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New Methodology for the N-Demethylation of Opiate Alkaloids

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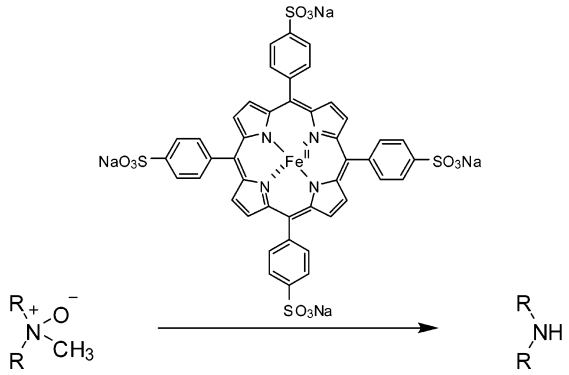


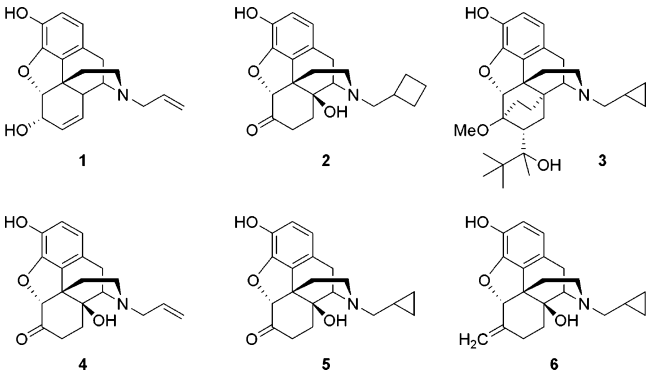
N-Demethylation is a key step in the preparation of a number of semisynthetic opiate pharmaceuticals. Herein we report a high-yielding, catalytic procedure for the N-demethylation of opiates which has a number of advantages over existing methods. For example, tetrasodium 5,10,15,20-tetra(4-sulfophenyl)-porphyrinatoiron(II) (0.3 molar equiv) effected the transformation of codeine methyl ether to the corresponding N-nor analogue in 91% yield. The catalyst was readily removed and recycled.

Introduction

The *N*-methyl group is a characteristic group associated with many naturally occurring alkaloids of biological significance, including the opiate alkaloids. In a number of semisynthetic pharmaceutical opiates this *N*-methyl group has been replaced by other alkyl substituents such as *N*-allyl, *N*-cyclopropylmethyl, and *N*-cyclobutylmethyl. A number of examples are depicted in Chart 1. Since these compounds are typically prepared from naturally occurring opiate precursors, a key step in their synthesis is the N-demethylation of these substrates.

N-Methyl alkaloids can be N-demethylated via a variety of procedures.[1] The von Braun reaction, in which the *N*-methyl amine is reacted with cyanogen bromide prior to cleavage of the resultant cyanamide, was developed in the early 1900s.[2] More recently chloroformates have been the reagents of choice for the N-demethylation of tertiary *N*-methyl amines. A range of different chloroformates have been developed which give rise to carbamates that can be cleaved under a variety of different reaction conditions.[3] Vinyl chloroformate has been one of the most effective members of this family for the N-demethylation of opiates.[4] An example of this is the conversion of oxymorphone to noroxymorphone in 98% yield. Diethyl azodicarboxy-

CHART 1. Nalorphine (1), Nalbuphine (2), Buprenorphine (3), Naloxone (4), Naltrexone (5), and Nalmefene (6)



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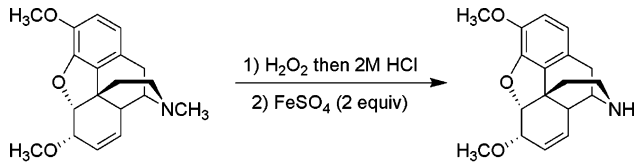
SCHEME 1. N-Demethylation of Codeine Methyl Ether with Use of a Nonclassical Polonovski Reaction



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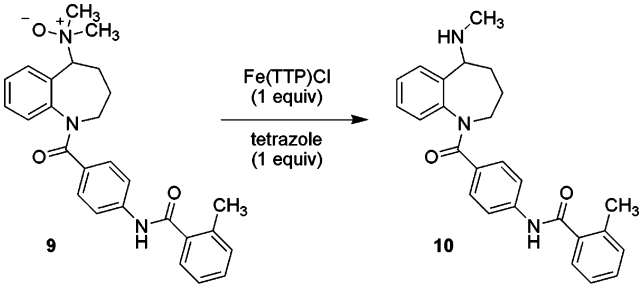
SCHEME 2. N-Demethylation of OPC-31260



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late has also been reported to be an effective reagent for the N-demethylation of thebaine to northebaine, though it has not seen widespread use for the N-demethylation of tertiary amines.[5]

More recently the "nonclassical" or iron salt mediated Polonovski reaction has been applied to the N-demethylation of opiate alkaloids.[6−9] In this procedure, the tertiary *N*-methyl amine was converted to the corresponding *N*-oxide prior to treatment with iron sulfate (2 molar equiv). A range of opiate and tropane alkaloids were successfully N-demethylated in this fashion in moderate to high yield. A high-yielding example of this procedure is the preparation of *N*-norcodeine methyl ether in 87% yield over two steps (Scheme 1).[6] The presence of excess iron sulfate presents purification problems, particularly with larger scale syntheses. In some cases, this problem could be overcome by the use of iron chelating agents such as EDTA and tetraphenylporphine (TPP). A range of other chemical, photochemical, and microbial procedures that have been used for the N-demethylation of alkaloids have been summarized in a recent review on this topic.[1]

Cytochrome P-450 enzymes effect a range of metabolic oxidation reactions including N-demethylation. A range of biomimetic oxidations modeled on cytochrome P-450's action have also been studied.[10] A relevant example of this was described by Otsubo and co-workers, who employed a metalloporphyrin-catalyzed demethylation reaction to prepare a metabolite (**10**) of the vasopressin V2 receptor antagonist, OPC-31260 (Scheme 2).[11] In this case the relevant *N*,*N*-dimethylalkylamine *N*-oxide was selectively demethylated in 86% yield by treatment with 5,10,15,20-tetraphenylporphyrinatoiron(III) chloride [Fe(III)(TPP)Cl]. The axial ligand of the iron complex proved to be an influential factor in this reaction, with tetrazole giving the best results.

TABLE 1. N-Demethylation of CME *N*-Oxide with Various Fe(III) Catalysts[a]

entry	catalyst	equiv	additive	reaction time (h)	isolated yield (%)
1	Fe(III)(TPP)Cl	1.0	tetrazole	48	24
2	Fe(III)(TPPS)Cl	1.0	tetrazole	120	0[b]
3	Fe(III)(TPPS)Cl	0.3		168	0[b]
4	$Fe_2(SO_4)_3.9H_2O$	0.3		168	0[b]

[a] Reactions were performed in methanol at room temperature. [b] No product was apparent from TLC and ^{1}H NMR analysis.

Herein we report a new procedure for the N-demethylation of opiate alkaloids that initially involves conversion to the corresponding *N*-oxide and then employs 5,10,15,20-tetra(4-sulfophenyl)porphyrinatoiron(II) [Fe(II)TPPS] as the catalyst of choice.

Results and Discussion

We initially evaluated the use of Fe(III)(TPP)Cl for the N-demethylation of opiate alkaloids. When codeine methyl ether *N*-oxide was treated with Fe(III)(TPP)Cl under the same conditions used by Otsubo and co-workers,[11] *N*-norcodeine methyl ether was isolated in 24% yield (entry 1, Table 1). The use of a stoichiometric amount of Fe(III)(TPPS)Cl and tetrazole failed to yield any of the desired N-demethylated product. Likewise, no *N*-norcodeine methyl ether was detected when substoichiometric amounts of either Fe(III)(TPPS)Cl or iron(III) sulfate were employed.

We also chose to investigate the use of Fe(II) porphyrins in N-demethylation reactions. This first necessitated the preparation of the desired porphyrins (Scheme 3), which are not commercially available. Tetrasodium 5,10,15,20-tetra(4-sulfonatophenyl)porphyrin (TPPS) was prepared in two steps via literature methodology.[13] The use of microwave irradiation (rather than conventional heating) greatly reduced the reaction time and slightly improved the yield of the initial reaction between pyrrole and benzaldehyde to form 5,10,15,20-tetraphenylporphyrin (TPP). Iron was incorporated by treating TPPS with iron(II) sulfate in a 1 M acetate buffer to form 5,10,15,20-tetra(4-sulfonatophenyl)porphyrinatoiron(II) as a tetrasodium salt.

Reaction of Fe(II)TPPS (0.3 molar equiv) with codeine methyl ether *N*-oxide hydrochloride proceeded very effectively, delivering a 91% yield of the *N*-norcodeine methyl ether after isolation and purification (entry 1, Table 2). By comparison, the corresponding reaction with 0.3 equiv of iron(II) sulfate heptahydrate produced only 52% of the *N*-nor product and 12% of the parent CME after the same reaction time (entry 2, Table 2). Fe(II)TPPS also proved to be an effective catalyst for the N-demethylation of dextromethorphan *N*-oxide, affording the *N*-nor product in 93% yield (entry 3, Table 2). Tetraphenylporphineiron(II) [Fe(II)TPP] also catalyzed the N-demethylation of dextromethorphan *N*-oxide, albeit in a slightly lower yield and longer reaction time than the sulfonated catalyst (entry 4, Table 2). In contrast with most of the Fe(III) catalysts evaluated

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SCHEME 3. Synthesis of Fe(II)TPPS

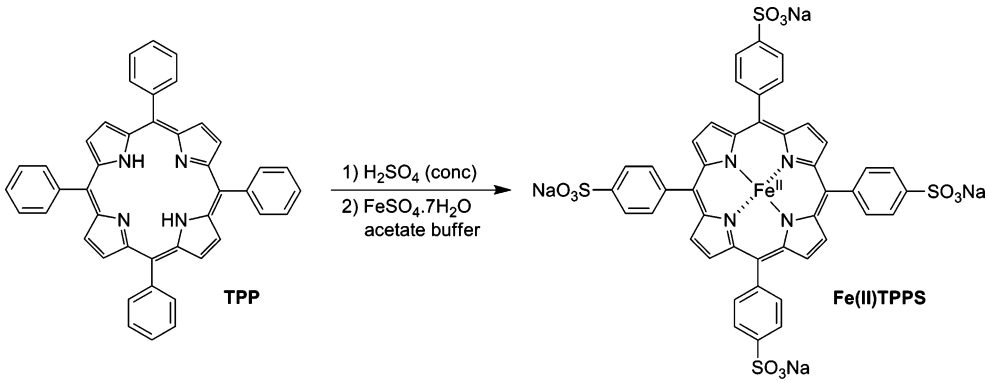
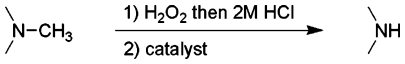


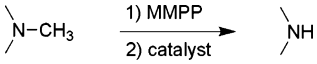
TABLE 2. *N*-Demethylation Reactions with Alternative Iron Catalysts



entry	substrate	catalyst	equiv	reaction time (h)	yield (%)[a]
1	codeine methyl ether	Fe(II)TPPS	0.3	72	91
2	codeine methyl ether	$FeSO_4 \cdot 7H_2O$	0.3	72	52[b]
3	dextromethorphan	Fe(II)TPPS	0.3	72	93
4	dextromethorphan	Fe(II)TPP	0.3	144	84
5	dextromethorphan	Hemin	0.3	192	23
6	dextromethorphan	hemin/dithio erythritol	0.3/1.0	168	47[c]
7	thebaine	Fe(II)TPPS	0.3	240	68

[a] Isolated yield over two steps after column chromatography. [b] CME (12%) was also isolated from this reaction. [c] Dextromethorphan (37%) was also isolated from this reaction.

TABLE 3. N-Demethylation with Use of Different Catalyst Loading



entry	Fe(II)TPPS (molar equiv)	reaction time (h)[a]	yield (%)[c]
1	1.0	44	84
2	0.3	72	85
3	0.2	120	80
4	0.1	264[d]	nd

[a] Reactions were monitored by TLC and worked up when CME *N*-oxide·HCl was consumed completely. [b] Isolated yield over two steps after column chromatography. [d] Some CME *N*-oxide·HCl still remained after 264 h of stirring.

TABLE 4. N-Demethylation of CME and Dextromethorphan with Fe(II)TPPS in Aqueous Alcohol

reactant	solvent (H_2O/methanol)	reaction time (h)	yield (%)[a]
CME	1:3	72	84
dextromethorphan	7:3	72	87

[a] Isolated yield after column chromatography.

previously, hemin produced a modest amount of *N*-nordextromethorphan (23%) though this may have resulted from the presence of trace amounts of Fe(II) in the reaction mixture. When this reaction was repeated with added dithioerythritol to increase the Fe(II) content, a higher yield on the N-demethylated product was isolated (47%, entry 6, Table 2). Thebaine *N*-oxide gave a lower yield of the desired N-demethylated product than the other alkaloids (entry 7, Table 2). The thebaine *N*-oxide isomers were present in a ratio of 65:35 by ^{1}H NMR. Caldwell and co-workers have reported that the major isomer (where the *N*-CH_3 group is axial) completely decomposed upon standing in solution for 5 days while the minor isomer (where the *N*-CH_3 group is equatorial) remained stable over this period.[12] Thus, the lower yield of the *N*-northebaine may have resulted from competing degradation processes over the course of the reaction (10 days).

Fe(II)TPPS clearly produced the most promising results of the iron catalysts that were evaluated in the initial study. The Fe(II)TPPS catalyst loading was further explored and the results of this investigation are described in Table 3. The use of a stoichiometric amount of Fe(II)TPPS shortened the reaction time to 44 h and gave a comparable yield of the corresponding N-demethylated product (entry 1, Table 3). Conversely the use of less than 0.3 molar equiv of the catalyst resulted in a significant increase in the time taken for the reaction to go to completion. In the reaction where Fe(II)TPPS (0.2 equiv) was used, the reaction time increased to 120 h, while the reaction with Fe(II)TPPS (0.1) failed to proceed to completion in 264 h (entries 3 and 4, Table 3). Comparable yields were obtained when 0.2, 0.3, and 1.0 equiv of the catalyst were used.

We have also been able to demonstrate that the Fe(II)TPPS catalyst can be recovered and reused. The same batch of catalyst was used for the N-demethylation of dextromethorphan *N*-oxide over four cycles. After the first cycle, Fe(II)TPPS was precipitated from the reaction mixture by the addition of diethyl ether. The catalyst was collected by suction filtration, washed with $CHCl_3/Et_2O$, dried in vacuo and then reused without further purification. Pure *N*-nordextromethorphan was isolated in yields of 87%, 94%, 97%, and 85%, respectively, following column chromatography.

We also wished to explore the possibility of performing N-demethylation reactions in aqueous systems. The results of this work are summarized in Table 4. The limiting factor in these experiments proved to be the water solubility of the substrate. However, once in solution the reactions with codeine methyl ether *N*-oxide and dextromethorphan *N*-oxide proceeded in good yield (84% and 87%, respectively).

Conclusions

In conclusion, Fe(II)TPPS is a promising reagent for the N-demethylation of *N*-methyl alkaloids, with 0.3 equiv affording excellent yields of the desired *N*-nor products. Furthermore, the high water solubility of the iron porphyrin catalyst facilitates

its removal at the completion of the reaction via precipitation and filtration following the addition of diethyl ether. As the N-demethylation of alkaloids has potential industrial applications, the principles of green chemistry have been given due consideration throughout the course of this research. The use of 0.3 equiv of Fe(II)TPPS rather than the 2.0 equiv of $FeSO_4$ commonly employed in the Polonovski approach, the capacity to recycle and reuse the catalyst, and the use of partially aqueous reaction media represent progress in this area.

Experimental Section

Synthesis of 5,10,15,20-Tetraphenylporphyrin (TPP). Pyrrole (0.7 mL, 10 mmol) and benzaldehyde (1.0 mL, 10 mmol) were dissolved in propionic acid (18.3 mL) in a 20 mL microwave vial. The vial was capped and irradiated in a microwave reactor (Biotage Initiator 2.0) at 200 °C for 15 min. The reaction mixture was cooled to 50 °C, filtered, and washed with methanol until the methanol washings were colorless. The resultant purple solid was dried in high vacuum to give pure TPP[13] (0.39 g) in 25% yield. ^{1}H NMR δ 8.91 (8H, s), 8.30−8.27 (8H, m), 7.87−7.78 (12H, m), −2.70 (2H, s); ESI-MS (70V) *m*/*z* 615.4 (M + H$^+$, 100%).

Synthesis of Tetrasodium 5,10,15,20-Tetra(4-sulfophenyl)-porphyrin (TPPS).[14] Tetraphenylporphyrin (TPP) (2.0 g, 3.25 mmol) and concentrated sulfuric acid (10 mL) were ground into a homogeneous paste with a mortar and pestle. The paste was transferred to a 100-mL round-bottomed flask and additional sulfuric acid (30 mL) was added. The mixture was heated in an oil bath (100−110 °C) for 4 h and then allowed to stand at room temperature for 18 h. The solution was filtered through a sintered frit and the filtrate was diluted carefully to 400 mL by addition of distilled water. The solution was stirred with CaO until a purple color persisted. Calcium sulfate was filtered off and washed with a minimum quantity of hot water. Crushed dry ice was added to the combined filtrate, which was filtered again. The filtrate was concentrated (to ∼150 mL) and the pH of the final solution was regulated at 8−10 by adding 1 M NaOH solution or 1 M HCl solution. The solution was again filtered to remove inorganic salt. The solution was cooled with liquid nitrogen until frozen then dried on a freeze dryer to give TPPS[14] (3.32 g) in quantitative yield. ^{1}H NMR (DMSO-d_6) δ 8.86 (8H, s), 8.18 (8H, d, J = 8.1 Hz), 8.06 (8H, d, J = 8.1 Hz), −2.90 (2H, s, NH); ESI-MS (20V) *m*/*z* 935.0 (M + H$^+$ − 4Na$^+$, 100%), 957.3 (M + H$^+$ + Na, 56%), 979.2 (M + H$^+$ + 2Na, 45%), 1001.1 (M + H$^+$ + 3Na, 28%), 1024.3 (M + H$^+$+ 4Na, 13%).

Synthesis of Tetrasodium 5,10,15,20-Tetra(4-sulfophenyl)-porphyrinatoiron(II) [Fe(II)TPPS]. Tetrasodium tetra(4-sulfophenyl)porphyrin (TPPS) (1.75 g, 1.71 mmol) and $FeSO_4$·$7H_2O$ (0.43 g, 1.63 mmol) were dissolved in 1 M acetate buffer (120 mL, pH 4). The resulting mixture was refluxed in an oil bath for 3.5 h and the reaction mixture was allowed to cool to room temperature. The reaction mixture was then stored at 4 °C overnight and filtered. The filtrate was poured into acetone (960 mL) and a precipitate formed. The precipitate was separated by centrifugation and then it was mixed with methanol (60 mL). Acetone (480 mL) was added and a second precipitate formed. The above procedure was repeated. The precipitate was finally filtered off and dried under high vacuum for 4 h to give Fe(II)TPPS[15] as a green solid (1.69 g, 92%). ESI-MS (70V): *m*/*z* 988.2 (M + H$^+$, 100%).

Synthesis of 5,10,15,20-Tetraphenylporphyrinatoiron(II) [Fe-(II)TPP]. TPP (200 mg, 0.33 mmol) and *N*,*N*-dimethylformamide (20 mL) were warmed in an oil bath under an atmosphere of nitrogen. The TPP was dissolved at 60−80 °C then ferrous acetate (71 mg, 0.41 mmol) was added and the reaction was refluxed for 10 min. The reaction was then cooled to room temperature and put into an ice bath for 15 min. The reaction mixture was diluted with deionized water (40 mL) and a precipitate formed. The solid was collected by suction filtration, washed well with deionized water, and dried by high vacuum to afford Fe(II)TPP[16] (182 mg, 84% yield). ESI-MS (70V): *m*/*z* 668.2 (M + H$^+$, 100%).

General Procedure for N-Demethylation. Codeine methyl ether (730 mg, 2.33 mmol) was dissolved in methanol (35 mL) and hydrogen peroxide (7.9 g, 30% w/v, 70 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 days. The excess H_2O_2 was deactivated with MnO_2 at 0 °C for 1 h and the solution was filtered through a Celite pad. The Celite pad was washed with additional methanol and the filtrate was evaporated in vacuo to give CME *N*-oxide. The CME *N*-oxide was dissolved in brine (10 mL), cooled on ice, and acidified to pH 1−2 with 6 M HCl. The resulting solution was extracted with $CHCl_3$ (4 × 20 mL). The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and then evaporated in vacuo to give CME *N*-oxide·HCl salt as an off-white solid. The crude CME *N*-oxide·HCl salt was dissolved in methanol (120 mL) and Fe(II)TPPS (690 mg, 0.64 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC with use of $CHCl_3$/MeOH/NH_4OH (85:15:1) as an eluent. After stirring at room temperature for 72 h, TLC showed complete consumption of the *N*-oxide. Methanol was removed in vacuo and the residue was taken up in a mixture of water (25 mL) and $CHCl_3$ (50 mL). The aqueous layer was then extracted with $CHCl_3$ (4 × 30 mL). The $CHCl_3$ extracts were combined, washed with brine (25 mL), dried ($MgSO_4$), and evaporated to afford a crude solid. After column chromatography on silica gel with a $CHCl_3$/MeOH/NH_4OH gradient (100:0:1 to 95:5:1), pure norcodeine methyl ether[17] was obtained as a pale yellow solid (631 mg) in 91% yield.

***N*-Norcodeine methyl ether:** mp 104−106 °C (lit.[17] mp 98−100 °C); ^{1}H NMR δ 6.69 (1H, d, J = 8.1 Hz), 6.56 (1H, d, J = 8.1 Hz), 5.79 (1H, d, J = 9.9 Hz), 5.34 (1H, dt, J = 9.9, 2.7 Hz), 5.01 (1H, dd, J = 5.7, 1.2 Hz), 3.88 (3H, s), 3.86−3.82 (1H, m), 3.72−3.69 (1H, m), 3.58 (3H, s), 3.09−3.02 (1H, m), 2.99−2.87 (3H, m), 2.63 (1H, m), 1.98−1.88 (2H, m); ^{13}C NMR δ 147.6, 142.1, 130.8, 130.6, 128.6, 127.1, 118.7, 113.4, 89.8, 75.9, 57.0, 56.4, 51.9, 44.3, 41.6, 38.5, 36.8, 31.5; ESI-MS (20 and 70 V) *m*/*z* 300 (M + H$^+$, 100%). HRMS $C_{18}H_{21}NO_3$ calcd for [M + H]$^+$ 300.1594, found 300.1595.

***N*-Nordextromethorphan.** The target compound was prepared from dextromethorphan (1.49 g, 5.2 mmol) with the general procedure described above. *N*-Nordextromethorphan[18] was purified by column chromatography on silica gel with a $CHCl_3$/MeOH/NH_4-OH gradient (100:0:1 to 95:5:1) to afford a pale yellow oil (1.31 g, 93%). ^{1}H NMR δ 7.05 (1H, d, J = 8.4 Hz), 6.80 (1H, d, J = 2.4 Hz), 6.72 (1H, dd, J = 8.4, 2.4 Hz), 4.43 (1H, br s), 3.78 (3H, s), 3.27 (1H, br s), 3.13 (1H, dd, J = 18.0, 6.0 Hz), 2.91 (1H, d, J = 18.0 Hz), 2.87−2.81 (1H, m), 2.64 (1H, t, J = 12.1 Hz), 2.32 (1H, d, J = 12.6 Hz), 1.74 (1H, dd, J = 12.6, 4.8 Hz), 1.68−1.62 (1H, m), 1.54−1.51 (1H, m), 1.43−1.25 (5H, m), 1.07 (1H, t, J = 12.6 Hz); ^{13}C NMR δ 158.3, 141.4, 129.7, 128.7, 111.3, 110.9, 55.2, 51.2, 45.5, 42.3, 39.0, 38.2, 36.9, 33.0, 26.8, 26.7, 22.1; ESI-MS (20V) *m*/*z* 300 (M + H$^+$, 85%), 102 (100%). HRMS $C_{17}H_{23}NO$ calcd for [M + H]$^+$ 258.1852, found 258.1850.

***N*-Northebaine.** The target compound was prepared from thebaine (47 mg, 0.15 mmol) with the general procedure described above. *N*-Northebaine[19] was purified by column chromatography

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on silica gel with a $CHCl_3$/MeOH/NH_4OH gradient (100:0:1 to 95:5:1) to afford the title compounds as a brown solid (31 mg, 69%). mp 148−153 °C (lit.[19] mp 157−158 °C); ^{1}H NMR δ 6.73 (1H, d, J = 8.1 Hz), 6.66 (1H, d, J = 8.1 Hz), 5.56 (1H, d, J = 6.3 Hz), 5.32 (1H, s), 5.09 (1H, d, J = 6.3 Hz), 3.98 (1H, d, J = 4.2 Hz), 3.91 (3H, s), 3.66 (3H, s), 3.25 (1H, dt, J = 13.5, 3.3 Hz), 3.17 (2H, br s), 2.99 (1H, dd, J = 13.5, 4.5 Hz), 2.23 (1H, br s), 2.14 (1H, dt, J = 12.6, 5.1 Hz), 1.89 (1H, dd, J = 12.6, 2.4 Hz); ^{13}C NMR δ 152.8, 145.0, 143.0, 133.3, 127.7, 119.4, 113.2, 110.8, 95.9, 89.2, 56.5, 55.1, 55.0, 53.9, 46.6, 40.3, 38.4, 37.5; ESI-MS (20V) m/z 298 (M + H^+, 100%), 152 (100%). HRMS $C_{18}H_{19}NO_3$ calcd for $[M + H]^+$ 298.1438, found 298.1443.

General Procedure for Catalyst Recovery and Reuse. Dextromethorphan (228 mg, 0.84 mmol) was dissolved in methanol (25 mL), magnesium bis(monoperoxyphthalate) hexahydrate (MMPP) (0.46 g, 0.93 mmol) was added, and the reaction mixture was stirred for 0.5 h at room temperature. Methanol (30 mL) was added and the solution was filtered through a plug of Celite. After washing with an additional 30 mL of methanol, the solution was evaporated in vacuo. The crude dextromethorphan *N*-oxide was redissolved in methanol (90 mL), Fe(II)TPPS (250 mg, 0.25 mmol) was added, and the reaction mixture was stirred at room temperature for 72 h. TLC (with $CHCl_3$/MeOH/NH_4OH, 85:15:1 as an eluent) showed complete consumption of the dextromethorphan *N*-oxide. The reaction mixture was poured into diethyl ether (270 mL) and the catalyst precipitated. The catalyst was collected by suction filtration with a Millipore filtration apparatus (0.45 μm filter paper), washed with $CHCl_3$/diethyl ether (4:1, 2 × 30 mL), and dried under vacuum prior to reuse. The filtrate was evaporated in vacuo and the residue partitioned between brine (15 mL) and $CHCl_3$ (30 mL). After further extraction of the aqueous layer with $CHCl_3$ (2 × 30 mL), the combined $CHCl_3$ extracts were evaporated to afford the crude N-nor product. Pure *N*-nordextromethorphan (188 mg, 87% yield) was obtaining following column chromatography on silica gel with a $CHCl_3$/MeOH/NH_4OH gradient (100:0:1 to 95:5:1).

This procedure was repeated with use of the recovered catalyst to afford *N*-nordextromethorphan: 203 mg (94%), 209 mg (97%), and 184 mg (85%), respectively.

General Procedure for N-Demethylation in Aqueous Alcohol. *N*-Norcodeine Methyl Ether. Codeine methyl ether (38 mg, 0.12 mmol) was dissolved in methanol (5 mL) and hydrogen peroxide (400 mg, 30% w/v, 3.6 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 days. Excess H_2O_2 was deactivated by stirring with MnO_2 for 1 h at 0 °C. The solution was then filtered through a Celite plug, which was further washed with methanol (10 mL). Evaporation of the solvent afforded CME *N*-oxide, which was dissolved in brine (5 mL), cooled on ice, and acidified to pH 1−2 with 6 M HCl. The resulting solution was extracted with $CHCl_3$ (4 × 10 mL). The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and then evaporated in vacuo to give CME *N*-oxide·HCl as an off-white solid. The crude CME *N*-oxide hydrochloride was dissolved in aqueous alcohol (1 mL of water and 3 mL of methanol) and Fe(II)TPPS (35 mg, 0.04 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC (eluted with $CHCl_3$/MeOH/NH_4OH, 85:15:1). After 72 h, TLC showed complete consumption of the CME *N*-oxide. After evaporation of the solvent under reduced pressure, the residue was partitioned between chloroform (15 mL) and water (5 mL). The aqueous layer was extracted with $CHCl_3$ (4 × 15 mL) and the combined $CHCl_3$ extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and evaporated to afford a crude product. After column chromatography on silica gel with a $CHCl_3$/MeOH/NH_4OH gradient (100:0:1 to 95:5:1), pure norcodeine methyl ether (30.5 mg) was obtained in 84% yield.

***N*-Nordextromethorphan.** The target compound was prepared from dextromethorphan (38 mg, 0.14 mmol) with the general procedure described above. Crude dextromethorphan *N*-oxide·HCl was dissolved in aqueous alcohol (3 mL of water, 7 mL of methanol) and stirred with Fe(II)-TPPS (40 mg, 0.04 mmol). *N*-Nordextromethorphan was purified by column chromatography with a $CHCl_3$/MeOH/NH_4OH gradient (100:0:1 to 95:5:1) to afford the title compound (31.5 mg) in 87% yield.

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Supporting Information Available: UV spectra of Fe(II)TPP and Fe(II)TPPS, and ^{1}H and ^{13}C NMR spectra of *N*-norcodeine methyl ether, *N*-northebaine, and *N*-nordextromethorphan. This material is available free of charge via the Internet at http://pubs.acs.org.

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