Synthesis of Rigid Morphinans Doubly Bridged at Ring C†

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As part of our studies directed toward the synthesis of new analgesics starting from thebaine-like morphinan-6,8-dienes, we have accomplished the synthesis of novel rigid morphinans doubly bridged at ring C via an intramolecular Diels–Alder reaction. These compounds (**5**–**8**) possess an additional 5β,7β-bridge linked over the 6α,14α-ethenoisomorphinan skeleton (Scheme I).

A suitable starting material[1] for the synthesis of these rigid adducts proved to be thebaine-5β-methanol (**3**), which is readily available via a two-step synthesis. Deprotonation[2] of thebaine followed by *in situ* reaction of the anion with methyl chloroformate yielded methyl thebaine-5β-carboxylate (**2**). Reduction of ester **2** with lithium aluminum hydride gave thebaine-5β-methanol (**3**). The hydroxymethyl group of **3** was converted almost quantitatively into ester **4a** with acryloyl chloride in the presence of triethylamine. Intramolecular Diels–Alder reaction of **4a** was achieved by heating the ester in boiling toluene for 3 weeks (70% conversion). The adduct was obtained in 48% yield after chromatographic separation, followed by crystallization from diethyl ether. In the ^{1}H NMR spectrum, two vinylic proton signals were present at δ 6.03 and δ 5.62, which indicates a 6α,14α-ethenoisomorphinan skeleton.[3] The 7β-position of the lactone group was established by analysis of the spin system and of the coupling constants of H-7α, H-8α, and H-8β [$J(7\alpha,8\alpha)$ = 13.4 Hz, $J(7\alpha,8\beta)$ = 3.5 Hz]. These data confirm the structure of adduct **5a**, in which the additional bridge formed by the lactone moiety links the 5β- with the 7β-position of the morphinan skeleton. This is expected, since the acrylate moiety of **4a** is connected with the methylene group in the 5β-position of the morphinan skeleton. Thus, cycloaddition gives the exclusive formation of adduct **5a**.

The usual Diels–Alder reaction[4] of thebaine (**1**) is fast (1–6 h) and yields the 7α-substituted adducts with only occasionally the 7β-substituted adduct as a minor side product.[5] The latter adduct is exclusively formed in the case of the intramolecular Diels–Alder reaction after prolonged heating. The slow reaction can be explained by the absence of advantageous secondary orbital overlap[6] and steric interactions during the cycloaddition.

To incorporate a methyl group at the 7α-position, thebaine-5β-methanol (**3**) was now esterified with methacryloyl chloride to methacrylate **4b**, which gave an intramolecular Diels–Alder adduct after 3 weeks of heating in boiling toluene. In the ^{1}H NMR spectrum, the signals of the vinylic protons were at positions δ 6.06 and 5.57 and the signal of the methyl group was found at δ 1.17. From these data and the strong resemblance with the spectrum of adduct **5a**, we concluded that the adduct **5b** has the expected structure with the methyl group in the 7α-position.

In order to obtain 5β,7β-disubstituted 6α,14α-ethenoisomorphinans, the hydrolysis of the lactone moiety was investigated under various conditions. All attempts to open the lactone bridge were unsuccessful. Obviously, the rigidity of the 6α,14α-ethenoisomorphinan structure brings the lactone group into a stable, six-membered ring system, which prevents the hydrolysis of the lactone. Another approach to obtain new congeners is reduction of the lactones **5a** and **5b** to cyclic ethers **6a** and **6b**, respectively. Reaction of **5a** and **5b** with lithium aluminum hydride yielded the lactols. The lactols were reduced with triethylsilane/boron trifluoride etherate[7a] to ethers **6a** and **6b**, respectively, each in approximately 75% yield. The mass spectra were in agreement with the proposed structures. The signals in the ^{1}H NMR spectrum of **6a** were in accordance with the 6α,14α-ethenoisomorphinan structure, and the two protons of the 7β-methylene group were found at δ 3.90 (dd) and 3.57 (dd). The signal of H-15ax was found at low field (δ 3.16), which is exceptional for this proton. Apparently, the downfield shift is due to the anisotropy of the oxygen of the 5β,7β-ether bridge.

In order to make these compounds suitable for biological screening, lactones **5a** and **5b** and ethers **6a** and **6b** were converted into the corresponding phenols.[8] Cleavage of the aryl methyl ether was performed with boron tribromide in chloroform[9] at room temperature. The phenols were obtained in about 75% yield upon crystallization from absolute ethanol. The conversion of the lactones **5a** and **5b** into the phenols **7a** and **7b** proved to be a clean "one-spot" reaction on TLC, in spite of the presence of other sensitive ether groups and the lactone group. Probably, the boron tribromide complex formation neccessary for cleaving the 6-methoxy group, which was observed in a 7α-substituted 6α,14α-ethenoisomorphinan,[10] is hindered by the presence of the 5β,7β-lactone bridge. Unexpectedly, the 3-*O*-demethylation of the ether adducts **6a** and **6b** to the phenolic ethers **8a** and **8b**, performed in the same way as for **5a** and **5b**, proceeded with difficulty. The reaction gave several side products besides the desired phenols. An explanation could be that the oxygen atoms of the 6-methoxy group and the cyclic ether coordinate with boron tribromide, thereby increasing the lability of these ether moieties relative to the 3-methoxy group. This results not only in the cleavage of the 3-methoxy group, but also in the cleavage of the other ethers. Therefore, the compounds **8a** and **8b** were prepared by lithium aluminum

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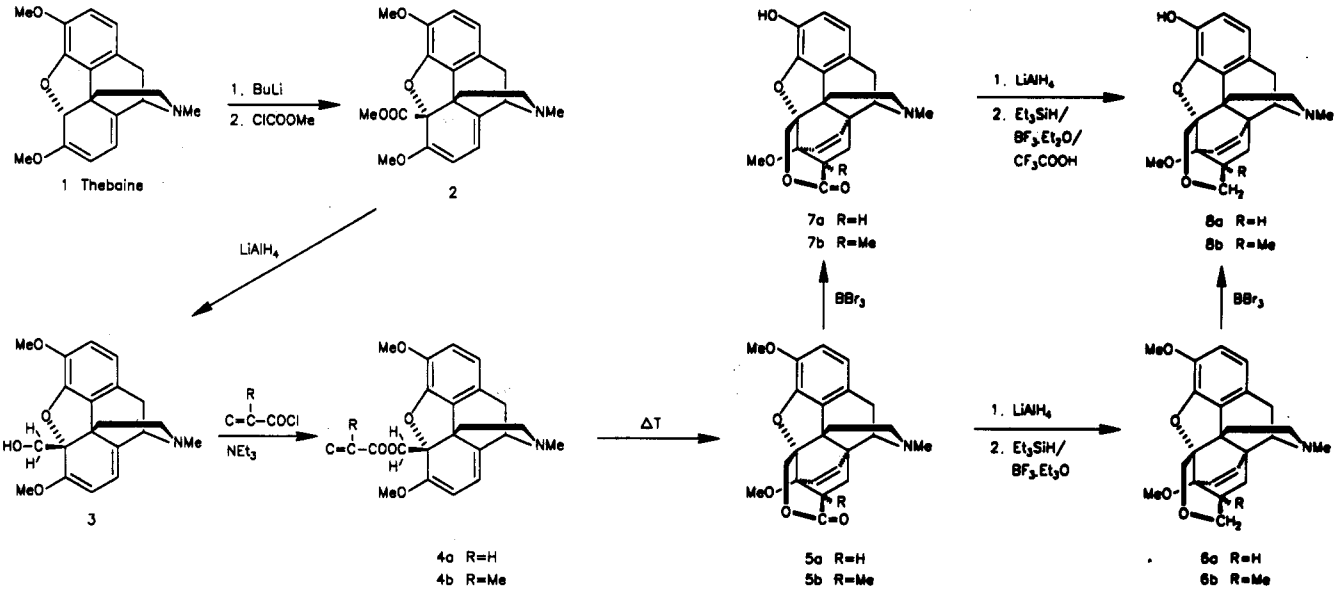
Scheme I. Synthesis of the Doubly-Bridged Morphinans (5–8) from Thebaine (1)



hydride reduction of **7a** and **7b** to the corresponding lactols. They were further reduced using the triethylsilane/boron trifluoride etherate method[7a] followed by treatment with trifluoroacetic acid[7b] to give the cyclic ethers **8a** and **8b** in an overall yield of 46% and 76%, respectively.

The structures of the phenols **7a**, **7b**, **8a**, and **8b** were confirmed by means of their NMR spectra and by comparison with those of the 3-methoxy counterparts. The results of the pharmacological screening of the phenol adducts **7a**, **7b**, **8a**, and **8b** will be published elsewhere.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained using a Varian VXR-400S spectrometer with $CDCl_3$ as solvent and TMS as reference. Mass spectra were determined using a VG 70-SE spectrometer. IR spectra were obtained from KBr disks using a Beckman IR 4210 spectrophotometer. Optical rotations were measured on a Perkin-Elmer P141 polarimeter in chloroform/ethanol (9:1). Melting points are uncorrected. Purification was performed by chromatography over Merck silica gel 60. Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent dichloromethane/methanol/25% ammonia (85:15:0.5)). The compounds were detected with UV (254 nm) and iodine vapor.

General Procedure for the Preparation of Acrylate Esters 4a and 4b. Acid chloride was added to a solution of thebaine-5β-methanol[1] (3) and triethylamine (3.7 mL, 27 mmol) in anhydrous THF (175 mL) at room temperature. After 4 h, water (10 mL) was added to the turbid solution, and the THF was evaporated. The residue was taken up in chloroform (100 mL) and washed with 1 M KOH (3 × 100 mL) and water (2 × 100 mL). After drying (Na_2SO_4), the solution was concentrated to yield **4a** or **4b**, respectively, as a foam. An analytical sample was chromatographed (eluent dichloromethane/methanol (98:2)) to give pure **4a** or **4b**. Attempts to crystallize the compounds were unsuccessful.

(–)-Thebaine-5β-methyl Acrylate (4a). Reaction of **3** (3.41 g, 10.0 mmol) with acryloyl chloride (1.2 mL, 15 mmol) yielded **4a** (3.71 g, 9.4 mmol, 94%). Column chromatography of 243 mg gave 165 mg of pure **4a**: $[\alpha]^{25}_D$ –368° (*c* 0.98); ^{1}H NMR δ 6.66 (d, 1H, H-2, J = 8.2 Hz), 6.62 (d, 1H, H-1, J = 8.2 Hz), 6.39 (dd, 1H, H_2C=CH-, J = 1.4, 17.3 Hz), 6.10 (dd, 1H, H_2C=C*H*-, J = 10.4, 17.4 Hz), 5.83 (dd, 1H, H_2C=CH-, J = 1.4, 10.5 Hz), 5.59 (d, 1H, H-8, J = 6.6 Hz), 5.17 (d, 1H, H-7, J = 6.7 Hz), 5.03 (d, 1H, 5β-CH_2, J = 11.0 Hz), 4.50 (d, 1H, 5β-CH_2, J = 11.0 Hz), 3.85 (s, 3H, 3-OMe), 3.66 (d, 1H, H-9, J = 6.8 Hz), 3.54 (s, 3H, 6-OMe), 3.30 (d, 1H, H-10β, J = 17.7 Hz), 2.78 (ddd, 1H, H-16ax, J = 3.5, 12.6, 12.6 Hz), 2.72–2.64 (m, 2H, H-10α, H-16eq), 2.45 (s, 3H, *N*-Me), 2.29 (ddd, 1H, H-15ax, J = 5.4, 12.4, 12.4 Hz), 1.72 (ddd, 1H, H-15eq, J = 1.6, 3.1, 11.5 Hz); ^{13}C NMR δ 165.21, 152.33, 143.09, 142.64, 133.88, 131.37, 128.10, 127.31, 119.74, 112.63, 112.26, 112.51, 98.13, 92.57, 62.41, 61.42, 56.27, 55.13, 47.35, 45.55, 42.19, 30.58, 29.37; HRMS (EI), *m/e* 395.1732 (calcd for $C_{23}H_{25}NO_5$ 395.1733); IR ν 1735 (C=O) cm^{-1}.

(–)-Thebaine-5β-methyl Methacrylate (4b). Reaction of **3** (3.41 g, 10.0 mmol) with methacryloyl chloride (1.5 mL, 15 mmol) yielded **4b** (3.89 g, 9.5 mmol, 95%). Column chromatography of 129 mg gave 98 mg of pure **4b**: $[\alpha]^{25}_D$ –372° (*c* 1.10); ^{1}H NMR δ 6.66 (d, 1H, H-2, J = 8.3 Hz), 6.62 (d, 1H, H-1, J = 8.3 Hz), 6.10 (m, 1H, H_2C=CMe–), 5.59 (d, 1H, H-8, J = 6.6 Hz), 5.56 (m, 1H, H_2C=CMe–), 5.18 (d, 1H, H-7, J = 6.6 Hz), 4.97 (d, 1H, 5β-CH_2, J = 11.0 Hz), 4.50 (d, 1H, 5β-CH_2, J = 11.0 Hz), 3.84 (s, 3H, 3-OMe), 3.63 (d, 1H, H-9, J = 7.0 Hz), 3.54 (s, 3H, 6-OMe), 3.28 (d, 1H, H-10β, J = 17.7 Hz), 2.83 (ddd, 1H, H-16ax, J = 3.7, 12.9, 12.9 Hz), 2.77–2.64 (m, 2H, H-10α, H-16eq), 2.44 (s, 3H, *N*-Me), 2.27 (ddd, 1H, H-15ax, J = 5.2, 12.4, 12.4 Hz), 1.92 (dd, 3H, H_2C=C*Me*–, J = 0.9, 1.6 Hz), 1.67 (ddd, 1H, H-15eq, J = 1.4, 3.2, 12.4 Hz); ^{13}C NMR δ 166.43, 152.50, 143.08, 142.61, 135.82, 133.89, 131.52, 127.36, 126.31, 119.74, 112.60, 112.27, 98.05, 92.61, 62.45, 61.47, 56.26, 55.13, 47.45, 45.46, 42.07, 31.59, 28.81, 18.27; HRMS (EI) *m/e* 409.1882 (calcd for $C_{24}H_{27}NO_5$ 409.1889); IR ν 1725 (C=O) cm^{-1}.

General Procedure for Preparation of Diels–Alder Adducts 5a and 5b. Crude compound **4a** or **4b** was dissolved in anhydrous toluene (75 mL) and boiled under reflux for 3 weeks. After being cooled to room temperature, the solution was filtered and concentrated. The residue was chromatographed (eluent dichloromethane/methanol (98.5:1.5)) to yield the adducts **5a** or **5b** and unreacted **4a** or **4b**, respectively. The adducts **5a** and **5b** were crystallized from diethyl ether.

(–)-4,5α-Epoxy-5β,7β-(methanoxymethano)-3,6-dimethoxy-*N*-methyl-6α,14α-ethenoisomorphinan-20-one (5a). Intramolecular Diels–Alder reaction (conversion 70%, HPLC) of **4a** (4.50 g, 11.4 mmol) yielded **5a** (2.16 g, 5.5 mmol, 48%) in addition to recovered **4a** (783 mg, 2.0 mmol, 18%): mp 204–206 °C; $[\alpha]^{25}_D$ –256° (*c* 1.03); ^{1}H NMR δ 6.63 (d, 1H, H-2, J = 8.3 Hz), 6.58 (dt, 1H, H-1, J = 0.9, 0.9, 8.3 Hz), 6.03 (d, 1H, H-18, J = 9.0 Hz), 5.62 (d, 1H, H-19, J = 9.3 Hz), 4.90 (d, 1H, 5β-CH_2, J = 11.4 Hz), 4.41 (d, 1H, 5β-CH_2, J = 11.4 Hz), 3.81 (s, 3H, 3-OMe), 3.57 (s, 3H, 6-OMe), 3.23 (d, 1H, H-10β, J = 18.0 Hz), 3.19 (d, 1H, H-9, J = 6.0 Hz), 2.86 (dd, 1H, H-8β, J = 3.5, 14.3 Hz), 2.84 (dd, 1H, H-7α, J = 3.3, 13.4 Hz), 2.59 (m, 1H, H-16eq), 2.47–2.39 (m, 2H, H-10α, H-16ax), 2.36 (s, 3H, *N*-Me), 2.33 (ddd, 1H, H-15ax, J = 5.5, 12.4, 12.4 Hz), 1.87 (dd, 1H, H-8α, J = 13.4, 14.3 Hz), 1.81 (ddd, 1H, H-15eq, J = 1.5, 3.6, 12.0 Hz); ^{13}C NMR δ 172.56, 145.69, 142.24, 138.62, 135.07, 127.57, 124.92, 120.29, 113.08, 92.61, 78.49, 65.28, 60.08, 56.37, 53.18, 47.80, 44.97, 43.44, 43.26, 42.19, 31.20, 27.64,

22.44; HRMS (EI) *m/e* 395.1726 (calcd for $C_{23}H_{25}NO_5$ 395.1733); IR ν 1750 (C=O) cm^{-1}.

(-)-4,5α-Epoxy-5β,7β-(methanoxymethano)-3,6-dimethoxy-7α,*N*-dimethyl-6α,14α-ethenoisomorphinan-20-one (5b). Intramolecular Diels-Alder reaction (conversion 65%, HPLC) of **4b** (2.42 g, 5.9 mmol) yielded **5b** (1.38 g, 3.4 mmol, 57%) in addition to recovered **4b** (580 mg, 1.4 mmol, 24%): mp 185–187 °C; $[\alpha]^{25}_D$ –297° (*c* 1.11); ^1H NMR δ 6.65 (d, 1H, H-2, *J* = 8.2 Hz), 6.58 (dt, 1H, H-1, *J* = 0.8, 0.8, 8.2 Hz), 6.06 (d, 1H, H-18, *J* = 9.0 Hz), 5.57 (d, 1H, H-19, *J* = 9.0 Hz), 4.84 (d, 1H, 5β-CH_2, *J* = 11.3 Hz), 4.39 (d, 1H, 5β-CH_2, *J* = 11.3 Hz), 3.82 (s, 3H, 3-OMe), 3.71 (s, 3H, 6-OMe), 3.22 (d, 1H, H-10β, *J* = 18.5 Hz), 3.15 (d, 1H, H-9, *J* = 6.4 Hz), 3.08 (d, 1H, H-8β, *J* = 13.9 Hz), 2.57 (m, 1H, H-16eq), 2.47–2.31 (m, 3H, H-10α, H-15ax, H-16ax), 2.34 (s, 3H, *N*-Me), 1.79 (m, 1H, H-15eq), 1.29 (d, 1H, H-8α, *J* = 13.9 Hz), 1.17 (s, 3H, 7α-Me); ^{13}C NMR δ 175.33, 145.52, 142.11, 136.76, 135.46, 127.71, 124.16, 120.28, 113.36, 93.81, 80.74, 64.95, 60.05, 56.56, 55.20, 47.73, 47.43, 44.89, 43.43, 43.25, 40.50, 27.40, 22.41, 22.14; HRMS (EI) *m/e* 409.1884 (calcd for $C_{24}H_{27}NO_5$ 409.1889); IR ν 1730 (C=O) cm^{-1}.

General Procedure for the Preparation of Ether Adducts 6a and 6b. Lithium aluminum hydride (95 mg, 1.3 mmol) was added to lactone **5a** or **5b** in 10 mL of anhydrous THF. After 15 min (complete conversion on TLC), water (1 mL) was added and the resulting mixture filtered. Drying (Na_2SO_4) and concentration of the filtrate gave the corresponding lactol. Boron trifluoride etherate (0.4 mL, 3.2 mmol) was added to a solution of the crude lactol and triethylsilane (0.5 mL, 3.1 mmol) in chloroform (10 mL), and the mixture was stirred overnight. The resulting mixture was diluted with water (25 mL), made alkaline using concentrated ammonia, and extracted with chloroform (2 × 10 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated. The product was purified by chromatography (eluent dichloromethane/methanol (99:1)) to give pure ether adduct **6a** or **6b**, which were crystallized from diethyl ether.

(-)-4,5α-Epoxy-5β,7β-(methanoxymethano)-3,6-dimethoxy-*N*-methyl-6α,14α-ethenoisomorphinan (6a). Lactone reduction of **5a** (150 mg, 0.38 mmol) yielded **6a** (101 mg, 0.27 mmol, 70%): mp 127–128 °C; $[\alpha]^{25}_D$ –180° (*c* 0.99); ^1H NMR δ 6.58 (d, 1H, H-2, *J* = 8.1 Hz), 6.53 (dt, 1H, H-1, *J* = 0.8, 0.8, 8.1 Hz), 6.06 (d, 1H, H-18, *J* = 8.9 Hz), 5.52 (d, 1H, H-19, *J* = 8.9 Hz), 4.16 (d, 1H, 5β-CH_2, *J* = 11.2 Hz), 3.90 (dd, 1H, 7β-CH_2, *J* = 2.1, 11.1 Hz), 3.81 (d, 1H, 5β-CH_2, *J* = 11.1 Hz), 3.80 (s, 3H, 3-OMe), 3.57 (dd, 1H, 7β-CH_2, *J* = 1.5, 11.1 Hz), 3.51 (s, 3H, 6-OMe), 3.25–3.19 (m, 2H, H-9, H-10α), 3.16 (ddd, 1H, H-15ax, *J* = 6.0, 13.0, 13.0 Hz), 2.57 (m, 1H, H-16eq), 2.53 (dd, 1H, H-8β, *J* = 3.7, 12.5 Hz), 2.41 (dd, 1H, H-10α, *J* = 6.9, 18.7 Hz), 2.39 (m, 1H, H-16ax), 2.39 (s, 3H, *N*-Me), 1.88 (m, 1H, H-7α), 1.61 (ddd, 1H, H-15eq, *J* = 1.7, 3.8, 13.4 Hz), 1.57 (dd, 1H, H-8α, *J* = 11.5, 12.5 Hz); ^{13}C NMR δ 146.16, 142.17, 137.32, 136.53, 127.72, 127.55, 119.54, 112.51, 93.78, 78.32, 65.16, 63.34, 61.05, 56.36, 52.65, 48.55, 45.37, 43.72, 43.00, 39.11, 29.70, 26.01, 22.45; HRMS (EI) *m/e* 381.1935 (calcd for $C_{23}H_{27}NO_4$ 381.1940). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 71.90; H, 6.86; N, 3.81. Found: C, 72.01; H, 6.92; N, 3.90.

(-)-4,5α-Epoxy-5β,7β-(methanoxymethano)-3,6-dimethoxy-7α,*N*-dimethyl-6α,14α-ethenoisomorphinan (6b). Lactone reduction of **5b** (414 mg, 1.01 mmol) yielded **6b** (328 mg, 0.83 mmol, 82%): mp 123–124 °C; $[\alpha]^{25}_D$ –177° (*c* 0.88); ^1H NMR δ 6.60 (d, 1H, H-2, *J* = 8.2 Hz), 6.54 (dt, 1H, H-1, *J* = 0.9, 0.9, 8.2 Hz), 6.01 (d, 1H, H-18, *J* = 9.0 Hz), 5.50 (d, 1H, H-19, *J* = 9.0 Hz), 4.13 (d, 1H, 5β-CH_2, *J* = 11.0 Hz), 3.82 (d, 1H, 5β-CH_2, *J* = 11.0 Hz), 3.81 (s, 3H, 3-OMe), 3.70 (d, 1H, 7β-CH_2, *J* = 10.9 Hz), 3.63 (s, 3H, 6-OMe), 3.31 (d, 1H, 7β-CH_2, *J* = 10.9 Hz), 3.21–3.18 (m, 3H, H-9, H-10β, H-15ax), 2.73 (d, 1H, H-8β, *J* = 12.5 Hz), 2.57 (m, 1H, H-16eq), 2.44–2.35 (m, 2H, H-10α, H-16ax), 2.39 (s, 3H, *N*-Me), 1.60 (ddd, 1H, H-15eq, *J* = 1.5, 4.0, 13.4 Hz), 1.10 (d, 1H, H-8α, *J* = 12.5 Hz), 0.70 (s, 3H, 7α-Me); ^{13}C NMR δ 146.06, 142.17, 136.93, 136.02, 127.68, 126.13, 119.58, 112.77, 95.17, 80.54, 70.99, 63.37, 61.13, 56.57, 55.04, 48.38, 45.33, 43.72, 43.65, 42.92, 38.04, 25.85, 22.48, 20.65; HRMS (EI) *m/e* 395.2090 (calcd for $C_{24}H_{29}NO_4$ 395.2097). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.57; H, 7.42; N, 3.50.

General Procedure for the Preparation of Phenols 7a and 7b. Adduct **5a** or **5b** dissolved in 10 mL of chloroform was added dropwise to a solution of boron tribromide (2.0 mL, 21 mmol) in 20 mL of chloroform and stirred at room temperature (complete conversion on TLC). Methanol (5 mL) was slowly added, and the solvent was removed under reduced pressure. Water (50 mL) was added to the residue, which was made alkaline (pH 8) using concentrated ammonia and extracted with chloroform (3 × 25 mL). The combined extracts were washed with brine and dried (Na_2SO_4), and the solvent was evaporated. Compounds **7a** and **7b** were recrystallized from absolute ethanol.

(-)-4,5α-Epoxy-3-hydroxy-5β,7β-(methanoxymethano)-6-methoxy-*N*-methyl-6α,14α-ethenoisomorphinan-20-one (7a). 3-*O*-Demethylation of **5a** (500 mg, 1.27 mmol) yielded **7a** (323 mg, 0.85 mmol, 67%): mp 290–293 °C dec; $[\alpha]^{25}_D$ –235° (*c* 0.97); ^1H NMR δ 6.61 (d, 1H, H-2, *J* = 8.1 Hz), 6.53 (d, 1H, H-1, *J* = 8.1 Hz), 5.99 (d, 1H, H-18, *J* = 9.0 Hz), 5.62 (d, 1H, H-19, *J* = 9.0 Hz), 4.85 (d, 1H, 5β-CH_2, *J* = 11.3 Hz), 4.63 (bs, 1H, 3-OH), 4.40 (d, 1H, 5β-CH_2, *J* = 11.3 Hz), 3.54 (s, 3H, 3-OMe), 3.22 (d, 1H, H-10β, *J* = 18.7 Hz), 3.21 (d, 1H, H-9, *J* = 6.6 Hz), 2.90–2.86 (m, 2H, H-7α, H-8β), 2.60 (dd, 1H, H-16eq, *J* = 5.0, 11.5 Hz), 2.48–2.39 (m, 2H, H-10α, H-16ax), 2.36 (s, 3H, *N*-Me), 2.33 (ddd, 1H, H-15ax, *J* = 5.8, 12.7, 12.7 Hz), 1.88 (m, 1H, H-8α), 1.82 (ddd, 1H, H-15eq, *J* = 1.7, 3.6, 13.0 Hz); ^{13}C NMR δ 172.50, 144.29, 138.96, 137.77, 134.95, 127.33, 124.56, 120.86, 116.58, 92.79, 78.66, 65.16, 60.09, 52.92, 48.16, 44.99, 43.44, 43.32, 41.53, 31.18, 27.59, 22.55; HRMS (EI) *m/e* 381.1590 (calcd for $C_{22}H_{23}NO_5$ 381.1576); IR ν 3390 (OH), 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.26; H, 6.08; N, 3.67. Found: C, 69.05; H, 6.05; N, 3.56.

(-)-4,5α-Epoxy-3-hydroxy-5β,7β-(methanoxymethano)-6-methoxy-7α,*N*-dimethyl-6α,14α-ethenoisomorphinan-20-one (7b). 3-*O*-Demethylation of **5b** (393 mg, 0.96 mmol) yielded **7b** (292 mg, 0.74 mmol, 77%): mp >300 °C dec; $[\alpha]^{25}_D$ –249° (*c* 1.01); ^1H NMR δ 6.62 (d, 1H, H-2, *J* = 8.2 Hz), 6.53 (dt, 1H, H-1, *J* = 0.8, 0.8, 8.2 Hz), 6.04 (d, 1H, H-18, *J* = 9.0 Hz), 5.56 (d, 1H, H-19, *J* = 9.0 Hz), 4.80 (d, 1H, 5β-CH_2, *J* = 11.2 Hz), 4.65 (bs, 1H, 3-OH), 4.39 (d, 1H, 5β-CH_2, *J* = 11.1 Hz), 3.69 (s, 3H, 6-OMe), 3.20 (d, 1H, H-10β, *J* = 18.5 Hz), 3.14 (d, 1H, H-9, *J* = 6.5 Hz), 3.07 (d, 1H, H-8β, *J* = 14.0 Hz), 2.58 (m, 1H, H-16eq), 2.45–2.31 (m, 3H, H-10α, H-15ax, H-16ax), 2.34 (s, 3H, *N*-Me), 1.79 (m, 1H, H-15eq), 1.29 (d, 1H, H-8α, *J* = 14.0 Hz), 1.17 (s, 3H, 7α-Me); ^{13}C NMR δ 175.35, 144.18, 137.58, 136.88, 135.35, 127.47, 123.82, 120.71, 116.34, 94.45, 80.75, 64.85, 60.07, 55.18, 48.07, 47.50, 44.90, 43.42, 43.31, 40.45, 27.32, 22.50, 22.16; HRMS (EI) *m/e* 395.1736 (calcd for $C_{23}H_{25}NO_5$ 395.1733); IR ν 3400 (OH), 1710 (C=O) cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.84; H, 6.38; N, 3.54. Found: C, 69.95; H, 6.21; N, 3.37.

General Procedure for the Preparation of Hydroxy Ethers 8a and 8b. Lithium aluminum hydride (95 mg, 1.3 mmol) was added to lactone **7a** or **7b** in 10 mL of anhydrous THF. After 15 min (complete conversion on TLC), water (1 mL) and subsequently one drop of acetic acid were added, and the resulting mixture was filtered. After concentration of the filtrate, the residue was dissolved in chloroform (25 mL) and washed with aqueous ammonia (pH 8, 25 mL) and brine. Drying (Na_2SO_4) and evaporation of the solvent gave the corresponding lactol. Boron trifluoride etherate (0.25 mL, 3.3 mmol) was added to a solution of the crude lactol and triethylsilane (0.5 mL, 3.1 mmol) in chloroform (10 mL). After the solution was stirred overnight, trifluoroacetic acid (1 mL, 17 mmol) was added and stirring continued for 4 h. The reaction mixture was worked up as described for **6a**. Hydroxy ethers **8a** and **8b** were purified by chromatography (eluent dichloromethane/methanol (98.5:1.5)).

(-)-4,5α-Epoxy-3-hydroxy-5β,7β-(methanoxymethano)-6-methoxy-*N*-methyl-6α,14α-ethenoisomorphinan (8a). Lactone reduction of **7a** (130 mg, 0.34 mmol) yielded **8a** (59 mg, 0.16 mmol, 46%): mp 179–181 °C dec; $[\alpha]^{25}_D$ –94° (*c* 0.50); ^1H NMR δ 6.56 (d, 1H, H-2, *J* = 8.2 Hz), 6.48 (d, 1H, H-1, *J* = 8.1 Hz), 6.02 (d, 1H, H-18, *J* = 8.9 Hz), 5.51 (d, 1H, H-19, *J* = 9.0 Hz), 5.3 (bs, 1H, 3-OH), 4.13 (d, 1H, 5β-CH_2, *J* = 11.0 Hz), 3.85 (dd, 1H, 7β-CH_2, *J* = 2.2, 11.0 Hz), 3.78 (d, 1H, 5β-CH_2, *J* = 11.0 Hz), 3.58 (dd, 1H, 7β-CH_2, *J* = 1.5, 11.0 Hz), 3.46 (s, 3H, 6-OMe), 3.24 (d, 1H, H-9, *J* = 7.1 Hz), 3.21 (d, 1H, H-10β, *J* = 19.4 Hz), 3.15 (ddd, 1H, H-15ax, *J* = 5.9, 13.0, 13.0 Hz), 2.57 (m, 1H, H-16eq), 2.54 (dd, 1H, H-8β, *J* = 3.8, 12.5 Hz), 2.45–2.37 (m, 2H, H-10α, H-16ax), 2.40 (s, 3H, *N*-Me), 1.96 (m, 1H, H-7α), 1.61 (ddd, 1H, H-15eq, *J* = 1.7, 3.8, 13.4 Hz), 1.58 (dd, 1H, H-8α, *J* = 11.4, 12.5 Hz); ^{13}C NMR δ 144.76, 137.93, 137.62, 136.23, 127.11, 126.87, 120.15, 115.97, 93.74, 78.55, 65.13, 63.16, 60.94, 51.95, 48.86, 45.38, 43.61,

43.08, 37.77, 29.49, 25.90, 22.61; HRMS (EI) *m/e* 367.1781 (calcd for $C_{22}H_{25}NO_4$ 367.1784); IR ν 3350 (OH) cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 72.40; H, 7.14; N, 3.67. Found: C, 72.46; H, 7.04; N, 3.52.

(−)-4,5α-Epoxy-3-hydroxy-5β,7β-(methanoxymethano)-6-methoxy-7α,*N*-dimethyl-6α,14α-ethenoisomorphinan (8b). Lactone reduction of **7b** (150 mg, 0.38 mmol) yielded **8b** (107 mg, 0.28 mmol, 74%): mp 238–242 °C dec; $[\alpha]^{25}_D$ −97° (*c* 0.61); ^1H NMR δ 6.57 (d, 1H, H-2, *J* = 8.1 Hz), 6.49 (d, 1H, H-1, *J* = 8.1 Hz), 5.99 (d, 1H, H-18, *J* = 9.0 Hz), 5.48 (d, 1H, H-19, *J* = 9.0 Hz), 4.10 (d, 1H, 5β-CH_2, *J* = 11.0 Hz), 3.81 (d, 1H, 5β-CH_2, *J* = 10.8 Hz), 3.69 (d, 1H, 7β-CH_2, *J* = 11.0 Hz), 3.61 (s, 3H, 6-OMe), 3.31 (d, 1H, 7β-CH_2, *J* = 10.9 Hz), 3.25–3.16 (m, 3H, H-9, H-10β, H-15ax), 2.72 (d, 1H, H-8β, *J* = 12.5 Hz), 2.59 (m, 1H, H-16eq), 2.45–2.37 (m, 2H, H-10α, H-16ax), 2.39 (s, 3H, *N*-Me), 1.60 (ddd, 1H, H-15eq, *J* = 1.5, 3.8, 13.2 Hz), 1.10 (d, 1H, H-8α, *J* = 12.5 Hz), 0.70 (s, 3H, 7α-Me); ^{13}C NMR δ 144.70, 137.74, 136.66, 136.05, 127.18, 125.65, 120.10, 115.63, 95.87, 80.55, 70.98, 63.24, 61.14, 55.04, 48.66, 45.36, 43.73, 43.67, 42.96, 37.92, 25.74, 22.63, 20.63; HRMS (EI) *m/e* 381.1931 (calcd for $C_{23}H_{27}NO_4$ 381.1940); IR ν 3400 (OH) cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 71.90; H, 6.86; N, 3.81. Found: C, 71.86; H, 7.05; N, 3.90.

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Supplementary Material Available: ^1H NMR spectra for compounds **4a**, **4b**, **5a**, and **5b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.