Synthesis of the AB ring system of clifednamide utilizing Claisen rearrangement and Diels-Alder reaction as key steps

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Electronic Supplementary Information

1) Attempts for the Preparation of the Wittig Reagent 8a

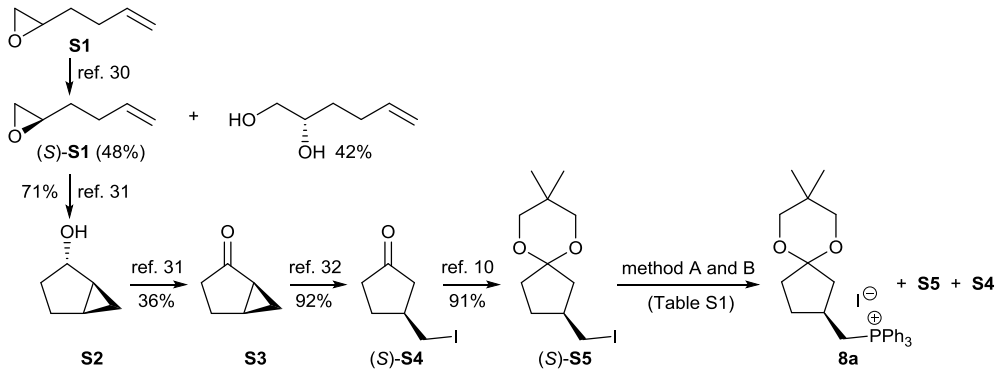


Table S1 Preparation of phosphonium iodide **8a** by using different conditions[a,b]

Method	*T* (°C)	*t* (h)	$NaHCO_3$[c]	**8a**	**S5**	**S4**	PPh_3
A	130	96	1	+			+
B	130	18	–	+	+	+	–
B	130	83	1	+	–	+	–
B	130	22	1	+	+	–	–
B	130	86	3	+	–	–	+
B	130	45	3	+	–	–	+

[a] Method A: PPh_3, $NaHCO_3$, MeCN, reflux; method B: PPh_3 (1.3 equiv.), MeCN, microwave, 300 W. [b] Products observed by TLC analysis, not isolated. [c] Number of drops.

[(2S)-(8,8-dimethyl-6,10-dioxaspiro[4.5]dec-2-yl)methyl]triphenylphosphonium iodide (8a). In a microwave reactor **S5** (10 mg, 0.03 mmol), 1 mL of CH_3CN, drops of $NaHCO_3$ and PPh_3 (11 mg, 0.04 mmol) were added. The mixture was heated at 130°C with a power of 300 W for the given time (Table S1). Then the solvent was evaporated and the crude product dissolved in 0.2 mL of CH_2Cl_2 and 10 mL of Et_2O. The solid was filtered and the filtrate concentrated

under reduced pressure to give a light brown solid. No yield in **8a** could be calculated because of the amount of PPh_3 remaining in the product.

2) Synthesis of precursors 16–18

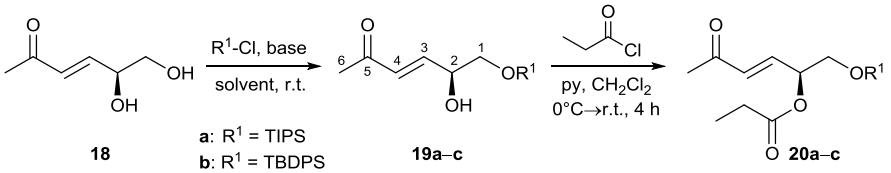
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (16). To a solution of di-*O*-isopropylidene-D-mannitol (2.00 g, 7.62 mmol) in CH_2Cl_2 (20 mL) at r.t. a satd. solution of $NaHCO_3$ (0.8 mL) and sodium periodate (2.45 g, 11.4 mmol) were slowly added, and the suspension was stirred for 4 h. After addition of $MgSO_4$, the reaction mixture was filtered and the filtrate concentrated under reduced pressure (max. 300 mbar) at 40 °C to give **16** (1.91 g, 14.6 mmol, 96%) as a light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.11 (dd, J = 8.8, 4.7 Hz, 1H, H_a-1), 4.18 (dd, J = 8.8, 7.4 Hz, 1H, H_b-1), 4.39 (ddd, J = 7.4, 4.7, 1.9 Hz, 1H, H-2), 9.73 (d, J = 1.9 Hz, 1H, H-3). The spectroscopic data were in accordance with those in the literature.[18]

(*S*,*E*)- and (*S*,*Z*)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one ((*E*)-17 and (*Z*)-17). To a solution of **8b** (9.40 g, 26.5 mmol) in CH_2Cl_2 (80 mL) at r.t. NEt_3 (4.91 mL, 3.57 g, 35.3 mmol) was added and the reaction mixture stirred for 10 min. Then a solution of **16** (2.30 g, 17.7 mmol) in CH_2Cl_2 (20 mL) was added and the reaction mixture heated at reflux for 4 h. After removal of the solvent under vacuum, the residue was purified by chromatography on SiO_2 with hexanes/EtOAc (15 : 1) to give in a first fraction (R_f = 0.67, hexanes/EtOAc 3 : 1) (*Z*)-**17** (285 mg, 1.67 mmol, 10%, purity >95% by ^{1}H NMR) and in a second fraction (R_f = 0.44, hexanes/EtOAc 3 : 1) (*E*)-**17** (1.80 g, 10.6 mmol, 60%, purity >95% by ^{1}H NMR) as yellow oils. (*Z*)-isomer **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.24 (s, 3H, H-1), 3.56 (ddd, J = 8.3, 6.8, 0.9 Hz, 1H, H_a-6), 4.22 (ddd, J = 8.3, 7.1, 1.1 Hz, 1H, H_b-6), 5.31–5.36 (m, 1H, H-5), 6.23–6.25 (m, 2H, H-3, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (CH_3), 26.5 (CH_3), 31.0 (C-1), 68.9 (C-6), 74.1 (C-5), 109.7 [$C(CH_3)_2$], 127.2 (C-3), 147.7 (C-4), 198.3 (C-2). The spectroscopic data were in accordance with those in the literature.[19] (*E*)-isomer **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.29 (s, 3H, H-1), 3.69 (dd, J = 8.1, 7.0 Hz, 1H, H_a-6), 4.21 (dd, J = 8.1, 6.4 Hz, 1H, H_b-6), 4.68 (dddd J = 7.0, 6.4, 5.8, 1.2 Hz, 1H, H-5), 6.32 (dd, J = 15.9, 1.2 Hz, 1H, H-3), 6.70 (dd, J = 15.9, 5.8 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (CH_3), 26.5 (CH_3), 27.4 (C-1), 68.9 (C-6), 75.1 (C-5), 110.2 [$C(CH_3)_2$], 131.1 (C-3), 143.2 (C-4), 198.0 (C-2). The spectroscopic data were in accordance with those in the literature.[19]

(*S*,*E*)-5,6-Dihydroxyhex-3-en-2-one (18). According to a literature procedure,[20] a solution of (*E*)-**17** (1.52 g, 8.93 mmol) in a mixture from AcOH/H_2O/THF (4 : 2 : 1, 21 mL) was heated at

reflux for 2 h and then extracted with CH_2Cl_2 (2 × 7 mL). The organic layer was extracted with H_2O (3 × 5 mL). The combined aqueous layers were concentrated under vacuum to give **18** (1.16 g, 8.93 mmol, quant.) as a yellow liquid. $[\alpha]_D^{20}$ –1.8 (*c* 1.00 in CH_2Cl_2). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3379 (s), 2924 (m), 1672 (vs), 1363 (m), 1262 (s), 1067 (m), 1033 (m), 978 (s), 903 (w), 722 (m), 650 (w). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, H-1), 3.59 (dd, *J* = 11.2, 6.9 Hz, 1H, H_a-6), 3.80 (dd, *J* = 11.2, 3.6 Hz, 1H, H_b-6), 4.43–4.51 (m, 1H, H-5), 6.40 (dd, *J* = 16.1, 1.7 Hz, 1H, H-3), 6.75 (dd, *J* = 16.1, 4.5 Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.6 (C-6), 65.5 (C-1), 71.7 (C-2), 130.7 (C-4), 144.5 (C-3), 198.6 (C-5). MS (CI) *m*/*z* 131.1 [22%, $(M + H^+)$], 113.1 [100, $(M - OH)^+$], 100.0 (6), 85.0 (5), 71.1 (3), 65.1 (1), 55.0 (1), 47.0 (2), 43.0 (5, $C_2H_3O^+$). HRMS (CI) *m*/*z* obsd 131.0706, calc. for $C_6H_{11}O_3$: 131.0703.

3) Synthesis of O-silylated 5-hydroxyhex-3-en-2-ones 19a–c and esters 20a–c



(*S*,*E*)-5-Hydroxy-6-((triisopropylsilyl)oxy)hex-3-en-2-one (19a). To a solution of **18** (6.14 g, 47.2 mmol) in DMF (66 mL) at 0 °C imidazole (3.53 g, 51.9 mmol) was added and the reaction mixture stirred at r.t. for 5 min. After addition of TIPSCl (11 mL, 9.91 g, 51.9 mmol), the reaction mixture was stirred for 20 h. H_2O (80 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure and the crude product purified by chromatography on SiO_2 with hexanes/EtOAc (10 : 1) to give **19a** (11.9 g, 41.6 mmol, 88%) as a colorless oil. R_f = 0.21. FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3450 (w), 2943 (s), 2866 (s), 1678 (m), 1632 (w), 1463 (m), 1363 (m), 1254 (m), 1113 (s), 1064 (m), 984 (m), 904 (vs), 882 (vs), 786 (m), 731 (vs), 683 (s), 650 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04–1.09 [m, 21H, $CH(CH_3)_2$], 2.27 (s, 3H, H-1), 2.80 (d, *J* = 3.8 Hz, 1H, OH), 3.61 (dd, *J* = 9.8, 7.3 Hz, 1H, H_a-6), 3.84 (dd, *J* = 9.8, 3.9 Hz, 1H, H_b-6), 4.37–4.44 (m, 1H, H-5), 6.38 (dd, *J* = 16.1, 1.1 Hz, 1H, H-3), 6.73 (dd, *J* = 16.1, 4.6 Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 [*C*H$(CH_3)_2$], 17.8 [CH(*C*H$_3)_2$], 27.5 (C-1), 66.5 (C-6), 71.6 (C-5), 130.6 (C-3), 144.5 (C-4), 198.2 (C-2). MS (ESI) *m*/*z* 309.2 $[M + Na]^+$, 187.1, 165.1, 113.1 $[M + H - C_9H_{22}OSi]^+$. HRMS (ESI) obsd 309.1852, calc. for $C_{15}H_{30}O_3SiNa^+$: 309.1856.

(*S*,*E*)-5-Hydroxy-6-[(*tert*-butyl(diphenyl)silyl)oxy]hex-3-en-2-one (19b). To a solution of **18** (930 mg, 7.15 mmol) in DMF (10 mL) Et_3N (1.10 mL) was added and the mixture stirred at

r.t. for 5 min. Then TBDPS-Cl (2.04 mL, 2.16 g, 7.86 mmol) was added dropwise, the reaction mixture stirred for 20 h and subsequently washed with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuum. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 5 : 1) to give **19b** (1.94 g, 5.13 mmol, 72%). R_f = 0.45 (hexanes/EtOAc, 3 : 1). FT-IR (ATR): $\tilde{\nu}$ = 2930 (w), 2857 (w), 1718 (m), 1472 (w), 1427 (m), 1361 (w), 1106 (vs), 998 (w), 821 (m), 740 (m), 700 (vs), 609 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 [s, 9H, $C(CH_3)_3$], 2.23 (s, 3H, 6-H), 2.76 (d, *J* = 4.2 Hz, 1H, OH), 3.59 (dd, *J* = 10.2, 6.8 Hz, 1H, 1-H_a), 3.78 (dd, *J* = 10.2, 3.9 Hz, 1H, 1-H_b), 4.38 – 4.47 (m, 1H, 2-H), 6.34 (dd, *J* = 16.1, 1.7 Hz, 1H, 4-H), 6.66 (dd, *J* = 16.1, 4.5 Hz, 1H, 3-H), 7.34 – 7.49 (m, 6H, *o*-H, *p*-H), 7.61 – 7.72 (m, 4H, *m*-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.3 [*C*$(CH_3)_3$], 26.8 [C(*C*$H_3)_3$], 27.4 (C-5), 66.9 (C-1), 71.5 (C-2), 127.9 (*o*-C), 130.1 (C-4), 130.6 (*p*-C), 132.6 (*i*-C), 135.5 (*m*-C), 144.5 (C-3), 198.1 (C-5) ppm. MS (EI): m/z = 338.2, 311.1 [M + H - C_4H_9]$^+$, 293.1 [M + H - C_4H_9 - H_2O], 233.1, 207.1, 199.1 [$C_{12}H_{11}OSi$]$^+$, 181.1, 155.1, 135.1, 121.0, 95.0, 77.0, 43.0. HRMS (ESI): calc. for $C_{22}H_{28}O_3SiNa^+$ 391.1700, found: 391.1713 [M + Na]$^+$.

(*S*,*E*)-5-Hydroxy-6-[(*tert*-butyl(dimethyl)silyl)oxy]hex-3-en-2-one (19c). To a solution of **18** (990 mg, 7.61 mmol) in CH_2Cl_2 (10 mL) Et_3N (1.18 mL, 847 mg, 8.37 mmol) and TBS-Cl (1.26 g, 8.37 mmol) were added and the reaction mixture was stirred at r.t. for 18 h. The mixture was then washed with H_2O (2 × 3 mL), a satd. solution of NH_4Cl (2 × 5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuum to give **19c** (1.31 g, 5.37 mmol, 71%, purity 85%) which was used without further purification. R_f = 0.87 (hexanes/EtOAc, 1 : 1). FT-IR (ATR): $\tilde{\nu}$ = 3445 (w), 2930 (w), 2858 (w), 1677 (m), 1361 (w), 1253 (m), 1105 (m), 980 (w), 903 (s), 836 (vs), 777 (s), 728 (vs), 649 (w) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.085 (s, 3H, $SiCH_3$), 0.090 (s, 3H, $SiCH_3$), 0.91 [s, 9H, $C(CH_3)_3$], 2.26 (s, 3H, 6-H), 2.72 (d, *J* = 3.8 Hz, 1H, OH), 3.52 (dd, *J* = 10.1, 6.9 Hz, 1H, 1-H_a), 3.75 (dd, *J* = 10.1, 3.8 Hz, 1H, 1-H_b), 4.35 – 4.41 (m, 1H, 2-H), 6.37 (dd, *J* = 16.1, 1.9 Hz, 1H, 4-H), 6.72 (dd, *J* = 16.1, 4.4 Hz, 1H, 3-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = -5.41 ($SiCH_3$), -5.38 ($SiCH_3$), 18.3 [*C*$(CH_3)_3$], 25.8 [C(*C*$H_3)_3$], 27.5 (C-6), 66.2 (C-1), 71.4 (C-2), 130.6 (C-4), 144.5 (C-3), 198.2 (C-5) ppm. MS (ESI): m/z = 267.1 [M + Na]$^+$, 227.2 [M – OH]$^+$, 171.1. HRMS (ESI): calc. for $C_{12}H_{24}O_3SiNa^+$ 267.1387, found: 267.1378 [M + Na]$^+$.

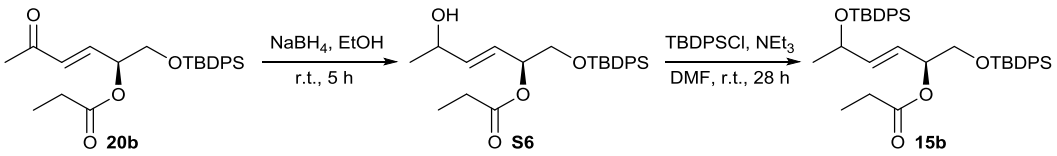
(1*S*,2*E*)-4-Oxo-1-{[(triisopropylsilyl)oxy]methyl}pent-2-enyl propionate (20a). To a solution of **19a** (1.14 g, 3.98 mmol) in CH_2Cl_2 (12 mL) at 0 °C pyridine (0.39 mL, 378 mg, 4.78 mmol) was added and the mixture stirred for 5 min. Then propionyl chloride (0.42 mL, 441 mg, 4.78 mmol) was added and the reaction mixture allowed to warm to r.t. over 4 h. The

reaction was quenched with H_2O (2 mL) and the mixture successively washed with H_2O (2 mL), a satd. solution of NH_4Cl (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under vacuum to give **20a** (1.36 g, 3.84 mmol, 97%, purity 97% by ^{1}H NMR), which was used without further purification. FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2943 (s), 2867 (s), 1744 (vs), 1682 (s), 1637 (w), 1463 (m), 1424 (w), 1361 (m), 1253 (m), 1175 (vs), 1130 (vs), 1069 (m), 979 (m), 902 (m), 882 (s), 785 (m), 726 (m), 683 (s), 650 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.09 [m, 21H, $CH(CH_3)_2$], 1.17 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.27 (s, 3H, H-5), 2.40 (q, J = 7.6 Hz, 2H, CH_2CH_3), 3.81 (dd, J = 10.3, 5.3 Hz, 1H, CH_aH_b), 3.87 (dd, J = 10.3, 6.0 Hz, 1H, CH_aH_b), 5.08 (dddd, J = 6.0, 5.3, 5.0, 1.6 Hz, 1H, H-1), 6.22 (dd, J = 16.2, 1.6 Hz, 1H, H-3), 6.78 (dd, J = 16.2, 5.0 Hz, 1H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.0 (CH_2CH_3), 11.9 ($CHCH_3$), 17.8 ($CHCH_3$), 27.1 (C-5), 27.6 (CH_2CH_3), 64.5 (CH_2), 72.9 (C-1), 131.1 (C-3), 142.0 (C-2), 173.4 (COO), 198.0 (C-4). MS (ESI) m/z 365.2 $[M + Na]^+$, 291.2, 271.2 $[M + H - COOCH_2CH_3]^+$, 191.1, 177.2, 165.1, 147.1, 137.1, 119.1, 95.1. HRMS (ESI) obsd 365.2120, calc. for $C_{18}H_{34}O_4SiNa^+$: 365.2119.

(*S*,*E*)-4-Oxo-1-{[(*tert*-butyl(diphenyl)silyl)oxy]methyl}pent-2-enyl propionate (20b). To a solution of **19b** (200 mg, 1.64 mmol) in CH_2Cl_2 (2 mL) at 0°C propionyl chloride (56.8 µL, 60.2 mg, 0.65 mmol) und pyridine (526 µL, 51.5 mg, 0.65 mmol) were added and the reaction mixture was allowed to r.t. over 2 h. The reaction was quenched with H_2O (1 mL) and the mixture successively washed with H_2O, a satd. solution of NH_4Cl and brine (1 mL each) and dried ($MgSO_4$). The solvent was removed under vacuum to give **20b** (253 mg, 0.53 mmol, 98%, puritiy 89% by ^{1}H NMR). R_f = 0.72 (hexanes/EtOAc, 3 : 1). $[\alpha]_D^{20}$ = –0.4 (c = 1.00, CH_2Cl_2). FT-IR (ATR): $\tilde{\nu}$ = 2933 (w), 2859 (w), 1743 (m), 1682 (m), 1463 (w), 1427 (m), 1362 (w), 1264 (vs), 1176 (m), 1113 (s), 978 (w), 800 (w), 735 (vs), 703 (vs) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 [s, 9H, $C(CH_3)_3$], 1.16 (dd, J = 7.6, 7.5 Hz, 3H, CH_2CH_3), 2.24 (s, 3H, 6-H), 2.36 (q, J = 7.5 Hz, 1H, $CH_{2a}CH_3$), 2.37 (q, J = 7.6 Hz, 1H, $CH_{2b}CH_3$), 3.76 (dd, J = 10.7, 5.0 Hz, 1H, 1-H_a), 3.81 (dd, J = 10.7, 6.1 Hz, 1H, 1-H_b), 5.57 (dddd, J = 6.1, 5.1, 5.0, 1.6 Hz, 1H, 2-H), 6.20 (dd, J = 16.1, 1.6 Hz, 1H, 4-H), 6.71 (dd, J = 16.1, 5.1 Hz, 1H, 3-H), 7.35 - 7.48 (m, 6H, *o*-H, *p*-H), 7.62 - 7.68 (m, 4H, *m*-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.0 (CH_2CH_3), 19.2 [$C(CH_3)_3$], 26.7 [$C(CH_3)_3$], 27.2 (C-6), 27.5 (CH_2CH_3), 64.7 (C-1), 72.8 (C-2), 127.8 (*o*-C), 129.88, 129.92 (*p*-C), 131.4 (C-4), 132.9, 133.0 (*i*-C), 135.5, 135.6 (*m*-C), 141.5 (C-3), 173.4 (COO), 197.8 (C-5) ppm. MS (ESI): m/z = 447.2 $[M + Na]^+$, 351.2 $[M + H - C_3H_5O_2]^+$, 291.1, 273.1 $[M + H - C_3H_5O_2 - C_6H_6]^+$, 269.1, 251.1, 227.1, 193.1, 163.1, 135.1, 95.1. HRMS (ESI): calc. for $C_{25}H_{32}O_4SiNa^+$ 447.1962, found: 447.1959 $[M + Na]^+$.

(*S*,*E*)-4-Oxo-1-{[(*tert*-butyl(dimethyl)silyl)oxy]methyl}pent-2-enyl propionate (20c). To a solution of **19c** (400 mg, 1.64 mmol) in CH_2Cl_2 (5 mL) at 0°C propionyl chloride (142 µL, 151 mg, 1.64 mmol) and pyridine (132 µL, 130 mg, 1.64 mmol) were added followed by addition of further propionyl chloride (20.0 µL, 0.23 mmol) after 2 h. The reaction was quenched with H_2O (2 mL) after stirring for a further 2 h and the mixture successively washed with H_2O, a satd. solution of NH_4Cl and brine (2 mL each). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 10 : 1) to give **20c** (303 mg, 1.01 mmol, 62%). R_f = 0.28 (hexanes/EtOAc, 10 : 1). FT-IR (ATR): $\tilde{\nu}$ = 2931 (m), 2858 (w), 1743 (s), 1681 (m), 1463 (w), 1361 (m), 1253 (s), 1175 (s), 1115 (s), 1082 (m), 978 (w), 911 (w), 837 (vs), 778 (s), 732 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 [s, 6H, $Si(CH_3)_2$], 0.89 [s, 9H, $C(CH_3)_3$], 1.17 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 2.27 (s, 3H, 6-H), 2.40 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 3.72 (dd, *J* = 10.7, 5.3 Hz, 1H, 1-H_a), 3.77 (dd, *J* = 10.7, 6.1 Hz, 1H, 1-H_b), 5.49 (dddd, *J* = 6.1, 5.3, 4.9, 1.5 Hz, 1H, 2-H), 6.22 (dd, *J* = 16.2, 1.5 Hz, 1H, 4-H), 6.74 (dd, *J* = 16.2, 4.9 Hz, 1H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = -5.31 ($SiCH_3$), -5.27 ($SiCH_3$), 9.2 (CH_2CH_3), 18.3 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 27.3 (C-6), 27.7 (CH_2CH_3), 64.1 (C-1), 73.0 (C-2), 131.5 (C-4), 141.8 (C-3), 173.5 (COO), 198.0 (C-5) ppm. MS (ESI): m/z = 323.2 $[M + Na]^+$, 249.1, 227.1, 191.1, 145.1, 133.1, 107.1, 95.0, 89.0. HRMS (ESI): ber. für $C_{15}H_{28}O_4SiNa^+$ 323.1649, gef. 323.1648 $[M + Na]^+$.

4) Synthesis of disilylated propionate 15b starting from 20b



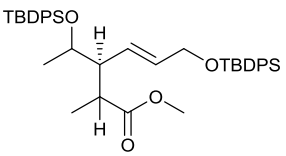
(1*S*,2*E*)-1-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-4-hydroxypent-2-enyl propionate (S6). To a solution of **20b** (330 mg, 0.78 mmol) in EtOH (3 mL) $NaBH_4$ (17.6 mg, 0.47 mmol) was added portionwise and the reaction mixture stirred at r.t. for 5 h. A 1 N solution of HCl (1 mL) and H_2O (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed to give **S6** (321 mg, 0.73 mmol, 94%, purity 98% by ^1H NMR). *dr* = 50 : 50 (by ^{13}C NMR). FT-IR (ATR): $\tilde{\nu}$ = 3363 (w), 2930 (w), 2857 (w), 1736 (m), 1427 (w), 1184 (m), 1111 (s), 1028 (m), 970 (w), 822 (m), 801 (m), 740 (m), 701 (vs), 6611 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.04 [s, 18H, $C(CH_3)_3$], 1.14 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 1.24 (d, *J* = 6.5 Hz, 6H, 6-H), 2.325 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 2.332 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 3.67 - 3.76 (m, 4H, 1-H), 4.24 - 4.31 (m, 2H,

5-H), 5.41 - 5.47 (m, 2H, 2-H), 5.63 (dddd, *J* = 15.6, 6.4, 2.9, 1.1 Hz, 2H, 3-H), 5.80 (dddd, *J* = 15.6, 5.7, 4.7, 1.1 Hz, 2H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.08 (CH_2CH_3), 18.2 [$C(CH_3)_3$], 22.1 (C-6), 25.7 [$C(CH_3)_3$], 26.7 (CH_2CH_3), 64.4 (C-1), 67.0, 67.1 (C-5), 72.9 (C-2), 123.9, 124.0 (C-3), 126.66, 126.67 (*o*-C), 128.69, 128.74 (*p*-C), 132.27, 132.33 (*i*-C), 134.4, 134.6 (*m*-C), 136.6, 136.7 (C-4), 172.6 (COO) ppm. MS (ESI): *m/z* = 449.2 $[M + Na]^+$, 375.2 $[M + Na - C_3H_5O_2]^+$, 277.2 $[M - C_3H_5O_2 - C_6H_5]^+$, 235.1, 221.1, 199.1, 173.1, 157.1, 117,1. HRMS (ESI): calc. for $C_{25}H_{34}O_4SiNa^+$ 449.2119, found: 449.2115 $[M + Na]^+$.

(1*S*,2*E*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)pent-2-enyl propionate (15b). To a solution of **S6** (310 mg, 0.73 mmol) in DMF (3 mL) Et_3N (0.14 mL, 103 mg, 1.02 mmol) and TBDPSCl (0.26 mL, 280 mg, 1.02 mmol) were successively added and the reaction mixture stirred at r.t. for 28 h. The solvent was then removed and the residue purified by chromatography on SiO_2 (hexanes/EtOAc, 100 : 1) to give **15b** (260 mg, 0.39 mmol, 54%). R_f = 0.26. *dr* = 51 : 49 (by ^{13}C NMR). FT-IR (ATR): $\tilde{\nu}$ = 2931 (w), 2858 (w), 1738 (m), 1462 (w), 1427 (m), 1362 (w), 1184 (m), 1110 (s), 1080 (s), 967 (m), 909 (w), 822 (m), 737 (s), 699 (vs), 610 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 - 1.05 [m, 18H, $C(CH_3)_3$], 1.07 - 1.17 (m, 6H, 6-H, CH_2CH_3), 2.23 - 2.36 (m, 2H, CH_2CH_3), 3.52 - 3.67 (m, 2H, 1-H), 4.20 - 4.31 (m, 1H, 5-H), 5.34 - 5.48 (m, 2H, 2-H, 3-H), 5.72 (dd, *J* = 14.4, 5.3 Hz, 1H, 4-H), 7.21 - 7.48 (m, 12H, *o*-H, *p*-H), 7.56 - 7.75 (m, 8H, *m*-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2 (CH_2CH_3), 19.2 [$C(CH_3)_3$], 24.0 (C-6), 26.6, 26.7 [$C(CH_3)_3$], 27.8 (CH_2CH_3), 65.5 (C-1), 69.4, 69.5 (C-5), 74.0, 74.2 (C-2), 123.9 (C-3), 127.4, 127.5, 127.68, 127.73 (*o*-C), 129.51. 129.54, 129.66, 129.72 (*p*-C), 133.4, 134.0, 134.4, 134.8 (*i*-C), 135.58, 135.64, 135.8 (*m*-C), 137.9, 138.2 (C-4), 173.5 (COO) ppm. MS (ESI): *m/z* = 687.3 $[M + Na]^+$, 610.2, 591.3 $[M - C_3H_5O_2]^+$, 462.4, 409.2 $[M - C_{16}H_{19}OSi]^+$, 335.2, 301.1, 235.1, 186.2, 157.1. HRMS (ESI): ber. für $C_{41}H_{52}O_4Si_2Na^+$ 687.3296, gef. 687.3280 $[M + Na]^+$.

Methyl (3*S*,4*E*)-6-{[*tert*-butyl(diphenyl)silyl]oxy}-3-(1-{[*tert*-butyl(diphenyl)silyl]oxy}-ethyl)-2-methylhex-4-enoate. To a solution of diisopropylamine (101 µL, 73.3 g, 0.72 mmol) in THF (2 mL) at –100°C a 1.6 M solution of *n*-BuLi in *n*-hexane (406 µL, 0.65 mmol) was added, the mixture warmed to r.t. for 5 min and then recooled to –100°C. Then a solution of **15b** (240 mg, 0.36 mmol) in THF (1 mL) was added dropwise followed by addition of TMSCl (50.0 µL, 43.1 mg, 0.40 mmol) and the reaction mixture was stirred for 1 h. Then it was warmed to r.t. and stirred for a further 3.5 h. After addition of a 0.1 M NaOH solution (1 mL), The mixture was stirred for 5 min. H_2O (1 mL) was then added and the mixture was extracted with Et_2O (3 × 2 mL). A 1 M solution of HCl (2 mL) was added and the aqueous layer extracted with Et_2O (1 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under vacuum.

The residue was taken up in Et_2O (5 mL) and transferred in the outer flask of the diazomethane generator. In the inner flask *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) (322 mg, 1.50 mmol) was dissolved in 2-(2-ethoxyethoxy)ethanol (carbitol) (2 mL). The outer flask was cooled to 0°C and a solution of KOH (37%, 2.5 mL) was added dropwise through a septum. After stirring at 0°C for 3 h, silica (158 mg, 3.76 mmol) was added to degrade excess diazald. The solvent was removed by a stream of N_2 and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 150 : 1 → 100 : 1) to give the product (141 mg, 0.18 mmol, 48%). R_f = 0.14 (hexanes/EtOAc, 100 : 1). *dr* = 53 : 44 : 3 : 0 (by ^{1}H NMR). FT-IR (ATR): $\tilde{\nu}$ = 2931 (w), 2857 (w), 1735 (m), 1461 (w), 1473 (m), 1362 (w), 1257 (w), 1191 (w), 1106 (s), 1051 (m), 974 (m), 909 (m), 822 (m), 734 (s), 700 (vs), 605 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.3 Hz, 3H, 2'-H), 0.98 (d, *J* = 6.5 Hz, 3H, 2'-H*), 0.98 (d, *J* = 6.8 Hz, 3H, 1''-H*), 1.027 [s, 18H, $C(CH_3)_3$], 1.034 [s, 9H, $C(CH_3)_3$], 1.07 [s, 9H, $C(CH_3)_3$], 1.08 (d, *J* = 7.2 Hz, 3H, 1''-H), 2.22 (ddd, *J* = 10.1, 9.9, 2.1 Hz, 1H, 3-H), 2.64 (ddd, *J* = 9.9, 6.8, 6.5 Hz, 1H, 3-H*), 2.85 (dq, *J* = 7.0, 6.8 Hz, 1H, 2-H*), 2.85 (dq, *J* = 10.1, 7.2 Hz, 1H, 2-H), 3.52 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.73 (dq, *J* = 6.6, 6.5 Hz, 1H, 1'-H*), 3.82 (dq, *J* = 6.3, 2.1 Hz, 1H, 1'-H), 4.15 (dd, *J* = 4.8, 1.6 Hz, 2H, 6-H*), 4.26 (dd, *J* = 4.5, 1.7 Hz, 2H, 6-H), 5.43 (ddt, *J* = 15.4, 9.9, 1.6 Hz, 1H, 4-H*), 5.60 (dt, *J* = 15.5, 4.5 Hz, 1H, 5-H), 5.61 (dt, *J* = 15.4, 4.8 Hz, 1H, 5-H*), 5.81 (ddt, *J* = 15.5, 10.1, 1.7 Hz, 1H, 4-H), 7.28 - 7.45 (m, 24H, *o*-H, *p*-H), 7.61 - 7.75 (m, 16H, *m*-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7 (C-1''*), 16.8 (C-1''), 19.2, 19.3, 19.35, 19.40 [$C(CH_3)_3$], 20.8 (C-2'*), 22.3 (C-2'), 26.78, 26.82, 27.0 [$C(CH_3)_3$], 40.2 (C-2*), 40.4 (C-2), 51.4 (OCH_3), 52.8 (C-3*), 53.3 (C-3), 64.1 (C-6), 64.3 (C-6*), 69.9 (C-1*), 70.7 (C-1), 126.69 (C-4*), 127.71 (C-4), 127.2, 127.3, 127.5, 127.60, 127.63, 127.7 (*o*-C), 129.2, 129.4, 129.57, 129.60, 129.64 (*p*-C), 133.1 (C-5), 133.4 (*i*-C), 133.5 (C-5), 133.7, 133.8, 133.9, 134.8, 135.1 (*i*-C), 135.5, 135.91, 135.93, 135.95, 136.01 (*m*-C), 176.3 (C-1*), 177.1 (C-1) ppm. MS (ESI): *m/z* = 701.3 [M + Na]$^+$, 601.3, 423.2 [M + H - $C_{16}H_{20}OSi$]$^+$, 379.2, 337.2, 283.2. HRMS (ESI): ber. für $C_{42}H_{54}O_4Si_2Na^+$ 701.3453, gef. 701.3444 [M + Na]$^+$.



5) Alternative route to disilylated derivative 15a (analogous to Scheme 4)

(*E*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-3-en-2-ol [(*E*)-22]. To a solution of (*E*)-**17** (200 mg, 1.18 mmol) in EtOH (2 mL) $NaBH_4$ (22.2 mg, 0.59 mmol) was added and the reaction mixture stirred at r.t. for 30 min. The reaction was quenched with H_2O (1 mL) and the mixture carefully filtered through SiO_2. The product was eluated from SiO_2 with EtOAc (10 mL) and the filtrate concentrated under vacuum to give (*E*)-**22** (200 mg, 1.18 mmol, quant.) in a diastereo-

meric ratio 62 : 38 (by ^{1}H NMR), which was reacted without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.279 (d, J = 6.4, 3H, H-1), 1.283 (d, J = 6.4, 3H, H*-1), 1.39 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.78 (br, 1H, OH), 3.56–3.63 (m, 1H, CH_aH$_b$), 4.06–4.14 (m, 1H, CH$_a$$H_b$), 4.28–4.39 (m, 1H, H-2), 4.47–4.55 (m, 1H, H-5), 5.61–5.71 (m, 1H, H-4), 5.83–5.92 (m, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (CH_3), 23.2 (CH_3*), 25.9 [C(CH_3)$_2$], 26.7 [C(CH_3)$_2$], 67.9 (CH_2), 69.4 (C-5), 76.49 (C-2), 76.52 (C-2*), 109.4 [C(CH_3)$_2$], 127.0 (C-4), 138.4 (C-3), 138.5 (C-3*). The spectroscopic data were in accordance with those in the literature.[33]

***tert*-Butyl({(*E*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-methylprop-2-enyl}oxy)diphenylsilane [(*E*)-23].** To a solution of (*E*)-**22** (198 mg, 1.16 mmol) in DMF (2 mL) imidazole (238 mg, 3.49 mmol) and TBDPSCl (454 µL, 480 mg, 1.75 mmol) were added and the reaction mixture stirred at r.t. for 3 h. The reaction was quenched with H_2O (3 mL) and toluene (3 mL) and the mixture extracted with toluene (3 × 7 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by chromatography on SiO_2 with hexanes/EtOAc (20 : 1) to give (*E*)-**23** (395 mg, 0.96 mmol, 83%) in a diastereomeric ratio 52 : 48 (by ^{1}H NMR). R_f = 0.38. FT-IR (ATR): ($\tilde{\nu}$ cm^{-1}) 2931 (w), 2858 (w), 1473 (w), 1428 (m), 1370 (m), 1216 (m), 1153 (m), 1109 (s), 1057 (s), 968 (m), 902 (m), 822 (m), 738 (s), 701 (vs), 613 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 [s, 9H, C(CH_3)$_3$], 1.07 [s, 9H, C(CH_3)$_3$], 1.15 (d, J = 6.4, 3H, H-6), 1.18 (d, J = 6.3, 3H, H*-6), 3.32–3.34 (m, 2H, CH_aH$_b$, CH_aH$_b$*), 3.90–4.04 (m, 2H, CH$_a$$H_b$, CH$_a$$H_b$*), 4.26–4.48 (m, 4H, H-2, H*-2, H-5, H*-5), 5.34 (ddd, J = 15.4, 7.6, 1.1, 1H, H*-3), 5.54 (ddd, J = 15.4, 7.2, 1.4, 1H, H-3), 5.75 (ddd, J = 15.4, 6.3, 0.9, 1H, H-4), 5.79 (ddd, J = 15.4, 5.0, 0.9, 1H, H*-4), 7.31–7.46 (m, 12H, *o*-H, *o*-H*, *p*-H, *p*-H*), 7.62–7.70 (m, 8H, *m*-H, *m*-H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 19.3 [C(CH_3)$_3$], 24.0, 24.2 (CH_3), 25.9, 26.0, 26.6, 26.7 [C(CH$_3$)$_2$], 26.98, 27.01 [C(CH$_3$)$_3$], 69.1 (C-5), 69.4, 69.5 (C-1), 69.7 (C-5), 76.5, 76.7 (C-2), 109.19, 109.23 [C(CH_3)$_2$], 126.0, 126.6 (C-3), 127.4, 127.5 (*o*-C), 129.5, 129.6 (*p*-C), 134.1, 134.4 (*i*-C), 135.86, 135.90 (*m*-C), 138.1, 138.5 (C-4).

(2*S*,3*E*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}hex-3-ene-1,2-diol (24). A solution of (*E*)-**23** (2.59 mg, 0.63 mmol) in a mixture from THF/HOAc/H_2O (1 : 4 : 2, 4.2 mL) was heated at reflux for 3 h. The solvent mixture was then removed under vacuum and the residue purified by chromatography on SiO_2 with hexanes/EtOAc (3 : 1) to give **24** (65.0 mg, 0.18 mmol, 28%) in a diastereomeric ratio 51 : 49 (by ^{13}C NMR). R_f = 0.49 (hexane/EtOAc, 1 : 1). FT-IR (ATR): ($\tilde{\nu}$ cm^{-1}) 3434 (w), 2930 (w), 2857 (w), 1737 (m), 1472 (w), 1427 (m), 1370 (w), 1236 (m), 1106 (m), 1040 (m), 969 (w), 822 (w), 737 (s), 701 (vs), 611 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 [s, 9H, C(CH_3)$_3$], 1.19 (d, J = 6.3 Hz, 3H, H-6), 3.30–3.37 (m, 1H, H$_a$-1), 3.50–3.52 (m, 1H, H$_b$-1), 4.05–4.12 (m, 1H, H-2), 4.30–4.37 (m, 1H, H-5), 5.37 (dddd, J = 15.5, 9.5, 6.3, 1.2, 1H, H-

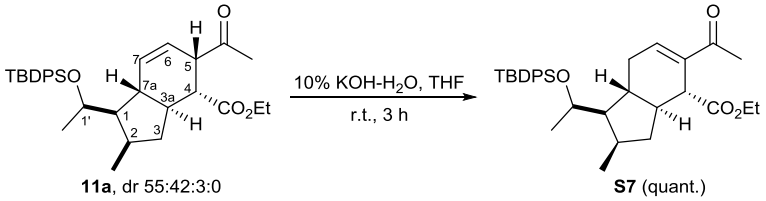
3), 5.73 (dddd, *J* = 15.5, 5.9, 2.7, 1.3, 1H, H-4), 7.33–7.40 (m, 4H, *o*-H), 7.40–7.45 (m, 2H, *p*-H), 7.63–7.69 (m, 4H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 [*C*$(CH_3)_3$], 24.3 (C-6), 27.0 [C(*C*$H_3)_3$], 66.25, 66.28 (C-1), 69.6, 69.7 (C-5), 72.46, 72.50 (C-2), 127.3 (C-3), 127.48, 127.55 (*o*-C), 129.6, 129.7 (*p*-C), 134.3, 134.4 (*i*-C), 135.9, 136.0 (*m*-C), 137.1, 137.3 (C-4). MS (ESI) *m/z* 393.2 $[M + Na]^+$, 331.1, 298.0, 270.0, 223.1, 175.1, 149.0, 137.1, 115.1. HRMS (ESI) obsd 393.1845, calc. for $C_{22}H_{30}O_3SiNa^+$: 393.1856.

(6*S*,7*E*)-3,3-Diisopropyl-2,9,12,12-tetramethyl-11,11-diphenyl-4,10-dioxa-3,11-disiladodec-7-en-6-ol (25). To a solution of **24** (303 mg, 0.82 mmol) in DMF (3 mL) Et_3N (0.13 mL, 91.0 mg, 0.90 mmol) was added followed by TIPSCl (0.19 mL, 173 mg, 0.90 mmol) after stirring for 5 min. The reaction mixture was stirred for 20 h and the reaction quenched with a satd. solution of NH_4Cl (1 mL). The aqueous layer was extracted with CH_2Cl_2 (8 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 with hexanes/EtOAc (30 : 1) to give **25** (201 mg, 0.22 mmol, 27%, purity 58% laut ^{1}H NMR) (*dr* = 52 : 48 by ^{1}H NMR). R_f = 0.46 (hexane/EtOAc, 20 : 1). FT-IR (ATR): ($\tilde{\nu}$ cm^{-1}) 2941 (m), 2864 (m), 1462 (m), 1427 (m), 1367 (w), 1106 (vs), 969 (m), 882 (s), 822 (m), 794 (w), 739 (m), 701 (vs), 687 (s), 612 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.08 [m, 60H, $CH(CH_3)_2$, $CH(CH_3)_2$*, $C(CH_3)_3$, $C(CH_3)_3$*], 1.15 (d, *J* = 6.3, 3H, CH_3), 1.17 (d, *J* = 6.3, 3H, CH_3*), 3.35 (dd, *J* = 9.8, 8.0, 1H, C*H*$_a$H$_b$*), 3.41 (dd, *J* = 9.8, 7.8, 1H, C*H*$_a$H$_b$), 3.55 (dd, *J* = 9.8, 3.6, 1H, CH$_a$*H*$_b$*), 3.60 (dd, *J* = 9.8, 3.8, 1H, CH$_a$*H*$_b$), 4.05–4.12 (m, 2H, H-6, H*-6), 4.28–4.36 (m, 2H, H-9, H-9*), 5.37 (ddd, *J* = 15.5, 6.4, 1.1, 1H, H*-7), 5.47 (ddd, *J* = 15.5, 6.1, 1.3, 1H, H-7), 5.76 (ddd, *J* = 15.5, 6.0, 1.3, 1H, H*-8), 5.78 (ddd, *J* = 15.5, 5.5, 1.3 Hz, 1H, H-8), 7.31–7.44 (m, 12H, *o*-H, *p*-H, *o*-H*, *p*-H*), 7.62–7.70 (m, 8H, *m*-H, *m*-H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.9 [*C*$H(CH_3)_2$], 18.0 [$CH(CH_3)_2$], 19.2 [*C*$(CH_3)_3$], 24.16, 24.24 (CH_3, CH_3*), 27.0 [C(*C*$H_3)_3$], 67.3 (CH_2*), 67.4 (CH_2), 69.5, 69.8 (C-9, C-9*), 72.4, 72.5 (C-6, C-6*), 126.8 (C-7), 127.1 (C-7*), 127.4, 127.5 (*o*-C, *o*-C*), 129.5, 129.6 (*p*-C, *p*-C*), 134.2, 134.3 (*i*-C, *i*-C*), 125.8, 135.9 (*m*-C, *m*-C*), 136.7, 136.9 (C-8, C-8*). MS (ESI) *m/z* 527.0 $[M + H]^+$, 449.3, 373.3, 351.2, 273.2, 255.2, 229.2, 213.2, 175.2, 149.1, 99.1. HRMS (ESI) obsd 549.3199, calc. for $C_{31}H_{50}O_3Si_2Na^+$: 549.3191.

(1*S*,4*E*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-({[ethyl(diisopropyl)silyl]oxy}methyl)pent-2-enyl propionate (15a). To a solution of **25** (188 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) at 0°C pyridine (30 µL, 33.9 mg, 0.4 mmol) was added and the mixture stirred for 5 min. Then propionyl chloride (40 µL, 39.6 mg, 0.43 mmol) was added and the reaction mixture allowed to warm to r.t. over 4 h. The reaction mixture was successively washed with a satd. solution of NH_4Cl (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under

vacuum. The residue was purified by chromatography on SiO_2 with hexanes/ EtOAc (100:1) to give **15a** (145.85 mg, 0.25 mmol, 70%, purity 97% by ^{1}H NMR) (*dr* 1:1).

6) Hydrolysis of derivative 11a



11a, dr 55:42:3:0 **S7** (quant.)

Reaction of **11a** with aqueous KOH in THF proceeded quantitatively, however, isomerization of the double bond occurred giving the bicyclic system **S7** rather than hydrolysis of the ester.

Ethyl (2*R*,3a*S*,4*R*,7a*R*)-5-acetyl-1-(1-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-4-carboxylate (S7). To a solution of **11a** (10 mg, 0.02 mmol) in THF (0.5 mL) a solution of 10% KOH (115 µL, 1.18 mg, 0.02 mmol) was added and the reaction mixture stirred for 3 h. After addition of a 4 N solution of HCl (1 mL) (pH = 1), the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give **S7** (10 mg, 0.02 mmol, quant.) as a colorless oil (*dr* 58 : 36 : 6 : 0 by ^{13}C NMR). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3071 (w), 3047 (w), 2957 (m), 2930 (m), 2892 (w), 2856 (m), 1731 (s), 1670 (s), 1631 (w), 1589 (w), 1473 (m), 1461 (m), 1427 (m), 1391 (w), 1373 (m), 1342 (w), 1319 (m), 1247 (m), 1194 (m), 1157 (s), 1108 (s), 1047 (m), 1026 (w), 1007 (w), 929 (w), 909 (w), 873 (w), 848 (w), 822 (m), 740 (m), 703 (vs), 649 (w), 609 (m), 568 (w), 542 (w). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 7.6 Hz, 3H, 2-CH_3*), 0.99 (d, J = 7.4 Hz, 3H, 2-CH_3), 1.01–1.07 (m, 20H, $C(CH_3)_3$, H_a-3, H_a*-3), 1.12 (d, J = 6.3 Hz, 3H, 1'-CH_3), 1.24–1.30 (m, 6H, CH_2CH_3, CH_2CH_3*), 1.50–1.82 (m, 4H, H-1, H*-1, H-3a, H*-3a), 1.98–2.27 (m, 10H, H-2, H*-2, H-7a, H*-7a, H_b-3, H_b*-3, H_a-7, H_a*-7), 2.31 (s, 3H, $COCH_3$*), 2.32 (s, 3H, $COCH_3$), 2.35–2.46 (m, 1H, H_b-7), 2.59–2.68 (m, 1H, H_b-7), 3.03–3.13 (m, 2H, H-4, H*-4), 3.98–4.05 (m, 1H, H-1'), 4.08–4.13 (m, 1H, H*-1'), 4.13–4.20 (m, 4H, CH_2CH_3, CH_2CH_3*), 6.96–7.02 (m, 2H, H-6, H*-6), 7.32–7.49 (m, 12H, *o*-H, *p*-H), 7.63–7.73 (m, 8-H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (CH_2CH_3, CH_2CH_3*), 17.7, 19.3 (2-CH_3, 2-CH_3*), 19.32, 19.5 [$C(CH_3)_3$], 22.3 (1'-CH_3), 23.9 (1'-CH_3*), 25.6 ($COCH_3$, $COCH_3$*), 27.2, 27.3, 27.4 [$C(CH_3)_3$], 32.4 (C-7), 33.3 (C-2), 34.0 (C-7), 35.0 (C-2), 39.2, 39.8 (C-3), 44.6, 45.1 (C-1), 49.0, 49.2 (C-4, C-4*), 53.4, 54.2 (C-3a, C-3a*), 60.6 (CH_2CH_3, CH_2CH_3*), 69.4, 70.4 (C-1', C-1'*), 127.48, 127.52, 127.70 (*o*-C), 129.57, 129.62, 129.75, 129.78 (*m*-C), 136.98, 136.09, 136.13 (*p*-C), 139.6, 139.7 (C-5, C-5*), 143.7, 143.8 (C-6, C-6*), 175.1, 175.2 (CO_2Et, CO_2Et*),

198.56, 198.63 (*C*$COCH_3$, *C*OCH_3*). MS (ESI) *m/z* 533.4 $[M - H]^+$, 231.1, 213.1, 203.1 $[M - C_{16}H_{19}OSi - C_{14}H_{20}O_2 - H]^+$, 185.1, 159.1, 117.1. HRMS (ESI) obsd 555.2897, calc. for $C_{33}H_{44}O_4SiNa^+$: 555.2901.

7) Deuteration experiments of derivative 20b

Tert-butyldiphenylsilyl ether **20b** was deprotonated with LDA and the reaction was quenched with D_2O. Chromatographic purification gave a pure fraction suitable for ^1H NMR investigation, where the signals of the olefinic protons H-2 and H-3 which remain unaffected by the deuteration were set to 1 as reference (Fig. S1a).

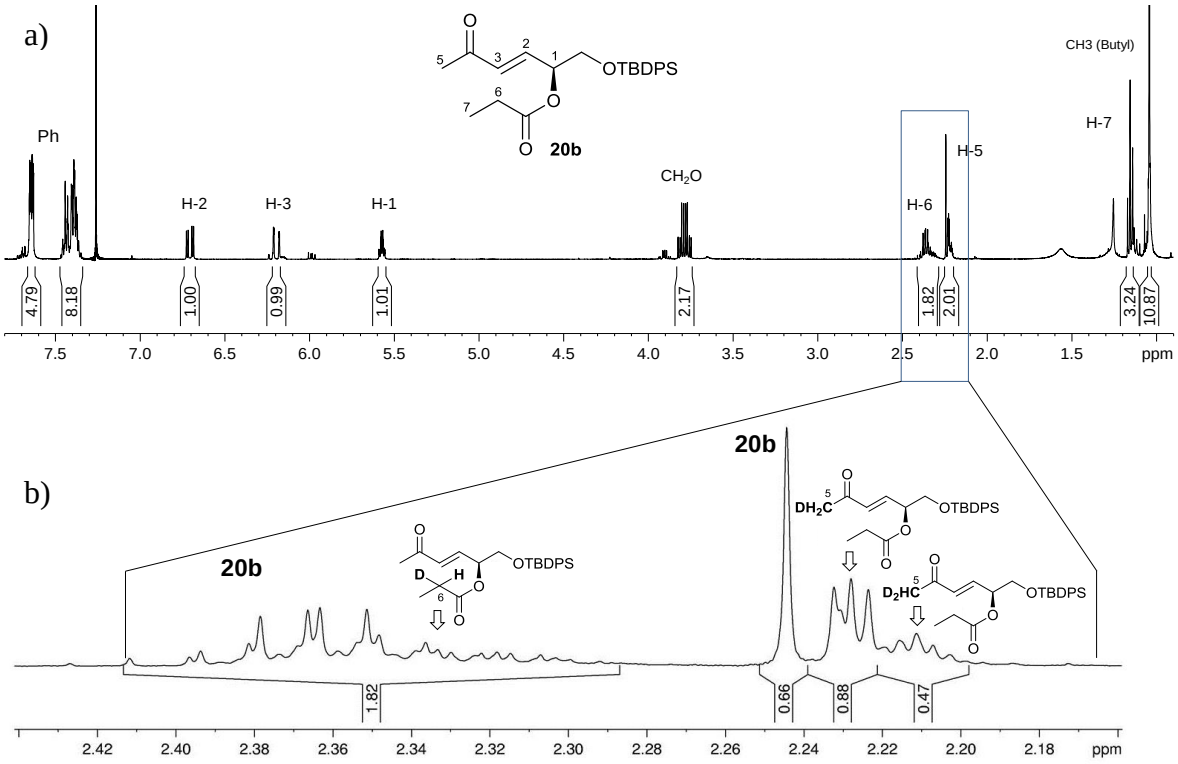


Fig. S1 ^1H NMR spectrum (500 MHz, $CDCl_3$) of starting silyl ether **20b** after deuteration (a) and detail of the spectrum showing the resolved region of protons H-5 and H-6 (b).

Integration of the H-5 protons in the range of δ = 2.20–2.25 ppm resulted in a value of 2.01 instead of the expected 3. That means, the derivative with fully deuterated CD_3 (no signal in the ^1H NMR spectrum) was obtain with 33% percentage. In contrast, double deuteration at position 6 proceeded with 9%, as shown by the integration value of 1.82 instead of 2 for the H-6 proton in the range of δ = 2.28–2.42 ppm. An H/D exchange[27] caused an upfield shift of the H-5 proton signals, allowing independent integration of the triplet for CH_2D and the quintet for CHD_2 formed by coupling between H and D (Fig. S1b). Thus, integration of signals for the deuteration

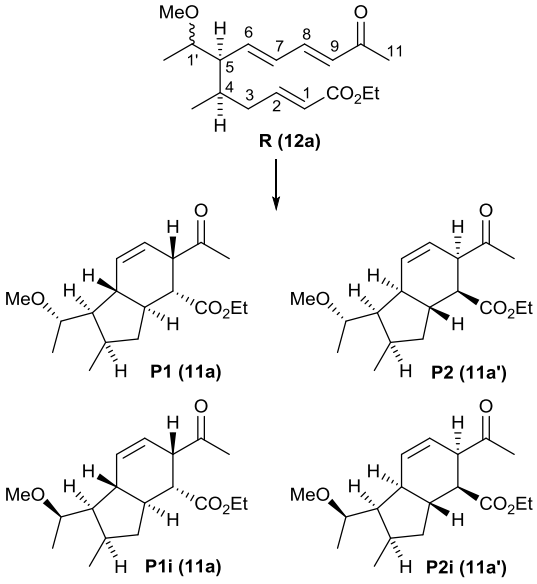
at position 5 gave a percentage of 13% (**20b**), of 25% monodeuterated and of 28% double deuterated derivative. The degree of deuteration is 87%.

8) Quantum-chemical investigation of the selective formation of 11a

As pointed out by Boeckman et al.[10] in a study on a similar compound, the conformation of the diastereomeric centres of **11a** can be understood by inspection of the different transition states leading from *E,E*-ketotriene ester **12a** to the final product. Here, we carried out a detailed quantum-chemical investigation of the different transition states, which underpins the formation of the intended diastereomer.

Our study is based on density functional theory (DFT). We employed the PBE and PBE0 density functionals[34] together with the def2-SVP and def2-TZVPP basis sets.[35] The D3 dispersion correction was used throughout.[36] The impact of solvation effects has been tested by applying the continuum solvation approach COSMO.[37] Computations were carried out with the TURBOMOLE V6.6 suite of programs,[38] using the multipole-accelerated RIJ technique[39] and appropriate auxiliary basis functions.[40]

Compound **11a** carries a bulky TBDPS group and both isomers resulting from the different stereochemistry at the C-1' centre have to be considered. The large configuration space of the TBDPS residue complicates the computations and we therefore decided to first investigate a simpler derivative, where TBDPS was replaced by methyl. Nonetheless, we also carried out computations on the full compound to check the effect of the much bulkier TBDPS residue.



Scheme S1 Simplified analogues of **12a**, **11a** and **11a'** with OMe group at the stereocentre C-1'.

The computations focus on the two transition states leading from triene **12a** to the compound **11a** and **11a'** (Scheme 6 of the article). For the initial computations we introduced the simplified

methyl-ether compounds **R**, **P1**, **P2**, **P1i**, and **P2i** (Scheme S1). The conformation of **R** was chosen somewhat arbitrary (the compound has a large number of conformers), it just defines the zero of the energy scale. This has no influence on our study, which focuses on differences in the energetics of the transition state structures and also of the final products. Of course, for the reactions leading to **P1i** and **P2i**, the corresponding isomer of **R** with different stereocentre in C-1' position was used.

We carried out an initial set of structure optimizations at the PBE+D3/def2-SVP level of theory. Second derivatives were computed for all determined structures at this level of theory to clearly identify these as minima or first-order saddle points. In addition these computations determined the zero-point vibrational energies of the compounds. To test these results, we increased both the size of the basis set (PBE-D3/def2-TZVPP) and changed to a hybrid functional (PBE0-D3/def2-TZVPP). Full structure optimizations were carried out for the model compounds, as well as computationally less demanding single point energy computations at the structures from the initial set of calculations (PBE+D3/def2-SVP). In addition, solvent stabilization energies were computed using the COSMO model (standard settings with $\varepsilon = 2.5$ to mimic toluene solvent). The results are summarized in Table S2.

Table S2 Computed reaction energies (RE) and activation energies (AE) for different computational settings (all values in kJ mol^{-1}). **A** PBE+D3/def2-SVP (full optimization), **B** PBE+D3/def2-TZVPP (full optimization), **C** PBE0+D3/def2-TZVPP (full optimization), **D** PBE+D3/def2-TZVPP (structures from setting **A**), **E** PBE+D3/def2-TZVPP with solvent effects (structures from setting **A**). All computed values include zero-point vibrational energies computed in setting **A**.

	A	**B**	**C**	**D**	**E**
RE(**P1**)	–121	–89	–121	–124	–115
RE(**P2**)	–115	–80	–111	–113	–104
AE(**P1**)	30	50	63	63	68
AE(**P2**)	43	61	74	74	78
RE(**P1i**)	–116	–85	–117	–119	–111
RE(**P2i**)	–107	–76	–106	–108	–102
AE(**P1i**)	35	52	66	66	70
AE(**P2i**)	45	62	75	76	79
ΔRE(**P1**,**P2**)	5	9	10	10	12
ΔAE(**P1**,**P2**)	12	11	11	11	9
ΔRE(**P1i**,**P2i**)	9	9	10	11	9
ΔAE(**P1**,**P2**)	10	10	10	9	9

Independent of the level of theory, we always predict a difference in activation energy of 10 kJ mol^{-1} in favor of the pathway leading to the expected product **P1** (or **P1i** for the alternative conformation of the OMe group). We took care that we only compare structures with very similar conformations at all centers that are not close to the reaction center. This makes our comparison valid even without a Boltzmann average over all structures from the energetically accessible conformational space. At the conditions of the Diels-Alder reaction (toluene reflux, T ≈ 384 K) and assuming an Arrhenius law $k \propto \exp(-\frac{\Delta E}{RT})$ for the competing reactions, the activation energy difference leads to an approximately 16 times larger reaction rate towards the desired product (we will see below that the activation energy difference is possibly even larger for the OTBDPS substituted compound). The activation energy is sizable (around 60 to 80 kJ mol^{-1}), in line with the rather harsh reaction conditions (toluene reflux and several days reaction time). In the initial setting (PBE+D3/def2-SVP) the activation barrier is somewhat underestimated, both the increase in basis set size and inclusion of exact exchange in the hybrid functional correct the estimate to higher energy (the difference between the activation energies leading to different product is not changed, however). Interestingly, the energy difference in the transition state structures persists for the products, too, see the reaction energies in Table S2. Therefore, the preference for **P1** should persist if the reaction is reversible and thermodynamically controlled.

In order to understand the stereochemical origin of the energy difference, we inspected the structures at the two transition states. Fig. S2 shows that the conformations of the two transition states mainly differ by the torsional angle between the centres C-5 and C-6. In the **P1** transition state, the hydrogens (marked in green in Fig. S2) are in anti position, and so are the carbon atoms C-7 and C-4, thus avoiding unfavorable interactions of the residues. In the alternative transition state leading to **P2**, the two highlighted hydrogens are in a nearly eclipsed conformation, leading to unfavorable interactions of the residues at C-4 and C-7 similar to the argument put forward by Boeckman et al.

In the next step, we investigated the transition states leading to the full compounds **11a** and **11a'**. Here, we optimized molecular structures at the PBE-D3/def2-SVP level (including determination of the second derivatives to verify the minimum or saddle point property of the stationary points and to determine the zero-point vibrational energy) and applied corrections by carrying out PBE0-D3/def2-TZVPP using the structures determined at the lower level of theory. Solvent effects were again included by the COSMO approach.

In Table S3 the results are summarized. Only one isomer regarding stereocentre C-1' has been considered. The transition structures are very similar to that of the model compound, but the

predicted difference in activation energy increases significantly to more than 30 kJ mol^{-1}. This is in line with the experimental observation of only a single diastereomer (except to the two possible configurations at C-1').

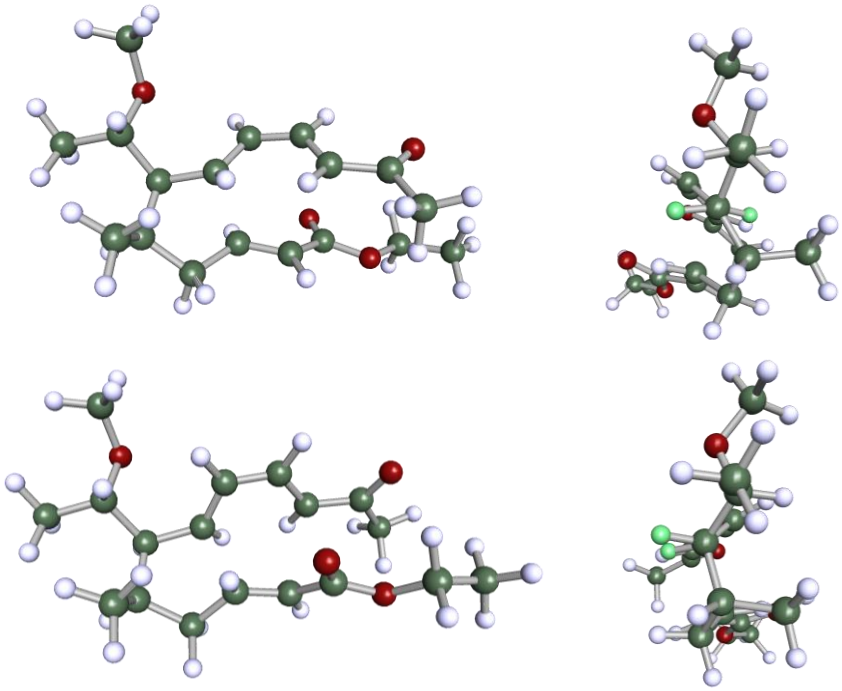


Fig. S2 Representations of the transition state structures leading to compound **P1** (upper row, front and side view) and to compound **P2** (lower row, front and side view). In the side view pictures, the hydrogens at atoms C-5 and C-6 have been marked in green to highlight the different conformation.

Table S3 Computed reaction energies (RE) and activation energies (AE, all energies in kJ mol^{-1}) for the reaction of **12** to **11a** or **11a'**. Only one isomer concerning the stereocentre C-1' has been considered.

	PBE+D3/def2-SVP	PBE0+D3/def2-TZVPP[a]	+ solvent effects[b]
RE(**11a**)	–107	–114	–110
RE(**11a'**)	–85	–87	–81
AE(**11a**)	36	66	68
AE(**11a'**)	64	99	104
ΔRE	22	27	29
ΔAE	28	33	36

[a] Based on PBE/def2-SVP structures and zero-point vibrational energies. [b] As previous column but with solvation energies included (COSMO, ε = 2.5).

9) Investigation of biological activities

Presumably the biosynthetic formation of secondary metabolites such as clifednamide is of advantage for the producing organisms. No biological activities have been reported from clifednamides so far, but since other polycyclic tetramate macrolactams were shown to be active against eukaryotes, we suppose that also clifednamides are biologically active. Since the biosynthesis of such a complex structure has evolved during evolution we also assume that simpler precursors at least may have a slight advantage for the producer. With the different precursors and bicyclic ester **11a** in hand we started a study on their biological acitivity. The inhibition of proliferation of L-929 mouse fibroblasts and the human KB-3-1 cervix carcinoma cell line was investigated in a standard MTT assay.[41] The results in Table S4 show that the possible biosynthetic precursors of the clifednamides indeed have antiproliferative activities in micromolar range with triene **12a** showing the highest potency (IC_{50} = 6 μM) against L-929 mouse fibroblasts (entry 6). Overall, the cytotoxicity increased from the more distant precursor **28** in the order **14a**, **13a** to triene **12a**. The inhibitory activity of the AB-ring system **11a** against L-929 mouse fibroblasts is poorer than that of triene **12a** (IC_{50} = 17 μM and 6 μM, resp.) while the cytotoxicity of **11a** and **12a** against the KB-3-1 cell line is in a similar range (IC_{50} = 9 μM and 11 μM, resp.).

Table S4 Cytotoxicities (IC_{50}) of clifednamide precursors against mouse fibroblast (L-929) and human cervix carcinoma (KB-3-1) cell lines[a]

Entry	Compounds	L-929 (μM)	KB-3-1 (μM)
1	**28**	25 ± 0	28 ± 2
2	**14a**	22 ± 5	24 ± 8
3	**32**[b]	26 ± 3	13 ± 0
4	**32**[c]	45 ± 7	18 ± 1
5	**13a**	16 ± 3	9 ± 2
6	**12a**	6 ± 1	11 ± 1
7	**11a**	17 ± 1	9 ± 3
8	**S7**	29 ± 4	24 ± 9

[a] IC_{50} values are calculated as mean ± S.D. of two assays in parallel. [b,c] Two diastereomers of alcohol **32** which could be separated but not assigned unambiguously.

Cytotoxicity assay. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used to measure growth and viability of cells which are capable of reducing it to a violet formazan product. 60 µL of serial dilutions of the test compounds were added to 120 µL aliquots

of a cell suspension (50 000 mL^{-1}) in 96-well microplates. Blank and solvent controls were incubated under identical conditions for 5 d. MTT in phosphate buffered saline (PBS) (20 µL) was added to a final concentration of 0.5 mg mL^{-1}. After 2 h, the precipitate of formazan crystals was centrifuged, and the supernatant discarded. The precipitate was washed with PBS (100 µL) and dissolved in isopropanol containing 0.4% hydrochloric acid (100 µL). The microplates were gently shaken for 20 min to ensure a complete dissolution of the formazan and finally measured at 595 nm using an ELISA plate reader. All experiments were carried out in two parallel experiments. Activity values were calculated as the mean with respect to the controls set to 100%.
Cell lines were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ) or American Type Culture Collection (ATCC) and cultivated in the media recommended by the supplier at 37 °C and 10% CO_2.

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10) Spectra

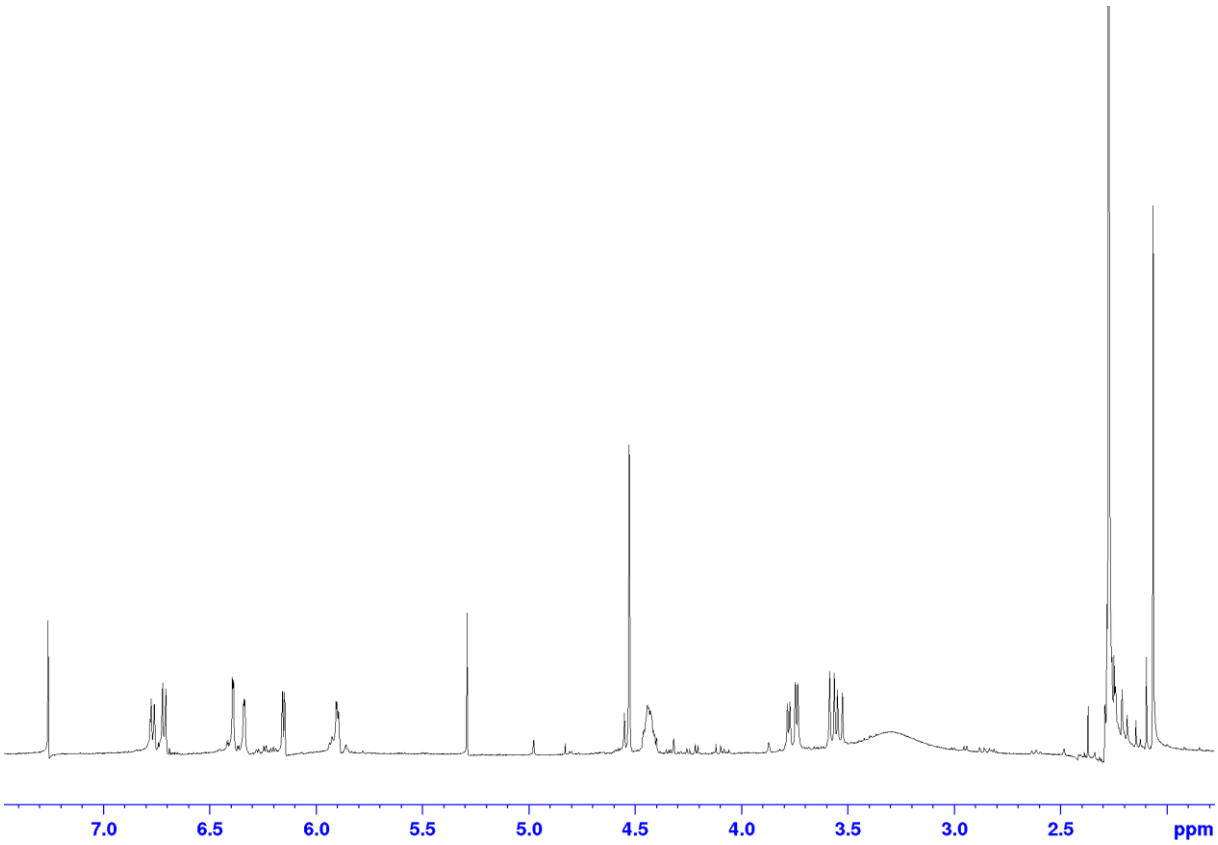


Fig. S3a ^{1}H NMR spectrum of **18**

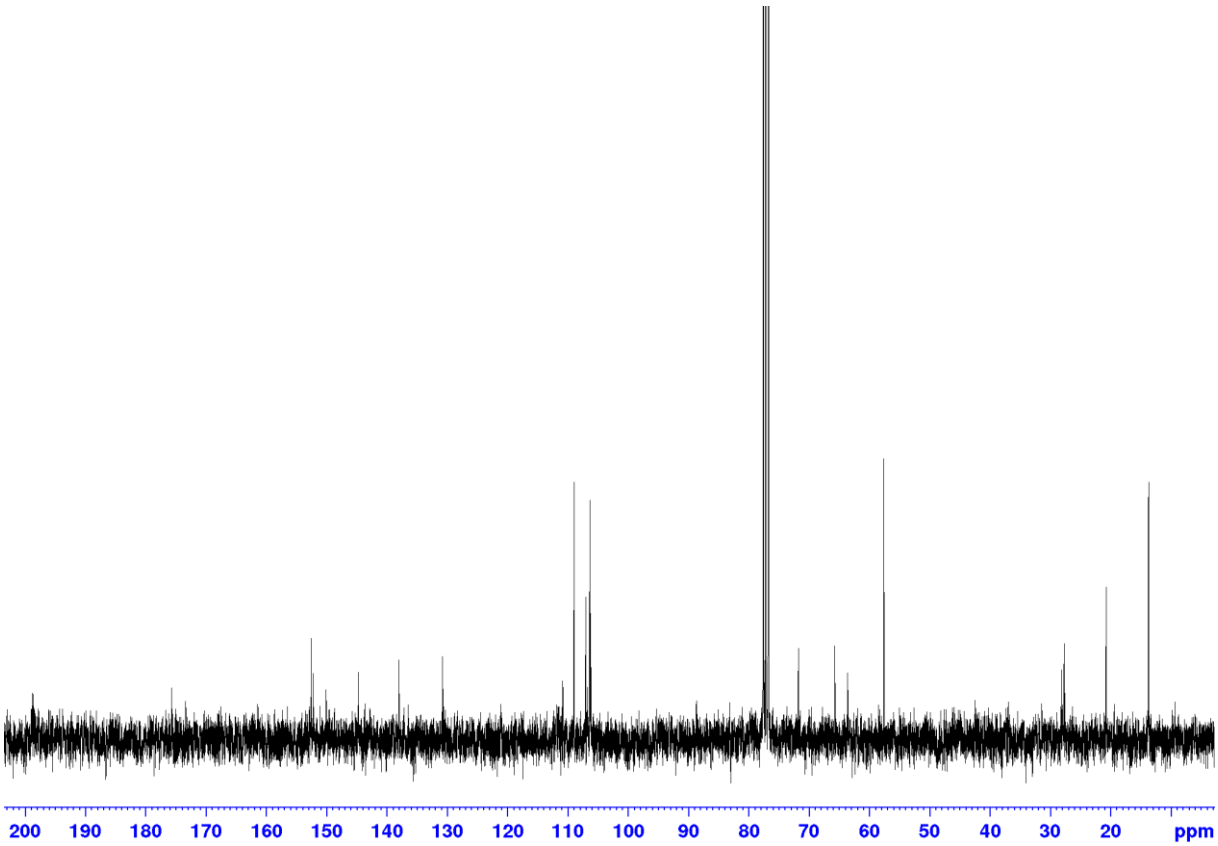


Fig. S3b ^{13}C NMR spectrum of **18**

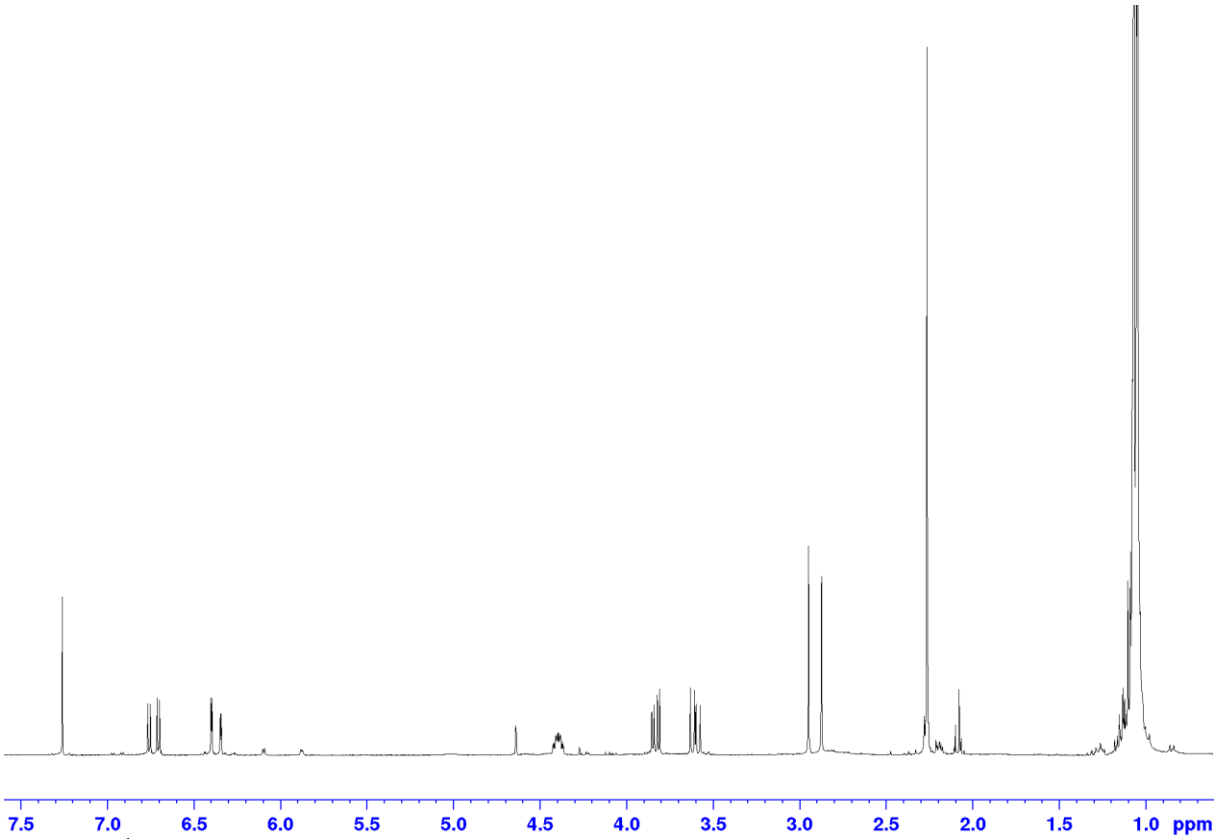


Fig. S4a ^{1}H NMR spectrum of **19a**

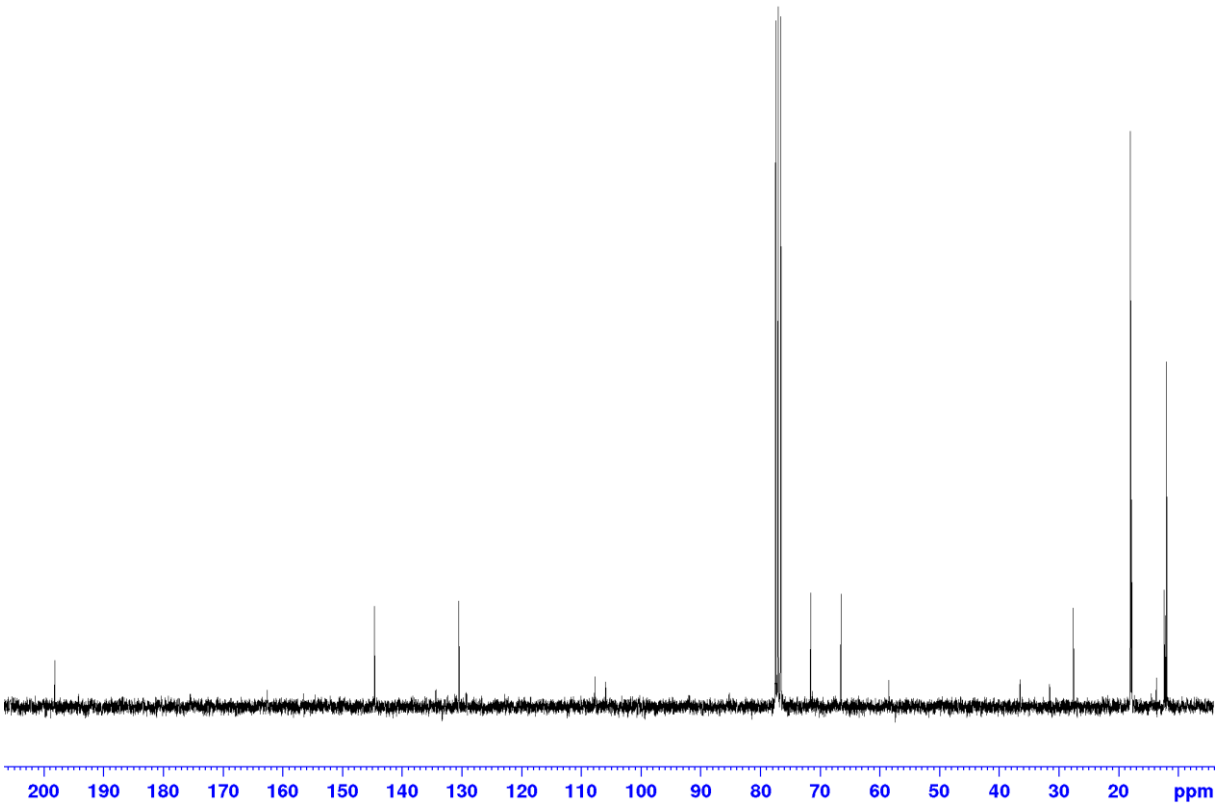


Fig. S4b ^{13}C NMR spectrum of **19a**

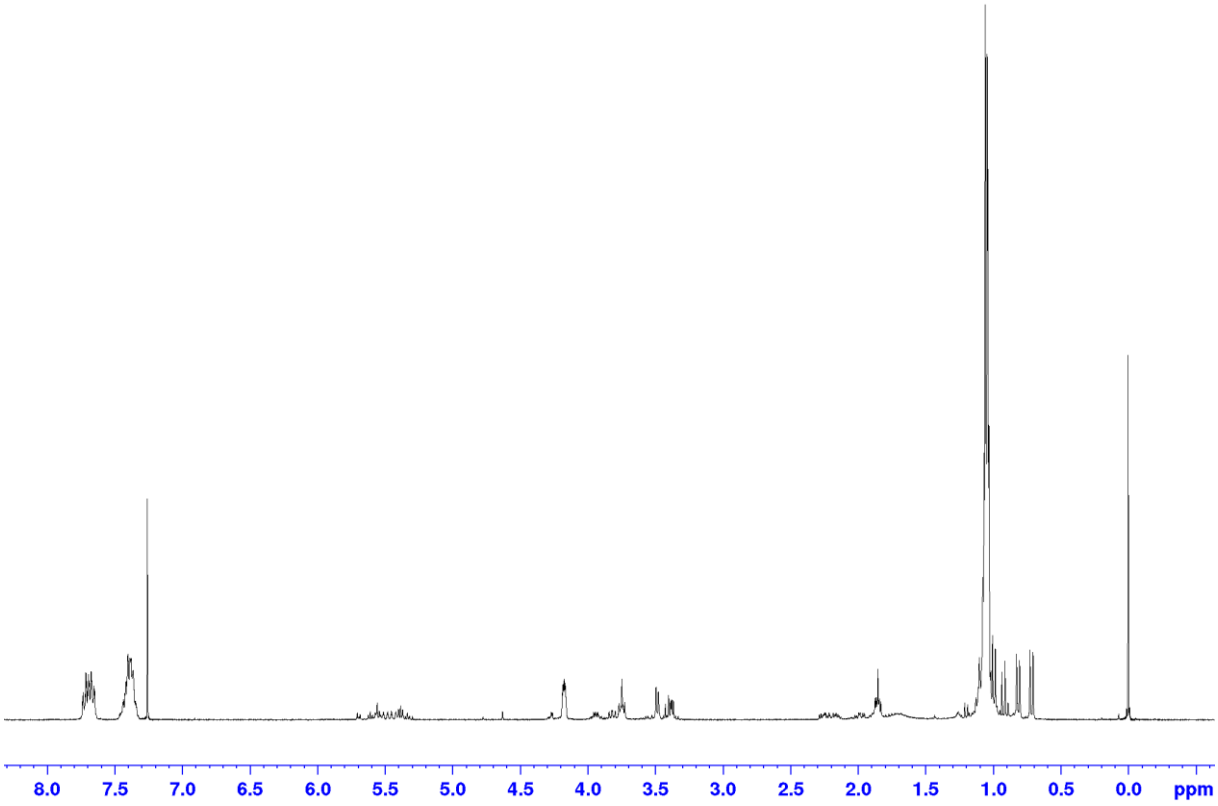


Fig. S5a ^{1}H NMR spectrum of **27**

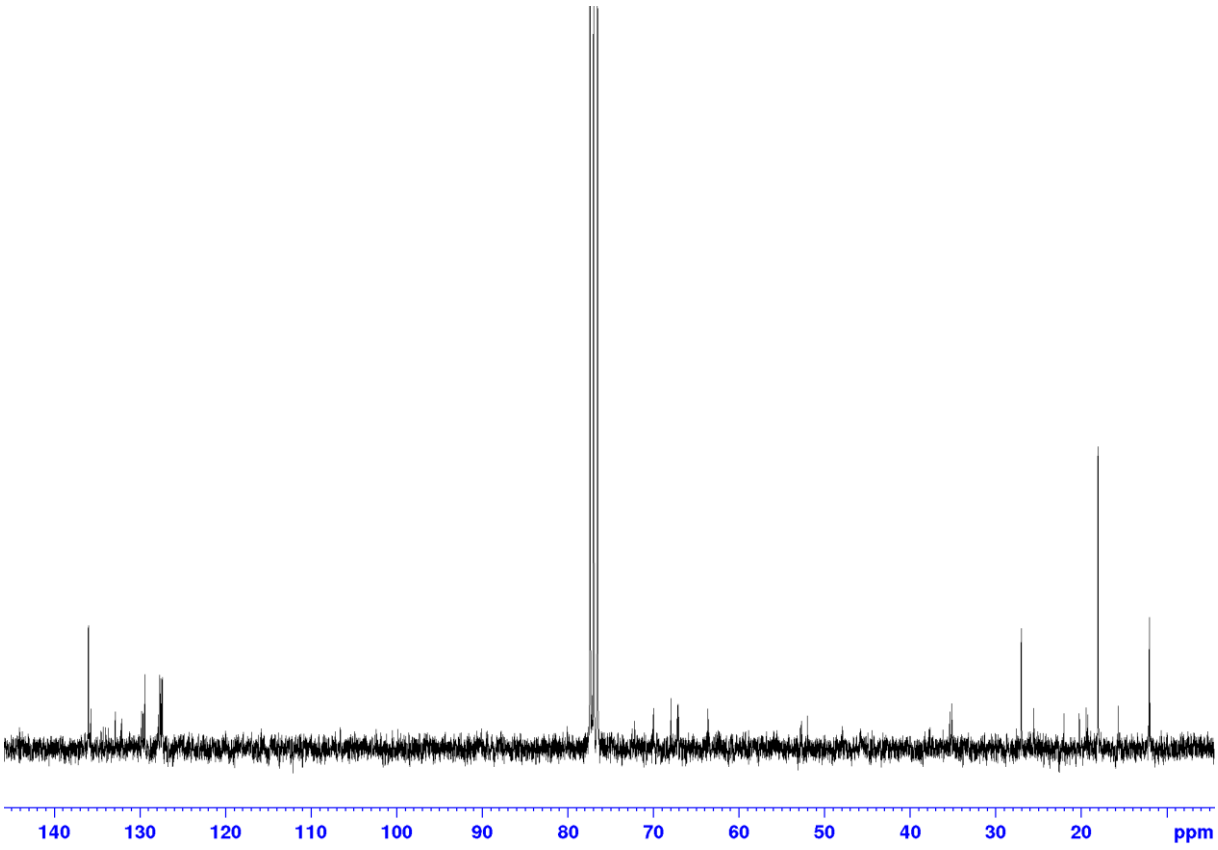


Fig. S5b ^{13}C NMR spectrum of **27**

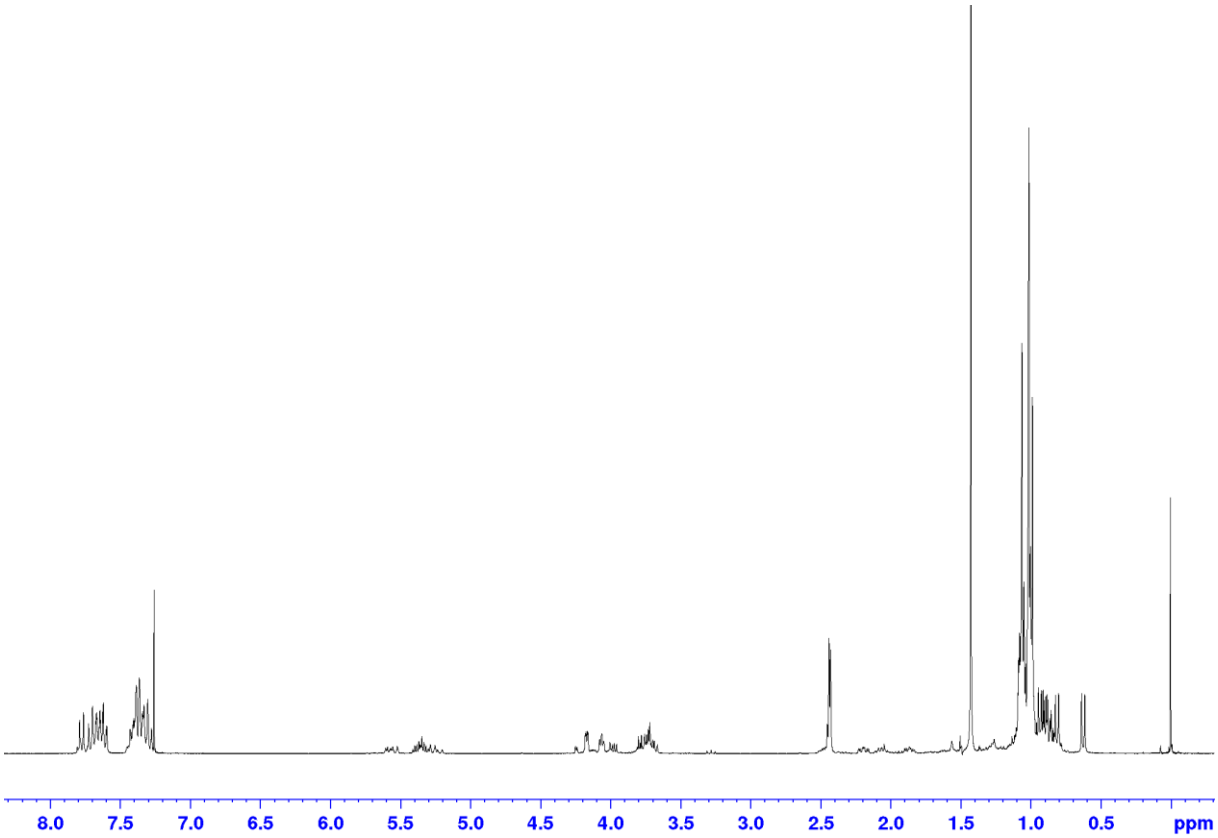


Fig. S6a ^{1}H NMR spectrum of **28**

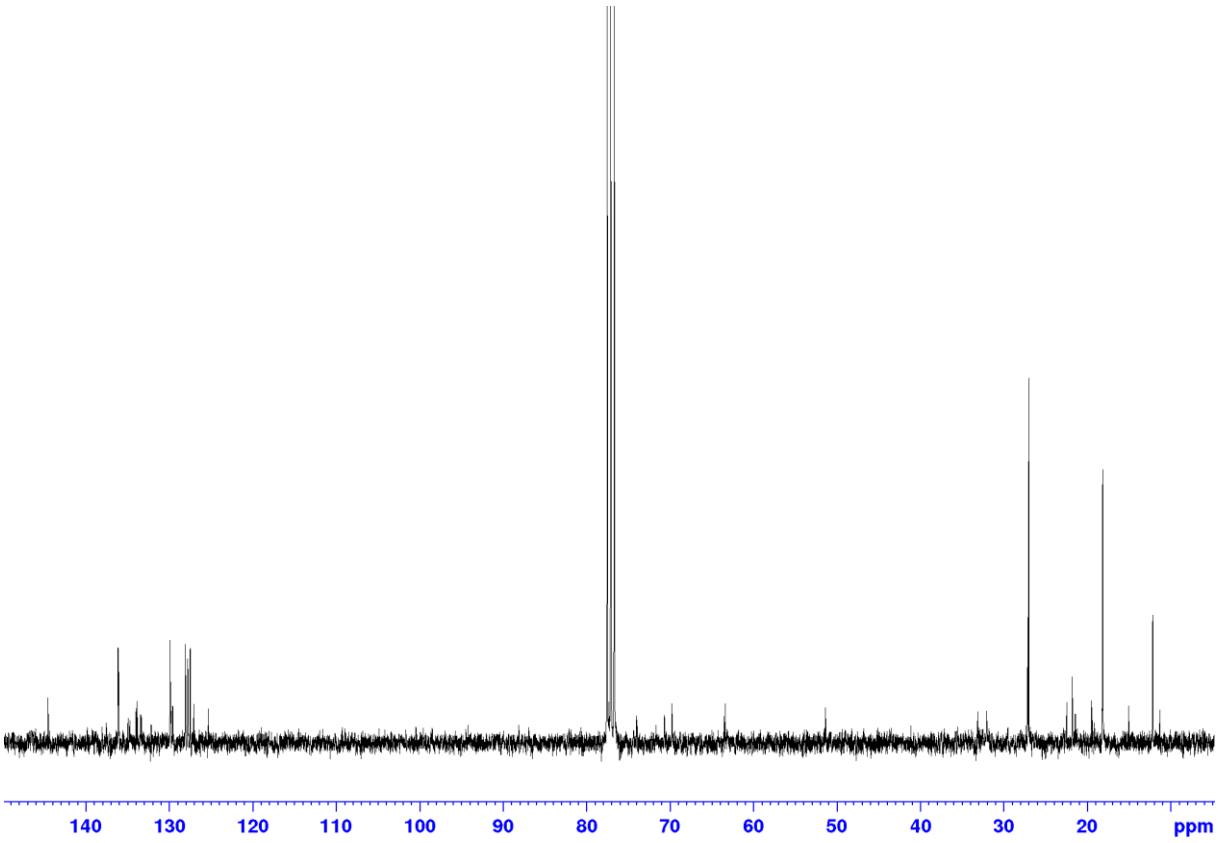


Fig. S6b ^{13}C NMR spectrum of **28**

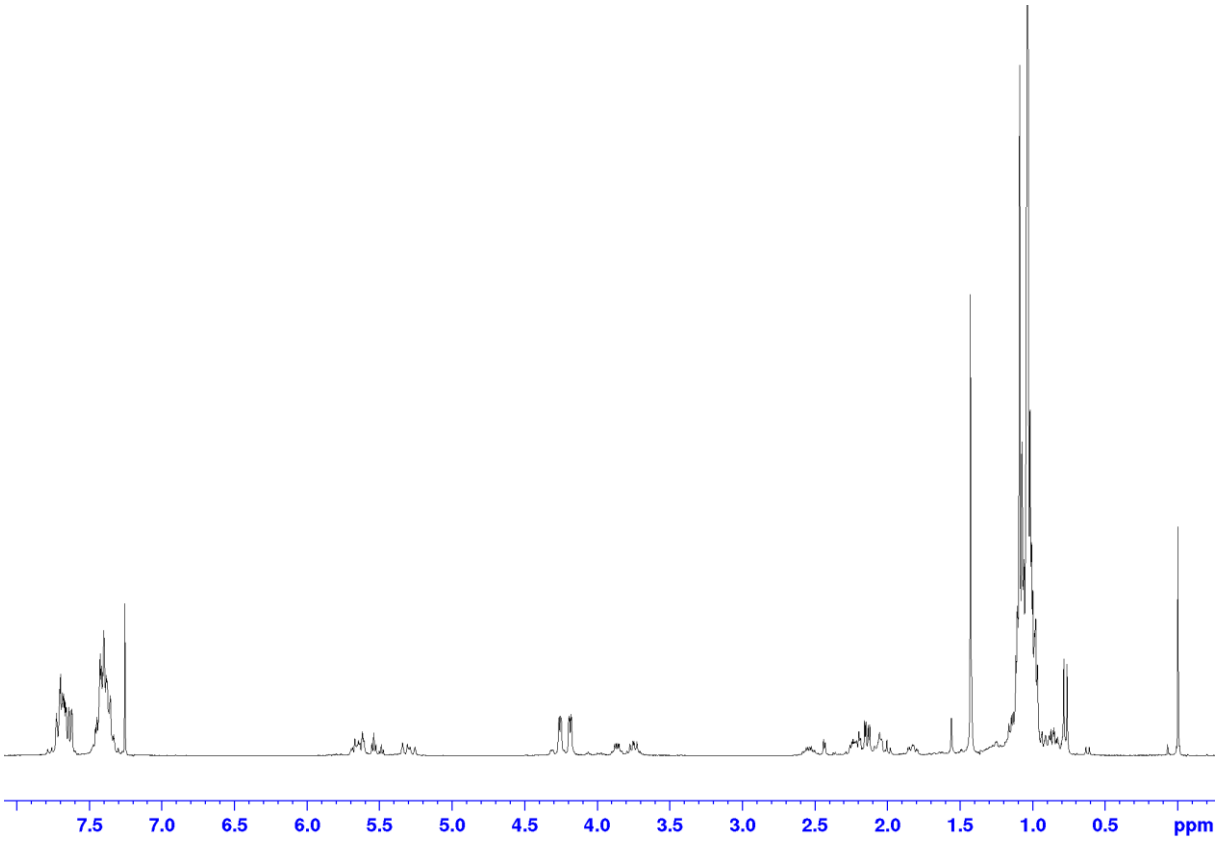


Fig. S7a ^{1}H NMR spectrum of **29**

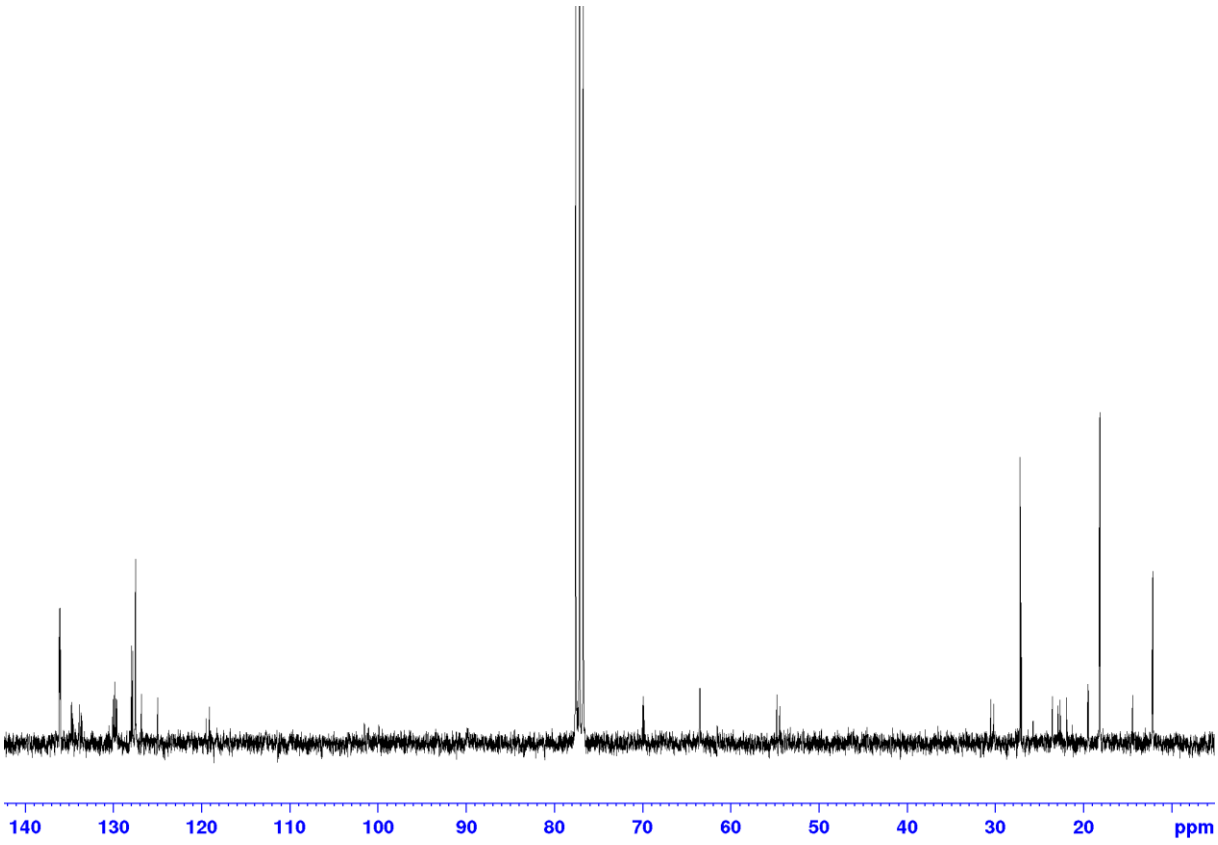


Fig. S7b ^{13}C NMR spectrum of **29**

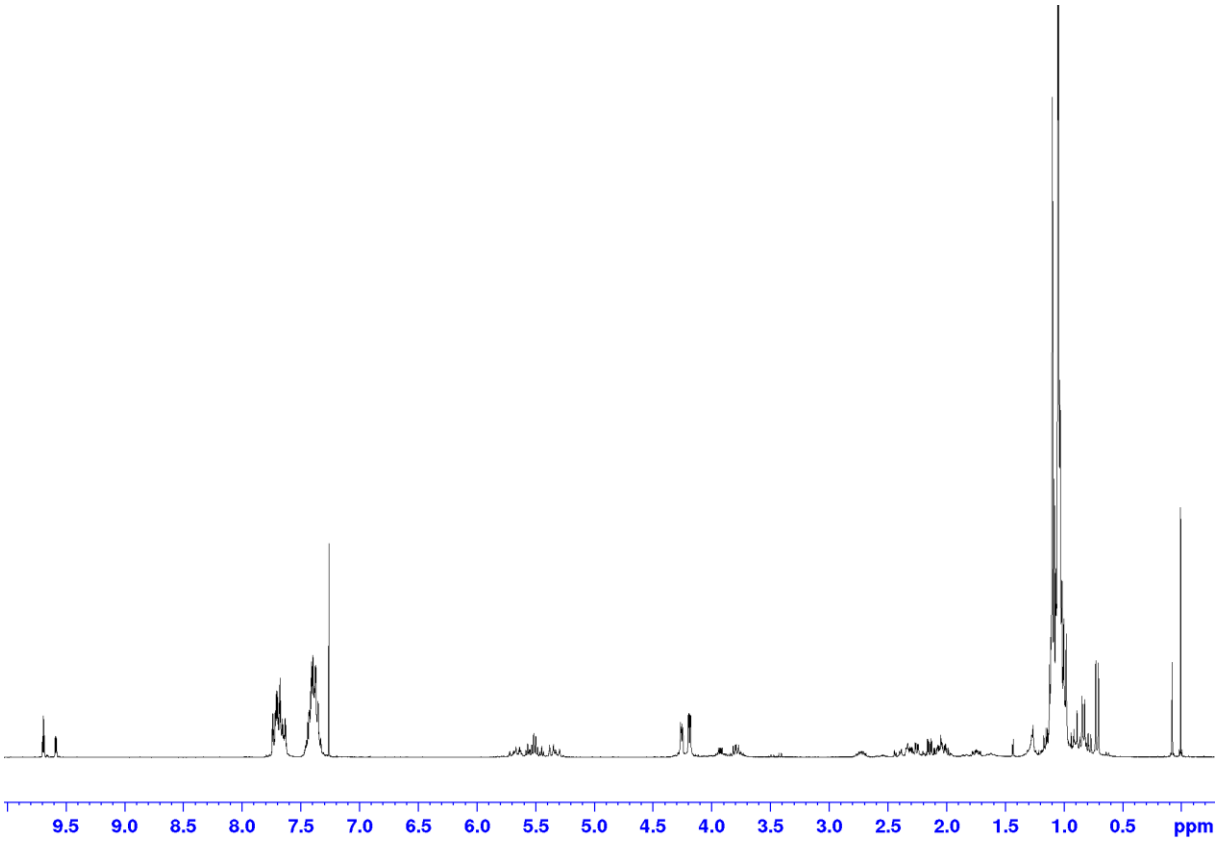


Fig. S8a ^{1}H NMR spectrum of **30**

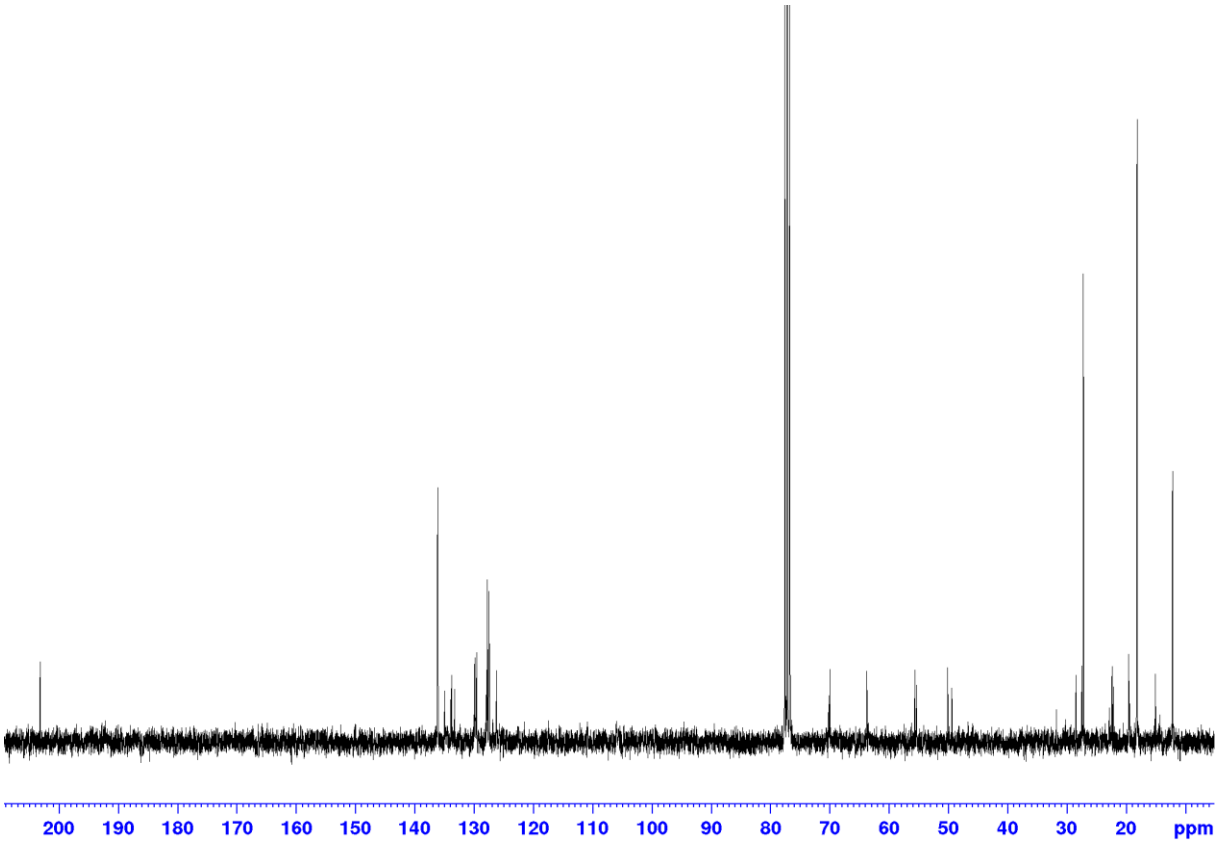


Fig. S8b ^{13}C NMR spectrum of **30**

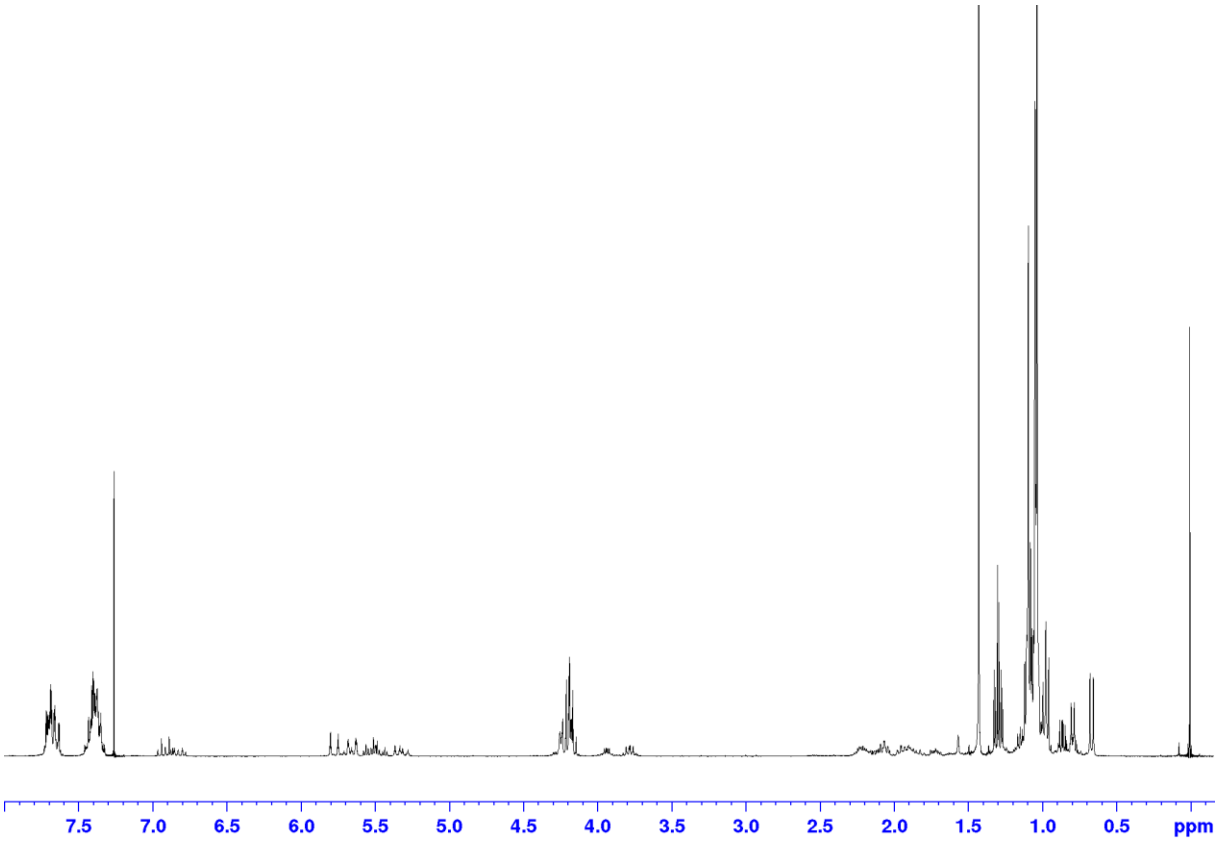


Fig. S9a ^{1}H NMR spectrum of **14a**

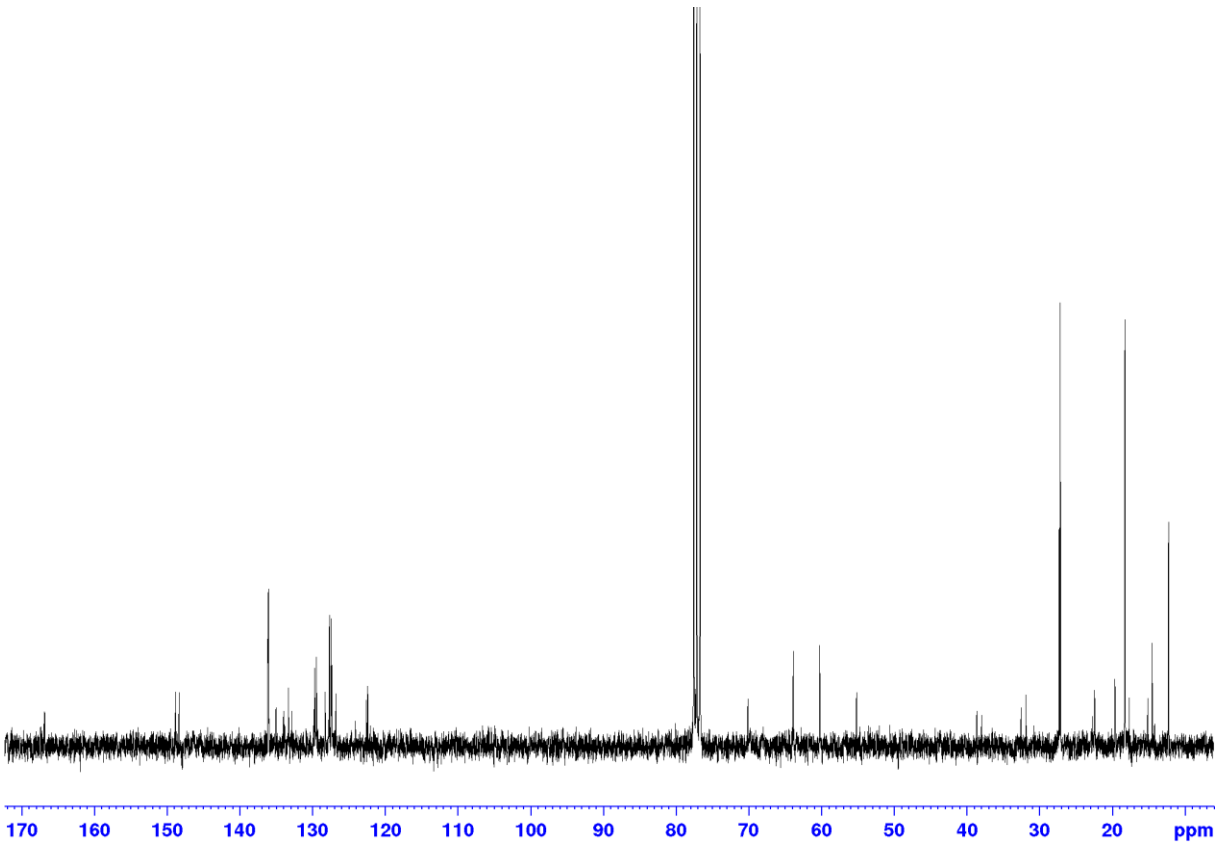


Fig. S9b ^{13}C NMR spectrum of **14a**

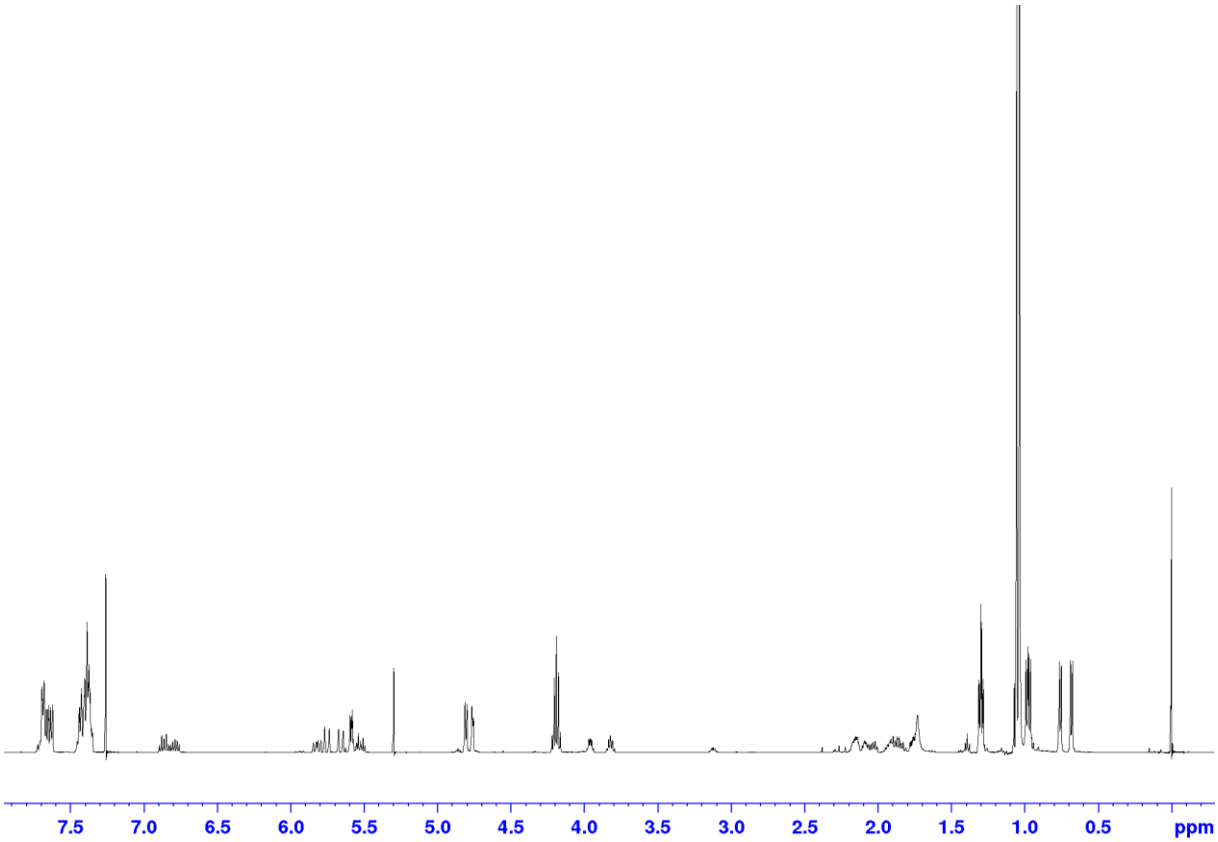


Fig. S10a ^{1}H NMR spectrum of **32**

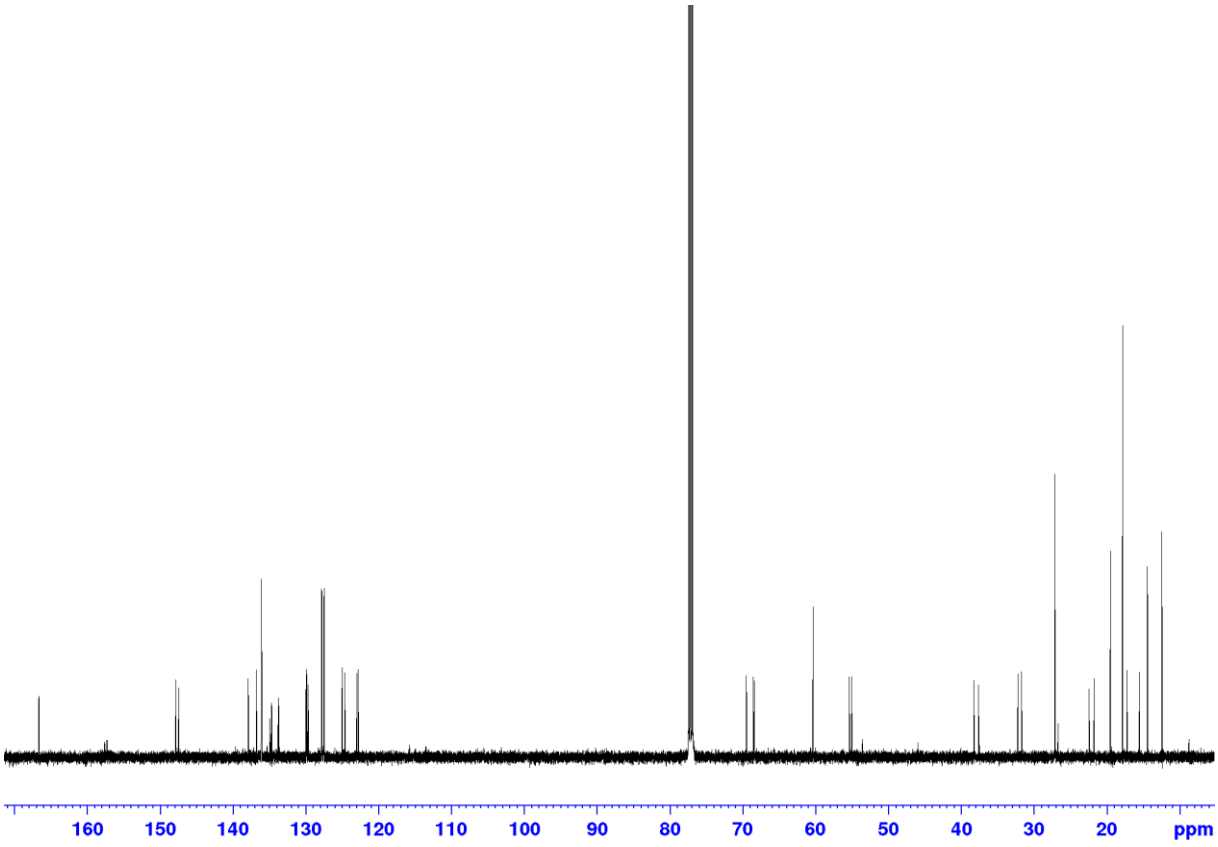


Fig. S10b ^{13}C NMR spectrum of **32**

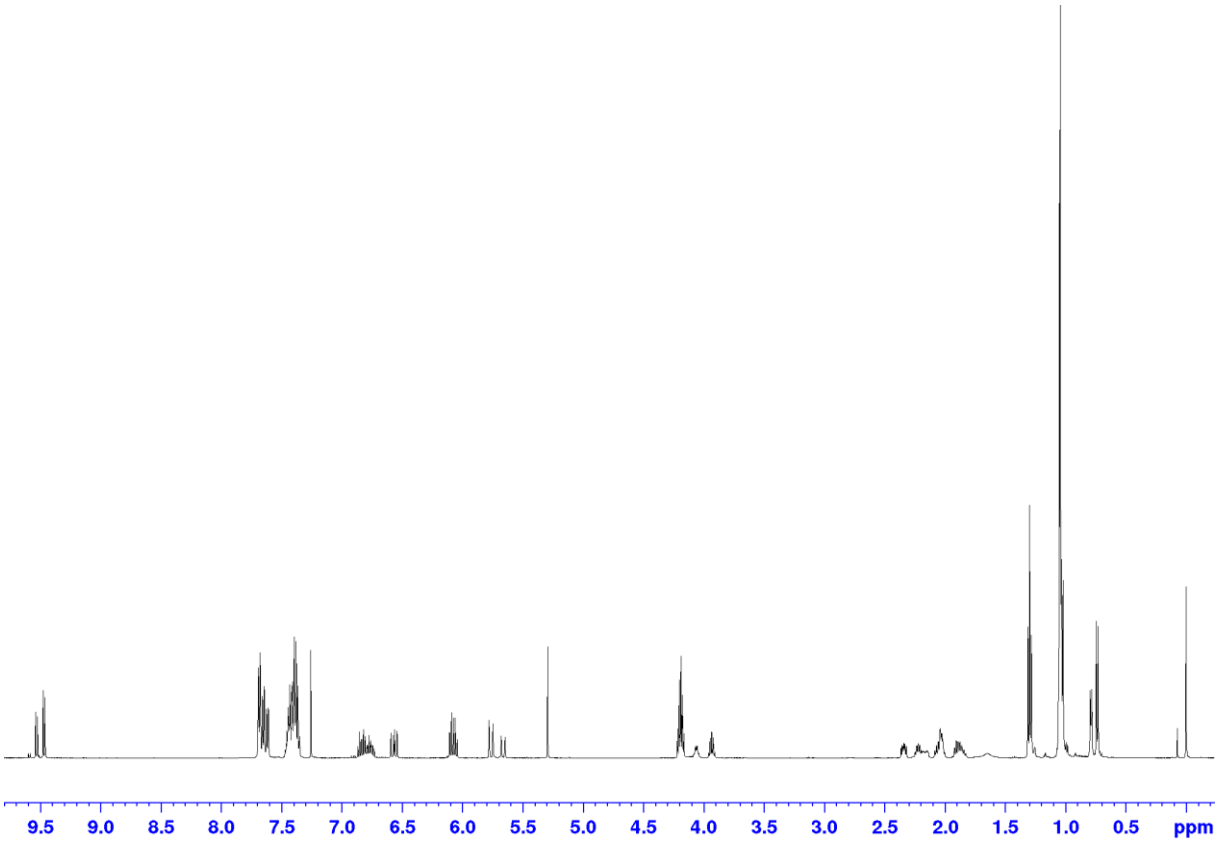


Fig. S11a ^{1}H NMR spectrum of **13a**

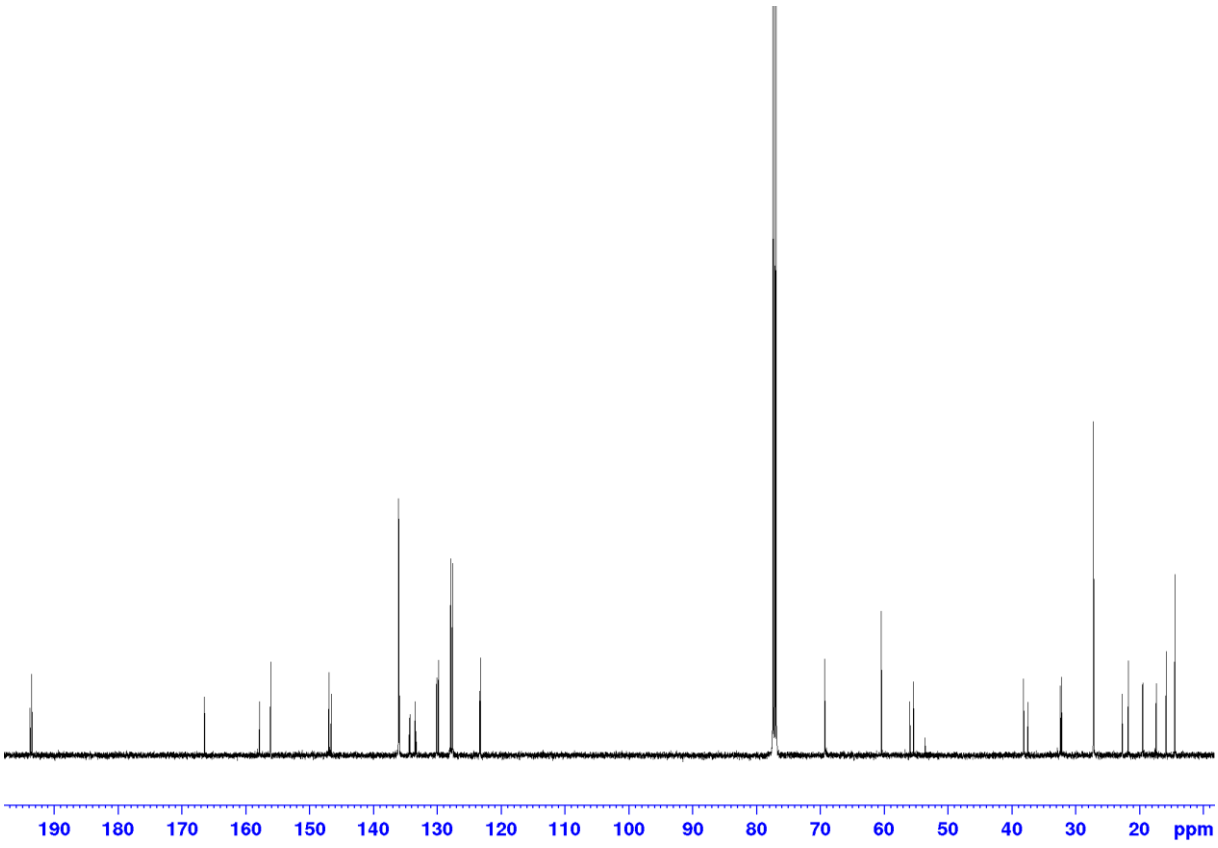


Fig. S11b ^{13}C NMR spectrum of **13a**

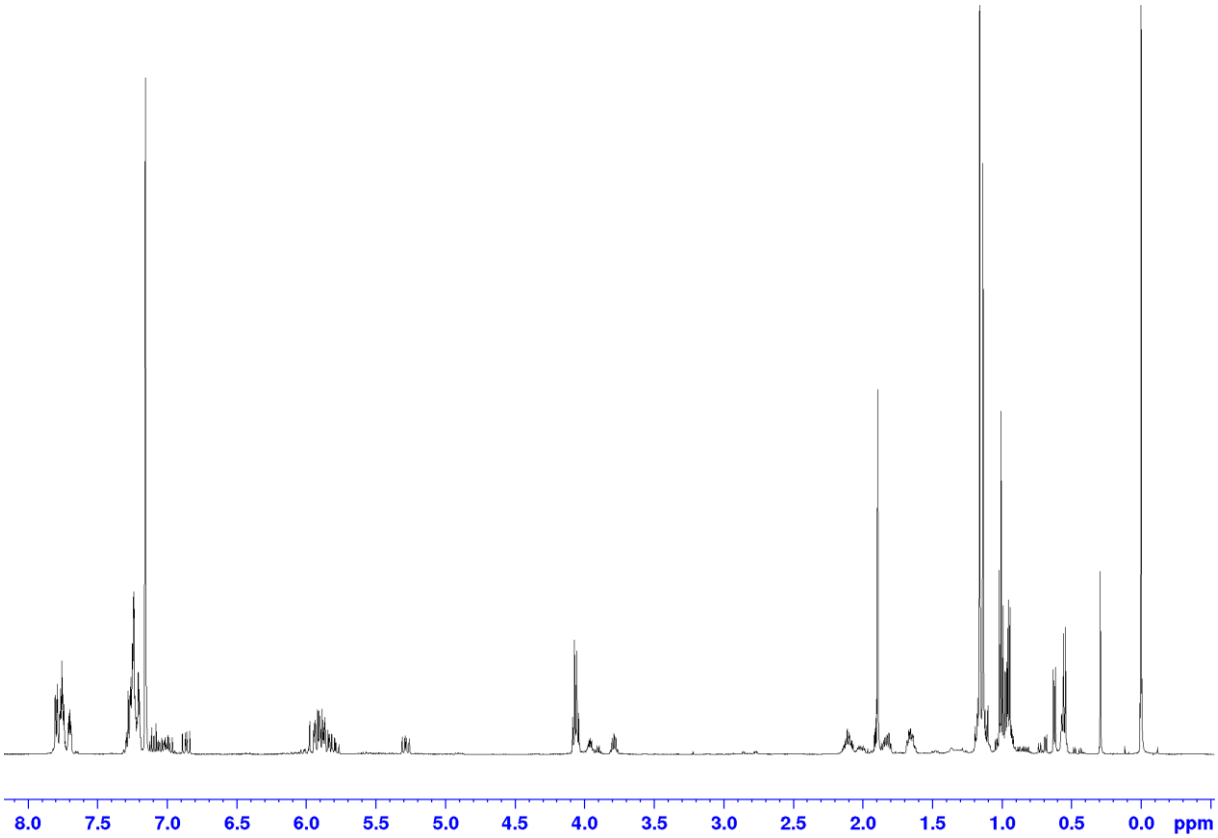


Fig. S12a ^{1}H NMR spectrum of **12a** in C_6D_6

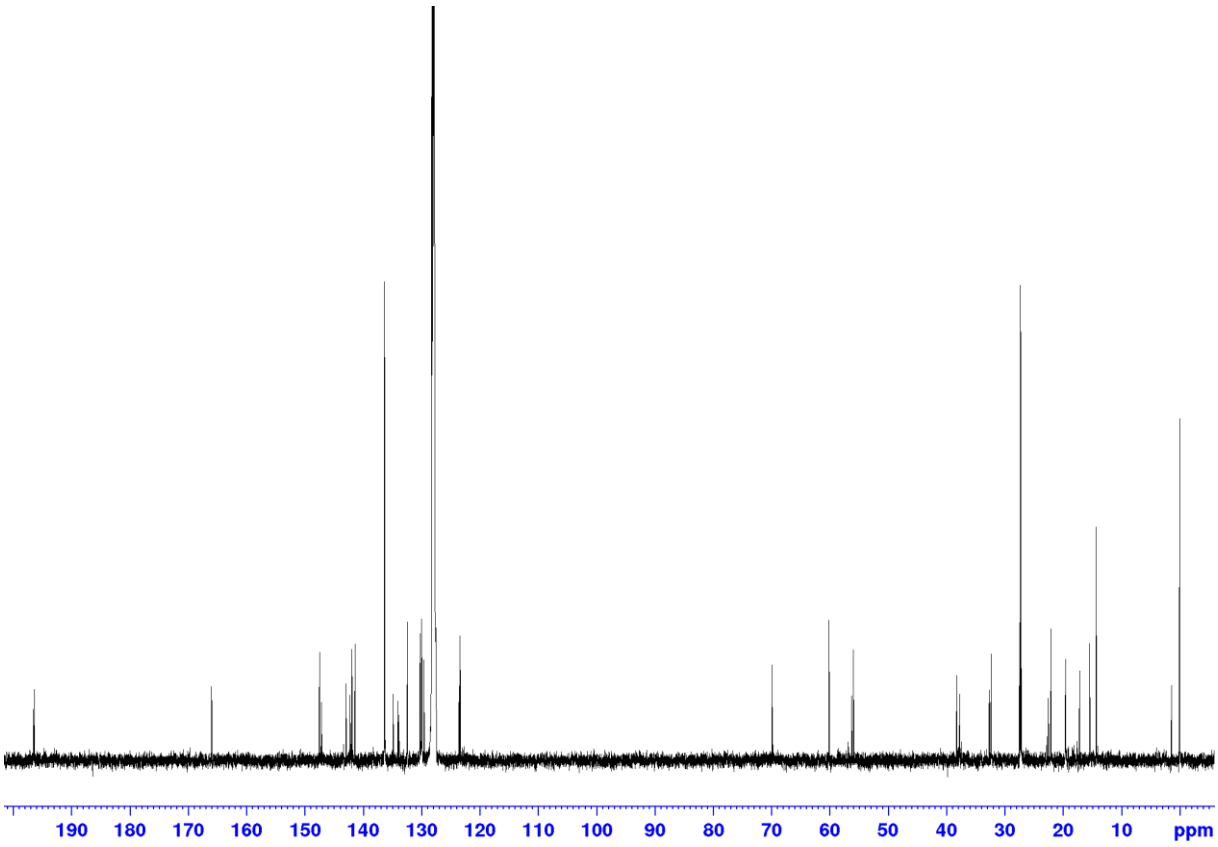


Fig. S12b ^{13}C NMR spectrum of **12a** in C_6D_6

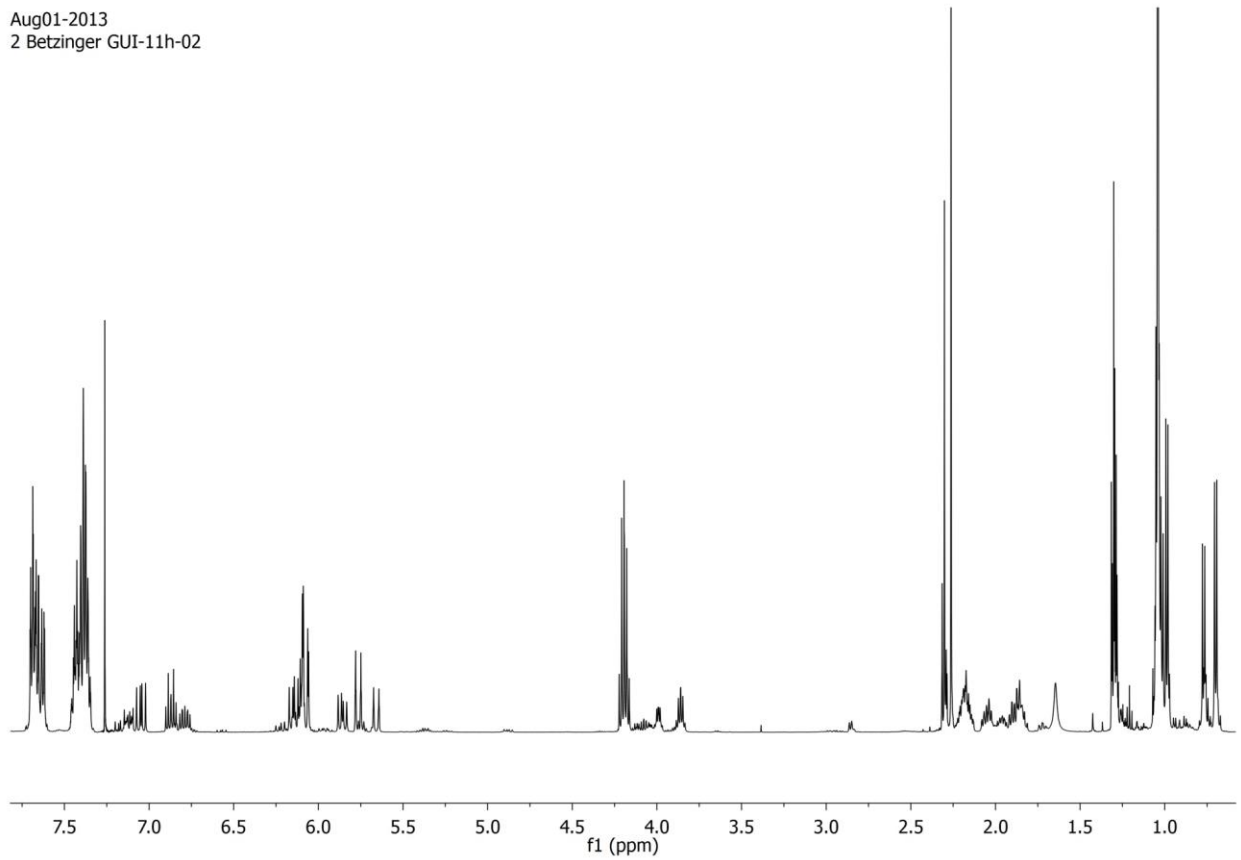


Fig. S12c ^{1}H NMR spectrum of **12a** in $CDCl_3$

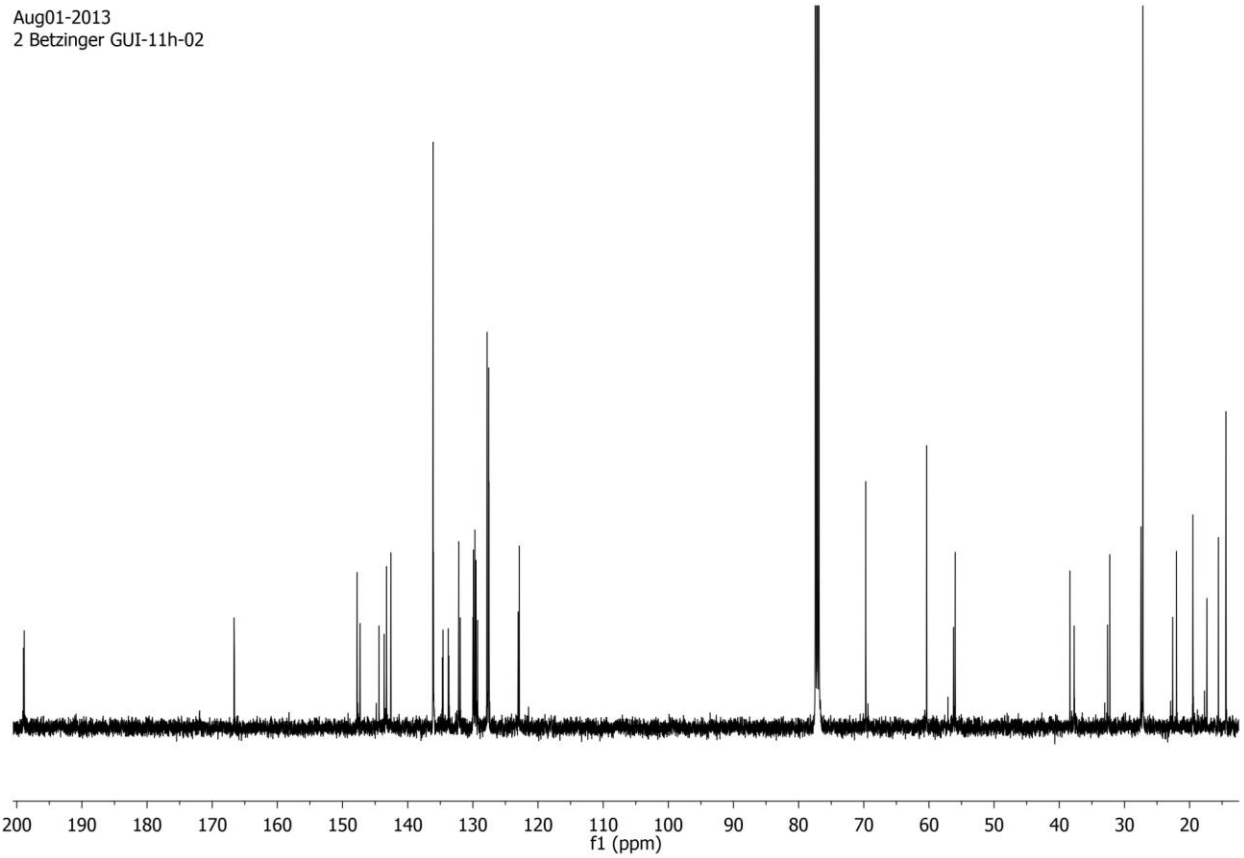


Fig. S12d ^{13}C NMR spectrum of **12a** in $CDCl_3$

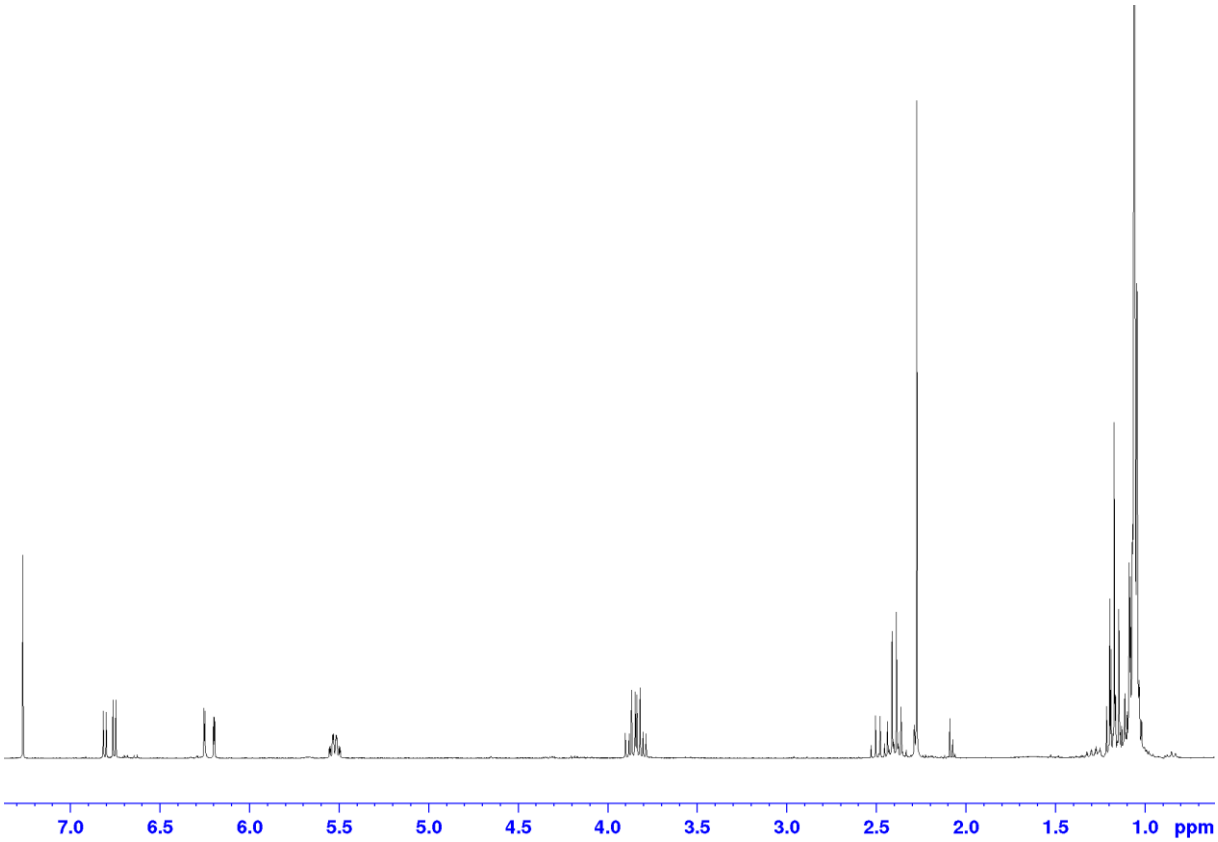


Fig. S13a ^{1}H NMR spectrum of **20a**

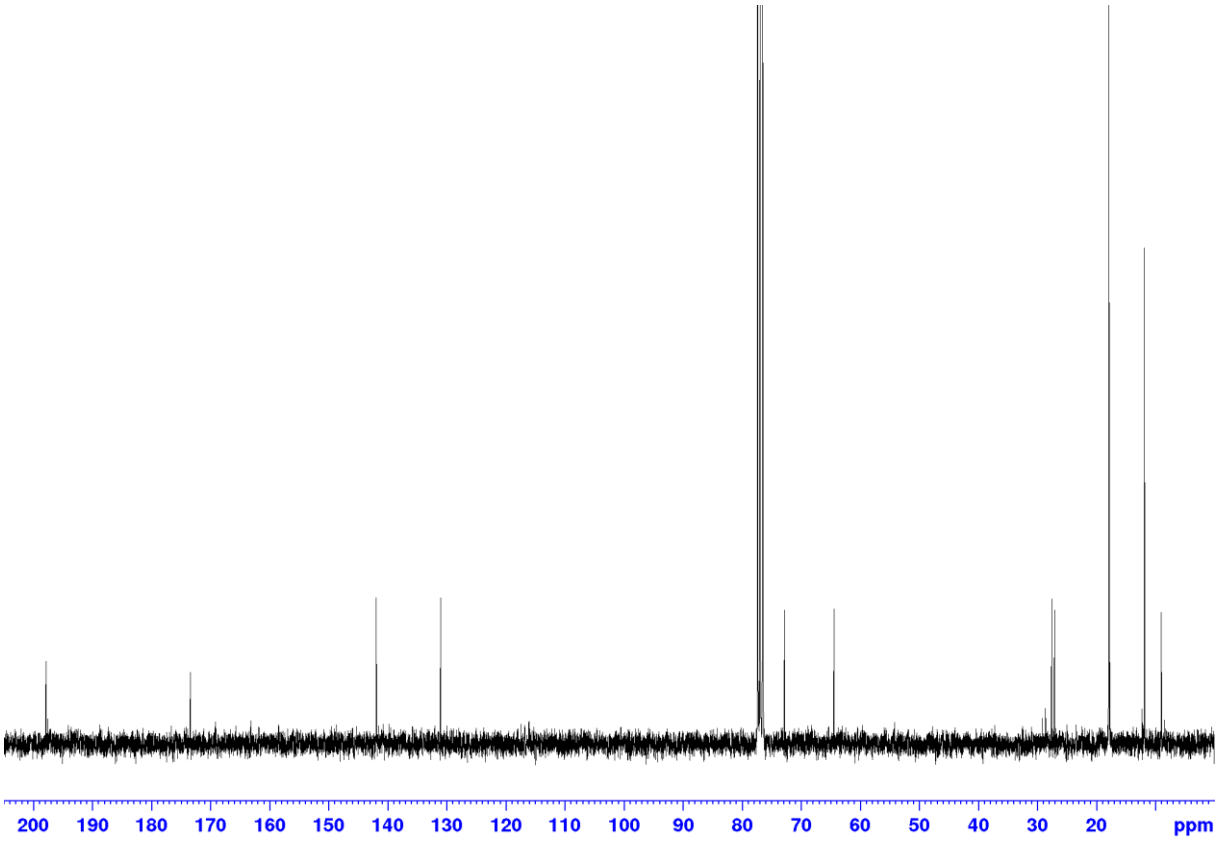


Fig. S13b ^{13}C NMR spectrum of **20a**

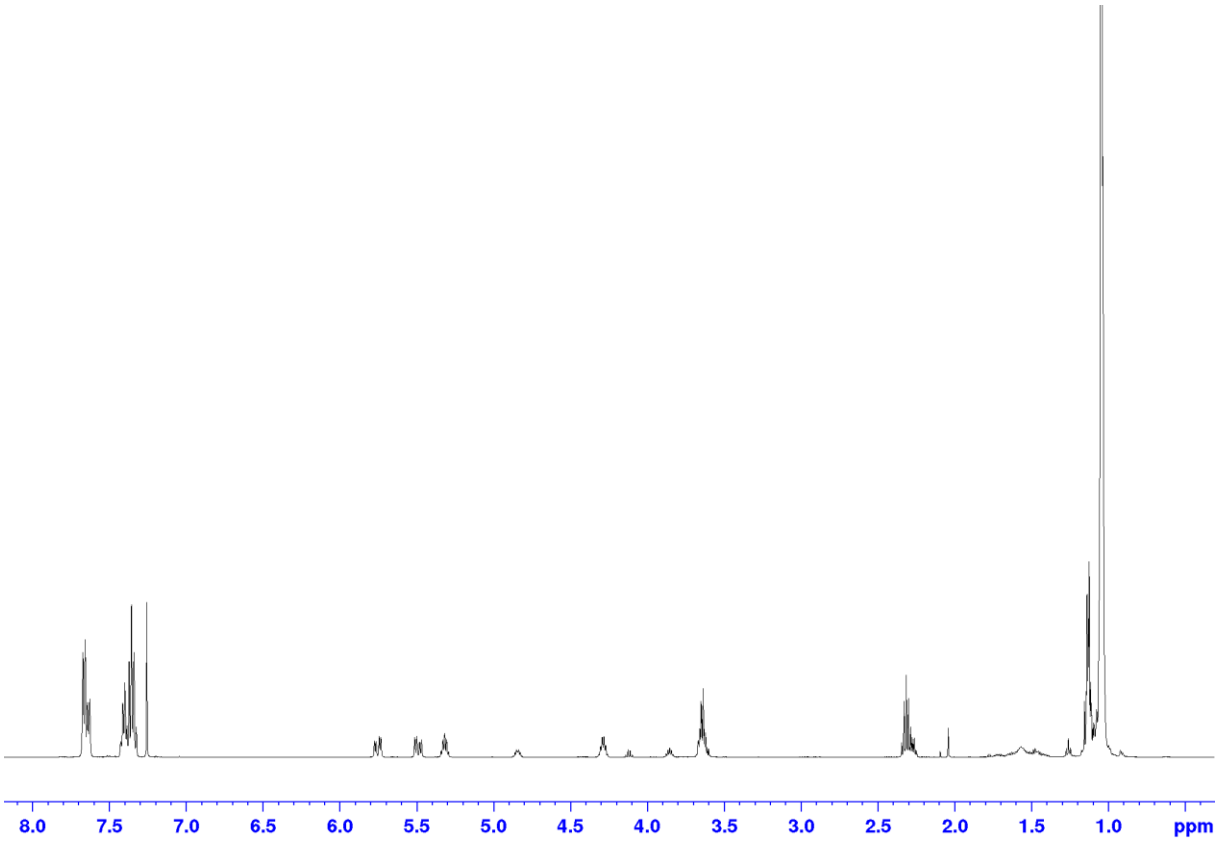


Fig. S14a ^{1}H NMR spectrum of **15a**

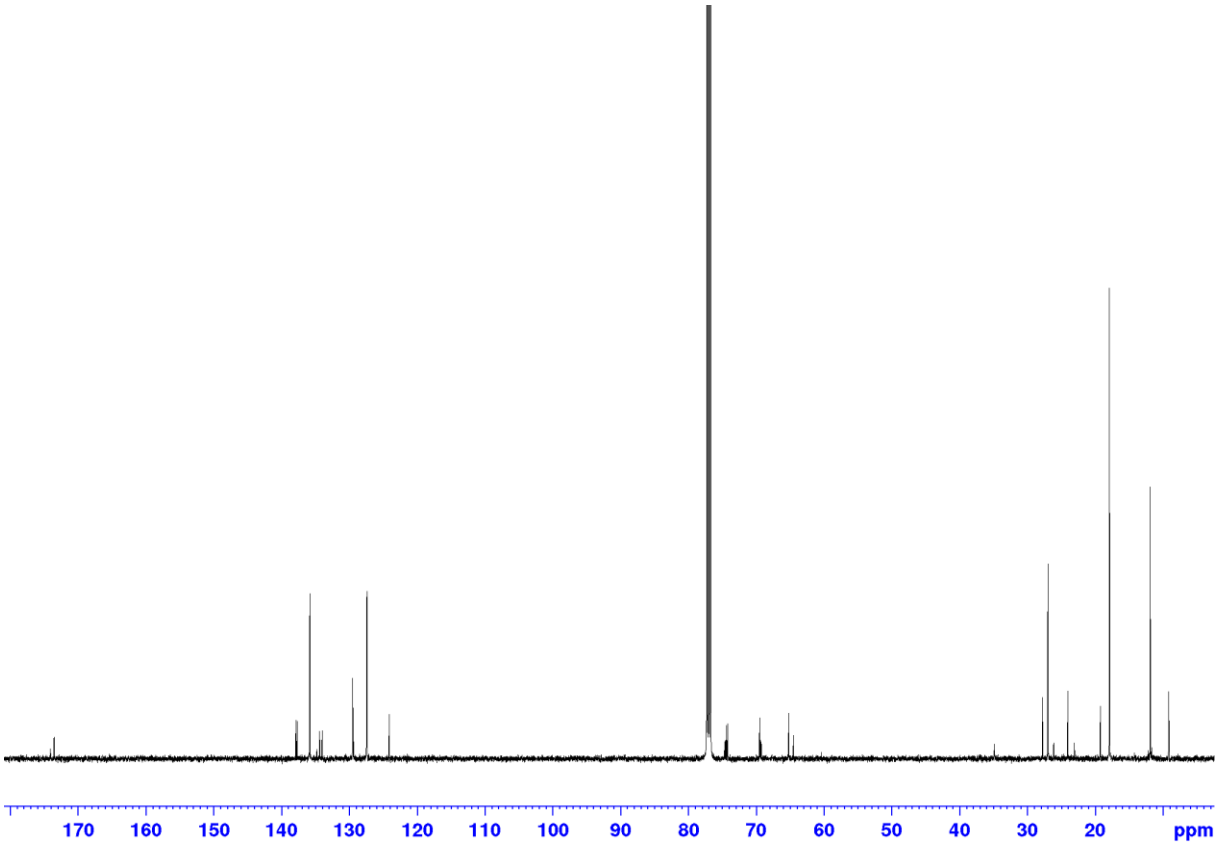


Fig. S14b ^{13}C NMR spectrum of **15a**

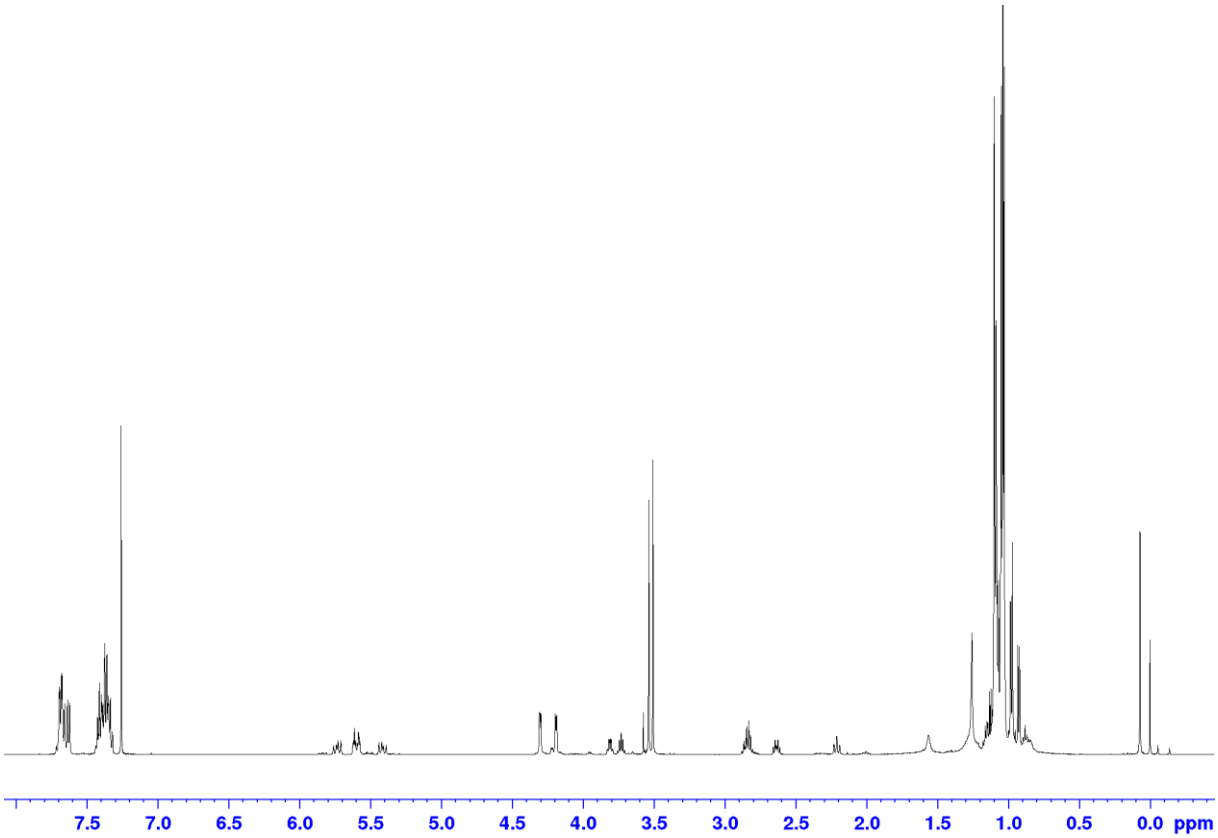


Fig. S15a ^{1}H NMR spectrum of **26**

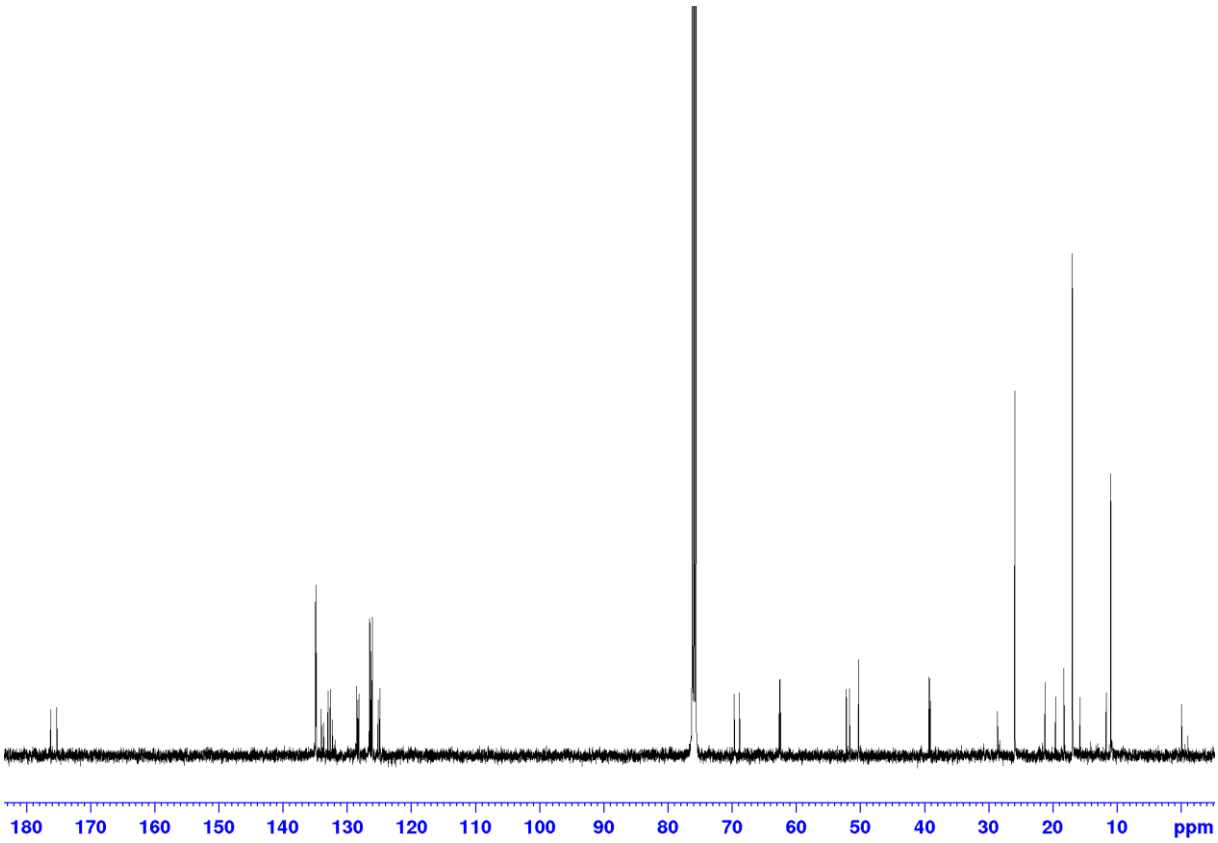


Fig. S15b ^{13}C NMR spectrum of **26**

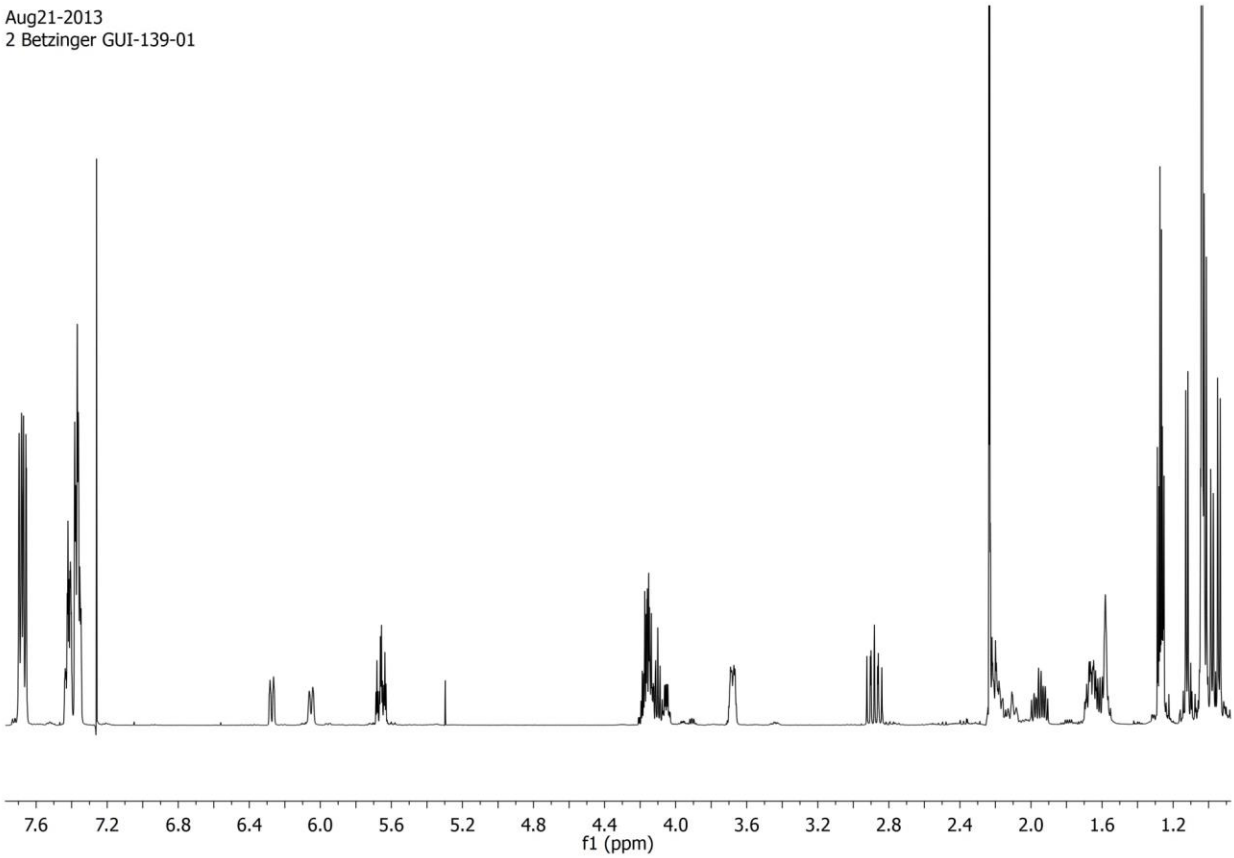


Fig. S16a ^{1}H NMR spectrum of **11a**

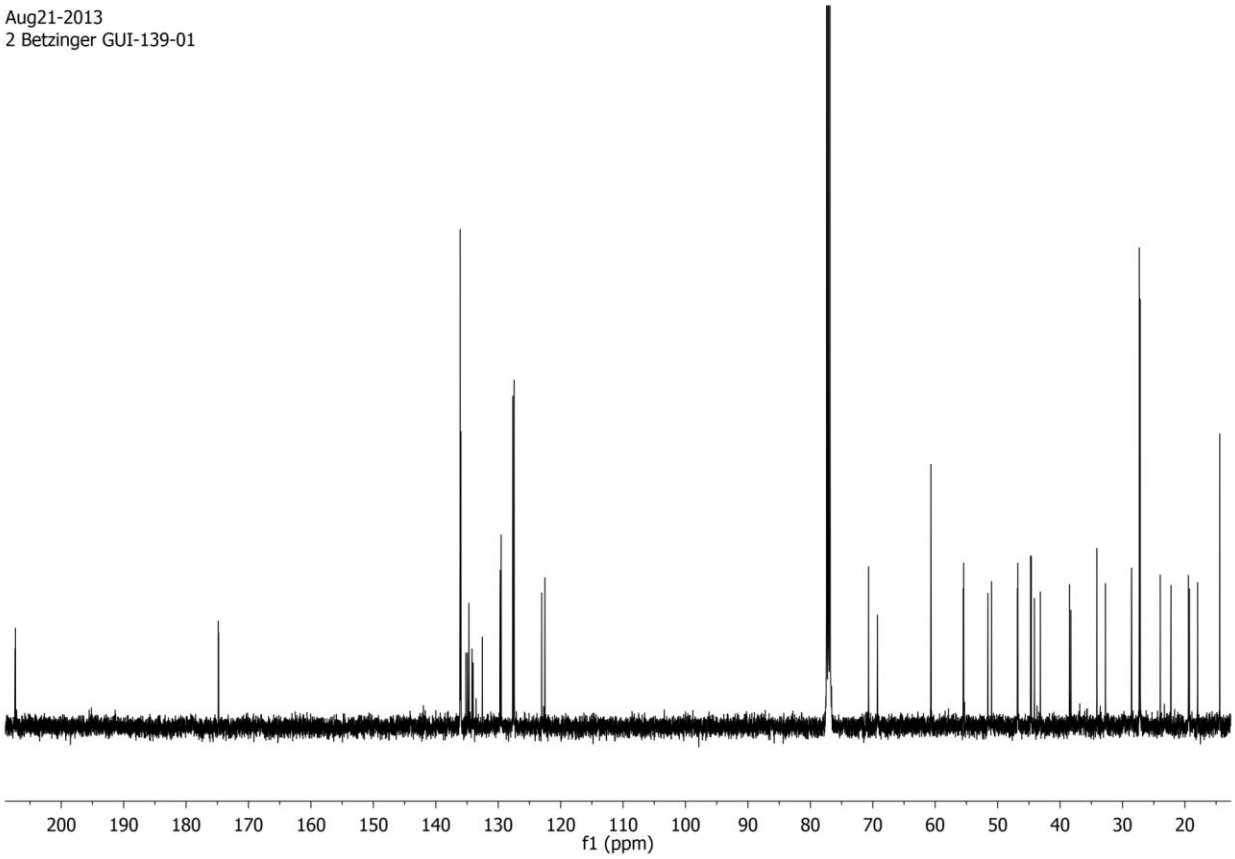


Fig. S16b ^{13}C NMR spectrum of **11a**

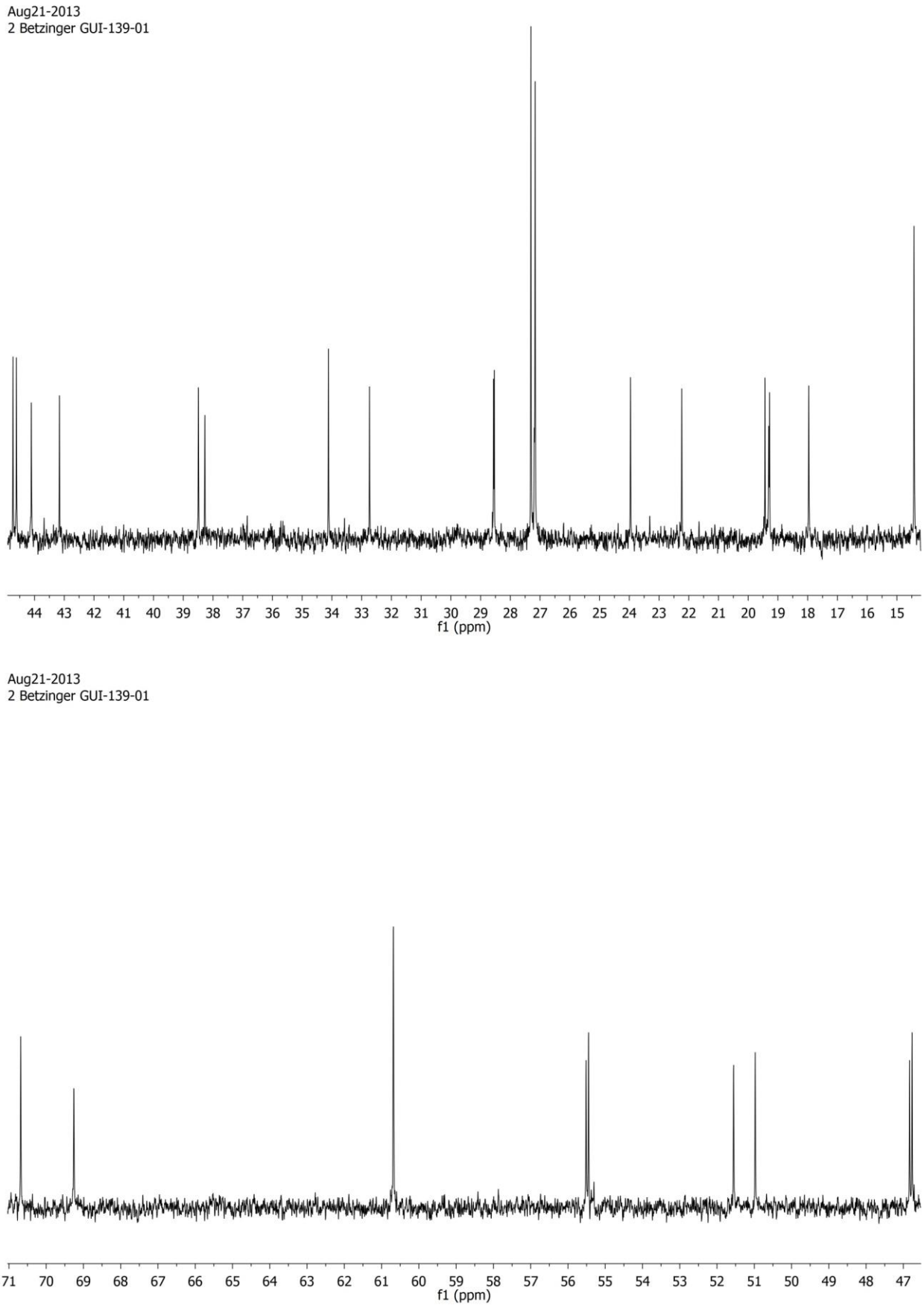
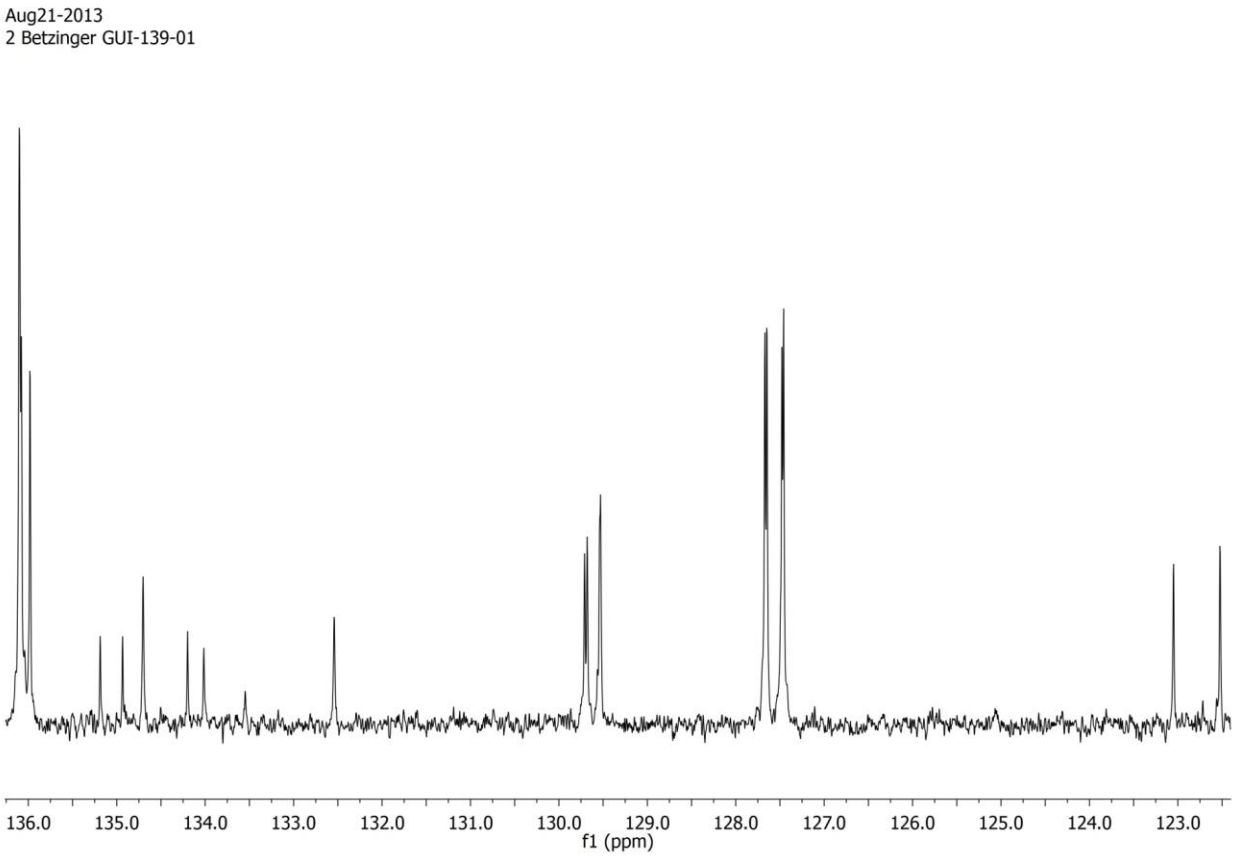


Fig. S16c ^{13}C NMR spectrum of **11a** (stretched regions between 14.5–45 and 47–71 ppm)



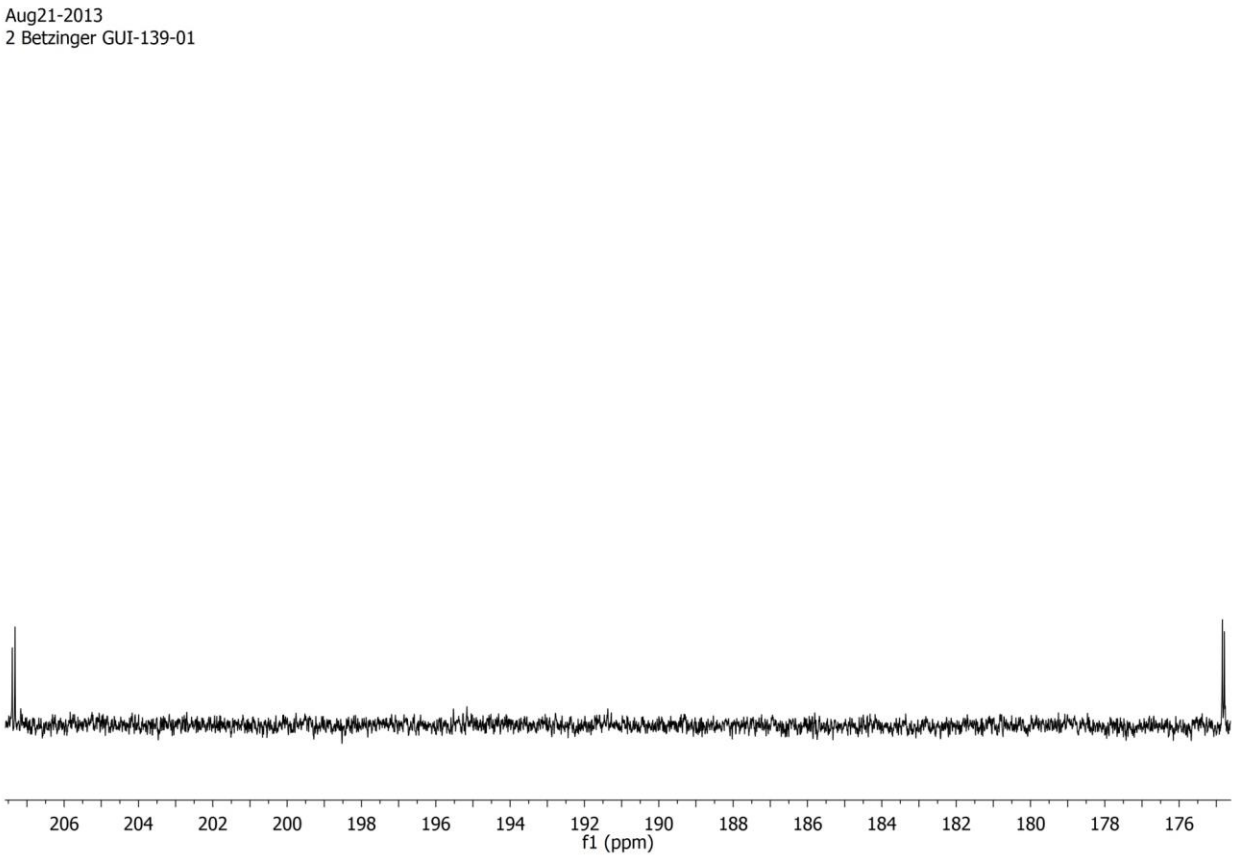


Fig. S16d ^{13}C NMR spectrum of **11a** (stretched regions between 122.5–136 and 175–207.5 ppm)

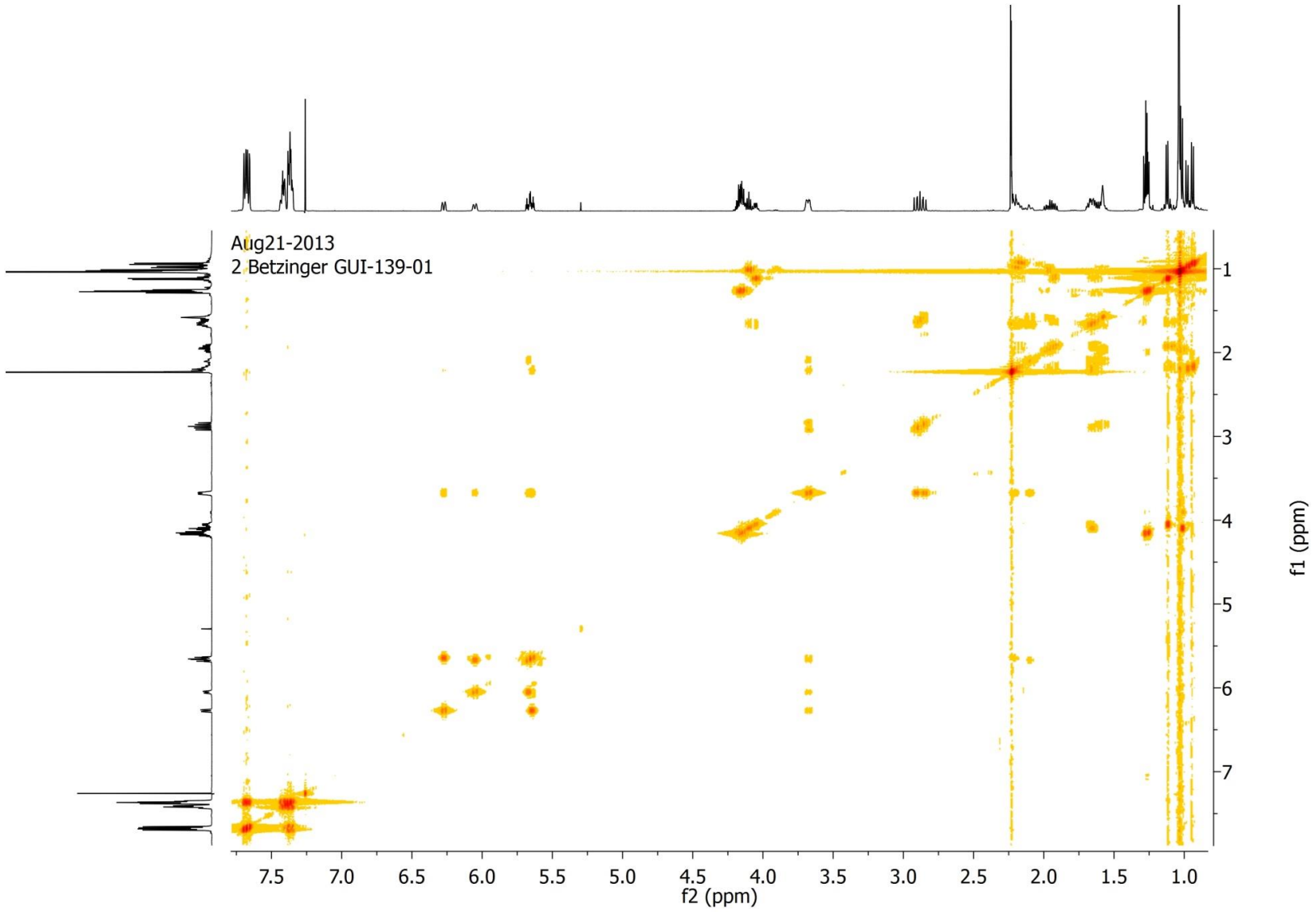


Fig. S16e 2D COSY spectrum of **11a**

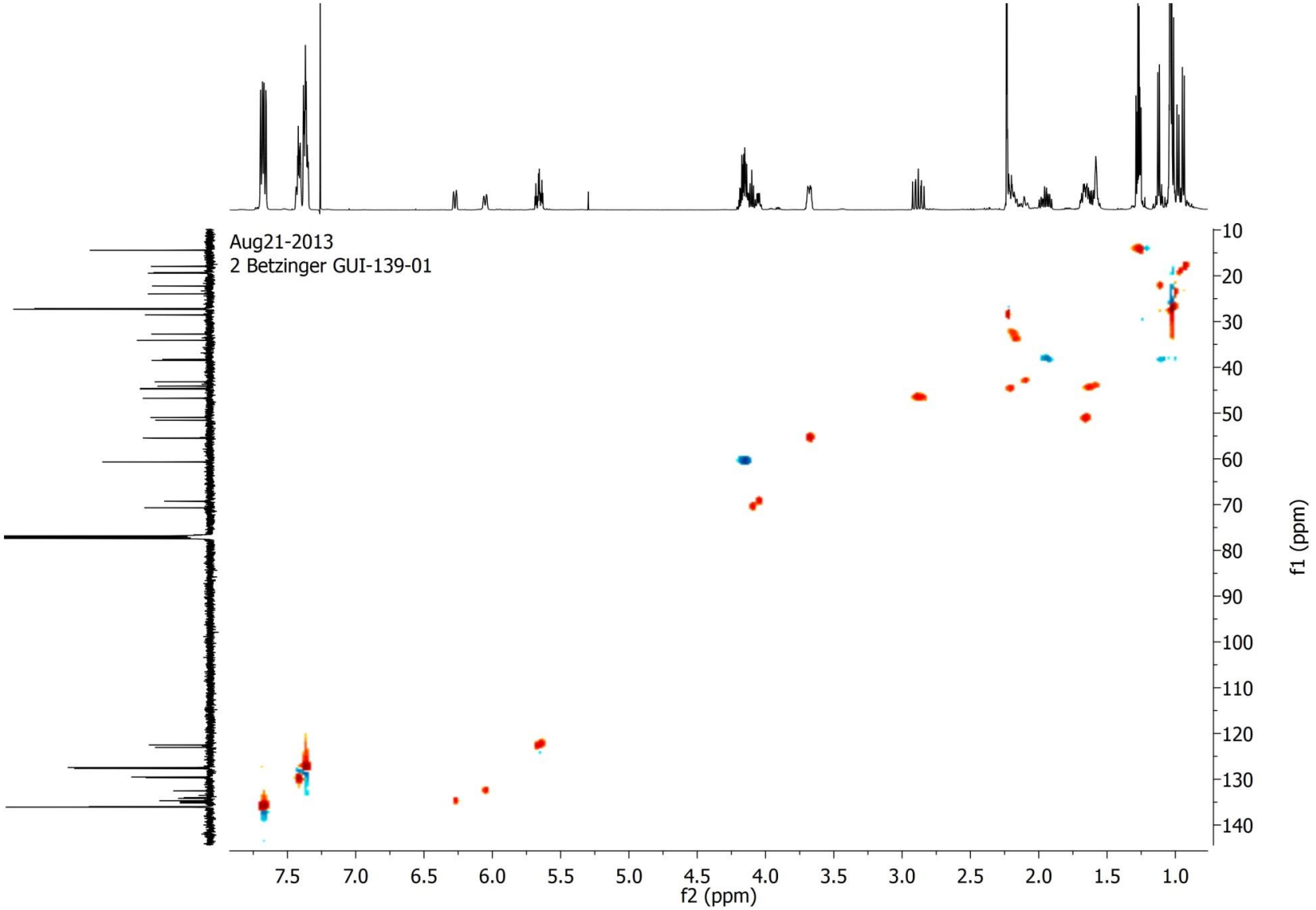


Fig. S16f HSQC spectrum of **11a**

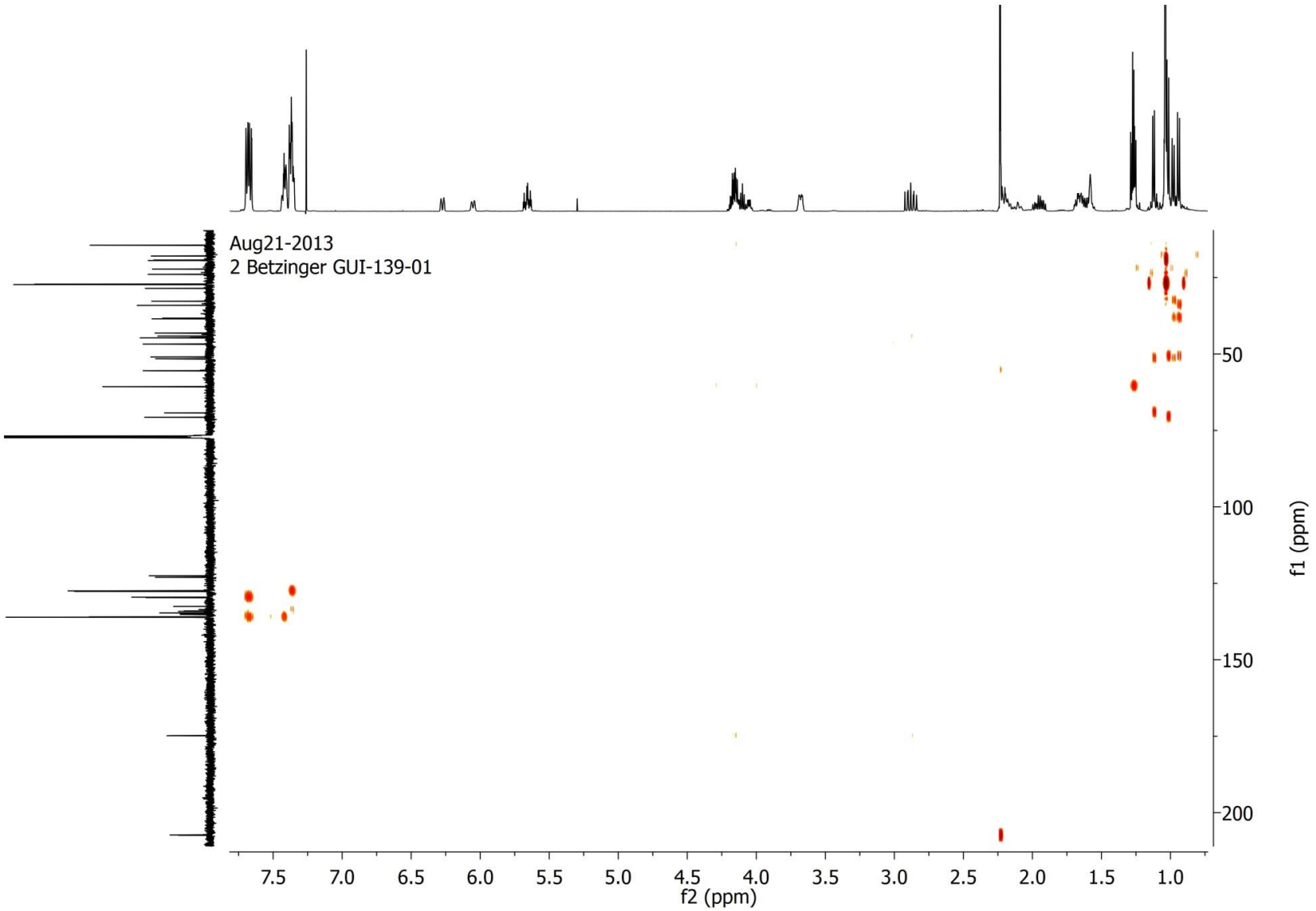


Fig. S16g HMBC spectrum of **11a**

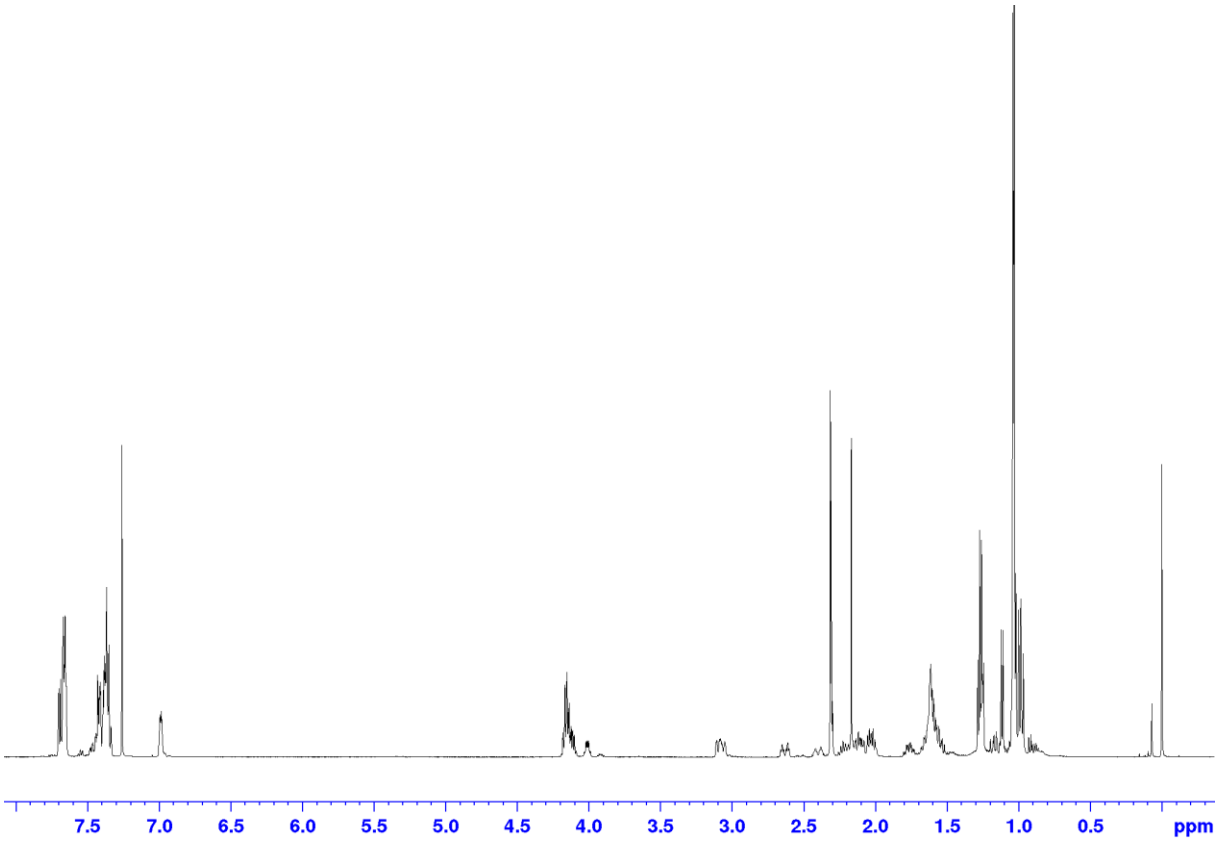


Fig. S17a ^{1}H NMR spectrum of **S7**

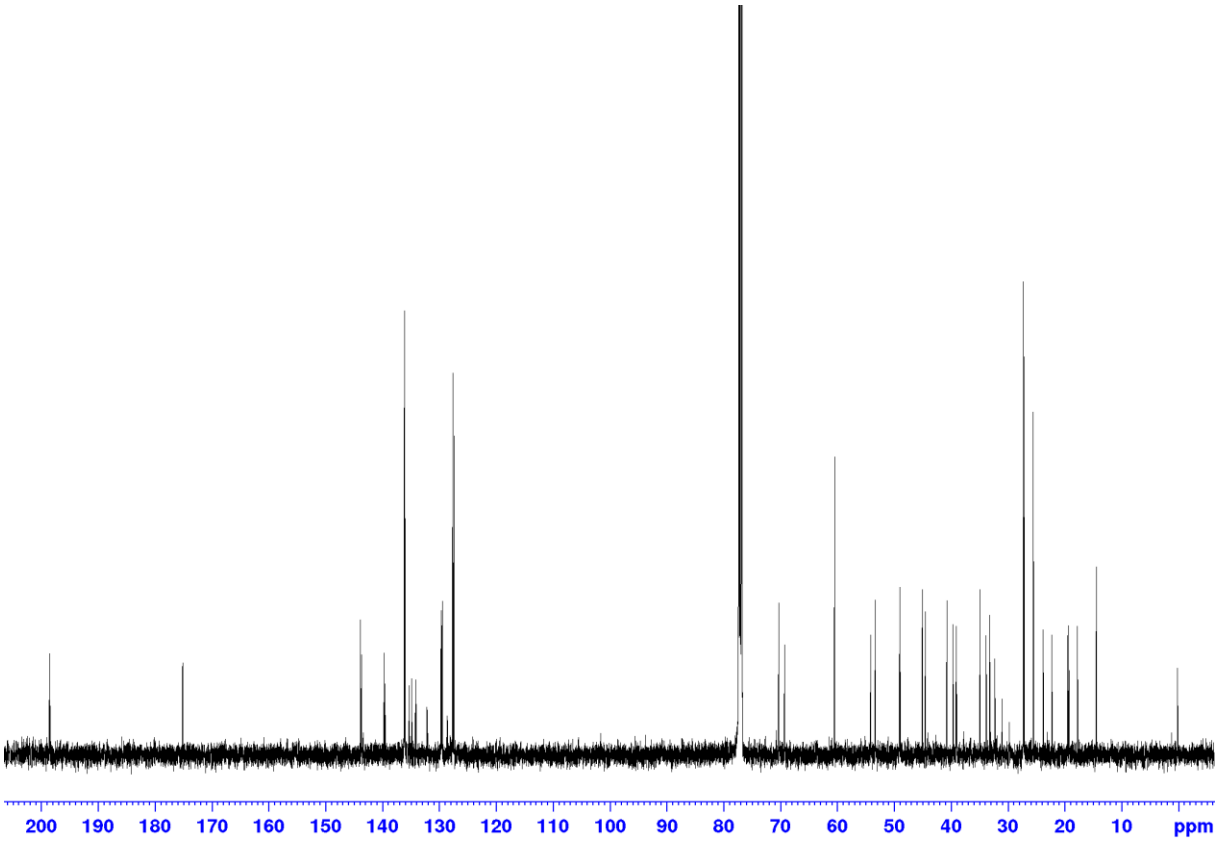


Fig. S17b ^{13}C NMR spectrum of **S7**