Synthetic transformations of isoquinoline alkaloids. Synthesis of new dihydrothebaine-hydroquinone derivatives*

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1-Bromo- and 1-iodo-6,14-*endo*-ethenodihydrothebaine-hydroquinones were obtained. The Heck reactions of these halides with various olefins were studied.

Key words: 6,14-*endo*-ethenotetrahydromorphinanes, dihydrothebaine-hydroquinone, alkaloids, bromination, iodination, olefins, the Heck reaction, indolizines.

6,14-*endo*-Ethenotetrahydro- and dihydromorphinanes synthesized by modification of thebaine adducts with various dienophiles constitute an important group of pharmacologically valuable agents and drugs. For instance, some of them (buprenorphine, diprenorphine, and etorphine) are efficient analgesics or opioid antagonists against drug overdose; others are of interest as selective ligands of opiate receptors for research purposes.[1—3] 6,14-*endo*-Ethenodihydrothebaine-hydroquinones prepared from thebaine and various benzoquinones have been used to obtain very promising analgesics deprived of side effects of morphine (lowered toxicity, no effect on respiration).[4—6] Transformations of morphine and codeine *via* modifications of substituents in aromatic ring A[7—10] gave two groups of pharmacologically promising agents, namely, 4-alkoxymorphinanes (cyprodime and analogs), which are specific antagonists to μ-receptors,[3,9] and 3-deoxy-3-carbamoylmorphinanes, which show an affinity for μ-opiate receptors.[10] Introduction of substituents into the C(1) and C(2) positions of ring A of morphinanes is restricted to the syntheses of 1-hydroxy-, 1-chloro-, and 2-dimethylamino derivatives of morphine, codeine, and 7-acetyl-*endo*-ethenotetrahydrothebaine. It has been demonstrated that even such slight structural modifications substantially change the analgesic properties of compounds.[7] In connection with this, a pressing problem is to obtain new 6,14-*endo*-ethenodihydrothebaine-hydroquinone derivatives containing various substituents in ring A and study their specific pharmacological activities.

The goal of the present work was to develop methods for the synthesis of new 6,14-*endo*-ethenodihydrothebaine-hydroquinone derivatives containing functionalized olefin substituents in aromatic ring A. The most convenient way of introducing such fragments is the Heck reaction of appropriate halo derivatives of *endo*-ethenodihydrothebaine-hydroquinone.

* Dedicated to the memory of Academician N. N. Vorozhtsov on the 100th anniversary of his birth.

Results and Discussion

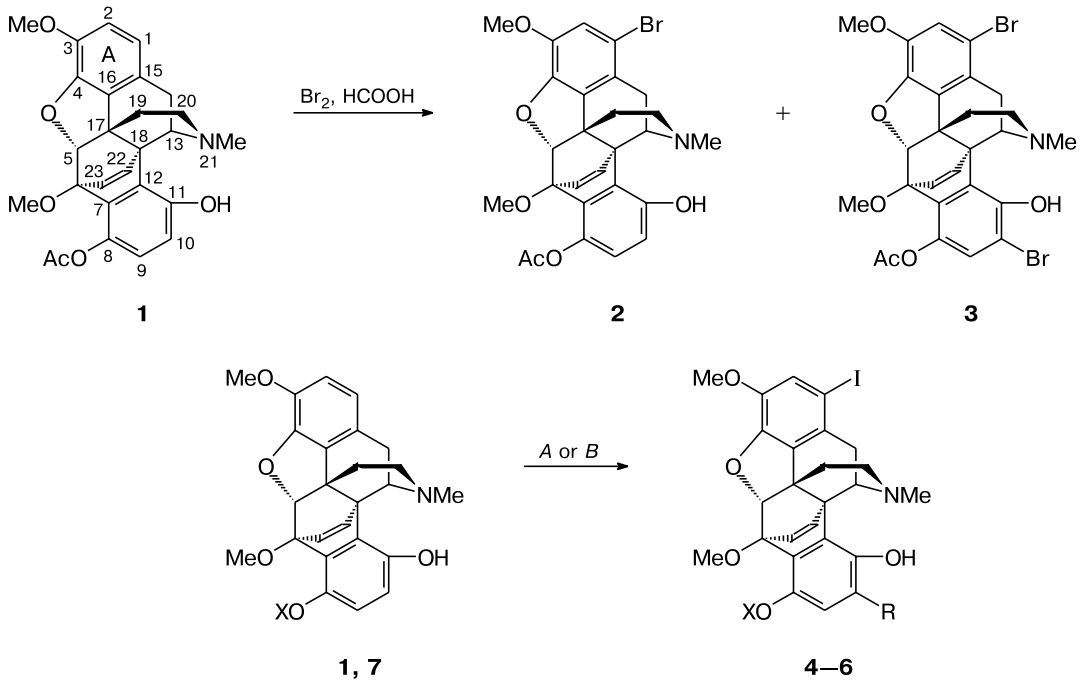
Treatment of dihydrothebaine-hydroquinone derivative **1** with bromine (1 equiv.) in formic acid at 0 °C gave 1-bromo derivative **2** in 25% yield (Scheme 1); the starting compound **1** was partially recovered. With an increase in the amount of bromine (1.1—1.5 equiv.), dibromide **3** was obtained along with bromide **2**. The optimal amount of bromine was 1.3 equiv. (total yield 85%; **2** : **3** = 1 : 1). At higher amounts of bromine, the yields of compounds **2** and **3** were 32 and 48% (1.4 equiv. Br_2) or 17 and 33% (1.5 equiv. Br_2), respectively.

Iodine was introduced into compound **1** through iodine chloride[11] (method *A*) or iodine in the presence of ammonium cerium nitrate[12] (method *B*). Heating of compound **1** with an excess of iodine chloride in formic acid proceeded slowly to give a mixture of three compounds (TLC data). The reaction products were 1-iodo-6,14-*endo*-etheno-7,8-(1-acetoxy-4-hydroxybenzo)dihydrothebaine (**4**) (yield 57%), 1-iodo-6,14-*endo*-etheno-7,8-(1,4-hydroquinono)dihydrothebaine (**5**) (yield 13%), and 5´-chloro-1-iodo-6,14-*endo*-etheno-7,8-(1,4-hydroquinono)dihydrothebaine (**6**) (yield 11%). Iodide **5** was the major product in the iodination of compound **1** or **7** with iodine in the presence of ammonium cerium nitrate. The yields were 62 and 52%, respectively (see Scheme 1, method *B*). The reaction was accompanied by hydrolysis of the acetoxy group.

The halogenation products were identified from ^1H and ^{13}C NMR, 2D COSY, and ^1H—^{13}C correlation spectra (COSY, COLOC). In the ^1H NMR spectra of com-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1206—1214, June, 2007.

Scheme 1



1 **2** **3** **1, 7** **4—6**

X = Ac (**1**), H (**7**)
R = H, X = Ac (**4**); R = X = H (**5**); R = Cl, X = H (**6**)

pounds **2**—**6**, a singlet for the proton of aromatic ring A appears at δ 6.84 (**2**, **3**) and 7.06—7.08 (**4**—**6**). The ^{13}C NMR spectra of compounds **2** and **3** show signals for the C(1) (δ 112—113, s) and C(2) atoms (δ 116, d). The ^{1}H—^{13}C COLOC spectra contain cross peaks between the signals of the above proton of the aromatic ring and the C(4) atom and between the signals for the C(1) atom (singlet in the ^{13}C JMod spectrum) and the H(14) proton (δ 3.03 and 2.25—2.44 in the spectrum of compound **2**). These couplings indicate introduction of the halogen atom into the C(1) position of ring A.* The location of the OH group at the C(11) atom and of the Br atom at the C(10) atom in compound **3** was confirmed by NOESY data for compounds **3** and **1**. Irradiation of the signal for the OH proton in compound **1** revealed NOE on the H(10) and H(13) protons; irradiation of the signal of the OH proton in compound **3** revealed NOE on the H(13) proton. In addition, the ^{1}H—^{13}C COLOC spectrum of compound **3** shows a cross peak between the signals for the H(9) and C(7) atoms.

The formation of 1-iodo derivatives **4**—**6** was unambiguously proved by ^{13}C NMR spectroscopy with consideration of increments of the substituent iodine atom.[13] The signal for the C(1) atom is shifted upfield to δ 85—87 (singlet in the ^{13}C NMR JMod spectrum), while the signals for the C(2) (doublet in the ^{13}C NMR spectrum) and C(15) atoms are shifted downfield (Δδ ~4—6) (Table 1).

It follows from the data obtained that the halogenation of 6,14-*endo*-ethenodihydrothebaine-hydroquinone derivatives occurs at the C(1) atom of the morphinane framework. Apparently, the attack of the reagent is directed by the O atom of the dihydrofuran ring. A similar substitution into the *meta*-position relative to the methoxy group has taken place in the chlorination and bromination of the aromatic ring of some morphinanes.[14—16]

Halodihydrothebaines **2**—**6** were used in the Heck reactions with ethyl acrylate, 2-methyl-5-vinylpyridine, styrene, and ethyl vinyl ether. A reaction of 1-iodo-*endo*-ethenodihydrothebaine **4** with ethyl acrylate in DMF in the presence of the catalytic system $Pd(OAc)_2$—tris(*o*-tolyl)phosphine and triethylamine as a base[16—18] gave 1-[2-(ethoxycarbonyl)ethenyl]-6,14-*endo*-etheno-7,8-(1-acetoxy-4-hydroxybenzo)dihydrothebaine (**8**) in 80% yield (Scheme 2). The yield of compound **8** from bromide **2** was 30%. The Heck reaction of dibromide **3** with ethyl acrylate under the above conditions gave products **9** and **10** in 13 and 6% yields, respectively. Analogous reactions of 1-iodo-*endo*-ethenodihydrothebaine-hydroquinones **5** and **6** with ethyl acrylate afforded the corresponding 1-[2-(ethoxycarbonyl)ethenyl]dihydrothebaine-hydroquinone derivatives **11** and **12** in 96 and 95% yields, respectively.

* The atomic numbering used in this paper for the morphinane framework is shown in Scheme 1.

Table 1. ^{13}C NMR spectra of dihydrothebaine **1** and halodihydrothebaines **2—6** (75.47 MHz, $CDCl_3$)

Atom	δ					
	1	**2**	**3**	**4**	**5**	**6**
C(1)	119.28	112.59	112.63*	85.75	87.12	86.96
C(2)	113.96	116.75	116.72	122.97	122.88	122.98
C(3)	142.34	143.48	143.50	143.68	143.49	143.03
C(4)	149.20	148.79	148.65	149.89	149.14	149.06
C(5)	93.66	94.11	93.71	94.10	97.27	96.98
C(6)	85.52	85.53	85.39	85.53	86.14	86.24
C(7)	128.31	127.96	131.67	127.92	121.76	123.69
C(8)	138.70	138.89	138.09	138.95	146.36	143.01
C(9)	122.06	122.34	112.71*	122.36	119.47	127.30
C(10)	118.79	119.10	125.56	119.10	116.82	116.96
C(11)	151.55	151.77	149.39	151.79	147.42	146.73
C(12)	131.71	131.72	128.51	131.81	129.24	121.14
C(13)	57.69	57.87	57.73	58.42	58.23	58.08
C(14)	22.43	24.30	24.32	28.71	28.56	28.58
C(15)	125.69	125.18	124.82	128.89	125.99	128.96
C(16)	131.86	133.04	132.55	132.85	132.88	132.44
C(17)	50.11	50.53	50.43	50.70	50.48	50.54
C(18)	50.07	50.00	50.40	50.15	50.10	50.41
C(19)	33.67	33.73	33.62	33.81	33.70	33.63
C(20)	44.87	44.85	44.69	44.90	44.79	44.64
N(21)Me	41.76	41.93	41.90	41.98	42.01	41.97
C(22)	136.40	136.44	136.20	136.49	137.32	137.14
C(23)	129.26	129.76	129.85	129.85	129.18	129.36
$\underline{C}H_3OC(6)$	55.09	55.23	55.30	55.22	55.68	55.75
$\underline{C}H_3OC(3)$	56.37	56.58	56.50	56.67	56.70	56.66
$CH_3\underline{C}O$	170.52	170.56	170.29	170.49	—	—
$\underline{C}H_3CO$	20.62	20.69	20.56	20.68	—	—

* The signals may be interchanged.

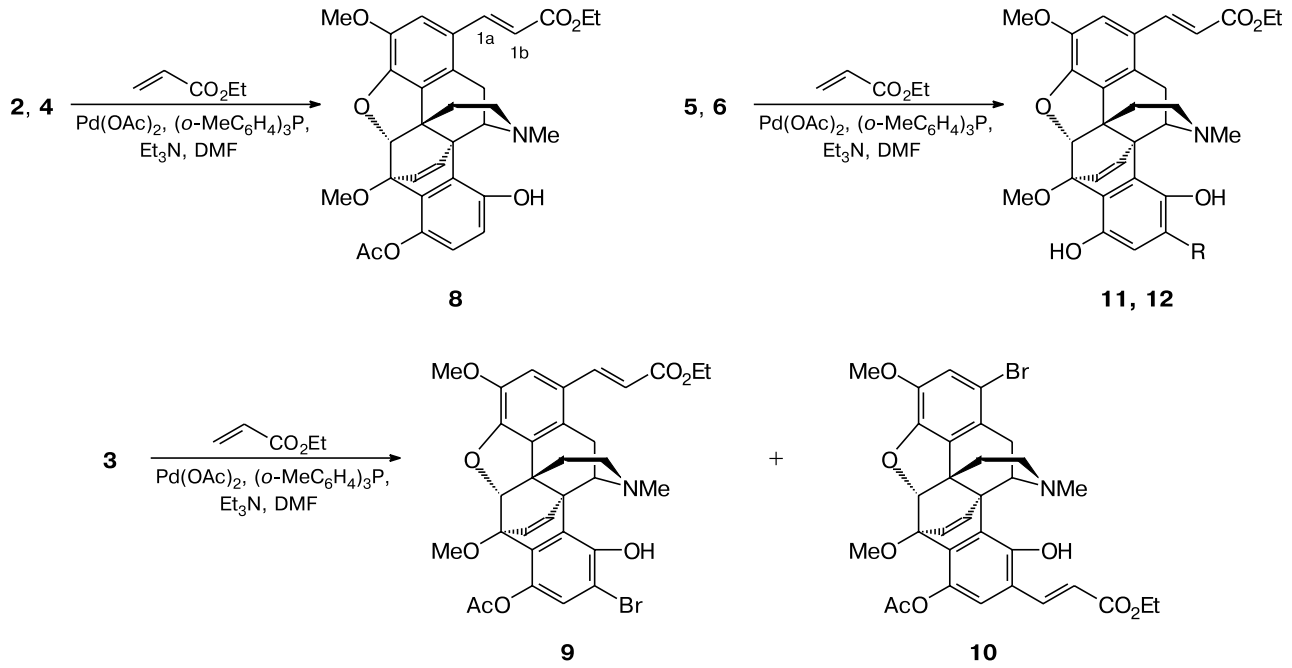
Condensation of 1-iododihydrothebaine derivatives **4** and **5** with 2-methyl-5-vinylpyridine or styrene under the above conditions gave the corresponding 1-[aryl(hetaryl)ethenyl]dihydrothebaine-hydroquinones **13—15** in 63—71% yields (Scheme 3).

A reaction of 1-iododihydrothebaine **5** with ethyl vinyl ether gave 1-acetyl-6,14-*endo*-etheno-7,8-(1-acetoxy-4-hydroxybenzo)dihydrothebaine (**16**) in 50% yield (Scheme 4). We did not isolate a product of arylation at the β-position of ethyl vinyl ether (compound **17**), although its formation (~3%) was detected by ^1H NMR spectroscopy (the presence of the H(1a) and H(1b) protons at the double bond). The ratio **16** : **17** was determined from the integral intensity ratio of the signal for the H(5) proton (δ 4.74 for **16** and δ 4.69 for **17**). Earlier,[18,19] analogous addition of aryl halides to vinyl ethers has been observed for aryl halides containing electron-donating substituents.

Because alkenyldihydrothebaine-hydroquinones **13** and **14** are accessible, we studied their transformations, in particular, for the synthesis of indolizinomorphinane derivatives. It should be noted that substituted indolizines work well as agonists of neuronal acetylcholine receptors (N-AChRs) and are very promising as regards a search for therapeutic means against the Alzheimer and Parkinson diseases and other problems of age-associated neurodegeneration.[20,21] To obtain indolizinomorphinane, we entered pyridinium salt **18** (prepared from compound **14** and phenacyl bromide) into a 1,3-dipolar cycloaddition reaction with ethyl propiolate in the presence of triethylamine. The reaction gave individual adduct **19** in 65% yield (Scheme 5). Its structure was proven by spectroscopic (including 2D-NMR) data. The ^1H NMR spectrum of compound **19** shows signals for the H(4′) and H(5′) protons of the indolizine fragment at δ 6.98 (dd, H(5′), J = 8.4 Hz, J = 1.6 Hz due to couplings with the H(4′) proton and the methyl protons at the C(6′) atom) and 8.09 (H(4′), J = 8.4 Hz). A singlet for the H(8′) proton appears at δ 7.80 (the $^1H—^{13}C$ COLOC spectrum exhibits a cross peak between the signals for the H(8′) and C(7′) atoms (δ 124.96)).

The structures of cross-coupling products **8—17** were identified from spectroscopic data (Table 2). The *E*-configuration of the double bond in compounds **8—15** and

Scheme 2

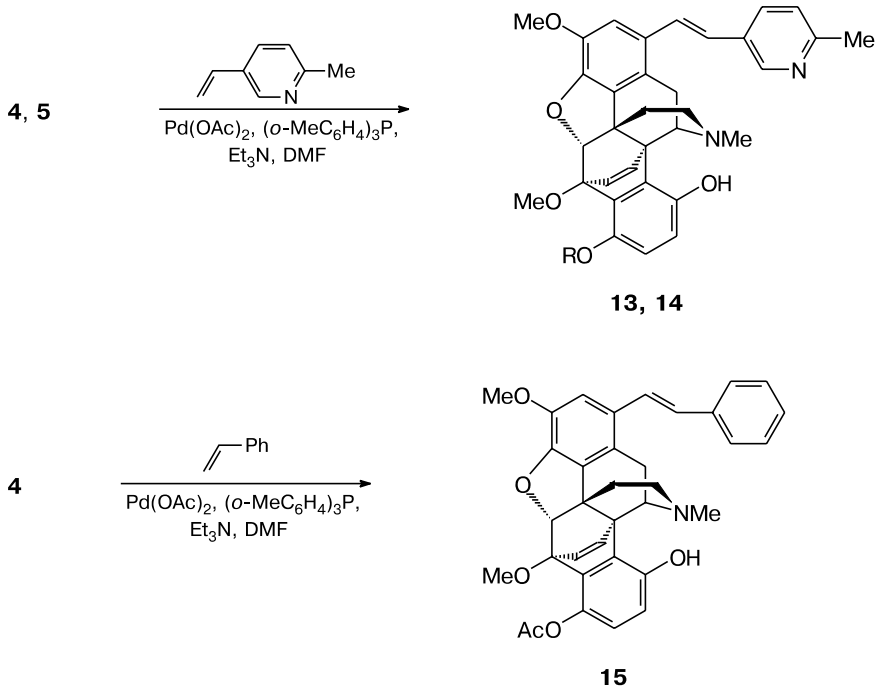


R = H (**11**), Cl (**12**)

17—**19** is evident from the ^{1}H NMR spectra. The H(1a) and H(1b) protons at the newly introduced double bond are manifested as doublets with coupling constants of 16—17 Hz, which corresponds to their *trans*-arrangement.

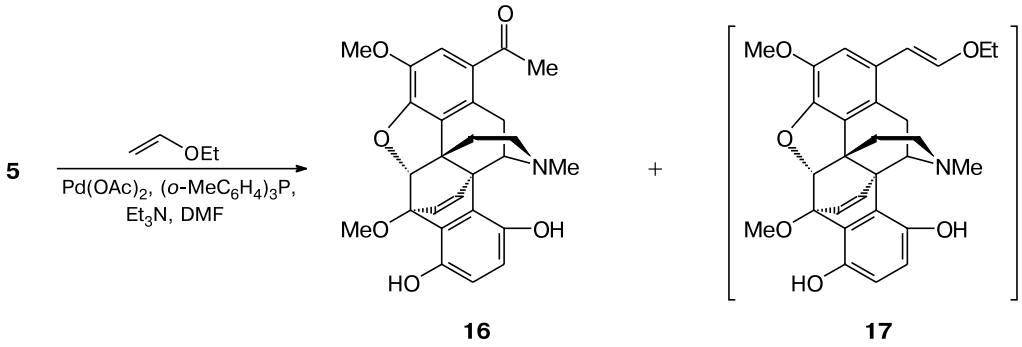
To sum up, we synthesized a number of bromo- and iododihydrothebaine-hydroquinones. By the Heck cross-coupling of these halides with ethyl acrylate, styrene, or 2-methyl-5-vinylpyridine, we obtained for the first time

Scheme 3



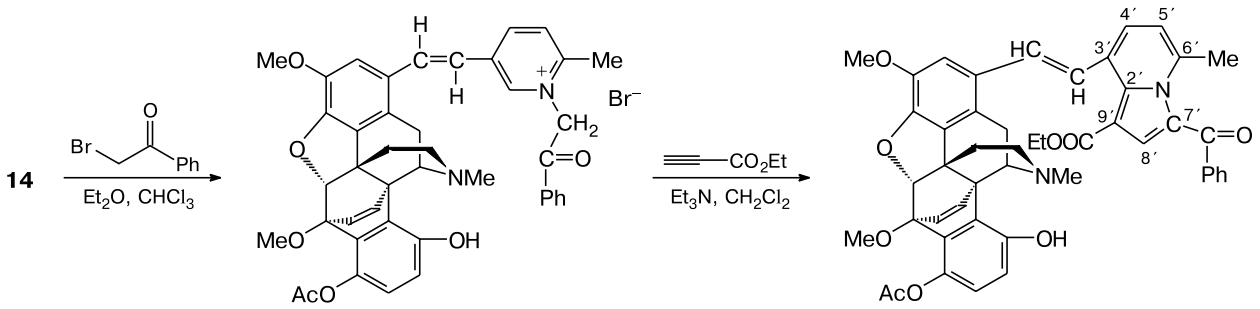
R = H (**13**), Ac (**14**)

Scheme 4



16 **17**

Scheme 5



18 **19**

ethenyl-substituted dihydrothebaine-hydroquinones in 30—96% yields. A reaction of 1-iododihydrothebaine-hydroquinone with ethyl vinyl ether gave the corresponding 1-acetyldihydrothebaine-hydroquinone. We demonstrated that 1-[(*E*)-pyridinylethenyl]dihydrothebaine-hydroquinone can be used in the synthesis of hybrid structures containing indolizine and isoquinoline fragments of alkaloids.

Experimental

NMR spectra were recorded in $CDCl_3$ on Bruker AC-200 (200.13 (^{1}H) and 50.32 MHz (^{13}C)), Bruker AV-300 (300.13 (^{1}H) and 75.47 MHz (^{13}C)), Bruker AM-400 (400.13 (^{1}H) and 100.78 MHz (^{13}C)), and Bruker DRX-500 spectrometers (500.13 (^{1}H) and 125.76 MHz (^{13}C)). For signal assignments in the NMR spectra, various types of proton-proton and carbon-proton correlation spectroscopy (COSY, COLOC, CORRD) and ^{1}H NMR 2D NOESY spectroscopy were used. Mass spectra were recorded on a Finnigan MAT-8200 high-resolution mass spectrometer (EI, 70 eV, injector temperature 270—300 °C); molecular masses and elemental compositions were determined. IR spectra were recorded on a VECTOR-22 instrument (KBr pellets). Electronic absorption spectra were recorded on an HP 8453 UV Vis spectrometer in ethanol.

The course of the reactions was monitored by TLC on Silufol UV-254 plates. Reaction products were isolated by column chromatography on silica gel (Acros, 0.035—0.070 mm, pore diameter 6 nm) with benzene—ethyl acetate and chloroform—ethanol as eluents.

Freshly distilled solvents and high-purity reagents were used. Ethyl acrylate, phenacyl bromide, ethyl propiolate, ethyl vinyl ether, and styrene were purchased from Aldrich; high-purity benzoquinone (TU-6-09-07-1638-87) was additionally purified by sublimation. Thebaine produced at the Chimkent chemical and pharmaceutical plant (Kazakhstan) was employed. Palladium diacetate was synthesized according to a known procedure;[22] ICl was prepared as described earlier.[23]

3,6-Dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (7) was obtained from an adduct of thebaine and benzoquinone (see Ref. 24). ^{1}H NMR ($CDCl_3$), δ: 1.62, 1.85 (both m, 1 H each, H(19)); 2.46—2.69 (m, 3 H, H(14), H(20)); 2.58 (s, 3 H, MeN(21)); 3.36 (d, 1 H, H(14), J = 19 Hz); 3.83 (s, 3 H, MeC(6)); 3.93 (s, 3 H, MeC(3)); 3.99 (d, 1 H, H(13), J = 7 Hz); 4.66 (m, 1 H, H(5)); 5.71 (d, 1 H, H(22), J = 8 Hz); 6.39 (m, 1 H, H(23)); 6.50—6.71 (m, 4 H, H(1), H(2), H(9), H(10)); 9.00 (s, 1 H, OH); 12.10 (br.s, 1 H, OH).

8-Acetoxy-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (1). Thebaine-hydroquinone **7** (3.78 g, 9 mol) was added to a mixture of acetic anhydride (7.56 mL) and pyridine (37.8 mL). The reaction mixture was kept at ~20 °C for 24 h and poured onto ice. The product was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, the solvent was removed, and the residue was recrystallized from ether to give compound **1** (3.167 g, 94%), m.p.

Table 2. ^{13}C NMR spectra of dihydrothebaine-hydroquinone derivatives **8** and **11**—**16** (75.47 MHz, $CDCl_3$)

Atom	δ						
	8	**11**	**12**	**13**	**14**	**15**	**16**
C(2)	111.59	111.80	111.91	110.31	110.31	110.39	118.21
C(3)	143.05	142.95	143.02	142.91	143.03	143.08	141.34
C(4)	151.62	150.88	150.78	148.97	149.72	151.83	147.33
C(5)	94.55	97.83	97.53	97.51	94.21	94.28	98.13
C(6)	85.55	87.21	87.04	87.22	85.59	85.70	87.22
C(7)	—	121.64	123.79	126.34	—	—	124.52
C(8)	138.88	146.38	143.04	146.32	138.85	138.93	146.52
C(9)	119.14	116.86	116.82	116.73	118.99	119.07	116.88
C(10)	122.34	119.55	127.49	119.39	122.27	122.35	119.60
C(11)	151.74	147.45	149.80	147.38	151.76	149.51	152.44
C(12)	—	—	121.02	121.86	—	—	—
C(13)	57.72	57.62	57.49	57.71	57.85	58.00	57.46
C(14)	21.64	21.54	21.58	21.49	21.66	21.74	28.42
C(15)	—	—	—	124.21	124.06	—	—
C(16)	—	132.54	132.13	130.33	—	—	—
C(17)	49.75	49.81	49.94	49.86	49.85	49.98	49.43
C(18)	50.18	50.01	50.25	50.06	50.21	50.33	49.84
C(19)	33.70	33.68	33.62	33.70	33.77	33.91	33.83
C(20)	44.86	44.82	44.68	44.91	44.98	45.11	44.55
N(21)Me	42.04	42.10	42.06	42.09	42.05	42.13	42.06
C(22)	136.63	137.48	137.30	137.45	136.61	136.74	137.92
C(23)	129.69	129.16	129.35	129.00	129.64	129.72	129.78
$\underline{C}H_3OC(3)$	56.31	56.47	56.45	56.59	56.50	56.61	56.95
$\underline{C}H_3OC(6)$	55.26	55.71	55.77	55.71	55.22	55.33	55.72
C(1a)	116.26	116.60	117.01	125.51	124.07	123.82	—
C(1b)	140.27	140.16	139.97	127.08	125.66	124.59	—
$CH_3\underline{C}OO$	170.58	—	—	—	170.59	170.69	—
$\underline{C}H_3COO$	20.71	—	—	—	20.71	20.81	—

Note. The other signals appear at δ 14.26 ($\underline{C}H_3CH_2COO$), 60.38 ($CH{=}CHCOO\underline{C}H_2CH_3$), 125.28, 126.27, 128.10, 131.60, 132.36 (C(1), C(7), C(12), C(15), C(16)), 167.23 ($CH{=}CH{-}\underline{C}OOEt$) (compound **8**); 14.25 ($\underline{C}H_3CH_2COO$), 60.41 ($CH{=}CHCOO\underline{C}H_2CH_3$), 125.59, 126.19, 126.59 (C(1), C(12), C(15)), 167.15 ($CH{=}CH{-}\underline{C}OOEt$) (**11**); 14.24 ($\underline{C}H_3CH_2COO$), 60.42 ($CH{=}CHCOO\underline{C}H_2CH_3$), 125.74, 126.23 (C(1), C(15)), 167.05 ($CH{=}CH{-}\underline{C}OOEt$) (**12**); 23.95 ($\underline{C}H_3C(6')$), 123.19 (C(5′)), 128.25 (C(1)), 129.29 (C(3′)), 132.22 (C(4′)), 147.37 (C(2′)), 157.08 (C(6′)) (**13**); 23.91 ($\underline{C}H_3C(6')$), 123.19 (C(5′)), 127.97, 128.21, 130.40, 131.83, 132.97 (C(1), C(3′), C(7), C(12), C(16)), 132.97 (C(4′)), 147.28 (C(2′)), 156.96 (C(6′)) (**14**); 126.31 (C(2′), C(6′)), 127.50, 128.20, 128.37, 128.60, 131.99, 132.11, 137.54 (C(1), C(7), C(12), C(15), C(16), C(1′), C(4′)), 128.70 (C(3′), C(5′)) (**15**); 24.19 ($\underline{C}H_3CO$), 198.19 ($CH_3\underline{C}O$), 126.22, 128.26, 128.99, 133.22 (C(1), C(12), C(15), C(16)) (**16**).

245—250 °C. ^1H NMR ($CDCl_3$), δ: 1.56, 1.85 (both m, 1 H each, H(19)); 2.24 (s, 3 H, MeCOO); 2.55 (s, 3 H, MeN); 2.58—2.67 (m, 3 H, H(14), H(20)); 3.36 (d, 1 H, H(14), J = 17 Hz); 3.63 (s, 3 H, MeC(6)); 3.79 (s, 3 H, MeC(3)); 4.01 (m, 1 H, H(13)); 4.58 (d, 1 H, H(5), J = 1 Hz); 5.65 (d, 1 H, H(22), J = 7.8 Hz); 6.30 (m, 1 H, H(23)); 6.55 (d, 1 H, H(1), J = 8.8 Hz); 6.65 (m, 2 H, H(2), H(10)); 6.74 (d, 1 H, H(9), J = 8 Hz). MS, m/z (I_{rel} (%)): 461 $[M]^+$ (31), 417 (54), 375 (19), 242 (98), 202 (19), 201 (57), 200 (100), 44 (92). High-resolution MS, found: m/z 461.18497 $[M]^+$. $C_{27}H_{27}NO_6$. Calculated: M = 461.18382.

8-Acetoxy-1-bromo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (2) and **8-acetoxy-1,10-dibromo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (3).** A 1 *M* solution of bromine (2.6 mL) in formic acid was added at 0 °C to a stirred solution of compound **1** (0.776 g, 1.7 mmol) in formic acid (11 mL). The reaction mixture was stirred at 0—5 °C for 2 h and poured into a Petri dish for free evaporation. The residue was treated with a saturated solution of $NaHCO_3$ (20 mL). The products were extracted with CH_2Cl_2 and the extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from ethanol. A 1 : 1 mixture of bromides **2** and **3** was filtered off (the total yield was 0.795 g (85%)). These compounds were separated in boiling benzene. Dibromide **3** (0.177 g, 17%) was filtered off hot. To isolate the individual monobromide, the mother liquor was concentrated to 5 mL and chromatographed on silica gel in benzene—ethyl acetate (10 : 3). The yield of compound **2** was 0.360 g (39%).

Compound **2**, m.p. 260—264 °C (from ether). ^1H NMR ($CDCl_3$), δ: 1.60, 1.85 (both m, 1 H each, H(19)); 2.24 (s, 3 H,

MeCOO); 2.30—2.80 (m, 3 H, H(14), H(20)); 2.59 (s, 3 H, MeN); 3.20 (d, 1 H, H(14), J = 19.2 Hz); 3.63 (s, 3 H, MeC(6)); 3.79 (s, 3 H, MeC(3)); 4.07 (d, 1 H, H(13), J = 6 Hz); 4.60 (m, 1 H, H(5)); 5.66 (d, 1 H, H(22), J = 8.4 Hz); 6.35 (m, 1 H, H(23)); 6.67 (d, 1 H, H(10), J = 8.8 Hz); 6.75 (d, 1 H, H(9), J = 8.8 Hz); 6.84 (s, 1 H, H(2)); 12.85 (br.s, 1 H, OH). MS, m/z (I_{rel} (%)): 539 $[M]^+$ (39), 498 (17), 286 (10), 244 (16), 243 (76), 202 (58), 201 (95), 115 (10), 44 (100). High-resolution MS, found: m/z 539.09469 $[M]^+$. $C_{27}H_{26}BrNO_6$. Calculated: M = 539.09439.

Compound **3**, m.p. 275—280 °C. Found (%): C, 52.00; H, 4.00; Br, 25.80; N, 2.26. $C_{27}H_{25}Br_2NO_6$. Calculated (%): C, 51.53; H, 4.04; Br, 25.00; N, 2.26. ^{1}H NMR ($CDCl_3$), δ: 1.58, 1.88 (both m, 1 H each, H(19)); 2.23 (s, 3 H, MeCOO); 2.54—2.63 (m, 2 H, H(14), H(20)); 2.69 (s, 3 H, MeN); 2.70 (m, 1 H, H(20)); 3.20 (d, 1 H, H(14), J = 19.5 Hz); 3.61 (s, 3 H, MeC(6)); 3.79 (s, 3 H, MeC(3)); 4.06 (d, 1 H, H(13), J = 6.5 Hz); 4.59 (d, 1 H, H(5), J = 1 Hz); 5.64 (d, 1 H, H(22), J = 8.5 Hz); 6.35 (m, 1 H, H(23)); 6.84 (s, 1 H, H(2)); 7.01 (s, 1 H, H(9)); 14.02 (s, 1 H, OH).

Iodination of *endo*-ethenobenzo[*i*]isomorphinane 1. ***A.*** A solution of ICl (1.11 g, 6.8 mmol) in formic acid (0.9 mL) was added dropwise to a stirred solution of compound **1** (4.6 mmol, 2.1 g) in formic acid (6 mL). The reaction mixture was heated with stirring for 9 h and poured into a Petri dish for free evaporation. The residue was treated with a saturated solution of $NaHCO_3$ and the product was extracted with chloroform. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with ether. The resulting amorphous precipitate (2.68 g) was dissolved in a minimum amount of chloroform and chromatographed on silica gel with $CHCl_3$—EtOH as an eluent (gradient from 100 : 0 to 10 : 1). Elution successively gave **8-acetoxy-1-iodo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (4)** (with $CHCl_3$ as the eluent), **1-iodo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (5)** ($CHCl_3$—EtOH, 100 : 0.5), and **10-chloro-1-iodo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (6)** ($CHCl_3$—EtOH, 100 : 1 → 10 : 1). The collected fractions were concentrated and the residues were triturated with ether.

Compound **4**. The yield was 1.52 g (57%), m.p. 253—255 °C. Found (%): C, 55.19; H, 4.42; I, 21.63; N, 2.38. $C_{27}H_{26}INO_6$. Calculated (%): C, 54.01; H, 4.41; I, 22.44; N, 2.03. ^{1}H NMR ($CDCl_3$), δ: 1.57, 1.85 (both m, 1 H each, H(19)); 2.24 (s, 3 H, MeCOO); 2.45 (m, 1 H, H(14)); 2.55 (m, 1 H, H(20)); 2.60 (s, 3 H, MeN); 2.66 (m, 1 H, H(20)); 3.12 (d, 1 H, H(14), J = 19.4 Hz); 3.64 (s, 3 H, MeC(6)); 3.80 (s, 3 H, MeC(3)); 4.06 (d, 1 H, H(13), J = 6.2 Hz); 4.60 (d, 1 H, H(5), J = 1.2 Hz); 5.67 (d, 1 H, H(22), J = 8.4 Hz); 6.36 (m, 1 H, H(23)); 6.67 (d, 1 H, H(10), J = 8.7 Hz); 6.76 (d, 1 H, H(9), J = 8.7 Hz); 7.06 (s, 1 H, H(2)); 12.75 (br.s, 1 H, OH).

Compound **5**. The yield was 0.36 g (13%), m.p. 232—235 °C. Found (%): C, 55.04; H, 4.40; I, 23.30; N, 2.56. $C_{25}H_{24}INO_5$. Calculated (%): C, 49.83; H, 4.50; I, 21.63; N, 2.34. ^{1}H NMR ($CDCl_3$), δ: 1.61, 1.83 (both m, 1 H each, H(19)); 2.42 (m, 1 H, H(14)); 2.49—2.62 (m, 1 H, H(20)); 2.58 (s, 3 H, MeN); 2.66 (m, 1 H, H(20)); 3.11 (d, 1 H, H(14), J = 19.2 Hz); 3.82 (s, 3 H, MeC(6)); 3.91 (s, 3 H, MeC(3)); 4.03 (d, 1 H, H(13), J = 6.2 Hz); 4.66 (m, 1 H, H(5)); 5.71 (d, 1 H, H(22), J = 8.4 Hz); 6.43 (m, 1 H, H(23)); 6.55 (d, 1 H, H(10), J = 8.4 Hz); 6.65 (d, 1 H, H(9), J = 8.4 Hz); 7.08 (s, 1 H, H(2)); 8.93 (s, 1 H, C(8)OH); 12.01 (br.s, 1 H, C(11)OH).

Compound **6**. The yield was 0.30 g (11%), m.p. 243—245 °C. ^{1}H NMR ($CDCl_3$), δ: 1.61, 1.86 (both m, 1 H each, H(19)); 2.43 (m, 1 H, H(14)); 2.50—2.60 (m, 1 H, H(20)); 2.61 (s, 3 H, MeN); 2.69 (m, 1 H, H(20)); 3.11 (d, 1 H, H(14), J = 19 Hz); 3.81 (s, 3 H, MeC(6)); 3.91 (s, 3 H, MeC(3)); 4.02 (d, 1 H, H(13), J = 6.2 Hz); 4.65 (d, 1 H, H(5), J = 0.9 Hz); 5.67 (d, 1 H, H(22), J = 8.4 Hz); 6.43 (m, 1 H, H(23)); 6.71 (s, 1 H, H(9)); 7.08 (s, 1 H, H(2)); 8.94 (s, 1 H, C(8)OH); 13.10 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 579 $[M]^+$ (77), 344 (22), 238 (19), 237 (55), 235 (100), 74 (16), 59 (25), 44 (84), 31 (53). High-resolution MS, found: m/z 579.03035 $[M]^+$. $C_{25}H_{23}ClINO_5$. Calculated: M = 579.03112.

B. Ammonium cerium(IV) nitrate (0.559 g, 1.02 mmol) and iodine (0.26 g, 1.02 mmol) were successively added to a stirred solution of compound **7** (0.7 g, 1.7 mmol) in acetonitrile (42 mL). The reaction mixture was stirred at 20 °C for 5 h and then at 30—35 °C for 9 h and concentrated in a Petri dish. The residue was treated with water and the product was extracted with chloroform. The extract was washed with $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was triturated with ether. The yield of **1-iodo-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (5)** was 0.46 g (52%). Compound **5** was also obtained by iodination of compound **1** (0.63 g) under analogous conditions. The yield was 0.5 g (62%).

The Heck reaction (general procedure). A two-neck flask fitted with a magnetic stirring bar was evacuated and filled with argon. This manipulation was repeated three times. The flask was successively charged under argon with bromo- or iododihydrothebaine (1 mmol), palladium diacetate (2 mol.%), tri(*o*-tolyl)phosphine (8 mol.%), and DMF (6 mL). Triethylamine (1.4 mmol) and ethyl acrylate (or 2-methyl-5-vinylpyridine, or styrene, or ethyl vinyl ether) (4 mmol) was added to the stirred resulting suspension. The reaction mixture was stirred at 150 °C for 9—10 h and poured into a Petri dish. The solid residue was dissolved in a minimum amount of chloroform and chromatographed on silica gel in $CHCl_3$—EtOH (gradient from 100 : 0 to 10 : 1). The successively eluted products were tri(*o*-tolyl)phosphine, the starting halide, and the reaction product (100 : 1 → 50 : 3). The product was rechromatographed and recrystallized.

8-Acetoxy-1-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (8). After repeated chromatography and recrystallization from ether, the yield of compound **8** was 80 (from iodide **4**) or 30% (from bromide **2**), m.p. 255—257 °C. ^{1}H NMR ($CDCl_3$), δ: 1.32 (m, 3 H, $COOCH_2C\underline{H}_3$); 1.55—1.65, 1.85 (both m, 1 H each, H(19)); 2.25 (s, 3 H, MeCOO); 2.56 (m, 1 H, H(20)); 2.61 (s, 3 H, MeN); 2.67 (m, 1 H, H(14)); 2.73 (m, 1 H, H(20)); 3.45 (m, 1 H, H(14), J = 19 Hz); 3.64 (s, 3 H, MeC(6)); 3.83 (s, 3 H, MeC(3)); 4.09 (m, 1 H, H(13)); 4.25 (q, 2 H, $COOC\underline{H}_2CH_3$, J = 7 Hz); 4.65 (d, 1 H, H(5), J = 1.2 Hz); 5.69 (d, 1 H, H(22), J = 8.3 Hz); 6.24 (d, 1 H, H(1b), J = 15.6 Hz); 6.37 (m, 1 H, H(23)); 6.67 (d, 1 H, H(9), J = 8.7 Hz); 6.76 (d, 1 H, H(10), J = 8.7 Hz); 6.97 (s, 1 H, H(2)); 7.77 (d, 1 H, H(1a), J = 15.6 Hz); 12.78 (br.s, 1 H, OH). MS, m/z (I_{rel} (%)): 559 $[M]^+$ (78), 517 (15), 516 (31), 327 (14), 316 (19), 244 (20), 243 (91), 202 (54), 201 (92), 44 (100). High-

resolution MS, found: m/z 559.21958 $[M]^+$. $C_{32}H_{33}NO_8$. Calculated: M = 559.22060.

8-Acetoxy-10-bromo-1-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (9) and **8-acetoxy-1-bromo-10-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (10).** ^{1}H NMR data for compounds **9** and **10** were obtained from the spectrum of a mixture of compounds **3**, **9**, and **10** (6 : 1 : 0.5).

Compound **9**, selected signals, δ: 1.32 (m, 3 H, $COOCH_2C\underline{H}_3$); 1.54—1.64, 1.89 (both m, 1 H each, H(19)); 2.23 (s, 3 H, MeCOO); 2.53—2.66 (m, 2 H, H(14), H(20)); 2.62 (s, 3 H, MeN); 2.71 (m, 1 H, H(20)); 3.45 (m, 1 H, H(14)); 3.63 (s, 3 H, MeC(6)); 3.79 (s, 3 H, MeC(3)); 4.07 (m, 1 H, H(13)); 4.25 (q, 2 H, $COOC\underline{H}_2CH_3$, J = 7 Hz); 4.60 (m, 1 H, H(5)); 5.65 (m, 1 H, H(22)); 6.24 (d, 1 H, H(1b), J = 16 Hz); 6.36 (m, 1 H, H(23)); 6.97 (s, 1 H, H(2)); 7.01 (s, 1 H, H(9)); 7.76 (d, 1 H, H(1a), J = 16 Hz); 14.01 (s, 1 H, OH).

Compound **10**, selected signals, δ: 1.32 (m, 3 H, $COOCH_2C\underline{H}_3$); 1.54—1.64, 1.89 (both m, 1 H each, H(19)); 2.23 (s, 3 H, MeCOO); 2.53—2.66 (m, 2 H, H(14), H(20)); 2.62 (s, 3 H, MeN); 2.71 (m, 1 H, H(20)); 3.45 (m, 1 H, H(14)); 3.63 (s, 3 H, MeC(6)); 3.79 (s, 3 H, MeC(3)); 4.07 (m, 1 H, H(13)); 4.22 (q, 2 H, $COOC\underline{H}_2CH_3$, J = 7 Hz); 4.60 (m, 1 H, H(5)); 5.65 (m, 1 H, H(22)); 6.36 (m, 1 H, H(23)); 6.52 (d, 1 H, H(1a), J = 16 Hz); 6.85 (s, 1 H, H(2)); 7.06 (s, 1 H, H(9)); 7.95 (d, 1 H, H(1b), J = 16 Hz); 14.01 (s, 1 H, OH).

1-[(*E*)-2-(Ethoxycarbonyl)ethenyl]-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (11). The yield was 95%, m.p. 254—257 °C. ^{1}H NMR ($CDCl_3$), δ: 1.33 (m, 3 H, $COOCH_2C\underline{H}_3$); 1.55—1.70, 1.84 (both m, 1 H each, H(19)); 2.46—2.76 (m, 3 H, H(14), H(20)); 2.59 (s, 3 H, Me); 3.44 (d, 1 H, H(14), J = 19 Hz); 3.85 (s, 3 H, MeC(6)); 3.92 (s, 3 H, MeC(3)); 4.06 (m, 1 H, H(13)); 4.26 (q, 2 H, $COOC\underline{H}_2CH_3$, J = 6.9 Hz); 4.72 (d, 1 H, H(5), J = 0.8 Hz); 5.73 (d, 1 H, H(22), J = 8.4 Hz); 6.25 (d, 1 H, H(1b), J = 15.8 Hz); 6.44 (m, 1 H, H(23)); 6.55 (d, 1 H, H(9), J = 8.8 Hz); 6.65 (d, 1 H, H(10), J = 8.8 Hz); 6.98 (s, 1 H, H(2)); 7.77 (d, 1 H, H(1a), J = 15.8 Hz); 8.92 (s, 1 H, C(8)OH); 12.00 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 517 $[M]^+$ (53), 474 (9), 316 (10), 202 (14), 201 (35), 200 (100), 44 (35). High-resolution MS, found: m/z 517.20640 $[M]^+$. $C_{30}H_{31}NO_7$. Calculated: M = 517.21004.

10-Chloro-1-[(*E*)-2-(ethoxycarbonyl)ethenyl]-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (12). The yield was 96%, m.p. 188—192 °C. ^{1}H NMR ($CDCl_3$), δ: 1.32 (m, 3 H, $COOCH_2C\underline{H}_3$); 1.54—1.69, 1.86 (both m, 1 H each, H(19)); 2.48—2.77 (m, 3 H, H(14), H(20)); 2.62 (s, 3 H, MeN); 3.44 (d, 1 H, H(14), J = 19.2 Hz); 3.85 (s, 3 H, MeC(6)); 3.91 (s, 3 H, MeC(3)); 4.05 (m, 1 H, H(13)); 4.25 (q, 2 H, $COOC\underline{H}_2CH_3$, J = 7 Hz); 4.70 (d, 1 H, H(5), J = 1.2 Hz); 5.70 (d, 1 H, H(22), J = 8.4 Hz); 6.24 (d, 1 H, H(1b), J = 15.7 Hz); 6.43 (m, 1 H, H(23)); 6.71 (s, 1 H, H(9)); 6.98 (s, 1 H, H(2)); 7.76 (d, 1 H, H(1a), J = 15.7 Hz); 8.94 (s, 1 H, C(8)OH); 13.08 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 551 $[M]^+$ (75), 508 (15), 327 (45), 238 (24), 237 (54), 235 (96), 44 (100). High-resolution MS, found: m/z 551.17040 $[M]^+$. $C_{30}H_{30}ClNO_7$. Calculated: M = 551.17106.

3,6-Dimethoxy-*N*-methyl-1-[(*E*)-2-(6-methylpyridin-3-yl)ethenyl]-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (13). The yield was 67%, m.p. 200—205 °C. ^{1}H NMR ($CDCl_3$), δ: 1.63, 1.85 (both m, 1 H each, H(19)); 2.50—2.75 (m, 3 H, H(14), H(20)); 2.56 (s, 3 H, MeC(6′)); 2.61 (s, 3 H, MeN(21)); 3.41 (d, 1 H, H(14), J = 18.8 Hz); 3.90 (s, 3 H, MeC(6)); 3.93 (s, 3 H, MeC(3)); 4.07 (m, 1 H, H(13)); 4.70 (m, 1 H, H(5), J = 0.8 Hz); 5.75 (d, 1 H, H(22), J = 8.7 Hz); 6.44 (m, 1 H, H(23)); 6.56 (d, 1 H, H(9), J = 8.7 Hz); 6.65 (d, 1 H, H(10), J = 8.7 Hz); 6.85 (d, 1 H, H(1b), J = 16.2 Hz); 7.00 (s, 1 H, H(2)); 7.15 (m, 2 H, H(1a), H(5′)); 7.74 (m, 1 H, H(4′)); 8.56 (m, 1 H, H(2′)); 12.11 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 536 $[M]^+$ (100), 493 (21), 346 (35), 345 (41), 292 (18), 202 (28), 201 (87), 83 (13), 44 (23). High-resolution MS, found: m/z 536.23134 $[M]^+$. $C_{33}H_{32}N_2O_5$. Calculated: M = 536.23111. IR, ν/cm^{-1}: 706, 732, 817, 841, 861, 926, 1103, 1120, 1558, 1597, 1615, 3348. UV, λ_{max}/nm (logε): 256 (2.45), 343 (3.09).

8-Acetoxy-3,6-dimethoxy-*N*-methyl-1-[(*E*)-2-(6-methylpyridin-3-yl)ethenyl]-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (14). The yield was 71%, m.p. 214 °C. ^{1}H NMR ($CDCl_3$), δ: 1.53—1.67, 1.76—1.94 (both m, 1 H each, H(19)); 2.25 (s, 3 H, MeCOO); 2.51—2.80 (m, 3 H, H(14), H(20)); 2.56 (s, 3 H, MeC(6′)); 2.63 (s, 3 H, MeN); 3.43 (m, 1 H, H(14), J = 18.8 Hz); 3.65 (s, 3 H, MeC(6)); 3.88 (s, 3 H, MeC(3)); 4.11 (m, 1 H, H(13)); 4.63 (m, 1 H, H(5), J = 0.8 Hz); 5.71 (d, 1 H, H(22), J = 8.1 Hz); 6.36 (m, 1 H, H(23)); 6.67 (d, 1 H, H(9), J = 8.4 Hz); 6.76 (d, 1 H, H(10), J = 8.4 Hz); 6.84 (d, 1 H, H(1a), J = 16.2 Hz); 6.98 (s, 1 H, H(2)); 7.11—7.19 (m, 2 H, H(1b), H(5′)); 7.73 (m, 1 H, H(4′)); 8,57 (m, 1 H, H(2′)); 12.90 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 578 $[M]^+$ (100), 535 (16), 492 (10), 345 (46), 344 (52), 291 (29), 243 (86), 202 (43), 201 (89), 83 (26), 44 (75). High-resolution MS, found: m/z 578.24738 $[M]^+$. $C_{35}H_{34}N_2O_6$. Calculated: M = 578.24167.

8-Acetoxy-3,6-dimethoxy-*N*-methyl-1-[(*E*)-2-phenylethenyl]-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (15). The yield was 63%, m.p. 155—161 °C. ^{1}H NMR ($CDCl_3$), δ: 1.53—1.66, 1.89 (both m, 1 H each, H(19)); 1.26 (s, 3 H, MeCOO); 2.58—2.78 (m, 3 H, H(14), H(20)); 2.63 (s, 3 H, MeN); 3.43 (m, 1 H, H(14), J = 19 Hz); 3.65 (s, 3 H, MeC(6)); 3.88 (s, 3 H, MeC(3)); 4.10 (m, 1 H, H(13)); 4.63 (m, 1 H, H(5), J = 0.8 Hz); 5.72 (d, 1 H, H(22), J = 8.4 Hz); 6.37 (m, 1 H, H(23)); 6.68 (d, 1 H, H(9), J = 8.4 Hz); 6.77 (d, 1 H, H(10), J = 8.4 Hz); 6.91 (d, 1 H, H(1b), J = 16 Hz); 7.00 (s, 1 H, H(2)); 7.14 (m, 1 H, H(5′), J = 16 Hz); 7.35 (m, 3 H, H(3′)—H(5′)); 7.49 (m, 2 H, H(2′), H(6′)); 12.94 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 563 $[M]^+$ (49), 520 (14), 495 (20), 331 (20), 330 (23), 243 (67), 202 (36), 201 (60), 91 (11), 44 (100). High-resolution MS, found: m/z 563.23222 $[M]^+$. $C_{35}H_{33}NO_6$. Calculated: M = 563.23077.

1-Acetyl-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinane-8,11-diol (16). The yield was 50%, m.p. 145—150 °C. ^{1}H NMR ($CDCl_3$), δ: 1.64, 1.82 (both m, 1 H each, H(19)); 2.44—2.70 (m, 3 H, H(14), H(20)); 1.54 (s, 3 H, MeCO); 2.59 (s, 3 H, MeN); 3.80 (d, 1 H, H(14), J = 20.5 Hz); 3.91 (s, 3 H, MeC(6)); 3.93 (s, 3 H, MeC(3)); 3.99 (m, 1 H, H(13)); 4.74 (m, 1 H, H(5), J = 1.3 Hz); 5.79 (d, 1 H, H(22), J = 8.5 Hz); 6.44 (m, 1 H, H(23)); 6.56 (d, 1 H, H(9), J = 8.6 Hz); 6.65 (d, 1 H, H(10), J = 8.6 Hz); 7.30 (s, 1 H, H(2)); 8.90 (s, 1 H, C(8)OH); 12.22 (br.s, 1 H, C(11)OH). MS, m/z (I_{rel} (%)): 461 $[M]^+$ (48), 260 (7), 214 (7), 203 (15), 202 (35), 201 (100), 44 (20). High-resolution MS, found: m/z 461.18277 $[M]^+$. $C_{27}H_{27}NO_6$. Calculated: M = 461.18382. IR, ν/cm^{-1}: 815, 843, 861, 939, 1592, 1620, 1670, 3424.

8-Acetoxy-1-{2-[(*E*)-(7-benzoyl-9-ethoxycarbonyl-6-methylindolizin-3-yl)]ethenyl}-3,6-dimethoxy-*N*-methyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[*i*]isomorphinan-11-ol (19). Phenacyl bromide (0.034 g, 0.17 mmol) in ether (1 mL) was added to a stirred solution of compound **14** (0.1 g, 0.17 mmol) in chloroform (3 mL). The reaction mixture was stirred at 50 °C for 8 h and concentrated *in vacuo*. The residue of salt **18** (0.148 g) was dissolved in CH_2Cl_2 (20 mL) and ethyl propiolate (0.031 mL, 0.3 mmol) was added with stirring. Then triethylamine (0.2 mmol) in CH_2Cl_2 (4 mL) was added dropwise for 10 min. The mixture was stirred at ~20 °C for 12 h, treated with water (20 mL), and alkalified with stirring with aqueous ammonia to pH 12. The organic layer was separated and the product from the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel. Fractions containing the product were concentrated *in vacuo* and the residue was treated with ether. The yield of compound **19** was 0.088 g (65%), m.p. 150—155 °C. Found (%): C, 72.72; H, 5.55; N, 3.53. $C_{48}H_{44}N_2O_9$. Calculated (%): C, 72.30; H, 5.67; N, 3.10. ^{1}H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, Me, J = 6.8 Hz); 1.63, 1.94 (both m, 1 H each, H(19)); 2.30 (s, 3 H, MeCOO); 2.61 (d, 3 H, MeC(6′), J = 1.6 Hz); 2.62—2.78 (m, 2 H, H(20)); 2.70 (s, 3 H, MeN(21)); 2.94 (m, 1 H, H(14)); 3.60 (d, 1 H, H(14), J = 19 Hz); 3.71 (s, 3 H, MeC(6)); 3.95 (s, 3 H, MeC(3)); 4.16 (m, 1 H, H(13)); 4.29 (q, 2 H, CH_2, J = 6.8 Hz); 4.68 (d, 1 H, H(5), J = 0.8 Hz); 5.77 (d, 1 H, H(22), J = 8.6 Hz); 6.41 (m, 1 H, H(23)); 6.71 (d, 1 H, H(9), J = 8.3 Hz); 6.80 (d, 1 H, H(10), J = 8.3 Hz); 6.98 (dd, 1 H, H(5′), J = 8.4 Hz, J = 1.6 Hz); 7.10 (d, 1 H, H(1a), J = 15.7 Hz); 7.23 (s, 1 H, H(2)); 7.33—7.74 (m, 5 H, Ph); 7.80 (s, 1 H, H(8′)); 8.09 (m, 1 H, H(4′)); 8.37 (d, 1 H, H(1b), J = 15.7 Hz). ^{13}C NMR, δ: 14.30 ($\underline{C}H_3CH_2$); 20.72 ($\underline{C}H_3COO$); 21.99 (C(14)); 23.35 ($\underline{C}H_3C(6')$); 33.92 (C(19)); 42.00 ($CH_3N(21)$); 45.02 (C(20)); 49.93 (C(17)); 50.30 (C(18)); 55.23 ($\underline{C}H_3OC(6)$); 56.18 ($\underline{C}H_3OC(3)$); 58.02 (C(13)); 60.27 ($CH_3\underline{C}H_2$); 85.65 (C(6)); 94.25 (C(5)); 107.26 (C(9′)); 111.50 (C(2)); 116.96 (C(5′)); 118.96 (C(10)); 122.26 (C(9)); 123.70 (C(15)); 124.16 (C(4′)); 124.96 (C(7′)); 126.09 (C(1a)); 126.45 (C(1b)); 128.55 (2 C_{Ph}); 128.39 (C(1)); 128.74 (C(3′)); 129.64 (C(23)); 130.20 (2 C_{Ph}); 131.29 (C(8′)); 132.60 (1 C_{Ph}); 136.76 (C(22)); 138.28, 138.36, 138.86, 139.14 (C(16), C(11), C(2′), C(6′)); 143.14 (C(3)); 149.41 (C(4)); 151.82 (C(8)); 164.23 ($\underline{C}OOEt$); 170.58 ($\underline{C}OOCH_3$); 182.65 ($\underline{C}OPh$).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 05-03-32365) and the Council on Grants of the President of the Russian Federation (Program for Support of Leading Scientific Schools, Grant NSh 1588.2006.3).

References

1. A. F. Casy and R. T. Parfitt, *Opioid Analgesics. Chemistry and Receptors*, Plenum Press, New York—London, 1986.
2. L. Maat, *Novel Thebainlike Morphinan-dienes and Their Diels—Alder Adducts*, in *Drugs of Abuse: Chemistry, Pharmacology, Immunology and AIDS*, Eds P. T. K. Phan and K. Rice, NIDA Research Monograph, 1990, 35.
3. H. Schmidhammer, *Progr. Med. Chem.*, 1998, **35**, 83.
4. K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1956, 1863.
5. G. A. Tolstikov, E. E. Shults, T. Sh. Mukhametyanova, and L. V. Spirikhin, *Zh. Org. Khim.*, 1991, **27**, 273 [*J. Org. Chem. USSR*, 1991, **27** (Engl. Transl.)].
6. G. A. Tolstikov, T. G. Tolstikova, E. E. Shults, T. Sh. Mukhametyanova, V. G. Popov, V. A. Davydova, D. N. Lazareva, and F. S. Zarudii, *Khim.-Farm. Zh.*, 1992, **11**, 39 [*Pharm. Chem. J.*, 1992, **11** (Engl. Transl.)].
7. K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3273.
8. H. Schmidhammer and A. Brossi, *J. Org. Chem.*, 1983, **48**, 1469.
9. M. Spetea, F. Schüllner, R. C. Moisa, I. P. Bersetei-Gurske, B. Schraml, C. Dörfler, M. D. Aceto, L. S. Harris, A. Coop, and H. Schmidhammer, *J. Med. Chem.*, 2004, **47**, 3243.
10. M. P. Wentland, Q. Lu, R. Lou, Y. Bu, B. I. Knapp, and J. M. Bidlack, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2107.
11. A. P. Terent´ev and L. A. Yanovskaya, *Reaktsii i metody issledovaniya organicheskikh soedinenii* [*Reactions and Methods of Investigations of Organic Compounds*], Goskhimizdat, Moscow, 1957, **6**, 7 (in Russian).
12. M. A. Rodriguez-Franco, I. Dorronsoro, A. I. Hernandez-Higueras, and G. Antequera, *Tetrahedron Lett.*, 2001, **42**, 863.
13. J. B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York—London, 1972.
14. K. Görlitzer and R. Schumann, *Pharmazie*, 1992, **47**, 893.
15. Y. Nan, W. Xu, K. Zaw, K. E. Hughes, L.-F. Huang, W. J. Dunn, III, L. Bauer, and H. N. Bhargava, *J. Heterocycl. Chem.*, 1997, **34**, 1995.
16. V. T. Bauman, E. E. Shults, M. M. Shakirov, and G. A. Tolstikov, *Zh. Org. Khim.*, 2007, **43**, 529 [*Russ. J. Org. Chem.*, 2007, **43** (Engl. Transl.)].
17. S. G. Davies and D. Pyatt, *Heterocycles*, 1989, **28**, 163.
18. S. G. Davies, C. J. Goodwin, D. Pyatt, and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1413.
19. S.-M. Anderson and A. Hallberg, *J. Org. Chem.*, 1987, **52**, 3529.
20. S. Hagishita, M. Yamada, K. Shirahase, T. Okada, Y. Murakami, Y. Ito, T. Matsuura, M. Wada, T. Kato, M. Ueno, Y. Chikazawa, K. Yamada, T. Uno, I. Teshirogi, and M. Ohtani, *J. Med. Chem.*, 1996, **39**, 3636.
21. L. E. Rueter, D. J. Anderson, C. A. Briggs, D. L. Donnelly-Roberts, G. A. Gintant, M. Gopalakrishnan, N. H. Lin, M. A. Osinski, G. A. Reinhart, M. J. Buckley, R. E. L. Martin, J. S. McDermott, L. C. Preusser, T. R. Seifert, Z. Su, B. F. Cox, M. W. Decker, and J. P. Sulliovan, *CNS Drug Rev.*, 2004, **10**, 167.
22. G. B. Shul´pin, *Organicheskie reaktsii, kataliziruemye kompleksami metallov* [*Organic Reactions Catalyzed by Metal Complexes*], Nauka, Moscow, 1988, 275 (in Russian).
23. *Organic Syntheses, Coll. Vol.* **2**, Ed. A. Blatt, New York, 1947, 196.
24. C. Schopf, K. von Gottberg, and W. Petri, *Justus Liebigs Annalen Chem.*, 1938, **536**, 216.

Received February 9, 2007;
in revised form May 23, 2007