Pergamon

Tetrahedron 54 (1998) 9143–9152

TETRAHEDRON

Studies on the Synthesis of β-Thevinone Derivatives★★

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Received 2 March 1998; revised 21 May 1998; accepted 3 June 1998

Abstract: The reactions of β-thevinone and β-dihydrothevinone with *tert.*-butylmagnesium chloride and *n*-propylmagnesium bromide were investigated. Further chemical transformations (*N*-demethylation, *N*-alkylation, *O*-demethylation) of the tertiary alcohols afforded the known β-buprenorphine and the hitherto unknown β-etorphine and β-dihydroetorphine. The by-products of these reactions were also isolated, their structures identified, and the mode of their formation was explained.

Keywords: Morphine alkaloids, Grignard reactions, 7β 6,14-ethenomorphinans, X-ray analysis

Our earlier results[1-5] in the field of alkaloids permitted the synthesis of novel derivatives of 7β-thevinone and 7β-dihydrothevinone. Literature reports[6,7] deal with the preparation of only a few 7β 6,14-ethenomorphinan analogues. Our primary aim was to synthesize the 7β-analogues of the pharmacologically active compounds: *buprenorphine*(7*R*,20*S*)[8,9] (Temgesic) (**1**), *etorphine*(7*R*,20*R*)[10,11] (Immobilon), (**2**) and *dihydroetorphine*(7*R*, 20*R*)[12] (**3**). The 7β-derivatives of *diprenorphine*[10,13] (Revivon) have been reported recently by our group[3].

** Dedicated to ***Professor Dr. Csaba Szántay*** on the occasion of his 70th birthday

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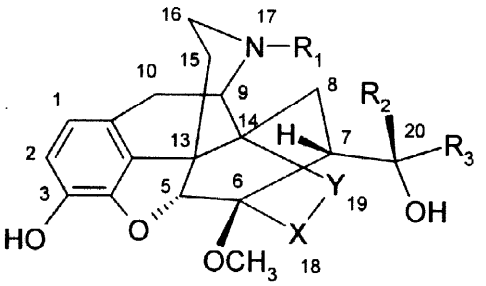
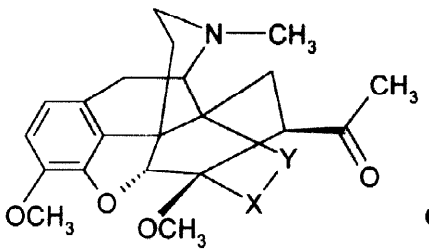
0040-4020/98/$19.00
PII: S0040-4020(98)00551-1



	R_1	R_2	R_3	X-Y	
1	CPM	tBu	CH_3	CH_2-CH_2	Buprenorphine
2	CH_3	nPr	CH_3	CH=CH	Etorphine
3	CH_3	nPr	CH_3	CH_2-CH_2	Dihydroetorphine

When studying the preparation of the 7β-analogues of buprenorphine from 7β-dihydrothevinone (**4b**) with *tert.*-butylmagnesium chloride (5 equivalent) in toluene-tetrahydrofuran Uff et al.[7] reported the formation of a single by-product **6** besides the major product **5** (31 %).



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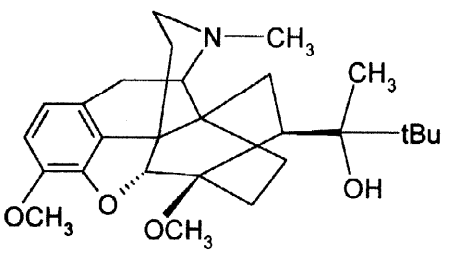

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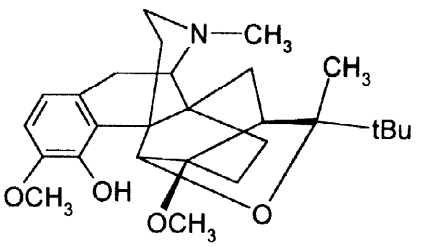
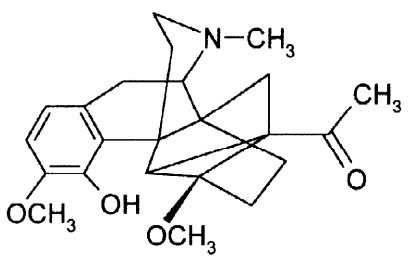


6

	X-Y
4a	CH=CH
4b	CH_2-CH_2

In our studies the Grignard reaction of β-dihydrothevinone (**4b**) with 6 molar equivalents of *tert.*-butylmagnesium chloride was carried out in toluene-ether and no formation of a compound structurally related to **6** was observed. The four products of the transformation were separated by column chromatography and their structures were established by means of NMR spectroscopic methods (^{1}H-NMR, ^{13}C-NMR). Besides the major product **5** compound **7** was produced on the alkaline action of the Grignard reagent (*t*BuMgCl) employed in excess and the Grignard reaction of this latter with the ketone **7** resulted in **8**. In the case of the reagent *t*BuMgCl a β-hydrogen transfer is also possible and this is responsible for the formation of compound **9**.



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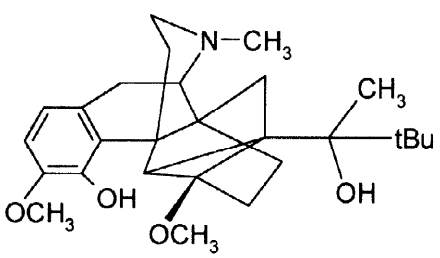

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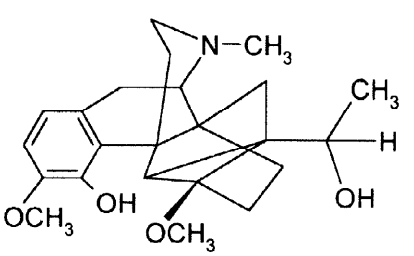

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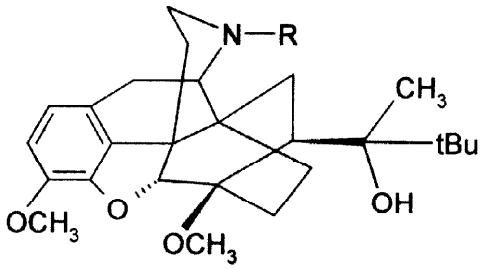

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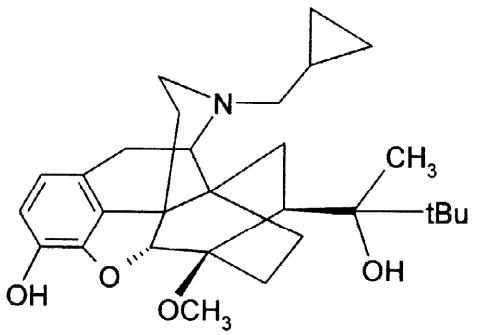
	R
10a	CN
10b	H
10c	CPM



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Treatment of **5** with cyanogen bromide and subsequent reaction of the resulting cyanamide **10a** with potassium hydroxide furnished the *N*-demethyl derivative **10b** whose structure was substantiated by means of X-ray analysis as shown on **Fig. 1**. The reaction of **10b** with cyclopropylmethyl bromide gave **10c** which was *O*-demethylated with potassium hydroxide/diethyleneglycol to afford 7β-buprenorphine(7*S*, 20*R*) (**11**).

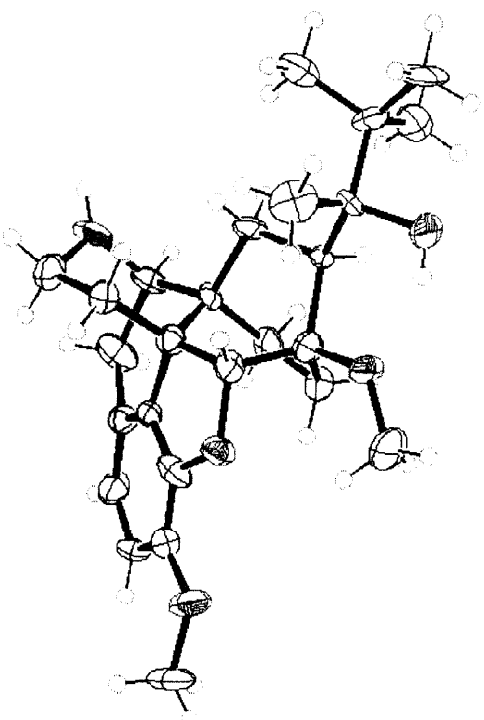
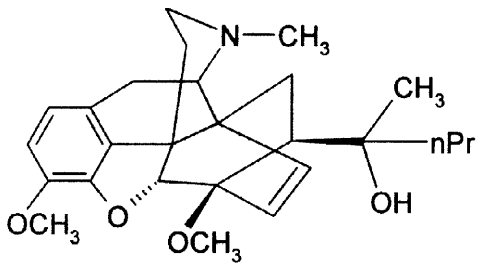


Figure 1. Structure of **10b** determined by X-ray analysis

Grignard reaction of β-thevinone (**4a**) with a sixfold excess of *n*-propylmagnesium bromide furnished again a four-component product mixture which was separated by column chromatography. Besides the normal Grignard adduct **12** compound **14** formed as the product of the Grignard-reduction and **13** and **15** were produced on the alkaline action of the excess reagent.



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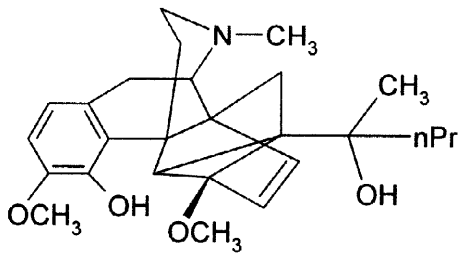

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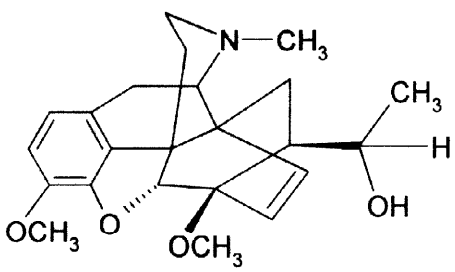

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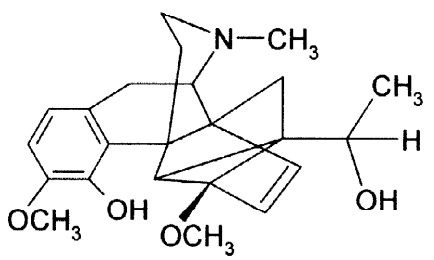

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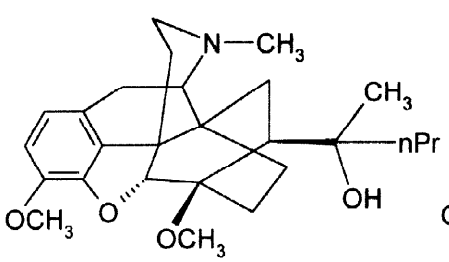
In the reaction of β-dihydrothevinone (**4b**) with *n*-propylmagnesium bromide the normal Grignard adduct **16** was accompanied by compounds **17** and **18**.



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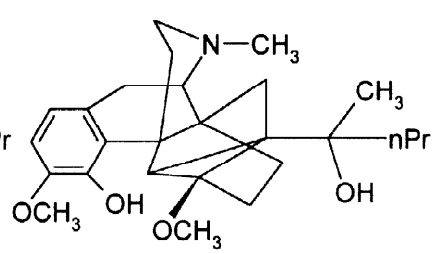

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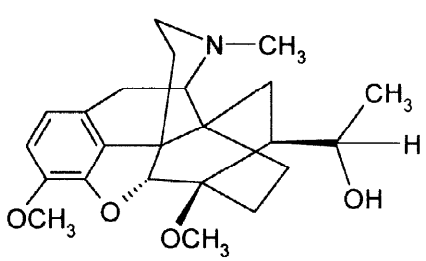

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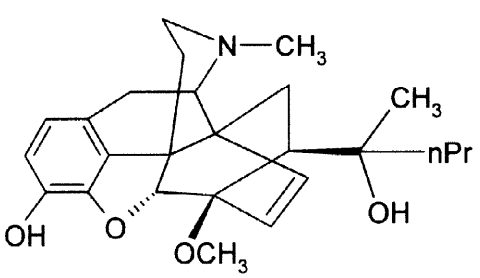

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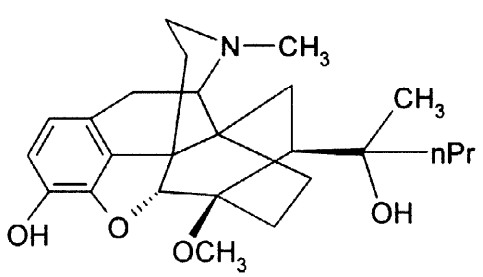

20

3-*O*-Demethylation of **12** and **16** afforded the 7β-analogues of etorphine(7*S*, 20*S*) (**19**) and dihydroetorphine(7*S*, 20*S*) (**20**) respectively.

Acknowledgements:

This work was supported, in part, by a grant (*OTKA reg. No.: T025047*) given by the *National Science Foundation* (Budapest, Hungary). The authors thank *Dr. Attila Bényei* for the X-ray analysis, *Mrs. Julianna Nagy* and *Mrs. Julianna Kabai* for their technical assistance.

EXPERIMENTAL

Melting points (uncorrected) were measured with a Büchi-apparatus in open capillary tubes. Thin layer chromatography was carried out on precoated Kieselgel 60 F_{254} plates (Merck 5719) by applying 10 μl of the 10 mg/ml chloroform solutions on the plates. Preceeding chromatography the chambers were saturated with the solvent systems for 30 min at 25 °C. The front height was 8 cm with the developing systems (v/v): benzene-methanol 8:2 [A]; chloroform-methanol 9:1 [B]; chloroform-acetone-diethyl amine 5:4:1 [C] and ethylacetate-chloroform-25 % NH_3 70:30:1 [D]. The chromatograms were visualized with a 254 nm UV lamp or with the Dragendorff reagent.

For column chromatography Kieselgel 60 (particle size 0.040-0.063 mm) was employed with the eluent system 9:1 chloroform-methanol.

^{1}H-NMR spectra were recorded with a Varian-Gemini-200 instrument at 20 °C in $CDCl_3$ (or in DMSO-d_6). For the ^{1}H-NMR examinations TMS (δ=0.00 ppm) was used as the internal standard. Carbon multiplicities could be determined with the aid of standard Varian APT (Attached Proton Test). Proton and carbon assignments based on COSY and HETCOR experiments. Abbreviations: cProp: protons of the cyclopropyl ring; [a]: deuterable. Mass spectra were obtained with a VG Trio-2 instrument by using the EI method (70 eV).

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

X-ray analysis: Enraf-Nonius MACH3 diffractometer.

Reaction of β-dihydrothevinone* (4b) *with tert.-butylmagnesium chloride: To the Grignard reagent prepared from magnesium shavings (1.46 g) and *tert.*-butylchloride (6.7 ml) in abs. toluene (9 ml) and abs. ether (31 ml) a solution of the β-dihydrothevinone (**4b**) (3.83 g, 10 mmol) in abs. toluene (36 ml) was dropwise added dropwise over a period of 1 h. Then the solution was stirred under gentle reflux for 1.5 h, allowed to cool to room temperature and poured into 150 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with toluene (3 x 50 ml), the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated to obtain a four-component product (TLC). The mixture was separated by column chromatography with eluent system toluene-methanol 8:2.

Fraction 1 (**5**): 1.5 g (34 %) — Mp. 188-189 °C [lit.[7] 188-189 °C] — R_{fA} = 0.69; R_{fB} = 0.77; R_{fC} = 0.90. — ^{1}H-NMR($CDCl_3$): δ = 0.88 (m, 1H, 19-H); 1.03 (s, 9H, 20-tBu); 1.10-1.30 (m, 2H, 18-H, 19-H); 1.40 (s, 3H, 20-CH_3); 1.45-1.70 (m, 3H, 8α-H, 15α-H, 18-H); 2.20-2.50 (m, 6H, 7α-H, 8β-H, 10α-H, 15β-H, 16α-H, 16β-H); 2.28 (s, 3H, NCH_3); 3.08 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 2.70 (d, $J_{9\alpha,10\alpha}$ = 6.38 Hz, 1H, 9α-H); 3.55 (s, 3H, 6-OCH_3); 3.89 (s, 3H, 3-OCH_3); 5.13 (d, $J_{5\beta,18}$ = 1.65 Hz, 1H, 5β-H); 6.03 (s[a], 1H, 20-OH); 6.58 (d, J = 8 Hz, 1H, 1-H); 6.73 (d, 1H, 2-H). — ^{13}C-NMR: δ = 21.69 (20-CH_3); 21.89 (C-10); 23.73 (C-18); 26.32 (tBu(CH_3)$_3$); 28. 04 (C-19); 33.13 (C-15); 33.82 (C-8); 35.65 (C-14); 40.04 (tBu-C); 43.72 (NCH_3); 43.89 (C-13); 44.78 (C-16); 48.59 (C-7); 52.76 (6-OCH_3); 56.97 (3-OCH_3); 62.28 (C-9); 81.40 (C-6); 94.48 (C-5); 79.13 (C-20); 114.56 (C-2); 119.18 (C-1); 128.41 (C-11); 133.79 (C-12); 141.81 (C-3); 146.24 (C-4). — MS (EI - 70 eV) m/z: 441 (10) [M^+], 384 (30); 352 (48); 326 (14); 340 (4); 135 (37); 91 (38); 57 (68); MS (TSP) m/z: 442 (100) $[M+1]^+$ — $C_{27}H_{39}NO_4$ (441.6). — Calcd.: C: 73.43; H: 8.90; N: 3.17; Found: C: 73.39; H: 8.92; N: 3.12.

Fraction 2 (**8**): 0.3 g (6.8 %) — Mp. 268-270 °C [diethyl ether] — R_{fA} = 0.46; R_{fB} = 0.40; R_{fC} = 0.89. — ^{1}H-NMR($CDCl_3$): δ = 1.02 (s, 9H, 20-tBu); 1.10 (m, 1H, 19-H); 1.30-1.60 (m, 3H, 8α-H, 18-H, 19-H); 1.41 (s,

3H, 20-CH_3); 1.80-2.20 (m, 4H, 15α-H, 15β-H, 16β-H, 18-H); 2.27 (s, 3H, NCH_3); 2.35 (m, 1H, 16α-H); 2.45-2.65 (m, 3H, 8β-H, 9α-H, 10α-H); 2.80 (s, 1 H, 5-H); 3.00 (d, $J_{10\beta,10\alpha}$ = 17 Hz, 1H, 10β-H); 3.33 (s, 3H, 6-OCH_3); 3.85 (s, 3H, 3-OCH_3); 5.00 (s[a], 1H, 20-OH); 6.10 (s[a], 1H, 4-OH); 6.58 (d, J = 8 Hz, 1H, 1-H); 6.68 (d, 1H, 2-H). — ^{13}C-NMR: δ = 19.34 (C-18); 21.93 (20-CH_3); 23.96 (C-10); 27.12 (tBu(CH_3)3); 28.61 (C-19); 33.49 (C-5); 34.83 (C-15); 30.05 (C-8); 38.96 (C-14); 39.50 (tBu-C); 43.32 (NCH_3); 42.05 (C-13); 45.71 (C-16); 43.06 (C-7); 54.06 (6-OCH_3); 55.76 (3-OCH_3); 58.50 (C-9); 78.67 (C-6); 69.95 (C-20); 107.93 (C-2); 117.45 (C-1); 127.35 (C-11); 132.12 (C-12); 143.42 (C-3); 144.59 (C-4). — MS (EI - 70 eV) m/z: 441 (3) [M^+], 408 (6); 383 (32); 340 (14); 312 (6); 277 (15); 240 (5); 217 (6); 176 (17); 149 (7); 108 (18); 57 (58). — $C_{27}H_{39}NO_4$ (441.6). — Calcd.: C: 73.43; H: 8.90; N: 3.17; Found: C: 73.40; H: 8.81; N: 3.11.

Fraction 3 (7): 0.3 g (7.8 %) — Mp. 167-169 °C — R_{fA} = 0.34; R_{fB} = 0.23; R_{fC} = 0.87. — ^{1}H-NMR($CDCl_3$): δ = 1.16 (m, 1H, 19-H); 1.40-1.80 (m, 4H, 8α-H, 15α-H, 15β-H, 19-H); 1.80-2.20 (m, 3H, 16β-H, 18-H); 2.26 (s, 3H, 20-CH_3); 2.29 (s, 3H, NCH_3); 2.35 (m, 1-H, 16α-H); 2.57 (dd, 1H, 10α-H); 2.70 (d, $J_{9\alpha,10\alpha}$ = 6.53 Hz, 1H, 9α-H); 2.90 (m, 1H, 8β-H); 3.00 (d, $J_{10\beta,10\alpha}$ = 18.3 Hz, 1H, 10β-H); 3.30 (s, 3H, 6-OCH_3); 3.39 (s, 1H, 5-H); 3.87 (s, 3H, 3-OCH_3); 5.82 (s[a], 1H, 4-OH); 6.62 (d, J = 8.1 Hz, 1H, 1-H); 6.69 (d, 1H, 2-H). — ^{13}C-NMR: δ = 19.86 (C-18); 23.74 (C-10); 27.66 (C-19); 28.95 (20-CH_3); 30.39 (C-8); 35.16 (C-15); 41.83 (C-14); 42.64 (C-13); 43.09 (NCH_3); 43.58 (C-5); 45.42 (C-16); 45.94 (C-7); 54.76 (6-OCH_3); 55.95 (3-OCH_3); 58.19 (C-9); 72.61 (C-6); 108.34 (C-2); 117.85 (C-1); 125.99 (C-11); 131.58 (C-12); 143.35 (C-3); 144.57 (C-4); 195.32 (C-20). — MS (EI - 70 eV) m/z: 383 (53) [M^+], 368 (53); 340 (33); 312 (15); 277 (17); 240 (14); 205 (9); 176 (43); 115 (20); 94 (14). — $C_{23}H_{29}NO_4$ (383.4). — Calcd.: C: 72.04; H: 7.62; N: 3.65; Found: C: 72.10; H: 7.58; N: 3.58.

Fraction 4 (9): 0.2 g (5.1 %) — Mp. 102-104 °C — R_{fA} = 0.26; R_{fB} = 0.18; R_{fC} = 0.72. — ^{1}H-NMR ($CDCl_3$): δ = 1.13 (m, 1H, 19-H); 1.30-1.60 (m, 3H, 8α-H, 15α-H, 19-H); 1.33 (d, 3H, 20-CH_3); 1.80-2.10 (m, 4H, 15β-H, 16β-H, 18-H); 2.20-2.40 (s[a], 1H, 20-OH); 2.30 (s, 3H, NCH_3); 2.30 (m, 1H, 16α-H); 2.45-2-75 (m, 3H, 8β-H, 9α-H, 10α-H); 2.48 (s, 1H, 5-H); 3.00 (d, $J_{10\beta,10\alpha}$ = 18.36 Hz, 1H, 10β-H); 3.30 (s, 3H, 6-OCH_3); 3.87 (s, 3H, 3-OCH_3); 4.13 (m, $J_{20,20Me}$ = 6.53 Hz, 1H, 20-H); 5.80 (s[a], 1H, 4-OH); 6.60 (d, J = 8.1 Hz, 1H, 1-H); 6.68 (d, 1H, 2-H). — NOE Data[1]: $f_{20\text{-}H}$ (5-H) = 5.7; $f_{20\text{-}H}$ (20-CH_3) = 5.6 — ^{13}C-NMR: δ = 19.31 (C-18); 21.79 (20-CH_3); 23.84 (C-10); 28.82 (C-8); 35.35 (C-5); 35.35 (C-15); 37.50 (C-7); 28.13 (C-19); 41.82 (C-14); 42.71 (C-13); 43.23 (NCH_3); 45.68 (C-16); 54.31 (6-OCH_3); 55.87 (3-OCH_3); 58.55 (C-9); 66.75 (C-6); 66.80 (C-20); 108.01 (C-2); 117.62 (C-1); 127.11 (C-11); 131.98 (C-12); 143.45 (C-3); 144.50 (C-4). — MS (EI - 70 eV) m/z: 385 (24) [M^+], 370 (84); 352 (100); 312 (16); 277 (14); 230 (23); 176 (25); 152 (14); 115 (20); 55 (31). — $C_{23}H_{31}NO_4$ (385.5). — Calcd.: C: 71.66; H: 8.11; N: 3.63; Found: C: 71.57; H: 8.06; N: 3.56.

Reaction of* 5 *with cyanogen bromide (**10a**): To a solution of the *N*-methyl compound (**5**) (3g, 6.8 mmol) in dry chloroform (30 ml) a solution of cyanogen bromide (0.85 g, 8 mmol) in chloroform (5 ml) was added. TLC examination showed that the reaction was complete after 24 h at room temperature. The solvent and the reagent excess were evaporated and the residual solid was crystallized from ethanol. 2.75 g (90 %) — Mp. 206-207 °C [lit.[7] 211 °C] — R_{fA} = 0.80; R_{fB} = 0.96; R_{fC} = 0.91. — ^{1}H-NMR ($CDCl_3$): δ = 0.85 (m, 1H, 19-H); 1.03 (s, 9H, 20-tBu); 1.18-1.35 (m, 2H, 18-H, 19-H); 1.40 (s, 3H, 20-CH_3); 3.24 (d, 1H, 10β-H); 3.44 (d, 1H, 9α-H); 3.54 (s, 3H, 6-OCH_3); 3.89 (s, 3H, 3-OCH_3); 5.13 (d, 1H, 5β-H); 5.81 (s[a], 1H, 20-OH); 6.63 (d, J = 8 Hz, 1H, 1-H); 6.77 (d, 1H, 2-H). — ^{13}C-NMR: δ = 21.71 (20-CH_3); 23.40 (C-19); 26.24 (20-tBu); 27.48 (C-10); 30.95 (C-18); 31.73 (C-8); 33.02 (C-15); 35.09 (C-14); 40.13 (C-16); 41.20 (20-tBu); 43.64 (C-13); 48.28 (C-7); 52.90 (6-OCH_3); 56.94 (3-OCH_3); 60.22 (C-9); 79.03 (C-20); 80.83 (C-6); 93.99 (C-5); 115.49 (C-2); 118.03 (N-CN); 119.87 (C-1); 125.57 (C-11); 131.80 (C-12); 142.72 (C-3); 146.60 (C-4). — MS (EI - 70 eV) m/z: 452 (18) [M^+], 395 (38); 363 (67); 337 (10); 255 (8); 165 (9); 101 (32); 57 (77); MS (TSP) m/z: 453 (3) [M+1]$^+$, 435 (100). — $C_{27}H_{36}N_2O_4$ (452.6). — Calcd.: C: 71.65; H: 8.02; N: 6.19; Found: C: 71.60; H: 8.10; N: 6.11.

[1] The irradiated proton is indicated in the subscript and the protons whose signals suffered intensity change is in brackets.

***Reaction of* 10a *with KOH* (10b)**: **10a** Was transformed into the *N*-demethyl derivative (**10b**) with KOH in diethyleneglycol as previously described in the literature[14]. —77 %— Mp. 185-186 °C. — R_{fA} = 0.38; R_{fB} = 0.38; R_{fC} = 0.81. — ^{1}H-NMR ($CDCl_3$): δ = 0.83 (m, 1H, 19-H); 1.03 (s, 9H, 20-tBu); 1.42 (s, 3H, 20-CH_3); 3.54 (s, 3H, 6-OCH_3); 3.88 (s, 3H, 3-OCH_3); 5.10 (d, 1H, 5β-H); 5.97 (s[a], 1H, 20-OH); 6.58 (d, J = 8 Hz, 1H, 1-H); 6.74 (d, 1H, 2-H). — ^{13}C-NMR: δ = 21.37 (20-CH_3); 23.62 (C-19); 26.07 (20-tBu); 27.88 (C-10); 32.34 (C-18); 33.12 (C-8); 33.70 (C-15); 34.65 (C-14); 36.26 (C-16); 39.83 (20-tBu); 44.53 (C-13); 48.36 (C-7); 52.50 (6-OCH_3); 54.86 (3-OCH_3); 56.74 (C-9); 78.85 (C-20); 81.00 (C-6); 94.55 (C-5); 114.60 (C-2); 119.05 (C-1); 128.03 (C-11); 133.42 (C-12); 141.82 (C-3); 146.20 (C-4). — MS (EI - 70 eV) m/z: 427 (55) [M^+], 370 (48); 336 (85); 312 (21); 251 (8); 226 (18); 204 (28); 175 (11); 123 (17); 101 (34); 83 (24); 57 (79); MS (TSP) m/z: 428 (100) $[M+1]^+$ — $C_{26}H_{37}NO_4$ (427.6). — Calcd.: C: 73.03; H: 8.72; N: 3.28; Found: C: 72.94; H: 8.69; N: 3.22.

***N-Alkylation of* 10b (10c)**: To a solution of **10b** (2.1g, 4.9 mmol) in dry *N,N*-dimethylformamide (12 ml) powdered sodium hydrogen carbonate (1.25 g, 14.8 mmol) and cyclopropylmethyl bromide (1.0 g, 7.4 mmol) were added. After stirring at 90-95 °C for 20 h the inorganic salts were removed by filtration. The filtrate was evaporated under diminished pressure, the residue was suspended in water, alkalized with a small volume of aqueous ammonia, extracted with chloroform and then dried (Na_2SO_4). After evaporation of the solvent the product (**10c**) was crystallized from ethanol. 1.68 g (72 %) — Mp. 150-151 °C. — R_{fA} = 0.86; R_{fB} = 0.91; R_{fC} = 0.90. — ^{1}H-NMR ($CDCl_3$): δ = 0.12 (m, 2H, cPropCH_{2syn}); 0.49 (m, 2H, cPropCH_{2anti}); 0.79 (m, 1H, cProp<u>CH</u>); 0.89 (m, 1H, 19-H); 1.04 (s, 9H, 20-tBu); 1.42 (s, 3H, 20-CH_3); 2.98 (d, 1H, 10β-H); 3.04 (d, 1H, 9α-H); 3.56 (s, 3H, 6-OCH_3); 3.89 (s, 3H, 3-OCH_3); 5.15 (d, 1H, 5β-H); 5.98 (s[a], 1H, 20-OH); 6.57 (d, 1H, 1-H); 6.73 (d, 1H, 2-H). — ^{13}C-NMR: δ = 3.10 (cPropCH_2); 3.79 (cPropCH_2); 9.36 (cPropCH); 21.49 (20-CH_3); 22.82 (C-10); 23.79 (C-19); 26.30 (20-tBu); 28.03 (C-18); 33.27 (C-8); 33.92 (C-15); 35.50 (C-14); 40.02 (20-tBu); 43.27 (C-16); 44.55 (C-13); 49.08 (C-7); 52.76 (6-OCH_3); 57.02 (C-9); 59.45 (3-OCH_3); 59.74 (N<u>C</u>H_2cProp); 79.11 (C-20); 81.55 (C-6); 94.70 (C-5); 114.70 (C-2); 119.26 (C-1); 128.51 (C-11); 134.12 (C-12); 141.90 (C-3); 146.36 (C-4). — MS (EI - 70 eV) m/z: 481 (9) [M^+], 440 (12); 424 (15); 392 (33); 366 (13); 310 (6); 101 (16); 83 (13); 55 (100); MS (TSP) m/z: 482 (100) $[M+1]^+$ — $C_{30}H_{43}NO_4$ (481.6). — Calcd.: C: 74.81; H: 9.00; N: 2.91; Found: C: 74.76; H: 8.95; N: 2.87.

Reaction of β-thevinone* (4a) *with n-propylmagnesium bromide: To the Grignard reagent prepared from magnesium shavings (1.90 g) and n-propyl bomide (9.8 ml) in abs. toluene (12 ml) and abs. ether (27 ml) a solution of the β-thevinone (**4a**) (4.90 g, 12.8 mmol) in abs. toluene (47 ml) was added dropwise over a period of 1 h. Then the solution was stirred under gentle reflux for 2 h, allowed to cool to room temperature and poured into 150 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with toluene (3 x 50 ml), the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated to obtain a four-component product (TLC). The mixture was separated by column chromatography with eluent system [B].

Fraction 1 (**12**): 0.54 g (10 %) — Mp.: 162-163 °C [diethyl ether] — R_{fA} = 0.68; R_{fB} = 0.85; R_{fC} = 0.87. — ^{1}H-NMR ($CDCl_3$): δ = 0.87 (t, 3H, Pr-CH_3); 0.93 (m, 1H, 8α-H); 1.20-1.54 (m, 5H, Pr-(CH_2)2), 8β-H); 1.40 (s, 3H, 20-CH_3); 1.70 (m, 1H, 15α-H); 1.95 (m, 1H, 7-H); 2.13-2.60 (m, 4H, 15β-H, 10α-H, 16-H(2)); 2.36 (s, 3H, NCH_3); 3.12 (d, 1H, 9α-H); 3.21 (d, 1H, 10β-H); 3.71 (s, 3H, 6-OCH_3); 3.82 (s, 3H, 3-OCH_3); 4.78 (s[a], 1H, 20-OH); 5.27 (d, $J_{5\beta,18}$ = 1.6 Hz, 1H, 5β-H); 5.33 (d, $J_{19,18}$ = 8.97 Hz, 1H, 19-H); 6.18 (dd, $J_{18,19}$ = 8.97 Hz, $J_{18,5\beta}$ = 1.60 Hz, 18-H); 6.51 (d, $J_{1,2}$ = 8.24 Hz, 1H, 1-H); 6.63 (d, 1H, 2-H). — NOE Data[1]: $f_{18\text{-}H}$ (19-H) = 10.8; $f_{18\text{-}H}$ (6-OCH3) = 11.3; $f_{18\text{-}H}$ (7α-H) = 2.8 — ^{13}C-NMR: δ = 14.36 (Pr-<u>CH_3</u>); 15.93 (Pr<u>CH_2</u>); 22.17 (C-10); 26.37 (C-8); 26.37 (20-CH_3); 29.97 (C-15); 42.55 (C-14); 43.57 (NCH_3); 44.79 (Pr<u>CH_2</u>); 45.22 (C-16); 46.34 (C-13); 55.15 (6-OCH_3); 56.87 (3-OCH_3); 60.87 (C-9); 75.57 (C-20); 85.28 (C-6); 94.86 (C-5); 114.20 (C-2); 119.42 (C-1); 127.94 (C-11); 130.61 (C-18); 134.36 (C-19); 136.05 (C-12); 142.32 (C-3); 147.55 (C-4). — MS (TSP) m/z: 426 (100) $[M+1]^+$. — $C_{26}H_{35}NO_4$ (425.6). — Calcd.: C: 73.38; H: 8.29; N: 3.29; Found: C: 73.35; H: 8.22; N: 2.21.

Fraction 2 (**13**): 0.40 g (7 %) — Mp. 203-204 °C — R_{fA} = 0.60; R_{fB} = 0.65; R_{fC} = 0.82. — ^{1}H-NMR($CDCl_3$): δ = 0.70 (d, 1H, 8α-H); 0.88 (t, 3H, Pr-CH_3); 1.20-1.60 (m, 4H, Pr-$(CH_2)_2$); 1.49 (s, 3H, 20-CH_3); 1.70 (m, 1H, 15β-H); 1.88 (ddd, 1H, 15β-H); 2.08 (ddd, 1H, 16β-H); 2.33 (s, 3H, NCH_3); 2.40 (m, 1H, 16α-H); 2.48 (d, 1H, 8β-H); 2.77 (dd, 1H, 10α-H); 2.95 (s, 1H, 5-H); 3.08 (d, 1H, 9α-H); 3.12 (d, $J_{10\beta,10\alpha}$ = 16 Hz, 1H, 10β-H); 3.44 (s, 3H, 6-OCH_3); 3.82 (s, 3H, 3-OCH_3); 4.72 (s[a], 1H, 20-OH); 5.60 (d, $J_{19,18}$ = 8.8 Hz, 1H, 19-H); 5.96 (d, 1H, 18-H); 6.55 (d, J = 8 Hz, 1H, 1-H); 6.63 (d, 1H, 2-H). — NOE Data[1]: $f_{19\text{-}H}$ (18-H) = 9.1; $f_{19\text{-}H}$ (9α-H) = 3.5; $f_{19\text{-}H}$ (10α-H) = 7.3; $f_{19\text{-}H}$ (8α-H) = 1.2; $f_{8\alpha\text{-}H}$ (8β-H) = 32.0; $f_{8\alpha\text{-}H}$ (9α-H) = 3.1; $f_{8\alpha\text{-}H}$ (19-H) = 3.7; $f_{8\alpha\text{-}H}$ (18-H) = 2.0 — ^{13}C-NMR: δ = 14.47 (Pr-CH_3); 16.14 (Pr-(CH_2)); 24.29 (C-10); 28.28 (20-CH_3); 31.78 (C-8); 31.85 (C-5); 32.63 (C-15); 40.16 (C-14); 40.65 (C-13); 43.31 (NCH_3); 44.69 (Pr-(CH_2)); 46.14 (C-7); 46.23 (C-16); 55.76 (6-OCH_3); 56.91 (3-OCH_3); 56.91 (C-9); 73.33 (C-20); 71.41 (C-6); 107.94 (C-2); 117.67 (C-1); 125.74 (C-18); 127.55 (C-11); 130.62 (C-19); 131.91 (C-12); 143.11 (C-3); 144.32 (C-4). — MS (TSP) m/z: 426 (100) $[M+1]^+$. — $C_{26}H_{35}NO_4$ (425.6). — Calcd.: C: 73.38; H: 8.29; N: 3.29; Found: C: 73.31; H: 8.32; N: 3.25.

Fraction 3 (**14**): 0.9 g (18 %) — oil — R_{fA} = 0.53; R_{fB} = 0.48; R_{fC} = 0.78. — ^{1}H-NMR($CDCl_3$): δ = 0.90 (s[a], 1H, 20-OH); 1.25 (d, 3H, 20-CH_3); 1.37 (d, 1H, 8α-H); 1.57 (m,1H, 15α-H); 1.71 (m, 1H, 7-H); 2.22-2.63 (m, 2H, 15β-H, 16β-H); 2.41 (s, 3H, NCH_3); 2.75 (m, 1H, 16α-H); 2.87 (m, 1H, 8β-H); 3.20 (d, 1H, 9α-H); 3.25 (d, 1H, 10β-H); 3.51 (s, 3H, 6-OCH_3); 3.81 (s, 3H, 3-OCH_3); 4.43 (m, 1H, 20-H); 5.24 (d, $J_{5\beta,18}$ = 1.57 Hz, 1H, 5β-H); 5.41 (d, $J_{19,18}$ = 8.98 Hz, 1H, 19-H); 6.07 (dd, $J_{18,19}$ = 8.98 Hz, $J_{18,5\beta}$ = 1.57 Hz, 1H, 18-H); 6.49 (d, 1H, 1-H); 6.62 (d, 1H, 2-H). — ^{13}C-NMR: δ = 22.22 (C-10); 22.99 (C-8); 23.76 (20-CH_3); 29.30 (C-15); 42.97 (C-14); 43.60 (NCH_3); 45.57 (C-16); 46.59 (C-13); 47.23 (C-7); 52.75 (6-OCH_3); 56.78 (3-OCH_3); 61.05 (C-9); 64.25 (C-20); 81.68 (C-6); 93.47 (C-5); 113.78 (C-2); 118.90 (C-1); 127.89 (C-11); 129.78 (C-18); 135.75 (C-19); 136.28 (C-12); 142.20 (C-3); 148.08 (C-4). — MS (TSP) m/z: 384 (100) $[M+1]^+$. — $C_{23}H_{29}NO_4$ (383.5). — Calcd.: C: 72.04; H: 7.62; N: 3.65; Found: C: 72.10; H: 7.55; N: 3.58.

Fraction 4 (**15**): 0.1 g (2 %) — oil — R_{fA} = 0.30; R_{fB} = 0.26; R_{fC} = 0.76. — ^{1}H-NMR ($CDCl_3$): δ = 0.75 (d, $J_{8\alpha,8\beta}$ = 12 Hz, 1H, 8α-H); 1.32 (d, 3H, 20-CH_3); 1.70 (m, 1H, 15α-H); 1.88 (m, 1H, 15β-H); 2.12 (m, 1H, 16β-H); 2.37 (s, 3H, NCH_3); 2.46 (m, 1H, 16α-H); 2.62 (d, 1H, 8β-H); 2.73 (s, 1H, 5-H); 2.82 (m, 1H, 10α-H); 3.09 (d, 1H, 10β-H); 3.17 (d, 1H, 9α-H); 3.42 (s, 3H, 6-OCH_3); 3.82 (s, 3H, 3-OCH_3); 4.23 (quar, 1H, 20-H); 5.58 (d, $J_{19,18}$ = 8.89 Hz, 1H, 19-H); 5.77 (s[a], 1H, 4-OH); 6.00 (d, 1H, 18-H); 6.55 (d, 1H, 1-H); 6.64 (d, 1H, 2-H). — ^{13}C-NMR: δ = 22.00 (20-CH_3); 24.36 (C-10); 27.92 (C-8); 32.72 (C-15); 34.50 (C-5); 39.36 (C-14); 40.18 (C-13); 43.17 (NCH_3); 45.68 (C-7); 46.20 (C-16); 55.78 (6-OCH_3); 56.82 (3-OCH_3); 56.97 (C-9); 66.29 (C-20); 69.57 (C-6); 108.01 (C-2); 117.68 (C-1); 125.69 (C-18); 127.20 (C-11); 130.11 (C-19); 131.69 (C-12); 143.14 (C-3); 144.34 (C-4). — MS (TSP) m/z: 384 (100) $[M+1]^+$. — $C_{23}H_{29}NO_4$ (383.5). — Calcd.: C: 72.04; H: 7.62; N: 3.65; Found: C: 72.12; H: 7.57; N: 3.61.

Reaction of β-dihydrothevinone* (4b) *with n-propylmagnesium bromide: To the Grignard reagent prepared from magnesium shavings (1.90 g) and n-propyl bomide (9.8 ml) in abs. toluene (12 ml) and abs. ether (27 ml) a solution of the β-dihydrothevinone (**4b**) (5.00 g, 13 mmol) in abs. toluene (47 ml) was added dropwise over a period of 1 h. Then the solution was stirred under gentle reflux for 2 h, allowed to cool to room temperature and poured into 150 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with toluene (3 x 50 ml), the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated to obtain a three-component product (TLC). The mixture was separated by column chromatography with eluent system [B].

Fraction 1 (**16**): 0.90 g (16 %) — Mp. 155-156 °C — R_{fA} = 0.67; R_{fB} = 0.88; R_{fC} = 0.91. — ^{1}H-NMR ($CDCl_3$): δ = 0.80-1.00 (m, 2H, 19-H); 0.92 (20-Pr-CH_3); 1.10-1.30 (m, 2H, 18-H); 1.37 (s, 3H, 20-CH_3); 1.30-1.80 (m, 4H, 20-Pr-$(CH_2)_2$); 2.00-2.50 (m, 8H, 7α-H, 8α-H, 8β-H, 10α-H, 15α-H, 15β-H, 16β-H, 16α-H); 2.31 (s, 3H, NCH_3); 2.73 (d, $J_{9\alpha,10\alpha}$ = 6.38 Hz, 1H, 9α-H); 3.10 (d, $J_{10\beta,10\alpha}$ = 18.43 Hz, 1H, 10β-H); 3.54 (s, 3H, 6-OCH_3); 3.88 (s, 3H, 3-OCH_3); 5.12 (d, $J_{5\beta,18}$ = 1.91 Hz, 1H, 5β-H); 5.20 (s[a], 1H, 20-OH); 6.58 (d, J = 8 Hz, 1H, 1-H); 6.72 (d, 1H, 2-H). — ^{13}C-NMR: δ = 14.49 (Pr-CH_3); 15.85 (Pr-(CH_2)); 21.83 (C-

10); 23.82 (C-18); 25.33 (20-CH_3); 28.26 (C-19); 31.74 (C-8); 32.96 (C-15); 35.56 (C-14); 43.29 (Pr-(CH_2)); 43.69 (NCH_3); 43.99 (C-13); 44.89 (C-16); 50.25 (C-7); 52.82 (6-OCH_3); 57.00 (3-OCH_3); 62.22 (C-9); 75.48 (C-20); 81.16 (C-6); 94.46 (C-5); 114.74 (C-2); 119.17 (C-1); 128.29 (C-11); 133.59 (C-12); 141.82 (C-3); 146.32 (C-4). — MS (EI - 70 eV) m/z: 427 (100) [M^+], 394 (40); 340 (63); 310 (68); 276 (31); 240 (40); 87 (27). — $C_{26}H_{37}NO_4$ (427.6). — Calcd.: C: 73.03; H: 8.72; N: 3.28; Found: C: 72.95; H: 8.74; N: 3.25.

Fraction 2 (**17**): 0.58 g (10 %) — Mp.: 179-180 °C — R_{fA} = 0.53; R_{fB} = 0.50; R_{fC} = 0.90. — ^{1}H-NMR($CDCl_3$): δ = 0.92 (t, 3H, 20-Pr-CH_3); 1.12 (m, 1H, 19-H); 1.24 (d, 1H, 8α-H); 1.42 (s, 3H, 20-CH_3); 1.35-1.65 (m, 6H, 15-H, 19-H, 20-Pr-(CH_2)2); 1.82-2.10 (m, 5H, 15-H, 16β-H, 8β-H, 18-H(2)); 2.30 (s, 3H, NCH_3); 2.24-2.40 (m, 1H, 16α-H); 2.47-2.69 (m, 3H, 8β-H, 9α-H, 10α-H); 2.86 (s, 1 H, 5-H); 3.00 (d, $J_{10\beta,10\alpha}$ = 17.6 Hz, 1H, 10β-H); 3.34 (s, 3H, 6-OCH_3); 3.87 (s, 3H, 3-OCH_3); 4.82 (s[a], 1H, 20-OH); 5.85 (s[a], 1H, 4-OH); 6.58 (d, 1H, 1-H); 6.68 (d, 1H, 2-H). — ^{13}C-NMR: δ = 14.64 (Pr-CH_3); 16.79 (Pr-CH_2); 19.55 (C-18); 23.93 (C-10); 26.18 (20-CH_3); 28.27 (C-19); 32.16 (C-5); 32.50 (C-8); 35.01 (C-15); 38.57 (C-14); 42.24 (C-13); 42.97 (C-7); 43.24 (N-CH_3); 45.03 (Pr-CH_2); 45.70 (C-16); 54.17 (6-OCH_3); 55.75 (3-OCH_3); 58.56 (C-9); 68.81 (C-6); 73.90 (C-20); 107.98 (C-2); 117.48 (C-1); 127.09 (C-11); 131.73 (C-12); 143.41 (C-3); 144.56 (C-4). — MS (TSP) m/z: 428 (100) $[M+1]^+$. — $C_{26}H_{37}NO_4$ (427.6). — Calcd.: C: 73.03; H: 8.72; N: 3.28; Found: C: 73.08; H: 8.63; N: 3.19.

Fraction 3 (**18**):— 0.10 g (2 %) — oil — R_{fA} = 0.15; R_{fB} = 0.13; R_{fC} = 0.67. — ^{1}H-NMR($CDCl_3$): δ = 0.92 (m, 1H, 19-H); 1.24 (d, 3H, 20-CH_3); 2.35 (s, 3H, NCH_3); 3.13 (d, 1H, 10β-H); 3.42 (s, 3H, 6-OCH_3); 3.88 (s, 3H, 3-OCH_3); 4.47 (m, 1H, 20-H); 5.16 (d, 1H, 5β-H); 6.56 (d, 1H, 1-H); 6.72 (d, 1H, 2-H). — MS (TSP) m/z: 386 (100) $[M+1]^+$. — $C_{23}H_{31}NO_4$ (385.5). — Calcd.: C: 71.66; H: 8.11; N: 3.63; Found: C: 71.58; H: 8.13; N: 3.57.

3-O-Demethylation

12 (1.3 g, 3.0 mmol) was added to a solution of 2.0 g potassium hydroxide in 20 ml diethylene glycol at 70 °C. The mixture was boiled at 210-220 °C under argon for 75 minutes. The reaction mixture was diluted with 50 ml of water and 3.0 g of ammonium chloride was added until precipitation of the phenol. The product was isolated by chloroform-methanol 9:1 extraction. The crude product was purified by column chromatography with the eluent system ethyl acetate-chloroform-25 % NH_3 70:30:1 [D].

7β-Etorphine (**19**): 0.57g (46 %) — Mp. 168-170 °C — R_{fB} = 0.50; R_{fC} = 0.51; R_{fD} = 0.37. — ^{1}H-NMR ($CDCl_3$): δ = 0.83 (t, 3H, Pr-CH_3); 1.20-2.05 (m, 6H, 8α-H, 15α-H, Pr-(CH_2)2); 1.40 (s, 3H, 20-CH_3); 2.10-2.60 (m, 6H, 7α-H, 8β-H, 10α-H, 15β-H, 16β-H, 16α-H); 2.37 (s, 3H, NCH_3); 3.18 (d, 1H, 9α-H); 3.20 (d, 1H, 10β-H); 3.68 (s, 3H, 6-OCH_3); 4.86 (s[a], 1H, 20-OH); 5.26 (d, $J_{5\beta,18}$ = 1.2 Hz, 1H, 5β-H); 5.35 (d, 1H, 19-H); 6.16 (dd, 1H, 18-H); 6.47 (d, J = 8 Hz, 1H, 1-H); 6.59 (d, 1H, 2-H). — ^{13}C-NMR: δ = 14.22 (Pr-$\underline{CH_3}$); 15.87 (Pr$\underline{CH_2}$); 22.21 (C-10); 26.18 (C-8); 26.41 (20-CH_3); 29.69 (C-15); 42.53 (C-14); 43.32 (NCH_3); 44.57 (Pr$\underline{CH_2}$); 45.15 (C-16); 46.46 (C-13); 51.25 (C-7); 54.94 (6-OCH_3); 60.78 (C-9); 75.98 (C-20); 85.19 (C-6); 94.59 (C-5); 116.38 (C-2); 119.67 (C-1); 126.33 (C-11); 129.90 (C-18); 134.52 (C-19); 135.18 (C-12); 138.62 (C-3); 146.12 (C-4). — MS (EI - 70 eV) m/z: 411 (77) [M^+]; 396 (7); 368 (4); 324 (24); 298 (10); 266 (4); 241 (7); 215 (41); 162 (15); 121 (18); 87 (23); 44 (100) — $C_{25}H_{33}NO_4$ (411.5). — Calcd.: C: 72.96; H: 8.08; N: 3.40; Found: C: 72.87; H: 8.12; N: 3.43.

11 and **20** were prepared from **10c** and **16** analogously to **19**

7β-Buprenorphine (**11**): 42 % Mp.: 214-215 °C, lit.[7] 216 °C — R_{fA} = 0.35; R_{fB} = 0.29; R_{fC} = 0.50. — ^{1}H-NMR ($CDCl_3$): δ = 0.09 (m, 2H, cProp$\underline{CH_2}_{syn}$); 0.47 (m, 2H, cProp$\underline{CH_2}_{anti}$); 0.78 (m, 1H, cProp$\underline{CH}$); 0.90 (m, 1H, 19-H); 0.99 (s, 9H, 20-tBu); 1.39 (s, 3H, 20-CH_3); 2.97 (d, 1H, 10β-H); 3.06 (d, 1H, 9α-H); 3.53 (s, 3H, 6-OCH_3); 5.14 (d, 1H, 5β-H); 6.03 (s[a], 1H, 20-OH); 6.53 (d, 1H, 1-H); 6.71 (d, 1H, 2-H). — ^{13}C-NMR: δ = 3.14 (cPropCH_2); 3.76 (cPropCH_2); 9.23 (cPropCH); 22.24 (20-CH_3); 23.24 (C-10); 23.70 (C-19);

26.23 (20-tBu); 28.28 (C-18); 33.34 (C-8); 33.85 (C-15); 35.61 (C-14); 40.19 (20-tBu); 43.23 (C-16); 44.87 (C-13); 48.79 (C-7); 52.54 (6-OCH_3); 59.35 (C-9); 59.66 ($N\underline{C}H_2$cProp); 79.29 (C-20); 81.58 (C-6); 94.54 (C-5); 117.19 (C-2); 119.43 (C-1); 126.95 (C-11); 133.43 (C-12); 138.21 (C-3); 145.26 (C-4). — MS (TSP) m/z: 467 (100) $[M+1]^+$ — $C_{29}H_{41}NO_4$ (467.6). — Calcd.: C: 74.48; H: 8.84; N: 3.00; Found: C: 74.39; H: 8.78; N: 2.95.

***7β-Dihydroetorphine* (20)**: (48 %) — Mp. 121-122 °C – R_{fA} = 0.40; R_{fB} = 0.49; R_{fC} = 0.50. — ^{1}H-NMR ($CDCl_3$): δ = 0.80-1.00 (m, 1H, 19-H); 0.85 (t, 3H, Pr-CH_3); 1.20-1.80 (m, 9H, 8α-H, 15α-H, 19-H, 18-H(2), Pr-$(CH_2)_2$); 1.37 (s, 3H, 20-CH_3); 2.00-2.50 (m, 6H, 7α-H, 8β-H, 10α-H, 15β-H, 16β-H, 16α-H); 2.31 (s, 3H, NCH_3); 2.75 (d, $J_{9\alpha,10\alpha}$ = 6.73 Hz, 1H, 9α-H); 3.10 (d, $J_{10\beta,10\alpha}$ = 17.82 Hz, 1H, 10β-H); 3.52 (s, 3H, 6-OCH_3); 5.11 (d, $J_{5\beta,18}$ = 1.2 Hz, 1H, 5β-H); 5.23 (s[a], 1H, 20-OH); 5.75 (s[a], 1H, 3-OH); 6.53 (d, J = 8 Hz, 1H, 1-H); 6.68 (d, 1H, 2-H). — ^{13}C-NMR: δ = 14.44 (Pr-CH_3); 15.85 (Pr-(CH_2)); 22.03 (C-10); 23.71 (C-18); 25.53 (20-CH_3); 28.24 (C-19); 31.61 (C-8); 32.74 (C-15); 35.65 (C-14); 43.19 (Pr-(CH_2)); 43.54 (NCH_3); 44.21 (C-13); 44.89 (C-16); 49.60 (C-7); 52.84 (6-OCH_3); 62.27 (C-9); 75.86 (C-20); 81.21 (C-6); 94.60 (C-5); 116.71 (C-2); 119.49 (C-1); 126.88 (C-11); 133.12 (C-12); 138.11 (C-3); 144.98 (C-4). — MS (TSP) m/z: 414 (100) $[M+1]^+$, (100) — $C_{25}H_{35}NO_4$ (413.5). — Calcd.: C: 72.61; H: 8.53; N: 3.39; Found: C: 72.55; H: 8.51; N: 3.35.

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