Electronic Supplementary Material (ESI) for Chemical Communications.

Benzimidazopurine nucleosides from N^6-aryl adenosine derivatives by $PhI(OAc)_2$-mediated C–N bond formation, *no metal needed*

*Sakilam Satishkumar and Mahesh K. Lakshman**

TABLE OF CONTENTS

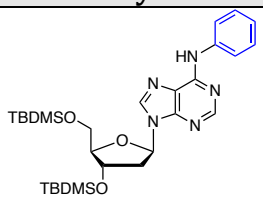
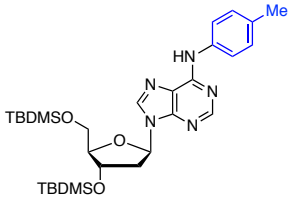
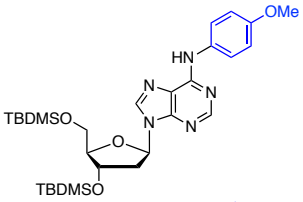
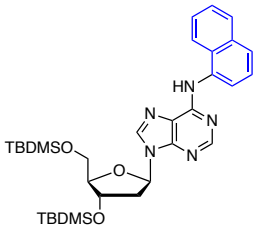
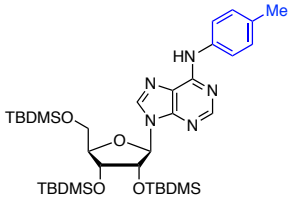
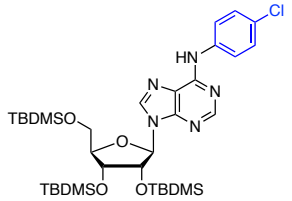
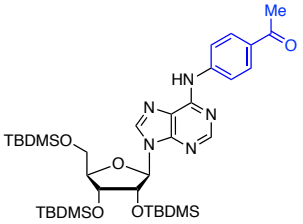
Information	Page
General Experimental Considerations	S-3
Table S1. Synthesis of the N^6-aryl 2'-deoxyadenosine and adenosine precursors	S-4
General procedure for the synthesis of the benzimidazopurine nucleoside derivatives	S-5
3',5'-Di-O-(*t*-Butyldimethylsilyl)-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (**2**)	S-6
3',5'-Di-O-(t-Butyldimethylsilyl)-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (**5**)	S-7
3',5'-Di-O-(*t*-Butyldimethylsilyl)-8-methoxy-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (**6**)	S-7
3',5'-Di-O-(*t*-Butyldimethylsilyl)-3*H*-naphtho[1',2':4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (**7**)	S-8
((9-(3',5'-di-*O*-*t*-butyldimethylsilyl-2'-deoxy-β-D-ribofuranosyl)-9H-purin-6-yl)imino)naphthalen-1(4*H*)-one (**7'**)	S-8
2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**8**)	S-9
2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-8-chloro-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**9**)	S-9
2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-8-acetyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**10**)	S-10
2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-8-cyano-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**11**)	S-11
2',3',5'-Tri-O-(*t*-butyldimethylsilyl)-10-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**12**)	S-11
3',5'-Di-O-acetyl-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (**13**)	S-12
2',3',5'-Tri-O-acetyl-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (**14**)	S-13
Radical inhibition experiments	S-13
General procedure for radical inhibition experiments using 1,1-DPE in HFIP	S-13
General procedure for radical inhibition experiments using BHT in HFIP	S-14
500 MHz ^{1}H NMR spectrum of compound **2** in $CDCl_3$	S-15

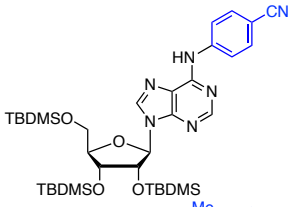
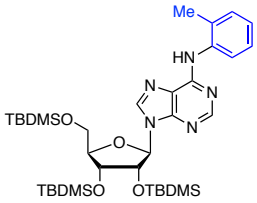
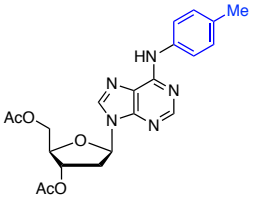
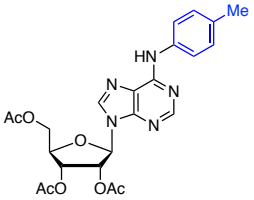
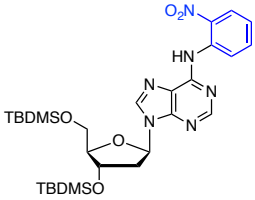
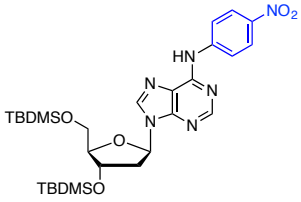
125 MHz ^{13}C NMR spectrum of compound **2** in $CDCl_3$	S-16
500 MHz ^{1}H NMR spectrum of compound **2** obtained from a 0.9 mmol reaction, in $CDCl_3$	S-17
500 MHz ^{1}H NMR spectrum of compound **5** in $CDCl_3$	S-18
125 MHz ^{13}C NMR spectrum of compound **5** in $CDCl_3$	S-19
500 MHz ^{1}H NMR spectrum of compound **6** in $CDCl_3$	S-20
125 MHz ^{13}C NMR spectrum of compound **6** in $CDCl_3$	S-21
500 MHz ^{1}H NMR spectrum of compound **7** in $CDCl_3$	S-22
125 MHz ^{13}C NMR spectrum of compound **7** in $CDCl_3$	S-23
gCOSY NMR spectrum of compound **7** in $CDCl_3$	S-24
Expansion of gCOSY NMR spectrum of compound **7** in $CDCl_3$	S-25
500 MHz ^{1}H NMR spectrum of compound **7′** in $CDCl_3$	S-26
125 MHz ^{13}C NMR spectrum of compound **7′** in $CDCl_3$	S-27
gCOSY NMR spectrum of compound **7′** in $CDCl_3$	S-28
Expansion of gCOSY NMR spectrum of compound **7′** in $CDCl_3$	S-29
HRMS spectrum of compound **7'**	S-30
500 MHz ^{1}H NMR spectrum of compound **8** in $CDCl_3$	S-31
125 MHz ^{13}C NMR spectrum of compound **8** in $CDCl_3$	S-32
500 MHz ^{1}H NMR spectrum of compound **9** in $CDCl_3$	S-33
125 MHz ^{13}C NMR spectrum of compound **9** in $CDCl_3$	S-34
500 MHz ^{1}H NMR spectrum of compound **10** in $CDCl_3$	S-35
125 MHz ^{13}C NMR spectrum of compound **10** in $CDCl_3$	S-36
500 MHz ^{1}H NMR spectrum of compound **10** obtained from a 0.9 mmol reaction, in $CDCl_3$	S-37
500 MHz ^{1}H NMR spectrum of compound **11** in $CDCl_3$	S-38
125 MHz ^{13}C NMR spectrum of compound **11** in $CDCl_3$	S-39
500 MHz ^{1}H NMR spectrum of compound **12** in $CDCl_3$	S-40
125 MHz ^{13}C NMR spectrum of compound **12** in $CDCl_3$	S-41
500 MHz ^{1}H NMR spectrum of compound **13** in $CDCl_3$	S-42
125 MHz ^{13}C NMR spectrum of compound **13** in $CDCl_3$	S-43
500 MHz ^{1}H NMR spectrum of compound **14** in $CDCl_3$	S-44
125 MHz ^{13}C NMR spectrum of compound **14** in $CDCl_3$	S-45
500 MHz ^{1}H NMR spectrum of iodobenzene isolated from one of the large-scale reactions, in $CDCl_3$	S-46

General experimental considerations

Reactions were conducted in screw-cap glass vials with Teflon-lined caps. Thin layer chromatography was performed on 200 μm aluminum-foil-backed silica gel plates. Column chromatography was performed using 100–200 mesh silica gel in all cases unless otherwise mentioned. Toluene was distilled over Na prior to use and acetonitrile was distilled over CaH_2. Hexanes and EtOAc, used for column chromatography, were distilled over $CaSO_4$. Xantphos, $Pd(OAc)_2$, $Pd_2(dba)_3$, Cs_2CO_3, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 2,2,2-trifluoroethanol (TFE), and all other reagents were obtained from commercial suppliers and used as received. All N^6-aryl adenine nucleosides were prepared by following literature procedures and this information is collected in Table S1. ^1H NMR spectra were obtained at 500 MHz in the solvents indicated under the individual compound headings and are referenced to residual protonated solvent resonances. ^{13}C NMR spectra were obtained at 125 MHz in the solvents indicated under the individual compound headings, and are referenced to the solvent resonances. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are in hertz (Hz). Standard abbreviations are used to designate resonance multiplicities.

Table S1. Synthesis of the N^6-aryl 2'-deoxyadenosine and adenosine precursors

Precursor synthesized	Yield	Method
	90%	Prepared from 3',5'-di-*O*-silyl 2'-deoxyadenosine and bromobenzene using $Pd_2(dba)_3$/Xantphos (e.g. F. N. Ngassa, K. A. DeKorver, T. S. Melistas, E. A.-H. Yeh and M. K. Lakshman, *Org. Lett.*, 2006, **8**, 4613–4616).
	58%	Prepared from the O^6-(benzotriazol-1-yl)-2'-deoxyinosine derivative and *p*-toluidine (e.g. S. Bae and M. K. Lakshman, *J. Am. Chem. Soc.*, 2007, **129**, 782–789).
	92%	Prepared from the O^6-(benzotriazol-1-yl)-2'-deoxyinosine derivative and *p*-anisidine (e.g. S. Bae and M. K. Lakshman, *J. Am. Chem. Soc.*, 2007, **129**, 782–789).
	94%	Prepared from 3',5'-di-*O*-silyl 2'-deoxyadenosine and 1-bromonaphthalene using $Pd_2(dba)_3$/Xantphos (e.g. F. N. Ngassa, K. A. DeKorver, T. S. Melistas, E. A.-H. Yeh and M. K. Lakshman, *Org. Lett.*, 2006, **8**, 4613–4616).
	73%	Prepared from 2',3',5'-tri-*O*-silyl 6-chloropurine riboside and *p*-toluidine using $Pd(OAc)_2$/Xantphos (e.g. P. F. Thomson, P. Lagisetty, J. Balzarini, E. De Clercq and M. K. Lakshman, *Adv. Synth. Catal.*, 2010, **352**, 1728–1735).
	73%	Prepared from 2',3',5'-tri-*O*-silyl 6-chloropurine riboside and *p*-chloroaniline using $Pd(OAc)_2$/Xantphos (e.g. P. F. Thomson, P. Lagisetty, J. Balzarini, E. De Clercq and M. K. Lakshman, *Adv. Synth. Catal.*, 2010, **352**, 1728–1735).
	93%	Prepared from 2',3',5'-tri-*O*-silyl 6-chloropurine riboside and *p*-aminoacetophenone using $Pd(OAc)_2$/Xantphos (e.g. P. F. Thomson, P. Lagisetty, J. Balzarini, E. De Clercq and M. K. Lakshman, *Adv. Synth. Catal.*, 2010, **352**, 1728–1735).

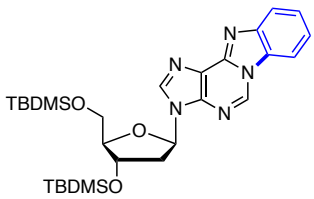
	84%	Prepared from 2',3',5'-tri-*O*-silyl 6-chloropurine riboside and *p*-cyanoaniline using $Pd(OAc)_2$/Xantphos (e.g. P. F. Thomson, P. Lagisetty, J. Balzarini, E. De Clercq and M. K. Lakshman, *Adv. Synth. Catal.*, 2010, **352**, 1728–1735).
	85%	Prepared from 2',3',5'-tri-*O*-silyl 6-chloropurine riboside and *o*-toluidine using $Pd(OAc)_2$/Xantphos (e.g. P. F. Thomson, P. Lagisetty, J. Balzarini, E. De Clercq and M. K. Lakshman, *Adv. Synth. Catal.*, 2010, **352**, 1728–1735).
	70%	Prepared from the O^6-(benzotriazol-1-yl)-2'-deoxyinosine derivative and *p*-toluidine (e.g. S. Bae and M. K. Lakshman, *J. Am. Chem. Soc.*, 2007, **129**, 782–789).
	72%	Prepared from 2',3',5'-tri-*O*-acetyl 6-bromopurine riboside and *p*-toluidine in MeOH (e.g. E. A. Véliz and P. A. Beal, *J. Org. Chem.*, 2001**, 66**, 8592-8598).
	95%	Prepared from 3',5'-di-*O*-silyl 2'-deoxyadenosine and *o*-*o*-bromonitrobenzene using $Pd_2(dba)_3$/Xantphos (e.g. F. N. Ngassa, K. A. DeKorver, T. S. Melistas, E. A.-H. Yeh and M. K. Lakshman, *Org. Lett.*, 2006, **8**, 4613–4616).
	94%	Prepared from 3',5'-di-*O*-silyl 2'-deoxyadenosine and *p*-iodonitrobenzene using $Pd_2(dba)_3$/Xantphos (e.g. F. N. Ngassa, K. A. DeKorver, T. S. Melistas, E. A.-H. Yeh and M. K. Lakshman, *Org. Lett.*, 2006, **8**, 4613–4616).

General procedure for the synthesis of the benzimidazopurine nucleoside derivatives

In a clean, dry, 8 mL vial equipped with a stirring bar were placed C–N product (0.05 mmol, 1 equiv.), HFIP (0.5 mL, 0.1M in the C–N product), and $PhI(OAc)_2$ (20.95 mg, 0.065 mmol, 1.3 equiv.). The vial was flushed with nitrogen and capped, stirred at room temperature. Reaction progress was monitored by TLC. After completion, the reaction mixture was

concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (see specific compound headings for details).

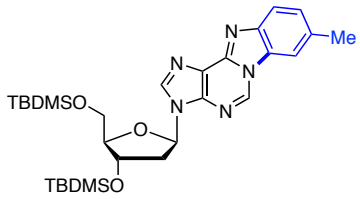
3',5'-Di-*O*-(*t*-Butyldimethylsilyl)-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (2)



Synthesized from the N^6-phenyl-2'-deoxyadenosine precursor (27.8 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **2** (25.6 mg, 92% yield) as a pale-brown solid. R_f (SiO_2 and 40% EtOAc in hexanes) = 0.30. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.39 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.56 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 6.56 (t, J = 6.4 Hz, 1H), 4.64–4.67 (m, 1H), 4.04–4.08 (m, 1H), 3.85 (dd, J = 4.3, 11.1 Hz, 1H), 3.79 (dd, J = 3.1, 11.1 Hz, 1H), 2.65 (app quint, J_{app} ~ 6.4 Hz, 1H), 2.51 (ddd, J = 4.2, 5.8, 13.0 Hz, 1H), 0.93 and 0.91 (2s, 18H), 0.13, 0.09, and 0.08 (3s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 144.5, 140.8, 139.2, 135.3, 127.7, 126.6, 123.4, 122.4, 120.7, 110.3, 88.3, 84.8, 72.1, 62.9, 41.7, 26.2, 26.0, 18.6, 18.2, −4.4, −4.5, −5.2, −5.3. HRMS (ESI/TOF) calcd for $C_{28}H_{44}N_5O_3Si_2$ $[M + H]^+$: 554.2977, found 554.2970.

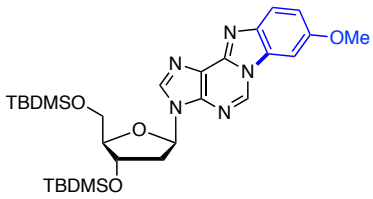
The larger-scale reaction was conducted with the N^6-phenyl-2'-deoxyadenosine precursor (500.3 mg, 0.9 mmol), HFIP (9.0 mL), and $PhI(OAc)_2$ (376.9 mg, 1.17 mmol, 1.3 equiv.). Chromatography on a 200–300 mesh silica gel column by elution with hexanes and then 5% EtOAc in hexanes gave iodobenzene (88.1 mg). Subsequent elution with 20% EtOAc in hexanes and then 70% EtOAc in hexanes gave product **2** (426.4 mg, 86% yield) as a pale brown solid.

3',5'-Di-*O*-(*t*-Butyldimethylsilyl)-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (5)



Synthesized from the N^6-(*p*-methylphenyl)-2'-deoxyadenosine precursor (28.5 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **5** (22.6 mg, 80% yield) as a brown solid. R_f (SiO_2 and 50% EtOAc in hexanes) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.26 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.73 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 6.55 (t, J = 6.3 Hz, 1H), 4.63–4.68 (m, 1H), 4.04–4.08 (m, 1H), 3.85 (dd, J = 4.4, 11.0 Hz, 1H), 3.79 (dd, J = 3.0, 11.2 Hz, 1H), 2.66 (app quint, J_{app} ~ 6.3 Hz, 1H), 2.57 (s, 3H), 2.52–2.48 (m, 1H), 0.93 and 0.91 (2s, 18H), 0.12, 0.08, and 0.07 (3s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 143.1, 140.5, 139.0, 135.2, 132.6, 128.1, 127.8, 123.5, 120.2, 110.2, 88.2, 84.8, 72.1, 63.0, 41.6, 26.2, 26.0, 22.0, 18.6, 18.2, −4.4, −4.5, −5.2, −5.3. HRMS (ESI/TOF) calcd for $C_{29}H_{46}N_5O_3Si_2$ $[M + H]^+$: 568.3134, found 568.3127.

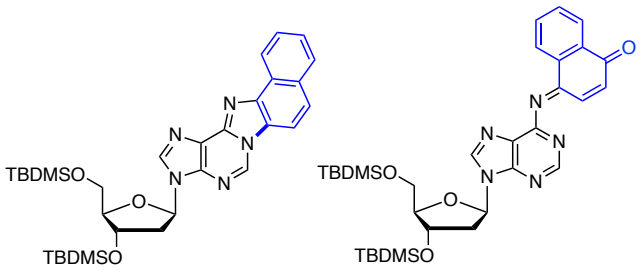
3',5'-Di-*O*-(*t*-Butyldimethylsilyl)-8-methoxy-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (6)



Synthesized from the N^6-(*p*-methoxyphenyl)-2'-deoxyadenosine precursor (29.3 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **6** (25.8 mg, 88% yield) as a brown solid. R_f (SiO_2 and 50% EtOAc in hexanes) = 0.31. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.25 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 1.9 Hz, 1H), 7.16 (dd, J = 2.2, 9.0 Hz, 1H), 6.54 (t, J = 6.3 Hz, 1H), 4.62–4.68 (m, 1H), 4.03–4.08 (m, 1H), 3.93 (s, 3H), 3.85 (dd, J = 4.4, 11.2 Hz, 1H), 3.79 (dd, J = 3.2, 11.0 Hz, 1H), 2.65 (app quint, J_{app} ~ 6.3 Hz, 1H), 2.52–2.49 (m, 1H), 0.93 and

0.91 (2s, 18H), 0.12, 0.083, and 0.077 (3s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 143.8, 140.1, 139.2, 138.9, 135.1, 127.9, 123.5, 121.1, 115.6, 94.3, 88.2, 84.7, 72.0, 62.9, 56.3, 41.6, 26.1, 26.05, 25.96, 18.6, 18.2, −4.4, −4.6, −5.2, −5.3. HRMS (ESI/TOF) calcd for $C_{29}H_{45}N_5O_4Si_2Na$ $[M + Na]^+$: 606.2902, found 606.2883.

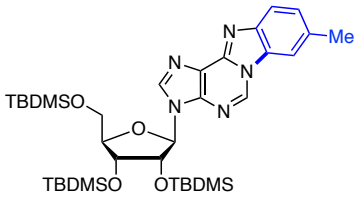
3',5'-Di-*O*-(*t*-Butyldimethylsilyl)-3*H*-naphtho[1',2':4,5]imidazo[2,1-*i*]purine 2'-deoxy-ribonucleoside (7) and ((9-(3',5'-di-*O*-*t*-butyldimethylsilyl-2'-deoxy-β-D-ribo-furanosyl)-9H-purin-6-yl)imino)naphthalen-1(4*H*)-one (7')



Synthesized from the N^6-(1-naphthyl)-2'-deoxyadenosine precursor (30.3 mg, 0.05 mmol), using MeCN (0.5 mL) as solvent. Chromatography on a 200–300 mesh silica gel column by sequential elution with 10% EtOAc in hexanes and 20% EtOAc in hexanes gave compound **7'** (3.8 mg, 12% yield) as a colorless gum. Then elution with 50% EtOAc in hexanes gave product **7** (11.4 mg, 38% yield) as a pale brown, thick gum. R_f (SiO_2 and 50% EtOAc in hexanes): **7'** = 0.56 and **7** = 0.34. ^{1}H NMR of **7'** (500 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H), 8.16 (d, J = 7.3 Hz, 1H), 7.76 (t, J = 7.3 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 10.2 Hz, 1H), 6.70 (d, J = 10.7 Hz, 1H), 6.57 (t, J = 6.6 Hz, 1H), 4.62–4.68 (m, 1H), 4.06–4.08 (m, 1H), 3.89 (dd, J = 11.5, 4.1 Hz, 1H), 3.80 (dd, J = 11.2, 3.4 Hz, 1H), 2.71 (app quint, $J_{app} \sim$ 6.5 Hz, 1H), 2.53–2.48 (m, 1H), 0.94 and 0.90 (2s, 18H), 0.13, 0.09, and 0.08 (3s, 12H). ^{13}C NMR of **7'** (125 MHz, $CDCl_3$): δ 185.1, 159.2, 158.4, 152.9, 152.0, 143.0, 135.5, 134.0, 133.6, 132.6, 132.1, 131.9, 127.0, 126.5, 125.5, 88.4, 84.9, 72.3, 63.1, 41.6, 26.2, 26.01, 18.7, 18.3, −4.4, −4.5, −5.1, −5.2. HRMS (ESI/TOF) of **7'** calcd for $C_{32}H_{46}N_5O_4Si_2$ $[M + H]^+$: 620.3083, found 620.3065. ^{1}H NMR of **7** (500 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.99 (d, J = 8.3 Hz,

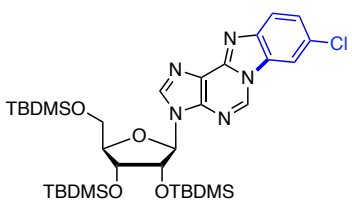
1H), 8.39 (s, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 6.63 (t, J = 6.3 Hz, 1H), 4.74–4.70 (m, 1H), 4.11–4.09 (m, 1H), 3.92 (dd, J = 4.1, 11.0 Hz, 1H), 3.84 (dd, J = 3.4, 11.2 Hz, 1H), 2.71 (app quint, J_{app} ~ 6.5 Hz, 1H), 2.61 (ddd, J = 3.9, 5.9, 10.0 Hz, 1H), 0.97 and 0.95 (2s, 18H), 0.16 and 0.13 (2s, 12H). ^{13}C NMR of **7** (125 MHz, $CDCl_3$): δ 143.4, 141.7, 140.0, 139.3, 134.5, 132.5, 128.5, 127.14, 127.07, 126.4, 124.0, 123.9, 123.6, 123.2, 109.8, 88.3, 84.9, 72.0, 63.0, 41.9, 26.2, 26.0, 18.7, 18.2, −4.4, −4.5, −5.1, −5.2. HRMS (ESI/TOF) of **7** calcd for $C_{32}H_{46}N_5O_3Si_2$ $[M + H]^+$: 604.3134, found 604.3118.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (8)



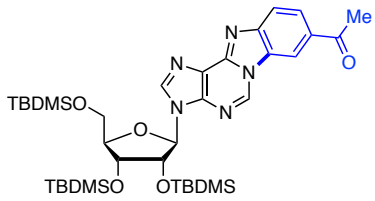
Synthesized from the N^6-(*p*-methylphenyl)adenosine precursor (35.0 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **8** (29.6 mg, 85% yield) as a pale-brown foam. R_f (SiO_2 and 20% EtOAc in hexanes) = 0.11. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.40 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 6.17 (d, J = 4.9 Hz, 1H), 4.59 (t, J = 4.6 Hz, 1H), 4.35 (t, J = 3.9 Hz, 1H), 4.18–4.16 (m, 1H), 4.02 (dd, J = 3.7, 11.5 Hz, 1H), 3.83 (dd, J = 2.7, 11.5 Hz, 1H), 2.58 (s, 3H), 0.97, 0.95, and 0.79 (3s, 27H), 0.16, 0.15, 0.12, 0.11, −0.03, and −0.22 (6s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 141.3, 140.1, 134.9, 133.1, 128.4, 127.2, 122.6, 119.3, 110.4, 88.5, 85.7, 71.9, 62.5, 26.1, 25.9, 25.7, 21.8, 18.6, 18.1, 17.9, −4.4, −4.6, −4.7, −5.0, −5.3. HRMS (ESI/TOF) calcd for $C_{35}H_{60}N_5O_4Si_3$ $[M + H]^+$: 698.3948, found 698.3932.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-8-chloro-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (9)



Synthesized from the N^6-(*p*-chlorophenyl)adenosine precursor (36.0 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **9** (32.1 mg, 89% yield) as a pale-brown foam. R_f (SiO_2 and 20% EtOAc in hexanes) = 0.15. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.42 (s, 1H), 7.99 (s, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.17 (d, J = 4.9 Hz, 1H), 4.57 (t, J = 4.4 Hz, 1H), 4.35 (t, J = 3.7 Hz, 1H), 4.18–4.17 (m, 1H), 4.02 (dd, J = 3.2, 11.2 Hz, 1H), 3.82 (dd, J = 1.5, 11.2 Hz, 1H), 0.97, 0.94, and 0.80 (3s, 27H), 0.16, 0.15, 0.12, 0.10, −0.02, and −0.20 (6s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.7, 142.8, 141.3, 140.2, 135.0, 128.2, 128.1, 127.4, 123.1, 121.2, 110.9, 88.8, 88.7, 85.8, 72.0, 62.6, 26.3, 26.0, 25.9, 18.8, 18.3, 18.1, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI/TOF) calcd for $C_{34}H_{56}ClN_5O_4Si_3Na$ $[M + Na]^+$: 740.3221, found 740.3227.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-8-acetyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (10)

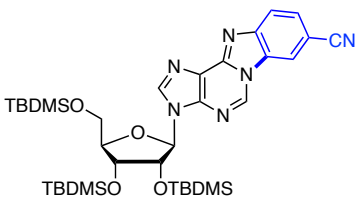


Synthesized from the N^6-(*p*-acetylphenyl)adenosine precursor (36.4 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 70% EtOAc in hexanes gave product **10** (33.2 mg, 91.4% yield) as a yellow solid. R_f (SiO_2 and 50% EtOAc in hexanes) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.66 (s, 1H), 8.45 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 4.4 Hz, 1H), 4.59 (t, J = 4.4 Hz, 1H), 4.36 (t, J = 4.1 Hz, 1H), 4.18–4.17 (m, 1H), 4.04 (dd, J = 3.6, 11.5 Hz, 1H), 3.83 (dd, J = 2.4, 11.2 Hz, 1H), 2.73 (s, 3H), 0.97, 0.94, and 0.81 (3s, 27H), 0.17, 0.15, 0.12, 0.10, −0.01, and −0.18 (6s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.2, 148.5, 146.9, 142.0, 140.5, 135.4, 131.5, 128.0, 127.4, 123.3, 120.0,

111.1, 88.90, 88.87, 85.7, 71.9, 62.6, 27.1, 26.3, 26.0, 25.9, 18.7, 18.3, 18.1, −4.2, −4.4, −4.5, −4.8, −5.2. HRMS (ESI/TOF) calcd for $C_{36}H_{60}N_5O_5Si_3$ $[M + H]^+$: 726.3897, found 726.3898.

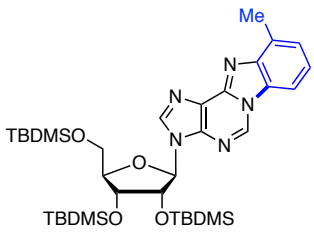
The larger-scale reaction was conducted with the N^6-(*p*-acetylphenyl)adenosine precursor (655.4 mg, 0.9 mmol), HFIP (9.0 mL), and $PhI(OAc)_2$ (376.9 mg, 1.17 mmol, 1.3 equiv.). Chromatography on a 200–300 mesh silica gel column by elution with hexanes and then 5% EtOAc in hexanes gave iodobenzene (82.2 mg). Subsequent elution with 20% EtOAc in hexanes and then 90% EtOAc in hexanes gave product **10** (608.5 mg, 93% yield) as a pale-yellow foamy solid.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-8-cyano-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (11)



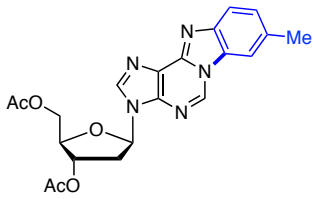
Synthesized from the N^6-(*p*-cyanophenyl)adenosine precursor (35.5 mg, 0.05 mmol), column chromatography by sequential elution with 20% EtOAc in hexanes and 50% EtOAc in hexanes gave product **11** (29.2 mg, 82% yield) as a brown foam. R_f (SiO_2 and 50% EtOAc in hexanes) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.53 (s, 1H), 8.36 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.85 (dd, J = 1.2, 8.5 Hz, 1H), 6.22 (d, J = 4.9 Hz, 1H), 4.59 (t, J = 4.4 Hz, 1H), 4.38 (t, J = 4.1 Hz, 1H), 4.22–4.20 (m, 1H), 4.06 (dd, J = 3.6, 11.5 Hz, 1H), 3.86 (dd, J = 2.4, 11.2 Hz, 1H), 1.00, 0.96, and 0.83 (3s, 27H), 0.20, 0.19, 0.14, 0.13, −0.02, and −0.16 (6s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 146.9, 142.0, 140.7, 135.1, 130.1, 127.6, 123.2, 121.5, 119.5, 115.4, 105.0, 88.85, 88.82, 85.8, 72.0, 62.6, 26.3, 26.0, 25.9, 18.8, 18.3, 18.1, −4.1, −4.4, −4.5, −4.8, −5.1. HRMS (ESI/TOF) calcd for $C_{36}H_{56}N_6O_4Si_3Na$ $[M + Na]^+$: 731.3563, found 731.3565.

2',3',5'-Tri-*O*-(*t*-butyldimethylsilyl)-10-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (12)



Synthesized from the N^6-(*o*-methylphenyl)adenosine precursor (35.0 mg, 0.05 mmol), column chromatography by sequential elution with 10% EtOAc in hexanes and 20% EtOAc in hexanes gave product **12** (30.4 mg, 87% yield) as a pale-orange gum. R_f (SiO_2 and 20% EtOAc in hexanes) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.53 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.40–7.33 (m, 2H), 6.19 (d, J = 4.4 Hz, 1H), 5.75–5.71 (m, 1H), 4.53 (t, J = 4.4 Hz, 1H), 4.37 (t, J = 4.4 Hz, 1H), 4.20–4.18 (m, 1H), 4.07 (dd, J = 3.2, 11.5 Hz, 1H), 3.85 (dd, J = 1.7, 11.5 Hz, 1H), 2.77 (s, 3H), 0.99, 0.94, and 0.83 (3s, 27H), 0.19, 0.18, 0.12, 0.11, 0.01, and −0.13 (6s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 143.8, 140.9, 139.6, 135.4, 131.0, 127.3, 127.0, 123.4, 122.4, 107.7, 88.82, 88.78, 85.6, 72.0, 62.6, 26.3, 26.1, 25.9, 18.8, 18.3, 18.1, 17.3, −4.1, −4.4, −4.5, −4.8, −5.1. HRMS (ESI/TOF) calcd for $C_{35}H_{60}N_5O_4Si_3$ $[M + H]^+$: 698.3948, found 698.3943.

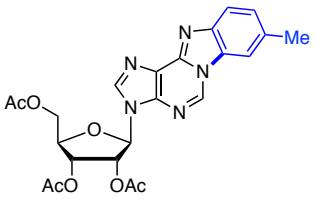
3',5'-Di-*O*-acetyl-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine 2'-deoxyribonucleoside (13)



Synthesized from the N^6-(*p*-methylphenyl)-2'-deoxyadenosine precursor (21.3 mg, 0.05 mmol), column chromatography by sequential elution with 50% EtOAc in hexanes, EtOAc, and then 10% MeOH in EtOAc gave product **13** (18.7 mg, 88% yield) as a white solid. R_f (SiO_2 and 50% EtOAc in hexanes) = 0.09. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.14 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.73 (s, 1H), 7.38 (d, J = 8.3 Hz, 1H), 6.52 (t, J = 6.8 Hz, 1H), 5.49–5.47 (m, 1H), 4.45–4.35 (m, 3H), 3.03 (app quint, J_{app} ~ 7.0 Hz, 1H), 2.70 (ddd, J = 2.9, 6.8, 11.9 Hz, 1H), 2.58 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.5, 143.9, 143.0,

140.4, 138.8, 135.5, 132.9, 128.3, 127.8, 123.9, 120.2, 110.3, 85.3, 82.9, 74.7, 64.0, 38.0, 22.0, 21.1, 21.0. HRMS (ESI/TOF) calcd for $C_{21}H_{22}N_5O_5$ [M + H]$^+$: 424.1615, found 424.1612.

2',3',5'-Tri-*O*-acetyl-8-methyl-3*H*-benzo[4,5]imidazo[2,1-*i*]purine ribonucleoside (14)



Synthesized from the N^6-(*p*-methylphenyl)adenosine precursor (24.1 mg, 0.05 mmol), column chromatography by sequential elution with 50% EtOAc in hexanes, EtOAc, and then 10% MeOH in EtOAc gave product **14** (20.6 mg, 86% yield) as a white solid. R_f (SiO_2 and 100% EtOAc) = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.13 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.73 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.25 (d, J = 4.9 Hz, 1H), 6.04 (t, J = 5.1 Hz, 1H), 5.64–5.69 (m, 1H), 4.54–4.46 (m, 2H), 4.42–4.40 (m, 1H), 2.58 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.0, 169.5, 143.7, 143.0, 140.4, 139.4, 135.8, 133.0, 128.4, 127.7, 124.2, 120.3, 110.3, 87.1, 73.4, 70.8, 63.3, 22.0, 21.0, 20.7, 20.6. HRMS (ESI/TOF) calcd for $C_{23}H_{24}N_5O_7$ [M + H]$^+$: 482.1670, found 424.1663.

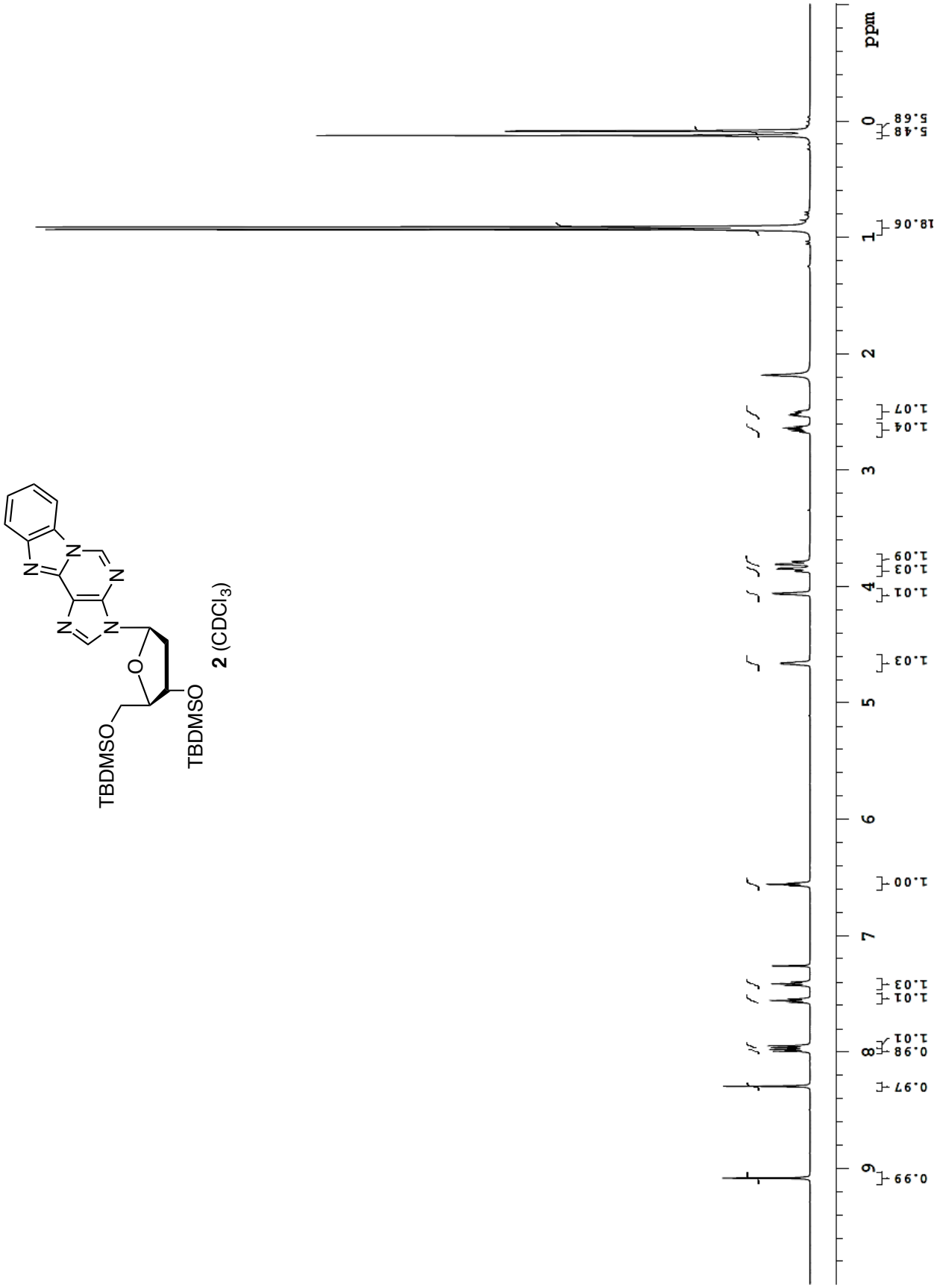
Radical inhibition experiments

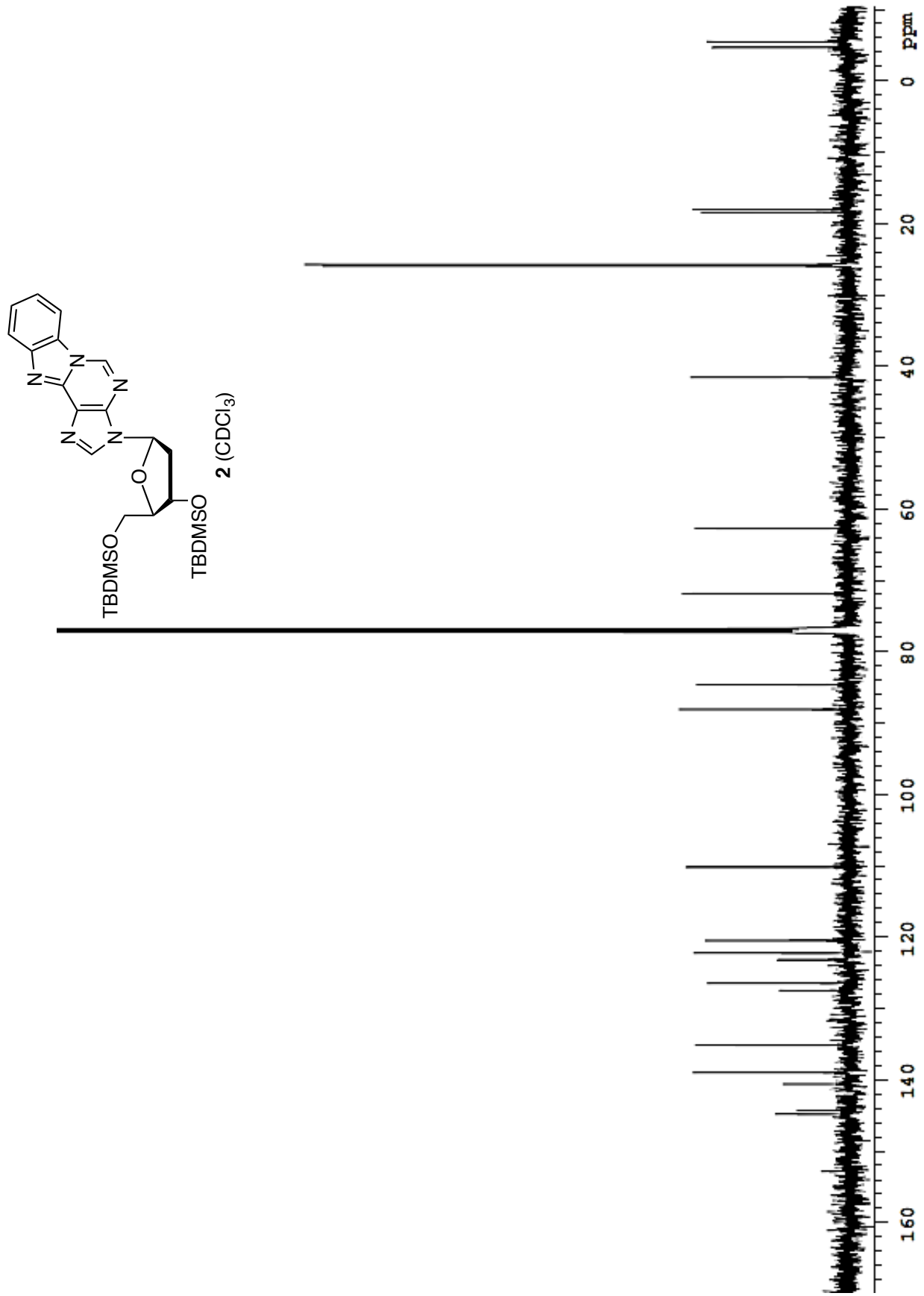
General procedure for radical inhibition experiments using 1,1-DPE in HFIP

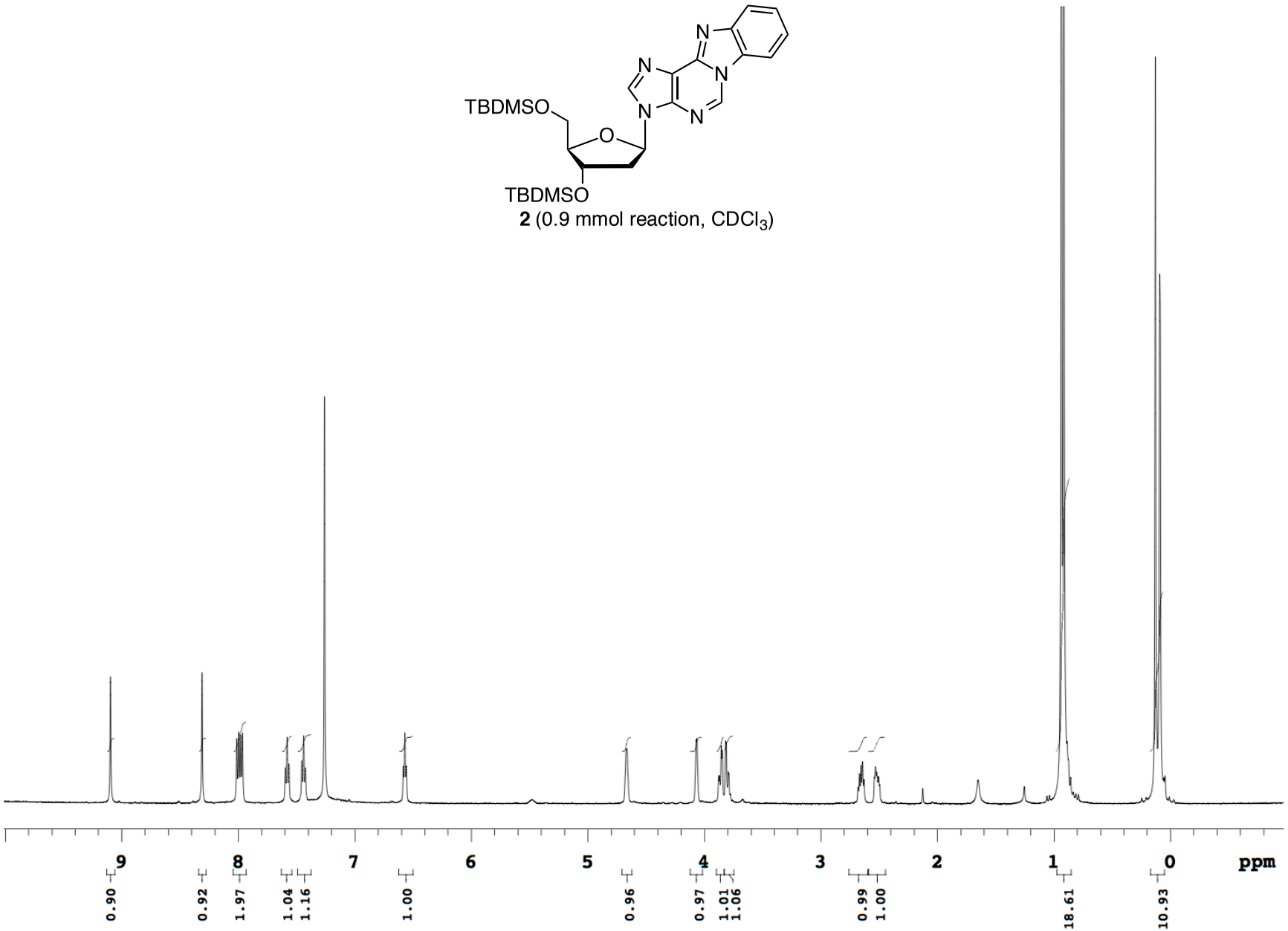
In a clean, dry, 8 mL vial equipped with a stirring bar were placed C–N product (0.05 mmol, 1.0 equiv.), 1,1-DPE (7.1μL, 0.05 mmol, 1.0 equiv.), HFIP (0.5 mL, 0.1 M in the C–N product) and $PhI(OAc)_2$ (20.9 mg, 0.065 mmol, 1.3 equiv.). The vial was flushed with nitrogen and capped, stirred at room temperature. Then, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel. Reaction times and yields of recovered starting materials are reported in Table 2 of the manuscript.

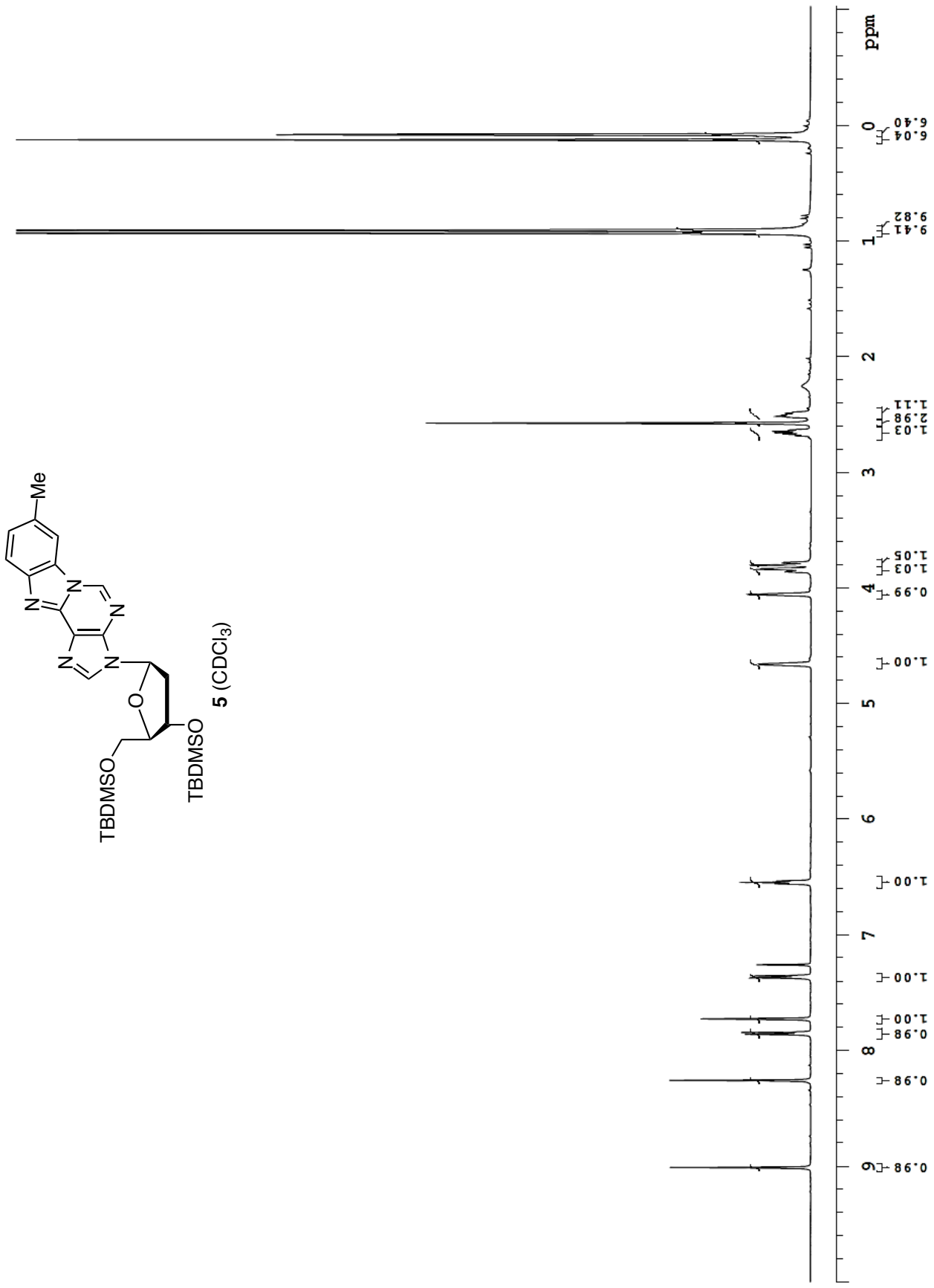
General procedure for radical inhibition experiments using BHT in HFIP

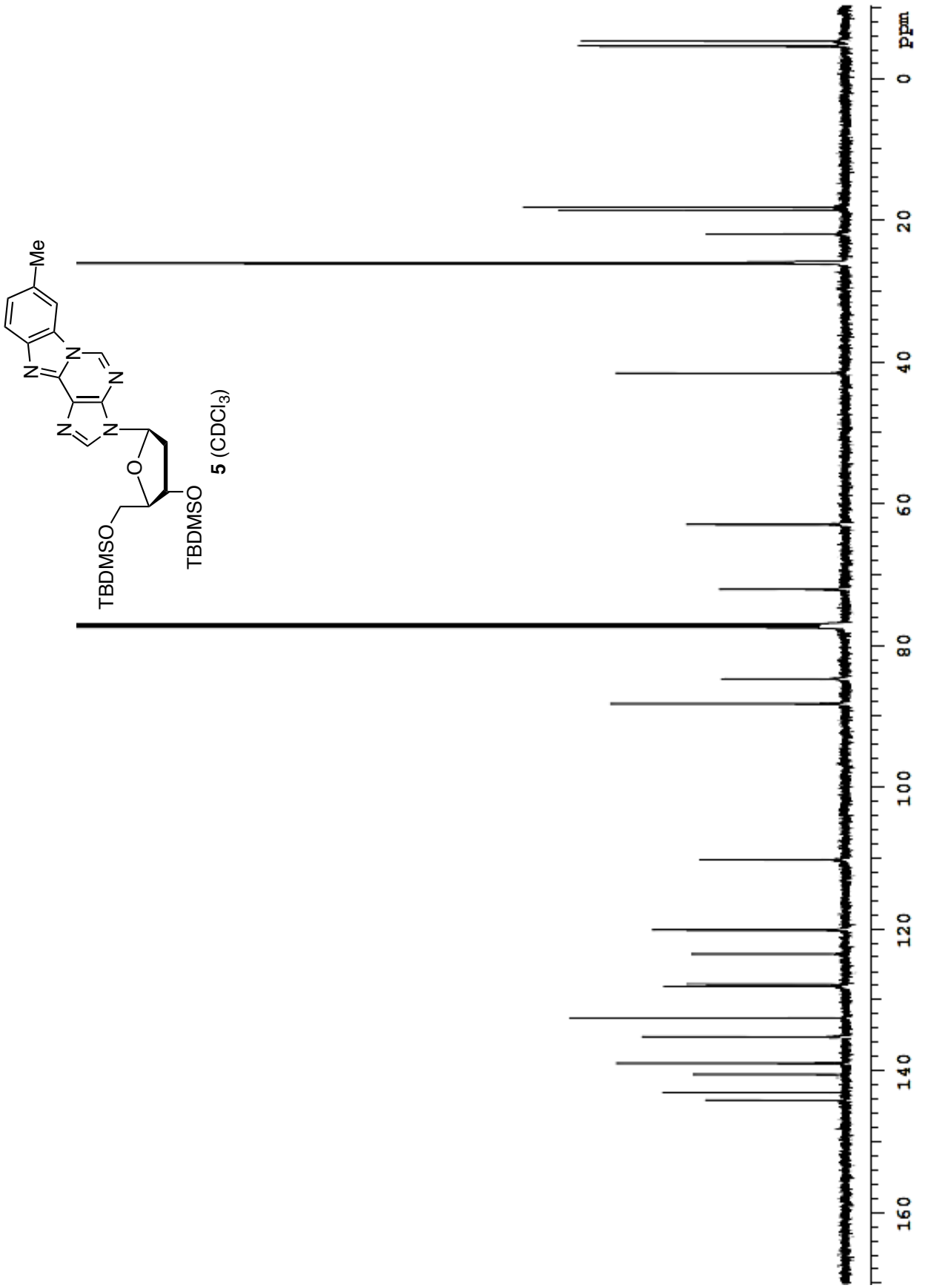
In a clean, dry, 8 mL vial equipped with a stirring bar were placed C–N product (0.05 mmol, 1.0 equiv.), BHT (11.0 mg, 0.05 mmol, 1.0 equiv.), HFIP (0.5 mL, 0.1 M in the C–N product) and $PhI(OAc)_2$ (20.9 mg, 0.065 mmol, 1.3 equiv.). The vial was flushed with nitrogen and capped, stirred at room temperature. Then, the reaction mixture was concentrated under reduced pressure and residue was purified by column chromatography on silica gel. Reaction times and yields of the recovered starting materials are reported in Table 2 of the manuscript.

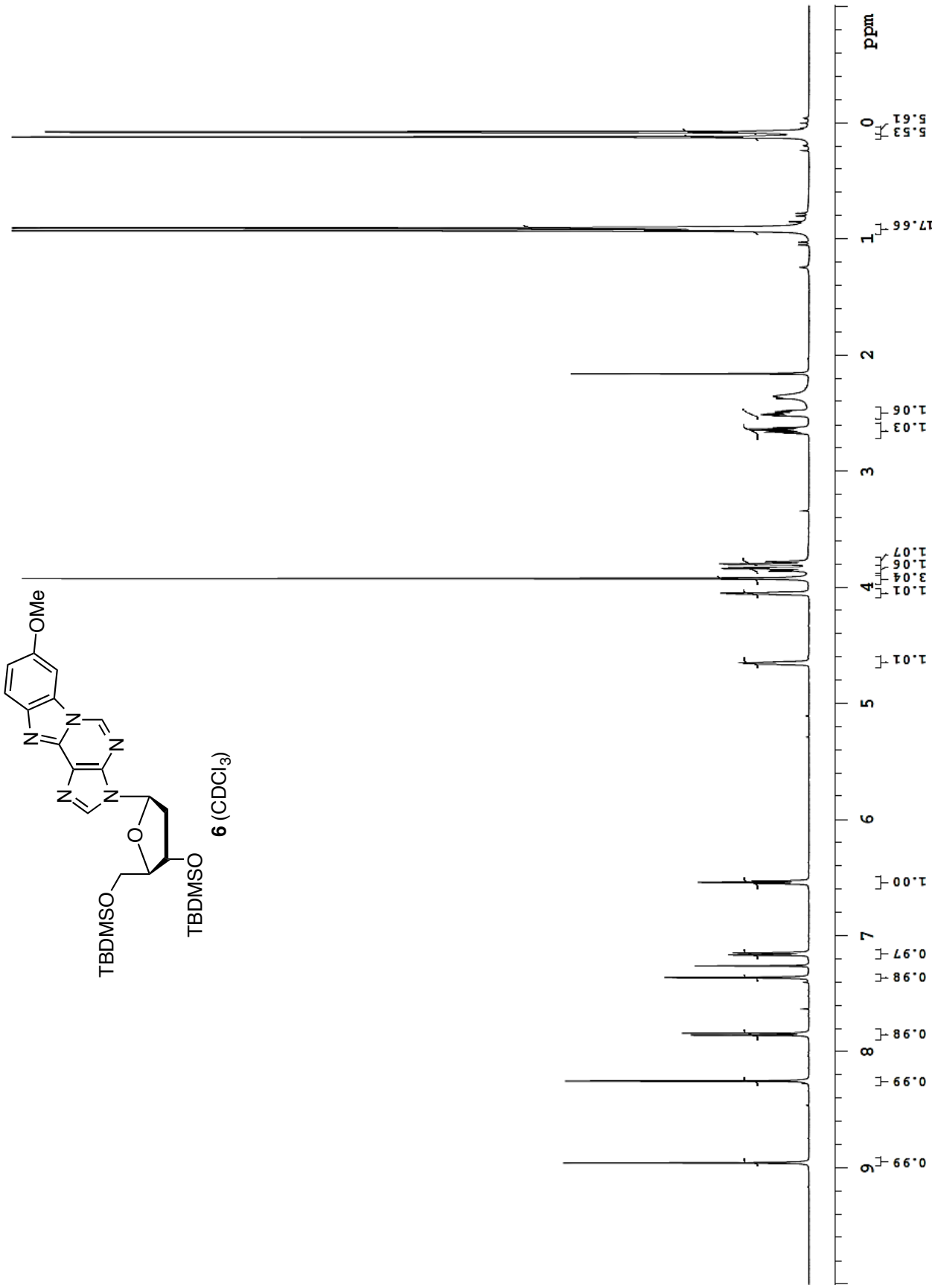

TBDMSO
TBDMSO
O
N
N
N
N
N
2 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
5.48
5.68
18.06
1.07
1.04
1.09
1.03
1.01
1.03
1.00
1.03
1.01
0.98
1.01
0.97
0.99

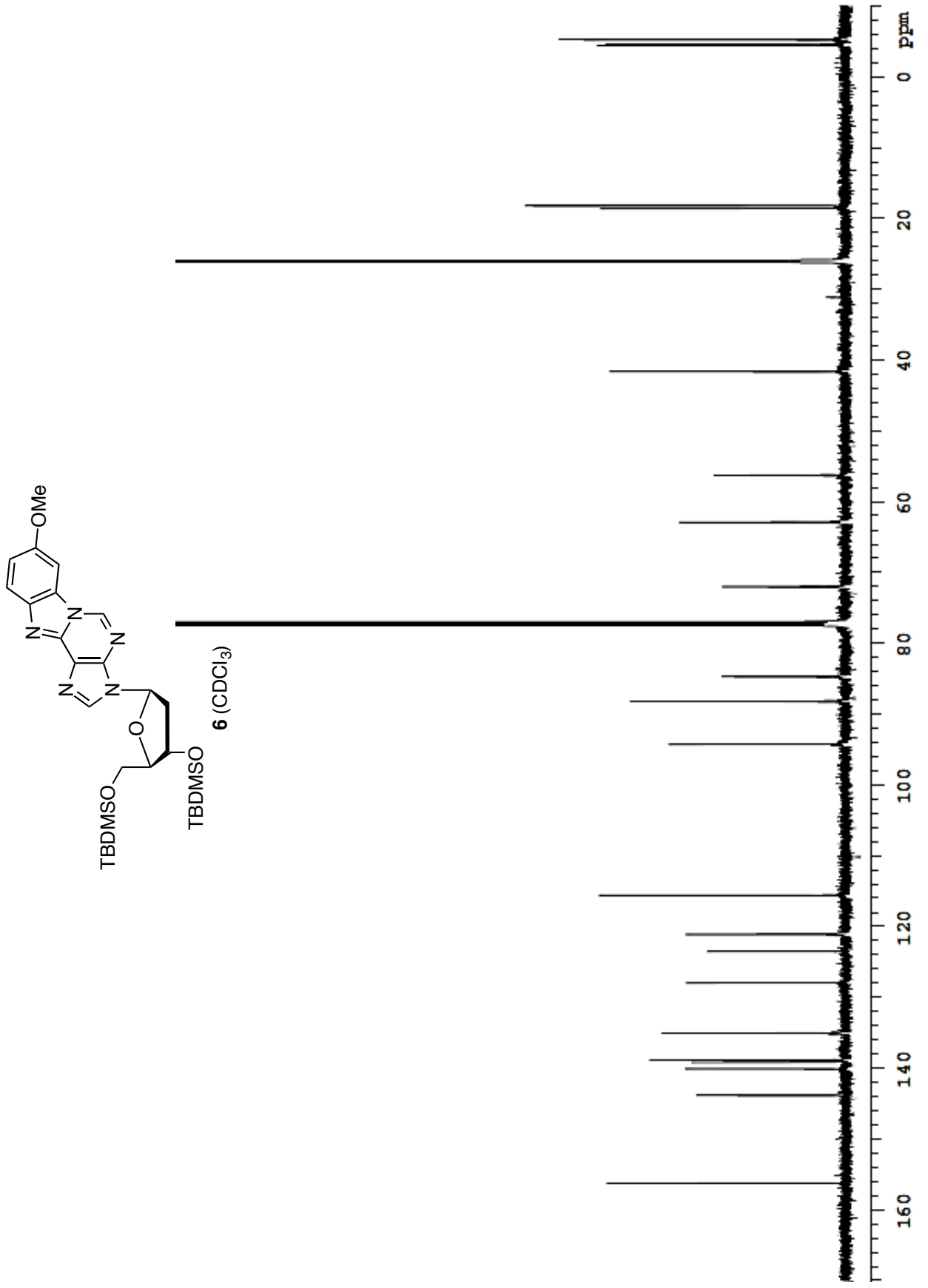

TBDMSO
TBDMSO
2 (CDCl3)
ppm
0
20
40
60
80
100
120
140
160

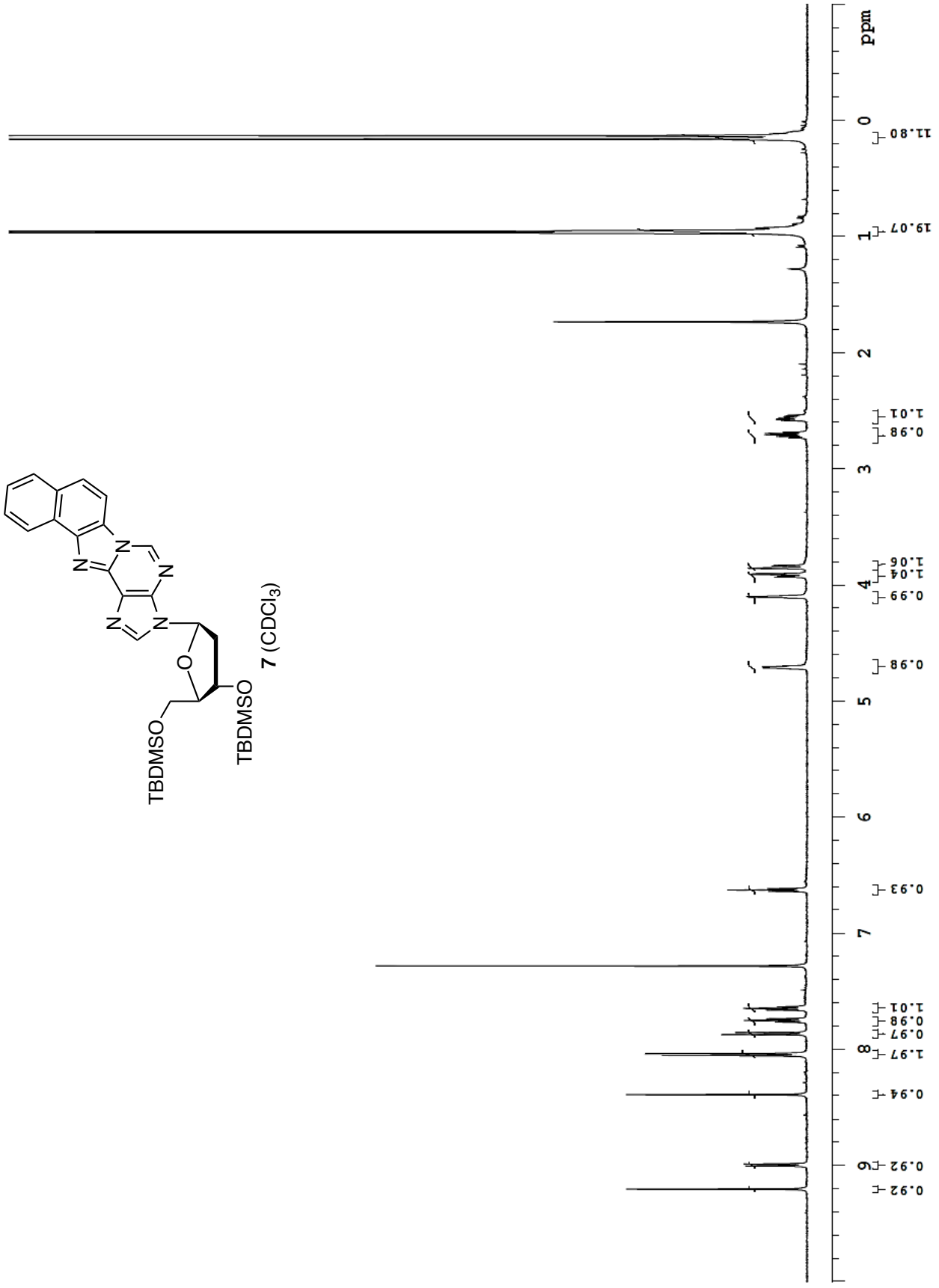

TBDMSO
TBDMSO
N
N
N
N
N
O
2 (0.9 mmol reaction, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
0.90
0.92
1.97
1.04
1.16
1.00
0.96
0.97
1.01
1.06
0.99
1.00
18.61
10.93

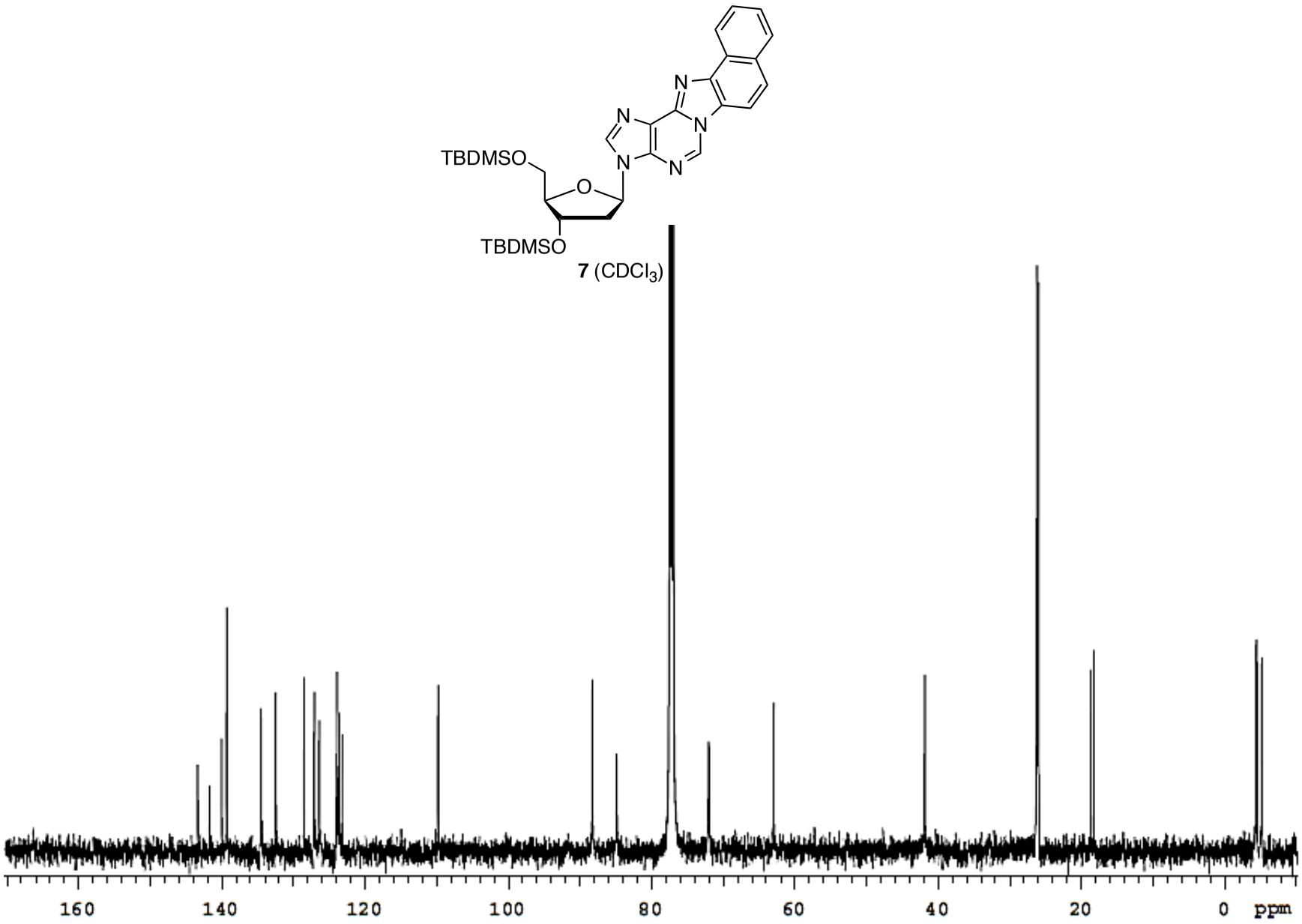

Me
N
N
N
N
N
O
TBDMSO
TBDMSO
5 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
6.40
6.04
9.82
9.41
1.11
2.98
1.03
1.05
1.03
0.99
1.00
1.00
1.00
0.98
1.00
0.98
0.98


Me
N
N
N
N
O
TBDMSO
TBDMSO
5 (CDCl3)
ppm
0
20
40
60
80
100
120
140
160

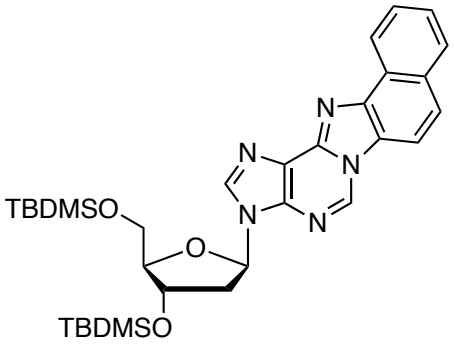

OMe
N
N
N
N
N
O
TBDMSO
TBDMSO
6 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
5.61
5.53
17.66
1.03
1.06
1.07
1.06
1.04
1.01
1.01
1.00
0.97
0.98
0.98
0.99
0.99


OMe
N
N
N
N
N
O
TBDMSO
TBDMSO
6 (CDCl3)
ppm
0
20
40
60
80
100
120
140
160

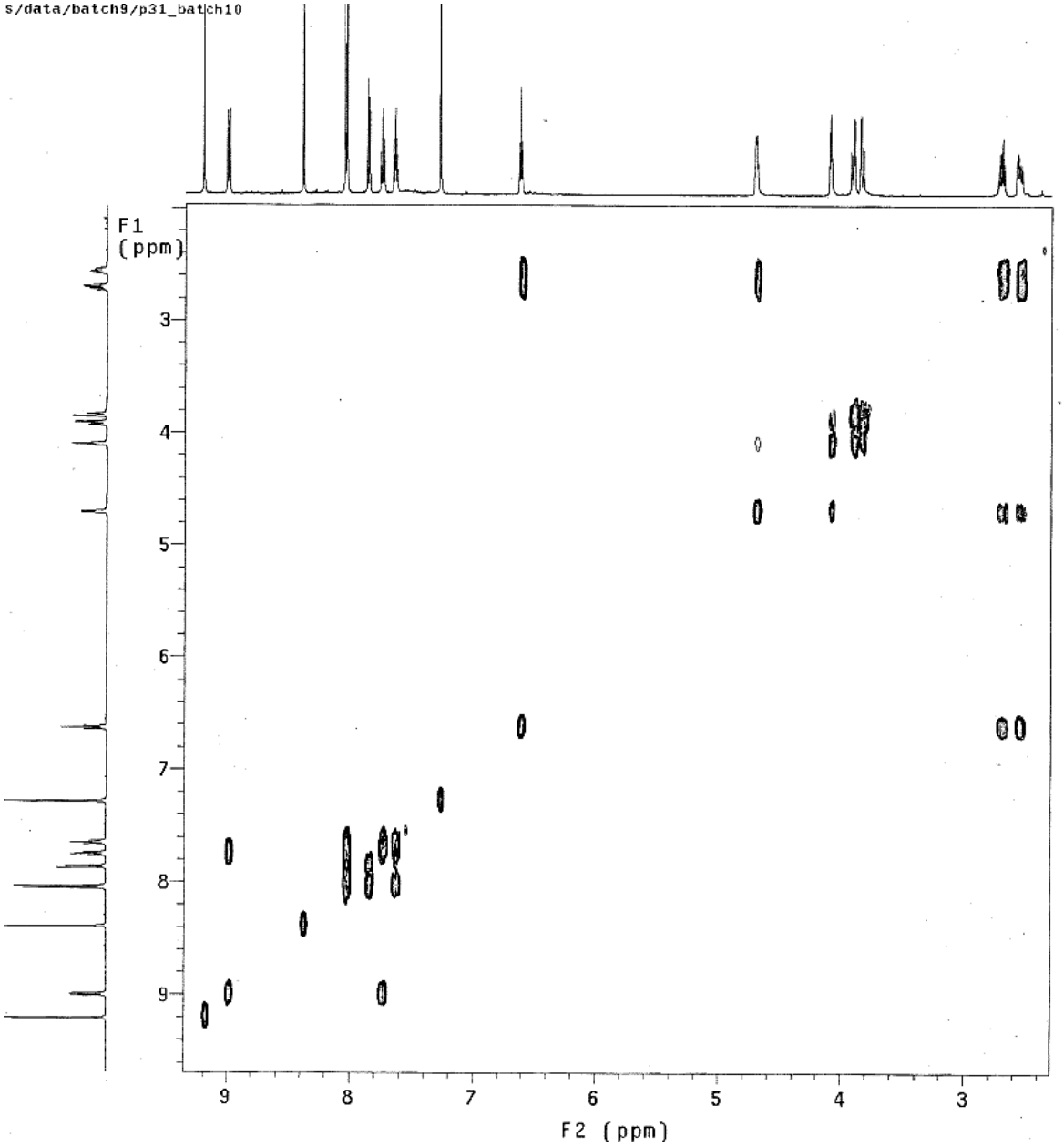

TBDMSO
TBDMSO
7 ($CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
11.80
19.07
1.01
0.98
1.06
1.04
0.99
0.98
0.93
1.01
0.98
0.97
1.97
0.94
0.92
6
0.92


TBDMSO
TBDMSO
O
N
N
N
N
N
7 (CDCl3)
160
140
120
100
80
60
40
20
0
ppm

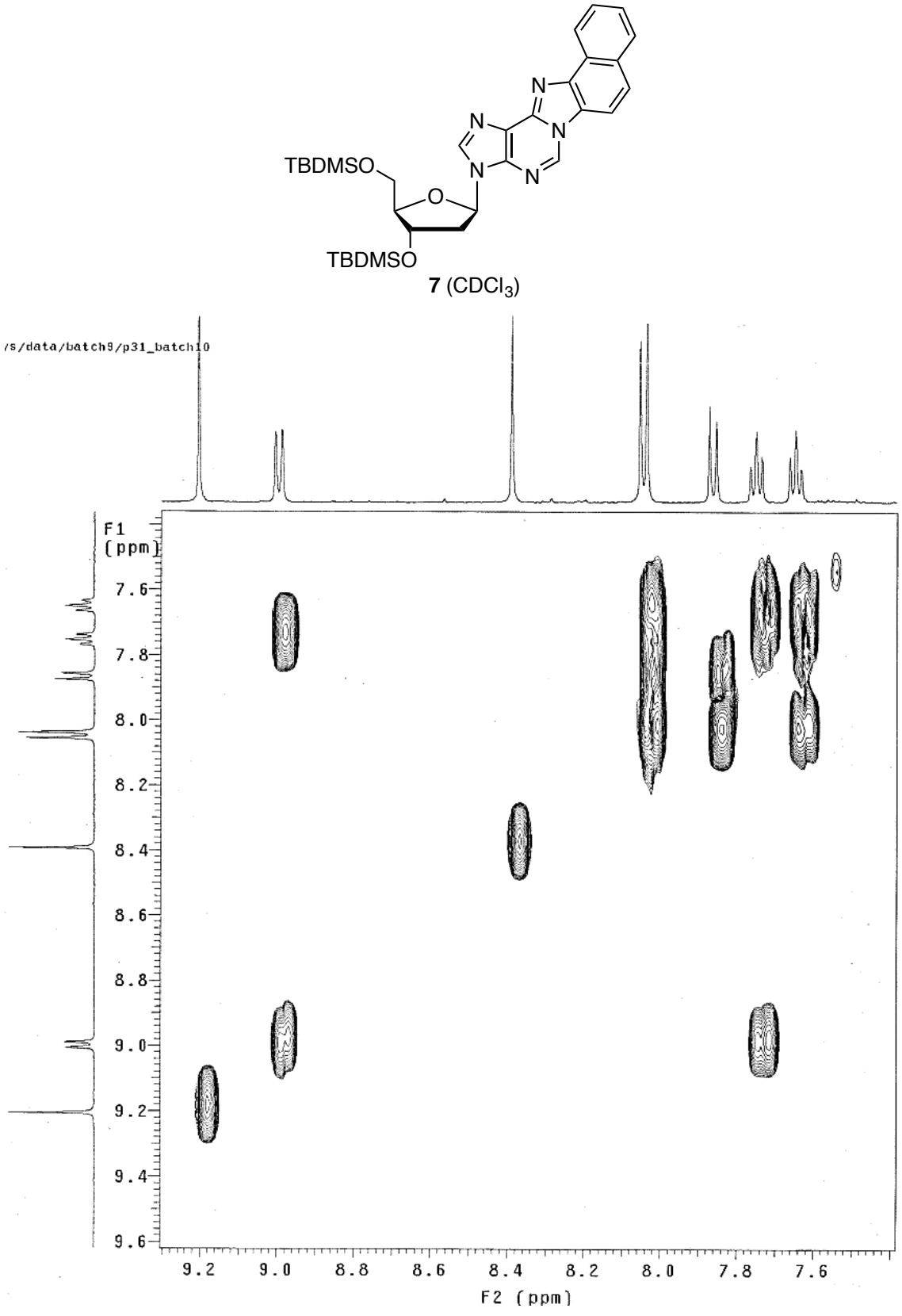
gCOSY NMR spectrum



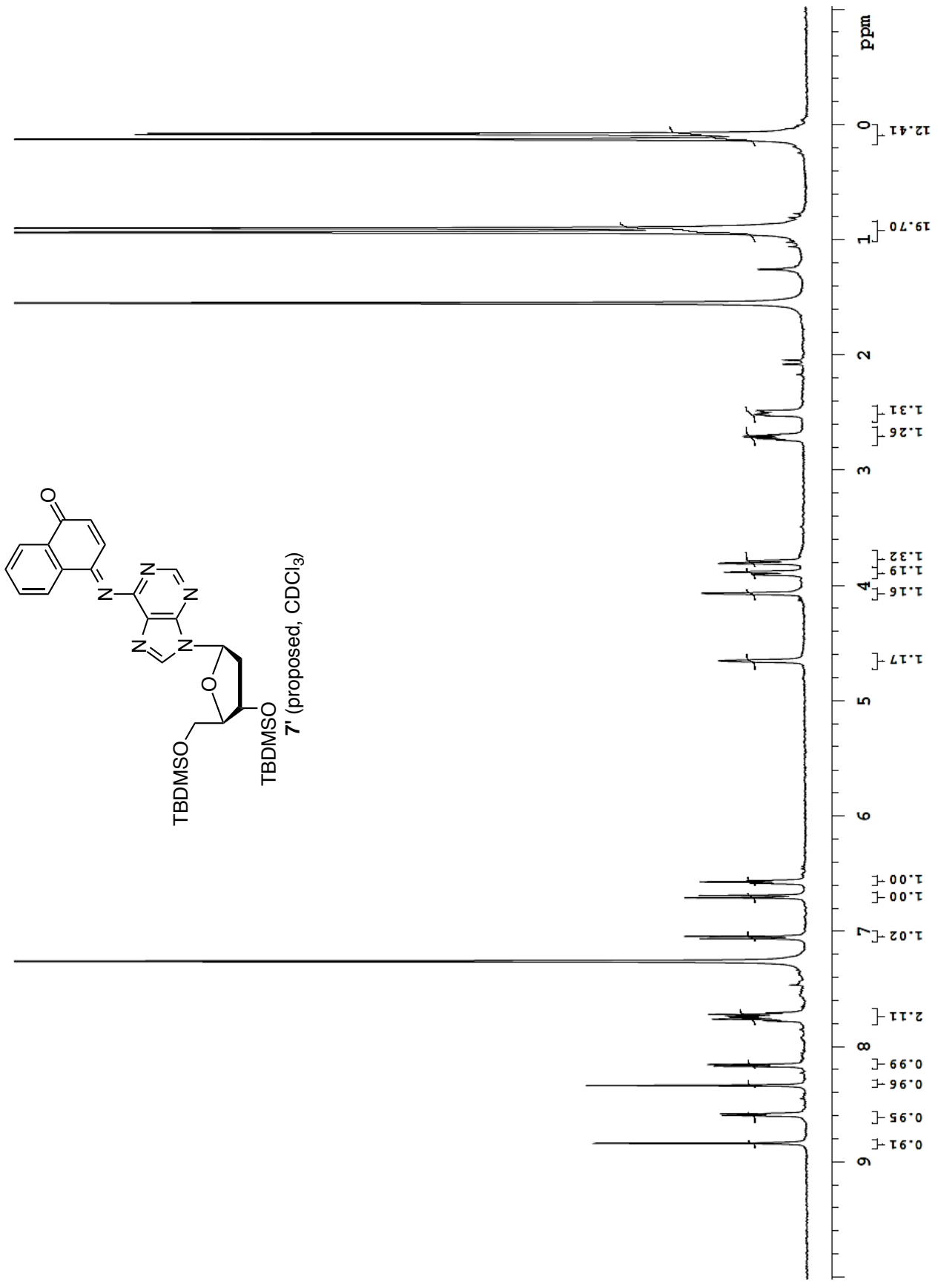
7 ($CDCl_3$)

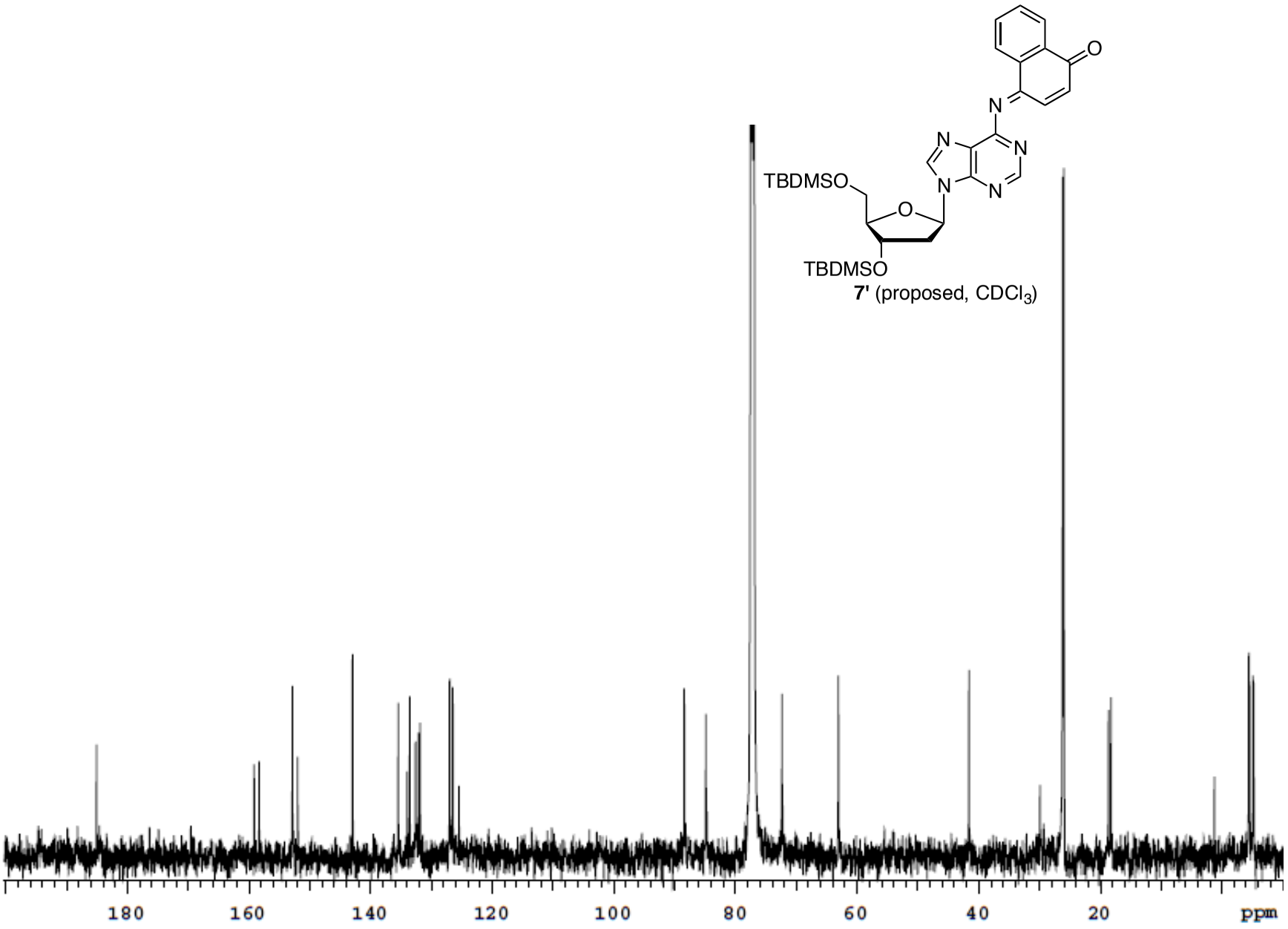


Expansion of the aromatic region in the gCOSY NMR spectrum



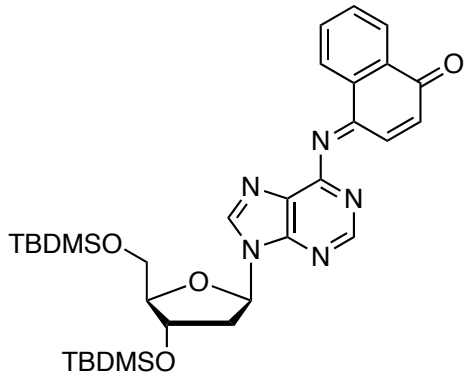
7 ($CDCl_3$)


TBDMSO
TBDMSO
7' (proposed, CDCl3)
ppm
12.41
19.70
1.31
1.26
1.32
1.19
1.16
1.17
1.00
1.00
1.02
2.11
0.99
0.96
0.95
0.91

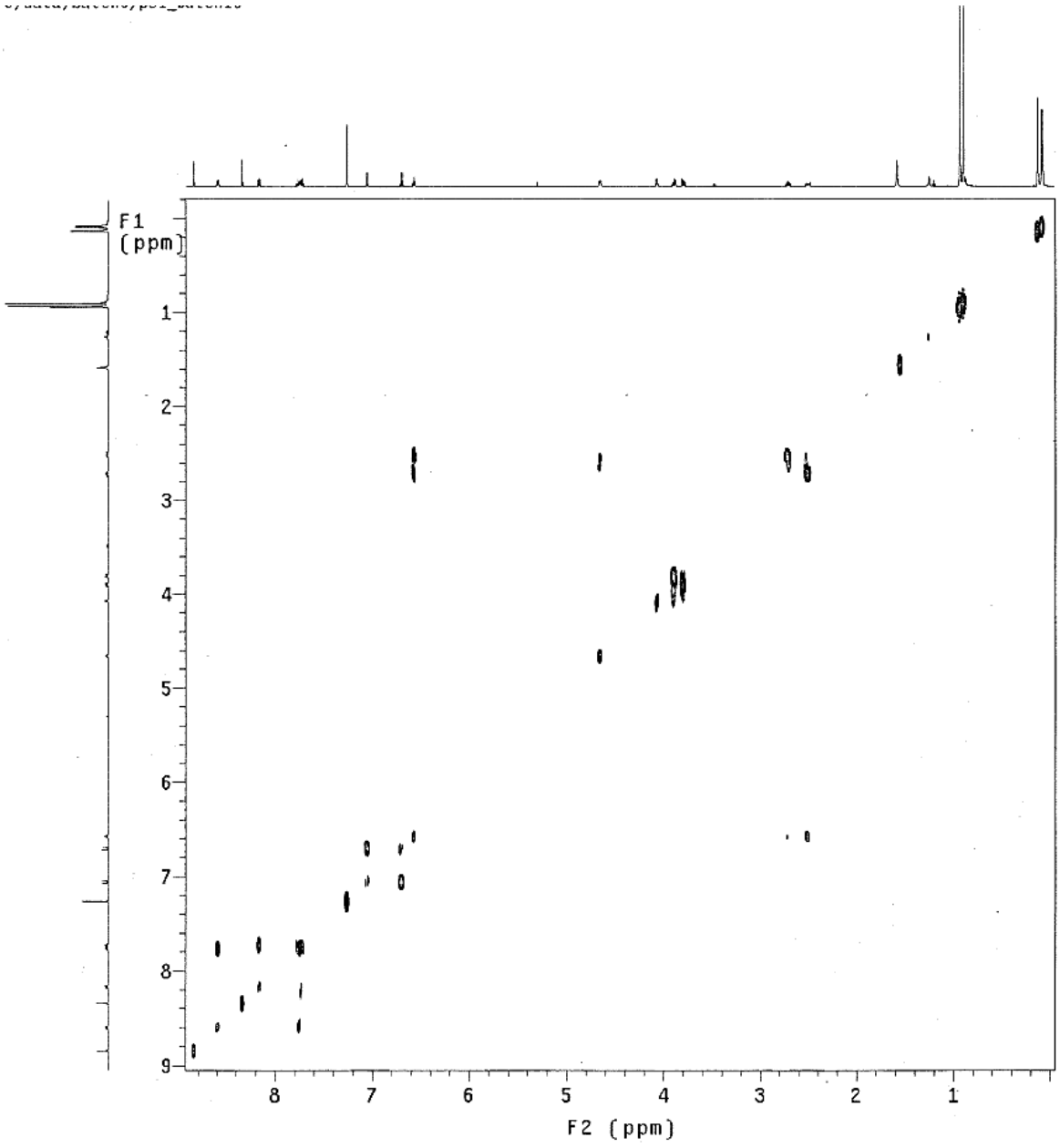


7' (proposed, $CDCl_3$)

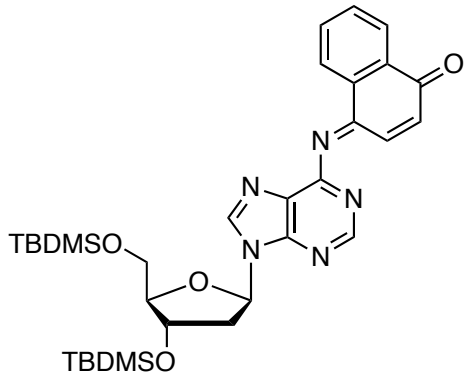
gCOSY NMR spectrum



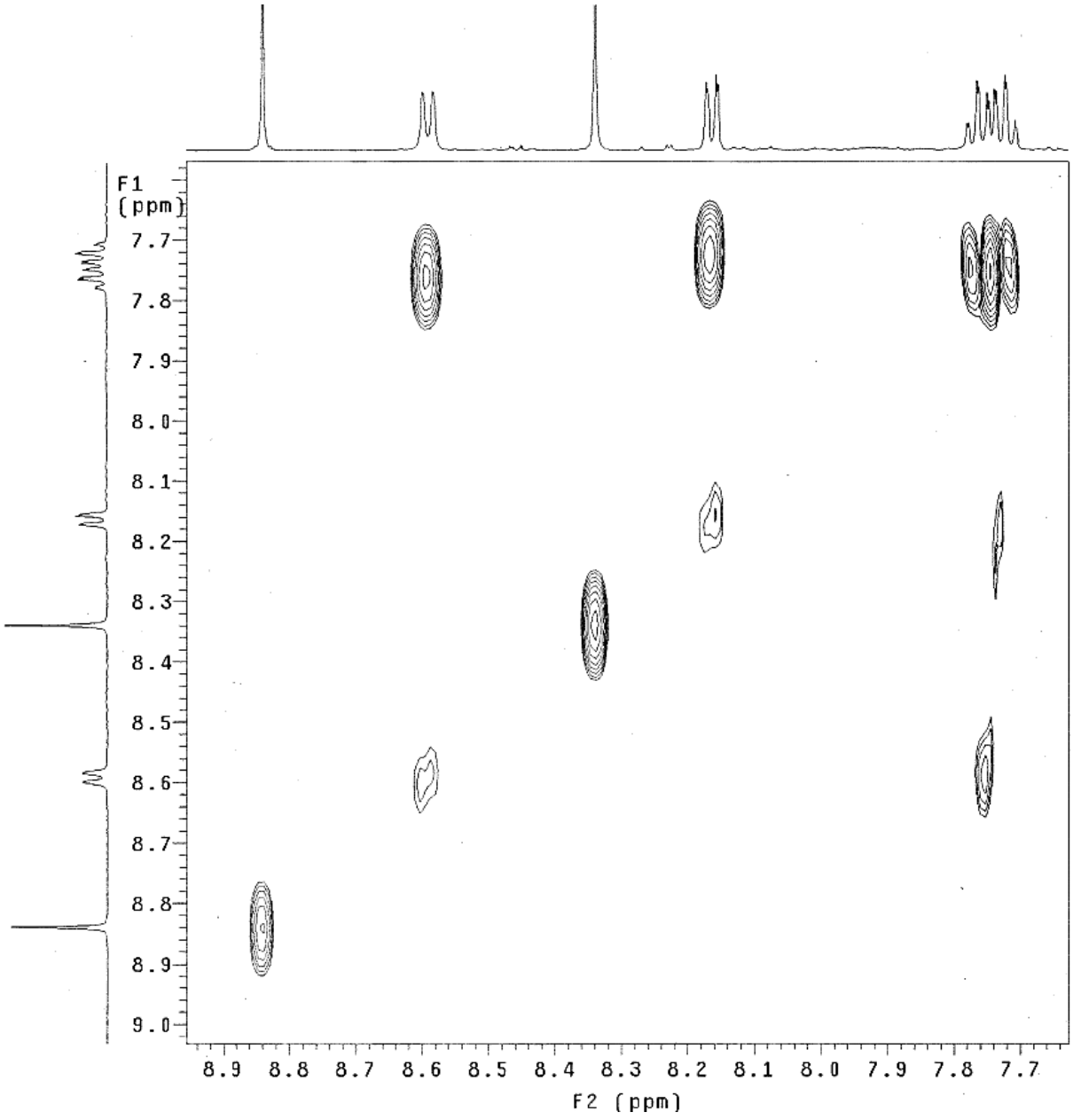
7' (proposed)

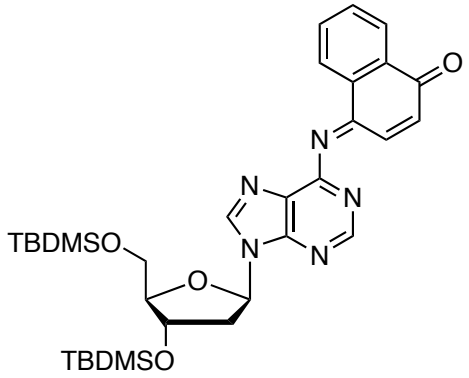


Expansion of the aromatic region in the gCOSY NMR spectrum



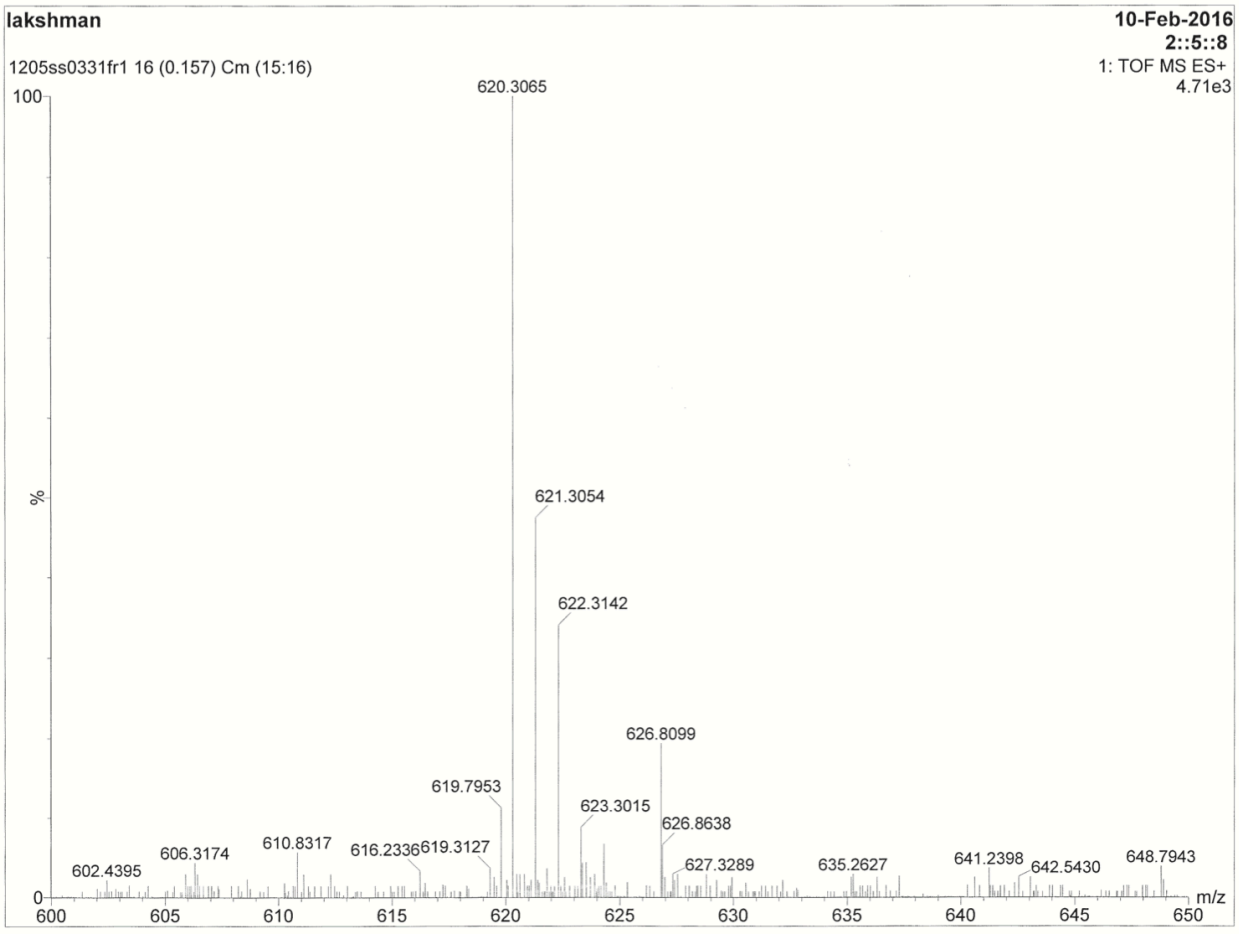
7' (proposed)

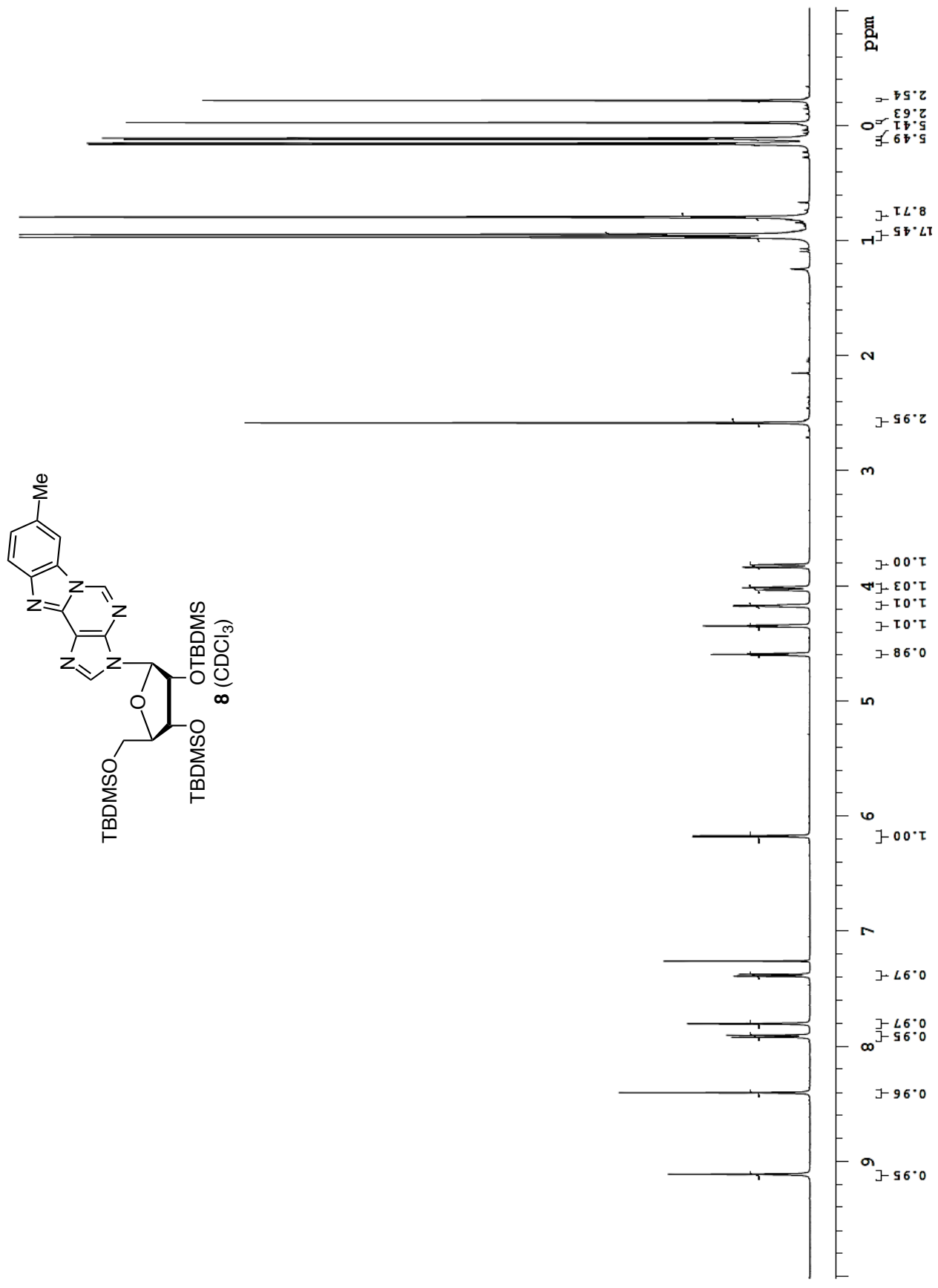


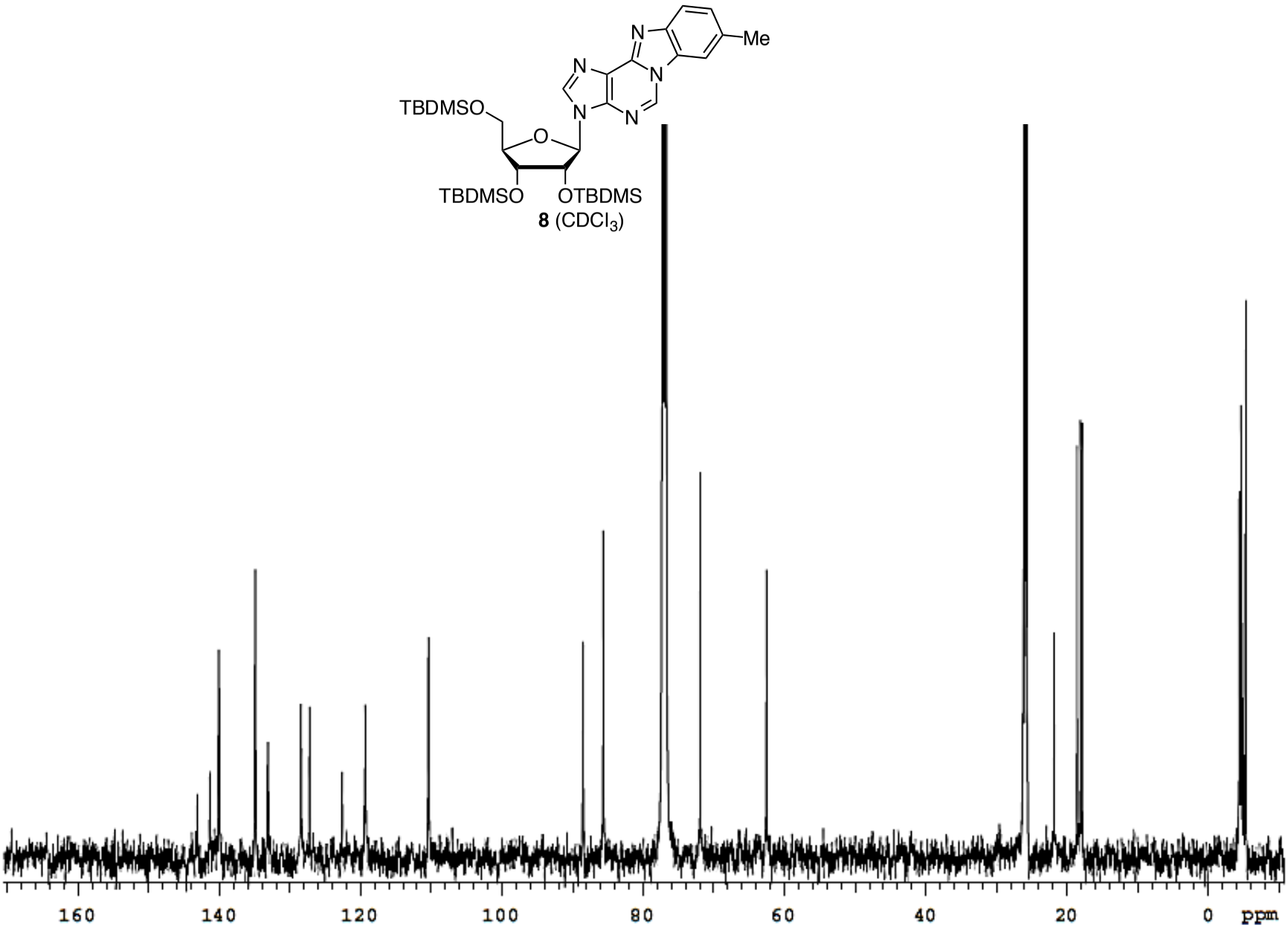


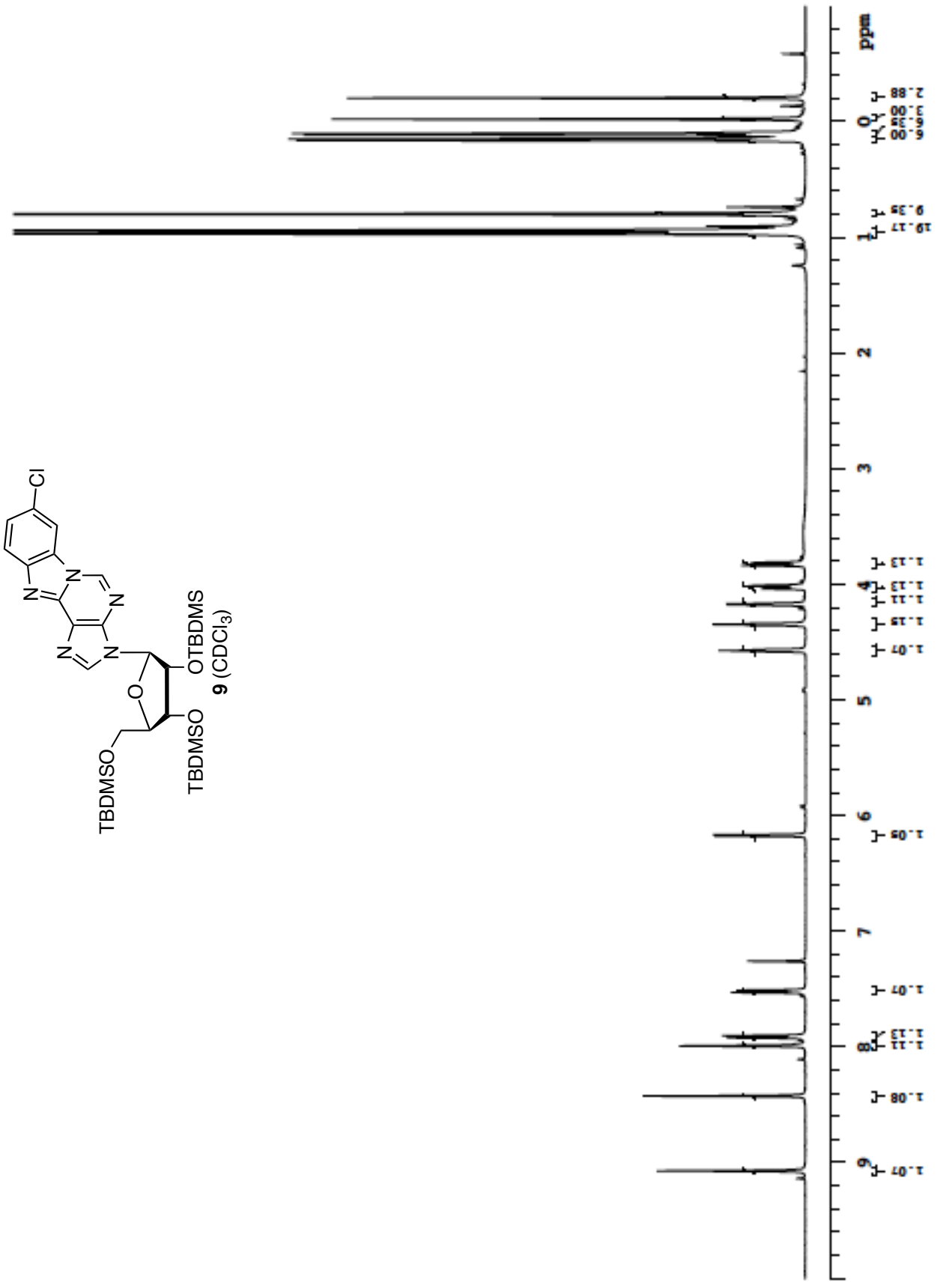
7' (proposed)

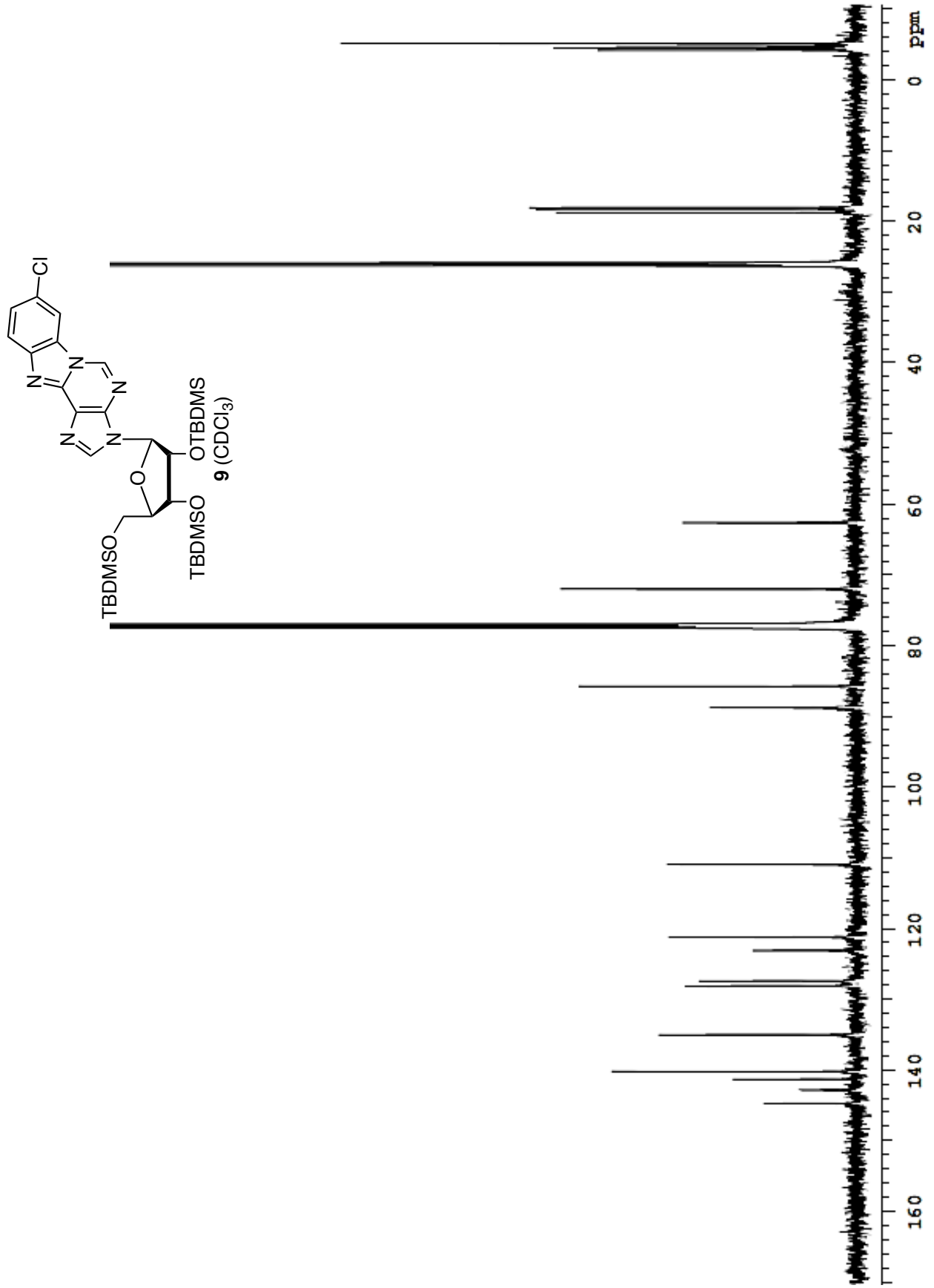
Calculated molecular mass $C_{32}H_{45}N_5O_4Si_2$: 619.3010
Calculated for $C_{32}H_{45}N_5O_4Si_2$ $[M]^+$: 619.3005
Calculated for $C_{32}H_{46}N_5O_4Si_2$ $[M + H]^+$: 620.3083

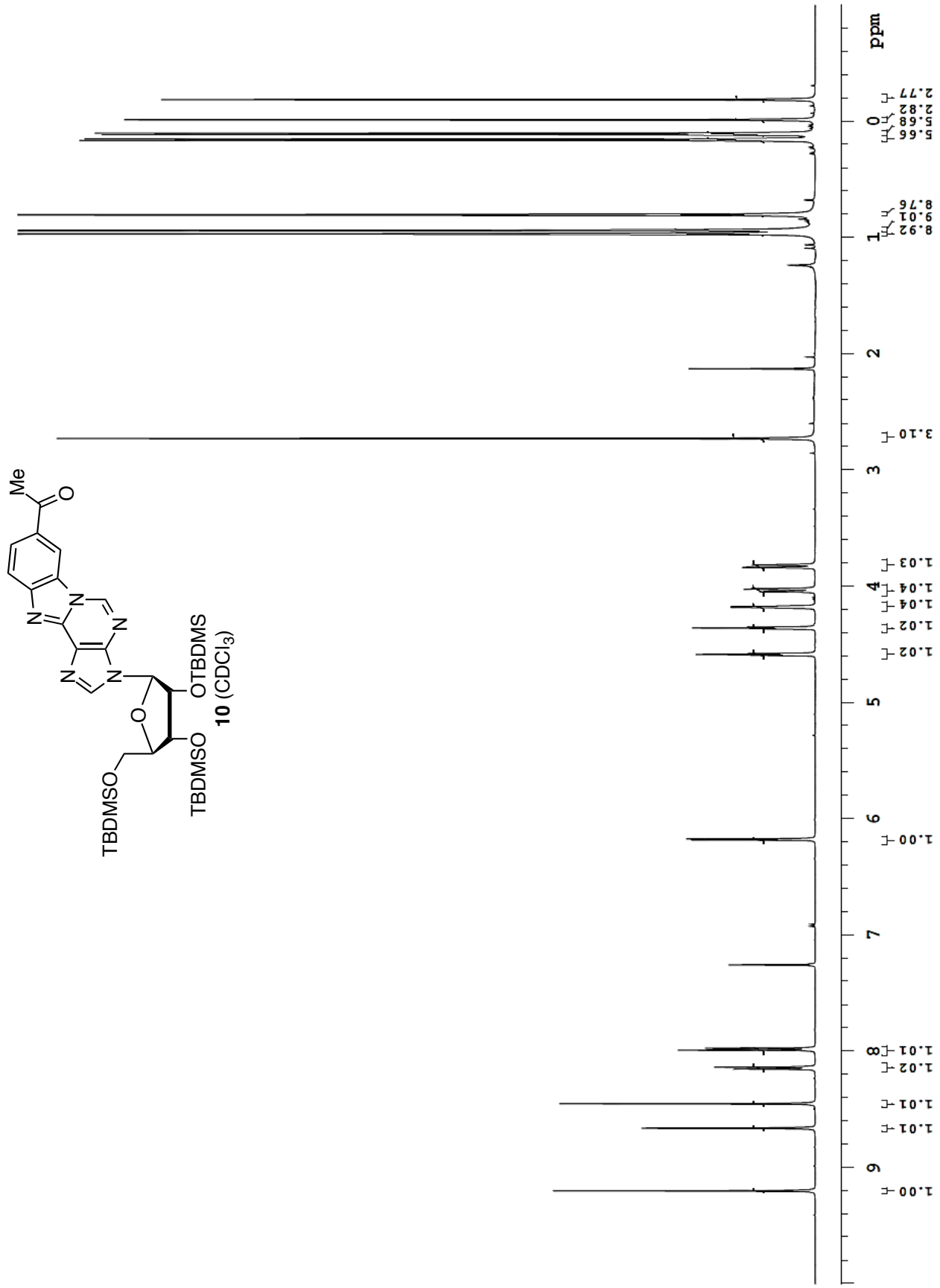


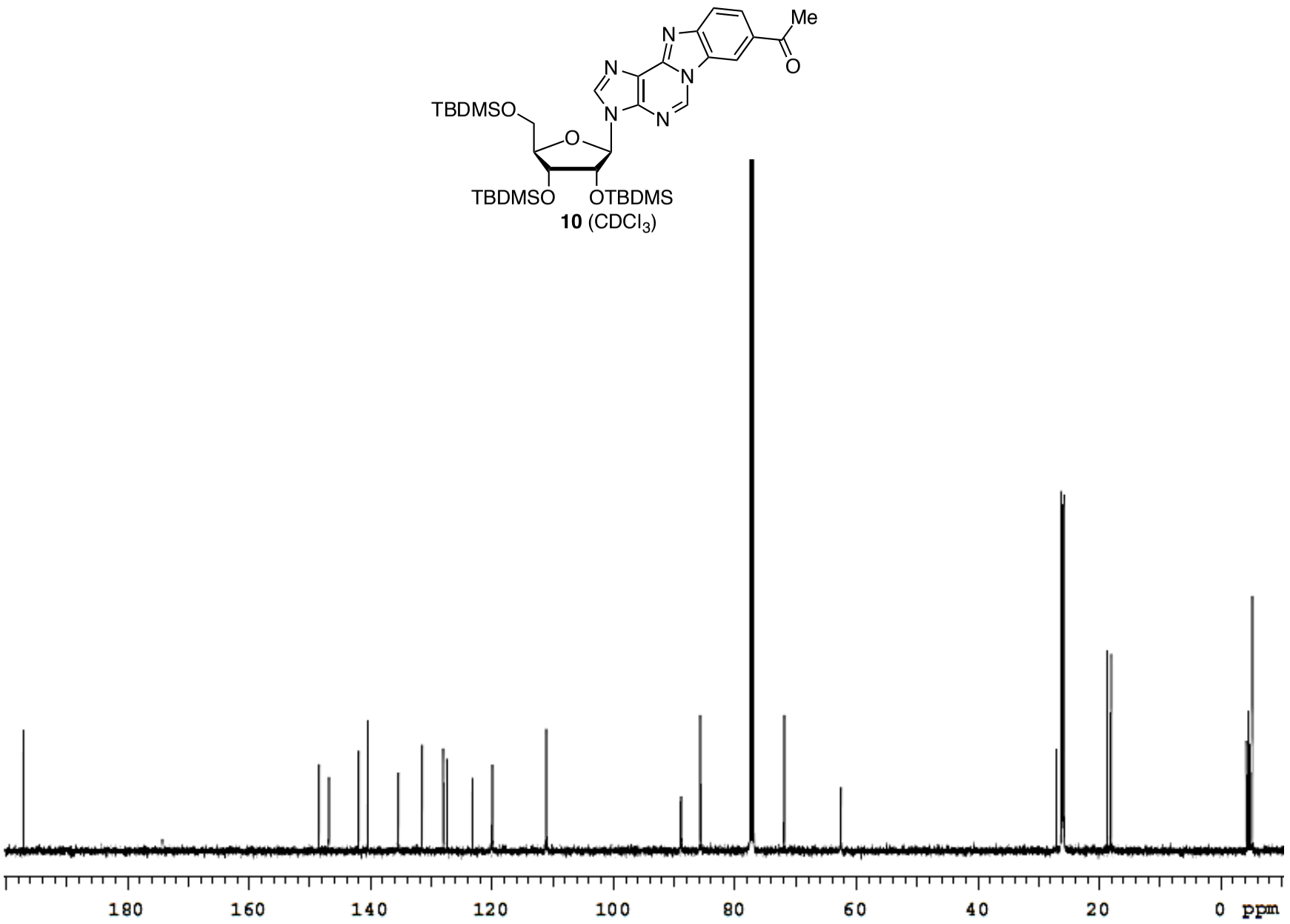

Me
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
8 (CDCl3)
ppm
0.95
0.96
0.97
0.95
0.97
0.97
1.00
0.98
1.01
1.01
1.03
1.00
2.95
8.71
17.45
5.49
5.41
2.63
2.54

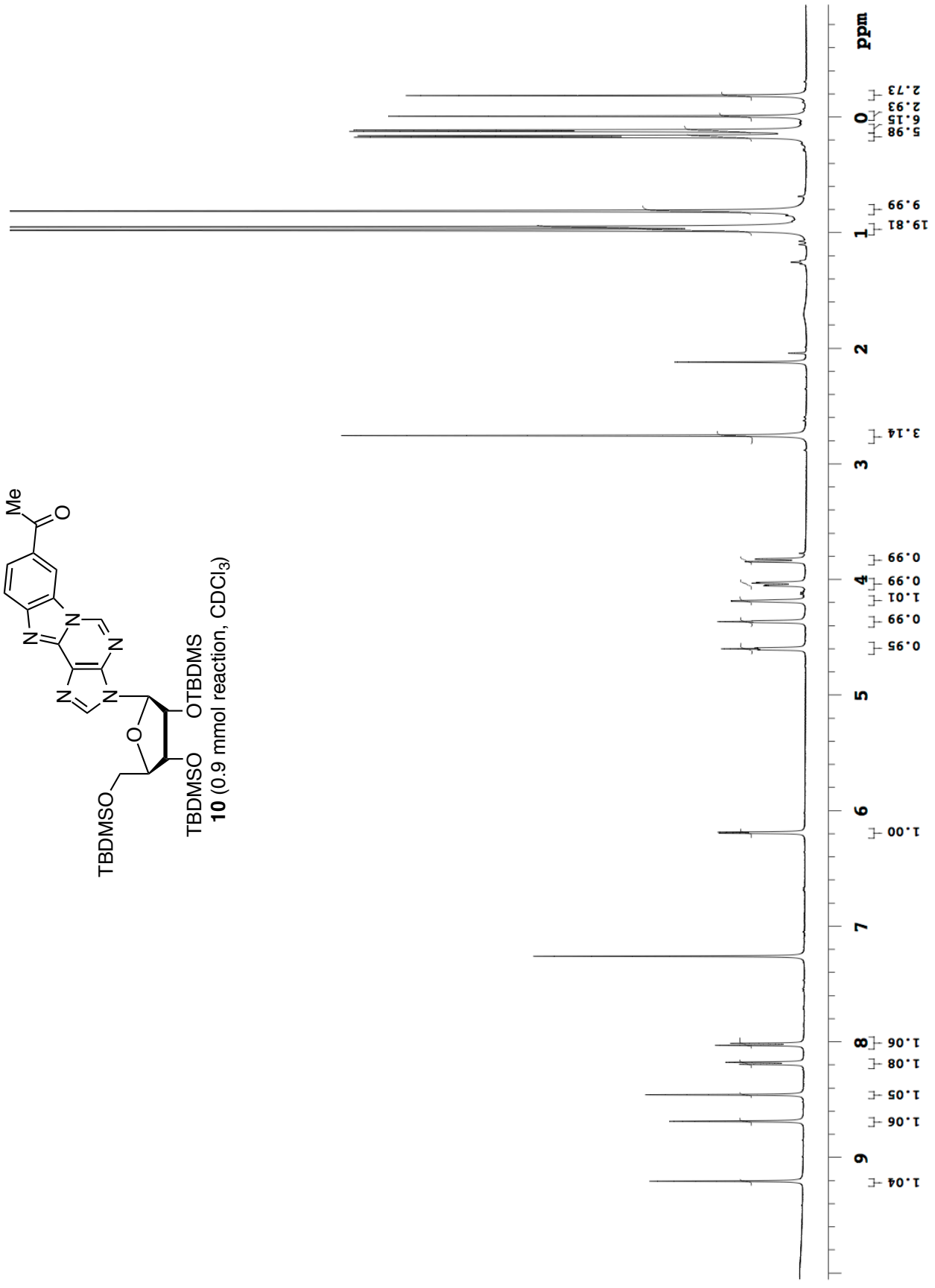

TBDMSO
TBDMSO
OTBDMS
Me
8 (CDCl3)
160
140
120
100
80
60
40
20
0
ppm

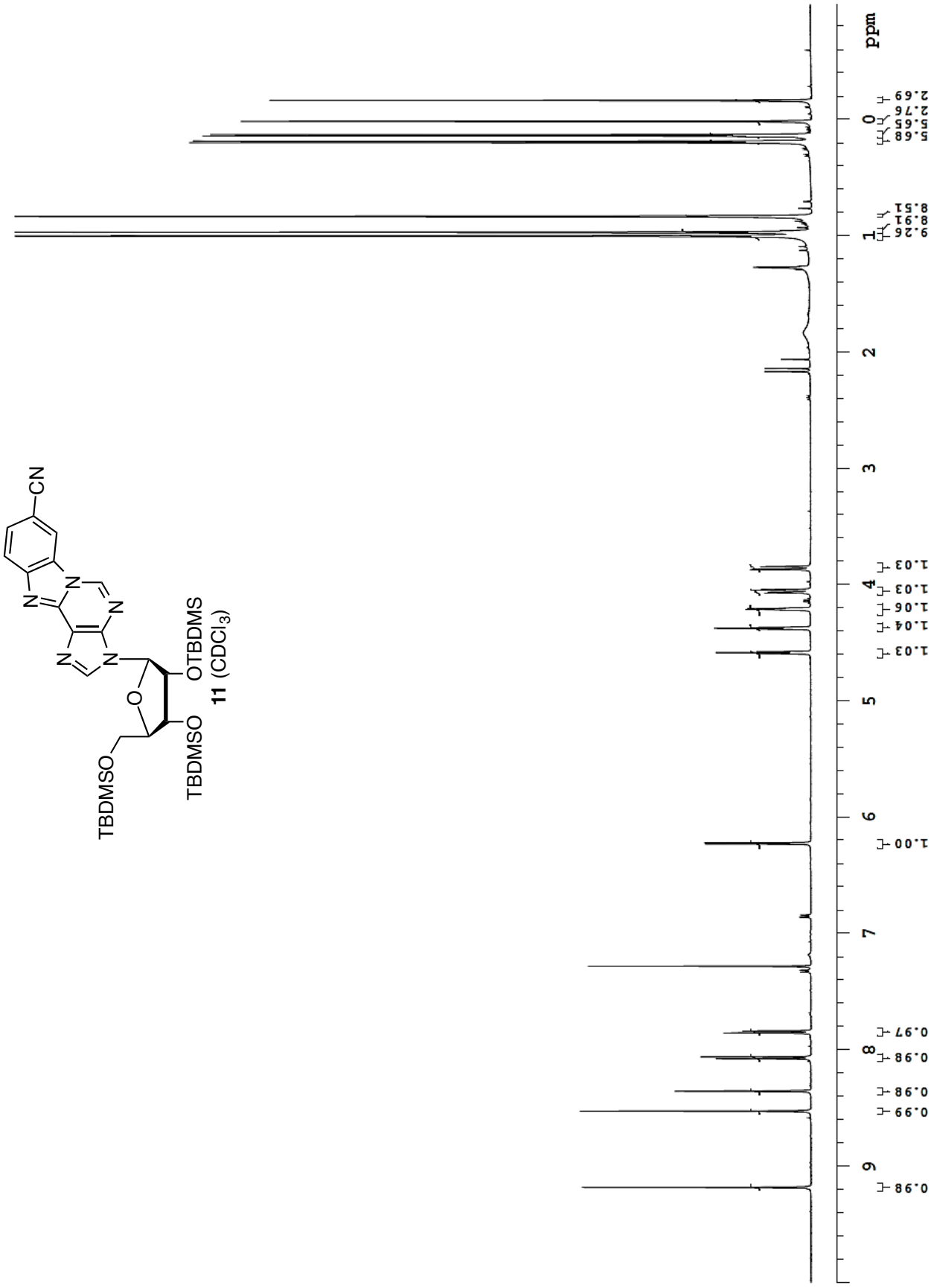

Cl
N
N
N
N
N
O
OTBDMS
TBDMSO
TBDMSO
9 (CDCl3)
ppm
19.17
9.39
6.00
5.39
3.00
2.88
1.07
1.13
1.11
1.13
1.13
1.07
1.09
1.07
1.13
1.11
1.08
1.07

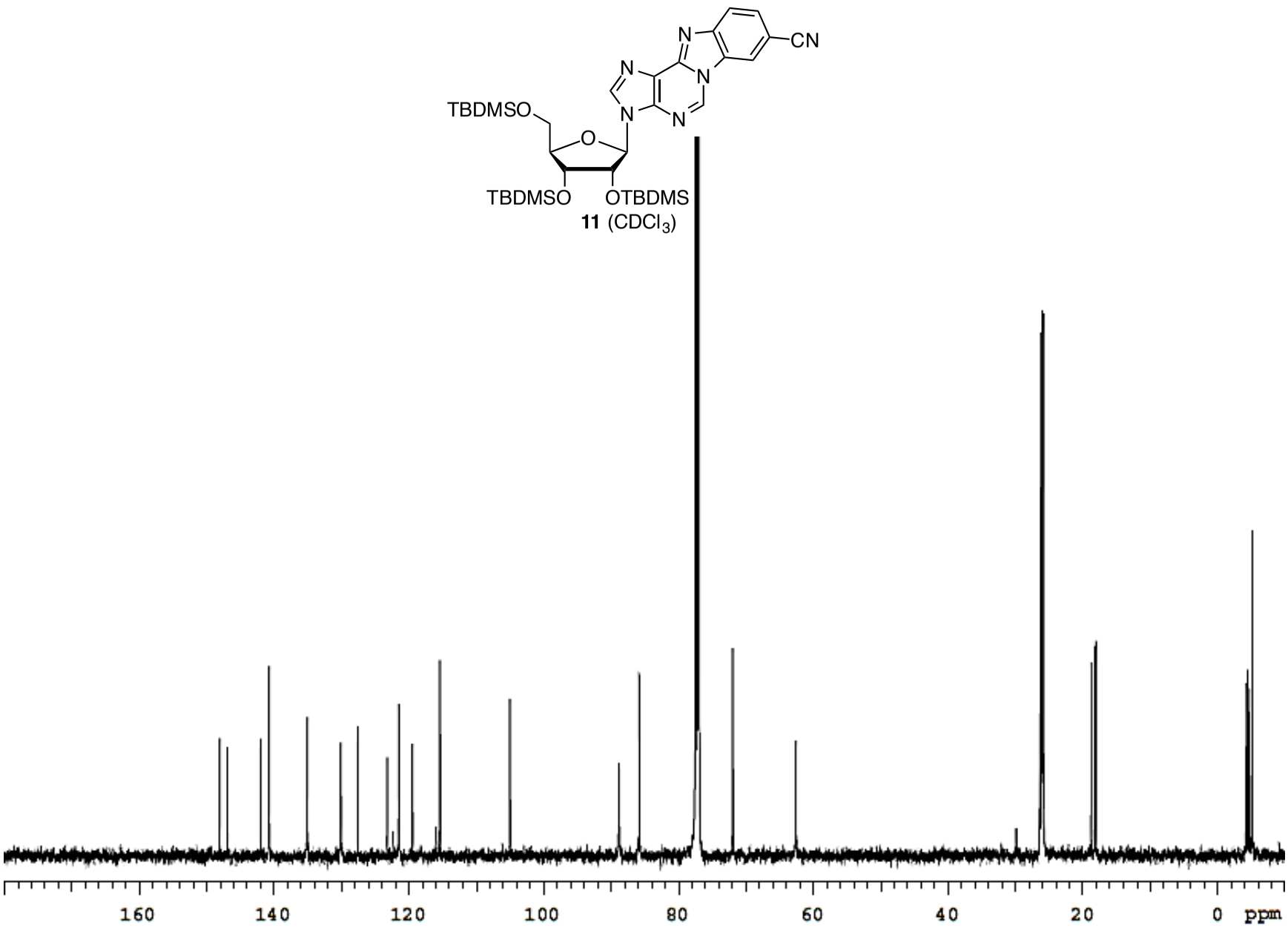

Cl
N
N
N
N
O
OTBDMS
TBDMSO
TBDMSO
9 (CDCl3)
ppm
0
20
40
60
80
100
120
140
160


Me
O
N
N
N
N
N
O
OTBDMS
TBDMSO
TBDMSO
10 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
2.77
2.82
5.68
5.66
8.76
9.01
8.92
3.10
1.03
1.04
1.04
1.02
1.02
1.00
1.01
1.02
1.01
1.01
1.00

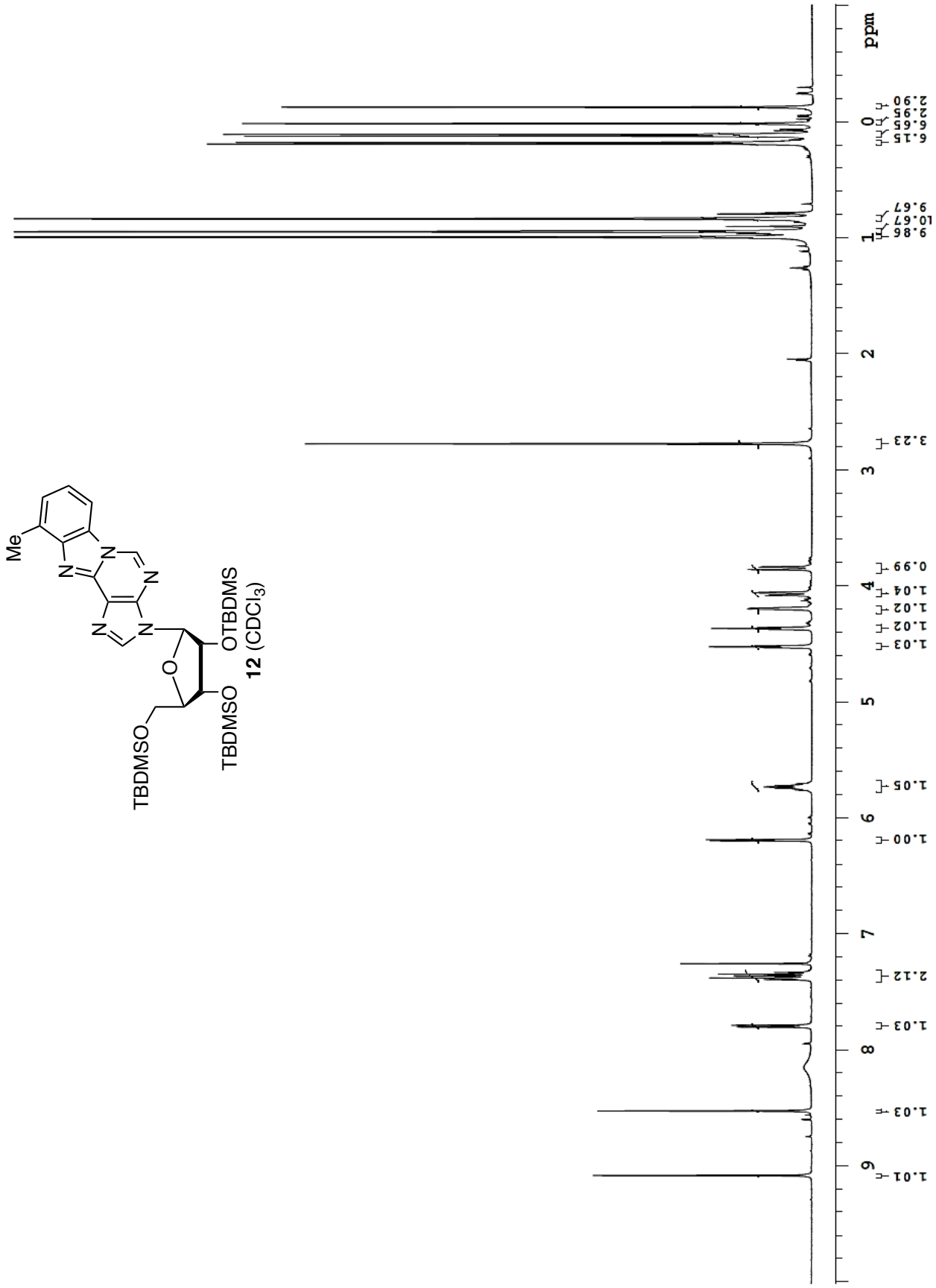

Me
O
N
N
N
N
N
TBDMSO
O
TBDMSO
OTBDMS
10 (CDCl3)
180
160
140
120
100
80
60
40
20
0 ppm

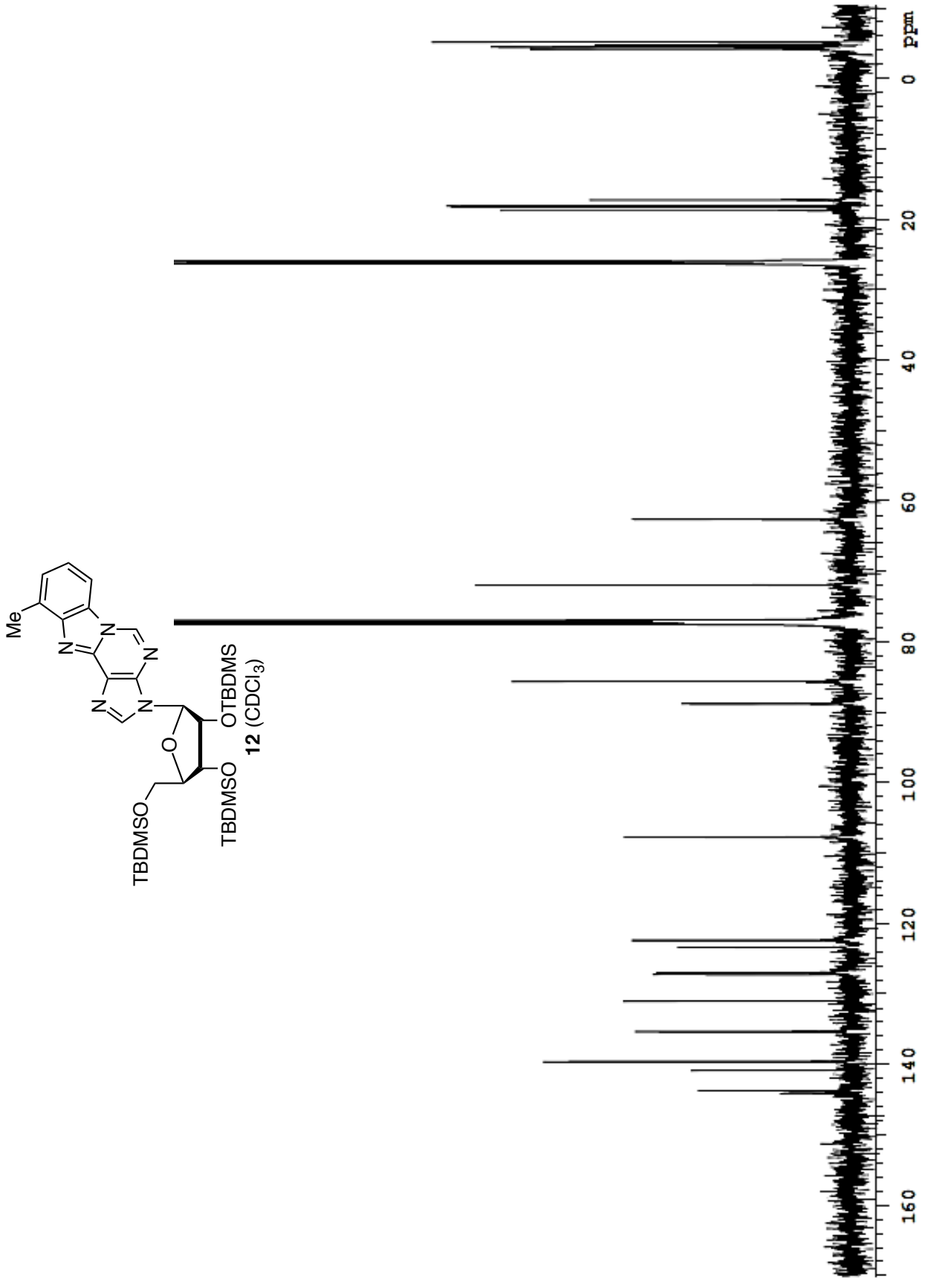

Me
O
N
N
N
N
N
O
TBDMSO
OTBDMS
TBDMSO
10 (0.9 mmol reaction, $CDCl_3$)
ppm
0
1
2
3
4
5
6
7
8
9
2.73
2.93
6.15
5.98
9.99
19.81
3.14
0.99
0.99
1.01
0.99
0.95
1.00
1.06
1.08
1.05
1.06
1.04

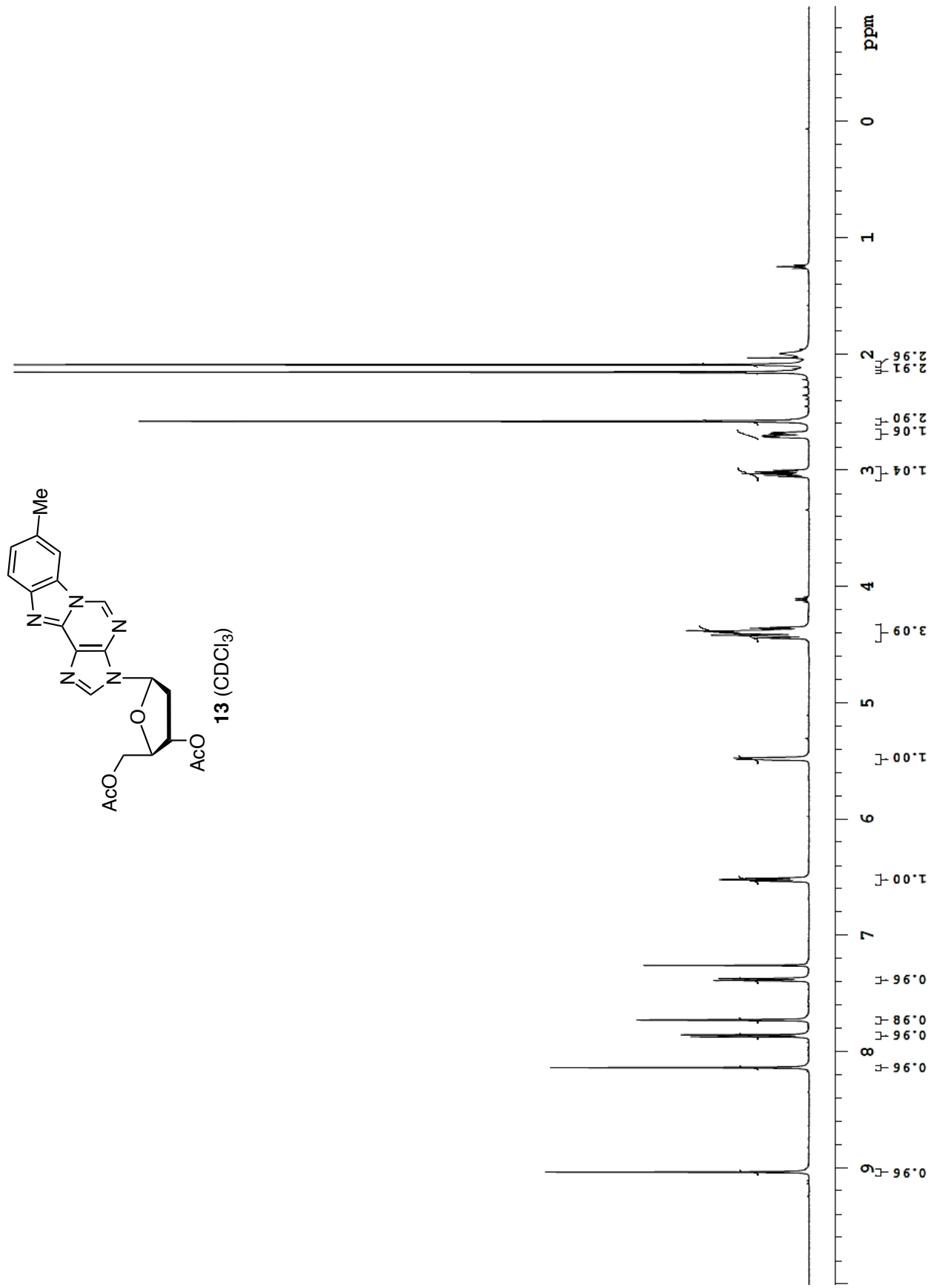

CN
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
11 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
9.26
8.91
8.51
5.68
5.65
2.76
2.69
1.03
1.03
1.06
1.04
1.03
1.00
0.97
0.98
0.98
0.99
0.98

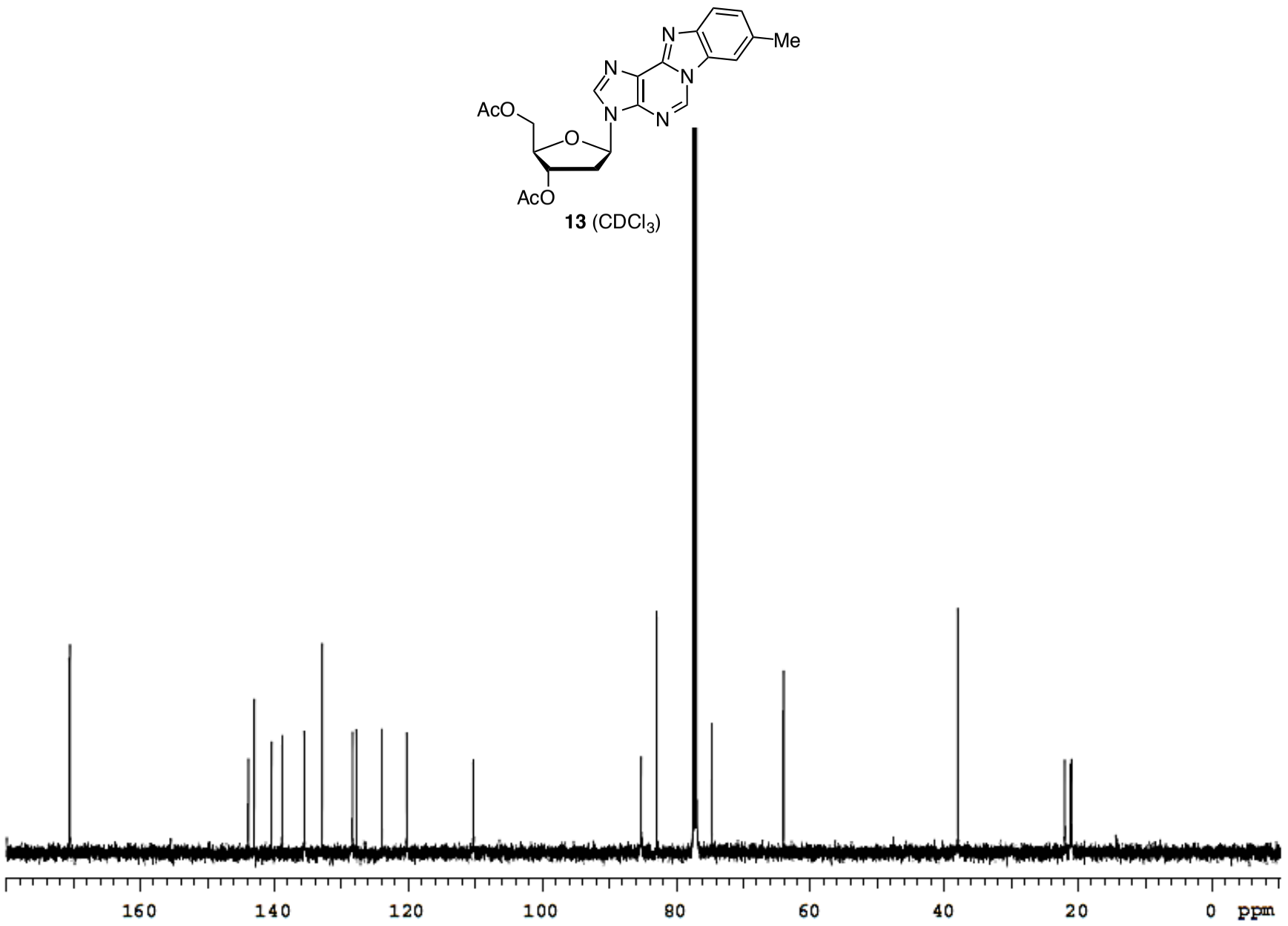

TBDMSO
TBDMSO
OTBDMS
CN
N
N
N
N
N
O
160
140
120
100
80
60
40
20
0
ppm

11 ($CDCl_3$)

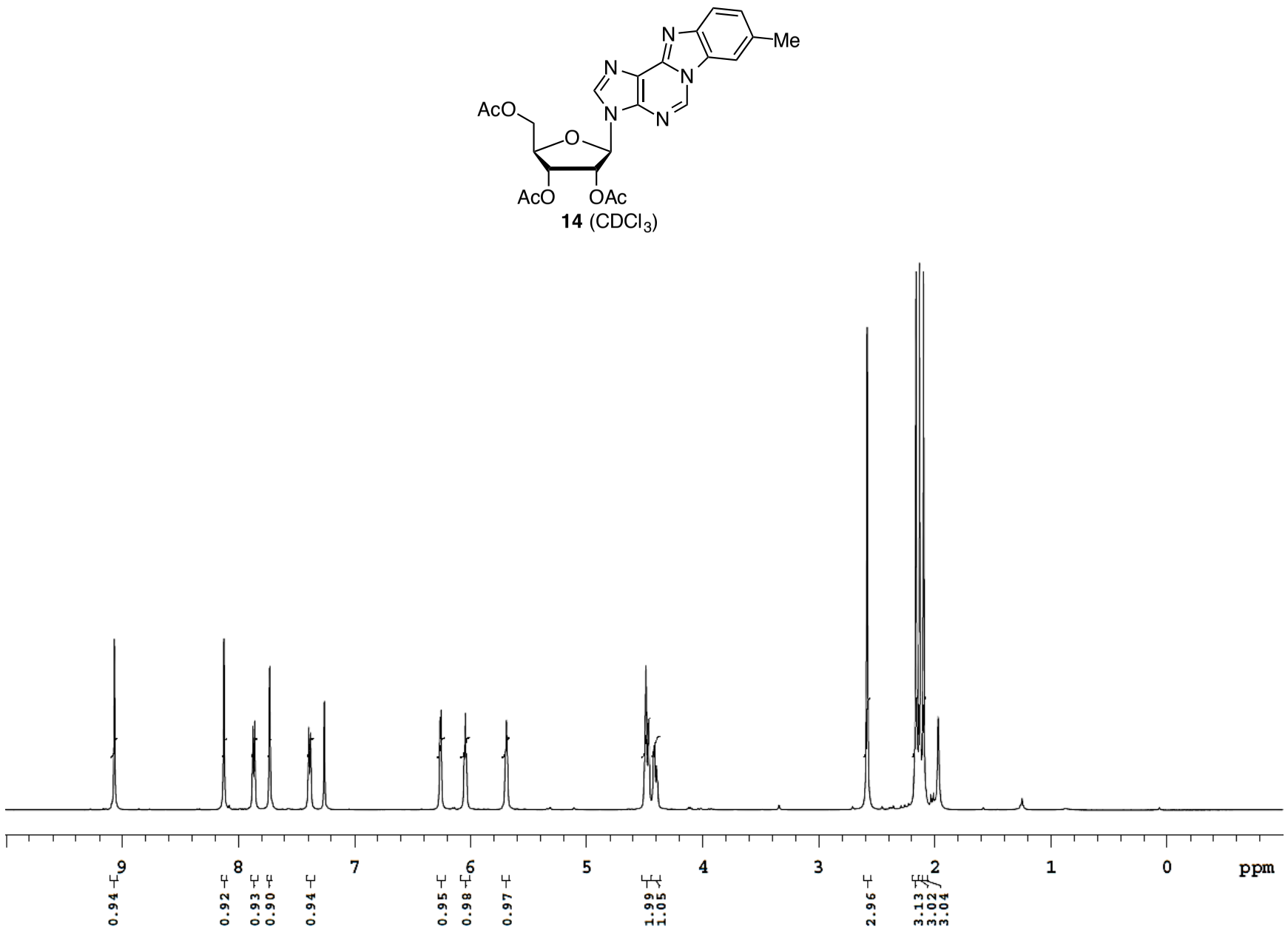

Me
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
12 (CDCl3)
ppm
9.86
10.67
9.67
6.15
6.65
2.95
2.90
3.23
0.99
1.04
1.02
1.02
1.03
1.05
1.00
2.12
1.03
1.03
1.01

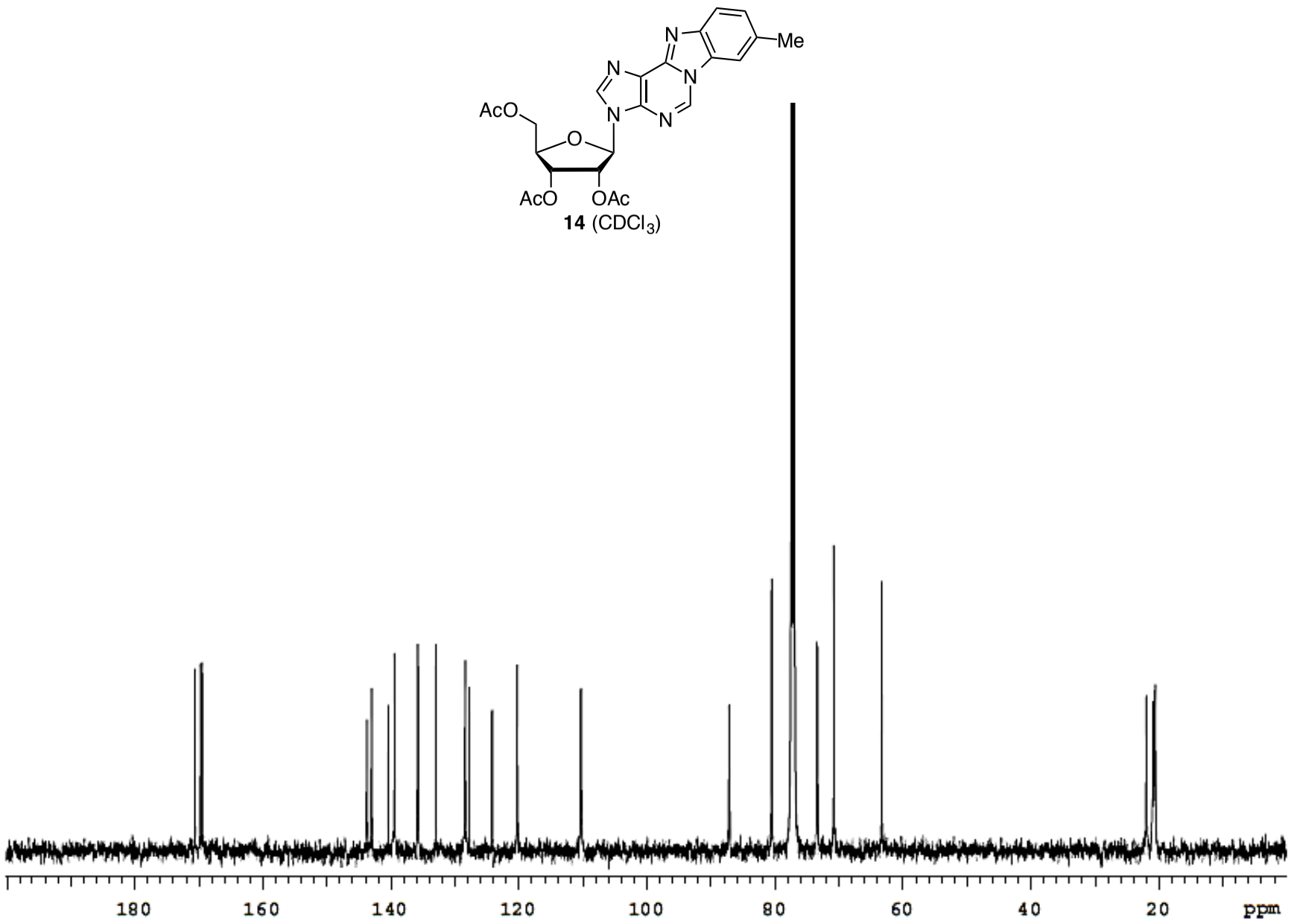

Me
N
N
N
N
N
O
TBDMSO
TBDMSO
OTBDMS
12 (CDCl3)
ppm
0
20
40
60
80
100
120
140
160

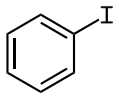

Me
N
N
N
N
N
O
AcO
AcO
13 (CDCl3)
ppm
0
1
2
3
4
5
6
7
8
9
2.96
2.91
1.06
2.90
1.04
3.09
1.00
1.00
0.96
0.98
0.96
0.96
0.96



13 ($CDCl_3$)


AcO
AcO
OAc
Me
14 (CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
0.94
0.92
0.93
0.90
0.94
0.95
0.98
0.97
1.99
1.05
2.96
3.13
3.02
3.04


Me
N
N
N
N
N
AcO
O
AcO
OAc
14 (CDCl3)
180
160
140
120
100
80
60
40
20
ppm



(Isolated from a 0.9 mmol reaction, $CDCl_3$)