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Synthesis of Buprenorphine from Oripavine via N-Demethylation of Oripavine Quaternary Salts

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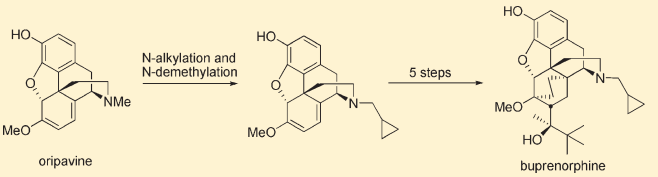
Supporting Information

ABSTRACT: Buprenorphine was synthesized from oripavine by a sequence involving the conversion of oripavine into its cyclopropylmethyl quaternary salt, N-demethylation with thiolate to *N*-cyclopropylmethyl nororipavine, and conversion of this material to the title compound by previously available methods. The new synthesis avoids toxic reagents used previously, is shorter, and proceeds in comparable yields. Experimental and spectral data are provided for all new compounds.



INTRODUCTION

Buprenorphine (**1**), Figure 1, is a semisynthetic opiate used to treat moderate to severe chronic pain at low dosages. At higher dosages it is used to treat opiate addiction, sometimes in combination therapy with naloxone (Suboxone). It acts as a partial agonist at the μ- and δ-receptors and has a competitive antagonist activity at the κ-receptors.

One of the current routes to buprenorphine is an eight-step sequence from thebaine (**2**) proceeding as shown in Scheme 1.[1] It employs cyanogen bromide in a von Braun N-demethylation[2] of **5** to *N*-nitrile **6**, which is then hydrolyzed to the secondary amine **7**. Alkylation of **7** with cyclopropylmethyl carbonyl chloride followed by lithium aluminum hydride reduction and then O-demethylation then furnishes buprenorphine (**1**). While this sequence is both efficient and performed at industrial scales it could be vastly improved by eliminating the cyanogen bromide step and replacing it with a milder as well as environmentally more benign protocol.

RESULTS AND DISCUSSION

In this paper we report on an improved synthesis of the title compound. The literature synthesis contains two demethylation steps: one N-demethylation of **5** performed with cyanogen bromide and the other, the final O-demethylation of **8**, accomplished with a KOH/digol. Various methods for O-demethylation of aryl alkyl ethers also reported in the literature employed thioethoxide,[3] thiopropoxide,[4] BBr_3,[5] or $NbCl_5$.[6] It would be beneficial if these demethylation steps could either be avoided or at least combined into one operation. To this end we examined the conversion of oripavine to the cyclopropylmethyl derivative **10** by thiolate-induced N-demethylation of the quaternary salts **9**, prepared as a mixture of *S*- and *R*-stereoisomers as shown in Scheme 2.[7]

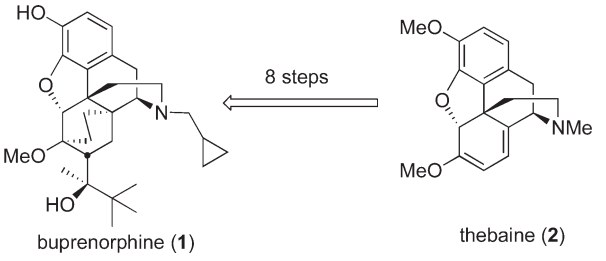


Figure 1. Buprenorphine synthesis from thebaine.

Oripavine was converted to its quaternary salts by heating with cyclopropylmethyl bromide in DMF (0.67 M mixture of oripavine). This procedure provided for a ratio of *S*- and *R*-isomers varying between 1.8:1 and 2.6:1, detected in aliquots from the reaction mixture; however, the solid precipitate consisted of almost pure *R*-isomer. The pure *R*-isomer was isolated from the mixture by careful precipitation, in an approximate yield of 20%.

The use of dimethylacetamide (DMA, 0.67 M mixture of oripavine) as solvent in the above quaternization provided a reaction mixture as a thick slurry. Isolation consisted of filtration and furnished 94% of mass as a solid in 98% purity by HPLC (*S*/*R* ratio = 1.5: 1). The use of *N*-methylpyrrolidone (NMP) and DMF as the solvent mixture (1:1, 0.84 M mixture of oripavine) provided cyclopropylmethyloripavine salt as a solid precipitate in 28% yield (*S*/*R* ratio = 0.26:1) and in 56% yield from mother liquor with a purity of 97% by HPLC (*S*/*R* ratio = 7.1:1).

The quaternization of oripavine proceeded quantitatively in various polar aprotic solvents, provided two cycles were used: the

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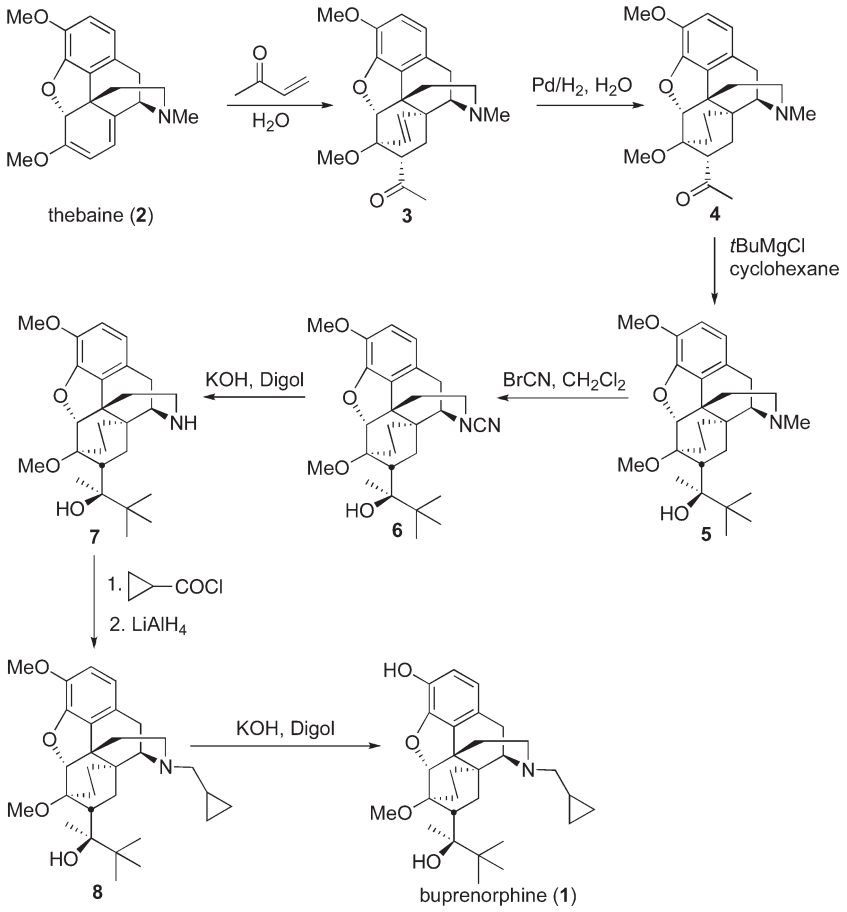
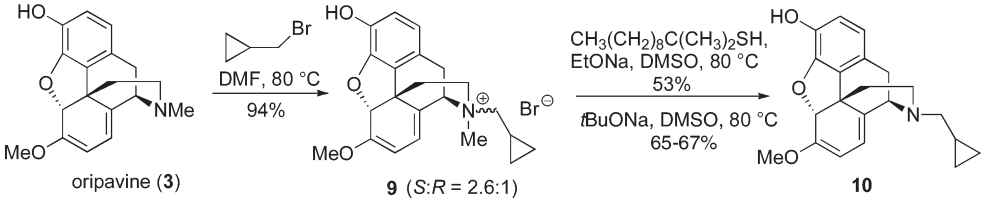
Scheme 1



Scheme 2



crude product was resubjected to treatment with additional cyclopropylmethyl bromide with heating in order to provide the full conversion. The mixture of diastereomeric salts **9** was used in the synthesis of *R*-methylnaltrexone as described recently.[8]

The use of thiolate anions, such as PhSNa, as soft nucleophiles for the N-demethylation of morphine alkaloids was previously reported.[9] The N-demethylation of the quaternary ammonium salt of oripavine was also performed with *tert*-dodecanethiol as the nucleophilic reagent and sodium ethoxide or sodium *tert*-butoxide as the base. We found that the diastereomers yielded *N*-methylcyclopropyl nororipavine at different rates and in different yields, as shown in Table 1, where the conditions and the yields are summarized.

In addition to the noticeable increase in yield in the experiments on small scale, the appearance and handling of the reaction mixtures during workup has significantly improved. It is also noteworthy to mention that the *R*-isomer of **9** reacts at a faster rate than the corresponding *S*-isomer.

Table 1. Summary of Conditions for the N-Demethylations of 9

entry	substrate/ (mg)	solvent	*T* (°C)	time (min)	base	yield (%)
1	(*R*) salt	DMSO	80	45	NaOEt	71[b]
2	(*R*) salt	DMSO	100	10	NaOEt	77[b]
3	(*S*) salt	DMSO	80	55	NaOEt	63[b]
4	(*S*,*R*) salt[a]	DMSO	80	55	NaO*t*-Bu	67[c]

[a] Mixture in 1.9/1 ratio. [b] Isolated by column chromatography, 200 mg scale. [c] Isolated by crystallization, 1 g scale.

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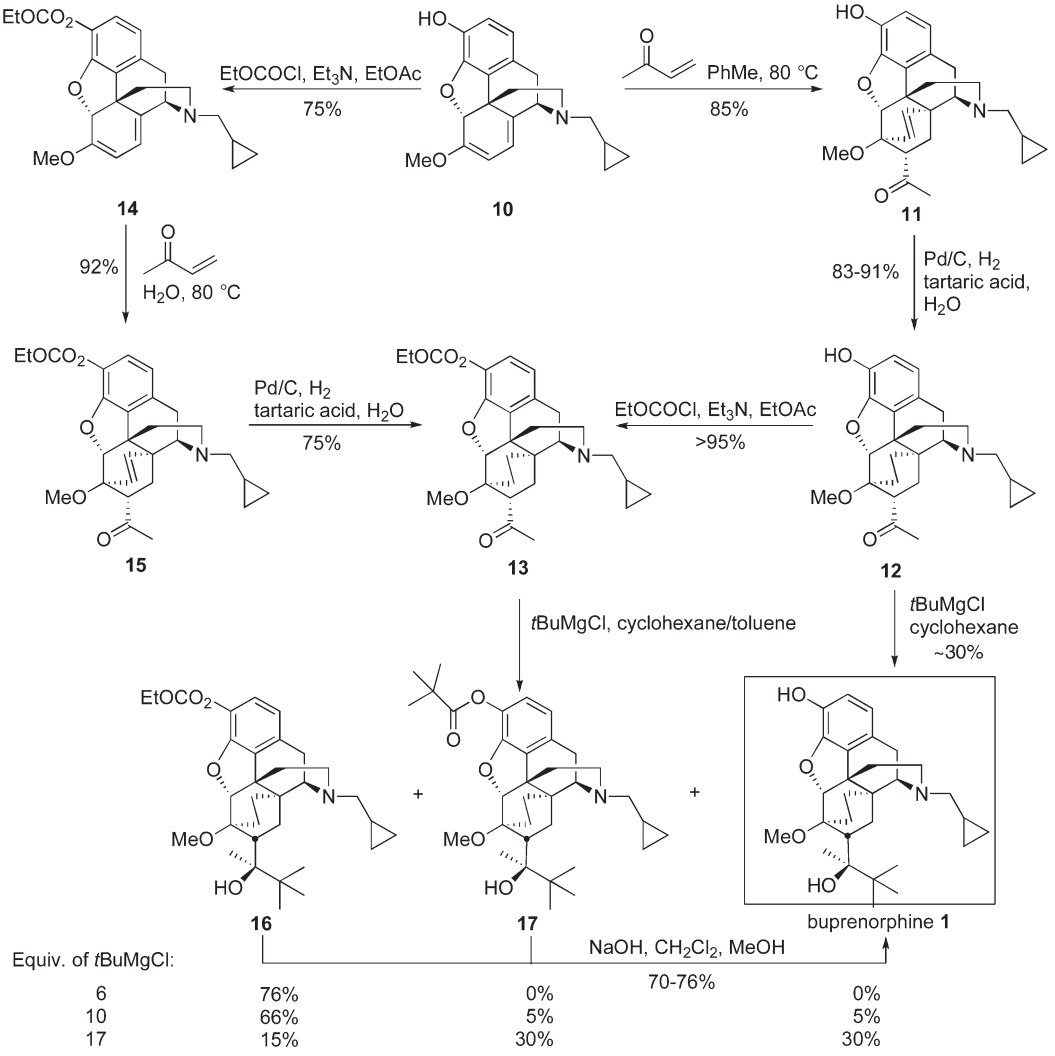
Scheme 3



With the *N*-cyclopropylmethyl nororipavine **10** in hand, we turned our attention to its conversion to buprenorphine. Two routes, depicted in Scheme 3, were investigated and compared in terms of overall efficiency. The Diels–Alder cycloaddition of methylvinyl ketone with the diene system of oripavine produced the adduct **11** in high yield.

A small amount (4–8%) of byproduct resulting from the 1,4-addition of the phenol to methyl vinyl ketone, namely compound **18**, Figure 2, was formed in this reaction, but the crude product was easily purified by crystallization (see the Experimental Section for the spectral data of the byproduct). Hydrogenation of **11** in water containing tartaric acid gave cleanly **12**, in which the phenol hydroxyl was protected as its ethyl carbonate **13**. The second route involved the protection of the phenol as its carbonate **14** prior to performing the Diels–Alder reaction that provided the cycloadduct **15** in 92% yield. Hydrogenation of **15** then furnished carbonate **13**, converging with the previous sequence. The comparison of the two routes provided the following conclusion: The overall yield of buprenorphine (**1**) via **11**, **12**, and **13** was 32%, while the route via **14** and **15** gave 23% overall yield of the title compound. The former route is more convenient because the intermediates **11** and **12** were crystalline, thus simplifying purification.

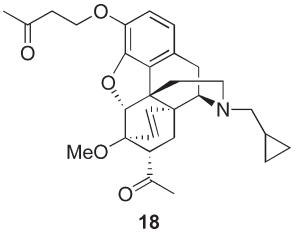


Figure 2. Byproduct from the Diels–Alder cycloaddition of unprotected nororipavine.

The attainment of **13** left only the Grignard addition to complete the synthesis. Ketone **13** was treated with 6 equiv of Grignard reagent, which was prepared as a slurry, to produce 76% of carbonate **16**, Scheme 3. When the reaction was performed with 10 equiv of Grignard reagent, the yield of **16** was diminished and a byproduct, identified as the pivalate ester **17**, appeared, along with ~5% of buprenorphine produced by the full cleavage of the

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carbonate. With 17 equiv of the Grignard reagent, the proportion of the pivalate **17** and buprenorphine increased to 30%, respectively, Scheme 3. The mixture of **16** and **17** obtained under any of these conditions was then treated with sodium hydroxide in methanol/dichloromethane to furnish buprenorphine, identical in all respects with the known standard. The direct conversion of the O-unprotected intermediate **12** to buprenorphine with excess Grignard reagent was also performed, as shown in Scheme 3. However, the yield of buprenorphine from **12** was never higher than ~30% at the expense of recovered starting material and a minor byproduct that was not further identified. If this reaction mixture was subjected to a second cycle, the yield of buprenorphine increased to 42%. This protocol was not investigated in detail in view of the much higher-yielding route via carbonate **13**. In the future, a better protecting group for the phenol may be an acetate as it would be more easily cleaved by the Grignard reagent.

■ CONCLUSIONS

The synthesis of buprenorphine described in this paper proceeds in seven chemical steps but is reducible to just four operations, as some of the steps may be combined without isolation of the intermediates. The major improvement over the previous synthesis is the elimination of cyanogen bromide as the agent of N-demethylation and avoidance of O-demethylation required in the route from thebaine. The synthesis is amenable to scale up and proceeds with the overall yield of 32% from oripavine.

■ EXPERIMENTAL SECTION

All nonaqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. All solvents were distilled unless otherwise noted. Analytical thin layer chromatography was performed on silica gel 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel (230−400 mesh). Melting points are uncorrected. IR spectra were obtained on a FT-IR spectrometer. Optical rotations was measured on a polarimeter at a wavelength of 589 nm. ^{1}H and ^{13}C spectra were recorded on a 300 and 600 MHz spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants (Hz), integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (C) relative to TMS.

***N*-Cyclopropylmethyl Oripavine Ammonium Bromide (9).** To a flame-dried, argon purged round-bottom flask with attached reflux condenser was charged a suspension of oripavine (**3**) (1.84 g, 6.18 mmol) in anhydrous DMF (10 mL). (Bromomethyl)cyclopropane (1.8 mL, 18.5 mmol, 3.0 equiv) was added in one portion to the vigorously stirred suspension of oripavine at room temperature. The reaction mixture was immersed in a preheated oil bath at 80 °C and allowed to stir under argon atmosphere for 12 h. The reaction mixture was cooled, and an aliquot was analyzed by HPLC (285 nm) and determined to contain approximately 4% (as determined by integration) of oripavine (as the HBr salt). $NaHCO_3$ (21 mg, 0.24 mmol, 4 mol %) was added to the reaction mixture and allowed to stir for 1 h prior to the addition of (bromomethyl)cyclopropane (0.30 mL, 3.1 mmol, 0.5 equiv) at room temperature. The reaction mixture was immersed in the preheated oil bath at 80 °C for an additional 8 h prior to analysis by HPLC (285 nm). It was observed that approximately 1% oripavine remained in the reaction mixture. The reaction mixture (fine beige slurry) was cooled to room temperature and filtered through a fine-fritted funnel. The filtered solid was washed with MeOH (1.5 mL), and the product precipitated by slow, inverse addition of the reaction mixture to a vigorously stirred volume of toluene (~100 mL). The precipitate was filtered and washed with toluene (2 × 10 mL), and the solid was collected and dried under vacuum to provide a slightly off-white solid in greater than quantitative yield. This crude material was triturated in acetone (50 mL) at room temperature for 2 h prior to a second filtration. The solid was collected and dried under vacuum to yield 2.60 g (94% yield) of *N*-cyclopropylmethyl oripavine ammonium bromide salt (**9**) as a white, free-flowing solid; mp 194−200 °C; isomeric ratio determined by HPLC (*S*:*R*) 2.6:1.

R-Isomer. mp 219−221 °C (EtOH); R_f 0.30 (DCM + 20% methanol); $[\alpha]^{20}_D$ −109.38 (*c* = 1, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.01 (d, *J* = 6.6 Hz, 1H), 5.42 (s, 1H), 5.29 (d, *J* = 6.6 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, 1H) 3.71 (m, 1H), 3.70 (m, 1H), 3.61 (s, 3H), 3.45 (dd, *J* = 13.5, 4.6 Hz, 1H), 3.39 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.29 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H) 3.19 (s, 3H), 3.06 (dd, *J* = 19.4, 7.2 Hz, 1H), 2.59 (ddd, *J* = 14.1, 14.1, 5.1 Hz, 1H), 1.86 (dd, *J* = 14.2, 2.9 Hz, 1H), 1.21 (m, 1H), 0.75 (m, 2H), 0.51 (m, 1H), 0.44 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.6, 143.5, 140.4, 132.6, 124.1, 122.5, 120.2, 119.8, 117.6, 96.1, 87.2, 68.1, 67.1, 55.6, 54.0, 46.1, 44.2, 31.5, 30.4, 5.1, 4.4, 4.2.

S-Isomer. mp 195−197 °C (MeOH + i-PrOH); R_f 0.28 (DCM + 20% methanol); $[\alpha]^{20}_D$ −43.73 (*c* = 1, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.98 (d, *J* = 6.6 Hz, 1H), 5.39 (s, 1H), 5.26 (d, *J* = 6.6 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 3.77 (d, *J* = 19.6 Hz, 1H), 3.64 (dd, *J* = 13.4, 6.1 Hz, 1H), 3.60 (s, 3H), 3.49 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.35 (m, 1H), 3.29 (s, 3H), 3.28 (m, 1H), 3.06 (dd, *J* = 19.5, 7.0 Hz, 1H), 2.56 (ddd, *J* = 14.0, 14.0, 4.5 Hz, 1H), 1.79 (d, *J* = 11.9 Hz, 1H), 1.21 (m, 1H), 0.72 (m, 2H), 0.52 (m, 1H), 0.39 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.6, 143.4, 140.4, 132.6, 124.1, 122.6, 120.2, 119.7, 117.6, 96.0, 87.3, 68.6, 63.9, 55.58, 54.0, 48.6, 43.7, 31.3, 30.6, 4.9, 4.6, 4.3; MS (FAB+) *m*/*z* (%): 55 (31), 98 (24), 112 (38), 239 (12), 352 (100); HRMS calcd for $C_{22}H_{26}NO_3^+$ 352.1907, found 352.1898.

***N*-Cyclopropylmethyl Nororipavine (10).** To a slurry of sodium *tert*-butoxide (0.67 g; 7.04 mmol) in freshly distilled DMSO (4.7 mL) was added *tert*-dodecanethiol (1.42 g; 7.04 mmol, distilled) in one portion. The resulting mixture was vigorously stirred and immersed in a preheated oil bath at 90 °C for 10 min prior to decreasing the temperature to 80 °C. A solution of *N*-cyclopropylmethyl oripavine ammonium bromide **9** (1.01 g, 2.34 mmol) in DMSO (4.7 mL) was added to the preformed mixture of *tert*-dodecanethiolate at 80 °C over 10 min. A sharp color change from a clear, slightly yellow solution to a brown colored mixture occurred after the addition of the first several drops of the *N*-cyclopropylmethyl oripavine ammonium bromide solution. The reaction mixture was allowed to stir at 80 °C for 40 min following the addition, and the progress was monitored by HPLC (285 nm). After the complete consumption of starting material, the reaction mixture was allowed to cool to room temperature with stirring and poured into H_2O (40 mL). The pH of the aqueous mixture was adjusted to pH 2 with HCl (6 M) and washed with hexanes (2 × 20 mL). The pH of the aqueous mixture (milky yellow suspension) was readjusted to pH 8 with NaOH (aq, 15%). A fine, white precipitate was observed upon pH adjustment and was cleared by extraction with EtOAc (1 × 20 mL, 1 × 10 mL). The pH of the aqueous phase was adjusted again to pH 8 (white precipitate was observed) and extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with H_2O (1 × 10 mL) and brine (1 × 10 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated to provide crude material, which was crystallized from acetone/cyclohexane mixture (1:1). The yield of the crystallization was 0.48 g (61%). The mother liquor was chromatographed on silica gel (20% MeOH/EtOAc) and crystallized from acetone/cyclohexane to afford additional 0.05 g

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(6%) of *N*-cyclopropylmethyl nororipavine **10** as a pale-yellow, crystalline solid; R_f 0.25 (20% MeOH/EtOAc); mp 165−166 °C (DCM), mp 166−167 °C (methanol); $[\alpha]^{20}_D$ −168.60 (*c* = 1, $CHCl_3$); IR (KBr) ν 3445, 2908, 1630, 1458, 1234, 1046, 1016, 926, 868 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.65 (d, *J* = 8.4 Hz, 1 H), 6.55 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 6.6 Hz, 1 H), 5.29 (s, 1 H), 5.07 (d, *J* = 6.6 Hz, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 3.61 (s, 3 H), 3.29 (d, *J* = 18.0 Hz, 1 H), 3.00 (dd, *J* = 12.6, 4.2 Hz, 1 H), 2.90 (m, 1 H), 2.76 (dd, *J* = 18.0, 7.2 Hz, 1 H), 2.55 (m, 2 H), 2.24 (m, 1 H), 1.71 (d, *J* = 11.4 Hz, 1 H), 0.97 (m, 1 H), 0.56 (d, *J* = 8.4 Hz, 2 H), 0.19 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.2, 143.1, 138.8, 133.2, 132.6, 126.7, 119.7, 116.5, 112.1, 96.4, 89.4, 58.57, 58.55, 54.9, 46.9, 43.8, 36.2, 31.2, 9.2, 3.9 (2 × CH_2); MS (+EI) *m*/*z* (%): 43 (100), 58(19), 84 (56), 227 (8), 282 (12), 337 (41); HRMS calcd for $C_{21}H_{23}NO_3$ 337.1678, found 337.1681.

[7α-Acetyl-17-(cyclopropylmethyl)-6,14-endo(etheno)tetrahydronororipavine]. *1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethenomorphinan-7-yl]ethanone (**11**).* Cyclopropylmethyl nororipavine **10** (157 mg; 0.53 mmol) was dissolved in toluene (2.4 mL), and methylvinyl ketone (0.8 mL) was added. The reaction mixture was stirred with a magnetic stirbar and heated to 80 °C. After 12 h, TLC (ethyl acetate) analysis indicated no starting material (R_f = 0.05) but the presence of **11** (R_f = 0.5) and the adduct **18** (R_f = 0.4). The reaction mixture was then concentrated in vacuo, and the resulting light brown solid was crystallized from hot EtOH (0.4 mL), yielding **11** (182 mg, 85%) as a white solid.

11: mp 211−214 °C (EtOH); R_f = 0.5 (ethyl acetate); $[\alpha]^{20}_D$ −236.47° (*c* = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3587, 3072, 3051, 3027, 3000, 2970, 2935, 2920, 2891, 2839, 2814, 2788, 1702, 1637, 1607, 1500, 1467, 1427, 1381, 1352, 1317, 1242, 1217, 1163, 1124, 1096, 1084, 1028, 932, 822, 786, 735; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.62 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 5.87 (d, *J* = 9.0 Hz, 1H), 5.59 (d, *J* = 9.0 Hz, 1H), 4.62 (s, 1 H), 3.60−3.57 (m, 4H), 3.11 (d, *J* = 18.6 Hz, 1H), 3.03 (dd, *J* = 12.6, 10.2 Hz, 1H), 2.95 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.73 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.45−2.38 (m, 3H), 2.35 (dd, *J* = 12.6, 6.6 Hz, 1H), 2.16 (s, 3H), 1.98 (ddd, *J* = 13.2, 13.2, 5.4 Hz, 1H), 1.86 (dd, *J* = 12.6, 2.4 Hz, 1H), 1.36 (dd, *J* = 12.6, 6.6 Hz, 1H), 0.85−0.83 (m, 1H), 0.56−0.49 (m, 2H), 0.17−0.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 209.3, 146.6, 137.4, 136.4, 134.1, 127.8, 125.7, 119.9, 116.3, 95.2, 81.3, 59.8, 57.1, 53.2, 50.7, 48.5, 44.0, 43.3, 33.5, 30.3, 30.0, 23.3, 9.5, 4.1, 3.5; MS (FAB+) *m*/*z* (%) 408 (18), 407 (13), 243 (22), 242 (100), 184 (11), 142 (19); HRMS (FAB+) calcd for $C_{25}H_{29}N_1O_4$: 407.2096. Found 407.2096.

[7α-Acetyl-17-(cyclopropylmethyl)-6,14-endo(etheno)tetrahydronororipavine]. *1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-(3-oxobutyl)-6-methoxy-6,14-ethenomorphinan-7-yl]ethanone (**18**).* This material was isolated by chromatography of combined filtrates left after the crystallization of **11**. First chromatography: hexane/ethyl acetate 4:1. Second chromatography: toluene/ethyl acetate 3:1.

18: Colorless oil. R_f = 0.5 (ethyl acetate); $[\alpha]^{20}_D$ −183.61° (*c* = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3484, 3421, 3406, 3075, 2997, 2924, 2835, 2813, 2777, 1712, 1629, 1600, 1497, 1444, 1384, 1357, 1250, 1205, 1170, 1103, 1054, 937, 796; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.64(d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 5.90 (d, *J* = 9.0 Hz, 1H), 5.60 (d, *J* = 9.0 Hz, 1H), 4.57 (s, 1 H), 4.40−4.20 (m, 2H), 3.61 (s, 3H), 3.58 (dd, *J* = 11.7, 6.3 Hz, 1H), 3.11 (d, *J* = 18.3 Hz, 1H), 3.08−2.90 (m, 2H), 2.87 (t, *J* = 6.6 Hz, 1H), 2.72 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.48−2.28 (m, 4H), 2.22 (s, 3H), 2.16 (s, 3H), 1.98 (ddd, *J* = 12.0, 12.0, 5.1 Hz, 1H), 1.85 (dd, *J* = 12.9, 2.7 Hz, 1H), 1.37 (dd, *J* = 12.0, 5.7 Hz, 1H), 0.91−0.77 (m, 1H), 0.57−0.47 (m, 2H), 0.19−0.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.3, 206.8, 148.6, 140.4, 136.4, 134.6, 129.2, 125.6, 119.6, 116.3, 95.6, 81.4, 65.2, 59.8, 56.9, 53.6, 50.8, 48.1, 43.9, 43.4, 43.2, 33.6, 30.60, 30.55, 29.9, 23.3, 9.5, 4.1, 3.4; MS (FAB+) *m*/*z* (%) 478 (100), 408 (26), 407 (16), 326 (14), 246 (28); HRMS from 408 fragment (FAB+) calcd for $C_{25}H_{30}N_1O_4$: 408.2174. Found 408.2142.

[7α-Acetyl-17-(cyclopropylmethyl)-6,14-endo(ethano)tetrahydronororipavine]. *1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]ethanone (**12**).* The Diels−Alder adduct **11** (1.64 g; 4.01 mmol), tartaric acid (642 mg; 4.01 mmol), and Pd/C (450 mg; 10 wt %) were suspended in deionized water (15 mL). The flask was then evacuated/refilled with H_2 gas (four cycles) and subjected to hydrogenation (1 atm.). The reaction mixture was then stirred at 80 °C for 16 h under 1 atm of hydrogen. TLC (ethyl acetate) analysis showed only traces of starting material (R_f = 0.5) and a majority of **12** (R_f = 0.4). The TLC sample was prepared by extraction of few drops of reaction mixture between ethyl acetate (0.5 mL) and a satd solution of $NaHCO_3$ (0.5 mL). The hot reaction mixture was then filtered through a 0.7 cm pad of Celite which was then washed with hot deionized water (70 °C, 2 × 2 mL). After the filtrate was cooled to room temperature, the pH was adjusted to 6.60−6.70 (40% KOH; 930 μL) with vigorous stirring. The resulting white precipitate was then filtered off and dried overnight under vacuum at 50 °C to yield a porous white solid (1.52 g). ^1H NMR showed that this material contains ∼3% of starting **11** and ∼3% of corresponding β-diastereomer. Chromatography (10 mL silica, hexane/ethyl acetate 1:1) of 150 mg of this material afforded 135 mg of pure **12**. It was determined that the crude material contained ∼10% water and inorganic impurities. The yield of **12** was estimated to be 1.37 g (83%).

12: mp 170−172 °C (EtOH), 166−168 °C (crude evaporated from ethyl acetate); R_f = 0.4 (ethyl acetate); $[\alpha]^{20}_D$ −109.93° (*c* = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3463, 3075, 2956, 2924, 2874, 2853, 2813, 2777, 1709, 1647, 1610, 1502, 1458, 1384, 1356, 1331, 1283, 1160, 1095, 1030, 958, 820, 702; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.70 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 8.1 Hz, 1H), 4.51 (d, *J* = 1.8 Hz, 1H), 3.43 (s, 3H), 3.10−3.04 (m, 2H), 2.97 (d, *J* = 18.3 Hz, 1H), 2.76 (ddd, *J* = 13.5, 11.4, 3.9 Hz, 1H), 2.65 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.37−2.23 (m, 7H), 2.05 (ddd, *J* = 12.6, 12.6, 5.7 Hz, 1H), 1.74 (dd, *J* = 13.2, 6.3 Hz, 1H), 1.69−1.40 (m, 3H), 1.30 (ddd, *J* = 12.3, 12.3, 8.7 Hz, 1H), 0.83−0.64 (m, 2H), 0.54−0.40 (m, 2H), 0.15−0.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.9, 145.3, 137.4, 132.4, 128.2, 119.7, 116.5, 94.8, 77.8, 59.8, 58.4, 52.1, 49.5, 46.7, 43.8, 35.5, 35.2, 33.6, 30.5, 28.6, 22.8, 17.6, 9.4, 4.1, 3.4; MS (+EI) *m*/*z* (%) 409 (6), 368 (5), 155 (2), 149 (4), 129 (5), 123 (4), 113 (7), 112 (9), 111 (6); HRMS (+EI) calcd for $C_{25}H_{31}N_1O_4$: 409.2253. Found 409.2261; Anal. Calcd for $C_{25}H_{31}N_1O_4$: C, 73.32; H, 7.63. Found C,73.22; H, 7.59.

[7α-Acetyl-17-(cyclopropylmethyl)-3-[(ethoxycarbonyl)oxy]-6,14-endo(ethano)tetrahydronororipavine]. *(1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-[(ethoxycarbonyl)oxy]-18,19-dihydro-6-methoxy-6,14-ethenomorphinan-7-yl]ethanone (**13**).* To a suspension of **12** (0.5 g, ∼1.21 mmol; ∼90% purity;) in warm toluene (10 mL, 40 °C) were added ethyl chloroformate (171 mg; 1.58 mmol) and triethylamine (271 μL, 1.94 mmol). Upon addition of triethylamine, most of **12** was dissolved and the reaction mixture turned a slight-yellow color followed by red. TLC (ethyl acetate/hexane 1:1) analysis after 10 min showed disappearance of starting material, a major spot corresponding to **13** (R_f = 0.3−0.4) and two spots of minor impurities (R_f = 0.4, 0.45). After being stirred for an additional 30 min at room temperature, the reaction mixture was filtered through a short pad of Celite, and triethylammonium hydrochloride and other inorganic material from the previous step were removed. The filter cake was then washed with toluene (2 × 2.5 mL) and the filtrate concentrated in vacuo. ^1H NMR of crude showed essentially pure **13** and traces of toluene. The crude product (520 mg) was then dissolved in EtOH (2.5 mL) at 55 °C and crystallized overnight in a freezer, giving 320 mg (∼61%) of white crystals with slight yellow tinge. When chromatography (30 mL silica, hexane/ethyl acetate 4:1) was used for purification, the yield of **13** was 498 mg (95%).

13: mp 105−107 °C (MeOH); R_f = 0.3−0.4 (ethyl acetate/hexane 1:1); $[\alpha]^{20}_D$ −148.51° (*c* = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3077, 2965, 2930, 2837, 2812, 2778, 2745, 2255, 1764, 1711, 1614, 1492, 1451, 1384, 1369, 1356, 1259, 1243, 1200, 1163, 1130, 1095, 1063, 1024, 993, 958,

878, 781, 731; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 4.51 (d, J = 1.5 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H) 3.38 (s, 3H), 3.09−2.98 (m, 3H), 2.74 (ddd, J = 13.5, 9.6, 3.9 Hz, 1H), 2.65 (dd, J = 12.0, 5.1 Hz, 1H), 2.37−2.23 (m, 7H), 2.05 (ddd, J = 12.6, 12.6, 5.4 Hz, 1H), 1.78−1.61 (m, 3H), 1.53 (dddd, J = 12.9, 12.9, ∼1, ∼1 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.29 (dd, J = 12.0, 6.0 Hz, 1H), 0.80−0.73 (m, 1H), 0.69−0.65 (m, 1H), 0.54−0.43 (m, 2H), 0.13−0.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.9, 153.2, 149.5, 134.6, 133.8, 131.9, 121.8, 119.3, 96.7, 77.6, 64.9, 59.8, 58.3, 52.4, 50.0, 46.1, 43.6, 35.4, 34.9, 33.9, 30.3, 28.6, 23.3, 16.6, 14.2, 9.4, 4.1, 3.4; MS (FAB+) m/z (%) 482 (100), 481 (78), 480 (2), 450 (21), 440 (25), HRMS (FAB+) calcd for $C_{28}H_{36}N_1O_6$: 482.2542. Found 482.2507. Anal. Calcd for $C_{28}H_{35}N_1O_6$: C, 69.83; H, 7.33. Found C, 69.53; H, 7.30.

Alternative Route. *17-(Cyclopropylmethyl)-3-[(ethoxycarbonyl)-oxy]norooripavine (**14**).* Cyclopropylmethylnorooripavine (400 mg; 1.19 mmol) was suspended in ethyl acetate (4 mL) at room temperature, and ethyl chloroformate (124 μL; 1.30 mmol) was added to suspension in one portion followed by Et_3N (215 μL; 1.54 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with ethyl acetate (50 mL), and washed with satd solution of $NaHCO_3$ (10 mL). The aqueous layer was re-extracted with ethyl acetate (10 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. Crystallization of crude product from acetone (3 mL) afforded white crystals of **14** (316 mg, 65%). The mother liquor was concentrated and crystallized from acetone/cyclohexane (0.5 mL, 1:1) giving an additional 15 mg (10%) of product. **14**: mp 157−158 °C (EtOH); R_f 0.33 (ethyl acetate +20% methanol); $[\alpha]^{20}_D$ −97.80 (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 2997, 2933, 2837, 1761, 1608, 1446, 1370, 1261, 1023, 866 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.59 (d, J = 6.4 Hz, 1H), 5.34 (s, 1H), 5.07 (d, J = 6.4 Hz, 1H), 4.33 (dq, J = 7.2, 0.9 Hz, 2H) 3.96 (d, J = 6.8 Hz, 1H), 3.62 (s, 3H), 3.28 (d, J = 18.1 Hz, 1H), 2.92 (dd, J = 13.0, 4.5 Hz, 1H), 2.81 (ddd, J = 12.7, 12.7, 3.0, 1H), 2.74 (dd, J = 18.1, 6.9 Hz, 1H), 2.50 (d, J = 6.4 Hz, 2H), 2.22 (ddd, J = 12.6, 12.6, 5.1 Hz, 1H), 1.77 (dd, J = 12.6, 1.7 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 0.93 (m, 1H), 0.57 (m, 2H), 0.17 (dd, J = 9.7, 4.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.2, 152.3, 147.5, 134.8, 133.5, 132.8, 132.3, 121.5, 119.3, 112.0, 96.3, 90.0, 64.9, 59.1, 58.4, 55.1, 46.5, 44.1, 36.6, 30.9, 14.2, 9.5, 3.9, 3.8; MS (+EI) m/z (%): 42 (23), 55 (45), 253 (25), 277 (41), 308 (23), 363 (100), 409 (14); HRMS calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1889.

[7α-Acetyl-17-(cyclopropylmethyl)-3-[(ethoxycarbonyl)-oxy]-6,14-endo(etheno)tetrahydronorooripavine]. *1-[(5α,7α)-17-(Cyclopropylmethyl)-4,5-epoxy-3-[(ethoxycarbonyl)oxy]-6-methoxy-6,14-ethenomorphinan-7-yl]ethanone (**15**).* Diene **14** (243 mg; 0.59 mmol) was suspended in distilled water (1.5 mL) at room temperature, and methylvinyl ketone (0.4 mL) was added. Sea sand (0.5 g) was added to the mixture in order to have a better mixing regime, and the mixture was stirred by magnetic stirring at 80 °C for 12 h. The mixture was then diluted with EtOH (10 mL), sea sand was filtered off, and the filtrate was concentrated in vacuo. Chromatography (11.5 mL silica, hexane/ethyl acetate 5:1→4:1) afforded 261 mg (92%) of **15** as a white oil.

Carbonate **15** was also prepared from **11** by the following procedure: The free phenol **11** (127 mg; 0.31 mmol) was suspended in ethyl acetate (2 mL) at room temperature, and ethyl chloroformate (39 μL; 0.41 mmol) was added to the suspension in one portion followed by Et_3N (70 μL; 0.50 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with ethyl acetate (40 mL), and washed with satd solution of $NaHCO_3$ (8 mL). The aqueous layer was re-extracted with ethyl acetate (8 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. Chromatography (8 mL silica, hexane/ethyl acetate 2:1) afforded **15** (135 mg, 90%) as a white oil.

15: R_f = 0.25 (hexane/ethyl acetate 3:1); $[\alpha]^{20}_D$ −200.85° (c = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3448, 3431, 3076, 2995, 2933, 2834, 2813, 2777, 1765, 1704, 1614, 1492, 1451, 1384, 1370, 1358, 1241, 1201, 1167, 1099, 1062, 1023, 977, 780; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 5.94 (d, J = 8.7 Hz, 1H), 5.60 (d, J = 9.0 Hz, 1H), 4.62 (s, 1 H), 4.28 (q, J = 7.2 Hz, 2H), 3.59−3.57 (m, 4H), 3.14 (d, J = 18.6 Hz, 1H), 3.00 (dd, J = 11.7, 9.6 Hz, 1H), 2.91 (dd, J = 9.3, 6.3 Hz, 1H), 2.73 (dd, J = 12.0, 4.5 Hz, 1H), 2.50−2.30 (m, 4H), 2.16 (s, 3H), 1.97 (ddd, J = 12.6, 12.6, 5.4 Hz, 1H), 1.90 (dd, J = 12.9, 2.7 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H), 0.83 (m, 1H), 0.54−0.50 (m, 2H), 0.17−0.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.2, 153.1, 150.8, 136.2, 135.5, 133.9, 131.9, 125.5, 121.4, 119.6, 97.1, 81.3, 77.5, 64.9, 59.8, 56.9, 53.9, 50.9, 48.2, 43.8, 43.2, 33.3, 30.8, 29.8, 23.7, 14.2, 9.5, 4.1, 3.4; MS (FAB+) m/z (%) 480 (100), 436 (21), 328 (14), 246 (31); HRMS (FAB+) calcd for $C_{28}H_{34}N_1O_6$: 480.2386. Found 480.2338.

Hydrogenation of **15** to **13**: Carbonate **15** (135 mg; 0.28 mmol), tartaric acid (42 mg; 0.28 mmol), and Pd/C (25 mg; 10 wt %) were suspended in deionized water (2 mL). The flask was then evacuated/refilled with H_2 gas (four cycles) and subjected to hydrogenation (1 atm). The reaction mixture was then stirred at 80 °C for 16 h. The hot reaction mixture was then filtered through a 0.5 cm pad of Celite which was then washed with hot deionized water (70 °C, 2 × 1 mL). After being cooling to room temperature, the filtrate was washed between ethyl acetate (15 mL) and has $NaHCO_3$ solution (5 mL). Organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography (8 mL silica, hexane/ethyl acetate 2:1) afforded **13** (113 mg, 75%) as a white solid, identical to the material obtained by the previous route.

*Buprenorphine (**1**).* *tert*-Butylmagnesium chloride was prepared from 2 g of Mg turnings, 6.94 mL of THF, 9.8 g of *t*-BuCl, and 24.5 mL of cyclohexane. An aliquot of Grignard reagent (∼1 mL) was dissolved in a solution of 1,10-phenatroline monohydrate (1−2 mg) in 4 mL of THF and titrated with a 1 M solution of menthol in THF until loss of purple color from the magnesium/phenantroline complex. The Grignard reagent was used as a slurry.

A solution of **13** (109 mg; 2.265 mmol) in toluene (1 mL) was added dropwise to a vigorously stirred suspension of *tert*-butylmagnesium chloride in hexane (2.3 mL; 1 M suspension) at room temperature. After the mixture was stirred 35 min, TLC (hexane/ethyl acetate 1:1) analysis showed the disappearance of all starting material and a major spot corresponding to **16** (R_f = 0.8), traces of buprenorphine (R_f = 0.6), and a byproduct (R_f = 0.1) not fully identified. This byproduct probably resulted from the reduction of the ketone, as it appeared to be a mixture of two diastereoisomers. The TLC sample was prepared by extraction of few drops of reaction mixture between ethyl acetate (0.5 mL) and satd $NaHCO_3$ (0.5 mL). The reaction was then quenched by careful addition of water (2 mL) to the reaction mixture at room temperature, which led to a release of isobutane and heat (∼45 °C). The reaction mixture was then diluted with ethyl acetate (30 mL) and extracted with satd NH_4Cl (4 mL). The aqueous layer (pH 7−8, paper) was then re-extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The content of **16** (estimated by ^{1}H NMR) was 84%. The crude mixture was then dissolved in MeOH (3 mL) and dichloromethane (2 mL), and 5% NaOH (0.91 mL; 5 equiv) was added dropwise. Immediately after addition of hydroxide, the reaction turned to a brown-red color. After 10 min, TLC (hexane/ethyl acetate 1:1) analysis showed complete hydrolysis of starting material and a major spot of buprenorphine R_f = 0.6 accompanied by two minor spots R_f = 0.65, 0.2. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with satd solution NH_4Cl (5 mL). The aqueous layer (pH 7−8, paper) was re-extracted with dichloromethane (10 mL). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. Chromatography (8 mL silica; hexane/ethyl acetate 4:1→2:1) afforded buprenorphine (**1**) as slightly yellow crystals (80 mg; 76%). mp 217−218 °C (MeOH); lit. mp 218.1 °C[10] (no solvent given) or 216 °C (EtOH). R_f 0.23 (EtOAc: hexane/1:2); $[\alpha]^{20}_D$ −104.17 (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 3583,

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3389, 2982, 2952, 2815, 1633, 1503, 1370, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 5.46 (bs, 1H), 4.47 (d, J = 1.2 Hz, 1H), 3.54 (s, 3H), 3.00 (bs, 1H), 2.99 (d, J = 13.4 Hz, 1H), 2.90 (m, 1H), 2.62 (dd, J = 11.9, 5.1 Hz, 1H), 2.37 (dd, J = 12.6, 6.0 Hz, 1H), 2.40−2.27 (m, 2H), 2.23 (dd, J = 18.3, 6.5 Hz, 1H), 2.17 (dd, J = 9.8, 9.8 Hz, 1H), 1.99 (ddd, J = 12.6, 12.6, 5.6 Hz, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.69 (dd, J = 12.8, 2.5 Hz, 1H), 1.38 (s, 3H), 1.32 (dd, J = 18.9, 9.2 Hz, 1H), 1.08 (m, 1H), 1.05 (s, 9H), 0.81 (m, 1H), 0.72 (m, 1H), 0.52−0.45 (m, 2H), 0.13 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 137.3, 132.6, 128.3, 119.6, 116.4, 96.9, 80.9, 79.7, 59.5, 58.3, 52.6, 46.5, 43.72, 43.66, 40.4, 35.9, 35.7, 33.4, 29.6, 26.4, 22.9, 20.1, 18.2, 9.5, 4.2, 3.3; MS (+EI) m/z (%): 55 (100), 71 (64), 149 (26), 366 (21), 378 (92), 410 (31), 435 (20), 449 (23), 467 (25); HRMS calcd for $C_{29}H_{41}NO_4$ 467.3036, found 467.3043.

*(2S)-2-[(−)-(5R,6R,7R,14S)-9α-Cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-[(ethoxycarbonyl)oxy]-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol (**16**).* mp 125−128 °C (MeOH); R_f = 0.8 (ethyl acetate/hexane 1:1); $[\alpha]^{20}_D$ −138.56° (c = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3443, 3077, 2979, 2954, 2928, 2878, 2846, 2812, 2777, 1763, 1614, 1491, 1451, 1402, 1384, 1370, 1338, 1303, 1247, 1201, 1164, 1134, 1077, 1021, 979, 877, 781, 731; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.93 (s, 1H), 4.47 (d, J = 1.5 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.51 (s, 3H), 3.05 (d, J = 10.8 Hz, 1H), 3.01 (s, 1H), 2.90 (ddd, J = 13.5, 9.9, 3.6 Hz, 1H), 2.63 (dd, J = 11.7, 5.1 Hz, 1H), 2.40−2.17 (m, 4H), 2.14 (dd, J = 9.9, 9.9 Hz, 1H), 1.99 (ddd, J = 12.9, 12.9, 5.7 Hz, 1H), 1.93−1.77 (m, 2H), 1.73 (dd, J = 12.6, 2.4 Hz, 1H), 1.40−1.28 (m, 7H), 1.17−0.97 (m, 10H), 0.85−0.77 (m, 1H), 0.73−0.64 (m, 1H), 0.56−0.45 (m, 2H), 0.17−0.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.2, 149.6, 134.8, 134.0, 131.9, 121.7, 119.3, 98.3, 80.7, 79.3, 64.9, 59.5, 58.1, 52.6, 46.3, 44.3, 43.5, 40.4, 35.9, 35.4, 33.4, 29.8, 26.4, 23.3, 19.9, 17.5, 14.19, 9.5, 4.2, 3.3; MS (FAB+) m/z (%) 538(69), 522(57), 482(37), 450(49), 438(17); HRMS (FAB+) calcd for $C_{32}H_{45}N_1O_6$: 539.3246. Found 539.3263.

17: mp 142−144 °C (MeOH); R_f = 0.9 (ethyl acetate/hexane 2:1); $[\alpha]^{20}_D$ −151.478° (c = 1, $CHCl_3$); IR (KBr, cm^{-1}) ν 3433, 3066, 2977, 2955, 2936, 2913, 2876, 2822, 2775, 1754, 1614, 1480, 1449, 1406, 1384, 1280, 1244, 1206, 1117, 1075, 1021, 960, 885, 783; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 5.94 (s, 1H), 4.43 (d, J = 1.5 Hz, 1H), 3.47 (s, 3H), 3.04 (d, J = 12.3 Hz, 1H), 3.00 (s, 1H), 2.90 (ddd, J = 13.8, 10.8, 3.6 Hz, 1H), 2.63 (dd, J = 11.7, 4.8 Hz, 1H), 2.40−2.23 (m, 4H), 2.12 (dd, J = 9.9, 9.9 Hz, 1H), 1.98 (ddd, J = 12.6, 12.6, 5.4 Hz, 1H), 1.94 (m, 1H), 1.82 (m, 1H), 1.72 (dd, J = 12.9, 2.4 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 9H), 0.99 (s, 9H), 0.85−0.77 (m, 1H), 0.69 (dddd, J = 12.6, 12.6, 3.6, 3.6 Hz, 1H), 0.56−0.45 (m, 2H), 0.17−0.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.4, 149.9, 134.3, 133.7, 131.8, 121.9, 119.3, 98.2, 80.7, 79.2, 59.5, 58.2, 52.5, 46.3, 44.5, 43.6, 40.3, 38.9, 36.0, 35.4, 33.4, 29.8, 27.2, 26.4, 23.3, 19.9, 17.4, 9.5, 4.2, 3.3; MS (FAB+) m/z (%) 552 (39), 551 (37), 550 (75), 534 (65), 494 (45); HRMS (FAB+) calcd for $C_{34}H_{50}N_1O_5$: 552.3689. Found 552.3666; Anal. Calcd for $C_{34}H_{49}N_1O_5$: C, 74.01; H, 8.95. Found C, 74.24; H, 9.15.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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