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János Marton [a] , Szilárd Miklòs [a] , Sàndor Hosztafi [a] & Sándor Makleit [b]

[a] Alkaloida Chemical Company Ltd. , H-4440, Tiszavasvári, Hungary

[b] Department of Organic Chemistry , L. Kossuth University , P. O. Box 20., H-4010, Debrecen, Hungary

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SYNTHESIS OF N-SUBSTITUTED 7β-DIPRENORPHINE DERIVATIVES#

János Marton[1], Szilárd Miklós[1], Sándor Hosztafi[1], and Sándor Makleit[2]*

[1] Alkaloida Chemical Company Ltd., H-4440 Tiszavasvári, Hungary

[2] Department of Organic Chemistry, L. Kossuth University, P. O. Box 20., H-4010 Debrecen, Hungary

Abstract: The separation of thevinone (**2a**) and β-thevinone (**2b**), as well as that of dihydrothevinone (**3a**) and β-dihydrothevinone (**3b**) was accomplished. By the application of various procedures numerous new *N*-substituted Diprenorphine analogues (**8a-f**) with 7*R* absolute configuration were synthesized. Detailed pharmacological investigation of the prepared compounds may contribute to a better understanding of the structure-activity relationship of morphine alkaloids.

Compounds belonging to the 6,14-ethenomorphinane family were first prepared by Sandermann[1a] and Schöpf[1b] et al, when investigating the reactions of thebaine with dienophiles (*p*-benzoquinone, 1,4-naphtoquinone and maleic anhydride). Bentley and Thomas reported[2] that the dihydro derivative of the

* To whom correspondence should be addressed

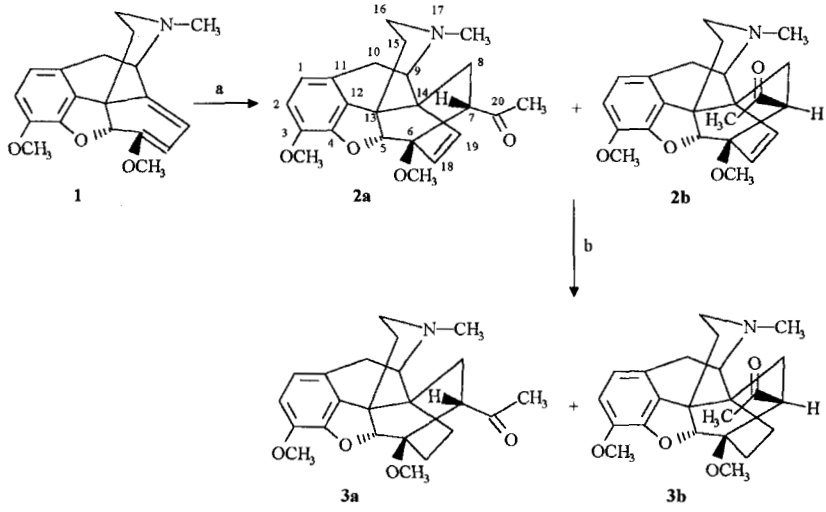
Diels-Alder adduct of thebaine with *p*-benzoquinone possessed an analgetic effect on rodents almost equal to that of pethidine. The results, published by Bentley and Hardy[3] in the early sixties, and showing that the substances produced in the addition reactions of thebaine and dienophiles possess extremely high analgetic activities generated considerable interest in the research of synthetic opioid alkaloids. The research of 6,14-ethenomorphinanes is one of the most promising field from both theoretical and practical points of view, as indicated by the published numerous review papers[4,5,6], as well as the discovery and development of such drugs like Buprenorphine, Diprenorphine and Etorphine. All of these compounds belong to the above group of alkaloids and are very important in pharmacology and in medicinal practice.

During our own research we have prepared Buprenorphine and Diprenorphine from *N*-formyl-*N*-demethylthebaine and *N*-benzyl-*N*-demethylthebaine *via* new intermediates[7], and numerous new *N*-substituted dihydronorthevinone derivatives and *N*-substituted Buprenorphine and Diprenorphine analogues have also been synthesized[8].

In the present work the separation of thevinone (**2a**) and β-thevinone (**2b**), as well as that of dihydrothevinone (**3a**) and β-dihydrothevinone (**3b**) was accomplished. In addition, studies of the Grignard reaction of **3b** and the *N*-demethylation, *N*-alkylation and *O*-demethylation of 7β-acetyl derivatives were carried out. Several new Diprenorphine analogues (**8a-f**) with 7*R* absolute configuration were also synthesized by employing hitherto unknown intermediates.

The [4+2] cycloaddition reaction of thebaine (**1**) and methyl vinyl ketone proceeds in a regio and stereoselective manner[9] to result in 7-acetyl derivatives

exclusively and the ratio of the 7α-acetyl (**2a**) and 7β-acetyl (**2b**) analogues was found to be 98 : 2. The 7β compounds have not been extensively studied; β-dihydrothevinone (**3b**) was prepared[10] by the reduction of β-thevinone (**2b**).



Scheme 1.

a: Methyl vinyl ketone, reflux; b: H_2/Pd-C, 55 °C, 6 bar, toluene or ethyl acetate[8]

The 7α and 7β cyano compounds were obtained in a 1 : 1 ratio in the Diels-Alder reaction[9] of thebaine (**1**) with acrylonitrile. With methyl acrylate 8 % of the 7β-methyl ester was isolated, and the 7β-hydrazide analogue was prepared by treatment with hydrazine hydrate. The 7β derivative of Buprenorphine was also synthesized and the intermediates to this substance were analysed[12,13] by means of ^{1}H-NMR spectroscopy.

Heterogeneous catalytic hydrogenation of the mixture of thevinone (**2a**) and β-thevinone (**2b**), obtained in the large-scale addition reaction of thebaine and

methyl vinyl ketone, gave a mixture of dihydrothevinone (**3a**) and β-dihydrothevinone (**3b**). Upon recrystallization of this mixture from ethanol dihydrothevinone partially crystallized, while the β-compound remained dissolved in the mother liquor. Following evaporation, preparation of the bitartarate-salt in aqueous medium led to the crystallization of the bitartarate of dihydrothevinone and the salt of the β-derivative remained, again, in solution. From the aqueous mother liquor the free base was isolated, and TLC showed a 1 : 3 ratio for dihydrothevinone and β-dihydrothevinone. Crystallization of this mixture from ethanol afforded crystalline β-dihydrothevinone, and this new procedure for the separation of the isomers proved to be much more efficient than the tedious method described[9] earlier.

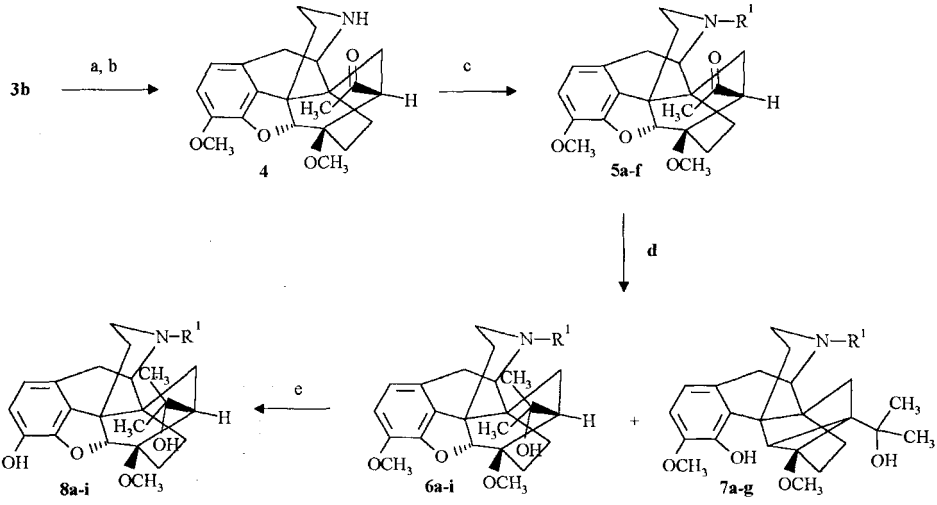
For the preparation of the target Diprenophine analogues three independent routes were applied:

Sequence A) **3b** → **4** → **5a-f** → **6a-f** → **8a-c**; compound **3b** was *N*-demethylated with DEAD, and then alkylated with the appropriate alkylating agent to obtain **5a-f**. Treatment of these latter compounds with MeMgI gave **6a-f**, whose *O*-demethylation with KOH/diethyleneglycol at 210 °C afforded **8a-c**.

Sequence B) **3b** → **6g** → **6h** → **6i** → **6a-f** → **8a-c**; **3b** was first reacted with MeMgI and the produced tertiary alcohol (**6g**) was *N*-demethylated according to the von Braun procedure to obtain **6h** and then **6i**. Following *N*-alkylation and *O*-demethylation of the resulting **6a-f** the target products **8a-c** were isolated.

Sequence C) **6g** → **6h** → **8i** → **8d-f**; the tertiary alcohol **6g** was treated with BrCN and the obtained cyanamide **6h** was reacted with KOH in hot (210 °C) diethyleneglycol. The produced **8i** is a suitable intermediate to **8d-f**.

For the synthesis of **8a-c** both of the reaction sequences A and B proved to be applicable, but **8d-f** could be more conveniently prepared on route C - due to the thermal instability of the *N*-substituents.The adduct formed in the reaction of β-dihydrothevinone (**3b**) and ethyl azodicarboxylate was split with pyridine



5-8	R^1
a	Cyclopropylmethyl
b	β-Phenylethyl
c	n-Propyl
d	Allyl
e	3,3-Dimethylallyl
f	Propargyl
g	Methyl
h	CN
i	H

Scheme 2.

a: DEAD, benzene, reflux; b: Pyridine hydrochloride, EtOH; c: R^1Br, dimethylformamide, 90-95 °C; d: MeMgI, diethylether-toluene; e: KOH, diethyleneglycol, 210 °C, N_2

chlorohydrate. β-Dihydronorthevinone (**4**) was purified by means of the preparation of the bitartarate salt, and the obtained new compound was *N*-alkylated, separately, with cyclopropylmethyl bromide, β-phenylethyl bromide, allyl bromide, dimethylallyl bromide and propargyl bromide to yield **5a**, **5b**, **5c**, **5d**, **5e** and **5f**, respectively.

Table 1. Physical data for compounds **5 - 8**

No	Yield [%]	M. P. [°C]	$[\alpha]_D^{25}$,i	No.	Yield [%]	M. P. [°C]	$[\alpha]_D^{25}$,i
5a	61	175-176[d]	-233,8	**7a**	8[a]	148-150[d]	-106.7[k]
5b	69	166-167[d]	-173,8	**7b**	12[a]	199-200[d]	-90.0[m]
5c	75	179-180[d]	-230,1	**7c**	7[a]	198-200[e]	-68.9
5d	46	196-197[d]	-208,0	**7d**	8[a]	oil	-161.4[m]
5e	63	82-83[d]	-225.0	**7e**	9[a]	oil	-90.3
5f	60	176-177[d]	-225,7	**7f**	13[a]	oil	-8.7[l]
6a	72[a]/68[b]	oil	-130,2	**7g**	13[a]	187-188[e]	-68.0[m]
6b	71[a]/73[b]	187-188[d]	-124,0	**8a**	60	240-242[d]	-156.3
6c	62[a]/64[b]	127-128[e]	-151,9	**8b**	62	281-282[f]	-106.2
6d	66[a]	118-119[e]	-90.0[k]	**8c**	56	255-256[d]	-157.6[m]
6e	62[a]	oil	-149,8	**8d**	65[c]	213-215[d]	-160.0[m]
6f	60[a]	oil	-160,3	**8e**	78[c]	73-75[h]	-76.0[n]
6g	67[a]	170-171[e]	-172,2	**8f**	70[c]	198-199[e]	-160.0[m]
6h	81[c]	200-202[d]	-161,0	**8g**	67	289-290[d]	-149.3
6i	60[c]	167-168[d]	-165.0	**8i**	65	305-307[g]	-40.0[p]

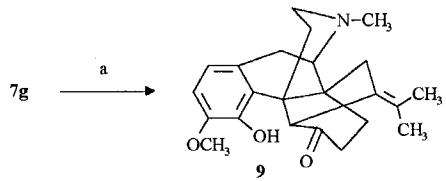
a: Sequence A, after chromatographic separation; b: Sequence B; c: Sequence C; d: ethanol; e: diethyl ether; f: hydrochloride; g: 1:1 (v/v) chloroform-ethanol ; h: bitartrate, i: c = 1, $CHCl_3$; k: c = 0.3, $CHCl_3$; l: c = 0.1, $CHCl_3$; m: c = 0.5, $CHCl_3$; n: c = 0.5, EtOH; p: c = 0.1, EtOH;

The Grignard reaction of the new compounds with MeMgI was also investigated. When dihydrothevinone (**3a**) was employed an exclusive formation of the corresponding tertiary alcohol was observed[8]. In the present studies, the Grignard reaction of the 7β-acetyl compounds with MeMgI gave two compounds in a ratio of 9 : 1 to 8 : 2.

Separation of this mixture by means of column chromatography gave 62-67 % of the tertiary alcohols **6a-g**, as the major products, and 7-13% of the minor compounds **7a-g**.

When studied the Grignard reaction of β-thevinone (**2b**) and methyl magnesium iodide Bentley et al[14] observed the formation of the expected tertiary alcohol, accompanied by another tertiary alcohol with opened ring E and carrying a C-4 phenolic hydroxyl group - as a result of the attack of the alkaline Grignard reagent.

^{1}H-NMR examination of the by-product **7g** formed in the reaction of β-dihydrothevinone (**3b**) with MeMgI showed that the two singlets at δ = 4.46 and 5.74 ppm disappeared upon deuteration and the signal between 4-5 ppm, characteristic of the 5β-H was also missing; indicating the opening of ring E.



Scheme 3.

a: 2N HCl, room temperature, 10 min

In the IR spectrum of **7g** an absorption at 2999 cm^{-1} characteristic of a cyclopropane skeletone was observed. For each of the tertiary alcohol **6g** and the by-products the molecular ion was detected at *m/z* 399 in the mass spectra.

Upon treatment of **7g** with 2N HCl a further rearrangement occurred to give rise to **9**, and this supports, again, the proposed structure of the by-product **7g**. Based on these data the structure of the related minor products **7a-f** were also essentially substantiated.

Table 2. ^{1}H-NMR and MS data for compounds **5 - 8**

Compound	^{1}H-NMR Data ($CDCl_3$)
5a $C_{26}H_{33}NO_4$ (423.5) 423 (100) [M^+]	0.1-0.8 (m, 5H, cProp), 0.85 (m, 1H, 8α-H), 2.28 (s, 3H, 7β-Ac), 3.43 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.96 (d, 1H, 5β-H), 6.53 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
5b $C_{30}H_{35}NO_4$ (473.6) 473 (<1%) [M^+], 382(100)	0.85 (m, 1H, H-8α), 2.27 (s, 3H, 7βAc), 3.42(s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.96 (d, 1H, 5β-H), 6.54 (d, 1H, 1-H), 6.70 (d, 1H, 2-H), 7.14-7.30 (m, 5H, Ar).
5c $C_{25}H_{33}NO_4$ (411.5) 411 (8) [M^+], 382(100)	0.88 (t, 3H, $\underline{CH_3}CH_2CH_2$), 2.28 (s, 3H, 7βAc), 3.43 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.94 (d, 1H, 5β-H), 6.54 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
5d $C_{25}H_{31}NO_4$ (409.5) 409 (100) [M^+]	0.85 (m, 1H, 8α-H), 2.28 (s, 3H, 7β-Ac), 3.42 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.93 (d, 1H, 5β-H), 5.05-5.22 (m, 2H, All), 5.65-5.86 (m, 1H, All), 6.54 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
5e $C_{27}H_{35}NO_4$ (437.6) 437 (8) [M^+], 69 (100)	0.85 (m, 1H, H-8α), 1.63 (s, 3H, Me), 1.72 (s, 3H, Me), 2.27 (s, 3H, 7β-Ac), 3.42 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.96 (d, 1H, 5β-H), 5.13 (t, 1H, All), 6.55 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
5f $C_{25}H_{29}NO_4$ (407.5) 407 (100) [M^+]	0.87 (m, 1H, 8α-H), 2.20 (t, 1H, Prop), 2.27 (s, 3H, 7β-Ac), 3.26 (d, 2H, Prop), 3.42 (s, 3H, 6-OCH_3), 3.87 (s 3H, 3-OCH_3), 4.96 (d, 1H, 5β-H), 6.55 (d, 1H, 1-H), 6.72 (d, 1H, 2-H).
6a $C_{27}H_{37}NO_4$ (439.6) 439 (80) [M^+], 398 (100)	0.10-0.80 (m, 5H, cProp), 0.92 (m, 1H, 8α-H), 1.20 (s, 3H, 20-Me), 1.44 (s, 3H, 20-Me), 3.54 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 5.09 (d, 1H, 5β-H), 5.20 (s[a], 1H, 20-OH), 6.56 (d, 1H, 1-H), 6.72 (d, 1H, 2-H).
6b $C_{31}H_{39}NO_4$ (489.6) [M^+] couldn't detected	0.85 (m, 1H, 8α-H), 1.16 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 3.54 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 3-OCH_3), 5.07 (d, 1H, 5β-H), 5.17 (s[a], 1H, 20-OH), 6.57 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 7.16-7.35 (m, 5H, Ar).

(continued)

Table 2. Continued

6c $C_{26}H_{37}NO_4$ (427.6) 427 (8) [M^+], 398 (100)	0.90 (t, 3H, $CH_3CH_2CH_2$), 1.18 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.54 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 5.08 (d, 1H, 5β-H), 5.17 (s[a], 1H, 20-OH), 6.57 (d, 1H, 1-H), 6.72 (d, 1H, 2-H).
6d $C_{26}H_{35}NO_4$ (425.6) 425 (54) [M^+], 366 (100)	0.86 (m, 1H, 8α-H), 1.19 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.53 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 5.08 (d, 1H, 5β-H), 5.14-5.25 (m, 2H, All), 5.16 (s[a], 1H, 20-OH), 5.68-5.90 (m, 1H, All), 6.57 (d, 1H, 1-H), 6.73 (d, 1H, 2-H).
6e $C_{28}H_{39}NO_4$ (453.6) 453 (80) [M^+], 394 (100)	0.87 (m, 1H, 8α-H), 1.20 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 1.65 (s, 3H, Me), 1.74 (s, 3H, Me), 3.54 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 5.08 (d, 1H, 5β-H), 5.14 (t, 1H, All), 5.20 (s[a], 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.73 (d, 1H, 2-H).
6f $C_{26}H_{33}NO_4$ (423.5) 423 (8) [M^+], 59 (100)	0.89 (m, 1H, 8α-H), 1.18 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 2.23 (t, 1H, Prop), 3.28 (d, 2H, Prop), 3.54 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 3-OCH_3), 5.08 (d, 1H, 5β-H), 5.18 (s[a], 1H, 20-OH), 6.57 (d, 1H, 1-H), 6.72 (d, 1H, 2-H).
6g $C_{24}H_{33}NO_4$ (399.5) 399 (26) [M^+], 366(22)	0.88 (m, 1H, 8α-H), 1.19 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 2.30 (s, 3H, NCH_3), 3.54 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 3-OCH_3), 5.07 (d, 1H, 5β-H), 5.20 (s[a], 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.73 (d, 1H, 2-H).
6h $C_{24}H_{30}N_2O_4$ (410.5) 410 (25) [M^+], 336(10)	0.86 (m, 1H, 8α-H), 1.23 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.54 (s, 3H, 6-OCH_3), 3.90 (s, 3H, 3-OCH_3), 4.85 (s[a], 1H, 20-OH), 5.08 (d, 1H, 5β-H), 6.64 (d, 1H, 1-H), 6.78 (d, 1H, 2-H).
6i $C_{23}H_{31}NO_4$ (385.5) 385 (65) [M^+], 367(20)	0.88 (m, 1H, 8α-H), 1.21 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 3.54 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 3-OCH_3), 5.06 (d, 1H, 5β-H), 5.14 (s[a] , 1H, 20-OH), 6.60 (d, 1H, 1-H), 6.75 (d, 1H, 2-H).
7a $C_{27}H_{37}NO_4$ (439.6) 439 (10) [M^+], 421(100)	0.05-0.80 (m, 5H, cProp), 1.38 (s, 3H, 20-Me), 1.44 (s, 3H, 20-Me), 3.35 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.50 (s[a], 1H, 4-OH), 5.74 (s[a], 1H, 20-H), 6.56 (d, 1H, 1-H), 6.68 (d, 1H, 2-H).

(continued)

Table 2. Continued

7b $C_{31}H_{39}NO_4$ (489.6) [M^+] couldn't detected	1.36 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.35 (s, 3H, 6-OCH_3), 3.84 (s, 3H, 3-OCH_3), 4.45 (s^a, 1H, 4-OH), 5.72 (s^a, 1H, 20-OH), 6.56 (d, 1H, 1-H), 6.68 (d, 1H, 2-H), 7.16-7.35 (m, 5H, Ar).
7c $C_{26}H_{37}NO_4$ (427.6) 427 (4) [M^+], 380(100)	0.89 (t, 3H, $\underline{CH_3}CH_2CH_2$), 1.37 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.35 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.47 (s^a, 1H, 4-OH), 5.75 (s^a, 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.67 (d, 1H, 2-H).
7d $C_{26}H_{35}NO_4$ (425.6) 425 (10) [M^+], 407 (100)	1.37 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.35 (s, 3H, 6-OCH_3), 3.86 (s, 3H, 3-OCH_3), 4.46 (s^a, 1H, 4-OH), 5.04-5.22 (m, 2H, All), 5.72 (s^a, 1H, 20-OH), 5.68-5.90 (m, 1H, All), 6.57 (d, 1H, 1-H), 6.73 (d, 1H, 2-H).
7e $C_{28}H_{39}NO_4$ (453.6) 453 (10) [M^+], 435 (100)	1.37 (s, 3H, 20-Me), 1.44 (s, 3H, 20-Me), 1.63 (s, 3H, Me), 1.74 (s, 3H, Me), 3.35 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.48 (s^a, 1H, 4-OH), 5.14 (t, 1H, All), 5.76 (s^a, 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.68 (d, 1H, 2-H).
7f $C_{26}H_{33}NO_4$ (423.5) 423 (13) [M^+], 405(100)	1.37 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 2.20 (t, 1H, Prop), 3.24 (d, 2H, Prop), 3.34 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.46 (s^a, 1H, 4-OH), 5.74 (s^a, 1H, 20-OH), 6.57 (d, 1H, 1-H), 6.68 (d, 1H, 2-H).
7g $C_{24}H_{33}NO_4$ (399.5) 399 (12) [M^+], 366(100)	1.37 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 2.57 (s, 3H, NCH_3), 3.33 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.46 (s^a, 1H, 4-OH), 5.74 (s^a, 1H, 20-OH), 6.58 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
8a $C_{26}H_{35}NO_4$ (425.6) 425 (55) [M^+], 384 (100)	0.10-0.80 (m, 5H, cProp), 0.90 (m, 1H, 8α-H), 1.20 (s, 3H, 20-Me), 1.44 (s, 3H, 20-Me), 3.52 (s, 3H, 6-OCH_3), 4.80 (s^a, 1H, 3-OH), 5.07 (s^a, 1H, 20-OH) 5.11 (d, 1H, 5β-H), 6.52 (d, 1H, 1-H), 6.68 (d, 1H, 2-H).
8b $C_{30}H_{37}NO_4$ (474.6) [M^+] couldn't detected	0.85 (m, 1H, 8α-H), 1.17 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 3.50 (s, 3H, 6-OCH_3), 5.05 (s^a, 1H, 20-OH), 5.15 (s, 1H, 5β-H), 5.40 (s^a, 1H, 3-OH), 6.52 (d, 1H, 1-H), 6.70 (d, 1H, 2-H), 7.12-7.34 (m, 5H, Ar).

(continued)

Table 2. Continued

8c $C_{25}H_{35}NO_4$ (413.5) 413 (6) [M^+], 384 (100)	0.90 (t, 3H, $\underline{CH_3}CH_2CH_2$), 1.18 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.51 (s, 3H, 6-OCH_3), 4.82 (s^a, 1H, 3-OH), 5.05 (s^a, 1H, 20-OH), 5.09 (d, 1H, 5β-H), 6.53 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
8d $C_{25}H_{33}NO_4$ (411.5) 411 (46) [M^+], 352 (100)	0.87 (m, 1H, 8α-H), 1.20 (s, 3H, 20-Me), 1.43 (s, 3H, 20-Me), 3.53 (s, 3H, 6-OCH_3), 4.95 (s^a, 1H, 3-OH), 5.07-5.23 (m, 2H, All), 5.10 (s^a, 1H, 20-OH), 5.15 (d, 1H, 5β-H), 5.65-5.90 (m, 1H, All), 6.53 (d, 1H, 1-H), 6.70 (d, 1H, 2-H).
8e $C_{27}H_{37}NO_4$ (439.6) 439 (4) [M^+], 380 (8), 69 (100)	0.90 (m, 1H, 8α-H), 1.22 (s, 3H, 20-Me), 1.45 (s, 3H, 20-Me), 1.67 (s, 3H, Me), 1.77 (s, 3H, Me), 3.54 (s, 3H, 6-OCH_3), 5.10 (d, 1H, 5β-H), 5.20 (s^a, 1H, 20-OH), 6.54 (d, 1H, 1-H), 6.73 (d, 1H, 2-H), 8.05 (s^a, 1H, 3-OH)
8f $C_{25}H_{31}NO_4$ (409.5) 409 (10) [M^+], 108 (100)	0.92 (m, 1H, 8α-H), 1.20 (s, 3H, 20-Me), 1.44 (s, 3H, 20-Me), 2.23 (t, 1H, Prop), 3.28 (d, 2H, Prop), 3.54 (s, 3H, 6-OCH_3), 5.08 (d, 1H, 5β-H), 5.20 (s^a, 1H, 20-OH), 6.53 (d, 1H, 1-H), 6.72 (d, 1H, 2-H), 8.03 (s^a, 1H, 3-OH)
8g $C_{23}H_{31}NO_4$ (385.5) 385 (100) [M^+]	0.90 (m, 1H, 8α-H), 1.18 (s, 3H, 20-Me), 1.42 (s, 3H, 20-Me), 2.30 (s, 3H, NCH_3), 3.52 (s, 3H, 6-OCH_3), 5.09 (d, 1H, 5β-H), 5.15 (s^a, 1H, 20-H), 5.20 (s^a, 1H, 3-OH), 6.53 (d, 1H, 1-H), 6.68 (d, 1H, 2-H)
8i[b] $C_{22}H_{29}NO_4$ (371.4) 371 (100) [M^+]	0.65 (m, 1H, 8α-H), 1.22 (s, 3H, 20-Me), 1.32 (s, 3H, 20-Me), 3.28 (s, 3H, 6-OCH_3), 4.50 (s^a, 1H, 20-OH), 4.94 (d, 1H, 5β-H), 6.42 (d, 1H, 1-H), 6.65 (d, 1H, 2-H), 8.90 (s^a, 1H, 3-OH)

a: exchangeable; b: in DMSO-d_6; Abbreviations: cProp: protons of the cyclopropyl ring; Ar: aromatic protons; All: protons of the allyl or 3,3-dimethylallyl groups; Prop: protons of the propargyl group

Detailed ^{1}H-NMR studies of the 7α and 7β-6,14-ethenomorphinane derivatives have been accomplished by Fulmor et al[15], Uff and coworkers[12], and Mazza[13] reported ^{1}H and ^{13}C NMR examination of derivatives carrying 7β substituents. The chemical shift value of the 5β proton is of diagnostic importance to establish the stereochemistry of carbon C-7.

Table 3. Chemical shifts (δ, ppm) and ν_{CO}(cm^{-1}) for 7-acetyl-6,14-ethenomorphinane derivatives

	7α-Acetyl[8]			7β-Acetyl		
N-substituent	7-Acetyl	5β-H	ν_{CO}	7-Acetyl	5β-H	ν_{CO}
Methyl	2.25	4.47	1709	2.27	4.97	1705
H	2.28	4.45	1705	2.30	4.80	1699
Cyclopropylmethyl	2.26	4.48	1701	2.28	4.96	1706
n-Propyl	2.25	4.47	1702	2.28	4.94	1709
β-Penylethyl	2.25	4.47	1706	2.27	4.96	1703
Allyl	2.25	4.50	1690	2.28	4.93	1706
3,3-Dimethylallyl	2.25	4.48	1705	2.27	4.96	1707
Propargyl	2.26	4.50	1700	2.27	4.96	1690

For the 5β proton of the 7α and 7β derivatives Fulmor reported[15] chemical shifts of 4.57 ± 0.05 and 5.07 ± 0.12 ppm, respectively. For the numerous new *N*-substituted 7-acetyl-6,14-ethenomorphinane derivatives we also observed that - in agreement with the above literature data - the chemical shift of the 5β proton of the 7β derivatives is larger than that of the 7α isomers. A similar phenomenon

was observed with the acetyl group, as well. The NMR and IR spectral data of the prepared compounds are summarized in Table 3.

The biological investigation of the prepared new derivatives will be the subject of a forthcoming paper.

Experimental

Melting points were measured with a Büchi-535 instrument and the data are uncorrected. The ^{1}H-NMR spectra were obtained with a Varian - Gemini - 200 spectrometer at 20 °C (internal standard TMS). Optical rotations were determined with a Polmat - A (Zeiss - Jena) polarimeter and the IR spectra were recorded with a Digilab FTS - 40 spectrometer. Column chromatography was performed on Kieselgel 60 (0.063 - 0.2 mm) adsorbed using a 9 : 1 (v/v) eluent for the separation of **6a-g** and **7a-g**. TLC was accomplished on precoated Kieselgel 60 F_{254} foils (Merck) with the following eluent systems (each v/v): 8 : 2 benzene - methanol, 9 : 1 chloroform - methanol, 5 : 4 : 1 chloroform - acetone - diethylamine. The spots were visualized with UV light or with the Draggendorf reagent.

The large-scale reaction of thebaine (**1**) and methyl vinyl ketone was executed according to a literature procedure[9]. Catalytic hydrogenation of the obtained mixture of **2a** and **2b** was performed without separation[8] to obtain a mixture of **3a** and **3b**.

Separation of (5R,6R,7S,9R,13S,14S) and (5R,6R,7R,9R,13S,14S)-7-acetyl-4,5-epoxy-18,19-dihydro-3,6-dimethoxy-17-methyl-6,14-ethenomorphinane (**3a** and **3b**)

By the hydrogenation of a mixture (10 kg) of thevinone (**2a**) and β-thevinone

(**2b**) 9157 g of dihydrothevinone (**3a**) was obtained. From the mother liquor a second corp (472 g) was obtained, which proved to be mostly β-dihydrothevinone. To the product 185 g L-(+) tartaric acid and water (5500 ml) were added, and the mixture was stirred at 70-80 °C until complete dissolution of the solid materials. The solution was then concentrated to its half volume under diminished pressure and cooled to room temperature, when the bitartarate of the 7α-derivative (**3a**) crystallized in 80-90 % purity and the filtrate was enriched in the 7β-isomer. Following alkalization of this mother liquor with 25 % aqueous ammonia the free base was extracted with chloroform. The combined chloroform extract was washed with water, dried (Na_2SO_4), concentrated and the residue was crystallized from ethanol to result in the selective crystallization of the 7β compound. Repeated recrystallization from ethanol afforded 92 g of β-dihydrothevinone (**3b**) of 98-99 % purity. Mp: 173-174 °C [lit.[10] mp 166 °C] - ^{1}H-NMR ($CDCl_3$): δ = 0.88 (m, 1H, 8α-H), 2.27 (s, 3H, 7β-Ac), 2.31 (s, 3H, NCH_3), 3.43 (s, 3H, 6-OCH_3), 3.88 (s, 3H, 3-OCH_3), 4.97 (d, 1H, 5β-H), 6.57 (d, 1H, 1-H), 6.72 (d, 1H, 2-H) - $[\alpha]_D^{25}$ = -196.0 (c = 1, $CHCl_3$) - MS (70 eV): m/z (%) = 383 (100) [M^+] - $C_{23}H_{28}NO_4$ (383.4).

The separation of the mixture of **2a** and **2b** was accomplished in an essentially similar way. **2b**: Mp: 206-208 °C (EtOH) [lit.[10] mp. 200-202 °C] - ^{1}H-NMR ($CDCl_3$): δ = 1.62 (m, 1H, 8α-H), 2.27 (s, 3H, 7β-Ac), 2.36 (s, 3H, NCH_3), 3.23 (d, J = 18 Hz, 1H, 10β-H), 3.60 (s, 3H, 6-OCH_3), 3.81 (s, 3H, 3-OCH_3), 4.98 (d, J = 1.3 Hz, 1H, 5β-H), 5.47 (d, J = 9 Hz, 1H, 19-H), 6.03 (dd, J_1 = 9 Hz, J_2 = 1.3 Hz, 18-H), 6.48 (d, 1H, 1-H), 6.62 (d, 1H, 2-H) - $[\alpha]_D^{25}$ = -232 (c = 1, $CHCl_3$) - MS (70 eV): m/z (%) = 381 (40) [M^+], 206(100) - $C_{23}H_{26}NO_4$ (381.4).

(5R,6R,7R,9R,13S,14S)-7-acetyl-4,5-epoxy-18,19-dihydro-3,6-dimethoxy-6,14-ethenomorphinane (**4**)

To a solution of **3b** (11.3 g, 29.5 mmol) in abs. benzene (150 ml) diethyl azodicarboxylate (7.5 ml, 48.2 mmol) was added and the mixture was refluxed for 16 hrs. After evaporation of the solvent the residue was taken up with ethanol (150 ml), pyridine chlorohydrate (4.5 g) was added, the mixture was stirred at room temperature for 24 hrs and then evaporated. The residue was dissolved in water (400 ml), 5 % HCl (150 ml) was added and extracted with ether (3 x 100 ml). The aqueous layer was alkalized with 25 % aqueous ammonia and extracted with chloroform (3 x 100 ml). The combined chloroform extract was washed with a saturated NaCl solution and then with water, dried over Na_2SO_4 and evaporated. From the residue the bitartarate salt (12.3 g, 80 %) was prepared, mp. 210-211 °C. For further experiments, as well as for analytical purposes the free base **4** was prepared and crystallized from ether, mp. 152-153 °C. ^{1}H-NMR ($CDCl_3$): δ = 0.85 (m, 1H, 8α-H), 2.30 (s, 3H, 7β-Ac), 3.43 (s, 3H, 6-OCH_3), 3.87 (s, 3H, 3-OCH_3), 4.80 (d, 1H, 5β-H), 6.56 (d, 1H, 1-H), 6.72 (d, 1H, 2-H) - $[\alpha]_D^{25}$ = -202.8 (c = 1, $CHCl_3$) - MS (70 eV): m/z (%) = 369 (100) [M^+] - $C_{22}H_{27}NO_4$ (369.4).

General procedure for the synthesis of (5R,6R,7R,9R,13S,14S)-7-Acetyl-4,5-epoxy-18,19-dihydro-3,6-dimethoxy-17-substituted-6,14-ethenomorphinanes **(5a-f)**

The syrupy free base **4** was prepared from the bitartarate salt (3 g, 5.8 mmol) and dissolved in abs. *N,N*-dimethylformamide (25 ml). This solution was treated with sodium hydrogen carbonate (1.75 g) and the alkyl bromide (8.7 mmol)

[cyclopropylmethyl bromide, β-phenylethyl bromide, n-propyl bromide, allyl bromide, 3,3-dimethylallyl bromide and propargyl bromide] and stirred at 90 °C for 20 hrs. After removal of the inorganic salt by filtration the solvent was distilled off, the residue was suspended in water, the pH was made alkaline by the addition of aqueous ammonia and the mixture was extracted with chloroform. The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated. The syrupy residue was crystallized from ethanol. The physical and ^{1}H-NMR spectral data of the products are collected in Table 1 and Table 2, respectively.

General procedure for the Grignard reaction of **5a-f** *with methyl magnesium iodide*

To the Grignard reagent prepared from magnesium shavings (0.35 g) and methyl iodide (0.9 ml) in abs. toluene (4 ml) and abs. ether (11 ml) a solution of 3.40 mmol of the *N*-substituted β-dihydronorthevinone derivative (**5a-f**) in abs. toluene (7 ml) was dropwise added over a period of 1 h. Then the solution was stirred under gentle reflux for 1 h, allowed to cool to room temperature and poured into 50 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with toluene (3 x 20 ml), the combined organic phase was washed with a saturated sodium chloride solution, dried (Na_2SO_4) and evaporated to obtain a two-component product (TLC). The physical and spectral data of the pure products obtained by means of column chromatography are summarized in Tables 1 and 2.

Rearrangement of **7g** *upon the action of acid*

A mixture of **7g** (0.2 g, 0.5 mmol) and 2N HCl (4 ml) was stirred for 10 min,

when TLC showed that the starting material had reacted. The reaction mixture was alkalized with 25 % aqueous ammonia, extracted with chloroform, dried over Na_2SO_4 and then evaporated. **9**: ^{1}H-NMR ($CDCl_3$): δ = 1.68 (s, 3H, 20-Me), 1.74 (s, 3H, 20-Me), 2.35 (s, 3H, NMe), 3.08 (d, J = 18 Hz, 1H, 10β-H), 3.82 (s, 3H, 3-OMe), 5.80 (s, deuterable, 1H, 4-OH), 6.63 (s, 2H, 1-H, 2-H) - MS (70 eV): m/z (%) = 367 (100) [M^+], 310 (30), 293 (12) - IR: ν_{CO} = 1700 cm^{-1} - mp. 287-290 °C [HCl] - $C_{23}H_{29}NO_4$ (367.4)

Reaction of **6g** *with cyanogen bromide*

To a solution of **6g** (3.9 g, 9.7 mmol) in chloroform (20 ml; previously dried over $CaCl_2$) was treated with cyanogen bromide (1.9 g, 18 mmol) at room temperature for 24 hrs. The solvent and the excess of the reagent were removed by evaporation, the residue was diluted with ethanol (50 ml) and the mixture was concentrated to its half volume. Upon cooling crystalline **6h** was separated, which was filtered off and dried. The product was then transformed into the corresponding *N*-demethyl derivative **6i** with KOH in diethyleneglycol as previously described in the literature[7,16].

N-Alkylation reactions

To a mixture of **6i** (1.1 g, 2.8 mmol), abs. *N,N*-dimethylformamide (6 ml) and $NaHCO_3$ (0.6 g) the required alkylating agent (4.2 mmol) [cyclopropylmethyl bromide, β-phenylethyl bromide, n-propyl bromide] was added, and it was stirred at 95 °C for 20 hrs. The inorganic salts were then filtered off, the solvent was evaporated under diminished pressure, the residue was suspended in water, alkalized with a small volume of aqueous ammonia, extracted with chloroform

and evaporated. The obtained syrupy products were crystallized from the suitable solvent.

Hydrolysis and *O*-demethylation of the cyanamide **6h** was carried out in one step as described in the literature[7] to obtain **8i**. *N*-Alkylation of this compound was carried out according to our procedure[8] by application of 1.1 equivalent of the alkylating agent to obtain **8d-f** with good yields.

O-demethylation of **6e** *in a nPrSH/NaH/N,N-dimethylformamide system*

To a suspension of NaH (0.23 g) in abs *N,N*-dimethylformamide (2 ml) n-propanethiol (0.12 ml) in abs. *N,N*-dimethylformamide (3 ml) was added under a N_2 atmosphere. After stirring for 5 min a solution of **6e** (0.4 g, 0.8 mmol) in *N,N*-dimethylformamide (3 ml) was added and the reaction mixture was boiled under reflux for 4 hrs. It was then cooled, acidified to pH = 2 with 1N HCl and extracted with ether (30 ml). The aqueous phase was alkalized with aqueous ammonia, extracted with a 9 : 1 (v/v) chloroform - methanol mixture and the organic layer was evaporated under diminished pressure. From the residue the bitartarate salt was prepared with L-(+) tartaric acid, which was filtered to obtain 0.36 g (70 %) **8e**.

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