Electronic Supplementary Material (ESI) for RSC Advances.

Transition metal-catalyzed redox isomerization of codeine and morphine in water

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General Information:

All transition metal-catalyzed reactions were carried out in sealed glass-vials under an atmosphere of nitrogen. Reagents were used as obtained from commercial suppliers without further purification.

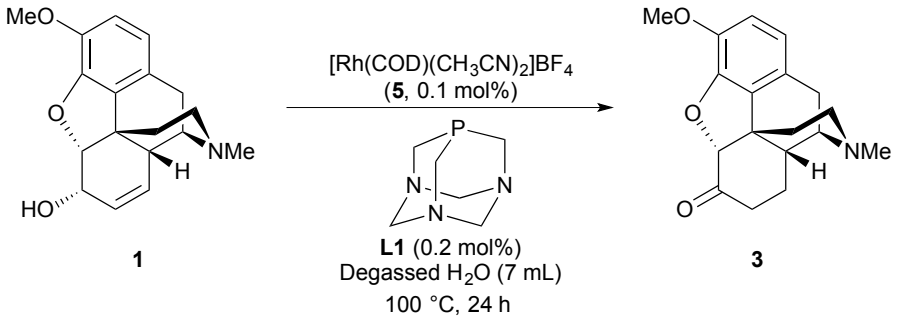
Reactions in 100 g scale were carried out in a 1 L jacketed cylindrical reactor, diameter 100 mm; Manufacturer: G. Diehm (accessories: turbine stirrer, 70 mm diameter; immersed temperature pocket / baffle, 10 mm diameter).

^{1}H NMR spectra were recorded at 400 MHz; ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Advance spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane using the residual solvent resonance ($CHCl_3$: δ_H 7.26 and $CDCl_3$: δ_C 77.2; or DMSO: δ_H 2.50 and DMSO-*d*$_6$: δ_C 39.5). Coupling constants (*J*) are given in Hz.

Codeine (**1**) and morphine (**2**) were used as obtained from suppliers (Codeine base and Morphine CPS from *Alcaliber S.A.*) without further purification. $[Rh(COD)(CH_3CN)_2]BF_4$ (**5**) and 1,3,5-triaza-7-phosphaadamantane (**L1**, PTA, 97%) were purchased from *Sigma-Aldrich* and used without further purification. Deionized H_2O was degassed by bubbling N_2 for 30 min before it was used.

UPLC chromatograms were recorder on a Waters UPLC equipment with a gradient pump and a MS detector (TQD), column Waters Acquity BEH C18 (1.7 μm, 2.1 x 50 mm) using a solution 10 mM of ammonium formate in H_2O as mobile phase A and MeOH as mobile phase B (flow rate of 0.4 mL/ min and at 30 °C). The rate of the mobile phases was changed from 90% A : 10% B (0 min) to 10% A : 90% B (10 min).

Synthesis and characterization of hydrocodone (3):



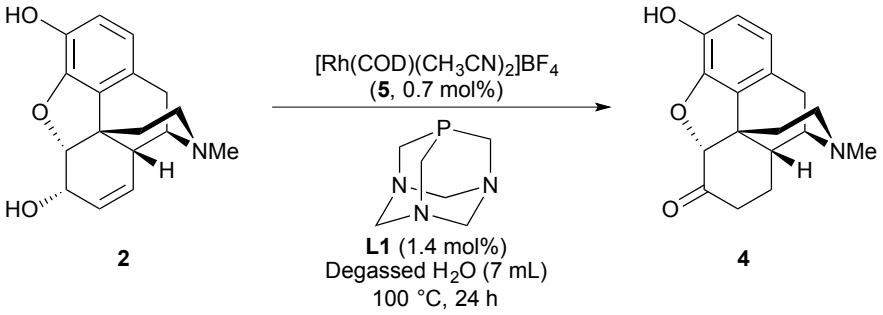
Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (**L1**) (5.4 mg, 0.033 mmol) and $[RhCOD(CH_3CN)_2]BF_4$ (**5**) (6.4 mg, 0.017 mmol) were stirred in deionized and degassed H_2O (10 mL) for some minutes prior to use until a clear solution was obtained.

Codeine base (**1**) (1.0 g, 3.34 mmol) was suspended in deionized and degassed H_2O (5 mL) and the suspension was heated to 100 °C. The catalyst solution (1.7 mM, 2 mL, 0.1 mol% Rh) was added and the reaction mixture was stirred vigorously at this temperature for 24 h. After cooling, the solid was filtered off and washed with H_2O (3 x 5 mL). The product **3** was dried under vacuum (< 2 mmHg) and obtained as an off-white solid (889 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.70 (d, *J*(H,H) = 8.2 Hz, 1H), 6.63 (d, *J*(H,H) = 8.2 Hz, 1H), 4.65 (s, 1H), 3.91 (s, 3H), 3.18 (dd, *J*(H,H) = 5.4, 2.8 Hz, 1H), 3.02 (d, *J*(H,H) = 18.5 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.43 (s, 3H), 2.42 – 2.26 (m, 3H), 2.19 (td, *J*(H,H) = 12.1, 3.5 Hz, 1H), 2.06 (td, *J*(H,H) = 12.1, 4.8 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.26 (qd, *J*(H,H) = 13.2, 3.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 208.0, 145.6, 143.0, 127.4, 126.5, 119.9, 114.8, 91.6, 59.4, 57.0, 47.1, 47.0, 43.1, 42.9, 40.4, 35.7, 25.7, 20.1.

Synthesis and characterization of hydromorphone (4):



Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (**L1**) (7.9 mg, 0.049 mmol) and $[RhCOD(CH_3CN)_2]BF_4$ (**5**) (9.3 mg, 0.025 mmol) were stirred in deionized and degassed H_2O (7 mL) for some minutes prior to use until a clear solution was obtained.

The catalyst solution (2.5 mM, 7 mL, 0.7 mol% Rh) was added to morphine CPS (**2**) (1.0 g, 3.50 mmol) and the suspension was heated to 100 °C and stirred vigorously at this temperature for 24 h. After cooling to room temperature, the solid was filtered off and washed with H_2O (3x5 mL). The product **4** was dried under vacuum (< 2 mmHg) and was obtained as white-grey solid (718 mg, 77%).

^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ = 9.10 (s, 1H), 6.54 (d, *J*(H,H) = 8.0 Hz, 1H), 6.50 (d, *J*(H,H) = 8.1 Hz, 1H), 4.80 (s, 1H), 3.06 (dd, *J*(H,H) = 5.0, 2.7 Hz, 1H), 2.87 (d, *J*(H,H) = 18.3 Hz, 1H), 2.56 – 2.39 (m, 3H), 2.29 (s, 3H), 2.23 – 2.12 (m, 2H), 2.05 – 1.96 (m, 2H), 1.80 – 1.74 (m, 1H), 1.52 – 1.44 (m, 1H), 1.05 – 0.95 (m, 1H).

^{13}C NMR (100 MHz, DMSO-d_6, TMS): δ = 208.7, 144.0, 139.3, 127.4, 124.5, 119.2, 117.0, 90.4, 58.3, 46.4, 46.2, 42.5, 41.4, 39.7, 34.8, 25.0, 19.6.

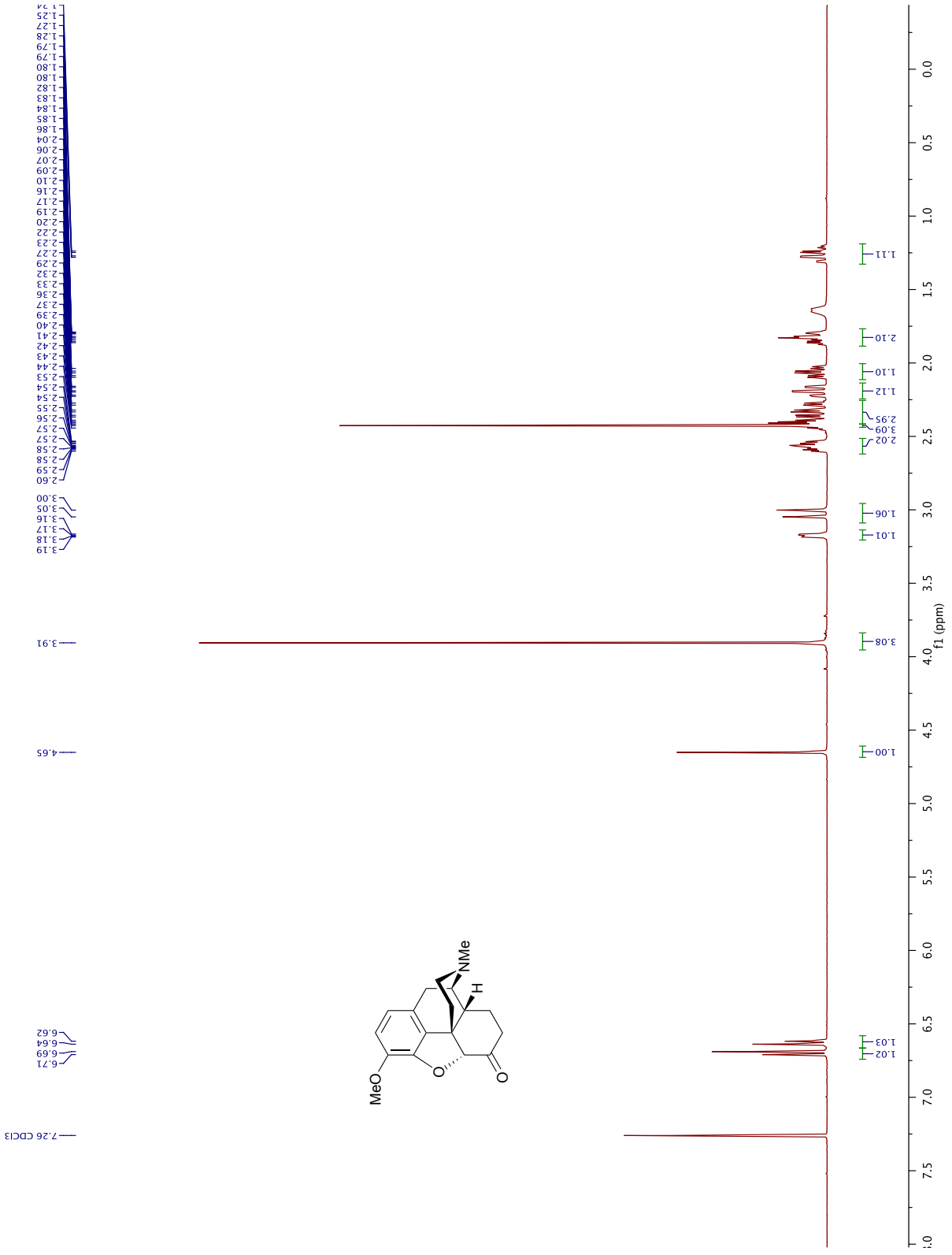
Synthesis hydrocodone (3) in 100 g scale:

Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (**L1**) (108 mg, 0.66 mmol) and $[RhCOD(CH_3CN)_2]BF_4$ (**5**) (128 mg, 0.34 mmol) were dissolved in deionized and degassed H_2O (20 mL) for some minutes prior to use until a clear solution was obtained.

Codeine (**1**) (100 g, 334 mmol) was suspended in deionized and degassed H_2O (500 mL) in a 1 L jacketed cylindrical reactor, and the suspension was heated at 100 °C. The catalyst solution (20 mL, 0.1 mol% Rh) was added and the reaction was stirred vigorously at this temperature for 24 h. After cooling, the solid was filtered off and washed with H_2O (3 x 100 mL). The solid was dried under vacuum (< 2 mmHg) to afford the title compound as off-white solid (90 g, 90%).

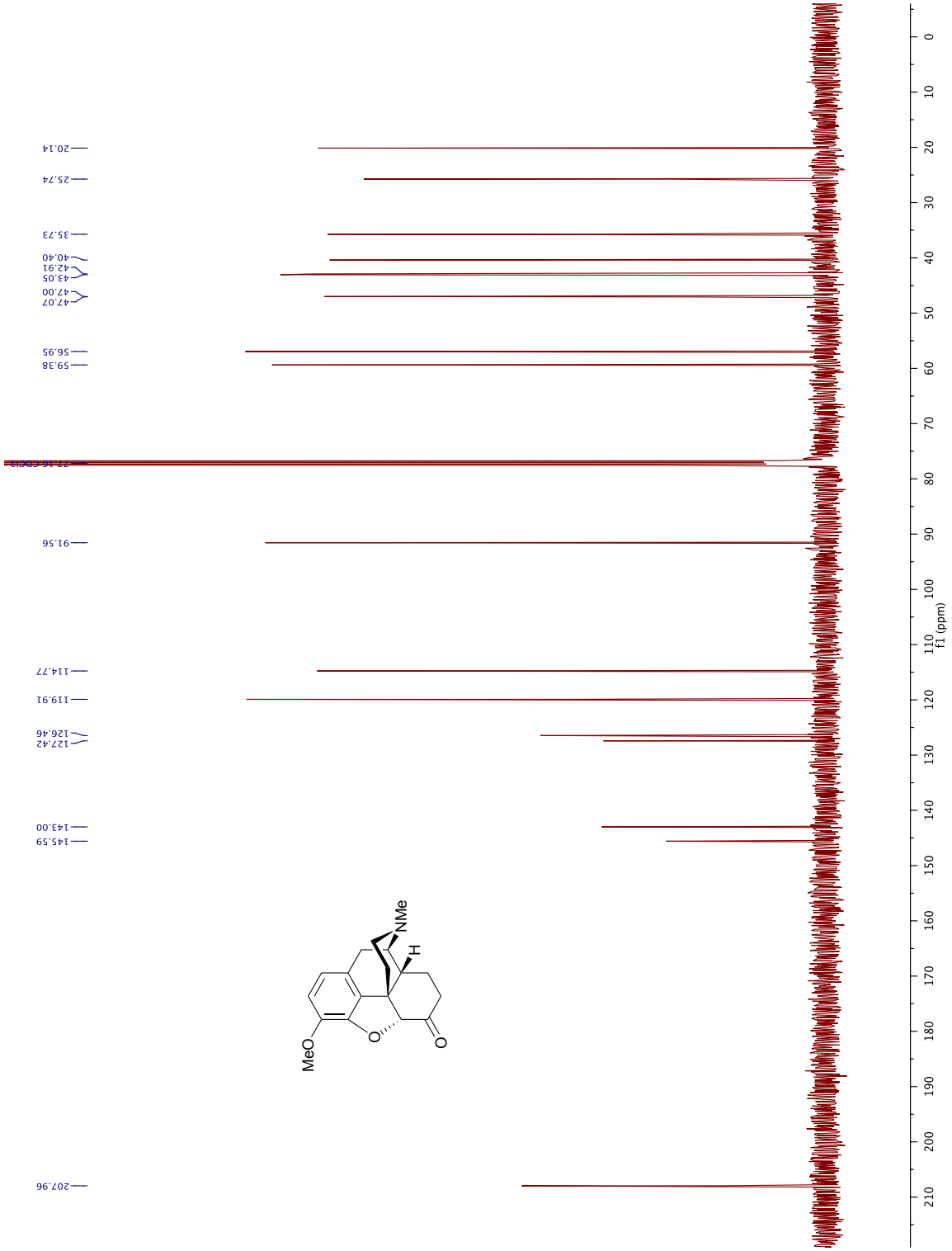
Hydrocodone (3)

^{1}H NMR (400 MHz, $CDCl_3$)



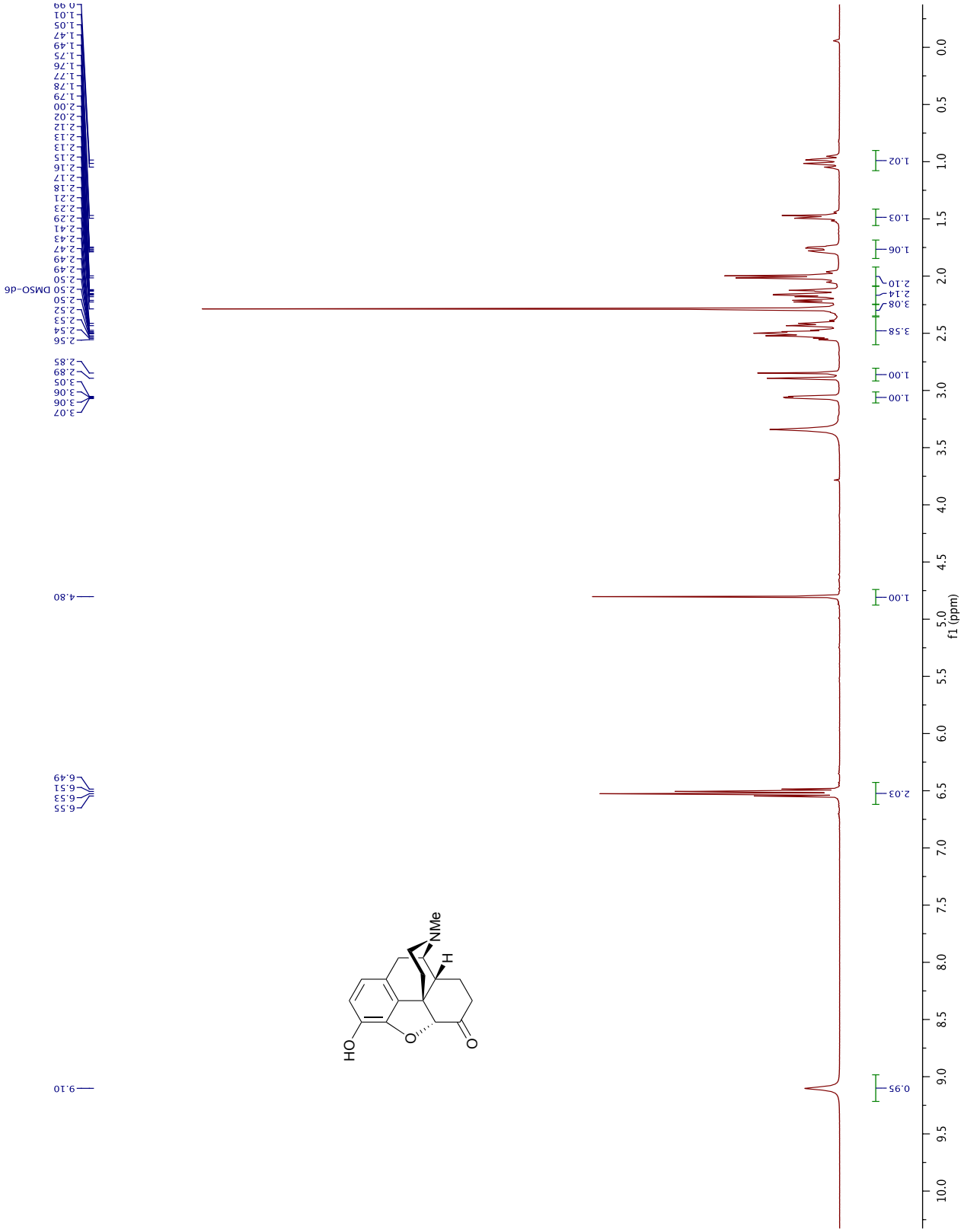
Hydrocodone (3)

^{13}C NMR (400 MHz, $CDCl_3$)



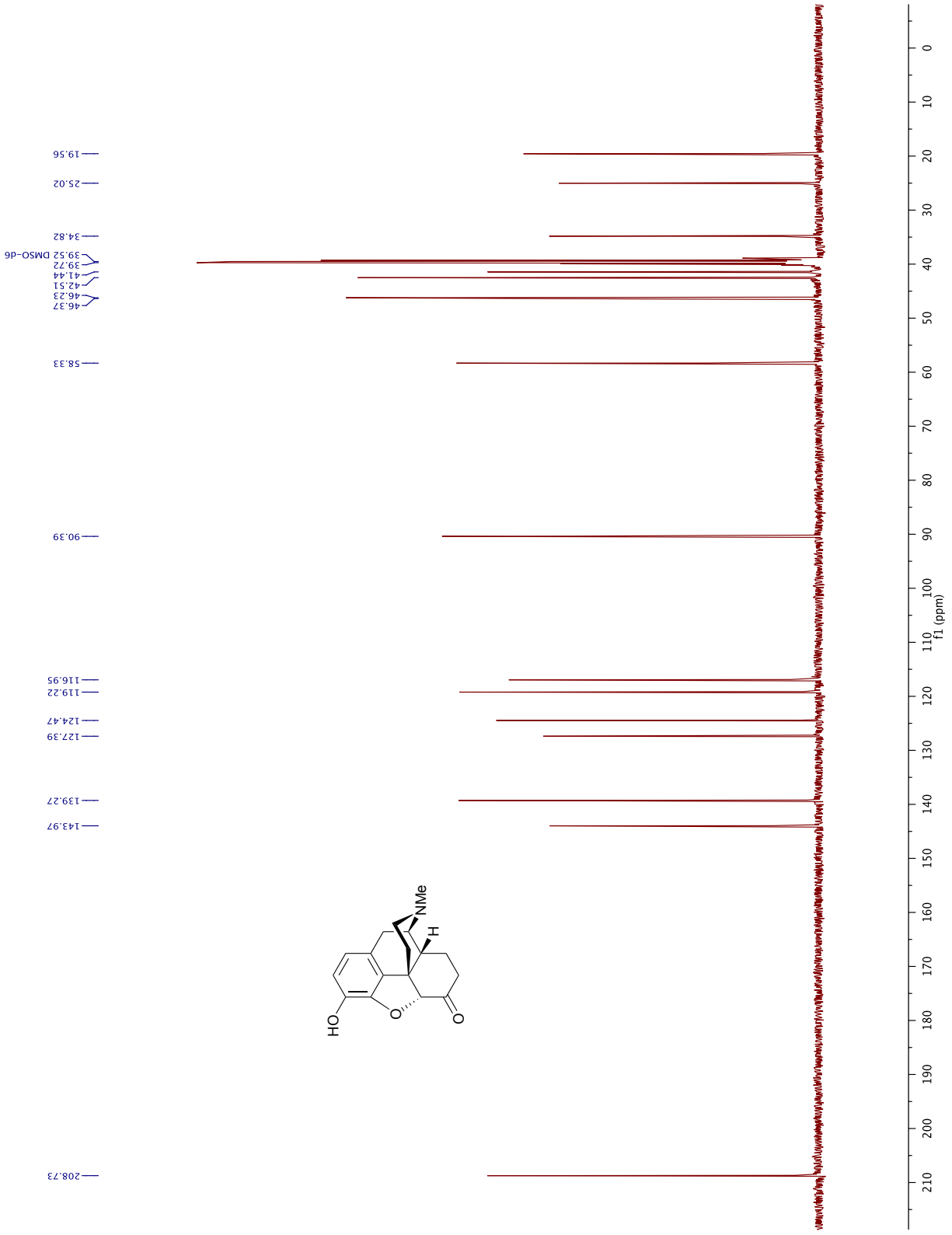
Hydromorphone (4)

^{1}H NMR (400 MHz, DMSO-d_6)



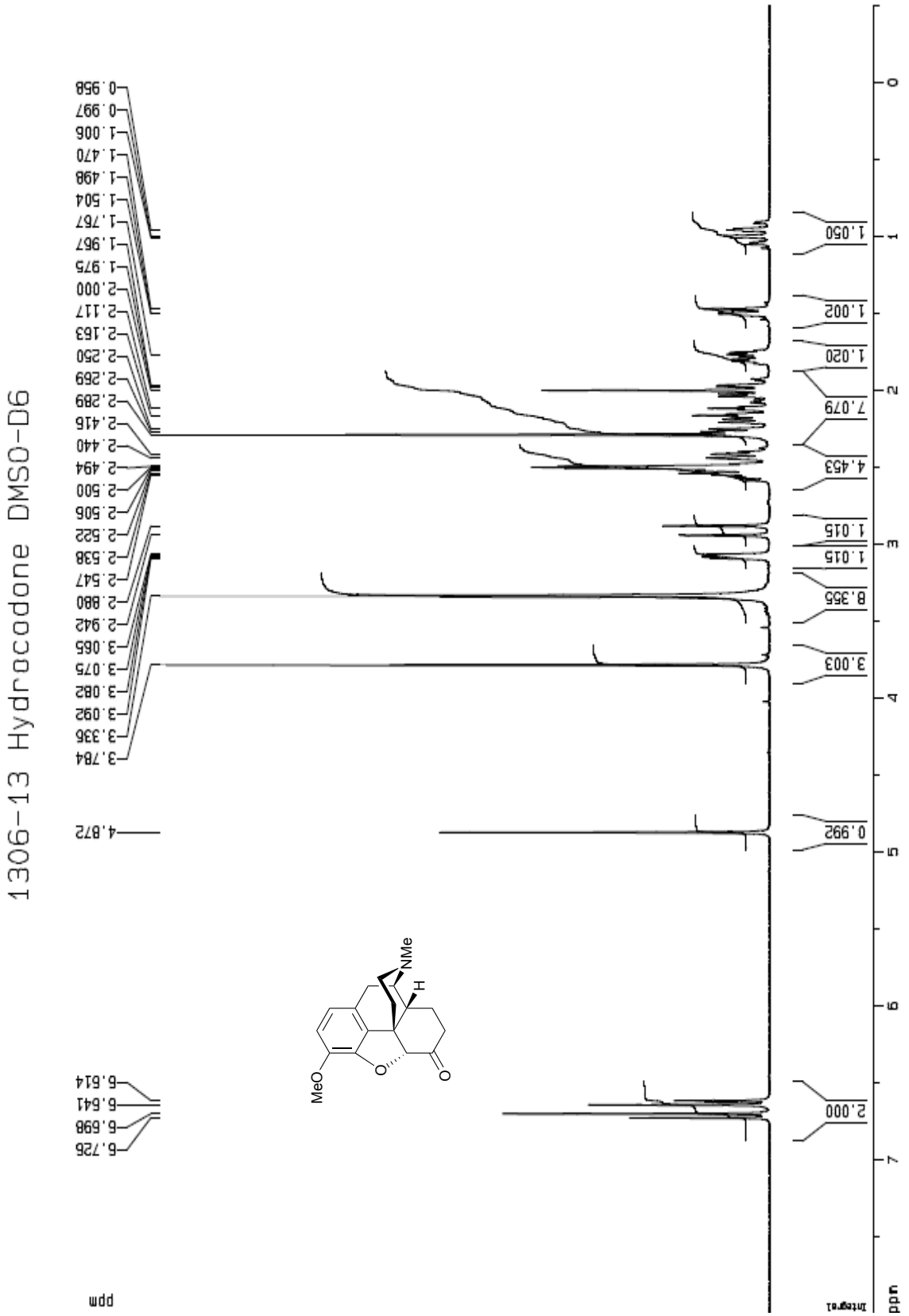
Hydromorphone (4)

^{13}C NMR (400 MHz, DMSO-d_6)

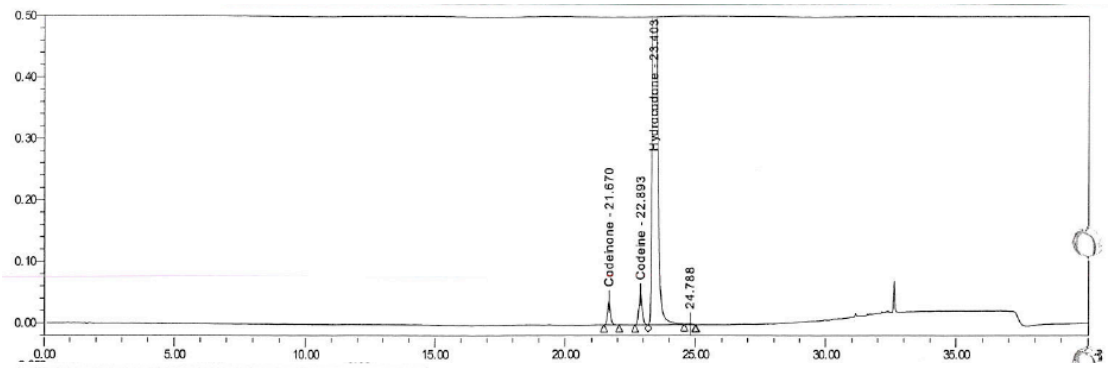


Hydrocodone (3) (100 g scale)

^{1}H NMR (400 MHz, DMSO-d_6)

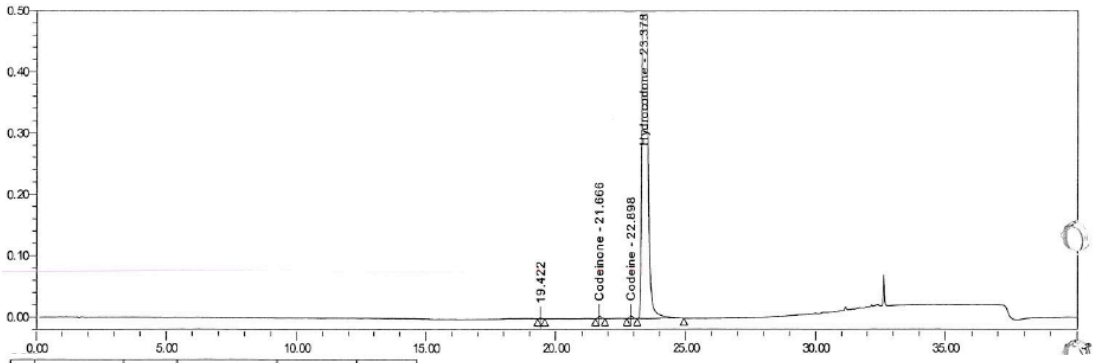


UPLC chromatogram of hydrocodone (3) (100 g scale, 0.1 mol% Rh)



	Name	RT (min)	Area (µV*sec)	Height (µV)	Area %
1	Codeinone	21.670	310166.9286	38025.37	2.4461
2	Codeine	22.893	446176.1963	49329.16	3.5187
3	Hydrocodone	23.403	11909235.9834	1080166.84	93.9194
4		24.788	14686.9709	1033.61	0.1158

UPLC chromatogram of hydrocodone (3) (100 g scale, 0.15 mol% Rh)



	Name	RT (min)	Area (µV*sec)	Height (µV)	Area %
1		19.422	10767.9204	1564.45	0.0761
2	Codeinone	21.666	41337.0412	5010.79	0.2920
3	Codeine	22.898	46790.7868	5166.90	0.3306
4	Hydrocodone	23.378	14055781.9607	1258448.09	99.3013