SUPPORTING INFORMATION

One-pot Total Synthesis of Cannabinol

via Iodine-mediated Deconstructive Annulation

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General Experimental Procedures. IR spectra were registered on an Avatar 370 FT-IR Techno-Nicolet apparatus. ^{1}H (500 and 400 MHz) and ^{13}C (125 and 100 MHz) NMR spectra were measured on Varian INOVA NMR spectrometers. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26, δ_C = 77.0; CD_3OD: δ_H = 3.34, δ_C = 55.0). Homonuclear ^{1}H connectivities were determined by the COSY experiment. One-bond heteronuclear ^{1}H-^{13}C connectivities were determined with the HSQC experiment. Two- and three-bond ^{1}H-^{13}C connectivities were determined by gradient 2D HMBC experiments optimized for a $^{2,3}J$ = 9 Hz. Low- and high-resolution ESIMS were obtained on a LTQ OrbitrapXL (Thermo Scientific) mass spectrometer. Silica gel 60 (70-230 mesh) used for gravity column chromatography (CC) was purchased from Macherey-Nagel. Flash chromatography was carried out on a Biotage apparatus, and a Knauer HPLC instrument equipped with Phenomenex LUNA silica gel and reverse phase columns (100 × 4.6 mm ID) was used for HPLC. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, visualized by staining with 5% H_2SO_4 in ethanol and heating. Organic phases were dried with Na_2SO_4 before evaporation. Chemical reagents and solvents were from Aldrich and were used without any further purification unless stated otherwise.

Pyrolysis of cannabichromene (3) in presence of silica gel. CBC (100 mg, 0.32 mmol) was adsorbed onto silica (200 mg) and heated to 150 °C by microwave (CEM Discover SP Microwave, 300 W) at regular intervals of 30 minutes for a total of 210 minutes, until complete consumption of the starting material by TLC (PE-EtOAc 9:1, Rf CBC= 0.27, Rf product mixture= 0.43). The crude product mixture was first purified by gravity column chromatography on silica gel using 9:1 PE-EtOAc solution as eluent to afford 68 mg of brown oil. Further HPLC purification (UV detector set at λ_{max} 227 nm; flow 0.8 mL/min) using as eluent a gradient from CH_3CN/H_2O (0.1% HCOOH) 7:3 to CH_3CN in 25 min afforded pure cannabicitran (**6**, 18.0 mg, 0.057 mmol, 17.8% yield), Δ^{8}-*iso*-*cis*-THC (**7**,

11.3 mg, 0.036 mmol, 11.2% yield), and cannabicyclol (**8**, 31.3 mg, 0.10 mmol, 31.2%). Cannabicitran,[1] Δ^8-*iso*-*cis*-THC,[2] and cannabicyclol[3] showed spectral properties identical to those reported in the literature.

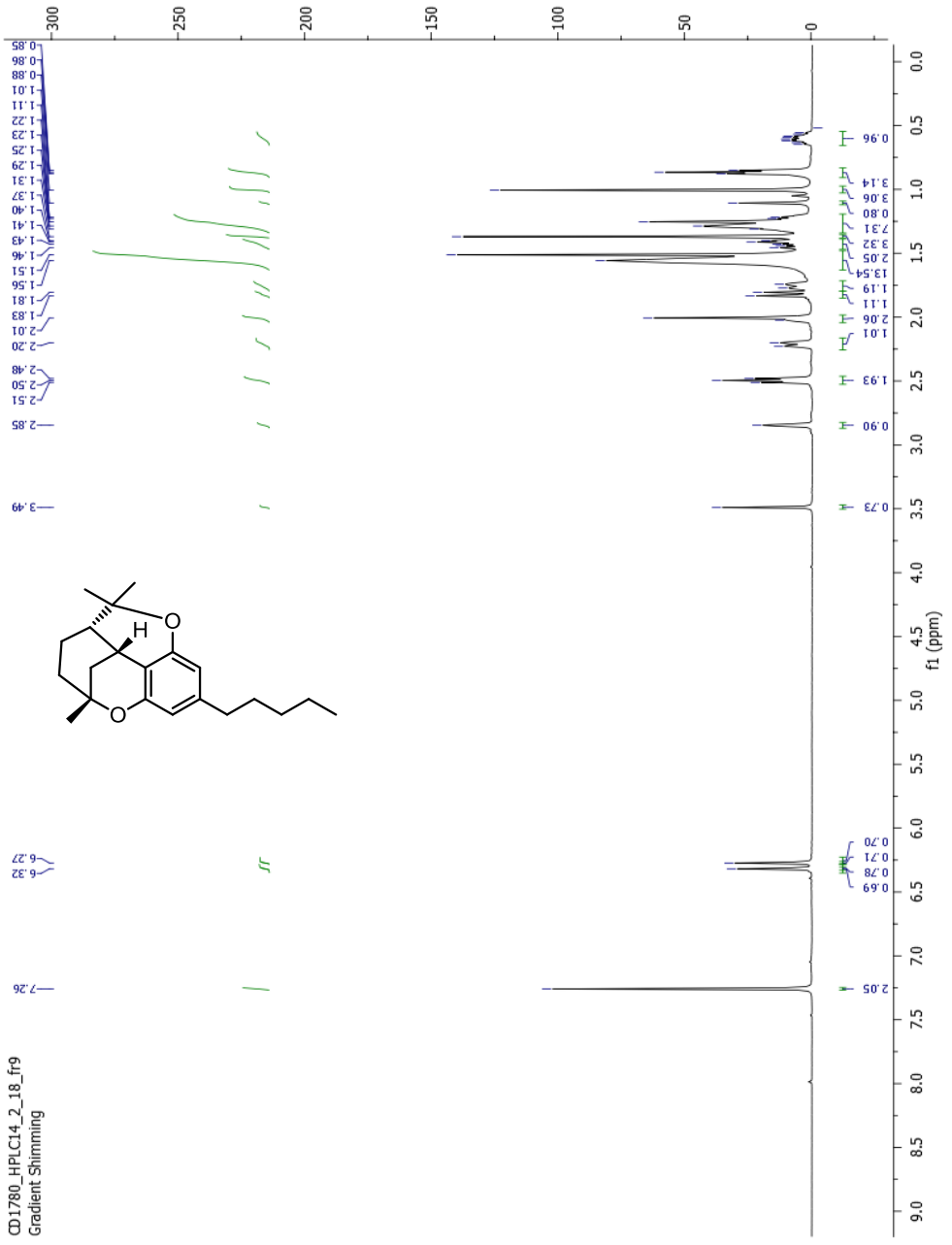

Figure S1. ^{1}H NMR spectrum of cannabicitran (**6**) in $CDCl_3$

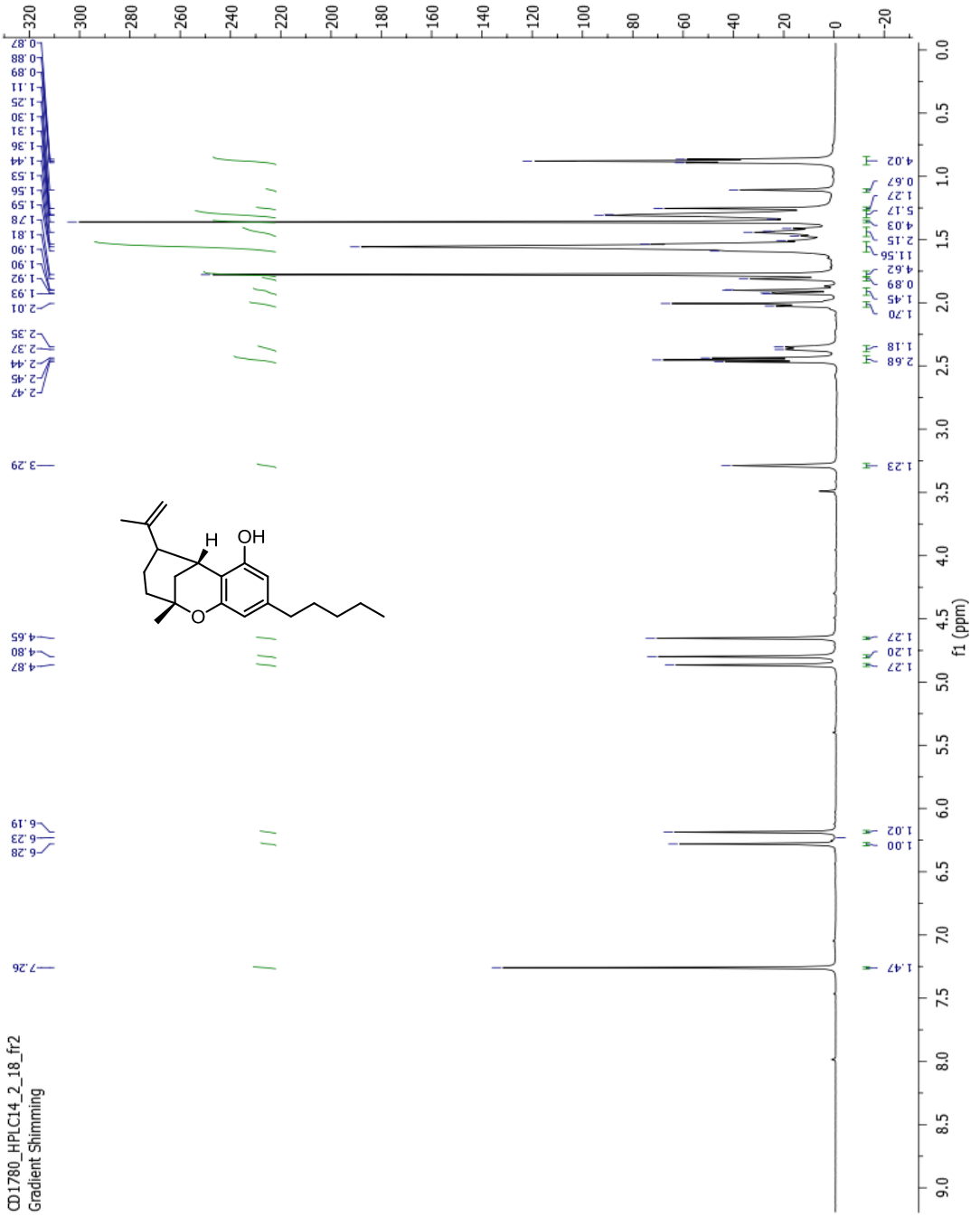

Figure S2. ^{1}H NMR spectrum of Δ^{8}-*iso-cis*-THC (**7**) in $CDCl_3$

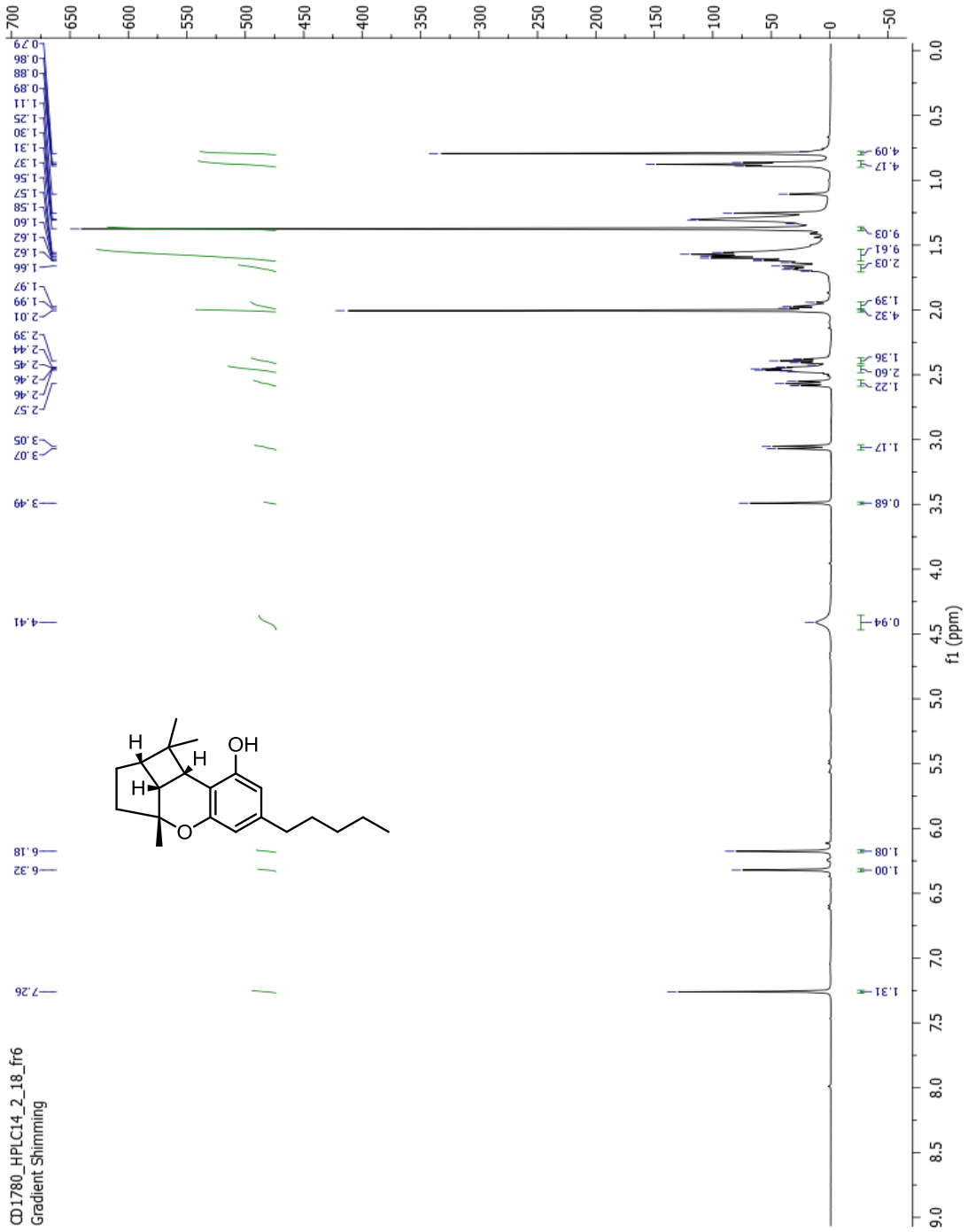

Figure S3. ^{1}H NMR spectrum of cannabicyclol (**8**) in $CDCl_3$

Iodine-mediated annulation of homo-isoprenylchromenes to benzo[*c*]chromenes: synthesis of CBN (5). To a stirred solution of CBC (300 mg, 0,954 mmol) in toluene (20 mL), iodine (472 mg, 1,860 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 9:1, Rf CBC= 0,27, Rf product= 0,29). After 3 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford CBN (**5**) as a brown oil (236 mg, 82%).

One-pot total synthesis of CBN. To a stirred solution of olivetol (**11**, 100 mg, 0,554 mmol) toluene (5mL), citral (**10**, 91 µL, 0,533 mmol) and *n*-butylamine (53 µL, 0,533 mmol) were added. The mixture was refluxed overnight, then cooled to room temperature. Dowex 50 W X 8 (200 mg) was added, and the solution was stirred for 10 minutes at room temperature then filtered over celite pad in a new round bottomed flask. To the filtered solution, iodine (268 mg, 1,066 mmol) was added. The mixture was refluxed for 3 hours, then quenched by addition of sat. Na_2SO_3 and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford CBN (**5**) as a brown oil (94 mg, 0.305 mmol, 55% yield).

The spectra obtained for cannabinol (**5**) matched those reported in the literature.[4]

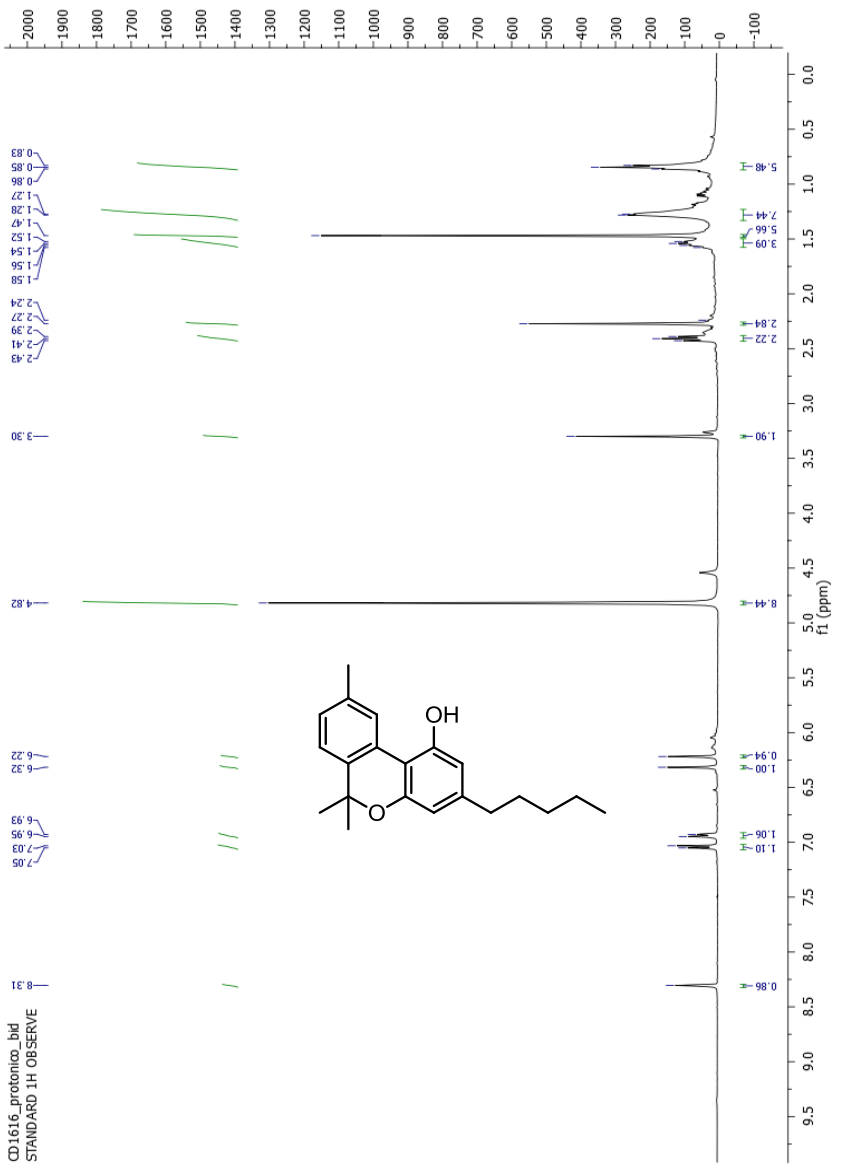

Figure S4. ^{1}H NMR spectrum of cannabinol (**5**) in CD_3OD

Synthesis of 14a. To a stirred solution of **13a** (260 mg, 0.914 mmol) in toluene (20 mL), iodine (463 mg, 1.828 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 9:1, Rf **13a**= 0.55, Rf product= 0.45). After 2 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 98:2 solution to obtain compound **14a** as a brown oil (207 mg, 80% yield). Compound **14a** was identified on the basis of a comparison of its spectral data with those reported in the literature.[5]

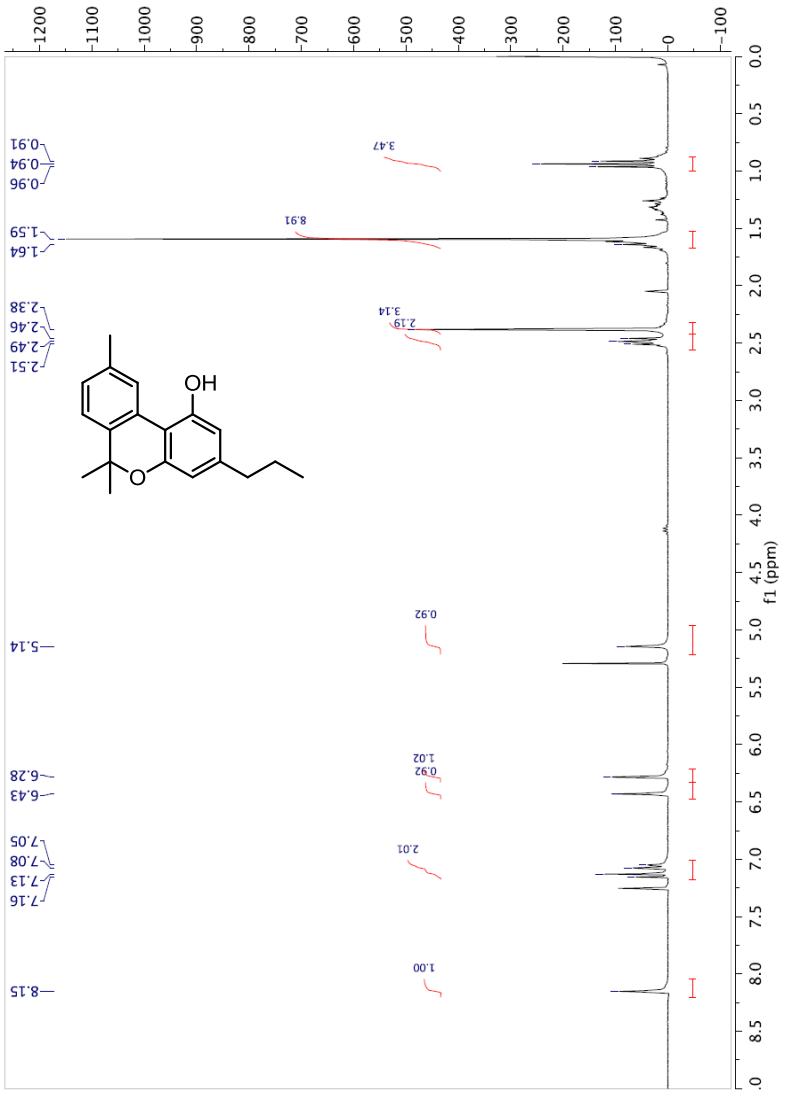

Figure S5. ^{1}H NMR spectrum of compound **14a** in $CDCl_3$

Synthesis of 14b: To a stirred solution of **13b** (300 mg, 1.161 mmol) in toluene (30 mL), iodine (590 mg, 2.323 mmol) was added. The mixture was refluxed and monitored by TLC (PE-CH_2Cl_2 6:4, Rf **13b**= 0.35, Rf product= 0.42). After 2 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford compound cannabiorcol (**14b**) as a brown solid (188 mg, 63%). Compound **14b** was identified on the basis of a comparison of its spectral data with those reported in the literature.[6]

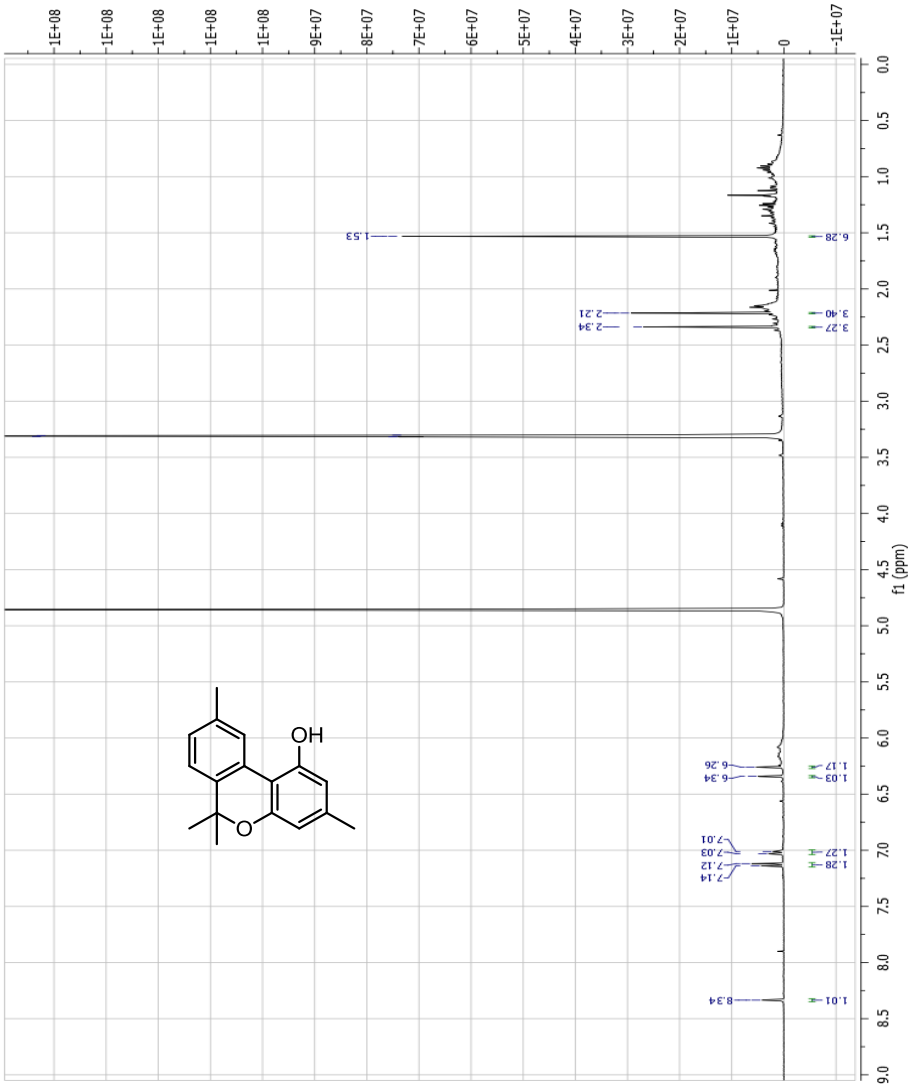

Figure S6. ^{1}H NMR spectrum of compound **14b** in $CDCl_3$

Synthesis of 14c: To a stirred solution of **13c** (200 mg, 0.540 mmol) in toluene (20 mL), iodine (273 mg, 1.080 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 9:1, Rf **13c**= 0.38, Rf product= 0.44). After 2 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford compound **14c** as a brown solid (165 mg, 83%). Compound **14c** was identified on the basis of a comparison of its spectral data with those reported in the literature.[7]

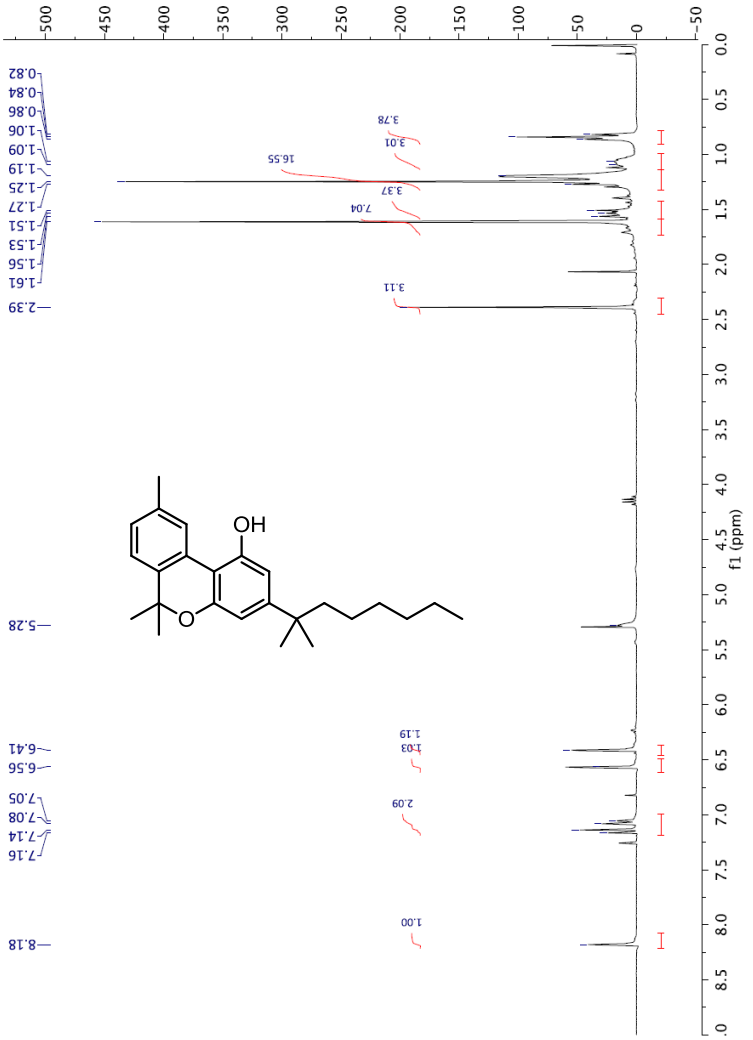

Figure S7. ^{1}H NMR spectrum of compound **14c** in $CDCl_3$

Synthesis of 14d: To a stirred solution of **13d** (280 mg, 0.774 mmol) in toluene (20 mL), iodine (393 mg, 1.549 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 9:1, Rf **13d** = 0.44, Rf product = 0.46). After 2 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford compound **14d** as dark yellow oil (113 mg, 41%).

ESIMS *m/z* 343 $[M - H]^-$; HRESIMS *m/z* $[M - H]^-$ 343.1700 (calcd for $C_{24}H_{23}O_2$, 343.1704).

^{1}H NMR (CD_3OD, 700 MHz): δ 8.34 (1H, s, H-8), 7.26-7.14 (overlapped, H-7, H-4' to H-8'), 7.03 (1H, d, *J* = 7.0 Hz, H-8), 6.36 (1H, s, H-2), 6.26 (1H, s, H-4), 2.88 (2H, t, *J* = 7.2 Hz, H-1′), 2.78 (2H, t, *J* = 7.2 Hz, H-2′), 2.34 (3H, s, H-11), 1.53 (6H, s, H-12, H-13).

^{13}C NMR (CD_3OD, 175 MHz): δ 156.5 (C-1), 155.7 (C-4a), 144.2 (C-10a), 143.1 (C-3), 141.8 (C-3'), 129.5 (C-8), 129.3 (C-6'), 128.3 (C-4', C-8'), 128.2 (C-5', C-7'), 126.9 (C-10), 123.3 (C-7), 110.7 (C-4), 110.5 (C-2), 109.8 (C-10b), 78.1 (C-6), 39.0 (C-1'), 38.6 (C-2'), 27.5 (C-12, C-13), 21.6 (C-11).

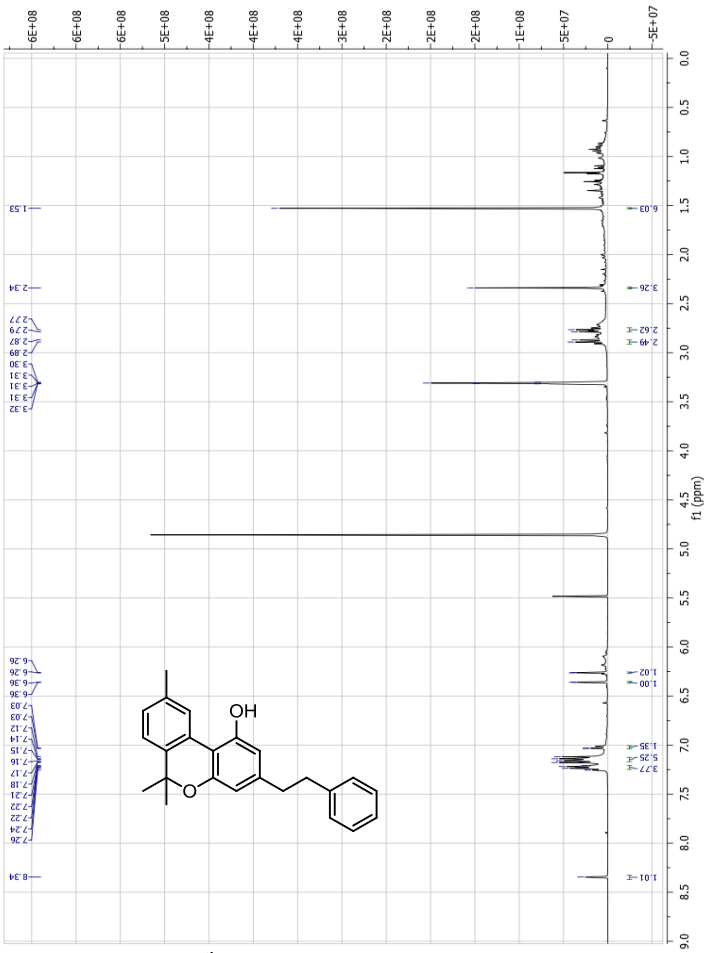

Figure S8. ^{1}H NMR spectrum of compound **14d** in CD_3OD

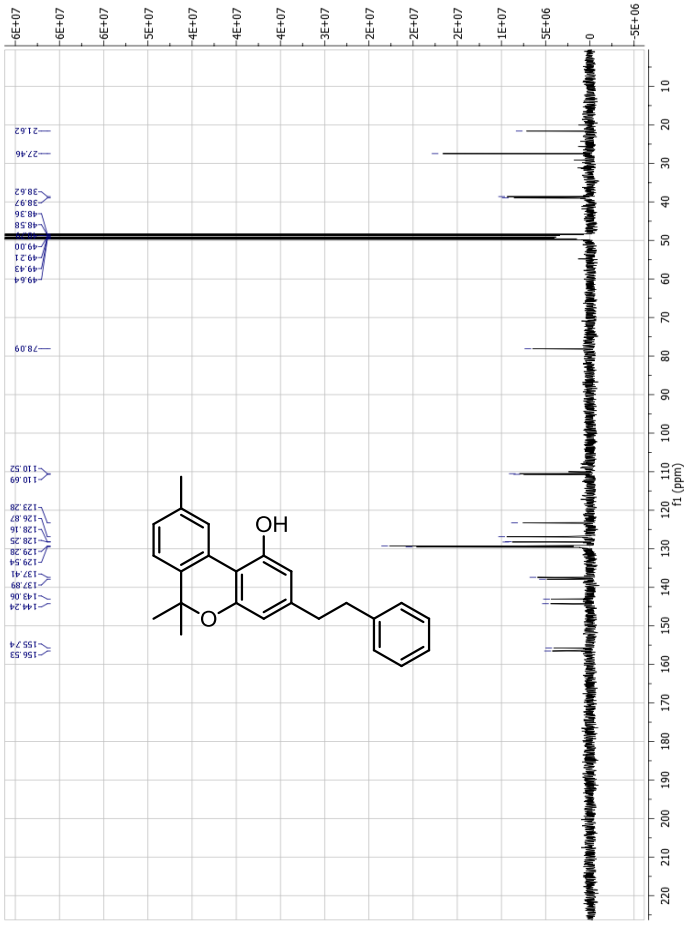

Figure S9. ^{13}C NMR spectrum of compound **14d** in CD_3OD

Reaction of CBC with *N*-iodosuccinimide. To a stirred solution of CBC (220 mg, 0.709 mmol) in toluene (15 mL), *N*-iodosuccinimide (318 mg, 1.418 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 95:5, Rf CBC= 0.16, Rf product mix A= 0.54, Rf product mix B= 0.32). After 3 hours, the reaction was quenched by addition of sat. Na_2SO_3 s.s. and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel with PE-EtOAc 95:5 solution to afford two major product mixtures (A: yellow oil, 132 mg; B: brown oil, 134 mg). Further HPLC purification of fraction A (UV detector set at λ_{max} 227 nm; flow 1.0 mL/min) using as eluent a gradient from MeOH/H_2O (0.1% HCOOH) 8:2 to MeOH in 15 min afforded pure compound **17** (85 mg, 21%). Further HPLC purification of fraction B (UV detector set at λ_{max} 227 nm; flow 1.0 mL/min) using as eluent a gradient from MeOH/H_2O (0.1% HCOOH) 6:4 to MeOH in 25 min afforded pure compounds **15** (64.3 mg, 20.6%) and **16** (21.1 mg, 5.6%).

Compound 15. ESIMS *m/z* 441 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 441.1290 (calcd for $C_{21}H_{30}IO_2$, 441.1285). ^{1}H NMR (CD_3OD, 700 MHz) δ 6.69 (1H, d, *J* = 10.0 Hz, H-1′), 6.32 (1H, s, H-4), 5.56 (1H, d, *J* = 10.0 Hz, H-2’), 5.10 (1H, t, *J* = 7.2 Hz, H-6’), 2.63 (2H, t, *J* = 7.5 Hz, H-1”), 2.09 (2H, m, H-5’), 1.66 (2H, overlapped, H-4’), 1.65 (3H, s, H-8’), 1.56 (3H, s, H-10’), 1.55 (2H, overlapped, H-2”), 1.37 (4H, m, H-3”-4”), 1.34 (3H, s, H-9’), 0.93 (3H, t, *J* = 6.4 Hz, H-5‴). ^{13}C NMR (CD_3OD, 175 MHz): δ 157.8 (C-1), 153.0 (C-5), 143.0 (C-3), 131.6 (C-7'), 127.5 (C-2'), 123.9 (C-6'), 117.5 (C-1'), 109.9 (C-6), 109.4 (C-4), 87.0 (C-2), 77.9 (C-3'), 40.9 (C-4'), 40.7 (C-1''), 31.3 (C-3''), 29.6 (C-2''), 25.1 (C-5'), 22.3 (C-8', C-4''), 17.2 (C-9'), 13.0 (C-5'').

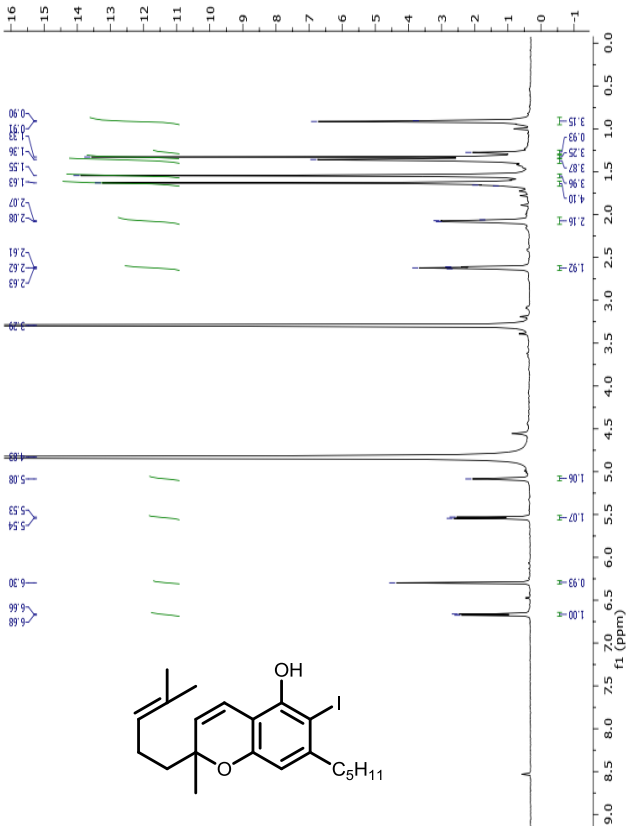

Figure S10. ^{1}H NMR spectrum of compound **15** in CD_3OD

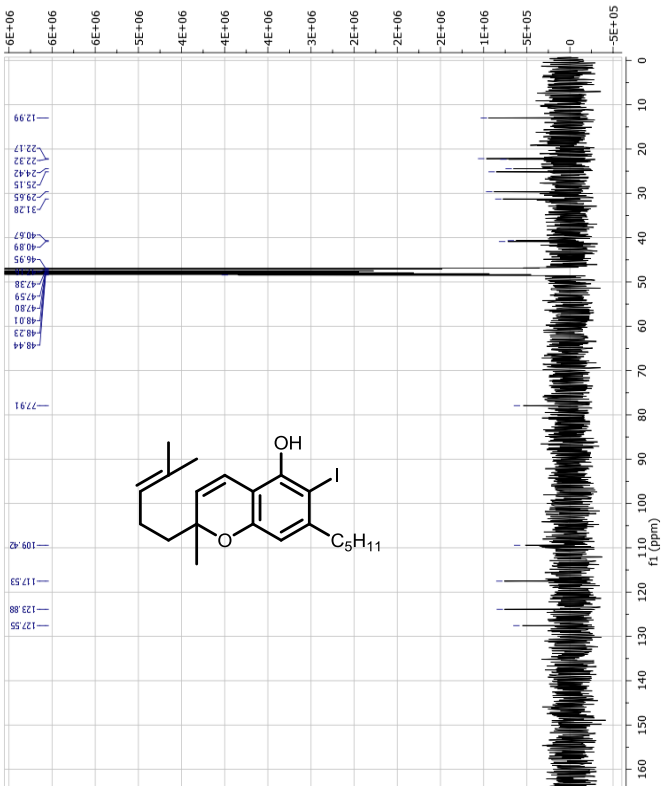

Figure S11. ^{13}C NMR spectrum of compound **15** in CD_3OD

Compound 16. ESIMS *m/z* 567 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 567.0241 (calcd. for $C_{21}H_{29}I_2O_2$, 567.0251).^{1}H NMR (CD_3OD, 700 MHz) δ 6.63 (1H, d, *J* = 10.0 Hz, H-1′), 5.57 (1H, d, *J* = 10.0 Hz, H-2’), 5.12 (1H, t, *J* = 7.1 Hz, H-6’), 3.10 (2H, t, *J* = 7.5 Hz, H-1”), 2.09 (1H, m, H-5’a), 2.03 (1H, m, H-5’b), 1.92 (1H, m, H-4’a),1.66 (1H, overlapped, H-4’b), 1.65 (3H, s, H-8’), 1.57 (3H, s, H-10’), 1.55 (2H, overlapped, H-2”), 1.40 (3H, s, H-9’), 1.37 (4H, m, H-3”-4”), 0.96 (3H, s, H-5″). ^{13}C NMR (CD_3OD, 175 MHz): δ 157.1 (C-1), 151.2 (C-5), 146.5 (C-3), 131.6 (C-7'), 128.6 (C-2'), 123.9 (C-6'), 117.5 (C-1'), 110.7 (C-6), 81.7 (C-2), 80.4 (C-3'), 79.0 (C-4), 41.4 (C-4'), 40.7 (C-1''), 31.3 (C-4''), 29.6 (C-2''), 25.1 (C-5'), 25.2 (C-8'), 22.3 (C-4''), 17.2 (C-9'), 13.0 (C-5'').

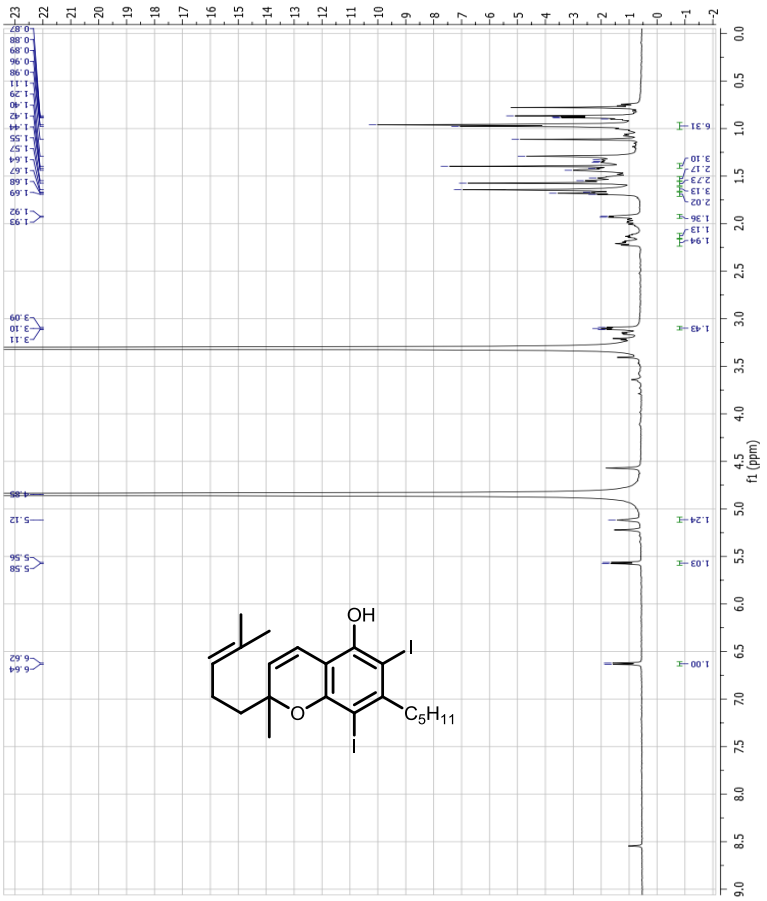

Figure S12. ^{1}H NMR spectrum of compound **16** in CD_3OD

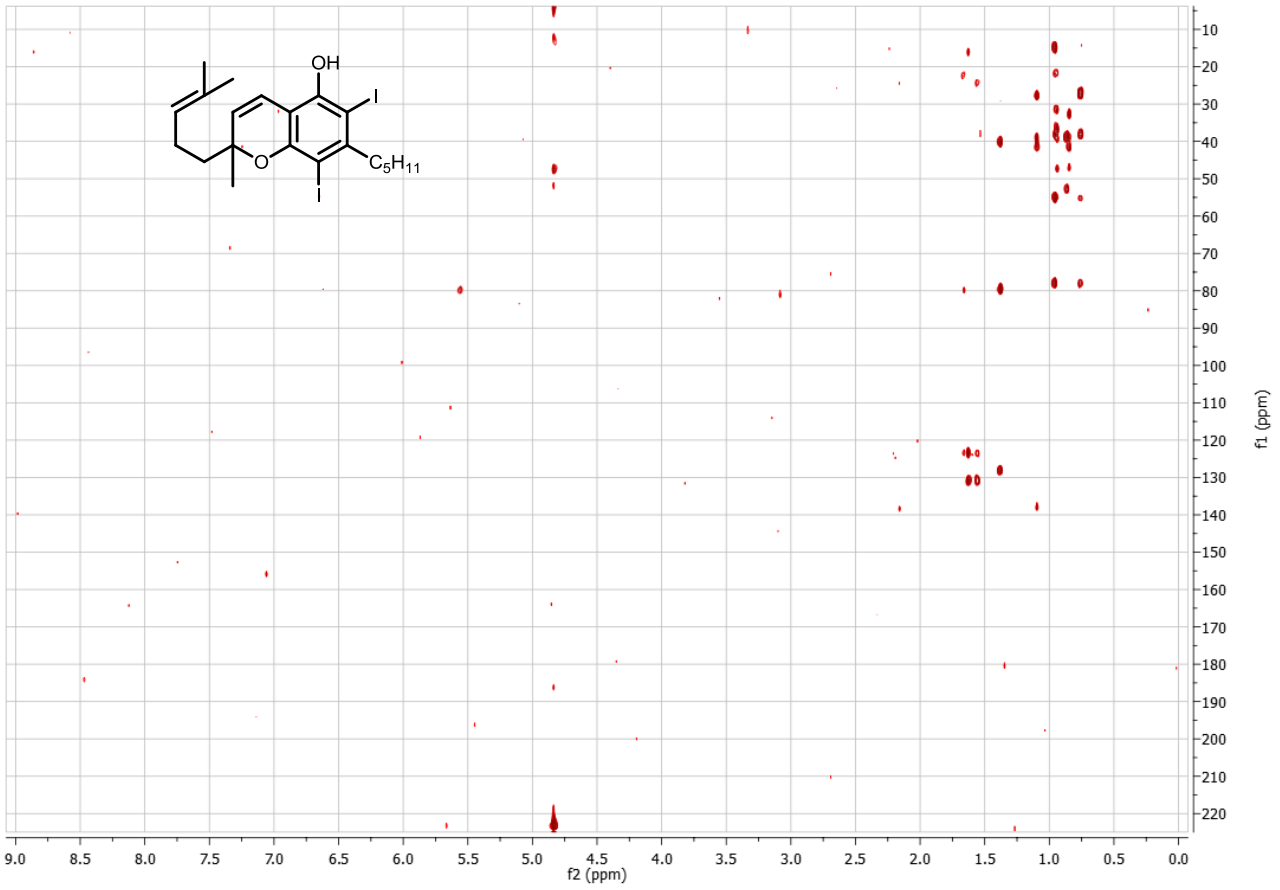

Figure S13. 2D NMR HMBC spectrum of compound **16** in CD_3OD

Compound 17. ESIMS *m/z* 567 $[M + H]^+$; HRESIMS m/z $[M + H]^+$ 567.0239 (calcd for $C_{21}H_{29}I_2O_2$, 567.0251).^{1}H NMR (CD_3OD, 700 MHz) δ 6.42 (1H, s, H-4), 4.98 (1H, bs, H-2'), 3.00 (1H, bs, H-1'), 2.76 (1H, m, H-1"a), 2.68 (1H, m, H-6'), 2.61 (1H, m, H-1"b), 2.16 (1H, td, *J* = 13.9, 6.8 Hz, H-4'a), 1.68 (1H, dd, *J* = 15.5, 5.6 Hz H-5'a), 1.55 (6H, s, H-8'-10'), 1.38-1.29 (6H, m, H-3"-4"-4'b-5'b), 1.07 (3H, s, H-9'), 0.92 (3H, t, *J* = 6.9 Hz, H-5‴), 0.53 (1H, qd, *J* = 12.7, 6.1 Hz, H-5); ^{13}C NMR (CD_3OD, 125 MHz): δ 157.7 (C-1), 153.2 (C-5), 143.0 (C-3), 109.7 (C-6), 109.4 (C-4), 87.3 (C-2), 86.2 (C-7'), 76.7 (C-3'), 45.1 (C-6'), 40.7 (C-1''), 35.1 (C-2'), 32.0 (C-4'), 31.3 (C-3''), 29.6 (C-2''), 28.1 (C-8'), 25.5 (C-1'), 23.5 (C-9'), 23.2 (C-10'), 22.4 (C-4''), 21.5 (C-5'), 13.0 (C-5'').

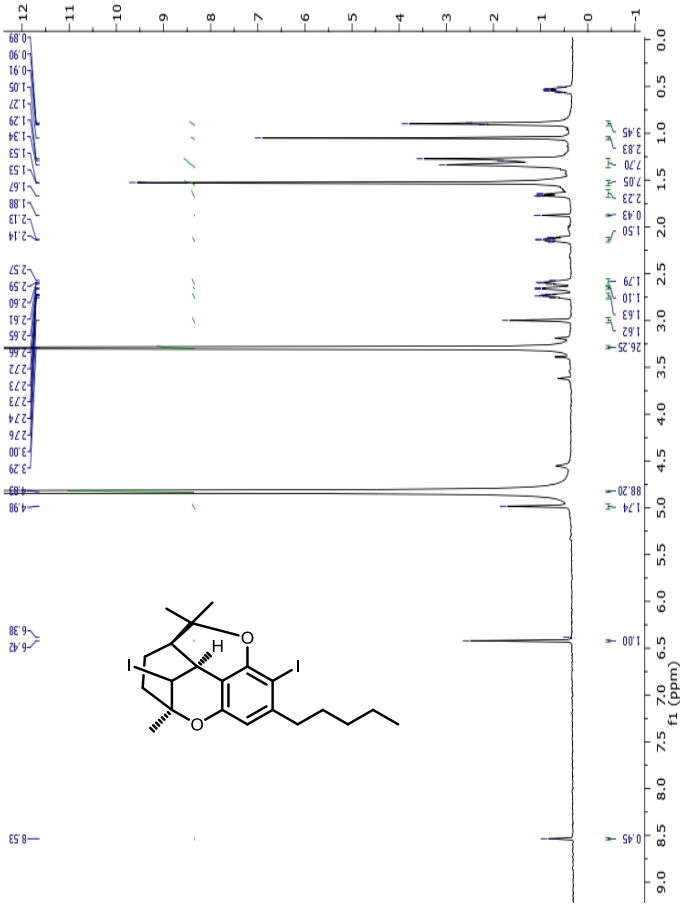

Figure S14. ^{1}H NMR spectrum of compound **17** in CD_3OD

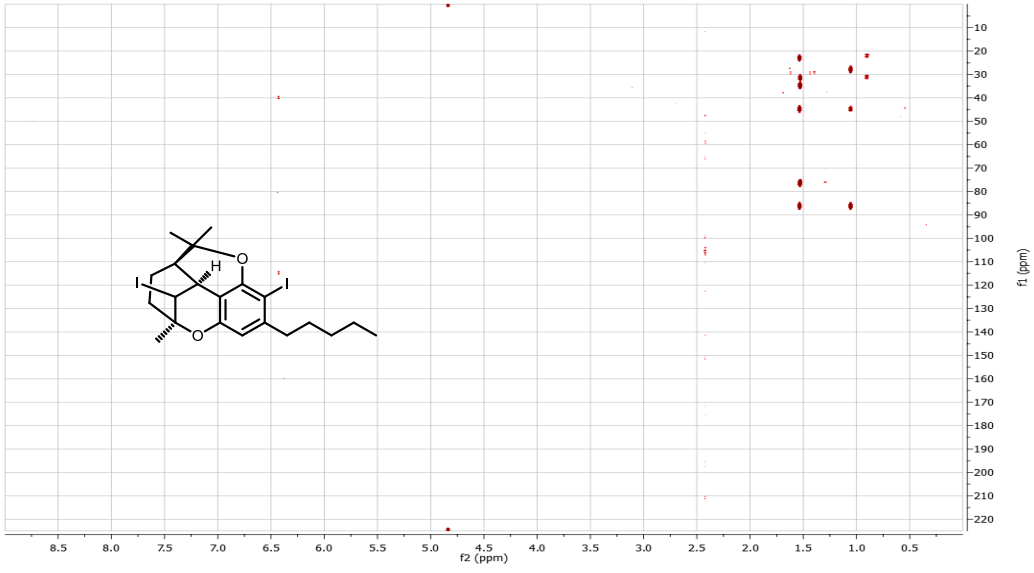

Figure S15. 2D HMBC NMR spectrum of compound **17** in CD_3OD

Reaction of pyranopyrones with iodine. To a stirred solution of ferprenine (300 mg, 1.035 mmol) in toluene (20 mL), iodine (515 mg, 2.03 mmol) was added. The mixture was refluxed and monitored by TLC (PE-EtOAc 9:1, Rf ferprenine= 0.40, Rf product mix= 0.54). After 3 hours, the reaction was quenched by addition of sat. Na_2SO_3 and extraction with EtOAc. After drying (Na_2SO_4) and evaporation, the residue was purified by gravity column chromatography on silica gel to afford 180 of brown oil. Further HPLC purification (UV detector set at λ_{max} 227 nm; flow 1.0 mL/min) using as eluent a gradient from CH_3CN/H_2O (0.1% HCOOH) 7:3 to CH_3CN in 20 min afforded pure compounds **19** (11.3 mg, 3.7%), **20a** (57.4 mg, 18.7%) and **20b** (61.9 mg, 20.2%). When the same reaction and purification conditions were applied to compound **21** (200 mg, 0.77 mmol), compounds **22a** and **22b** (mixture 66.3 mg, 33.2%) were obtained.

Compound 19. ESIMS *m/z* 293 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 293.1181 (calcd. for $C_{19}H_{17}O_3$, 293.1172).^{1}H NMR (CD_3OD, 500 MHz) δ 8.41 (1H, s, H-13), 7.95 (1H, d, *J* = 8.0 Hz, H-1), 7.66 (1H, t, *J* = 8.0 Hz, H-2), 7.39 (2H, overlapped, H-3, H-4), 7.23 (1H, d, *J* = 7.8 Hz, H-16), 7.19 (1H, d, *J* = 7.8 Hz, H-15), 2.38 (3H, s, H-17), 1.77 (6H, s, H-18-19). ^{13}C NMR (CD_3OD, 125 MHz) δ 164.5 (C-9), 159.8 (C-7), 152.3 (C-5), 144.2 (C-11), 137.9 (C-14), 132.2 (C-2), 131.2 (C-6), 129.4 (C-15), 124.8 (C-13), 124.7 (C-3), 123.7 (C-1), 123.5 (C-12), 122.5 (C-16), 116.1 (C-4), 101.9 (C-8), 81.1 (C-10), 25.2 (C-18, C-19), 20.0 (C-17).

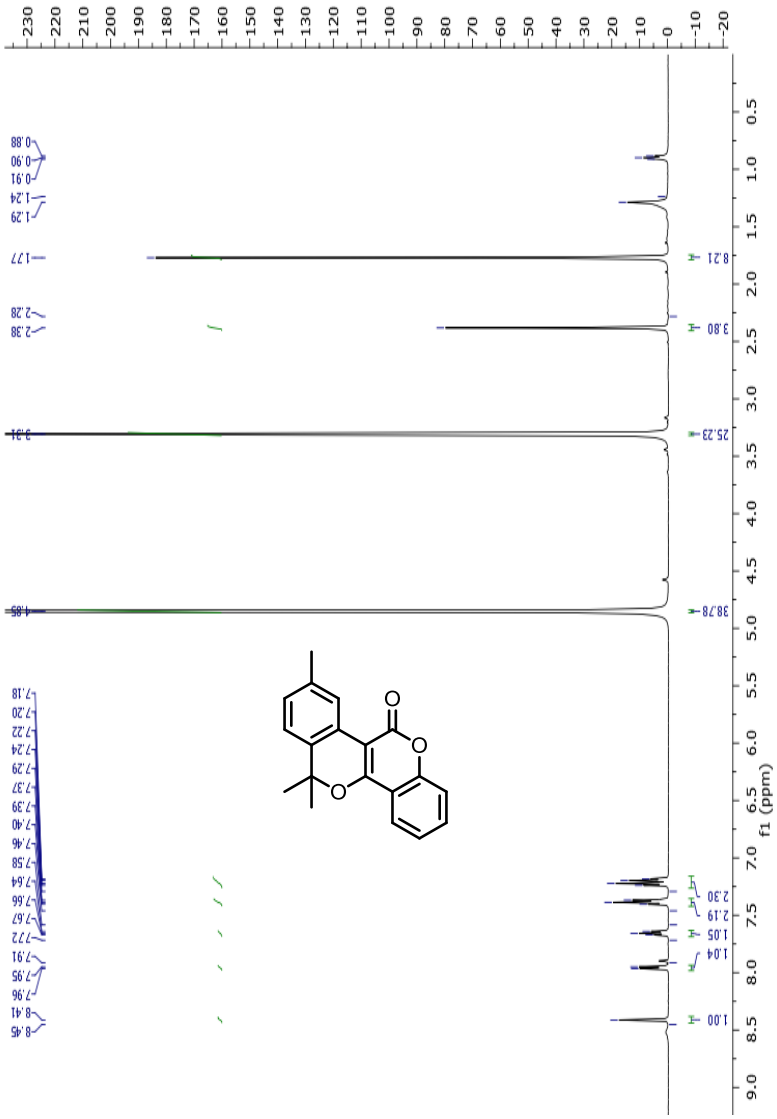

Figure S16. ^{1}H NMR spectrum of compound **19** in CD_3OD

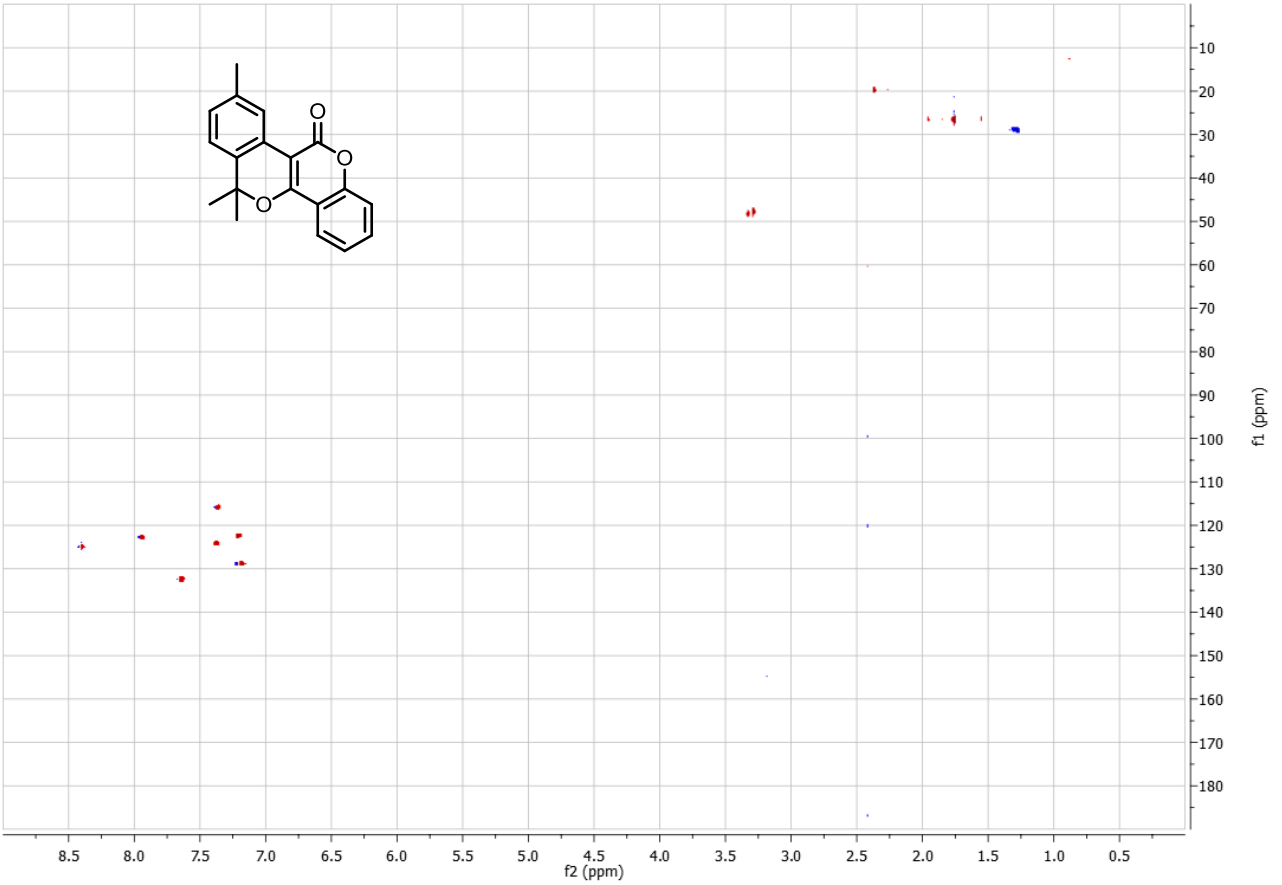

Figure S17. 2D NMR HSQC spectrum of compound **19** in CD_3OD

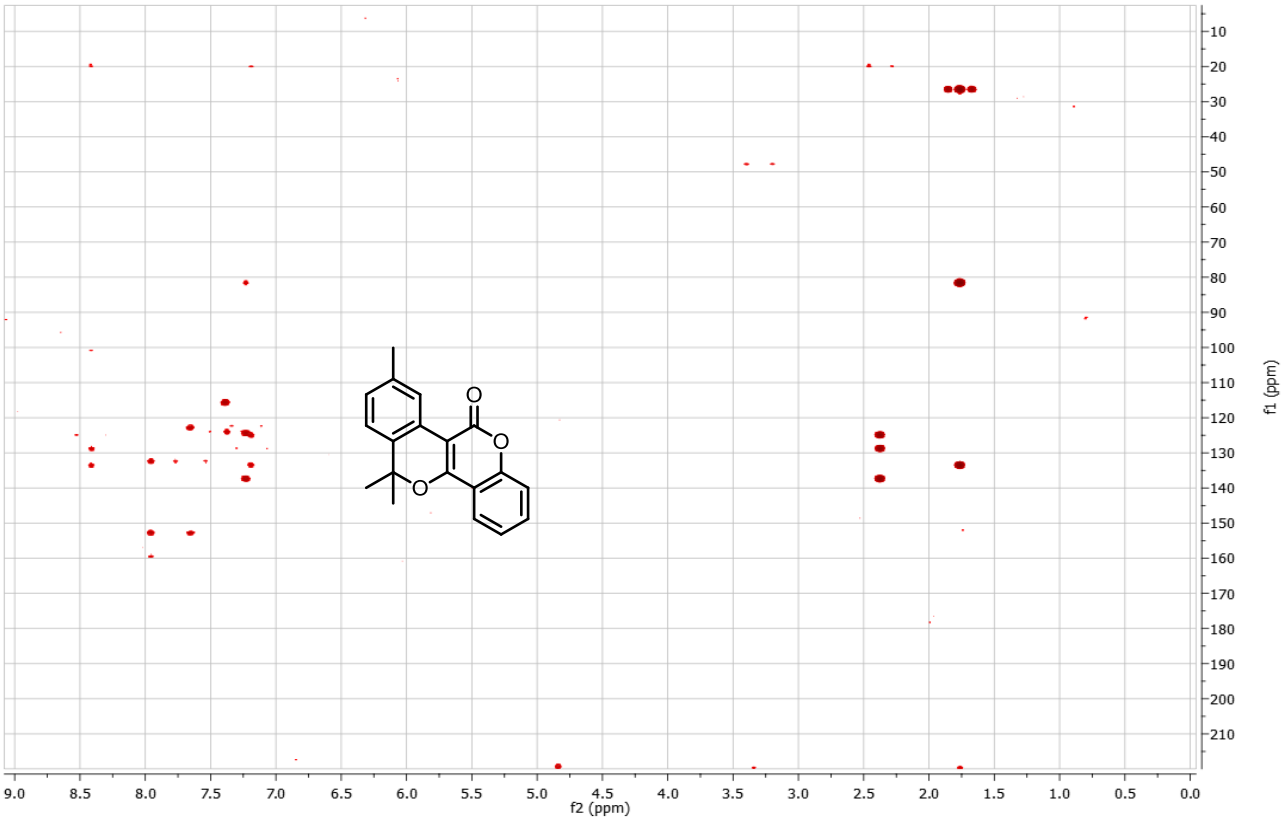

Figure S18. 2D NMR HMBC spectrum of compound **19** in CD_3OD

Compound 20a. ESIMS *m/z* 297 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 297.1501 (calcd for $C_{19}H_{21}O_3$, 297.1485).^{1}H NMR (CD_3OD, 500 MHz) δ 7.86 (1H, d, *J* = 7.8 Hz, H-1), 7.58 (1H, t, *J* = 7.8 Hz, H-3), 7.31 (1H, t, *J* = 7.8 Hz, H-2), 7.29 (1H, d, *J* = 7.8 Hz, H-4), 4.18 (1H, bs, H-12), 2.57 (1H, dd, *J* = 14.9, 5.4 Hz, H-14a), 2.12 (1H, dt, *J* = 13.8, 2.4 Hz, H-15a), 1.96 (1H, dd, *J* = 13.3, 2.2 Hz, H-11a), 1.93 (3H, s, H-19), 1.89 (1H, overlapped, H-11b), 1.81 (1H, overlapped, H-14b), 1.69 (3H, s, H-18), 1.67 (1H, overlapped, H-15b), 1.53 (3H, s, H-17); ^{13}C NMR (CD_3OD, 125 MHz) δ 164.5 (C-9), 162.1 (C-7), 153.2 (C-5), 130.1 (C-3), 127.4 (C-13), 123.0 (C-16), 122.3 (C-2), 120.6 (C-1), 114.6 (C-4), 79.4 (C-10), 38.2 (C-15), 34.7 (C-11), 28.7 (C-12), 25.3 (C-17), 20.5 (C-14), 18.2 (C-18), 17.8 (C-19).

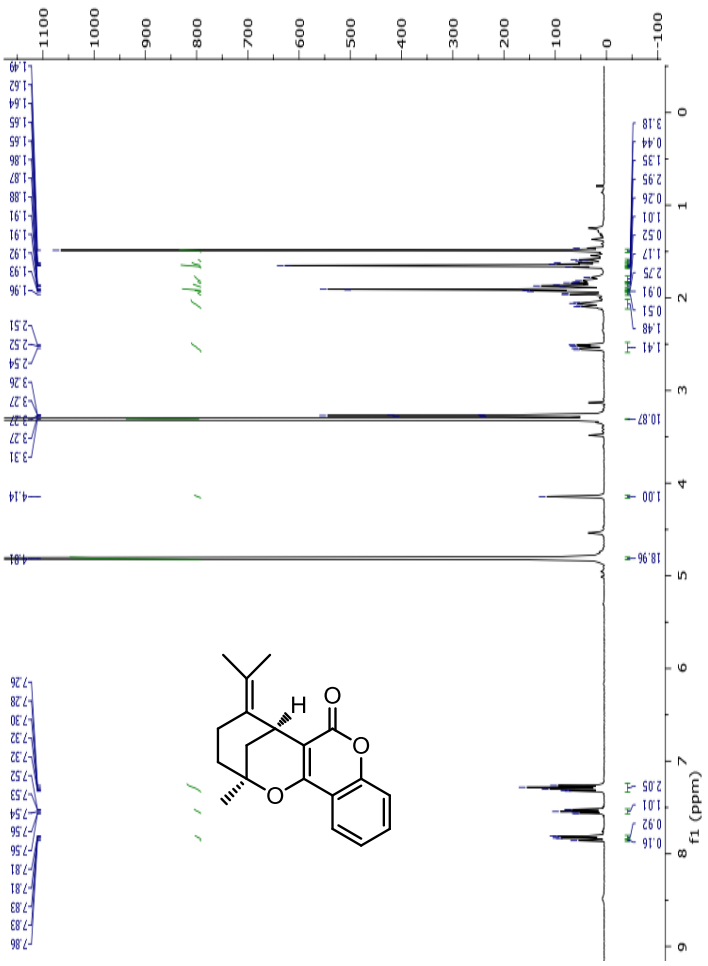

Figure S19. ^{1}H NMR spectrum of compound **20a** in CD_3OD

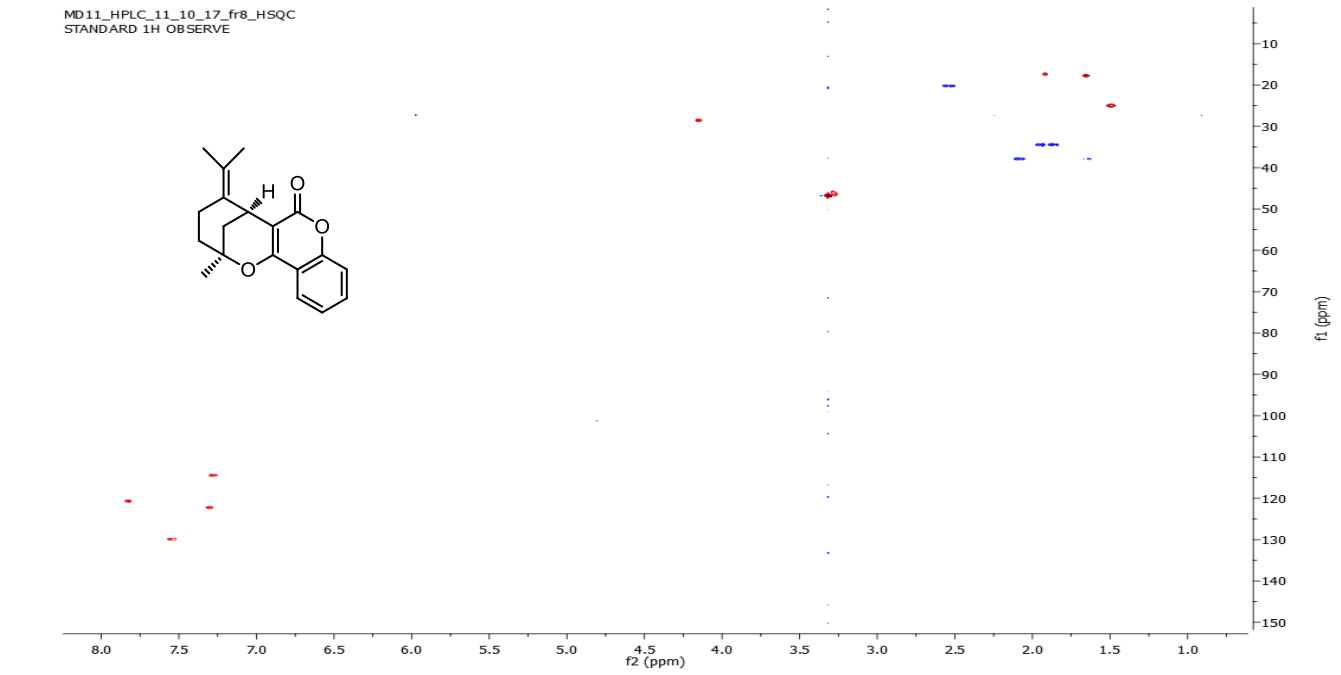

Figure S20. 2D HSQC NMR spectrum of compound **20a** in CD_3OD

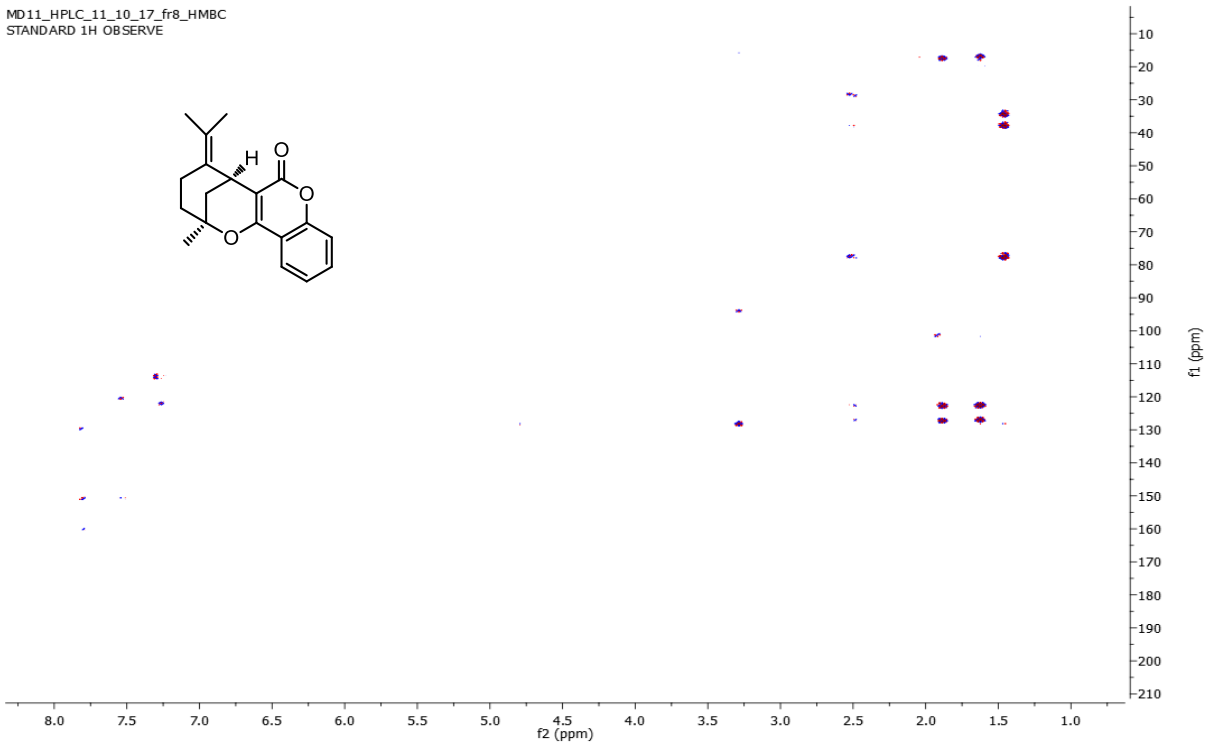

Figure S21. 2D HMBC NMR spectrum of compound **20a** in CD_3OD

Compound 20b. ESIMS *m/z* 297 $[M + H]^+$; HRESIMS *m/z* $[M + H]^+$ 297.1481 (calcd for $C_{19}H_{21}O_3$, 297.1485).^{1}H NMR (CD_3OD, 500 MHz) δ 7.81 (1H, d, *J* = 7.8 Hz, H-1), 7.57 (1H, t, *J* = 7.9 Hz, H-3), 7.32 (1H, overlapped, H-2), 7.30 (1H, overlapped, H-4), 5.32 (1H, t, *J* = 3.1 Hz, H-14), 3.69 (1H, t, *J* = 3.3 Hz, H-12), 2.54-2.51 (3H, overlapped, H-11-16), 2.11 (1H, dd, *J* = 13.02, 3.3 Hz, H-15a) 1.88 (1H, d, *J* = 13.0 Hz, H-15b), 1.65 (3H, s, H-17), 1.12 (3H, d, *J* = 6.8 Hz, H-19), 1.00 (3H, d, *J* = 6.8 Hz, H-18); ^{13}C NMR (CD_3OD, 125 MHz) δ 164.9 (C-9), 162.1 (C-7), 153.6 (C-5), 150.7 (C-13), 132.9 (C-3), 125.3 (C-2), 123.6 (C-1), 117.4 (C-4), 116.3 (C-14), 105.3 (C-8), 80.4 (C-10), 41.6 (C-11), 35.6 (C-15), 33.7 (C-16), 30.1 (C-12), 28.3 (C-17), 22.7 (C-18), 21.1 (C-19).

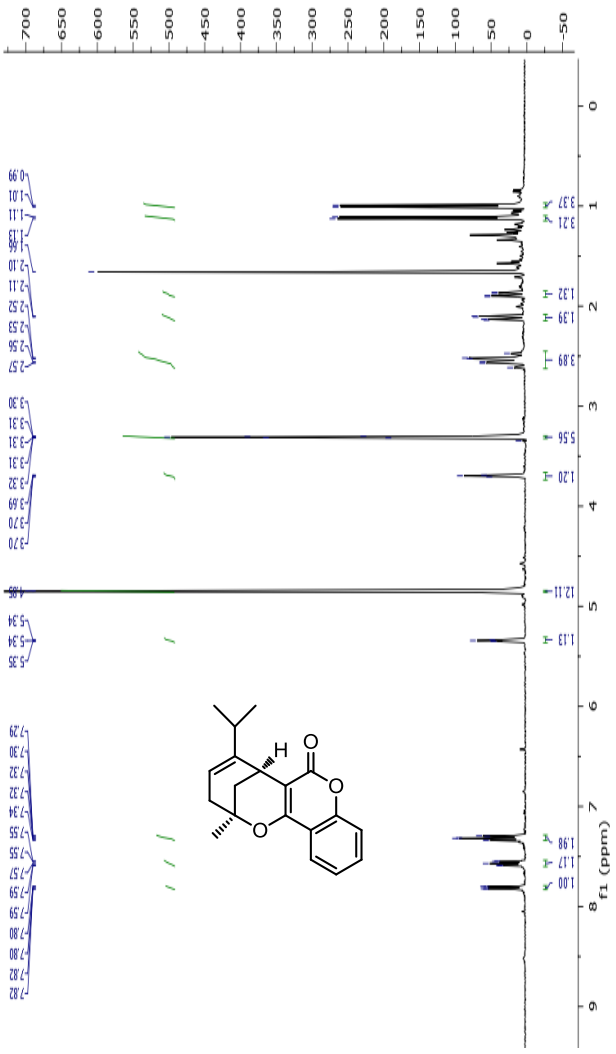

Figure S22. ^{1}H NMR spectrum of compound **20b** in CD_3OD

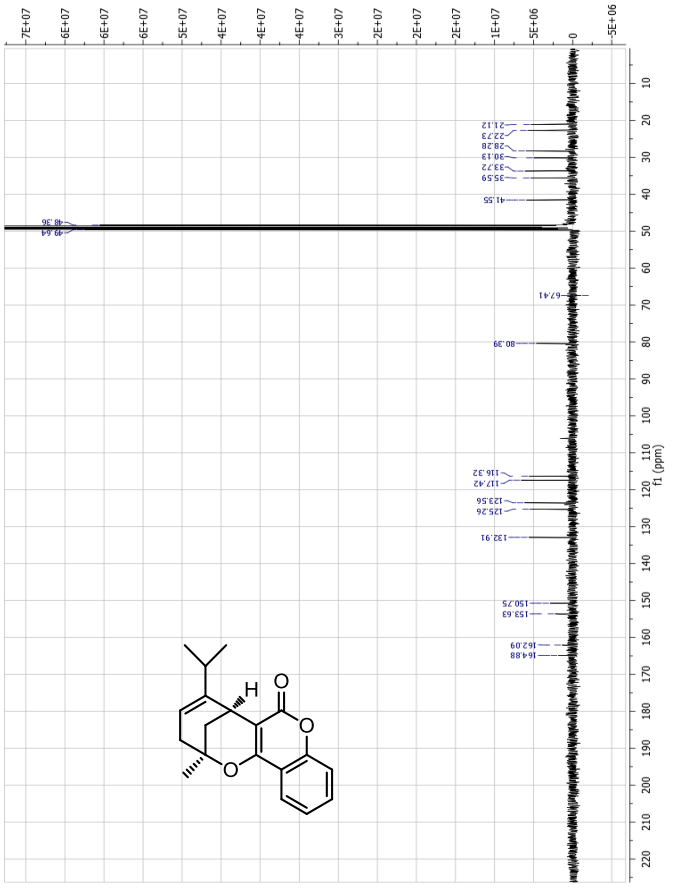

Figure S23. ^{13}C NMR spectrum of compound **20b** in CD_3OD

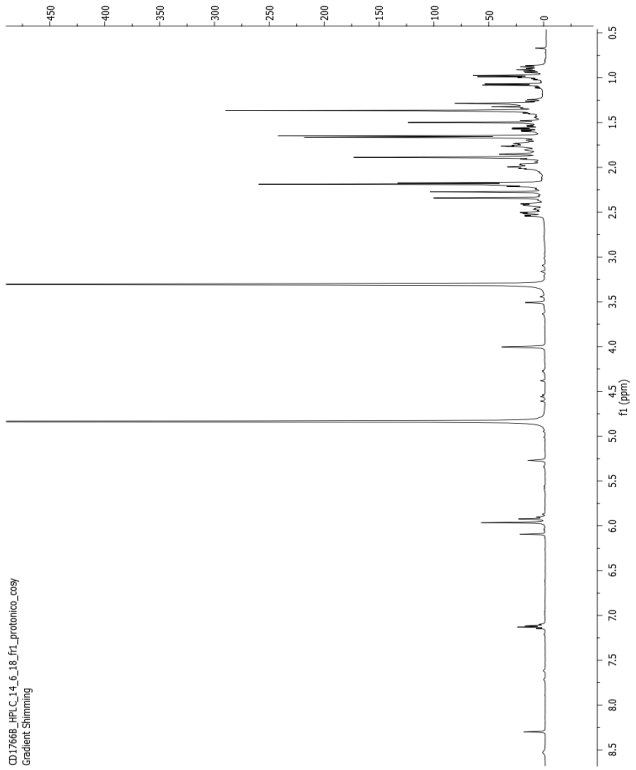

Figure S24. ^{1}H NMR spectrum of the mixture **22a/b** in CD_3OD

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