Supporting Information for

Synthesis of the Tetracyclic Core of Daphnilactone B-Type and Yuzurimine-Type Alkaloids

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Content :

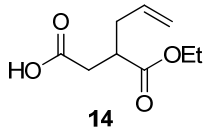
I General Information

All required fine chemicals were used directly without purification unless mentioned. Compounds lacking experimental details were prepared according to the literature as cited and are in agreement with published spectra. THF and Et_2O were distilled from Na and benzophenone at atmospheric pressure. Dichloromethane, toluene, diisopropylamine, diisopropylethylamine, and triethylamine were distilled from CaH_2 at atmospheric pressure. Triflic anhydride was distilled over a small amount of phosphorus pentoxide (P_2O_5) at atmospheric pressure prior to use. Methanol was distilled over 4 Å molecular sieves at atmospheric pressure. Infrared spectra were recorded with an ABB Bomen MB series spectrometer by applying substrates as thin films onto a KBr plate. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were measured with a Bruker AC-300 spectrometer. ^{1}H (400 MHz) NMR and ^{13}C (100 MHz) NMR spectra were measured with a Varian AS-400 spectrometer. NMR spectra are given in ppm as referenced to $CDCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). 2D experiments (COSY, NOESY) were measured with a Varian AS-400 spectrometer. ^{1}H NMR coupling constants are reported in Hertz and refer to apparent multiplicities and not true coupling constants. Data are reported as followed: chemical shift, multiplicity (s=singulet, br. s=broad singulet, d=doublet, t=triplet, q=quartet, qn=quintet, m=mutiplet, dd=doublets of doublets, etc.), coupling constant. Mass spectra were recorded with a VG Micromass ZAB-2F spectrometer or with a Synapt MS (Tof). Silia-P Silicycle (40-63 μm) silica gel was used for column chromatography, while Silicycle 60 Å silica gel plates (250 μm) were used for TLC analysis. All reactions were conducted under nitrogen or argon in flame-dried glassware and concentrations were performed under reduced pressure using a rotary evaporator.

Usual Reaction Work-up and Purification. After addition of the indicated aqueous solution, layers were separated. The aqueous phase was extracted with the indicated solvent, and the combined organic

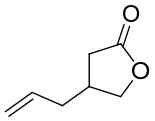
phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using silica gel with the indicated eluent.

II Synthesis of 3 and Cyclization to 1



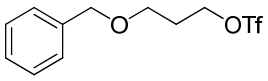
14

3-(Ethoxycarbonyl)hex-5-enoic acid (14). *n*-BuLi (2.50 M in hexanes, 5.75 mL, 14.4 mmol) was added dropwise to a solution of *i*-Pr_2NH (2.10 mL, 14.7 mmol) in THF (15 mL) at –78 ºC. The mixture was stirred for 30 min at –78 ºC then a solution of ester **13** (1.00 g, 6.84 mmol) in THF (10 mL) was added at –78 ºC. The reaction mixture was stirred for 2 h at 0 ºC then cooled at –78 ºC and a solution of 3-bromopropene (0.69 mL, 8.2 mmol) in THF (5.0 mL) was added. The reaction mixture was allowed to warm up to rt and stirred for 18 h. Water was added and THF was removed under reduced pressure. Aqueous HCl (1 N) was added at 0 ºC until an acidic pH (2-3) was obtained. The usual work-up (EtOAc) and purification (20% EtOAc in hexanes containing 1% AcOH) gave **14** (709 mg, 56%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.78-5.64 (m, 1H), 5.11-5.06 (m, 2H), 4.15 (q, *J*=7.0 Hz, 2H), 2.94-2.85 (m, 1H), 2.74 (dd, *J*=17.0, 9.0 Hz, 1H), 2.50 (dd, *J*=17.0, 5.0 Hz, 1H), 2.48-2.40 (m, 1H), 2.34-2.25 (m, 1H), 1.25 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 178.2 (s), 174.0 (s), 134.1 (d), 117.9 (t), 60.8 (t), 40.4 (d), 35.7 (t), 34.7 (t), 14.0 (q); IR (film) ν (cm^{-1}) 3361-2876, 3079, 2982, 2936, 1734, 1711, 1443, 1418, 1226, 1178; MS (EI) *m*/*z* (rel %) 187 $[MH]^+$ (2), 168 $[M\text{-}H_2O]^+$ (7), 140 (54), 123 (67), 112 (100); HRMS (EI) calcd for $C_9H_{15}O_4$ $[MH]^+$ 187.0970, found 187.0981.



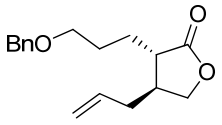
6

4-Allyldihydrofuran-2(3*H*)-one (6). The protocol was adapted from a reported procedure.[1] KOH (13.6 g, 206 mmol), $CaCl_2$ (27.0 g, 244 mmol), and $NaBH_4$ (9.23 g, 244 mmol) were added to a solution of **14** (17.5 g, 93.7 mmol) in abs. EtOH (1.04 L) at 0 ºC. The mixture was stirred for 20 h at rt then aqueous HCl (2 N) was added until an acidic pH (2-3) was obtained. The solution was stirred for 18 h at rt then EtOH was removed under reduced pressure. The usual work-up (EtOAc) and purification (10 to 30% EtOAc in hexanes) afforded **6** (10.1 g, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.71 (ddt, *J*=17.0, 9.5, 7.0 Hz, 1H), 5.12-5.07 (m, 2H), 4.38 (t, *J*=8.0 Hz, 1H), 3.98 (dd, *J*=8.5, 5.5 Hz, 1H), 2.68-2.57 (m, 2H), 2.27-2.17 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 176.8 (s), 134.1 (d), 117.4 (t), 72.4 (t), 36.8 (t), 34.4 (d), 33.6 (t); IR (film) ν (cm^{-1}) 3079, 2978, 2909, 1779, 1173, 1013, 919; MS (EI) *m*/*z* (rel %) 98 $[M-CO]^+$ (21), 84 (79), 67 (100); HRMS (EI) calcd for $C_7H_{10}O_2$ $[M]^+$ 126.0681, found 126.0684.



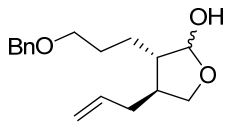
3-(Benzyloxy)propyl trifluoromethanesulfonate. Tf_2O (759 μL, 4.51 mmol) was added to a solution of 3-(benzyloxy)propan-1-ol[2] (500 mg, 3.01 mmol) and Et_3N (423 μL, 3.01 mmol) in DCM (40 mL) at 0 °C. The solution was stirred for 1.5 h at 0 °C then the solution was concentrated under reduced pressure. The usual purification (0 to 10% Et_2O in hexane) afforded **$BnO(CH_2)_3OTf$** (880 mg, 97%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40-7.29 (m, 5H), 4.70 (t, *J*=6.0 Hz, 2H), 4.52 (s, 2H), 3.60 (t, *J*=6.0 Hz, 2H), 2.11 (qn, *J*=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8

(s), 128.4 (d), 127.7 (d), 127.6 (d), 118.6 (q, $J_{C\text{-}F}$=320 Hz), 74.7 (t), 73.1 (t), 64.7 (t), 29.6 (t); IR (film) ν (cm^{-1}) 3090, 3066, 3033, 2937, 2868, 1412, 1246, 1206, 1147, 934; MS (EI) *m*/*z* (rel %) 298 $[M]^+$ (72), 107 (83), 91 (100); HRMS (EI) calcd for $C_{11}H_{13}F_3O_4S_1$ $[M]^+$ 298.0487, found 298.0498.



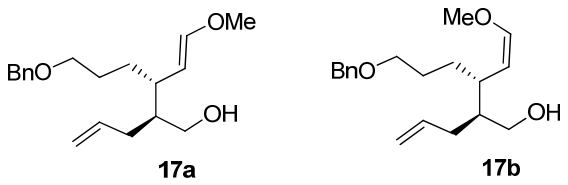
15

***rel*-(3*S*,4*S*)-4-Allyl-3-(3-benzyloxypropyl)dihydrofuran-2(3*H*)-one (15).** A solution of **6** (1.58 g, 12.5 mmol) in THF (35 mL) was added dropwise to a solution of KHMDS (0.5 M in toluene, 26.3 mL, 13.2 mmol) in THF (50 mL) at -78 ºC. The solution was stirred for 1 h at -78 °C then this solution was transferred via cannula to a solution of **$BnO(CH_2)_3OTf$** (6.52 g, 21.9 mmol) in THF (70 mL) at -78 ºC. The mixture was stirred for 1 h at -78 ºC then water was added and the mixture was allowed to warm up to rt. Saturated aqueous NaCl was added. The usual work-up (EtOAc) and purification (15% EtOAc in hexane) afforded **15** (2.77 g, 81%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38-7.28 (m, 5H), 5.77-5.64 (m, 1H), 5.13-5.07 (m, 2H), 4.50 (s, 2H), 4.34 (dd, *J*=9.0, 7.0 Hz, 2H), 3.85 (dd, *J*=9.0, 7.0 Hz, 1H), 3.54-3.45 (m, 2H), 2.42-2.22 (m, 3H), 2.19-2.08 (m, 1H), 1.86-1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.8 (s), 138.2 (s), 133.9 (d), 128.1 (d), 127.4 (d), 127.3 (d), 117.6 (t), 72.6 (t), 70.6 (t), 69.6 (t), 44.1 (d), 39.9 (d), 36.4 (t), 26.6 (t), 25.9 (t); IR (film) ν (cm^{-1}) 3030, 2917, 2859, 1773, 1453, 1361, 1165, 1101, 1017, 919; MS (EI) *m*/*z* (rel %) 275 $[MH]^+$ (2), 274 $[M]^+$ (1), 183 $[M\text{-}C_7H_7]^+$ (54), 168 (38), 167 (37), 127 (94), 91 (100); HRMS (EI) calcd for $C_{17}H_{22}O_3$ $[M]^+$ 274.1569, found 274.1573.



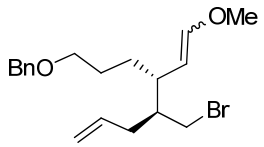
16

***rel*-(3*S*,4*S*)-4-Allyl-3-(3-benzyloxypropyl)tetrahydrofuran-2-ol (16).** A solution of DIBAL-H (1.0 M in DCM, 25.8 mL, 25.8 mmol) was added dropwise to a solution of **15** (6.44 g, 23.5 mmol) in Et_2O (200 mL) at -78 ºC. The solution was stirred for 1.5 h at -78 °C. MeOH (5.0 mL) was added and the mixture was warmed up at rt. Saturated aqueous Rochelle salt was added then the mixture was stirred for 2 h at rt. The usual work-up (Et_2O) and purification (60% Et_2O in hexane) afforded an inseparable 1:1.5 mixture of diastereomers **16** (6.37 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) mixture of diastereomers δ (ppm) 7.38-7.26 (m, 5H), 5.81-5.67 (m, 1H), 5.38 (t, *J*=4.0 Hz) and 5.16 (t, *J*=3.0 Hz) (1H), 5.07-4.97 (m, 2H), 4.51 (s, 2H), 4.17 (t, *J*=8.5 Hz), 4.00 (t, *J*=8.0 Hz), 3.69 (t, *J*=8.5 Hz), 3.51-3.42 (m), and 3.27 (d, *J*=3.0 Hz) (5H), 2.41-2.30 (m, 1H), 2.19-2.09 (m, 1H), 2.00-1.86 (m, 1H), 1.81-1.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.2 (s), 136.4 (d), 136.2 (d), 128.1 (d), 127.5 (d), 127.4 (d), 127.3 (d), 115.8 (t), 115.8 (t), 103.7 (d), 98.5 (d), 72.7 (t), 72.0 (t), 71.5 (t), 70.2 (t), 69.9 (t), 51.4 (d), 49.0 (d), 44.2 (d), 40.7 (d), 36.7 (t), 36.5 (t), 28.7 (t), 28.0 (t), 27.8 (t), 24.1 (t); IR (film) ν (cm^{-1}) 3435-3381, 3064, 3029, 2936, 2858, 1453, 1360, 1099, 1027, 1005, 914; MS (EI) *m*/*z* (rel %) 276 $[M]^+$ (1), 258 $[M\text{-}H_2O]^+$ (2), 217 (100); HRMS (EI) calcd for $C_{17}H_{24}O_3$ $[M]^+$ 276.1725, found 276.1734.



***rel*-(2*S*,3*S*)-2-Allyl-6-(benzyloxy)-3-((*E*)-2-methoxyvinyl)hexan-1-ol (17a) and *rel*-(2*S*,3*S*)-2-Allyl-6-(benzyloxy)-3-((*Z*)-2-methoxyvinyl)hexan-1-ol (17b).** A solution of KHMDS (0.5 M in toluene, 83.0 mL, 41.5 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride (14.3 g, 41.8 mmol) in THF (200 mL) at 0 ºC. The solution was stirred for 1 h at rt. The mixture was cooled at 0 ºC then a solution of **16** (4.62 g, 16.7 mmol) in THF (50 mL) was added. The solution was stirred for 18 h at rt. Water was added and THF was removed under reduced pressure. Saturated aqueous $NaHCO_3$ was added. The usual work-up (EtOAc) and purification (10 to 30% EtOAc in hexane) afforded mixture of *E/Z*-isomers **17a** and **17b** (4.37 g, 86%) as a pale yellow oil. A small portion of the mixture of isomers was separated for characterization: **17a** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35-7.24 (m, 5H), 6.23 (d, *J*=12.5 Hz, 1H), 5.80 (ddt, *J*=17.0, 10.0, 7.0 Hz, 1H), 5.09-5.01 (m, 2H), 4.49 (s, 2H), 4.48 (dd, *J*=12.5, 10.0 Hz, 1H), 3.67 (dt, *J*=11.0, 5.5 Hz, 1H), 3.55 (dt, *J*=11.0, 5.5 Hz, 1H), 3.51 (s, 3H), 3.45 (t, *J*=6.0 Hz, 2H), 2.14 (t, *J*=7.0 Hz, 2H), 2.01-1.91 (m, 1H), 1.74-1.42 (m, 4H), 1.38-1.30 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 147.8 (d), 138.4 (s), 137.5 (d), 128.2 (d), 127.5 (d), 127.4 (d), 116.0 (t), 103.9 (d), 72.7 (t), 70.2 (t), 63.2 (t), 55.8 (q), 45.1 (d), 38.9 (d), 33.7 (t), 29.5 (t), 27.7 (t); IR (film) δ (cm^{-1}) 3617-3203, 3066, 3032, 2934, 2860, 1650, 1453, 1206, 1101, 937; MS (EI) *m*/*z* (rel %) 304 $[M]^+$ (1), 303 $[M-H]^+$ (2), 181 (53), 137 (72), 91 (100); HRMS (EI) calcd for $C_{19}H_{28}O_3$ $[M]^+$ 304.2038, found 304.2033. **17b** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38-7.24 (m, 5H), 6.01 (d, *J*=6.5 Hz, 1H), 5.92-5.78 (m, 1H), 5.10-5.00 (m, 2H), 4.50 (s, 2H), 4.14 (dd, *J*=10.5, 6.5 Hz, 1H), 3.65-3.53 (m, 2H), 3.55 (s, 3H), 3.45 (dd, *J*=6.5, 5.0 Hz, 2H), 2.55 (qd, *J*=10.5, 3.0 Hz, 1H), 2.26-2.11 (m, 2H), 1.94-1.90 (m, 1H), 1.75-1.62 (m, 2H), 1.59-1.46 (m, 1H), 1.40-1.30 (m, 1H),

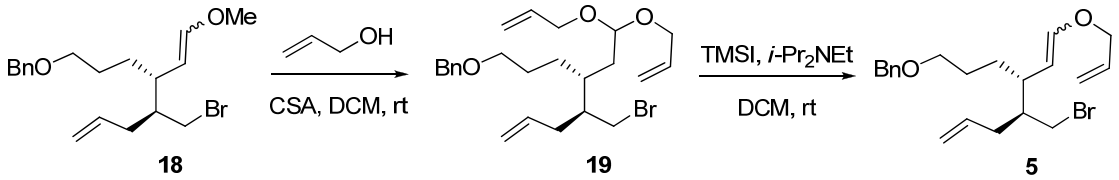
1.25-1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.0 (d), 138.6 (s), 137.7 (d), 128.2 (d), 127.5 (d), 127.4 (d), 115.9 (t), 109.4 (d), 72.7 (t), 70.3 (t), 63.3 (t), 59.5 (q), 44.8 (d), 34.7 (d), 33.7 (t), 29.2 (t), 27.6 (t); IR (film) ν (cm^{-1}) 3529-3282, 3065, 3028, 2934, 2857, 1661, 1454, 1259, 1102, 911; MS (EI) *m*/*z* (rel %) 304 $[M]^+$ (2), 273 $[M\text{-}OCH_3]^+$ (3), 181 (63), 91 (100); HRMS (EI) calcd for $C_{19}H_{27}O_3$ $[M\text{-}H]^+$ 303.1960, found 303.1955.



18

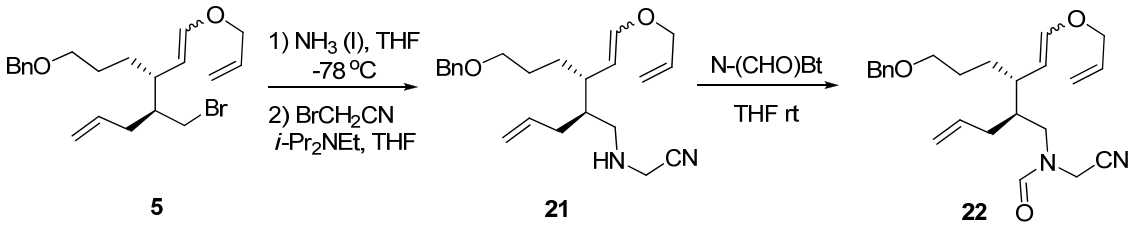
***rel*-(4*R*,5*S*)-1-Benzyloxy-5-(bromomethyl)-4-(2-methoxyvinyl)oct-7-ene (18).** Bromine (780 μL, 15.1 mmol) was added to a solution of PPh_3 (3.95 g, 15.1 mmol) and imidazole (1.96 g, 28.8 mmol) in DCM (70 mL) (the solution was protected from light) at 0 ºC. The solution was stirred for 20 min at 0 ºC then a solution of **17** (4.37 g, 14.4 mmol) in DCM (40 mL) was added. The mixture was stirred for 3 h at rt then saturated aqueous NaCl and 10% $NaHSO_3$ aqueous solution were added. The usual work-up (DCM) and purification (5 to 10% Et_2O in hexane) afforded a mixture of *E*/*Z*-isomers **18** (4.37 g, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of *E*/*Z*-isomers δ (ppm) 7.38-7.28 (m, 5H), 6.29 (d, *J*=12.5 Hz) and 6.00 (d, *J*=6.5 Hz) (1H), 5.71 (ddt, *J*=17.0, 10.0, 7.0 Hz, 1H), 5.12 (d, *J*=17.0 Hz, 1H), 5.07 (d, *J*=10.0 Hz, 1H), 4.50 (s, 2H), 4.38 (dd, *J*=12.5, 10.5 Hz) and 4.05 (dd, *J*=10.0, 6.5 Hz) (1H), 3.57-3.49 (m, 4H), 3.46 (t, *J*=6.0 Hz, 2H), 3.38 (dd, *J*=10.0, 6.5 Hz, 1H), 2.71-2.61 (m) and 2.03 (tdd, *J*=10.0, 7.0, 3.5 Hz) (1H), 2.31-2.16 (m, 2H), 1.75-1.44 (m, 4H), 1.33-1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.4 (d), 147.7 (d), 138.4 (s), 138.3 (s), 136.0 (d), 135.7 (d), 128.2 (d), 128.2 (d), 127.5 (d), 127.5 (d), 127.4 (d), 127.3 (d), 117.1 (t), 117.0 (t), 107.4 (d), 102.9 (d), 72.7 (t), 72.6 (t), 70.2 (t), 70.1 (t), 59.4 (q), 55.8 (q), 44.4 (d), 44.0 (d), 39.7 (d), 37.5 (t), 37.1 (t),

35.5 (d), 33.9 (t), 33.9 (t), 29.0 (t), 28.8 (t), 27.6 (t), 27.3 (t); IR (film) ν (cm^{-1}) 3062, 3028, 2999, 2934, 2855, 1650, 1453, 1438, 1208, 1102, 936, 916; MS (CI:NH_3) *m*/*z* (rel %) 386 $[MNH_4]^+$ (47, ^{81}Br), 384 $[MNH_4]^+$ (46, ^{79}Br), 369 $[MH]^+$ (15, ^{81}Br), 367 $[MH]^+$ (14, ^{79}Br), 91 (100); HRMS (CI:NH_3) calcd for $C_{19}H_{28}{}^{79}BrO_2$ $[MH]^+$ 367.1273, found 367.1266.



***rel-(4R,5S)*-1-Benzyloxy-4-(2-(allyloxy)vinyl)-5-(bromomethyl)oct-7-ene (5).** Camphorsulfonic acid (220 mg, 0.948 mmol) was added to a solution of **18** (1.74 g, 4.74 mmol) and allyl alcohol (6.44 mL, 94.7 mmol) in DCM (45 mL) at rt. The solution was stirred for 18 h at rt then saturated aqueous $NaHCO_3$ was added. The usual work-up (DCM) afforded **19** (2.06 g, 96%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38-7.28 (m, 5H), 5.99-5.85 (m, 2H), 5.79-5.65 (m, 1H), 5.28 (d, *J*=17.5 Hz, 2H), 5.16 (d, *J*=10.5 Hz, 2H), 5.11-5.04 (m, 2H), 4.66 (t, *J*=5.5 Hz, 1H), 4.50 (s, 2H), 4.15-4.07 (m, 2H), 4.04-3.97 (m, 2H), 3.47 (t, *J*=6.5 Hz, 2H), 3.40 (d, *J*=6.0 Hz, 2H), 2.25-2.16 (m, 1H), 2.12-2.02 (m, 1H), 1.95-1.83 (m, 2H), 1.74-1.55 (m, 4H), 1.49-1.38 (m, 1H), 1.35-1.23 (m, 1H); MS (CI:NH_3) *m*/*z* (rel %) 470 $[MNH_4]^+$ (20, ^{81}Br), 468 $[MNH_4]^+$ (19, ^{79}Br), 412 (100, ^{81}Br), 410 (98, ^{79}Br), 395 (36, ^{81}Br), 393 (30, ^{79}Br); HRMS (CI:NH_3) calcd for $C_{24}H_{39}N^{79}BrO_3$ $[MNH_4]^+$ 468.2113, found 468.2122. Following a protocol adapted from a reported procedure,[3] iodotrimethylsilane (1.30 mL, 9.13 mmol) was added to a solution of **19** (2.06 g, 4.56 mmol) and *i*-Pr_2NEt (4.00 mL, 22.8 mmol) in DCM (50 mL) at 0 ºC. The solution was stirred for 3 h at rt then saturated aqueous $NaHCO_3$ was added. The usual work-up (Et_2O) and purification (0 to 10% Et_2O in hexane) afforded a mixture of *E*/*Z*-isomers **5** (1.45 g, 81%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) as a mixture of *E*/*Z*-isomers δ (ppm)

7.38-7.25 (m, 5H), 6.22 (d, *J*=12.5 Hz) and 6.07 (d, *J*=6.5 Hz) (1H), 6.00-5.64 (m, 2H), 5.35-5.05 (m, 4H), 4.50 (s, 2H), 4.46 (dd, *J*=12.5, 10.5 Hz) and 4.08 (dd, *J*=10.5, 6.5 Hz) (1H), 4.21 (t, *J*=5.5 Hz, 2H), 3.57-3.52 (m), 3.48-3.43 (m) and 3.40-3.33 (m) (4H), 2.72 (ddt, *J*=10.0, 7.0, 3.0 Hz) and 2.01 (ddt, *J*=10.0, 7.0, 3.5 Hz) (1H), 2.29-2.20 (m, 2H), 1.74-1.43 (m, 4H), 1.32-1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.2 (d), 147.1 (d), 146.1 (d), 146.0 (d), 138.5 (s), 138.4 (s), 136.0 (d), 135.8 (d), 133.9 (d), 133.8 (d), 133.3 (d), 133.3 (d), 128.2 (d), 128.2 (d), 127.5 (d), 127.4 (d), 127.3 (d), 117.3 (t), 117.3 (t), 117.1 (t), 117.0 (t), 107.6 (d), 105.0 (d), 72.8 (t), 72.7 (t), 72.5 (t), 70.2 (t), 70.1 (t), 70.0 (t), 44.6 (d), 44.1 (d), 39.8 (d), 37.4 (t), 37.0 (t), 35.6 (d), 34.0 (t), 29.0 (t), 28.9 (t), 27.6 (t), 27.4 (t); IR (film) ν (cm^{-1}) 3075, 3063, 3028, 2926, 2856, 1666, 1646, 1453, 1425, 1361, 1162, 1100, 920; MS (CI:NH_3) *m*/*z* (rel %) 412 $[MNH_4]^+$ (23, ^{81}Br), 410 $[MNH_4]^+$ (22, ^{79}Br), 395 $[MH]^+$ (12, ^{81}Br), 393 $[MH]^+$ (10, ^{79}Br), 245 (67), 227 (58), 91 (100); HRMS (CI:NH_3) calcd for $C_{21}H_{30}{}^{79}BrO_2$ $[MH]^+$ 393.1429, found 393.1435.

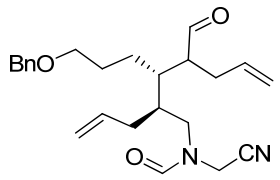


5 21 22

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)hexyl)-*N*-(cyanomethyl)formamide (22).** NH_3 (g) was condensed (60 mL) in a solution of **5** (1.52 g, 3.86 mmol) in THF (15 mL) in a sealed tube at -78 ºC. The solution was stirred for 72 h at rt then cooled at -78 ºC to decrease pressure and allow the opening of the sealed tube. The sealed tube was opened and the mixture was allowed to warm up to rt. After complete NH_3 evaporation, saturated aqueous $NaHCO_3$ was added and THF was removed under reduced pressure. Water was added then the usual work-up (EtOAc) afforded **20** (1.27 g, 100%) as a

colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of *E*/*Z*-isomers δ (ppm) 7.34-7.23 (m, 5H), 6.14 (d, *J*=12.5 Hz) and 6.04 (d, *J*=6.5 Hz) (1H), 5.99-5.69 (m, 2H), 5.34-5.17 (m, 2H), 5.08-4.98 (m, 2H), 4.53 (dd, *J*=12.5, 10.0 Hz) and 4.11 (dd, *J*=10.5, 6.5 Hz) (1H), 4.49 (s, 2H), 4.22-4.17 (m, 2H), 3.46 (t, *J*=6.0 Hz) and 3.44 (t, *J*=6.0 Hz) (2H), 2.79-2.48 (m, 2H), 2.19-2.04 (m, 2H), 1.97-1.89 (m) and 1.71-1.20 (m) (6H). Bromoacetonitrile (270 μL, 4.05 mmol) was added to a solution of **20** (1.27 g, 3.86 mmol) and *i*-Pr_2NEt (0.71 mL, 4.05 mmol) in THF (70 mL). The solution was stirred for 18 h at rt. Water was added and THF was removed under reduced pressure. Saturated aqueous $NaHCO_3$ was added then the usual work-up (EtOAc) afforded **21** (1.46 g) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of *E*/*Z*-isomers δ (ppm) 7.38-7.23 (m, 5H), 6.16 (d, *J*=12.5 Hz) and 6.07 (d, *J*=6.5 Hz) (1H), 6.00-5.67 (m, 2H), 5.35-5.19 (m, 2H), 5.07-4.99 (m, 2H), 4.53 (dd, *J*=12.5, 10.0 Hz) and 4.12 (dd, *J*=10.5, 6.5 Hz) (1H), 4.49 (s, 2H), 4.23 (d, *J*=5.5 Hz) and 4.20 (d, *J*=5.5 Hz) (2H), 3.60-3.41 (m, 4H), 2.78-2.49 (m, 2H), 2.23-2.09 (m, 2H), 2.00-1.90 (m) and 1.73-1.43 (m) (5H), 1.38-1.19 (m, 2H). A solution of amine **21** (1.42 g, 3.86 mmol) in THF (84 mL) was treated with *N*-formylbenzotriazole[4] (738 mg, 5.02 mmol). The mixture was stirred for 20 h at rt then aqueous NaOH (2 N) was added. The solution was stirred for 15 min at rt then water was added and THF was removed under reduced pressure. The usual work-up (DCM) and purification (0 to 40% EtOAc in hexanes) afforded **22** (1.02 g, 67% over 3 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of *E*/*Z*-isomers and rotamers δ (ppm) 8.11 (s) and 8.00 (s) (1H), 7.38-7.26 (m, 5H), 6.19 (d, *J*=12.5 Hz) and 6.08 (d, *J*=6.5 Hz) (1H), 6.00-5.84 (m, 1H), 5.75-5.60 (m, 1H), 5.36-5.21 (m, 2H), 5.11-5.03 (m, 2H), 4.53-4.46 (m, 1H), 4.49 (s, 2H), 4.37-4.04 (m, 4H), 3.47-3.13 (m, 2H), 3.45 (t, *J*=6.0 Hz, 2H), 2.64-2.55 (m) and 2.17-1.95 (m) (3H), 1.80-1.65 (m, 2H), 1.63-1.44 (m, 2H), 1.40-1.24 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 162.6 (d), 162.5 (d), 162.4 (d), 147.5 (d), 147.2 (d), 146.1 (d), 138.3 (s), 138.3 (s), 136.2 (d), 136.0 (d), 135.2 (d), 135.1 (d), 133.5 (d), 133.1 (d), 128.1 (d), 127.4 (d), 127.3 (d), 117.5 (t), 117.3 (t), 117.2 (t), 116.8 (t), 114.5 (s), 107.3 (d), 103.8 (d), 72.6 (t), 72.5 (t), 70.0 (t), 69.6 (t), 48.7 (t),

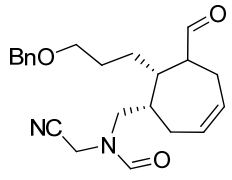
48.5 (t), 43.7 (t), 43.2 (t), 39.9 (d), 39.6 (d), 38.8 (d), 38.2 (d), 35.8 (t), 35.4 (t), 35.3 (t), 34.1 (d), 33.8 (d), 33.6 (t), 33.3 (t), 33.0 (t), 32.8 (t), 30.2 (t), 29.8 (t), 28.8 (t), 27.8 (t), 27.6 (t), 27.5 (t), 27.3 (t); IR (film) ν (cm^{-1}) 3077, 3032, 2937, 2861, 1681, 1428, 1163, 1096, 920; MS (EI) *m*/*z* (rel %) 355 $[M-C_3H_5]^+$ (2), 311 (10), 247 (19), 163 (62), 91 (100); HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ $[M]^+$ 396.2413, found 396.2417.



4

***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(3-(benzyloxy)propyl)-4-formylhept-6-enyl)-*N*-(cyanomethyl)formamide (4).** A solution of **22** (508 mg, 1.28 mmol) in toluene (26 mL) was heated at 150 ºC in a sealed tube for 120 h. The solution was concentrated under reduced pressure. The usual purification using silica gel saturated with Et_3N (30 to 40% EtOAc in hexane) afforded an inseparable mixture of diastereoisomers **4** (381 mg, 75%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of diastereoisomers and rotamers δ (ppm) 9.66 (d, *J*=2.0 Hz) and 9.63 (d, *J*=2.5 Hz) (1H), 8.08 (s), 8.07 (s), 7.97 (s) and 7.96 (s) (1H), 7.36-7.26 (m, 5H), 5.77-5.60 (m, 2H), 5.11-5.03 (m, 4H), 4.48 (s) and 4.47 (s) (2H), 4.28-4.01 (m, 2H), 3.49-3.42 (m, 2H), 3.26 (t, *J*=7.0 Hz, 2H), 2.52-2.41 (m, 2H), 2.35-2.05 (m, 2H), 1.99-1.80 (m, 3H), 1.70-1.41 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.0 (d), 204.8 (d), 204.4 (d), 204.0 (d), 162.5 (d), 138.3 (s), 138.1 (s), 135.8 (d), 135.1 (d), 134.7 (d), 128.3 (d), 127.6 (d), 127.4 (d), 117.9 (t), 117.7 (t), 117.5 (t), 117.4 (t), 117.2 (t), 114.5 (s), 72.9 (t), 72.7 (t), 70.0 (t), 70.0 (t), 69.7 (t), 69.4 (t), 52.4 (d), 52.3 (d), 52.0 (d), 49.2 (t), 49.1 (t), 44.4 (t), 44.2 (t), 37.8 (d), 37.4 (d), 37.0 (d), 36.7 (d), 36.6 (d), 36.3 (d), 35.8 (t), 32.8 (t), 32.7 (t), 31.7 (t), 31.0 (t), 30.1 (t), 28.7 (t), 28.4 (t), 23.9 (t), 23.8 (t), 23.6

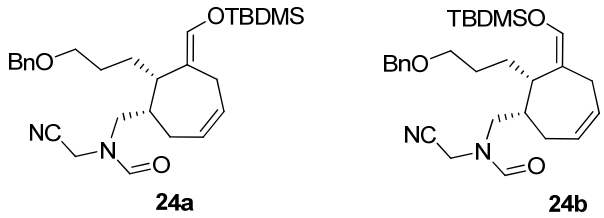
(t), 23.5 (t); IR (film) ν (cm^{-1}) 3073, 2936, 2863, 1719, 1681, 1430, 1101, 918; MS (EI) *m*/*z* (rel %) 396 $[M]^+$ (2), 367 $[M\text{-}CHO]^+$ (7), 328 (15), 277 (18), 91 (100); HRMS (EI) calcd for $C_{24}H_{32}N_2O_3$ $[M]^+$ 396.2413, found 396.2401.



23

***N*-((*rel*-(1*S*,7*S*)-7-(3-(Benzyloxy)propyl)-6-formylcyclohept-3-enyl)methyl)-*N*-(cyanomethyl)form-amide (23).** Following the reported procedure,[5] Grubbs' catalyst 2nd generation (41 mg, 5 mol%) was added to a solution of **4** (381 mg, 0.961 mmol) in DCM (160 mL). The solution was stirred for 18 h at rt then concentrated under reduced pressure. The usual purification (20 to 50% EtOAc in hexane) afforded a mixture of diastereoisomers **23** (303 mg, 86%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) as a mixture of diastereoisomers and rotamers δ (ppm) 9.71 (s), 9.65 (s), and 9.63 (s) (1H), 8.17 (s), 8.09 (s), 8.01 (s), and 8.00 (s) (1H), 7.38-7.26 (m, 5H), 5.83-5.61 (m, 2H), 4.57 (d, *J*=17.5 Hz), 4.19 (d, *J*=17.5 Hz), 4.08 (d, *J*=17.5 Hz), and 4.60-4.06 (m) (2H), 4.49 (s) and 4.47 (s) (2H), 3.78 (dd, *J*=14.0, 10.0 Hz), 3.49-3.34 (m), 3.32-3.20 (m), and 3.07 (dd, *J*=14.0, 6.0 Hz) (4H), 2.62-2.50 (m, 2H), 2.43-2.15 (m), 2.10-2.00 (m), 1.83 (dd, *J*=14.0, 7.0 Hz), and 1.77-1.32 (m) (9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 205.6 (d), 204.5 (d), 203.8 (d), 203.4 (d), 162.6 (d), 162.4 (d), 162.2 (d), 138.2 (s), 131.3 (d), 130.7 (d), 129.1 (d), 128.3 (d), 128.0 (d), 127.6 (d), 127.5 (d), 114.7 (s), 114.6 (s), 72.9 (t), 72.9 (t), 72.7 (t), 70.3 (t), 70.2 (t), 69.5 (t), 56.5 (d), 56.0 (d), 51.7 (t), 51.3 (d), 50.0 (t), 47.4 (t), 44.8 (t), 43.7 (d), 41.5 (d), 41.1 (d), 38.5 (d), 38.2 (d), 36.3 (d), 36.1 (d), 35.3 (t), 33.7 (d), 33.5 (d), 30.5 (t), 29.6 (t), 28.8 (t), 28.4 (t), 28.2 (t), 27.6 (t), 27.1 (t), 27.1 (t), 24.1 (t), 23.9 (t), 23.7 (t), 22.4 (t), 22.1 (t), 21.2

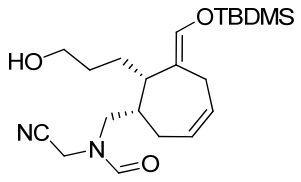
(t), 21.0 (t); IR (film) ν (cm^{-1}) 3028, 2940, 2868, 1719, 1678, 1435, 1180, 1097; MS (EI) *m*/*z* (rel %) 368 $[M]^+$ (5), 340 (3), 277 (8), 91 (100); HRMS (EI) calcd for $C_{22}H_{28}N_2O_3$ $[M]^+$ 368.2100, found 368.2108.



24a **24b**

***N*-((*rel*-(1*S*,7*S*,*E*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (24a) and *N*-((*rel*-(1*S*,7*S*,*Z*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (24b).** TBSOTf (284 μL, 1.24 mmol) was added to a solution of **23** (304 mg, 0.825 mmol) and *i*-Pr_2NEt (287 μL, 1.65 mmol) in DCM (16.5 mL) at 0 ^oC. The solution was stirred for 18 h at rt then saturated aqueous Na_2CO_3 and saturated aqueous NaCl were added. The usual work-up (DCM) and purification using silica gel saturated with Et_3N (0 to 40% EtOAc in hexane) afforded *E*-**24a** (187 mg) and *Z*-**24b**[6] (63 mg) (63% global yield) as a colorless oils. *E*-**24a** and *Z*-**24a** both exist as a mixture of rotamers and were separated at this stage. However, due to the instability of the products, full characterization was not possible and both isomers were carried through the sequence separately. Only the sequence with the major isomer *E*-**24a** is reported thereafter: *E*-**24a (major)** ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (s) and 8.00 (s) (1H), 7.38-7.28 (m, 5H), 6.05 (s, 1H), 5.82-5.75 (m, 1H), 5.57-5.52 (m, 1H), 4.49 (s, 2H), 4.32 (d, *J*=17.5 Hz, 1H), 4.14 (d, *J*=17.5 Hz, 1H), 3.46 (t, *J*=5.5 Hz, 2H), 3.33-3.19 (m, 2H), 3.10 (dd, *J*=17.5, 6.5 Hz, 1H), 2.70-2.64 (m, 1H), 2.12-1.92 (m, 4H), 1.71-1.56 (m, 2H), 1.49-1.34 (m, 2H), 0.91 (s, 9H), 0.11 (s, 6H). *Z*-**24b (minor)** ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.14 (s) and 8.02 (s) (1H),

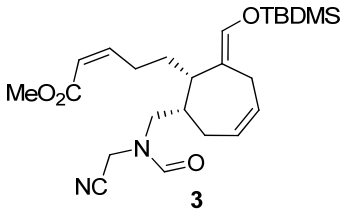
7.38-7,28 (m, 5H), 6.13 (s) and 6.10 (s) (1H), 5.71-5.65 (m, 1H), 5.57-5.50 (m, 1H), 4.59 (d, *J*=17.5 Hz, 1H), 4.49 (s, 2H), 4.19 (d, *J*=2.0 Hz) and 4.09 (d, *J*=17.5 Hz) (1H), 3.45 (t, *J*=6.0 Hz, 2H), 3.38-3.23 (m, 2H), 2.99-2.95 (m, 1H), 2.79-2.73 (m, 1H), 2.47 (dd, *J*=18.0, 7.0 Hz, 1H), 2.09-1.88 (m, 3H), 1.68-1.27 (m, 4H), 0.90 (s, 9H), 0.12 (s) and 0.11 (s) (6H).



25

***N*-((*rel*-(1*S*,7*S*,*E*)-6-((*tert*-Butyldimethylsilyloxy)methylene)-7-(3-hydroxypropyl)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (25).** A solution of Me_2BBr (1.0 M in DCM, 3.87 mL, 3.87 mmol) was added to a solution of **24a** (187 mg, 0.387 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (795 mg, 3.87 mmol) in DCM (8.0 mL) at -25 ^{o}C. The solution was stirred for 2 h at -25 ^{o}C then saturated aqueous $NaHCO_3$ (2.0 mL) was added at -25 ^{o}C. The mixture was stirred for 15 min at rt and saturated aqueous NaCl was added. The usual work-up (DCM) and purification using silica gel saturated with Et_3N (10 to 100% EtOAc in hexane) afforded **25** (110 mg, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) as a mixture of rotamers δ (ppm) 8.19 (s) and 8.03 (s) (1H), 6.07 (s) and 6.04 (s) (1H), 5.80-5.74 (m, 1H), 5.56-5.52 (m, 1H), 4.31 (d, *J*=17.5 Hz), 4.17 (d, *J*=17.5 Hz), and 4.17 (d, *J*=3.3 Hz) (2H), 3.63-3.57 (m, 2H), 3.33 (dd, *J*=14.5, 7.0 Hz, 1H), 3.24 (dd, *J*=14.5, 8.0 Hz, 1H), 3.11 (dd, *J*=17.5, 6.5 Hz, 1H), 2.65-2.63 (m) and 2.54-2.49 (m) (1H), 2.12-2.05 (m, 2H), 2.00-1.89 (m) and 1.78 (br s) (3H), 1.61-1.54 (m, 2H), 1.43-1.36 (m, 2H), 0.90 (s, 9H), 0.11 (s) and 0.10 (s) (6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8 (d), 162.6 (d), 135.0 (d), 134.7 (d), 130.1 (d), 129.3 (d), 126.9 (d), 126.4 (d), 121.0 (s), 119.6 (s), 114.5 (s), 62.1 (t), 61.7 (t), 50.2 (t), 46.3 (t), 43.5 (d), 42.3 (d),

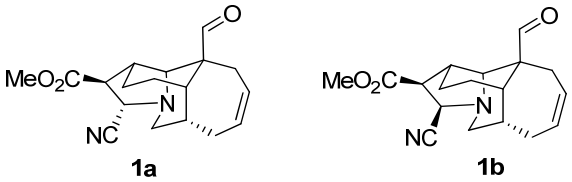
40.3 (d), 39.6 (d), 36.0 (t), 30.3 (t), 30.2 (t), 30.0 (t), 29.0 (t), 28.6 (t), 25.6 (q), 25.1 (t), 24.5 (t), 21.8 (t), 20.2 (t), 18.2 (s), -5.3 (q), -5.4 (q); IR (film) ν (cm^{-1}) 3611-3132, 2956, 2930, 2889, 2859, 1673, 1465, 1433, 1402, 1253, 1179; MS (EI) *m*/*z* (rel %) 392 $[M]^+$ (10), 335 $[M-C_4H_9]^+$ (17), 249 (34), 74 (100); HRMS (EI) calcd for $C_{21}H_{36}N_2O_3Si$ $[M]^+$ 392.2495, found 392.2503.



3

(*Z*)-Methyl 5-(*rel*-(1*S*,7*S*,*E*)-2-((*tert*-butyldimethylsilyloxy)methylene)-7-((*N*-(cyanomethyl)form-amido)methyl)cyclohept-4-enyl)pent-2-enoate (3). Oxalyl chloride (32 μL, 0.36 mmol) was added to a solution of DMSO (40 μL, 0.56 mmol) in DCM (3.5 mL) at -78 °C. After 5 min at -78 °C, a solution of **25** (110 mg, 0.280 mmol) in DCM (1.5 mL) was added and the reaction mixture was stirred 1.5 h at -78 °C. Triethylamine (195 μL, 1.40 mmol) was added and the reaction mixture was allowed to warm to rt over 3 h. Saturated aqueous $NaHCO_3$ was added then the usual work-up (DCM) afforded **26** (100 mg of crude material). A solution of KHMDS (0.5 M in toluene, 0.56 mL, 0.28 mmol) was added to a solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (94 mg, 0.28 mmol) and 18-crown-6 ether (169 mg, 0.640 mmol) in THF (3.0 mL) at -78 °C. After 20 min at -78 °C, a solution of **26** (100 mg of crude material) in THF (2.0 mL) was added and the reaction mixture was allowed to warm to rt over 2 h. Saturated aqueous $NaHCO_3$ was added. The usual work-up (EtOAc) and purification using silica gel saturated with Et_3N (5 to 20% acetone in toluene) afforded **3** (44.6 mg, 39% over 2 steps) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) as a mixture of rotamers δ (ppm) 8.18 (s), and 8.04 (s) (1H), 6.26 (dt, *J*=11.5, 8.0 Hz, 1H), 6.06 (s, 1H), 5.82-5.79 (m, 2H), 5.56-5.51 (m, 1H), 4.38 (d,

J=17.5 Hz, 1H), 4.12 (d, *J*=17.5 Hz, 1H), 3.70 (s, 3H), 3.34-3.23 (m, 2H), 3.02 (dd, *J*=17.0, 6.0 Hz, 1H), 2.84-2.79 (m, 1H), 2.66-2.60 (m, 1H), 2.54-2.48 (m, 1H), 2.20-2.16 (m, 1H), 2.09-2.02 (m, 3H), 1.73-1.65 (m, 1H), 1.49-1.40 (m, 1H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ (ppm) 166.6 (s), 162.7 (d), 149.5 (d), 135.1 (d), 130.4 (d), 126.3 (d), 120.0 (d), 119.2 (s), 114.6 (s), 51.1 (q), 49.5 (t), 44.5 (d), 38.6 (d), 30.3 (t), 28.8 (t), 27.1 (t), 26.2 (t), 25.8 (t), 25.6 (q), 18.3 (s), -5.3 (q), -5.3 (q); IR (film) ν (cm^{-1}) 2952, 2928, 2857, 1720, 1680, 1462, 1437, 1406, 1254, 1198, 1177, 1154; MS (ESI) *m*/*z* (rel %) 469 $[MNa]^+$ (100), 353 (12), 130 (7); HRMS (ESI) calcd for $C_{24}H_{38}N_2NaO_4Si$ $[MNa]^+$ 469.2498, found 469.2488.

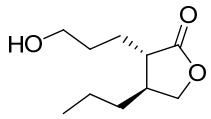


1a **1b**

Methyl *rel*-(1*R*,2*S*,3*S*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyltetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadec-8-ene-2-carboxylate (1a) and Methyl *rel*-(1*R*,2*S*,3*R*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyl-tetracyclo[9.3.1.0^{4,15}.0^{6,12}]pentadec-8-ene-2-carboxylate (1b). *NB: in order to follow the reaction, the following quantities were split into 8 NMR tubes, thus containing ca. 4 mg of **3** per tube. All tube contents were pooled for work-up and purification*. Triflic anhydride (21 μL, 0.122 mmol, freshly distilled over P_2O_5) was added to a solution of **3** (32.0 mg, 0.0716 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (44.1 mg, 0.215 mmol) in CD_2Cl_2 (7.2 mL) at rt. After 5 min at rt, a NMR spectra of each sample were recorded to ensure completion of the Vilsmeier-Haack cyclization. In rare cases where the cyclization was not completed, triflic anhydride (4 μL, 0.022 mmol) was added and the reaction was monitored by NMR once again after 5 min. *i*-Pr_2NEt (100 μL, 0.573 mmol) was then added. After 15 min at rt, NMR spectra of each sample were recorded to ensure completion of the

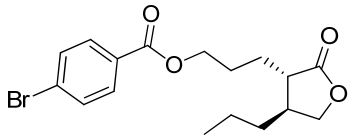
intramolecular cycloaddition. NMR tube contents were then pooled and an aqueous saturated solution of $NaHCO_3$ was added. The usual work-up (EtOAc) and purification (2 to 10% MeCN in toluene) afforded two separable diastereoisomers **1a** (4.7 mg) and **1b** (5.1 mg) (44% global yield) as yellow oils: **1a** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.39 (s, 1H), 5.65-5.57 (m, 2H), 4.27 (d, *J*=8.0 Hz, 1H), 3.74 (s, 3H), 3.42 (br s, 1H), 3.35 (dd, *J*=8.0, 6.0 Hz, 1H), 3.29 (dd, *J*=14.0, 6.5 Hz, 1H), 2.94 (dd, *J*=14.0, 9.0 Hz, 1H), 2.75-2.63 (m, 2H), 2.31-2.11 (m, 4H), 1.64-1.52 (m, 2H), 1.50-1.35 (m, 2H), 1.15-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.1 (d), 170.5 (s), 128.8 (d), 124.4 (d), 120.9 (s), 61.2 (d), 57.8 (d), 55.4 (d), 53.9 (t), 52.5 (q), 50.3 (s), 38.5 (d), 36.3 (t), 34.2 (d), 33.2 (d), 31.7 (t), 28.1 (t), 18.6 (t); IR (film) ν (cm^{-1}) 3016, 2928, 2885, 1725, 1438, 1241, 1204, 1170; MS (ESI) *m*/*z* (rel %) 315 $[MH]^+$ (100), 288 $[M\text{-}CN]^+$ (11), 198 (5); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$ 315.1709, found 315.1714. **1b** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.39 (s, 1H), 5.70-5.59 (m, 2H), 4.31 (br s, 1H), 3.75 (s, 3H), 3.41 (dd, *J*=14.0, 8.5 Hz, 1H), 3.33 (dd, *J*=9.0, 6.0 Hz, 1H), 3.18 (dd, *J*=14.0, 5.5 Hz, 1H), 3.13 (br s, 1H), 2.81-2.74 (m, 1H), 2.55-2.47 (m, 1H), 2.35-2.19 (m, 4H), 1.72-1.45 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 201.2 (d), 169.7 (s), 128.9 (d), 124.9 (d), 117.3 (s), 61.6 (d), 54.7 (d), 52.2 (q), 52.2 (d), 50.3 (s), 49.7 (t), 37.5 (d), 36.4 (t), 34.6 (d), 34.0 (d), 32.6 (t), 28.3 (t), 19.1 (t); IR (film) ν (cm^{-1}) 3016, 2956, 2930, 2889, 1722, 1439, 1203, 1177; MS (ESI) *m*/*z* (rel %) 315 $[MH]^+$ (100), 288 $[M\text{-}CN]^+$ (13), 198 (6); HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$ 315.1709, found 315.1704.

III Synthesis of 28



27

***rel*-(3*S*,4*S*)-3-(3-Hydroxypropyl)-4-propyldihydrofuran-2(3*H*)-one (27).** A solution of **15** (255 mg, 0.930 mmol) and $Pd(OH)_2$ on carbon (20%, 65 mg, 10 mol%) in MeOH (12.5 mL) was stirred under hydrogen atmosphere for 1.5 h. The mixture was filtered on Celite® and concentrated under reduced pressure. The usual purification (60% EtOAc in hexane) afforded **27** (121 mg, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.40 (dd, *J*=9.0, 7.0 Hz, 1H), 3.82 (t, *J*=8.5 Hz, 1H), 3.68 (q, *J*=5.5 Hz, 2H), 2.32-2.18 (m, 2H), 1.83-1.56 (m, 6H), 1.44-1.26 (m, 3H), 0.94 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 179.8 (s), 71.7 (t), 61.9 (t), 44.9 (d), 40.6 (d), 34.7 (t), 29.5 (t), 25.2 (t), 20.1 (t), 13.9 (q); IR (film) ν (cm^{-1}) 3621-3188, 2957, 2931, 2872, 1769, 1183, 1164, 1057, 1016; MS (CI:NH_3) *m*/*z* (rel %) 187 $[MH]^+$ (100), 169 (67), 125 (20); HRMS (CI:NH_3) calcd for $C_{10}H_{19}O_3$ $[MH]^+$ 187.1334, found 187.1338.



28

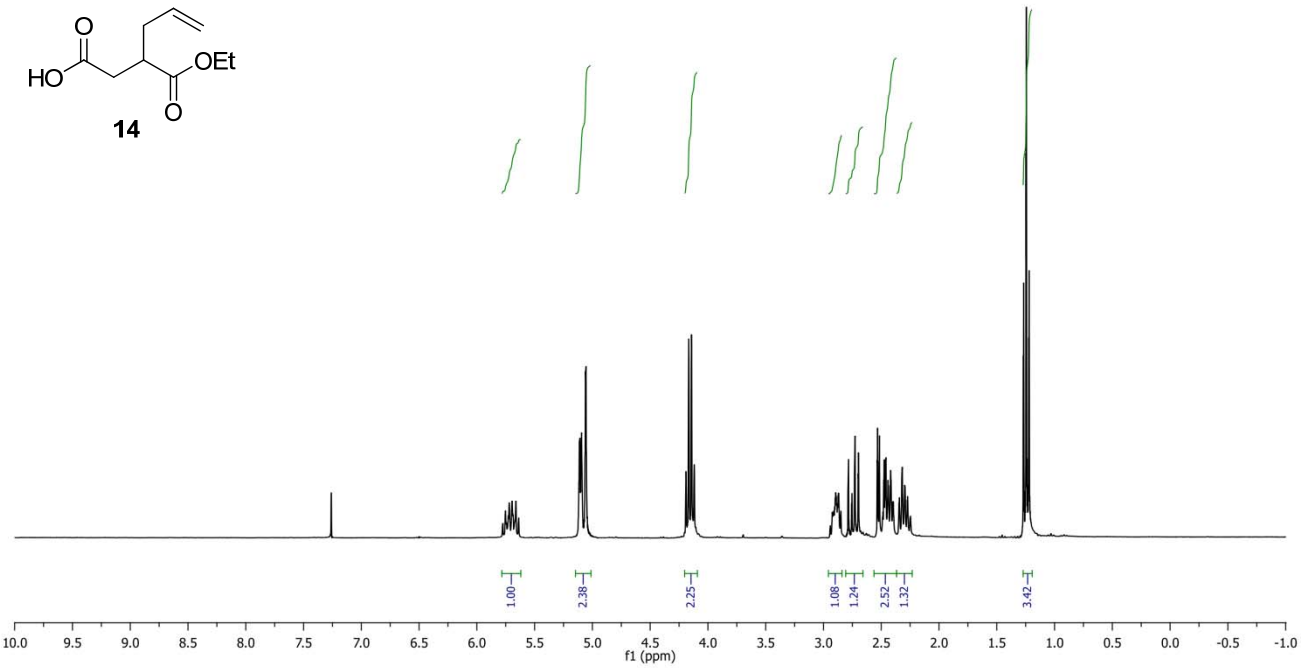
3-(*rel*-(3S,4S)-2-Oxo-4-propyltetrahydrofuran-3-yl)propyl 4-bromobenzoate (28). 4-Bromobenzoyl chloride (113 mg, 0.516 mmol) and *N*,*N*-dimethyl-4-aminopyridine (3.2 mg, 0.03mmol) was added to a solution of **27** (107 mg, 0.568 mmol) and Et_3N (79 μL, 0.568 mmol) in DCM (19 mL). The solution was stirred for 18 h at rt then saturated aqueous $NaHCO_3$ was added. The usual work-up (DCM) and

purification (20% EtOAc in hexane) afforded **28** (149 mg, 78%) as white crystals[7]: m.p.=46-48 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.90 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.5 Hz, 2H), 4.40 (dd, *J*=9.0, 7.0 Hz, 1H), 4.35 (t, *J*=6.0 Hz, 2H), 3.82 (t, *J*=8.5, Hz, 1H), 2.31-2.20 (m, 2H), 2.11-2.00 (m, 1H), 1.95-1.73 (m, 3H), 1.68-1.55 (m, 1H), 1.45-1.26 (m, 3H), 0.93 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.7 (s), 165.6 (s), 131.5 (d), 130.9 (d), 128.9 (s), 127.8 (s), 71.4 (t), 64.6 (t), 44.6 (d), 40.7 (d), 34.7 (t), 25.7 (t), 25.6 (t), 20.2 (t), 14.0 (q); IR (film) ν (cm^{-1}) 2959, 2933, 2914, 2872, 1773, 1720, 1590, 1272, 1102, 1011; MS (EI) *m*/*z* (rel %) 370 $[M]^+$ (2, ^{81}Br), 368 $[M]^+$ (2, ^{79}Br), 202 (8, ^{81}Br), 200 (8, ^{79}Br), 185 (100); HRMS (EI) calcd for $C_{17}H_{21}{}^{79}BrO_4$ $[M]^+$ 368.0623, found 368.0615.

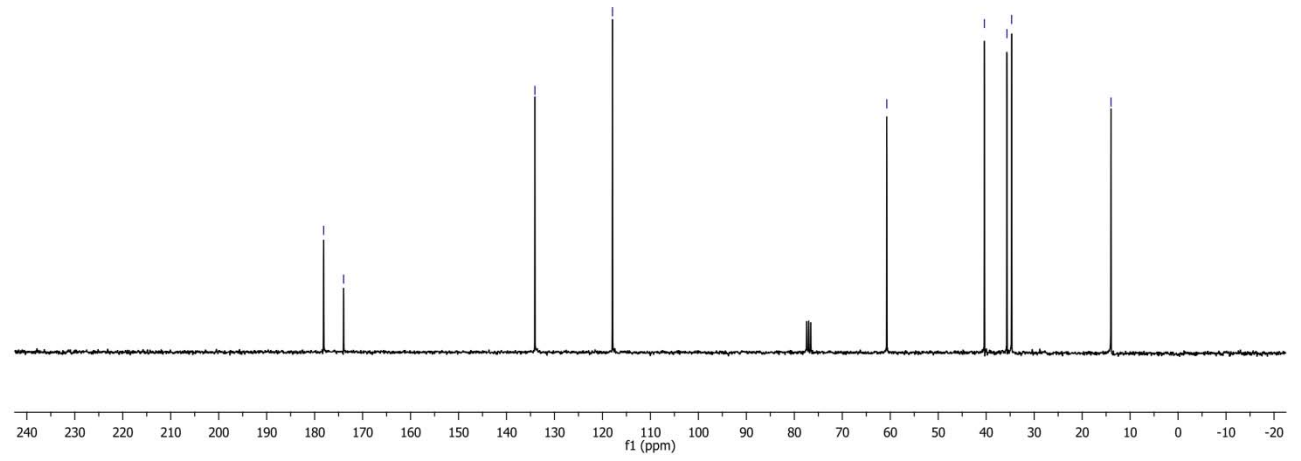
IV ^{1}H and ^{13}C NMR Spectra for Compounds 1a, 1b, 3-6, 14-25, 27, and 28

3-(Ethoxycarbonyl)hex-5-enoic acid (14)

^{1}H NMR spectrum

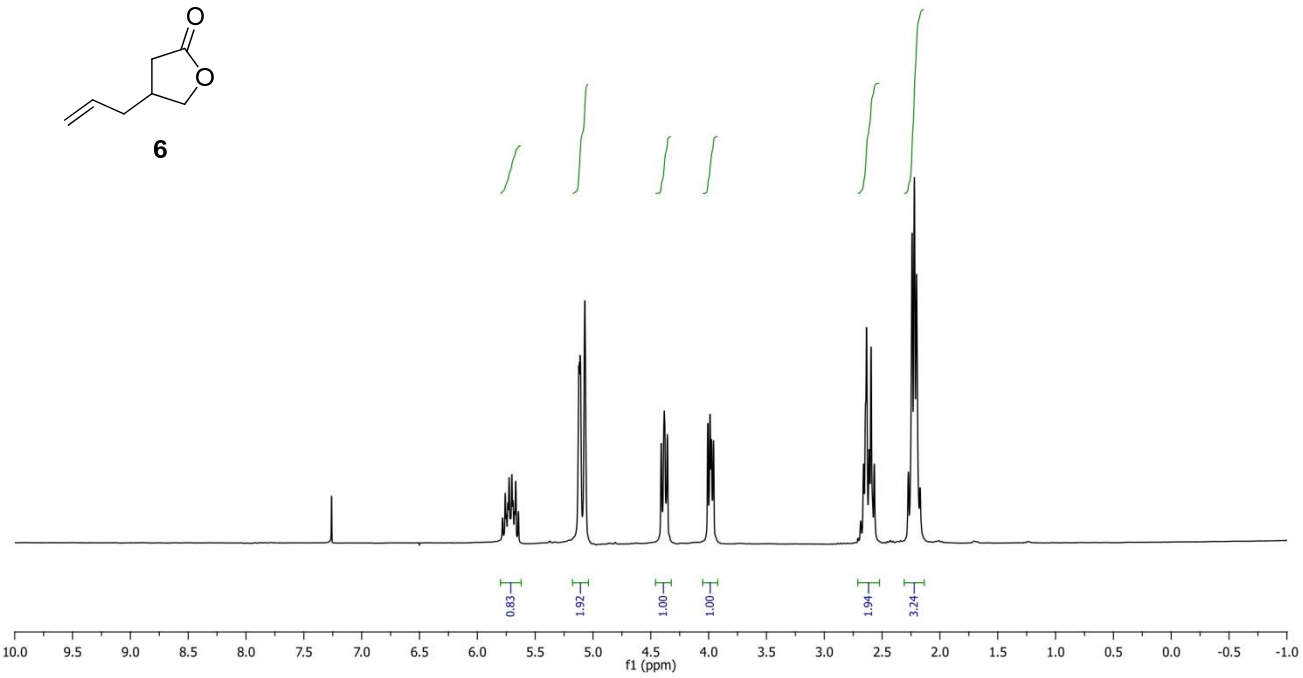


^{13}C NMR spectrum

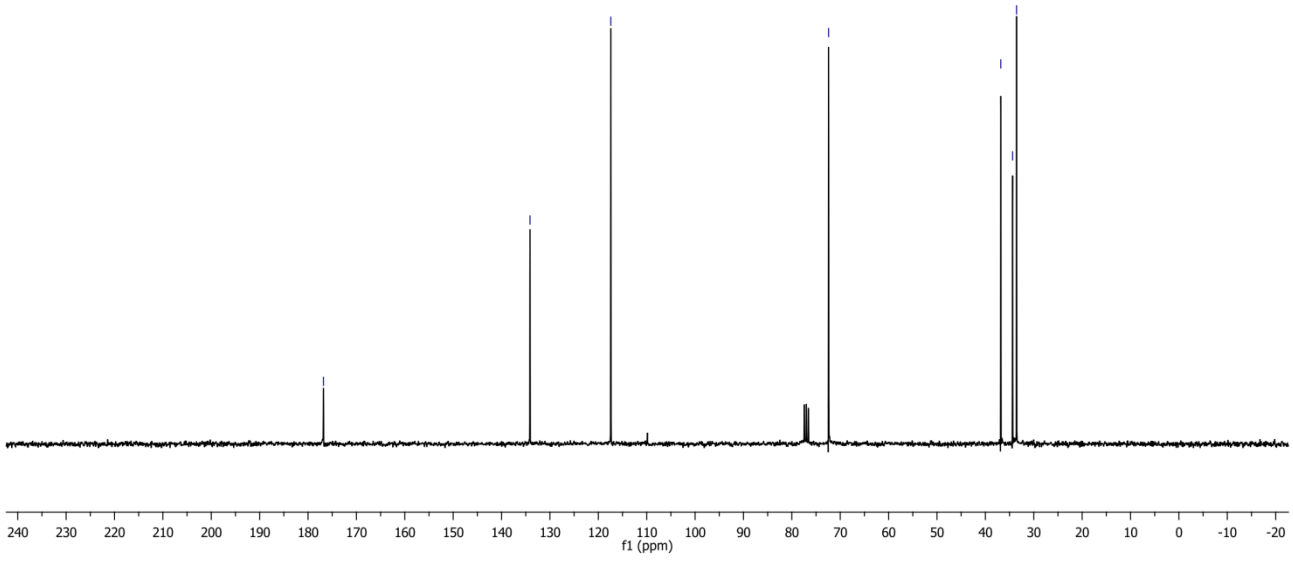


4-Allyldihydrofuran-2(3*H*)-one (6)

^{1}H NMR spectrum

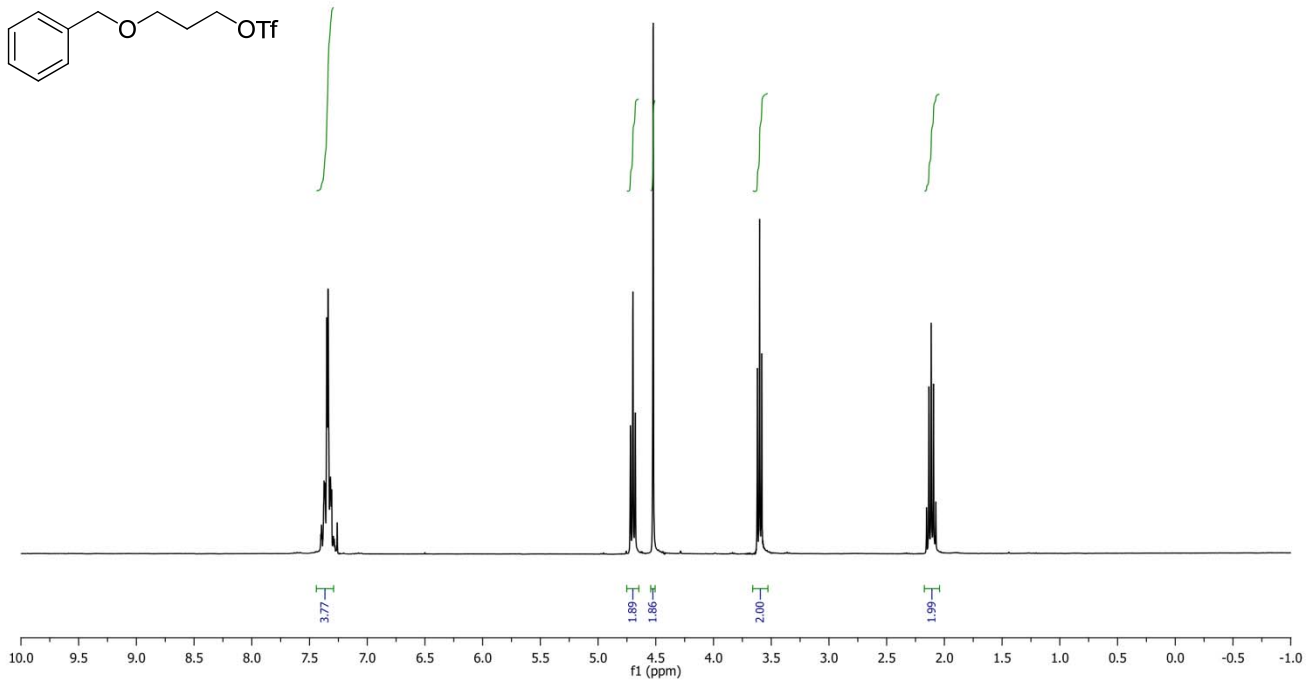


^{13}C NMR spectrum

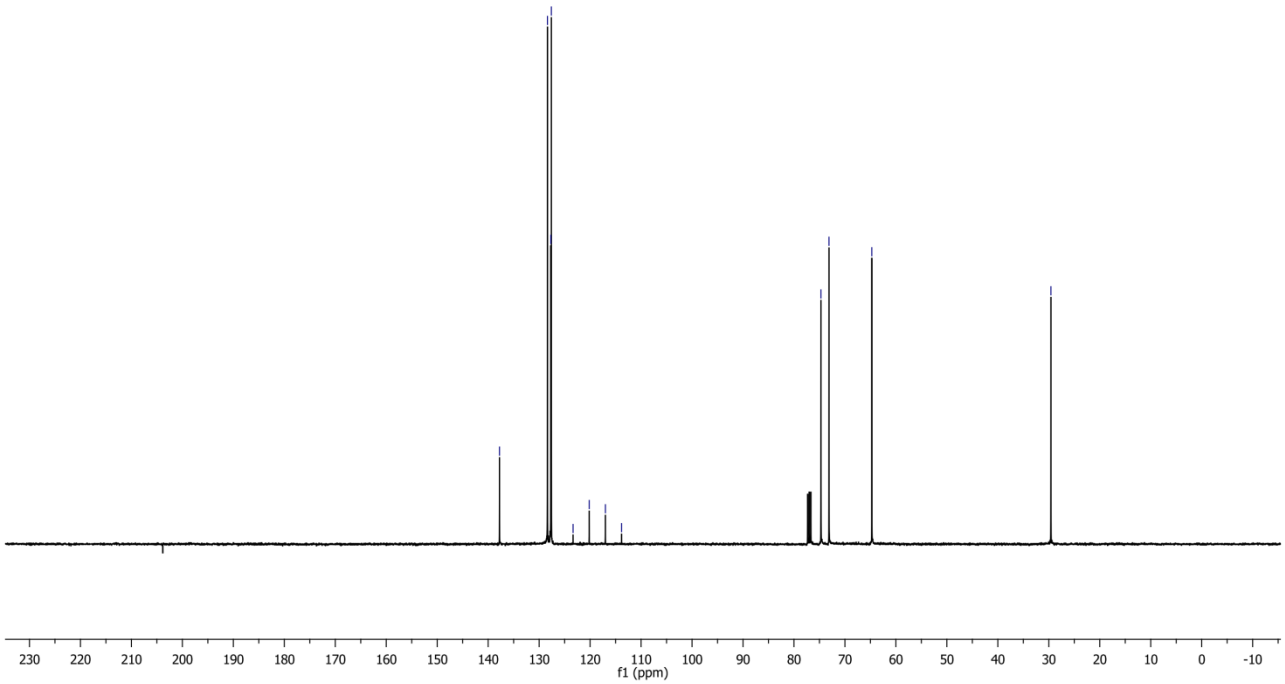


3-(Benzyloxy)propyl trifluoromethanesulfonate

^{1}H NMR spectrum

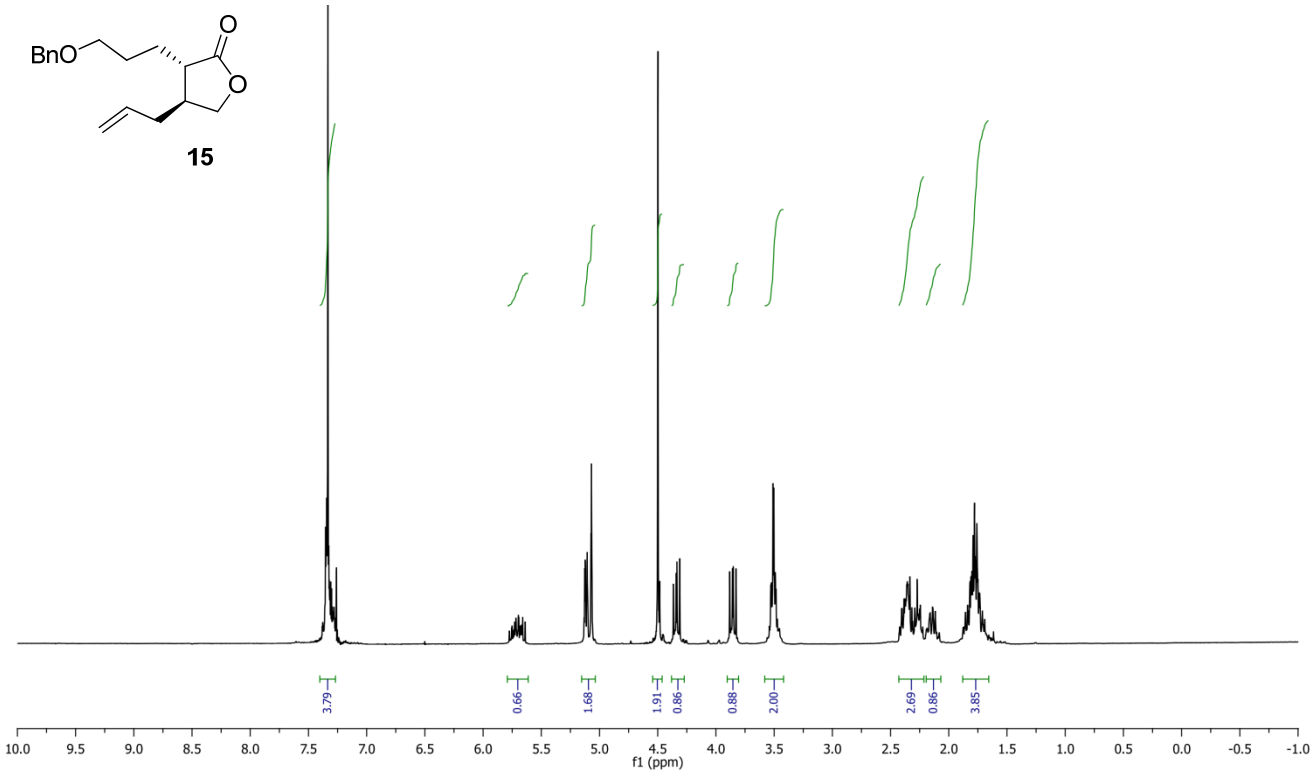


^{13}C NMR spectrum

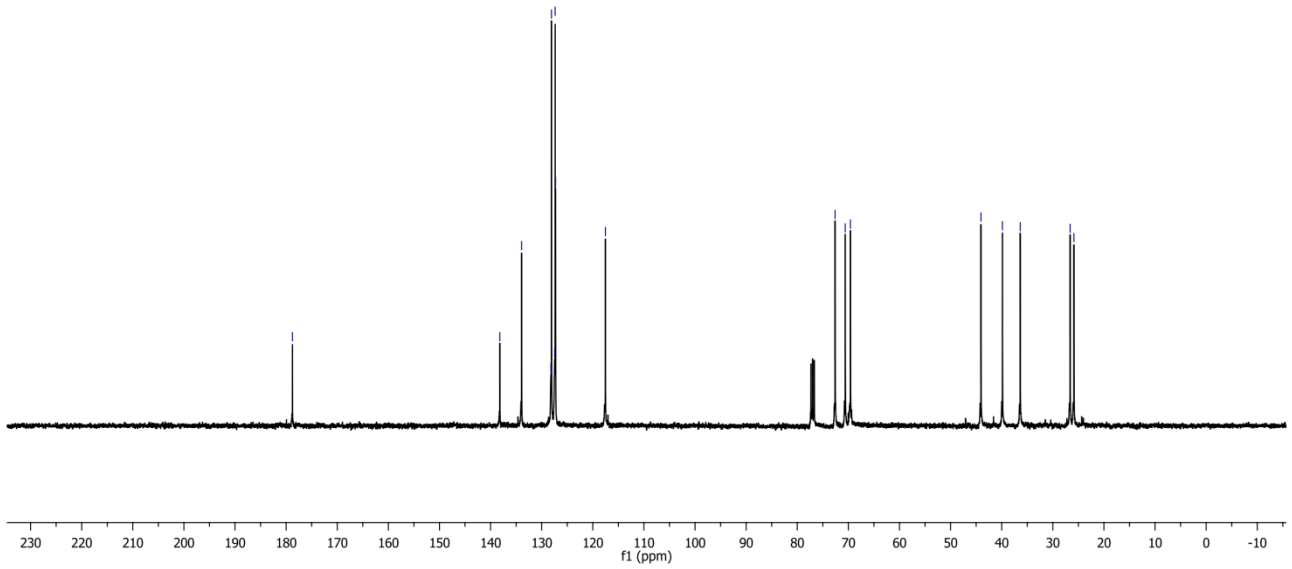


***rel*-(3*S*,4*S*)-4-Allyl-3-(3-benzyloxypropyl)dihydrofuran-2(3*H*)-one (15)**

^{1}H NMR spectrum

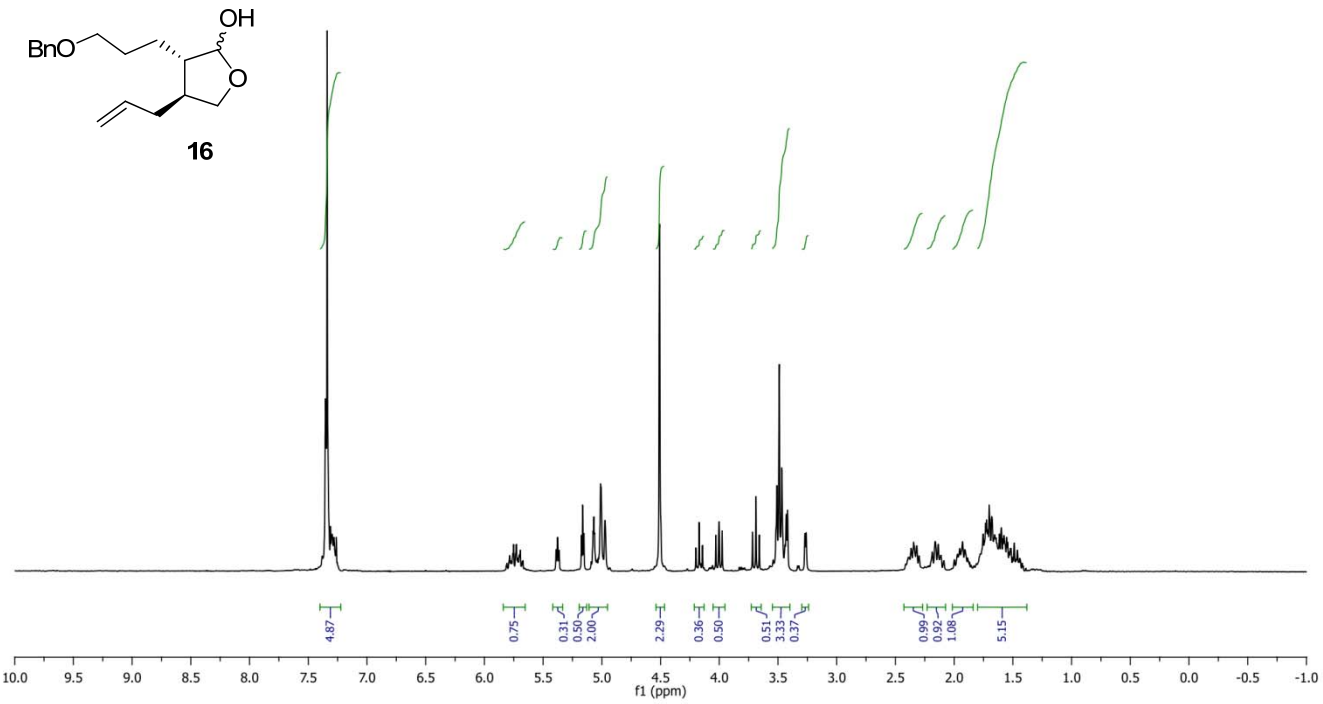


^{13}C NMR spectrum

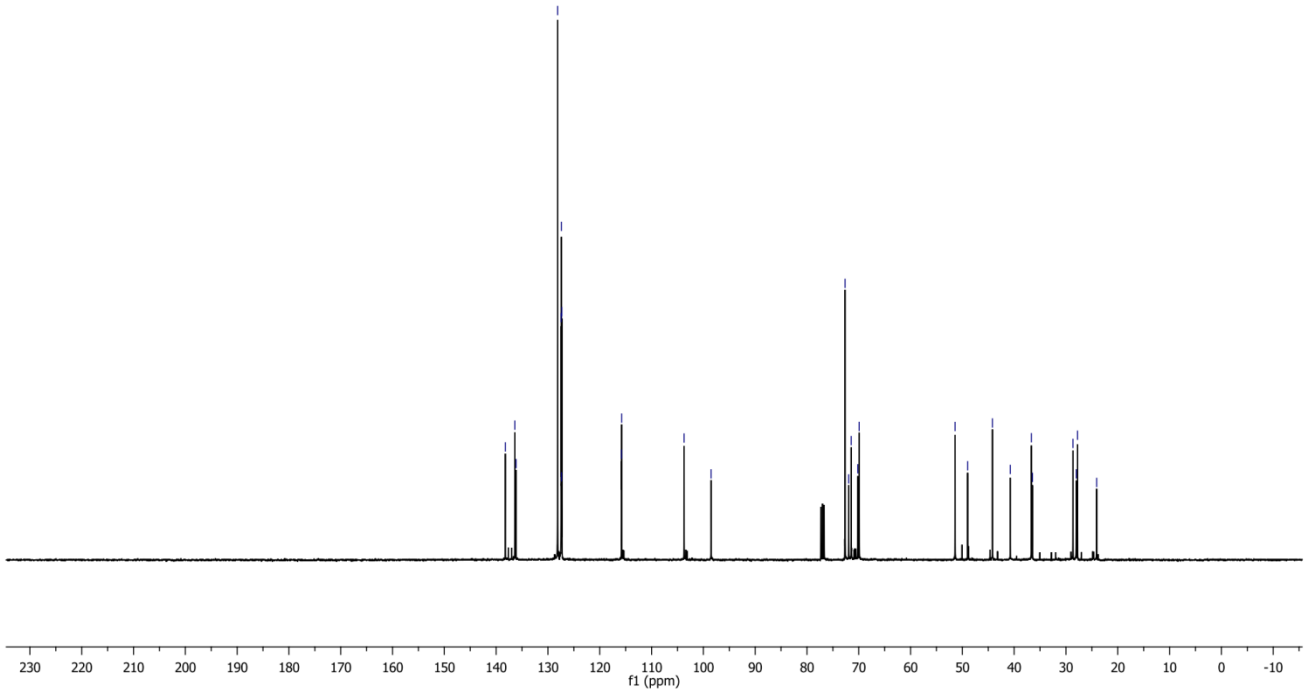


***rel*-(3*S*,4*S*)-4-Allyl-3-(3-benzyloxypropyl)tetrahydrofuran-2-ol (16)**

^{1}H NMR spectrum

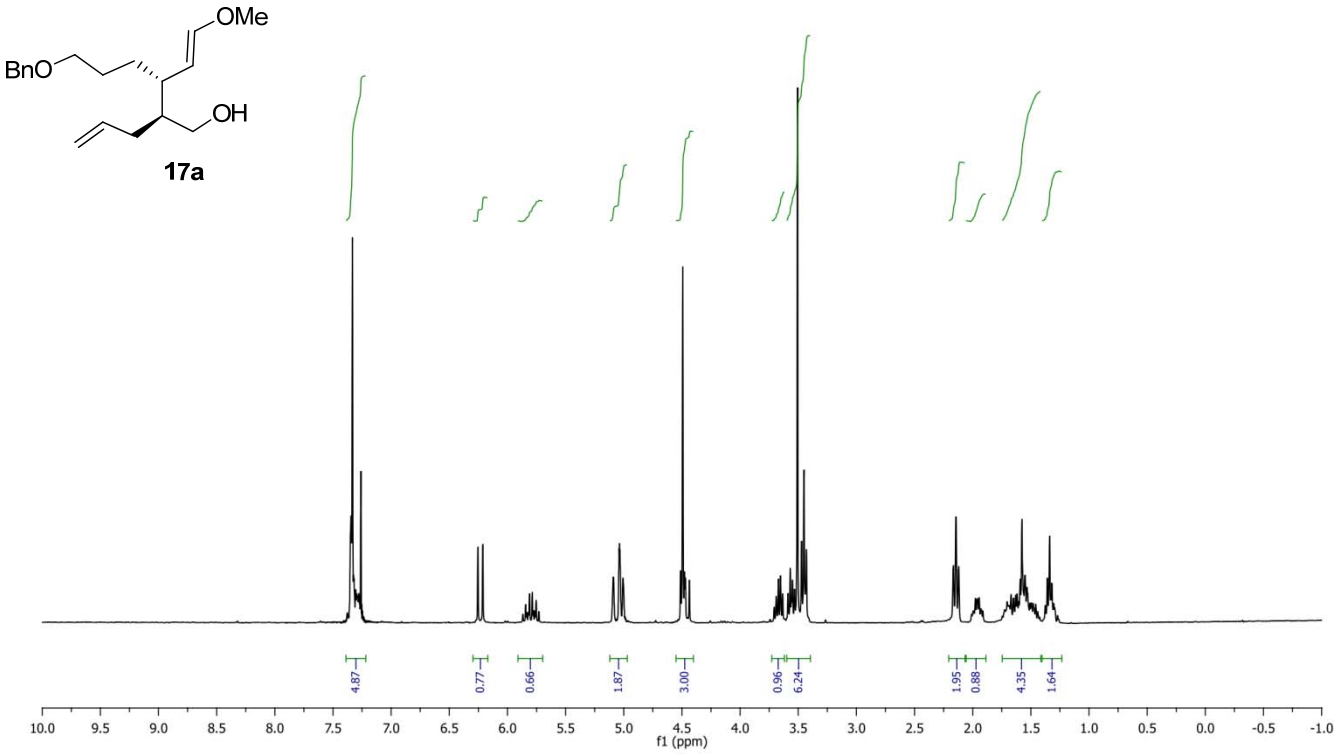


^{13}C NMR spectrum

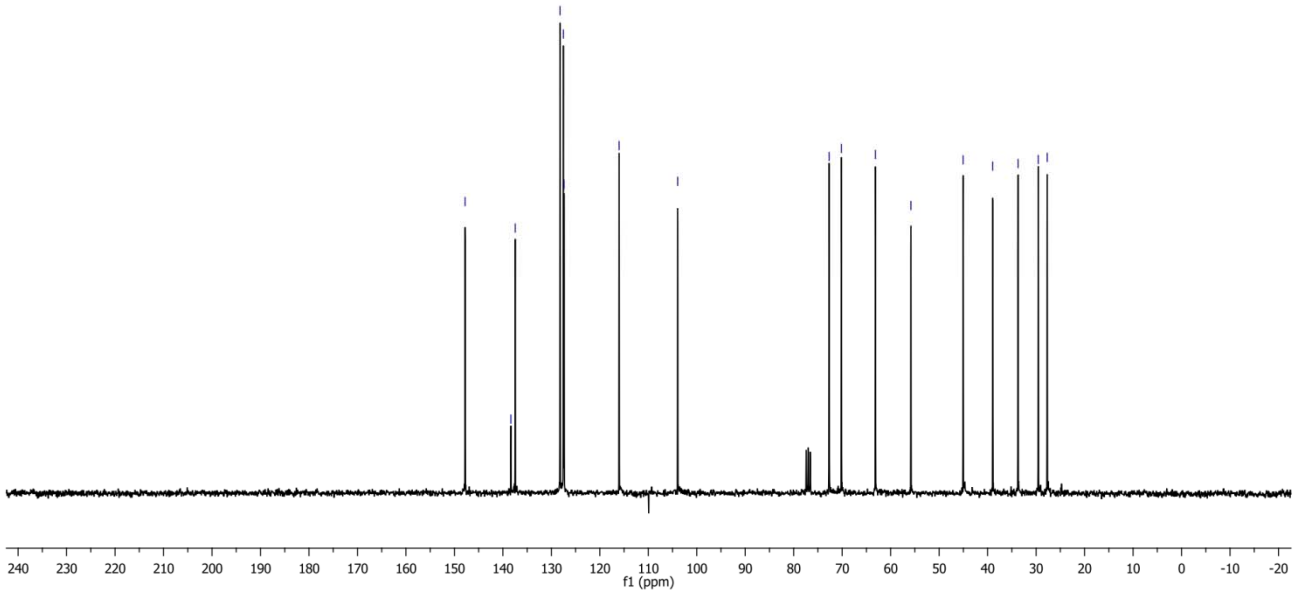


***rel*-(2*S*,3*S*)-2-Allyl-6-(benzyloxy)-3-((*E*)-2-methoxyvinyl)hexan-1-ol (17a)**

^{1}H NMR spectrum

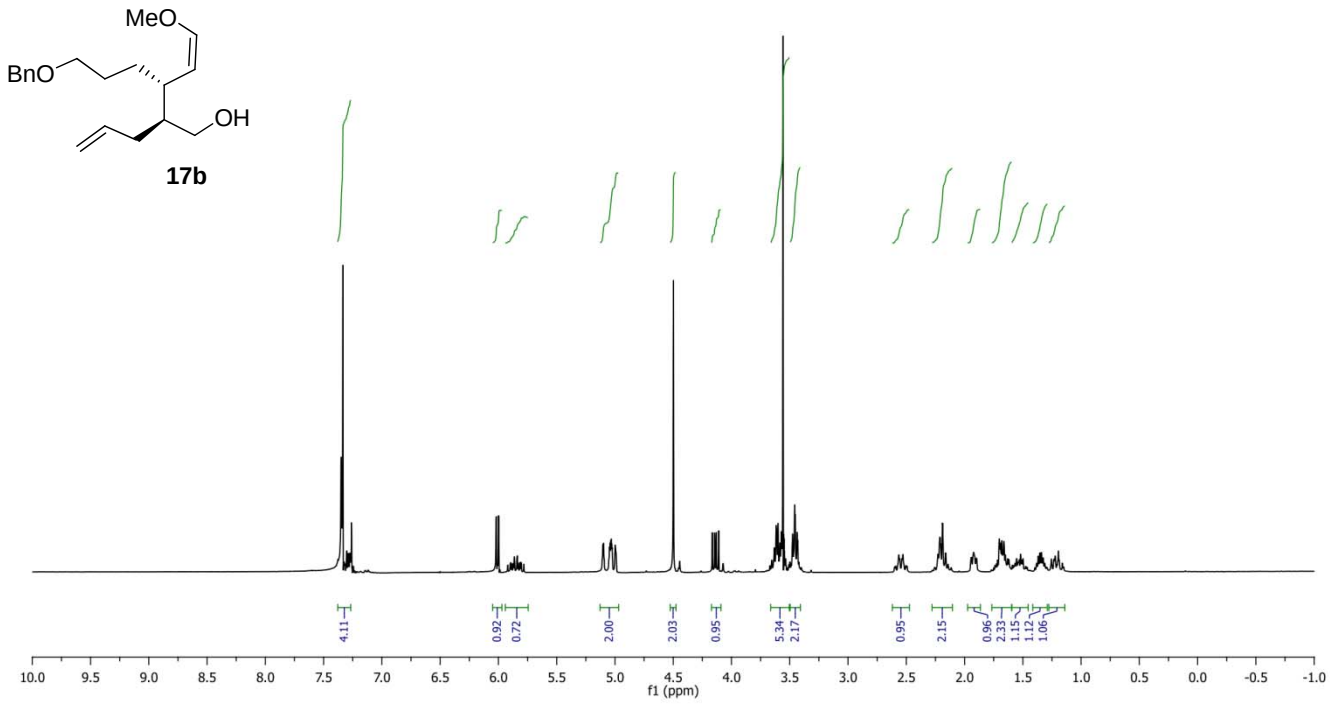


^{13}C NMR spectrum

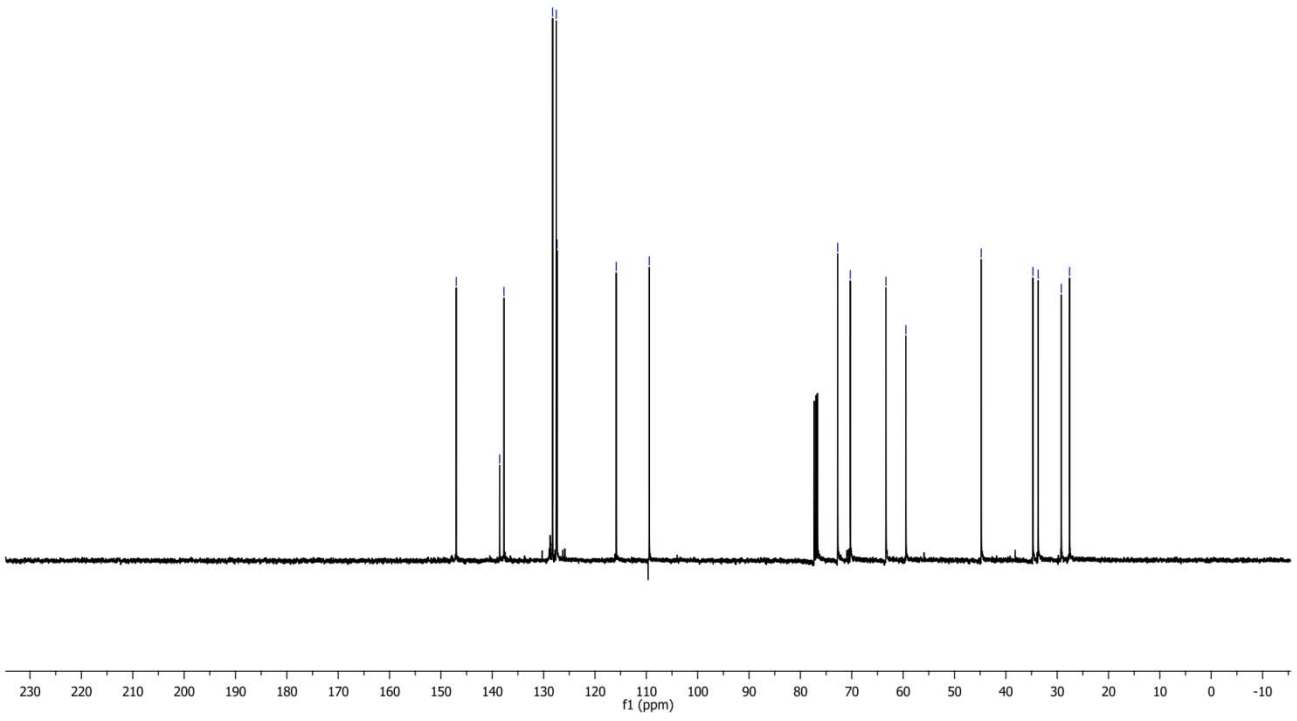


***rel*-(2*S*,3*S*)-2-Allyl-6-(benzyloxy)-3-((*Z*)-2-methoxyvinyl)hexan-1-ol (17b)**

^{1}H NMR spectrum

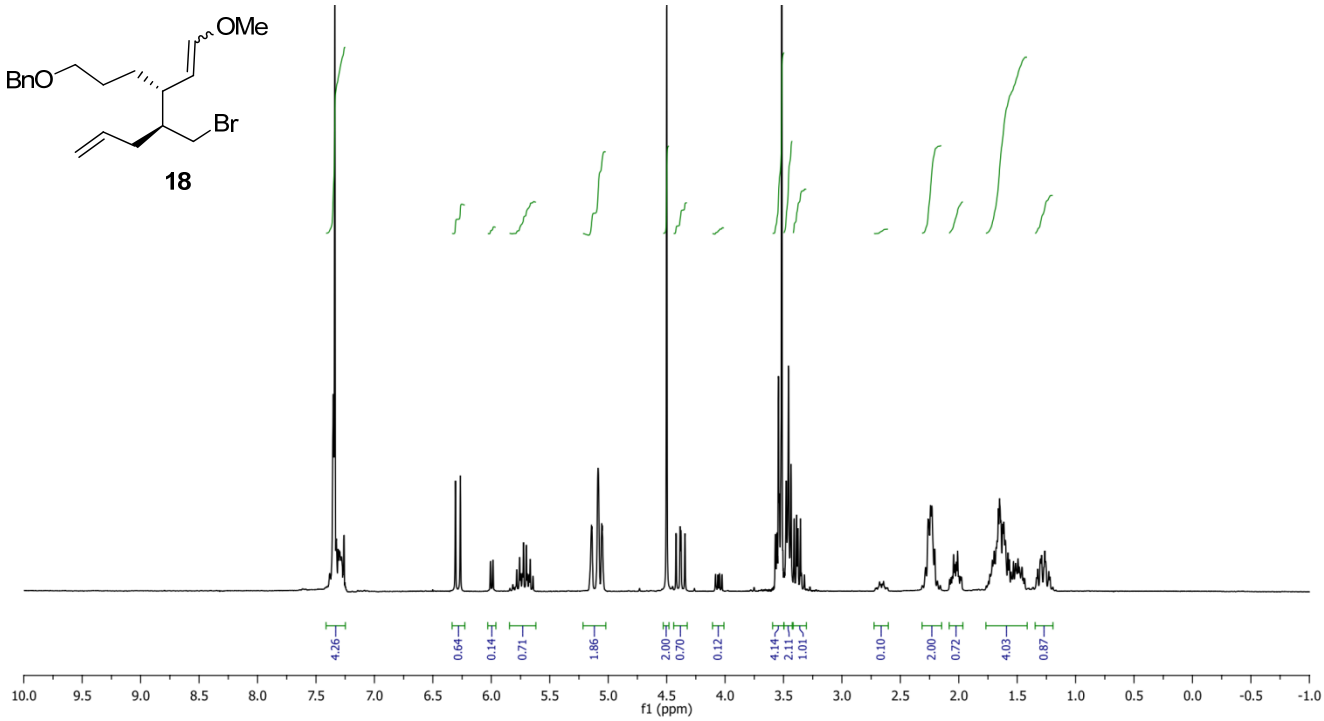


^{13}C NMR spectrum

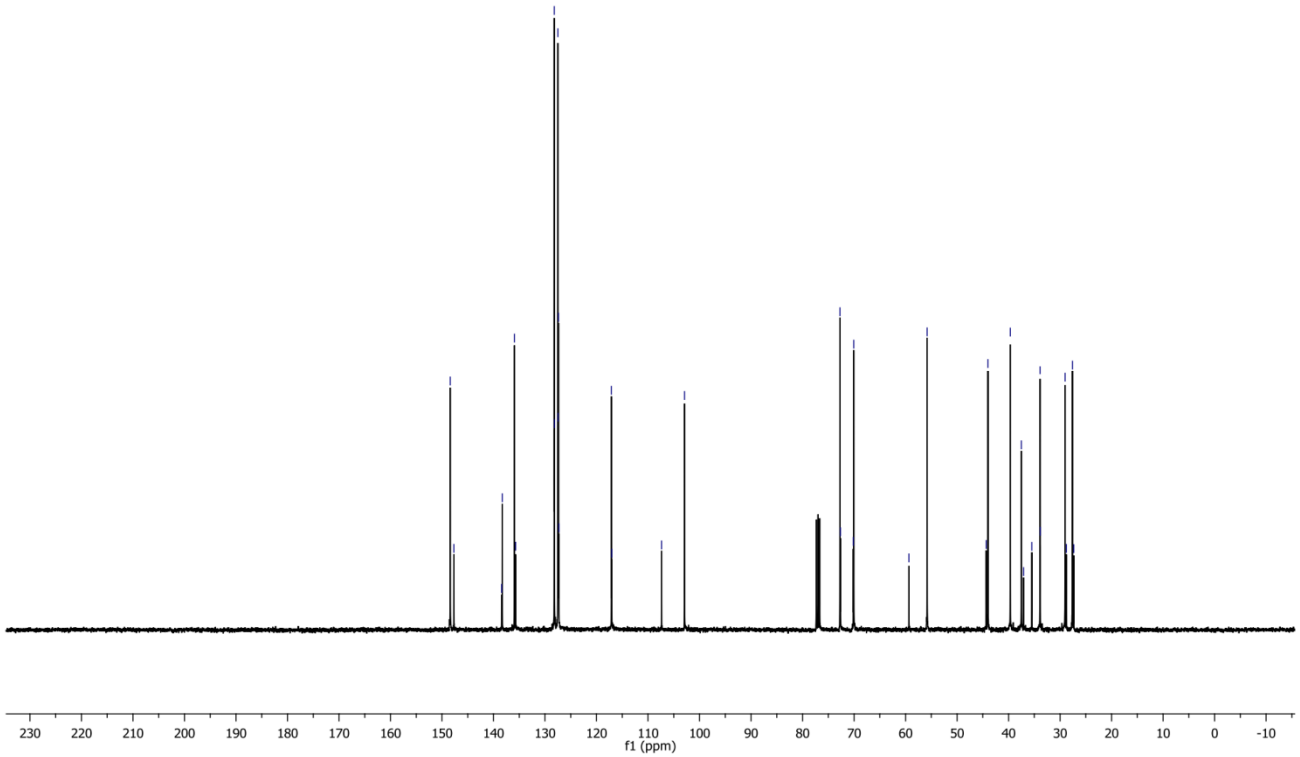


***rel*-(4*R*,5*S*)-1-Benzyloxy-5-(bromomethyl)-4-(2-methoxyvinyl)oct-7-ene (18)**

^{1}H NMR spectrum

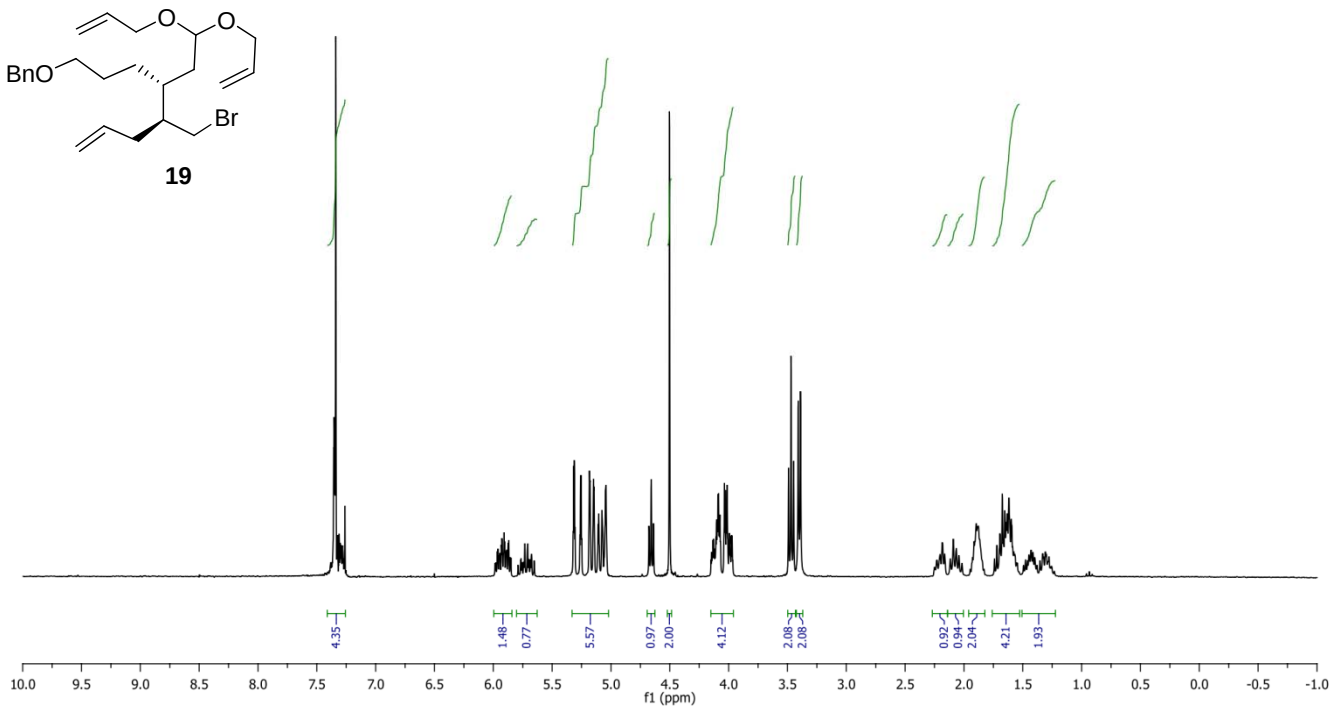


^{13}C NMR spectrum



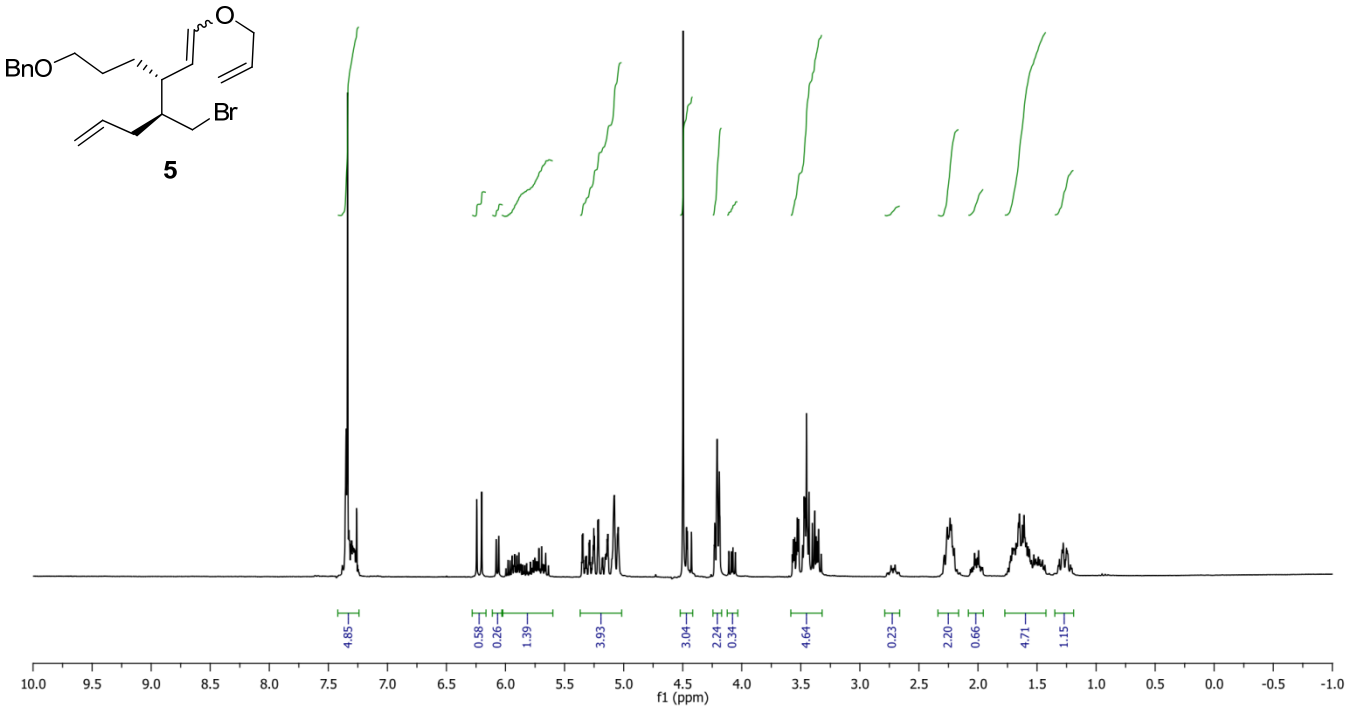
***rel*-(4*R*,5*S*)-4-(2,2-bis(Allyloxy)ethyl)-1-benzyloxy-5-(bromomethyl)-)oct-7-ene (19)**

^{1}H NMR spectrum

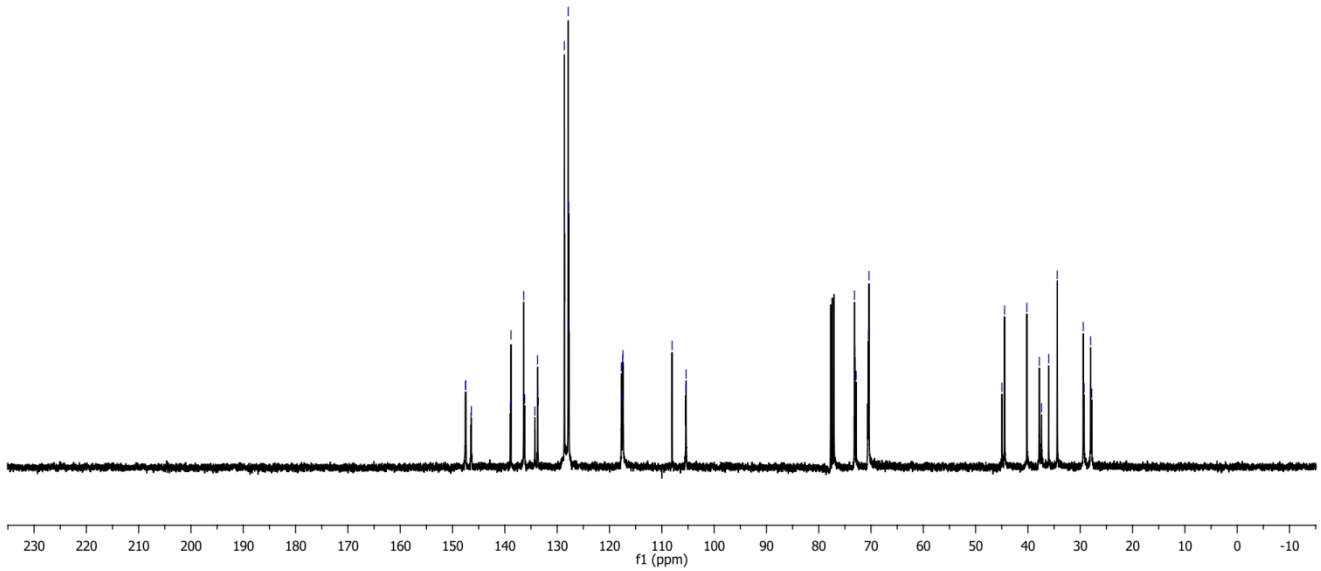


***rel-(4R,5S)*-1-Benzyloxy-4-(2-(allyloxy)vinyl)-5-(bromomethyl)oct-7-ene (5)**

^{1}H NMR spectrum

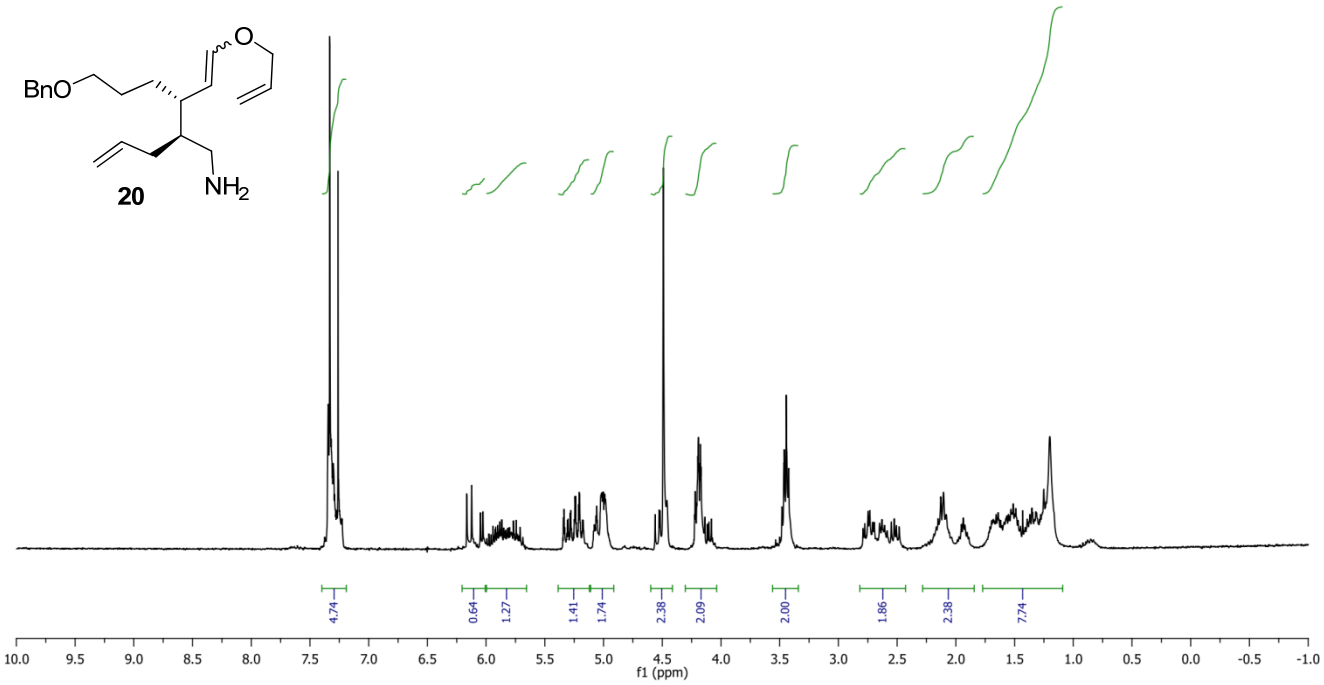


^{13}C NMR spectrum



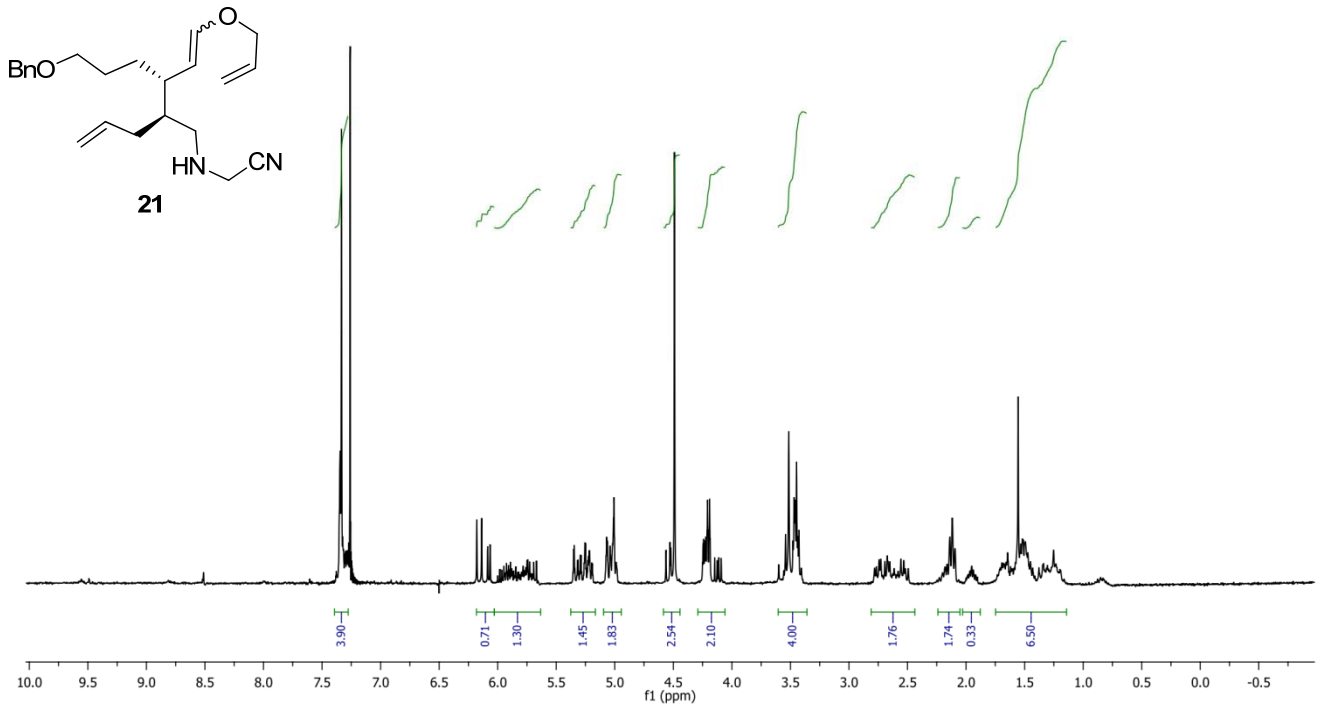
***rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)hexan-1-amine (20)**

^{1}H NMR spectrum



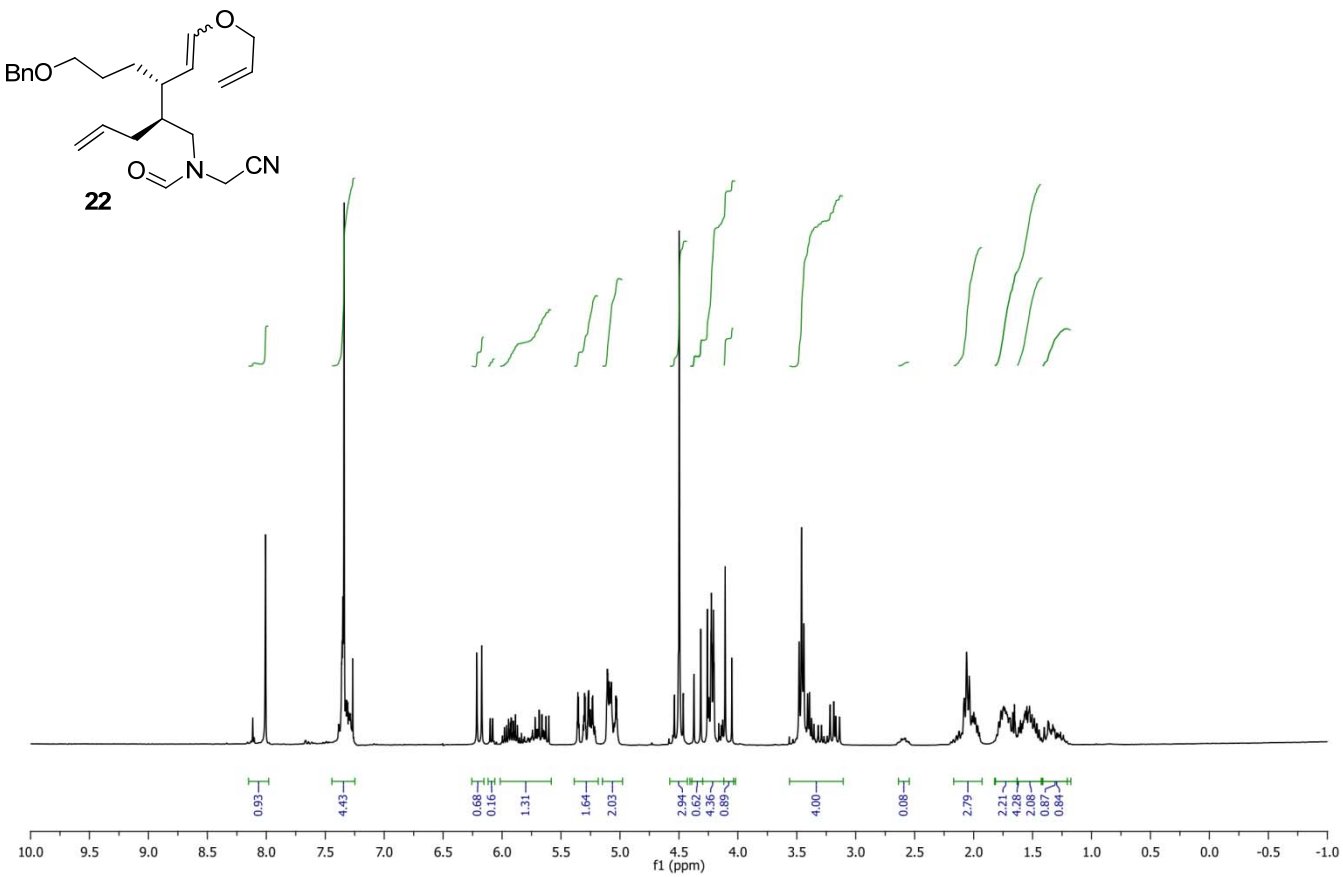
2-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)hexylamino)acetonitrile (21)

^{1}H NMR spectrum

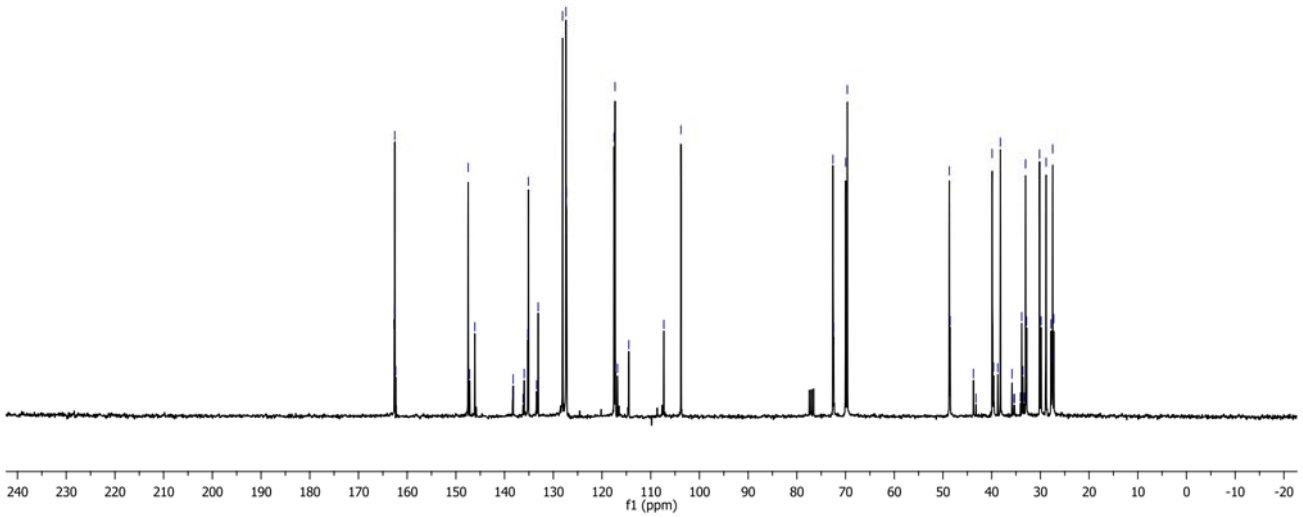


***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(2-(allyloxy)vinyl)-6-(benzyloxy)hexyl)-*N*-(cyanomethyl)formamide (22)**

^{1}H NMR spectrum



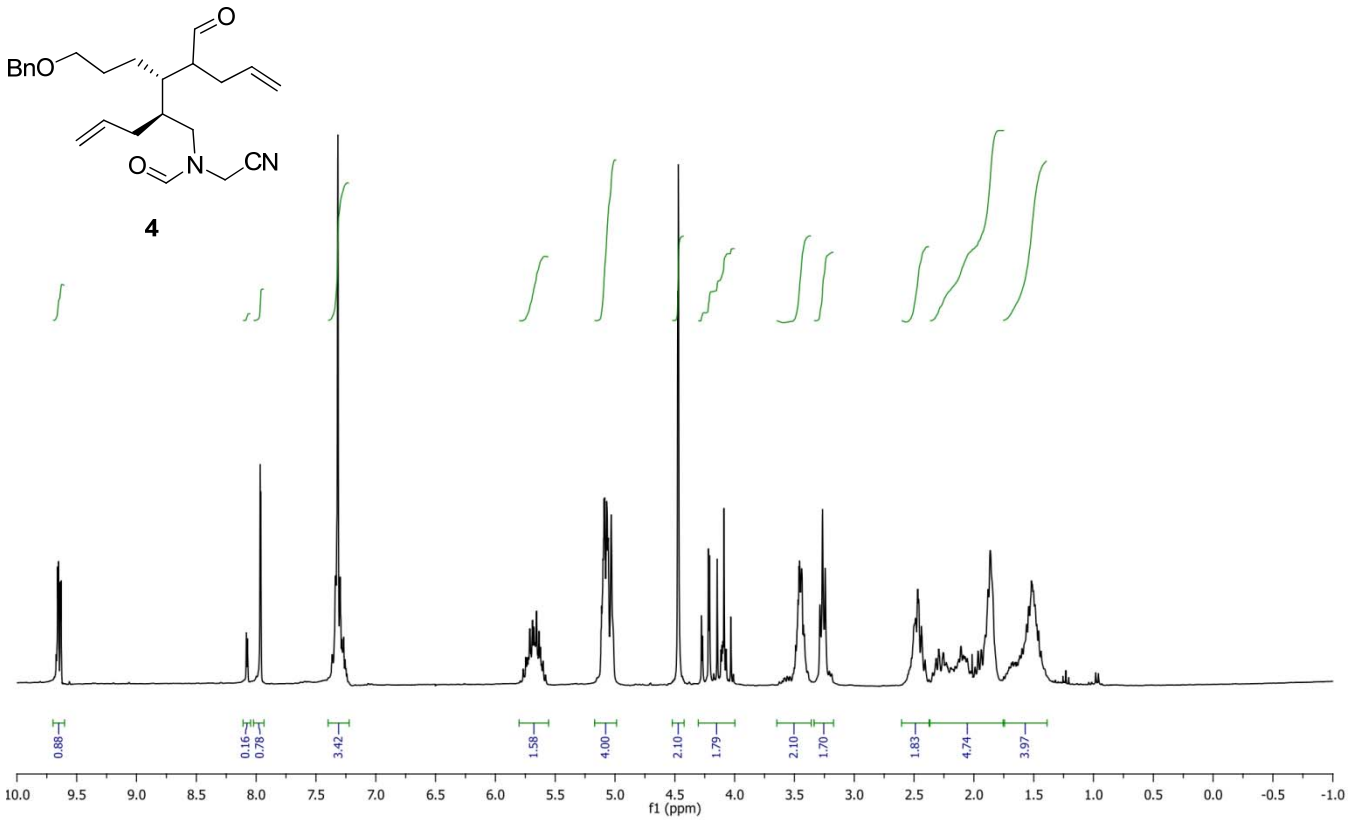
^{13}C NMR spectrum



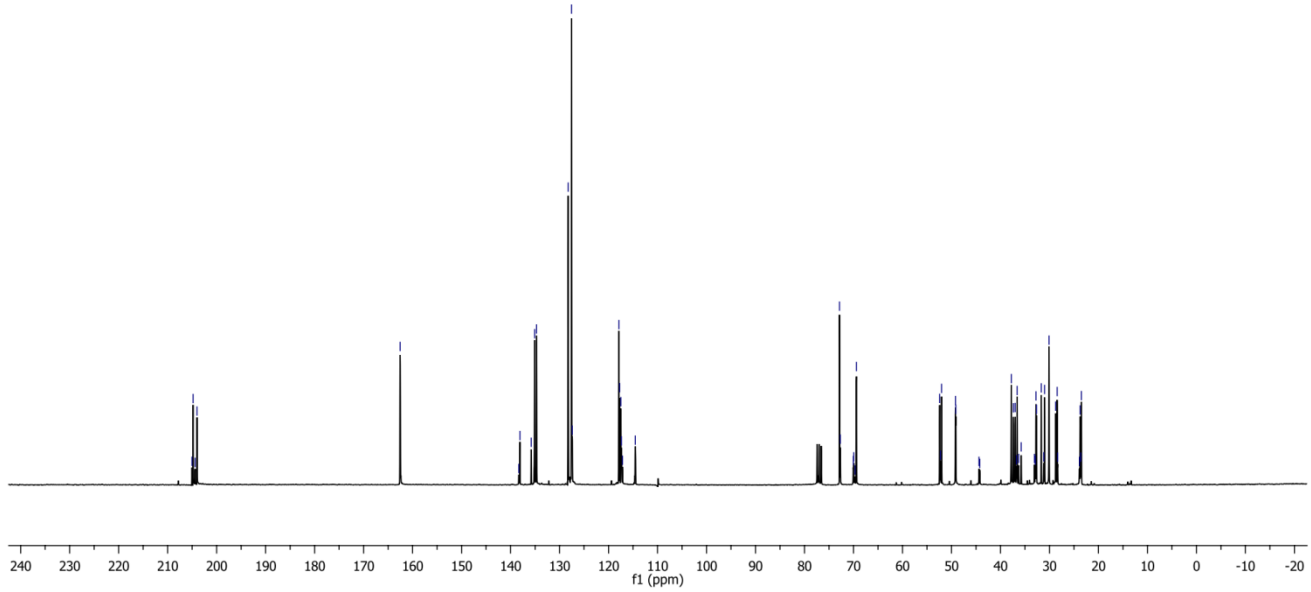
***N*-(*rel*-(2*S*,3*S*)-2-Allyl-3-(3-(benzyloxy)propyl)-4-formylhept-6-enyl)-*N*-(cyanomethyl)formamide**

(4)

^{1}H NMR spectrum

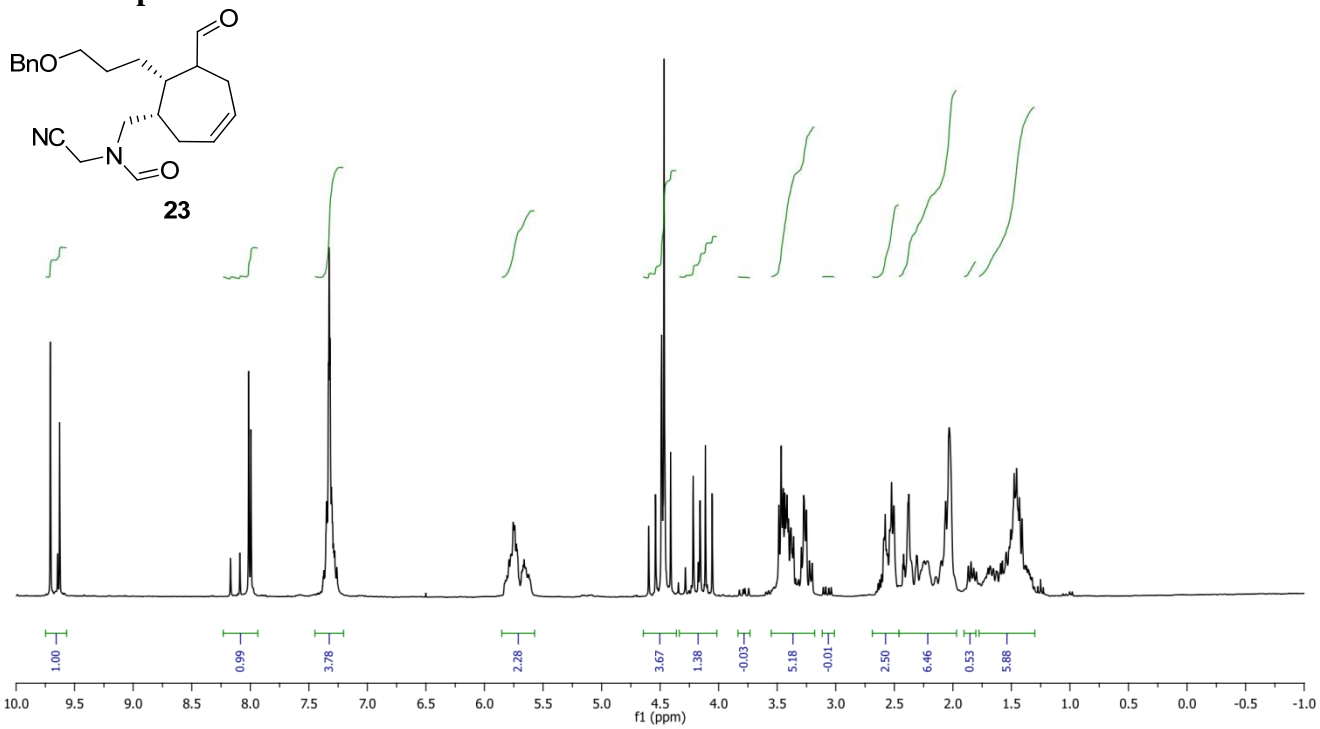


^{13}C NMR spectrum

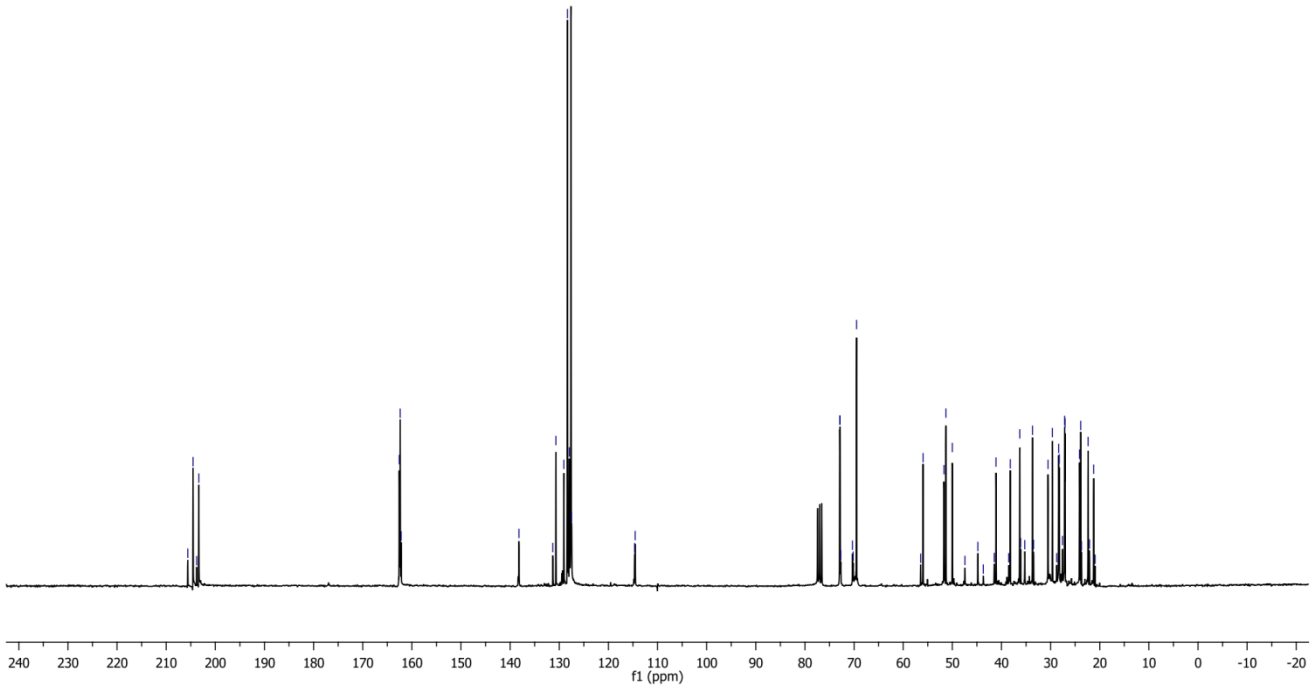


***N*-((*rel*-(1*S*,7*S*)-7-(3-(Benzyloxy)propyl)-6-formylcyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (23)**

^{1}H NMR spectrum

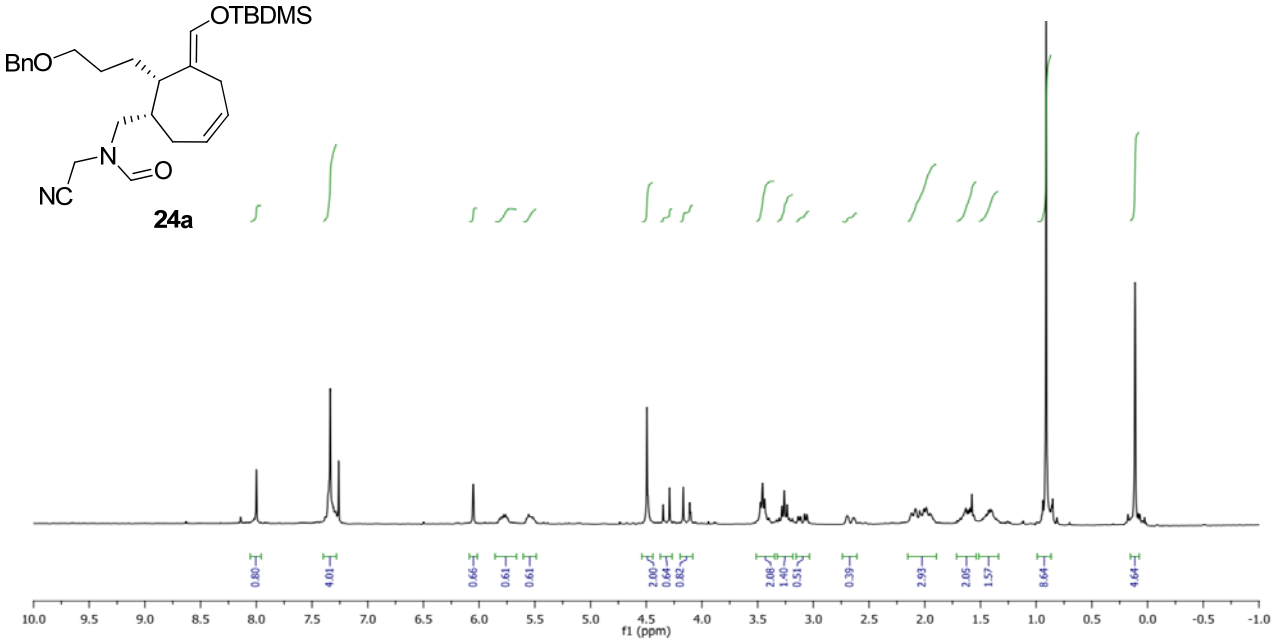


^{13}C NMR spectrum



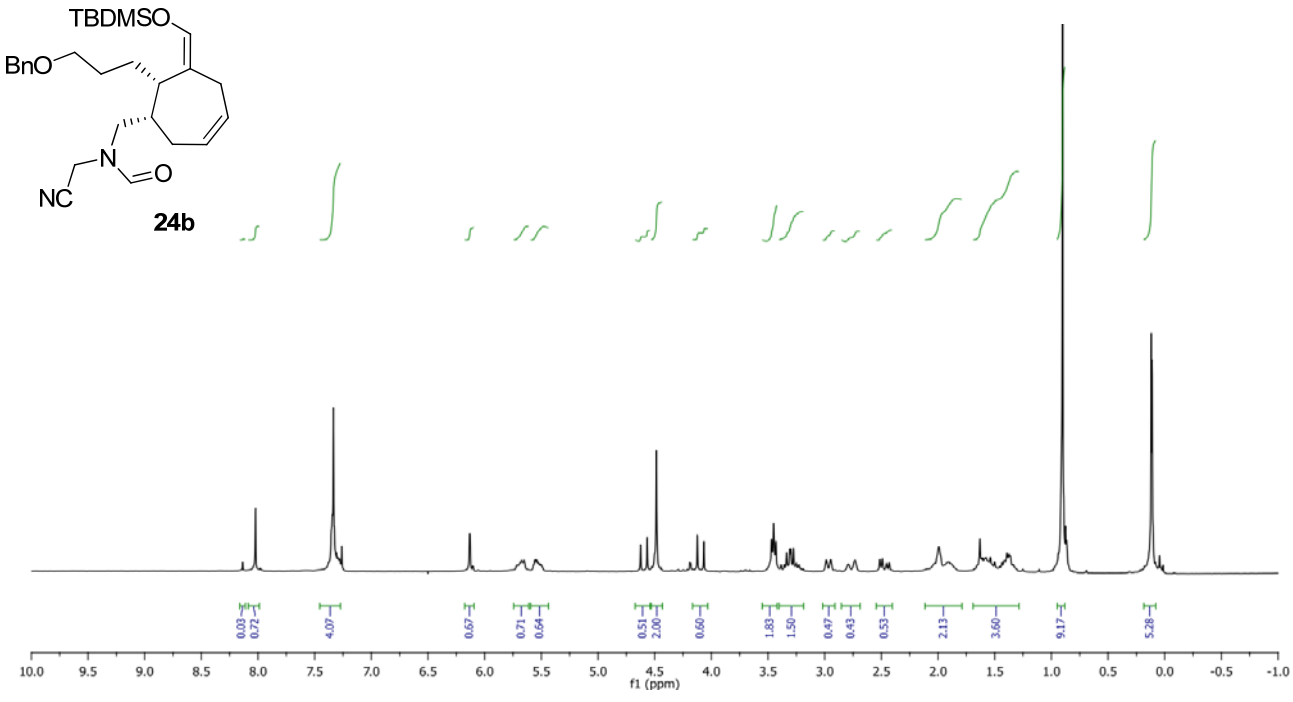
***N*-((*rel*-(1*S*,7*S*,*E*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (24a)**

^{1}H NMR spectrum



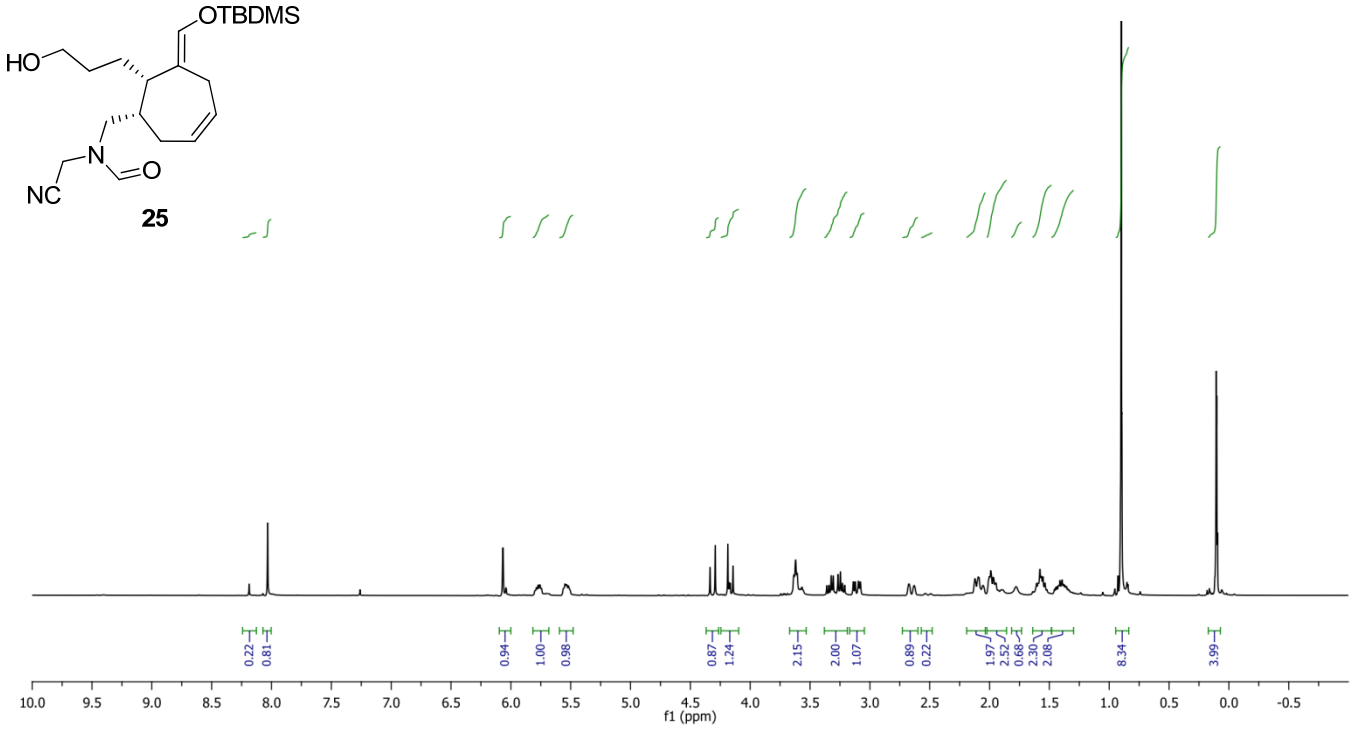
***N*-(((1*S*,7*S*,*Z*)-7-(3-(Benzyloxy)propyl)-6-((*tert*-butyldimethylsilyloxy)methylene)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (24b)**

^{1}H NMR spectrum

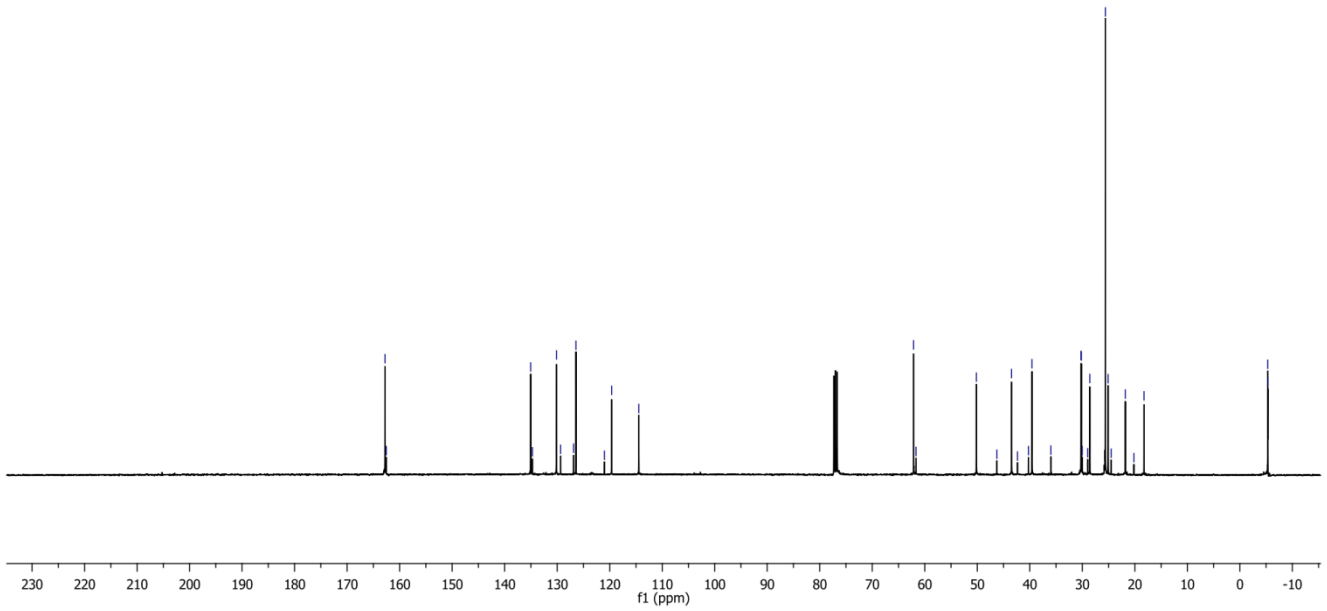


***N*-((*rel*-(1*S*,7*S*,*E*)-6-((*tert*-Butyldimethylsilyloxy)methylene)-7-(3-hydroxypropyl)cyclohept-3-enyl)methyl)-*N*-(cyanomethyl)formamide (25)**

^{1}H NMR spectrum

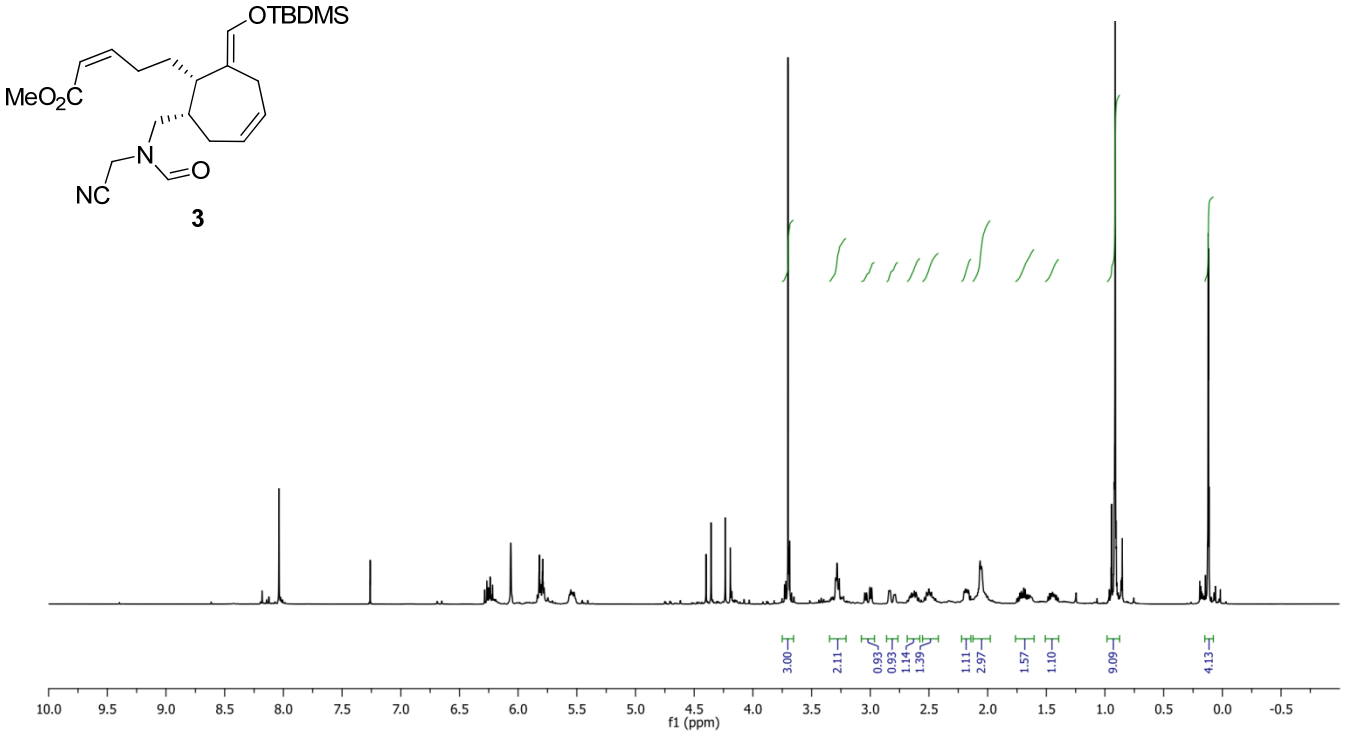


^{13}C NMR spectrum

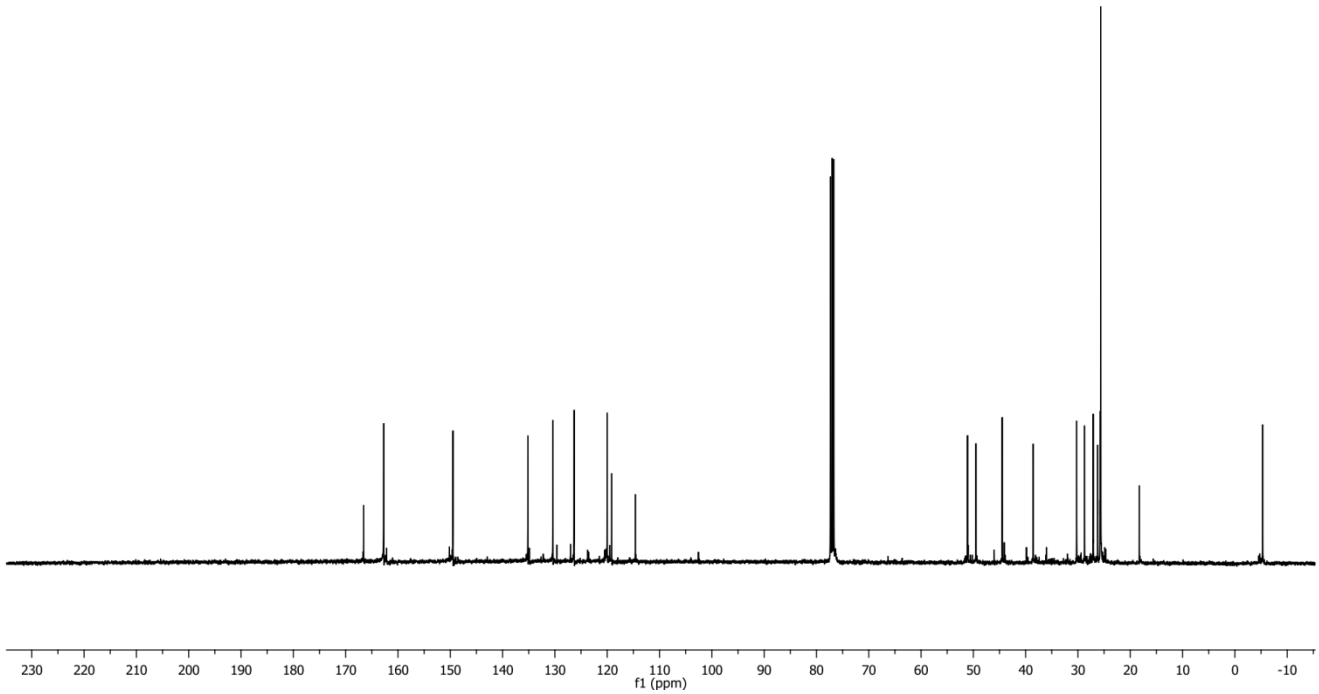


(*Z*)-Methyl 5-(*rel*-(1*S*,7*S*,*E*)-2-((*tert*-butyldimethylsilyloxy)methylene)-7-((*N*-(cyanomethyl)formamido)methyl)cyclohept-4-enyl)pent-2-enoate (3)

^{1}H NMR spectrum

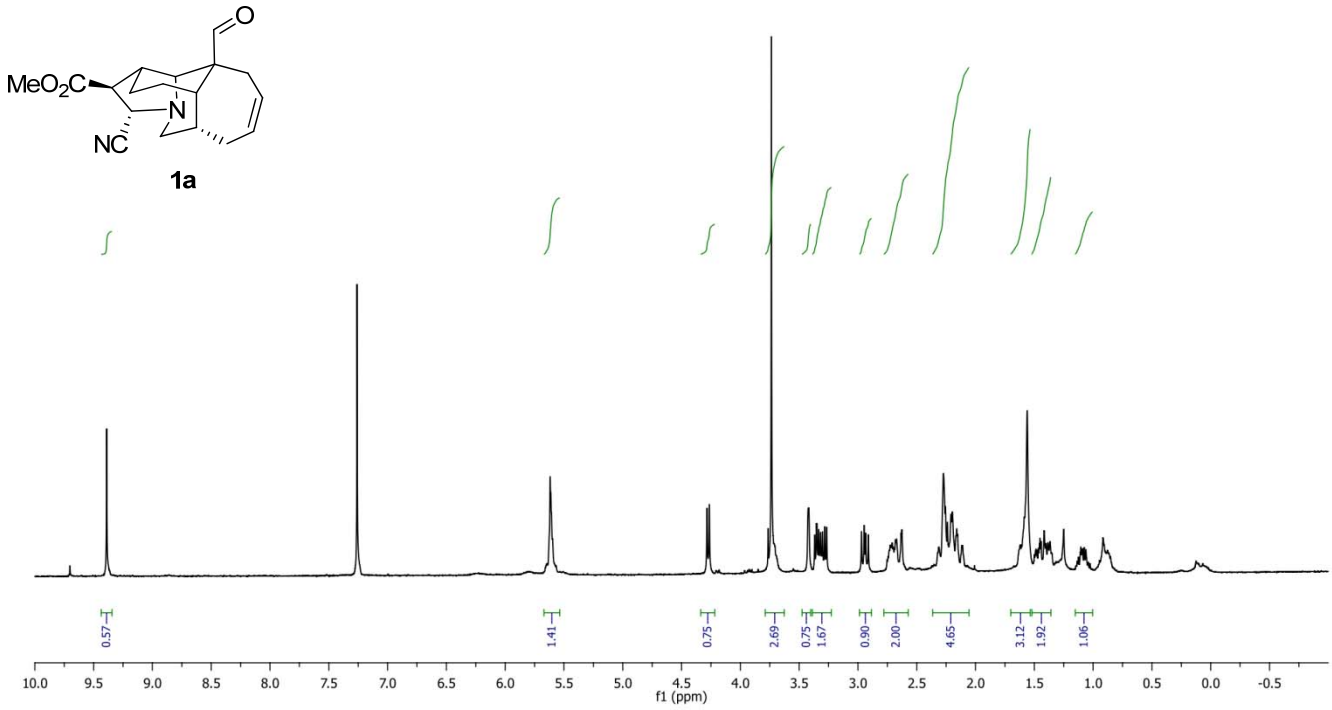


^{13}C NMR spectrum

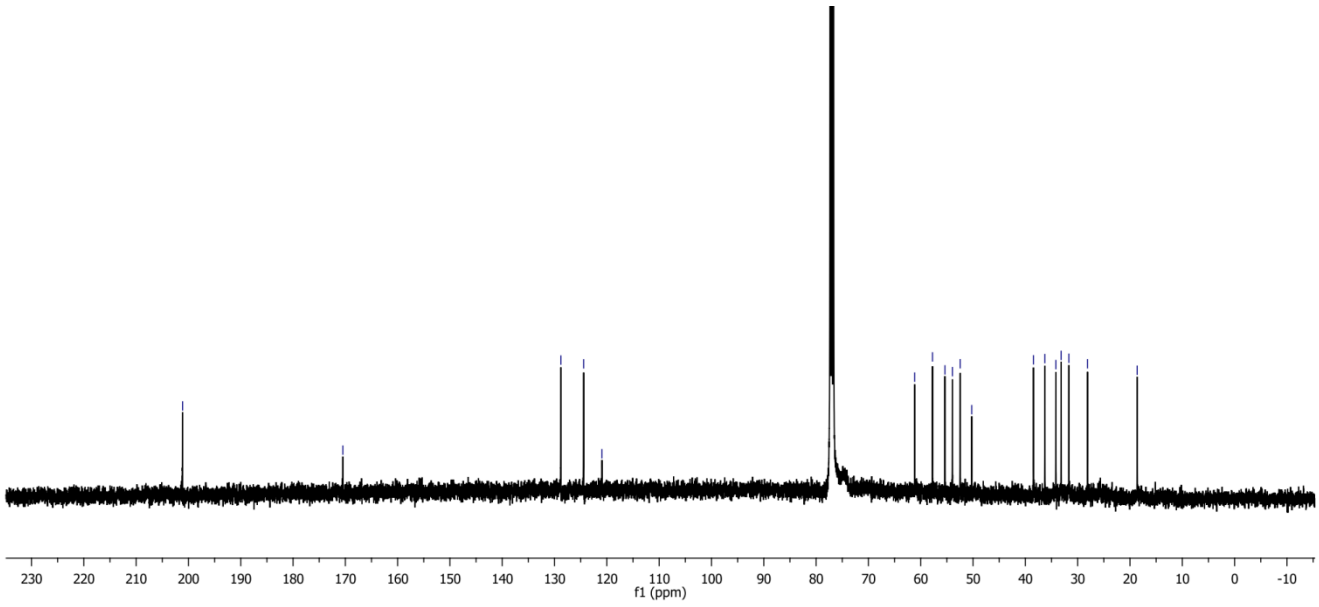


Methyl *rel*-(1*R*,2*S*,3*S*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyltetracyclo[9.3.1.$0^{4,15}$.$0^{6,12}$]pentadec-8-ene-2-carboxylate (1a)

^{1}H NMR spectrum

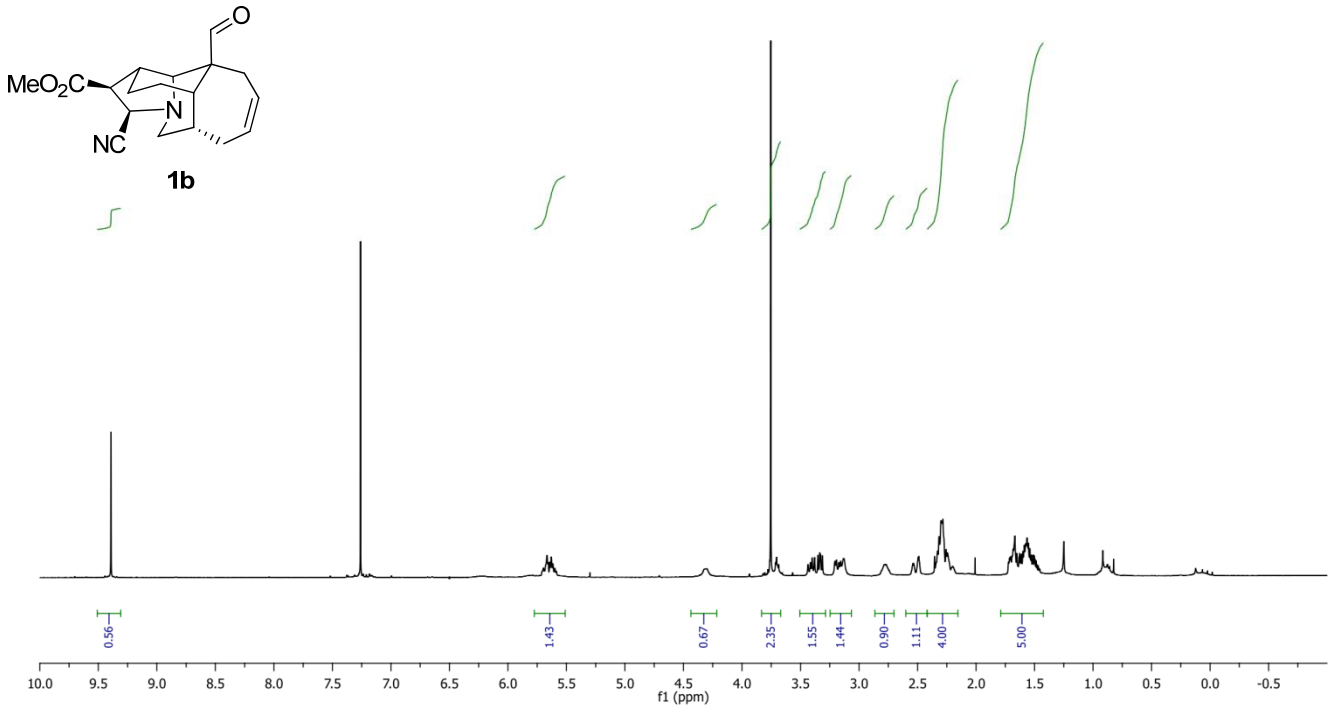


^{13}C NMR spectrum

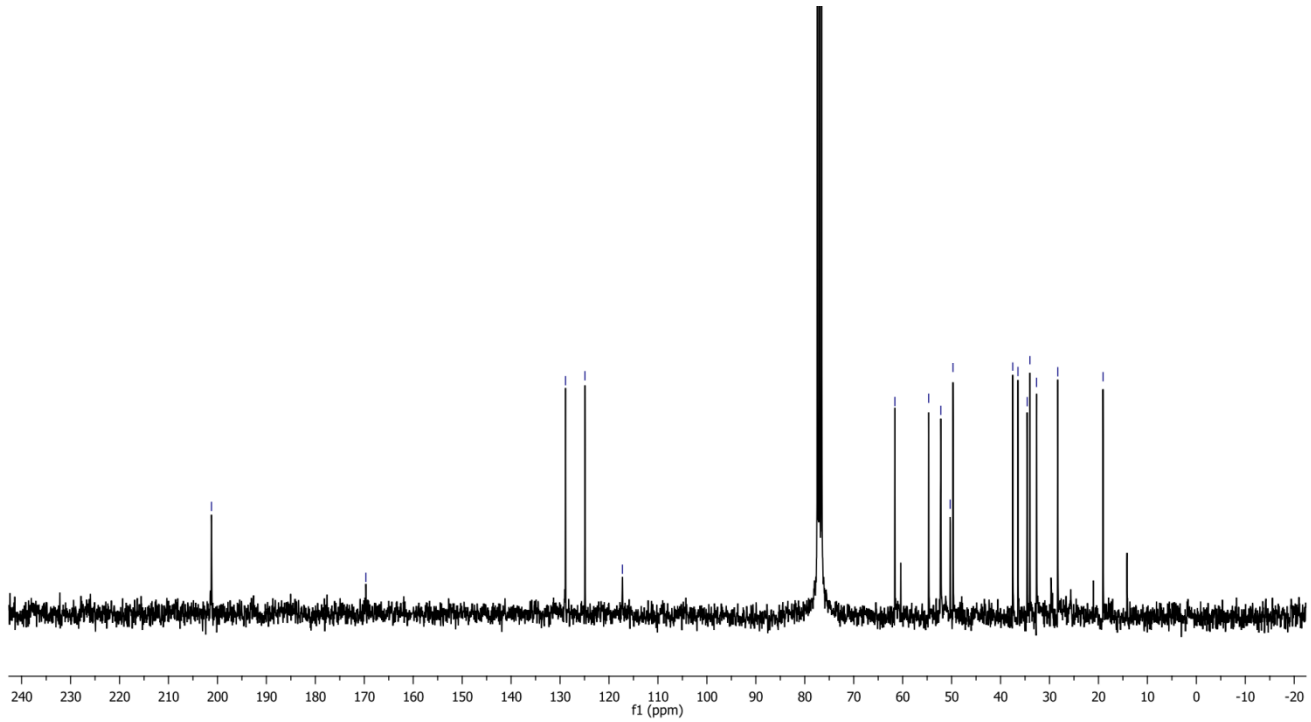


Methyl *rel*-(1*R*,2*S*,3*R*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyltetracyclo[9.3.1.$0^{4,15}$.$0^{6,12}$]pentadec-8-ene-2-carboxylate (1b)

^{1}H NMR spectrum

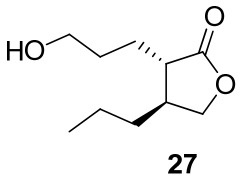


^{13}C NMR spectrum



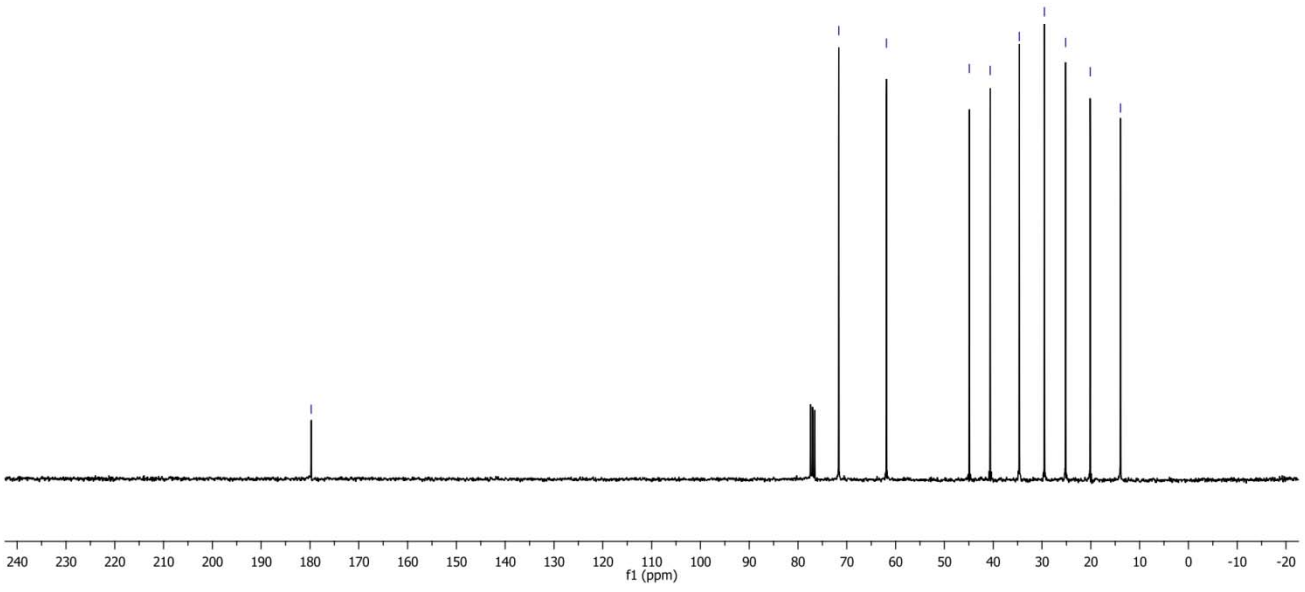
***rel*-(3*S*,4*S*)-3-(3-Hydroxypropyl)-4-propyldihydrofuran-2(3*H*)-one (27)**

^{1}H NMR spectrum



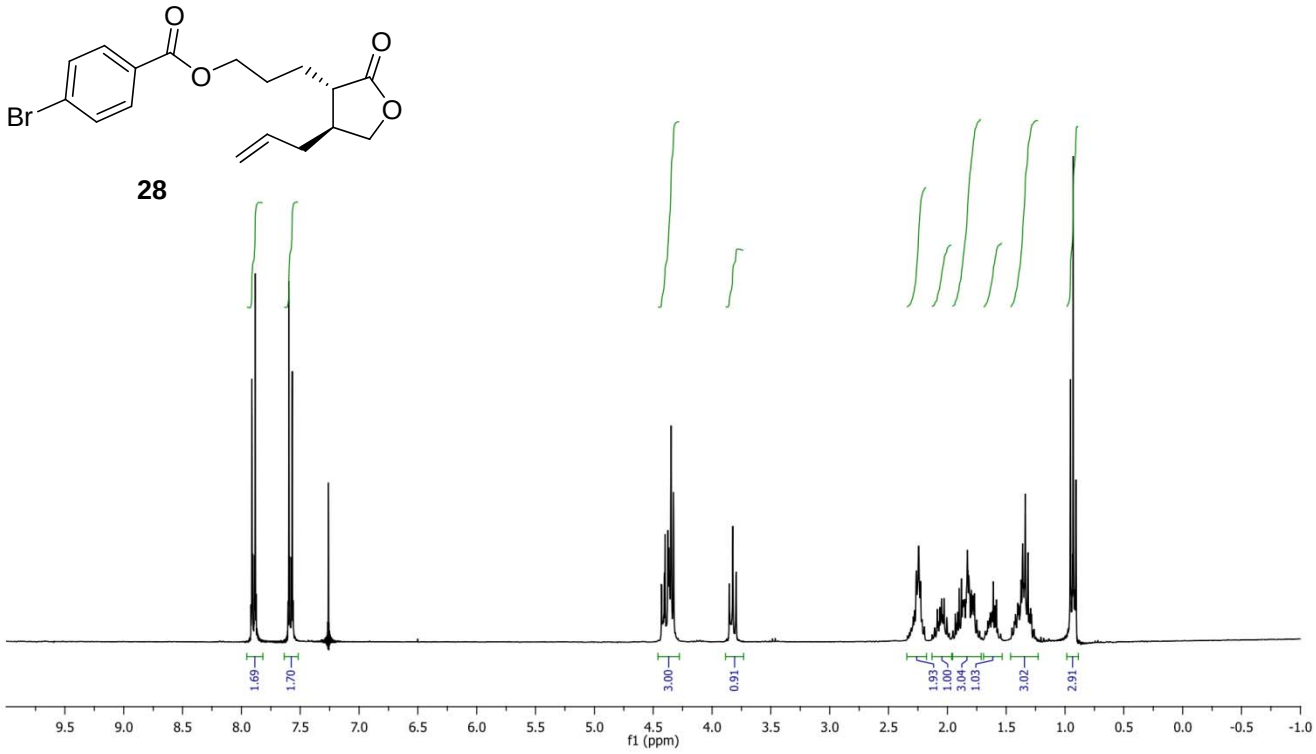
27

^{13}C NMR spectrum



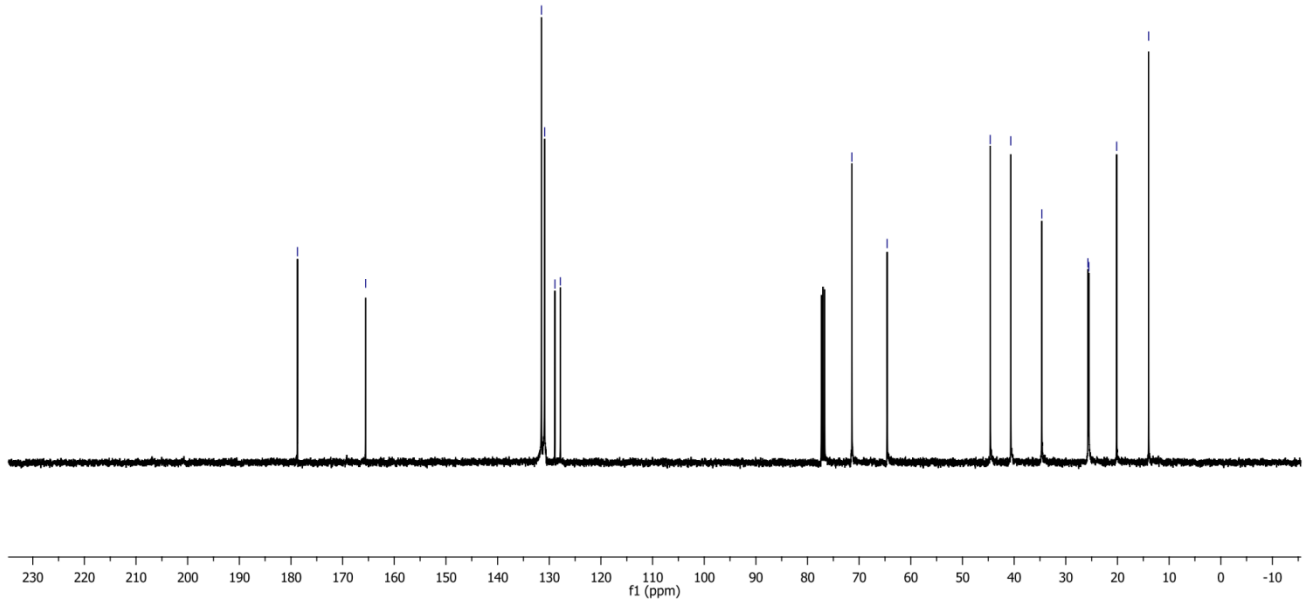
3-(*rel*-(3S,4S)-2-Oxo-4-propyltetrahydrofuran-3-yl)propyl 4-bromobenzoate (28)

^{1}H NMR spectrum

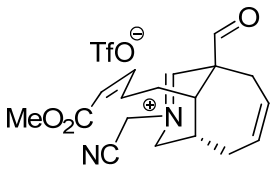


28

^{13}C NMR spectrum



V ^{1}*H Spectrum of Iminium Ion 29*

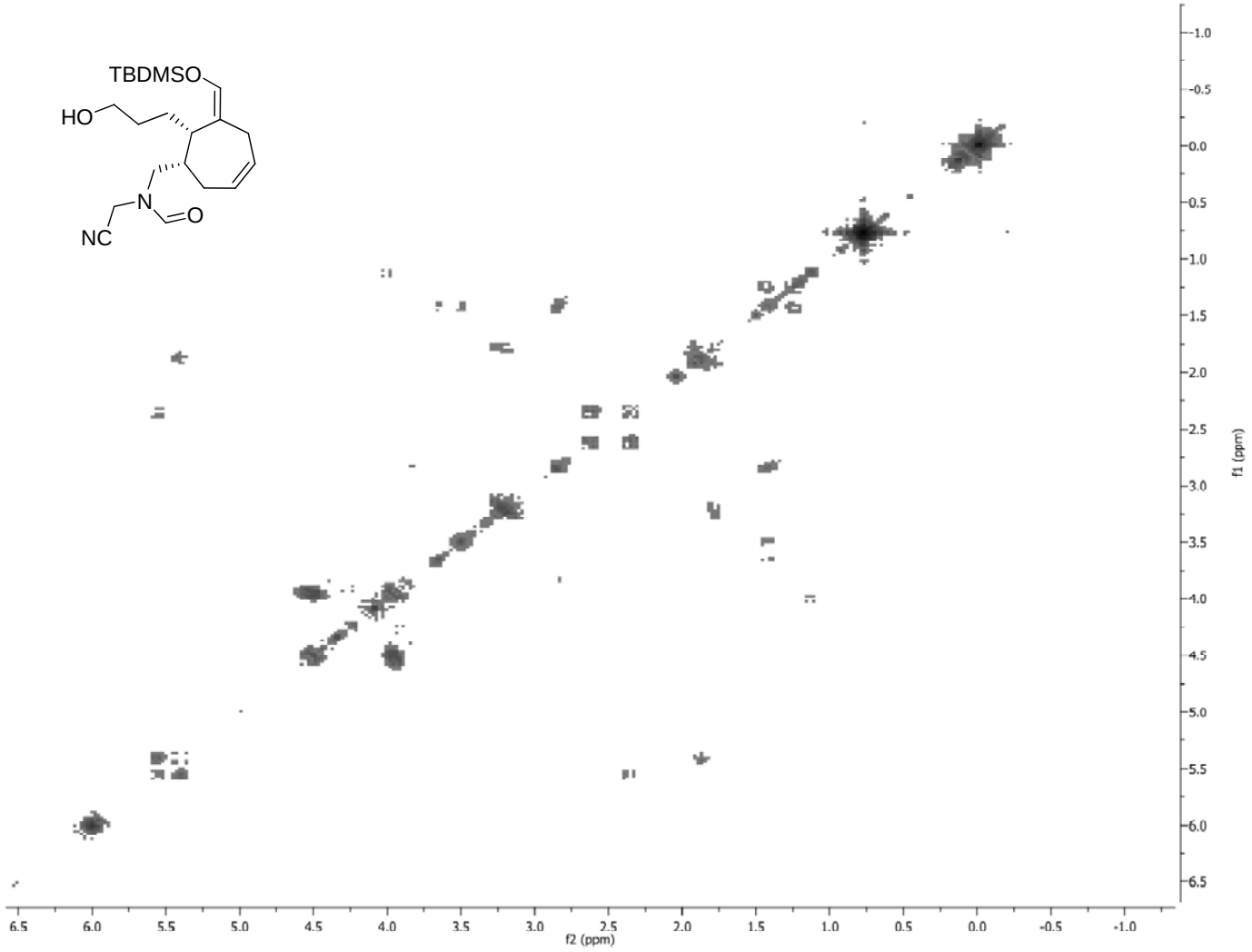


29

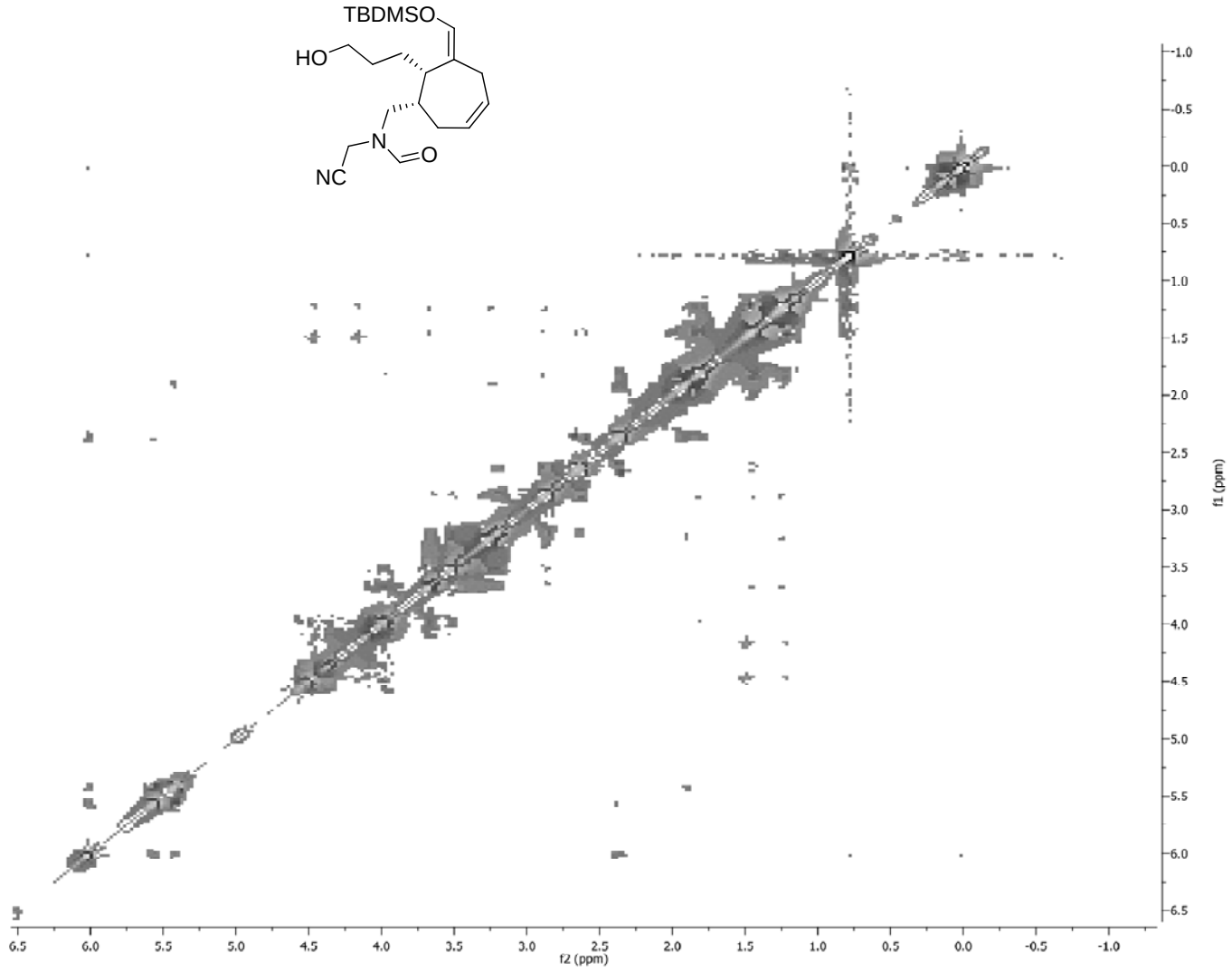
VI COSY and NOESY Spectra of Isomer of 25 and of 1a and 1b

_N_-((_rel_-(1_S_,7_S_,_Z_)-6-((_tert_-Butyldimethylsilyloxy)methylene)-7-(3-hydroxypropyl)cyclohept-3-enyl)methyl)-_N_-(cyanomethyl)formamide (isomer of 25)

COSY spectrum

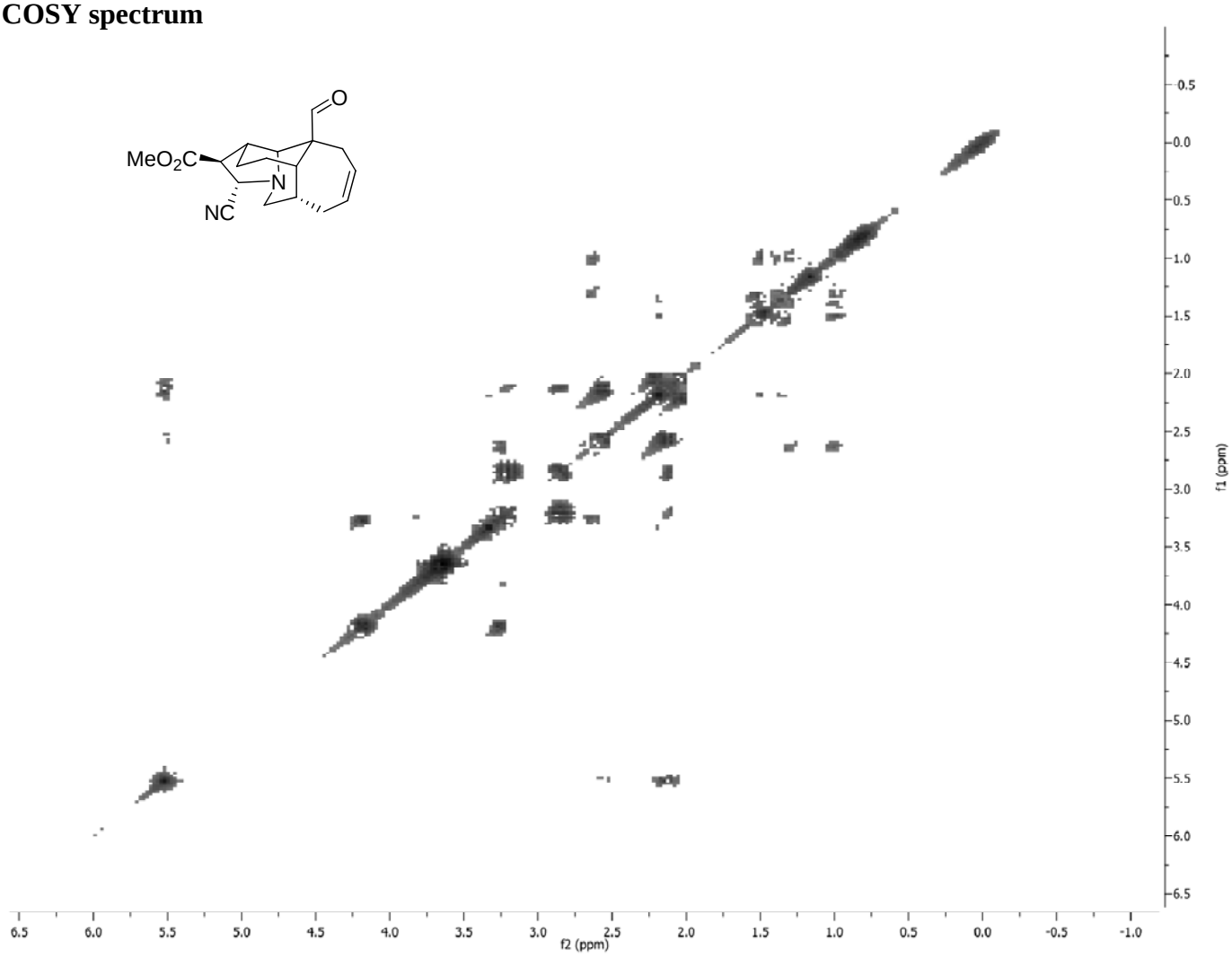


NOESY spectrum

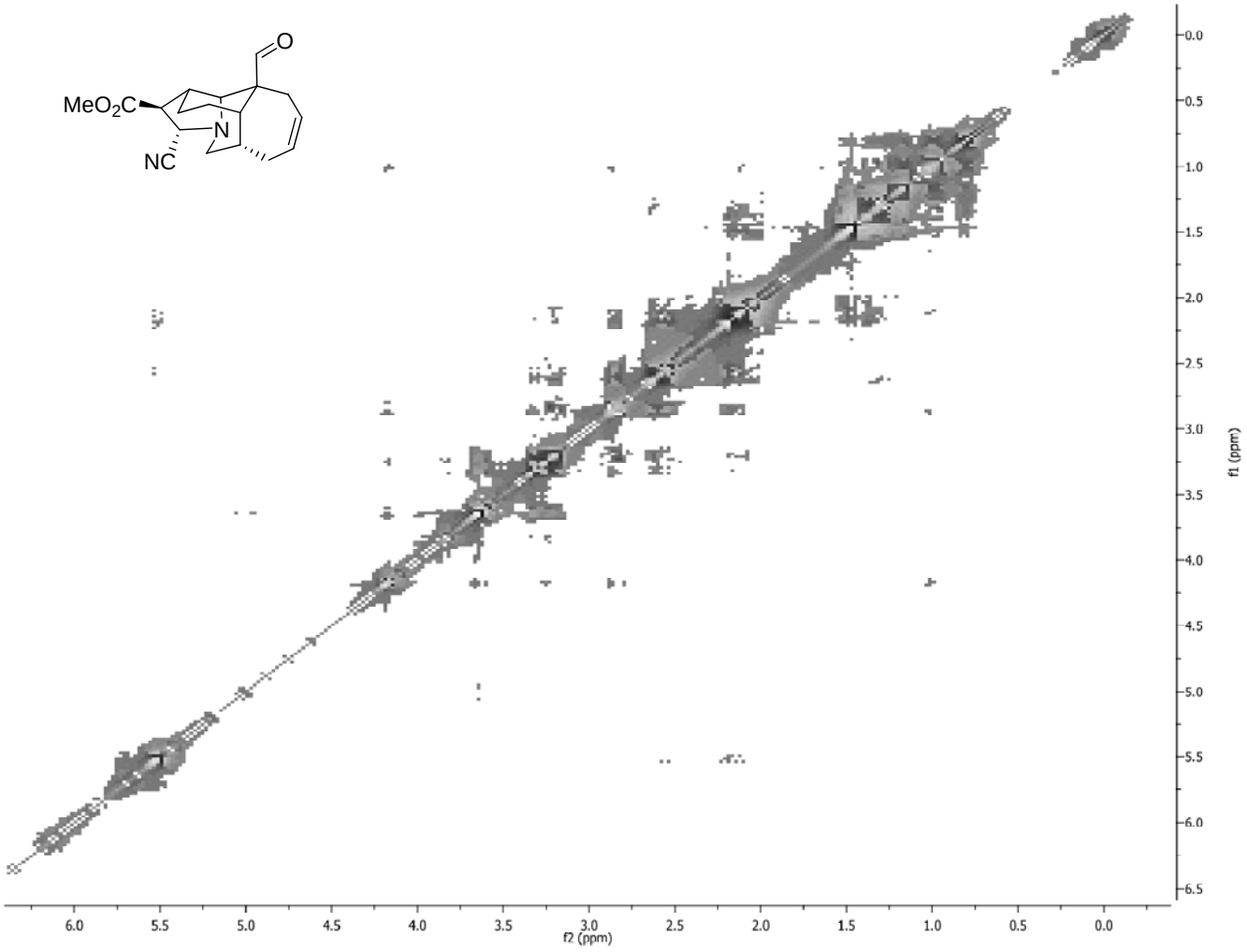


Methyl *rel*-(1*R*,2*S*,3*S*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyltetracyclo[9.3.1.$0^{4,15}$.$0^{6,12}$]pentadec-8-ene-2-carboxylate (1a)

COSY spectrum

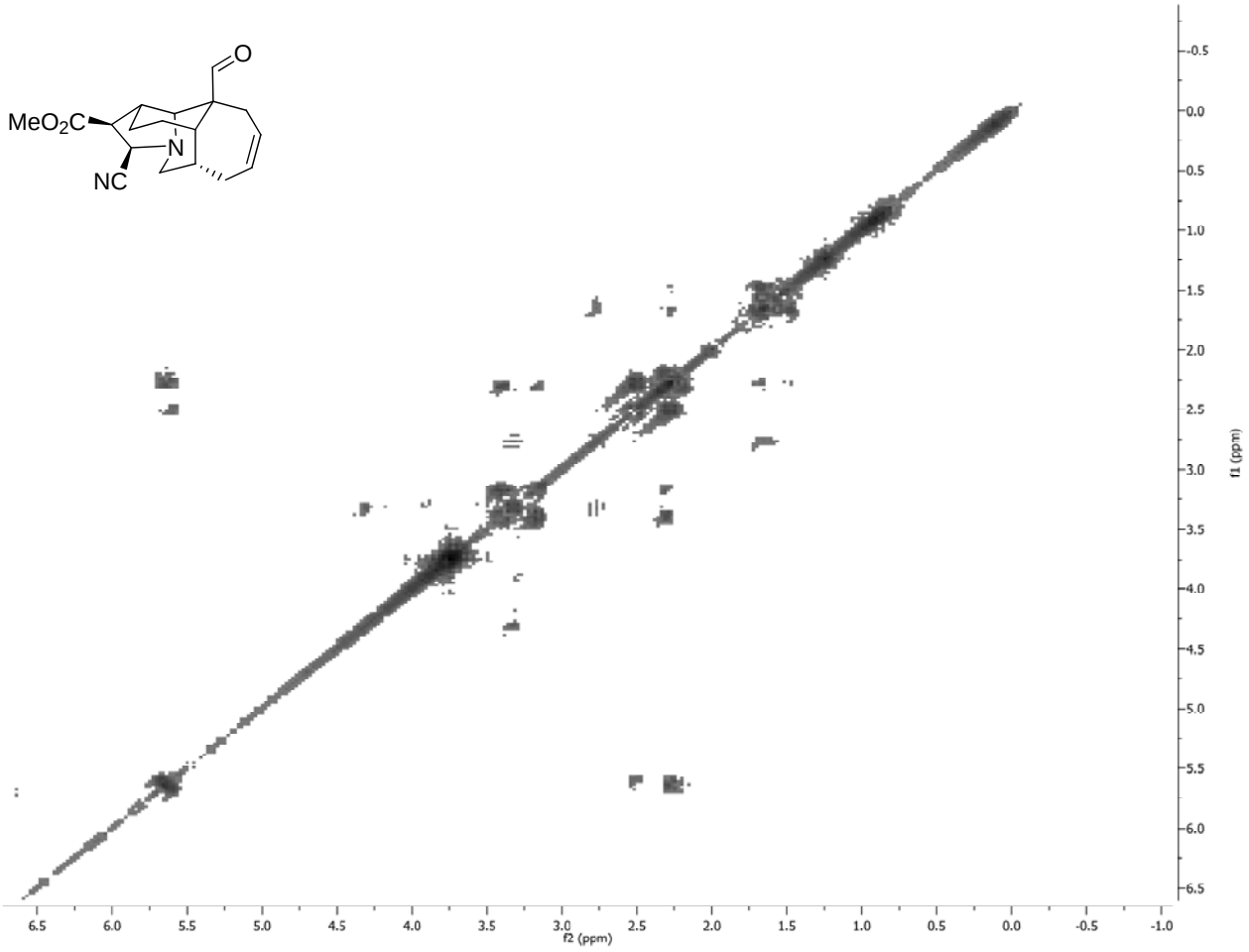


NOESY spectrum

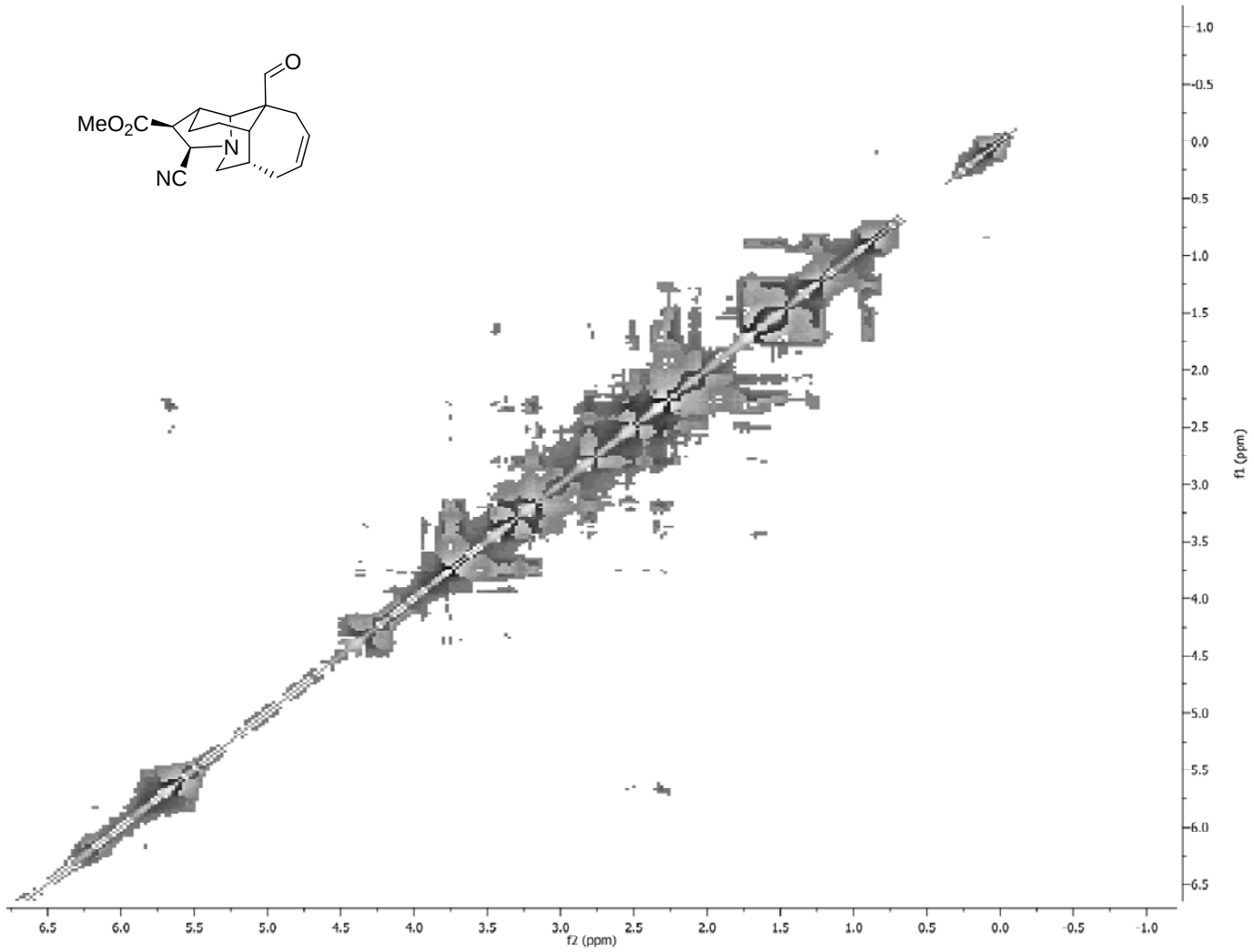


Methyl *rel*-(1*R*,2*S*,3*R*,6*S*,11*S*,12*S*,15*S*)-4-aza-3-cyano-11-formyltetracyclo[9.3.1.$0^{4,15}$.$0^{6,12}$]pentadec-8-ene-2-carboxylate (1b)

COSY spectrum



NOESY spectrum



VII References

(1) Robin, J.-P.; Landais, Y. *Tetrahedron* **1992**, 48, 819.

(2) Venkateswar Reddy, G.; Sateesh Chandra Kumar, R.; Suresh Babu, K.; Madhusudana Rao, J. *Tetrahedron Lett.* **2009**, *50*, 4117.

(3) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893.

(4) (a) Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503. (b) Pasqua, A. E.; Matheson, M.; Sewell, A. L.; Marquez, R. *Org. Process Res. Dev.* **2011**, *15*, 467.

(5) Hanna, I.; Ricard, L. *Org. Lett.* **2000**, *2*, 2651.

(6) The *Z* stereochemistry was assigned from a NOESY experiment with **25b** obtained by debenzylation of compound **24b**.

(7) An ORTEP representation of **28** could be found in the Supporting Information. Crystallographic data for this compound has been deposited with the Cambridge Crystallographic Data Centre (CCDC no 842628). The coordinates can be obtained on http://www.ccdc.cam.ac.uk/deposit.