Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 2, pp 369–382, 1997

PII: S0968-0896(96)00257-X
0968-0896/97 $17.00+0.00

New Nepenthone and Thevinone Derivatives†‡

János Marton,[a] Csaba Simon,[a] Sándor Hosztafi,[a] Zoltán Szabó,[a] Árpád Márki,[b] Anna Borsodi[b] and Sándor Makleit[c,*]

[a]*Alkaloida Chemical Company Ltd., P.O. Box 1, Tiszavasvári, H-4440 Hungary*
[b]*Institute of Biochemistry, Biological Research Center, Hungarian Academy of Sciences, Post Office Box 521, Szeged, Hungary*
[c]*Department of Organic Chemistry, Lajos Kossuth University, Post Office Box 20, Debrecen, H-4010 Hungary*

Abstract—The diastereoselective reaction of thevinone (**2a**) and nepenthone (**2c**) and their dihydro derivatives (**2b** and **d**) with Grignard reagents afforded new N-substituted (20*S*)- and (20*R*)-phenyl-6,14-ethenomorphinan derivatives (**6a–y**). The Grignard reaction of the N-substituted-*N*-demethyl derivatives **4a–f** and **4m–r** with methylmagnesium iodide resulted in the (20*R*)-phenyl tertiary alcohols **5a–f** and **5m–r**, respectively, but the conversion of **4g–l** and that of the *N*-substituted-dihydrothevinone derivatives with phenylmagnesium bromide afforded the (20*S*)-phenyl derivatives **5g–l** and **5s–y**, respectively. The *N*-cyclopropylmethyl-, *N*-β-phenylethyl-, and *N*-propyl derivatives were prepared by the 3-O-demethylation of compounds **5**. For the synthesis of the *N*-allyl-, *N*-dimethylallyl-, and *N*-propargyl compounds **2a–d** were reacted with the corresponding Grignard reagent, and treatment of the products with cyanogen bromide gave the cyanamides **8a–d**. These latter compounds were transformed into **10a,b,d**, whose alkylation led to the target derivatives **6d–f, j–l, p–r**, and **w–y**. The biochemical investigation of these substances showed that the affinities to the δ-opioid receptors were high, but the selectivity was low. In two cases (**6c** and **11d**) a μ-opioid receptor specificity was observed.

Introduction

Study of 6,14-ethenomorphinans is one of the most promising fields of research of morphine alkaloids, as demonstrated by the discovery and development of the agonist etorphine (**1a**), the antagonist diprenorphine (**1b**), and the mixed agonist–antagonist buprenorphine (**1c**). Most recently, a selective binding of dihydroetorphine to the μ-opioid receptors has also been reported.[1]

The present work was aimed at the synthesis of selective opioid derivatives belonging to the group of the so-called Bentley compounds, carrying a bulky phenyl group at position C-20. The tertiary alcohol, prepared by Bentley et al.[2] from thevinone by treatment with phenylmagnesium bromide and subsequent 3-O-demethylation, was found to be 34 times as active as morphine in *tail pressure* tests on rats. Bentley and his associates[3] supposed that the reactions of thevinone (**2a**) and its analogues with Grignard reagents proceed via six-membered chelate intermediates. Compound **7a** derived as stereochemically homogeneous from the 7α-benzoyl compound **2c** and methyllithium, and the Grignard adduct **7b** available from the 7α-acetyl derivative with phenylmagnesium bromide are in diastereoisomeric relation[4] [(20*R*) and (20*S*), respectively].

By utilizing the advantages in the mechanism of the Grignard reaction we have prepared a series of new (20*S*) and (20*R*)-phenyl-6,14-ethenomorphinan derivatives from thevinone (**2a**) and nepenthone (**2c**). Nepenthone (**2c**) was obtained according to a method published in the literature,[5] and dihydronepenthone was first synthesized by our group.[6]

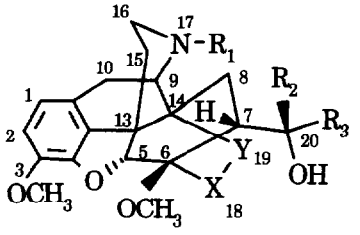
Chemistry

The target compounds were prepared by various independent procedures. N-Demethylation of thevinone (**2a**), dihydrothevinone (**2b**), nepenthone (**2c**), and dihydronepenthone (**2d**) with diethyl azodicarboxylate (DEAD) in benzene gave rise to compounds **3a–d**, whose N-alkylation in *N,N*-dimethylformamide in the presence of sodium hydrogen carbonate led to the desired N-substituted-*N*-demethyl derivatives **4a–r** with high yields.[7,8]

Treatment of **4a–f** and **4m–r** with methylmagnesium iodide afforded the N-substituted tertiary alcohols **5a–f** and **5m–r**, respectively, with (20*R*) absolute configuration.

Compounds **4g–l** and the N-substituted derivatives of dihydrothevinone[7,8] were reacted with phenylmagnesium bromide to obtain, in accordance with the mechanism of the Grignard reaction, the (20*S*)-tertiary

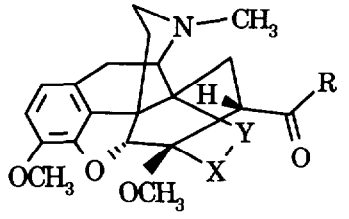
†Morphine alkaloids Part 137. For Part 136 see: Hosztafi, S.; Makleit, S. Synthesis of new apomorphine derivatives containing halogen (Cl, Br) in ring-D (*Synth. Commun.* **1996**, *26*, 3909).
‡This work was a part of the Ph.D. Thesis: Marton, J. Diels–Alder reaction of morphinandienes I. Kossuth University, Debrecen, Hungary, 1995.
Key words: thevinone; nepenthone; 6,14-ethenomorphinans; μ-opioid receptor specificity.



1

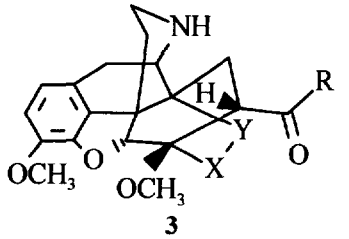
1	R_1	R_2	R_3	X-Y	
a	CH_3	n-Pr	CH_3	CH=CH	Etorphine
b	CPM	CH_3	CH_3	CH_2-CH_2	Diprenorphine
c	CPM	*t*-Bu	CH_3	CH_2-CH_2	Buprenorphine

alcohols **5g–l** and **5s–y**, respectively. The Grignard reactions of the 7α-benzoyl compounds with methylmagnesium iodide, and those of the 7α-acetyl derivatives with phenylmagnesium bromide were carried out with high diastereoselectivity; the diastereoisomeric pair of the product could only be detected or isolated in a very few cases. The major product of the reaction



2

2	R	X-Y
a	CH_3	CH=CH
b	CH_3	CH_2-CH_2
c	Ph	CH=CH
d	Ph	CH_2-CH_2

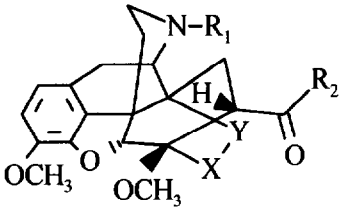


3

3	X-Y	R
a	CH=CH	CH_3
b	CH_2-CH_2	CH_3
c	CH=CH	Ph
d	CH_2-CH_2	Ph

of nepenthone (**2c**) with methylmagnesium iodide was **7a**, but by column chromatography of the mother liquor 5% of **7b** could also be isolated. Based on our experiences in the field of 6,14-ethenomorphinanes, 3-O-demethylation with the KOH/diethylene glycol system was accomplished only in the case of the *N*-cyclopropylmethyl, *N*-(β-phenylethyl), and *N*-(n-propyl) derivatives to afford compounds **6** with 42–63% yield.

The other route employed was the von-Braun reaction leading to N-demethylation, as well. The starting ketones **2a–d** were first reacted with methylmagnesium iodide or phenylmagnesium bromide and the resulting tertiary alcohols (**7a–d**) were treated with cyanogen bromide in chloroform to furnish the cyanoamides **8a–d**. The reaction of these latter compounds with potassium hydroxide gave the *N*-demethyl derivatives **9a–d**, which were then alkylated giving rise to the N-substituted compounds **5a–y** with good yields. A clear advantage of this procedure is that hydrolysis of the cyanoamide and O-demethylation can be carried out as a one-pot procedure, permitting the preparation of **10a,b,d**, which are suitable for converting into derivatives (**6d–f**, **j–l**, **w–y**) containing allyl, 3,3-dimethylallyl and propargyl N-substituents. The above procedure gave **7c**, **8c**, and **9c** but the 3-O-demethylation failed. Treatment of **8c** with KOH in diethylene glycol at 210 °C resulted in an uncontrollable decomposition of the educt. Attempted 3-O-demethylation of **5m–r** with various methods reported for the cleavage of aryl-methyl ethers (i.e. nPrSH/NaH/DMF and diphenyl-phosphine/BuLi) failed, and thus no suitable method for the preparation of the (20*R*) derivatives **6m–r** could be found. 3-O-Demethylation of **5a** and **c** with KOH/diethylene glycol resulted in **12b** and **d** in a longer reaction time (2 h). For structural assignment **5c** was converted with formic acid[9,10] into **12a**. In the ^{1}H NMR spectra of **12b–c** the signal characteristic of the 3-OCH_3 function was missing, but otherwise the spectra were similar to that of **12a**. The presence of the C-6 keto group in these molecules was assigned according to the IR spectra. Thus, the tertiary alcohols **5** undergo rearrangement accompanied by



4

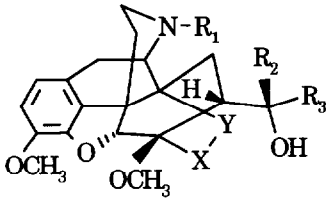
4	X-Y	R_1	R_2
a	CH=CH	CPM	Ph
b	CH=CH	β-Phe	Ph
c	CH=CH	n-Pr	Ph
d	CH=CH	Allyl	Ph
e	CH=CH	diMe-Allyl	Ph
f	CH=CH	Propargyl	Ph
g	CH=CH	CPM	CH_3
h	CH=CH	β-Phe	CH_3
i	CH=CH	n-Pr	CH_3
j	CH=CH	Allyl	CH_3
k	CH=CH	diMe-Allyl	CH_3
l	CH=CH	Propargyl	CH_3
m	CH_2-CH_2	CPM	Ph
n	CH_2-CH_2	β-Phe	Ph
o	CH_2-CH_2	n-Pr	Ph
p	CH_2-CH_2	Allyl	Ph
q	CH_2-CH_2	diMe-Allyl	Ph
r	CH_2-CH_2	Propargyl	Ph

elimination of water under both acidic and alkaline conditions.

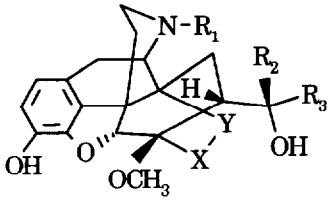
Materials and Methods

Membrane preparation

The rat membrane preparation was according to Pasternak[11] with a small modification (40 000 *g* and Braun Teflon-glass homogenizer instead of 49 000 *g* and Polytron homogenizer, respectively). Rats (Wistar strain) were killed by decapitation. The brains without cerebellum were removed and then homogenized in 20 volumes (wt/vol) of ice-cold buffer (Tris–HCl 50 mM, pH 7.4) with Braun Teflon-glass homogenizer were filtered on four layers of gauze and centrifuged with Sorvall RC5C centrifuge (40 000 *g* 4 °C 20 min). The pellet was resuspended in buffer (50 mM Tris–HCl, pH 7.4) and incubated (37 °C, 30 min). Centrifugation was repeated. The pellet was resuspended in 5 × volumes of buffer (50 mM Tris–HCl, 0.32 M sucrose

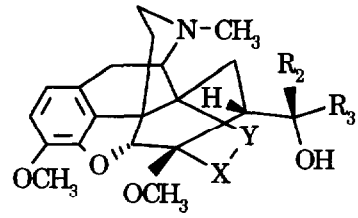


5

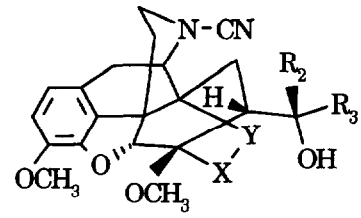


6

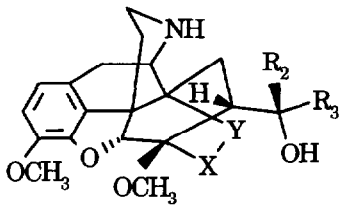
5-6	X-Y	R_1	R_2	R_3
a	CH=CH	CPM	Ph	CH_3
b	CH=CH	β-Phe	Ph	CH_3
c	CH=CH	n-Pr	Ph	CH_3
d	CH=CH	Allyl	Ph	CH_3
e	CH=CH	diMe-Allyl	Ph	CH_3
f	CH=CH	Propargyl	Ph	CH_3
g	CH=CH	CPM	CH_3	Ph
h	CH=CH	β-Phe	CH_3	Ph
i	CH=CH	n-Pr	CH_3	Ph
j	CH=CH	Allyl	CH_3	Ph
k	CH=CH	diMe-Allyl	CH_3	Ph
l	CH=CH	Propargyl	CH_3	Ph
m	CH_2-CH_2	CPM	Ph	CH_3
n	CH_2-CH_2	β-Phe	Ph	CH_3
o	CH_2-CH_2	n-Pr	Ph	CH_3
p	CH_2-CH_2	Allyl	Ph	CH_3
q	CH_2-CH_2	diMe-Allyl	Ph	CH_3
r	CH_2-CH_2	Propargyl	Ph	CH_3
s	CH_2-CH_2	CPM	CH_3	Ph
t	CH_2-CH_2	β-Phe	CH_3	Ph
v	CH_2-CH_2	n-Pr	CH_3	Ph
w	CH_2-CH_2	Allyl	CH_3	Ph
x	CH_2-CH_2	diMe-Allyl	CH_3	Ph
y	CH_2-CH_2	Propargyl	CH_3	Ph



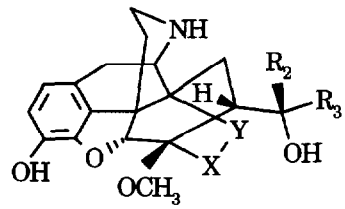
7a-d



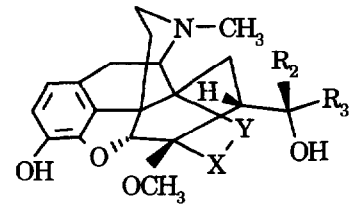
8a-d



9a-d



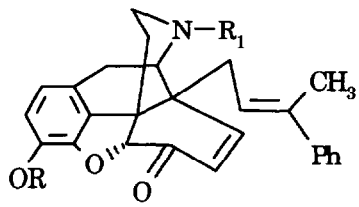
10-a-d



11a-d

7-11	X-Y	R_2	R_3	C-20
a	CH=CH	Ph	CH_3	R
b	CH=CH	CH_3	Ph	S
c	CH_2-CH_2	Ph	CH_3	R
d	CH_2-CH_2	CH_3	Ph	S

pH 7.4). The membranes were stored at −70 °C. Before the using membranes were diluted and centrifuged (40 000 *g*, 4 °C, 20 min) and then the pellet was resuspended in 50 mL buffer (200–300 μg/mL protein). The protein concentration was determined according to Bradford.[12]



12

12	R_1	R
a	n-Pr	CH_3
b	CPM	H
c	n-Pr	H

Receptor binding assays

The frozen membranes were thawed at room temperature and centrifuged in 50 mM Tris–HCl buffer (40 000 *g*, 20 min, 4 °C). Ligand binding experiments were carried out in 50 mM Tris–HCl buffer (pH 7.4) at a final volume of 1 mL containing 100 μL radioligand, 100 μL unlabelled ligand and about 0.3–0.5 mg protein. When [^{3}H]EKC was applied 100 μL DADLE–DAMGO (10–5 M) mixture was used to block μ and δ opioid receptors. In the receptor binding assays the following tritiated ligands were used: [^{3}H]deltorphin II (20 Ci/mmol, Isotope Lab. BRC),[13] [^{3}H]DAMGO (59 Ci/mmol, Amersham),[14] and [^{3}H]EKC (15 Ci/mmol, New England Nuclear) (Table 1). Incubations were started by addition of membrane suspension and continued in a shaking water bath until steady-state was achieved. The reaction was terminated by rapid filtration on Brandel M24 R cell harvester through Whatmann GF/C or GF/B filters and washed with 3 × 5 mL of ice-cold Tris–HCl (pH 7.4) buffer. The filters were dried at 37 °C in the heating room, and the bound radioactivity was determined in a toluene based scintillation cocktail in Beckman 5000 TD spectrophotometer.

Table 1. Experimental procedures of receptor binding assay

Labelled compound	Specific radioactivity (Ci/mmol)	Temperature (°C)	Incubation time (min)	Concentration (nM)	Filter type
[^{3}H]DAMGO[a]	60	35	45	0.5	C
[^{3}H]EKC[b]	15	24	40	1.5	B
[^{3}H]DT[c]	20	35	45	2.0	C

[a]DAMGO: (D-Ala^2-(Me)Phe^4-Gly^5-ol)enkephalin.
[b]EKC: Ethylketocyclazocine.
[c]DT: Tyr-D-Ala-Phe-Glu-Val-Gly-NH_2.

The total binding was defined as that measured in the absence of a competing agent. Nonspecific binding was determined in the presence of 10 μL unlabelled naloxone. All assays were carried out at least three times in duplicate. Competition data were analyzed by the LIGAND 3.1.4.[15] program utilizing a nonlinear least squares fitting algorithm.

Results

Biochemistry

First, the delta receptor affinity of compounds were examined with labelled deltorphin II. In that case when K_i values were less then 100 nM further competition studies were carried out with [^{3}H]DAMGO (μ opioid receptor agonist) and [^{3}H]EKC (κ opioid receptor agonist). Only four compounds (**6h**, **6b**, **5o**, and **5p**) showed K_i values greater than 100 nM. The remaining six ligands possess high affinity (K_i: 5–60 nM) toward the delta, mu, and kappa opioid receptors as well (Table 2). These ligands did not show any opioid receptor type selectivity except **6c** (δ/μ 15.0, κ/μ 5.0) and **11d** (δ/μ 17.7, κ/μ 17.0), which are somewhat mu selective ligands.

Experimental

Melting points (uncorrected) were measured with a Büchi-apparatus in open capillary tubes. The purity of the synthesized compounds were checked by TLC. For column chromatography Kieselgel 60 (particle size 0.063–0.2 mm) was employed with an eluent system $CHCl_3$: MeOH (9:1). The optical rotation values were measured with a Polmat-A (Zeiss, Jena) polarimeter.

^{1}H NMR spectra were recorded with a Varian-Gemini-200 instrument at 20 °C in $CDCl_3$ (or in the case of **10** in DMSO-d_6). For the ^{1}H NMR examinations TMS (δ = 0.00 ppm) was used as the internal standard. In the cases of **12a–c** the proton and carbon assingnments are based on COSY-45 and HETCOR experiments. Abbreviations: cProp: protons of the cyclopropyl ring; Ar: aromatic protons; Ph: protons of the C-20-phenyl group; All: protons of the allyl or 3,3-dimethyallyl groups; Prop: protons of the propargyl group; [a]: deuterable. Mass spectra were obtained with a VG Trio-2 instrument by using the EI method (70 eV), or occasionally by means of the 'thermospray technique' (TSP).

The elemental analyses were carried out at the Department of Organic Chemistry, Lajos Kossuth University with a Carlo Erba automatic analyser.

Table 2. Opioid receptor binding results

Unlabelled compounds	K_i (nM)		
	[^{3}H]DT II	[^{3}H]DAMGO	[^{3}H]EKC
6h	262.8	—	—
6b	106.4	—	—
6v	14.8	1.0	1.7
6c	61.4	4.1	20.7
11d	5.3	0.3	5.1
11c	7.2	2.8	10.7
6i	38.9	7.2	8.3
5o	280.5	—	—
5p	194.5	—	—
5m	32.5	27.5	35.5

Typical procedure for the preparation of compounds 3a–c

To a soln of the *N*-methyl derivatives **3a–c** (17.3 mmol) in abs benzene (89 mL) diethyl azodicarboxylate (5.1 mL) was added, the mixture was heated under reflux for 7 h and then evapd. The residue was dissolved in EtOH (56 mL), pyridinium chloride (1.8 g) added and the reaction mixture stirred for 8 h at room temperature. The hydrochloride that precipitated was filtered off. It was washed with cold EtOH and air dried.

3a [*N*-demethylthevinone]. Yield 68%, mp 347–348 °C [HCl] [EtOH] (Lit.[2]: 350 °C). ^{1}H NMR ($CDCl_3$): δ 1.40 (dd, 1H, 8α-H), 3.62 (s, 1H, 6-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 5.56 (d, 1H, 19-H), 5.92 (dd, 1H, 18-H), 6.54 (d, 1H, 1-H), 6.67 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 367 (100) [M$^+$]. $[\alpha]_D^{25}$ [HCl] −217.0° (H_2O, *c* 0.5). $C_{22}H_{25}NO_4$ (367.4).

3b [*N*-demethylnepenthone]. Yield 71%, mp 238–240 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.50 (dd, 1H, 8α-H), 3.45 (s, 1H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.64 (d, 1H, 5β-H), 5.54 (d, 1H, 19-H), 6.12 (dd, 1H, 18-H), 6.53 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.40–8.02 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 429 (58), 148 (100). $[\alpha]_D^{25}$ [HCl] −206.0° (H_2O, *c* 0.5). $C_{27}H_{27}NO_4$ (429.5) calcd C 75.50; H 6.34; N 3.26; Found C 75.58; H 6.30; N 3.17.

3c [*N*-demethyldihydronepenthone]. Yield 82% [HCl] mp 151–152 °C [hexane]. ^{1}H NMR ($CDCl_3$): δ 0.80 (m, 1H, 8α-H), 3.25 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.54 (d, 1H, 5β-H), 6.63 (d, 1H, 1-H), 6.76 (d, 1H, 2-H), 7.40–8.05 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 431 (5) [M$^+$], 104 (100). $[\alpha]_D^{25}$ −111.0° ($CHCl_3$, *c* 0.1). $C_{27}H_{29}NO_4$ (431.5) calcd C 75.15; H 6.77; N 3.25; Found C 75.20; H 6.85; N 3.18.

General method for the preparation of compounds 4a–r

The hydrochloride salts of the *N*-demethyl derivatives (*N*-demethyl-dihydrothevinone[7] and **3a–c**; 7.4 mmol) were converted into the syrupy free bases and dissolved in abs DMF (20 mL). To this soln $NaHCO_3$ (1.9 g), and 11.1 mmol of the *N*-alkylating agent (cyclopropylmethyl bromide, β-phenylethyl bromide, *n*-propyl bromide, allyl bromide, 3,3-dimethylallyl bromide and propargyl bromide) were added and the reaction mixture stirred at 90 °C (oil-bath) for 20 h. After filtration of the inorganic salts the filtrate was concd, the residue suspended in water, alkalized with 25% aq NH_4OH and extracted with $CHCl_3$. The combined organic layer was washed with water, dried over

Na_2SO_4 and concd. The residual crude product was crystallized from the appropriate solvent.

(5*R*,6*R*,7*S*,9*R*,13*S*,14*R*)-7-Benzoyl-4,5-epoxy-3,6-dimethoxy-17-substituted-6,14-ethenomorphinan derivatives (4a–f) [*N*-demethyl-N-substituted-nepenthone derivatives]

4a: Yield 74%, mp 136–137 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.13–0.83 (m, 5H, cProp), 1.50 (dd, 1H, 8α-H), 3.48 (s, 3H, 6-OCH_3), 3.85 (s, 3H, 3-OCH_3), 4.70 (d, 1H, 5β-H), 5.72 (d, 1H, 19-H), 6.13 (dd, 1H, 18-H), 6.54 (d, 1H, 1-H), 6.67 (d, 1H, 2-H), 7.43–8.04 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 483 (14) [M^+], 105 (100). $[\alpha]_D^{25}$ −247.0° ($CHCl_3$, *c* 1). $C_{31}H_{33}NO_4$ (483.6) calcd C 76.99; H 6.88; N 2.90; Found C 76.91; H 6.93; N 2.83.

4b: Yield 83%. The residual crude product was dissolved in EtOH and the pH adjusted to 2 with satd HCl/EtOH. The solvent was evapd and the residue treated with Et_2O. The produced hydrochloride salt was filtered off, mp 221–223 °C [HCl] [diethylether]. ^{1}H NMR ($CDCl_3$): δ 1.30 (dd, 1H, 8α-H), 3.47 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.65 (d, 1H, 5β-H), 5.53 (d, 1H, 19-H), 6.10 (dd, 1H, 18-H), 6.53 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.05–7.35 (m, 5H, Ar), 7.40–8.00 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 442 (40) [M-91]$^+$, 105 (100). $[\alpha]_D^{25}$ −151.5° ($CHCl_3$, *c* 1). $C_{35}H_{35}NO_4$ (533.6) calcd C 78.77; H 6.61; N 2.62; Found C 78.68; H 6.70; N 2.68.

4c: Yield 55%, mp 129–130 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, $CH_3CH_2CH_2$), 1.45 (m, 1H, 8α-H), 3.47 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.68 (d, 1H, 5β-H), 5.57 (d, 1H, 19-H), 6.10 (dd, 1H, 18-H), 6.53 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 7.40–8.02 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 471 (13) [M^+], 105 (100). $[\alpha]_D^{25}$ −230.8° ($CHCl_3$, *c* 1). $C_{30}H_{33}NO_4$ (471.6) calcd C 76.41; H 7.05; N 2.97; Found C 76.36; H 7.12; N 3.05.

4d: Yield 69%, mp 104–105 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.45 (dd, 1H, 8α-H), 3.48 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.68 (d, 1H, 5β-H), 5.05–5.28 (m, 2H, All), 5.56 (d, 1H, 19-H), 5.67–5.90 (m, 1H, All), 6.10 (dd, 1H, 18-H), 6.54 (d, 1H, 1-H), 6.66 (d, 1H, 2-H), 7.40–8.02 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 469 (15) [M^+], 105 (100). $[\alpha]_D^{25}$ −246.9° ($CHCl_3$, *c* 1). $C_{30}H_{31}NO_4$ (469.5) calcd C 76.73; H 6.65; N 2.98; Found C 76.65; H 6.70; N 3.05.

4e: Yield 86%, oil. ^{1}H NMR ($CDCl_3$): δ 1.44 (dd, 1H, 8α-H), 1.67 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.47 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.68 (d, 1H, 5β-H), 5.15 (t, 1H, All), 5.57 (d, 1H, 19-H), 6.09 (dd, 1H, 18-H), 6.55 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.40–8.04 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 497 (12) [M^+], 105 (100). $[\alpha]_D^{25}$ −221.0° ($CHCl_3$, *c* 1). $C_{32}H_{35}NO_4$ (497.6).

4f: Yield 56%, mp 126–127 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.48 (dd, 1H, 8α-H), 2.22 (t, 1H, Prop), 3.34 (d, 2H, Prop), 3.47 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.67 (d, 1H, 5β-H), 5.57 (d, 1H, 19-H), 6.12 (dd, 1H, 18-H), 6.54 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.40–7.98 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 467 (18) [M^+], 105 (100). $[\alpha]_D^{25}$ −236.9° ($CHCl_3$, *c* 1). $C_{30}H_{29}NO_4$ (467.5) calcd C 77.07; H 6.25; N 3.00; Found C 76.98; H 6.31; N 3.09.

(5*R*,6*R*,7*S*,9*R*,13*S*,14*R*)-7-Acetyl-4,5-epoxy-3,6-dimethoxy-17-substituted-6,14-ethenomorphinan derivatives (4g–l) [*N*-demethyl-N-substituted-thevinone derivatives]

4g: Yield 58%, mp 95–96 °C [EtOH] (Lit.[16]: oil). ^{1}H NMR ($CDCl_3$): δ 0.10–0.92 (m, 5H, cProp), 1.34 (dd, 1H, 8α-H), 2.14 (s, 3H, 7α-Ac), 3.61 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.59 (d, 1H, 19-H), 5.90 (dd, 1H, 18-H), 6.52 (d, 1H, 1-H), 6.63 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 421 (80) [M^+], 246 (100). $[\alpha]_D^{25}$ −238.3° ($CHCl_3$, *c* 1); (Lit.[16]: $[\alpha]_D^{20}$ −145° (CH_2Cl_2, *c* 0.67)). $C_{26}H_{31}NO_4$ (421.5).

4h: Yield 76%, mp 136–137 °C [EtOH] (Lit.[2]: 137 °C). ^{1}H NMR ($CDCl_3$): δ 1.25 (dd, 1H, 8α-H), 2.13 (s, 3H, 7α-Ac), 3.58 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.56 (d, 1H, 5β-H), 5.55 (d, 1H, 19-H), 5.88 (dd, 1H, 18-H), 6.53 (d, 1H, 1-H), 6.88 (d, 1H, 2-H), 7.14–7.33 (m, 5H, Ar). MS (EI 70 eV) *m/z* 471 (4) [M]$^+$, 380 (100). $[\alpha]_D^{25}$ −195.1° ($CHCl_3$, *c* 1). $C_{30}H_{33}NO_4$ (471.6).

4i: Yield 51%, mp 94–95 °C [EtOH] (Lit.[2]: oil). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, $CH_3CH_2CH_2$), 1.35 (m, 1H, 8α-H), 2.14 (s, 3H, 7α-Ac), 3.59 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.58 (d, 1H, 19-H), 5.90 (dd, 1H, 18-H), 6.52 (d, 1H, 1-H), 6.63 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 409 (80) [M^+], 380 (100). $[\alpha]_D^{25}$ −236.0° ($CHCl_3$, *c* 1). $C_{25}H_{31}NO_4$ (409.5).

4j: Yield 53%, mp 92–94 °C [EtOH] (Lit.[2]: oil). ^{1}H NMR ($CDCl_3$): δ 1.34 (dd, 1H, 8α-H), 2.14 (s, 3H, 7α-Ac), 3.60 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 5.07–5.27 (m, 2H, All), 5.56 (d, 1H, 19-H), 5.67–5.84 (m, 1H, All), 5.90 (dd, 1H, 18-H), 6.52 (d, 1H, 1-H), 6.64 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 407 (100) [M^+], 232 (90). $[\alpha]_D^{25}$ −237.5° ($CHCl_3$, *c* 1). $C_{25}H_{29}NO_4$ (407.5).

4k: Yield 87%, oil (Lit.[2]: oil). ^{1}H NMR ($CDCl_3$): δ 1.30 (dd, 1H, 8α-H), 1.65 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.13 (s, 3H, 7α-Ac), 3.58 (s, 3H, 6-OCH_3), 3.80 (s, 3H, 3-OCH_3), 4.56 (d, 1H, 5β-H), 5.15 (t, 1H, All), 5.54 (d, 1H, 19-H), 5.87 (dd, 1H, 18-H), 6.51 (d, 1H, 1-H), 6.62 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 435 (48) [M^+], 177 (100). $[\alpha]_D^{25}$ −193.0° ($CHCl_3$, *c* 1). $C_{27}H_{33}NO_4$ (435.5).

4l: Yield 56%, mp 119–120 °C [EtOH] (Lit.[2]: oil). ^{1}H NMR ($CDCl_3$): δ 1.37 (dd, 1H, 8α-H), 2.13 (s, 3H, 7α-Ac), 2.24 (t, 1H, Prop), 3.34 (d, 2H, Prop), 3.59 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.58 (d, 1H, 19-H), 5.92 (dd, 1H, 18-H), 6.53 (d, 1H, 1-H), 6.64 (d, 1H, 2-H). MS (EI 70 eV) *m/z* 405

(40) [M$^+$], 230 (100). $[\alpha]_D^{25}$ −239.1° ($CHCl_3$, *c* 1). $C_{25}H_{27}NO_4$ (405.5).

(5*R*,6*R*,7*S*,9*R*,13*S*,14*S*)-7-Benzoyl-4,5-epoxy-18,19-dihydro-3,6-dimethoxy-17-substituted-6,14-ethenomorphinan derivatives (4m–r) [*N*-demethyl-N-substituted-dihydronepenthone derivatives]

4m: Yield 72% mp 104–105 °C [hexane]. ^{1}H NMR ($CDCl_3$): δ 0.10–0.80 (m, 5H, cProp), 0.85 (m, 1H, 8α-H), 3.21 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 6.58 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.40–8.05 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 485 (25) [M$^+$], 105 (100). $[\alpha]_D^{25}$ −173.5° ($CHCl_3$, *c* 1). $C_{31}H_{35}NO_4$ (485.6) calcd C 76.67; H 7.26; N 2.88; Found C 76.58; H 7.30; N 2.95.

4n: Yield 84%, oil. ^{1}H NMR ($CDCl_3$): δ 0.79 (m, 1H, 8α-H), 3.20 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 6.57 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.08–7.34 (m, 5H, Ar), 7.42–8.04 (m, 5H, 20-Ph). MS (TSP) *m/z* 536 (100) [M + 1]$^+$. $[\alpha]_D^{25}$ −125.0° ($CHCl_3$, *c* 0.5). $C_{35}H_{37}NO_4$ (535.6).

4o: Yield 54%, mp 103–104 °C [hexane]. ^{1}H NMR ($CDCl_3$): δ 0.79 (m, 1H, 8α-H), 0.87 (t, 3H, $CH_3CH_2CH_2$), 3.22 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 6.59 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.40–8.04 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 473 (8) [M$^+$], 444 (100). $[\alpha]_D^{25}$ −220.0° ($CHCl_3$, *c* 0.1). $C_{30}H_{35}NO_4$ (473.6) calcd C 76.08; H 7.45; N 2.96; Found C 75.97; H 7.50; N 3.02.

4p: Yield 81%, mp 112–113 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.78 (m, 1H, 8α-H), 3.20 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 5.03–5.23 (m, 2H, All), 5.63–5.84 (m, 1H, All), 6.60 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.40–8.03 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 471 (22) [M$^+$], 105 (100). $[\alpha]_D^{25}$ −174.2° ($CHCl_3$, *c* 1). $C_{30}H_{33}NO_4$ (471.6) calcd C 76.41; H 7.05; N 2.97; Found C 76.50; H 7.12; N 2.88.

4q: Yield 90%, mp 160–163 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.78 (m, 1H, 8α-H), 1.63 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 3.20 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 5.10 (t, 1H, All), 6.59 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 7.38–8.03 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 499 (8) [M$^+$], 105 (100). $[\alpha]_D^{25}$ −145.0° (EtOH, *c* 0.5). $C_{32}H_{37}NO_4$ (499.6) calcd C 76.92; H 7.46; N 2.80; Found C 76.85; H 7.52; N 2.87.

4r: Yield 52%, mp 143–146 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.82 (m, 1H, 8α-H), 2.22 (t, 1H, Prop), 3.21 (s, 3H, 6-OCH_3), 3.30 (d, 2H, Prop), 3.88 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 6.62 (d, 1H, 1-H), 6.75 (d, 1H, 2-H), 7.40–8.03 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 469 (55) [M$^+$], 105 (100). $[\alpha]_D^{25}$ −196.0° ($CHCl_3$, *c* 1). $C_{30}H_{31}NO_4$ (469.5) calcd C 76.73; H 6.65; N 2.98; Found C 76.80; H 6.58; N 2.94.

Typical procedure for the preparation of (5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*R*)-4,5-epoxy-α-phenyl-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5a–f) and (5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*R*)-4,5-epoxy-α-phenyl-18,19-dihydro-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5m–r) [reaction of *N*-demethyl-N-substituted-nepenthone- and dihydronepenthone derivatives with methylmagnesium iodide]

To a suspension of the Grignard reagent (prepared from 0.8 g of Mg-shavings and 2 mL of MeI in a mixture of 5 mL of abs toluene and 11 mL of abs tetrahydrofuran) a solution of the *N*-demethyl-N-substituted derivative (**4a–f** and **4m–r**; 5.3 mmol) in abs toluene (18 mL) was added over a period of 1 h. Then the reaction mixture is stirred under reflux for 1 h, cooled to ambient temperature, and poured into 120 mL of satd aq NH_4Cl soln. Following extraction with toluene (3 × 40 mL) the combined organic layer was washed with satd aq NaCl, dried (Na_2SO_4), and concd. The residual product was crystallized from the appropriate solvent.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*R*)-4,5-Epoxy-α-phenyl-3,6-dimethoxy-α-metyl-17-substituted-6, 14-ethenomorphinan-7-methanol derivatives (5a–f)

5a: Yield 85%, mp 140–141 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.13–0.95 (m, 5H, cProp), 1.22 (dd, 1H, 8α-H), 1.60 (s, 3H, 20-CH_3), 3.70 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.50 (d, 1H, 5β-H), 4.87 (d, 1H, 19-H), 5.02 (dd, 1H, 18-H), 5.90 (s[a], 1H, 20-OH), 6.40 (d, 1H, 1-H), 6.53 (d, 1H, 2-H), 7.08–7.38 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 499 (17) [M$^+$], 378 (100). $[\alpha]_D^{25}$ −220.9° ($CHCl_3$, *c* 1). $C_{32}H_{37}NO_4$ (499.6) calcd C 76.92; H 7.46; N 2.80; Found C 76.87; H 7.39; N 2.75.

5b: Yield 83%, oil. ^{1}H NMR ($CDCl_3$): δ 1.02 (dd, 1H, 8α-H), 1.48 (s, 3H, 20-CH_3), 3.58 (s, 3H, 6-OCH_3), 3.76 (s, 3H, 3-OCH_3), 4.47 (d, 1H, 5β-H), 4.82 (d, 1H, 19-H), 4.96 (dd, 1H, 18-H), 5.88 (s[a], 1H, 20-OH), 6.42 (d, 1H, 1-H), 6.53 (d, 1H, 2-H), 7.12–7.40 (m, 10H, 20-Ph, Ar). MS (EI 70 eV) *m/z* 458 (100) [M-91]$^+$ $[\alpha]_D^{25}$ −175.0° ($CHCl_3$, *c* 1). $C_{36}H_{39}NO_4$ (549.7).

5c: Yield 74%, mp 120–121 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, 3H, $CH_3CH_2CH_2$), 1.20 (dd, 1H, 8α-H), 1.52 (s, 3H, 20-CH_3), 3.68 (s, 3H, 6-OCH_3), 3.77 (s, 3H, 3-OCH_3), 4.49 (d, 1H, 5β-H), 4.86 (d, 1H, 19-H), 5.00 (dd, 1H, 18-H), 5.82 (s[a], 1H, 20-OH), 6.40 (d, 1H, 1-H), 6.54 (d, 1H, 2-H), 7.10–7.37 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 487 (20) [M$^+$], 366 (100). $[\alpha]_D^{25}$ −252.8° ($CHCl_3$, *c* 1). $C_{31}H_{37}NO_4$ (487.6) calcd C 76.36; H 7.65; N 2.87; Found C 76.40; H 7.74; N 2.94.

5d: Yield 67%, mp 139–140 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.20 (dd, 1H, 8α-H), 1.53 (s, 3H, 20-CH_3), 3.70 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.50 (d, 1H, 5β-H), 4.85 (d, 1H, 19-H), 5.00 (dd, 1H, 18-H), 5.12–5.32 (m, 2H, All), 5.75–5.98 (m, 1H, All), 5.94 (s[a], 1H, 20-OH), 6.42 (d, 1H, 1-H), 6.55 (d, 1H, 2-H), 7.08–7.37 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 485 (15)

[M$^+$], 364 (100). $[\alpha]_D^{25}$ −244.6° ($CHCl_3$, *c* 1). $C_{31}H_{35}NO_4$ (485.6) calcd C 76.67; H 7.26; N 2.88; Found C 76.65; H 7.32; N 2.93.

5e: Yield 68%, mp 169–170 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.17 (dd, 1H, 8α-H), 1.52 (s, 3H, 20-CH_3), 1.68 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 3.70 (s, 3H, 6-OCH_3), 3.76 (s, 3H, 3-OCH_3), 4.48 (d, 1H, 5β-H), 4.85 (d, 1H, 19-H), 4.98 (dd, 1H, 18-H), 5.24 (t, 1H, All), 5.84 (s[a], 1H, 20-OH), 6.42 (d, 1H, 1-H), 6.54 (d, 1H, 2-H), 7.12–7.36 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 513 (30) [M$^+$], 392 (100). $[\alpha]_D^{25}$ −265.0° ($CHCl_3$, *c* 1). $C_{33}H_{39}NO_4$ (513.6) calcd C 77.16; H 7.65; N 2.73; Found C 77.21; H 7.58; N 2.81.

5f: Yield 71%, mp 155–156 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.24 (dd, 1H, 8α-H), 1.52 (s, 3H, 20-CH_3), 2.30 (t, 1H, Prop), 3.34 (d, 2H, Prop), 3.70 (s, 3H, 6-OCH_3), 3.77 (s, 3H, 3-OCH_3), 4.51 (d, 1H, 5β-H), 4.87 (d, 1H, 19-H), 4.98 (dd, 1H, 18-H), 5.96 (s[a], 1H, 20-OH), 6.42 (d, 1H, 1-H), 6.55 (d, 1H, 2-H), 7.08–7.37 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 483 (40) [M$^+$], 362 (100). $[\alpha]_D^{25}$ −239.8° ($CHCl_3$, *c* 1). $C_{31}H_{33}NO_4$ (483.6) calcd C 76.99; H 6.88; N 2.90; Found C 76.87; H 6.91; N 2.95.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*R*)-4,5-Epoxy-α-phenyl-18,19-dihydro-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5m–r)

5m: Yield 70%, mp 143–145 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.10–0.85 (m, 5H, cProp), 1.60 (s, 3H, 20-CH_3), 3.44 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.34 (d, 1H, 5β-H), 6.13 (s[a], 1H, 20-OH), 6.47 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.16–7.62 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 501 (45) [M$^+$], 380 (100). $[\alpha]_D^{25}$ −156.8° ($CHCl_3$, *c* 1). $C_{32}H_{39}NO_4$ (501.6) calcd C 76.62; H 7.84; N 2.79; Found C 76.54; H 7.80; N 2.82.

5n: Yield 80%, oil. ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 3H, 20-CH_3), 3.40 (s, 3H, 6-OCH_3), 3.80 (s, 3H, 3-OCH_3), 4.30 (d, 1H, 5β-H), 6.12 (s[a], 1H, 20-OH), 6.45 (d, 1H, 1-H), 6.63 (d, 1H, 2-H), 7.13–7.57 (m, 10H, 20-Ph, Ar). MS (EI 70 eV) *m/z* 460 (18) [M-91]$^+$, 206 (100). $[\alpha]_D^{25}$ −113.4° ($CHCl_3$, *c* 1). $C_{36}H_{41}NO_4$ (551.7).

5o: Yield 73%, mp 110–111 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, $CH_3CH_2CH_2$), 1.63 (s, 3H, 20-CH_3), 3.45 (s, 3H, 6-OCH_3), 3.85 (s, 3H, 3-OCH_3), 4.36 (d, 1H, 5β-H), 6.14 (s[a], 1H, 20-OH), 6.52 (d, 1H, 1-H), 6.67 (d, 1H, 2-H), 7.18–7.62 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 489 (10) [M$^+$], 460 (100). $[\alpha]_D^{25}$ −166.0° ($CHCl_3$, *c* 1). $C_{31}H_{39}NO_4$ (489.6) calcd C 76.04; H 8.03; N 2.86; Found C 75.98; H 8.12; N 2.92.

5p: Yield 67%, mp 152–153 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H, 20-CH_3), 3.43 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.34 (d, 1H, 5β-H), 5.10–5.28 (m, 2H, All), 5.73–5.96 (m, 1H, All), 6.13 (s[a], 1H, 20-OH), 6.50 (d, 1H, 1-H), 6.66 (d, 1H, 2-H), 7.16–7.62 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 487 (42) [M$^+$], 366 (100). $[\alpha]_D^{25}$ −145.2° ($CHCl_3$, *c* 0.5). $C_{31}H_{37}NO_4$ (487.6) calcd C 76.36; H 7.65; N 2.87; Found C 76.28; H 7.73; N 2.95.

5q: Yield 61%, mp 126–128 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H, 20-CH_3), 1.68 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 3.43 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.34 (d, 1H, 5β-H), 5.22 (t, 1H, All), 6.13 (s[a], 1H, 20-OH), 6.50 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.14–7.60 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 515 (33) [M$^+$], 394 (100). $[\alpha]_D^{25}$ −99.9° (EtOH, *c* 0.5). $C_{33}H_{41}NO_4$ (515.6) calcd C 76.86; H 8.01; N 2.72; Found C 76.78; H 7.96; N 2.76.

5r: Yield 65%, mp 170–171 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H, 20-CH_3), 2.27 (t, 1H, Prop), 3.30 (d, 2H, Prop), 3.43 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.36 (d, 1H, 5β-H), 6.11 (s[a], 1H, 20-OH), 6.49 (d, 1H, 1-H), 6.67 (d, 1H, 2-H), 7.20–7.60 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 499 (25) [M$^+$], 452 (100). $[\alpha]_D^{25}$ −147.5° ($CHCl_3$, *c* 1). $C_{32}H_{37}NO_4$ (499.6) calcd C 76.92; H 7.46; N 2.80; Found C 76.85; H 7.37; N 2.75.

General method for the preparation of (5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*S*)-4,5-epoxy-α-phenyl-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5g–l) and (5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*S*)-4,5-epoxy-α-phenyl-18,19-dihydro-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5s–y) [reaction of *N*-demethyl-N-substituted-thevinone- and dihydrothevinone derivatives with phenylmagnesium bromide]

To a suspension of the Grignard reagent (prepared from 0.52 g of Mg-shavings, and 2.3 mL of freshly distilled bromobenzene in a mixture of 5 mL of abs toluene and 10 mL of abs ether) a soln of the *N*-demethyl-N-substituted derivative (**4g–l** or *N*-demethyl-N-substituted-dihydrothevinone;[7] 3.5 mmol) in abs toluene (18 mL) was added and the reaction mixture stirred under reflux for 1 h. After cooling, it was poured onto 65 mL satd aq NH_4Cl, extracted with toluene (3 × 20 mL), the combined organic layer was washed with satd aq NaCl, and dried (Na_2SO_4). Evapn of the solvent gave a residue, which was crystallized from the appropriate solvent.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*S*)-4,5-Epoxy-α-phenyl-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5g–l)

5g: Yield 67%, mp 159–160 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.35–0.75 (m, 5H, cProp), 1.44 (s, 3H, 20-CH_3), 3.80 (s, 3H, 6-OCH_3), 3.85 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.35 (s[a], 1H, 20-OH), 5.45 (d, 1H, 19-H), 6.03 (dd, 1H, 18-H), 6.47 (d, 1H, 1-H), 6.62 (d, 1H, 2-H), 7.18–7.48 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 499 (32) [M$^+$], 378 (100). $[\alpha]_D^{25}$ −138.1° ($CHCl_3$, *c* 1). $C_{32}H_{37}NO_4$ (499.6).

5h: Yield 74%, mp 162–164 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.57 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.59 (d, 1H, 5β-H), 5.32 (s[a], 1H, 20-OH), 5.43 (d, 1H, 19-H), 6.03 (dd, 1H, 18-H), 6.47 (d, 1H, 1-H), 6.62 (d, 1H, 2-H), 6.98–7.16 (m, 5H, Ar), 7.27–7.50 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 458 (100) [M-91]$^+$, TSP: 550 (100)

$[M+1]^+$. $[\alpha]_D^{25}$ −94.4° ($CHCl_3$, *c* 1). $C_{36}H_{39}NO_4$ (549.7).

5i: Yield 68%, mp 187–188 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 0.57 (dd, 1H, 8α-H), 0.69 (t, 3H, $C\underline{H}_3CH_2CH_2$), 1.43 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.28 (s[a], 1H, 20-OH), 5.43 (d, 1H, 19-H), 6.03 (dd, 1H, 18-H), 6.46 (d, 1H, 1-H), 6.62 (d, 1H, 2-H), 7.15–7.48 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 487 (33) [M^+], 366 (100). $[\alpha]_D^{25}$ −132.7° ($CHCl_3$, *c* 1). $C_{31}H_{37}NO_4$ (487.6).

5j: Yield 69%, mp 202–203 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 0.58 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 3.85 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 4.97–5.14 (m, 2H, All), 5.30 (s[a], 1H, 20-OH), 5.44 (d, 1H, 19-H), 5.52–5.60 (m, 1H, All), 6.04 (dd, 1H, 18-H), 6.49 (d, 1H, 1-H), 6.63 (d, 1H, 2-H), 7.16–7.50 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 485 (22) [M^+], 70 (100). $[\alpha]_D^{25}$ −126.9° ($CHCl_3$, *c* 1). $C_{31}H_{35}NO_4$ (485.6).

5k: Yield 80%, oil. ^1H NMR ($CDCl_3$): δ 0.56 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 1.54 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.80 (s, 3H, 6-OCH_3), 3.84 (s, 3H, 3-OCH_3), 4.58 (d, 1H, 5β-H), 5.00 (t, 1H, All), 5.32 (s[a], 1H, 20-OH), 5.43 (d, 1H, 19-H), 6.02 (dd, 1H, 18-H), 6.47 (d, 1H, 1-H), 6.62 (d, 1H, 2-H), 7.07–7.63 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 513 (3) [M^+], 344 (100). $[\alpha]_D^{25}$ −88.2° ($CHCl_3$, *c* 1). $C_{33}H_{39}NO_4$ (513.6).

5l: Yield 73%, mp 260–261 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 0.63 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 2.17 (t, 1H, Prop), 3.25 (d, 2H, Prop), 3.82 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.60 (d, 1H, 5β-H), 5.32 (s[a], 1H, 20-OH), 5.47 (d, 1H, 19-H), 6.04 (dd, 1H, 18-H), 6.49 (d, 1H, 1-H), 6.63 (d, 1H, 2-H), 7.18–7.48 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 483 (15) [M^+], 68 (100). $[\alpha]_D^{25}$ −119.8° ($CHCl_3$, *c* 1). $C_{31}H_{33}NO_4$ (483.6).

(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*S*)-4,5-epoxy-α-phenyl-18,19-dihydro-3,6-dimethoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives (5s–y)

5s: Yield 72%, mp 159–160 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 0.35–0.75 (m, 5H, cProp), 1.80 (s, 3H, 20-CH_3), 3.62 (s, 3H, 6-OCH_3), 3.91 (s, 3H, 3-OCH_3), 4.44 (d, 1H, 5β-H), 5.54 (s[a], 1H, 20-OH), 6.53 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 7.22–7.58 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 501 (48) [M^+], 380 (100). $[\alpha]_D^{25}$ −71.1° ($CHCl_3$, *c* 0.5). $C_{32}H_{39}NO_4$ (501.6).

5t: Yield 74%, mp 185–187 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.82 (s, 3H, 20-CH_3), 3.63 (s, 3H, 6-OCH_3), 3.90 (s, 3H, 3-OCH_3), 4.46 (d, 1H, 5β-H), 5.57 (s[a], 1H, 20-OH), 6.55 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 6.98–7.22 (m, 5H, Ar), 7.28–7.60 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 551 (2) [M^+], 460 (100). $[\alpha]_D^{25}$ −57.4° ($CHCl_3$, *c* 0.5). $C_{36}H_{41}NO_4$ (551.7).

5v: Yield 68%, mp 132–133 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 0.63 (t, 3H, $C\underline{H}_3CH_2CH_2$), 1.80 (s, 3H, 20-CH_3), 3.61 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.43 (d, 1H, 5β-H), 5.52 (s[a], 1H, 20-OH), 6.53 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 7.16–7.55 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 489 (10) [M^+], 460 (100). $[\alpha]_D^{25}$ −63.4° ($CHCl_3$, *c* 0.5). $C_{31}H_{39}NO_4$ (489.6).

5w: Yield 70%, mp 170–171 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 3.60 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.43 (d, 1H, 5β-H), 4.93–5.08 (m, 2H, All), 5.43–5.67 (m, 1H, All), 5.52 (s[a], 1H, 20-OH), 6.53 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 7.20–7.55 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 487 (33) [M^+], 121 (100). $[\alpha]_D^{25}$ −36.0° ($CHCl_3$, *c* 0.1). $C_{31}H_{37}NO_4$ (487.6).

5x: Yield 82%, oil. ^1H NMR ($CDCl_3$): δ 1.47 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.80 (s, 3H, 20-CH_3), 3.60 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.42 (d, 1H, 5β-H), 4.94 (t, 1H, All), 5.52 (s[a], 1H, 20-OH), 6.54 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.23–7.65 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 515 (40) [M^+], 393 (100). $[\alpha]_D^{25}$ −56.5° ($CHCl_3$, *c* 0.1). $C_{33}H_{41}NO_4$ (515.6).

5y: Yield 65%, mp 205–206 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.78 (s, 3H, 20-CH_3), 2.14 (t, 1H, Prop), 3.16 (d, 2H, Prop), 3.60 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.44 (d, 1H, 5β-H), 5.52 (s[a], 1H, 20-OH), 6.53 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.22–7.55 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 485 (80) [M^+], 452 (100). $[\alpha]_D^{25}$ −119.0° ($CHCl_3$, *c* 0.1). $C_{31}H_{35}NO_4$ (485.6).

Preparation of compounds **7a–d** from the corresponding ketones (**3a–d**) with phenylmagnesium bromide or methylmagnesium iodide was accomplished as described above in the general procedures.

7a: Yield 78%, mp 147–148 °C [EtOH] (Lit.[3] mp: 152 °C). ^1H NMR ($CDCl_3$): δ 1.25 (dd, 1H, 8α-H), 1.53 (s, 3H, 20-CH_3), 2.37 (s, 3H, NCH_3), 3.72 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.52 (d, 1H, 5β-H), 4.87 (d, 1H, 19-H), 5.02 (dd, 1H, 18-H), 5.86 (s[a], 1H, 20-OH), 6.43 (d, 1H, 1-H), 6.56 (d, 1H, 2-H), 7.08–7.37 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 459 (25) [M^+], 164 (100). $[\alpha]_D^{25}$ −235.3° ($CHCl_3$, *c* 1). $C_{29}H_{33}NO_4$ (459.6). By column chromatography of the mother liquor 5% of **7b** could be isolated.

7b: Yield 76%, mp 213–214 °C [EtOH] (Lit.[3] mp: 208 °C). ^1H NMR ($CDCl_3$): δ 0.62 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 2.22 (s, 3H, NCH_3), 3.83 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.60 (d, 1H, 5β-H), 5.34 (s[a], 1H, 20-OH), 5.47 (d, 1H, 19-H), 6.05 (dd, 1H, 18-H), 6.52 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 7.20–7.50 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 459 (40) [M^+], 164 (100). $[\alpha]_D^{25}$ −134.5° ($CHCl_3$, *c* 1). $C_{29}H_{33}NO_4$ (459.6).

7c: Yield 72%, mp 173–174 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.62 (s, 3H, 20-CH_3), 2.34 (s, 3H, NCH_3), 3.44 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 4.35 (d, 1H, 5β-H), 6.14 (s[a], 1H, 20-OH), 6.50 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 7.18–7.58 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 461 (44) [M^+], 340 (100). $[\alpha]_D^{25}$ −121.1° ($CHCl_3$, *c* 1). $C_{29}H_{35}NO_4$ (461.6) calcd C 75.46; H 7.64; N 3.03; Found C 75.38; H 7.70; N 2.95.

7d: Yield 79%, mp 203–204 °C [EtOH] (Lit.[3] mp: 202 °C). ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 2.14 (s, 3H, NCH_3), 3.60 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.44 (d, 1H, 5β-H), 5.54 (s[a], 1H, 20-OH), 6.55 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 7.20–7.56 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 461 (71) [M^+], 340 (100). $[\alpha]_D^{25}$ −72.6° ($CHCl_3$, *c* 1). $C_{29}H_{35}NO_4$ (461.6).

General method for the reaction of compounds 7a–d with cyanogen bromide

Compounds **7a–d** (50 mmol) were dissolved in 100 mL of $CHCl_3$ (previously dried over $CaCl_2$), 10 g cyanogen bromide was added and the reaction mixture heated under reflux for 10 h. The excess of the reagent and the solvent were removed by evapn under diminished pressure, the residue was taken up with EtOH (150 mL) and the resulting solution evapd to its half-volume. The product (**8a–d**) crystallized from the solution upon cooling was filtered off and dried.

8a: Yield 90%, mp 205–206 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.38 (dd, 1H, 8α-H), 1.54 (s, 3H, 20-CH_3), 3.70 (s, 3H, 6-OCH_3), 3.78 (s, 3H, 3-OCH_3), 4.49 (d, 1H, 5β-H), 4.80 (d, 1H, 19-H), 5.11 (dd, 1H, 18-H), 5.67 (s[a], 1H, 20-OH), 6.47 (d, 1H, 1-H), 6.60 (d, 1H, 2-H), 7.10–7.35 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 470 (12) [M^+], 121 (100). $[\alpha]_D^{25}$ −295.0° ($CHCl_3$, *c* 1). $C_{29}H_{30}N_2O_4$ (470.5).

8b: Yield 93%, mp 258–259 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.74 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 3.83 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.60 (d, 1H, 5β-H), 5.17 (s[a], 1H, 20-OH), 5.40 (d, 1H, 19-H), 6.13 (dd, 1H, 18-H), 6.54 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 7.23–7.48 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 470 (23) [M^+], 121 (100). $[\alpha]_D^{25}$ −119.8° ($CHCl_3$, *c* 0.5). $C_{29}H_{30}N_2O_4$ (470.5).

8c: Yield 92%, mp 218–219 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.64 (s, 3H, 20-CH_3), 3.48 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.37 (d, 1H, 5β-H), 5.95 (s[a], 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.74 (d, 1H, 2-H), 7.20–7.60 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 472 (8) [M^+], 121 (100). $[\alpha]_D^{25}$ −130.6° ($CHCl_3$, *c* 1). $C_{29}H_{32}N_2O_4$ (472.5).

8d: Yield 94%, mp 222–224 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 3.42 (s, 3H, 6-OCH_3), 3.90 (s, 3H, 3-OCH_3), 4.43 (d, 1H, 5β-H), 5.37 (s[a], 1H, 20-OH), 6.62 (d, 1H, 1-H), 6.76 (d, 1H, 2-H), 7.23–7.53 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 472 (12) [M^+], 121 (100). $[\alpha]_D^{25}$ −73.7° ($CHCl_3$, *c* 1). $C_{29}H_{32}N_2O_4$ (472.5).

General method for the hydrolysis of compounds 8a–d

Potassium hydroxide (4.6 g) was dissolved in diethylene glycol (32 mL) at 105 °C, the solution cooled to 70 °C, and a suspension of the cyanoamide **8a–d** (10.6 mmol) in diethylene glycol (32 mL) added. The reaction mixture was stirred vigorously at 170 °C for 75 min, cooled, poured into 300 mL of ice-water and stirred for 30 min. The crystalline precipitate (**9a–d**) was filtered off, dried in a vacuum desiccator over $CaCl_2$, and purified by precipitating from a $CHCl_3$ solution with ethanol.

9a: Yield 90%, mp 208–210 °C [$CHCl_3$–EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.22 (dd, 1H, 8α-H), 1.57 (s, 3H, 20-CH_3), 3.68 (s, 3H, 6-OCH_3), 3.79 (s, 3H, 3-OCH_3), 4.00 (s[a], 1H, NH), 4.56 (d, 1H, 5β-H), 4.83 (d, 1H, 19-H), 5.13 (dd, 1H, 18-H), 5.73 (s[a], 1H, 20-OH), 6.50 (d, 1H, 1-H), 6.63 (d, 1H, 2-H), 7.13–7.40 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 445 (26) [M^+], 121 (100). $[\alpha]_D^{25}$ −187.3° (EtOH, *c* 0.1). $C_{28}H_{31}NO_4$ (445.5).

9b: Yield 90%, mp 254–255 °C [$CHCl_3$–EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.63 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.57 (d, 1H, 5β-H), 5.29 (s[a], 1H, 20-OH), 5.42 (d, 1H, 19-H), 6.08 (dd, 1H, 18-H), 6.50 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 7.18–7.48 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 445 (15) [M^+], 121 (100). $[\alpha]_D^{25}$ −114.9° ($CHCl_3$, *c* 1). $C_{28}H_{31}NO_4$ (445.5).

9c: Yield 92%, mp 128–130 °C [$CHCl_3$–EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3H, 20-CH_3), 3.42 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.32 (d, 1H, 5β-H), 6.07 (s[a], 1H, 20-OH), 6.52 (d, 1H, 1-H), 6.67 (d, 1H, 2-H), 7.15–7.58 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 447 (45) [M^+], 414 (100). $[\alpha]_D^{25}$ −89.2° ($CHCl_3$, *c* 0.5). $C_{28}H_{33}NO_4$ (447.5).

9d: Yield 94%, mp 229–230 °C [$CHCl_3$–EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 3.60 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.39 (d, 1H, 5β-H), 5.53 (s[a], 1H, 20-OH), 6.56 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.20–7.57 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 447 (32) [M^+], 121 (100). $[\alpha]_D^{25}$ −46.0° ($CHCl_3$, *c* 1). $C_{28}H_{33}NO_4$ (447.5).

For the preparation of **10a–d** the 3-O-demethylation procedure described for **6a–c** (vide infra) was applied, and the progress of the reaction was monitored by TLC. O-Demethylation proceeded following the hydrolysis of the cyanoamide, and a complete conversion was observed in ca 70–75 min reaction time.

10a: Yield 64%, mp 294–295 °C [$CHCl_3$–EtOH]. ^{1}H NMR (DMSO-d_6): δ 1.03 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 3.10 (s, 3H, 6-OCH_3), 4.44 (d, 1H, 5β-H), 4.70 (s[a], 1H, 20-OH), 5.10 (d, 1H, 19-H), 5.38 (dd, 1H, 18-H), 6.28 (d, 1H, 1-H), 6.40 (d, 1H, 2-H), 7.10–7.48 (m, 5H, 20Ph), 8.74 (s[a], 1H, 3-OH). MS (EI 70 eV) *m/z* 431 (18) [M^+], 121 (100). $[\alpha]_D^{25}$ −213.9° (EtOH, *c* 0.1). $C_{27}H_{29}NO_4$ (431.5).

10b: Yield 66%, mp 295–297 °C [$CHCl_3$–EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.62 (dd, 1H, 8α-H), 1.43 (s, 3H, 20-CH_3), 3.80 (s, 3H, 6-OCH_3), 4.56 (d, 1H, 5β-H), 5.22 (s[a], 1H, 20-OH), 5.40 (d, 1H, 19-H), 6.03 (dd, 1H, 18-H), 6.45 (d, 1H, 1-H), 6.60 (d, 1H, 2-H), 7.27–7.46 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 431 (30) [M^+], 121 (100). $[\alpha]_D^{25}$ −258.0° (EtOH, *c* 0.1). $C_{27}H_{29}NO_4$ (431.5).

10d: Yield 62%, mp 308–310 °C [$CHCl_3$–EtOH]. ^1H NMR (DMSO-d_6): δ 1.62 (s, 3H, 20-CH_3), 3.05 (s, 3H, 6-OCH_3), 4.28 (d, 1H, 5β-H), 5.04 (s[a], 1H, 20-OH), 6.38 (d, 1H, 1-H), 6.56 (d, 1H, 2-H), 7.12–7.54 (m, 5H, 20Ph), 8.93 (s[a], 1H, 3-OH). MS (EI 70 eV) *m/z* 433 (12) [M^+], 105 (100). $[\alpha]_D^{25}$ −12.6° (EtOH, *c* 0.1). $C_{27}H_{31}NO_4$ (433.5).

For the preparation of **11a–d** the O-demethylation procedure described for **6a–c** (vide infra) was employed and the progress of the reaction monitored by TLC.

11a: Yield 50%, mp 104–105 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.25 (dd, 1H, 8α-H), 1.52 (s, 3H, 20-CH_3), 2.37 (s, 3H, NCH_3), 3.70 (s, 3H, 6-OCH_3), 4.52 (d, 1H, 5β-H), 4.70 (s[a], 1H, 3-OH), 4.85 (d, 1H, 19-H), 4.97 (dd, 1H, 18-H), 5.80 (s[a], 1H, 20-OH), 6.38 (d, 1H, 1-H), 6.53 (d, 1H, 2-H), 7.14–7.45 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 445 (100) [M^+]. $[\alpha]_D^{25}$ −218.0° (EtOH, *c* 0.1). $C_{28}H_{31}NO_4$ (445.5).

11b: Yield 56%, mp 260–261 °C [EtOH]. (Lit.[2] mp: 252 °C). ^1H NMR ($CDCl_3$): δ 0.63 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 2.23 (s, 3H, NCH_3), 3.83 (s, 3H, 6-OCH_3), 4.62 (d, 1H, 5β-H), 4.73 (s[a], 1H, 3-OH), 5.30 (s[a], 1H, 20-OH), 5.46 (d, 1H, 19-H), 6.02 (dd, 1H, 18-H), 6.47 (d, 1H, 1-H), 6.60 (d, 1H, 2-H), 7.18–7.47 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 445 (33) [M^+], 121 (100). $[\alpha]_D^{25}$ −111.8° ($CHCl_3$, *c* 1). $C_{28}H_{31}NO_4$ (445.5).

11c: Yield 25%, mp 238–240 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.58 (s, 3H, 20-CH_3), 2.32 (s, 3H, NCH_3), 3.43 (s, 3H, 6-OCH_3), 4.36 (d, 1H, 5β-H), 4.66 (s[a], 1H, 3-OH), 6.07 (s[a], 1H, 20-OH), 6.45 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 7.17–7.58 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 447 (32) [M^+], 105 (100). $[\alpha]_D^{25}$ −136.4° (EtOH, *c* 0.1). $C_{28}H_{33}NO_4$ (447.5).

11d: Yield 58%, mp 243–245 °C [EtOH]. ^1H NMR ($CDCl_3$): δ 1.78 (s, 3H, 20-CH_3), 2.14 (s, 3H, NCH_3), 3.57 (s, 3H, 6-OCH_3), 4.45 (d, 1H, 5β-H), 4.68 (s[a], 1H, 3-OH), 5.45 (s[a], 1H, 20-OH), 6.52 (d, 1H, 1-H), 6.69 (d, 1H, 2-H), 7.21–7.55 (m, 5H, 20Ph). MS (EI 70 eV) *m/z* 447 (25) [M^+], 121 (100). $[\alpha]_D^{25}$ −73.9° (EtOH, *c* 0.1). $C_{28}H_{33}NO_4$ (447.5).

General method for the preparation of compounds 6a–c, g–i, and s–v

Potassium hydroxide (3.9 g) was dissolved at 105 °C in 32 mL diethylene glycol under a nitrogen atmosphere. The solution was cooled to 70 °C and a suspension of the aryl-methyl ether (**5a–c**, **g–i**, and **s–v**; 2.6 mmol) in diethylene glycol (4 mL) added. The temperature of the reaction mixture was raised to 210–220 °C and stirred for 90 min. After cooling it was poured into 150 mL satd aq NH_4Cl, extracted with ether (3 × 50 mL), dried (Na_2SO_4) and concd. The residue was dissolved in hot EtOH, the solution decolorized with charcoal, filtered and the pH adjusted to 2 with satd HCl/EtOH. The produced hydrochloride salt was filtered off.

General method for the preparation of compounds 6d–f, j–l, and w–y

To a soln of the N-demethyl derivative **10a**, **b**, or **d** (3.5 mmol) in abs. DMF (9 mL) $NaHCO_3$ (1.10 g) and 3.85 mmol of the alkylating agent (allyl bromide, 3,3-dimethylallyl bromide and propargyl bromide) were added and the reaction mixture stirred at 90 °C (oil-bath) for 20 h. After filtration of the inorganic salts the solvent was distilled off under reduced pressure, the residue suspended in water, alkalized with 25% aq NH_4OH and extracted with $CHCl_3$. The combined organic layer was washed with water, dried (Na_2SO_4) and concd. The residue was crystallized from the appropriate solvent, or isolated in form of the hydrochloride salt.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*R*)-4,5-Epoxy-α-phenyl-3-hydroxy-6-methoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives

6a: Yield 52%, mp 238–240 °C [HCl] [EtOH]. ^1H NMR ($CDCl_3$): δ 0.10–0.95 (m, 5H, cProp), 1.22 (dd, 1H, 8α-H), 1.53 (s, 3H, 20-CH_3), 3.68 (s, 3H, 6-OCH_3), 4.53 (d, 1H, 5β-H), 4.87 (d, 1H, 19-H), 4.94 (dd, 1H, 18-H), 4.97 (s[a], 1H, 3-OH), 5.86 (s[a], 1H, 20-OH), 6.35 (d, 1H, 1-H), 6.52 (d, 1H, 2-H), 7.08–7.36 (m, 5H, 20-Ph). MS (TSP) *m/z* 486 (100) $[M+1]^+$. $[\alpha]_D^{25}$ −289.0° ($CHCl_3$, *c* 0.1). $C_{31}H_{35}NO_4$ (485.6) calcd [HCl] C 71.32; H 6.95; N 2.68; Found C 71.25; H 6.88; N 2.61.

6b: Yield 60%, mp 254–255 °C [HCl] [EtOH]. ^1H NMR ($CDCl_3$): δ 1.02 (dd, 1H, 8α-H), 1.47 (s, 3H, 20-CH_3), 3.65 (s, 3H, 6-OCH_3), 4.48 (d, 1H, 5β-H), 4.67 (s[a], 1H, 3-OH), 4.81 (d, 1H, 19-H), 4.93 (dd, 1H, 18-H), 5.82 (s[a], 1H, 20-OH), 6.36 (d, 1H, 1-H), 6.52 (d, 1H, 2-H), 7.10–7.40 (m, 10H, 20-Ph, Ar). MS (EI 70 eV) *m/z* 535 (4) [M^+], 444 (100). $[\alpha]_D^{25}$ −155.1° (EtOH, *c* 0.1). $C_{35}H_{37}NO_4$ (535.6) calcd [HCl]: C 73.48; H 6.69; N 2.45; Found C 73.35; H 6.61; N 2.50.

6c: Yield 58%, mp 266–267 °C [HCl] [EtOH]. ^1H NMR (DMSO-d_6): δ 0,85 (t, 3H, $CH_3CH_2CH_2$), 1,42 (s, 3H, 20-CH_3), 3.34 (s, 3H, 6-OCH_3), 4.48 (d, 1H, 5β-H), 4.73 (s[a], 1H, 20-OH), 5.17 (d, 1H, 19-H), 5.38 (dd, 1H, 18-H), 6.30 (d, 1H, 1-H), 6.41 (d, 1H, 2-H), 7.08–7.50 (m, 5H, 20-Ph), 8.73 (s[a], 1H, 3-OH). MS (EI 70 eV) *m/z* 473 (68) [M^+], 352 (100). $[\alpha]_D^{25}$ −249.6° ($CHCl_3$, *c* 0.5). $C_{30}H_{35}NO_4$ (473.6) calcd [HCl] C 70.64; H 7.11; N 2.75; Found C 70.50; H 7.13; N 2.78.

6d: Yield 65%, mp 243–245 °C [HCl] [EtOH]. ^1H NMR ($CDCl_3$): δ 1.20 (dd, 1H, 8α-H), 1.53 (s, 3H, 20-CH_3), 3.65 (s, 3H, 6-OCH_3), 4.51 (d, 1H, 5β-H), 4.67 (s[a], 1H, 3-OH), 4.84 (d, 1H, 19-H), 4.96 (dd, 1H, 18-H), 5.12–5.30 (m, 2H, All), 5.75–6.00 (m, 1H, All), 5.88 (s[a], 1H, 20-OH), 6.38 (d, 1H, 1-H), 6.52 (d, 1H, 2-H), 7.10–7.40 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 471 (10) [M^+], 241 (100). $[\alpha]_D^{25}$ −36.7° (EtOH, *c* 0.1). $C_{30}H_{33}NO_4$ (471.6) calcd [HCl] C 70.92; H 6.75; N 2.76; Found C 70.95; H 6.82; N 2.70.

6e: Yield 68%, mp 192–194 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.20 (dd, 1H, 8α-H), 1.25 (s, 3H, CH_3), 1.52 (s, 3H, 20-CH_3), 1.80 (s, 3H, CH_3), 3.68 (s, 3H, 6-OCH_3), 4.53 (d, 1H, 5β-H), 4.70 (s[a], 1H, 3-OH), 4.85 (d, 1H, 19-H), 4.97 (dd, 1H, 18-H), 5.23 (t, 1H, All), 5.80 (s[a], 1H, 20-OH), 6.38 (d, 1H, 1-H), 6.53 (d, 1H, 2-H), 7.12–7.40 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 499 (80) [M^+], 378 (100). $[\alpha]_D^{25}$ −50.5° (EtOH, *c* 0.1). $C_{32}H_{37}NO_4$ (499.6) calcd [HCl] C 71.69; H 7.14; N 2.61; Found C 71.57; H 7.20; N 2.64.

6f: Yield 74%, mp 148–149 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.20 (dd, 1H, 8α-H), 1.50 (s, 3H, 20-CH_3), 2.30 (t, 1H, Prop), 3.34 (d, 2H, Prop), 3.67 (s, 3H, 6-OCH_3), 4.52 (d, 1H, 5β-H), 4.60 (s[a], 1H, 3-OH), 4.88 (d, 1H, 19-H), 4.98 (dd, 1H, 18-H), 5.80 (s[a], 1H, 20-OH), 6.38 (d, 1H, 1-H), 6.53 (d, 1H, 2-H), 7.12–7.40 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 469 (25) [M^+], 89 (100). $[\alpha]_D^{25}$ −265.0° ($CHCl_3$, *c* 0.1). $C_{30}H_{31}NO_4$ (469.5) calcd C 76.73; H 6.65; N 2.98; Found C 76.68; H 6.70; N 3.03.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*R*,20*S*)-17-Substituted-4,5-epoxy-α-phenyl-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol derivatives

6g: Yield 63%, mp 257–258 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.40–0.95 (m, 5H, cProp), 0.65 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 4.50 (s[a], 1H, 3-OH), 4.62 (d, 1H, 5β-H), 5.26 (s[a], 1H, 20-OH), 5.45 (d, 1H, 19-H), 6.02 (dd, 1H, 18-H), 6.43 (d, 1H, 1-H), 6.58 (d, 1H, 2-H), 7.20–7.47 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 485 (46) [M^+], 364 (100). $[\alpha]_D^{25}$ −73.0° (EtOH, *c* 0.1). $C_{31}H_{35}NO_4$ (485.6) calcd [HCl] C 71.32; H 6.95; N 2.68; Found C 71.35; H 6.87; N 2.73.

6h: Yield 62%, mp 252–253 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.55 (dd, 1H, 8α-H), 1.44 (s, 3H, 20-CH_3), 3.80 (s, 3H, 6-OCH_3), 4.60 (d, 1H, 5β-H), 5.20 (s[a], 1H, 3-OH), 5.37 (s[a], 1H, 20-OH), 5.42 (d, 1H, 19-H), 5.98 (dd, 1H, 18-H), 6.42 (d, 1H, 1-H), 6.54 (d, 1H, 2-H), 6.95–7.15 (m, 5H, Ar), 7.20–7.50 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 444 (100) [M-91]$^+$ $[\alpha]_D^{25}$ −92.2° (EtOH, *c* 0.1). $C_{35}H_{37}NO_4$ (535.6) calcd [HCl] C 73.48; H 6.69; N 2.45; Found C 73.45; H 6.75; N 2.53.

6i: Yield 54%, mp 255–256 °C [HCl] [EtOH]. ^{1}H NMR (DMSO-d_6): δ 0.86 (t, 3H, $CH_3CH_2CH_2$), 1.38 (s, 3H, 20-CH_3), 3.55 (s, 3H, 6-OCH_3), 4.76 (d, 1H, 5β-H), 5.33 (d, 1H, 19-H), 5.84 (dd, 1H, 18-H), 6.42 (d, 1H, 1-H), 6.56 (d, 1H, 2-H), 7.15–7.48 (m, 5H, 20-Ph), 8.45 (s[a], 1H, 20-OH), 9.10 (s[a], 1H, 3-OH). MS (EI 70 eV) *m/z* 473 (90) [M^+], 352 (100). $[\alpha]_D^{25}$ −103.3° (EtOH, *c* 0.1). $C_{30}H_{35}NO_4$ (473.6) calcd [HCl] C 70.64; H 7.11; N 2.75; Found C 70.57; H 7.20; N 2.84.

6j: Yield 52%, mp 230–232 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.58 (dd, 1H, 8α-H), 1.58 (s, 3H, 20-CH_3), 3.82 (s, 3H, 6-OCH_3), 4.50 (s[a], 1H, 3-OH), 4.62 (d, 1H, 5β-H), 5.00–5.15 (m, 2H, All), 5.25 (s[a], 1H, 20-OH), 5.42 (d, 1H, 19-H), 5.50–5.70 (m, 1H, All), 6.00 (dd, 1H, 18-H), 6.44 (d, 1H, 1-H), 6.61 (d, 1H, 2-H), 7.20–7.45 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 471 (58) [M^+], 241 (100). $[\alpha]_D^{25}$ −100.0° (EtOH, *c* 0.1). $C_{30}H_{33}NO_4$ (471.6) calcd C 76.41; H 7.05; N 2.97; Found C 76.48; H 7.13; N 2.89.

6k: Yield 64%, mp 219–220 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.55 (dd, 1H, 8α-H), 1.42 (s, 3H, 20-CH_3), 1.53 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.80 (s, 3H, 6-OCH_3), 4.55 (s[a], 1H, 3-OH), 4.60 (d, 1H, 5β-H), 4.98 (t, 1H, All), 5.24 (s[a], 1H, 20-OH), 5.43 (d, 1H, 19-H), 5.98 (dd, 1H, 18-H), 6.44 (d, 1H, 1-H), 6.58 (d, 1H, 2-H), 7.18–7.47 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 449 (100) [M^+]. $[\alpha]_D^{25}$ −117.2° ($CHCl_3$, *c* 1). $C_{32}H_{37}NO_4$ (499.6) calcd C 76.92; H 7.46; N 2.80; Found C 76.95; H 7.53; N 2.89.

6l: Yield 62%, mp 250–251 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.62 (dd, 1H, 8α-H), 1.42 (s, 3H, 20-CH_3), 2.16 (t, 1H, Prop), 3.24 (d, 2H, Prop), 3.82 (s, 3H, 6-OCH_3), 4.61 (d, 1H, 5β-H), 4.70 (s[a], 1H, 3-OH), 5.25 (s[a], 1H, 20-OH), 5.44 (d, 1H, 19-H), 6.02 (dd, 1H, 18-H), 6.44 (d, 1H, 1-H), 6.60 (d, 1H, 2-H), 7.22–7.47 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 469 (100) [M^+]. $[\alpha]_D^{25}$ −99.6° (EtOH, *c* 0.1). $C_{30}H_{31}NO_4$ (469.5) calcd C 76.73; H 6.65; N 2.98; Found C 76.65; H 6.71; N 3.07.

(5*R*,6*R*,7*R*,9*R*,13*S*,14*S*,20*S*)-4,5-Epoxy-α-phenyl-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-17-substituted-6,14-ethenomorphinan-7-methanol derivatives

6s: Yield 58%, mp 262–263 °C [HCl] [EtOH]. ^{1}H NMR (DMSO-d_6) [HCl]: δ 0.32–0.84 (m, 5H, cProp), 1.52 (s, 3H, 20-CH_3), 3.45 (s, 3H, 6-OCH_3), 4.46 (d, 1H, 5β-H), 4.54 (s[a], 1H, 3-OH), 5.03 (s[a], 1H, 20-OH), 6.51 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 7.08–7.58 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 487 (61) [M^+], 366 (100). $[\alpha]_D^{25}$ −76.5° (EtOH, *c* 0.1). $C_{31}H_{37}NO_4$ (487.6) calcd [HCl] C 71.04; H 7.31; N 2.67; Found C 71.17; H 7.34; N 2.75.

6t: Yield 61%, mp 264–265 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 3.58 (s, 3H, 6-OCH_3), 4.47 (d, 1H, 5β-H), 4.83 (s[a], 1H, 3-OH), 5.48 (s[a], 1H, 20-OH), 6.49 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 6.95–7.20 (m, 5H, Ar), 7.25–7.58 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 537 (3) [M^+], 446 (100). $[\alpha]_D^{25}$ −67.1° (EtOH, *c* 0.1). $C_{35}H_{39}NO_4$ (537.7) calcd [HCl] C 73.22; H 7.02; N 2.44; Found C 73.15; H 7.10; N 2.51.

6v: Yield 42%, mp 253–255 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.63 (t, 3H, $CH_3CH_2CH_2$), 1.80 (s, 3H, 20-CH_3), 3.57 (s, 3H, 6-OCH_3), 4.46 (d, 1H, 5β-H), 4.64 (s[a], 1H, 3-OH), 5.42 (s[a], 1H, 20-OH), 6.50 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 7.18–7.54 (m, 5H, 20-Ph). MS (TSP) *m/z* 476 (100) [M+1]$^+$ $[\alpha]_D^{25}$ −31.5° (EtOH, *c* 0.1). $C_{30}H_{37}NO_4$ (475.6) calcd [HCl] C 70.36; H 7.48; N 2.74; Found C 70.25; H 7.39; N 2.80.

6w: Yield 58%, mp 259–260 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, 20-CH_3), 3.58 (s, 3H, 6-OCH_3), 4.45 (d, 1H, 5β-H), 4.82 (s[a], 1H, 3-OH),

4.93–5.10 (m, 2H, All), 5.45 (s[a], 1H, 20-OH), 5.50–5.65 (m, 1H, All), 6.50 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 7.18–7.55 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 473 (50) [M^+], 352 (100). $[\alpha]_D^{25}$ −74.4° (EtOH, *c* 0.1). $C_{30}H_{35}NO_4$ (473.6) calcd [HCl] C 70.64; H 7.11; N 2.75; Found C 70.57; H 7.15; N 2.81.

6x: Yield 61%, mp 239–240 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.78 (s, 3H, 20-CH_3), 3.55 (s, 3H, 6-OCH_3), 4.45 (d, 1H, 5β-H), 4.90 (s[a], 1H, 3-OH), 5.02 (t, 1H, All), 5.45 (s[a], 1H, 20-OH), 6.51 (d, 1H, 1-H), 6.71 (d, 1H, 2-H), 7.23–7.56 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 501 (60) [M^+], 380 (100). $[\alpha]_D^{25}$ −45.0° ($CHCl_3$, *c* 0.1). $C_{32}H_{39}NO_4$ (501.6) calcd [HCl] C 71.42; H 7.49; N 2.60; Found C 71.46; H 7.54; N 2.69.

6y: Yield 75%, mp 104–105 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 3H, 20-CH_3), 2.13 (t, 1H, Prop), 3.14 (d, 2H, Prop), 3.55 (s, 3H, 6-OCH_3), 4.44 (d, 1H, 5β-H), 4.80 (s[a], 1H, 3-OH), 5.48 (s[a], 1H, 20-OH), 6.48 (d, 1H, 1-H), 6.67 (d, 1H, 2-H), 7.22–7.45 (m, 5H, 20-Ph). MS (EI 70 eV) *m/z* 471 (45) [M^+], 459 (100). $[\alpha]_D^{25}$ −70.0° (EtOH, *c* 0.1). $C_{30}H_{33}NO_4$ (471.6) calcd [HCl] C 70.92; H 6.75; N 2.76; Found C 70.90; H 6.71; N 2.65.

12a: Compound **5c** (0.2 g, 0.4 mmol) was heated under reflux with 2 mL of 98% formic acid[9] for 3 h. The reaction mixture was cooled to room temperature and then alkalized with 25% aq NH_4OH with external cooling in an ice-water bath. Yield 0.15 g (82%), mp 78–80 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, $CH_3CH_2CH_2$), 1.52 (m, 2H, $CH_3CH_2CH_2$), 1.62 (m, 1H, 15-H), 2.01 (s, 3H, CH_3), 2.26 (m, 2H, $CH_3CH_2CH_2$), 2.34–2.55 (m, 3H, 15-H, 16-H, 10α-H), 2.82 (m, 0.5H, $CH_2C=$), 3.12 (d, 1H, 10β-H), 3.18 (d, 1H, 9α-H), 3.42 (m, 0.5H, $CH_2C=$), 3.83 (s, 3H, 3-OCH_3), 4.70 (s, 1H, 5β-H), 5.62 (t, 1H, $CH_2CH=C(CH_3)Ph$), 6.12 (d, 1H, 8-H), 6.57 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 6.68 (d, 1H, 7-H), 7.17–7.38 (m, 5H, 20-Ph). ^{13}C NMR 11.73 (CH_3), 16.62 ($=C(Ph)CH_3$), 20.69 (CH_2), 22.76 (C-10), 28.71 (C-15), 34.78 (CH_2-CH=), 44.05 (C-16), 45.26 (C-14), 46.42 (C-13), 56.55 (N-CH_2), 56.93 (OCH_3), 59.92 (C-9), 88.31 (C-5), 114.92 (C-2), 119.67 (C-1), 121.76 (CH), 125.09 (C-11), 131.93 (C-12), 132.66 (C-7), 139.78 (>C=), 143.72 (C-3), 144.44 (C-4), 153.77 (C-8), 194.27 (C-6), aromatic: 125.71; 127.18; 128.47; 144.44. MS (EI 70 eV) *m/z* 455 (75) [M^+], 426 (100). $C_{30}H_{33}NO_3$ (455.6).

12b: 3-O-Demethylation of **5a** with KOH/diethylene glycol (2 h) afforded **12b**. Yield 50%, mp 163–164 °C [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.17 (m, 2H, cPropCH$_2$syn), 0.56 (m, 2H, cPropCH$_2$anti), 0.89 (m, 1H, cPropCH), 1.62 (m, 1H, 15-H), 2.02 (s, 3H, NCH_3), 2.24 (m, 2H, NCH_2), 2.28–2.40 (m, 2H, 15-H, 16-H), 2.50 (dd, 1H, 10α-H), 2.85 (m, 1H, 16-H), 2.93 (m, 1H, CH_2-CH=), 3.08 (d, 1H, 10β-H), 3.32 (m, 1H, CH_2-CH=), 3.42 (d, 1H, 9α-H), 4.71 (s, 1H, 5β-H), 5.63 (t, 1H, $CH_2CH=C(CH_3)Ph$), 6.11 (d, 1H, 8-H), 6.53 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 6.68 (d, 1H, 7-H), 7.18–7.39 (m, 5H, 20-Ph). ^{13}C NMR 3.37 (cPropCH$_2$), 3.79 (cPropCH$_2$), 9.22 (cPropCH), 16.53 (CH_2-CH=C(Ph)CH_3), 22.37 (C-10), 28.43 (C-15), 34.88 (CH_2-CH=C(Ph)CH_3), 44.29 (C-16), 45.31 (C-14), 46.55 (C-13), 59.05 (NCH_2), 59.41 (C-9), 88.45 (C-5), 117.17 (C-2), 120.06 (C-1), 121.78 (CH_2-CH=C(Ph)CH_3), 125.64 (C-11), 131.30 (C-12), 132.24 (C-7), 138.40 (C-3), 139.77 (>C=), 142.76 (C-4), 154.81 (C-8), aromatic: 127.08; 128.37; 143.65. IR (KBr) (cm^{-1}) ν_{CO} 1677; $\nu_{C\ C}$ 1622. MS (EI 70 eV) *m/z* 453 (75) [M^+], 356 (100). $[\alpha]_D^{25}$ −25.6° (EtOH, *c* 0.1). $C_{30}H_{31}NO_3$ (453.5).

12c: 3-O-Demethylation of **5c** with KOH/diethylene glycol (2 h) furnished **12c**. Yield 53%, mp 263–264 °C [HCl] [EtOH]. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H, $CH_3CH_2CH_2$), 1.50 (m, 2H, $CH_3CH_2CH_2$), 1.62 (m, 1H, 15-H), 2.00 (s, 3H, CH_3), 2.25 (m, 2H, $CH_3CH_2CH_2$), 2.32–2.52 (m, 3H, 15-H, 16-H, 10α-H), 2.68 (m, 1H, 16-H), 2.76 (m, 0.5H, $CH_2C=$), 3.12 (d, 1H, 10β-H), 3.18 (d, 1H, 9α-H), 3.53 (m, 0.5H, $CH_2C=$), 4.69 (s, 1H, 5β-H), 5.62 (t, 1H, $CH_2CH=C(CH_3)Ph$), 6.10 (d, 1H, 8-H), 6.55 (d, 1H, 1-H), 6.64 (d, 1H, 2-H), 6.68 (d, 1H, 7-H), 7.22–7.40 (m, 5H, 20-Ph). ^{13}C NMR 11.79 (CH_3), 16.71 ($=C(Ph)CH_3$), 20.75 (CH_2), 22.88 (C-10), 28.60 (C-15), 34.59 (CH_2-CH=), 44.12 (C-16), 45.66 (C-14), 46.68 (C-13), 56.55 (N-CH_2), 60.15 (C-9), 88.61 (C-5), 117.19 (C-2), 120.26 (C-1), 121.68 (CH=), 125.88 (C-11), 131.22 (C-12), 132.31 (C-7), 138.34 (C-3), 139.99 (>C=), 142.61 (C-4), 154.37 (C-8), 195.09 (C-6), aromatic: 125.66; 127.20; 128,46; 143.65. IR (KBr) (cm^{-1}) ν_{CO} 1680; $\nu_{C\ C}$ 1612. MS (EI 70 eV) *m/z* 441 (46) [M^+], 244 (100). $C_{29}H_{31}NO_3$ (441.5).

Acknowledgements

This work was supported in part by grants OMFB 9297–07–0036; OTKA I/3 reg. No.: 1722 and T 0413991. The authors thank Mrs Julianna Nagy and Mrs Julianna Kabai for technical assistance, Mrs Katalin Horváth for measuring the ^{1}H NMR spectra, Mrs Katalin Treszkó and Mrs Mária Orosz for recording mass spectra and Dr Gizella B. Szabó (Analytical Laboratory of L. Kossuth University, Debrecen) for performing the microanalyses.

References

1. Wang, D.-X.; Lu, X.-Q.; Qin, B.-Y. *J. Pharm. Pharmacol.* **1995**, *47*, 669.

2. Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *69*, 3281.

3. Bentley, K. W.; Hardy, D. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3273.

4. Fulmor, W.; Lancaster, J. E.; Morton, G. O.; Brown, J. J.; Howell, C. F.; Nora, C. T.; Hardy, R. A. J. *J. Am. Chem. Soc.* **1967**, *89*, 3322.

5. Bentley, K. W.; Ball, J. C. *J. Org. Chem.* **1958**, *23*, 1720.

6. Marton, J.; Szabó, Z.; Simon, C.; Hosztafi, S.; Makleit, S. *Liebigs Ann. Chem.* **1996**, 1653.

7. Marton, J.; Szabó, Z.; Hosztafi, S. *Liebigs Ann. Chem.* **1993**, 915.

8. Marton, J.; Hosztafi, S.; Berényi, S.; Simon, C.; Maklcit, S. *Monatsh. Chem.* **1994**, *125*, 1229.

9. Lewis, J. W.; Readhead, M. J. *Tetrahedron* **1968**, 24, 1829.

10. Valhari, M. U.; Rahman, A. U.; Memon, M. U.; Nachnani, F. C.; Khan, M. Y. *Sci. Int. (Lahore)* **1992**, *4*, 53.

11. Pasternak, G. W.; Wilson, H. A., Snyder, S. H. *Mol. Pharmacol.* **1975**, *11*, 340.

12. Bradford, M. *Anal. Biochem.* **1976**, *72*, 248.

13. Búzás, B.; Tóth, G.; Cavagnero, S.; Hruby, V. J.; Borsodi, A. *Life Sci.* **1992**, *50*, PL71.

14. Handa, B. K.; Lane, A. C.; Lord, J. A. H.; Morgan, B. A.; Rance, M. J.; Smith, C. F. C. *Eur. J. Pharm.* **1981**, *70*, 531.

15. Munson, P. J.; Rodbard, D. *Anal. Biochem.* **1980**, *107*, 220.

16. Klein, P.; Nelson, W. L.; Yao, Y.-H.; Simon, E. J. *J. Med. Chem.* **1990**, *33*, 2286.

(*Received in U.S.A.* 2 *August* 1996; *accepted* 20 *September* 1996)