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Synthesis of neopine and its 5β- and 7-substituted derivatives (chemistry of opium alkaloids, part XL#)

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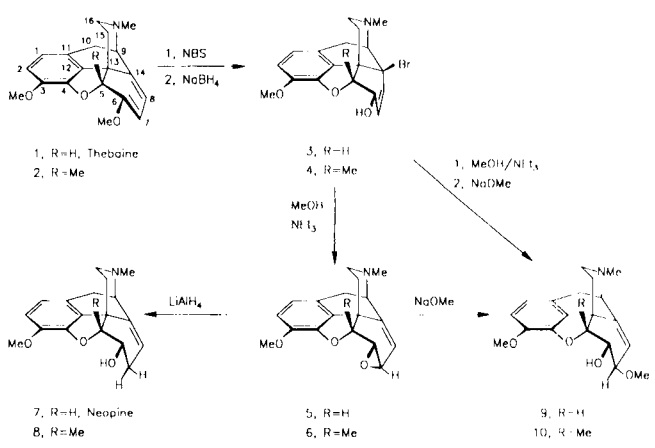
Abstract. Heating 14β-bromocodeine (**3**) with methanol and triethylamine yielded 6α,7α-epoxy-6-deoxyneopine (**5**). The epoxide **5** was reduced to neopine (**7**) with lithium aluminium hydride, whereas reaction of **5** with sodium methoxide gave 7β-methoxyneopine (**9**). Similar reactions were performed with 14β-bromo-5β-methylcodeine (**4**), yielding the corresponding 5β-methyl derivatives **6**, **8** and **10**. Acetylation of **3** and **4** gave 6α-*O*-acetyl-14β-bromocodeine (**11**) and its 5β-methyl analogue **12**, respectively, from which the ortho esters **13** and **14** were obtained after treatment with methanol. Acid hydrolysis of **13** or, better, solvolysis of **11** in water yielded a mixture of 6α-*O*-acetyl-7α-hydroxyneopine (**15**) and 7α-acetoxyneopine (**17**). Under the same conditions **12** and **14** gave the 5β-methyl analogues **16** and **18**.

Introduction

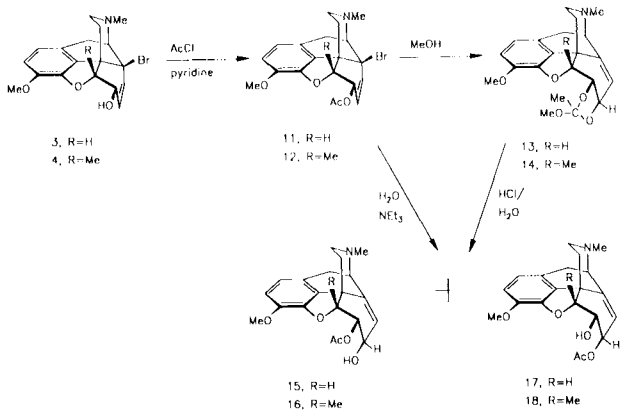
There is a great interest in novel classes of morphinans for biological screening with regard to the interaction with different types of opioid receptor[1]. An important class of morphinans are the rigid Diels–Alder adducts of thebaine and its analogues[2,3]. Several of the latter compounds are easily obtained from neopine and derivatives thereof[4,5]. Natural sources of neopine, which is a minor alkaloid (less than 0.1%) from *Papaver somniferum* L.[6], are limited. Some syntheses of neopine have been described earlier. Reduction of neopinone yields a mixture of isomers which are difficult to separate[7]. A synthesis starting from 14β-chlorocodeine gives neopine in good yield[8]. We have developed a new synthesis of neopine starting from readily available thebaine, which provides also access to a number of 7-substituted neopine derivatives. Starting from 5β-methylthebaine, 5β-methylneopine and the corresponding 5β-methyl analogues were prepared. The 7α-substituted compounds in particular are convenient starting materials for the synthesis of 7-substituted morphinan-6,8-dienes[9].

Results and discussion

For the synthesis of neopine and some of its derivatives we started from thebaine (**1**) and 5β-methylthebaine (**2**)[9], which were readily converted into 14β-bromocodeine (**3**) and 14β-bromo-5β-methylcodeine (**4**), respectively. *Okuda* et al.[10] reported that compound **3** afforded three products when it was stirred in a mixture of methanol and tetrahydrofuran. One of these products, isolated in 40% yield, was identified as 7-methoxyneopine (**9**). They suggested that the methoxy group was at the 7β-position. However, in our hands four products were obtained. TLC analysis indicated that the three minor compounds were the same as published earlier[10]. The mass spectrum of the main product showed a molecular weight of 297, indicating that it was not methoxy morphinan **9**. This was confirmed by the ^{1}H-NMR spectrum, which demonstrated the absence of the signal of the 7-methoxy group. The spectrum showed one vinylic proton at δ 5.82 (d) and the signal of H-5 at δ 4.95 (d). They form the "head" and "tail" of a linear ABCD system; of the two "inner" protons, the one coupled to the vinylic proton was found at δ 3.71 (dd), and the one next to H-5 at δ 3.41 (dd). From the three coupling constants, the position of H-9 at δ 3.59, and other spectral data, we concluded that the main product was 6α-7α-epoxy-6-deoxyneopine (**5**). This epoxide was described earlier[11], isolated in 4% yield as an intermediate in the hydrolysis of **3**. The ^{1}H-NMR spectrum was in all aspects identical to that of our compound. This result induced us to investigate the optimization of the yield of **5**. When **3** was refluxed in methanol and triethylamine for



Scheme 1. Synthesis of neopine and derivatives **5**–**10** *from thebaine* (**1**) *and 5β-methylthebaine* (**2**).



Scheme 2. Synthesis of 7α-substituted neopine derivatives **13–18** *starting from* **3** *and* **4**.

three minutes, the yield of **5** was 47% after flash column chromatography. In analogy to this reaction, the 5β-methyl compound **4** gave 6α,7α-epoxy-5β-methyl-6-deoxyneopine (**6**) in 35% yield under the same conditions, but after 1 hour reaction time. An internal S_N2' reaction explains the formation of the 6α,7α-epoxy ring and the double bond between the 8- and 14-position[12]. The epoxides **5** and **6** are valuable intermediates for the synthesis of neopine and the 7β-substituted derivatives. Reduction of **5** with lithium aluminium hydride gave neopine in quantitative yield, which was fully characterized by ^1H and ^{13}C NMR. Obviously, the hydride reagent attacks selectively at the 7β position. 5β-Methylneopine was synthesized in a similar way starting from **6**.

When the epoxide **5** was treated with methanol in the presence of sulfuric acid, 7β-methoxyneopine (**9**) was obtained in 16% yield. The configuration of the methoxy group at position C-7 was established by analysis of the spin system and the coupling constants of the ^1H NMR spectrum. The reaction of the epoxide with sodium methoxide gave the desired morphinan **9** in good yield. However, the best results (total yield 52%) were obtained when 14β-bromocodeine was converted into **9** via the epoxide **5** in a one-pot reaction. In this way **4** gave 7β-methoxy-5β-methylneopine (**10**) in a total yield of 54%.

In order to block the epoxide formation and to get into the 7α-substituted neopine series, we esterified the hydroxyl group at the 6α-position of **3** and **4** with acetyl chloride and pyridine, giving 6α-*O*-acetyl-14β-bromocodeine (**11**) and 6α-*O*-acetyl-14β-bromo-5β-methylcodeine (**12**), respectively (Scheme 2).

Refluxing **11** or **12** in methanol and triethylamine for 30 min and 1 hour, respectively, gave in both cases one main product (TLC). The molecular weights were in agreement with the replacement of the bromo substituent by a methoxy group. The IR and ^{13}C-NMR spectrum showed that no carbonyl group was present. In the ^1H-NMR spectra of the products the signal of a methoxy group was found at δ 3.2, besides those of the aromatic methoxy group and the signal of a methyl group was found at δ 0.9. Furthermore, in both cases only one vinylic proton was observed and the signal of H-9 was found at δ 3.6. We concluded from all these data that the main products of the methanolysis of **11** and **12** were the cyclic ortho esters 6α,7α-(1-methoxy-ethylidenedioxy)-6-deoxyneopine (**13**) and its 5β-methyl analogue **14** (Scheme 2)[13]. Both products contain a new chiral centre, the 'central' carbon atom of the ortho ester, and the diastereomeric ratio in our products was found to be about 9:1 (^1H NMR). Presumably, there is an equilibrium between the acetyl group, methanol, and an unstable hemi ortho ester. Nucleophilic attack of the hydroxyl group of the hemi ortho ester at C-7, followed by an allylic rearrangement and expulsion of a bromide ion, promoted by methanol, results in the found ortho esters.

Acidic hydrolysis of **13** gave a mixture of two major products (ratio **15**/**17** 3:2), which were separated by column chromatography. The molecular weight of each of the two products was 357, and the IR spectra of the compounds showed the presence of both a carbonyl group and a hydroxyl group. From this, combined with the data from ^1H and ^{13}C NMR, we conclude that the products are 6α-*O*-acetyl-7α-hydroxyneopine (**15**) and 7α-acetoxyneopine (**17**). The position of the acetyl group was established mainly from the ^1H-NMR spectrum by the analysis of the spin system of H-5 to H-8. In the spectrum of the first fraction, the signals of H-6 and H-7 were found at δ 4.37 and δ 5.52, respectively, while these signals were found at δ 5.58 and δ 4.56, respectively, for the second fraction. Probably, the down-field shifts of H-7 (first fraction) and H-6 (second fraction) are caused by the position of the acetyl group. This discriminates between the two components in which the acetoxy group is either at the 6α position (**15**, second fraction) or at the 7α position (**17**, first fraction). Additional evidence for the acetyl group positions was found from their signals at δ 1.50 and at δ 2.10. The 0.6-ppm-upfield position for the 6α-acetyl signal can be explained by the shielding effect of the aromatic nucleus. The formation of **15** and **17** is in agreement with the general mechanism for the hydrolysis of an ortho ester[14]. We have indications from the lithium aluminium hydride reduction of both **15** and **17** that a third product is 7α-hydroxyneopine. We made no attempts to isolate this diol. In a similar way **14** yielded a mixture (ratio **16**/**18** 15:1) from which 6α-*O*-acetyl-7α-hydroxy-5β-methylneopine (**16**) and 7α-acetoxy-5β-methylneopine (**18**) were isolated.

Reaction of **11** or **12** with methanol results in the formation of the ortho esters **13** or **14**, respectively. Replacement of methanol by water may yield the above-mentioned acetyl-neopine derivatives in a one-pot reaction. Thus, **11** or **12** was refluxed in water and triethylamine with THF as cosolvent. The reactions were complete in about 4 hours. In both cases the two main products were the expected neopines **15** and **17** and their 5β-methyl analogues **16** and **18**.

In summary, neopine and a number of diverse neopine derivatives are now readily available starting from 14β-bromocodeine and its 5β-methyl analogue.

Experimental

Mass spectra were measured using a VG 70-SE mass spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400S spectrometer with $CDCl_3$ as solvent and tetramethylsilane as reference. Optical rotations were measured using a Perkin–Elmer P-141 polarimeter with chloroform/ethanol (9:1) as solvent, unless stated otherwise. IR spectra were obtained from KBr discs using a Beckman IR-4210 spectrophotometer. Melting points are uncorrected. Column chromatography was performed over silica with dichloromethane/methanol as eluent.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent dichloromethane/methanol/25% ammonia, 85:15:0.5). The compounds were detected with iodine vapour.

(+)-14β-Bromocodeine (**3**)

3 Was prepared from thebaine (**1**) according to the procedure described in Ref. 9.

(+)-14β-Bromo-5β-methylcodeine (**4**)

4 Was prepared from 5β-methylthebaine (**2**) according to the procedure described in Ref. 9.

(−)-6α,7α-Epoxy-6-deoxyneopine (**5**)

A solution of 14β-bromocodeine (**3**, 4.20 g, 11.1 mmol) in anhydrous methanol (80 ml) and triethylamine (8 ml) was boiled for 3 min. Methanol (50 ml) was removed under reduced pressure, water (25 ml) was added and the aqueous layer was extracted with chloroform (3×50 ml). The combined organic layers were washed with water (2×150 ml) and a saturated solution of NaCl (150 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to yield 3.30 g as a foam. The product was purified by flash column chromatography (97:3) yielding 1.57 g (5.3 mmol, 47%) of **5**. M.p. 58–60°C; $[\alpha]_D^{25}$-75° (*c* 1.01). MS: 297 (M^+, 100), 268 (52), 241(51), 212(25), 188 (18), 146 (60). High-resolution mass: *m/z* 297.1363; calcd. for $C_{18}H_{19}NO_3$: 297.1365. ^1H NMR: δ 1.79 [ddd, 1H, H-15eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 3.5 Hz, *J*(15eq, 16eq) 1.6 Hz], 2.02 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.5 Hz, *J*(15ax, 16eq) 5.1 Hz], 2.43 (s, 3H, *N*-Me), 2.58 (m, 1H, H-16eq), 2.64 [dd, 1H, H-10α, *J*(10α, 9) 6.9 Hz, *J*(10α, 10β) 18.0 Hz], 2.76 [ddd, 1H, H-16ax, *J*(16ax, 16eq) 12.6 Hz], 3.27 (d, 1H, H-10β), 3.42 [dd, 1H, H-7β, *J*(7β, 6β) 3.8 Hz, *J*(7β, 8) 3.5 Hz], 3.59 (d, 1H, H-9), 3.71 [dd, 1H, H-6β, *J*(6β, 5β) 3.7 Hz], 3.87 (s, 3H, 3-OMe), 4.95 (d, 1H, H-5β), 5.82 (d, 1H, H-8), 6.57 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.68 (d, 1H, H-2). ^{13}C NMR: δ 145.14 (C-4), 144.11, 142.39 (C-3, C-14), 133.16 (C-12), 127.00 (C-11), 119.18 (C-1), 113.46, 111.84 (C-2, C-8), 88.75 (C-5), 61.38 (C-9), 56.53 (3-OMe), 52.65, 50.37 (C-6, C-7), 45.95 (C-13), 42.65 (C-16), 42.31 (*N*-Me), 36.30 (C-15), 28.66 (C-10).

(−)-6α,7α-Epoxy-5β-methyl-6-deoxyneopine (**6**)

4 (0.744 g, 1.899 mmol) was added to a mixture of anhydrous methanol (14 ml) and triethylamine (1.4 ml) and refluxed for 1 h. Water (25 ml) was added to the reaction mixture and the aqueous layer was extracted with chloroform (1×40 ml, 2×20 ml). The combined chloroform layers were washed with water (2×80 ml) and a saturated solution of NaCl (80 ml). Drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a crude product as a foam. Purification by flash column chromatography (98:2) yielded 0.206 g (0.662 mmol, 35%) of pure **6**. M.p. 48–50°C; $[\alpha]_D^{25}$-66° (*c* 0.99). MS: 311 (M^+, 76), 296 (22), 282 (31), 268 (40), 255 (73), 160 (100). High-resolution mass: *m/z* 311.1522; calcd. for $C_{19}H_{21}NO_3$: 311.1521. ^1H NMR: δ 1.64 [ddd, 1H, H-15eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 3.4 Hz, *J*(15eq, 16eq) 1.8 Hz] 1.68 (s, 3H, 5β-Me), 1.98 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.4 Hz, J(15ax, 16eq) 5.4 Hz], 2.42 (s, 3H, *N*-Me), 2.60 (m, 2H, H-16eq, H-10α), 2.71 [ddd, 1H, H-16ax, *J*(16ax, 16eq) 12.5 Hz], 3.27 [d, 1H, H-10β, *J*(10β, 10α) 18.0 Hz], 3.33 [dd, 1H, H-7β, *J*(7β, 8) 3.5 Hz], 3.48 [d, 1H, H-6β, *J*(6β, 7β) 4.0 Hz], 3.57 [d, 1H, H-9, *J*(9, 10α) 6.8 Hz] 3.85 (s, 3H, 3-OMe), 5.79 (d, 1H, H-8), 6.55 [d, 1H, H-1, J(1, 2) 8.2 Hz], 6.65 (d, 1H, H-2). ^{13}C NMR: δ 144.40, 144.00 (C-4, C-14), 142.08 (C-3), 135.30 (C-12), 126.64 (C-11), 118.64 (C-1), 112.60, 112.32 (C-2, C-8), 91.52 (C-5), 61.86 (C-9), 59.45, 50.23 (C-6, C-7), 56.26 (3-OMe), 45.96 (C-16), 44.02 (C-13), 42.27 (*N*-Me), 32.14 (C-15), 28.91 (C-10), 20.56 (5β-Me).

(+)-Neopine (**7**)

Lithium aluminium hydride (50 mg, 1.3 mmol) was added to a solution of 6α,7α-epoxy-6-deoxyneopine (**5**, 0.214 g, 0.722 mmol) in 5 ml of anhydrous ether and 3 ml of anhydrous THF. After 15 min a 15% solution of NaOH (30 ml) was added to the reaction mixture and the aqueous layer was extracted with chloroform (1×50 ml, 2×20 ml). The combined organic layers were washed with water (2×100 ml) and a saturated solution of NaCl (100 ml). After drying (Na_2SO_4), chloroform was removed under reduced pressure and 0.216 g (0.720 mmol, 100%) of product was obtained as a foam. Compound **9** was crystallized from ethanol as the hydrobromide salt (**9**·HBr, 0.206 g, 0.540 mmol, 75%).
M.p. 282–284°C (**9**·HBr) (Ref. 15: 284–286°C); $[\alpha]_D^{25}$ +7° (**9**·HBr, c 1.01, H_2O, Ref. 15: $[\alpha]_D^{25}$ +17°, c 3.696). MS 299 (M^+, 67), 284 (14), 254 (14), 254 (53), 149 (33), 62 (100). High-resolution mass: *m/z* 299.1511; calcd. for $C_{18}H_{21}NO_3$: 299.1521. ^1H NMR: δ 1.82 (m, 1H, H-15eq), 1.98 [ddd, 1H, H-15ax, *J*(15ax, 15eq) 12.4 Hz, *J*(15ax, 16ax) 12.4 Hz, *J*(15ax, 16eq) 4.9 Hz], 2.29 [dt, 1H, H-7β, *J*(7β, 6β) 2.6 Hz, *J*(7β, 7α) 17.4 Hz, *J*(7β, 8) 2.6 Hz], 2.36 [ddd, 1H, H-7α, *J*(7α, 6β) 3.4 Hz, *J*(7α, 8) 5.8 Hz], 2.47 (s, 3H, *N*-Me), 2.63 [m, 1H, H-16eq, *J*(16eq, 16ax) 13.1 Hz], 2.72 (m, 1H, H-10α), 2.74 (m, 1H, H-16ax), 3.26 [d, 1H, H-10β, *J*(10β, 10α) 18.3 Hz], 3.64 [d, 1H, H-9, *J*(9, 10α) 6.4 Hz], 3.87 (s, 3H, 3-OMe), 4.24 (m, 1H, H-6β), 4.66 [d, 1H, H-5β, *J*(5β, 6β) 4.3 Hz], 5.54 (dd, 1H, H-8), 6.61 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.70 (d, 1H, H-2). ^{13}C NMR: 145.26 (C-4), 141.77 (C-3), 137.80 (C-14), 132.08 (C-12), 126.47 (C-11), 119.62 (C-1), 113.36, 112.66 (C-2, C-8), 90.48 (C-5), 66.70 (C-6), 61.44 (C-9), 56.45 (3-OMe), 45.88 (C-13), 41.99 (*N*-Me), 41.97 (C-16) 36.32 (C-15), 28.27 (C-10), 27.20 (C-7). IR: ν_{max}^{KBr} 3420 (OH) cm^{-1}.

(−)-5β-Methylneopine (**8**)

Lithium aluminium hydride (50 mg, 1.316 mmol) was added to a solution of **6** (0.206 g, 0.662 mmol) in 15 ml of THF. After 15 min a solution of 15% NaOH (30 ml) was added and the aqueous layer was extracted with chloroform (1×50 ml, 2×25 ml). The combined organic layers were washed with water (2×100 ml) and a saturated solution of NaCl (100 ml). After drying (Na_2SO_4) and removal of the chloroform, 0.196 g (0.626 mmol, 95%) of product was obtained. Crystallization from anhydrous diethyl ether yielded pure **8** (0.167 g, 0.534 mmol, 81%). M.p. 127–128.5°C; $[\alpha]_D^{25}$-2° (*c* 0.99) MS: 313 (M^+, 100), 298 (40), 268 (48), 199 (12), 149 (16). High-resolution mass: *m/z* 313.1669; calcd. for $C_{19}H_{23}NO_3$: 313.1678. ^1H NMR: δ 1.56 (s, 1H, 5β-Me), 1.71 (m, 1H, H-15eq), 1.95 [ddd, 1H, H-15ax, *J*(15ax, 15eq) 12.0 Hz *J*(15ax, 16ax) 12.0 Hz, *J*(15ax, 16eq) 5.9 Hz], 2.27 [ddd, 1H, H-7α, *J*(7α, 6β) 3.1 Hz, *J* (7α, 7β) 17.3 Hz, *J*(7α, 8) 6.1 Hz], 2.35 [dt, 1H, H-7β, *J*(7β, 6β) 2.4 Hz, *J*(7β, 8) 2.4 Hz], 2.44 (s, 3H, *N*-Me), 2.61 (m, 1H, H-16eq), 2.64 (m, 1H, H-10α), 2.67 (m, 1H, H-16ax), 3.23 [d, 1H, H-10β, *J*(10β, 10α) 18.0 Hz], 3.57 [d, 1H, H-9, *J*(9,10α) 6.4 Hz] 3.86 (s, 3H, 3-OMe), 3.98 (bs, 1H, H-6β), 5.49 (dd, 1H, H-8), 6.60 [d, 1H, H-1, *J*(1,2) 8.2 Hz], 6.68 (d, 1H, H-2). ^{13}C NMR: δ 144.78 (C-4), 141.16 (C-3), 138.70 (C-14), 126.81 (C-11), 119.28 (C-1), 112.63, 111.98 (C-8, C-2), 93.47 (C-5), 73.94 (C-6), 61., 78 (C-9), 56.21 (3-OMe), 45.84 (C-16), 43.65 (C-13), 42.28 (*N*-Me), 32.68 (C-15), 29.01 (C-10) 26.84 (C-7), 19.80 (5β-Me). IR: ν_{max}^{KBr} 3170 (OH) cm^{-1}.

(−)-7β-Methoxyneopine (**9**)

3 (1.501 g, 3.971 mmol) was added to a solution of anhydrous methanol (30 ml) and triethylamine (2.75 ml). After 3 min refluxing (complete conversion, TLC) the solution was allowed to cool to room temperature. Sodium (1.0 g) was reacted with methanol (25 ml) and the resulting mixture was added to the crude reaction mixture. After 1 h the conversion of **5** was complete (TLC). Water (75 ml) was added and the aqueous layer was extracted with chloroform (1×125 ml, 2×50 ml). The combined organic layers were washed with water (2×200 ml) and a saturated solution of NaCl (200 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to yield 1.094 g of crude product. Purification by column chromatography (96:4) gave **9** (0.673 g, 2.046 mmol, 52%). M.p. 84–86°C; $[\alpha]_D^{25}$ -131° (c, 1.00). MS: 329 (M^+, 100), 314 (26), 298 (30), 254 (50). High-resolution mass: *m/z* 329.1621; calcd. for $C_{19}H_{23}NO_4$: 329.1627. ^1H NMR: δ 1.80 [ddd, 1H, H-15eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 3.7 Hz, *J*(15eq, 16eq) 1.7 Hz], 2.09 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.7 Hz, *J*(15ax, 16eq) 4.9 Hz], 2.46 (s, 3H, *N*-Me) 2.58 [m, 1H, H-16eq, *J*(16eq, 16ax) 13.1 Hz], 2.80 [dd, 1H, H-10α, J(10α, 10β) 18.2 Hz], 2.81 (ddd, 1H, H-16ax), 3.24 (d, 1H, H-10β), 3.42 (s, 3H, 7-OMe), 3.58 [d, 1H, H-9, *J*(9,10α) 6.8 Hz], 3.87 (s, 3H, 3-OMe), 3.87 (m, 1H, H-7α), 4.32 [t, 1H, H-6β, *J*(6β, 5) 3.9 Hz, *J*(6β, 7α) 3.9 Hz], 4.83 (d, 1H, H-5β), 5.79 [d, 1H, H-8, *J*(8,7α) 5.5 Hz], 6.61 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.70 (d, 1H, H-2). ^{13}C NMR δ 145.70 144.22 (C-4, C-14), 141.86 (C-3), 131.96 (C-12), 126.67 (C-11), 119.53 (C-1), 113.80, 113.50 (C-8, C-2), 89.16 (C-5), 75.70, 68.11 (C-7, C-6), 61.68 (C-9), 56.70, 56.45 (3-OMe, 7-OMe), 45.67 (C-16), 42.72 (C-13), 42.04 (*N*-Me), 36.22 (C-15), 29.00 (C-10). IR: ν_{max}^{KBr} 3490 (OH) cm^{-1}.

(−)-7β-Methoxy-5β-methylneopine (**10**)

4 (0.590 g, 1.505 mmol) was dissolved in anhydrous methanol (15 ml) and triethylamine (1 ml) and refluxed for 1 h. Sodium (1.0 g) was reacted with methanol (25 ml) and the resulting mixture was added to the reaction mixture. After 3 h stirring at room temperature, water (50 ml) was added and the aqueous layer was extracted with chloroform (1×100 ml, 2×25 ml). The combined chloroform layers were washed with water (2×150 ml) and a saturated solution of NaCl (150 ml). Drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a foam. Crystallization from anhydrous diethyl ether yielded pure **10** (0.279 g, 0.813 mmol, 54%). M.p. 153.5–155°C. $[\alpha]_D^{25}$ −80° (c 1.00). MS: 343 (M^+, 100), 328 (33), 312 (20), 268(31), 190 (20). High-resolution mass: *m/z* 343.1786; calcd. for $C_{20}H_{25}NO_4$: 343.1784. ^1H NMR: δ 1.65 [ddd, 1H, H-15 eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 3.5 Hz, *J*(15eq, 16eq) 1.9 Hz], 1.67 (s, 3H, 5β-Me), 2.02 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.5 Hz, *J*(15ax, 16eq) 5.2 Hz], 2.44 (s, 3H, *N*-Me), 2.61 (m, 1H, H-16eq), 2.75 [dd, 1H, H-10α, J(10α, 9) 6.7 Hz, *J*(10α, 10β) 18.9 Hz], 2.78 [m, 1H, H-16ax, *J*(16ax, 16eq) 12.7 Hz], 3.23 (d, 1H, H-10β), 3.40 (s, 3H, 7-OMe), 3.56 (d, 1H, H-9), 3.80 [dd, 1H, H-7α, *J*(7α, 6β) 3.0 Hz, *J*(7α, 8) 5.8 Hz], 3.85 (s, 3H, 3-OMe), 4.03 (m, 1H, H-6β), 5.77 (d, 1H, H-8), 6.58 [d, 1H, H-1, *J*(1, 2) 8.3 Hz], 6.68 (d, 1H, H-2). ^{13}C NMR: δ 144.67 (C-4), 143.47, 141.25 (C-3, C-14), 133.59 (C-12), 126.78 (C-11), 119.25 (C-1), 113.69, 112.69 (C-2, C-8), 93.22 (C-5), 76.36, 74.08 (C-6, C-7), 62.13 (C-9), 56.77, 56.21 (3-OMe, 7-OMe),

45.60 (C-16), 44.30 (C-13), 42.04 (*N*-Me), 32.12 (C-15), 28.73 (C-10), 20.23 (5β-Me). IR: ν_{max}^{KBr} 3140 (OH) cm^{-1}.

(+)-6α-O-Acetyl-14β-bromocodeine (**11**)

Acetyl chloride (4 ml, 56.25 mmol) in 15 ml of chloroform was added dropwise to 14β-bromocodeine (**3**) (9.10 g, 24.07 mmol) in 150 ml of dichloromethane and 4 ml of pyridine. After 1 h stirring, water and ice were added and the solution was made alkaline with concentrated ammonia. After separation, the aqueous layer was extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water (2×250 ml), a saturated solution of NaCl (250 ml), and dried (Na_2SO_4). The solvents were evaporated under reduced pressure to yield **11** (9.69 g, 23.07 mmol, 96%). An analytical sample was crystallized from methanol. M.p. 133.5–134°C (Ref. 11: 153–154°C[a]); $[\alpha]_D^{25}$ +9° (*c* 1.00). MS: 419/421 (1:1; M^+, 5), 340 (82), 298 (28), 281 (100), 266 (54), 254 (18). High-resolution mass: *m/z*-Br 340.1547; calcd. for $C_{20}H_{22}NO_4$: 340.1549. ^1H NMR: δ 1.83 (m, 1H, H-15eq), 2.15 (s, 3H, CO*Me*), 2.34 [m, 1H, H-15ax, *J*(15ax, 15eq) 12.3 Hz, *J*(15ax, 16ax) 12.3 Hz, *J*(15ax, 16eq) 3.7 Hz], 2.44 (s, 3H, *N*-Me), 2.47 [m, 1H, H-10α, *J*(10α, 10β) 18.2 Hz, *J*(10α, 9) 5.8 Hz], 2.61–2.71 (m, 2H, H-16ax, H-16eq), 3.18 (d, 1H, H-10β), 3.29 (d, 1H, H-9), 3.85 (s, 3H, 3-OMe), 5.07 [dd, 1H, H-5β, *J*(5β, 6β), 7.1 Hz, *J*(5β, 7) 0.9 Hz], 5.43 [ddd, 1H, H-6β, *J*(6β, 7) 3.2 Hz, *J*(6β, 8) 2.0 Hz], 5.70 [ddd, 1H, H-8, *J*(8.7) 9.8 Hz], 5.90 (ddd, 1H, H-7), 6.55 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.67 (d, 1H, H-2). ^{13}C NMR: δ 170.20 (C = O), 145.28 (C-4), 142.66 (C-3), 131.63 (C-7), 131.25 (C-12), 130.50 (C-8), 125.84 (C-11), 119.11 (C-1), 114.73 (C-2), 85.55 (C-5), 67.00 (C-6, C-14), 65.24 (C-9), 56,86 (3-OMe), 48.82 (C-16), 46.20 (C-13), 43.07 (*N*-Me), 32.08 (C-15), 23.20 (C-10), 20.65 (CO*Me*). IR: ν_{max}^{KBr} 1735 (C = O) cm^{-1}

(+)-6α-O-Acetyl-14β-bromo-5β-methylcodeine (**12**)

12 was prepared according to the procedure described for **11**. 5.96 g (15.2 mmol) of **4** yielded 6.53 g (99%) of crystalline **12**. An analytical sample was recrystallized from methanol. M.p. 144–145°C; $[\alpha]_D^{25}$ +85° (*c* 1.00). MS: 433/435 (1:1; M^+, 7) 354 (69) 312 (35), 295 (100), 280 (65), 154 (27). High resolution mass: *m/z* 433.0887; calcd. for $C_{21}H_{24}NO_4Br$: 433.0889. ^1H NMR: δ 1.68 (m, 1H, H-15eq), 1.78 (s, 3H, 5β-Me), 2.14 (s, 3H, CO*Me*), 2.30 [ddd, 1H, H-15ax, J(15ax, 15eq) 11.8 Hz, *J*(15ax, 16ax) 11.8 Hz, *J*(15ax, 16eq) 3.7 Hz], 2.45 (s, 3H, *N*-Me), 2.46 [m, 1H, H-10α, *J*(10α, 9) 5.8 Hz, *J*(10α, 10β) 18.5 Hz], 2.55 [ddd, 1H, H-16ax, *J*(16ax, 15eq) 12.3 Hz, *J*(16ax, 16eq) 12.3 Hz], 2.67 (m, 1H, H-16eq), 3.14 (d, 1H, H-10β), 3.23 (d, 1H, H-9), 3.85 (s, 3H, 3-OMe), 5.38 [t, 1H, H-6β, *J*(6β, 7) 2.6 Hz, *J*(6β, 8) 2.8 Hz], 5.59 [dd, 1H, H-7, *J*(7,8) 9.8 Hz], 5.92 (ddd, 1H, H-8), 6.55 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.67 (d, 1H, H-2). ^{13}C NMR: δ 170.65 (C = O), 144.13 (C-4), 142.18 (C-3), 131.34 (C-7), 132.00 (C-12), 130.33 (C-8), 125.74 (C-11), 118.76 (C-1), 113.54 (C-2), 91.61 (C-5), 70.71, 67.77 (C-14, C-6), 65.94 (C-9), 56.33 (3-OMe), 49.15 (C-13), 46.32 (C-16), 42.97 (*N*-Me), 28.65 (C-15), 23.30 (C-10), 21.73 (5β-Me), 20.83 (CO*Me*). IR: ν_{max}^{KBr} 1735 (C = O) cm^{-1}.

6α, 7α-(1-Methoxyethylidenedioxy)-6-deoxyneopine (**13**)

11 (0.52 g, 1.24 mmol) was dissolved in a mixture of anhydrous methanol (30 ml) and triethylamine (1 ml) and refluxed for 30 min. After cooling, water (25 ml) was added and the aqueous layer was extracted with chloroform (1×50 ml, 2×25 ml). The combined organic layers were washed with water (2×100 ml) and a saturated solution of NaCl (100 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure to yield 0.4 g of crude product. Purification by column chromatography (97:3) gave pure **13** (0.16 g, 0.43 mmol, 35%). Two diastereoisomers were formed in a ratio of about 9:1. MS: 371 (M^+, 95) 339 (47), 296 (39), 280 (64), 254 (100), 241 (97) 225 (45), 152 (36). High-resolution mass: *m/z* 371.1738; calcd for $C_{21}H_{25}NO_5$: 371.1733. ^1H NMR: δ 0.96 [s, 3H, 6α-O-7α-O-C(OMe)*Me*], 1.84 [ddd, 1H, H-15eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 4.2 Hz, *J*(15eq, 16eq) 2.2 Hz], 1.90 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.1 Hz, *J*(15ax, 16eq) 5.0 Hz], 2.44 (s, 3H, *N*-Me), 2.62 (m, 1H, H-16eq), 2.62 (m, 1H, H-10α), 2.69 [ddd, 1H, H-16ax, *J*(16ax, 16eq) 12.5 Hz], 3.22 (s, 3H, 6α-O-7α-O-C(*OMe*)Me), 3.28 [d, 1H, H-10β, *J*(10β, 10α) 17.9 Hz], 3.62 [d, 1H, H-9, *J*(9, 10α) 6.4 Hz], 3.88 (s, 3H, 3-OMe), 4.75 [ddd, 1H, H-6β, *J*(6β, 5) 5.3 Hz, *J*(6β, 7β) 4.5 Hz, *J*(6β, 8) 0.8 Hz], 4.78 (d, 1H, H-5β), 4.88 [dd, 1H, H-7β, *J*(7β, 8) 1.7 Hz], 5.40 (d, 1H, H-8), 6.58 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.70 (d, 1H, H-2). ^{13}C NMR: δ 145.88 (C-4), 142.24 (C-3), 137.69 (C-14), 131.64 (C-12), 126.27 (C-11), 121.27 (6α-O-7α-O-*C*(OMe)Me), 119.08 (C-1), 115.11 (C-8), 114.28 (C-2), 87.09 (C-5), 74.43, 73.68 (C-6, C-7), 61.66 (C-9), 56.89 (3-OMe), 49.13 (C-13), 46.18 (C-16), 42.34 (*N*-Me), 41.00 (6α, 7α-O_2C(O*Me*)Me), 36.34 (C-15), 17.14 (C-10), 24.72 (6α, 7α-O_2C(OMe)*Me*).

6α,7α-(1-Methoxyethylidenedioxy)-5β-methyl-6-deoxyneopine (**14**)

12 (2.00 g, 4.61 mmol) was added to a mixture of anhydrous methanol (75 ml) and triethylamine (4 ml) and refluxed for 1 h. Methanol (50 ml) was partly removed under reduced pressure. Water (25 ml) was added and the aqueous layer was extracted with chloroform (1×50 ml, 2×25 ml). The combined organic layers were washed with water (2×100 ml), a saturated solution of NaCl (100 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 1.77 g crude product as a foam. Purification by flash column chromatography (97:3) yielded pure **14** (1.01 g, 2.62 mmol, 57%). The ^1H NMR spectrum showed two diastereoisomers in a ratio of about 9:1. MS: 385 (M^+, 86), 370 (22), 353 (53), 338 (29), 326 (29), 310 (31), 294 (44), 270 (56), 255 (100). High-resolution mass: *m/z* 385.1891; calcd. for $C_{22}H_{27}NO_5$: 385.1889. ^1H NMR: δ 0.92 (s, 3H, 6α-O-7α-O-C(OMe)*Me*), 1.56 (s, 1H, 5β-Me), 1.68 [m, 1H, H-15eq, *J*(15eq, 15ax) 11.9 Hz, *J*(15eq, 16eq) 2.5 Hz], 1.88 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.1 Hz, *J*(15ax, 16eq) 5.8 Hz], 2.44 (s, 3H, *N*-Me), 2.58 [dd, 1H, H-10α, *J*(10α, 9) 6.3 Hz, *J*(10α, 10β) 18.4 Hz], 2.63 (m, 1H, H-16eq), 2.69 [dd, 1H, H-16ax, *J*(16ax, 16eq) 12.5 Hz, *J*(16ax, 15eq) 3.4 Hz], 3.20 (s, 3H, 6α-O-7α-O-C(*OMe*)Me), 3.28 (d, 1H, H-10β), 3.61 (d, 1H, H-9), 3.87 (s, 3H, 3-OMe), 4.45 [dd, 1H, H-6β, *J*(6β, 7β) 4.6 Hz, *J*(6β, 8) 0.8 Hz], 4.80 [dd, 1H, H-7β, *J*(7β, 8) 1.4 Hz], 5.38 (s, 1H, H-8), 6.56 [d, 1H, H-1, *J*(1, 2) 8.3 Hz], 6.67 (d, 1H, H-2). ^{13}C NMR: δ 145.39 (C-4), 141.92 (C-3), 138.16 (C-14), 132.72 (C-12), 126.23 (C-11), 121.23 (6α-O-7α-O-*C*(OMe)Me), 118.74 (C-1), 115.14 (C-8), 113.52 (C-2), 90.29 (C-5), 81.32, 73.82 (C-6, C-7), 62.02 (C-9), 56.68 (3-OMe), 49.20 (6α,7α-O_2C(*OMe*)Me), 46.00 (C-13), 42.71 (C-16), 42.26 (*N*-Me), 32.23 (C-15), 27.28 (C-10), 24.57 (6α,7α-O_2C(OMe)*Me*), 20.36 (5β-Me).

(−)-6α-O-Acetyl-7α-hydroxyneopine (**15**) *and (−)-7α-acetoxyneopine* (**17**)

(a). Compounds **15** *and* **17** *from* **11**. 6α-*O*-Acetyl-14β-bromocodeine (4.31 g, 10.26 mmol) was dissolved in 80 ml of THF, 60 ml of water, and 4 ml of triethylamine and refluxed for 4 h. Most of the THF was evaporated under reduced pressure and the aqueous residue extracted with chloroform (60 ml, 2×20 ml). The organic layers were combined and washed with water (2×100 ml) and a saturated solution of NaCl (100 ml), and dried (Na_2SO_4). The solvent was evaporated to give 3.51 g (96%) crude product. The product was redissolved in dichloromethane and ethyl acetate. Compound **15** crystallized after evaporation of dichloromethane (0.61 g, 17%). Further separation by column chromatography (95:5) yielded **17** (0.73 g, 2.04 mmol, 20%) and **15** (0.82, 2.30 mmol, 22%).

15 M.p. 130–132°C; $[\alpha]_D^{25}$ -5° (*c* 1.01). MS: 357 (M^+, 94), 298 (56), 254 (100), 241 (45). High-resolution mass: *m/z* 357.1569; calcd. for $C_{20}H_{23}NO_5$: 357.1576. ^1H NMR: δ 1.50 (s, 3H, CO*Me*), 1.84 [ddd, 1H, H-15eq, *J*(15eq, 15ax) 12.6 Hz, *J*(15eq, 16ax) 3.7 Hz, *J*(15eq, 16eq) 1.8 Hz], 1.95 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.4 Hz, *J*(15ax, 16eq) 5.1 Hz], 2.45 (s, 3H, *N*-Me), 2.61 [m, 1H, H-16eq, *J*(16eq, 16ax) 12.6 Hz], 2.70 (m, 1H, H-16ax), 2.72 [dd, 1H, H-10α, *J*(10α, 9) 6.5 Hz, *J*(10α, 10β) 18.1 Hz], 3.27 (d, 1H, H-10β), 3.64 (d, 1H, H-9), 3.85 (s, 3H, 3-OMe), 4.56 [dd, 1H, H-7β, *J*(7β, 6β) 2.7 Hz, *J*(7β, 8) 1.4 Hz], 4.79 [d, 1H, H-5, *J*(5, 6β) 4.4 Hz], 5.47 [t, 1H, H-8, *J*(8, 6β) 1.3 Hz], 5.58 (ddd, 1H, H-6β), 6.59 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.66 (d, 1H, H-2). ^{13}C NMR: δ 171.08 (C = O), 145.42 (C-4), 142.02 (C-3), 137.81 (C-14), 131.63 (C-12), 126.70 (C-11), 119.75, 118.68 (C-1, C-8), 114.40 (C-2), 87.22 (C-5), 71.91 (C-6), 65.88 (C-7), 61.20 (C-9), 56.99 (3-OMe), 45.95 (C-16), 42.73 (C-13), 42.11 (*N*-Me), 35.87 (C-15), 27.17 (C-10), 20.22 (CO*Me*). IR: ν_{max}^{KBr} 3450 (OH), 1745 (C = O) cm^{-1}.

17 M.p. 90–91°C; $[\alpha]_D^{25}$ -54° (c 0.99). MS: 357 (M^+, 100), 298, (61), 280 (58), 254 (92), 241 (50). High-resolution mass: *m/z* 357.1574; calcd. for $C_{20}H_{23}NO_5$: 375.1576. ^1H NMR: δ 1.80 [m, 1H, H-15eq, *J*(15eq, 15ax) 12.5 Hz, *J*(15eq, 16ax) 3.5 Hz, *J*(15eq, 15eq) 1.6 Hz], 1.96 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.4 Hz, *J*(15ax, 16eq) 5.1 Hz], 2.10 (s, 3H, CO*Me*), 2.44 (s, 3H, *N*-Me), 2.58 [dd, 1H, H-16eq, *J*(16ax, 16eq) 12.6 Hz], 2.74 (m, 2H, H-10α, H-16ax), 3.24 [d, 1H, H-10β, *J*(10β, 10α) 18.1 Hz], 3.64 [d, 1H, H-9, *J*(9, 10α) 6.4 Hz], 3.87 (s, 3H, 3-OMe), 4.37 (m, 1H, H-6β), 4.74 [d, 1H, H-5, *J*(5,6β) 4.4 Hz], 5.39 (s, 1H, H-8), 5.51 [dd, 1H, H-7β, *J*(7β, 6β) 2.6 Hz, *J*(7β, 8) 1.4 Hz], 6.62 [d, 1H, H-1, *J*(1, 2) 8.2 Hz], 6.72 (d, 1H, H-2). ^{13}C

[a] The only physical property of **11** described in Ref. 9 deviates strongly from our findings.

NMR: δ 170.30 (C = O), 145.46 (C-4), 141.87 (C-3), 139.80 (C-14), 131.36 (C-12), 126.53 (C-11), 119.75 (C-1), 114.08, 113.83 (C-2, C-8), 88.67 (C-5), 69.87, 69.04 (C-6, C-7), 61.09 (C-9), 56.58 (3-OMe), 45.74 (C-13), 42.83 (C-16), 42.16 (*N*-Me), 36.19 (C-15), 27.62 (C-10), 21.08 (CO*Me*). IR: ν_{max}^{KBr} 3450 (OH), 1735 (C = O) cm^{-1}.

(b). Compounds **15** *and* **17** *by hydrolysis of* **13**. **13** (0.36 g, 0.97 mmol) was dissolved in 15 ml of 2N HCl. After 2 h stirring, chloroform (20 ml) was added and the aqueous layer was made alkaline with concentrated ammonia. After separation, the aqueous layer was extracted with chloroform (2×10 ml). The combined organic layers were washed with water (2×40 ml) and a saturated solution of NaCl (40 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield 0.27 crude product as a foam. Separation by column chromatography (96:4) yielded **17** (0.10 g, 29%) and **15** (0.07 g, 20%), in all respects identical with the compounds described above.

(+)-6α-O-Acetyl-7α-hydroxy-5β-methylneopine (**16**)

12 (21.70 g, 50.0 mmol) was dissolved in 250 ml of THF, 250 ml of water, and 35 ml of triethylamine and refluxed for 4 h. Most of the THF was evaporated under reduced pressure and the aqueous residue extracted with chloroform (250 ml, 2×100 ml). The organic layers were combined and washed with water (2×400 ml) and a saturated solution of NaCl (400 ml), and dried (Na_2SO_4). The solvent was evaporated and the foam (18.13 g) redissolved in 20 ml ethyl acetate and 10 ml dichloromethane. Evaporation of dichloromethane resulted in crystallization of **16** (8.49 g, 22.9 mmol, 46%). An analytical sample was recrystallized from ethyl acetate. M.p. 205–206°C; $[\alpha]_D^{25}$ +36° (*c* 1.00). MS: 371 (M^+, 100), 312 (50), 294 (52), 282 (35), 268 (72), 255 (48). High-resolution mass: *m/z* 371.1735; calcd. for $C_{21}H_{25}NO_5$: 371.1733. ^1H NMR: δ 1.47 (s, 3H, CO*Me*), 1.65 (s, 3H, 5β-Me), 1.70 [m, 1H, H-15eq, *J*(15eq, 15ax) 12.2 Hz, *J*(15eq, 16ax) 3.6 Hz, *J* (15eq, 16eq) 2.6 Hz], 1.89 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 11.7 Hz, *J*(15ax, 16eq) 6.3 Hz], 2.44 (s, 3H, *N*-Me), 2.64 [m, 1H, H-16eq, *J*(16ax, 16eq) 12.3 Hz], 2.64 (m, 1H, H-16ax), 2.69 [dd, 1H, H-10α, 7 (10α, 9) 6.6 Hz, *J*(10α, 10β) 18.0 Hz], 3.25 (d, 1H, H-10β), 3.60 (d, 1H, H-9), 3.84 (s, 3H, 3-OMe), 4.53 [dd, 1H, H-7β, *J*(7β, 6β) 3.0 Hz, *J*(7β, 8) 1.3 Hz], 5.33 [dd, 1H, H-6β, *J*(6β, 8) 1.4 Hz], 5.42 (t, 1H, H-8), 6.59 [d, 1H, H-1, *J*(1, 2) 8.1 Hz], 6.66 (d, 1H, H-2). ^{13}C NMR: δ 170.81 (C = O), 144.91 (C-4), 141.46 (C-3), 138.91 (C-14), 132.79 (C-12), 126.97 (C-11), 119.28 (C-1), 117.86 (C-8), 113.50 (C-2), 91.17 (C-5), 66.24 (C-6, C-7), 61.59 (C-9), 56.62 (3-OMe), 45.75 (C-13), 44.32 (C-16), 42.21 (*N*-Me), 32.12 (C-15), 27.03 (C-10), 20.12, 19.75 (5β-Me, CO*Me*). IR: ν_{max}^{KBr} 3160 (OH), 1735 (C = O) cm^{-1}.

(−)-7α-Acetoxy-5β-methylneopine (**18**)

Compound **14** (1.01 g, 2.62 mmol) was dissolved in 50 ml of 2N HCl and stirred for 6 h. The solution was made alkaline with concentrated ammonia and extracted with chloroform (1×75 ml, 2×25 ml). The combined organic layers were washed with water (2×100 ml) and a saturated solution of NaCl (100 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The yield was 0.94 g (97%) of crude product as a foam, which was redissolved in dichloromethane (10 ml) and ethyl acetate (20 ml). After evaporation of dichloromethane, **16** (0.48 g, 1.30 mmol, 50%) crystallized. The filtrate was concentrated and separated by column chromatography (96:4) yielding 0.031 g (0.084 mmol, 3%) of 7α-acetoxy compound **18**. M.p. 83–86°C; $[\alpha]_D^{25}$ -8° (*c* 0.51). MS: 371 (M^+, 100), 328 (47), 312 (44), 294 (66), 268 (56), 255 (98). High-resolution mass: *m/z* 371.1728; calcd. for $C_{21}H_{25}NO_5$: 371.1733. ^1H NMR: δ 1.63 (s, 3H, 5β-Me), 1.69 [m, 1H, H-15eq, *J*(15eq, 15ax) 12.2 Hz, *J*(15eq, 16ax) 3.7 Hz, *J*(15eq, 16eq) 1.8 Hz], 1.94 [ddd, 1H, H-15ax, *J*(15ax, 16ax) 12.3 Hz, *J*(15ax, 16eq) 5.2 Hz], 2.09 (s, 3H, CO*Me*), 2.45 (s, 3H, *N*-Me), 2.63 [m, 1H, H-16eq, *J*(16eq, 16ax) 13.3 Hz], 2.69 (m, 1H, H-10α), 2.74 (m, 1H, H-16ax), 3.25 [d, 1H, H-10β, *J*(10β, 10α) 18.1 Hz], 3.61 [d, 1H, H-9, *J*(9, 10α) 6.5 Hz], 3.86 (s, 3H, 3-OMe), 4.12 (m, 1H, H-6β), 5.36 [t, 1H, H-8, *J*(8, 6β) 1.4 Hz, *J*(8, 7β) 1.4 Hz], 5.51 [dd, 1H, H-7β, *J*(7β, 6β) 2.8 Hz], 6.59 [d, 1H, H-1, *J*(1, 2) 8.3 Hz], 6.70 (d, 1H, H-2). ^{13}C NMR: δ 170.26 (C = O), 144.90 (C-4), 141.27, 140.07 (C-3, C-14), 132.26 (C-12), 126.46 (C-11), 119.50 (C-1), 114.11, 113.20 (C-2, C-8), 92.46 (C-5), 75.50 (C-7), 70.09 (C-6), 61.52 (C-9), 56.36 (3-OMe), 45.57(C-13), 44.32 (C-16), 42.06 (*N*-Me), 31.97 (C-15), 27.64 (C-10), 21.10, 19.58 (CO*Me*, 5β-Me). IR: ν_{max}^{KBr} 3440 (OH), 1730 (C = O) cm^{-1}.

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