Supporting Information

Next Generation Total Synthesis of Vancomycin

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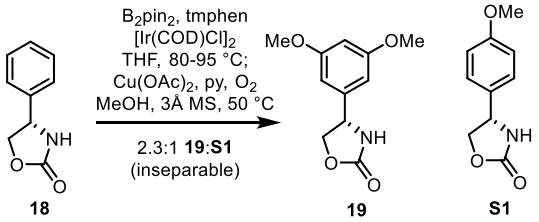
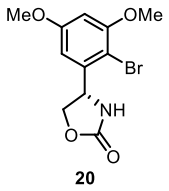


(*S*)-4-(3,5-Dimethoxyphenyl)oxazolidin-2-one (19). An oven-dried 1 L pressure flask was cooled under Ar and charged with (*S*)-4-phenyl-oxazolidin-2-one (**18**, 20.0 g, 123 mmol, 1 equiv), bis(pinacolato)diboron (B_2pin_2, 62.3 g, 245 mmol, 2 equiv), $[Ir(COD)Cl]_2$ (404 mg, 0.613 mmol, 0.5 mol %), and 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen, 288 mg, 1.23 mmol, 1 mol %), followed by anhydrous THF (400 mL, 20 vol). The reaction flask was sealed and stirred at 80 ˚C under Ar **(Caution: H_2 buildup)**. After 12 h at 80 ˚C, the temperature was reduced to 50 ˚C and the reaction mixture was carefully vented, sparged with Ar for 5 min, resealed, and warmed to 95 ˚C. After 24 h at 95 ˚C,* the reaction mixture was concentrated under reduced pressure. The resulting brown solid was combined with anhydrous $Cu(OAc)_2$ (22.0 g, 123 mmol, 1 equiv), flame-dried 3Å MS (powder, 50 g, 2.5 wt equiv), MeOH (600 mL, 30 vol), and pyridine (30 mL, 368 mmol, 3 equiv). The reaction mixture was sparged with O_2 for 10 min at room temperature, then stirred at 50 ˚C under O_2 for 30 h, at which point LC/MS indicated complete consumption of the monomethoxylated intermediate [*m/z* 320 (pos.)]. The reaction mixture was filtered, washing the filter cake with MeOH (3 x 100 mL) and PhMe (3 x 100 mL), and the filtrate was concentrated under reduced pressure. The crude residue was diluted with CH_2Cl_2 (500 mL) and concentrated aqueous NH_4OH (200 mL), stirred for 1 h at room temperature, and the layers were separated. The aqueous was extracted with $CHCl_3$ (5 x 300 mL). The combined organic layers were concentrated under reduced pressure, co-evaporated with H_2O (3 x 1 L, rotary evaporation at 60 ˚C), redissolved in CH_2Cl_2 (500 mL), washed with aqueous 1 N HCl (500 mL), and concentrated under reduced pressure to yield crude **19** as a red-orange oil (23 g, 2.3:1 **19**:**S1** by NMR),** used directly in the next step. For **19**: $[\alpha]_D^{23}$ +40 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.2 Hz, 1H), 6.39 (t, *J* = 2.3 Hz, 2H), 6.34 (br s, 1H, N-H), 4.90–4.82 (m, 1H), 4.68 (t, *J* = 8.7 Hz, 1H), 4.13 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 160.0, 142.0, 103.8, 100.4, 72.4, 56.4, 55.5; IR (powder) ν_{max} 3213, 2968, 2837, 1760, 1716, 1599, 1474, 1430, 1407, 1344, 1300, 1259, 1225, 1205, 1168, 1154, 1109, 1062, 1033, 986, 923, 836, 797, 763, 718, 686, 664, 627 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}NO_4$, 224.0923; found, 224.0928.

*Conversion to the desired di-*meta*-borylated intermediate was estimated to be >66% by crude NMR: ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 8.16 (s, 1H, *para*-proton of desired) versus 5.25–4.00 (3H, aliphatic protons of all products derived from **18**).

5% of the crude reaction product was removed for optimization of the following reaction. This is accounted for in the reported yield of **20 in the following step.

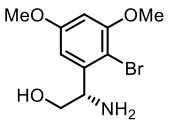


(*S*)-4-(2-Bromo-3,5-dimethoxyphenyl)oxazolidin-2-one (20). The crude mixture of **19** and **S1** from the previous step was dissolved in CH_3CN (500 mL, 25 vol) and cooled to 0 ˚C, then treated portionwise with N-bromosuccinimide* (NBS, 12.9 g, 72.5 mmol, 0.62 equiv). After 15 min following addition of the final portion of NBS, the reaction mixture was quenched

with the addition of saturated aqueous sodium thiosulfate ($Na_2S_2O_3$, 50 mL) and concentrated under reduced pressure to 200 mL total volume, diluted with H_2O (300 mL) and further concentrated to remove CH_3CN. The precipitate was filtered. washed with H_2O (2 x 100 mL), triturated with Et_2O (3 x 100 mL), and purified by column chromatography [350 g SiO_2, wet-load CH_2Cl_2, eluted with 10% acetone–CH_2Cl_2 (3 L)] to provide **20** (16.4 g, 47% overall from **18**, 3 steps)** as a white solid. For **20**: $[\alpha]_D^{23}$ +107 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.65 (d, *J* = 2.7 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 6.19 (br s, 1H, N-H), 5.35 (ddd, *J* = 9.0, 6.2, 1.3 Hz, 1H), 4.91 (t, *J* = 8.9 Hz, 1H), 4.09 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 160.0, 157.2, 141.1, 102.5, 101.9, 99.6, 71.5, 56.5, 55.8, 55.6; IR (thin film) ν_{max} 3244, 2937, 1759, 1721, 1589, 1455, 1438, 1420, 1342, 1319, 1290, 1238, 1204, 1167, 1132, 1080, 1032, 993, 932, 840, 763, 723, 646, 614 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}BrNO_4$, 302.0028; found, 302.0034.

*NBS was added in 1–2 g portions until **19** was fully consumed, monitoring by LC/MS 15 min post-addition of each portion. Excess NBS and extended reaction times lead to dibromination.

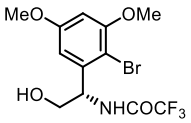
Impure batches of **20 can be further purified by recrystallization from PhMe. Recrystallization prior to chromatography was unsuccessful.



21

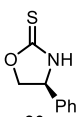
(*S*)-2-Amino-2-(2-bromo-3,5-dimethoxyphenyl)ethan-1-ol (21). A solution of **20** (10.7 g, 35.4 mmol, 1 equiv) in dioxane (50 mL, 5 vol) at 80 ˚C was treated with aqueous 6 N NaOH (50 mL, 5 vol) and the reaction mixture was warmed at reflux for 18 h, at which point TLC (10% MeOH–CH_2Cl_2) indicated complete consumption of **20**. The reaction mixture was concentrated at 60 ˚C under reduced pressure to remove dioxane, diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (5 x 200 mL).* The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **21** (10.2 g, quant) as an off-white solid, which used without further purification. For **21**: $[\alpha]_D^{23}$ +41 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 6.74 (d, *J* = 2.7 Hz, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 4.48 (dd, *J* = 7.8, 4.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (dd, *J* = 10.9, 4.0 Hz, 1H), 3.43 (dd, *J* = 10.9, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.5, 158.0, 144.0, 105.5, 104.6, 99.5, 67.1, 57.5, 56.7, 56.0; IR (film) ν_{max} 3382, 2921, 2849, 1586, 1448, 1417, 1352, 1331, 1310, 1282, 1258, 1222, 1200, 1163, 1128, 1077, 1021, 945, 927, 830, 801, 744, 696, 643, 628, 611 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}BrNO_3$, 276.0235; found, 276.0240.

*The solubility of **21** is ca. 10 g/L in CH_2Cl_2. The product gradually dissolves over the course of multiple extractions.



22

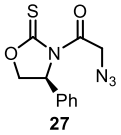
(*S*)-*N*-(1-(2-Bromo-3,5-dimethoxyphenyl)-2-hydroxyethyl)-2,2,2-trifluoroacetamide (22). A stirred suspension of **21** (10.2 g, approximately 35.4 mmol, 1.0 equiv) in MeOH (200 mL, 20 vol) was treated with methyl trifluoroacetate ($MeOCOCF_3$, 4.63 mL, 46.0 mmol, 1.3 equiv) dropwise at room temperature. The reaction mixture was stirred for 1 h at room temperature, at which point TLC (10% MeOH–CH_2Cl_2) indicated full consumption of **21**. The reaction mixture was concentrated and dried under reduced pressure to provide **22** (13.2 g, quant/2 steps) as an off-white solid. For **22**: mp 169–172 ˚C: R_f 0.40 (33% EtOAc–hexanes); $[\alpha]_D^{23}$ +45 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 6.59 (d, *J* = 2.7 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 5.49 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.86 (s, 3H), 3.82 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 11.6, 8.9 Hz, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 161.6, 158.9 (^2J C-F = 38 Hz), 158.3, 140.4, 117.5 (^1J C-F = 285 Hz), 105.5, 104.4, 99.8, 63.9, 57.5, 56.8, 56.0; IR (film) ν_{max} 3312, 2938, 1691, 1591, 1455, 1420, 1362, 1330, 1291, 1234, 1205, 1164, 1080, 1046, 874, 829 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}BrF_3NO_4$, 369.9902; found, 369.9907.



30

(*S*)-4-Phenyloxazolidine-2-thione (30). A solution of (*S*)-(+)-2-phenylglycinol (15.3 g, 111 mmol) in anhydrous THF (60 mL, 4 vol) was treated with 1,1'-thiocarbonyldiimidazole (24.8 g, 139 mmol, 1.25 equiv) portionwise (exothermic) and the reaction mixture was stirred at room temperature for 15 min, at which point TLC (100% EtOAc, ninhydrin stain) indicated complete consumption of (*S*)-(+)-2-phenylglycinol . The homogeneous red solution was treated with aqueous 1 N HCl (300 mL, 2.7 equiv) and THF was removed by rotary evaporation (40 ˚C) to yield an orange suspension that was extracted with CH_2Cl_2 (4 x 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated by rotary evaporation (40 ˚C) to yield an orange waxy solid (21.63 g) sufficiently pure for use in the next step.

Optional purification for **30** (odorous): Crude **30** was suspended in Et_2O (200 mL) and extracted with aqueous 1 N NaOH (130 mL) and aqueous 0.2 N NaOH (2 x 50 mL). The combined aqueous layers were acidified with addition of aqueous 6 N HCl (35 mL, 180 mmol) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure (**odorous**) to yield analytically pure **30** as a beige solid (13.5 g, 67%). The spectral data for **30** were in accordance with the literature values.[1] For **30**: $[\alpha]_D^{25}$ +83 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.42–7.34 (m, 3H), 7.30–7.27 (m, 2H), 5.13 (dd, *J* = 8.9, 6.9 Hz, 1H), 4.95 (t, *J* = 8.9 Hz, 1H), 4.38 (dd, *J* = 8.9, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 189.7, 137.7, 129.32, 129.11, 126.1, 77.5.

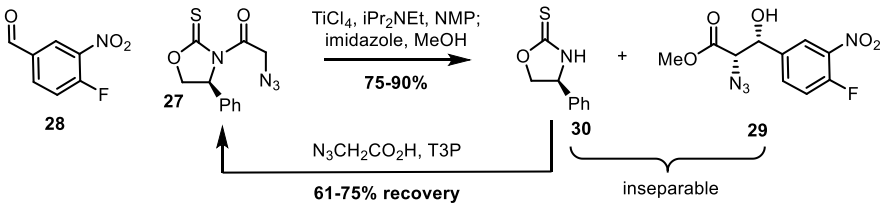


27

(*S*)-2-Azido-1-(4-phenyl-2-thioxooxazolidin-3-yl)ethan-1-one (27) (unstable toward base, silica gel, moisture). The crude product **30** [111 mmol (assuming quant yield)], anhydrous CH_2Cl_2 (40 mL, 2 vol) and 2-azidoacetic acid (20 g, 65 wt % in Et_2O,* 123 mmol, 1.1 equiv)** were stirred at 0 ˚C to obtain a homogeneous yellow solution. *i*-Pr_2NEt (51 mL, 292 mmol, 2.6 equiv) was added at 0 ˚C, causing a color change to dark brown and producing a white vapor in the reaction headspace. The reaction mixture was treated with T3P (50 wt % in EtOAc, 93 g, 146 mmol, 1.3 equiv) dropwise by addition funnel, then warmed to room temperature and stirred for 15 min, at which point TLC (100% CH_2Cl_2) indicated trace **30** remaining (important note: TLC must be eluted immediately after spotting from reaction mixture as product reverts to starting material on SiO_2). The reaction mixture was poured over vigorously stirred aqueous 1 N HCl (400 mL, 1.37 equiv with respect to *i*-Pr_2NEt), stirred for 5 min at room temperature, and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phase was dried over Na_2SO_4 and concentrated (40 ˚C) to yield a thick red oil that was purified by column chromatography (240 g SiO_2, wet-load minimal CH_2Cl_2, gradient 50–80% CH_2Cl_2-hexanes, rapid elution) to provide **27** as a yellow oil (15.5 g, 53% over 2 steps) that crystallized over several days under high vacuum, identical to the known compound.[2] For **27**: $[\alpha]_D^{23}$ +24 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–7.36 (m, 3H), 7.36–7.31 (m, 2H), 5.73 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.96–4.83 (m, 3H), 4.57 (dd, *J* = 9.3, 3.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.9, 168.5, 137.9, 129.5, 126.3, 75.2, 62.3, 54.7.

*2-Azidoacetic acid was prepared according to the literature method.[3] In order to avoid loss of the reagent during isolation, the Et_2O used during its extraction was not fully removed by rotary evaporation.

Incomplete conversion and/or deacylation is occasionally observed when only a small excess (1.1 equiv) of 2-azidoacetic acid is used. Increasing the amounts of all reagents by 50% relative to the limiting reagent **30 improves conversion. Partial diacylation of **27** was observed upon aging the reaction mixture at room temperature, and upon exposure to SiO_2.

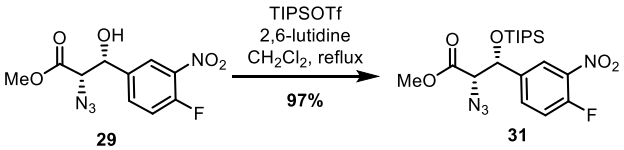


Methyl (2*S*,3*R*)-2-Azido-3-(4-fluoro-3-nitrophenyl)-3-hydroxypropanoate (29). The reaction has been conducted on scales from 10.0–23.7 g (75–90%) and a representative procedure follows. Compound **27** (23.7 g, 90.4 mmol) was dissolved in anhydrous CH_2Cl_2 (900 mL, 0.1 M concentration) and cooled to –78 ˚C under Ar to yield a light yellow solution. $TiCl_4$ (10.4 mL, 95 mmol, 1.05 equiv) was added dropwise to yield a light orange solution. After 15 min, *i*-Pr_2NEt (17.4 mL, 99

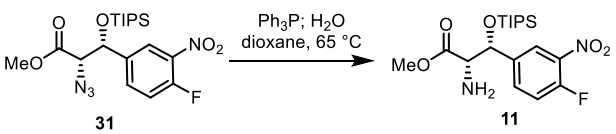
mmol, 1.1 equiv) was added dropwise, resulting in an instant color change to black. The reaction mixture was stirred for 1 h, then anhydrous *N*-methyl-2-pyrrolidone (NMP, 17.4 mL, 181 mmol, 2.0 equiv) was added dropwise. After 15 min, a solution of 4-fluoro-3-nitrobenzaldehyde (**28**, 20.0 g, 117 mmol, 1.3 equiv) in anhydrous CH_2Cl_2 (20 mL, 1 vol) was added dropwise. The reaction mixture was warmed to –20 ˚C and held for 2 h at the same temperature, at which point LC/MS indicated trace **27** remaining [**27** *m/z* = 263 (pos.), <1% Liquid Chromatography Area Percent (LCAP) at 254 nm]. A solution of imidazole (31.0 g, 452 mmol, 5.0 equiv) in anhydrous MeOH (150 mL, 5 vol) was added in one portion at –20 ˚C and the reaction mixture was warmed to room temperature, producing a dark red solution. After 2 h at room temperature, LC/MS indicated complete methanolysis of the intermediate aldol product [*m/z* = 404 (pos.)]. The reaction mixture was diluted with saturated aqueous NH_4Cl* (200 mL) and stirred for 5 min at room temperature to yield a thick orange suspension that was vacuum-filtered through a pad of Celite. The filter cake was washed with CH_2Cl_2 (3 × 200 mL), and the combined filtrate was concentrated by rotary evaporation (50 ˚C) to yield a thick orange slurry that was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to yield a thick red oil. Column chromatography (370 g SiO_2, wet-load minimal CH_2Cl_2, 60% CH_2Cl_2/hexanes until aldehyde **28** fully eluted, then 10% EtOAc–CH_2Cl_2) afforded a mixture** of the aldol product (**29**) and the recovered chiral auxiliary (**30**) as a yellow oil (36 g). No attempt was made to separate **29** from **30**. Instead, the crude product mixture was subjected to the conditions of the previous acylation step assuming 70% recovery of **30**. Two rounds of column chromatography (800 g SiO_2 each, wet-load CH_2Cl_2, 100% CH_2Cl_2 until **27** elutes, then 10% EtOAc–CH_2Cl_2) provided **29** (19.2 g, 75%, typically 75–90%) as a yellow oil and **27** (14.5 g, 61% recovery, typically 61–75%) as a yellow oil that crystallized on standing. For **29**: $[\alpha]_D^{23}$ –73 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.70 (ddd, *J* = 8.7, 4.2, 2.4 Hz, 1H), 7.31 (dd, *J* = 10.4, 8.6 Hz, 1H), 5.29 (d, *J* = 3.8 Hz, 1H), 4.07 (d, *J* = 3.8 Hz, 1H), 3.83 (s, 3H), 3.33 (br s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.8, 155.2 (d, *J* = 265.9 Hz), 137.2 (d, *J* = 7.5 Hz), 136.7 (d, *J* = 4.1 Hz), 133.5 (d, *J* = 8.8 Hz), 124.1 (d, *J* = 2.6 Hz), 118.8 (d, *J* = 21.1 Hz), 72.7, 67.0, 53.4; IR (film) ν_{max} 3499, 2114, 1738, 1619, 1595, 1536, 1499, 1437, 1348, 1265, 1208, 1138, 1084, 1012, 905, 833, 812, 756, 728, 699, 669 cm^{-1}; HRMS (ESI-TOF) *m/z* [M+HCO_2^-]$^-$ calcd for $C_{10}H_9FN_4O_5$, 329.0534; found, 329.0533.

*Substitution of saturated aqueous L-tartaric acid (200 mL) for aqueous NH_4Cl prevents precipitation of TiO_2, resulting in a more convenient workup. The aqueous layer is subsequently concentrated to remove MeOH, extracted with $CHCl_3$ (4 x 200 mL), dried over Na_2SO_4 and purified as above to afford the products in reduced yield (64% yield of **29** on 15.4 g scale).

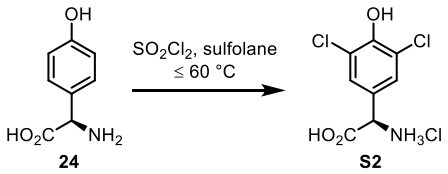
The title compound **29 is practically inseparable from the recovered auxiliary **30** by column chromatography. Reacylation of the chiral auxiliary facilitates chromatographic separation. No undesired acylation of **29** was observed under the conditions employing T3P.



Methyl (2*S*,3*R*)-2-Azido-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoate (31). A stirred solution of **29** (19.2 g, 67.6 mmol) in anhydrous CH_2Cl_2 (92 mL) at room temperature was treated with 2,6-lutidine (9.0 mL, 76 mmol, 1.13 equiv) followed by TIPSOTf (19 mL, 70 mmol, 1.04 equiv). The orange reaction mixture was warmed at reflux (oil bath temp = 55 ˚C) for 46 h, at which point LC/MS indicated >90% conversion. The reaction mixture was cooled to room temperature, diluted with aqueous 0.5 N HCl (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL), dried over Na_2SO_4, filtered, and concentrated. Column chromatography (SiO_2, wet-load minimal CH_2Cl_2, 20% EtOAc–hexanes) afforded **31** as a light-yellow oil (29.0 g, 97%). For **31**: $[\alpha]_D^{25}$ –94 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.14 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.73 (ddd, *J* = 8.7, 4.2, 2.3 Hz, 1H), 7.32 (dd, *J* = 10.5, 8.5 Hz, 1H), 5.49 (d, *J* = 3.6 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 3.5 Hz, 1H), 1.29–0.87 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.5, 155.2 (d, *J* = 265.9 Hz), 138.2 (d, *J* = 3.9 Hz), 137.0 (d, *J* = 7.5 Hz), 133.7 (d, *J* = 8.5 Hz), 124.3 (d, *J* = 2.5 Hz), 118.9 (d, *J* = 21.1 Hz), 75.4, 67.7, 52.8, 17.76, 17.74, 17.69, 12.39, 12.33; IR (neat) ν_{max} 2947, 2868, 2115, 1748, 1619, 1595, 1539, 1499, 1462, 1436, 1348, 1303, 1265, 1203, 1104, 1068, 1016, 999, 882, 816, 753, 680 cm^{-1}; HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{19}H_{29}FN_4O_5Si$, 329.0534; found, 329.0533.

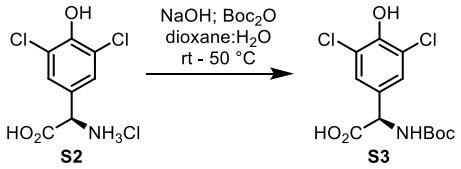


Methyl (2*S*,3*R*)-2-Amino-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoate (11). Compound **31** (29.0g, 65.8 mmol) was co-evaporated with dioxane (100 mL) to remove residual EtOAc, then dissolved in dioxane (125 mL, 5 vol). The stirred reaction mixture at room temperature was treated with Ph_3P (16 g, 60 mmol, 0.91 equiv) in one portion, resulting in steady gas evolution and a slight exotherm. The reaction mixture was stirred for 1 h at room temperature, at which point TLC (30% EtOAc–hexanes) indicated trace **31** remained. Deionized H_2O (25 mL, ca. 1 vol) was added and the reaction mixture was stirred at 65 ˚C for 12 h. The reaction mixture was then concentrated by rotary evaporation at 60 ˚C and co-evaporated with dioxane (100 mL). Column chromatography (two rounds, first round 500 g SiO_2, wet-load minimal CH_2Cl_2, 30% EtOAc–hexanes, second round 300 g SiO_2, dry-load SiO_2, 30% EtOAc–hexanes, then 100% EtOAc once pure **11** began to elute) afforded **11** (21.8 g, 80%) as a yellow solid after co-evaporation with hexanes. For **11**: $[\alpha]_D^{25}$ +3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.14 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.70 (ddd, *J* = 8.6, 4.2, 2.3 Hz, 1H), 7.34–7.12 (m, 1H), 5.34 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.47 (d, *J* = 3.0 Hz, 1H), 1.57 (br s, 2H, NH_2), 1.01 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 154.9 (d, *J* = 265.0 Hz), 139.4 (d, *J* = 4.0 Hz), 136.8 (d, *J* = 7.3 Hz), 133.7 (d, *J* = 8.6 Hz), 124.3 (d, *J* = 2.7 Hz), 118.0 (d, *J* = 21.0 Hz), 74.9, 61.5, 52.2, 17.9, 17.8, 12.4; IR (thin film) ν_{max} 2945, 2867, 1740, 1681, 1619, 1594, 1537, 1463, 1436, 1347, 1245, 1204, 1164, 1141, 1096, 1066, 998. 922, 882, 821, 743, 681, 609 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{31}FN_2O_5Si$, 415.2065; found, 415.2065.



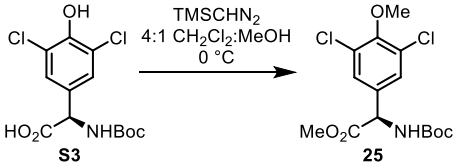
Methyl (*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dichloro-4-methoxyphenyl)acetate (S2). The reaction has been conducted on scales of 10–100 g (68–82%) and a representative procedure follows. A stirred suspension of (*D*)-4-hydroxyphenylglycine (**24**, 17.7 g, 107 mmol, 1 equiv) in sulfolane (177 mL, 10 vol) at 30 ˚C was treated with SO_2Cl_2 (25 mL, 268 mmol, 2.5 equiv) dropwise (exothermic) such that the internal temperature of the reaction mixture did not exceed 60 ˚C. During the course of the addition, **24** fully dissolved and a new precipitate formed. The reaction mixture was stirred for an additional 30 min at 60 ˚C, diluted with PhMe (700 mL) with vigorous stirring, and cooled to room temperature. The precipitate was collected by filtration, washed with PhMe (3 x 150 mL) and Et_2O (3 x 150 mL), and dried under high vacuum to yield **S2** (hydrochloride salt, 21.6 g, 75%, typically 68–82%) as a white solid.

Optional purification for compound **S2**: A solution of crude **S2** (ca. 7 g) in aqueous 1 N HCl (100 mL) was adjusted to pH 5 with saturated aqueous NH_4OH. The resulting precipitate was collected by filtration, washed with H_2O (3 x 30 mL), acetone (4 x 30 mL), and Et_2O (50 mL), and dried to provide (*R*)-2-amino-2-(3,5-dichloro-4-hydroxyphenyl)acetic acid (zwitterionic form, 5.0 g) as a fine white solid with spectra matching those reported in the literature.[4] Literature data for zwitterionic form: R_f 0.40 (BuOH:AcOH:H_2O 4:1:5); mp 222–225 ˚C; $[\alpha]_D^{20}$ –127 (*c* 1.0, 1 N HCl); ^{1}H NMR (300 MHz, CD_3OD) δ 7.43 (s, 2H), 4.47 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.9, 151.2, 132.7, 129.3, 123.4, 58.6.



(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dichloro-4-hydroxyphenyl)acetic Acid (S3). A stirred suspension of **S2** (hydrochloride salt, 17.8 g, 65.3 mmol, 1 equiv) in dioxane (100 mL, 5.6 vol) was treated with aqueous 1 N NaOH (163 mL, 163 mmol, 2.5 equiv). The resulting dark purple-brown suspension was stirred at room temperature until all solids dissolved (1 h), then treated with a solution of Boc_2O (22.5 mL, 98 mmol, 1.5 equiv) in dioxane (10 mL). The reaction mixture was stirred for 1 h at room temperature, then warmed at 50 ˚C for 30 min, at which point TLC (10% AcOH–EtOAc) indicated complete consumption of starting material. The reaction mixture was concentrated under reduced pressure at 50 ˚C to remove dioxane, cooled to room temperature, and washed with CH_2Cl_2 (4 x 100 mL). The aqueous layer was diluted with CH_2Cl_2 (200 mL) and adjusted to pH < 1 with conc. HCl (15 mL) while stirring at room temperature. The aqueous layer was removed and back-extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic layer was dried over Na_2SO_4, filtered and concentrated to yield **S3** (23.7 g, 108% theoretical, containing traces of solvent) as a hygroscopic light tan

foam, used directly in the next step. The spectral data for **S3** were in accordance with the literature values.[50] Literature data: R_f 0.75 (BuOH:AcOH:H_2O 4:1:5); mp 60–62 ˚C; $[\alpha]_D^{22}$ –122 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.28 (s, 9H), 5.01 (d, *J* = 6.0 Hz, 1H), 5.70 (br s, 1H), 7.36 (s, 2H), 8.07 (d, *J* = 6.0 Hz, 1H); HR-FAB-MS *m/z* $[M+Na]^+$ calcd for $C_{13}H_{15}O_5NCl_2Na$, 358.0238; found 358.0225.

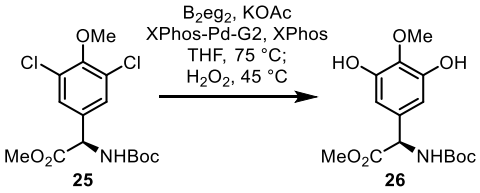


Methyl (*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dichloro-4-methoxyphenyl)acetate (25). A stirred solution of crude **S3** (ca. 65.3 mmol, 1 equiv) in CH_2Cl_2 (80 mL, 4 vol) and MeOH (20 mL, 1 vol) at 0 ˚C was treated with $TMSCHN_2$* (2 M/hexanes, 131 mL, 262 mmol, 4.0 equiv) dropwise over 15 min (gas evolution), and the resulting bright yellow solution was stirred at 0 ˚C. Complete consumption of **S3** and an intermediate mono-methylated product was observed 30 min post-addition (TLC, 15% EtOAc–hexanes). The reaction mixture was immediately** quenched by dropwise addition of AcOH (vigorous gas evolution) until no further bubbling was observed. The reaction mixture was concentrated under a stream of air and co-evaporated with heptane (2 x 100 mL). Column chromatography [230 g SiO_2, wet-load 33% CH_2Cl_2–hexanes, eluted with hexanes (500 mL), 5% acetone–hexanes (1 L), 7% acetone–hexanes (1 L), and 10% acetone–hexanes (1 L)] provided **25** (18.5 g, 84% for 2 steps, >99% ee) as a light tan solid. For **25:** known compound,[4] literature data: R_f 0.52 (33% EtOAc–hexane); mp 106–108 ˚C; $[\alpha]_D^{25}$ –130 (c 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 2H), 5.66 (d, *J* = 7.0 Hz, 1H), 5.22 (br d, *J* = 7.0 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 154.4, 152.1, 134.4, 129.6, 127.2, 80.6, 60.6, 56.3, 53.1, 28.3.

Compound **25** was analyzed by chiral SFC on a Daicel IG column (3 mm, 4.6 x 250 mm) under isocratic conditions [5% MeOH/CO_2 (4 mL/min), 1600 psi back pressure] at 30 °C. The enantiomers were detected by UV (220 nm), R_t 2.15 min (**25**), 2.37 min (*ent*-**25**).

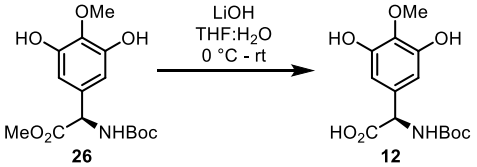
*Attempts to methylate **S3** using more conventional reagents produced **25** with lower optical purity (e.g., Cs_2CO_3, Me_2SO_4, DMF, 0 ˚C, 15 min, 94% ee).

$TMSCHN_2$ is capable of racemizing **25 under reaction-like conditions [1 equiv **25** (>99% ee)**,** 2 equiv $TMSCHN_2$, 4:1 CH_2Cl_2/MeOH (0.67 M), room temperature, 15 min, 96% ee]. The reaction must therefore be quenched immediately upon completion.



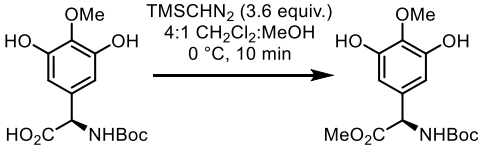
Methyl (*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dihydroxy-4-methoxyphenyl)acetate (26). The reaction has been conducted on scales up to 7 g (88–94% yield) and a representative procedure follows. An oven-dried pressure flask was cooled to room temperature under Ar, charged with **25** (5.00 g, 13.7 mmol, 1 equiv), bis(ethyleneglycolato)diboron (B_2eg_2, 5.8 g, 41.2 mmol, 3 equiv), XPhos-Pd-G2* (Strem Chemicals, 540 mg, 0.68 mmol, 5 mol %), XPhos (654 mg, 1.4 mmol, 10 mol %), anhydrous KOAc (8.1 g, 82 mmol, 6 equiv), and THF (140 mL, 28 vol). The reaction vessel was sealed and stirred at 75 ˚C under Ar for 1 h, at which point LC/MS indicated no starting material [*m/z* 264 (pos.)] or monoborylated intermediate [*m/z* 274 (pos.)] remained. The reaction mixture was cooled to room temperature and stirred on a room temperature water bath as H_2O_2 (30% aqueous solution, 7.1 mL, 69 mmol, 5 equiv) was added dropwise (**exothermic, vigorous bubbling**) over 5 min. The resulting tan suspension was resealed and stirred at 45 ˚C under Ar for 2 h, at which point LC/MS indicated no mono-oxidized boronic acid intermediate [*m/z* 354 (neg.)] remained. The reaction mixture was cooled to room temperature, quenched with the addition of saturated aqueous $Na_2S_2O_3$ (30 mL), and THF was removed under reduced pressure at 30 ˚C. The reaction mixture was diluted with H_2O (70 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (200 mL), dried over Na_2SO_4, filtered and concentrated. Column chromatography [200 g SiO_2, wet-load CH_2Cl_2, eluted with CH_2Cl_2 (200 mL), 10% EtOAc–CH_2Cl_2 (3 L,

until the UV active spot directly above the desired product eluted completely), and 20% EtOAc–CH_2Cl_2 (2 L)] provided **26** (4.0 g, 89%, typically 88–94%, 99% ee) as a tan foam. For **26**: $[\alpha]_D^{23}$ –100 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 6.37 (s, 2H), 4.99 (s, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.2, 157.4, 151.9, 136.8, 133.3, 107.8, 80.8, 60.7, 59.0, 52.8, 28.6; IR (thin film) ν_{max} 3409, 1692, 1600, 1502, 1438, 1345, 1265, 1160, 1054, 995, 851, 734, 702 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_7$, 327.1396; found, 328.1394.
Compound **26** was analyzed by chiral SFC on a Daicel IC column (3 µm, 4.6 x 250 mm) under isocratic conditions [15% MeOH-CO_2 (4 mL/min), 1600 psi backpressure] at 30 °C. The enantiomers were detected by UV (220 nm), R_t 1.61 min (**26**), 2.08 min (*ent*-**26**).
*XPhos-Pd-G2 was purchased from Strem Chemicals (light grey solid). Batches received from another supplier (light yellow solid) gave inferior results.



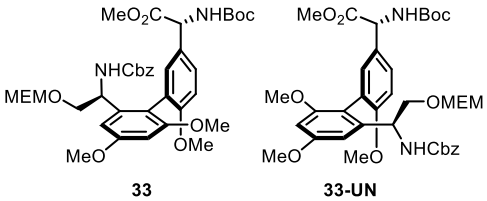
26 **12**

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dihydroxy-4-methoxyphenyl)acetic Acid (12). A stirred solution of **26** (3.67 g, 11.2 mmol, 1 equiv) in THF (40 mL, 11 vol) at room temperature was treated with H_2O (40 mL, 11 vol). The resulting suspension was sparged with Ar, cooled to 0 ˚C and $LiOH{\cdot}H_2O$ (2.4 g, 46 mmol, 5 equiv) was added. The reaction mixture was slowly warmed to room temperature while stirring under Ar. After 2 h at room temperature, LC/MS indicated complete consumption of starting material [*m/z* 326 (neg.)]. The reaction mixture was quenched with the addition of solid NH_4Cl (6.5 g, 121 mmol, 11 equiv) and THF was removed by rotary evaporation at 45 ˚C. The aqueous phase was washed with CH_2Cl_2 (3 x 30 mL), diluted with EtOAc (100 mL) and stirred at room temperature with dropwise addition of aqueous 6 N HCl (10 mL). The aqueous layer was removed and back-extracted with EtOAc (100 mL), and the combined EtOAc extracts were washed with saturated aqueous NaCl (200 mL), dried over Na_2SO_4, filtered and concentrated to yield **12** (3.50 g, 99%, ≥98% ee*, hygroscopic and sensitive to air oxidation) as a light tan foam, which used without further purification. For **12**: known compound,[5] literature data: $[\alpha]_D^{25}$ –89 (*c* 0.8, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.41 (s, 2H), 4.92 (s, 1H), 3.76 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.3, 157.3, 151.8, 136.5, 135.1, 107.8, 80.6, 60.7, 28.7, 28.5.
*The enantiomeric excess of **12** was determined by conversion to the corresponding methyl ester **26** as follows:



12 (≥98% ee) **26** **98% ee**

A solution of **12** (33.0 mg, 0.11 mmol, 1.0 equiv) in 80% CH_2Cl_2–MeOH (2 mL, 60 vol) at 0 ˚C was treated with $TMSCHN_2$ (2 M/hexane, 0.2 mL, 0.4 mmol, 3.6 equiv) dropwise. The reaction mixture was stirred for 10 min at 0 ˚C, quenched by dropwise addition of AcOH (0.1 mL), and concentrated under reduced pressure. PTLC (SiO_2, 20% EtOAc–CH_2Cl_2) provided **26** (27.5 mg, 83%, 98% ee) as a light tan oil. The enantiomeric excess of **26** was determined by chiral SFC as described above.

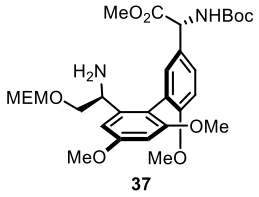


33 **33-UN**

Methyl (*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-((*R*)-2',4',6-trimethoxy-6'-((*S*)-3-oxo-1-phenyl-2,7,9,12-tetraoxa-4-azatridecan-5-yl)-[1,1'-biphenyl]-3-yl)acetate (33). A mixture of **32**[6] (37.5 mg, 0.100 mmol), **14** (68.0 mg, 0.147 mmol),

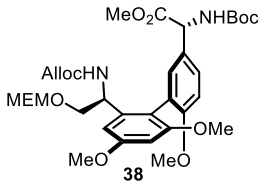
$Pd_2(dba)_3$ (9.3 mg, 0.010 mmol), (*R*)-BINAP(O)[7] (16.0 mg, 0.0251 mmol) and aqueous 1 M Na_2CO_3 (0.30 mL, 0.30 mmol) in PhMe (2.0 mL) was sparged with Ar at room temperature, then stirred at 70 °C for 2 h under Ar. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), washed with saturated aqueous NH_4Cl (5 mL) and saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (SiO_2, 30–50% EtOAc–hexanes) followed by PTLC (50% EtOAc–hexanes, 3x solvent elution) provided **33** (59.8 mg, 84%) as a yellow foam and its unnatural atropisomer **33-UN** (2.9 mg, 4%) as a yellow foam (88% combined yield, 21:1 dr; typically 15–21:1 dr, 72–95% combined yield and conducted on up to 8 g scale). For **33** (natural atropisomer): $[\alpha]_D^{23}$ –48 (*c* 1.0, MeOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.23 (br s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.52 (overlapping peaks, 2H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.67 (br d, *J* = 8.4 Hz, 1H), 5.22 (br d, *J* = 5.0 Hz, 1H), 5.11 (m, 2H), 4.58 (q, *J* = 5.6 Hz, 1H), 4.54 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.57 (m, 1H), 3.51 (m, 3H), 3.43 (m, 2H), 3.33 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.8, 159.8, 157.8, 157.6, 155.3, 155.2, 140.2, 135.9, 130.6, 129.1, 128.1 (2C), 128.0 (2C), 127.7, 127.1, 125.2, 118.8, 110.3, 102.4, 97.4, 94.8, 79.1, 71.2, 69.6, 66.6, 66.4, 58.4, 57.5, 55.4, 55.1, 54.9, 51.9, 51.2, 28.0 (3C); IR (film) ν_{max} 3349, 2934, 2361, 2340, 1702, 1505, 1257, 1159, 1054, 1033 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{37}H_{48}N_2O_{12}Si$, 713.3280; found, 713.3278.

For **33-UN** (unnatural atropisomer): $[\alpha]_D^{25}$ –6.4 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.24 (m, 6H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.45 (dd, *J* = 13.7, 2.2 Hz, 1H), 5.61–5.43 (m, 2H), 5.26 (d, *J* = 7.3 Hz, 1H), 5.02 (s, 2H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.51 (s, 2H), 3.81 (s, 3H), 3.76 (d, *J* = 3.2 Hz, 1H), 3.71 (s, 4H), 3.66 (s, 3H), 3.52 (d, *J* = 6.1 Hz, 4H), 3.44 (t, *J* = 4.6 Hz, 2H), 3.33 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 160.4, 158.4, 158.1, 155.9, 155.8, 140.8, 136.5, 131.3, 129.7, 128.6, 128.3, 127.7, 125.8, 119.4, 110.9, 103.0, 98.0, 95.4, 79.7, 71.8, 70.2, 67.1, 66.9, 59.0, 59.0, 58.1, 56.0, 55.7, 55.5, 52.5, 51.8, 28.6; IR (film) ν_{max} 2930, 1709, 1603, 1504, 1458, 1259, 1203, 1155, 1028, 842, 699 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{37}H_{48}N_2O_{12}Si$, 713.3280; found, 713.3282.



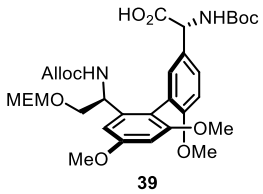
37

Compound 37. A suspension of 10% Pd/C (0.9 mg, 15% w/w) and **33** (60 mg, 0.0842 mmol) in MeOH (2 mL) was sparged with N_2 for 5 min at room temperature, then sparged with H_2 for 5 min at room temperature. The solution was stirred for an additional 30 min under H_2, then filtered through a pad of Celite, rinsing with EtOAc. The solvent was removed under reduced pressure to provide **37** as an oil that was carried forward without purification.



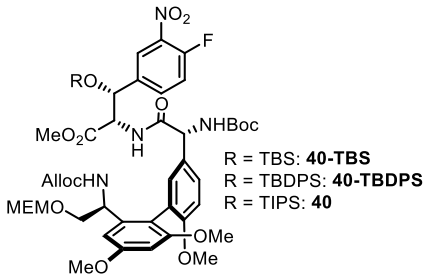
38

Compound 38. A mixture of **37** (from above, 0.0842 mmol), $NaHCO_3$ (44 mg, 0.53 mmol, 6 equiv), THF (3 mL), and H_2O (3 mL) at room temperature was treated with allyl chloroformate (28 µL, 0.26 mmol, 3 equiv). The reaction mixture was stirred at room temperature for 12 h, extracted with EtOAc (200 mL, 100 mL), and the combined organic layers were washed with saturated aqueous NaCl (200 mL), dried over Na_2SO_4, and concentrated in vacuo. Column chromatography (SiO_2, 1 × 9 cm, 50% EtOAc–hexanes) provided **38** (48.8 mg, 87% over 2 steps) as a white foam. For **38**: $[\alpha]_D^{26}$ –36 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.43 (br s, 1H), 5.89 (br s, 1H), 5.64 (br s, 1H), 5.28 (d, *J* = 17.4 Hz, 1H), 5.22–5.11 (m, 2H), 4.68–4.42 (m, 6H), 3.83 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.63–3.43 (m, 5H), 3.37 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 160.4, 158.4, 158.1, 155.9, 155.6 140.9, 133.1, 131.3, 129.7, 127.7, 125.8, 118.1, 110.9, 103.1, 97.9, 95.4, 79.6, 71.9, 70.2, 67.0, 66.0, 59.1, 58.1, 56.0, 55.5, 52.5, 51.8, 28.6; IR (film) ν_{max} 3351, 2933, 1701, 1504, 1256, 1202, 1157, 1032, 811 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{33}H_{46}N_2O_{12}$, 663.3124; found, 663.3126.



39

Compound 39. A solution of **38** (164.8 mg, 0.249 mmol) in 50% THF–H_2O (12 mL) at 0 ˚C was treated with LiOH·H_2O (31.3 mg, 0.746 mmol, 3.0 equiv). The reaction mixture was stirred for 2 h, acidified with the addition of aqueous 0.1 N HCl, and extracted with $CHCl_3$ (3 x 7 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide **39**, which was typically carried forward without purification.

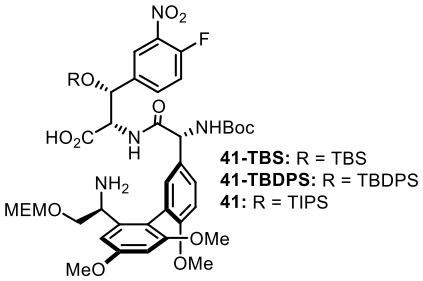


Compounds **40-TBS** and **40-TBDPS** were synthesized under identical reaction conditions. A representative procedure for the synthesis of **40-TBS** is provided: A solution of **39** (0.0736 mmol) and ethyl (2*R*,3*R*)-2-amino-3-[(4-fluoro-3-nitro)phenyl]-3-[(tertbutyldimethylsilyl)oxy]propionate[8] (41 mg, 0.11 mmol, 1.5 equiv) in THF (4 mL) at 0 ˚C was treated sequentially with *i*-Pr_2NEt (38 µL, 0.2208 mmol, 3.0 equiv) and DEPBT (66 mg, 0.2208 mmol, 3.0 equiv), and the reaction mixture was allowed to warm to room temperature and stirred for 14 h. The reaction was quenched with the addition of saturated aqueous NH_4Cl (10 mL) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (5 x 10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (SiO_2, 1 × 15 cm, 50% EtOAc–hexanes) provided **24** (72 mg, 97% over 2 steps) as a yellow foam. For **40-TBS**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.0 Hz, 1H), 7.39 (s, 1H), 7.13 (s, 1H), 7.07–7.00 (m, 1H), 6.95 (t, *J* = 9.6 Hz, 1H), 6.79 (s, 1H), 6.60 (d, *J* = 6.1 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.21 (s, 1H), 5.91 (s, 1H), 5.67 (d, *J* = 8.6 Hz, 1H), 5.36–5.27 (m, 2H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 4.86 (d, *J* = 9.2 Hz, 1H), 4.71–4.45 (m, 4H), 3.84 (s, 3H), 3.74 (s, 3H), 3.69 (s, 2H), 3.61 (s, 3H), 3.56 (dd, *J* = 3.7, 2.7 Hz, 2H), 3.50–3.46 (m, 2H), 3.37 (s, 3H), 1.40 (s, 9H), 0.84 (s, 9H), 0.00 (s, 3H), –0.19, (s, 3H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{48}H_{68}FN_4O_{16}Si$, 1003.4378; found, 1003.4383.

Compound **40-TBDPS**: ^{1}H NMR (600 MHz, CD_3OD) 7.67–7.62 (m, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.46–7.42 (m, 1H), 7.42–7.38 (m, 1H), 7.37–7.27 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.21–7.10 (m, 2H), 7.07–6.85 (m, 2H), 6.72 (s, 1H), 6.47 (s, 1H), 5.95 (td, *J* = 10.9, 5.3 Hz, 1H), 5.36–5.25 (m, 2H), 5.18 (t, *J* = 9.7 Hz, 2H), 4.71 (s, 1H), 4.58 (dd, *J* = 14.6, 8.7 Hz, 2H), 4.49 (d, *J* = 24.6 Hz, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 3.74–3.63 (m, 1H), 3.64–3.41 (m, 8H), 3.35 (s, 3H), 1.44 (s, 9H), 1.06 (s, 9H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{58}H_{72}FN_4O_{16}Si$, 1127.4691; found, 1127.4692.

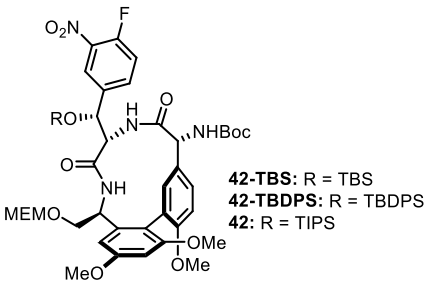
Compound **40**: The reaction has been conducted on scales of 0.3–9.7 g (86–92%) and a representative procedure follows. A solution of **39** (656 mg, 1.01 mmol, 1 equiv) and **11** (545 mg, 1.31 mmol, 1.3 equiv) in EtOAc (4 mL, 6 vol) was treated with DMTMM (364 mg, 1.31 mmol, 1.3 equiv) and stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O (10 mL) and PhMe (5 mL) and stirred at room temperature until all solids dissolved. The aqueous layer was discarded and the organic layer was washed with saturated aqueous NaCl, filtered through Na_2SO_4, and concentrated under reduced pressure. Column chromatography (40 g SiO_2, wet-load PhMe, 60–80% Et_2O–hexanes until **11** fully eluted, then 0–100% EtOAc–Et_2O) provided **40** (973 mg, 92%) as a yellow foam. For **40**: $[\alpha]_D^{25}$ –5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.26–7.17 (m, 2H), 7.15–7.06 (m, 1H), 6.90 (dd, *J* = 10.6, 8.5 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 6.47–6.41 (m, 2H), 5.91–5.86 (m, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 5.34–5.24 (m, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.04 (d, *J* = 6.3 Hz, 1H), 4.83 (d, *J* = 8.9 Hz, 1H), 4.59–4.50 (m, 4H), 3.83 (s, 3H), 3.75 (s, 3H), 3.69

(s, 3H), 3.61 (q, *J* = 5.0 Hz, 1H), 3.54 (m, 5H), 3.51–3.44 (m, 3H), 3.37 (s, 3H), 1.40 (s, 9H), 1.05–0.91 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 169.3, 159.8, 157.69, 157.67, 155.2, 155.0, 153.5, 140.4, 137.0, 136.3, 133.6, 132.4, 131.2, 128.9, 128.3, 125.4, 123.5, 118.7, 117.6, 117.3, 110.2, 110.2, 102.6, 97.1, 94.8, 79.2, 72.3, 71.3, 69.6, 66.4, 65.3, 58.5 (2C), 57.8, 55.2, 55.1, 54.9, 52.0, 51.1, 27.9 (2C), 17.4 (3C), 17.3 (3C), 11.7 (3C); IR (film) ν_{max} 3315, 2943, 1676, 1538, 1505, 1349, 1202, 1160, 1105, 1034, 735, 684 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{51}H_{73}FN_4O_{16}Si$, 1045.4848; found, 1045.4833**.**



41-TBS: R = TBS
41-TBDPS: R = TBDPS
41: R = TIPS

Compounds **41-TBS, 41-TBDPS,** and **41** were synthesized under identical reaction conditions. A representative procedure for the synthesis of **41** is provided: A stirred solution of **40** (8.61 g, 8.2 mmol, 1.0 equiv) in CH_2Cl_2 (82 mL) at 0 ˚C under Ar was treated with $PhSiH_3$ (7.1 ml, 57 mmol, 7.0 equiv) followed by $Pd(PPh_3)_4$ (0.95 g, 0.82 mmol, 10 mol %). The reaction mixture was stirred at 0 ˚C for 1 h and concentrated under reduced pressure. Column chromatography (SiO_2, 5–10% MeOH–CH_2Cl_2) provided the semi-pure amine (7.79 g) as a yellow solid that was dissolved in 50% THF–H_2O (330 mL), cooled to 0 ˚C, and treated with LiOH·H_2O (1.04 g, 24.6 mmol, 3.0 equiv). The reaction mixture was stirred at 0 ˚C for 3 h, acidified with 1 N HCl (23 mL), and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 x 180 mL), and the combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide **41** (7.53 g, 97%/2 steps), which was carried forward without purification.



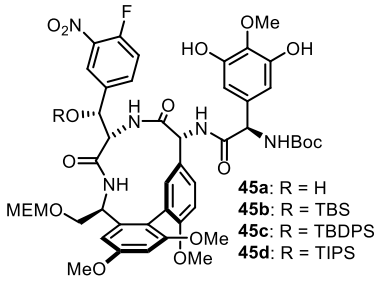
42-TBS: R = TBS
42-TBDPS: R = TBDPS
42: R = TIPS

Compounds **42-TBS** and **42-TBDPS** were prepared under identical reaction conditions. A representative procedure for the synthesis of **42-TBS** is provided**:** Crude **41-TBS** (0.0452 mmol, 1 equiv) was dissolved in THF (45.2 mL, 1 mM concentration) at 0 ˚C and treated with DEPBT (67.6 mg, 0.226 mmol, 5 equiv), followed by N-methylmorpholine (NMM, 50 µL, 0.45 mmol, 10 equiv). The reaction mixture was stirred at room temperature for 48 h, then concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with saturated aqueous NH_4Cl (10 mL) and saturated aqueous NaCl (10 mL), and dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, 2 × 10 cm, 67% EtOAc–hexanes) to afford **42-TBS** (26.1 mg, 65% over 3 steps from **40-TBS**) as a yellow solid. For **42-TBS**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.6 Hz, 1H), 7.67 (s, 1H), 7.19 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.06–6.94 (m, 2H), 6.86 (d, *J* = 11.5 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.49–6.41 (m, 1H), 6.23 (d, *J* = 6.7 Hz, 1H), 5.94 (d, *J* = 11.0 Hz, 1H), 5.11 (s, 1H), 5.09 (s, 1H), 4.86 (d, *J* = 6.7 Hz, 1H), 4.83–4.76 (m, 2H), 4.51 (d, *J* = 7.9 Hz, 1H), 4.28–4.22 (m, 1H), 4.03 (d, *J* = 11.1 Hz, 1H), 3.88 (s, 4H), 3.80 (s, 1H), 3.76 (d, *J* = 14.0 Hz, 2H), 3.73 (d, *J* = 4.6 Hz, 3H), 3.70 (s, 2H), 3.66 (t, *J* = 3.5 Hz, 1H), 3.64 (s, 1H), 3.61–3.59 (m, 1H), 3.35 (d, *J* = 2.2 Hz, 1H), 3.24 (s, 3H), 1.52 (s, 2H), 1.39–1.24 (m, 9H), 0.83 (s, 9H), 0.00 (s, 3H), -0.18 (s, 3H); LRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{43}H_{59}FN_4O_{13}Si$, 909.4; found, 909.4.

Compound **42-TBDPS**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75–7.62 (m, 2H), 7.62–7.48 (m, 6H), 7.47–7.39 (m, 4H), 7.39–7.28 (m, 8H), 7.20 (t, *J* = 7.2 Hz, 3H), 7.17–7.09 (m, 3H), 6.97–6.90 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.64–6.55 (m, 1H), 6.48–6.39 (m, 1H), 6.24 (d, *J* = 11.4 Hz, 1H), 6.09 (d, *J* = 7.1 Hz, 1H), 5.62 (d, *J* = 11.3 Hz, 1H), 5.01 (s, 1H), 4.77–4.64 (m, 3H), 4.53–4.39 (m, 1H), 4.32–4.19 (m, 2H), 3.97–3.86 (m, 6H), 3.81–3.76 (m, 4H), 3.75–3.68 (m, 10H), 3.64 (s, 1H), 3.61–3.58 (m, 1H),

3.56–3.53 (m, 2H), 3.37–3.34 (m, 2H), 3.19 (s, 3H), 1.48–1.40 (m, 9H), 1.04–0.97 (m, 9H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{53}H_{64}FN_4O_{13}Si$, 1011.4218; found, 1011.4224

Compound **42**. A solution of **41** (10.3 g, 11.3 mmol, 1 equiv) in NMP (56 mL, 0.2 M) was added to a stirred suspension of **44**[8] (8.3 g, 21 mmol, 1.9 equiv) and *i*-Pr_2NEt (5.9 mL, 34 mmol, 3 equiv) in NMP (56 mL, final [**41**] = 0.1 M) over 30 min by syringe pump. The reaction mixture was stirred for 2 h post-addition, then diluted with PhMe (400 mL) and washed with 0.5 N HCl (400 mL) and saturated aqueous NaCl (400 mL) and dried over Na_2SO_4. Column chromatography (500 g SiO_2, 30% acetone–hexanes) provided **42** (6.3 g, 61%) as a white solid. For **42**: $[\alpha]_D^{26}$ +16 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.7, 2.6 Hz, 2H), 6.99–6.80 (m, 4H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.20 (t, *J* = 9.1 Hz, 2H), 5.53 (d, *J* = 11.9 Hz, 1H), 5.13–4.96 (m, 2H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 7.1 Hz, 1H), 4.52–4.46 (m, 1H), 4.26–4.23 (m, 1H), 4.13–4.09 (m, 1H), 3.87 (d, *J* = 1.4 Hz, 4H), 3.81 (d, *J* = 3.0 Hz, 2H), 3.77–3.66 (m, 10H), 3.65 (s, 1H), 3.62–3.58 (m, 3H), 3.51 (d, *J* = 4.9 Hz, 1H), 3.36 (d, *J* = 2.3 Hz, 1H), 3.31 (s, 3H), 1.44–1.24 (m, 9H), 1.02–0.89 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 165.4, 160.2, 158.4, 157.0, 156.3, 154.7, 138.5, 137.2, 136.6, 135.3, 133.6, 127.4, 127.1, 124.4, 123.4, 121.2, 118.9, 113.1, 104.4, 97.8, 96.6, 79.8, 74.0, 71.9, 69.4, 67.9, 67.1, 61.3, 58.9, 55.9, 55.8, 55.4, 20.1, 28.4 (3C), 17.9 (6C), 12.0 (3C); IR (film) ν_{max} 2935, 2868, 1670, 1539, 1463, 1349, 1260, 1160, 1097, 1023, 803, 684 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{46}H_{65}FN_4O_{13}Si$, 929.4374; found, 929.4344. The 2D ^1H–^1H ROESY spectrum of **42** [600 MHz, CD_3OD, 1:1 mixture of conformers (A and B)] displayed the following diagnostic NOE crosspeaks: conformer A δ 8.27/5.28, 8.27/4.14, 7.84/5.28, 7.84/4.14, 6.92/4.75, 6.92/4.14, 5.28/4.14, 4.75/4.14; conformer B δ 8.09/4.99, 8.09/4.48, 7.72/4.99, 7.72/4.48, 5.27/4.99, 5.27/4.48, 4.99/4.48.



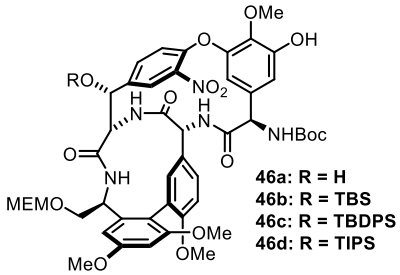
Compound **45a**: A solution of **45b** (54 mg, 0.05 mmol) in THF (0.5 mL) was treated with AcOH (6 µL, 0.105 mmol, 20 equiv) and Bu_4NF (1.0 M in THF, 0.1 mL, 0.1 mmol, 20 equiv). The reaction mixture was stirred at room temperature for 48 h, then concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 20% acetone–CH_2Cl_2) to afford **45a** (35 mg, 74%) as a white solid: ^1H NMR (600 MHz, CD_3OD, 5:1 mixture of conformers, major conformer given) δ 8.24 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.82 (ddd, *J* = 8.7, 4.1, 2.3 Hz, 1H), 7.39 (dd, *J* = 10.9, 8.7 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.39 (s, 2H), 5.19 (s, 1H), 5.04 (d, *J* = 2.8 Hz, 1H), 4.74 (s, 2H), 4.52–4.38 (m, 2H), 4.34 (d, *J* = 2.9 Hz, 1H), 3.88 (s, 3H), 3.86–3.80 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.64 (s, 1H), 3.58 (t, *J* = 4.9 Hz, 3H), 3.37 (s, 4H), 1.42 (s, 9H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{46}H_{55}FN_5O_{17}$, 968.3571; found, 968.3571.

Compounds **45b**–**d** were synthesized under identical reaction conditions and a representative procedure for the synthesis of **45d** is provided**.** A solution of **42** (2.41g, 2.59 mmol, 1 equiv) in 75% HCO_2H–CH_2Cl_2 (16 ml) was stirred for 18 h at room temperature, then concentrated under a stream of N_2. The residue was neutralized with addition of saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (3 x 60 mL). The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to provide the crude amine (2.13 g), which was used without purification. The amine **12** (0.98 g, 3.11 mmol, 1.2 equiv), and *i*-Pr_2NEt (0.86 ml, 7.77 mmol, 3.0 equiv) were dissolved in THF (26 mL) at room temperature and treated with DEPBT (1.16 g, 3.89 mmol, 1.5 equiv) in one portion. The reaction mixture was stirred at room temperature for 18 h, diluted with saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Two rounds of column chromatography (SiO_2, 40–80% EtOAc–hexanes) provided **45d** (1.98 g, 68%) as a light yellow solid. For **45d**: $[\alpha]_D^{27}$ +15 (*c* 1.0, MeOH); ^1H NMR (600 MHz, CD_3OD, 2:1 mixture of conformers) major conformer δ 8.25 (dd, *J* = 7.0, 2.2 Hz, 1H), 8.15–8.07 (m, 1H), 7.83–7.80 (dt, *J* = 8.8, 3.0 Hz, 1H), 7.77–7.65 (m, 1H), 7.48–7.34 (m, 2H), 7.24 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.04–6.98 (m, 2H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.74 (s, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.37 (s, 2H), 5.26 (d, *J* =

2.2 Hz, 1H), 5.02 (d, *J* = 28.7 Hz, 2H), 4.69 (q, *J* = 6.7 Hz, 2H), 4.37 (dd, *J* = 9.1, 4.3 Hz, 1H), 4.16 (d, *J* = 2.3 Hz, 1H), 3.87 (s, 4H), 3.81 (s, 2H), 3.79 (d, *J* = 3.2 Hz, 2H), 3.76 (d, *J* = 5.6 Hz, 4H), 3.71 (d, *J* = 5.2 Hz, 6H), 3.67 (s, 1H), 3.65 (s, 4H), 3.61 (s, 1H), 3.57 (t, *J* = 4.9 Hz, 3H), 3.50 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.37 (s, 3H), 1.42–1.29 (m, 9H), 1.02–0.88 (m, 21H); minor conformer δ 8.09 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.68 (br m, 1H), 7.37 (t, *J* = 9.6 Hz, 1H), 7.13 (br s, 1H), 6.90 (br d, *J* = 8.5 Hz, 1H), 6.74 (s, 1H), 6.54 (s, overlaps with major conformer, 1H), 6.37 (s, overlaps with major conformer, 1H), 5.43 (br s, 1H), 5.13 (br s, 1H), 4.53–4.40 (br s, 1H), 4.16 (s, overlaps with major conformer, 1H), 3.90–3.40 (numerous peaks overlap with major conformer), 3.34 (s, 3H), 1.52–1.20 (peaks overlap with major conformer, 9H, ^{t}Bu), 1.02–0.87 (peaks overlap with major conformer, 21H, Si^{i}Pr$_3$); ^{13}C NMR (151 MHz, CD_3OD) δ 171.0, 170.4, 167.3, 159.9, 157.9, 156.8, 155.4, 153.6, 150.2, 150.0, 138.0, 137.3, 136.3, 135.1, 133.2, 126.5, 125.4, 124.5, 123.8, 123.3, 121.0, 117.8, 112.3, 106.0, 104.3, 97.1, 96.8, 95.0, 94.8, 79.2, 73.5, 71.1, 71.0, 66.6, 66.4, 61.4, 59.7, 58.9, 57.3, 54.4, 54.3, 54.2, 49.9, 16.6 (3C), 16.5 (6C), 11.9 (3C); IR (film) ν_{max} 2939, 2869, 1655, 1503, 1349, 1160, 1101, 1050, 843, 735, 686 cm^{-1}; HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{55}H_{74}FN_5O_{17}Si$, 1124.4906; found, 1124.4875.

For **45b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.0, 2.3 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.83 (ddd, *J* = 8.7, 4.0, 2.3 Hz, 1H), 7.43 (dd, *J* = 10.7, 8.7 Hz, 1H), 7.24 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.04 (dd, *J* = 5.6, 3.2 Hz, 2H), 6.90 (d, *J* = 2.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.37 (s, 2H), 5.18–5.14 (m, 1H), 5.08 (s, 1H), 4.78–4.69 (m, 2H), 4.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.24 (dd, *J* = 2.4, 1.0 Hz, 1H), 3.81 (d, *J* = 6.9 Hz, 3H), 3.78–3.77 (m, 3H), 3.76–3.72 (m, 7H), 3.71 (s, 1H), 3.68 (s, 3H), 3.61–3.57 (m, 1H), 3.39 (s, 2H), 3.37–3.35 (m, 1H), 1.46–1.37 (m, 9H), 0.90 (s, 9H), 0.04 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 160.4, 160.3, 158.3, 157.2, 154.8, 150.5, 146.4, 141.8, 138.1, 137.9, 136.9, 135.6, 135.3, 133.47, 133.44, 124.0, 123.7, 123.2, 121.4, 118.2, 112.7, 108.9, 106.5, 104.8, 97.2, 95.5, 95.2, 85.7, 73.2, 72.8, 72.4, 71.5, 71.4, 67.18, 67.12, 67.1, 63.4, 61.4, 59.4, 59.3, 57.77, 57.70, 54.8, 54.78, 54.77, 54.75, 54.74, 54.65, 54.64, 54.63, 54.4, 50.33, 50.31, 26.9, 24.8, 24.8, 24.7, 17.5, –5.9, –6.3; HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{52}H_{69}FN_5O_{17}Si$, 1082.4436; found, 1082.4449.

For **45c**: ^{1}H NMR (600 MHz, CD_3OD) δ 7.63 (d, *J* = 6.1 Hz, 1H), 7.61 (d, *J* = 6.6 Hz, 1H), 7.54 (ddd, *J* = 8.7, 4.0, 2.3 Hz, 2H), 7.50–7.46 (m, 3H), 7.44–7.31 (m, 8H), 7.29–7.18 (m, 4H), 7.14 (dd, *J* = 10.8, 8.7 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.95 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.83 (d, *J* = 2.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 6.56 (s, 1H), 6.38 (s, 2H), 5.07 (d, *J* = 9.4 Hz, 1H), 5.04 (d, *J* = 2.3 Hz, 1H), 4.64 (d, *J* = 9.4 Hz, 1H), 4.61–4.54 (m, 2H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.36 (dd, *J* = 8.8, 4.2 Hz, 1H), 4.15 (d, *J* = 2.5 Hz, 1H), 3.94 (s, 2H), 3.86 (d, *J* = 3.2 Hz, 4H), 3.80–3.78 (m, 3H), 3.76 (d, *J* = 2.1 Hz, 5H), 3.75–3.68 (m, 5H), 3.66–3.63 (m, 5H), 3.62–3.59 (m, 1H), 3.58–3.56 (m, 1H), 3.56–3.53 (m, 1H), 3.36 (s, 3H), 1.41 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (151 MHz, CD_3OD) δ 170.9, 160.5, 160.3, 158.3, 157.3, 150.7, 150.58, 150.51, 135.76, 135.75, 135.6, 134.1, 132.3, 131.9, 131.8, 131.7, 130.1, 130.0, 129.8, 129.7, 128.6, 128.5, 127.8, 127.6, 127.5, 127.32, 127.31, 127.0, 125.0, 124.9, 123.7, 122.0, 121.3, 112.6, 107.4, 106.5, 106.4, 104.9, 104.7, 97.5, 97.2, 95.4, 95.2, 95.0, 74.9, 73.4, 71.59, 71.52, 71.3, 67.1, 67.0, 66.8, 59.3, 57.7, 54.8, 54.7, 54.6, 54.4, 26.9, 26.1, 26.0, 18.6; HRMS (ESI-TOF) *m/z* [M+H]$^+$ calcd for $C_{62}H_{73}FN_5O_{17}Si$, 1206.4749; found, 1206.4750.



Compounds **46a**–**d** were synthesized under identical reaction conditions. A representative procedure used for the synthesis of **46d** is provided. For compound **46d**, the reaction has been conducted on scales between 7.6 mg–118.6 mg (54–71%, 6–7:1 dr). Cs_2CO_3 (343.7 mg, 2.1 mmol, 20 equiv), $CaCO_3$ (105.6 mg, 2.1 mmol, 20 equiv) and 4Å MS (593 mg, 5 wt equiv) were flame dried under high vacuum, cooled to room temperature under Ar, and suspended in anhydrous DMF (21 mL). Compound **45d** (118.6 mg, 0.45 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through Celite, washed with EtOAc (2 x 20 mL), and concentrated

under reduced pressure. Column chromatography (SiO_2, wet-load CH_2Cl_2, 40–70% EtOAc–hexanes), followed by HPLC (C18, 10 x 250 mm, 3 mL/min, 65–75% CH_3CN–H_2O + 0.7%, R_t (minor) = 24.7 min, R_t (major) = 26.5 min) provided **46d** [62.9 mg, 54% (less polar)] as a white solid and its atropisomer **46d-UN** [10.5 mg, 9%, unnatural atropisomer (more polar)] as a white solid.

For **46a** (natural atropisomer)**:** ^{1}H NMR (600 MHz, CD_3OD) δ 8.29 (d, *J* = 2.1 Hz, 1H), 7.90 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.19 (dd, *J* = 17.4, 8.4 Hz, 2H), 7.08 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.68–6.64 (m, 2H), 5.48 (s, 1H), 5.31 (s, 1H), 5.17 (s, 1H), 4.81–4.77 (m, 2H), 4.68 (s, 1H), 4.40 (dd, *J* = 7.9, 4.2 Hz, 1H), 4.11–4.06 (m, 2H), 3.98 (s, 3H), 3.97–3.94 (m, 1H), 3.91 (s, 3H), 3.80–3.73 (m, 2H), 3.72 (s, 3H), 3.69–3.64 (m, 4H), 3.60 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.40 (s, 3H), 1.45 (s, 9H), HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{46}H_{54}N_5O_{17}$, 948.3509; found, 948.3515.

For **46b** (natural atropisomer): ^{1}H NMR (600 MHz, CD_3OD) δ 8.82 (d, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 8.28 (d, *J* = 2.2, Hz, 1H), 7.84 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.70–6.61 (m, 2H), 5.43 (s, 1H), 5.39 (s, 1H), 5.15 (s, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 4.64 (s, 1H), 4.39 (s, 1H), 4.11–4.08 (m, 1H), 3.96 (s, 3H), 3.94–3.89 (m, 4H), 3.76–3.73 (m, 2H), 3.70 (s, 3H), 3.65 (d, *J* = 1.6 Hz, 3H), 3.61–3.57 (m, 2H), 3.38 (s, 3H), 1.42 (s, 9H), 0.91 (s, 9H), 0.07 (d, *J* = 19.7 Hz, 6H); ^{13}C NMR (151 MHz, CD_3OD) δ 171.4, 170.0, 167.2, 159.9, 158.1, 156.9, 155.7, 151.7, 150.9, 147.8, 142.4, 139.8, 137.5, 135.9, 135.0, 133.8, 133.6, 126.1, 124.5, 123.7, 121.5, 120.7, 111.9, 109.5, 104.5, 103.4, 96.8, 95.2, 78.9, 72.8, 71.0, 66.6, 66.6, 62.7, 59.6, 57.3, 55.8, 54.4, 54.3, 54.1, 53.8, 51.2, 26.8, 24.3, 17.3, –6.6, –6.7; HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{52}H_{67}N_5O_{17}Si$, 1084.4193; found, 1084.4194.

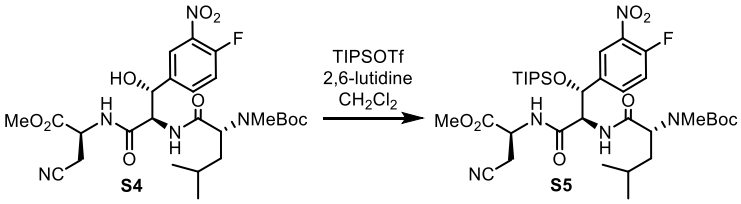
For **46b-UN** (unnatural atropisomer): ^{1}H NMR (600 MHz, CD_3OD) δ 8.98 (d, *J* = 6.2 Hz, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.03 (s, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.94 (s, 1H), 6.65 (d, *J* = 2.4 Hz, 2H), 5.46 (d, *J* = 28.0 Hz, 2H), 5.34 (d, *J* = 2.3 Hz, 1H), 4.78–4.71 (m, 2H), 4.38 (s, 1H), 4.10 (s, 1H), 3.92 (s, 4H), 3.89 (s, 3H), 3.74 (dd, *J* = 5.8, 3.8 Hz, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.60–3.57 (m, 2H), 3.38 (s, 3H), 1.49–1.29 (m, 9H), 0.94 (s, 9H), 0.10 (d, *J* = 9.8 Hz, 6H); LRMS (ESI) m/z $[M+Na^+]$ calcd for $C_{52}H_{67}N_5O_{17}Si$, 1084.4; found, 1084.4

For **46c** (natural atropisomer)**:** ^{1}H NMR (600 MHz, CD_3OD) δ 7.75 (t, *J* = 2.2, 0.4 Hz, 1H), 7.74 (s, 1H), 7.60–7.55 (m, 2H), 7.51–7.47 (m, 2H), 7.45–7.42 (m, 2H), 7.39–7.35 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.97 (s, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.63 (s, 1H), 5.38 (d, *J* = 22.8 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.60 (s, 3H), 4.51 (s, 1H), 4.39 (s, 1H), 4.03 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.88 (dd, *J* = 10.2, 4.3 Hz, 2H), 3.81–3.74 (m, 3H), 3.73 (s, 23H), 3.67–3.61 (m, 3H), 3.41 (s, 3H), 3.37 (d, *J* = 2.2 Hz, 3H), 1.42 (s, 9H), 1.14 (s, 9H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{62}H_{72}N_5O_{17}Si$, 1186.4687; found, 1186.4687.

For **46d** (natural atropisomer): $[\alpha]_D^{28}$ +19 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.26 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.05–6.96 (m, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.68–6.61 (m, 2H), 5.53 (s, 1H), 5.42 (s, 1H), 5.15 (s, 1H), 4.76–4.71 (m, 2H), 4.55 (s, 1H), 4.39 (s, 1H), 4.06 (s, 1H), 3.96 (s, 4H), 3.92–3.84 (m, 4H), 3.73 (q, *J* = 4.9 Hz, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.38 (s, 3H), 1.45–1.27 (m, 9H), 1.15–1.03 (m, 21H); ^{13}C NMR (151 MHz, CD_3OD) δ 172.0, 170.4, 167.6, 160.4, 158.6, 157.4, 156.2, 152.3, 151.5, 148.6, 142.9, 140.6, 137.8, 136.5, 135.5, 134.4, 126.6, 125.0, 124.2, 122.2, 121.3, 112.4, 110.0, 104.9, 104.3, 97.3, 95.6 (2C), 79.4, 73.7, 71.6, 69.2, 67.0, 66.8, 63.2, 60.2, 57.8, 56.2, 54.8, 54.6 (2C), 54.5, 51.7, 28.1 (3C), 17.2 (6C), 12.1 (3C); IR (film) ν_{max} 2937, 1659, 1581, 1535, 1505, 1463, 1348, 1264, 1200, 1161, 1108, 1032, 734, 702 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{55}H_{73}N_5O_{17}Si$, 1104.4843; found, 1104.4843. The 2D ^{1}H–^{1}H ROESY spectrum of natural atropisomer **46d** (600 MHz, CD_3OD) displayed the following diagnostic NOE crosspeaks: δ 8.26/5.53, 8.26/4.06.

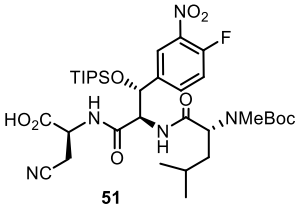
For **46d-UN** (unnatural atropisomer): $[\alpha]_D^{26}$+14 (c 0.5, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.18 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.00 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 2H), 5.60 (s, 1H), 5.48 (s, 1H), 5.30–5.26 (m, 1H), 4.75–4.71 (m, 2H), 4.64 (s, 1H), 4.39 (s, 1H), 4.08 (s, 1H), 3.97 (d, *J* = 13.1 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 4H), 3.73 (q, *J* = 4.6 Hz, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.38 (s, 3H), 1.44 (s, 9H), 1.16–1.04 (m, 21H); ^{13}C NMR (151 MHz, CD_3OD) δ 175.9, 171.8, 169.8, 167.1, 159.9, 158.2, 156.9, 155.8, 152.2, 150.9, 147.1, 142.0 140.6, 137.3, 135.6, 133.9, 129.8, 129.0, 126.2, 124.1, 123.7, 120.9, 112.0,

108.6, 104.5, 103.1, 96.8, 95.1 (2C), 79.1, 73.0, 71.1 (2C), 66.6, 66.3, 59.7, 57.3, 55.6, 54.4, 54.2, 53.9, 51.2, 28.9, 26.8 (3C), 16.7 (6C), 11.8 (3C); IR (film) ν_{max} 2926, 1656, 1581, 1536, 1507, 1460, 1349, 1261, 1200, 1161, 1103, 1021, 652, 608 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{55}H_{73}N_5O_{17}Si$, 1104.4843; found, 1104.4840. The 2D ^1H-^1H ROESY spectrum of unnatural atropisomer **46d-UN** (600 MHz, CD_3OD) displayed the following diagnostic NOE crosspeaks: δ 7.78/5.60, 7.78/4.08.

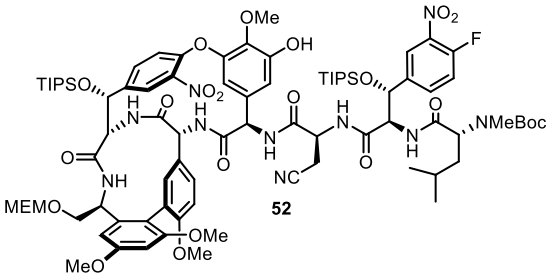


A solution of **S4**[8] (155 mg, 0.267 mmol) in CH_2Cl_2 (8 mL) at 0 ˚C was treated with 2,6-lutidine (186 µL, 1.60 mmol, 6 equiv) and TIPSOTf (216 µL, 0.800 mmol, 3 equiv). The reaction mixture was stirred at 0 °C for 12 h, quenched by addition of saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (SiO_2, 1 × 15 cm, 33% EtOAc–hexanes) provided **S5** (176 mg, 90%) as a colorless foam. For **S5**: $[\alpha]_D^{25}$ +37 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers, integration relative to -OMe (3H) peak at 3.78 ppm) δ 8.04 (s, 0.7H), 7.74–7.71 (m, 1H), 7.32 (s, 0.6H), 6.93 (s, 0.6H), 6.59 (s, 0.24H), 6.48 (s, 0.6H), 6.23 (s, 0.1H), 5.59 (broad overlapping peaks, 1H), 4.94 (br s, 0.9H), 4.66 (br s, 1H), 4.45 (br s, 0.6H), 3.79 (s, 3H, -OMe), 2.94 (q, *J* = 9.6, 7.5 Hz, 2H), 2.73 (s, 3H, -NMe), 1.69–1.64 (m, 2H), 1.42 (s, 9H), 1.12–1.07 (m, 3H), 1.04 (d, *J* = 7.2 Hz, 9H), 0.99 (d, *J* = 7.1 Hz, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 170.7, 168.1, 155.6, 153.8, 136.6, 136.3, 133.2, 123.8, 118.4, 115.1, 80.5, 71.7, 59.9, 59.4, 53.0, 48.4, 36.1, 30.8, 27.8 (3C), 24.4, 22.6, 21.3, 17.4 (6C), 13.7, 11.7 (3C); IR (film) ν_{max} 2949, 2869, 1751, 1672, 1540, 1366, 1348, 1254, 1151, 1106, 685, 609 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{35}H_{56}FN_5O_9Si$, 738.3904; found, 738.3910.

*The dr of **S4** as prepared by the reported method was typically 4–9:1; thus, we purified **S4** additionally by HPLC (Luna C18(2) 100 Å, 100 x 30 mm, 65–75% CH_3CN–H_2O + 0.7% TFA, 10 mL/min, ≤15 mg/injection) to ≥95:5 dr prior to TIPS protection. Separation of the corresponding diastereomers of **S5** by HPLC or PTLC was unsuccessful.

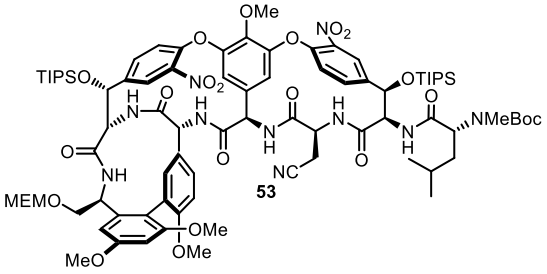


Compound 51. A solution of **S5** (111.1 mg, 0.15 mmol, 1 equiv) in 50% *t*-BuOH–H_2O (4 mL) was cooled to 0 °C, treated with $LiOH{\cdot}H_2O$ (12.6 mg, 0.30 mmol, 2 equiv), and stirred for 45 min. The reaction mixture was then acidified with aqueous 1 N HCl and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide **51** as a white foam, which was carried forward without purification.



Compound 52. A solution of **46d** (9.9 mg, 0.009 mmol, 1 equiv) in CH_2Cl_2 (0.3 mL) was treated with formic acid (0.3 mL) and stirred at room temperature for 12 h. The reaction mixture was concentrated under a stream of N_2, diluted with $CHCl_3$

(10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was combined with **51** (0.018 mmol, 2 equiv), dissolved in THF (0.2 mL), cooled to 0 ˚C, and treated sequentially with solid $NaHCO_3$ (4.5 mg, 0.054 mmol, 6 equiv) and DEPBT (10.8 mg, 0.036 mmol, 4 equiv). The reaction mixture was stirred for 48 h at 0 ˚C, diluted with $CHCl_3$ (10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 100% EtOAc) provided **52** (9.9 mg, 64% over 2 steps) as a yellow solid. For **52**: $[\alpha]_D^{28}$ +19 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.25 (d, *J* = 2.2 Hz, 1H), 8.13 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.85 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.64 (br s, 1H), 7.19–7.08 (m, 2H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.64 (overlapping peaks, 2H), 6.59 (s, 1H), 5.80 (s, 1H), 5.53 (s, 1H), 5.35 (t, *J* = 6.5 Hz, 1H), 5.34 (br s, 1H), 5.21 (s, 1H), 4.80 (d, *J* = 6.1 Hz, 1H), 4.73 (overlapping peaks, 3H), 4.58 (s, 1H), 4.55 (br s, 1H), 4.38 (br s, 1H), 4.06 (s, 1H), 4.01–3.98 (m, 2H), 3.97 (s, 3H), 3.91 (s, 1H), 3.90 (s, 3H), 3.87 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.75–3.71 (m, 2H), 3.70 (s, 3H), 3.65 (s, 1H), 3.63–3.54 (m, 3H), 3.38 (s, 3H), 2.99–2.87 (m, 2H), 2.59 (s, 3H), 1.64–1.57 (m, 1H), 1.43 (s, 9H), 1.14–1.00 (m, 42H), 0.99–0.94 (m, 3H), 0.90 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 173.3, 170.6, 169.3, 167.9, 167.2, 159.9, 158.2, 156.9, 155.3, 153.5, 151.9, 151.1, 142.5, 140.1, 137.3, 136.6, 136.5, 135.0, 133.9, 132.6, 129.0, 126.2, 126.1, 124.4 (2C), 124.2, 124.1, 123.8, 121.6, 120.8, 117.6, 117.5, 116.1, 112.0, 109.9, 104.5, 96.8, 95.1 (2C), 79.8, 73.2, 71.1 (2C), 66.6, 66.3, 62.8, 59.8, 57.3 (2C), 54.9, 54.5, 54.4, 54.2 (2C), 51.2, 48.9, 36.1 31.2, 26.8 (2C), 21.9, 20.2, 16.7 (12C), 16.5 (6C), 12.6, 11.6 (3C); IR (film) ν_{max} 2926, 2866, 1652, 1537, 1508, 1349, 1260, 1101, 1022, 800, 685 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{84}H_{117}FN_{10}O_{23}Si_2$, 1709.7888; found, 1709.7819.

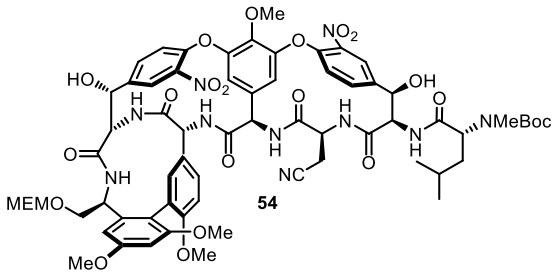


53

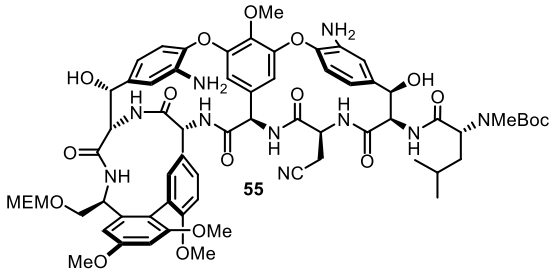
Compound 53. A vial containing Cs_2CO_3 (35.2 mg, 0.108 mmol, 18 equiv), $CaCO_3$ (12.0 mg, 0.12 mmol, 20 equiv), 4Å MS (20.4 mg, 2 wt equiv) was flame dried under high vacuum and cooled to room temperature under Ar. A solution of **52** (10.2 mg, 0.006 mmol) in DMF (1.0 mL) was added, and the vial and syringe used to transfer **52** were rinsed with additional DMF (0.5 mL). The reaction mixture was stirred at room temperature for 10 h, filtered through a plug of Celite, and quenched with the addition of saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic phase was washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 75% EtOAc–hexanes) provided **53** (6.0 mg, 59%) as a white solid and its atropisomer (0.6 mg, 5.9%) as a white solid. Typically, the ratio of atropisomers was 10–11:1. For **53**: $[\alpha]_D^{25}$ +14 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.15 (overlapping peaks, 2H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.07–7.03 (m, 3H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 5.78 (d, *J* = 4.9 Hz, 1H), 5.70 (d, *J* = 2.0 Hz, 1H), 5.59 (s, 1H), 5.48 (s, 1H), 5.24 (d, *J* = 4.9 Hz, 1H), 5.16 (s, 1H), 4.92 (d, *J* = 11.8 Hz, 1H), 4.72 (s, 2H), 4.63 (s, 1H), 4.39 (s, 1H), 4.27 (s, 3H), 4.16 (s, 1H), 4.01–3.97 (m, 1H), 3.90 (s, 3H), 3.85 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.74–3.69 (m, 5H), 3.64 (s, 3H), 3.57 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.37 (s, 3H), 2.96 (dd, *J* = 17.3, 4.4 Hz, 1H), 2.86 (s, 3H), 2.62 (dd, *J* = 17.4, 10.0 Hz, 1H), 1.55–1.29 (m, 12H), 1.26–1.19 (m, 3H), 1.16–1.08 (m, 30H), 1.05 (d, *J* = 7.5 Hz, 9H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.92–0.88 (m, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 172.4, 170.0, 169.4, 169.0, 167.6, 167.0, 160.0, 158.1, 157.3, 156.6, 153.1, 152.9, 148.0, 147.7, 143.4, 139.9, 138.4, 138.3, 137.2, 135.0, 134.5, 132.8, 132.7, 129.0, 126.0, 125.6, 125.5, 124.5, 124.0, 123.8, 122.0, 120.8, 115.8, 112.1, 106.3, 104.8, 104.4, 96.8, 95.0 (2C), 80.2, 76.4, 73.3, 72.1, 71.1, 66.5, 66.1, 63.3, 60.7, 58.8, 57.3, 55.1, 54.4, 54.3, 53.4, 51.2, 49.6, 35.0, 28.4, 27.0 (3C), 24.0, 22.1 (2C), 19.7, 16.9 (3C), 16.8 (6C), 16.7 (3C), 11.9 (3C), 11.4 (3C); IR (film) ν_{max} 3291, 2924, 2855, 1656, 1536, 1462, 1261, 1086, 1020, 801, 739, 704, 634 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{85}H$-$N_{10}O_{23}Si_2$, 1689.7823; found, 1689.7849. The 2D ^{1}H-^{1}H ROESY spectrum of **53** (600 MHz, CD_3OD, natural atropisomer) displayed the following diagnostic NOE crosspeaks: δ 8.15/5.59, 8.15/4.16, 7.77/5.78.

For **53-UN** (unnatural atropisomer): ^{1}H NMR (600 MHz, CD_3OD) δ 8.22 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.3 Hz,

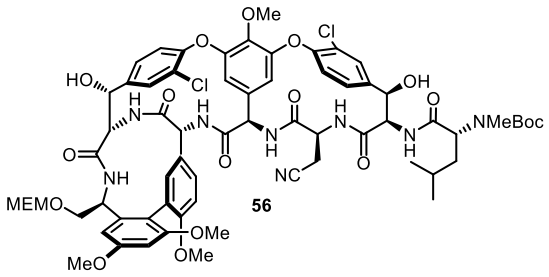
1H), 7.81 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.10–7.06 (m, 1H), 7.04–7.00 (m, 2H), 6.89 (dd, *J* = 13.6, 2.3 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 5.76 (d, *J* = 4.8 Hz, 1H), 5.69 (s, 1H), 5.58 (s, 1H), 5.45 (s, 1H), 5.36–5.33 (m, 1H), 5.22 (d, *J* = 4.8 Hz, 1H), 4.72 (s, 2H), 4.58 (s, 2H), 4.24 (s, 3H), 4.12 (d, *J* = 5.4 Hz, 1H), 4.01–3.95 (m, 1H), 3.89 (s, 3H), 3.85 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.75–3.68 (m, 5H), 3.63 (d, *J* = 1.1 Hz, 3H), 3.57 (dd, *J* = 5.3, 4.3 Hz, 2H), 3.37 (s, 3H), 2.92 (dd, *J* = 17.2, 5.1 Hz, 1H), 2.85 (s, 3H), 2.61 (dd, *J* = 17.3, 9.7 Hz, 1H), 1.57–1.27 (m, 12H), 1.22–1.18 (m, 3H), 1.13–1.03 (m, 39H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.92–0.88 (m, 3H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{85}HN_{10}O_{23}Si_2$, 1689.7823; found, 1689.7822.



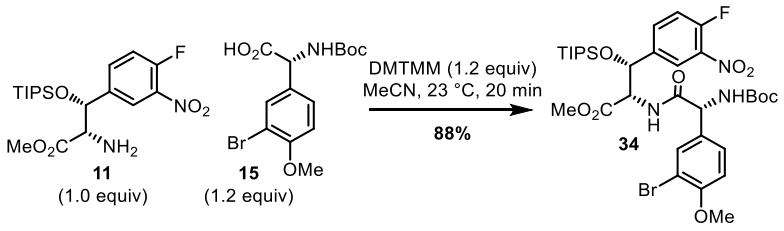
Compound 54. A solution of **53** (4.5 mg, 0.0027 mmol) in THF (0.4 mL) was treated with HOAc (2.4 µL, 0.043 mmol, 16 equiv) and Bu_4NF (1 M in THF, 32 µL, 0. 0.032 mmol, 12 equiv). The reaction mixture was stirred at room temperature for 12 h, diluted with saturated aqueous NH_4Cl (5 mL), extracted with $CHCl_3$ (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 10% MeOH–CH_2Cl_2) provided **54** (3.6 mg, 98%) as a white solid. For **54**: $[\alpha]_D^{26}$ +29 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.29 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.88 (s, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.09–7.04 (m, 2H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 5.96 (s, 1H), 5.70 (s, 1H), 5.48 (d, = 5.0 Hz, 1H), 5.42 (s, 1H), 5.33 (d, *J* = 1.5 Hz, 1H), 4.77 (s, 2H), 4.65 (s, 1H), 4.58 (s, 1H), 4.37 (dd, *J* = 7.8, 4.3 Hz, 1H), 4.21 (s, 3H), 4.14 (dd, *J* = 9.2, 7.1 Hz, 1H), 4.08–4.03 (m, 1H), 3.93 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.89 (s, 3H), 3.78–3.67 (m, 6H), 3.64 (s, 3H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.38 (s, 3H), 2.85 (s, 1H), 2.80 (s, 3H), 2.66 (dd, *J* = 17.7, 8.3 Hz, 1H), 1.56–1.29 (m, 12H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 173.6, 172.7, 170.5, 169.8, 169.7, 168.2, 167.8, 160.4, 158.6, 157.5, 153.4, 153.3, 148.2, 147.6, 143.7, 141.0, 140.8, 139.0, 138.3, 138.0, 135.4, 134.2, 133.7, 133.5, 132.7, 126.7, 126.2, 125.7, 124.7, 124.4, 124.0, 122.8, 121.1, 116.1, 112.4, 107.2, 105.1, 104.9, 97.2, 95.4, 80.7, 72.5, 71.5, 70.3, 67.1, 66.8, 63.3, 60.9, 59.7, 57.8, 55.3, 54.9, 54.8, 54.6, 54.5, 53.4, 51.6, 35.0, 27.5 (3C), 24.3, 22.5, 17.2, 17.1, 11.9; IR (film) ν_{max} 3278, 2924, 2854, 1651, 1535, 1464, 1348, 1260, 1235, 1086, 1021, 800, 736, 702, 622 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{67}H_{80}N_{10}O_{23}$, 1377.5187; found, 1377.5163.



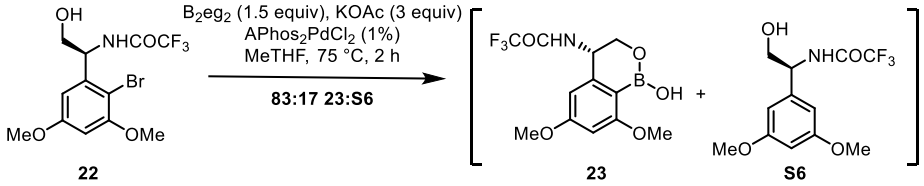
Compound 55. A solution of **54** (5.3 mg, 0.0039 mmol) in 0.4 mL degassed acetone was treated with 0.08 mL degassed saturated aqueous NH_4Cl, followed by Zn^0 (nanopowder, 20.1 mg, 0.31 mmol, 80 equiv). The reaction mixture was stirred at room temperature for 4 h before the solvent was removed under a stream of N_2. The residue was suspended in EtOAc and purified by passage through a short plug of SiO_2 (10% MeOH–CH_2Cl_2), providing **55** as an air-sensitive white solid that was carried forward without further purification.



Compound 56. A solution of crude **55** (0.0039 mmol) in CH_3CN (0.2 mL) was treated with HBF_4 (0.1 mM in CH_3CN, 1.2 µL, 0.0096 mol, 2.5 equiv) at 0 ˚C, and the reaction mixture was stirred at 0 ˚C for 2 min before the dropwise addition *t*-BuONO (0.1 mM in CH_3CN, 1.3 µL, 0.0096 mol, 2.5 equiv). The resulting mixture was stirred at 0 ˚C for 30 min, cooled to –35 ˚C, and stirred vigorously as a chilled (0 ˚C) suspension of CuCl (38.1 mg, 0.39 mmol, 100 equiv) and $CuCl_2$ (62.1 mg, 0.46 mmol, 120 equiv) in 50% CH_3CN–H_2O (0.2 mL) was added dropwise. The heterogeneous mixture was warmed to room temperature and stirred for 45 min, quenched with saturated aqueous NH_4Cl (4 mL) and $NaHCO_3$ (4 mL), and extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 10% MeOH–CH_2Cl_2) provided **56** (2.8 mg, 54% over 2 steps) as a white solid. The spectral data for **56** were in accordance with the literature values.[9] For **56**: $[\alpha]_D^{27}$ +32 (c 0.4, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 9.11 (d, -CONH-, *J* = 5.8 Hz, 1H), 8.28 (d, -CONH-, *J* = 5.8 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.64–7.59 (m, 2H), 7.56 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.32 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.94–6.88 (m, 2H), 6.63 (d, *J* = 2.3 Hz, 1H), 5.82 (br s, 1H), 5.68 (s, 1H), 5.47 (s, 1H), 5.37 (d, *J* = 5.1 Hz, 1H), 5.22 (s, 1H), 4.98–4.93 (m, 1H), 4.93–4.78 (2 m, 2H, obscured by H_2O), 4.76 (s, 2H), 4.62 (d, *J* = 5.7 Hz, 1H), 4.39–4.30 (m, 1H), 4.15 (s, 3H), 4.10–4.02 (m, 2H), 3.93 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.88 (s, 3H), 3.78–3.69 (m, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.58 (t, *J* = 4.7 Hz, 2H), 3.37 (s, 3H), 2.79 (br dd, J = 16.6, 5.8 Hz, 1H, obscured by -NMe), 2.78 (s, 3H), 2.60 (dd, *J* = 17.1, 8.2 Hz, 1H), 1.88–1.80 (m, 1H), 1.55 (s, 9H), 1.37–1.25 (m, 2H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H); IR (film) ν_{max} 3308, 2927, 1651, 1583, 1505, 1420, 1318, 1261, 1236, 1156, 1061, 1027, 803, 614 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{67}H_{80}Cl_2N_8O_{19}$, 1355.4682; found, 1355.4678.

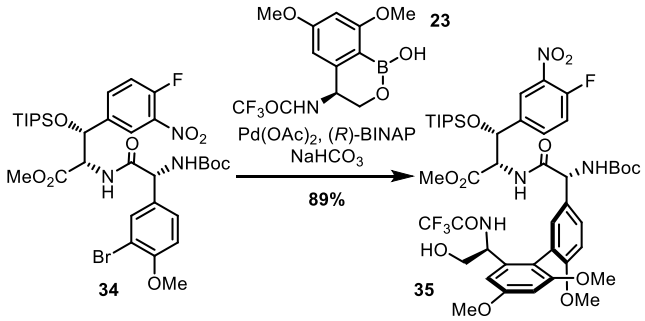


Methyl (2*S*,3*R*)-2-((*R*)-2-(3-Bromo-4-methoxyphenyl)-2-((*tert*-butoxycarbonyl)amino)acetamido)-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoate (34). A stirred solution of **11** (2.16 g, 4.85 mmol, 1 equiv) and **15**[6] (2.08 g, 5.77 mmol, 1.2 equiv) in CH_3CN (58 mL) was treated with DMTMM (1.60 g, 5.78 mmol, 1.2 equiv). The resulting suspension was stirred for 20 min at room temperature, diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (80 g SiO_2, 15–20% EtOAc–hexanes) provided **34** (3.24 g, 88%) as a yellow solid: mp 67–70 ˚C; R_f 0.67 (65% EtOAc–hexanes); $[\alpha]_D^{24}$ –39.0 (*c* 1.06, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 5.2 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.19–7.13 (m, 2H), 7.08 (dd, *J* = 10.1, 8.6 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.37 (br s, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 5.45 (d, *J* = 1.8 Hz, 1H), 5.04 (br s, 1H), 4.68–4.66 (m, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 1.39 (s, 9H), 0.93 (s, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0, 169.58, 169.56, 156.2, 155.8, 155.0, 154.0, 137.87, 137.84, 136.82, 136.77, 132.85, 132.80, 132.1, 127.5, 123.5, 118.5, 118.3, 112.4, 112.2, 80.3, 73.2, 58.6, 58.5, 56.3, 53.0, 29.7, 28.3, 17.88, 17.84, 17.78, 12.38, 12.33; IR ν_{max} 3351, 2923, 2867, 1742, 1672, 1620, 1601, 1539, 1495, 1463, 1438, 1348, 1286, 1257, 1206, 1165, 1102, 1056, 1020, 914, 883, 808 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{33}H_{48}BrFN_3O_9Si$, 756.2327; found, 756.2326.



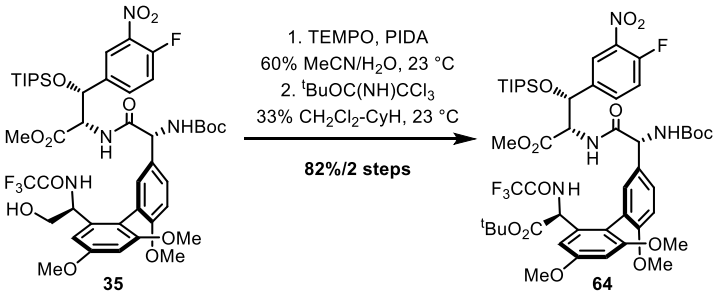
(*S*)-2,2,2-Trifluoro-*N*-(1-hydroxy-6,8-dimethoxy-3,4-dihydro-1*H*-benzo[*c*][1,2]oxaborinin-4-yl)acetamide (23). The reaction has been conducted on scales from 1.5–37 g (81 – 85%) and a representative procedure follows. An oven-dried round-bottom flask was charged with **22** (5.16 g, 13.8 mmol, 1 equiv), B_2eg_2 (2.94 g, 21 mmol, 1.5 equiv), $APhos_2PdCl_2$ (98 mg, 0.14 mmol, 0.01 equiv), and anhydrous KOAc (4.0 g, 41 mmol, 3 equiv). The vessel was flushed with Ar and MeTHF (92 mL, 18 vol) was added. The resulting suspension was sparged with Ar while stirring at room temperature for 10 min, and then stirred at 75 ˚C for 2 h, at which point LC/MS indicated full consumption of **22**. The resulting suspension was cooled to room temperature and saturated aqueous $NaHCO_3$ (138 mL, 138 mmol, 10 equiv) was added. The mixture was stirred at room temperature for 30 min, and the aqueous layer was removed. NMR analysis of the organic layer indicated that the ratio of **23** to **S6** was 83:17,* with no additional byproducts detected (approximately 83% yield of **23**, used directly in the next step as a solution in MeTHF). An analytically pure sample of **23** was obtained by PTLC (SiO_2, 60% EtOAc–hexanes) as a white solid. For **23**: mp 134–137 ˚C; R_f 0.32 (60% EtOAc–hexanes); $[\alpha]_D^{23}$ +117 (*c* 1.06, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.1 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.44 (s, 1H), 5.09 (dt, *J* = 8.5, 2.8 Hz, 1H), 4.33–4.27 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 164.7, 156.9 ($^2J_{CF}$ = 38 Hz), 146.2, 115.9 ($^1J_{CF}$ = 287 Hz), 106.6, 105.1, 98.6, 66.6, 55.8, 55.7, 50.1; IR ν_{max} 3304, 2955, 1716, 1697, 1598, 1580, 1551, 1459, 1428, 1367, 1338, 1281, 1257, 1206, 1192, 1157, 1123, 1079, 1049, 977, 929, 911, 837 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{12}H_{12}BF_3NO_5$, 317.0797; found, 317.0798.

*The following resonance was used for quantitation of **S6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.79 (s, 6H, -OMe x 2).



Methyl (2*S*,3*R*)-2-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-((*S*)-2'-((*S*)-2-hydroxy-1-(2,2,2-trifluoroacetamido)ethyl)-4',6,6'-trimethoxy-[1,1'-biphenyl]-3-yl)acetamido)-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoate (35). The reaction has been conducted on scales up to 25 g (82–93%) and a representative procedure follows. An oven-dried round-bottom flask was charged with **34** (3.7 g, 4.89 mmol, 1 equiv), $Pd(OAc)_2$ (312 mg, 1.39 mmol, 0.3 equiv), and (*R*)-BINAP (1.0 g, 1.62 mmol, 0.35 equiv). The vessel was flushed with Ar and MeTHF (46 mL, 12 vol) was added. The reaction mixture was stirred at room temperature for 10 min while sparging with Ar, then treated with saturated aqueous $NaHCO_3$ (degassed, 23 mL, ca. 23 mmol, 5 equiv) and warmed at 75 ˚C. The crude MeTHF solution of **23** and **S6** from the previous step (approximately 11.5 mmol, 2.3 equiv) was added over 1 h to the stirred reaction mixture at 75 ˚C by addition funnel. The reaction mixture was stirred for an additional 1 h at 75 ˚C, cooled to room temperature, and the aqueous layer was removed. The organic layer was dried over Na_2SO_4, filtered through Celite, and the flask and filter cake were rinsed with EtOAc. The combined organic phase was concentrated under reduced pressure and the residue was purified by column chromatography (200 g SiO_2, wet-load CH_2Cl_2, 35–60% EtOAc–hexanes) to provide **35** (4.23 g, 89%) as a light gray solid: mp 100–103 ˚C; R_f 0.27 (50% EtOAc–hexanes); $[\alpha]_D^{24}$ –5.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.27–7.22 (m, 2H), 7.14 (br s, 1H), 7.09–7.01 (m, 2H), 6.89–6.85 (m, 2H), 6.49 (m, 2H), 5.91 (br s, 1H), 5.43 (s, 1H), 5.08 (br s, 1H), 4.83–4.78 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.63–3.57 (m, 5H), 2.11 (br s, 1H), 1.39 (s, 7.8H, Boc), 1.25 (s, 1.2H, Boc), 1.06–0.95 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 169.8, 160.6, 158.5, 158.0, 157.1, 156.9, 156.6, 156.4, 155.9, 155.8, 154.1, 138.5, 137.82, 136.76, 136.72, 133.86, 133.83, 131.5, 129.6, 128.7, 125.6, 124.2, 119.4,

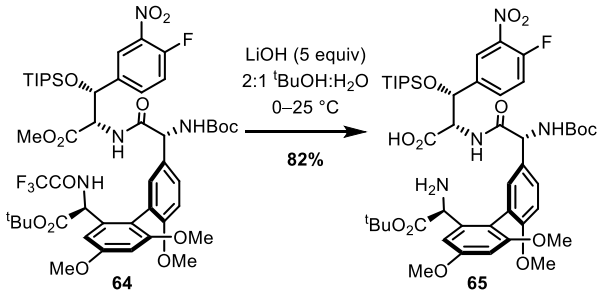
118.3, 118.2, 116.8, 114.9, 110.9, 103.4, 97.9, 80.0, 73.0, 64.2, 58.6, 58.5, 55.73, 55.65, 55.4, 53.5, 52.5, 29.8, 28.3, 17.9, 17.8, 12.3; IR (film) ν_{max} 3415, 3328, 2942, 2871, 1746, 1709, 1677, 1608, 1538, 1502, 1465, 1348, 1319, 1260, 1201, 1158, 1102, 1065, 815 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{45}H_{61}F_4N_4O_{13}Si$, 969.3941; found, 969.3967.



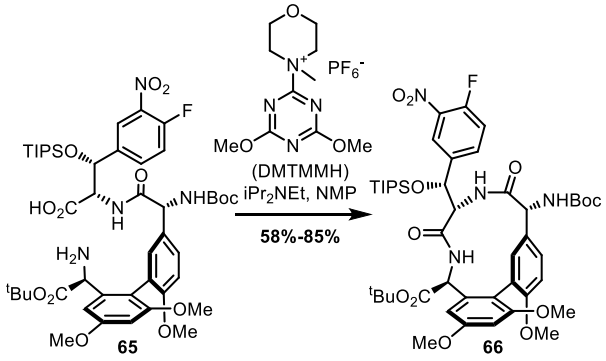
(2*S*,3*R*)-2-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-((*R*)-2'-((S)-carboxy(2,2,2-trifluoroacetamido)methyl)-4',6,6'-trimethoxy-[1,1'-biphenyl]-3-yl)acetamido)-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoic Acid (63). A solution of **35** (26.0 g, 26.8 mmol, 1 equiv) and TEMPO (2.5 g, 16 mmol, 0.6 equiv) in CH_3CN (390 mL, 15 vol) was diluted with H_2O (260 mL, 10 vol) and $PhI(OAc)_2$ (PIDA, 21.6 g, 67 mmol, 2.5 equiv) was added in one portion. The reaction mixture was stirred at room temperature for 2 h, and a second portion of PIDA (1.7 g, 5.3 mmol, 0.2 equiv) was added. Stirring was continued for 1 h, at which point the ratio of **63**:aldehyde intermediate was >98:2 by LC/MS integration at 254 nm. The reaction mixture was quenched with the addition of saturated aqueous sodium thiosulfate ($Na_2S_2O_3$, 100 mL) and concentrated at 40 ˚C under reduced pressure to remove CH_3CN. The reaction mixture was extracted with CH_2Cl_2 (3 x 200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography [400 g SiO_2, wet-load CH_2Cl_2, 3–10% MeOH–CH_2Cl_2] provided semi-pure **63** (25 g) as an orange solid. An analytically pure sample of **63** was obtained by PTLC (SiO_2, 10% MeOH–CH_2Cl_2) from a 30 mg scale reaction in 86% isolated yield. For **63**: mp 120–123 ˚C; R_f 0.20 (5% MeOH–CH_2Cl_2); $[\alpha]_D^{20}$ +51 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.45 (br s, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 9.5 Hz, 1H), 7.05 (s, 1H), 7.03 (s, 1H), 7.01 (s, 1H), 6.90 (br s, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 5.82 (br s, 1H), 5.37 (d, *J* = 2.8 Hz, 1H), 5.33 (d, *J* = 7.8 Hz, 1H), 5.02 (br s, 1H), 4.79 (d, *J* = 8.6 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H), 1.42 (s, 9H), 1.03 – 0.93 (m, 21H); ^{13}C NMR (151 MHz, CD_3OD) δ 173.3 172.9, 170.6, 162.0, 160.0, 159.7, 157.8, 157.5, 157.3, 156.7, 154.9, 139.1, 138.2, 138.1, 137.9, 135.29, 135.23, 132.5, 130.4, 129.9, 126.7, 125.2, 121.6, 118.9, 118.8, 118.3, 116.4, 112.2, 105.3, 99.8, 80.7, 74.3, 59.6, 59.3, 56.2, 56.1, 55.9, 55.5, 52.9, 28.6, 18.37, 18.35, 13.4; IR (film) ν_{max} 3367, 2921, 2851, 1711, 1678, 1608, 1538, 1489, 1462, 1348, 1264, 1203, 1160, 1103, 1063, 1032, 911, 884, 835 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{45}H_{59}F_4N_4O_{14}Si$, 983.3733; found, 983.3755.

Methyl (2*S*,3R)-2-((R)-2-((*S*)-2'-((S)-2-(*tert*-Butoxy)-2-oxo-1-(2,2,2-trifluoroacetamido)ethyl)-4',6,6'-trimethoxy-[1,1'-biphenyl]-3-yl)-2-((*tert*-butoxycarbonyl)amino)acetamido)-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoate (64). A stirred solution of **63** from the previous step (25 g, ca. 26 mmol) in CH_2Cl_2 (25 mL, 1 vol) was diluted with cyclohexane (CyH, 50 mL, 2 vol) and *tert*-butyl trichloroacetimidate (1.1 mL, 6.1 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 5 h at room temperature, then a second portion of *tert*-butyl trichloroacetimidate (20.0 mL, 112 mmol, 4 equiv) was added. After 24 h, the ratio of **64**:**63** was 93:7 (93% conv) by LC/MS at 254 nm. A second portion of *tert*-butyl trichloroacetimidate (10 mL, 52 mmol, 2 equiv) was added, and the reaction mixture was stirred for an additional 24 h (95% conv), diluted with hexanes (25 mL), and filtered, rinsing the precipitated trichloroacetamide with minimal 30% CH_2Cl_2–hexanes. The filtrate was concentrated at 45 ˚C under reduced pressure and and the residue was purified by column chromatography [500 g SiO_2, wet-load CH_2Cl_2, flushed with 10 L CH_2Cl_2 (until trichloroacetamide fully eluted), then 5% acetone–CH_2Cl_2 (5 L)] to provide **64** (23.0 g, 82%) as a yellow foam: mp 91–94 ˚C; R_f 0.39 (30% EtOAc–hexanes); $[\alpha]_D^{19}$ +39 (*c* 0.61, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.29–7.26 (m, 2H), 7.21–7.14 (m, 2H), 6.99 (dd, *J* = 10.5, 8.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.09 (d, *J* = 6.4 Hz, 1H), 5.41 (br s, 1H), 5.27 (d, *J* = 8.3 Hz, 1H), 5.03 (d, *J* = 6.5 Hz, 1H), 4.82 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.67 (s, 3H), 3.59 (s, 3H), 1.41 (s, 9H), 1.34 (s, 9H), 1.01–0.93 (m, 21H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 169.7, 169.0, 160.6, 159.0, 158.1, 155.8, 155.7, 155.6, 155.5, 154.0, 137.8, 136.8, 136.7, 136.0, 133.97, 133.92, 131.5, 129.3, 129.0, 124.8, 124.0, 120.4, 118.1, 117.9, 116.6, 114.7, 110.7, 102.5, 99.0, 83.6, 79.7,

73.0, 58.6, 58.5, 55.7, 55.6, 55.5, 54.3, 52.4, 29.7, 28.3, 27.7, 17.8, 12.2; IR (film) ν_{max} 3356, 2924, 2866, 1731, 1711, 1679, 1608, 1539, 1489, 1463, 1367, 1347, 1261, 1203, 1156, 1101, 1067, 882, 835 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{49}H_{67}F_4N_4O_{14}Si$, 1039.4359; found, 1039.4379.



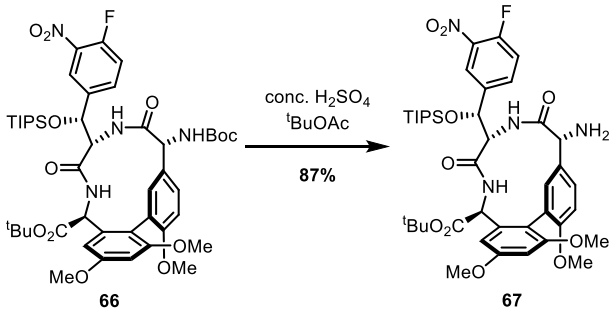
(2*S*,3*R*)-2-((*R*)-2-((*S*)-2'-((*S*)-1-Amino-2-(*tert*-butoxy)-2-oxoethyl)-4',6,6'-trimethoxy-[1,1'-biphenyl]-3-yl)-2-((*tert*-butoxycarbonyl)amino)acetamido)-3-(4-fluoro-3-nitrophenyl)-3-((triisopropylsilyl)oxy)propanoic Acid (65). Compound **64** (23.0 g, 22 mmol, 1 equiv) was dissolved in *t*-BuOH (400 mL, 20 vol) at 35 ˚C , diluted with H_2O (200 mL, 10 vol), and cooled to 0 ˚C. Solid $LiOH·H_2O$ (4.6 g, 110 mmol, 5 equiv) was added in one portion at 0 ˚C, and the reaction mixture was slowly warmed to room temperature and stirred for 4 h, at which point LC/MS indicated <3% of the trifluoroacetamide-protected free acid intermediate remained (*m/z* 1023 (neg) = $[M-H]^-$). The reaction mixture was immediately quenched with solid NH_4Cl (12 g) and concentrated at 50 ˚C under reduced pressure to remove *t*-BuOH. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (500 g SiO_2, wet-load EtOAc, 5–20% MeOH–EtOAc) provided **65** (16.5 g, 82%) as an off-white solid. For **65**: mp 156–160 ˚C (dec); R_f 0.36 (5% MeOH–CH_2Cl_2); $[\alpha]_D^{19}$ +12 (*c* 0.73, $CHCl_3$); ^1H NMR (600 MHz, CD_3OD) δ 8.13 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.72 (br s, 1H), 7.44 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.32 (t, *J* = 9.0 Hz, 1H), 7.09–7.06 (m, 2H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 5.67 (br s, 1H), 5.02 (s, 1H), 4.58 (s, 1H), 4.34 (br s, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 1.49 (s, 9H), 1.37 (s, 9H), 1.11–0.99 (m, 21H); ^{13}C NMR (151 MHz, CD_3OD) δ 174.5, 172.6, 169.2, 162.3, 160.5, 159.4, 157.3, 156.5, 154.8, 141.8, 138.2, 138.2, 134.77, 134.72, 134.2, 132.9, 131.0, 129.7, 125.3, 124.9, 122.4, 118.9, 118.7, 112.7, 102.8, 100.6, 84.7, 81.1, 79.4, 75.4, 62.0, 59.9, 56.28, 56.20, 56.0, 54.8, 28.7, 27.9, 18.7, 13.6; IR (film) ν_{max} 3428, 2961, 2942, 2923, 2867, 1727, 1679, 1608, 1538, 1463, 1389, 1367, 1348, 1263, 1203, 1157, 1093, 884, 838 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{46}H_{66}FN_4O_{13}Si$, 929.4380; found, 929.4411.



***tert*-Butyl (3*S*,6*S*,9*R*)-9-((*tert*-Butoxycarbonyl)amino)-6-((*R*)-(4-fluoro-3-nitrophenyl)((triisopropylsilyl)oxy)methyl)-16,24,26-trimethoxy-5,8-dioxo-4,7-diaza-1(1,3),2(1,2)-dibenzenacyclononaphane-3-carboxylate (66).** The reaction has been conducted on scales up to 16.4 g and a representative procedure follows. A solution of **65** (1.0 g, 1.1 mmol, 1 equiv) in NMP (5.4 mL, 5 vol) was added over 15 min by syringe pump to a stirred suspension of DMTMMH[10] (831 mg, 2.2 mmol, 2 equiv), NMP (5.4 mL, final [**65**] = 0.1 M), and *i*-Pr_2NEt (0.57 mL, 3.2 mmol, 3 equiv). The resulting solution was stirred for an additional 10 min at room temperature, diluted with PhMe (40 mL, color change to green), washed sequentially with 1 N aqueous HCl (40 mL, color change to yellow), H_2O (2 x 40 mL), and saturated aqueous NaCl (40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (40 g SiO_2, wet-load CH_2Cl_2, 20–30% acetone–hexanes) followed by a second chromatography (40 g SiO_2, wet-load CH_2Cl_2, 0–20% EtOAc–CH_2Cl_2) provided **66** (834 mg,

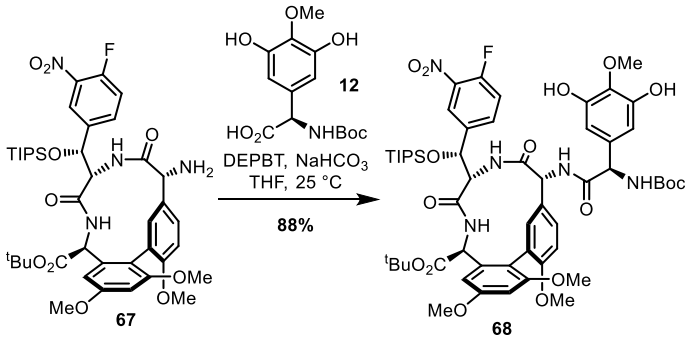
85%) as a white solid:* mp 143–146 ˚C; R_f 0.31 (2% MeOH–CH_2Cl_2); $[\alpha]_D^{24}$ +7.3 (*c* 0.68, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD, 2:1 mixture of conformers): major conformer δ 8.05 (d, *J* = 6.4 Hz, 1H), 7.79 (ddd, *J* = 8.7, 4.1, 2.3 Hz, 1H), 7.39 (dd, *J* = 10.8, 8.6 Hz, 1H), 7.33–7.28 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.81 (br s, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.33–6.25 (s, 1H), 5.35 (s, 1H), 5.05 (br s, 1H), 4.61 (br m, 1H), 4.24 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 1.54 (s, 9H), 1.31 (s, 9H), 1.07–0.93 (overlapping peaks, 21H); minor conformer δ 8.29 (d, *J* = 6.9 Hz, 1H), 7.88 (s, 1H), 7.44 (t, *J* = 9.7 Hz, 1H), 7.23–7.19 (m, 1H), 7.04 (overlapping peaks, 1H), 6.88 (s, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 2.2 Hz, 1H), 5.38 (s, 1H), 4.74 (s, 1H), 4.14 (d, *J* = 1.9 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 1.50 (s, 9H), 1.38 (s, 9H), 1.08–0.92 (overlapping peaks, 21H); ^{13}C NMR (151 MHz, CD_3OD) δ 174.5, 172.6, 169.2, 162.3, 160.5, 159.4, 157.3, 156.5, 154.8, 141.8, 138.28, 138.23, 134.77, 134.72, 134.2, 132.9, 131.0, 129.7, 125.3, 124.9, 122.4, 118.9, 118.7, 112.7, 102.8, 100.6, 84.7, 81.1, 79.4, 75.4, 62.0, 59.9, 56.28, 56.20, 56.0, 54.8, 28.7, 27.9, 18.7, 13.6; IR (film) ν_{max} 3394, 3290, 2944, 2869, 1739, 1705, 1659, 1600, 1582, 1541, 1467, 1422, 1391, 1364, 1308, 1249, 1201, 1156, 1107, 1064, 1028, 832, 818 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M+H]^+$ calcd for $C_{46}H_{64}FN_4O_{12}Si$, 911.4274; found, 911.4282. The 2D ^{1}H–^{1}H ROESY spectrum of **66** [600 MHz, CD_3OD, 2:1 mixture of conformers] displayed the following diagnostic NOE crosspeaks: major conformer δ 8.05/5.05, 8.05/4.61, 7.79/5.05, 7.79/4.61, 5.05/4.61; minor conformer δ 8.29/5.38, 8.29/4.14, 7.88/5.38, 7.88/4.14, 6.87/4.74, 6.87/4.14, 5.38/4.74, 5.38/4.14, 4.74/4.14. The structure, relative stereochemistry, and cis amide conformation of **66** (CCDC 2014740) were confirmed with a single-crystal X-ray structure determination conducted on crystals grown from methanol (colorless plates). The structure has been deposited with the Cambridge Crystallographic Data Center.

*On occasion, an intensely yellow DMTMMH-derived byproduct coeluted with the desired product [^{1}H NMR (600 MHz, $CDCl_3$) δ 4.05 (s, 6H, -OMe × 2)]. This byproduct is conveniently removed by trituration with Et_2O.

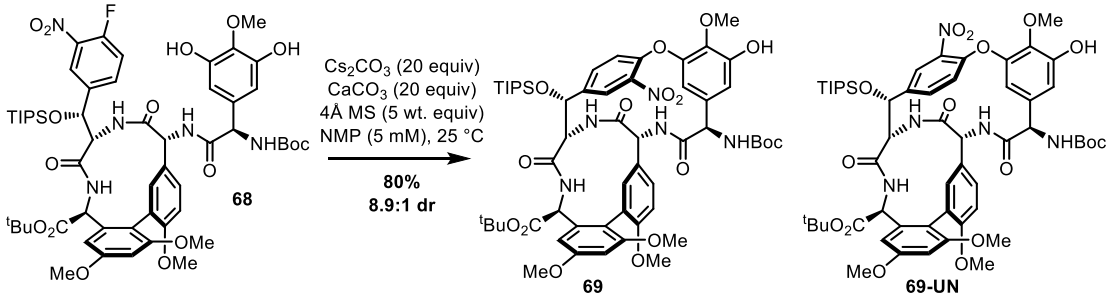


***tert*-Butyl (3*S*,6*S*,9*R*)-9-Amino-6-((*R*)-(4-fluoro-3-nitrophenyl)((triisopropylsilyl)oxy)methyl)-16,24,26-trimethoxy-5,8-dioxo-4,7-diaza-1(1,3),2(1,2)-dibenzenacyclononaphane-3-carboxylate (67).** The reaction was typically conducted on scales of 0.9–6.9 g (84–88%) and a representative procedure follows. Compound **66** (0.97 g, 1.1 mmol, 1.0 equiv) was dissolved in *tert*-butyl acetate (20 mL, 20 vol) at 60 ˚C, cooled to room temperature, and treated with conc. H_2SO_4 (0.4 mL, 2% v/v). The reaction mixture was closely monitored by LC/MS until <1% **66** remained based on UV absorbance at 254 nm (1.75 h), then added carefully to a stirred solution of saturated aqueous $NaHCO_3$ (50 mL), rinsing with EtOAc. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (25 g SiO_2, wet-load CH_2Cl_2, 0–10% MeOH–CH_2Cl_2) provided **67** as a yellow solid (0.75 g, 87%). For **67**: $[\alpha]_D^{23}$ –29 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD, 1.2:1 mixture of conformers) major conformer: δ 8.30 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.89 (ddd, *J* = 8.7, 4.1, 2.3 Hz, 1H), 7.44 (dd, *J* = 10.8, 8.7 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 5.42 (d, *J* = 1.5 Hz, 1H), 4.82 (s, 1H), 4.12 (d, *J* = 1.7 Hz, 1H), 4.09 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.35 (s, 1H, overlapping with minor conformer), 1.51 (s, 9H), 1.08–0.92 (m, 21H, overlapping with minor conformer); minor conformer: δ 8.03 (d, *J* = 6.6 Hz, 1H), 7.75 (ddd, *J* = 8.6, 4.1, 2.3 Hz, 1H), 7.48 (br d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 10.9, 8.6 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.78 (br s, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 4.61 (s, 1H), 4.56 (s, 1H), 4.29 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 3.35 (s, 1H, overlapping with major conformer), 1.32 (s, 9H), 1.09–0.93 (m, 21H, overlapping with major conformer); ^{13}C NMR (126 MHz, CD_3OD) δ 175.9, 171.5, 170.9, 169.1, 161.7, 161.6, 160.0, 160.0, 158.5, 158.1, 157.4, 157.2, 155.3, 155.1, 140.4, 140.3, 138.29, 138.23, 138.1, 137.5, 136.7, 136.4, 134.9, 134.8, 132.6, 130.9, 130.6, 127.7, 126.5, 125.49, 125.43, 124.6, 123.0, 122.7, 119.5, 119.3, 114.5, 112.4, 105.5, 104.9, 99.7, 99.4, 83.0, 82.6, 74.7, 62.7, 57.0, 56.9, 56.7, 56.26, 56.24, 56.0, 55.8, 28.3, 28.0, 18.5, 18.47, 18.43, 18.3, 13.56, 13.52; IR (thin film) ν_{max} 2957, 2867, 2366, 2330, 2139, 2107, 1738, 1668,

1578, 1538, 1468, 1349, 1248, 1200, 1154, 1114, 1084, 1029, 944, 918, 882, 843, 808, 756, 713, 680, 652, 633, 617 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M+H]^+$ calcd for $C_{41}H_{55}FN_4O_{10}Si$, 811.3750; found, 811.3740.



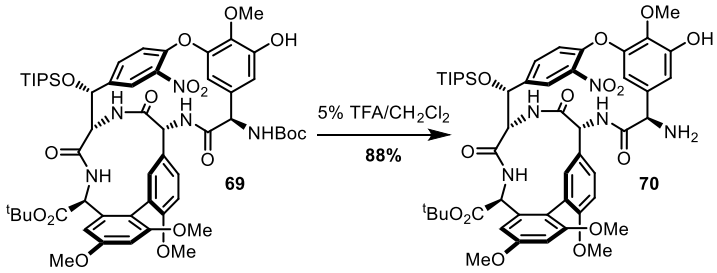
***tert*-Butyl (3*S*,6*S*,9*R*)-9-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(3,5-dihydroxy-4-methoxyphenyl)acetamido)-6-((R)-(4-fluoro-3-nitrophenyl)((triisopropylsilyl)oxy)methyl)-16,24,26-trimethoxy-5,8-dioxo-4,7-diaza-1(1,3),2(1,2)-dibenzenacyclononaphane-3-carboxylate (68).** A stirred suspension of **67** (50.0 mg, 0.062 mmol, 1.0 equiv), **12** (25 mg, 0.080 mmol, 1.3 equiv), and $NaHCO_3$ (21 mg, 0.25 mmol, 4.0 equiv) in THF (0.4 mL) at room temperature was treated with DEPBT (37 mg, 0.12 mmol, 2.0 equiv) in one portion. The reaction mixture was stirred at room temperature for 75 h, diluted with saturated aqueous $NaHCO_3$ (0.5 mL), and stirred vigorously for 10 min at room temperature before removal of THF under a stream of N_2. The reaction mixture was extracted with EtOAc (0.5 mL), dried over Na_2SO_4, and concentrated under a stream of N_2. PTLC (SiO_2, 40% acetone–hexanes) provided **68** (59.8 mg, 88%) as a light tan solid. For **68**: mp 180–185 ˚C (dec); R_f 0.45 (5% MeOH–CH_2Cl_2); $[\alpha]_D^{24}$ –24 (*c* 0.74, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD, 1:1 mixture of conformers) δ 8.27 (dd, *J* = 7.1, 2.3 Hz, 1H), 8.08 (br s, 1H), 7.86 (ddd, *J* = 8.7, 4.0, 2.3 Hz, 1H), 7.78–7.74 (m, 1H), 7.42 (dd, *J* = 10.8, 8.7 Hz, 1H), 7.37 (t, *J* = 9.3 Hz, 1H), 7.25 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.91 (s, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.54 (s, 2H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.36 (s, 2H), 6.31 (s, 1H), 5.37 (d, *J* = 2.0 Hz, 1H), 5.06–5.01 (m, 1H), 4.76 (s, 1H), 4.27 (s, 1H), 4.17 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (overlapping singlets, 6H), 3.75 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H), 1.41 (s, 9H), 1.32 (d, *J* = 10.9 Hz, 9H), 1.05–0.87 (m, 42H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.2, 173.8, 171.8, 170.2, 169.7, 166.4, 160.24, 160.15, 158.6, 158.5, 157.40, 157.3, 156.2, 155.4, 154.4, 154.2, 150.0, 149.7, 137.2, 136.8, 136.4, 136.2, 135.6, 135.0, 134.7, 134.5, 134.2, 134.0, 130.9, 127.8, 126.3, 125.5, 124.6, 124.2, 123.0, 121.7, 121.2, 119.0, 118.8, 113.7, 107.2, 106.5, 104.0, 103.5, 99.4, 99.1, 82.5, 81.9, 80.4, 80.1, 74.1, 69.8, 67.9, 61.3, 60.5, 60.45, 57.5, 56.1, 56.0, 55.89, 55.83, 55.78, 55.65, 55.5, 55.4, 54.6, 54.0, 53.5, 28.4, 28.0, 17.93, 17.87, 17.80, 17.78, 12.1; IR (film) ν_{max} 3370, 2942, 2868, 1745, 1679, 1659, 1605, 1538, 1502, 1462, 1391, 1365, 1350, 1327, 1253, 1201, 1157, 1099, 1062, 909, 838 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M+H]^+$ calcd for $C_{55}H_{71}FN_5O_{16}Si$, 1104.4649; found, 1104.4629.



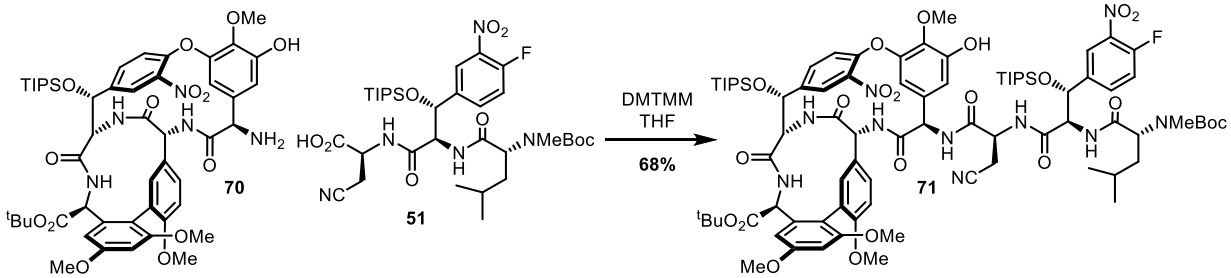
Compound 69. The reaction has been conducted on scales of 20–480 mg (66–84%, 7–9:1 dr) and a representative procedure follows. Cs_2CO_3 (3.0 g, 9 mmol, 20 equiv), $CaCO_3$ (900 mg, 9 mmol, 20 equiv) and 4Å MS (2.5 g, 5 wt equiv) were flame dried under high vacuum, cooled to room temperature under Ar, and suspended in anhydrous NMP (90 mL). Solid **68** (480 mg, 0.45 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred at room temperature for 20.5 h, diluted with PhMe (500 mL), and washed sequentially with aqueous 0.4 N HCl (500 mL), aqueous 0.2 N HCl (300 mL), and H_2O (3 x 400 mL). The organic layer was concentrated under reduced pressure and the crude product was purified

by chromatography (16 g SiO_2, wet-load CH_2Cl_2, gradient 8–15% acetone–CH_2Cl_2). The mixed fractions were further purified by PTLC (SiO_2, 15% acetone–CH_2Cl_2) to provide **69** [340 mg, 72%, natural atropisomer (less polar)] and **69-UN** [38 mg, 8%, unnatural atropisomer (more polar)]. For **69** (natural atropisomer): $[\alpha]_D^{23}$ +5.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ 8.29 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.17–7.13 (d, *J* = 9.0 Hz 1H), 7.00 (s, 1H), 6.99 (s, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.65 (s, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 5.61 (s, 1H), 5.46 (m, 1H), 5.15 (s, 1H), 4.71 (s, 1H), 4.07 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 2.63 (s, 1H), 2.18 (s, 1H), 1.53 (s, 9H), 1.41 (s, 7H), 1.25 (s, 2H), 1.12 (m, 3H), 1.06 (d, *J* = 7.2 Hz, 9H), 1.03 (d, *J* = 7.2 Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.5, 170.4, 170.2, 170.1, 166.4, 160.2, 158.9, 157.6, 155.4, 151.4, 150.3, 149.0, 142.8, 140.6, 136.0, 135.8, 135.5, 135.4, 134.3, 127.4, 126.5, 125.6, 123.2, 122.0, 121.2, 113.0, 110.1, 105.2, 104.1, 99.0, 82.0, 80.1, 73.6, 63.1, 61.6, 57.1, 56.3, 55.9, 55.8, 55.41, 54.40, 53.5, 32.0, 31.0, 29.8, 29.4, 28.4, 28.0, 18.0, 17.9, 17.9, 12.3; IR (film) ν_{max} 2938, 1664, 1581, 1535, 1490, 1350, 1264, 1159, 1036, 733, 702 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{55}H_{71}N_5O_{16}Si$, 1086.4743; found, 1086.4729. The 2D ^{1}H-^{1}H ROESY spectrum of natural atropisomer **69** (600 MHz, CD_3OD) displayed the following diagnostic NOE crosspeaks: δ 8.31/5.63, 8.31/4.09.

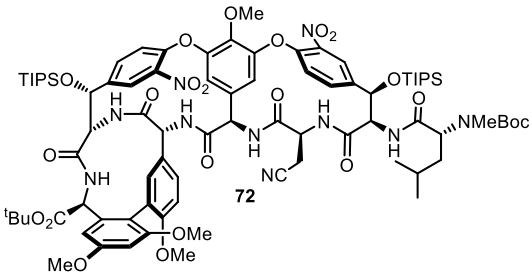
For **69-UN** (unnatural atropisomer): $[\alpha]_D^{23}$ +6.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ 8.20 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.20–7.13 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.64 (s, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 5.67 (s, 1H), 5.48 (br s, 1H), 5.28 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 4.09 (s, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 3.61 (s, 3H), 1.53 (s, 9H), 1.42 (s, 7H), 1.34 (s, 2H), 1.20–1.13 (s, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.1 Hz, 9H), 1.08 (d, *J* = 7.1 Hz, 9H); ^{13}C NMR (151 MHz, CD_3OD) δ 171.5, 171.3, 168.7, 161.7, 160.4, 158.7, 157.2, 153.8, 152.2, 148.9, 143.7, 142.4, 138.5, 137.6, 137.2, 137.0, 131.5, 128.6, 127.8, 126.8, 125.7, 124.6, 122.7, 113.8, 109.9, 105.8, 105.4, 99.8, 83.1, 81.2, 74.6, 70.6, 64.3, 62.2, 61.5, 61.2, 58.2, 56.6, 56.3, 56.0, 28.6, 28.3, 18.58, 18.56, 13.5; IR (thin film) ν_{max} 3278, 2958, 2866, 1656, 1579, 1537, 1504, 1463, 1364, 1324, 1257, 1228, 1199, 1156, 1102, 1080, 1037, 882, 859, 837, 812, 751, 681, 651 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{55}H_{71}N_5O_{16}Si$, 1086.4743; found, 1086.4717. The 2D ^{1}H-^{1}H ROESY spectrum of unnatural atropisomer **69-UN** (600 MHz, CD_3OD) displayed the following diagnostic NOE crosspeaks: δ 7.80/5.67, 7.80/4.09.



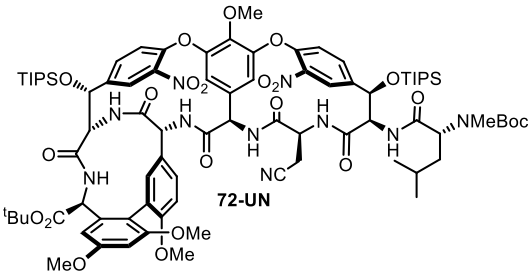
Compound 70. Compound **69** (20 mg, 0.018 mmol) was suspended in CH_2Cl_2 (0.4 mL) and treated with trifluoroacetic acid (20 µL, 5% v/v). The resulting homogeneous solution was stirred at room temperature for 4 h, at which point the ratio of **69:70** was 5:95 according to LC/MS. The reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (1 mL), diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3 x 3 mL). PTLC (SiO_2, 3% MeOH–EtOAc) provided **69** (0.9 mg, 5% recovered starting material) and **70** (15.9 mg, 88%) that was carried forward without further purification. For **70**: HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{50}H_{63}N_5O_{14}Si$, 986.4219; found, 986.4227.



Compound 71. A stirred solution of **70** (15.0 mg, 15.2 µmol, 1.0 equiv) and **51** (20.0 mg, 27.1 µmol, 1.78 equiv) in anhydrous THF (200 µL) at 0 ˚C was treated with DMTMM (8.4 mg, 30 µmol, 2 equiv) in one portion. The reaction mixture was stirred at 0–5 ˚C for 45 h, diluted with H_2O (0.5 mL) and the THF was removed under a stream of N_2. The aqueous layer was extracted with CH_2Cl_2 (4 x 0.5 mL) and the combined organic layers were purified directly by PTLC (SiO_2, 15% acetone–CH_2Cl_2) to provide **71** (17.5 mg, 68%) as a white solid. For **71**: $[\alpha]_D^{23}$ +31 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ 8.28 (d, *J* = 2.2 Hz, 1H), 8.15 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.83 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.65 (br s, 1H), 7.20 (br s, 1H), 7.14 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.00 (d, *J* = 6.7 Hz, 1H), 6.99 (s, 1H), 6.96 (br s, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.58 (s, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 5.98 (br s, 1H), 5.61 (s, 1H), 5.35 (br s, 1H), 5.18 (s, 1H), 4.79 (d, *J* = 6.3 Hz, 2H), 4.71 (s, 1H), 4.55 (s, 1H), 4.51 (br s, 2H), 4.08 (s, 1H), 3.98 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H), 3.62 (br s, 3H), 3.07–2.83 (m, 2H), 2.57 (s, 3H), 1.53 (s, 9H), 1.47–1.26 (m, 9H), 1.17–0.93 (m, 42H), 0.97–0.92 (br m, 3H), 0.87–0.81 (br m, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 172.0, 171.0, 170.3, 170.0, 169.9, 168.6, 168.4, 167.4, 160.4, 159.0, 157.5, 152.5, 151.6, 142.7, 140.7, 137.0, 135.6, 135.5, 134.4, 126.7, 126.6, 124.8, 123.6, 122.13, 121.11, 118.1, 117.9, 112.6, 104.2, 98.0, 81.6, 73.5, 63.0, 60.2, 56.8, 55.2, 54.98, 54.92, 54.64, 54.61, 54.5, 36.5, 28.1, 27.2, 26.9, 24.5, 22.2, 20.1, 17.2, 17.1, 17.0, 13.7, 12.1, 12.0; IR (thin film) ν_{max} 2958, 2866, 1656, 1579, 1537, 1504, 1463, 1364, 1324, 1257, 1228, 1199, 1156, 1102, 1080, 1037, 882, 859, 837, 812, 751, 681, 651 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{84}H_{115}FN_{10}O_{22}Si_2$, 1691.7788; found, 1691.7797.



72

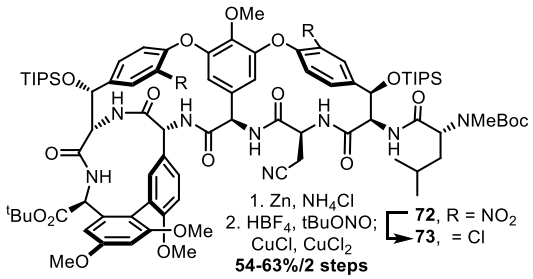


72-UN

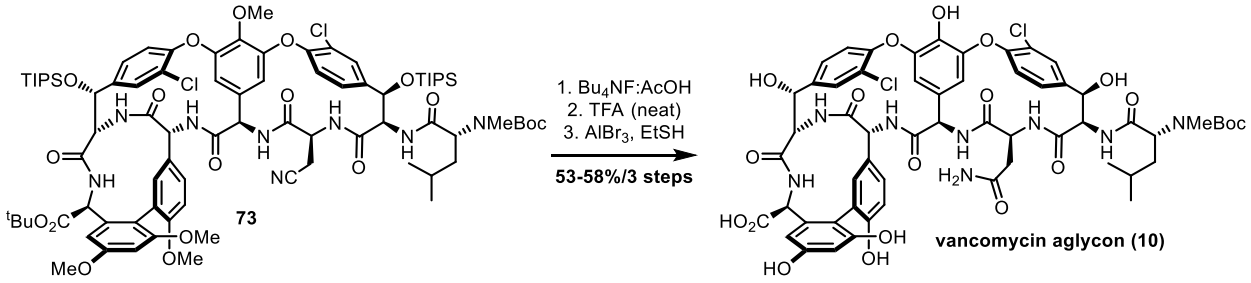
Compound 72. Cs_2CO_3 (169 mg, 0.52 mmol, 20 equiv), $CaCO_3$ (52.0 mg, 0.52 mmol, 20 equiv) and powdered 4Å MS (220 mg, 5 wt equiv, oven dried prior to use) were flame dried under high vacuum, cooled to room temperature under Ar, and suspended in anhydrous DMF (4.2 mL). The stirred suspension was treated with a solution of **71** (44 mg, 0.026 mmol) in anhydrous DMF (0.4 mL) and the vial and syringe used to transfer **71** were rinsed with additional anhydrous DMF (2 x 0.3 mL). The reaction mixture was stirred for 2.5 h at room temperature, diluted with EtOAc (100 mL) and washed sequentially with aqueous 1 N HCl, H_2O, and saturated aqueous NaCl (100 mL each), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. PTLC (SiO_2, 50% EtOAc–hexanes) provided **72** (natural atropisomer, less polar, 33.3 mg, 77%) as a white solid. The unnatural atropisomer required additional purification by HPLC (C_{18}, 100% CH_3CN, 3 mL/min, broad peak eluting from 10–50 min post-injection) to provide **72-UN** (2.3 mg, 5%) as an off-white film. For **72** (natural atropisomer): $[\alpha]_D^{25}$ +26 (*c* 0.36, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ 8.20 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.11–7.04 (m, 2H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.7 (m, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 5.77 (d, *J* = 4.9 Hz, 1H), 5.70 (s, 1H), 5.67 (s, 1H), 5.46 (s, 1H), 5.24 (d, *J* = 4.8 Hz, 1H), 5.13 (s, 1H), 4.91 (d, *J* = 11.1 Hz, 1H), 4.70 (s, 1H), 4.62 (s, 1H), 4.26 (s, 3H), 4.14 (d, *J* = 2.2 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 2.93 (dd, *J* = 17.3, 4.6 Hz, 1H), 2.86 (s, 3H), 2.63 (s, 1H), 2.60 (dd, *J* = 18.0, 10.2 Hz, 1H), 2.18 (s, 2H), 2.01 (s, 1H), 1.55 (s, 9H), 1.51 (s, 9H), 1.29 (s, 7H), 1.25 (s, 2H), 1.25–1.03 (m, 42H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.93–0.81 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.2, 176.9, 171.4, 170.6, 170.0, 169.2, 167.4, 166.0, 160.3, 158.9, 157.6, 157.3, 153.6, 153.5, 149.4, 148.7, 143.9, 141.1, 140.5, 139.5, 138.6, 135.8, 135.5, 134.1, 132.6, 132.2, 130.1, 129.8, 127.5, 126.3, 125.9, 125.8, 124.3, 123.3, 122.2, 121.2, 116.0, 113.2, 105.5, 99.2, 82.2, 81.7, 73.7, 72.4, 69.7, 62.2, 59.0, 57.1, 56.1, 56.03, 56.01, 55.4, 54.4, 54.0, 49.4, 36.2, 35.9, 33.9, 32.0, 31.0, 28.4, 28.0, 27.3, 25.7, 25.0, 24.8, 23.2, 22.8, 21.9, 18.17, 18.15, 18.02, 18.01, 14.2, 12.4, 12.2, 1.1; IR (film) ν_{max} 3744, 3737, 3676, 3650, 1693, 1665, 1652, 1638, 1632, 1576, 1560, 1536, 1506, 1492, 1469 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{84}H_{114}N_{10}O_{22}Si_2$, 1671.7726; found, 1671.7701. The 2D ^{1}H-^{1}H ROESY spectrum of **72** (600 MHz, CD_3OD, natural atropisomer) displayed the following diagnostic NOE crosspeaks: δ 8.20/5.70, 8.20/4.14, 7.78/5.77.

For **72-UN** (unnatural atropisomer): ^{1}H NMR (600 MHz, CD_3OD) δ 9.31 (d, -CONH-, *J* = 5.8 Hz, 1H) 8.82 (d, -CONH-, *J* = 6.8 Hz, 1H), 8.26 (overlapping peaks, 2H), 8.00 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.3 Hz, 1H),

7.02 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 6.08 (s, 1H), 5.92 (s, 1H), 5.78 (d, *J* = 4.8 Hz, 1H), 5.67 (d, *J* = 1.5 Hz, 1H), 5.47–5.43 (m, 1H), 5.12–5.03 (m, 2H), 4.78 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 5.8 Hz, 1H), 4.18 (s, 3H), 4.13 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.19 (s, 1H), 2.85 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.79 (s, 3H), 2.58 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.18 (s, 1H), 2.03 (q, *J* = 5.3, 3.8 Hz, 1H), 1.87 (t, *J* = 12.9 Hz, 1H), 1.52 (s, 18H), 1.29 (s, 3H), 1.26–1.03 (m, 42H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.89 (m, 3H); HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{84}H_{114}N_{10}O_{22}Si_2$, 1671.7726; found, 1671.7697. The 2D ^{1}H-^{1}H ROESY spectrum of **72-UN** (600 MHz, CD_3OD, unnatural atropisomer) displayed the following diagnostic NOE crosspeaks: δ 8.82/7.02, 8.82/5.67, 8.82/4.14.

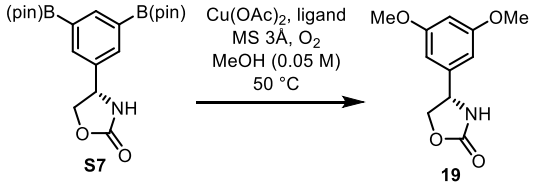


Compound 73. The reaction has been conducted on scales of 5–36 mg (54–63%) and a representative procedure follows. A stirred solution of **72** (6.0 mg, 3.6 µmol, 1 equiv) in acetone (0.6 mL) was treated with saturated aqueous NH_4Cl (0.1 mL), sparged with Ar for 10 min, then treated with Zn^0 (nano-powder, 19 mg, 0.29 mmol, 80 equiv). The reaction mixture was stirred at room temperature for 30 min, concentrated under a stream of N_2, and co-evaporated with EtOAc (1 mL) under a stream of N_2. The crude residue was suspended in EtOAc (1 mL), filtered through a short SiO_2 plug (200 mg SiO_2, rinsing with EtOAc), and concentrated under a stream of N_2 to provide the crude aniline as a white, air-sensitive solid that was immediately carried forward without further purification. The crude aniline was dissolved in CD_3CN (0.2 mL), cooled to 0 ˚C, and treated with HBF_4 (0.1 mM in CD_3CN, 108 µL, 11 µmol, 3 equiv) followed immediately by ^{t}BuONO (0.1 mM in CD_3CN, 108 µL, 11 µmol, 3 equiv). The resulting yellow solution was stirred at 0 ˚C for 30 min, cooled to –35 ˚C, and stirred vigorously as a chilled (0 ˚C) suspension of CuCl (35 mg, 360 µmol, 100 equiv) and $CuCl_2$ (58 mg, 430 µmol, 120 equiv) in 50% CD_3CN–H_2O (0.2 mL) was added dropwise by syringe. The reaction mixture was gradually warmed to 5 ˚C over the course of 2.5 h, diluted with EtOAc (3 mL) and washed with saturated aqueous NH_4HCO_3 (2 x 3 mL) and saturated aqueous NaCl (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 35% acetone–hexanes) provided **73** (3.8 mg, 63%/2 steps, typically 54–63%) as a white solid. For **73**: $[\alpha]_D^{23}$ +14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.78 (d, *J* = 6.6 Hz, 1H), 7.71 (d, *J* = 10.4 Hz, 1H), 7.60 (overlapping peaks, 2H), 7.55 (s, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 7.04 (d, *J* = 3.3 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 1H), 6.71 (d, *J* = 2.3 Hz, 1H), 6.60 (d, *J* = 9.8 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 5.79–5.75 (m, 1H), 5.69 (overlapping peaks, 2H), 5.54 (s, 1H), 5.43–5.38 (m, 1H), 5.35 (td, *J* = 4.4, 2.1 Hz, 1H), 5.19 (br s, 1H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.64 (dd, *J* = 9.1, 6.5 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.16 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 2.90 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.82 (s, 3H), 2.80 (s, 1H), 2.68 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.60 (s, 1H), 2.16–2.12 (m, 2H), 2.09 (s, 1H), 1.68 (ddd, *J* = 14.1, 9.1, 5.0 Hz, 1H), 1.61–1.55 (m, 2H), 1.53 (s, 9H), 1.51 (s, 10H), 1.37–1.26 (m, 15H), 1.24–1.18 (m, 6H), 1.17–1.00 (m, 36H), 0.92 (d, *J* = 6.6 Hz, 4H), 0.90–0.86 (m, 2H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.0, 173.2, 171.4, 170.8, 170.1, 169.9, 169.3, 167.7, 166.2, 160.3, 159.0, 157.6, 157.3, 153.1, 152.8, 152.7, 150.7, 141.0, 138.6, 138.1, 135.8, 135.5, 131.7, 130.4, 130.1, 129.8, 129.5, 127.7, 127.4, 127.0, 126.1, 125.9, 124.5, 124.3, 123.1, 121.2, 116.0, 113.2, 107.3, 105.2, 104.3, 99.1, 82.3, 81.5, 73.7, 72.4, 64.0, 61.8, 59.5, 57.1, 56.3, 55.9, 55.4, 55.2, 54.6, 49.5, 39.6, 39.0, 37.2, 37.1, 36.0, 35.8, 32.0, 30.3, 30.2, 29.9, 29.89, 29.86, 29.81, 29.7, 29.68, 29.61, 29.5, 29.49, 29.47, 29.44, 29.42, 29.39, 29.34, 28.4, 28.0, 27.39, 27.35, 25.7, 24.7, 23.4, 22.8, 21.6, 18.19, 18.16, 18.07, 18.01, 14.2, 12.4, 12.2, 1.1; IR (film) ν_{max} 3389, 3374, 3325, 3310, 2924, 2863, 1695, 1661, 1606, 1507, 1461, 1366, 1325, 1241, 1200, 1160, 1113, 1062, 1039, 708, 657, 608 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calculated for $C_{84}H_{114}Cl_2N_8O_{18}Si_2$, 1649.7245; found, 1649.7214.



Vancomycin Aglycon (10). A stirred solution of **73** (3.0 mg, 1.8 µmol, 1 equiv) in THF (0.1 mL) was treated with 1.1:1 AcOH:Bu_4NF (1.1:1 M in THF, 9 µL, 9.9 µmol AcOH, 9.0 µmol Bu_4NF, 5.5 equiv AcOH, 5.0 equiv Bu_4NF), stirred at room temperature for 42 h, and concentrated under a stream of N_2. The residue was dissolved in neat TFA (0.3 mL), stirred at room temperature for 24 h, and concentrated under a stream of N_2. The residue was then treated with solid $AlBr_3$ (100 mg) and EtSH (0.2 mL, exothermic), stirred at room temperature for 24 h, cooled to 0 ˚C, and quenched with MeOH (0.5 mL, exothermic). The resulting suspension was stirred until homogeneous and concentrated under N_2 to provide an orange oil (0.2 mL). The oil was suspended in H_2O (0.5 mL) and passed through a short reverse-phase C18 SiO_2 plug, eluting with 50% CH_3CN–H_2O. HPLC purification (Cosmosil 5C_{18}-AR-II, 4.6ID x 250 mm, 1.5 mL/min, 25% CH_3CN–H_2O + 0.07% TFA, R_t = 5 min) provided **10** (1.3 mg, 58% for 3 steps, typically 53–58%) as a white film. The spectral data for **10** was in accordance with the literature values, and the ^{1}H NMR of synthetic **10** was in full agreement with that of an authentic sample of **10** derived from deglycosylation of vancomycin hydrochloride. For **10**: $[\alpha]_D^{23}$ +58 (*c* 0.1, CH_3OH) ^{1}H NMR (600 MHz, CD_3OD) δ 8.96 (d, -CONH-, *J* = 6.3 Hz, 1H), 8.71 (d, -CONH-, *J* = 5.8 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.66 (s, 2H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.03 (br s, 1H), 5.97 (br s, 1H), 5.36 (s, 1H), 5.33 (d, *J* = 1.6 Hz, 1H), 5.26 (d, *J* = 3.5 Hz, 1H), 4.75 (d, *J* = 6.4 Hz, 1H), 4.70 (d, *J* = 5.7 Hz, 1H), 4.26 (d, *J* = 9.2 Hz, 1H), 4.17 (s, 1H), 4.01 (t, *J* = 7.2 Hz, 1H), 2.95 (d, *J* = 15.8 Hz, 1H), 2.77 (s, 3H), 1.99 (br m, 1H), 1.93–1.82 (m, 1H), 1.71–1.54 (m, 2H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 175.7, 174.9, 172.5, 171.8, 171.7, 170.10, 169.4, 168.9, 159.2, 158.1, 156.6, 153.4, 151.5, 149.9, 148.3, 142.5, 141.1, 137.5, 137.2, 136.0, 132.3 130.3, 129.2, 128.8, 128.5, 127.9, 127.3, 127.2, 125.5, 125.3, 122.4, 118.9, 118.4, 107.8, 106.6, 104.0, 74.3, 73.4, 72.3, 63.9, 62.1, 59.6, 58.6, 56.5, 55.4, 52.7, 40.4, 36.5, 33.0, 25.5, 23.1, 22.8; IR (film) ν_{max} 3301, 1669, 1646, 1510, 1434, 1203, 1139 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{53}H_{52}Cl_2N_8O_{17}$, 1143.9602; found, 1143.2887.

Figure S1: Optimization of the Chan-Lam methoxylation enroute to **19**.

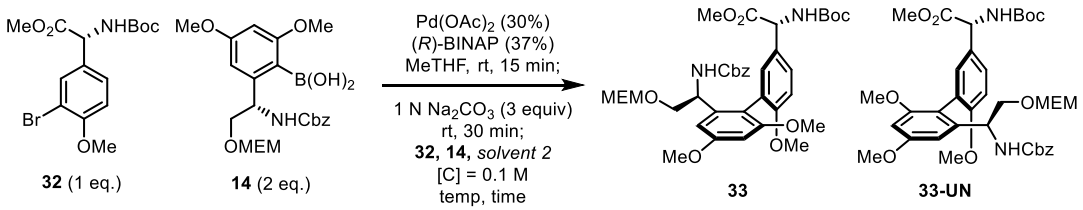


equiv Cu	ligand	L:Cu	time	yield
1	none	-	12 h (50 °C) + 36 h (65 °C)	75%
2	Et_3N	2:1	4 h	66%
2	DMAP	2:1	4 h	76%
2	imidazole	2:1	4 h	trace
2	pyr	2:1	4 h	88%
1	pyr	1:1	12 h	86%
1	**pyr**	**3:1**	**12 h**	**91%**
1	pyr	5:1	12 h	91%

Optimization experiments were performed according to the procedure detailed above for the conversion of **18** to **19**. In order to control for reaction variability in the C-H borylation step, all Chan-Lam couplings were conducted using aliquots from the same crude borylation product mixture. Reactions were carried out until the monomethoxylated intermediate (*m/z* 320 [pos.]) was fully consumed (monitored by LC/MS). Following removal of Cu salts by aqueous workup, the yield

of **19** from the diborylated intermediate was determined by NMR integration relative to internal standard (di-*tert*-butylbiphenyl).

Figure S2: Select conditions examined for the atroposelective Suzuki coupling of **32** and **14**.

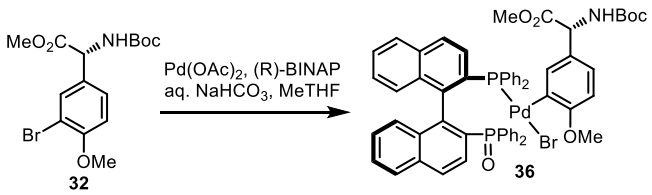


solvent 2	temp	time	dr	yield	deviation from standard conditions
MeOH	90 °C	15 min	1.1:1	97%*	P(*o*-tol)$_3$ (1.5 equiv), Pd_2dba_3 (0.3 equiv)
MeTHF	rt	18 h	18:1	38%	preformed oxidative addition complex
PhMe	**70 °C**	**2 h**	**15:1**	**75%**	**none**
PhMe	70 °C	2 h	15:1	59%*	[C] = 0.2 M
MeTHF	70 °C	2 h	15:1	52%*	[C] = 0.2 M, 15% Pd, 18% (*R*)-BINAP
MeTHF	70 °C	2 h	<1:20	37%*	(*S*)-BINAP
MeTHF	70 °C	2 h	2.2:1	55%	(*S*)-Xyl-SDP
MeTHF	rt	18 h	2.6:1	24%	(*S*)-Xyl-SDP

*Isolated yield (combined yield for both atropisomers)

Standard procedure: A solution of $Pd(OAc)_2$ (0.3 equiv), (*R*)-BINAP (0.37 equiv), and MeTHF ([Pd] = 0.06 M) was stirred at room temperature under Ar for 15 min, treated with 1 N aqueous Na_2CO_3 (3 equiv), and stirred for an additional 30 min at room temperature. During this period, the color of the organic layer typically turned dark red. A solution of **32**[6] (20 mg, 1 equiv) and **14**[9] (2 equiv) in solvent 2 (final [**32**] = 0.1 M) was then added, and the reaction mixture was immediately warmed to 70 ˚C (preheated oil bath), stirred for 2 h under Ar, and cooled to room temperature. The reaction yield and diastereoselectivity were determined by LC/MS integration at 254 nm relative to internal standard (di-*tert*-butylbiphenyl). Additionally, the following ligands were surveyed and did not show substantial improvement from (*R*)-BINAP: (*R*)-C3-TunePhos, (*R*)-SEGPHOS, (*R*)-Tol-BINAP.

Figure S3: Comparison of methods for generation of **36**.

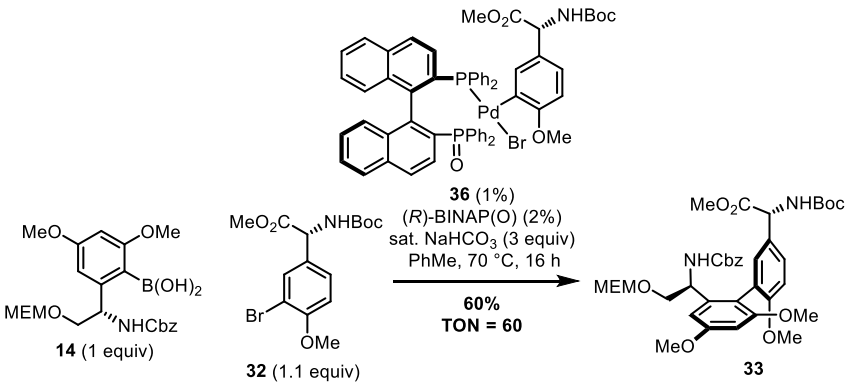


Compound 36, Method A. A solution of $Pd(OAc)_2$ (11.0 mg, 0.049 mmol, 1 equiv), (*R*)-BINAP (32.0 mg, 0.051 mmol, 1.05 equiv) and **32**[6] (60.0 mg, 0.16 mmol, 3.3 equiv) in PhMe (1 mL) was stirred at room temperature under Ar for 30 min, then treated with saturated aqueous $NaHCO_3$ (degassed with Ar, 150 µL, 3 equiv) and warmed at 80 ˚C. The reaction mixture immediately turned deep red, then faded to light orange over the course of 15 min at 80 ˚C. The reaction mixture was stirred for 1.5 h total at 80 ˚C, cooled to room temperature, and the aqueous layer was removed. PTLC (SiO_2, 40% acetone–hexanes) provided **36** (49 mg, 91%) as a tan solid. For **36**: $[\alpha]^{23}_D$ +36 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, CD_2Cl_2, mixture of rotamers) δ 8.38 (d, *J* = 7.2 Hz, 1H), 8.36 (d, *J* = 7.1 Hz, 1H), 8.27 – 8.19 (overlapping peaks, 3H), 8.12 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.04 (dd, *J* = 12.3, 8.6 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.88 (overlapping peaks, 4H), 7.74 (overlapping peaks, 4H), 7.67 – 6.46 (overlapping peaks, 46H), 6.44 (d, *J* = 7.6 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 6.16 (d, *J* = 8.1 Hz, 1H), 6.11 (dd, *J* = 3.6, 2.2 Hz, 1H), 6.08 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.06 (d, *J* = 8.6 Hz, 1H), 5.82 (s, 1H), 4.96 (d, *J* = 7.5 Hz, 1H), 4.77 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 7.5 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 3.42 (s, 3H), 3.20 (s, 3H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2, mixture of rotamers) δ 172.2, 171.9, 161.5, 160.91, 160.90, 154.6, 154.5, 144.8, 143.1, 142.9, 142.8, 142.77, 142.71, 141.8, 138.88, 138.80, 137.0, 136.9, 136.5, 136.4, 136.3, 135.3, 135.28, 135.27, 135.03, 135.01, 134.9, 134.8, 134.7, 134.6, 134.55, 134.52, 134.50, 134.3, 134.08, 134.07, 134.03, 133.99,

133.97, 133.96, 133.89, 133.82, 133.66, 133.60, 133.54, 133.50, 133.4, 133.36, 133.32, 133.2, 133.1, 133.13, 133.10, 133.08, 133.05, 133.01, 132.99, 132.98, 132.96, 132.94, 132.90, 132.83, 132.81, 132.7, 132.63, 132.4, 132.38, 132.31, 132.30, 132.28, 132.26, 132.13, 132.11, 132.05, 132.00, 131.99, 131.96, 131.90, 131.5, 131.47, 131.41, 131.40, 131.32, 131.30, 131.05, 131.03, 130.99, 130.96, 130.95, 130.3, 130.27, 130.20, 130.1, 130.0, 129.89, 129.83, 129.79, 129.72, 129.66, 129.64, 129.62, 129.61, 129.5, 129.48, 129.44, 129.42, 129.37, 129.33, 129.2, 129.17, 129.15, 129.14, 129.11, 129.06, 129.05, 129.01, 128.96, 128.91, 128.8, 128.78, 128.73, 128.71, 128.70, 128.66, 128.61, 128.60, 128.48, 128.42, 128.3, 128.26, 128.24, 128.22, 128.21, 128.18, 128.16, 128.15, 128.08, 128.05, 128.03, 128.01, 127.97, 127.95, 127.87, 127.86, 127.79, 127.78, 127.77, 127.70, 127.66, 127.64, 127.59, 127.55, 127.4, 127.31, 127.30, 127.2, 127.16, 127.14, 127.12, 127.11, 127.09, 127.08, 127.06, 127.04, 127.01, 126.98, 126.91, 126.85, 126.83, 126.81, 126.80, 126.7, 126.6, 126.15, 126.12, 125.8, 125.5, 122.9, 122.4, 109.7, 108.5, 79.3, 79.2, 57.1, 56.9, 55.0, 54.7, 52.1, 51.9, 34.6, 34.5, 31.9, 31.5, 29.6, 29.3, 29.0, 28.1, 28.0, 25.2, 22.6, 20.4, 13.9; IR (film) ν_{max} 3066, 2224, 2146, 1944, 1744, 1714, 1586, 1481, 1436, 1333, 1308, 1162, 817, 746, 720, 699, 641, 605 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M-Br]^+$ calcd for $C_{59}H_{52}BrNO_6P_2Pd^{102}$, 1034.2326; found 1034.2291.

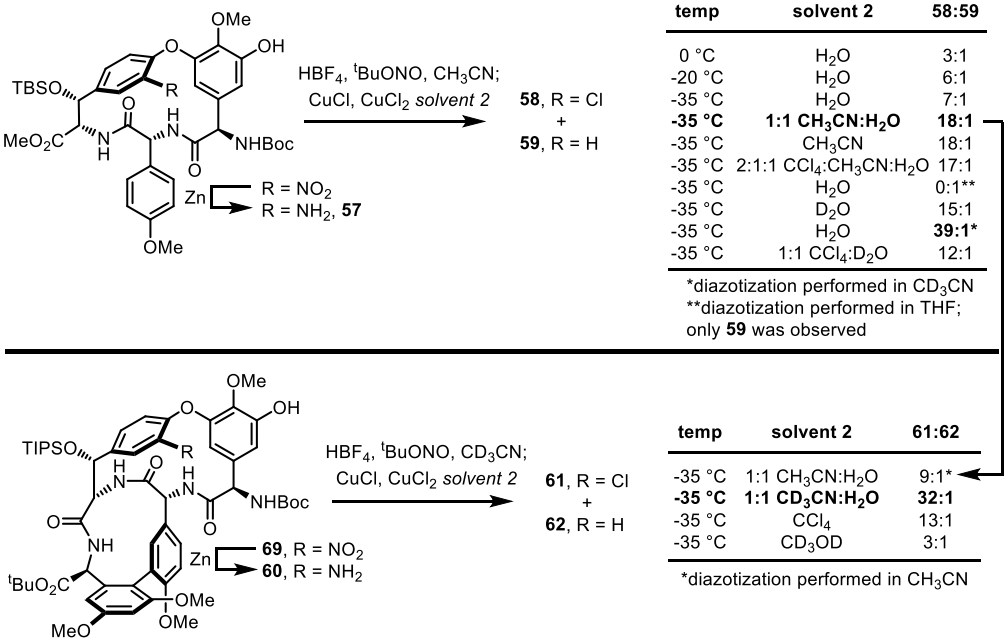
Method B. A solution of Pd_2dba_3 (416 mg, 0.45 mmol, 1 equiv), (*R*)-BINAP(O) (639 mg, 1.0 mmol, 2.2 equiv), and **32** (374 mg, 1.0 mmol, 2.2 equiv) in PhMe (5 mL) was sparged with Ar for 2 min, then warmed to 80 ˚C under Ar. After 1.5 h, the reaction mixture was cooled to room temperature and the product purified directly by chromatography (40 g SiO_2, wet-load CH_2Cl_2, gradient 0-100% EtOAc-CH_2Cl_2) to provide **36** (240 mg, 24%) as a light green solid.

Figure S4: Demonstration of catalytic competence of **36**.



A mixture of aryl bromide **32**[6] (89 mg, 0.24 mmol, 1.1 equiv), oxidative addition complex **36** (2.4 mg, 0.002 mmol, 1 mol %), (*R*)-BINAP(O)[7] (2.8 mg, 0.005 mmol, 2 mol %), PhMe (0.5 mL, degassed) and saturated aqueous $NaHCO_3$ (0.65 mL, 3 equiv) was warmed to 70 ˚C under Ar. A solution of **14**[9] (100 mg, 0.22 mmol, 1 equiv) in PhMe (0.3 mL, degassed) was added over 4 h by syringe pump. The reaction mixture was stirred for an additional 12 h at 70 ˚C, cooled to room temperature, and the aqueous layer was removed. The organic layer was subjected to chromatography directly (5.4 g SiO_2, wet-load PhMe, isocratic 50% EtOAc-hexanes) to provide **33** (85 mg, 60% yield with respect to **14**, TON = 60 for **36**) as a white foam.

Figure S5: Optimization of the Sandmeyer chlorination reaction.



temp	solvent 2	58:59
0 °C	H_2O	3:1
-20 °C	H_2O	6:1
-35 °C	H_2O	7:1
-35 °C	**1:1 CH_3CN:H_2O**	**18:1**
-35 °C	CH_3CN	18:1
-35 °C	2:1:1 CCl_4:CH_3CN:H_2O	17:1
-35 °C	H_2O	0:1**
-35 °C	D_2O	15:1
-35 °C	H_2O	**39:1***
-35 °C	1:1 CCl_4:D_2O	12:1

*diazotization performed in CD_3CN
diazotization performed in THF; only **59 was observed

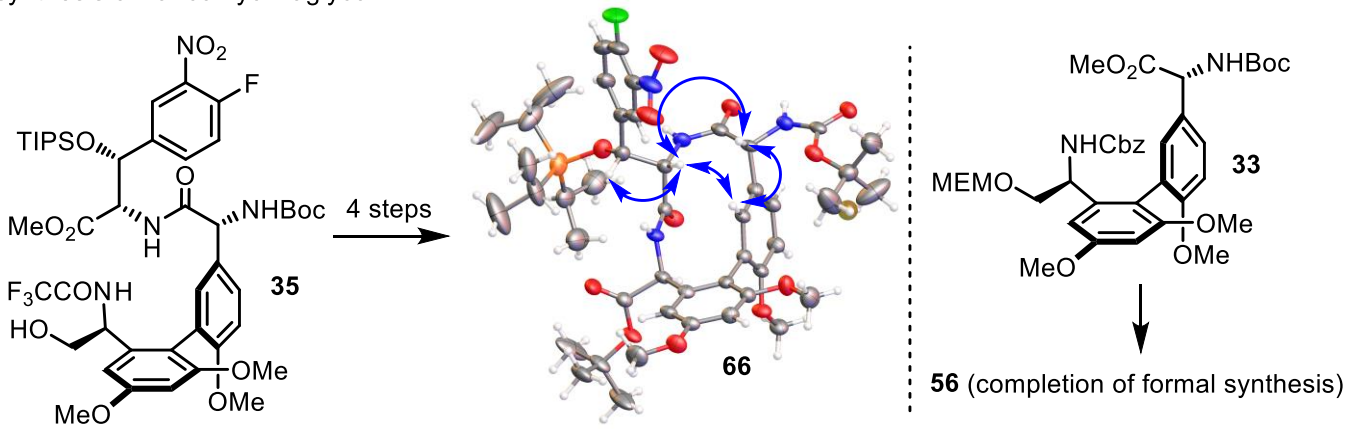
temp	solvent 2	61:62
-35 °C	1:1 CH_3CN:H_2O	9:1*
-35 °C	**1:1 CD_3CN:H_2O**	**32:1**
-35 °C	CCl_4	13:1
-35 °C	CD_3OD	3:1

*diazotization performed in CH_3CN

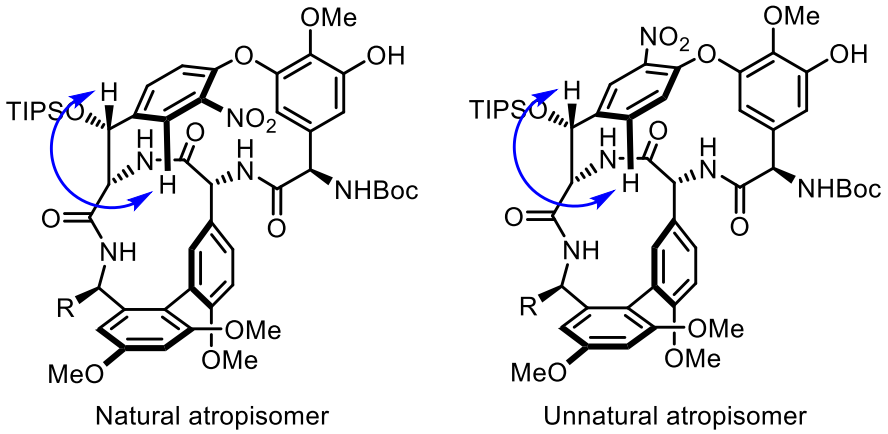
General procedure: A solution of nitroaromatic **58** or **61** (2-3 mg, 1 equiv) in acetone (0.5 mL) was treated with saturated aqueous NH_4Cl (0.1 mL), sparged with Ar for 10 min, then treated with Zn (nano-powder, 20 equiv). The reaction mixture was stirred at room temperature for 1 h, concentrated under a stream of N_2, and co-evaporated with EtOAc (1 mL). The crude residue was suspended in EtOAc (1 mL), filtered through a short SiO_2 plug (200 mg SiO_2, rinsing with EtOAc), and concentrated under a stream of N_2. The resulting crude aniline **57** or **60** was dissolved in the specified solvent (CH_3CN or CD_3CN, 0.3 mL), cooled to 0 ˚C, and treated with HBF_4 (0.1 M stock solution in CH_3CN or CD_3CN, prepared by dilution of 50% aqueous HBF_4, 1.3 equiv) followed immediately by ^{t}BuONO (0.1 mM stock solution in CH_3CN or CD_3CN, 1.3 equiv). The resulting yellow solution was stirred at 0 ˚C for 30 min, cooled to the specified temperature, and stirred vigorously as a chilled (0 ˚C) suspension of CuCl (50 equiv) and $CuCl_2$ (60 equiv) in solvent 2 (0.5 mL) was added dropwise. The reaction mixture was gradually warmed to room temperature over the course of 2 h, at which point the ratio of **58:59** or **61:62** was determined by LC/MS integration at 235 nm.

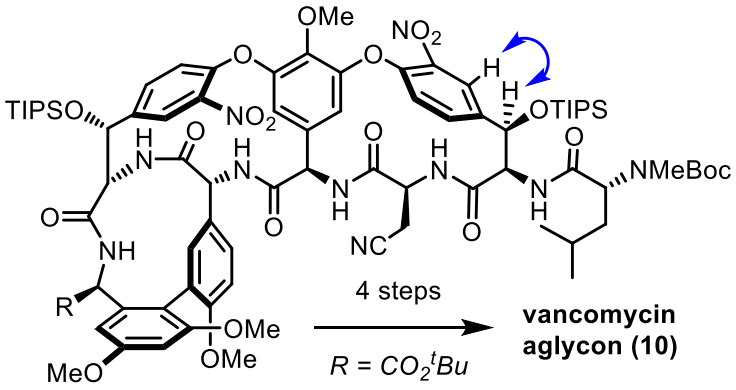
Figure S6: Methods used for assignment of atropisomers

The stereochemical outcome of the Suzuki coupling (i.e. the AB biaryl stereochemistry) could not be assigned directly for **35** or **33**. With **35**, the stereochemistry was unambiguously established by X-ray crystallography following elaboration to the AB macrocycle **66**. Diagnostic nOes[S11] are shown in blue for **66** and used to assign stereochemistry in the downstream intermediate **42** of **33**. This was confirmed upon conversion to **56**, a known intermediate in the total synthesis of vancomycin aglycon.



The atropisomer stereochemistry of the CD and DE diaryl ethers (for both R = MEM and R = $CO_2{}^tBu$), including that of the model studies with **46a-d**, **48b-d**, and **50a-d**, were established by observation of the indicated diagnostic ^1H-^1H ROESY nOe correlations. For the natural atropisomer, it is the aryl CH ortho to the nitro group that exhibits a strong nOe with the benzylic -CHOTIPS (CHOR), whereas it is the aryl CH para to the nitro group for the unnatural atropisomer. Additional correlations that support the assigned structures are indicated in the SI experimentals and documented in the presented ROESY NMR data. These assignments were confirmed upon conversion to **56** (R = MEM), a known intermediate in a prior total synthesis of vancomycin aglycon, and with the next generation total synthesis of vancomycin aglycon for **69** and **72.**





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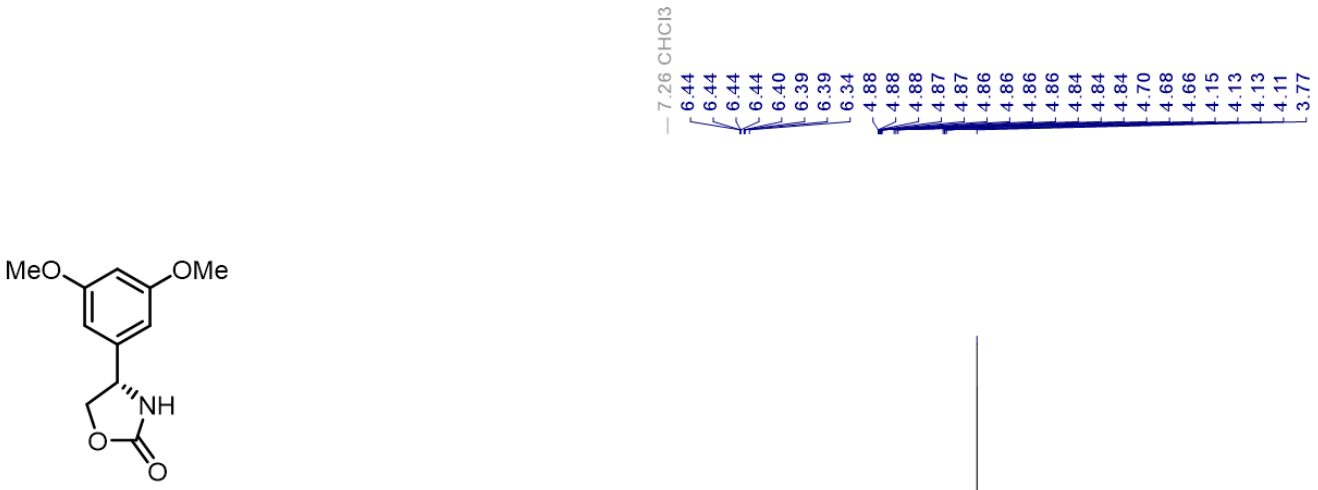
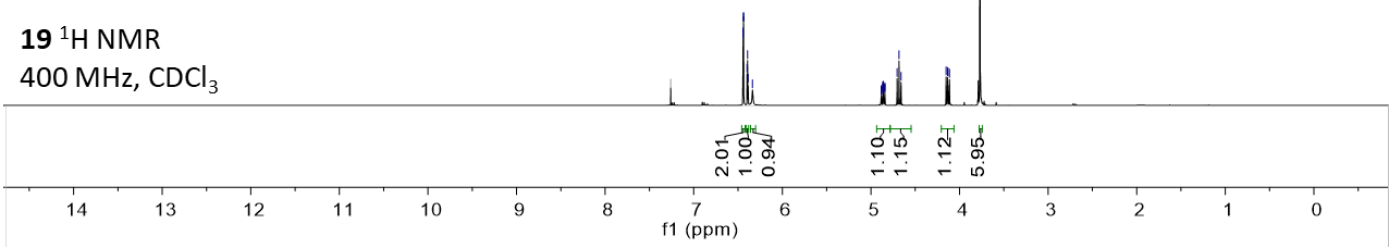
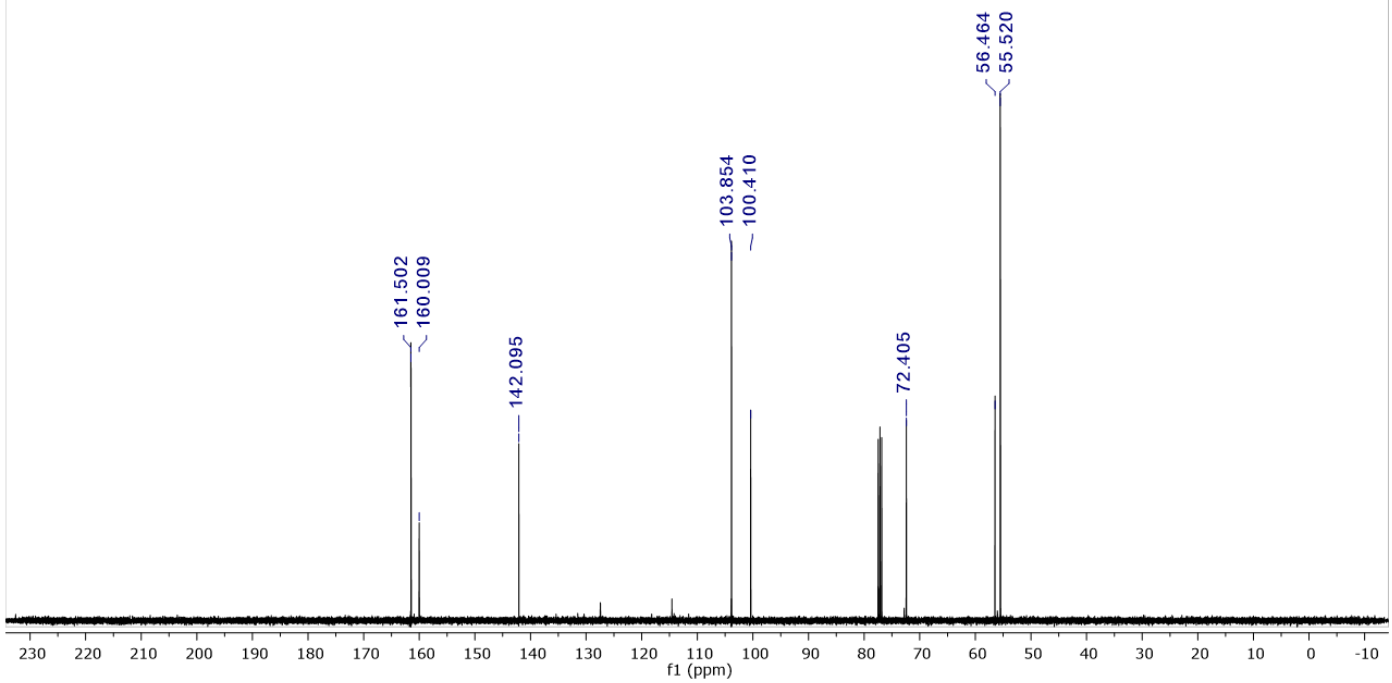
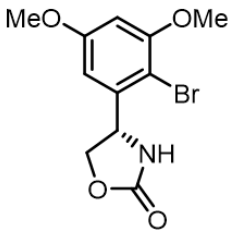


19 ^{1}H NMR
400 MHz, $CDCl_3$



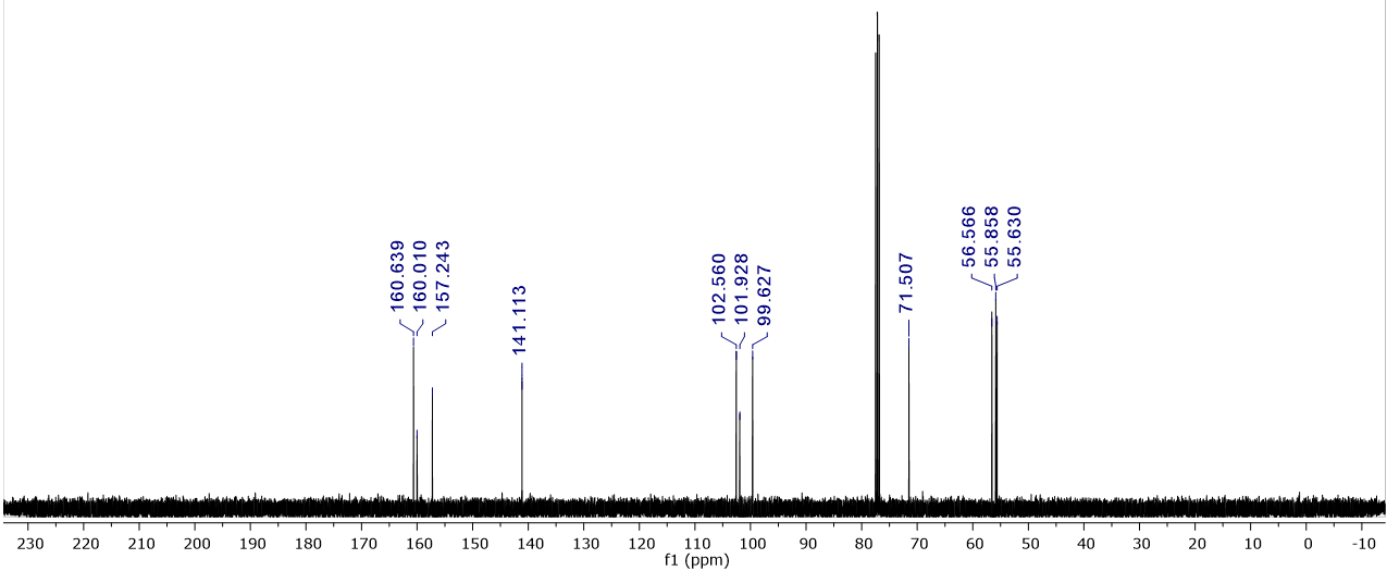
19 ^{13}C NMR
100 MHz, $CDCl_3$

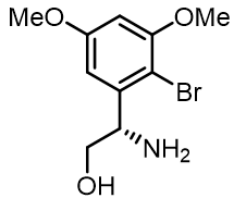




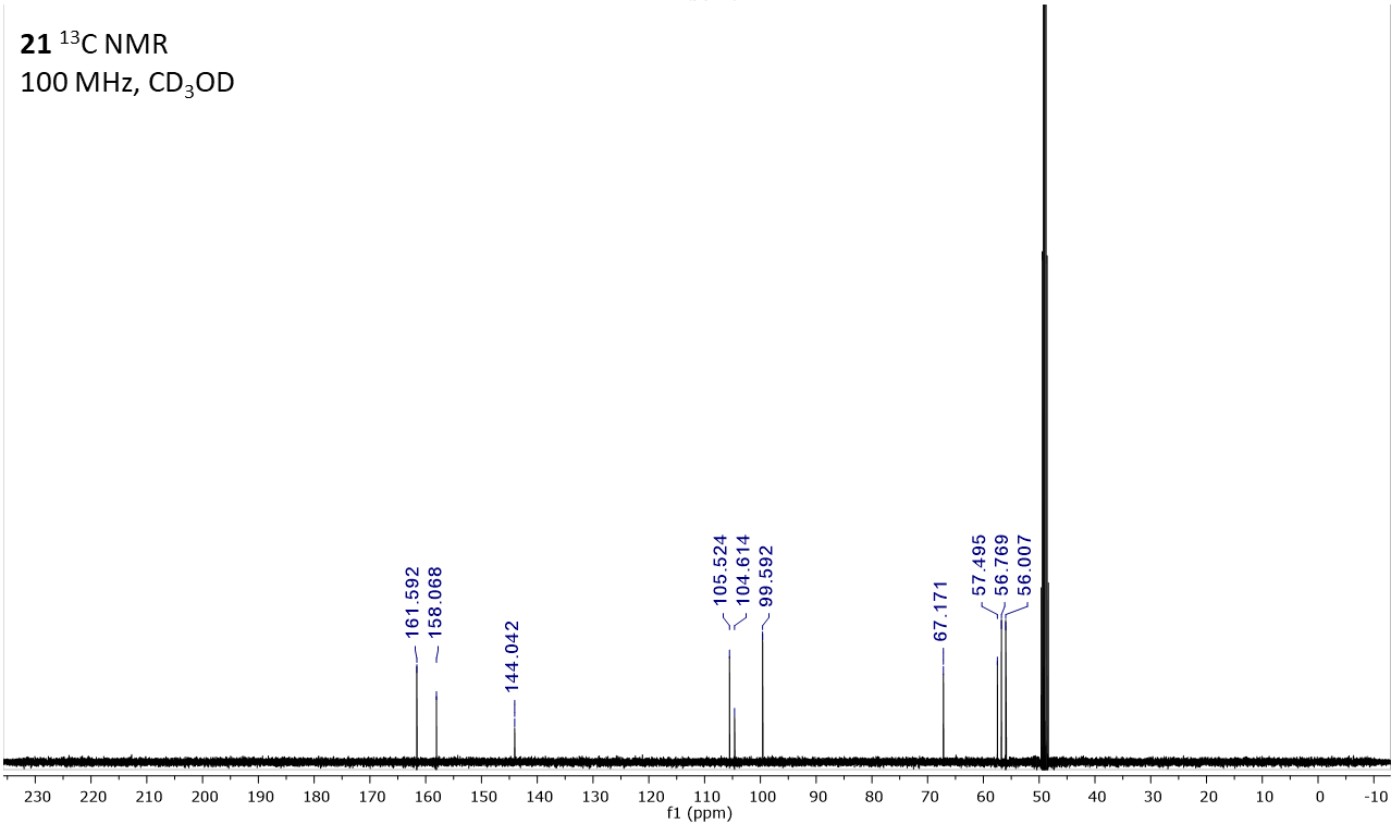
20 ^{1}H NMR
600 MHz, $CDCl_3$

20 ^{13}C NMR
100 MHz, $CDCl_3$

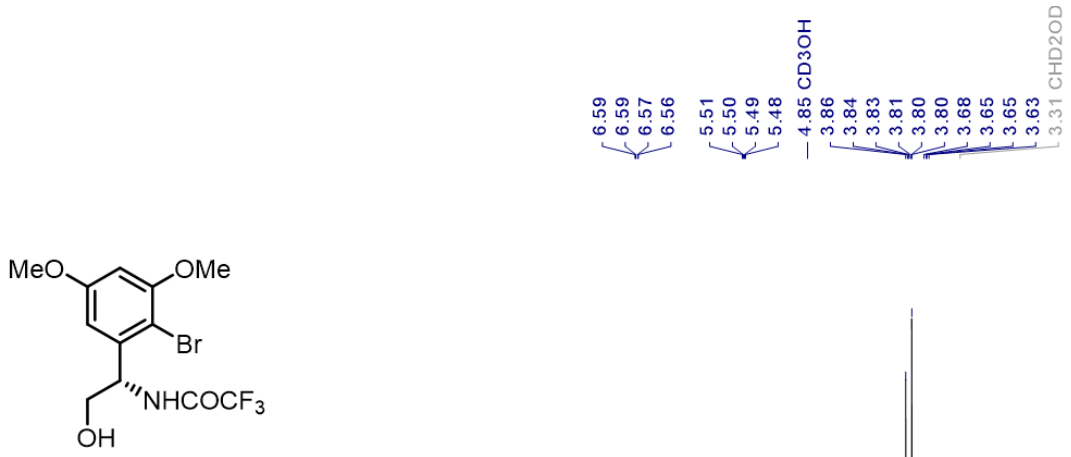




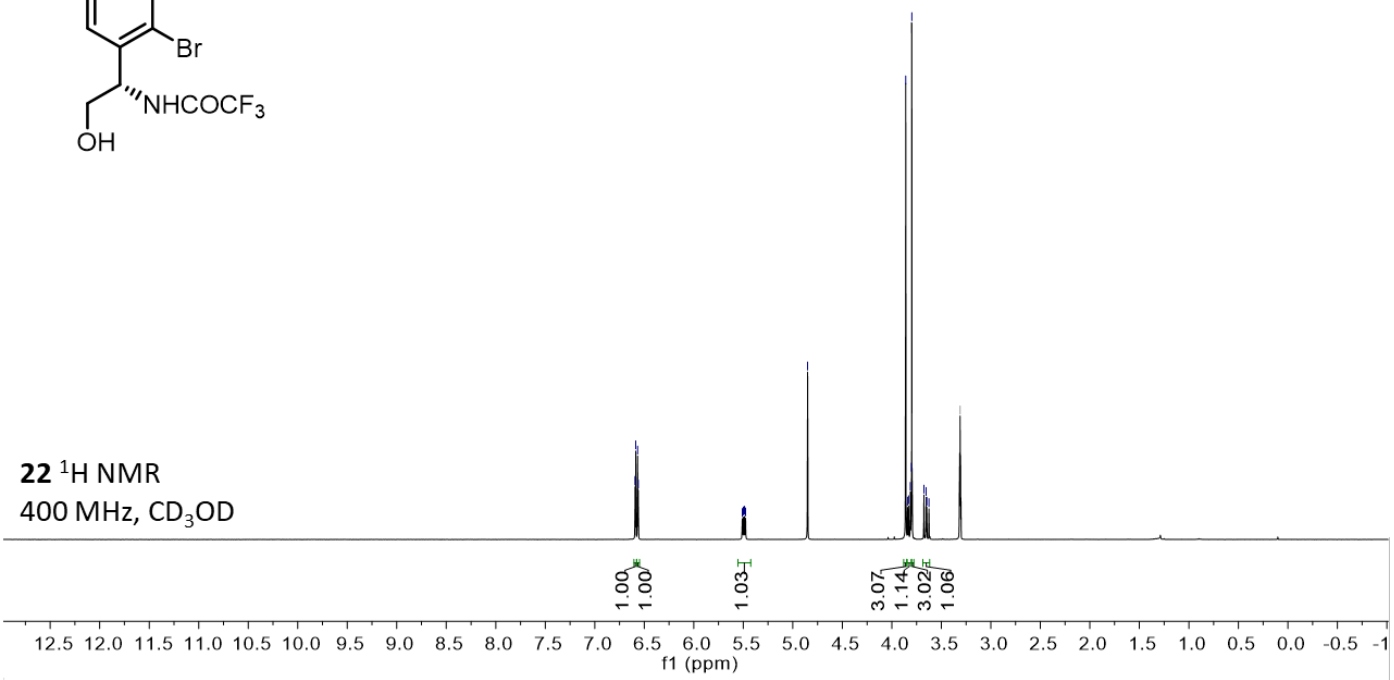
21 ^{1}H NMR
400 MHz, CD_3OD



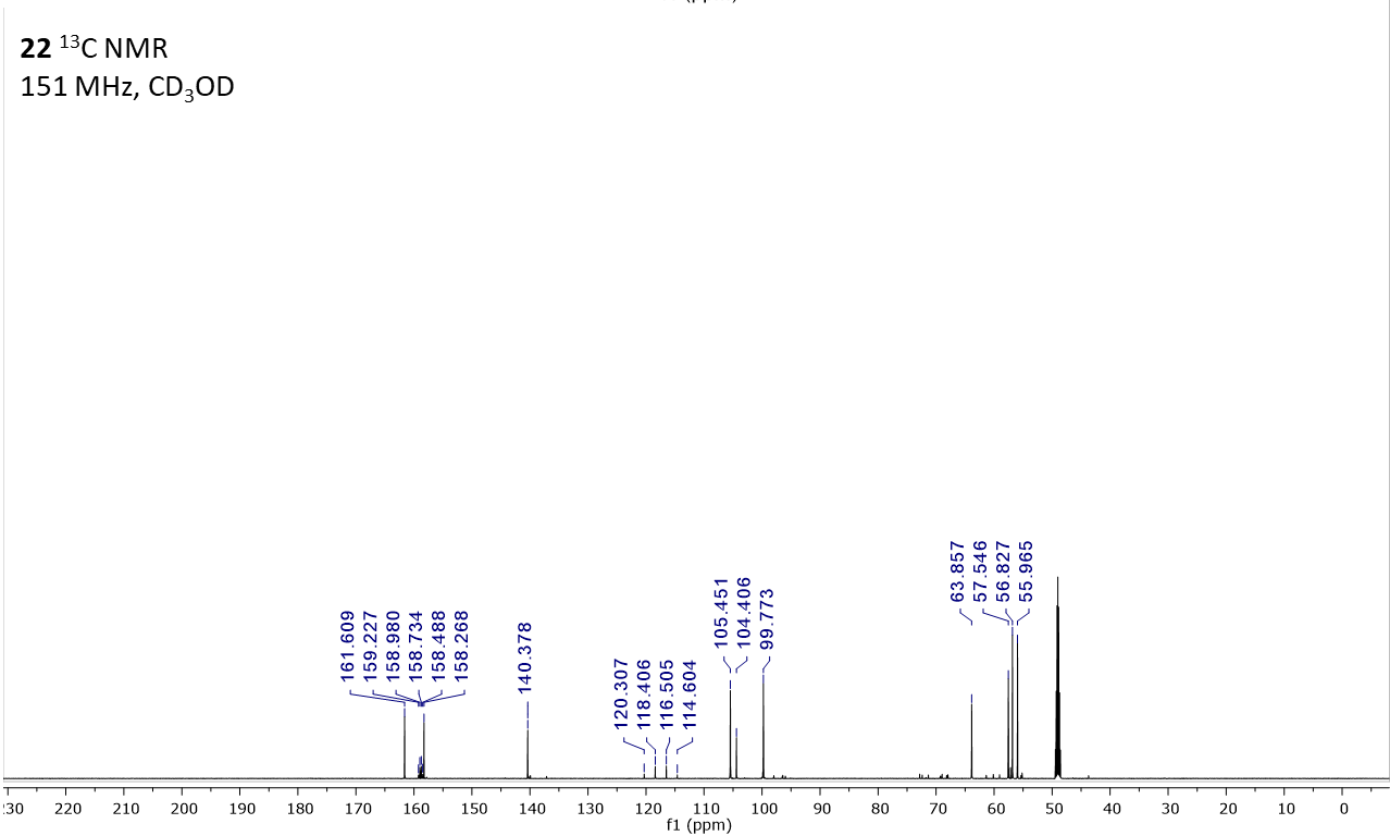
21 ^{13}C NMR
100 MHz, CD_3OD

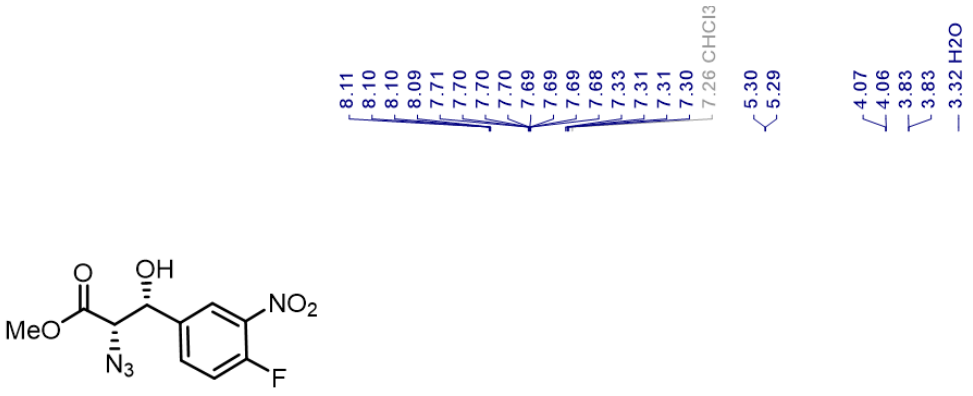


22 ^{1}H NMR
400 MHz, CD_3OD



22 ^{13}C NMR
151 MHz, CD_3OD





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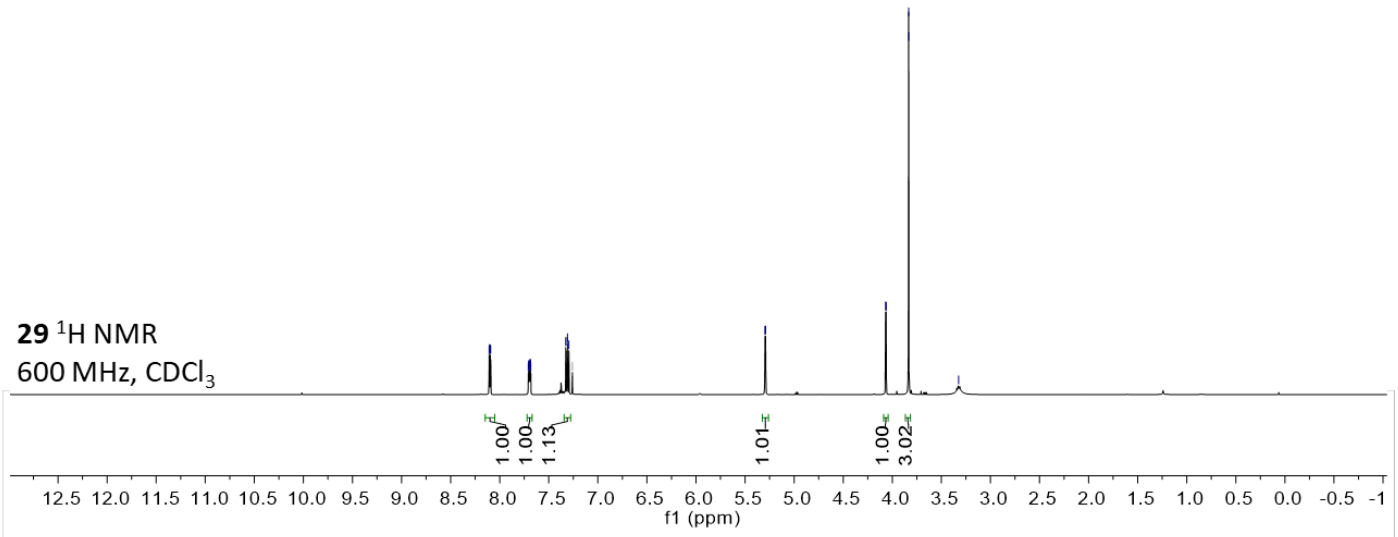
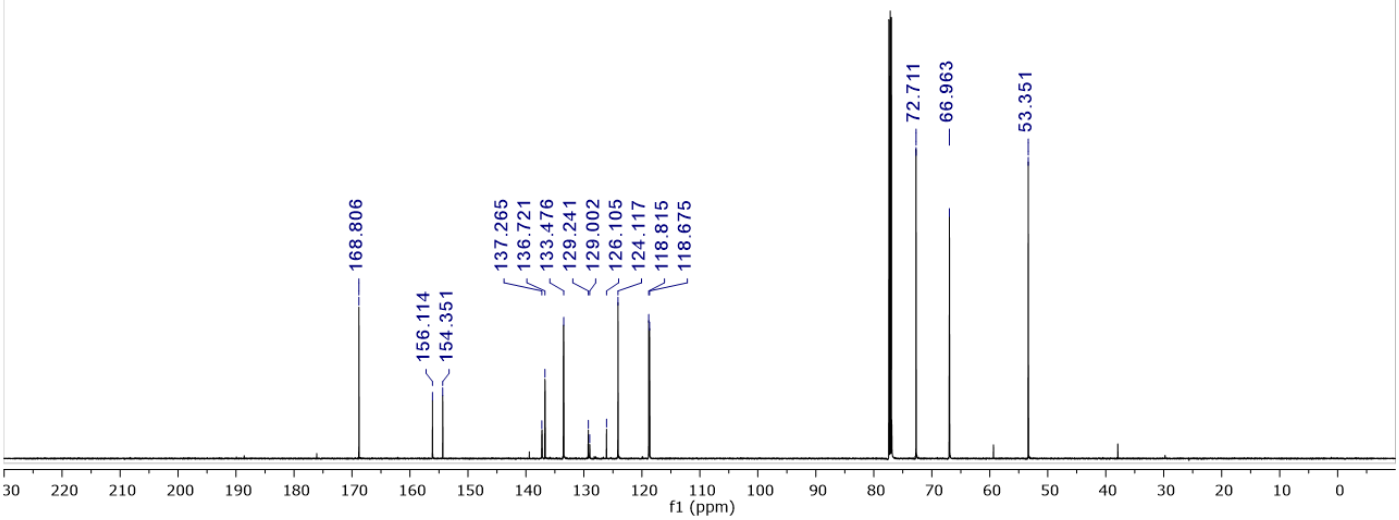
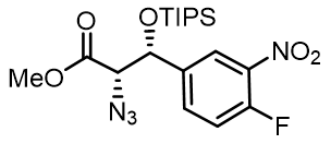
600 MHz, $CDCl_3$



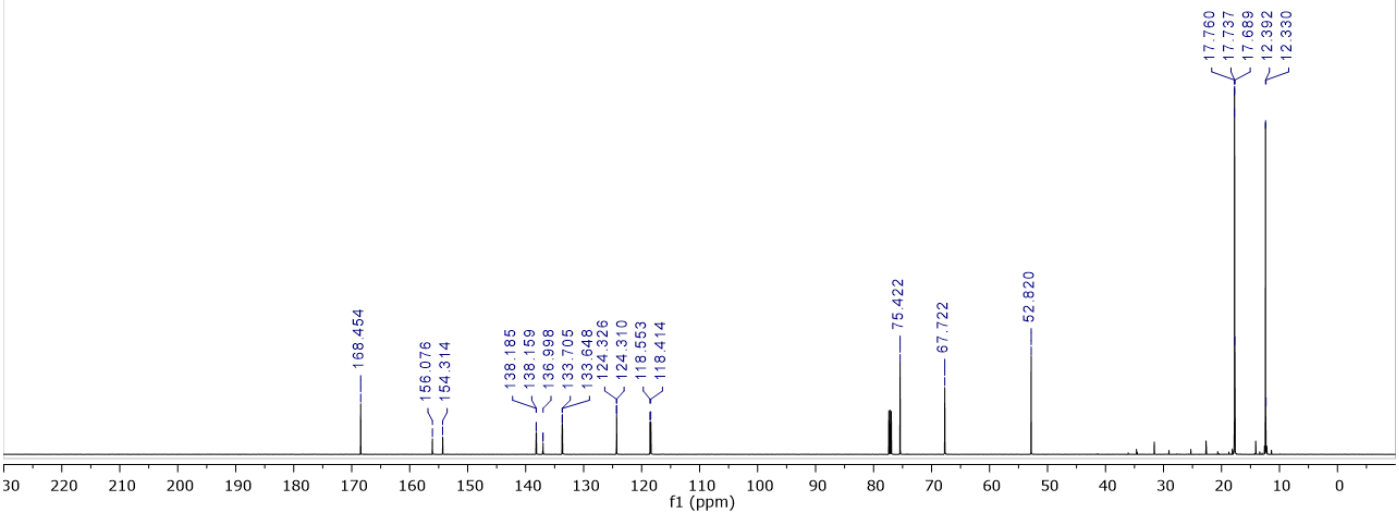
29 ^{13}C NMR
151 MHz, $CDCl_3$

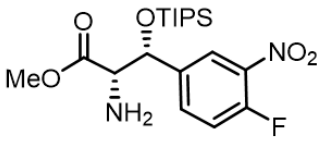




31 ^{1}H NMR
400 MHz, $CDCl_3$

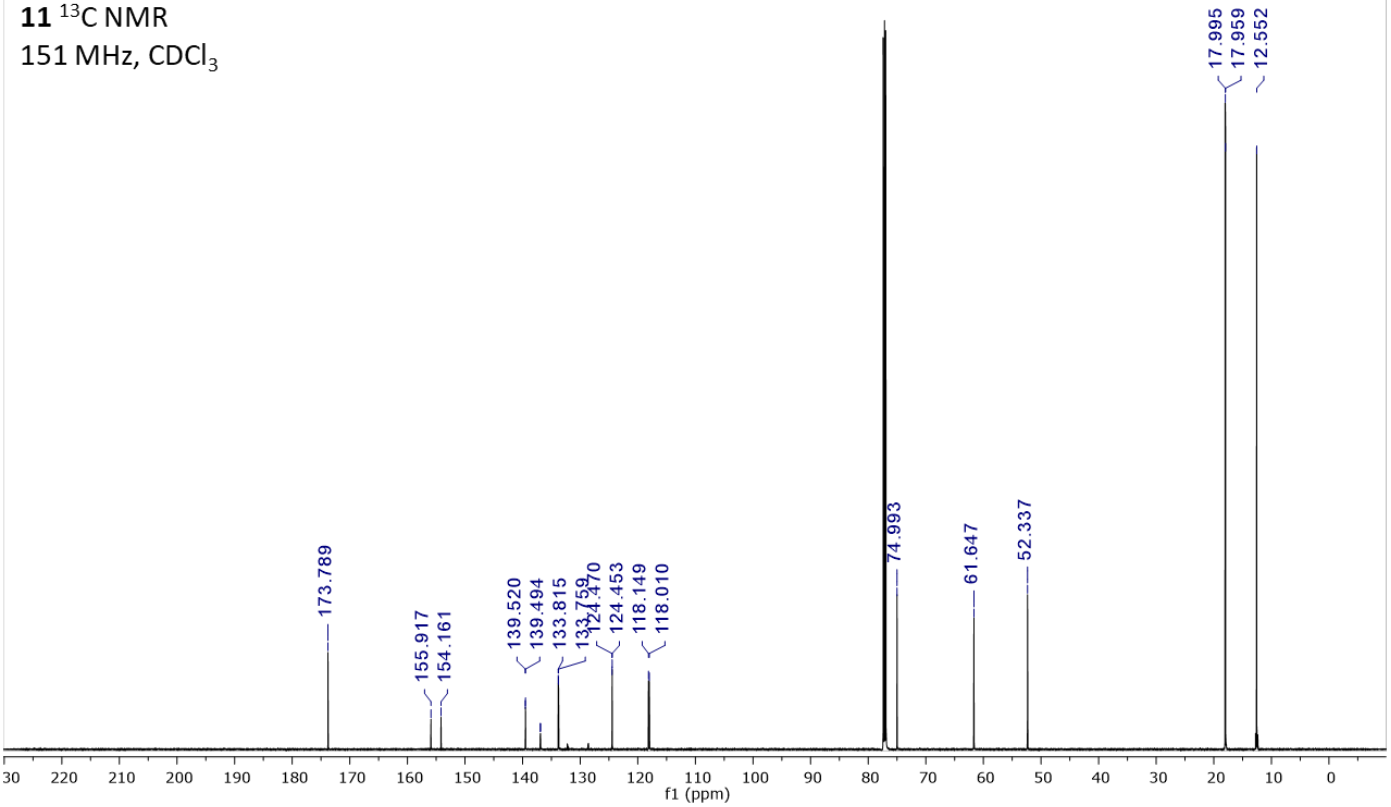
31 ^{13}C NMR
100 MHz, $CDCl_3$

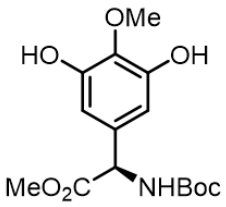




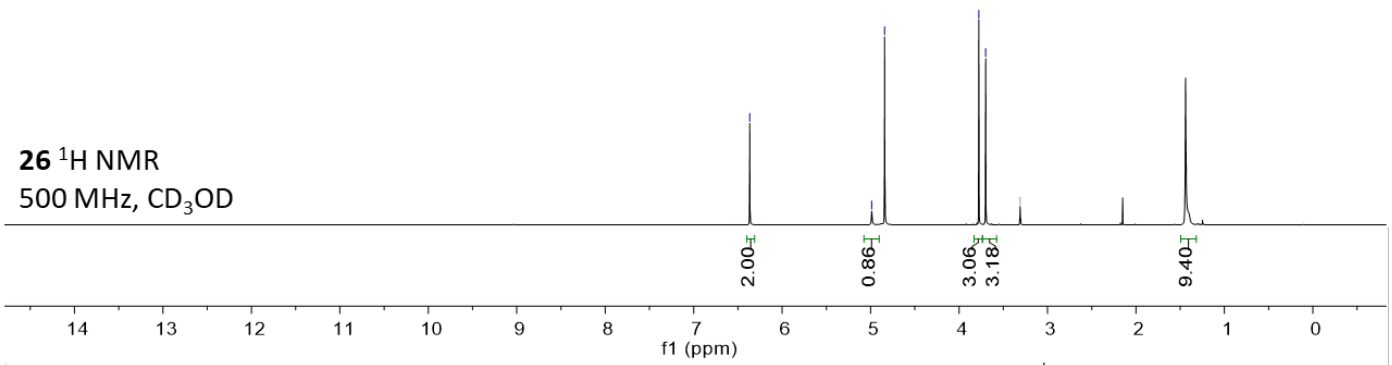
11 ^{1}H NMR
600 MHz, $CDCl_3$

11 ^{13}C NMR
151 MHz, $CDCl_3$

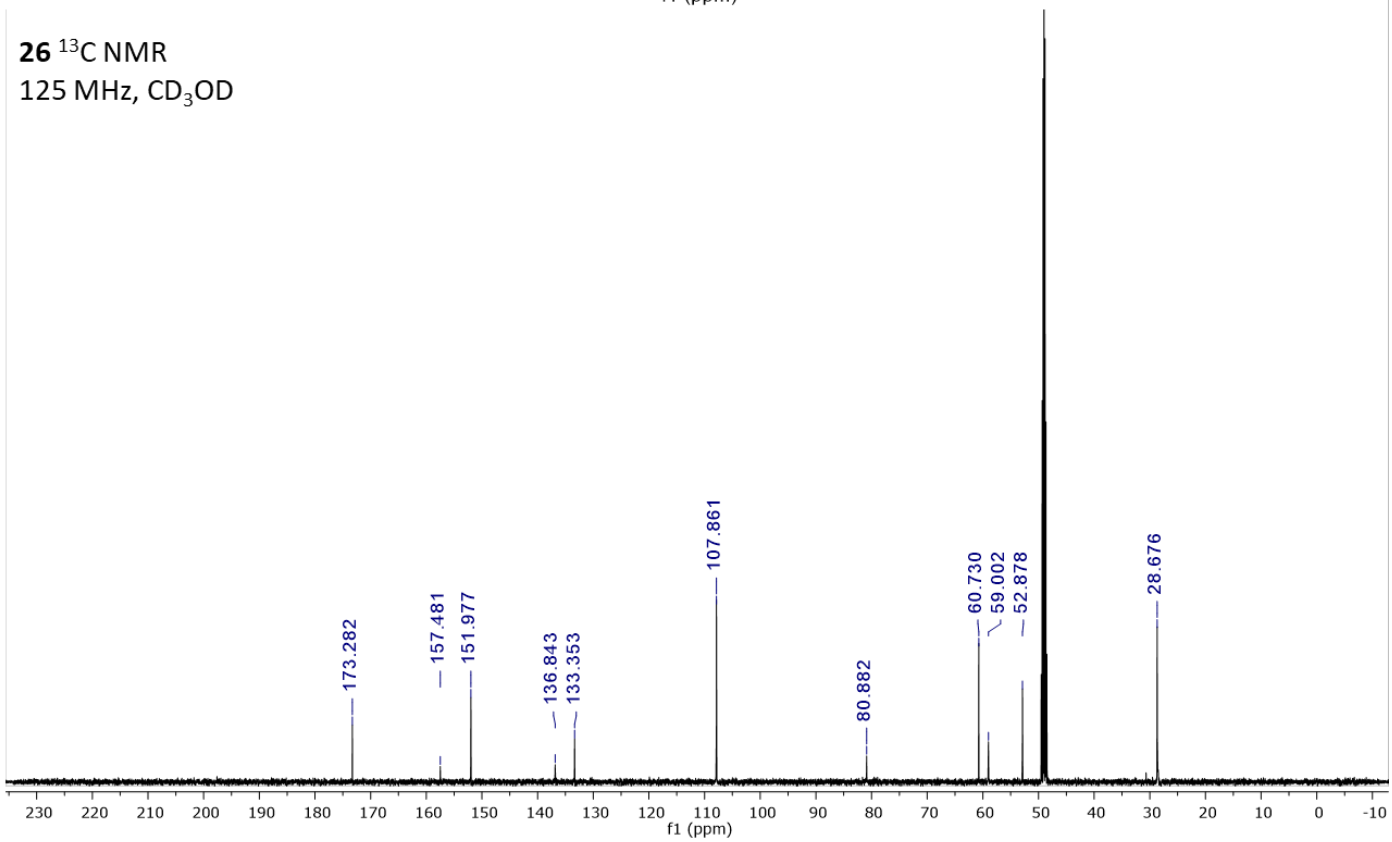


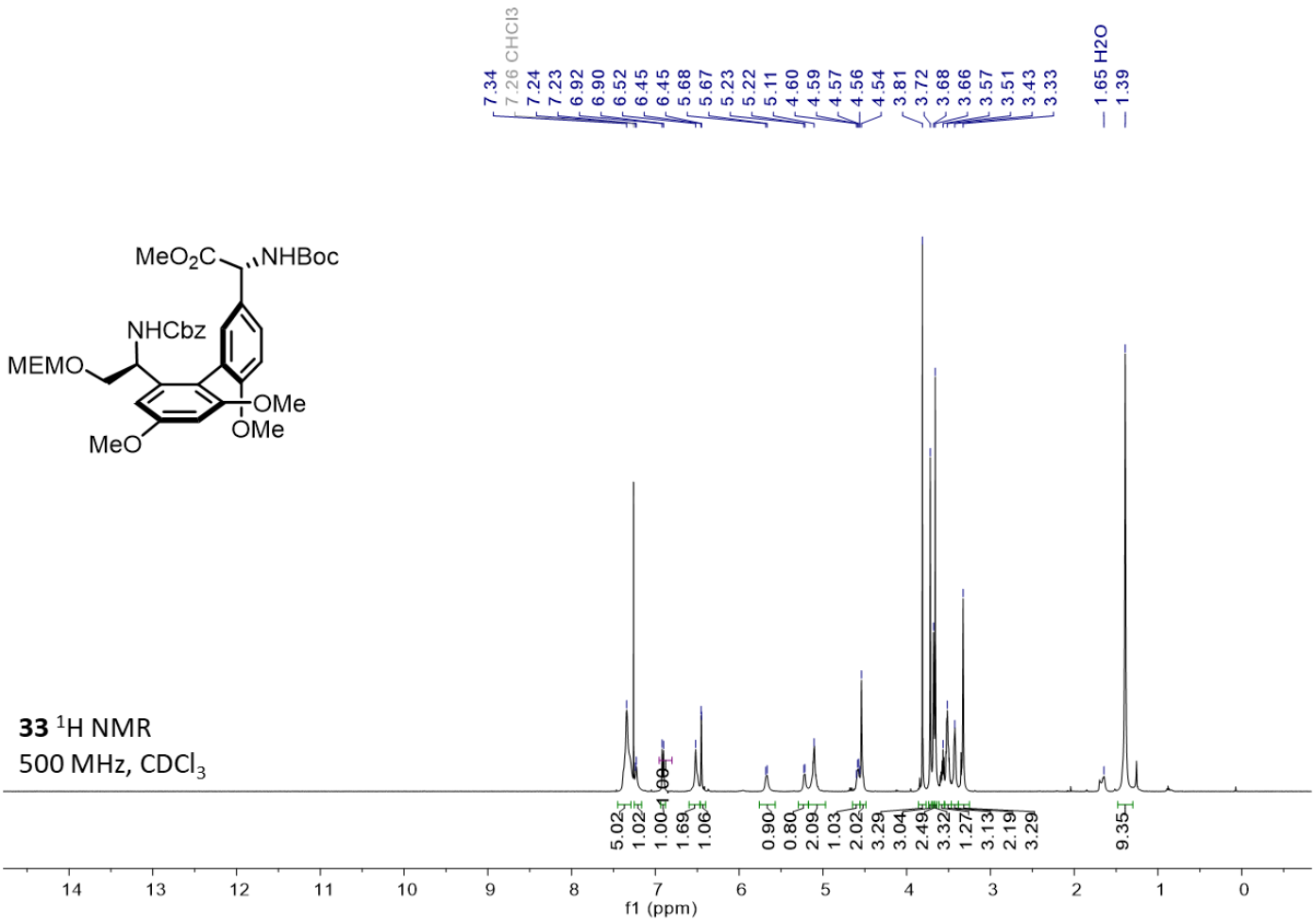


26 ^{1}H NMR
500 MHz, CD_3OD

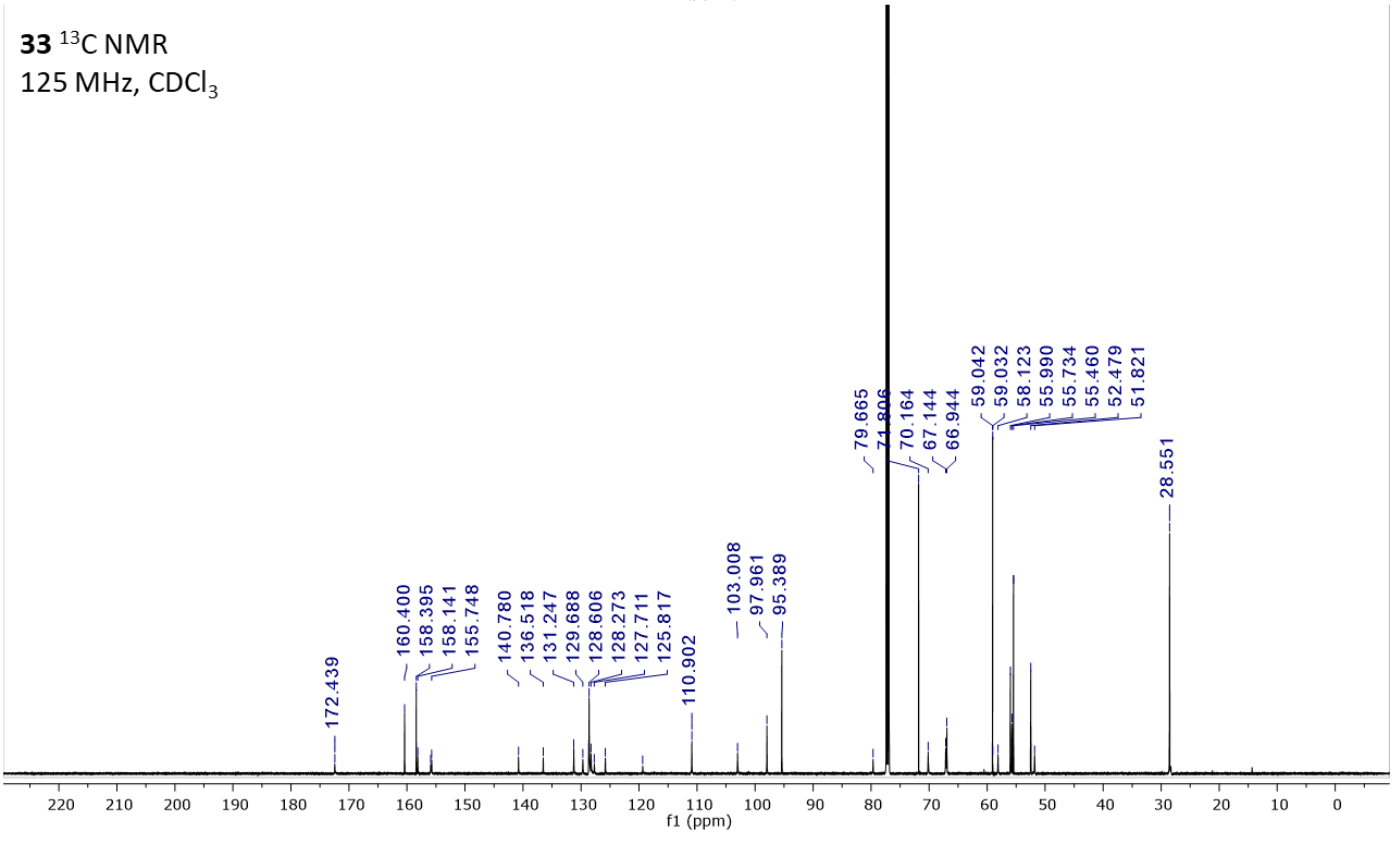


26 ^{13}C NMR
125 MHz, CD_3OD

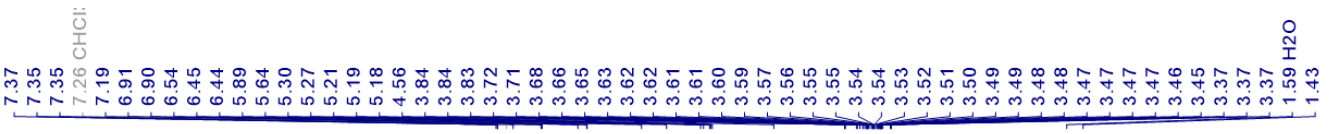


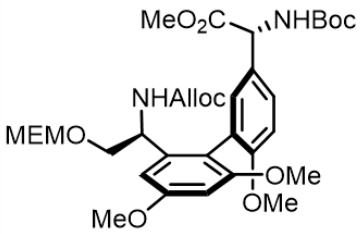


33 ^{1}H NMR
500 MHz, $CDCl_3$



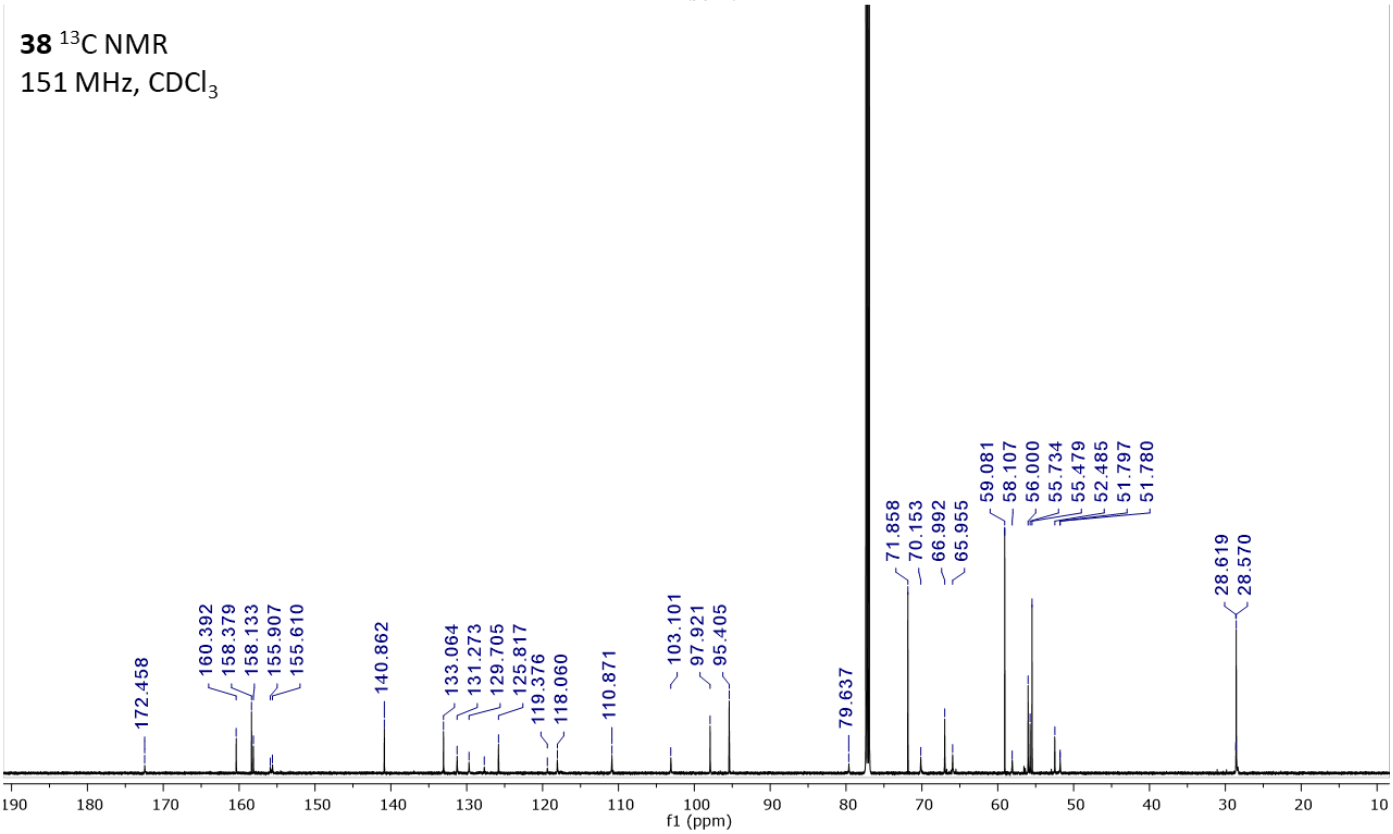
33 ^{13}C NMR
125 MHz, $CDCl_3$

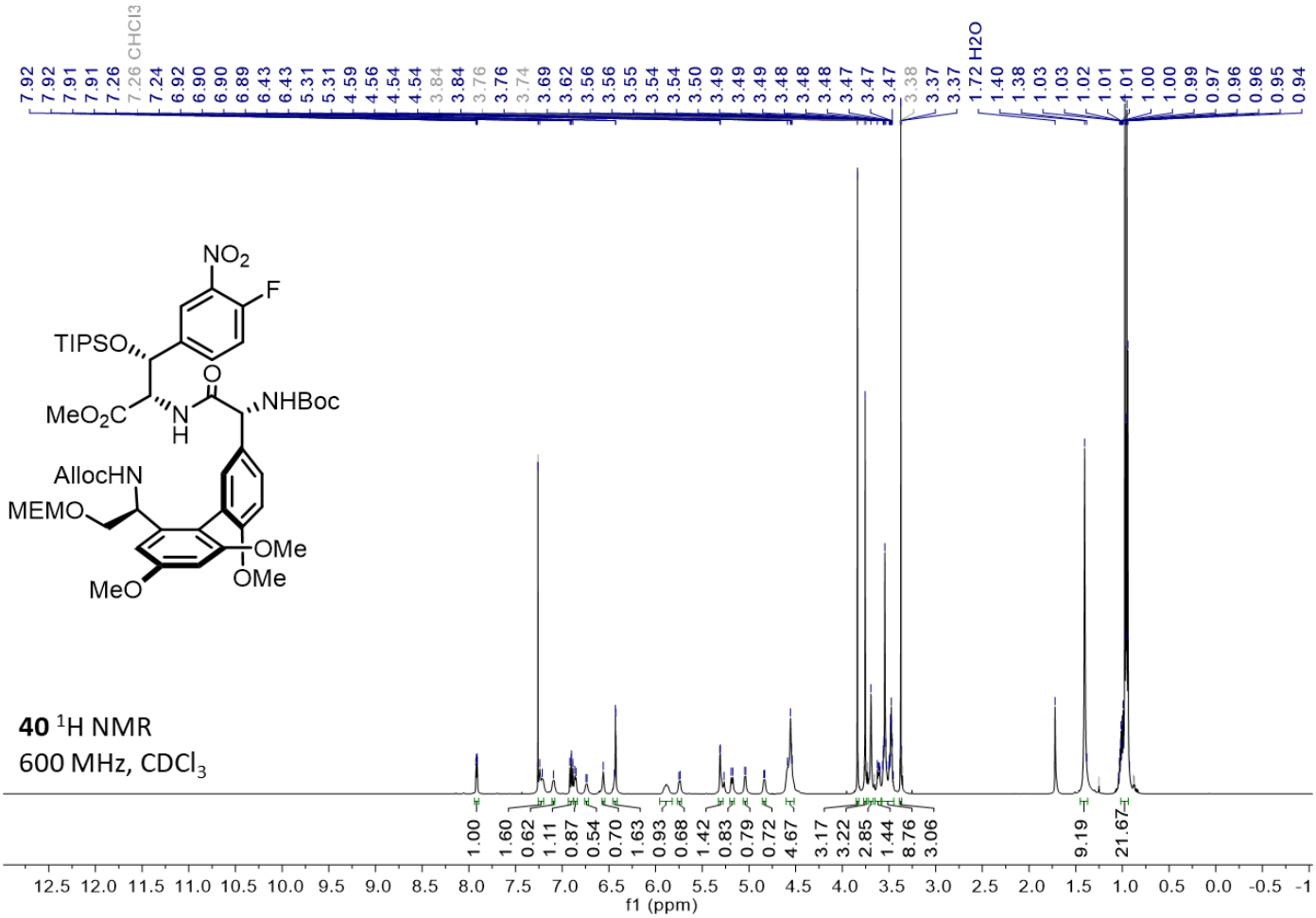


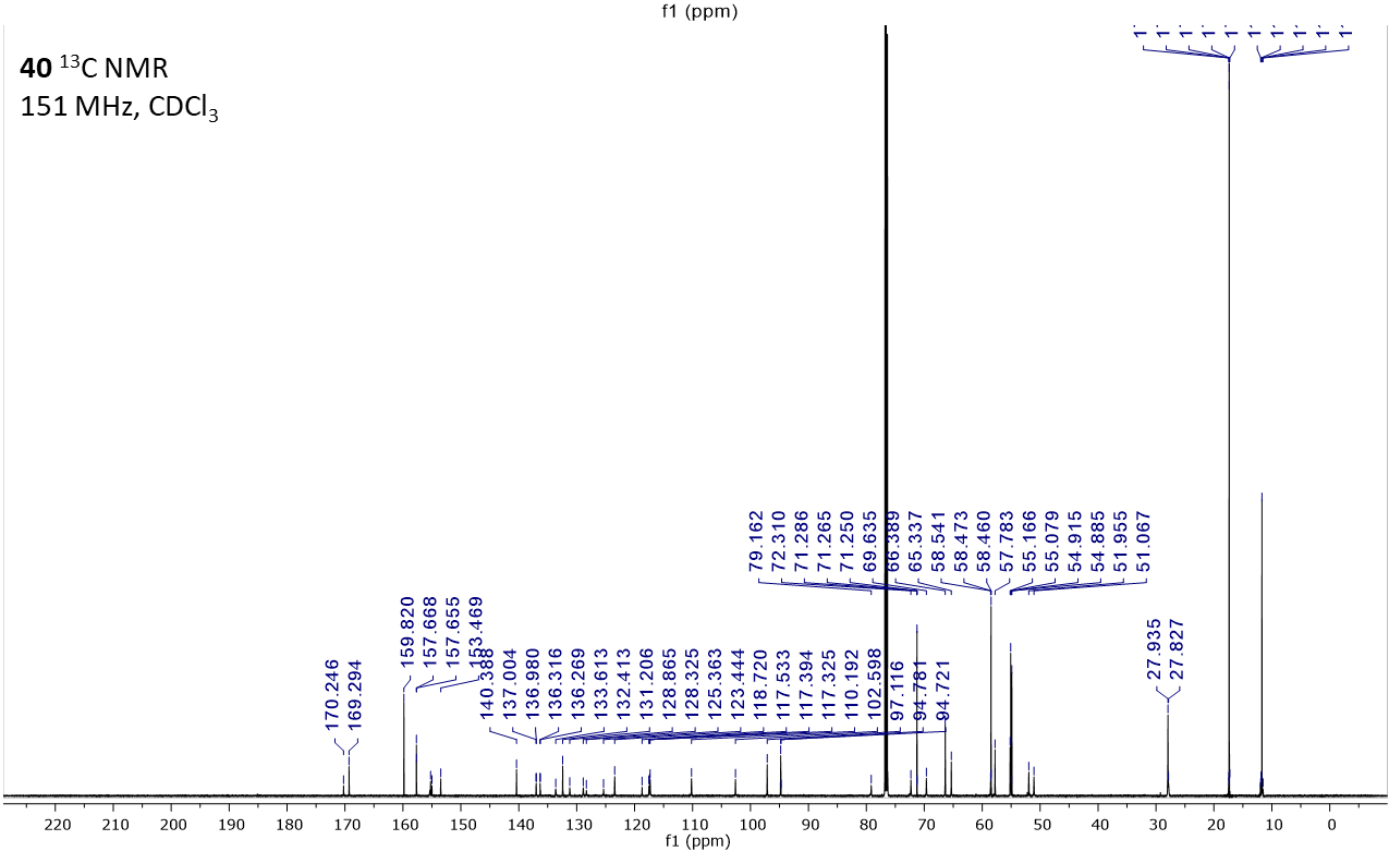


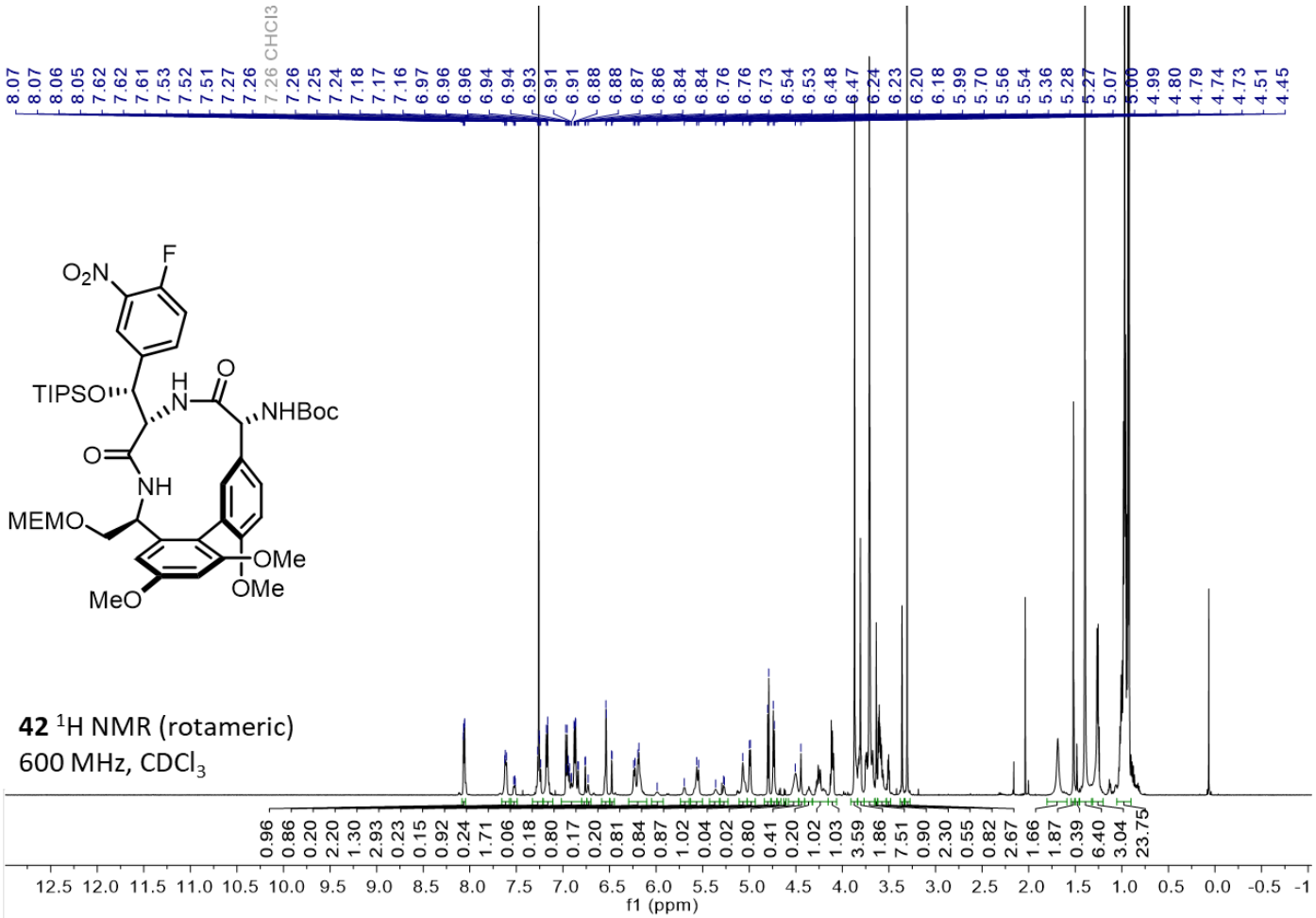
38 ^{1}H NMR
600 MHz, $CDCl_3$

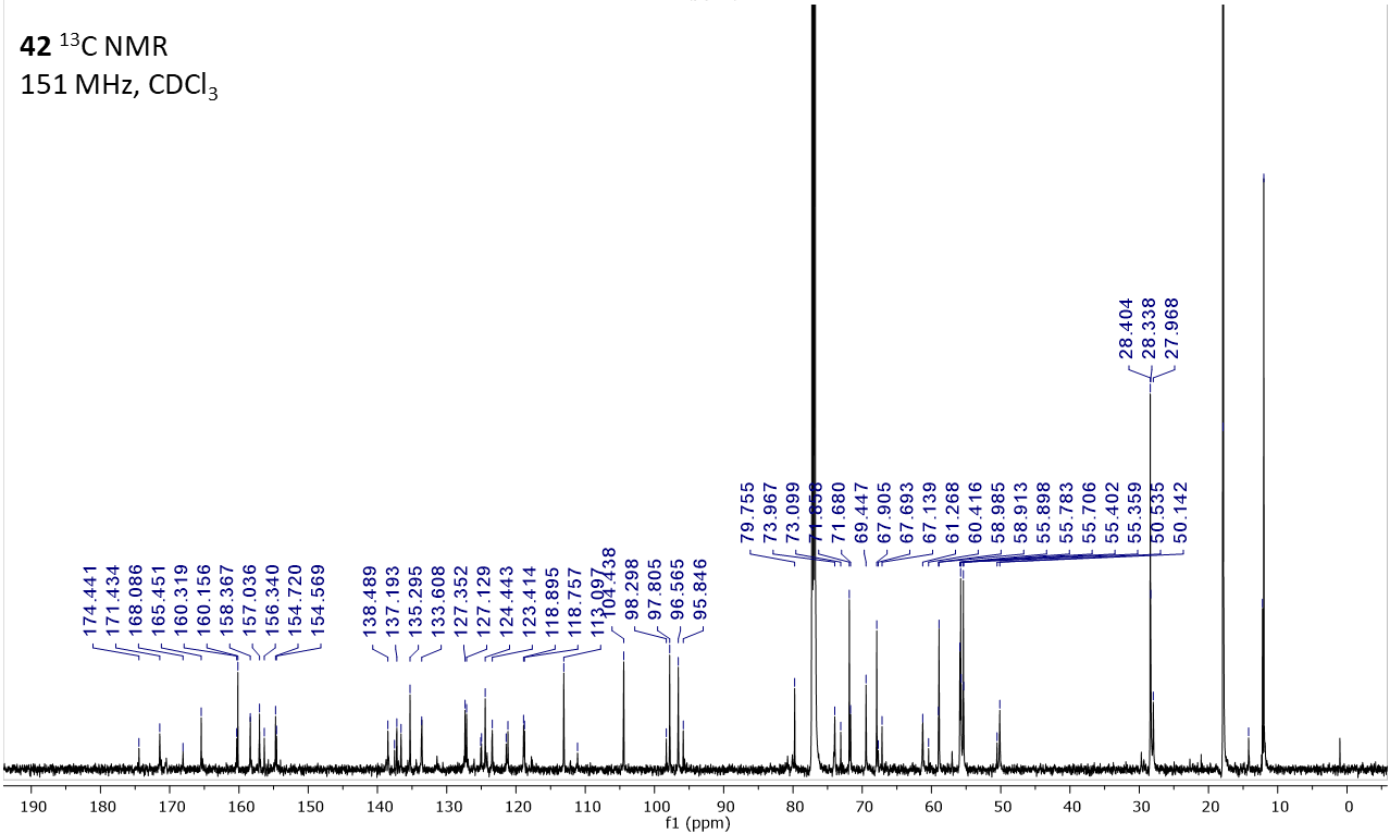
38 ^{13}C NMR
151 MHz, $CDCl_3$

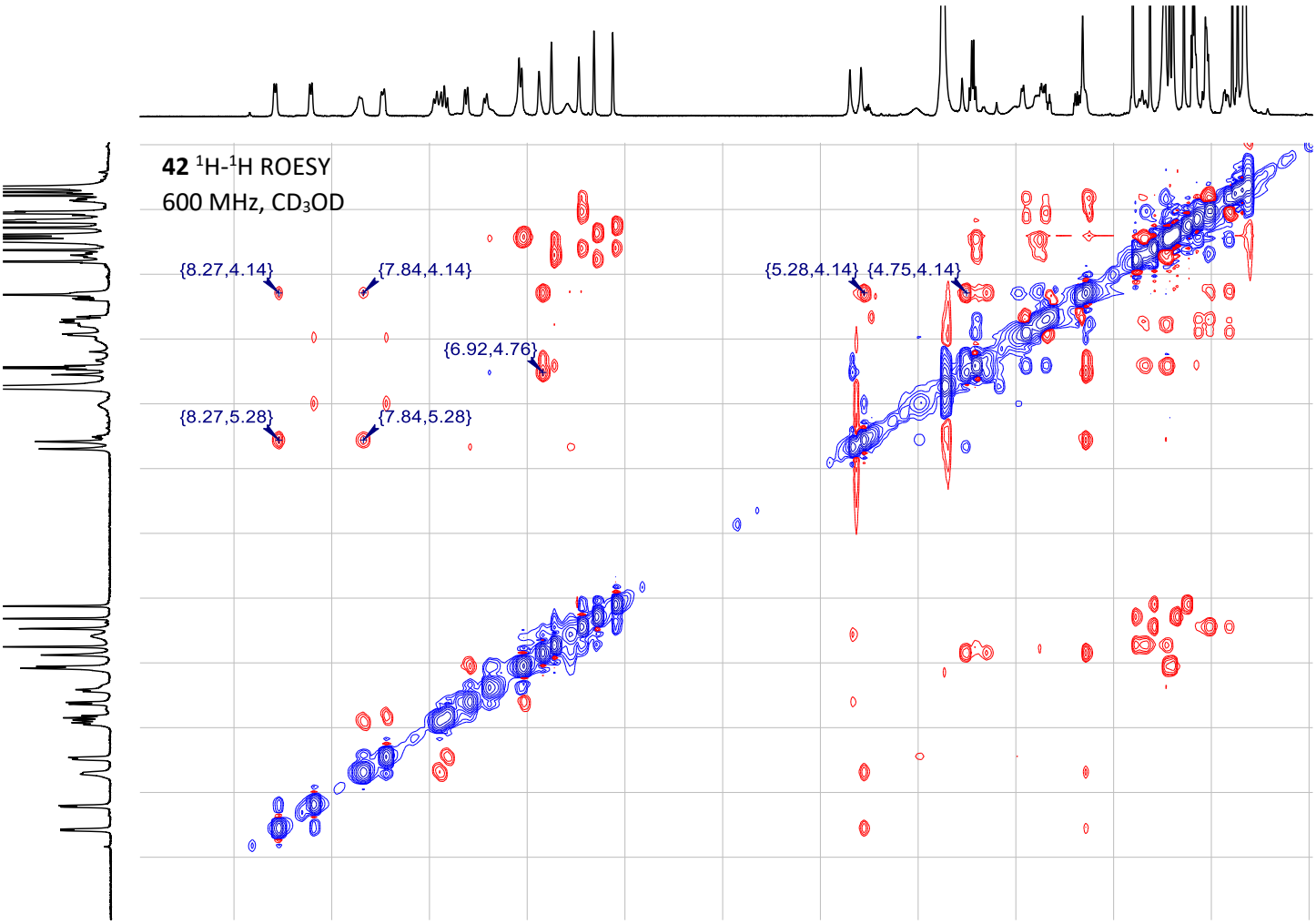


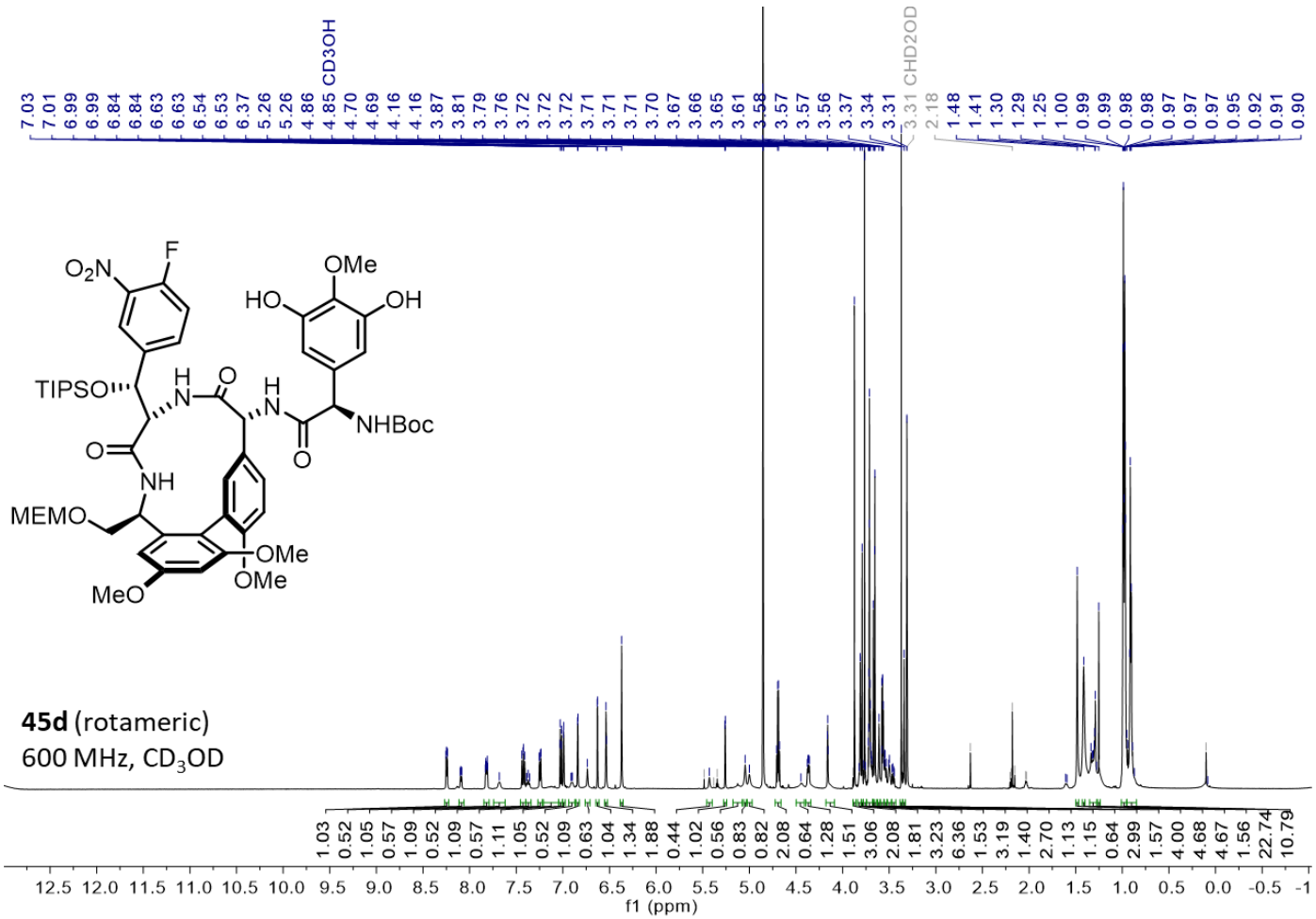

7.92 7.92 7.91 7.91 7.26 CHCl3 7.24 6.92 6.90 6.90 6.89 6.43 5.31 5.31 4.59 4.56 4.54 4.54 3.84 3.84 3.76 3.76 3.74 3.69 3.62 3.56 3.56 3.55 3.54 3.54 3.50 3.49 3.49 3.49 3.48 3.48 3.48 3.47 3.47 3.47 3.38 3.37 3.37 1.72 H2O 1.40 1.38 1.03 1.03 1.02 1.01 1.01 1.00 1.00 0.99 0.97 0.96 0.96 0.95 0.94
NO2
F
TIPSO
O
MeO2C
N
H
NHBoc
AllocHN
MEMO
OMe
OMe
MeO
40 1H NMR
600 MHz, CDCl3
1.00 1.60 0.62 1.11 0.87 0.54 0.70 1.63 0.93 0.68 1.42 0.83 0.79 0.72 4.67 3.17 3.22 2.85 1.44 8.76 3.06 9.19 21.67
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

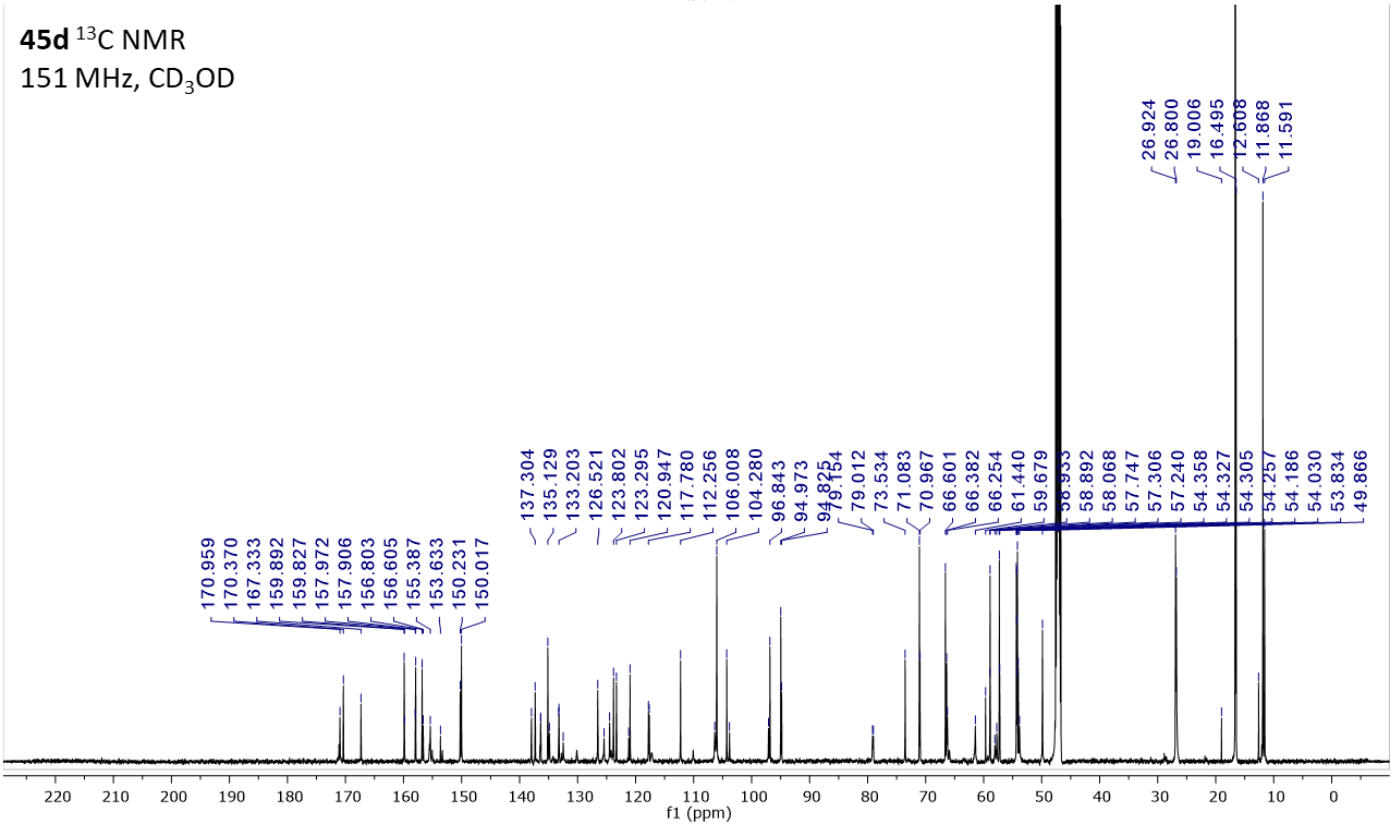

40 13C NMR
151 MHz, CDCl3
79.162 72.310 71.286 71.265 71.250 69.635 66.389 65.337 58.541 58.473 58.460 57.783 55.166 55.079 54.915 54.885 51.955 51.067
170.246 169.294 159.820 157.668 157.655 153.469 140.388 137.004 136.980 136.316 136.269 133.613 132.413 131.206 128.865 128.325 125.363 123.444 118.720 117.533 117.394 117.325 110.192 102.598 97.116 94.781 94.721 27.935 27.827
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

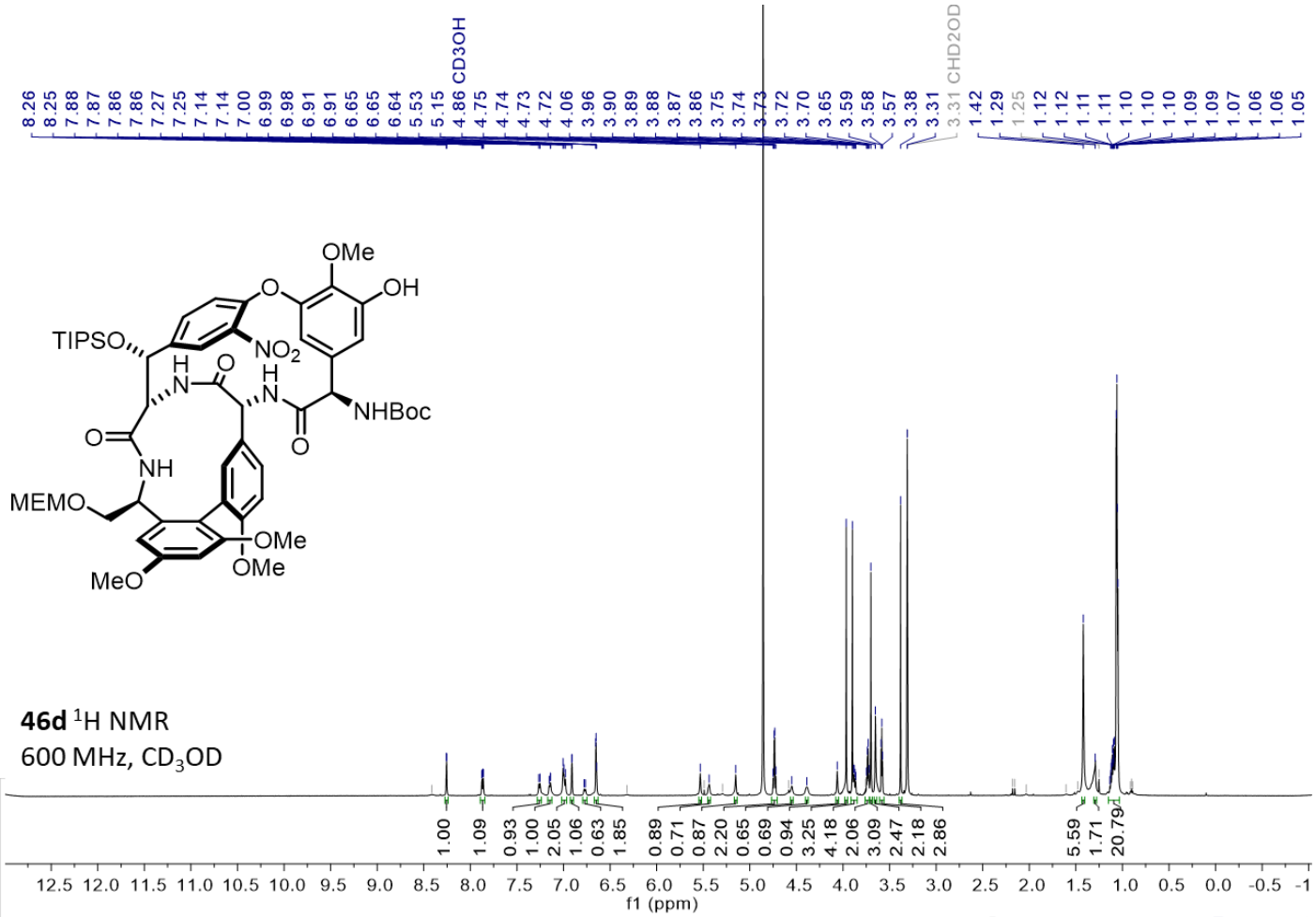

42 ^{1}H NMR (rotameric)
600 MHz, $CDCl_3$
f1 (ppm)

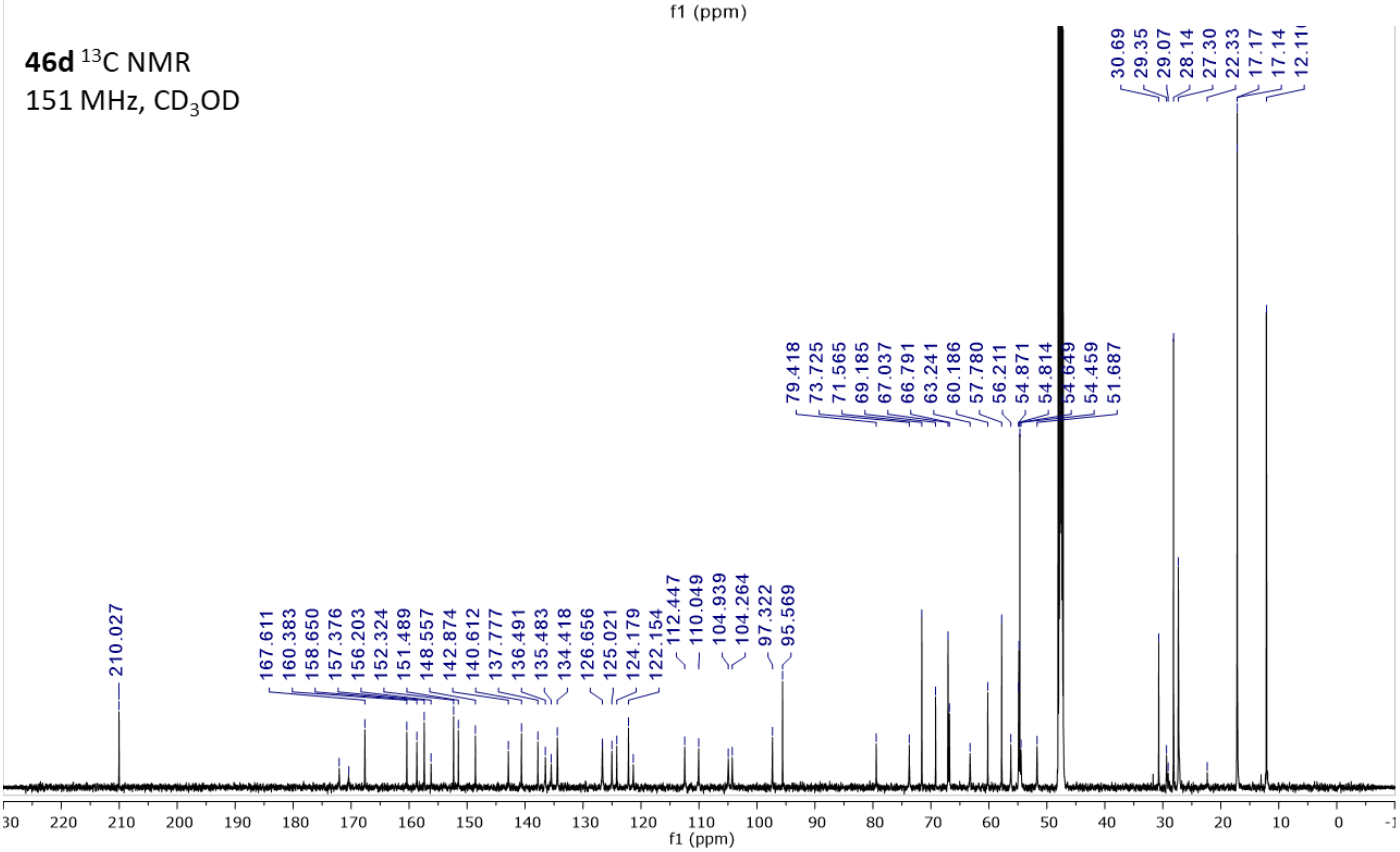

42 ^{13}C NMR
151 MHz, $CDCl_3$
f1 (ppm)

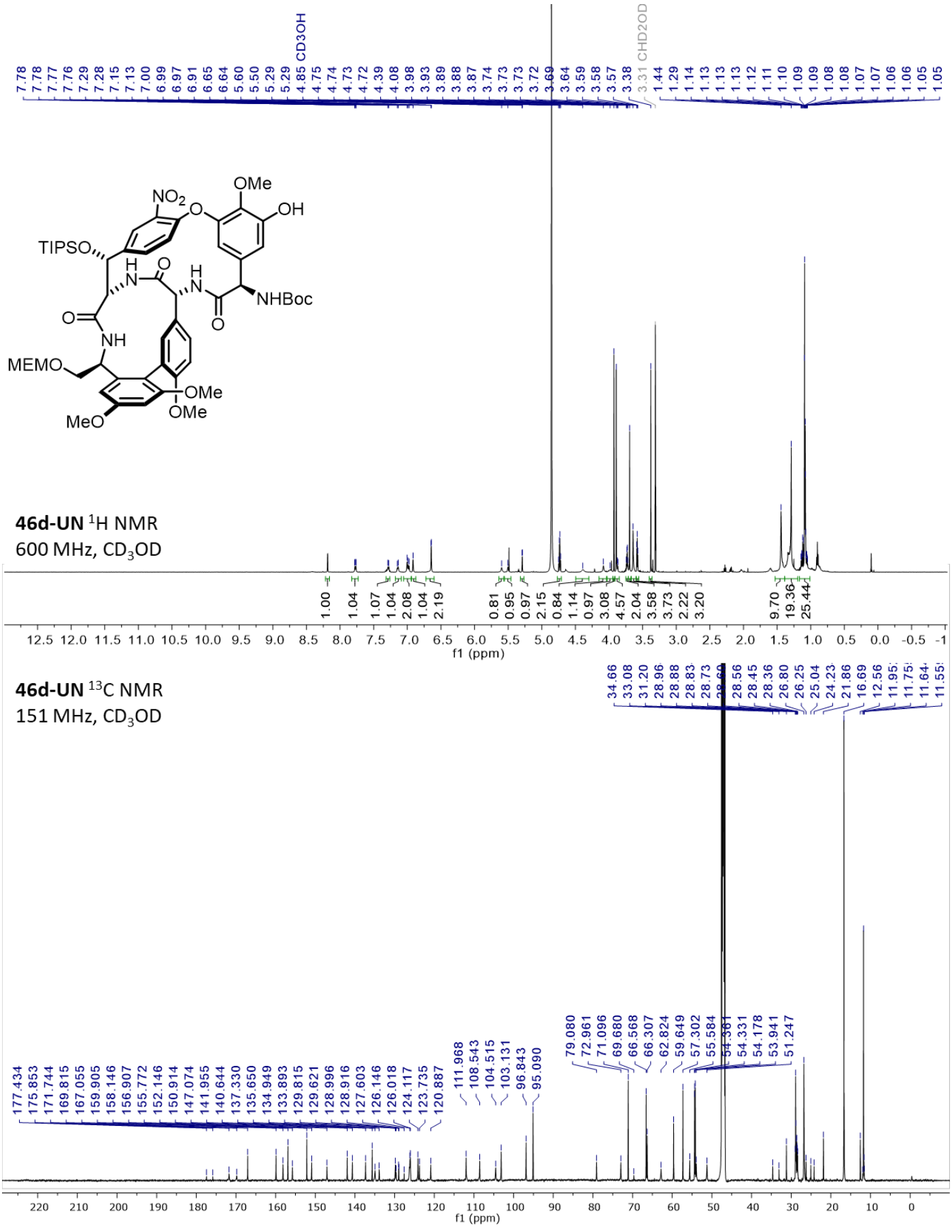

42 ¹H-¹H ROESY
600 MHz, CD₃OD
{8.27,4.14}
{7.84,4.14}
{6.92,4.76}
{8.27,5.28}
{7.84,5.28}
{5.28,4.14}
{4.75,4.14}

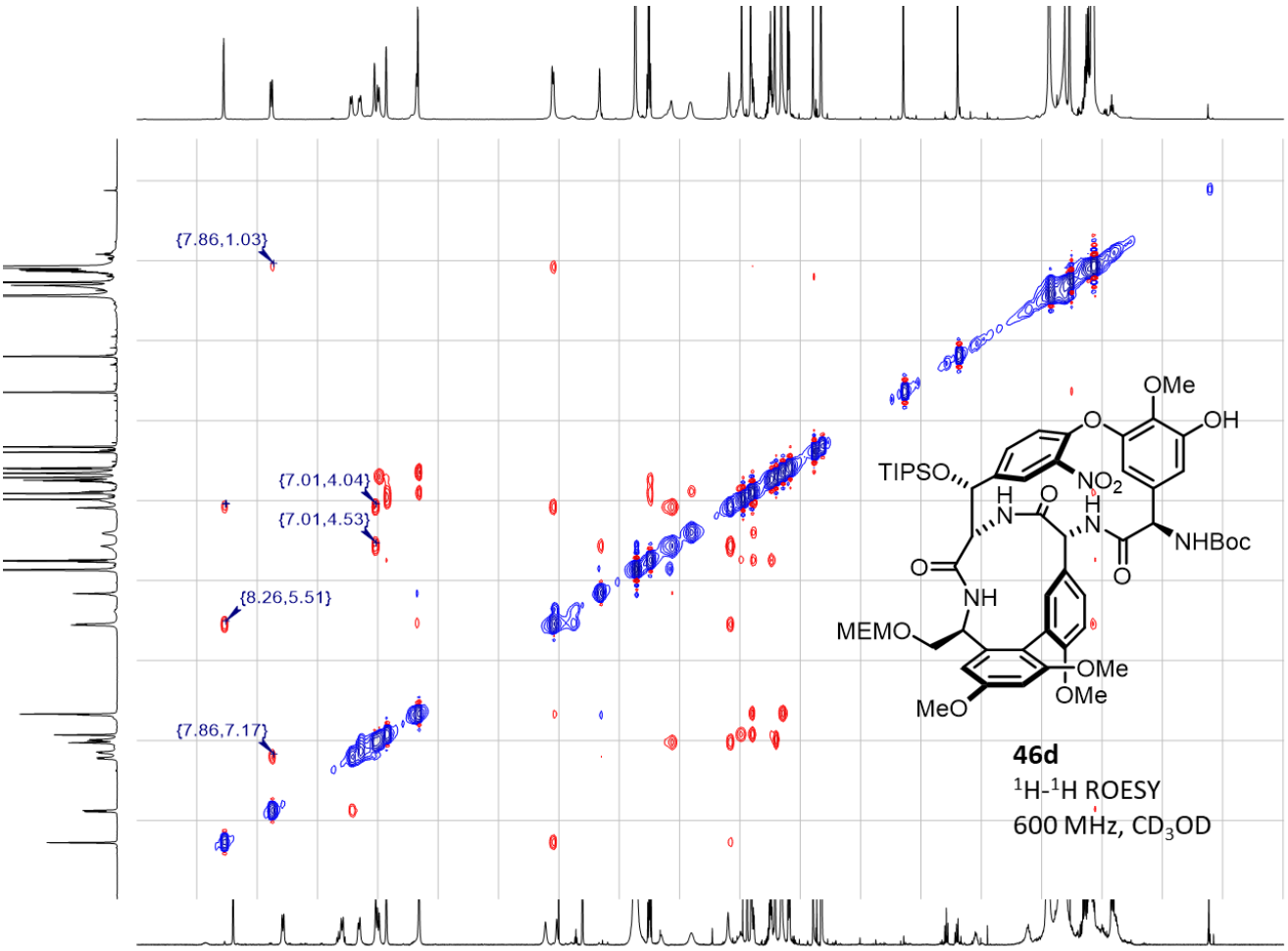

7.03 7.01 6.99 6.99 6.84 6.84 6.63 6.63 6.54 6.53 6.37 5.26 5.26 4.86 4.85 CD3OH 4.70 4.69 4.16 4.16 3.87 3.81 3.79 3.76 3.72 3.72 3.72 3.71 3.71 3.71 3.70 3.67 3.66 3.65 3.61 3.58 3.57 3.57 3.56 3.37 3.34 3.31 3.31 CHD2OD 2.18 1.48 1.41 1.30 1.29 1.25 1.00 0.99 0.99 0.98 0.98 0.97 0.97 0.97 0.95 0.92 0.91 0.90
O2N
F
OMe
HO
OH
TIPSO
H
N
O
H
N
NHBoc
O
O
NH
MEMO
OMe
OMe
MeO
45d (rotameric)
600 MHz, CD3OD
1.03 0.52 1.05 0.57 1.09 0.52 1.09 0.57 1.11 1.05 0.52 1.09 0.63 1.04 1.34 1.88 0.44 1.02 0.56 0.83 0.82 2.08 0.64 1.28 1.51 3.06 2.08 1.81 3.23 6.36 1.53 3.19 1.40 2.70 1.13 1.15 0.64 2.99 1.57 4.00 4.68 4.67 1.56 22.74 10.79
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

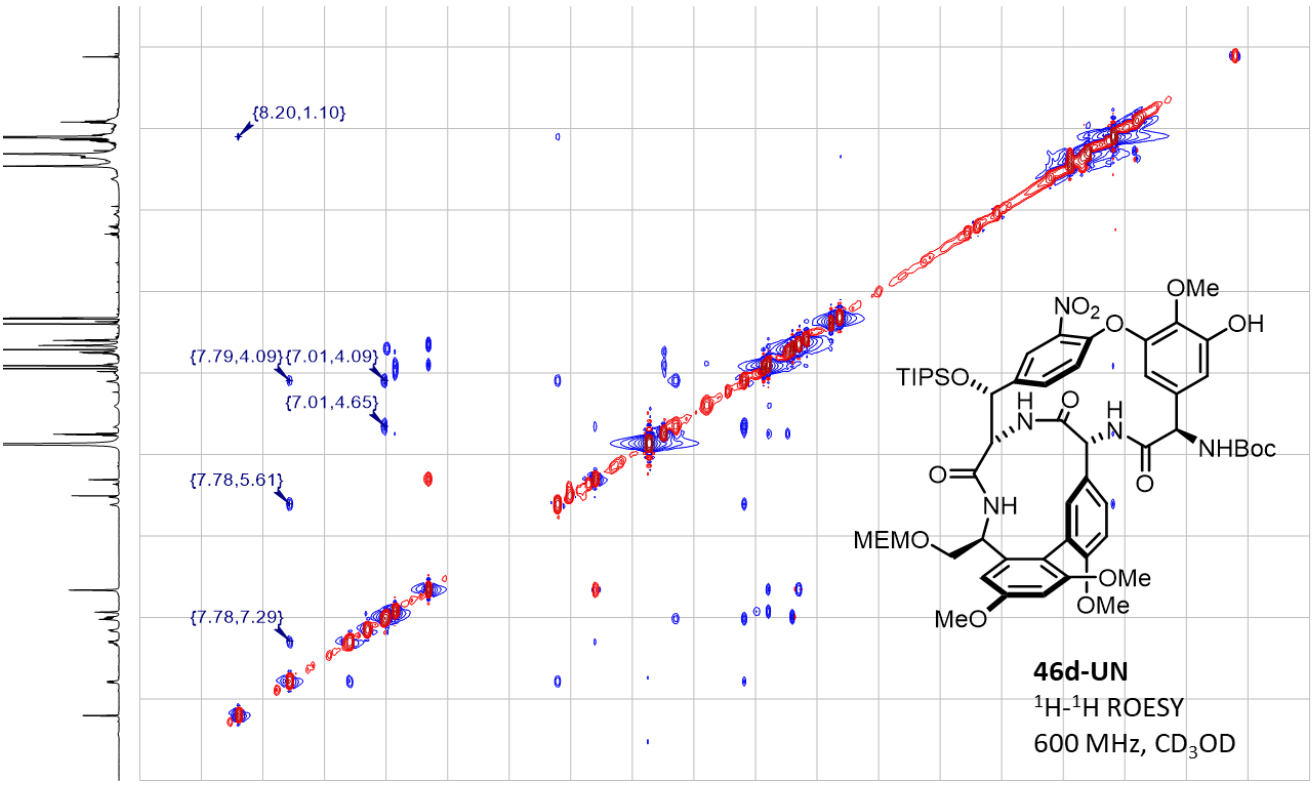

45d 13C NMR
151 MHz, CD3OD
26.924 26.800 19.006 16.495 12.608 11.868 11.591
137.304 135.129 133.203 126.521 123.802 123.295 120.947 117.780 112.256 106.008 104.280 96.843 94.973 94.825 79.154 79.012 73.534 71.083 70.967 66.601 66.382 66.254 61.440 59.679 58.933 58.892 58.068 57.747 57.306 57.240 54.358 54.327 54.305 54.257 54.186 54.030 53.834 49.866
170.959 170.370 167.333 159.892 159.827 157.972 157.906 156.803 156.605 155.387 153.633 150.231 150.017
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

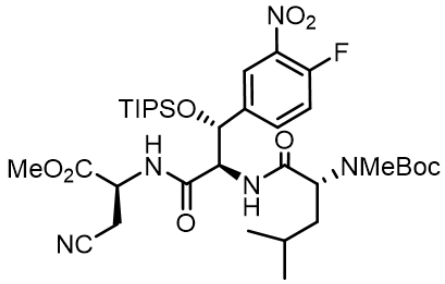

OMe
OH
TIPSO
NO2
NHBoc
NH
MEMO
OMe
OMe
MeO
46d 1H NMR
600 MHz, CD3OD
f1 (ppm)


46d 13C NMR
151 MHz, CD3OD
f1 (ppm)


CD3OH
CHD2OD
OMe
OH
NO2
O
TIPSO
H
N
O
NHBoc
NH
MEMO
OMe
OMe
MeO
46d-UN 1H NMR
600 MHz, CD3OD
f1 (ppm)
46d-UN 13C NMR
151 MHz, CD3OD
f1 (ppm)

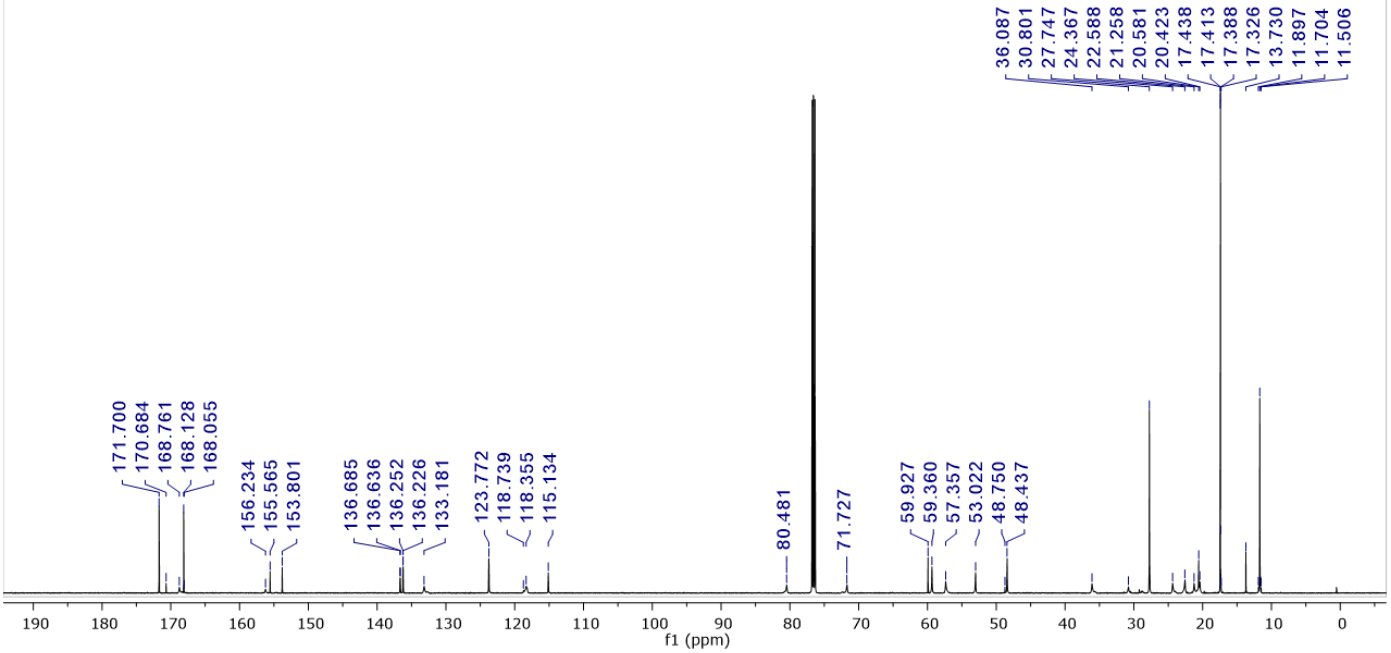

{7.86,1.03}
{7.01,4.04}
{7.01,4.53}
{8.26,5.51}
{7.86,7.17}
OMe
OH
TIPSO
NO2
NHBoc
NH
MEMO
OMe
OMe
MeO
46d
1H-1H ROESY
600 MHz, CD3OD

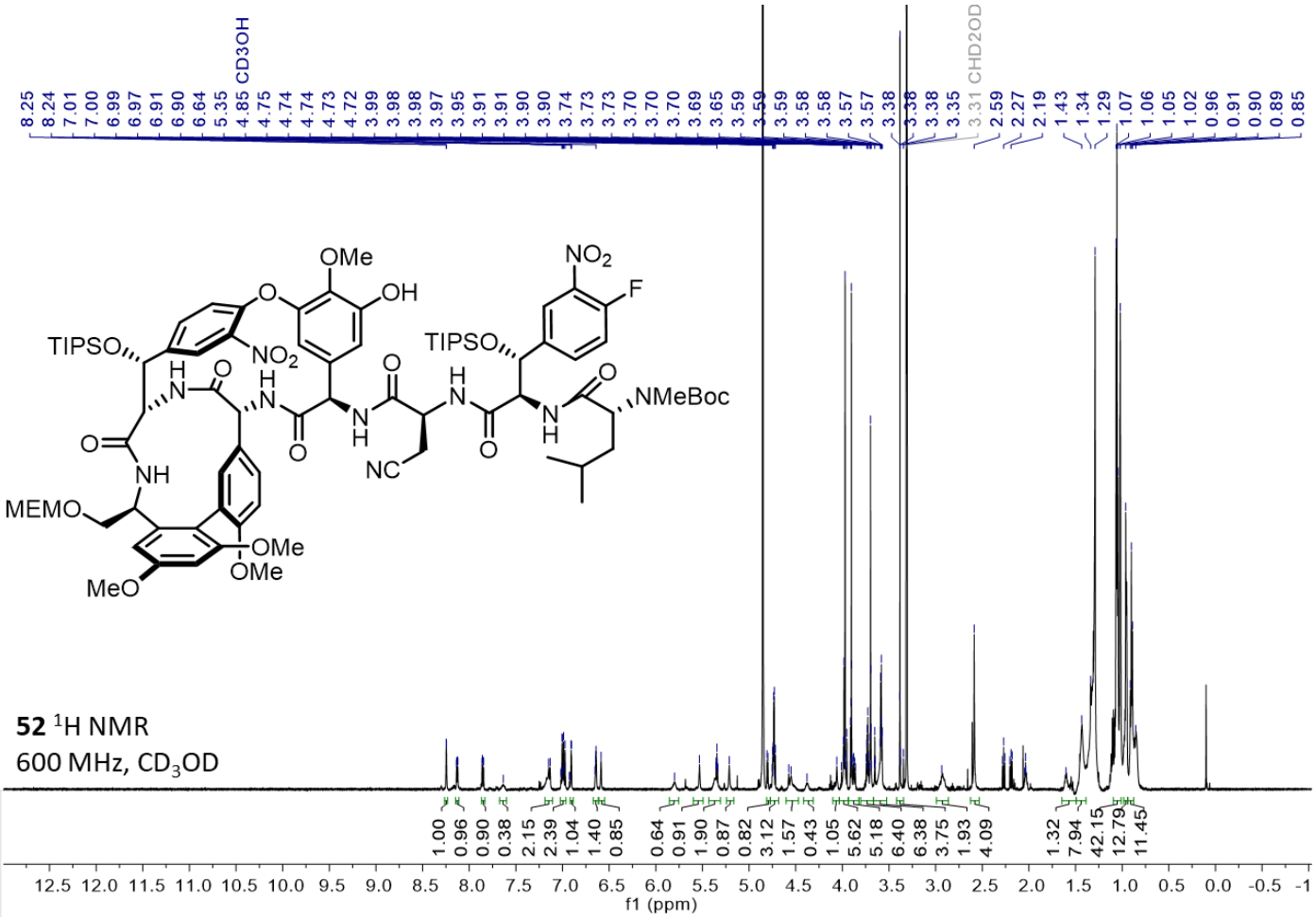

{8.20,1.10}
{7.79,4.09}{7.01,4.09}
{7.01,4.65}
{7.78,5.61}
{7.78,7.29}
NO2
OMe
OH
TIPSO
NHBoc
NH
MEMO
OMe
OMe
MeO
46d-UN
1H-1H ROESY
600 MHz, CD3OD



S5 ^{1}H NMR
600 MHz, $CDCl_3$

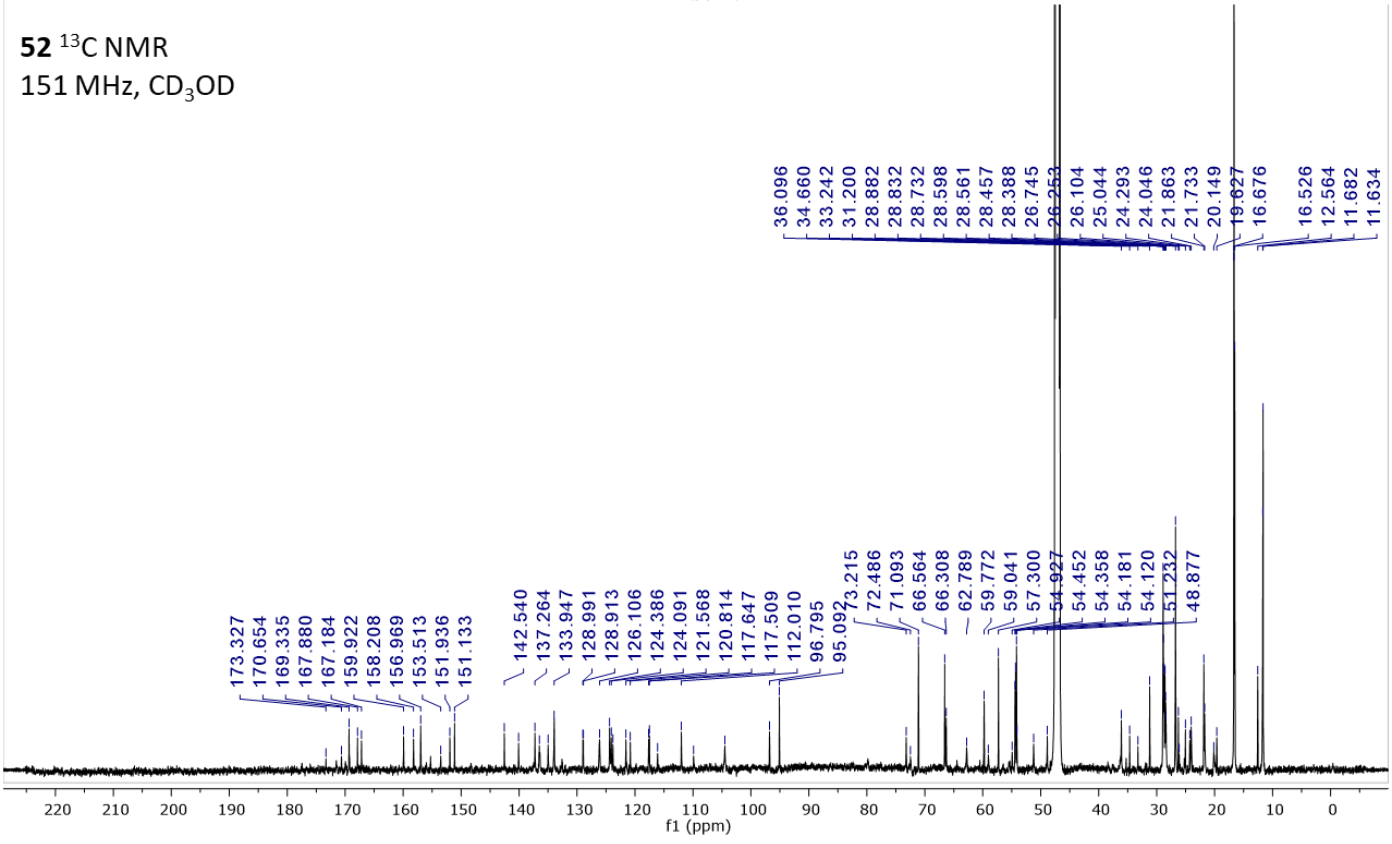
S5 ^{13}C NMR
151 MHz, $CDCl_3$

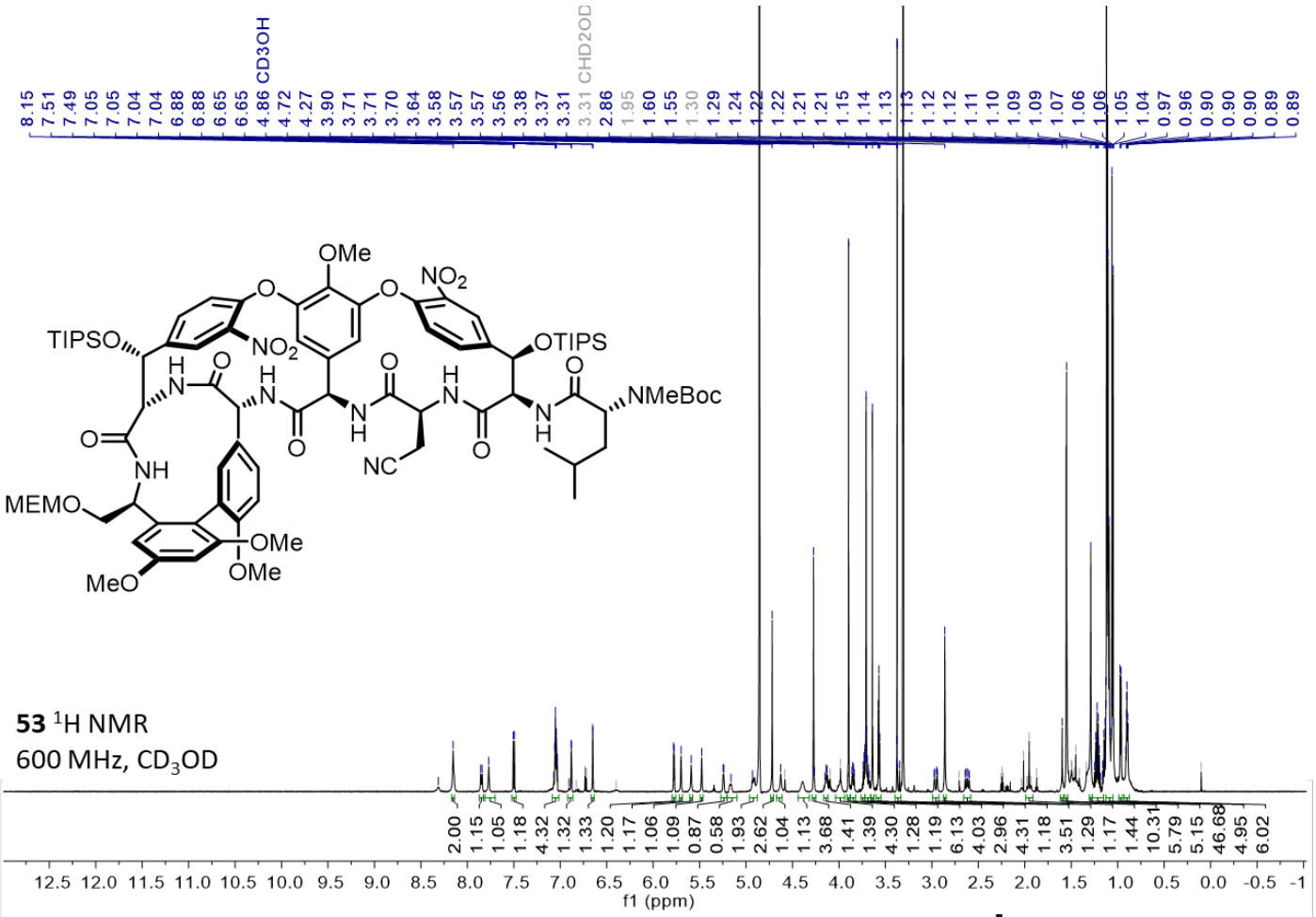




52 ^{1}H NMR
600 MHz, CD_3OD

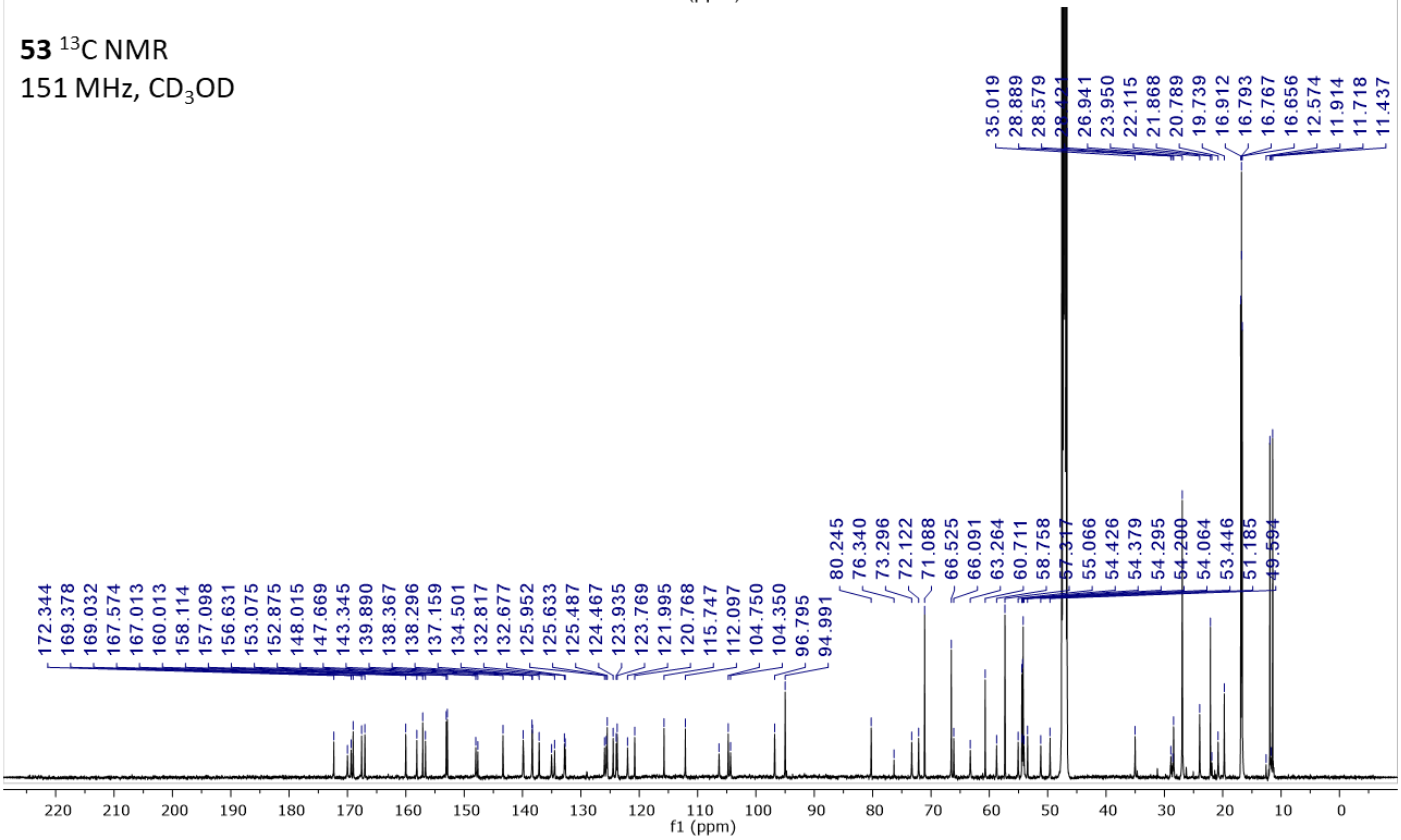
52 ^{13}C NMR
151 MHz, CD_3OD

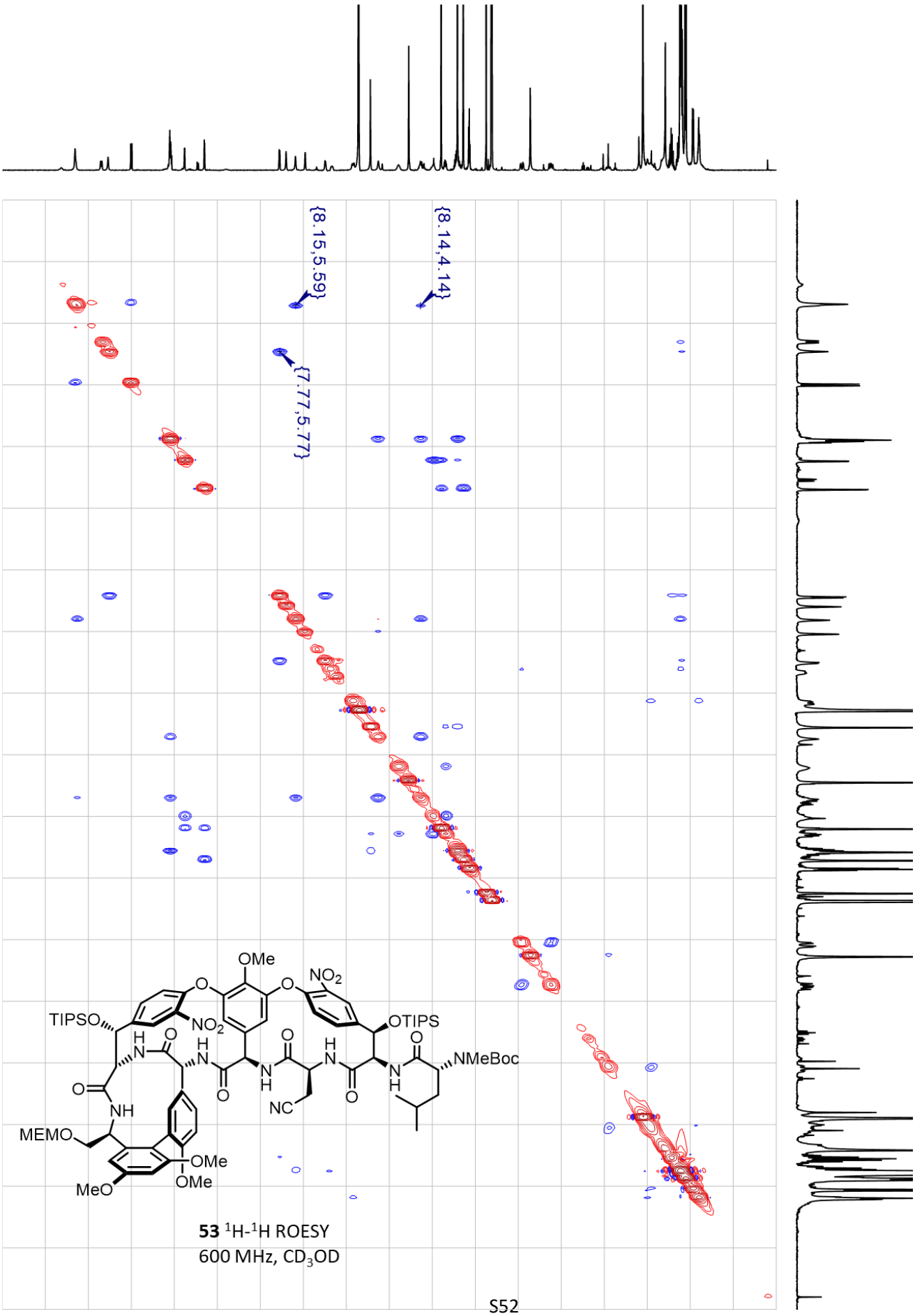




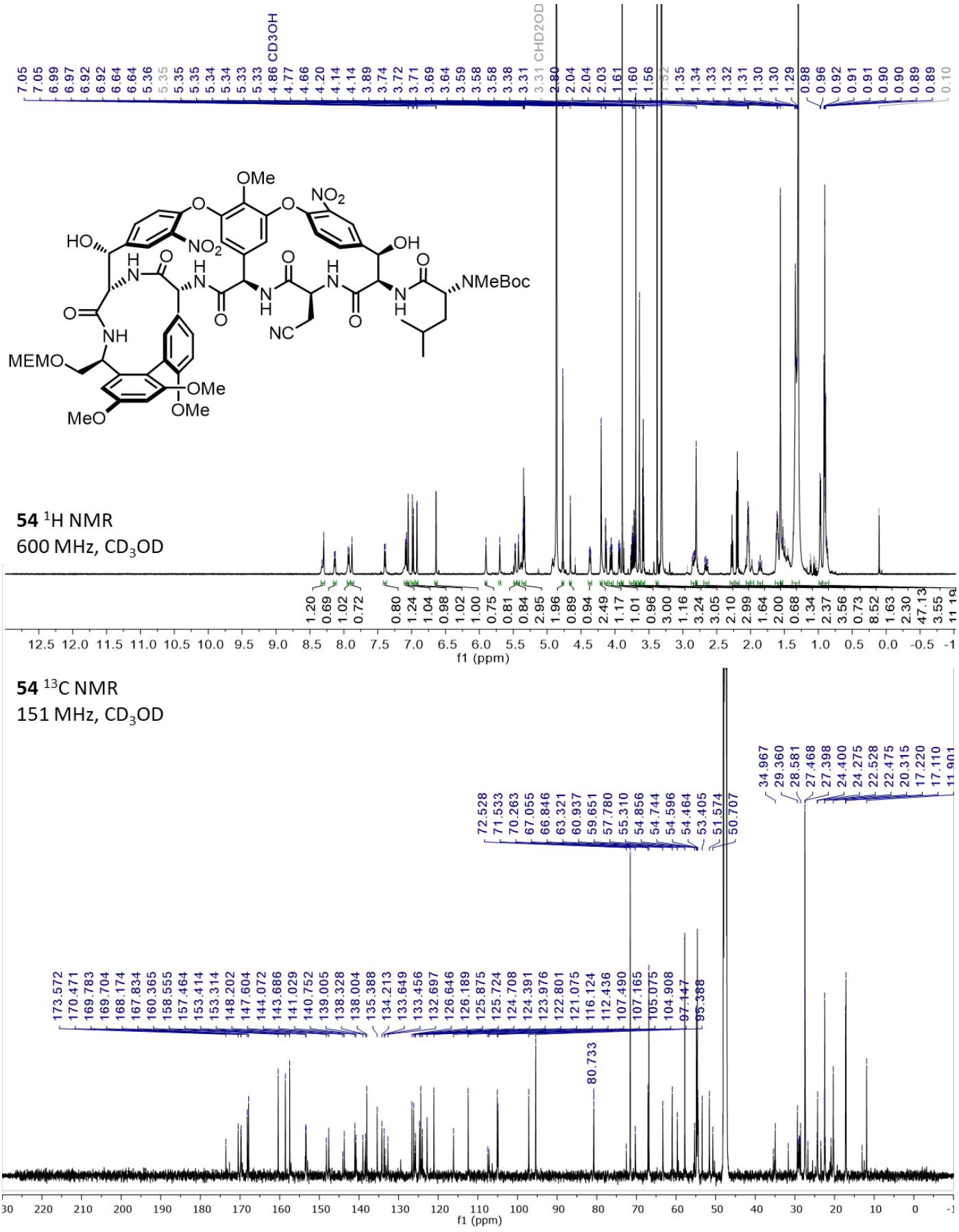
53 ^{1}H NMR
600 MHz, CD_3OD

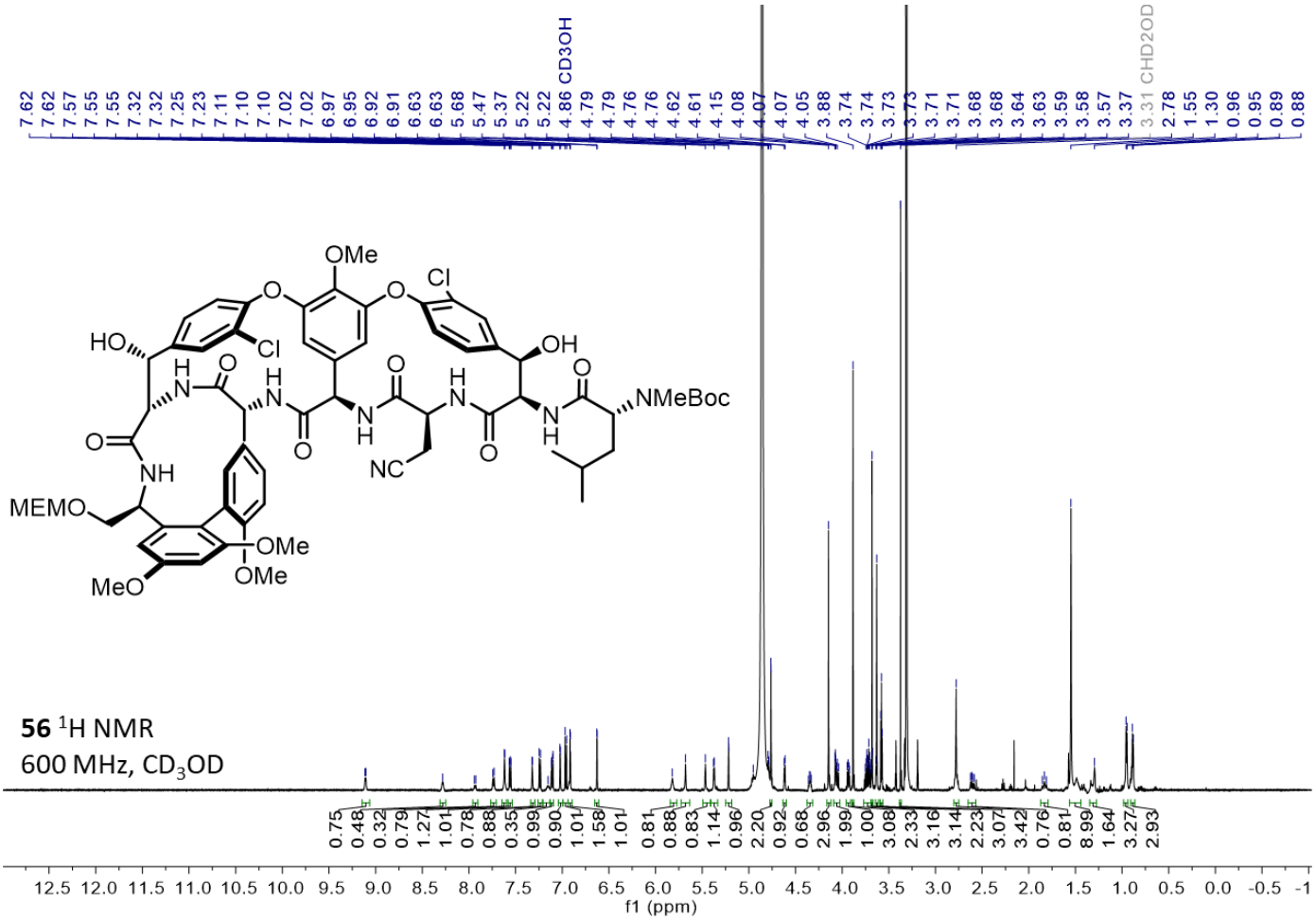
53 ^{13}C NMR
151 MHz, CD_3OD

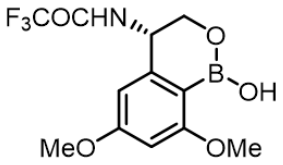




53 ^{1}H-^{1}H ROESY
600 MHz, CD_3OD

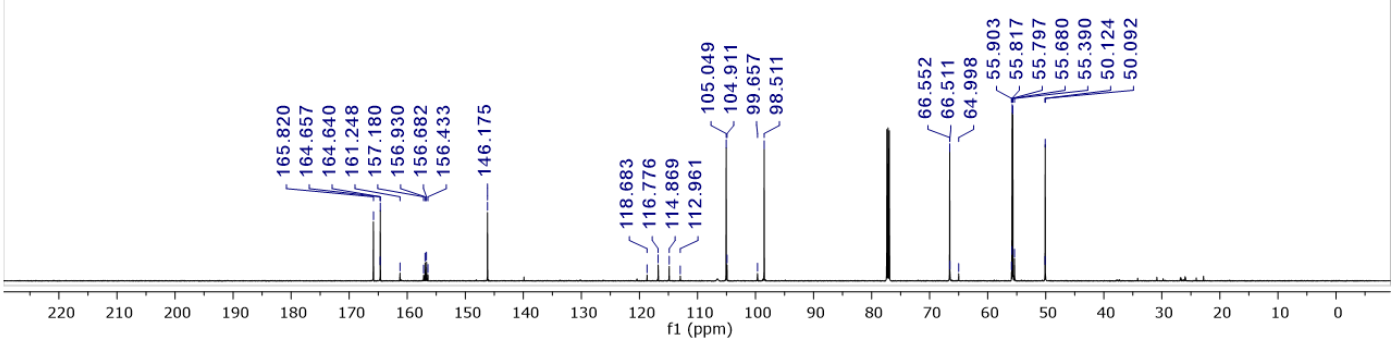

OMe
NO2
NO2
HO
OH
NMeBoc
NC
MEMO
OMe
OMe
MeO
54 1H NMR
600 MHz, CD3OD
f1 (ppm)
54 13C NMR
151 MHz, CD3OD
f1 (ppm)

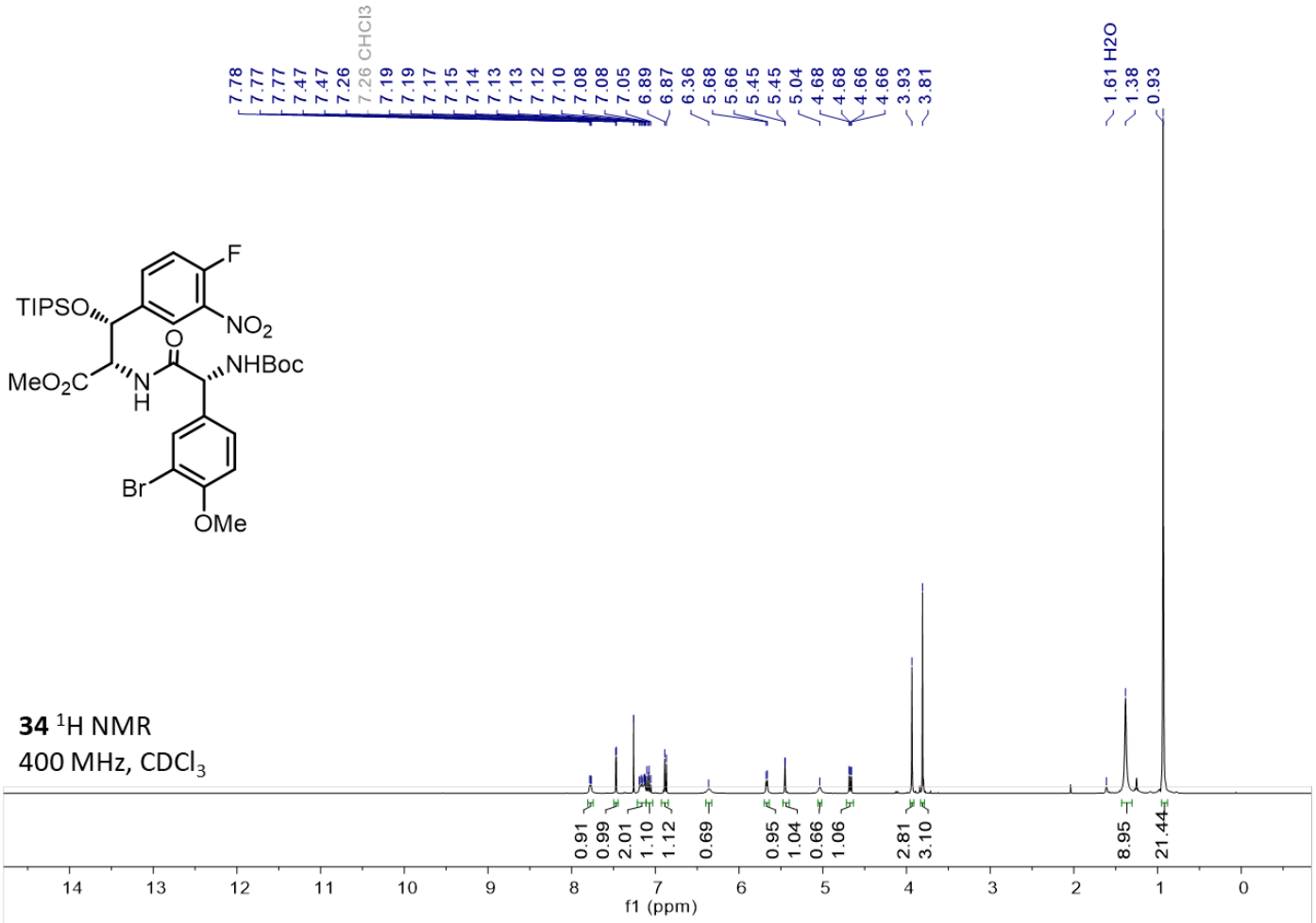

7.62 7.62 7.57 7.55 7.55 7.32 7.32 7.25 7.23 7.11 7.10 7.10 7.02 7.02 6.97 6.95 6.92 6.91 6.63 6.63 5.68 5.47 5.37 5.22 5.22 4.86 CD3OH 4.79 4.79 4.76 4.76 4.62 4.61 4.15 4.08 4.07 4.07 4.05 3.88 3.74 3.74 3.73 3.73 3.71 3.71 3.68 3.68 3.64 3.63 3.59 3.58 3.57 3.37 3.31 CHD2OD 2.78 1.55 1.30 0.96 0.95 0.89 0.88
OMe
Cl
HO
Cl
OH
NMeBoc
NC
MEMO
OMe
OMe
MeO
56 1H NMR
600 MHz, CD3OD
0.75 0.48 0.32 0.79 1.27 1.01 0.78 0.88 0.35 0.99 0.90 1.01 1.58 1.01 0.81 0.88 0.83 1.14 0.96 2.20 0.92 0.68 2.96 1.99 1.00 3.08 2.33 3.16 3.14 2.23 3.07 3.42 0.76 0.81 8.99 1.64 3.27 2.93
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



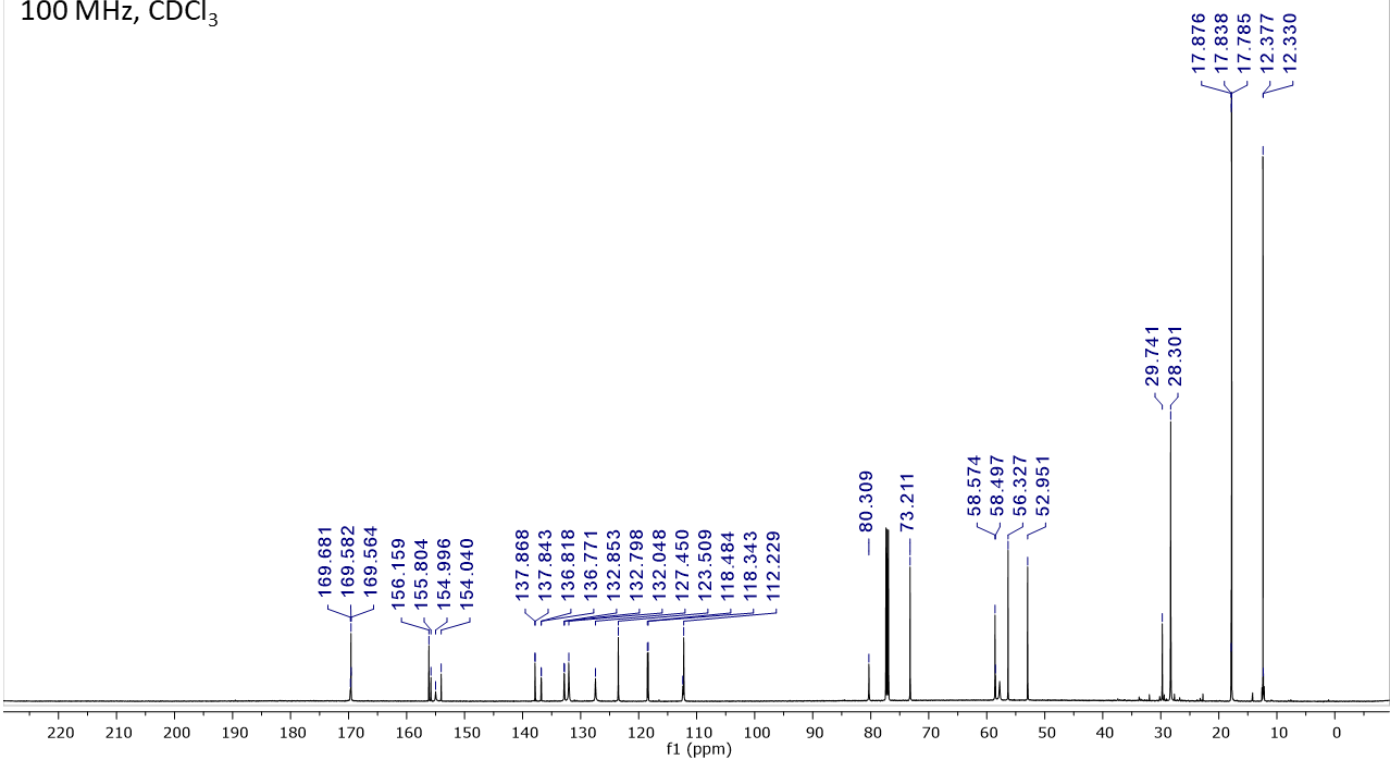
23 ^{1}H NMR
600 MHz, $CDCl_3$

23 ^{13}C NMR
151 MHz, $CDCl_3$

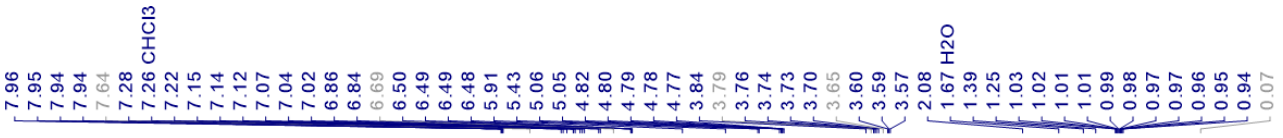


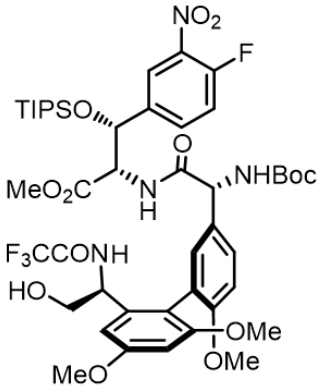


34 ^{1}H NMR
400 MHz, $CDCl_3$

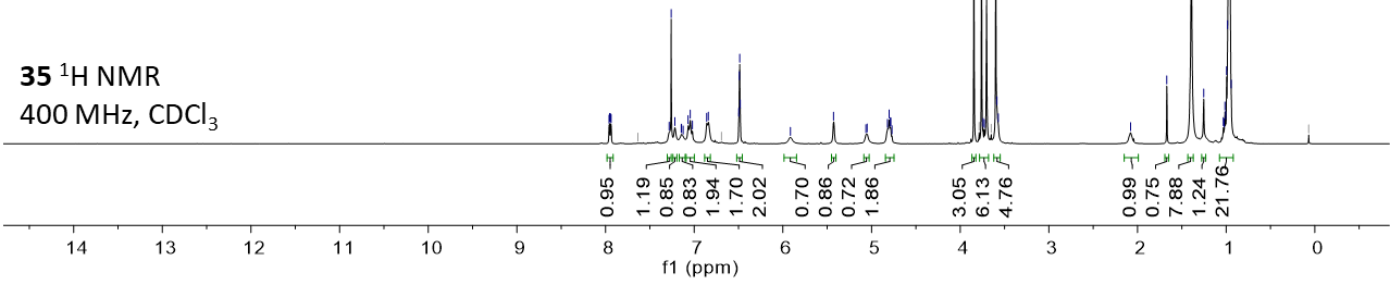


34 ^{13}C NMR
100 MHz, $CDCl_3$

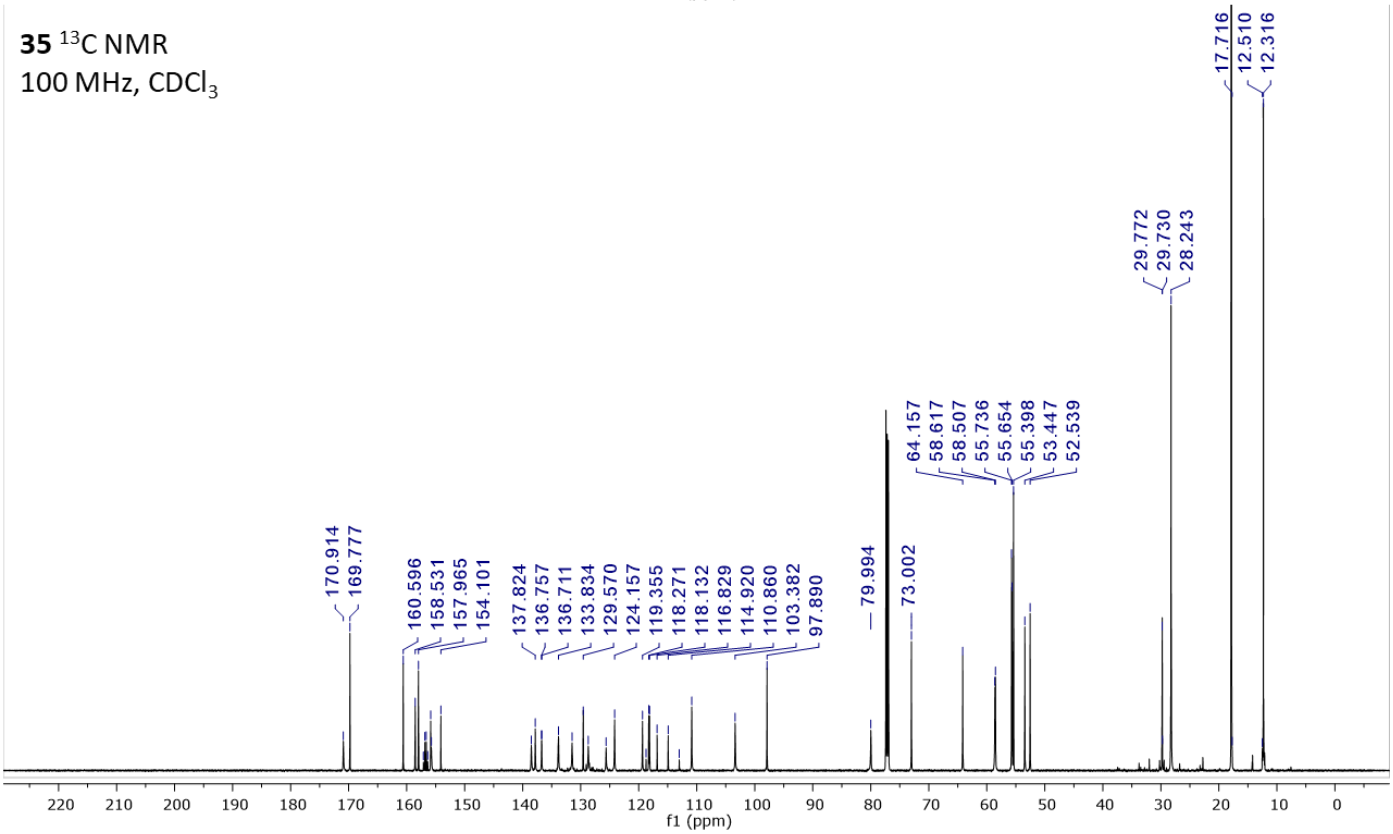


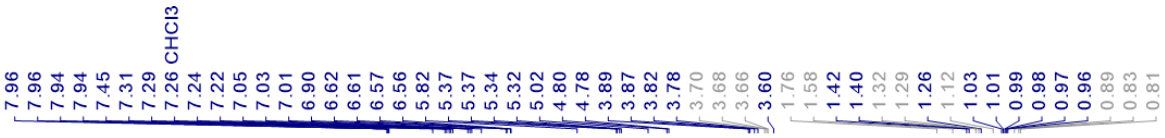


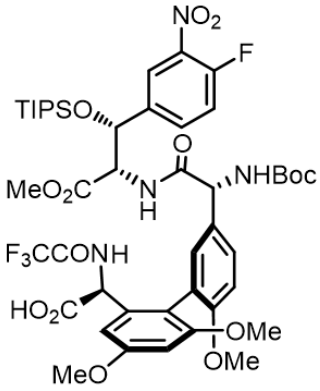
35 ^{1}H NMR
400 MHz, $CDCl_3$



35 ^{13}C NMR
100 MHz, $CDCl_3$

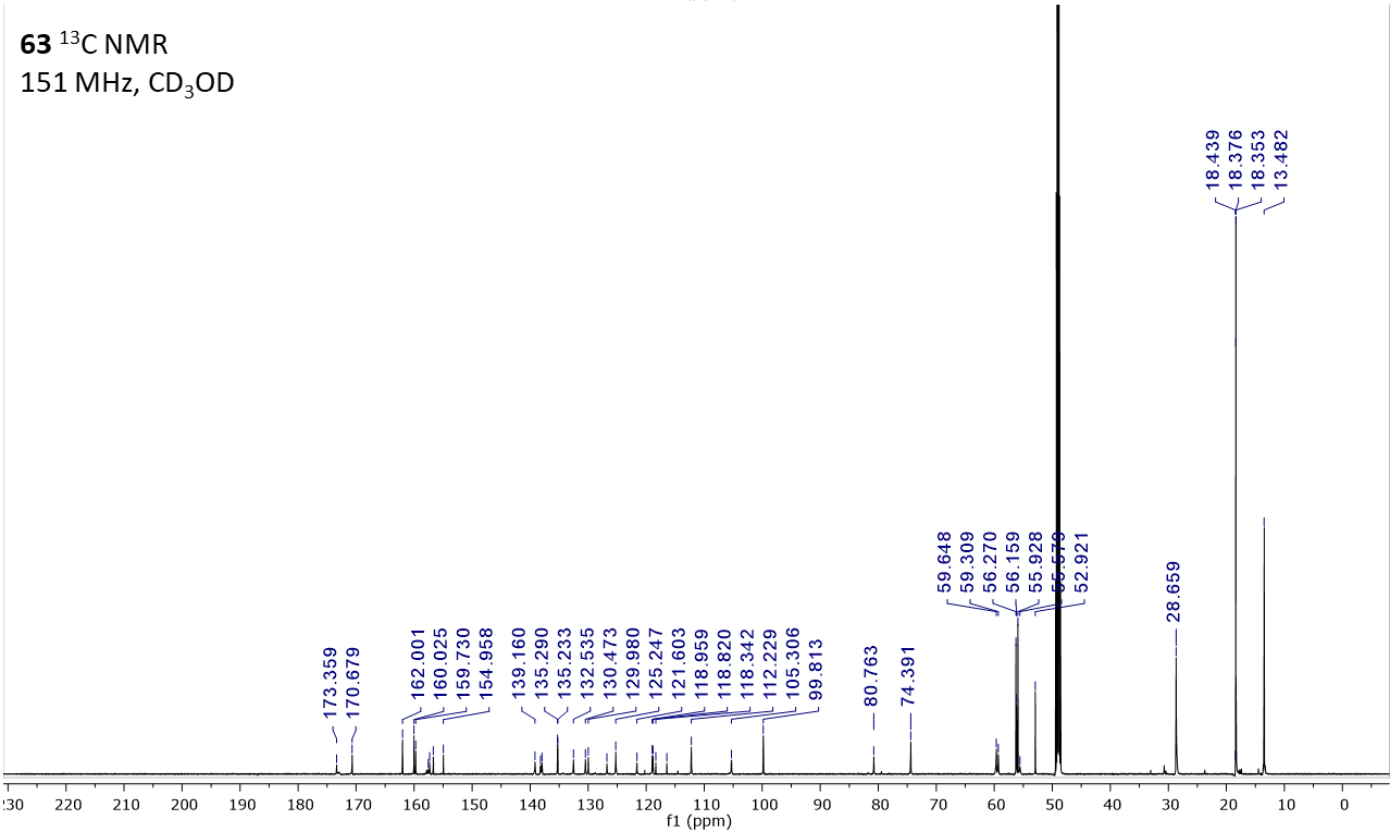


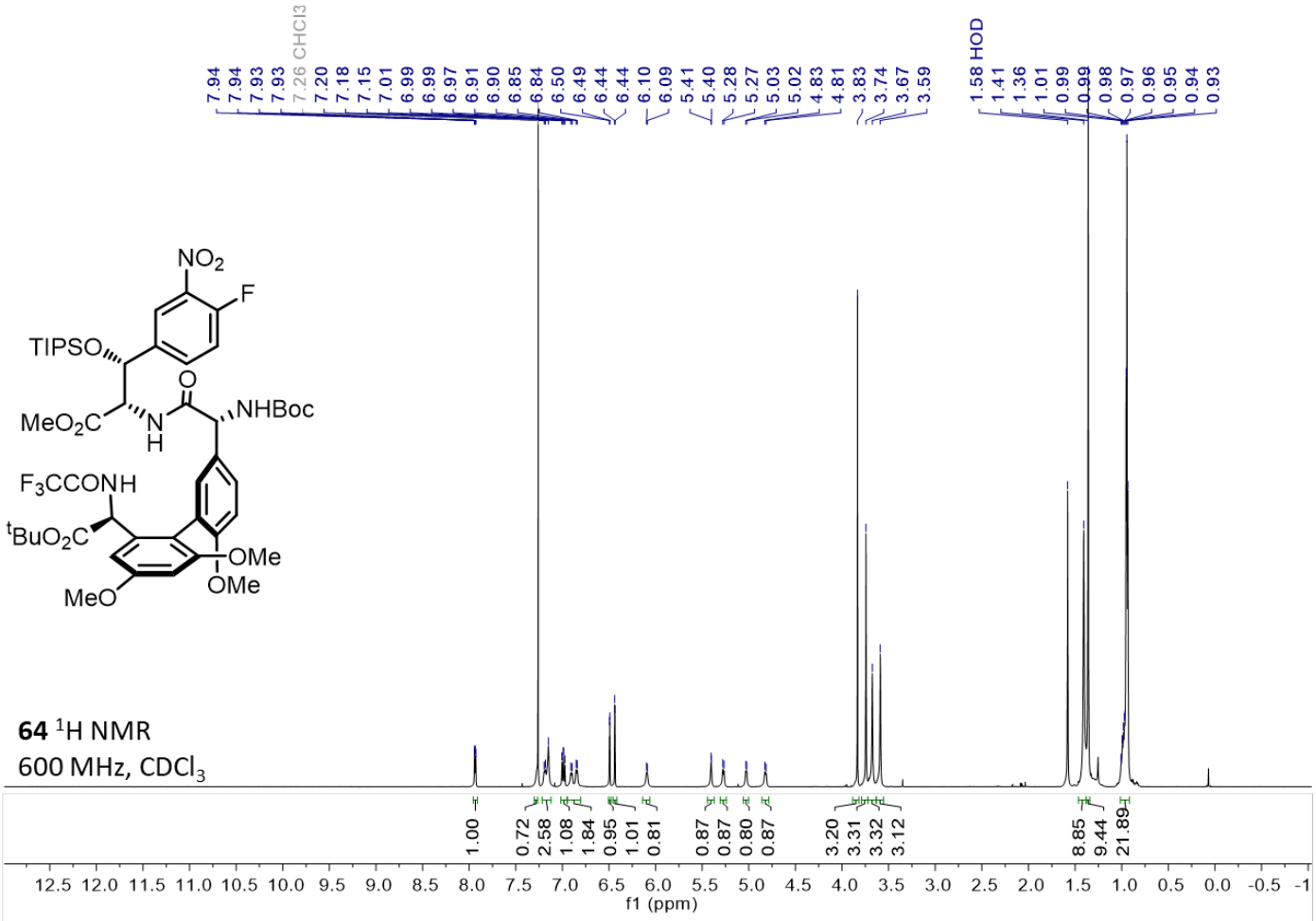




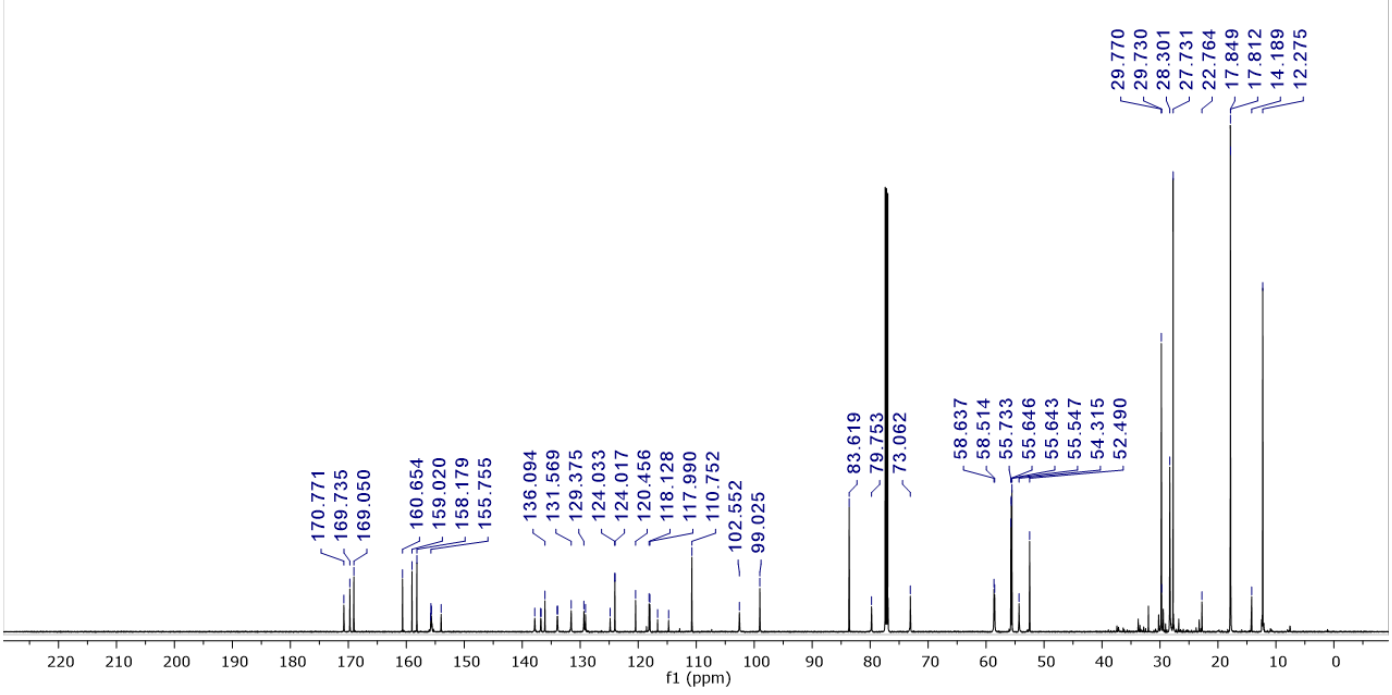
63 ^{1}H NMR
400 MHz, $CDCl_3$

63 ^{13}C NMR
151 MHz, CD_3OD

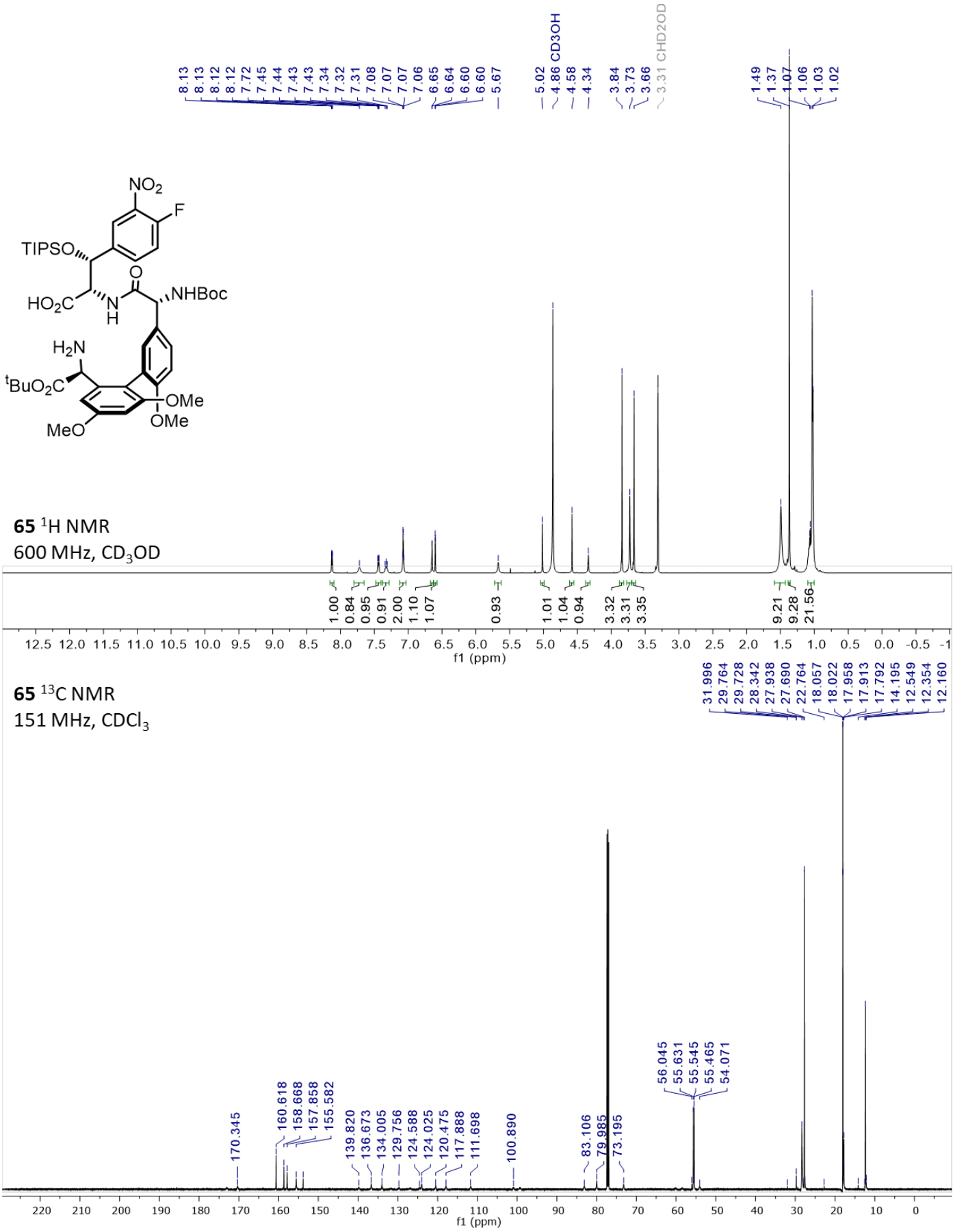


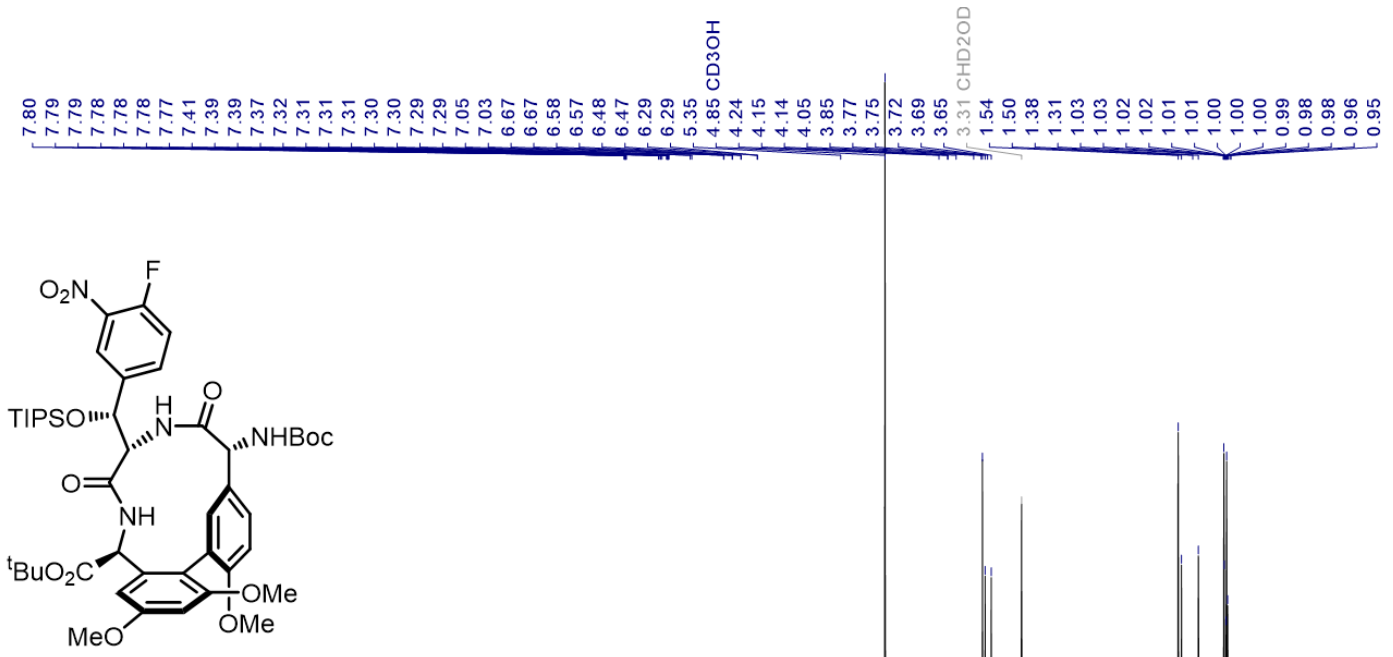


64 ^{1}H NMR
600 MHz, $CDCl_3$

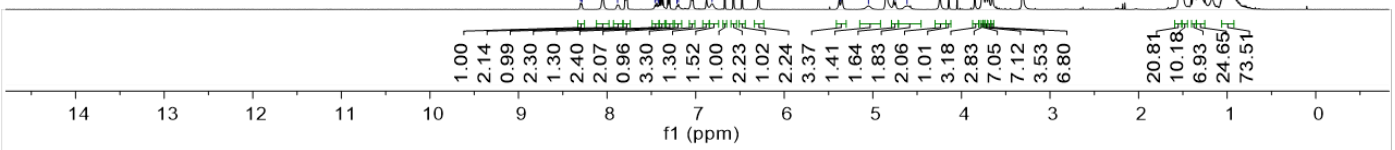


64 ^{13}C NMR
151 MHz, $CDCl_3$

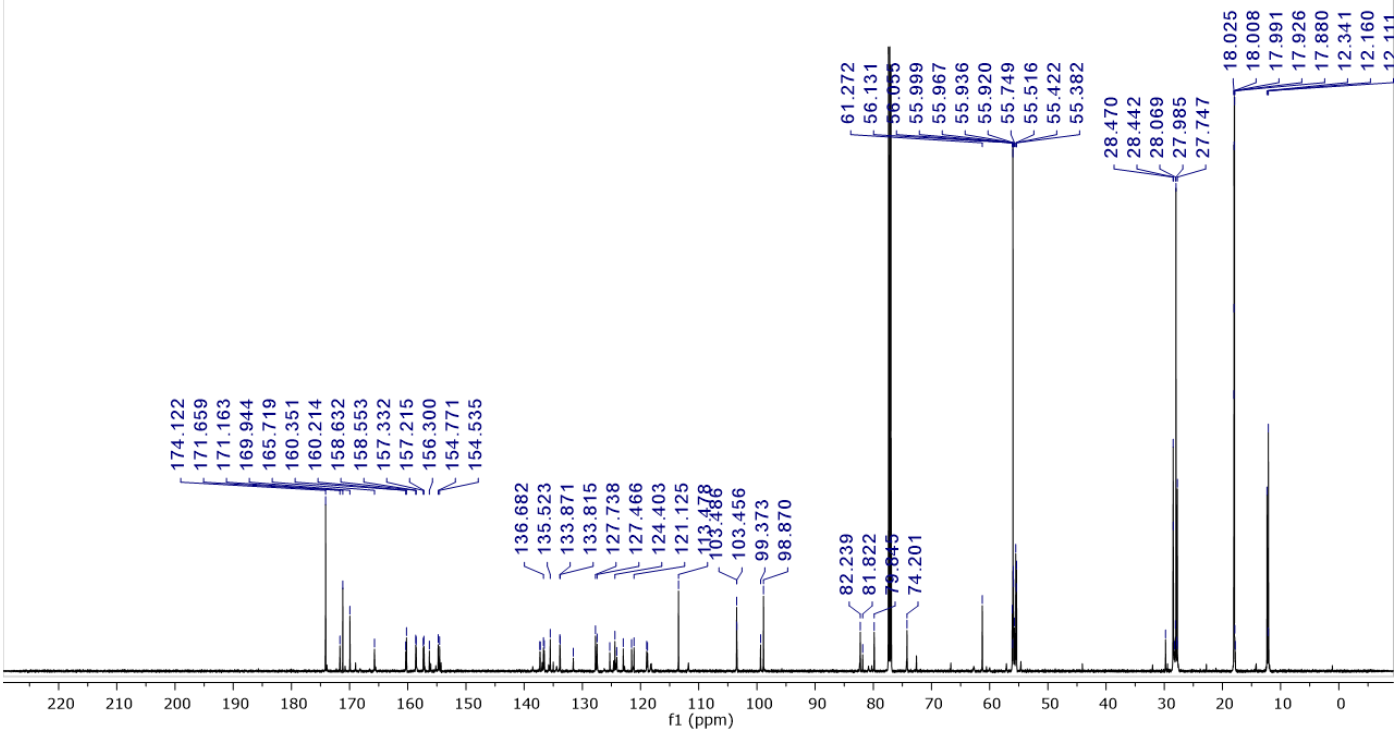

8.13
8.13
8.12
8.12
7.72
7.45
7.44
7.43
7.43
7.34
7.32
7.31
7.08
7.07
7.07
7.06
6.65
6.64
6.60
6.60
5.67
5.02
4.86 CD3OH
4.58
4.34
3.84
3.73
3.66
3.31 CHD2OD
1.49
1.37
1.07
1.06
1.03
1.02
NO2
F
TIPSO
HO2C
N
H
O
NHBoc
H2N
tBuO2C
OMe
OMe
MeO
65 1H NMR
600 MHz, CD3OD
1.00
0.84
0.95
0.91
2.00
1.10
1.07
0.93
1.01
1.04
0.94
3.32
3.31
3.35
9.21
9.28
21.56
f1 (ppm)
65 13C NMR
151 MHz, CDCl3
31.996
29.764
29.728
28.342
27.938
27.690
22.764
18.057
18.022
17.958
17.913
17.792
14.195
12.549
12.354
12.160
170.345
160.618
158.668
157.858
155.582
139.820
136.673
134.005
129.756
124.588
124.025
120.475
117.888
111.698
100.890
83.106
79.985
73.195
56.045
55.631
55.545
55.465
54.071
f1 (ppm)

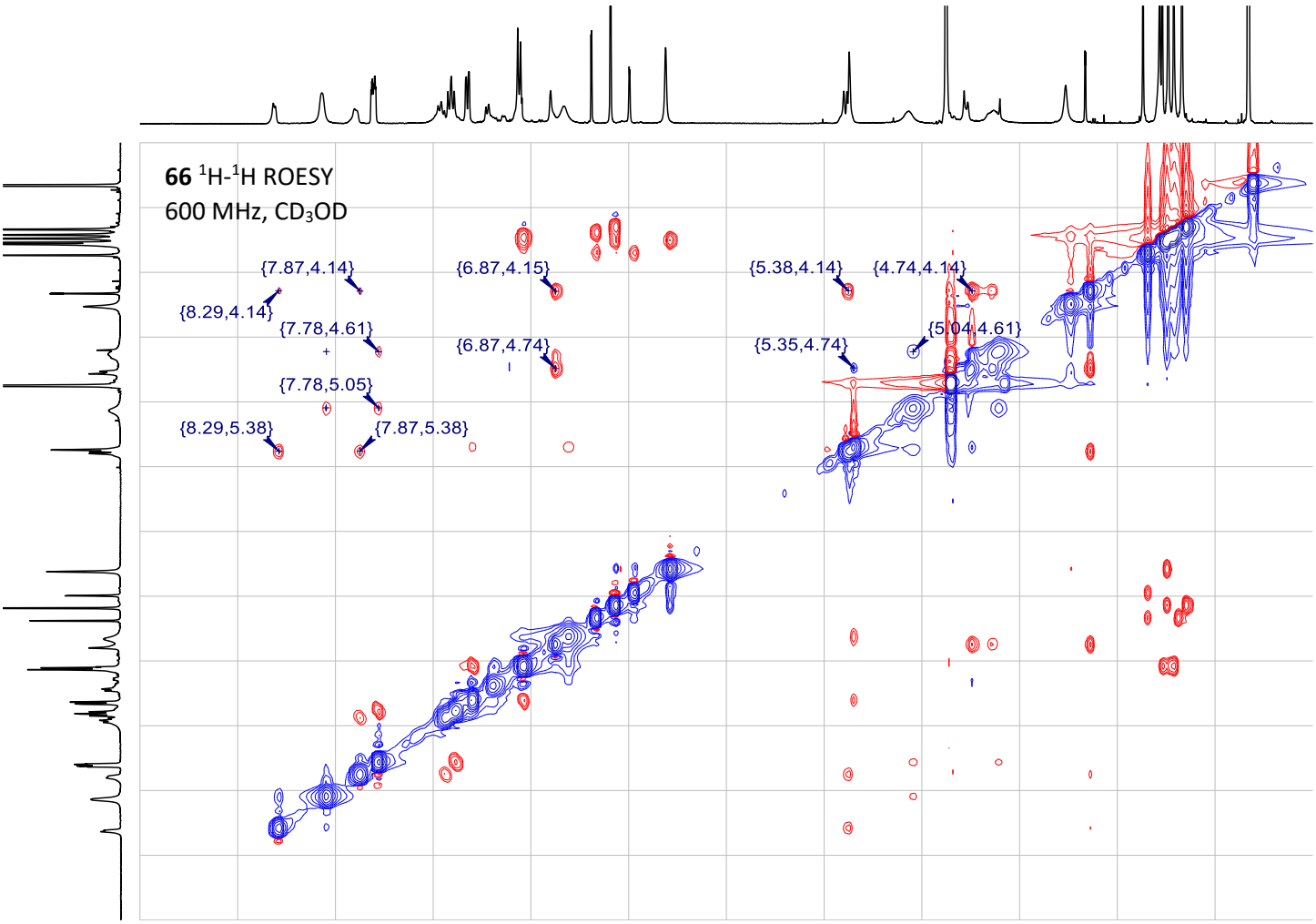


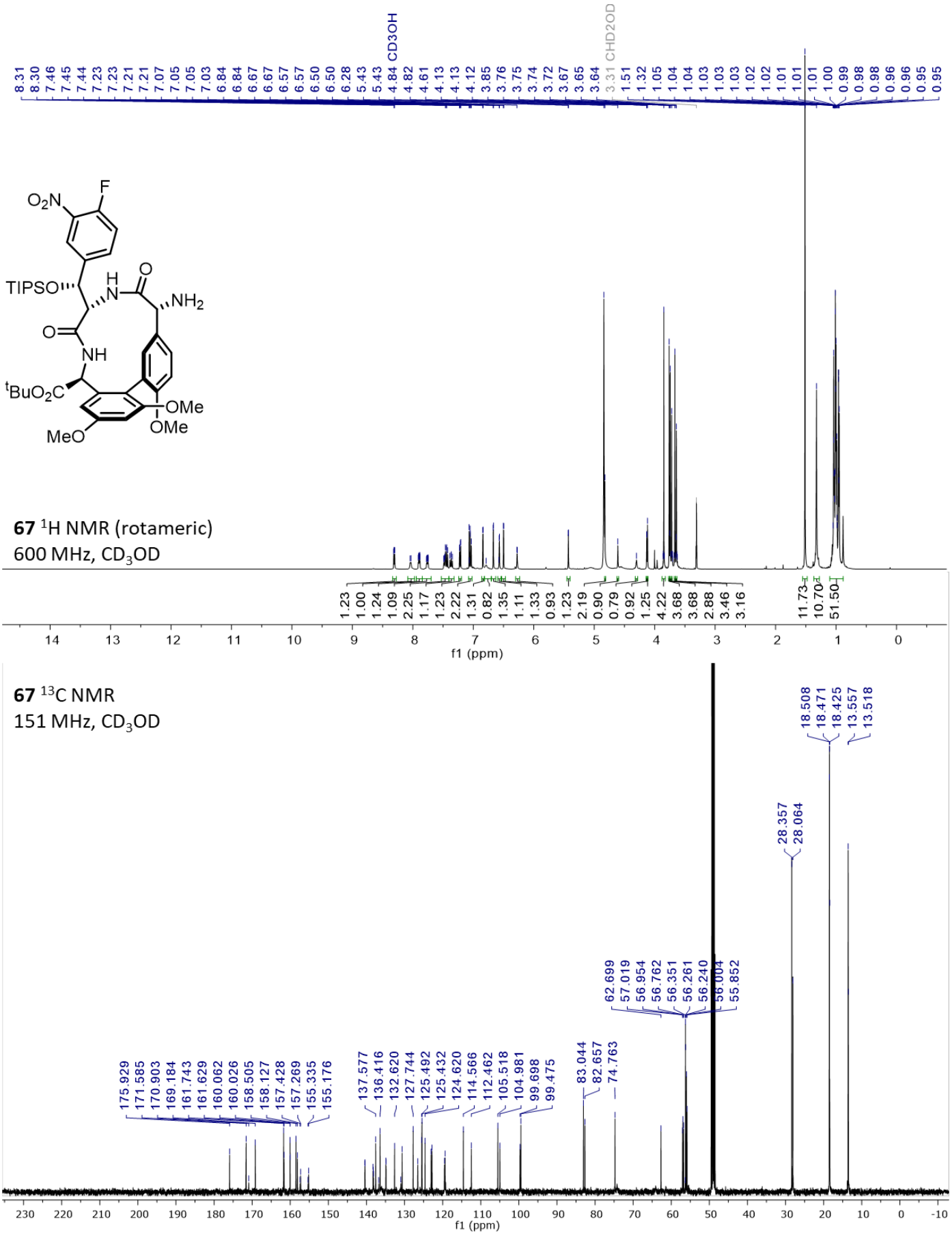
66 ^{1}H NMR (rotameric)
600 MHz, CD_3OD

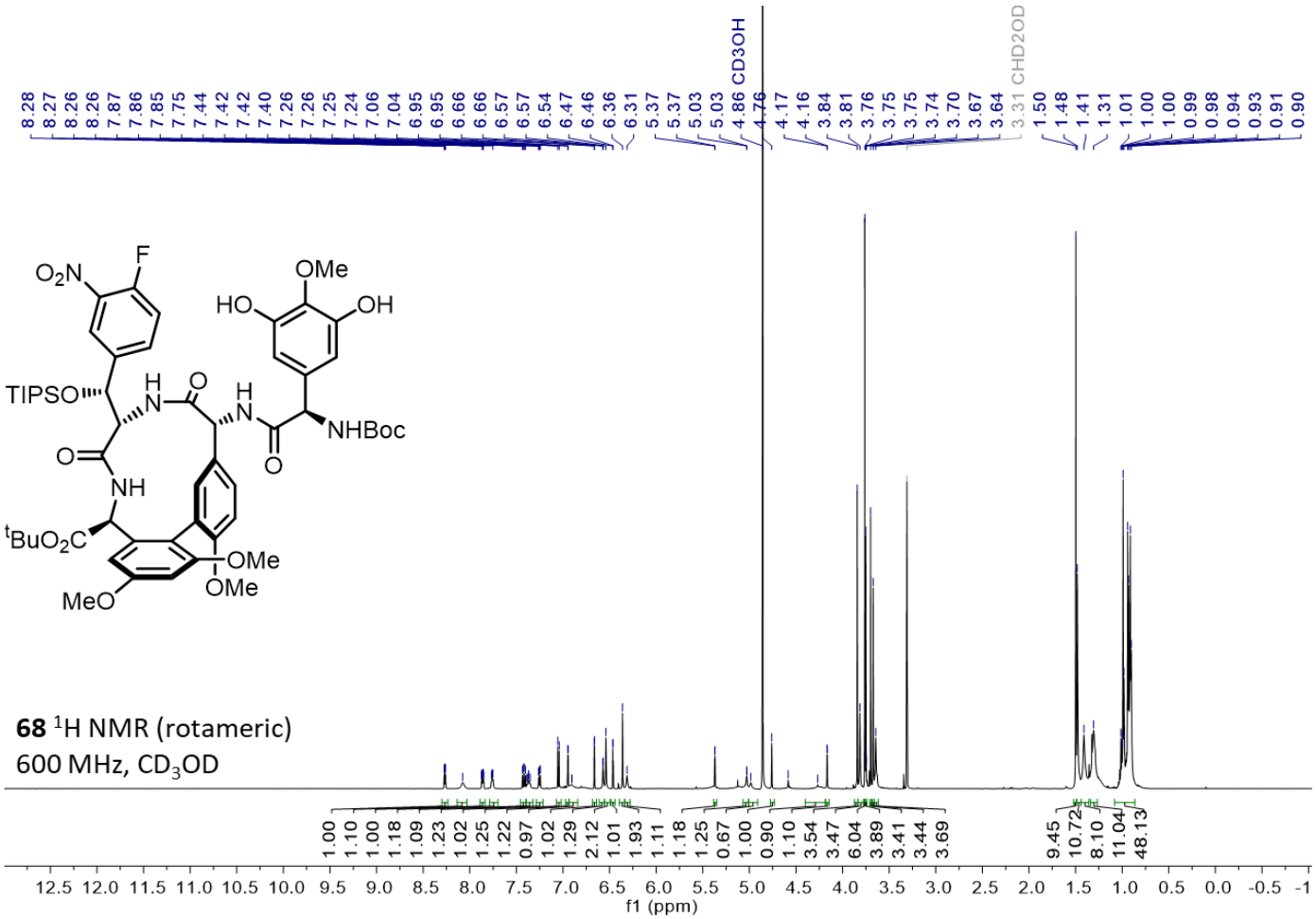


66 ^{13}C NMR
151 MHz, $CDCl_3$

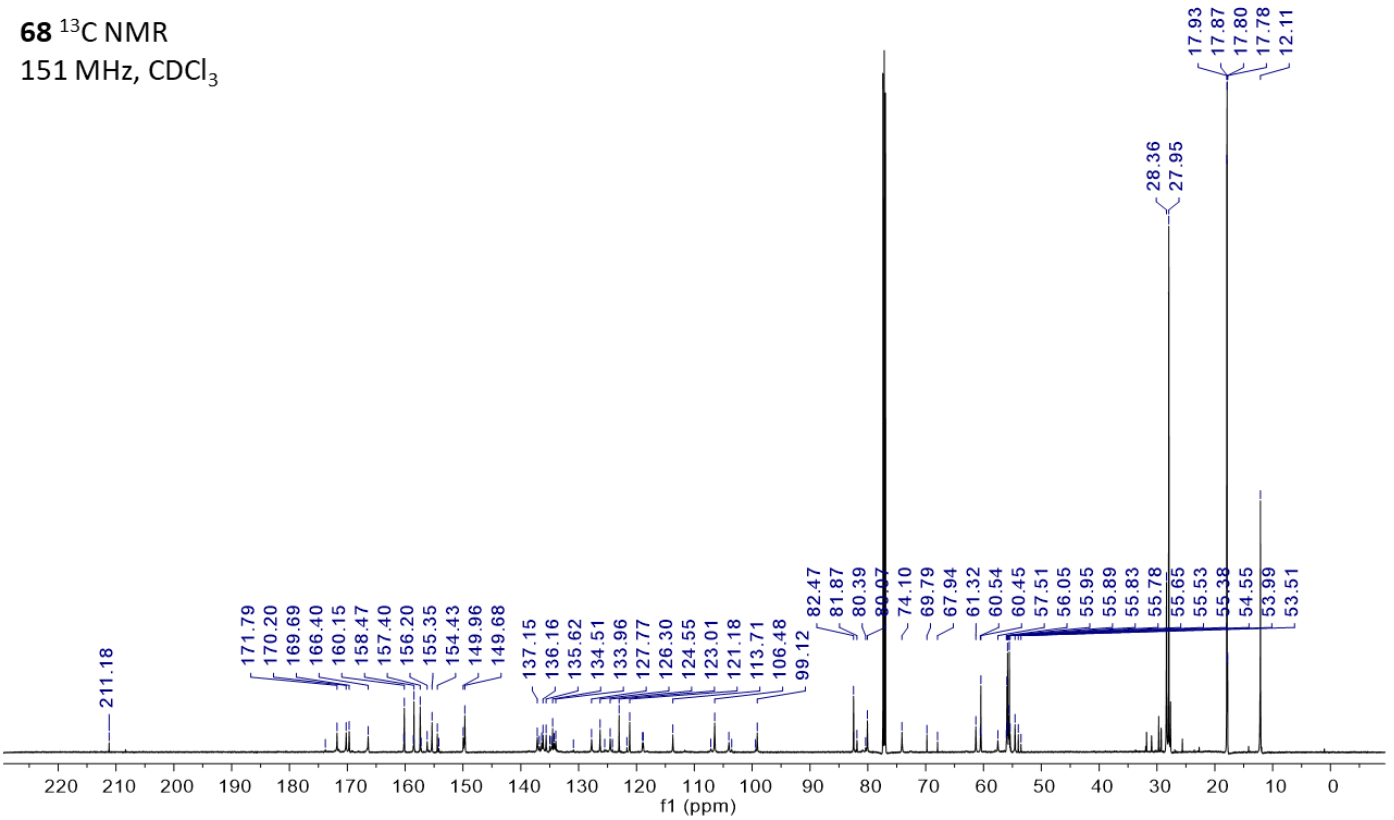



66 ^{1}H-^{1}H ROESY
600 MHz, CD_3OD
{7.87,4.14}
{8.29,4.14}
{7.78,4.61}
{7.78,5.05}
{8.29,5.38}
{7.87,5.38}
{6.87,4.15}
{6.87,4.74}
{5.38,4.14}
{4.74,4.14}
{5.35,4.74}
{5.04,4.61}

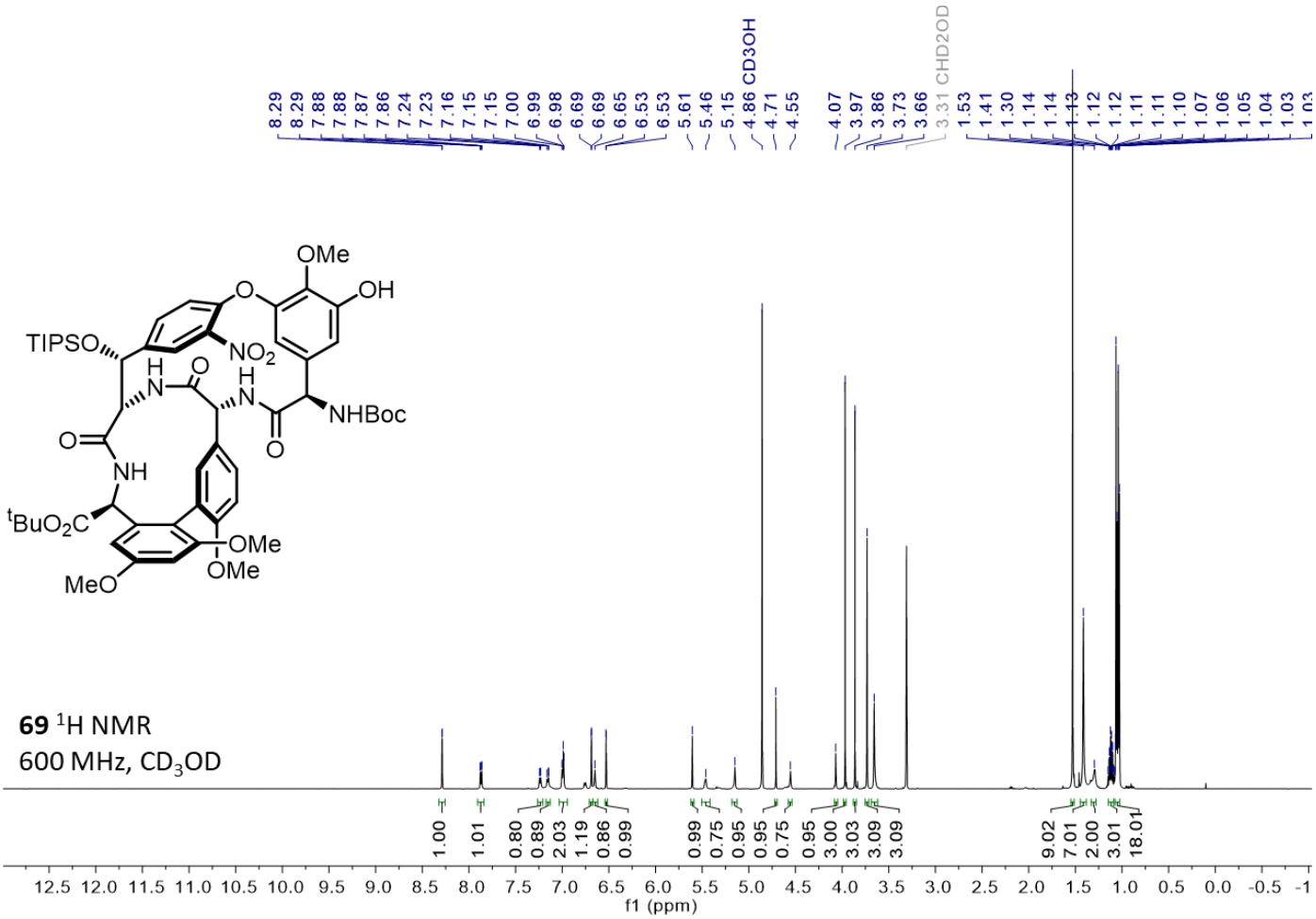

CD3OH
CHD2OD
TIPSO
NH2
NH
tBuO2C
OMe
OMe
MeO
67 1H NMR (rotameric)
600 MHz, CD3OD
f1 (ppm)
67 13C NMR
151 MHz, CD3OD
f1 (ppm)

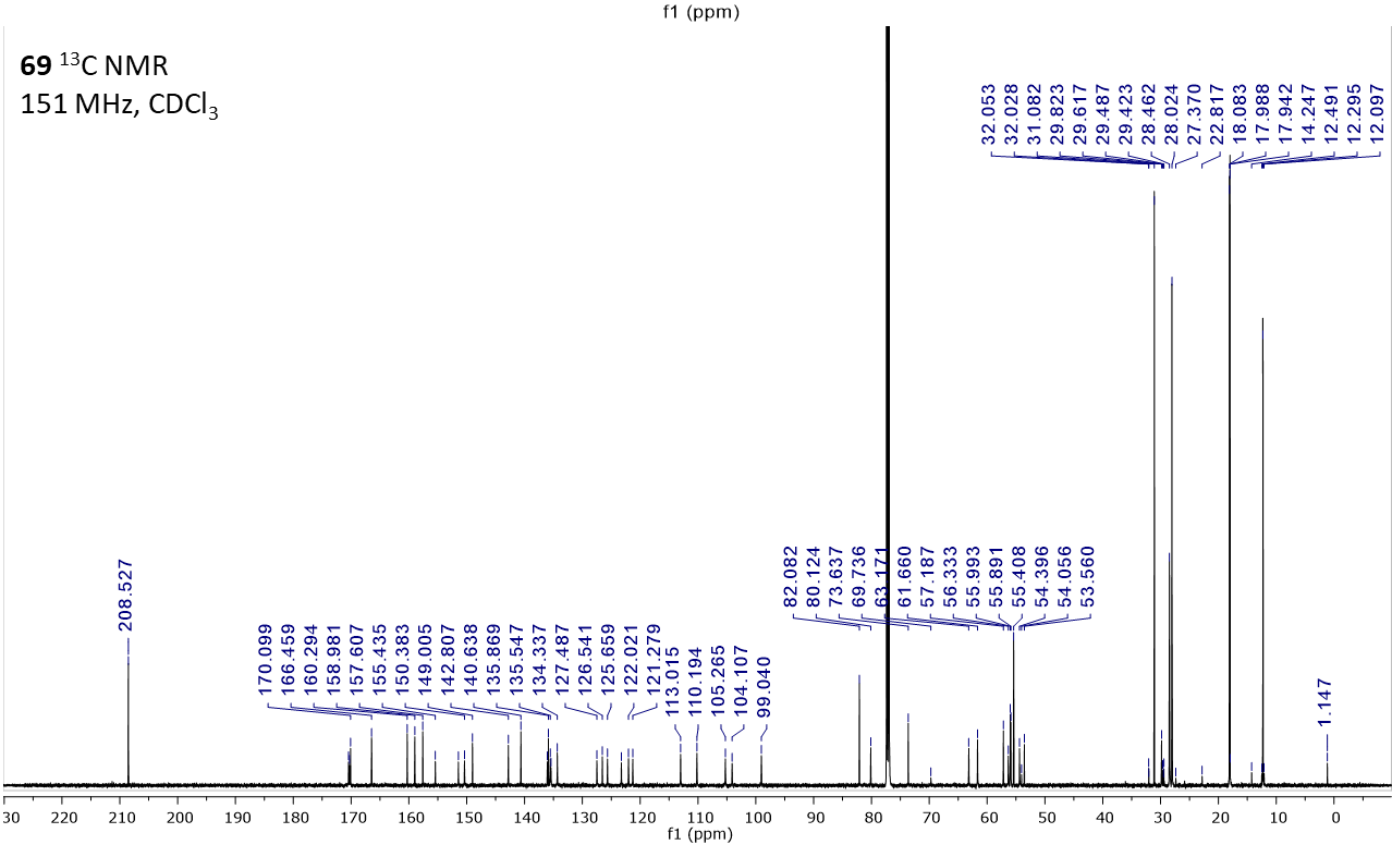


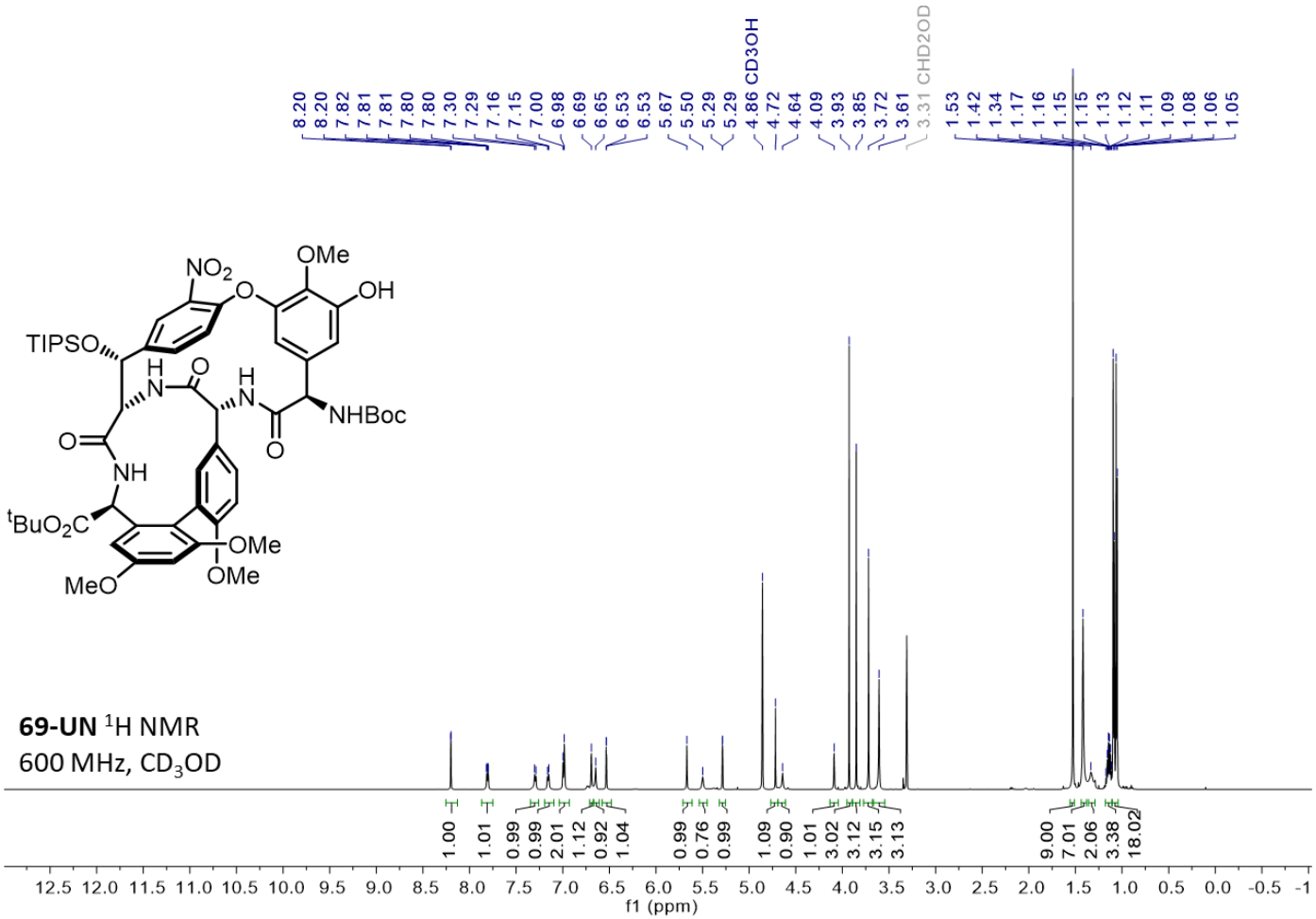
68 ^{1}H NMR (rotameric)
600 MHz, CD_3OD

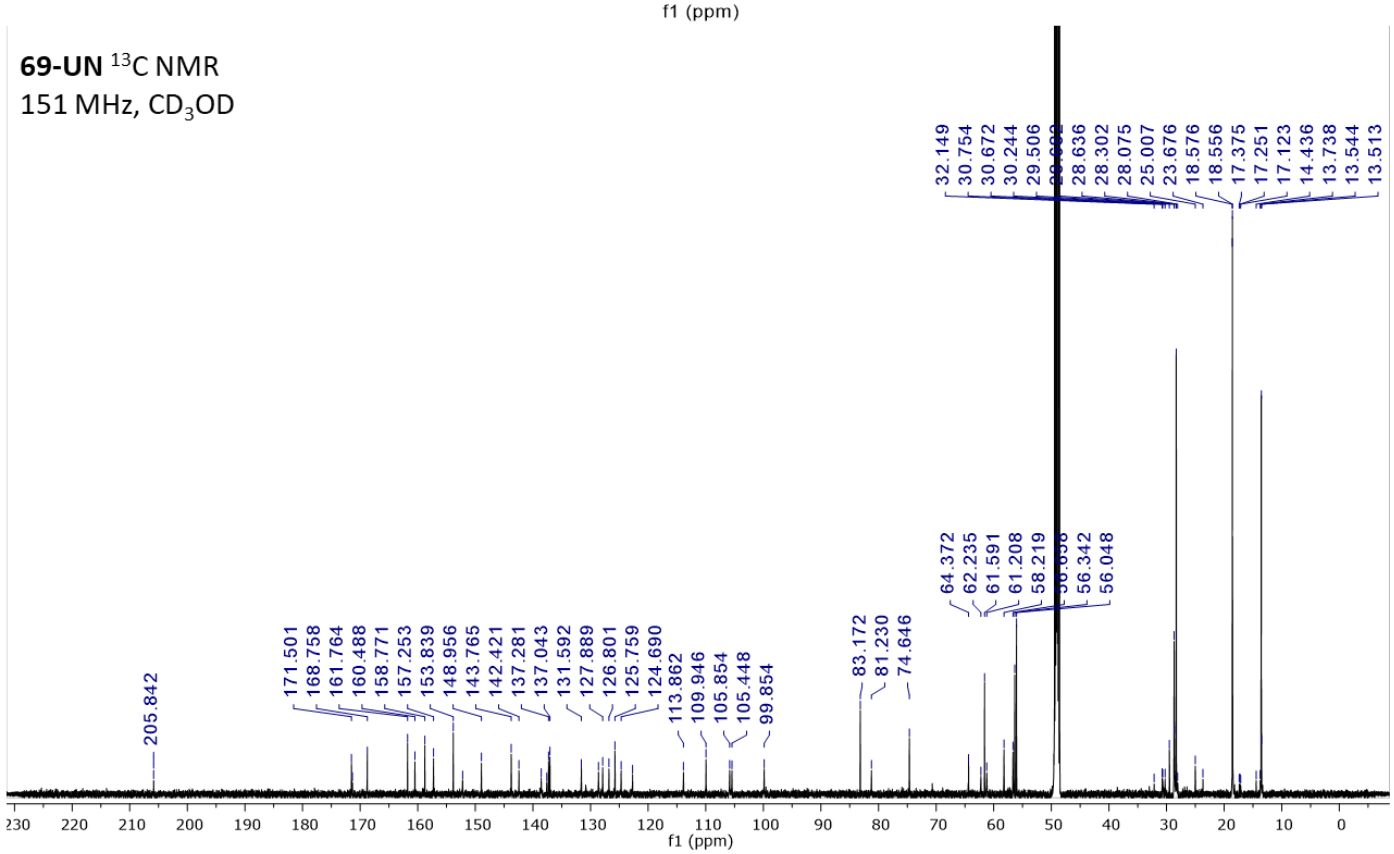


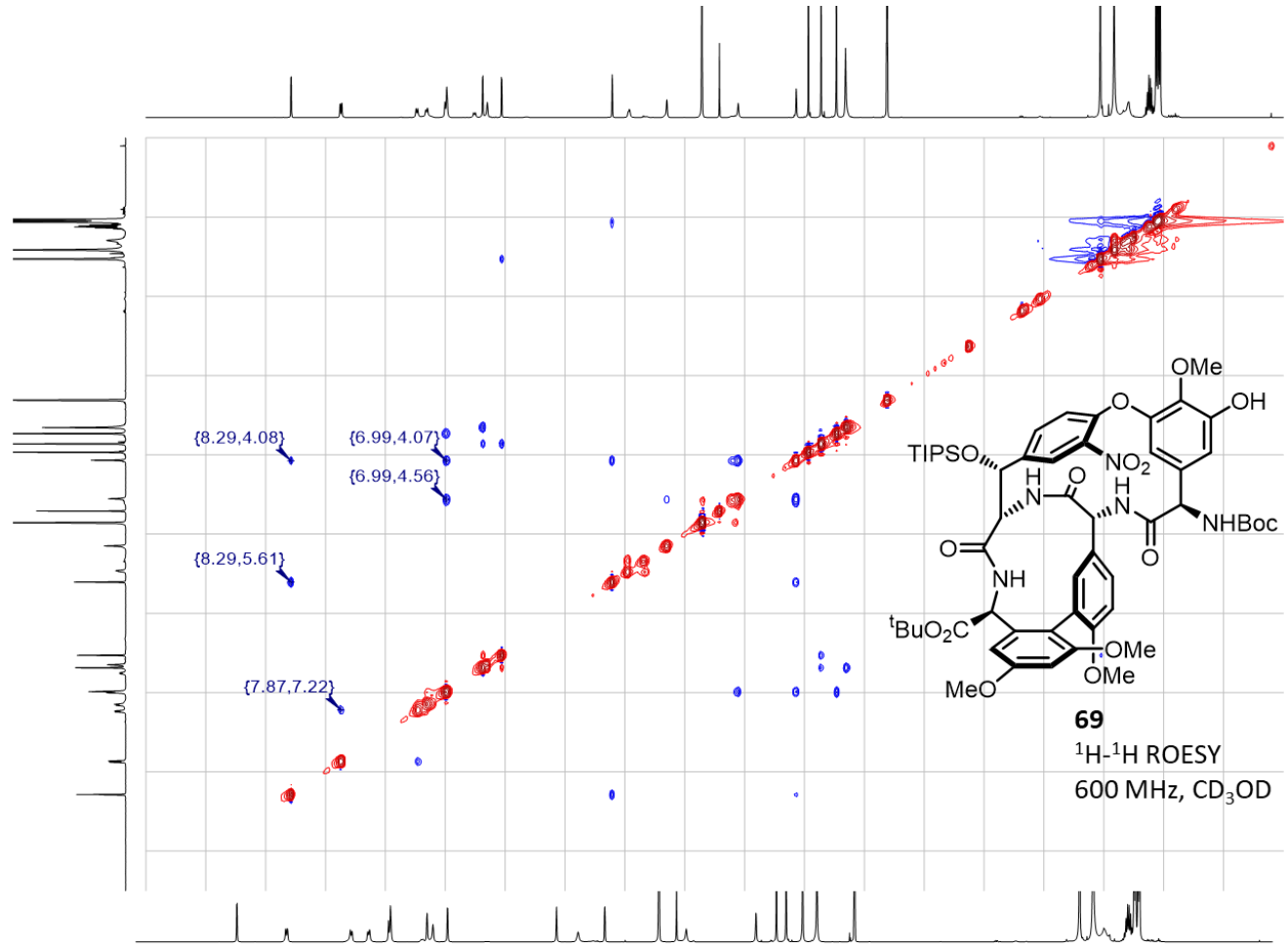
68 ^{13}C NMR
151 MHz, $CDCl_3$

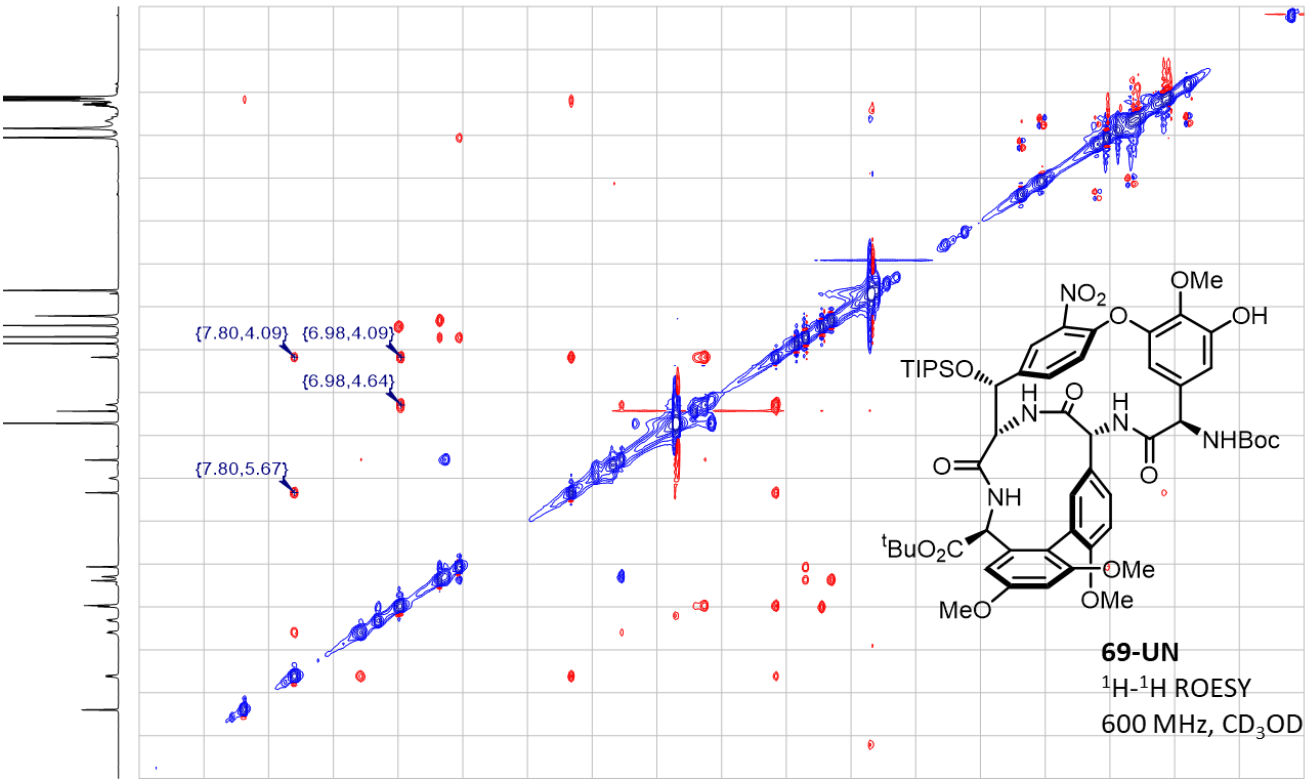

OMe
OH
TIPSO
NO2
NHBoc
tBuO2C
OMe
OMe
MeO
69 1H NMR
600 MHz, CD3OD
CD3OH
CHD2OD
f1 (ppm)

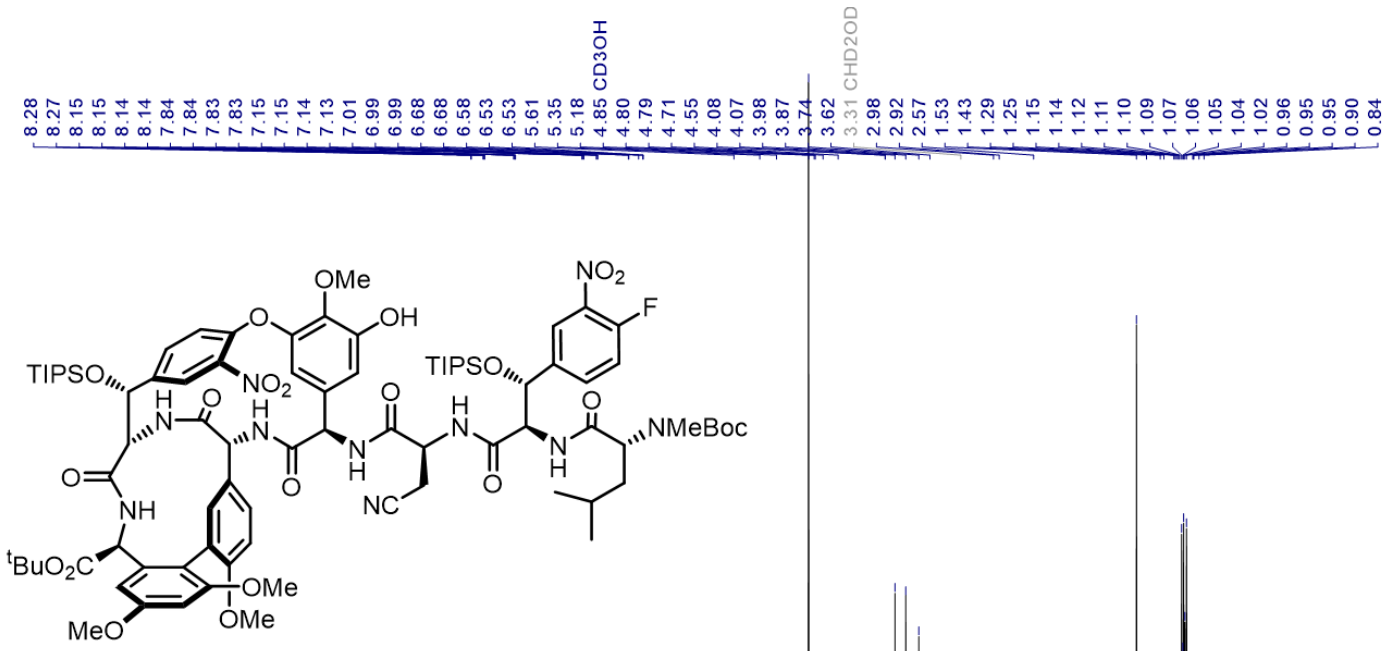

69 13C NMR
151 MHz, CDCl3
f1 (ppm)


8.20
8.20
7.82
7.81
7.81
7.80
7.80
7.30
7.29
7.16
7.15
7.00
6.98
6.69
6.65
6.53
6.53
5.67
5.50
5.29
5.29
4.86 CD3OH
4.72
4.64
4.09
3.93
3.85
3.72
3.61
3.31 CHD2OD
1.53
1.42
1.34
1.17
1.16
1.15
1.15
1.13
1.12
1.11
1.09
1.08
1.06
1.05
NO2
OMe
OH
TIPSO
NHBoc
NH
tBuO2C
OMe
OMe
MeO
69-UN 1H NMR
600 MHz, CD3OD
1.00
1.01
0.99
0.99
2.01
1.12
0.92
1.04
0.99
0.76
0.99
1.09
0.90
1.01
3.02
3.12
3.15
3.13
9.00
7.01
2.06
3.38
18.02
f1 (ppm)


69-UN 13C NMR
151 MHz, CD3OD
32.149
30.754
30.672
30.244
29.506
28.636
28.302
28.075
25.007
23.676
18.576
18.556
17.375
17.251
17.123
14.436
13.738
13.544
13.513
64.372
62.235
61.591
61.208
58.219
56.342
56.048
205.842
171.501
168.758
161.764
160.488
158.771
157.253
153.839
148.956
143.765
142.421
137.281
137.043
131.592
127.889
126.801
125.759
124.690
113.862
109.946
105.854
105.448
99.854
83.172
81.230
74.646
f1 (ppm)

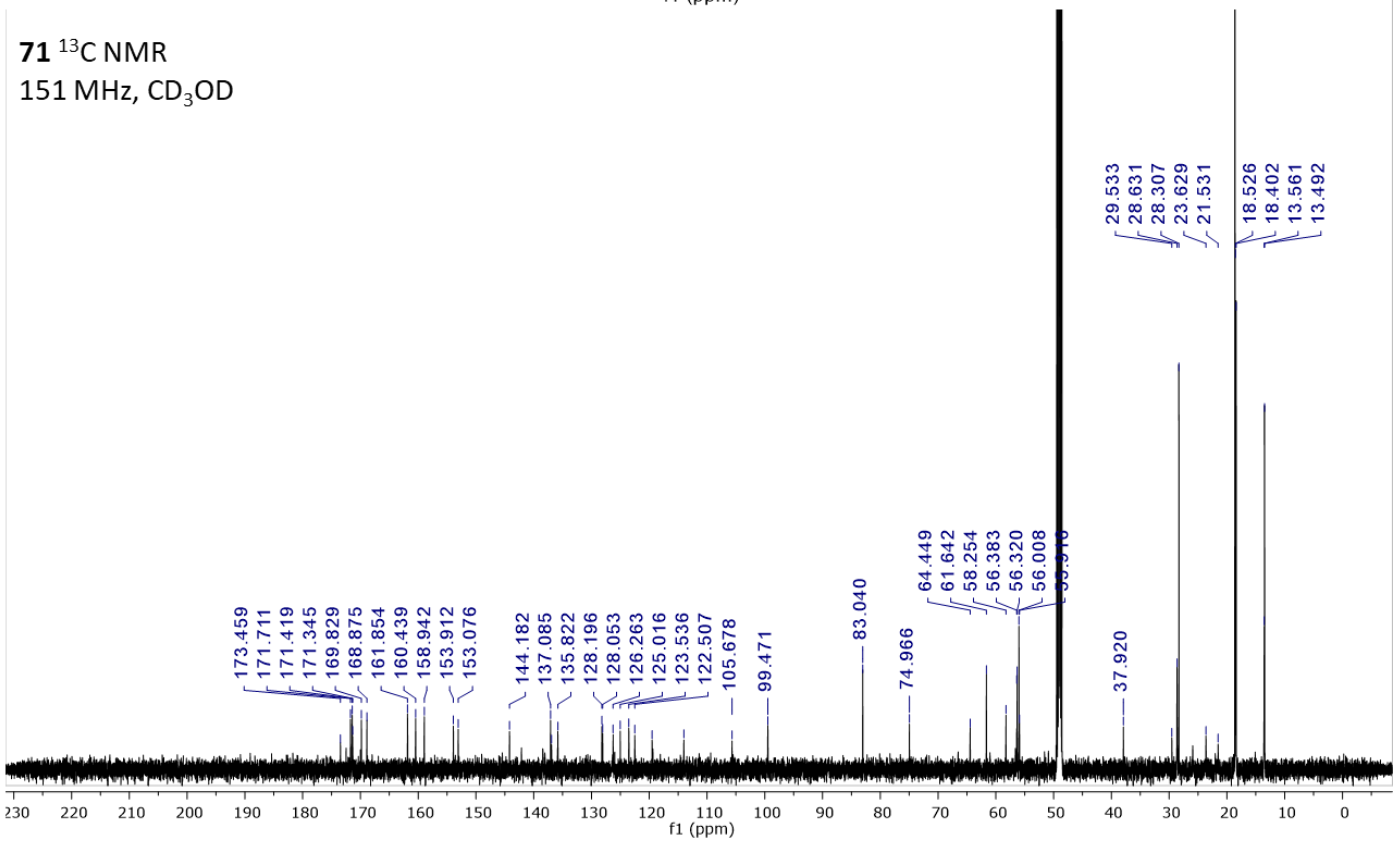

{8.29,4.08}
{6.99,4.07}
{6.99,4.56}
{8.29,5.61}
{7.87,7.22}
OMe
OH
TIPSO
NO2
NHBoc
NH
tBuO2C
OMe
OMe
MeO
69
1H-1H ROESY
600 MHz, CD3OD

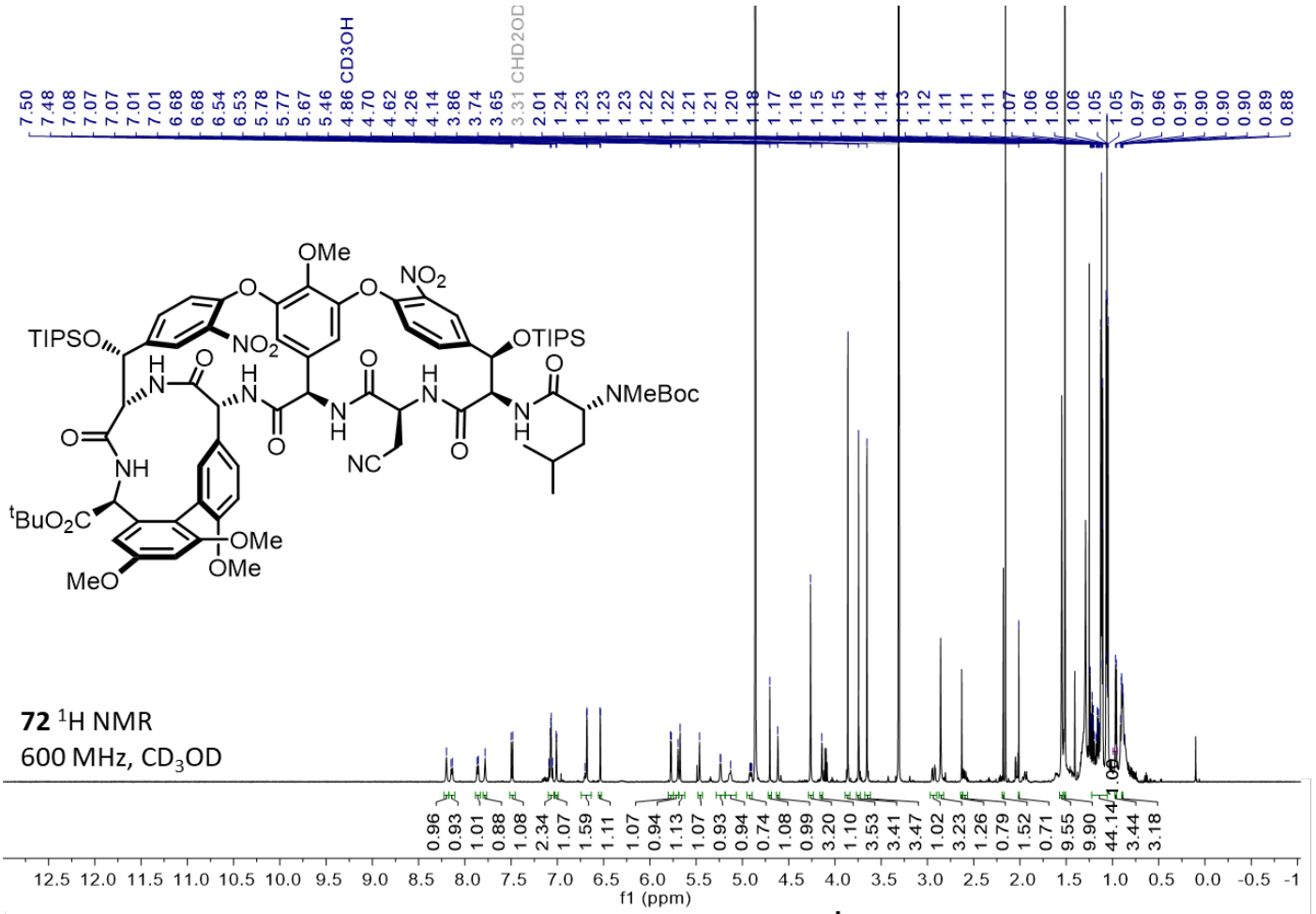

{7.80,4.09}
{6.98,4.09}
{6.98,4.64}
{7.80,5.67}
NO2
OMe
OH
TIPSO
NHBoc
NH
tBuO2C
OMe
OMe
MeO
69-UN
1H-1H ROESY
600 MHz, CD3OD

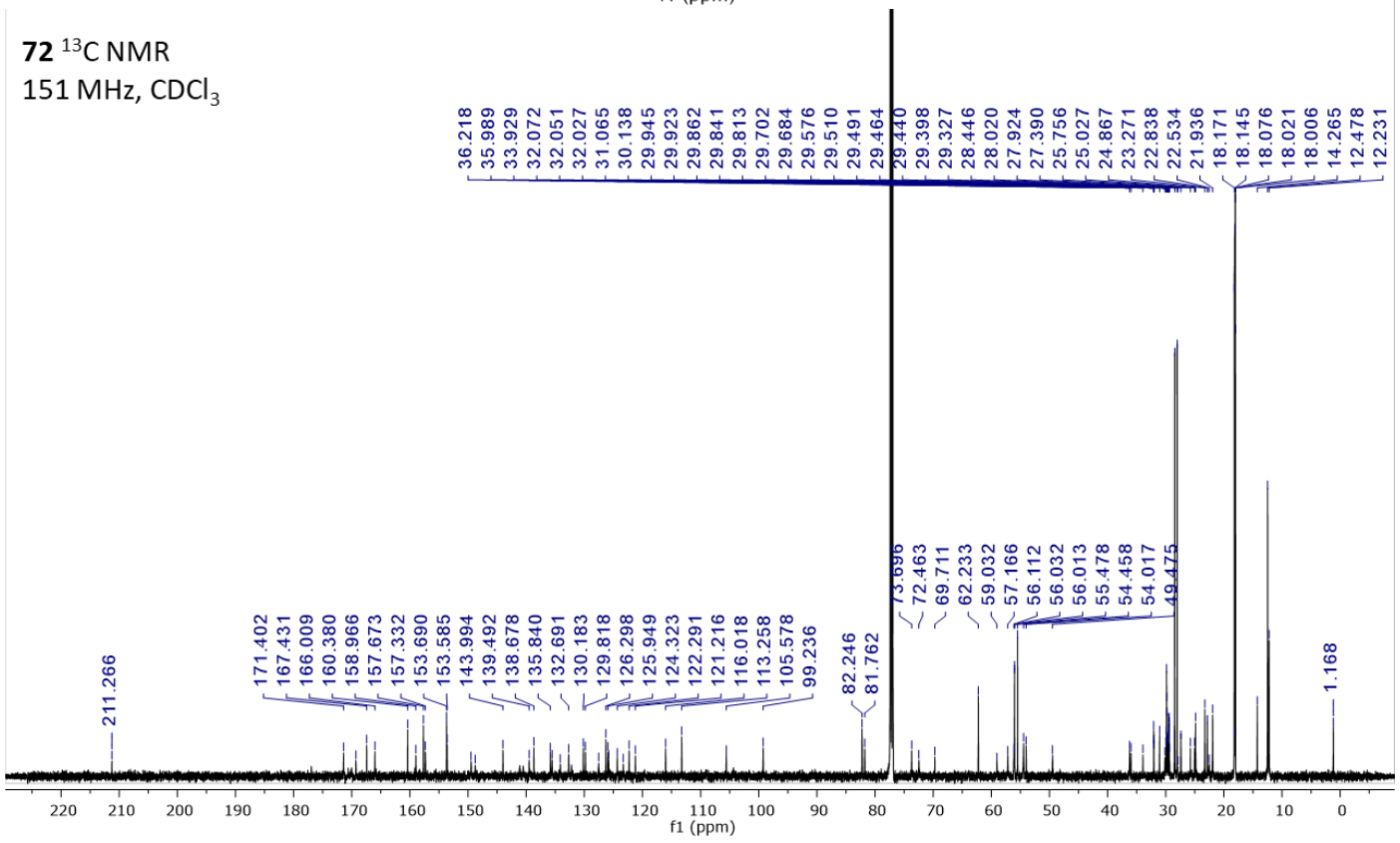


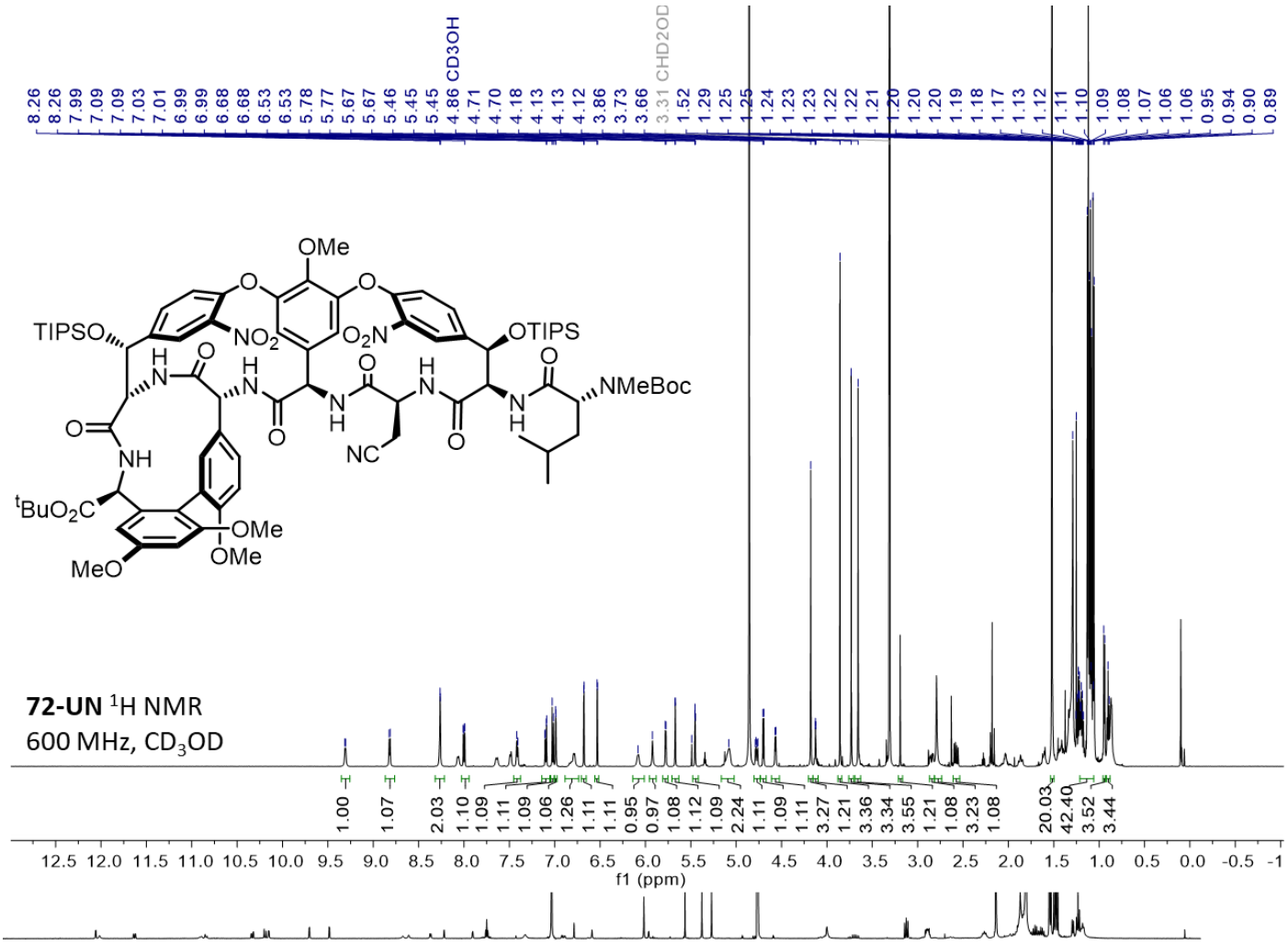
71 ^{1}H NMR
600 MHz, CD_3OD

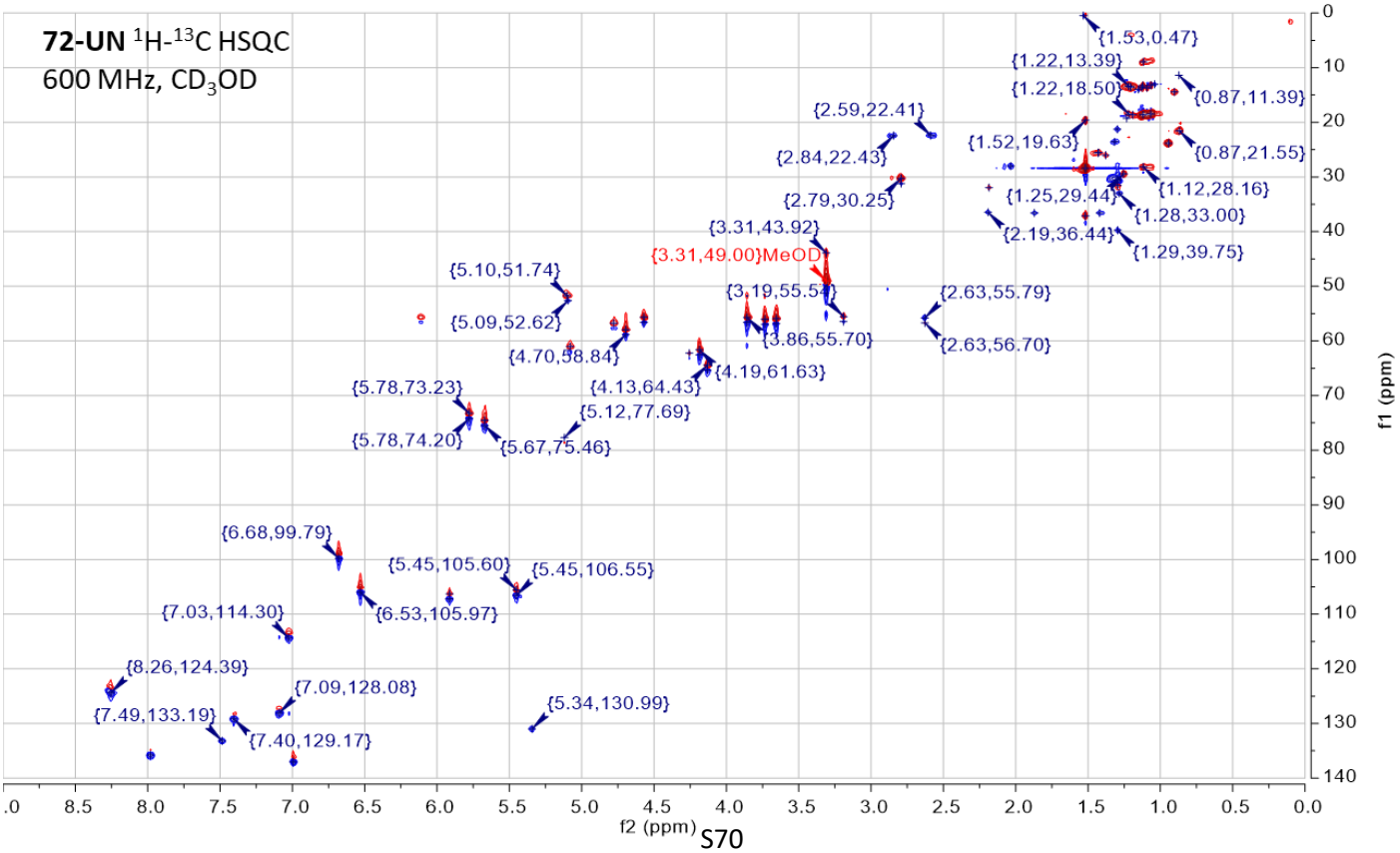
71 ^{13}C NMR
151 MHz, CD_3OD

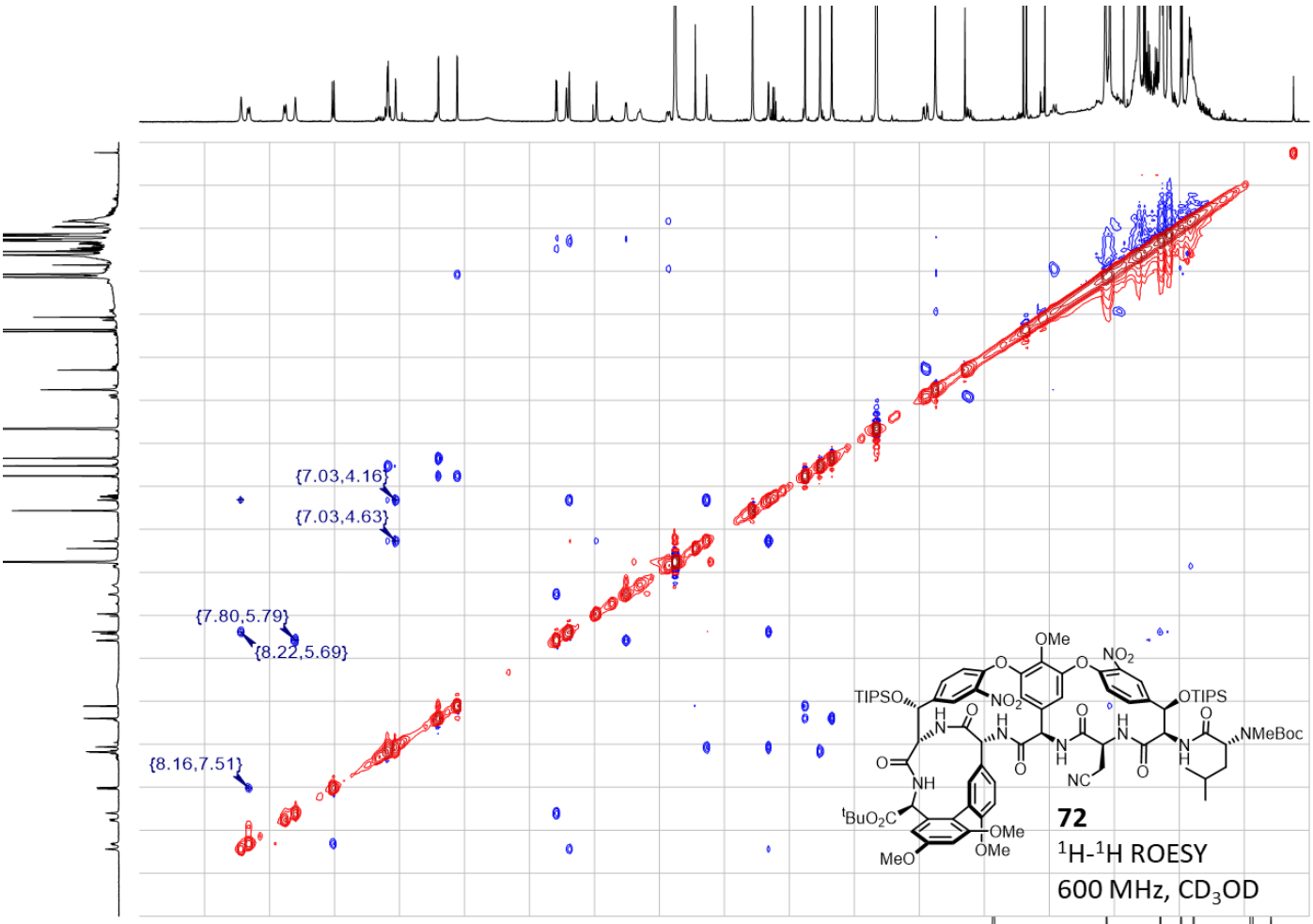


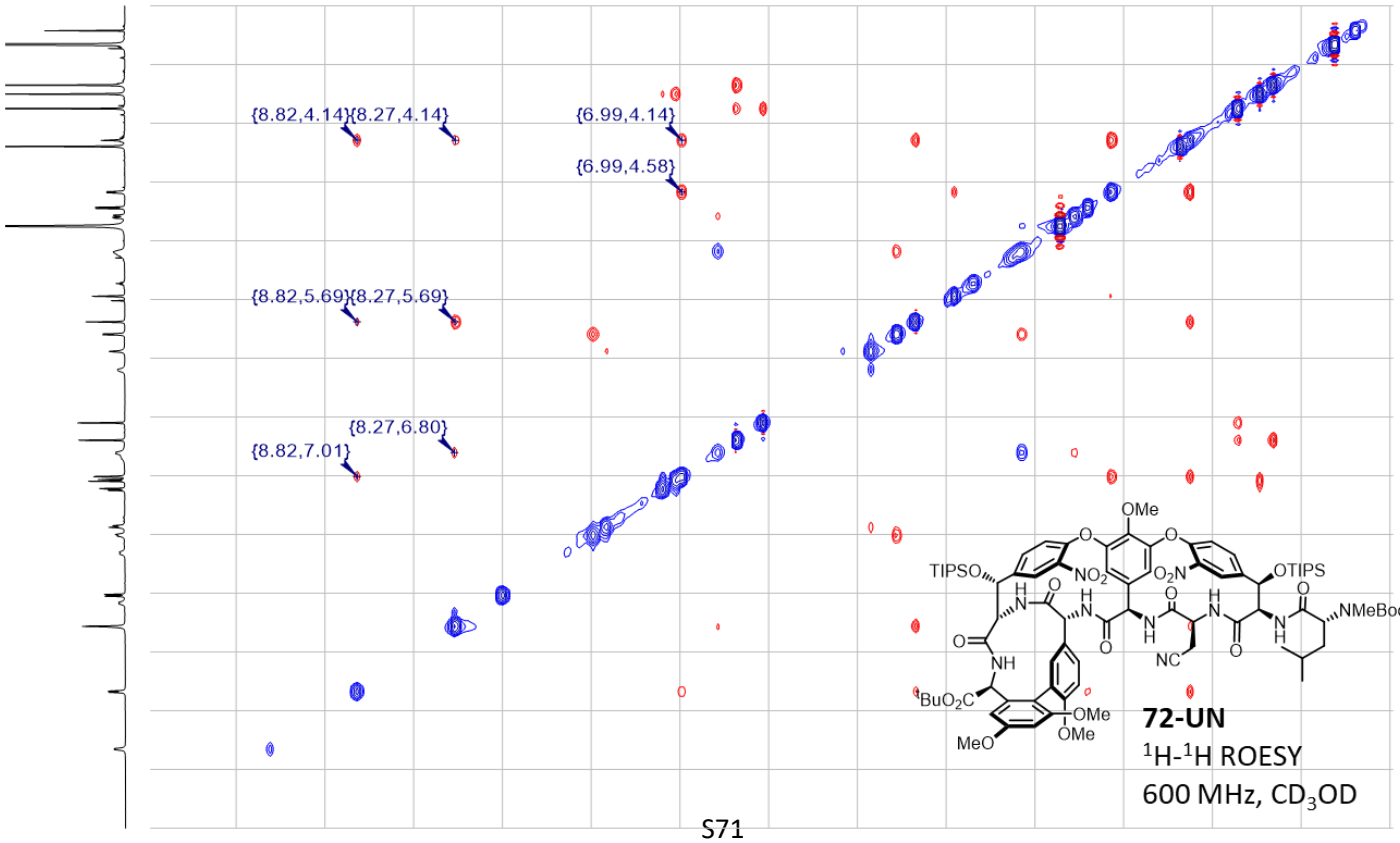

OMe
NO2
TIPSO
NO2
OTIPS
NMeBoc
NC
tBuO2C
OMe
OMe
MeO
CD3OH
CHD2OD
72 1H NMR
600 MHz, CD3OD
f1 (ppm)

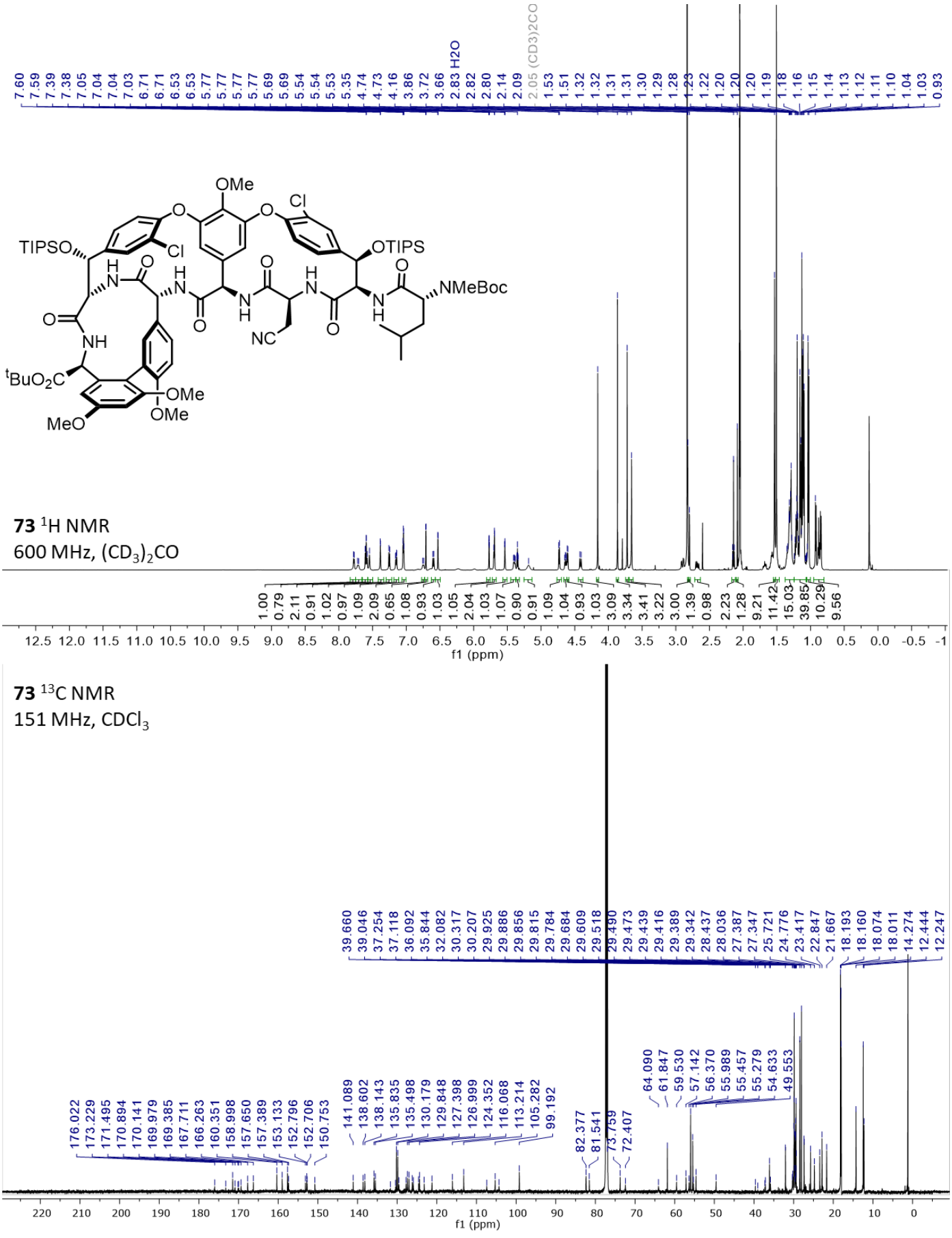

72 13C NMR
151 MHz, CDCl3
f1 (ppm)

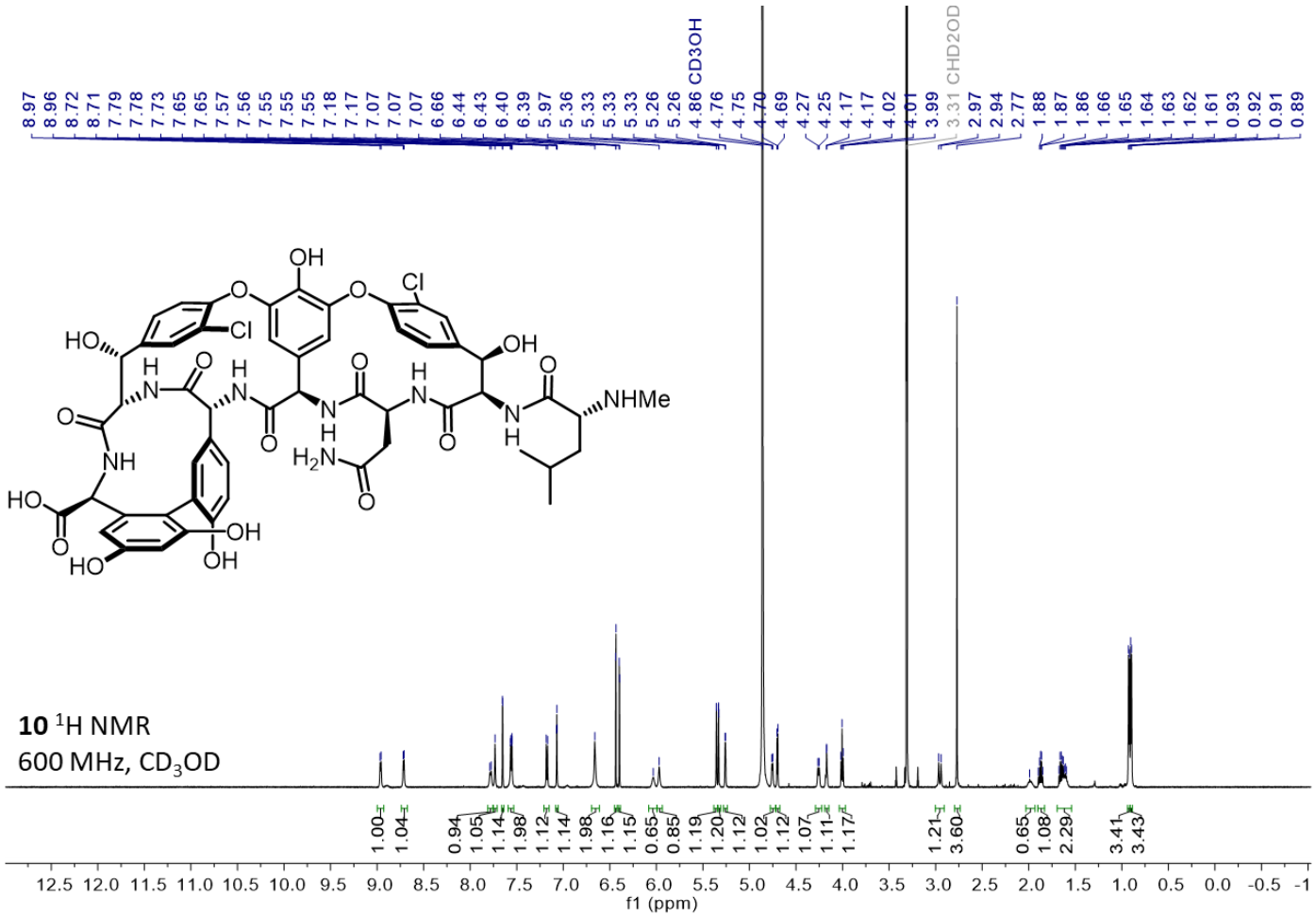

CD3OH
CHD2OD
OMe
TIPSO
OTIPS
NMeBoc
NC
NH
tBuO2C
OMe
OMe
MeO
72-UN 1H NMR
600 MHz, CD3OD
f1 (ppm)

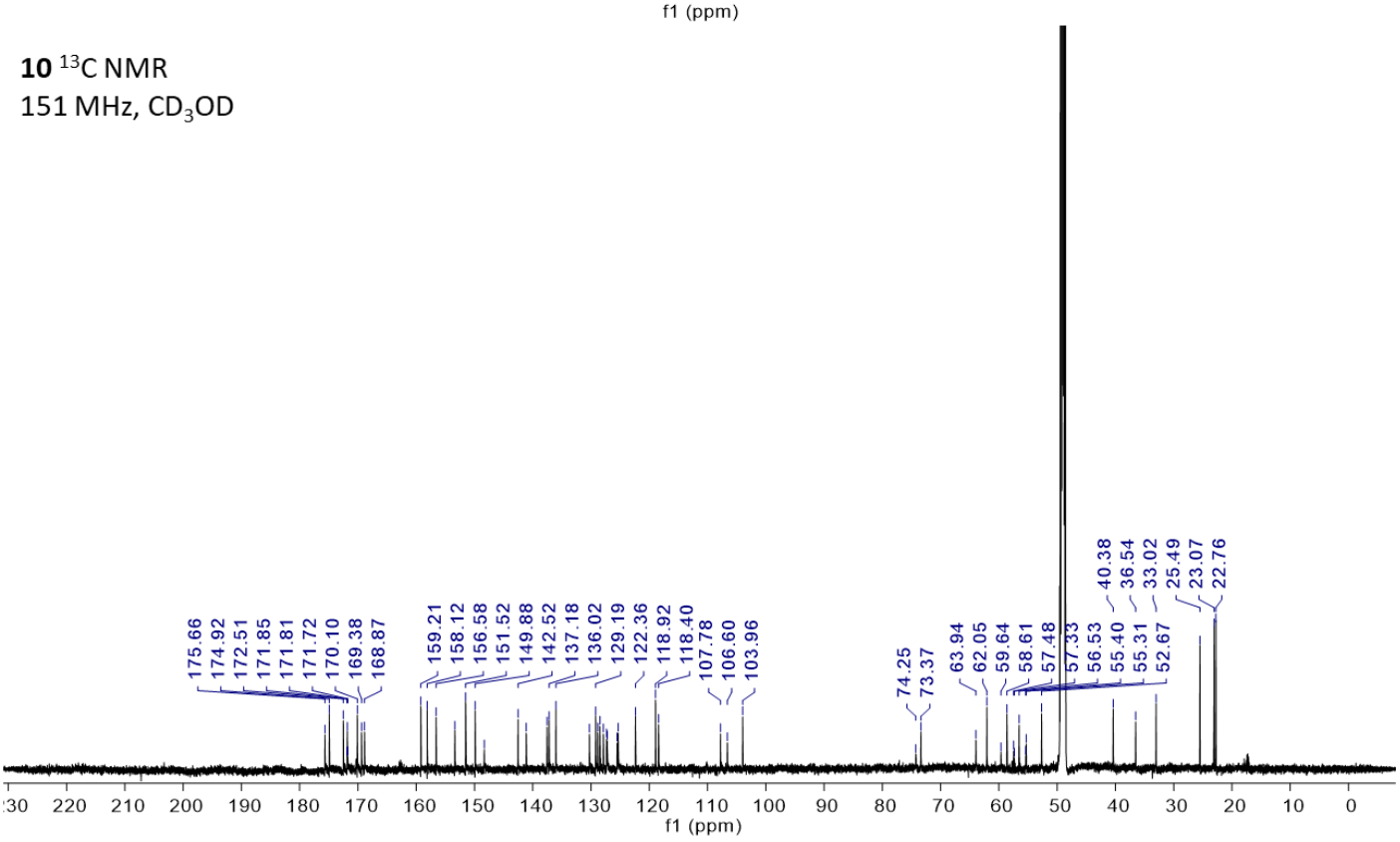

72-UN 1H-13C HSQC
600 MHz, CD3OD
{1.53,0.47}
{1.22,13.39}
{1.22,18.50}
{0.87,11.39}
{2.59,22.41}
{2.84,22.43}
{1.52,19.63}
{0.87,21.55}
{2.79,30.25}
{1.25,29.44}
{1.12,28.16}
{1.28,33.00}
{3.31,43.92}
{2.19,36.44}
{1.29,39.75}
{3.31,49.00}MeOD
{5.10,51.74}
{3.19,55.54}
{2.63,55.79}
{5.09,52.62}
{3.86,55.70}
{2.63,56.70}
{4.70,58.84}
{4.19,61.63}
{4.13,64.43}
{5.78,73.23}
{5.12,77.69}
{5.78,74.20}
{5.67,75.46}
{6.68,99.79}
{5.45,105.60}
{5.45,106.55}
{6.53,105.97}
{7.03,114.30}
{8.26,124.39}
{7.09,128.08}
{7.49,133.19}
{7.40,129.17}
{5.34,130.99}
f2 (ppm)
f1 (ppm)


{7.03,4.16}
{7.03,4.63}
{7.80,5.79}
{8.22,5.69}
{8.16,7.51}
OMe
NO2
TIPSO
NO2
OTIPS
NMeBoc
NC
NH
tBuO2C
OMe
OMe
MeO
72
1H-1H ROESY
600 MHz, CD3OD

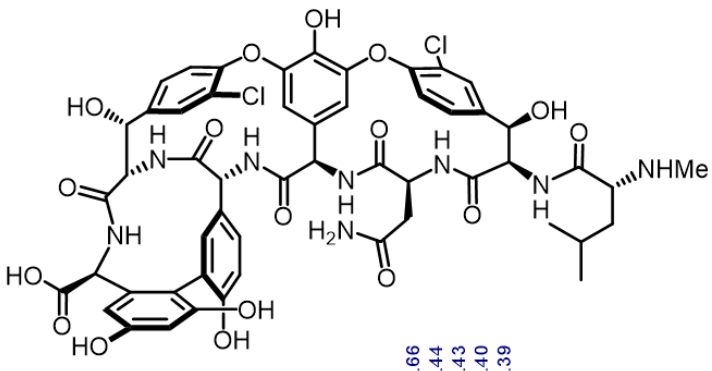

{8.82,4.14}{8.27,4.14}
{6.99,4.14}
{6.99,4.58}
{8.82,5.69}{8.27,5.69}
{8.27,6.80}
{8.82,7.01}
OMe
TIPSO
NO2
O2N
OTIPS
NMeBoc
NC
NH
tBuO2C
OMe
OMe
MeO
72-UN
1H-1H ROESY
600 MHz, CD3OD


OMe
Cl
TIPSO
Cl
OTIPS
NMeBoc
NC
NH
tBuO2C
OMe
OMe
MeO
73 1H NMR
600 MHz, (CD3)2CO
f1 (ppm)
73 13C NMR
151 MHz, CDCl3
f1 (ppm)


8.97 8.96 8.72 8.71 7.79 7.78 7.73 7.65 7.57 7.56 7.55 7.55 7.55 7.18 7.17 7.07 7.07 7.07 6.66 6.44 6.43 6.40 6.39 5.97 5.36 5.33 5.33 5.33 5.26 5.26 4.86 CD3OH 4.76 4.75 4.70 4.69 4.27 4.25 4.17 4.17 4.02 4.01 3.99 3.31 CHD2OD 2.97 2.94 2.77 1.88 1.87 1.86 1.66 1.65 1.64 1.63 1.62 1.61 0.93 0.92 0.91 0.89
OH
Cl
HO
Cl
OH
NHMe
NH
HO
OH
OH
HO
10 1H NMR
600 MHz, CD3OD
1.00 1.04 0.94 1.05 1.14 1.98 1.12 1.14 1.98 1.16 1.15 0.65 0.85 1.19 1.20 1.12 1.02 1.12 1.07 1.11 1.17 1.21 3.60 0.65 1.08 2.29 3.41 3.43
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


10 13C NMR
151 MHz, CD3OD
175.66 174.92 172.51 171.85 171.81 171.72 170.10 169.38 168.87 159.21 158.12 156.58 151.52 149.88 142.52 137.18 136.02 129.19 122.36 118.92 118.40 107.78 106.60 103.96 74.25 73.37 63.94 62.05 59.64 58.61 57.48 57.33 56.53 55.40 55.31 52.67 40.38 36.54 33.02 25.49 23.07 22.76
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

10 (synthetic) ^{1}H NMR
600 MHz, CD_3OD



10 (natural) ^{1}H NMR
600 MHz, CD_3OD