A viscous oil was obtained, 2.68 g, and the crude yield was determined via ^1H NMR (with an internal standard) to be >90%. The crude mixture was distilled in a Kugelrohr apparatus under vaccum: ^1H NMR ($CDCl_3$) δ 7.2 (s, 2 H), 6.95 (s, 1 H), 2.65 (q, 4 H), 1.28 (t, 6 H); MS (relative intensity) **M** + 2, 268 (2.32), M + 1, 267 (22.74), M, 266 (100). Anal. Calcd for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.34; H, 9.73.

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Registry No. 4, 108-67-8; **5a**, 934-74-7; **5b**, 2050-24-0; **5c**, 102-25-0; **6**, 556-96-7; **8**, 25570-02-9; **9**, 84980-70-1; **10**, 36919-84-3.

Selective O-Demethylation of 7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine

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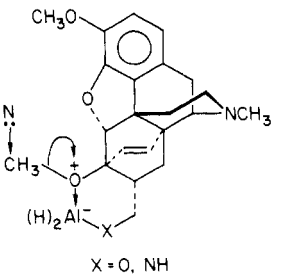
The remarkable opioid agonist/antagonist properties of several 7α-(1-hydroxy-1-methylalkyl)-6,14-*endo*-ethenotetrahydrooripavines[1] prompted us to synthesize 7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine (**6**). This key intermediate can be converted to a new series of potential analgesics by acylation of the 7α-aminomethyl function, can be used to prepare potential selective irreversible labels of opioid receptors,[2] and can be attached to an appropriate support to form an affinity chromatography matrix for opioid receptor purification.[3]

7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (**4**) was synthesized from thebaine (**1**) as shown in Scheme I. The Diels–Alder addition of acrolein in refluxing benzene gave the previously reported 7α-formyl derivative (**2**).[4] Reaction of **2** with hydroxylamine hydrochloride gave the aldoxime **3** that was treated with LAH in THF to yield the 7α-aminomethyl product (**4**). A previous attempt to prepared **4** by reduction of the corresponding 7α-carboxamide with LAH gave only rearrangement products.[5] The conversion of **4** to **6** by selective O-demethylation at the 3-position had been accomplished in 7α-tertiary alcohol analogues by reaction with potassium hydroxide in diethylene glycol at 200–210 °C.[1] Instead of these harsh conditions, we wished to find a more facile selective 3-O-demethylation procedure.

Treatment of codeine with boron tribromide in chloroform has been found to selectively demethylate the phenolic ether to give morphine in high yield.[6] This established the stability of the oxide bridge toward brief exposure to strongly acidic conditions but did not show what effect this treatment would have on the 6-methoxy group. Brief treatment of **4** with BBr_3 in chloroform at room temperature afforded **6** by selective 3-O-demethylation as shown by the loss of the NMR singlet at δ 3.83 that had been previously assigned to this group.[7] Recently, Jacobson and co-workers have reported the analogous selective 3-O-demethylation of 7α-amino-4,16-*endo*-ethenotetrahydrothebaine with boron tribromide in $CHCl_3$.[8] In order to determine whether a nitrogen atom in the 7α-function plays a vital role in these selective 3-O-demethylations, 7α-methyl-6,14-*endo*-ethenotetrahydrothebaine (**11**) was synthesized from **8** via the tosylate **10** as outlined in Scheme I. Treatment of **11** with boron tribromide gave multiple products. Thus, an amino group in the 7α-position of these compounds appears necessary for selective 3-O-demethylation. This suggests that the formation of a boron complex with the appropriate 7α-substituent blocks reaction at the 6-position.

Occasionally, the NMR spectrum of the crude 7α-aminomethyl product **4** formed by the LAH/THF reduction of **3** showed a loss in the intensity of the singlet (δ 3.56) that had been assigned to the 6-methoxy function.[7] This totally unexpected selective 6-O-demethylation was traced to the presence of residual chloroform that had not been removed during the workup of **3**. The addition of CCl_4, $CHCl_3$, or CH_2Cl_2 to a THF solution of **3** prior to reduction with LAH afforded **5** in good yields. Furthermore, **4** was 6-*O*-demethylated to **5** by treatment with LAH/THF/chlorinated methane. Therefore, the aldoxime appears to be reduced to an amine/aluminum complex before demethylation occurs.

In order to ascertain whether this surprising demethylation was unique to compounds containing a 7α-aminomethyl function, 7α-formyl-6,14-*endo*-ethenotetrahydrothebaine (**2**) was subjected to the same conditions. The aldehyde was reduced cleanly to the 7α-hydroxymethyl compound **8** in the absence of chlorinated methane, while the addition of chlorinated methane gave the diol **9**. Additionally, **8** was converted to **9** by inclusion of a chlorinated methane in the reduction medium. This suggests initial reduction of the aldehyde to the primary alcohol followed by 6-O-demethylation of the 7α-(hydroxymethyl)/aluminum complex. To prove that an electron-rich atom associated with the 7α-substitutent is required for demethylation, the 7α-methyl compound **11** was treated with LAH/THF/chlorinated methane. This reaction gave only starting material. Thus, a six-membered ring aluminum complex as shown below, or a variation of it, undoubtedly plays a major role is this unusual demethylation, but the role of the chlorinated methane is less clear. It may be necessary for the generation of the nucleophile required by a S_N2 demethylation process. No solid evidence concerning the fate of the 6-methyl group has been obtained.



X = O, NH

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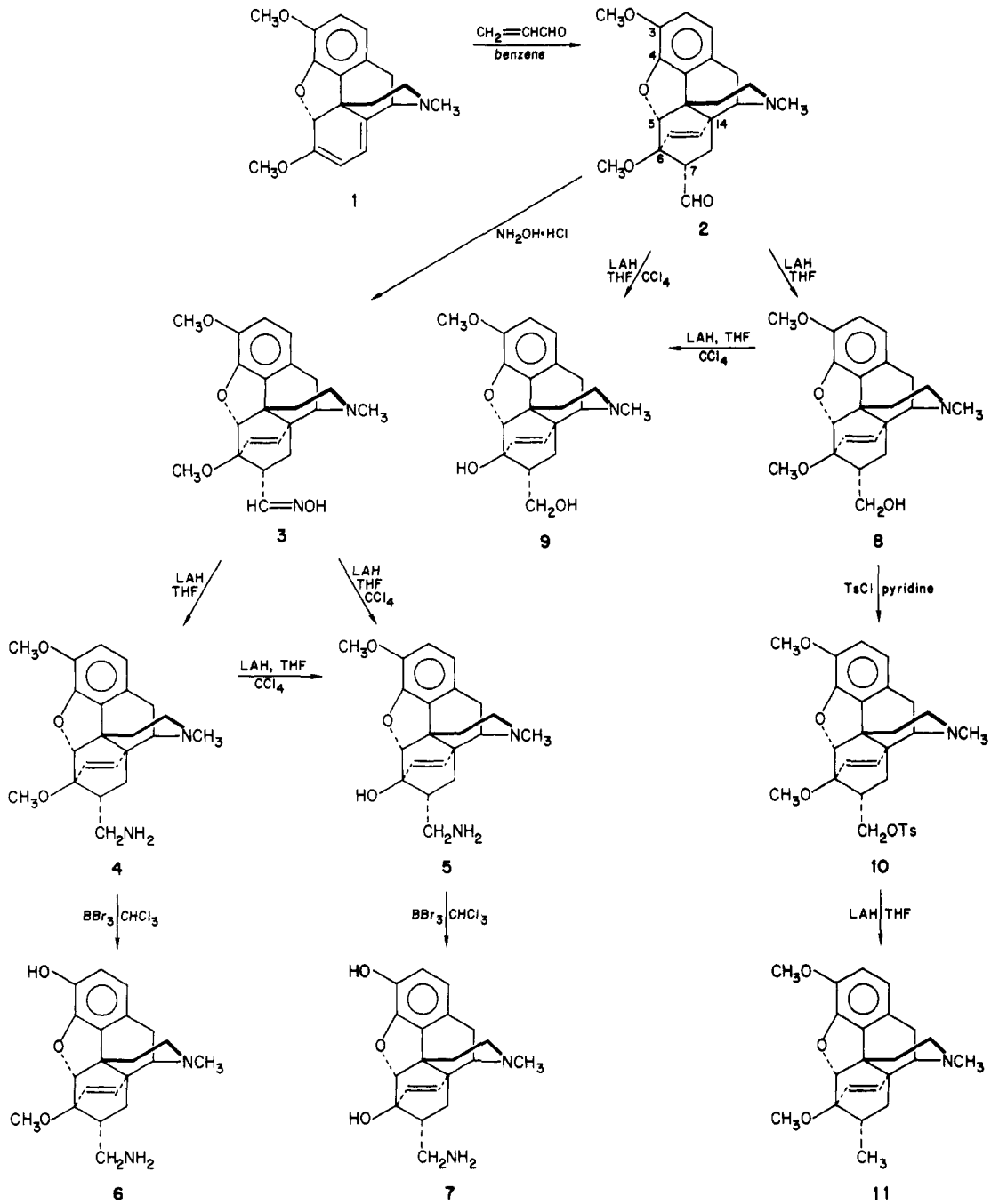
Scheme I



Because O-demethylation often has a profound effect on the pharmacological properties of opiates,[9] the previously unavailable 6-desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (**5**) and 6-desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine (**7**) that was prepared by reaction of **5** with BBr_3 and their derivatives may possess unique physiological profiles.

Experimental Section

Infrared spectra were recorded on a Pye Unicam 3-100 infrared spectrophotometer. ^1H NMR spectra were determined on an IBM NR/80 spectrometer. Elemental analyses were performed by Galbraith Laboratories. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. TLC was performed on Merck percoated silica gel 60 F-254 plates.

7α-Formyl-6,14-*endo*-ethenotetrahydrothebaine (2).[4] A mixture of thebaine (1, 5.0 g, 16.1 mmol), acrolein (15 mL, 0.22 mol), and benzene (100 mL) was refluxed for 16 h. The benzene and excess acrolein were removed under reduced pressure to yield a viscous, yellow oil. Crystallization from ethanol gave colorless needles (4.98 g, 84%): mp 118–120 °C; ^1H NMR ($CDCl_3$)[7] δ 3.83 (3 H, s, 3-OCH_3), 3.64 (3 H, s, 6-OCH_3), 2.39 (3 H, s, N-CH_3), 4.64 (1 H, s, 5α proton), 5.89 and 5.57 (2 H, ABq, J = 10 Hz, vinylic protons); IR (KBr) 1710, 2790 cm^{-1}.

7α-(Hydroximinomethyl)-6,14-*endo*-ethenotetrahydrothebaine (3). A mixture of **2** (4.00 g, 10.9 mmol), hydroxylamine hydrochloride (1.52 g, 21.9 mmol), ethanol (35 mL), and water (35 mL) was refluxed for 8 h. The solution was refrigerated for 15 h, after which the crystalline product was filtered, washed with cold ethanol, and air dried to yield 4.75 g (104%) of the hydrochloride salt. The salt was dissolved in 1 M NaOH (50 mL)/$CHCl_3$ (50 mL), and the pH of the aqueous phase was adjusted to 9.3 with NH_4Cl. The organic phase was separated, washed with 10% NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a viscous, yellow tinted oil. After

(9) *Quantitative Structure Activity Relationships of Analgesics, Narcotic Antatonists, and Hallucinogens*; Barnett, G.; Trsic, M.; Willette, R. E., Eds.; National Institute on Drug Abuse Research Monograph No. 22; U.S. Government Printing Office: Washington, DC, 1978.

addition of 25 mL of diethyl ether, a white precipitate formed. The powdery solid was filtered, washed with ether, and air dried to yield 3.63 g (87%): mp 178–183 °C; ^{1}H NMR ($CDCl_3$)[7] δ 3.82 (3 H, s, 3-OCH_3), 3.50–3.55 (3 H, m, 6-OCH_3), 2.43 (3 H, s, N-CH_3), 4.66 (1 H, s, 5α proton), 5.42 to 5.95 (2 H, m, vinylic protons).

7α-(Aminomethyl)-6,14-*endo* ethenotetrahydrothebaine Benzoic Acid Salt (4). A solution of **3** (500 mg, 1.31 mmol) in THF (6 mL, distilled from LAH) was added dropwise to a mixture of LAH (155 mg, 4.08 mmol) in THF (6 mL). The solution was refluxed for 20 h, then carefully quenched in 30 mL of 1 M H_2SO_4. The solution was made basic with 10 M NaOH and extracted 3 times with $CHCl_3$. The organic layers were combined, washed several times with 10% NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a viscous, yellow tinted oil. The oil was dissolved in ether (25 mL) and benzoic acid (0.32 g, 2.6 mmol), as a solution in 25 mL of ether, was added. The resultant white precipitate was filtered, washed with ether, and air dried to yield 493 mg of the benzoic acid salt (77%). The salt was recrystallized from methanol/ether: mp 208–214 °C; TLC (2-propyl alcohol/concentrated NH_4OH, 10:1), one product, R_f 0.42; ^{1}H NMR (D_2O)[7] δ 3.82 (3 H, s, 3-OCH_3), 3.56 (3 H, s, 6-OCH_3), 2.39 (3 H, s, N-CH_3); ^{1}H NMR ($CDCl_3$) free base, δ 4.84 (1 H, s, 5α proton), 5.60 and 5.74 (2 H, ABq, J = 8 Hz, vinylic protons). Anal. Calcd for $C_{29}H_{34}N_2O_5$: C, 70.99; H, 6.99; N, 5.71. Found: C, 70.80; H, 6.88; N, 5.51.

6-Desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (5). A solution of **3** (500 mg, 1.31 mmol) in THF (6 mL, distilled from LAH) and CCl_4 (0.5 mL, 5.2 mmol) was added dropwise to a mixture of LAH (740 mg, 19.5 mmol) in THF (6 mL). After the mixture was refluxed for 17 h, it was treated in the same manner as **4** to yield 334 mg of a white solid (74%). Recrystallization from ethanol gave colorless crystals: mp 216–218 °C; TLC (2-propyl alcohol/concentrated NH_4OH, 10:1), one product, R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 3.82 (3 H, s, 3-OCH_3), 2.37 (3 H, s, N-CH_3), 4.35 (1 H, s, 5α proton), 5.37 and 5.79 (2 H, ABq, J = 9 Hz, vinylic protons). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.91; H, 7.43; N, 7.91.

7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine Benzoic Acid Salt (6). A solution of the free base of **4** (751 mg, 2.04 mmol) in $CHCl_3$ (20 mL) was added to 1 M BBr_3 in $CHCl_3$ (20 mmol). The mixture was stirred at ambient temperature for 15 min, then quenched in 50 mL of ice cold dilute NH_4OH solution, and stirred at 0 °C for 30 min. The layers were separated, and the aqueous phase was extracted 3 times with 15-mL portions of $CHCl_3$. The $CHCl_3$ layers were combined, washed with 10% NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a light brown solid. The solid was dissolved in methanol (2 mL)/ether (20 mL), and a solution of benzoic acid (0.40 g, 3.3 mmol) in 20 mL of ether was added. The resultant precipitate was filtered, washed with ether, and air dried to yield 520 mg of a light brown solid. The salt was recrystallized from methanol–ether: mp 220–224 °C; ^{1}H NMR (D_2O)[7] δ 3.61 (3 H, s, 6-OCH_3), 2.41 (3 H, s, N-CH_3); 5.60 and 5.75 (2 H, ABq, J = 9 Hz, vinylic protons); ^{1}H NMR ($CDCl_3$) free base, δ 3.57 (3 H, s, 6-OCH_3), 2.36 (3 H, s, N-CH_3), 4.58 (1 H, s, 5α proton), 5.43 and 5.70 (2 H, ABq, J = 9 Hz, vinylic protons). Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.56; H, 6.77; N, 5.88. Found: C, 70.38; H, 6.89; N, 5.72.

6-Desmethyl-7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine (7). A solution of **5** (550 mg, 1.55 mmol) in $CHCl_3$ (2 mL) was added to 1 M BBr_3 in $CHCl_3$ (31 mmol). The mixture was stirred at ambient temperature for 2 h, then quenched in 20 mL of ice cold, dilute NH_4OH solution, and stirred at 0 °C for 15 min. The layers were separated, and the organic phase was extracted with 1 M NaOH (20 mL). The aqueous layers were combined and concentrated to 20 mL. The pH of the concentrate was adjusted to 9.9 with NaOH. The solution was saturated with NaCl and then extracted 5 times with 15-mL portions of $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 384 mg of a light brown solid (72%): ^{1}H NMR ($CDCl_3$) δ 2.35 (3 H, s, N-CH_3), 4.33 (1 H, s, 5α proton), 5.33 and 5.72 (2 H, ABq, J = 9 Hz, vinylic protons).

7α-(Hydroxymethyl)-6,14-*endo*-ethenotetrahydrothebaine (8).[10] A solution of **2** (500 mg, 1.36 mmol) in THF (6 mL) was added dropwise to a mixture of LAH (260 mg, 6.85 mmol) in THF (6 mL). The mixture was refluxed for 8.5 h and subjected to the standard workup to yield 403 mg of a colorless, viscous oil (80%): ^{1}H NMR ($CDCl_3$) δ 3.83 (3 H, s, 3-OCH_3), 3.71 (3 H, s, 6-OCH_3), 2.36 (3 H, s, N-CH_3), 4.57 (1 H, s, 5α proton), 5.49 and 5.91 (2 H, ABq, J = 9 Hz, vinylic protons).

6-Desmethyl-7α-(hydroxymethyl)-6,14-*endo*-ethenotetrahydrothebaine (9). A solution of **2** (500 mg, 1.36 mmol), CCl_4 (0.5 mL, 5.2 mmol), and 6 mL of THF was added dropwise to a mixture of LAH (775 mg, 20.4 mmol) in THF (6 mL). The mixture was refluxed for 8.5 h and subjected to the standard workup to yield a colorless, viscous oil which by TLC (dichloromethane/methanol, 20:1) showed two products: R_f 0.26 and 0.16. The two products were separated by chromatography on silica gel. The NMR of the faster moving product was identical with **8**, while the NMR of the less mobile product indicated demethylation at the 6 position: ^{1}H NMR ($CDCl_3$)[7] δ 3.83 (3 H, s, 3-OCH_3), 2.38 (3 H, s, N-CH_3), 4.35 (1 H, s, 5α proton), δ 5.40 and 5.70 (2 H, ABq, J = 10 Hz, vinylic protons).

7α-(((*p*-Toluenesulfonyl)oxy)methyl)-6,14-*endo*-ethenotetrahydrothebaine (10).[10] To a solution of compound **8** (1.07 g, 2.91 mmol) in pyridine (15 mL, dried over NaOH) at 0 °C was added *p*-toluenesulfonyl chloride (1.11 g, 5.82 mmol). After 96 h at 5 °C, the reaction mixture was added with stirring to 300 mL of ice water upon which a pink precipitate immediately formed. The solid was filtered, washed with 400 mL of water, and air dried to yield 1.47 g of a spongy, pink solid (96%). Recrystallization from ethanol gave pink tinted needles: mp 129–130 °C; NMR ($CDCl_3$)[7] δ 3.81 (3 H, s, 3-OCH_3), 3.48 (3 H, s, 6-OCH_3), 2.45 (3 H, s, Ts-CH_3), 2.36 (3 H, s, N-CH_3), 4.53 (1 H, s, 5α proton), 5.43 and 5.61 (2 H, ABq, J = 9 Hz, vinylic protons).

7α-Methyl-6,14-*endo*-ethenotetrahydrothebaine (11). Compound **10** (100 mg, 0.19 mmol) was added to LAH (75 mg, 2.0 mmol) in THF (5 mL, dried over 3-Å molecular sieves). The mixture was refluxed for 41 h and then subjected to the usual workup to yield 42 mg of a powdery brown solid (65%): ^{1}H NMR ($CDCl_3$)[7] δ 3.80 (3 H, s, 3-OCH_3), 3.49 (3 H, s, 6-OCH_3), 2.34 (3 H, s, N-CH_3), 0.79 (3 H, d, J = 7.2 Hz, 7α-methyl), 4.58 (1 H, s, 5α proton), 5.40 and 5.64 (2 H, ABq, J = 10 Hz, vinylic protons).

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(10) Intermediate previously reported by Bentley et al. (ref 5), but no details of synthesis or characterization were given.

Facile Stereoselective Reductions of Enediones and Cage Diketones Using $NaBH_4$–$CeCl_3$

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The use of sodium borohydride and of lithium aluminum hydride for the reduction of ketone and aldehyde carbonyl functionalities is a standard technique in synthetic organic chemistry.[1-3] Sodium borohydride is the more selective of the two reagents. Recently, Luche and co-workers have

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