Inhibition of Chikungunya Virus-Induced Cell Death by Salicylate-Derived Bryostatin Analogs Provides Additional Evidence for a PKC-Independent Pathway

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Supporting Information

Table of Contents

Standard Deviations Associated with Cell-Protective Assay

Compound	Bryo 1	1	2	3	4	5	6	7	8	9
R[a]	-	H	Br		OMe	OMe	MeO OMe	OiPr	OiPr	iPrO OiPr
PKCδ[b] K_i (nM)	1.1	18	28	9.1	4.0	5.1	1.3	2.7	3.4	1.9
CHIKV EC_{50} (μM)[c]	>50	6.7±0.2	5±0.2	2.0±0.06	3.7±0.2	2.0±0.7	1.4±0.4	2.8±0.9	2.0±0.6	3.5±0.3
CHIKV CC_{50} (μM)[c]	>50	12±4	25.5±3.6	12.4	>50	>50	>50	>50	>50	>50

Compound	10	11	12	13	14	15	16	17	18
R	C_6H_{13}	HN	H N	CO_2Me	CO_2iPr	O NEt_2	O O S NEt_2	O O S NEt_2	O–N
PKCδ K_i (nM)	4.4	>250	12	3.3	7.6	7.9	5.9	3.6	2.8
CHIKV EC_{50} (μM)	3.8±3.1	3.7±0.1	3.2±0.8	2±1	3.4±0.3	>5.9	2.2±0.4	3.1±1.8	2.3±0.9
CHIKV CC_{50} (μM)	>50	41±9	9.5±1.2	16.3±1.3	>50	5.9±1.2	>50	>50	8.6±0.8

Figure S1. Reproduction of Figure 2 in the main text with standard deviations included

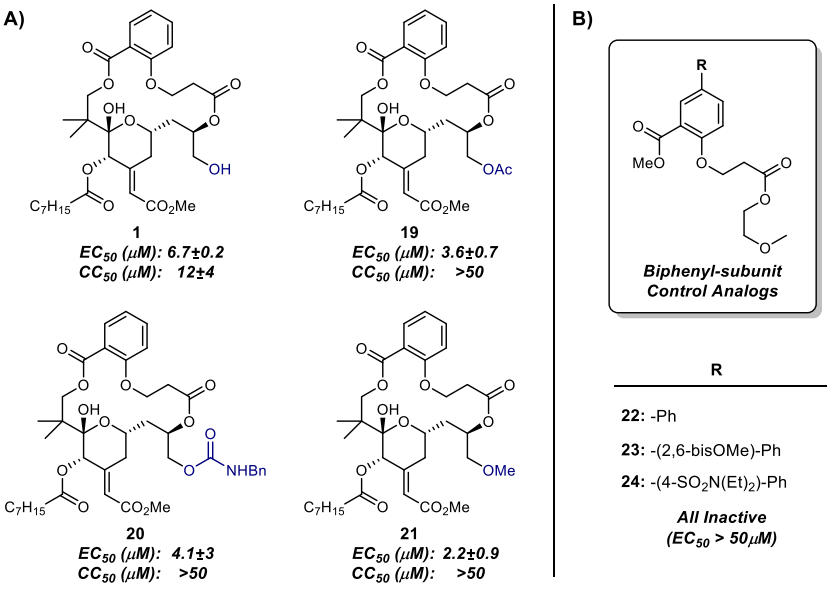


Figure S2. Reproduction of Figure 4 in the main text with standard deviations included

General Synthetic Methods

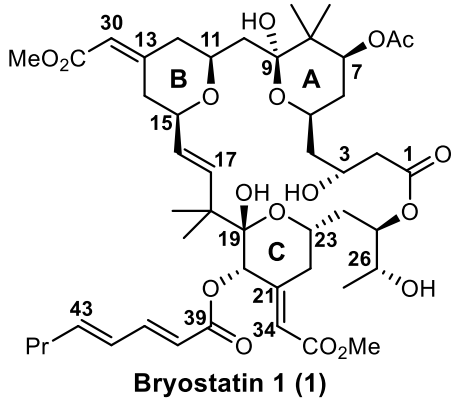
Unless otherwise noted, all reactions were run under a nitrogen atmosphere in flame-dried glassware. Reactions were stirred using Teflon-coated magnetic stirrer bars. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates with fluorescent indicator from Merck. Plates were visualized by treatment with UV, acidic *p*-anisaldehyde stain, or $KMnO_4$ stain with gentle heating. Products were purified by column chromatography using the solvent systems indicated. Silica gel 60, 230-400 mesh, was purchased from Fisher Scientific.

When necessary, solvents and reagents were purified before use. Tetrahydrofuran (THF), diethyl ether (ether), benzene, toluene (PhMe), and dichloromethane were passed through an alumina drying column (Solv-Tek Inc. or Innovative Technologies) using nitrogen pressure. Anhydrous dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetone, acetonitrile (MeCN), and methanol (MeOH) were obtained from Sigma-Aldrich. Ethyl acetate (EtOAc), petroleum ether, pentane, hexanes, MeOH, ether, dichloromethane, MeCN, PhMe, and THF were obtained from Fischer Scientific. Powdered 4Å molecular sieves (< 5 micron) were purchased from Aldrich and stored/activated as indicated. Amine bases (NEt_3, pyridine, diisopropylamine, diisopropylethylamine [Hünig's base]) were distilled over CaH_2 under nitrogen. Sodium borodeuteride was purchased from Cambridge Isotope Laboratories, and acetic acid-2-^{13}C was obtained from Isotec. All other reagents were purchased from commercial suppliers (Aldrich, Acros) and were either used as received without additional purification or were purified using standard methods. Preparative HPLC was carried out using an MeCN:H_2O gradient using a Shimadzu Prominence system equipped with a Restek 18 column (5 μm, 21 x 250 mm). NMR spectra were measured on a Varian INOVA 500 (^1H at 500 MHz, ^{13}C at 125 MHz), a Varian 400 (^1H at 400 MHz, ^{13}C at 100 MHz), or a Varian INOVA 600 MHz (^1H at 500 MHz, ^{13}C at 150 MHz) magnetic resonance spectrometer, as noted. ^1H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm; benzene = 7.16 ppm)[1] as follows: chemical shift (δ), (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, hept. = heptet, b = broad, *app* = apparent), integration, coupling constant(s) in Hz, proton ID [when available, designated by carbon number]). Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. Proton assignments were made via 2D spectroscopy (COSY, HSQC, and/or HMBC) or analogy. ^{13}C chemical shifts are reported relative to the residual deuterated solvent ^{13}C signals ($CDCl_3$ = 77.16 ppm, C_6D_6 = 128.06 ppm).[1] Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier Transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). Optical rotation data were obtained using a JASCO P-2000 Polarimeter are reported as $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\boldsymbol{T}}$ (*c* = grams/100 mL), where D indicates the sodium D line (589 nm) and T indicates temperature (all optical rotation values were obtained at ambient temperature, ca. 22-25 °C). Unless otherwise indicated, optical rotations are the average (± standard deviation) of 10 individual measurements. Optical rotations were not recorded for isomeric mixtures. High resolution mass spectra were obtained at the Vincent Coates Mass Spectrometry Laboratory, Stanford, CA 94305.

[1] Gottlieb, H.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

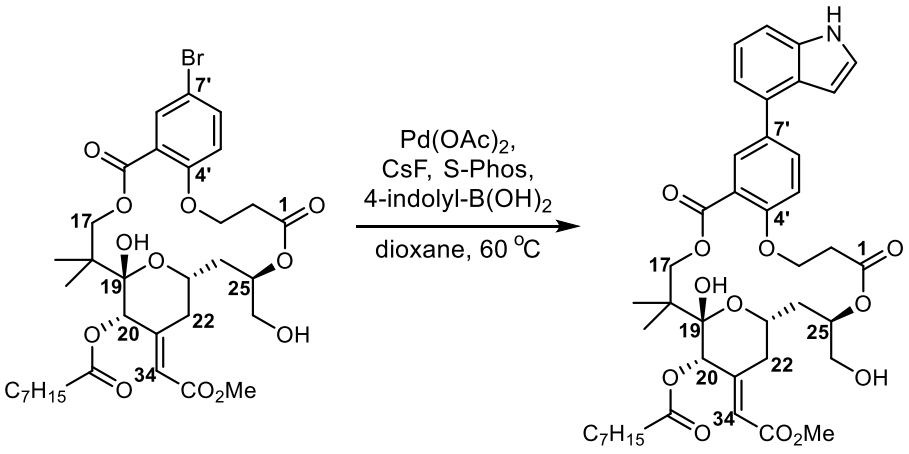
Experimental Methods; Characterization and Spectroscopic Data

For ease of comparison, all proton assignments are given by carbon number as it corresponds to the bryostatin 1 scaffold (see Figure S5). For instance, the carbons of the C20 octanoyl chain are both designated as C39-C46, even though not all analogs contain 46 carbons.



Bryostatin 1 (1)

Figure S3. Bryostatin 1 carbon numbering



2 ***43%*** **12**

Procedure for C7'-(4-indolyl) analog 12

$Pd(OAc)_2$ (1.8 mg, 8.0 µmol), S-Phos (7.7 mg, 19 µmol), and 4-indolylboronic acid (5.6 mg, 35 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (9.7 mg, 64 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **2** (4.9 mg, 6.9 µmol) was dissolved in 200 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd^0 solution (having stirred 20 min; dark red solution) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. TLC analysis showed consumption of starting material. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The now light orange reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→70% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 24.7 minutes. The C7'-(4-indolyl)-substituted analog **12** was obtained as a white solid (2.20 mg,[2] 42.7%).

*Characterization Data for C7'-(4-indolyl) analog **12**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.31 (s, 1H, NH), 8.19 (d, 1H, *J* = 2.4 Hz, Ar), 7.82 (dd, 1H, *J* = 8.6, 2.4 Hz, Ar), 7.40 (d, 1H, *J* = 8.5 Hz, indole), 7.28- 7.25 (m, 2H, indole), 7.18 (d, 1H, *J* = 8.6 Hz, Ar), 7.18 (dd, 1H, *J* = 7.3, 0.9 Hz, indole), 6.71-6.69 (m, 1H, indole), 6.01 (d, 1H, *J* = Hz, C34), 5.43-5.39 (m, 1H, C25), 5.32 (s, 1H, C20), 5.24 (s, 1H, C19-OH), 4.65-4.55 (m, 2H, C3), 4.44 (d, 1H, *J* = 11.4 Hz, C17), 4.34 (*app* t, 1H, *J* = 11.4 Hz, C23), 4.23 (d, 1H, *J* = 11.4 Hz, C17), 3.83 (ddd, 1H, *J* = 12.0, 4.7, 3.4 Hz, C26), 3.73 (dd, 1H, *J* = 14.3, 2.5 Hz, C22), 3.71 (s, 3H, CO_2Me), 3.64 (*app* dt, 1H, *J* = 12.3, 6.2 Hz, C26), 2.64-2.60 (m, 2H, C2), 2.37-2.26 (m, 2H, C40), 2.20 (*app* t, 1H, *J* = 13.5 Hz, C22), 2.04 (*app* t, 1H, *J* = 13.5 Hz, C24), 1.87 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.84 (dd, 1H, *J* = 6.8, 4.5 Hz, C26-OH), 1.64-1.57 (m, 2H, C41), 1.31-1.24 (m, 8H, C42-C45), 1.14 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.88 (t, 3H, *J* = 6.8 Hz, C46) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 170.7, 166.9, 166.3, 154.7, 151.8, 136.4, 136.1, 133.9, 132.7, 132.5, 126.0, 124.8, 123.6, 122.5, 119.8, 119.6, 116.9, 110.7, 102.0, 100.1, 73.5, 72.2, 71.5, 67.3, 65.6, 65.4, 51.3, 41.5, 35.9, 35.0, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm

IR (thin film): 3475, 2929, 1720, 1611, 1486, 1435, 1372, 1336, 1259, 1232, 1174, 1153, 1089, 1061, 1004, 914, 754, 730, 647 cm^{-1}

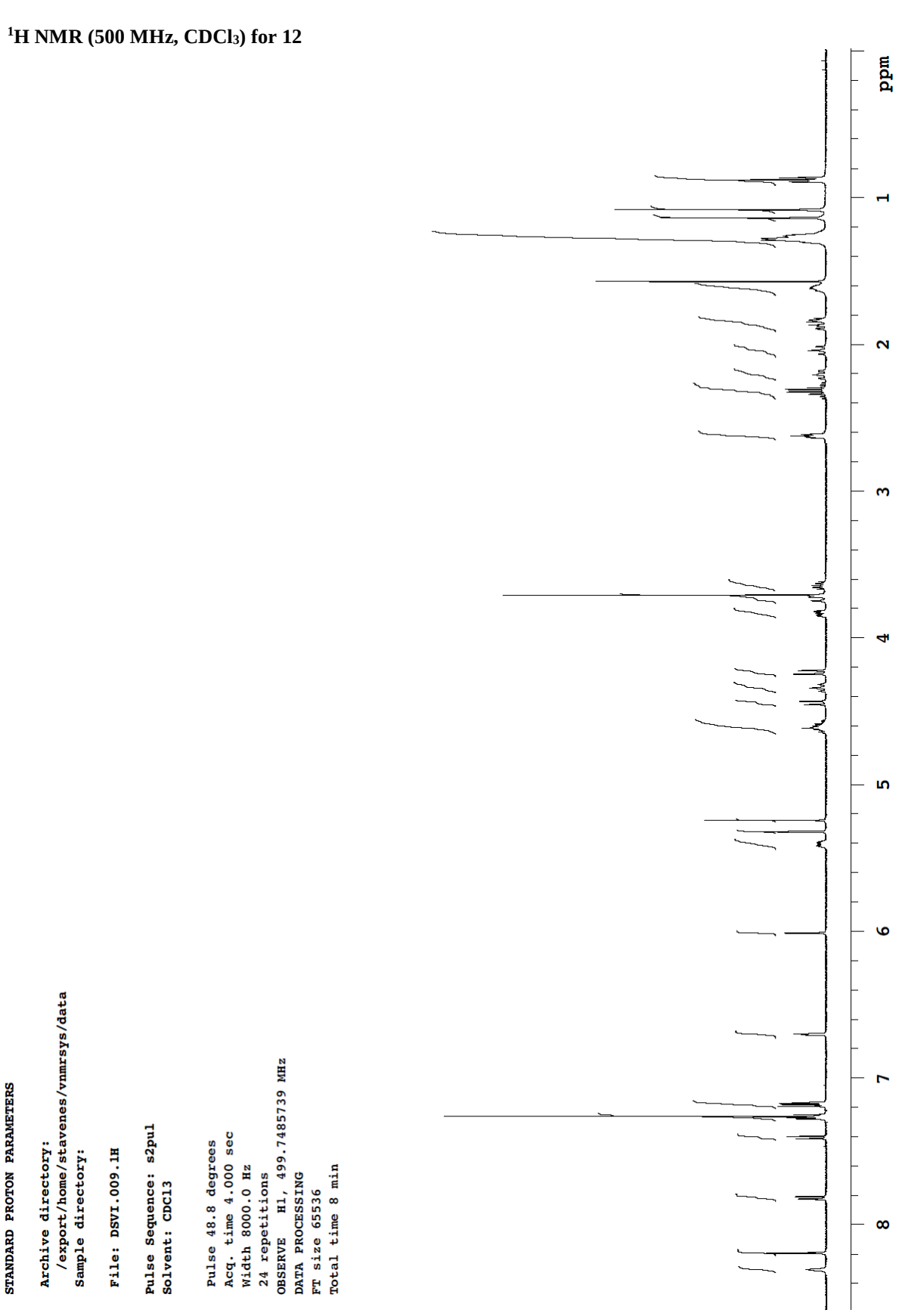
HRMS (ES+, *m/z)* calculated for $C_{41}H_{51}NNaO_{12}^+$: 772.3303, Found: 772.3302

$[\alpha]_D^{23.9\,°C}$ = -42.7 ± 0.6° (*c* = 0.3, CH_2Cl_2)

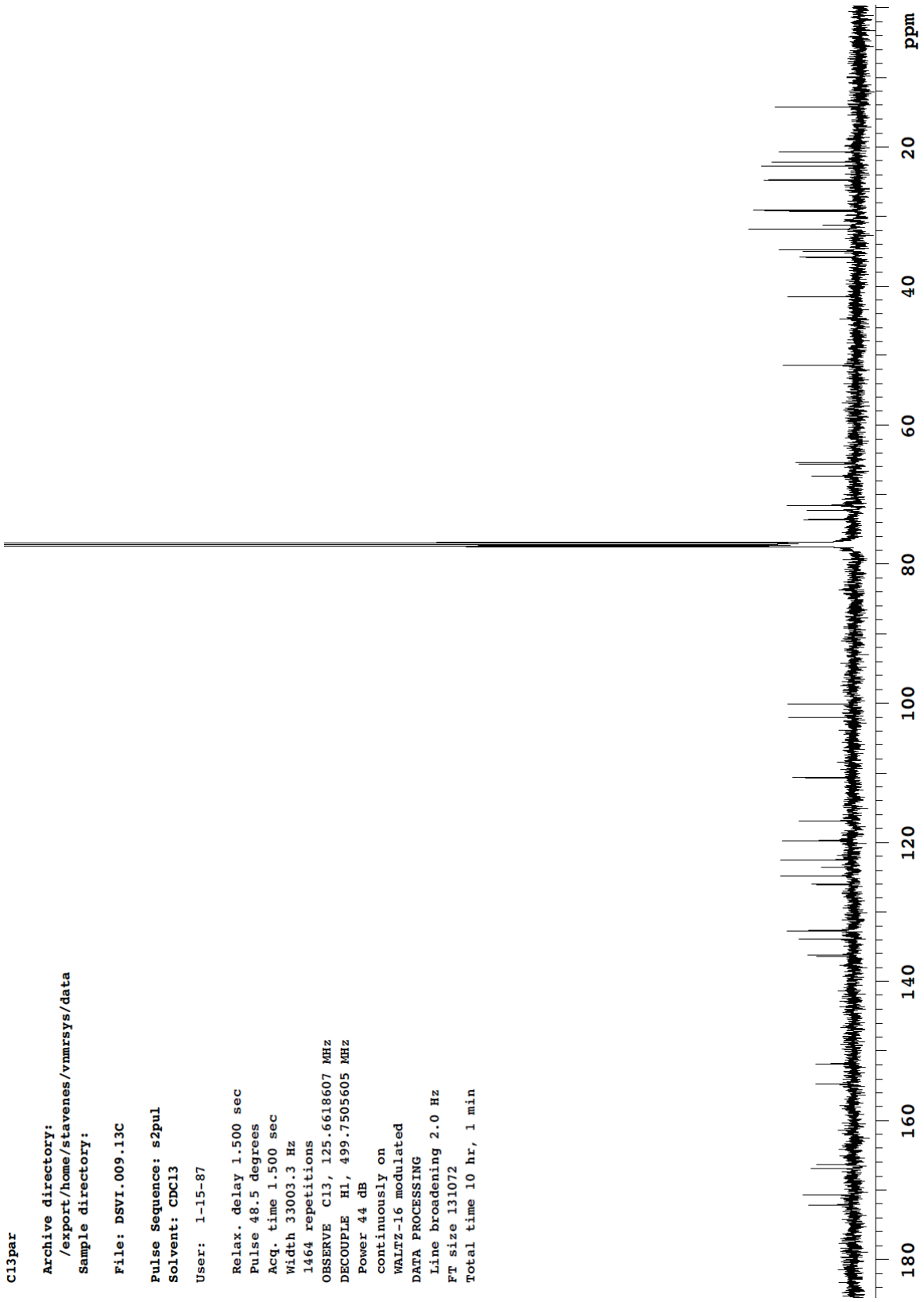
[2] Final amount of analog **12** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

R_f = 0.45 (70% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV (slightly fluorescent blue)

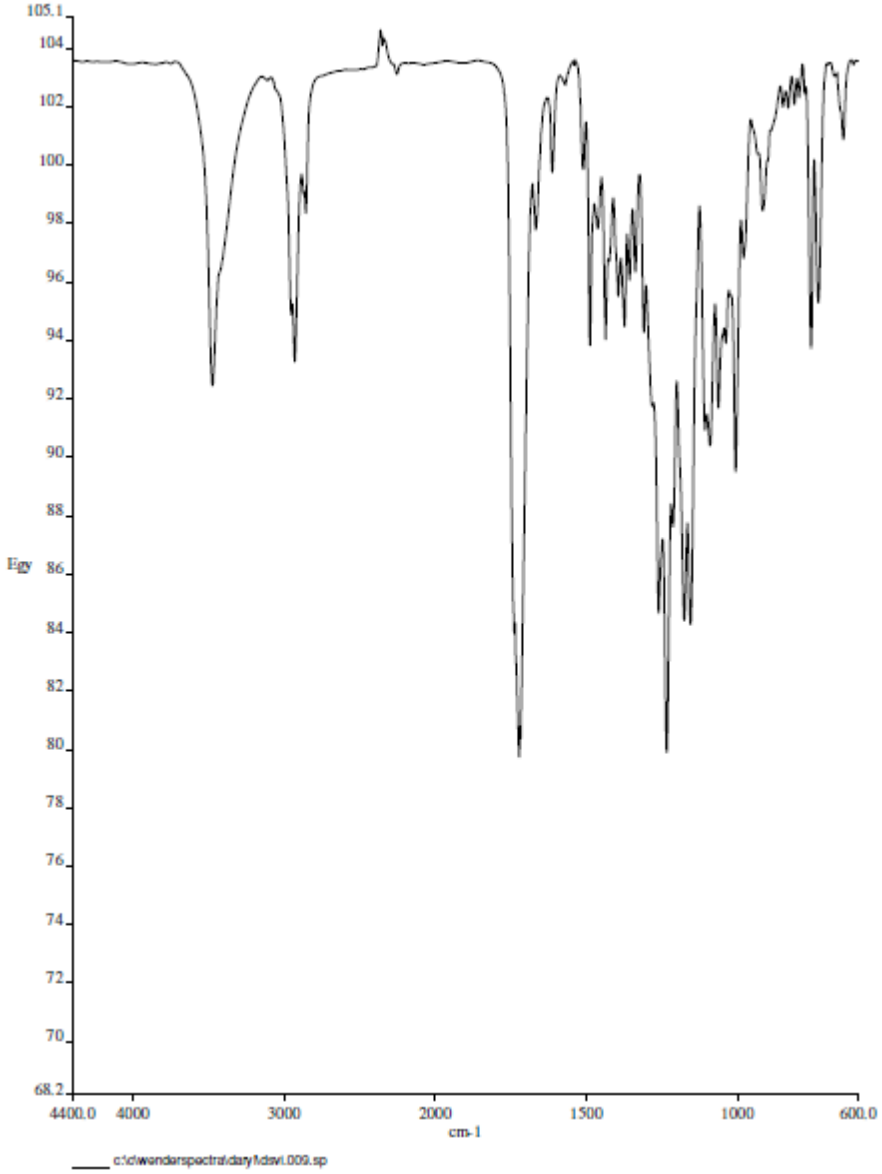
^{1}H NMR (500 MHz, $CDCl_3$) for 12



^{13}C NMR (125 MHz, $CDCl_3$) for 12



IR for 12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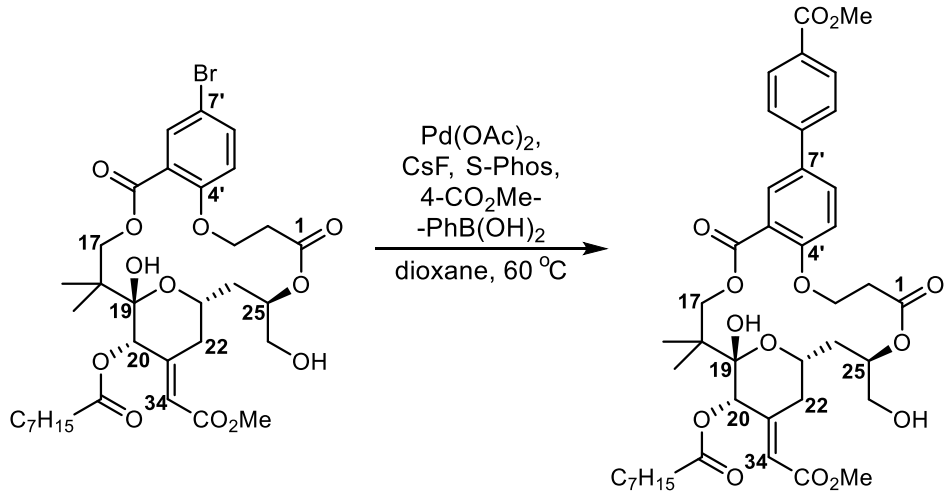


2 ***38%*** **13**

Procedure for C7'-(4-CO_2Me)-Ph analog 13

$Pd(OAc)_2$ (1.8 mg, 8.0 µmol), S-Phos (6.9 mg, 17 µmol), and 4-CO_2Me-phenyl boronic acid (6.3 mg, 35 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (9.6 mg, 63 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **2** (4.8 mg, 6.7 µmol) was dissolved in 200 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd^0 solution (having stirred 20 min; dark red solution) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. TLC analysis revealed appearance of product, but a number of small impurities made it difficult to determine whether or not starting material remained. Heated an additional 45 min at 60 ºC. The now light orange reaction mixture was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 29.8 minutes, but had an inseparable shoulder peak. ^{1}H NMR showed that this peak contained an ~2.3:1 mix of product to unreacted starting material. This mixture was exposed to the same conditions as above using the following amounts: $Pd(OAc)_2$ (1.6 mg, 7.1 µmol); S-Phos (6.6 mg, 16 µmol); boronic acid (5.7 mg, 32 µmol); CsF (7.6 mg, 50 µmol). Two hrs at 60 ºC was sufficient to consume the remaining starting material. HPLC purification as above then furnished the methyl benzoate-substituted analog **13** as a white solid (1.99 mg,[3] 38.4%).

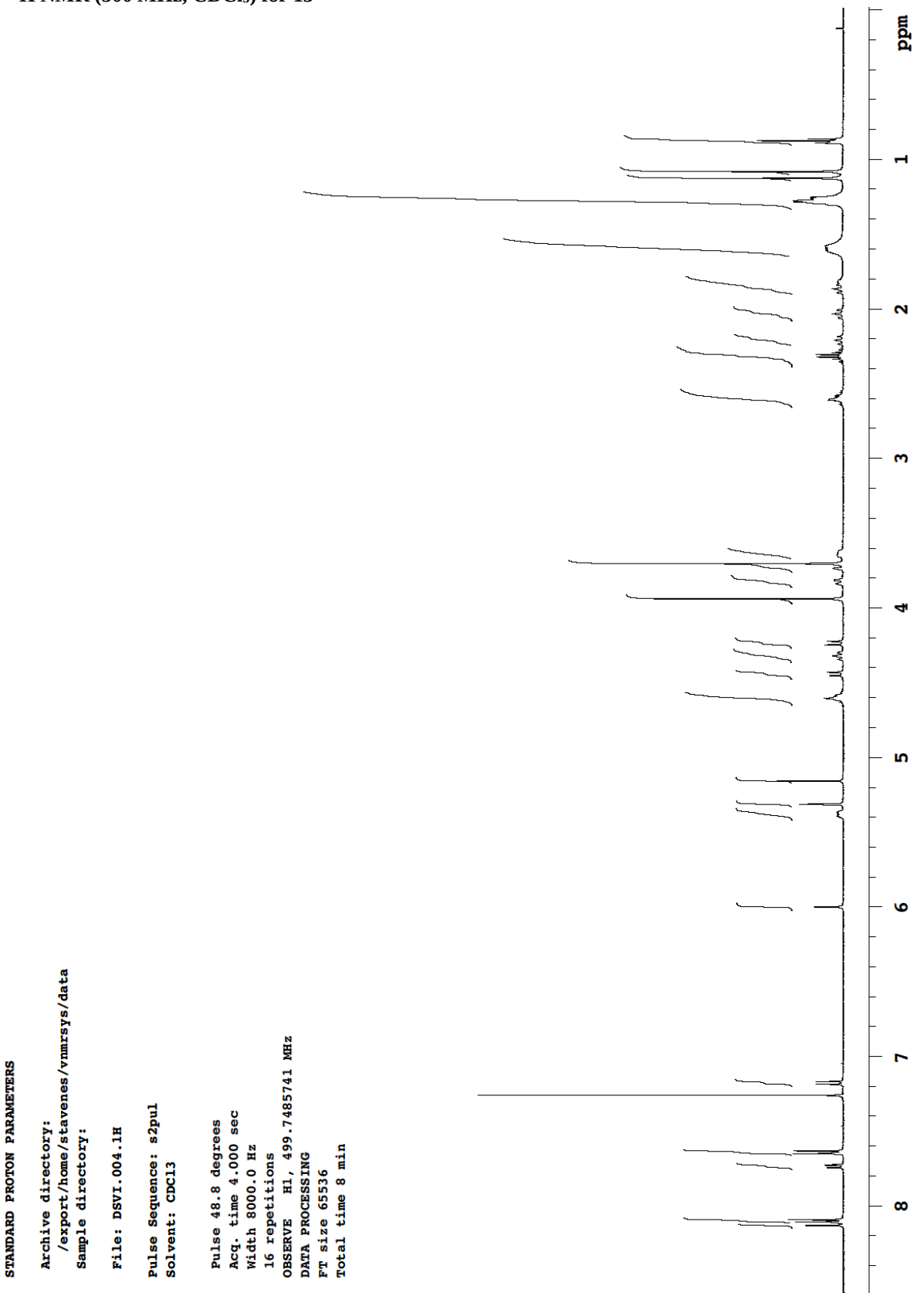
*Characterization Data for C7'-(4-CO_2Me)-Ph analog **13**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.13 (d, 1H, *J* = 2.3 Hz, Ar), 8.10 (d, 2H, *J* = 8.4 Hz, C_6H_4R), 7.73 (dd, 1H, *J* = 8.6, 2.5 Hz, Ar), 7.64 (d, 2H, *J* = 8.4 Hz, C_6H_4R), 7.18 (d, 1H, *J* = 8.9 Hz, Ar), 6.00 (s, 1H, C34), 5.41-5.35 (m, 1H, C25), 5.31 (s, 1H, C20), 5.15 (s, 1H, C19-OH), 4.64-4.56 (m, 2H, C3), 4.44 (d, 1H, *J* = 11.5 Hz, C17), 4.32 (*app* t, 1H, *J* = 11.5 Hz, C23), 4.23 (d, 1H, *J* = 11.5 Hz, C17), 3.94 (s, 3H, ArCO_2Me), 3.83 (d, 1H, *J* = 11.5 Hz, C26), 3.75-3.70 (m, 1H, C22), 3.70 (s, 3H, CO_2Me), 3.67-3.61 (m, 1H, C26), 2.64-2.54 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.21 (*app* t, 1H, *J* = 12.8 Hz, C22), 2.03 (*app* t, 1H, *J* = 12.8 Hz, C24), 1.87 (*app* t, 1H, *J* = 12.8 Hz, C24), 1.82 (br s, 1H, C26-OH), 1.65-1.54 (m, 2H, C41), 1.31-1.23 (m, 8H, C42-C45), 1.12 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.87 (t, 3H, *J* = 7.2 Hz, C46) ppm

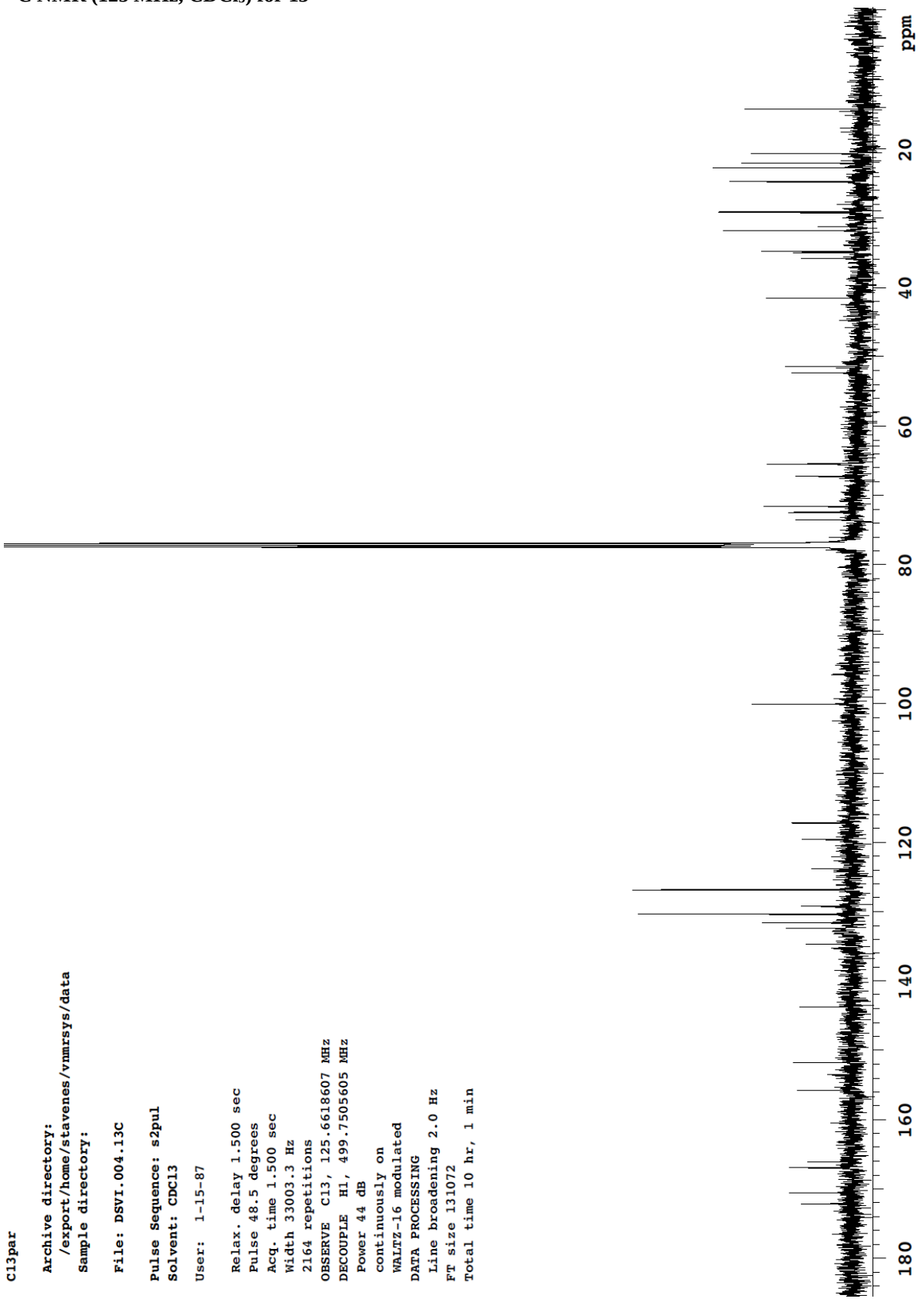
[3] Final amount of analog **13** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 170.5, 167.0, 166.9, 166.0, 155.8, 151.8, 143.7, 134.7, 132.4, 131.6, 130.4, 129.3, 126.9, 123.8, 119.6, 117.2, 100.1, 73.5, 72.4, 71.6, 67.2, 65.5, 65.4, 52.3, 51.4, 41.5, 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm
IR (thin film): 3475, 2929, 1721, 1608, 1488, 1434, 1372, 1262, 1232, 1182, 1155, 1106, 1045, 1004, 773, 730 cm^{-1}
HRMS (ES+, *m/z)* calculated for $C_{41}H_{52}NaO_{14}^{+}$: 791.3249, Found: 791.3252
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23.1\,^{\circ}C}} =$ -59.9 ± 0.8° (*c* = 0.2, CH_2Cl_2)
$\mathbf{R}_f$ = 0.40 (70% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV (slightly fluorescent blue)

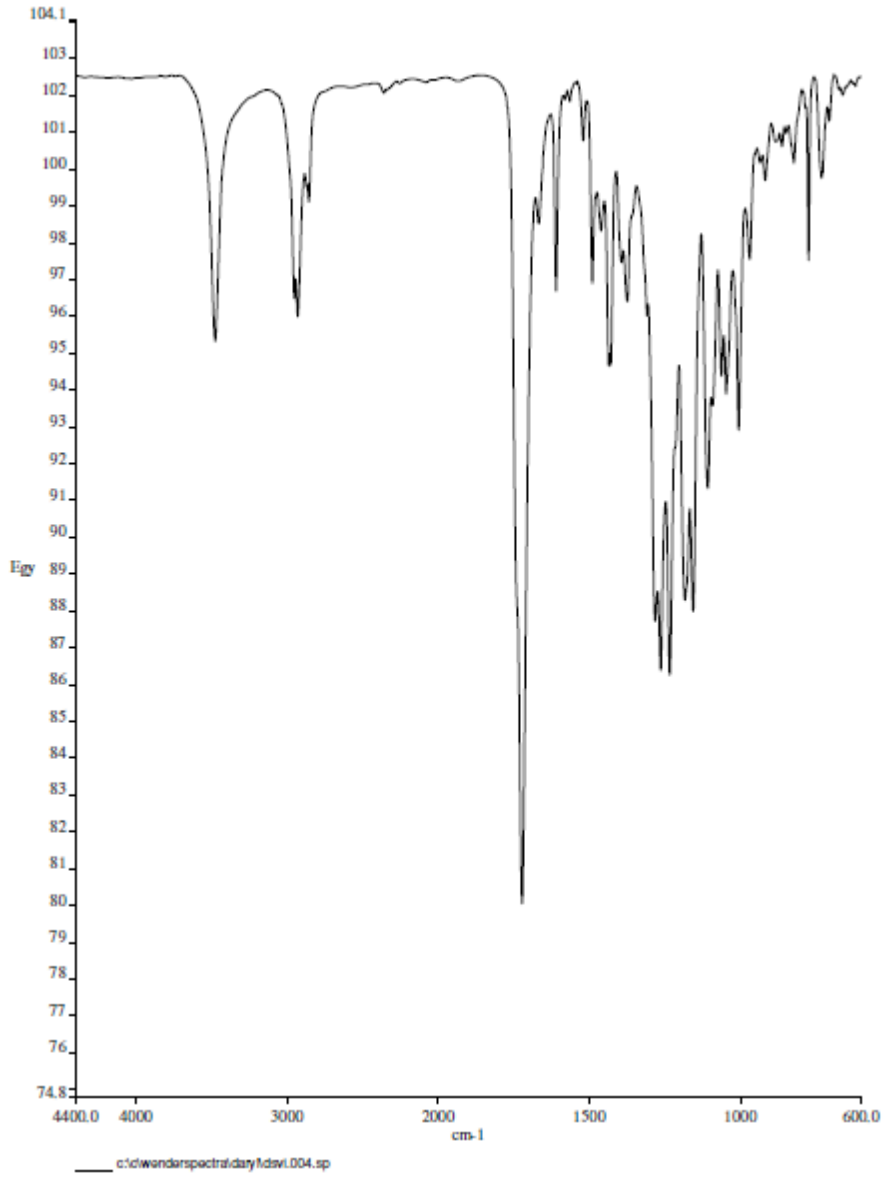
^{1}H NMR (500 MHz, $CDCl_3$) for 13



^{13}C NMR (125 MHz, $CDCl_3$) for 13



IR for 13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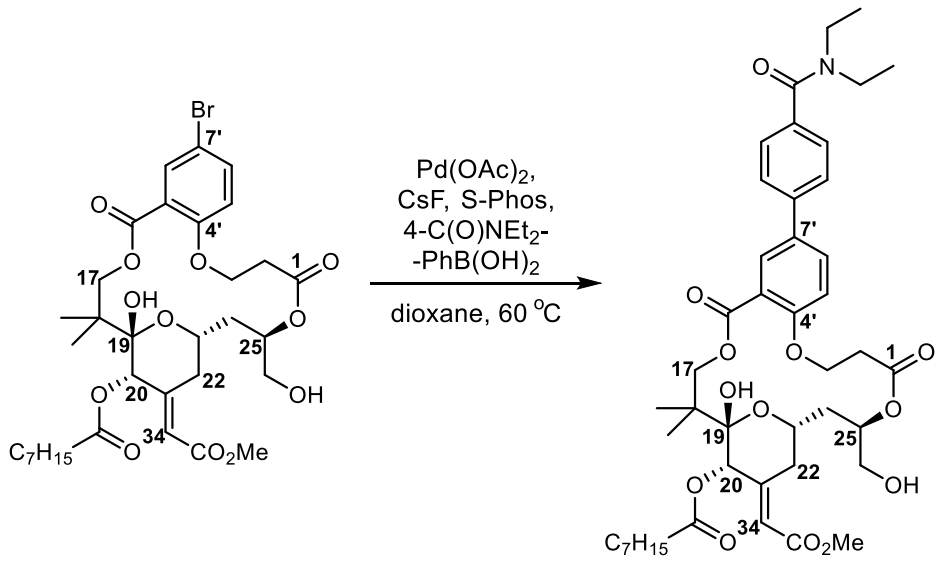


2 ***52%*** **15**

Procedure for C7'-(4-C(O)N(Et)$_2$)-Ph analog 15

$Pd(OAc)_2$ (2.2 mg, 9.8 µmol), S-Phos (7.7 mg, 19 µmol), and 4-methoxycarbamoylphenyl boronic acid (8.0 mg, 36 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (10.6 mg, 70 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **2** (4.7 mg, 6.6 µmol) was dissolved in 200 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd^0 solution (having stirred 20 min; dark red solution) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The now light orange reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (60→90% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H_2O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 14.9 minutes. The C7'-(4-methoxylcarbamoylphenyl)-substituted analog **15** was obtained as a white solid (2.74 mg,[4] 51.5%).

*Characterization Data for C7'-(4-C(O)N(Et)$_2$)-Ph analog **15**:*

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.09 (s, 1H, Ar), 7.70 (d, 1H, *J* = 9.0 Hz, Ar), 7.59 (d, 2H, *J* = 7.9 Hz, C_6H_4R), 7.44 (d, 2H, *J* = 7.9 Hz, C_6H_4R), 7.16 (d, 1H, *J* = 8.7 Hz, Ar), 6.00 (s, 1H, C34), 5.40-5.36 (m, 1H, C25), 5.31 (s, 1H, C20), 5.16 (s, 1H, C19-OH), 4.61-4.56 (m, 2H, C3), 4.43 (d, 1H, *J* = 11.2 Hz, C17), 4.32 (*app* t, 1H, *J* = 11.7 Hz, C23), 4.24 (d, 1H, *J* = 11.4 Hz, C17), 3.82 (dd, 1H, *J* = 11.9, 2.9 Hz, C26), 3.73-3.69 (m, 1H, C22), 3.70 (s, 3H, CO_2Me), 3.63 (dd, 1H, *J* = 12.0, 5.7 Hz, C26), 3.56 (br s, 2H, NEt), 3.30 (br s, 2H, NEt), 2.64-2.54 (m, 2H, C2), 2.36-2.26 (m, 2H, C40), 2.21 (*app* t, 1H, *J* = 12.7 Hz, C22), 2.03 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.86 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.64-1.58 (m, 2H, C41), 1.32-1.22 (m, 11H, C42-C45, NEt), 1.14 (br s, 3H, NEt), 1.12 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.88 (t, 3H, *J* = 7.3 Hz, C46) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 171.1, 170.6, 166.9, 166.1, 155.4, 151.8, 140.2, 136.4, 135.2, 132.2, 131.4, 127.1, 127.0, 123.7, 119.6, 117.2, 100.1, 73.5, 72.4, 71.5, 67.3, 65.5, 65.4, 51.3, 43.5 (br, NEt), 41.5, 39.4 (br, NEt), 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.4, 14.2 (br, NEt), 13.1 (br, NEt) ppm

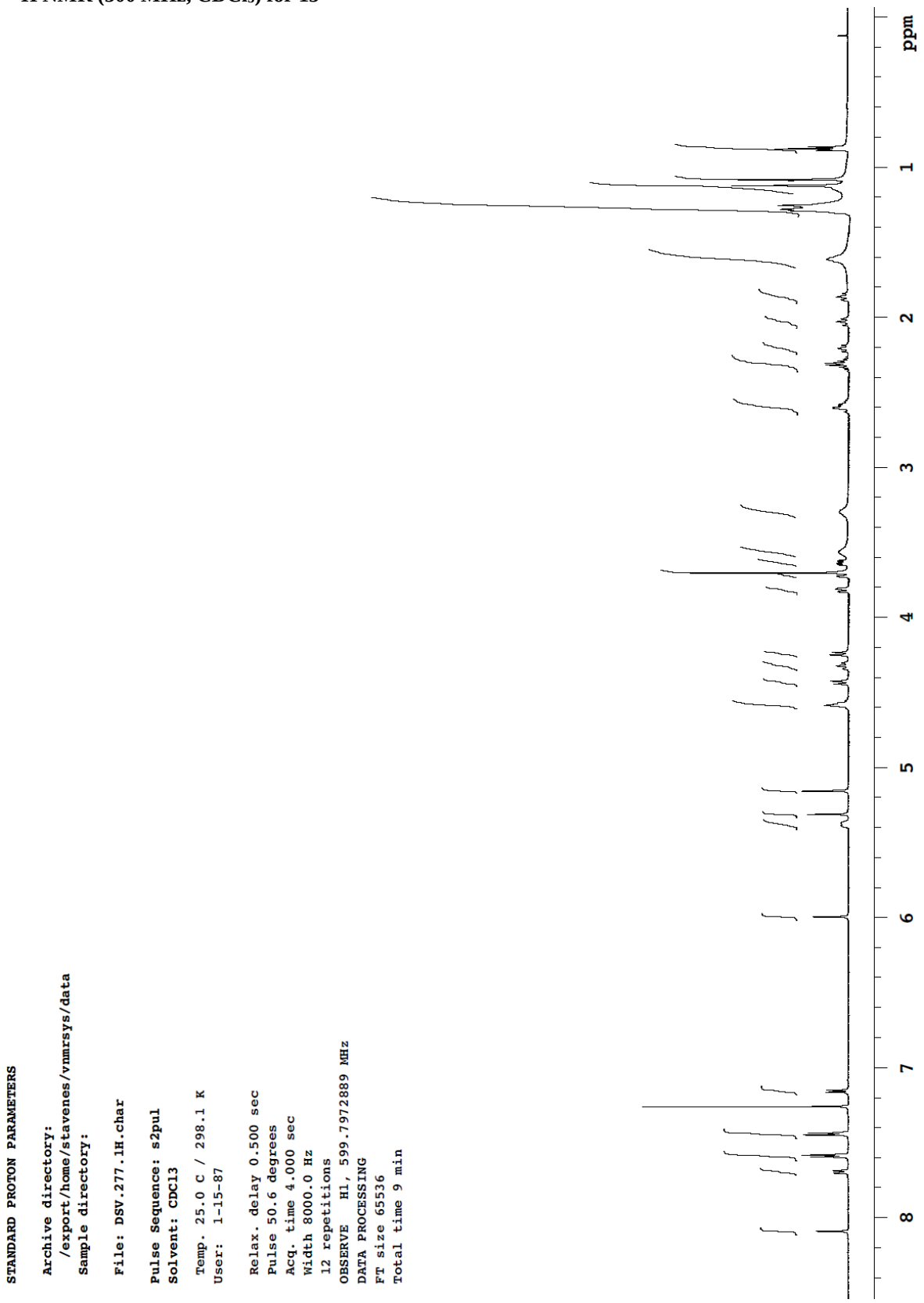
IR (thin film): 3473, 2930, 2360, 1718, 1610, 1424, 1374, 1232, 1155, 1090, 1062, 1004 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{44}H_{59}NNaO_{13}^+$: 832.3879, Found: 832.3888

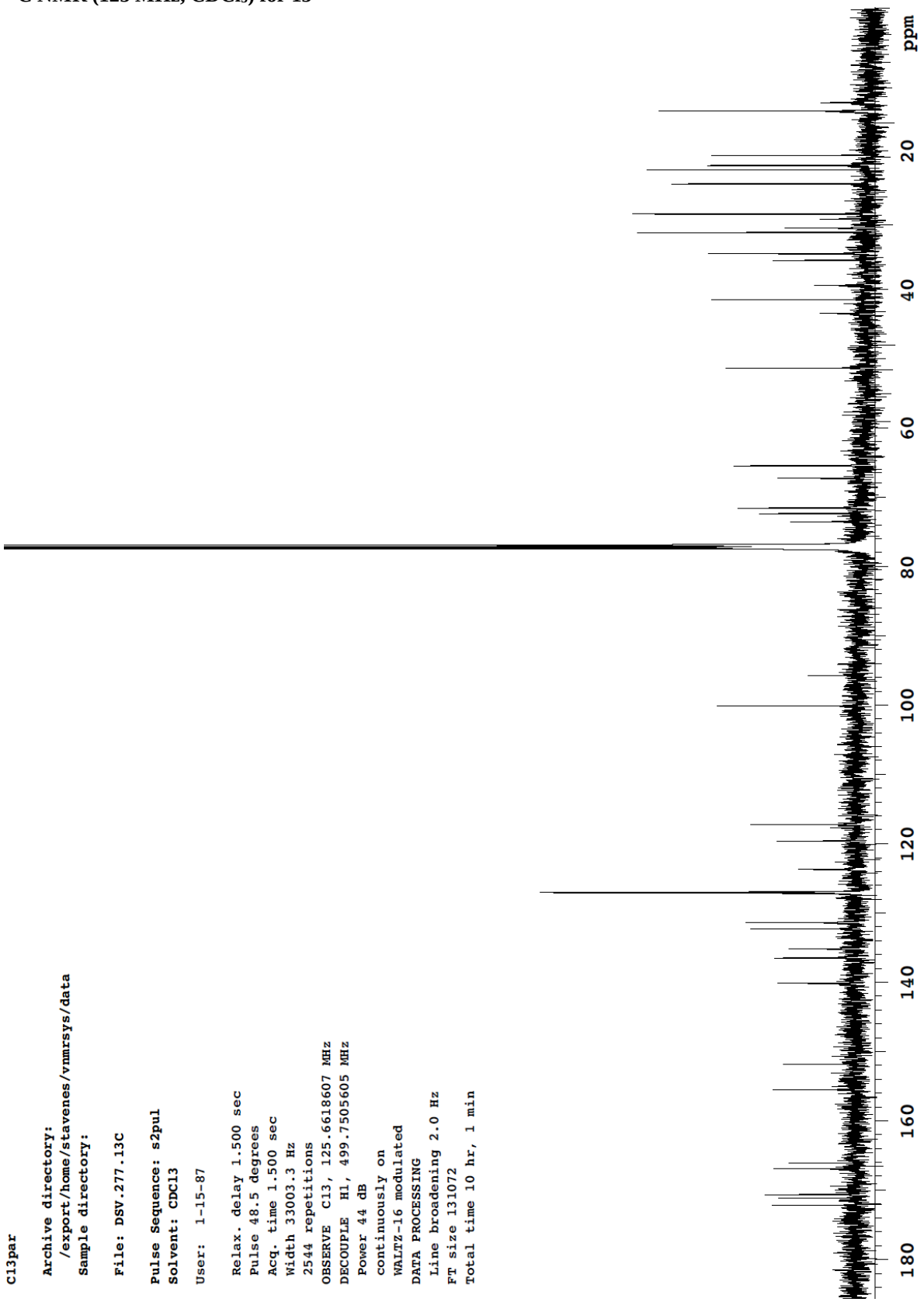
[4] Final amount of analog **15** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23.2\ ^{\circ}C}}$ = -54.5 ± 0.8° (*c* = 0.3, CH_2Cl_2)
$\mathbf{R}_f$ = 0.10 (70% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV (slightly fluorescent blue)

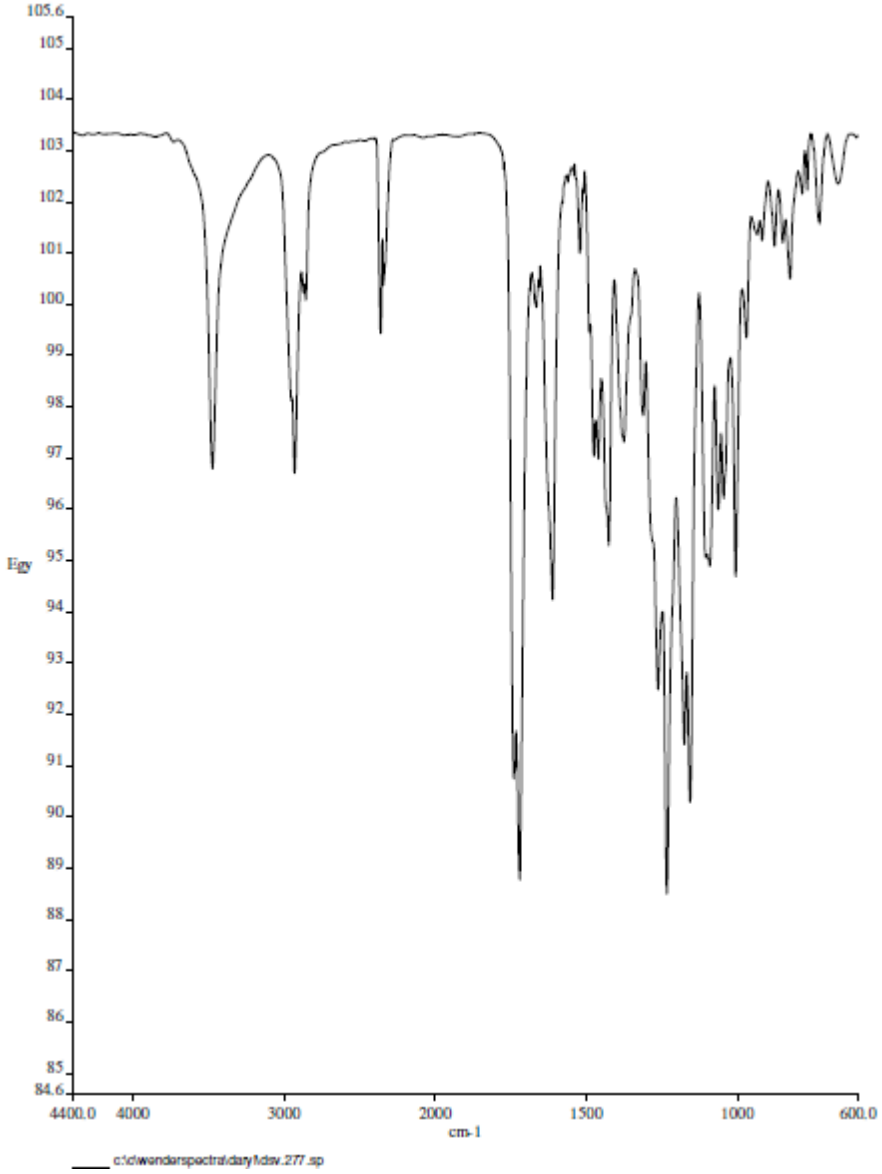
^{1}H NMR (500 MHz, $CDCl_3$) for 15



^{13}C NMR (125 MHz, $CDCl_3$) for 15



IR for 15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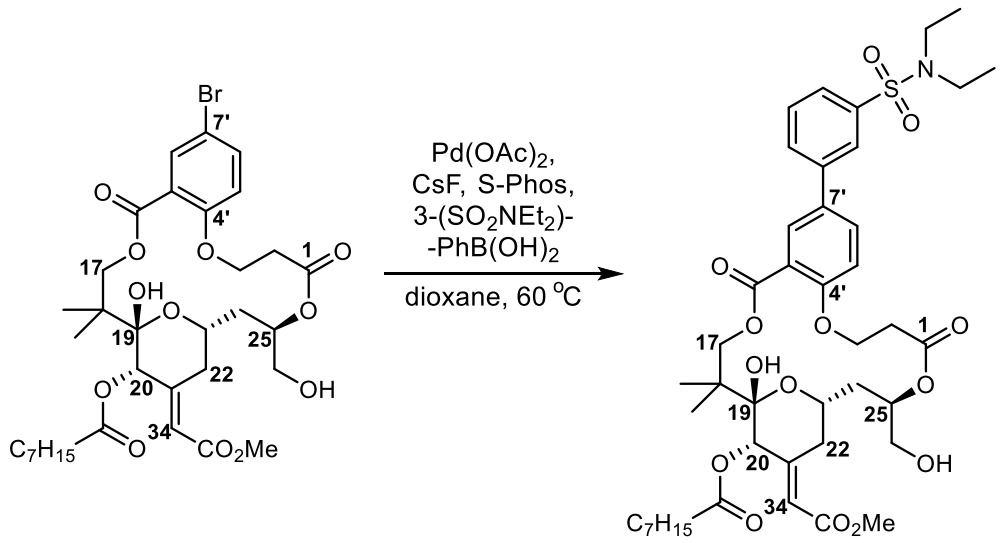


2 ***26%*** **17**

Procedure for C7'-(3-$SO_2N(Et)_2$)-Ph analog 17

$Pd(OAc)_2$ (1.9 mg, 8.4 µmol), S-Phos (6.8 mg, 17 µmol), and 3-diethylsulfamoylphenyl boronic acid (8.6 mg, 34 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (7.2 mg, 47 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **2** (4.8 mg, 6.7 µmol) was dissolved in 200 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd^0 solution (having stirred 20 min; dark red solution) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. TLC analysis showed consumption of starting material. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The now light orange reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H_2O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 18.1 minutes. The C7'-(3-diethylsulfamoylphenyl)-substituted analog **17** was obtained as a white solid (1.46 mg,[5] 25.7%).

*Characterization Data for C7'-(3-$SO_2N(Et)_2$)-Ph analog **17**:*

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.09 (d, 1H, *J* = 2.4 Hz, Ar), 7.89 (s, 1H, C_6H_4R), 7.78 (d, 1H, *J* = 8.1 Hz, C_6H_4R), 7.74 (d, 1H, *J* = 8.1 Hz, C_6H_4R), 7.71 (dd, 1H, *J* = 8.6, 2.5 Hz, Ar), 7.56 (t, 1H, *J* = 7.9 Hz, C_6H_4R), 7.18 (d, 1H, *J* = 8.7 Hz, Ar), 6.00 (s, 1H, C34), 5.40-5.35 (m, 1H, C25), 5.32 (s, 1H, C20), 5.13 (s, 1H, C19-OH), 4.63-4.56 (m, 2H, C3), 4.45 (d, 1H, *J* = 11.1 Hz, C17), 4.32 (*app* t, 1H, *J* = 11.1 Hz, C23), 4.24 (d, 1H, *J* = 11.1 Hz, C17), 3.82 (dd, 1H, *J* = 12.2, 3.2 Hz, C26), 3.74-3.70 (m, 1H, C22), 3.71 (s, 3H, CO_2Me), 3.64 (dd, 1H, *J* = 12.0, 5.6 Hz, C26), 3.27 (4H, quart., *J* = 7.2 Hz, NEt_2), 2.66-2.55 (m, 2H, C2), 2.37-2.26 (m, 2H, C40), 2.22 (*app* t, 1H, *J* = 13.4 Hz, C22), 2.03 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.85 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.65-1.59 (m, 2H, C41), 1.32-1.21 (m, 8H, C42-C45), 1.15 (t, 6H, *J* = 7.1 Hz, NEt_2), 1.13 (s, 3H, C18-Me), 1.09 (s, 3H, C18-Me), 0.88 (t, 3H, *J* = 7.1 Hz, C46) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 170.6, 166.9, 166.0, 155.8, 151.8, 141.3, 140.5, 134.2, 132.4, 131.5, 130.7, 129.8, 126.0, 125.4, 123.9, 119.6, 117.3, 100.1, 73.5, 72.5, 71.6, 67.2, 65.5, 65.4, 51.4, 42.3, 41.5, 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.3, 14.2 ppm

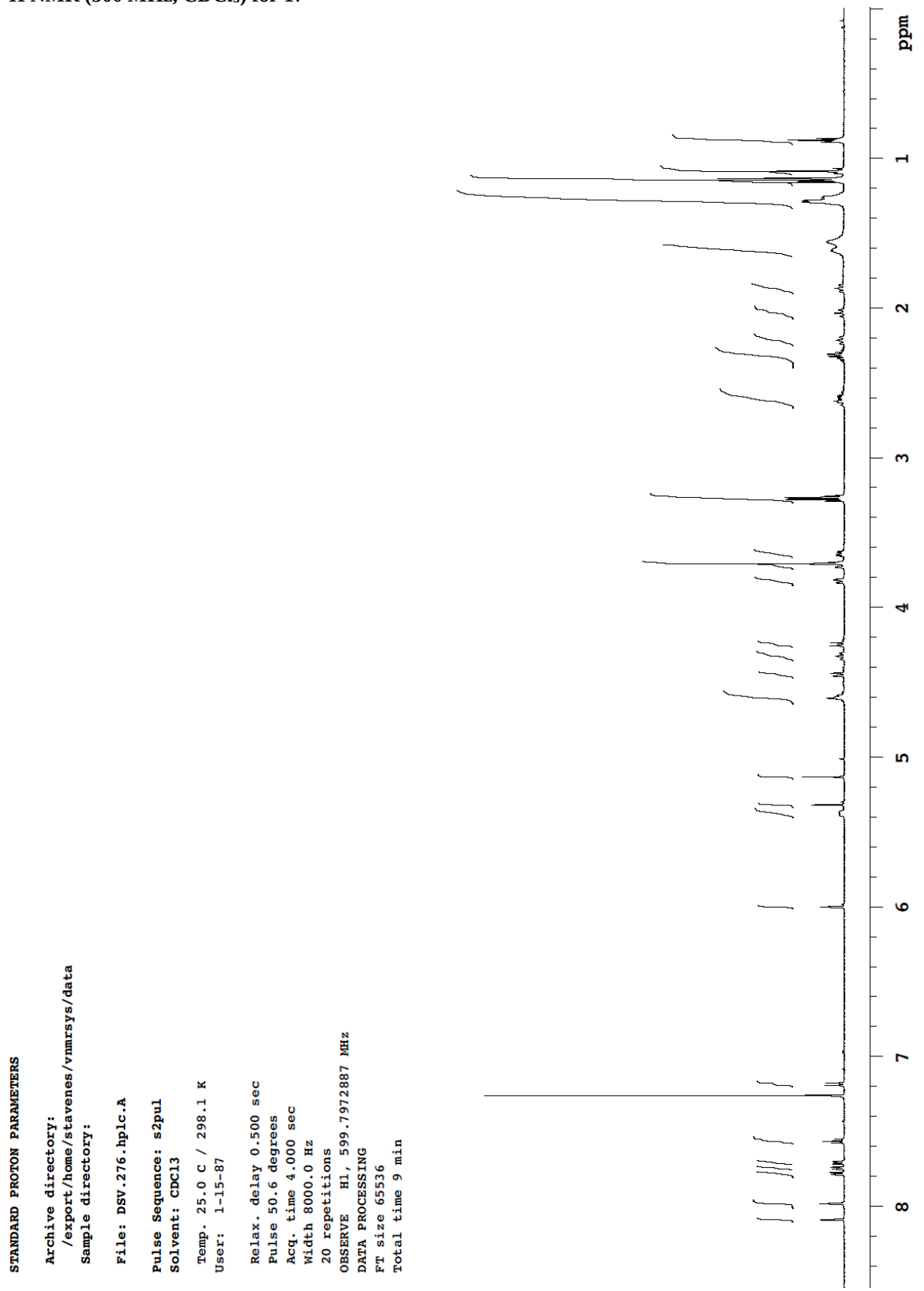
IR (thin film): 3478, 2931, 1720, 1470, 1433, 1232, 1153, 1105, 1058, 1005, 701 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{43}H_{59}NNaO_{14}S^+$: 868.3548, Found: 868.3552

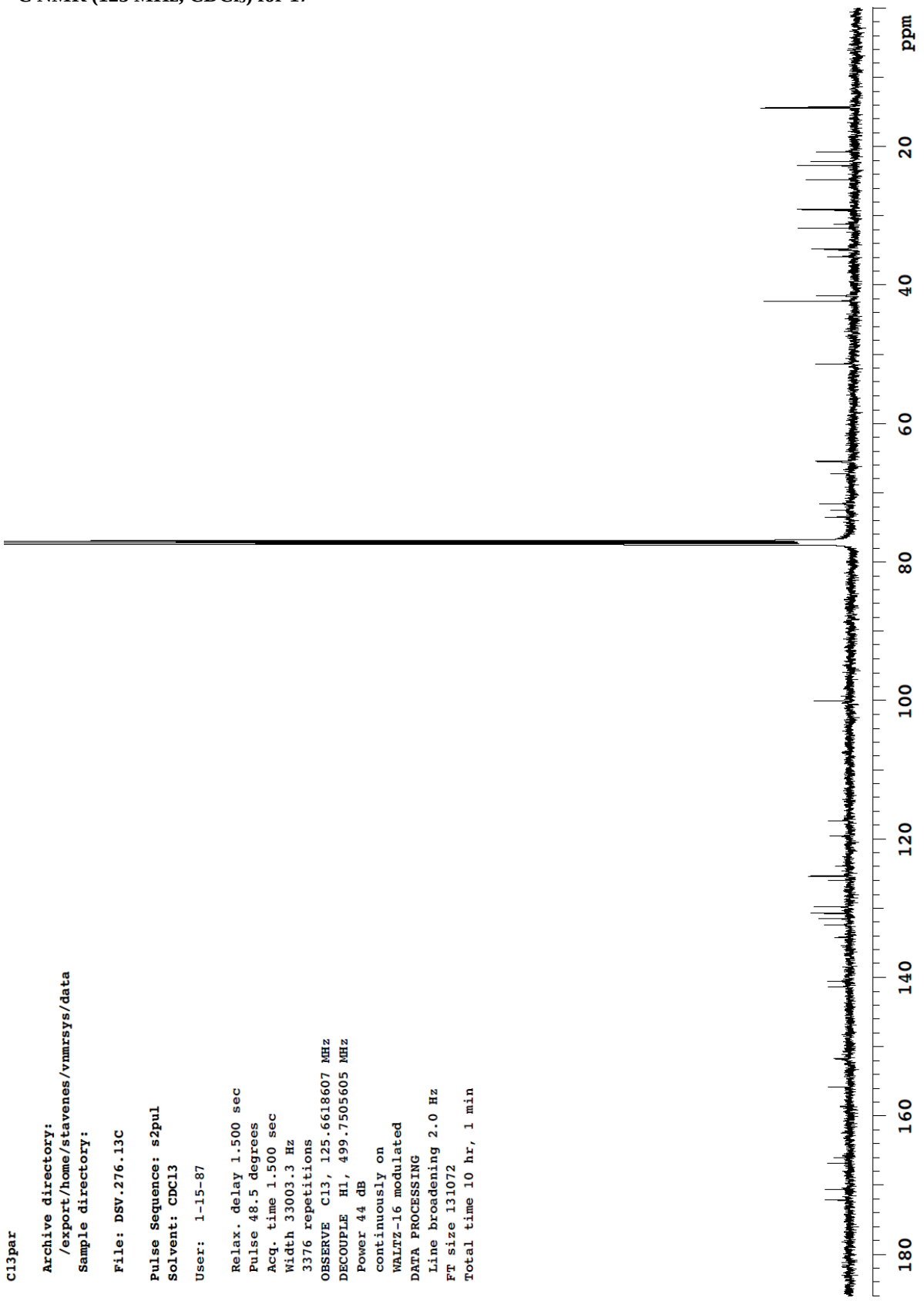
[5] Final amount of analog 17 was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{22.9\ ^{\circ}C}}$ = -19.8 ± 0.6° (*c* = 0.3, CH_2Cl_2)
$\mathbf{R}_f$ = 0.40 (70% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV (slightly fluorescent blue)

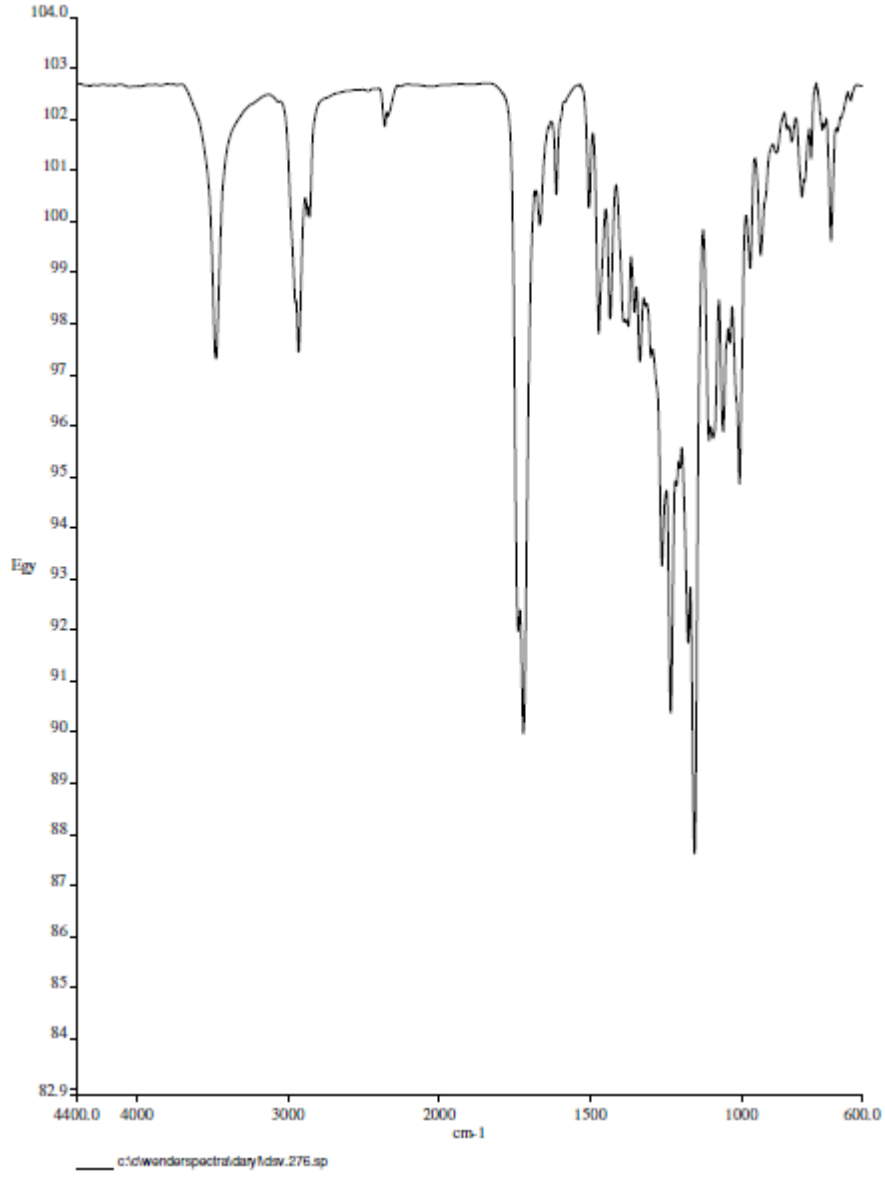
^{1}H NMR (500 MHz, $CDCl_3$) for 17



^{13}C NMR (125 MHz, $CDCl_3$) for 17



IR for 17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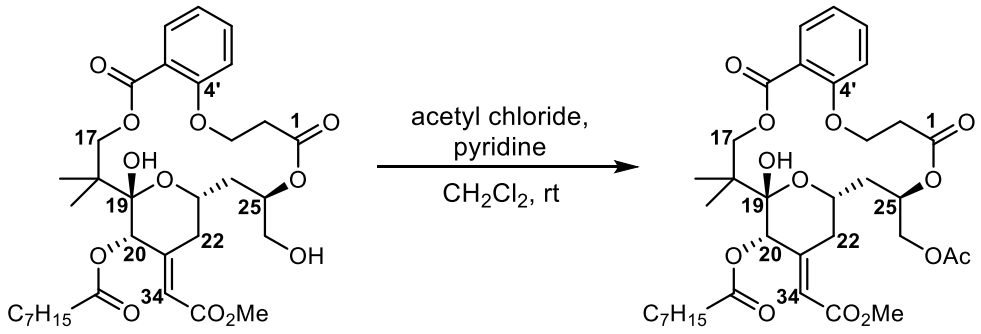


1 *41%* **19**

Procedure for C26-OAc analog 19

Dissolved salicylate-derived analog **1** (4.1 mg, 6.5 µmol) in 350 µL dry CH_2Cl_2 before adding pyridine (2.1 µL, 26 µmol) and acetyl chloride (0.7 µL, 9.7 µmol) respectively in one portion each. Stirred reaction mixture 2 hrs at rt at which point all starting material was consumed. Reaction was quenched with 1 mL sat. NH_4Cl and diluted with 1 mL water and 1 mL ether. Phases were separated. Aqueous phase was further extracted with four 1 mL aliquots of ether. Combined organic phases were washed with 1 mL brined, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (25→50% ethyl acetate:pentane). The C26-acetate analog **19** was obtained as a white solid (1.77 mg, [6] 40.6%).

*Characterization Data for C26-OAc analog **19**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (dd, 1H, *J* = 8.0, 2.0 Hz, Ar), 7.47 (ddd, 1H, *J* = 8.3, 7.4, 1.8 Hz, Ar), 7.11 (*app* t, 1H, *J* = 7.6 Hz, Ar), 7.08 (d, 1H, *J* = 8.4 Hz, Ar), 6.00 (d, 1H, *J* = 1.8 Hz, C34), 5.52-5.46 (m, 1H, C25), 5.28 (s, 1H, C20), 5.20 (s, 1H, C19-OH), 4.56-4.47 (m, 2H, C3), 4.39 (d, 1H, *J* = 11.4 Hz, C17), 4.31 (dd, 1H, *J* = 12.2, 3.1 Hz, C26), 4.29 (*app* t, 1H, *J* = 11.3 Hz, C23), 4.23 (d, 1H, *J* = 11.3 Hz, C17), 4.05 (dd, 1H, *J* = 12.2, 5.4 Hz, C26), 3.73 (dd, 1H, *J* = 13.8, 2.2 Hz, C22), 3.70 (s, 3H, CO_2Me), 2.54-2.45 (m, 2H, C2), 2.36-2.25 (m, 2H, C40), 2.17 (*app* t, 1H, *J* = 12.3 Hz, C22), 2.06 (s, 3H, OAc), 1.99 (*app* t, 1H, *J* = 12.3 Hz, C24), 1.84 (*app* t, 1H, *J* = 12.3 Hz, C24), 1.64-1.54 (m, 2H, C41), 1.31-1.23 (m, 8H, C42-C45), 1.10 (s, 3H, C18-Me), 1.07 (s, 3H, C18-Me), 0.88 (t, 3H, *J* = 7.1 Hz, C46) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 170.7, 169.3, 166.9, 156.0, 151.7, 133.8, 132.8, 123.6, 122.9, 119.7, 117.1, 100.1, 73.4, 72.1, 67.7, 67.5, 65.5, 65.2, 51.3, 41.4, 35.9, 34.8,[7] 31.8, 31.0, 29.2, 29.0, 24.8, 22.7, 22.1, 21.0, 20.6, 14.2 ppm

IR (thin film): 3471, 2928, 1748, 1602, 1452, 1375, 1295, 1229, 1173, 1127, 1046, 1005, 759 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{35}H_{48}NaO_{13}^+$: 699.2987, Found: 699.2992

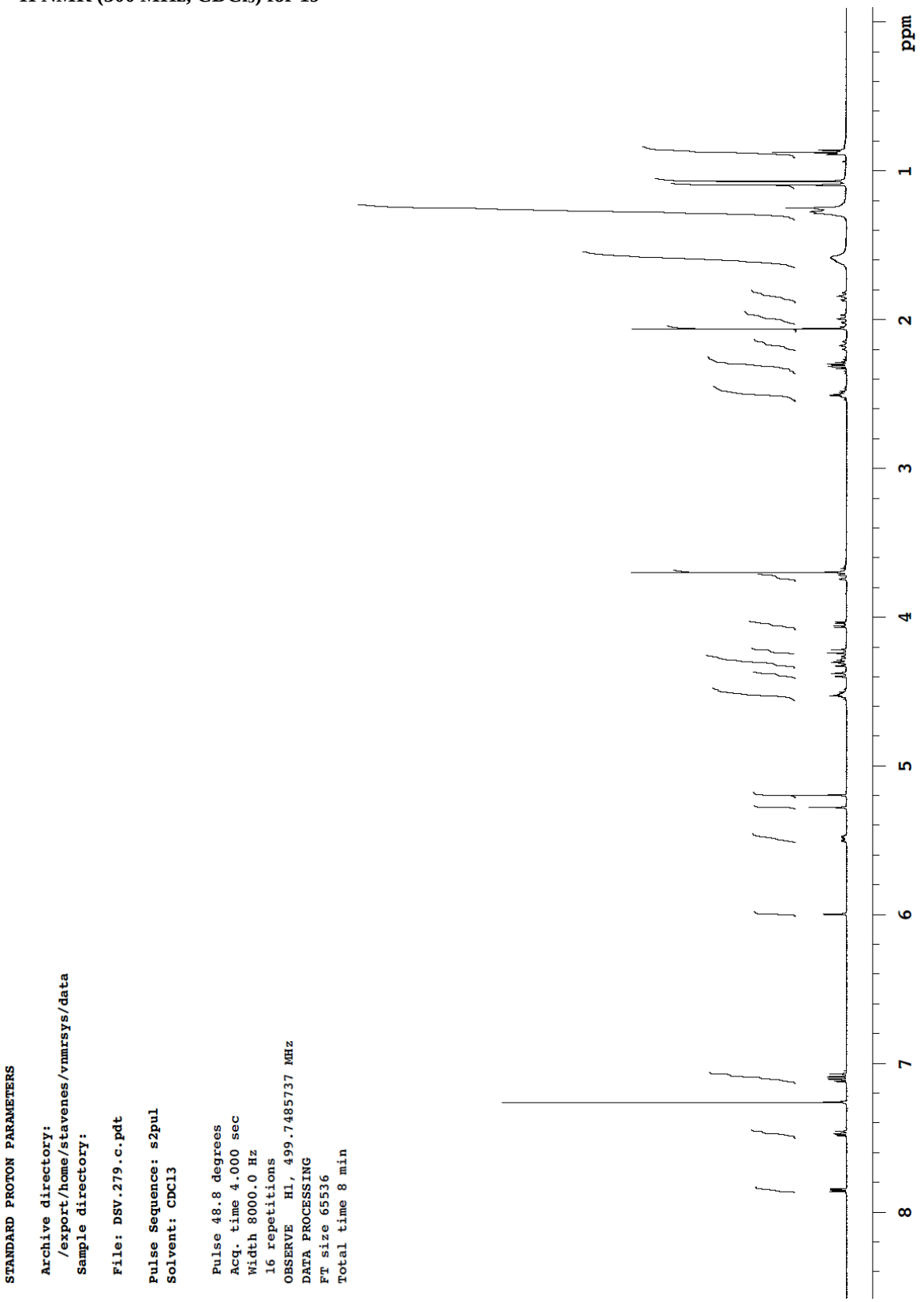
$[\alpha]_D^{23.5\,°C} = 6.1 \pm 0.4°$ (*c* = 0.3, CH_2Cl_2)

$\mathbf{R}_f$ = 0.35 (60% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV

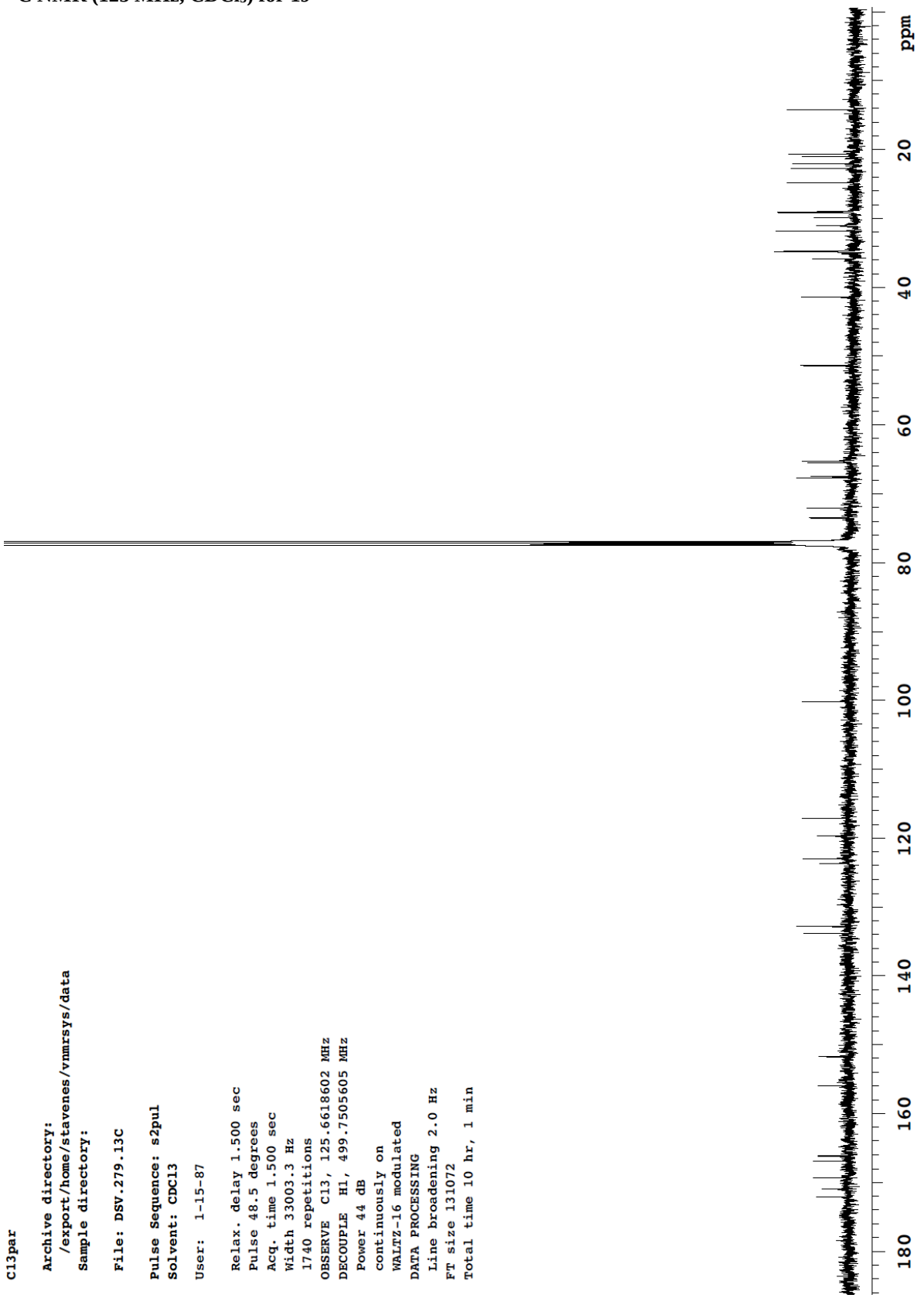
[6] Final amount of analog **19** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

[7] Suspected to be two unresolved resonances based on analogy to related analogs.

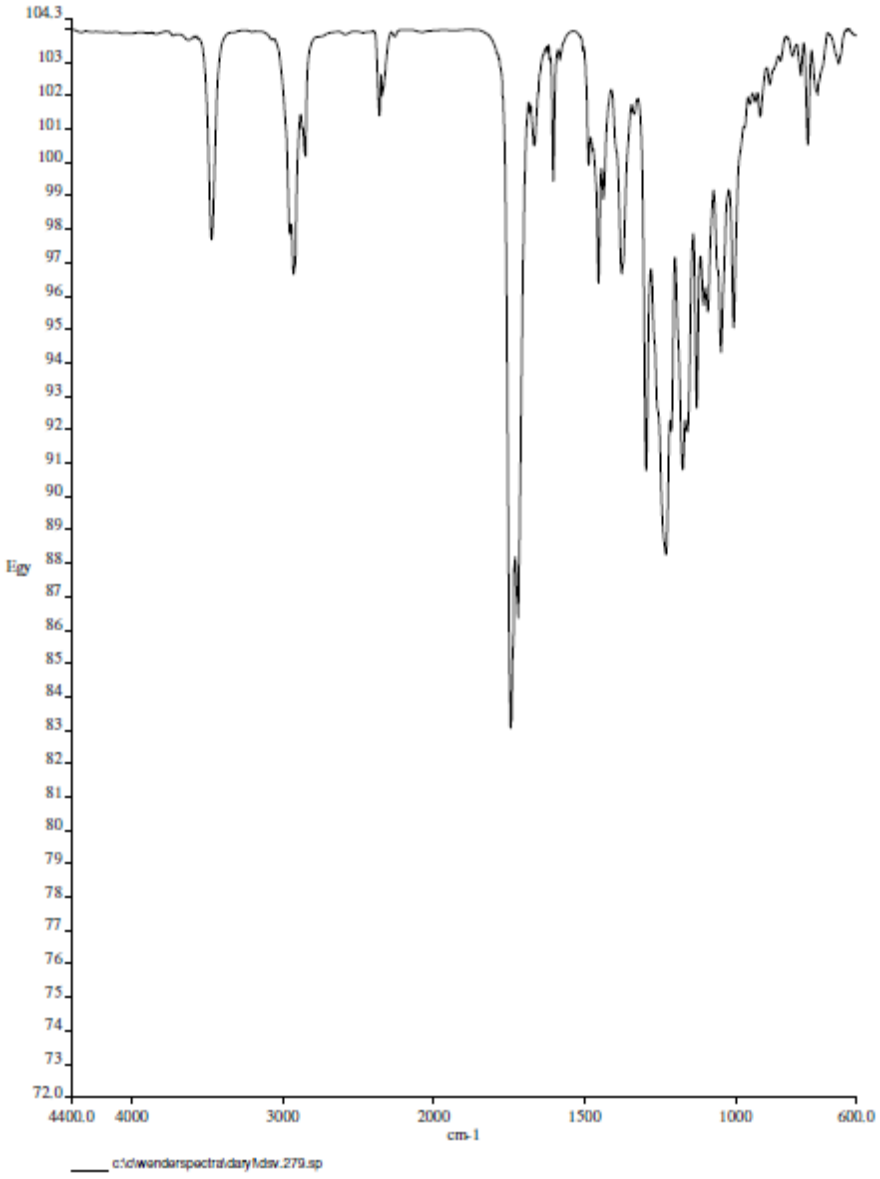
^{1}H NMR (500 MHz, $CDCl_3$) for 19



^{13}C NMR (125 MHz, $CDCl_3$) for 19



IR for 19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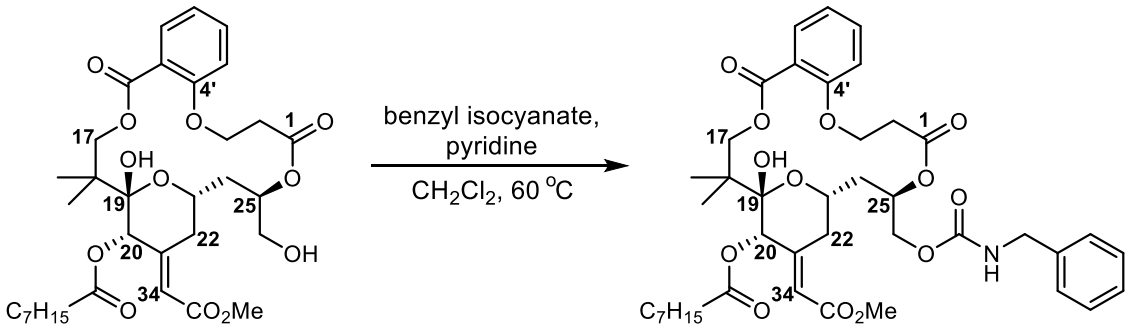


1 ***80%*** **20**

Procedure for C26-O(CO)NHBn analog 20

Dissolved salicylate-derived analog **1** (3.6 mg, 5.7 µmol) in 350 µL dry CH_2Cl_2 before adding pyridine (1.8 µL, 23 µmol) and benzyl isocyanate (1.1 µL, 8.5 µmol) respectively in one portion each. Stirred reaction mixture 2 hrs at rt; no visible reaction by TLC. Additional pyridine (2.0 µL, 25 µmol) and benzyl isocyanate (1.1 µL, 8.5 µmol) was added, flushed vial with Ar, capped, heated to 60 °C for 2 hrs; only ~10% conversion. Added additional pyridine (5.0 µL, 62 µmol) and benzyl isocyanate (2.5 µL, 20 µmol), heated under Ar at 50 °C for 10 hrs to finally achieve complete consumption of starting material. Reaction was quenched with 1 mL sat. NH_4Cl and diluted with 1 mL water and 1 mL ether. Phases were separated. Aqueous phase was further extracted with four 1 mL aliquots of ether. Combined organic phases were washed with 1 mL brined, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (25→35→50% ethyl acetate:pentane). The C26-benzyl carbamate analog **20** was obtained as a white solid (3.47 mg, [8] 79.7%).

*Characterization Data for C26-O(CO)NHBn analog **20**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (dd, 1H, *J* = 7.8, 1.8 Hz, Ar), 7.47 (ddd, 1H, *J* = 8.2, 7.5, 1.9 Hz, Ar), 7.37-7.30 (m, 3H, Ph), 7.30-7.25 (m, 2H, Ph), 7.11 (*app* t, 1H, *J* = 7.7 Hz, Ar), 7.08 (d, 1H, *J* = 8.6 Hz, Ar), 5.99 (d, 1H, *J* = 1.9 Hz, C34), 5.52-5.46 (m, 1H, C25), 5.28 (s, 1H, C20), 5.19 (s, 1H, C19-OH), 5.05 (t, 1H, *J* = 6.3 Hz, NH), 4.53-4.46 (m, 2H, C3), 4.39 (d, 1H, *J* = 11.3 Hz, C17), 4.35 (d, 2H, *J* = 6.2 Hz, NHBn), 4.31 (dd, 1H, *J* = 12.2, 3.2 Hz, C26), 4.27 (*app* t, 1H, *J* = 11.3 Hz, C23), 4.22 (d, 1H, *J* = 11.3 Hz, C17), 4.11 (dd, 1H, *J* = 12.6, 5.8 Hz, C26), 3.74-3.70 (m, 1H, C22), 3.70 (s, 3H, CO_2Me), 2.51-2.41 (m, 2H, C2), 2.36-2.24 (m, 2H, C40), 2.16 (*app* t, 1H, *J* = 12.7 Hz, C22), 1.98 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.84 (*app* t, 1H, *J* = 12.7 Hz, C24), 1.64-1.56 (m, 2H, C41), 1.31-1.24 (m, 8H, C42-C45), 1.09 (s, 3H, C18-Me), 1.06 (s, 3H, C18-Me), 0.87 (t, 3H, *J* = 7.1 Hz, C46) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 169.4, 166.9, 166.1, 156.2, 156.0, 151.7, 138.3, 133.8, 132.8, 128.8, 127.7, 127.6, 123.7, 122.9, 119.7, 117.3, 100.1, 73.5, 72.1, 68.1, 67.6, 66.2, 65.3, 51.3, 45.3, 41.4, 35.8, 34.8,[9] 31.8, 31.0, 29.2, 29.0, 24.8, 22.7, 22.1, 20.6, 14.2 ppm

IR (thin film): 3471, 2928, 2855, 1718, 1602, 1522, 1453, 1376, 1295, 1237, 1174, 1127, 1104, 1045, 1004, 916, 758, 733, 699 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{41}H_{53}NNaO_{13}^+$: 790.3409, Found: 790.3415

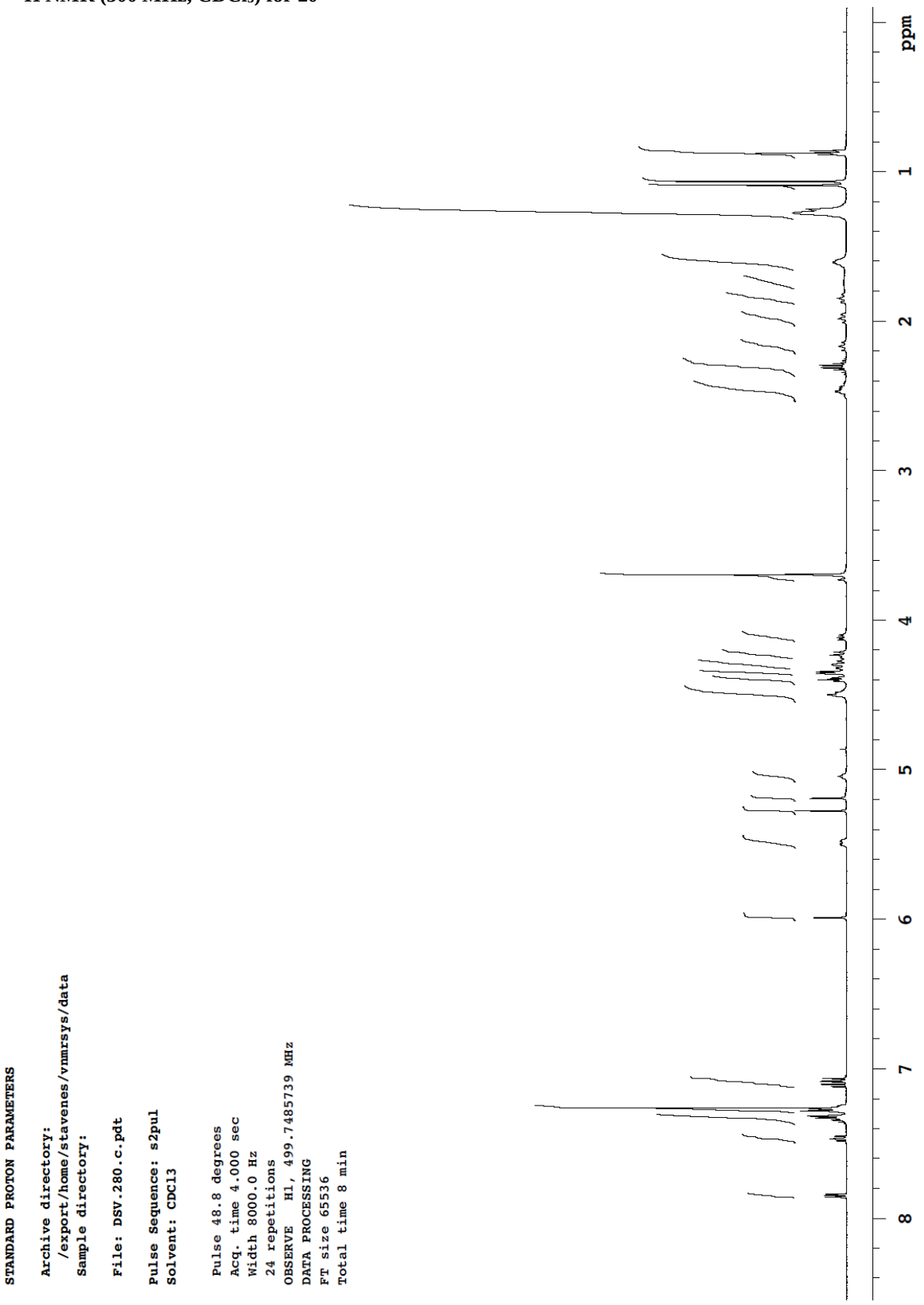
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23.6\ °C}} = 17.6 \pm 0.8°$ (*c* = 0.3, CH_2Cl_2)

$\mathbf{R}_f$ = 0.20 (40% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV

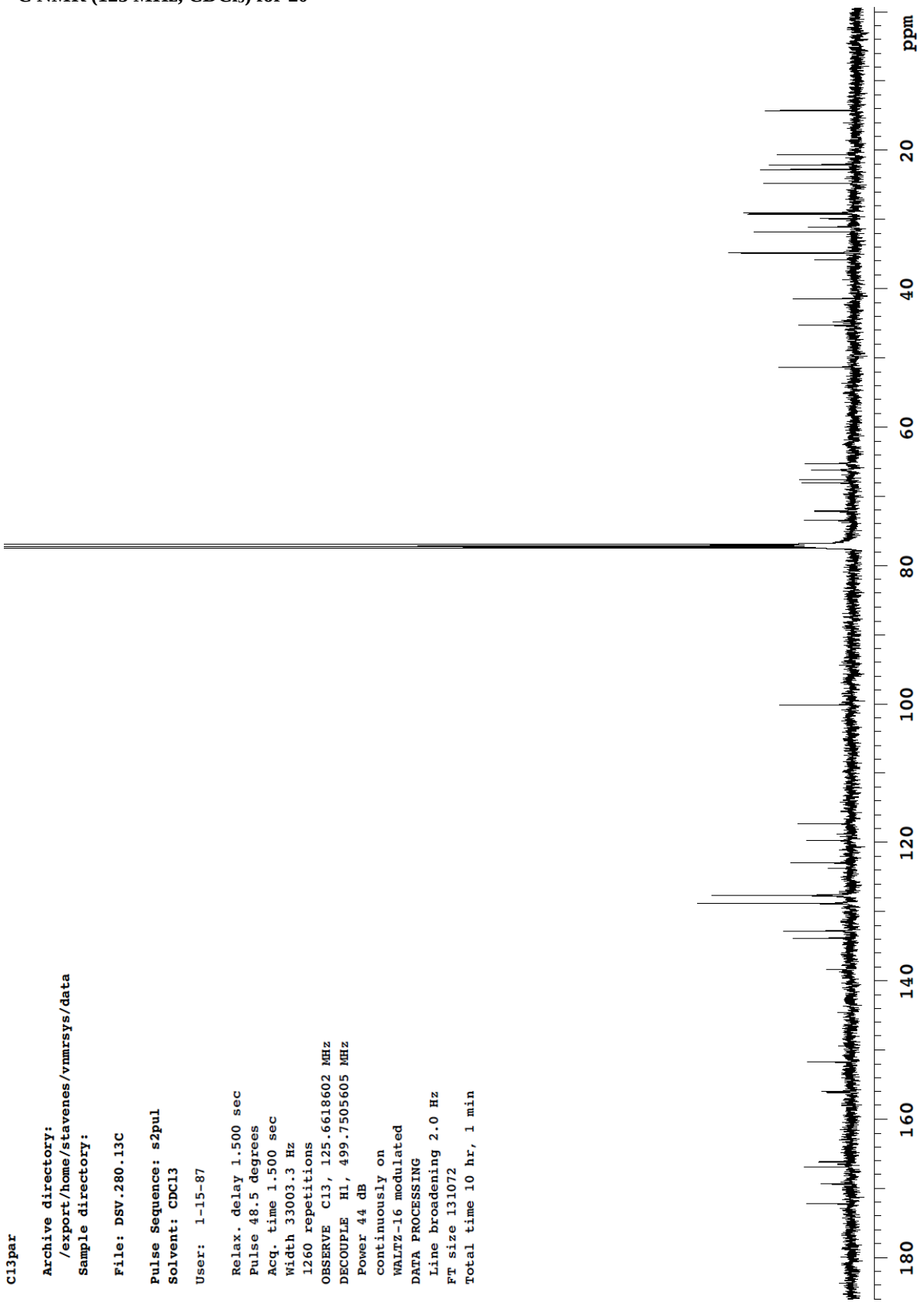
[8] Final amount of analog **20** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

[9] Suspected to be two unresolved resonances based on analogy to related analogs.

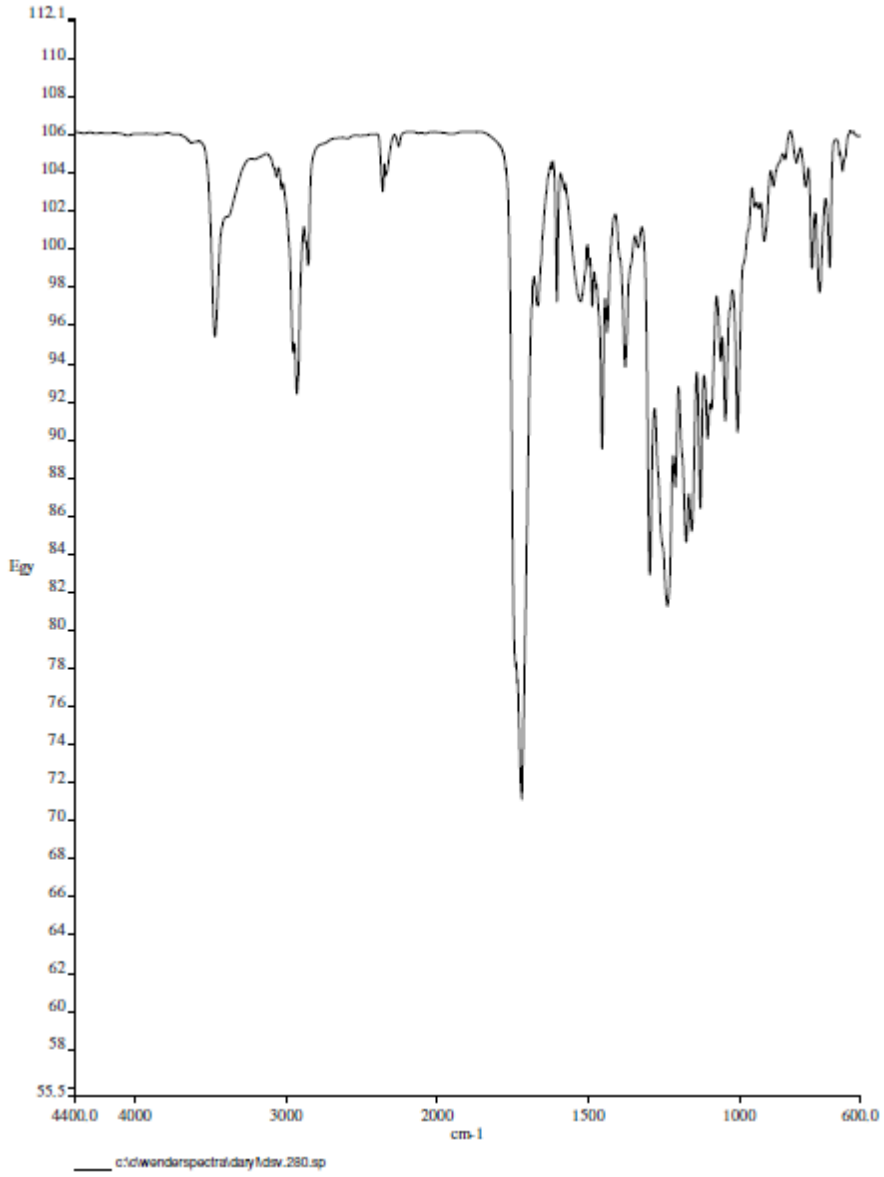
^{1}H NMR (500 MHz, $CDCl_3$) for 20



^{13}C NMR (125 MHz, $CDCl_3$) for 20



IR for 20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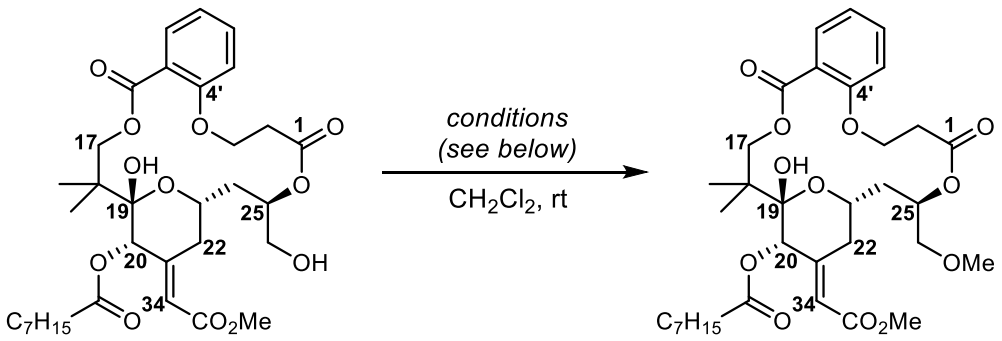


1 *17%* **21**

Procedure for C26-OMe analog 21

Dissolved salicylate-derived analog **1** (3.6 mg, 5.7 µmol) in 420 µL dry CH_2Cl_2 before adding 2,6-bis-*tert*-butyl-4-methylpyridine (4.8 µL, 23 µmol) and MeOTf (122 µL of freshly prepared 50 mM stock solution in dry CH_2Cl_2, 6.6 µmol) respectively in one portion each. No reaction after one hr at rt under Ar. Added 2.8 mg KCl (38 µmol) then 1.1 µL methyl iodide (18 µmol) in one portion each, diluted with 150 µL dry THF. Capped, heated to 60 °C for 2 hrs; ~30% conversion observed by TLC. Added additional 10 mg substituted pyridine (49 µmol), 5 mg KCl (67 µmol) then 2.5 µL methyl iodide (40 µmol), capped, heated to 60 °C for 12 hrs; still only ~30% conversion observed by TLC.[10] Reaction was quenched with 1 mL sat. NH_4Cl and diluted with 1 mL water and 1 mL ether. Phases were separated. Aqueous phase was further extracted with four 1 mL aliquots of ether. Combined organic phases were washed with 1 mL brined, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. Crude mixture was dissolved in 350 µL dry CH_2Cl_2. Proton sponge (11 mg, 51 µmol) and trimethyloxonium tetrafluoroborate (30 µL of 1.0 M solution in DCM, 30 µmol) were added in one portion each. Reaction was flushed with Ar, capped, and heated to 50 °C for 2 hrs. Reaction appeared to be at ~50 % conversion, though some byproducts were beginning to appear. Addition of more Me_3OBF_4 (15 µL) and 2 hrs of stirring at rt provided no additional conversion. Quenched and extracted the reaction mixture as above. The crude residue was purified via flash chromatography over a silica pipet column (25→40→60% ethyl acetate:pentane). ^{1}H NMR revealed peaks suspected to correspond to the product (including a large singlet for the C26-OMe), but this was mixed with starting material and other byproducts. Crude mixture was dissolved in 600 µL dry CH_2Cl_2. Proton sponge (12 mg, 56 µmol) and trimethyloxonium tetrafluoroborate (4 mg, 27 µmol) were added in one portion each. Reaction was stirred 3 hrs at rt under Ar. After ~30 min, reaction turned red-orange. Quenched and extracted the reaction mixture as above. The crude residue was purified via flash chromatography over a silica pipet column (25→35→50% ethyl acetate:pentane). The product was then further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 34.0 minutes. The C26-methoxy analog **21** was obtained as a white solid (0.61 mg, [11] 16.9%).

*Characterization Data for C26-OMe analog **21**:*

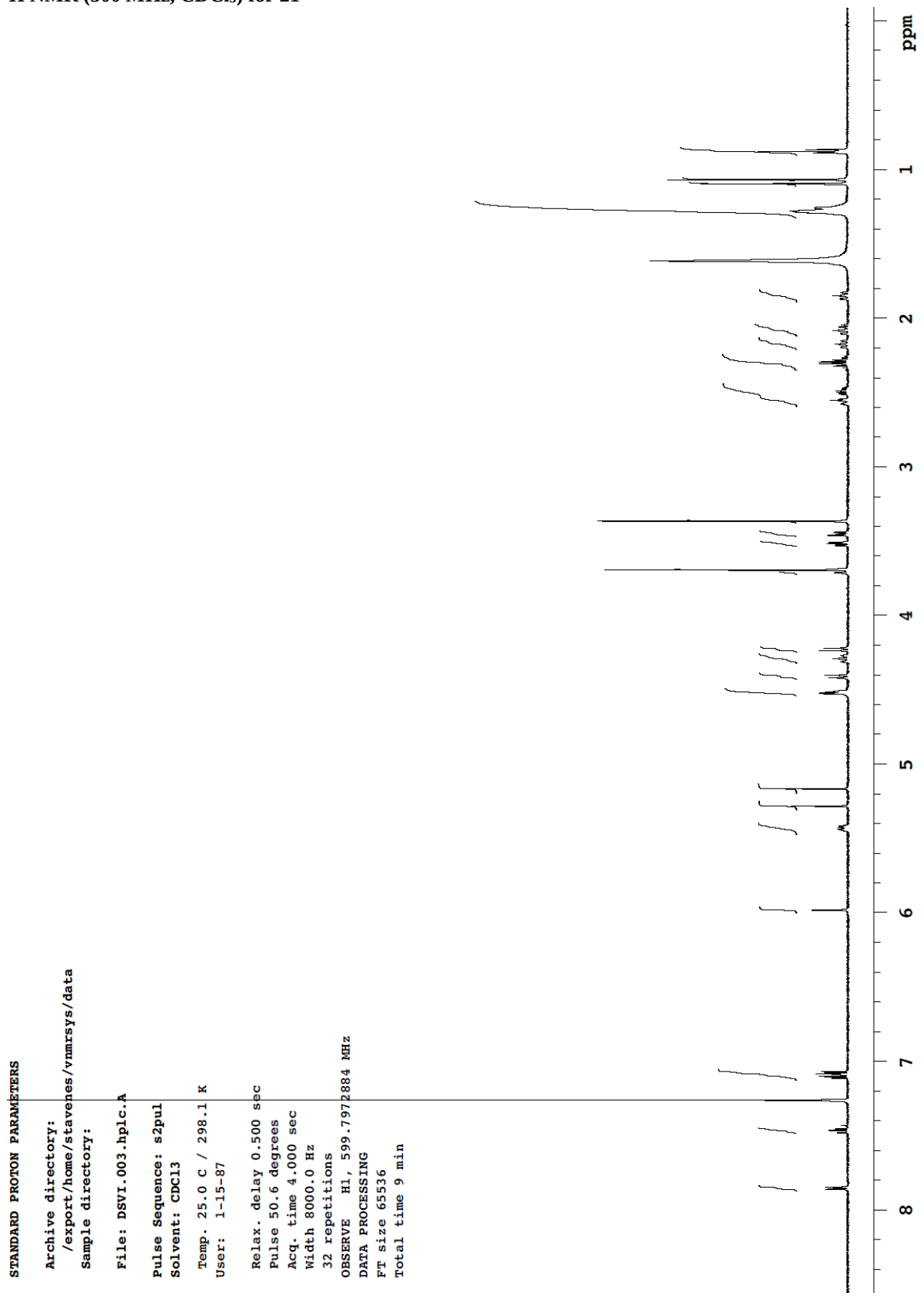
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86 (dd, 1H, *J* = 8.0, 1.9 Hz, Ar), 7.46 (*app* t, 1H, *J* = 8.2 Hz, Ar), 7.10 (*app* t, 1H, *J* = 7.6 Hz, Ar), 7.08 (d, 1H, *J* = 8.7 Hz, Ar), 5.98 (d, 1H, *J* = 1.7 Hz, C34), 5.45-5.40 (m, 1H, C25), 5.28 (s, 1H, C20), 5.17 (s, 1H, C19-OH), 4.54-4.50 (m, 2H, C3), 4.41 (d, 1H, *J* = 11.3 Hz, C17), 4.29 (*app* t, 1H, *J* = 11.3 Hz, C23), 4.23

[10] While the quality of the methyl triflate is still suspected to have been low (hence the switch to MeI), the observed methylation is believed to have arisen from the original methylating reagent. The above procedure is clearly not optimized, but a fresh bottle of methyl triflate would appear to be functional if the reaction was heated slightly. It is speculated that one could achieve a much higher yield with this approach.

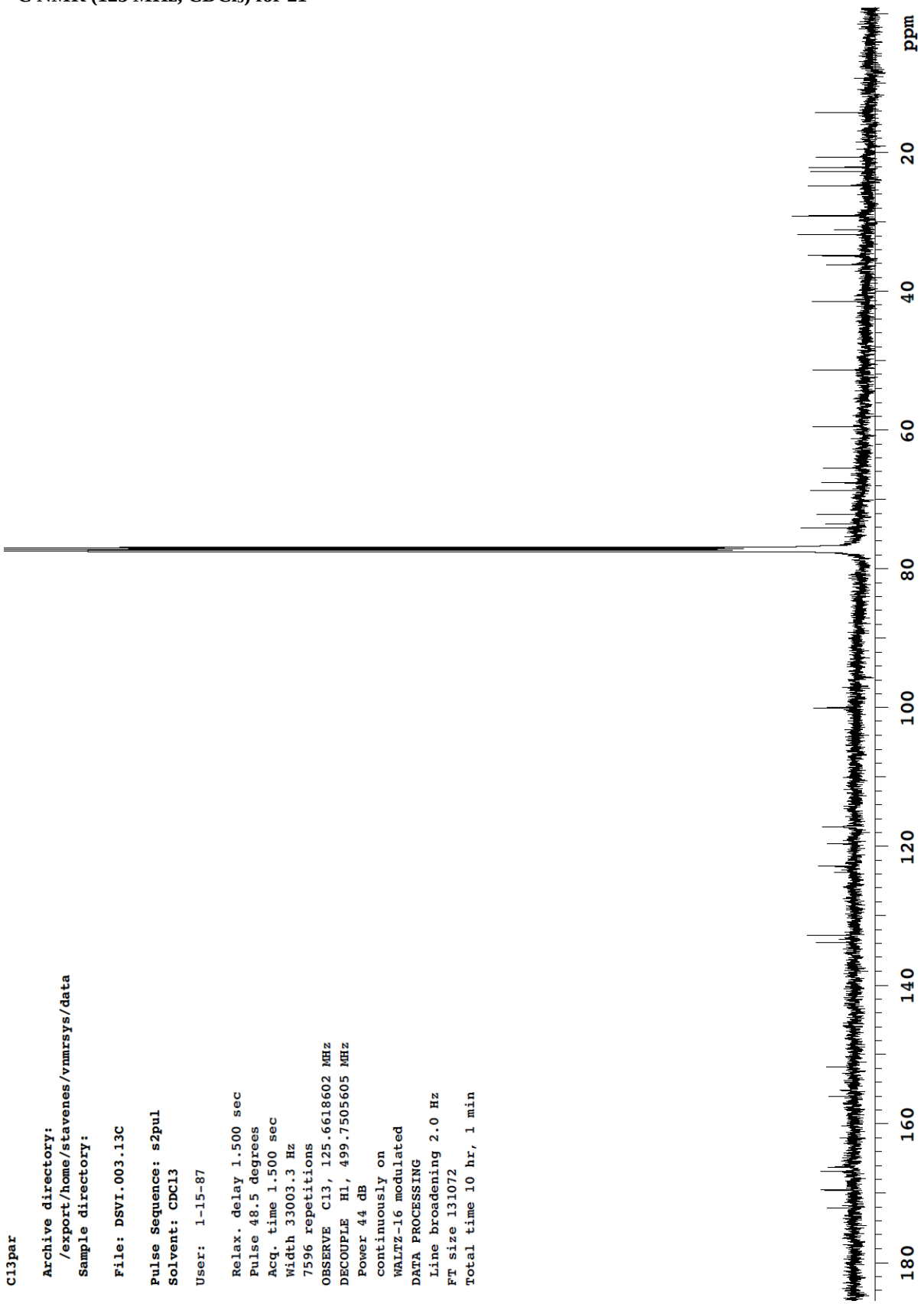
[11] Final amount of analog **21** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

(d, 1H, *J* = 11.3 Hz, C17), 3.72-3.68 (m, 1H, C22), 3.69 (s, 3H, CO_2Me), 3.52 (dd, 1H, *J* = 10.7, 4.0 Hz, C26), 3.45 (dd, 1H, *J* = 10.7, 4.3 Hz, C26), 3.36 (s, 3H, C26-OMe), 2.59-2.46 (m, 2H, C2), 2.35-2.25 (m, 2H, C40), 2.17 (*app* t, 1H, *J* = 13.0 Hz, C22), 2.08 (*app* t, 1H, *J* = 13.0 Hz, C24), 1.85 (*app* t, 1H, *J* = 13.0 Hz, C24), 1.64-1.58 (m, 2H, C41), 1.32-1.22 (m, 8H, C42-C45), 1.10 (s, 3H, C18-Me), 1.07 (s, 3H, C18-Me), 0.88 (t, 3H, *J* = 6.6 Hz, C46) ppm
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.1, 169.5, 166.9, 166.2, 156.0, 151.8, 133.8, 132.8, 123.7, 122.9, 119.7, 117.2, 100.0, 74.2, 73.5, 72.1, 68.6, 67.6, 65.4, 59.5, 51.3, 41.4, 36.1, 34.9, 34.8, 31.8, 31.1, 29.2, 29.0, 24.8, 22.7, 22.1, 21.0, 20.6, 14.2 ppm
IR (thin film): 3474, 2928, 1719, 1602, 1452, 1377, 1295, 1230, 1175, 1127, 1102, 1043, 1005, 759 cm^{-1}
HRMS (ES+, *m/z)* calculated for $C_{34}H_{48}NaO_{12}^+$: 671.3038, Found: 671.3044
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{23.5\ ^{\circ}C}} = 14.2 \pm 2.2°$ (*c* = 0.04, CH_2Cl_2)
$\mathbf{R_f}$ = 0.65 (60% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV

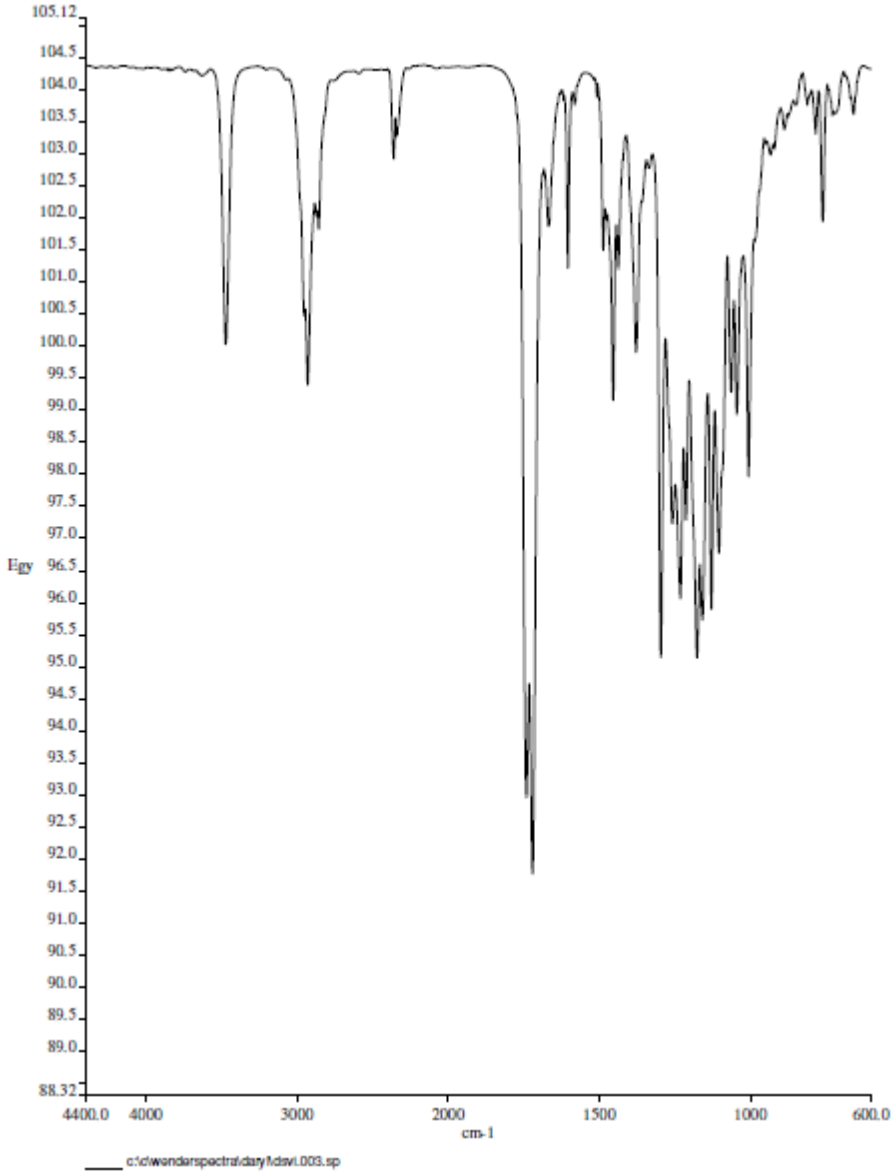
^{1}H NMR (500 MHz, $CDCl_3$) for 21



^{13}C NMR (125 MHz, $CDCl_3$) for 21



IR for 21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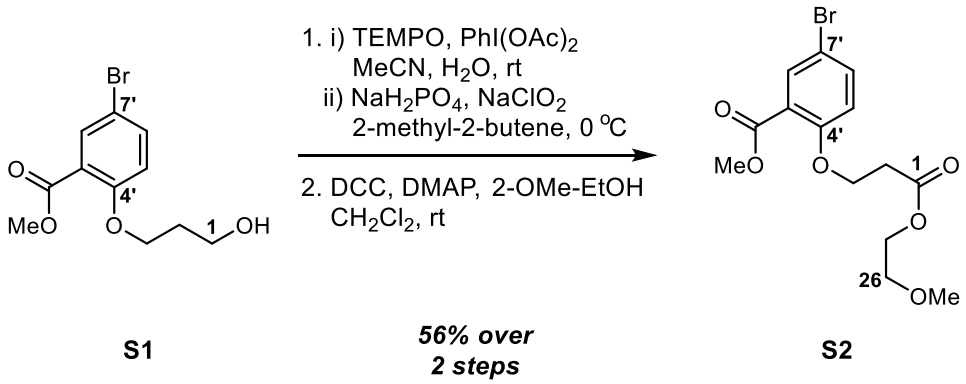


S1 ***56% over 2 steps*** **S2**

Procedure for C7'-Br top piece-only analog S2

C1 alcohol **S1** (126.3 mg, 0.44 mmol; see ref. 9b in the test for preparation of **S1**) was dissolved in 9.5 mL MeCN under an inert atmosphere before adding 1.5 mL water. TEMPO (20 mg, 0.13 mmol) and $PhI(OAc)_2$ (420 mg, 1.3 mmol) were added respectively in one portion each. The light red-orange reaction mixture was stirred for 1 hr at room temp at which point starting material had been consumed by TLC analysis. 2-Methyl-2-butene (2.3 mL, 22 mmol), water (1.0 mL), and NaH_2PO_4 (520 mg, 4.4 mmol) were added respectively, one portion each. The biphasic mixture was cooled to 0 °C before adding $NaClO_2$ (320 mg, 3.5 mmol) in one portion. The reaction was stirred vigorously for 45 min at 0 °C, starting as a dark red solution and slowly fading to a lighter red-orange with time. The reaction was quenched by pouring into 10 mL sat. $Na_2S_2O_3$. This mixture was diluted with 10 mL ether, and the phases were separated. The aqueous phase was extracted with four 10 mL portions of ether. The combined organic phases were washed with 10 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated *in vacuo*. This mixture was taken up in ~10 mL PhMe and re-concentrated three times in order to remove residual AcOH. The resultant crude yellow oil was moved on without further purification.

Half of the crude C1 carboxylic acid (0.22 mmol max.) was dissolved in 1.1 mL dry CH_2Cl_2 in under nitrogen. 2-Methoxyethanol (26 µL, 0.33 mmol), DCC (68 mg, 0.33 mmol), and DMAP (40 mg, 0.33 mmol) were added respectively in one portion each. The reaction mixture quickly turned cloudy with white precipitate. Reaction was stirred for 40 hrs at rt. Quenched the reaction with 2 mL 1:1 sat. NH_4Cl:water then diluted with 2 mL ether. The phases were separated, and the aqueous phase was extracted with 2 mL of ether three times. Collected organic phases were then washed with 2 mL brine before drying over anhydrous sodium sulfate, filtering to remove solids, and concentrating under vacuum. Crude ^{1}H NMR revealed some free phenol, the result of elimination to the acrylate. The crude product was purified via flash chromatography over silica (30→90% ethyl acetate:pentane, 15% increments). A second round of chromatography was required to get a sufficiently pure sample for characterization (10→50% ethyl acetate:pentane, 10% increments) The desired top piece-only analog **S2** was obtained as an off-white solid (43 mg, 56% over 2 steps).

*Characterization Data for C7'-Br top piece-only analog **S2**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (d, 1H, *J* = 2.5 Hz, Ar), 7.53 (dd, 1H, *J* = 8.8, 2.6 Hz, Ar), 6.89 (d, 1H, *J* = 8.9 Hz, Ar), 4.30 (t, 2H, *J* = 6.6 Hz, C3), 4.28 (*app* t, 2H, *J* = 4.7 Hz, C25), 3.86 (s, 3H, CO_2Me), 3.60 (*app* t, 2H, *J* = 4.7 Hz, C26), 3.37 (s, 3H, OMe), 2.88 (t, 2H, *J* = 6.6 Hz, C2) ppm

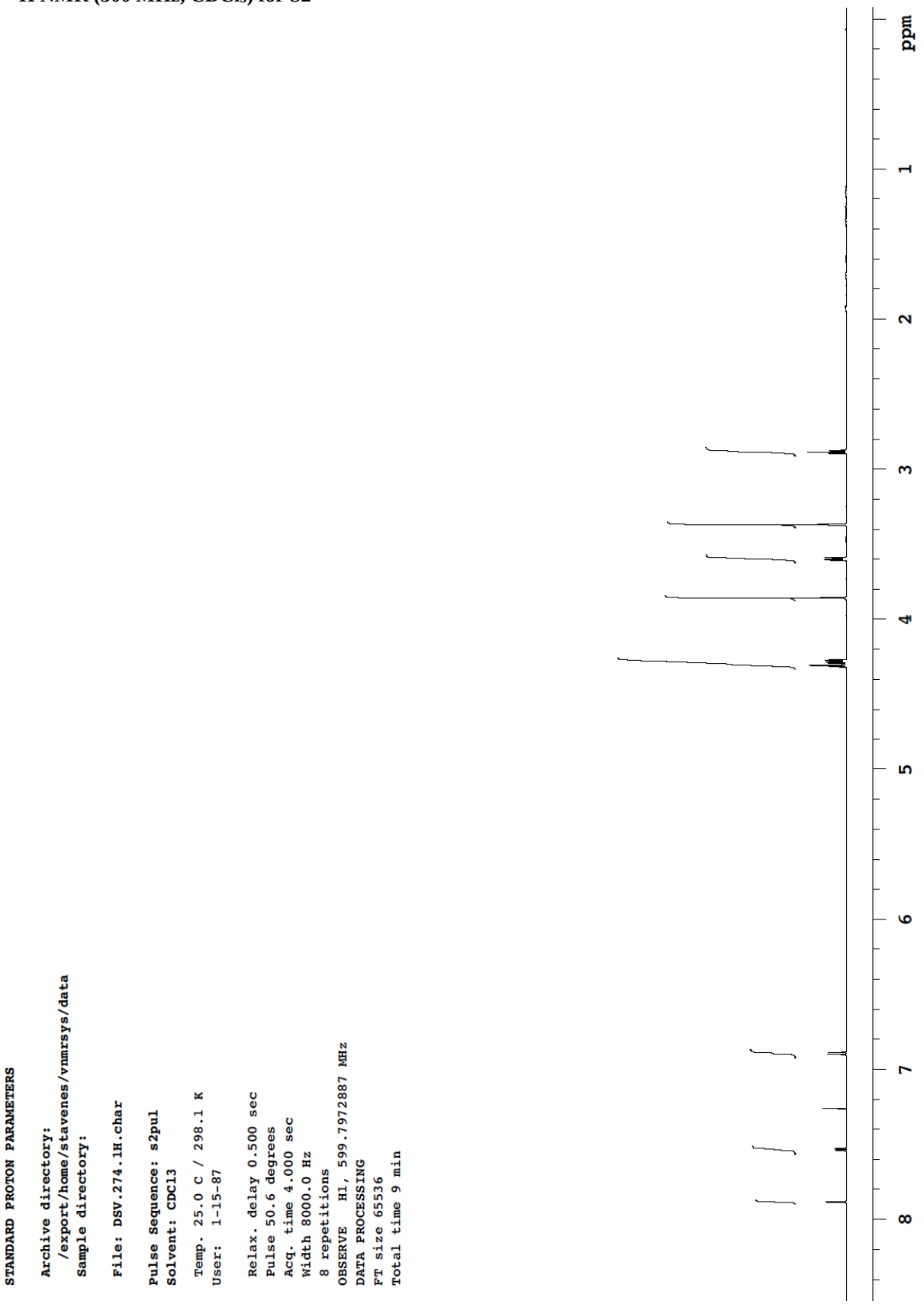
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.9, 165.4, 157.3, 136.1, 134.4, 122.6, 115.9, 113.1, 70.4, 65.2, 64.0, 59.1, 52.3, 34.5 ppm

IR (thin film): 2932, 1731, 1592, 1488, 1470, 1435, 1392, 1298, 1278, 1243, 1181, 1128, 1099, 1031, 966, 803, 783, 686, 642 cm^{-1}

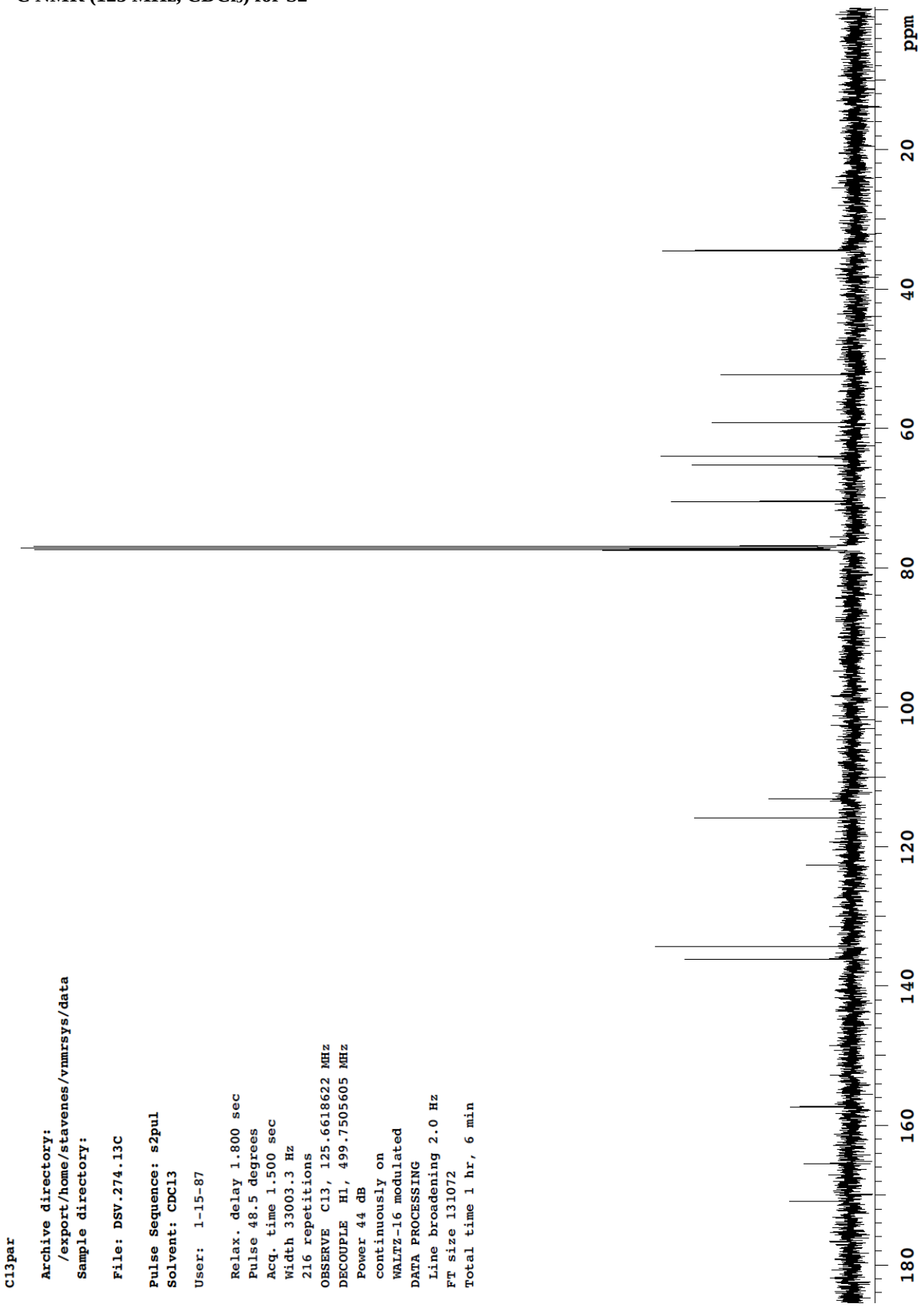
HRMS (ES+, *m/z)* calculated for $C_{14}H_{17}BrNaO_6^+$: 383.0101, Found: 383.0103

R_f = 0.60 (60% EtOAc in pentane), one yellow spot, $KMnO_4$ + UV

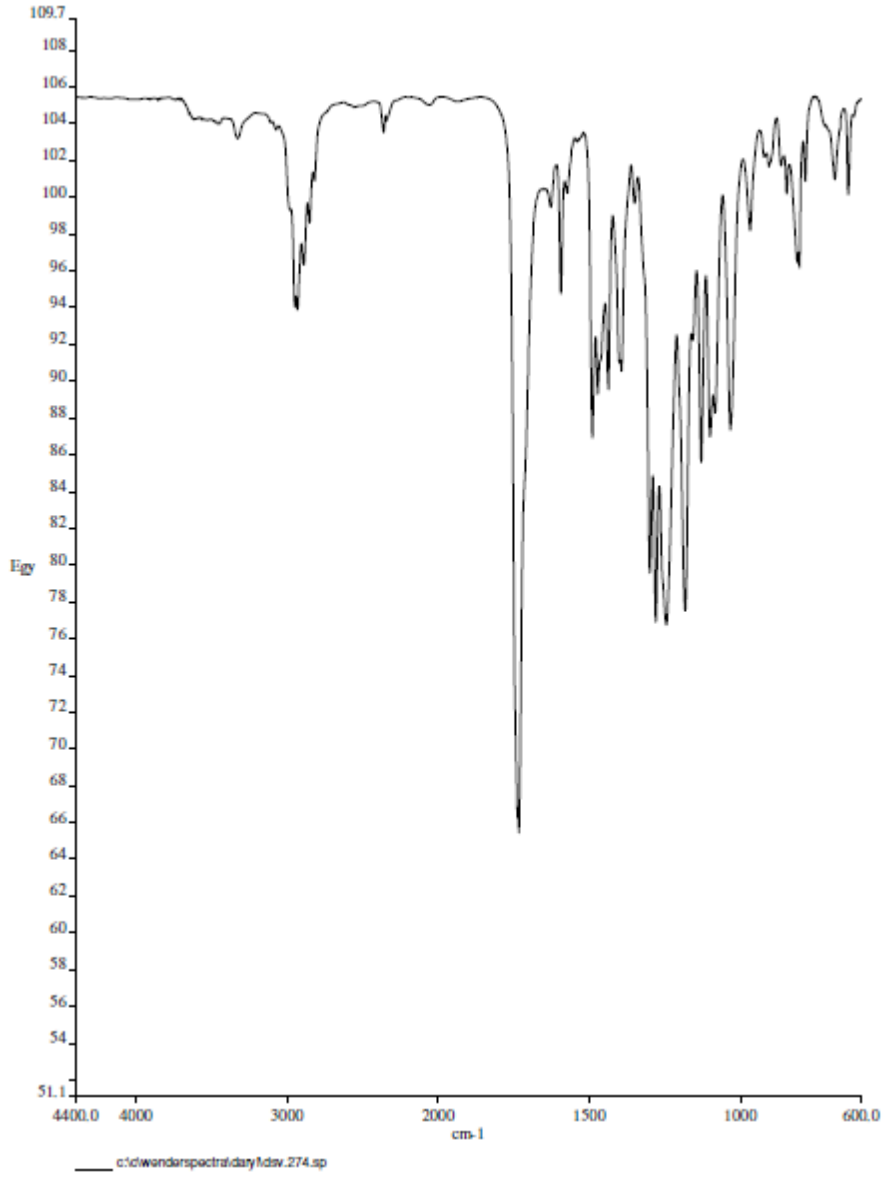
^{1}H NMR (500 MHz, $CDCl_3$) for S2



^{13}C NMR (125 MHz, $CDCl_3$) for S2



IR for S2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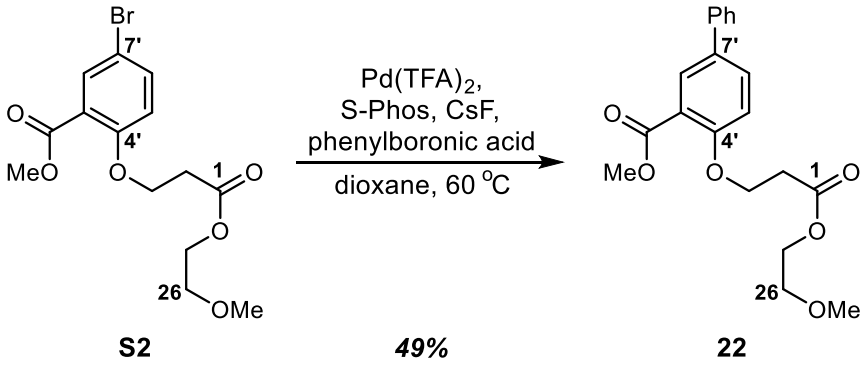


S2 ***49%*** **22**

Procedure for C7'-Ph top piece-only analog 22

$Pd(O_2CCF_3)_2$ (5.1 mg, 15 µmol), S-Phos (12 mg, 29 µmol), and phenylboronic acid (8.8 mg, 72 µmol) were dissolved in 600 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (27 mg, 178 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **S2** (10.3 mg, 29 µmol) was dissolved in 400 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd^0 solution (having stirred 20 min) was transferred via syringe into the starting material solution over the course of 15 seconds. TLC analysis showed consumption of starting material. The vial was flushed with Ar, capped, and heated 2.5 hrs at 60 ºC. The reaction mixture was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over silica (10→50% ethyl acetate:pentane, 10% increments, loaded residue with PhMe). The resultant off-white solid was further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 9.0 minutes. The desired top piece-only analog **22** was obtained as a white solid (5.03 mg,[12] 49.1%).

*Characterization Data for C7'-Ph top piece-only analog **22**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.02 (d, 1H, *J* = 2.5 Hz, Ar), 7.68 (dd, 1H, *J* = 8.6, 2.7 Hz, Ar), 7.56 (*app* d, 2H, *J* = 7.8 Hz, Ph), 7.43 (*app* t, 2H, *J* = 7.8 Hz, Ph), 7.33 (*app* t, 1H, *J* = 7.8 Hz, Ph), 6.89 (d, 1H, *J* = 8.8 Hz, Ar), 4.38 (t, 2H, *J* = 6.6 Hz, C3), 4.30 (*app* t, 2H, *J* = 4.8 Hz, C25), 3.89 (s, 3H, CO_2Me), 3.62 (*app* t, 2H, *J* = 4.9 Hz, C26), 3.38 (s, 3H, OMe), 2.93 (t, 2H, *J* = 6.6 Hz, C2) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.0, 166.9, 157.6, 139.8, 134.1, 131.9, 130.4, 129.0, 127.3, 126.9, 121.2, 114.5, 70.5, 65.1, 64.0, 59.1, 52.2, 34.6 ppm

IR (thin film): 2948, 1734, 1610, 1484, 1451, 1399, 1314, 1277, 1235, 1181, 1128, 1083, 1033, 763, 699 cm^{-1}

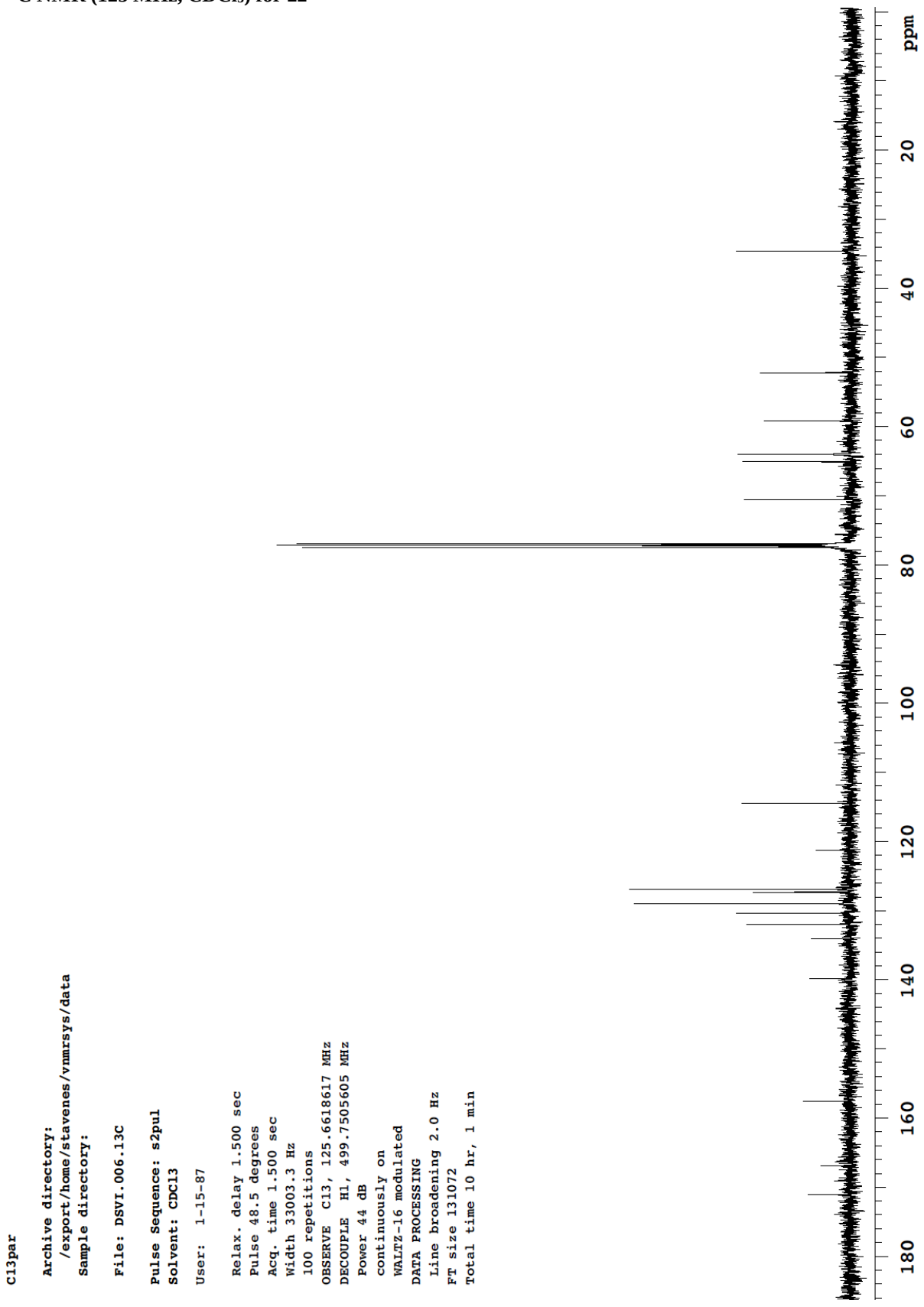
HRMS (ES+, *m/z)* calculated for $C_{20}H_{22}NaO_6^+$: 381.1309, Found: 381.1310

R_f = 0.45 (50% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV

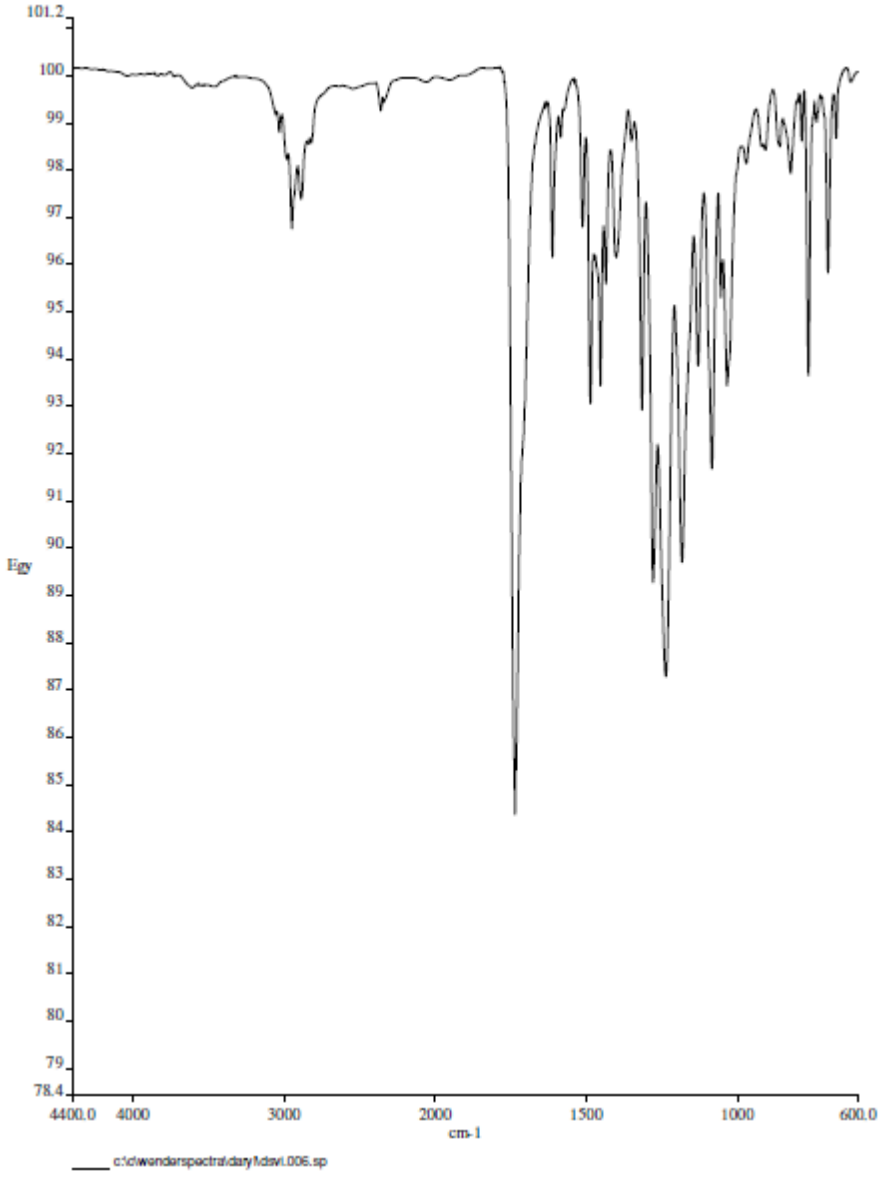
[12] Final amount of analog **22** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

^{1}H NMR (500 MHz, $CDCl_3$) for 22

^{13}C NMR (125 MHz, $CDCl_3$) for 22



IR for 22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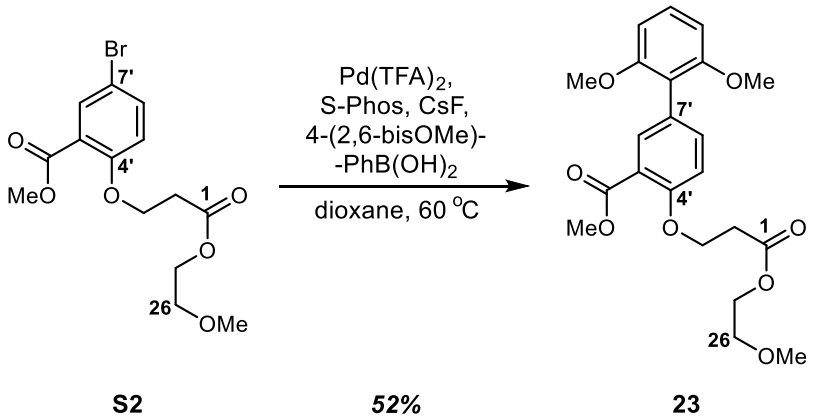


S2 ***52%*** **23**

Procedure for C7'-(2,6-bisOMe)-Ph top piece-only analog 23

$Pd(O_2CCF_3)_2$ (5.5 mg, 17 µmol), S-Phos (13.5 mg, 33 µmol), and 2,6-(bismethoxy)phenylboronic acid (13.4 mg, 74 µmol) were dissolved in 600 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (22.1 mg, 145 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **S2** (10.9 mg, 30 µmol) was dissolved in 400 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd^0 solution (having stirred 20 min) was transferred via syringe into the starting material solution over the course of 15 seconds. TLC analysis showed consumption of starting material. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The reaction mixture was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (30→50→60% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 7.3 minutes. The desired top piece-only analog **23** was obtained as a white solid (6.53 mg,[13] 51.7%).

*Characterization Data for C7'-(2,6-bisOMe)-Ph top piece-only analog **23**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (d, 1H, *J* = 2.3 Hz, Ar), 7.44 (dd, 1H, *J* = 8.6, 2.2 Hz, Ar), 7.27 (t, 1H, *J* = 8.6 Hz, $C_6H_3R_2$), 7.03 (d, 1H, *J* = 8.6 Hz, Ar), 6.63 (d, 2H, *J* = 8.3 Hz, $C_6H_3R_2$), 4.38 (t, 2H, *J* = 6.7 Hz, C3), 4.29 (*app* t, 2H, *J* = 4.5 Hz, C25), 3.84 (s, 3H, CO_2Me), 3.73 (s, 6H, Ar-bisOMe), 3.61 (*app* t, 2H, *J* = 4.3 Hz, C26), 3.39 (s, 3H, C26-OMe), 2.92 (t, 2H, *J* = 6.7 Hz, C2) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.1, 167.0, 157.8, 157.0, 136.2, 134.5, 128.9, 126.7, 120.2, 118.0, 113.4, 104.2, 70.5, 64.8, 63.9, 59.1, 56.0, 51.9, 34.7 ppm

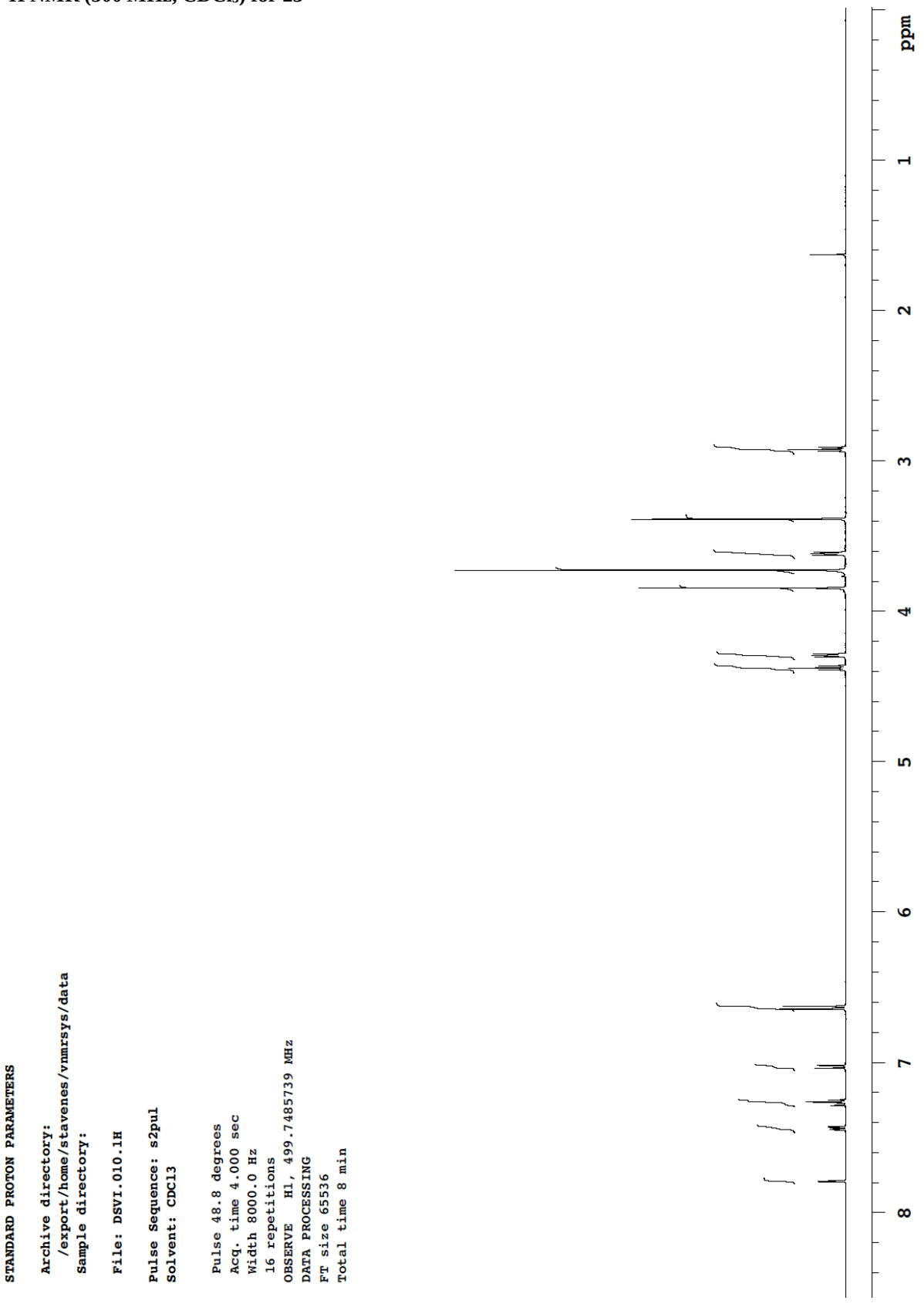
IR (thin film): 2948, 2837, 1734, 1593, 1507, 1472, 1434, 1401, 1308, 1247, 1182, 1109, 1029, 821, 783, 735 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{22}H_{26}NaO_8^+$: 441.1520, Found: 441.1524

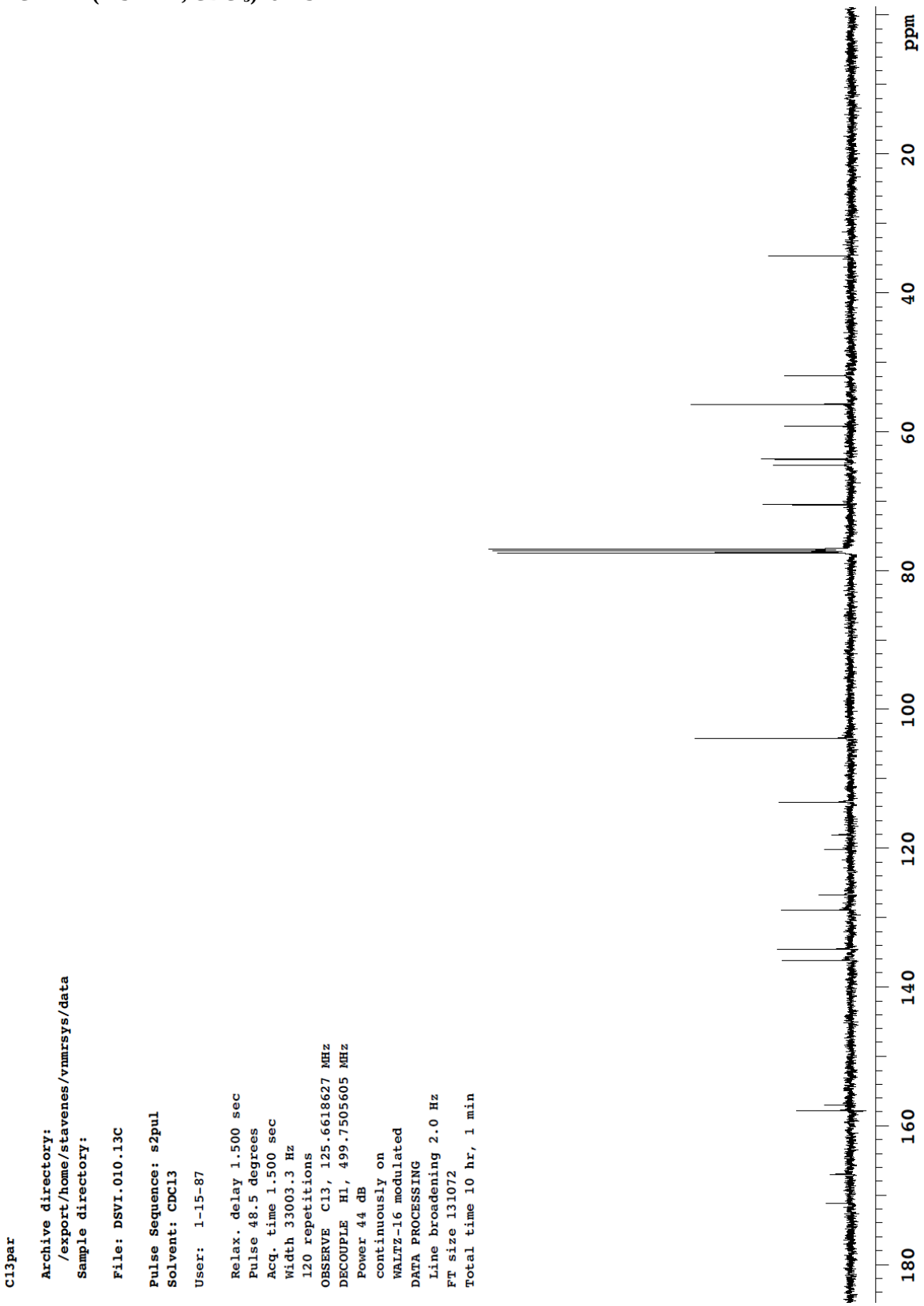
R_f = 0.25 (60% EtOAc in pentane), one red spot, *p*-anisaldehyde + UV

[13] Final amount of analog **23** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

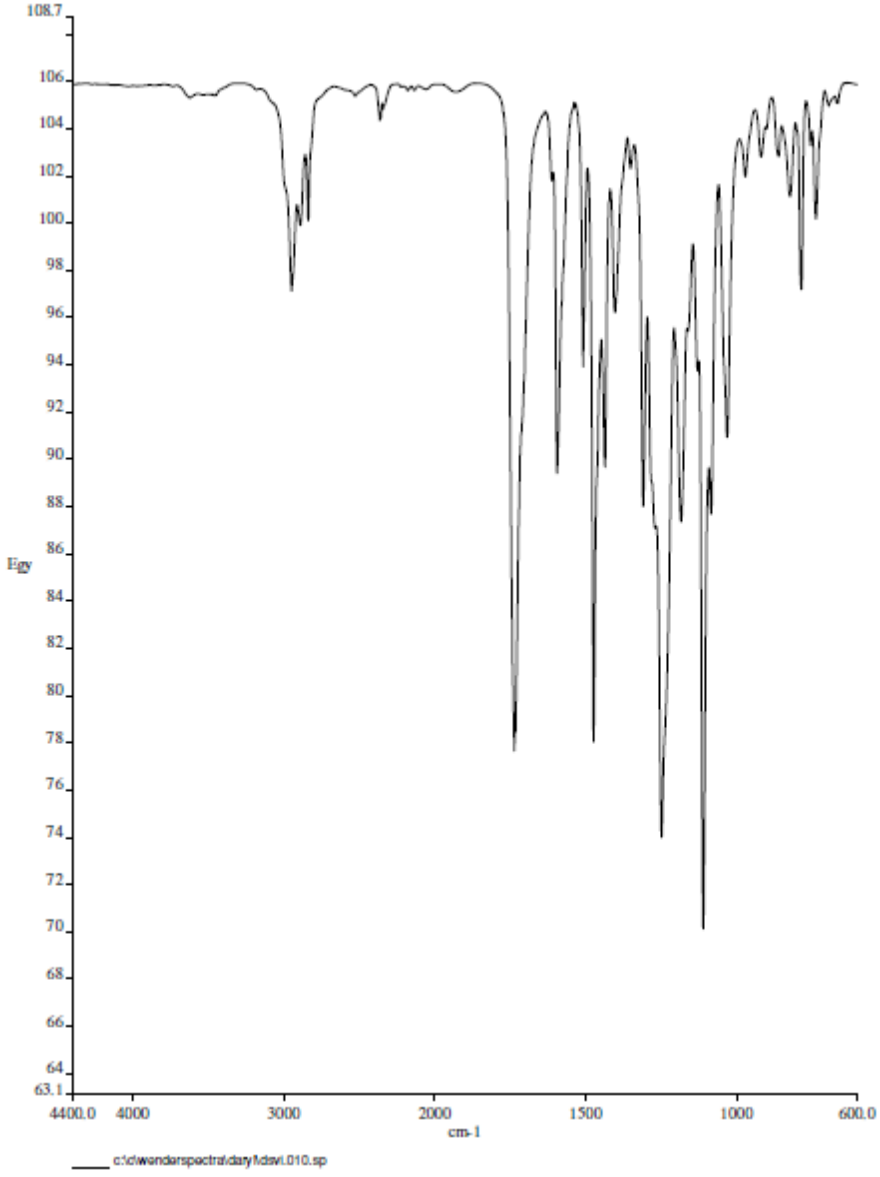
^{1}H NMR (500 MHz, $CDCl_3$) for 23



^{13}C NMR (125 MHz, $CDCl_3$) for 23



IR for 23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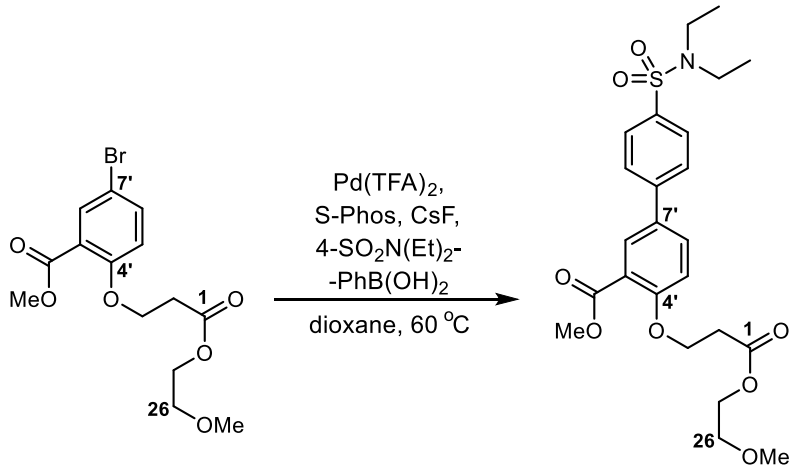


Procedure for C7'-(4-$SO_2N(Et)_2$)-Ph top piece-only analog 24

$Pd(O_2CCF_3)_2$ (5.9 mg, 17 µmol), S-Phos (13.0 mg, 32 µmol), and 4-diethylsulfamoylphenyl boronic acid (20.3 mg, 79 µmol) were dissolved in 600 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (23.8 mg, 158 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide **S2** (11.4 mg, 32 µmol) was dissolved in 500 µL dioxane under N_2; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd^0 solution (having stirred 20 min) was transferred via syringe into the starting material solution over the course of 15 seconds. TLC analysis showed consumption of starting material. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The reaction mixture was filtered through a plug of celite, eluting with ~30 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (20→30→50→60% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (60→100% MeCN:H_2O, 40 min run, residue loaded with a 2:1 mixture of MeOH to MeCN + 10% DMSO). Product eluted at 9.0 minutes. The desired top piece-only analog **24** was obtained as a white solid (3.64 mg,[14] 23.3%).

Characterization Data for C7'-(4-$SO_2N(Et)_2$)-Ph top piece-only analog 24*:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.04 (d, 1H, *J* = 2.5 Hz, Ar), 7.85 (dt, 2H, *J* = 8.6, 2.2 Hz, Ar), 7.70 (dd, 1H, *J* = 8.7, 2.5 Hz, Ar), 7.67 (dt, 2H, *J* = 8.7, 2.2 Hz, Ar), 7.11 (d, 1H, *J* = 8.6 Hz, Ar), 4.39 (t, 2H, *J* = 6.5 Hz, C3), 4.30 (*app* t, 2H, *J* = 4.5 Hz, C25), 3.90 (s, 3H, CO_2Me), 3.62 (*app* t, 2H, *J* = 4.3 Hz, C26), 3.38 (s, 3H, C26-OMe), 3.27 (q, 4H, *J* = 7.1 Hz, $N(Et)_2$ –CH_2-), 2.94 (t, 2H, *J* = 6.4 Hz, C2), 1.15 (t, 6 H, *J* = 7.2 Hz, $N(Et)_2$ –CH_3) ppm

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.8, 166.4, 158.2, 143.5, 138.8, 132.0, 130.5, 127.6, 127.1, 121.2, 114.3, 70.3, 64.8, 63.9, 59.0, 52.1, 42.0, 34.4, 14.2 ppm

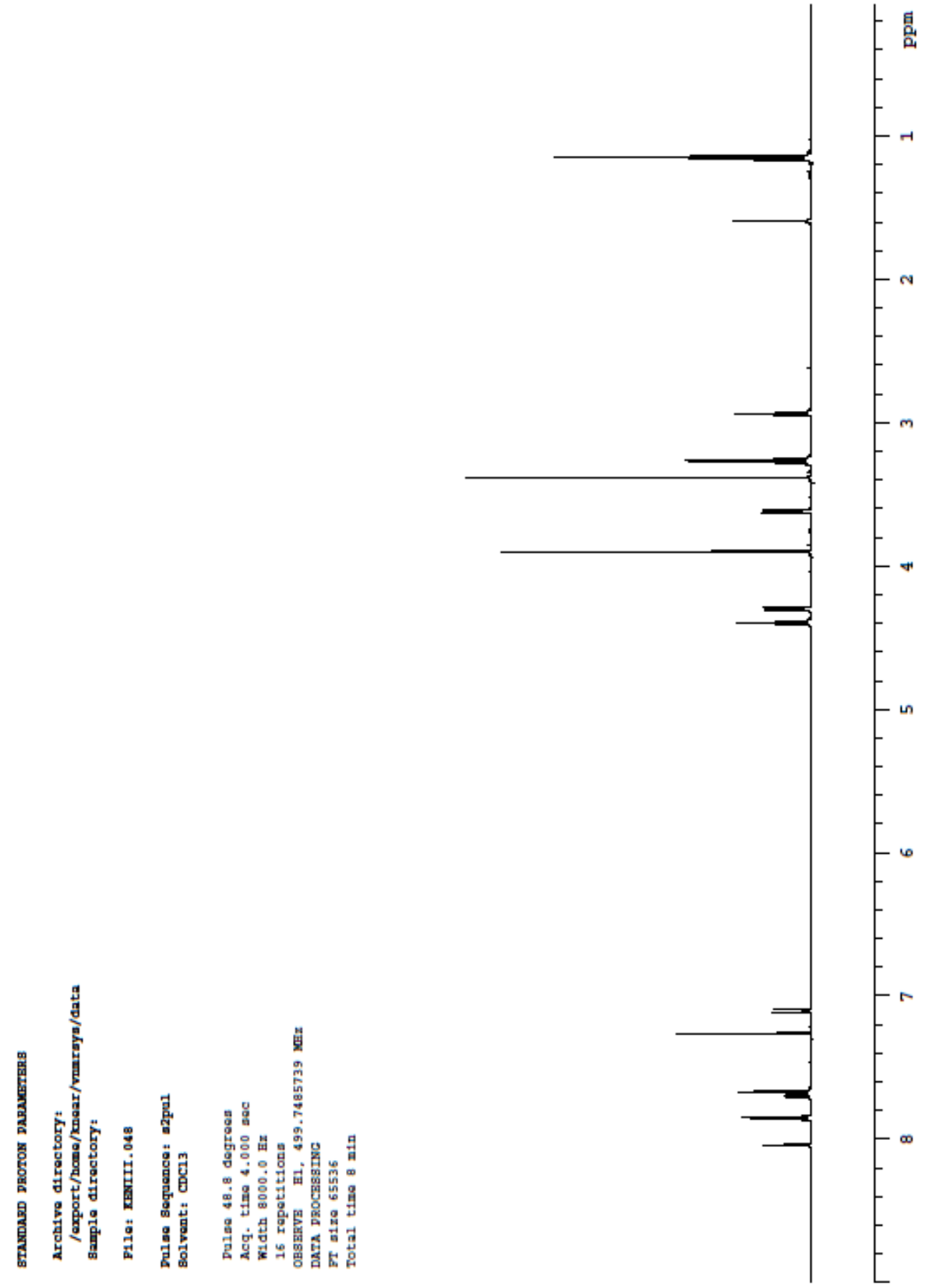
IR (thin film): 2947, 1735, 1610, 1511, 1486, 1438, 1384, 1333, 1279, 1239, 1182, 1084, 1020, 933, 818, 786, 699, 648 cm^{-1}

HRMS (ES+, *m/z)* calculated for $C_{24}H_{31}NaNO_8S^+$: 516.1663 Found: 516.1657

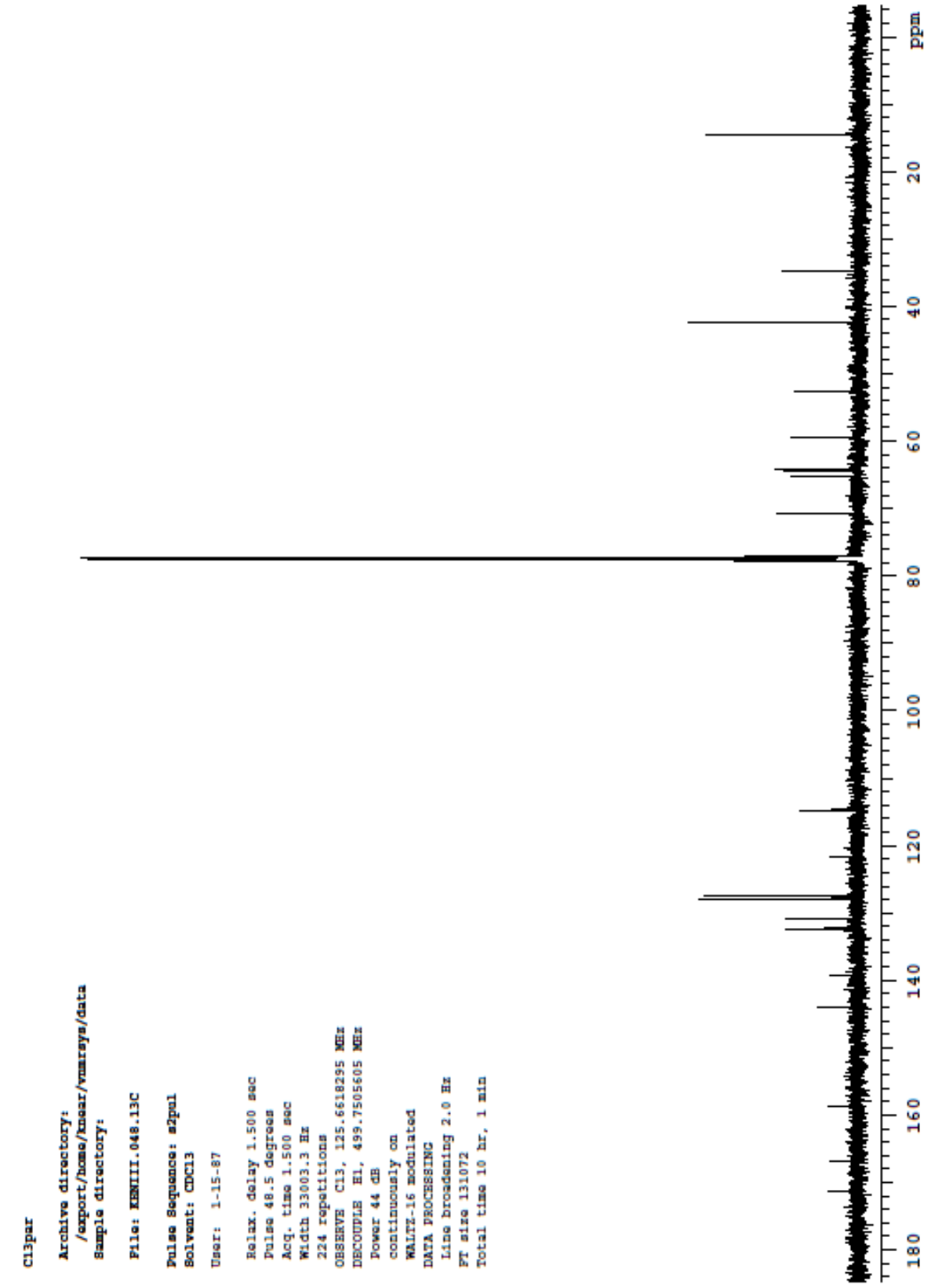
R_f = 0.20 (50% EtOAc in pentane), one pink spot, $KMnO_4$ + UV

[14] Final amount of analog **24** was determined by quantitative ^{1}H NMR using dimethyl terephthalate as an external standard and benzene as an internal standard.

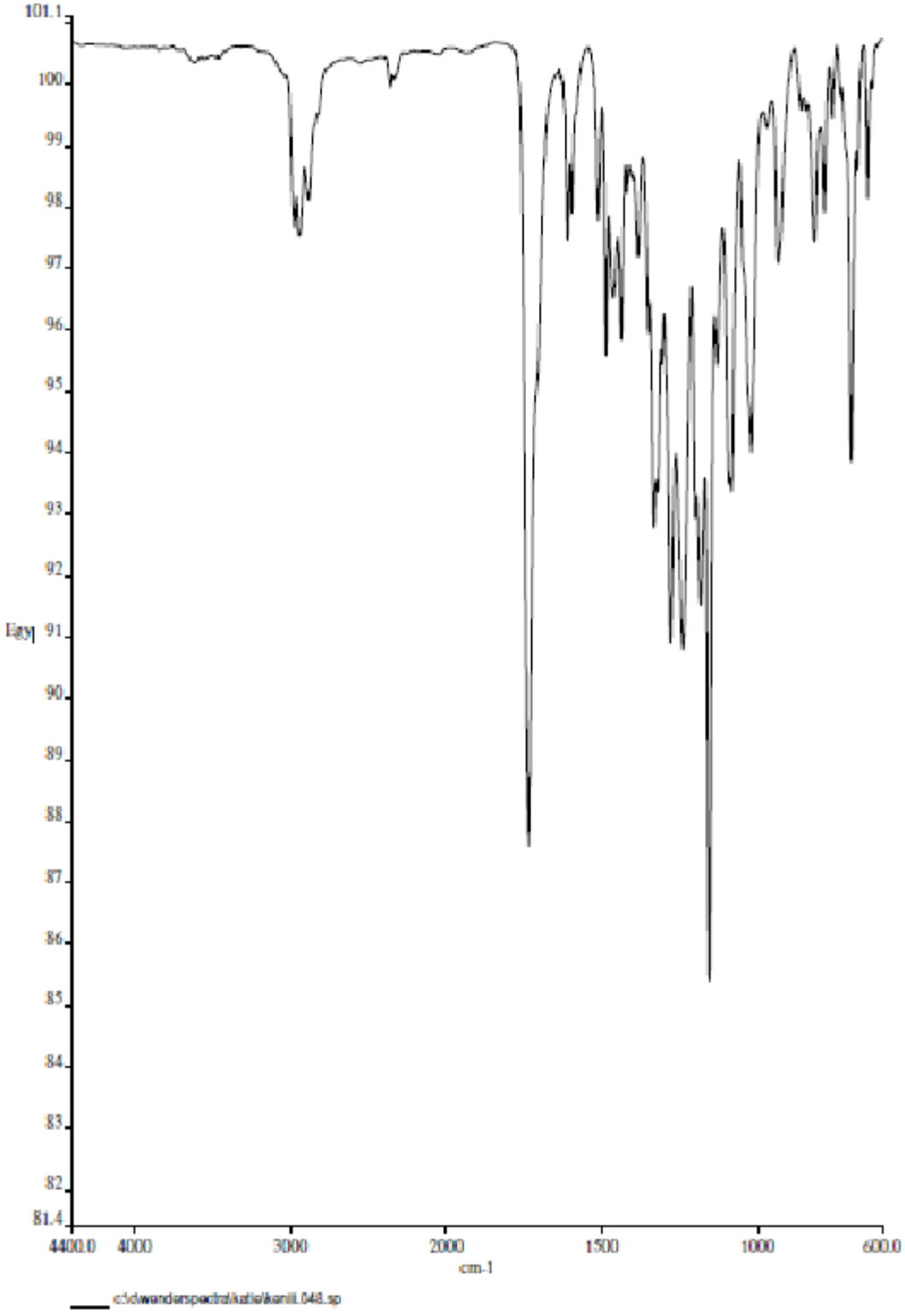
^{1}H NMR (500 MHz, $CDCl_3$) for 24



^{13}C NMR (125 MHz, $CDCl_3$) for 24



IR for 24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