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Practical and High-Yield Syntheses of Dihydromorphine from Tetrahydrothebaine and Efficient Syntheses of (8*S*)-8-Bromomorphide

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Abstract: A practical method for the conversion of tetrahydrothebaine to dihydromorphine in 92% yield is described. The procedure should allow more efficient production of opium products and may be easily modified for large-scale synthesis. The conversion of codeine to (8*S*)-8-bromomorphide, a potentially valuable intermediate to 6-demethoxyoripavine and derivatives, is also described. The absolute configuration of (8*S*)-8-bromomorphide was determined by a single-crystal X-ray diffraction study of the hydrobromide salt.

Narcotic drugs and their antagonists derived from the opium poppy, *Pavaver somniferum*, are essential for the effective practice of modern medicine. The chemistry of these drugs has been extensively investigated, and one goal has been their more efficient and economical production.[1] This has taken on heightened significance in recent years with steadily increasing demands[2] on the finite supply of opium available only through labor-intensive processes.[3] These studies have resulted in efficient routes for interconversion of many of the drugs and derivatives. However, in some manufacturing processes, byproducts of no medical value are produced. One example is tetrahydrothebaine (**1**, THT, Scheme 1) produced in the commercial hydrogenation of thebaine (**2**, Scheme 2) to 8,14-dihydrothebaine (**3**, Scheme 2) in a process for the production of dihydrocodeinone (**4**, Scheme 2).[4] Tetrahydrothebaine (**1**) also results from the hydrogenation of codeine methyl ether (**5**, Scheme 1), a byproduct of no medical utility that is produced in the commercial methylation of morphine (**6**, Scheme 2) to codeine (**7**, Scheme 1).[4] Codeine (**7**) is the most widely used opiate[2] in U.S. medicine and about 90%, or more than 35 000 kg, was produced by this process in 2001. Thus, THT (**1**) is obtained as (or derived from) a byproduct in two important manufacturing processes for medical narcotics. Its recycling to useful medications would be very desirable.

An efficient process for the complete O-demethylation of THT (**1**) would provide dihydromorphine (**8**, DHM, Scheme 1), a direct precursor of the pharmacologically useful hydromorphone (**9**, Scheme 2). DHM (**8**) is also a starting material for dihydrocodeinone (**4**) via phenolic methylation[4] to dihydrocodeine (**10**, Scheme 1) and oxidation[5,6] of the alcohol function. Dihydrocodeinone (**4**) is an important drug, being the third most widely prescribed opium product in the U.S.[2] Dihydrocodeinone (**4**) is convertible[7] in high yield to codeine (**7**), morphine (**6**), and thebaine (**2**) on which the entire spectrum of opium-derived medical narcotics and their antagonists is based.

We have now examined the conversion of THT (**1**) to DHM (**8**) using material from the catalytic reduction[8] of 89 kg of thebaine (**2**) to 8,14-dihydrothebaine (**3**) accomplished at Merck and Co. in 1947. The latter was required for the synthesis of methyldihydromorphinone (metapon, **11**, Scheme 2)[9] and related compounds in an early opiate program[10,11] aimed at the development of strong analgesics with fewer side effects than morphine (**6**). Crude crystalline THT (**1**) hydrochloride trihydrate from the Merck reduction showed about 7% of a higher R_f spot on thin-layer chromatography (TLC) that we identified as neopine methyl ether (**12**, Scheme 2) from the NMR spectrum, by comparison with the original sample of Small.[8] Hydrogenation of the crude mixture converted the neopine methyl ether (**12**) to the desired THT (**1**) that was purified to give starting material for O-demethylation to DHM (**8**).

The O-demethylation of THT (**1**) with refluxing 48% aqueous HBr for 1.0 h to give dihydromorphine (**8**) has been previously described.[4] We followed the reaction by TLC at 5 min intervals and found darkening and at least six impurities developing from the beginning and increasing to the end of reaction. We modified the O-demethylation by heating with 15% HBr in acetic acid, using conditions similar to those employed by Small for the conversion of neopine (**13**, Scheme 2) into neomorphine (**14**, Scheme 2).[12] Small-scale experiments resulted in copious evolution of HBr from the reaction mixture and the separation of crystalline material that was identified as 6-acetyldihydromorphine hydrobromide (**15**·HBr, Scheme 1). We next studied heating THT (**1**) in 15% HBr in acetic acid at 100 °C in a sealed hydrogenation bottle (under 20 psi) in order to avoid the loss of HBr. As described below, this gave a 95% yield of chromatographically homogeneous, analytically pure HBr salt on a 0.1

[†] National Institutes of Health.
[‡] Naval Research Laboratory.

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(10) White, W. C. *National Research Council Report of Committee on Drug Addiction 1929−1941 and Collected Reprints 1930−1941*; National Academy of Sciences: Washington, DC, 1941. The chemical research component of this program began in 1929 at the University of Virginia in Charlottsville under the direction of Dr. Lyndon Small. It was relocated to the National Institute of Health (then singular) in 1939, and opioid research at NIH has continued to the present. The contemporary successor to Dr. Small's group is the Laboratory of Medicinal Chemistry, NIDDK, NIH, Bethesda, MD, Dr. Kenner C. Rice, Chief.
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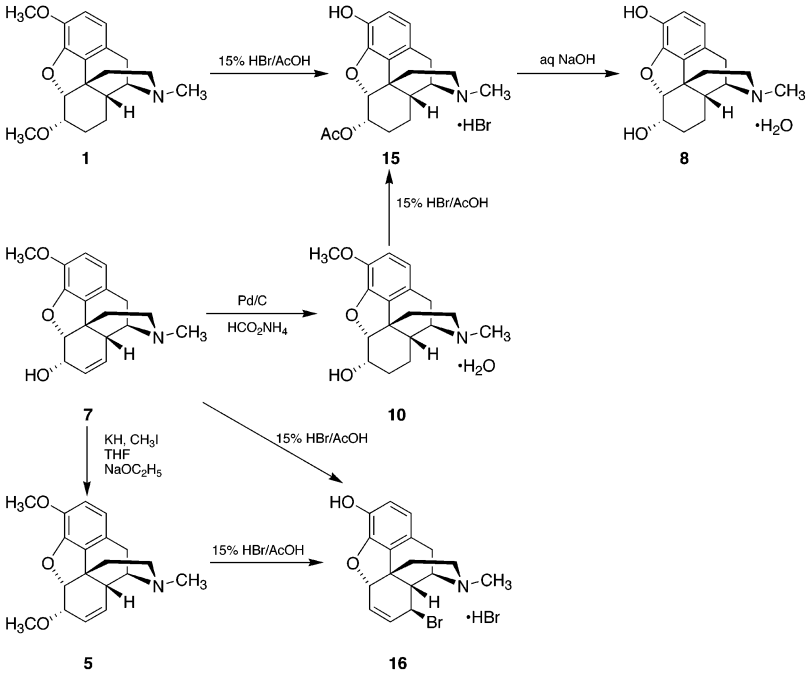
SCHEME 1



mol scale merely by filtering and washing. Hydrolysis of the acetyl group with aqueous NaOH followed by neutralization to pH 9−9.5 followed by filtering and washing then gave chromatographically and analytically pure hydrated DHM (**8**) in 97% yield from its HBr salt and 92% yield from THT (**1**).

We next examined the O-demethylation of dihydrocodeine (**10**) that had previously been described with 48% HBr.[13] Upon exposure to 15% HBr in acetic acid as described for THT (**1**), 6-acetyldihydromorphine (**15**)·HBr was produced in 94% yield. We also examined the reaction of codeine methyl ether (**5**)[14] and codeine (**7**) under the same conditions used to convert THT (**1**) to 6-acetyldihydromorphine (**15**). In both cases, the product was (8*S*)-8-bromomorphide (**16**, Scheme 1) hydrobromide that separated from the reaction mixture in 90% and 98% yield, respectively. (8*S*)-8-Bromomorphide (**16**) is a potentially useful intermediate for the synthesis of 6-demethoxyoripavine (**17**, Scheme 2) analogous to bromocodide (**18**, Scheme 2) in the synthesis of 6-demethoxythebaine (**19**, Scheme 2).[15] A minor impurity produced in the conversion of codeine (**7**) to (8*S*)-8-bromomorphide (**16**) was isolated and identified as desoxymorphine C (**20**, Scheme 2) that proved identical with an authentic sample[16] from Small's collection. Our samples of (8*S*)-8-bromomorphide (**16**) were spectroscopically and chromatographically identical with an authentic sample[17] from Small's work prepared by the method of Schryver and Lees.[18] X-ray analysis of our sample of (8*S*)-8-bromomorphide (**16**) then verified the C_8 bromine position and determined that the absolute configuration at C_8 was *S*.[19]

In summary, we have developed a practical, high-yielding conversion of THT (**1**) to DHM (**8**) that gives an analytically and chromatographically pure intermediate and product. This procedure should allow more efficient production of opium products and be easily modified for large-scale synthesis. We also described facile conversion of the readily available codeine to (8*S*)-8-bromomorphide (**16**), a potentially valuable chemical intermediate. The structure and absolute configuration of **16**·HBr were determined by X-ray crystallographic analysis.

Experimental Section

TLC analyses were carried out on Analtech silica gel GHLF 0.25 mm plates with UV and I_2 detection, using $CHCl_3$/MeOH/NH_4OH (80:18:2) as the solvent system. Column chromatography was carried out with silica gel (ICN SiliTech 32−63, 60 Å), using $CHCl_3$/MeOH/NH_4OH (100:10:1) as the solvent system. Melting points were determined in open glass capillaries on a Thomas-Hoover melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) and HRMS were recorded on JEOL SX 102a. Optical rotations were measured with a Perkin-Elmer polarimeter 341 using the solvents, concentrations, and wavelengths specified. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

Purification of Crude Crystalline Tetrahydrothebaine (1, THT) Hydrochloride. A crude crystalline tetrahydrothebaine (**1**) hydrochloride trihydrate (40 g) mixture, containing about 7% of neopine methyl ether (**12**), was obtained from Merck and Co. in 1947. The mixture was dissolved in 150 mL of water. To this solution was added 3.1 g of 5% Pd/C. The reaction mixture was hydrogenated for 1 h at 40 psi and then was filtered through a pad of Celite. To the yellow solution was added 4 g of NaOH, and then 0.8 g of $NaBH_4$ was added. The reaction mixture was stirred for 1 h. The product, tetrahydrothebaine (**1**), was extracted with ether and dried over Na_2SO_4. The filtrate was evaporated and dissolved in 100 mL of a mixture of

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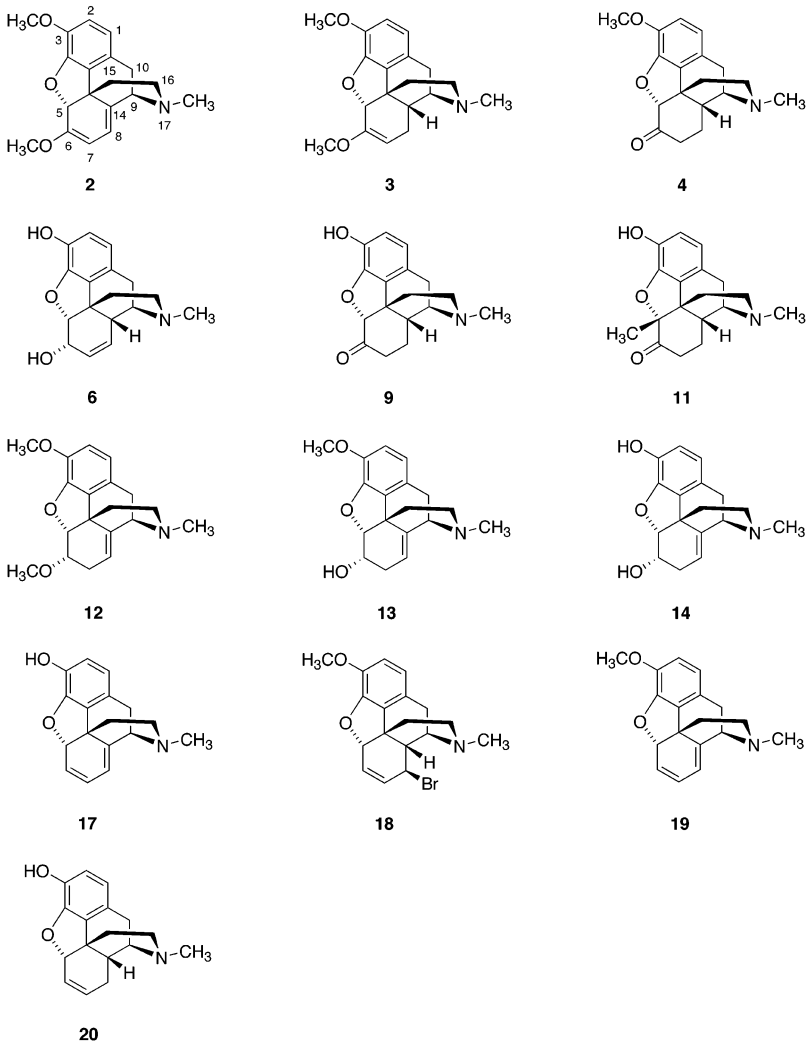
SCHEME 2



2-propanol/ether (80:20) with the help of a hot water bath or ultrasound. The addition of 10.5 mL of 36.5% HCl gave 38.9 g of **1**·HCl·$3H_2O$ salt [mp 112−113 °C (lit.[20] (crystals from acetone) mp 115−116 °C)]. The salt was converted to the free base by treatment with 1.7 M NaOH (300 mL), and **1** was isolated by extraction with ether and evaporation of the solvent to give chromatographically pure **1** (30.5 g, 0.097 mol). Treatment of a portion of this material with ether gave crystals: mp 80−81 °C (lit.[20] mp 83 °C). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.46; H, 7.94; N, 4.39.

6-Acetyldihydromorphine Hydrobromide (15·HBr). (a) From Tetrahydrothebaine (1). A solution of 30% HBr in acetic acid (150 mL) was added to a solution of tetrahydrothebaine (**1**, 31.50 g, 0.10 mol) in glacial acetic acid (150 mL). The reaction mixture was stirred for 5 h at 100 °C at 20 psi (in a 1 L hydrogenation bottle, 2002 Ace Glass catalog no. 8648-157; using a #25 Teflon screw cap, Ace Glass catalog no. 5846-5). Crystalline material appeared in about 1 h. The mixture was cooled to room temperature, and ether (400 mL) was added. The reaction mixture was refrigerated overnight (5 °C). The mixture was filtered, and the crystals were washed with a mixture of ether and acetic acid (4:3, 210 mL) until a few drops of the wash solution diluted with an equal volume water gave a negative $AgNO_3$ test, to afford 33.54 g (82%) of chromatographically and analytically pure **15**·HBr. The filtrate was evaporated to a thick slurry and filtered, and the collected solid was washed with the mixture of ether and acetic acid (4:3, 21 mL) to afford 5.46 g (13%) of **15**·HBr as a second crop (total yield 39.00 g, 95%). The salt was converted to free base **15** by heating with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The free base was recrystallized from MeOH: mp 241 °C (lit.[12] mp 245 °C); ^{1}H NMR (free base) δ 6.68 (d, 1H, J = 8.1 Hz, H-2), 6.58 (d, 1H, J = 8.1 Hz, H-1), δ 5.30 (ddd, 1H, J = 5.8, 5.5, 2.7 Hz, H-6), 4.63 (d, 1H, J = 5.8 Hz, H-5), 3.14−3.11 (m, 1H, H-9), 3.01 (d, 1H, J = 18.6 Hz, H-10α), 2.56 (dd, 1H, J = 12.3, 3.6 Hz, H-16β), 2.41 (s, 3H, NCH_3), 2.39 (dd, 1H, J = 18.6, 5.4 Hz, H-10β), 2.30−2.21 (m, 2H, H-14), 2.30−2.21 (m, 1H, H-16α), 1.89 (dt, 1H, J = 12.3, 4.8 Hz, H-15β), 1.83 (s, 3H, $-CH_3$), 1.72−1.61 (m, 1H, H-8β), 1.72−1.61 (m, 1H, H-15α), 1.53−1.36 (m, 2H, H-7α), 1.53−1.36 (m, 2H, H-7β), 1.09−1.26 (H-8α, m, 1H); MS (FAB) m/z 330 [M + 1]$^+$. Anal. Calcd for $C_{19}H_{24}BrNO_4$: C, 55.62; H, 5.90; N, 3.41. Found: C, 55.57; H, 5.95; N, 3.33. The ^{1}H NMR spectrum of **15** base was identical to that of an authentic sample of 6-acetyldihydromorphine (**15**) originally synthesized from neopine (**13**) by Small.[12]

(b) From Dihydrocodeine (10). Dihydrocodeine (**10**, 1.00 g, 3 mmol), obtained by catalytic reduction of codeine (**7**) with Pd/C in MeOH, was dissolved in a mixture of 5 mL of glacial acetic acid and 5 mL of 30% HBr in acetic acid. The mixture was treated as shown above for tetrahydrothebaine (**1**). Compound **15**·HBr (1.15 g) was obtained from **10** in 94% yield.

Dihydromorphine (8)·1.1H_2O. 6-Acetyldihydromorphine·HBr (**15**·HBr, 39.00 g, 95 mmol) was dissolved in 10% NaOH solution (200 mL) and refluxed under nitrogen for 30 min. The aqueous solution was cooled and adjusted to pH 7 with 36% hydrochloric acid (25 mL) and then made alkaline (pH 9−9.5)

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with NH_4OH (2 mL). The crystals that formed were washed with ice−water (60 mL) and dried in vacuo at 40 °C to give a cream-colored solid (**8**·1.1H_2O, 26.36 g, 90%), mp 151−152 °C (lit.[12] mp 155−157 °C). The combined filtrate was evaporated to 100 mL, and 1 mL of NH_4OH was added to pH 9−9.5. A second crop crystallized and was washed with 10 mL of ice−water. The crystals were dried under reduced pressure at 40 °C to afford 1.91 g (6.6%), for a total yield of 97% (28.27 g). The overall yield of dihydromorphine·1.1H_2O (**8**) from tetrahydrothebaine (**1**) was 92%. The ^{1}H NMR spectrum was identical with material synthesized by Small[12] and with the literature:[21] ^{1}H NMR δ 6.66 (d, 1H, J = 8.0 Hz, H-2), 6.55 (d, 1H, J = 8.0 Hz, H-1), 4.60 (d, 1H, J = 5.2 Hz, H-5), 4.00 (m, 1H, H-6), 3.13−3.10 (m, 1H, H-9), 2.97 (d, 1H, J = 18.4 Hz, H-10α), 2.56 (dd, 1H, J = 12.4, 3.8 Hz, H-16β), 2.41 (s, 3H, $-CH_3$), 2.40 (dd, 1H, J = 18.4, 6.0 Hz, H-10β), 2.33−2.22 (m, 1H, H-16α), 2.33−2.22 (m, 1H, H-14), 1.93 (dt, 1H, J = 12.4, 5.2 Hz, H-15β), 1.69 (ddd, 1H, J = 12.4, 3.8, 1.9 Hz, H-15α), 1.50−1.41 (m, 3H, H-7α), 1.50−1.41 (m, 3H, H-7β), 1.50−1.41 (m, 3H, H-8β), 1.12−1.03 (m, 1H, H-8α); MS (FAB) m/z 288 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{21}NO_3$·1.1 H_2O: C, 66.47; H, 7.66; N, 4.56. Found: C, 66.44; H, 7.66; N, 4.54.

(8*S*)-8-Bromomorphide (16) Hydrobromide from Codeine (7) via Codeine Methyl Ether (5). Codeine methyl ether (**5**) was prepared from codeine (**7**) by the method of Barber and Rapoport.[14]

A solution of 30% HBr in acetic acid (5 mL) was added to a solution of codeine methyl ether (**5**, 1.00 g, 3.2 mmol) in glacial acetic acid (5 mL). The procedure was the same as that used for the preparation of **15**·HBr. The **16**·HBr crystals were obtained as a gray solid from the reaction mixture (1.24 g, 90%), mp 193−194 °C. The HBr salt (1.2 g, 2.8 mmol) was converted to the free base with Na_2CO_3 solution. Column chromatography of the crude material using $CHCl_3$/MeOH/NH_4OH (100:10:1) gave a microcrystalline powder of **16** (0.7 g, 72%). It was recrystallized from MeOH to give **16**·H_2O as a crystalline solid: mp 114−115 °C; $[\alpha]^{20}_D$ +55.8 (*c* 1, MeOH) [lit.[18] mp 169−170 °C for anhydrous **16**, $[\alpha]^{20}_D$ +65.9 (*c* 2.8, MeOH)], an authentic anhydrous sample[17] from Small's collection showed $[\alpha]^{20}_D$ +61.0 (*c* 1.1, MeOH) and it sintered and darkened at 164 °C; ^{1}H NMR δ 6.69 (d, 1H, J = 8.0 Hz, H-2), 6.59 (d, 1H, J = 8.0 Hz, H-1), 6.05 (dd, 1H, J = 10.4, 1.9 Hz H-7α), 5.63 (dt, 1H, J = 10.4, 2.5 Hz, H-6), 5.05−5.03 (m, 1H, H-5), 4.11 (dd, 1H, J = 9.9, 1.9 Hz, H-8β), 3.60 (dd, 1H, J = 6.3, 3.0 Hz, H-9), 3.06 (d, 1H, J = 18.9 Hz, H-10α), 2.75 (dd, 1H, J = 9.9, 3.0 Hz, H-14), 2.56 (m, 1H, H-16β), 2.46 (dd, 1H, J = 18.9, 6.3 Hz, H-10β), 2.45 (s, 3H,-CH_3), 2.30 (dt, 1H, J = 12.4, 3.6 Hz, H-16α), 1.96 (dt, 1H, J = 12.4, 4.9 Hz, H-15β), 1.77 (ddd, 1H, J = 12.6, 3.6, 1.9 Hz, H-15α); MS (FAB) m/z 348 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{18}BrNO_2$·H_2O: C, 57.15; H, 5.36; N, 3.91. Found: C, 57.39; H, 5.25; N, 3.93. A sample of **16**·HBr, crystallized slowly from methanol in a diethyl ether atmosphere (mp 197−198 °C), was used for X-ray structure analysis to unequivocally determine its structure (Figure 1). The hydrate **16**·H_2O was found to be identical with an authentic sample[17] using TLC, MS, and ^{1}H NMR.[19]

(8*S*)-8-Bromomorphide (16) Hydrobromide from Codeine·H_2O (7). A solution of 30% HBr in acetic acid (7.5 mL) was added to a solution of codeine·H_2O (**3**, 1.58 g, 5 mmol) in glacial acetic acid (7.5 mL). The procedure was the same as that used for the preparation of **15**·HBr. The **16**·HBr crystals from the reaction mixture were obtained as a white solid (2.10 g, 98%). TLC of the crude material showed 2 minor impurities at R_f 0.26 and 0.55. The impurity of R_f 0.55 was isolated by column chromatography with solvent: $CHCl_3$/MeOH/NH_4OH (100:10:1). It was identified as desoxymorphine C (**20**, Scheme 2), which was found to be identical with Small's sample[16] using TLC, MS, and ^{1}H NMR. Free base **20** was crystallized from ethyl acetate: mp 192−193 °C (lit.[16] mp 189−190 °C); ^{1}H NMR δ 6.65 (d, 1H, J = 8.0 Hz, H-2), 6.56 (d, 1H, J = 8.0 Hz, H-1), 5.83 (m, 1H, H-6), 5.63 (m, 1H, H-7), 4.92 (s, 1H, H-5), 3.18 (dd, 1H, J = 6.0, 2.7 Hz, H-9), 3.01 (d, 1H, J = 18.4 Hz, H-10α), 2.63 (m, 1H, H-16β), 2.53−2.44 (m, 2H, H-10β), 2.53−2.35 (m, 2 H, H-14), 2.42 (s, 3H, $-CH_3$), 2.32 (dt, 1H, J = 12.1, 3.8 Hz, H-16α), 2.00−1.87 (m, 2H, H-8α), 1.96 (dt, 1H, J = 12.4, 5.2 Hz, H-15β), 1.77 (ddd, 1H, J = 12.4, 3.8, 1.9 Hz, H-15α), 1.52 (m, 1H, H-8β); HRMS (DEI$^+$) m/z 269.1403, $C_{17}H_{19}NO_2$ requires 269.1416.

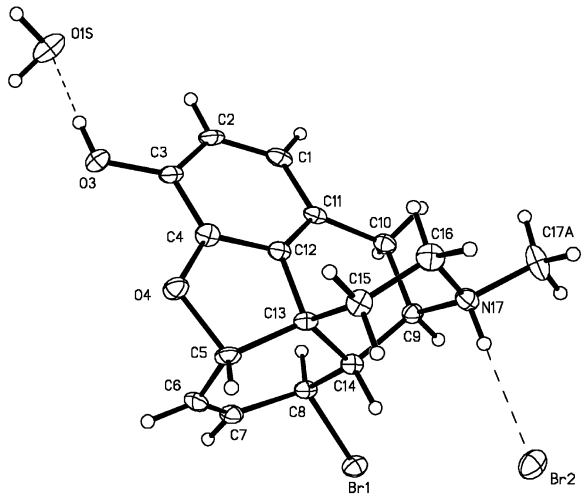

FIGURE 1. X-ray of (8*S*)-8-bromomorphide (**16**·HBr) with displacement parameters at the 20% probability level.

Single-crystal X-ray diffraction analysis of (8*S*)-8-bromomorphide (16)·HBr: $C_{17}H_{18}NO_2Br^+Br^-$·H_2O, FW = 447.17 (0.24 × 0.23 × 0.12 mm^{-1}), monoclinic space group $P2_1$, a = 8.351(1) Å, b = 11.825(1) Å, c = 8.946(1) Å, β = 96.67°, V = 877.41(8) Å^3, Z = 2, ρ_{calc} = 1.69 mg mm^{-3}, λ(Mo Kα) = 0.710 73 Å, μ = 4.633 mm^{-1}, $F(000)$ = 448, T = 193 K, R_1 = 0.027 for 3322 observed ($I > 2\sigma I$) reflections and 0.030 for the full set of 3533 reflections. Data were collected using a Bruker SMART 1K CCD detector mounted on a Bruker P4 diffractometer equipped with an incident beam monochromator. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved and refined with the aid of the programs in the SHELXTL-plus system of programs.[22] The full-matrix least-squares refinement on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H atoms. Most of the H atoms were included using a riding model. Coordinates only were refined for hydrogens on the nitrogen atom, the hydroxyl oxygen atom and the water molecule. The absolute configuration was determined experimentally from the anomalous scattering of the bromine atoms.[23] Atomic coordinates have been deposited with the Cambridge Crystallographic Data Base, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

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Supporting Information Available: Details of the X-ray structure of (8*S*)-8-bromomorphide·HBr (**16**·HBr), including tables of crystal data, atomic coordinates, bond lengths and angles, positional and anisotropic thermal parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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