Electronic Supplementary Information

Bulky phosphazenium cation catalysis for dehydrative condensation of phosphoric acid with alcohols

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General Method.

^{1}H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or Varian INOVA-500 (500 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) or Varian INOVA-500 (125 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). ^{31}P NMR spectra were measured on a Varian Mercury-300 spectrometer (121 MHz). Chemical shifts were reported as δ value in ppm downfield from 85% H_3PO_4. All experiments were carried out under an atmosphere of dry nitrogen. Chemical materials were obtained from commercial supplies and used without further purification. Phosphoric acid (crystal, 99.999+%) was purchased from Aldrich. Tetrakis[tris(dimethylamino)-phosphoranilidenamino]phosphonium hydroxide (**1**) was prepared from commercially available tetrakis[tris(dimethylamino)phosphoranilidenamino]phosphonium chloride (purchased from Aldrich) by the known procedure using anion-exchange resin (OH^- form).[1] All products in Tables 2 and 3 are known.[2,3]

General Procedure for the Dehydrative Condensation of Phosphoric acid with Alcohols in NMP–*o*-Xylene (1:1 v/v) (Table 2).

The reaction was carried out in a 30-mL flask fitted with a pressure-equalized addition funnel (containing a cotton plug and ca. 2.0 g of molecular sieves 4A, and functioning as a Soxhlet extractor) surmounted by a reflux condenser. A solution of an alcohol (2.0 mmol), phosphoric acid (crystal, 3.0 mmol) and tetrakis[tris(dimethylamino)phosphoranilidenamino]phosphonium hydroxide (**1**, 0.20 mmol) in NMP–*o*-xylene (1:1 v/v, 10 mL) was heated at azeotropic reflux condition with the removal of water. After 10 h of heating, the reaction mixture was allowed to cool to ambient temperature.

For the condensation of stearyl alcohol, oleyl alcohol, diethyleneglycol dodecyl ether and β-cholestanol, after the solvents were removed under reduced pressure, **1** was removed by purification using cation-exchange resin (DOWEX® 50WX2-200, H^+ form, 20 mL) using chloroform–methanol (1:1 v/v) (for stearyl alcohol and β-cholestanol) or methanol (for oleyl alchohol and diethylene glycol dodecyl ether) as an eluent. Then excess phosphoric acid was removed by extraction using 1 M aqueous HCl (50 mL) and diethyl ether (60 mL × 5). The products were analyzed by ^{1}H NMR and ^{31}P NMR.

For the condensation of 2',3'-*O*-isopropylidene uridine (entry 6), the crude product was analyzed by RP-HPLC using a Shimadzu Model LC-6A instrument [Nomura Chemical Develosil ODS-HG-5 column (4.6 × 250 mm), 0.02 M aqueous NH_4OAc–MeOH (3:1 v/v), flow rate = 0.75 mL/min, retention time = 6.2 min] without purification.

General Procedure for the Dehydrative Condensation of Phosphoric acid with Alcohols in NMP–*n*-PrCN (1:1 v/v) (Table 3).

The reaction was carried out in a 30-mL flask fitted with a pressure-equalized addition funnel (containing a cotton plug and ca. 2.0 g of molecular sieves 4A, and functioning as a Soxhlet extractor) surmounted by a reflux condenser. A solution of an alcohol (0.50 mmol), phosphoric acid (crystal, 4.0 mmol) and **1** (0.20 mmol) in NMP–*n*-PrCN (1:1 v/v, 10 mL) was heated at azeotropic reflux condition with the removal of water for 2 h. After cooling the reaction mixture to ca. 60 °C, the alcohol (0.50 mmol) was added. After 2 h of stirring at azeotropic reflux, the reaction mixture was cooled to ca. 60 °C and the alcohol (0.50 mmol) was added. Furthermore, after 2 h of stirring at azeotropic

reflux, the reaction mixture was cooled to ca. 60 °C and the alcohol (0.50 mmol) was added. After 4 h of stirring at azeotropic reflux, the reaction mixture was cooled to ambient temperature and the solvents were removed under reduced pressure.

For the condensation of stearyl alcohol (entries 1 and 2), **1** was removed by purification using cation-exchange resin (DOWEX® 50WX2-200, H^+ form, 20 mL) using chloroform–methanol (1:1 v/v) as an eluent, and then excess phosphoric acid was removed by extraction using 1 M aqueous HCl (50 mL) and diethyl ether (60 mL × 5). The product was analyzed by ^{1}H NMR and ^{31}P NMR.

For the condensation of 2',3'-*O*-isopropylidene ribonucleosides (entries 3–6), the resultant crude product was purified by anion-exchange chromatography (DOWEX® 1X2-200, HCO_2^- form, 20 mL) using 0–0.5 M aqueous ammonium formate as an eluent. The product was anaylyzed by ^{31}P NMR. Yields were estimated by UV analysis in 0.04 M aqueous Tris•AcOH. TOD: 2',3'-*O*-isopropylidene uridine 5'-*O*-monophosphate 1.66×10^4; 2',3'-*O*-isopropylidene adenosine 5'-*O*-monophosphate 2.20×10^4; 2',3'-*O*-isopropylidene cytidine 5'-*O*-monophosphate 1.28×10^4; 2',3'-*O*-isopropylidene guanosine 5'-*O*-monophosphate 1.99×10^4.

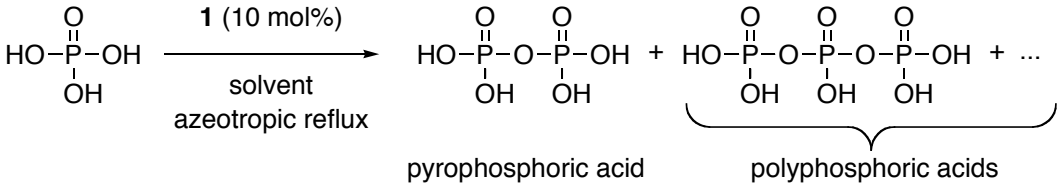
Comparison of the Reactivity in NMP–*o*-Xylene versus in NMP–*n*-PrCN

The reaction of phosphoric acid (3.0 mmol) with stearyl alcohol (2.0 mmol) in the presence of **1** (0.20 mmol) was conducted in NMP–*o*-xylene (1:1 v/v) and in NMP–*n*-PrCN (1:1 v/v) (10 mL) at 145 °C (bath temperature) for 10 h. In the case of the reaction in NMP–*n*-PrCN, stearyl alcohol was added in four portions. Since *o*-xylene did not reflux at 145 °C (bath temperature), the generated water was not removed in NMP–*o*-xylene azeotropically. Therefore, the reaction in NMP–*o*-xylene gave a very poor result.

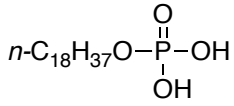
Solvents	Conversion yield of Stearyl phoshate [%]
NMP–*o*-xylene (1:1 v/v)	4
NMP–*n*-PrCN (1:1 v/v)	95

Reaction of Phosphoric Acid in the Absence of Alcohols.

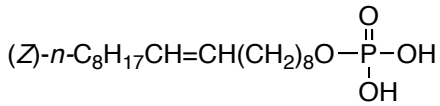
When the reaction of phosphoric acid with **1** (10 mol%) in NMP–*o*-xylene was conducted in the absence of alcohols for 2 h, pyrophosphoric acid was produced in 4% yield along with polyphosphoric acids (84% yield). The reaction in NMP–*n*-PrCN produced pyrophosphoric acid in 23% yield along with polyphosphoric acids (17% yield) (^{31}P NMR analysis). We could not observe the generation of the proposed intermediates **3** and **5**.



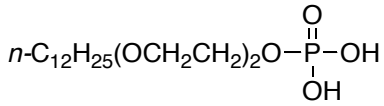
solvent	pyrophosphoric acid	polyphosphoric acids
NMP–*o*-xylene (1:1 v/v)	4%	84%
NMP–*n*-PrCN (1:1 v/v)	23%	17%



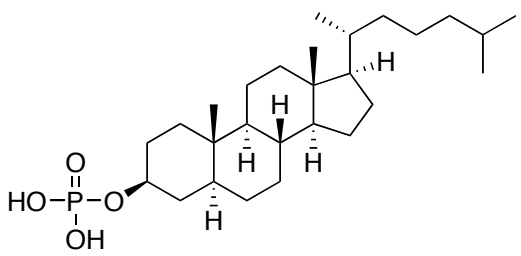
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H, –CH_2CH_3), 1.27–1.43 (m, 30H), 1.66 (quint, *J* = 6.5 Hz, 2H, –$CH_2CH_2OPO_3H_2$), 3.96 (dt, *J* = 6.5, 6,5 H, 2H, –$CH_2CH_2OPO_3H_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 29.3, 29.3, 29.4, 29.6, 29.7, 29.8, 29.8, 29.8, 30.3, 32.0, 68.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 2.69; HRMS (FAB) calcd for $C_{18}H_{38}O_4P$ [$(M–H)^-$] 349.2508, found 349.2507.



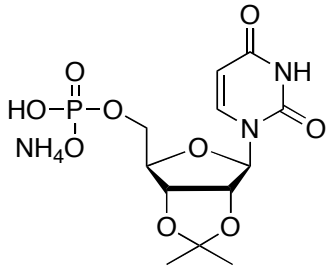
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H, –CH_2CH_3), 1.20–1.45 (m, 24H), 1.95–2.10 (m, 4H, –CH_2CH=$CHCH_2$–), 4.03 (dt, *J* = 6.5, 6.5 Hz, 1H, –$CH_2OPO_3H_2$), 4.04 (dt, *J* = 6.5, 6.5 Hz, 1H, –$CH_2OPO_3H_2$), 5.34 (t, *J* = 5.5 Hz, 2H, –C*H*=C*H*–); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.3, 27.2, 29.2, 29.2, 29.3, 29.3, 29.4, 29.5, 29.7, 29.7, 29.8, 30.1, 31.9, 68.3, 129.8, 129.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 2.01; HRMS (FAB) calcd for $C_{18}H_{36}O_4P$ [$(M–H)^-$] 347.2351, found 347.2352.



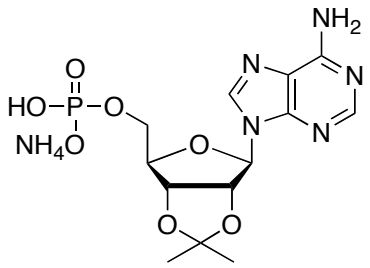
^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (t, *J* = 7.0 Hz, 3H, –CH_2CH_3), 1.22–1.38 (m, 18H), 1.56 (quint, *J* = 7.0 Hz, 2H, –$CH_2CH_2CH_2O$–), 3.47 (t, *J* = 6.6 Hz, 2H), 3.58 (dd, *J* = 3.0, 5.5 Hz, 2H), 3.64 (m, 2H), 3.69 (dt, *J* = 1.0, 5.0 Hz, 2H), 4.08 (td, *J* = 5.0, 7.5 Hz, 2H, –$CH_2OPO_3H_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.6, 25.9, 29.2, 29.2, 29.4, 29.4, 29.5, 29.6, 29.6, 31.8, 66.1, 69.7, 70.0, 70.1, 71.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 1.10; HRMS (FAB) calcd for $C_{16}H_{34}O_6P$ [$(M–H)^-$] 353.2093, found 353.2064.



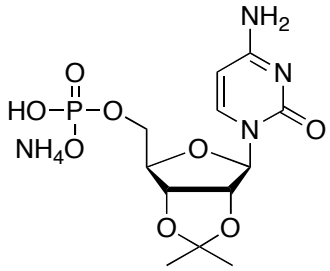
^{1}H NMR (500 MHz, CD_3OD) δ 0.68 (s, 3H, –CH_3), 0.84 (s, 3H, –CH_3), 0.87 (d, J = 6.5 Hz, 6H, –CH(CH_3)$_2$), 0.92 (d, J = 6.0 Hz, 3H, –CHCH_3), 0.95–1.42 (m, 19H), 1.44 (d, J = 11.5 Hz, 1H), 1.47–1.62 (m, 5H), 1.65–1.78 (m, 3H), 1.83 (m, 1H), 1.94 (br d, J = 12.5 Hz, 1H), 1.99 (td, J = 3.0, 12.5 Hz, 1H), 4.16 (m, 1H, –CHOPO$_3$H$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 12.3, 18.8, 21.4, 22.6, 22.8, 24.1, 24.3, 28.0, 28.3, 28.7, 29.3, 32.1, 35.4, 35.6, 35.7, 36.0, 36.3, 37.0, 39.6, 40.2, 42.7, 44.8, 54.4, 56.6, 56.6, 78.8; ^{31}P NMR (121 MHz, CD_3OD) δ –0.48; HRMS (FAB) calcd for $C_{27}H_{48}O_4P$ [(M–H)$^-$] 467.3290, found 467.3283.



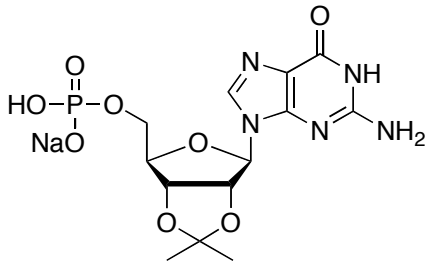
^{1}H NMR (500 MHz, CD_3OD) δ 1.34 (s, 3H, –CH_3), 1.54 (s, 3H, –CH_3), 4.05 (m, 2H, H-5'), 4.37 (m, 1H, H-4'), 4.88 (dd, J = 3.0, 6.0 Hz, 1H, H-3'), 4.93 (dd, J = 3.0, 6.0 Hz, 1H, H-2'), 5.76 (d, J = 8.0 Hz, 1H, H-5), 5.98 (d, J = 3.0 Hz, 1H, H-1'), 7.93 (d, J = 8.0 Hz, 1H, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 22.1 66.1, 82.6, 85.7, 86.4, 93.2, 103.1, 114.9, 143.4, 152.3, 166.3; ^{31}P NMR (121 MHz, CD_3OD) δ –0.14; HRMS (FAB) calcd for $C_{12}H_{16}N_2O_9P$ [(M–H)$^-$] 363.0593, found 363.0593.



^{1}H NMR (500 MHz, CD_3OD) δ 1.37 (s, 3H, –CH_3), 1.60 (s, 3H, –CH_3), 4.02 (t, J = 4.0 Hz, 2H, H-5'), 4.49 (m, 1H, H-4'), 5.11 (br d, J = 6.0 Hz, 1H, H-3'), 5.31 (dd, J = 3.0, 6.0 Hz, 1H, H-2'), 6.22 (d, J = 3.0 Hz, 1H, H-1'), 8.19 (s, 1H, H-2), 8.50 (s, 1H, H-8); ^{13}C NMR (125 MHz, CD_3OD) δ 25.6, 27.6, 66.4, 83.4, 85.9, 86.8, 91.8, 115.1, 120.0, 141.4, 150.5, 153.9, 157.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ –0.13; HRMS (FAB) calcd for $C_{13}H_{19}N_5O_7P$ [(M+H)$^+$] 388.1022, found 388.1040.



^{1}H NMR (500 MHz, CD_3OD) δ 1.38 (s, 3H, –CH_3), 1.57 (s, 3H, –CH_3), 4.02 (ddd, J = 5.0, 6.0, 11.5 Hz, 1H, H-5'), 4.08 (ddd, J = 4.0, 5.0, 11.5 Hz, 1H, H-5'), 4.44 (m, 1H, H-4'), 4.93 (dd, J = 2.5, 6.5 Hz, 1H, H-3'), 4.97 (dd, J = 2.5, 6.5 Hz, 1H, H-2'), 5.86 (d, J = 2.5 Hz, 1H, H-1'), 6.14 (d, J = 7.5 Hz, 1H, H-5), 7.90 (d, J = 7.5 Hz, 1H, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 25.5, 27.3, 66.0, 82.1, 86.0, 86.8, 95.0, 96.2, 115.2, 144.6, 155.2, 165.2; ^{31}P NMR (121 MHz, CD_3OD) δ –0.28; HRMS (FAB) calcd for $C_{12}H_{19}N_3O_8P$ [$(M+H)^+$] 364.0910, found 364.0890.



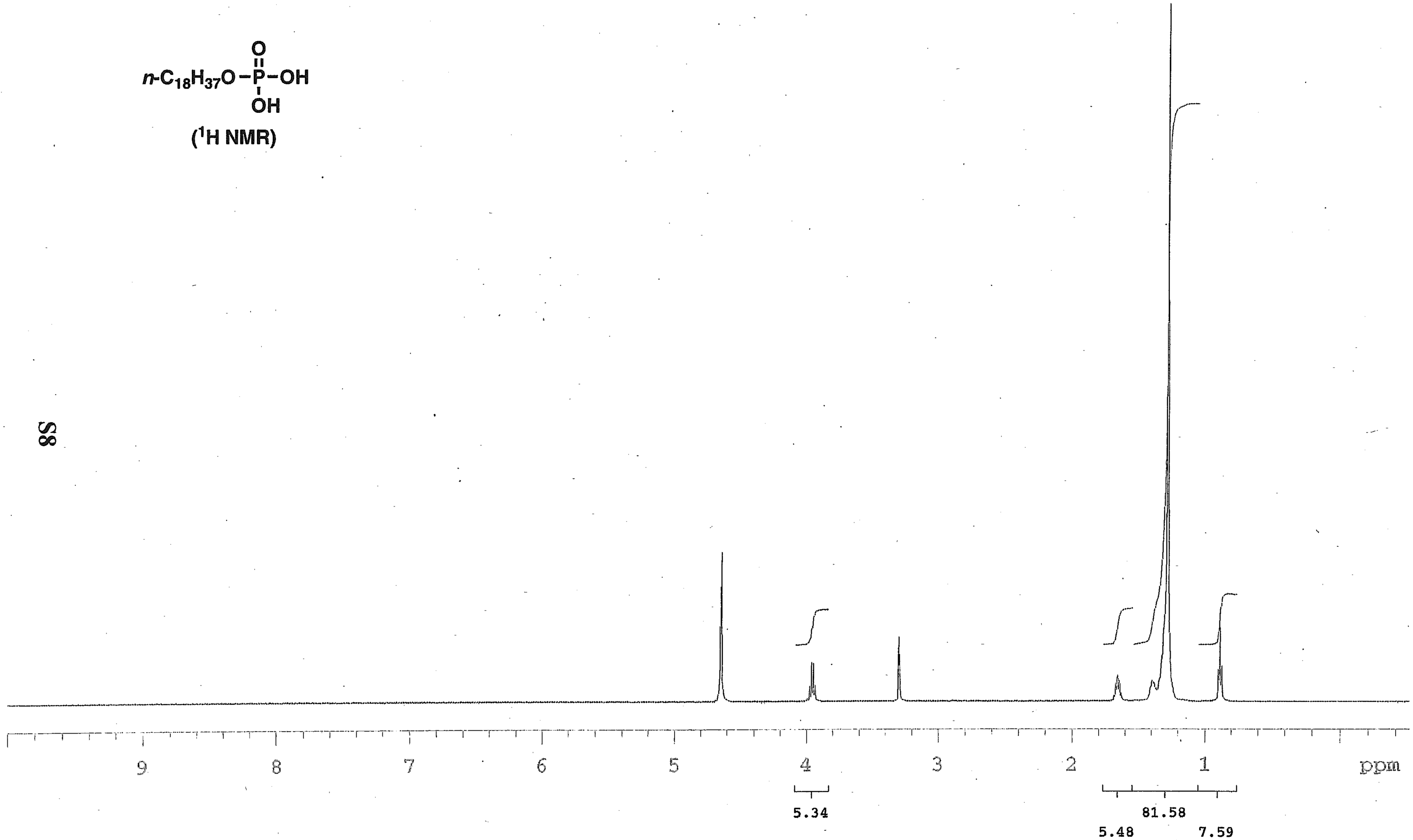
^{1}H NMR (500 MHz, CD_3OD) δ 1.36 (s, 3H, –CH_3), 1.59 (s, 3H, –CH_3), 3.95 (m, 2H, H-5'), 4.44 (m, 1H, H-4'), 5.11 (dd, J = 1.5, 6.0 Hz, 1H, H-3'), 5.22 (dd, J = 3.5, 6.0 Hz, 1H, H-2'), 6.04 (d, J = 3.5 Hz, 1H, H-1'), 8.11 (s, 1H, H-8); ^{13}C NMR (125 MHz, CD_3OD) δ 25.7, 27.6, 65.7, 83.3, 85.8, 86.8, 90.8, 115.0, 119.0, 137.1, 152.8, 162.7, 169.8; ^{31}P NMR (121 MHz, CD_3OD) δ 3.18; HRMS (FAB) calcd for $C_{13}H_{19}N_5O_8P$ [$(M+H)^+$] 404.0971, found 404.0949.

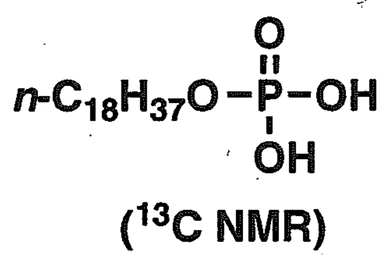
References

(1) *EP Pat.*, 791 600, 1997.

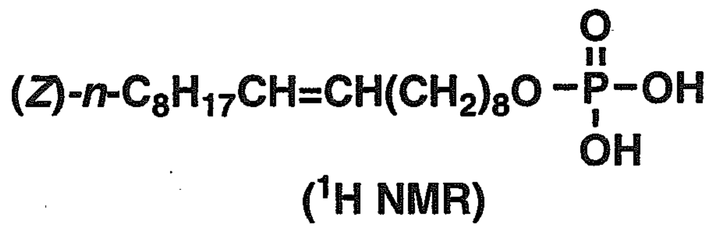
(2) A. Sakakura, M. Katsukawa and K. Ishihara, *Org. Lett.* 2005, **7**, 1999.

(3) A. Sakakura, M. Katsukawa and K. Ishihara, *Angew. Chem. Int. Ed.* 2005, **46**, 1423.


n-C18H37O-P(=O)(OH)-OH
(1H NMR)
8S
9
8
7
6
5
4
3
2
1
ppm
5.34
81.58
5.48
7.59



(^{13}C NMR)

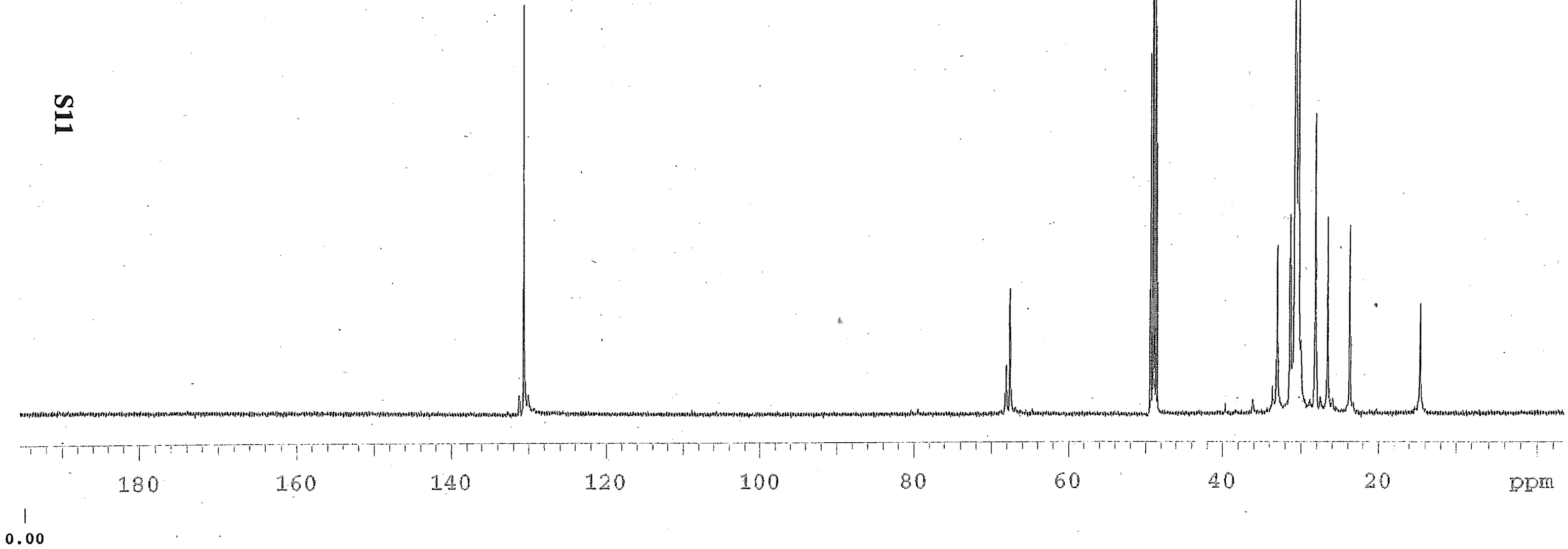

O
(Z)-n-C8H17CH=CH(CH2)8O-P-OH
OH

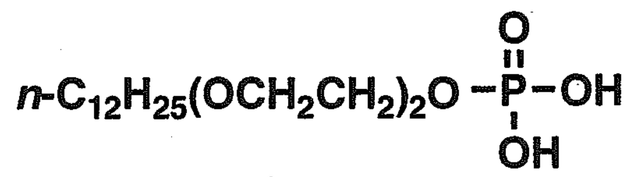
(^{1}H NMR)

9
8
7
6
5
4
3
2
1
ppm
4.26
5.74
8.91
7.13
64.83
9.12

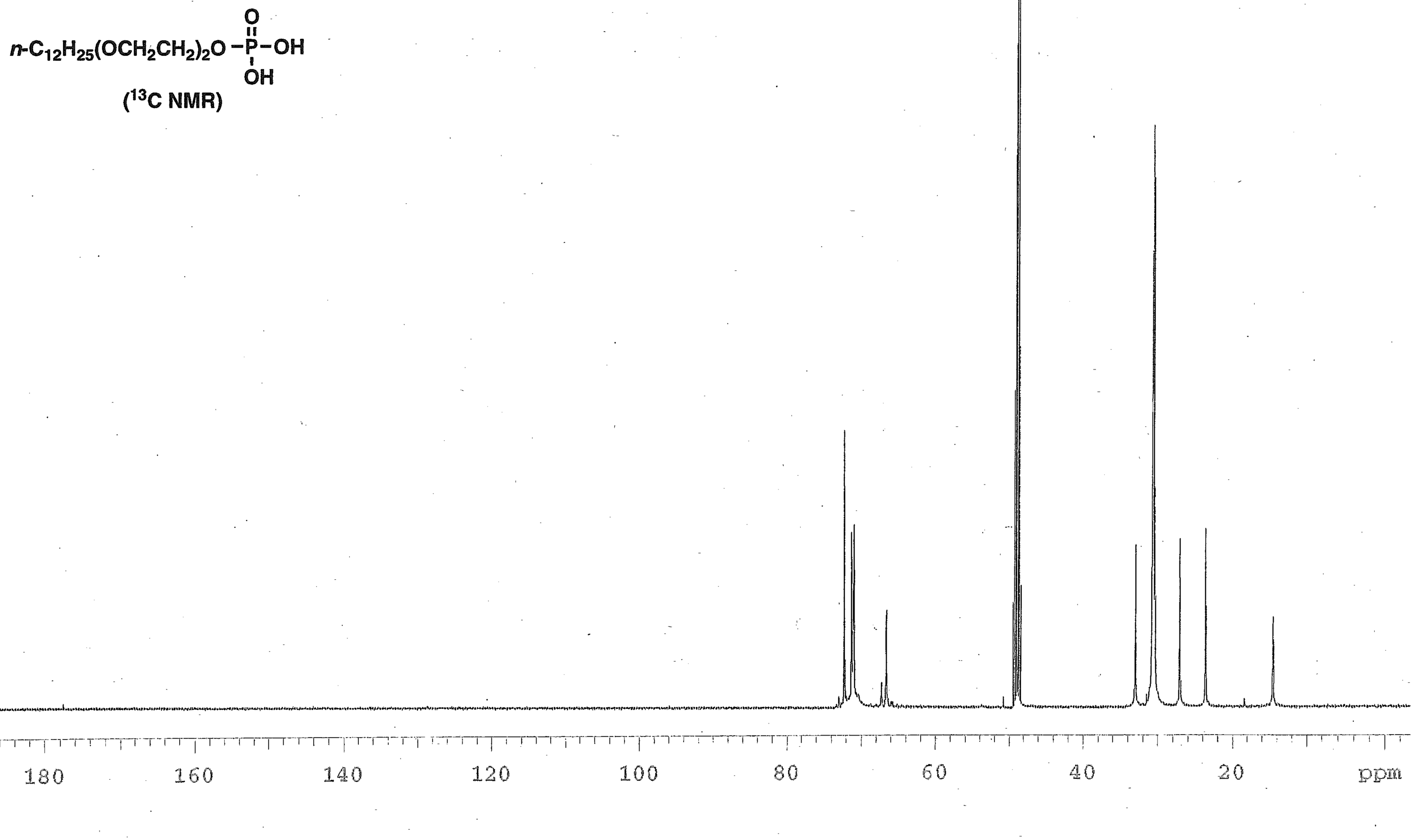
(*Z*)-*n*-$C_8H_{17}CH{=}CH(CH_2)_8O-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-OH$

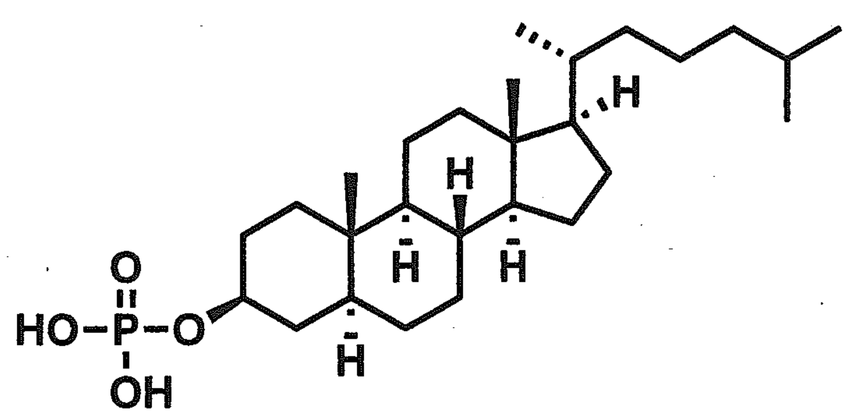
(^{13}C NMR)



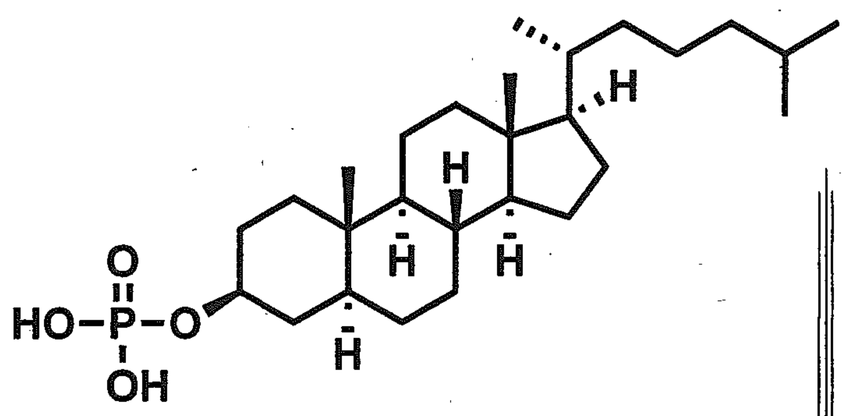


(^{1}H NMR)

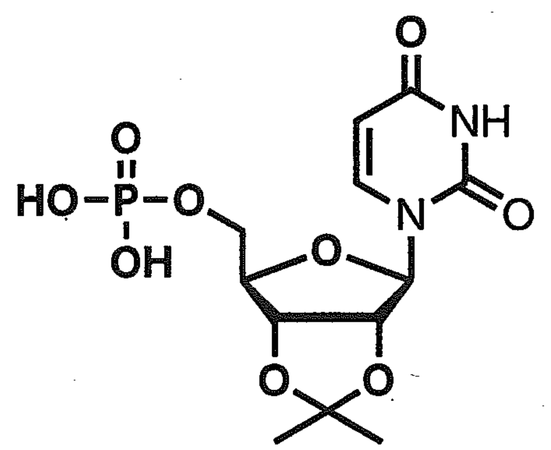

n-C12H25(OCH2CH2)2O-P(=O)(OH)-OH
(13C NMR)
180
160
140
120
100
80
60
40
20
ppm
0.00



(^{1}H NMR)

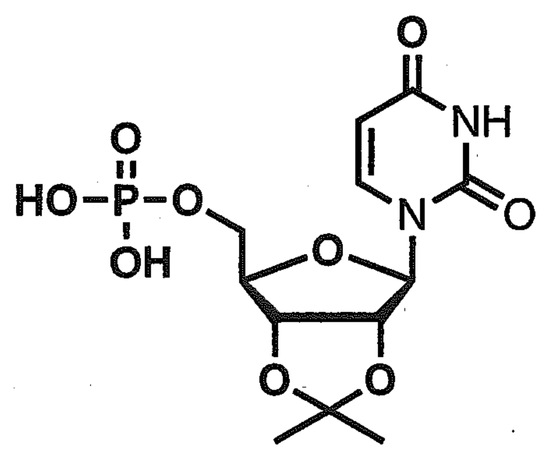


(^{13}C NMR)


O
NH
HO–P–O
OH
O
N
O
O
O

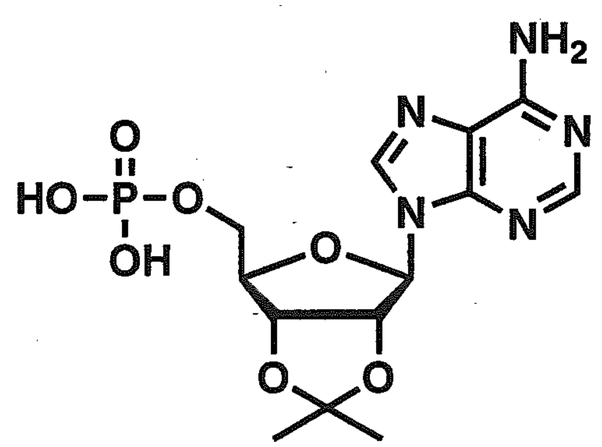
(^{1}H NMR)

1.932
9
8
7
6
5
4
3
2
1
ppm
7.06
7.78
7.08
8.14
8.02
15.22
23.22
23.48


O
NH
HO–P–O
O
OH
N
O
O
O

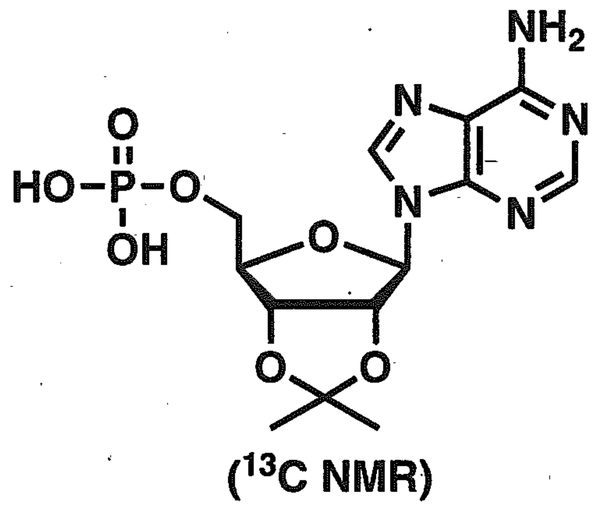
(^{13}C NMR)

49.346
49.176
49.000
48.830
48.660
S17
180
160
140
120
100
80
60
40
20
ppm
0.00


NH2
N
N
N
N
HO–P–O
O
OH
O
O
O

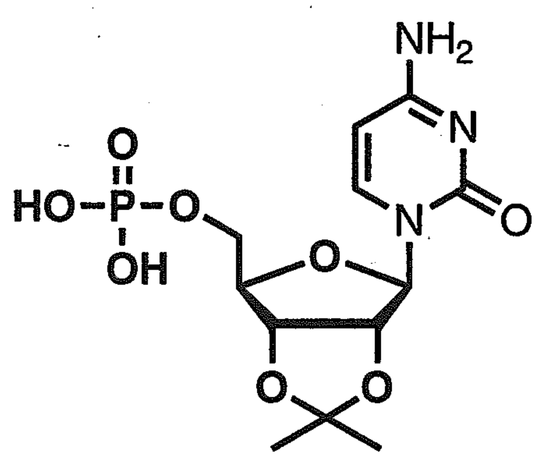
(^{1}H NMR)

9
8
7
6
5
4
3
2
1
ppm
10.33
6.64
6.17
7.05
9.18
6.53
13.40
19.94
20.77

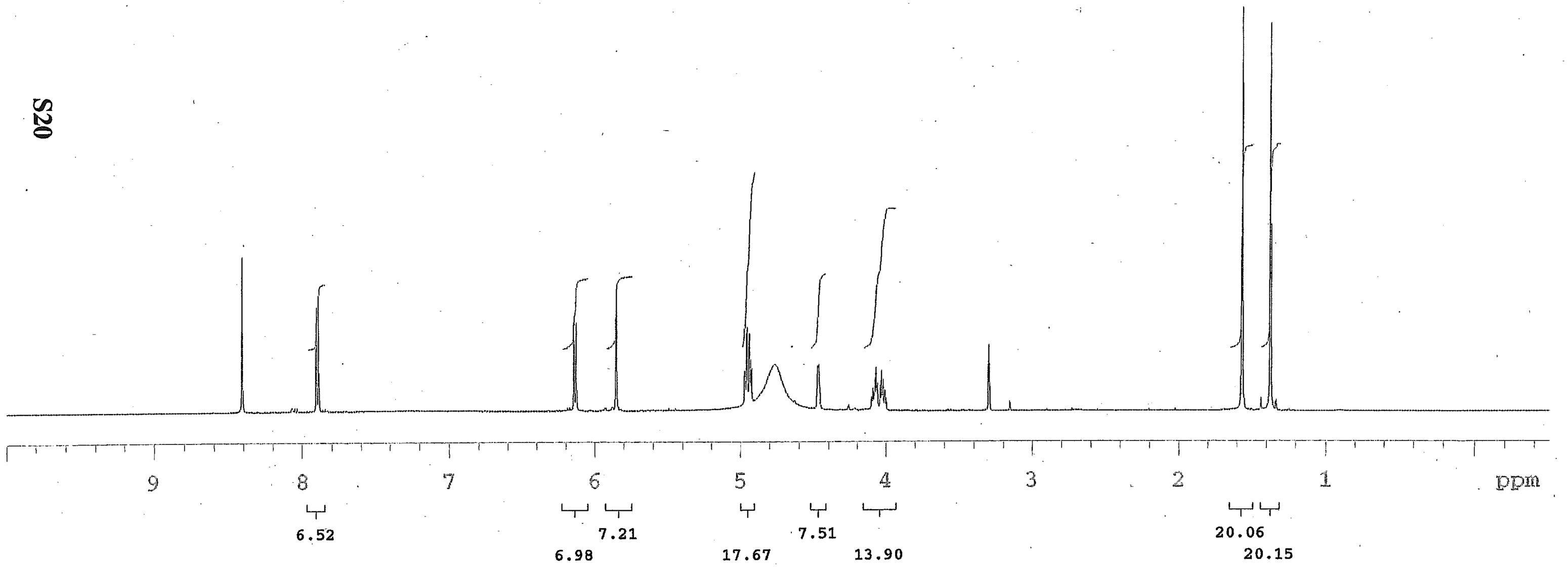

NH2
N
N
N
N
HO–P–O
O
OH
O
O
O

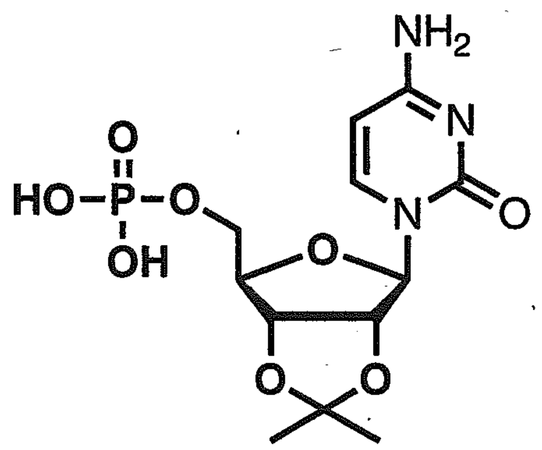
(^{13}C NMR)

49.340
49.170
49.000
48.830
48.660
180
160
140
120
100
80
60
40
20
ppm
0.00


NH2
N
HO–P–O
O
OH
O
N
O
O
O

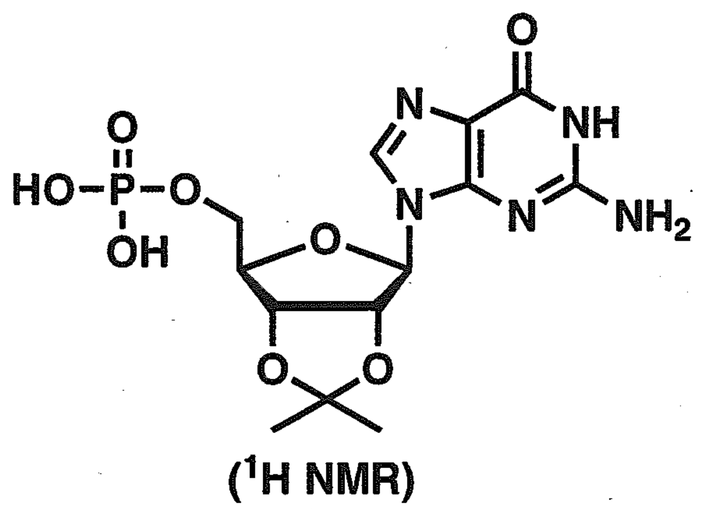
(^{1}H NMR)


9
8
7
6
5
4
3
2
1
ppm
6.52
6.98
7.21
17.67
7.51
13.90
20.06
20.15


NH2
N
O
HO–P–O
OH
O
N
O
O
O

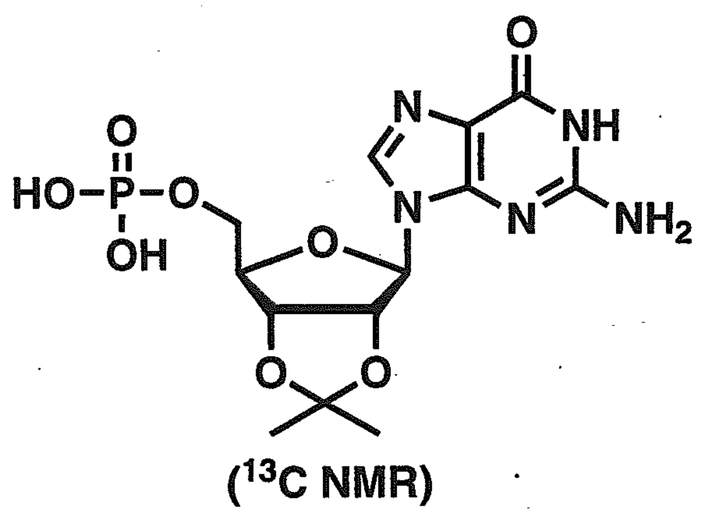
(^{13}C NMR)

49.340
49.170
49.000
48.824
48.654
180
160
140
120
100
80
60
40
20
ppm
0.00


HO–P–O
OH
O
N
NH
N
N
NH2
O
O
O

(^{1}H NMR)

9
8
7
6
5
4
3
2
1
ppm
6.77
7.24
7.64
7.37
7.53
15.54
23.88
24.02


HO–P–O
OH
O
N
NH
N
N
NH2
O
O
O

(^{13}C NMR)

49.340
49.170
49.000
48.830
48.660
180
160
140
120
100
80
60
40
20
ppm
0.00