Supplementary Material (ESI) for Chemical Communications

Supporting information

Phosphate mediated biomimetic synthesis of tetrahydroisoquinoline alkaloids

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General

All reagents were obtained from commercial sources and used as received unless otherwise stated. TLC was performed on Kieselgel 60 F_{254} precoated plastic plates and compounds visualised by exposure to UV light, potassium permanganate, phosphomolybdic acid (PMA) or ninhydrin.

Flash column chromatography was carried out using silica gel (particule size 40-63 μm). Both analytical and preparative HLPC were performed on a Varian Prostar instrument equipped with an autosampler, a UV-visible detector and a DiscoveryBIO wide Pore C18-10 Supelco column (25 × 0.46 cm for analytical scale work and 25 × 2.12 cm for preparative scale). Elutions were monitored at 280 nm and carried out according to either of the following gradients. Gradient **1**: 5% to 40% of acetonitrile/water (0.1% TFA) and gradient **2**: 5% to 90% of acetonitrile/water (0.1% TFA). Diasteromeric excesses were calculated by HPLC chromatography following gradient method **1** or **2**.

^{1}H and ^{13}C NMR specta were recorded at 298 K at the field indicated using Bruker AMX 300, AMX 400, Avance 500 and Avance 600 machines. Coupling constants were measured in Hertz (Hz) and referenced to the deuterated solvent used. Infrared spectra were recorded on Perkin Elmer Spectrum 100 FTIR spectrometer. Optical rotations were recorded on a Perkin Elmer model 343 polarimeter at 589 nm, quoted in deg cm^2 g^{-1} and conc (*c*) in g/100 mL. Mass spectra were recorded on Thermo Finnegan MAT 900XP and Micro Mass Quattro LC electrospray mass spectrometers VG ZAB 2SE.

Procedure A. Pictet-Spengler biomimetic reaction

Amine (1 eq.) and aldehyde (1.2 eq.) were added to 10 mL of a 1:1 mixture of acetonitrile/potassium phosphate buffer (0.1 M solution at pH 6). The resulting solution was stirred at 50 ºC for 12 h. The crude product was extracted with dichloromethane (3 × 20 mL) which was evaporated *in vacuo*, then purified by preparative HPLC (by either gradient **1** or **2**) and fractions containing the desired product were combined, concentrated and co-evaporated with methanol (3 × 20 mL).

4-Hydroxyphenylacetaldehyde[1] **(2).** The reaction was carried out under anhydrous conditions. To a solution of 2-(4-hydroxyphenyl)ethanol (500 mg, 3.62 mmol) in DMSO (5 mL) was added diisopropylethylamine (1.30 mL, 7.46 mmol) and then a solution of

SO_3.pyridine (1.15 g, 7.23 mmol) in DMSO (5 mL) over 30 min. The mixture was stirred for 1 h at rt and quenched by the addition of ice-cold water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers were combined and concentrated under reduced pressure. The crude material was purified using silica flash chromatography (eluent 20% EtOAc in hexane). Fractions containing the desired product were combined and concentrated under reduced pressure to yield **2** as a colourless oil (217 mg, 44% yield). ^{1}H NMR (500 MHz; $CDCl_3$) δ 3.62 (2H, d, *J* 2.4 Hz, C*H*$_2$), 5.00 (1H, s, OH), 6.84 (2H, d, *J* 8.4 Hz, 3-H, 5-H), 7.08 (2H, d, *J* 8.4 Hz, 2-H, 6-H), 9.72 (1H, t, *J* 2.4 Hz, C*H*O); ^{13}C NMR (125 MHz; $CDCl_3$) δ 49.8 (*C*H$_2$), 116.0 (C-3, C-5), 123.9 (C-1), 131.0 (C-2, C-6), 155.0 (C-4), 200.0 (*C*HO); *m/z* [HRMS ES+] found MH^+ 137.05978. $C_8H_9O_2$ requires 137.06025.

1-(4-Hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[2] **(*rac*-norcoclaurine) (3).** Compound **3** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (370 mg, 1.95 mmol) and 4-hydroxyphenylacetaldehyde **2** (310 mg, 2.28 mmol). Racemic norcoclaurine **3** (330 mg, 63%) was isolated as a pale yellow solid by preparative HPLC (gradient **1**, r_t (retention time) 11.8 min). Mp. 220–222 °C (H_2O) (Lit.[2] 256–258 °C (EtOH)); ν_{max} (neat)/cm^{-1} 3488, 3101, 1613, 1516; ^{1}H NMR (500 MHz; D_2O) δ 2.83–3.00 (3H, m, 4-H$_2$, NCHC*H*H), 3.24 (1H, app. quintet, *J* 6.4 Hz, 3-*H*H), 3.35 (1H, dd, *J* 14.7 and 5.5 Hz, NCHCH*H*), 3.47 (1H, app. quintet, *J* 6.4 Hz, 3-H*H*), 4.59 (1H, dd, *J* 9.0 and 5.7 Hz, 1-H), 6.67 (1H, s, 8-H), 6.73 (1H, s, 5-H), 6.88 (2H, d, *J* 8.4 Hz, 3'-H, 5'-H), 7.16 (2H, d, *J* 8.4 Hz, 2'-H, 6'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.4 (C-4), 38.8 (C-9), 39.6 (C-3), 56.6 (C-1), 114.2 (C-8), 116.2 (C-5), 116.3 (C-3', C-5'), 123.7 (C-8a), 124.2 (C-4a), 127.2 (C-1'), 131.3 (C-2', C-6'), 143.2 (C-7), 144.4 (C-6), 155.3 (C-4'). *m/z* [HRMS ES+] found MH^+ 272.12734. $C_{16}H_{18}NO_3$ requires 272.12867.

1-Methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol[3] **(4a).** Compound **4a** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and ethanal (36 μL, 0.64 mmol). The reaction mixture was purified by preparative HPLC (gradient **1**, r_t 10.5 min) to give **4a** as a pale yellow solid (71 mg, 75%). Mp. 147–149 °C (H_2O); ν_{max} (neat)/cm^{-1} 3285, 2992, 2845, 1625, 1531; ^{1}H NMR (500 MHz; D_2O) δ 1.57 (3H, d, *J* 6.8 Hz, CH_3), 2.86–2.96 (2H, m, 4-H$_2$), 3.34 (1H, m, 3-*H*H), 3.48 (1H, m, 3-H*H*), 4.45 (1H, q, *J* 6.8 Hz, 1-H), 6.69 (1H, s, 5-H), 6.72 (1H, s, 8-H); ^{13}C NMR (125 MHz; D_2O) δ 18.9 (CH_3), 24.5 (C-4), 39.6 (C-3), 51.2 (C-1), 113.6 (C-8), 116.0 (C-5),

123.8 (C-4a), 125.5 (C-8a), 143.4 (C-7), 144.1 (C-6); *m/z* [HRMS CI] found MH^+ 180.10157. $C_{10}H_{14}NO_2$ requires 180.10245.

1-Cyclopropyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol (4b). Compound **4b** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and cyclopropanecarboxaldehyde (48 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 10.8 min) to give **4b** as a pale yellow solid (65 mg, 60%). Mp. 210–212 °C (H_2O); ν_{max} (neat)/cm^{-1} 3100, 2992, 2845, 1625, 1531; ^{1}H NMR (500 MHz; D_2O) δ 0.58 (1H, m, cyclopropyl 2'-*H*H), 0.74–0.78 (2H, m, cyclopropyl 2'-H*H* and 3'-*H*H), 1.01 (1H, m, cyclopropyl 3'-H*H*), 1.14–1.18 (1H, m, 1'-H), 2.94–2.98 (1H, m, 4-*H*H), 3.00–3.04 (1H, m, 4-H*H*), 3.31–3.35 (1H, m, 3-*H*H), 3.56–3.60 (1H, m, 3-H*H*), 3.63 (1H, d, *J* 10.7 Hz, 1-H), 6.74 (1H, s, 5-H), 7.06 (1H, s, 8-H); ^{13}C NMR (125 MHz; D_2O) δ 0.0 (cyclopropyl C-3'), 3.3 (cyclopropyl C-2'), 12.0 (cyclopropyl C-1'), 22.0 (C-4), 38.0 (C-3), 58.4 (C-1), 111.6 (C-8), 113.5 (C-5), 121.7 (C-4a), 122.2 (C-8a), 140.9 (C-7), 142.0 (C-6); *m/z* [HRMS EI] found M^+ 205.11052. $C_{12}H_{15}NO_2$ requires 205.11028.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol[4] **(4c).** Compound **4c** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and benzaldehyde (65 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 12.2 min) to give **4c** as a pale yellow solid (96 mg, 75%). Mp. 208–214 °C (H_2O) (Lit.[4] 115–117 °C (EtOAc/diethylamine)); ν_{max} (neat)/cm^{-1} 3097, 1611, 1532; ^{1}H NMR (500 MHz; D_2O) δ 3.02–3.18 (2H, m, 4-H_2), 3.37–3.53 (2H, m, 3-H_2), 5.65 (1H, s, 1-H), 6.36 (1H, s, 8-H), 6.84 (1H, s, 5-H), 7.24–7.53 (5H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ 24.3 (C-4), 39.6 (C-3), 59.3 (C-1), 115.3 (C-8), 115.8 (C-5), 123.1 (C-8a), 125.0 (C-4a), 129.6, 130.1, 130.3, 136.5, 143.5 (C-7), 144.7 (C-6); *m/z* [HRMS CI] found MH^+ 242.11737. $C_{15}H_{16}NO_2$ requires 242.11810.

1-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[5] **(4d).** Compound **4d** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 4-nitrobenzaldehyde (96 mg 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 13.2 min) to give **4d** as a pale yellow solid (77 mg, 51%). Mp. 210–212 °C (H_2O); ν_{max} (neat)/cm^{-1} 3136, 2780, 1611, 1521, 1351; ^{1}H NMR (500 MHz; D_2O) δ 3.00–3.17 (2H, m, 4-H_2), 3.40–3.50 (2H, m, 3-H_2), 5.79 (1H, s, 1-H), 6.31 (1H, s, 8-H), 6.82 (1H, s, 5-H), 7.55 (2H, d, *J* 6.0 Hz, 2'-H, 6'-H), 8.25 (2H, d, *J* 6.0 Hz, 3'-H, 5'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.2 (C-4), 39.8 (C-3), 58.2 (C-1), 115.1 (C-8), 115.9 (C-5), 121.9 (C-8a),

124.6 (C-3', C-5'), 124.9 (C-4a), 131.4 (C-2', C-6'), 143.3 (C-1'), 143.6 (C-7), 145.0 (C-6), 148.7 (C-4'); *m/z* [HRMS CI] found MH^+ 287.10383. $C_{15}H_{15}N_2O_4$ requires 287.10318.

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[4a] (4e). Compound **4e** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 4-methoxybenzaldehyde (78 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 13.2 min) to give **4e** as a pale yellow solid (44 mg, 31%). Mp. 198–200 °C (H_2O) (Lit.[4a] 94–96 °C (EtOAc/diethylamine)); ν_{max} (neat)/cm^{-1} 3136, 1611, 1521; ^{1}H NMR (500 MHz; D_2O) δ 3.03–3.13 (2H, m, 4-H_2), 3.38–3.48 (2H, m, 3-H_2), 3.85 (3H, s, OMe), 5.62 (1H, s, 1-H), 6.38 (1H, s, 8-H), 6.83 (1H, s, 5-H), 7.04 (2H, d, *J* 7.0 Hz, 3'-H, 5'-H), 7.27 (2H, d, *J* 7.0 Hz, 2'-H, 6'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.3 (C-4), 39.3 (C-3), 55.8 (OMe), 58.7 (C-1), 114.9 (C-3', C-5'), 115.3 (C-8), 115.8 (C-5), 123.4 (C-8a), 124.9 (C-4a), 129.0 (C-1'), 131.6 (C-2', C-6'), 143.5 (C-7), 144.7 (C-6), 160.2 (C-4'); *m/z* [HRMS EI] found M^+ 271.11955. $C_{16}H_{17}NO_3$ requires 271.12029.

1-(4-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[6] (4f). Compound **4f** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 4-hydroxybenzaldehyde (78 mg, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 11.0 min) to give **4f** as a pale yellow solid (47 mg, 35%). Mp. 198–200 °C (H_2O); ν_{max} (neat)/cm^{-1} 3032, 1611, 1516; ^{1}H NMR (500 MHz; D_2O) δ 2.96–3.11 (2H, m, 4-H_2), 3.35–3.46 (2H, m, 3-H_2), 5.55 (1H, s, 1-H), 6.33 (1H, s, 8-H), 6.78 (1H, s, 5-H), 6.87 (2H, d, *J* 8.4 Hz, 3'-H, 5'-H), 7.15 (2H, d, *J* 8.4 Hz, 2'-H, 6'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.3 (C-4), 39.4 (C-3), 58.8 (C-1), 115.2 (C-8), 115.5 (C-5), 115.8 (C-3', C-5'), 123.4 (C-8a), 124.9 (C-4a), 128.3 (C-1'), 131.7 (C-2', C-6'), 143.4 (C-7), 144.6 (C-6), 157.1 (C-4'); *m/z* [HRMS CI] found MH^+ 258.11245. $C_{15}H_{16}NO_3$ requires 258.11302.

1-(3-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[7] (4g). Compound **4g** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 3-hydroxybenzaldehyde (78 mg, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 11.0 min) to give **4g** as a pale yellow solid (109 mg, 80%). Mp. 106–108 °C (H_2O); ν_{max} (neat)/cm^{-1} 3100, 2820, 1594, 1530; ^{1}H NMR (500 MHz; D_2O) δ 2.92–3.09 (2H, m, 4-H_2), 3.32–3.47 (2H, m, 3-H_2), 5.48 (1H, s, 1-H), 6.28 (1H, s, 8-H), 6.74 (1H, s, 5-H), 6.80 (1H, s, 2'-H), 6.83 (1H, d, *J* 7.6 Hz, 6'-H), 6.91 (1H,

d, *J* 8.2 Hz, 4'-H), 7.26 (1H, dd, *J* 8.2 and 7.6 Hz, 5'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.3 (C-4), 39.8 (C-3), 59.2 (C-1), 115.2 (C-8), 115.7 (C-5), 116.8 (C-2'), 117.1 (C-4'), 121.9 (C-6'), 122.9 (C-8a), 124.8 (C-4a), 130.9 (C-5'), 138.1 (C-1'), 143.4 (C-7), 144.7 (C-6), 156.4 (C-3'); *m/z* [HRMS CI] found MH^+ 258.11281. $C_{15}H_{16}NO_3$ requires 258.11302.

1-(2-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol (4h). Compound **4h** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 2-hydroxybenzaldehyde (70 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 12.2 min) to give **4h** as a pale yellow solid (117 mg, 86%). Mp. 121–123 °C (H_2O); ν_{max} (neat)/cm^{-1} 3200, 3150, 3027, 2835, 1606, 1531, 1505; ^{1}H NMR (500 MHz; D_2O) δ 2.94–3.08 (2H, m, 4-H_2), 3.34–3.41 (2H, m, 3-H_2), 5.74 (1H, s, 1-H), 6.34 (1H, s, 8-H), 6.78 (1H, s, 5-H), 6.90 (1H, t, *J* 7.6 Hz, 5'-H), 6.98–7.02 (2H, m, 3'-H and 6'-H), 7.34 (1H, t, *J* 7.6 Hz, 4'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.4 (C-4), 39.9 (C-3), 55.2 (C-1), 114.7 (C-3'), 115.9 (C-5), 116.1 (C-8), 120.7 (C-5'), 122.6 (C-8a), 122.8 (C-4a), 124.8 (C-1'), 131.7 (C-4'), 131.7 (C-6'), 143.5 (C-7), 144.5 (C-6), 154.6 (C-2'); *m/z* [HRMS CI] found MH^+ 258.11313. $C_{15}H_{16}NO_3$ requires 258.11302.

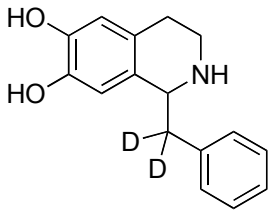
1-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[4a] **(4i).** Compound **4i** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 4-bromobenzaldehyde (118 mg, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 15.0 min) to give **4i** as a pale yellow solid (80 mg, 47%). Mp. 228–232 °C (H_2O) (Lit.[4a] 116–118 °C (EtOAc/diethylamine)); ν_{max} (neat)/cm^{-1} 3150, 3100, 1613, 1535; ^{1}H NMR (500 MHz; D_2O) δ 3.02–3.15 (2H, m, 4-H_2), 3.40–3.50 (2H, m, 3-H_2), 5.67 (1H, s, 1-H), 6.38 (1H, s, 8-H), 6.85 (1H, s, 5-H), 7.26 (2H, d, *J* 8.4 Hz, 2'-H, 6'-H), 7.66 (2H, d, *J* 8.4 Hz, 3'-H, 5'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.5 (C-4), 39.8 (C-3), 58.8 (C-1), 115.5 (C-8), 116.1 (C-5), 123.0 (C-4'), 124.3 (C-8a), 125.3 (C-4a), 132.2 (C-3', C-5'), 132.6 (C-2', C-6'), 135.9 (C-1'), 143.9 (C-7), 145.1 (C-6); *m/z* [HRMS ES+] found MH^+ 322.0278. $C_{15}H_{15}{}^{81}BrNO_2$ requires 322.0266.

1-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol (4j). Compound **4j** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 4-fluorobenzaldehyde (68 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 13.1 min) to give **4j** as a pale yellow solid (56 mg, 41%). Mp. 218–220 °C (H_2O); ν_{max} (neat)/cm^{-1} 3250, 3127, 1609, 1535, 1507; ^{1}H NMR (500 MHz; D_2O) δ 3.01–3.18 (2H, m, 4-H_2), 3.37–3.51 (2H, m, 3-H_2), 5.69 (1H, s, 1-H),

6.39 (1H, s, 8-H), 6.85 (1H, s, 5-H), 7.20–7.25 (2H, t, *J* 8.8 Hz, 3'-H, 5'-H), 7.35–7.39 (2H, dd, *J* 8.8 and 5.3 Hz, 2'-H, 6'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.3 (C-4), 39.5 (C-3), 58.5 (C-1), 115.3 (C-8), 115.9 (C-5), 116.4 (d, $^2J_{CF}$ 21.9 Hz, C-3', C-5'), 123.0 (C-8a), 125.0 (C-4a), 132.2 (d, $^3J_{CF}$ 8.8 Hz, C-2', C-6'), 133.0 (C-1'), 143.5 (C-7), 144.8 (C-6), 163.8 (d, $^1J_{CF}$ 220 Hz, C-4'); *m/z* [HRMS CI] found MH^+ 260.10923. $C_{15}H_{15}FNO_2$ requires 260.10868.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol[3a] **(4k).** Compound **4k** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and phenylacetaldehyde (75 µL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 13.5 min) to give **4k** as a pale yellow solid (98 mg, 73%). Mp. 186–190 °C (H_2O) (Lit.[8] 233–236 °C); ν_{max} (neat)/cm^{-1} 3442, 3028, 1599, 1529; ^{1}H NMR (500 MHz; D_2O) δ 2.85–2.96 (2H, m, 4-H_2), 3.00 (1H, dd, *J* 14.5 and 9.2 Hz, NCHC*H*H), 3.26 (1H, app. quintet, *J* 6.4 Hz, 3-*H*H), 3.40–3.50 (2H, m, 3-H*H* and NCHCH*H*), 4.65 (1H, dd, *J* 9.2 and 5.7 Hz, 1-H), 6.67 (1H, s, 8-H), 6.73 (1H, s, 5-H), 7.28 (2H, d, *J* 7.0 Hz, 2'-H, 6'-H Ph), 7.30–7.45 (3H, m, 3'-H, 4'-H, 5'-H, Ph); ^{13}C NMR (125 MHz; D_2O) δ 24.4 (C-4), 39.6 (NCH*C*H_2), 39.7 (C-3), 56.5 (C-1), 114.1 (C-8), 116.1 (C-5), 123.6 (C-8a), 124.1 (C-4a), 128.2 (C-4'), 129.6 (C-3', C-5'), 129.9 (C-2', C-6'), 135.4 (C-1'), 143.2 (C-7), 144.4 (C-6); *m/z* [HRMS CI] found MH^+ 256.13256. $C_{16}H_{18}NO_2$ requires 256.13375.

1-Phenyl[$^2H_2$]methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol (4k-$^2H_2$).



Phenylacetaldehyde (30 µL, 0.26 mmol) was stirred at room temperature in 4 mL of a 1:1 mixture of acetonitrile/D_2O phosphate buffer (0.1 M in D_2O at pH 6) for 1 h. Dopamine hydrochloride (**1**.HCl) (40 mg, 0.21 mmol) was added and the resulting solution stirred at 50 ºC for 12 h. The crude product was washed with dichloromethane (3 × 20 mL) and evaporated *in vacuo*, then purified by preparative HPLC (gradient **1**, r_t = 13.7 min) to give **4k-$^2H_2$** as a pale yellow glassy solid (45 mg, 83%) containing deuterium at CD_2Ph (90%). ^{1}H NMR (600 MHz; CD_3OD) δ 2.87–3.02 (2H, m, 4-H_2), 3.26 (1H, app. quintet, *J* 6.2 Hz, 3-*H*H), 3.45 (1H, app. quintet, *J* 6.0 Hz, 3-H*H*), 4.66 (1H, s, 1-H), 6.58 (1H, s, 8-H), 6.63

(1H, s, 5-H), 7.30–7.41 (5H, m, Ph); ^{13}C NMR (150 MHz; CD_3OD) δ 25.7 (C-4), 40.5–40.7 (m, NCH*C*H$_2$), 40.9 (C-3), 57.7 (C-1), 114.2 (C-8), 116.2 (C-5), 123.6 (C-8a), 123.7 (C-4a), 128.8 (C-4'), 130.3 (C-3', C-5'), 130.6 (C-2', C-6'), 136.6 (C-1'), 145.7 (C-7), 146.9 (C-6); *m/z* [HRMS CI] found MH$^+$ 258.14749. $C_{16}H_{16}D_2NO_2$ requires 258.14630.

1-Thiophen-2-yl-1,2,3,4-tetrahydroisoquinoline-6,7-diol[9] (4l). Compound **4l** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 2-thiophenecarboxaldehyde (64 μL, 0.68 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 11.8 min) to give **4l** as a pale yellow solid (102 mg, 79%). Mp. 218–220 °C (H_2O); ν_{max} (neat)/cm^{-1} 3300, 3116, 1614, 1587, 1533; ^{1}H NMR (500 MHz; D_2O) δ 2.97–3.10 (2H, m, 4-H$_2$), 3.38–3.55 (2H, m, 3-H$_2$), 5.96 (1H, s, 1-H), 6.54 (1H, s, 8-H), 6.78 (1H, s, 5-H), 7.14 (1H, dd, *J* 5.0 and 3.6 Hz, 4'-H), 7.18–7.20 (1H, m, 3'-H), 7.56 (1H, d, *J* 5.0 Hz, 5'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.1 (C-4), 39.1 (C-3), 53.8 (C-1), 115.4 (C-8), 115.8 (C-5), 123.2 (C-8a), 124.4 (C-4a), 127.9 (C-4'), 129.1 (C-5'), 130.9 (C-3'), 139.1 (C-2'), 143.4 (C-7), 145.0 (C-6); *m/z* [HRMS CI] found MH$^+$ 248.07380. $C_{13}H_{14}NO_2S$ requires 248.07452.

1-Pyridin-3-yl-1,2,3,4-tetrahydroisoquinoline-6,7-diol[4a] (4m). Compound **4m** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and 3-pyridinecarboxaldehyde (60 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 7.7 min) to give **4m** as a glassy solid (99 mg, 77%). ν_{max} (neat)/cm^{-1} 3064, 1615, 1531; ^{1}H NMR (500 MHz; D_2O) δ 2.99–3.11 (2H, m, 4-H$_2$), 3.37 (1H, app. quintet, *J* 6.4 Hz, 3-*H*H), 3.45 (1H, app. quintet, *J* 6.4 Hz, 3-H*H*), 5.98 (1H, s, 1-H), 6.29 (1H, s, 8-H), 6.79 (1H, s, 5-H), 8.11 (1H, dd, *J* 8.1 and 5.7 Hz, 5'-H), 8.56 (1H, d, *J* 8.1 Hz, 4'-H), 8.76 (1H, s, 2'-H), 8.84 (1H, d, *J* 5.7 Hz, 6'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.0 (C-4), 39.5 (C-3), 55.3 (C-1), 114.8 (C-8), 116.2 (C-5), 119.5 (C-8a), 125.3 (C-4a), 128.3 (C-5'), 136.8 (C-3'), 142.9 (C-2'), 143.0 (C-6'), 144.0 (C-7), 145.6 (C-6), 148.8 (C-4'); *m/z* [HRMS ES+] found MH$^+$ 243.11263. $C_{14}H_{15}N_2O_2$ requires 243.11335.

1,2,3,4-tetrahydro-(1,4-bisisoquinolinyl)-6,7-diol (4n). Compound **4n** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (50 mg, 0.264 mmol) and isoquinoline-4-carboxaldehyde (49 mg, 0.31 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 15.8 min) to give **4n** as a pale yellow solid (68 mg, 88%). Mp. 203–205 °C (H_2O); ν_{max} (neat)/cm^{-1} 3100, 1610, 1531; ^{1}H NMR (500 MHz; D_2O) δ 3.00–3.20 (2H, m, 4-H$_2$), 3.46–3.54 (2H, m, 3-H$_2$), 6.17 (1H, s, 1-H), 6.39 (1H, s,

8-H), 6.87 (1H, s, 5-H), 7.99 (1H, app. t, *J* 7.6 Hz, 6'-H or 7'-H), 8.20–8.31 (3H, m, 6'-H or 7'-H, 5'-H, 8'-H), 9.09 (1H, d, *J* 1.6 Hz, 3'-H), 9.13 (1H, d, *J* 1.6 Hz, 1'-H); ^{13}C NMR (125 MHz; D_2O) δ 24.1 (C-4), 39.4 (C-3), 55.6 (C-1), 115.0 (C-8), 116.3 (C-5), 120.0, 120.6, 125.4, 129.0, 130.0, 130.5, 131.4, 137.1, 138.0, 144.1, 145.1, 145.6 (C-1'), 149.6 (C-3'); *m/z* [HRMS ES+] found MH^+ 293.1276. $C_{18}H_{17}N_2O_2$ requires 293.1290.

1-(Ferrocene)-1,2,3,4-tetrahydroisoquinoline-6,7-diol (4o). Compound **4o** was prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (50 mg, 0.264 mmol) and ferrocenecarboxaldehyde (137 mg, 0.640 mmol). The product was purified by preparative HPLC (gradient **2**, r_t = 12.8 min) to give **4o** as a black solid (40 mg, 44%). Mp. 183–185 °C (H_2O); ν_{max} (neat)/cm^{-1} 3101, 1605, 1532; ^{1}H NMR (600 MHz; CD_3OD) δ 2.70–2.90 (2H, m, 4-H_2), 3.10–3.25 (2H, m, 3-H_2), 3.60 (1H, s, H-C_5H_4), 4.16 (1H, s, H-C_5H_4), 4.20 (5H, s, C_5H_5), 4.26 (1H, s, H-C_5H_4), 4.34 (1H, s, H-C_5H_4), 5.37 (1H, s, 1-H), 6.52 (1H, s, 5-H), 6.87 (1H, s, 8-H); ^{13}C NMR (150 MHz; CD_3OD) δ 25.1 (C-4), 38.6 (C-3), 56.4 (C-1), 68.1, 69.6, 70.5, 70.8, 70.9 and 86.3 (C-ferrocene), 115.9 (C-8), 116.0 (C-5), 122.6 (C-8a), 123.6 (C-4a), 145.4 (C-7), 147.2 (C-6); *m/z* [HRMS ES+] found MH^+ 350.0848. $C_{19}H_{20}FeNO_2$ requires 350.0844.

2-(3-Nitrophenyl)-ethylamine (5f). The reaction was carried out under anhydrous conditions. To a solution of 3-nitrophenylacetonitrile (1.00 g, 6.17 mmol) in THF was added a solution of borane-THF (1 M; 15 mL, 15 mmol). The mixture was heated at reflux for 7 h, cooled to 0 °C and methanol (10 mL) was added dropwise. The solution was concentrated under vacuum and co-evaporated with methanol (3 × 30 mL). Methanol (15 mL) and 3 M HCl (20 mL) were added to the crude residue and the resulting suspension was stirred at room temperature for 4 h and subsequently washed with diethyl ether (3 × 30 mL). The aqueous layer was made basic with 6 M NaOH and extracted with diethyl ether (3 × 30 mL). The organic layers were dried (Na_2SO_4) and concentrated to yield a pale yellow oil that was recrystallised from a conc. HCl/isopropanol mixture to give **5f** (1.02 g, 100%) as colourless crystals. Mp. 180–182 °C (isopropanol); ν_{max} (neat)/cm^{-1} 2889, 1601, 1520, 1345; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.86 (2H, t, *J* 6.9 Hz, C*H*$_2$CH$_2$NH$_2$), 3.05 (2H, t, *J* 6.9 Hz, CH$_2$C*H*$_2$NH$_2$), 7.48 (1H, t, *J* 7.6 Hz, 5'-H), 7.55 (1H, d, *J* 7.6 Hz, 6'-H), 8.05–8.10 (2H, m, 2'-H and 4'-H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 39.7 (*C*H$_2$CH$_2$NH), 43.2 (CH$_2$*C*H$_2$NH), 121.5, 123.7, 129.4, 135.2, 142.1 (C-1'), 148.5 (C-3'); *m/z* [HRMS CI] found MH^+ 167.08251. $C_8H_{11}N_2O_2$ requires 167.08205.

2-(3-Aminophenyl)ethylamine[10] **(5g).** To **5f** (1.00 g, 6.02 mmol) in isopropanol (5 mL) was added 10% Pd/C (5 mg). The reaction mixture was purged with N_2, then H_2 and stirred at rt for 24 h. The reaction mixture was subsequently filtered, concentrated and purified by silica chromatography (eluent 25% MeOH in CH_2Cl_2) to give **5g** (625 mg, 76%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3332, 3200, 2910, 1602, 1490; ^{1}H NMR (500 MHz; D_2O) δ 2.93 (2H, t, *J* 7.4 Hz, C*H*$_2$CH$_2$NH$_2$), 3.28 (2H, t, *J* 7.4 Hz, CH$_2$C*H*$_2$NH$_2$), 6.70–6.82 (3H, m, Ph), 7.25 (1H, t, *J* 7.4 Hz, 5'-H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 33.3 (*C*H$_2$CH$_2$N), 41.2 (CH$_2$*C*H$_2$N), 115.8 and 116.2 (C-2', C-4'), 120.5 (C-6'), 130.7 (C-5'), 138.6 (C-1'), 147.3 (C-3'); *m/z* [HRMS EI] found M$^+$ 136.09961. $C_8H_{12}N_2$ requires 136.10004.

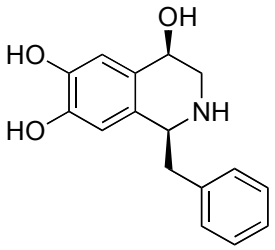
1-Benzyl-1,2,3,4-tetrahydroisoquinoline-6,7,8-triol (6a). Compound **6a** was prepared according to procedure **A** using 5-hydroxydopamine hydrochloride (**5a**.HCl) (20 mg, 0.097 mmol) and phenylacetaldehyde (17 μL, 0.15 mmol). The product was purified by preparative HPLC (gradient **1**, r_t = 13.3 min) to give **6a** as a pale yellow solid (2.5 mg, 9%). ^{1}H NMR (500 MHz; D_2O) δ 2.86–2.98 (2H, m, 4-H$_2$), 3.00–3.07 (1H, m, NCHC*H*H), 3.26–3.34 (1H, m, 3-*H*H), 3.46–3.56 (2H, m, 3-H*H* and NCHCH*H*), 4.85 (1H, m, 1-H), 6.39 (1H, s, 5-H), 7.32–7.45 (5H, m, Ph); *m/z* [HRMS ES+] found MH$^+$ 272.1278. $C_{16}H_{18}NO_3$ requires 272.1287.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline-6-ol[9,11] **(6c).** Compound **6c** was prepared according to procedure **A** using **5c** (50 mg, 0.36 mmol) and phenylacetaldehyde (52 mg, 0.43 mmol). The product was purified by preparative HPLC (gradient **2**, r_t = 12.5 min) to give **6c** as a colourless solid (64 mg, 74%). Mp. 210–212 °C (H_2O); ν_{max} (neat)/cm^{-1} 3033, 1623, 1584, 1504; ^{1}H NMR (600 MHz; CD_3OD) δ 2.98–3.13 (3H, m, 4-H$_2$ and NCHC*H*H), 3.27–3.33 (1H, m, 3-*H*H), 3.47–3.53 (2H, m, 3-H*H* and NCHCH*H*), 4.73 (1H, dd, *J* 8.5 and 6.2 Hz, 1-H), 6.66 (1H, s, 5-H), 6.67 (1H, d, *J* 6.7 Hz, 7-H), 6.98 (1H, d, *J* 6.7 Hz, 8-H), 7.30–7.42 (5H, m, Ph); ^{13}C NMR (150 MHz; CD_3OD) δ 26.3 (C-4), 40.4 (C-3), 41.1 (NCH*C*H$_2$), 57.7 (C-1), 115.4 (C-5), 115.9 (C-7), 123.3 (C-8a), 128.6, 129.0, 130.1, 130.5, 133.8 (C-4a), 136.5, 158.5 (C-6); *m/z* [HRMS ES+] found MH$^+$ 240.1380. $C_{16}H_{18}NO$ requires 240.1388.

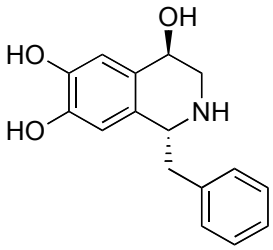
1-Benzyl-1,2,3,4-tetrahydroisoquinoline-6-ylamine (6g). Compound **6g** was prepared according to procedure **A** using **5g** (90 mg, 0.66 mmol) and phenylacetaldehyde (110 mg, 0.92 mmol). The product was purified by preparative HPLC (gradient **2**, r_t 10.5 min) to

give **6g** as a glassy solid (82 mg, 52%). ν_{max} (neat)/cm^{-1} 3010, 2950, 2828, 1620, 1584, 1506; ^{1}H NMR (500 MHz; D_2O) δ3.00–3.16 (3H, m, 4-H_2 and NCHC*H*H), 3.28 (1H, app. quintet, *J* 6.5 Hz, 3-*H*H), 3.39 (1H, dd, *J* 14.3 and 6.4 Hz, NCHCH*H*), 3.49 (1H, m, 3-H*H*), 4.75–4.79 (1H, m, 1-H), 7.06 (1H, dd, *J* 8.4 and 2.2 Hz, 7-H), 7.11 (1H, d, *J* 8.4 Hz, 8-H), 7.12 (1H, s, 5-H), 7.20–7.32 (5H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ26.2 (C-4), 40.0 (C-3), 40.9 (NCH*C*H_2), 57.5 (C-1), 121.7 (C-7), 123.6 (C-5), 128.9, 130.0 (C-8), 130.2, 130.7, 132.3 (C-8a), 134.3 (C-4a), 135.2 (C-6), 136.2; *m/z* [HRMS ES+] found MH$^+$ 239.1540. $C_{16}H_{19}N_2$ requires 239.1548.

(1*S*,4*R*)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline-4,6,7-triol and (1*R*,4*R*)-1-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6,7-triol (8a).



8a (1*S*,4*R*)



8a (1*R*,4*R*)

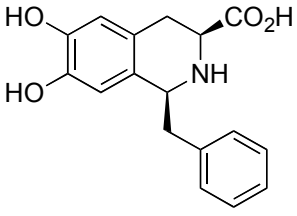
Compound **8a** (both isomers) were prepared according to procedure **A** using (-)-norepinephrine (90 mg, 0.53 mmol) and phenylacetaldehyde (75 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t (1*S*,4*R*) 6.7 min, r_t (1*R*,4*R*) 7.2 min) to give **8a** (1*S*,4*R*) minor isomer (39 mg, 27%) and **8a** major isomer (1*R*,4*R*) (61 mg, 43%). Compound **8a** minor isomer (1*S*,4*R*): $[\alpha]^{25}_D$ = -16 (*c* 0.1, MeOH); ν_{max} (neat)/cm^{-1} 3032, 1606, 1528; ^{1}H NMR (500 MHz; D_2O) δ3.13 (1H, dd, *J* 14.7 and 9.2 Hz, NCHC*H*H), 3.36 (1H, dd, *J* 13.1 and 3.1 Hz, 3-*H*H), 3.43 (1H, dd, *J* 13.1 and 3.4 Hz, 3-H*H*), 3.63 (1H, dd, *J* 14.7 and 4.9 Hz, NCHCH*H*), 4.74 (1H, dd, *J* 9.2 and 4.9 Hz, 1-H), 4.88 (1H, dd, *J* 3.4 and 3.1 Hz, 4-H), 6.87 (1H, s, 8-H), 6.94 (1H, s, 5-H), 7.34–7.45 (5H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ39.2 (NCH*C*H_2), 47.5 (C-3), 57.1 (C-1), 62.6 (C-4), 113.5 (C-8), 116.7 (C-5), 123.9 (C-8a), 125.8 (C-4a), 128.2 (C-4'), 129.6 (C-3', C-5'), 129.9 (C-2', C-6'), 135.1 (C-1'), 144.7 (C-7), 145.4 (C-6); *m/z* [HRMS ES+] found MH$^+$ 272.1289. $C_{16}H_{18}NO_3$ requires 272.1287.

Compound **8a** major isomer (1*R*,4*R*): $[\alpha]^{25}_D$ = +56 (*c* 0.1, MeOH); Mp. 138–140 °C (H_2O); ν_{max} (neat)/cm^{-1} 3033, 1607, 1528; ^{1}H NMR (500 MHz; D_2O) δ3.07 (1H, dd, *J* 14.4 and 8.4 Hz, NCHC*H*H), 3.24–3.34 (2H, m, 3-*H*H and NCHCH*H*), 3.58 (1H, dd, *J*

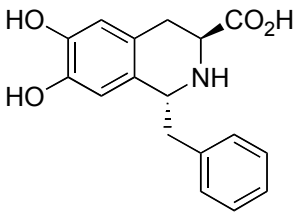
13.4 and 3.3 Hz, H-3-H*H*), 4.73 (1H, dd, *J* 8.4 and 6.8 Hz, 1-H), 4.87 (1H, t, *J* 3.3 Hz, 4-H), 6.48 (1H, s, 8-H), 6.92 (1H, s, 5-H), 7.22–7.40 (5H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ 39.2 (NCH*C*H_2), 44.5 (C-3), 55.8 (C-1), 62.3 (C-4), 114.2 (C-8), 116.5 (C-5), 123.6 (C-8a), 125.2 (C-4a), 128.2 (C-4'), 129.6 (C-3', C-5'), 129.9 (C-2', C-6'), 135.2 (C-1'), 144.8 (C-7), 145.0 (C-6); *m/z* [HRMS ES+] found MH^+ 272.1285. $C_{16}H_{18}NO_3$ requires 272.1287.

The stereochemistry of the two isomers was tentatively assigned from NOESY experiments shown in Figures 3 and 5 (together with for example COSY experiments (Figures 4 and 6) to establish peak identification), and consideration of molecular models and pseudo-axial or equatorial orientations of the protons on the heterocyclic ring. For the CH_2Ph group in **8a** (1*S*,4*R*) no NOE was observed with 3-H_2, suggesting the CH_2Ph is pseudo-equatorial, while an NOE is observed between 1-H and 3-*H*H (and both protons are probably pseudo-axial and below the ring as drawn). However, in **8a** (1*R*,4*R*) the CH_2Ph (CH_2 group) does give an NOE to 3-*H*H (the proton below the ring as drawn). In addition, no NOE is observed between 1-H and 3-H (both groups probably pseudo-equatorial). Proton 4-H shows NOEs to both 3-H_2s in **8a** (1*R*,4*R*) and **8a** (1*S*,4*R*), suggesting it is pseudo-equatorial in both isomers.

(1*S*,3*S*)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and (1*R*,3*S*)-1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (8b)[12].



8b (1*S*,3*S*)



8b (1*R*,3*S*)

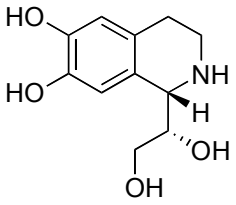
Compound **8b** (both isomers) were prepared according to procedure **A** using 3,4-dihydroxyphenyl-L-alanine (104 mg, 0.53 mmol) and phenylacetaldehyde (75 µL, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t (1*S*,3*S*) 7.0 min, r_t (1*R*,3*S*) 7.7 min) to give **8b** (1*S*,3*S*) (56 mg, 35%) and **8b** (1*R*,3*S*) (48 mg, 30%) as pale yellow solids. Compound **8b** (1*S*,3*S*): $[\alpha]^{25}_D$ = -79 (*c* 0.1, MeOH); Mp 140–142 °C (H_2O); ν_{max} (neat)/cm^{-1} 3033, 1700, 1612, 1529; ^{1}H NMR (500 MHz; D_2O) δ 3.05 (1H, dd, *J* 14.6

and 9.6 Hz, NCHC*H*H), 3.12 (1H, dd, *J* 16.9 and 12.2 Hz, 4-*H*H), 3.22 (1H, dd, *J* 16.9 and 5.1 Hz, 4-H*H*), 3.66 (1H, dd, *J* 14.6 and 4.9 Hz, NCHCH*H*), 4.10 (1H, dd, *J* 12.2 and 5.1 Hz, 3-H), 4.72 (1H, dd, *J* 9.6 and 4.9 Hz, 1-H), 6.76 (1H, s, 5-H), 6.92 (1H, s, 8-H), 7.36–7.49 (5H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ 28.3 (C-4), 39.1 (NCH*C*H_2), 55.2 (C-3), 57.7 (C-1), 113.5 (C-8), 116.0 (C-5), 123.2 (C-8a), 123.4 (C-4a), 128.3, 129.7, 129.9, 135.3, 143.8 (C-7), 144.6 (C-6), 171.6 (C=O); *m/z* [HRMS ES-] found [M-H] 298.1069. $C_{17}H_{16}NO_4$ requires 298.1079.

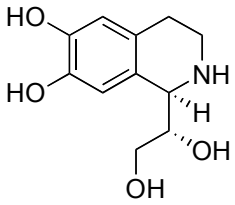
Compound **8b** (1*R*,3*S*): $[\alpha]^{25}_D$ = -72 (*c* 0.1, MeOH); Mp 136–138 °C (H_2O); ν_{max} (neat)/cm^{-1} 3100, 1611, 1531; ^{1}H NMR (500 MHz; D_2O) δ 3.05 (1H, dd, *J* 17.4 and 10.0 Hz, 4-*H*H), 3.15–3.22 (2H, m, NCHCH_2), 3.28 (1H, dd, *J* 17.4 and 6.0 Hz, 4-H*H*), 4.38 (1H, dd, *J* 10.0 and 6.0 Hz, 3-H), 4.79 (1H, m, 1-H), 6.22 (1H, s, 8-H), 6.72 (1H, s, 5-H), 7.12 (2H, d, *J* 7.6 Hz, 2'-H, 6'-H), 7.30–7.40 (3H, m, Ph); ^{13}C NMR (125 MHz; D_2O) δ 27.5 (C-4), 40.0 (NCH*C*H_2), 51.1 (C-3), 56.2 (C-1), 114.6 (C-8), 116.0 (C-5), 122.2 (C-8a), 122.6 (C-4a), 128.1 (C-4'), 129.4 (C-3'), 130.1 (C-2'), 135.4 (C-1'), 143.2 (C-7), 144.6 (C-6), 171.5 (C=O); *m/z* [HRMS ES+] found $[MH]^+$ 300.1235. $C_{17}H_{18}NO_4$ requires 300.1236.

The stereochemistry of the two isomers was established by NOESY experiments shown in Figures 7 and 9 (together with for example COSY experiments (Figures 8 and 10) to establish peak identification). Notably, for **8b** (1*S*,3*S*) an NOE was noted between 1-H and 3-H that was not present in **8b** (1*R*,3*S*).

(1*S*,1'*S*)-1-(1,2-Dihydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol and (1*R*,1'*S*)-1-(1,2-Dihydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol[13] (8c).



8c (1*S*,1'*S*)



8c (1*R*,1'*S*)

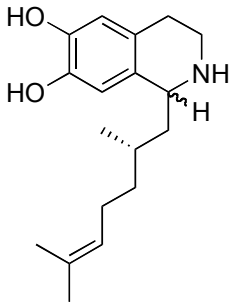
Compound **8c** (both isomers) were prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (83 mg, 0.64 mmol). The product was purified by preparative HPLC (gradient **1**, r_t (1*S*,1'*S*) 11.6 min, r_t (1*R*,1'*S*) 12.0 min) to give **8c** (1*S*,1'*S*) (31 mg, 26%) and

8c (1*R*,1'*S*) (80 mg, 68%) as glassy solids. Compound **8c** minor isomer (1*S*,1'*S*): $[\alpha]^{25}_{D}$ = +46 (*c* 0.1, MeOH); ν_{max} (neat)/cm^{-1} 3085, 1603, 1530; ^{1}H NMR (600 MHz; CD_3OD) δ 2.78–2.82 (1H, m, 4-*H*H), 2.98–3.11 (2H, m, 3-*H*H and 4-H*H*), 3.59 (1H, dd, *J* 11.6 and 3.1 Hz, C*H*HOH) 3.63 (1H, m, 3-H*H*), 3.68 (1H, dd, *J* 11.6 and 2.8 Hz, CHHOH), 4.22 (1H, m, NHCHC*H*OH), 4.64 (1H, d, *J* 4.5 Hz, 1-H), 6.61 (1H, s, 8-H), 6.64 (1H, s, 5-H); ^{13}C NMR (150 MHz; CD_3OD) δ 26.3 (C-4), 42.3 (C-3), 60.4 (C-1), 63.9 (CH_2OH), 71.5 (NCH*C*H), 113.6 (C-8), 116.2 (C-5), 121.4 (C-8a), 125.2 (C-4a), 146.0 (C-7), 146.6 (C-6); *m/z* [HRMS ES+] found $[MH]^+$ 226.1082. $C_{11}H_{16}NO_4$ requires 226.1079.

Compound **8c** major isomer (1*R*,1'*S*): $[\alpha]^{25}_{D}$ = -11 (*c* 0.1, MeOH); ν_{max} (neat)/cm^{-1} 3097, 1614, 1531; ^{1}H NMR (600 MHz; CD_3OD) δ 2.85–3.02 (2H, m, 4-H_2), 3.30–3.36 (1H, m, 3-*H*H), 3.57 (1H, app. quintet, *J* 6.3 Hz, 3-H*H*), 3.78 (2H, m, CH_2OH), 3.96–4.00 (1H, m, NHCHC*H*OH), 4.46 (1H, d, *J* 3.5 Hz, 1-H), 6.62 (1H, s, 5-H), 6.73 (1H, s, 8-H); ^{13}C NMR (150 MHz; CD_3OD) δ 25.4 (C-4), 40.0 (C-3), 57.3 (C-1), 63.9 (CH_2OH), 72.4 (NCH*C*H), 113.7 (C-8), 116.5 (C-5), 121.5 (C-8a), 124.8 (C-4a), 146.0 (C-7), 146.9 (C-6); *m/z* [HRMS ES+] found $[MH]^+$ 226.1072. $C_{11}H_{16}NO_4$ requires 226.1079.

The stereochemistry of the two isomers was established by comparison to previous reports and NMR data for **8c**.[13]

(1*RS*,2'*S*)-1-[2,6-Dimethylhept-5-enyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (8d).



Compound **8d** (both isomers as a diastereomeric mixture) were prepared according to procedure **A** using dopamine hydrochloride (**1**.HCl) (100 mg, 0.527 mmol) and (S)-(-)-citronellal (115 μL, 0.64 mmol). The product was purified by preparative HPLC (gradient **2**, r_t 14.0 min) to give **8d** (as a 1:1 mixture of (1*R*,2'*S*) and (1*S*,2'*S*) isomers) (66 mg, 43%) as a pale yellow oil. ν_{max} (neat)/cm^{-1} 3100, 2966, 2852, 1617, 1531; ^{1}H NMR (600 MHz; D_2O) δ 1.07 (3H, m, CHCH_3), 1.25–2.20 (7H, m, 3 × CH_2, C*H*CH_3), 1.57 (1.5H, s, CH_3, one diastereoisomer), 1.62 (1.5H, s, CH_3, one diastereoisomer), 1.66 (1.5H, s, CH_3, one

diastereoisomer), 1.68 (1.5H, s, CH_3, one diastereoisomer), 3.85–3.02 (2H, m, 4-H_2), 3.30–3.32 (1H, m, 3-*H*H), 3.46–3.50 (1H, m, 3-H*H*), 4.40–4.43 (1H, m, 1-H), 5.10–5.16 (1H, m, CH=C), 6.61 (1H, s, 5-H), 6.62 (1H, s, 8-H); ^{13}C NMR (150 MHz; D_2O) δ 18.0, 18.5, 20.5, 26.0 (signals superimposed), 26.1, 26.4, 30.2, 30.5, 37.4, 38.7, 40.1, 40.8, 43.1, 43.4, 54.15, 54.24, 113.8, 114.1, 116.2, 116.3, 123.5, 123.6, 124.7, 124.8, 125.3, 132.5, 145.7, 145.9, 146.6, 146.7; *m/z* [HRMS ES+] found $[MH]^+$ 290.2113. $C_{18}H_{28}NO_2$ requires 290.2120.

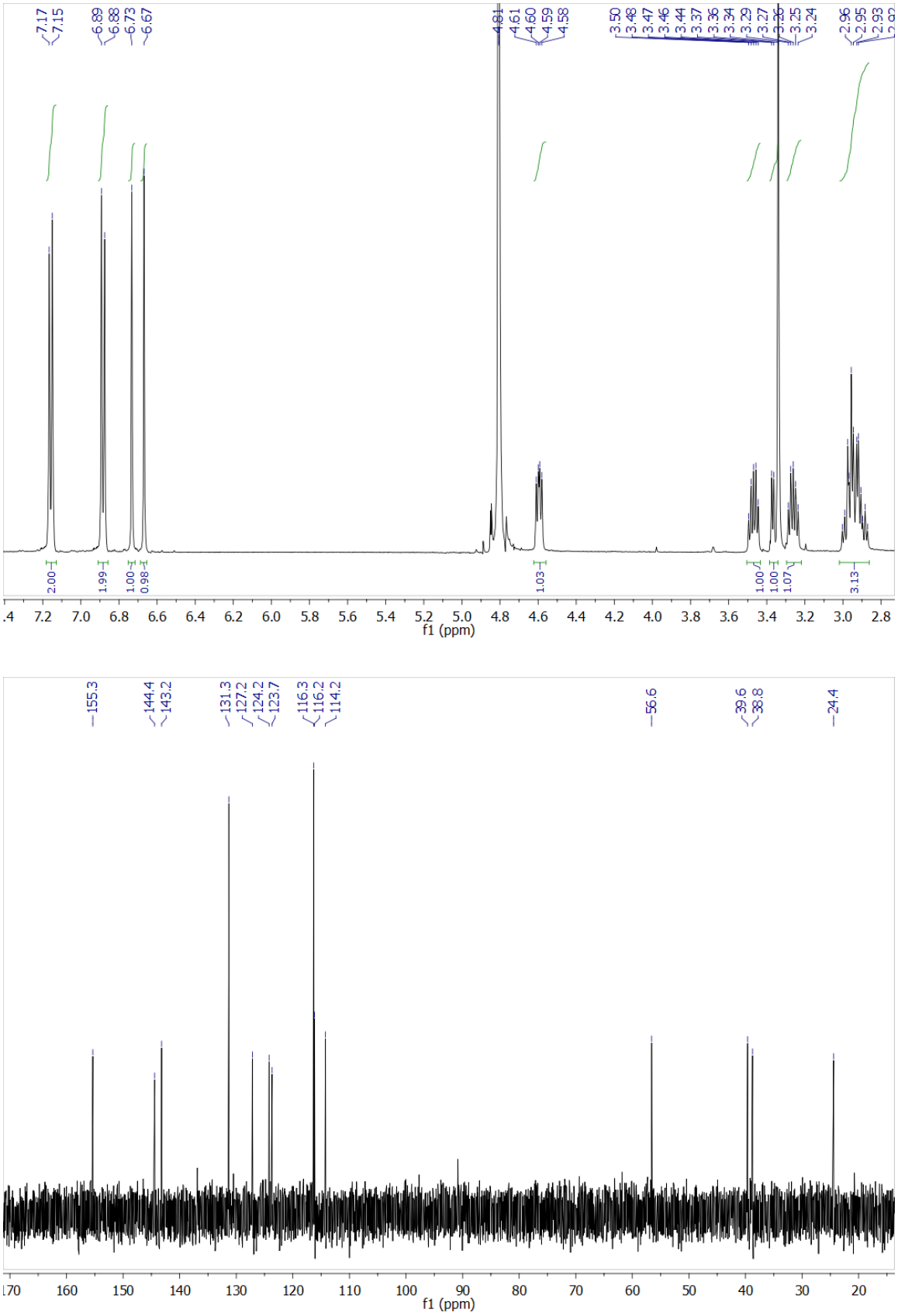


Figure 1: ^{1}H NMR and ^{13}C NMR of norcoclaurine **3**

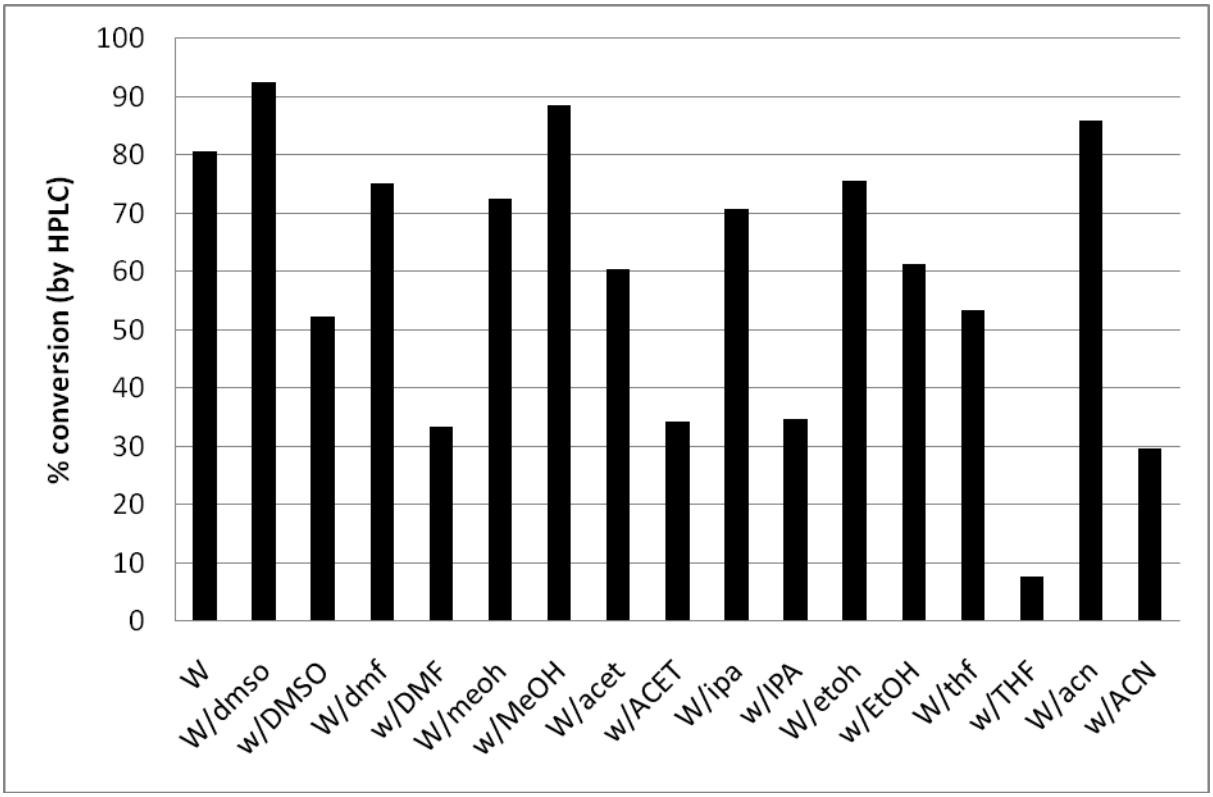


Figure 2: Production of norcoclaurine in different reaction solvents. **W is 0.1 M KP_i at pH 6.** *Conditions*: dopamine (4 mM), 4-HPAA (4.8 mM), SOLVENT A/solvent b (10 mL), 50 ºC, 1 h. **SOLVENT A/solvent b** represents a 2:1 mixture of SOLVENT A and solvent b.

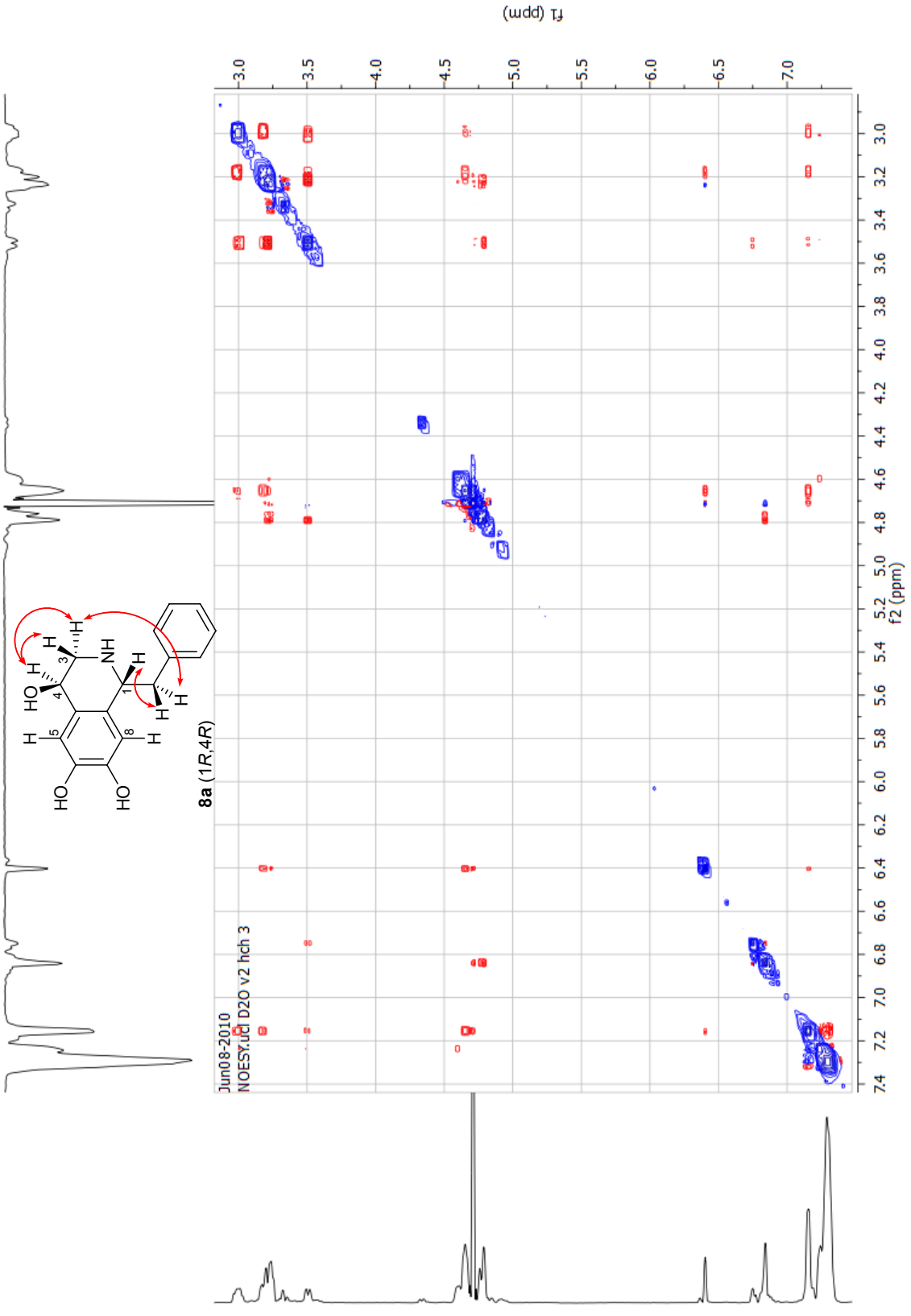


Figure 3: NOESY NMR of **8a** (1*R*,4*R*)

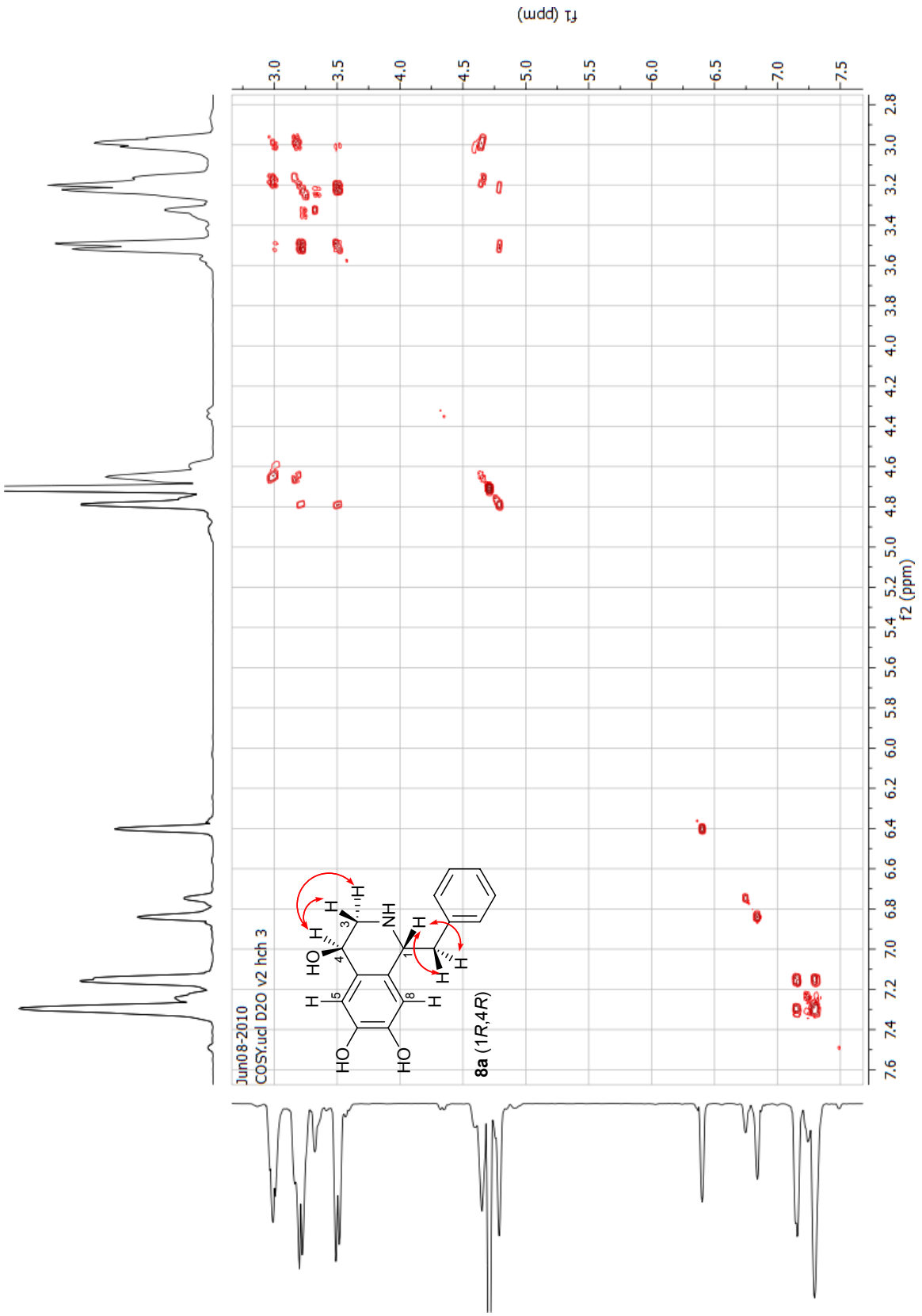


Figure 4: COSY NMR of **8a** (1*R*,4*R*)

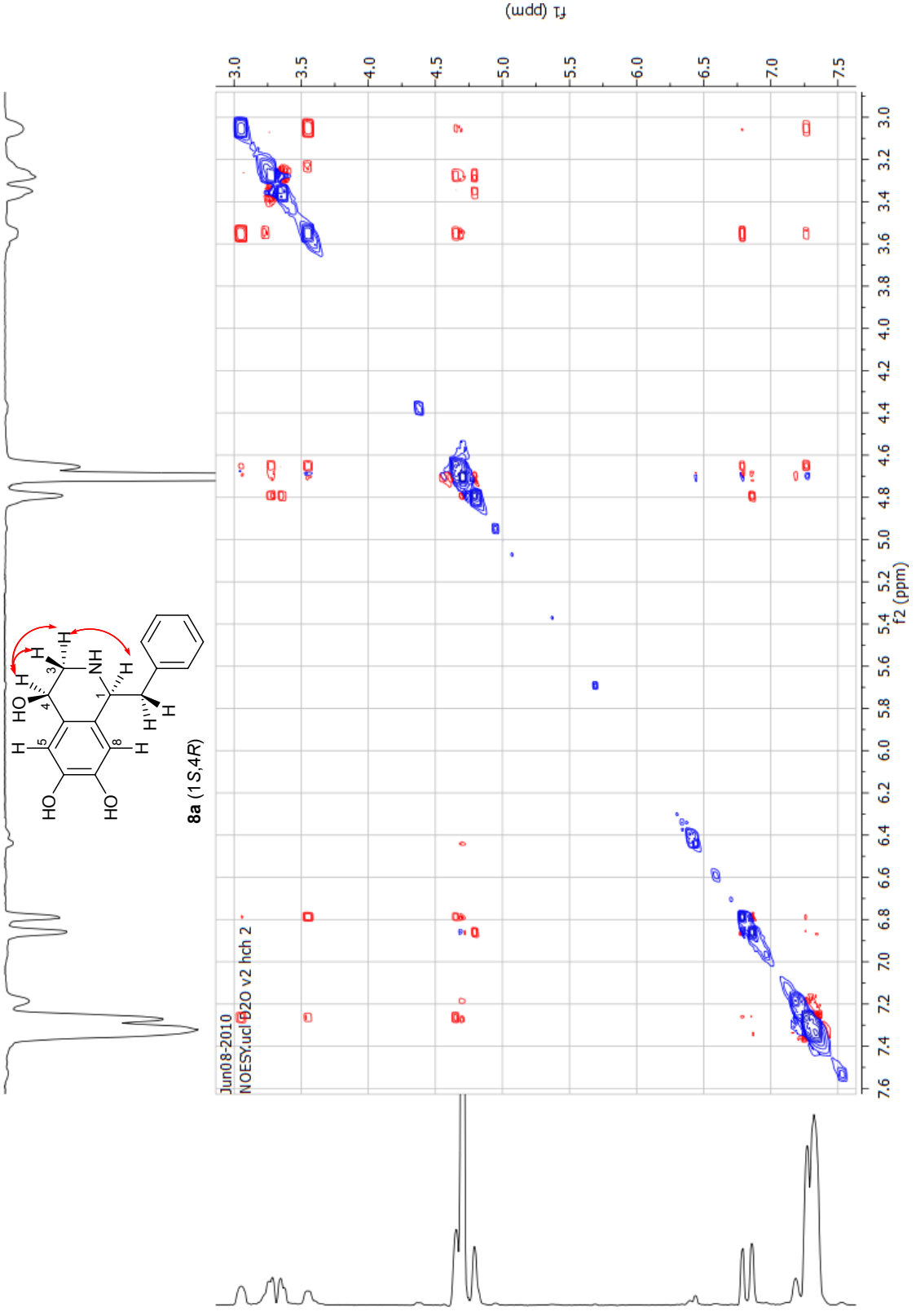


Figure 5: NOESY NMR of **8a** (1*S*,4*R*)

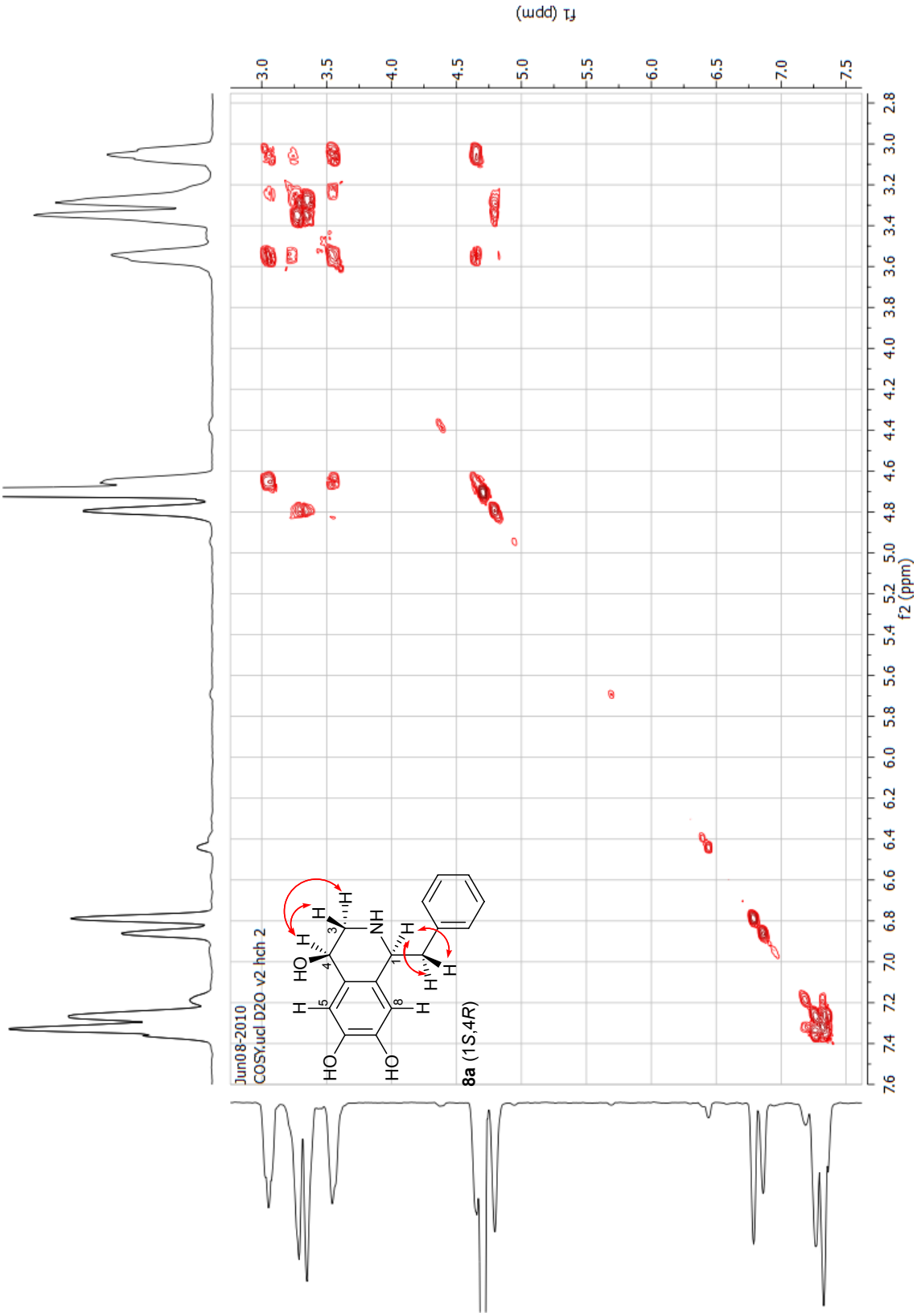


Figure 6: COSY NMR of **8a** (1*S*,4*R*)

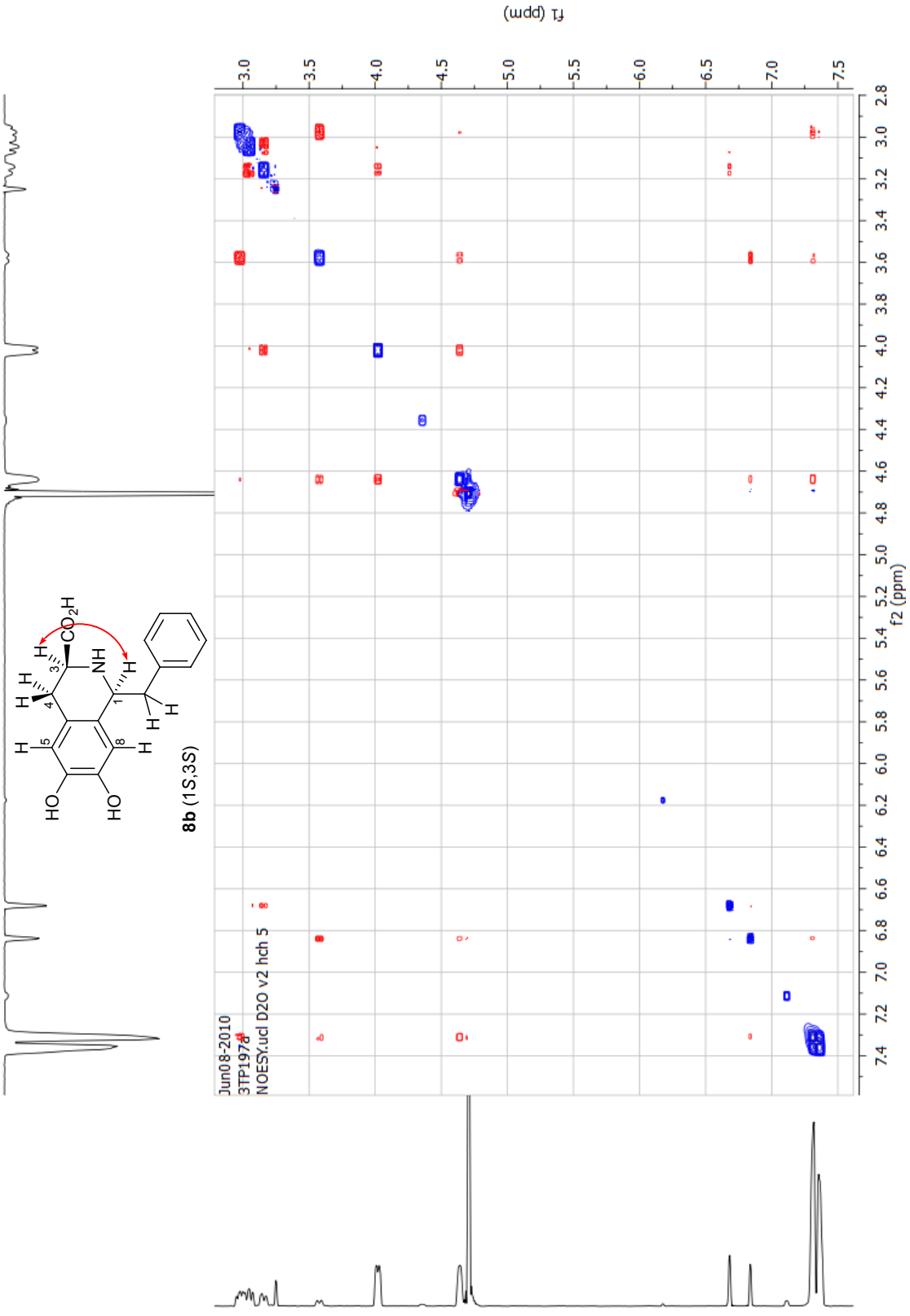


Figure 7: NOESY NMR of **8b** (1*S*,3*S*)

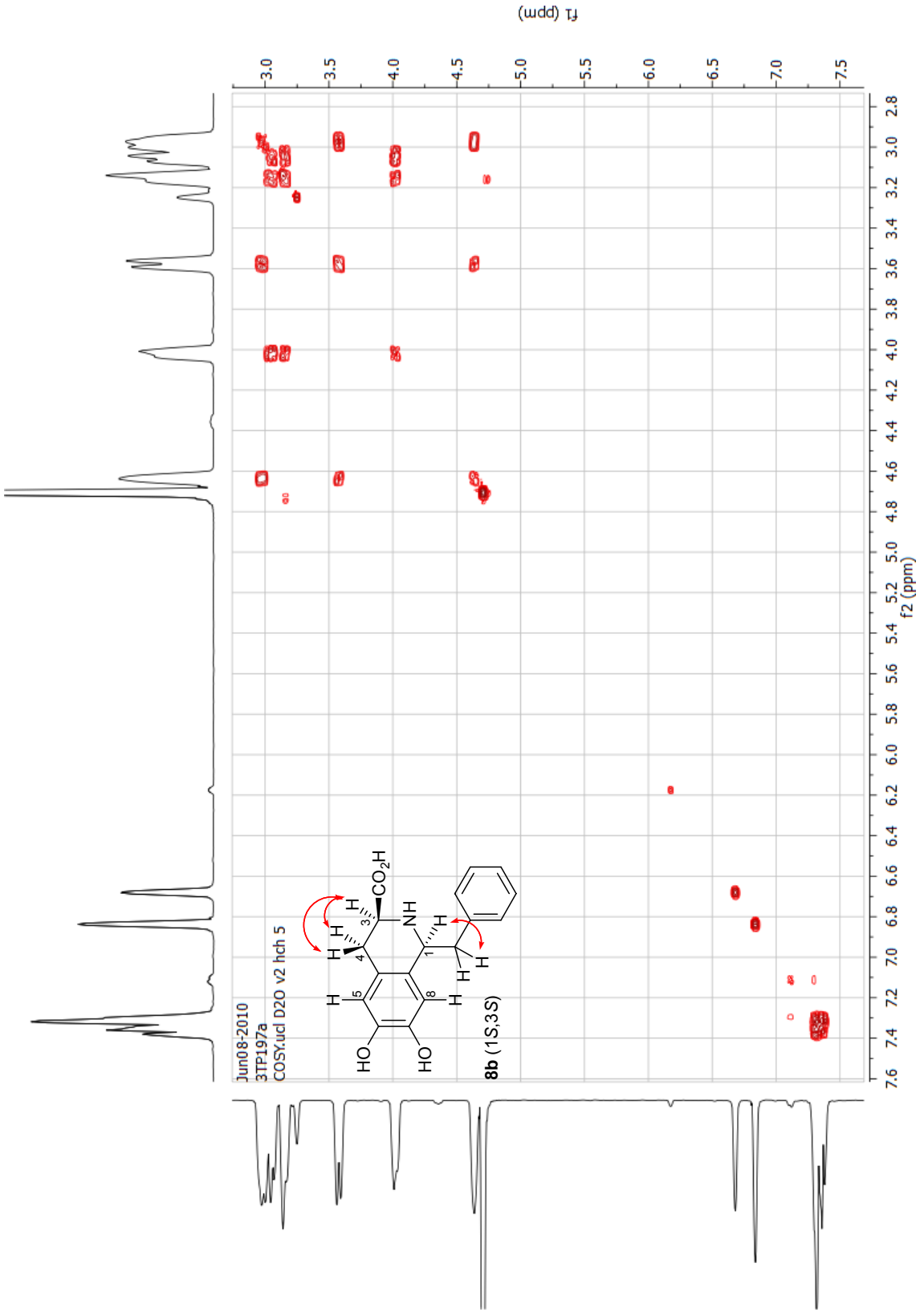


Figure 8: COSY NMR of **8b** (1*S*,3*S*)

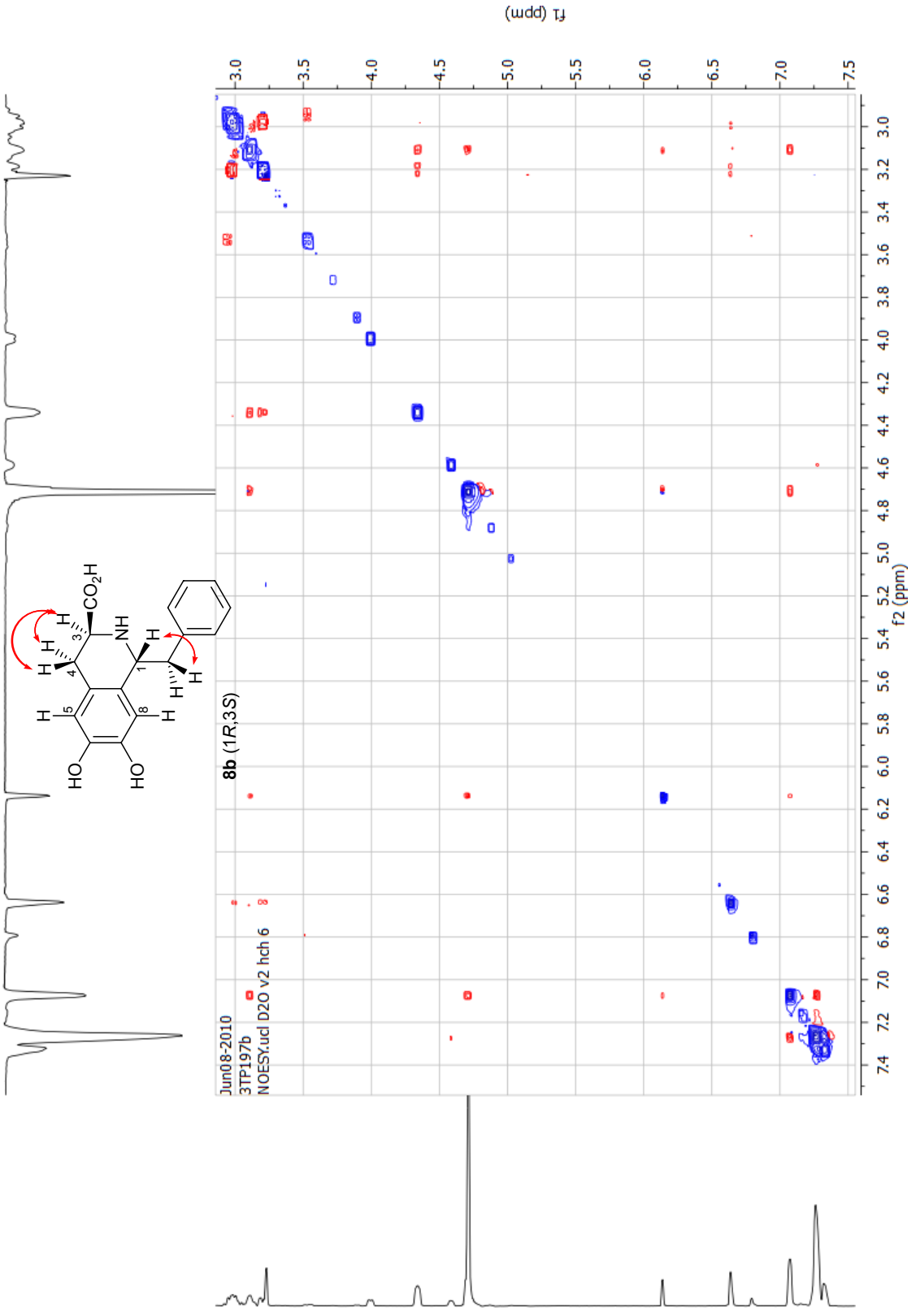


Figure 9: NOESY NMR of **8b** (1*R*,3*S*)

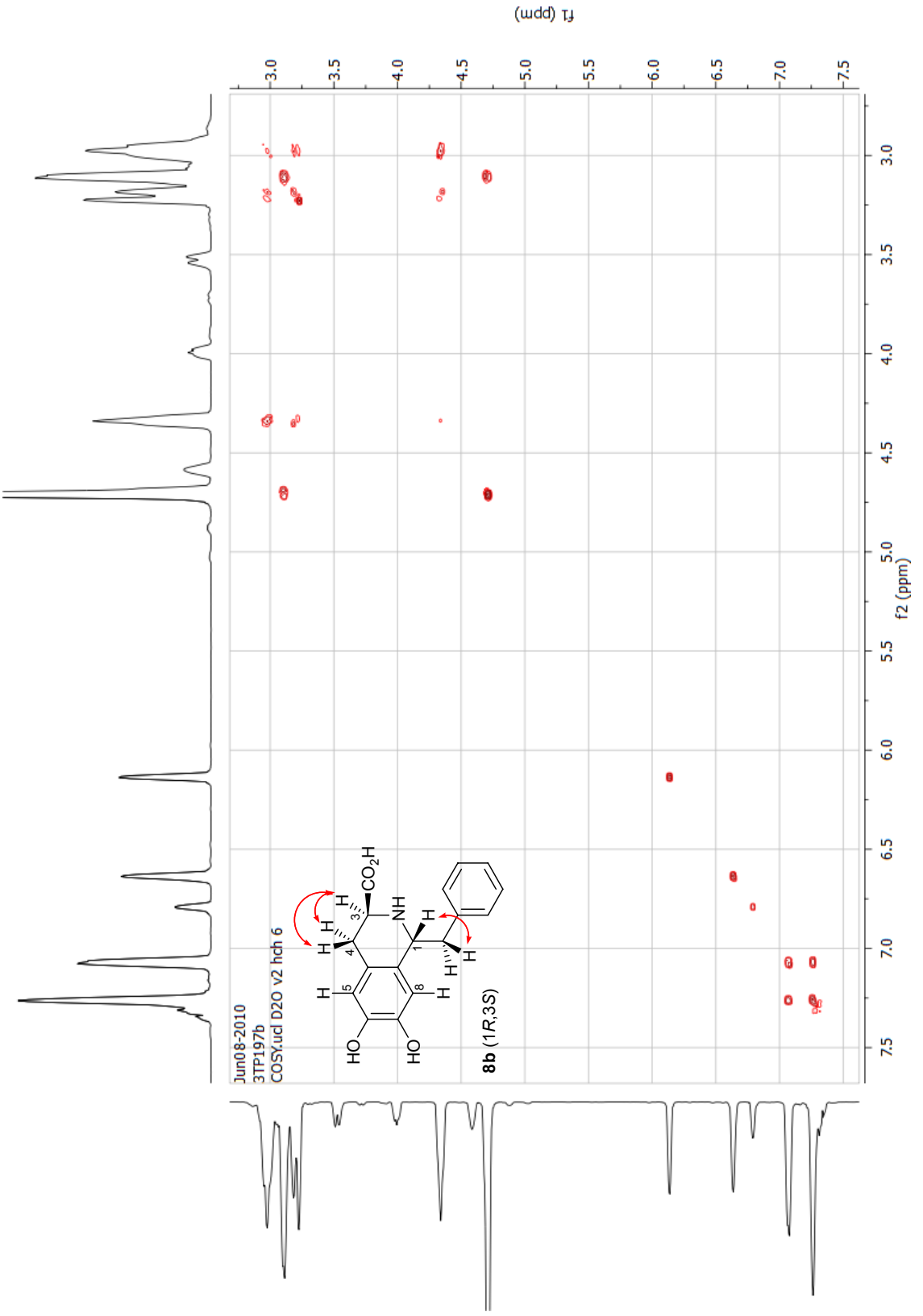


Figure 10: COSY NMR of **8b** (1*R*,3*S*)

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