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Research Article

Synthesis of deuterium-labelled etorphine and dihydroetorphine

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Abstract: The synthesis of deuterium-labelled [$^2H_6$]-etorphine and [$^2H_6$]-dihydroetorphine from codeine is described. The isotopically labelled compounds are used as internal standards in gas chromatography–mass spectrometry (GC–MS) assays. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: deuterium labelled; etorphine; dihydroetorphine

Introduction

The increased availability of the analgesic opioid alkaloids (morphine derivatives) on the illicit drug market has become a serious societal problem.[1–4] Morphine derivatives are increasingly abused psychoactive drugs and well documented in literature. The continuing designer drug exploration of homologous series and their widespread consumption has resulted in an increasing number of reports regarding abuse and intoxication.

Etorphine, invented in 1963 by a research group at McFarlan–Smith and Co., is a synthetic cousin of morphine and 1500–3000 times more powerful.[5] Etorphine, which 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. Studies by Carr indicated that in humans, etorphine is a morphine-like drug with a high abuse potential.[6] As a close relative, dihydroetorphine (DHE) has been employed as opiate painkiller for human usage in China.

DHE is one of the strongest known analgesic opioid alkaloids and is 1000–12 000 times more potent than morphine.[7] Onset of the analgesic effect of DHE in rodents is rapid, 5–15 min following parenteral administration. The duration of action is short; the analgesic effect disappears within 120 min after administration. Clinical reports in China show that sublingual doses of DHE, 20–180 μg, cause a strong analgesic effect with only mild side effects, such as dizziness, somnolence, nausea, vomiting, constipation, and shortness of breath.

Stable isotope-labelled internal standards for controlled drugs analyses in Taiwan are extremely difficult to acquire. Numerous researchers are interested in the preparation of deuterium-labelled control drugs as internal standards for gas chromatography–mass spectrometry (GC–MS) analysis.[8–11] This work describes the synthetic routes to, and characterization of, [$^2H_6$]-etorphine and [$^2H_6$]-DHE, and presents their characteristic analytical data. The synthetic method presented is promising for synthesizing a wide variety of morphine-based drugs. These compounds have never been investigated in literature.

Results and Discussion

Although etorphine and DHE have been readily prepared via several synthetic routes,[5,12–16] preparing [$^2H_6$]-etorphine and [$^2H_6$]-DHE has not been described previously. Scheme 1 presents the general synthetic scheme for preparing [$^2H_6$]-etorphine and [$^2H_6$]-DHE. Deuterium-labelled codeine methyl ether (**2**) was prepared by treating codeine with sodium hydride in tetrahydrofuran, in which the codeine sodium salt was methylated with [$^2H_3$]-methyl iodide to give 4,5α-epoxy-3,6α-[$^2H_3$]-dimethoxy-17-methylmorphin-7-ene (**2**)

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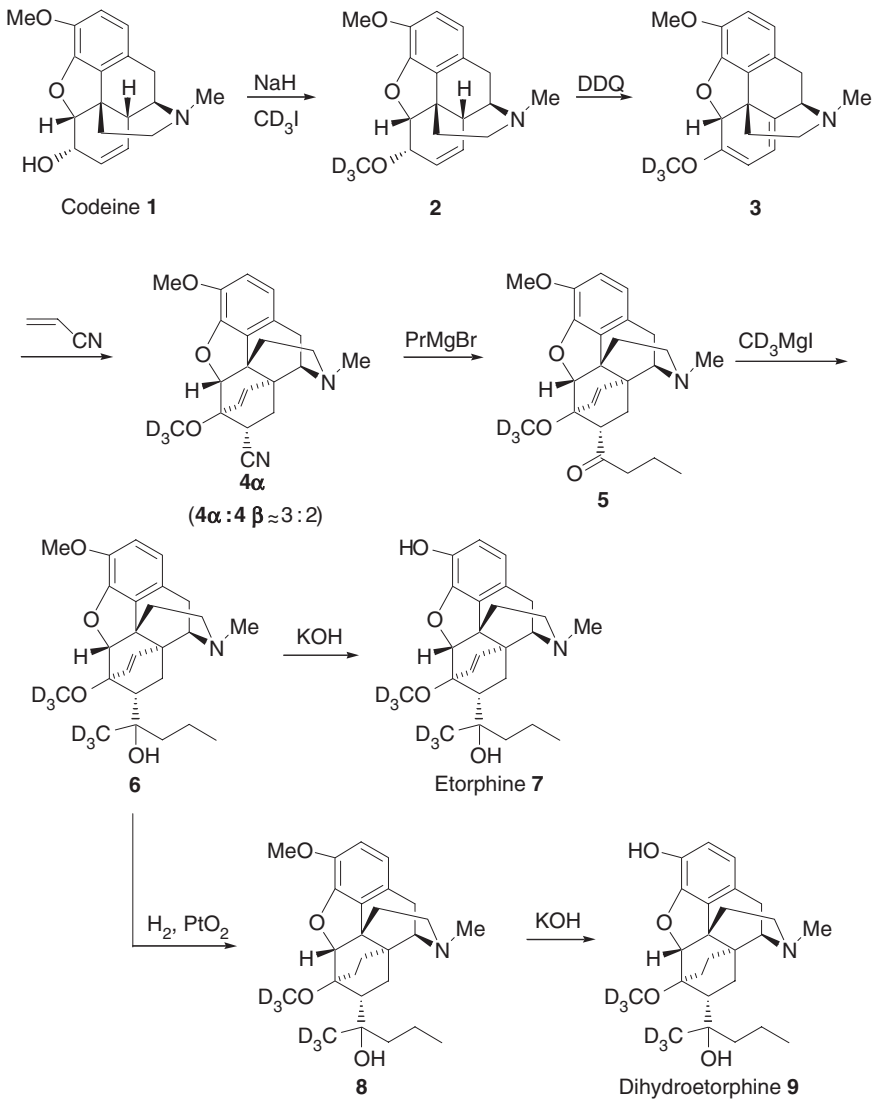

Scheme 1

in a 98% yield. 4,5α-Epoxy-3,6-dimethoxy-17-methyl-morphina-6,8(14)-diene (**3**) was successfully prepared by oxidizing compound **2** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The crude product **3** was utilized for the next step in the Diels–Alder reaction without further purification. The Diels–Alder reaction was applied to prepare 4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-ethenomorphinane-7-carbonitrile (**4**) by treating compound **3** and acrylonitrile under reflux.[17] Purification then gave **4α** (9%), **4β** (6%), and recovered compound **2** (26%). Compound **4α** was used to prepare 1-(4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-etheno-morphinan-7α-yl)-[$^2H_3$]-butan-1-one (**5**) in a 23% yield by a reaction of compound **4α** with *n*-propylmagnesium bromide. Compound **5** reacted with [$^2H_3$]-methylmagnesium iodide to produce 2-(4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-ethenomorphinan-7α-yl)-1,1,1-[$^2H_3$]-pentan-2-ol (**6**) in a 97% yield.[16] The diastereomers of compound **6** were not determined. A solution of compound **6** and potassium hydroxide in diethylene glycol was stirred at 210°C for 2.5 h to give [$^2H_6$]-etorphine (**7**) in a 33% yield. Compound **6** was reduced by hydrogenation in methanol in the presence of PtO_2 under a hydrogen atmosphere (60 psi) for 30 days using hydrogenation apparatus (Parr) to yield 2-(4,5-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6,14-ethanomorphinan-7-yl)-1,1,1-[$^2H_3$]-pentan-2-ol (**8**) in a 15% yield. This reaction progressed very slowly, and compound **8** must be purified by preparative thin-layer chromatography. Compound **8** was treated with potassium hydroxide to produce [$^2H_6$]-HDE (**9**) in a 20% yield.

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Experimental

General

^{1}H NMR spectra were acquired at 400 MHz (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 obtained on a Micromass Platform II mass spectrometer at 70 eV. High-resolution mass spectra (HRMS) were obtained on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on a JASCO FT/IR 410 spectrometer. All reactions were performed in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium–benzophenone in argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. Flash column chromatography was performed using MN basic aluminium oxide, which was purchased from Macherey-Nagel.

All reactions were initially optimized using unlabelled compounds.

Synthesis of 4,5α-epoxy-3,6α-[$^2H_3$]-dimethoxy-17-methyl-morphin-7-ene (2). An excess of sodium hydride (3.80 g, 95.0 mmol, 60% dispersion in mineral oil) was added to a solution of codeine (7.12 g, 23.8 mmol) and [$^2H_3$]-iodomethane (4.14 g, 28.6 mmol) in tetrahydrofuran (250 mL) and stirred in an argon atmosphere at 0°C for 2 h. The reaction mixture was poured into a saturated ammonium chloride solution (200 mL), and basified by adding a saturated sodium bicarbonate solution. The resulting aqueous mixture was extracted with ethyl acetate, and the extracts were dried over anhydrous sodium sulfate. Evaporation then gave a crude solid that was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (3:7) as the mobile phase, giving compound **2** as a white crystalline solid (7.35 g, 23.3 mmol). Yield: 98%. M.p. 133.4–134.4°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.63 (d, $J = 8.1$ Hz, 1H), 6.51 (d, $J = 8.2$ Hz, 1H), 5.73 (d, $J = 9.8$ Hz, 1H), 5.33 (d, $J = 9.8$ Hz, 1H), 4.99 (d, $J = 5.9$ Hz, 1H), 3.82 (s, 3H), 3.79–3.76 (m, 1H), 3.36–3.34 (m, 1H), 3.06 (d, $J = 18.6$ Hz, 1H), 2.66 (s, 1H), 2.56 (m, 1H), 2.45 (s, 3H), 2.43–2.41 (m, 1H), 2.33–2.27 (d, $J = 18.6$ Hz, 1H), 2.12–2.03 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 147.6, 142.1, 130.8, 130.5, 128.7, 126.9, 118.7, 113.4, 89.4, 76.0, 58.9, 56.4, 46.5, 43.4, 43.1, 41.3, 36.0, 20.5. IR (KBr): 3026, 2978, 2791, 2238, 2194, 2052, 1831, 1603, 1495, 788, 669 cm^{-1}. MS *m/z*: 316 (M^+, 100), 301 (15), 282 (58), 229 (46), 141 (55). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{20}D_3NO_3$, 316.1863; found, 316.1867.

Synthesis of 4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-ethenomorphinane-7-carbonitrile (4). A mixture of codeine methyl ether **2** (1.54 g, 4.9 mmol) and DDQ (1.20 g, 5.3 mmol) in benzene (50 mL) was refluxed under an argon atmosphere for 26 h. The solvent was removed via evaporation under reduced pressure. The resulting brown solid was suspended in sodium bicarbonate solution, and extracted with chloroform. The extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated to give a crude product **3**. Crude product **3** was boiled under reflux with acrylonitrile (50 mL) for 3 h. The excess acrylonitrile was removed by evaporation under reduced pressure to give a crude product that was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (1:9, 3:7) as the mobile phase, giving **4-α** (161 mg, 0.44 mmol, 9%), **4-β** (103 mg, 0.28 mmol, 6%) and recovered compound **2** (414 g, 1.3 mmol, 26%). **4-α**: M.p. 163–164°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.64 (d, $J = 8.1$ Hz, 1H), 6.56 (d, $J = 8.2$ Hz, 1H), 5.98 (d, $J = 8.8$ Hz, 1H), 5.65 (d, $J = 8.8$ Hz, 1H), 4.50 (s, 1H), 3.82 (s, 3H), 3.24–3.19 (m, 3H), 2.90–2.83 (m, 1H), 2.58–2.42 (m, 1H), 2.40 (s, 3H), 1.95–1.80 (m, 2H), 1.56 (d, $J = 13.1$ Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 147.5, 142.1, 137.5, 133.5, 127.7, 126.4, 120.2, 119.8, 113.8, 92.9, 79.4, 59.8, 56.6, 46.9, 45.3, 43.4, 42.5, 36.6, 33.1, 32.2, 31.7, 21.2. IR (KBr): 2938, 2855, 2766, 2235, 2073, 1636, 1601, 1503, 776 cm^{-1}. MS *m/z*: 367 (M^+, 100), 349 (28), 314 (15), 297 (6), 258 (10), 216 (17), 192 (64), 165 (10), 115 (7). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{22}H_{21}D_3N_2O_3$, 367.1972; found, 367.1967. **4-β**: M.p. 180.4–181.5°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.64 (d, $J = 8.0$ Hz, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 5.94 (d, $J = 8.9$ Hz, 1H), 5.56 (d, $J = 8.8$ Hz, 1H), 3.82 (s, 3H), 3.21–3.07 (m, 3H), 2.81 (d, $J = 11.7$ Hz, 1H), 2.46–2.30 (m, 6H), 1.92 (s, d, $J = 13.4$ Hz, 1H), 1.56 (t, $J = 11.7$ Hz, 1H). IR (KBr): 2936, 2788, 2232, 2069, 1628, 1598, 1500, 795, 288 cm^{-1}. MS *m/z*: 367 (M^+, 100), 349 (37), 314 (18), 297 (8), 258 (26), 216 (28), 192 (37), 165 (23), 115 (14). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{22}H_{21}D_3N_2O_3$, 367.1972; found, 367.1972.

Synthesis of 1-(4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-ethenomorphinan-7α-yl)-butan-1-one (5). Bromopropane (0.5 mL, 2.7 mmol) was slowly added to a suspension mixture of magnesium (53 mg, 2.2 mmol) in anhydrous diethyl ether (25 mL) under an argon atmosphere, and was then refluxed for 30 min. To the refluxing mixture was added a solution of compound **4α** (161 mg, 0.4 mmol) in anhydrous diethyl ether (5 mL), and refluxed

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for an additional 5 h. Following cooling, the reaction mixture was poured into a saturated ammonium chloride solution, and then extracted using diethyl ether. The extracts were concentrated under reduced pressure to give a residue; a 1 N HCl solution (20 mL) was added to this residue. The resulting aqueous solution was stirred at 60°C for 30 min. Following cooling, the solution was basified by adding 2 N NaOH, and then extracted with diethyl ether. The extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to yield a crude product. The crude product was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (1:19, 1:9) as the mobile phase and gave compound **5** (43 mg, 0.1 mmol). Yield: 23%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.63 (d, $J = 8.0$ Hz, 1H), 6.54 (d, $J = 8.1$ Hz, 1H), 5.93 (d, $J = 8.8$ Hz, 1H), 5.56 (d, $J = 8.8$ Hz, 1H), 4.54 (s, 1H), 3.81 (s, 3H), 3.24–3.17 (m, 2H), 2.90–2.81 (m, 2H), 2.54–2.32 (m, 8H), 2.08–1.85 (m, 2H), 1.57–1.25 (m, 4H), 0.88–0.84 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 210.8, 148.1, 141.8, 135.5, 134.1, 128.2, 125.8, 119.3, 113.7, 95.9, 81.5, 60.0, 56.7, 50.0, 47.4, 45.6, 43.5, 43.2, 33.4, 30.2, 29.6, 22.4, 16.8, 14.0. IR (KBr): 2924, 2840, 2971, 2224, 2073, 1705, 1627, 1595, 1500, 957, 774 cm^{-1}. MS *m/z*: 412 (M^+, 100), 394 (40), 341 (74), 315 (20), 237 (94), 165 (71), 124 (33), 71 (51). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{25}H_{28}D_3NO_4$, 412.2438; found, 412.2439.

Synthesis of 2-(4,5α-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6α,14α-ethenomorphinan-7α-yl)-1,1,1-[$^2H_3$]-pentan-2-ol (6). The [$^2H_3$]-iodomethane (0.2 mL, 3.2 mmol) was slowly added to a suspension mixture of magnesium (57 mg, 2.0 mmol) in anhydrous diethyl ether (10 mL) under an argon atmosphere, and was then refluxed for 30 min to prepare Grignard reagent [$^2H_3$]–MeMgI. To the [$^2H_3$]-MeMgI solution, a solution of compound **5** (198 mg, 0.5 mmol) in anhydrous diethyl ether (10 mL) was added, and stirred at room temperature for 15 h. The reaction mixture was poured into a saturated ammonium chloride solution, and the solution was then basified using a saturated sodium bicarbonate solution. The resulting basic solution was extracted with diethyl ether. The extracts were dried over anhydrous magnesium sulfate, and the solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (1:9, 1:5) as the mobile phase to yield compound **6** (203 mg, 0.5 mmol). The diastereomers of compound **6** were not identified. Yield : 97%. M.p. 149.5–150.7°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.63 (d, $J = 8.0$ Hz, 1H), 6.52 (d, $J = 8.0$ Hz, 1H), 5.95 (d, $J = 8.7$ Hz, 1H), 5.43 (d, $J = 8.8$ Hz, 1H), 4.55 (s, 1H), 4.48 (s, 1H), 3.80 (s, 3H), 3.23 (d, $J = 18.5$ Hz, 1H), 3.12 (d, $J = 6.2$ Hz, 1H), 2.85–2.80 (t, $J = 11.0$ Hz, 1H), 2.51–2.49 (m, 1H), 2.37 (s, 3H), 2.01–1.99 (m, 2H), 1.84 (d, $J = 11.5$ Hz, 1H), 1.60 (s, 1H), 1.53–1.46 (m, 1H), 1.29–1.16 (m, 5H), 0.88–0.84 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 148.1, 141.7, 135.0, 128.4, 125.2, 119.1, 114.0, 98.9, 84.0, 75.3, 60.0, 56.9, 49.9, 47.1, 45.5, 43.5, 42.8, 39.4, 33.6, 30.7, 29.6, 22.2, 16.8, 15.1. IR (KBr): 3498, 2925, 2869, 2801, 2225, 2073, 1626, 1599, 1498, 793, 709 cm^{-1}. MS *m/z*: 431 (M^+, 73), 413 (13), 388 (15), 341 (100), 324 (8), 315 (55), 256 (60), 167 (61), 124 (23), 57 (22). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{26}H_{29}D_6NO_4$, 431.2937; found, 431.2941.

Synthesis of 4,5-epoxy-19-(1-hydroxy-1-[$^2H_3$]-methyl-butyl)-6-[$^2H_3$]-methoxy-17-methyl-6,14-ethanomorphin-7-en-3-ol (7) (Etorphine). A mixture of potassium hydroxide (100 mg) in diethylene glycol (1 mL) was heated at 70°C until it becomes clear. To this clear solution, compound **6** (28 mg, 0.06 mmol) was added and stirred at 210°C for 2.5 h. After cooling to room temperature, a saturated solution of ammonium chloride solution (5 mL) was added, and extracted using chloroform. The extracts were dried over anhydrous magnesium sulfate, and the solvent was then removed under reduced pressure to generate a crude product. The crude product was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (1:9, 1:3) as the mobile phase to give compound **7** (10 mg, 0.02 mmol). Yield : 33%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.60 (d, $J = 7.8$ Hz, 1H), 6.47 (d, $J = 8.2$ Hz, 1H), 5.92 (d, $J = 8.9$ Hz, 1H), 5.42 (d, $J = 8.8$ Hz, 1H), 4.55 (s, 1H), 4.53 (s, 1H), 3.22–3.13 (m, 2H), 2.80 (t, $J = 6.2$ Hz, 1H), 2.51 (m, 1H), 2.37 (s, 3H), 2.00–1.96 (m, 3H), 1.85 (d, $J = 12.0$ Hz, 1H), 1.52–1.45 (m, 1H), 1.29–1.20 (m, 5H), 0.85 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 146.7, 137.5, 135.1, 134.0, 127.7, 124.8, 119.7, 116.2, 99.3, 84.0, 75.5, 60.1, 49.8, 47.5, 45.6, 43.5, 42.9, 39.3, 33.4, 30.7, 29.7, 22.6, 16.6, 15.0. IR (KBr): 3439, 2953, 2928, 2235, 2073, 1719, 1606, 1454, 1103, 957, 795 cm^{-1}. MS *m/z*: 417 (M^+, 100), 399 (5), 327 (56), 301 (23), 256 (15), 167 (24), 90 (12). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{25}H_{27}D_6NO_4$, 417.2780; found, 417.2780.

Synthesis of 2-(4,5-epoxy-3,6-[$^2H_3$]-dimethoxy-17-methyl-6,14-ethanomorphinan-7-yl)-1,1,1-[$^2H_3$]-pentan-2-ol (8). A mixture of compound **6** (142 mg, 0.33 mmol) and PtO_2 (30 mg) in methanol (30 mL) under hydrogen atmosphere (60 psi) was reacted for 30 days using a hydrogenation apparatus (Parr). The reaction mixture was filtered through celite to remove catalyst

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PtO_2. The filtrate was concentrated, and purified by preparative thin-layer chromatography (TLC) using ethyl acetate as the mobile phase to yield compound **8** (30 mg, 0.07 mmol). Yield: 15%. ^{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), 3.14 (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), 1.05 (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, 49.0, 46.1, 45.2, 39.0, 36.0, 35.5, 32.0, 29.8, 21.9, 18.0, 16.5, 14.0. IR (KBr): 3513, 3493, 2963, 2933, 2260, 2068, 1599, 1496, 1441, 1255, 798, 557 cm^{-1}. MS *m/z*: 433 (M^+, 97), 415 (41), 397 (100), 343 (36), 313 (11), 90 (9), 48 (10). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{26}H_{31}D_6NO_4$, 433.3093; found, 433.3100.

Synthesis of 4,5α-epoxy-7α-(1-hydroxy-1-[$^2H_3$]-methylbutyl)-6-[$^2H_3$]-methoxy-17-methyl-6α-, 14α-ethanomorphinan-3-ol (9) (Dihydroetorphine). A mixture of potassium hydroxide (100 mg) in diethylene glycol (1 mL) was heated at 70°C until it becomes clear. To this clear solution, compound **8** (9.6 mg, 0.02 mmol) was added and stirred at 210°C for 2 h. After cooling to room temperature, a saturated ammonium chloride solution (5 mL) was added, and extracted using chloroform. The extracts were dried over anhydrous magnesium sulfate, and the solvent was then removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography using basic aluminium oxide as the stationary phase and ethyl acetate–hexane (1:9, 1:3) as the mobile phase to give compound **9** (1.6 mg, 0.004 mmol). Yield : 20%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.71 (d, $J = 7.5$ Hz, 1H), 6.54 (d, $J = 7.1$ Hz, 1H), 4.64 (s, 1H), 4.42 (s, 1H), 3.12 (d, $J = 18.2$ 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, 3H), 0.91 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 145.5, 137.2, 132.0, 128.4, 119.5, 116.7, 97.5, 80.3, 61.3, 48.9, 46.6, 45.2, 43.4, 39.0, 36.1, 35.4, 31.9, 29.7, 21.9, 18.0, 16.9, 15.0. IR (KBr): 3459, 2958, 2928, 2874, 2230, 2077, 1636, 1458, 1242, 1139, 952 cm^{-1}. MS *m/z*: 419 (M^+, 54), 401 (100), 383 (68), 376 (22), 245 (3), 167 (5), 90 (9). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{25}H_{29}D_6NO_4$, 419.2937; found, 419.2944.

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