

Autoxidation of Salvinorin A under Basic Conditions

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Supporting Information

Compound	Experimental	¹ H NMR spectrum
3	S2	S6
4a	S3	S7
4b	S3	S8
4c	S4	S9
8b	S4	S10
9a	S4	
9d	S4	S11

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 [³H]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 μ mol) in minimal CH₂Cl₂ (\approx 250 μ L), and oxygen bubbled through the resulting orange solution for 20 minutes, after which time TLC (Et₂O) 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 CH₂Cl₂. Drying (MgSO₄) 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 CH₂Cl₂, which was dried (MgSO₄) and filtered. MeOH (10 mL) and Me₃SiCHN₂ in Et₂O (2.0 M, 200 μ L) 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 μ m silica gave a compound which was tentatively assigned as **4c**. Further elution gave **4a**, followed by **4b**.

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

TLC (Et₂O): R_f = 0.69;

$[\alpha]_D^{14}$ +58 (c 0.7, CH₂Cl₂);

UV (CH₃CN): 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;

¹H NMR (400 MHz, CDCl₃): 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, CO₂CH₃), 3.11 (1H, ddd, J = 14.8, 2.9, 1.2 Hz, H-11 α), 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-7 β), 2.02 (1H, dd, J = 15.0, 12.2 Hz, H-11 β), 1.98 (1H, dddd, J = 14.3, 9.7, 7.7, 6.4 Hz, H-7 α), 1.77-1.67 (1H, m, H-6b), 1.72 (3H, s, H-19), 1.67 (3H, s, H-20);

¹³C NMR (100 MHz, CDCl₃): 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 (CH₃, CO₂CH₃), 44.9 (CH, C-8), 42.3 (C, C-5), 37.7 (C, C-9), 36.8 (CH₂, C-11), 30.3 (CH₃, C-19), 28.3 (CH₂, C-6), 24.4 (CH₃, C-20), 21.9 (CH₂, C-7);

HRESIMS [M + Na]⁺ m/z 409.1265 (calcd for C₂₁H₂₂O₇Na⁺, 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, CH₂Cl₂);

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

¹H NMR (500 MHz, CDCl₃): 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, CO₂CH₃), 3.68 (3H, s, CO₂CH₃), 3.65 (3H, s, CO₂CH₃), 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-7 β , 8), 2.01 (1H, dd, $J = 13.7, 5.5$ Hz, H-11 α), 1.84 (1H, ddd, $J = 13.7, 12.0, 0.8$ Hz, H-11 β), 1.74-1.63 (2H, m, H-6a, 7 α), 1.52-1.48 (1H, m, H-6b), 1.38 (3H, s, H-19), 1.30 (3H, s, H-20);

¹³C NMR (100 MHz, CDCl₃): 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 (CH₃, CO₂CH₃), 51.9 (CH, C-4), 51.7 (CH₃, CO₂CH₃), 51.4 (CH₃, CO₂CH₃), 50.5 (CH, C-8), 44.6 (CH₂, C-11), 38.7 (C, C-5), 36.9 (C, C-9), 35.1 (CH₂, C-6), 32.4 (CH₂, C-3), 18.8 (CH₃, C-19), 18.2 (CH₂, C-7), 15.6 (CH₃, C-20);

HRESIMS [M + Na]⁺ m/z 473.1783 (calcd for C₂₃H₃₀O₉Na⁺, 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, CH₂Cl₂);

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;

¹H NMR (500 MHz, CDCl₃): 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, CO₂CH₃), 3.66 (3H, s, CO₂CH₃), 3.64 (3H, s, CO₂CH₃), 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-7 β), 2.02 (1H, dd, $J = 14.5, 11.9$ Hz, H-11 β), 1.94-1.86 (2H, m, H-6 β , 7 α), 1.80 (1H, dd, $J = 14.4, 2.1$ Hz, H-11 α), 1.48 (3H, s, H-20), 1.32-1.27 (1H, m, H-6 α), 1.29 (3H, s, H-19);

¹³C NMR (125 MHz, CDCl₃): 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 (CH₃, CO₂CH₃), 51.7 (CH₃, CO₂CH₃), 51.7 (CH, C-4), 51.5 (CH₃, CO₂CH₃), 46.5 (CH₂, C-11), 44.4 (CH, C-8), 38.5 (C, C-5), 35.8 (C, C-9), 32.2 (CH₂, C-3), 31.6 (CH₂, C-6), 25.1 (CH₃, C-20), 18.2 (CH₃, C-19), 18.2 (CH₂, C-7);

HRESIMS [M + Na]⁺ m/z 473.1780 (calcd for C₂₃H₃₀O₉Na⁺, 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;

^1H 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-11 α), 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-7 α), 1.86 (1H, dd, $J = 14.9, 11.8$ Hz, H-11 β), 1.78 (1H, dq, $J = 14.4, 3.8$ Hz, H-7 β), 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 $[\text{M} + \text{Na}]^+$ m/z 473.1781 (calcd for $\text{C}_{23}\text{H}_{30}\text{O}_9\text{Na}^+$, 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% $\text{H}_2\text{SO}_4/\text{MeOH}$ added dropwise until effervescence ceased. The solution was concentrated to ≈ 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): $R_f = 0.53$;

^1H 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-7 α), 1.73-1.53 (m, obscured by H_2O & OH), 1.66 (3H, s, H-20), 1.32 (3H, s, H-19), 0.90 (1H, d, $J = 1.6$ Hz, H-10);

^1H NMR ($[\text{CD}_3]_2\text{CO}$) and ^{13}C NMR (CDCl_3) matched literature values.⁴

Salvinorin C (9a).

UV (CH_3CN): λ_{max} ($\log \epsilon$) 208 (4.10) nm.

^1H 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): $\bar{\nu}_{\text{max}}$ 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-11 α), 2.50-2.45 (1H, m, H-6 α), 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-7 β), 1.82 (1H, dtd, $J = 15.0, 13.2, 3.3$ Hz, H-7 α), 1.70 (3H, s, H-19), 1.60 (1H, ddd, $J = 13.0, 11.1, 0.8$ Hz, H-11 β), 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-6 β);

^{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);

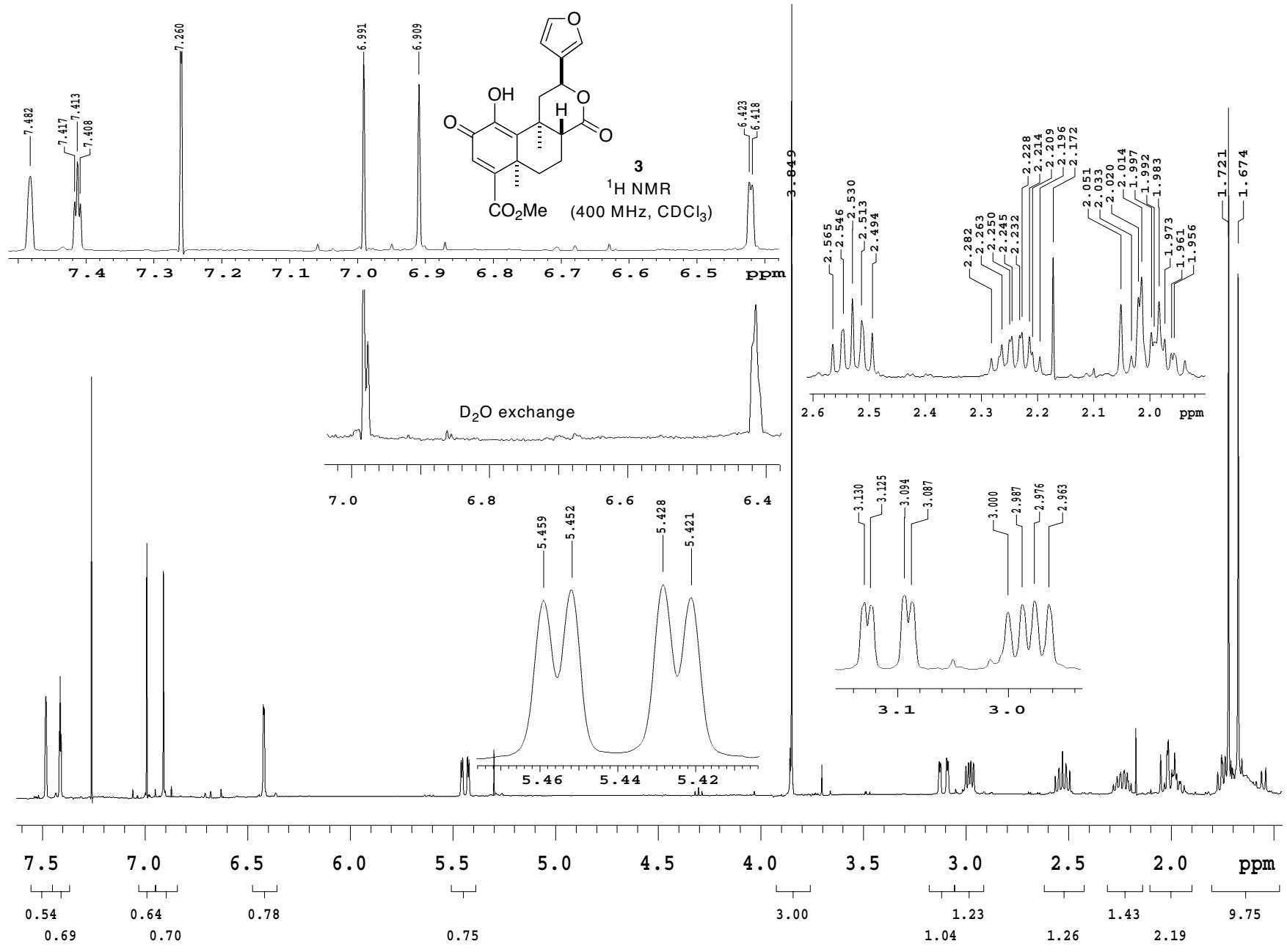
HRESIMS $[\text{M} + \text{Na}]^+$ m/z 413.1588 (calcd for $\text{C}_{21}\text{H}_{26}\text{O}_7\text{Na}^+$, 413.1571).

References

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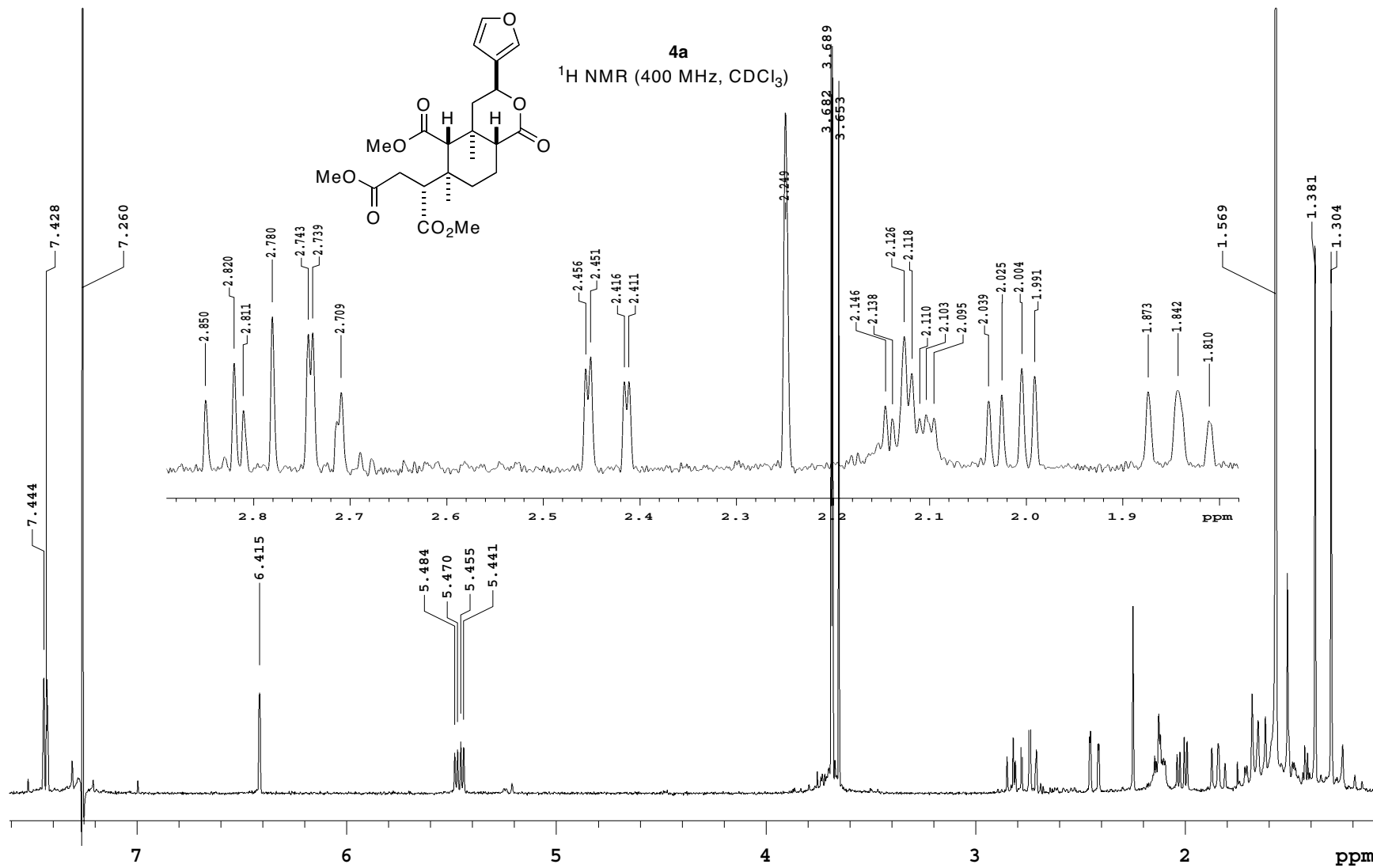
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9S

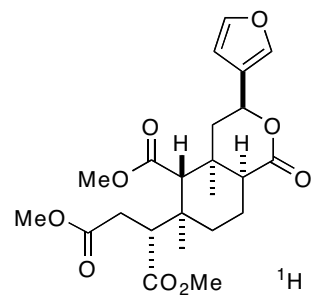


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LS

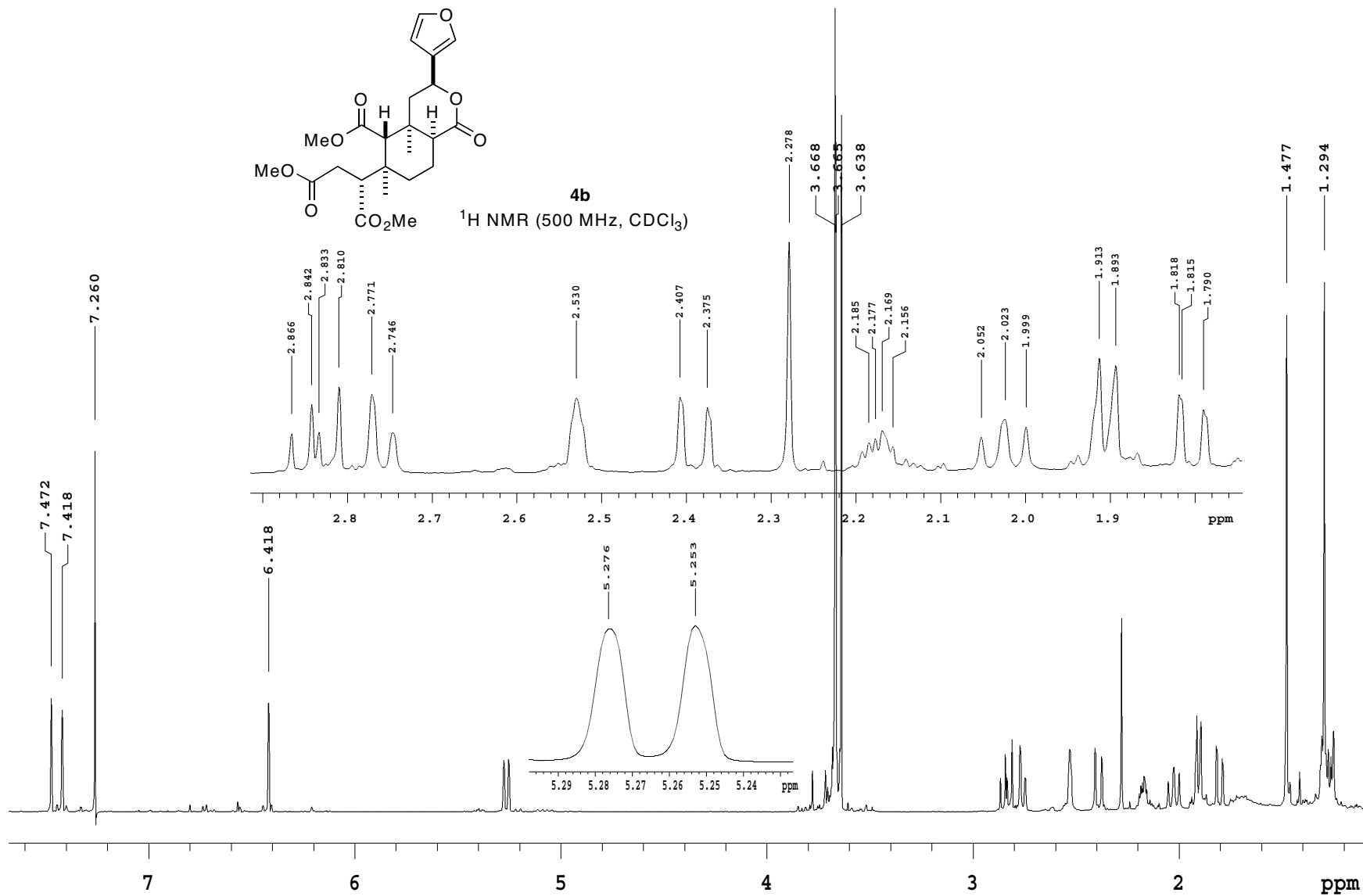


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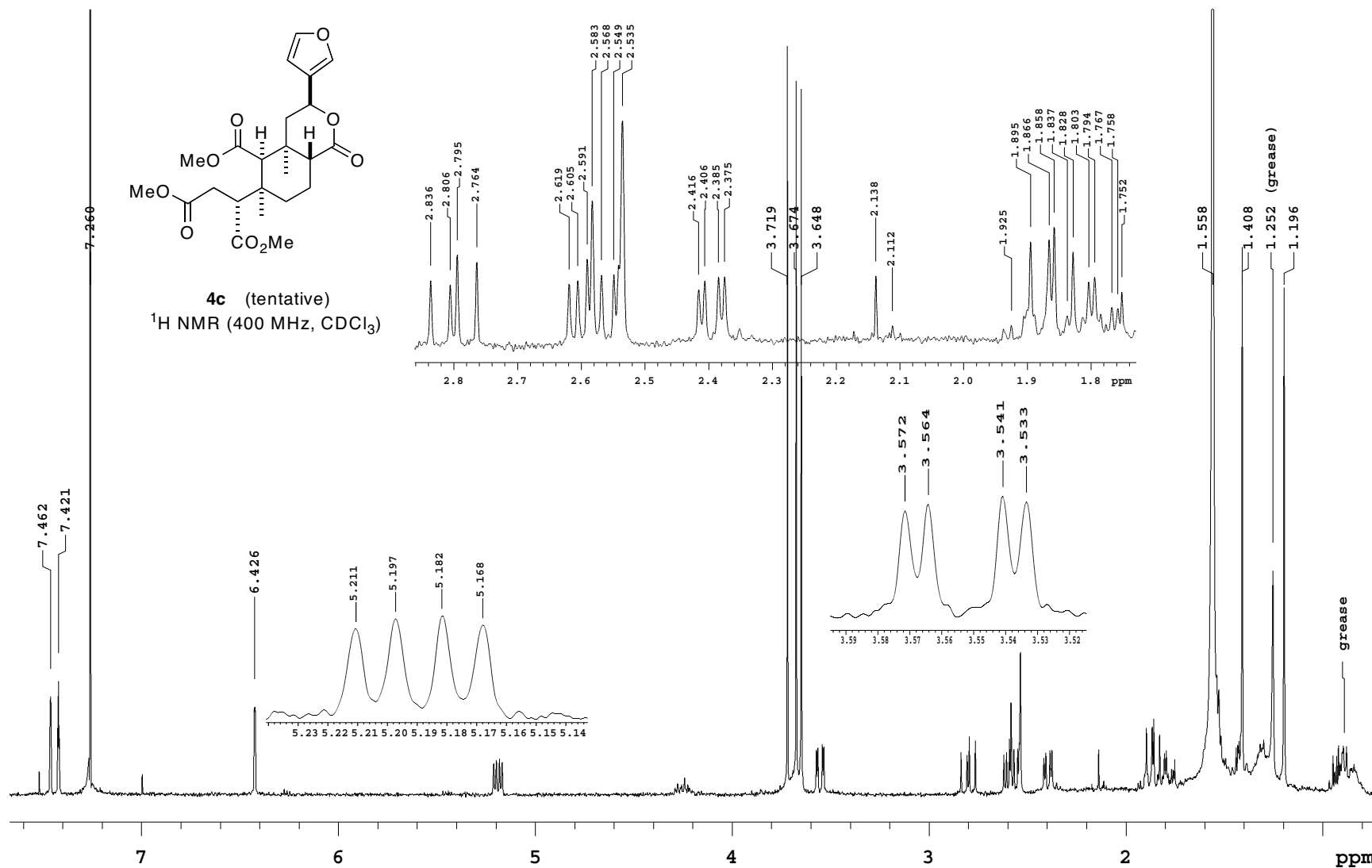


¹H NMR (500 MHz, CDCl₃)

85

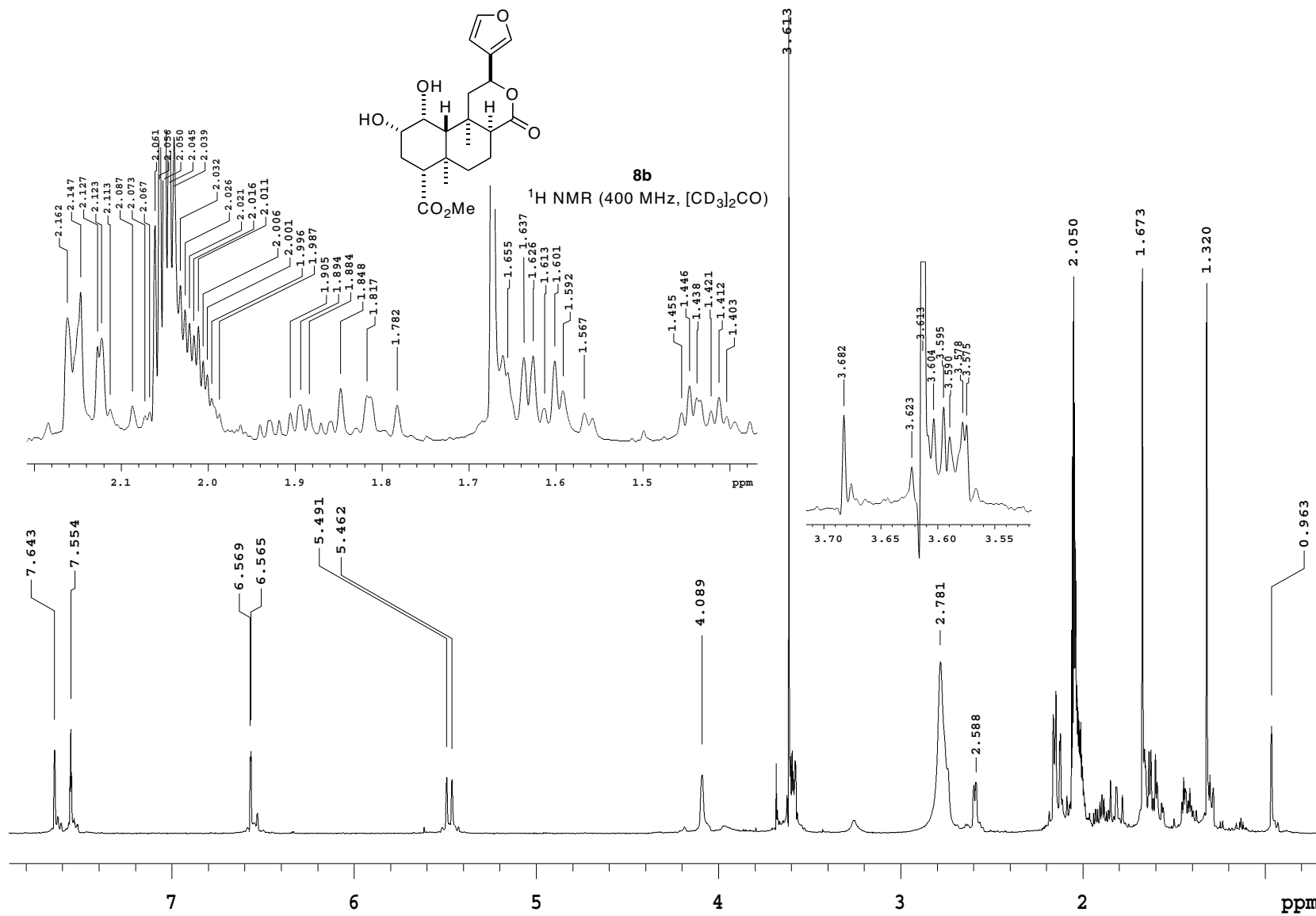


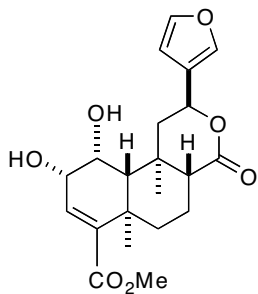
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OTIS





9d

¹H NMR (400 MHz, CDCl₃)

T1S

