Novel "Reverse Kahne-Type Glycosylation": Access to O-, N- and C-Linked Epipodophyllotoxin Conjugates.

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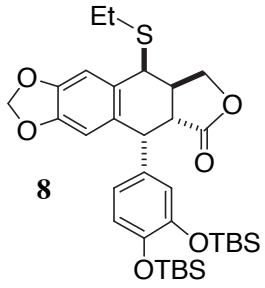
SUPPORTING INFORMATION



8

Using Br_2Mg-OEt_2 as Lewis Acid

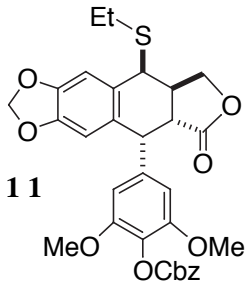
To a solution of SEM ether **7** (195 mg, 0.27 mmol) in Et_2O (4 mL) and PhH (1 mL) was added $MgBr_2$-OEt_2 complex (127 mg 0.49 mmol) under Ar. EtSH (61 μL, 0.82 mmol) was then added at 0 °C, dropwise, via syringe. After 8 h (0 °C→rt), additional Br_2Mg-OEt_2 (40 mg, 0.15 mmol) and EtSH (20 μL; 0.27 mmol) were added. Within 3 h the reaction was judged to be complete by TLC, and was quenched by the addition of sat'd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10→30% EtOAc-hexanes) gave **8** (68 mg, 40%) in a first fraction, and **9** (64 mg, 40%) in a second fraction.

For **8**: $[\alpha]^{21}_D$ -100.5 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.89 (s, 9 H), 0.95 (s, 9 H), 1.33 (t, *J* = 7 Hz, 3 H), 2.46-2.64 (m, 2 H), 3.05-3.17 (m, 1 H), 3.20 (dd, *J* = 5, 14 Hz, 1 H), 4.14 (d, *J* = 4 Hz, 1 H), 4.36 (m, 2 H), 4.45 (d, *J* = 5 Hz, 1 H), 5.90 (d, *J* = 1 Hz, 1 H), 5.92 (d, *J* = 1 Hz, 1 H), 6.37 (s, 1 H), 6.40 (d, *J* = 2 Hz, 1 H), 6.56 (dd, *J* = 2, 8 Hz, 1 H), 6.65 (d, *J* = 8 Hz, 1 H), 6.89 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.3, -4.2, -4.1, -4.0, 15.0, 18.3, 18.4, 25.8, 25.9, 28.2, 37.4, 42.0, 42.7, 47.2, 69.7, 101.3, 109.7, 109.9, 120.1, 123.4, 123.7, 130.0, 132.1, 133.3, 145.7, 146.0, 147.0, 147.6, 174.4; HRMS (FAB, 3-NBA/NaI) calcd for $C_{33}H_{48}O_6Si_2SNa$ 651.2608, obsd 651.2611.

For **9**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.90 (s, 9 H), 0.95 (s, 9 H), 2.06 (bs, 1 H), 2.71-2.83 (m, 3 H), 4.56 (dd, *J* = 6, 9 Hz, 1 H), 4.50 (d, *J* = 3 Hz, 1 H), 4.06 (t, *J* = 9 Hz, 1 H), 4.72 (d, *J* = 9 Hz, 1 H), 5.92 (s, 1 H), 5.93 (s, 1 H), 6.44 (s, 1 H), 6.53-6.59 (m, 2 H), 6.66 (d, *J* = 8 Hz, 1 H), 7.11 (s, 1 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.3, -4.2, -4.1, -4.0, 18.3, 18.4, 25.8, 25.9, 40.5, 43.1, 45.2, 71.4, 72.8, 101.3, 106.1, 109.8, 120.1, 123.4, 123.5, 132.0, 132.9, 133.0, 145.7, 146.1, 147.5, 147.7, 174.4.

Using F_3B-OEt_2 as Lewis Acid

To a solution of **7** (170 mg, 0.24 mmol) and EtSH (106 μL, 1.43 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added F_3B-OEt_2 (88 μL, 0.71 mmol). After being stirred for 1 h at 0 °C, the reaction mixture was quenched by addition of sat'd $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10% EtOAc-hexanes) gave **8** (125 mg, 83%).

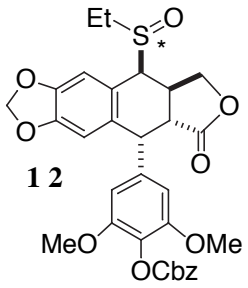


11

To a solution of 4'-O-Cbz-epipodophyllotoxin (500 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) were added ethanethiol (208 μL, 2.82 mmol) and F_3B-OEt_2 (237 μL, 1.88 mmol) at 0 °C. After 1 h at 0°C, the reaction mixture was partitioned between CH_2Cl_2 and aq. $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and evaporated to give **11** (510 mg, 94% yield) of sufficient purity to be used directly in the next step:

R_f 0.6 (1:1 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34 (t, *J* = 7.5 Hz, 3 H), 2.50-2.60 (m, 2 H), 3.03-3.11 (m, 1 H), 3.24 (dd, *J* = 5, 14 Hz, 1 H), 3.67 (s, 6 H), 4.18 (d, *J* = 4.5 Hz, 1 H), 4.35-4.39 (m, 2 H), 4.56 (d, *J* = 5 Hz, 1 H), 5.24 (s, 2 H), 5.92 (d, *J* = 1 Hz, 1 H), 5.94 (d, *J* = 1 Hz, 1 H), 6.30 (s, 2 H), 6.40 (s, 1 H), 6.91 (s, 1 H), 7.30-7.42 (m, 5 H), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 28.2, 37.5, 42.0, 43.7, 47.2,

56.2, 69.8, 70.2, 101.4, 107.8, 109.8, 110.0, 128.2, 128.25, 128.4, 128.5, 130.3, 130.7, 135.0, 138.7, 147.2, 147.6 151.3, 153.0, 174.4.

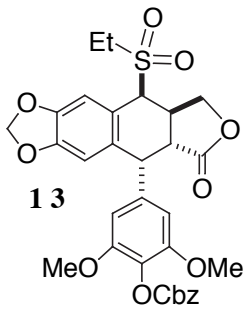


1 2

To a solution of **11** (400 mg, 0.69 mmol) in CH_2Cl_2 (50 mL) at –78° C, was added, dropwise, a solution of m-CPBA (180 mg, 60% w/w, 0.69 mmol) in CH_2Cl_2 (20 ml). Reaction was complete in 5 min (TLC). The reaction mixture was partitioned between CH_2Cl_2 and aq. $NaHCO_3$, then dried (Na_2SO_4), filtered and evaporated. Column chromatography (100% EtOAc) afforded the major diastereomer of sulfoxide(s) **12** (272 mg) in a first fraction, and the minor diastereomer (27 mg) in a second fraction (total yield: 73%). The major diastereomer was used for subsequent conjugation/glycosidation reactions.

Major Diastereomer: $[\alpha]^{25}_D$ –169 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (t, *J* = 7.5 Hz, 3 H), 2.55-2.63 (m, 1 H), 2.78-2.87 (m, 1 H), 3.21-3.30 (m, 1 H), 3.55 (dd, *J* = 5, 14 Hz, 1 H), 3.66 (s, 6 H), 4.07 (d, *J* = 4 Hz, 1 H), 4.44 (t, *J* = 9 Hz, 1 H), 4.65 (d, *J* = 5 Hz, 1 H), 5.03 (dd, *J* = 9, 11 Hz, 1 H), 5.24 (s, 2 H), 5.98 (s, 2 H), 6.22 (s, 2 H), 6.52 (s, 1 H), 6.77 (s, 1 H), 7.30-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.6, 35.9, 42.9, 44.1, 44.4, 56.2, 63.8, 67.6, 70.3, 101.8, 107.7, 109.3, 111.2, 122.9, 128.2, 128.4, 128.47, 128.54, 133.2, 135.0, 138.4, 147.3, 148.9, 151.5, 153.0, 173.5; IR (ATR) 1769, 1601, 1505, 1484, 1239, 1130 cm^{-1}; HRMS (FAB, 3-NBA/NaI) calcd. for $C_{31}H_{30}0_{10}NaS$ [M+Na^+] 617.1457; obsd 617.1450. Anal. Calcd for $C_{31}H_{30}O_{10}S$: C, 62.62; H, 5.05; Found: C, 62.68; H, 5.18.

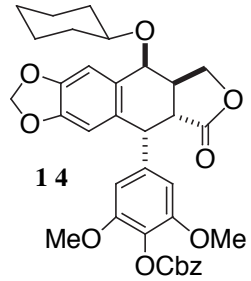
Minor Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7 Hz, 3 H), 2.71-2.95 (m, 2 H), 3.19-3.32 (m, 1 H), 3.67 (s, 6 H), 3.78 (dd, *J* = 6, 15 Hz, 1 H), 4.04 (d, *J* = 5 Hz, 1 H), 4.38 (app t, *J* = 9 Hz, 1 H), 4.54 (dd, *J* = 9, 11 Hz, 1 H), 4.70 (d, *J* = 6 Hz, 1 H), 5.24 (s, 2 H), 5.96 (d, *J* = 1 Hz, 1 H), 6.01 (d, *J* = 1 Hz, 1 H), 6.25 (s, 2 H), 6.59 (s, 1 H), 6.67 (s, 1 H), 7.32-7.43 (m, 5 H).



1 3

To a solution of **11** (50 mg, 80 μmol) in CH_2Cl_2 (3 mL) at 0 °C was added m-CPBA (46 mg, 70% w/w, 0.19 mmol) in CH_2Cl_2 (2 mL). After 30 min, the reaction was quenched by addition of sat'd $NaHCO_3$ (aq) and extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (40% EtOAc-hexanes) gave **13** (45 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7 Hz, 3 H), 2.94-3.06 (m, 2 H), 3.10-3.23 (m, 1 H), 3.65 (s, 6 H), 3.99 (dd, *J* = 6, 14 Hz, 1 H), 4.45 (dd, *J* = 8, 9 Hz, 1 H), 4.49 (d, *J* = 5 Hz, 1 H), 4.70 (d, *J* = 6 Hz, 1 H), 4.94 (dd, *J* = 9, 11 Hz, 1 H), 5.24 (s, 2 H), 5.99 (d, *J* = 1 Hz, 1 H), 6.01 (d, *J* = 1 Hz, 1 H), 6.19 (s, 2 H), 6.57 (s, 1 H), 6.89 (s, 1 H), 7.31-7.41 (m, 5 H).



1 4

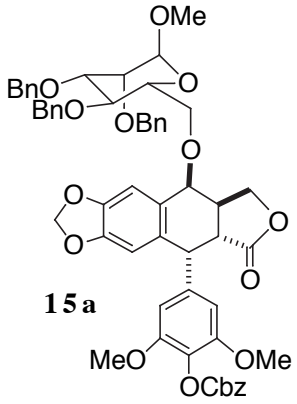
To a solution of **12** (20.0 mg, 0.034 mmol) and cyclohexyl alcohol (17 μL, 0.17 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added AgOTf (18 mg, 0.07 mmol). The resulting suspension was stirred for 16 h at rt. A bicarbonate quench and extractive workup (CH_2Cl_2) were followed by drying (Na_2SO_4), filtration and evaporation. Column chromatography (20% EtOAc/hexanes) afforded **14** as a single C_4-*S*-diastereomer (15.7 mg, 75%). Alternatively, the use of MeOTf (5 eq.) as promoter, under the same reaction conditions, led to a 70% yield of **14**, after 24 h.

R_f 0.6 (1:1 EtOAc/hexanes), $[\alpha]^{25}_D$ –196 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.16-1.43 (m, 4 H), 1.53-1.62 (m, 2 H), 1.72-1.83 (m, 2 H), 1.89-1.97 (m, 1 H), 2.00-2.08 (m, 1 H), 2.75-2.83 (m, 1 H), 3.32 (m, 1 H), 3.37 (dd, *J*= 5, 14 Hz, 1 H), 3.66 (s, 6 H), 4.24 (dd, *J* = 9, 11 Hz, 1 H), 4.36 (t, *J* = 9 Hz, 1 H), 4.60 (d, *J* = 4 Hz, 1 H), 4.61 (d, *J* = 5 Hz, 1 H), 5.25 (s, 2 H), 5.94 (d, *J* = 1.2 Hz, 1H), 5.97 (d, *J* = 1.2 Hz, 1 H), 6.28 (s, 2 H), 6.50 (s, 1 H), 6.81 (s, 1 H), 7.30-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2, 24.3, 25.6, 32.4, 33.2, 38.5, 41.2, 44.0, 56.2, 67.8, 70.3, 71.0, 77.5, 101.4, 107.7, 109.4, 110.5, 128.2, 128.3,

128.4, 128.5, 130.7, 131.8, 135.1, 138.4, 147.2, 148.1, 151.5, 153.1, 175.0; HRMS (FAB, 3-NBA/NaI) calcd for $C_{35}H_{36}0_{10}Na$ [M+Na^+] 639.2204; obsd 639.2206.

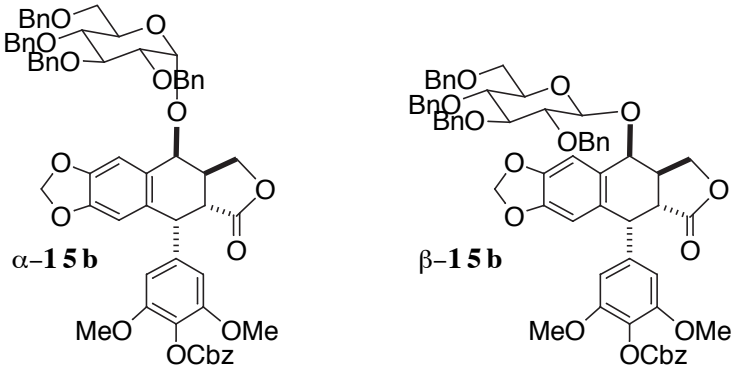
Typical Procedure for "Reverse Kahne-Type Glycosidation/Conjugation."

To a solution of sulfoxide **12** (10 mg, 17 μmol) and 2,6-di-*tert*-butyl-4-methylpyridine (7.0 mg, 34 μmol) in CH_2Cl_2 (1 mL) at –78° C, was added trifluoromethanesulfonic anhydride (5.0 μL, 25 μmol). After 10 min, a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (24 mg, 50 μmol) in CH_2Cl_2 (0.5 mL) was added via cannula, and the reaction mixture was left stirring for 3 h (-78° C). The reaction mixture was diluted with CH_2Cl_2 and washed with water, followed by drying (Na_2SO_4), filtration and evaporation. Flash chromatography (0→50% EtOAc/hexanes) afforded the desired compound (15 mg, 91% yield) as a single (C_4-*S*) diastereomer.



15a

R_f 0.4 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –7.0 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.73-2.81 (m, 1 H), 3.27 (s, 3 H), 3.37 (dd, *J* = 5, 14 Hz, 1 H), 3.62-3.70 (m, 1 H), 3.67 (s, 6 H), 3.71-3.74 (m, 2 H), 3.76-3.79 (m, 1 H), 3.85-3.88 (m, 2 H), 4.31 (t, *J* = 8 Hz, 1 H), 4.38 (dd, *J* = 8, 11 Hz, 1 H), 4.47 (d, *J* = 4 Hz, 1 H), 4.56 (d, *J* = 11 Hz), 4.58 (d, *J* = 5 Hz, 1 H), 4.59 (s, 2 H), 4.68 (d, *J* = 1.5 Hz, 1 H), 4.75 (d, *J* = 12.5 Hz, 1 H), 4.79 (d, *J* = 12.5 Hz, 1 H), 4.89 (d, *J* = 11 Hz, 1 H), 5.25 (s, 2 H), 5.89 (d, *J* = 1.2 Hz, 1 H), 5.94 (d, *J* = 1.2 Hz, 1 H), 6.27 (s, 2 H), 6.50 (s, 1 H), 7.05 (s, 1 H), 7.20-7.43 (m, 20 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.5, 40.9, 43.9, 54.8, 56.2, 67.7, 69.9, 70.3, 72.1 (2 C), 72.5, 74.1, 74.7, 74.9, 75.4, 80.2, 99.2, 101.4, 107.7, 110.3, 110.4, 127.6 (2 C), 127.7, 128.0 (3 C), 128.2, 128.4 (5 C), 128.5, 129.5, 131.8, 135.1, 138.3, 138.32, 138.35, 138.5, 146.8, 148.2, 151.4, 153.1, 174.9; HRMS (FAB, 3-NBA/NaI) calcd for $C_{57}H_{56}0_{15}Na$ [M+Na^+] 1003.3516; obsd 1003.3501.

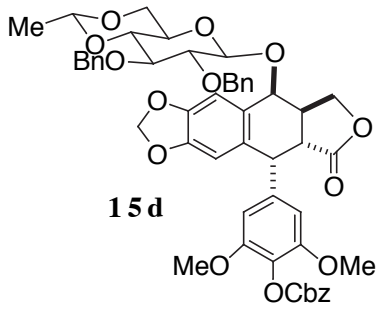


Following the typical glycosidation procedure (but allowing the reaction to proceed from -78 °C to -40°C over 5 h), from sulfoxide **12** (10 mg, 17 μmol) and 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (α:β = 3:1 in $CDCl_3$-from integration of the anomeric carbons in the ^{13}C NMR spectrum) was obtained **15b** (12 mg, 68%; α:β = 2:1). The anomers could be separated by conventional chromatography (33% EtOAc/hexanes) with the minor, β-anomer eluting first. In each case, the anomeric protons were first identified by correlating them with the anomeric carbons through a 2D HMQC experiment. Then the anomeric stereochemistry, and the stereochemistry at C_4 of the aglycon, were established by identifying the appropriate coupling constants using double quantum-filtered, phase-sensitive COSY experiments.

For β-**15b** *(first-eluting):* ^1H NMR (500 MHz, $CDCl_3$) δ 2.80-2.87 (m, 1 H), 3.26 (dd, *J* = 5, 14 Hz, 1 H), 3.43 (app t, *J* = 8 Hz, 1 H), 3.45-3.57 (m, 2 H), 3.60-3.73 (m, 3 H), 3.67 (s, 6 H), 4.23 (t, *J* = 8 Hz, 1H), 4.49 (app t, *J* = 9 Hz, 1 H), 4.53-4.58 (m, 5 H), 4.61 (d, *J* = 5 Hz, 1 H), 4.64 (d, *J* = 8 Hz, 1 H), 4.79 (d, *J* = 11 Hz, 1 H), 4.83 (d, *J* = 11 Hz, 1 H), 4.91 (d, *J* = 11 Hz, 1 H), 4.92 (d, *J* = 4 Hz, 1 H), 5.26 (s, 2 H), 5.90 (d, *J* = 1 Hz, 1 H), 5.96 (d, *J* = 1 Hz, 1 H), 6.27 (s, 2 H), 6.54 (s, 1 H), 6.91 (s, 1 H), 7.02-7.43 (m, 25 H); HRMS (FAB, 3-NBA/NaI) calcd for $C_{63}H_{60}0_{15}Na$ [$M+Na^+$] 1079.3830; obsd 1079.3786.

For α-**15b** *(second-eluting):* ^1H NMR (500 MHz, $CDCl_3$) δ 2.75-2.81 (m, 1 H), 3.38 (dd, *J* = 5, 14 Hz, 1 H), 3.52-3.59 (m, 3 H), 3.63-3.73 (m, 2 H), 3.66 (s, 6 H), 3.87 (appt, *J* = 9 Hz, 1 H), 4.12 (t, *J* = 8 Hz, 1 H), 4.39 (d, *J* = 10 Hz, 1 H), 4.50 (d, *J* = 12 Hz, 1 H), 4.55-4.68 (m, 4 H), 4.75-4.84 (m, 4 H), 4.93 (d, *J* = 11 Hz, 1 H), 4.95(d, *J* = 3 Hz, 1 H), 5.25 (s, 2 H), 5.88 (s, 1 H), 5.93 (s, 1 H), 6.26 (s, 2 H), 6.46 (s, 1 H), 7.01 (s, 1 H), 7.05-7.42 (m, 25 H).

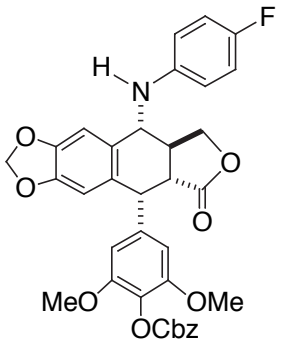
When the same glycosidation was carried out on the β-silyl glycoside; namely, trimethylsilyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside, and sulfoxide **12** (20 mg, 34 μmol) exclusively β-**15b** (23 mg, 65%) was obtained (Table 1, entry **c**).



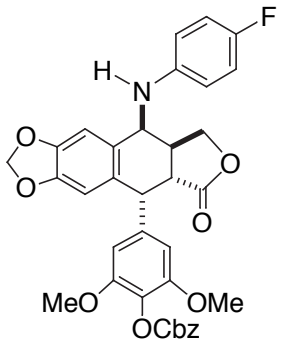
15d

Following the typical reverse glycosylation procedure (from -78 to -40° C over 5 h) from sulfoxide **12** (20 mg, 34 μmol) and trimethylsilyl 4,6-*O*-ethylidene-2,3-*O*-benzyl-β-D-glucopyranoside was obtained **15d** (22 mg, 74%) after flash chromatography (10→50% EtOAc-hexanes).

$[\alpha]^{25}_{D}$ –88.2 (*c* 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, *J* = 5 Hz, 3 H), 2.81-2.88 (m, 1 H), 3.24 (dd, *J* = 5, 14 Hz, 1 H), 3.27-3.31 (m, 1 H), 3.37 (t, *J* = 8 Hz, 1 H), 3.43 (t, *J* = 9 Hz, 1 H), 3.55 (t, *J* = 10 Hz, 1 H), 3.64 (t, *J* = 9 Hz, 1 H), 3.66 (s, 6 H), 4.16 (dd, *J* = 5, 10 Hz, 1H), 4.22 (t, *J* = 8 Hz, 1 H), 4.39 (app t, *J* = 10 Hz, 1 H), 4.51 (d, *J* = 11 Hz, 1 H), 4.57 (d, *J* = 11 Hz, 1 H), 4.60 (d, *J* = 5 Hz, 1 H), 4.73 (q, *J* = 5 Hz, 1 H), 4.75 (d, *J* = 8 Hz, 1 H), 4.76 (d, *J* = 11 Hz, 1 H), 4.86 (d, *J* = 11 Hz, 1 H), 4.89 (d, *J* = 3 Hz, 1 H), 5.25 (s, 2 H), 5.90 (s, 1 H),), 5.97 (s, 1 H), 6.26 (s, 2 H),), 6.54 (s, 1 H),), 6.82 (s, 1 H), 6.98-7.42 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 37.5, 41.2, 44.0, 56.1, 66.0, 67.8, 68.2, 70.3, 73.4, 75.0, 75.4, 80.9, 81.0, 81.6, 99.5, 101.6, 102.3, 107.6, 109.2, 110.7, 127.6, 127.7, 127.8, 128.0, 128.18, 128.22, 128.3, 128.4, 128.5, 128.6, 132.0 (2 C), 135.0, 137.8, 138.2, 138.5, 147.2, 148.7, 151.5, 153.1, 174.6; HRMS (FAB, 3-NBA/LiI) calcd. for $C_{51}H_{50}0_{15}Li$ [M+Li^+] 909.3310; obsd. 909.3285.



(*4R*)-**15e**



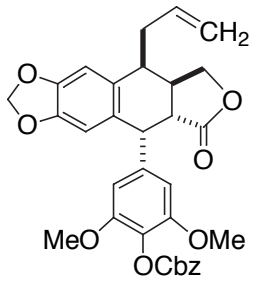
(*4S*)-**15e**

Following the typical reverse glycosylation procedure (but allowing the reaction to proceed from -78 °C to -40°C over 4 h), from sulfoxide **12** (20 mg, 34 μmol) and *p*-fluoroaniline was obtained **15e** (15 mg, 72% total yield) as a 2:1 mixture of (4*S*):(4*R*)-diastereomers. Following initial purification by flash chromatography (EtOAc/hexanes), the diastereomers could be cleanly separated by preparative HPLC (3→5% i-PrOH/hexanes).

(4*S*)-**15e** (*major, first-eluting on HPLC*): R_f 0.5 (1:1 EtOAc/hexanes); $[\alpha]^{25}_{D}$ –217 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 1 H), 2.92-3.00 (m, 1 H), 3.16 (dd, *J* = 5, 14 Hz, 1 H), 3.69 (s, 6 H),

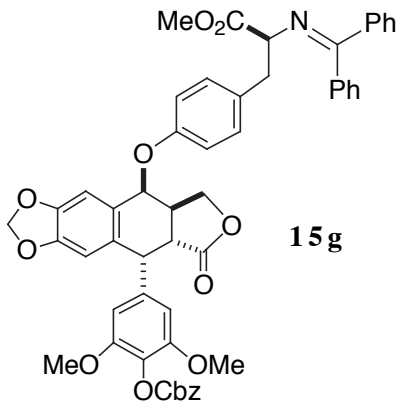
3.99 (dd, *J* = 9, 11 Hz, 1 H), 4.37 (t, *J* = 8.5 Hz, 1 H), 4.58 (d, *J* = 4 Hz, 1 H), 4.62 (d, *J* = 5 Hz, 1 H), 5.25 (s, 2 H), 5.95 (d, *J* = 1 Hz, 1 H),. 5.96 (d, *J* = 1 Hz, 1 H), 6.34 (s, 2 H), 6.47 (dd, *J* = 4, 8.5 Hz, 2 H), 6.52 (s, 1 H), 6.74 (s, 1 H), 6.93 (bt, *J* = 8.5 Hz, 2 H), 7.30-7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.6, 41.8, 43.6, 53.3, 56.2, 68.8, 70.3, 101.6, 107.7, 109.1, 110.0, 113.1 (d, *J* = 7 Hz), 116.1 (d, *J* = 22.5 Hz), 128.2, 128.43, 128.46, 128.5, 130.7, 131.3, 135.1, 138.1, 143.7, 147.8, 148.3, 151.5, 153.1, 156.1 (d, *J*= 232 Hz), 174.6; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -126.9 (bs); HRMS (FAB, 3-NBA/NaI) calcd for $C_{35}H_{30}FN0_9Na$ [M+Na^+] 650.1802; obsd 650.1785.

(4*R*)-**15e** (*minor, second-eluting on HPLC*): R_f 0.5 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –203 (*c* 0.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (s, 1 H), 3.61-3.69 (m, 1 H), 2.92 (dd, *J* = 5, 14 Hz, 1 H), 3.71 (s, 6 H), 3.95 (t, *J* = 9.5 Hz, 1 H), 4.24 (t, *J* = 8.5 Hz, 1 H), 4.61 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 5 Hz, 1 H), 5.26 (s, 2 H), 5.94 (d, *J* = 1 Hz, 1 H),. 5.95 (d, *J* = 1 Hz, 1 H), 6.40 (s, 2 H), 6.52 (s, 1 H), 6.63-6.69 (br, 2 H), 6.92 (bt, *J* = 8.5 Hz, 2 H), 7.13 (bs, 1 H), 7.30-7.44 (m, 5 H); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -125.8 (bs).



15f

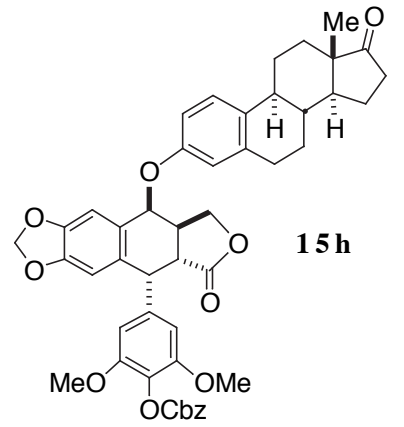
Carrying out the typical sulfoxide activation procedure from sulfoxide **12** (10 mg, 17 μmol) and allyltrimethylsilane, was obtained **15f** (8 mg, 85%), after column chromatography (25% EtOAc/hexanes). R_f 0.6 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –104 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.38-2.45 (m, 1 H), 2.52-2.61 (m, 1 H), 2.88-2.96 (m, 1 H), 3.07 (dd, *J* = 5, 14 Hz, 1 H), 3.24-3.29 (m, 1 H), 3.67 (s, 6 H), 4.21-4.28 (m, 2 H), 4.58 (d, *J* = 5 Hz, 1 H), 5.10 (br d, *J* = 10.5 Hz, 1 H), 5.12 (br d, *J* = 17.5 Hz, 1 H), 5.24 (s, 2 H), 5.79 (ddt, *J* = 6.5, 10, 17 Hz, 1 H), 5.93 (d, *J* = 1 Hz, 1 H), 5.94 (d, *J* = 1 Hz, 1 H), 6.30 (s, 2 H), 6.45 (s, 1 H), 6.71 (s, 1 H), 7.30-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.0, 37.7, 38.5, 42.3, 44.1, 56.2, 68.9, 70.3, 101.3, 107.9, 108.7, 110.2, 116.9, 128.2, 128.3, 128.4, 128.4, 130.5, 133.1, 135.1, 136.6, 139.1, 146.9, 147.2, 151.4, 153.1, 174.9; HRMS (FAB, 3-NBA/NaI) calcd for $C_{32}H_{30}0_9Na$ [M+Na^+] 581.1787; obsd 581.1767.



15g

Following the typical sulfoxide activation procedure from **12** (15 mg, 25 μmol) and N-benzophenone imine, L-tyrosine, methyl ester was obtained **15g** (14 mg, 64%) after column chromatography (30% EtOAc/hexanes).

R_f 0.5 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –332 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.95-3.03 (m, 1 H); 3.05-3.32 (br, 1 H); 3.24 (bd, *J* = 10 Hz, 1 H); 3.44 (dd, *J* = 5, 14 Hz, 1 H), 3.67 (s, 6 H); 3.75 (bs, 3 H); 4.11 (dd, *J* = 9, 11 Hz, 1 H); 4.20-4.34 (br, 1 H); 4.31 (t, *J* = 9 Hz, 1 H); 4.70 (d, *J* = 5 Hz, 1 H); 5.25 (s, 2 H); 5.36 (d, *J* = 4 Hz, 1 H); 5.91 (d, *J* = 1.2 Hz, 1 H); 5.95 (d, *J* = 1.2 Hz, 1 H); 6.55 (s, 1 H); 6.61 (s, 1 H); 6.63-6.74 (br, 2 H); 6.75 (d, *J* = 8 Hz, 2 H); 7.02 (bd, *J* = 5 Hz, 2 H); 7.29-7.43 (m, 11 H); 7.62 (br, 2 H); IR (ATR): 1768, 1736, 1658, 1600, 1506, 1230, 1130 cm^{-1}; HRMS (FAB, 3-NBA) calcd for $C_{52}H_{46}NO_{12}$ $[M+H^+]$ 876.2975; obsd 876.2991.

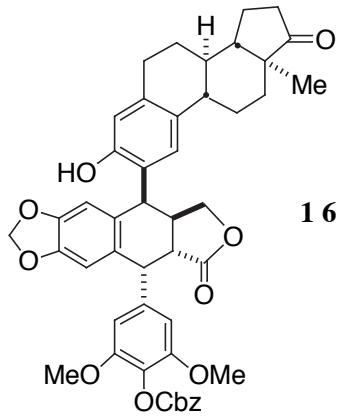


15h

Following the typical sulfoxide activation/conjugation procedure at -78 °C was obtained **15h** (9.9 mg, 75%) from **12** (10 mg, 17 μmol) and estrone, after column chromatography (25% EtOAc/hexanes):

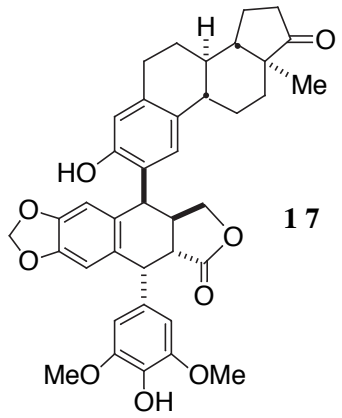
R_f 0.5 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –56 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (s, 3 H), 1.40-1.68 (m, 6 H), 1.90-2.20 (m, 4 H), 2.20-2.25 (m, 1 H), 2.38-2.43 (m, 1 H), 2.50 (dd, *J* = 8, 18 Hz, 1 H), 2.85-2.91 (m, 2 H), 2.95-3.05 (m, 1 H), 3.45 (dd, *J* = 5, 14 Hz, 1 H), 3.68 (s, 6 H), 4.13 (dd, *J* = 9, 11 Hz, 1 H), 4.32 (t, *J* = 9 Hz, 1 H), 4.71 (d, *J* = 5 Hz, 1 H), 5.26 (s, 2 H), 5.43 (d, *J* = 4 Hz, 1 H), 5.94 (d, *J* = 1.2 Hz, 1 H), 5.97 (d, *J* = 1.2 Hz, 1 H), 6.34 (s, 2 H), 6.56 (s, 1 H), 6.67 (d, *J* = 3 Hz, 1 H), 6.71 (dd, *J* = 3, 8 Hz, 1

H), 6.72 (s, 1 H), 7.22 (d, *J* = 8 Hz, 1 H), 7.32-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 21.5, 25.8, 26.7, 29.6, 31.4, 35.8, 38.1, 38.2, 41.6, 43.8, 43.9, 47.9, 50.4, 56.2, 67.6, 70.3, 72.8, 101.6, 107.6, 109.4, 110.2, 112.8, 115.8, 126.7, 128.2-128.5 (4 C), 129.0, 131.9, 133.5, 135.0, 137.9, 138.4, 147.3, 148.7, 151.6, 153.1, 156.3, 174.5, 220.7; IR (ATR): 1770, 1736, 1602, 1484, 1235, 1131 cm^{-1}; HRMS (FAB, 3-NBA/NaI) calcd for $C_{47}H_{46}O_{11}Na$ [M+Na$^+$] 809.2893; obsd 809.2905.



16

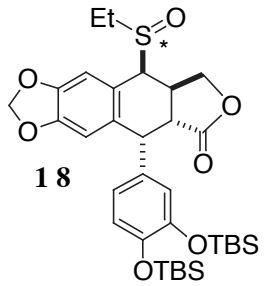
Starting from **12** (15 mg, 25 μmol), the same procedure as for the synthesis of **15h** was initially followed. Thus, after 3 h at –78 ^{o}C, TLC analysis showed primarily one fast moving spot (R_f 0.5 in 1:1 EtOAc/hexanes) presumed to be the O-estrone adduct, **15h**. The reaction mixture was then allowed to slowly warm to 0 ^{o}C over the course of 3 h. The upper spot gradually vanished, and a prominent lower spot was observed at R_f 0.25 in 1:1 EtOAc/hexanes. This was taken as evidence of an O→C-glycosyl rearrangement. Following work-up, column chromatography (40% EtOAc/hexanes) gave **16** (14 mg, 71%). $[\alpha]^{25}_D$ –108 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3 H), 1.40-2.20 (m, 12 H), 2.49 (dd, *J* = 8, 18 Hz, 1 H), 2.80-2.88 (m, 2 H), 2.96 (dd, *J* = 5, 14 Hz, 1 H), 3.03-3.16 (m, 1 H), 3.45 (dd, *J* = 9, 10 Hz, 1 H), 3.69 (s, 6 H), 4.38 (t, *J* = 9 Hz, 1 H), 4.72 (d, *J* = 5 Hz, 1 H), 4.79 (d, *J* = 5 Hz, 1 H), 5.25 (s, 2 H), 5.58 (bs, 1 H), 5.90 (d, *J* = 1.2 Hz, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 6.31 (s, 1 H), 6.41 (s, 2 H), 6.45 (s, 1 H), 6.49 (s, 1 H), 6.54 (s, 1 H), 7.31-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.5, 26.0, 26.3, 29.1, 31.4, 35.8, 36.5, 38.1, 39.0, 41.1, 43.7, 44.0, 48.0, 50.2, 56.2, 70.3, 70.4, 101.2, 107.9, 109.7, 109.8, 114.6, 124.8, 128.2-128.5 (6 C), 131.6 (2 C), 133.1, 135.0, 136.6, 139.3, 147.1, 147.3, 151.4, 153.2, 175.5, 221.2; IR (ATR): 3411 (br), 1770, 1734, 1601, 1482, 1226, 1130 cm^{-1}.



17

A solution of **16** (5.0 mg, 6.4 μmol) in EtOAc (2 mL) and was hydrogenated (1 atm) at rt for 3 h over 10% Pd/C (3 mg). After filtration through Celite and evaporation, column chromatography (70% EtOAc/hexanes) afforded clean **17** (4.1 mg, 100 %).

R_f 0.05 (1:1 EtOAc/hexanes); $[\alpha]^{25}_D$ –53 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (s, 3 H), 1.22-1.64 (m, 6 H), 1.84-1.89 (m, 1 H), 1.90-2.06 (m, 3 H), 2.06-2.16 (m, 2 H), 2.49 (dd, *J* = 8, 19 Hz, 1 H), 2.80-2.86 (m, 2 H), 2.93 (dd, *J* = 5, 14 Hz, 1 H), 3.09-3.18 (m, 1 H), 3.44 (dd, *J* = 9, 11 Hz, 1 H), 3.79 (s, 6 H), 4.38 (t, *J* = 9 Hz, 1 H), 4.69 (d, *J* = 5 Hz, 1 H), 4.80 (d, *J* = 6 Hz, 1 H), 4.86 (bs, 1 H), 5.39 (s, 1 H), 5.88 (d, *J* = 1.2 Hz, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 6.34 (s, 1 H), 6.39 (s, 2 H), 6.43 (s, 1 H), 6.48 (s, 1 H), 6.56 (s, 1 H); HRMS [FAB, *o*-nitrophenyl octyl ether (ONPOE)] calcd for $C_{39}H_{40}O_9$ [$M^{+\bullet}$] 652.2672; obsd 652.2651.



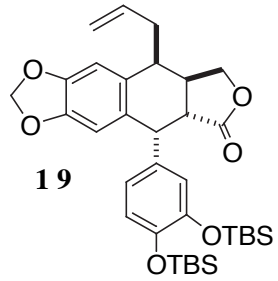
18

Sulfide **8** (100 mg, 0.16 mmol) was treated with m-CPBA (40 mg, 70% w/w, 1.0 equiv.) in CH_2Cl_2 (10 mL) at-78 °C as for the conversion of **11** to **12** (*vide supra*). Flash chromatography (50% EtOAc-hexanes) gave **18** as two separable diastereomers (8:1, 98 mg, 86% total yield):

Major Diastereomer (first-eluting): $[\alpha]^{21}_D$ -231.6 (*c* 0.5, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 9 H), 1.36 (t, *J* = 7 Hz, 3 H), 2.53-2.60 (m, 1 H), 2.78-2.85 (m, 1 H), 3.26-3.34 (m, 1 H), 3.45 (dd, *J* = 6, 14 Hz, 1 H), 4.07 (d, *J* = 4 Hz, 1 H), 4.42 (app t, *J* = 8 Hz, 1 H), 4.55 (d, *J* = 6 Hz, 1 H), 4.98 (dd, *J* = 9, 11 Hz, 1 H), 5.94 (s, 1 H), 5.97 (s, 1 H), 6.27 (d, *J* = 2 Hz, 1 H), 6.48 (s, 1 H), 6.54 (dd, *J* = 2, 8 Hz, 1 H), 6.65 (d, *J* = 8 Hz, 1 H), 6.77 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.4, -4.2 (2 C), -4.1, 7.5, 18.3, 18.4, 25.7, 25.8, 35.6, 42.8, 43.1, 44.1, 64.6,

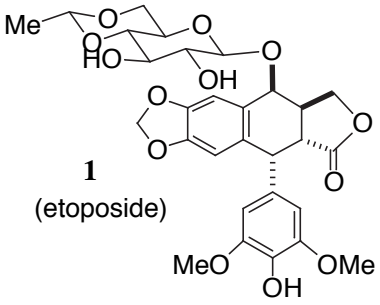
67.9, 101.7, 109.2, 111.2, 120.1, 122.2, 123.1, 123.7, 133.0, 134.4, 145.9, 146.0, 147.0, 148.9, 173.5; HRMS (FAB, 3-NBA/LiI) calcd. for $C_{33}H_{48}0_7SSi_2Li$ [M+Li^+] 651.2819; obsd. 651.2827.

Minor Diastereomer(second-eluting): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.88 (s, 9 H), 0.94 (s, 9 H), 1.42 (t, *J* = 8 Hz, 3 H), 2.72-2.79 (m, 1 H), 2.84-2.91 (m, 1 H), 3.25-3.33 (m, 1 H), 3.71 (dd, *J* = 6, 14 Hz, 1 H), 4.01 (d, *J* = 5 Hz, 1 H), 4.36 (t, *J* = 8 Hz, 1 H), 4.53 (dd, *J* = 9, 11 Hz, 1 H), 4.59 (d, *J* = 6 Hz, 1 H), 5.94 (s, 1 H), 5.97 (s, 1 H), 6.33 (d, *J* = 2 Hz, 1 H), 6.55 (s, 1 H), 6.56 (app dd, *J* = 2, 8 Hz, 1 H), 6.64 (s, 1 H), 6.65 (app d, *J* = 8 Hz, 1 H).



19

Following the typical epipodophyllotoxin conjugation protocol, from sulfoxide **18** (20 mg, 34 μmol) and allyltrimethylsilane was obtained **19** (14 mg, 75%) after flash chromatography (10% EtOAc-hexanes). $[\alpha]^{25}_D$ –127.2 (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.88 (s, 9 H), 0.95 (s, 9 H), 2.37-2.42 (m, 1 H), 2.52-2.58 (m, 1 H), 2.92-3.00 (m, 1 H), 3.02 (dd, *J* = 5, 14 Hz, 1 H), 3.21-3.24 (m, 1 H), 4.21-4.23 (m, 2 H), 4.47 (d, *J* = 5 Hz, 1 H), 5.09 (br d, *J* = 10 Hz, 1 H), 5.12 (br d, *J* = 17.5 Hz, 1 H), 5.80 (ddt, *J* = 7, 10, 17 Hz, 1 H), 5.88 (d, *J* = 1 Hz, 1 H), 5.90 (d, *J* =1 Hz, 1 H), 6.35 (d, *J* = 2 Hz, 1 H), 6.42 (s, 1 H), 6.61 (dd, *J* = 2, 8 Hz, 1 H), 6.65 (d, *J* = 8 Hz, 1 H), 6.70 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.3, -4.2 (2 C), -4.1, 18.3, 18.4, 25.8, 25.9, 35.8, 37.7, 38.6 42.1, 43.1, 69.0, 101.1, 108.6, 110.2, 116.8, 120.0, 123.4, 123.8, 131.7, 132.8, 133.6, 136.7, 145.5, 145.9, 146.86, 146.88, 174.9; HRMS (FAB, 3-NBA/LiI) calcd. for $C_{34}H_{48}0_6Si_2Li$ [M+Li^+] 615.3149; obsd. 615.3150.

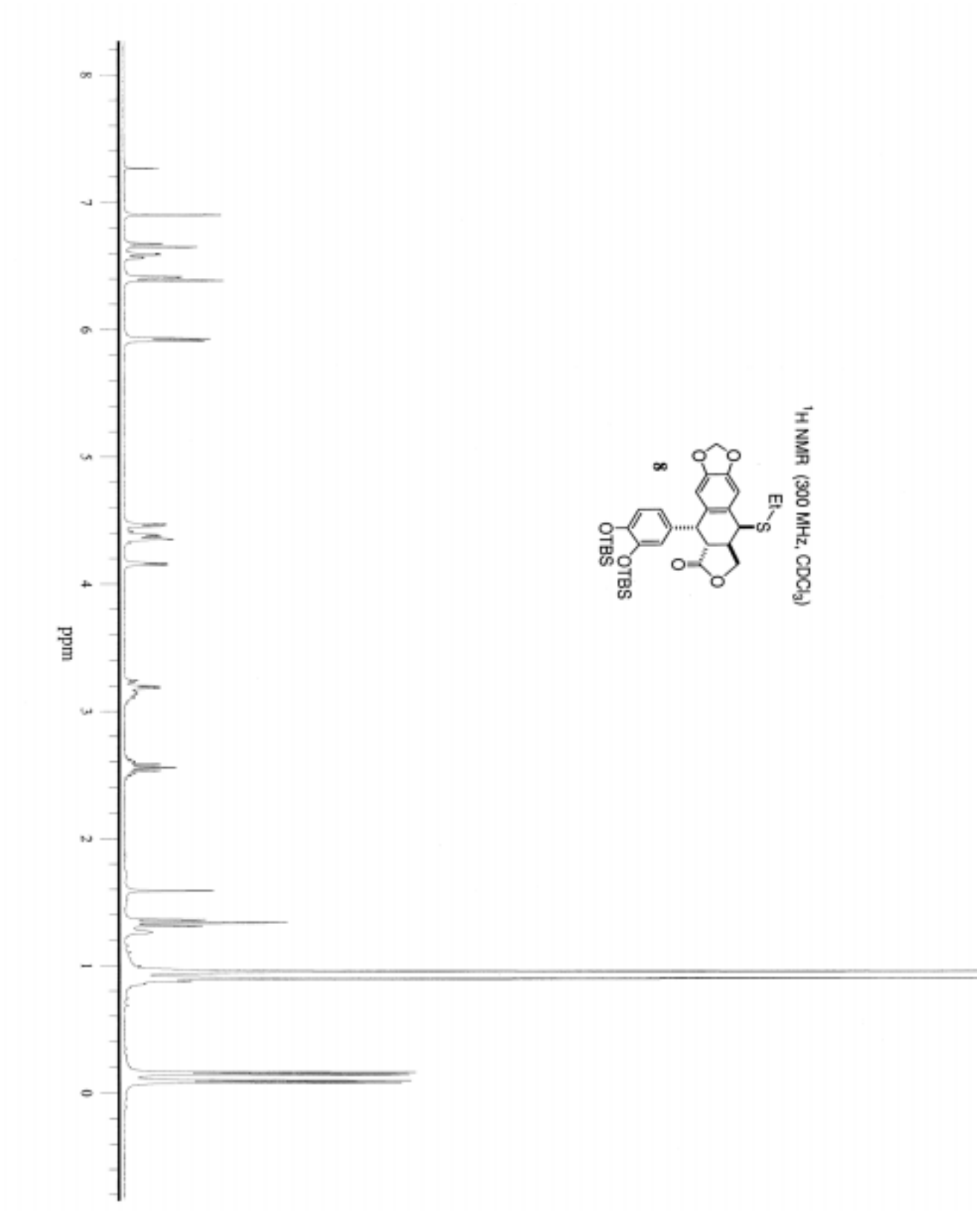


1
(etoposide)

To a solution of **15d (**30 mg, 34 μmol) in MeOH-EtOAc (1:1; 10 mL) containing 0.5% CF_3COOH was added 10% Pd/C (15 mg). The reaction mixture was hydrogenated at 50 psi for 12 h. After filtration

through Celite, residual TFA was neutralized with bicarbonate, and the MeOH was evaporated, in vacuo, to facilitate extraction. After partitioning between H_2O and CH_2Cl_2, the organics were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (50→100% EtOAc/hexanes) provided **1** (20 mg, 85%), which was identical to an authentic sample (from Sigma, see spectra below).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (d, *J* = 5 Hz, 3 H), 1.57 (bs, 2 H), 2.84-2.91 (m, 1 H), 3.24 (dd, *J* = 5, 14 Hz, 1 H), 3.31-3.34 (m, 2 H), 3.43 (app t, *J* = 8 Hz, 1 H), 3.57 (d, *J* = 10 Hz, 1 H), 3.72-3.75 (m, 1H), 3.75 (s, 6 H), 4.21 (t, *J* = 8 Hz, 1H), 4.40 (dd, *J* = 9, 11 Hz, 1 H), 4.60 (d, *J* = 5 Hz, 1 H), 4.65 (d, *J* = 8 Hz, 1 H), 4.16 (dd, *J* = 4, 10 Hz, 1 H), 4.74 (q, *J* = 5 Hz, 1 H), 4.90 (d, *J* = 3 Hz, 1 H), 5.39 (bs, 1 H), 5.97 (d, *J* = 1. Hz, 1 H), 5.99 (d, *J* = 1. Hz, 1 H), 6.25 (s, 2 H), 6.54 (s, 1 H), 6.81 (s, 1 H).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OTBS
OTBS
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8
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5
4
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2
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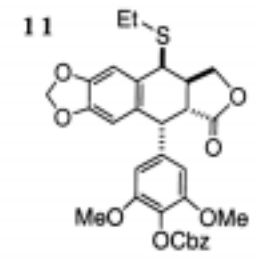

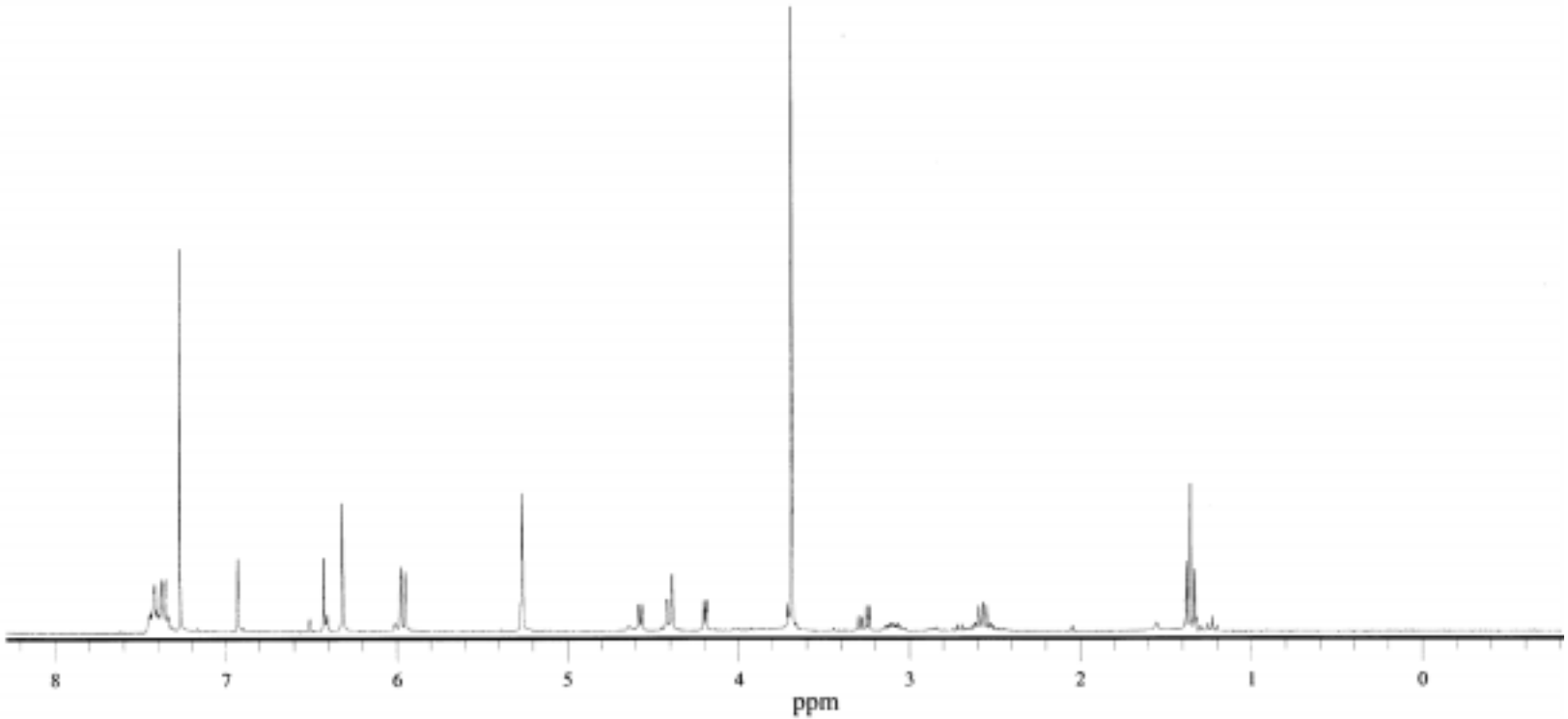

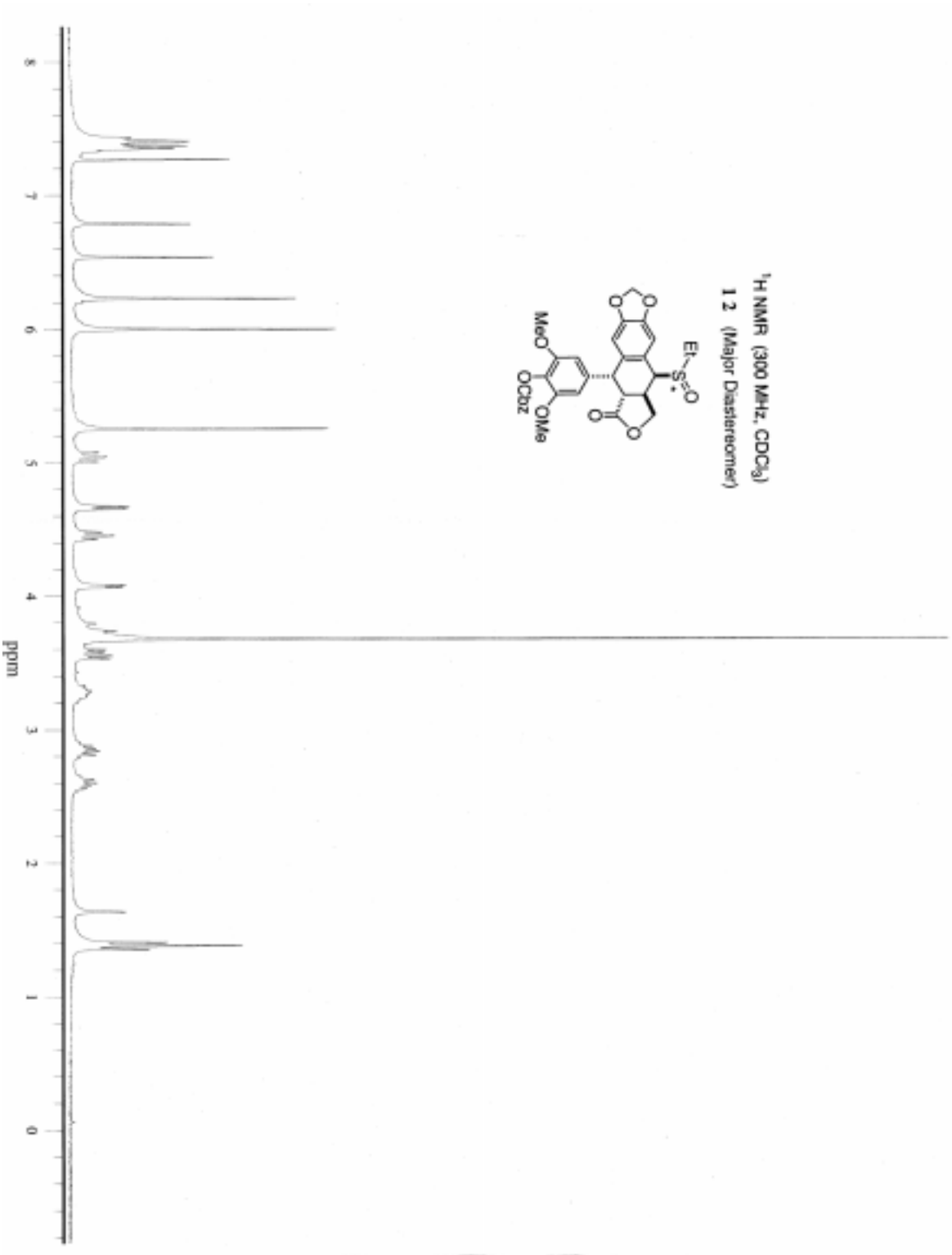
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MeO
OMe
OCbz
ppm
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7
6
5
4
3
2
1
0

GE NMR Instruments /home/omega/data/sjc-XI-40-1 Mon Feb 14 12:18:53 2000 Page 1
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OCbz
OMe
Et
S
O
ppm
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1
2
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4
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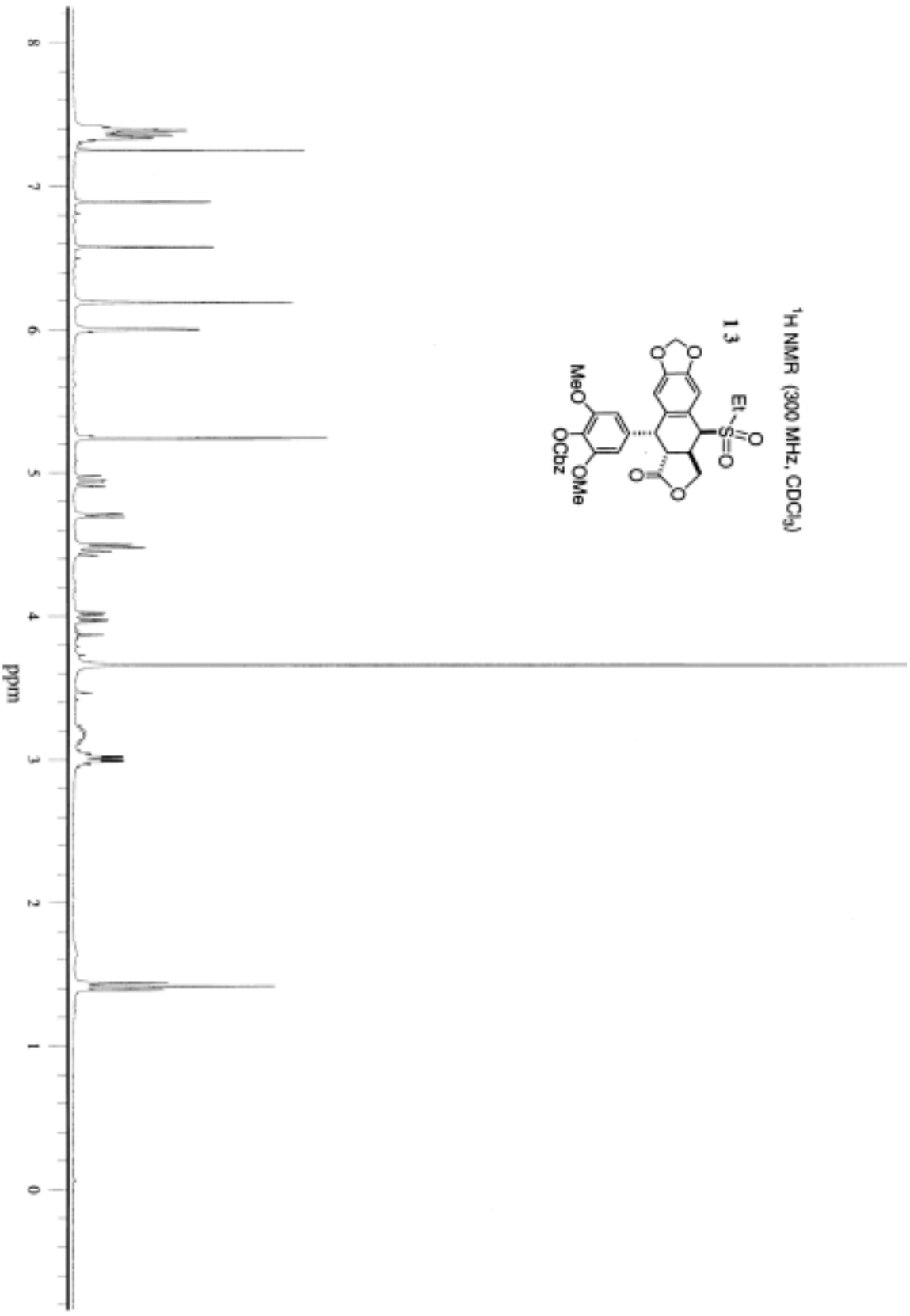
6
7
8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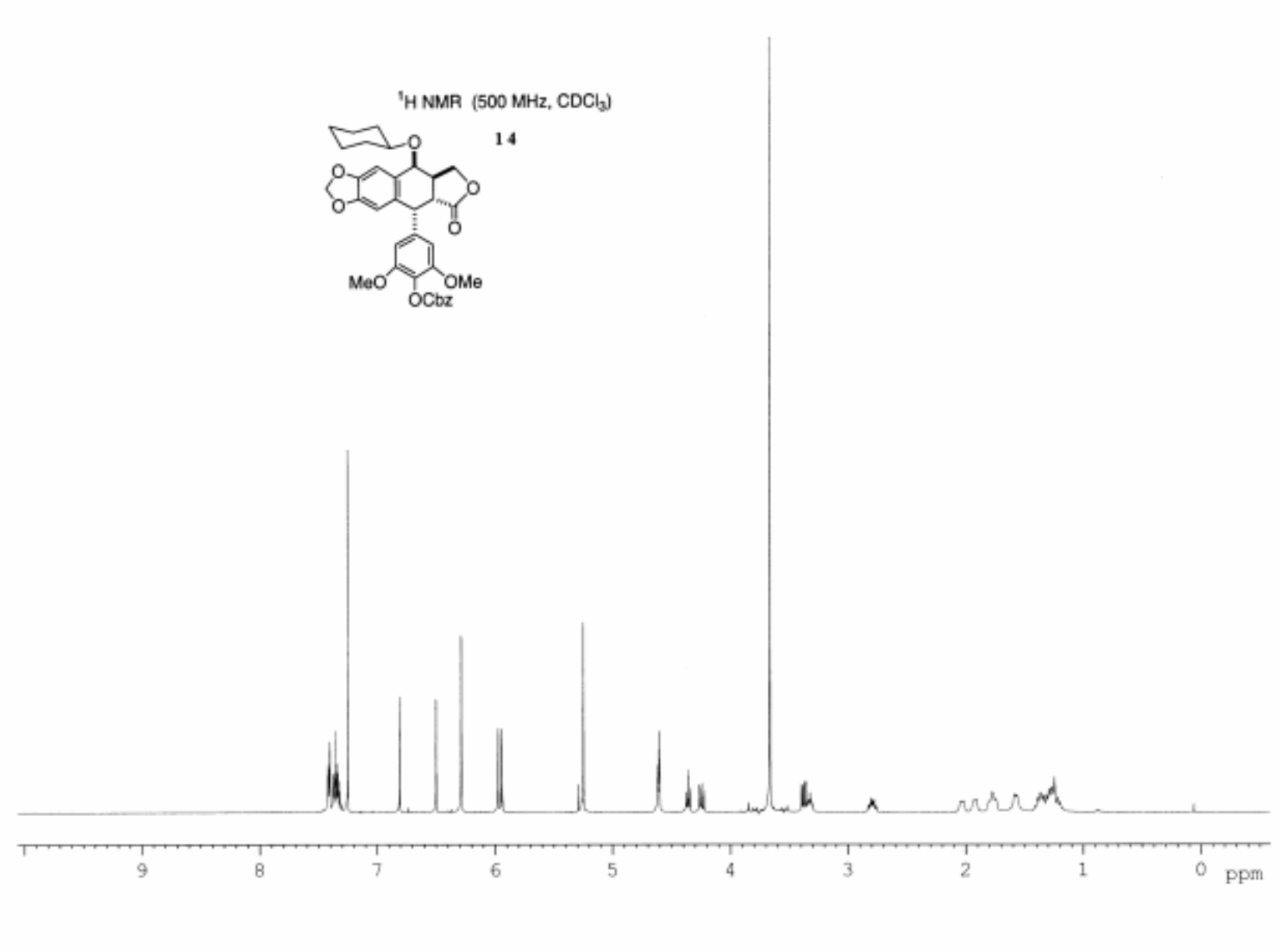
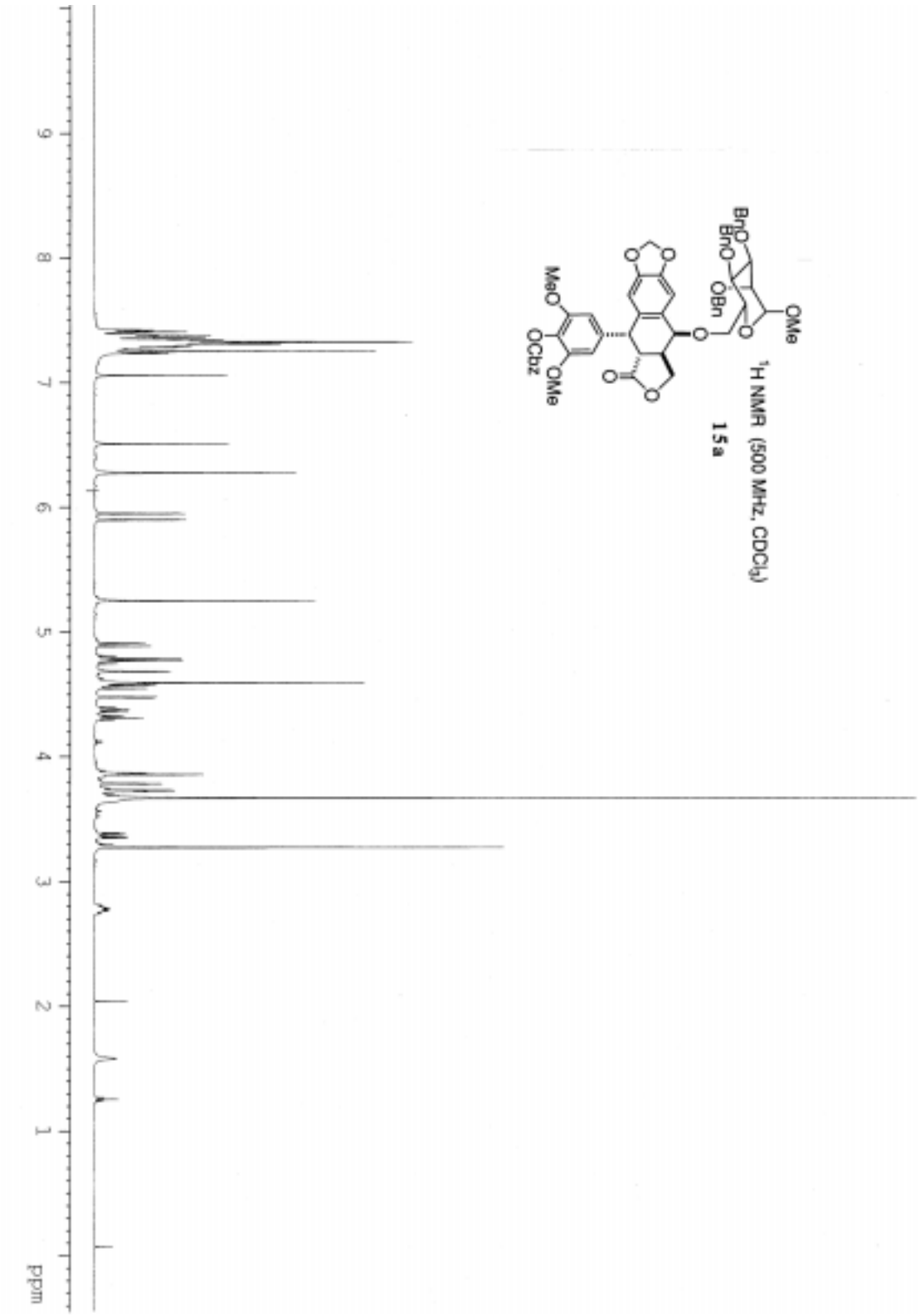
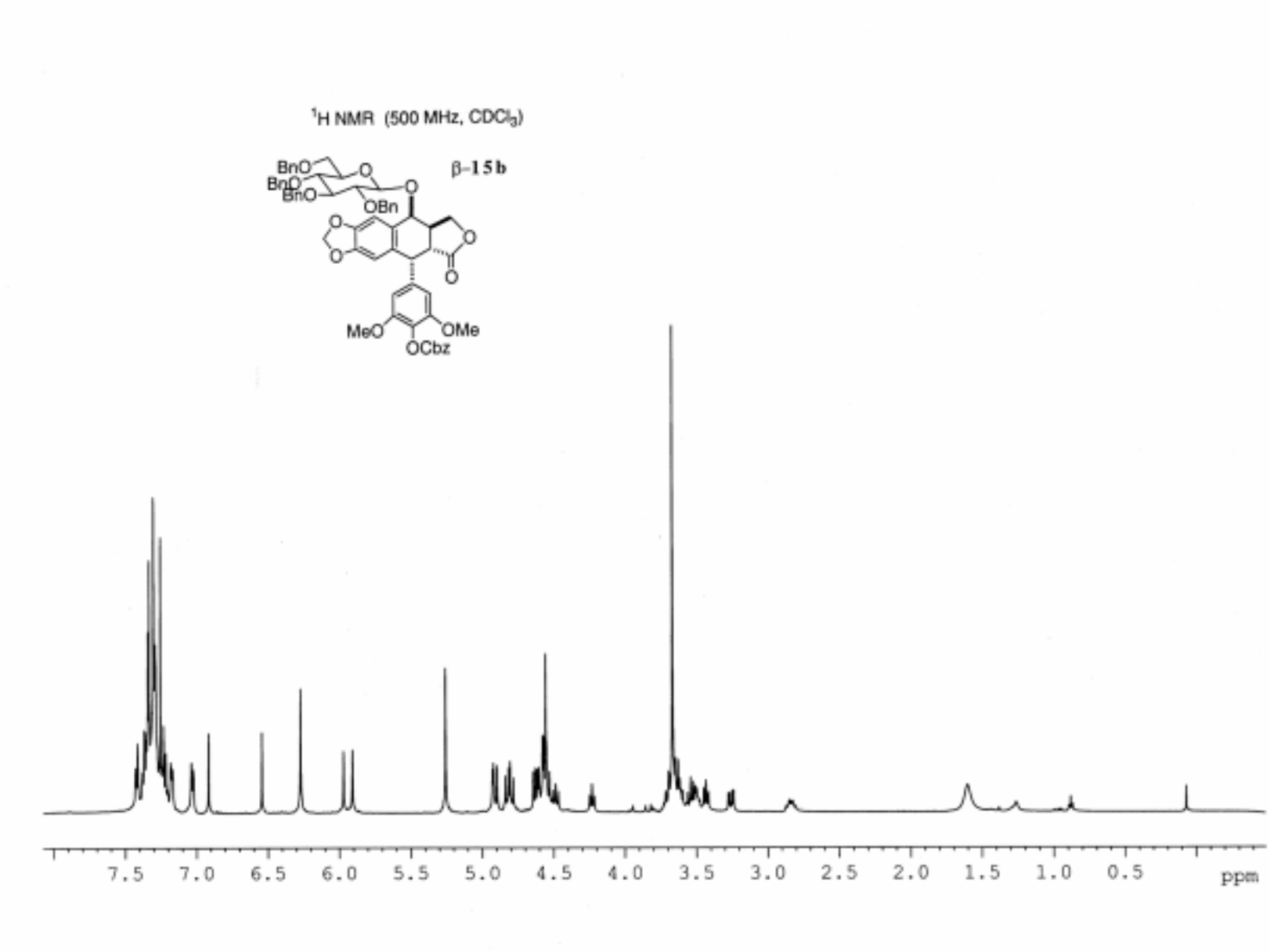
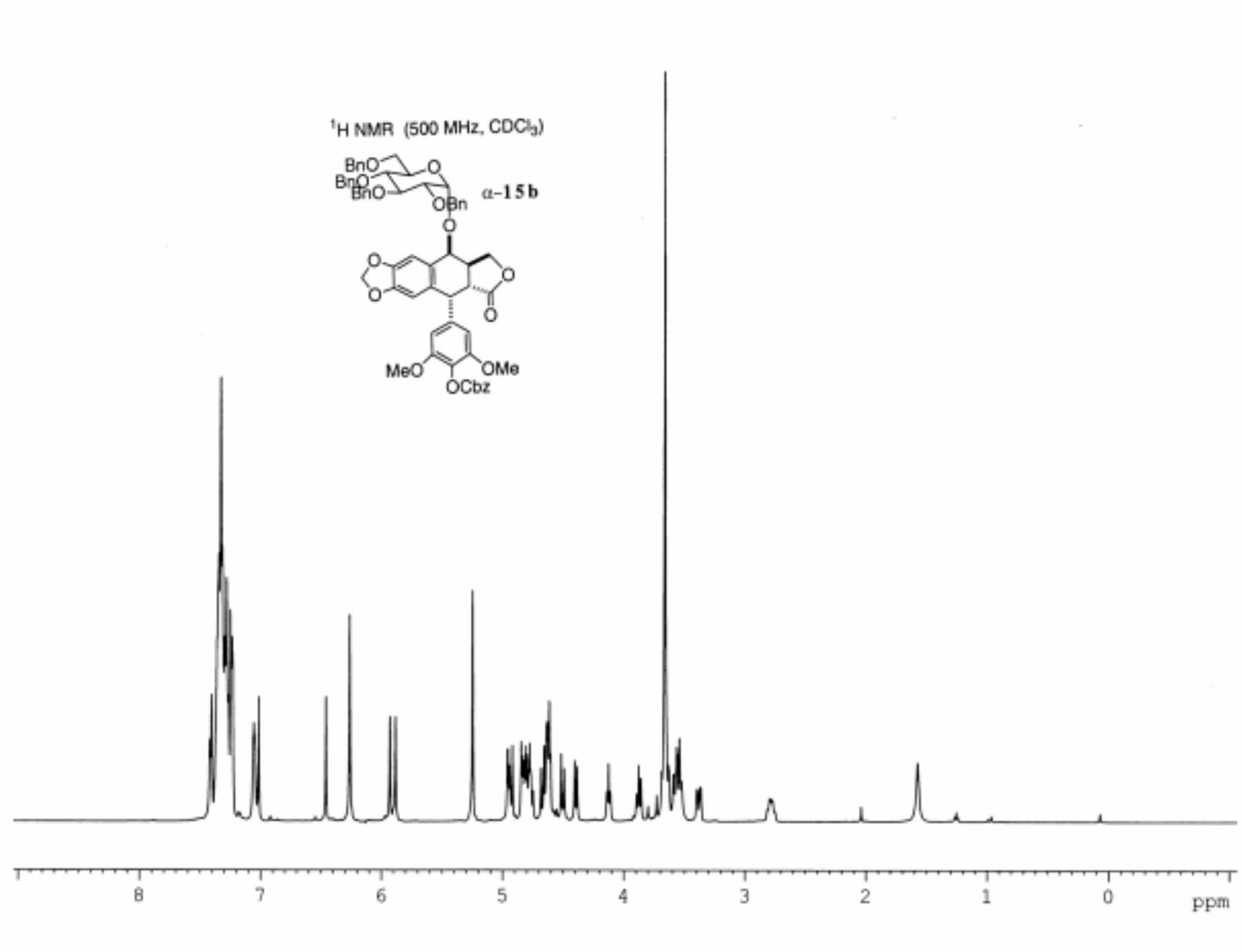
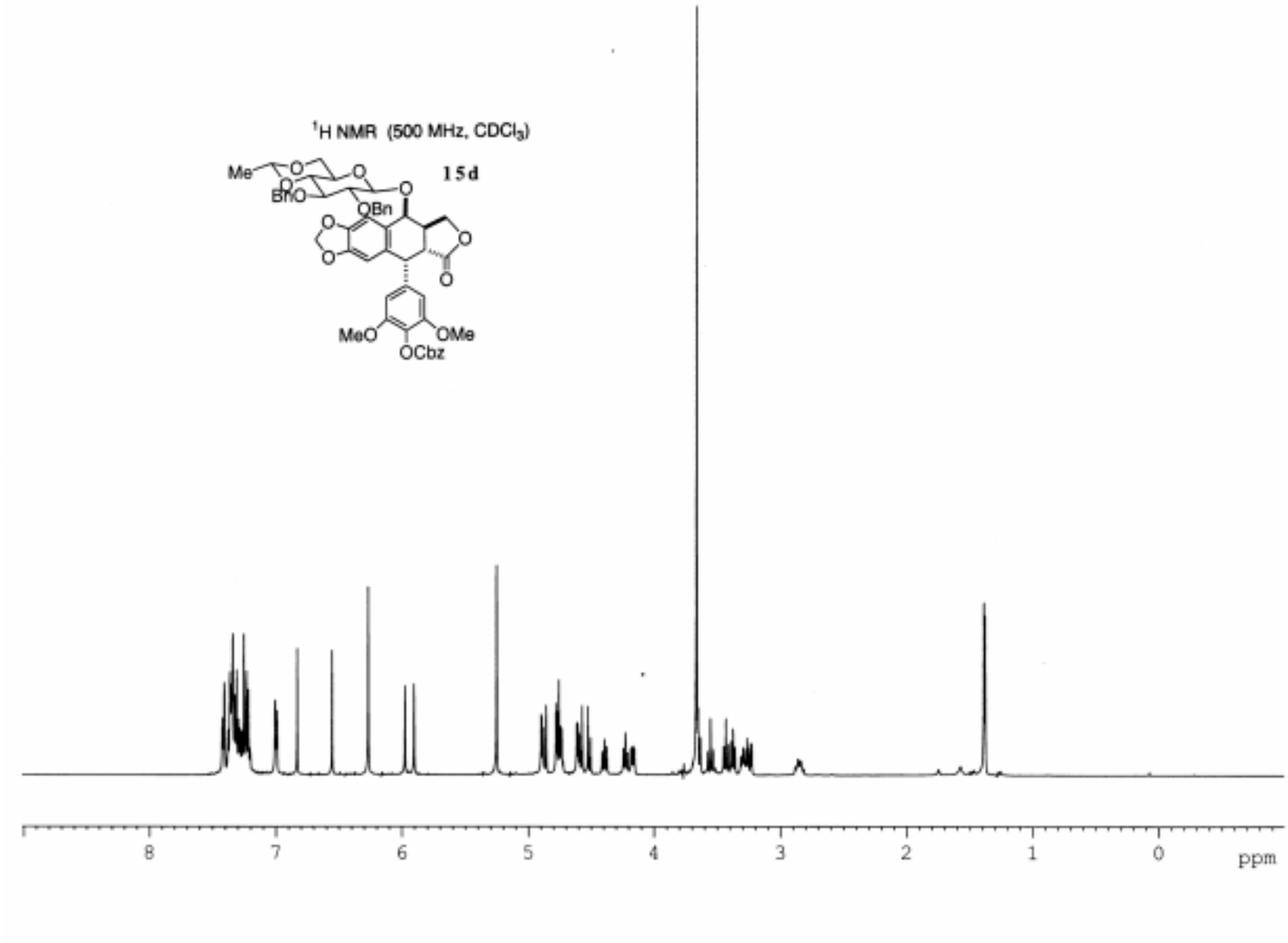
0

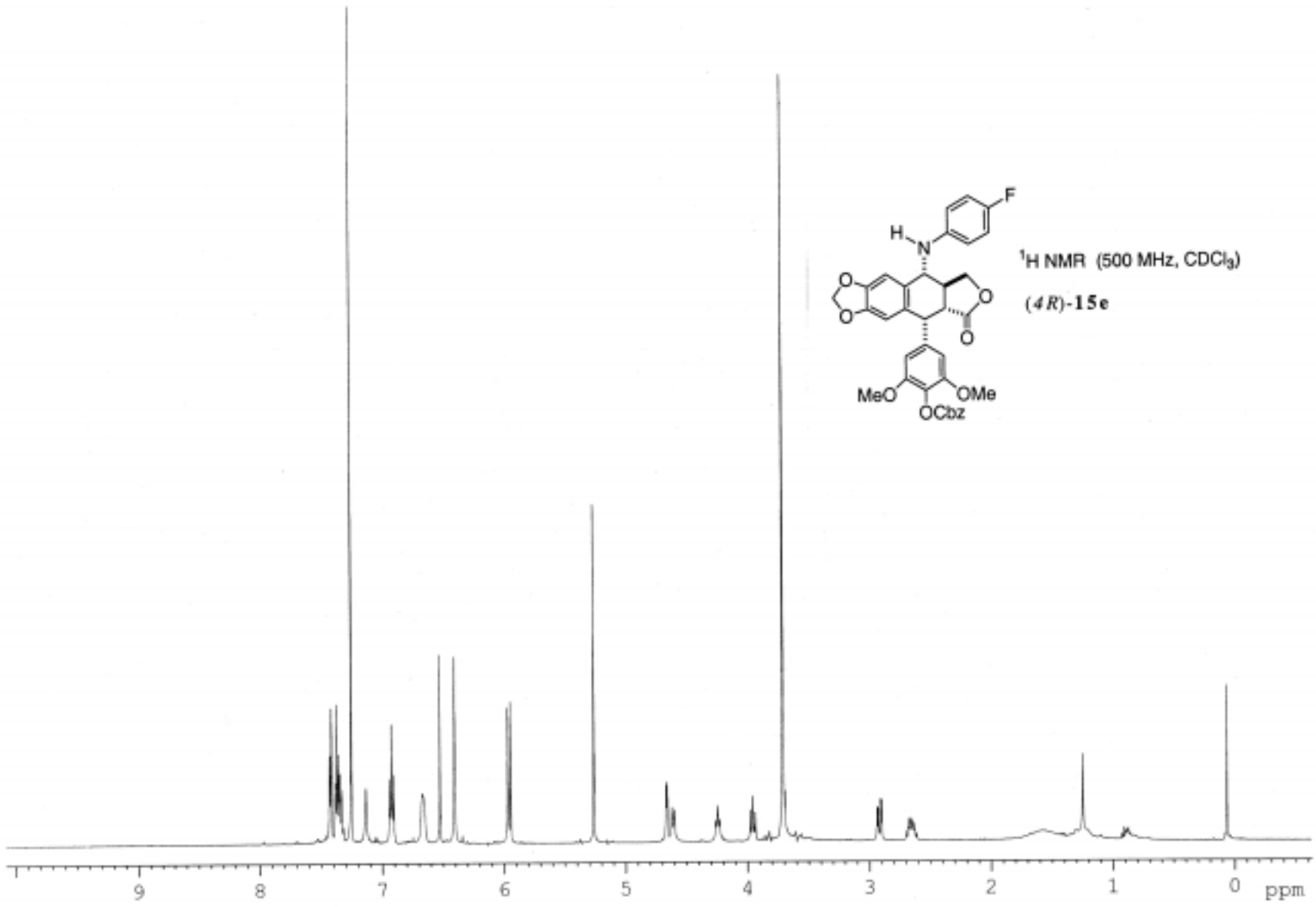

^{1}H NMR (500 MHz, $CDCl_3$)
14
MeO
OMe
OCbz
9
8
7
6
5
4
3
2
1
0
ppm


BnO
BnO
OBn
OMe
MeO
OCbz
OMe
O
O
O
O
O
O
O
O
O
O
^{1}H NMR (500 MHz, CDCl$_3$)
15a
9
8
7
6
5
4
3
2
1
ppm


^{1}H NMR (500 MHz, $CDCl_3$)
β-15b
BnO
BnO
BnO
OBn
O
O
O
O
O
MeO
OMe
OCbz
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

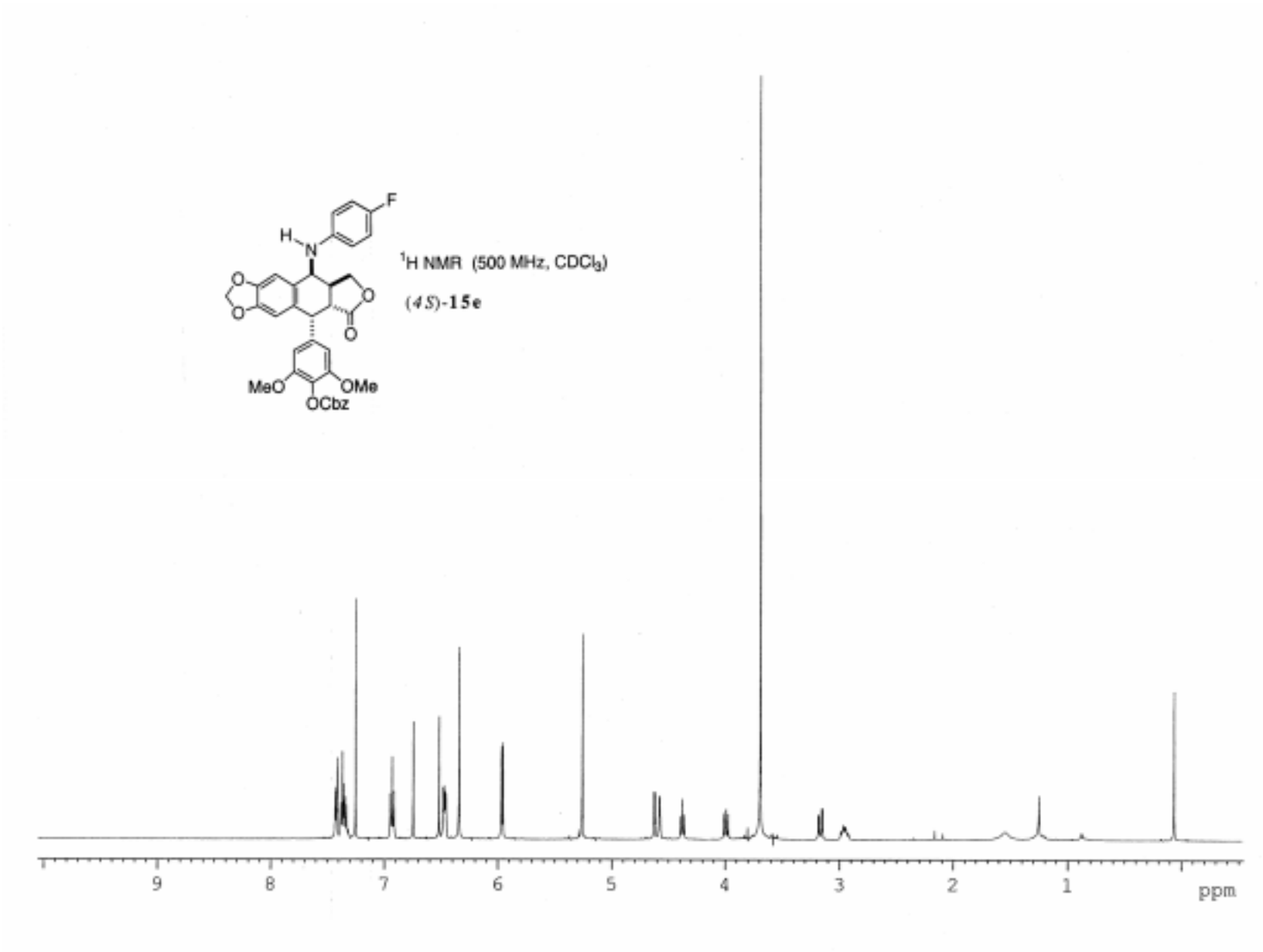

^{1}H NMR (500 MHz, $CDCl_3$)
α-15b
BnO
BnO
BnO
OBn
O
O
O
O
O
O
MeO
OMe
OCbz
8
7
6
5
4
3
2
1
0
ppm

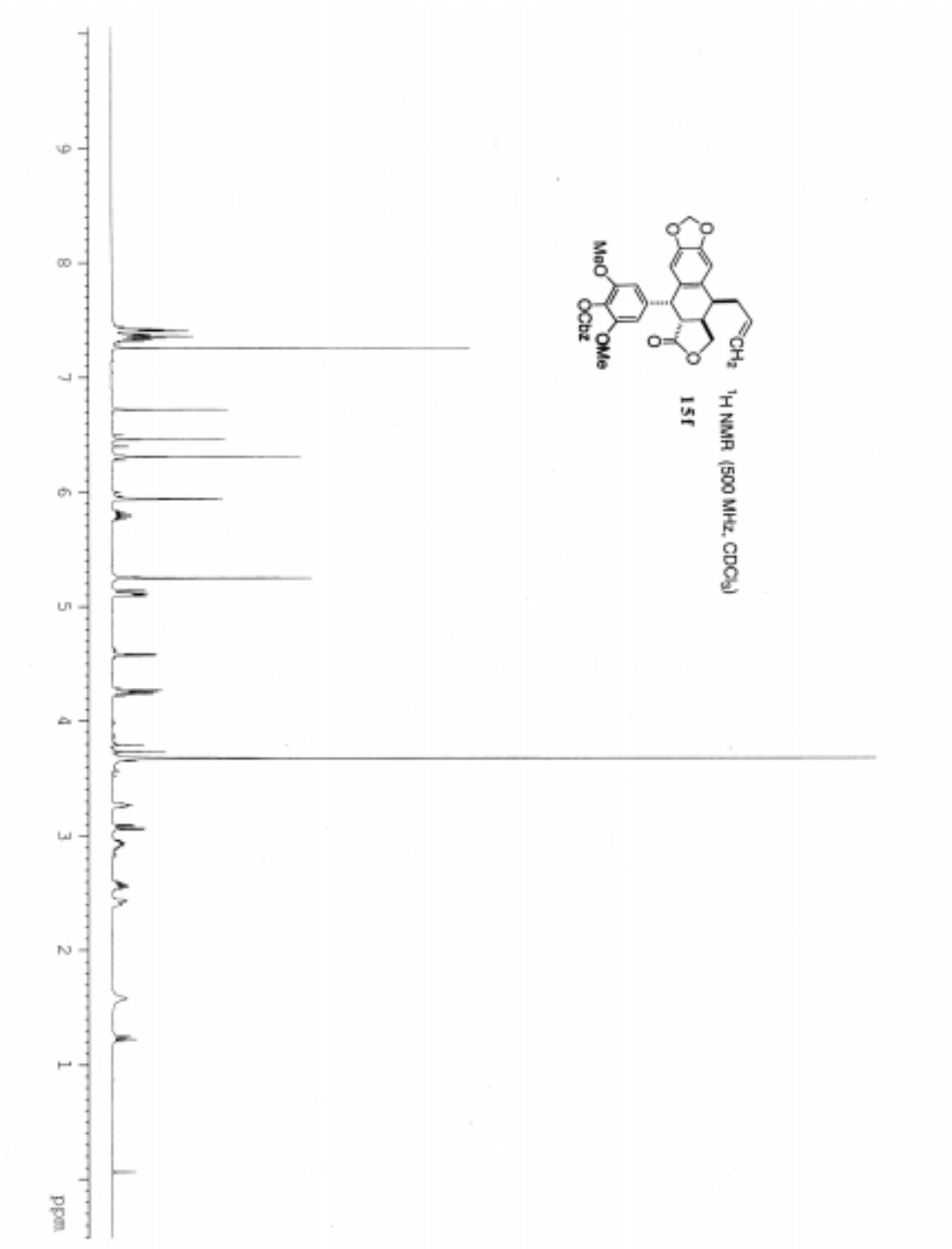

^{1}H NMR (500 MHz, CDCl$_3$)
15d
Me
BnO
OBn
MeO
OMe
OCbz
8
7
6
5
4
3
2
1
0
ppm

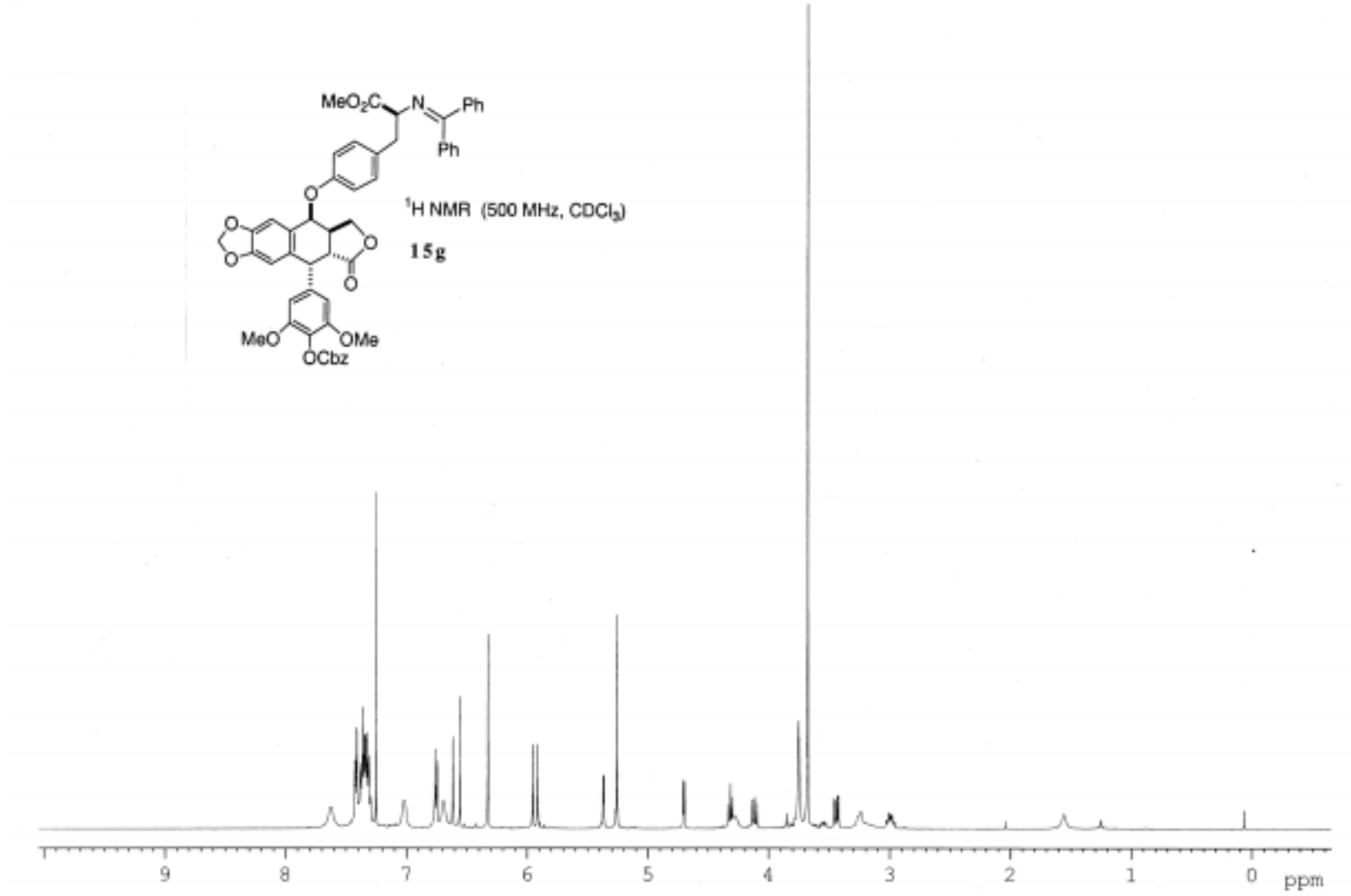


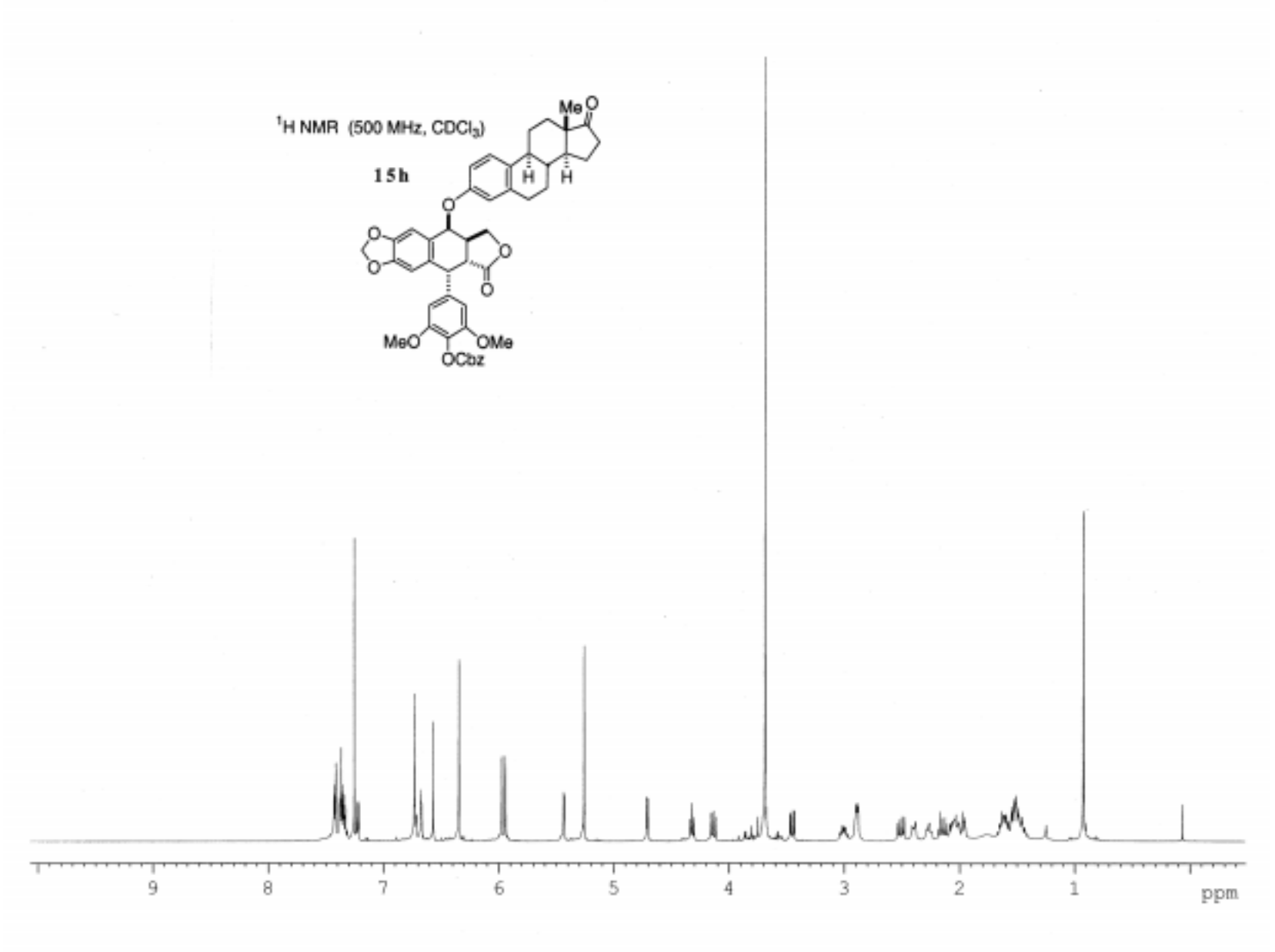
^{1}H NMR (500 MHz, $CDCl_3$)

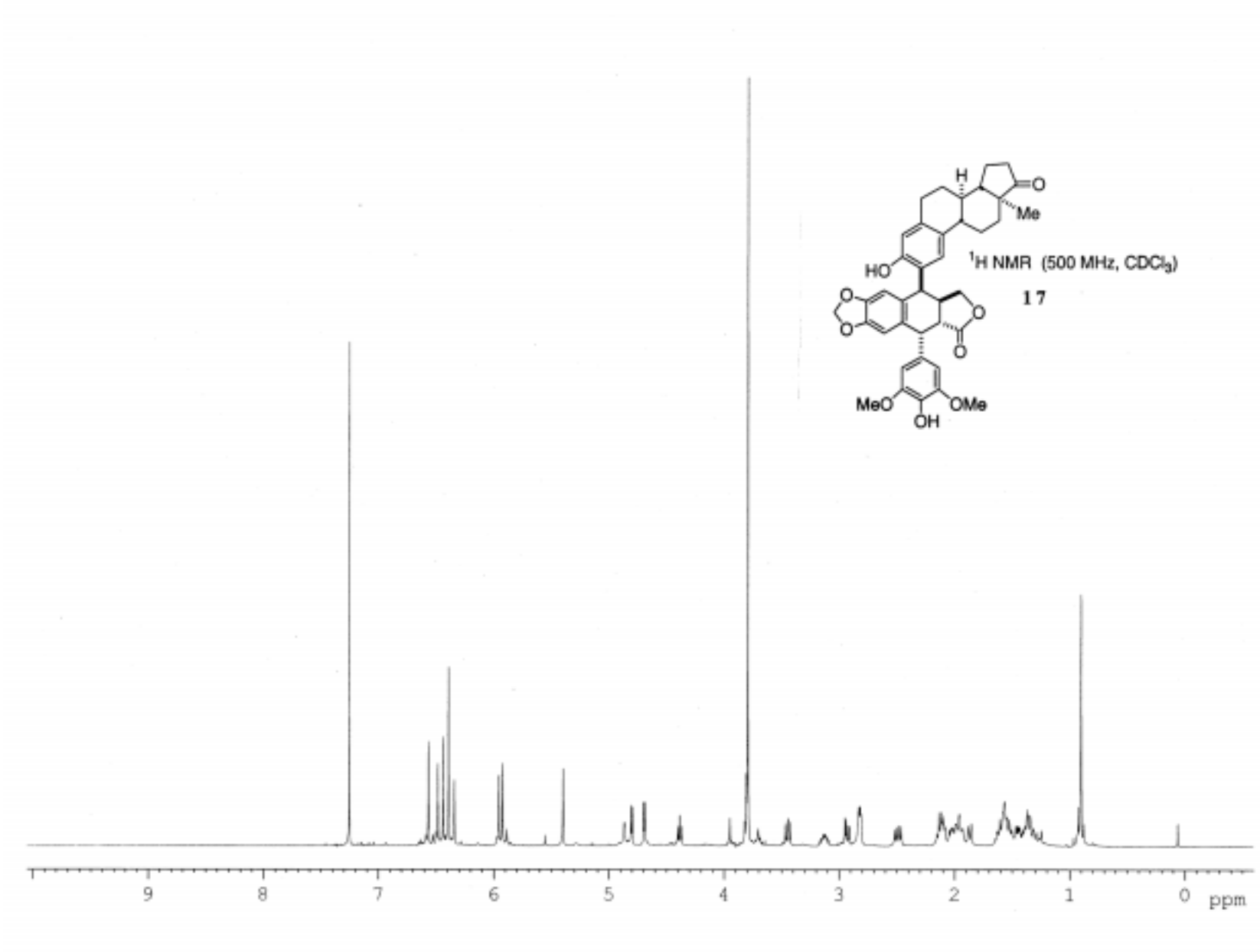
(*4R*)-**15e**

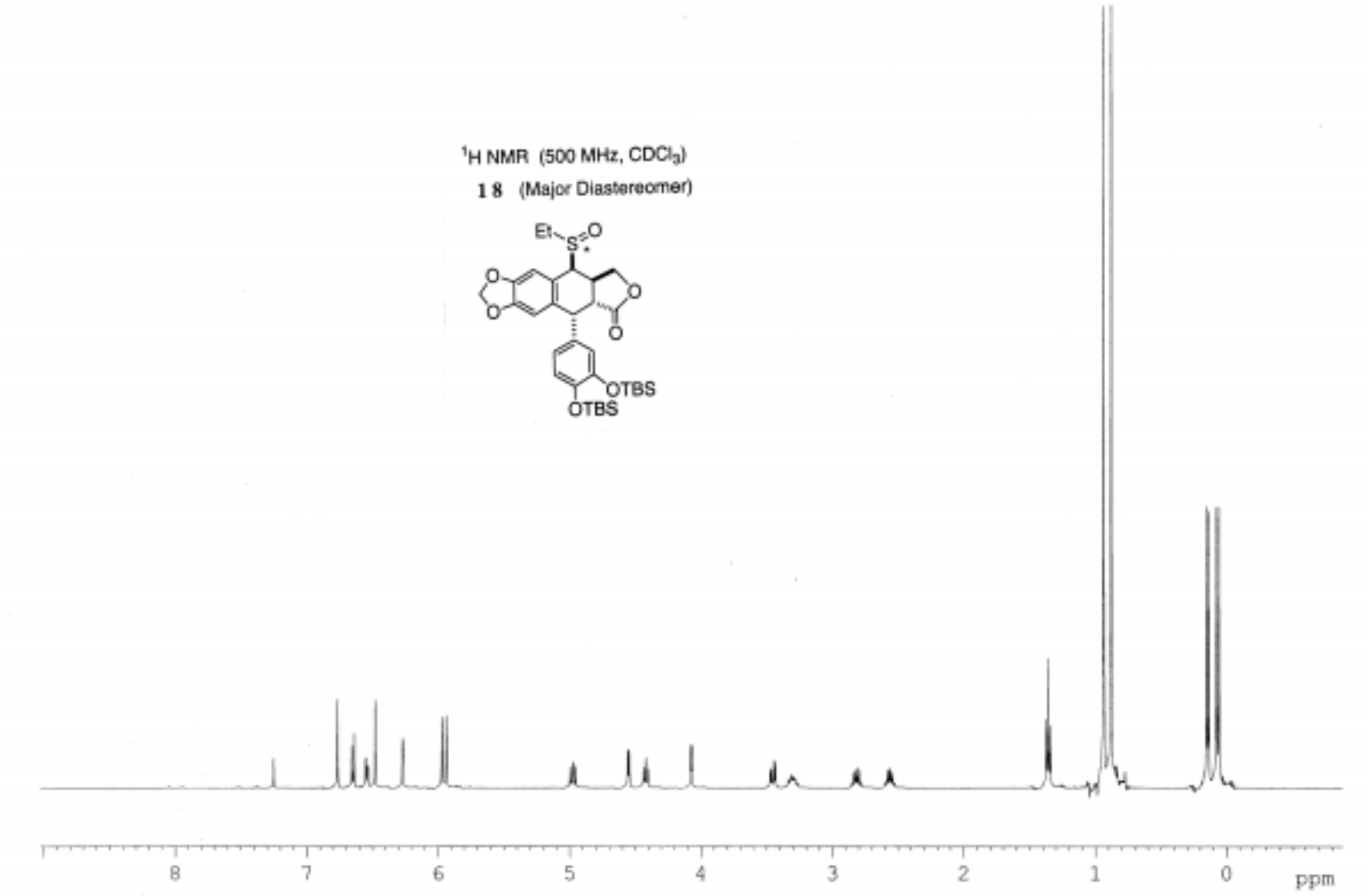

F
H
N
O
O
O
O
MeO
OMe
OCbz
^{1}H NMR (500 MHz, CDCl$_3$)
(4S)-15e
9
8
7
6
5
4
3
2
1
ppm

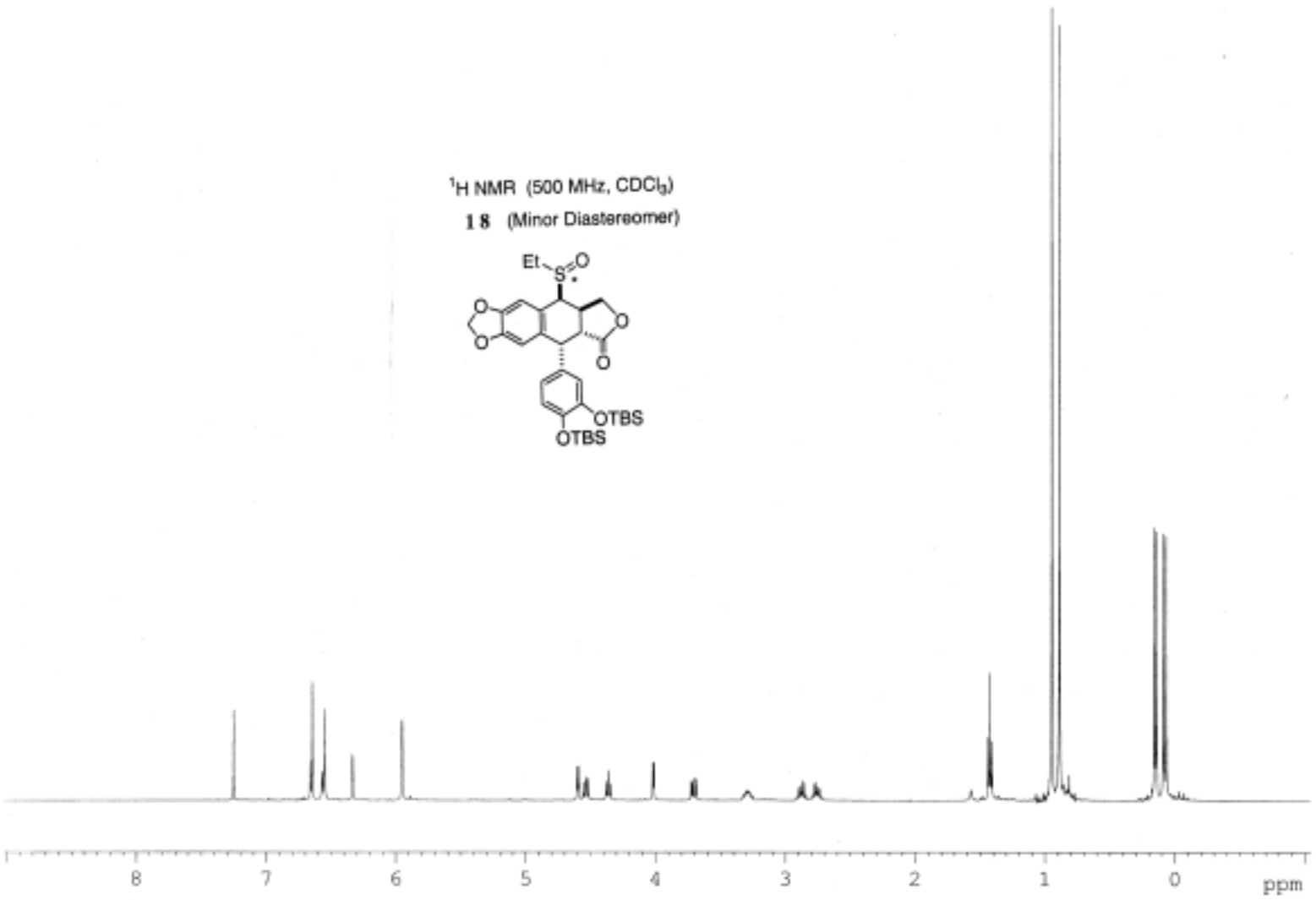

MeO
OCbz
OMe
CH2
151
1H NMR (500 MHz, CDCl3)
ppm
9
8
7
6
5
4
3
2
1

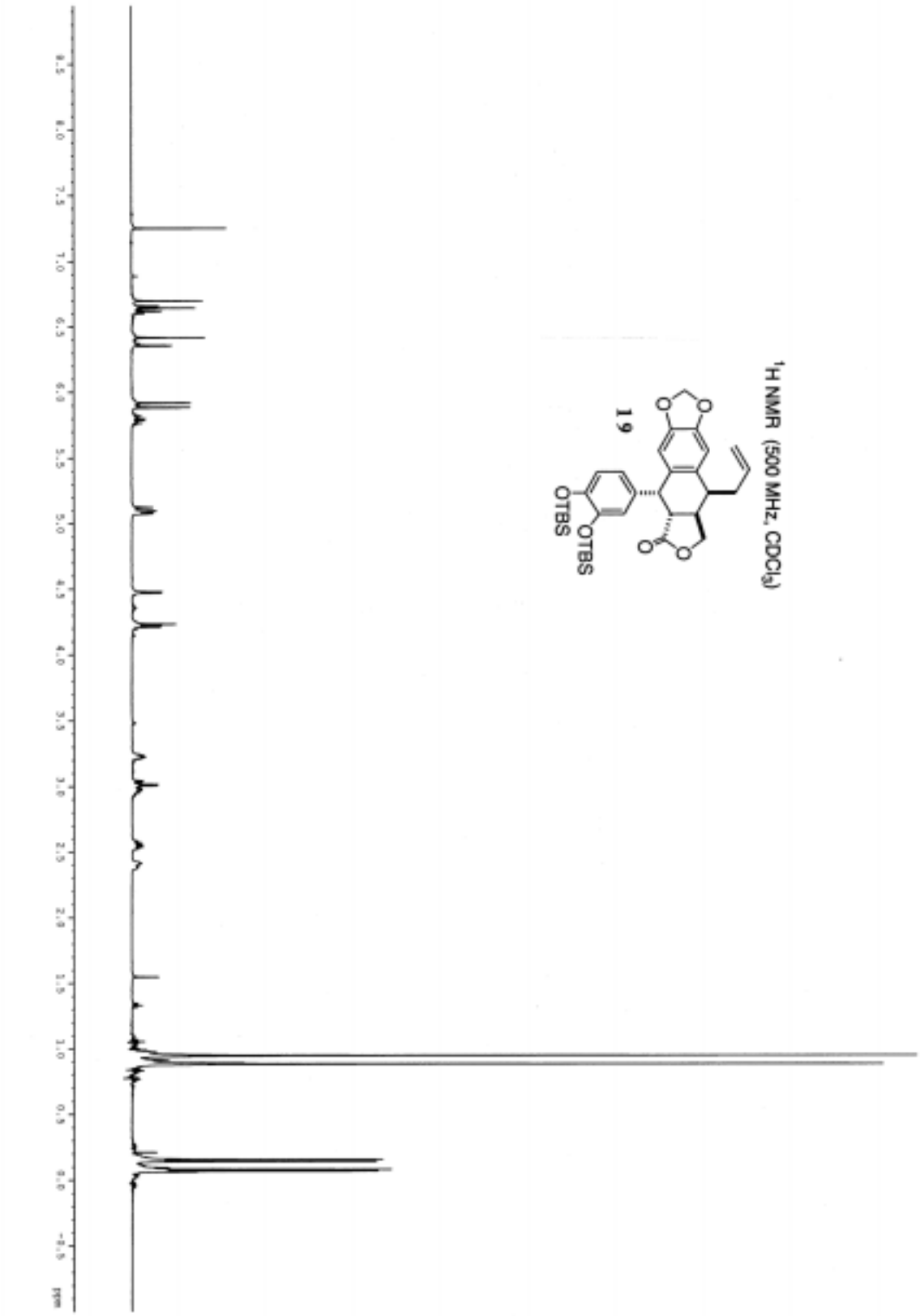

MeO2C
N
Ph
Ph
O
O
O
O
O
MeO
OMe
OCbz
1H NMR (500 MHz, CDCl3)
15g
9
8
7
6
5
4
3
2
1
0
ppm

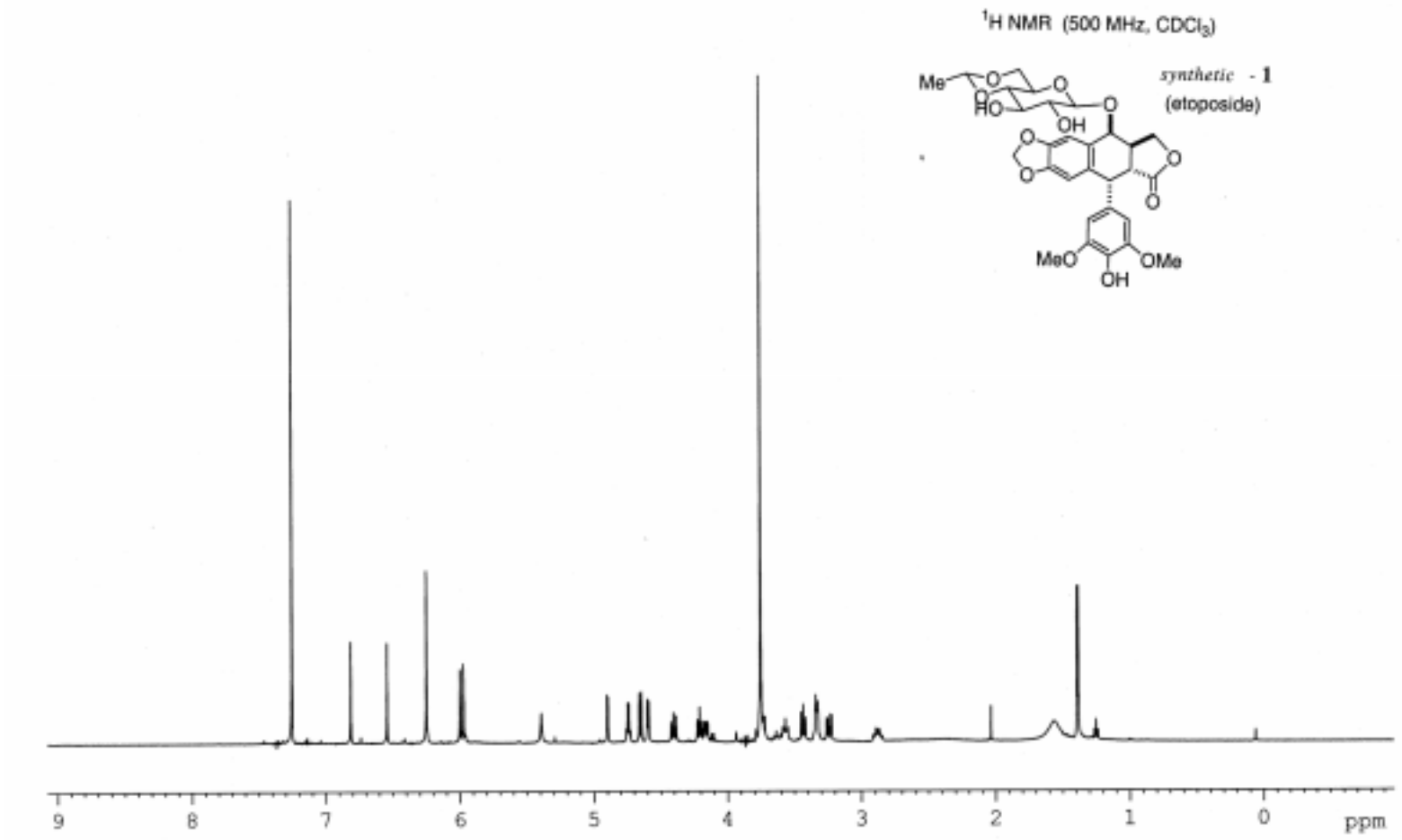

^{1}H NMR (500 MHz, CDCl$_3$)
15h
Me
O
H
H
O
O
O
O
O
MeO
OMe
OCbz
9
8
7
6
5
4
3
2
1
ppm

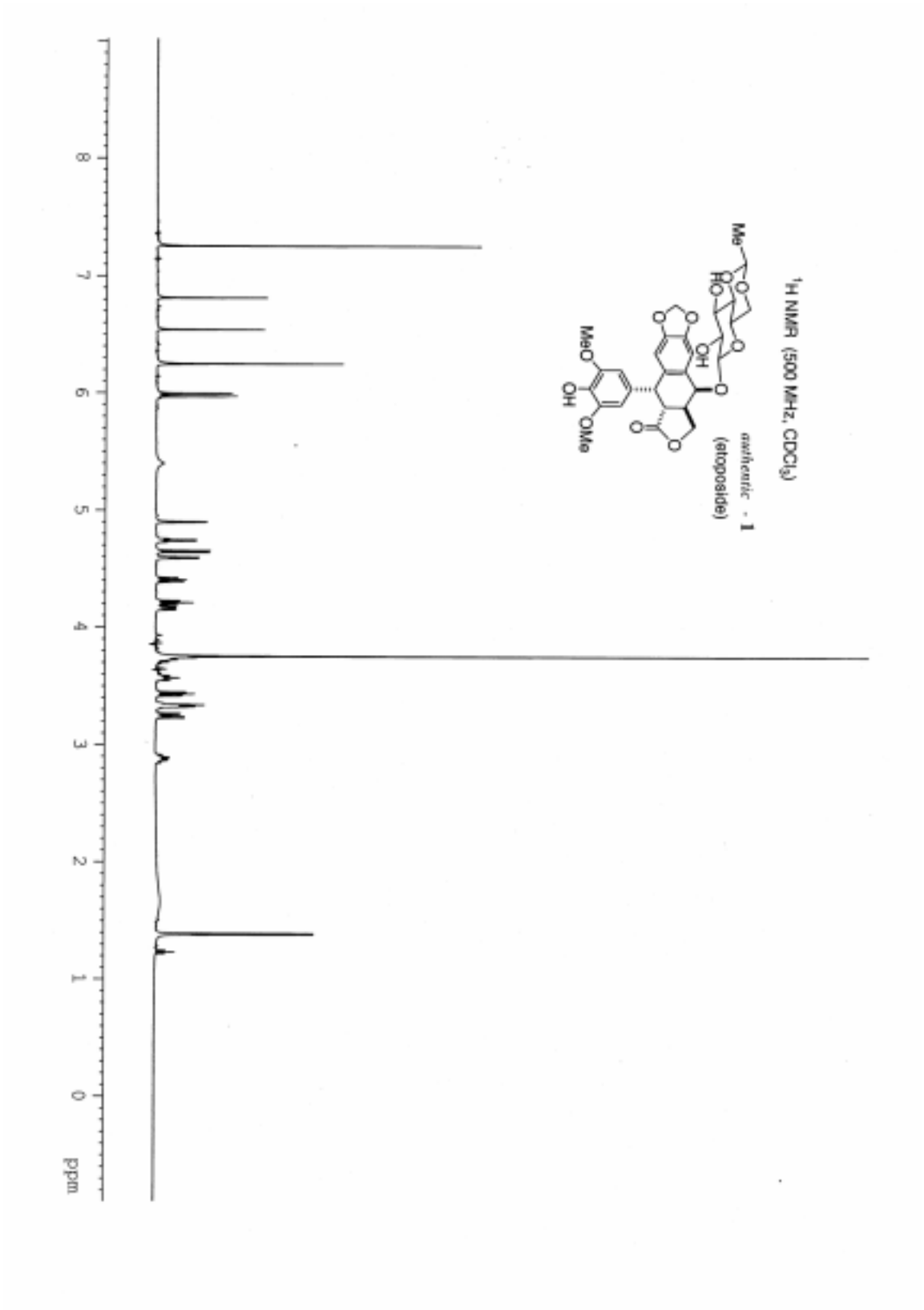

H
O
Me
HO
O
O
O
O
MeO
OMe
OH
^{1}H NMR (500 MHz, CDCl$_3$)
17
9
8
7
6
5
4
3
2
1
0
ppm


^{1}H NMR (500 MHz, $CDCl_3$)
18 (Major Diastereomer)
Et
S
O
O
O
O
O
OTBS
OTBS
8
7
6
5
4
3
2
1
0
ppm


^{1}H NMR (500 MHz, $CDCl_3$)
18 (Minor Diastereomer)
Et
S
O
O
O
O
O
OTBS
OTBS
8
7
6
5
4
3
2
1
0
ppm


^{1}H NMR (500 MHz, CDCl$_3$)
19
OTBS
OTBS


^{1}H NMR (500 MHz, $CDCl_3$)
synthetic - 1
(etoposide)
Me
HO
OH
MeO
OMe
OH
9
8
7
6
5
4
3
2
1
0
ppm


^{1}H NMR (500 MHz, CDCl$_3$)
Me
HO
OH
MeO
OH
OMe
synthesis - 1
(etoposide)
8
7
6
5
4
3
2
1
0
ppm