A Novel and Efficient Synthesis of 14-Alkoxy-Substituted Indolo- and Benzofuromorphinans in the Series of Selective δ Opioid Receptor Antagonists

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A novel and more efficient synthesis of 14-alkoxy-substituted indolo- and benzofuro-morphinans in three steps starting from either naltrindole (**1**) or naltriben (**2**), using methoxymethyl or silyl protecting groups, is reported. The 14-*O*-alkyl group is introduced at the penultimate step of the procedure. This is an additional advantage of the described procedure since the late introduction of the 14-*O*-alkyl group makes it much easier to produce a greater diversity of 14-alkoxy derivatives in this series of δ opioid receptor antagonists. Thus, compounds **14**–**19**, **20**–**25**, and **27**–**29** were synthesized.

Introduction. – Opioid antagonists have been indispensable as tools in opioid research. For example, the chief criterion for the classification of an agonist effect as being opioid-receptor-mediated is the ability of the known opioid antagonists naloxone and naltrexone to reversibly antagonize this effect in a competitive fashion. The usefulness of naloxone and naltrexone for this purpose stems from the fact that they are universal opioid antagonists; that is, they are capable of antagonizing the agonist effects mediated by multiple opioid receptor types.

In addition to their uses as pharmacological tools, selective, non-peptide opioid antagonists have been described as having potential clinical applications in the treatment of a variety of disorders where endogenous opioids play a modulatory role. These include, *e.g.*, disorders of food intake, shock, constipation, mental disorders, CNS injury, alcoholism, drug addiction, and immune function (immune stimulation or suppression) [1].

Non-peptide, competitive, δ-selective opioid antagonists (*e.g.*, naltrindole (NTI; **1**)) have been found to have immunosuppressive potency and less toxicity than the presently used immunosuppressive compound cyclosporin [2–4]. Such immunosuppressive agents can be used after organ transplantation to suppress the rejection of the foreign organ and also in the treatment of autoimmune diseases (*e.g.*, rheumatoid arthritis).

Development of morphine tolerance and physical dependence is markedly suppressed by the administration of NTI (**1**) before and during morphine treatment [5]. These effects are produced by NTI at dosages that do not block the antinociceptive effects due to interactions at μ receptors. NTI seems also to block the ability of cocaine to produce positive reinforcement in rats [6][7]. NTI was also found to produce a marked and long-lasting antitussive effect in mice and rats which was not antagonized by the irre-

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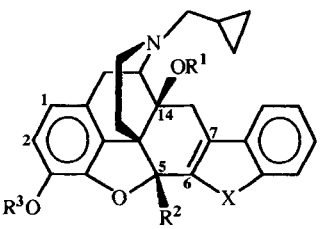
versible μ antagonist β-FNA [8]. Naltriben (NTB; **2**), the benzofuro derivative of NTI, is able to distinguish between δ receptor subtypes and is selective for the δ_2 site [9] but shows also agonist effects like NTI [10].

Introduction of a 14β-ethoxy and a 5β-methyl group onto the NTI molecule resulted in a pure opioid antagonist (HS 378 (**3**)) with somewhat lower δ potency but much higher δ selectivity in the MVD due to very low μ and κ affinities [11]. A recent study suggests that a 5-Me group is not necessary for high δ opioid receptor antagonism and selectivity; 14-*O*-methyl- and 14-*O*-ethylnaltrindole (**4** and **5**, resp.) exhibited increased δ receptor antagonism in comparison to HS 378 while retaining antagonist purity [12].

Such 14-alkoxy-substituted indolo- and benzofuro-morphinans are usually prepared by reaction of the corresponding 14-alkoxymorphinan-6-ones with either phenylhydrazine to form indolomorphinans or with *O*-phenylhydroxylamine to form benzofuromorphinans [11–13]. The synthesis of these 14-alkoxymorphinan-6-one precursors involves seven to ten steps starting from thebaine, whereby the 14-*O*-alkyl group is introduced at an early step of the procedure [11][13][14]. Recently, a new and efficient synthesis of 14-*O*-methyl- and 14-*O*-ethylnaloxone and -naltrexone in three steps, starting from either naloxone or naltrexone, has been described [15]. Introduction of 14-*O*-alkyl groups different from Me or Et (*e.g.*, allyl, cinnamyl (= (*E*)-3-phenylprop-2-enyl), benzyl) involves one more synthetic step (ketalization of the 6-keto function), since the 14-*O*-alkylation does not proceed as smoothly when other alkylating reagents than dimethyl or diethyl sulfate are used [16].

The objective of this work was to find a new process which would facilitate the preparation of 14-*O*-substituted indolo-morphinans and benzofuro-morphinans. Here,



1 $R^1 = R^2 = R^3 = H$, X = NH (NTI)
2 $R^1 = R^2 = R^3 = H$, X = O (NTB)
3 R^1 = Et, R^2 = Me, R^3 = H, X = NH (HS 378)
4 R^1 = Me, $R^2 = R^3$ = H, X = NH
5 R^1 = Et, $R^2 = R^3$ = H, X = NH
6 $R^1 = R^2$ = H, $R^3 = MeOCH_2$, X = O
7 $R^1 = R^2$ = H, $R^3 = MeOCH_2$, X = $MeOCH_2N$
8 R^1 = Me, R^2 = H, $R^3 = MeOCH_2$, X = O
9 $R^1 = PhCH{=}CHCH_2$, R^2 = H, $R^3 = MeOCH_2$, X = O
10 $R^1 = 2\text{-}FC_6H_4CH_2$, R^2 = H, $R^3 = MeOCH_2$, X = O
11 $R^1 = 2,6\text{-}Cl_2C_6H_3CH_2$, R^2 = H, $R^3 = MeOH_2$, X = O
12 $R^1 = 3\text{-}(NO_2)C_6H_4CH_2$, R^2 = H, $R^3 = MeOCH_2$, X = O
13 R^1 = 2-naphthylmethyl, R^2 = H, $R^3 = MeOCH_2$, X = O
14 R^1 = Me, $R^2 = R^3$ = H, X = O
15 $R^1 = PhCH{=}CHCH_2$, $R^2 = R^3$ = H, X = O
16 $R^1 = 2\text{-}FC_6H_4CH_2$, $R^2 = R^3$ = H, X = O
17 $R^1 = 2,6\text{-}Cl_2C_6H_3CH_2$, $R^2 = R^3$ = H, X = O
18 $R^1 = 3\text{-}(NO_2)C_6H_4CH_2$, $R^2 = R^3$ = H, X = O
19 R^1 = 2-naphthylmethyl, $R^2 = R^3$ = H, X = O
20 $R^1 = 2\text{-}ClC_6H_4CH_2$, $R^2 = R^3$ = H, X = O
21 $R^1 = 3\text{-}ClC_6H_4CH_2$, $R^2 = R^3$ = H, X = O
22 $R^1 = 4\text{-}ClC_6H_4CH_2$, $R^2 = R^3$ = H, X = O
23 $R^1 = PhCH_2$, $R^2 = R^3$ = H, X = O
24 $R^1 = CH_2{=}CHCH_2$, $R^2 = R^3$ = H, X = O
25 $R^1 = MeCH{=}CHCH_2$, $R^2 = R^3$ = H, X = O
26 $R^1 = 2\text{-}ClC_6H_4CH_2$, R^2 = H, $R^3 = MeOCH_2$, X = $MeOCH_2N$
27 $R^1 = 2\text{-}ClC_6H_4CH_2$, $R^2 = R^3$ = H, X = NH
28 $R^1 = CH_2{=}CHCH_2$, $R^2 = R^3$ = H, X = NH
29 $R^1 = CH_2{=}CHCH_2$, $R^2 = R^3$ = H, X = $CH_2{=}CHCH_2N$

we report on a novel and more efficient synthesis of 14-alkoxy-substituted indolo- and benzofuro-morphinans in three steps starting from either NTI (**1**) or NTB (**2**), whereby the 14-*O*-alkyl group is introduced at the penultimate step of the procedure [17]. An additional advantage of this new procedure is the late introduction of the 14-*O*-alkyl group which makes it much easier and less costly to produce a greater diversity of 14-alkoxy derivatives in this series of δ opioid receptor antagonists.

Results. – Protection of the 3-OH group of NTB (**2**) and of both the 3-OH and indole N-atom of NTI (**1**) with methoxymethyl bromide gave $MeOCH_2$-protected derivatives **6** and **7**, respectively. Subsequent 14-*O*-alkylation of the protected NTB derivative, **6** with dimethyl sulfate, cinnamyl bromide, 2-fluorobenzyl bromide, 2,6-dichlorobenzyl bromide, 3-nitrobenzyl bromide, and 2-naphthylmethyl bromide in DMF using NaH as base afforded 14-*O*-alkylated derivatives **8**–**13**, respectively. Acid hydrolysis (MeOH/1N HCl) yielded the desired 14-alkoxy-substituted benzofuro-morphinans **14**–**19**. Essentially the same procedure – with the exception that the 3-*O*-protected 14-*O*-alkyl intermediates were not isolated – was employed to prepare compounds **20**–**22** from **2**.

The triisopropylsilyl protecting group instead of $MeOCH_2$ was used to synthesize compounds **23**–**25**, also without isolation of intermediates. Thus, NTB (**2**) was silylated in DMF prior to the 14-*O*-alkylation with benzyl bromide, allyl bromide, and (*E*)-but-2-enyl bromide in the presence of NaH. Acid hydrolysis (EtOH/1N HCl) of the 3-*O*-protected 14-*O*-alkyl intermediates gave benzofuro-morphinans **23**–**25**.

The 14-*O*-alkylation of the $MeOCH_2$-protected NTI derivative **7** with 2-chlorobenzyl bromide in DMF employing NaH as base gave 14-*O*-alkylated morphinan **26** which was hydrolyzed (MeOH/1N HCl) to yield 14-alkoxy-substituted indolo-morphinan **27**. The 14-*O*-allylated derivative **28** was prepared from NTI (**1**) employing the $MeOCH_2$ protecting group without isolation of the intermediates. Isobutyldimethylsilyl protection of only 3-OH was used for the synthesis of 1′,14-*O*-diallyl-substituted indolo-morphinan **29** without isolation of intermediates, analogously to the preparation of **23**–**25**.

Biological and pharmacological evaluation is in progress and will be published elsewhere.

Experimental Part

General. Column chromatography (CC): silica gel *60* (230–440 mesh). Melting-point: *Thomas-Hoover* capillary apparatus; uncorrected. IR Spectra: *Paragon-1000-FT-IR* spectrometer; in cm^{-1}. ^1H-NMR Spectra: *Varian-400* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, *J* in Hz. All compounds exhibited NMR data consistent with those of the structures assigned. Mass spectra: *Micromass Quattro LC*. Elemental analyses were performed at the *Canadian Microanalytical Service Ltd.*, Delta, B.C.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)benzofuro[2′,3′:6,7]morphinan-14-ol (**6**). NaH (426 mg, 17.7 mmol; obtained from 710 mg of 60% NaH dispersion in oil by washings with hexane) was added to a soln. of naltriben methanesulfonate (**2** · $MeSO_3H$; 2.0 g, 3.9 mmol) in 30 ml of anh. DMF (30 ml) at 0°. The resulting mixture was stirred at 0° for 20 min and then at r.t. for another 60 min. After cooling to 0°, $MeOCH_2Br$ (653 ml, 8 mmol) was added, and stirring was continued for 15 min at 0° and then for additional 120 min at r.t. Excess NaH was destroyed by addition of MeOH and H_2O. The resulting mixture was extracted with AcOEt (4 × 50 ml), the combined org. phase washed with H_2O (2 × 50 ml) and brine, dried (Na_2SO_4), and evaporated, and the oil crystallized from MeOH: 1.0 g (56%) of **6**. M.p. 129–130°. ^1H-NMR ($CDCl_3$): 7.45 (*d*, *J* = 8.3, 1 arom. H); 7.37 (*d*, *J* = 8.3, 1 arom. H); 7.25 (*m*, 1 arom. H); 7.16 (*m*, 1 arom. H); 6.86 (*d*, *J* = 8.3, 1 arom. H); 6.60 (*d*, *J* = 8.3, 1 arom. H); 5.63 (*s*, H–C(5)); 5.17, 5.06 (2*d*, *J* = 6.6, 6.6, OCH_2O); 3.42 (*s*, MeO). Anal. calc. for $C_{28}H_{29}NO_5$ · 0.2 MeOH (465.95): C 72.69, H 6.45, N 3.01; found: C 72.58, H 6.28, N 3.00.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)-1'-(methoxymethyl)indolo-[2',3':6,7]morphinan-14-ol (**7**). As described for **6**, with NaH (492 mg, 20.5 mmol; from 820 mg of 60% dispersion in oil), naltrindole hydrochloride (**1** · HCl; 1.5 g, 3.3 mmol), and DMF (30 ml; 15 min at 0°, 30 min at r.t.), and then with $MeOCH_2Br$ (1.27 g, 10.2 mmol; 30 min at 0°, 120 min at r.t.). Workup (3 × 60 ml) of AcOEt and CC (silica gel, CH_2Cl_2/MeOH/conc. NH_4OH soln. 245:10:1) afforded 500 mg (30%) of pure **7**. Colorless foam. ^{1}H-NMR ($CDCl_3$): 7.44 (*m*, 2 arom. H); 7.20 (*m*, 1 arom. H); 7.07 (*m*, 1 arom. H); 6.82 (*d*, *J* = 8, 1 arom. H); 6.58 (*d*, *J* = 8, 1 arom. H); 5.81 (*s*, H–C(5)); 5.79, 5.50 (2*d*, *J* = 10.8, 10.8, NCH_2O); 5.12, 5.50 (2*d*, *J* = 6.4, 6.4, OCH_2O); 3.41, 3.33 (2*s*, 2 MeO). Anal. calc. for $C_{30}H_{34}N_2O_5$ (502.61): C 71.9, H 6.82, N 5.57; found: C 71.92, H 6.94, N 5.34.

3-O-Protected 14-O-Alkoxybenzofuro-morphinans. NaH (36 mg, 1.5 mmol; obtained from 60 mg of 60% NaH dispersion in oil by washings with hexane) was added to a soln. of **6** (300 mg, 0.64 mmol) in anh. DMF (6 ml) at 0°. After stirring at 0° for 15 min, stirring was continued for another 30 min at r.t. The mixture was cooled again to 0°, the alkylating reagent (1 mmol) added at once, and stirring continued for 15 min at 0° and then for 3 h at r.t. Excess NaH was destroyed with MeOH and H_2O, the mixture extracted with AcOEt (3 × 30 ml), the combined org. phase washed with H_2O (2 × 30 ml) and brine (2 × 30 ml), dried (Na_2SO_4), and evaporated, and the oily residue purified either by crystallization or by CC (silica gel, CH_2Cl_2/MeOH/conc. NH_4OH soln. 240:10:1).

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-methoxy-3-(methoxymethoxy)benzofuro[2',3':6,7]-morphinan (**8**): 280 mg (91%). Colorless foam after CC. ^{1}H-NMR ((D_6)DMSO): 7.56 (*d*, *J* = 8.1, 1 arom. H); 7.52 (*d*, *J* = 8.1, 1 arom. H); 7.32 (*dd*, *J* = 8, 8, 1 arom. H); 7.23 (*dd*, *J* = 8, 8, 1 arom. H); 6.79 (*d*, *J* = 8.2, 1 arom. H); 6.64 (*d*, *J* = 8.2, 1 arom. H); 5.64 (*s*, H–C(5)); 5.05, 5.00 (2*d*, *J* = 6.4, 6.4, OCH_2O); 3.32 (MeO). Anal. calc. for $C_{29}H_{31}NO_5 \cdot 0.2$ MeOH (479.98): C 73.07, H 6.68, N 2.92; found: C 72.94, H 6.60, N 2.92.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)-14-{[(E)-3-phenylprop-2-enyl]oxy}-benzofuro[2',3':6,7]morphinan (**9**): 200 mg (53%). Colorless crystals. M.p. 156–159° (MeOH). ^{1}H-NMR ($CDCl_3$): 7.47 (*d*, *J* = 8, 1 arom. H); 7.33 (*d*, *J* = 8, 1 arom. H); 7.28–7.07 (*m*, 7 arom. H); 6.84 (*d*, *J* = 8.4, 1 arom. H); 6.59 (*d*, *J* = 8.4, 1 arom. H); 6.38 (*d*, *J* = 16, 1 olef. H); 6.13 (*m*, 1 olef. H); 5.68 (*s*, H–C(5)); 5.16, 5.06 (2*d*, *J* = 6.4, 6.4, OCH_2O); 4.46, 4.11 (2*m*, CH_2O–C(14)); 3.42 (*s*, MeO). Anal. calc. for $C_{37}H_{37}NO_5 \cdot 0.1$ AcOEt (584.52): C 76.85, H 6.52, N 2.40; found: C 76.70, H 6.48, N 2.41.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-[(2-fluorobenzyl)oxy]-3-(methoxymethoxy)benzofuro-[2',3':6,7]morphinan (**10**): 215 mg (58%). Colorless foam after CC. ^{1}H-NMR ((D_6)DMSO): 7.56 (*d*, *J* = 8, 1 arom. H); 7.49 (*d*, *J* = 8, 1 arom. H); 7.31 (*m*, 1 arom. H); 7.21 (*m*, 1 arom. H); 6.81 (*d*, *J* = 8.4, 1 arom. H); 6.67 (*d*, *J* = 8.4, 1 arom. H); 5.72 (*s*, H–C(5)); 5.06, 5.01 (2*d*, *J* = 6.4, 6.4, OCH_2O); 4.89, 4.57 (2*d*, *J* = 11.6, 11.6, $ArCH_2O$); 3.33 (*s*, MeO). Anal. calc. for $C_{35}H_{34}FNO_5$ (567.66): C 74.06, H 6.04, N 2.47; found: C 73.71, H 5.92, N 2.42.

17-(Cyclopropylmethyl)-6,7-didehydro-14-[(2,6-dichlorobenzyl)oxy]-4,5α-epoxy-3-(methoxymethoxy)benzo-furo[2',3':6,7]morphinan (**11**): 300 mg (75%). Colorless crystals. M.p. 180–182° (MeOH). ^{1}H-NMR ($CDCl_3$): 7.41 (*d*, *J* = 8.1, 1 arom. H); 7.33 (*d*, *J* = 8.3, 1 arom. H); 7.23 (*m*, 1 arom. H); 7.14 (*m*, 2 arom. H); 7.03, 7.01 (2*d*, *J* = 7.3, 7.3, 2 arom. H); 6.84 (*d*, *J* = 8.3, 1 arom. H); 6.59 (*d*, *J* = 8.3, 1 arom. H); 5.56 (*s*, H–C(5)); 5.32, 4.68 (2*d*, *J* = 8.7, 8.7, $ArCH_2O$); 5.16, 5.05 (2*d*, *J* = 6.6, 6.6, OCH_2O); 3.41 (*s*, MeO).

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)-14-[(3-nitrobenzyl)oxy]benzofuro-[2',3':6,7]morphinan (**12**): 100 mg (26%). Colorless foam after CC. ^{1}H-NMR ($CDCl_3$): 8.25 (*s*, 1 arom. H); 7.55 (*d*, *J* = 7.8, 1 arom. H); 7.47 (*d*, *J* = 8.3, 1 arom. H); 7.28 (*m*, 4 arom. H); 7.15 (*m*, 1 arom. H); 6.87 (*d*, *J* = 8.3, 1 arom. H); 6.62 (*d*, *J* = 8.3, 1 arom. H); 5.66 (*s*, H–C(5)); 5.17, 5.07 (2*d*, *J* = 6.6, 6.6, OCH_2O); 4.92, 4.44 (2*d*, *J* = 11.5 $ArCH_2O$); 3.42 (*s*, MeO).

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)-14-(2-naphthylmethoxy)benzofuro-[2',3':6,7]morphinan (**13**): 285 mg (73%). Colorless crystals. M.p. 198–201° (AcOEt). ^{1}H-NMR ($CDCl_3$): 7.72–7.08 (*m*, 11 arom. H); 6.86 (*d*, *J* = 8.3, 1 arom. H); 6.62 (*d*, *J* = 8.3, 1 arom. H); 5.68 (*s*, H–C(5)); 5.17, 5.07 (2*d*, *J* = 6.6, 6.6, OCH_2O); 5.01, 4.57 (2*d*, *J* = 11.2, 11.2, $ArCH_2O$); 3.42 (*s*, MeO). Anal. calc. for $C_{39}H_{37}NO_5 \cdot 0.2$ AcOEt (617.35): C 77.43, H 6.30, N 2.27; found: C 77.40, H 6.27, N 2.27.

Benzofuro-morphinans **14–19**. A soln. of **8**, **9**, **10**, **11**, **12**, or **13** (< 0.5 mmol) in MeOH (4 ml) and 1N HCl (2 ml) was refluxed for 1 h. After cooling, the soln. was alkalinized with conc. NH_4OH soln. and extracted with AcOEt (3 × 15 ml), the combined org. phase washed with H_2O (2 × 15 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated, and the oily residue purified by crystallization or by CC.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-methoxybenzofuro[2',3':6,7]morphinan-3-ol Hydro-chloride (**14** · HCl): 70 mg (36%) of **14** · HCl. M.p. > 240° (dec.). ^{1}H-NMR ((D_6)DMSO): 9.47 (*s*, OH); 9.17 (br. *s*, NH^+); 7.61 (*d*, *J* = 8, 1 arom. H); 7.53 (*d*, *J* = 8, 1 arom. H); 7.36 (*dd*, *J* = 8, 8, 1 arom. H); 7.27 (*dd*, *J* = 8,

8, 1 arom. H); 6.72 (*d*, *J* = 8.4, 1 arom. H); 6.65 (*d*, *J* = 8.4, 1 arom. H); 5.90 (*s*, H–C(5)); 3.35 (*s*, MeO). Anal. calc. for $C_{27}H_{27}NO_4 \cdot HCl \cdot 1.5\,H_2O$ (493.00): C 65.78, H 6.34, N 2.84; found: C 65.89, H 6.20, N 2.85.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-{[(E)-3-phenylprop-2-enyl]oxy}benzofuro[2',3':6,7]morphinan-3-ol 2-Hydroxybenzoate (**15** · HOC_6H_4COOH): 100 mg (53%) of **15** · HOC_6H_4COOH. M.p. > 170° (dec.). ^{1}H-NMR ($CDCl_3$): 7.94 (*d*, *J* = 8, 1 arom. H); 7.35 (*d*, *J* = 8, 1 arom. H); 7.30–6.73 (*m*, 12 arom. H); 6.56 (*d*, *J* = 8, 1 arom. H); 5.96 (*s*, 2 olef. H); 5.55 (*s*, H–C(5)); 4.33–4.02 (*m*, CH_2O–C(14)). Anal. calc. for $C_{35}H_{33}NO_4 \cdot HOC_6H_4COOH \cdot 1$ MeOH (701.82): C 73.57, H 6.18, N 2.00; found: C 73.56, H 5.96, N 2.06.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-[(2-fluorobenzyl)oxy]benzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**16** · HCl): 110 mg (70%) of **16** · HCl. M.p. > 215° (dec.). ^{1}H-NMR ($CDCl_3$): 9.45 (*s*, OH); 9.04 (br. *s*, NH^+); 7.54 (*d*, *J* = 8.4, 1 arom. H); 7.31–6.73 (*m*, 7 arom. H); 6.71 (*d*, *J* = 8.2, 1 arom. H); 6.66 (*d*, *J* = 8.2, 1 arom. H); 5.98 (*s*, H–C(5)); 4.81, 4.84 (2*d*, *J* = 12, ArCH_2O). Anal. calc. for $C_{33}H_{30}FNO_4 \cdot HCl \cdot 1.4\,H_2O$ (585.29): C 67.72, H 5.82, N 2.39; found: C 67.63, H 5.56, N 2.51.

17-(Cyclopropylmethyl)-6,7-didehydro-14-[(2,6-dichlorobenzyl)oxy]-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol (**17**): 70 mg (51%). Colorless crystals. M.p. 193–195° (dec.). ^{1}H-NMR ($CDCl_3$): 7.42 (*d*, *J* = 8.3, 1 arom. H); 7.33 (*d*, *J* = 8, 1 arom. H); 7.24 (*m*, 1 arom. H); 7.14 (*m*, 2 arom. H); 7.03, 7.01 (2*d*, *J* = 7.3, 1 arom. H); 6.64 (*d*, *J* = 8.1, 1 arom. H); 6.56 (*d*, *J* = 8.1, 1 arom. H); 5.58 (*s*, H–C(5)); 5.32, 4.68 (2*d*, *J* = 8.6, ArCH_2O). Anal. calc. for $C_{33}H_{29}Cl_2NO_4$ (574.51): C 68.79, H 5.09, N 2.44; found: C 68.97, H 5.05, N 2.44.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-[(3-nitrobenzyl)oxy]benzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**18** · HCl): 50 mg (66%) of **18** · HCl. M.p. > 230° (dec.). ^{1}H-NMR ((D_6)DMSO): 9.40 (*s*, OH); 9.15 (br. *s*, NH^+); 7.84 (*s*, 1 arom. H); 7.60 (*d*, *J* = 8.8, 1 arom. H); 7.53 (*d*, *J* = 7.6, 1 arom. H); 7.45 (*d*, *J* = 8, 1 arom. H); 7.23 (*d*, *J* = 7.6, 1 arom. H); 7.19 (*d*, *J* = 7.6, 1 arom. H); 6.98 (*m*, 1 arom. H); 6.88 (*d*, *J* = 7.6, 1 arom. H); 6.69 (*d*, *J* = 8.3, 1 arom. H); 6.66 (*d*, *J* = 8.3, 1 arom. H); 6.03 (*s*, H–C(5)); 4.98, 4.87 (2*d*, *J* = 14, 14, ArCH_2O). Anal. calc. for $C_{33}H_{30}N_2O_6 \cdot HCl$ (587.08): C 67.52, H 5.32, N 4.77; found: C 67.78, H 5.26, N 4.76.

17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14-(2-naphthylmethoxy)benzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**19** · HCl): 150 mg (84%) of **19** · HCl. M.p. > 215° (dec.). ^{1}H-NMR ((D_6)DMSO): 9.42 (*s*, OH); 9.00 (br. *s*, NH^+); 7.68–6.85 (*m*, 11 arom. H); 6.71 (*d*, *J* = 8, 1 arom. H); 6.67 (*d*, *J* = 8, 1 arom. H); 6.04 (*s*, H–C(5)); 4.92 (*s*, ArCH_2O). Anal. calc. for $C_{37}H_{33}NO_4 \cdot HCl \cdot 0.3$ MeOH (601.75): C 74.45, H 5.90, N 2.33; found: C 74.47, H 5.76, N 2.35.

Preparation of **20–22**. To a stirred soln. of naltriben methanesulfonate (**2** · $MeSO_3H$; 256 mg, 0.5 mmol) in anh. DMF (10 ml) was added NaH (60% dispersion in oil; 100 mg, 2.5 mmol) at 0°. The soln. was stirred for 1 h at 20° and then cooled to 0° prior to addition of $MeOCH_2Br$ (125 mg, 1.0 mmol). The mixture was warmed up to r.t. during 1 h and cooled again to 0° before NaH (60% dispersion in oil; 100 mg, 2.5 mmol) was added. After 1 h, the corresponding chlorobenzyl bromide (1.0 mmol) was added to the soln. and the resulting mixture stirred for 4 h at 20°. Then MeOH (5 ml) and AcOEt (5 ml) were slowly added at 0°, followed by addition of sat. aq. NH_4Cl soln. (20 ml). The mixture was extracted with AcOEt (3 × 50 ml), the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated, and the oil dissolved in EtOH (5 ml) and 1N HCl (1.5 ml) and refluxed for 1 h. The mixture was alkalinized with 1N NH_4OH and extracted with AcOEt (3 × 50 ml), the combined org. layer washed with brine, dried (MgSO4), and evaporated, and the crude product purified by CC (silica gel, hexane/$CHCl_3$ 3:1, 1:1, and 1:3, then $CHCl_3$, then $CHCl_3$/AcOEt 4:1 and 1:1, and finally AcOEt): **20**, **21**, or **22** as oil. A soln. of this oil in Et_2O (5 ml) was treated with 1M HCl/Et_2O (2 ml) at 0° to provide the corresponding hydrochloride salts.

14-[(2-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**20** · HCl): 236 mg (87%) of **20** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.45–6.90 (*m*, 8 arom. H); 6.72 (*d*, *J* = 8.4, 1 arom. H); 6.68 (*d*, *J* = 8.4, 1 arom. H); 5.72 (*s*, H–C(5)); 4.96, 4.55 (2*d*, *J* = 11.6, 11.6, ArCH_2O).

20 · HCl: M.p. > 220° (dec.). ^{1}H-NMR ((D_6)DMSO): 9.40 (*s*, OH); 8.59 (br. *s*, NH^+); 7.56–6.90 (*m*, 8 arom. H); 6.66 (*m*, 2 arom. H); 6.03 (*s*, H–C(5)); 4.74 (*s*, ArCH_2O). Anal. calc. for $C_{33}H_{30}ClNO_4 \cdot HCl \cdot 1.5\,H_2O$ (603.52): C 65.67, H 5.68, N 2.32; found: C 65.72, H 5.48, N 2.25.

14-[(3-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**21** · HCl): 232 mg (86%) of **21** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.50–7.05 (*m*, 8 arom. H); 6.69 (*d*, *J* = 8.4, 1 arom. H); 6.58 (*d*, *J* = 8.4, 1 arom. H); 5.68 (*s*, H–C(5)); 4.81, 4.35 (2*d*, *J* = 11.6, 11.6, ArCH_2O).

21 · HCl: M.p. > 230° (dec.). ^{1}H-NMR ((D_6)DMSO): 9.40 (*s*, OH); 8.59 (br. *s*, NH^+); 7.53–6.90 (*m*, 8 arom. H); 6.65 (*s*, 2 arom. H); 6.03 (*s*, H–C(5)); 4.74, 4.62 (2*d*, *J* = 13.6, 13.6, ArCH_2O). Anal. calc. for $C_{33}H_{30}ClNO_4 \cdot HCl \cdot 1.5\,H_2O$ (603.52): C 65.67, H 5.68, N 2.32; found: C 65.31, H 5.37, N 2.33.

14-[(4-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**22** · HCl): 224 mg (83%) of **22** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.45–6.95 (*m*, 8 arom. H); 6.65–6.50 (*m*, 2 arom. H); 5.72 (*s*, H–C(5)); 4.78, 4.25 (2*d*, J = 11.6, 11.6, ArCH_2O).

22 · HCl: M.p. > 229° (dec.). Anal. calc. for $C_{33}H_{30}ClNO_4 \cdot HCl \cdot 1.2\,H_2O$ (598.11): C 66.27, H 5.63, N 2.34; found: C 66.21, H 5.57, N 2.17.

Preparation of **23**–**25**. To a stirred soln. of naltriben methanesulfonate (**2** · $MeSO_3H$; 256 mg, 0.5 mmol) and (i-Pr)$_2$EtN (260 mg, 2.0 mmol) in anh. DMF (10 ml) was added (i-Pr)$_3$SiCl (145 mg, 0.75 mmol) at 0°. The soln. was stirred for 1 h at 20°, and then cooled to 0° prior to addition of NaH (60%; 120 mg, 3.0 mmol). After 1 h, the alkylating reagent (1.0 mmol) was added dropwise. The resulting mixture was stirred for 2 h at 20°, and then MeOH (5 ml) and AcOEt (5 ml) were slowly added at 0°. After 30 min, the mixture was extracted with AcOEt (3 × 50 ml), the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated, and the oil dissolved in EtOH (10 ml) and 1N HCl (2 ml) and refluxed for 5 h. The mixture was alkalinized with 1N NH_4OH and extracted with AcOEt (3 × 50 ml), the combined org. phase washed with brine, dried ($MgSO_4$), and evaporated, and the oil purified by CC (silica gel, hexane/$CHCl_3$ 3:1 and 3:2, then $CHCl_3$/AcOEt 3:1 and 1:1, then AcOEt): **23**, **24**, or **25** as oil. A soln. of this oil in Et_2O (5 ml) was treated with 1M HCl/Et_2O (2 ml) at 0° to provide the corresponding hydrochloride salts.

14-(Benzyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**23** · HCl): 206 mg (82%) of **23** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.60–7.05 (*m*, 9 arom. H); 6.80–6.60 (*m*, 2 arom. H); 5.72 (*s*, H–C(5)); 4.95, 4.52 (2*d*, J = 11.6, 11.6, PhCH_2O).

23 · HCl: M.p. 255–270° (dec.). Anal. calc. for $C_{33}H_{31}NO_4 \cdot HCl \cdot 0.8\,H_2O$: C 71.23, H 6.09, N 2.52; found: C 71.32, H 5.78, N 2.35.

14-(Allyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**24** · HCl): 106 mg (46%) of **24** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.50–7.08 (*m*, 4 arom. H); 6.70–6.45 (*m*, 2 arom. H); 5.75 (*m*, 1 olef. H); 5.65 (*s*, H–C(5)); 5.02 (*m*, 2 olef. H); 4.81 (br. *s*, OH); 4.25, 3.90 (*m*, CH_2O).

24 · HCl: M.p. 280–290° (dec.). Anal. calc. for $C_{29}H_{29}NO_4 \cdot HCl \cdot 1.1\,H_2O$: C 68.05, H 6.34, N 2.74; found: C 67.94, H 5.95, N 2.53.

14-{[(E)-But-2-enyl]oxy}-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxybenzofuro[2',3':6,7]morphinan-3-ol Hydrochloride (**25** · HCl): 45 mg (19%) of **25** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.48–7.08 (*m*, 4 arom. H); 6.66–6.48 (*m*, 2 arom. H); 5.62 (*s*, H–C(5)); 5.40 (*m*, 2 olef. H); 4.20, 3.82 (2*m*, CH_2O); 1.48, 1.52 (2*m*, Me). LC-MS: 470.3 ([M + 1]$^+$).

25 · HCl: M.p. 245–260° (dec.).

14-[(2-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-3-(methoxymethoxy)-1'-(methoxymethyl)indolo[2',3':6,7]morphinan (**26**). NaH (36 mg, 1.5 mmol; obtained from 60 mg of 60% NaH dispersion in oil by washings with hexane) was added to a soln. of **7** (300 mg, 0.68 mmol) in anh. DMF (5 ml) at 0°. The resulting mixture was stirred at 0° for 15 min and at r.t. for another 30 min. After cooling to 0°, 2-chlorobenzyl bromide (205 mg, 1 mmol) was added, and stirring was continued at first at 0° for 15 min and then at r.t. for 3 h. Excess NaH was destroyed by addition of MeOH and H_2O. The resulting mixture was extracted with AcOEt (3 × 30 ml), the combined org. phase washed with H_2O (2 × 40 ml) and brine (2 × 30 ml), dried (Na_2SO_4), and evaporated: 370 mg (96%) of **26**, pure by TLC and NMR. Colorless foam. ^{1}H-NMR ($CDCl_3$): 7.56 (*m*, 1 arom. H); 7.44 (*m*, 1 arom. H); 7.37–7.17 (*m*, 3 arom. H); 7.01 (*m*, 1 arom. H); 6.91 (*m*, 1 arom. H); 6.83 (*d*, J = 8.2, 1 arom. H); 6.59 (*d*, J = 8.2, 1 arom. H); 5.90 (*s*, H–C(5)); 5.82, 5.55 (2*d*, J = 11.2, 11.2, NCH_2O); 5.13, 5.03 (2*d*, J = 6.4, 6.4, OCH_2O); 4.98, 4.56 (2*d*, J = 13, 13, ArCH_2O); 3.40, 3.26 (2*s*, 2 MeO).

14-[(2-Chlorobenzyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride (**27** · HCl). A soln. of **26** (300 mg, 0.48 mmol) in MeOH (5 ml) and 1N HCl (3 ml) was refluxed for 1 h. After cooling, the soln. was alkalinized with conc. NH_4OH soln. and extracted with AcOEt (3 × 20 ml). The combined org. phase was washed with H_2O (2 × 20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated to give a colorless foam. To a soln. of this foam in a small amount of methanol, HCl/Et_2O soln. was added. The formed crystals were collected and washed with cold MeOH: 120 mg (43%) of **27** · HCl. M.p. > 250° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 11.38 (*s*, NH); 9.38 (*s*, OH); 8.76 (br. *s*, NH^+); 7.34–6.85 (*m*, 8 arom. H); 6.72 (*d*, J = 8, 1 arom. H); 6.64 (*d*, J = 8, 1 arom. H); 5.93 (*s*, H–C(5)); 4.80, 4.67 (2*d*, J = 13, 13, ArCH_2O). Anal. calc. for $C_{33}H_{31}N_2O_3 \cdot HCl$ (575.54): C 68.87, H 5.60, N 4.87; found: C 68.81, H 5.59, N 4.77.

14-(Allyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride (**28** · HCl). To a stirred soln. of naltrindole hydrochloride (**1** · HCl; 220 mg, 0.5 mmol) in anh. DMF (10 ml), NaH (60% dispersion in oil; 160 mg, 4.0 mmol) was added at 0°. The soln. was stirred for 1 h at 20°, and then cooled to 0° prior to addition of $MeOCH_2Br$ (250 mg, 2.0 mmol). The mixture was warmed up to r.t. during 1 h

and cooled again to 0° before NaH (60%; 100 mg, 2.5 mmol) was added. After 1 h, allyl bromide (242 mg, 2.0 mmol) was added, and the resulting mixture was stirred for 4 h at 20°. Then MeOH (5 ml) and AcOEt (5 ml) were slowly added at 0°, followed by addition of sat. aq. NH_4Cl soln. (20 ml). The mixture was extracted with AcOEt (3 × 50 ml), the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated, and the oil dissolved in EtOH (5 ml) and 6N HCl (1 ml) and refluxed for 2 h. The mixture was alkalinized with 1N NH_4OH and extracted with AcOEt (3 × 50 ml), the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated, and the crude product purified by CC (silica gel, hexane/$CHCl_3$ 3:1, 1:1, and 1:3, then $CHCl_3$, then $CHCl_3$/AcOEt 3:1 and 1:1, and finally AcOEt): **28** (53 mg, 23%; free base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.50–7.00 (*m*, 4 arom. H); 6.65–6.45 (*m*, 2 arom. H); 5.80 (*m*, 1 olef. H); 5.75 (*s*, H–C(5)); 5.18–4.85 (*m*, 2 olef. H); 4.25, 3.95 (2*m*, CH_2O). LC-MS: 455.4 ($[M + 1]^+$).

A soln. of the free base **28** (53 mg) in anh. Et_2O (5 ml) was treated with 1M HCl/Et_2O (1 ml) at 0°. Isolation of the precipitate provided **28** · HCl. M.p. 270–285° (dec.).

1'-Allyl-14-(allyloxy)-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride (**29** · HCl). Isobutyldimethylsilyl chloride (114 mg, 0.75 mmol) was added at 0° to a stirred soln. of naltrindole methanesulfonate (**1** · $MeSO_3H$; 255 mg, 0.5 mmol) and (i-Pr)$_2$EtN (260 mg, 2.0 mmol) in anh. DMF (10 ml). The resulting soln. was stirred at 20° for 1 h and then cooled to 0° prior to the addition of NaH (60% dispersion in oil; 120 mg, 3.0 mmol). After 1 h, isobutyldimethylsilyl chloride (114 mg, 0.75 mmol) was added. The resulting mixture was stirred for 1 h at 20° and then cooled to 0° before adding NaH (60% dispersion in oil; 120 mg, 3.00 mmol). After 1 h, allyl bromide (1.51 mg, 1.25 mmol) was added. The mixture was stirred for 2 h at 20° and then quenched with sat. aq. NH_4Cl soln. and extracted with AcOEt (3 × 30 ml). The combined org. phase was washed with brine, dried ($MgSO_4$), and evaporated to give a yellow oil which was dissolved in MeOH (6 ml) and 1N HCl (2 ml) and refluxed for 6 h. The mixture was alkalinized with 1N NH_4OH and extracted with AcOEt (3 × 30 ml), the combined org. layer washed with brine, dried ($MgSO_4$), and evaporated. This crude product was purified by CC (silica gel, hexane/$CHCl_3$ 3:1 and 1:1, then $CHCl_3$/AcOEt 3:1 and 1:1, then AcOEt): 106 mg (42%) of **29** (base). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.40 (*d*, *J* = 8.4, 1 arom. H); 7.24 (*m*, 1 arom. H); 7.15 (*m*, 1 arom. H); 7.03 (*m*, 1 arom. H); 6.57 (*d*, *J* = 8.4, 1 arom. H); 6.50 (*d*, *J* = 8.4, 1 arom. H); 6.08 (*m*, 1 olef. H); 5.76 (*m*, 1 olef. H); 5.72 (*s*, H–C(5)); 5.15–4.75 (*m*, 6 H, CH_2N, 4 olef. H); 4.24, 3.92 (2*dd*, *J* = 12.4, 4.8, CH_2O). LC-MS: 495.5 ($[M + 1]^+$).

The free base **29** was dissolved in Et_2O (5 ml) and treated with 1M HCl/Et_2O (2 ml) at 0°. Isolation of the precipitate provided **29** · HCl. M.p. 225–229° (dec.).

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