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IMPROVED SYNTHESIS OF DIHYDROTHEBAINONE AND ITS 14β-EPIMER

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Abstract: An improved synthesis for the preparation of diastereomerically pure dihydrothebainone (**1**) from thebaine (**3**) is reported. A 41% overall yield was realized over three steps via direct transformation of dihydrothebaine-Φ (**4**) to thebainone-A (**6**) with 6N HCl.

Dihydrothebainone (**1**) and β-dihydrothebainone (**2**) have been shown to be important intermediates in the synthesis of opiates,[1] in particular codeine. The syntheses of both isomers of dihydrothebainone have been documented since 1920 and several groups since that time have investigated various aspects of the synthesis.[2] Recently in our labs we needed to prepare a significant amount of diastereomerically pure dihydrothebainone (**1**) from commercially available thebaine (**3**). Upon reviewing the literature, it became evident that no single reference was able to provide adequate experimental, analytical and spectroscopic

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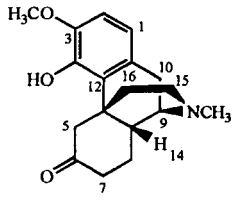
data for the preparation of **1** (or **2**) in reasonable yields. We now report our findings for the preparation of both isomers of dihydrothebainone (**1** and **2**) from **3** including the direct conversion of **4** to **6** in 51% yield avoiding intermediate **5**.



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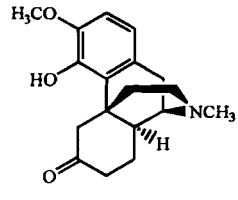

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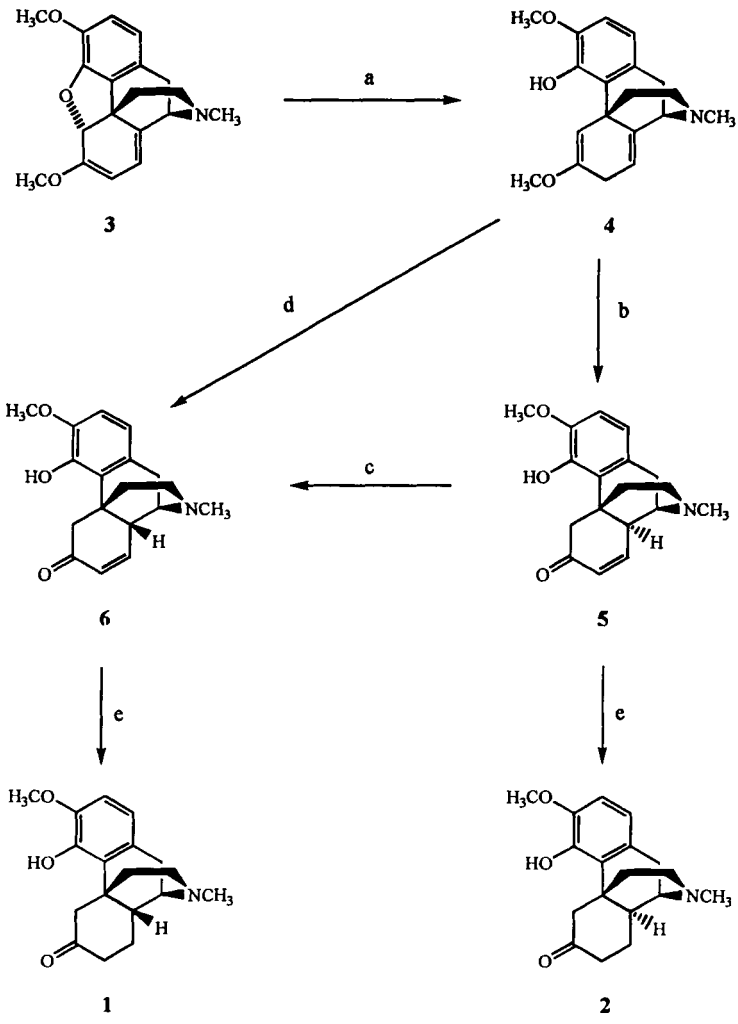
The synthesis of **1** and **2** is outlined in Scheme I. Treatment of commercially available thebaine (**3**) with sodium (2 eq) in liquid ammonia[2a] only resulted in the formation of dihydrothebaine-Φ^3 (**4**) in approximately 75% yield. We have found that the addition of a third equivalent of sodium is necessary to reproducibly and cleanly generate **4** in nearly quantitative yields. The crude material isolated from this reaction is sufficiently pure by TLC as well as ^{1}H and ^{13}C NMR spectroscopy to use without further purification, however, crystals of the product can be obtained from acetone/water.

Hydrolysis of **4** under acidic conditions is the key step in the preparation of diastereomerically pure (at the C-14 center) **1** or **2**. Initial observations reported by Small *et al.*[4] found the hydrolysis of **4** in 1N HCl to prepare β-thebainone-A (**5**) generated a "colored, varnish-like substance". However, hydrolysis utilizing $KHSO_4$ was more successful in generating the desired product. Contrary to Small *et al.*[4], Sawa *et al.*[5] later showed that treatment of **4** with 5% HCl (96 °C, 45 min)

Scheme I



(a) **4**: NH_3/Na (95%); (b) **5**: 5% HCl, 95 °C, 35 min (45%) or $KHSO_4$, 25 °C, 18 h (38%); (c) **6**: conc. HCl, 95 °C, 35 min (35%); (d) **6**: 6N HCl, 95 °C, 35 min (51%); (e) **1** or **2**: 1.5% PtO_2, EtOH, 1 atm H_2, 1.5 h (85%).

formed **5** in 53% yield. In our hands, treatment of **4** with 5% HCl (95 °C, 35 min) or $KHSO_4$ (25 °C, 24 h) gave **5** in 45% and 38%, respectively. A 56% yield was reported[5] for the isomerization of **5** to thebainone-A (**6**) by treatment with concentrated HCl (95 °C, 35 min). Upon repeating this procedure we have found that under these conditions the reaction mixture consists of several materials including the desired product and unreacted β-isomer. After chromatography a 35% yield of **6** was obtained with an overall yield of 20% for the previous two steps. Considering the cost of the thebaine starting material and the poor yield of the hydrolysis and isomerization steps, we re-examined these two steps in an effort to devise a reproducible, higher yielding synthesis of **6**. We have found that treatment of **4** with 6N HCl, under similar conditions as reported above (95 °C, 35 min), directly gave **6** in 52% overall yield after chromatography with less than 5% of the β-isomer detected as determined by both TLC and ^1H NMR analysis.[6]

Catalytic hydrogenation of enones **5** and **6** was effected by treatment with platinum oxide (1.5 wt. %) in ethanol at room temperature under 1 atm hydrogen to give the desired dihydrothebainones with only trace amounts of ketone reduction. The structures of both targets and all intermediate compounds have been characterized by ^1H, ^{13}C NMR and IR spectroscopies, mass spec, optical rotation and microanalysis and are consistent with literature values.

In summary, past preparations of diastereomerically pure dihydrothebainone (**1**) from thebaine (**3**) relied on the synthesis of the intermediate β- thebainone-A (**5**) which was subsequently isomerized to thebainone-A (**6**) in

low overall yields. We report herein our findings for the synthesis of **1** from **3** in 41% overall yield over three steps via the direct transformation of dihydrothebaine-Φ (**4**) to thebainone-A (**6**) with 6N HCl.

Experimental Section

Proton and carbon NMR spectra were obtained on a Bruker AC 300 spectrometer at 300 MHz and 75 MHz, respectively. Proton spectra were referenced to tetramethylsilane as an internal standard, and the carbon spectra were referenced to chloroform-*d* (purchased from Cambridge Isotopes). All ^{13}C spectra are proton decoupled. Mass spectra were obtained on a Shimadzu Mass Spectrometer model QP5000 interfaced with a Shimadzu GC 17A gas chromatograph. DI mass spectra were obtained starting at a temperature of 35 °C with a temperature gradient of 30 °C per min up to a maximum temperature of 300 °C. Chemical ionization mode used ultra high purity methane as the ionization gas. The IR spectrometer used was a single beam Perkin-Elmer Spectrum 1000 FT-IR. All spectra obtained were prepared in $CDCl_3$ at a concentration of 10 mg/mL. A solvent blank of $CDCl_3$ was subtracted from the sample using computerized FT techniques. All spectra were acquired with a total of 4 accumulations at a resolution of 4.00 cm^{-1}.

Elemental analyses were obtained from QTI, Inc. of Whitehouse, NJ. Optical rotation analyses were obtained on a Perkin-Elmer 243b polarimeter. Melting points were obtained on a Mel-Temp II apparatus and are uncorrected.

Reaction of Thebaine (3) with NH_3/Na. A 1 L three-neck round-bottomed flask fitted with a dry ice condenser and nitrogen bubbler was charged with thebaine (**3**,

50.0 g, 0.161 mol) and liquid ammonia (500 mL) while immersed in a dry ice/acetone bath (-78 °C). Sodium metal (11.12 g, 0.483 mol, 3.0 eq) was slowly added portionwise over a 45 min period. The intermediate rust-orange color was replaced with a permanent deep blue color and the reaction mixture was stirred for an additional 30 min. The dry ice bath was removed while maintaining the dry ice condenser and the reaction was allowed to stir for 1 h under nitrogen while reaching a final temperature of approximately -45 °C. Methanol (20 mL) was slowly added to quench any unreacted sodium to give a clear mustard yellow solution. The resulting solution was poured over crushed ice (250 mL) and solid carbon dioxide (50 g) was then added in three portions causing the desired product to precipitate. The product was extracted with ether (3 x 400 mL) and the combined organics were washed with saturated brine and dried over anhydrous sodium sulfate. Concentration under vacuum (40 °C) gave dihydrothebaine-Φ (**4**, 50.0 g, 0.160 mol, 99% yield) as a pale pink solid. The product was recrystallized from acetone/water to yield pure white needles: mp 145 - 147 °C; $[\alpha]^{23}{}_{D} = +27.8°$ (*c* = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 6.68 (d, J = 8.3 Hz, H_2), 6.59 (d, J = 8.3 Hz, H_1), 6.11 (s, H_5), 6.00 (s, *OH*), 5.62 (m, H_7), 3.85 (s, C_3-OCH_3), 3.63 (s, C_6-OCH_3), 3.43 (m, H_9), 3.18 (d, J = 17.4 Hz, H_{10e}), 2.85 (dd, J = 17.5, 5.6 Hz, H_{10a}), 2.74 (m, H_{14}), 2.55 (dm, J = 12.1 Hz, H_{16e}), 2.40 (s, NCH_3), 2.31 (dt, J = 12.3, 2.9, H_{16a}), 2.04 (dm, J = 11.9 Hz, H_{15e}), 1.85 (dt, J = 12.5, 4.7 Hz, H_{15a}); ^{13}C NMR {^{1}H} ($CDCl_3$) δ 152.5 (C_8), 145.2 (C_3), 143.4 (C_4), 138.0 (C_6), 131.1 (C_7), 128.9 (C_{11}), 118.9 (C_1), 115.3 (C_{12}), 108.8 (C_2), 61.7 (C_9), 56.4 (OCH_3), 54.1 (C_5), 48.4 (C_{16}), 42.4 (NCH_3), 40.7 (C_{14}), 39.5 (C_{13}), 31.4 (C_{15}), 28.6 (C_{10}); MS

(CI) *m/z* (relative intensity) 314 (100, MH^+), 298 (12); IR ($CDCl_3$) 3525.2 (w), 2936.8 (w), 2356.1 (vs), 1660.1 (w), 1482.4 (s),1439.9 (m), 1277.7 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.01; H, 7.32; N, 4.27. TLC analysis R_f = 0.26 (90/10 dichloromethane/methanol).

Hydrolysis of Dihydrothebaine-Φ (4) with 5% HCl. Dihydrothebaine-Φ (**4**, 25.0 g, 0.080 mol) was dissolved in 5% HCl (400 mL) and heated to 95 °C for 30 min after which time the reaction was cooled in an ice bath and quenched with concentrated ammonium hydroxide (200 mL) which precipitated the product as a white solid. Toluene (400 mL) was added and the aqueous layer extracted with additional toluene (2 x 300 mL). The combined organics were washed with saturated brine and dried over anhydrous sodium sulfate. The solution was concentrated under vacuum (40 °C) to give a purple colored foam (19.4 g). The crude material was chromatographed on a 16 x 12 cm column of silica gel, eluting the product using a gradient of 98:2 to 95:5 dichlormethane:methanol. All fractions containing the desired pure material were combined and concentrated under vacuum (40 °C) to give β-thebainone-A (**5**, 8.95 g, 0.030 mol, 37%). The product obtained was crystallized from acetonitrile/water (25/75) to give the desired product (8.0 g, 0.027 mol, 33%) as fine white needles: mp 99 - 100 °C; $[\alpha]^{23}{}_D$ = +114.4° (*c* = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 6.97 (dd, J = 8.1, 1.8 Hz, H_8), 6.74 (d, J = 8.2 Hz, H_2), 6.67 (d, J = 8.2 Hz, H_1), 6.19 (dd, J = 7.2, 2.7 Hz, H_7), 6.00 (s, *OH*), 4.12 (d, J = 17.6 Hz, H_{5e}), 3.88 (s, OCH_3), 3.21 (m, H_9), 3.15 (d, J = 18.0 Hz, H_{10e}), 2.87 (dd, J = 18.2, 5.7 Hz, H_{10a}), 2.83 (m, H_{14}), 2.61 (d, J =

17.5, H_{5a}), 2.42 (dd, J = 8.4, 3.1 Hz, H_{16e}), 2.37 (s, NCH_3), 2.20 - 2.05 (m, H_{16a}), 1.59 (d, J = 11.4 Hz, H_{15}); ^{13}C NMR {^{1}H} ($CDCl_3$) δ 200.5 (C_6), 154.2 (C_8), 145.0 (C_3), 144.1 (C_4), 130.8 (C_{11}), 129.9 (C_7), 127.5 (C_{12}), 118.9 (C_1), 109.3 (C_2), 58.0 (C_9), 56.4 (OCH_3), 48.2 (C_5), 47.3 (C_{16}), 43.5 (NCH_3), 43.1 (C_{14}), 38.4 (C_{13}), 28.8 (C_{15}), 27.5 (C_{10}); MS (CI) *m/z* (relative intensity) 300 (100, MH^+); 162 (12); IR ($CDCl_3$) 3525.2 (w), 2936.8 (w), 2240.0 (vw), 1669.4 (vs), 1484.1 (s),1440.1 (m), 1284.1 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3 - H_2O$: C, 67.78; H, 7.30; N, 4.41. Found: C, 67.78; H, 7.21; N, 4.22. TLC analysis R_f = 0.42 (90/10 dichloromethane/methanol).

Hydrolysis of β-Thebainone-A (5) with concentrated HCl to Prepare (6). β-Thebainone-A (21.0 g, 0.070 mol) was dissolved in concentrated HCl (110 mL) and heated at 95 °C for 35 min. The reaction was immediately cooled in an ice bath and water (100 mL) was then slowly added. The aqueous phase was basified with concentrated ammonium hydroxide (100 mL) which immediately formed a precipitate. The aqueous layer was extracted with dichloromethane (3 x 200 mL) and the combined organics were washed with saturated brine and dried with anhydrous sodium sulfate. The organics were concentrated under vacuum (40 °C) to give thebainone-A (19.9 g) as a brown foam. The crude material was chromatographed on a 16 x 12 cm column of silica gel, eluting the product using a gradient of 98:2 to 95:5 to 90:10 dichloromethane:methanol. All fractions containing the desired pure material were combined and concentrated under vacuum (35 °C) to give thebainone-A (**6**, 7.48 g, 0.025 mol, 36%): thebainone-A

was readily crystallized from acetonitrile to give pure white crystals: mp 128 - 130 °C; $[\alpha]^{23}_D$ = -45.9° (*c* = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 6.70 (d, J = 1.8 Hz, H_8), 6.65 (d, J = 8.3 Hz, H_2), 6.55 (d, J = 8.3 Hz, H_1), 6.02 (s, *OH*), 5.90 (dt, J = 9.9, 0.9 Hz, H_7), 4.28 (d, J = 15.6 Hz, H_{5e}), 3.81 (s, OCH_3), 3.23 (m, H_9), 3.02 (d, J = 18.0 Hz, H_{10e}), 2.90 (d, J = 3.0 Hz, H_{14}), 2.65 (dd, J = 18.0, 4.9 Hz, H_{10a}), 2.55 (dq, J = 11.8, 1.9 Hz, H_{16e}), 2.43 (s, NCH_3), 2.38 (d, J = 15.6, H_{5a}), 2.00 - 1.80 (m, H_{15}), 1.79 (dt, J = 8.3, 3.7 Hz, H_{16a}); ^{13}C NMR {^{1}H} ($CDCl_3$) δ 199.6 (C_6), 149.7 (C_8), 145.1 (C_3), 144.8 (C_4), 131.2 (C_7), 130.6 (C_{11}), 123.1 (C_{12}), 118.6 (C_1), 109.1 (C_2), 56.4 (C_9), 56.3 (OCH_3), 49.3 (C_5), 47.5 (C_{14}), 47.4 (C_{16}), 42.9 (NCH_3), 40.8 (C_{13}), 36.7 (C_{15}), 24.7 (C_{10}); MS (CI) *m/z* (relative intensity) 300 (100, MH^+); IR ($CDCl_3$) 3517.4 (w), 2929.0 (w), 2843.9 (w, sh), 1678.8 (vs), 1485.9 (s), 1436.1 (m), 1279.5 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3 \cdot 0.5\ H_2O$: C, 70.11; H, 7.19; N, 4.54. Found: C, 70.20; H, 7.23; N, 4.57. TLC analysis R_f = 0.20 (90/10 dichloromethane/methanol).

Hydrolysis of Dihydrothebaine-Φ (4) with 6N HCl to Prepare (6).

Dihydrothebaine-Φ (**4**, 750 mg, 2.39 mmol) was dissolved in 6N HCl (15 mL) and heated at 95 °C for 35 min. The reaction was immediately cooled in an ice bath and water (10 mL) was then slowly added. The aqueous phase was basified with concentrated ammonium hydroxide (20 mL) which immediately precipitated the product. The aqueous layer was extracted with dichloromethane (3 x 40 mL) and the combined organics were washed with saturated brine and dried with anhydrous

sodium sulfate. The organics were concentrated under vacuum (40 °C) to give crude thebainone-A (660 mg) as a tan foam. The crude material was chromatographed on a 2.5 x 15 cm column of silica gel, eluting the product using 98:2 dichloromethane:methanol. All fractions containing the desired pure material were combined and concentrated under vacuum (40 °C) to give thebainone-A (**6**, 370 mg, 1.24 mmol, 52%) and β-thebainone-A (**5**, 60 mg, 0.02 mmol, 8%). Spectral data for **5** and **6** were consistent with previously prepared samples.

Hydrogenation of Thebainone-A (6). A solution of thebainone-A (7.48 g, 0.025 mol) was prepared in ethanol (400 mL) to which was added platinum oxide (1.5 wt %). The resulting solution was purged with hydrogen for 5 minutes and then placed under 1 atm hydrogen for 1.5 h. The solution was filtered through Celite® to remove the catalyst and the solvent removed under vacuum (40 °C) to give crude dihydrothebainone (**1**, 7.1 g). The crude material was chromatographed on a 6.5 x 3.5 cm column of silica gel, eluting the product using 90:10 dichloromethane:methanol. All fractions containing the desired pure material were combined and concentrated under vacuum (40 °C) to give dihydrothebainone (**1**, 6.33 g, 0.021 mol, 84%): mp 116 - 118 °C; $[\alpha]^{23}_{D}$ = -65.4° (*c* = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 6.68 (d, J = 8.2 Hz, H_2), 6.60 (d, J = 8.2 Hz, H_1), 6.15 (s, *OH*), 4.25 (dd, J = 13.7, 2.2 Hz, H_{5e}), 3.83 (s, OCH_3), 3.06 (m, H_9), 2.99 (d, J = 18.5 Hz, H_{10e}), 2.70 (dd, J = 18.6, 6.1 Hz, H_{10a}), 2.51 (m, H_{16e}), 2.45 (s, NCH_3), 2.42 (m, H_{7e}), 2.28 (m, H_{7a}), 2.25 (d, J = 13.3 Hz, H_{5a}), 2.24 (m, H_{14}), 2.05 (m, H_{16a}),

2.01 - 1.56 (m, 4H, $H_{8\&15}$); ^{13}C NMR {^{1}H} ($CDCl_3$) δ 210.9 (C_6), 145.2 (C_3), 145.0 (C_4), 130.4 (C_{11}), 123.0 (C_{12}), 118.7 (C_1), 109.2 (C_2), 57.5 (OCH_3), 56.3 (C_9), 50.8 (C_5), 46.9 (C_{16}), 45.2 (C_{14}), 42.8 (NCH_3), 41.4 (C_7), 41.3 (C_{13}), 38.7 (C_{15}), 27.3 (C_8), 27.0 (C_{10}); MS (CI) *m/z* (relative intensity) 302 (100, MH^+); 164 (8); IR ($CDCl_3$) 3516.2 (w), 2932.4 (w), 1711.3 (m), 1483.9 (s), 1439.2 (s), 1281.6 (vs), 1056.7 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_3$ - 0.75 H_2O: C, 68.66; H, 7.84; N, 4.45. Found: C, 68.43; H, 7.51; N, 4.47. TLC analysis R_f = 0.13 (90/10 dichloromethane/methanol).

Hydrogenation of β-Thebainone-A (5). The procedure utilized above for the preparation of **1** was similarly used to prepare **2**: mp 82 - 84 °C; $[\alpha]^{23}_D$ = -47.4° (*c* = 1, ethanol); ^{1}H NMR ($CDCl_3$) δ 6.72 (d, J = 8.3 Hz, H_2), 6.64 (d, J = 8.4 Hz, H_1), 6.11 (s, *OH*), 3.95 (d, J = 14.7 Hz, H_{5e}), 3.85 (s, OCH_3), 3.15 (d, J = 18.5 Hz, H_{10e}), 2.95 (m, H_9), 2.79 (dd, J = 17.8, 5.5 Hz, H_{10a}), 2.51 (m, H_{16e}), 2.42 (m, H_{7e}), 2.31 (s, NCH_3), 2.28 (m, H_{7a}), 2.25 (d, J = 13.3 Hz, H_{5a}), 2.14 (m, H_{14}), 2.01 (m, H_{16a}), 1.95 - 1.56 (m, 4H, $H_{8\&15}$); ^{13}C NMR {^{1}H} ($CDCl_3$) δ 211.9 (C_6), 144.9 (C_4), 143.4 (C_3), 130.7 (C_{11}), 127.8 (C_{12}), 118.4 (C_1), 109.3 (C_2), 57.3 (C_9), 56.1 (OCH_3), 50.5 (C_5), 46.9 (C_{16}), 46.4 (C_{14}), 42.5 (NCH_3), 41.1 (C_7), 39.9 (C_{13}), 30.3 (C_{15}), 26.3 (C_8), 28.1 (C_{10}); MS (CI) *m/z* (relative intensity) 302 (100, MH^+); IR ($CDCl_3$) 3522.8 (w), 2938.6 (w), 1703.6 (m), 1483.9 (s),1439.8 (s), 1280.6 (vs), 1060.8 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_3$ - 0.12 H_2O: C, 71.21; H, 7.71; N, 4.65. Found: C, 70.91; H, 7.77; N, 5.01. TLC analysis R_f = 0.40 (90/10 dichloromethane/methanol).

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