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Synthetic Transformations of Isoquinoline Alkaloids. Synthesis of 1-Halo Derivatives of *endo*-Ethenotetrahydrothebaine and Their Behavior in the Heck Reaction

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Abstract—Bromination of *endo*-ethenotetrahydrothebaine derivatives having a pyrrolidine ring fused at the C^7–C^8 bond, namely 1'-substituted 4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4' : 7,8]morphinan-2',5'-diones, 1'-aryl-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4' : 7,8]morphinans, and 4,5α-epoxy-6α,14-etheno-2'α-hydroxy-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4' : 7,8]morphinan-5'-one, with molecular bromine in formic acid smoothly afforded the corresponding 1-bromo derivatives. Iodination of 4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]-morphinan-2',5'-dione with iodine(I) chloride gave 4,5α-epoxy-6α,14-etheno-1-iodo-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4' : 7,8]morphinan-2',5'-dione. The resulting 1-halo derivatives were brought into the Heck reaction with acrylic acid esters to obtain 1-[(*E*)-2-(alkoxycarbonyl)ethenyl]-substituted compounds. Demethylation of the 6-methoxy group in 1-bromo-*endo*-ethenotetrahydrothebaines was accomplished using boron(III) bromide in chloroform.

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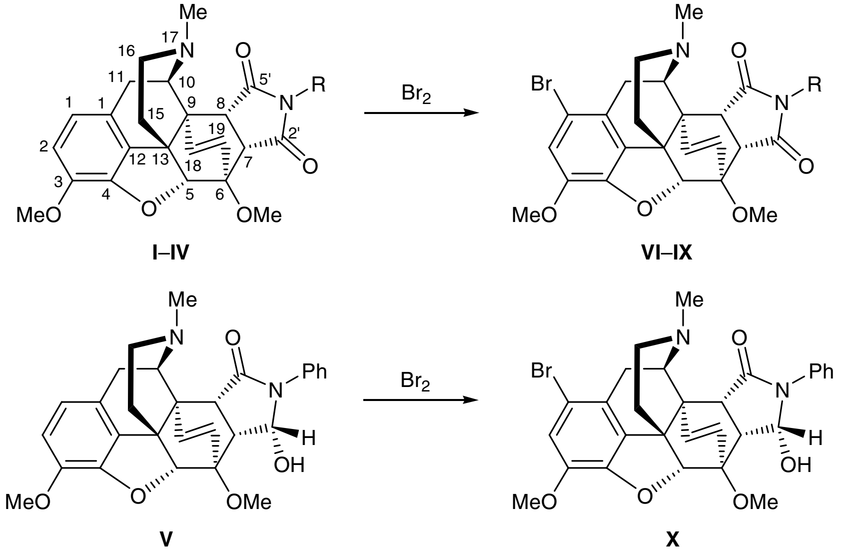
Morphinan alkaloids constitute one of the most important groups of non-endogenous ligands for opiate receptors and exhibit properties of agonists or antagonists. Enhancement or weakening of these properties depends on substituents in different positions of the morphinan skeleton. Introduction into morphinan alkaloid molecules of additional heterocyclic fragments via fusion at the C^6–C^7 or C^7–C^8 bond gave rise to quite promising pharmacologically active agents. For example, indolo- and pyrrolomorphinans were shown to be selective κ-, μ-, and δ-opioid receptor agonists and antagonists [1–6]. Thebaine derivatives having a thiolane 1,1-dioxide [7, 8], *N*-arylpyrrolidine-2,5-dione [9], or *N*-arylpyrrolidine fragment [10, 11] are promising analgesics. Annelation of an *N*-aryl-2,5-dioxopyrrolidine moiety at the C^7–C^8 bond of 6,7,8,14-tetrahydrothebaine produces a number of selective μ-opioid agonists [9]. Less attention was given to modification of the A ring, though it is well known that variation of substituents on C^3 and C^4 of the aromatic A ring essentially affects pharmacological properties of alkaloids. 4-Alkoxy-substituted morphinans (such as Cyprodime and its analogs) are specific μ-receptor antagonists [1, 12]; 3-deoxy-3-carboxamidonaltrexone showed a high affinity for μ-opioid receptors [13]. Examples of modification of the 1- and 2-positions of the morphinan skeleton are limited to the synthesis of 1-hydroxy, 1-chloro, and 2-methylamino derivatives. Such modifications essentially affect the analgesic activity [14, 15].

The goal of the present work was to develop procedures for the synthesis of halogen derivatives of *endo*-6,14-etheno-6,7,8,14-tetrahydrothebaine containing 2,5-dioxopyrrolidine, 5-hydroxy-2-oxopyrrolidine, and pyrrolidine fragments fused at the C^7–C^8 bond and examine the behavior of some halogen derivatives in the Heck reaction.

By treatment of 2,5-dioxopyrrolidine derivatives **I**–**IV** and 5-hydroxy-2-oxopyrrolidine derivative **V** with 1.5 equiv of bromine in formic acid at 0°C we obtained the corresponding 1-bromo-*endo*-ethenotetrahydrothebaines **VI**–**X** (Scheme 1). In the bromination of *N*-aryl-substituted compounds **I** and **II**, both free

Scheme 1.



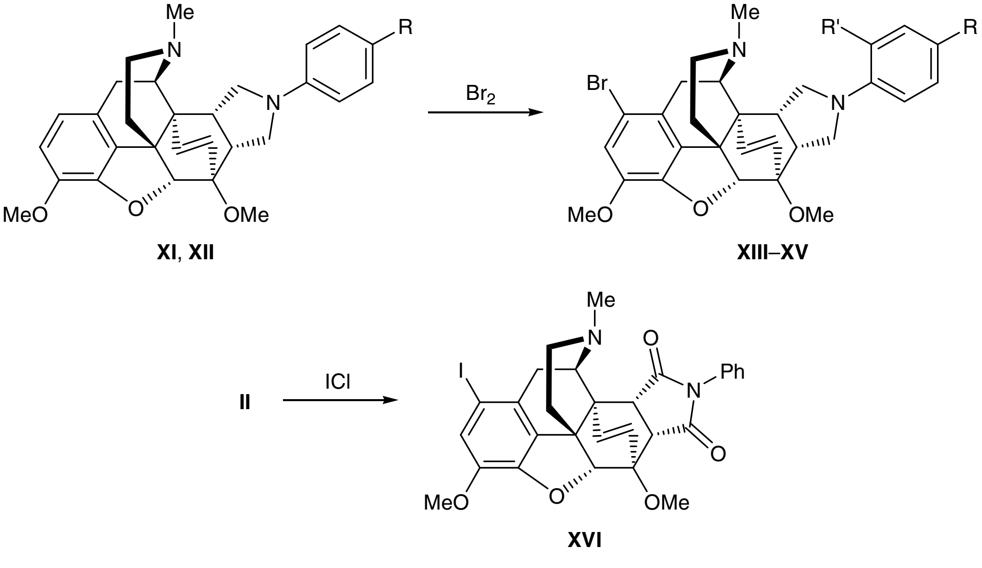
I, **VI**, R = 4-BrC_6H_4; **II**, **VII**, R = Ph; **III**, **VIII**, R = Me; **IV**, **IX**, R = H.

bases **VI** and **VII** and their hydrobromides were isolated. The latter were converted into the free bases by treatment with alkali to pH 9–10, so that the overall yield of bromides **VI**–**X** was 81–94%.

The bromination of *endo*-ethenotetrahydrothebaines **XI** and **XII** with a fused pyrrolidine ring followed a more complex pattern. In the reaction with 1'-(4-bromophenyl) derivative **XI**, the product composition strongly depended on the reactant ratio. 1-Bromo-1'-(4-bromophenyl)thebaine **XIII** was formed as the only product in the reaction of compound **XI** with 1.8 equiv of bromine in formic acid (yield 86%), while the reaction of **XI** with a larger amount of bromine gave 71% of tribromo derivative **XIV** (Scheme 2). The bromination of 1'-phenyl-substituted analog **XII** was less selective. Compound **XIII** was obtained in 85% yield in the reaction of **XII** with 1.5 equiv of bromine. Our attempts to isolate monobromo derivative **XV** using lesser excess of bromine (1–1.5 equiv) were unsuccessful.

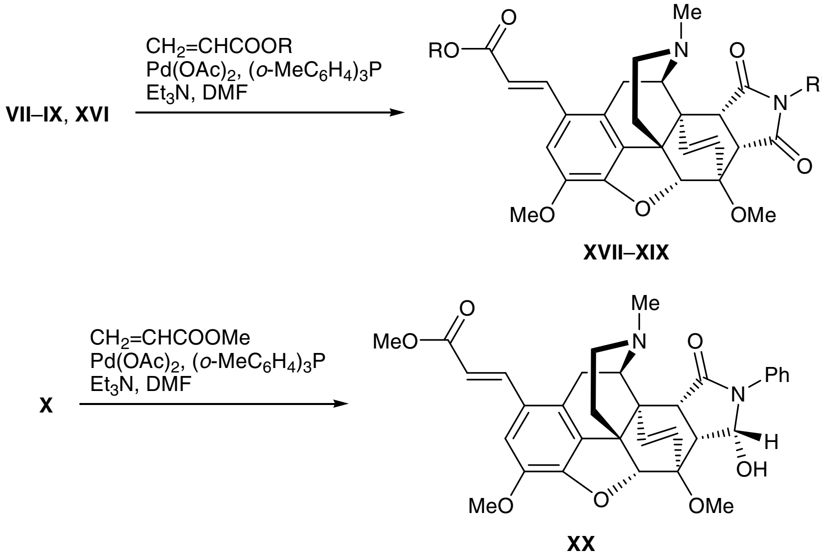
The iodination of compound **II** was performed with the use of iodine(I) chloride which is known as con-

Scheme 2.



XI, R = Br; **XII**, R = H; **XIII**, R = Br, R' = H; **XIV**, R = R' = Br; **XV**, R = R' = H.

Scheme 3.



XVII, R = Et, R' = Ph; **XVIII**, R = Et, R' = Me; **XIX**, R = Me, R' = H.

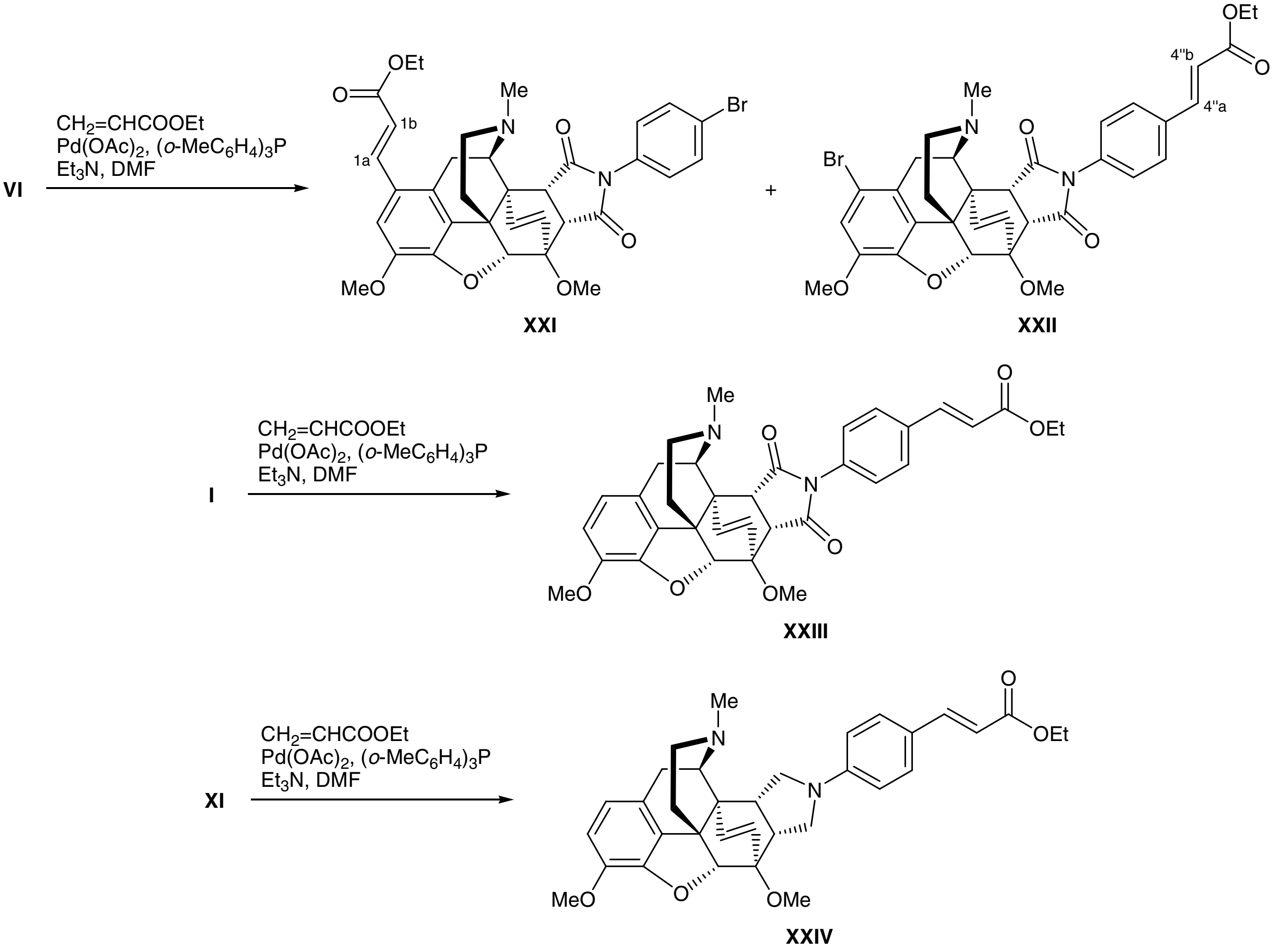
venient reagent for the introduction of iodine into molecules of aromatic compounds [16]. The reaction of **II** with excess ICl in a mixture of acetic and formic acids occurred at a low rate and resulted in the formation of a complex mixture of products (according to the TLC data). We succeeded in isolating the major product, 1-iodo derivative **XVI**, in 41% yield.

The structure of the halogenation products was determined by analysis of their ^{1}H and ^{13}C NMR and two-dimensional ^{1}H–^{13}C correlation spectra (COSY, COLOC). Compounds **VI–X** and **XIII–XV** showed in the ^{1}H NMR spectra a singlet at δ 6.79–6.86 ppm from proton in the aromatic A ring. The ^{13}C NMR spectra of these compounds contained a singlet from C^1 at δ_C 112–113 ppm and a doublet from C^2 (δ_C 116 ppm). The C^1 signal in the spectra of the initial compounds is located at δ_C 118–119 ppm; thus replacement of hydrogen on C^1 by bromine leads to an upfield shift of the C^1 signal. In addition, the existence of ^{13}C–^{1}H correlations through two and three bonds (J = 10 Hz) between 2-H (a singlet in the ^{1}H NMR spectrum) and C^4 and between C^1 (a singlet in the ^{13}C NMR spectrum) and protons on C^{10} (δ 3.03 and 2.25–2.44 ppm in the ^{1}H NMR spectrum of **XIV**) indicates that the bromine atom is attached to C^1. The formation of 1-iodo derivative **XVI** unambiguously follows from the ^{13}C NMR spectrum with account taken of substituent increments [17]. The C^1 signal shifts upfield to δ_C 85.5 ppm, while the C^2 and C^{11} signals appear in a weaker field ($\Delta\delta_C$ ~5 ppm). Our results showed that the halogenation of *endo*-ethenotetrahydrothebaine derivatives occurs at the C^1 atom with high selectivity. Presumably, the electrophilic attack on the A ring is controlled by the effect of the ether moiety in the *para* position with respect to C^1. Analogous substitution pattern (at the *meta* position with respect to the methoxy group) was observed in the chlorination and bromination of the aromatic ring in some morphinan derivatives [18, 19].

1-Halogen-substituted tetrahydrothebaine derivatives **VI–X** and **XVI** were brought into the Heck reaction with ethyl and methyl acrylates. The reaction of 1-iodo derivative **XVI** with ethyl acrylate in DMF in the presence of $Pd(OAc)_2$ as catalyst, tris(*o*-tolyl)phosphine as ligand, and triethylamine as base [20, 21] gave 1-[2-(ethoxycarbonyl)ethenyl]-*endo*-ethenotetrahydrothebaine **XVII** as a single stereoisomer (yield 50%; Scheme 3). In the reaction with 1-bromo analog **VII**, compound **XVII** was formed in 19% yield. The yields of cross-coupling products **XVII–XX** in the reactions of bromo derivatives **VII–X** with acrylates depended on the substitution pattern in the fused pyrrolidine fragment. The maximal yield (30%) was attained in the reaction with 1'-phenyl-2'-hydroxy-5'-oxo derivative **XX**. Compound **IX** having no substituent on the $N^{1'}$ atom gave rise to 22% of cross-coupling ptoduct **XIX** in the Heck reaction with methyl acrylate.

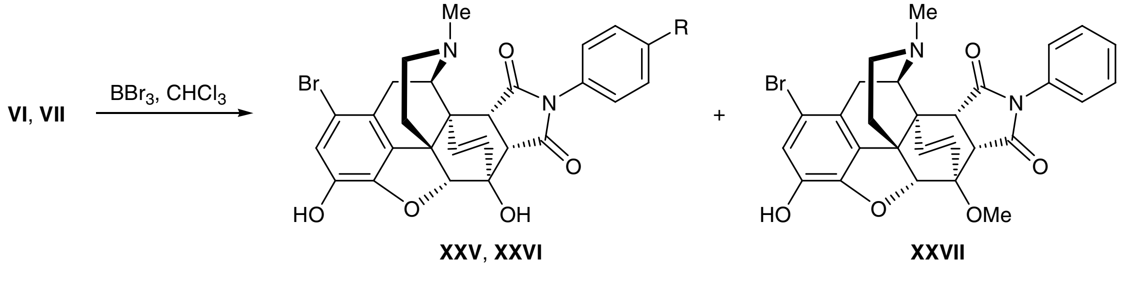
We also examined the effect of palladium catalyst on the yield of cross-coupling products. The reaction of bromide **IX** with ethyl acrylate using bis(diben-

Scheme 4.



zylideneacetone)palladium [Pd(dba)$_2$] as catalyst and tris(*o*-tolyl)phosphine as ligand, other conditions being equal, gave 40% of ester **XIX**, but the reaction was accompanied by decomposition of the morphinan skeleton to an appreciable extent. We failed to raise the yield of the cross-coupling product by varying the ligand nature [(Bu)$_3$P, Ph$_3$P, and tris(2-furyl)phosphine were tried]. Dibromo derivative **VI** reacted with ethyl acrylate to form a mixture of compounds **XXI** and **XXII** in 5 and 23% yield, respectively (Scheme 4). This means that the bromine atom in the aromatic ring at the nitrogen atom of the pyrrolidine fragment is more reactive. The same follows from the results obtained in the reaction of **I** with ethyl acrylate. Under standard conditions [Pd(OAc)$_2$, (*o*-MeC$_6$H$_4$)$_3$P, Et$_3$N; Scheme 3], compound **XXIII** was formed in 50% yield (Scheme 4). *endo*-Ethenotetrahydrothebaines having a fused pyrrolidine ring are less active in the Heck

Scheme 5.



XXV, R = Br; **XXVI**, R = H.

reaction than their 2,5-dioxopyrrolidine and 2-hydroxy-5-oxopyrrolidine analogs. The reaction of **XI** with ethyl acrylate gave 20% of compound **XXIV** in which the ester fragment is attached to the aromatic ring at the pyrrolidine nitrogen atom (Scheme 4). The Heck reaction with bromide **XIII** was slow, and the reaction mixture contained cross-coupling products at the 4''-position. In all cases, except for compounds **XVII**–**XXIV**, an appreciable amount of the initial bromide was isolated from the reaction mixture. The use of tris-(2-furyl)phosphine as ligand favored decomposition of the morphinan skeleton. The composition of the reaction mixtures was determined from the ^{1}H NMR spectra. Compounds **XVII** and **XIX** were isolated as individual substances.

The structure of acrylic acid derivatives **XVII**–**XXIV** was established on the basis of their spectral parameters. The *E* configuration of the double bond in the acrylic acid moiety follows from the ^{1}H NMR data. The 1a-H (4''a-H) and 1b-H (4''b-H) protons resonated as doublets with a coupling constant ^{3}J of 16–17 Hz, which is typical of their *trans* orientation with respect to the double bond. Introduction of a 2-(ethoxycarbonyl)ethenyl substituent into the position *1* of the morphinan skeleton induces a downfield shift of the 2-H, 5-H, and 10-H signals, as well as of the 3-OMe signal, as compared to the initial bromo derivative. In the JMOD ^{13}C NMR spectra we observed a downfield shift of the C^{1} signal (δ_C 125–126 ppm, s) and upfield shift of the C^{2} signal (δ_C 111–112 ppm, d). The presence of a 2-(ethoxycarbonyl)ethenyl group on C$^{4''}$ leads to a downfield shift of the 2''-H, 6''-H, 7-H, 8-H, 18-H, and 19-H signals. The *endo* arrangement of the ethene bridge in the bromination and arylation products is confirmed by considerable difference in the chemical shifts of 18-H and 19-H, as well as by the existence of *W*-coupling between 5-H and 19-H (^{4}J = 1.4–1.5 Hz).

It is known that 3-hydroxy tetrahydrothebaine derivatives (2',5'-dioxopyrrolo[3',4':7,8]oripavines) exhibit the strongest analgesic activity and the highest selectivity for μ-opiate receptors [22]. Treatment of dibromo-*endo*-ethenotetrahydrothebaine **VI** with excess BBr$_3$ in chloroform resulted in demethylation of both methoxy groups with formation of tetrahydrooripavine derivative **XXV** in 94% yield (Scheme 5). The reaction of bromide **VII** with BBr$_3$ gave 67% of compound **XXVI** and 18% of oripavine **XXVII**. These results confirmed our previous data [10] on the effect of fused 2,5-dioxopyrrolidine ring on the demethylation of tetrahydrothebaine derivatives.

EXPERIMENTAL

The NMR spectra were recorded from solutions in CDCl$_3$ on Bruker AC-200 (200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C), AV-300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C), AM-400 (400.13 MHz for ^{1}H and 100.78 MHz for ^{13}C), and DRX-500 spectrometers (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C). Signals were assigned using various proton–proton and carbon–proton shift correlation techniques (COSY, COLOC, CORRD) and two-dimensional ^{1}H NOESY spectra. The high-resolution mass-spectra (electron impact, 70 eV) were obtained on a Finnigan MAT-8200 mass spectrometer (ion source temperature 270–300°C); the molecular weights and the elemental compositions were determined from the high-resolution mass spectra. The progress of reactions was monitored by TLC using Silufol UV-254 plates. The products were isolated by column chromatography on silica gel (eluent chloroform–ethanol).

Compounds **I**, **V**, **XII** [10], **II** [23], and **XI** [24] were synthesized by known methods. Compound **IV** was prepared as described in [25].

4,5α-Epoxy-6α,14-etheno-3,6-dimethoxy-1',17-dimethyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo-[3',4':7,8]morphinan-2',5'-dione (III). A solution of 1.97 g (6 mmol) of thebaine in 50 ml of ethanol was added to a solution of 0.46 g (6 mmol) of *N*-methylmaleimide in 25 ml of ethanol. The mixture was heated for 5 h under reflux (TLC) and cooled, and the precipitate of adduct **III** was filtered off. Yield 1.68 g (67%), mp 302–304°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 1.85–1.98 m (2H, 15-H), 2.39–2.50 m (2H, 10-H, 16-H), 2.42 s (3H, 17-CH$_3$), 2.51–2.58 m (1H, 16-H), 2.84 s (3H, 1'-CH$_3$), 3.04 d (1H, 8-H, *J* = 8.0 Hz), 3.23 d (1H, 10-H, *J* = 19.2 Hz), 3.68 s (3H, 6-OCH$_3$), 3.78 s (3H, 3-OCH$_3$), 3.96 d (1H, 9-H, *J* = 6.4 Hz), 4.19 d (1H, 7-H, *J* = 8.0 Hz), 4.63 d (1H, 5-H, *J* = 1.4 Hz), 5.34 d (1H, 18-H, *J* = 8.4 Hz), 5.71 m (1H, 19-H), 6.54 d (1H, 1-H, *J* = 8.2 Hz), 6.61 d (1H, 2-H, *J* = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.24 (C^{10}), 24.51 (1'-CH$_3$), 33.43 (C^{15}), 41.46 (C^{8}), 42.30 (17-CH$_3$), 43.13 (C^{7}), 44.80 (C^{13}), 44.93 (C^{16}), 47.75 (C^{14}), 51.64 (6-OCH$_3$), 56.25 (3-OCH$_3$), 56.84 (C^{9}), 80.47 (C^{6}), 90.89 (C^{5}), 113.40 (C^{2}), 119.77 (C^{1}), 127.46 (C^{11}), 128.64 (C^{19}), 132.52 (C^{12}), 133.39 (C^{18}), 141.94 (C^{3}), 147.68 (C^{4}), 174.07 (C$^{5'}$), 177.32 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 422 (100), 310 (58), 255 (37), 247 (74), 204 (65), 44 (34). Found: $[M]^+$ 422.18641. $C_{24}H_{25}N_2O_5$. Calculated: *M* 422.18416.

4,5α-Epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (IV). mp 328–330°C (from ethanol); published data [25]: mp 330°C (from DMF–Et$_2$O. ^{1}H NMR spectrum, δ, ppm: 1.88–1.93 m (2H, 15-H), 2.42 s (3H, 17-CH$_3$), 2.43–2.59 m (3H, 10-H, 16-H), 3.02 d (1H, 8-H, *J* = 8.6), 3.23 d (1H, 10-H, *J* = 16 Hz), 3.67 s (3H, 6-OCH$_3$), 3.80 s (3H, 3-OCH$_3$), 3.95 d (1H, 9-H, *J* = 6.4 Hz), 4.23 d (1H, 7-H, *J* = 8.4 Hz), 4.61 d (1H, 5-H, *J* = 1.2 Hz), 5.42 d (1H, 18-H, *J* = 8.2 Hz), 5.84 m (1H, 19-H), 6.55 d (1H, 1-H, *J* = 8.8 Hz), 6.63 d (1H, 2-H, *J* = 8.8 Hz), 7.51 s (1H, 1'-H). ^{13}C NMR spectrum, δ_C, ppm: 22.31 (C^{10}), 33,52 (C^{15}), 42.86 (C^7), 43.14 (C^8), 43.57 (17-CH3), 44.87 (C^{16}), 44.99 (C^{13}), 47.77 (C^{14}), 51.76 (6-OCH$_3$), 56.36 (3-OCH$_3$), 56.75 (C^9), 80.40 (C^6), 90.94 (C^5), 113.60 (C^2), 119.86 (C^1), 127.48 (C^{11}), 128.84 (C^{19}), 132.50 (C^{12}), 133.50 (C^{18}), 142.04 (C^3), 147.77 (C^4), 173.50 (C$^{5'}$), 176.91 (C$^{2'}$).

1-Bromo-1'-(4-bromophenyl)-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (VI). *a.* A solution of 2.7 mmol of bromine in 2.7 ml of formic acid was added dropwise under stirring at 0°C to a solution of 1.0 g (1.8 mmol) of compound **I** in 22 ml of formic acid. The mixture was stirred for 1.5 h at 0–5°C, and the precipitate of hydrobromide **VI**·HBr was filtered off and recrystallized from ethanol. Yield 0.94 g (73.4%). The mother liquor was poured onto a Petri dish, and the dry residue was treated with 20 ml of a saturated solution of sodium carbonate. The product was extracted into methylene chloride (3×20 ml), the extracts were combined, washed with a solution of NaCl, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from alcohol. Yield of **VI** 0.36 g (26%), mp 280–283°C. ^{1}H NMR spectrum, δ, ppm: 1.85–2.07 m (2H, 15-H), 2.32–2.68 m (3H, 10-H, 16-H), 2.45 s (3H, 17-CH$_3$), 3.07 d (1H, 10-H, *J* = 19.0 Hz), 3.18 d (1H, 8-H, *J* = 8.5 Hz), 3.68 s (3H, 6-OCH$_3$), 3.79 s (3H, 3-OCH$_3$), 4.05 d (1H, 9-H, *J* = 6.5 Hz), 4.40 d (1H, 7-H, *J* = 8.5 Hz), 4.68 d (1H, 5-H, *J* = 1.5 Hz), 5.45 d (1H, 18-H, *J* = 8.8 Hz), 5.87 d.d (1H, 19-H, *J* = 8.8, 1.5 Hz), 6.82 s (1H, 2-H), 7.01–7.09 m (2H, 2''-H, 6''-H), 7.47–7.55 m (2H, 3''-H, 5''-H). ^{13}C NMR spectrum, δ_C, ppm: 24.16 (C^{10}), 33.44 (C^{15}), 41.21 (C^8), 42.07 (17-CH$_3$), 43.15 (C^7), 44.82 (C^{16}), 44.99 (C^{13}), 48.14 (C^{14}), 51.59 (6-OCH$_3$), 56.38 (3-OCH$_3$), 56.88 (C^9), 80.52 (C^6), 90.81 (C^5), 113.10 (C^1), 116.25 (C^2), 122.26 (C$^{4''}$), 126.71 (C^{11}), 127.70 (2C, C$^{2''}$, C$^{6''}$), 129.41 (C^{19}), 132.04 (C$^{3''}$), 132.08 (C$^{5''}$), 133.42 (C^{12}), 133.50 (C^{18}), 142.99 (C^3), 147.17 (2C, C^4, C$^{1''}$), 172.41 (C$^{5'}$), 175.73 (C$^{2'}$).

Hydrobromide **VI**·HBr. mp 243–249°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 1.87 m (1H, 15-H), 2.15 m (1H, 15-H), 2.60–3.30 m (3H, 10-H, 16-H), 3.13 br.s (3H, 17-CH$_3$), 3.40–3.70 m (2H, 8-H, 10-H), 3.66 s (3H, 6-OCH$_3$), 3.83 s (3H, 3-OCH$_3$), 4.80 m (1H, 9-H), 4.84 d.d (1H, 5-H, *J* = 1.5 Hz), 5.25 d (1H, 18-H, *J* = 9 Hz), 5.43 m (1H, 7-H), 5.91 m (1H, 19-H), 6.90 s (1H, 2-H), 7.03 m (2H, 2''-H, 6''-H), 7.47 m (2H, 3''-H, 5''-H). Found, %: C 47.30; H 3.40; Br 33.40; N 3.48. $C_{29}H_{27}Br_3N_2O_5$. Calculated, %: C 48.00; H 3.70; Br 33.00; N 3.80.

b. Hydrobromide **VI**·HBr, 0.94 g, was added to 15 ml of a saturated solution of sodium carbonate (pH 8–9). The mixture was extracted with methylene chloride (3×30 ml), the combined extracts were washed with water, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from alcohol. Yield of free base **VI** 0.84 g (89.5%).

1-Bromo-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (VII). A solution of 15 mmol of bromine in 15 ml of formic acid was added dropwise under stirring at 0°C to a solution of 5.0 g (10 mmol) of compound **II** in 72.3 ml of formic acid. The mixture was stirred for 1.5 h at 0–5°C, and the yellow precipitate was filtered off and recrystallized from ethanol. Yield of hydrobromide **VII**·HBr 4.22 g (64%). The filtrate was combined with the mother liquor and evaporated, the residue was treated with 20 ml of a saturated solution of sodium carbonate, the mixture was extracted with methylene chloride (3×100 ml), the extracts were combined, washed with a solution of sodium chloride, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from ethanol. Yield of free base **VII** 2.0 g (30.4%), mp 283–286°C. ^{1}H NMR spectrum, δ, ppm: 1.84–2.07 m (2H, 15-H), 2.31–2.67 m (3H, 10-H, 16-H), 2.45 s (3H, 17-CH$_3$), 3.08 d (1H, 10-H, *J* = 19.8 Hz), 3.19 d (1H, 8-H, *J* = 8.2 Hz), 3.69 s (3H, 6-OCH$_3$), 3.79 s (3H, 3-OCH$_3$), 4.06 d (1H, 9-H, *J* = 6.3 Hz), 4.38 d (1H, 7-H, *J* = 8.2 Hz), 4.69 d (1H, 5-H, *J* = 1.5 Hz), 5.47 d (1H, 18-H, *J* = 8.9 Hz), 5.89 m (1H, 19-H), 6.82 s (1H, 2-H), 7.09–7.18 m (2H, 2''-H, 6''-H), 7.30–7.46 m (3H, 3''-H, 4''-H, 5''-H). ^{13}C NMR spectrum, δ_C, ppm: 24.15 (C^{10}), 33.46 (C^{15}), 41.21 (C^8), 42.02 (17-CH3), 43.14 (C^7), 44.83 (C^{16}), 44.99 (C^{13}), 48.14 (C^{14}), 51.56 (6-OCH$_3$), 56.40 (3-OCH$_3$), 56.88 (C^9), 80.55 (C^6), 90.91 (C^5), 113.06 (C^1), 116.27

(C^{2}), 126.22 (2C, C$^{2''}$, C$^{6''}$), 126.83 (C^{11}), 128.47 (C$^{4''}$), 128.87 (2C, C$^{3''}$, C$^{5''}$), 129.38 (C^{19}), 133.57 (2C, C^{12}, C^{18}), 142.98 (C^{3}), 147.22 (2C, C^{4}, C$^{1'}$), 172.74 (C$^{5'}$), 176.08 (C$^{2'}$).

Hydrobromide **VII**·HBr. mp 270–280°C. ^{1}H NMR spectrum, δ, ppm: 2.12–2.22 m (2H, 15-H), 2.68–2.81 m (1H, 16-H), 2.83–3.02 m (2H, 10-H, 16-H), 3.13 br.s (3H, 17-CH$_3$), 3.53–3.65 m (2H, 9-H, 10-H), 3.68 s (3H, 6-OCH$_3$), 3.83 s (3H, 3-OCH$_3$), 4.78–4.87 m (2H, 5-H, 8-H), 5.28–5.37 m (2H, 7-H, 18-H), 5.94 m (1H, 19-H), 6.90 s (1H, 2-H), 7.13 m (2H, 2''-H, 6''-H), 7.28–7.39 m (3H, 3''-H, 4''-H, 5''-H). Found, %: C 53.39; H 3.90; Br 25.00; N 4.03. $C_{29}H_{28}Br_2N_2O_5$. Calculated, %: C 54.00; H 4.30; Br 24.80; N 4.30.

1-Bromo-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-1',17-dimethyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (VIII). A solution of 2.4 mmol of bromine in 2.4 ml of formic acid was added under stirring at 0°C to a solution of 0.68 g (1.6 mmol) of compound **III** in 11 ml of formic acid. The mixture was stirred for 1.5 h at 0–5°C and evaporated, and the residue was treated with 20 ml of a saturated solution of sodium carbonate. The product was extracted into methylene chloride (4×20 ml), the extract was washed with a solution of NaCl, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 0.73 g (91%), mp 266–270°C. ^{1}H NMR spectrum, δ, ppm: 1.83–1.97 m (2H, 15-H), 2.33–2.44 m (2H, 10-H, 16-H), 2.44 s (3H, 17-CH$_3$), 2.55 m (1H, 16-H), 2.84 s (3H, 1'-CH$_3$), 3.01 d (1H, 8-H, J = 8.8 Hz), 3.05 d (1H, 10-H, J = 19.0 Hz), 3.66 s (3H, 6-OCH$_3$), 3.77 s (3H, 3-OCH$_3$), 4.02 d (1H, 9-H, J = 6.2 Hz), 4.18 d (1H, 7-H, J = 8.8 Hz), 4.62 d (1H, 5-H, J = 1.5 Hz), 5.34 d (1H, 18-H, J = 8.4 Hz), 5.74 d.d (1H, 19-H, J = 8.4, 1.5 Hz), 6.80 s (1H, 2-H). ^{13}C NMR spectrum, δ$_C$, ppm: 24.03 (C^{10}), 24.60 (17-CH$_3$), 33.32 (C^{15}), 41.22 (C^{8}), 42.09 (C^{7}), 43.13 (1'-CH$_3$), 44.59 (C^{13}), 44.77 (C^{16}), 48.03 (C^{14}), 51.60 (6-OCH$_3$), 56.31 (3-OCH$_3$), 56.85 (C^{9}), 80.33 (C^{6}), 91.03 (C^{5}), 112.96 (C^{1}), 116.06 (C^{2}), 126.72 (C^{11}), 129.19 (C^{19}), 133.26 (C^{18}), 133.59 (C^{12}), 142.89 (C^{3}), 147.08 (C^{4}), 173.88 (C$^{5'}$), 177.08 (C$^{2'}$). Mass spectrum, m/z (I_{rel}, %): 500 $[M]^+$ (76), 388 (25), 247 (100), 204 (79), 176 (21), 44 (39). Found: $[M]^+$ 500.09507. $C_{24}H_{25}BrN_2O_5$. Calculated: M 500.09472.

1-Bromo-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (IX). A solution of 3.8 mmol of bromine in 3.8 ml of formic acid was added under stirring at 0°C to a solution of 1.0 g (2.5 mmol) of compound **IV** in 16 ml of formic acid. The mixture was stirred for 2 h at 0–5°C and poured onto a Petri dish. After evaporation of the solvent, the residue was treated with 20 ml of a saturated solution of sodium carbonate. The product was extracted into methylene chloride (4×20 ml), the extracts were combined, washed with a solution of sodium chloride, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from alcohol. Yield 0.96 g (81%), mp 293–297°C. ^{1}H NMR spectrum, δ, ppm: 1.81–1.94 m (2H, 15-H), 2.30–2.46 m (2H, 10-H, 16-H), 2.44 s (3H, 17-CH$_3$), 2.42 d.d.d (1H, 16-H, J = 12.6, 4.8, 1.5 Hz), 3.04 d (1H, 10-H, J = 15.2 Hz), 3.05 d (1H, 8-H, J = 8.6 Hz), 3.65 s (3H, 6-OCH$_3$), 3.78 s (3H, 3-OCH$_3$), 3.98 d (1H, 9-H, J = 6.8 Hz), 4.24 d (1H, 7-H, J = 8.6 Hz), 4.61 d (1H, 5-H, J = 1.2 Hz), 5.44 d (1H, 18-H, J = 8.4 Hz), 5.84 d.d (1H, 19-H, J = 8.4, 1.2 Hz), 6.81 s (1H, 2-H), 8.08 s (1H, 1'-H). ^{13}C NMR spectrum, δ$_C$, ppm: 24.04 (C^{10}), 33.33 (C^{15}), 42.61 (C^{7}), 43.10 (C^{8}), 43.31 (17-CH$_3$), 44.62 (C^{13}), 44.76 (C^{16}), 47.99 (C^{14}), 51.68 (6-OCH$_3$), 56.40 (3-OCH$_3$), 56.42 (C^{9}), 80.22 (C^{6}), 91.12 (C^{5}), 113.00 (C^{1}), 116.35 (C^{2}), 126.78 (C^{11}), 129.31 (C^{19}), 133.34 (C^{18}), 133.58 (C^{12}), 142.94 (C^{3}), 147.16 (C^{4}), 173.55 (C$^{5'}$), 176.88 (C$^{2'}$). Mass spectrum, m/z (I_{rel}, %): 486 $[M]^+$ (66), 388 (15), 233 (100), 190 (77), 162 (26), 59 (24), 44 (46). Found: $[M]^+$ 486.07740. $C_{23}H_{23}BrN_2O_5$. Calculated: M 486.07907.

1-Bromo-4,5α-epoxy-6α,14-etheno-2'α-hydroxy-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-5'-one (X). A solution of 0.75 mmol of bromine in 0.75 ml of formic acid was added under stirring at 0°C to a solution of 0.22 g (0.5 mmol) of compound **V** in 5 ml of formic acid. The mixture was stirred for 2 h at 0–5°C, poured onto a Petri dish, and evaporated. The residue was treated with 20 ml of a saturated solution of sodium carbonate, the mixture was extracted with methylene chloride (4×20 ml), the extract was washed with a solution of sodium chloride, dried over MgSO$_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 0.22 g (86%), mp 175–180°C. ^{1}H NMR spectrum, δ, ppm: 1.83 d.d.d (1H, 15-H, J = 12.4, 4.2, 1.8 Hz), 1.92–2.07 m (1H, 15-H), 2.33–2.52 m (3H, 8-H, 10-H, 16-H), 2.42 s (3H, 17-CH$_3$), 2.53–2.66 m (1H, 16-H), 3.02 d (1H, 10-H, J = 18.0 Hz), 3.57 s (3H, 6-OCH$_3$), 3.80 s (3H, 3-OCH$_3$), 4.18 d (1H, 9-H, J = 6.7 Hz), 4.30 d.d (1H, 7-H, J = 4.6, 8.0 Hz), 4.57 m (1H, 5-H), 5.38 s (1H, 2'-OH), 5.48 d

(1H, 18-H, *J* = 9.0 Hz), 5.79 m (1H, 19-H), 6.81 s (1H, 2-H), 7.14–7.22 m (2H, 2"-H, 6"-H), 7.42–7.26 m (3H, 3"-H, 4"-H, 5"-H). ^{13}C NMR spectrum, δ_C, ppm: 24.22 (C^{10}), 32.98 (C^{15}), 43.07 (17-CH_3), 43.56 and 43.88 (C^7, C^8), 45.11 (C^{13}), 45.37 (C^{16}), 48.18 (C^{14}), 51.79 (6-OCH_3), 56.48 (2C, 3-OCH_3, C^9), 79.37 (C^6), 84.24 ($C^{2'}$), 92.16 (C^5), 112.77 (C^1), 116.21 (C^2), 123.96 (2C, $C^{2''}$, $C^{6''}$), 126.55 ($C^{4''}$), 126.93 (C^{11}), 128.32 (C^{19}), 128.97 (2C, $C^{3''}$, $C^{5''}$), 133.80 (C^{12}), 134.29 (C^{18}), 136.61 ($C^{1''}$), 142.83 (C^3), 147.26 (C^4), 173.72 ($C^{5'}$). Found, %: C 61.10; H 5.00; Br 14.90; N 4.50. $C_{29}H_{29}BrN_2O_5$. Calculated, %: C 61.59; H 5.13; Br 14.16; N 4.95.

1-Bromo-1'-(4-bromophenyl)-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan (XIII). *a*. A solution of 4 mmol of bromine in 4 ml of formic acid was added under stirring at 0°C to a solution of 1.0 g (2.2 mmol) of compound **XII** in 15 ml of formic acid. The mixture was stirred for 2.5 h at 0–5°C and evaporated, the residue was treated with 20 ml of a saturated solution of sodium carbonate, and the product was extracted into methylene chloride (4×20 ml). The extract was washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 1.14 g (85%), mp 188–190°C.

b. A solution of 3.4 mmol of bromine in 3.4 ml of formic acid was added under stirring at 0°C to a solution of 1.0 g (1.9 mmol) of compound **XI** in 13 ml of formic acid. The mixture was stirred for 2.5 h at 0–5°C, poured onto a Petri dish, and evaporated. The residue was treated with 20 ml of a saturated solution of sodium carbonate, and the product was extracted into methylene chloride, the extract was washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from diethyl ether. Yield 0.94 g (86%), mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 1.84 d.d.d (1H, 15-H, *J* = 12.8, 4.2, 1.5 Hz), 2.14 m (1H, 15-H), 2.29–2.42 m (2H, 10-H, 16-H), 2.40 s (3H, 17-CH_3), 2.55 m (1H, 16-H), 2.76–2.84 m (2H, 2'-H, 5'-H), 3.06 d (1H, 10-H, *J* = 19.0 Hz), 3.13 m (1H, 8-H), 3.24 d (1H, 9-H, *J* = 7.2 Hz), 3.37–3.48 m (2H, 2'-H, 5'-H), 3.55 s (3H, 6-OCH_3), 3.78 s (3H, 3-OCH_3), 3.80–3.99 m (1H, 7-H), 4.62 d (1H, 5-H, *J* = 1.5 Hz), 5.32 d (1H, 18-H, *J* = 9 Hz), 5.80 m (1H, 19-H), 6.39–6.44 m (2H, 2"-H, 6"-H), 6.79 s (1H, 2-H), 7.22–7.27 m (2H, 3"-H, 5"-H). ^{13}C NMR spectrum, δ_C, ppm: 24.02 (C^{10}), 32.77 (C^{15}), 40.11 (C^7), 42.58 (C^8), 43.55 (17-CH_3), 45.16 (C^{13}), 48.28 (C^{14}), 49.83 (C^{16}), 50.98 ($C^{2'}$), 51.77 (6-OCH_3), 52.85 ($C^{5'}$), 56.40 (3-OCH_3), 59.03 (C^9), 81.12 (C^6), 93.54 (C^5), 108.28 ($C^{4''}$), 112.44 (C^1), 114.31 (2C, $C^{3''}$, $C^{5''}$), 115.87 (C^2), 127.00 (C^{11}), 129.86 (C^{19}), 131.51 (2C, $C^{2''}$, $C^{6''}$), 134.29 (C^{18}), 135.00 (C^{12}), 142.94 (C^3), 146.80 (C^4), 147.21 ($C^{1''}$).

1-Bromo-1'-(2,4-dibromophenyl)-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan (XIV). A solution of 4.8 mmol of bromine in 4.8 ml of formic acid was added under stirring at 0°C to a solution of 1.0 g (2 mmol) of compound **XI** in 13 ml of formic acid. The mixture was stirred for 2 h at 0–5°C, poured onto a Petri dish, and evaporated. The residue was treated with 20 ml of a saturated solution of sodium carbonate, the product was extracted into methylene chloride (4×20 ml), the extract was washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was recrystallized from alcohol. Yield 1.21 g (71%), mp 130–133°C. ^{1}H NMR spectrum, δ, ppm: 1.81 d.d.d (1H, 15-H, *J* = 13.0, 3.2, 1.0 Hz), 2.15 t.d (1H, 15-H, *J* = 13.0, 5.5 Hz), 2.28 d.d (1H, 10-H, *J* = 18.8, 6.4 Hz), 2.37 s (3H, 17-CH_3), 2.38 d.d.d (1H, 16-H, *J* = 12.8, 10.2, 1.5 Hz), 2.54 m (1H, 16-H, *J* = 12.8, 4.4, 1.4 Hz), 2.66 t (1H, 2'-H, *J* = 8.7 Hz), 2.76 m (1H, 8-H), 2.88 d.d (1H, 5'-H, *J* = 9.8, 8.0 Hz), 3.03 d (1H, 10-H, *J* = 18.8 Hz), 3.18 m (1H, 9-H, *J* = 6.4 Hz), 3.52 s (3H, 6-OCH_3), 3.55–3.57 m (2H, 2'-H, 5'-H), 3.78 s (3H, 3-OCH_3), 4.64 d (1H, 5-H, *J* = 1.3 Hz), 5.35 d (1H, 18-H, *J* = 8.8 Hz), 5.84 d.d (1H, 19-H, *J* = 8.8, 1.3 Hz), 6.78 s (1H, 2-H), 6.80 d (1H, 6"-H, *J* = 8.9 Hz), 7,27 d.d (1H, 5"-H, *J* = 8.9, 1.8 Hz), 7.60 d (1H, 3"-H, *J* = 1.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.92 (C^{10}), 32.72 (C^{15}), 40.10 (C^7), 42.30 (C^8), 43.52 (17-CH_3), 44.44 (C^{14}), 45.06 (C^{16}), 48.69 (C^{13}), 51.86 (6-OCH_3), 52.89 ($C^{5'}$), 53.28 ($C^{2'}$), 56.52 (3-OCH_3), 58.84 (C^9), 81.32 (C^6), 93.97 (C^5), 112.39 (C^1), 114.40 ($C^{2''}$), 116.13 (C^2), 117.93 ($C^{4''}$), 120.84 ($C^{6''}$), 127.05 (C^{11}), 130.17 (C^{19}), 130.63 ($C^{5''}$), 134.36 (C^{18}), 135.29 (C^{12}), 135.96 ($C^{3''}$), 142.92 (C^3), 147.26 ($C^{1''}$), 147.43 (C^4). Found, %: C 50.55; H 4.40; Br 34.30; N 4.20. $C_{29}H_{29}Br_3N_2O_3$. Calculated, %: C 50.20; H 4.20; Br 34.60; N 4.00.

4,5α-Epoxy-6α,14-etheno-1-iodo-3,6-dimethoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (XVI). A solution of 0.778 g (5 mmol) of ICl in 0.8 ml of acetic acid was added dropwise under stirring to a solution of 1.17 g (2.4 mmol) of compound **II** in 3 ml of formic acid. The mixture was stirred for 12 h at 35–40°C, poured onto a Petri dish, and evaporated. The solid residue was treated with 10 ml of a saturated solution of sodium carbonate, the product was extracted into chloroform (4×20 ml), the extract was washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated on a Petri dish, and the residue was ground with ethanol. The precipitate was filtered off and dissolved in chloroform, the undissolved material was filtered off, and the filtrate was subjected to chromatography on silica gel using chloroform–ethanol as eluent (gradient elution, 100:0 to 50:1). A fraction containing compound **XVI** (chloroform, chloroform–ethanol, 100:1) was evaporated, and the residue was recrystallized from ethyl acetate. Yield 0.6 g (41%), mp 286–289°C. ^{1}H NMR spectrum, δ, ppm: 1.85–2.01 m (2H, 15-H), 2.27 d.d (1H, 10-H, *J* = 18.8, 6.4 Hz), 2.39–2.52 m (1H, 16-H), 2.45 s (3H, CH_3N), 2.58 d.d.d (1H, 16-H, *J* = 12.4, 4.6, 1.8 Hz), 3.00 d (1H, 10-H, *J* = 18.8 Hz), 3.18 d (1H, 8-H, *J* = 9.2 Hz), 3.69 s (3H, 6-OCH_3), 3.79 s (3H, 3-OCH_3), 4.06 d (1H, 9-H, *J* = 6.4 Hz), 4.37 d (1H, 7-H, *J* = 9.2 Hz), 4.67 d (1H, 5-H, *J* = 1.4 Hz), 5.45 d (1H, 18-H, *J* = 8.8 Hz), 5.89 d.d (1H, 19-H, *J* = 8.8, 1.4 Hz), 7.04 s (1H, 2-H), 7.11–7.16 m (2H, 2''-H, 6''-H), 7.29–7.34 m (1H, 4''-H), 7.35–7.42 m (2H, 3''-H, 5''-H). ^{13}C NMR spectrum, δ_C, ppm: 28.62 (C^{10}), 33.55 (C^{15}), 41.38 (C^{8}), 42.00 (C^{7}), 43.17 (17-CH_3), 44.89 (C^{16}), 45.17 (C^{13}), 48.27 (C^{14}), 51.61 (6-OCH_3), 56.51 (3-OCH_3), 57.40 (C^{9}), 80.59 (C^{6}), 86.52 (C^{1}), 90.96 (C^{5}), 122.54 (C^{2}), 126.25 ($C^{6''}$), 126.28 ($C^{2''}$), 128.44 ($C^{4''}$), 128.86 (2C, $C^{3''}$, $C^{5''}$), 129.37 (C^{19}), 130.62 (C^{11}), 131.63 (C^{12}), 133.34 (C^{3}), 133.56 (C^{18}), 143.22 (C^{4}), 148.36 ($C^{1''}$), 172.71 ($C^{5'}$), 176.04 ($C^{2'}$). Found, %: C 57.70; H 4.30; I 20.2; N 4.44. $C_{29}H_{27}IN_2O_5$. Calculated, %: C 57.00; H 4.40; I 20.82; N 4.59.

Heck reaction (*general procedure*). A two-necked flask equipped with a magnetic stirrer was evacuated and filled with argon, and this procedure was repeated thrice. The flask was charged in a stream of argon in succession with 1 mmol of the corresponding bromo or iodo derivative, 2 mol % of palladium(II) acetate, 8 mol % of tris(*o*-tolyl)phosphine, and 1.5 ml of DMF. Triethylamine, 1.4 mmol, and ethyl or methyl acrylate, 4 mmol, were then added to the resulting suspension under stirring, and the mixture was stirred for 5–9 h at 100–150°C and poured onto a Petri dish. After evaporation of the solvent, the solid residue was dissolved in a minimal amount of chloroform, and the solution was applied to a column charged with silica gel using chloroform–ethanol (100:0 to 10:1) as eluent. We isolated (in the order of elution) tris(*o*-tolyl)phosphine, the initial halogen derivative, and a mixture of the initial halogen derivative and cross-coupling product (chloroform–ethanol, 100:1 to 50:3). To isolate the pure cross-coupling product or increase its fraction, its mixture with the initial compound was subjected to repeated chromatographic separation and recrystallization.

Ethyl (*E*)-3-(4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5'-dioxo-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1-yl)prop-2-enoate (XVII) was isolated by repeated column chromatography, followed by recrystallization from diethyl ether. Yield 50% from iodide **XVI** or 19% from bromide **VII**, mp 269–274°C (from diethyl ether). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.0 Hz), 1.87–2.03 m (2H, 15-H), 2.41–2.49 m (1H, 16-H), 2.46 s (3H, 17-CH_3), 2.50–2.62 m (2H, 10-H, 16-H), 3.18 d (1H, 8-H, *J* = 7.8 Hz), 3.30 d (1H, 10-H, *J* = 18.8 Hz), 3.70 s (3H, 6-OCH_3), 3.83 s (3H, 3-OCH_3), 4.07 m (1H, 9-H), 4.24 q (2H, OCH_2, *J* = 7.0 Hz), 4.39 d (1H, 7-H, *J* = 7.8 Hz), 4.72 d (1H, 5-H, *J* = 1.5 Hz), 5.46 d (1H, 18-H, *J* = 8.8 Hz), 5.88 d.d (1H, 19-H, *J* = 8.8, 1.5 Hz), 6.22 d (1H, 1b-H, *J* = 15.9 Hz), 6.93 s (1H, 2-H), 7.11–7.16 (2H, 2''-H, 6''-H), 7.28–7.33 m (1H, 4''-H), 7.34–7.40 m (2H, 3''-H, 5''-H), 7.76 d (1H, 1a-H, *J* = 15.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.26 (CH_3), 21.50 (C^{10}), 33.52 (C^{15}), 41.35 (C^{8}), 42.14 (C^{7}), 43.21 (17-CH_3), 44.82 (C^{13}), 44.84 (C^{16}), 47.74 (C^{14}), 51.63 (6-OCH_3), 56.26 (3-OCH_3), 56.79 (C^{9}), 60.33 (CH_2), 80.63 (C^{6}), 91.47 (C^{5}), 111.59 (C^{2}), 116.49 (C^{1b}), 125.85 (C^{1}), 126.24 (2C, $C^{6''}$, $C^{2''}$), 128.02 (C^{11}), 128.44 ($C^{4''}$), 128.86 (2C, $C^{3''}$, $C^{5''}$), 129.28 (C^{19}), 131.61 (C^{12}), 133.11 (C^{3}), 133.68 (C^{18}), 140.52 (C^{1a}), 142.65 (C^{4}), 150.03 ($C^{1''}$), 167.18 (C=O), 172.69 ($C^{5'}$), 176.04 ($C^{2'}$). Mass spectrum, *m*/*z* (I_{rel}, %): 582 $[M]^+$ (100), 553 (6), 408 (19), 336 (10), 327 (23), 309 (7), 266 (6), 238 (18), 176 (15), 121 (9), 44 (20). Found: $[M]^+$ 582.24025. $C_{34}H_{34}N_2O_7$. Calculated: *M* 582.23658.

Ethyl (*E*)-3-(4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-1',17-dimethyl-2',5'-dioxo-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1-yl)prop-2-enoate (XVIII). The initial amount of palladium(II) acetate was increased by a factor of 4, and two additional portions of palladium(II) acetate (0.9 mol %) and ethyl acrylate (2.64 mmol) were added during the process (reaction time 14 h). Yield 14%. ^{1}H NMR spectrum (from the spectrum of a 1:1 mixture of **XVIII** and **VIII**), δ, ppm: 1.31 t (3H, $CH_2C\mathbf{H}_3$, *J* = 6.8 Hz), 1.80–2.02 m (2H, 15-H), 2.28–2.62 m (3H, 10-H, 16-H), 2.44 s (3H, 17-CH_3), 2.85 s (3H, 1'-CH_3), 2.99–3.12 m (2H, 9-H, 10-H), 3.67 s (3H, 6-OCH$_3$), 3.81 s (3H, 3-OCH$_3$), 4.02 d (1H, 8-H, *J* = 6.2 Hz), 4.18 d (1H, 7-H, *J* = 6.2 Hz), 4.21 q (2H, OCH$_2$, *J* = 6.8 Hz), 4.68 m (1H, 5-H), 5.35 d (1H, 18-H, *J* = 8.2 Hz), 5.74 m (1H, 19-H), 6.22 d (1H, 1b-H, *J* = 16.0 Hz), 6.91 s (1H, 2-H), 7.75 d (1H, 1a-H, *J* = 16.0 Hz).

Methyl (*E*)-3-(4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5'-dioxo-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1-yl)prop-2-enoate (XIX) was isolated by repeated column chromatography of a fraction containing compounds **XIX** and **IX** and was additionally recrystallized from ethanol. Yield 22% (under standard conditions), 40% [in the presence of Pd(dba)$_2$ instead of Pd(OAc)$_2$]; mp 203–205°C. ^{1}H NMR spectrum, δ, ppm: 1.83–2.02 m (2H, 15-H), 2.38 m (1H, 16-H), 2.48 s (3H, 17-CH$_3$), 2.57 m (1H, 10-H), 2.62 m (1H, 16-H), 3.06 d (1H, 8-H, *J* = 8.4 Hz), 3.33 d (1H, 10-H, *J* = 18.7 Hz), 3.68 s (6H, 6-OCH$_3$), 3.79 s (3H, COOCH$_3$), 3.83 s (3H, 3-OCH$_3$), 4.03 d (1H, 9-H, *J* = 6.4 Hz), 4.28 d (1H, 7-H, *J* = 8.4 Hz), 4.69 d (1H, 5-H, *J* = 1.5 Hz), 5.45 d (1H, 18-H, *J* = 8.9 Hz), 5.86 d.d (1H, 19-H, *J* = 8.9, 1.5 Hz), 6.25 d (1H, 1b-H, *J* = 16.8 Hz), 6.92 s (1H, 2-H), 7.80 d (1H, 1a-H, *J* = 16.8 Hz), 8.56 s (1H, 1'-H). ^{13}C NMR spectrum, δ_C, ppm: 21.45 (C^{10}), 33.38 (C^{15}), 42.74 (C^8), 43.18 (17-CH$_3$), 43.46 (C^7), 44.46 (C^{16}), 44.82 (C^{13}), 47.64 (C^{14}), 51.23 (6-OCH$_3$), 51.28 (COO**C**H$_3$), 56.23 (3-OCH$_3$), 56.68 (C^9), 80.32 (C^6), 91.64 (C^5), 111.59 (C^2), 116.03 (C^{1b}), 125.74 (C^1), 129.29 (C^{11}), 129.28 (C^{19}), 131.61 (C^{12}), 133.11 (C^3), 133.68 (C^{18}), 140.43 (C^{1a}), 150.06 (C^4), 167.60 (C=O), 173.30 (C$^{5'}$), 176.66 (C$^{2'}$). Mass spectrum, *m/z* (I_{rel}, %): 492 $[M]^+$ (100), 477 (23), 313 (14), 233 (45), 190 (31), 162 (11), 59 (13), 44 (27), 43 (33). Found: $[M]^+$ 492.18900. $C_{27}H_{28}N_2O_7$. Calculated: *M* 492.18964.

Methyl (*E*)-3-(4,5α-epoxy-6α,14-etheno-2'-hydroxy-3,6-dimethoxy-17-methyl-5'-oxo-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1-yl)prop-2-enoate (XX). The initial amount of palladium(II) acetate was increased by a factor of 4, and two additional portions of Pd(II) acetate (0.9 mol %) and methyl acrylate (2.64 mmol) were added during the process (reaction time 14 h). Yield 30%. ^{1}H NMR spectrum (from the spectrum of a 1 : 1 mixture of compounds **XX** and **X**), δ, ppm: 1.90 m (1H, 15-H), 2.22 m (1H, 15-H), 2.28–2.62 m (2H, 10-H, 16-H), 2.61 s (3H, 17-CH$_3$), 2.88 m (1H, 16-H), 2.99 d (1H, 10-H, *J* = 18.8 Hz), 3.12 m (1H, 8-H), 3.67 s (3H, 6-OCH$_3$), 3.74 s (3H, COOCH$_3$), 3.84 s (3H, 3-OCH$_3$), 4.40 m (1H, 7-H), 4.56 m (1H, 2'-H), 4.67 d (1H, 5-H, *J* = 1.4 Hz), 5.35 s (1H, 2'-OH), 5.48 d (1H, 18-H, *J* = 8.2 Hz), 5.92 d.d (1H, 19-H, *J* = 8.2, 1.4 Hz), 6.32 d (1H, 1b-H, *J* = 16.0 Hz), 6.89 s (1H, 2-H), 7.12–7.21 m (1H, 4''-H), 7.24–7.31 m (2H, 2''-H, 6''-H), 7.38–7.40 m (2H, 3''-H, 5''-H), 7.68 d (1H, 1a-H, *J* = 16.0 Hz).

Ethyl (*E*)-3-[1'-(4-bromophenyl)-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5'-dioxo-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1-yl]prop-2-enoate (XXI) and ethyl (*E*)-3-[4-(1-bromo-4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5'-dioxo-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1'-yl)phenyl]prop-2-enoate (XXII) were synthesized following the general procedure. After heating for 5–6 h, additional portions of Pd(OAc)$_2$ (1.2 mol %), tris(*o*-tolyl)phosphine (4.8 mol %), triethylamine (0.6 mmol), and ethyl acrylate (3.2 mmol) were added. The reaction mixture was heated at 150°C.

Compound **XXI**. Yield 5%. ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH$_2$C**H**$_3$, *J* = 7 Hz), 1.95 m (1H, 15-H), 2.14 m (1H, 15-H), 2.42–2.51 m (2H, 10-H, 16-H), 2.59 s (3H, 17-CH$_3$), 2.74–2.87 m (1H, 16-H), 3.08 d (1H, 10-H, *J* = 19.5 Hz), 3.23 d (1H, 8-H, *J* = 8.2 Hz), 3.67 s (3H, 6-OCH$_3$), 3.80 s (3H, 3-OCH$_3$), 4.07–4.30 m (3H, 9-H, OCH$_2$), 4.67–4.77 m (1H, 7-H), 4.71 d (1H, 5-H, *J* = 1.5 Hz), 5.40 d (1H, 18-H, *J* = 8.7 Hz), 5.86 m (1H, 19-H), 6.38 d (1H, 1b-H, *J* = 16.6 Hz), 6.84 s (1H, 2-H), 7.17–7.28 m (2H, 2''-H, 6''-H), 7.47–7.56 m (2H, 3''-H, 5''-H), 7.61 d (1H, 1a-H, *J* = 16.6 Hz).

Compound **XXII**. Yield 23%. ^{1}H NMR spectrum, δ, ppm: 1.28 m (3H, CH$_2$C**H**$_3$), 1.95 m (1H, 15-H), 2.14 m (1H, 15-H), 2.42–2.61 m (2H, 10-H, 16-H), 2.59 s (3H, 17-CH$_3$), 2.75–2.94 m (1H, 16-H), 3.23 d (1H, 8-H, *J* = 8.2 Hz), 3.33 d (1H, 10-H, *J* = 20 Hz), 3.67 s (3H, 6-OCH$_3$), 3.83 s (3H, 3-OCH$_3$), 4.28 d (1H, 9-H, *J* = 6.4 Hz), 4.30 q (2H, OCH$_2$), 4.72 m (1H, 7-H), 4.74 d (1H, 5-H, *J* = 1.4 Hz), 5.43 d (1H, 18-H, *J* = 8.8 Hz), 5.88 d.d (1H, 19-H, *J* = 8.8, 1.4 Hz), 6.23 d (1H, 4''b-H, *J* = 15 Hz), 6.95 s (1H, 2-H), 7.01–7.11 m (2H, 2''-H, 6''-H), 7.47–7.56 m (2H, 3''-H, 5''-H), 7.73 d (1H, 4''a-H, *J* = 15 Hz).

Ethyl (*E*)-3-[4-(4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5'-dioxo-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1'-yl)phenyl]prop-2-enoate (XXIII) was synthesized as described above. Yield 50%, mp 245–250°C (from diethyl ether–ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH$_2$C**H**$_3$, *J* = 7.0 Hz), 1.91–2.08 m (2H, 15-H), 2.47 s (3H, 17-CH$_3$), 2.50–2.68 m (3H, 10-H, 16-H), 3.19 d (1H, 8-H, J = 8.2 Hz), 3.28 d (1H, 10-H, J = 20.0 Hz), 3.74 s (3H, 6-OCH$_3$), 3.84 s (3H, 3-OCH$_3$), 4.05 d (1H, 9-H, J = 8.2 Hz), 4,27 q (2H, OCH$_2$, J = 7.0 Hz), 4.46 d (1H, 7-H, J = 8.2 Hz), 4.72 d (1H, 5-H, J = 1.4 Hz), 5.55 d (1H, 18-H, J = 8.8 Hz), 5.78 d.d (1H, 19-H, J = 8.8, 1.5 Hz), 6.43 d (1H, 4''b-H, J = 15.9 Hz), 6.60 d (1H, 1-H, J = 8.2 Hz), 6.68 d (1H, 2-H, J = 8.2 Hz), 7.25 d (2H, 2''-H, 6''-H, J = 8.9 Hz), 7.55 d (2H, 3''-H, 5''-H, J = 8.9 Hz), 7.66 d (1H, 4''a-H, J = 15.9 Hz).

Ethyl (*E*)-3-[4-(4,5α-epoxy-6α,14-etheno-3,6-dimethoxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-1'-yl)phenyl]prop-2-enoate (XXIV). Yield 20%. ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, CH$_2$C**H**$_3$, J = 7.0 Hz), 1.86 m (1H, 15-H), 2.10–2.30 m (1H, 15-H), 2.33–2.65 m (3H, 10-H, 16-H), 2.41 s (3H, 17-CH$_3$), 2.72–2.95 m (2H, 2'-H, 5'-H), 3.08–3.31 m (3H, 8-H, 9-H, 10-H), 3.40–3.51 m (2H, 2'-H, 5'-H), 3.56 s (3H, 6-OCH$_3$), 3.80 s (3H, 3-OCH$_3$), 3.90 d (1H, 7-H, J = 8.0 Hz), 4.21 q (2H, OCH$_2$, J = 7.0 Hz), 4.64 d (1H, 5-H, J = 1.5 Hz), 5.32 d (1H, 18-H, J = 8.6 Hz), 5.78 d.d (1H, 19-H, J = 8.6, 1.5 Hz), 6.18 d (1H, 4''b-H, J = 16.0 Hz), 6.41 d (1H, 1-H, J = 9.0 Hz), 6.46–6.72 m (3H, 2''-H, 6''-H), 7.15–7.28 m (2H, 3''-H, 5''-H), 7.58 d (1H, 4''a-H, J = 16.0 Hz).

Demethylation of compounds VI and VII (*general procedure*). Compound **VI** or **VII**, 2 mmol, was dissolved in 20 ml of chloroform, and 20 ml of a 1 M solution of BBr$_3$ in chloroform was added under stirring. The mixture was stirred for 3 h at room temperature, poured into dilute (1 : 1) aqueous ammonia, cooled to 3–5°C, and stirred for 30 min at 0°C. The organic phase was separated, and the aqueous phase was extracted with chloroform (2×15 ml). The extracts were combined with the organic phase, washed with a saturated solution of sodium chloride, dried over magnesium sulfate, and evaporated. The residue was ground with diethyl ether, and the precipitate (compound **XXV** from **VI** or compounds **XXVI** and **XXVII** from **VII**) was filtered off. An analytical sample of **XXV** was obtained by recrystallization from ethanol.

1-Bromo-1'-(4-bromophenyl)-4,5α-epoxy-6α,14-etheno-3,6-dihydroxy-17-methyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (XXV). Yield 94%, mp 200–205°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 1.80 m (1H, 15-H), 1.98 m (1H, 15-H), 2.27–2.43 m (2H, 10-H, 16-H), 2.42 s (3H, 17-CH$_3$), 2.55 m (1H, 16-H), 2.99 m (1H, 10-H), 3.11 m (2H, 8-H), 3.94 d (1H, 9-H, J = 6.9 Hz); 4.35 d (1H, 7-H, J = 9.2 Hz), 4.46 d (1H, 5-H, J = 1.4 Hz), 5.37 d (1H, 18-H, J = 9.2 Hz), 5.81 d.d (1H, 19-H, J = 9.2, 1.4 Hz), 6.81 s (1H, 2-H), 7.01 m (2H, 2''-H, 6''-H), 7.47–7.53 m (4H, 3''-H, 5''-H, OH). ^{13}C NMR spectrum, δ_C, ppm: 24.04 (C^{10}), 32.24 (C^{15}), 41.15 (C^8), 42.92 (17-CH$_3$), 44.55 (C^{13}), 44.94 (C^7), 45.39 (C^{16}), 47.92 (C^{14}), 56.69 (C^9), 75.74 (C^6), 95.17 (C^5), 113.38 (C^1), 120.01 (C^2), 122.49 (C$^{4''}$), 125.85 (C^{11}), 127.51 (2C, C$^{2''}$, C$^{6''}$), 129.82 (C^3), 130.56 (C^{19}), 131.84 (2C, C$^{3''}$, C$^{5''}$), 132.47 (C^{12}), 133.72 (C^{18}), 138.90 (C^4), 145.67 (C$^{1''}$), 175.31 (C$^{5'}$), 175.90 (C$^{2'}$). Mass spectrum, *m*/*z* (I_{rel}, %): 612 [M]$^+$ (16), 440 (11), 363 (29), 362 (60), 361 (42), 360 (100), 307 (18), 305 (16), 162 (16), 160 (21), 84 (15), 83 (23), 58 (19), 44 (59), 42 (42). Found: [M]$^+$ 611.98961. $C_{34}H_{34}Br_2N_2O_7$. Calculated: M 611.989664.

1-Bromo-4,5α-epoxy-6α,14-etheno-3,6-dihydroxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (XXVI) was isolated by column chromatography using chloroform–ethanol (100:1) as eluent. Yield 67%, mp 203–210°C (from diethyl ether). ^{1}H NMR spectrum, δ, ppm: 1.78 m (1H, 15-H), 2.10 m (1H, 15-H), 2.29–2.48 m (2H, 10-H, 16-H), 2.45 s (3H, 17-CH$_3$), 2.68 m (1H, 16-H), 2.98 d (1H, 8-H, J = 8.4 Hz), 3.10 d (1H, 10-H, J = 18.8 Hz), 3.99 d (1H, 9-H, J = 6.2 Hz), 4.38 d (1H, 7-H, J = 8.4 Hz), 4.51 d (1H, 5-H, J = 1.4 Hz), 5.40 d (1H, 18-H, J = 8.6 Hz), 5.85 d.d (1H, 19-H, J = 8.6, 1.4 Hz), 6.85 s (1H, 2-H), 7.11 m (2H, 2''-H, 6''-H), 7.32–7.46 m (5H, 3''-H, 4''-H, 5''-H, OH). ^{13}C NMR spectrum, δ_C, ppm: 24.26 (C^{10}), 32.33 (C^{15}), 41.16 (C^8), 43.11 (17-CH$_3$), 44.81 (C^{13}), 45.02 (C^7), 45.54 (C^{16}), 48.07 (C^{14}), 56.83 (C^9), 75.92 (C^6), 95.40 (C^5), 113.50 (C^1), 120.12 (C^2), 125.92 (C^{11}), 126.18 (2C, C$^{2''}$, C$^{6''}$), 128.85 (C$^{4''}$), 129.06 (2C, C$^{3''}$, C$^{5''}$), 130.93 (C^{19}), 131.02 (C^3), 133.45 (C^{12}), 133.73 (C^{18}), 139.11 (C^4), 145.88 (C$^{1''}$), 176.00 (C$^{5'}$), 176.53 (C$^{2'}$). Mass spectrum, *m*/*z* (I_{rel}, %): 534 [M]$^+$ (30), 363 (27), 362 (56), 360 (51), 307 (28), 281 (30), 280 (100), 224 (21), 160 (25), 44 (57), 42 (51). Found: [M]$^+$ 534.07737. $C_{27}H_{23}BrN_2O_5$. Calculated: M 534.07907.

1-Bromo-4,5α-epoxy-6α,14-etheno-3-hydroxy-6-methoxy-17-methyl-1'-phenyl-2',5',7β,8β-tetrahydro-1'*H*-14α-pyrrolo[3',4':7,8]morphinan-2',5'-dione (XXVII). ^{1}H NMR spectrum, δ, ppm (from the spectrum of mixture **XXVI**/**XXVII**): 1.87–1.99 m (1H, 15-H), 1.99–2.15 m (1H, 15-H), 2.34–2.55 m (2H, 10-H, 16-H), 2.50 s (3H, 17-CH$_3$), 2.61–2.73 m (1H, 16-H), 3.06 d (1H, 10-H, J = 18.8 Hz), 3.16 d (1H, 8-H, J = 8.2 Hz), 3.78 s (3H, OCH$_3$), 4.04 d (1H, 9-H, J = 6.4 Hz), 4.43 d (1H, 7-H, J = 8.2 Hz), 4.53 d (1H, 5-H, J = 1.4 Hz), 5.47 d (1H, 18-H, J = 8.6 Hz), 5.93 d.d (1H, 19-H, J = 8.6, 1.4 Hz), 6.86 s (1H, 2-H), 6.92 s (1H, OH), 7.12–7.19 m (2H, 2''-H, 6''-H), 7.35–7.50 m (3H, 3''-H, 4''-H, 5''-H).

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