A Facile Synthesis and Structural Verification of Etorphine and Dihydroetorphine from Codeine

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In this study, an improved process for the synthesis of etorphine and dihydroetorphine from codeine with an overall yield of 2.7% and 1.5% respectively is described. The structure of 19-propylthevinol **7** was verfied by X-ray structure analysis. This result is promising for synthesizing various morphine-based drugs.

Keywords: Etorphine; Dihydroetorphine; Codeine; Morphine; Thebaine.

1. INTRODUCTION

Etorphine is a synthetic analogue of morphine and 1500-3000 times more powerful.[1] Etorphine can be produced from thebaine is most often used to immobilize elephants and other large mammals. Etorphine is only available legally for veterinary use and is strictly governed by law. In humans, etorphine is a morphine-like drug with a high abuse potential.[2] A close relative, dihydroetorphine (DHE) is one of the strongest known analgesic opioid alkaloids and is 1000-12000 times more potent than morphine.[3] Clinical reports in China show that sublingual doses of DHE, 20-180 μg, cause a strong analgesic effect with only mild side effects.

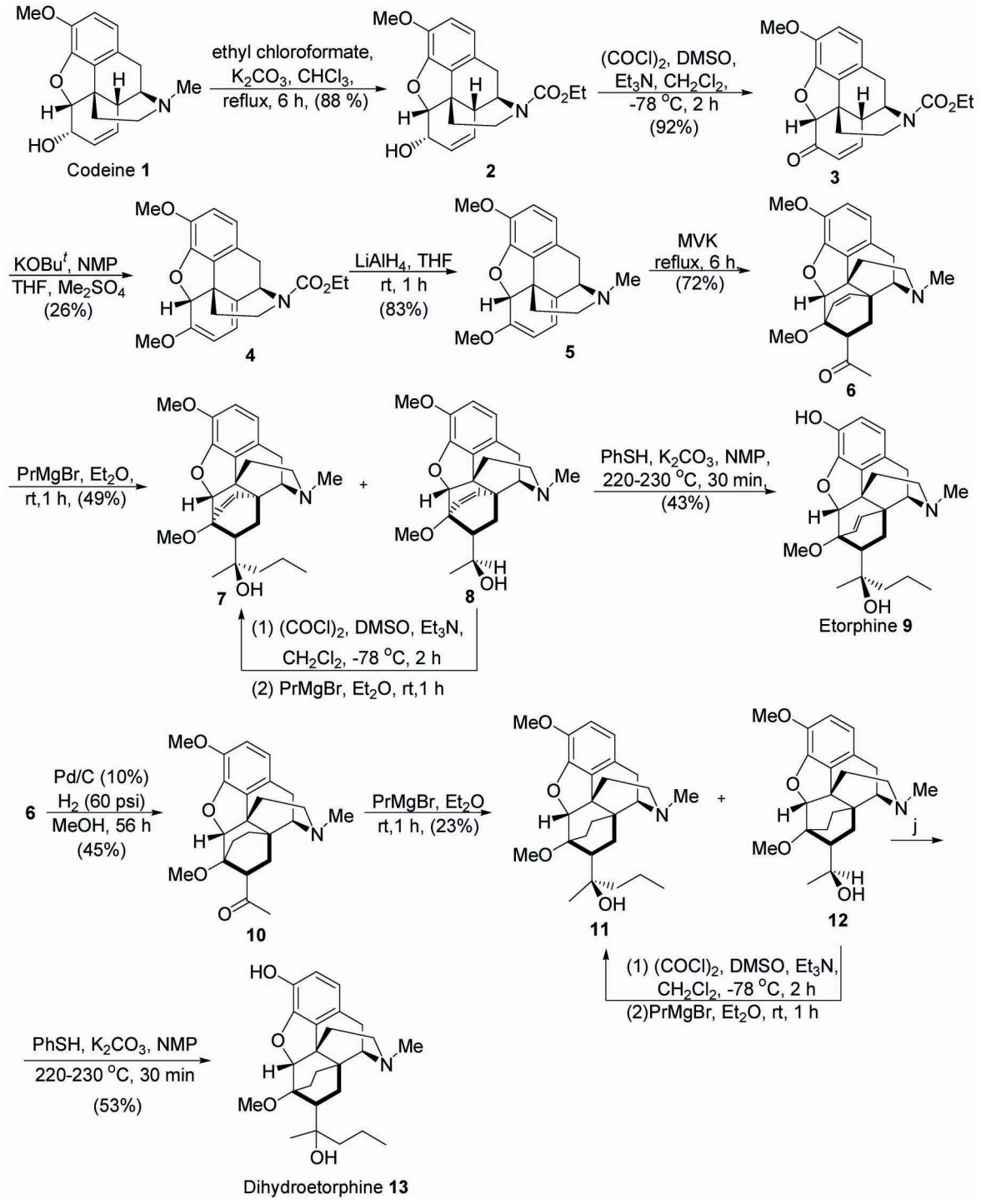
On the illicit drug market the increased availability of the analgesic opioid alkaloids has become a serious social problem.[4-7] Morphine derivatives are increasingly abused psychoactive drugs and well documented in literature. The widespread consumption and the continuing exploration of designer drug's homologous series has resulted in an increasing number of reports regarding abuse and intoxication. Therefore in 2008, we synthesized the deuterium-labelled etorphine and dihydroetorphine started from codeine and acrylonitrile as the internal standard in the screening of drug abuser, but the yield of several steps were poor.[8]

The synthetic study of morphine-thebaine group has been reported by Bentley and Hardy in 1967,[9-14] and by Rapoport in 1975.[15] We modified the Rapoport's and Bentley's procedures to use a facile and promising method to prepare etorphine and dihydroetorphine eventhough some steps in low yields. The synthetic method presented in this work is promising for synthesizing a wide variety of morphine-based drugs.

2. RESULTS AND DISCUSSION

The improved process adopted for the synthesis of etorphine and dihydroetorphine free base is shown in Scheme I. The codeine free base **1** was employed as the starting material and formed from codeine phosphate supplied by the National Bureau of Controlled Drugs, Taiwan. The oxidation of codeine to α,β-unsaturated ketone has been reported,[16-23] but the yields were unsatisfied. Therefore, *N*-carboethoxylation of the tertiary amine of codeine **1** using ethylchloroformate gave *N*-carboethoxycodeine **2** in good yield (88%) by using ethyl chloroformate and potassium carbonate in chloroform.[24] Swern oxidation of *N*-carboethoxycodeine **2** formed the α,β-unsaturated ketone **3** in high yield (92%). The carbonyl group of **3** was converted to the vinyl methyl ether by reaction with potassium *tert*-butoxide and dimethyl sulfate to give **4**. If the tertiary amine was not converted to the carbamate, a low yield product will obtained.[25] Following reduction of ethyl carbamate by $LiAlH_4$ produced thebaine **5**, which was conducted a Diels-Alder reaction with methyl vinyl ketone to yield an adduct **6**.[9,26-31] Compound **6** reacted with Grignard reagent (PrMgBr) to give alcohol **7**.[10,14,26,28,32] An efficient protocol reported in the literature for demethylation of **7** to etorphine **9** in good purity using KOPh[33] was therefore attempted. Dihydroetorphine **13** was prepared through the reduction of **6**,[10,26,31,34-35] and then follow the same proce-

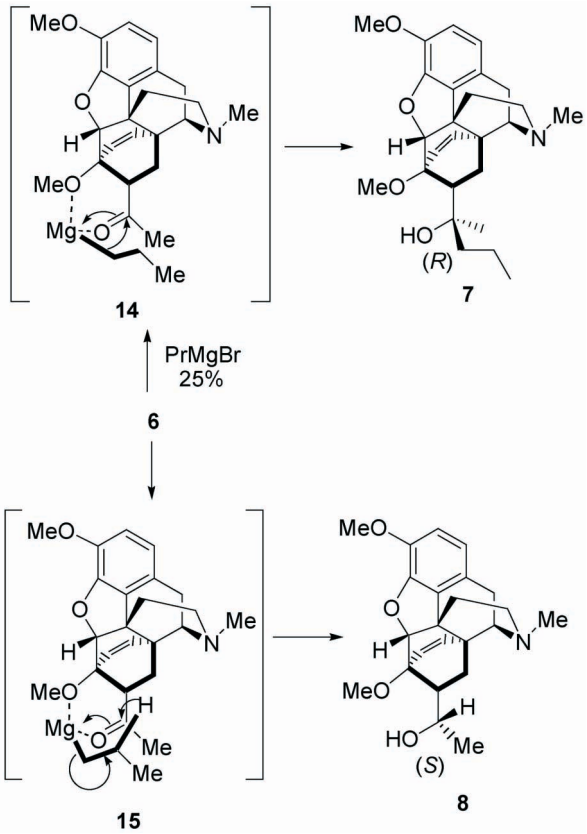
Scheme I Synthesis of etorphine and dihydroetorphine



dures as the preparation of **9**.

The Grignard reaction of compound **6** produced stereospecific product **7** in 25% yield, and the stereospecific reduction product **8** in 50% yield, due to the stereohiderence of compound **6** (Scheme II).[24] Compound **8** was converted to **6** by Swern oxidation, and repeated the Grignard reaction to obtain compound **6**. In intermediate **14**, the propyl group added to carbonyl group through the less hin-

Scheme **II** Grignard reaction of compound **6**



dered *Re*-face, and give the compound **7**. The absolute structure was determined by an analysis of the X-ray crystal structure (Fig. 1).[32] The intermediate **14** has a four member ring transition state that is a disfavor pathway to give a minor product. In the intermediate **15**, the β-hydrogen was added to carbonyl group through a six member ring transition state to give a reduction product **8**.

3. CONCLUSION

In this study, we established the facile preparation of etorphine and dihydroetorphine from codeine with 2.7% and 1.5% overall yields respectively. The structure of 19-propylthevinol **7** was verified by X-ray structure analysis. This work is promising for synthesizing a wide variety of morphine-based drugs.

4. EXPERIMENTAL

4.1. General Chemical Procedures

All reactions were carried out in anhydrous solvents. Tetrhydrofuran and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. ^{1}H NMR spectra were acquired at 400 (indicated in each case), and ^{13}C NMR were acquired at 100.6 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were determined on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on a JASCO FT/IR 410 spectrometer. Flash column chromatography was performed using MN silica gel 60 (70-230 mesh) purchased from Macherey-Nagel.

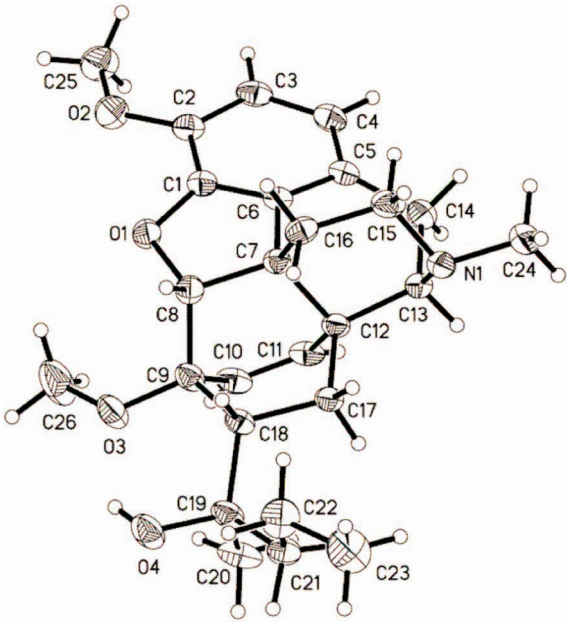


Fig. 1. X-ray structure of **7**. (The Cambridge Crystallographic Data Centre deposition number CCDC 750865).

4.2. Preparation of etorphine 9

Synthesis of *N*-carboethoxycodeine 2

A mixture of codeine **1** (3.00 g, 10.03 mmol), ethyl chloroformate (5.75 mL, 60.18 mmol) and anhydrous K_2CO_3 (1.59 g, 11.54 mmol) in $CHCl_3$ (300 mL) was refluxed for 6 h. After completion of the reaction (TLC, 6 h), the reaction mass was cooled to room temperature and filtered through celite bed. It was washed with more of $CHCl_3$ (10 mL) and the combined filtrate was concentrated under reduced pressure to yield a white solid (**2**) (3.80 g, 89%) which was directly used in the next reaction without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.68-6.66 (d, J = 8.2 Hz, 1H), 6.57-6.55 (d, J = 8.2 Hz, 1H), 5.74

(b, 1H), 5.28 (b, 1H), 4.94-4.80 (m, 2H), 4.17-3.98 (m, 4H), 3.82 (s, 3H), 3.03-2.52 (m, 5H), 1.93-1.89 (m, 2H), 1.30-1.24 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 155.4, 146.4, 142.5, 134.5, 129.9, 127.0, 125.8, 120.0, 113.2, 91.2, 66.1, 61.6, 56.3, 50.4, 43.4, 39.7, 37.4, 35.5, 29.6, 14.8. MS *m/z*: 357.2 (M^+, 75), 241.1 (74), 209.0 (100), 181.1 (34), 115.1 (17), 102.0 (21), 88.1 (22.6).

Synthesis of *N*-carboethoxycodeinone 3

To solution of DMSO (1.67 mL, 23.54 mmol) in CH_2Cl_2 (90 mL) at -78 ºC was added dropwise a solution of oxalyl chloride (1.1 mL, 12.84 mmol) in CH_2Cl_2 (8 mL) over period of 40 min. It was further stirred at the same temperature for 10 min. A solution of codeine (3.00 g, 10.03 mmol) in CH_2Cl_2 (20 mL) was then added over a period of 45 min at -78 ºC, and stirred for 2 h. Triethylamine (7.44 mL, 53.50 mmol) was added dropwise to reaction mass at -78 ºC and allowed to warm up to the room temperature. Water (100 mL) was added to the reaction mass and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were washed with brine, separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford *N*-carboethoxycodeinone (**3**) as white foam (2.75 g, 92%) which was used directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.71-6.89 (d, *J* = 8.2 Hz, 1H), 6.65-6.60 (m, 2H), 6.12-6.10 (d, *J* = 10.2 Hz, 1H), 5.03-5.02 (b, 1H), 4.68 (s, 1H), 4.20-3.98 (m, 3H), 3.84 (m, 2H), 1.33-1.23 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 194.1, 155.6, 147.2, 145.0, 142.9, 133.3, 127.9, 124.8, 120.5, 115.1, 87.8, 61.8, 56.8, 50.3, 43.6, 40.4, 38.1, 33.6, 29.4, 14.8. MS *m/z*: 355.1 (M^+, 100), 250.9 (33), 240.0 (93), 225.1 (66), 210.9 (28), 115.0 (25), 78.1 (40).

Synthesis of *N*-carboethoxythebaine 4

Potassium *tert*-butoxide (3.50 g, 31.26 mmol) was added to a mixture of *N*-methylpyrrolidone (14 mL) and THF (14 mL) in a 100 mL single neck flask and stirred at room temperature for 30 min to form a pale yellow solution. The flask was cooled to 0 ºC in an ice bath and *N*-carboethoxycodeinone (**3**) (3.70 g, 10.42 mmol) in THF (19 mL) was added dropwise over a period of 30 min and allowed to warm to room temperature. It was further stirred for 2 h and then again cooled to 0 ºC. Dimethyl sulfate (2.77 mL, 29.18 mmol) was added dropwise to the reaction mixture over 15 min and allowed to stir at room temperature for 2 h. After the completion of the reaction, water (25 mL) was added and extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (50 mL), brine (30 mL), and separated. It was then dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford crude product as foam. After short path column purification, the crude material was dissolved in minimum amount of ether and slowly added to hexanes at room temperature. It was ultrasonicated to get a clear solution and stored in deep freezer to get white solid which was filtered and washed with cold hexanes to get pure product (**4**) (1.00 g, 26%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.69-6.67 (d, *J* = 8.2 Hz, 1H), 6.60-6.58 (d, *J* = 8.2 Hz, 1H), 5.63-5.58 (m, 1H), 5.29 (s, 2H), 5.22-5.02 (m, 2H), 4.16-4.02 (m, 3H), 3.84 (s, 3H), 3.59 (s, 3H), 3.26-2.99 (m, 3H), 2.11-2.03 (m, 1H), 1.80-1.74 (m, 1H), 1.29-1.27 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 155.2, 153.0, 144.9, 143.1, 132.5, 130.1, 126.6, 119.6, 113.1, 112.0, 95.8, 88.8, 61.5, 56.4, 55.1, 52.6, 52.2, 46.3, 38.1, 37.3, 14.7. MS *m/z*: 369.2 (M^+, 100), 341.1 (13), 326.1 (14), 294.1 (29), 264.0 (24), 241.0 (24).

Synthesis of thebaine 5

$LiAlH_4$ (200 mg, 5.28 mmol) was weighed in an oven dried 50 mL single neck flask under argon atmosphere. It was cooled to 0 ºC and dry THF (10 mL) was added dropwise and stirred for 10 minutes. A solution of *N*-carbethoxythebaine (**4**) (1.50 g, 4.06 mmol) in THF (15 mL) was added dropwise over a period of 15 min and the resulting slurry was warmed to room temperature and stirred for 1 h. After the completion of the reaction, the flask was cooled to 0 ºC, and carefully quenched with aqueous THF. It was then filtered over celite, washed with EtOAc (3 × 15 mL) and concentrated under reduced pressure to afford a crude product (**5**) (1.00 g, 83%) which was used for further reaction without any purification. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.66-6.64 (d, *J* = 8.2 Hz, 1H), 6.60-6.58 (d, *J* = 8.2 Hz, 1H), 5.56-5.54 (d, *J* = 6.4 Hz, 1H), 5.29 (s, 2H), 5.04-5.02 (d, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 3.61-3.59 (d, *J* = 8.6 Hz, 1H), 3.59 (s, 3H), 3.33-3.28 (d, *J* = 18.0 Hz, 1H), 2.83-2.59 (m, 3H), 2.45 (s, 3H), 2.23-2.16 (m, 1H), 1.70 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 152.5, 144.8, 142.8, 133.3, 132.4, 127.7, 119.2, 112.8, 111.6, 95.9, 89.2, 60.8, 56.4, 55.0, 46.1, 42.5, 37.1, 29.5. MS *m/z*: 311.1 (M^+, 100), 296.1 (76), 254.0 (11), 242.0 (14), 139.3 (9).

Synthesis of thevinone 6

The crude thebaine (**5**) (1.00 g, 3.19 mmol) was refluxed in methyl vinyl ketone (30 mL) for 3 h and the reaction was monitored by TLC. At the end of 3 h, more methyl vinyl ketone (10 mL) was added and further refluxed overnight. The flask was cooled to room temperature and the solvents were pumped off under reduced pres-

sure to afford a crude product which was purified by column chromatography on basic alumina to afford the title compound as a pure white solid (**6**) (1.00 g, 2.62 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.62-6.60 (d, J = 8.2 Hz, 1H), 6.53-6.51 (d, J = 8.1 Hz, 1H), 5.57-5.55 (d, J = 8.8 Hz, 1H), 5.56 (d, J = 1.2 Hz, 1H), 3.80 (s, 3H), 3.58 (s, 3H), 3.23-3.17 (m, 1H), 2.91-2.90 (t, J = 2.4 Hz, 1H), 2.49-2.38 (m, 2H), 2.34 (s, 3H), 2.23-2.19 (m, 2H), 2.17 (s, 3H), 1.96-1.81 (m, 1H), 1.38-1.31 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 209.3, 148.2, 142.0, 136.1, 134.2, 128.1, 126.2, 119.6, 113.6, 95.4, 81.4, 60.1, 56.8, 53.7, 50.8, 47.7, 45.7, 43.7, 43.4, 33.6, 30.7, 30.1, 22.6.

Synthesis of 19-propylthevinol 7

Bromopropane (1.5 mL, 16.79 mmol) was slowly added to a suspension mixture of magnesium (0.26 g, 10.5 mmole) in anhydrous ditheyl ether (25 mL) under an argon atmosphere, and was then refluxed for 30 min. After cooling to room temperature, a solution of compound thevinone (1.00 g, 2.6 mmol) in benzene (25 mL) was added dropwise, and the contents were stirred at room temperature for 1 h. The reaction mixture was poured into a saturated ammonium chloride solution, and then basified using a saturated sodium bicarbonate solution. The resulting basic solution was extracted with diethyl ether (3 × 15 mL) and the combined extracts were dried over anhydrous magnesium sulfate. Concentration of the solvents under reduced pressure afforded crude product which was purified by flash column chromatography using basic Al_2O_3 as the stationary phase and ethyl acetate/hexanes as a mobile phase to yield pure 19-propylthevinol **7** (0.55 g, 49%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.63-6.61 (d, J = 8.1 Hz, 1H), 6.52-6.50 (d, J = 8.2 Hz, 1H), 5.98-5.96 (d, J = 9.0 Hz, 1H), 5.45-5.43 (d, J = 8.9 Hz, 1H), 4.90 (s, 1H), 4.55 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.24-3.19 (d, J = 18.6 Hz, 1H), 3.12-3.11 (d, J = 6.5 Hz, 1H), 2.84-2.79 (m, 1H), 2.40-2.34 (m, 1H), 2.37 (s, 3H), 1.99-1.84 (m, 1H), 1.55-1.15 (m, 3H), 0.96 (s, 3H), 0.92-0.88 (t, J = 7.2 Hz, 1H), 0.80-0.77 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 148.1, 141.7, 135.2, 134.3, 128.4, 125.2, 119.2, 113.7, 98.9, 84.1, 74.9, 60.0, 56.8, 55.2, 47.1, 46.7, 45.5, 43.6, 43.3, 42.8, 33.6, 30.6, 24.1, 22.2, 15.9, 14.8. IR (KBr): 3492, 2936, 2837, 2798, 1625, 1598, 1498, 781, 754 cm^{-1}. MS *m/z*: 425.3 (M^+, 59), 338.2 (100), 311.1 (33), 296.1 (19), 250.2 (47), 229.1 (31), 189.1 (22), 164.1 (44). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{26}H_{35}NO_4$, 425.2566; found, 425.2568.

Synthesis of etorphine 9

In a magnetically stirred mixture of the compound **7** (212 mg, 0.5 mmol), PhSH (51.2 μL, 0.5 mmol) and K_2CO_3 (34.5 mg, 0.25 mmol) in dry NMP (1.0 mL) was heated 220-230 ºC under Ar for 30 minutes. The cold reaction mixture was neutralized with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous magnesium sulfate. Concentration of the solvents under reduced pressure afforded crude product which was purified by flash column chromatography using neutral silica gel as the stationary phase and ethyl acetate-hexane as a mobile phase to yield etorphine (89 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.61-6.59 (d, J = 8.1 Hz, 1H), 6.48-6.46 (d, J = 8.0 Hz, 1H), 5.95-5.93 (d, J = 8.8 Hz, 1H), 5.44-5.41 (d, J = 8.9 Hz, 1H), 4.88 (s, 1H), 4.57 (s, 1H), 3.74 (s, 3H), 3.22-3.17 (d, J = 18.5 Hz, 1H), 3.12-3.11 (d, J = 6.5 Hz, 1H), 2.82-2.75 (m, 1H), 2.39 (s, 3H), 2.50-2.30 (m, 1H), 2.00-1.80 (m, 2H), 1.60-1.10 (m, 2H), 1.99-1.84 (m, 1H), 1.55-1.15 (m, 3H), 0.90 (s, 3H), 0.82-0.77 (t, J = 8.1 Hz, 1H), 0.82-0.77 (m, 1H). IR (KBr): 3433, 3242, 2955, 2930, 1716, 1635, 1606, 1455, 1159, 785 cm^{-1}. MS *m/z*: 411.2 (M^+, 100), 324.2 (83), 297.1 (26), 250.2 (18), 215.1 (96), 164.1 (50), 121.1 (22). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{25}H_{33}NO_4$, 411.2410; found, 411.2415.

4.3. Preparatipn of dihydroetorphine 13

Synthesis of 1-(4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethano-morphinan-7-yl)-ethanone 10

A 10% of Pd/C (60 mg, 10 wt%) was weighed in a Parr glass vessel and carefully wet with methanol. A solution of **6** (0.10 g, 0.26 mmol) in methanol (5 mL) was added and then flushed three times with hydrogen gas. The vessel was finally charged with hydrogen gas (60 psi) and shaken mechanically for 56 h. After completion of the reaction (TLC, 12 h), the reaction mixture was filtered through a pad of celite and washed with excess methanol (2 × 5 mL). The filtrate was concentrated under reduced pressure to afford a crude product which was purified by using basic aluminum oxide as the stationary phase and ethyl acetate-hexanes as mobile phase (1:4) to give **10** (45 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.71-6.69 (d, J = 8.1 Hz, 1H), 6.59-6.57 (d, J = 8.1 Hz, 1H), 4.47 (s, 1H), 3.86 (s, 3H), 3.43 (s, 3H), 3.11-3.01 (m, 2H), 2.72-2.65 (m, 2H), 2.44-2.32 (m, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.05-1.97 (m, 1H), 1.78-1.62 (m, 2H), 1.55-1.45 (m, 2H), 1.33-1.21 (m, 1H), 0.78-0.64 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 210.8, 146.7, 141.8, 132.4, 128.7, 119.2, 113.9, 94.6, 61.3,

56.7, 52.2, 49.5, 45.8, 45.2, 43.5, 35.6, 35.2, 33.8, 30.4, 28.6, 22.0, 17.5. MS *m/z*: 383.2 (M^+, 100), 368.2 (27), 340.2 (49), 320.1 (30), 277.1 (25), 176.1 (27).

Synthesis of 2-(4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethano-morphinan-7-yl)-pentan-2-ol 11

Bromopropane (0.15 mL, 1.68 mmol) was slowly added to a suspension mixture of magnesium (25 mg, 1.05 mmol) in anhydrous ditheyl ether (25 mL) under an argon atmosphere, and was then refluxed for 30 min. After cooling to room temperature, a solution of compound **10** (0.10 g, 0.26 mmol) in dirthyl ether (3 mL) was added dropwise, and the contents were stirred at room temperature for 1 h. The reaction mixture was poured into a saturated ammonium chloride solution (5 mL), and then basified using a saturated sodium bicarbonate solution. The resulting basic solution was extracted with diethyl ether (3 × 5 mL) and the combined extracts were dried over anhydrous magnesium sulfate. Concentration of the solvents under reduced pressure afforded crude product which was purified by flash column chromatography using basic Al_2O_3 as the stationary phase and ethyl acetate/hexane (1:9) as a mobile phase to yield pure 19-propylthevinol (0.55 g, 49%) as a white solid **11** (25 mg , 23%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.67 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.69 (s, 1H), 4.40 (s, 1H), 3.88 (s, 3H), 3.53 (s, 3H), 3.14 (d, *J* = 18.2 Hz, 1H), 2.75 (t, *J* = 6.2 Hz, 1H), 2.65 (d, *J* = 6.2 Hz, 1H), 2.42 (m, 1H), 2.31 (s, 3H), 2.25 (d, *J* = 18.5 Hz, 1H), 2.04 (m, 1H), 1.91 (t, *J* = 8.0 Hz, 1H), 1.77-1.66 (m, 8H), 1.25 (m, 1H), 1.14 (s, 3H), 1.05 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 147.0, 141.6, 132.5, 128.8, 119.0, 114.3, 97.0, 80.3, 61.3, 56.9, 52.6, 49.1, 46.1, 45.1, 43.5, 39.0, 36.0, 35.5, 32.0, 29.8, 25.5, 21.9, 18.0, 16.9. IR (KBr): 3508, 3498, 2967, 2953, 1490, 1447, 1257, 820 cm^{-1}. MS *m/z*: 427 (M^+, 74), 409 (45), 394 (100), 340 (57), 326 (2), 310 (24), 256 (13), 176 (10), 87 (14). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{26}H_{37}NO_4$, 427.2723; found, 427.2714.

Synthesis of dihydroetorphine 13

In a magnetically stirred mixture of the compound **11** (400 mg, 0.94 mmol), PhSH (96.0 μL, 0.94 mmol) and K_2CO_3 (65 mg, 0.47 mmol) in dry NMP (1.0 mL) was heated 220-230 ºC under Ar for 30 minutes. The cold reaction mixture was neutralized with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous magnesium sulfate. Concentration of the solvents under reduced pressure afforded crude product which was purified by flash column chromatography using neutral silica gel as the stationary phase and ethyl acetate-hexane as a mobile phase to yield dihydroetorphine **13** (205 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.70 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.40 (s, 1H), 3.97 (s, 1H), 3.84 (s, 1H), 3.51 (s, 3H), 3.12 (d, *J* = 18.5 Hz, 1H), 2.80-2.69 (m, 2H), 2.21-2.10 (m, 5H), 2.05-1.90 (m, 1H), 1.90 (t, *J* = 10.0 Hz, 1H), 1.77-1.56 (m, 8H), 1.38-0.95 (m, 6H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 145.6, 137.6, 131.9, 119.5, 116.7, 97.3, 80.3, 61.4, 52.7, 48.9, 46.4, 45.2, 43.4, 38.7, 35.2, 33.9, 31.9, 29.7, 25.4, 21.6, 16.9, 16.0, 15.0. IR (KBr): 3429, 3233, 2958, 2928, 1719, 1636, 1456, 1296, 1157, 952 cm^{-1}. MS *m/z*: 413 (M^+, 57), 395 (100), 380 (81), 338 (38), 326 (4), 312 (9), 242 (8), 176 (8), 73 (18). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{25}H_{35}NO_4$, 413.2566; found, 413.2728.

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