Synthetic Transformations of Isoquinoline Alkaloids. Catalytic Alkinylation of 6,14-*endo*-Ethenotetrahydrothebaine and 6,14-*endo*-Ethenodihydrothebaine Hydroquinone Derivatives

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Abstract

An efficient method is developed for the synthesis of 1-alkinyl substituted tetrahydro- and dihydrothebaine derivatives *via* Pd-catalysed Sonogashira reaction.

INTRODUCTION

The introduction of additional cyclic fragments into the molecules of morphinane alkaloids by means of a Diels–Alder reaction of thebaine with various dienophils at the key stage represents a promising approach aimed at their structural modification [1]. According to the data published [2], the introduction of the arylsuccinimide fragment into the thebaine molecule results in the formation of selective μ-opioid agonists. High efficient analgetic agents were obtained upon annulation of N-(4-bromophenyl)-succinimide with respect to $C^{7,8}$ bond of the morphine skeleton [3].

There are derivatives of 6,14-*endo*-ethenodihydrothebaine hydroquinone among promising analgesics those do not exhibit respiratory depression in contrast to morphine [4]. As the result of transformations of thebaine adducts with unsaturated ketones, 6,14-*endo*-ethenoisomorphinanes (orvinols) were obtained, strong copied ligands those found application in medicine (buprenorphine), as well as in veterinary medicine (ethorphine and diprenorphine) [1, 5]. Various groups of buprenorphine analogues and derivatives substituted at $C^{5,17,18,20}$ positions were synthesized and studied during last years [5–11].

In order to extend the range of functional derivatives of 6,14-*endo*-ethenodihydrothebaine hydroquinone and 6,14-*endo*-ethenotetrahydrothebaine and to study their properties we investigated the possibility for the synthesis of morphinane derivatives containing alkinyl fragments. It should be noted that acethylene derivatives of various structural types including nitrogen-containing compounds, are considered to be efficient as antitumor agents [12, 13].

RESULTS AND DISCUSSION

Nowadays the most efficient method for obtaining aryl- and hetarylacetylenes is presented by Pd-catalysed alkinylation of arylhalogenides (Sonogashira reaction) [14]. Iodo derivatives of ethenodihydrothebaine hydroquinone **1–3** and tetrahydrothebaine **4** whose synthesis we described in [15, 16] were exposed to a cross-coupling reaction with phenylacetylene, 2-propine-1-ol and trimethylsilylacetilene.

The reaction was carried out in benzene solution with the use of catalytic amounts of dichlorobis(triphenylphoshine)palladium and copper iodide as catalysts as well as triethylamine as a base. The condensation of 6,14-*endo*-ethenodihydrothebaine hydroquinones **1**, **2** with phenylacetylene or propargyl alcohol resulted in the formation of corresponding 1-acetylenyl-6,14-*endo*-ethenodihydrothebaine hydro-

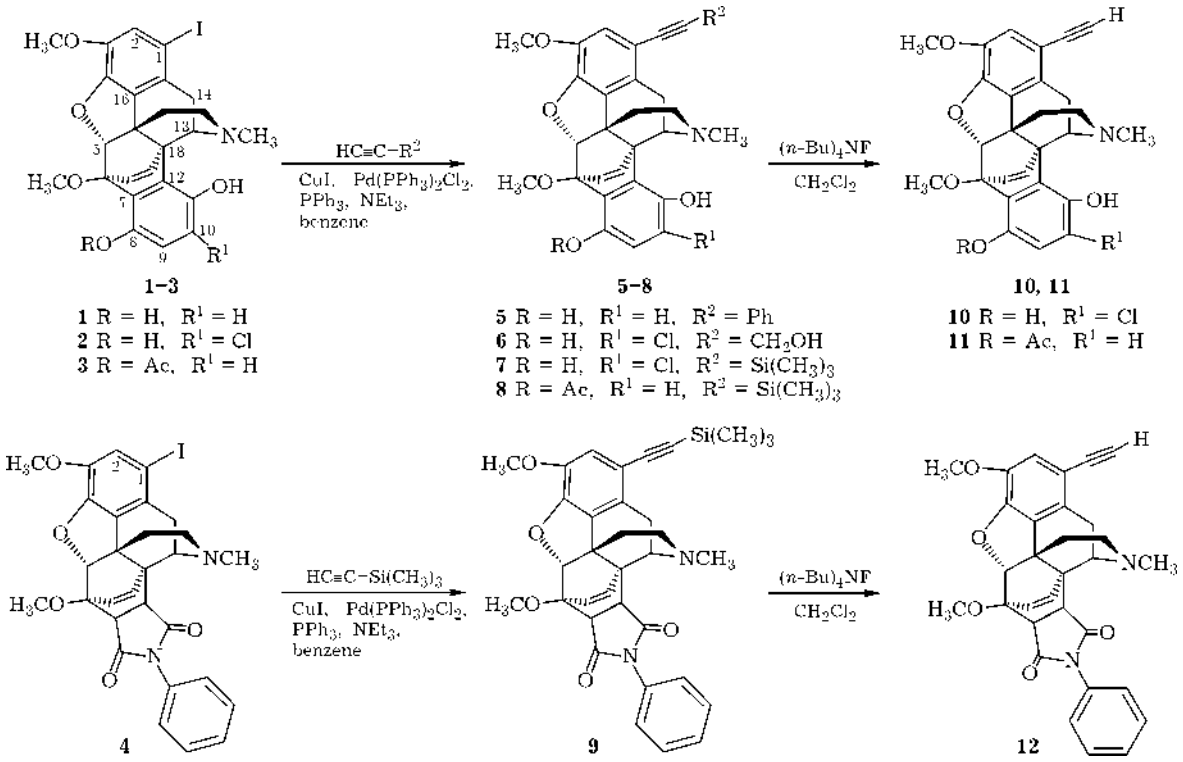
quinones **5**, **6** (with the yield of 44 and 75 %, respectively) (Scheme 1). The products of coupling reactions between iodomorphinanes **2–4** with trimethylsilylacetylene such as 1-trimethylsilylethynyl-6,14-*endo*-ethenodihydrothebaine hydroquinones **7**, **8** and 1-trimethylsilylethynyl-6,14-*endo*-etheno-(N-phenylsuccinimido)-tetrahydrothebaine **9** were obtained with the yield amounting to 90, 84 and 68 %, respectively. The reaction of iodides with trimethylsylilacetylene was brought to completion using 2.5-fold surplus of acetylene (with repeated addition) as well as increasing the duration of the process.

It was established that dihydrothebaine derivatives such as **1**, **3** demonstrate a higher reactivity in the cross coupling reaction as compared to succinimido annulated thebaine tetrahydro derivative **4**. Upon desililation of compounds **7–9** with the use of tetra-*n*-butylammonium fluoride in CH_2Cl_2 medium the formation of corresponding 1-ethinyldihydrothebaine hydroquinones **10**, **11** (with the yield of 50 and 71 %, respectively) and 1-ethinyldihydrothebaine **12** (with the yield amounting to 70 %) is observed.

EXPERIMENTAL

The NMR spectra of the compounds dissolved in $CDCl_3$ were obtained by use of a Bruker AC-200 [with operation frequencies of 200.13 (^{1}H) and 50.32 (^{13}C) MHz], an AV-300 [with operation frequencies of 300.13 (^{1}H) and 75.47 (^{13}C) MHz], AM-400 [with operation frequencies of 400.13 (^{1}H) and 100.78 (^{13}C) MHz] as well as a Bruker DRX-500 [with operation frequencies of 500.13 (^{1}H) and 125.76 (^{13}C) MHz] NMR spectrometers. The assignment of NMR signals was carried out using various types of proton-proton and carbon-proton shift correlation spectroscopy (COSY, COLOC, CORRD) as well as ^{1}H NMR 2D Overhauser effect spectroscopy (NOESY).

For the registration of mass spectra, the determination of molecular mass and elemental composition a Finnigan MAT-8200 high-resolution mass spectrometer was used with the ionisation voltage of 70 eV (the evaporator temperature being at 270–300 °C). IR spectra were registered by means of a VECTOR-22 spec-



Scheme 1.

trometer, using KBr tablet method. Absorption UV spectra were registered with the help of an HP 8453 UV VIS spectrometer for the samples dissolved in ethanol.

The reaction process was monitored using a TLC technique with Silufol UV-254 plates. The reaction products were isolated with the help of a column chromatography technique on silica gel (benzoethylacetate and chloroform-ethanol mixture being used as eluents).

3,6-Dimethoxy-N-methyl-1-phenylethinyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[i]isomorphinane-8,11-diol (5). A two-necked flask supplied with a magnetic stirrer was evacuated and filled then with argon. The operation was repeated three times running. Under argon flow into the flask were succesively loaded 0.167 g (0.3 mmol) of compound **1**, 0.001 g (0.006 mmol, 2 mol. %) of CuI, 0.004 g (0.006 mmol, 2 mol. %) $Pd(PPh_3)_2Cl_2$, 0.004 g (0.0084 mmol, 2.8 mol. %) PPh_3, 1.5 mL of benzene. The mixture was then evacuated and under argon flow there were added 0.24 mL (1.6 mmol) of NEt_3 and 0.045 mL (0.42 mmol) of phenylacetylene. Then the mixture was stirred on heating (60 °C) under argon flow during 6 h and after this it was poured into a Petri dish for free evaporation. The product was extracted with chloroform. The organic extracts joined together were washed out with water and dried over magnesium sulphate. After evaporation in vacuum the residue obtained was dissolved in a minimum amount of chloroform. Then the solution was chromatographed on silica gel (chloroform-alcohol mixture being used as an eluent). The product obtained was triturated in ethylacetate, and then filtered on cooling. The yield of compound 5 amounted to 0.119 g (75 %), m.p. being at 240–245 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.64 m (1H, H^{19}); 1.86 m (1H, H^{19}); 2.55–2.69 m (2H, $H^{14,20}$), 2.60 s (3H, $C\underline{H}_3$–N); 2.78 m (1H, H^{20}); 3.41 d (1H, H^{14}, J = 19.4); 3.85 s (3H, $C\underline{H}_3O$–C^6); 3.93 s (3H, $C\underline{H}_3O$–C^3); 4.06 d (1H, H^{13}, J = 6.0); 4.71 d (1H, H^5, J = 1.3); 5.75 d (1H, H^{22}, J = 8.6); 6.41 m (1H, H^{23}); 6.56 d (1H, H^{10}, J = 8.4); 6.65 d (1H, H^9, J = 8.4); 6.90 s (1H, H^2); 7.30–7.37 m (3H, $H^{3',4',5'}$), 7.52 m (2H, $H^{2',6'}$), 8.92 s (1H, C^8–O$\underline{H}$), 12.07 broadened s (1H, C^{11}–O$\underline{H}$). ^{13}C NMR spectrum (δ, ppm): 22.42 (C^{14}), 33.67 (C^{19}), 42,01 ($\underline{C}H_3$–N^{21}), 44.85 (C^{20}), 50.14 (C^{18}), 50.18 (C^{17}); 55.67 ($\underline{C}H_3O$–C^6), 56.54 ($\underline{C}H_3O$–C^3), 57.72 (C^{13}), 87.02 (C^{1a}), 87.27 (C^6), 92.69 (C^{1b}), 97.55 (C^5), 114.11 (C^1), 116.75 (C^{10}), 117.15 (C^2), 119.77 (C^9), 121.74 (C^{12}), 123.20 ($C^{1'}$), 126.34 (C^7), 128.13 ($C^{4'}$), 128.30 ($C^{3',5'}$), 128.78 (C^{15}), 128.85 (C^{23}), 131.30 ($C^{2',6'}$), 132.25 (C^{16}), 137.54 (C^{22}), 142.50 (C^3), 146.47 (C^8), 147.49 (C^{11}), 149.45 (C^4). Mass spectrum, m/z (I_{rel}, %): 519 $[M]^+$ (79), 476 (20), 329 (34), 328 (39), 202 (44), 201 (100), 44 (40). Found: $[M]^+$ 519.20400 $C_{33}H_{29}NO_5$. Calculated: M 519.20456.

1-(3-Hydroxyprop-1-inyl)-3,6-dimethoxy-N-methyl-10-chloro-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[i]isomorphinane-8,11-diol (6). Compound **6** was obtained under the conditions described from 0.257 g (0.5 mmol) of compound **2**, 0.002 g (0.01 mmol, 2 mol. %) of CuI, 0.007 g (0.001 mmol, 2 mol. %) of $Pd(PPh_3)_2Cl_2$, 0.0015 g (0.003 mmol, 0.6 mol. %) of PPh_3, 2 mL of benzene, 0.4 mL (2.9 mmol) of NEt_3, and 0.1 mL (1.7 mmol) of propargyl alcohol. The mixture was stirred on heating (60 °C) under argon flow during 6 h and after this it was poured into a Petri dish for free evaporation. The product was extracted with chloroform. The organic extracts joined together were washed out with water and dried over magnesium sulphate. After evaporation in vacuum the residue obtained was dissolved in a minimum amount of chloroform. Then the solution was chromatographed on silica gel (chloroform-alcohol mixture being used as an eluent). The yield of compound **6** amounted to 0.106 g (44 %), m.p. being at 223–225 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.62 m (1H, H^{19}); 1.85 m (1H, H^{19}); 2.43–2.78 m (3H, $H^{14,20,20}$), 2.61 s (3H, $C\underline{H}_3$–N^{21}); 3.33 d (1H, H^{14}, J = 19.4); 3.80 s (3H, $C\underline{H}_3O$–C^6); 3.90 s (3H, $C\underline{H}_3O$–C^3); 4.02 d (1H, H^{13}, J = 6.4); 4.53 s (2H, $C\underline{H}_2OH$); 4.68 d (1H, H^5, J = 0.9); 5.67 d (1H, H^{22}, J = 8.8); 6.39 m (1H, H^{23}); 6.71 s (1H, H^9); 6.81 s (1H, H^2); 8.96 s (1H, C^8–O$\underline{H}$), 13.25, 13.25 broadened s (1H, C^{11}–O$\underline{H}$). ^{13}C NMR spectrum (δ, ppm): 22.47 (C^{14}), 33.56 (C^{19}), 41.97 ($\underline{C}H_3$–N^{21}), 44.66 (C^{20}), 50.05 (C^{18}), 50.54 (C^{17}), 51.60 (CH_2OH); 55.76 ($\underline{C}H_3O$–C^6), 56.48 ($\underline{C}H_3O$–C^3), 56.50 (C^{13}), 83,14 (C^{1b}), 87.05 (C^6), 90.55 (C^{1a}), 97.25 (C^5), 113.52 (C^1), 116.95 (C^9), 117.54 (C^2), 121.10 (C^{12}), 123.74 (C^7), 127.57 (C^{10}), 128.66 (C^{15}), 129,07 (C^{23}), 131.76 (C^{16}), 137.26 (C^{22}), 142.46 (C^3), 143.07 (C^8), 146.77 (C^{11}), 149.47 (C^4).

Mass spectrum, m/z (I_{rel}, %): 507 $[M]^+$ (78), 464 (17), 282 (37), 272 (39), 237 (51), 235 (100), 165 (6), 128 (7), 44 (87). Found: $[M]^+$ 507.14543 $C_{28}H_{26}NO_6Cl$. Calculated: M 507.14485.

3,6-Dimethoxy-N-methyl-1-(2-trimethylsilyl)-10-chloro-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[i]isomorphinane-8,11-diol (7). Compound **7** was obtained under the conditions described above from 0.308 g (0.53 mmol) of compounds 2, 0.002 g (0.011 mmol, 2.1 mol. %) of CuI, 0.002 g (0.003 mmol, 0.6 mol. %) of $Pd(PPh_3)_2Cl_2$, 0.0041 g (0.008 mmol, 1.6 mol. %) of PPh_3, 3 mL of benzene, 0.23 mL (1.5 mmol) of NEt_3, 0.1 mL (0.7 mmol) of trimethylsilylacetylene. The mixture was stirred on heating (60 °C) under argon flow during 12 h, and then it was put into a Petri dish and dried in air. The product was extracted with chloroform. The organic extracts joined together were washed out with water and dried over magnesium sulphate. After evaporation in vacuum the residue obtained was triturated with diethyl ether. The yield of compound **7** amounted to 0.264 g (90 %), m.p. being at about 240–245 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 0.26 c (9H, $(CH_3)_3Si$); 1.43 m (1H, H^{19}); 1.83 m (1H, H^{19}); 2.45–2.72 m (3H, $H^{14,20,20}$), 2.62 s (3H, $C\underline{H}_3$–N^{21}); 3.35 d (1H, H^{14}, J = 19.7); 3.81 s (3H, $C\underline{H}_3O$–C^6); 3.90 s (3H, $C\underline{H}_3O$–C^3); 4.02 d (1H, H^{13}, J = 6.2); 4.68 d (1H, H^5, J = 0.9); 5.71 d (1H, H^{22}, J = 8.4); 6.39 m (1H, H^{23}); 6.71 s (1H, H^9); 6.83 s (1H, H^2); 8.97 s (1H, C^8–O$\underline{H}$), 13.27 broadened s (1H, C^{11}–O$\underline{H}$). ^{13}C NMR spectrum (δ, ppm): 0.028 ($(\underline{C}H_3)_3Si$), 22.28 (C^{14}), 33.53 (C^{19}), 41.93 ($\underline{C}H_3$–N^{21}), 44.62 (C^{20}), 50.03 (C^{18}), 50.52 (C^{17}), 55.75 ($\underline{C}H_3O$–C^6), 56.36 ($\underline{C}H_3O$–C^3), 57.50 (C^{13}), 87.02 (C^6), 97.24 (C^5), 97.70 (C^{1b}), 102.46 (C^{1a}), 114.14 (C^1), 116.90 (C^9), 117.31 (C^2), 121.09 (C^{12}), 123.68 (C^7), 127.58 (C^{10}), 128.77 (C^{15}), 128.98 (C^{23}), 131.60 (C^{16}), 137.32 (C^{22}), 142.36 (C^3), 143.06 (C^8), 146.73 (C^{11}), 149.40 (C^4). Mass spectrum, m/z (I_{rel}, %): 549 $[M]^+$ (97), 506 (29), 325 (52), 248 (17), 237 (61), 235 (100), 165 (8), 73 (65), 44 (91). Found: $[M]^+$ 549.17380 $C_{30}H_{32}NO_5SiCl$. Calculated: M 549.17381.

8-Acetoxy-3,6-dimethoxy-N-methyl-1-(2-trimethylsilylethinyl)-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[i]isomorphinane-11-ol (8). Compound **8** was obtained under the conditions described above from 0.274 g (0.5 mmol) of compounds **3**, 0.002 g (0.01 mmol, 2.1 mol. %) of CuI, 0.002 g (0.003 mmol, 0.6 mol. %) of $Pd(PPh_3)_2Cl_2$, 0.004 g (0.0078 mmol, 1.6 mol. %) of PPh_3, 3 mL of benzene, 0.23 mL (1.5 mmol) of NEt_3, 0.1 mL (0.7 mmol) of trimethylsilylacetylene. After 6 h passed, another 0.1 mL aliquot (0.7 mmol) of trimethylsilylacetylene was added, the stirring was then continued for 6 h more (at 60 °C). The reaction mixture was put into a Petri dish and dried in air. Chloroform and water were added to the residue obtained. An organic layer was washed out with water and dried over magnesium sulphate. After evaporation the residue obtained was dissolved in a minimum amount of chloroform. The solution was chromatographed on silica gel (chloroform-alcohol mixture being used as an eluent). The yield of compound **8** amounted to 0.170 g (84 %), m.p. being at 235–240 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 0.25 s (9H, $(CH_3)_3Si$); 1.56 m (1H, H^{19}); 1.84 m (1H, H^{19}); 2.24 s (3H, CH_3COO); 2.53–2.75 m (3H, $H^{14,20,20}$), 2.62 s (3H, $C\underline{H}_3$–N^{21}); 3.32 d (1H, H^{14}, J = 19.3); 3.63 s (3H, $C\underline{H}_3O$–C^6); 3.79 s (3H, $C\underline{H}_3O$–C^3); 4.07 d (1H, H^{13}, J = 6.6); 4.62 m (1H, H^5); 5.68 d (1H, H^{22}, J = 8.5); 6.31 m (1H, H^{23}); 6.66 d (1H, H^9, J = 9.3); 6.75 d (1H, H^{10}, J = 9.3); 6.81 s (1H, H^2); 8.86 s (1H, C^8–O$\underline{H}$). ^{13}C NMR spectrum(δ, ppm): 0.17 ($(\underline{C}H_3)_3Si$), 20,70 ($\underline{C}H_3COO$), 22.36 (C^{14}), 33.68 (C^{19}), 41.89 ($\underline{C}H_3$–N^{21}), 44.82 (C^{20}), 50.08 (C^{17}), 50.28 (C^{18}), 55.22 ($\underline{C}H_3O$–C^6), 56.29 ($\underline{C}H_3O$–C^3), 57.73 (C^{13}), 85.58 (C^6), 94.27 (C^5), 97.31 (C^1), 102.85 (C^{1b}), 113.64 (C^{1a}), 117.21 (C^2), 119.06 (C^9), 122.26 (C^{10}), 128.21 (C^7), 128.83 (C^{15}), 129.39 (C^{23}), 131.69 (C^{12}), 131.93 (C^{16}), 136.70 (C^{22}), 138.83 (C^8), 142.42 (C^3), 150.25 (C^4), 155.82 (C^{11}), 170.56 ($CH_3\underline{C}OO$). Mass spectrum, m/z (I_{rel}, %): 557 $[M]^+$ (81), 514 (36), 324 (31), 244 (21), 243 (100), 202 (46), 201 (80), 73 (66), 44 (92). Found: $[M]^+$ 557.22290 $C_{32}H_{35}NO_6Si$. Calculated: M 557.22335.

1-(2-Trimethylsilylethinyl)-7β,8β-[N'-(phenyl)succinimido]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (9). Compound **9** was obtained under the conditions described above from 0.714 g (1.4 mmol) of compound **4**, 0.006 g (0.03 mmol, 2.1 mol. %) of CuI, 0.006 g (0.009 mmol, 0.6 mol. %) of $Pd(PPh_3)_2Cl_2$, 0.011 g (0.023 mmol, 1.6 mol. %) of PPh_3, 7.5 mL of benzene, 0.61 mL (4 mmol) of NEt_3, 0.257 mL (1.8 mmol) of trimethylsilylacetylene. After 6 h passed, another 0.257 mL aliquot (1.8

mmol) of trimethylsilylacetylene and 1 mL of benzene were added, the stirring was then continued for 6 h more, on heating under argon flow. The reaction mixture was put into a Petri dish and dried in air. Chloroform and water were added to the residue obtained. An organic layer was washed out with water and dried over magnesium sulphate. After evaporation the residue obtained was dissolved in a minimum amount of chloroform. The solution was chromatographed on silica gel (chloroform-alcohol mixture being used as an eluent). The yield of compound **9** amounted to 0.461 g (68 %), m.p. being at 234–236 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.24 s (9H, $(CH_3)_3Si$); 1.83–2.04 m (2H, H^{15}); 2.40–2.64 m (3H, $H^{10,16,16}$), 2.45 s (3H, $C\underline{H}_3–N^{17}$); 3.18 m (2H, $H^{8,10}$); 3.68 s (3H, $C\underline{H}_3O–C^6$); 3.78 s (3H, $C\underline{H}_3O–C^3$); 4.06 d (1H, H^9, *J* = 5.8); 4.37 d (1H, H^7, *J* = 7.5); 4.70 m (1H, H^5); 5.47 d (1H, H^{18}, *J* = 9.2); 5.83 m (1H, H^{19}); 6.78 s (1H, H^2); 7.09–7.17 м (2H, $H^{2',6'}$); 7.28–7.43 m (3H, $H^{3',4',5'}$). ^{13}C NMR spectrum (δ, ppm): 0.01 ($(\underline{C}H_3)_3Si$), 22.14 (C^{10}), 33.37 (C^{15}), 41.16 (C^8), 42.09 (C^7), 43.12 ($\underline{C}H_3–N^{17}$), 44.48 (C^{13}), 44.99 (C^{16}), 47.81 (C^{14}), 51.48 ($\underline{C}H_3O–C^6$), 56.07 ($\underline{C}H_3O–C^3$), 56.69 (C^9), 80.55 (C^6), 90.98 (C^5), 97.17 (C^{1b}), 102.85 (C^{1a}), 114.11 (C^1), 116.57 (C^2), 126.19 ($C^{2',6'}$), 128.40 ($C^{4'}$), 128.83 ($C^{3',5'}$), 128.94 (C^{19}), 130.58 (C^{11}), 131.57 ($C^{1'}$), 132.48 (C^{12}), 133.64 (C^{18}), 141.92 (C^3), 148.61 (C^4), 172.78 ($C^{5'}$), 176.11 ($C^{4'}$). Mass spectrum, *m/z* (I_{rel}, %): 580 $[M]^+$ (100), 406 (16), 326 (19), 325 (52), 266 (23), 203 (8), 174 (9), 121 (9), 73 (45), 44 (18), 28 (27). Found: $[M]^+$ 580.23789 $C_{34}H_{36}N_2O_5Si$. Calculated: *M* 580.23933.

3,6-Dimethoxy-N-methyl-10-chloro-1-ethinyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo-[i]isomorphinane-8,11-diol (10). To a solution of 0.47 g (0.8 mmol) of compound **7** in 2 mL of methylene chloride was added a solution of 0.308 g (1.2 mmol) of $(n\text{-Bu})_4NF$ in 1.6 mL of methylene chloride, dropwise upon stirring. The reaction mixture was stirred at a room temperature during 15 min (with a TLC monitoring); then it was washed out with water, and an organic layer was dried over magnesium sulphate. After evaporation in vacuum, the residue was dissolved in a minimum amount of chloroform and the solution was chromatographed on silica gel. The product obtained was triturated with ethyl acetate. The yield of compound **10** amounted to 0.287 g (71 %), m.p. being at about 230–232 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.50–1.92 m (2H, $H^{19,19}$); 2.43–2.80 m (3H, $H^{14,20,20}$), 2.60 s (3H, $C\underline{H}_3–N^{21}$); 3.24 s (1H, H^{1b}); 3.34 d (1H, H^{14}, *J* = 19.4); 3.81 s (3H, $C\underline{H}_3O–C^6$); 3.90 s (3H, $C\underline{H}_3O–C^3$); 4.03 d (1H, H^{13}, *J* = 6.4); 4.68 d (1H, H^5, *J* = 0.7); 5.69 d (1H, H^{22}, *J* = 8.4); 6.4 m (1H, H^{23}); 6.70 s (1H, H^9); 6.85 s (1H, H^2); 8.94 s (1H, $C^8–O\underline{H}$), 13.19 broadened s (1H, $C^{11}–O\underline{H}$). ^{13}C NMR spectrum (δ, ppm): 22.35 (C^{14}), 33.54 (C^{19}), 41.91 ($\underline{C}H_3–N$), 44.62 (C^{20}), 50.02 (C^{18}), 50.51 (C^{17}), 55.74 ($\underline{C}H_3O–C^6$), 56.46 ($\underline{C}H_3O–C^3$), 57.45 (C^{13}), 87.03 (C^6), 97.26 (C^5), 80.41, 81.23, 112.99 ($C^{1,1a,1b}$), 116.91 (C^9), 117.76 (C^2), 121.07 (C^{12}), 123.70 (C^7), 127.56 (C^{10}), 129.09 (C^{23}), 129,12 (C^{15}), 131.74 (C^{16}), 137.26 (C^{22}), 142.39 (C^3), 143.06 (C^8), 146.73 (C^{11}), 149.61 (C^4). Mass spectrum, *m/z* (I_{rel}, %): 477 $[M]^+$ (31), 434 (19), 252 (28), 242 (34), 237 (54), 235 (100), 74 (14), 59 (19), 44 (72). Found: 477.13370 $C_{27}H_{24}NO_5Cl$. Calculated: *M* 477.13429.

8-Acetoxy-3,6-dimethoxy-N-methyl-1-ethinyl-4,5α-epoxy-6α,18α-*endo*-ethenobenzo[i]-isomorphinane-11-ol (11). To a solution of 0.24 g (0.43 mmol) of compounds **8** in 1 mL of methylene chloride was added a solution of 0.155 g (0.6 mmol) of $(n\text{-Bu})_4NF$ in 1 mL of methylene chloride, dropwise upon stirring. The reaction mixture was stirred at room temperature during 15 min, and washed out with water; an organic layer was dried then over magnesium sulphate. After evaporation in vacuum, the residue was dissolved in a minimum amount of chloroform and the solution was chromatographed on silica gel. The product was triturated with diethyl ether, the precipitate formed was filtered. The yield of compound **11** amounted to 0.1 g (50 %), m.p. being at 225–227 °C. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.59 m (1H, H^{19}); 1.86 m (1H, H^{19}); 2.25 s (3H, CH_3COO); 2.50–2.86 m (3H, $H^{10,16,16}$), 2.61 s (3H, $C\underline{H}_3–N^{21}$); 3.41 d (1H, H^{14}, *J* = 19.7); 3.63 s (3H, $C\underline{H}_3O–C^6$); 3.80 s (3H, $C\underline{H}_3O–C^3$); 4.09 d (1H, H^{13}, *J* = 7.0); 4.65 m (1H, H^5); 5.68 d (1H, H^{22}, *J* = 8.9); 6.34 m (1H, H^{23}); 6.67 d (1H, H^{10}, *J* = 8.4); 6,67 d (1H, H^9, *J* = 8.4); 6.88 s (1H, H^2); 12.82 s (1H, $C^8–O\underline{H}$). ^{13}C NMR spectrum (δ, ppm): 20.66 ($\underline{C}H_3COO$), 22.56 (C^{14}), 33.59 (C^{19}), 41.95 ($\underline{C}H_3–N$), 44.82 (C^{20}), 50.02 (C^{17}), 50.28 (C^{18}), 55.21 ($\underline{C}H_3O–C^6$),

56.40 ($\underline{C}H_3O-C^3$), 57.70 (C^{13}), 76.86 (C^{1b}), 80.61 (C^6), 85.55 (C^{1a}), 94.45 (C^5), 112.14 (C^1), 118.05 (C^2), 119.16 (C^9), 122.37 (C^{10}), 129.56 (C^{23}), 128.07, 130.16, 131.56, 132.36 ($C^{7,12,15,16}$), 136.57 (C^{22}), 138.93 (C^8), 142.63 (C^3), 151,07 (C^4), 151.76 (C^{11}), 170.54 ($CH_3\underline{C}OO$).

1-Ethinyl-7α,8α-[N'-(phenyl)succinimido]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (12). To a solution of 0.6 g (1 mmol) of compound **9** in 4 mL of methylene chloride was added a solution of 0.4 g (1.5 mmol) of $(n\text{-Bu})_4NF$ in 2 mL of methylene chloride, dropwise upon stirring. The reaction mixture was stirred at room temperature during 15 min, a precipitate was filtered. An organic layer was washed out with water and dried then over magnesium sulphate. After evaporation in vacuum, the residue was triturated with methylene chloride medium. The yield of compound **12** amounted to 0.367 g (70 %), m.p. being at 270–273 °C. ^{1}H NMR spectrum (DMSO, δ, ppm, *J*, Hz): 2.10 m (1H, H^{15}), 2.28 m (1H, H^{15}); 2.44–2.60 m (3H, $H^{10,16,16}$), 2.49 s (3H, $C\underline{H}_3-N^{17}$); 3.08 d (1H, H^{10}, J = 18.8), 3.54 s (3H, $C\underline{H}_3O-C^6$), 3.72 s (3H, $C\underline{H}_3O-C^3$), 3.98 d (1H, H^9, J = 6.4), 3.77 d (1H, H^8, J = 7.5), 4.13 s (1H, H^{1b}), 4.31 d (1H, H^7, J = 7.5); 4.93 m (1H, H^5); 5.50 d (1H, H^{18}, J = 8.8); 5.69 m (1H, H^{19}); 6.81 s (1H, H^2); 7.09 m (2H, $H^{2',6'}$); 7.37 m (1H, $H^{4'}$), 7.44 m (3H, $H^{3',5'}$). ^{13}C NMR spectrum (δ, ppm): 21.75 (C^{10}), 32.27 (C^{15}), 40.66 (C^8), 42.28 (C^7), 42.96 ($\underline{C}H_3-N^{17'}$), 44.53 (C^{13}), 44.64 (C^{16}), 47.18 (C^{14}), 50.58 ($\underline{C}H_3O-C^6$), 56.06 ($\underline{C}H_3O-C^3$), 56.49 (C^9), 80.50 (C^6), 80.53 (C^{1b}), 81.85 (C^{1a}), 89.22 (C^5), 112.58 (C^1), 116.93 (C^2), 126.89 ($C^{2',6'}$), 128.35 ($C^{4'}$), 128.81 ($C^{3',5'}$), 129.18 (C^{19}), 130.89 (C^{11}), 132.20 ($C^{1'}$), 133.23 (C^{12}), 133.68 (C^{18}), 141.48 (C^3), 148.50 (C^4), 173.18 ($C^{5'}$), 176.27 ($C^{4'}$). Mass spectrum, m/z (I_{rel}, %): 508 $[M]^+$(100), 503(21), 335(44), 311(41), 268(41), 255(49), 174(19), 121(16), 58(22), 44(61), 28(21). Found: $[M]^+$ 508.18865. $C_{31}H_{28}N_2O_5$. Calculated: *M* 508.19981.

CONCLUSION

Thus, as the result of the work carried out an approach has been for the first time proposed to synthesize modified morphinane derivatives containing acethylene substituents in the aromatic nucleus, with the use of a palladium catalysed cross coupling reaction.

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