydro-3,6-dimethoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphinane* (**8c**). Alcohol **6** (550 mg, 1.3 mmol) was treated with benzyl bromide for 24 h according to *G.P. A*. CC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/AcOEt 1:1) gave **8c** (550 mg, 83%). $R_f$ 0.83 (AcOEt/$CH_2Cl_2$ 1:1). $^1$H-NMR: 0.13–0.21 (*m*, $NCH_2CH(CH_2CH_2)$); 0.42–0.61 (*m*, $NCH_2CH(CH_2CH_2)$); 0.78–0.94 (*m*, $NCH_2CH(CH_2CH_2)$); 3.08 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.58 (*s*, MeO–C(6)); 3.74–3.83 (*m*, $H_\alpha$–C(5′)); 3.82 (*s*, MeO–C(3)); 4.56 (*s*, $PhCH_2O$–C(5′)); 4.65 (*d*, *J* = 1.4, H–C(5)); 5.31 (*d*, *J* = 8.7, H–C(19)); 5.73 (*d*, *J* = 8.7, H–C(18)); 6.49 (*d*, *J* = 8.1, H–C(1)); 6.62 (*d*, *J* = 8.1, H–C(2)); 7.23–7.41 (*Ph*$CH_2O$–C(5′)). EI-MS: 525 (82, $M^+$), 510 (7, $[M - CH_3]^+$).

*(5β,5′β,6*R*,7*R*,8*R*,14α)-5′-(Benzyloxy)-17-(Cyclopropylmethyl)-4′,5′,7,8-tetrahydro-6-methoxy-4,5-epoxy-6,14-etheno-3′*H*-cyclopenta[7,8]morphin-3-ol* (**4d**). Ether **8c** (540 mg, 1.1 mmol) was treated according to *G. P. B:* **4d** (360 mg, 68%). $R_f$ 0.57 (AcOEt/$CH_2Cl_2$ 1:1). $^1$H-NMR: 0.13–0.22 (*m*, $NCH_2CH(CH_2)CH_2$)); 0.41–0.62 (*m*, $NCH_2CH(CH_2CH_2)$); 0.76–0.92 (*m*, $NCH_2CH(CH_2CH_2)$); 3.07 (*d*, *J* = 18.5, $H_\beta$–C(10)); 3.57

(*s*, MeO–C(6)); 3.74–3.83 (*m*, $H_\alpha$–C(5′)); 4.53 (*s*, PhC$H_2$O–C(5′)); 4.66 (*d*, *J* = 1.4, H–C(5)); 5.31 (*d*, *J* = 8.8, H–C(19)); 5.69 (*d*, *J* = 8.8, H–C(18)); 6.46 (*d*, *J* = 8.1, H–C(1)); 6.61 (*d*, *J* = 8.1, H–C(2)); 7.26–7.38 (Ph$CH_2$O–C(5′)). $^{13}$C-NMR: 146.6, 138.9, 137.7, 135.6, 134.5, 129.7, 128.3, 127.8, 127.4, 127.3, 119.7, 116.3, 92.3, 82.0, 81.7, 71.7, 59.7, 54.6, 50.8, 49.0, 48.1, 45.5, 44.4, 41.1, 33.0, 32.5, 25.7, 22.8, 9.4, 4.7, 2.7. EI-MS: 511 (100, $M^+$), 496 (7, $[M-CH_3]^+$). HR-MS: 511.2740 ($C_{33}H_{37}NO_4^+$; calc. 511.2723). Anal. calc. for $C_{33}H_{37}NO_4 \cdot HCl$: C 72.31, H 6.99, Cl 6.47, N 2.56; found: C 72.12, H 7.21, Cl 6.66, N 2.79.

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