Electronic Supplementary Material (ESI) for Chemical Communications.

Diversely C8-functionalized adenine nucleosides *via* their underexplored carboxaldehydes

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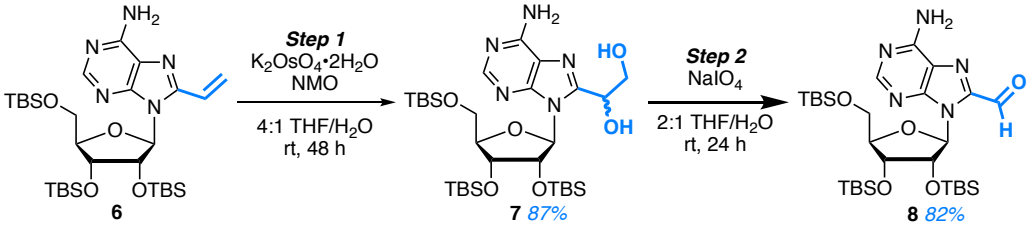
General Experimental Considerations

THF was distilled over $LiAlH_4$, stored over Na, and distilled over Na prior to use. CH_2Cl_2 and DME were distilled over CaH_2, and toluene was distilled over Na. For reactions that were performed under a nitrogen atmosphere, glassware was flame dried under vacuum. LDA (2.0 M solution in heptane/THF/EtPh), DIBAL-H (1.0 M in PhMe), LHMDS (1.0 M in THF), NaHMDS (0.6 M in PhMe), and KHMDS (0.5 M in PhMe) were obtained from commercial sources. For reactions requiring NaH, dry NaH (95%) was used. All other reagents were obtained from commercial sources and used without further purification. Thin layer chromatography was performed on 200 µm aluminum-foil-backed silica plates and column chromatographic purifications were performed on 200–300 mesh silica gel. ^{1}H NMR spectra were recorded at 500 MHz in either $CDCl_3$, or CD_2Cl_2, or CD_3OD, and are referenced to the residual proton resonance of the solvent. ^{13}C NMR spectra were recorded at 125 MHz in either $CDCl_3$, or CD_2Cl_2, or CD_3OD, and are referenced to the solvent resonance. ^{19}F NMR spectra were recorded at 470 MHz with $CFCl_3$ as the internal standard. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz (Hz).

Two-Step Synthesis of 8-formyl-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (8)



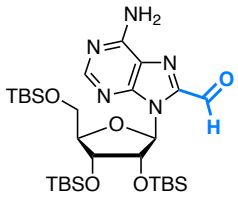
Step 1. In a clean, dry, 25 mL round-bottom flask equipped with a stir bar were placed the silyl-protected 8-vinyl nucleoside **6**[1] (846 mg, 1.33 mmol, 1.00 equiv.) and NMO (202.6 mg, 1.73 mmol, 1.30 equiv.) in THF (9.5 mL). A solution of K_2OsO_4•$2H_2O$ (24.5 mg, 0.0665 mmol, 5.0 mol%) in H_2O (2.4 mL) was added to the mixture that was then stirred at room temperature for 24 h. Another aliquot of NMO (202.6 mg, 1.73 mmol, 1.30 equiv.) and K_2OsO_4•$2H_2O$ (24.5 mg, 0.0665 mmol, 5.0 mol%) were added to the mixture and the stirring was continued for an additional 24 h. The reaction was quenched with 10% aq. Na_2SO_3 (10 mL) and the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with 1% aq. $NaHSO_3$ (3 × 50 mL), and brine (20 mL). The organic layer dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 50% EtOAc

in hexanes followed by EtOAc gave 775.4 mg (87% yield) of the diastereomeric mixture of products **7a** and **7b** as light-brown solid. R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.40. ^{1}H NMR of the *early*-eluting diastereomer **7a** ($CDCl_3$, 500 MHz): δ8.30 (s, 1H, Ar-H), 6.08 (d, *J* = 4.9 Hz, 1H, H-1'), 5.45 (t, *J* = 4.6 Hz, 1H, H-2'), 5.43 (s, 2H, NH_2), 5.01 (dt, *J* = 7.4, 3.8 Hz, 1H, CH), 4.64 (t, *J* = 4.2 Hz, 1H, H-3'), 4.20 (dt, *J* = 11.8, 3.2 Hz, 1H, CH), 4.10–4.02 (m, 2H, H-4', CH), 3.98 (dd, *J* = 11.3, 5.3 Hz, 1H, H-5'), 3.70 (dd, *J* = 11.3, 3.8 Hz, 1H, H-5'), 3.48 (s, 1H, OH), 3.43 (s, 1H, OH), 0.96, 0.79, and 0.77 (3s, 27H, *t*-Bu), 0.18, 0.15, –0.01, –0.04, –0.08, and –0.27 (6s, 18H, SiMe). ^{1}H NMR of the *late*-eluting diastereomer **7b** ($CDCl_3$, 500 MHz): δ8.31 (s, 1H, Ar-H), 6.08 (d, *J* = 6.3 Hz, 1H, H-1'), 5.47–5.36 (m, 3H, H-2', NH_2), 5.03 (dt, *J* = 7.8, 3.9 Hz, 1H, CH), 4.44 (dd, *J* = 4.1, 2.6 Hz, 1H, H-3'), 4.17 (dt, *J* = 11.8, 4.0 Hz, 1H, CH), 4.15–4.10 (m, 1H, H-4'), 4.08–4.02 (m, 2H, CH, H-5'), 3.74 (dd, *J* = 11.0, 4.0 Hz, 1H, H-5'), 3.60 (d, *J* = 7.9 Hz, 1H, OH), 3.40 (dd, *J* = 8.7, 4.6 Hz, 1H, OH), 0.95, 0.86, and 0.75 (3s, 27H, *t*-Bu), 0.16, 0.14, 0.06, 0.04, –0.08, and –0.40 (6s, 18H, SiMe).

Note. The NMR data listed above were obtained from the diol diastereomers, **7a** and **7b**, that were separated by column chromatography from a small-scale reaction.

Step 2. In a clean, dry, 50 mL round-bottom flask equipped with a stir bar was placed the diastereomeric mixture of diols **7a** and **7b** (0.900 g, 1.343 mmol, 1.00 equiv.) in THF (24.7 mL). A solution of $NaIO_4$ (574.6 mg, 2.686 mmol, 2.00 equiv.) in H_2O (12.3 mL) was added to the mixture that was then stirred for 16 h at room temperature. The mixture was diluted with water (20 mL) and washed with CH_2Cl_2 (2 $\times$ 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 10% acetone in hexanes gave 702.9 mg (82% yield) of silyl-protected 8-formyladenosine **8**, as a pale-yellow solid. R_f (SiO_2/30% EtOAc in hexanes): 0.50. ^{1}H NMR ($CDCl_3$, 500 MHz): δ9.99 (s, 1H, CHO), 8.39 (s, 1H, Ar-H), 6.80 (d, *J* = 5.5 Hz, 1H, H-1'), 5.89 (br s, 2H, NH_2), 5.37 (dd, *J* = 5.5, 4.6 Hz, 1H, H-2'), 4.60 (dd, *J* = 4.4, 3.4 Hz, 1H, H-3'), 4.08 (dt, *J* = 6.8, 3.5 Hz, 1H, H-4'), 4.03 (dd, *J* = 10.8, 6.6 Hz, 1H, H-5'), 3.72 (dd, *J* = 10.8, 4.0 Hz, 1H, H-5'), 0.97, 0.82, and 0.76 (3s, 27H, *t*-Bu), 0.16 (s, 6H, SiMe), 0.01, –0.04, –0.07, and 0.38 (4s, 12H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ183.0, 157.3, 155.4, 151.4, 145.2, 121.1, 88.8, 85.7, 73.3, 72.3, 62.5, 26.1, 26.0, 25.8, 18.5, 18.3, 18.0, –4.2, –4.35, –4.36, –5.0, –5.2, –5.3. HRMS (ESI/TOF): m/z calcd for $C_{29}H_{56}N_5O_5Si_3$ $[M + H]^+$ 638.3584, found 638.3607.

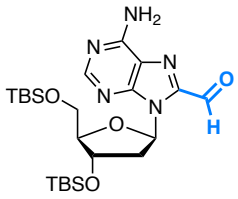
One-Step Synthesis of 8-Formyl-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (8)



In a flame-dried 250 mL round-bottom flask containing a stir bar, a 2.0 M solution of LDA in heptane/THF/EtPh (7.5 mL, 15 mmol, 5.0 equiv.) was added to dry THF (27.0 mL) at –78 °C, under a nitrogen atmosphere. A solution of silyl-protected adenosine **1**[2] (1.83 g, 3.00 mmol, 1.00 equiv.) in dry THF (33.0 mL) was added slowly so that the external bath temperature did not rise above –70 °C, and the mixture was stirred at –78 °C for 1 h. DMF (5.81 mL, 75.0 mmol, 25.0 equiv.) was then added dropwise and the mixture was stirred at –78 °C for an additional 2.5 h. The reaction was quenched with water (40 mL) and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 10% EtOAc in hexanes followed by 15% EtOAc in hexanes gave 1.57 g (82% yield) of silyl-protected 8-formyladenosine **8**, as a pale-yellow solid. The NMR data were identical to that reported above.

Note. Although this material is stable for about a month in a freezer, it is best to use it soon after preparation.

3',5'-Di-*O*-(*tert*-butyldimethylsilyl)-8-formyl-2'-deoxyadenosine (9)

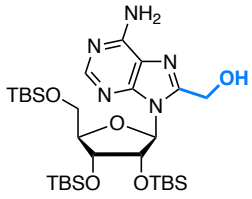


In a flame-dried 100 mL round-bottom flask containing a stir bar, a 2.0 M solution of LDA in heptane/THF/EtPh (7.5 mL, 15 mmol, 5.0 equiv.) was added to dry THF (27.0 mL), at –78 °C, under a nitrogen atmosphere. A solution of silyl-protected 2'-deoxyadenosine **2**[3] (1.44 g, 3.00 mmol, 1.00 equiv.) in dry THF (33.0 mL) was added slowly so that the external bath temperature did not rise above –70 °C, and the mixture was stirred at –78 °C for 1 h. DMF (5.81 mL, 75.0 mmol, 25.0 equiv.) was then added dropwise and the mixture was stirred at –78 °C for an additional 2.5 h. The reaction was quenched with water (40 mL) and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in hexanes followed by 40% EtOAc in hexanes gave 1.325 g (87% yield) of silyl-protected 8-formyl-2'-deoxyadenosine **9**, as a pale-yellow solid.

R_f (SiO_2/50% EtOAc in hexanes): 0.38. ^{1}H NMR ($CDCl_3$, 500 MHz): δ9.99 (s, 1H, CHO), 8.39 (s, 1H, Ar-H), 7.13 (t, *J* = 6.6 Hz, 1H, H-1'), 5.99 (br s, 2H, NH_2), 4.86 (dt, *J* = 6.2, 4.3 Hz, 1H, H-3'), 3.96 (app q, J_{app} ~ 4.8 Hz, 1H, H-4'), 3.91 (dd, *J* = 10.7, 5.7 Hz, 1H, H-5'), 3.71 (dd, *J* = 10.7, 4.6 Hz, 1H, H-5'), 3.39 (dt, *J* = 13.0, 6.4 Hz, 1H, H-2'), 2.29 (ddd, *J* = 13.0, 7.1, 4.6 Hz, 1H, H-2'), 0.94 and 0.82 (2s, 18H, *t*-Bu), 0.14 (s, 6H, SiMe), –0.01 and –0.05 (2s, 6H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ183.3, 157.5, 155.6, 151.2, 144.7, 121.0, 87.9, 84.6, 72.4, 62.9, 38.4, 26.01, 25.99, 18.5, 18.2, –4.47, –4.57, –5.27, –5.32. HRMS (ESI/TOF): m/z calcd for $C_{23}H_{42}N_5O_4Si_2$ [M + H]$^+$ 508.2770, found 508.2767.

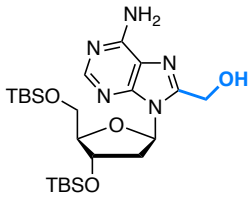
Note. Although this material is stable for about a month in a freezer, it is best to use it soon after preparation.

8-Hydroxymethyl-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (5)[2]



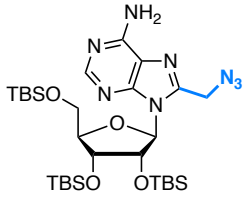
In a 50 mL round-bottom flask equipped with a stir bar, a solution of silyl-protected 8-formyladenosine **8** (0.638 g, 1.00 mmol, 1.00 equiv.) was prepared in MeOH (20.0 mL). $NaBH_4$ (83.3 mg, 2.20 mmol, 2.20 equiv.) was added in a single portion to the flask with stirring, and the mixture was stirred at room temperature for a total of 1 h. The reaction was quenched with saturated aq. NH_4Cl (20 mL) and water (20 mL), and then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ (20 mL), deionized water (20 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 25% EtOAc in hexanes, 35% EtOAc in hexanes, and 50% EtOAc in hexanes gave 544.2 mg (85% yield) of carbinol **5**, as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.28 (s, 1H, Ar-H), 5.93 (br s, 2H, NH_2), 5.92 (d, *J* = 5.8 Hz, 1H, H-1'), 5.33 (t, *J* = 5.0 Hz, 1H, H-2'), 4.95–4.88 (m, 2H, OCH_2), 4.49 (t, *J* = 5.0 Hz, 1H, H-3'), 4.09 (dt, *J* = 5.9, 3.2 Hz, 1H, H-4'), 4.01 (dd, *J* = 11.1, 5.9 Hz, 1H, H-5'), 3.72 (dd, *J* = 11.1, 3.9 Hz, 1H, H-5'), 0.95, 0.83, and 0.76 (3s, 27H, *t*-Bu), 0.16, 0.14, 0.03, –0.01, –0.07, and –0.37 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 155.4, 153.1, 152.7, 151.1, 118.5, 88.6, 85.7, 72.8, 72.3, 62.5, 57.2, 26.1, 26.0, 25.8, 18.5, 18.3, 18.0, –4.2, –4.4, –4.5, –5.0, –5.3, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{29}H_{58}N_5O_5Si_3$ [M + H]$^+$ 640.3740, found 640.3745.

8-Hydroxymethyl-3',5'-di-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (10)



In a 100 mL round-bottom flask equipped with a stir bar, a solution of silyl-protected 8-formyl 2'-deoxyadenosine **9** (1.016 g, 2.00 mmol, 1.00 equiv.) was prepared in MeOH (40.0 mL). $NaBH_4$ (166.5 mg, 4.40 mmol, 2.20 equiv.) was added in a single portion to the flask with stirring, and the mixture was stirred at room temperature for a total of 1 h. The reaction was quenched with saturated aq. NH_4Cl (20 mL) and water (20 mL), and then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ (20 mL), deionized water (20 mL), and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 50% EtOAc in hexanes, 75% EtOAc in hexanes, and EtOAc gave 0.897 g (88% yield) of carbinol **10**, as a pale-yellow solid. R_f (SiO_2/50% EtOAc in hexanes): 0.12. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.29 (s, 1H, Ar-H), 6.42 (t, J = 6.8 Hz, 1H, H-1'), 5.68 (br s, 2H, NH_2), 4.91 (ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 14.3 Hz, 2H, OCH_2), 4.71 (dt, J = 6.8, 3.5 Hz, 1H, H-3'), 4.29–4.22 (br s, 1H, OH), 3.95 (app q, J_{app} ~ 4.0 Hz, 1H, H-4'), 3.90 (dd, J = 11.2, 4.4 Hz, 1H, H-5'), 3.72 (dd, J = 11.1, 3.8 Hz, 1H, H-5'), 3.18 (dt, J = 13.4, 6.8 Hz, 1H, H-2'), 2.32 (ddd, J = 12.2, 7.2, 4.4 Hz, 1H, H-2'), 0.92 and 0.86 (2s, 18H, *t*-Bu), 0.124, 0.118, 0.04, and 0.02 (4s, 12H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 155.2, 152.8, 152.6, 151.0, 118.3, 87.7, 84.5, 72.0, 62.7, 57.8, 39.1, 26.06, 26.01, 18.6, 18.2, –4.4, –4.6, –5.31, –5.33. HRMS (ESI/TOF): m/z calcd for $C_{23}H_{44}N_5O_4Si_2$ $[M + H]^+$ 510.2926, found 510.2926.

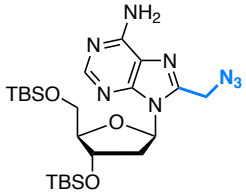
8-Azidomethyl-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (11)



In an 8 mL vial equipped with a stir-bar, a solution of silyl-protected 8-hydroxymethyladenosine **5** (0.300 g, 0.469 mmol, 1.00 equiv.) was prepared in dry THF (3.0 mL). DPPA (404 μL, 1.87 mmol, 4.00 equiv.) and DBU (350 μL, 2.34 mmol, 4.99 equiv.) were added. The vial was sealed, and the mixture was stirred at room temperature for 6 h. The mixture was diluted with deionized H_2O (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 15% EtOAc in hexanes and 30% EtOAc in hexanes gave 280.6 mg (90% yield) of the azido nucleoside **11**, as a white solid. R_f (SiO_2/50% EtOAc in hexanes): 0.69. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.30 (s,

1H, Ar-H), 5.90 (d, *J* = 5.7 Hz, 1H, H-1'), 5.86 (br s, 2H, NH_2), 5.38 (t, *J* = 5.0 Hz, 1H, H-2'), 4.64 (s, 2H, CH_2), 4.52 (dd, *J* = 4.2, 3.4 Hz, 1H, H-3'), 4.08 (dt, *J* = 6.1, 3.2 Hz, 1H, H-4'), 4.00 (dd, *J* = 11.1, 6.0 Hz, 1H, H-5'), 3.71 (dd, *J* = 11.1, 3.9 Hz, 1H, H-5'), 0.95, 0.82, and 0.78 (3s, 27H, *t*-Bu), 0.16, 0.14, 0.02, –0.02, –0.06, and –0.33 (6s, 18H, SiMe). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ155.3, 152.6, 151.2, 147.9, 119.2, 88.8, 85.8, 73.0, 72.2, 62.4, 47.5, 26.1, 26.0, 25.8, 18.5, 18.3, 18.1, –4.2, –4.36, –4.4, –5.1, –5.2, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{29}H_{56}N_8NaO_4Si_3$ $[M + Na]^+$ 687.3625, found 687.3630.

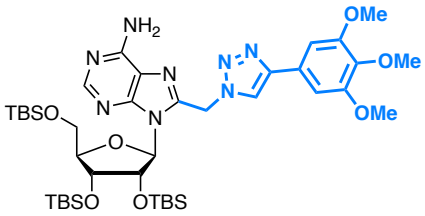
8-Azidomethyl-3',5'-di-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (12)



In a 25 mL round-bottom flask equipped with a stir bar, a solution of silyl-protected 8-hydroxymethyl 2'-deoxyadenosine **10** (0.800 g, 1.57 mmol, 1.00 equiv.) was prepared in dry THF (10.5 mL). DPPA (1.35 mL, 6.26 mmol, 3.99 equiv.) and DBU (1.20 mL, 8.02 mmol, 5.11 equiv.) were added. The flask was stoppered and the mixture was stirred at room temperature for 6 h. The mixture was diluted with deionized H_2O (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 30% EtOAc in CH_2Cl_2 and 50% EtOAc in CH_2Cl_2 gave 797.6 mg (95 % yield) of the azido nucleoside **12**, as a white solid. R_f (SiO_2/30% EtOAc in hexanes): 0.65. ^1H NMR ($CDCl_3$, 500 MHz): δ8.29 (s, 1H, Ar-H), 6.37 (t, *J* = 6.8 Hz, 1H, H-1'), 6.09 (s, 2H, NH_2), 4.73 (dt, *J* = 6.4, 3.7 Hz, 1H, H-3'), 4.71–4.65 (m, 2H, CH_2), 3.93 (app q, J_{app} ~ 4.3 Hz, 1H, H-4'), 3.87 (dd, *J* = 11.1, 4.9 Hz, 1H, H-5'), 3.69 (dd, *J* = 11.1, 4.0 Hz, 1H, H-5'), 3.28 (dt, *J* = 13.3, 6.7 Hz, 1H, H-2'), 2.29 (ddd, *J* = 13.2, 6.6, 3.9 Hz, 1H, H-2'), 0.92 and 0.83 (2s, 18H, *t*-Bu), 0.123, 0.118, 0.01, and –0.02 (4s, 12H, SiMe). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ155.6, 152.9, 151.1, 147.3, 119.1, 87.7, 84.5, 72.0, 62.6, 47.8, 39.0, 26.04, 26.02, 18.5, 18.2, –4.5, –4.6, –5.28, –5.33. HRMS (ESI/TOF): m/z calcd for $C_{23}H_{43}N_8O_3Si_2$ $[M + H]^+$ 535.2991, found 535.2982.

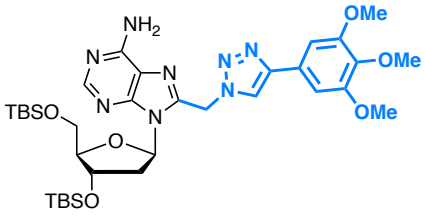
8-[(3,4,5-Trimethoxy-1*H*-1,2,3-triazol-4-yl)methyl]-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (13)

In an 8 mL vial equipped with a stir bar, a solution of silyl-protected 8-azidomethyladenosine **11** (0.200 g, 0.301 mmol, 1.00 equiv.) and 3,4,5-trimethoxyethynylbenzene[4] (115.6 mg, 0.601 mmol,



2.00 equiv.) in CH_2Cl_2 (1.5 mL) was prepared. To this stirred solution at room temperature, sodium ascorbate (11.9 mg, 0.060 mmol, 20 mol%), $CuSO_4 \bullet 5H_2O$ (7.5 mg, 0.030 mmol, 10 mol%), and H_2O (1.3 mL) were added, and the stirring was continued at room temperature for 3 h. The mixture was diluted with deionized H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 30% EtOAc in hexanes and 50% EtOAc in hexanes gave 242.4 mg (94% yield) of triazole **13**, as a white solid. R_f (SiO_2/EtOAc): 0.74. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.31 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.05 (s, 2H, Ar-H), 6.12 (br s, 2H, NH_2), 6.07–6.02 (m, 2H, H-1', NCH), 5.88 (d, J = 15.9 Hz, 1H, NCH), 5.23 (dd, J = 5.5, 4.6 Hz, 1H, H-2'), 4.48 (t, J = 3.9 Hz, 1H, H-3'), 4.12 (app q, J_{app} ~ 3.9 Hz, 1H, H-4'), 3.98 (dd, J = 11.4, 4.6 Hz, 1H, H-5'), 3.91 (s, 6H, OMe), 3.87 (s, 3H, OMe), 3.74 (dd, J = 11.4, 3.4 Hz, 1H, H-5'), 0.96, 0.79, and 0.74 (3s, 18H, *t*-Bu), 0.17, 0.14, 0.02, –0.05, –0.06, and –0.38 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 155.6, 153.8, 153.1, 151.1, 148.4, 146.0, 138.4, 126.2, 120.1, 119.3, 103.3, 88.6, 85.8, 73.5, 71.9, 62.2, 61.1, 56.4, 47.4, 26.1, 25.9, 25.8, 18.4, 18.3, 18.0, –4.2, –4.4, –4.5, –5.1, –5.3, –5.5. HRMS (ESI/TOF): m/z calcd for $C_{40}H_{69}N_8O_7Si_3$ [M + H]$^+$ 857.4592, found 857.4604.

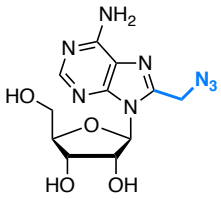
8-[(3,4,5-Trimethoxy-1*H*-1,2,3-triazol-4-yl)methyl]-3',5'-di-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (14)



In an 8 mL vial equipped with a stir bar, a solution of silyl-protected 8-azidomethyl-2'-deoxyadenosine **12** (0.100 g, 0.187 mmol, 1.00 equiv.) and 3,4,5-trimethoxyethynyl-benzene[4] (71.9 mg, 0.374 mmol, 2.00 equiv.) in CH_2Cl_2 (0.9 mL) was prepared. To this stirred solution at room temperature, sodium ascorbate (7.4 mg, 0.037 mmol, 20 mol%), $CuSO_4 \bullet 5H_2O$ (4.7 mg, 0.019 mmol, 10 mol%), and H_2O (0.8 mL) were added, and the stirring was continued at room temperature for 3 h. The mixture was diluted with deionized H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered, and evaporated under

reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 30% EtOAc in hexanes and 50% EtOAc in hexanes gave 128.5 mg (95% yield) of the triazole **14**, as a white solid. R_f (SiO_2/EtOAc): 0.35. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.32 (s, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.05 (s, 2H, Ar-H), 6.49 (t, *J* = 6.6 Hz, 1H, H-1'), 6.04 (d, *J* = 15.7 Hz, 1H, NCH), 5.89 (d, *J* = 15.7 Hz, 1H, NCH), 5.54 (br s, 2H, NH_2), 4.77 (dt, *J* = 6.3, 4.2 Hz, 1H, H-3'), 3.96 (app q, J_{app} ~ 4.0 Hz, 1H, H-4'), 3.91 (s, 6H, OMe), 3.91–3.87 (m, 1H, H-5'), 3.87 (s, 3H, OMe), 3.73 (dd, *J* = 11.3, 3.9 Hz, 1H, H-5'), 3.20 (dt, *J* = 13.2, 6.6 Hz, 1H, H-2'), 2.29 (ddd, *J* = 13.1, 6.5, 4.3 Hz, 1H, H-2'), 0.92 and 0.80 (2s, 18H, *t*-Bu), 0.12 (s, 6H, SiMe), –0.01 and –0.05 (2s, 6H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ155.7, 153.7, 153.2, 150.9, 148.2, 145.6, 138.3, 126.0, 120.4, 119.0, 103.0, 87.8, 84.7, 71.8, 62.5, 61.0, 56.3, 47.6, 39.2, 25.92, 25.91, 18.4, 18.1, –4.5, –4.7, –5.41, –5.44. HRMS (ESI/TOF): m/z calcd for $C_{34}H_{54}N_8NaO_6Si_2$ $[M + Na]^+$ 749.3597, found 749.3594.

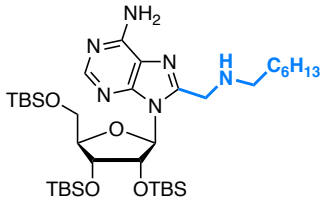
8-Azidomethyladenosine (15)



To a stirred solution of silyl-protected 8-azidomethyladenosine **11** (0.100 g, 0.150 mmol, 1.00 equiv.) in dry THF (1.5 mL), in a 4 mL polypropylene vial, Et_3N•3HF (123 μL, 0.755 mmol, 5.03 equiv.) was added. The mixture was stirred at room temperature for 16 h and then evaporated under a stream of nitrogen gas using a polyethylene pipette. The residual material was suspended in CH_2Cl_2 (2 mL), sonicated, and centrifuged. The supernatant liquid was carefully removed using a Pasteur pipette. The process was repeated several times and the resulting material was dried under high vacuum to give 47.1 mg (97% yield) of the desilylated product **15**, as a white solid. R_f (SiO_2/5% MeOH in EtOAc): 0.34. ^{1}H NMR (CD_3OD, 500 MHz): δ8.16 (s, 1H, Ar-H), 5.96 (d, *J* = 7.3 Hz, 1H, H-1'), 4.94 (dd, *J* = 7.2, 5.3 Hz, 1H, H-2'), 4.75 (ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 15.0 Hz, 2H, NCH_2), 4.34 (dd, *J* = 5.2, 1.5 Hz, 1H, H-3'), 4.20 (app q, J_{app} ~ 2.0 Hz, 1H, H-4'), 3.89 (dd, *J* = 12.6, 2.3 Hz, 1H, H-5'), 3.74 (dd, *J* = 12.6, 2.5 Hz, 1H, H-5'). ^{13}C{^{1}H} NMR (5:1 CD_3OD/DMSO-d_6, 125 MHz): δ157.6, 153.6, 151.2, 148.6, 119.9, 90.9, 88.9, 74.5, 72.9, 63.9, 48.0. HRMS (ESI/TOF): m/z calcd for $C_{11}H_{15}N_8O_4$ $[M + H]^+$ 323.1211, found 323.1216.

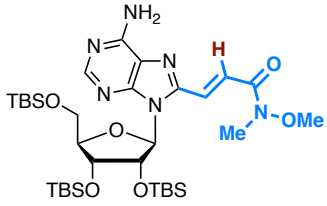
Reductive amination of 8-formyladenosine 8 with *n*-heptylamine, yielding compound 16

In a 25 mL round-bottom flask equipped with a stir bar, a solution of silyl-protected 8-formyladenosine **8** (0.130 g, 0.204 mmol, 1.00 equiv.) in dry CH_2Cl_2 (10.0 mL) was prepared. To



this mixture were added 4 Å MS (0.275 g) followed by *n*-heptylamine (38.0 µL, 0.256 mmol, 1.26 equiv.). The mixture was stirred at room temperature for 16 h, then evaporated under reduced pressure, and dried under high vacuum. The residue was dissolved in dry MeOH (10.0 mL) and $NaBH_4$ (19.3 mg, 0.510 mmol, 2.50 equiv.) was added in a single portion. The mixture was stirred at room temperature for a total of 1 h. The reaction was quenched with deionized H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. Evaporation of the filtrate under reduced pressure and drying under high vacuum gave 150.0 mg (quantitative yield) of the *N*-heptyl aminomethyl adenosine **16**, as a pale-yellow solid. R_f (SiO_2/30% EtOAc in hexanes): 0.37. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.26 (s, 1H, Ar-H), 5.98 (d, *J* = 5.4 Hz, 1H, H-1'), 5.55 (t, *J* = 4.7 Hz, 1H, H-2'), 5.39 (br s, 2H, NH_2), 4.60–4.55 (m, 1H, H-3'), 4.07–4.01 (m, 4H, NCH_2, H-4', H-5'), 3.70 (dd, *J* = 15.5, 8.0 Hz, 1H, H-5'), 2.69 (t, *J* = 7.2 Hz, 2H, CH_2), 1.52 (quint, *J* = 7.1 Hz, 2H, CH_2), 1.37–1.21 (m, 8H, CH_2), 0.96 (s, 9H, *t*-Bu), 0.88 (t, *J* = 6.8 Hz, 3H, CH_3), 0.82 and 0.79 (2s, 18H, *t*-Bu), 0.164, 0.161, 0.01, –0.04, –0.06, and –0.33 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 155.1, 152.40, 152.35, 151.3, 119.3, 88.7, 85.3, 72.4, 72.3, 62.5, 50.1, 46.9, 32.0, 30.2, 29.4, 27.4, 26.2, 26.0, 25.9, 22.8, 18.5, 18.3, 18.1, 14.3, –4.2, –4.3, –4.4, –4.9, –5.2, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{36}H_{73}N_6O_4Si_3$ $[M + H]^+$ 737.4996, found 737.5010.

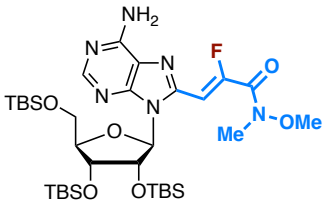
3-(2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)adenosin-8-yl)-*N*-methoxy-*N*-methylacrylamide (17)



In a 50 mL round-bottom flask containing a stir bar, a 1.0 M suspension of NaH (96.0 mg, 4.00 mmol, 4.00 equiv.) in anhydrous THF (4.0 mL) was prepared under a nitrogen atmosphere, and the suspension was cooled to 0 °C. To this was added a 0.25 M solution of BT-sulfone **A** (0.601 g, 2.00 mmol, 2.00 equiv.) in anhydrous THF (8.0 mL). The yellow suspension was stirred at 0 °C for 2 min and then a solution of silyl-protected 8-formyladenosine **8** (0.638 g, 1.00 mmol, 1.00 equiv.) in anhydrous THF (6.0 mL) was added dropwise at 0 °C, under nitrogen. The mixture was stirred at room temperature for 1 h. The reaction was quenched with deionized H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with deionized water (10 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and

evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in CH_2Cl_2, 50% EtOAc in CH_2Cl_2, followed by 75% EtOAc in CH_2Cl_2 gave 593 mg (82% yield) of the Weinreb amide **17** (*E*-isomer only), as a white solid. R_f (SiO_2/50% EtOAc in hexanes): 0.21. ^{1}H NMR ($CDCl_3$, 500 MHz): δ8.28 (s, 1H, Ar-H), 7.78 (d, *J* = 15.2 Hz, 1H, =CH_{trans}), 7.70 (d, *J* = 15.3 Hz, 1H, =CH_{trans}), 6.17 (br s, 2H, NH_2), 5.99 (d, *J* = 5.6 Hz, 1H, H-1'), 5.47 (t, *J* = 4.8 Hz, 1H, H-2'), 4.53 (t, *J* = 3.6 Hz, 1H, H-3'), 4.12–4.07 (m, 1H, H-4'), 4.03 (dd, *J* = 10.7, 7.3 Hz, 1H, H-5'), 3.81 (s, 3H, OMe), 3.73 (dd, *J* = 10.9, 4.1 Hz, 1H, H-5'), 3.34 (s, 3H, NMe), 0.96, 0.82, and 0.75 (3s, 27H, *t*-Bu), 0.17, 0.16, 0.01, –0.04, –0.07, and –0.36 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 165.6, 155.6, 152.8, 151.0, 148.2, 128.0, 124.8, 120.6, 88.8, 85.7, 72.6, 72.5, 62.5, 62.4, 32.8, 26.2, 26.0, 25.9, 18.5, 18.4, 18.1, –4.2, –4.37, –4.45, –5.0, –5.2, –5.3. HRMS (ESI/TOF): m/z calcd for $C_{33}H_{62}N_6NaO_6Si_3$ $[M + Na]^+$ 745.3931, found 745.3937.

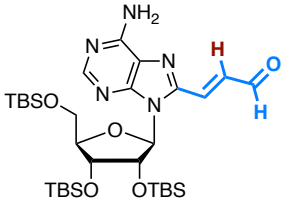
2-Fluoro-3-(2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosin-8-yl)-*N*-methoxy-*N*-methylacryl-amide (18)



In a 50 mL round-bottom flask containing a stir bar, a 1.05 M suspension of NaH (85.3 mg, 3.55 mmol, 3.99 equiv.) in anhydrous THF (3.4 mL) was prepared, and the suspension and cooled to 0 °C. To this was added a 0.25 M solution of BT-sulfone **B** (0.566 g, 1.78 mmol, 2.0 equiv.) in anhydrous THF (7.0 mL). The yellow suspension was stirred at 0 °C for 2 min and then a solution of silyl-protected 8-formyl adenosine **8** (0.567 g, 0.889 mmol, 1.00 equiv.) in anhydrous THF (5.3 mL) was added at 0 °C, under nitrogen. The mixture was stirred at room temperature for 45 min. The reaction was quenched with deionized H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1 N $NaHCO_3$ (15 mL), deionized water (10 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 25% EtOAc in hexanes, 35% EtOAc in hexanes, and 50% EtOAc in hexanes gave 0.195 g (30% yield) of the fluoro olefin Weinreb amide **18** (*Z*-isomer ≥ 99%), as a white solid. A fraction containing a significant amount of product and some impurities was also obtained. Chromatography of the impure fraction on a silica gel column by eluting with 20–40% EtOAc in hexanes, with 5% increments of EtOAc, gave and additional 0.330 g (50% yield) of the pure

product **18** (*Z*-isomer ≥ 99%), also as a white solid. The total amount of product **18** obtained was 0.525 g (80% yield). R_f (SiO_2/10% EtOAc in CH_2Cl_2): 0.36. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.29 (s, 1H, Ar-H), 6.94 (d, $^3J_{FH}$ = 30.8 Hz, 1H, =CH), 6.10 (br s, 2H, NH_2), 5.89 (d, J = 5.5 Hz, 1H, H-1'), 5.42 (t, J = 4.8 Hz, 1H, H-2'), 4.52 (t, J = 3.7 Hz, 1H, H-3'), 4.11–4.06 (m, 1H, H-4'), 4.01 (dd, J = 10.8, 7.1 Hz, 1H, H-5'), 3.82 (s, 3H, OMe), 3.73 (dd, J = 10.9, 4.1 Hz, 1H, H-5'), 3.32 (s, 3H, NMe), 0.96, 0.82, and 0.76 (3s, 27H, *t*-Bu), 0.16, 0.15, 0.01, –0.04, –0.06, and –0.35 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 161.7 (d, $^2J_{CF}$ = 26.4 Hz), 155.5, 155.0 (d, $^1J_{CF}$ = 294.6 Hz), 152.9, 150.2, 144.0 (d, J_{CF} = 5.8 Hz), 120.8, 102.7 (d, $^2J_{CF}$ = 3.1 Hz), 89.0, 85.6, 72.7, 72.4, 62.5, 62.4, 34.1, 26.2, 26.0, 25.9, 18.5, 18.4, 18.0, –4.1, –4.2, –4.3, –4.9, –5.0, –5.3. ^{19}F NMR ($CDCl_3$, 470 MHz): δ –100.64 (d, $^3J_{FH}$ = 16.7 Hz, *E*-isomer), –107.53 (d, $^3J_{FH}$ = 30.9 Hz, *Z*-isomer). Whereas the ^{1}H and ^{13}C spectra did not show discernible resonances for the minor *E*-isomer, a resonance corresponding to it was observed in the ^{19}F NMR. HRMS (ESI/TOF): m/z calcd for $C_{33}H_{62}FN_6O_6Si_3$ $[M + H]^+$ 741.4017, found 741.4033.

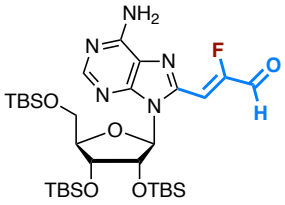
3-(2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)adenosin-8-yl)acrylaldehyde (19)



In a flame-dried 5 mL round-bottom flask equipped with a stir bar, a solution of the silyl-protected Weinreb amide **17** (0.100 g, 0.138 mmol, 1.00 equiv.) was prepared in dry CH_2Cl_2 (0.82 mL), under a nitrogen atmosphere, and cooled to –60 to –50 °C. A 1.0 M solution of DIBALH in PhMe (304 μL, 0.304 mmol, 2.20 equiv.) was added dropwise to the stirred, cooled mixture. The reaction was allowed to proceed at –60 to –50 °C for 1 h. The reaction was quenched by the addition of deionized H_2O (15 mL) at 5 °C. The mixture was diluted with 15% aq. NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in CH_2Cl_2 followed by 30% EtOAc in CH_2Cl_2 gave 49.3 mg (54% yield, 67% based on recovered starting material) of enone **19** (*E*-isomer only), as a yellow solid. Subsequently, 20 mg (20%) of starting material **17**, was also isolated as a yellow solid. R_f (SiO_2/30% EtOAc in CH_2Cl_2): 0.63. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 9.80 (d, J = 7.8 Hz, 1H, CHO), 8.29 (s, 1H, Ar-H), 7.64 (d, J = 15.5 Hz, 1H, =CH_{trans}), 7.24 (dd, J = 15.5, 7.8 Hz, 1H, =CH_{trans}), 5.99 (d, J = 5.0 Hz, 1H, H-1'), 5.69 (br s, 2H, NH_2),

5.45 (t, J = 4.6 Hz, 1H, H-2'), 4.60 (t, J = 3.8 Hz, 1H, H-3'), 4.12 (app q, J_{app} ~ 4.2 Hz, 1H, H-4'), 4.03 (dd, J = 11.2, 5.5 Hz, 1H, H-5'), 3.75 (dd, J = 11.2, 3.9 Hz, 1H, H-5'), 0.97, 0.80, and 0.78 (3s, 27H, *t*-Bu), 0.20, 0.17, 0.00, –0.03, –0.05, and –0.32 (6s, 18H, SiMe). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 125 MHz): δ 192.8, 156.6, 154.0, 151.3, 146.8, 136.3, 134.7, 121.1, 89.0, 86.0, 73.6, 72.4, 62.6, 26.2, 26.0, 25.9, 18.6, 18.5, 18.2, –4.2, –4.38, –4.4, –5.0, –5.3, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{31}H_{57}N_5NaO_5Si_3$ $[M + Na]^+$ 686.3560, found 686.3580.

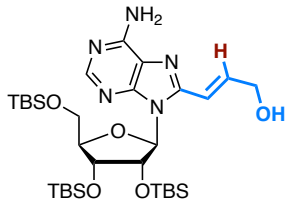
2-Fluoro-3-(2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosin-8-yl)acrylaldehyde (20)



In a flame-dried 5 mL round-bottom flask equipped with a stir bar, a solution of the silyl-protected Weinreb amide **18** (0.100 g, 0.135 mmol, 1.00 equiv.) was prepared in dry CH_2Cl_2 (0.8 mL), under a nitrogen atmosphere, and cooled to –70 to –60 °C. A 1.0 M solution of DIBALH in PhMe (340 μL, 0.340 mmol, 2.52 equiv.) was added dropwise to the stirred, cooled mixture. The reaction was allowed to proceed at –70 to –60 °C for 1 h. The reaction was quenched by the addition of deionized H_2O (15 mL) at 5 °C. The mixture was diluted with 15% aq. NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in CH_2Cl_2 gave 66.9 mg (73% yield) of fluoroenone **20** (*E*/*Z* ratio 1:17), as a yellow solid. R_f (SiO_2/30% EtOAc in CH_2Cl_2): 0.63. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.49 (d, J = 14.2 Hz, 1H, CHO), 8.32 (s, 1H, Ar-H), 6.97 (d, $^3J_{FH}$ = 28.6 Hz, 1H, $=CH_{trans}$), 6.18 (br s, 2H, NH_2), 5.92 (d, J = 5.1 Hz, 1H, H-1'), 5.42 (t, J = 4.7 Hz, 1H, H-2'), 4.55 (t, J = 4.0 Hz, 1H, H-3'), 4.12 (dt, J = 5.4, 3.8 Hz, 1H, H-4'), 4.00 (dd, J = 11.3, 5.6 Hz, 1H, H-5'), 3.74 (dd, J = 11.3, 3.9 Hz, 1H, H-5'), 0.96, 0.80, and 0.77 (3s, 27H, *t*-Bu), 0.18, 0.15, 0.00, –0.03, –0.05, and –0.32 (6s, 18H, SiMe). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ183.7 (d, $^2J_{CF}$ = 27.7 Hz), 156.9 (d, $^1J_{CF}$ = 285.9 Hz), 156.1, 154.0, 150.3, 142.6 (d, J_{CF} = 7.4 Hz), 121.4, 110.6 (d, $^2J_{CF}$ = 3.0 Hz), 89.0, 85.7, 73.2, 72.0, 62.3, 26.2, 26.0, 25.9, 18.5, 18.4, 18.1, –4.1, –4.3, –4.4, –5.0, –5.2, –5.4. ^{19}F NMR ($CDCl_3$, 470 MHz): δ–116.29 (t, $^3J_{FH}$ = 17.2 Hz, *E*-isomer), –117.50 (dd, $^3J_{FH}$ = 28.2, 13.9 Hz, *Z*-isomer). Whereas the ^1H and ^{13}C spectra did not show discernible resonances for the minor *E*-isomer, a resonance corresponding to it was observed in the ^{19}F NMR. HRMS data

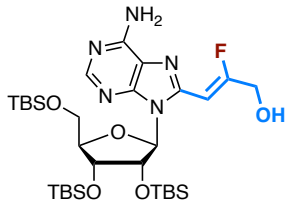
could not be obtained on this compound. However, HRMS data could be obtained for its reduction product (**22**).

2',3',5'-Tri-*O*-(*tert*-butyldimethylsilyl)-8-(3-hydroxypropen-1-yl)adenosine (21)



In a flame-dried 5 mL round-bottom flask equipped with a stir bar, a solution of the silyl-protected Weinreb amide **17** (0.120 g, 0.166 mmol, 1.00 equiv.) was prepared in dry CH_2Cl_2 (0.98 mL), under a nitrogen atmosphere, and cooled to –60 to –50 °C. A 1.0 M solution of DIBALH in PhMe (415 μL, 0.415 mmol, 2.50 equiv.) was added dropwise to the stirred, cooled mixture. The reaction was allowed to proceed at –60 to –50 °C for 1 h. The reaction was quenched by the addition of deionized H_2O (15 mL) at 5 °C. The mixture was diluted with 15% aq. NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure, and dried under high vacuum. The crude material was dissolved in EtOH (3.3 mL) and $CeCl_3 \bullet 7H_2O$ (136 mg, 0.365 mmol, 2.20 equiv.) followed by $NaBH_4$ (13.8 mg, 0.365 mmol, 2.20 equiv.) were added. The mixture was stirred at room temperature for 1 h and then quenched with deionized H_2O (15 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in hexanes followed by 50% EtOAc in hexanes gave 88.9 mg (80% yield) of the allylic alcohol **21** (*E*-isomer only), as a yellow solid. R_f (SiO_2/20% EtOAc in CH_2Cl_2): 0.41. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (s, 1H, Ar-H), 7.07 (dt, J = 15.6, 4.0 Hz, 1H, $=CH_{trans}$), 6.80 (d, J = 15.6 Hz, 1H, $=CH_{trans}$), 5.89 (d, J = 5.5 Hz, 1H, H-1'), 5.74 (br s, 2H, NH_2), 5.50 (t, J = 4.8 Hz, 1H, H-2'), 4.55 (t, J = 3.1 Hz, 1H, H-3'), 4.44 (d, J = 3.7 Hz, 2H, OCH_2), 4.09–4.03 (m, 2H, H-4', H-5'), 3.71 (app q, J_{app}~ 7.2 Hz, 1H, H-5'), 0.95, 0.83, and 0.76 (3s, 27H, *t*-Bu), 0.16 (s, 6H, SiMe), 0.01, –0.04, –0.08, and –0.37 (4s, 12H, SiMe). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 155.0, 152.3, 150.8, 149.8, 140.9, 119.8, 115.8, 88.7, 85.6, 72.53, 72.46, 62.8, 62.6, 26.2, 26.1, 25.9, 18.5, 18.4, 18.1, –4.2, –4.4 (2C), –5.0, –5.2, –5.3. HRMS (ESI/TOF): m/z calcd for $C_{31}H_{60}N_5O_5Si_3$ $[M + H]^+$ 666.3897, found 666.3898.

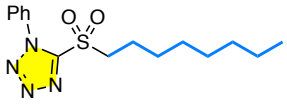
8-(2-Fluoro-3-hydroxypropen-1-yl)-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (22)



In a flame-dried 5 mL round-bottom flask equipped with a stir bar, a solution of the silyl-protected Weinreb amide **18** (0.100 g, 0.135 mmol, 1.00 equiv.) was prepared in dry CH_2Cl_2 (0.8 mL), under a nitrogen atmosphere, and cooled to –70 to –60 °C. A 1.0 M solution of DIBALH in PhMe (340 μL, 0.340 mmol, 2.52 equiv.) was added dropwise to the stirred, cooled mixture. The reaction was allowed to proceed at –70 to –60 °C for 1 h. The reaction was quenched by the addition of deionized H_2O (15 mL) at 5 °C. The mixture was diluted with 15% aq. NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure, and dried under high vacuum. The crude material was dissolved in EtOH (2.7 mL) and $CeCl_3 \bullet 7H_2O$ (125.6 mg, 0.337 mmol, 2.50 equiv.) followed by $NaBH_4$ (12.7 mg, 0.336 mmol, 2.49 equiv.) were added. The mixture was stirred at room temperature for 1 h and quenched with deionized H_2O (15 mL). The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in hexanes gave 74.9 mg (81% yield) of the fluorinated allylic alcohols **22** (E/Z ratio 1:22), as a yellow solid. R_f (SiO_2/50% EtOAc in hexanes): 0.55. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.26 (s, 1H, Ar-H), 6.14 (br s, 2H, NH_2), 6.13 (d, $^3J_{HF}$ = 33.3 Hz, 1H, =CH_{trans}), 5.79 (d, J = 5.4 Hz, 1H, H-1'), 5.49 (t, J = 4.8 Hz, 1H, H-2'), 4.56–4.52 (m, 1H, H-3'), 4.37 (d, J = 8.7 Hz, 2H, OCH_2), 4.08–4.00 (m, 2H, H-4', H-5'), 3.70 (app q, J_{app} ~ 8.2 Hz, 1H, H-5'), 0.95, 0.82, and 0.76 (3s, 27H, *t*-Bu), 0.154, 0.147, 0.00, –0.04, –0.08, and –0.36 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 166.2 (d, $^1J_{CF}$ = 281.1 Hz), 155.0, 152.5, 150.1, 145.3, 119.6, 94.0 (d, $^2J_{CF}$ = 5.1 Hz), 89.1, 85.6, 72.5, 72.4, 62.6, 60.5 (d, $^2J_{CF}$ = 32.1 Hz), 26.2, 26.0, 25.9, 18.5, 18.4, 18.0, –4.2, –4.38, –4.42, –5.0, –5.2, –5.4. ^{19}F NMR ($CDCl_3$, 470 MHz): δ –99.47 (d, $^3J_{FH}$ = 31.7 Hz, *Z*-isomer). HRMS (ESI/TOF): m/z calcd for $C_{31}H_{58}FN_5NaO_5Si_3$ $[M + Na]^+$ 706.3622, found 706.3628.

Synthesis of Other Olefination Reagents

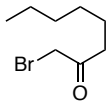
5-(Octylsulfonyl)-1-phenyl-1*H*-tetrazole (C)[5]



PT-sulfone **C** was synthesized by a modification of a previously reported procedure.[6] In a 25 mL round-bottom flask equipped with a stir bar, a

stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (712.8 mg, 4.00 mmol, 1.00 equiv.) in dry DMF (8.0 mL) was cooled to 0 °C, under a nitrogen atmosphere. NaH (124.8 mg, 5.20 mmol, 1.30 equiv.) was added and the mixture was stirred for 45 min at 0 °C. 1-Bromooctane (0.830 mL, 4.80 mmol, 1.20 equiv.) was added to the mixture and the stirring was continued for 1 h at room temperature, under a nitrogen atmosphere. The mixture was diluted with EtOAc (30 mL), washed with deionized H_2O (15 mL), and brine (20 mL). The aqueous layer was separated and extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with brine (20 mL × 2), dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure and dried under high vacuum. Without further purification the crude material was dissolved in EtOH (8.0 mL) and $(NH_4)_6Mo_7O_{24}•4H_2O$ (494.4 mg, 0.40 mmol, 10 mol%) was added. To this stirred solution at 0 °C, a 30% (w/w) solution of H_2O_2 (4.10 mL, 40.1 mmol, 10.0 equiv.) was added dropwise, and the reaction was allowed to proceed at room temperature for 4 h. The reaction mixture was diluted with deionized H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 5% EtOAc in CH_2Cl_2 gave 1.195 g (93% yield) of the olefination reagent **C**, as a white solid.

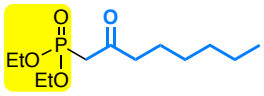
1-Bromooctan-2-one[7]



This compound was synthesized by a modification of a previously reported procedure.[8] In a 50 mL round-bottom flask equipped with a stir bar, bromine (0.860 mL, 16.8 mmol, 1.05 equiv.) was added dropwise to a stirred solution of 2-octanone (2.50 mL, 16.0 mmol, 1.00 equiv.) in MeOH (25.0 mL), while maintaining the bath temperature at –10 °C. The stirring was continued at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was re-cooled to 0 °C and H_2O (5.00 mL) followed by H_2SO_4 (8.75 mL) were added, and the resulting solution was stirred at room temperature for 16 h. The mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ (3 × 30 mL), water (10 mL), brine (15 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure and dried under high vacuum for 30 min. Vacuum

distillation of the crude material at 120 °C gave 2.783 g (84% yield) of 1-bromooctan-2-one as a colorless liquid.

Diethyl (2-oxooctyl)phosphonate (D)[9]



This compound was synthesized by modification of a previously reported procedure.[10] In a 100 mL round-bottom flask equipped with a stir bar, $P(OEt)_3$ (10.56 mL, 61.58 mmol, 5.00 equiv.) was added to a stirred solution of 1-bromooctan-2-one (2.55 g, 12.3 mmol, 1.00 equiv.) in PhMe (50.0 mL), and the mixture was heated at reflux for 24 h. The mixture was cooled and concentrated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 20% EtOAc in CH_2Cl_2 and 50% EtOAc in CH_2Cl_2 gave 1.848 g (57% yield) of product **D** as a colorless oil.

Optimizations of the olefination conditions were necessary in order to prepare the following compounds.

8-(Non-1-enyl)-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (**23**)

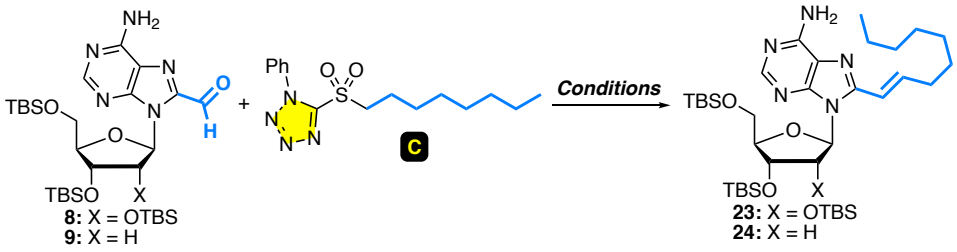
3',5'-Di-*O*-(*tert*-butyldimethylsilyl)-8-(non-1-enyl)-2'-deoxyadenosine (**24**)

8-(3-Oxonon-1-enyl)-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (**25**)

3',5'-Di-*O*-(*tert*-butyldimethylsilyl)-8-(3-oxonon-1-enyl)-2'-deoxyadenosine (**26**)

The two tables on the following two pages show these optimizations, following which the desired products were prepared.

Table S1 Julia-Kocienski olefination reactions of 8-formyladenine nucleosides **8** and **9** with PT-sulfone **C**

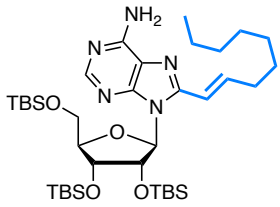


Entry	Aldehyde	Conditions[a]	Conversion[b]	Yield,[c] *E/Z* ratio[d]
1	**8**	LiHMDS, 2:1 THF-PhMe, –78 °C, 5 h	21%	**23:** –, –
2	**8**	NaHMDS, 2:1 THF-PhMe, –78 °C, 5 h	33%	**23:** –, –
3	**8**	KHMDS, 2:1 THF-PhMe, –78 °C, 5 h	42%	**23:** –, –
4[e]	**8**	KHMDS, 2:1 THF-PhMe, –78 °C, 5 h	38%	**23:** –, –
5[f]	**8**	KHMDS, 2:1 THF-PhMe, –78 °C, 5 h	45%	**23:** –, –
6[e]	**8**	KHMDS, DME, –78 °C, 5 h	83%	**23:** –, –
7[e]	**8**	KHMDS, DME, –78 °C, 5 h then –30 to –20 °C, 2 h	93%	**23:** –, –
8[e]	**8**	KHMDS, DME, –78 °C, 5 h then –30 to –20 °C, 2 h and then 16 h at rt	97%	**23:** –, –
9[e,g]	**8**	KHMDS, DME, –78 °C, 2 h then –60 °C, 1 h and then 16 h at rt	100%	**23:** 68%, *E*-isomer only
10[e]	**9**	KHMDS, DME, –60 to –50 °C, 4 h	98%	**24:** 47%, 16.6:1
11[e,g]	**9**	KHMDS, DME, –60 to –50 °C, 4 h	93%	**24:** 52%, 6.4:1

[a] Reactions were conducted with 0.0784 mmol of aldehyde **8** or **9** at a concentration of 8.80 mM in the solvent, with 2.0 equiv. of sulfone **C**, and 3.0 equiv. of base. [b] Conversions were calculated from the ^{1}H NMR data of the crude products. [c] Yields reported are of isolated and purified products. [d] *E*/*Z* ratios were determined from the ^{1}H NMR data of purified products. [e] KHMDS (5.0 equiv.) was used. [f] KHMDS (7.0 equiv.) was used. [g] Reaction was conducted with 0.313 mmol of the aldehyde.

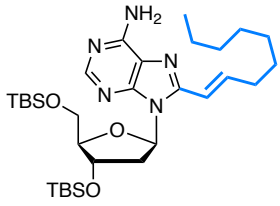
8-(Non-1-enyl)-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (23)

To a stirring solution of the silyl-protected adenosine-8-carbaldehyde (0.200 g, 0.313 mmol, 1.00 equiv.) in anhydrous DME (35.6 mL), prepared in a flame-dried 100 mL round-bottom flask, was



added the PT-sulfone **C** (202.2 mg, 0.627 mmol, 2.00 equiv.), and the mixture was cooled to –78 °C, under a nitrogen atmosphere. A 0.5 M solution of KHMDS in PhMe (3.1 mL, 1.6 mmol, 5.1 equiv.) was added to the mixture, at which time the mixture changed to a brown color. The mixture was then stirred at –78 °C for 2 h, followed by –60 °C for 1 h, and finally at room temperature for 16 h (by which time the color had changed to a yellow). The reaction was quenched with ice-cold deionized H_2O (30 mL), at which time the color of the mixture turned to a pale-yellow, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by sequential elution with 25% EtOAc in hexanes and 35% EtOAc in hexanes gave 156.9 mg (68% yield) of the C8 nonenyl adenosine derivative **23** (*E*-isomer >99%), as a pale-yellow solid. R_f (SiO_2/30% EtOAc in hexanes): 0.30. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (s, 1H, Ar-H), 6.96 (dt, *J* = 15.5, 7.1 Hz, 1H, =CH_{trans}), 6.50 (dt, *J* = 15.6, 1.5 Hz, 1H, =CH_{trans}), 5.88 (d, *J* = 5.6 Hz, 1H, H-1'), 5.72 (s, 2H, NH_2), 5.49 (dd, *J* = 5.4, 4.5 Hz, 1H, H-2'), 4.57 (dd, *J* = 4.2, 2.6 Hz, 1H, H-3'), 4.10–4.05 (m, 2H, H-4', H-5'), 3.73 (dd, *J* = 14.2, 7.3 Hz, 1H, H-5'), 2.31 (qd, *J* = 7.4, 1.4 Hz, 2H, CH_2), 1.51 (quint, *J* = 7.3 Hz, 2H, CH_2), 1.39–1.22 (m, 8H, CH_2), 0.96 (s, 9H, *t*-Bu), 0.88 (t, *J* = 7.0 Hz, 3H, Me), 0.83 and 0.76 (2s, 18H, *t*-Bu), 0.16 (s, 6H, SiMe), 0.02, –0.03, –0.08, and –0.38 (4s, 12H, SiMe). ^{13}C{^{1}H} NMR (CD_2Cl_2, 125 MHz): δ 155.3, 152.2, 151.1, 150.5, 143.2, 120.2, 116.6, 88.8, 85.7, 72.83, 72.78, 63.0, 33.7, 32.2, 29.63, 29.58, 29.1, 26.2, 26.1, 26.0, 23.1, 18.6, 18.5, 18.2, 14.3, –4.2, –4.38, –4.42, –5.0, –5.3, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{37}H_{72}N_5O_4Si_3$ $[M + H]^+$ 734.4887, found 734.4890.

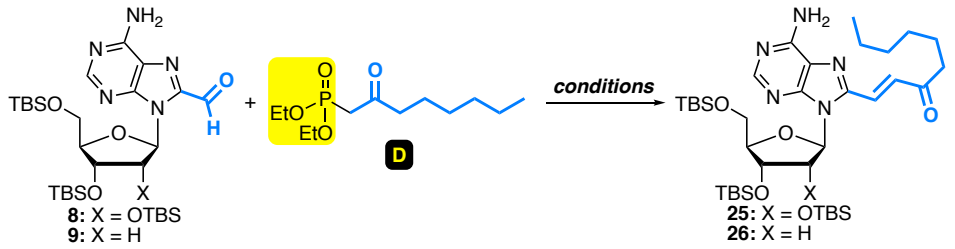
3',5'-Di-*O*-(*tert*-butyldimethylsilyl)-8-(non-1-enyl)-2'-deoxyadenosine (24)



To a stirring solution of the silyl-protected 2'-deoxyadenosine-8-carbaldehyde **9** (159.1 mg, 0.313 mmol, 1.00 equiv.) in anhydrous DME (35.6 mL), prepared in a flame-dried 100 mL round-bottom flask, was added the PT-sulfone **C** (202.2 mg, 0.627 mmol, 2.00 equiv.), and the mixture was maintained at –60 to –50 °C, under a nitrogen atmosphere. A 0.5 M solution of KHMDS in PhMe (3.1 mL, 1.6 mmol, 5.1 equiv.) was added to the mixture at which time the mixture changed to a brown color. The mixture was stirred at –60 to –50 °C over 4 h (by which

time the color had changed to a yellow). The reaction was quenched with ice-cold deionized H_2O (30 mL), at which time the color of the mixture turned to a pale-yellow, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column by elution with 20% EtOAc in CH_2Cl_2 gave 13.3 mg (7% yield) of the faster-eluting *Z*-isomer **24a**, as a pale-yellow, viscous oil. Subsequently, 85.5 mg (45% yield) of the later-eluting *E* isomer **24b** was obtained, also as a pale-yellow, viscous oil. R_f (SiO_2/50% EtOAc in hexanes): *Z* isomer = 0.42 and *E* isomer = 0.42. ^{1}H NMR of (*Z*)-**24a** ($CDCl_3$, 500 MHz): δ 8.27 (s, 1H, Ar-H), 6.53 (dt, *J* = 11.8, 1.5 Hz, 1H, =CH_{cis}), 6.35 (t, *J* = 7.0 Hz, 1H, H-1'), 6.18 (dt, *J* = 11.8, 7.4 Hz, 1H, =CH_{cis}), 5.56 (s, 2H, NH_2), 4.81–4.74 (m, 1H, H-3'), 3.93–3.88 (m, 2H, H-4', H-5'), 3.70 (app q, $J_{app} \sim$ 6.3 Hz, 1H, H-5'), 3.39 (dt, *J* = 13.3, 6.7 Hz, 1H, H-2'), 2.70–2.61 (m, 2H, CH_2), 2.17 (ddd, *J* = 13.1, 6.8, 3.9 Hz, 1H, H-2'), 1.47 (quint, *J* = 7.2 Hz, 2H, CH_2), 1.33–1.22 (m, 8H, CH_2), 0.92 (s, 9H, *t*-Bu), 0.88–0.83 (m, 3H, Me), 0.85 (s, 9H, *t*-Bu), 0.125, 0.121, 0.02, –0.01 (4s, 12H, SiMe). ^{13}C{^{1}H} NMR of (*Z*)-**24a** (CD_2Cl_2, 125 MHz): δ 155.2, 152.2, 150.6, 149.2, 144.0, 120.0, 115.9, 87.7, 84.1, 72.5, 63.1, 38.3, 32.2, 30.0, 29.7, 29.60, 29.57, 26.1, 26.0, 23.1, 18.6, 18.3, 14.3, –4.5, –4.6, –5.3, –5.4. HRMS (ESI/TOF) of (*Z*)-**24a**: m/z calcd for $C_{31}H_{57}N_5NaO_3Si_2$ $[M + Na]^+$ 626.3892, found 626.3892. ^{1}H NMR of (*E*)-**24b** ($CDCl_3$, 500 MHz): δ 8.23 (s, 1H, Ar-H), 6.97 (dt, *J* = 15.4, 7.1 Hz, 1H, =CH_{trans}), 6.57 (dt, *J* = 15.5, 1.5 Hz, 1H, =CH_{trans}), 6.32 (t, *J* = 6.7 Hz, 1H, H-1'), 5.69 (br, 2H, NH_2), 4.80 (dt, *J* = 6.2, 3.8 Hz, 1H, H-3'), 3.94 (dt, *J* = 5.7, 4.3 Hz, 1H, H-4'), 3.88 (dd, *J* = 10.8, 6.1 Hz, 1H, H-5'), 3.69 (dd, *J* = 10.8, 4.7 Hz, 1H, H-5'), 3.58 (dt, *J* = 13.1, 6.5 Hz, 1H, H-2'), 2.33–2.29 (m, 2H, CH_2), 2.19 (ddd, *J* = 13.2, 6.8, 4.1 Hz, 1H, H-2'), 1.53 (quint, *J* = 7.3 Hz, 2H, CH_2), 1.38–1.25 (m, 8H, CH_2), 0.93 (s, 9H, *t*-Bu), 0.88 (t, *J* = 7.0 Hz, 3H, Me), 0.83 (s, 9H, *t*-Bu), 0.14 (s, 6H, SiMe), 0.00 and –0.04 (2s, 6H, SiMe). ^{13}C{^{1}H} NMR of (*E*)-**24b** (CD_2Cl_2, 125 MHz): δ 155.5, 152.1, 151.0, 150.2, 142.8, 120.0, 117.0, 87.8, 84.3, 72.8, 63.3, 37.9, 33.7, 32.3, 29.7, 29.6, 29.2, 26.10, 26.07, 23.1, 18.7, 18.4, 14.3, –4.46, –4.56, –5.27, –5.32. HRMS (ESI/TOF) of (*Z*)-**24b**: m/z calcd for $C_{31}H_{57}N_5NaO_3Si_2$ $[M + Na]^+$ 626.3892, found 626.3892.

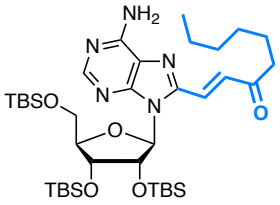
Table S2 Horner-Wadsworth-Emmons reactions of 8-formyladenine nucleosides **8** and **9** with phosphonate **D**



Entry	Aldehyde	Conditions[a]	Conversion[b]	Yield,[c] *E/Z* ratio[d]
1	**8**	$Ba(OH)_2$, THF-H_2O, rt, 16 h	100%	**25:** 85%, *10:1*
2	**8**	$Ba(OH)_2$, THF-H_2O, rt, 1 h	100%	**25:** 86%, *10:1*
3[e]	**8**	*1st run*: $Ba(OH)_2$, THF-H_2O, rt, 1 h	90%	–
		2nd run: $Ba(OH)_2$, THF-H_2O, rt, 1 h	100%	**25:** 83%, *25:1*[f]
4	**9**	$Ba(OH)_2$, THF-H_2O, rt, 2 h	95%	**26:** 77% (81%),[g] *E*-isomer only
5[h]	**9**	$Ba(OH)_2$, THF-H_2O, rt, 4 h	100%	**26:** 82%, *19.3:1*
6[i]	**9**	*1st run*: $Ba(OH)_2$, THF-H_2O, rt, 4 h	90%	–
		2nd run: $Ba(OH)_2$, THF-H_2O, rt, 2 h	100%	**26:** 89%, *8.5:1*[f]

[a] Reactions were conducted with 0.0780 mmol of aldehyde in 0.66 mL of THF and 10 μL of H_2O, with 1.0 equiv. of phosphonate **D**, and 0.80 equiv. of base. [b] %Conversions were calculated from the ^1H NMR data of the crude products. [c] Yields reported are of isolated and purified products. [d] *E/Z* ratios were determined from the ^1H NMR data of purified products. [e] Reaction was conducted with 0.3135 mmol of aldehyde in 3.4 mL of THF and 40 μL of H_2O. [f] After isolation in the first run, the crude product was subjected to reaction with 0.20 equiv. each of phosphonate **D** and $Ba(OH)_2$ in 3.4 mL of THF and 10 μL of H_2O. [g] Yield based on recovered starting material. [h] Reaction was conducted with 1.2 equiv. of phosphonate **D** and 1.0 equiv. of $Ba(OH)_2$. [i] Reaction was conducted with 1.2 equiv. of phosphonate **D** and 1.0 equiv. of $Ba(OH)_2$ in 3.6 mL of THF and 40 μL of H_2O. [j] Reaction was conducted with 0.20 equiv. each of phosphonate **D** and $Ba(OH)_2$ in 3.6 mL of THF and 40 μL of H_2O.

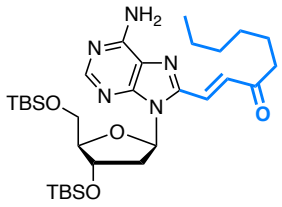
8-(3-Oxonon-1-enyl)-2',3',5'-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (25)



In an 8 mL vial, $Ba(OH)_2$ (43.0 mg, 0.251 mmol, 0.801 equiv.) was added to a stirred solution of phosphonate **D** (82.8 mg, 0.313 mmol, 1.00 equiv.) in THF (1.0 mL), at room temperature. The suspension was stirred at room temperature for 30 min and a solution of silyl-protected 8-formyladenosine **8** (0.200 g, 0.313 mmol, 1.00 equiv.) in 40:1 THF-water (1.64 mL) was added, at which point the mixture became a sludge. Therefore, additional THF (0.80 mL) was added, and the mixture was vigorously stirred at room temperature for 1 h. The mixture was diluted with

deionized H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude product mixture showed 10% of unreacted 8-formyladenosine **8** and the desired product in an *E*/*Z* ratio of 10:2. Because of the presence of the starting material, the mixture was subjected to reaction again with HWE reagent **D**. This was done by initially preparing a solution of phosphonate **D** (16.6 mg, 62.8 μmol, 0.200 equiv.) in THF (0.40 mL). Then, $Ba(OH)_2$ (10.8 mg, 63.0 μmol, 0.201 equiv.) was added to the mixture that was stirred at room temperature for 30 min. To the ensuing suspension, a solution of the crude product mixture obtained above in THF (3.0 mL) and water (10.0 μL) was added slowly, and the mixture was stirred for 1 h at room temperature. The reaction mixture was worked up exactly as described above. Chromatography of the crude material on a silica gel column by sequential elution with 5% EtOAc in hexanes, 10% EtOAc in hexanes, and 20% EtOAc in hexanes gave 195 mg (83% yield) of nucleoside enone **25** (E/Z ratio 32:1), as an off-white solid. R_f (SiO_2/50% EtOAc in hexanes): 0.52. ^{1}H NMR of (*E*)-**25a** ($CDCl_3$, 500 MHz): δ 8.26 (s, 1H, Ar-H), 7.58 (d, *J* = 15.5 Hz, 1H, =CH_{trans}), 7.34 (d, *J* = 15.5 Hz, 1H, =CH_{trans}), 6.31 (s, 2H, NH_2), 5.94 (d, *J* = 5.4 Hz, 1H, H-1'), 5.49 (t, *J* = 4.7 Hz, 1H, H-2'), 4.54 (t, *J* = 3.3 Hz, 1H, H-3'), 4.09–4.00 (m, 2H, H-4', H-5'), 3.72 (dd, *J* = 10.4, 3.4 Hz, 1H, H-5'), 2.63 (t, *J* = 7.3 Hz, 2H, CH_2), 1.66 (quint, *J* = 7.2 Hz, 2H, CH_2), 1.35–1.25 (m, 8H, CH_2), 0.94 (s, 9H, *t*-Bu), 0.86 (t, *J* = 6.5 Hz, 3H, Me), 0.80 and 0.74 (2s, 18H, *t*-Bu), 0.15, 0.14, –0.01, –0.06, –0.09, and –0.38 (6s, 18H, SiMe). ^{13}C{^{1}H} NMR of (*E*)-**25a** ($CDCl_3$, 125 MHz): δ 199.4, 156.0, 153.2, 151.0, 147.5, 132.8, 126.3, 120.6, 88.7, 85.7, 72.6, 72.4, 62.5, 42.4, 31.7, 29.1, 26.1, 26.0, 25.8, 22.6, 18.4, 18.3, 18.0, 14.2, –4.2, –4.4 (2C), –5.0, –5.3, –5.4. HRMS (ESI/TOF): m/z calcd for $C_{37}H_{69}N_5NaO_5Si_3$ $[M + Na]^+$ 770.4499, found 770.4515. ^{1}H NMR of (*Z*)-**25b** ($CDCl_3$, 500 MHz): δ 6.87 (d, *J* = 12.3 Hz, 1H, =CH_{cis}), 6.40 (d, *J* = 12.4 Hz, 1H, =CH_{cis}), 6.11 (s, 2H, NH_2), 5.89 (d, *J* = 5.6 Hz, 1H, H-1'), 5.33 (t, *J* = 4.8 Hz, 1H, H-2'), 4.53-4.50 (m, 1H, H-3'), 2.56 (t, *J* = 7.4 Hz, 2H, CH_2), 0.94 and 0.82 (2s, 18H, *t*-Bu), 0.13, 0.01, –0.03, and –0.36 (4s, 12H, SiMe). ^{13}C{^{1}H} NMR of (*Z*)-**25b** ($CDCl_3$, 125 MHz): δ 205.0, 155.7, 152.9, 150.6, 146.8, 137.6, 120.6, 88.6, 73.0, 72.2, 62.5, 42.7, 31.8, 29.0, 26.1, 26.0, 24.2, –5.2, –5.4. Only discernible NMR resonances of the minor isomer (*Z*)-**25b** are listed.

3',5'-Di-*O*-(*tert*-butyldimethylsilyl)-8-(3-oxonon-1-enyl)-2'-deoxyadenosine (26)



In an 8 mL vial, $Ba(OH)_2$ (53.7 mg, 0.313 mmol, 1.00 equiv.) was added to a solution of phosphonate **D** (99.4 mg, 0.376 mmol, 1.20 equiv.) in THF (1.00 mL), at room temperature. The suspension was stirred at room temperature for 30 min and a solution of silyl-protected 8-formyl-2'-deoxyadenosine **9** (0.159 g, 0.313 mmol, 1.00 equiv.) in 40:1 THF-water (1.64 mL) was added, at which point the mixture became a sludge. Therefore, additional THF (1.0 mL) was added and the mixture was vigorously stirred at room temperature for 4 h. The mixture was diluted with deionized H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude product mixture showed ca. 10% of unreacted 8-formyl-2'-deoxyadenosine **9**. Because of the presence of the starting material, the mixture was subjected to reaction again with HWE reagent **D**. This was done by initially preparing a solution of phosphonate **D** (16.6 mg, 62.8 μmol, 0.200 equiv.) in THF (0.50 mL). Then, $Ba(OH)_2$ (10.8 mg, 63.0 μmol, 0.201 equiv.) was added to the mixture that was stirred at room temperature for 30 min. To the ensuing suspension, a solution of the crude product mixture obtained above in THF (3.1 mL) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was worked up exactly as described above. Chromatography of the crude material on a silica gel column by sequential elution with 20% EtOAc in hexanes and 40% EtOAc in hexanes gave 173.1 mg (89% yield) of nucleoside enone **26** (*E*/*Z* ratio 8.5:1) as a yellow solid. R_f (SiO_2/50% EtOAc in hexanes): 0.37. ^{1}H NMR of (*E*)-**26a** ($CDCl_3$, 500 MHz): δ8.28 (s, 1H, Ar-H), 7.66 (d, *J* = 15.5 Hz, 1H, $=CH_{trans}$), 7.37 (d, *J* = 15.5 Hz, 1H, $=CH_{trans}$), 6.40 (t, *J* = 6.6 Hz, 1H, H-1'), 5.94 (br, 2H, NH_2), 4.79 (dt, *J* = 5.9, 4.0 Hz, 1H, H-3'), 3.96 (app q, $J_{app} \sim 4.8$ Hz, 1H, H-4'), 3.85 (dd, *J* = 10.9, 6.1 Hz, 1H, H-5'), 3.68 (dd, *J* = 11.0, 4.8 Hz, 1H, H-5'), 3.55 (dt, *J* = 13.1, 6.5 Hz, 1H, H-2'), 2.65 (t, *J* = 7.4 Hz, 2H, CH_2), 2.27 (ddd, *J* = 13.1, 6.6, 4.2 Hz, 1H, H-2'), 1.67 (quint, *J* = 7.3 Hz, 2H, CH_2), 1.36–1.28 (m, 8H, CH_2), 0.93 (s, 9H, *t*-Bu), 0.88 (t, *J* = 6.8 Hz, 3H, Me), 0.79 (s, 9H, *t*-Bu), 0.14 (s, 6H, SiMe), –0.03 and –0.07 (2s, 6H, SiMe). ^{13}C{^{1}H} NMR of (*E*)-**26a** ($CDCl_3$, 125 MHz): δ199.5, 155.9, 153.2, 151.0, 147.2, 132.2, 126.9, 120.5, 87.9, 84.4, 72.5, 63.0, 42.8, 38.1, 31.8, 29.1, 26.03, 26.00, 24.1, 22.7, 18.5, 18.2, 14.2, –4.5, –4.6, –5.27, –5.31. HRMS (ESI/TOF): m/z calcd for $C_{31}H_{56}N_5O_4Si_2$ $[M + H]^+$ 618.3865, found 618.3875. ^{1}H NMR of (*Z*)-**26b** ($CDCl_3$, 500 MHz): δ6.96 (d, *J* = 12.3 Hz, 1H, $=CH_{cis}$),

6.44 (d, J = 12.3 Hz, 1H, =CH_{cis}), 6.34 (t, J = 6.9 Hz, 1H, H-1'), 5.79 (br, 2H, NH_2), 4.73 (dt, J = 6.4, 3.3 Hz, 1H, H-3'), 4.11 (app q, $J_{app} \sim$ 7.1 Hz, 1H, H-4'), 3.90 (dd, J = 14.4, 4.1 Hz, 1H, H-5'), 3.27 (dt, J = 14.0, 7.2 Hz, 1H, H-2'), 2.57 (t, J = 7.4 Hz, 2H, CH_2), 1.61 (quint, J = 7.4 Hz, 2H, CH_2), 1.30–1.20 (m, 8H, CH_2), 0.91 and 0.85 (2s, 18H, *t*-Bu), 0.11 (s, 6H, SiMe), 0.02 and 0.00 (2s, 6H, SiMe). $^{13}C\{^1H\}$ NMR of (*Z*)-**26b** ($CDCl_3$, 125 MHz): δ 204.4, 155.5, 153.0, 150.6, 146.6, 137.0, 122.6, 119.9, 87.6, 84.2, 72.0, 62.7, 43.0, 38.8, 31.8, 29.0, 26.1, 24.1, 22.6, –5.2. Only the clearly discernible NMR resonances of the minor isomer (*Z*)-**26b** are listed.

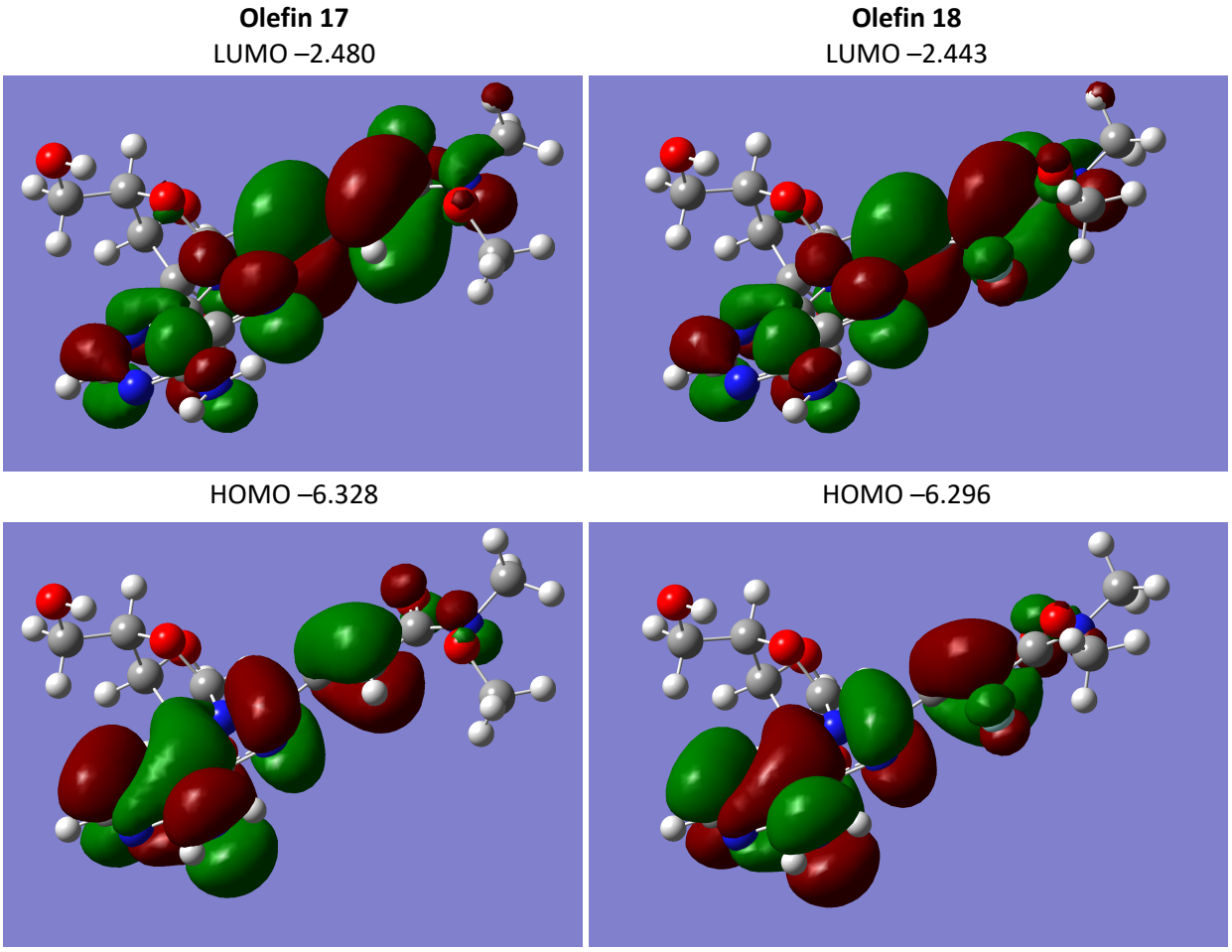
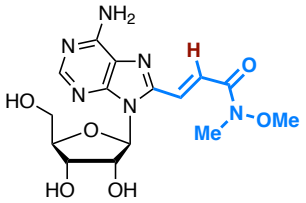
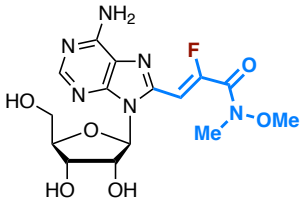
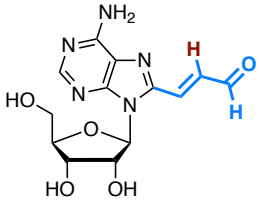
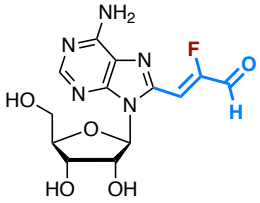


Fig. S1 Computed HOMO and LUMO orbitals of Weinreb enamides **17** and **18** (with OH groups).

Table S3 Calculated parameters for compound pairs **17**/**18** and **19**/**20**

	
E_{LUMO} = –2.480 eV	E_{LUMO} = –2.443 eV
E_{HOMO} = –6.328 eV	E_{HOMO} = –6.296 eV
Global hardness η = 1.924	Global hardness η = 1.927
Chemical potential μ = 4.404	Chemical potential μ = 4.369
Softness σ = 0.520 eV^{-1}	Softness σ = 1/η = 0.519 eV^{-1}
Electrophilicity index ω = 5.04 eV	Electrophilicity index ω = 4.95 eV

	
E_{LUMO} = –2.951 eV	E_{LUMO} = –3.060 eV
E_{HOMO} = –6.606 eV	E_{HOMO} = –6.611 eV
Global hardness η = 1.828	Global hardness η = 1.776
Chemical potential μ = 4.779	Chemical potential μ = 4.836
Softness σ = 0.547 eV^{-1}	Softness σ = 0.563 eV^{-1}
Electrophilicity index ω = 6.25 eV	Electrophilicity index ω = 6.59 eV

References

1 (*a*) R. M. Moriarty, W. R. Epa and A. K. Awasthi, *Tetrahedron Lett.*, 1990, **31**, 5877–5880; (*b*) P. Lagisetty, L. Zhang and M. K. Lakshman, *Adv. Synth. Catal.*, 2008, **350**, 602–608.

2 H. Hayakawa, K. Haraguchi, H. Tanaka and T. Miyasaka, *Chem. Pharm. Bull.*, 1987, **35**, 72–79.

3 D. B. Gophane and S. T. Sigurdsson, *Beilstein J. Org. Chem.*, 2015, **11**, 219–227.

4 T. A. Khandaker, J. D. Hess, R. Aguilera, G. Andrei, R. Snoeck, D. Schols, P. Pradan and M. K. Lakshman, *Eur. J. Org. Chem.*, 2019, 5610–5623.

5 C. R. Reddy and B. Latha, *Tetrahedron: Asymmetry*, 2011, **22**, 1849–1854.

6 N. Dussart, H. V. Trinh and D. Gueyrard, *Org. Lett.*, 2016, **18**, 4790–4793.

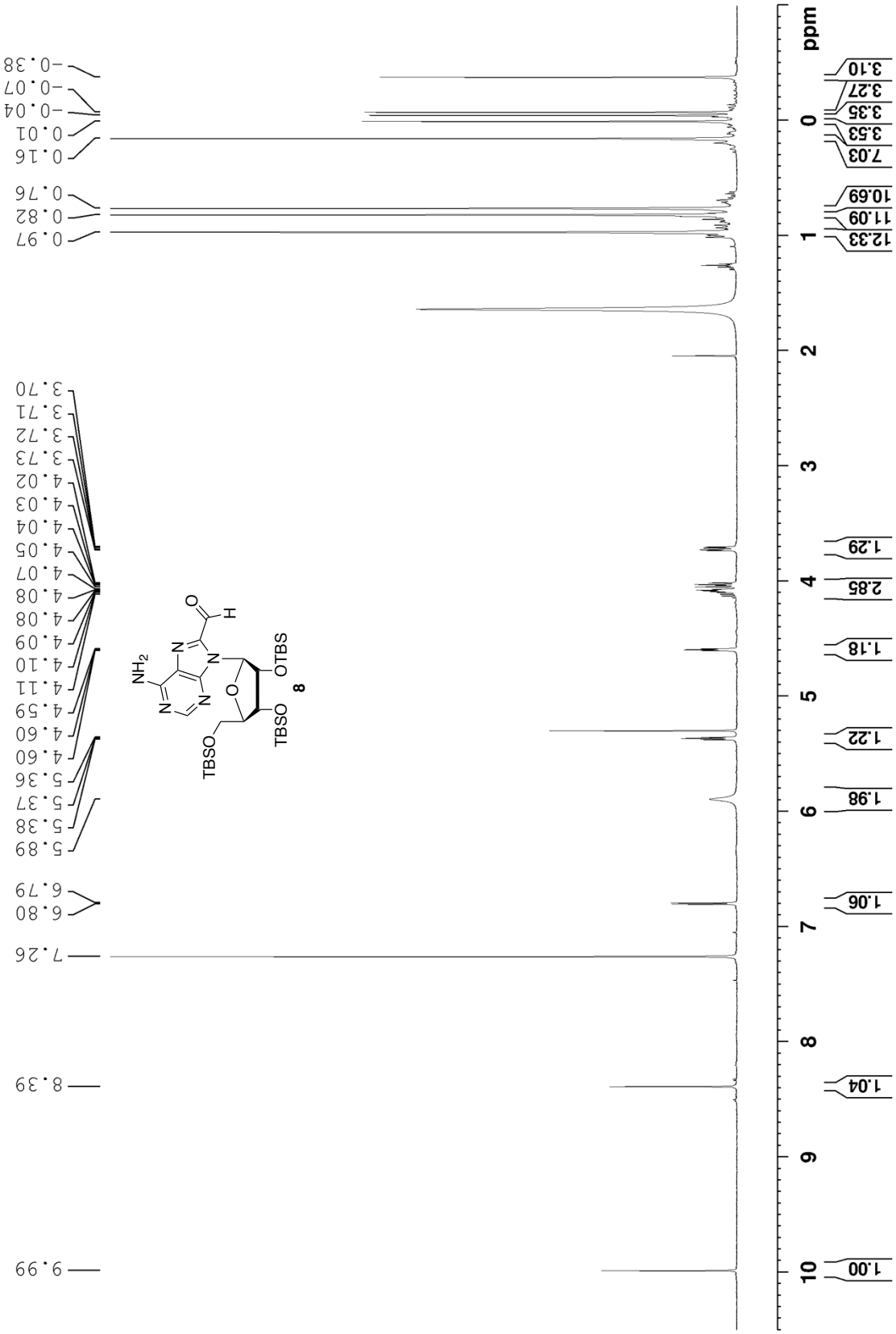
7 H. Bronstein, M. Hurhangee, E. C. Fregoso, D. Beatrup, Y. W. Soon, Z. Huang, A. Hadipour, P. S. Tuladhar, S. Rossbauer, E.-H. Sohn, S. Shoaee, S. D. Dimitrov, J. M. Frost, R. S. Ashraf, T. Kirchartz, S. E. Watkins, K. Song, T. Anthopoulos, J. Nelson, B. P. Rand, J. R. Durrant and I. McCulloch, *Chem. Mater.*, 2013, **25**, 4239–4249.

8 W.-Y. Wong, X.-Z. Wang, Z. He, K.-K. Chan, A. B. Djurišić, K.-Y. Cheung, C.-T. Yip, A. M.-C. Ng, Y. Y. Xi, C. S. K. Mak and W.-K. Chan, *J. Am. Chem. Soc.*, 2007, **129**, 14372–14380.

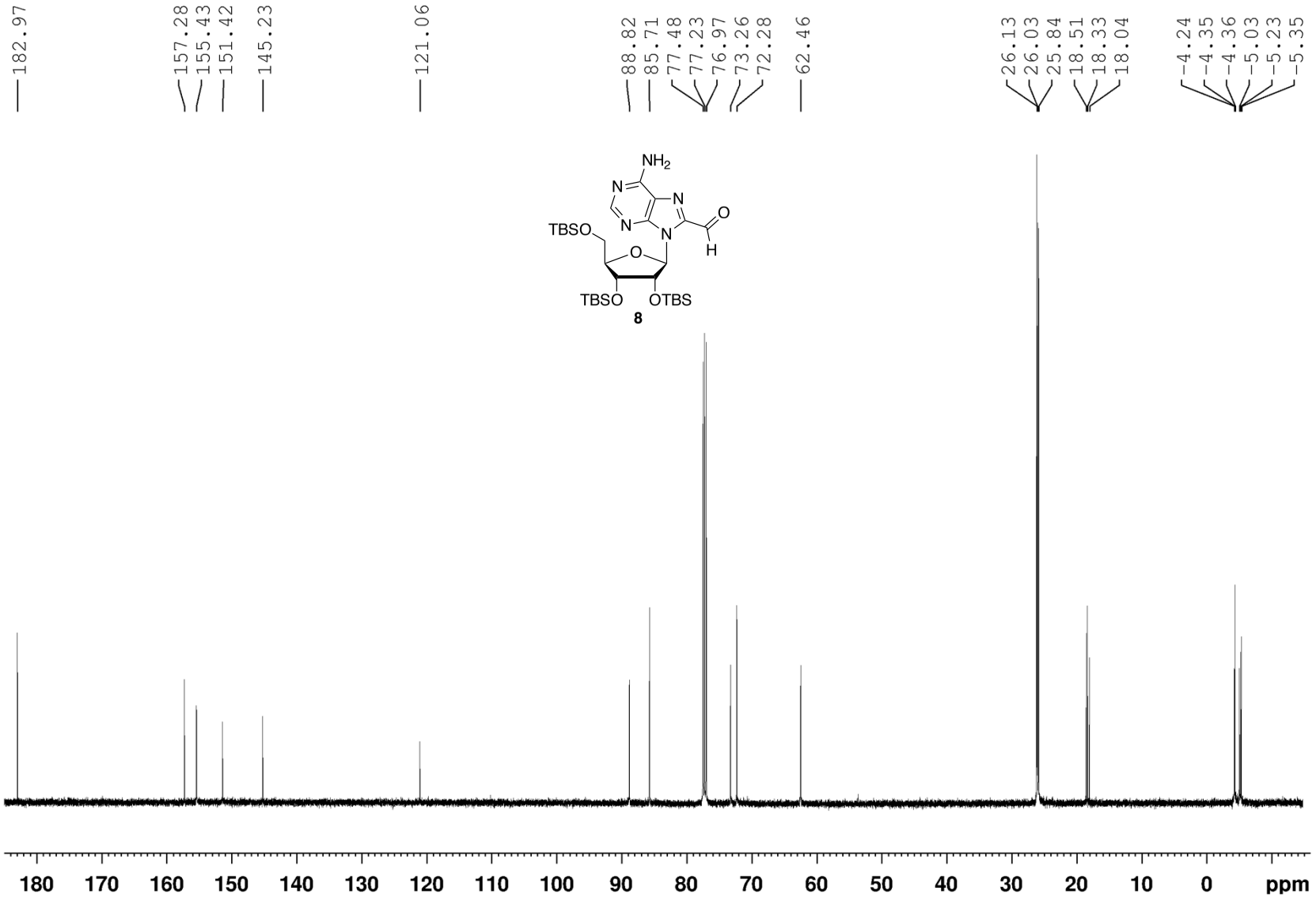
9 P. Zhou, B. Hu, L. Li, K. Rao, J. Yang and F. Yu, *J. Org. Chem.*, 2017, **82**, 13268–13276.

10 L. G. Meimetis, D. E. Williams, N. R. Mawji, C. A. Banuelos, A. A. Lal, J. J. Park, A. H. Tien, J. G. Fernandez, N. J. de Voogd, M. D. Sadar and R. J. Andersen, *J. Med. Chem.*, 2012, **55**, 503–514.

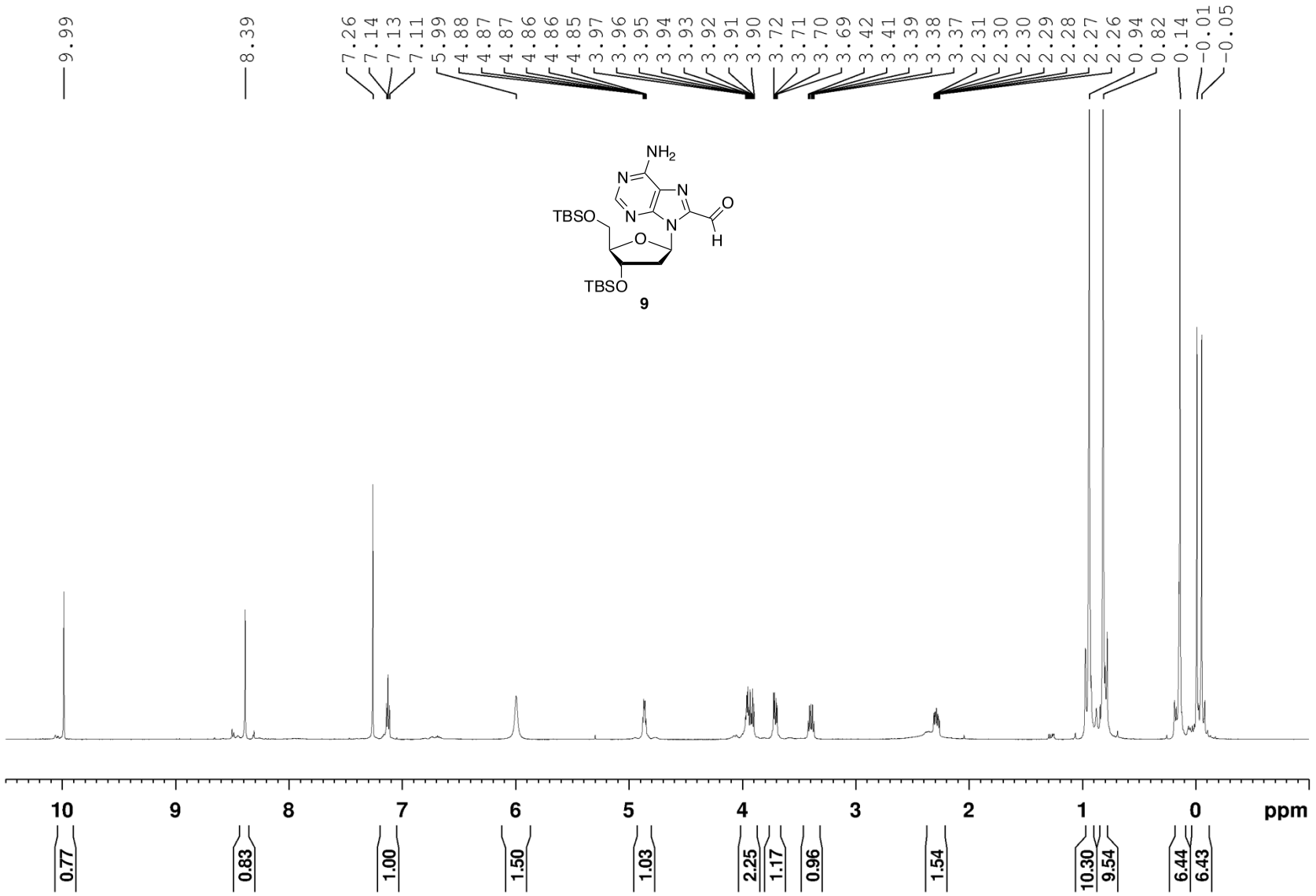
500 MHz ^{1}H NMR spectrum of compound **8** in $CDCl_3$



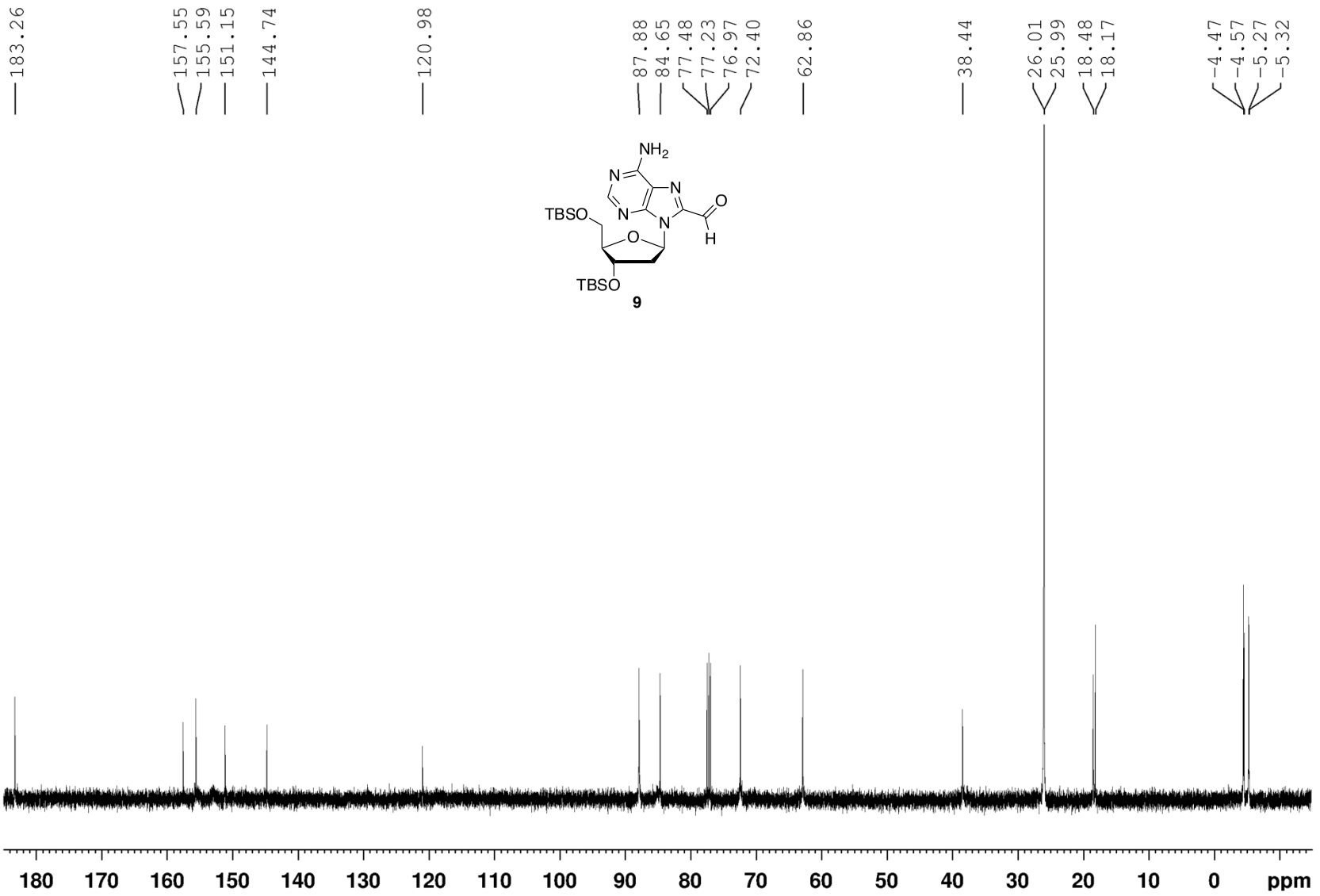
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **8** in $CDCl_3$



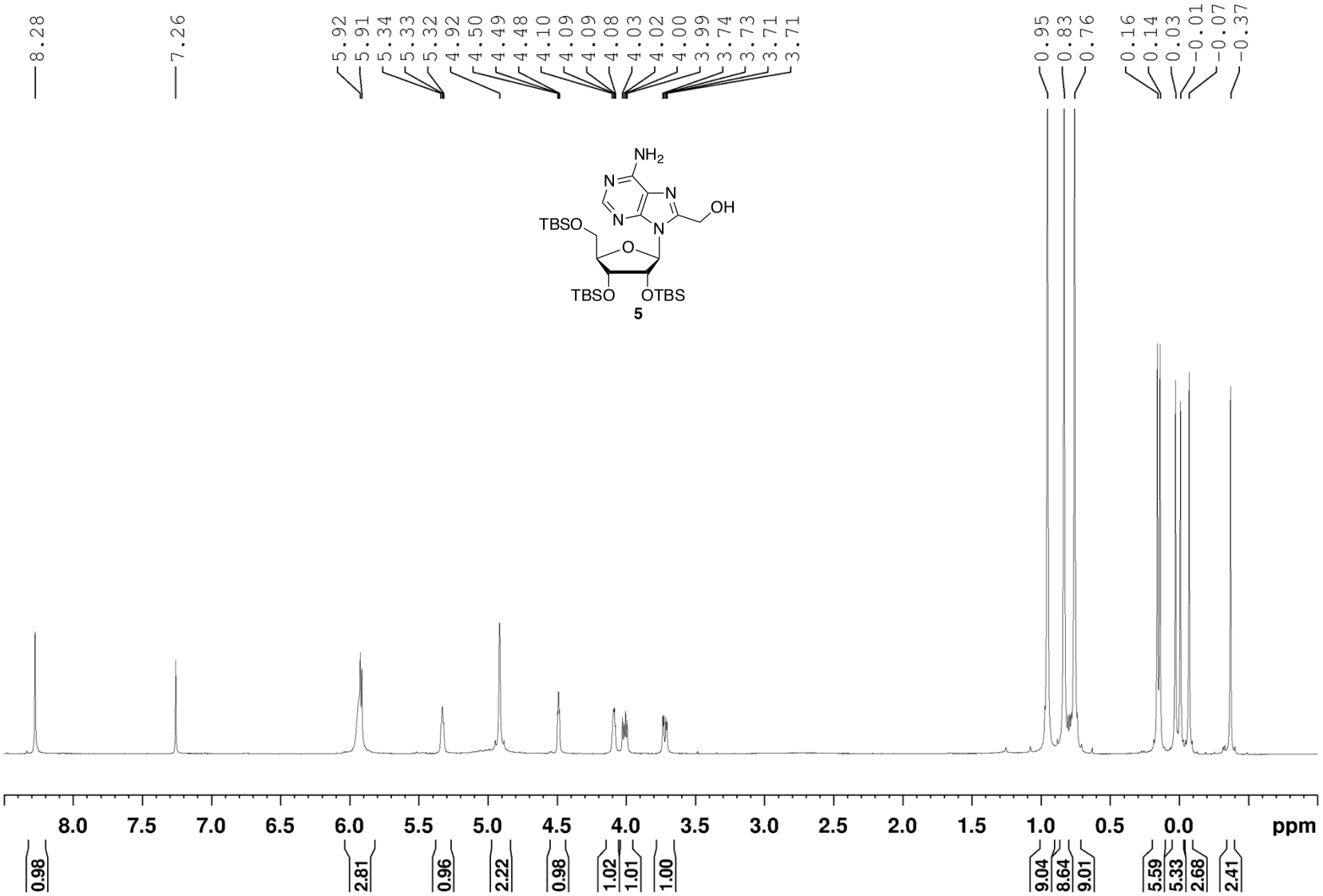
500 MHz ^{1}H NMR spectrum of compound **9** in $CDCl_3$



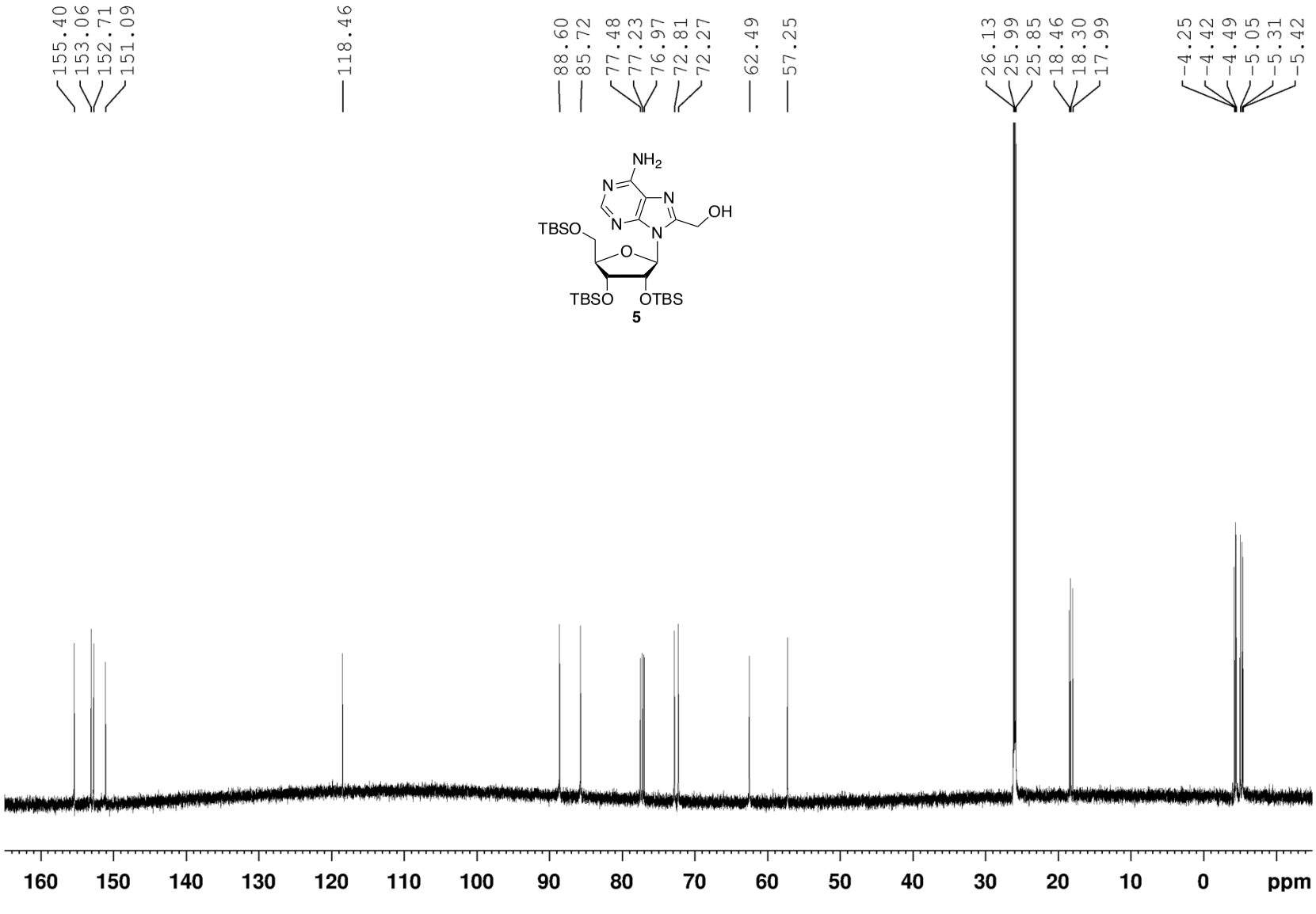
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **9** in $CDCl_3$



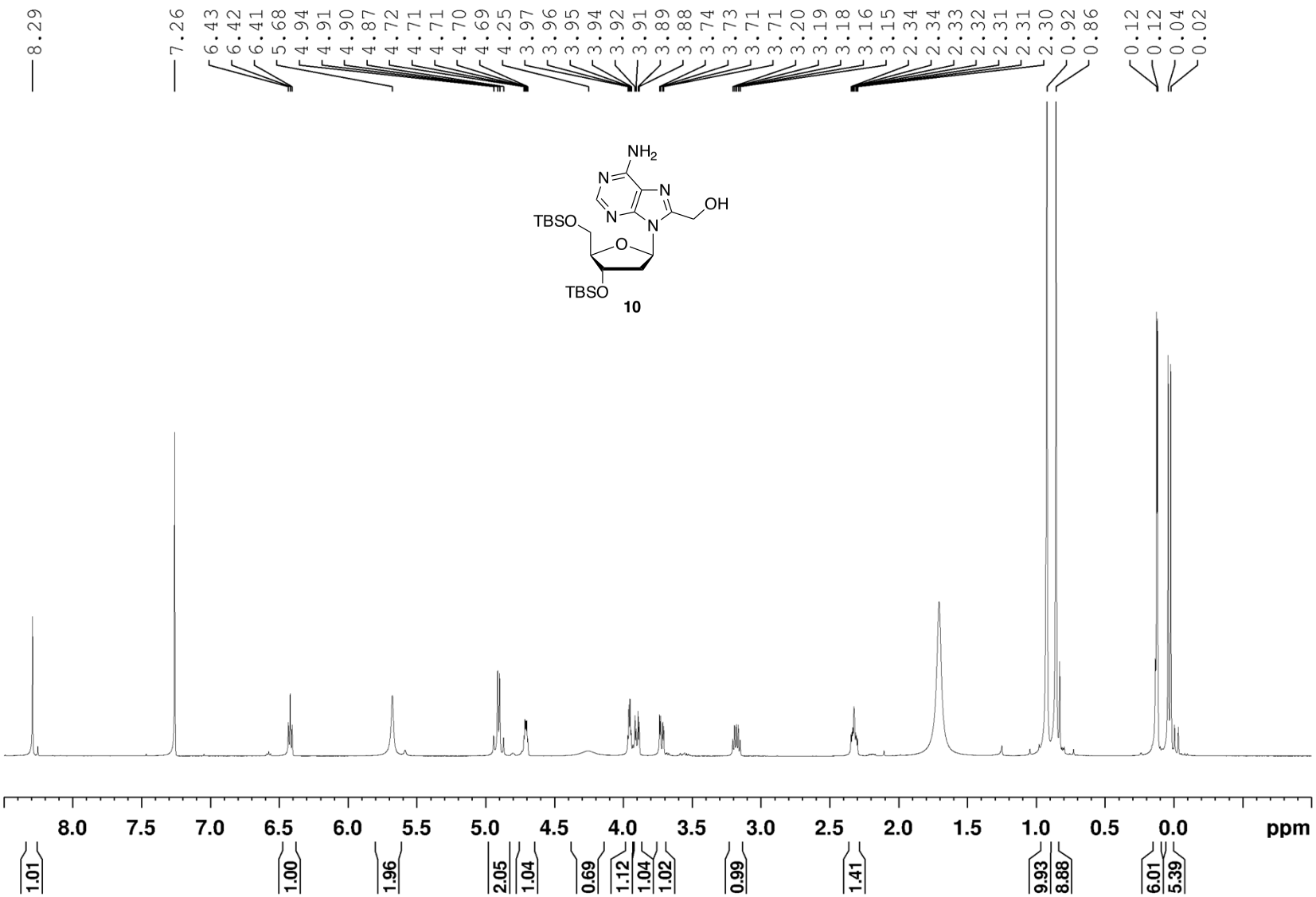
500 MHz ^{1}H NMR spectrum of compound **5** in $CDCl_3$



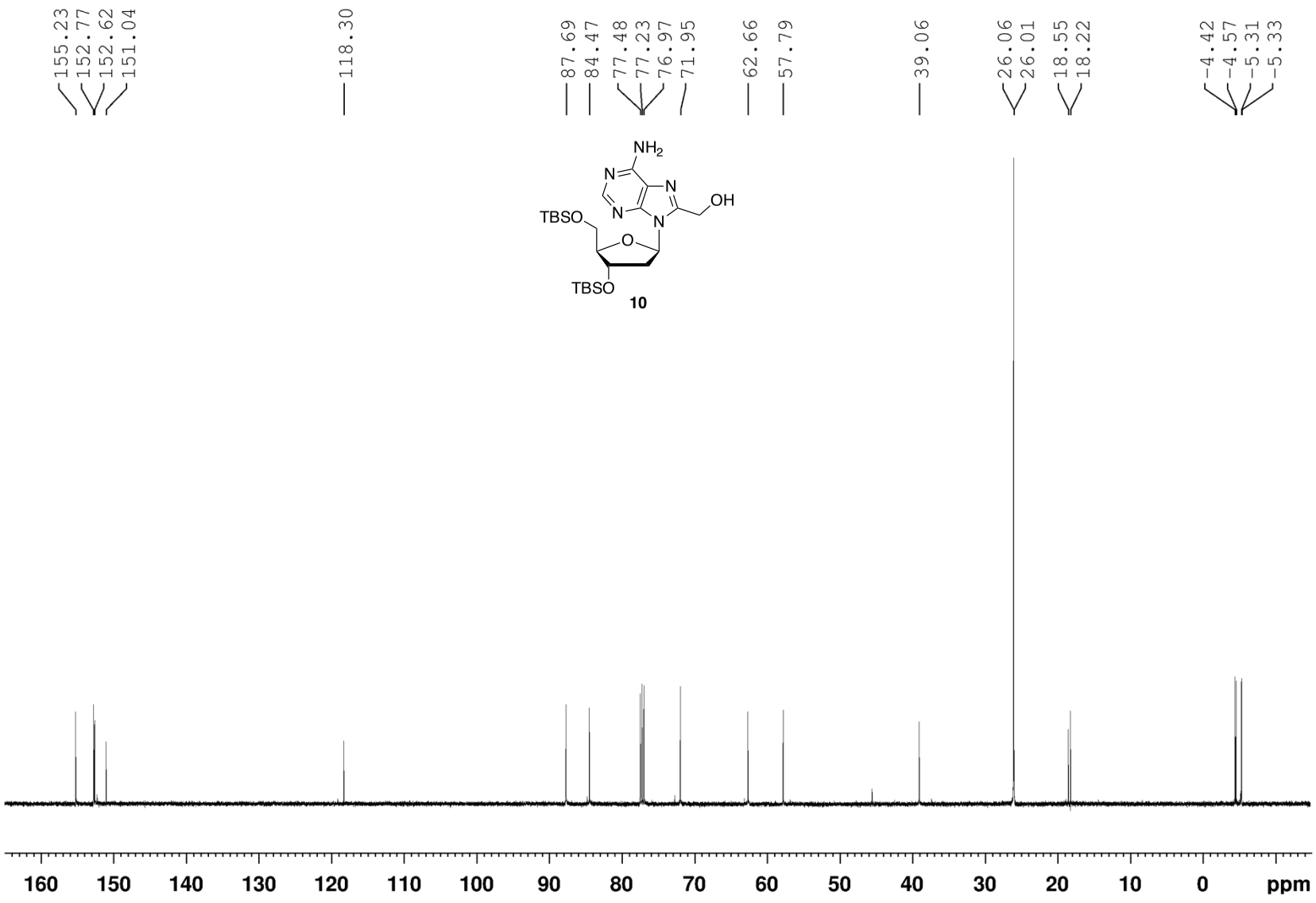
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **5** in $CDCl_3$



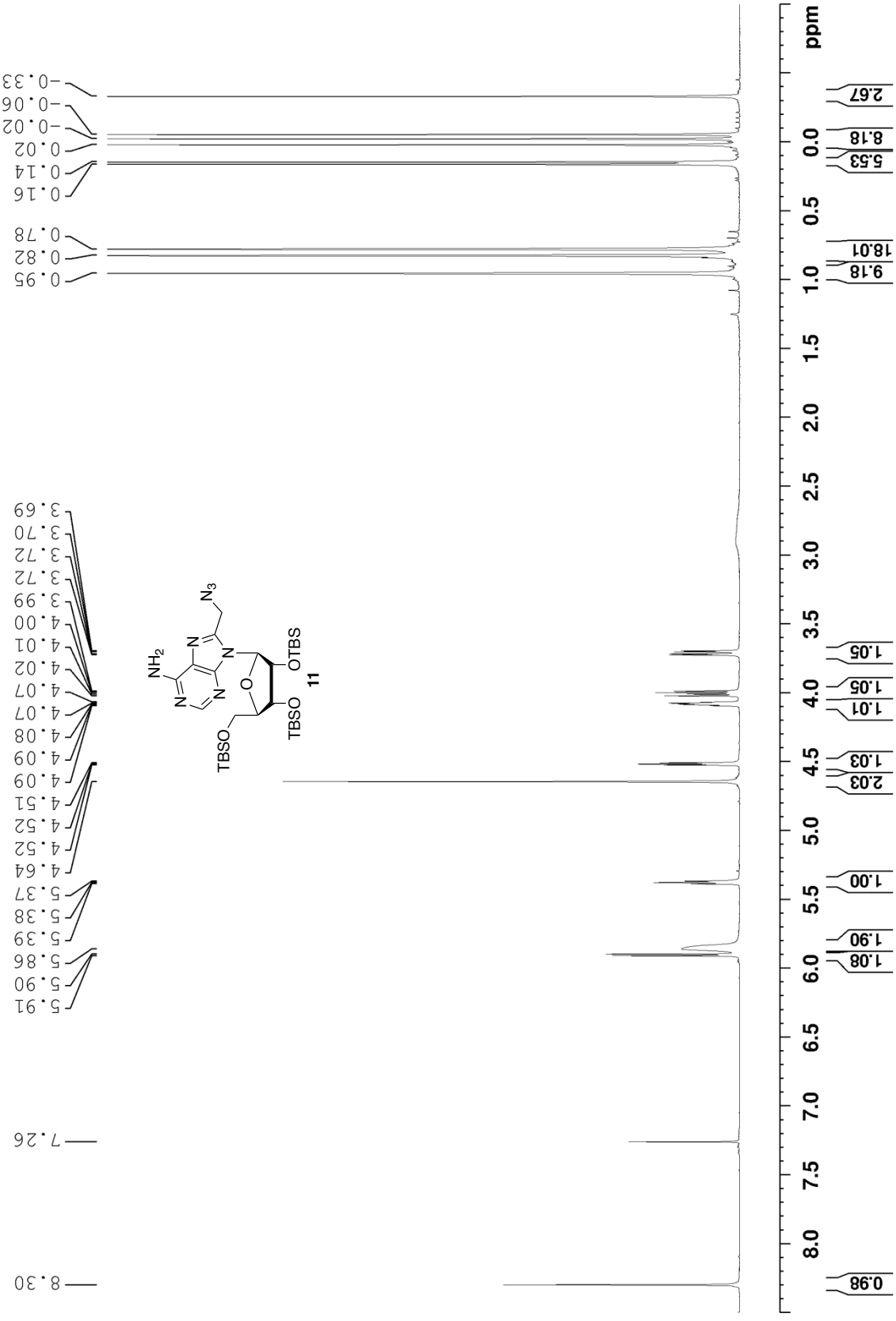
500 MHz ^{1}H NMR spectrum of compound **10** in $CDCl_3$



125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **10** in $CDCl_3$



500 MHz ^{1}H NMR spectrum of compound **11** in $CDCl_3$



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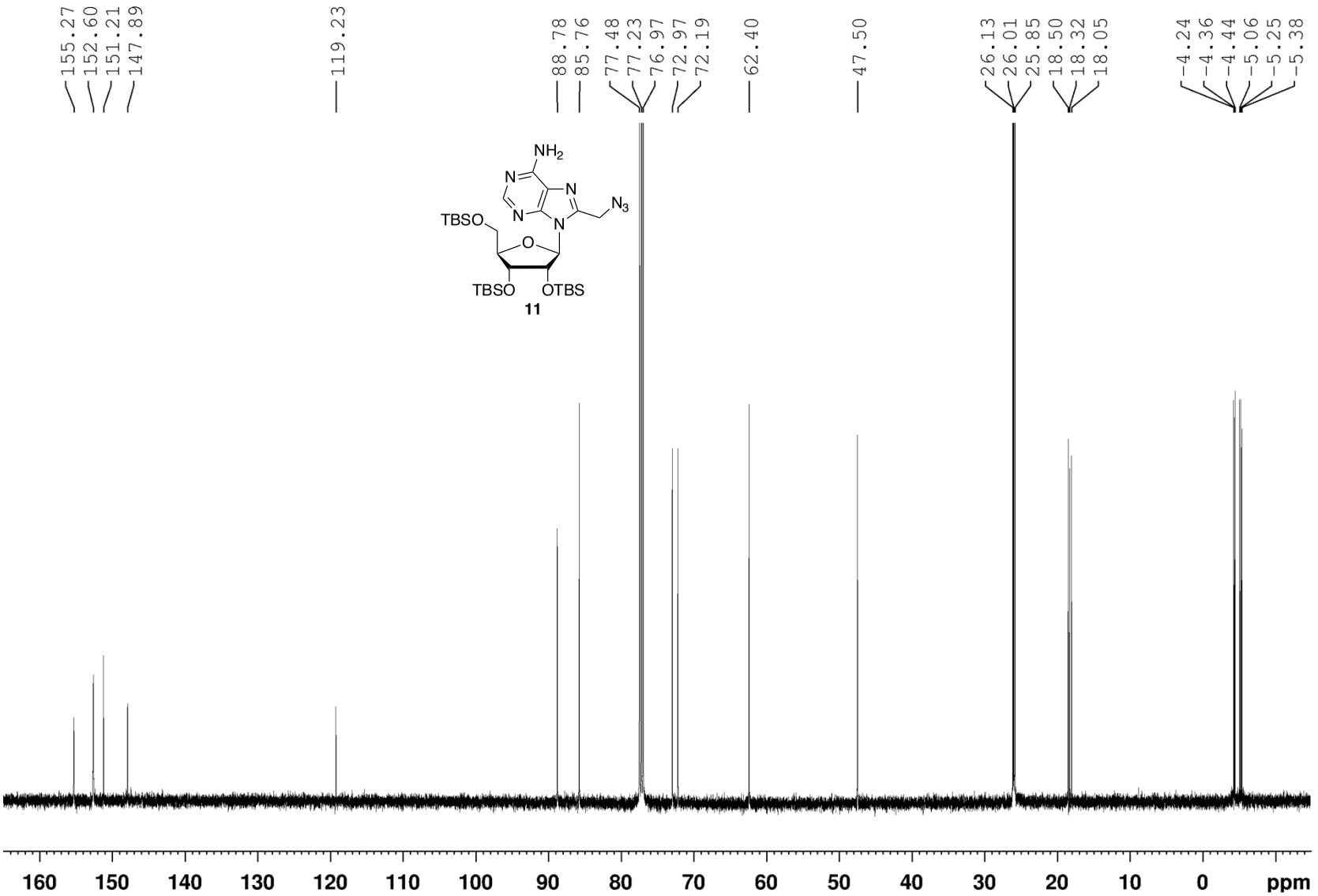
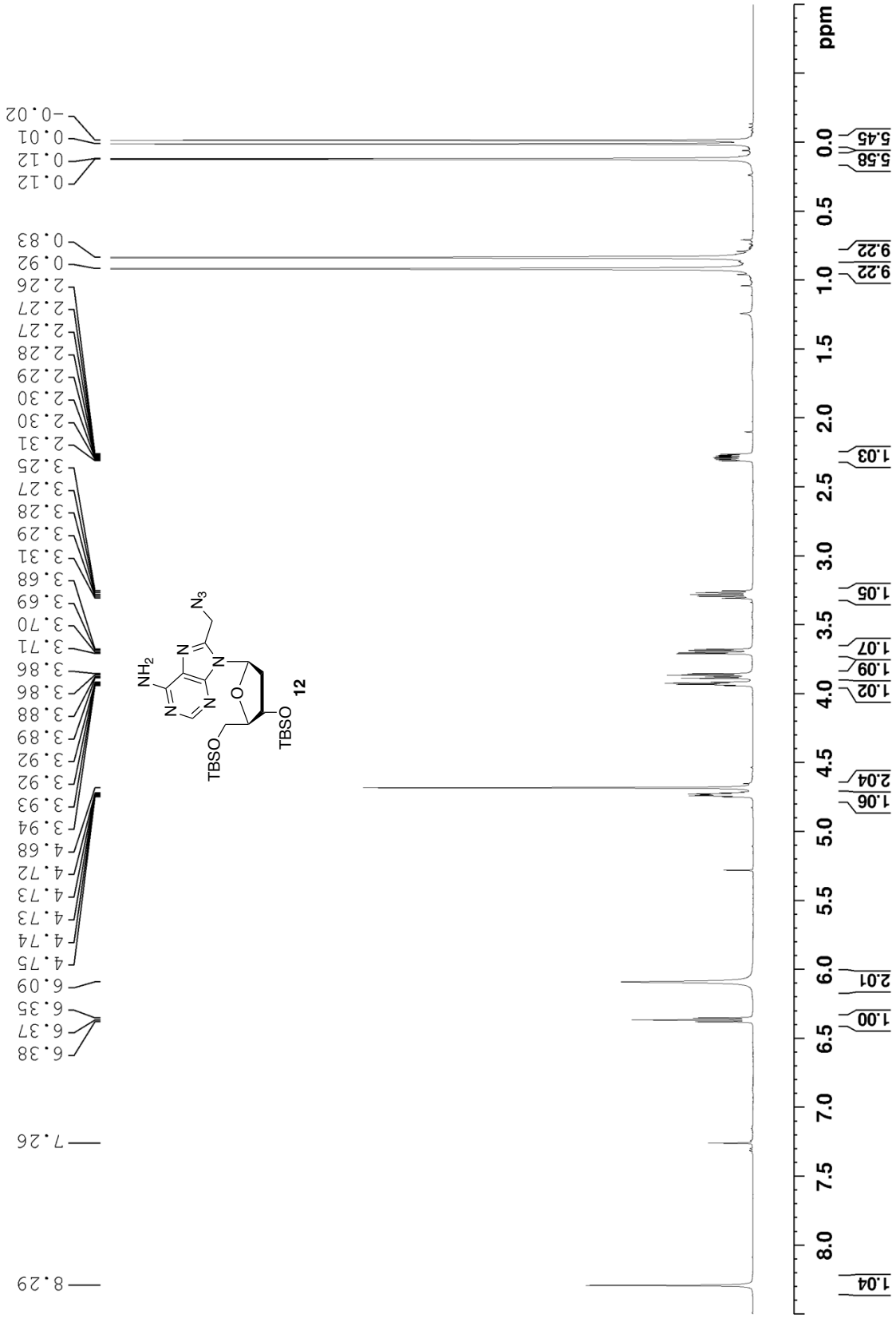
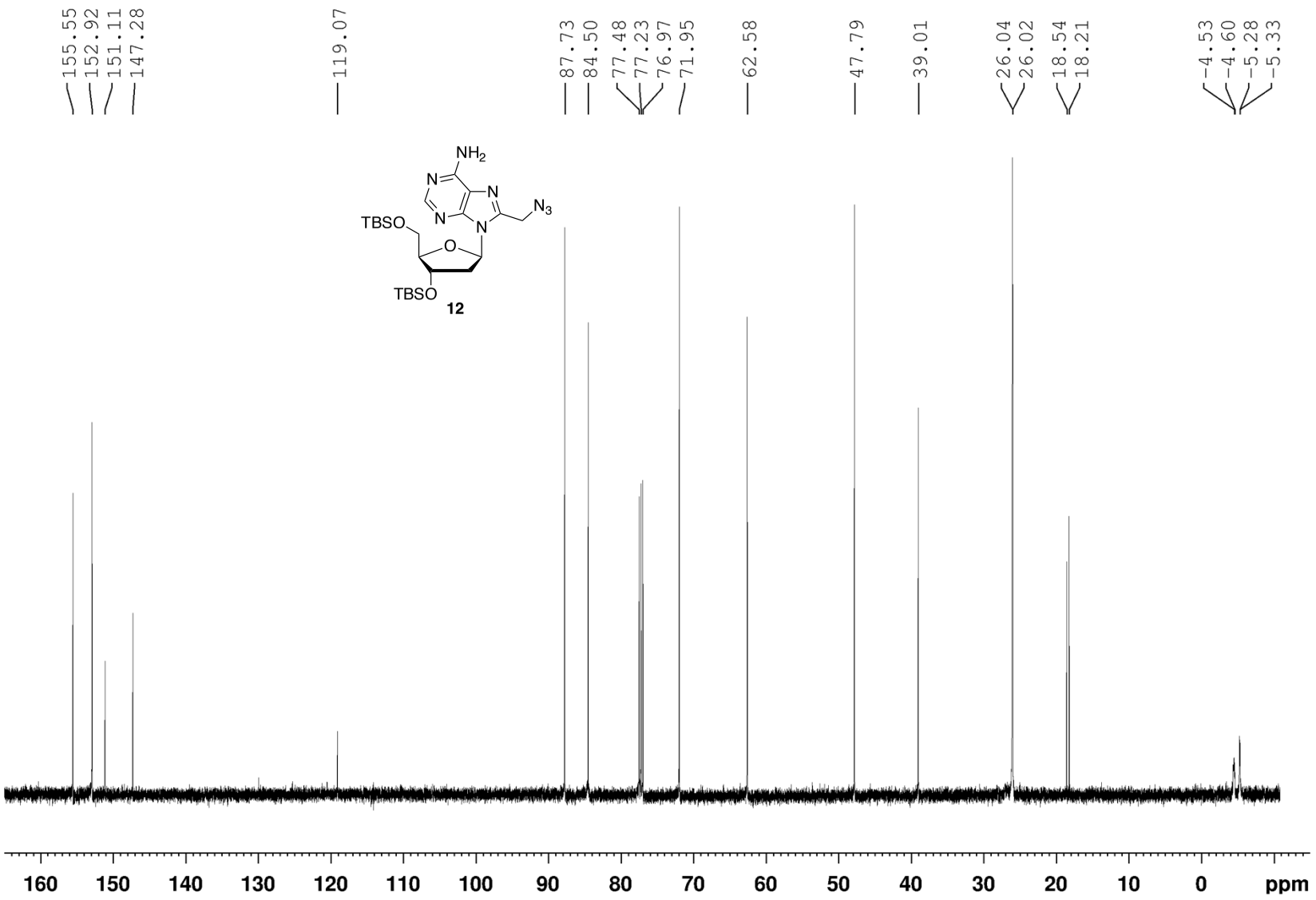


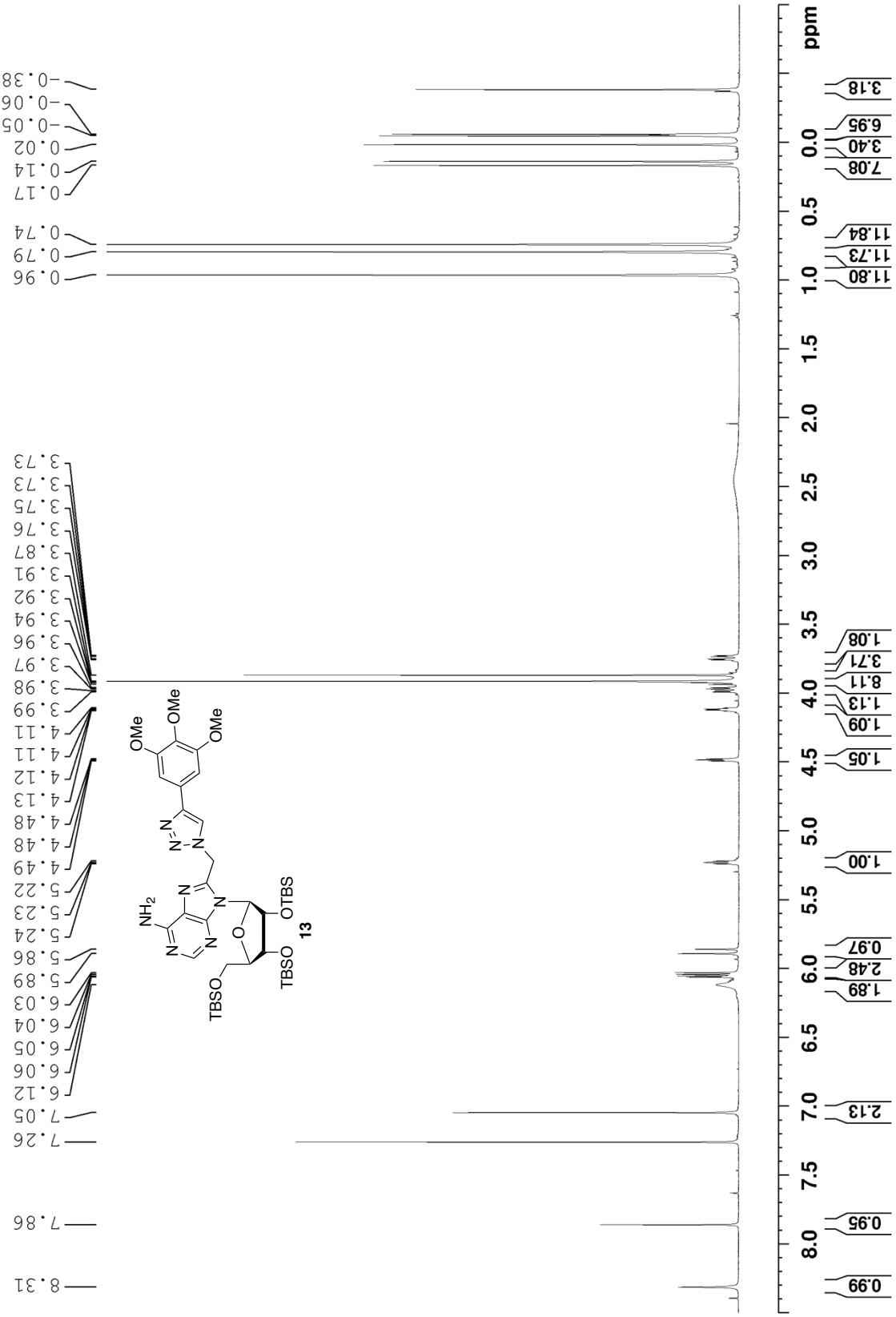
500 MHz ^{1}H NMR spectrum of compound **12** in $CDCl_3$



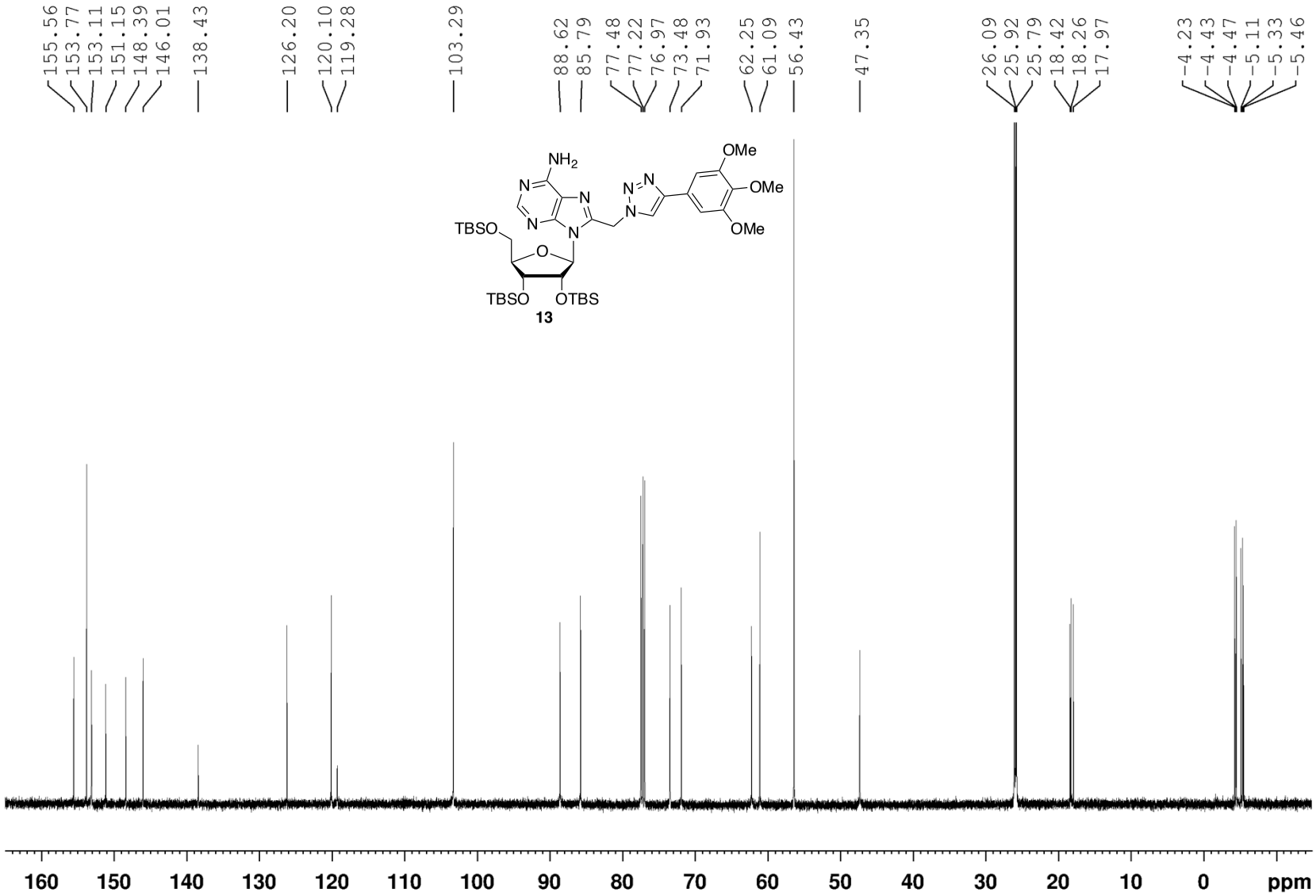
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **12** in $CDCl_3$



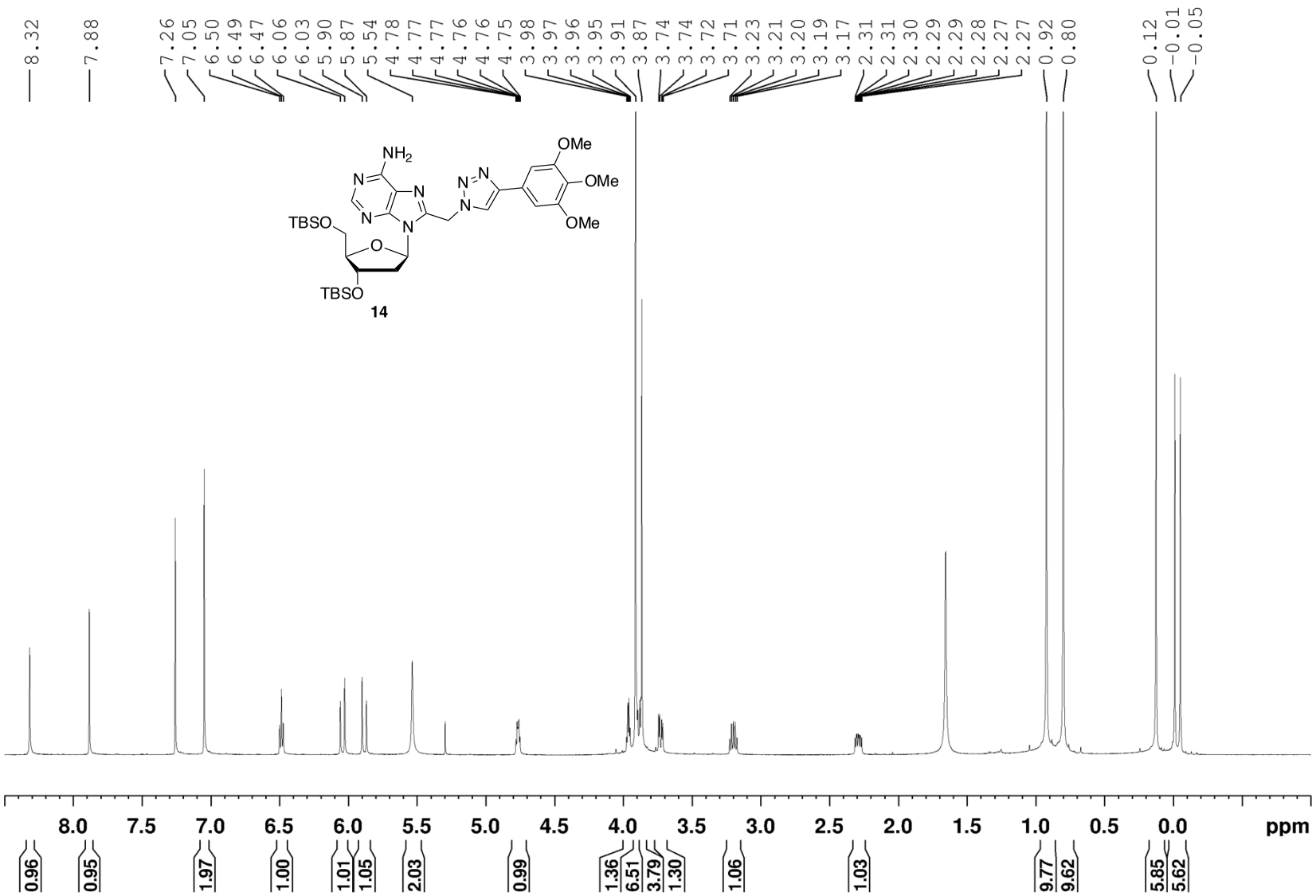
500 MHz ^{1}H NMR spectrum of compound **13** in $CDCl_3$



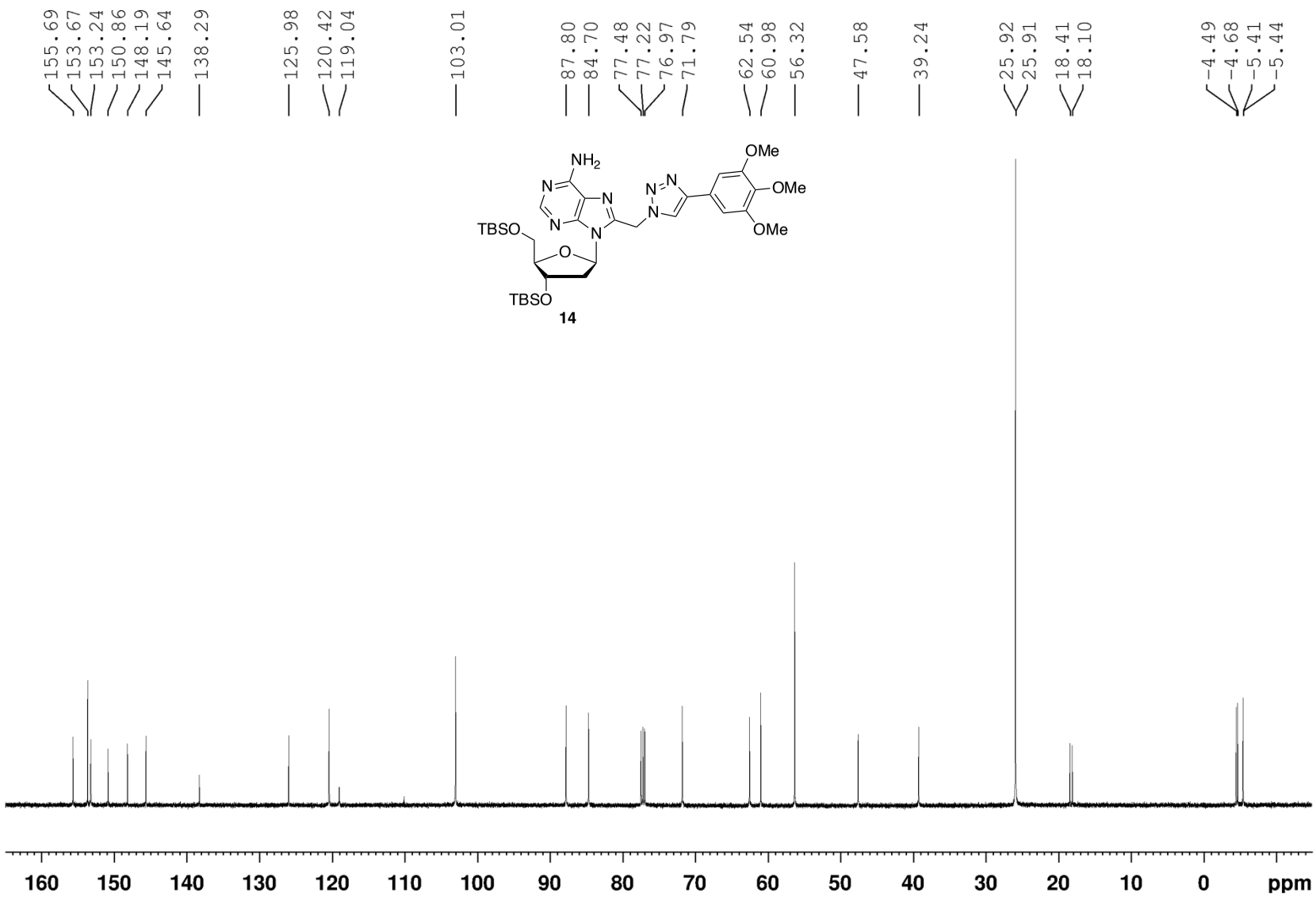
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **13** in $CDCl_3$



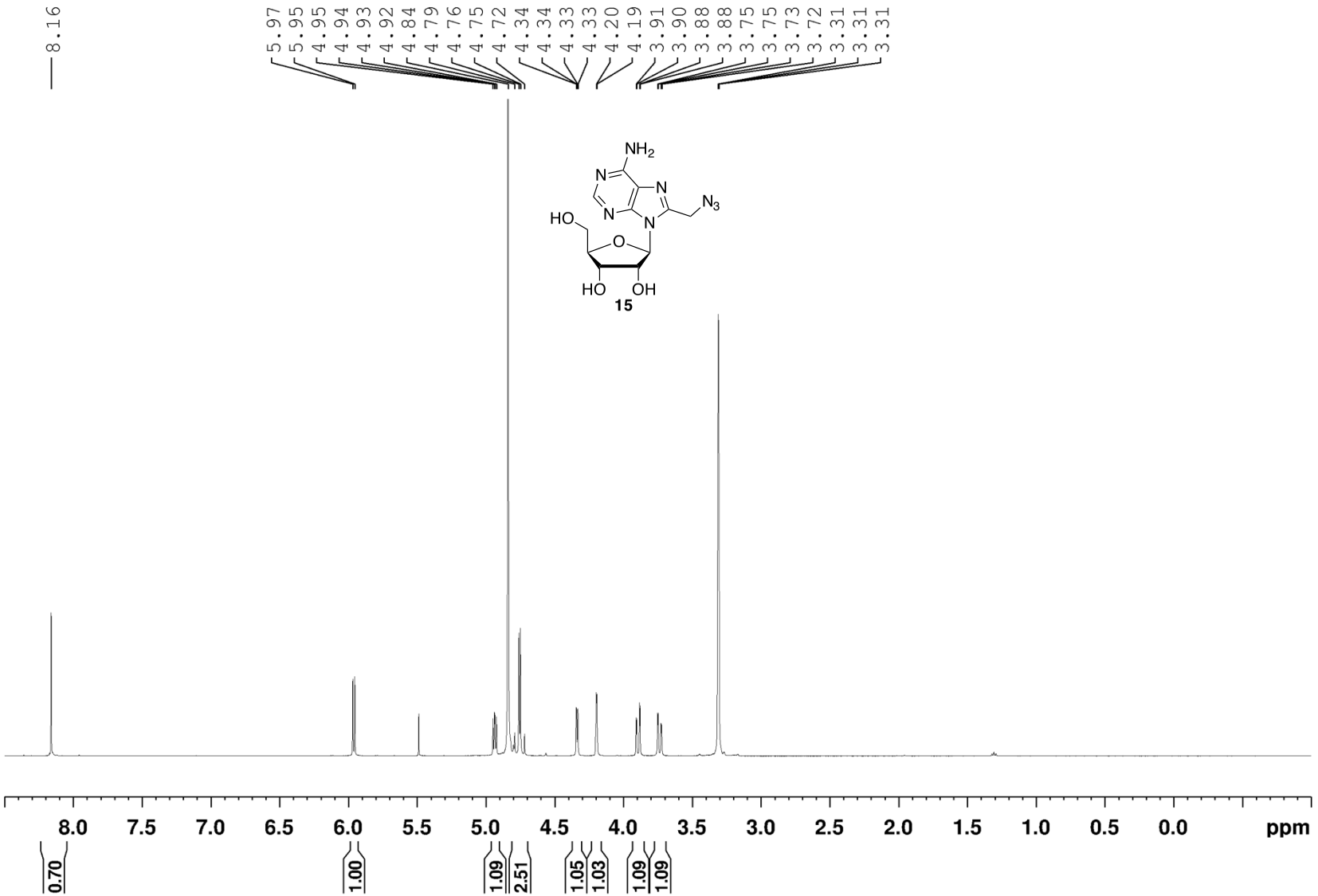
500 MHz ^{1}H NMR spectrum of compound **14** in $CDCl_3$



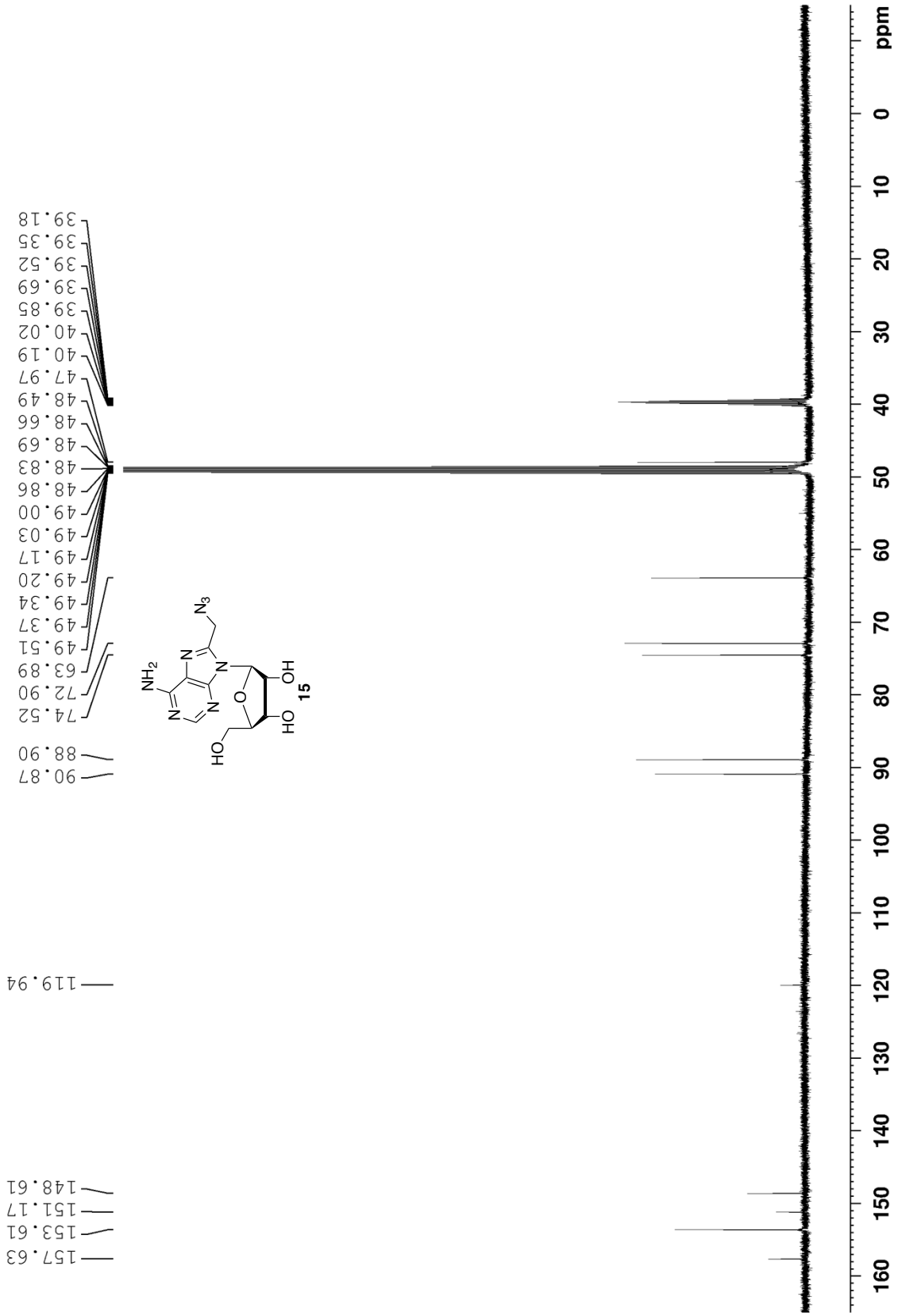
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **14** in $CDCl_3$



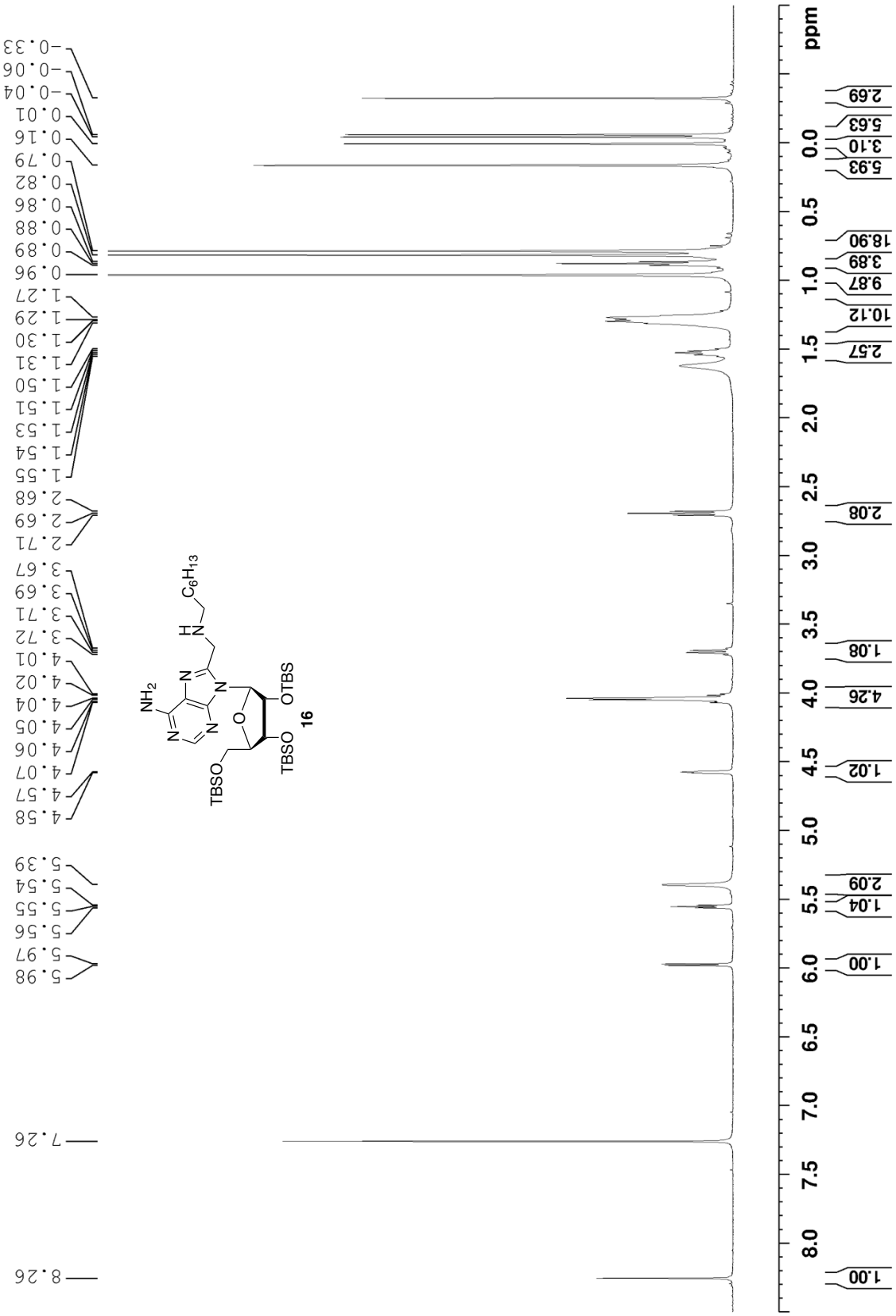
500 MHz ^{1}H NMR spectrum of compound **15** in CD_3OD



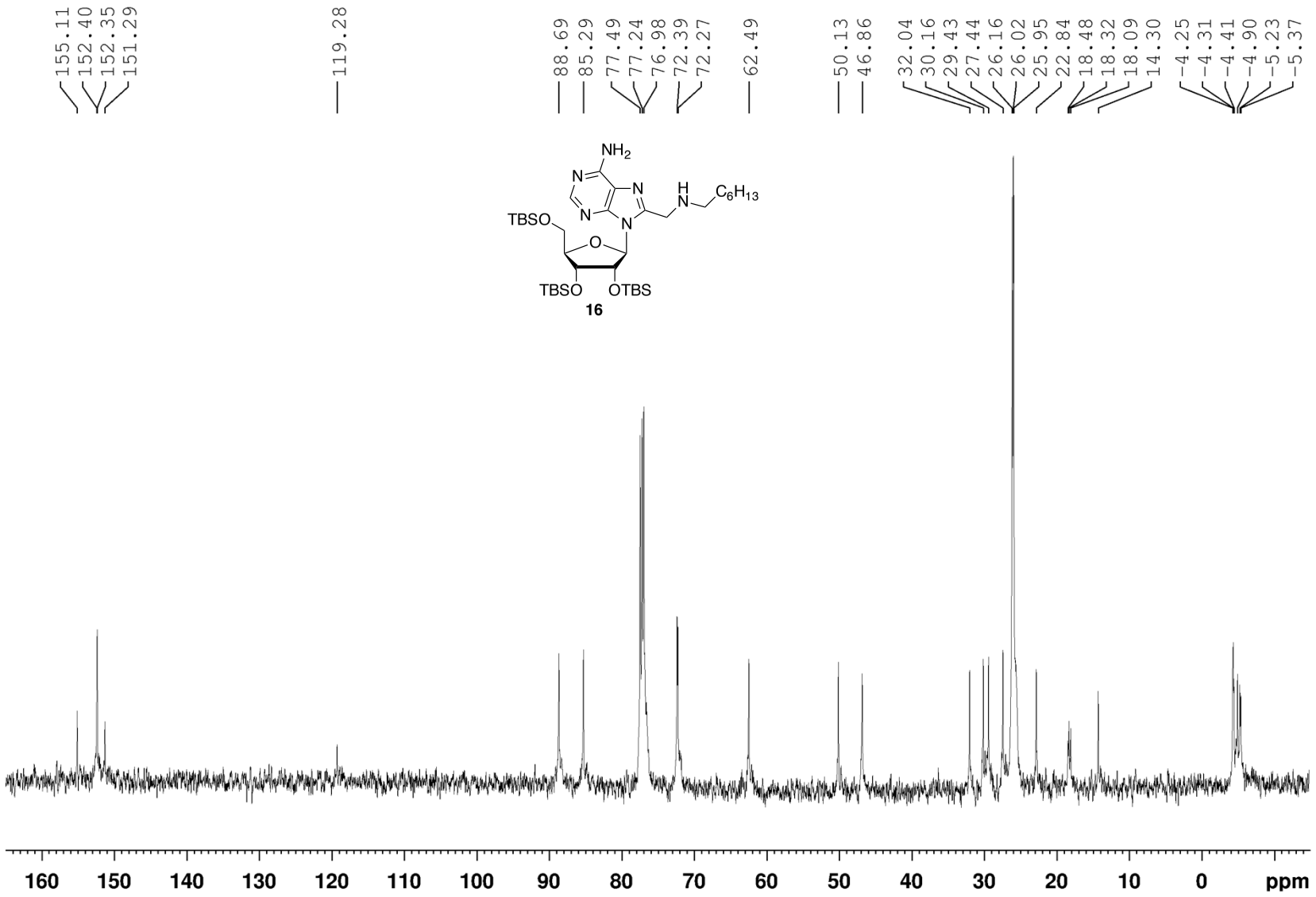
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **15** in 5:1 CD_3OD/DMSO-*d*6



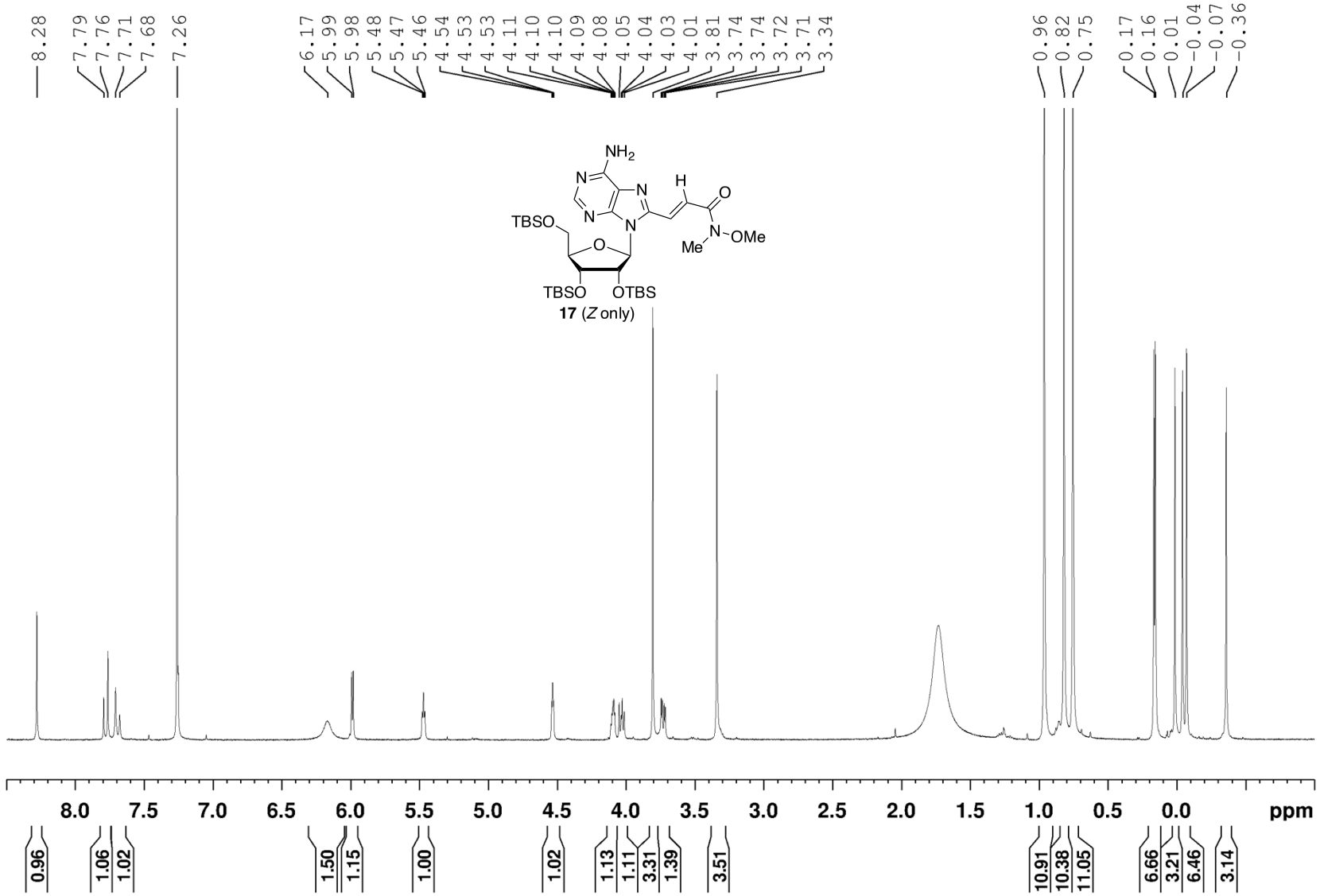
500 MHz ^{1}H NMR spectrum of compound **16** in CDCl3



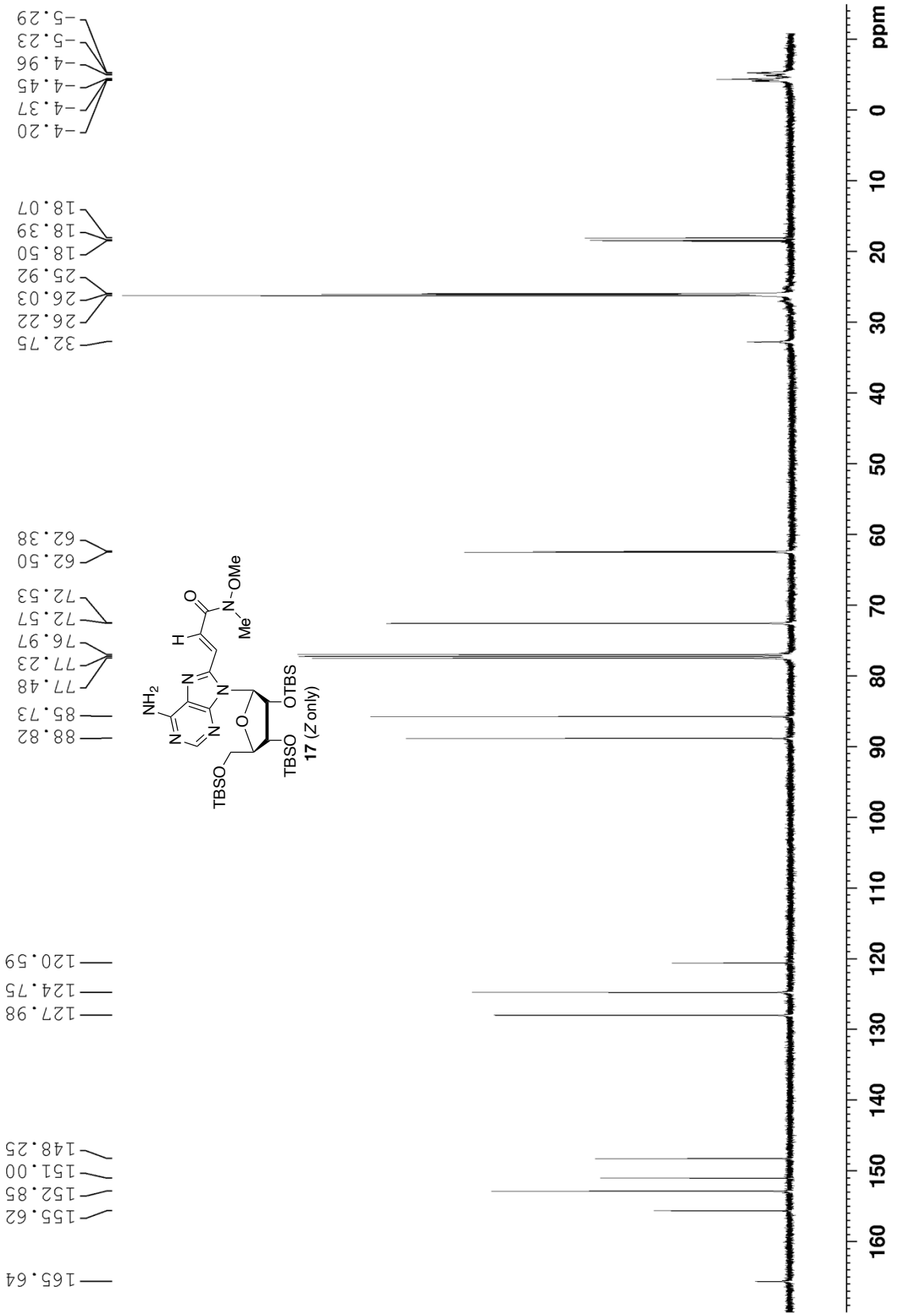
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **16** in $CDCl_3$



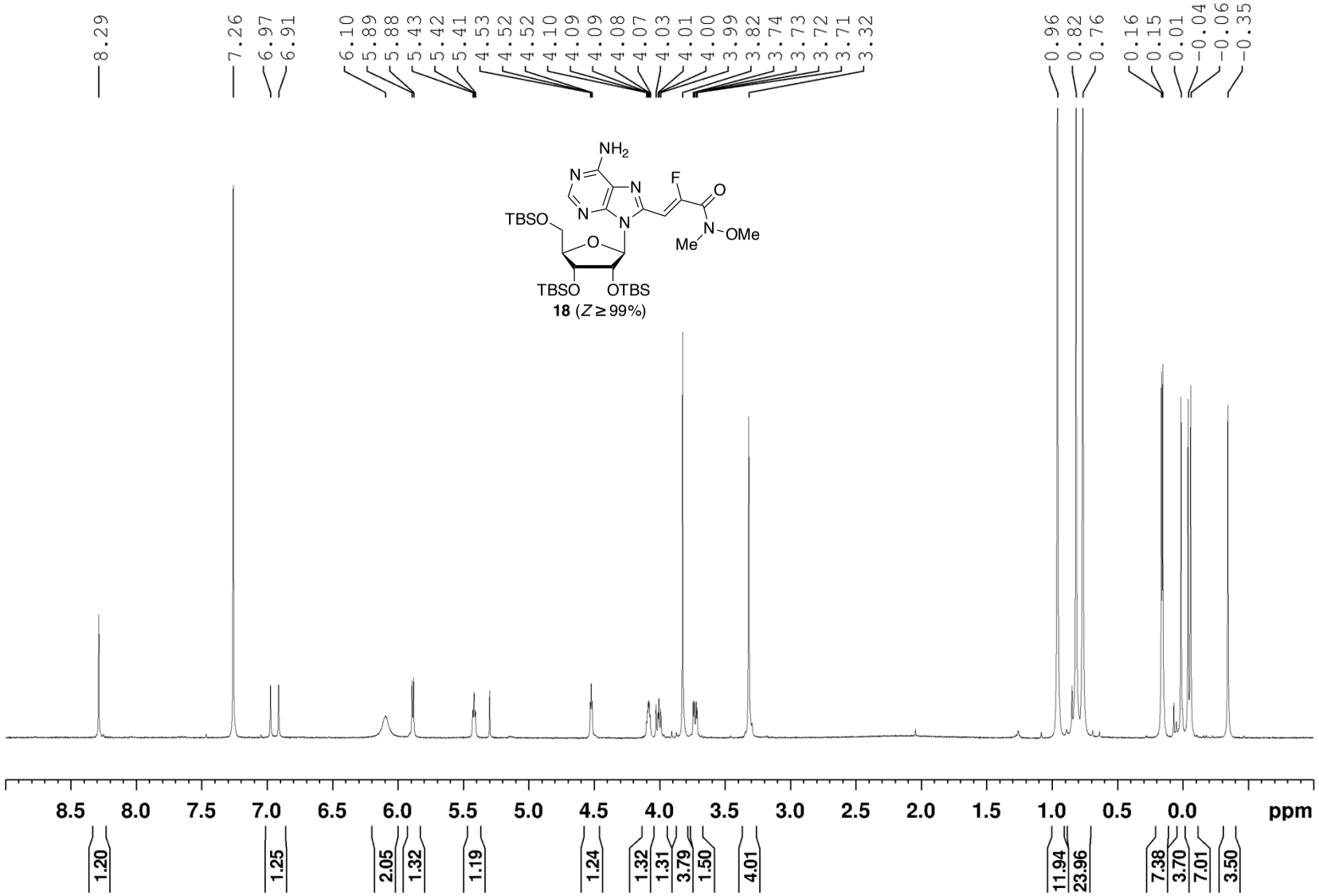
500 MHz ^{1}H NMR spectrum of compound **17** in $CDCl_3$



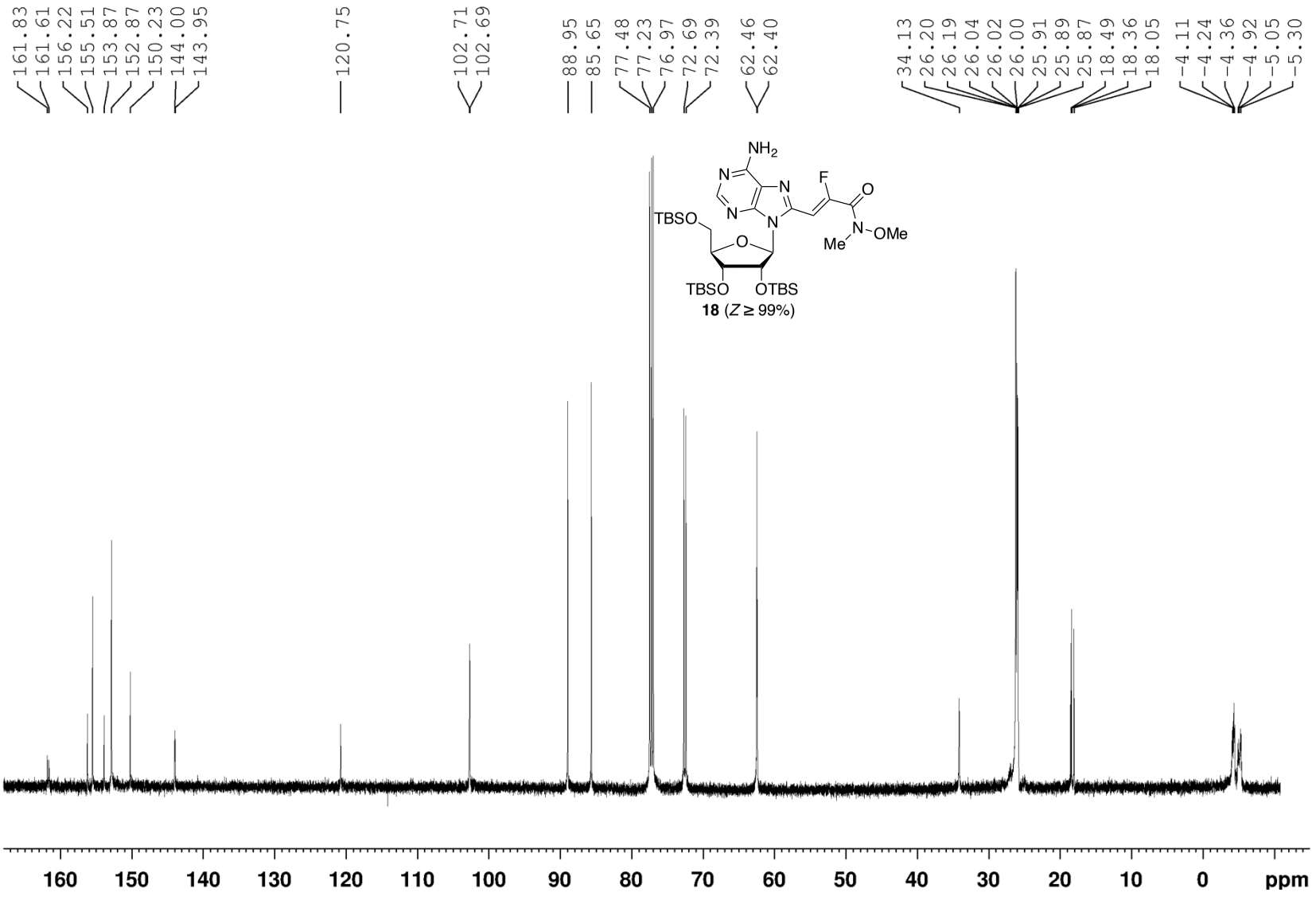
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **17** in $CDCl_3$



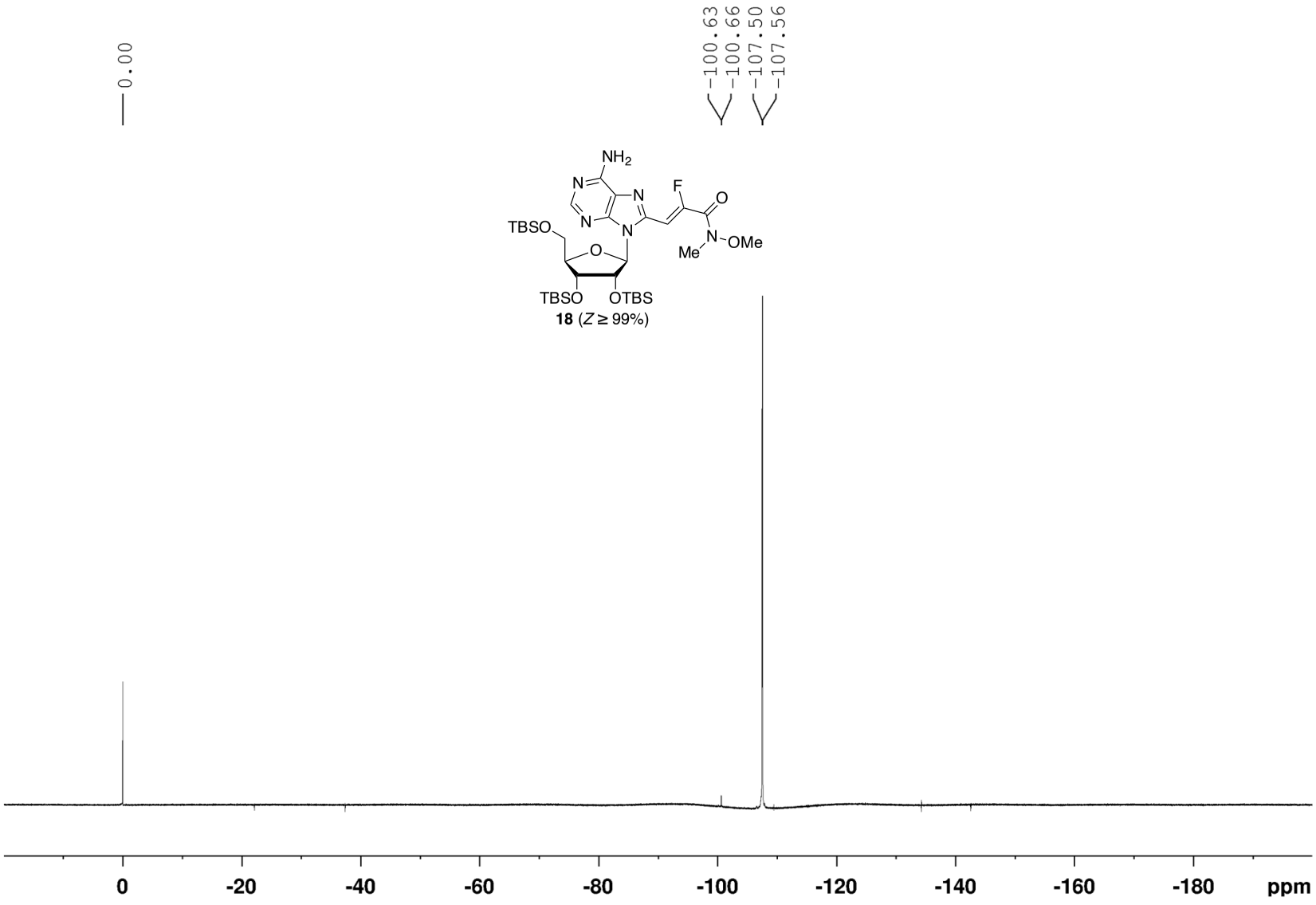
500 MHz ^{1}H NMR spectrum of compound **18** in $CDCl_3$



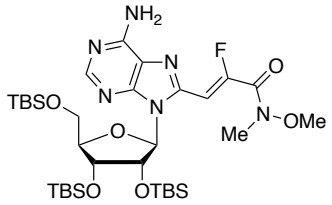
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **18** in $CDCl_3$



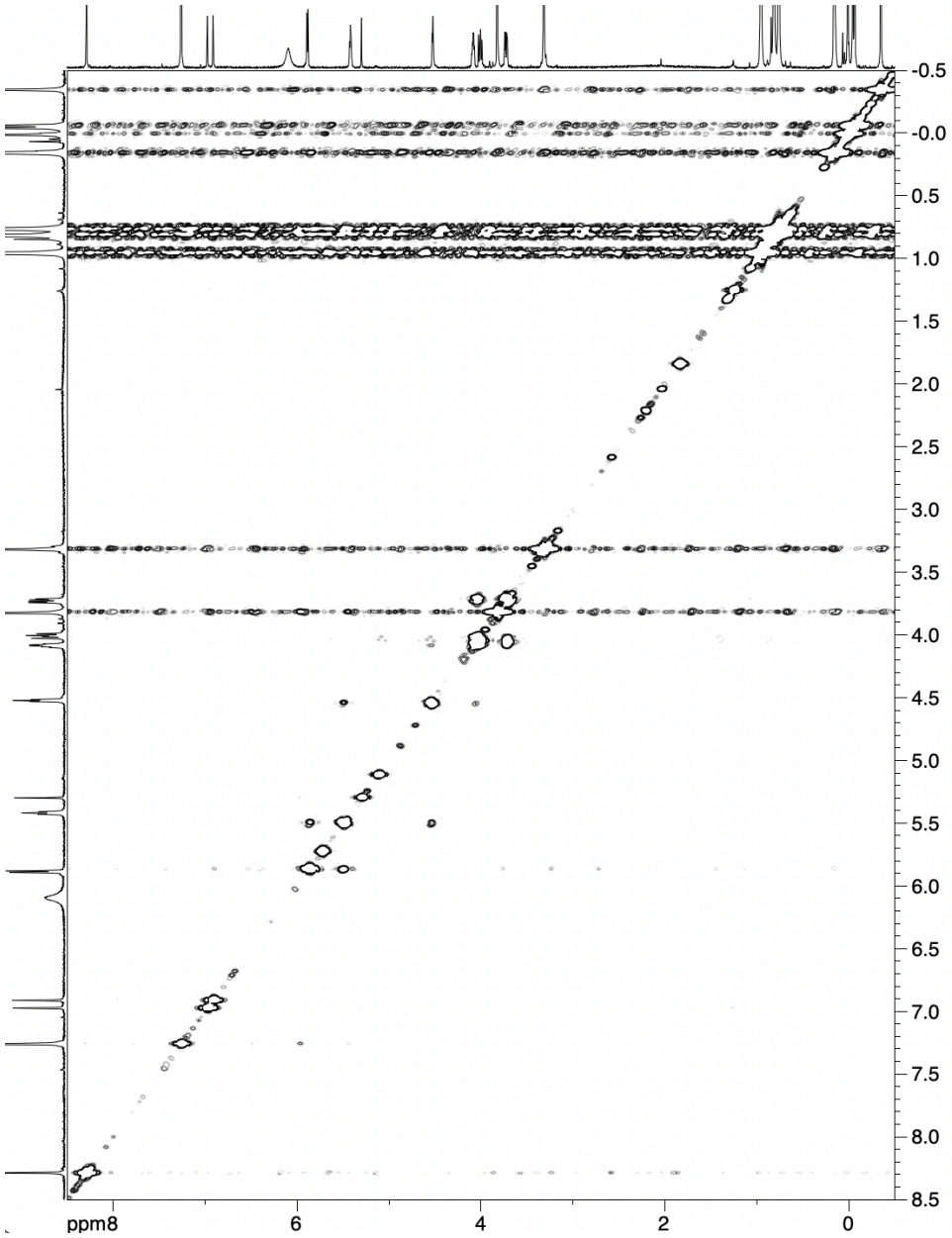
470 MHz $^{19}F\{^{1}H\}$ NMR spectrum of compound **18** in $CDCl_3$



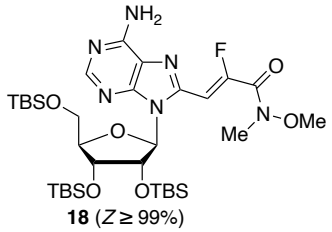
gCOSY spectrum of compound **18** in $CDCl_3$



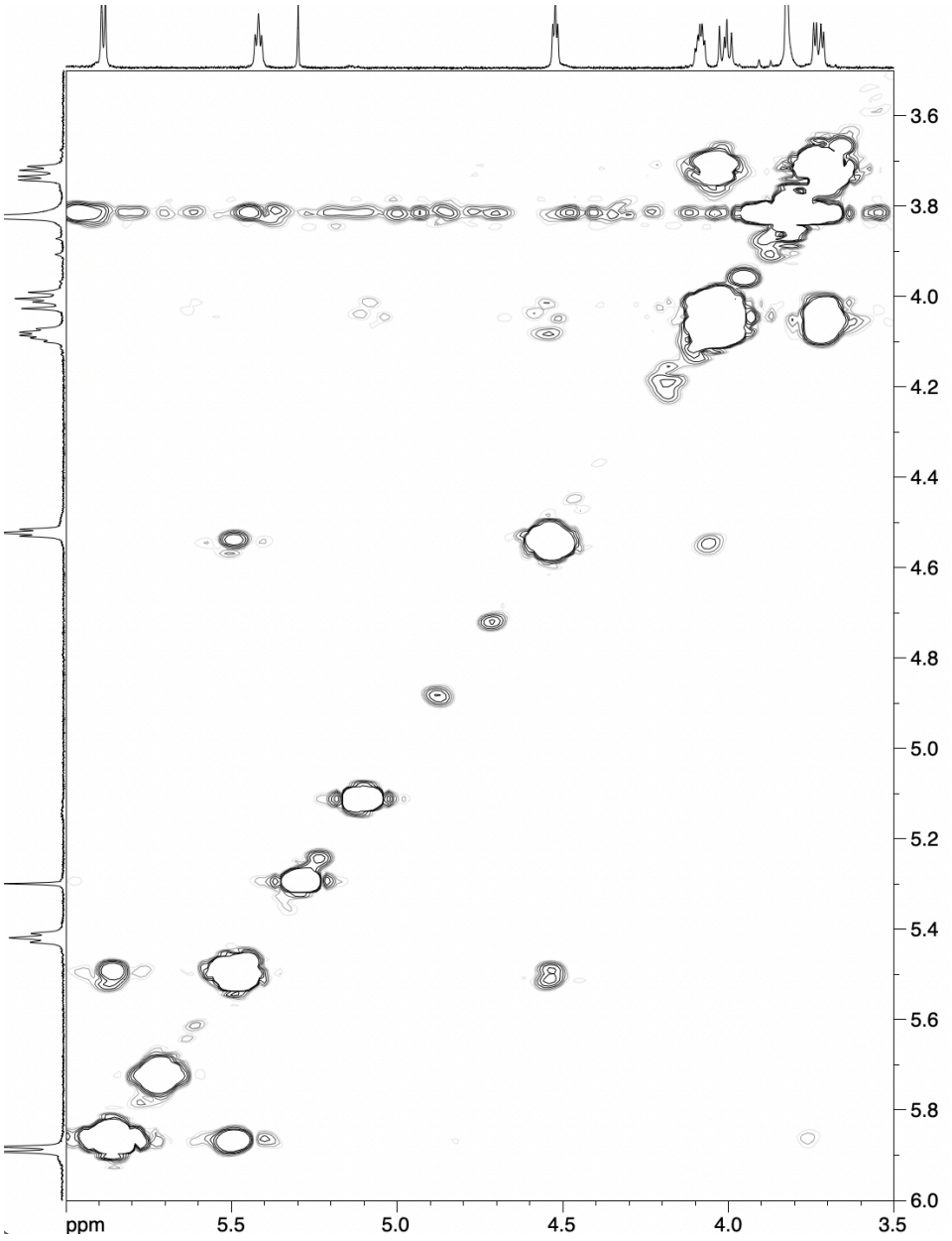
18 ($Z \geq 99\%$)



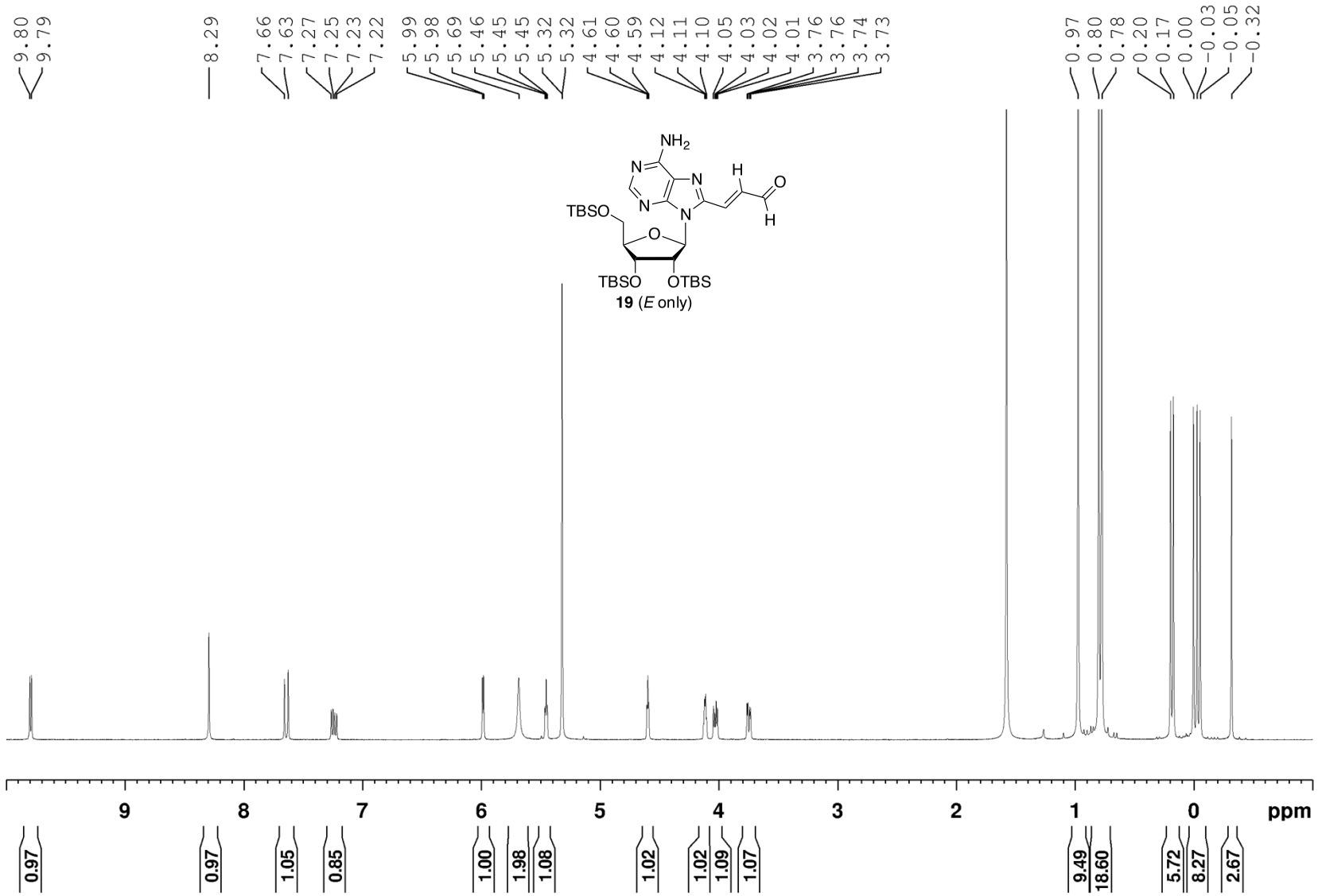
Expansion of gCOSY spectrum of compound **18** in $CDCl_3$



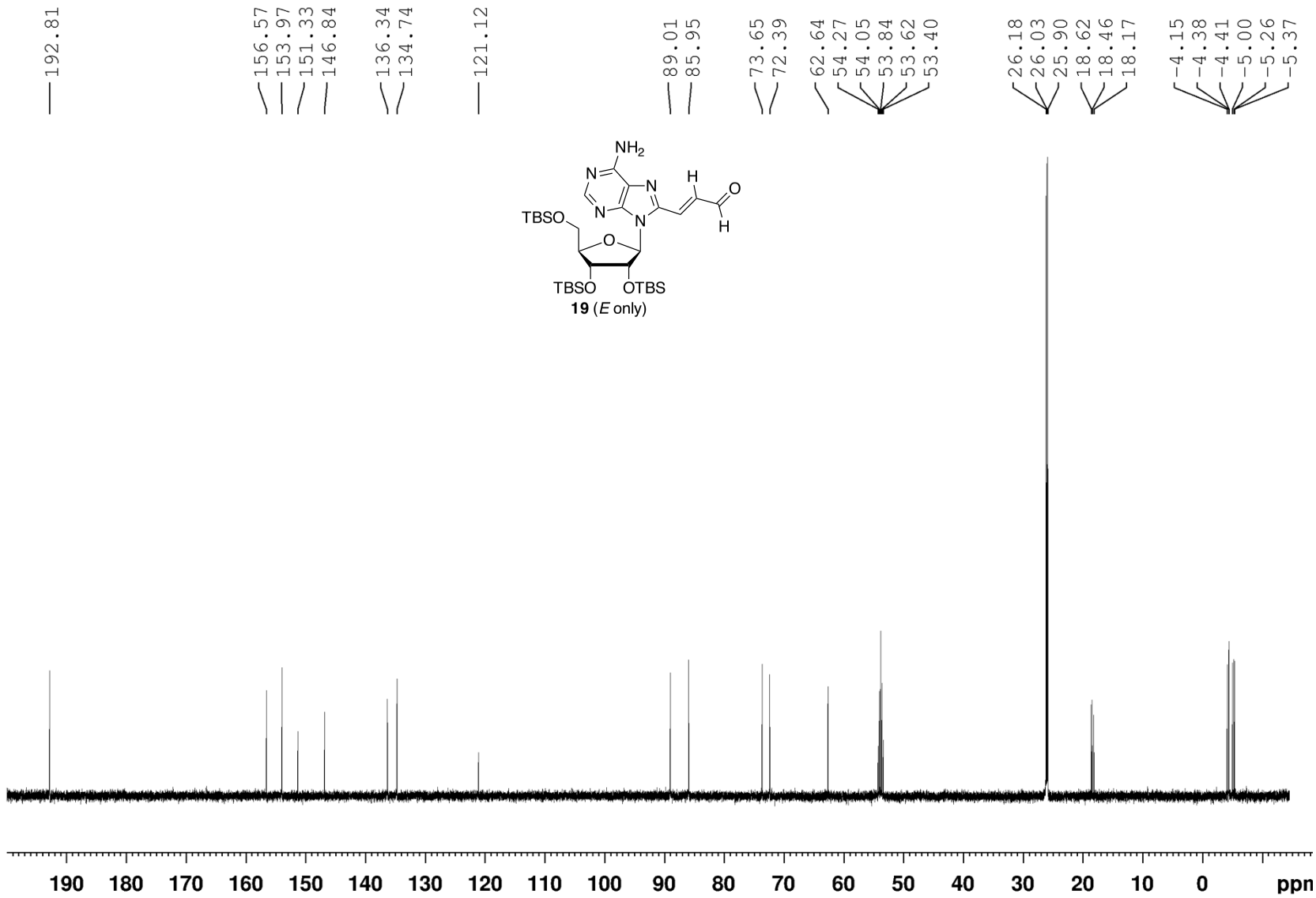
18 ($Z \geq 99\%$)



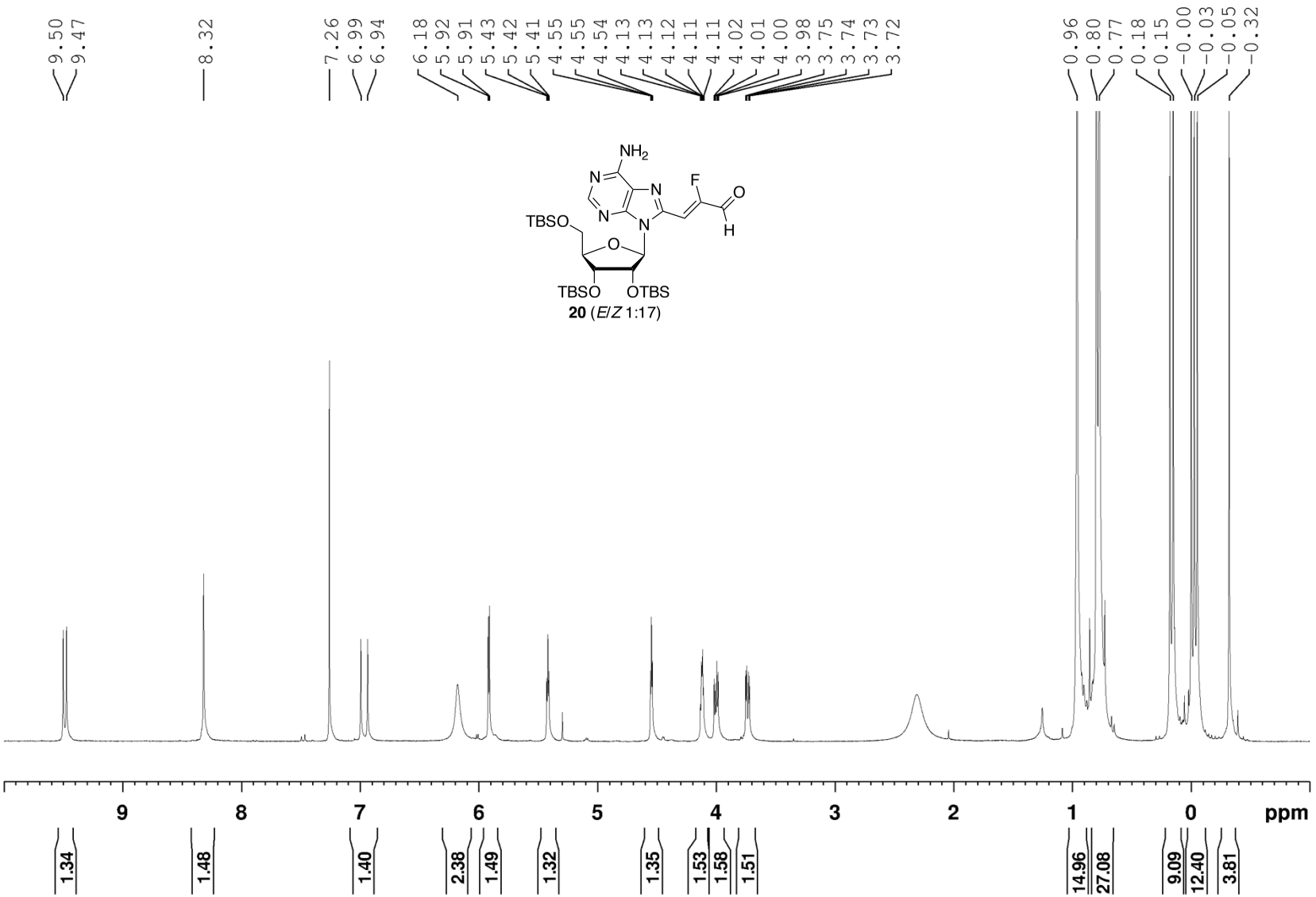
500 MHz ^{1}H NMR spectrum of compound **19** in CD_2Cl_2



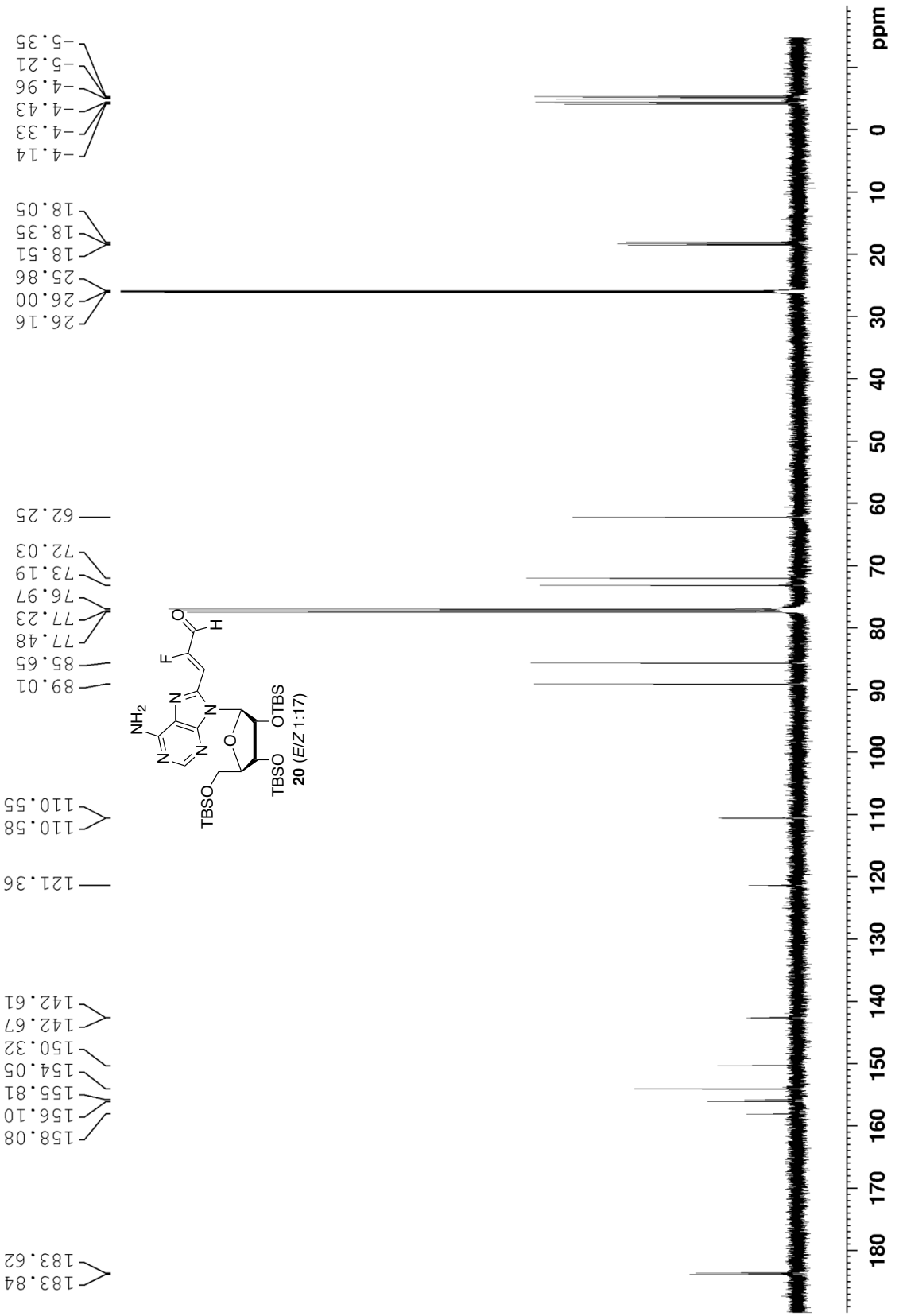
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **19** in CD_2Cl_2



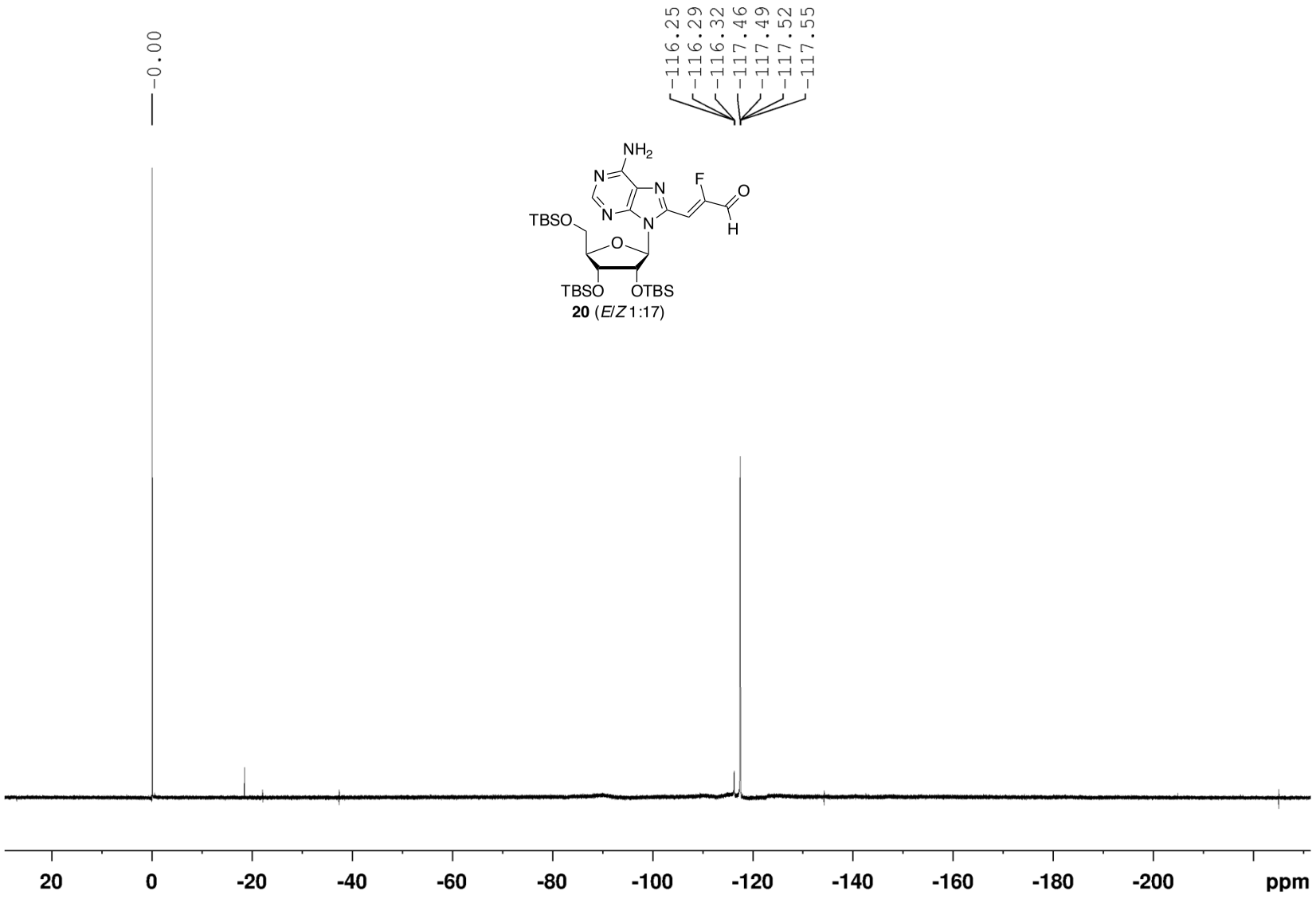
500 MHz ^{1}H NMR spectrum of compound **20** in $CDCl_3$



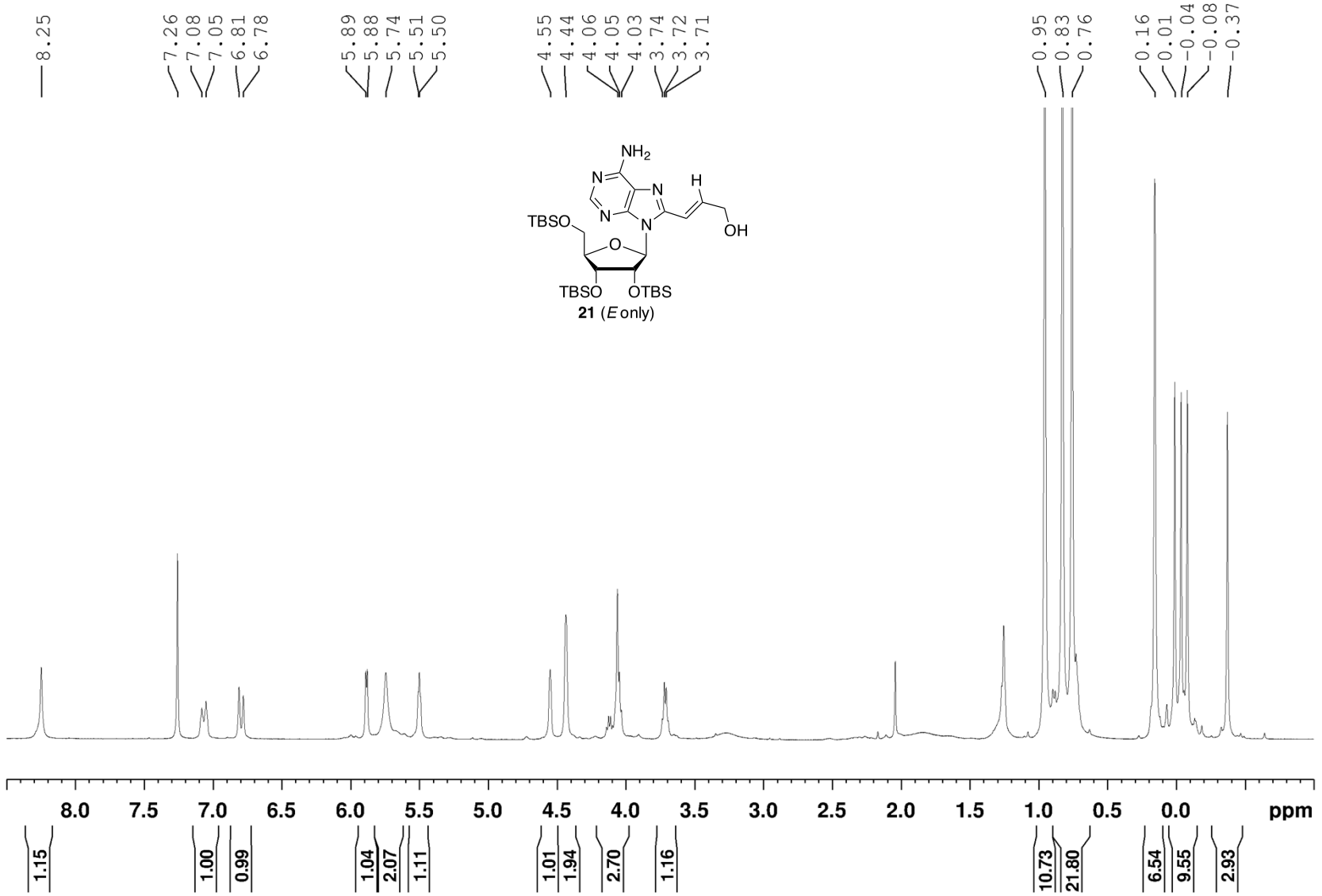
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **20** in $CDCl_3$



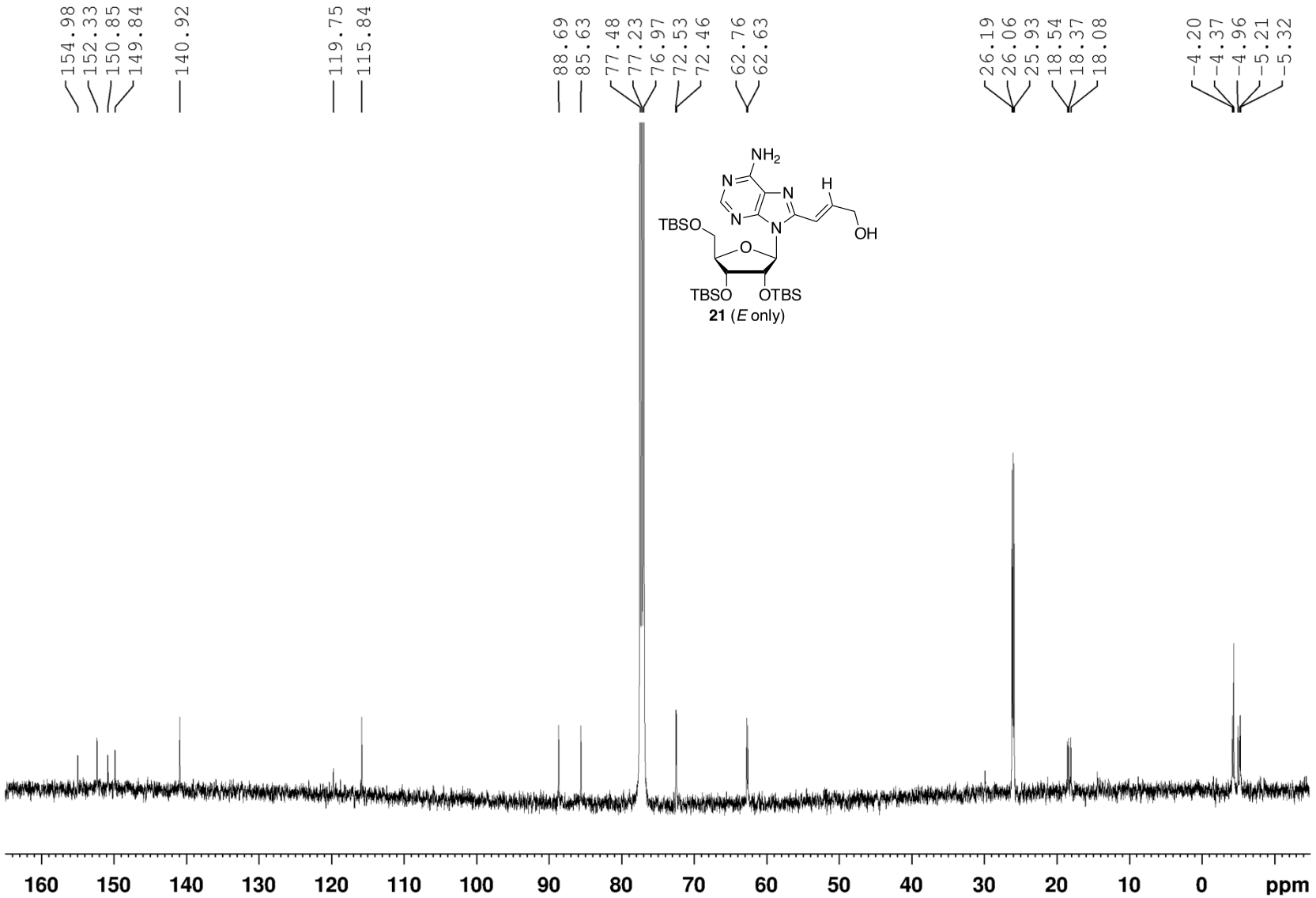
470 MHz $^{19}F\{^{1}H\}$ NMR spectrum of compound **20** in $CDCl_3$



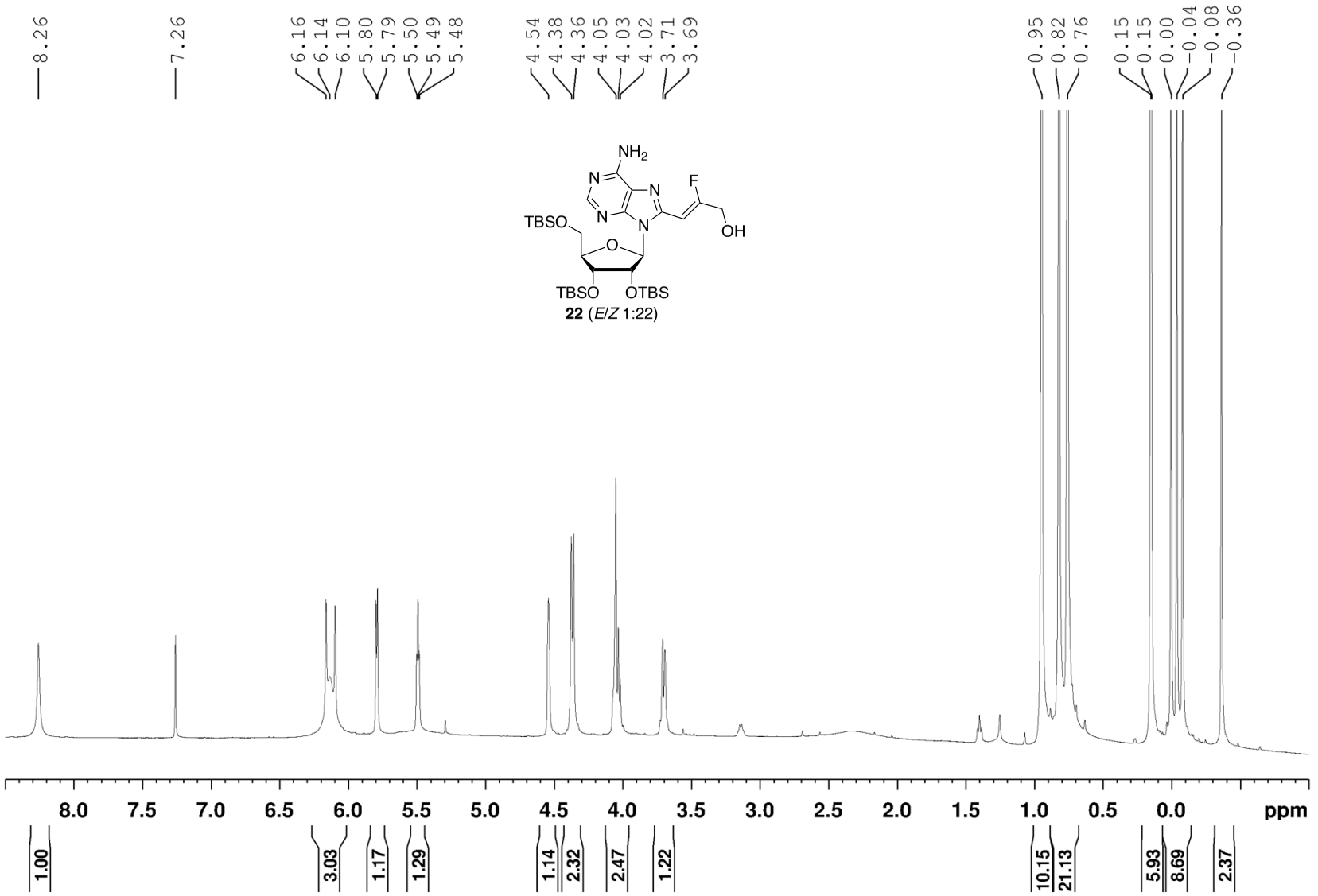
500 MHz ^{1}H NMR spectrum of compound **21** in $CDCl_3$



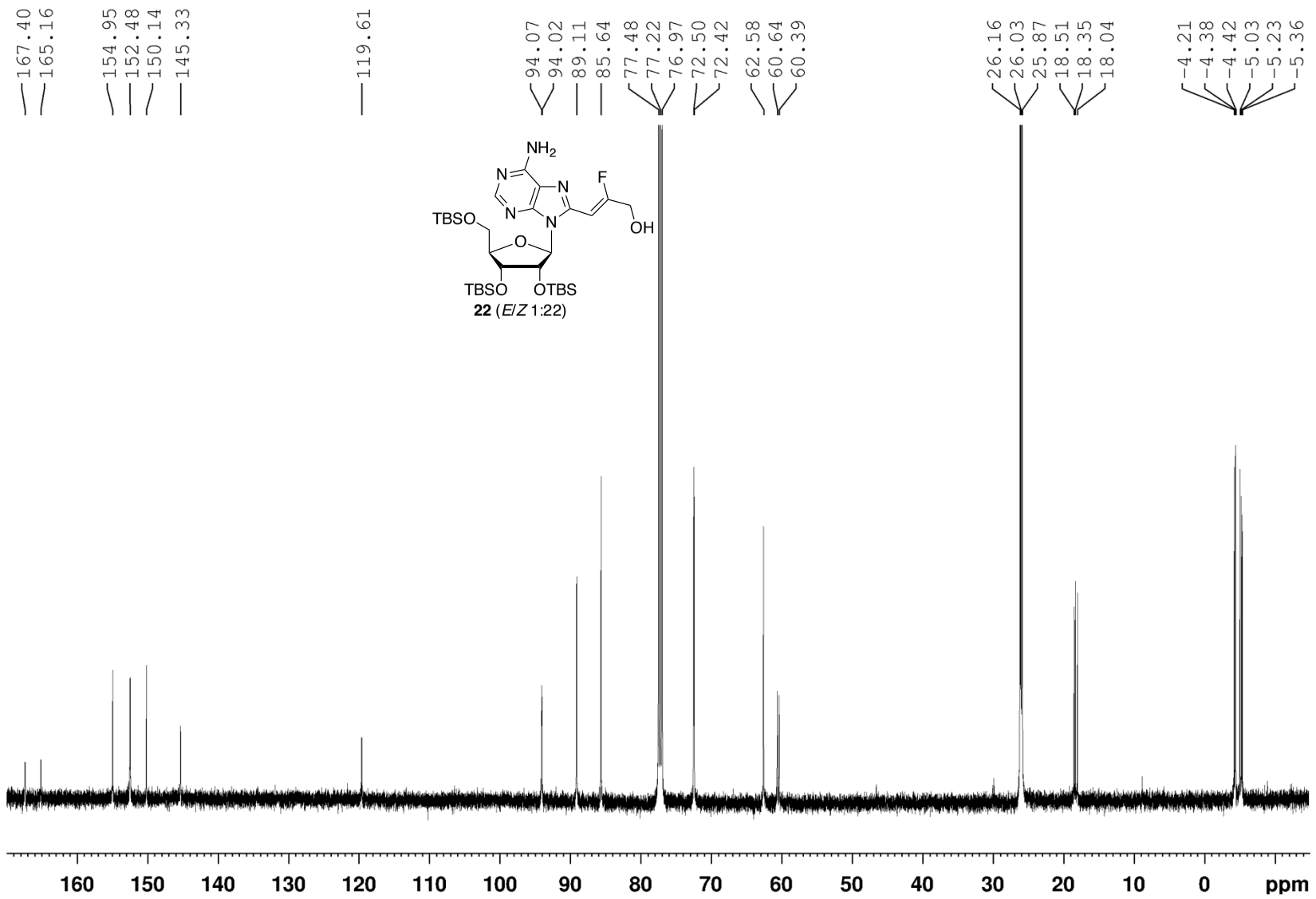
125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **21** in $CDCl_3$



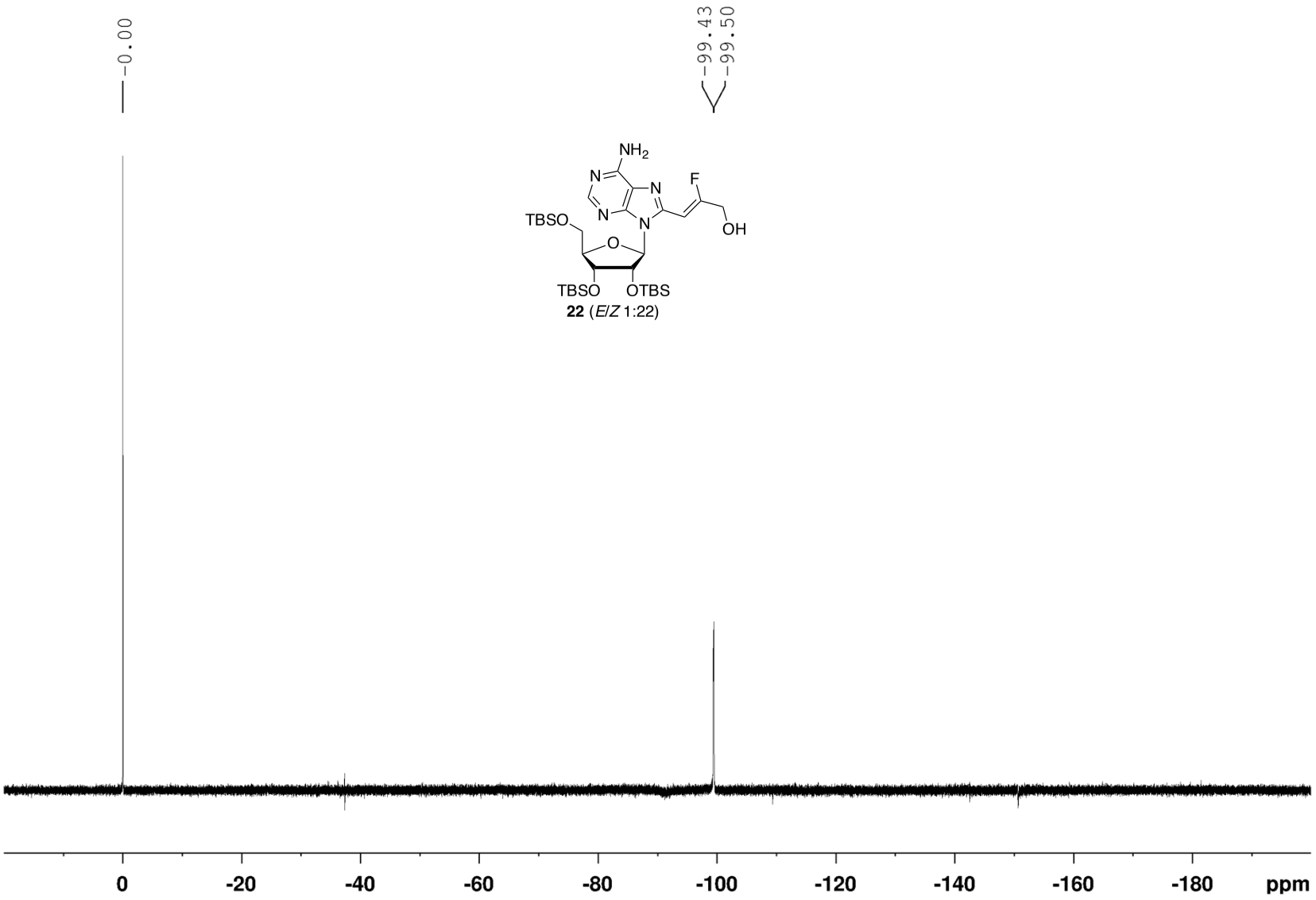
500 MHz ^{1}H NMR spectrum of compound **22** in $CDCl_3$



125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **22** in $CDCl_3$

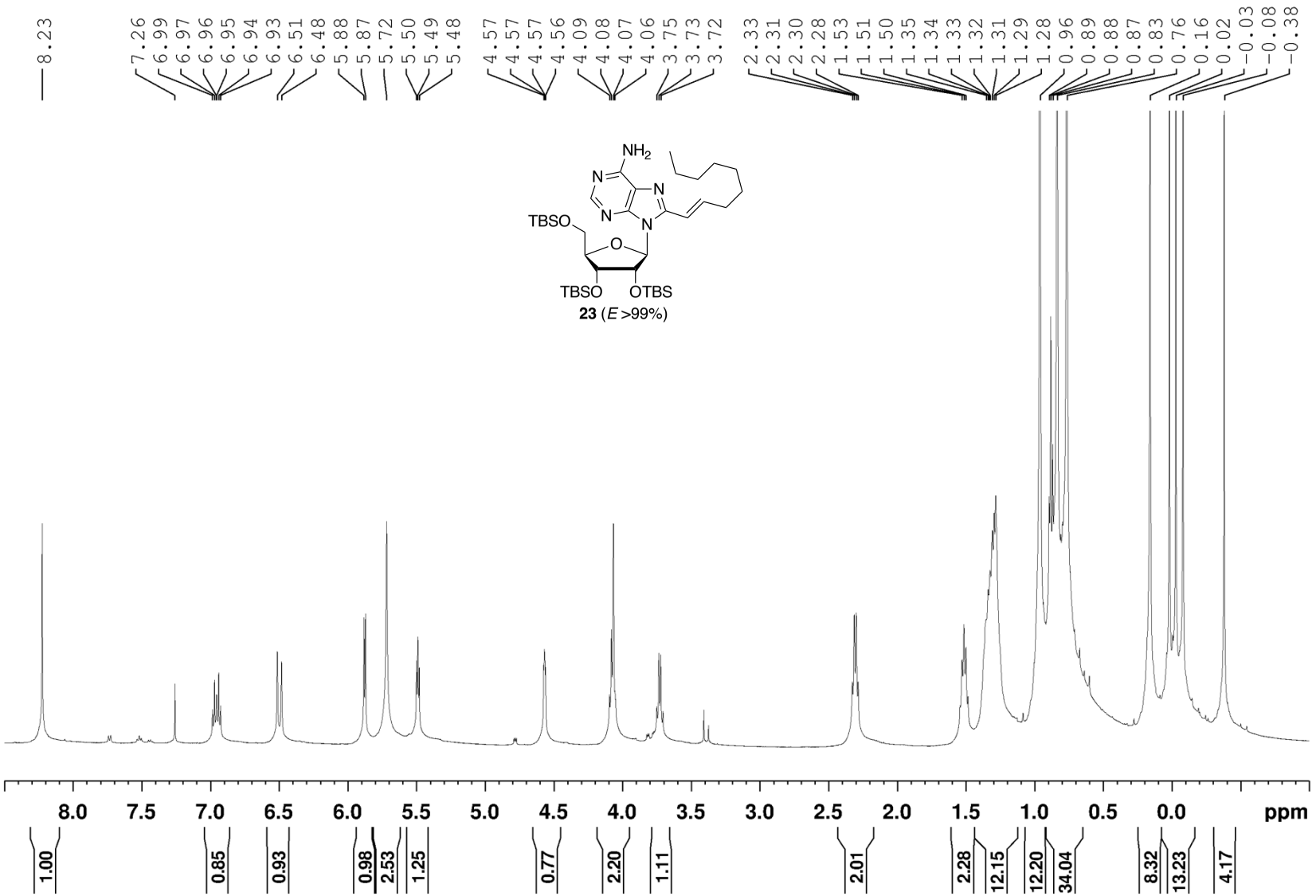


470 MHz $^{19}F\{^{1}H\}$ NMR spectrum of compound **22** in $CDCl_3$

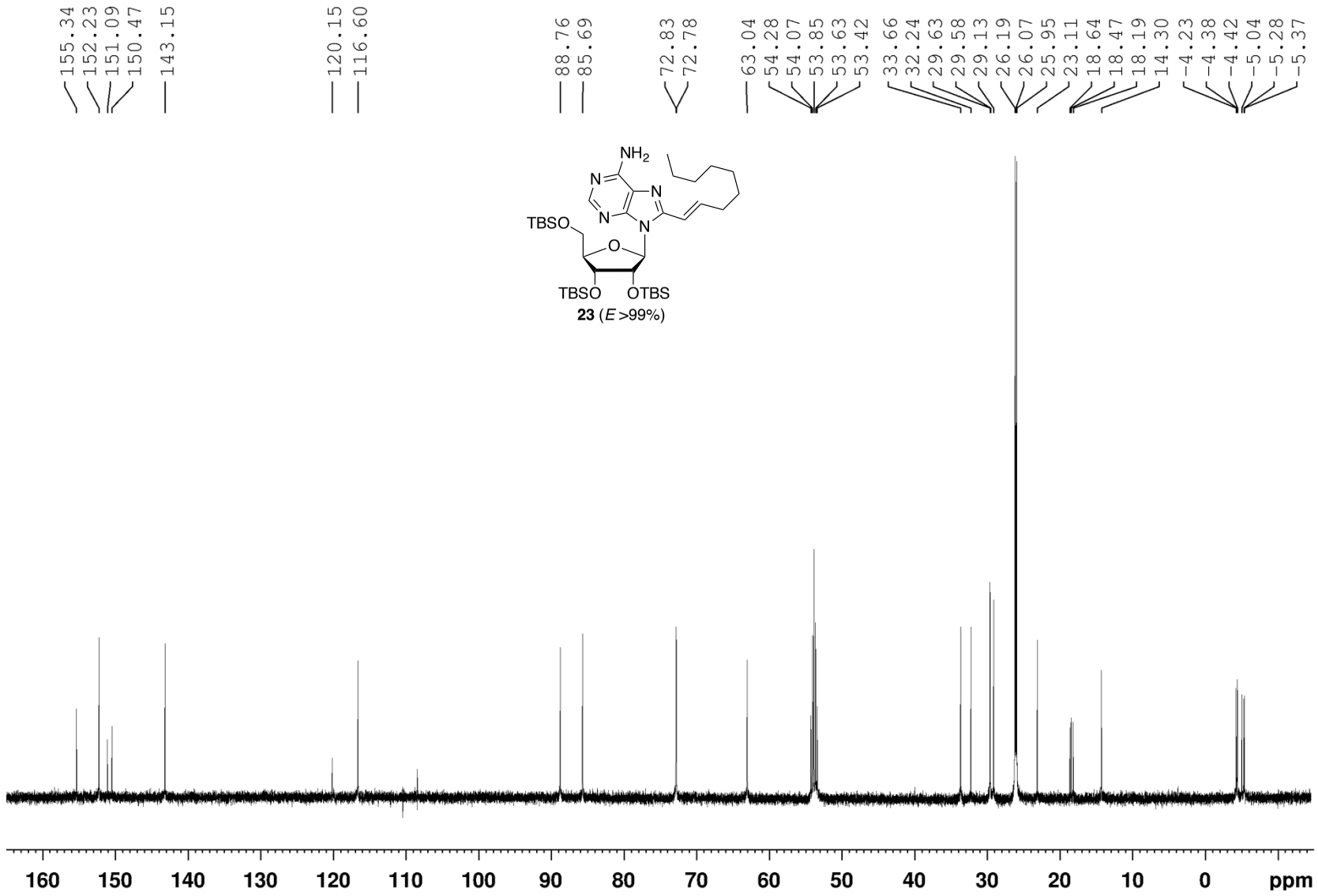


22 (*E*/*Z* 1:22)

500 MHz ^{1}H NMR spectrum of compound **23** in $CDCl_3$

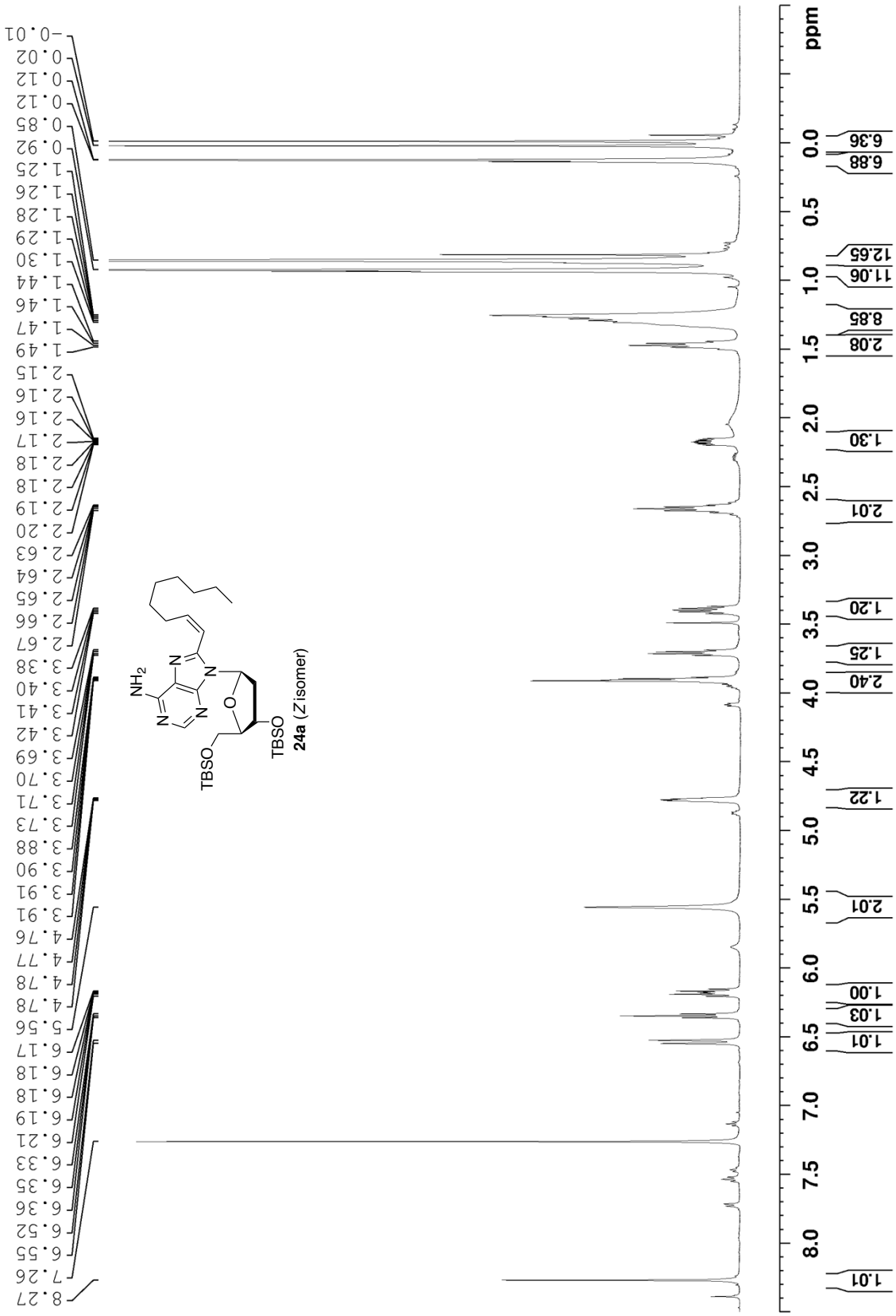


125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **23** in CD_2Cl_2

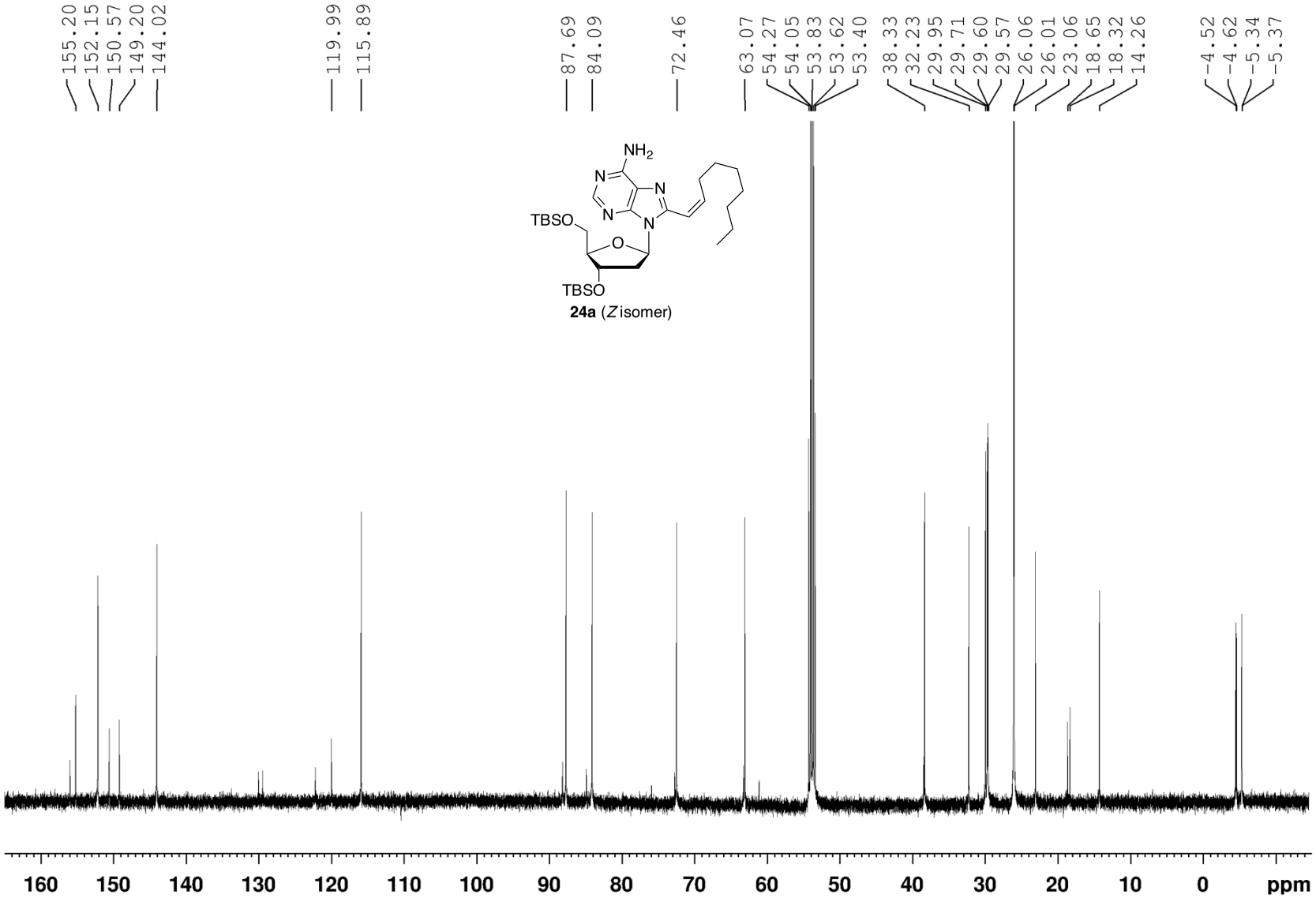


23 (*E* >99%)

500 MHz ^{1}H NMR spectrum of compound **24a** in $CDCl_3$

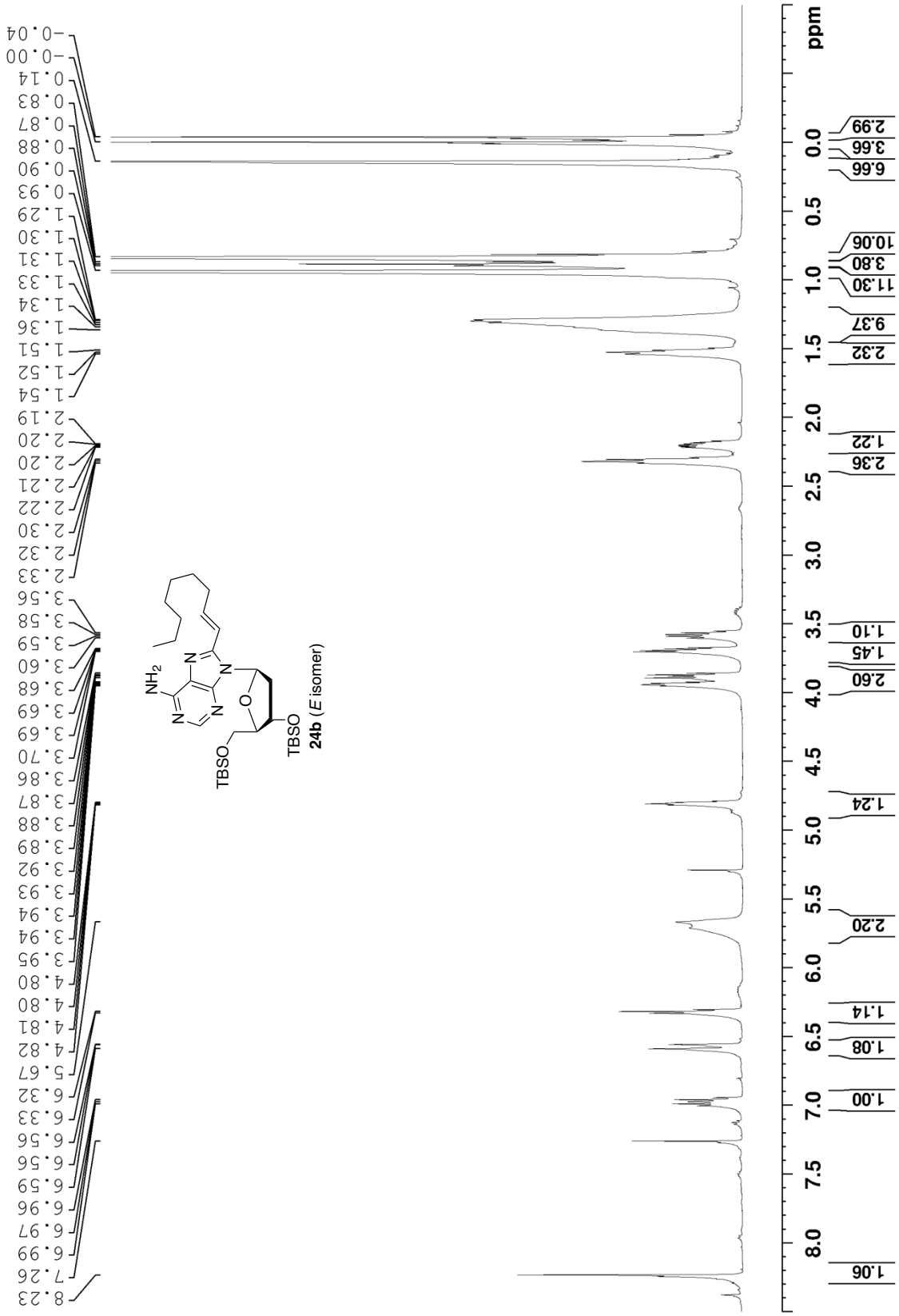


125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **24a** in CD_2Cl_2

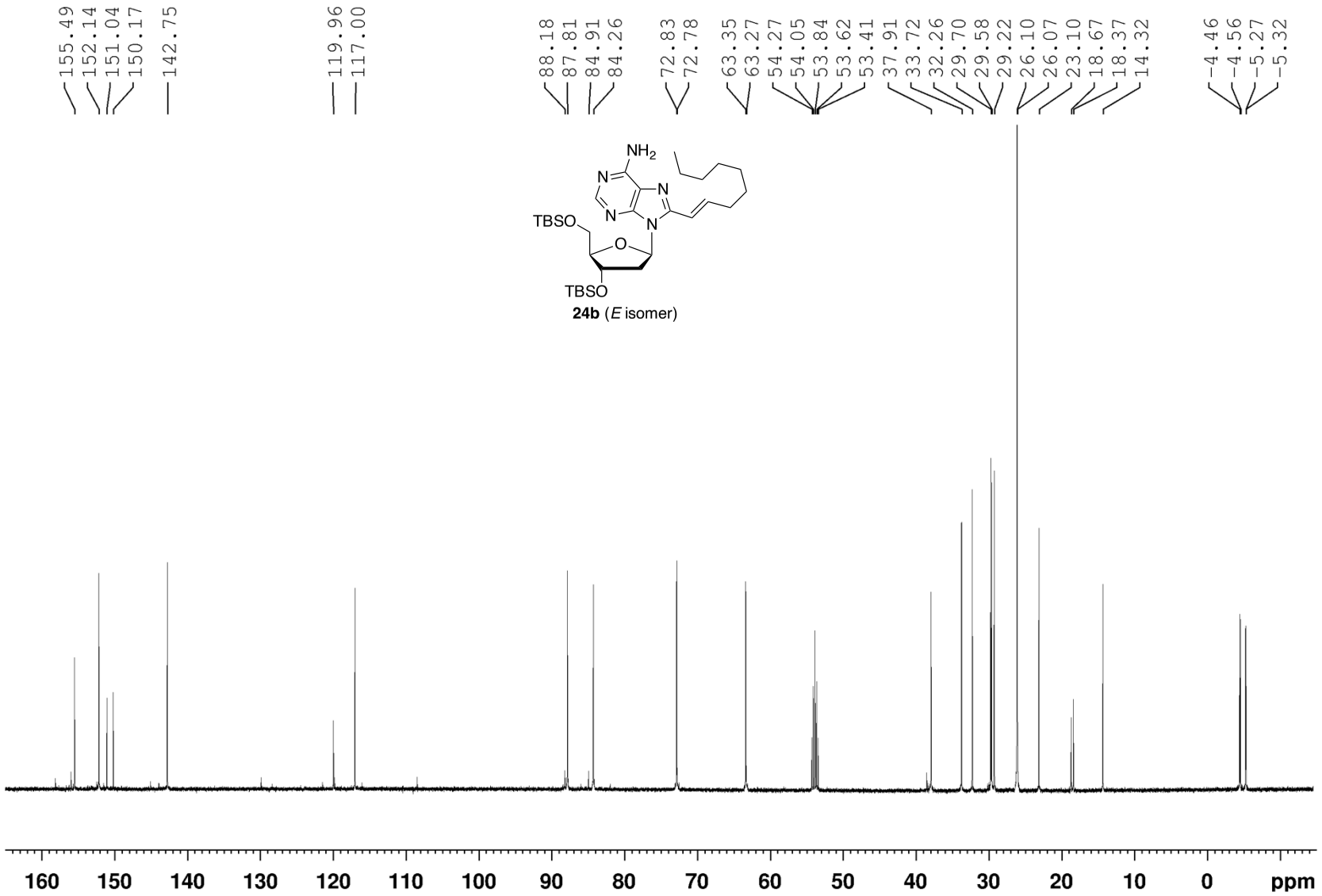


24a (*Z* isomer)

500 MHz ^{1}H NMR spectrum of compound **24b** in $CDCl_3$

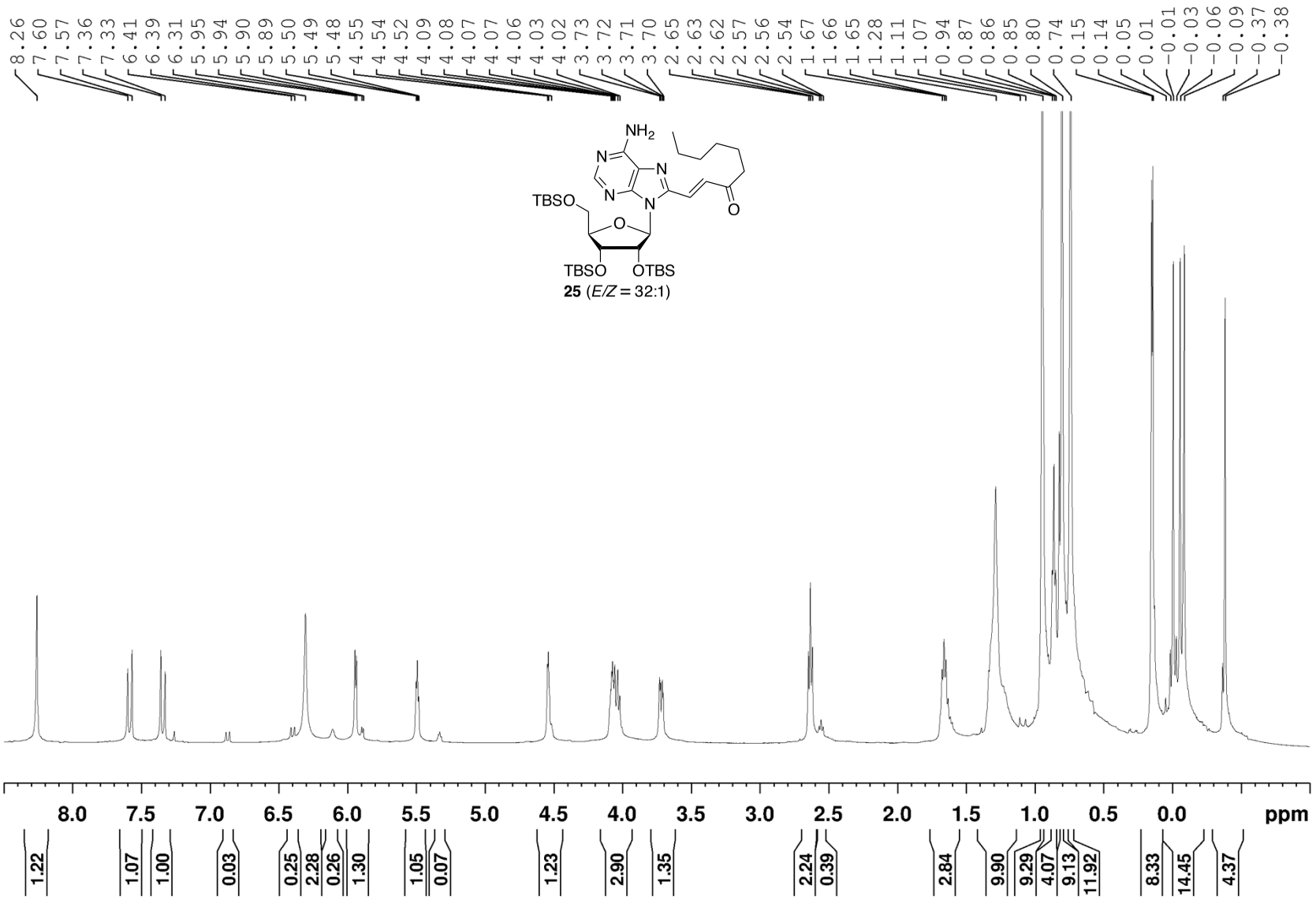


125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **24b** in CD_2Cl_2

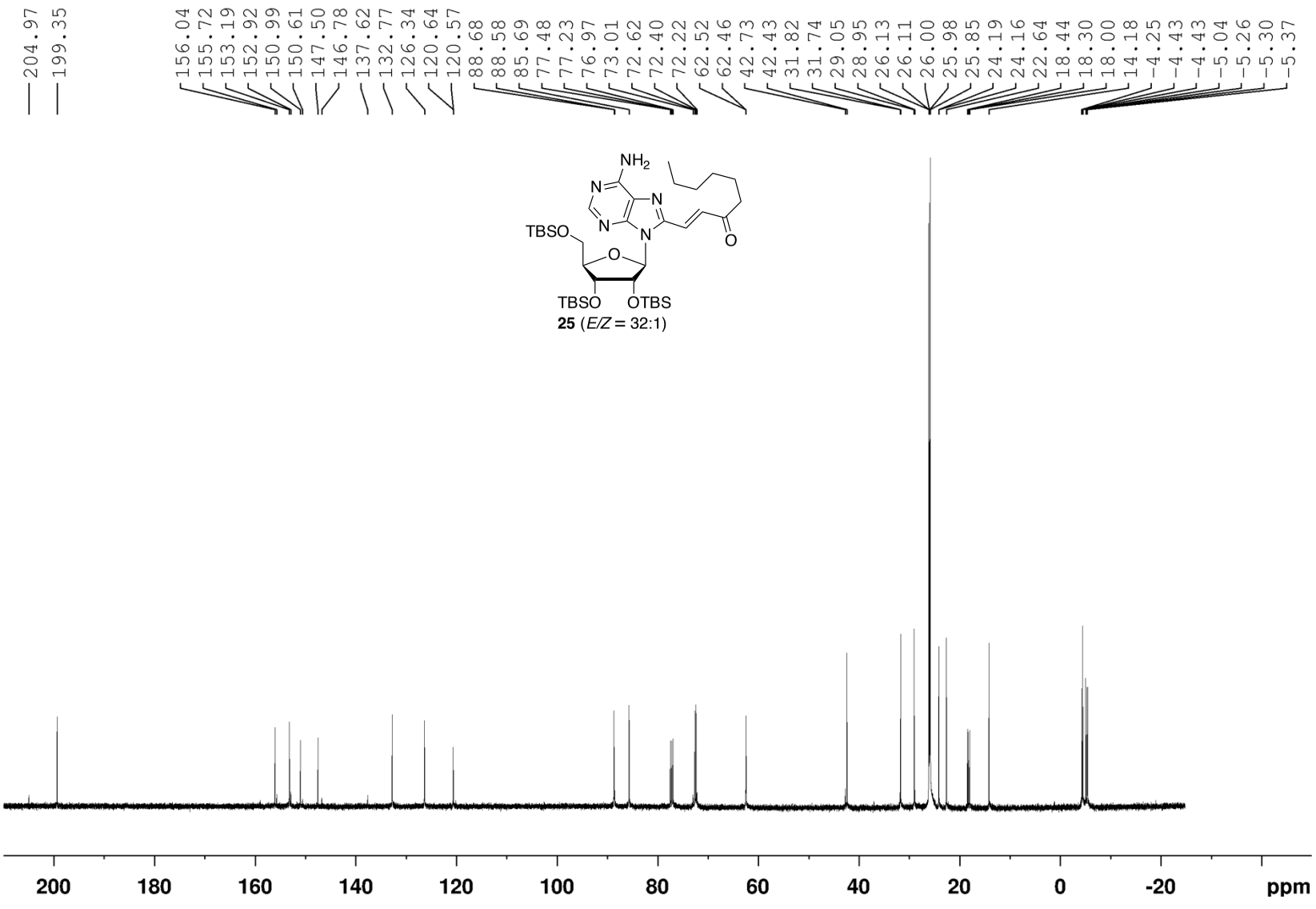


24b (*E* isomer)

500 MHz ^{1}H NMR spectrum of compound **25** in $CDCl_3$

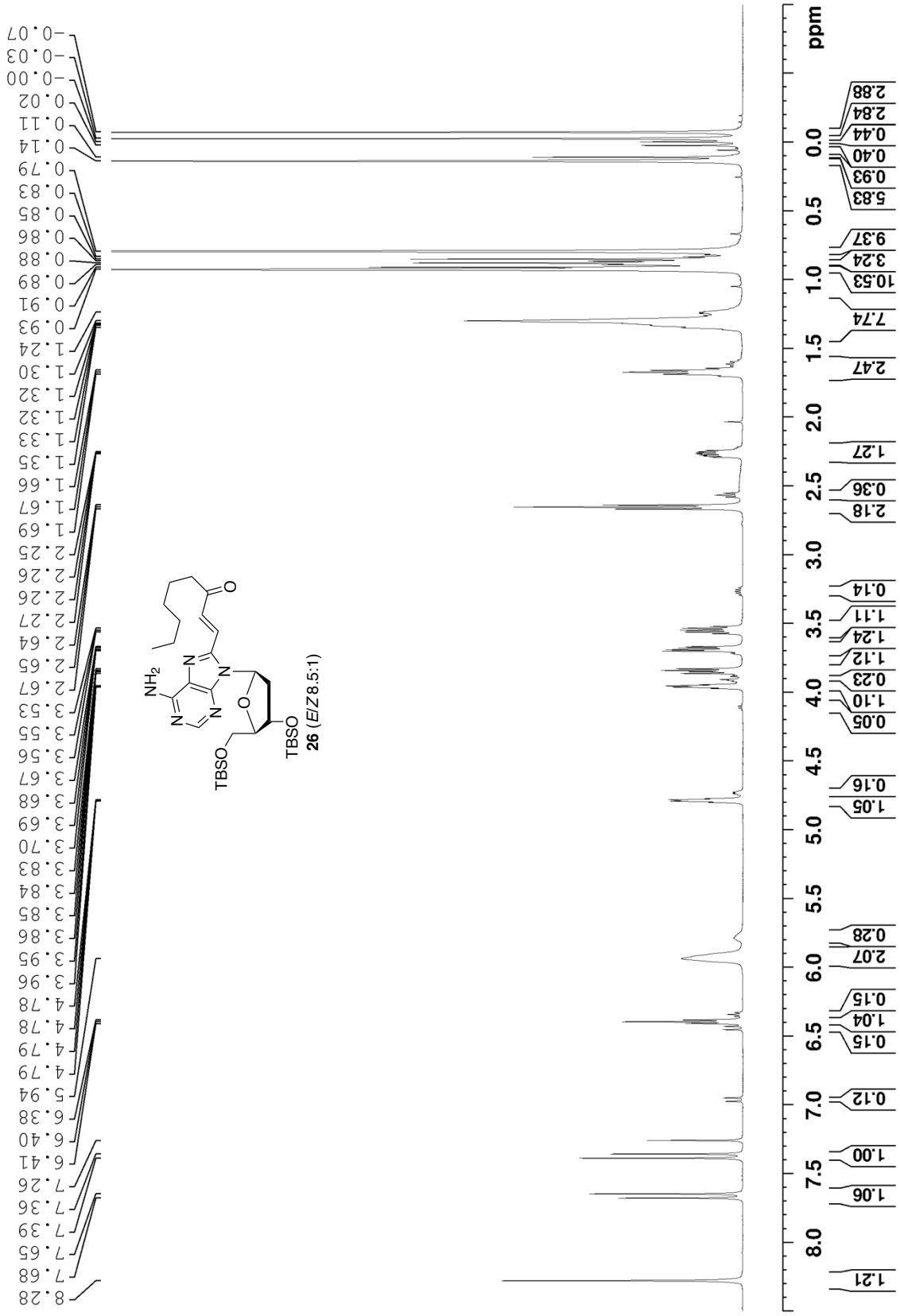


125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **25** in $CDCl_3$



25 (*E*/*Z* = 32:1)

500 MHz ^{1}H NMR spectrum of compound **26** in $CDCl_3$



125 MHz $^{13}C\{^{1}H\}$ NMR spectrum of compound **26** in $CDCl_3$