Supporting Information II

Conformational analysis of peptides 15 and 16:

^{1}H NMR spectra of tetra peptide **15** showed a well dispersed spectrum in both amide and alpha regions. Down field resonance for NH-2 and NH-3 which is >7 indicated that they have participated in intramolecular hydrogen bonding. Solvent titration studies confirmed their participation in H-bonding as they showed <3.5 ppm change in chemical shift values. The $^3J_{\text{NH-C}\beta\text{H}} > 8.5$ Hz for all the four residues, suggest that NH and C_βH protons are in *ap* arrangement, corresponding to CO-N-C_β-$C_\alpha(\phi) \sim \pm 120°$. $^3J_{\text{C}\alpha\text{H-C}\beta\text{H}} > 10$ Hz and < 5 Hz very clearly demonstrated the presence of predominantly a single conformation around Cα-Cβ (θ). The characteristic nOes for 12/10 helix which are C_βH(1)/NH(3), C_βH(1)/C$\alpha H_{(pro\text{-}R)}$(3) and NH(2)/NH(3) observed from ROESY spectrum qualifies the proposed 12/10 helical structure.

^{1}H NMR spectra of hexa peptide **16**, the extended structure of **15**, highly dispersed in the amide and C_αH region, with chemical shift (δ) dispersion of 2.59 and 0.71 ppm respectively, indicate the presence of a well defined structure. Down field resonance for NH-2, NH-3, NH-4 and NH-5 which is >7 indicated that they have participated in intramolecular hydrogen bonding. Solvent titration studies confirmed their participation in H-bonding as they showed <3.6 ppm change in chemical shift values. The observation of $J_{\text{NH-C}\beta\text{H}} > 8.5$ Hz and $J_{\text{C}\alpha\text{H-C}\beta\text{H}} > 10$ Hz and < 5 Hz and distinct NOe correlations indicate, $\phi \sim 120°$ and $\theta \sim 60°$ respectively. Apart from the hydrogen bonded NHs resulted from titration studies and derived dihedral angles from ^{1}H NMR coupling constants and the observation of nOes C_βH(1)/NH(3), C_βH(1)/C$\alpha H_{(pro\text{-}R)}$(3), C_βH(3)/NH(5), C_βH(3)/C$\alpha H_{(pro\text{-}R)}$(5), NH(2)/NH(3) and NH(4)/NH(5) from ROESY experiment provide compelling evidence for the presence of extended 12/10-helix for the peptide **16**.

Experimental Section:

(1*R*)-1-[(3a*S*,4*R*,6*R*,6a*S*)-6-(2,4-Difluorophenyl)-6-hydroxy-2,2-dimethylperhydrofuro[3,4-*d*][1,3]dioxol-4-yl]ethane-1,2-diol (47): A mixture of **46** (12.26 g, 32.9 mmol) and 60% aq. AcOH (85 mL) was stirred at room temperature for 6 h. The reaction mixture was neutralized with solid $NaHCO_3$ and sat. aq. $NaHCO_3$ solution (pH = 7) and extracted with EtOAc (3 x 300 mL). Organic layers were dried (Na_2SO_4), evaporated and residue purified the by column chromatography (Silica gel, 50% EtOAc in petroleum ether) to give **47** (8.16 g, 75%) as a colorless syrup; IR (neat): 3390, 2986, 2939, 1618, 1466, 1378, 1212, 1035, 893 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); δ 7.49 (m, 1H, Ar-H), 6.91-6.79 (m, 2H, Ar-H), 4.96 (m, 2H, C_2H, C_3H), 4.30 (m, 1H, C_6H), 3.90-3.87 (m, 3H, $C_{6'}H$, C_4H, C_5H), 1.29 (s, 3H, Me), 1.24 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.2, 161.3, 133.3 (4C), 113.1, 86.8, 79.6, 79.5, 78.8, 69.5, 63.9, 25.8, 25.0; HRMS (ESI): *m/z* calculated for $C_{15}H_{18}O_6F_2$ (M^++Na) 355.0969, found 355.0976.

Methyl (3*S*)-3-[(3a*S*,4*R*,6*S*,6a*R*)-6-(2,4-difluorophenyl)-2,2-dimethylperhydrofuro [3,4-*d*][1,3]dioxol-4-yl]-3-(benzylamino)propanoate (51) and methyl (3*R*)-3-[(3a*S*,4*R*,6*S*,6a*R*)-6-(2,4-difluorophenyl)-2,2-dimethylperhydrofuro [3,4-*d*][1,3]dioxol-4-yl]-3-(benzylamino)propanoate (52): A mixture of **50** (6 g, 17.6 mmol) and benzylamine (4.81 mL, 44.1 mmol), as described for **24/25**, was stirred at room temperature for 12 h and purified the reaction mixture by column chromatography. First eluted (Silica gel, 15% EtOAc in petroleum ether) was **52** (1.57 g, 20%) as a pale yellow syrup; $[\alpha]_D$ = +149.02 (*c* 0.75, $CHCl_3$); IR (Neat): 3356, 2988, 2938, 2838, 2833, 1736, 1438, 1375, 1194, 1097, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44 (m, 1H, ArH), 7.38-7.19 (m, 5H, ArH), 6.88-6.75 (m, 2H, ArH), 4.91 (m, 1H, C_1H), 4.88 (m, 1H C_3H), 4.79 (m, 1H C_2H), 3.94-3.65 (m, 4H, C_4H, $C_\beta H$, $BnCH_2$), 3.66 (s, 3H, OMe), 2.86 (m, 1H, $C_\alpha H$), 2.67 (m, 1H, $C_{\alpha'}H$), 1.44 (s, 3H, Me), 1.27 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.9, 162.0, 160.4, 128.2 (10C), 112.7-111.4 (3C), 82.9, 81.5, 80.7, 76.6 (2C), 51.4, 25.1, 24.3; HRMS (ESI): *m/z* calculated for $C_{24}H_{28}NO_5F_2$ (M^++H) 448.1935, found 448.1929.

Second eluted (Silica gel, 20% EtOAc in petroleum ether) was **51** (3.22 g, 41%) as a pale yellow syrup; $[\alpha]_D$ = 171.4 (*c* 0.33, $CHCl_3$); IR (Neat): 3370, 2991, 2937, 2899, 1739, 1444, 1160, 1087, 1020, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.45 (m, 1H,

Difluorophenyl), 7.39-7.20 (m, 5H, Ar-H), 6.89-6.77 (m, 2H, Difluorophenyl), 4.93 (d, 1H, *J* = 3.9 Hz, C_1H), 4.85 (dd, 1H, *J* = 3.4, 6.1 Hz, C_3H), 4.80 (dd, 1H, *J* = 3.7, 6.1 Hz, C_2H), 3.97 (d, 1H, *J* = 13.2 Hz, $BnCH_2$), 3.91 (d, 1H, *J* = 13.2 Hz, $BnCH_2$), 3.80 (dd, 1H, *J* = 3.4, 8.2 Hz, C_4H), 3.70 (s, 3H, COOMe), 3.60 (m, 1H, $C_\beta H$), 2.83 (dd, 1H, *J* = 4.9, 15.2 Hz, $C_\alpha H$), 2.62 (dd, 1H, *J* = 5.8, 15.2 Hz , $C_{\alpha'}H$), 1.43 (s, 3H, Me), 1.23 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 162.0, 159.7, 128.3-128.1(10C), 112.9-111.4 (3C), 83.6, 81.7, 80.7, 76.9 (2C), 51.5, 25.2, 24.4; HRMS (ESI): *m/z* calculated for $C_{24}H_{28}NO_5F_2$ (M^++H) 448.1935, found 448.1924.

Boc-(*S*)-β-Caa(diFP)-OCH_3 (3): A mixture of **51** (3.5 g, 7.82 mmol) in methanol (10 mL) was treated with 10% Pd-C (0.35 g) as described for **26** gave *methyl (3S)-3-[(3aS,4R,6S,6aR)-6-(2,4-difluorophenyl)-2,2-dimethylperhydrofuro [3,4-d][1,3]dioxol-4-yl]-3-aminopropanoate* (**53**) as a yellow liquid, which was used as such for the next reaction.

A solution of **53** (2.80 g, 7.84 mmol) and Et_3N (2.7 mL, 19.6 mmol) in CH_2Cl_2 (20 mL) was treated with Boc_2O (1.8 mL, 7.84 mmol) as described for **5** gave **3** (3.2 g, 89%) as a white solid; m.p. 112-115 °C, $[\alpha]_D$ = +21.9 (*c* 1.3, $CHCl_3$); IR (Neat): 3443, 2979, 1712, 1626, 1500, 1371, 1206, 1108, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 303K, 500 MHz): δ 7.24 (m, 1H, Ar-H), 6.88-6.86 (m, 2H, Ar-H), 5.30 (d, 1H, *J* = 8.1 Hz, NH), 4.98 (d, 1H, *J* = 3.7 Hz, C_1H), 4.81 (dd, 1H, *J* = 3.5, 6.2, Hz, C_3H), 4.80 (d, 1H, *J* = 3.7 Hz, C_2H), 4.50 (dddd, 1H, *J* = 4.8, 6.4, 6.7, 8.1 Hz, $C_\beta H$), 3.87 (dd, 1H, *J* = 3.5, 4.8 Hz, C_4H), 3.68 (s, 3H, COOMe), 2.86 (dd, 1H, *J* = 6.7, 16.1 Hz, $C_\alpha H$), 2.80 (dd, 1H, *J* = 6.4, 16.1 Hz, $C_{\alpha'}H$), 1.47 (s, 3H, Me), 1.45 (s, 9H, Boc), 1.25 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 163.0, 159.6, 155.4, 129.8, 129.6 (2C), 129.5, 113.0, 111.8, 111.4, 81.6, 81.1,80.3, 79.2,76.6, 46.9, 28.4 (3C), 25.1, 24.1; HRMS (ESI): *m/z* calculated for $C_{22}H_{29}NO_7F_2$ (M^++Na) 480.1809, found 480.1830.

Boc-(*R*)-β-Caa(diFP)-OCH_3 (4): A solution of **52** (1 g, 2.23 mmol) in methanol (5 mL) was treated with 10% Pd-C (0.10 g) as described for **26** to give *methyl (3R)-3-[(3aS,4R,6S,6aR)-6-(2,4-difluorophenyl)-2,2-dimethylperhydrofuro [3,4-d][1,3]dioxol-4-yl]-3-aminopropanoate* (**54**) as a syrup, which was used as such for the next reaction.

As described for the synthesis of **5**, a solution of **54** (0.79 g, 2.22 mmol) in CH_2Cl_2 (20 mL) was treated with Boc_2O (0.50 mL, 2.22 mmol) and Et_3N (0.77 mL, 5.5

mmol) in CH_2Cl_2 (30 mL) to give **4 (**0.95 g, 94%) as a yellow syrup;$[\alpha]_D$ = +139.8 (*c* 0.6, $CHCl_3$); IR (Neat): 3437, 2922, 1736, 1627, 1468, 1372, 1270, 1167, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (m, 1H, Ar-H), 6.87-6.82 (m, 2H, Ar-H), 5.56 (d, 1H, *J* = 8.7 Hz, NH), 4.95 (d, 1H, *J* = 4.0 Hz, C_1H), 4.85 (dd, 1H, *J* = 6.1, 3.5 Hz, C_3H), 4.79 (dd, 1H, *J* = 6.1, 4.0 Hz, C_2H), 4.53 (m, 1H, $C_\beta H$), 3.84 (m, 1H, C_4H), 3.69 (s, 3H, COOMe), 2.84 (m, 2H, $C_\alpha H$, $C_{\alpha'}H$), 1.46 (s, 3H, Me), 1.45 (s, 9H, Boc), 1.27 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.2, 162.1, 160.4, 155.6, 129.6 (2C), 128.7, 127.8, 112.9, 111.6, 111.4, 81.4, 80.9 (2C), 79.2, 76.6, 47.1, 28.3 (3C), 25.0, 24.0; HRMS (ESI): *m/z* calculated for $C_{22}H_{29}NO_7F_2$ (M^++Na) 480.1809, found. 480.1822.

Boc-(*S*)-β-Caa(diFP)-OH (55): As described for **28**, a solution of **3** (0.65 g, 1.42 mmol) gave **55** (0.57 g, 90%) as a white solid, m.p.55-59 °C**;** $[\alpha]_D$ = +46.1 (*c* 0.33, $CHCl_3$); IR (Neat): 3442, 2982, 1715, 1627, 1507, 1471, 1272, 1166, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24 (m, 1H, Ar-H), 6.90-6.85 (m, 2H, Ar-H), 5.42 (d, 1H, *J* = 8.7 Hz, NH), 4.99 (d, 1H, *J* = 4.0 Hz, C_1H), 4.82 (m, 2H, C_2H, C_3H), 4.48 (m, 1H, $C_\beta H$), 3.90 (m, 1H, C_4H), 2.86 (m, 2H, $C_\alpha H$, $C_{\alpha'}H$), 1.48 (s, 3H, Me), 1.46 (s, 9H, Boc), 1.27 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.0, 163.0, 159.6, 155.8, 129.8, 129.6 (2C), 129.5, 113.0, 111.8, 111.4, 81.6, 81.0, 80.3, 79.6, 46.7, 28.3 (3C), 25.1, 24.1; HRMS (ESI): *m/z* calculated for $C_{21}H_{27}NO_7F_2$ (M^++Na) 466.1653, found 466.1644.

Boc-(R)-β-Caa(diFP)-OH (56): As described for the synthesis of **28**, a solution of **4** (0.350 g, 0.765 mmol) gave **56** (0.33 g) in 97% yield as a white solid, m.p. 141-145 °C; $[\alpha]_D$ = +187.1 (*c* 0.35, $CHCl_3$); IR (KBr): 3349, 2982, 1745, 1691, 1592, 1419, 1172, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.23 (m, 1H, Ar-H), 6.88-6.83 (m, 2H, Ar-H), 5.58 (d, 1H, *J* = 8.2 Hz, NH), 4.97 (d, 1H, *J* = 4.0 Hz, C_1H), 4.87 (dd, 1H, *J* = 6.1, 3.4 Hz, C_3H), 4.81 (dd, 1H, *J* = 6.1, 4.0 Hz, C_2H), 4.54 (m, 1H, $C_\beta H$), 3.88 (m, 1H, C_4H), 2.89 (m, 2H, $C_\alpha H$, $C_{\alpha'}H$), 1.50 (s, 3H, Me), 1.46 (s, 9H, Boc), 1.27 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.6, 162.2, 160.5, 155.8, 129.6 (4C), 113.0, 111.6, 111.5, 81.4, 80.8, 80.7, 79.6, 46.9, 28.3 (3C), 25.0, 24.1; HRMS (ESI): *m/z* calculated for $C_{21}H_{27}NO_7F_2$ (M^++Na) 466.1653, found 466.1655.

Boc-(*S*)-β-Caa(diFP)-(*R*)-β-Caa(diFP)-OH (60): As described for **28**, a solution of **59** (0.3 g, 0.38 mmol) gave **60** (0.276 g, 94%) as a white solid, which was used as such for further reaction.

Boc-[(*S*)-β-Caa(diFP)-(*R*)-β-Caa(diFP)]$_2$-OH (62): As described for **28**, a solution of **13** (0.13 g, 0.09 mmol) gave **62** (0.116 g, 91%) as a white solid, which was used as such for further reaction.

Boc-(*R*)-β-Caa(diFP)-(*S*)-β-Caa(diFP)-OMe (63): A mixture of **56** (0.3 g, 0.677 mmol), HOBt (0.109 g, 0.812 mmol) and EDCI (0.155 g, 0.81 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 15 min and treated with **57** (0.31 g, 0.677 mmol; obtained from **3** on exposure to TFA) and DIPEA (0.23 mL, 1.35 mmol) under nitrogen atmosphere for 8 h. Workup as described for **36** and purification by column chromatography (Silica gel, 60% EtOAc in petroleum ether) gave **63** (0.34 g, 64%) as a white solid. m.p. 105-106 °C; $[\alpha]_D$ = +150.8 (c 0.35, $CHCl_3$); IR(KBr): 3435, 2982, 1732, 1628, 1507, 1376, 1207, 1108, 994 cm^{-1} **;** ^{1}H NMR ($CDCl_3$, 303K, 500 MHz): δ 7.27-7.17 (m, 2H, Ar-H)**,** 6.89-6.81 (m, 4H, Ar-H), 6.52 (d, 1H, *J* = 7.8 Hz, NH-2), 5.71 (d, 1H, *J* = 9.3 Hz, NH-1), 4.94 (d, 1H, *J* = 3.4 Hz, C_1H-2), 4.88 (m, 1H, C_3H-1), 4.82 (d, 1H, *J* = 4.1 Hz, C_1H-1), 4.77 (m, 2H, C_3H, C_2H-2), 4.75 (m, 1H, C_βH-2), 4.62 (m, 1H, C_2H-1), 4.49 (m, 1H, C_βH-1), 3.90 (dd, 1H, *J* = 3.0, 5.8 Hz, C_4H-2), 3.85 (m, 1H, C_4H-1), 3.67 (s, 3H, COOMe), 2.83 (m, 2H, C_αH, $C_{\alpha'}$H-2), 2.72 (dd, 1H, *J* = 6.3, 14.7 Hz, C_αH-1), 2.62 (dd, 1H, *J* = 7.1, 14.7 Hz, $C_{\alpha'}$H-1), 1.48 (s, 3H, Me), 1.44 (s, 9H, Boc), 1.43 (s, 3H, Me), 1.25 (s, 3H, Me), 1.21 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 170.3, 163.0 (2C), 159.7 (2C), 155.8, 129.8-129.2 (8C), 113.0, 112.7, 111.8, 111.6, 111.5, 111.3, 81.6, 81.5, 80.8 (2C),, 80.5, 80.2, 79.0, 76.6, 47.5, 45.8, 28.4 (3C), 25.2, 25.1, 24.2, 24.0; HRMS (ESI): *m/z* calculated for $C_{38}H_{46}N_2O_{11}F_4$ (M^++Na) 805.2935, found 805.2941.

Boc-[(*R*)-β-Caa(diFP)-(*S*)-β-Caa(diFP)]$_2$-OMe (15): A mixture of **64** (0.1 g, 0.13 mmol), HOBt (0.020 g, 0.15 mmol) and EDCI (0.028 g, 0.15 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 °C for 15 min and treated with **65** (0.10 g, 0.13 mmol; obtained from **63** on exposure to TFA) and DIPEA (0.045 mL, 0.26 mmol) under nitrogen atmosphere for 8 h. Workup as described for **36** and purification by column chromatography (Silica gel 1.6% MeOH in $CHCl_3$) afforded **15** (0.09 g, 48%) as a white solid; m.p. 82-85 °C; $[\alpha]_D$ =

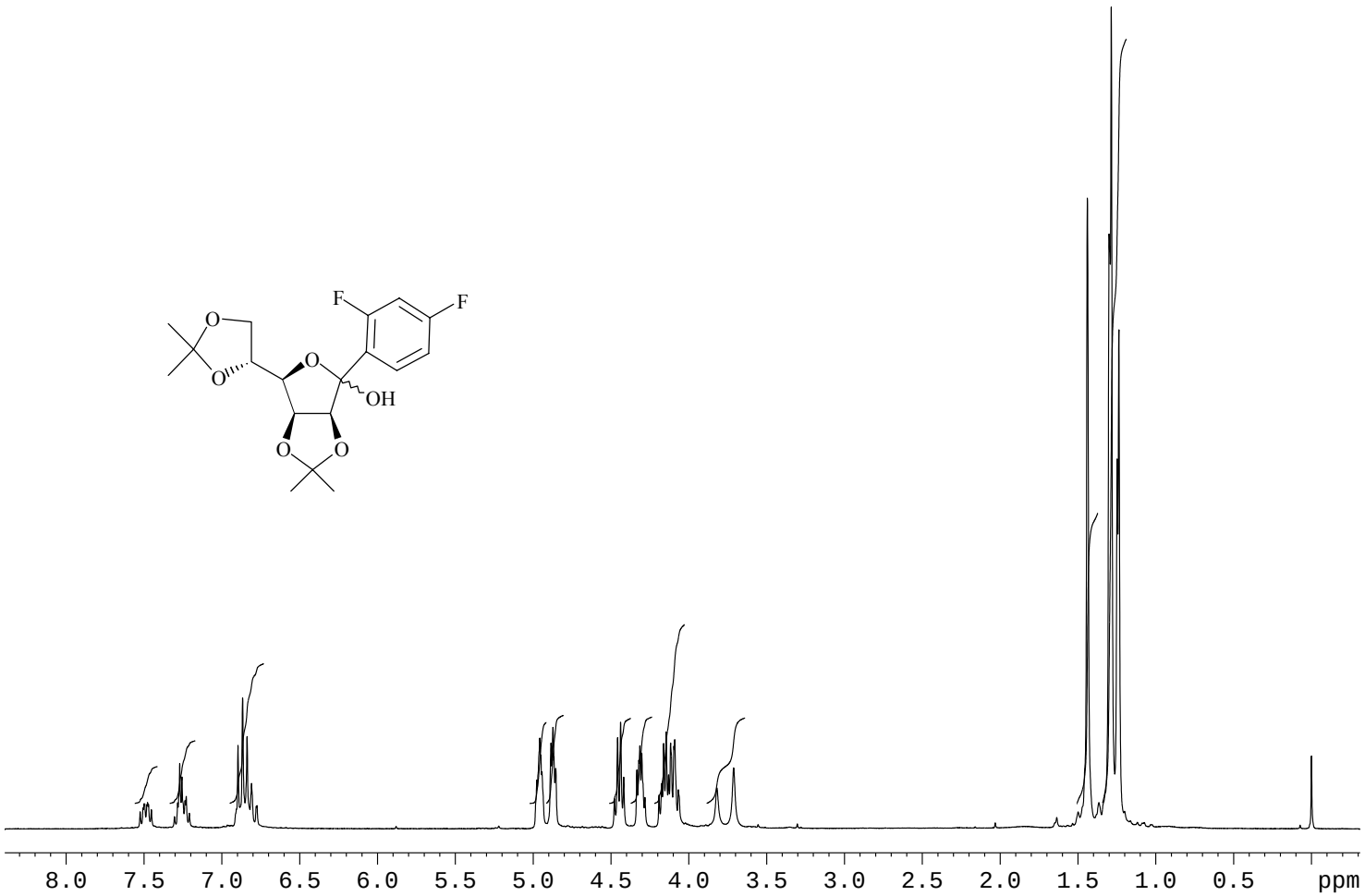
+29.50 (c 0.95, $CHCl_3$); IR(KBr): 3433, 2928, 1733, 1664, 1516, 1470, 1207, 1107, 996 cm^{-1}; ^1H NMR ($CDCl_3$, 303K, 500 MHz): δ 7.25-7.18 (m, 2H, Ar-H), 6.88-6.80 (m, 4H, Ar-H), 6.92 (d, 1H, NH-2), 5.83 (d, 1H, *J* = 9.2 Hz, NH-1), 4.96 (d, 1H, C_1H-2), 4.95 (d, 1H, *J* = 3.8 Hz, C_1H-1), 4.81 (m, 1H, C_2H-1), 4.81 (m, 2H, C_2H, C_3H-2), 4.72 (m, 1H, $C_\beta H$-2), 4.54 (m, 1H, $C_\beta H$-1), 4.66 (dd, 1H, *J* = 4.0, 6.1 Hz, C_2H-1), 3.96 (dd, 1H, C_4H-2), 3.84 (m, 1H, C_4H-1), 2.84 (m, 2H, $C_\alpha H$, $C_{\alpha'}H$-2), 2.76 (m, 1H, $C_\alpha H$-1), 2.65 (dd, 1H, *J* = 7.5, 13.5 Hz, $C_{\alpha'}H$-1), 1.48 (s, 6H, Me), 1.45 (s, 6H, Me), 1.44 (s, 9H, Boc), 1.26 (s, 12H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.2, 170.7, 170.2, 170.0, 162.1 (4C), 160.4 (4C), 156.6, 129.7-129.2 (16C), 112.9-112.6 (4C), 111.9-111.3 (8C), 81.8, 81.5, 81.4 (2C), 81.1, 80.9, 80.8, 80.6, 80.4, 79.9, 78.8, 76.6, 76.5, 48.8, 46.4, 46.2, 45.5, 28.4 (3C), 25.3 (2C), 25.0, 24.9, 24.5, 24.3, 24.0, 23.6; HRMS (ESI): *m/z* calculated for $C_{70}H_{80}N_4O_{19}F_8$ (M^++Na) 1455.5186, found 1455.5137.

Boc-(*R*)-β-Caa(diFP)-(*S*)-β-Caa(diFP)-OH (64): As described for **28**, a solution of **63** (0.13 g, 0.166 mmol) gave **64** (0.12 g, 95%) as a white solid, which was used as such for further reaction.

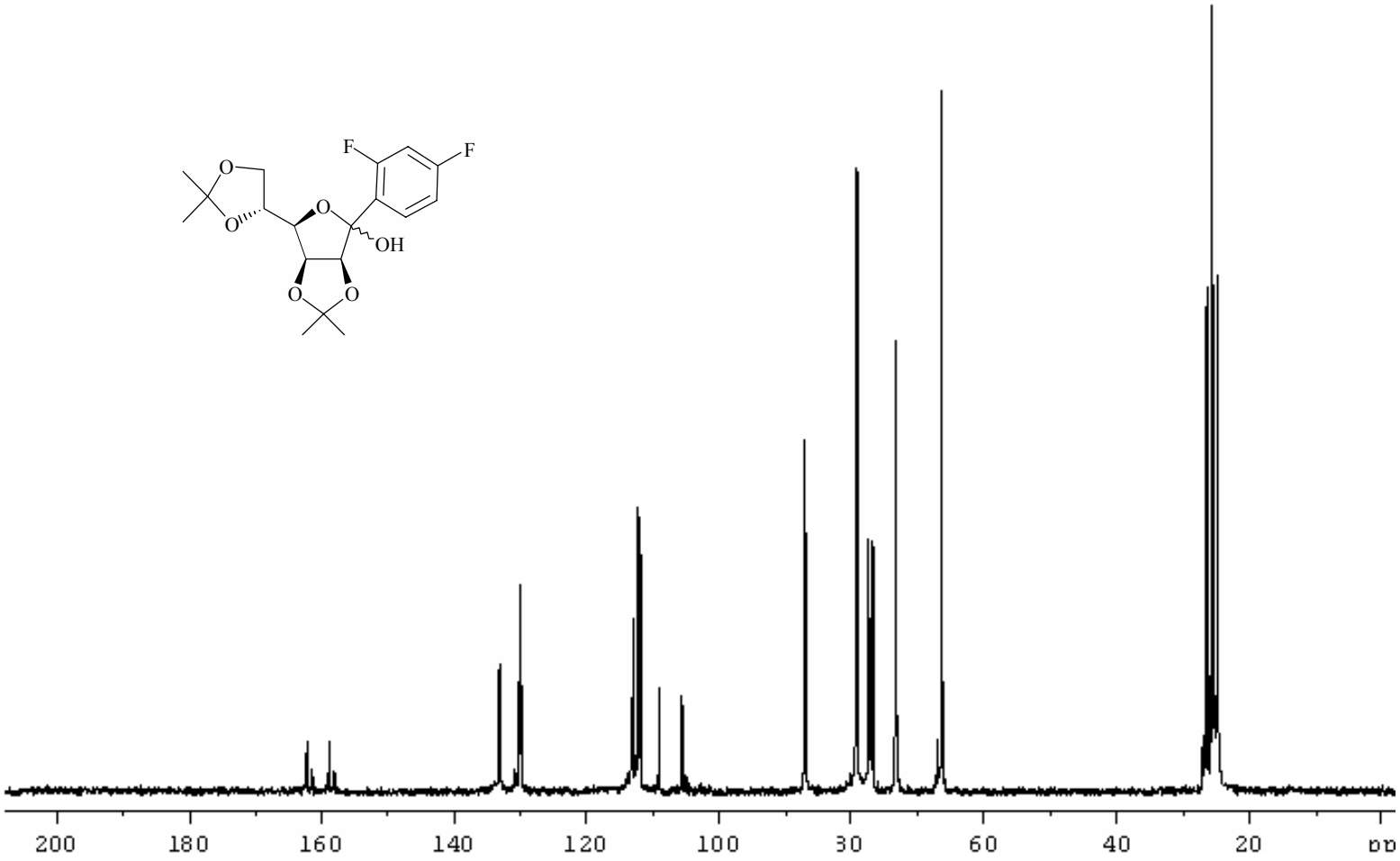
Boc-[(*R*)-β-Caa(diFP)-(*S*)-β-Caa(diFP)]$_3$-OCH$_3$ (16): As described for **28**, a solution of **15** (0.07, 0.048 mmol) gave *Boc-[(R)-β-Caa(diFP)-(S)-β-Caa(diFP)]$_2$-OH* (**66**; 0.06 g, 87%) as a white solid, which was used as such for further reaction.

A mixture of **66** (0.05 g, 0.035 mmol), HOBt (0.005 g, 0.04 mmol) and EDCI (0.008 g, 0.04 mmol) in CH_2Cl_2 (6 mL) was stirred at 0 °C for 15 min and treated with **65** (0.027 g, 0.035 mmol) and DIPEA (0.01 mL, 0.07 mmol) under nitrogen atmosphere for 8 h. Workup as described for **36** and purification by column chromatography (Silica gel, 1.8% MeOH in $CHCl_3$) afforded **16** (0.03 g, 41%) as a white solid; m.p. 151-153 °C; $[\alpha]_D$ = +346.0 (c 0.20, $CHCl_3$); IR(KBr): 3434, 2931, 2857, 1737, 1653, 1471, 1271, 1109,998, 787; ^1H NMR ($CDCl_3$, 303K, 500 MHz): δ 8.55 (d, 1H, *J* = 9.0 Hz, NH-5), 8.47 (d, 1H, *J* = 8.5 Hz, NH-3), 8.36 (d, 1H, *J* = 9.1 Hz, NH-2), 8.35 (d, 1H, *J* = 9.9 Hz, NH-4), 7.25-7.05 (m, 6H, Ar-H), 6.88-6.71 (m, 12H, Ar-H), 6.72 (m, 1H, NH-6), δ 5.96 (d, 1H, *J* = 10.1 Hz, NH-1), 5.24 (dd, 1H, *J* = 3.5, 6.0 Hz, C_3H-4), 5.15 (dd, 1H, *J* = 3.5, 6.0 Hz, C_3H-2), 4.96 (d, 1H, *J* = 4.2 Hz, C_1H-6), 4.93 (m, 5H, C_1H-1, C_1H-2, C_1H-3, C_1H-5, C_3H-5), 4.87 (m, 1H, C_1H-4), 4.85 (m, 1H, C_3H-1), 4.84 (m, 2H, $C_\beta H$-3, C_3H-3),

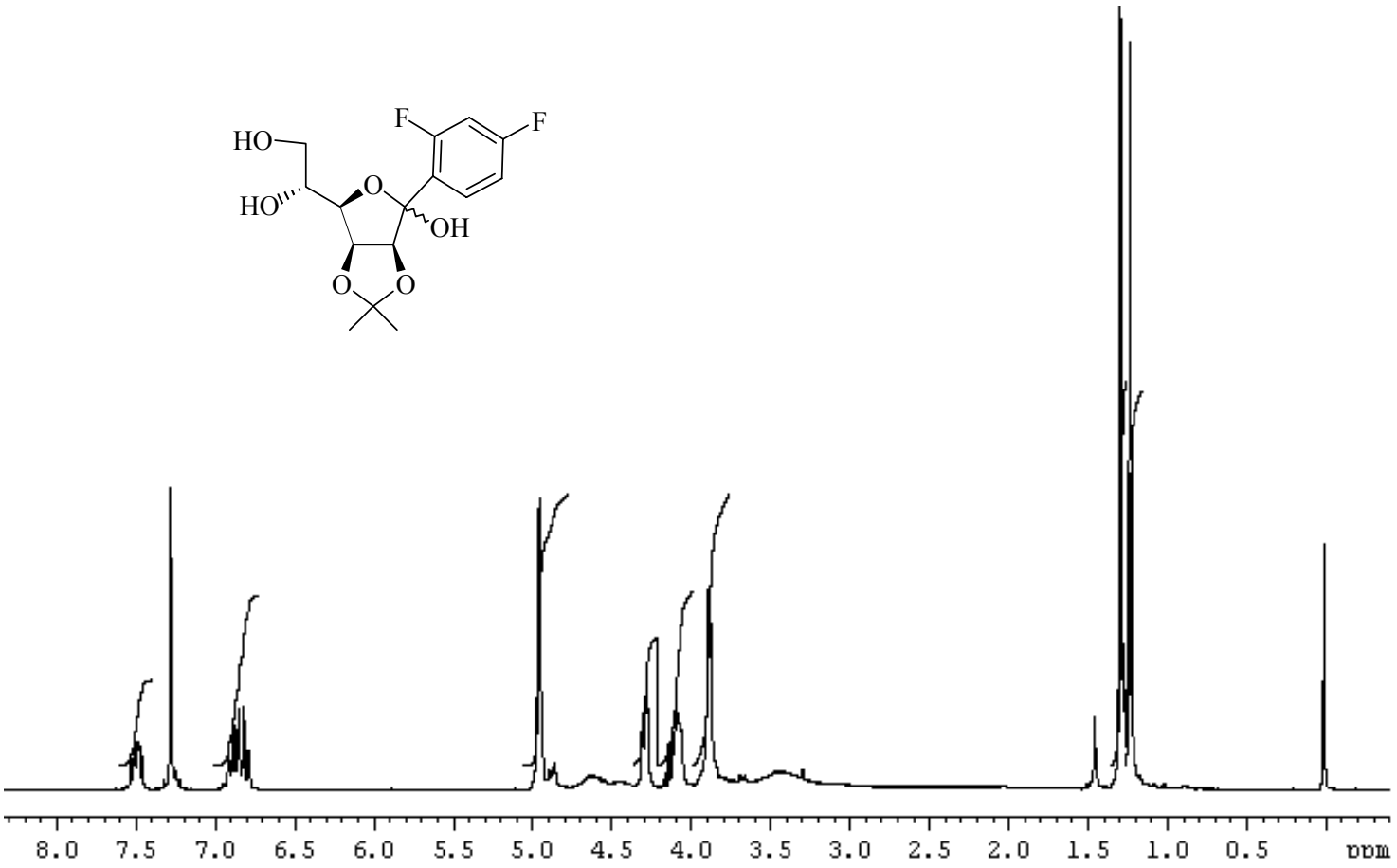
4.83 (m, 2H, C_{β}H-5, C_3H-5), 4.82 (m, 4H, C_{β}H-2, C_3H-2, C_2H-6, C_3H-6), 4.74 (m, 1H, C_2H-1), 4.73 (m, 1H, C_2H-5), 4.71 (m, 1H, C_{β}H-6), 4.70 (m, 1H, C_{β}H-1), 4.66 (dd, 1H, *J* = 4.4, 6.0 Hz, C_2H-3), 4.63 (m, 1H, C_{β}H-4), 3.97 (dd, 1H, *J* = 3.6, 8.0 Hz, C_4H-6), 3.95 (dd, 1H, *J* = 3.5, 9.2 Hz, C_4H-2), 3.87 (dd, 1H, *J* = 3.5, 9.5 Hz, C_4H-4), 3.75 (m, 2H, C_4H-1, C_4H-3), 3.72 (s, 3H, COOMe), 3.71 (m, 1H, C_4H-5), 3.01 (m, 2H, $C_{\alpha}H_{(pro\text{-}R)}$-6, $C_{\alpha}H_{(pro\text{-}S)}$-6), 2.95 (dd, 1H, *J* = 3.8, 12.0, Hz, $C_{\alpha}H_{(pro\text{-}S)}$-3), 2.84 (m, 2H, $C_{\alpha}H_{(pro\text{-}S)}$-1, $C_{\alpha}H_{(pro\text{-}S)}$-5), 2.77 (dd, 1H, *J* = 3.7, 13.2 Hz, $C_{\alpha}H_{(pro\text{-}S)}$-2), 2.69 (dd, 1H, *J* = 3.4, 12.6 Hz, $C_{\alpha}H_{(pro\text{-}S)}$-4), 2.54 (dd, 1H, *J* = 5.0, 13.2 Hz, $C_{\alpha}H_{(pro\text{-}R)}$-2), 2.50 (m, 1H, $C_{\alpha}H_{(pro\text{-}R)}$-1), 2.49 (dd, 1H, *J* = 5.0, 12.6 Hz, $C_{\alpha}H_{(pro\text{-}R)}$-4), 2.46 (dd, 1H, *J* =10.8, 12.7 Hz, $C_{\alpha}H_{(pro\text{-}R)}$-5), 2.30 (m, 1H, $C_{\alpha}H_{(pro\text{-}R)}$-3), 1.51 (s, 3H, Me), 1.50 (s, 3H, Me), 1.47 (s, 9H, Boc), 1.47 (s, 3H, Me), 1.44 (s, 6H, Me), 1.37 (s, 3H, Me), 1.31 (s, 3H, Me), 1.27 (s, 3H, Me), 1.26 (s, 3H, Me), 1.23 (s, 3H, Me), 1.21 (s, 3H, Me), 1.20 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.4, 171.0, 170.9, 170.4, 170.1, 169.6, 162.1 (6C), 160.4 (6C), 156.9, 129.7-129.0 (24C), 113.1-111.2 (18C), 82.3-76.4 (20C), 49.6, 47.3, 47.1, 46.7, 46.6, 45.3, 28.3 (3C), 25.4, 25.3, 25.2, 25.0, 24.9, 24.8, 24.5, 24.4, 24.3, 23.9, 23.8, 23.7; HRMS (ESI): *m/z* calculated for $C_{102}H_{114}N_6O_{27}F_{12}$ (M^++Na) 2105.7432, found 2105.7457.



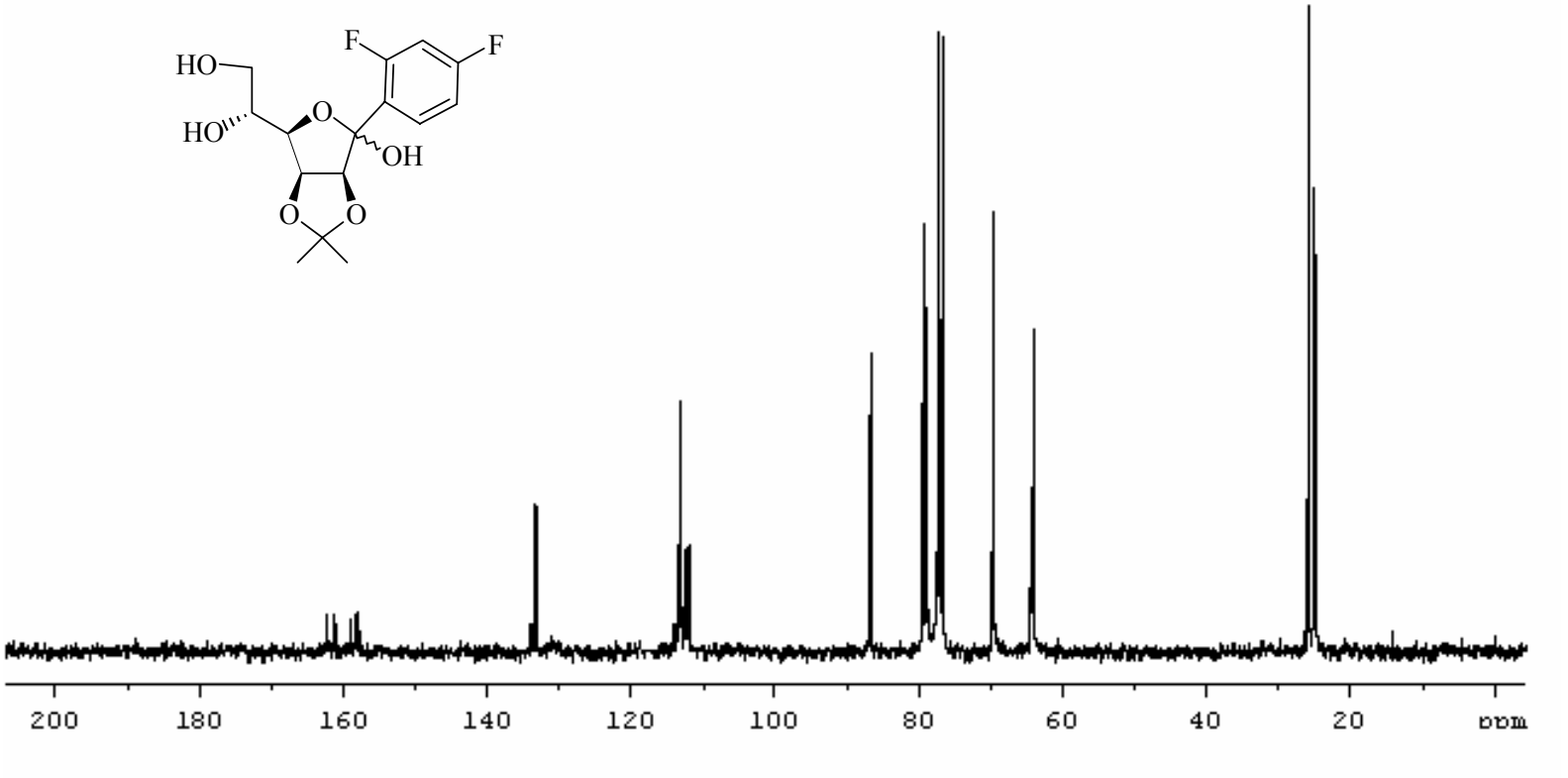
Supporting Fig 65: **^{1}H NMR Spectrum of 46 ($CDCl_3$, 294 K, 300 MHz)**



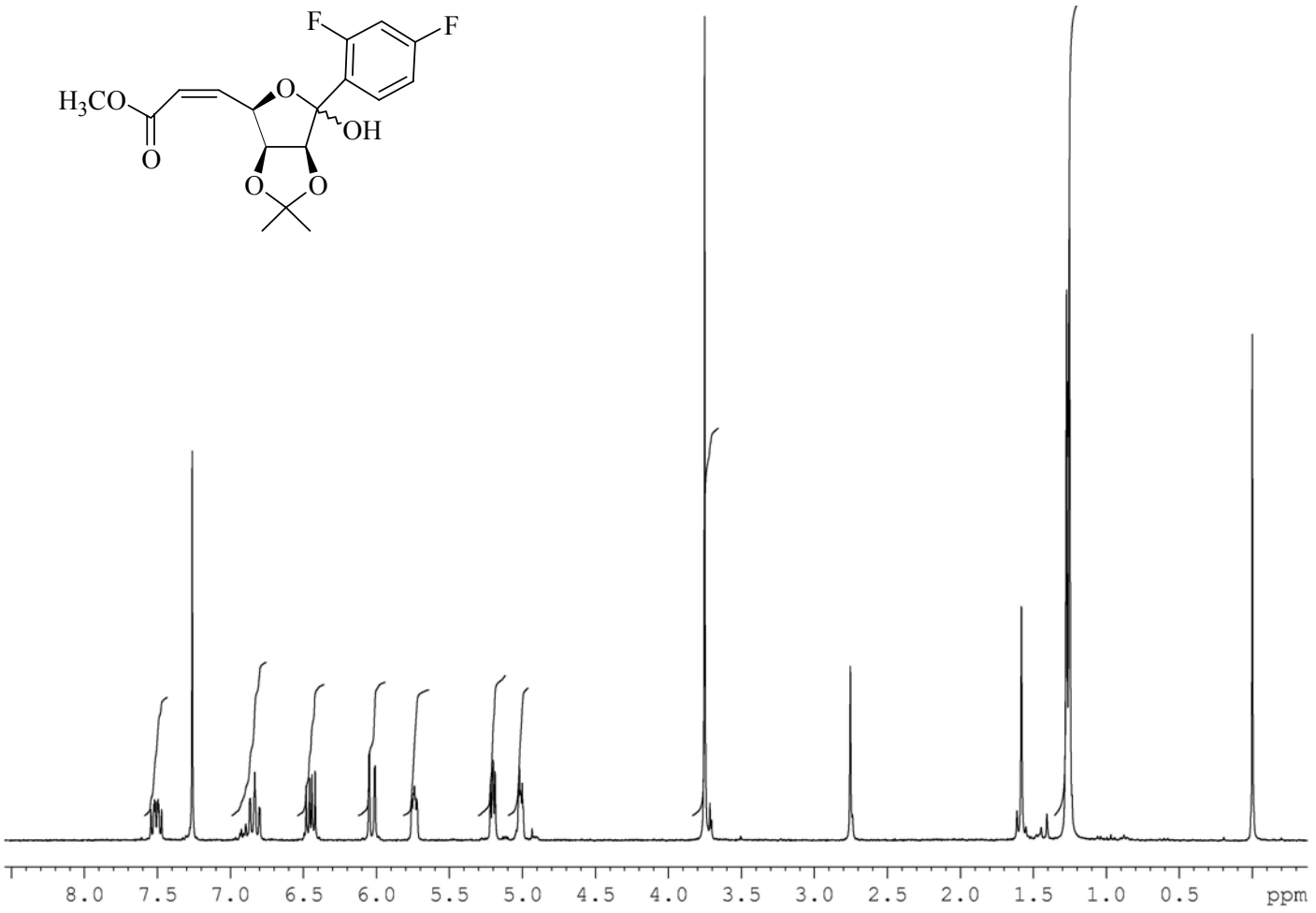
Supporting Fig 66: **^{13}C NMR Spectrum of 46 ($CDCl_3$, 294 K, 75 MHz)**



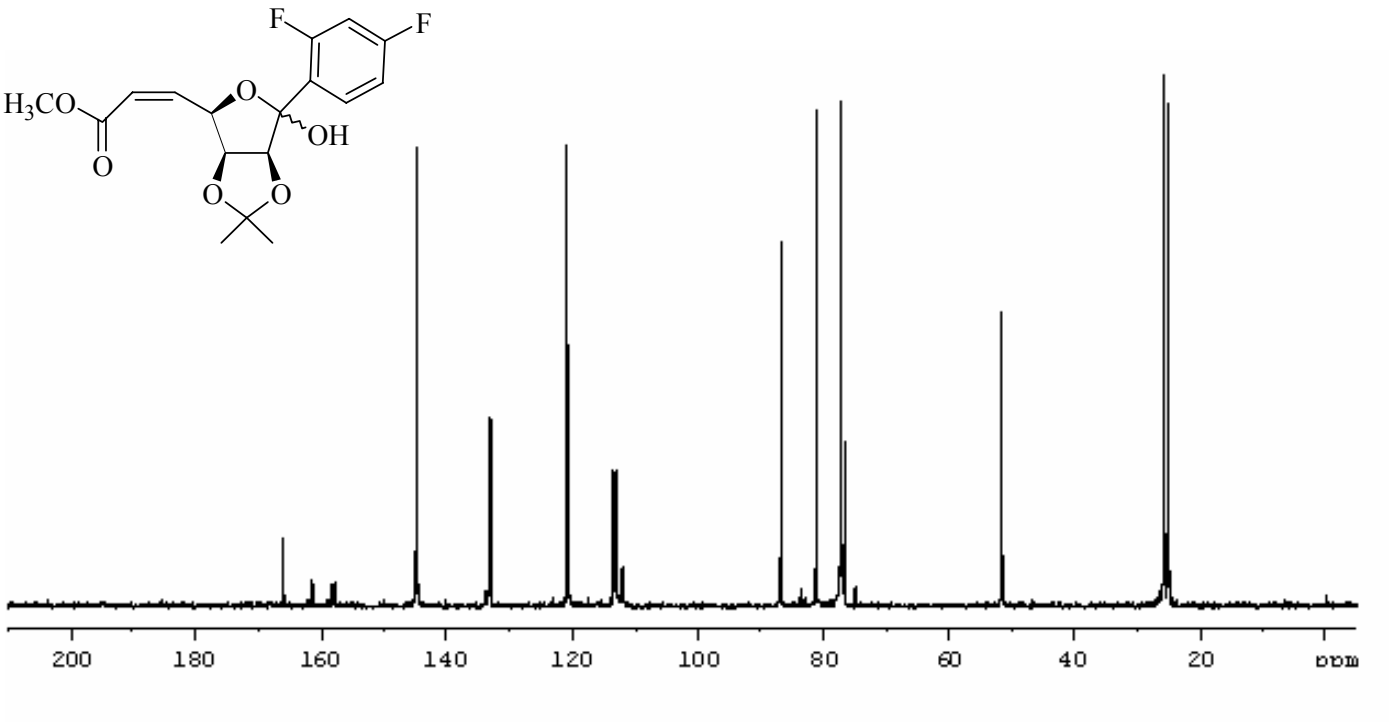
Supporting Fig 67: **^{1}H NMR Spectrum of 47 ($CDCl_3$, 294 K, 300 MHz)**



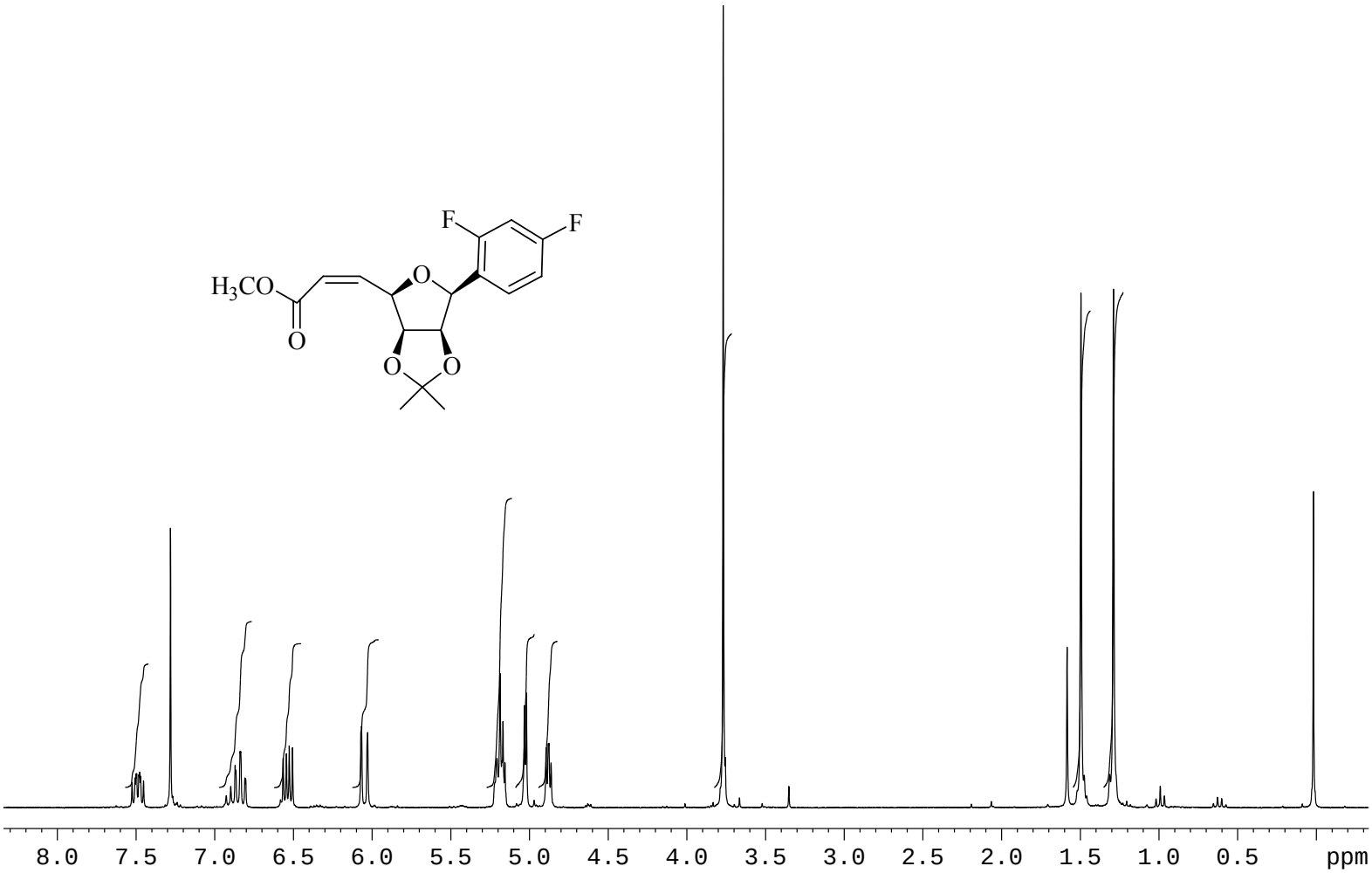
Supporting Fig 68: **^{13}C NMR Spectrum of 47 ($CDCl_3$, 294 K, 75 MHz)**



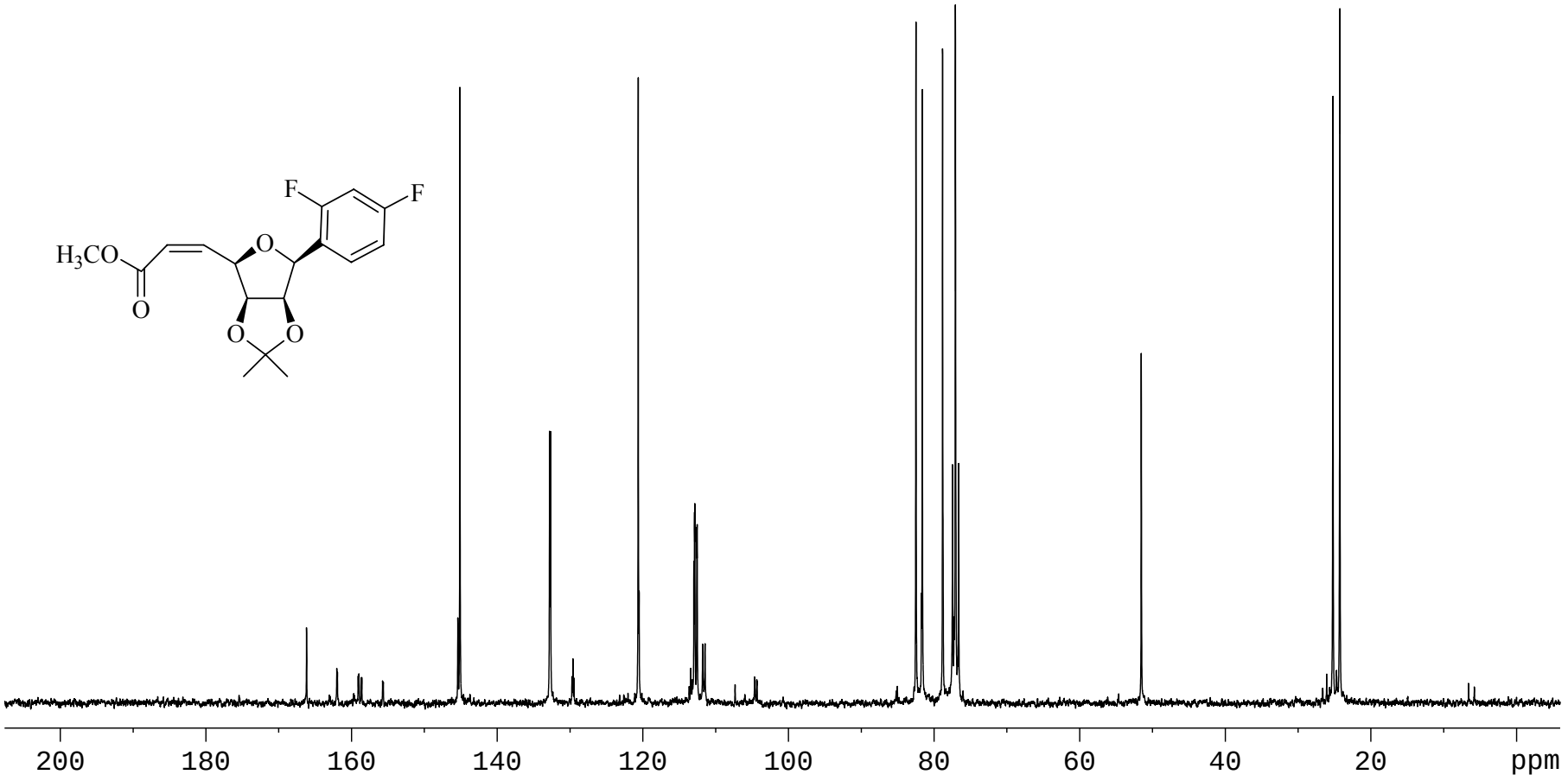
Supporting Fig 69: **^{1}H NMR Spectrum of 49 ($CDCl_3$, 294 K, 300 MHz)**



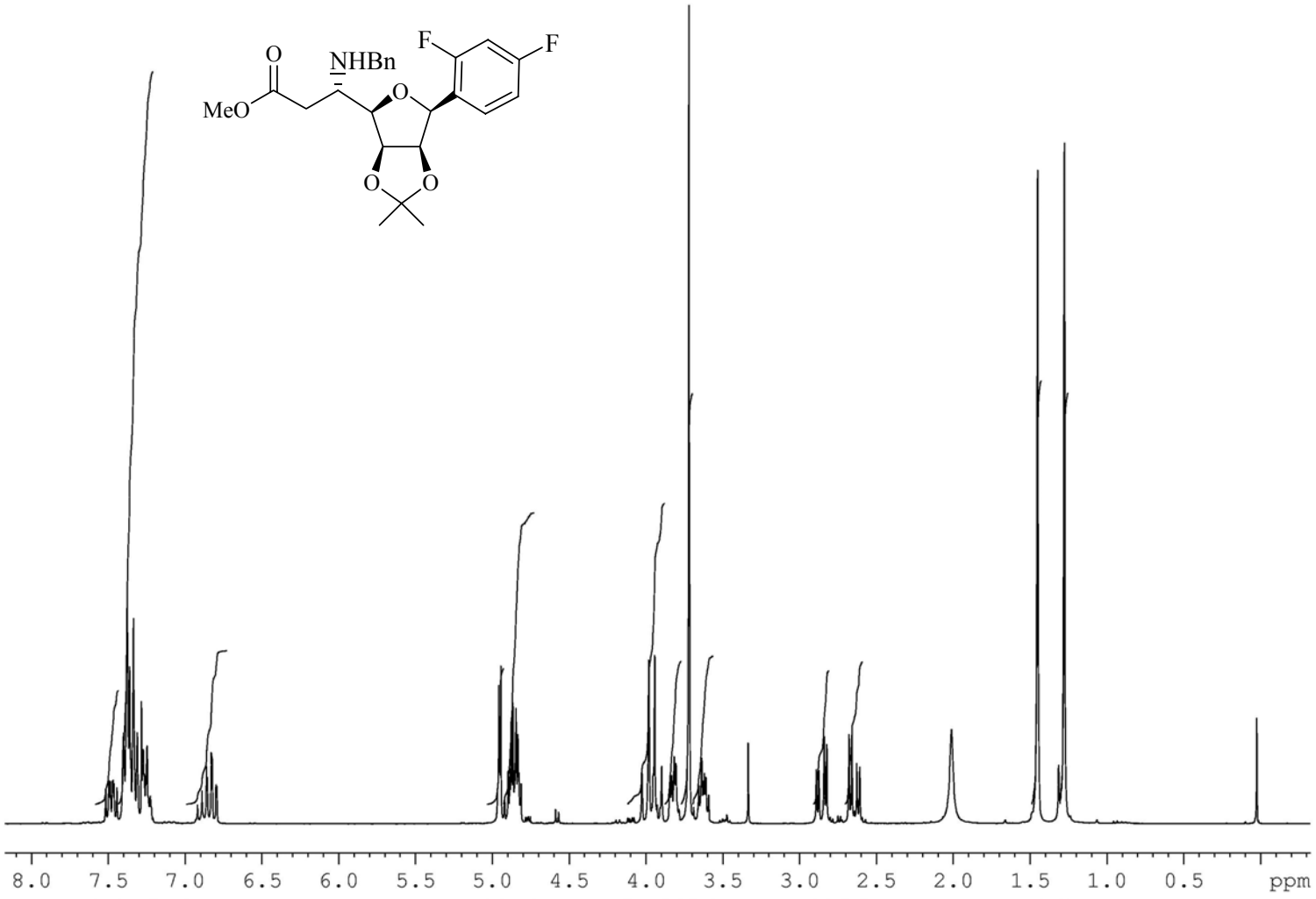
Supporting Fig 70: **^{13}C NMR Spectrum of 49 ($CDCl_3$, 294 K, 75 MHz)**



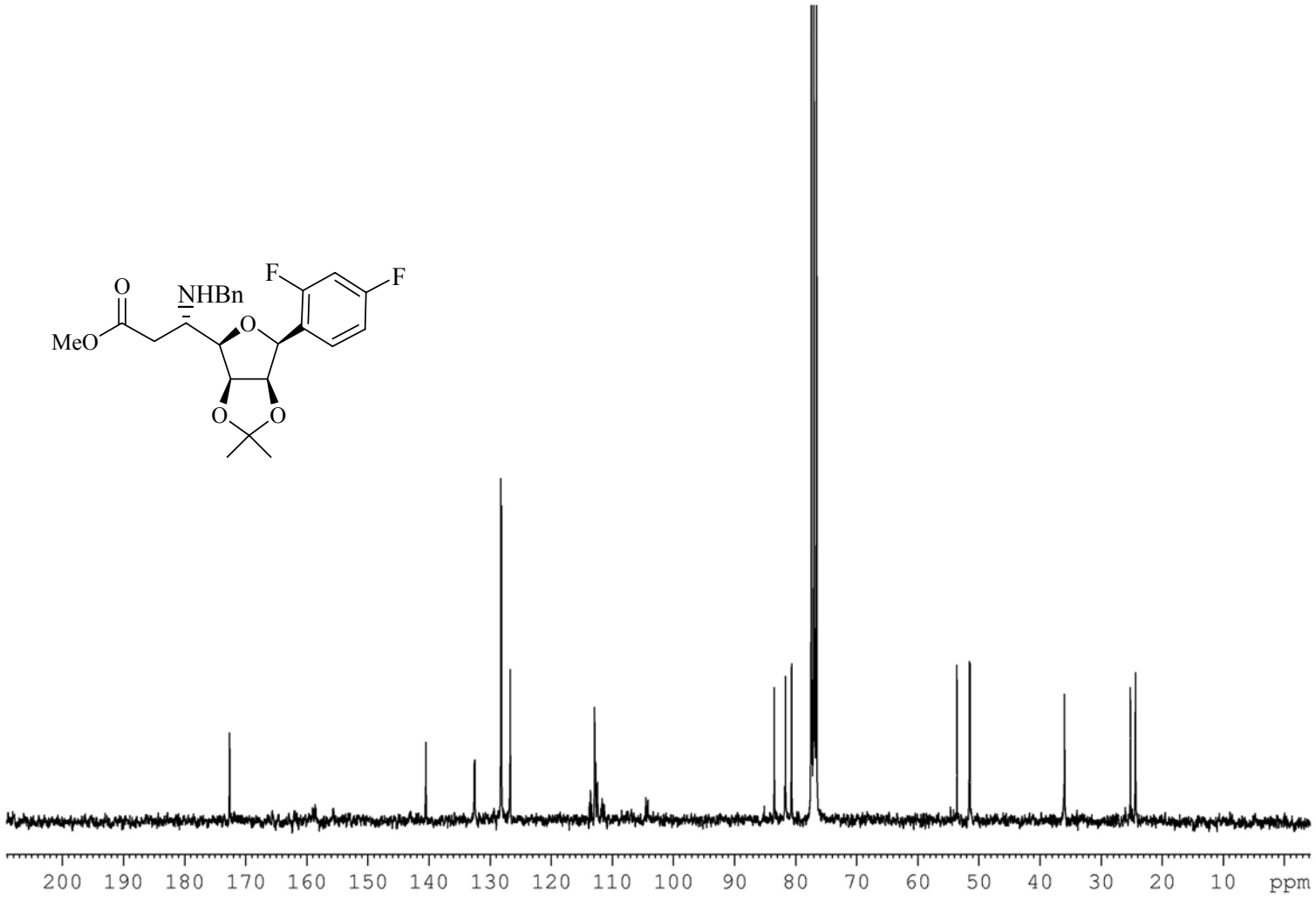
Supporting Fig 71: **^{1}H NMR Spectrum of 50 ($CDCl_3$, 294 K, 300 MHz)**



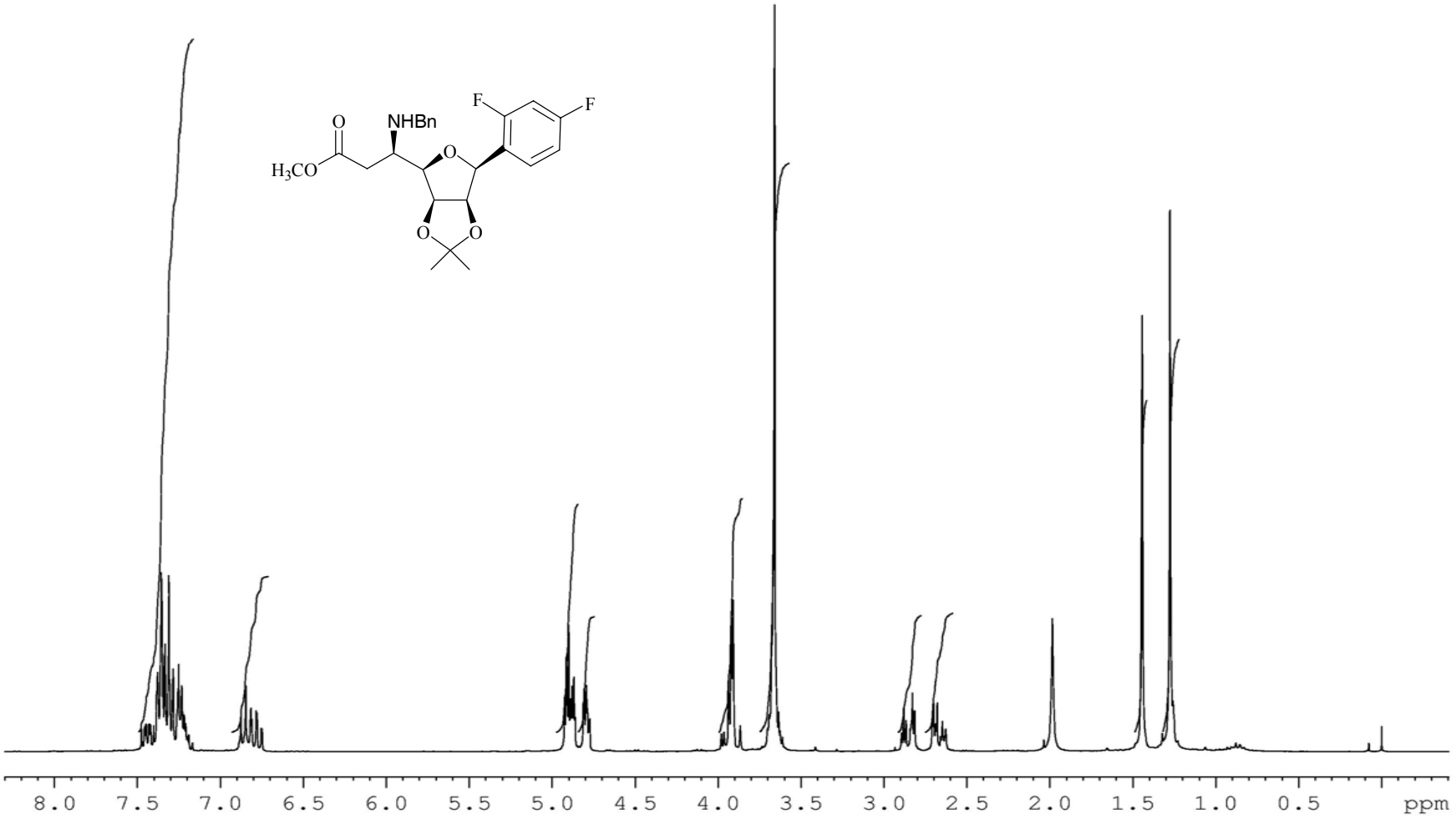
Supporting Fig 72: **^{13}C NMR Spectrum of 50 ($CDCl_3$, 294 K, 75 MHz)**



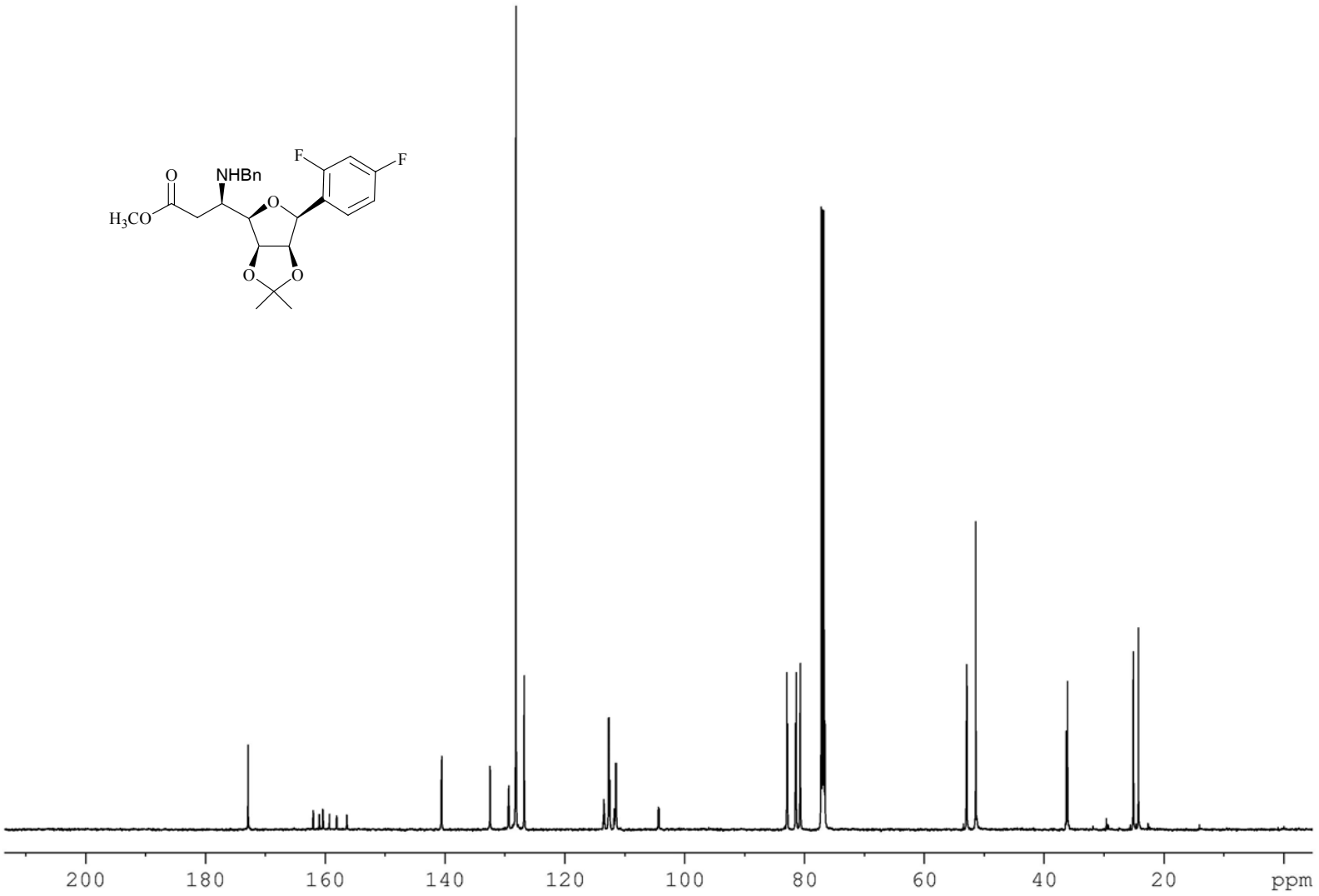
Supporting Fig 73: **^{1}H NMR Spectrum of 51 ($CDCl_3$, 294 K, 300 MHz)**



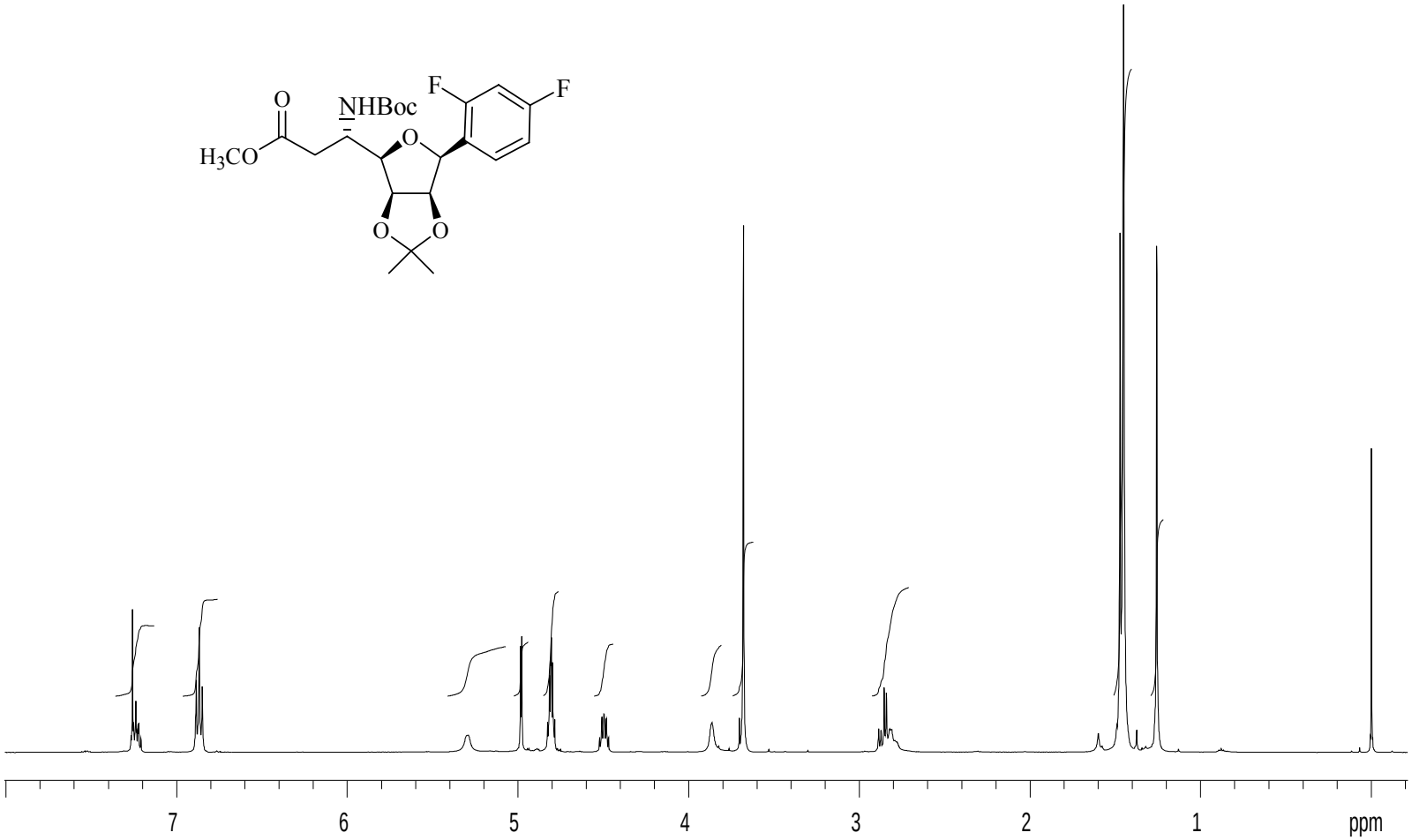
Supporting Fig 74: ^{13}**C NMR Spectrum of 51 (CDCl$_3$, 294 K, 75 MHz)**



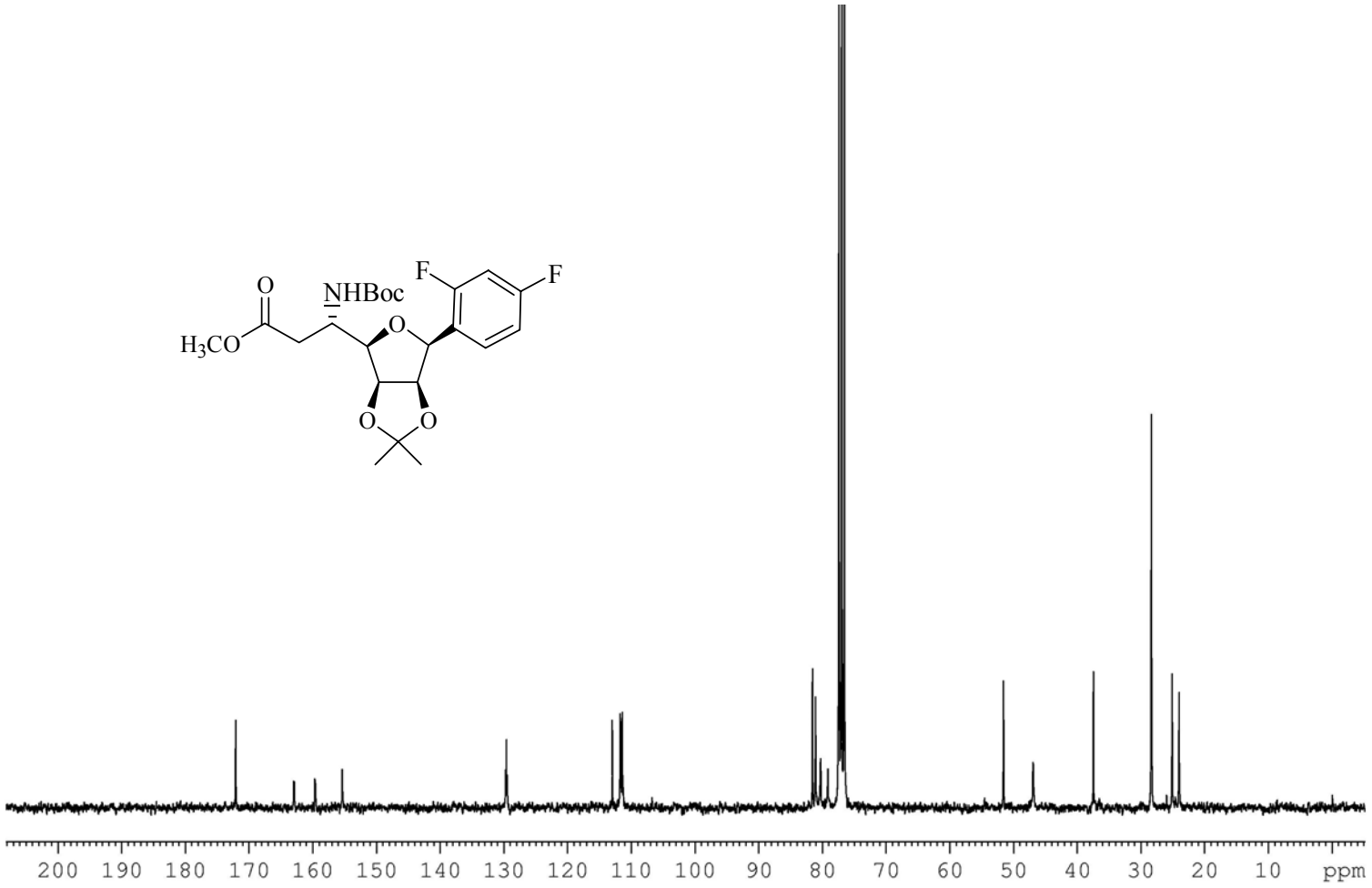
Supporting Fig 75: **^{1}H NMR Spectrum of 52 ($CDCl_3$, 294 K, 300 MHz)**



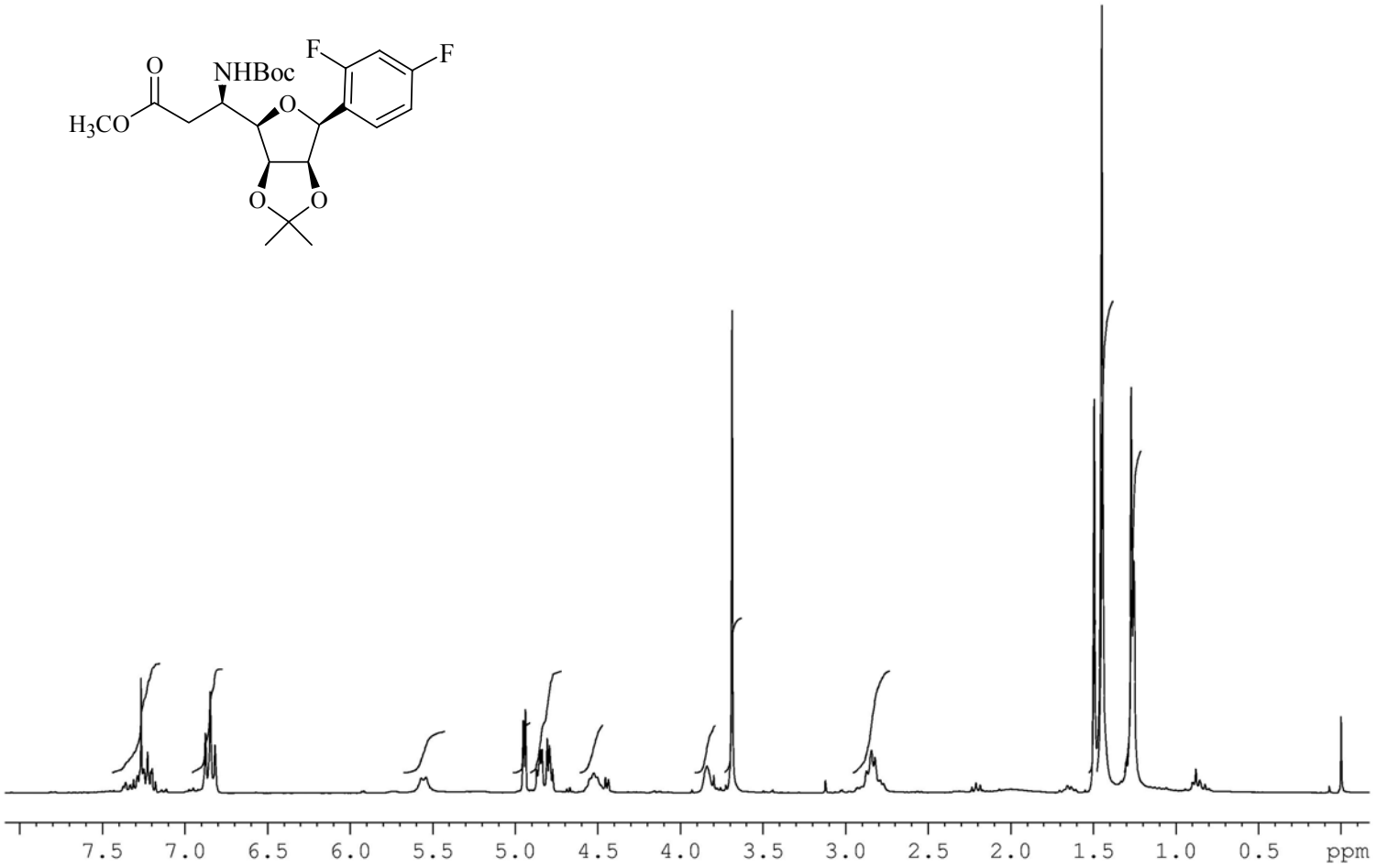
Supporting Fig 76: ^{13}C NMR Spectrum of 52 ($CDCl_3$, 298 K, 150 MHz)



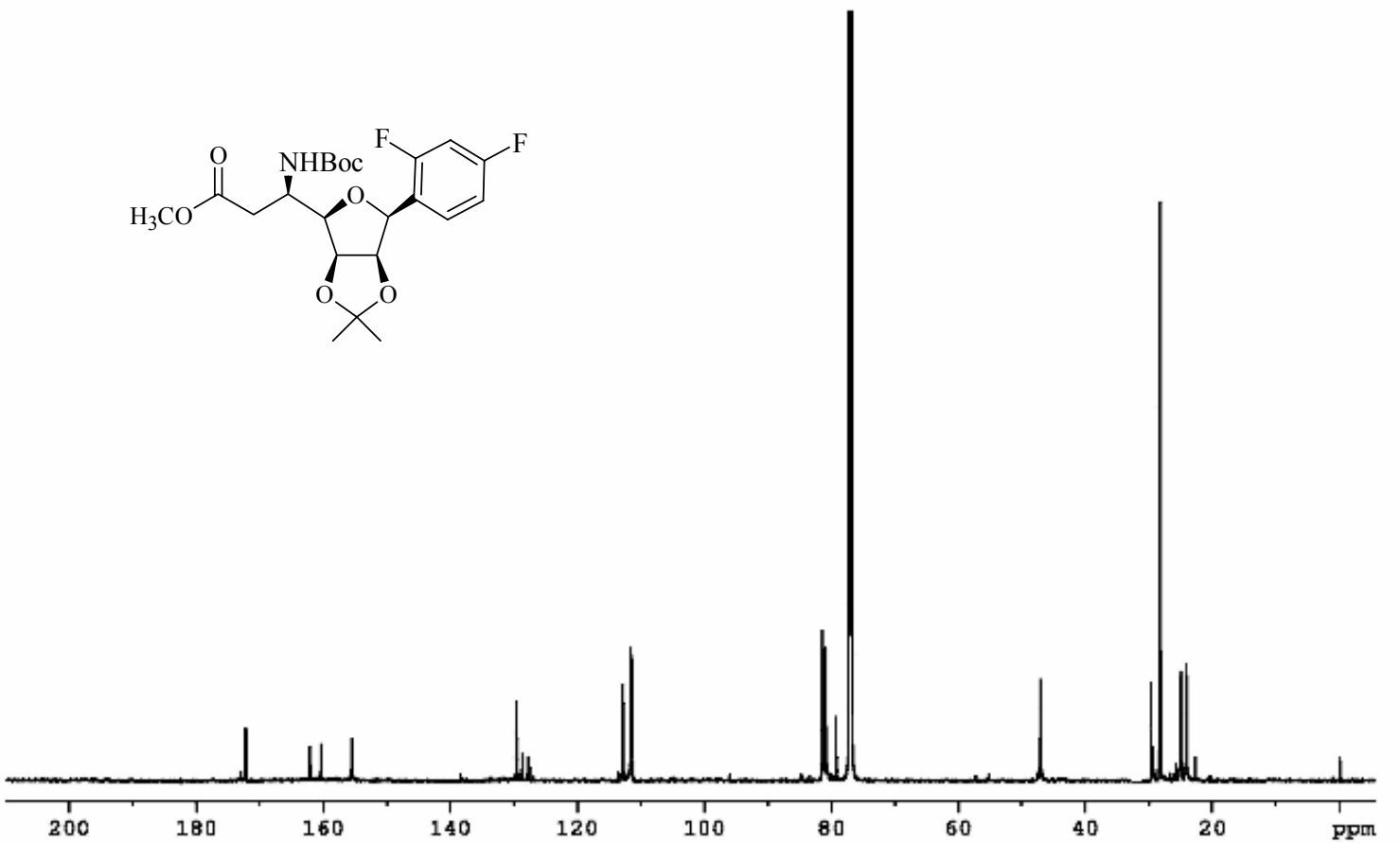
Supporting Fig 77: ^{1}H NMR Spectrum of 3 ($CDCl_3$, 303 K, 500 MHz)



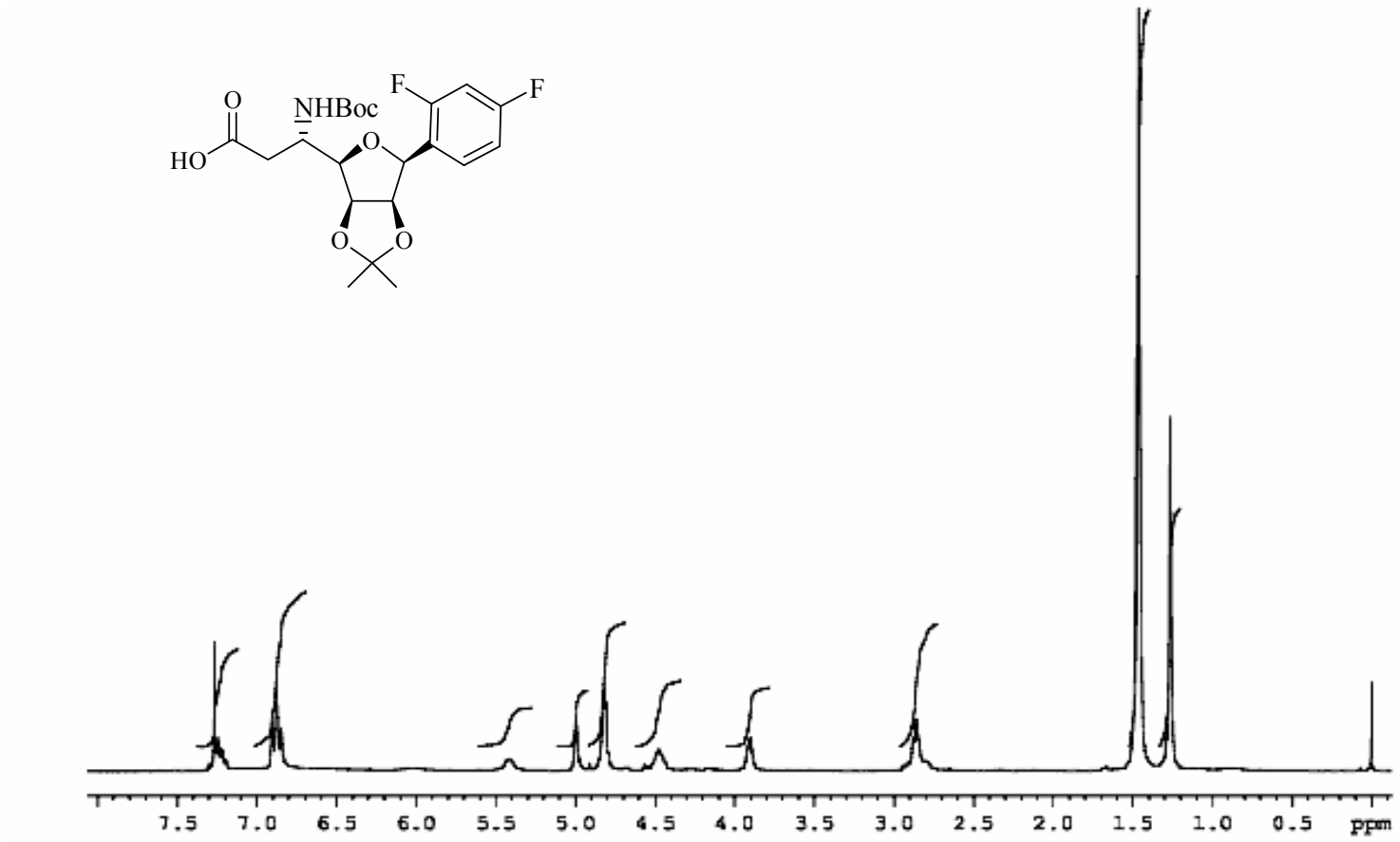
Supporting Fig 78: ^{13}C NMR Spectrum of 3 ($CDCl_3$, 294 K, 75 MHz)



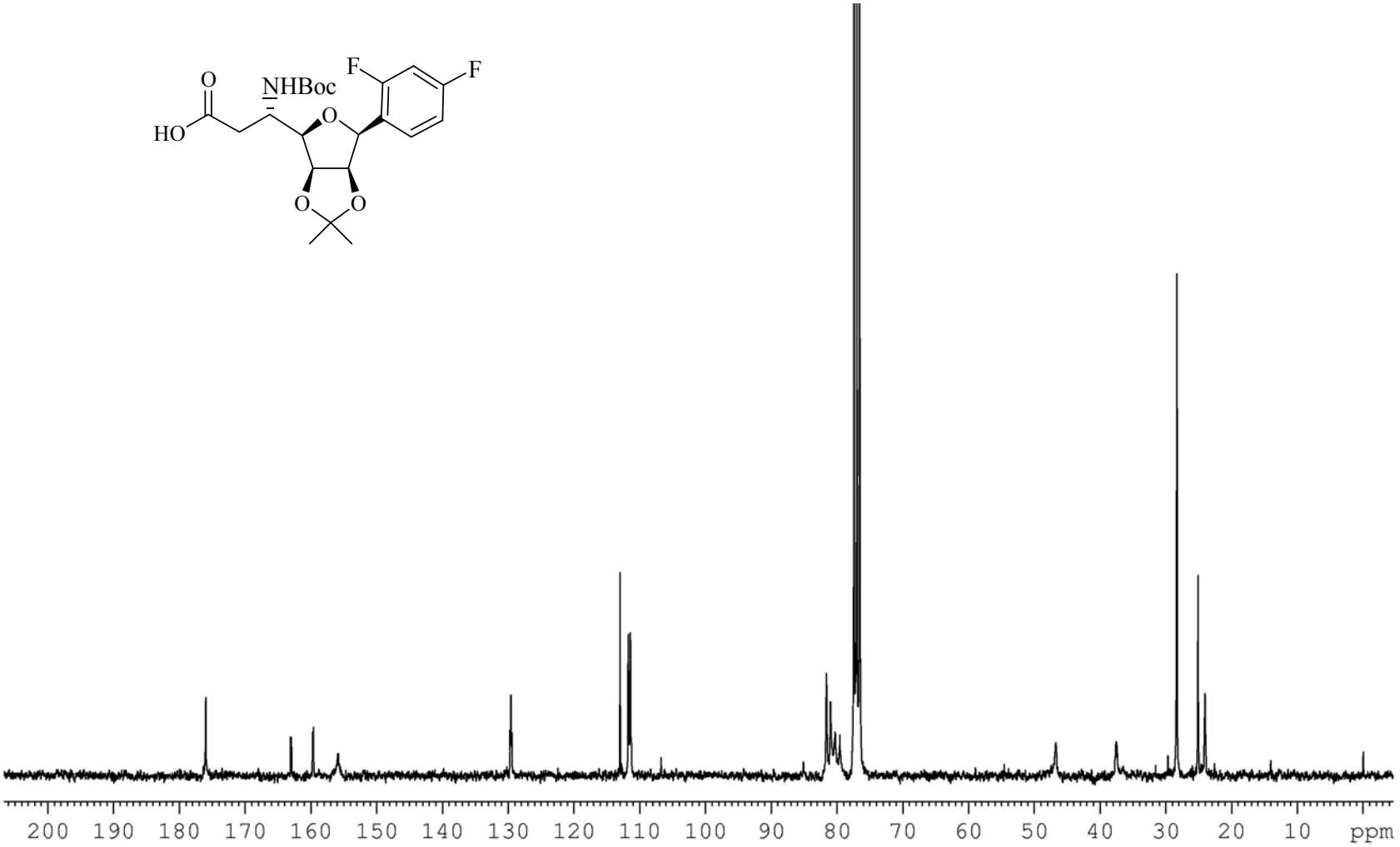
Supporting Fig 79: ^{1}H NMR Spectrum of 4 ($CDCl_3$, 294 K, 300 MHz)



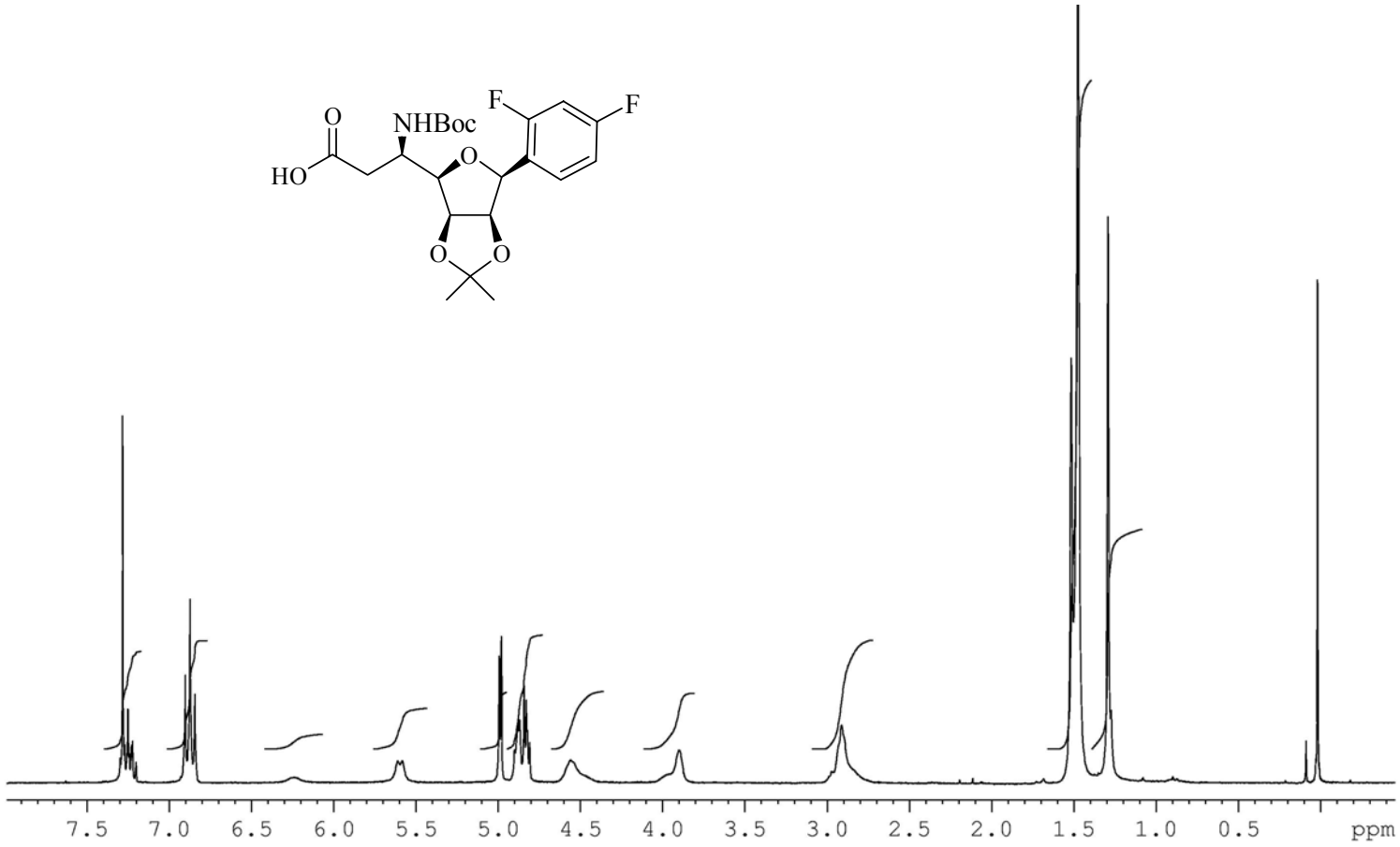
Supporting Fig 80: ^{13}C NMR Spectrum of 4 ($CDCl_3$, 294 K, 75 MHz)



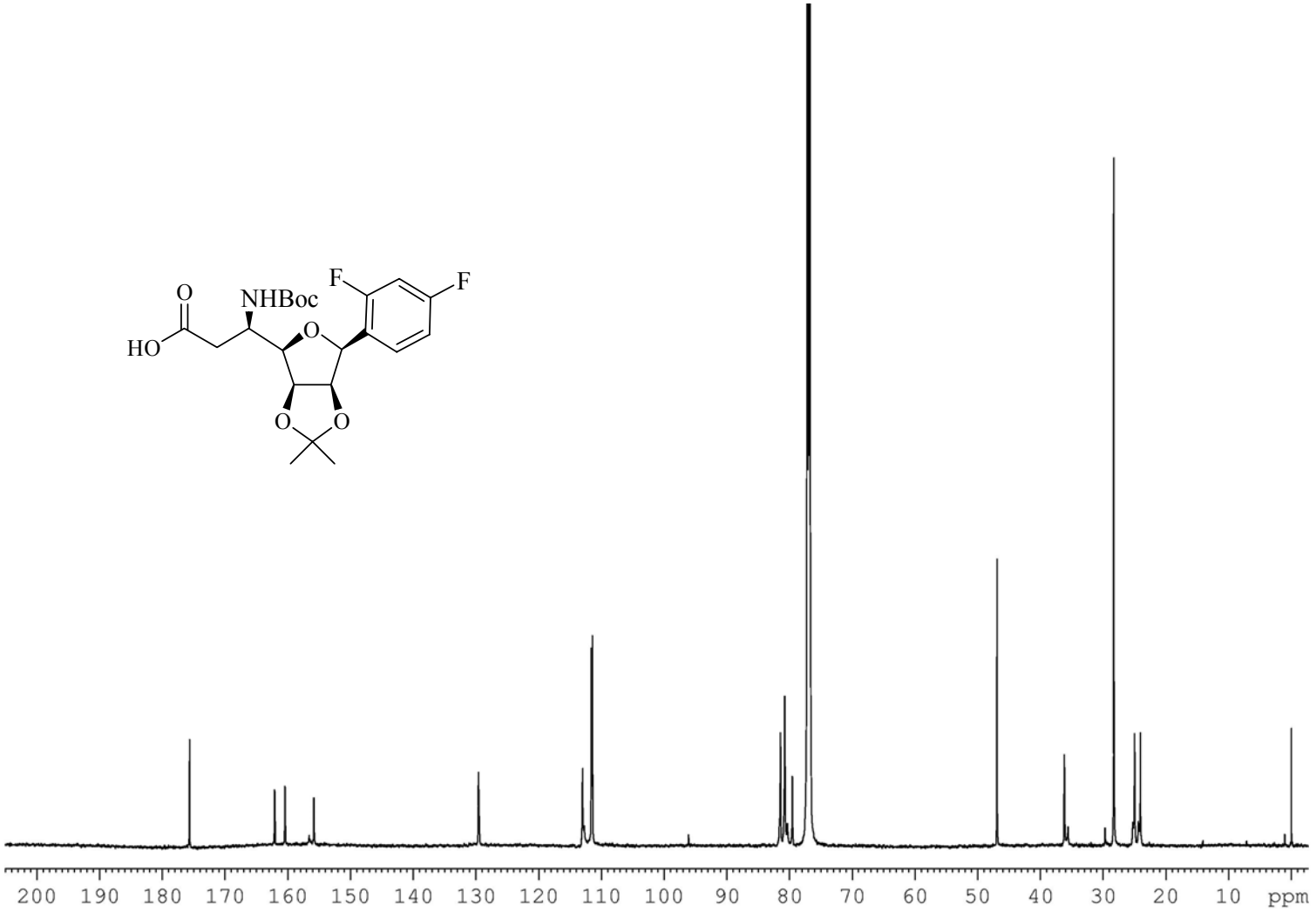
Supporting Fig 81: ^{1}H NMR Spectrum of 55 ($CDCl_3$, 294 K, 300 MHz)



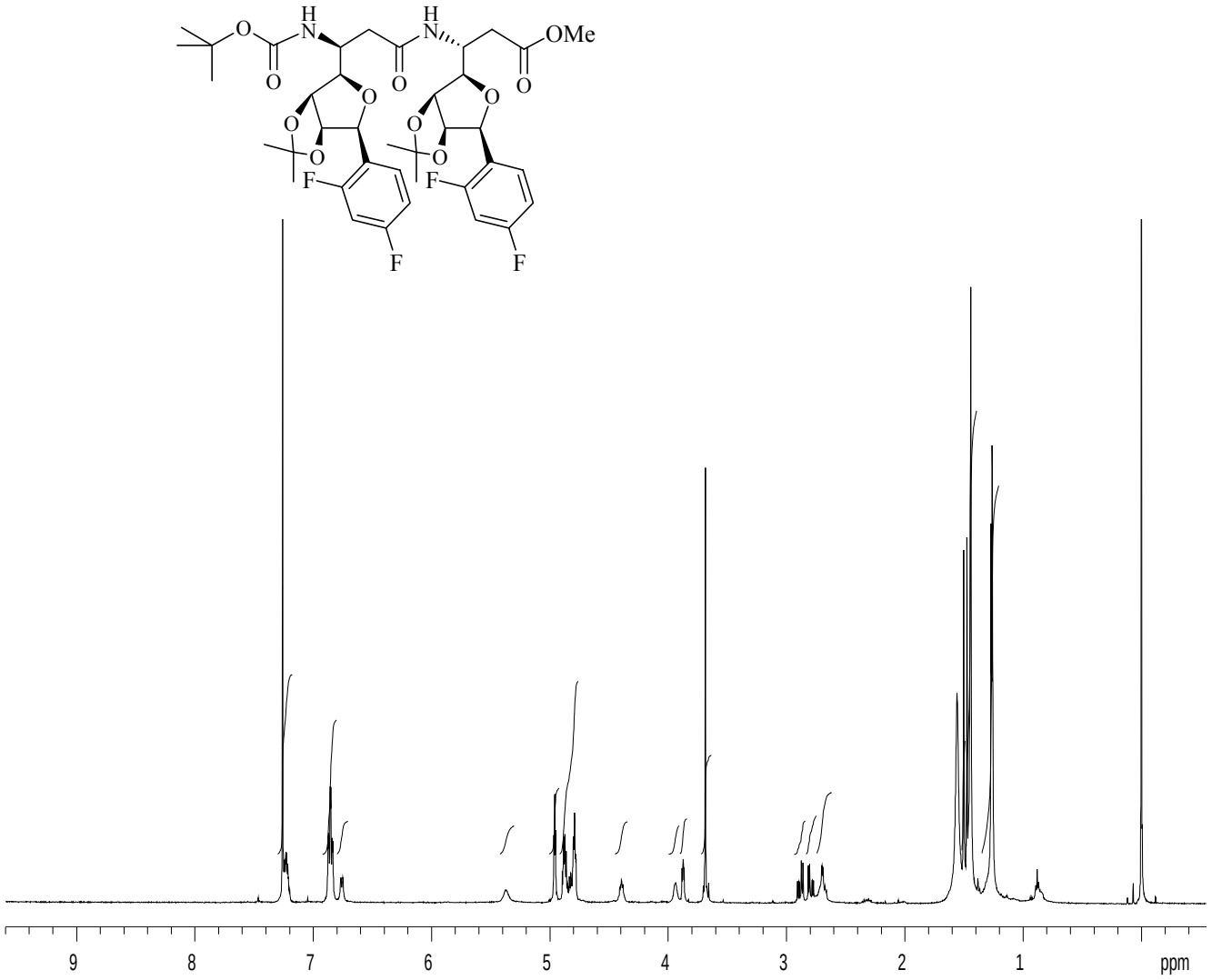
Supporting Fig 82: ^{13}C NMR Spectrum of 55 ($CDCl_3$, 294 K, 75 MHz)



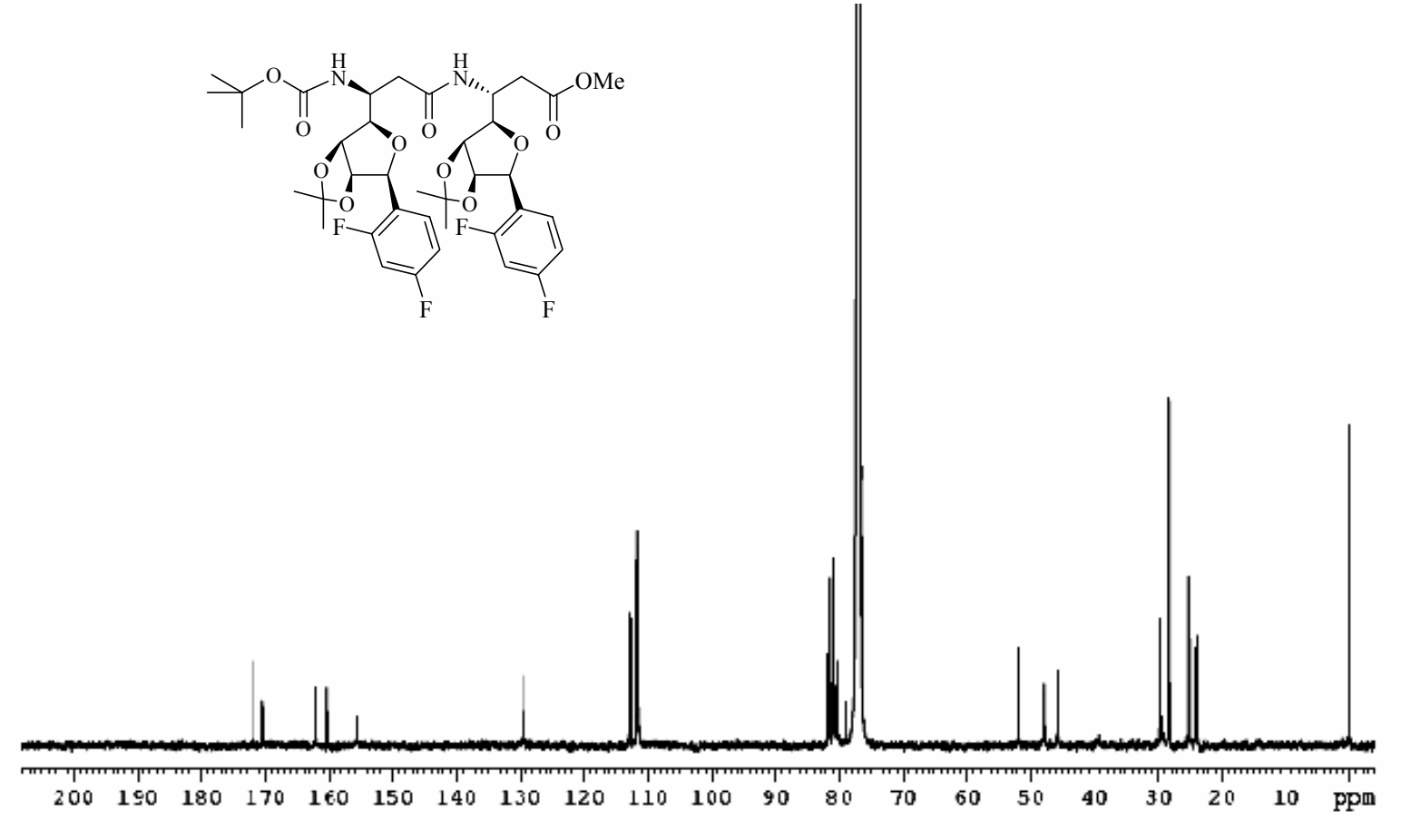
Supporting Fig 83: ^{1}H NMR Spectrum of 56 ($CDCl_3$, 294 K, 300 MHz)



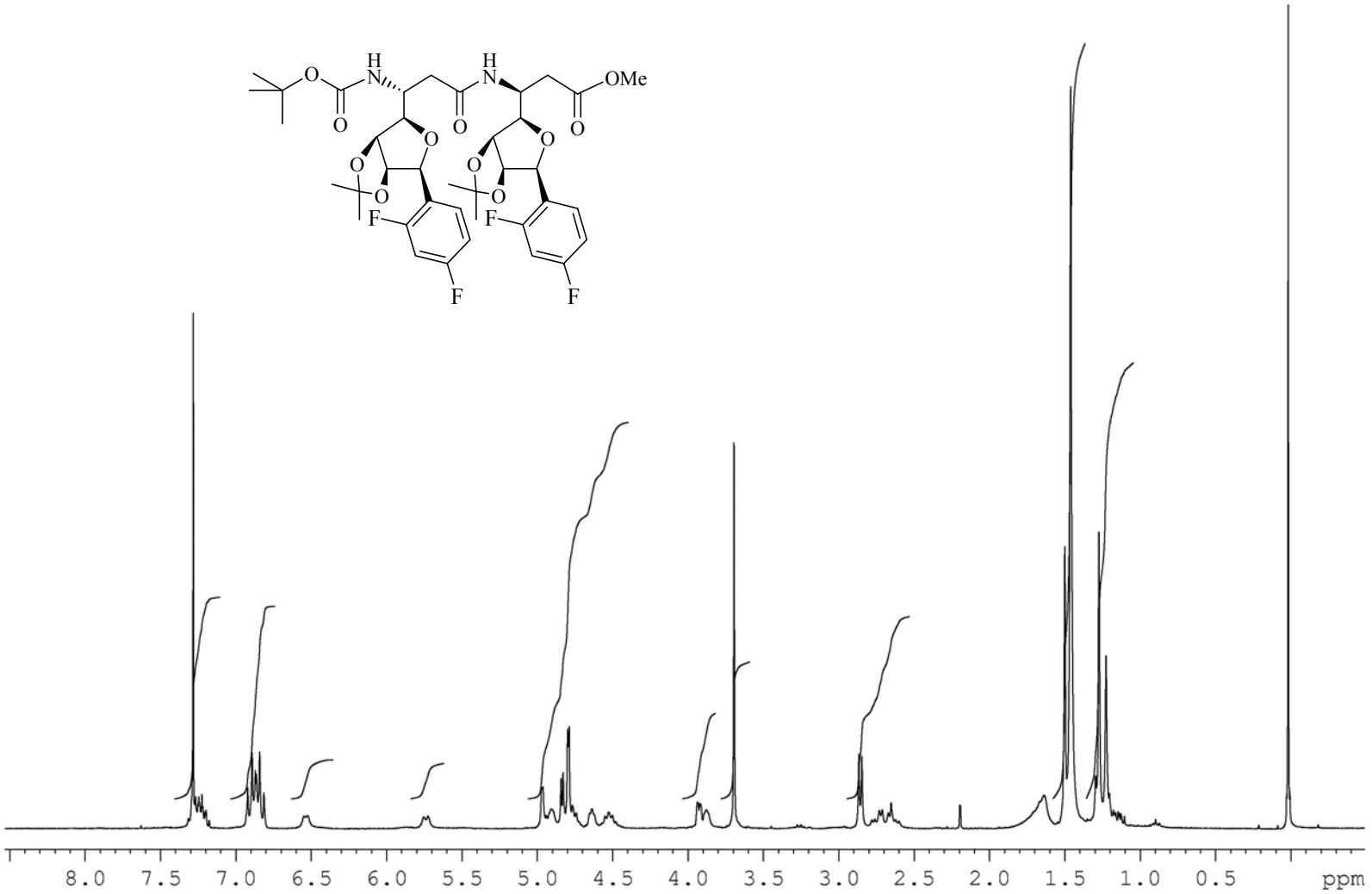
Supporting Fig 84: ^{13}C NMR Spectrum of 56 ($CDCl_3$, 294 K, 75 MHz)



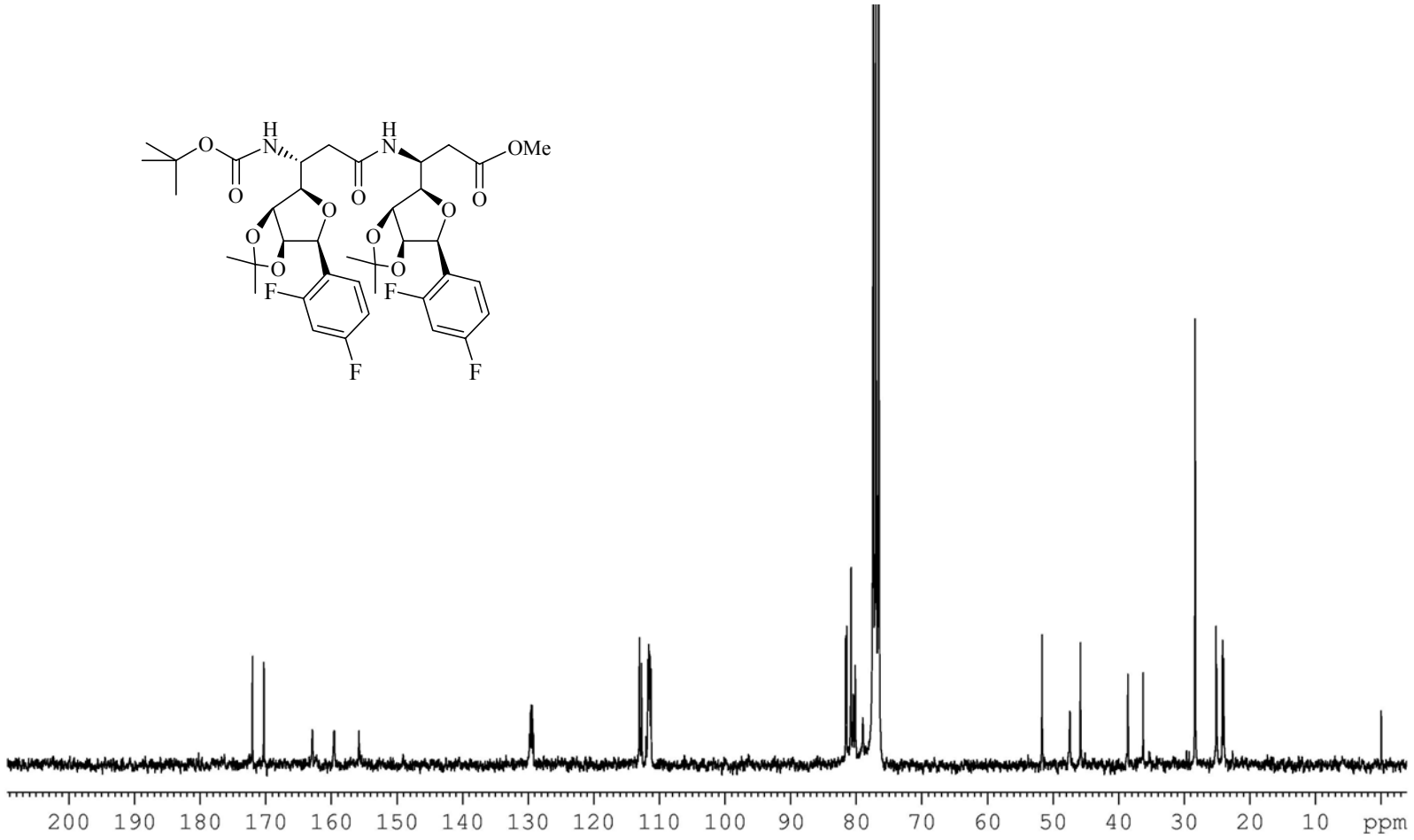
Supporting Fig 85: ^{1}H NMR Spectrum of 59 ($CDCl_3$, 303 K, 500 MHz)



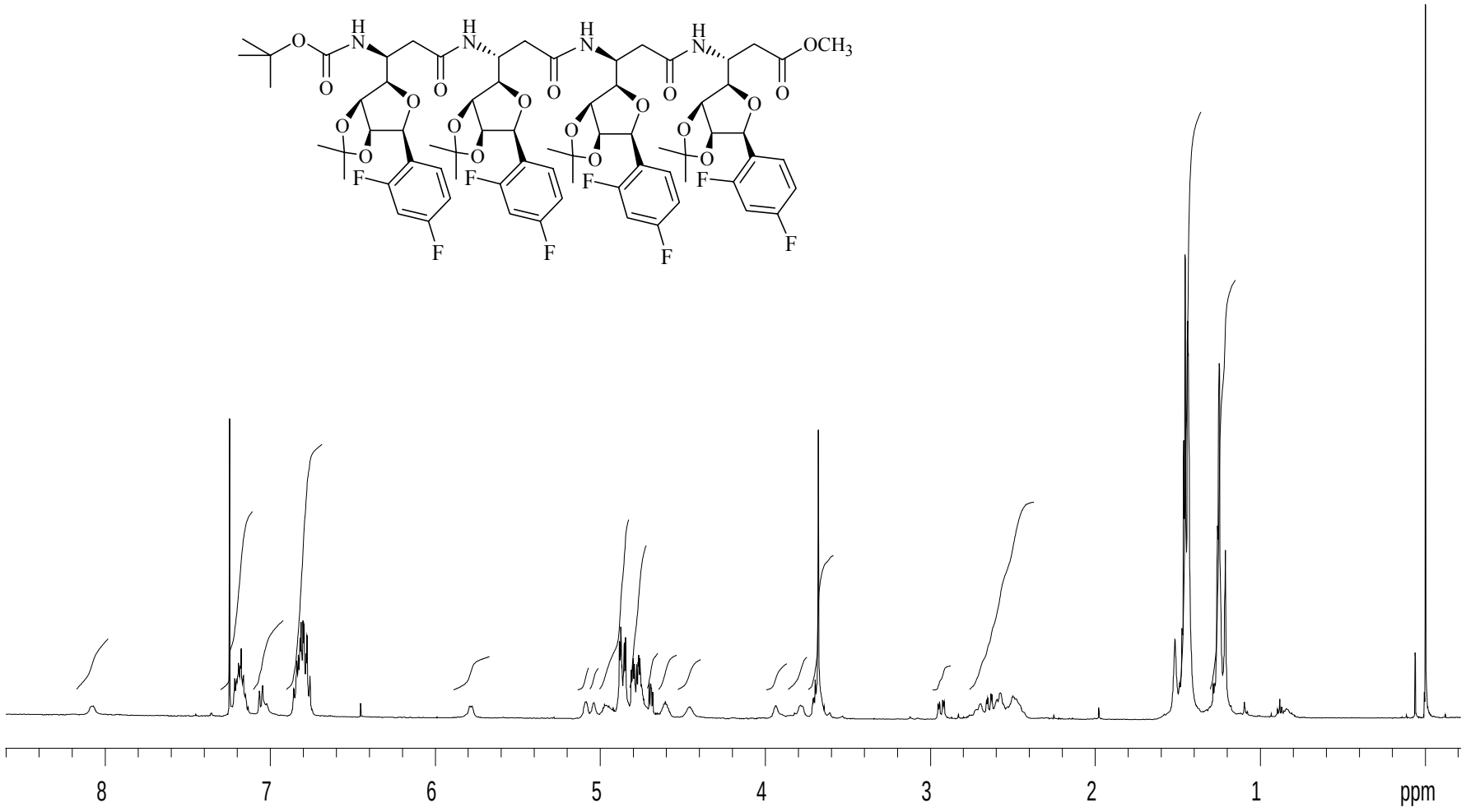
Supporting Fig 86: ^{13}C NMR Spectrum of 59 ($CDCl_3$, 298 K, 150 MHz)



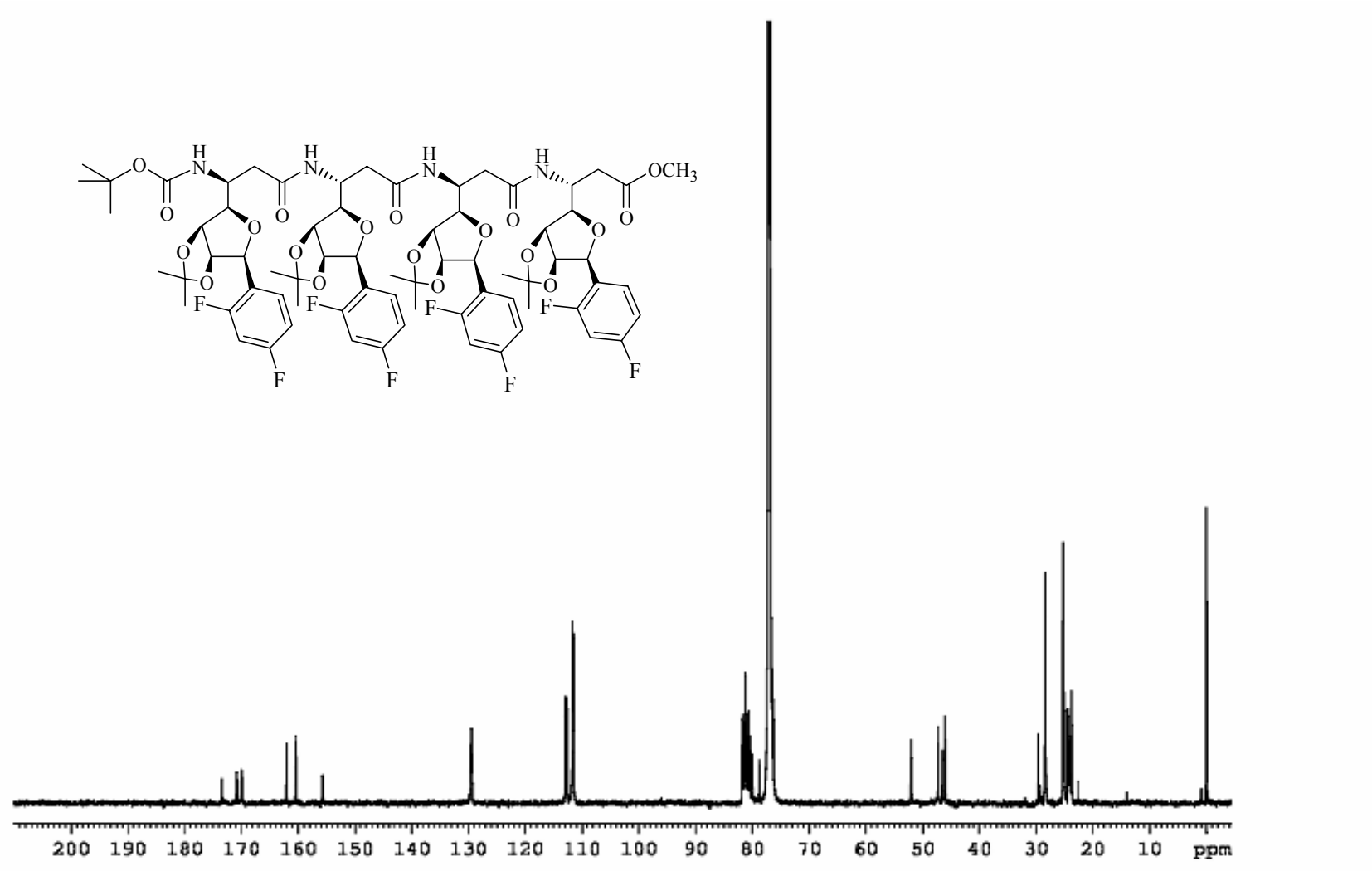
Supporting Fig 87: ^{1}H NMR Spectrum of 63 ($CDCl_3$, 294 K, 300 MHz)



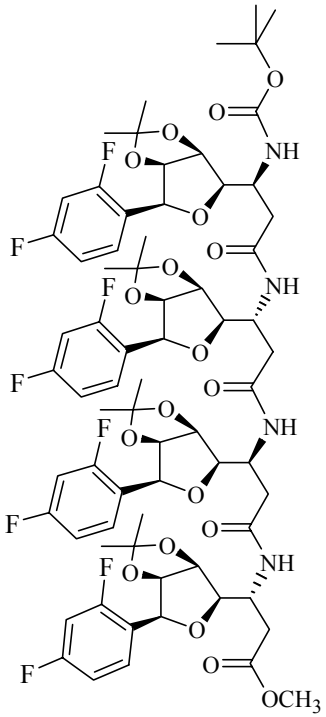
Supporting Fig 88: ^{13}C NMR Spectrum of 63 ($CDCl_3$, 298 K, 150 MHz)

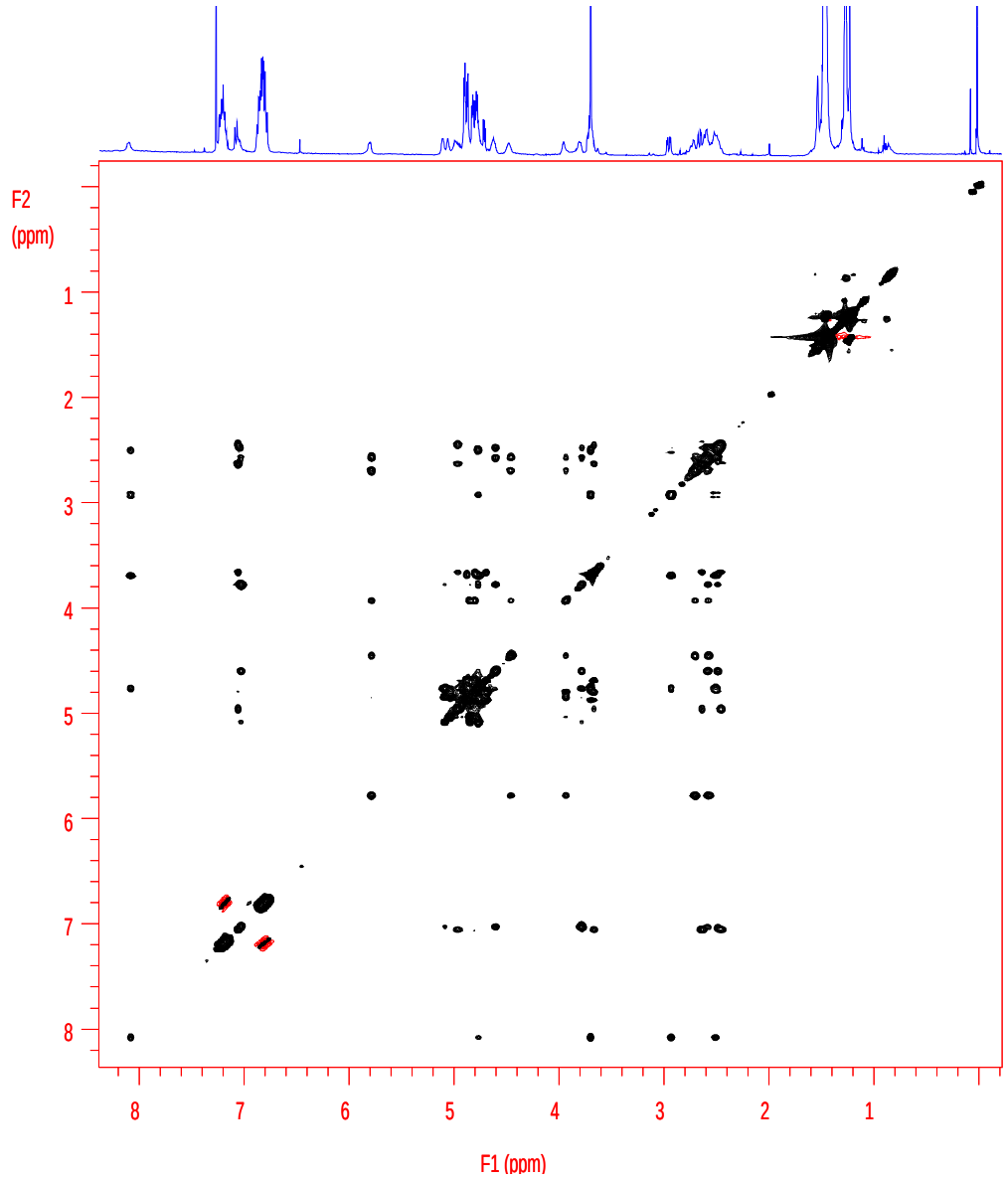


Supporting Fig 89: **^{1}H NMR Spectrum of 13 ($CDCl_3$, 303 K, 500 MHz)**

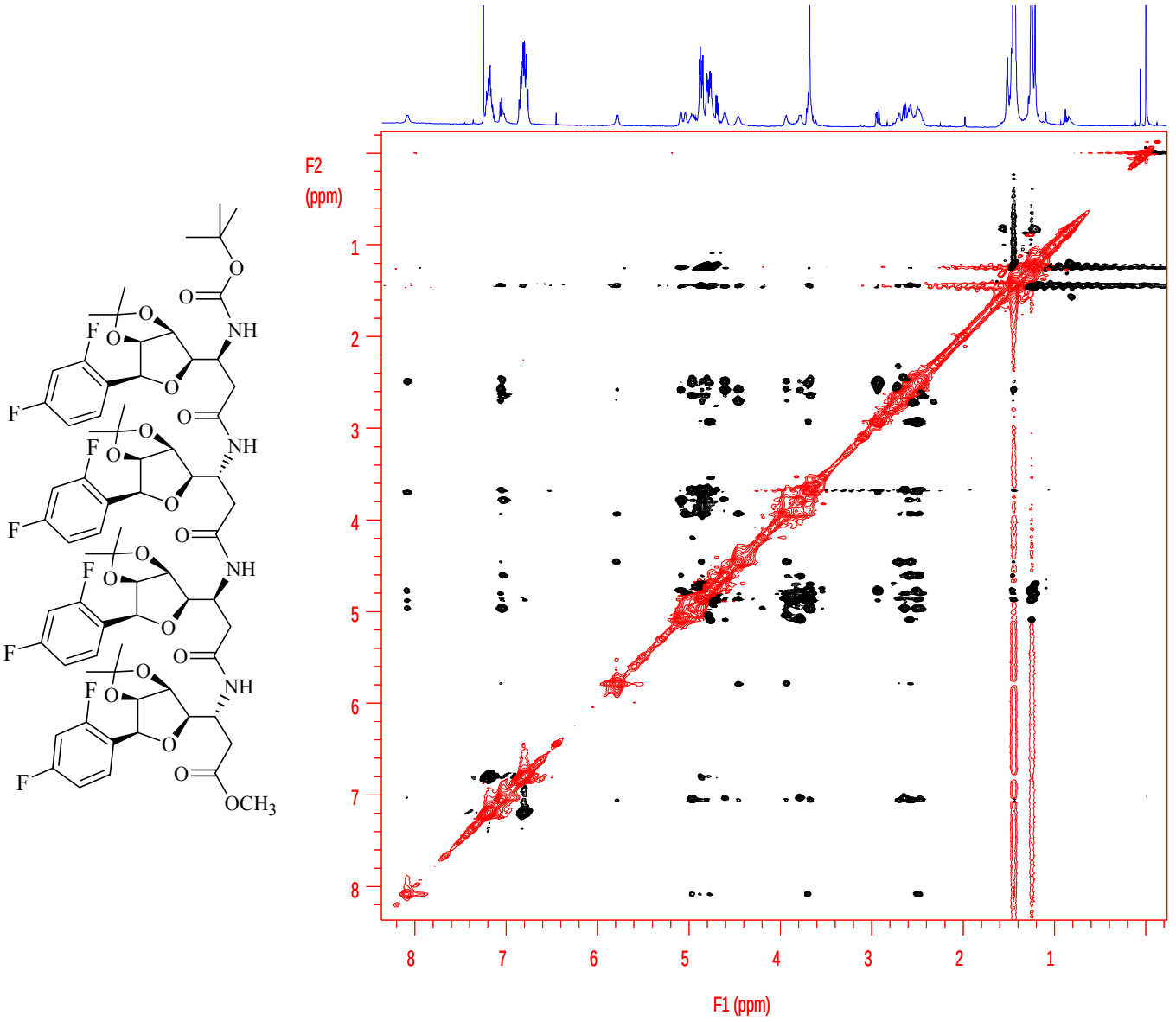


Supporting Fig 90: ^{13}C NMR Spectrum of 13 ($CDCl_3$, 298 K, 150 MHz)

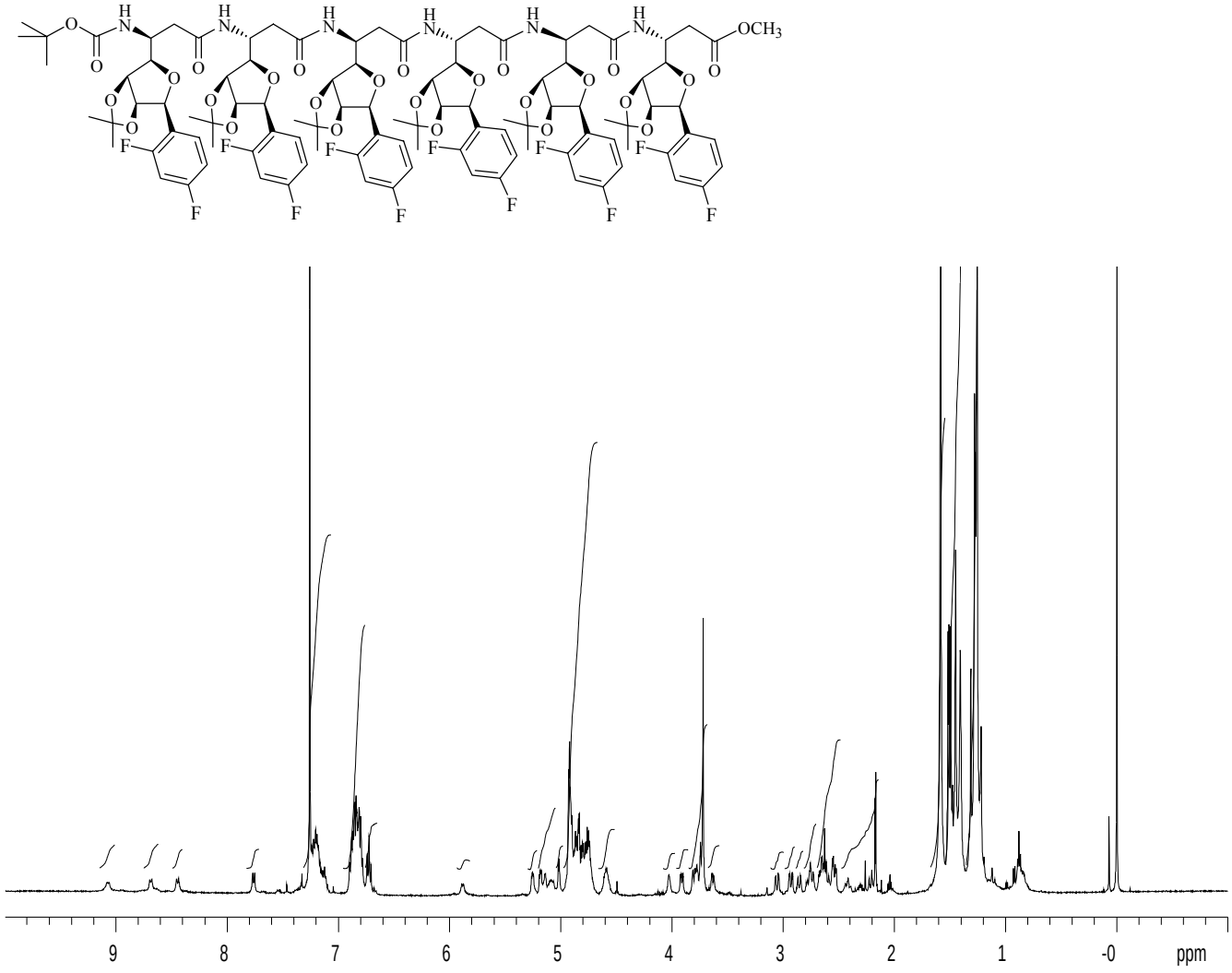




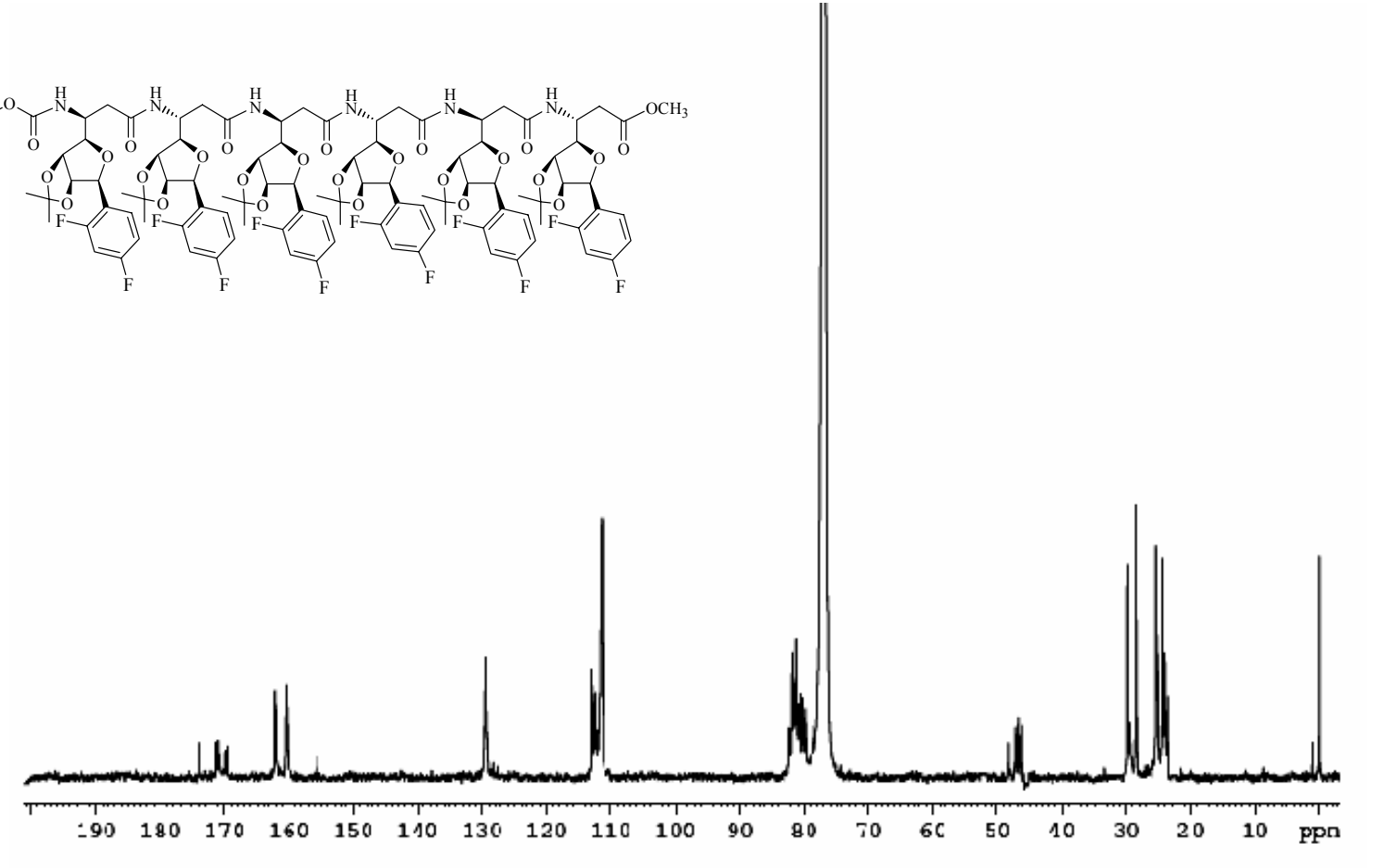
Supporting Fig 91: **TOCSY Spectrum of 13 ($CDCl_3$, 303 K, 500 MHz)**



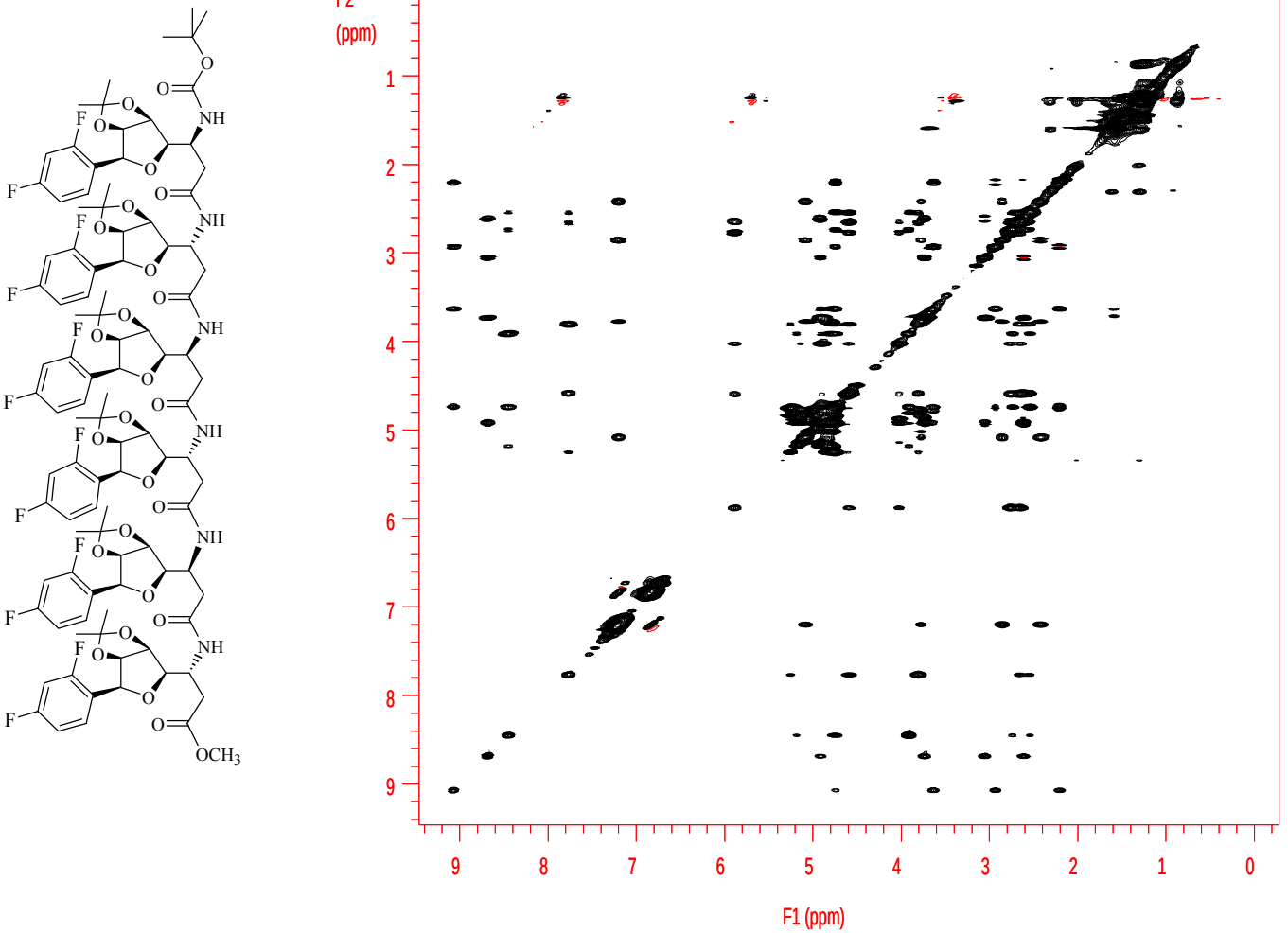
Supporting Fig 92: **ROESY Spectrum of 13 ($CDCl_3$, 303 K, 500 MHz)**



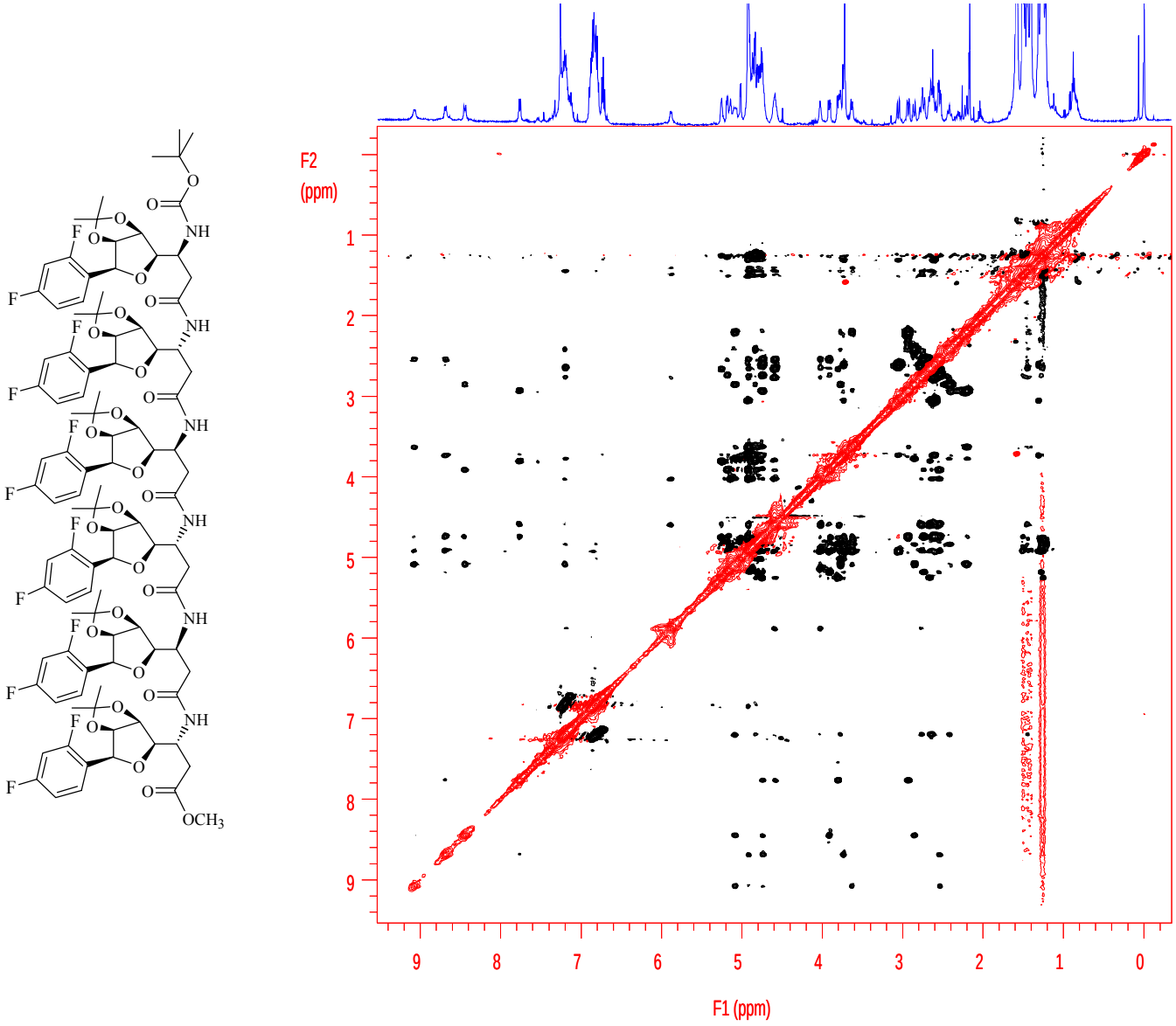
Supporting Fig 93: **^{1}H NMR Spectrum of 14 ($CDCl_3$, 303 K, 500 MHz)**



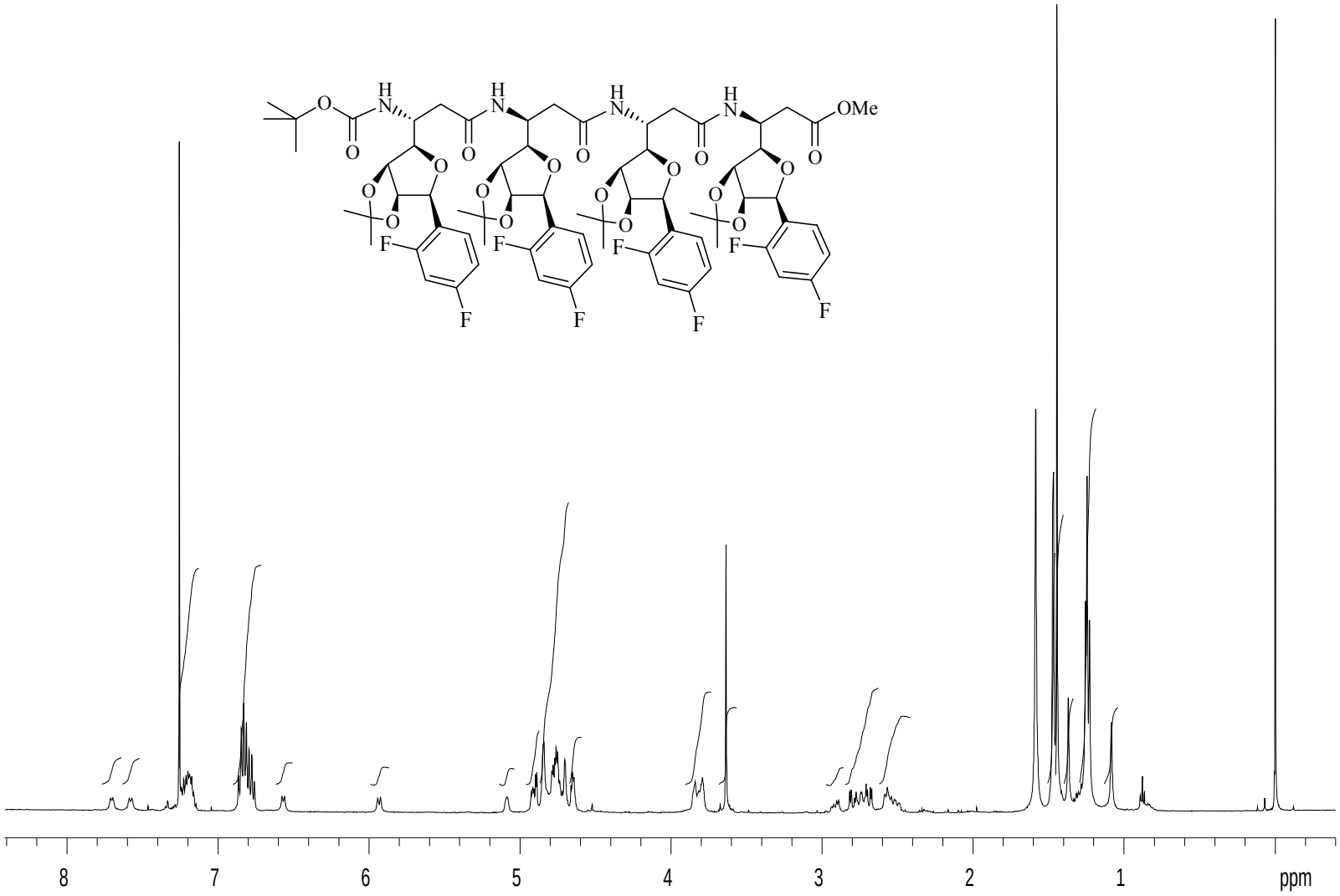
Supporting Fig 94: ^{13}**C NMR Spectrum of 14 ($CDCl_3$, 303 K, 150 MHz)**



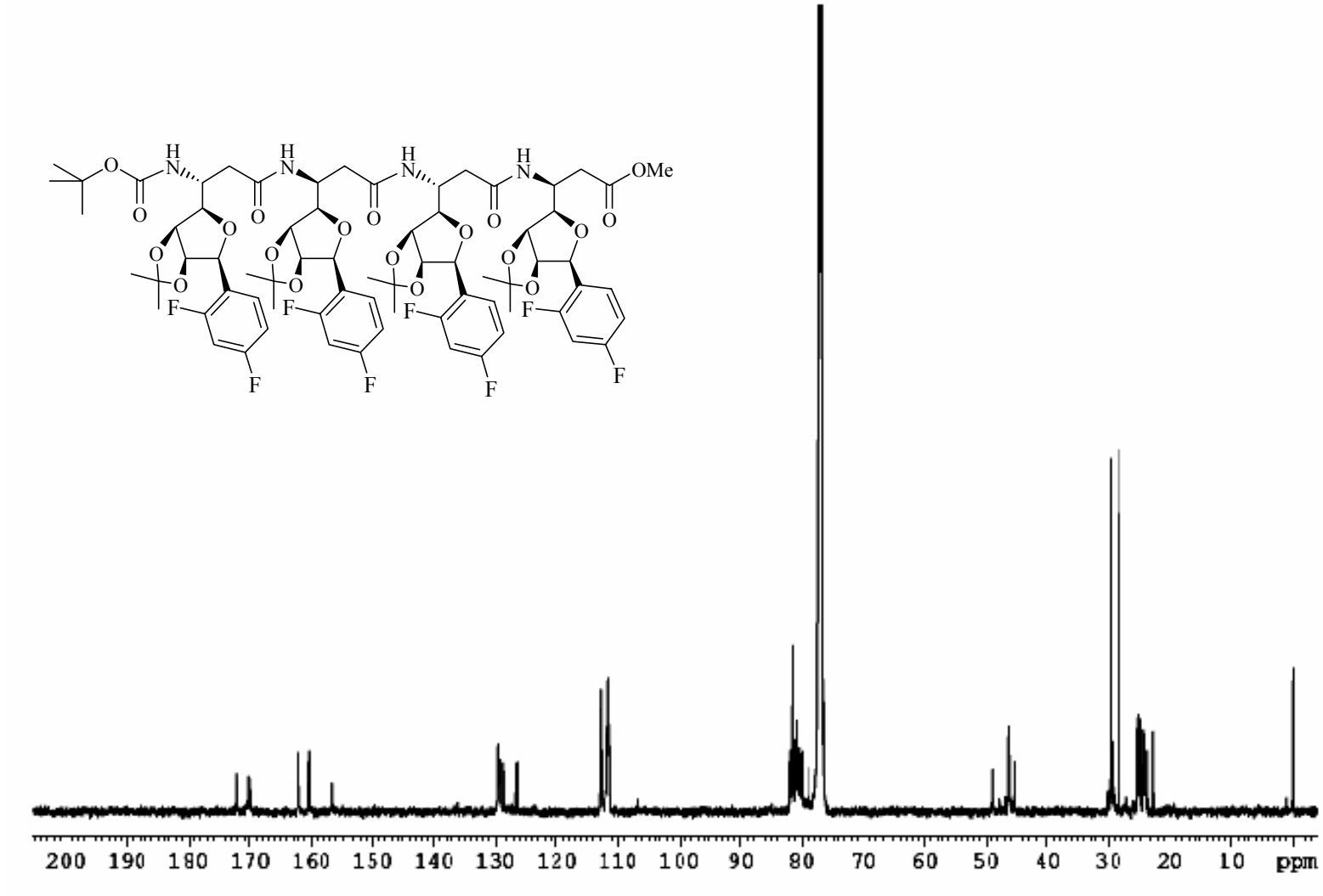
Supporting Fig 95: **TOCSY Spectrum of 14 ($CDCl_3$, 303 K, 500 MHz)**



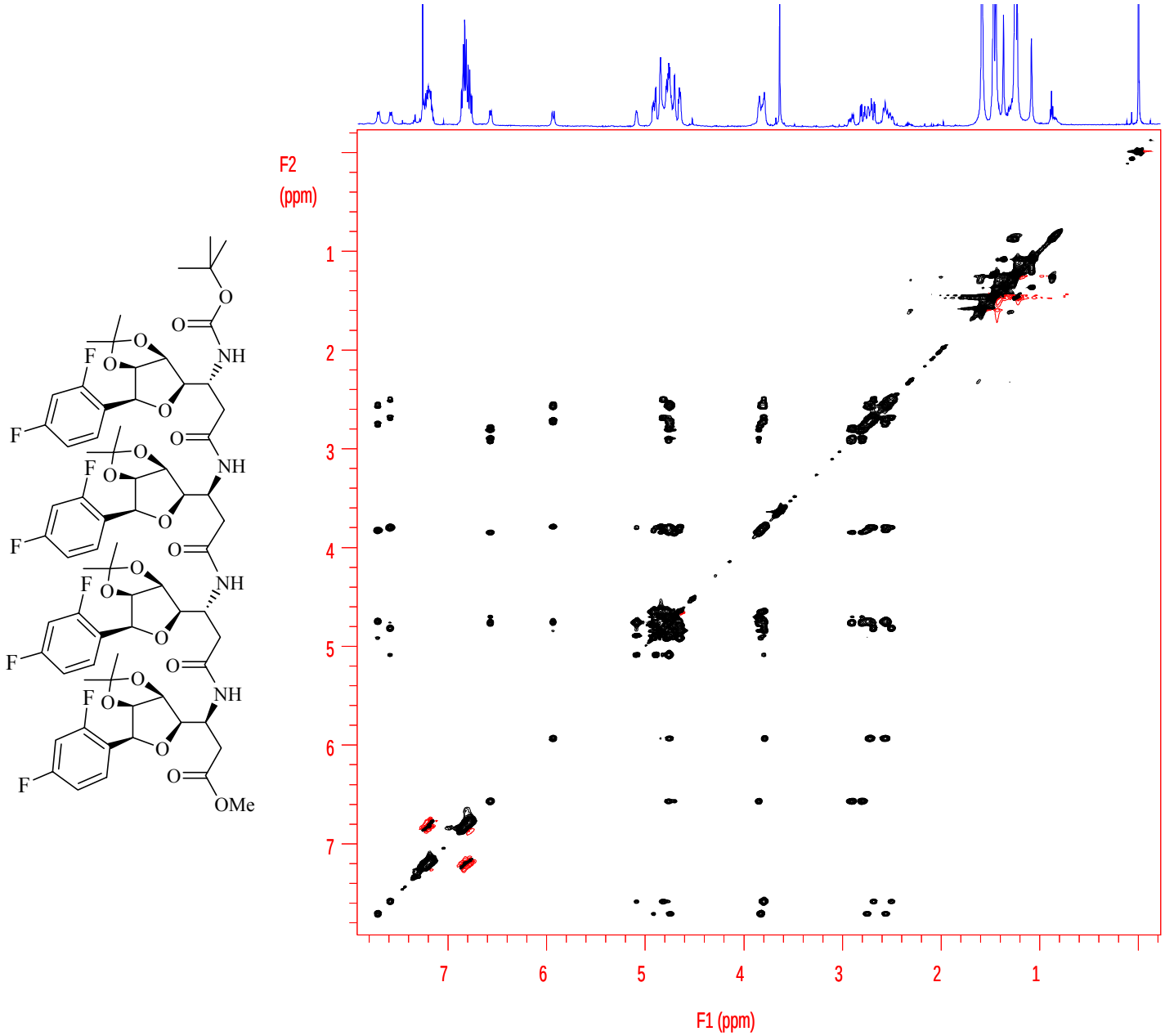
Supporting Fig 96: **ROESY Spectrum of 14 ($CDCl_3$, 303 K, 500 MHz)**



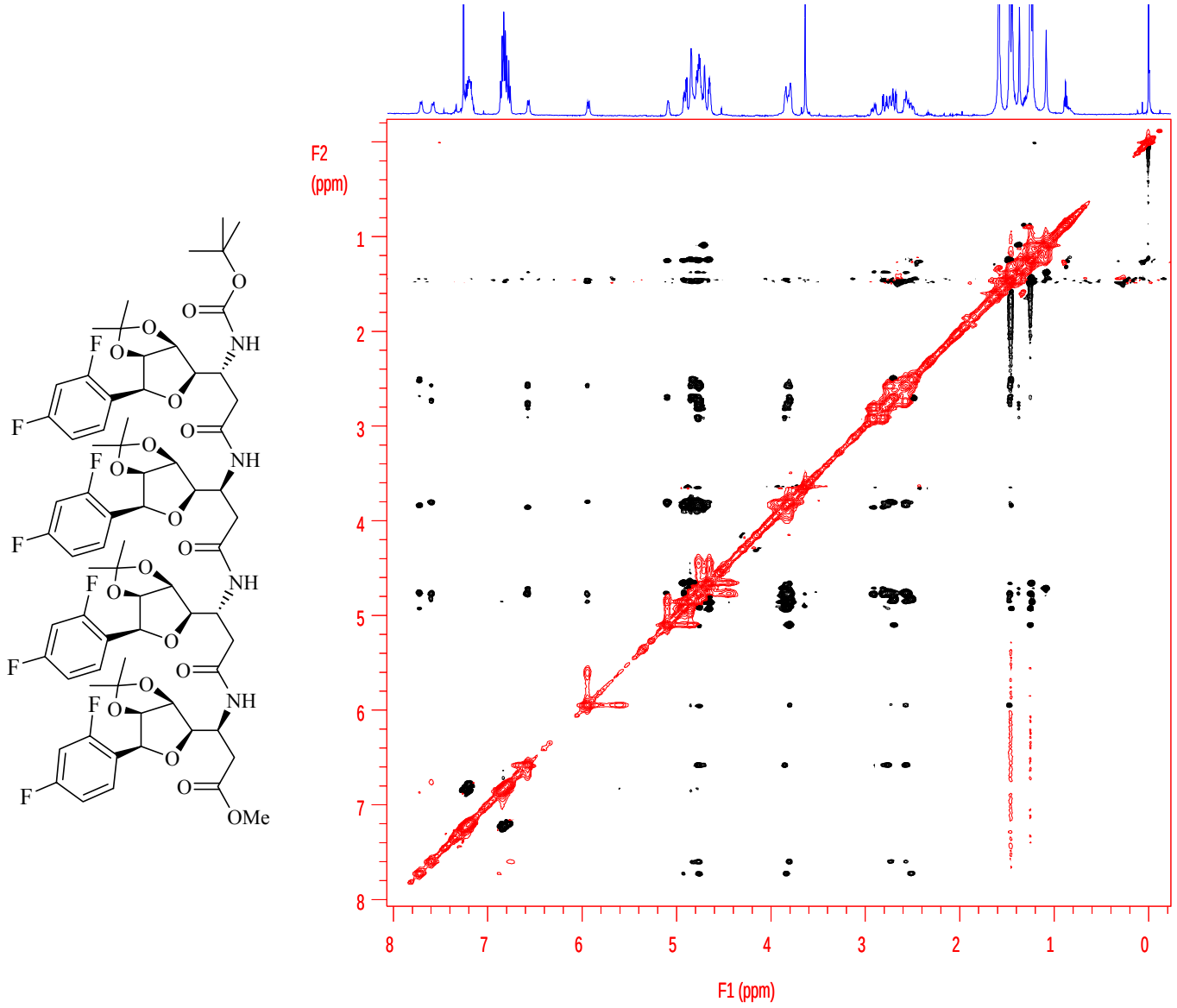
Supporting Fig 97: ^{1}H NMR Spectrum of 15 ($CDCl_3$, 303 K, 500 MHz)



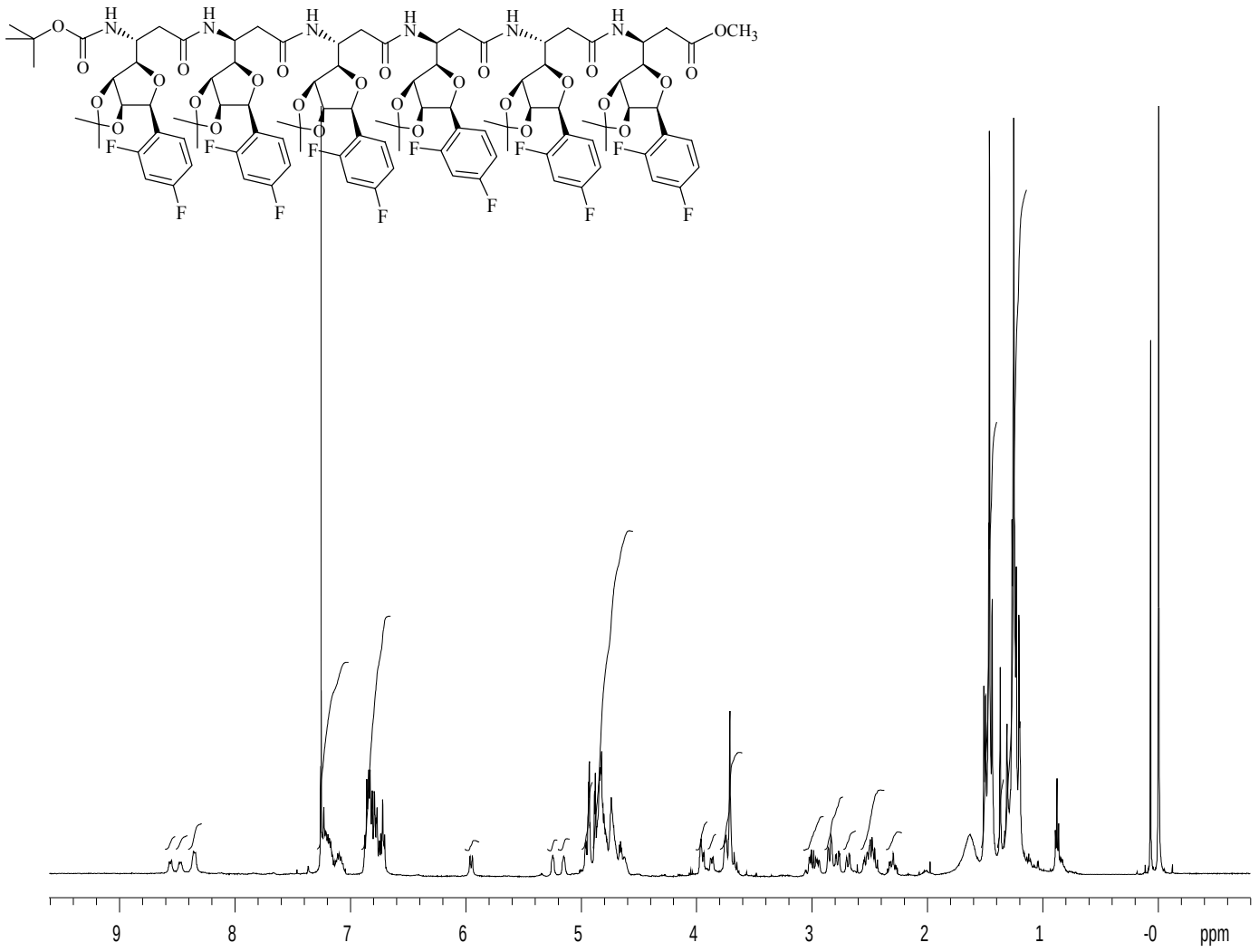
Supporting Fig 98: ^{13}C NMR Spectrum of 15 ($CDCl_3$, 298 K, 150 MHz)



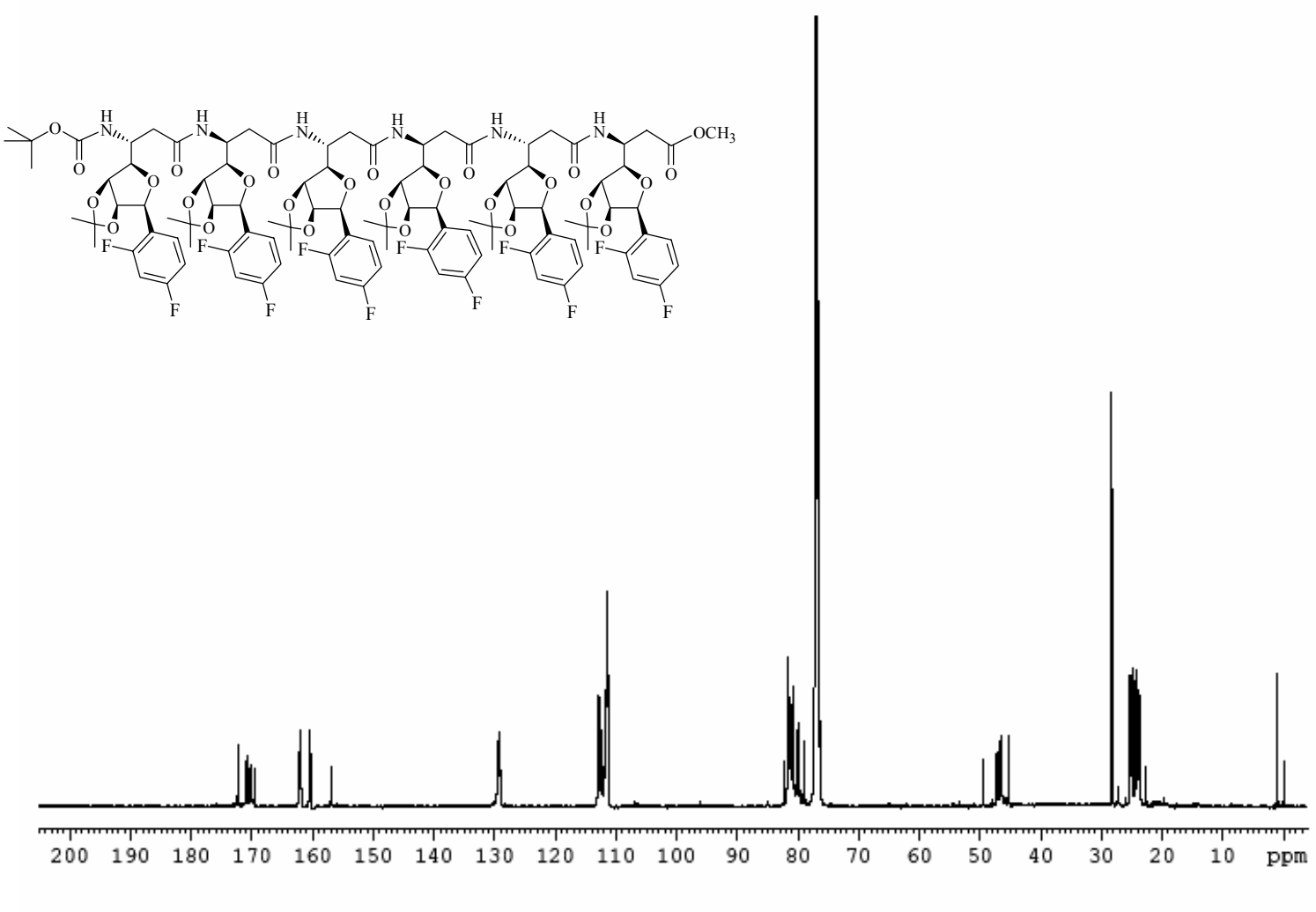
Supporting Fig 99: TOCSY Spectrum of 15 ($CDCl_3$, 303 K, 500 MHz)



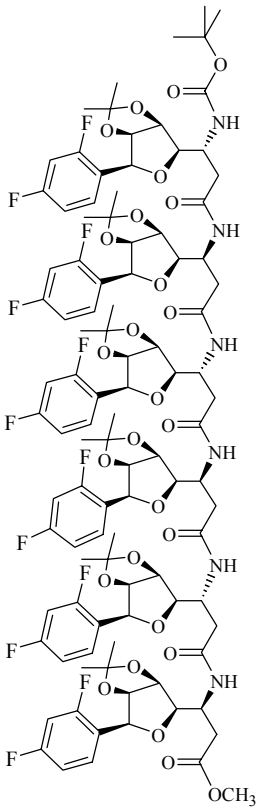
Supporting Fig 100: ROESY Spectrum of 15 ($CDCl_3$, 303 K, 500 MHz)

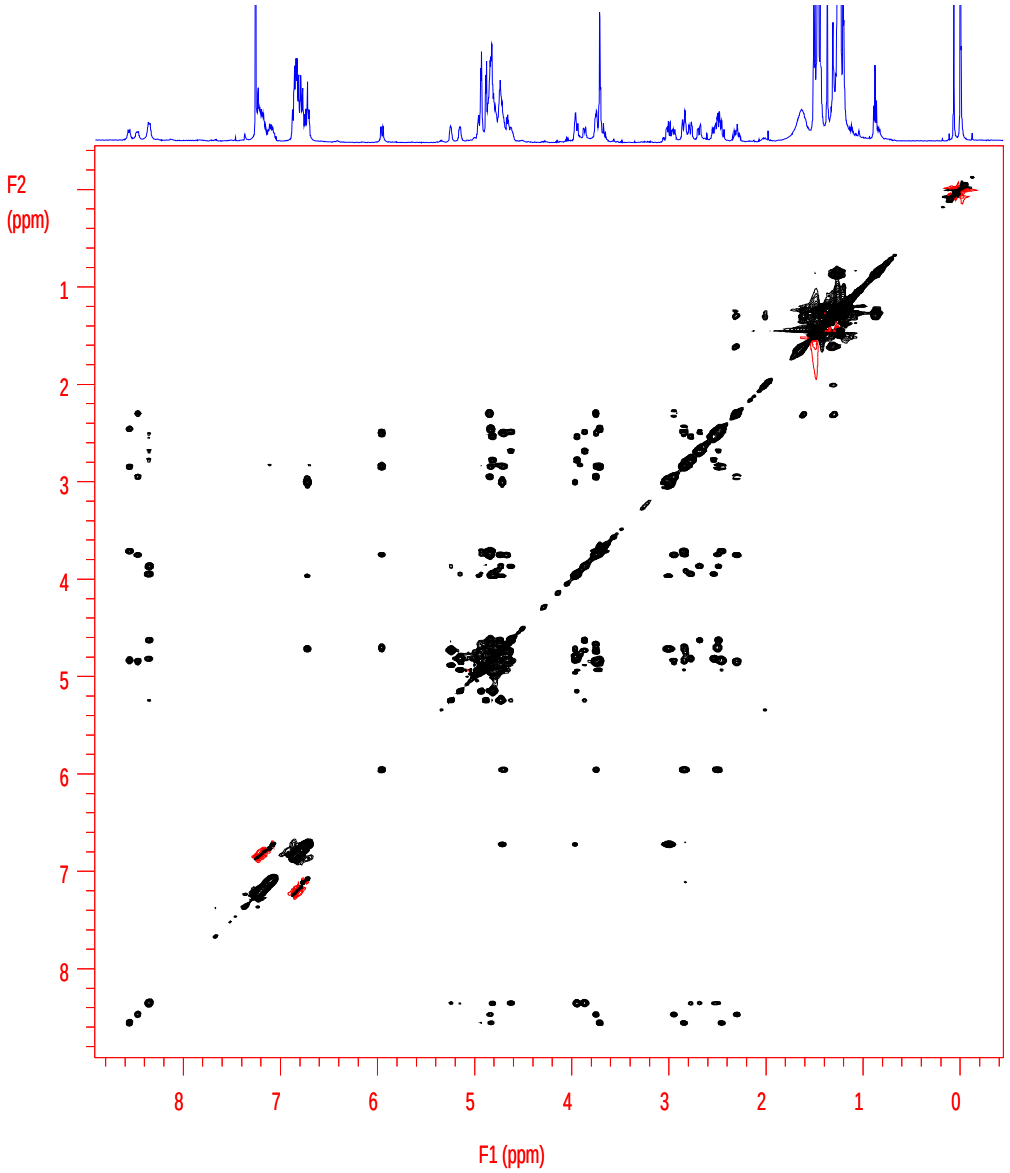


Supporting Fig 101: ^{1}H NMR Spectrum of 16 ($CDCl_3$, 303 K, 500 MHz)

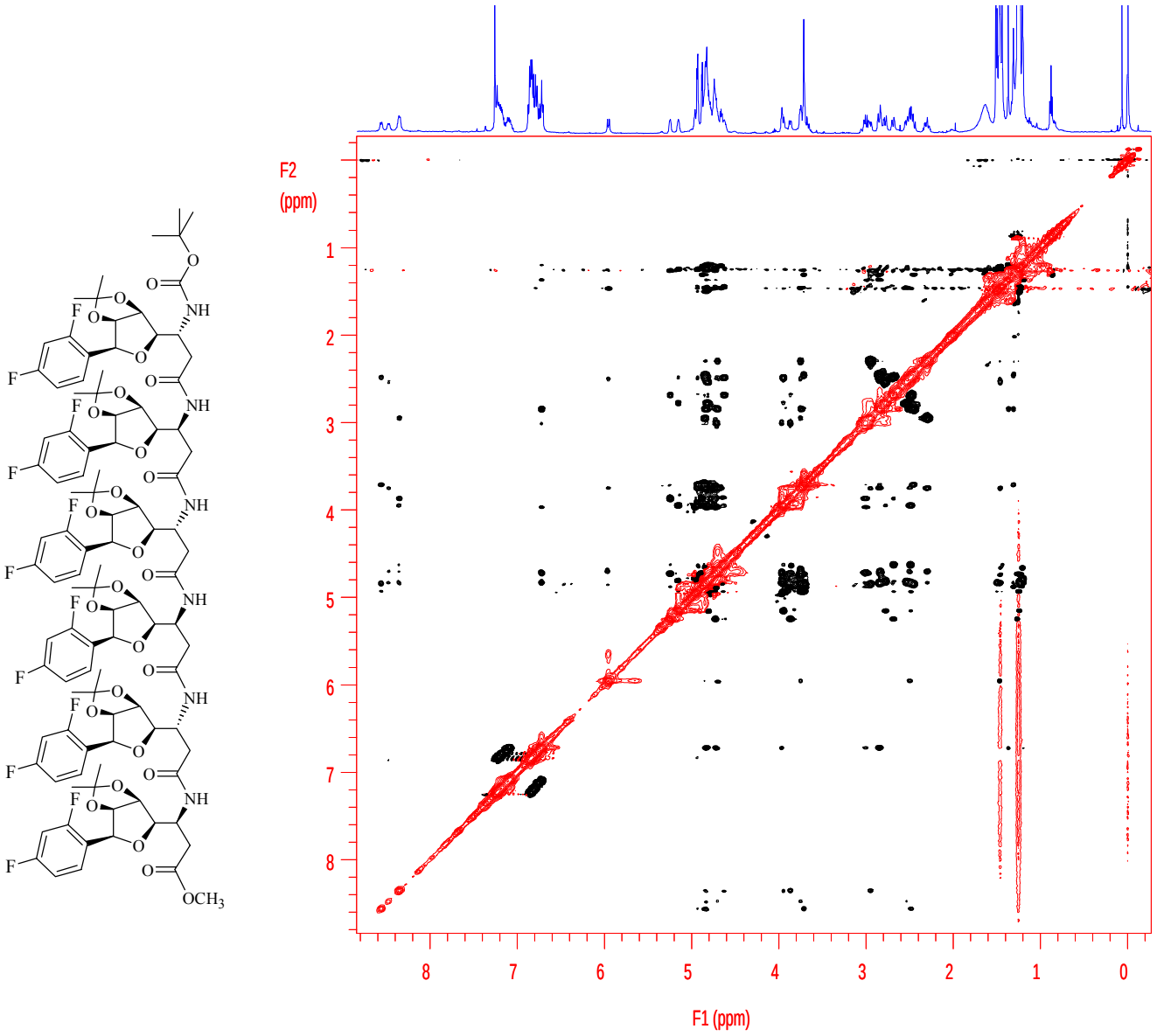


Supporting Fig 102: ^{13}C NMR Spectrum of 16 ($CDCl_3$, 298 K, 150 MHz)



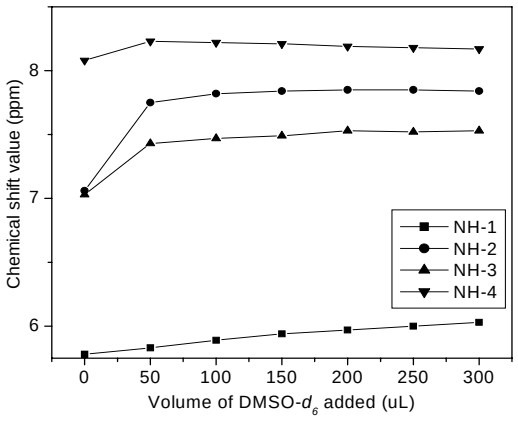


Supporting Fig 103: TOCSY Spectrum of 16 ($CDCl_3$, 303 K, 500 MHz)

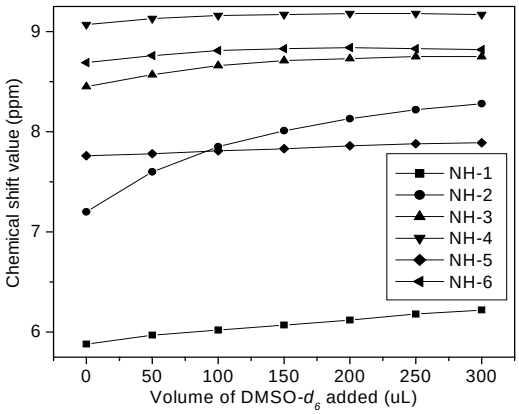


Supporting Fig 104: ROESY Spectrum of 16 ($CDCl_3$, 303 K, 500 MHz)

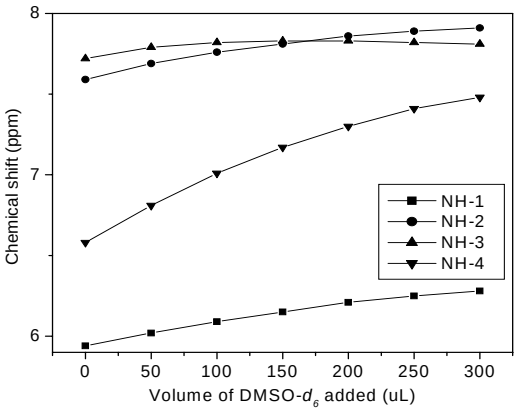
(13)



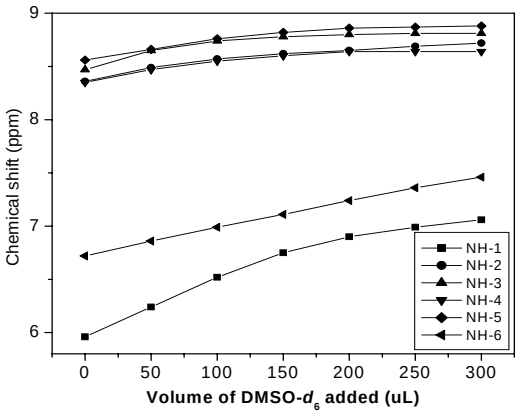
(14)



(15)



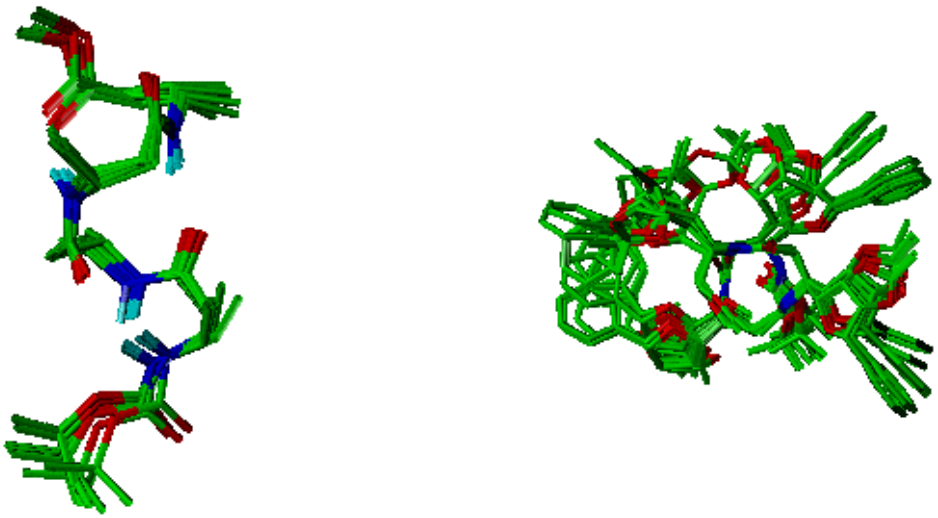
(16)



Supporting Fig 105: **Solvent titration plots of 13-16**

Molecular Dynamics:

Supporting Fig 106: Superimposed 20 minimum energy structures for 13 (A) side view and (B) top view :



A **B**

Supporting Table 6: Distance constraints used in MD calculations for 13, derived from ROESY experiment in $CDCl_3$ (500 MHz, 303 K)

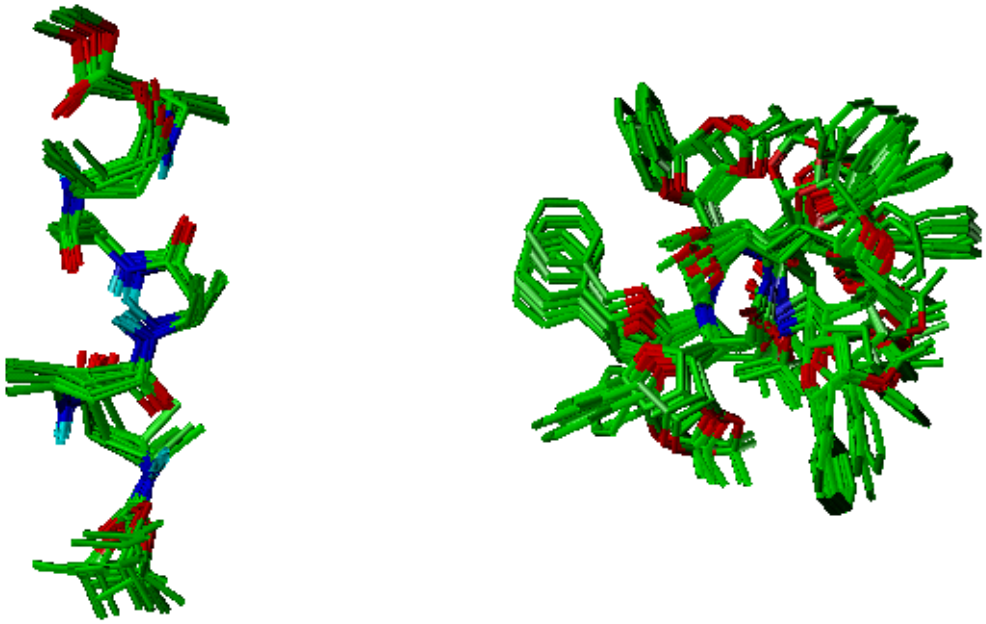
Residue	Atom	Residue	Atom	Lower bound	upper bound
1	NH	1	$C_\alpha H$ (*pro-S*)	2.80	3.64
1	NH	1	$C_\alpha H$ (*pro-R*)	2.77	3.64
1	NH	2	NH	2.83	3.46
1	$C_\beta H$	2	NH	2.79	3.32
1	$C_\alpha H$ (*pro-S*)	1	$C_4 H$	2.83	3.46

1	$C_{\alpha}H$ (*pro-S*)	1	C_3H	2.41	2.94
1	$C_{\alpha}H$ (*pro-S*)	2	NH	2.89	3.07
1	$C_{\alpha}H$ (*pro-R*)	1	C_4H	2.45	3.00
1	$C_{\alpha}H$ (*pro-R*)	1	C_3H	2.70	3.30
1	$C_{\alpha}H$ (*pro-R*)	2	NH	2.19	2.67
1	C_4H	2	NH	2.85	3.49
2	NH	2	C_4H	2.49	3.04
2	NH	2	C_3H	2.72	3.32
2	NH	2	$C_{\alpha}H$ (*pro-R*)	2.51	3.07
2	$C_{\beta}H$	3	NH	2.35	2.88
2	$C_{\beta}H$	3	$C_{\alpha}H$ (*pro-R*)	2.33	2.84
2	$C_{\beta}H$	4	NH	2.72	3.33
2	$C_{\alpha}H$ (*pro-S*)	2	C_3H	2.34	2.87
2	$C_{\alpha}H$ (*pro-S*)	3	NH	2.21	2.71
2	$C_{\alpha}H$ (*pro-R*)	2	C_3H	2.30	2.82

3	NH	3	C_4H	2.25	2.75
3	NH	4	NH	3.13	3.83
3	$C_\alpha H$ (*pro-S*)	3	C_4H	2.52	3.08
3	$C_\alpha H$ (*pro-R*)	3	C_4H	2.88	3.52
3	$C_\alpha H$ (*pro-R*)	4	NH	2.42	2.96
4	NH	4	C_4H	2.38	2.91
4	$C_\alpha H$ (*pro-S*)	4	C_4H	2.46	3.00
4	$C_\alpha H$ (*pro-R*)	4	C_4H	2.20	2.69

Supporting Fig 107: Superimposed 20 minimum energy structures for 14

(A) side view and (B) top view:



A **B**

Supporting Table 7: Distance constraints used in MD calculations for 13, derived from ROESY experiment in $CDCl_3$ (500 MHz, 303 K)

Residue	Atom	Residue	Atom	Lower bound	upper bound
1	$C_\alpha H$ (*pro-R*)	1	NH	3.28	4.01
1	$C_\alpha H$ (*pro-S*)	1	NH	3.09	3.78
1	C_4H	1	NH	2.72	3.33
1	C_3H	1	NH	3.02	3.69
1	C_1H	1	C_4H	2.03	2.48
1	C_4H	1	$C_\alpha H$ (*pro-S*)	3.04	3.72

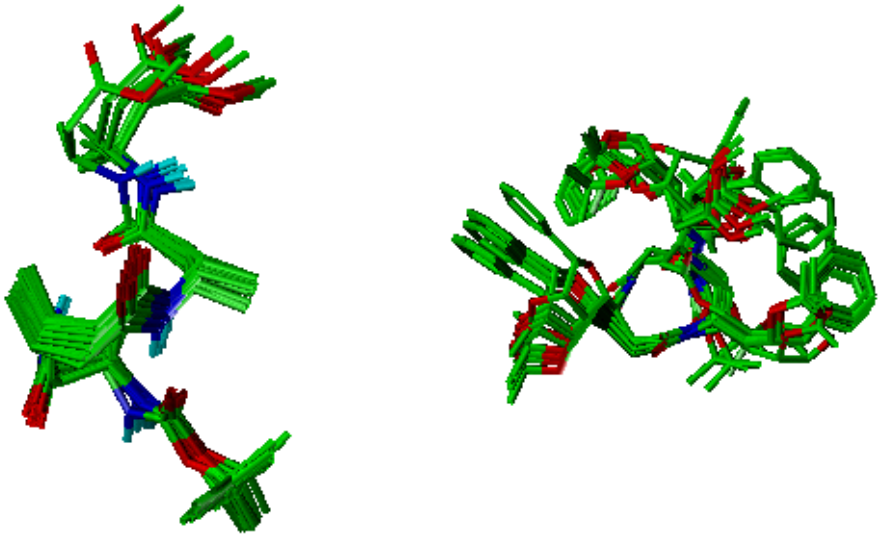
1	C_4H	1	$C_\alpha H$ (*pro-R*)	2.59	3.17
1	C_4H	3	$C_\alpha H$ (*pro-R*)	2.46	3.01
1	$C_\alpha H$ (*pro-R*)	2	NH	2.45	2.99
1	$C_\alpha H$ (*pro-S*)	2	NH	2.80	3.42
2	$C_\beta H$	4	$C_\alpha H$ (*pro-R*)	2.37	2.90
2	C_1H	2	C_4H	1.89	2.13
2	C_4H	2	$C_\alpha H$ (*pro-S*)	2.07	2.53
2	C_4H	2	$C_\alpha H$ (*pro-R*)	2.83	3.46
2	$C_\alpha H$ (*pro-R*)	2	NH	2.86	3.50
2	C_3H	2	$C_\alpha H$ (*pro-S*)	2.62	3.19
2	C_3H	2	$C_\alpha H$ (*pro-R*)	2.43	2.97
2	C_4H	4	$C_\alpha H$ (*pro-R*)	2.77	3.38
2	$C_\beta H$	3	NH	2.65	3.24
2	$C_\beta H$	4	NH	2.81	3.44
2	$C_\alpha H$ (pro-S)	3	NH	2.56	3.13
3	C_1H	3	C_4H	2.03	2.48

3	C_4H	3	$C_\alpha H$ (*pro-S*)	2.74	3.35
3	C_3H	3	C_1H	2.14	2.61
3	C_3H	3	$C_\beta H$	2.60	3.18
3	C_4H	3	NH	2.43	2.96
3	NH	4	NH	3.55	4.34
3	$C_\alpha H$ (*pro-R*)	4	NH	2.81	3.44
4	C_3H	4	NH	3.24	3.96
4	C_4H	4	NH	2.83	3.46
4	C_4H	4	$C_\alpha H$ (*pro-S*)	2.88	3.52
4	C_4H	4	$C_\alpha H$ (*pro-R*)	2.27	2.77
4	C_1H	4	C_4H	1.85	2.26
4	$C_\beta H$	6	$C_\alpha H$ (*pro-R*)	2.23	2.72
4	$C_\beta H$	5	NH	2.73	3.33
4	$C_\alpha H$ (*pro-S*)	5	NH	2.26	2.77
4	$C_\beta H$	6	NH	2.74	3.35
5	C_3H	5	C_1H	2.56	3.12

5	C_3H	5	$C_\beta H$	2.77	3.39
5	C_3H	5	$C_\alpha H$ (*pro-S*)	2.21	2.70
5	C_3H	5	$C_\alpha H$ (*pro-S*)	2.22	2.71
5	C_1H	5	C_4H	1.70	2.08
5	C_4H	5	$C_\alpha H$ (*pro-S*)	2.68	3.28
5	C_4H	5	NH	2.24	2.74
5	NH	6	NH	3.15	3.85
5	$C_\alpha H$ (*pro-R*)	6	NH	2.72	3.33
6	C_4H	6	NH	2.56	3.12
6	C_1H	6	C_4H	1.70	2.08
6	C_4H	6	$C_\alpha H$ (*pro-S*)	2.46	3.01
6	C_4H	6	$C_\alpha H$ (*pro-R*)	3.25	3.97

Supporting Fig 108: Superimposed 20 minimum energy structures for 15

(A) side view and (B) top view:



A **B**

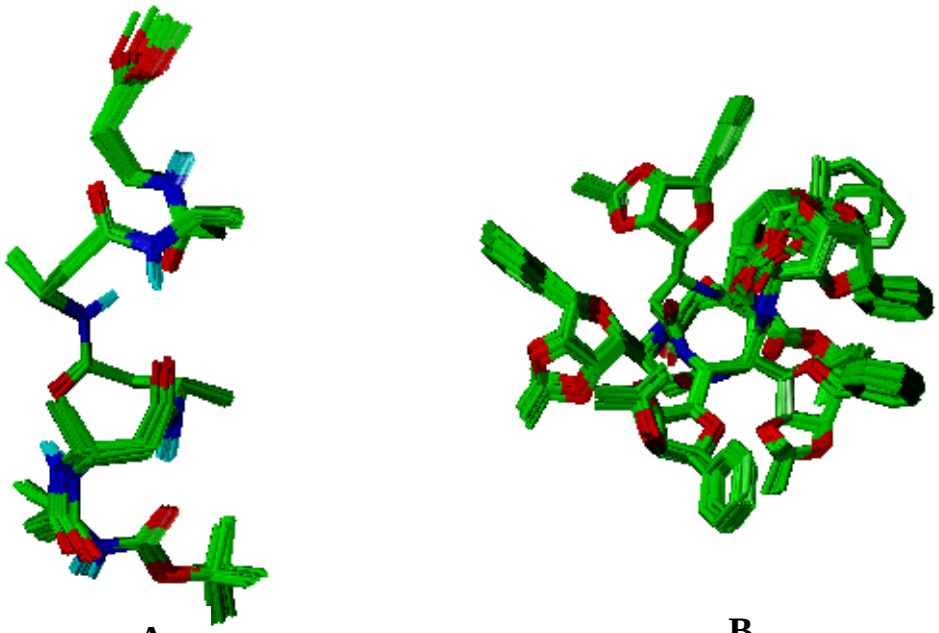
Supporting Table 8: Distance constraints used in MD calculations for 15, derived from ROESY experiment in $CDCl_3$ (500 MHz, 303 K)

Residue	Atom	Residue	Atom	Lower bound	upper bound
1	NH	1	$C_\alpha H$ (*pro-R*)	2.43	2.97
1	NH	1	C_4H	2.32	2.84
1	NH	2	C_3H	2.52	3.08
1	$C_\beta H$	2	NH	2.22	2.72
1	$C_\beta H$	3	NH	2.22	2.72
1	C_4H	1	$C_\alpha H$ (*pro-S*)	1.95	2.34

1	C_4H	1	$C_\alpha H$ (*pro-R*)	2.11	2.57
1	$C_\alpha H$ (*pro-S*)	2	NH	2.40	2.93
2	NH	2	C_4H	2.17	2.93
2	C_3H	2	$C_\alpha H$ (*pro-S*)	2.06	2.51
2	$C_\alpha H$ (*pro-R*)	3	NH	2.22	2.71
2	C_3H	4	$C_\alpha H$ (*pro-R*)	2.43	2.97
3	C_4H	3	NH	2.56	3.16
3	C_4H	3	$C_\alpha H$ (*pro-S*)	2.38	2.91
3	C_4H	3	$C_\alpha H$ (*pro-R*)	2.25	2.75
3	C_4H	3	C_1H	2.06	2.51
3	$C_\alpha H$ (*pro-S*)	4	NH	2.11	2.58
4	C_4H	4	NH	2.16	2.64
4	C_3H	4	$C_\alpha H$ (*pro-S*)	2.48	3.03
4	C_4H	4	$C_\alpha H$ (*pro-S*)	2.31	2.82

Supporting Fig 109: Superimposed 20 minimum energy structures for 16

(A) side view and (B) top view:



A **B**

Supporting Table 9: Distance constraints used in MD calculations for 16, derived from ROESY experiment in $CDCl_3$ (500 MHz, 303 K)

Residue	Atom	Residue	Atom	Lower bound	upper bound
1	NH	1	$C_\alpha H$ (*pro-R*)	2.44	2.98
1	NH	1	C_4H	2.49	3.04
1	NH	2	C_3H	2.69	3.01
1	$C_\beta H$	2	NH	2.75	3.36
1	$C_\beta H$	3	NH	2.66	3.25
1	$C_\beta H$	3	$C_\alpha H$ (*pro-R*)	2.30	2.81

1	C_4H	1	$C_\alpha H$ (*pro-S*)	2.07	2.53
1	C_4H	1	$C_\alpha H$ (*pro-R*)	2.37	2.90
2	NH	2	C_4H	2.54	3.10
2	C_4H	2	$C_\alpha H$ (*pro-S*)	2.49	3.04
2	C_3H	2	$C_\alpha H$ (*pro-S*)	2.11	2.57
2	$C_\alpha H$ (*pro-R*)	3	NH	2.69	3.29
2	$C_\beta H$	3	NH	2.58	3.26
2	C_3H	4	$C_\alpha H$ (*pro-R*)	2.49	3.04
3	C_4H	3	NH	2.56	3.16
3	C_4H	3	$C_\alpha H$ (*pro-S*)	2.34	2.87
3	C_4H	3	$C_\alpha H$ (*pro-R*)	2.06	2.51
3	$C_\beta H$	5	NH	2.35	2.86
3	$C_\beta H$	5	$C_\alpha H$ (*pro-R*)	1.96	2.39
3	$C_\alpha H$ (*pro-S*)	4	NH	2.42	2.96
4	C_4H	4	NH	2.28	2.79
4	$C_\alpha H$ (*pro-R*)	4	NH	3.13	3.83

4	C_3H	4	C_1H	2.62	3.2
4	C_3H	4	$C_\alpha H$ (*pro-S*)	2.01	2.46
4	C_4H	4	$C_\alpha H$ (*pro-S*)	2.51	3.06
4	C_1H	4	C_4H	2.11	2.57
4	C_3H	6	$C_\alpha H$ (*pro-R*)	2.69	3.28
4	$C_\alpha H$ (*pro-R*)	5	NH	2.42	2.96
5	C_4H	5	NH	2.31	2.82
5	C_3H	5	NH	2.67	3.27
5	$C_\beta H$	6	NH	2.11	2.58
5	$C_\alpha H$ (*pro-S*)	6	NH	2.00	2.44
5	$C_\alpha H$ (*pro-R*)	6	NH	2.82	3.45
5	C_4H	6	$C_\alpha H$ (*pro-R*)	2.04	2.50
5	C_4H	6	$C_\alpha H$ (*pro-S*)	2.32	2.83
6	C_4H	6	NH	2.35	2.87
6	$C_\alpha H$ (*pro-R*)	6	NH	2.49	3.05
6	C_4H	6	$C_\alpha H$ (*pro-S*)	2.16	2.64

Supporting Table 10: Antibacterial activities of peptides 13-16

Compounds	MIC (ug/ml)					
	S. aureus		*E.faecalis*		*E.faecium*	*E.coli*
	DRCC035	DRCC019	DRCC034	DRCC153	DRCC154	DRCC018
13	>32	>32	>32	>32	>32	>32
14	>32	>32	>32	>32	>32	>32
15	>32	>32	>32	>32	>32	>32
16	>32	>32	>32	>32	>32	>32