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ORIGINAL PAPER

# A facile and improved synthesis of desomorphine and its deuterium-labeled analogue

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**Abstract** This work describes a convenient and improved process for the synthesis of desomorphine from codeine. The proposed method affords the highly pure opiate without the aid of chromatographic purification, and provides a simple route for the synthesis of [$^2H_3$] deuterium-labeled desomorphine.

**Keywords** Opiates · Desomorphine · Deuterium · Controlled drugs · Internal standard

## Introduction

The active constituent of opium, i.e. morphine, is responsible for its pain-relieving properties and has been used very effectively for this purpose. Although morphine is an extremely effective analgesic, its use has to be limited because of certain undesirable effects of which "physical addiction" is the most serious [1–3]. A considerable amount of research has been directed towards synthesis of analogues that are completely devoid of this drawback. Desomorphine (**3**; Fig. 1) [4], a derivative of morphine, has similar sedative and analgesic effects. It is around ten times more potent than morphine with a rapid onset of action [5–7]. Additionally, desomorphine has a short duration of action, with relatively less nausea and respiratory depression than can be caused by an equivalent dose of morphine. However, the fact that it has abuse potential raises the possibility that it may become a future threat [8]. Internal standards are therefore essential for the detection and quantification of the drug in the samples of abusers. Deuterium-labeled internal standards are particularly effective for mass spectrometry analyses and quantification [9]. Selective ion monitoring, which is based on combined gas chromatography and mass spectrometry, is usually used as a very sensitive method for estimating specific assays of controlled substances in urine samples. It utilizes corresponding site-specific deuterium-labeled compounds as internal standards [10–12]. Many studies of the preparation of deuterium-labeled control drugs as internal standards for use in GC–MS analysis have been published [13–17].

Most of the synthetic routes to desomorphine (**3**) that are described in the literature have low yields and involve tedious reaction processes [18, 19]. This study describes an improved process for the synthesis of desomorphine with higher yield and purity (>99% by GC) without the need for purification by column chromatography. The process was optimized for synthesizing deuterium-labeled desomorphine [$^2H_3$]-**3** with very high purity.

## Results and discussion

Scheme 1 describes the protocol for the synthesis of desomorphine. A codeine-free base **2** was generated from codeine phosphate supplied by the National Bureau of Controlled Drugs, Taiwan. The C-14 hydroxy group of **2** was deoxygenated by converting it into a better leaving group and then displacing with hydride [20]. Tosylation and mesylation of codeine were therefore performed, affording the corresponding tosylate or mesylate **4**. The latter method

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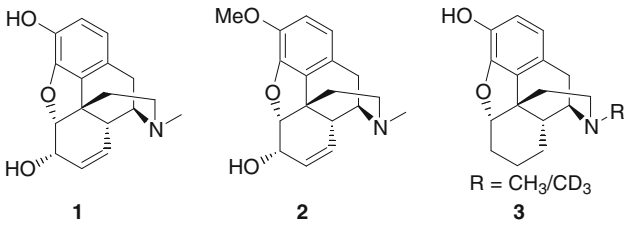



**Fig. 1** Structures of analgesic opiates: **1** morphine, **2** codeine, **3** desomorphine

was adopted because it had a higher yield and a shorter reaction time. However, the mesylate **4** was found to be unstable upon storage, and was therefore used immediately in the next step. Treatment of **4** with two equivalents of lithium aluminum hydride in THF at room temperature for a short time (1.5 h) afforded deoxycodeine (**5**) in high yield [21]. The use of fewer $LiAlH_4$ equivalents with a longer reaction time or refluxing the reaction mixture, gave more side-products, as observed by TLC.

Hydrogenation of **5** over $H_2/PtO_2$ in a Parr shaker (4 bar) afforded highly pure **6** in quantitative yield [22, 23]. The final demethylation of **6** was attempted using methods that have been reported elsewhere [22, 24, 25]. A mixture of products with low conversion of the starting material was observed using most of the reported methods. An efficient protocol for the high-yield demethylation of morphine to codeine with good purity using $BBr_3$ was therefore attempted [26]. A modification of the established procedure, using 1.5 equivalents of the reagent instead of excess $BBr_3$ (6.0 equivalents), afforded desomorphine (**3**) in acceptable yield and very high purity. All reaction products were analyzed by GC–MS and shown to be over 99% pure. The overall yield of the process was 38%, but no column purification was required in any stage.

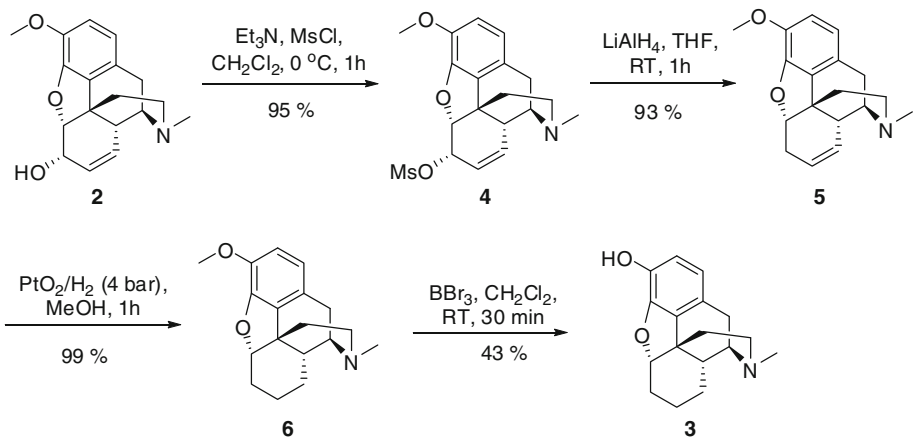
The synthetic route was modified to incorporate deuterium into desomorphine (Scheme 2). *N*-Methylation with $[^2H_3]$-$CH_3$ is a convenient method for installing deuterium in desomorphine. It involves transforming the methyl group to a carbamate [27], followed by reduction with $LiAlD_4$. *N*-Carbothoxylation of the tertiary amine of desocodeine (**6**) using ethyl chloroformate gave *N*-carbethoxydesocodeine (**7**) in good yield, which was converted back to deuterium-labeled desocodeine $[^2H_3]$-**6** by refluxing with $LiAlD_4$. Demethylation of $[^2H_3]$-**6** with $BBr_3$ as described above formed *d*-desomorphine $[^2H_3]$-**3**.

In summary, a short and efficient route for the synthesis of desomorphine and its deuterium analogue is described. The process affords highly pure desomorphine without the need for column purification, with an overall yield of 38%.

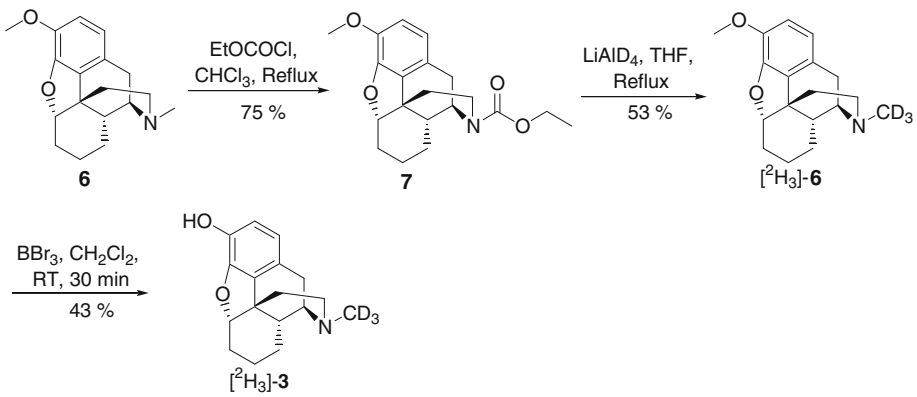
## Experimental

All reactions were carried out in anhydrous solvents. THF was distilled from sodium-benzophenone under argon. $CH_2Cl_2$ and hexane were distilled from $CaH_2$. $^1H$ NMR spectra were obtained at 400 MHz and $^{13}C$ NMR spectra were obtained at 100.5 MHz using a Bruker Avance 400 MHz NMR spectrometer. Chemical shifts ($\delta$) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Infrared spectra were recorded using an ATI Mattson spectrometer. An Agilent 7890AGC/5975CMS gas chromatograph–mass spectrometer equipped with a FID detector, split/splitless injector, and chemstation software was used for this study. A DB-35MS capillary column (30 m × 0.25 mm i.d., film thickness 0.25 μm) in a pulsed splitless mode was utilized for the separation of the analytes. Helium with a flow rate of 1.0 $cm^3$ $min^{-1}$ was used as a carrier gas. The temperature program for the experiments was as follows. The initial column temperature was held at 50 °C for 1 min and then raised at 5 °C $min^{-1}$ to 100 °C and maintained for 1 min and further ramped at 5 °C $min^{-1}$ to a final temperature of 250 °C and held for 20 min. The temperature of injection port and transfer line was held at 290 and 280 °C, respectively. To determine the

**Scheme 1**



**Scheme 2**




retention times and characteristic mass fragments, electron impact (EI) mass spectra of the analytes were recorded by total ion monitoring. For quantitative analysis, the chosen diagnostic mass fragments were monitored in the selected ion monitoring (SIM) mode: codeine ($t_R = 38.6$ min; $m/z = 299, 229, 162$); deoxycodeine ($t_R = 34.7$ min; $m/z = 283, 229, 214$); desocodeine ($t_R = 34.2$ min; $m/z = 285, 270, 228$); [$^2H_3$]-desocodeine ($t_R = 34.2$ min; $m/z = 288, 273, 228$); desomorphine ($t_R = 34.5$ min; $m/z = 271, 228, 214$). Optical rotations were measured using a JASCO P-1010 polarimeter at the indicated temperature using a sodium lamp (D line, 589 nm).

*Deoxycodeine* (**5**)
$LiAlH_4$ (0.73 g, 19.1 mmol) was weighed in an oven-dried flask. Dry THF (54 $cm^3$) was then added at 0 °C. To the stirred slurry was added 3.60 g solid codeine mesylate (9.6 mmol) at the same temperature in three portions over 15 min. The reaction mixture was then stirred at 0 °C for 30 min and at r.t. for 1 h. After completion of the reaction (TLC, 1 h), the reaction mixture was cooled to 0 °C and carefully quenched with aqueous THF. The resulting slurry was filtered through a pad of Celite and washed with excess EtOAc (2 × 15 $cm^3$); the filtrate was concentrated under reduced pressure to afford a white solid product (2.50 g, 93%), which was directly used for the next reaction without further purification; m.p.: 80 °C ([21], 81–82 °C).

*Desomorphine* (**3**)
A solution of 2.50 g desocodeine (8.77 mmol) in 25 $cm^3$ $CH_2Cl_2$ was added over 2 min to a well-stirred solution of 10.53 $cm^3$ $BBr_3$ (1 M in $CH_2Cl_2$, 10.53 mmol) that was maintained at temperatures in the range 23–26 °C. Stirring was continued for further 30 min at 23–26 °C. The reaction mixture was then poured into a well-stirred mixture of 60 $cm^3$ ice-water and 13 $cm^3$ of concentrated (28–30%) ammonia. The two-phase system was kept at −5 °C for 0.5 h (with continuous stirring) and extracted with excess of $CH_2Cl_2$ (2 × 30 $cm^3$). The combined organic extracts were concentrated to afford crude material, which was extracted with 10 $cm^3$ 2 M NaOH solution. The aqueous solution was washed with $CH_2Cl_2$ and then acidified to pH ~1 with 2 M HCl. The acidic solution was again washed with $CH_2Cl_2$ and made slightly alkaline with concentrated (28–30%) ammonia (pH ~8). The turbid solution was extracted with $CH_2Cl_2$ (2 × 30 $cm^3$) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford the product as a white solid (1.00 g, 43%); m.p.: 196 °C ([28], 188–189 °C).

*N-Carboethoxydesocodeine* (**7**, $C_{20}H_{25}NO_4$)
A mixture of 1.00 g desocodeine (3.5 mmol), 2.00 $cm^3$ ethyl chloroformate (21.1 mmol), and 0.56 g anhydrous $K_2CO_3$ (4.0 mmol) in 100 $cm^3$ $CHCl_3$ was refluxed for 6 h. After completion of the reaction (TLC, 6 h), the reaction solution was cooled to room temperature and filtered through a Celite bed. It was washed with 10 $cm^3$ $CHCl_3$ and the combined filtrate was concentrated under reduced pressure to yield a colorless viscous liquid, which was used directly in the next reaction without purification (0.90 g, 75%). $[\alpha]_D^{20} = -172.8$ °$cm^2g^{-1}$ ($c = 0.69$, $CH_2Cl_2$); IR (KBr): $\bar{\nu} = 2{,}931, 1{,}693, 1{,}502, 1{,}432, 1{,}319, 1{,}272, 1{,}224, 1{,}130, 1{,}099, 937$ $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, mixture of rotamers): $\delta = 6.74$–$6.76$ (m, 2H), 6.64–6.66 (m, 2H), 4.58–4.62 (m, 2H), 4.12–4.18 (m, 2H), 3.89–4.10 (m, 1H), 3.87 (s, 3H), 2.83–3.02 (m, 1H), 2.67–2.82 (m, 2H), 2.14–2.18 (m, 1H), 2.00–2.05 (m, 1H), 1.69–1.72 (m, 2H), 1.54–1.67 (m, 2H), 1.19–1.32 (m, 5H), 0.82–0.85 (m, 1H) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 155.5, 155.3, 144.1, 143.8, 129.1, 125.8, 125.6, 119.2, 119.1, 113.4, 113.3, 89.3, 61.3, 56.3, 51.4, 51.1, 42.6, 42.5, 41.9, 38.6, 34.9, 34.7, 29.1, 28.6, 24.8, 24.7, 21.3, 17.2, 17.1$ ppm; EI–MS: $m/z = 343.2$ ($M^+$, 100), 227.1, 195.1.

*[$^2H_3$]-Desocodeine* ([$^2H_3$]-**6**, $C_{18}H_{20}D_3NO_2$)
$LiAlD_4$ (62 mg, 1.46 mmol) was weighed in an oven-dried 50-$cm^3$ single neck flask at atmosphere argon. It was cooled to 0 °C and 5 $cm^3$ dry THF were added dropwise with stirring over 10 min. A solution of 0.50 g *N*-carbethoxydesocodeine (1.5 mmol) in 5 $cm^3$ THF was added dropwise over a period of 15 min, and the resulting slurry was warmed to room temperature and refluxed for 1 h.

After the completion of the reaction, the flask was cooled to 0 °C, and the system was carefully quenched by adding aqueous THF. It was then filtered over Celite, washed with EtOAc ($3 \times 15$ $cm^3$) and concentrated under reduced pressure to afford [$^2H_3$]-desocodeine (0.22 g, 53%) as a colorless solid. M.p.: 106 °C; $[\alpha]_D^{20} = -86.4$ °$cm^2g^{-1}$ ($c = 0.61$, $CH_2Cl_2$); IR (KBr): $\bar{\nu} = 2{,}929$, 2,377, 2,348, 2,308, 2,227, 2,167, 2,038, 1,608, 1,502, 1,440, 1,274 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 6.71$–6.73 (d, $J = 8.1$ Hz, 1H), 6.63–6.65 (d, $J = 8.1$ Hz, 1H), 4.60–4.62 (t, $J = 7.6$ Hz, 1H), 3.87 (s, 3H), 2.99–3.06 (m, 2H), 2.50–2.52 (m, 1H), 2.35–2.41 (dd, $J = 5.3$, 18.3 Hz, 1H), 2.13–2.19 (m, 3H), 1.78–1.81 (m, 1H), 1.70–1.71 (m, 1H), 1.56–1.58 (m, 1H), 1.46–1.50 (m, 1 H), 1.18–1.26 (m, 2H), 0.84–0.96 (m, 1H) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 144.1$, 143.6, 130.3, 127.1, 118.6, 112.9, 89.6, 59.7, 56.4, 47.5, 43.2, 42.4, 35.5, 29.3, 24.9, 21.7, 20.2 ppm; EI–MS: $m/z = 288.1$ ($M^+$, 100).

*[$^2H_3$]-Desomorphine* ([$^2H_3$]-**3**, $C_{17}H_{18}D_3NO_2$)

The conversion of [$^2H_3$]-**6** (200 mg) to [$^2H_3$]-**3** (80 mg) was performed in a similar fashion as described earlier. M.p.: 196 °C; $[\alpha]_D^{20} = -80.3$ °$cm^2g^{-1}$ ($c = 0.60$, $CH_2Cl_2$); IR (KBr): $\bar{\nu} = 3{,}397$, 2,929, 2,856, 2,048, 1,606, 1,500, 1,448, 1,322, 1,249, 1,159, 1,047 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 6.66$–6.80 (d, $J = 8.1$ Hz, 1H), 6.57–6.59 (d, $J = 8.1$ Hz, 1H), 4.56–4.60 (t, $J = 8.1$ Hz, 1H), 3.14–3.16 (m, 1H), 2.98–3.03 (d, $J = 18.4$ Hz, 1H), 2.61–2.65 (dd, $J = 3.8$, 12.0 Hz, 1H), 2.40–2.46 (dd, $J = 5.5$, 18.4 Hz, 1H), 2.23–2.28 (m, 2H), 2.04–2.07 (m, 1H), 1.80–1.91 (m, 1H), 1.61–1.68 (m, 1H), 1.40–1.58 (m, 2H), 1.20–1.24 (m, 3H), 0.88–0.91 (m, 1H) ppm; $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 143.0$, 140.4, 129.9, 125.5, 118.9, 116.9, 89.5, 59.6, 47.5, 35.0, 29.3, 24.9, 21.6, 20.3 ppm; EI–MS: $m/z = 274.1$ ($M^+$, 100).

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## References

1. Aldrich JV, Vigil-Cruz SC (2003) Narcotic analgesics. In: Abraham D (ed) Burger's medicinal chemistry and drug discovery, vol 6. Wiley, New York, pp 329–481
2. Casy AF, Parfitt RT (1986) Opioid analgesics, chemistry and receptors. Plenum, New York
3. Tagliaro D, Franchi R, Dorizzi M, Marigo M (1989) J Chromatogr 488:215
4. Small LF, Morris DE (1933) J Am Chem Soc 55:2874
5. Bognar R, Makleit S (1958) Arzneim Forsch 8:323
6. Janssen PA (1962) Br J Anaesth 34:260
7. Sargent LJ, May EL (1970) J Med Chem 13:1061
8. Savchuk SA, Barsegyan SS, Barsegyan IB, Kolesov GM (2008) J Anal Chem 63:361
9. Hsu FF, Lakshmi V, Rothman N, Bhatnager VK, Hayes RB, Kashyap R, Parikh DJ, Kashyap SK, Turk J, Zenser T, Davis B (1996) Anal Biochem 234:183
10. Wang WL, Darwin WD, Cone EJ (1994) J Chromatogr B 660:279
11. Wu AH (1995) Ann Clin Lab Sci 25:319
12. Wu YH, Lin KL, Chen SC, Chang YZ (2008) J Chromatogr B 870:192
13. Shaikh AC, Wang YY, Chen C (2007) J Label Compd Radiopharm 50:660
14. Chen YJ, Chen C (2007) J Labelled Comp Radiopharm 50:1143
15. Shaikh AC, Chen C (2008) J Labelled Comp Radiopharm 51:72
16. You ZY, Chen YJ, Wang YY, Chen C (2008) J Chin Chem Soc 55:663
17. Srimurugan S, Murugan K, Chen C (2009) Chem Pharm Bull 57:1421
18. Mosettig E, Cohen FL, Small LF (1932) J Am Chem Soc 54:793
19. Eddy NB, Howes HA (1935) J Pharmacol Exp Ther 55:257
20. Beyerman HC, Crabbendam PR, Lie TS, Maat L (1984) J R Neth Chem Soc 103:112
21. Stork G, Clarke FH (1956) J Am Chem Soc 78:4619
22. Kugita H, Takeda M (1965) Chem Pharm Bull 13:1422
23. Rapoport H, Bonner RM (1951) J Am Chem Soc 73:2872
24. Rapoport H, Bonner RM (1951) J Am Chem Soc 73:5485
25. Coop A, Janetka JW, Lewis JW, Rice KC (1998) J Org Chem 63:4392
26. Rice KC (1977) J Med Chem 20:164
27. Peet NP (1980) J Pharm Sci 69:1447
28. Small LF, Yuen KC, Eilers LK (1933) J Am Chem Soc 55:3869