Further Investigations into the N-Demethylation of Oripavine using Zero-valent Iron as a Redox Catalyst.

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General N-Demethylation Procedure

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Table A Specifications for Iron Catalysts used
General Experimental
Stainless steel powders 303-L and 316-L were purchased from Alfa Aesar. Iron powder was from Höganäs Sweden. m-CPBA was purchased from Sigma-Aldrich. All reactions were conducted under an atmosphere of nitrogen. Chloroform and 2-propanol (Merck) were used as supplied. Both solvents were degassed before use: sonicated for 10 minutes under vacuum and then back-filled with nitrogen. Reactions were monitored using thin layer chromatography (TLC) with pre-coated Merck 5554 Kieselgel 60F<sub>254</sub> aluminum plates using CHCl<sub>3</sub>/MeOH/NH₄OH (170:30:1) as the mobile phase. The spots were visualized using both UV light and molybdate stain. <sup>1</sup>H and <sup>13</sup>C NMR were recorded at 400 and 100 MHz, respectively. Chemical shifts (δ ppm) were referenced using solvent residual peaks.

Synthesis of Oripavine-<sub>N</sub>-oxide hydrochloride (6)
To a stirred solution of oripavine (1.92 g, 6.47 mmol) in CHCl<sub>3</sub> (200 mL) and MeOH (1 mL) at -20 °C was added m-CPBA (1.54 g of a max 77% reagent) portionwise over 10 min. The solution was then left to stir for a further 20 minutes. Ice-cold H<sub>2</sub>O (100 mL) was added; the pH of the aqueous phase was adjusted to 2–3 via the addition of 10% HCl. The layers were separated; the aqueous phase was extracted with CHCl<sub>3</sub> (20 mL x 2), saturated with NaCl, and extracted with CHCl<sub>3</sub>/2-propanol (3:1, 50 mL x 4). The CHCl<sub>3</sub>/2-propanol (3:1) extracts were combined, dried (Na₂SO₄), filtered and concentrated to give 6 as an off-white solid, 2.43 g. <sup>1</sup>H NMR of the solid was consistent with the desired product 6 with approximately 0.5 molar equivalent of 2-propanol. This material was used in the subsequent step without further purification. <sup>1</sup>H NMR (D<sub>2</sub>O) δ 6.80–6.70 (m, 2H), 6.08, 5.98 (each d, J = 6.7 Hz, 1H), 5.56, 5.55 (each s, 1H), 5.32, 5.29 (each d, J = 6.7 Hz, 1H), 4.79–4.74 (m, 1H), 3.85–3.57 (m, 9H), 3.33, 3.18 (each dd, J = 7.2, 1H), 2.70–2.47 (m, 1H), 2.18–1.98 (m, 1H).

General Procedure for N-Demethylation
To a mixture of oripavine-<sub>N</sub>-oxide hydrochloride (100 mg, 0.263 mmol) and iron powder (varying amounts; see Tables 1 and 2) was added solvent (10 mL). The reaction mixture was then stirred at the specified temperature until complete consumption of 6 (via TLC analysis). The mixture was concentrated to dryness and the remaining residue was subjected to column chromatography on silica gel. Elution with a gradient of CHCl<sub>3</sub>/MeOH (24:1–17:3) gave oripavine followed by N-nororipavine, both as the corresponding hydrochloride.

The above procedure was repeated substituting iron powder with stainless steel powder 303-L or 316-L (see Table 3).

N-Nororipavine Hydrochloride (7·HCl): Off-white solid, mp >200 °C dec; [α]<sub>D</sub><sup>24</sup> -188 (c 1.0, 10% HOAc); [lit.<sup>1</sup> [α]<sub>D</sub><sup>24</sup> -194 (c 0.83, 10% HOAc)]; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 6.79–6.73 (m, 2H), 5.90 (d, J = 6.6 Hz, 1H), 5.50 (s, 1H), 5.25 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.0, 1H), 3.64 (s, 3H), 3.46–3.22 (m, 4H), 2.31 (ddd, J = 6.0, 13.3 and 13.3 Hz, 1H), 2.08–2.01 (m, 1H); <sup>13</sup>C NMR (D<sub>2</sub>O/CF<sub>3</sub>CO₂D) δ 153.0, 142.8, 138.6, 132.0, 124.4, 124.2, 120.8, 117.3, 117.0, 96.1, 87.7, 55.1, 53.2, 44.6, 37.0, 33.5, 33.1; MS (ESI) m/z 284 [M+H]+; HRMS C₁₇H₁₈NO₃ calcd for [M+H]<sup>+</sup> 284.1281, found 284.1287.
Figure 1. $^1$H NMR of Oripavine-N-oxide Hydrochloride (6) in D$_2$O
Figure 1A. $^1$H NMR of Oripavine-N-oxide Hydrochloride (6) in D$_2$O (Expansion)
Figure 1B. $^1$H NMR of Oripavine-$N$-oxide Hydrochloride (6) in D$_2$O (Expansion)
Figure 2. $^1$H NMR of N-Nororipavine (6) Hydrochloride in D$_2$O
Figure 2A. $^1$H NMR of N-Nororipavine (7) Hydrochloride in D$_2$O (Expansion)
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Figure 4A. $^{13}$C NMR of N-Nororipavine (7) Hydrochloride in D$_2$O + TFA (Expansion)
Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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Figure 4B. $^{13}$C NMR of N-Nororipavine (7) Hydrochloride in D$_2$O + TFA (Expansion)
Figure 5. High Resolution MS of N-Nororipavine (7)
### Table A. Specifications for Iron and Stainless Steel Catalysts

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<th>Catalyst</th>
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<td>Mn</td>
<td>Si</td>
<td>(MnO)</td>
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