

Studies toward the Pharmacophore of Salvinorin A, a Potent κ Opioid Receptor Agonist

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Supporting Information

Table of Contents

	Experimental	NMR spectra
Salvinorin A (1)	S2	
8- <i>epi</i> -Salvinorin A (8- <i>epi</i> - 1)	S2	S9
Salvinorin B formate (3)	S3	S10
Salvinorin C (6)		S11
(4 <i>R</i>)-3,4-Dihydrosalvinorin E (8)		S12
(4 <i>R</i>)-3,4-Dihydrosalvinorin C (9)		S13
13,14,15,16-Tetrahydrosalvinorin A (10)	S3	S14
Salvinorin A lactol (11)	S4	S15
17-Deoxysalvinorin A (12)	S4	S16
8,17-Didehydro-17-deoxysalvinorin A (13)	S4	S17
<i>O</i> -Demethyl-18-deoxysalvinorin A (15)	S5	S18
1-Deoxysalvinorin A (18)	S6	S19
IUPAC/NIST Chemical Identifiers (INChIs)	S7	
References	S7	

Experimental Section.

Optical rotations: JASCO DIP-1000 digital polarimeter. IR spectra: Bio-Rad FTS 165 FT-IR spectrophotometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz): Varian Inova 400 and Unity Plus 400. HRESIMS: Bruker 4.7T BiOAPEX FTMS. TLC: Merck silica gel 60 F₂₅₄ plates, visualized with phosphomolybdic acid in EtOH unless otherwise indicated ($hR_f = R_f \times 100$). HPLC: Spherex 5 μm silica column (250 \times 10 mm), flow rate 2 mL min⁻¹. Flash column chromatography (FCC): 6 mL of Scharlau silica gel 60 (particle size 0.04 – 0.06 mm). Commercial ethanethiol and DMPU (Aldrich, 98%) were stored over 4Å sieves. ‘Petrol’ refers to the fraction boiling at 40-60 °C. ‘Standard drying’ refers to drying over MgSO₄, filtration and evaporation under reduced pressure.

Radioligand Binding Assays. Performed as previously detailed¹⁻³ using cloned receptors stably expressed in HEK 293 cells. κ : rat KORs with [^3H]diprenorphine (50 Ci/mmol, PerkinElmer Inc) or [^3H]U69,593 (41.4 Ci/mmol, PerkinElmer Inc) as radioligand. δ : human DORs with [^3H]DADLE {Enkephalin (2-D-Alanine-5-D-Leucine), [Tyrosyl-3,5- ^3H (N)]-} (51.5 Ci/mmol, PerkinElmer Inc) as radioligand. μ : human MORs with [^3H]diprenorphine as radioligand. K_i values were calculated using Prism 4.01 (GraphPad Software, Inc) as the mean \pm SEM of quadruplicate ($n \geq 4$) determinations. Nonspecific binding was defined using 10 μM naloxone.

Calcium Flux Functional Assay. Performed as previously detailed^{4,5} using cloned rat KORs stably expressed in HEK 293 cells, cotransfected with the universal G protein G α_{16} . Ca²⁺ mobilization was quantified using a 96-well FlexStationII with the calcium flux assay kit (Molecular Devices Corp, Sunnyvale, CA). EC₅₀ and E_{max} values were calculated using Prism 4.01 (GraphPad Software, Inc), as the mean \pm SEM of quadruplicate ($n \geq 4$) determinations.

Salvinorin A (1). ^1H NMR (CDCl₃): δ 7.40 (1H, br s, H-16), 7.38 (1H, t, $J = 1.8$ Hz, H-15), 6.37 (1H, dd, $J = 1.8, 0.8$ Hz, H-14), 5.51 (1H, dd, $J = 11.7, 5.3$ Hz, H-12), 5.13 (1H, m, H-2), 3.72 (3H, s, CO₂CH₃), 2.75 (1H, m, H-4), 2.49 (1H, dd, $J = 13.5, 5.3$ Hz, H-11a), 2.29 (2H, m, H-3), 2.17 (1H, br s, H-10), 2.16 (3H, s, OCOCH₃), 2.15 (1H, m, H-7a), 2.07 (1H, dd, $J = 11.6, 3.1$ Hz, H-8), 1.78 (1H, m, H-6a), 1.63 (1H, m, H-7b), 1.57 (1H, m, H-6b), 1.57 (1H, ddd, $J = 13.5, 11.7, 0.8$ Hz, H-11b), 1.44 (3H, s, H-20), 1.10 (3H, s, H-19).

8-*epi*-Salvinorin A (8-*epi*-1). Distilled DMPU (60 °C / 0.1 mmHg) was added to **1** (21.4 mg, 49.5 μmol) and NaHCO₃ (30.1 mg, 358 μmol), and stirred at 150 °C for 2 h. The resultant amber solution was cooled to rt, diluted in EtOAc, neutralized dropwise with 10% HCl, and washed (10% HCl \times 4, then brine). Standard drying followed by FCC (30% - 50% EtOAc/petrol gradient) monitored by TLC ($hR_f = 40$ (**1**), 50 (8-*epi*-**1**) in Et₂O) gave 8-*epi*-**1** as a clear resin (10.8 mg, 51% (81% borsm)); $[\alpha]_{\text{D}}^{13} -53^\circ$ (c 0.6, CHCl₃); **FTIR (film)**: 2951, 1732, 1238, 1202, 1161, 876 cm⁻¹; ^1H NMR (CDCl₃): δ 7.43 (1H, br s, H-16), 7.38 (1H, t, $J = 1.7$ Hz, H-15), 6.37 (1H, d, $J = 1.7$ Hz, H-14), 5.25 (1H, dd, $J = 12.0, 2.2$ Hz, H-12), 5.09 (1H, m, H-2), 3.69 (3H, s, CO₂CH₃), 2.75 (1H, m, H-4), 2.45 (1H, dd, $J = 5.0, 2.2$ Hz, H-8), 2.36 (1H, dd, $J = 15.0, 2.2$ Hz, H-11a), 2.26 (2H, m, H-3), 2.24 (1H, br s, H-10), 2.17 (1H, m, H-7a), 2.15 (3H, s, OCOCH₃), 2.00 (1H, td, $J = 13.7, 3.9$ Hz, H-6a), 1.83 (1H, tdd, $J = 14.2, 5.0, 3.9$ Hz, H-7b), 1.62 (3H, s, H-20), 1.54 (1H, dt, $J = 13.7, 3.4$ Hz, H-6b), 1.50 (1H, dd, $J = 15.0, 12.0$ Hz, H-11b), 1.07 (3H, s, H-19);

¹³C NMR (CDCl₃): δ 202.3 (C, C-1), 173.4 (C, C-17), 171.8 (C, C-18), 169.8 (C, OCOCH₃), 143.6 (CH, C-15), 139.7 (CH, C-16), 123.3 (C, C-13), 108.5 (CH, C-14), 75.2 (CH, C-2), 70.1 (CH, C-12), 64.1 (CH, C-10), 52.9 (CH, C-4), 51.8 (CH₃, CO₂CH₃), 48.0 (CH₂, C-11), 45.2 (CH, C-8), 42.2 (C, C-5), 34.7 (C, C-9), 33.9 (CH₂, C-6), 30.6 (CH₂, C-3), 24.6 (CH₃, C-20), 20.5 (CH₃, OCOCH₃), 17.6 (CH₂, C-7), 15.2 (CH₃, C-19); **HRESIMS [M + Na⁺] m/z** 455.1683 (calcd for C₂₃H₂₈O₈Na⁺, 455.1676).

Salvinorin B formate (3). A mixture of Ac₂O (0.25 mL) and HCO₂H (0.7 mL) was stirred at 45 °C for 40 minutes. Pyridine (1 mL) was added to **2** (18.0 mg, 46.1 μmol), warmed to 45 °C until fully dissolved, then cooled to 0 °C. The cooled anhydride mixture was added dropwise by pipette, causing violent bubbling. The solution was warmed to room temperature and stirred for 30 minutes, when TLC indicated completion (*hR_f* = 85 (**3**), 65 (**2**) in 20% acetone/CH₂Cl₂, visualized in KMnO₄). The reaction mixture was cooled to 0 °C, diluted dropwise with water, and extracted into EtOAc. The organic layer was washed (1% HCl, water, 5% NaHCO₃ and brine). Standard drying and FCC (2-4% MeOH/CH₂Cl₂ gradient) gave **3** as a clear resin (13.8 mg, 72%); [α]_D²⁶ -54° (*c* 0.6, CH₂Cl₂); **FTIR (film):** 2952, 1726, 1278, 1163, 875 cm⁻¹; **¹H NMR (CDCl₃):** δ 8.14 (1H, s, CHO), 7.41 (1H, br s, H-16), 7.40 (1H, t, *J* = 1.8 Hz, H-15), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz, H-14), 5.54 (1H, dd, *J* = 11.7, 5.2 Hz, H-12), 5.26 (1H, m, H-2), 3.73 (3H, s, CO₂CH₃), 2.76 (1H, m, H-4), 2.51 (1H, dd, *J* = 13.5, 5.2 Hz, H-11a), 2.35 (2H, m, H-3), 2.18 (1H, d, *J* = 0.8 Hz, H-10), 2.17 (1H, m, H-7a), 2.08 (1H, dd, *J* = 11.5, 3.0 Hz, H-8), 1.80 (1H, m, H-6a), 1.67 (1H, m, H-7b), 1.58 (1H, ddd, *J* = 13.5, 11.7, 0.8 Hz, H-11b), 1.58 (1H, m, H-6b), 1.46 (3H, s, H-20), 1.13 (3H, s, H-19); **¹³C NMR (CDCl₃):** δ 200.8 (C, C-1), 171.4 (C, C-18), 171.0 (C, C-17), 159.4 (CH, CHO), 143.7 (CH, C-15), 139.4 (CH, C-16), 125.1 (C, C-13), 108.3 (CH, C-14), 74.5 (CH, C-2), 72.0 (CH, C-12), 64.1 (CH, C-10), 53.5 (CH, C-4), 52.0 (CH₃, CO₂CH₃), 51.3 (CH, C-8), 43.4 (CH₂, C-11), 42.1 (C, C-5), 38.1 (CH₂, C-6), 35.5 (C, C-9), 30.6 (CH₂, C-3), 18.1 (CH₂, C-7), 16.4 (CH₃, C-19), 15.2 (CH₃, C-20); **HRESIMS [M + Na⁺] m/z** 441.1525 (calcd for C₂₂H₂₆O₈Na⁺, 441.1520).

13,14,15,16-Tetrahydrosalvinorin A (10). To a solution of **1** (20.3 mg, 46.9 μmol) in 50% CH₂Cl₂/MeOH (6 mL) was added 5% Rh/C (25.3 mg), and the suspension agitated under H₂ (4 atm) at room temperature for 90 minutes, when TLC indicated completion (*hR_f* = 46 (**10**), 74 (**1**) in 20% acetone/CH₂Cl₂). The solution was filtered through diatomite filter aid and evaporated in vacuo. FCC (10% acetone/CHCl₃) gave **10** (13-epimers, 1:1) as a clear resin (12 mg, 59%). For characterisation, the less polar epimer was separated by HPLC in EtOAc; [α]_D¹⁹ -39° (*c* 0.4, CHCl₃); **FTIR (film):** 2953, 1730, 1235, 1165 cm⁻¹; **¹H NMR (CDCl₃):** δ 5.14 (1H, dd, *J* = 11.4, 8.6 Hz, H-2), 4.44 (1H, ddd, *J* = 11.7, 6.9, 5.0 Hz, H-12), 3.85 (1H, td, *J* = 8.5, 5.0 Hz, H-15a), 3.78 (1H, dd, *J* = 9.0, 7.6 Hz, H-16a), 3.74 (1H, dt, *J* = 8.5, 7.4 Hz, H-15b), 3.72 (3H, s, CO₂CH₃), 3.54 (1H, dd, *J* = 9.0, 6.7 Hz, H-16b), 2.73 (1H, m, H-4), 2.43 (1H, m, H-13), 2.30 (2H, m, H-3), 2.19 (1H, dd, *J* = 13.3, 5.0 Hz, H-11a), 2.17 (3H, s, OCOCH₃), 2.15 (1H, m, H-7a), 2.12 (1H, br s, H-10), 2.08 (1H, dddd, *J* = 12.6, 8.7, 7.4, 5.0 Hz, H-14a), 1.95 (1H, dd, *J* = 11.5, 3.1 Hz, H-8), 1.81 (1H, ddt, *J* = 12.6, 8.3, 7.4 Hz, H-14b), 1.76 (1H, m, H-6a), 1.60 (1H, m, H-7b), 1.54 (1H, m, H-6b), 1.35 (3H, s, H-20), 1.26 (1H, ddd, *J* = 13.3, 11.7, 0.8 Hz, H-11b), 1.09 (3H, s, H-19); **¹³C NMR (CDCl₃):** δ 202.0 (C, C-1), 171.5 (C, C-18), 171.3 (C, C-17), 169.9 (C, OCOCH₃), 78.2 (CH, C-12), 75.0 (CH, C-2), 68.8 (CH₂, C-16), 68.0 (CH₂, C-15), 64.0 (CH, C-10), 53.5 (CH, C-4), 52.0 (CH₃,

CO₂CH₃), 51.4 (CH, C-8), 45.1 (CH, C-13), 42.0 (C, C-5), 41.2 (CH₂, C-11), 38.1 (CH₂, C-6), 35.1 (C, C-9), 30.8 (CH₂, C-3), 28.2 (CH₂, C-14), 20.6 (CH₃, OCOCH₃), 18.1 (CH₂, C-7), 16.3 (CH₃, C-19), 15.1 (CH₃, C-20); **HRESIMS** [M + Na⁺] *m/z* 459.1984 (calcd for C₂₃H₃₂O₈Na⁺, 459.1989).

Salvinorin A lactol (11). A solution of **1** (15.8 mg, 36.5 μmol) in dry THF (1 mL) was warmed until fully dissolved, then cooled to -78 °C. DIBALH (1M in THF, 0.5 mL, 500 μmol) was added dropwise. The solution was stirred for 25 minutes, then quenched (sat. aq. NH₄Cl dropwise), evaporated in vacuo until thick, diluted in water and extracted into Et₂O (× 3). Washing (sat. aq. NaCl), standard drying and FCC (6-10% acetone/CH₂Cl₂ gradient) monitored by TLC (*hRf* = 28 (**11**), 64 (**1**) in 10% acetone/CH₂Cl₂) gave **11** as a clear resin (10.4 mg, 65% (81% borsm)); **FTIR (film)**: 3446, 2953, 1730, 1237, 1161, 875 cm⁻¹; **¹H NMR, major (17β) anomer (CDCl₃)**: δ 7.36 (1H, br s, H-16), 7.34 (1H, t, *J* = 1.8 Hz, H-15), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz, H-14), 5.12 (1H, m, H-2), 4.87 (1H, dd, *J* = 11.6, 2.4 Hz, H-12), 4.80 (1H, d, *J* = 8.7 Hz, H-17), 3.70 (3H, s, CO₂CH₃), 2.74 (1H, m, H-4), 2.25 (2H, m, H-3), 2.14 (3H, s, OCOCH₃), 2.11 (1H, dd, *J* = 13.2, 2.4 Hz, H-11a), 2.07 (1H, d, *J* = 0.9 Hz, H-10), 1.80 (1H, ddd, *J* = 13.8, 6.9, 3.2 Hz, H-7a), 1.70 (1H, dt, *J* = 13.5, 3.2 Hz, H-6a), 1.58 (1H, m, H-6b), 1.38 (3H, s, H-20), 1.37 (1H, m, H-7b), 1.21 (1H, ddd, *J* = 13.2, 11.6, 0.9 Hz, H-11b), 1.12 (1H, m, H-8), 1.08 (3H, s, H-19); **¹³C NMR, major (17β) anomer (CDCl₃)**: δ 202.5 (C, C-1), 171.9 (C, C-18), 169.9 (C, OCOCH₃), 143.0 (CH, C-15), 139.1 (CH, C-16), 126.2 (C, C-13), 108.8 (CH, C-14), 94.2 (CH, C-17), 75.0 (CH, C-2), 66.2 (CH, C-12), 65.4 (CH, C-10), 53.6 (CH, C-4), 52.1 (CH, C-8), 51.8 (CH₃, CO₂CH₃), 44.7 (CH₂, C-11), 42.4 (C, C-5), 38.8 (CH₂, C-6), 35.6 (C, C-9), 30.8 (CH₂, C-3), 20.6 (CH₃, OCOCH₃), 17.6 (CH₂, C-7), 16.7 (CH₃, C-19), 15.0 (CH₃, C-20).

17-Deoxysalvinorin A (12). To a stirred solution of lactol **11** (18.3 mg, 42.1 μmol), in dry CH₂Cl₂ (1 mL) under Ar, was added Et₃SiH (20 μL, 125 μmol). The solution was cooled to 0 °C, and BF₃•Et₂O (10 μL, 79 μmol) was added. The light brown solution was stirred at 0 °C for 2 h, when TLC indicated completion (*hRf* = 72 (**12/13**), 38 (**11**) in 10% acetone/CH₂Cl₂; 24 (**12**), 42 (**13**) in 2% acetone/CH₂Cl₂). The reaction was quenched (0.5 mL sat. NaHCO₃), and partitioned between Et₂O and brine. Standard drying and FCC (0-4% acetone/CH₂Cl₂ gradient) gave enol ether **13** (4.1 mg, 23%) along with **12** as a clear resin (8.4 mg, 48%); [α]_D²⁰ -81° (*c* 0.4, CH₂Cl₂); **FTIR (film)**: 2950, 1730, 1236, 1201, 1161, 875 cm⁻¹; **¹H NMR (CDCl₃)**: δ 7.33 (2H, m, H-15 & 16), 6.34 (1H, t, *J* = 1.4 Hz, H-14), 5.14 (1H, dd, *J* = 10.7, 9.4 Hz, H-2), 4.70 (1H, dd, *J* = 11.6, 2.5 Hz, H-12), 3.70 (3H, s, CO₂CH₃), 3.58 (2H, d, *J* = 7.6 Hz, H-17), 2.77 (1H, m, H-4), 2.26 (2H, m, H-3), 2.15 (3H, s, OCOCH₃), 2.12 (1H, dd, *J* = 13.1, 2.6 Hz, H-11a), 2.09 (1H, d, *J* = 1.0 Hz, H-10), 1.66 (2H, m, H-6), 1.48 (1H, m, H-8), 1.38 (3H, s, H-20), 1.30 (2H, m, H-7), 1.19 (1H, ddd, *J* = 13.1, 11.6, 1.0 Hz, H-11b), 1.08 (3H, s, H-19); **¹³C NMR (CDCl₃)**: δ 202.5 (C, C-1), 171.9 (C, C-18), 169.9 (C, OCOCH₃), 142.9 (CH, C-15), 138.9 (CH, C-16), 127.0 (C, C-13), 108.7 (CH, C-14), 75.0 (CH, C-2), 67.5 (CH, C-12), 67.1 (CH₂, C-17), 65.6 (CH, C-10), 53.8 (CH, C-4), 51.8 (CH₃, CO₂CH₃), 46.4 (CH, C-8), 45.4 (CH₂, C-11), 42.7 (C, C-5), 39.0 (CH₂, C-6), 34.6 (C, C-9), 30.8 (CH₂, C-3), 20.6 (CH₃, OCOCH₃), 19.6 (CH₂, C-7), 16.8 (CH₃, C-19), 13.7 (CH₃, C-20); **HRESIMS** [M + Na⁺] *m/z* 441.1881 (calcd for C₂₃H₃₀O₇Na⁺, 441.1884).

8,17-Didehydro-17-deoxysalvinorin A (13). To a solution of lactol **11** (15.1 mg, 34.7 μmol) in

CH₂Cl₂ were added Et₃SiH (25 μL, 156 μmol) and Amberlyst 15 resin (22 mg). The sealed flask was stirred at rt for 24 h. Filtration, evaporation and FCC (1% acetone/CH₂Cl₂) gave **13** as a clear resin (11.0 mg, 76%); $[\alpha]_D^{23}$ -60° (c 0.5, CH₂Cl₂); **FTIR (film)**: 2927, 1731, 1237, 1203, 1164, 875 cm⁻¹; **¹H NMR (CDCl₃)**: δ 7.38 (1H, br s, H-16), 7.36 (1H, t, *J* = 1.9 Hz, H-15), 6.36 (1H, dd, *J* = 1.9, 0.8 Hz, H-14), 6.26 (1H, d, *J* = 1.8 Hz, H-17), 5.12 (1H, dd, *J* = 11.0, 9.0 Hz, H-2), 4.78 (1H, dd, *J* = 11.7, 2.1 Hz, H-12), 3.70 (3H, s, CO₂CH₃), 2.72 (1H, m, H-4), 2.33 (1H, dd, *J* = 13.6, 2.1 Hz, H-11a), 2.28 (2H, m, H-3), 2.27 (1H, m, H-7a), 2.16 (3H, s, OCOCH₃), 2.12 (1H, d, *J* = 0.8 Hz, H-10), 1.94 (1H, ddd, *J* = 14.6, 4.6, 2.6 Hz, H-7b), 1.69 (1H, ddd, *J* = 13.2, 4.4, 2.6 Hz, H-6a), 1.52 (3H, s, H-20), 1.50 (1H, td, *J* = 13.2, 4.6 Hz, H-6b), 1.40 (1H, ddd, *J* = 13.6, 11.6, 0.8 Hz, H-11b), 1.15 (3H, s, H-19); **¹³C NMR (CDCl₃)**: δ 202.9 (C, C-1), 172.0 (C, C-18), 169.9 (C, OCOCH₃), 143.2 (CH, C-15), 139.3 (CH, C-16), 137.1 (CH, C-17), 125.8 (C, C-13), 117.0 (C, C-8), 108.7 (CH, C-14), 75.2 (CH, C-2), 66.6 (CH, C-12), 65.5 (CH, C-10), 53.5 (CH, C-4), 51.7 (CH₃, CO₂CH₃), 44.4 (CH₂, C-11), 42.8 (C, C-5), 40.1 (CH₂, C-6), 34.1 (C, C-9), 30.6 (CH₂, C-3), 22.8 (CH₃, C-20), 22.6 (CH₂, C-7), 20.6 (CH₃, OCOCH₃), 15.4 (CH₃, C-19); **HRESIMS** [M + Na⁺] *m/z* 439.1728 (calcd for C₂₃H₂₈O₇Na⁺, 439.1727).

O-Demethyl-18-deoxysalvinorin A (15). To dry EtSH (1.5 mL, 20.2 mmol) at 0 °C, stirred rapidly under a stream of Ar, was added n-BuLi in hexanes (2.1M, 8 mL, 16.9 mmol). Immediate, violent gas evolution was accompanied by the sudden formation of white solid. The flask was swirled, mixing the precipitate into a slurry, and rapid stirring continued while the remaining n-BuLi was added. After warming to room temperature, the solution was evaporated under reduced pressure, and finally dried under high vacuum at 50 °C for 30 min, giving LiSEt as a white powder.

1 (42.2 mg, 97.6 μmol) and LiSEt (13.7 mg, 201 μmol) under Ar were dissolved in DMPU (1 mL). The yellow solution was stirred at 55 °C for 23 h, when TLC indicated consumption of **1** and intermediate **2** (*hRf* = 0 smearing to 20 (**14**), 63 (**2**), 71 (**1**) in 1% H₂SO₄/10% MeOH/CH₂Cl₂). The cooled solution was diluted in EtOAc and washed (10% HCl × 3, then water), then extracted into 1% NaHCO₃ (× 3). The pooled aqueous fractions were acidified at 0 °C with 10% HCl, then extracted into CH₂Cl₂ (× 3). Standard drying gave an amber resin, which was treated with Ac₂O (0.4 mL) in pyridine (1 mL) and catalytic DMAP at room temperature for 17 h. After cooling to 0 °C and quenching (water), the solution was diluted in EtOAc and washed (10% HCl and sat. NH₄Cl). Standard drying gave acids **14** (H-8α:β, ~1.4:1) as an amber resin (29.7 mg, 73% over two steps). The mixed acids (35.2 mg, 84.0 μmol) were stirred in dry THF (1 mL) under Ar in a flask fitted with a reflux condenser. BH₃•THF (1.0 M, 110 μL, 110 μmol) was added dropwise; the solution was heated to 55 °C and stirred at this temperature for 90 minutes, when TLC indicated completion (*hRf* = 0 smearing to 30 (**14**), 56 (**15**, 8-*epi*-**15**) in 1% NEt₃/EtOAc). The solution was cooled to room temperature, quenched with water (dropwise), and evaporated in vacuo to give a cloudy paste. This was diluted in sat. NaHCO₃ and extracted into CH₂Cl₂ (×3). Standard drying and FCC (10-25% acetone/Et₂O gradient) monitored by TLC (*hRf* = 30 (8-*epi*-**15**), 20 (**15**) in Et₂O) gave 8-*epi*-**15** (8.4 mg, 25%) along with **15** as a clear resin (7.7 mg, 23%); $[\alpha]_D^{25}$ -19° (c 0.3, CH₂Cl₂); **FTIR (film)**: 3468, 2944, 1727, 1237, 1162, 875 cm⁻¹; **¹H NMR (CDCl₃)**: δ 7.41 (1H, br s, H-16), 7.39 (1H, t, *J* = 1.9 Hz, H-15), 6.38 (1H, dd, *J* = 1.9, 0.8 Hz, H-14), 5.52 (1H, dd, *J* = 11.7, 5.3 Hz, H-12), 5.15 (1H, dd, *J* = 12.3, 7.6

Hz, H-2), 3.94 (1H, dd, $J = 10.3, 3.9$ Hz, H-18a), 3.49 (1H, dd, $J = 10.3, 8.0$ Hz, H-18b), 2.54 (1H, ddd, $J = 12.3, 7.0, 2.6$ Hz, H-3a), 2.49 (1H, dd, $J = 13.3, 5.3$ Hz, H-11a), 2.17 (1H, d, $J = 0.9$ Hz, H-10), 2.16 (3H, s, OCOCH₃), 2.16 (1H, m, H-7a), 2.06 (1H, dd, $J = 12.1, 3.0$ Hz, H-8), 1.99 (1H, dt, $J = 13.3, 3.3$ Hz, H-6a), 1.89 (1H, m, H-4), 1.80 (1H, q, $J = 12.3$ Hz, H-3b), 1.64 (1H, dddd, $J = 14.0, 13.5, 12.1, 3.4$ Hz, H-7b), 1.58 (1H, ddd, $J = 13.3, 11.7, 0.9$ Hz, H-11b), 1.45 (3H, s, H-20), 1.43 (1H, m, H-6b), 0.96 (3H, s, H-19); ¹³C NMR (CDCl₃): δ 203.6 (C, C-1), 171.3 (C, C-17), 170.0 (C, OCOCH₃), 143.7 (CH, C-15), 139.4 (CH, C-16), 125.2 (C, C-13), 108.4 (CH, C-14), 76.0 (CH, C-2), 72.1 (CH, C-12), 64.5 (CH, C-10), 61.7 (CH₂, C-18), 51.5 (CH, C-8), 50.8 (CH, C-4), 43.4 (CH₂, C-11), 41.9 (C, C-5), 38.1 (CH₂, C-6), 35.3 (C, C-9), 31.8 (CH₂, C-3), 20.6 (CH₃, OCOCH₃), 18.1 (CH₂, C-7), 16.7 (CH₃, C-19), 15.3 (CH₃, C-20); HRESIMS [M + Na⁺] m/z 427.1729 (calcd for C₂₂H₂₈O₇Na⁺, 427.1727).

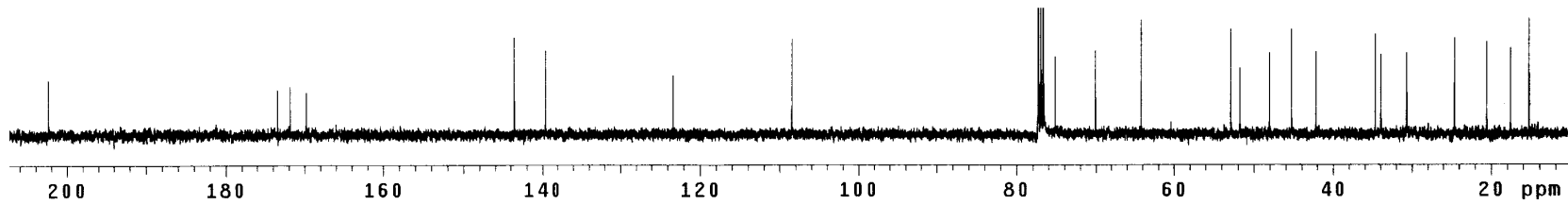
1-Deoxysalvinorin A (18). A solution of NaBH₄ (11.6 mg, 307 μmol) and **1** (108 mg, 249 μmol) in dry EtOH (9 mL)/CH₂Cl₂ (2 mL) was stirred under Ar at 40 °C. The cloudy solution gradually cleared. At 4 h, TLC indicated completion ($hRf = 45$ (**1**), 25 (8-*epi*-**7**), 14 (**7**) in Et₂O). The solution was evaporated in vacuo, and the residue partitioned between brine and CH₂Cl₂ (× 3). Standard drying gave an impure ~1:1 mixture of **7** and 8-*epi*-**7** (103 mg). This crude mixture and 1,1'-thiocarbonyldiimidazole (118 mg, 662 μmol) were dissolved in dry DMF and stirred under Ar at 90 °C for 6 h, when TLC indicated completion ($hRf = 86$ (**16**), 62 (7/8-*epi*-**7**) in 40% acetone/ CH₂Cl₂). The cooled solution was diluted in EtOAc/Et₂O and washed (10% HCl × 3, then brine). Standard drying followed by FCC (1-5% acetone/ CH₂Cl₂ gradient) gave the cyclic thionocarbonates **16** (H-8α:β, ~1:2), as a clear resin (72 mg, 67% over two steps). The thionocarbonate mixture was dissolved in dry toluene (2 mL). The resulting cloudy solution was stirred under Ar at 80 °C. A solution of freshly distilled Bu₃SnH (150 μL, 550 μmol) and AIBN (5.4 mg, 33 μmol) in dry toluene (2 mL) was added in small portions over 4 h; the solution gradually cleared. After a further 2 h, TLC indicated completion ($hRf = 70$ (byproduct), 55 (**16**), 20 (**17**/8-*epi*-**17**) in 10% acetone/ CH₂Cl₂). The solution was cooled and loaded directly onto silica gel, rinsing the flask with CH₂Cl₂ (× 2). Repeated FCC (50-70% EtOAc/petrol gradient) monitored by TLC ($hRf = 47$ (8-*epi*-**17**), 40 (**17**) in Et₂O) gave 8-*epi*-**17** (15.5 mg, 25%) along with **17** (13.5 mg, 22%) as a clear resin, which was dissolved in pyridine (0.3 mL) and Ac₂O (0.3 mL) with a crystal of DMAP. The solution was stirred at rt for 2.5 h, when TLC indicated completion ($hRf = 74$ (**18**) in Et₂O, visualized in KMnO₄), then evaporated in vacuo. FCC (60% Et₂O/*n*-pentane) gave **18** as a clear resin (12.3 mg, 82%); $[\alpha]_D^{21} -8^\circ$ (c 0.1, CH₂Cl₂); FTIR (film): 2952, 1729, 1365, 1245, 1153, 1024, 875 cm⁻¹; ¹H NMR (CDCl₃): δ 7.43 (1H, br s, H-16), 7.42 (1H, t, $J = 1.8$ Hz, H-15), 6.41 (1H, dd, $J = 1.9, 1.0$ Hz, H-14), 5.47 (1H, ddd, $J = 11.2, 5.6, 0.7$ Hz, H-12), 4.74 (1H, tt, $J = 11.0, 5.5$ Hz, H-2), 3.66 (3H, s, CO₂CH₃), 2.28 (1H, dd, $J = 13.5, 5.9$ Hz, H-11a), 2.18 (1H, dd, $J = 10.9, 3.5$ Hz, H-4), 2.15 (1H, dd, $J = 10.0, 3.5$ Hz, H-8), 2.09 (1H, dq, $J = 14.2, 3.4$ Hz, H-7a), 2.05 (3H, s, OCOCH₃), 1.92 (1H, m, H-1a), 1.89 (2H, m, H-3), 1.74 (1H, dt, $J = 13.5, 3.3$ Hz, H-6a), 1.65 (1H, m, H-7b), 1.64 (1H, dd, $J = 13.6, 11.5$ Hz, H-11b), 1.50 (1H, td, $J = 12.8, 11.2$ Hz, H-1b), 1.31 (1H, td, $J = 13.6, 3.7$ Hz, H-6b), 1.11 (3H, s, H-19), 1.10 (1H, dd, $J = 12.9, 2.2$ Hz, H-10), 1.06 (3H, s, H-20); ¹³C NMR (CDCl₃): δ 172.7 (C, C-18), 171.9 (C, C-17), 170.5 (C, OCOCH₃), 143.8 (CH, C-15), 139.4 (CH, C-16), 125.6 (C, C-13), 108.4 (CH, C-14), 71.8 (2 × CH, C-2 & 12), 54.2 (CH, C-4), 52.9 (CH, C-

10), 51.5 (CH₃, CO₂CH₃), 51.2 (CH, C-8), 43.9 (CH₂, C-11), 38.0 (CH₂, C-6), 36.9 (C, C-9), 36.2 (C, C-5), 29.6 (CH₂, C-3), 26.7 (CH₂, C-1), 21.3 (CH₃, OCOCH₃), 18.2 (CH₂, C-7), 15.0 (CH₃, C-19), 14.6 (CH₃, C-20); **HRESIMS** [M + Na⁺] *m/z* 441.1893 (calcd for C₂₃H₃₀O₇Na⁺, 441.1884).

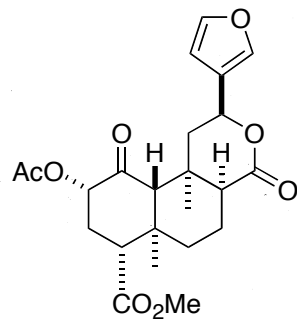
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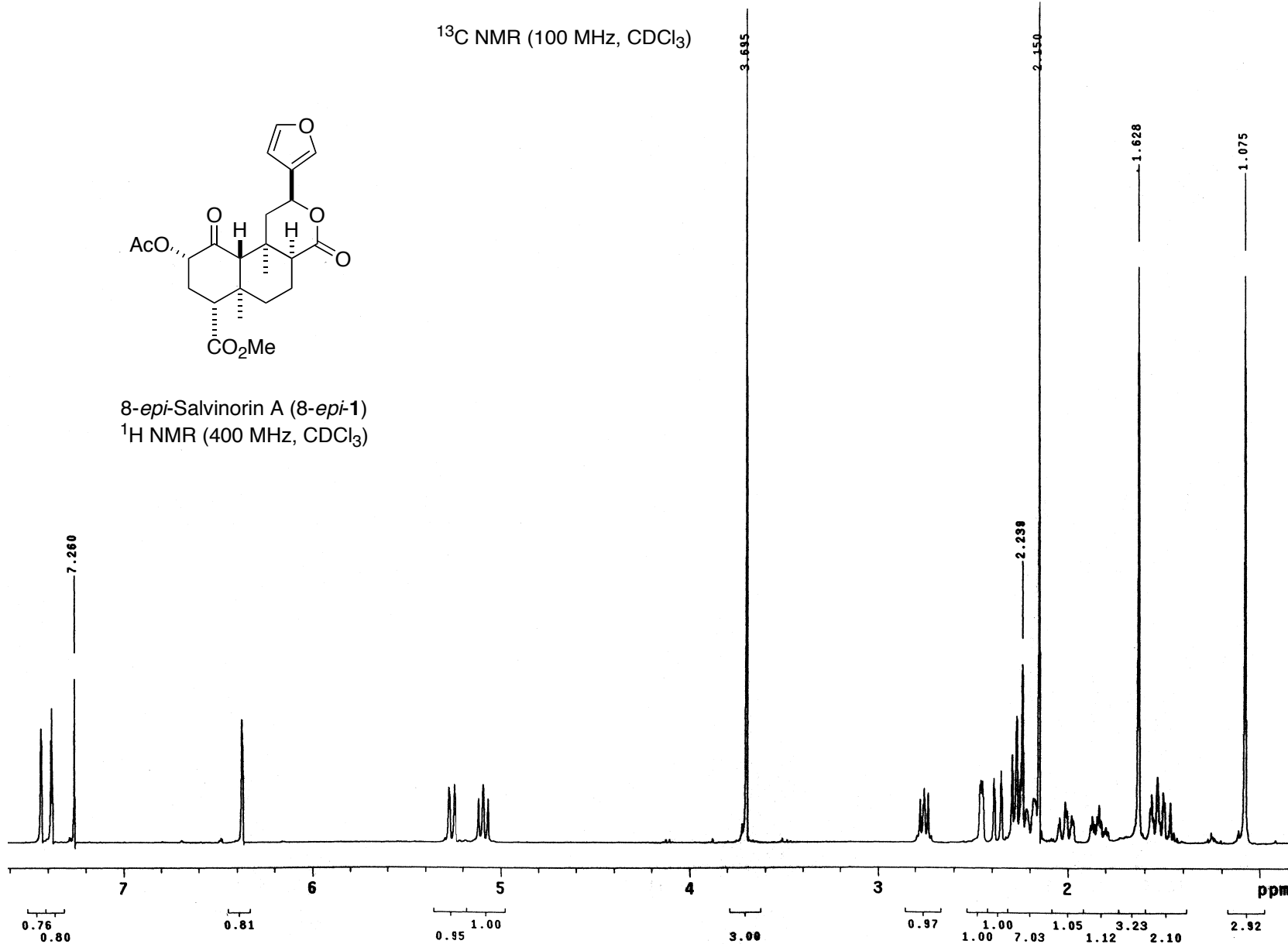
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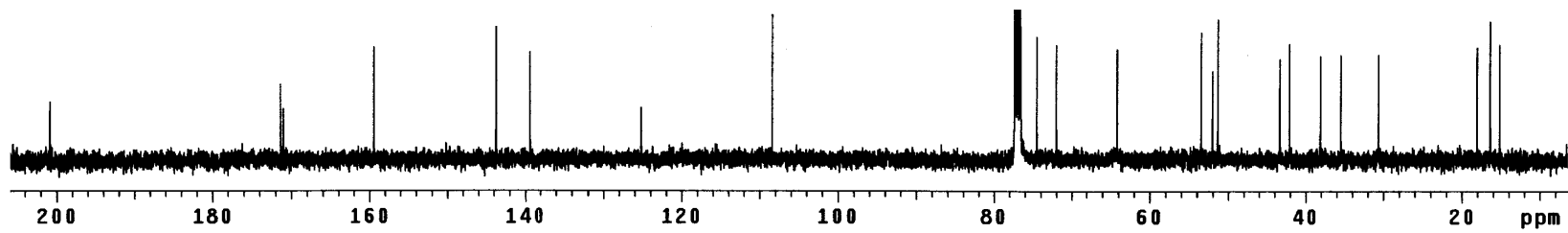


^{13}C NMR (100 MHz, CDCl_3)

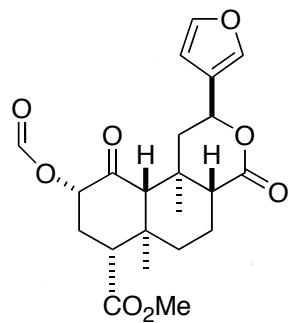


8-*epi*-Salvinorin A (8-*epi*-1)
 ^1H NMR (400 MHz, CDCl_3)

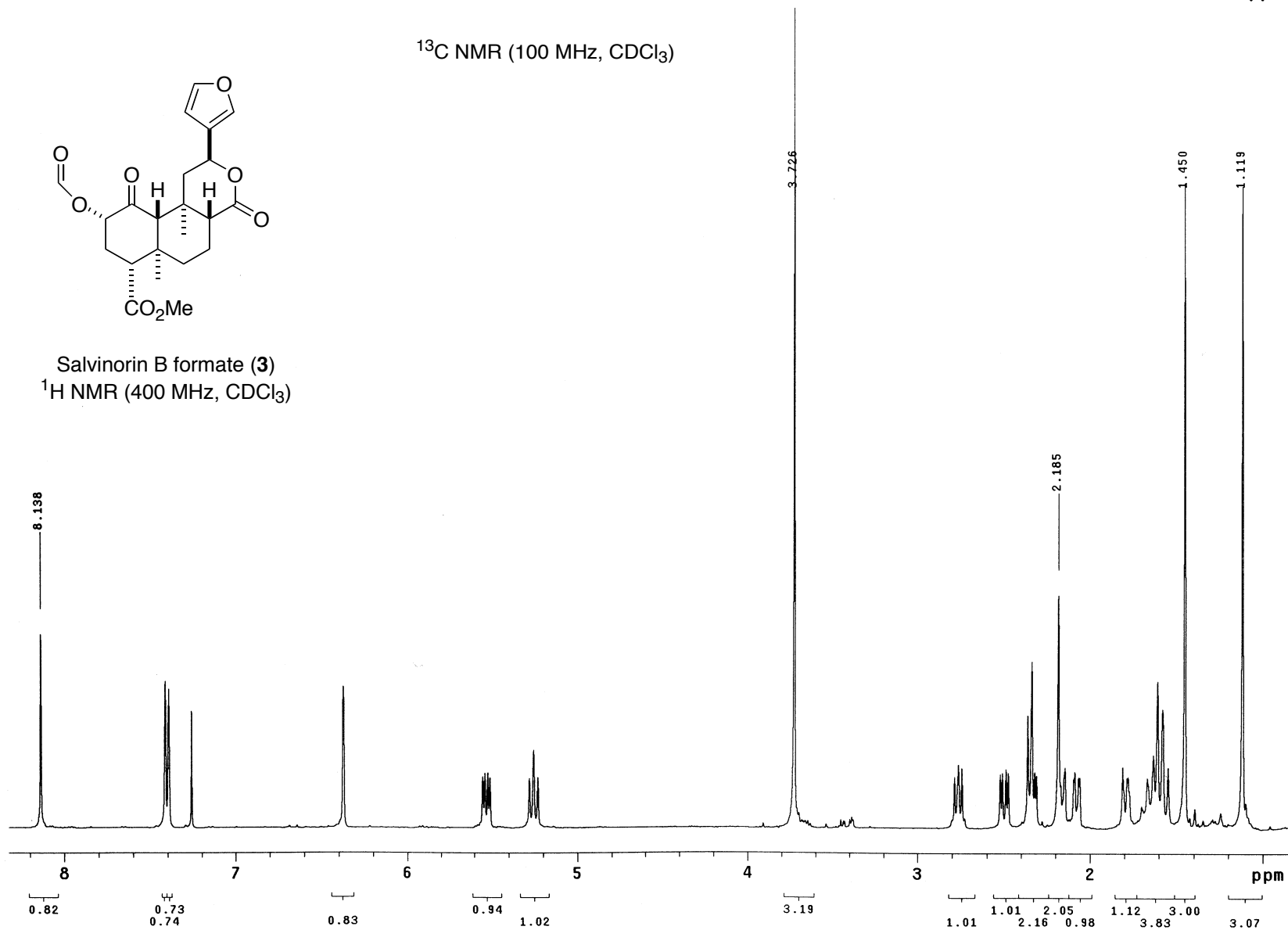




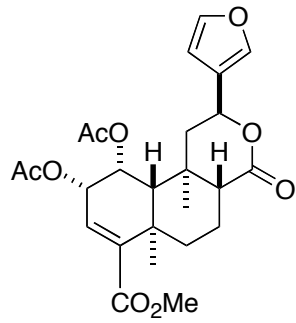
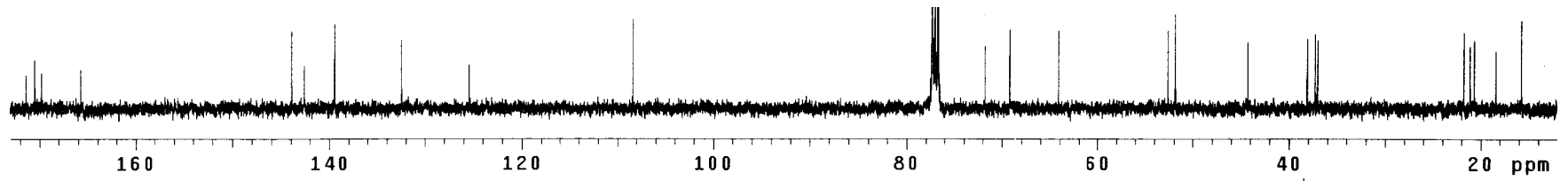
^{13}C NMR (100 MHz, CDCl_3)



Salvinorin B formate (**3**)
 ^1H NMR (400 MHz, CDCl_3)

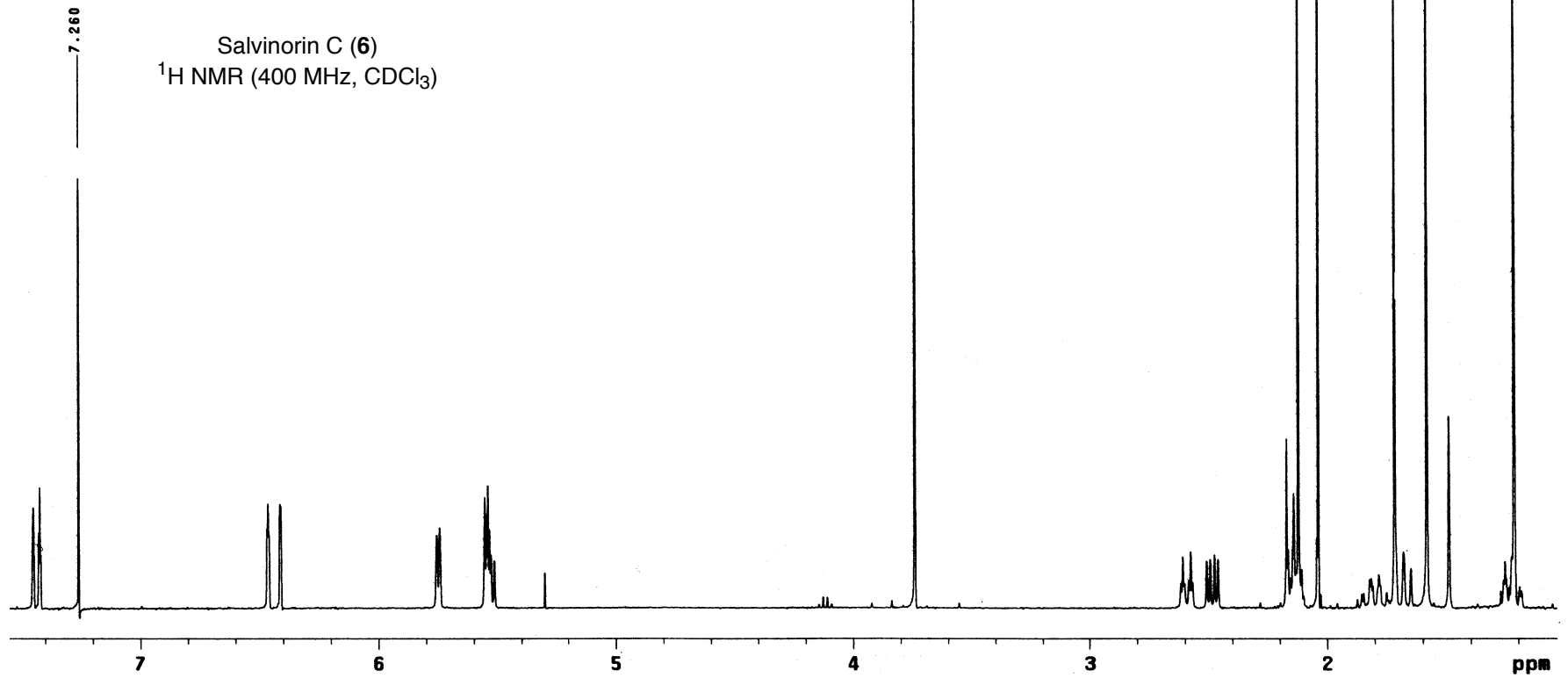


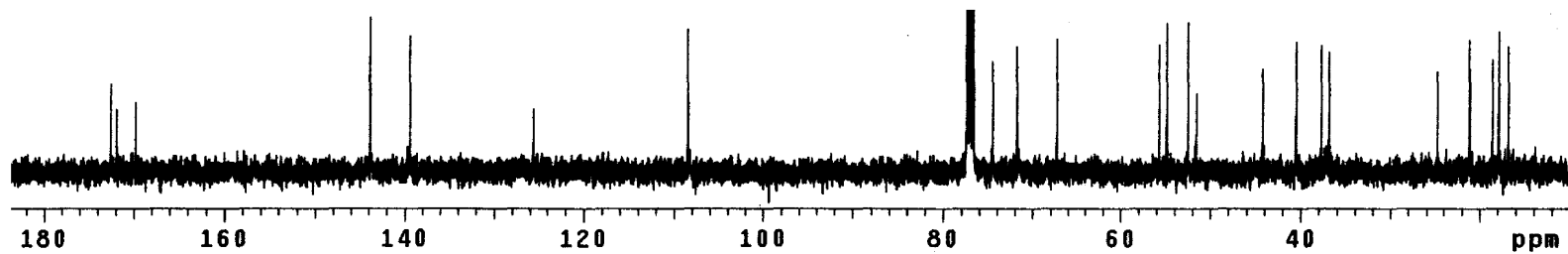
S10



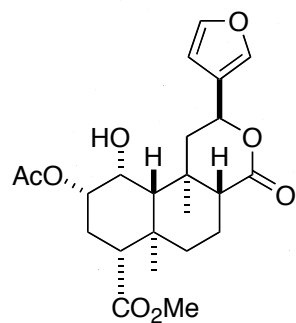
Salvinorin C (6)
 ^1H NMR (400 MHz, CDCl_3)

IIS

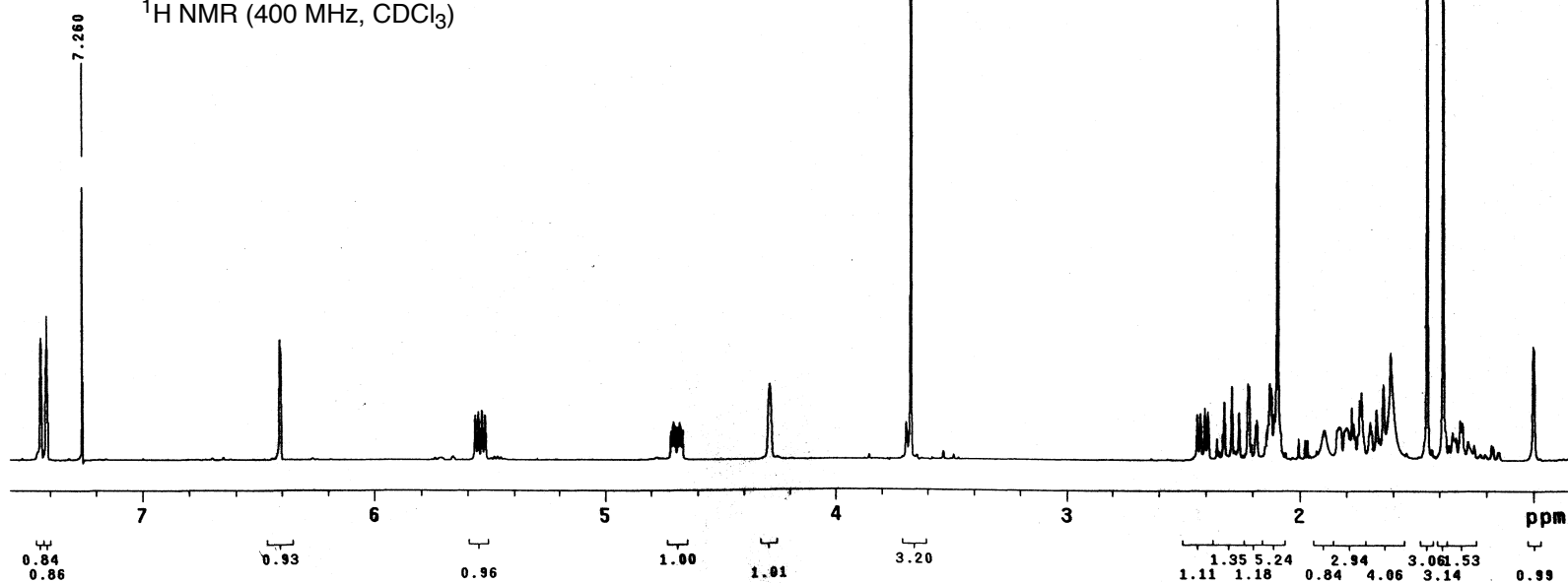


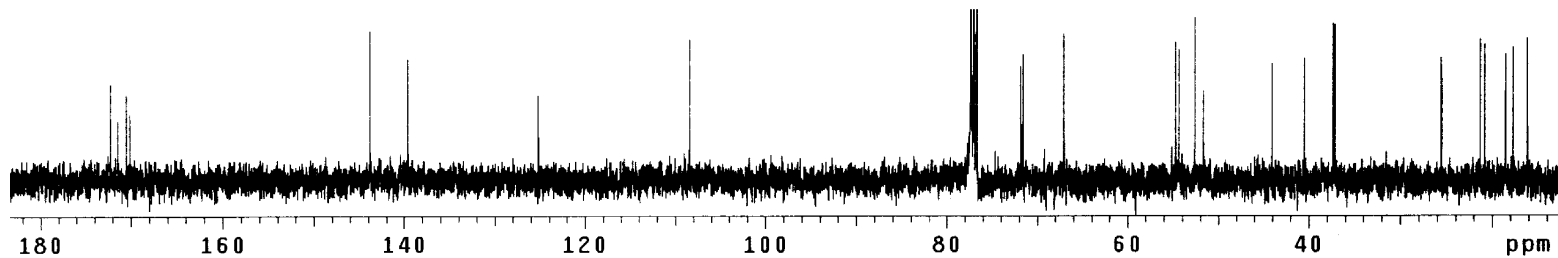


^{13}C NMR (100 MHz, CDCl_3)

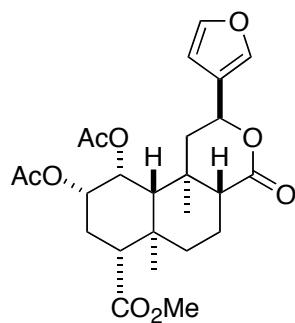


(4*R*)-3,4-Dihydrosalvinorin E (**8**)
 ^1H NMR (400 MHz, CDCl_3)

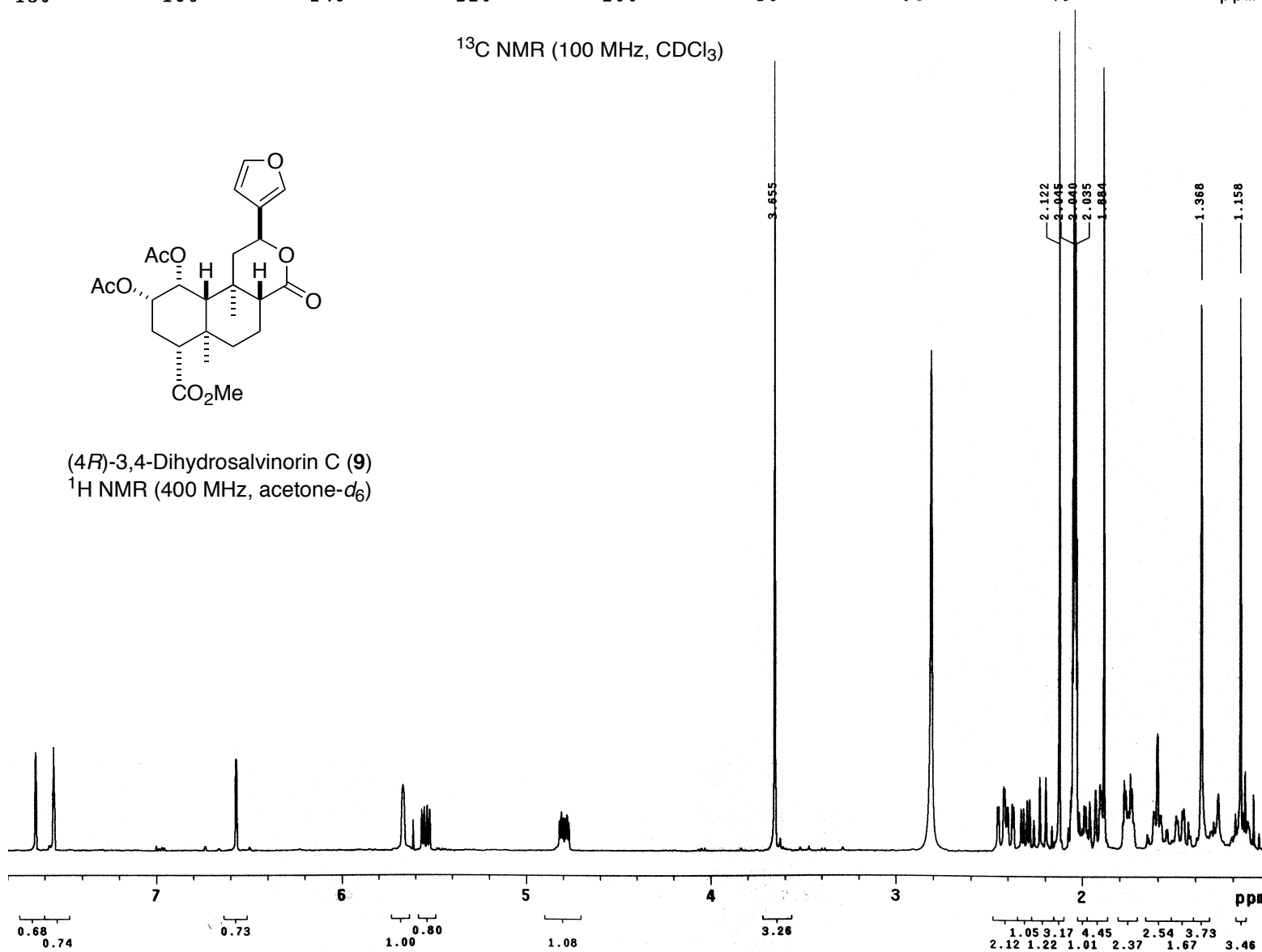


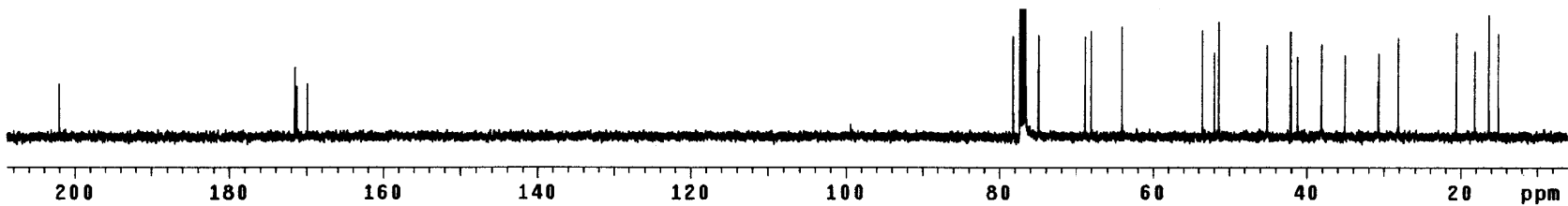


^{13}C NMR (100 MHz, CDCl_3)

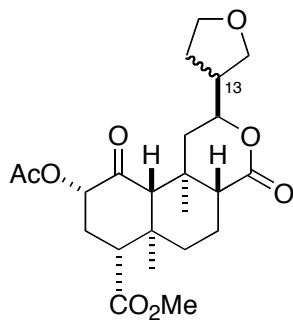


(4*R*)-3,4-Dihydrosalvinorin C (**9**)
 ^1H NMR (400 MHz, $\text{acetone-}d_6$)



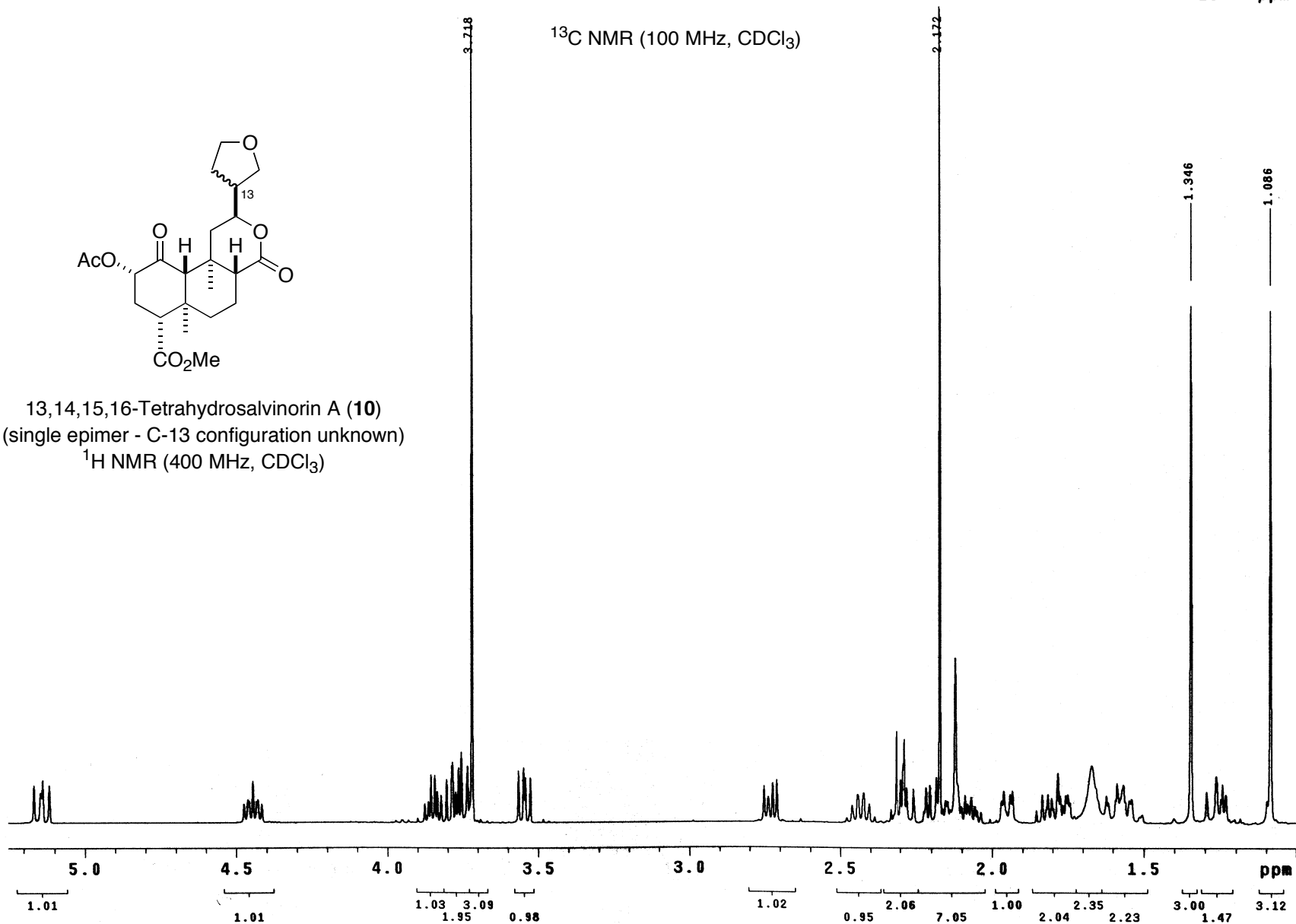


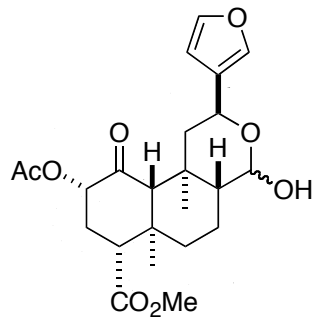
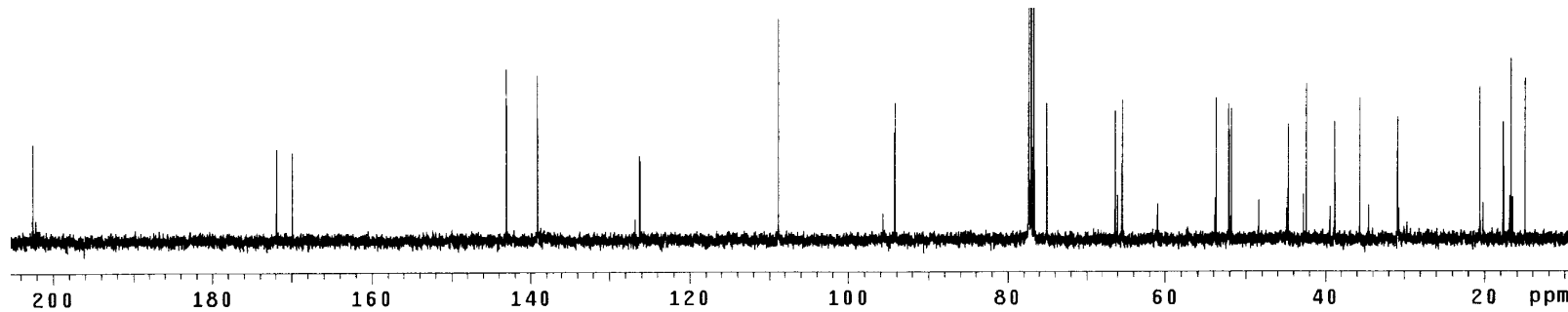
^{13}C NMR (100 MHz, CDCl_3)



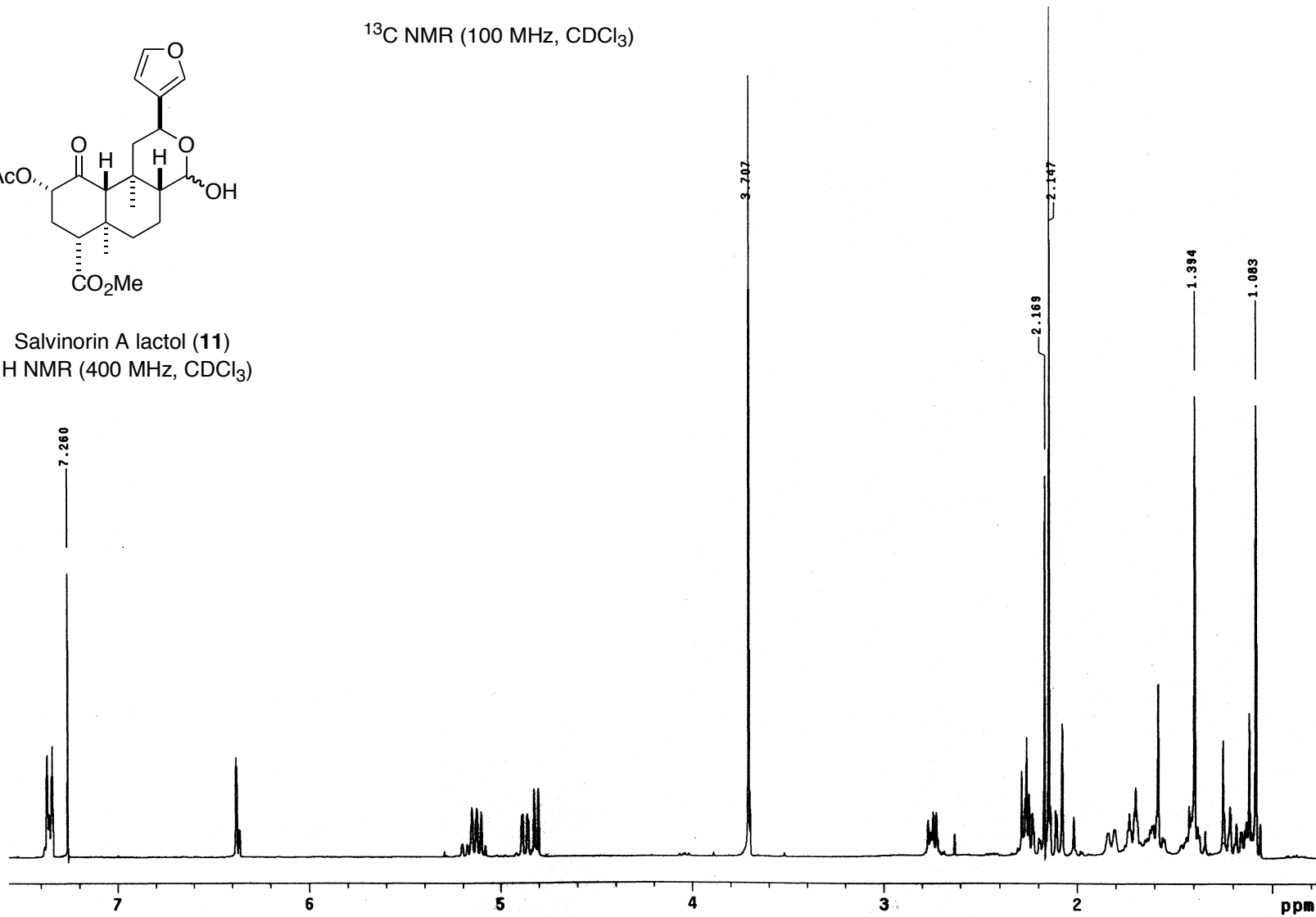
13,14,15,16-Tetrahydroalvalnorin A (**10**)
(single epimer - C-13 configuration unknown)

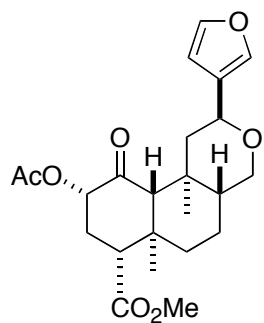
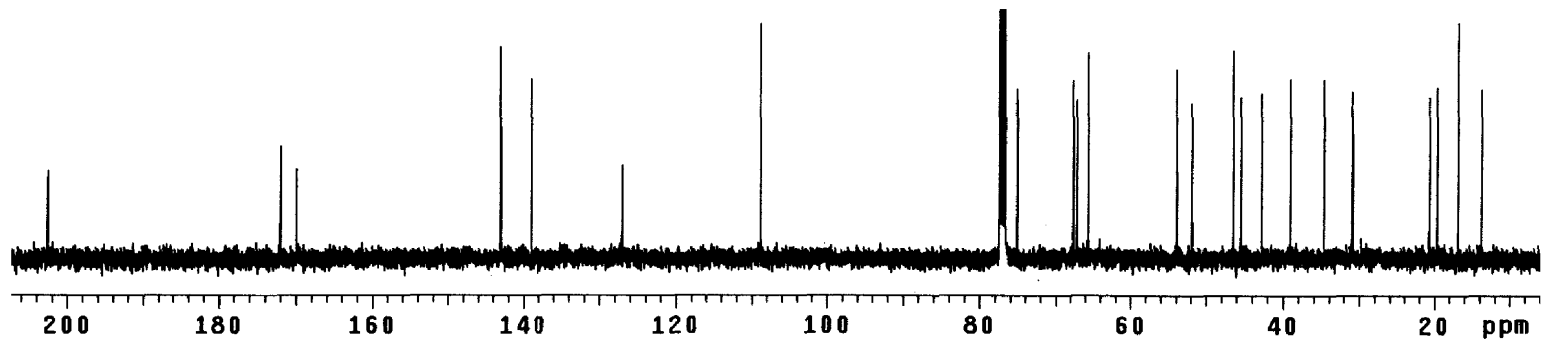
^1H NMR (400 MHz, CDCl_3)



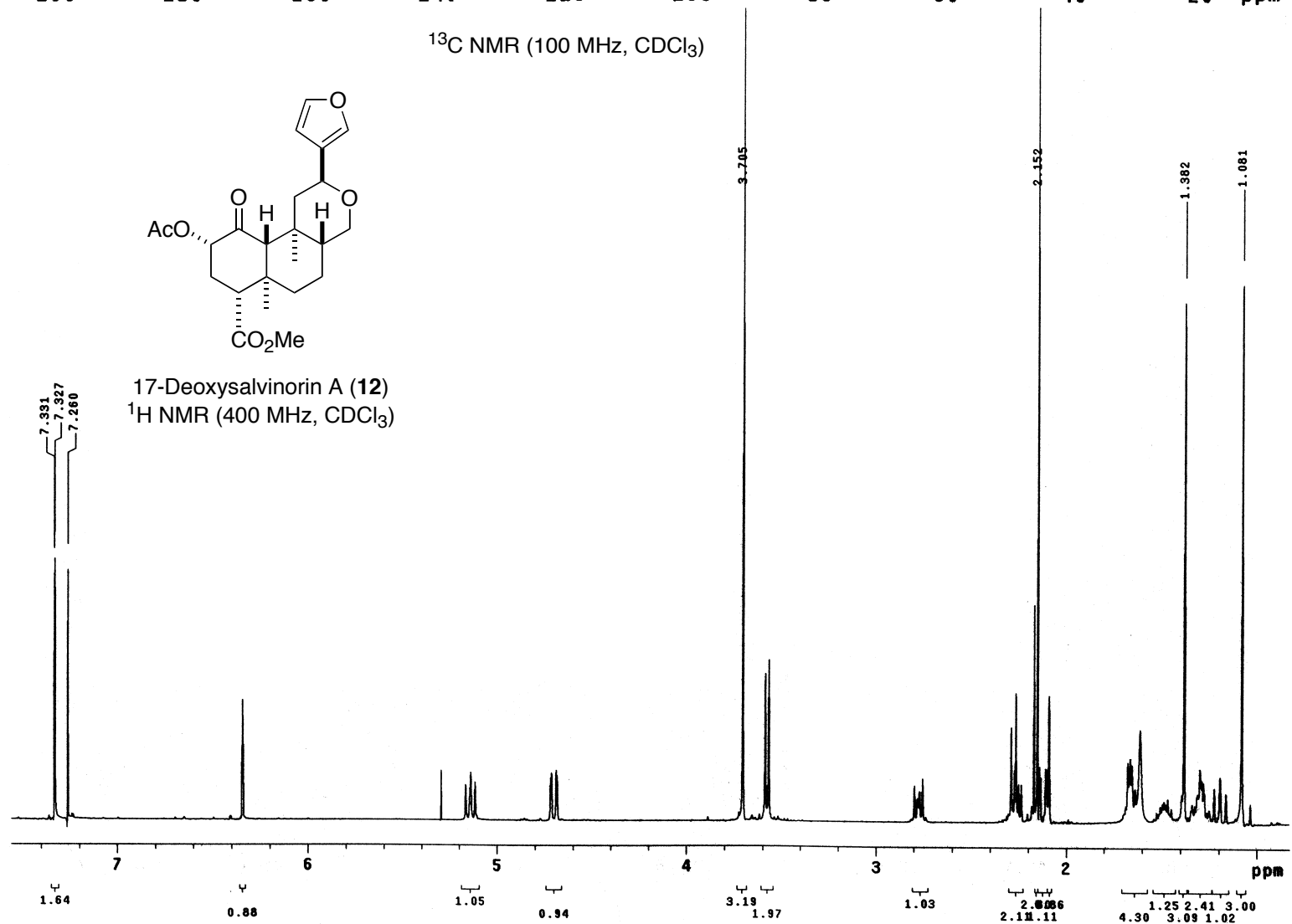


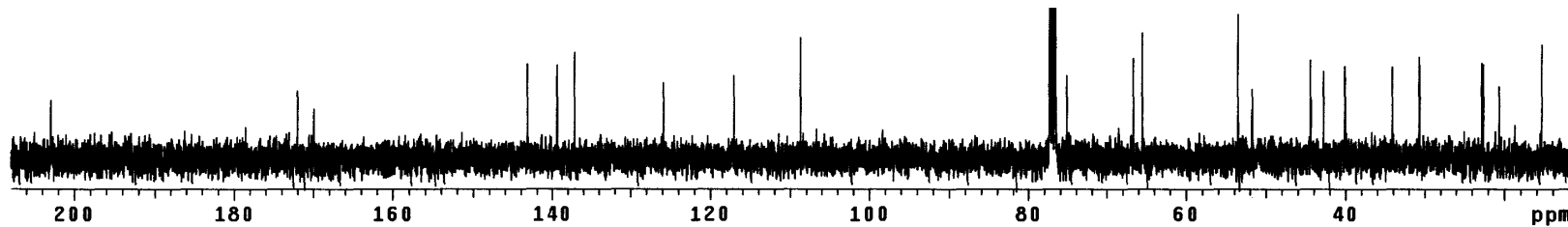
Salvinorin A lactol (11)
¹H NMR (400 MHz, CDCl₃)



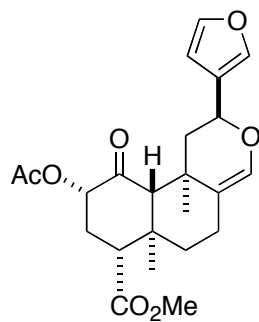


¹H NMR (400 MHz, CDCl₃)



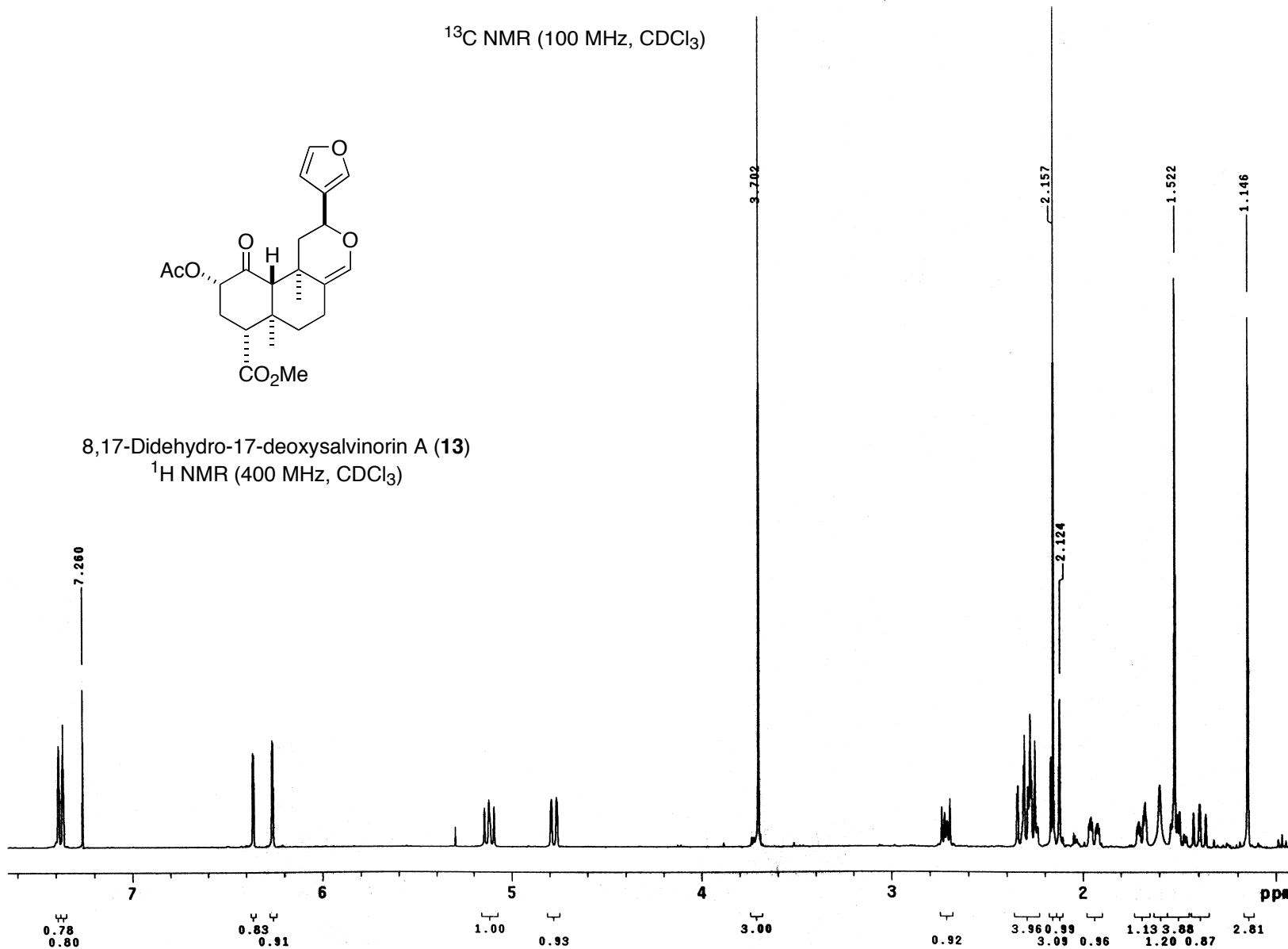


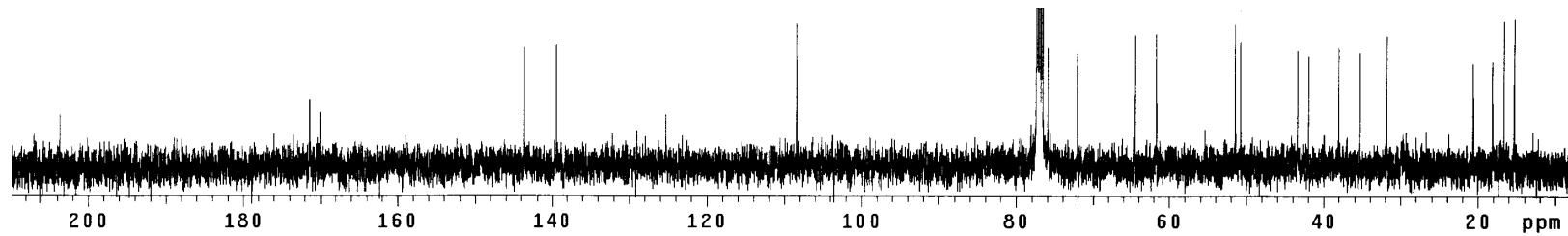
^{13}C NMR (100 MHz, CDCl_3)



8,17-Didehydro-17-deoxysalvinorin A (**13**)

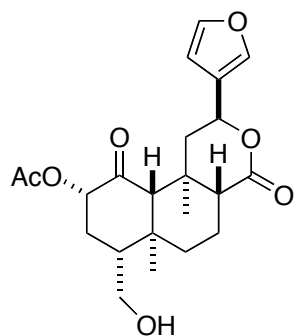
^1H NMR (400 MHz, CDCl_3)



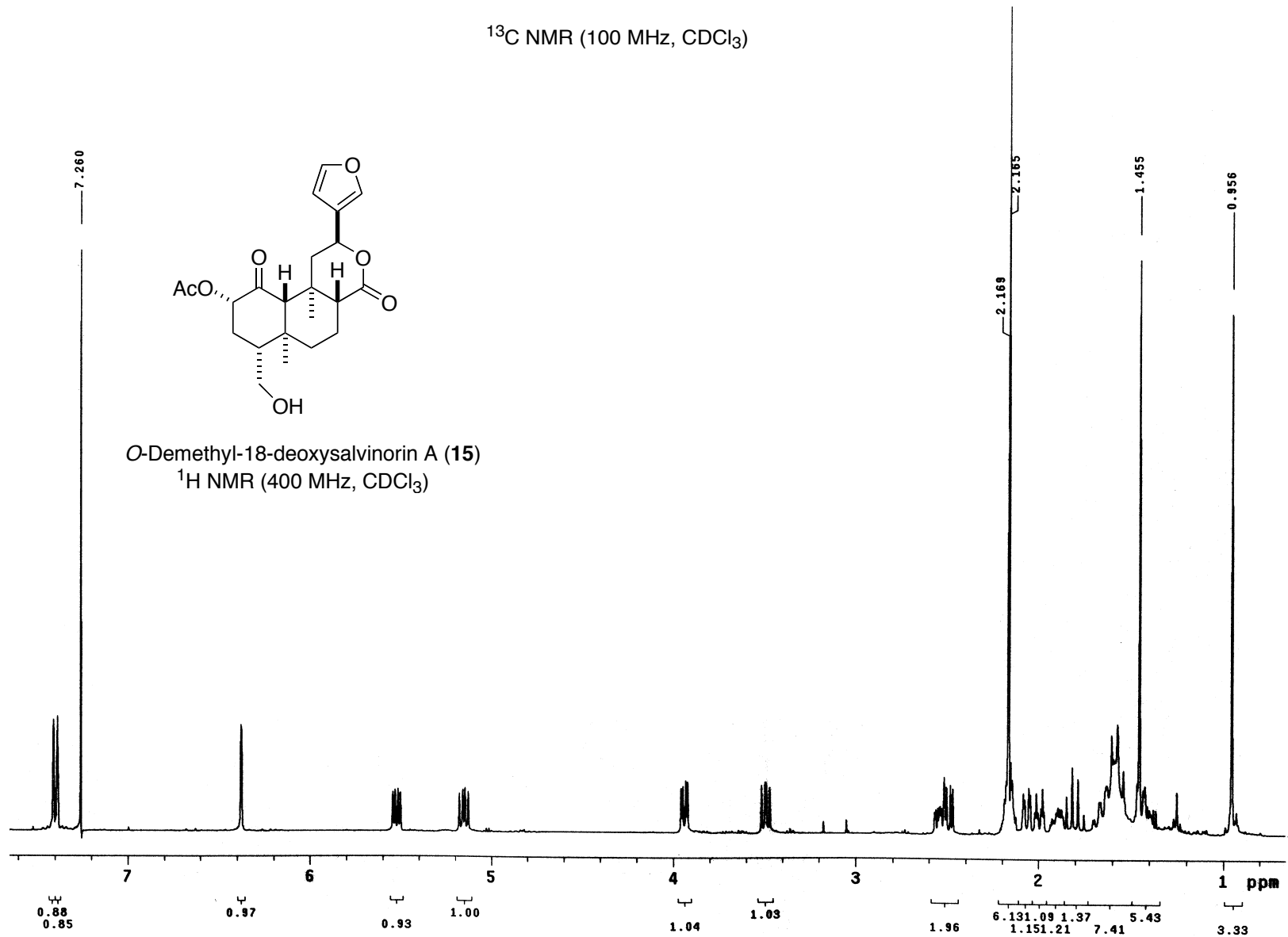


^{13}C NMR (100 MHz, CDCl_3)

818



O-Demethyl-18-deoxysalvinorin A (**15**)
 ^1H NMR (400 MHz, CDCl_3)



0.88
0.85

0.97

0.93

1.00

1.04

1.03

1.96

6.131.09 1.37
1.151.21 7.41

5.43

3.33

7

6

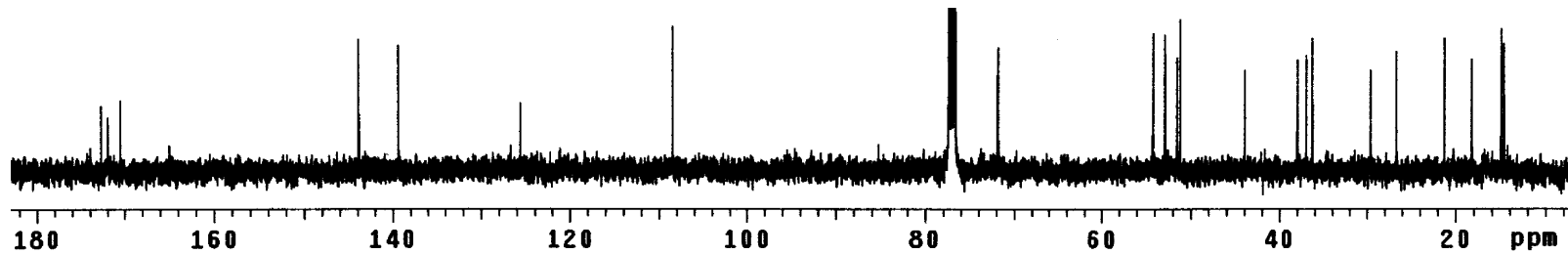
4

3

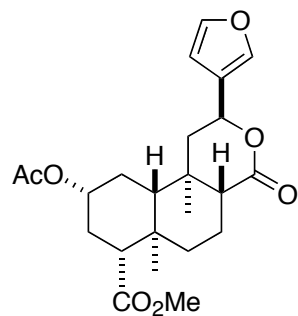
2

1

ppm



^{13}C NMR (100 MHz, CDCl_3)



1-Deoxysalvinorin A (**18**)
 ^1H NMR (400 MHz, CDCl_3)

