Boron Tribromide-Catalyzed Rearrangement of 7,7-Diphenylhydromorphone to 6,7-Diphenylmorphine: A Novel Conversion of Ketones to Allylic Alcohols

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A novel boron tribromide-catalyzed rearrangement of ketones to allylic alcohols was discovered in the 7-phenylmorphinan-6-one system. The reaction involved the stereospecific migration of an axial 7β-phenyl (or a hydrogen) to the C-6 carbonyl carbon, followed by the elimination of the H-8 proton leading to the generation of allylic alcohols. A possible mechanistic pathway for this rearrangement is discussed.

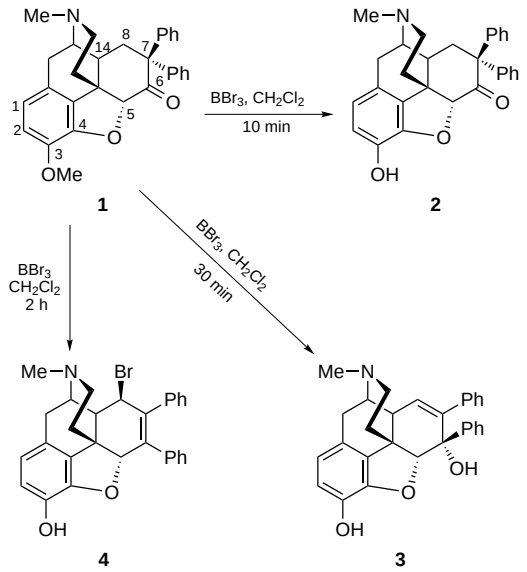
Under acidic conditions, branched or ring-constrained ketones are liable to skeletal rearrangement.[1] In a few cases, some bicyclic ketones have been reported to undergo Wagner−Meerwein rearrangement[2] leading to the formation of allylic compounds.[3−6] Here we report on a novel ketone to allylic alcohol rearrangement in the 7-phenylmorphinan-6-one system that is catalyzed by boron tribromide (BBr_3).

Results and Discussion

When diphenylhydrocodone **1**, a byproduct from the preparation of 7-phenylhydrocodone,[7] was subjected to boron tribromide treatment at room temperature (Scheme 1), an unexpected product **3** was isolated (52%) instead of the desired demethylation product **2**. The structure of **3** was characterized by the disappearance of the C-6 carbonyl group and the presence of an allylic alcohol functionality. The proton COSY spectrum of **3** indicated a proton−proton coupling pattern of $H_{10\alpha}-H_{10\beta}-H_9-H_{14}-H_8$. On the basis of the observation of the positive NOE between H_5 and *ortho* protons of the 6-phenyl group, the C-6 chiral center of **3** was assigned as the *S* configuration (6β-phenyl).

Further investigation showed that the reaction of **1** with boron tribromide rapidly afforded the demethylation product **2** as it was isolated as a major component (43%) when the reaction was quenched within 10 min. However, if the reaction proceeded longer than 30 min, the rearrangement product **3** was predominant. Compound **4** was obtained as a major product (39%) when the reaction proceeded beyond 1 h. The stereochemistry of the 8β-bromo group was deduced from the coupling constant (J_{H8-H14} = 9.6 Hz) which suggested a *trans* relationship for these protons.[8] In addition, the C-5 proton of **4** was found to be involved in long-range coupling (J_{H5-H8} = 1.6 Hz) to the H-8 due to the presence of the double bond between C-6 and C-7.

Scheme 1



From independent experiments, we have found that **3** and **4** also can be prepared from **2** and **3**, respectively, under similar conditions. The formation of **4** from **3** appears to be an example of *anti* S_N2' reaction,[9,10] which also supports the structure assignment of **3**.

Since ketone **1** has two phenyl groups at the C-7 position, 7α-methyl-7β-phenylhydrocodone[7] (**5**) was subjected to boron tribromide treatment in order to elucidate the stereopreference for migration of the C-7 substituents. The reaction of **5** with boron tribromide (Scheme 2) afforded both ketone **6** (59%) and the rearrangement product **7** (22%). The stereochemistry of **7** at the 6-position was confirmed by the positive NOE between H_5 and *ortho* protons of the 6-phenyl group. The formation of the 6β-phenyl isomer **7** and the absence of its 6α epimer suggested a stereospecific migration of the 7β-phenyl group.

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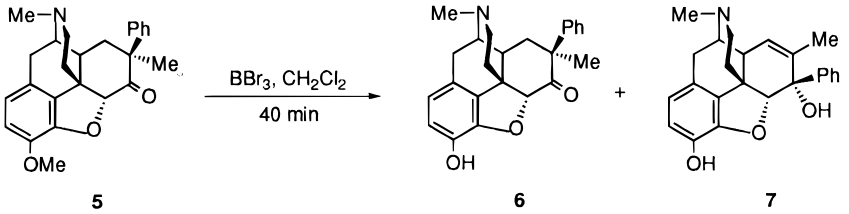
Scheme 2



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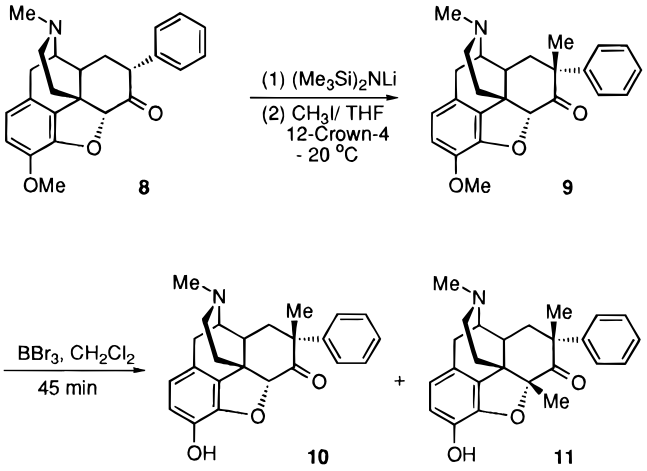
To further validate this observation, the reaction of the C-7 epimer **9** with boron tribromide was investigated (Scheme 3). Compound **9** was obtained by methylation

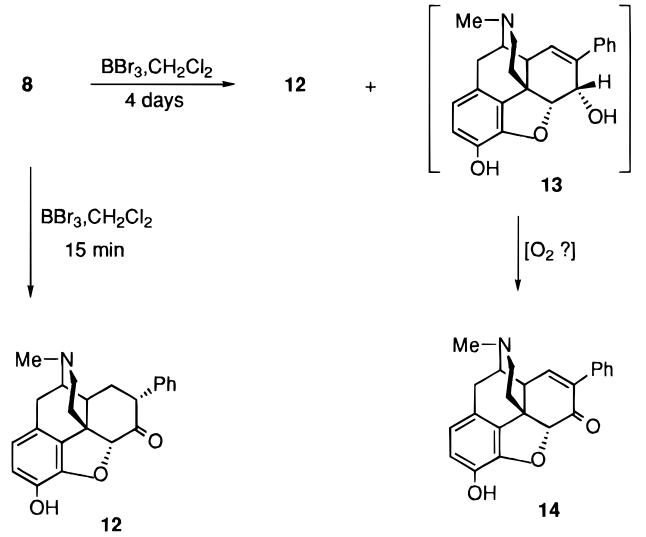
Scheme 3



of the lithium enolate of monophenyl ketone[7] **8** with methyl iodide. The stereochemistry at the C-7 position was confirmed by the positive proton NOE signals between H_5 and 7-methyl group, as well as between H_{14} and 7-methyl group. The stereochemistry of **9** is reasonable in view of the fact that the β face of the enolate is more accessable than the α face. Treatment of **9** with boron tribromide afforded **10** (29%), together with a minor amount (15%) of **11**. The 5-methyl group of **11** is likely derived from methyl bromide. Of significance was the finding that no 7-methyl or 7-phenyl migration product was isolated, supporting the idea that stereoelectronic factors are important in the rearrangement.

The reaction of ketone **8** with boron tribromide was also studied (Scheme 4). At room temperature, the

Scheme 4



reaction (15 min) led to the formation of **12** (26%). On prolonged treatment (4 days) of **8** with boron tribromide the α,β-conjugated ketone **14** (12%) in addition to **12** (8%) was isolated. It should be noted that the boron tribromide treatment of **8** led to the formation of a large amount of highly polar material which resulted in the low recovery of reaction material. A possible pathway leading to **14** may involve rearrangement of **12** to the allylic alcohol **13**, followed by air oxidation to the ketone.

The reactions of 7-phenylmorphinan-6-ones (**1**, **5**, **8**) with boron tribromide appear to be new examples of Lewis acid-catalyzed ketone to allylic alcohol rearrangements.[1,3–6] A proposed mechanism (Figure 1) of this rearrangement may involve the coordination of the carbonyl group by boron tribromide (step i), which would promote migration of the axial 7β-phenyl group (step ii). Migration of the 7β-phenyl would be expected because it is perpendicular to the sp^2 plane of C-6 center. The carbonium ion intermediate that is formed through this process would be expected to eliminate the *pro*-S proton (axial $H_{8\alpha}$, perpendicular to the sp^2 plane of C-7) to form the allylic product (step iii), which would yield **3** upon hydrolysis, or afford **4** through an *anti* S_N2' reaction (step iv).

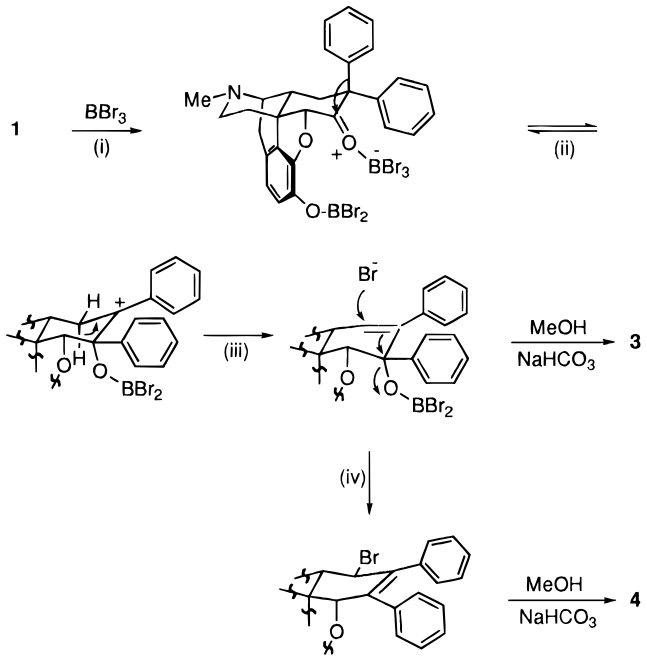


Figure 1.

The finding that ketone **9** did not undergo the ketone to allylic alcohol rearrangement when treated with boron tribromide is consistent with this mechanism, as its 7α-phenyl group occupies an equatorial position and is thus not available to migrate. Although the 7β-methyl group of **9** is in an axial position that is favorable for migration, the low migratory aptitude of a methyl group compared

to a phenyl group may be responsible for the failure of **9** to undergo the rearrangement.

Experimental Section

Reagents were from Aldrich Chemicals unless otherwise noted. 7,7-Diphenylhydrocodone, 7α-phenylhydrocodone, and 7*β*-methyl-7α-phenylhydrocodone were prepared according to the procedures that we have reported previously.[7] All reactions were performed under N_2. Spinning thin-layer chromatography (TLC) was performed on silica gel (EM Science Silica Gel 60, PF254). Chromatographic solvent systems are reported as volume/volume ratios. NMR data were collected at room temperature (18−20 °C) on a 300 MHz spectrometer. The δ (ppm) scale was in reference to the deuterated solvent. Coupling constants are reported in Hz. Proton NMR peak assignments were derived from COSY spectra. Melting points were determined in open capillary tubes and are uncorrected. Elemental analysis was performed by MHW Laboratory (Phoenix, AZ).

7,7-Diphenylhydromorphone (2). Boron tribromide (1 M in CH_2Cl_2, 0.85 mL, 0.85 mmol) was added over 5 min with stirring to diphenylhydrocodone[7] **1** (120 mg, 0.27 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 10 min after addition. Methanol (4 mL) was added and after stirring for 30 min the solution was adjusted to pH 8 with aqueous $KHCO_3$ (10%) and extracted with CH_2Cl_2−MeOH (95/5, 4 × 25 mL). The combined organic layer was washed with water to pH 7, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on a spinning TLC (1 mm silica gel plate, ethyl acetate) to afford **2** (50 mg, 43%): IR (KBr) 3444.5, 2930, 1718.3, 1496.3, 1447.0, 1384.3, 1250.8, 1030.8, 700.3 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 7.47−7.52 (t, 2H, J = 7.5, H-Ph), 7.31−7.419 (m, 3H, H-Ph), 7.06−7.09 (m, 3H, H-Ph), 6.60−6.64 (m, 4H, H-1,2 and H-Ph), 5.01 (s, 1H, H-5), 3.17−3.20 (m, 1H, H-9), 2.99−3.05 (d, 1H, J = 6, H-10), 2.67−2.72 (dd, 1H, J = 3.9, 13.8, H-8*β*), 2.57−2.64 (m, 1H, H-14), 2.39−2.47 (dd, 1H, J = 6, 18, H-10), 2.31−2.38 (m, 1H, H-D ring), 2.29 (s, 3H, H-NMe), 2.02−2.18 (dd, 1H, J = 16.8, 30.3, H-8α), 2.062−2.12 (m, 1H, H-D ring), 1.54−2.67 (dt, 1H, J = 5.4, H-D ring), 1.45−1.51 (m, 1H, H-D ring); ^{13}C NMR (CD_3COCD_3) δ 207.88, 144.84, 144.34, 140.39, 139.40, 129.29, 129.12, 128.95, 128.32, 128.22, 127.98, 126.91, 125.62, 120.47, 118.35, 91.76, 63.57, 59.34, 54.09, 47.12, 42.74, 38.45, 36.19, 35.66, 20.23; MS (HRFAB) m/z 438.2057 $[M + H]^+$, (calcd for $C_{29}H_{28}NO_3$ $[M + H]^+$ = 438.2049). 7,7-Diphenylhydromorphone (**2**) (48 mg, 0.11 mmol) was treated with Et_2O·HCl in a minimum amount of CH_2Cl_2. The resulting precipitate was crystallized from MeOH-Et_2O to give **2**·HCl (48 mg, 90%): mp 240 °C dec; ^1H NMR (CD_3OD) δ 7.52−7.57 (t, 2H, J = 7.2, H-Ph), 7.41−7.46 (m, 1H, H-Ph), 7.32−7.34 (d, 2H, J = 7.2, H-Ph), 7.07−7.09 (m, 3H, H-Ph), 6.80 (s, 2H, H-1,2), 6.53−6.56 (m, 2H, H-Ph), 5.23 (s, 1H, H-5), 4.06−4.08 (m, 1H, H-9), 3.19−3.34 (m, 2H, H-10, H-D ring), 3.04−3.19 (m, 2H, H-10, H-D ring), 2.91 (s, 3H, H-NMe), 2.91−2.96 (m, 1H, H-14), 2.77−2.83 (dd, 1H, J = 3.6, 14.7, H-8*β*), 2.03−2.13 (t, 1H, J = 13.6, H-8α), 1.84−1.96 (m, 2H, H-D ring); ^{13}C NMR (CD_3OD) δ 207.77, 144.70, 143.04, 141.18, 137.96, 130.13, 129.11, 128.59, 128.55, 127.93, 127.14, 125.96, 121.65, 121.31, 119.26, 90.86, 63.28, 61.84, 45.30, 40.78, 35.06; MS (FAB) m/z 438.2 $[M + H]^+$; Anal. Calcd for $C_{29}H_{28}NO_3$·HCl·$^2/_3H_2O$: C, 69.98; H, 6.36; N, 3.40; Cl, 8.61. Found: C, 69.98; H, 6.52; N, 3.21; Cl, 8.45.

6*β*,7-Diphenylmorphine (3). Boron tribromide in CH_2Cl_2 (1 M, 1.2 mL, 1.2 mmol) was added over 5 min to a solution of 7,7-diphenylhydrocodone (**1**) (168 mg, 0.37 mmol) in CH_2Cl_2 (5 mL). After stirring for 25 min at room temperature, the reaction was quenched with methanol (5 mL) and stirred for 30 min. The mixture was adjusted to pH 8 with aqueous $KHCO_3$ (10%), extracted with CH_2Cl_2−MeOH (95/5, 4 × 25 mL), and washed with water to pH 7. The solvent was evaporated under reduced pressure, and the residue was chromatographed on a spinning TLC (silica gel, 1 mm, 3/97, MeOH−CH_2Cl_2) to afford **3** (84 mg, 52%): ^1H NMR (CD_3COCD_3) δ 7.66−7.69 (m, 2H, H-Ph), 7.40−7.45 (m, 2H, H-Ph), 7.30−7.39 (m, 1H, H-Ph), 7.00−7.10 (m, 3H, H-Ph), 6.71−6.75 (m, 2H, H-Ph), 6.57−6.64 (2d, 2H, J = 5.8, H-1,2), 5.74−5.75 (d, 1H, J = 3, H-8), 4.88 (s, 1H, H-5), 3.39−3.43 (m, 1H, H-9), 3.00−3.06 (d, 1H, J = 6, H-10), 2.65−2.70 (m, 1H, H-14), 2.40−2.48 (dd, 1H, J = 6, H-10), 2.37−2.43 (m, 1H, H-D ring), 2.25−2.30 (m, 1H, H-D ring), 1.69−1.76 (m, 1H, H-D ring), 1.54−1.70 (m, 1H, H-D ring); ^{13}C NMR (CD_3COCD_3) δ 145.33, 143.21, 140.91, 139.31, 132.46, 130.76, 129.38, 129.13, 128.87, 128.38, 127.67, 127.41, 127.10, 126.27, 120.76, 117.82, 99.04, 76.06, 59.30, 46.75, 44.45, 43.10, 42.53, 36.80, 20.56; MS (HRFAB) m/z 438.2065 $[M + H]^+$ (calcd for $C_{29}H_{27}NO_3$ $[M + H]^+$ = 438.2050). The free base **3** (84 mg, 0.19 mmol) was treated with Et_2O·HCl in a minimum amount of CH_2Cl_2 and the precipitate was recrystallized twice from MeOH-ether to afford **3**·HCl (40 mg, 44%), mp 223 °C dec; ^1H NMR (CD_3OD) δ 7.71−7.74 (m, 2H, H-Ph), 7.45−7.50 (m, 2H, H-Ph), 7.36−7.41 (m, 1H, H-Ph), 7.07-7.15 (m, 3H, H-Ph), 6.74−6.79 (m, 4H, H-1,2 and H-Ph), 5.71−5.72 (d, 1H, J = 2.1), 5.18 (s, 1H, H-5), 4.20−4.23 (m, 1H, H-9), 3.30−3.34 (m, 1H, H-10), 3.19−3.25 (m, 1H, H-11), 3.06−3.12 (m, 1H, H-11), 3.00−3.09 (dd, 1H, J = 7.2, 20.4, H-10), 2.86−2.86 (m, 1H, H-14), 2.10−2.14 (m, 1H, H-12), 1.80−1.90 (m, 1H, H-12). The proton NMR in CD_3COCD_3 has a similar pattern but the chemical shift of the 14 proton is 3.55 instead of 2.85 ppm; three D_2O exchangeable protons were observed in CD_3COCD_3 at: 13.2, 8.2, and 4.5 ppm; ^{13}C NMR (CD_3OCD_3 at AC-300) δ 147.36 (q), 145.10 (q), 143.52 (q), 140.28 (q), 130.41 (q), 129.47 (t), 129.08 (t), 128.50 (t), 127.83 (t), 127.75 (t), 127.53 (t), 126.81 (t), 123.43 (q), 121.42 (t), 118.77 (t), 97.63 (t), 75.46 (q), 61.17 (t), 47.40 (s), 43.02 (q), 41.20 (p); ^{13}C NMR (CD_3OD): δ 147.22, 146.03, 141.41, 139.97, 139.68, 130.42, 129.34, 128.87, 128.72, 128.38, 127.69, 127.59, 126.59, 123.30, 121.11, 118.61, 97.76, 76.66, 61.47, 43.26, 40.79; ^{13}C NMR (D_2O) δ 145.84, 145.47, 140.42, 139.39, 138.53, 130.54, 129.87, 129.61, 128.77, 128.51, 128.40, 128.37, 127.72, 124.47, 121.60, 118.61, 97.27, 76.90, 61.25, 47.77, 41.54, 40.05, 33.43, 33.39, 21.61. Anal. Calcd for $C_{29}H_{28}NO_3$•HCl: C, 73.49; H, 5.95; N, 2.96. Found: C, 73.23; H, 5.98; N, 2.73.

8*β*-Bromo-6,7-didehydro-4,5α-epoxy-6,7-diphenyl-17-methylmorphinan-3-ol (4). A CH_2Cl_2 solution of boron tribromide (1 M, 0.6 mL, 0.6 mmol) was added over 5 min to a solution of 7,7-diphenylhydrocodone **1** (64 mg, 0.21 mmol) in CH_2Cl_2 (1 mL). After the mixture was stirred for 2 h, methanol (3 mL) was added and the stirring was continued for 30 min. The solution was adjusted to pH 8 with aqueous $KHCO_3$ (10%) and then extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with water to pH 7, dried ($MgSO_4$), and filtered. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on a spinning TLC plate (1 mm, silica gel, ethyl acetate) to afford **4** (27 mg, 39%): ^1H NMR (CD_3COCD_3) δ 7.06−7.10 (m, 3H, H-Ph), 6.93−7.00 (m, 5H, H-Ph), 6.64−6.74 (m, 4H, H-1,2 and H-Ph), 5.42−5.43 (d, 1H, J = 1.64, H-5), 4.78−4.81 (dd, 1H, J = 1.64, 9.6, H-8α), 3.64−3.70 (m, 1H, H-9), 3.09−3.15 (d, 1H, J = 18.7, H-10), 3.02−3.06 (dd, 1H, J = 2.82, 9.6, H-14), 2.59−2.67 (dd, 1H, J = 4.98, 18.7, H-10), 2.52−2.56 (dd, 1H, J = 3.98, 11.0, H-11), 2.44 (s, 3H, H-NMe), 2.26−2.35 (td, 1H, J = 3.22, 12, 12, H-D ring), 2.09−2.18(td, 1H, J = 4.90, 12, 12, H-D ring), 1.71−1.75 (m, 1H, H-D ring); ^{13}C NMR (CD_3COCD_3) δ 143.40 (q), 141.54 (q), 141.03 (q), 140.88 (q), 140.78 (q), 137.27 (q), 130.47 (t), 129.82 (q), 129.71 (t), 128.15 (t), 127.90 (t), 127.15 (t), 127.05 (t), 126.41 (q), 120.26 (t), 118.21 (t), 90.85 (t), 58.67 (t), 55.55 (t), 50.27 (t), 47.27 (s), 43.41 (p), 35.64 (s), 20.09 (s); MS (HRFAB) m/z 500.1222 $[M + H]^+$ (calcd for $C_{29}H_{27}NO_2Br$, $[M + H]^+$ 500.1225).

7α-Methyl-7*β*-phenylhydromorphone (6) and 7-methyl-6*β*-phenylmorphine (7). To a solution of 7α-methyl-7*β*-phenylhydrocodone[7] (**5**) (280 mg, 0.72 mmol) in CH_2Cl_2 was added boron tribromide (2.8 mL, 2.8 mmol, 1 M in CH_2Cl_2) over 5 min at 0 °C, and the mixture was stirred for 40 min. Methanol (15 mL) was added, and the mixture was stirred for another 40 min. The solution was adjusted to pH 8 with saturated $NaHCO_3$ (aq) and extracted with chloroform (3 × 40 mL), and the solvent was removed to afford crude product (290 mg). Chromatographic separation (spinning TLC, 2 mm silica gel plate, 3% EtOH in $CHCl_3$) afforded **6** (159 mg, 59%)

and **7** (60 mg, 22%). **6**: ^{1}H NMR ($CDCl_3$) δ 7.14−7.30 (m, 5H, H-Ph), 6.61−6.71 (2d, J = 8.4, 2H, H-1,2), 4.87 (s, 1H, H-5), 3.39 (m, 1H, H-9), 3.05−3.11 (d, J = 18.3, 1H, H-10β), 2.82−2.87 (m, 1H, H-14), 2.53−2.60 (m, 1H, H-D ring), 2.49 (s, 3H, H-NMe), 2.42−2.49 (m, 1H, H-10α), 2.17−2.25 (m, 1H, H-8β), 1.79 (m, 1H, H-D ring), 1.16−1.66 (m, 1H, H-D ring), 1.40−1.49 (t, J = 13.5, 1H, H-8α), 1.14 (s, 3H, H-Me); MS (FAB) m/z 376.2 $[M + H]^+$. Compound **6** (199 mg, 0.53 mmol) was dissolved in $CHCl_3$ (5 mL) and MeOH (2 mL) and treated with Et_2O·HCl to afford crude hydrochloride, which then was recrystallized (i-PrOH) to afford **6**·HCl (147 mg, 67%): mp 251 °C dec; MS (FAB) m/z 376.2 $[M - Cl]^+$. Anal. Calcd for $C_{24}H_{25}NO_3$·HCl: C, 69.98; H, 6.36; N, 3.40; Cl, 8.61. Found: C, 69.78; H, 6.52; N, 3.15; Cl, 8.43.

7: ^{1}H NMR ($CDCl_3$) δ 7.19−7.43 (m, 5H, H-Ph), 6.53−6.64 (2d, J = 7.8, 2H, H-1,2), 5.34 (m, 1H, H-8), 4.82 (s, 1H, H-5), 3.43 (m, 1H, H-9), 3.01−3.07 (d, J = 18.9, 1H, H-10β), 2.77 (m, 1H, H-14), 2.54−2.57 (m, 1H, H-D ring), 2.46 (s, 3H, H-NMe), 2.41−2.54 (m, 1H, H-D ring), 2.37 (m, 1H, H-10α), 1.85 (m, 1H, H-D ring), 1.65−1.70 (m, 1H, H-D ring), 1.56 (s, 3H, H-Me); ^{13}C NMR ($CDCl_3$) δ 19.92 (p), 21.07 (s), 36.21 (t), 41.30 (s), 43.43 (p), 43.91 (s), 47.37 (p), 59.80 (t), 75.41 (t), 97.35 (t), 118.32 (t), 120.92 (t), 124.81 (t), 126.29 (q), 127.03 (t), 128.24 (t), 129.36 (t), 131.42 (q), 139.21 (q), 141.82 (q), 143.56 (q), 144.80 (q); MS (FAB) m/z 376.2 $[M + H]^+$. 7-Methyl-6β-phenylmorphine **7** (60 mg, 0.16 mmol) was dissolved in $CHCl_3$−MeOH (4 mL, 3:1), and Et_2O·HCl was added to afford crude hydrochloride which was recrystallized (i-PrOH−-Et_2O) to afford **7**·HCl (41 mg, 62%): mp = 237 °C dec; MS (FAB) m/z 376.2 [M-Cl]$^+$. Anal. Calcd for $C_{24}H_{25}NO_3$·HCl: C, 69.98; H, 6.36; N, 3.40; Cl, 8.61. Found: C, 69.98; H, 6.52; N, 3.21; Cl, 8.45.

7β-Methyl-7α-phenylhydrocodone (9). To a solution of 7α-phenylhydrocodone[7] (**8**) (220 mg, 0.58 mmol) in THF (15 mL) was added lithium bis(trimethylsilyl)amide (1 M in THF, 2.0 mL, 2.00 mmol) and 12-crown-4 (100 mg, 0.57 mmol) at −23 °C, and the resulting solution was stirred for 5 min. Methyl iodide (123 mg, 0.86 mmol) was added over 5 min, and the reaction was stirred for 23 h. Triethylamine (3 mL) was added, and the resulting mixture was kept at 50−60 °C for 4 h. Upon filtration, the filtrate was removed at reduced pressure and the residue was subjected to spinning TLC separation (silica gel, 1 mm) with the elution of EtOH (4%) in $CHCl_3$ to afford compound **9** (48%). ^{1}H NMR ($CDCl_3$) δ 7.18−7.26 (m, 3H, H-Ph), 6.99−7.00 (m, 2H, H-Ph), 6.68−6.67 (2d, J = 8.1, 2H, H-1,2), 5.05 (s, 1H, H-5), 3.91 (s, 3H, H-OMe), 3.38 (m, 1H, H-9), 3.05−3.12 (d, J = 18.3, 1H, H-10), 2.59 (s, 3H, H-NMe), 1.70 (s, 3H, H-Me); MS (FAB) m/z 390.1 $[M + H]^+$.

7β-Methyl-7α-phenylhydromorphone (10) and 5β,7β-dimethyl-7α-phenylhydromorphine (11). A CH_2Cl_2 solution (1 M) of boron tribromide (0.6 mL, 0.6 mmol) was added over 5 min to a solution of 7β-methyl-7α-phenylhydrocodone (**9**) (60 mg, 0.15 mmol) in CH_2Cl_2 at 0 °C. After stirring for 45 min, methanol (10 mL) was added, and the mixture was stirred for 1 h. The solution was washed with saturated $NaHCO_3$ (aq) and extracted with chloroform (3 × 30 mL), and the solvent was removed in reduced pressure. Chromatographic separation on a spinning TLC (1 mm silica gel plate, eluted with EtOH (1%) in $CHCl_3$ afforded **10** (17 mg, 29%) and **11** (9 mg, 15%). **10**: ^{1}H NMR ($CDCl_3$) δ 7.19−7.25 (m, 5H, H-Ph), 6.94−6.97 (2d, J = 8.4, 2H, H-1,2), 4.93 (s, 1H, H-5), 3.26 (m, 1H, H-9), 3.02−3.09 (m, 1H, H-10β), 2.46 (s, 3H, H-NMe), 1.61 (s, 3H, H-Me); MS (FAB) m/z 376.1 $[M + H]^+$, m/z 374.1 $[M - H]^-$. Compound **10** was dissolved in $CHCl_3$ (3 mL), treated with Et_2O·HCl, and filtered. After recrystallization twice from i-PrOH, **10**·HCl was collected: mp = 234−240 °C dec; MS (FAB) m/z 376.2 $[M - Cl]^+$. Anal. Calcd for $C_{24}H_{25}NO_3$·1.5HCl: C, 66.45; H, 6.18; N, 3.22. Found: C, 66.51; H, 5.89; N, 3.19.

11: ^{1}H NMR ($CDCl_3$) δ 7.15−7.22 (m, 3H, H-Ph), 6.78−6.81 (m, 2H, H-Ph), 6.66−6.76 (2d, J = 7.8, 2H, H-1,2), 3.27−3.28 (m, 1H, H-9), 2.99−3.06 (d, J = 18.3, 1H, H-10β), 2.79−2.85 (m, 1H), 2.66−2.71 (m, 1H), 1.69 (s, 3H, H-Me), 1.61 (s, 3H, H-Me); ^{13}C NMR ($CDCl_3$) δ 215.76, 144.79, 144.17, 139.05, 129.14, 128.77, 128.62, 127.39, 125.83, 120.90, 118.29, 95.88, 59.87, 53.62, 46.88, 43.29, 39.87, 37.12, 32.10, 22.99, 20.95, 20.58; MS (FAB) m/z 390.1 $[M + H]^+$, m/z 388.0 $[M - H]^-$; MS (HRFAB) m/z 390.2054 (calcd for $C_{25}H_{28}NO_3$ m/z = 390.2069).

7α-Phenylhydromorphone (12). Boron tribromide in CH_2Cl_2 (1 M, 0.4 mL, 0.4 mmol) was added over 5 min to a solution of 7α-phenylhydrocodone[7] (**8**) (80 mg, 0.26 mmol) in CH_2Cl_2 (5 mL). After stirring for 15 min at room temperature, the reaction was quenched with methanol (5 mL) and stirred for 30 min. The mixture was adjusted to pH 8 with aqueous $KHCO_3$ (10%), extracted with CH_2Cl_2−MeOH (95/5, 4 × 25 mL), and washed with water to pH 7. The solvent was evaporated under reduced pressure, and the residue was chromatographed on a spinning TLC plate (silica gel, 1 mm, 3/97, MeOH−CH_2Cl_2) to afford **12** (25 mg, 26%): ^{1}H NMR (CD_3COCD_3) δ 7.12−7.23 (m, 3H, 7-Ph), 6.94−6.98 (m, 2H, H-Ph), 6.53−6.64 (2d, 2H, J = 1.8, H-1,2), 4.95 (s, 1H, H-5), 3.89−3.95 (dd, 1H, J = 4.2, 13.8, H-7β), 3.15−3.18 (m, 1H, H-9), 2.97−3.03 (d, 1H, J = 18.3, H-10), 2.83−2.89 (m, 1H, H-14), 2.47−2.50 (m, 1H, H-D ring), 2.35 (s, 3H, H-Me), 2.29−2.37 (dd, 1H, J = 5.7,18.3), 2.13−2.17 (m, 1H, H-8β), 1.92−1.99 (m, 1H, H-D ring), 1.62−1.65 (m, 1H, H-D ring), 1.55−1.68 (m, 1H, H-8α). 7α-Phenylhydromorphone (**12**) (25 mg) was treated with Et_2O·HCl in a minimum amount of CH_2Cl_2 (0.5 mL) and recrystallized twice from MeOH-ether to afford **12**·HCl (15 mg). ^{1}H NMR (CD_3OD): δ 7.19−7.30 (m, 3H, H-Ph), 6.96−6.99 (m, 2H, H-ph), 6.75 (s, 2H, H-1,2), 5.119 (s, 1H, H-5), 3.96−4.02 (m, 1H, H-7β), 3.30−3.37 (m, 1H, H-D ring), 3.20−3.25 (m, 1H, H-10), 3.02−3.11 (m, 1H, H-10), 3.00 (s, 3H, H-NMe), 2.80−2.90 (m, 1H, H-9), 2.40−2.50 (m, 1H, H-D ring), 2.12-2.20 (m, 1H, H-8β), 1.99−2.06 (m, 1H, H-D ring), 1.58−1.70 (m, 1H, H-8α); MS (FAB) m/z 362 $[M + H]^+$. Anal. Calcd for $C_{23}H_{23}NO_3$·HCl·1.5H_2O: C, 65.01; H, 6.40; N, 3.29. Found: C, 65.16; H, 6.36; N, 3.29.

7α-Phenylhydromorphone (12) and 6,7-Didehydro-4,5α-epoxy-17-methyl-7-phenylmorphinan-6-one (14). Reaction of 7α-phenylhydrocodone **8** with boron tribromide. 7α-Phenylhydrocodone[7] (**8**) (220 mg, 0.587 mmol) in CH_2Cl_2 (10 mL) was treated with boron tribromide (1 M in CH_2Cl_2, 2.4 mL) at room temperature for 4 days under N_2. Methanol (25 mL) was added, and the mixture was stirred for 30 min at room temperature and then refluxed for 30 min. The solution was adjusted to pH 8 with saturated $NaHCO_3$ (aq) and extracted with chloroform (4 × 30 mL). The organic layers were combined and washed with water (20 mL), and the solvent was removed under reduced pressure. The residue was subjected to spinning TLC separation (silica gel, 2 mm plate) by eluting with EtOH (5%) in $CHCl_3$ to afford α,β-unsaturated ketone **14** (26.8 mg, 12.7%) and 7α-phenylhydromorphone (**12**) (17.8 mg, 8.3%). **14**: ^{1}H NMR ($CDCl_3$) δ 7.18−7.23 (m, 3H, H-Ph), 7.05−7.08 (m, 2H, H-Ph), 6.81 (d, J = 1.8, 1H, H-8), 6.48−6.60 (2d, J = 8.1, 2H, H-1,2), 4.82 (s, 1H, H-5), 3.51−3.54 (dd, J = 3, 5.7, 1H, H-9), 3.36−3.38 (m, 1H, H-14), 3.03−3.09 (d, J = 18.0, 1H, H-10), 2.40 (m, 3H, H-NMe), 1.54 (s, 3H, H-Me); ^{13}C NMR ($CDCl_3$) δ 193.3, 147.7, 143.1, 139.5, 136.9, 130.6, 128.9, 128.8, 128.6, 128.4, 128.2, 126.1, 120.5, 117.9, 90.08, 59.50, 47.01, 43.54, 43.01, 41.40, 34.44, 30.36, 20.64; IR (KBr) 1733.8 (m, C=O) cm^{-1}; MS (FAB) m/z 360.2 $[M + H]^+$; MS (HRFAB) m/z 359.1524 (calcd for $C_{23}H_{21}NO_3$ m/z = 359.1521).

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Supporting Information Available: Copies of ^{1}H NMR spectra of **4**, **9**, **11**, and **14** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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