Autoxidation of Salvinorin A under Basic Conditions

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Supporting Information

General Experimental Methods. NMR peaks assignments were based on HMQC, HMBC and COSY data. Stereochemical assignments (α vs β) were based on coupling constants where possible (peaks whose stereochemistry could not be unambiguously assigned on this basis are listed as "a" and "b"). Radioligand binding assays were performed as previously detailed,[1] using cloned opioid receptors stably expressed in HEK 293 cells, with [^{3}H]diprenorphine (50 Ci/mmol, PerkinElmer Inc) as radioligand for all subtypes. IUPAC International Chemical Identifiers (InChIs)[2] were created using winChI version 1.[3]

Autoxidation of 1a. Oxygen was bubbled through a solution of KOH in MeOH (1 M, 2 mL) for 5 min. This was then added to a solution of **1a** (31.7 mg, 73.3 μmol) in minimal CH_2Cl_2 ($\approx$ 250 μL), and oxygen bubbled through the resulting orange solution for 20 minutes, after which time TLC (Et_2O) showed no **1a** (R_f = 0.54) or **1b** (R_f = 0.42). 10% HCl was added dropwise until an opaque white colour persisted. The solution was diluted in 0.05 M NaOH and extracted into CH_2Cl_2. Drying ($MgSO_4$) and evaporation *in vacuo* gave enedione **3** as a resin (14.9 mg, 53%). The aqueous layer was acidified with 10% HCl until opaque white, then extracted into CH_2Cl_2, which was dried ($MgSO_4$) and filtered. MeOH (10 mL) and Me_3SiCHN_2 in Et_2O (2.0 M, 200 μL) were added. The yellow solution was stirred for 30 min, then evaporated *in vacuo*. Flash column chromatography on silica gel (50% EtOAc/petrol) gave a mixture of the seco triesters **4a**, **4b** and **4c** (12.2 mg, 37%) which cospotted by TLC (R_f = 0.45). Repeated HPLC (36% EtOAc/petrol) on 5 μm silica gave a compound which was tentatively assigned as **4c**. Further elution gave **4a**, followed by **4b**.

Deacetyl-1,10-didehydrosalvinorin G (3).

TLC (Et_2O): R_f = 0.69;

$[\alpha]_D^{14}$ +58 (c 0.7, CH_2Cl_2);

UV (CH_3CN): λ_{max} (log ε) 215 (4.30), 249 (3.77), 324 (3.57) nm;

FTIR (film): $\bar{\nu}_{max}$ 3373, 3149, 2955, 1726, 1651, 1601, 1504, 1456, 1435, 1408, 1380, 1331, 1244, 1203, 1162, 1068, 1022, 911, 875, 793, 736, 703 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, br s, H-16), 7.41 (1H, t, J = 1.8 Hz, H-15), 6.99 (1H, s, H-3), 6.91 (1H, s, OH), 6.42 (1H, dd, J = 2.0, 0.9 Hz, H-14), 5.44 (1H, dd, J = 12.3, 2.9 Hz, H-12), 3.85 (3H, s, CO_2CH_3), 3.11 (1H, ddd, J = 14.8, 2.9, 1.2 Hz, H-11α), 2.98 (1H, ddd, J = 9.7, 5.4, 1.2 Hz, H-8), 2.53 (1H, ddd, J = 14.1, 7.7, 6.3 Hz, H-6a), 2.24 (1H, dtd, J = 14.6, 7.4, 5.3 Hz, H-7β), 2.02 (1H, dd, J = 15.0, 12.2 Hz, H-11β), 1.98 (1H, dddd, J = 14.3, 9.7, 7.7, 6.4 Hz, H-7α), 1.77-1.67 (1H, m, H-6b), 1.72 (3H, s, H-19), 1.67 (3H, s, H-20);

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7 (C, C-2), 173.2 (C, C-17), 165.4 (C, C-18), 157.5 (C, C-4), 145.0 (C, C-1), 143.6 (CH, C-15), 140.0 (C, C-10), 139.6 (CH, C-16), 128.2 (CH, C-3), 124.5 (C, C-13), 108.4 (CH, C-14), 70.9 (CH, C-12), 52.6 (CH_3, CO_2CH_3), 44.9 (CH, C-8), 42.3 (C, C-5), 37.7 (C, C-9), 36.8 (CH_2, C-11), 30.3 (CH_3, C-19), 28.3 (CH_2, C-6), 24.4 (CH_3, C-20), 21.9 (CH_2, C-7);

HRESIMS [M + Na]$^+$ m/z 409.1265 (calcd for $C_{21}H_{22}O_7Na^+$, 409.1258).

1-Methoxy-2-*O*-methyl-2-oxo-1,2-secosalvinorin B (4a).

HPLC (36% EtOAc/ petrol): t_R = 17.4 min;

$[\alpha]_D^{24}$ +6 (*c* 0.1, CH_2Cl_2);

FTIR (film): $\bar{\nu}_{max}$ 2953, 1732, 1506, 1436, 1393, 1373, 1261, 1226, 1202, 1163, 1137, 1079, 1025, 875, 792 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (1H, br s, H-16), 7.43 (1H, t, J = 1.9 Hz, H-15), 6.41 (1H, m, H-14), 5.46 (1H, dd, J = 11.6, 5.4 Hz, H-12), 3.69 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 2.82 (1H, dd, J = 15.9, 11.8 Hz, H-3a), 2.72 (1H, dd, J = 11.8, 2.0 Hz, H-4), 2.43 (1H, dd, J = 15.9, 2.0 Hz, H-3b), 2.25 (1H, s, H-10), 2.17-2.08 (2H, m, H-7β, 8), 2.01 (1H, dd, J = 13.7, 5.5 Hz, H-11α), 1.84 (1H, ddd, J = 13.7, 12.0, 0.8 Hz, H-11β), 1.74-1.63 (2H, m, H-6a, 7α), 1.52-1.48 (1H, m, H-6b), 1.38 (3H, s, H-19), 1.30 (3H, s, H-20);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0 (C, C-2/18), 172.5 (C, C-2/18), 171.7 (C, C-1), 171.0 (C, C-17), 143.8 (CH, C-15), 139.6 (CH, C-16), 125.1 (C, C-13), 108.5 (CH, C-14), 71.6 (CH, C-12), 58.6 (CH, C-10), 52.0 (CH_3, CO_2CH_3), 51.9 (CH, C-4), 51.7 (CH_3, CO_2CH_3), 51.4 (CH_3, CO_2CH_3), 50.5 (CH, C-8), 44.6 (CH_2, C-11), 38.7 (C, C-5), 36.9 (C, C-9), 35.1 (CH_2, C-6), 32.4 (CH_2, C-3), 18.8 (CH_3, C-19), 18.2 (CH_2, C-7), 15.6 (CH_3, C-20);

HRESIMS $[M + Na]^+$ *m/z* 473.1783 (calcd for $C_{23}H_{30}O_9Na^+$, 473.1782).

8-*epi*-1-Methoxy-2-*O*-methyl-2-oxo-1,2-secosalvinorin B (4b).

HPLC (36% EtOAc/petrol): t_R = 18.3 min;

$[\alpha]_D^{23}$ +4 (*c* 0.4, CH_2Cl_2);

FTIR (film): $\bar{\nu}_{max}$ 2953, 1733, 1504, 1436, 1392, 1361, 1247, 1200, 1166, 1091, 1062, 1025, 998, 968, 909, 875, 849, 794, 735 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (1H, br s, H-16), 7.42 (1H, t, J = 1.8 Hz, H-15), 6.42 (1H, dd, J = 1.8, 0.7 Hz, H-14), 5.26 (1H, dd, J = 12.0, 2.1 Hz, H-12), 3.67 (3H, s, CO_2CH_3), 3.66 (3H, s, CO_2CH_3), 3.64 (3H, s, CO_2CH_3), 2.84 (1H, dd, J = 15.9, 11.9 Hz, H-3a), 2.76 (1H, dd, J = 11.9, 1.6 Hz, H-4), 2.53 (1H, dd, J = 4.6, 2.8, H-8), 2.39 (1H, dd, J = 16.0, 1.8 Hz, H-3b), 2.28 (1H, br s, H-10), 2.19-2.14 (1H, m, H-7β), 2.02 (1H, dd, J = 14.5, 11.9 Hz, H-11β), 1.94-1.86 (2H, m, H-6β, 7α), 1.80 (1H, dd, J = 14.4, 2.1 Hz, H-11α), 1.48 (3H, s, H-20), 1.32-1.27 (1H, m, H-6α), 1.29 (3H, s, H-19);

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8 (C, C-18), 173.2 (C, C-17), 172.6 (C, C-2), 172.2 (C, C-1), 143.7 (CH, C-15), 139.7 (CH, C-16), 123.6 (C, C-13), 108.4 (CH, C-14), 69.8 (CH, C-12), 57.8 (CH, C-10), 51.9 (CH_3, CO_2CH_3), 51.7 (CH_3, CO_2CH_3), 51.7 (CH, C-4), 51.5 (CH_3, CO_2CH_3), 46.5 (CH_2, C-11), 44.4 (CH, C-8), 38.5 (C, C-5), 35.8 (C, C-9), 32.2 (CH_2, C-3), 31.6 (CH_2, C-6), 25.1 (CH_3, C-20), 18.2 (CH_3, C-19), 18.2 (CH_2, C-7);

HRESIMS $[M + Na]^+$ *m/z* 473.1780 (calcd for $C_{23}H_{30}O_9Na^+$, 473.1782).

10-*epi*-1-Methoxy-2-*O*-methyl-2-oxo-1,2-secosalvinorin B (4c).

HPLC (36% EtOAc/petrol): t_R = 17.0 min;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, br s, H-16), 7.42 (1H, t, J = 1.8 Hz, H-15), 6.42 (1H, dd, J = 1.9, 0.9 Hz, H-14), 5.19 (1H, dd, J = 11.7, 5.4 Hz, H-12), 3.72 (3H, s, CO_2CH_3), 3.67 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 3.55 (1H, dd, J = 12.3, 2.9 Hz, H-4), 2.80 (1H, dd, J = 16.6, 12.3 Hz, H-3a), 2.59 (1H, dd, J = 14.9, 5.5 Hz, H-11α), 2.56 (1H, dd, J = 16.6, 2.9 Hz, H-3b), 2.53 (1H, br s, H-10), 2.39 (1H, dd, J = 12.6, 3.7 Hz, H-8), 1.94-1.83 (1H, m, H-7α), 1.86 (1H, dd, J = 14.9, 11.8 Hz, H-11β), 1.78 (1H, dq, J = 14.4, 3.8 Hz, H-7β), 1.60-1.41 (2H, m, H-6 [obscured by H_2O]), 1.41 (3H, s, H-19), 1.20 (3H, s, H-20);

HRESIMS $[M + Na]^+$ m/z 473.1781 (calcd for $C_{23}H_{30}O_9Na^+$, 473.1782).

(4*R*,8*S*)-Dideacetyl-3,4-dihydrosalvinorin C (8b). Enedione **3** (41.3 mg, 107 μmol) and $NaBH_4$ (10 mg, 264 μmol) were dissolved in CH_2Cl_2 (500 μL), followed by EtOH (2 mL), and stirred under Ar at 40 °C. The initial orange colour faded to faint yellow within 1 h. After 4 h, TLC (Et_2O) showed no **3** (R_f = 0.69). The solution was cooled to 0 °C, and 0.5% H_2SO_4/MeOH added dropwise until effervescence ceased. The solution was concentrated to $\approx$ 500 μL *in vacuo*, then partitioned between brine (acidified with 10% HCl) and CH_2Cl_2. Drying ($MgSO_4$), evaporation *in vacuo* and flash column chromatography on silica gel (70-100% Et_2O/petrol) gave **8b** (15.7 mg, 37%);

TLC (Et_2O): R_f = 0.53;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, dt, J = 1.7, 0.9 Hz, H-16), 7.42 (1H, t, J = 1.7 Hz, H-15), 6.41 (1H, dd, J = 1.9, 0.9 Hz, H-14), 5.29 (1H, dd, J = 11.7, 1.5 Hz, H-12), 4.07 (1H, br s, H-1), 3.65 (3H, s, CO_2CH_3), 3.54 (1H, ddd, J = 11.1, 4.7, 3.2 Hz, H-2), 2.45 (1H, br d, J = 4.7 Hz, H-8), 2.23-2.10 (4H, m), 1.90 (1H, tdd, J = 14.4, 5.5, 4.0 Hz, H-7α), 1.73-1.53 (m, obscured by H_2O & O*H*), 1.66 (3H, s, H-20), 1.32 (3H, s, H-19), 0.90 (1H, d, J = 1.6 Hz, H-10);

^{1}H NMR ($[CD_3]_2CO$) and ^{13}C NMR ($CDCl_3$) matched literature values.[4]

Salvinorin C (9a).

UV (CH_3CN): λ_{max} (log ε) 208 (4.10) nm.

^{1}H and ^{13}C NMR ($CDCl_3$) matched literature values.[4]

Dideacetylsalvinorin C (9d). To **9a** (5.8 mg, 12.2 μmol) and Na_2CO_3 (5.1 mg, 41.1 μmol) in CH_2Cl_2 (1 mL) was added MeOH (1 mL), and the solution stirred at rt for 2 h, when TLC (10% acetone/CH_2Cl_2) showed considerable **9a** (R_f = 0.60). The solution was heated at 45 °C with a reflux condenser for a further 90 min, when TLC showed no **9a**. The solution was partitioned between brine (acidified with 10% HCl) and CH_2Cl_2. Drying ($MgSO_4$), evaporation *in vacuo* and flash column chromatography on silica gel (33 - 50% EtOAc/petrol, then 25% MeOH/CH_2Cl_2) gave **9d** as a resin (4.1 mg, 86%);

TLC (10% acetone/CH_2Cl_2): R_f = 0.18;

$[\alpha]_D^{18}$ +27 (*c* 0.2, CH_2Cl_2);

FTIR (film): $\bar{\nu}_{max}$ 3456, 2951, 1714, 1504, 1435, 1379, 1314, 1229, 1177, 1144, 1075, 1049, 1027, 949, 875, 788, 736, 685 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, m, H-16), 7.42 (1H, t, J = 1.8 Hz, H-15), 6.48 (1H, dd, J = 2.5, 1.6 Hz, H-4), 6.40 (1H, dd, J = 1.9, 0.9 Hz, H-14), 5.60 (1H, dd, J = 11.1, 5.9 Hz, H-12), 4.32 (1H, br d, J = 5.1 Hz, H-1), 4.28 (1H, dd, J = 5.1, 2.4 Hz, H-2), 3.73 (3H, s, CO_2CH_3), 2.49 (1H, dd, J = 13.2, 6.0 Hz, H-11α), 2.50-2.45 (1H, m, H-6α), 2.38 (1H, br d, J = 2.1 Hz, OH), 2.33 (1H, br d, J = 5.9 Hz, OH), 2.14-2.10 (1H, m, H-8), 2.09 (1H, dq, J = 14.6, 3.6 Hz, H-7β), 1.82 (1H, dtd, J = 15.0, 13.2, 3.3 Hz, H-7α), 1.70 (3H, s, H-19), 1.60 (1H, ddd, J = 13.0, 11.1, 0.8 Hz, H-11β), 1.47 (3H, s, H-20), 1.22 (1H, d, J = 1.0 Hz, H-10), 1.16 (1H, tdd, J = 13.3, 3.6, 0.9 Hz, H-6β);

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (C, C-17), 166.6 (C, C-18), 143.9 (CH, C-15), 142.2 (C, C-4), 139.3 (CH, C-16), 135.3 (CH, C-3), 125.8 (C, C-13), 108.4 (CH, C-14), 71.8 (CH, C-12), 69.6 (CH, C-2), 65.6 (CH, C-1), 54.1 (CH, C-10), 51.8 (CH, C-8), 51.7 (CH_3, CO_2CH_3), 44.4 (CH_2, C-11), 37.49 (C, C-5/9), 37.45 (C, C-5/9), 37.0 (CH_2, C-6), 22.1 (CH_3, C-19), 18.4 (CH_2, C-7), 16.3 (CH_3, C-20);

HRESIMS $[M + Na]^+$ *m/z* 413.1588 (calcd for $C_{21}H_{26}O_7Na^+$, 413.1571).

References

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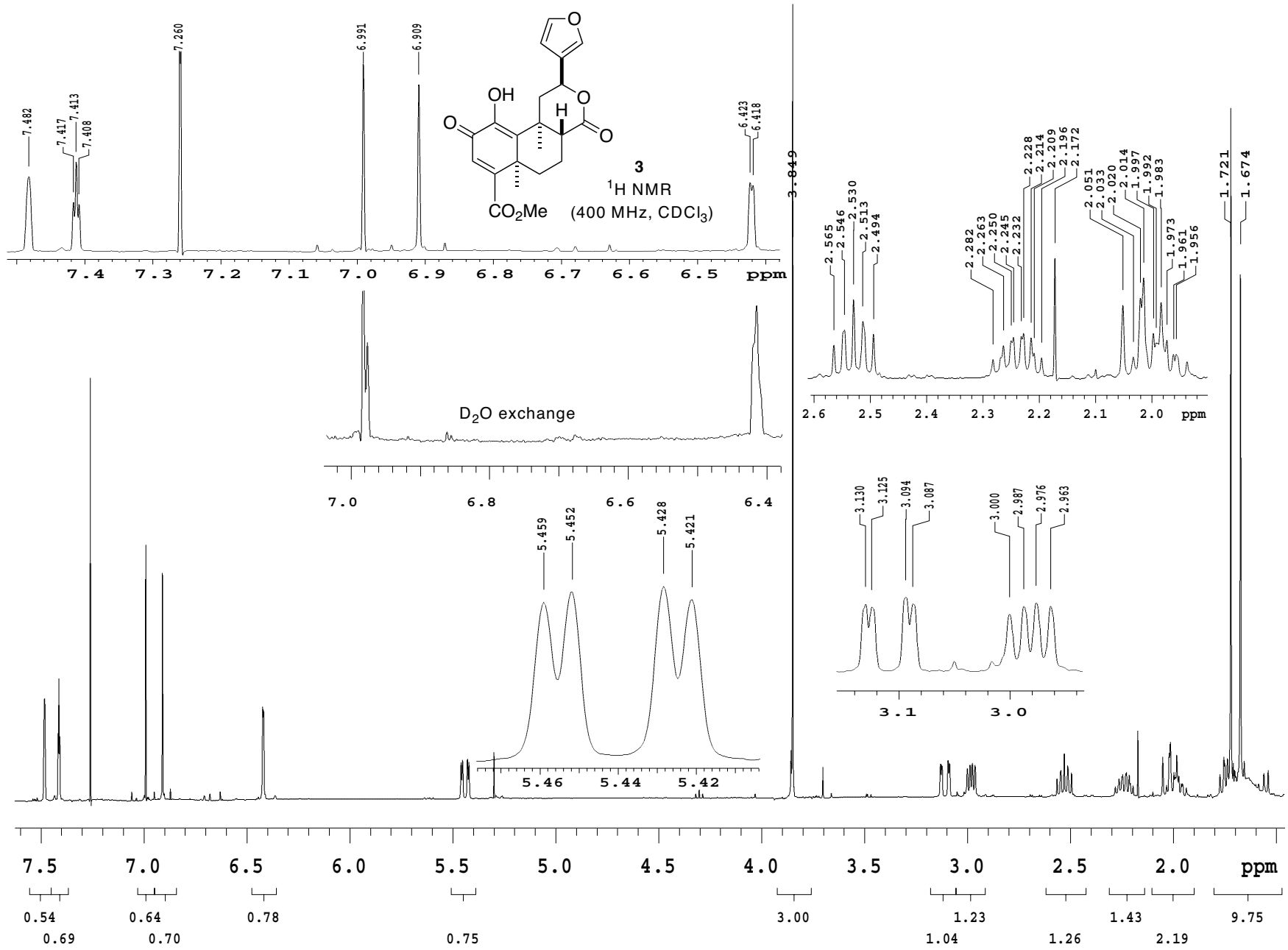
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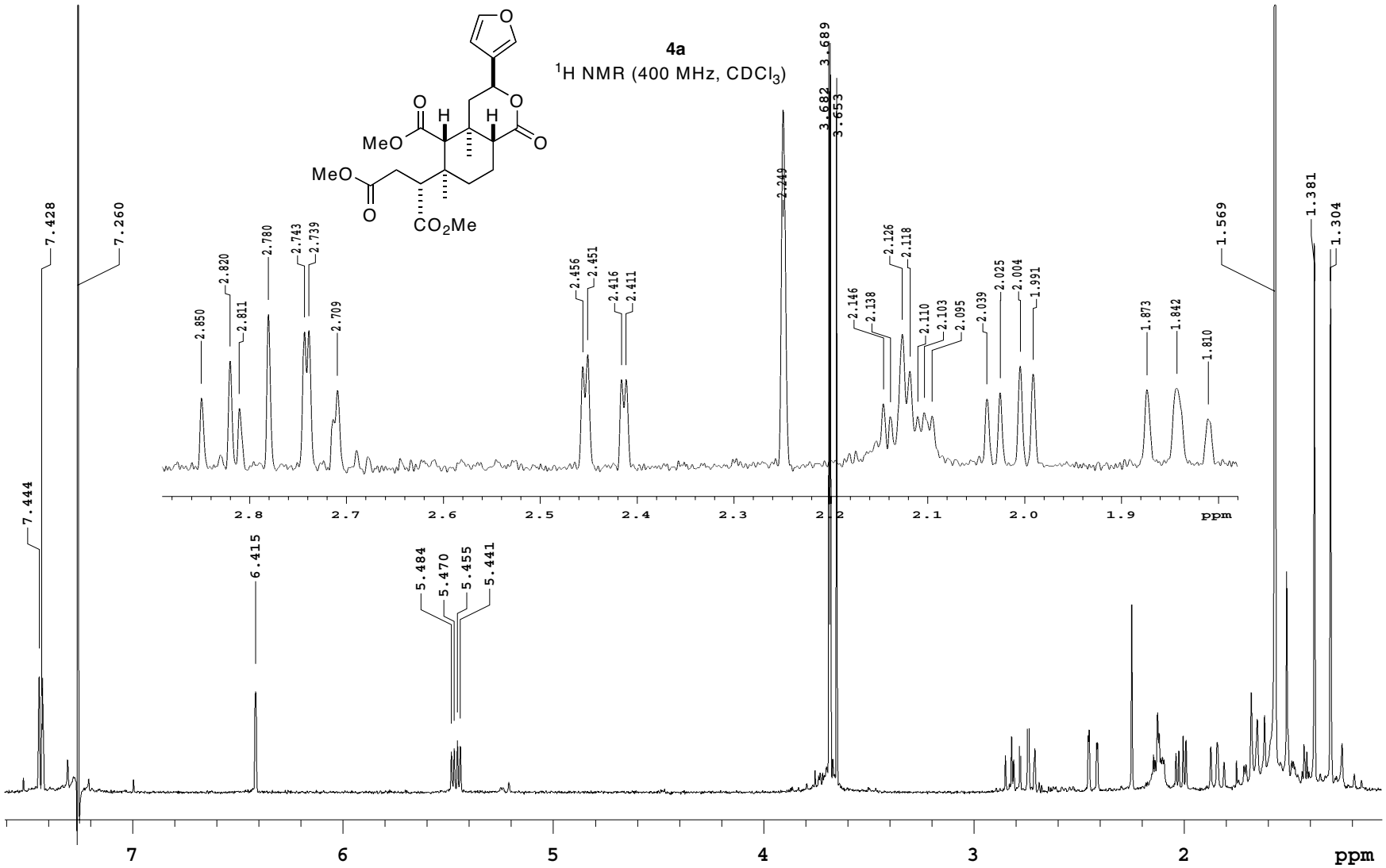

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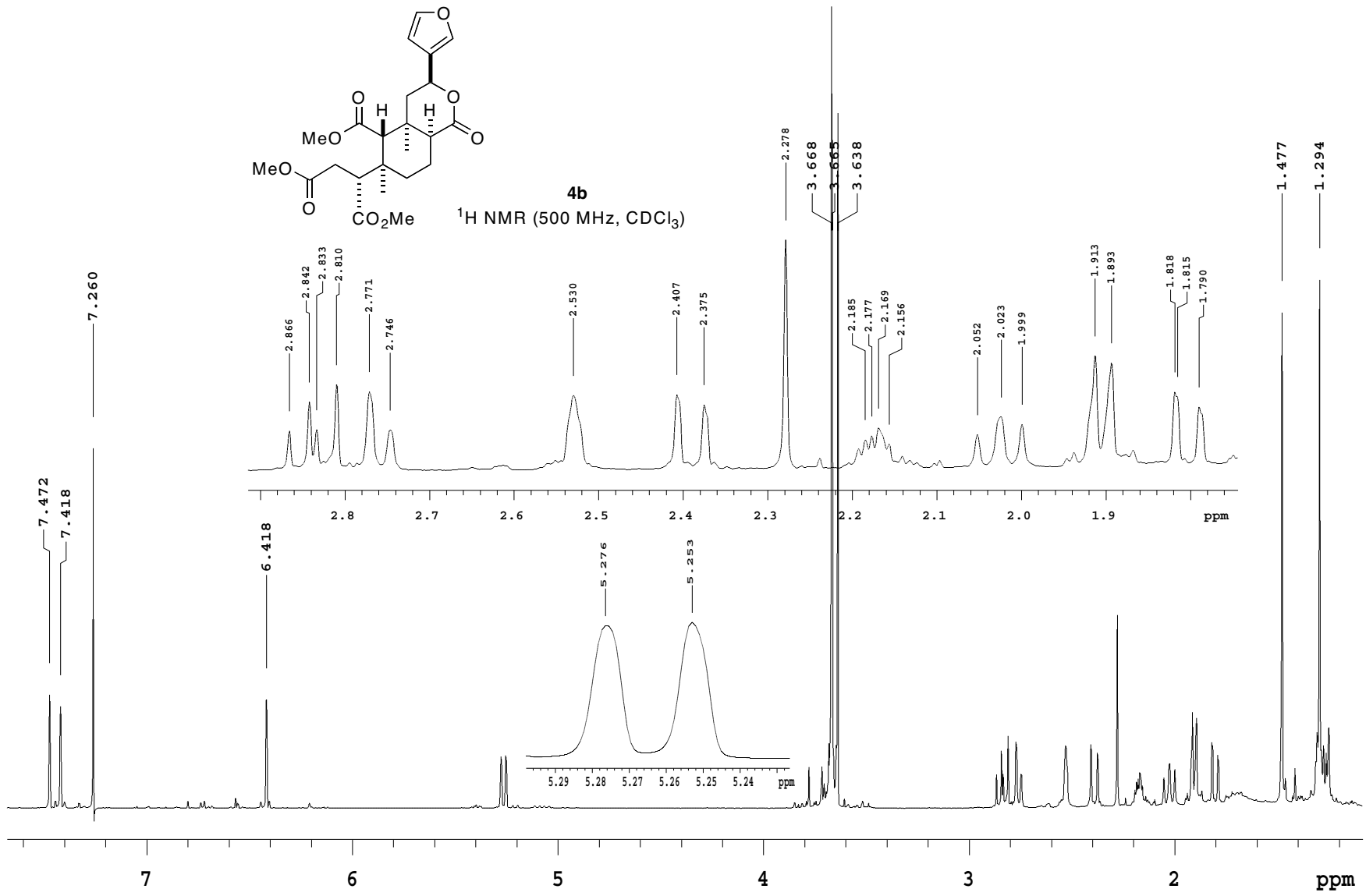

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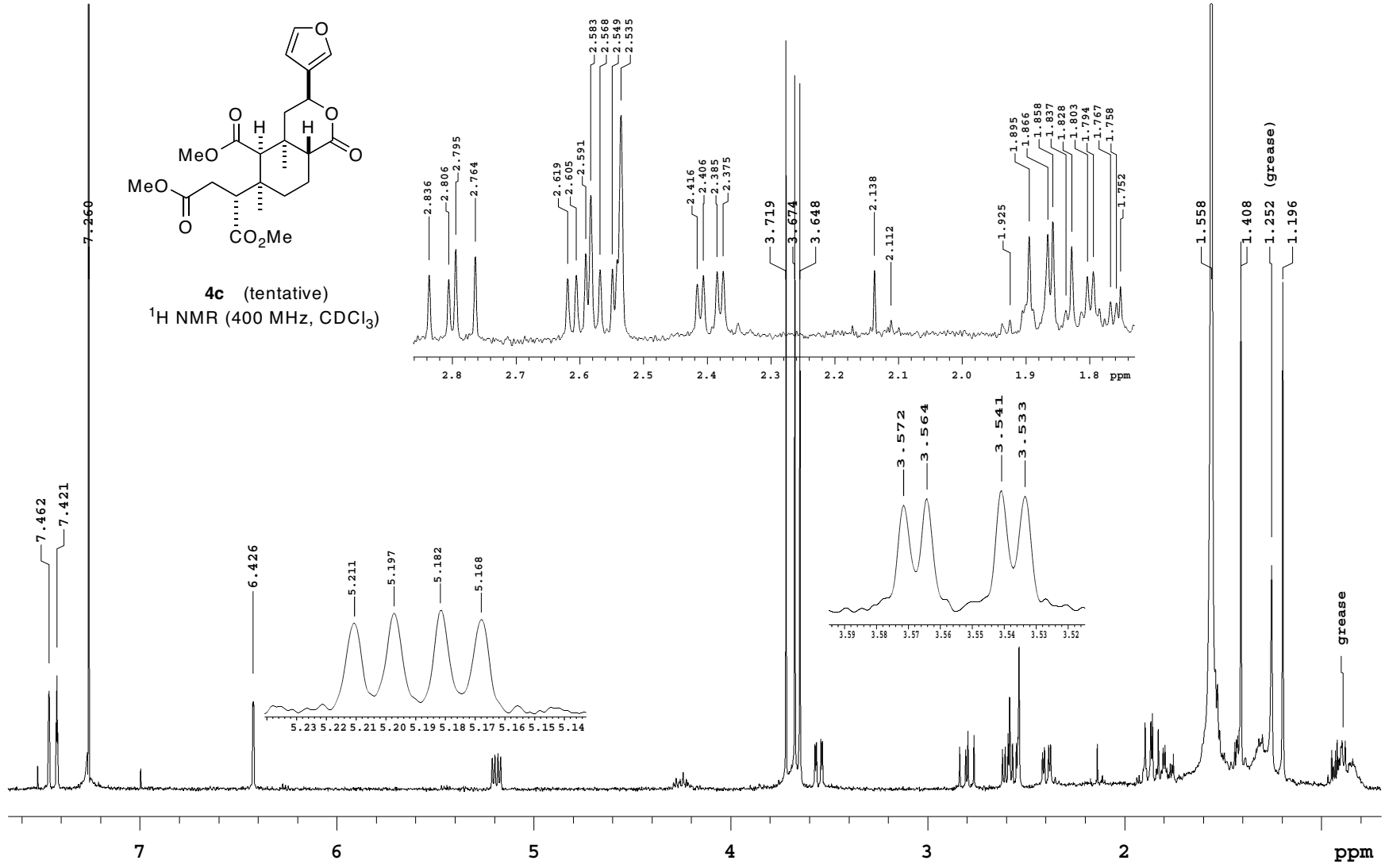

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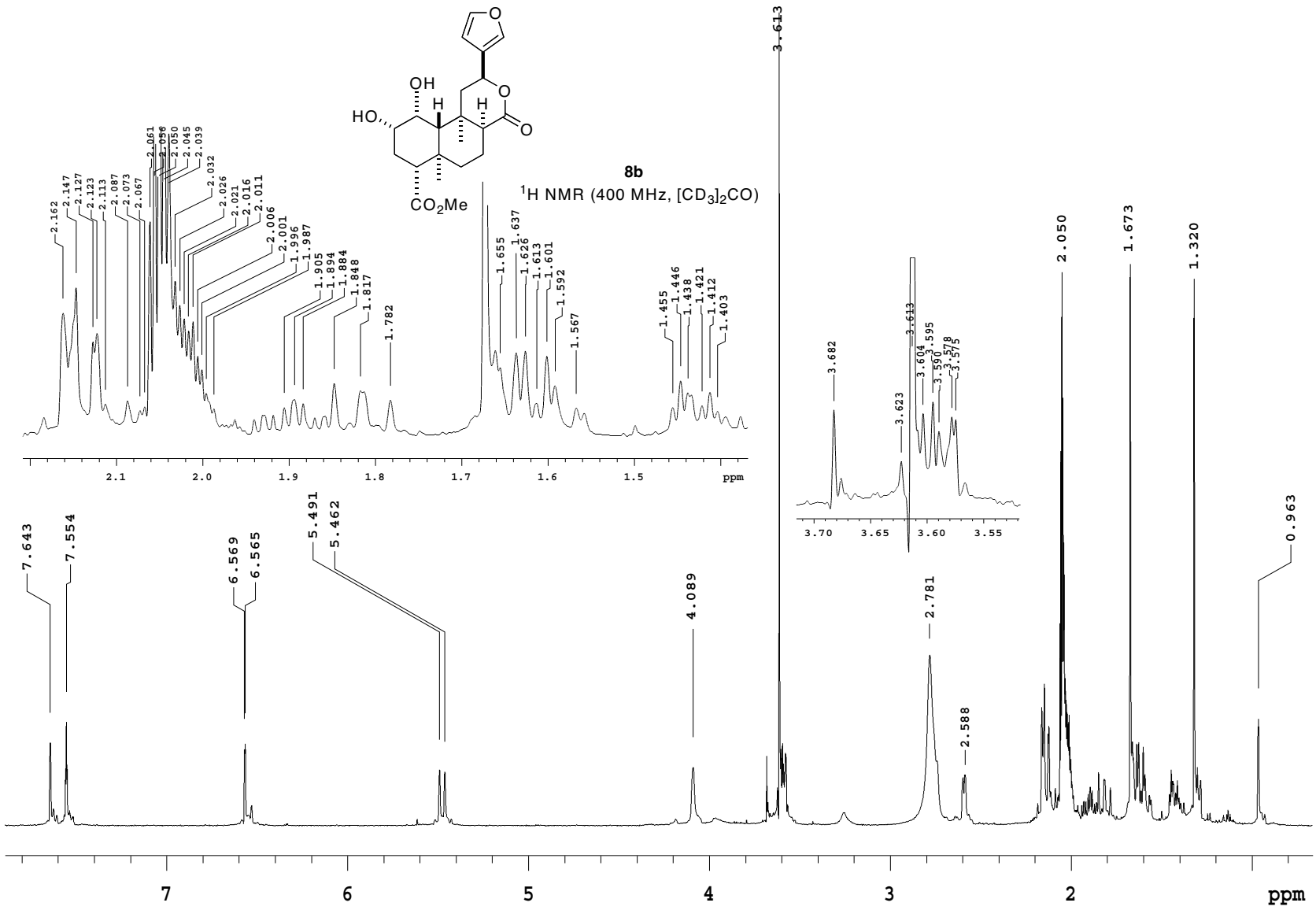

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