Determination of Absolute Configuration of Phosphinic Analogues of Glutamate

Bruno Commare,[ab#] Delphine Rigault,[a#] Isabelle A. Lemasson,[a] Patrick Deschamps,[c] Alain Tomas,[c] Pascal Roussel,[d] Isabelle Brabet,[e,f] Cyril Goudet,[e,f] Jean-Philippe Pin,[e,f] Frédéric R. Leroux,[b] Françoise Colobert[b*] and Francine C. Acher[a*]*

[a] Laboratoire de Chimie & Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Université Paris Descartes, Sorbonne Paris Cité, 45, rue des Saints-Pères 75270, Paris cedex 06, France. Tel: +33 142 86 33 21 ; Fax +33 142 86 83 87; E-mail: francine.acher@parisdescartes.fr
[b] Syncat, UMR CNRS 7509, Université de Strasbourg, 25, rue Becquerel 76087, Strasbourg, France. Fax: +33 368 852742 ; Tel: +33 368 8527 46; E-mail: francoise.colobert@unistra.fr; frederic.leroux@unistra.fr
[c] Laboratoire de Cristallographie et RMN Biologiques, UMR CNRS 8015, Université Paris Descartes, 4 avenue de l''Observatoire, 75270 Paris cedex 06, France. Fax:+33 153 73 97 32 ; Tel: +33 153 73 98 40, +33 153 73 98 51 ; E-mail: patrick.deschamps@parisdescartes.fr; E-mail: alain.tomas@parisdescartes.fr
[d] Unité de Catalyse et Chimie du solide, UMR CNRS 8012, École Nationale Supérieure de Chimie de Lille BP 90108 – 59652 Villeneuve d'Ascq cedex, France. Fax: +33 320 43 68 14; Tel : +33 320 33 64 34; E-mail: pascal.roussel@ensc-lille.fr
[e] Institut de Génomique Fonctionnelle, Centre National de la Recherche Scientifique Unité Mixte de Recherche 5203, Université de Montpellier, F-34094 Montpellier, France. Tel: +33 434 35 92 77 ; Fax: +33 467 54 24 32 ; E-mail :cyril.goudet@igf.cnrs.fr
[f] Inserm Unité 661, F-34094 Montpellier, France.

Supplementary Information

1. General information

All chemicals and solvents were purchased from commercial suppliers (Acros, Aldrich, Alpha Aesar, Chembridge etc) and used as received. Z-L-Vinyl glycine methyl ester was purchased from Ascent Scientific Ltd (North Somerset, UK). Most solvents were purchased from Carlo Erba-SDS. Prior to use, tetrahydrofuran (THF) was distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from CaH_2. Solid Lewis acids were flame-dried in the reaction flask under vacuum and under argon before use. All reactions were carried out under argon atmosphere, and were monitored by thin layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on aluminium. Column chromatography was performed with Merck Kieselgel 60 (200–500 mm); the solvent systems were given (s/s v:v).

^{1}H (250.13, 400.14 or 500.16 MHz), ^{13}C (62.9, 100.62 or 125.78 MHz), ^{31}P ($^{31}P_{cpd}$ meaning ^{31}P spectrum without $J_{H\text{-}P}$ coupling, 101.25, 161.98 or 202.47 MHz) and ^{19}F (376.46 MHz) NMR spectra were recorded on an ARX250, Avance II 400 Bruker or an Avance II 500 Bruker spectrometers. Chemical shifts (δ, ppm) are given with reference to residual ^{1}H or ^{13}C of deuterated solvents (CD_3OD 3.31, 49.0; D_2O 4.80; $CDCl_3$ 7.27, 77.00 ; $(CD_3)_2CO$ 2.05, 29.84 and 206.26, $(CD_3)_2SO$ 2.50, 39.52) or external reference (H_3PO_4 95%). Signal multiplicity is described as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Broad singlets, for instance, are described as bs. Coupling constants (*J*) are given in Hz.

Optical rotations were measured at the sodium D line (589 nm) at 20 °C with a Perkin-Elmer 341 polarimeter using a 1 dm path length cell. Specific optical rotation $[\alpha]_D$ is defined by $[\alpha]_D = (\alpha_{obs} \times 100)/(l \times c)$, where abs is the observed optical rotation in degrees, ℓ is the path length in dm, and *c* is the sample concentration in grams of product per 100 mL of solution. $[\alpha]_D$ is given without units, although it should be expressed in ° x mL x dm^{-1} x g^{-1}.

Mass spectra (MS) were recorded with a LCQ-advantage (ThermoFinnigan) mass spectrometer with positive (ESI+) or negative (ESI-) electrospray ionization (ionization tension 4.5 kV, injection temperature 240 °C).

HPLC analyses were carried out on a Gilson analytical instrument with a 321 pump, column temperature was controlled with an Igloo-CIL Peltier effect thermostat, eluted peaks were detected at 210 and 220 nm by a UV-vis 156 detector, and retention times are reported in minutes. A Daicel Crownpak CR(+) column (150 mm - 4 mm) eluted with pH 1.0 perchloric acid (hydrochloric acid for semi-preparative) at a 0.4 mL/min flow rate and at 4°C was used. HPLC-MS analyses were performed on a Thermo Finnigan LCQ Advantage Instrument as described above, equipped for HPLC with a Phenomenex RP Polar column (250 mm × 4.6 mm, 4 μm). Products were eluted with a water-acetonitrile mobile phase at 40°C and a 0.4 mL/min flowrate and detected by mass and UV at 210 nm. The following gradient using 100% A for 10 min, linear increase from 0 to 100% B between 10 and 20 min, 100% B from 20 to 30 min (solvent A (water / acetonitrile / formic acid 950 : 50 : 1) and solvent B (water / acetonitrile / formic acid 900 : 100 : 1)).

Purity of the tested compounds was established by analytical HPLC-MS and was at least 95%.

Infrared (IR) spectra were recorded on a diamond ATR spectrometer using neat samples. Infrared frequencies are reported in wavenumbers (cm^{-1}), and intensities were determined qualitatively and are reported as strong (s), medium (m) or weak (w). Solid Lewis acids were flame-dried in the reaction flask under vacuum and under argon before use.

Cation exchange resin: Dowex AG 50W-X4, H^+, 50-100 mesh, water elution. The deposit was carried out in aqueous solution at pH 1-2. Anion exchange resin: Dowex AG 1-X4, AcO^-, 200-400 mesh, water, hydrochloric acid, acetic acid or formic acid aqueous solution elution. The deposit was carried out in boiled aqueous solution at pH 8-9.The pure water used for anion exchange resins was previously boiled to be degazed. Product visualization was achieved using TLC plates with 2% (w/v) ninhydrin in ethanol. The resins were purchased from Biorad. A Gilson persistatic pump coupled with a Gilson automatic collector were used for elution.

Melting points were determined with a Büchi 530 apparatus.

Pharmacology: Cell transfection and second messenger determination

HEK293 cells were transiently transfected by electroporation, as described elsewhere (1). mGlu4 receptor was cotransfected with a chimeric G_q/G_i protein, allowing the monitoring of receptor activity by measurements of $[Ca]_i$; and EAAC1, a glutamate transporter, to avoid the influence of extracellular glutamate. After 24 h, cells were loaded with Ca-sensitive fluorescent dye Fluo-4-AM (Invitrogen, Cergy Pontoise, France), and $[Ca]_i$ determinations were performed, as described previously (2). All points are realized in triplicate. Data were analyzed using the Prism software (GraphPad, La Jolla, CA, USA).

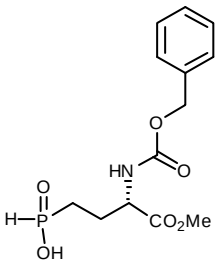
(1) Brabet, I., Parmentier, M. L., De Colle, C., Bockaert, J., Acher, F., and Pin, J. P. (1998) Comparative effect of L-CCG-I, DCG-IV and gamma-carboxy-L-glutamate on all cloned metabotropic glutamate receptor subtypes. *Neuropharmacology* **37,** 1043–1051

(2) Goudet, C., Gaven, F., Kniazeff, J., Vol, C., Liu, J., Cohen-Gonsaud, M., Acher, F., Prezeau, L., and Pin, J. P. (2004) Heptahelical domain of metabotropic glutamate receptor 5 behaves like rhodopsin-like receptors. *Proc. Natl. Acad. Sci.U. S. A.* **101,** 378–383

2. Experimental part

- ((*S*)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)phosphinic acid **2**

A mixture of hypophosphorous acid (1.44 g, 21.8 mmol, 10.9 eq), *N*-benzyloxycarbonyl-L-α-vinylglycine methyl ester (507 mg, 2 mmol, 1 eq) and AIBN (8 mg, 0.05 mmol, 0.025 eq) in MeOH (20 mL) was refluxed at 80 °C for 5 h. MeOH was evaporated under vacuum and the residue was treated with water (20 mL) and extracted with EtOAc (3x30 mL). The organic layers were washed with water (3x10 mL), dried over $MgSO_4$, filtered and evaporated under vacuum to afford **2** (610 mg, 1.9 mmol, 95% yield).

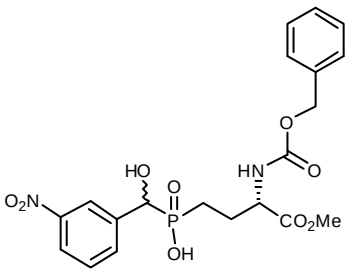


$C_{13}H_{18}NO_6P$
M=315.26 g/mol
White solid

NMR ^{1}H (500 MHz; $CDCl_3$) δ : 7,33 (m, 5H, H_{Ar}) ; 7.12 (d, $J_{H\text{-}P}$ = 555.0 Hz, 1H, *H*-P) ; 4.41 (m, 1H, C*H*) ; 5.09 (s, 2H, OCH_2) ; 3.74 (s, 3H, OCH_3) ; 1.92 (m, 4H, *(*CH_2*)*$_2$). **NMR ^{31}P (202 MHz; $CDCl_3$)** δ : 36.9 (d, $J_{P\text{-}H}$ = 551 Hz). **NMR $^{31}P_{cpd}$ (202 MHz; $CDCl_3$)** δ : 36,9

- ((*S*)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)(hydroxy(3-nitrophenyl)methyl)phosphinic acid **4a**

To a solutiton of 3-nitrobenzaldehyde **3a** (453 mg, 3.0 mmol, 2.7 eq) and **2** (352 mg, 1.1 mmol, 1 eq) in DCM (12 mL) was added at 0 °C dropwise *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.45 mL, 6 mmol, 5.5 eq). The mixture was allowed to warm to 25 °C and stirred for 12 h. At 0 °C, 1 M HCl (30 mL) was added to quench the reaction. The compound was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 20 mL) and a saturated solution of NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford crude **4a** (511 mg, 1.1 mmol).

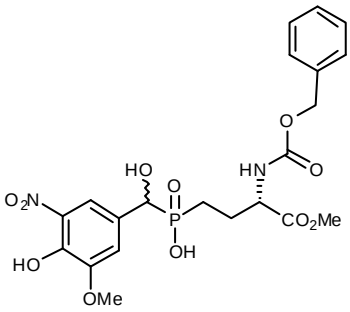


$C_{20}H_{23}N_2O_9P$
M=466.38 g/mol
Yellowish solid

NMR $^{31}P_{cpd}$ (101 MHz; MeOD) δ : 48.4. **SM (ESI$^-$)** m/z : 465.1 $[M\text{-}H]^-$

- ((*S*)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutyl)(hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl)phosphinic acid **4b**

To a solutiton of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde **3b** (568 mg, 2.8 mmol, 2.7 eq) and **2** (292 mg, 0.9 mmol, 1 eq) in DCM (12 mL) was added at 0 °C dropwise *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.45 mL, 6 mmol, 5.5 eq). The mixture was allowed to warm to 25 °C and stirred for 12 h. At 0 °C, 1 M HCl (30 mL) was added to quench the reaction. The compound was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 20 mL) and a saturated solution of NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford crude **4b** (575 mg, 1.1 mmol).



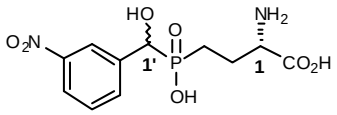
$C_{21}H_{25}N_2O_{11}P$
M=512.40 g/mol
Yellowish solid

^{31}P NMR (101 MHz ; MeOD) δ (ppm) : 49.3

- (2*S*)-2-amino-4-(hydroxy(hydroxy(3-nitrophenyl)methyl)phosphoryl)butanoic acid **LSP1-2093**

A solution of **4a** (575 mg, 1.1 mmol) in 6 M HCl was refluxed for 5 h. Then, the mixture was cooled to 25 °C and the solvent was evaporated under vacuum. The residue was diluted in EtOAc (50 mL) and extracted with 1 M HCl (2 x 80 mL). The combined aqueous layers were washed with EtOAc (2 x 30 mL) and the solvent was evaporated under vacuum to afford crude product which was purified by cation exchange resin chromatography.

Cation exchange resin chromatography: crude compound were deposited on a Dowex AG 50W-X4, H^+, 50-100 mesh. The compound was eluted with water to afford **LSP1-2093** (60 mg, 0.19 mmol, 17% yield on 2 steps).



$C_{11}H_{15}N_2O_7P$
M=318.22g/mol
White solid

NMR ^{1}H (500 MHz; D_2O) δ : 8.27 (s, 1H, H_{Ar}) ; 8.17 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.80 (d, *J* = 7.5 Hz, 1H, H_{Ar}) ; 7.60 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 4.98 (d, $J_{H\text{-}P}$ = 9.5 Hz, 1H, $H_{1'}$) ; 4.03 (m, 1H, H_1) ; 2.10 (m, 2H, PCH_2CH_2) ; 1.70 (m, 2H, PCH_2CH_2). **NMR ^{13}C (126 MHz; D_2O)** δ : 173.5 (Cq) ; 149.3 (Cq_{Ar}) ;

141.6 (Cq_{Ar}) ; 134.9 (CH_{Ar}) ; 130.9 (CH_{Ar}) ; 124.2 (CH_{Ar}) ; 123.0 (CH_{Ar}) ; 73.6 (d, J_{C-P} = 107 Hz, $C_{1'}$) ; 55.1 (d, J_{C-P} = 13.9 Hz, C_1) ; 24.7 (PCH_2CH_2) ; 23.8 (d, J_{C-P} = 90.0 Hz, PCH_2CH_2). **NMR $^{31}P_{cpd}$ (101 MHz; D_2O)** δ : 49.7. **MS (ESI$^-$)** m/z : 317.2 $[M-H]^-$

The diastereomers of LSP1-2093 were separated by HPLC with the preparative Crownpack column with a 2.0 mL.min^{-1} flow, a 2 mL injection loop, and a dual UV detection at 210 and 254 nm, at 25 °C. 3 injections were performed; each injection prepared at pH 2 with 9.0 mg of **LSP1-2093** in 1.8 mL of diluted solution of HCl. The diastereomer with the shortest retention time was named **I** and the other one **II**. 12 mg of pure **LSP1-2093 dia I** and 12 mg of pure **LSP1-2093 dia II** were obtained.

LSP1-2093 Dia I

^{1}H NMR (500 MHz; D_2O) δ : 8.22 (s, 1H, H_{Ar}) ; 8.14 (d, J = 7.0 Hz, 1H, H_{Ar}) ; 7.76 (d, J = 7.6 Hz, 1H, H_{Ar}) ; 7.56 (d, J = 7.6 Hz, 1H, H_{Ar}) ; 5.04 (d, J_{H-P} = 9.5 Hz, 1H, $H_{1'}$) ; 4.07 (t, J = 6.0 Hz, 1H, H_1) ; 2.11 (m, 2H, PCH_2CH_2) ; 1.83 (m, 2H, PCH_2CH_2). **MS (ESI$^-$)** m/z : 317.1 $[M-H]^-$. **HPLC-MS**: Rt = 8.14 min. **HPLC (Crownpak):** Rt = 16.7 min (T = 21 °C, detection λ = 210 / 254 nm). **$[\alpha]_D^{20}$** - 2.0 (c = 0.6, H_2O)

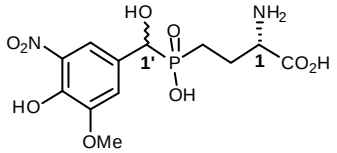
LSP1-2093 Dia II

^{1}H NMR (500 MHz; D_2O) δ : 8.22 (s, 1H, H_{Ar}) ; 8.14 (d, J = 6.9 Hz, 1H, H_{Ar}) ; 7.75 (d, J = 6.3 Hz, 1H, H_{Ar}) ; 7.56 (d, J = 7.4 Hz, 1H, H_{Ar}) ; 5.06 (d, J_{H-P} = 8.5 Hz, 1H, $H_{1'}$) ; 4.06 (bs, 1H, H_1) ; 2.12 (dd, J_{H-P} = 23.3 Hz, J = 10.0 Hz, 2H, PCH_2CH_2) ; 1.94 (d, J_{H-P} = 11.7 Hz; 1H, PCH_2CH_2) ; 1.78 (d, J_{H-P} = 12.0 Hz; 1H, PCH_2CH_2). **MS (ESI$^-$)** m/z : 317.1 $[M-H]^-$. **HPLC-MS**: Rt = 8.10 min. **HPLC (Crownpak):** Rt = 21.4 min (T = 21 °C, detection λ = 210 / 254 nm). **$[\alpha]_D^{20}$** + 29.0 (c = 0.6, H_2O)

- (2*S*)-2-amino-4-(hydroxy(hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl)phosphoryl)butanoic acid **LSP1-2111**

A solution of **4b** (575 mg, 1.1 mmol) in 6 M HCl was refluxed for 5 h. Then, the mixture was cooled to 25 °C and the solvent was evaporated under vacuum. The residue was diluted in EtOAc (50 mL) and extracted with 1 M HCl (2 x 80 mL). The combined aqueous layers were washed with EtOAc (2 x 30 mL) and the solvent was evaporated under vacuum to afford crude product which was purified by cation exchange resin chromatography.

Cation exchange resin chromatography: crude compound were deposited on a Dowex AG 50W-X4, H^+, 50-100 mesh. The compound was eluted with water to afford **LSP1-2111** (196 mg, 0.54 mmol, 60% yield on 2 steps) of desired product were collected.



$C_{12}H_{17}N_2O_9P$
M=364.24/mol
White solid

^{1}H NMR (500 MHz ; D_2O) δ (ppm) : 7.54 (s, 1H, H_{Ar}) ; 7.18 (s, 1H, H_{Ar}) ; 4.82 (d, J_{H-P} = 8.5 Hz, 1H, $H_{1'}$) ; 4.03 (m, 1H, H_1) ; 3.79 (s, 3H, OC*H*$_3$) ; 2.07 (m, 2H, PCH_2CH_2) ; 1.80 (m, 2H, PCH_2CH_2). **^{13}C NMR (125 MHz ; D_2O)** δ (ppm) : 171.3 (Cq) ; 149.0 (Cq_{Ar}) ; 143.7 (Cq_{Ar}) ; 133.9 (Cq_{Ar}) ; 128.6 (Cq_{Ar}) ; 116.2 (CH_{Ar}) ; 114.1 (CH_{Ar}) ; 71.0 (d, J_{C-P} = 109 Hz, $C_{1'}$) ; 56.5 (O*C*H$_3$) ;53.1 (d, J_{C-P} = 14.7 Hz, C_1) ; 22.7 (PCH_2CH_2) ; 21.6 and 21.3 (dd, J_{C-P} = 90 Hz, PCH_2CH_2). **^{31}P NMR (202 MHz ; D_2O)** δ (ppm) : 42.4. **HPLC-MS (ESI)** m/z ; (λ=254 nm): Rt = 7.40 min ; 363.03 $[M-H]^-$

The diastereomers of LSP1-2093 were separated by HPLC with the preparative Crownpack column with a 2.0 mL.min^{-1} flow, a 2 mL injection loop, and a dual UV detection at 210 and 254 nm, at 25 °C. 7 injections were performed; each injection prepared at pH 2 with 5.0 mg of **LSP1-2111** in 1.8 mL of diluted solution of HCl. The diastereomer with the shortest retention time was named **I** and the other one **II**. 15 mg of pure **LSP1-2111 dia I** and 14 mg of pure **LSP1-2111 dia II** were obtained.

LSP1-2111 Dia I

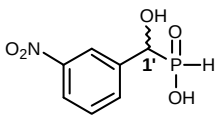
^{1}H NMR (500 MHz ; DMSO) δ (ppm) : 7.49 (s, 1H, H_{Ar}) ; 7.32 (s, 1H, H_{Ar}) ; 4.82 (d, J_{H-P} = 9.2 Hz, 1H, $H_{1'}$) ; 3.98 (m, 1H, H_1) ; 3.86 (s, 3H, OC*H*$_3$) ; 2.07 (m, 2H, PCH_2CH_2) ; 1.80 (m, 2H, PCH_2CH_2). **HPLC (Crownpak):** Rt = 21.4 min (T = 21 °C, detection λ = 210 / 254 nm). **$[\alpha]_D^{20}$** + 2.0 (c = 0.8, H_2O)

LSP1-2111 Dia II

^{1}H NMR (500 MHz ; DMSO) δ (ppm) : 7.49 (s, 1H, H_{Ar}) ; 7.33 (s, 1H, H_{Ar}) ; 4.83 (d, J_{H-P} = 8.4 Hz, 1H, $H_{1'}$) ; 3.98 (m, 1H, H_1) ; 3.86 (s, 3H, OC*H*$_3$) ; 2.06 (m, 2H, PCH_2CH_2) ; 1.91 (m, 1H, PCH_2CH_2) ; 1.72 (m, 1H, PCH_2CH_2). **HPLC (Crownpak):** Rt = 25.0 min (T = 21 °C, detection λ = 210 / 254 nm). **$[\alpha]_D^{20}$** + 25.0 (c = 0.7, H_2O)

- (hydroxy(4-nitrophenyl)methyl)phosphinic acid **(±)-5**

To a stirring solution of 4-nitrobenzaldehyde **3** (2 g, 13.2 mmol, 1 eq) and hypophosphorous acid (50% in water, 4.4 g, 66.2 mmol, 5 eq) in THF (30 mL) was added dropwise at 0 °C BSA (13 mL, 53 mmol, 4 eq). The mixture was allowed to warm up to 25 °C within 12 h. At 0 °C, 1 M HCl (10 mL) was added to quench the reaction. The compound was extracted with EtOAc (3x30 mL) and combined organic layers were washed with 1 M HCl and a saturated solution of NaCl, dried over Na_2SO_4, filtered and evaporated under vacuum to afford **(±)-5** (1.56 g, 7.2 mmol, 54% yield).

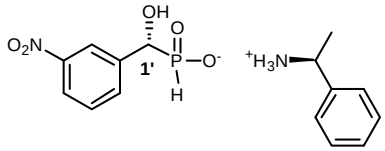


$C_7H_8NO_5P$
M=217.12 g/mol
Orange oil

NMR ^{1}H (500 MHz; MeOD) δ : 8.35 (s, 1H, H_{Ar}) ; 8.19 (d, *J* = 8.2 Hz, 1H, H_{Ar}) ; 7.84 (d, *J* = 7.9 Hz, 1H, H_{Ar}) ; 7.62 (t, *J* = 8.1 Hz, 1H, H_{Ar}) ; 6.9 (d, $J_{H\text{-}P}$ = 555 Hz, 1H, *H*-P) ; 5.06 (d, $J_{H\text{-}P}$ = 9.0 Hz, 1H, $H_{1'}$). **NMR ^{31}P (202 MHz; MeOD)** δ : 29.6 (d, $J_{P\text{-}H}$ = 555 Hz). **NMR $^{31}P_{cpd}$ (202 MHz; MeOD)** δ : 29.6

- (*S*)-1-phenylethylamonium-(*R*)-(hydroxy(3-nitrophenyl)methyl)phosphinate **7a**

The (±)-phosphinic acid **(±)-5** (1.05 g, 4.84 mmol, 1 eq) and (*S*)-methylbenzylamine (586 mg, 4.84 mmol, 1 eq) were stirred in MeOH (10 ml) for 12 h. The solvent was evaporated under vacuum and the product crystallized in a mixture of MeOH/acetonitrile (10 mL, 1:1) to afford **7a** (461 mg, 1.36 mmol, 28% yield).

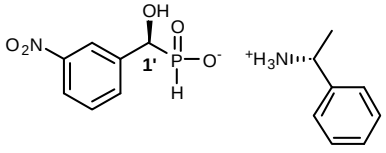


$C_{15}H_{19}N_2O_5P$
M=338.30 g/mol
White cristals

NMR ^{1}H (250 MHz; MeOD) δ : 8.30 (s, 1H, H_{Ar}) ; 8.10 (d, *J* = 8.3 Hz, 1H, H_{Ar}) ; 7.82 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.55 (t, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.44 (m, 5H, H_{Ar}) ; 6.85 (d, $J_{H\text{-}P}$ = 508 Hz, *H*-P) ; 4.73 (d, $J_{H\text{-}P}$ = 9.7 Hz, 1H, $H_{1'}$) ; 4.40 (q, *J* = 6.9 Hz, 1H, C*H*NH_2) ; 1.63 (d, *J* = 6.7 Hz, 3H, CH_3). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.6 (Cq_{Ar}) ; 143.2 (Cq_{Ar}) ; 140.1 (Cq_{Ar}) ; 134.3 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH_{Ar}) ; 130.0 (CH_{Ar}) ; 130.3 and 127.7 (CH_{Ar}) ; 122.8 (CH_{Ar}) ; 122.7 (d, $J_{C\text{-}P}$ = 5.3 Hz, CH_{Ar}) ; 74.9 (d, $J_{C\text{-}P}$ = 100 Hz, $C_{1'}$) ; 52.3 (*C*HNH_2) ; 21.0 (*C*H_3). **NMR ^{31}P (101 MHz; MeOD)** δ : 18.8 (d, $J_{P\text{-}H}$ = 508 Hz). **NMR $^{31}P_{cpd}$ (101 MHz; MeOD)** δ : 18.8. **HRMS (ESI$^+$)** m/z : Calculated for $C_{15}H_{20}N_2O_5P$ $[M+H]^+$: 339.1110. Found 339.1112. **Mp :** 187 °C. **$[\alpha]_D^{20}$** - 3.0 (c = 2.0, MeOH)

- (*R*)-1-phenylethylamonium-(*S*)-(hydroxy(3-nitrophenyl)methyl)phosphinate **7b**

The (±)-phosphinic acid **(±)-5** (1.02 g, 4.70 mmol, 1 eq) and (*R*)-methylbenzylamine (570 mg, 4.70 mmol, 1 eq) were stirred in MeOH (10 ml) for 12 h. The solvent was evaporated under vacuum and the product crystallized in a mixture of MeOH/acetonitrile (10 mL, 1:1) to afford **7b** (514 mg, 1.52 mmol, 32% yield).



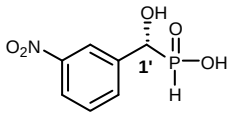
$C_{15}H_{19}N_2O_5P$
M=338.30 g/mol
White cristals

NMR ^{1}H (250 MHz; MeOD) δ : 8.30 (s, 1H, H_{Ar}) ; 8.10 (d, *J* = 8.2 Hz, 1H, H_{Ar}) ; 7.82 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.55 (t, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.44 (m, 5H, H_{Ar}) ; 6.85 (d, $J_{H\text{-}P}$ = 510 Hz, *H*-P) ; 4.73 (d, $J_{H\text{-}P}$

= 9.7 Hz, 1H, $H_{1'}$) ; 4.41 (q, *J* = 6.9 Hz, 1H, C*H*NH_2) ; 1.60 (d, *J* = 6.7 Hz, 3H, CH_3). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.5 (Cq_{Ar}) ; 143.1 (Cq_{Ar}) ; 140.0 (Cq_{Ar}) ; 134.3 (d, $J_{C\text{-}P}$ = 4.3 Hz, CH_{Ar}) ; 130.0 (CH_{Ar}) ; 130.2 and 127.6 (CH_{Ar}) ; 122.7 (CH_{Ar}) ; 122.6 (d, $J_{C\text{-}P}$ = 5.1 Hz, CH_{Ar}) ; 74.9 (d, $J_{C\text{-}P}$ = 102 Hz, $C_{1'}$) ; 52.3 (*C*HNH_2) ; 20.9 (*C*H_3). **NMR ^{31}P (101 MHz; MeOD)** δ : 24.2 ($J_{P\text{-}H}$ = 510 Hz). **NMR $^{31}P_{cpd}$ (101 MHz; MeOD)** δ : 24.2. **HRMS (ESI$^+$)** m/z : Calculated for $C_{15}H_{20}N_2O_5P$ $[M+H]^+$: 339.1110. Found 339.1111. **Mp :** 187°C. **$[\alpha]_D^{20}$**: + 3.7 ° (c = 2.0, MeOH)

- ((*R*)-hydroxy(3-nitrophenyl)methyl)phosphinic acid **(*R*)-5**

7a (461 mg, 1.36 mmol, 1 eq) was treated with a cation exchange resin (Dowex AG50W4, 50-100mesh, H^+ form, 1g) in MeOH (20 mL) for 12 h. Resin was removed by filtration and the solvent was evaporated under vacuum to afford **(*R*)-5** (289 mg, 1.33 mmol, 98% yield).

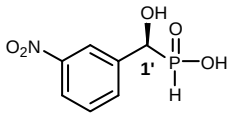


$C_7H_8NO_5P$
M=217.12 g/mol
Orange solid

NMR ^{1}H (250 MHz; MeOD) δ : 8.33 (s, 1H, H_{Ar}) ; 8.17 (d, *J* = 8.1 Hz, 1H, H_{Ar}) ; 7.84 (d, *J* = 8.1 Hz, 1H, H_{Ar}) ; 7.61 (t, *J* = 8.1 Hz, 1H, H_{Ar}) ; 6.90 (d, $J_{H\text{-}P}$ = 554 Hz, *H*-P) ; 5.05 (d, $J_{H\text{-}P}$ = 8.1 Hz, 1H, $H_{1'}$). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.5 (Cq_{Ar}) ; 140.2 (Cq_{Ar}) ; 134.3 (d, $J_{C\text{-}P}$ = 3.8 Hz, CH_{Ar}) ; 130.4 (CH_{Ar}) ; 130.0 (CH_{Ar}) ; 122.7 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_{Ar}) ; 72.2 (d, $J_{C\text{-}P}$ = 110 Hz, $C_{1'}$). **NMR ^{31}P (101 MHz; MeOD)** δ : 29.3 (d, $J_{P\text{-}H}$ = 555 Hz). **NMR $^{31}P_{cpd}$ (101 MHz ; MeOD)** δ : 29.3. **MS (ESI$^-$)** m/z : 216.0 $[M-H]^-$. **$[\alpha]_D^{20}$**: + 27.1 (c = 2.0, MeOH)

- ((*S*)-hydroxy(3-nitrophenyl)methyl)phosphinic acid **(*S*)-5**

7b (514 mg, 1.52 mmol, 1 eq) was treated with a cation exchange resin (Dowex AG50W4, 50-100mesh, H^+ form, 1g) in MeOH (20 mL) for 12 h. Resin was removed by filtration and the solvent was evaporated under vacuum to afford **(*S*)-5** (361 mg, 1.66 mmol, quantitative yield).



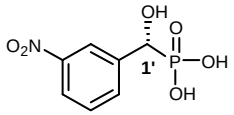
$C_7H_8NO_5P$
M=217.12 g/mol
Orange solid

NMR ^{1}H (250 MHz; MeOD) δ : 8.35 (s, 1H, H_{Ar}) ; 8.19 (d, *J* = 7.9 Hz, 1H, H_{Ar}) ; 7.85 (d, *J* = 7.9 Hz, 1H, H_{Ar}) ; 7.63 (t, *J* = 7.9 Hz, 1H, H_{Ar}) ; 6.90 (d, $J_{H\text{-}P}$ = 555 Hz, *H*-P) ; 5.06 (d, $J_{H\text{-}P}$ = 8.5 Hz, 1H, $H_{1'}$).

NMR ^{13}C (63 MHz; MeOD) δ : 149.2 (Cq_{Ar}) ; 140.0 (Cq_{Ar}) ; 134.3 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_{Ar}) ; 130.4 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH_{Ar}) ; 130.0 (CH_{Ar}) ; 122.5 (d, $J_{C\text{-}P}$ = 5.0 Hz, CH_{Ar}) ; 72.3 (d, $J_{C\text{-}P}$ = 109 Hz, $C_{1'}$). **NMR ^{31}P (101 MHz; MeOD)** δ : 28.7 (d, $J_{P\text{-}H}$ = 549 Hz). **NMR $^{31}P_{cpd}$ (101 MHz; MeOD)** δ : 28.7. **MS (ESI$^-$)** m/z : 216.0 [M-H]$^-$. **[α]$_D^{20}$**: - 27.4 (c = 2.0, MeOH)

- (*R*)-(hydroxy(3-nitrophenyl)methyl)phosphonic acid **(*R*)-9**

A solution of (*R*) phosphinic acid **(*R*)-5** (30 mg, 0.14 mmol, 1eq), DMSO (27 µL, 0.14 mmol, 1 eq) and iodine (0.4 mg, 0.0014 mmol, 0.01 eq) in THF (2ml) was heated at 60 °C for 5 h. After cooling to 25 °C, the mixture was evaporated to dryness and the residue was washed with DCM (5x20 mL). The insoluble material was dissolved in MeOH and evaporated under vacuum to afford **(*R*)-9** (30 mg, 0.13 mmol, 93% yield).

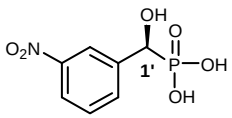


$C_7H_8NO_6P$
M=233.12 g/mol
Orange oil

NMR ^{1}H (250 MHz; MeOD) δ : 8.41 (s, 1H, H_{Ar}) ; 8.15 (d, *J* = 7.5 Hz, 1H, H_{Ar}) ; 7.89 (d, *J* = 7.5 Hz, 1H, H_{Ar}) ; 7.58 (t, *J* = 8.0 Hz, 1H, H_{Ar}) ; 5.05 (d, $J_{H\text{-}P}$ = 14.3 Hz, 1H, $H_{1'}$). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.5 (Cq_{Ar}) ; 142.9 (Cq_{Ar}) ; 134.6 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_{Ar}) ; 130.1 (CH_{Ar}) ; 123.3 (CH_{Ar}) ; 123.1 (d, $J_{C\text{-}P}$ = 4.5 Hz, CH_{Ar}) ; 71.3 (d, $J_{C\text{-}P}$ = 161 Hz, $C_{1'}$). **NMR $^{31}P_{cpd}$ (202 MHz; MeOD)** δ : 18.7. **SM (ESI$^-$)** m/z : 232.2 [M-H]$^-$. **[α]$_D^{20}$**: + 19.7 (c = 1.0, MeOH)

- (*S*)-(hydroxy(3-nitrophenyl)methyl)phosphonic acid **(*S*)-9**

A solution of (*S*) phosphinic acid **(*S*)-5** (30 mg, 0.14 mmol, 1eq), DMSO (27 µL, 0.14 mmol, 1 eq) and iodine (0.4 mg, 0.0014 mmol, 0.01 eq) in THF (2ml) was heated at 60 °C for 5 h. After cooling to 25 °C, the mixture was evaporated to dryness and the residue was washed with DCM (5x20 mL). The insoluble material was dissolved in MeOH and evaporated under vacuum to afford **(*S*)-9** (23 mg, 0.1 mmol, 71% yield).

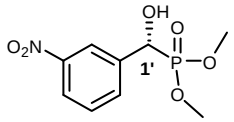


$C_7H_8NO_6P$
M=233.12 g/mol
Orange oil

NMR ^{1}H (250 MHz; MeOD) δ : 8.41 (s, 1H, H_{Ar}) ; 8.15 (d, *J* = 7.5 Hz, 1H, H_{Ar}) ; 7.88 (d, *J* = 7.5 Hz, 1H, H_{Ar}) ; 7.57 (t, *J* = 7.5 Hz, 1H, H_{Ar}) ; 5.05 (d, $J_{H\text{-}P}$ = 14.0 Hz, 1H, $H_{1'}$). **NMR ^{13}C (63 MHz; MeOD)** δ : 149.5 (Cq_{Ar}) ; 142.9 (Cq_{Ar}) ; 134.6 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_{Ar}) ; 130.0 (CH_{Ar}) ; 123.3 (CH_{Ar}) ; 123.1 (d, $J_{C\text{-}P}$ = 4.9 Hz, CH_{Ar}) ; 71.3 (d, $J_{C\text{-}P}$ = 163 Hz, $C_{1'}$). **NMR $^{31}P_{cpd}$ (101 MHz; MeOD)** δ : 18.8. **MS (ESI$^-$)** m/z : 232.0 [M-H]$^-$. **[α]$_D^{20}$**: - 23.0 (c = 1.0, MeOH)

- Synthesis of (*R*)-dimethyl (hydroxy(3-nitrophenyl)methyl)phosphonate **(*R*)-10**

To a solution of (*R*)-phosphonic acid **(*R*)-9** (30 mg, 0.13 mmol, 1 eq) in a mixture of solvent DCM/MeOH (1 mL : 37 µl, 0.90 mmol, 7 eq) was added dropwise at 25 °C diazomethane (1 M in toluene, 320 µl, 0.65 mmol, 5 eq). After stirring for 1 h, the solvent was evaporated under vacuum and the crude residue was purified by column chromatography on silica gel (DCM/ AcOEt 2:8) to afford **(*R*)-10** (4 mg, 0.015 mmol, 12% yield).

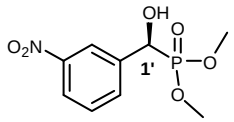


$C_9H_{12}NO_6P$
M=261.17 g/mol
Orange oil

NMR ^{1}H (250 MHz; MeOD) δ : 8.38 (s, 1H, H_{Ar}) ; 8.18 (d, J = 8.2 Hz, 1H, H_{Ar}) ; 7.88 (d, J = 7.6 Hz, 1H, H_{Ar}) ; 7.62 (t, J = 7.8 Hz, 1H, H_{Ar}) ; 5.27 (d, $J_{H\text{-}P}$ = 13.7 Hz, 1H, $H_{1'}$) ; 3.78 and 3.76 (d, $J_{H\text{-}P}$ = 10.5 Hz, 6H, OCH_3). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.5 (Cq_{Ar}) ; 141.3 (Cq_{Ar}) ; 134.4 (d, $J_{C\text{-}P}$ = 5.5 Hz, CH_{Ar}) ; 130.4 (CH_{Ar}) ; 123.8 (d, $J_{C\text{-}P}$ = 3.4 Hz, CH_{Ar}) ; 122.9 (d, $J_{C\text{-}P}$ = 5.8 Hz, CH_{Ar}) ; 70.0 (d, $J_{C\text{-}P}$ = 165 Hz, $C_{1'}$) ; 54.9 and 54.30 (d, $J_{C\text{-}P}$ = 7.3 Hz, OCH_3). **NMR $^{31}P_{cpd}$ (202 MHz; MeOD)** δ : 20.5. **SM (ESI$^+$)** m/z : 262.1 $[M+H]^+$. **$[\alpha]_D^{20}$**: + 35.0 (c = 1.0, MeOH)

- (*S*)-dimethyl (hydroxy(3-nitrophenyl)methyl)phosphonate **(*S*)-10**

To a solution of (*S*)-phosphonic acid **(*S*)-9** (23 mg, 0.1 mmol, 1 eq) in a mixture of solvent DCM/MeOH (1 mL : 28 µl, 0.69 mmol, 7 eq) was added dropwise at 25 °C diazomethane (1 M in toluene, 250 µl, 0.50 mmol, 5 eq). After stirring for 1 h, the solvent was evaporated under vacuum and the crude residue was purified by column chromatography on silica gel (DCM/ EtOAc 2:8) to afford **(*S*)-10** (17 mg, 0.07 mmol, 67% yield).

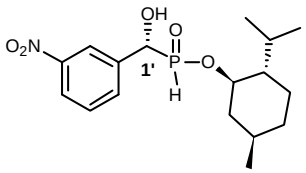


$C_9H_{12}NO_6P$
M=261.17 g/mol
Orange oil

NMR ^{1}H (250 MHz; MeOD) δ : 8.38 (s, 1H, H_{Ar}) ; 8.19 (d, J = 8.0 Hz, 1H, H_{Ar}) ; 7.88 (d, J = 8.0 Hz, 1H, H_{Ar}) ; 7.62 (t, J = 8.0 Hz, 1H, H_{Ar}) ; 5.26 (d, $J_{H\text{-}P}$ = 13.7 Hz, 1H, $H_{1'}$) ; 3.80 and 3.78 (d, $J_{H\text{-}P}$ = 10.0 Hz, 6H, OCH_3). **NMR ^{13}C (126 MHz; MeOD)** δ : 149.7 (Cq_{Ar}) ; 141.4 (Cq_{Ar}) ; 134.5 (d, $J_{C\text{-}P}$ = 5.3 Hz, CH_{Ar}) ; 130.5 (CH_{Ar}) ; 123.9 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH_{Ar}) ; 123.0 (d, $J_{C\text{-}P}$ = 6.0 Hz, CH_{Ar}) ; 70.2 (d, $J_{C\text{-}P}$ = 166 Hz, $C_{1'}$) ; 54.5 and 54.3 (d, $J_{C\text{-}P}$ = 7.1 Hz, OCH_3). **NMR $^{31}P_{cpd}$ (101 MHz; MeOD)** δ : 23.0. **MS (ESI$^+$)** m/z : 264.1 $[M+Na]^+$. **$[\alpha]_D^{20}$** - 23.2 (c = 1.0, MeOH)

- Synthesis of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ((*R*)-hydroxy(3-nitrophenyl)methyl)phosphinate **(*R*)-8a** & **(*R*)-8a'**

To a stirring solution of **(*R*)-5** (235 mg, 1.08 mmol, 1 eq) in THF (10 mL) were added PPh_3 polymer bound (200-400 mesh, 3 mmol triphenylphosphine/g resin, 718 mg, 2.16 mmol, 2 eq) and (-)-menthol (676 mg, 4.33 mmol, 4 eq). The mixture was cooled at 0 °C and diisopropylazadicarboxylate (425 µl, 2.16 mmol, 2 eq) was added. The mixture was then stirred at reflux for 2 h. The mixture was diluted in EtOAc and filtrated on Celite. The crude compound was purified by column chromatography on silica gel (EtOAc) to afford majoratory **(*R*)-8a** and **(*R*)-8a'** (62 mg, 0.174 mmol, 21% yield).

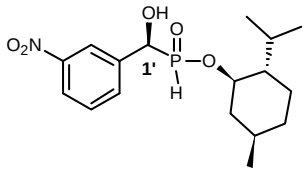


$C_{17}H_{26}NO_5P$
M=355.36 g/mol
Orange oil

NMR $^{31}P_{cpd}$ (101 MHz; MeOD) δ : 34.85 and 28.41 (20%), 33.18 and 30.36 (80%)

- (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl ((S)-hydroxy(3-nitrophenyl)methyl)phosphinate **(*S*)-8b** & **(*S*)-8b'**

To a stirring solution of **(*S*)-5** (178 mg, 0.82 mmol, 1 eq) in THF (10 mL) were added PPh_3 polymer bound (200-400 mesh, 3 mmol triphenylphosphine/g resin, 547 mg, 1.65 mmol, 2 eq) and (-)-menthol (515 mg, 3.29 mmol, 4 eq). The mixture was cooled at 0 °C and diisopropylazadicarboxylate (324 µl, 3.29 mmol, 2 eq) was added. The mixture was then stirred at reflux for 2 h. The mixture was diluted in EtOAc and filtered PPh_3 on Celite. The crude compound was purified by column chromatography on silica gel (EtOAc) to afford majoratory **(*S*)-8b** and **(*S*)-8b'** (62 mg, 0.174 mmol, 21% yield).

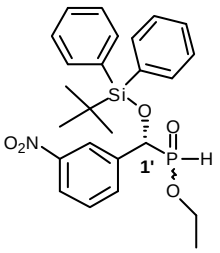


$C_{17}H_{26}NO_5P$
M=355.36 g/mol
Orange oil

NMR $^{31}P_{cpd}$ (101 MHz; MeOD) δ : 35.07 and 28.13 (90%), 32.98 and 30.50 (10%)

- ethyl ((*R*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)phosphinate **(*R*)-11**

To a solution of **(*R*)-5** (4.12 g, 19.0 mmol, 1 eq) in THF (100 mL) was added at 0 °C successively NEt_3 (5.3 mL, 38.0 mmol, 2 eq) and TBDPSCl (5.9 mL, 22.8 mmol, 1.21 eq). The reaction mixture was stirred at 25 °C for 12 h. Then, the solvent was evaporated under vacuum and the crude compound was dissolved in EtOH (80 mL). At 0°C, PivCl (5.5 mL, 28.5 mmol, 1.5 eq) and pyridine (4.9 mL, 40 mmol, 2.1 eq) were added successively dropwise to the reaction mixture which was stirred for 1 h at 25 °C. After evaporation of solvent under vacuum, the crude residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 1:1) to afford a mixture of 2 diastereomers **(*R*)-11 (**4.6 g, 9.5 mmol, 50% yield over 2 steps).



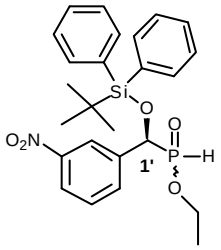
$C_{25}H_{30}NO_5PSi$
M=483.57 g/mol
Yellowish oil

Rf = 0.43 (SiO_2; EtOAc/cyclohexane 1:1; UV). **NMR ^{1}H (400 MHz; $CDCl_3$)** δ : 8.20 (s, 1H, H_{Ar}) ; 8.11 and 8.10 (d, J = 6.8 Hz, 2H, H_{Ar}) ; 8.04 (s, 1H, H_{Ar}) ; 7.69 (d, J = 7.0 Hz, 4H, H_{Ar}) ; 7.61 (d, J = 8.2 Hz, 1H, H_{Ar}) and 7.58 (d, J = 6.5 Hz, 1H, H_{Ar}) ; 7.44 (m, 12H, H_{Ar}) ; 7.34 (m, 2H, H_{Ar}) ; 7.23 (m, 4H, H_{Ar}) ; 6.95 (d, $J_{H\text{-}P}$ = 559 Hz, 1H, *H*-P) and 6.89 (d, $J_{H\text{-}P}$ = 556 Hz, 1H, *H*-P) ; 5.07 (d, $J_{H\text{-}P}$ = 5.6 Hz, 1H, $H_{1'}$) and 4.96 (d, $J_{H\text{-}P}$ = 9.9 Hz, 1H, $H_{1'}$) ; 4.01 (m, 4H, CH_2CH_3) ; 1.24 (m, 6H, CH_2CH_3) ; 1.15 and 1.13 (s, 18H, *t*-Bu). **NMR ^{13}C (126 MHz; $CDCl_3$)** δ : 148.0 and 147.9 (Cq_{Ar}) ; 137.6 and 137.3 (Cq_{Ar}) ; 135.8 (x2), 135.7 (x2), 135.7 (x2) and 135.6 (x2) (CH_{Ar}) ; 133.4 and 133.1 (d, $J_{C\text{-}P}$ = 4.8 Hz, CH_{Ar}) ; 131.8 (x2), 131.6 and 131.5 (Cq_{Ar}) ; 130.4, 130.2 (x2) and 130.1 (CH_{Ar}) ; 129.2 and 129.0 (CH_{Ar}) ; 127.9 (x2), 127.8 (x2), 127.7 (x2) and 127.6 (x2) (CH_{Ar}) ; 123.1 and 122.9 (d, $J_{C\text{-}P}$ = 2.2 Hz, CH_{Ar}) ; 122.3 (d, $J_{C\text{-}P}$ = 5.5 Hz, CH_{Ar}) and 122.2 (d, $J_{C\text{-}P}$ = 4.6 Hz, CH_{Ar}) ; 73.2 (d, $J_{C\text{-}P}$ = 115.3 Hz, $C_{1'}$) and 72.9 (d, $J_{C\text{-}P}$ = 113.1 Hz, $C_{1'}$) ; 63.4 and 63.1 (d, $J_{C\text{-}P}$ = 7.7 Hz, CH_2CH_3) ; 26.8 and 26.7 (*t*-Bu) ; 19.2 (x2)(Cq *t*-Bu) ; 16.1 and 16.0 (d, $J_{C\text{-}P}$ = 2.1 Hz, CH_2CH_3). **NMR $^{31}P_{cpd}$ (202 MHz; $CDCl_3$)** δ : 31.9 and 31.4. **HRMS (ESI$^+$)** m/z : Calculated for $C_{25}H_{30}NO_5PSiNa$ $[M+Na]^+$: 506.1529. Found 506.1518. **IR** ν_{max}/cm^{-1} : 2930, 1531, 1428, 1351, 1239, 1113, 961, 908, 809, 730

- ethyl ((*S*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)phosphinate **(*S*)-11**

To a solution of **(*S*)-5** (4.94 g, 22.8 mmol, 1 eq) in THF (100 mL) was added at 0 °C successively NEt_3 (6.3 mL, 45.5 mmol, 2 eq) and TBDPSCl (5.9 mL, 22.8 mmol, 1.21 eq). The reaction mixture was stirred at 25 °C for 12 h. Then, the solvent was evaporated under vacuum and the crude compound was dissolved in EtOH (80 mL). At 0 °C, PivCl (6.5 mL, 34.2 mmol, 1.5 eq) and pyridine

(5.8 mL, 47.8 mmol, 2.1 eq) were added successively dropwise to the reaction mixture which was stirred for 1 h at 25 °C. After evaporation of solvent under vacuum, the crude residue was purified by column chromatography on silica gel (EtOAc/cyclohexane 1:1) to afford a mixture of 2 diastereomers **(*S*)-11 (**5.7 g, 11.8 mmol, 52% yield over 2 steps).

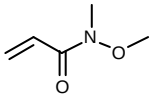


$C_{25}H_{30}NO_5PSi$
M=483.57 g/mol
Yellowish oil

Rf = 0.52 (SiO_2; EtOAc/cyclohexane 1:1; UV). **NMR ^{1}H (400 MHz; $CDCl_3$)** δ : 8.20 (s, 1H, H_{Ar}) ; 8.11 and 8.10 (d, *J* = 7.0 Hz, 2H, H_{Ar}) ; 8.05 (s, 1H, H_{Ar}) ; 7.69 (d, *J* = 7.0 Hz, 4H, H_{Ar}) ; 7.61 (d, *J* = 9.1 Hz, 1H, H_{Ar}) and 7.59 (d, *J* = 6.5 Hz, 1H, H_{Ar}) ; 7.44 (m, 12H, H_{Ar}) ; 7.34 (m, 2H, H_{Ar}) ; 7.23 (m, 4H, H_{Ar}) ; 6.96 (d, $J_{H\text{-}P}$ = 558 Hz, 1H, *H*-P) and 6.90 (d, $J_{H\text{-}P}$ = 558 Hz, 1H, *H*-P) ; 5.07 (d, $J_{H\text{-}P}$ = 5.4 Hz, 1H, $H_{1'}$) and 4.97 (d, $J_{H\text{-}P}$ = 9.6 Hz, 1H, $H_{1'}$) ; 4.01 (m, 4H, C*H*$_2$CH$_3$) ; 1.23 (m, 6H, CH$_2$C*H*$_3$) ; 1.15 and 1.13 (s, 18H, *t*-Bu). **NMR ^{13}C (100 MHz; $CDCl_3$)** δ : 148.2 and 148.1 (Cq_{Ar}) ; 137.8 and 137.5 (Cq_{Ar}) ; 136.0 (x4), 135.9 (x2) and 135.8 (x2) (CH_{Ar}) ; 133.6 and 133.3 (d, $J_{C\text{-}P}$ = 4.2 Hz, CH_{Ar}) ; 132.1, 132.0, 131.8 and 131.7 (Cq_{Ar}) ; 130.6, 130.4 (x2) and 130.3 (CH_{Ar}) ; 129.4 and 129.2 (CH_{Ar}) ; 128.1 (x2), 128.0 (x4) and 127.9 (x2) (CH_{Ar}) ; 123.3 and 123.2 (CH_{Ar}) ; 122.5 (d, $J_{C\text{-}P}$ = 5.4 Hz, CH_{Ar}) and 122.4 (d, $J_{C\text{-}P}$ = 4.4 Hz, CH_{Ar}) ; 73.5 (d, $J_{C\text{-}P}$ = 115.3 Hz, $C_{1'}$) and 73.1 (d, $J_{C\text{-}P}$ = 112.4 Hz, $C_{1'}$) ; 63.5 and 63.2 (d, $J_{C\text{-}P}$ = 7.4 Hz, *C*H$_2$CH$_3$) ; 27.0 and 26.9 (*t*-Bu) ; 19.5 (x2)(Cq *t*-Bu) ; 16.1 and 16.0 (d, $J_{C\text{-}P}$ = 3.0 Hz, CH$_2$*C*H$_3$). **NMR $^{31}P_{cpd}$ (161 MHz; $CDCl_3$)** δ : 31.9 and 31.4. **HRMS (ESI$^+$)** m/z : Calculated for $C_{25}H_{30}NO_5PSiNa$ $[M+Na]^+$: 506.1529. Found 506.1523. **IR** ν_{max}/cm^{-1} : 2932, 2860, 1530, 1347, 1236, 1107, 1045, 907, 733, 702, 502

- N-methoxy-N-methylacrylamide

To a stirring solution of *N*,*O*-dimethylhydroxylamine (2 g, 20.5 mmol, 1.1 eq) and acryloyl chloride (1.51 mL, 18.7 mmol, 1 eq) in $CHCl_3$ (40 mL) was added dropwise at 0 °C anhydrous pyridine (3.3 mL, 41.3 mmol, 2.2 eq). After stirring 1.5 h at 25 °C, the solvent was evaporated. The residue was dissolved in 1 M HCl and aqueous layer was extracted with a mixture of DCM/Et_2O (3x30 mL, 1:1). The combined organic layers were washed with a saturated solution of $NaHCO_3$ and a saturated solution of NaCl, dried over Na_2SO_4, filtered and evaporated under vacuum to afford desired compound (1.4 g, 12.2 mmol, 65% yield).

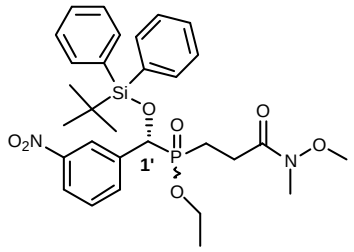


$C_5H_9NO_2$
M=115.13 g/mol
Yellowish oil

NMR ^{1}H (400 MHz; $CDCl_3$) δ : 6.74 (dd, *J* = 17.3 Hz, *J* = 10.4 Hz, 1H, C*H*) ; 6.44 (dd, *J* = 17.1 Hz, *J* = 2 Hz, 1H, CH_2) ; 5.76 (dd, *J* = 10.3 Hz, *J* = 2 Hz, 1H, CH_2) ; 3.27 (s, 3H, OCH_3) ; 3.72 (s, 3H, NCH_3). **NMR ^{13}C (100 MHz; $CDCl_3$)** δ : 166.5 (Cq) ; 129.0 (*C*H) ; 125.9 (*C*H_2) ; 61.8 (O*C*H_3); 32.4 (N*C*H_3)

- ethyl ((*R*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-(methoxy(methyl)amino)-3-oxopropyl)phosphinate **(*R*)-13**

To a stirring deoxygenated solution of **(*R*)-11** (4.58 g, 9.5 mmol, 1 eq) in THF (120 mL) was added at -78 °C freshly prapared LiHMDS (6.30 mL in THF (15 mL), 10.4 mmol, 1.1 eq). After 5 min, N-methoxy-N-methylacrylamide (1.31 g, 11.4 mmol, 1.2 eq) was added to the mixture which was allowed to warm up to 25 °C within 12 h. The reaction mixture was quenched with a saturated solution of NaCl, extracted with EtOAc (3x30 mL) then combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting oil was purified by column chromatography on silica gel (EtOAc) to afford a mixture of 2 diastereomers **(*R*)-13** (1.2 g, 2.0 mmol, 41% yield).

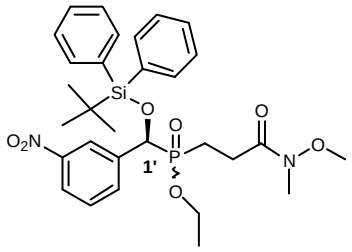


$C_{30}H_{39}N_2O_7PSi$
M=598.70 g/mol
Yellowish oil

Rf = 0.41 (SiO_2; EtOAc; UV). **NMR ^{1}H (500 MHz; $CDCl_3$)** δ : 8.00 and 7.98 (m, 2H, H_{Ar}) ; 7.94 (d, *J* = 8.4 Hz, 2H, H_{Ar}) ; 7.64 (m, 4H, H_{Ar}) ; 7.55 and 7.50 (d, *J* = 7.5 Hz, 2H, H_{Ar}) ; 7.38 (m, 6H, H_{Ar}) ; 7.31 (m, 6H, H_{Ar}) ; 7.22 (m, 2H, H_{Ar}) ; 7.11 (m, 4H, H_{Ar}) ; 5.03 (d, $J_{H\text{-}P}$ = 9.3 Hz, 1H, $H_{1'}$) and 4.98 (d, $J_{H\text{-}P}$ = 12.6 Hz, 1H, $H_{1'}$) ; 3.89 (m, 4H, CH_2CH$_3$) ; 3.58 and 3.54 (s, 6H, OCH_3) ; 3.11 and 3.09 (s, 6H, NCH_3) ; 2.57 (m, 4H, PCH$_2$CH_2) ; 2.01 (m, 4H, PCH_2CH$_2$) ; 1.14 (m, 6H, CH$_2$CH_3) ; 1.08 and 1.06 (s, 18H, *t*-Bu). **NMR ^{13}C (126 MHz; $CDCl_3$)** δ : 172.4 and 172.3 (Cq) ; 147.8 and 147.7 (Cq_{Ar}) ; 139.2 and 139.1 (Cq_{Ar}) ; 136.1 (x4), 135.9 (x2) and 135.8 (x2) (CH_{Ar}) ; 133.6 and 133.5 (d, $J_{C\text{-}P}$ = 4.3 Hz, CH_{Ar}) ; 132.2, 132.1, 131.8 and 131.7 (Cq_{Ar}) ; 130.2 (x2), 130.1 and 130.0 (CH_{Ar}) ; 129.0 and 128.8 (CH_{Ar}) ; 127.8 (x2), 127.7 (x2), 127.6 (x2) and 127.5 (x2) (CH_{Ar}) ; 122.7 and 122.6 (d, $J_{C\text{-}P}$ = 2.5 Hz, CH_{Ar}) ; 122.6 (d, $J_{C\text{-}P}$ = 4.2 Hz, CH_{Ar}) and 122.5 (d, $J_{C\text{-}P}$ = 4.9 Hz, CH_{Ar}) ; 74.5 (d, $J_{C\text{-}P}$ = 110.6 Hz, $C_{1'}$) and 74.2 (d, $J_{C\text{-}P}$ = 109.7 Hz, $C_{1'}$) ; 61.8 and 61.4 (d, $J_{C\text{-}P}$ = 7.0 Hz, *C*H$_2$CH$_3$) ; 61.3 and 61.2 (O*C*H$_3$) ; 32.4 (x2) (N*C*H$_3$) ; 27.1 and 27.0 (*t*-Bu) ; 24.3 and 24.1(PCH$_2$*C*H$_2$) ; 19.8 and 19.1 (d, $J_{C\text{-}P}$ = 92.0 Hz, P*C*H$_2$CH$_2$) ; 19.4 (x2) (Cq *t*-Bu) ; 16.7 and 16.6 (d, $J_{C\text{-}P}$ = 5.7 Hz, CH$_2$*C*H$_3$). **NMR $^{31}P_{cpd}$ (202 MHz; $CDCl_3$)** δ : 49.6 and 48.6. **HRMS (ESI$^+$)** m/z : Calculated for $C_{30}H_{40}N_2O_7PSi$ $[M+H]^+$: 599.2342. Found 599.2331. **IR** ν_{max}/cm^{-1} : 2932, 1663, 1530, 1427, 1351, 1233, 1112, 1032, 910, 823, 731

- ethyl ((*S*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-(methoxy(methyl)amino)-3-oxopropyl)phosphinate **(*S*)-13**

To a stirring deoxygenated solution of **(*S*)-11** (5.39 g, 11.2 mmol, 1 eq) in THF (150 mL) was added at -78 °C freshly prapared LiHMDS (10.3 mL in THF (15 mL), 12.3 mmol, 1.1 eq). After 5 min, N-methoxy-N-methylacrylamide (1.54 g, 13.4 mmol, 1.2 eq) was added to the mixture which was allowed to warm up to 25 °C within 12 h. The reaction mixture was quenched with a saturated solution of NaCl, extracted with EtOAc (3x30 mL) then combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting oil was purified by column chromatography on silica gel (EtOAc) to afford a mixture of 2 diastereomers **(*S*)-13** (2.45 g, 4.1 mmol, 37% yield).



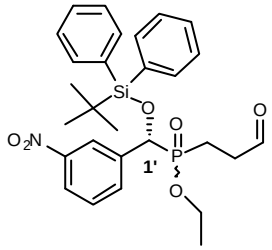
$C_{30}H_{39}N_2O_7PSi$
M=598.70 g/mol
Yellowish oil

Rf = 0.49 (SiO_2; EtOAc ; UV). **NMR ^{1}H (400 MHz; $CDCl_3$)** δ : 8.03 (m, 4H, H_{Ar}) ; 7.70 (m, 4H, H_{Ar}) ; 7.61 and 7.56 (d, J = 7.3 Hz, 2H, H_{Ar}) ; 7.38 (m, 12H, H_{Ar}) ; 7.29 (m, 2H, H_{Ar}) ; 7.18 (m, 4H, H_{Ar}) ; 5.08 (d, $J_{H\text{-}P}$ = 9.2 Hz, 1H, $H_{1'}$) and 5.04 (d, $J_{H\text{-}P}$ = 12.7 Hz, 1H, $H_{1'}$) ; 3.93 (m, 4H, CH_2CH$_3$) ; 3.61 and 3.51 (s, 6H, OCH_3) ; 3.18 and 3.16 (s, 6H, NCH_3) ; 2.62 (m, 4H, PCH$_2$CH_2) ; 2.07 (m, 4H, PCH_2CH$_2$) ; 1.21 (m, 6H, CH$_2$CH_3) ; 1.14 and 1.13 (s, 18H, *t*-Bu). **NMR ^{13}C (100 MHz; MeOD)** δ : 199.1 and 199.0 (Cq) ; 148.0 (x2) (Cq_{Ar}) ; 139.1 and 139.0 (Cq_{Ar}) ; 136.1 (x4) and 136.0 (x4) (CH_{Ar}) ; 133.7 and 133.6 ($J_{C\text{-}P}$ = 4.2 Hz, CH_{Ar}) ; 132.1, 132.0 and 131.9 (x2) (Cq_{Ar}) ; 130.5 (x2) and 130.3 (x2) (CH_{Ar}) ; 129.2 and 129.0 (CH_{Ar}) ; 128.1 (x2), 128.0 (x2), 127.9 (x2) and 127.8 (x2) (CH_{Ar}) ; 123.1 and 123.0 (d, $J_{C\text{-}P}$ = 2.2 Hz, CH_{Ar}) ; 122.7 and 122.6 (d, $J_{C\text{-}P}$ = 4.7 Hz, CH_{Ar}) ; 74.3 and 74.1 (d, $J_{C\text{-}P}$ = 110.8 Hz, $C_{1'}$) ; 62.2 and 61.7 (d, $J_{C\text{-}P}$ = 7.0 Hz, CH$_2$CH$_3$) ; 61.4 and 61.3 (OCH$_3$); 32.6 (x2) (NCH$_3$) ; 27.1 (x2) (*t*-Bu) ; 24.5 and 24.3 (PCH$_2$CH$_2$) ; 19.6 and 19.5 (Cq *t*-Bu) ; 17.7 and 16.7 (d, $J_{C\text{-}P}$ = 92.4 Hz, PCH$_2$CH$_2$) ; 16.8 and 16.7 (d, $J_{C\text{-}P}$ = 5.2 Hz, CH$_2$$CH_3$). **NMR $^{31}P_{cpd}$ (161 MHz; MeOD)** δ : 49.6 and 48.6. **HRMS (ESI$^+$)** m/z : Calculated for $C_{30}H_{39}N_2O_7PSiNa$ $[M+Na]^+$: 621.2162. Found 621.2156. **IR** ν_{max}/cm^{-1} : 2933, 2862, 1664, 1528, 1350, 1233, 1110, 1031, 824, 698, 502

- ((*R*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-oxopropyl)phosphinate **(*R*)-14**

To a stirring solution of **(*R*)-13** (1.2 g, 2.0 mmol, 1 eq) in DCM (50 mL) was added at -78 °C DIBAL (1 M in toluene, 4.0 mL, 4.0 mmol, 2 eq). The mixture was stirred at -78 °C for 2 h. The reaction mixture was stopped by addition of a saturated solution of potassium (30 mL) and compound was extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting oil was purified by column chromatography on silica gel

(EtOAc/cyclohexane 8:2) to afford a mixture of 2 diastereomers **(*R*)-14** (849 mg, 1.57 mmol, 78% yield).

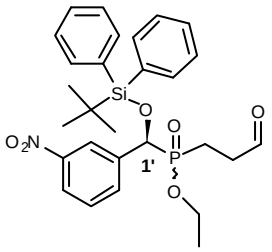


$C_{28}H_{34}N_2O_6PSi$
M=539.63 g/mol
Yellowish oil

Rf = 0.57 (SiO_2; EtOAc ; UV). **NMR ^{1}H (500 MHz; $CDCl_3$)** δ : 9.71 and 9.68 (s, 2H, H_{Al}) ; 8.11 and 8.04 (m, 4H, H_{Ar}) ; 7.69 (m, 4H, H_{Ar}) ; 7.61 and 7.58 (d, J = 7.5 Hz, 2H, H_{Ar}) ; 7.42 (m, 12H, H_{Ar}) ; 7.30 (t, $J_{H\text{-}P}$ = 7.0 Hz, 2H, H_{Ar}) ; 7.19 (t, $J_{H\text{-}P}$ = 7.0 Hz, 4H, H_{Ar}) ; 5.09 (d, $J_{H\text{-}P}$ = 7.9 Hz, 1H, $H_{1'}$) and 5.02 (d, $J_{H\text{-}P}$ = 11.9 Hz, 1H, $H_{1'}$) ; 3.87 (m, 4H, CH_2CH_3) ; 2.60 (m, 4H, PCH_2CH_2) ; 1.98 (m, 4H, PCH_2CH_2) ; 1.19 (m, 6H, CH_2CH_3) ; 1.13 and 1.12 (s, 18H, *t*-Bu). **NMR ^{13}C (126 MHz; $CDCl_3$)** δ : 199.1 and 199.0 (C_{Al}) ; 148.0 (x2) (Cq_{Ar}) ; 139.1 and 139.0 (Cq_{Ar}) ; 136.1 (x4) and 136.0 (x4) (CH_{Ar}) ; 133.7 and 133.5 ($J_{C\text{-}P}$ = 4.2 Hz, CH_{Ar}) ; 132.1, 132.0 and 131.9 (x2) (Cq_{Ar}) ; 130.4 (x2) and 130.3 (x2) (CH_{Ar}) ; 129.1 and 129.0 (CH_{Ar}) ; 128.1 (x2), 127.9 (x2), 127.8 (x2) and 127.7 (x2) (CH_{Ar}) ; 123.0 and 122.9 (d, $J_{C\text{-}P}$ = 2.3 Hz, CH_{Ar}) ; 122.7 and 122.5 (d, $J_{C\text{-}P}$ = 4.7 Hz, CH_{Ar}) ; 74.3 and 74.1 (d, $J_{C\text{-}P}$ = 110.9 Hz, $C_{1'}$) ; 62.1 and 61.7 (d, $J_{C\text{-}P}$ = 7.0 Hz, CH_2CH_3) ; 35.7 (d, $J_{C\text{-}P}$ = 3.5 Hz, PCH_2CH_2) and 35.6 (d, $J_{C\text{-}P}$ = 4.1 Hz, PCH_2CH_2) ; 27.1 (x2) (*t*-Bu) ; 19.5 and 19.4 (Cq *t*-Bu) ; 17.6 (d, $J_{C\text{-}P}$ = 91.7 Hz, PCH_2CH_2) and 16.7 (d, $J_{C\text{-}P}$ = 92.8 Hz, PCH_2CH_2) ; 16.8 and 16.7 (d, $J_{C\text{-}P}$ = 5.2 Hz, CH_2CH_3). **NMR $^{31}P_{cpd}$ (202 MHz; $CDCl_3$)** δ : 48.8 and 48.3. **HRMS (ESI$^+$)** m/z : Calculated for $C_{28}H_{35}N_2O_6PSi$ $[M+H]^+$: 540.1971. Found 540.1960. **IR** ν_{max}/cm^{-1} : 2970, 1724, 1530, 1427, 1393, 1351, 1230, 1035, 909, 822

- ethyl ((*S*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-oxopropyl)phosphinate **(*S*)-14**

To a stirring solution of **(*S*)-13** (2.39 g, 4.0 mmol, 1 eq) in DCM (70 mL) was added at -78 °C DIBAL (1 M in toluene, 8.0 mL, 8.0 mmol, 2 eq). The mixture was stirred at -78 °C for 2 h. The reaction mixture was stopped by addition of a saturated solution of potassium (40 mL) and compound was extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting oil was purified by column chromatography on silica gel (EtOAc/cyclohexane 8:2) to afford a mixture of 2 diastereomers **(*S*)-14** (1.51 g, 2.80 mmol, 70% yield).

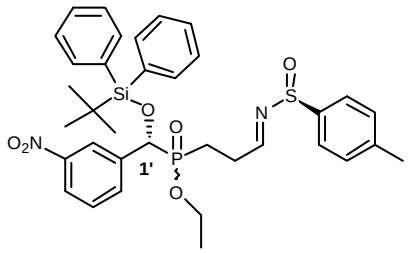


$C_{28}H_{34}N_2O_6PSi$
M=539.63 g/mol
Yellowish oil

Rf = 0.44 (SiO_2; EtOAc ; UV). **NMR ^{1}H (400 MHz; $CDCl_3$)** δ : 9.72 and 9.60 (s, 2H, H_{Al}) ; 8.11 and 8.05 (m, 4H, H_{Ar}) ; 7.70 (t, *J* = 6.0 Hz, 4H, H_{Ar}) ; 7.60 (m, 2H, H_{Ar}) ; 7.42 (m, 12H, H_{Ar}) ; 7.30 (t, *J* = 7.6 Hz, 2H, H_{Ar}) ; 7.19 (t, *J* = 7.5 Hz, 4H, H_{Ar}) ; 5.09 (d, J_{H-P} = 8.4 Hz,1H, $H_{1'}$) and 5.02 (d, J_{H-P} = 12.2 Hz, 1H, $H_{1'}$) ; 3.90 (m, 4H, CH_2CH_3) ; 2.60 (m, 4H, PCH_2CH_2) ; 1.97 (m, 4H, PCH_2CH_2) ; 1.19 (m, 6H, CH_2CH_3) ; 1.12 (s, 18H, *t*-Bu). **NMR ^{13}C (100 MHz; $CDCl_3$)** δ : 199.1 and 199.0 (C_{Al}) ; 148.0 (x2) (Cq_{Ar}) ; 139.1 and 139.0 (Cq_{Ar}) ; 136.1 (x4) and 136.0 (x4) (CH_{Ar}) ; 133.7 and 133.6 (J_{C-P} = 4.4 Hz, CH_{Ar}) ; 132.1, 132.0 and 131.9 (x2) (Cq_{Ar}) ; 130.5 (x2) and 130.3 (x2) (CH_{Ar}) ; 129.2 and 129.0 (CH_{Ar}) ; 128.1 (x2), 128.0 (x2), 127.8 (x2) and 127.7 (x2) (CH_{Ar}) ; 123.1 and 123.0 (d, J_{C-P} = 2.2 Hz, CH_{Ar}) ; 122.7 (d, J_{C-P} = 4.5 Hz, CH_{Ar}) and 122.6 (d, J_{C-P} = 5.1 Hz, CH_{Ar}) ; 74.3 and 74.1 (d, J_{C-P} = 110.7 Hz, $C_{1'}$) ; 62.2 and 61.7 (d, J_{C-P} = 7.1 Hz, CH_2CH_3) ; 35.8 (d, J_{C-P} = 3.6 Hz, PCH_2CH_2) and 35.7 (d, J_{C-P} = 4.3 Hz, PCH_2CH_2) ; 27.1 (x2) (*t*-Bu) ; 19.6 and 19.5 (Cq *t*-Bu) ; 17.7 (d, J_{C-P} = 92.0 Hz, PCH_2CH_2) and 16.7 (d, J_{C-P} = 93.0 Hz, PCH_2CH_2) ; 16.8 and 16.7 (d, J_{C-P} = 5.4 Hz, CH_2CH_3). **NMR $^{31}P_{cpd}$ (161 MHz; $CDCl_3$)** δ : 48.8 and 48.3. **HRMS (ESI$^+$)** m/z : Calculated for $C_{28}H_{34}N_2O_6PSiNa$ $[M+Na]^+$: 562.1791. Found 562.1785. **IR** ν_{max}/cm^{-1} : 2952, 1760, 1738, 1598,1493, 1440, 1199, 1177, 1090

- ethyl ((*R*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)((E)-3-((*p*-tolylsulfinyl)imino)propyl)phosphinate **(*R*)-15**

To a stirring solution of **(*R*)-14** (849 mg, 1.6 mmol, 1 eq) and (*S*)-(+)-*p*-toluensulfinamide (244 mg, 1.6 mmol, 1 eq) in DCM (25 mL) was added $Ti(OEt)_4$ (1.65 mL, 7.9 mmol, 5 eq). The mixture was heated at 50 °C for 24 h. After cooling to 0 °C, water (20 mL) was added to the mixture to stop the reaction. The turbid solution was filtered through Celite and washed with DCM (3x20 mL). After decantation, the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to afford crude sulfinylimine **(*R*)-15** (919 mg, 1.36 mmol, 85% yield) used in next step without further purification.

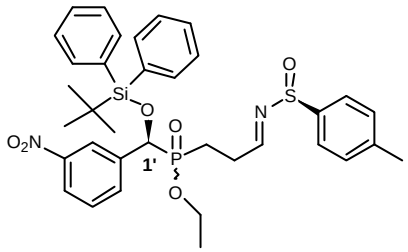


$C_{35}H_{41}N_2O_6PSSi$
M=676.83 g/mol
Yellowish oil

HRMS (ESI$^+$) m/z : Calculated for $C_{35}H_{42}N_2O_6PSSi$ $[M+H]^+$: 677.2270. Found 677.2254.

- ethyl ((*S*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)((E)-3-((*p*-tolylsulfinyl)imino)propyl)phosphinate **(*S*)-15**

To a stirring solution of **(*S*)-14** (1.36 g, 2.5 mmol, 1 eq) and (*S*)-(+)-*p*-toluensulfinamide (400 mg, 2.5 mmol, 1 eq) in DCM (40 mL) was added $Ti(OEt)_4$ (2.7 mL, 12.9 mmol, 5 eq). The mixture was heated at 50 °C for 24 h. After cooling to 0 °C, water (20 mL) was added to the mixture to stop the reaction. The turbid solution was filtered through Celite and washed with DCM (3x30 mL). After decantation, the aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to afford crude sulfinylimine **(*S*)-15** (1.79 mg, 2.6 mmol, quantitative yield) used in next step without further purification.

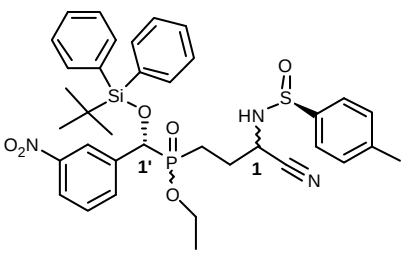


$C_{35}H_{41}N_2O_6PSSi$
M=676.83 g/mol
Yellowish oil

LC-MS: 2.77 min; $[M]^+$ = 676.94

- ethyl ((*R*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-cyano-3-(4-methylphenylsulfinamido)propyl)phosphinate **(1*RS*, 1'*R*)-16**

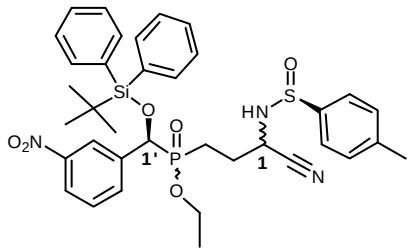
In a round-bottom flask was dissolved sulfinylimine **(*R*)-15** (919 mg, 1.4 mmol, 1 eq) in THF (25 mL). In a separate Schlenk flask, to a stirring solution of diethylaluminium cyanide (6.25 mL, 6.25 mmol, 4.6 eq) was added at -78 °C *i*-PrOH (0.21 mL, 2.8 mmol, 2 eq). This solution was allowed to reach to 25 °C, stirred for 30 min, and cannulated into the solution of **(*R*)-15** at -78 °C. The reaction mixture was brought to 25 °C, and stirred for 24 h. Then cooled to -78 °C and solution of NH_4Cl (20 mL) was added to stop the reaction. The suspension was filtered through Celite, extracted with EtOAc (3x10 mL) and washed with a saturated solution of NaCl (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to afford crude **(1*RS*, 1'*R*)-16** (943 mg, 1.34 mmol) used in next step without further purification.



$C_{36}H_{42}N_3O_6PSSi$
M=703.86 g/mol
Yellowish solid

- ethyl ((*S*)-((tert-butyldiphenylsilyl)oxy)(3-nitrophenyl)methyl)(3-cyano-3-(4-methylphenylsulfinamido)propyl)phosphinate **(1*RS*, 1'*S*)-16**

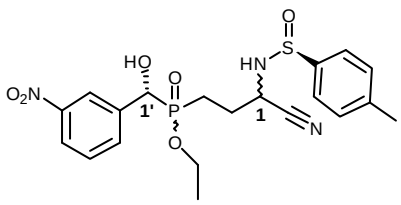
In a round-bottom flask was dissolved sulfinylimine **(*S*)-15** (1.7 g, 2.5 mmol, 1 eq) in THF (30 mL). In a separate Schlenk flask, to a stirring solution of diethylaluminium cyanide (11.6 mL, 11.6 mmol, 4.6 eq) was added at -78 °C *i*-PrOH (0.38 mL, 5.0 mmol, 2 eq). This solution was allowed to reach to 25 °C, stirred for 30 min, and cannulated into the solution of **(*S*)-15** at -78 °C and the reaction mixture was brought to 25 °C, and stirred for 24 h. The reaction mixture was cooled to -78 °C and a saturated solution of NH_4Cl (30 mL) was added to stop the reaction. The suspension was filtered through Celite, extracted with EtOAc (3x30 mL) and washed with a saturated solution of NaCl (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to afford crude **(1*RS*, 1'*S*)-16** (1.68 g, 2.4 mmol) used in next step without further purification.



$C_{36}H_{42}N_3O_6PSSi$
M=703.86 g/mol
Yellowish solid

- ethyl (3-cyano-3-(4-methylphenylsulfinamido)propyl)((*R*)-hydroxy(3-nitrophenyl)methyl)phosphinate **(1*RS*, 1'*R*)-17**

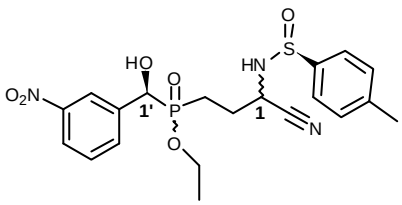
To a solution of **(1*RS*, 1'*R*)-16** (932 mg, 1.3 mmol, 1 eq) in THF (25 mL) was added at 0 °C successively AcOH (0.1 mL, 1.6 mmol, 1.2 eq) and $TBAF.3H_2O$ (507 mg, 1.6 mmol, 1.2 eq) . The reaction mixture was maintained at 25 °C for 12 h. Water (10 mL) was added to the mixture to stop the reaction. After decantation, the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers was dried over Na_2SO_4, filtered and evaporated under vacuum to afford crude residue **(1*RS*, 1'*R*)-17** (1.03 g, 2.2 mmol) used in next step without further purification.



$C_{20}H_{24}N_3O_6PS$
M=465.46 g/mol
Yellowish solid

- ethyl (3-cyano-3-(4-methylphenylsulfinamido)propyl)((*S*)-hydroxy(3-nitrophenyl)methyl)phosphinate **(1*RS*, 1'*S*)-17**

To a solution of **(1*RS*, 1'*S*)-16** (1.68 g, 2.4 mmol, 1 eq) in THF (25 mL) was added at 0 °C successively AcOH (0.15 mL, 2.64 mmol, 1.1 eq) and TBAF (1 M in THF, 2.64 mL, 2.64 mmol, 1.1 eq) . The reaction mixture was maintained at 25 °C for 12 h. Water (10 mL) was added to the mixture to stop the reaction. The organic and aqueous layers were separated and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layers was dried over Na_2SO_4, filtered and evaporated under vacuum to afford crude residue **(1*RS*, 1'*S*)-17** (929 mg, 2.0 mmol) used in next step without further purification.

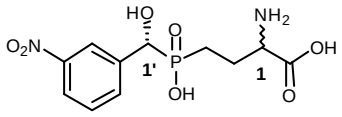


$C_{20}H_{24}N_3O_6PS$
M=465.46 g/mol
Yellowish solid

LC-MS: 1.75 min; $[M-H]^-$ = 463.92

- 2-amino-4-(hydroxy((*R*)-hydroxy(3-nitrophenyl)methyl)phosphoryl)butanoic acid **(1*RS*, 1'*R*)-LSP1-2093**

A solution of **(1*RS*, 1'*R*)-17** (1.03 g, 2.2 mmol, 1 eq) in 6 M HCl (50 mL) was refluxed for 24 h. After cooling to 25 °C, solvent was evaporated under vacuum. The crude residue was dissolved in 1 M HCl and washed with EtOAc (3 x 30 mL). The water was evaporated and the residue was purified on cation exchange resin chromatography (Dowex AG 50W-X4, H^+, 50-100 mesh). The compound was eluted with water to afford **(1*RS*, 1'*R*)-LSP1-2093** (76 mg, 0.24 mmol, 18% over 3 steps).

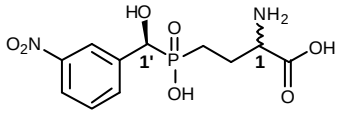


$C_{11}H_{15}N_2O_7P$
M=318.22 g/mol
Yellowish solid

NMR ^{1}H (500 MHz; D_2O) δ : 8.31 (s, 1H, H_{Ar}) ; 8.21 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.84 (d, *J* = 8.1 Hz, 1H, H_{Ar}) ; 7.64 (t, *J* = 8.1 Hz, 1H, H_{Ar}) ; 5.04 (d, J_{H-P} = 9.4 Hz, 1H, $H_{1'}$) ; 4.08 (m, 1H, H_1) ; 2.19 (m, 2H, PCH_2CH_2) ; 1.83 (m, 2H, PCH_2CH_2). **NMR ^{13}C (126 MHz; D_2O)** δ : 172,1 (Cq) ; 147.9 (Cq_{Ar}) ; 140.2 (Cq_{Ar}) ; 133.5 (CH_{Ar}) ; 129.5 (CH_{Ar}) ; 122.7 (CH_{Ar}) ; 121.6 (CH_{Ar}) ; 72.2 (d, J_{C-P} = 105 Hz, $C_{1'}$) ; 53.7 (d, J_{C-P} = 12.5 Hz, C_1) ; 23.3 (PCH_2CH_2) ; 22.5 and 22.4 (d, J_{C-P} = 90.0 Hz, PCH_2CH_2). **NMR $^{31}P_{cpd}$ (202 MHz; D_2O)** δ : 38.0. **HRMS (ESI$^-$)** m/z : Calculated for $C_{11}H_{14}N_2O_7P$ $[M-H]^-$: 317.0544. Found 333.0355. **LC-MS (ESI)** m/z ; (λ=254 nm): Rt = 2.71 min ; 319.07 $[M+H]^+$; 317.05 $[M-H]^-$

- 2-amino-4-(hydroxy((*S*)-hydroxy(3-nitrophenyl)methyl)phosphoryl)butanoic acid **(1*RS*, 1'*S*)-LSP1-2093**

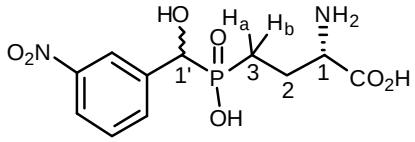
A solution of **(1*RS*, 1'*S*)-17** (929 mg, 2.0 mmol, 1 eq) in 6 M HCl (50 mL) was refluxed for 24 h. After cooling to 25 °C, solvent was evaporated under vacuum. The crude residue was dissolved in 1 M HCl and washed with EtOAc (3x30 mL). The water was evaporated and the residue was purified on cation exchange resin chromatography (Dowex AG 50W-X4, H^+, 50-100 mesh). The compound was eluted with water to afford **(1*RS*, 1'*S*)-LSP1-2093** (23 mg, 0.07 mmol, 3% over 3 steps).



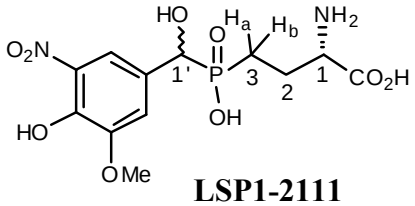
$C_{11}H_{15}N_2O_7P$
M=318.22 g/mol
Yellowish solid

NMR ^{1}H (500 MHz; D_2O) δ : 8.32 (s, 1H, H_{Ar}) ; 8.23 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.85 (d, *J* = 8.0 Hz, 1H, H_{Ar}) ; 7.65 (t, *J* = 8.0 Hz, 1H, H_{Ar}) ; 5.03 (d, $J_{H\text{-}P}$ = 9.9 Hz, 1H, $H_{1'}$) ; 4.07 (m, 1H, H_1) ; 2.20 (m, 2H, PCH_2CH_2) ; 1.81 (m, 2H, PCH_2CH_2). **NMR ^{13}C (126 MHz; D_2O)** δ : 172,2 (Cq) ; 147.9 (Cq_{Ar}) ; 140.3 (Cq_{Ar}) ; 133.5 (CH_{Ar}) ; 129.5 (CH_{Ar}) ; 122.7 (CH_{Ar}) ; 121.6 (CH_{Ar}) ; 72.3 (d, $J_{C\text{-}P}$ = 106 Hz, $C_{1'}$) ; 53.9 (d, $J_{C\text{-}P}$ = 13.9 Hz, C_1) ; 23.6 (PCH_2CH_2) ; 22.6 and 22.4 (dd, $J_{C\text{-}P}$ = 89.5 Hz, PCH_2CH_2). **NMR $^{31}P_{cpd}$ (202 MHz; D_2O)** δ : 37.7. **HRMS (ESI$^-$)** m/z : Calculated for $C_{11}H_{14}N_2O_7P$ $[M\text{-}H]^-$: 317.0544. Found 317.0544. **LC-MS (ESI)** m/z ; (λ=254 nm): Rt = 2.74 min ; 319.07 $[M+H]^+$; 317.05 $[M\text{-}H]^-$

3. Analytical characteristics of LSP1-2093 and LSP1-2111



LSP1-2093

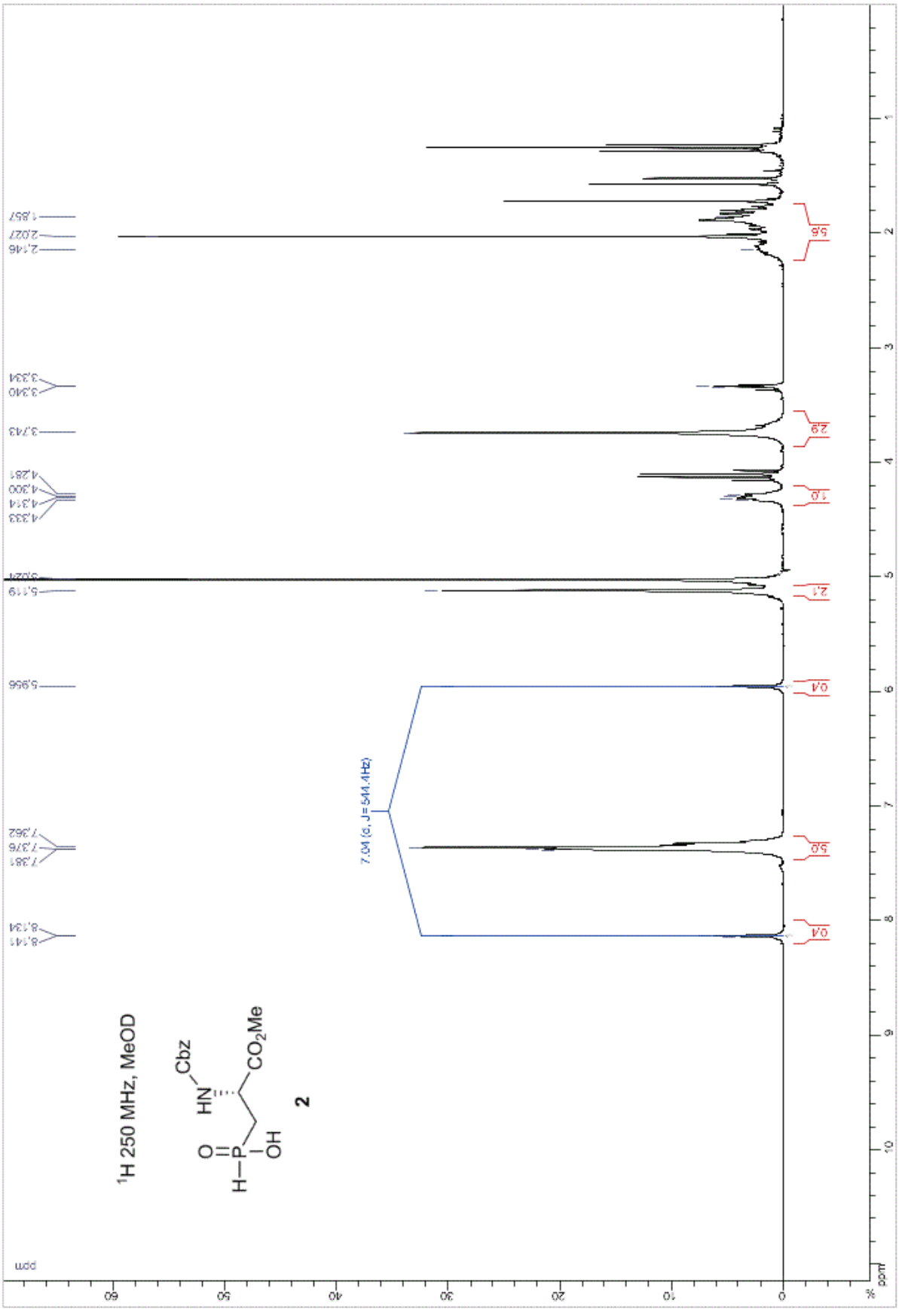


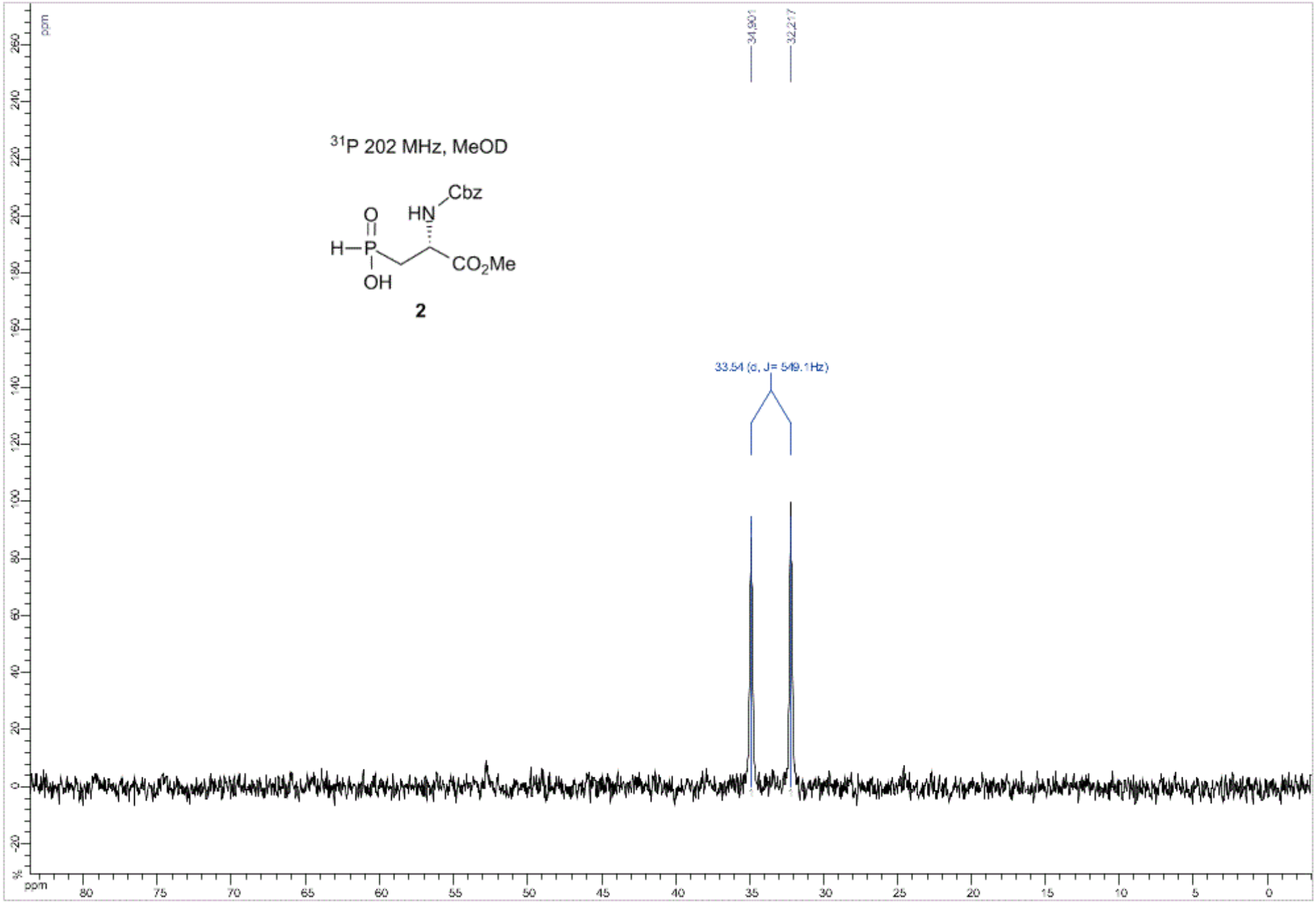
LSP1-2111

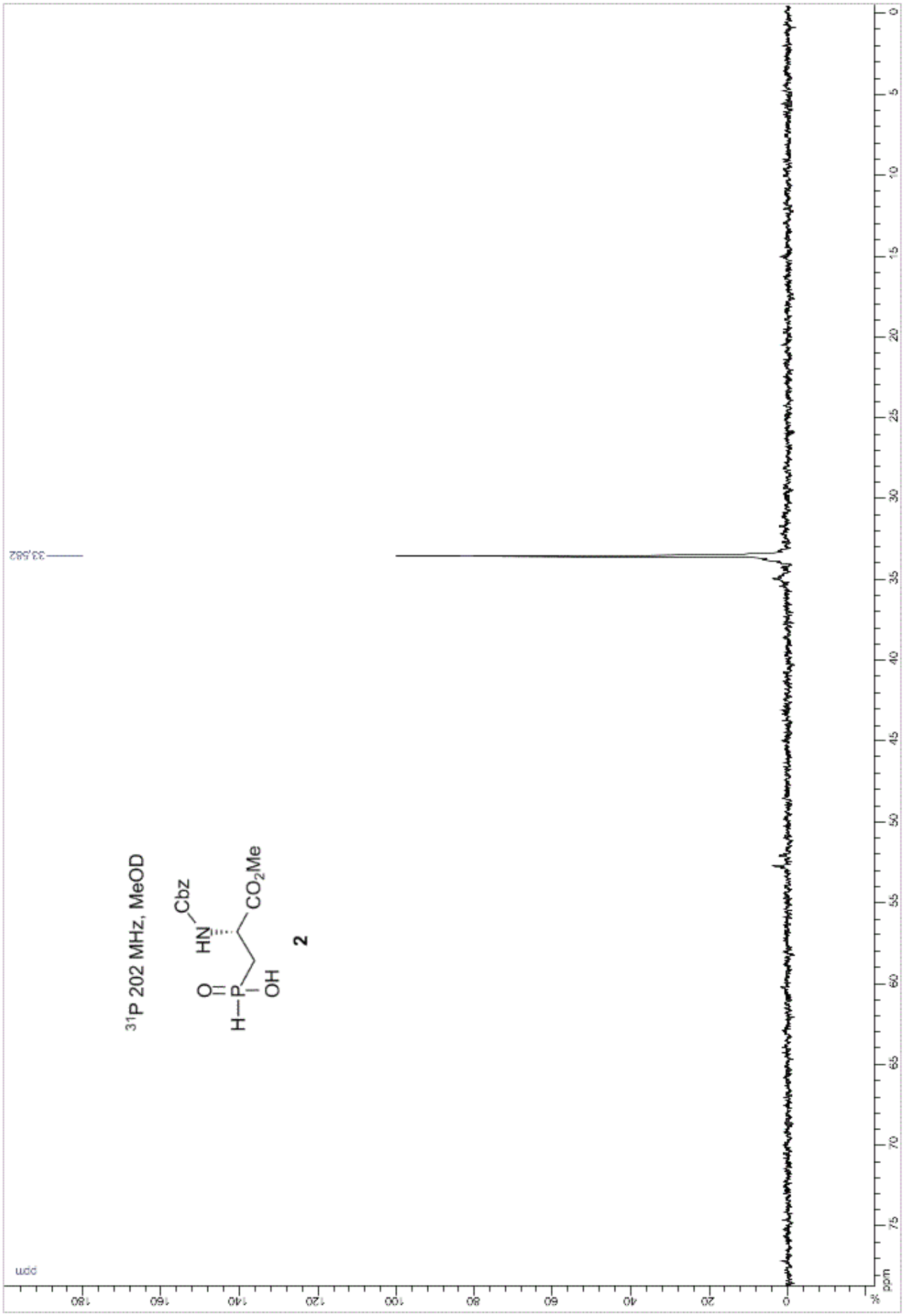
Table 1. Analytical characteristics that differentiate Dia I and Dia II of **LSP1-2093** and **LSP1-2111**

Compounds	HPLC Crownpak Rt (min)	$[\alpha]_D^{20}$ (H_2O, c 0.6-0.8)	^1H NMR of H_{3a} and H_{3b} (ppm)
LSP1-2093			
LSP1-2093 Dia I	16.7	-2	1.83 (m, 2H)
LSP1-2093 Dia II	21.4	+29	1.78 (d, J_{H-P} = 12.0 Hz; 1H) and 1.94 (d, J_{H-P} = 11.7 Hz; 1H)
LSP1-2111			
LSP1-2111 Dia I	21.4	+2	1.80 (m, 2H)
LSP1-2111 Dia II	25.0	+25	1.72 (m, 1H) and1.91 (m, 1H)

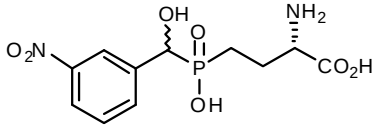
4. 1H, 13C & ^{31}P Nuclear Magnetic Resonance Specta



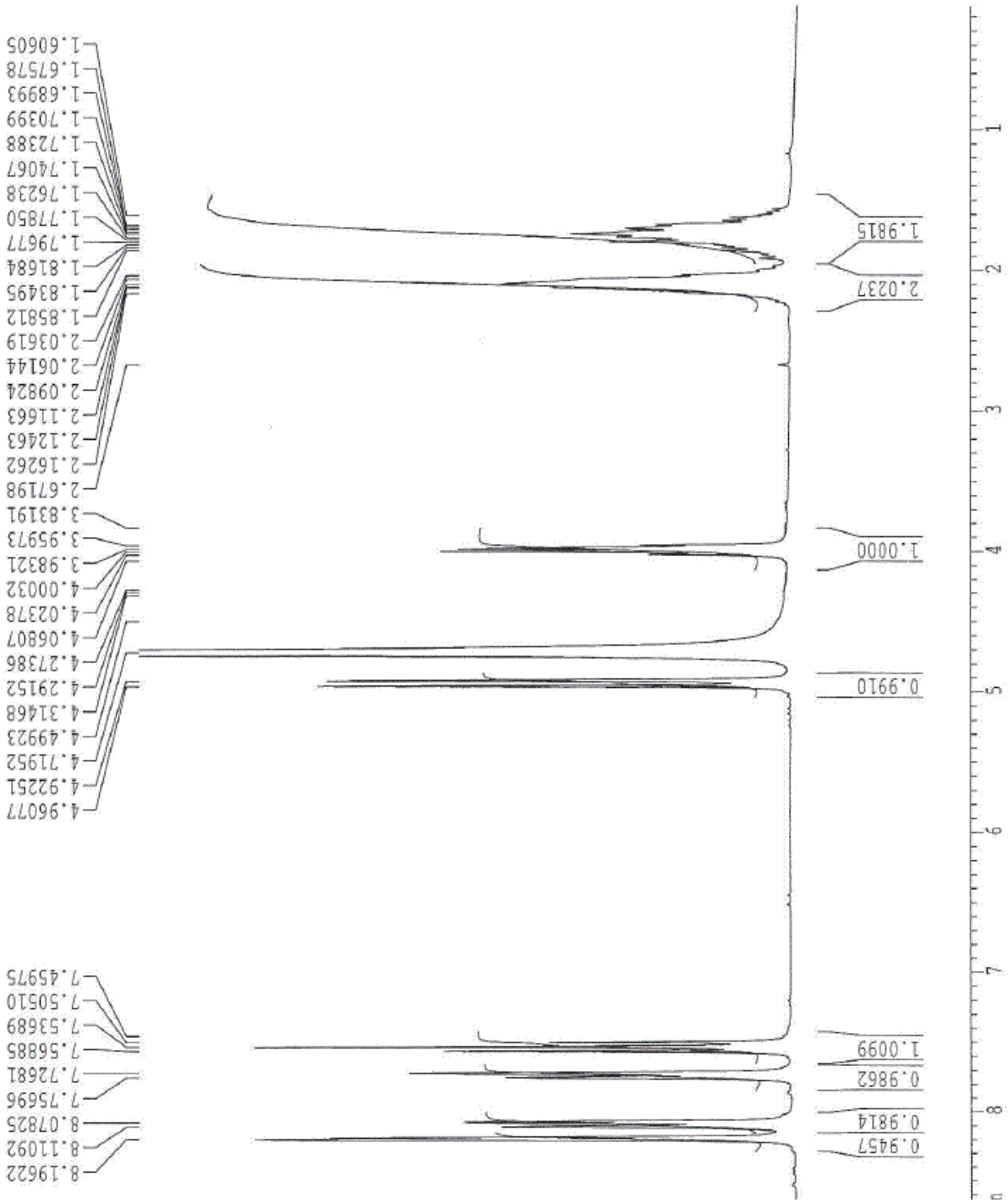

31P 202 MHz, MeOD
Cbz
HN
O
H—P
OH
CO2Me
2
34.901
32.217
33.54 (d, J= 549.1Hz)
ppm
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
%
-20
0
20
40
60
80
100
120
140
160
180
200
220
240
260


^{31}P 202 MHz, MeOD
33.582
Cbz
HN
CO2Me
O
H—P
OH
2
ppm
ppm

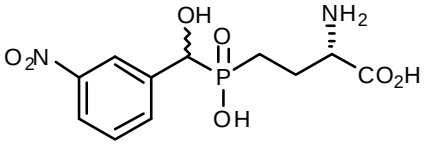
^{1}H NMR, 250 MHz, D_2O



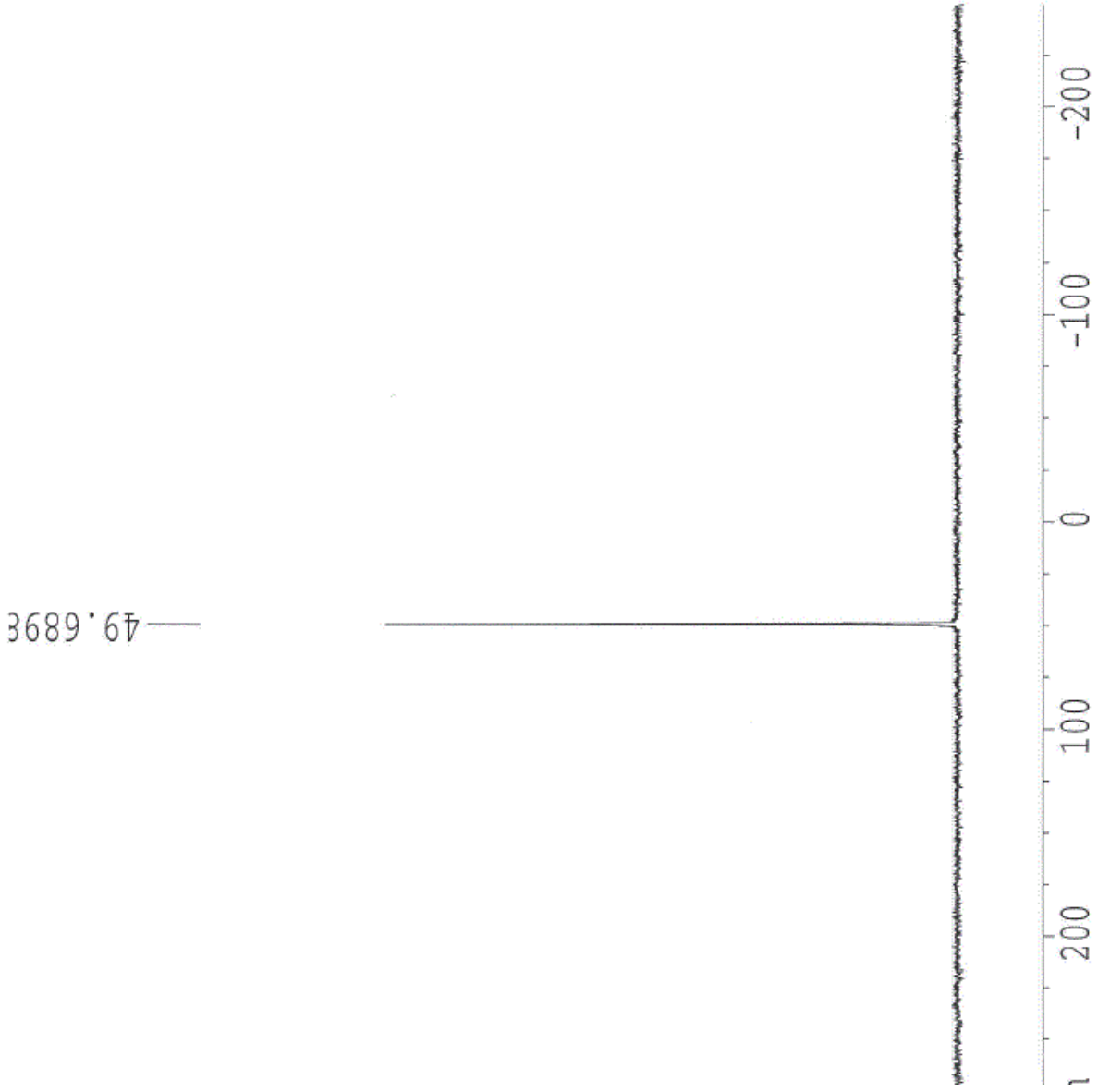
LSP1-2093



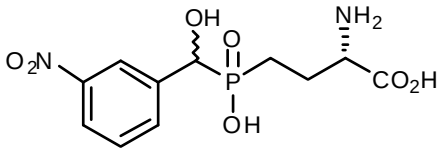
^{31}P NMR, 101 MHz, D_2O



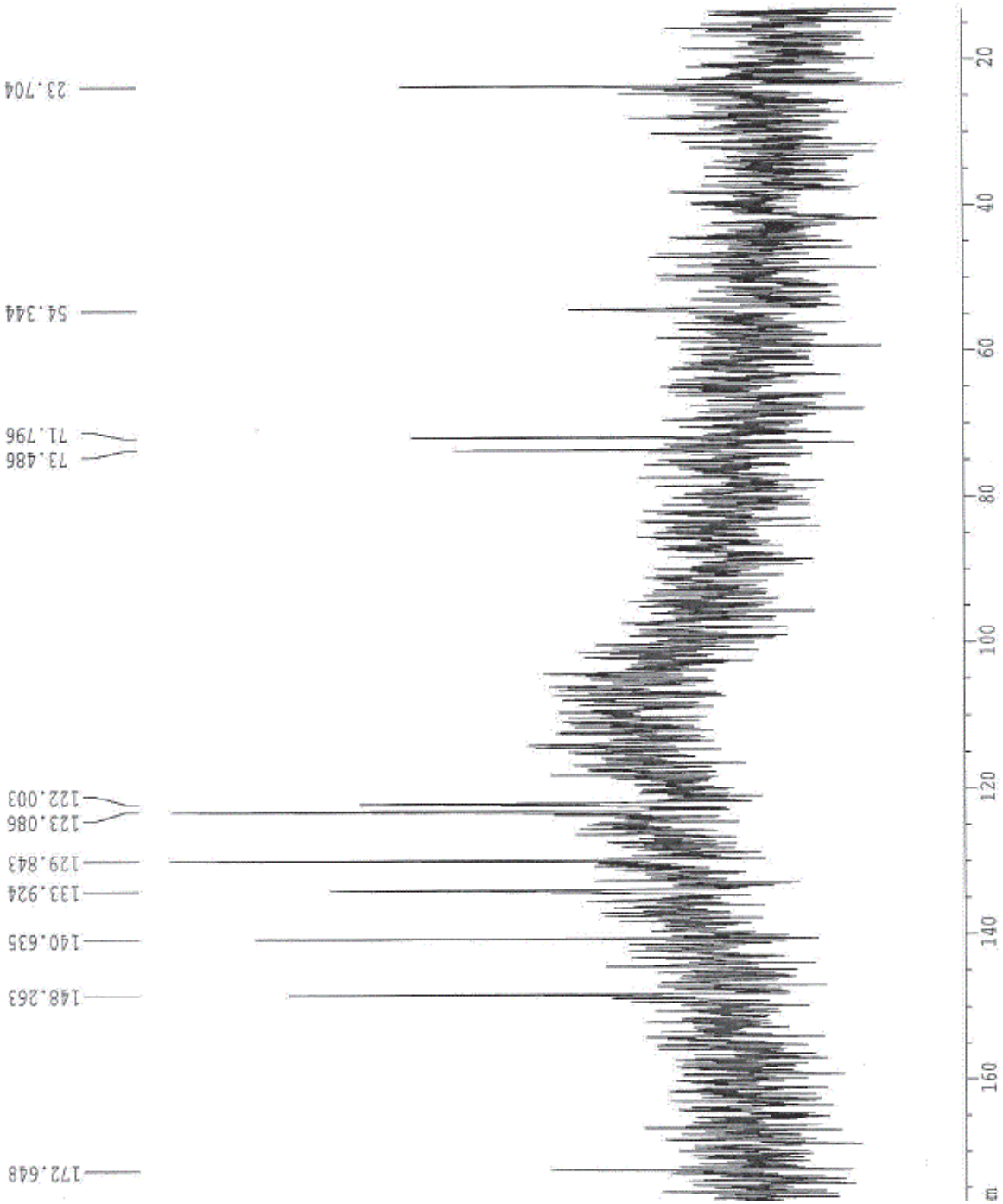
LSP1-2093



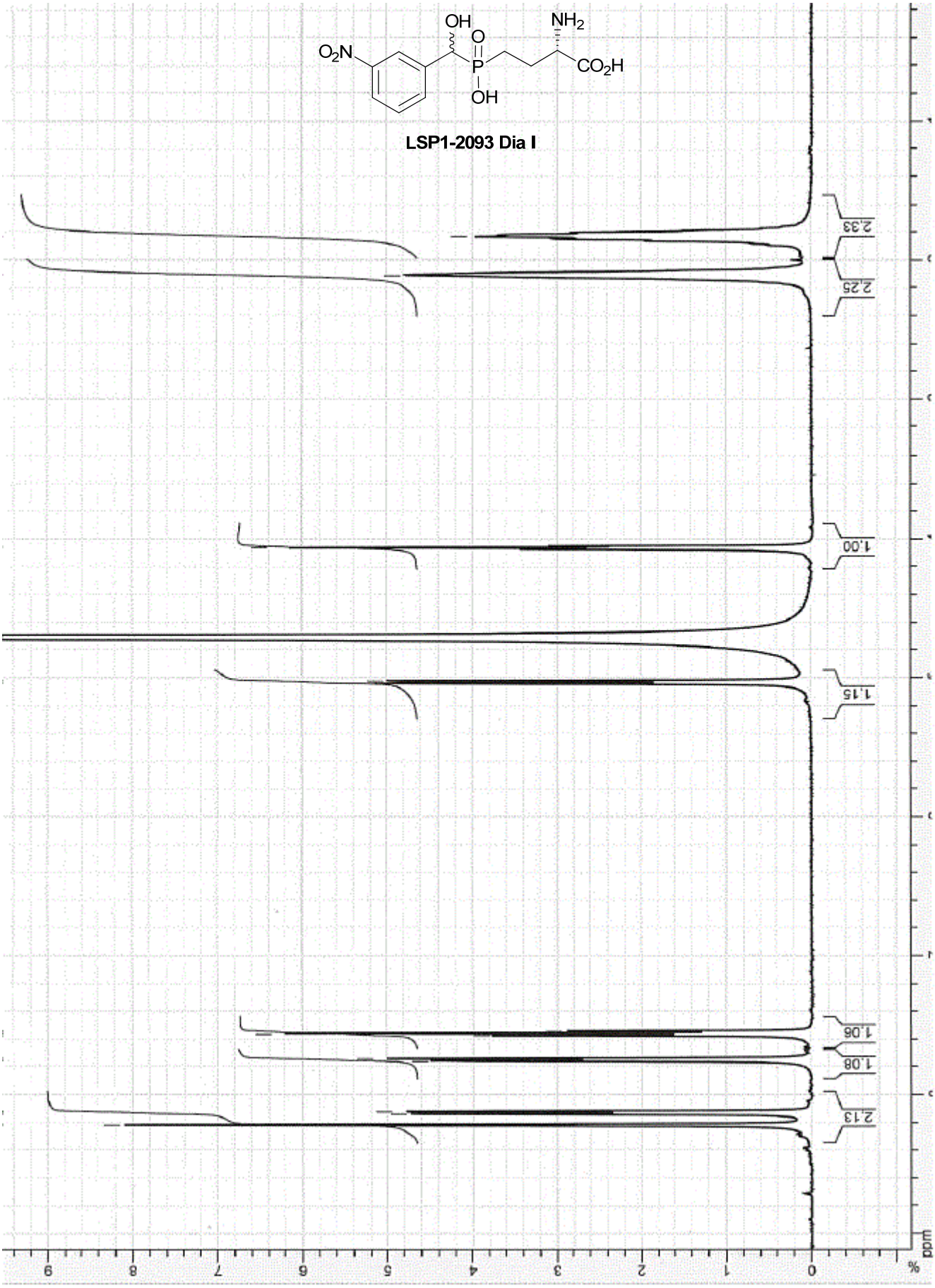
^{13}C NMR, 63 MHz, D_2O



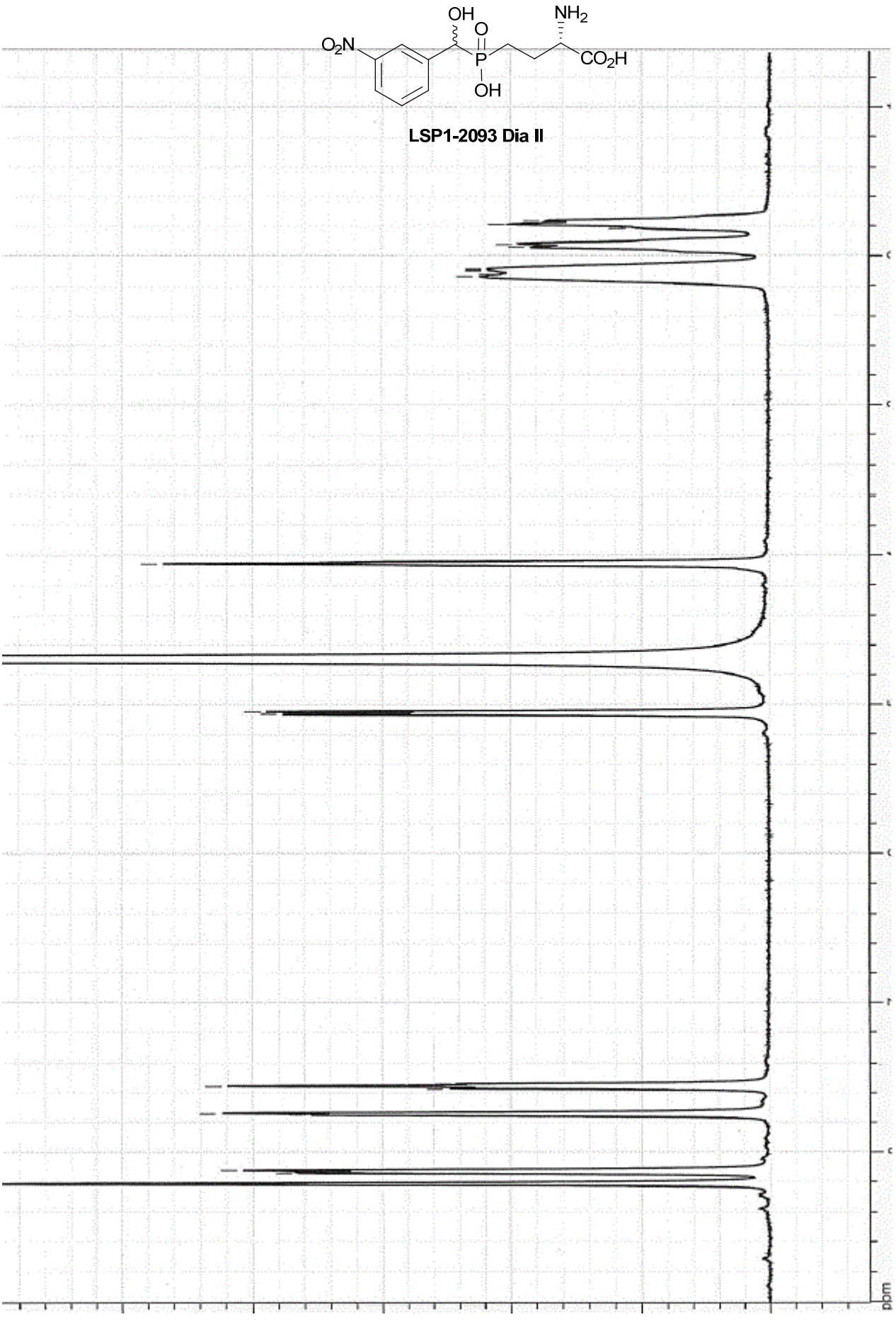
LSP1-2093

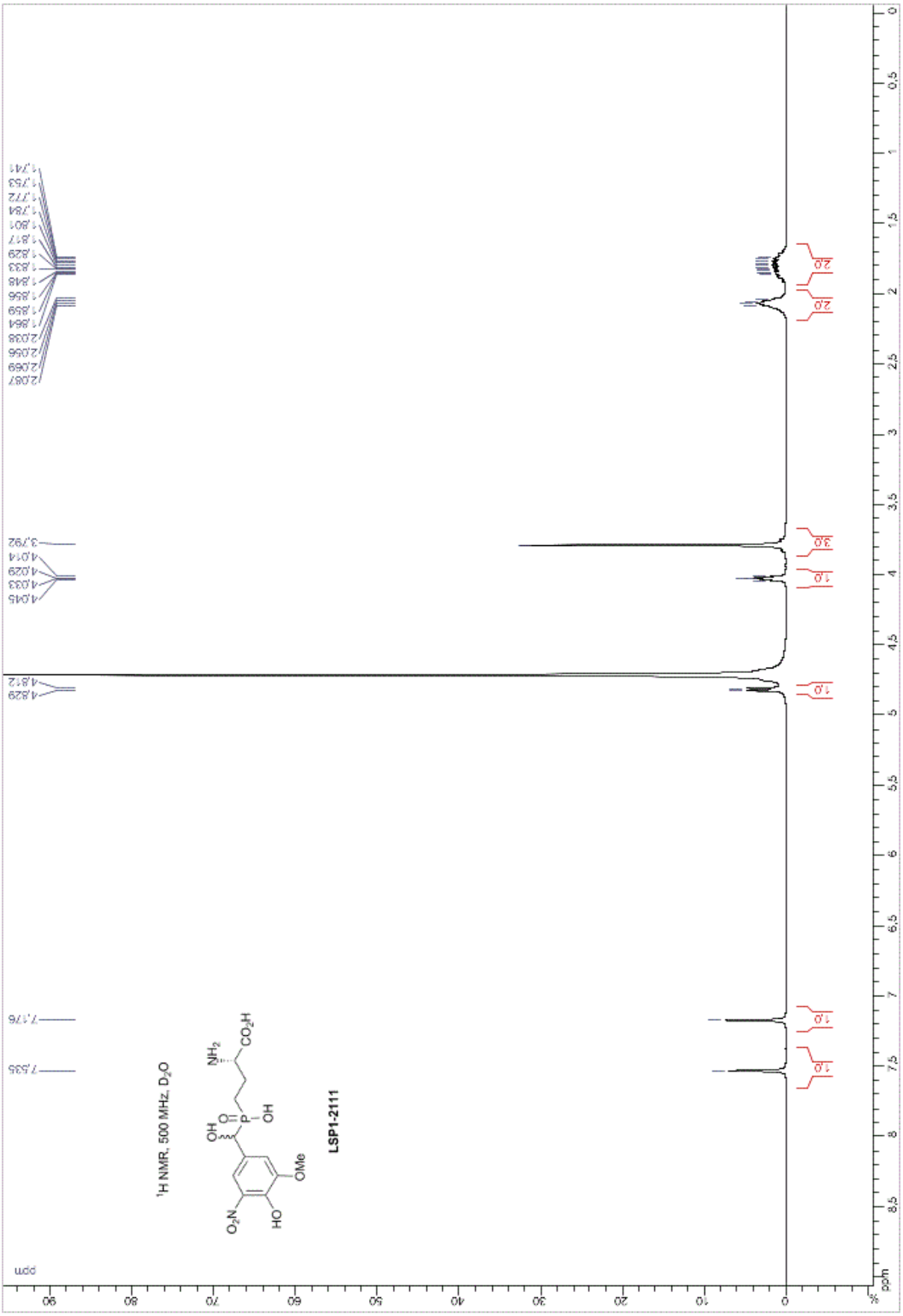


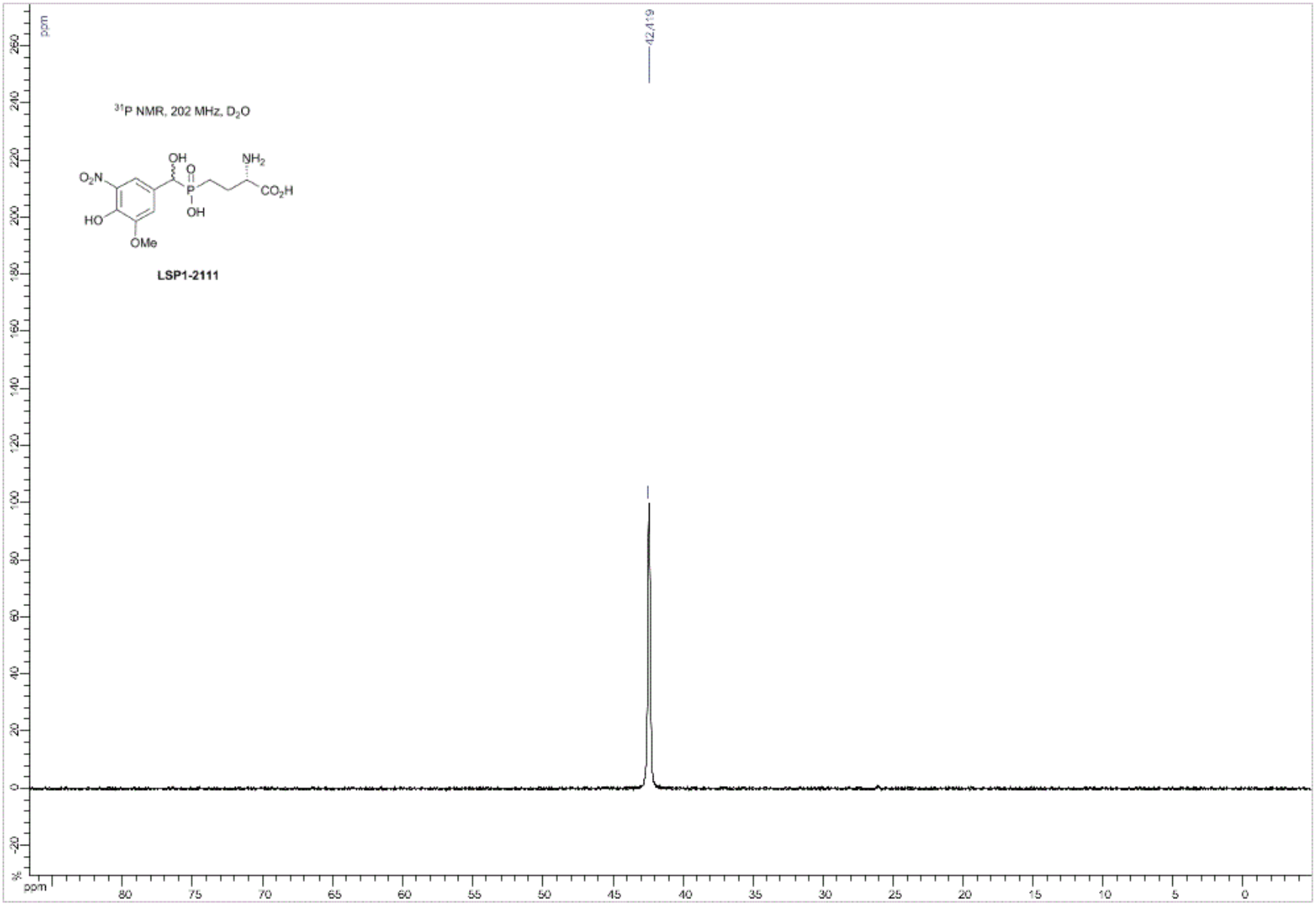
^{1}H NMR, 500 MHz, D_2O

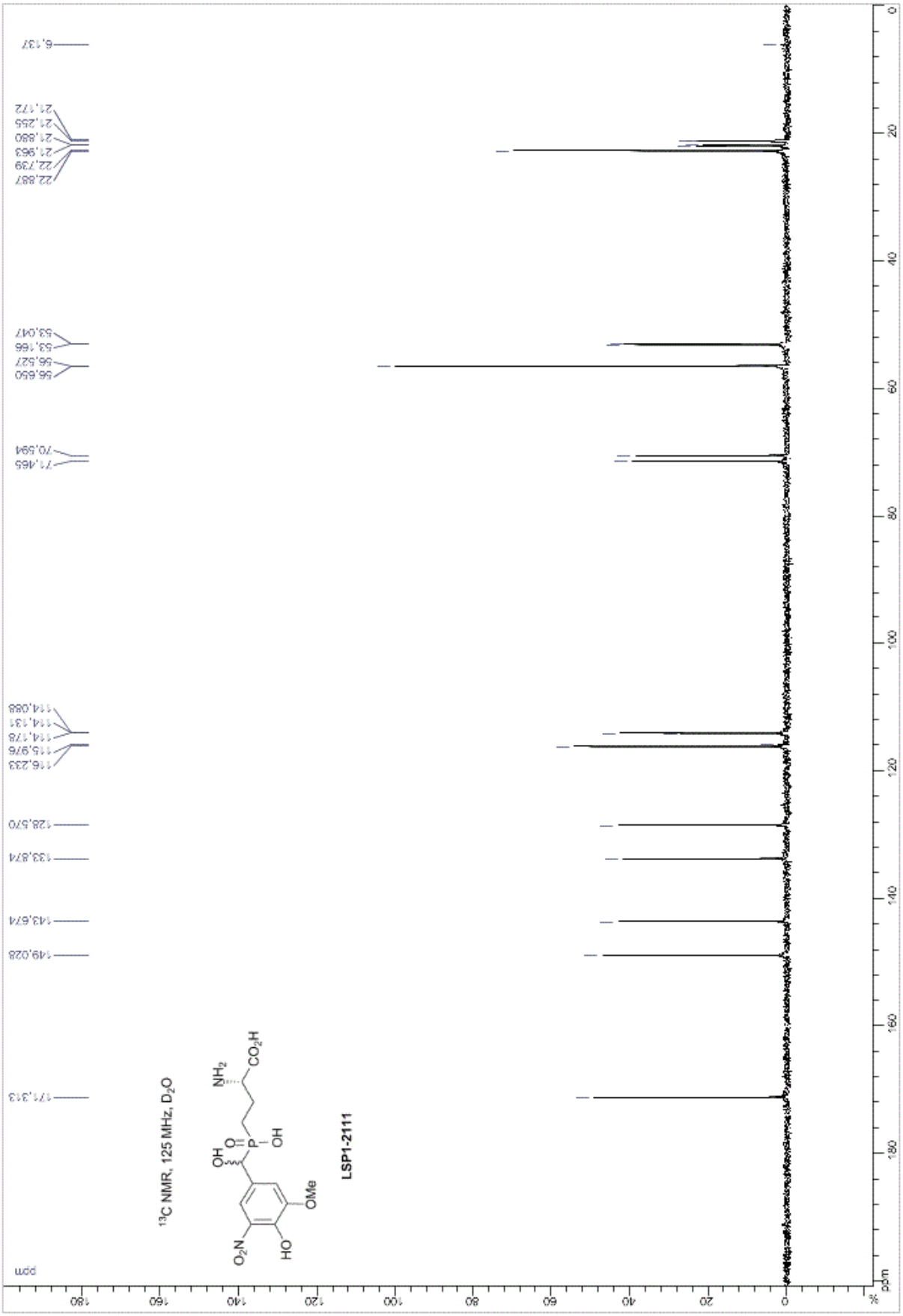


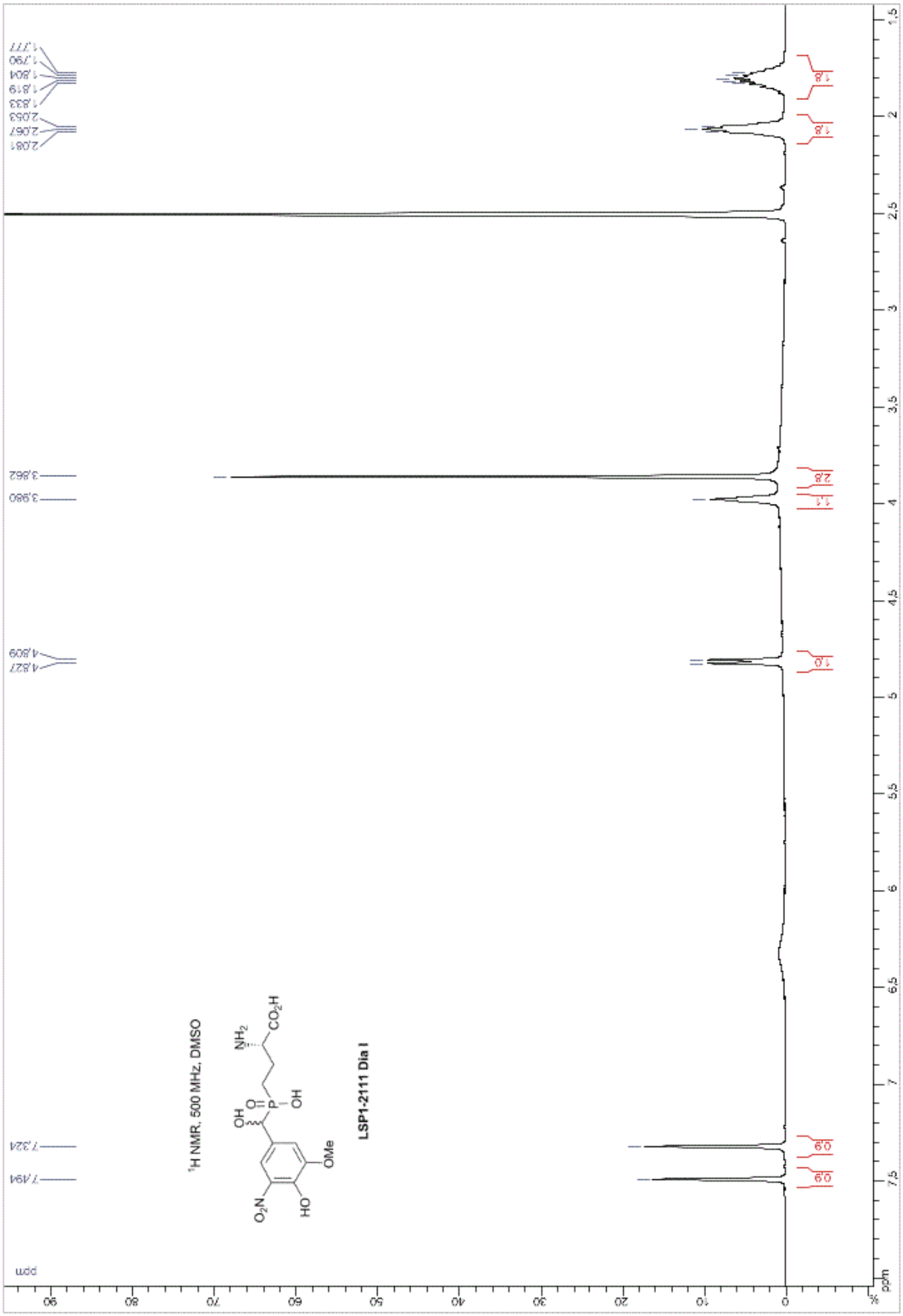
^{1}H NMR, 500 MHz, D_2O

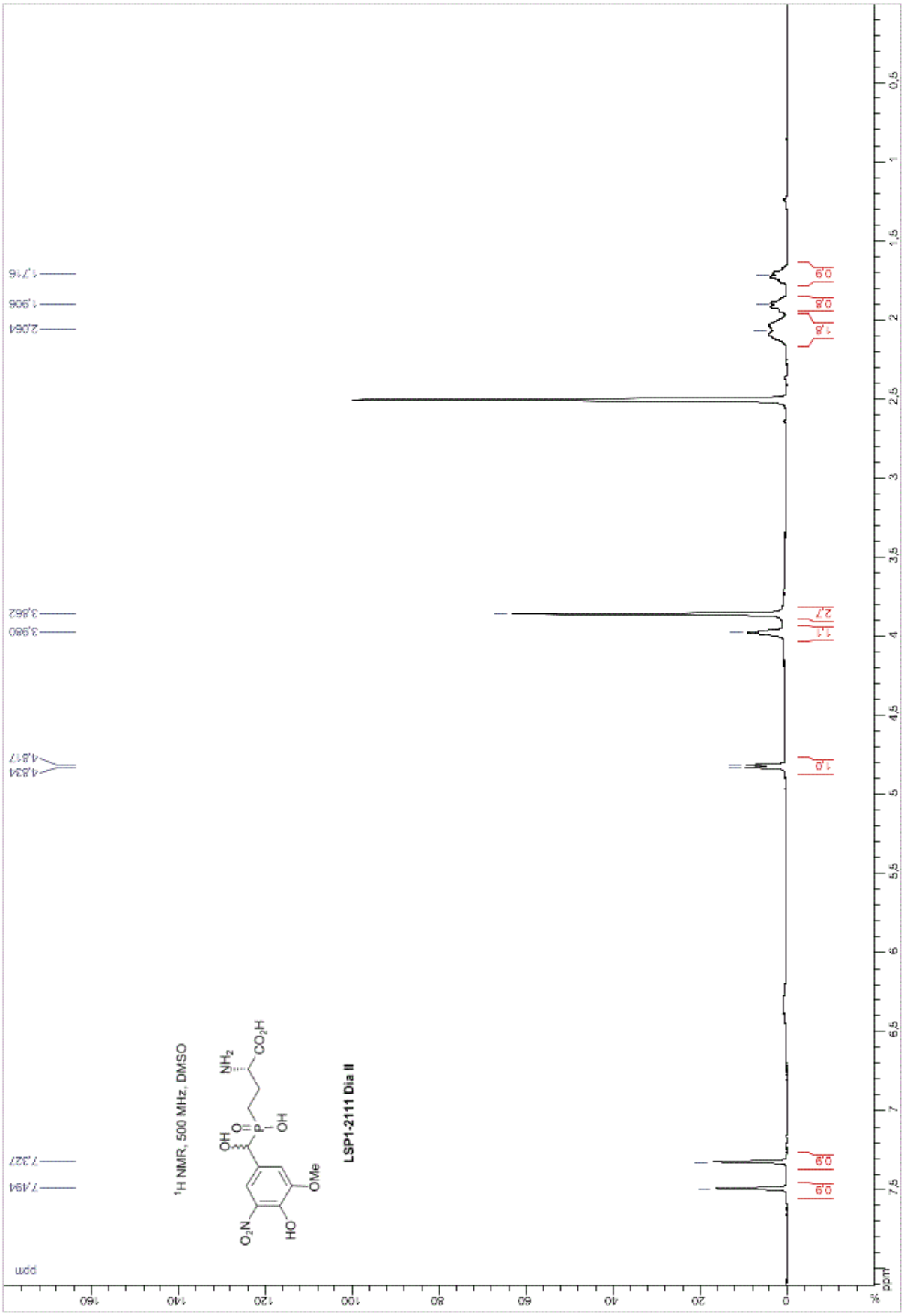


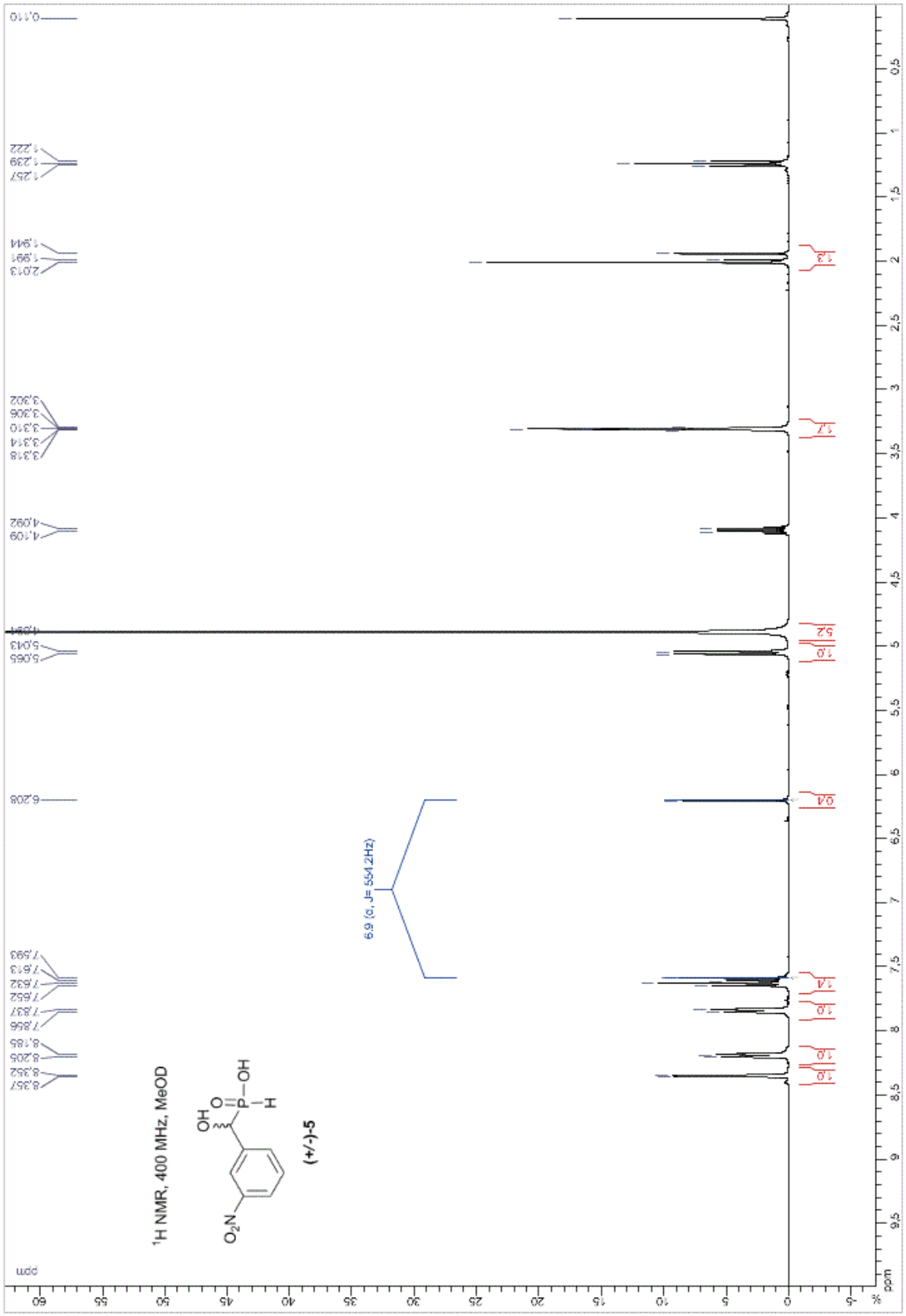

LSP1-2111
^{1}H NMR, 500 MHz, D_2O
ppm

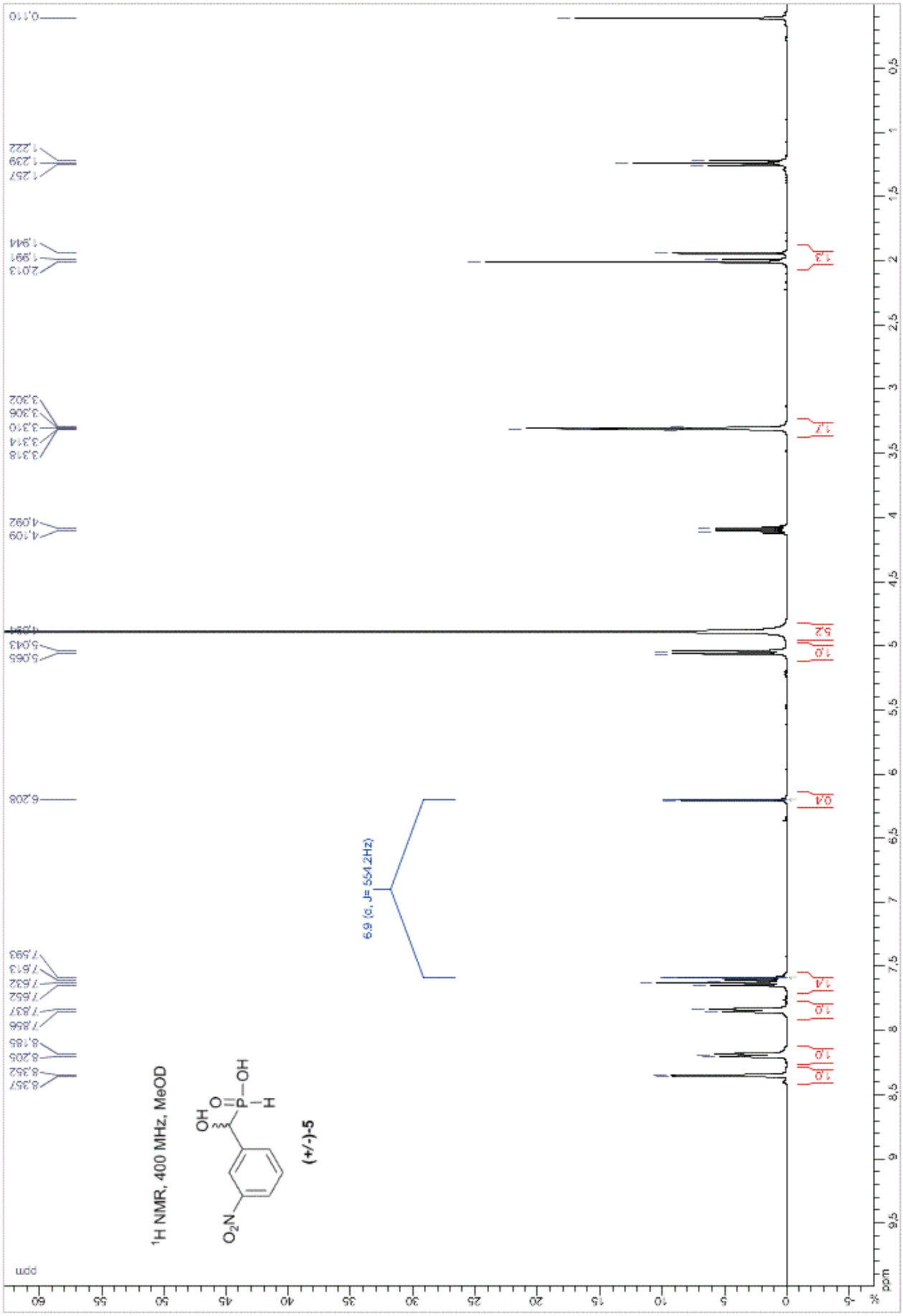

ppm
42.419
^{31}P NMR, 202 MHz, D_2O
OH
O
NH_2
O_2N
P
CO_2H
HO
OH
OMe
LSP1-2111
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
%
ppm
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

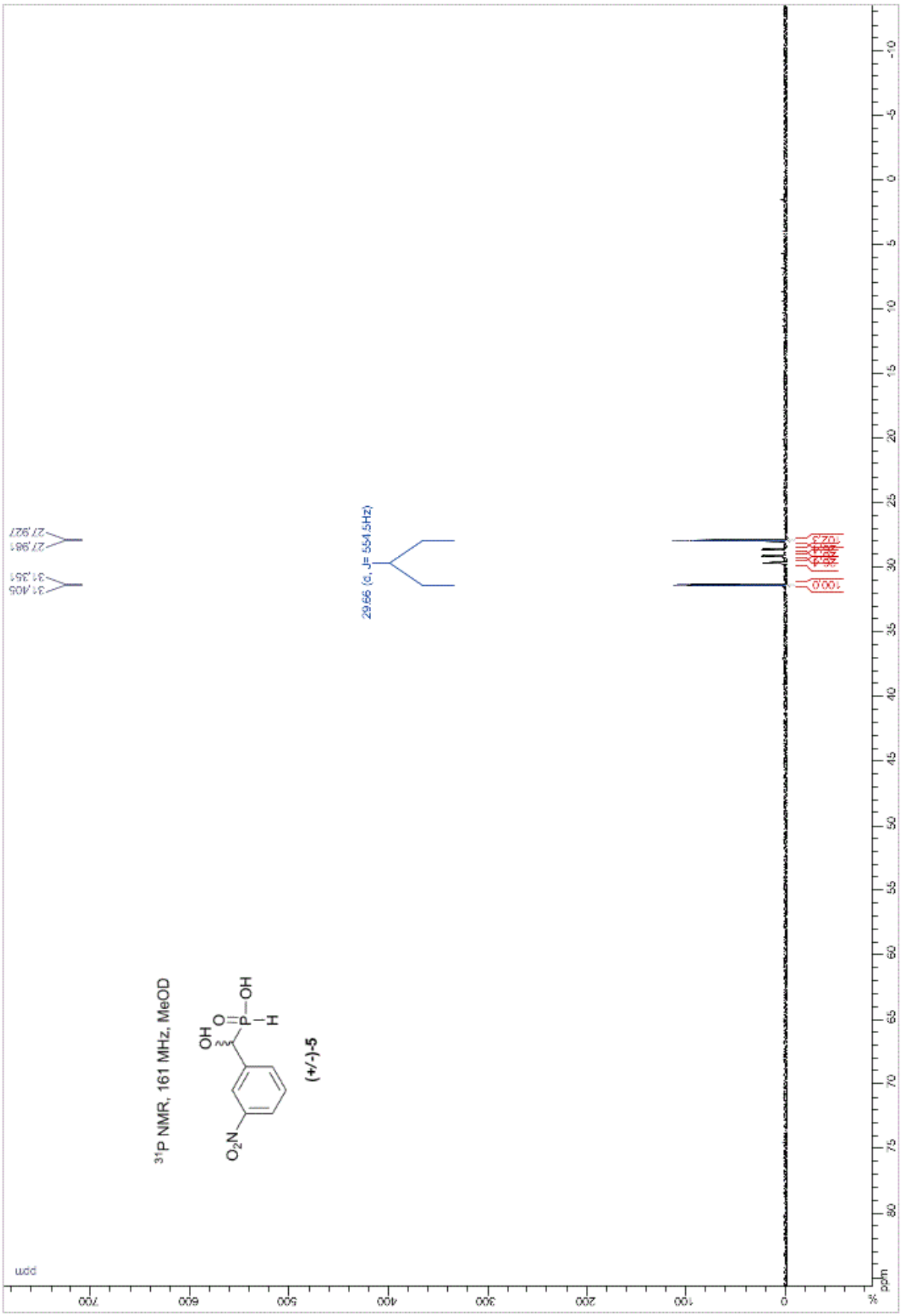

LSP1-2111
^{13}C NMR, 125 MHz, D_2O
ppm
6.137
21.172
21.255
21.880
21.963
22.739
22.887
53.047
53.166
56.527
56.650
70.594
71.465
114.088
114.131
114.178
115.976
116.233
128.570
133.874
143.674
149.028
171.313

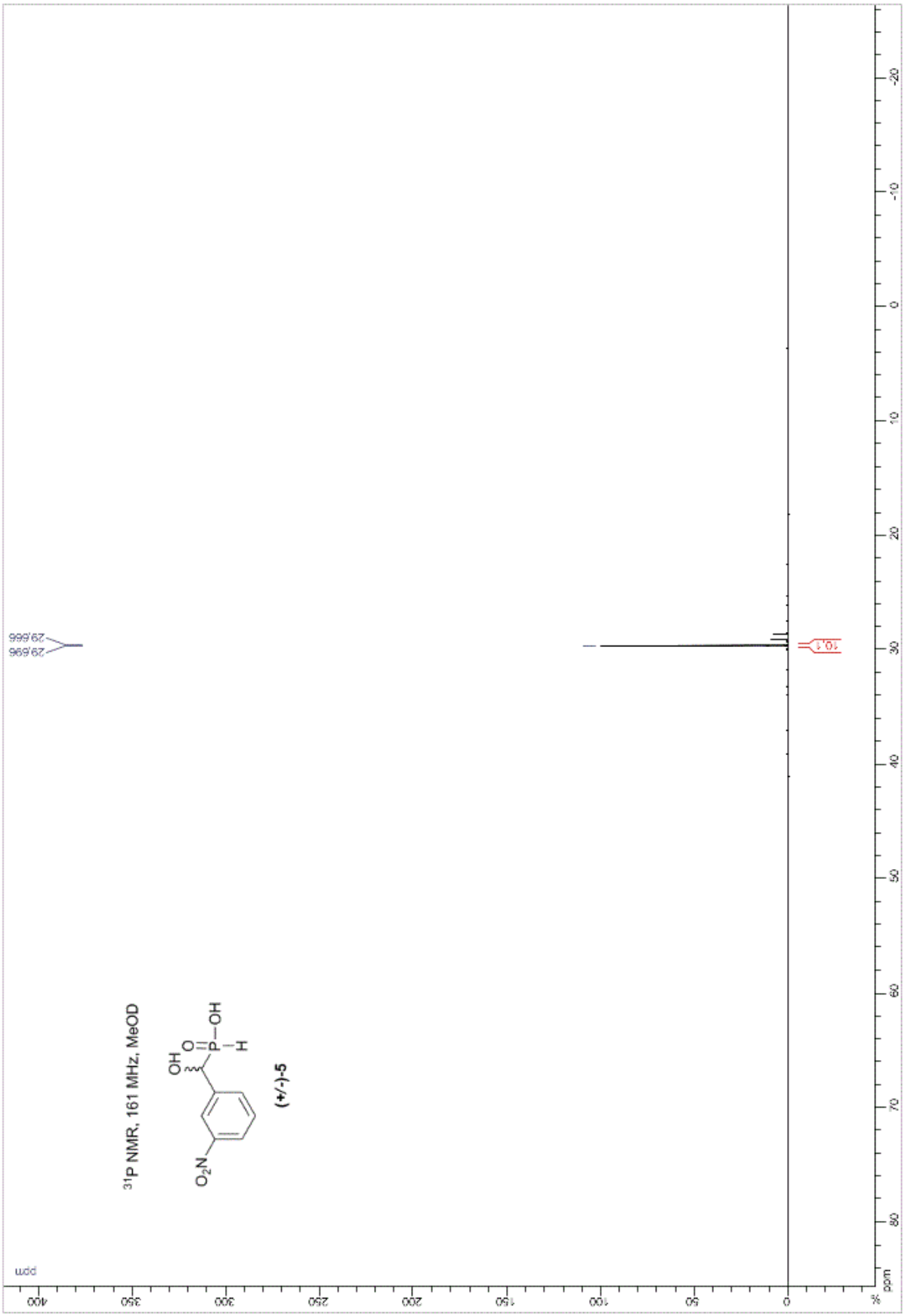

LSP1-2111 Dia I
^{1}H NMR, 500 MHz, DMSO
ppm
7,494
7,324
4,827
4,809
3,980
3,862
2,081
2,067
2,053
1,833
1,819
1,804
1,790
1,777
0,9
0,9
1,0
1,1
2,8
1,8
1,8

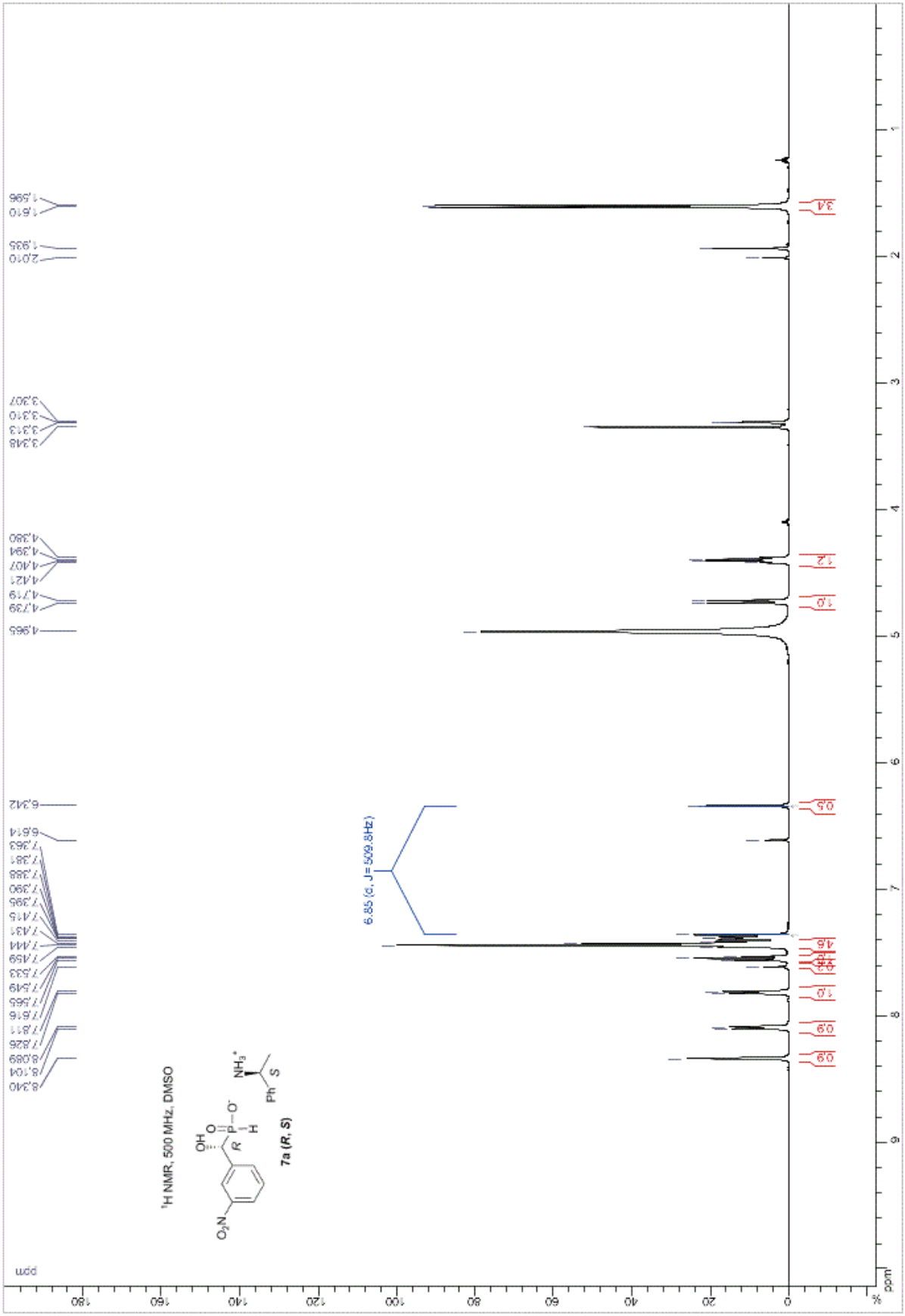

LSP1-2111 Dia II
1H NMR, 500 MHz, DMSO
7,459
7,327
4,834
4,817
3,980
3,862
2,064
1,906
1,716
ppm

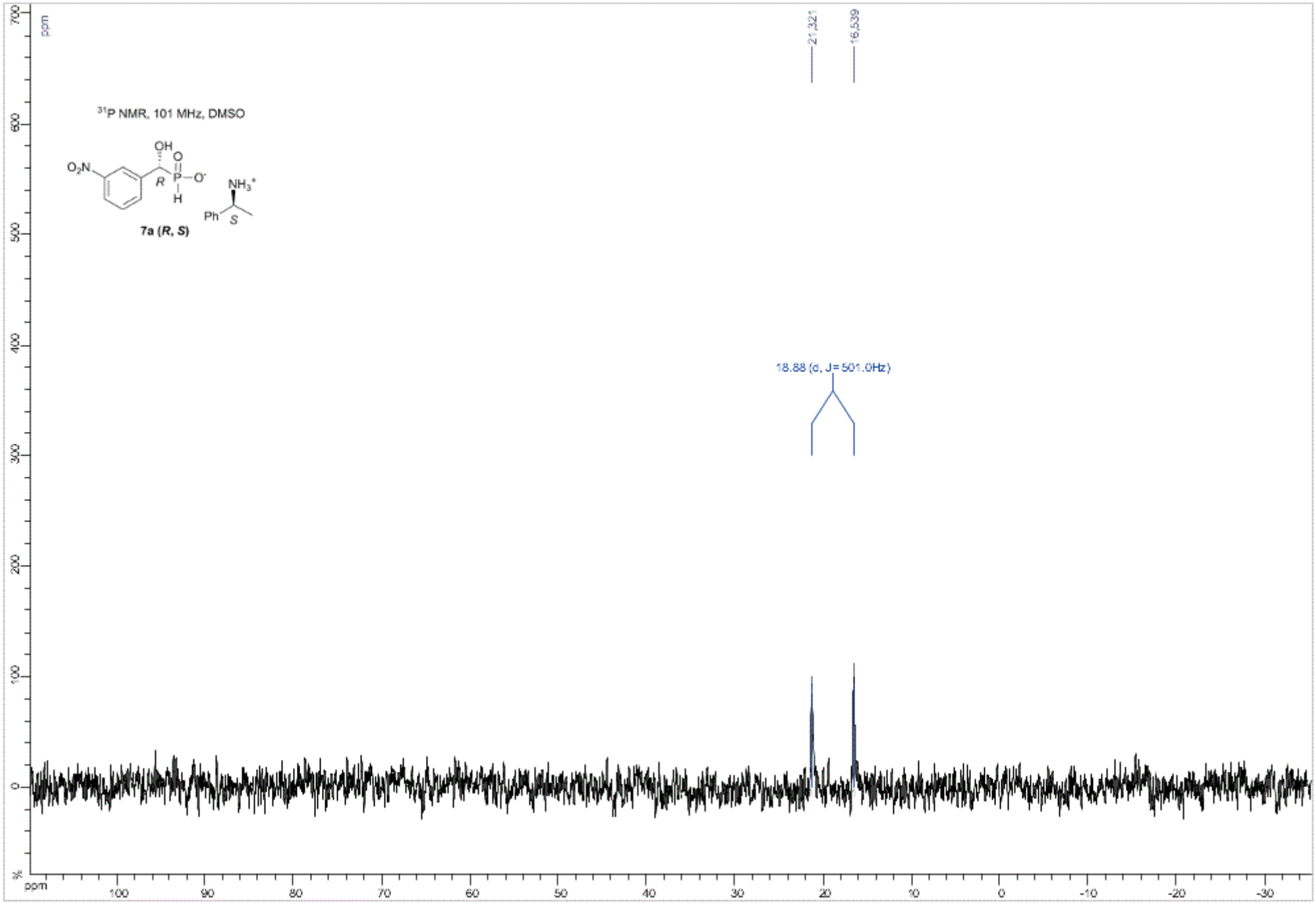

^{1}H NMR, 400 MHz, MeOD
(+/-)-5
6.9 (d, J= 554.2Hz)
ppm

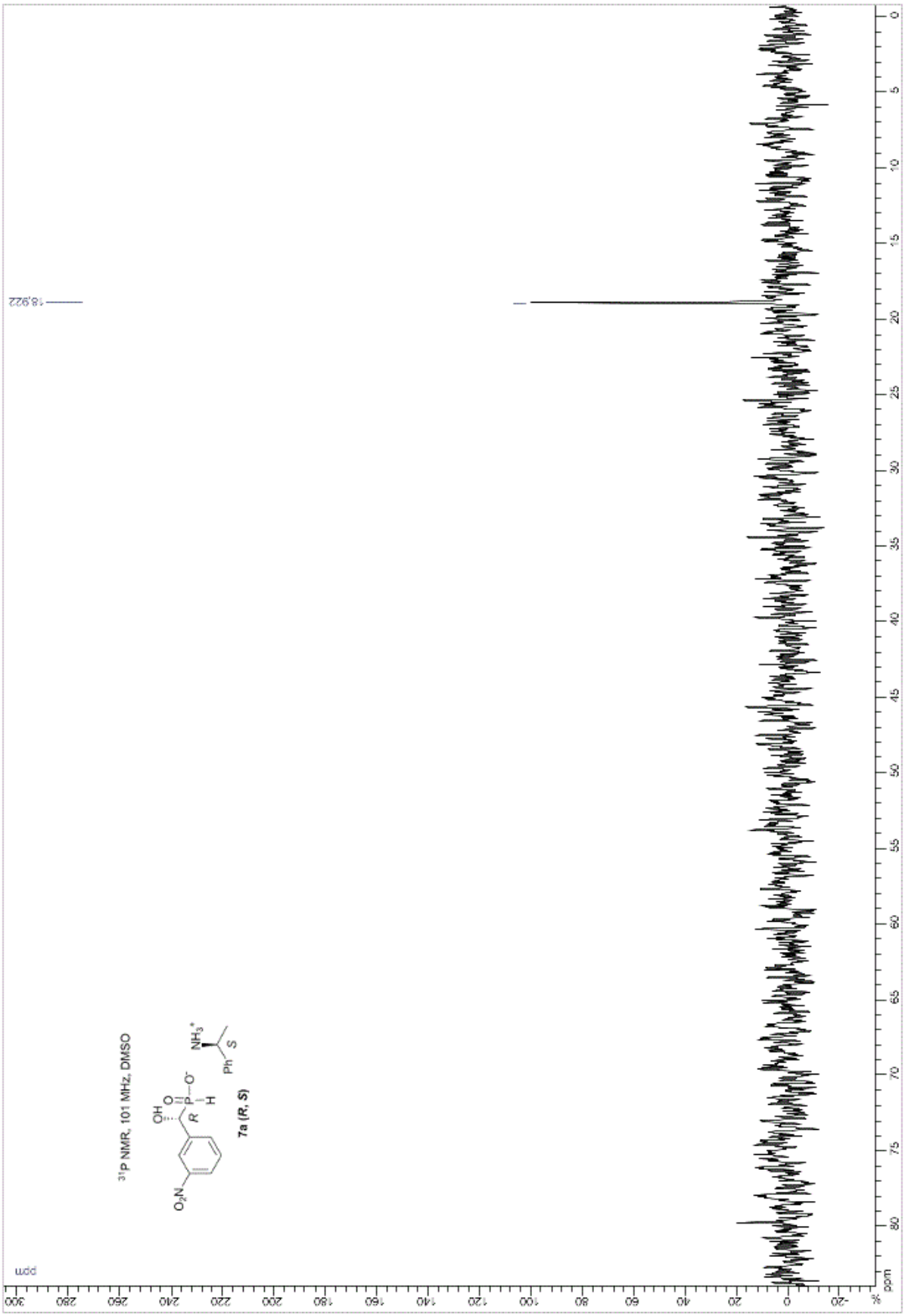

^{1}H NMR, 400 MHz, MeOD
(+/-)-5
6.9 (d, J= 554.2Hz)

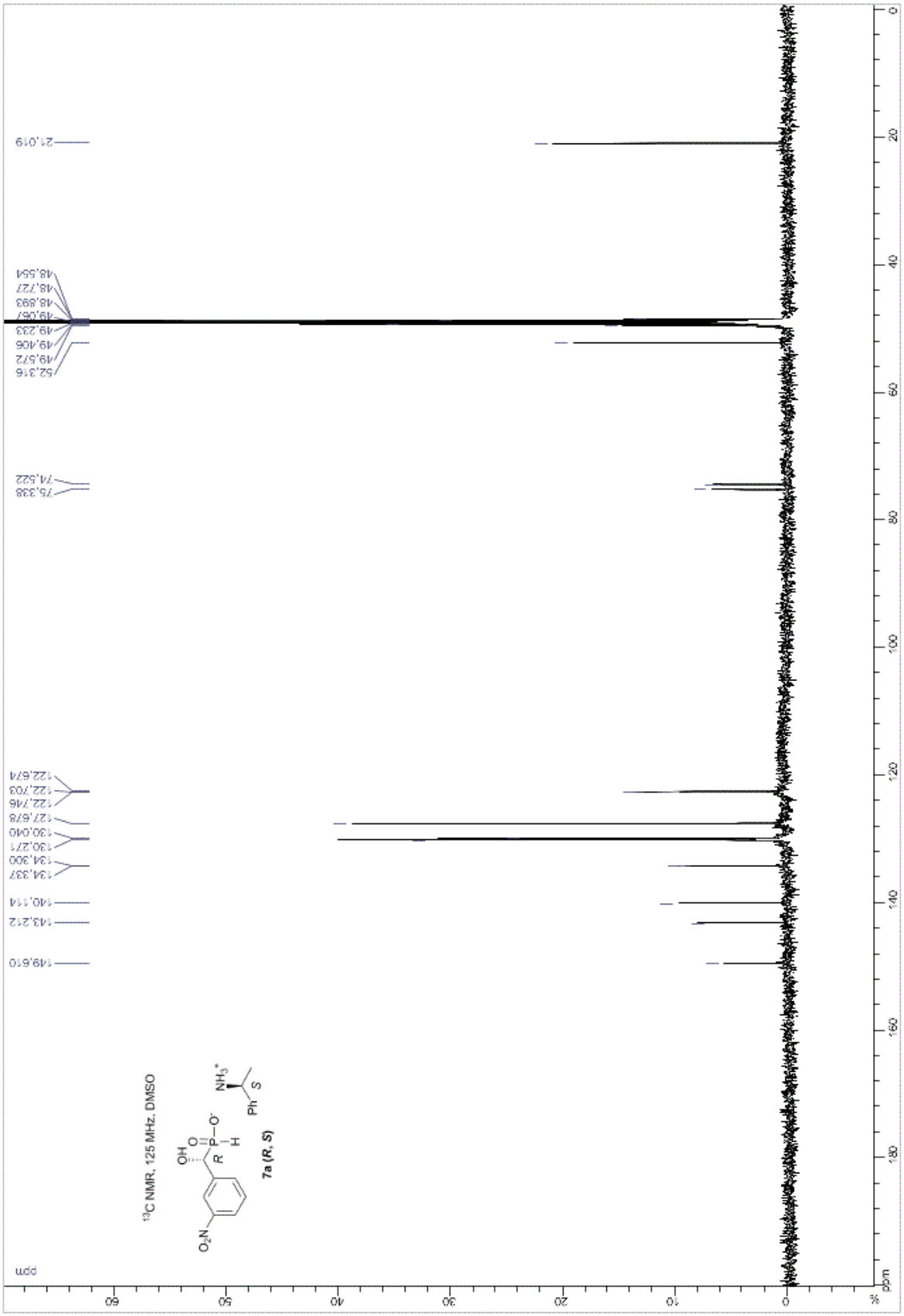

31.405
31.361
27.981
27.927
2966 (d, J= 554.5Hz)
1000
ppm
^{31}P NMR, 161 MHz, MeOD
(+/-)-5

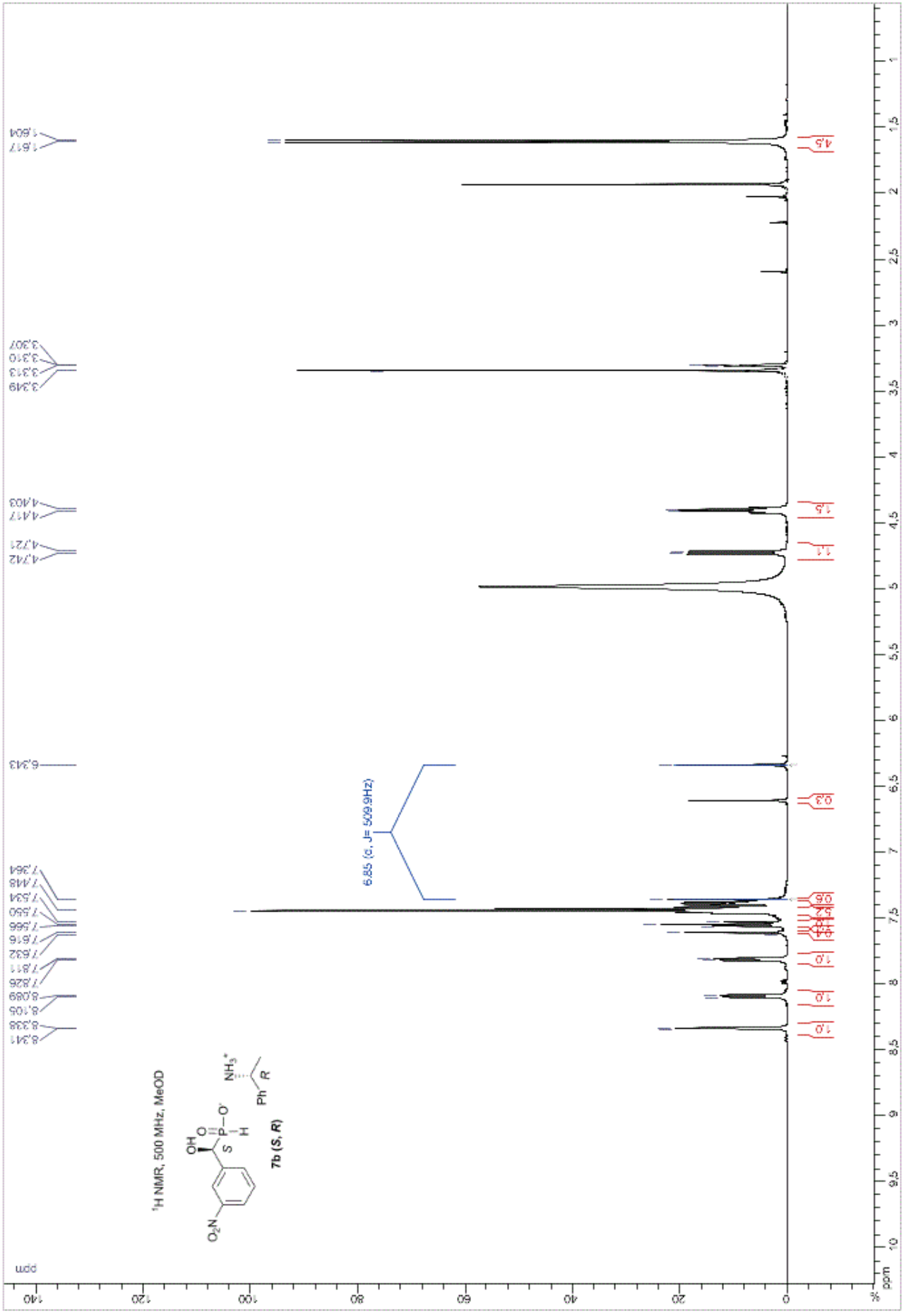

31P NMR, 161 MHz, MeOD
(+/-)-5
29,696
29,666
10,1
ppm

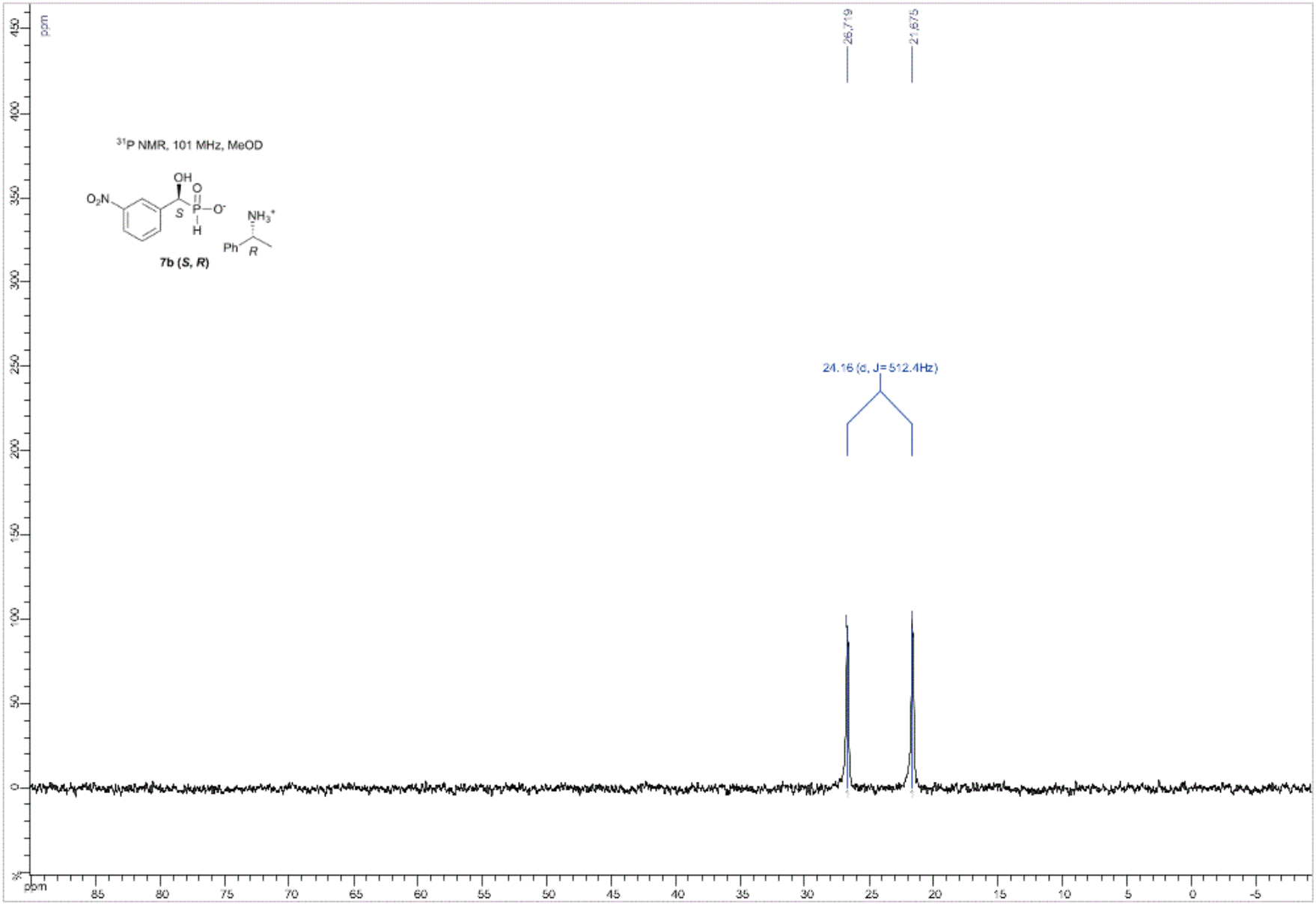

1H NMR, 500 MHz, DMSO
7a (R, S)
6.85 (d, J= 509.8Hz)
ppm

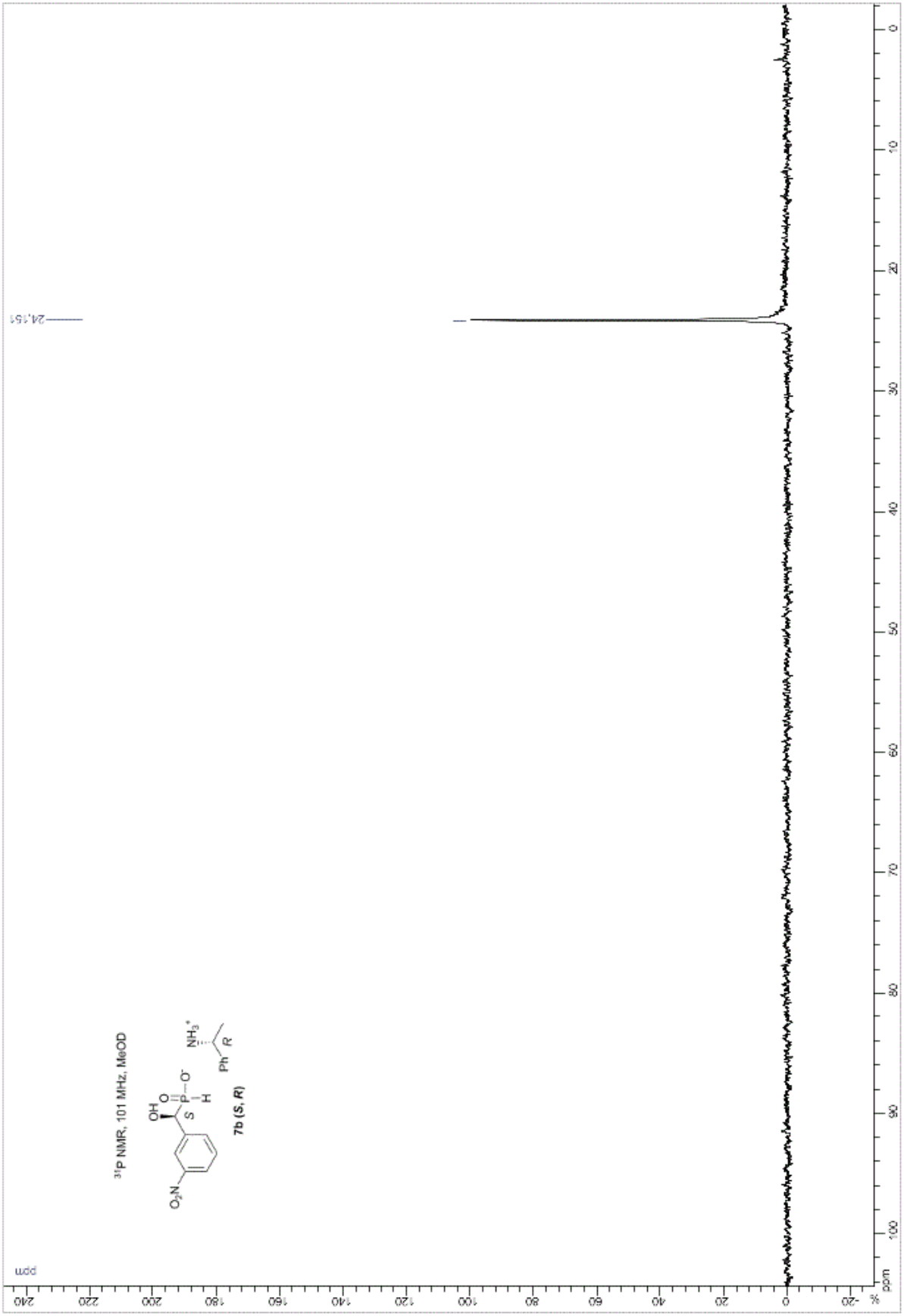

ppm
21,321
16,539
31P NMR, 101 MHz, DMSO
7a (R, S)
18.88 (d, J= 501.0Hz)
%
ppm
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30

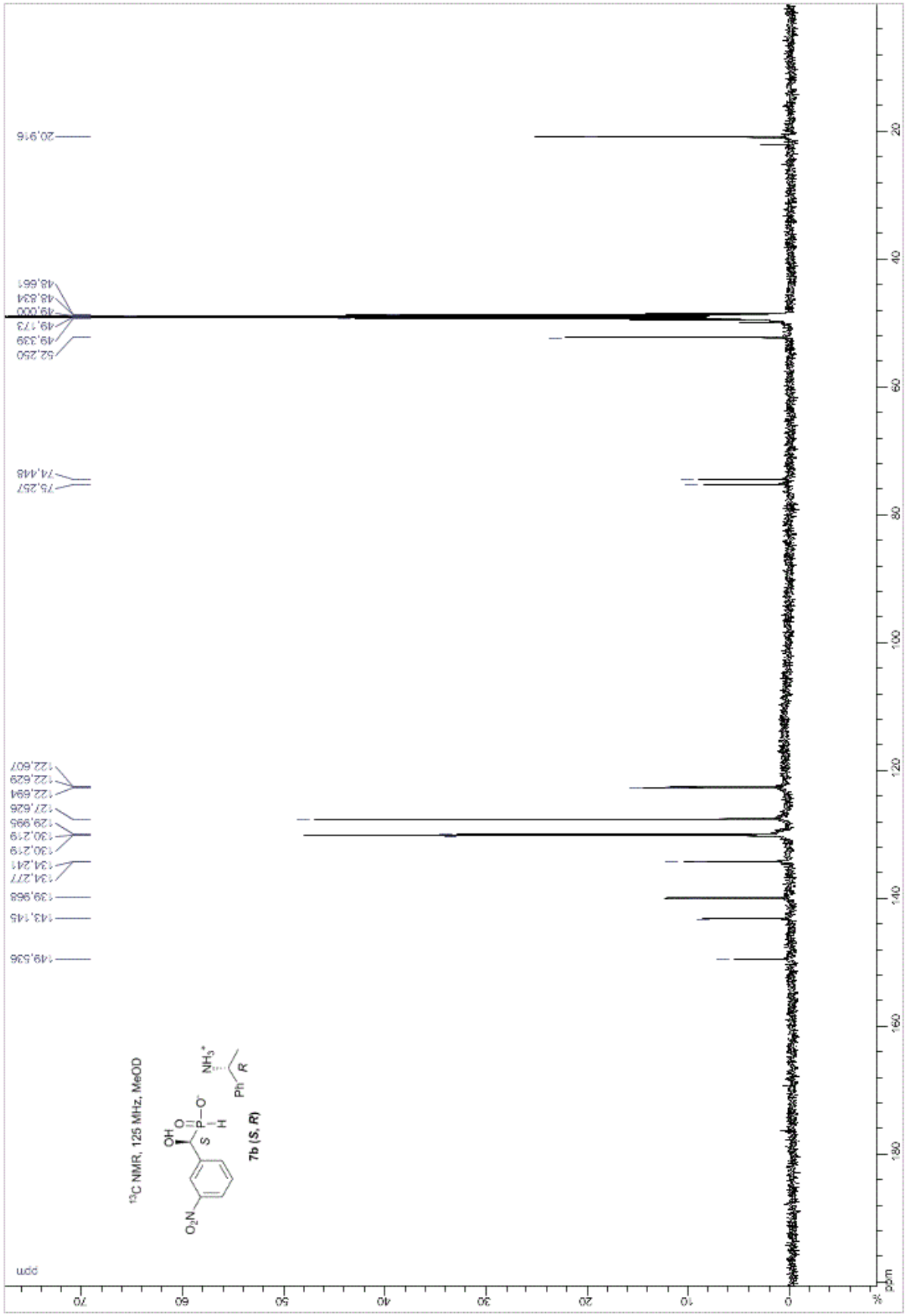

18.922
^{31}P NMR, 101 MHz, DMSO
7a (R, S)
ppm

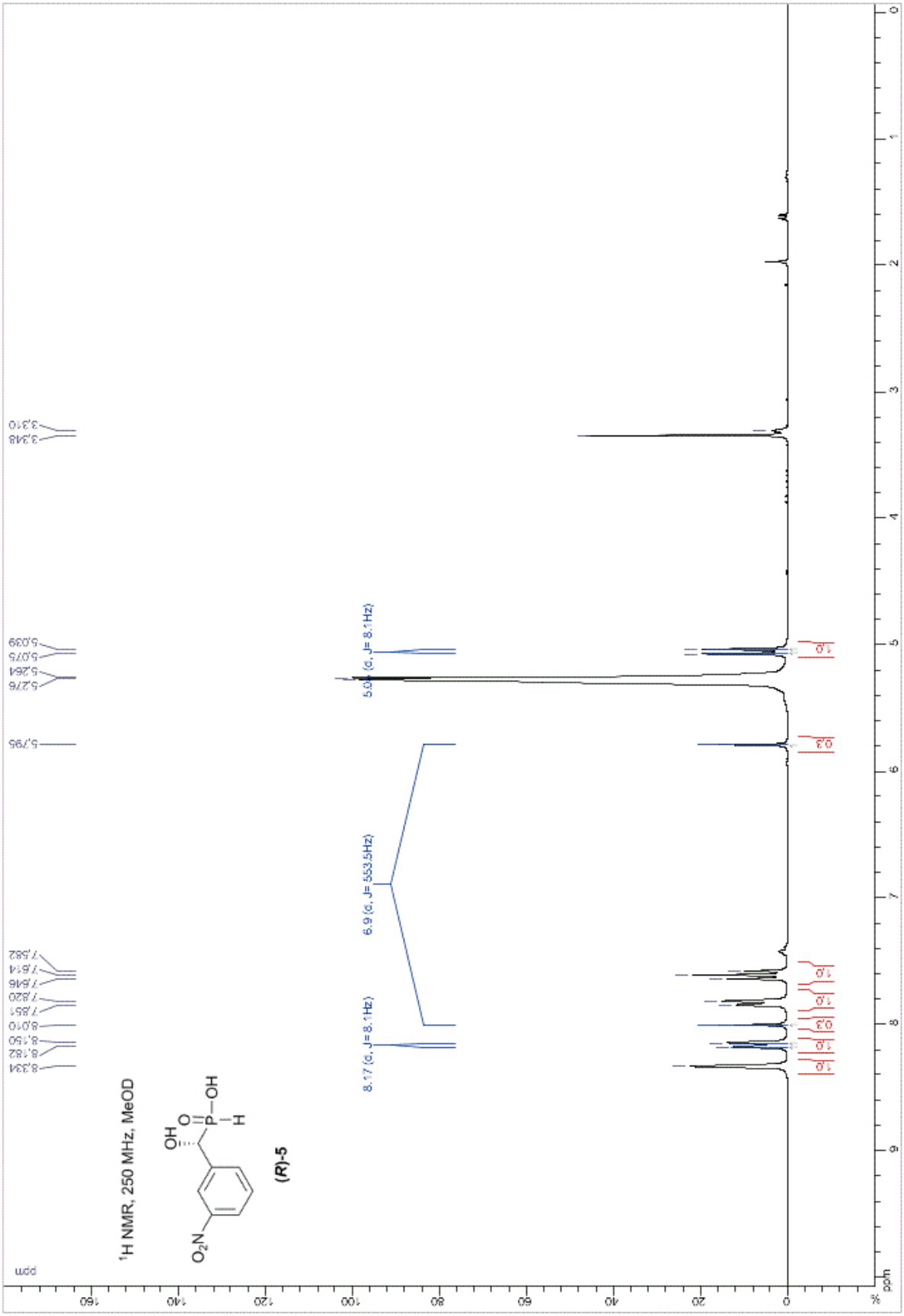

udd
^{13}C NMR, 125 MHz, DMSO
7a (R, S)
21,019
48,554
48,727
48,893
49,067
49,233
49,406
49,572
52,316
74,522
75,338
122,674
122,703
122,746
127,678
130,040
130,271
134,300
134,337
140,114
143,212
149,610
ppm

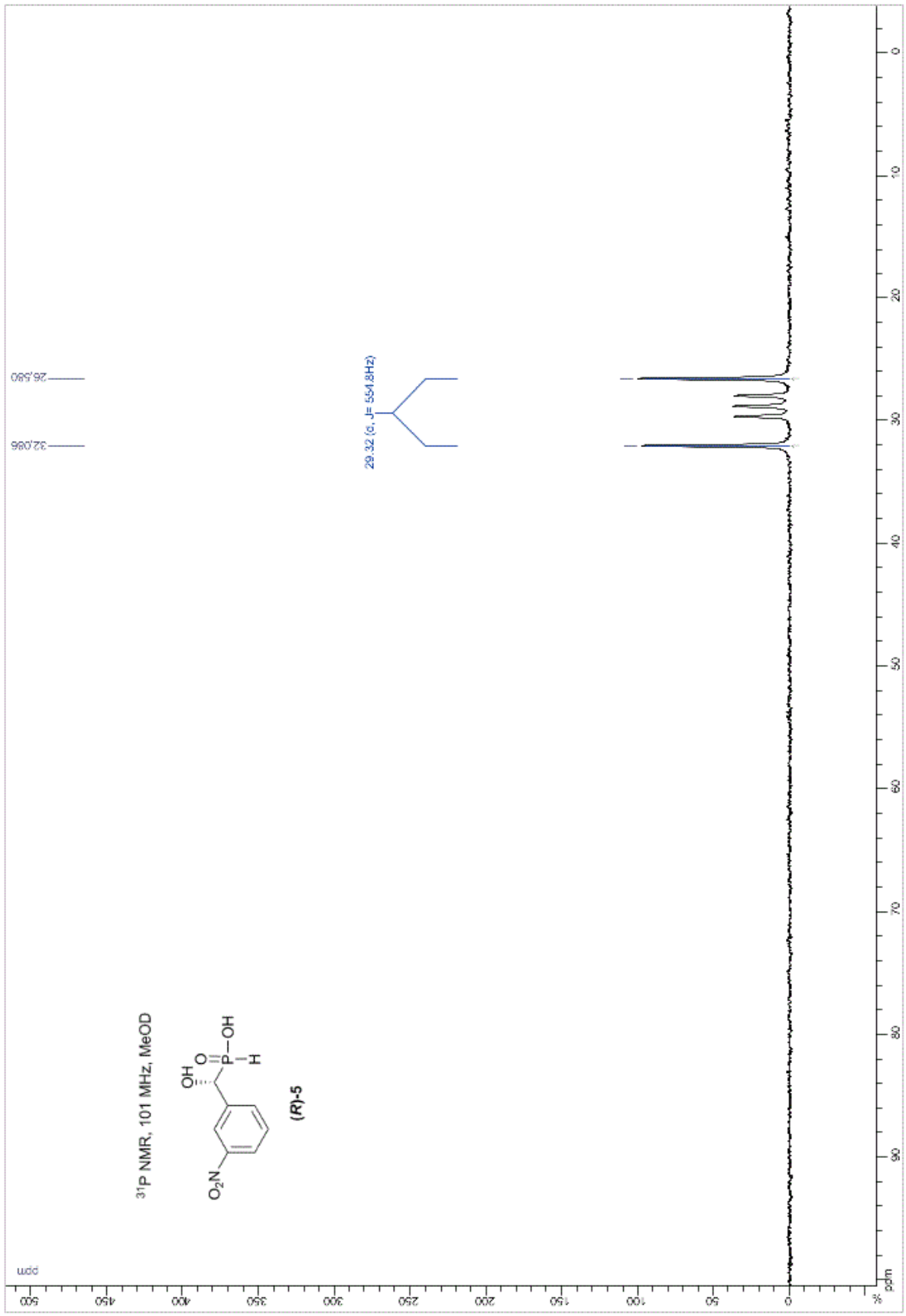

1H NMR, 500 MHz, MeOD
7b (S, R)
6.85 (d, J= 509.9Hz)
8.341
8.338
8.105
8.089
7.826
7.811
7.632
7.616
7.566
7.550
7.534
7.448
7.364
6.343
4.742
4.721
4.417
4.403
3.349
3.313
3.310
3.307
1.817
1.804
ppm

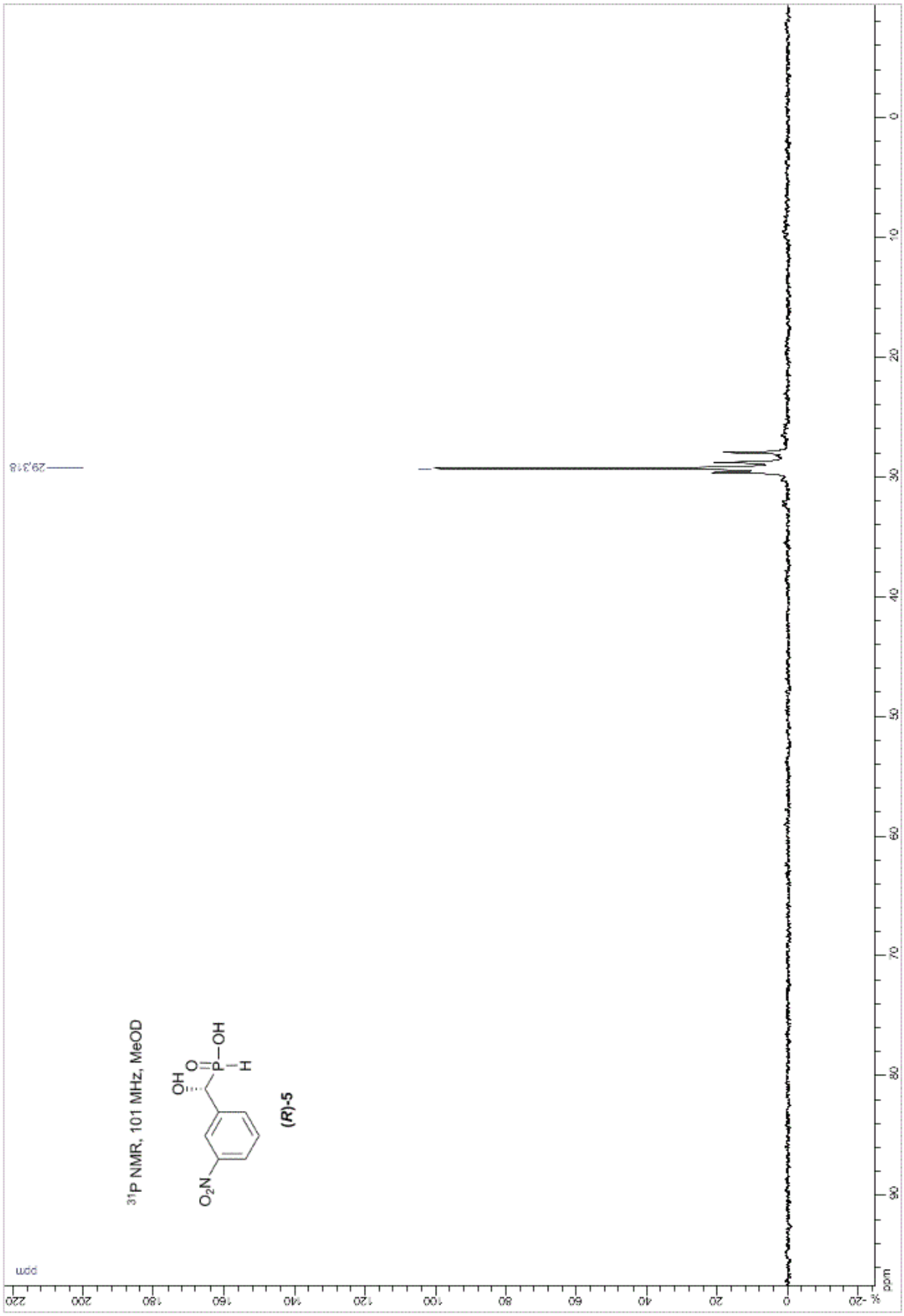

26.719
21.675
^{31}P NMR, 101 MHz, MeOD
7b (S, R)
24.16 (d, J= 512.4Hz)
ppm

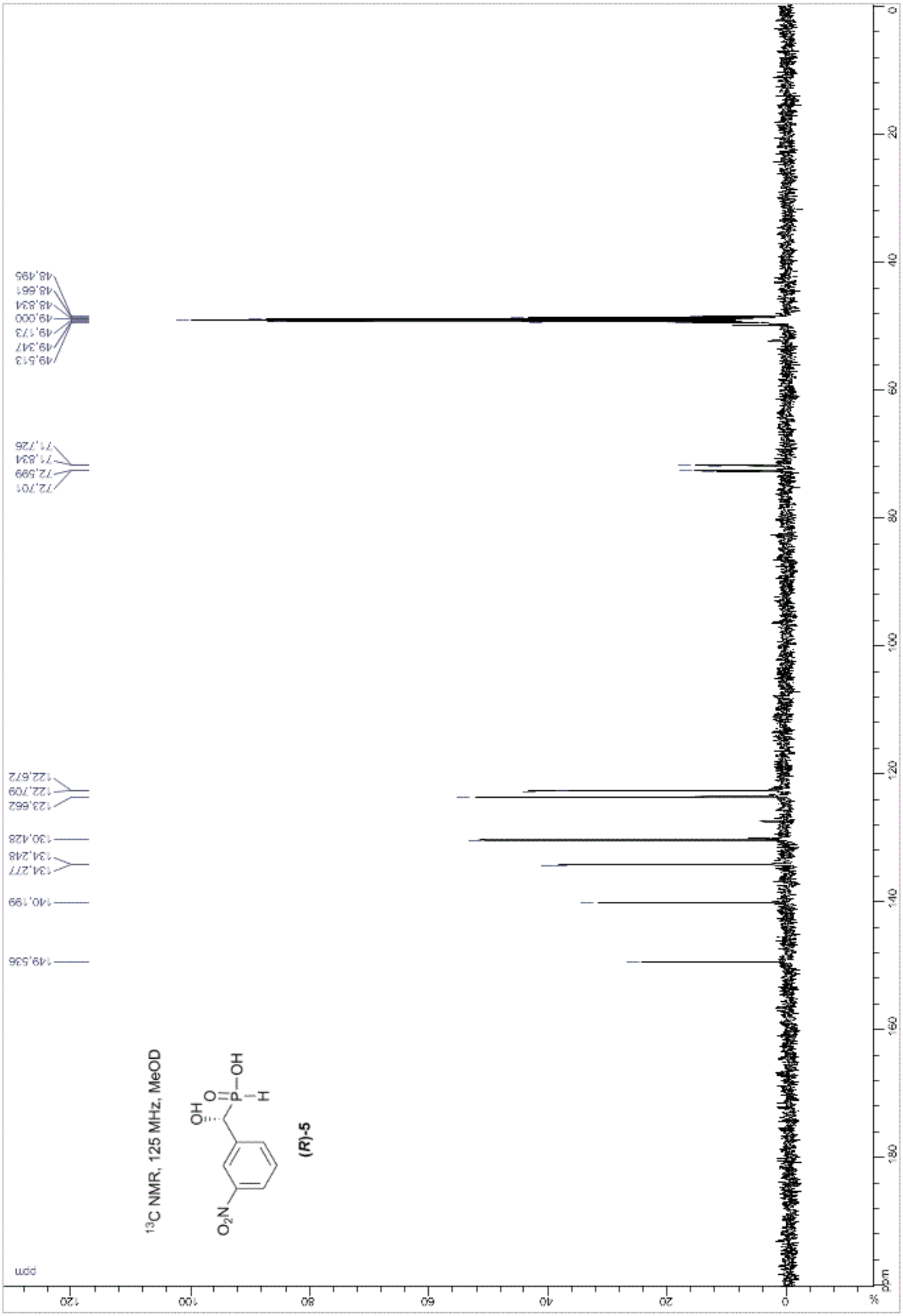

24,151
^{31}P NMR, 101 MHz, MeOD
7b (S, R)
ppm

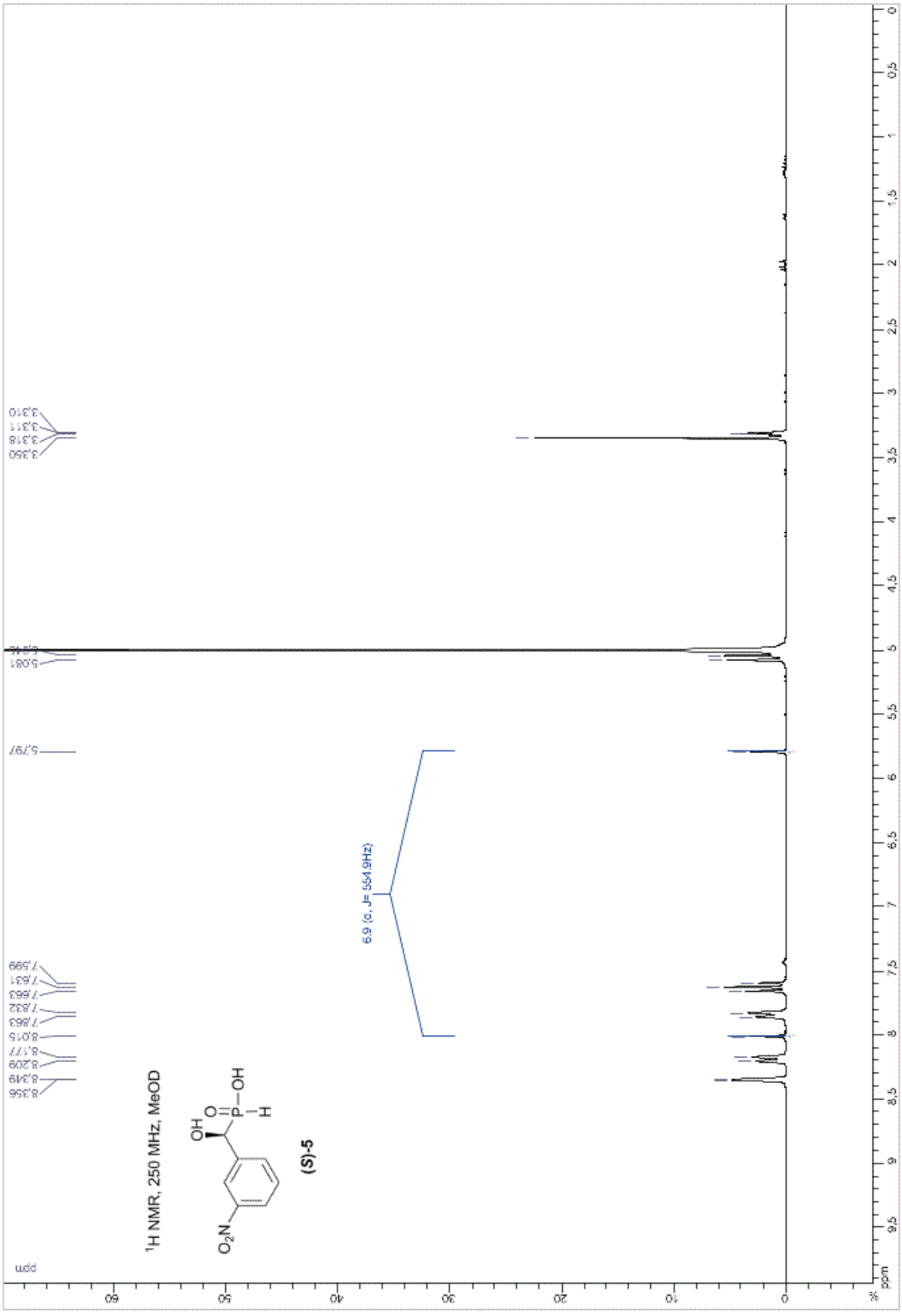

20,916
48,661
48,834
49,000
49,173
49,339
52,260
74,448
75,257
122,607
122,629
122,694
127,626
129,995
130,219
130,219
134,241
134,277
139,968
143,145
149,536
ppm
^{13}C NMR, 125 MHz, MeOD
7b (S, R)

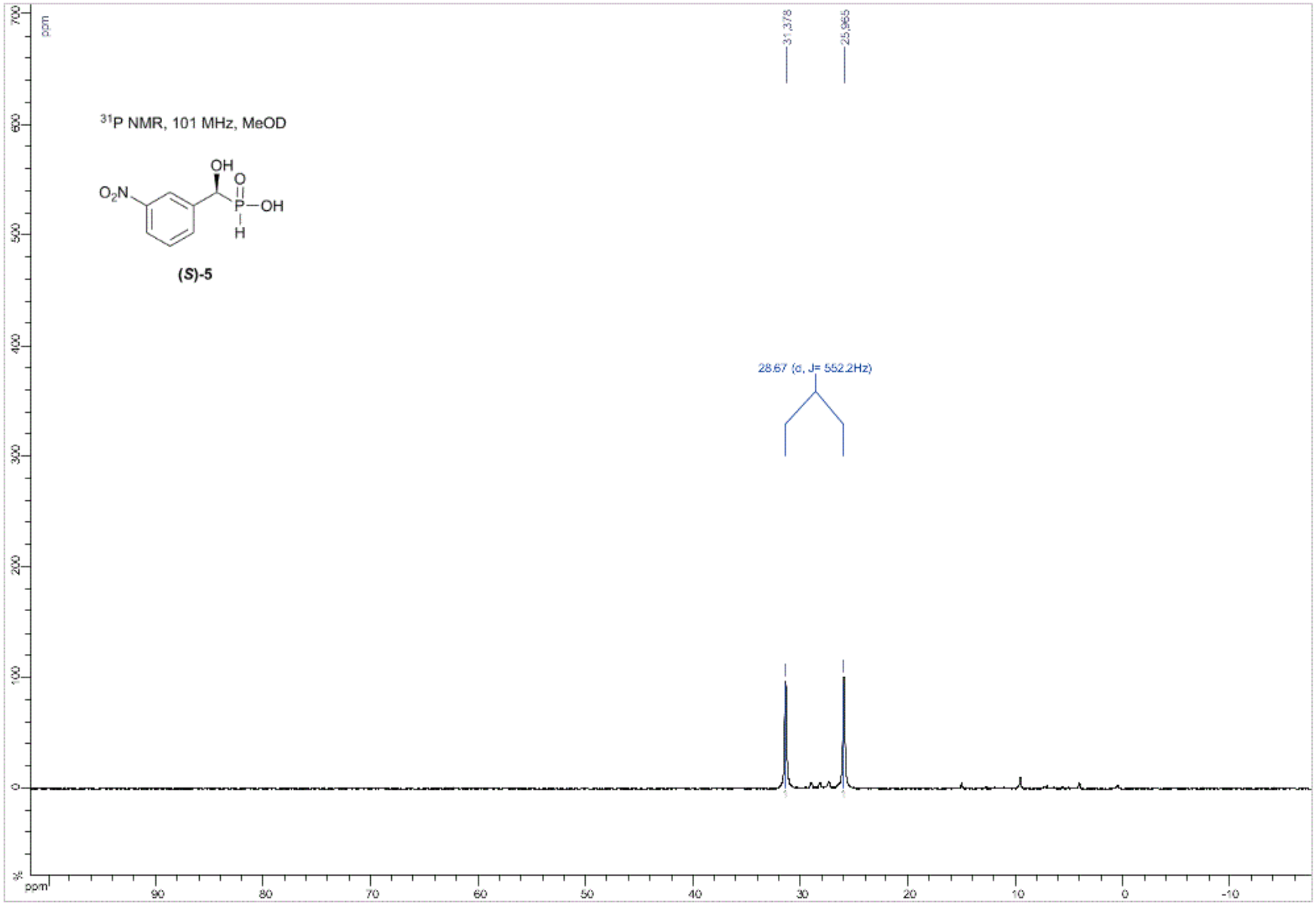

^{1}H NMR, 250 MHz, MeOD
(R)-5
8.334
8.182
8.160
8.010
7.851
7.820
7.646
7.614
7.582
5.795
5.276
5.264
5.075
5.039
3.348
3.310
8.17 (d, J= 8.1Hz)
6.9 (d, J= 553.5Hz)
5.04 (d, J= 8.1Hz)
ppm

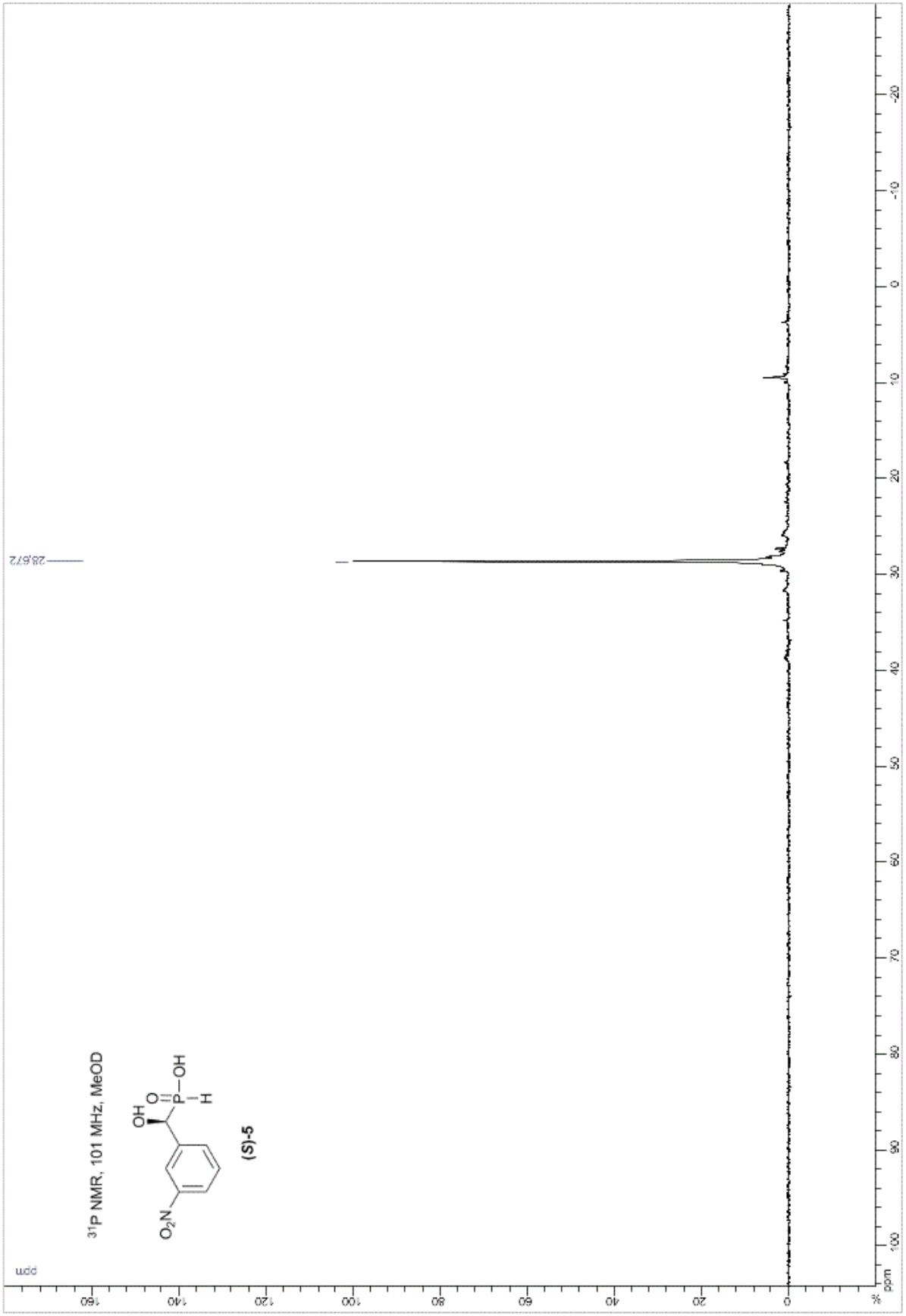

32.086
26.580
29.32 (d, J= 554.8Hz)
^{31}P NMR, 101 MHz, MeOD
(R)-5
ppm

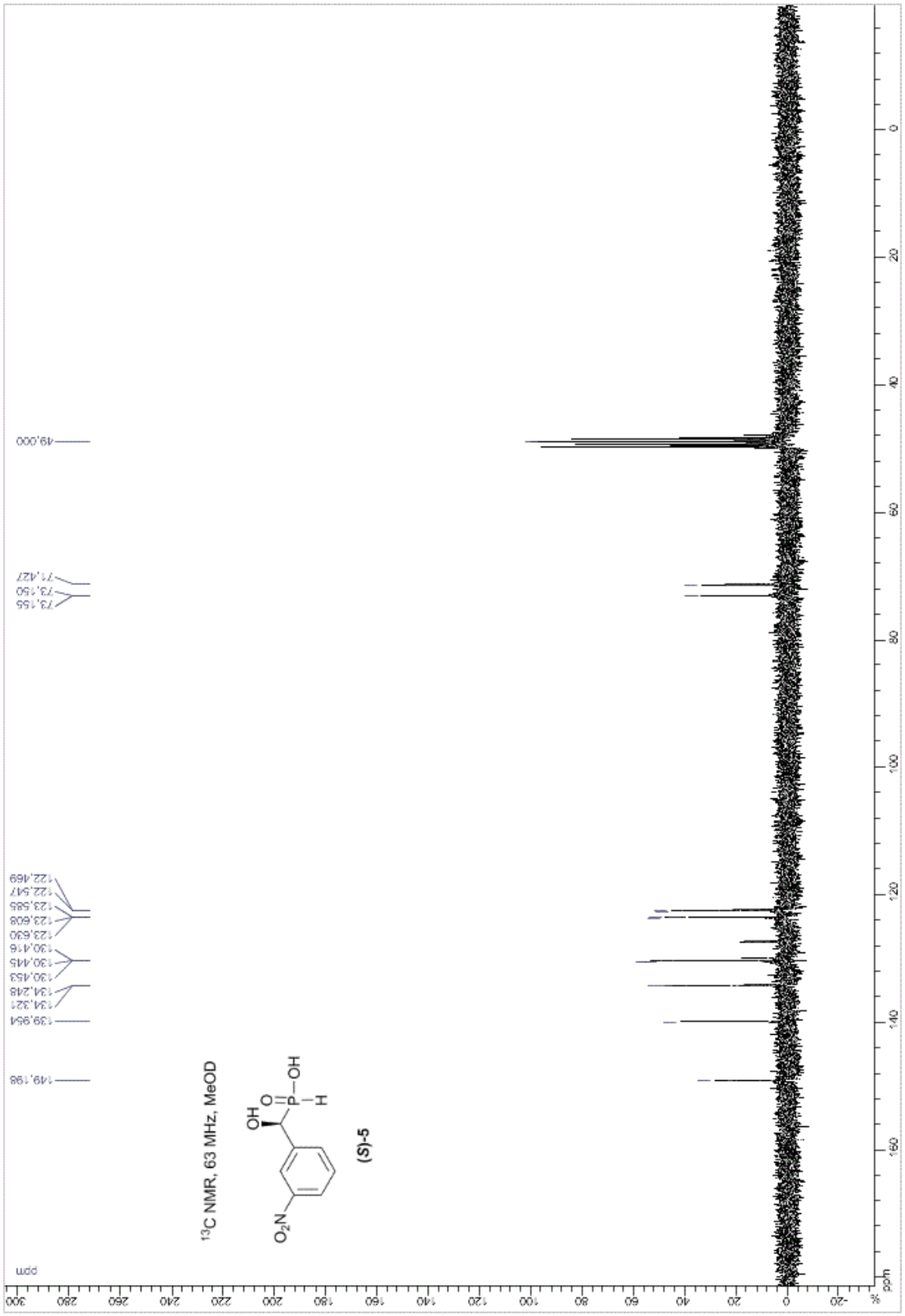

^{31}P NMR, 101 MHz, MeOD
(R)-5
29.318
ppm

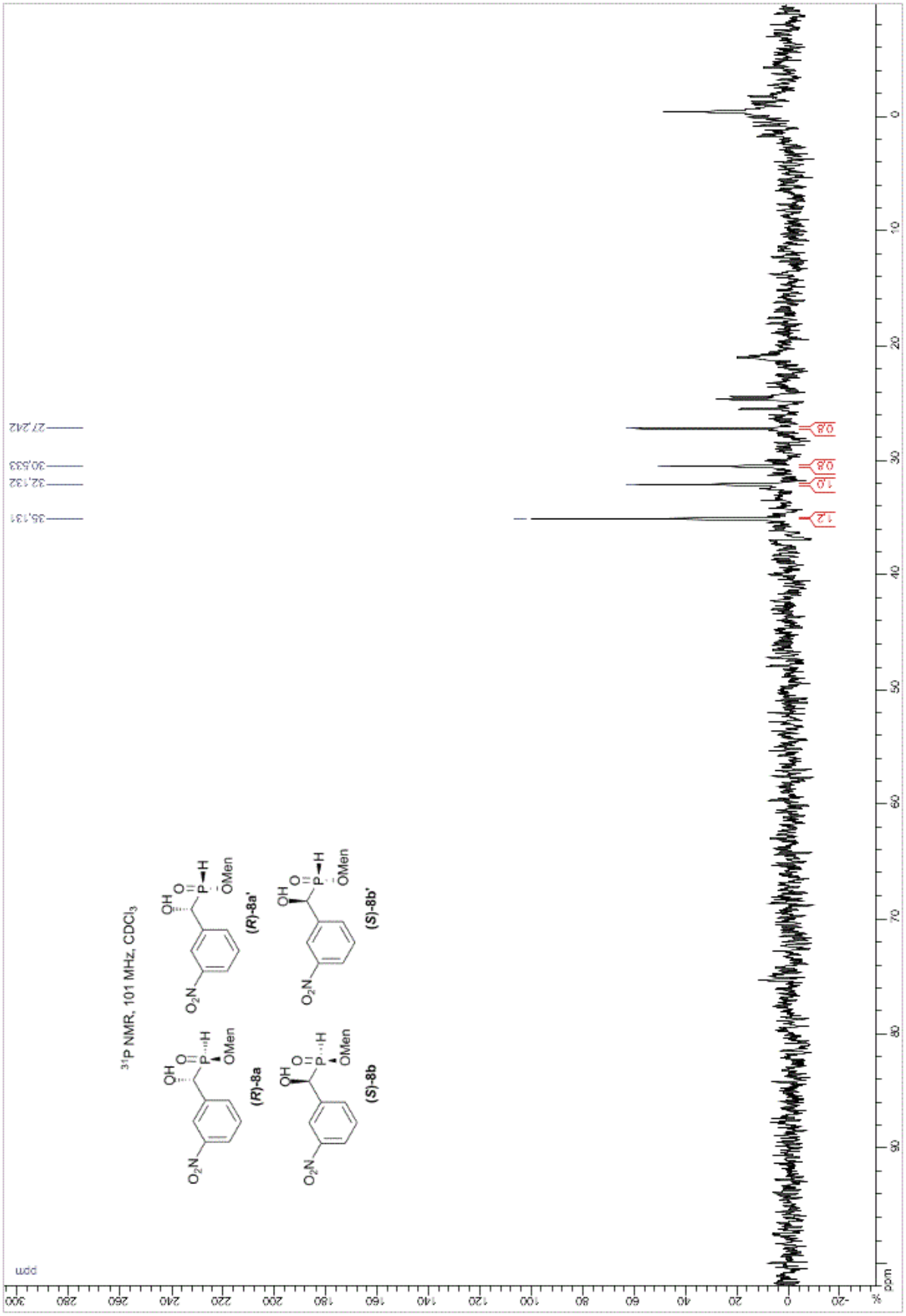

^{13}C NMR, 125 MHz, MeOD
(R)-5
149,536
140,199
134,277
134,248
130,428
123,662
122,709
122,672
72,701
72,599
71,834
71,726
49,513
49,347
49,173
49,000
48,834
48,661
48,496
ppm

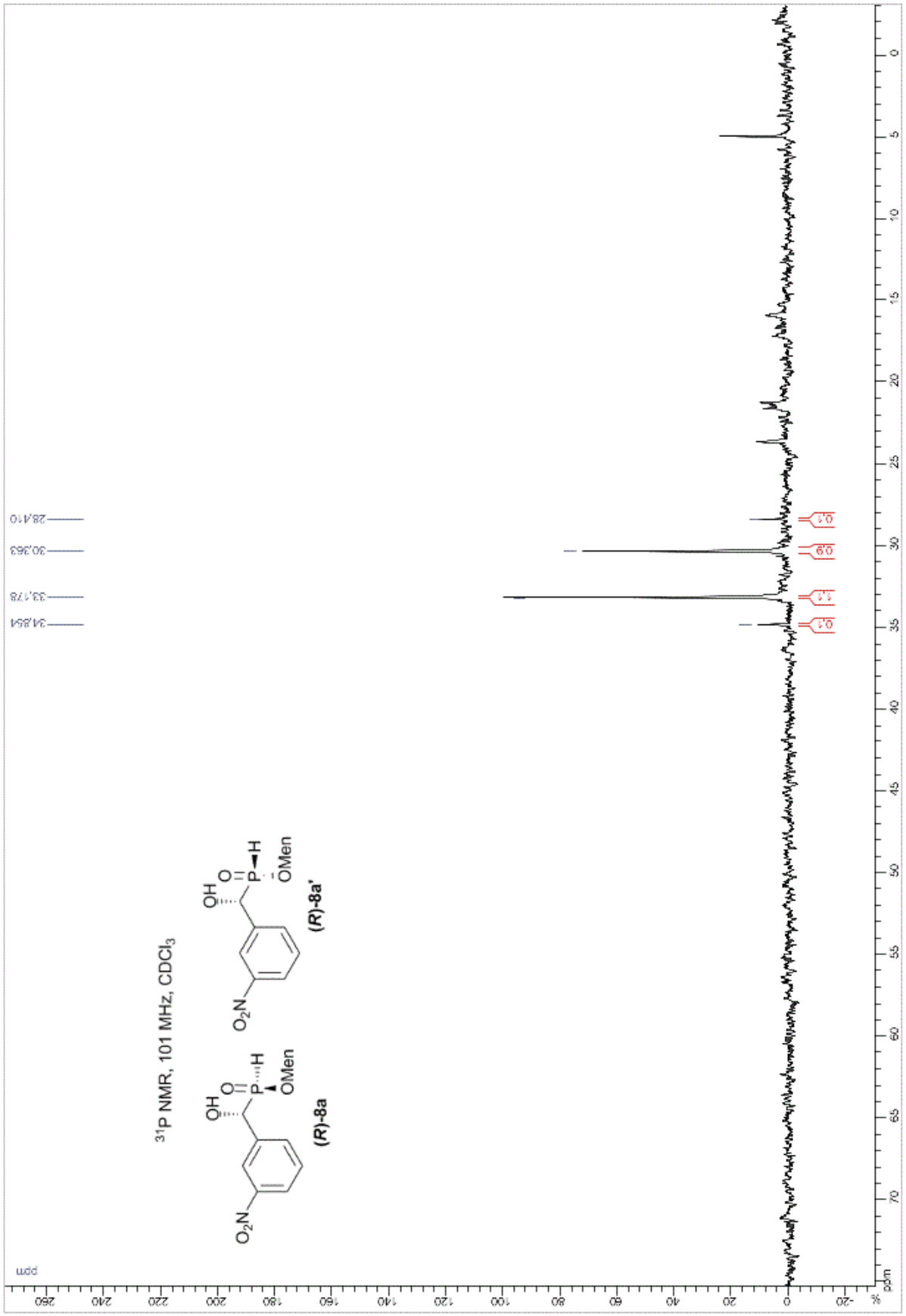

udd
ppm
^{1}H NMR, 250 MHz, MeOD
(S)-5
6.9 (d, J= 554.9Hz)
8.356
8.349
8.209
8.177
8.015
7.863
7.832
7.663
7.631
7.599
5.797
5.081
3.350
3.318
3.311
3.310

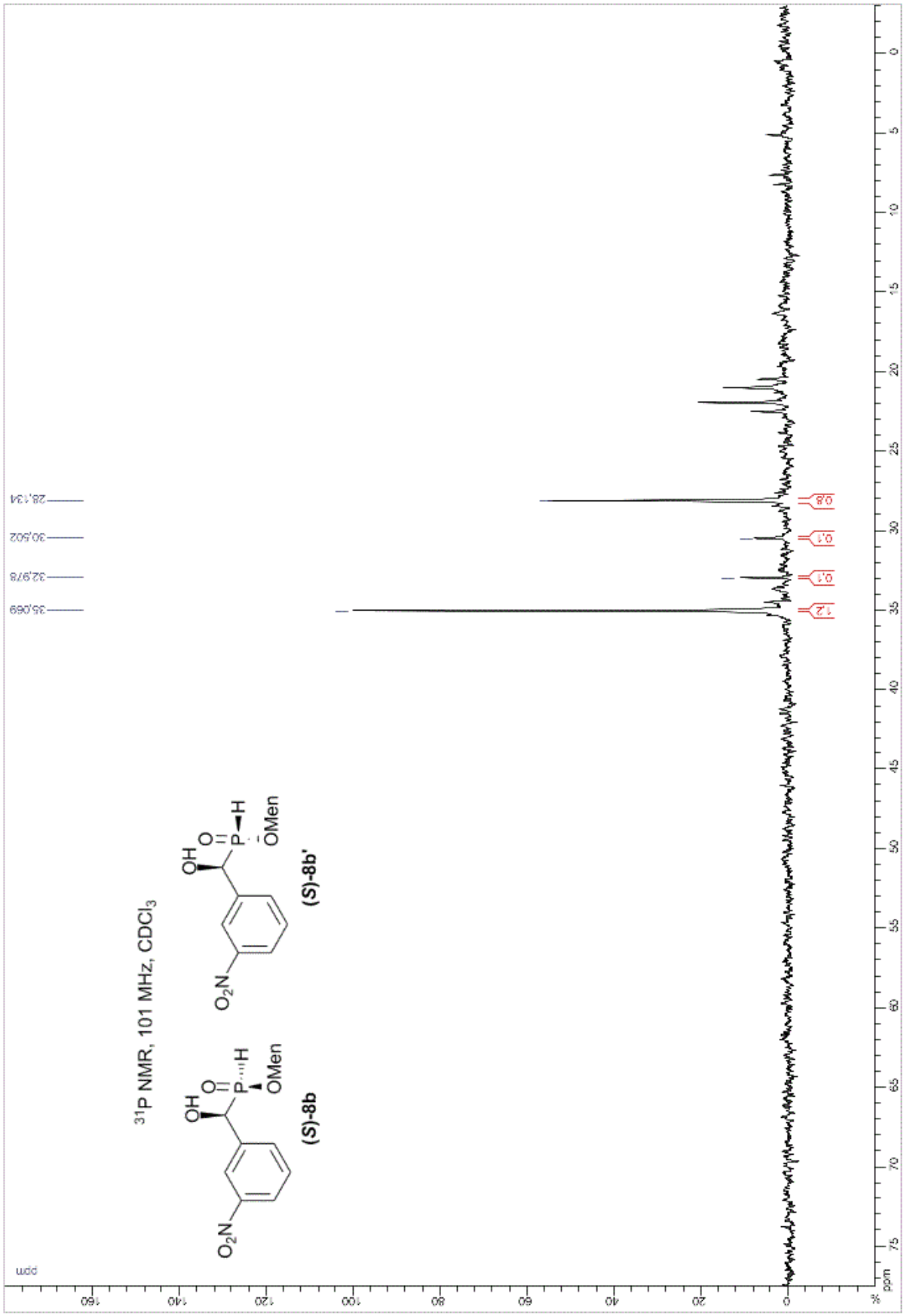

31.378
25.965
^{31}P NMR, 101 MHz, MeOD
OH
O
O_2N
P—OH
H
(S)-5
28.67 (d, J= 552.2Hz)
ppm
700
600
500
400
300
200
100
0
%
ppm
90
80
70
60
50
40
30
20
10
0
-10

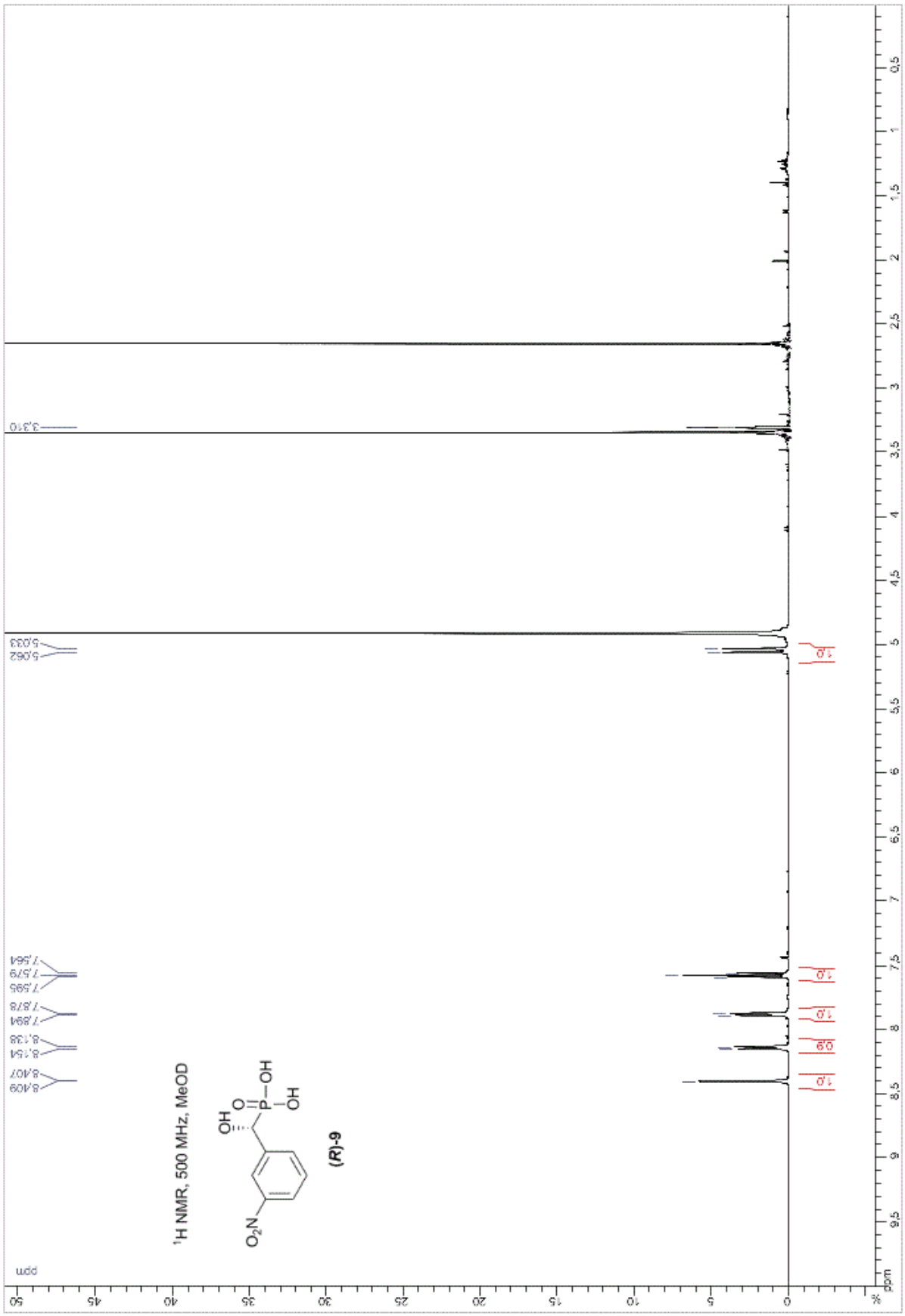

28.572
^{31}P NMR, 101 MHz, MeOD
(S)-5
ppm

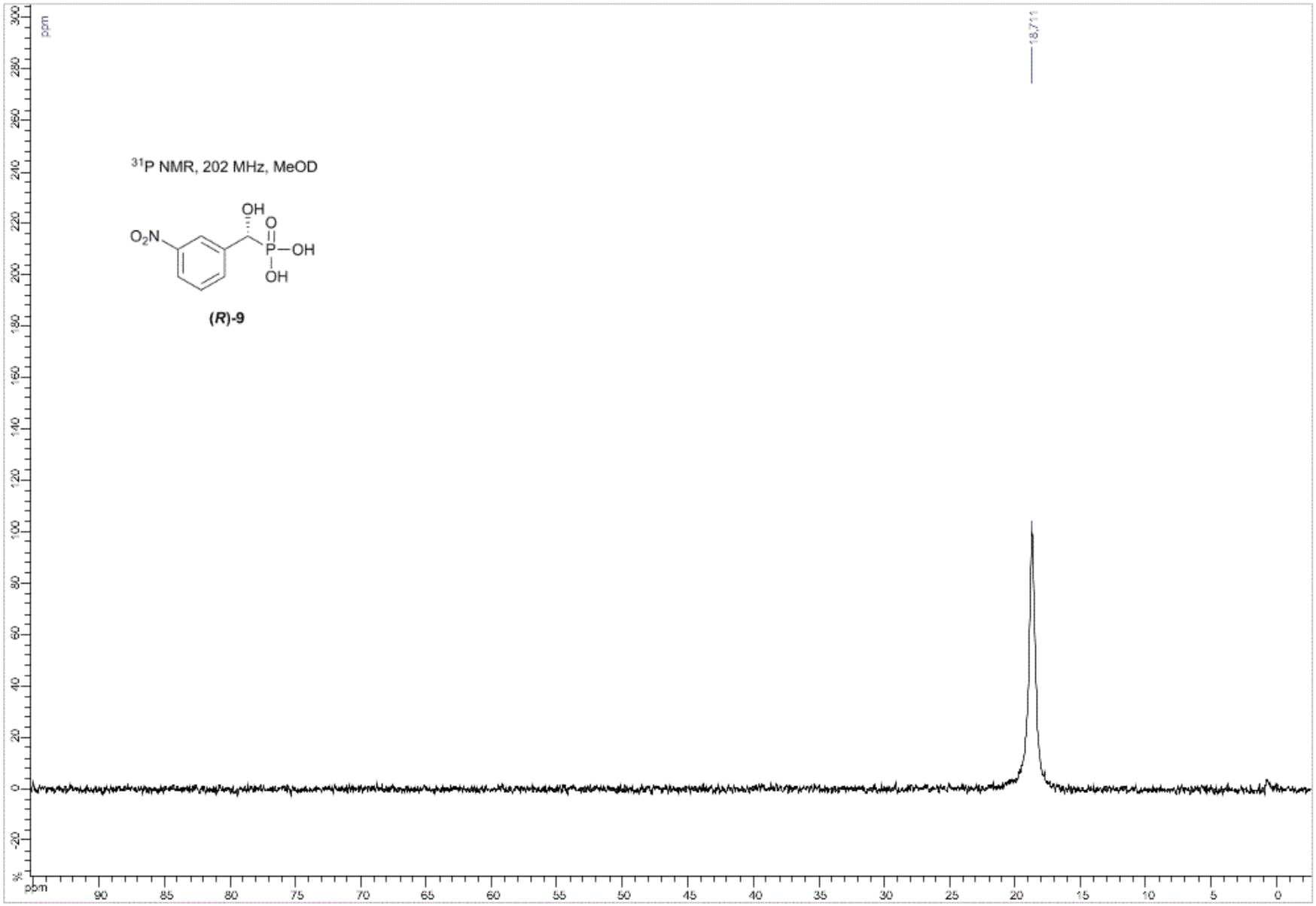

^{13}C NMR, 63 MHz, MeOD
(S)-5
149,198
139,954
134,321
134,248
130,453
130,445
130,416
123,630
123,608
123,585
122,547
122,469
73,555
73,150
71,427
49,000
ppm

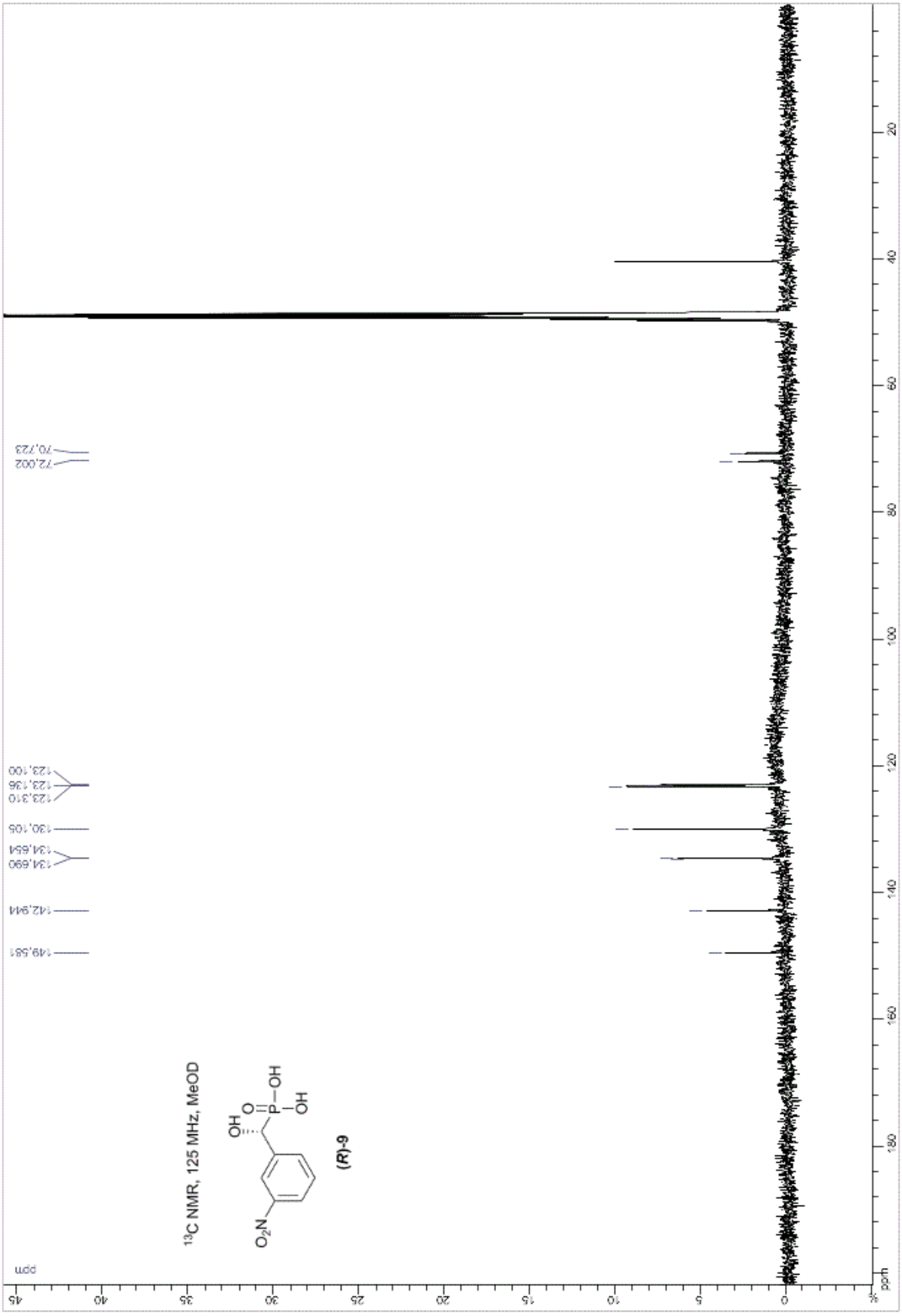

31P NMR, 101 MHz, CDCl3
(R)-8a
(R)-8a'
(S)-8b
(S)-8b'
ppm
35,131
32,132
30,533
27,242
1,2
1,0
0,8
0,8
0,8

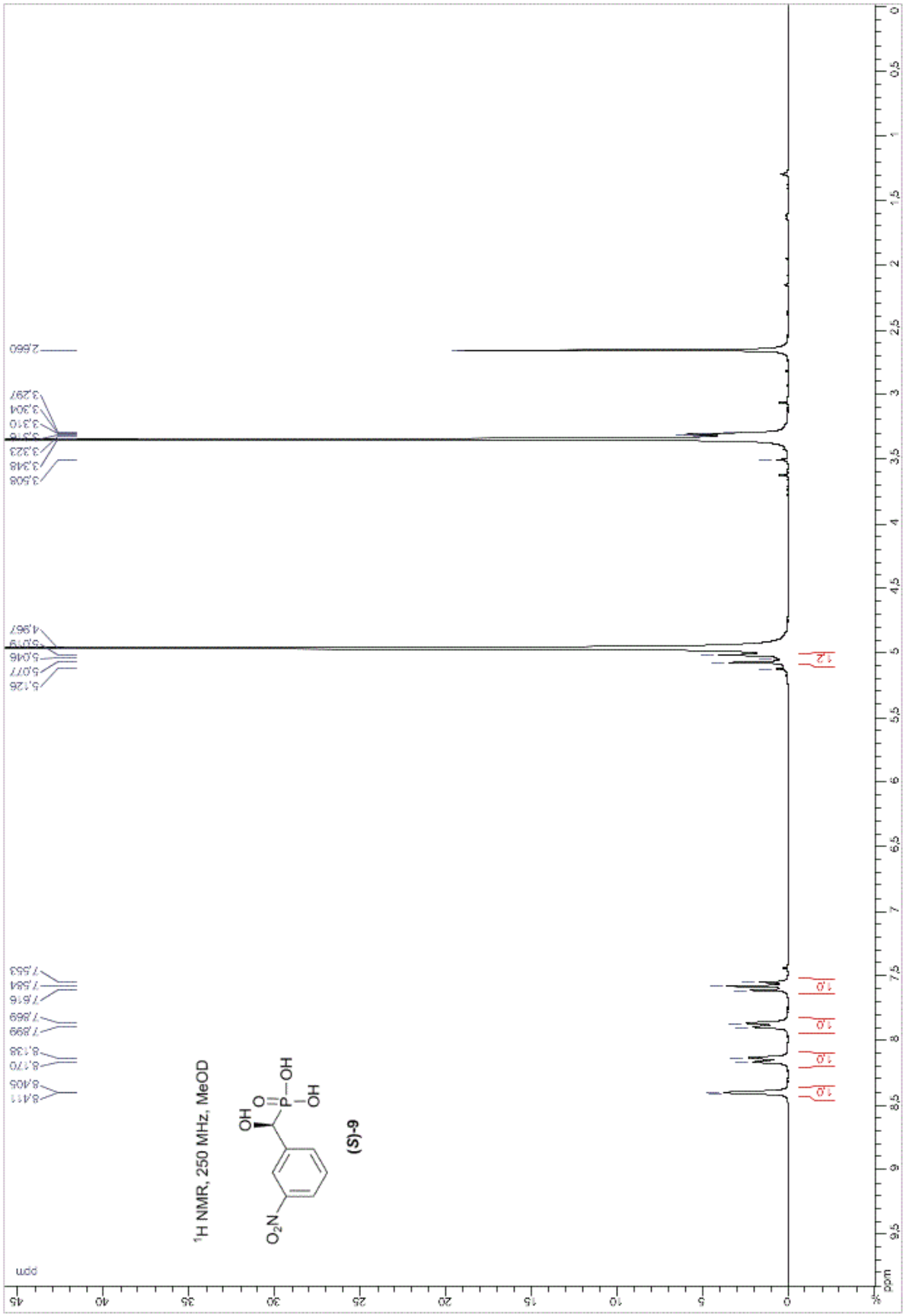

^{31}P NMR, 101 MHz, $CDCl_3$
(R)-8a
(R)-8a'
OMen
OH
O
P
H
O_2N
34,854
33,178
30,363
28,410
0,1
1,1
0,9
0,1
ppm

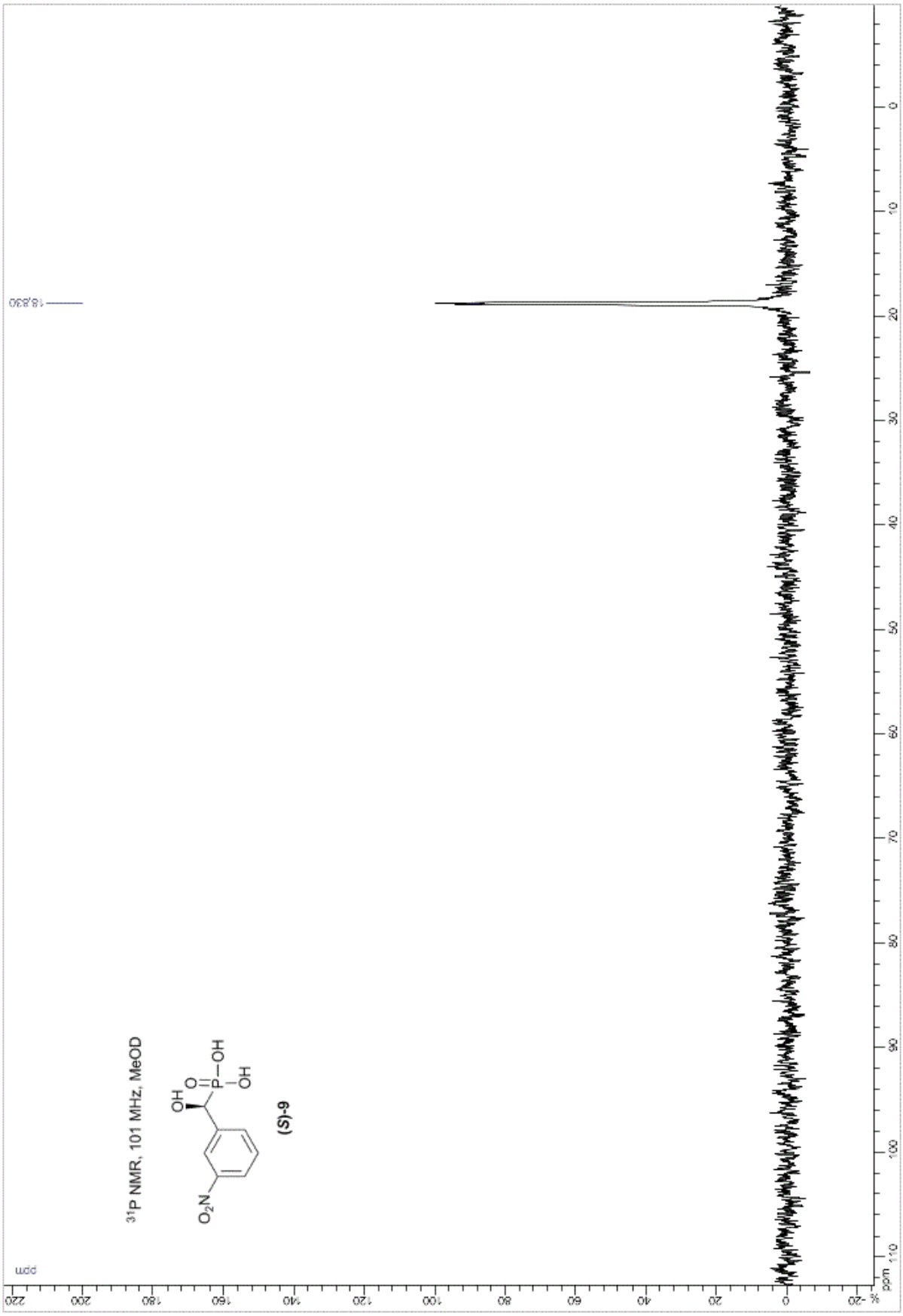

^{31}P NMR, 101 MHz, $CDCl_3$
(S)-8b
(S)-8b'
35,069
32,978
30,502
28,134
1,2
0,1
0,1
0,8
ppm

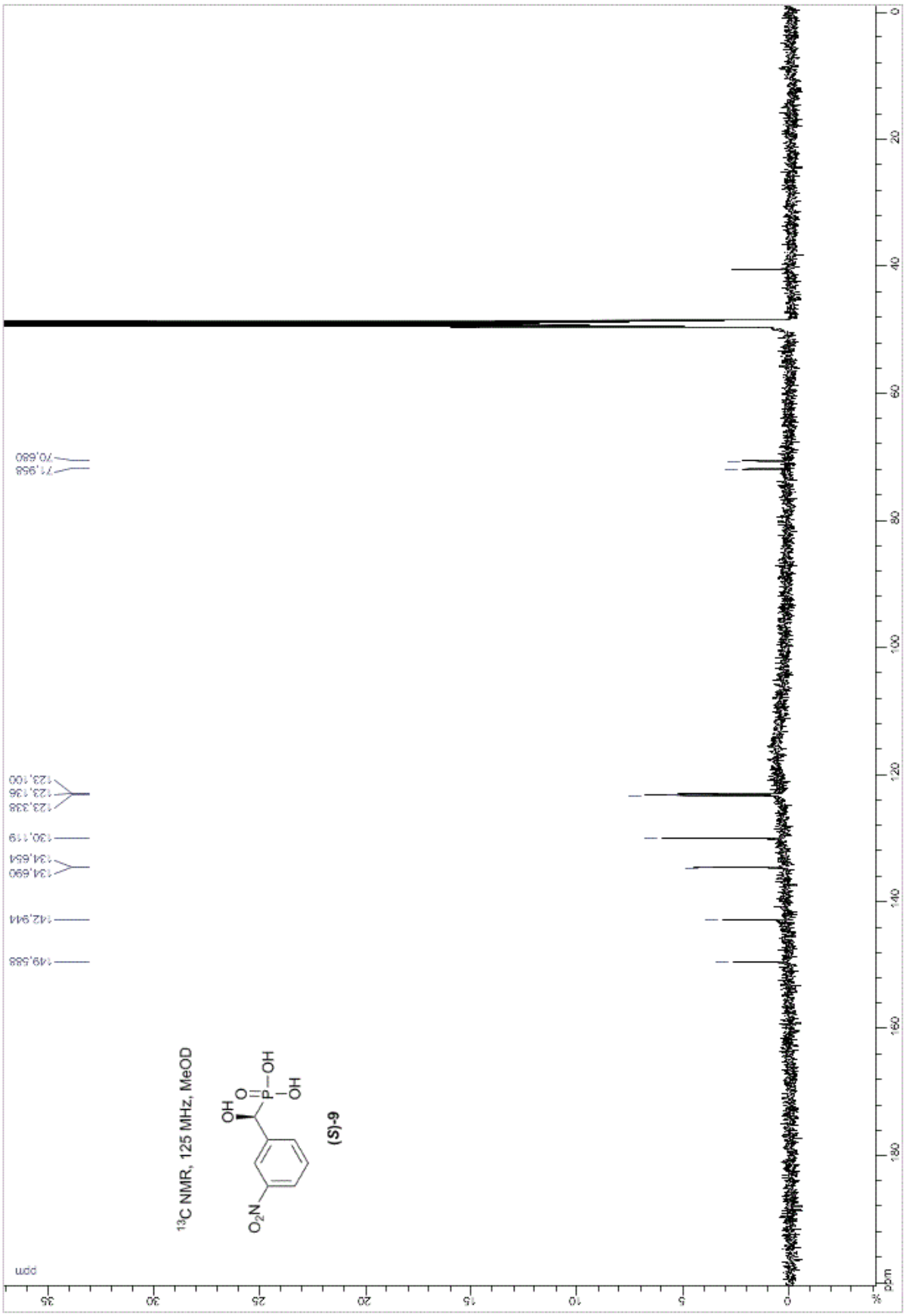

^{1}H NMR, 500 MHz, MeOD
(R)-9
8,409
8,407
8,154
8,138
7,894
7,878
7,595
7,579
7,564
5,062
5,033
3,310
1,0
1,0
1,0
1,0
0,9
1,0
ppm

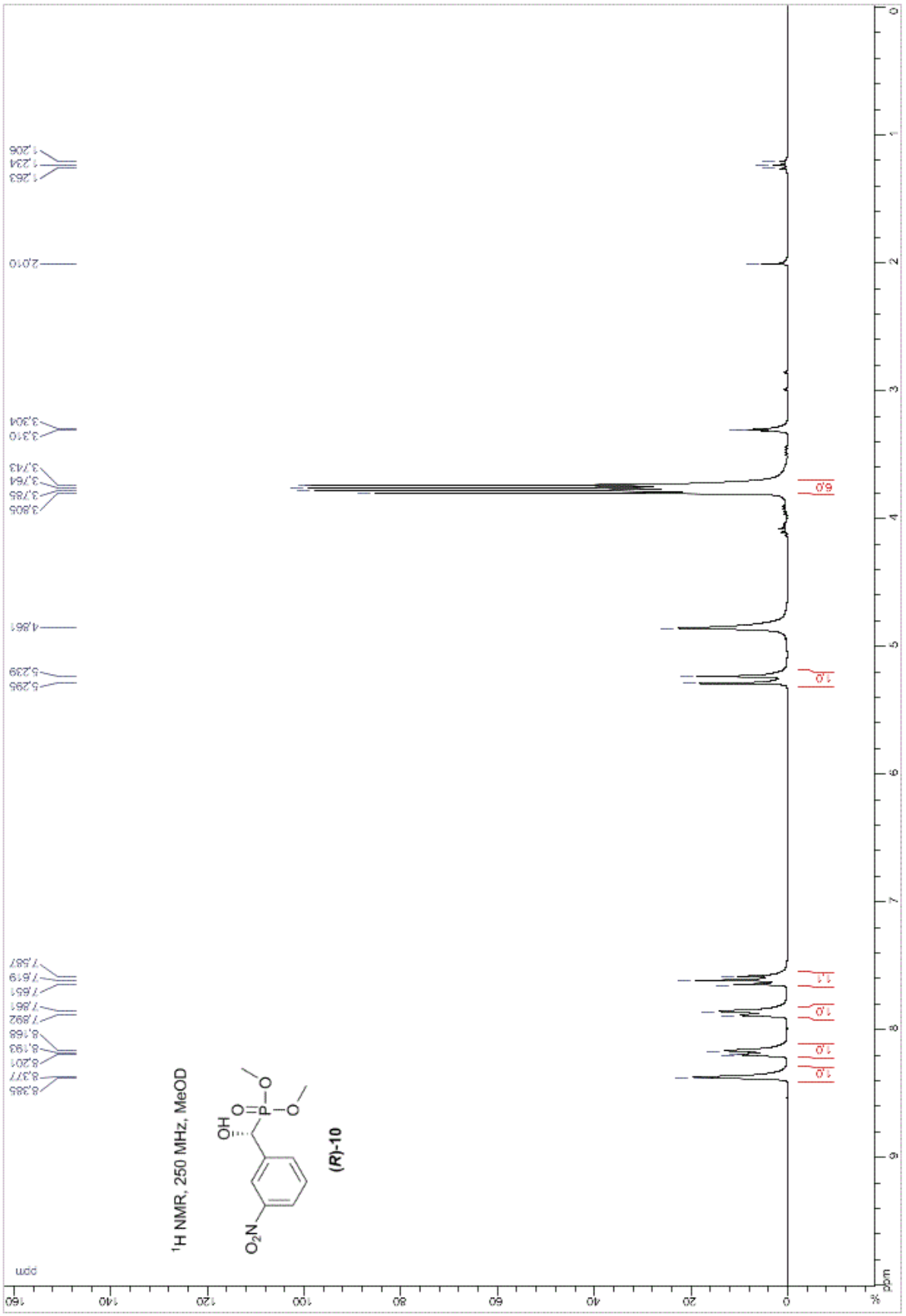

ppm
18,711
^{31}P NMR, 202 MHz, MeOD
OH
O
O_2N
P—OH
OH
(*R*)-9
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
%
ppm
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

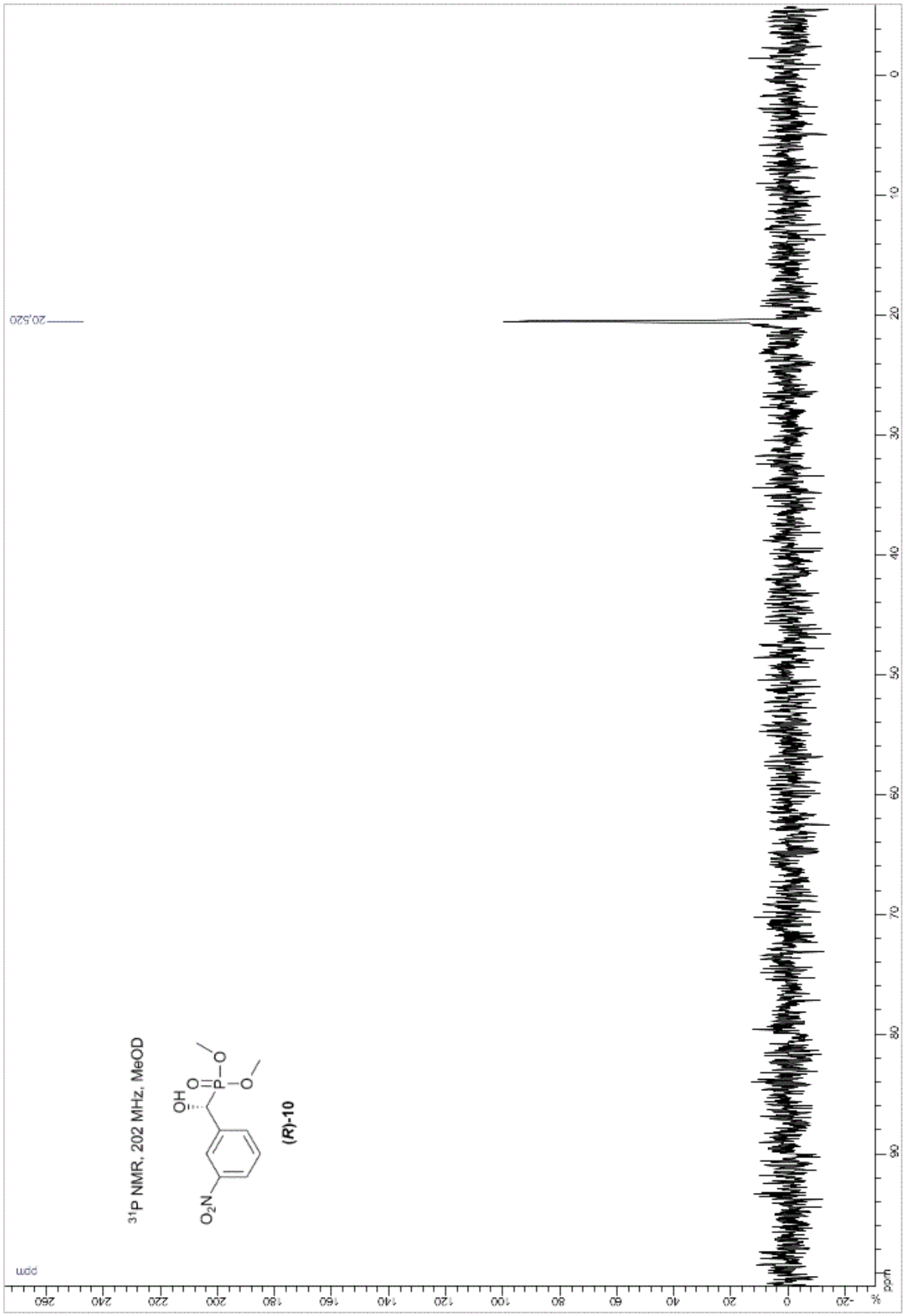

^{13}C NMR, 125 MHz, MeOD
(R)-9
149,581
142,944
134,690
134,654
130,105
123,310
123,136
123,100
72,002
70,723
ppm

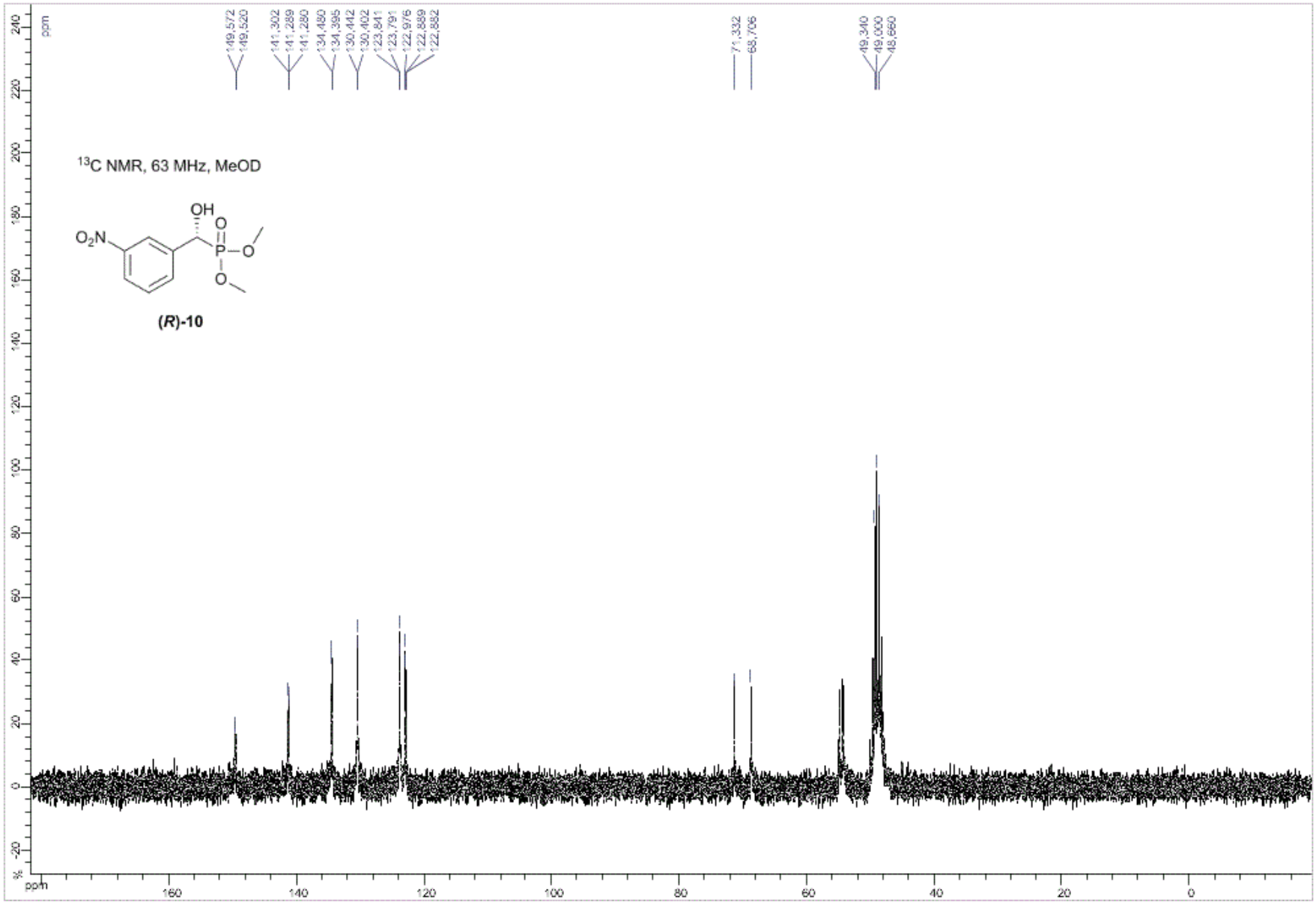

^{1}H NMR, 250 MHz, MeOD
(S)-9
8,411
8,405
8,170
8,138
7,899
7,869
7,816
7,584
7,553
5,126
5,077
5,046
4,967
3,508
3,348
3,323
3,310
3,304
3,297
2,660
1,0
1,0
1,0
1,0
1,0
1,2
ppm

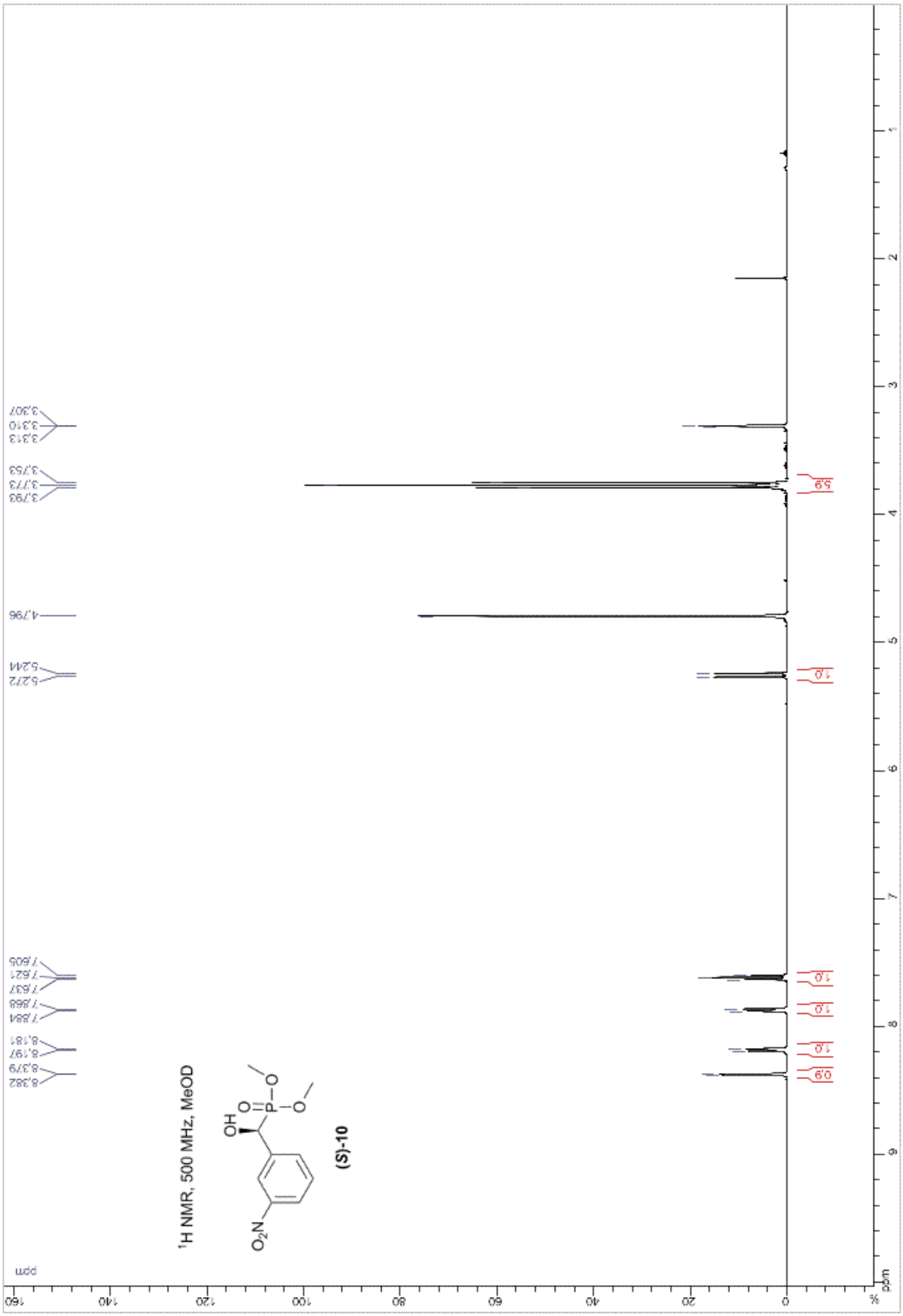

18,830
ppm
^{31}P NMR, 101 MHz, MeOD
(S)-9


^{13}C NMR, 125 MHz, MeOD
(S)-9
149,588
142,944
134,690
134,654
130,119
123,338
123,136
123,100
71,958
70,690
ppm

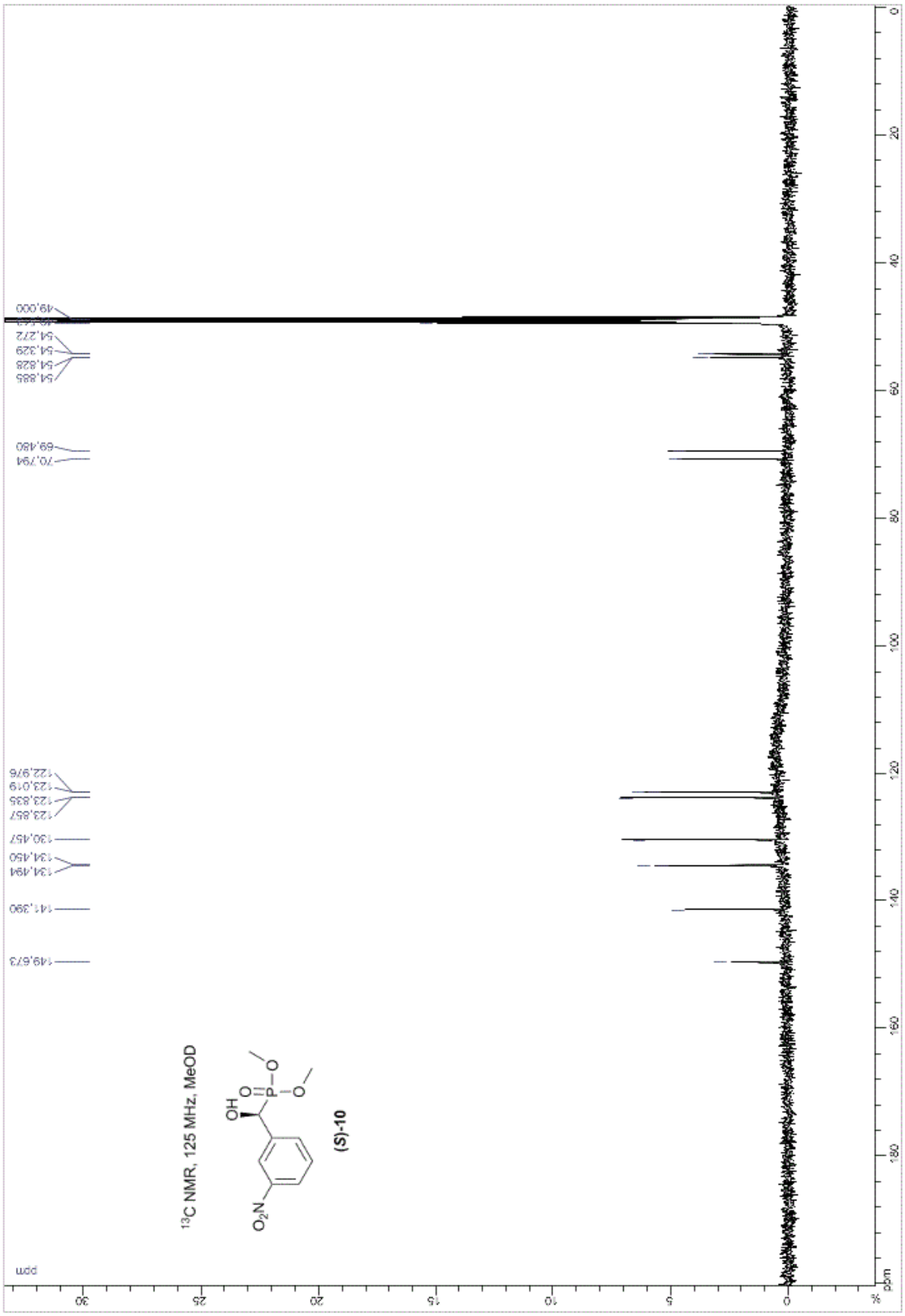

1H NMR, 250 MHz, MeOD
(R)-10
8,385
8,377
8,201
8,193
8,168
7,892
7,861
7,651
7,619
7,587
5,295
5,239
4,861
3,805
3,785
3,764
3,743
3,310
3,304
2,010
1,263
1,234
1,206
6,0
1,0
1,1
1,0
1,0
1,0
ppm

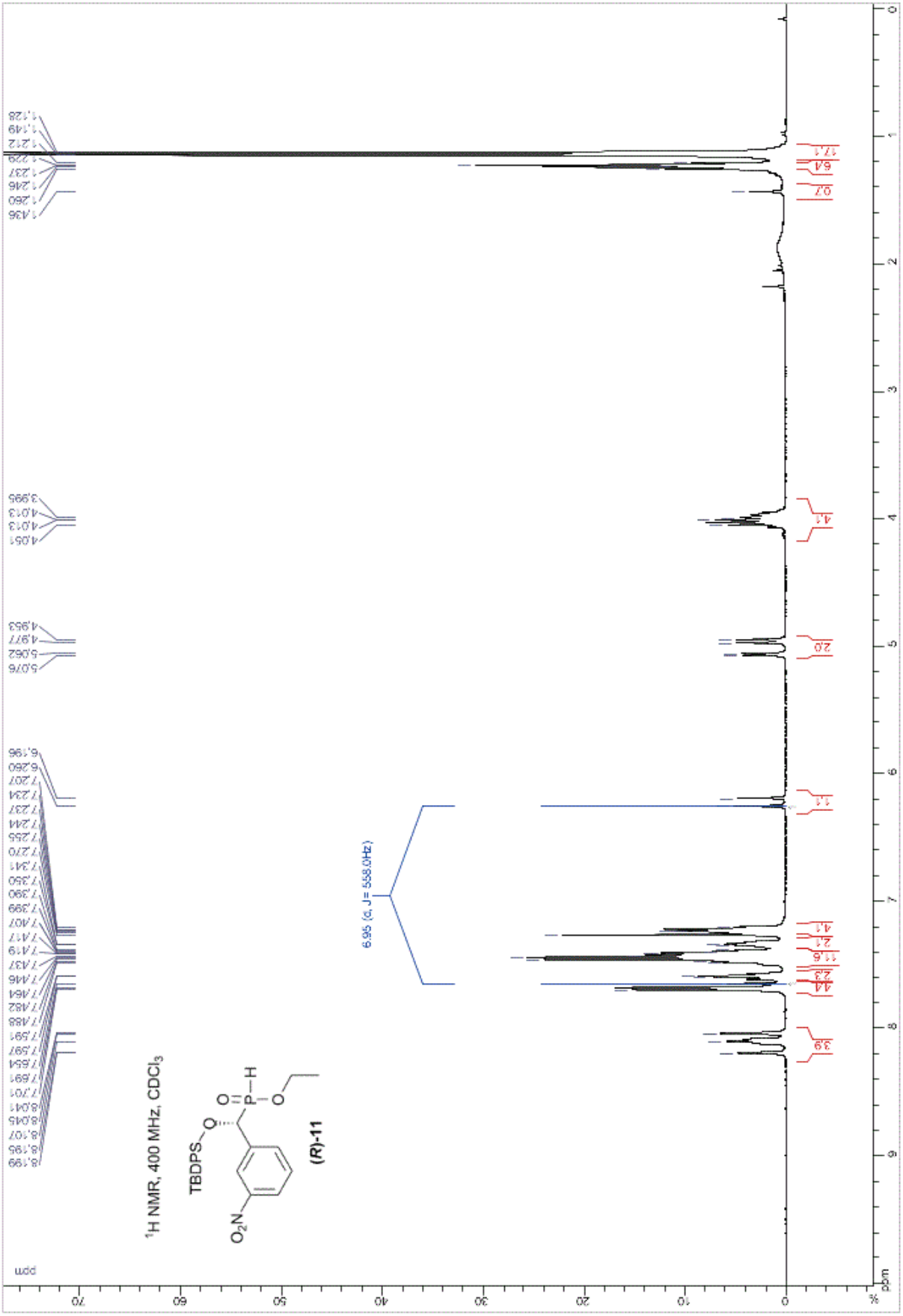

^{31}P NMR, 202 MHz, MeOD
(R)-10
20.520
ppm

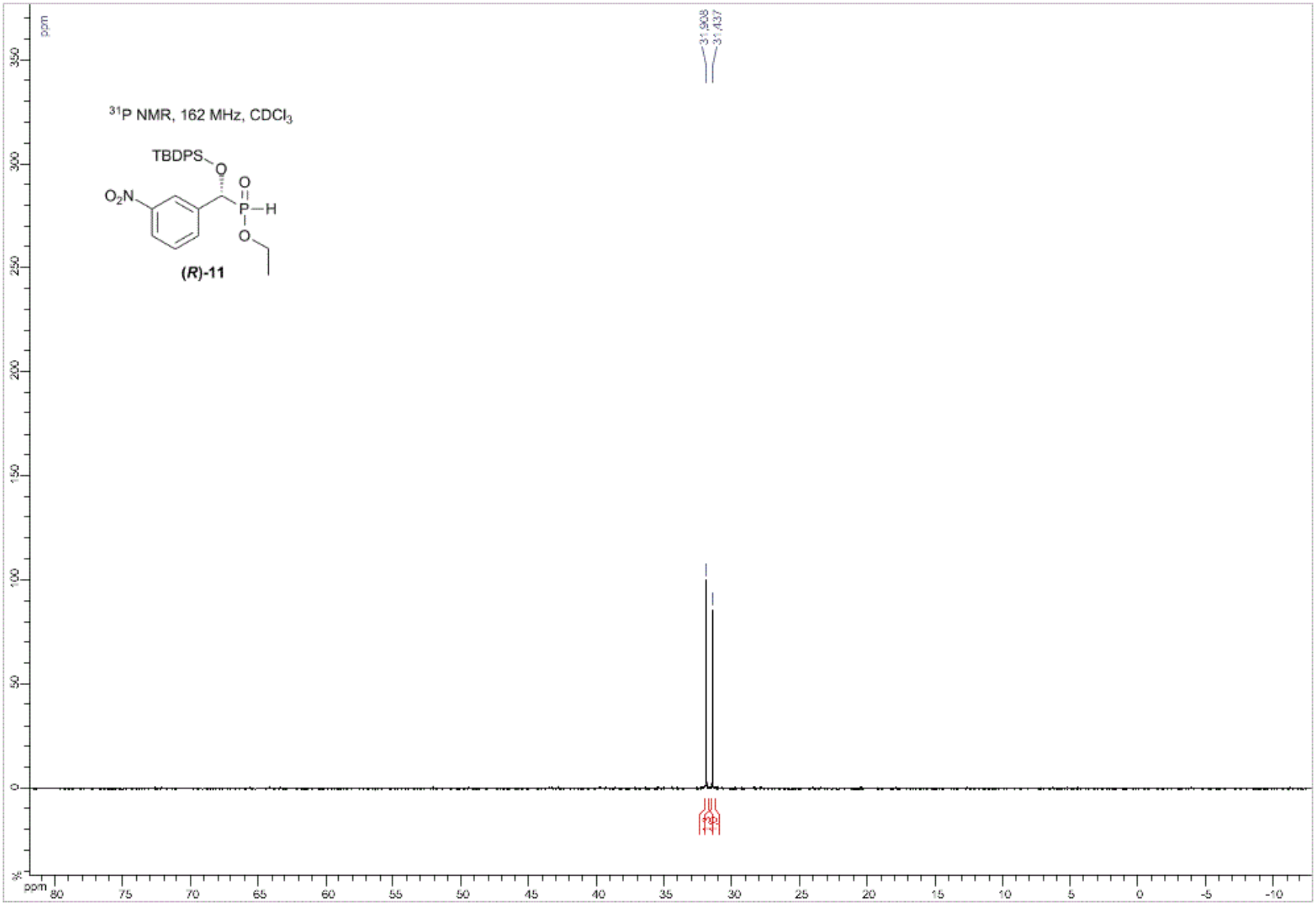

149,572
149,520
141,302
141,289
141,280
134,480
134,395
130,442
130,402
123,841
123,791
122,976
122,889
122,882
71,332
68,706
49,340
49,000
48,660
ppm
^{13}C NMR, 63 MHz, MeOD
OH
O
O_2N
P
O
O
(*R*)-10

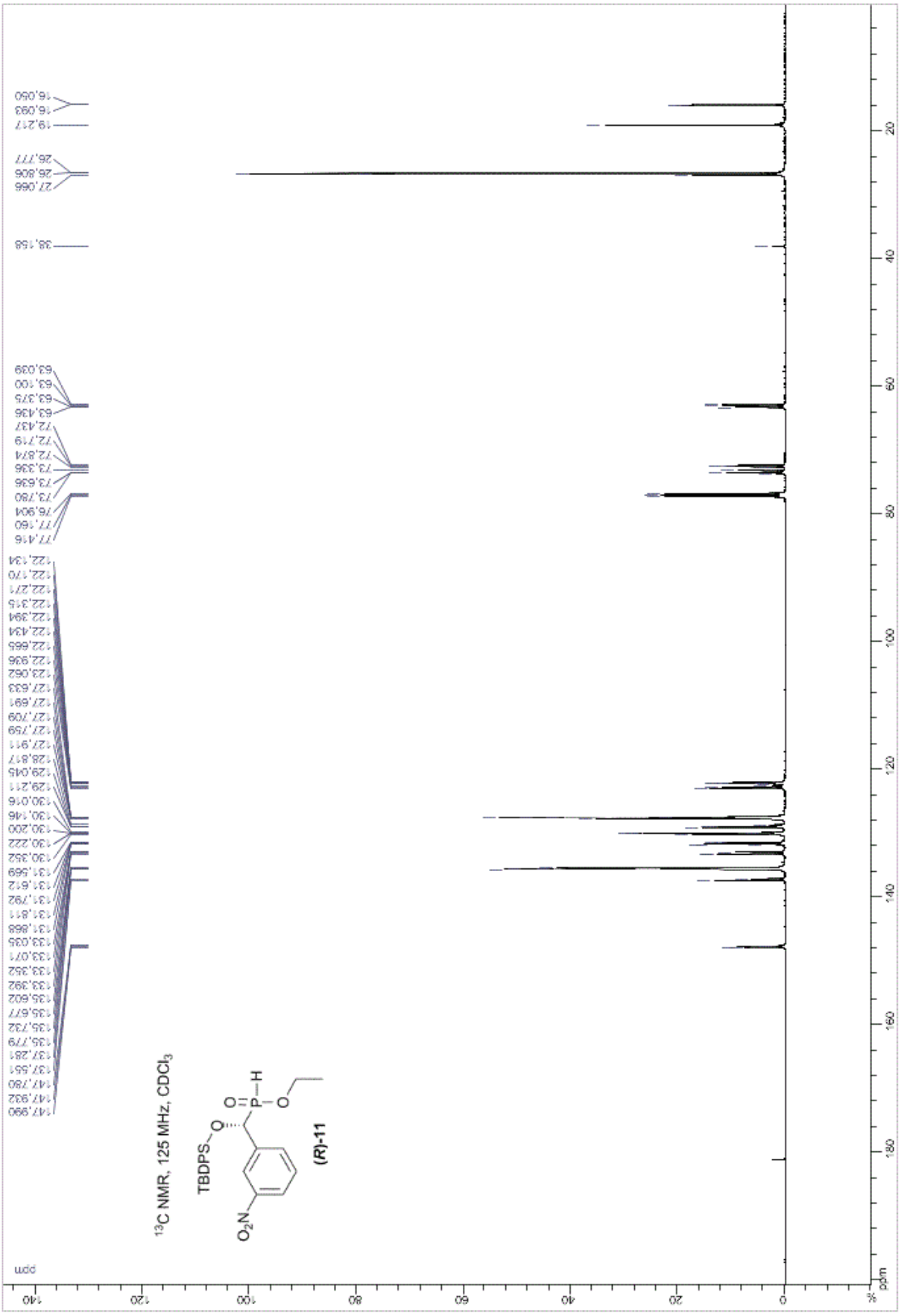

^{1}H NMR, 500 MHz, MeOD
(S)-10
8,382
8,379
8,197
8,181
7,884
7,868
7,637
7,621
7,605
5,272
5,244
4,796
3,793
3,773
3,753
3,313
3,310
3,307
0,9
1,0
1,0
1,0
1,0
5,9
1,0
ppm

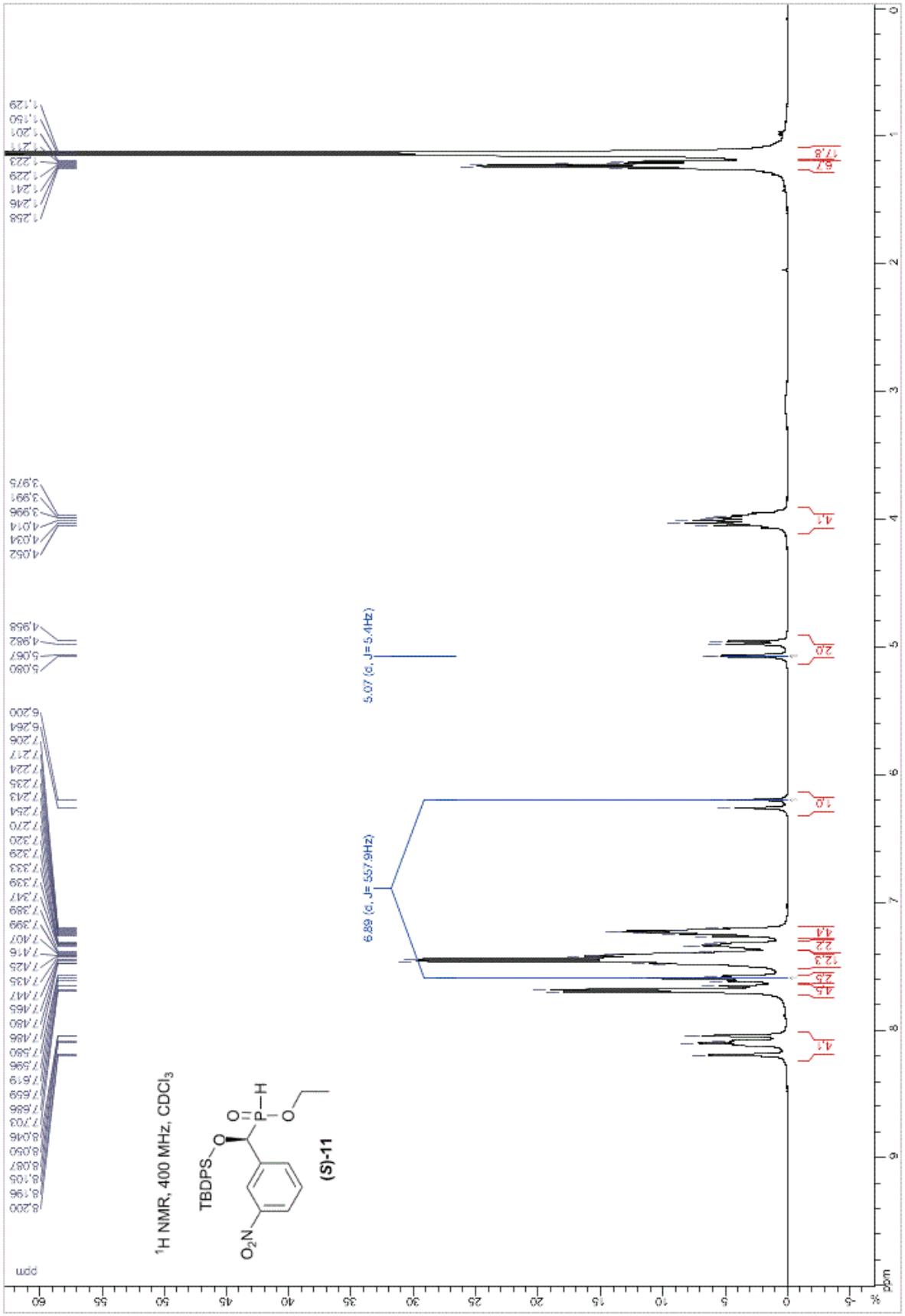
^{31}P NMR, 101 MHz, MeOD
(S)-10
22.997
ppm
pdm

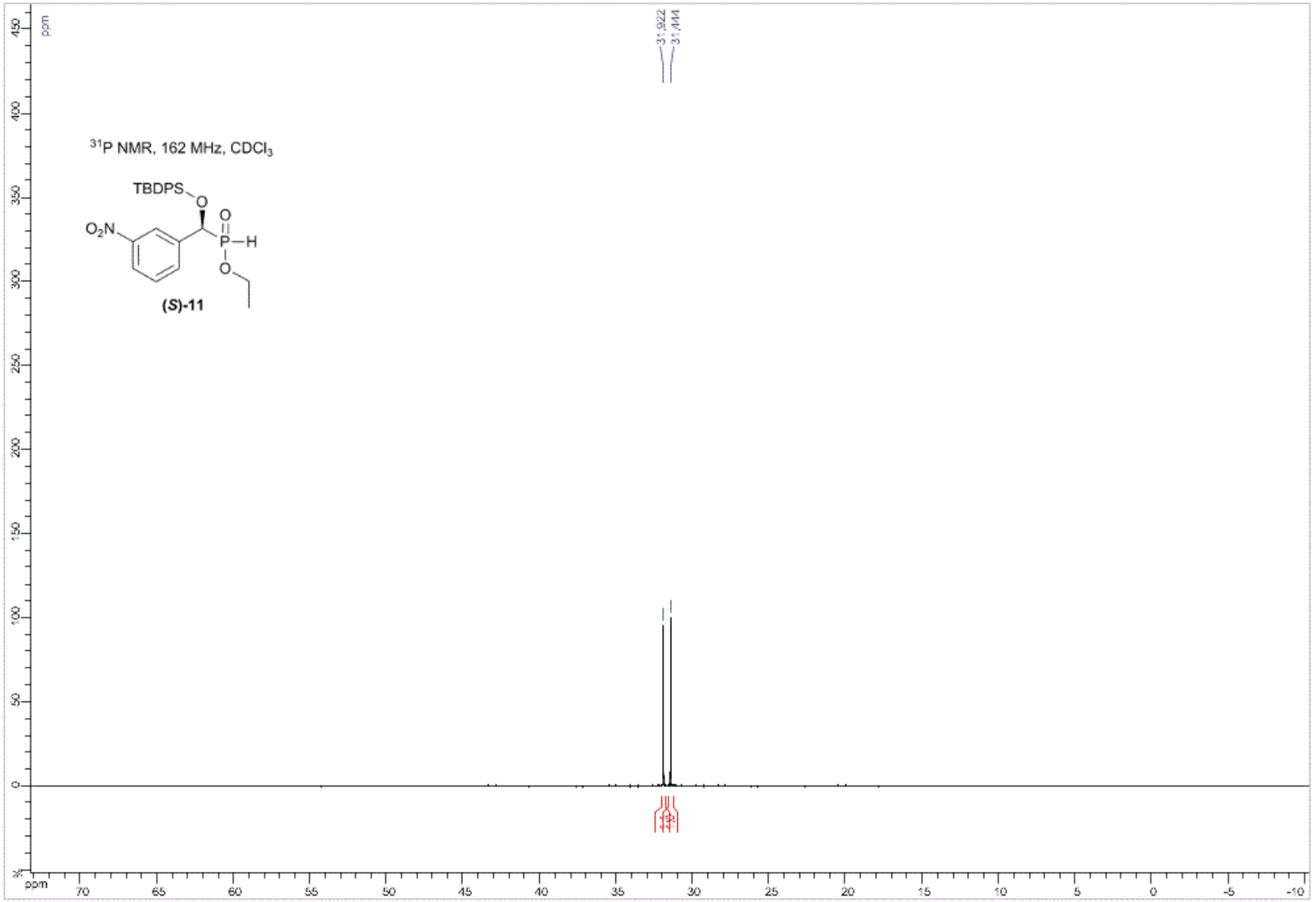

^{13}C NMR, 125 MHz, MeOD
(S)-10
149,673
141,390
134,494
134,450
130,457
123,857
123,835
123,019
122,976
70,794
69,480
54,885
54,828
54,329
54,272
49,000
ppm

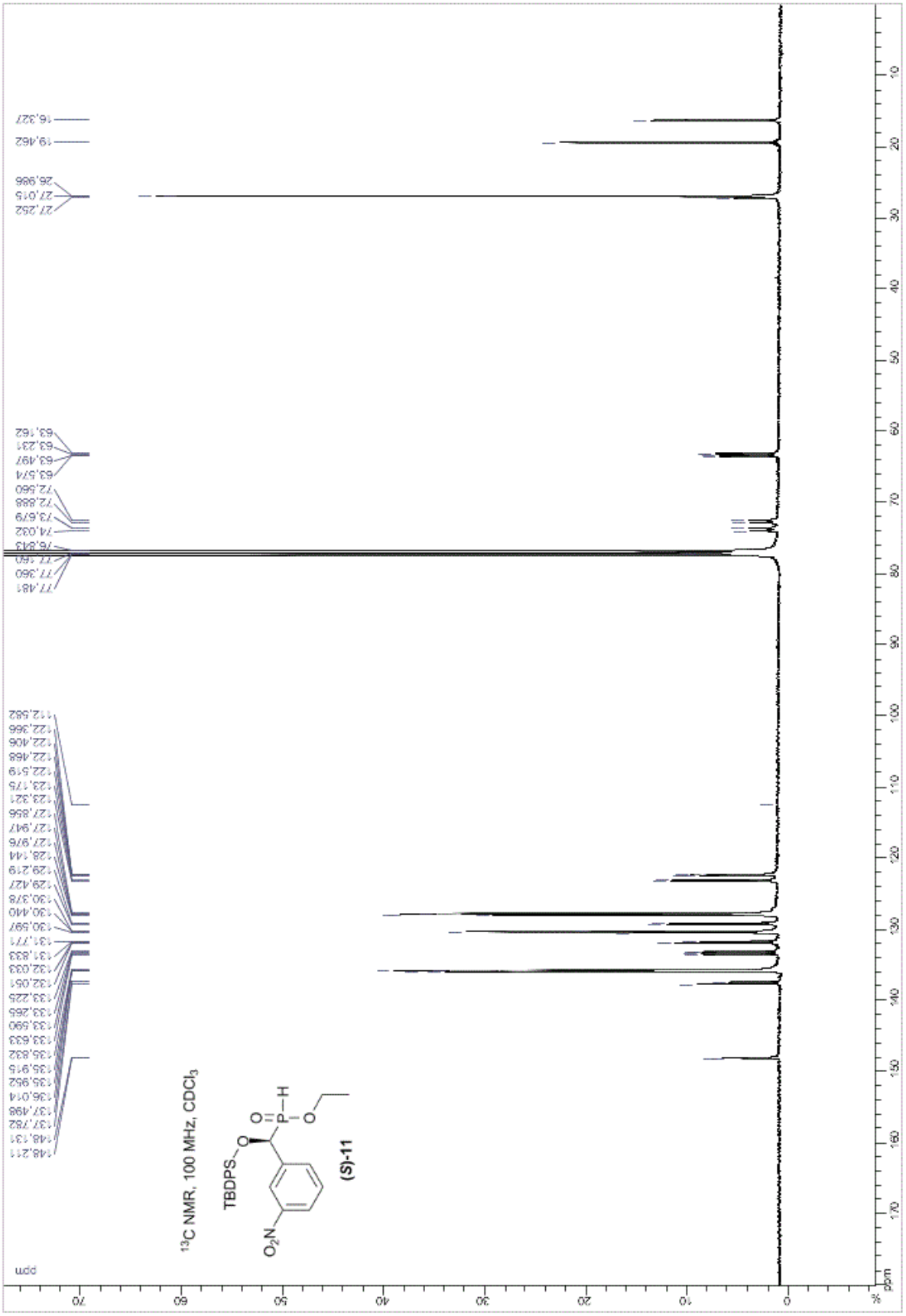

^{1}H NMR, 400 MHz, CDCl$_3$
TBDPS
O_2N
(R)-11
6.95 (d, J= 558.0Hz)
ppm

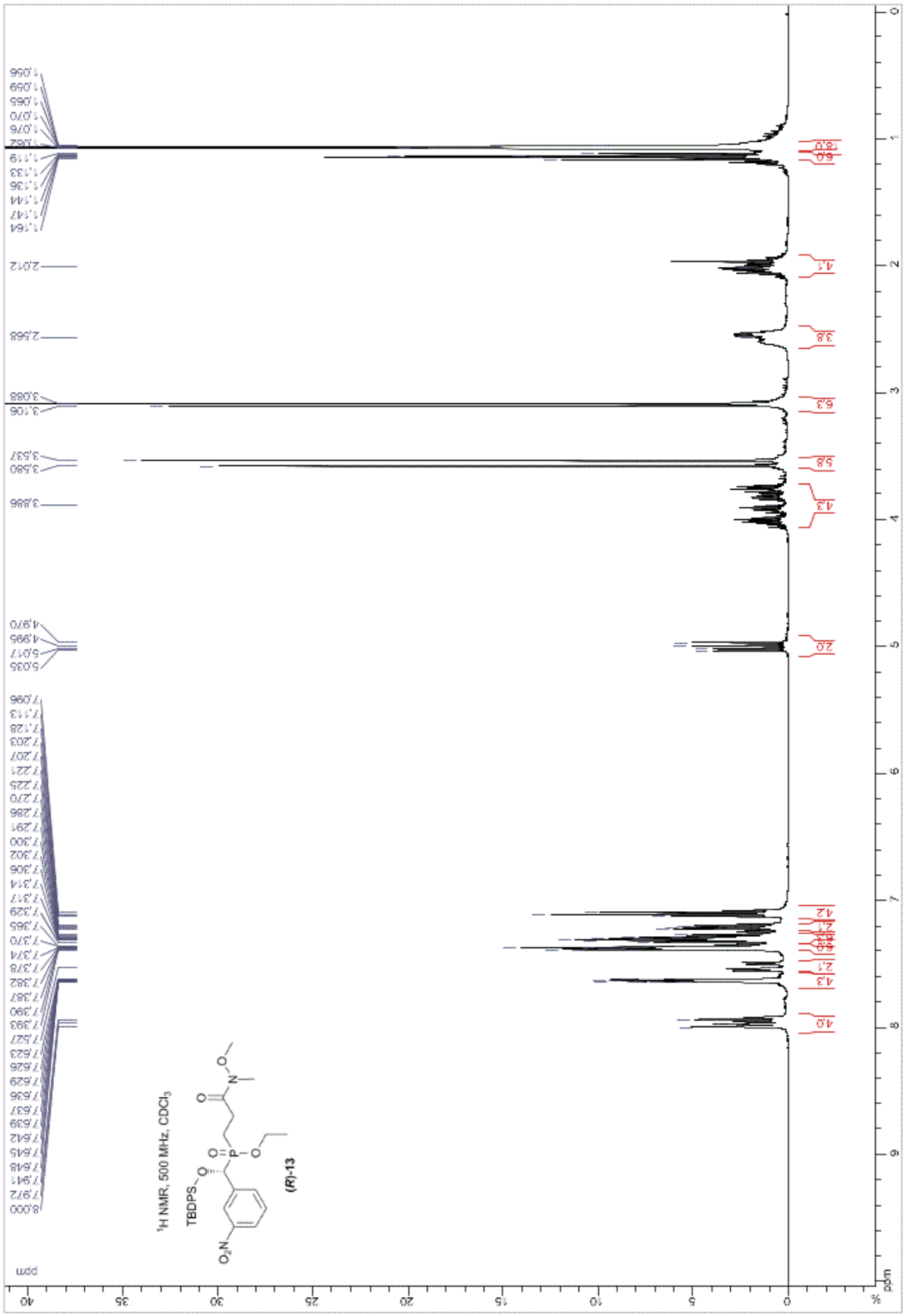

^{31}P NMR, 162 MHz, $CDCl_3$
TBDPS
O_2N
(*R*)-11
31.908
31.437
ppm

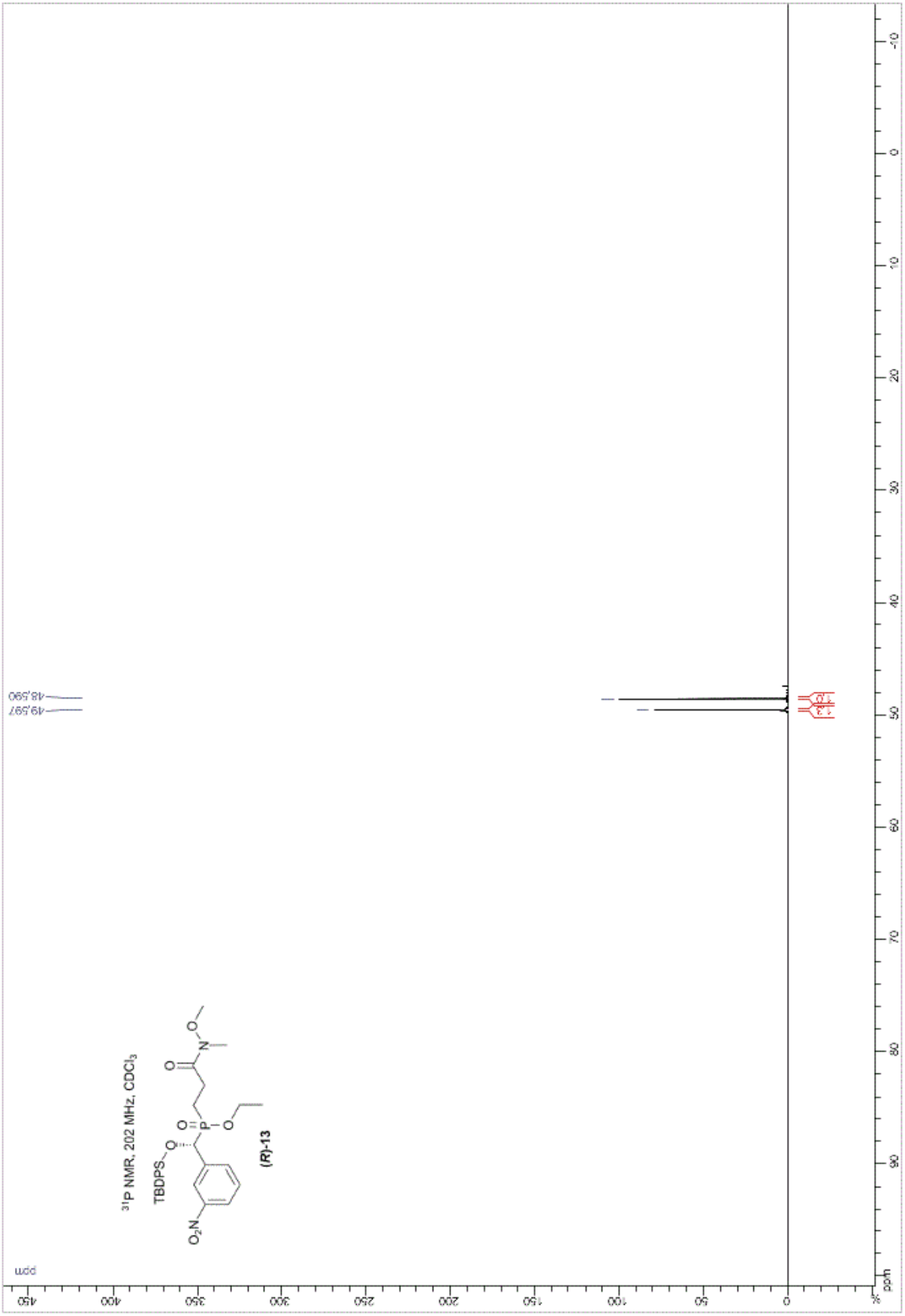

^{13}C NMR, 125 MHz, $CDCl_3$
TBDPS
O_2N
(R)-11
ppm

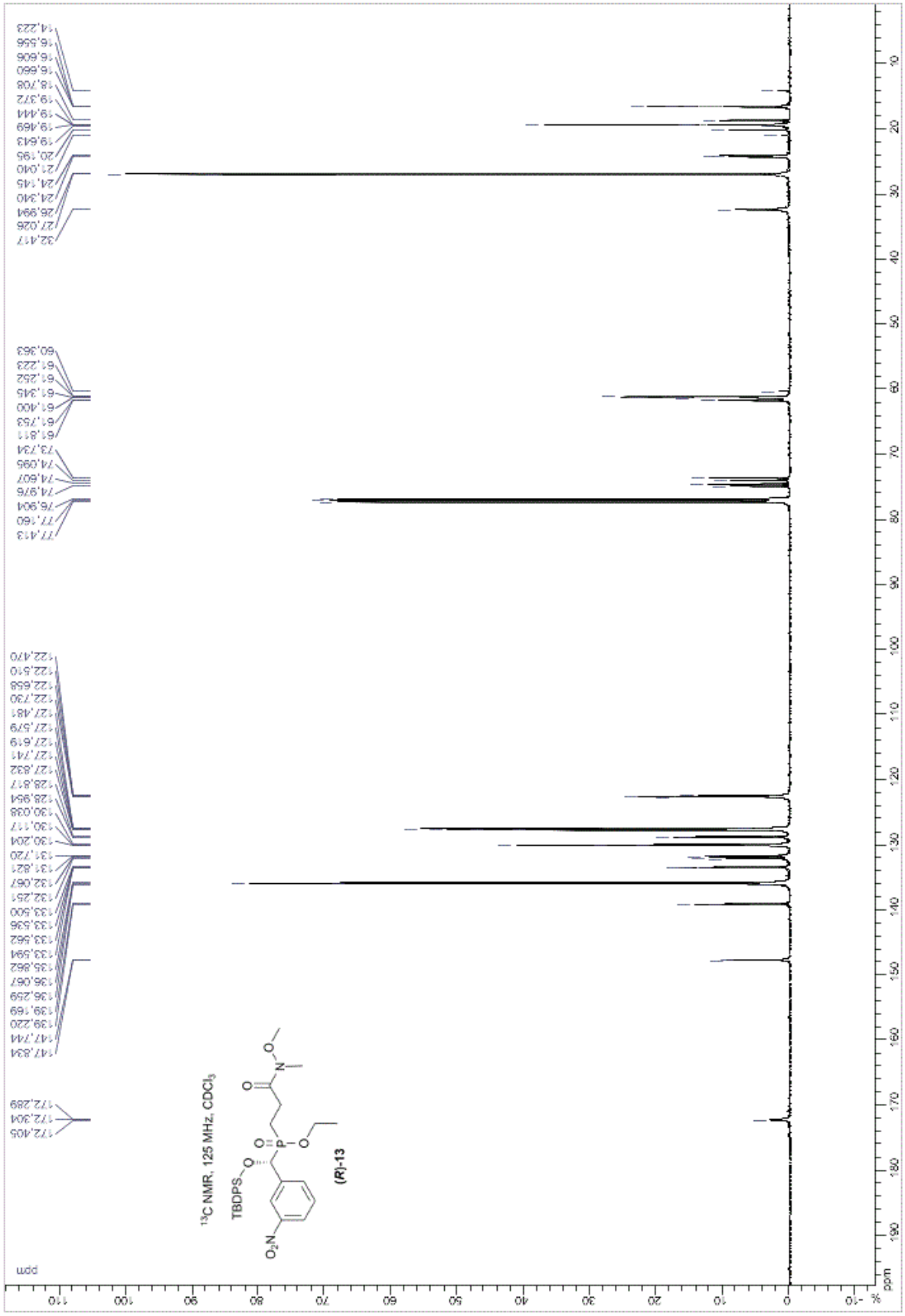

^{1}H NMR, 400 MHz, $CDCl_3$
TBDPS
O_2N
(S)-11
6.89 (d, J= 557.9Hz)
5.07 (d, J= 5.4Hz)
ppm

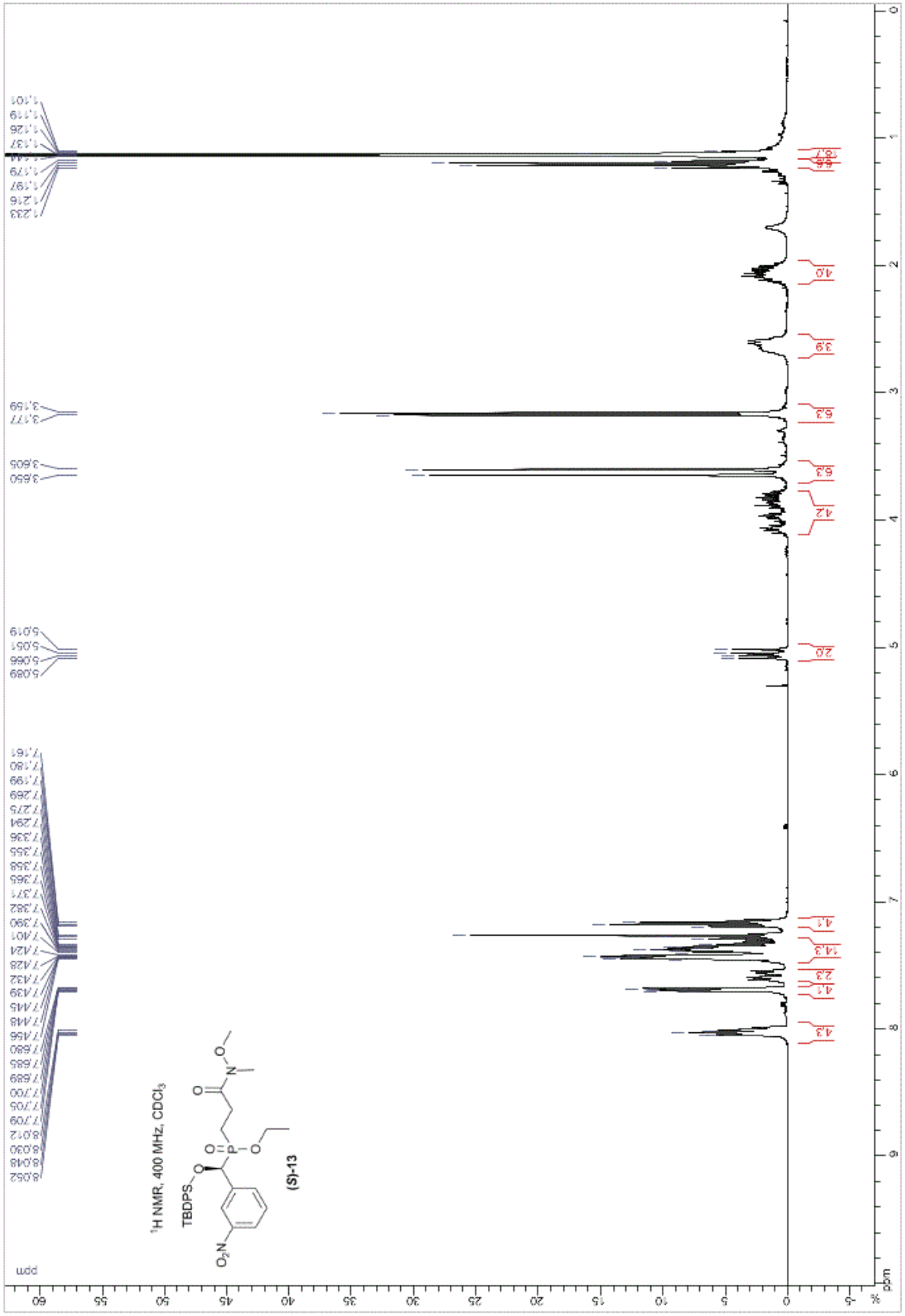

31.922
31.444
^{31}P NMR, 162 MHz, $CDCl_3$
TBDPS
O
O_2N
O
P
H
O
(S)-11
ppm
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10

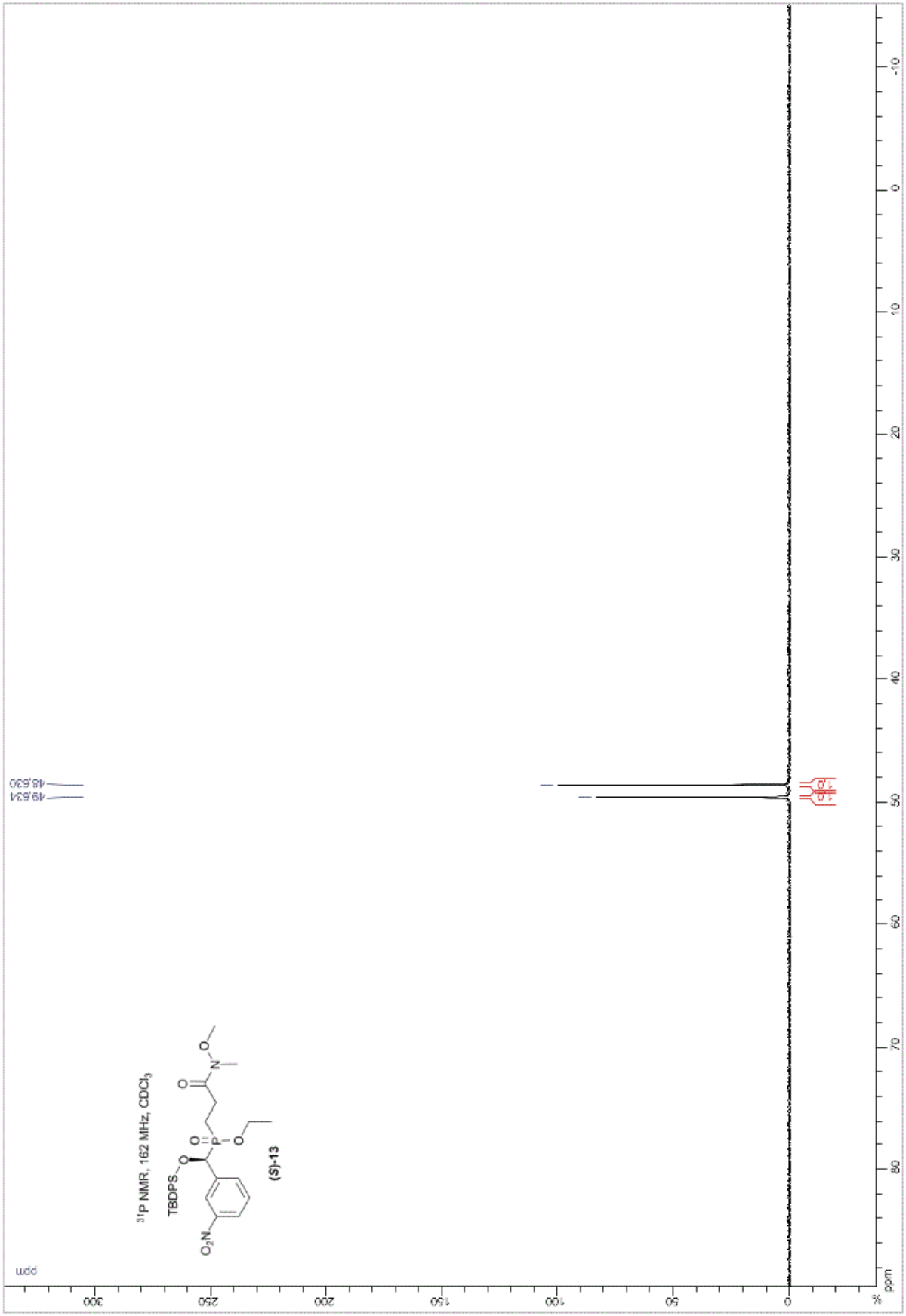

udd
^{13}C NMR, 100 MHz, $CDCl_3$
TBDPS
O
P
H
O
O_2N
(S)-11
ppm

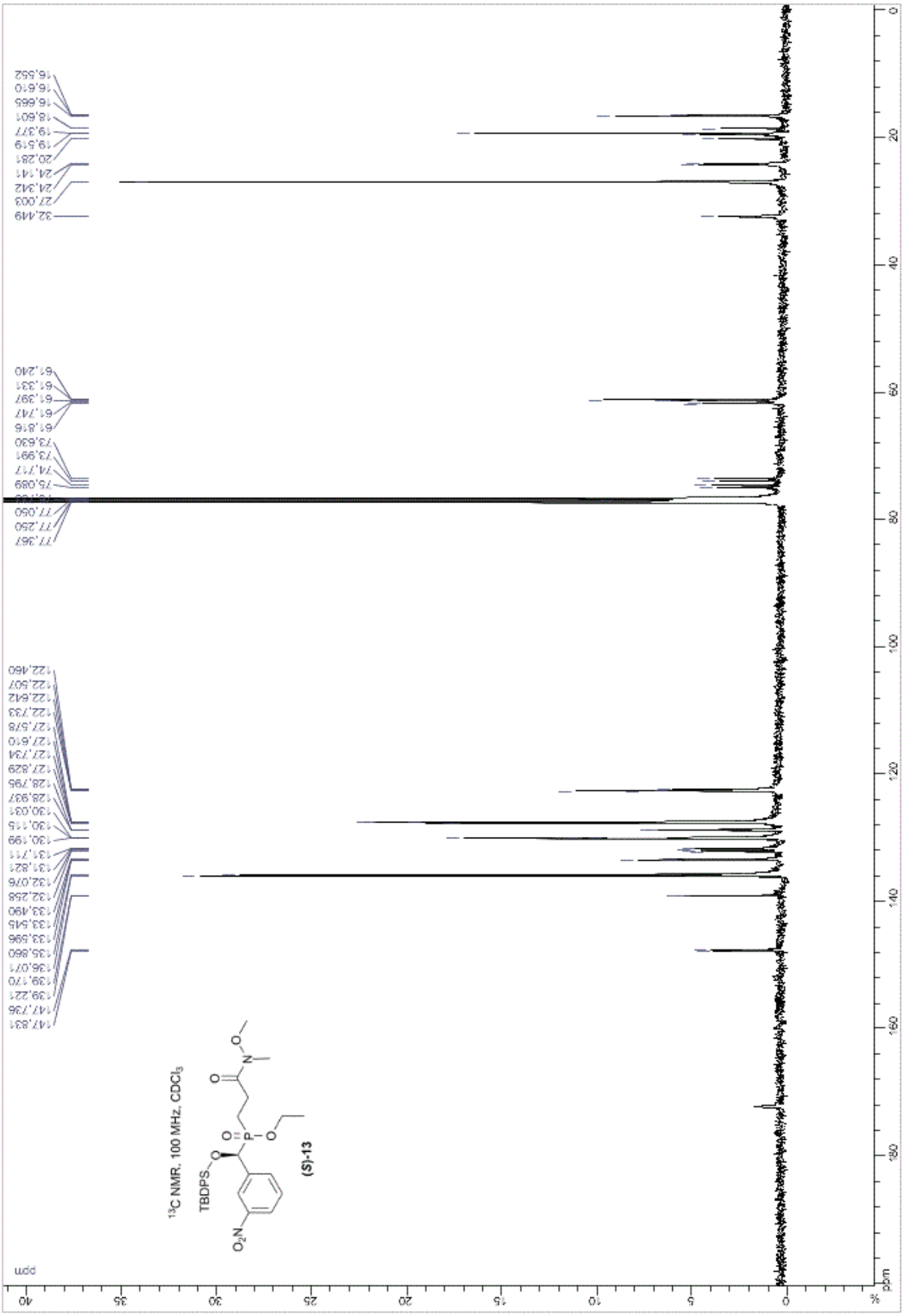

^{1}H NMR, 500 MHz, $CDCl_3$
TBDPS
(R)-13

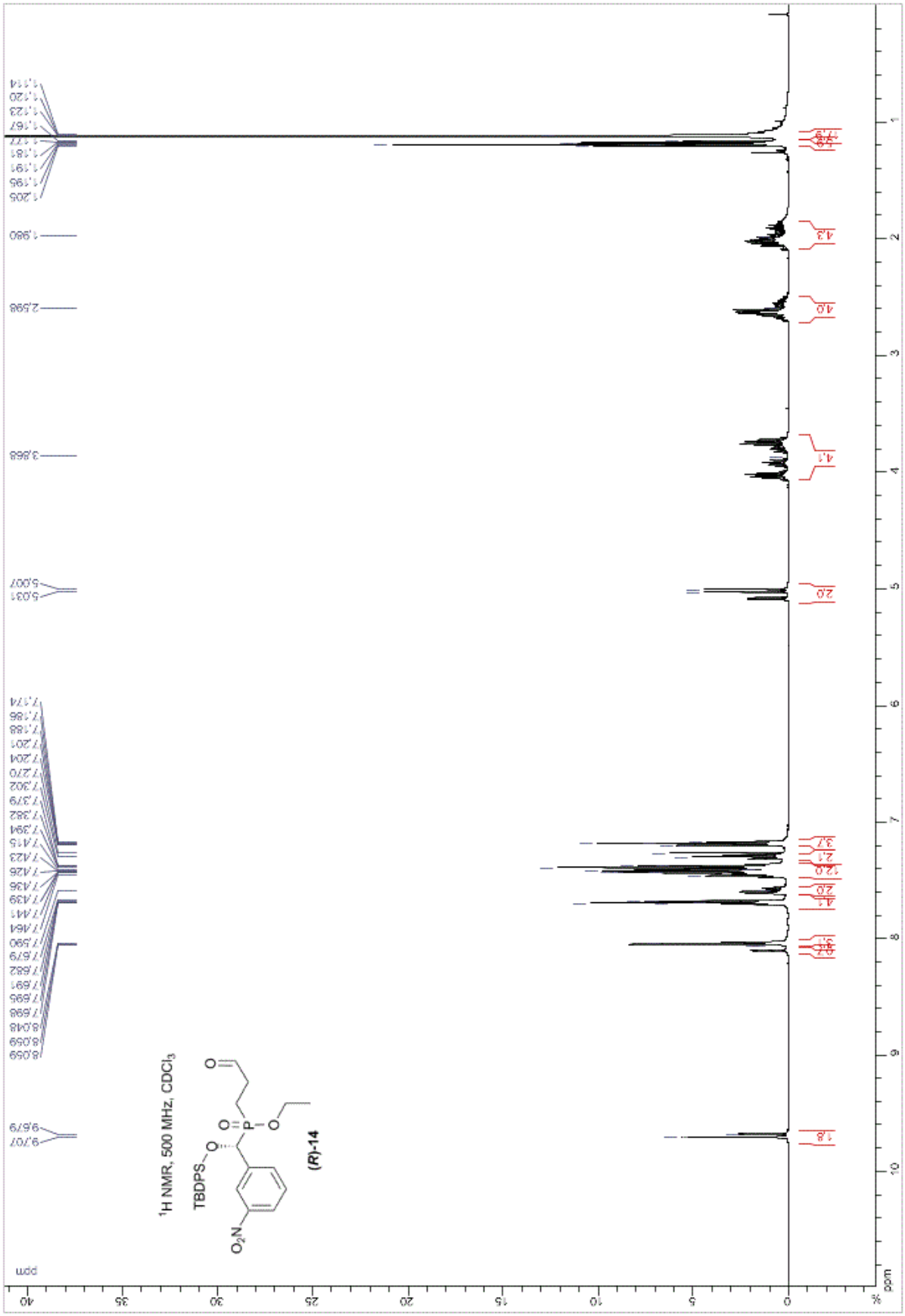

49.597
48.590
^{31}P NMR, 202 MHz, $CDCl_3$
TBDPS
O_2N
(R)-13
ppm

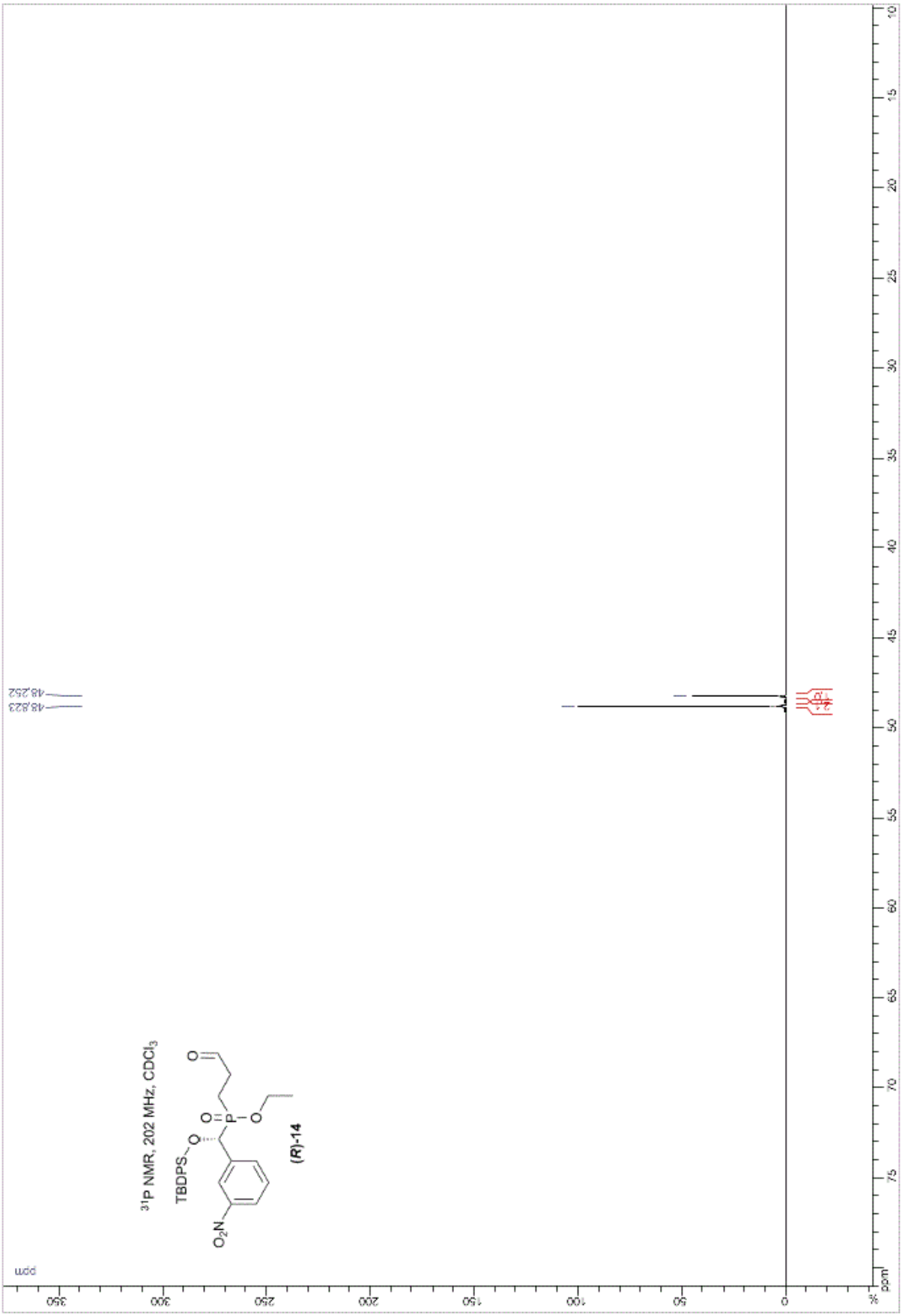

^{13}C NMR, 125 MHz, $CDCl_3$
TBDPS
O_2N
(R)-13

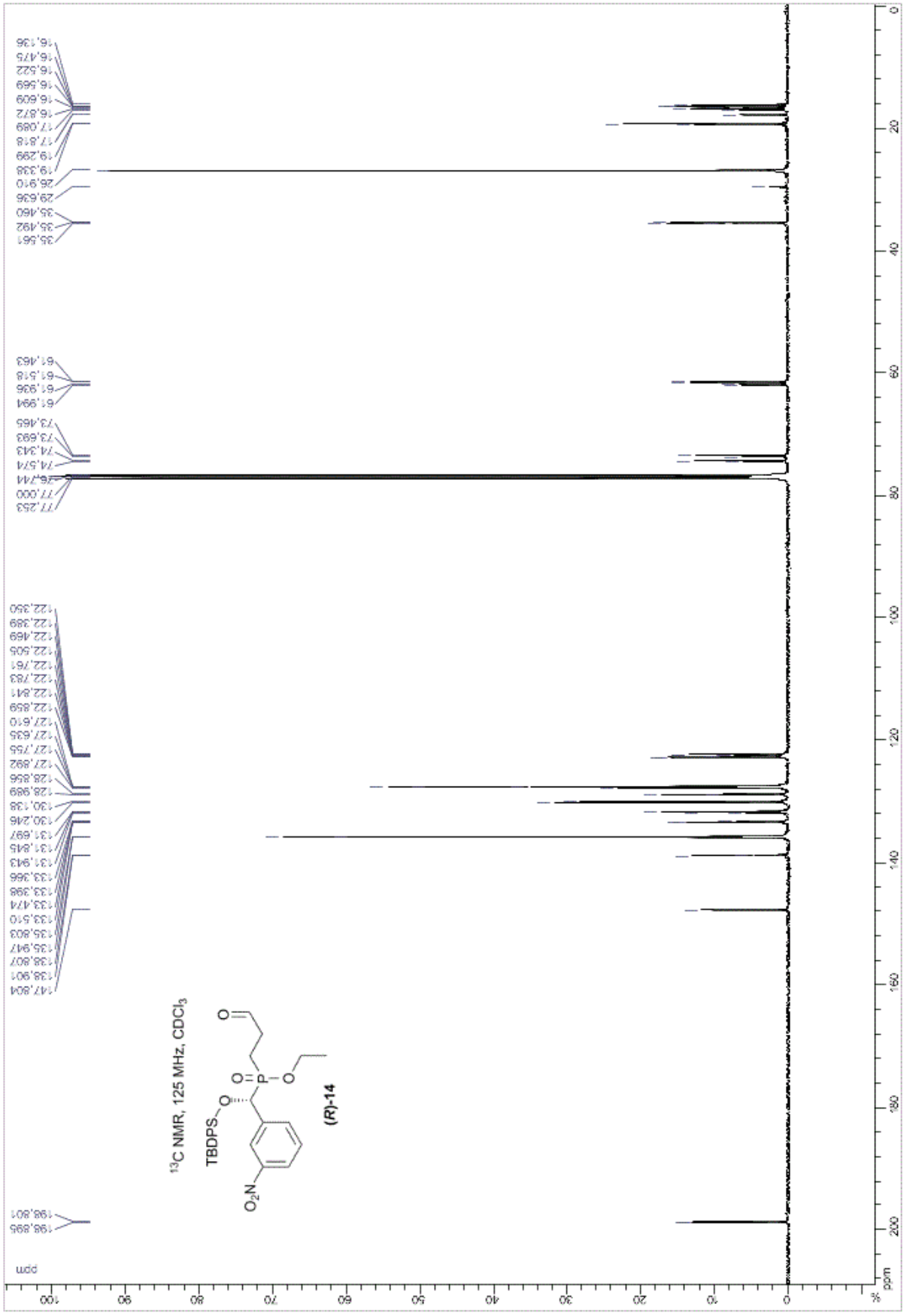

^{1}H NMR, 400 MHz, CDCl$_3$
TBDPS
(S)-13
ppm

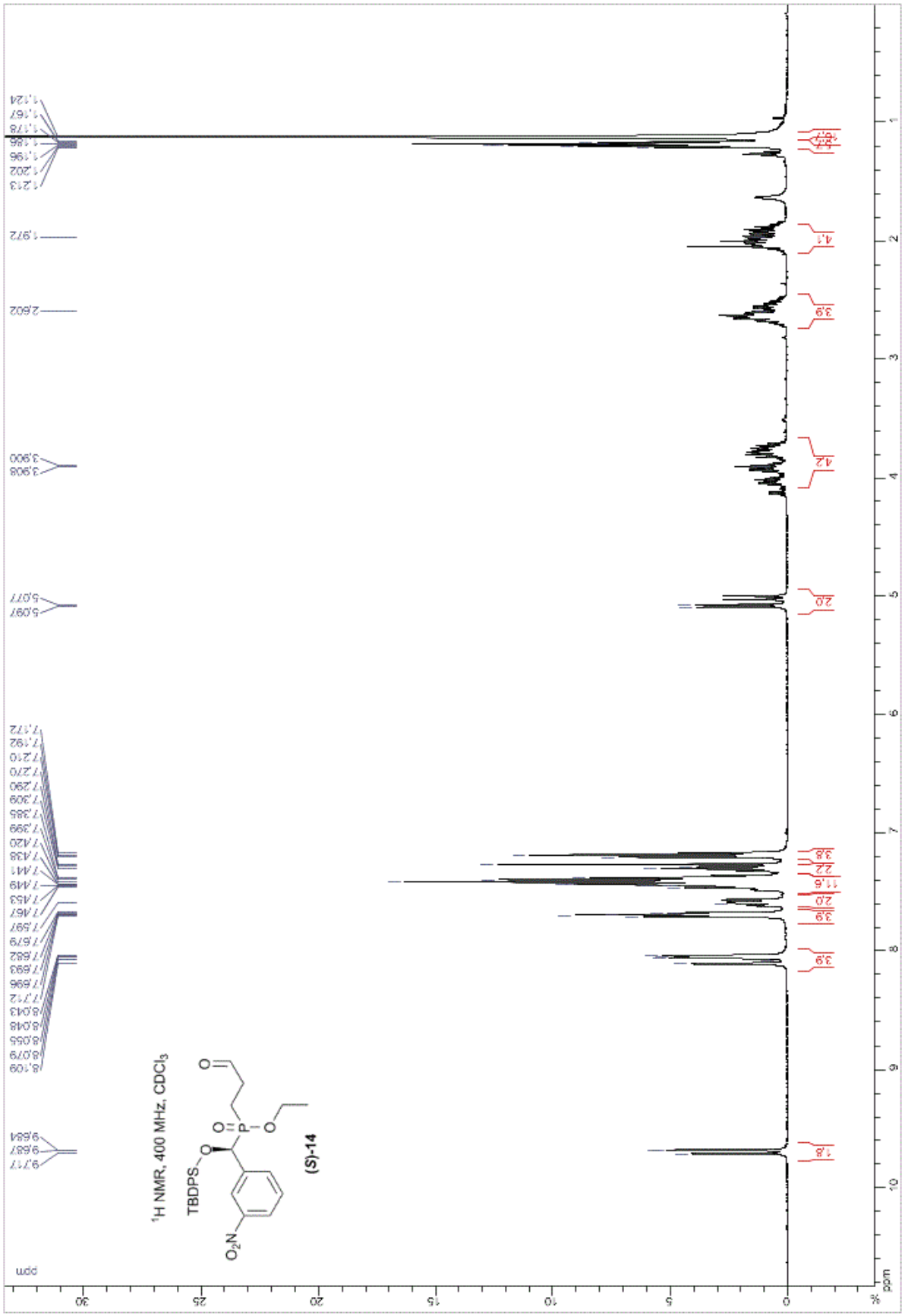

49.634
48.630
ppm
^{31}P NMR, 162 MHz, $CDCl_3$
TBDPS
O_2N
(S)-13

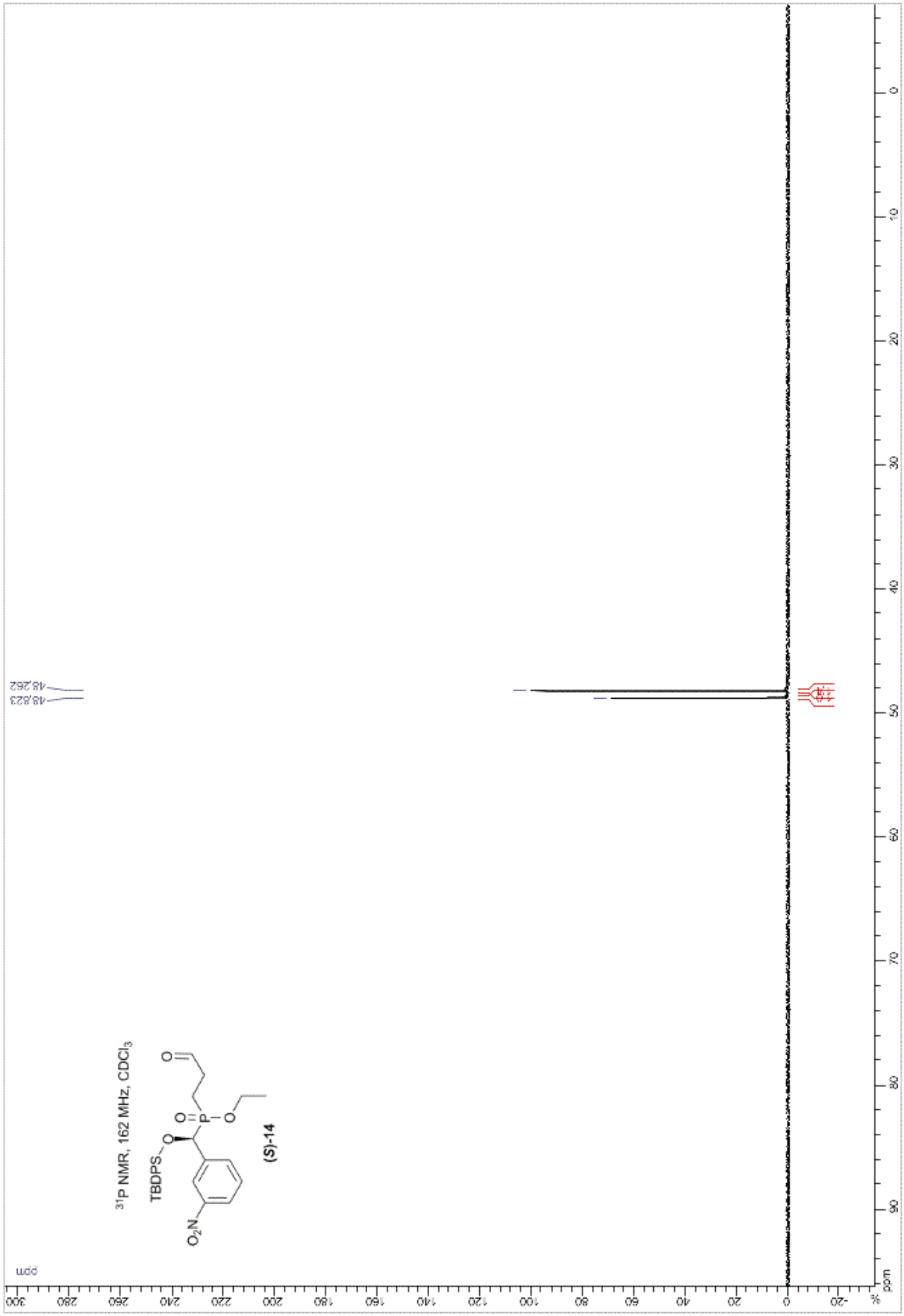

^{13}C NMR, 100 MHz, $CDCl_3$
TBDPS
(S)-13

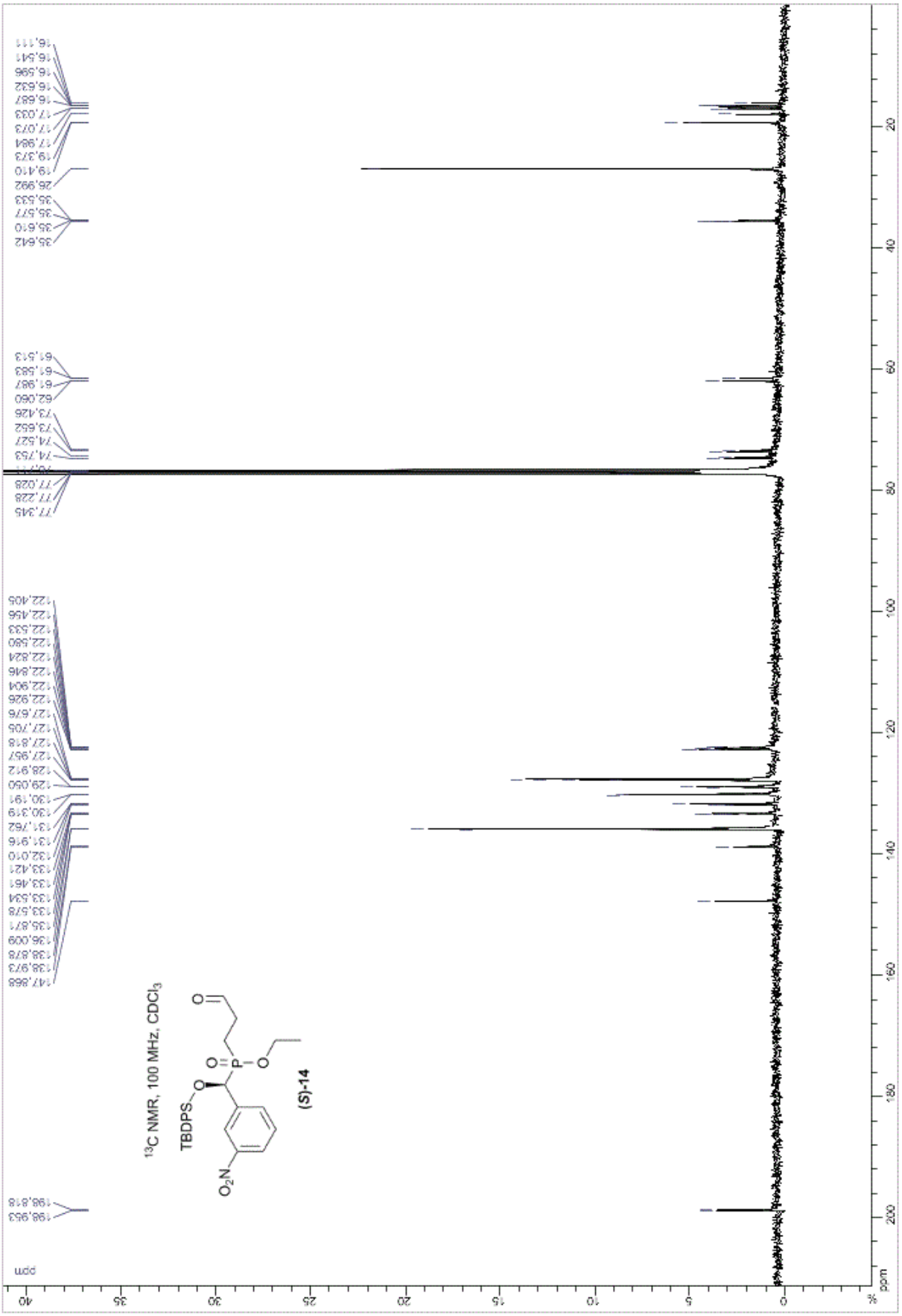

^{1}H NMR, 500 MHz, $CDCl_3$
TBDPS
O_2N
(R)-14
ppm

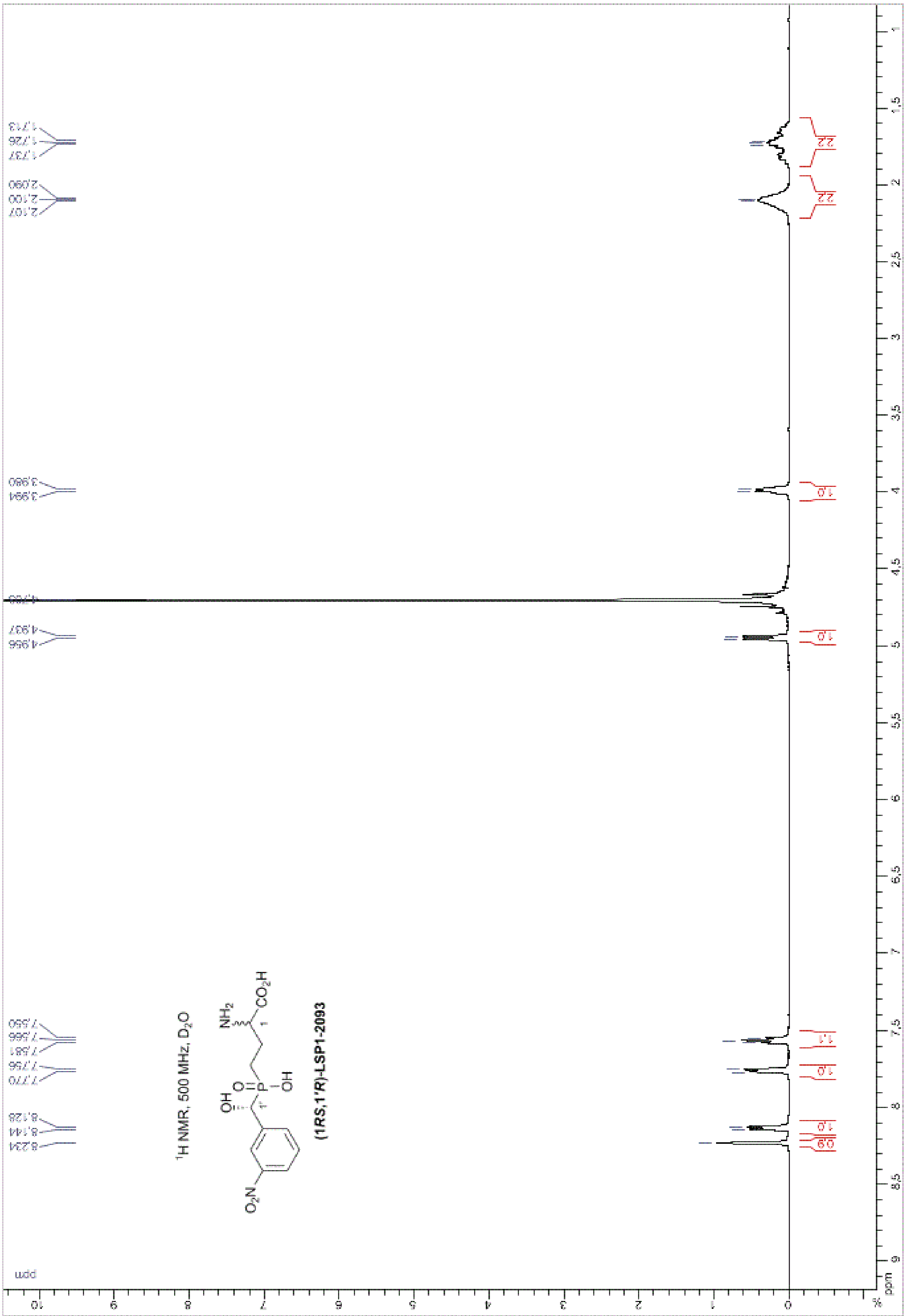

^{31}P NMR, 202 MHz, $CDCl_3$
TBDPS
O_2N
(R)-14
18.252
18.823
ppm


^{13}C NMR, 125 MHz, $CDCl_3$
TBDPS
O_2N
(R)-14
ppm

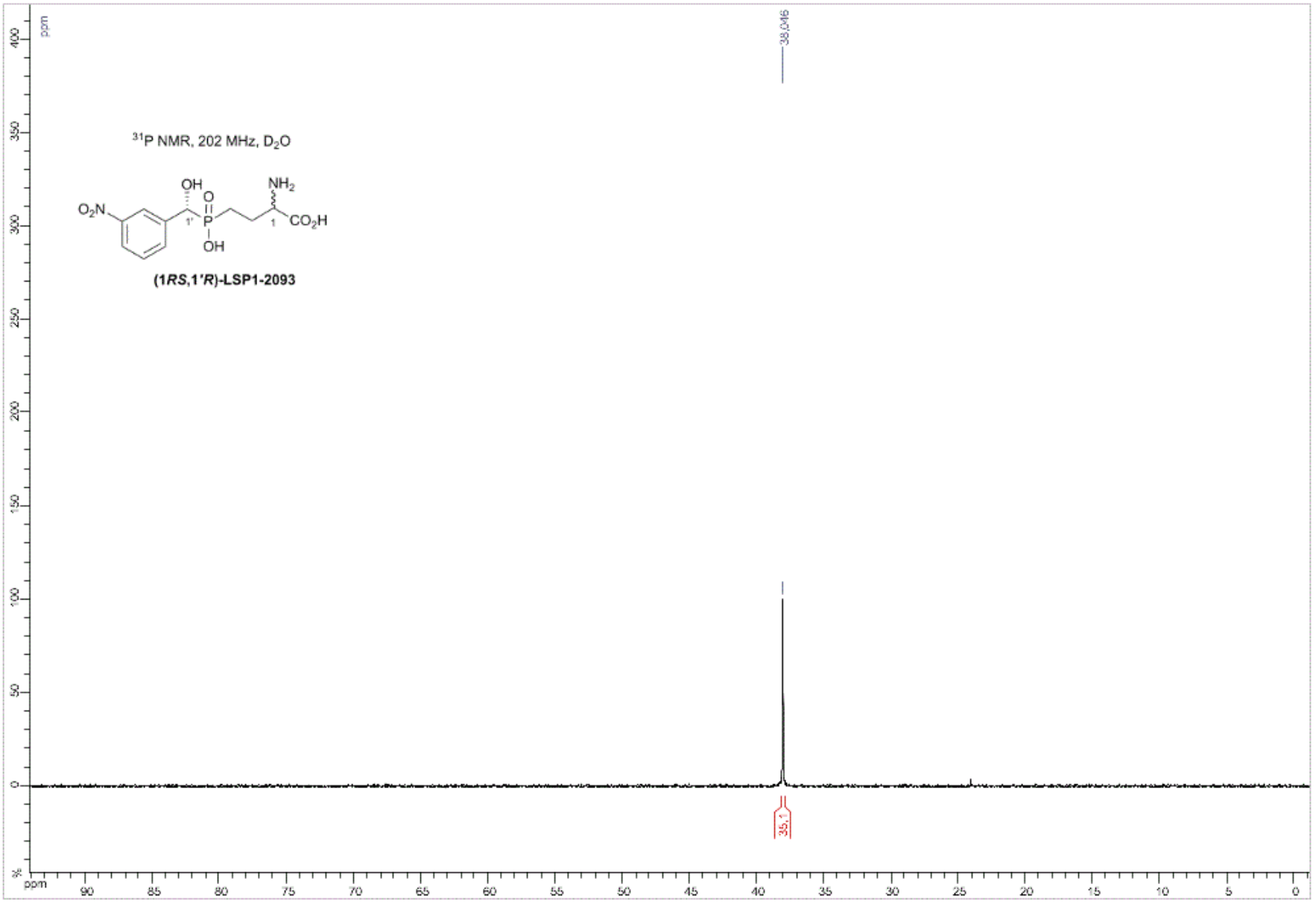

^{1}H NMR, 400 MHz, $CDCl_3$
TBDPS
O_2N
(S)-14
ppm

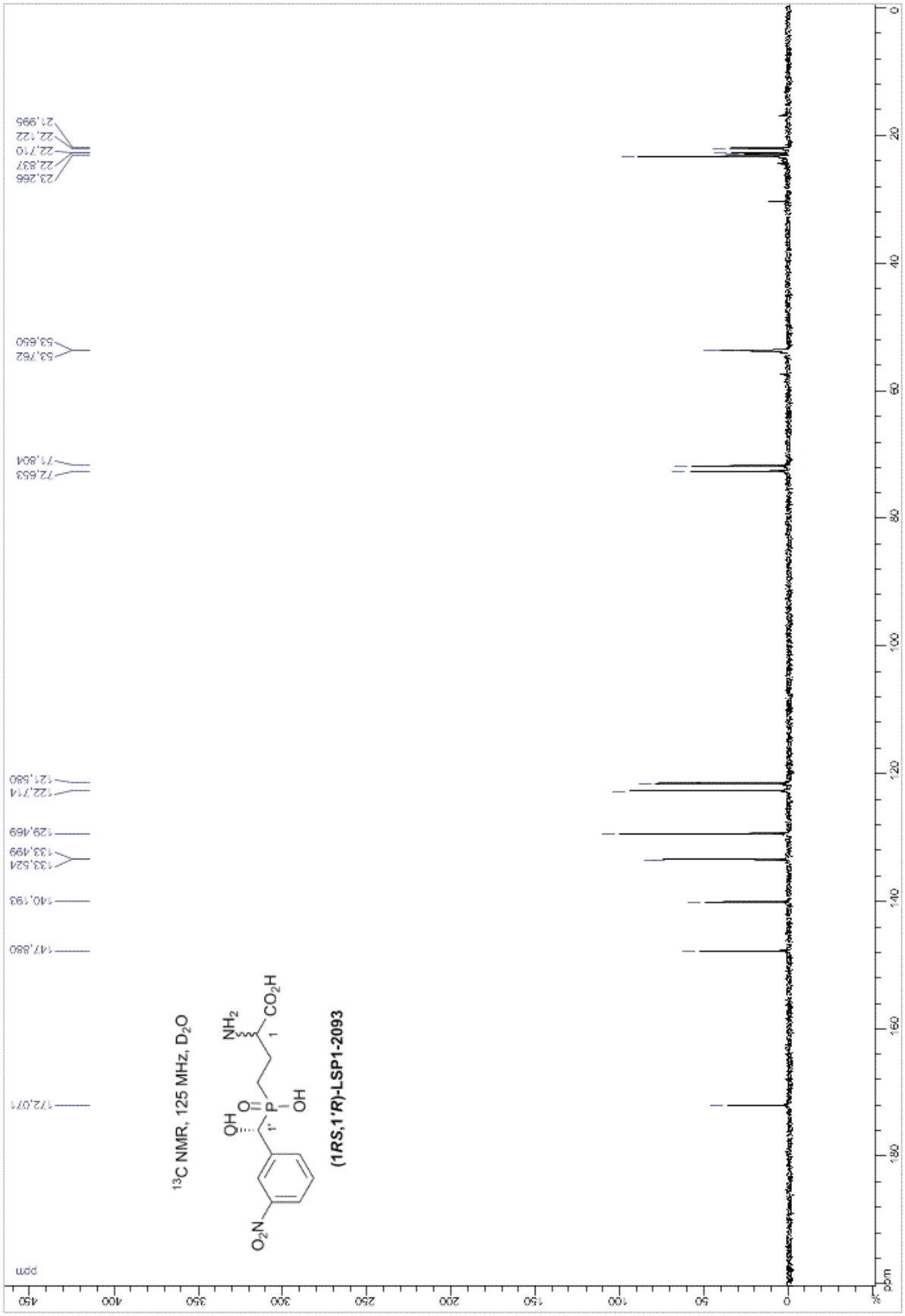

^{31}P NMR, 162 MHz, $CDCl_3$
TBDPS
O_2N
(S)-14
48.823
48.262
ppm

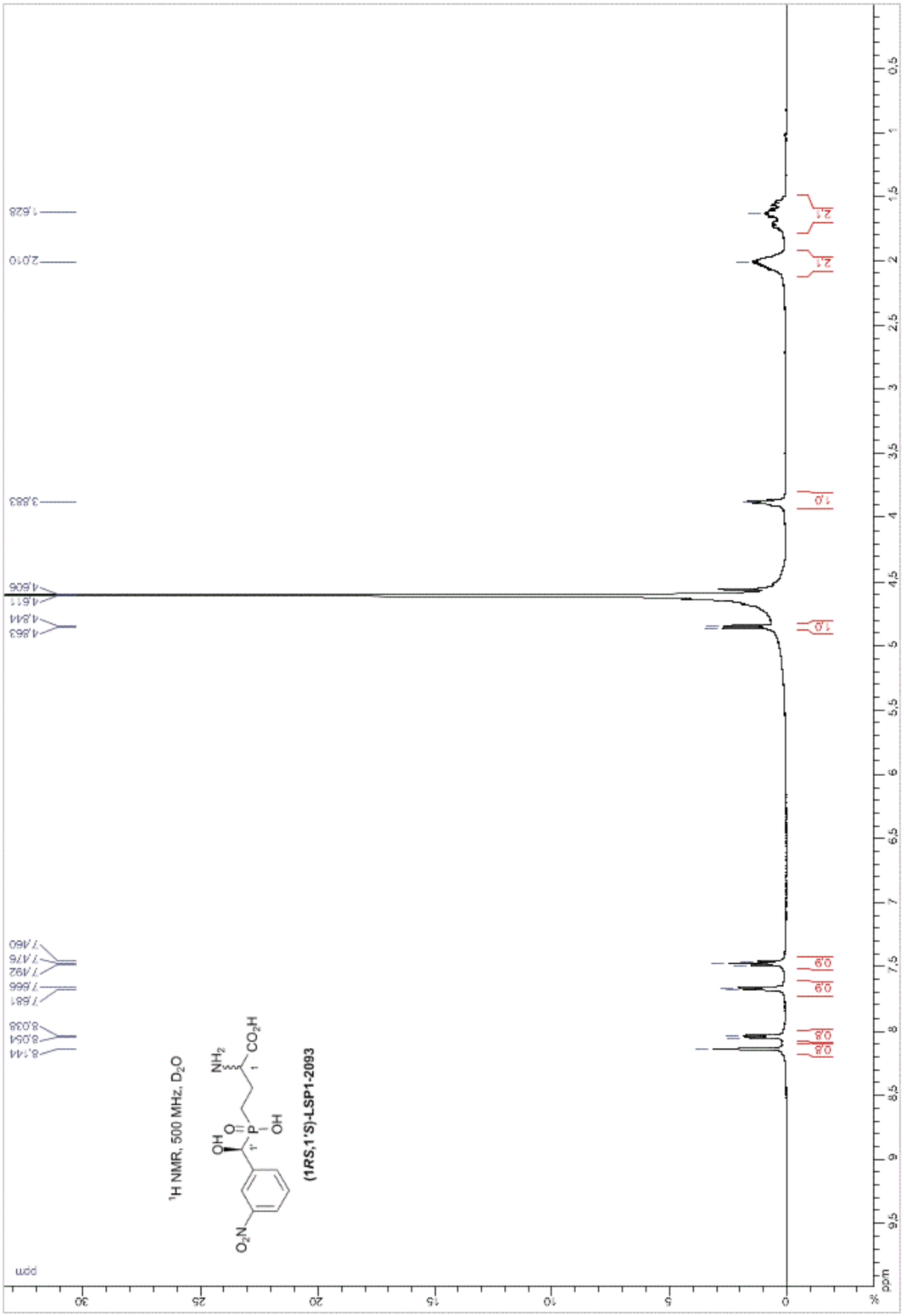

^{13}C NMR, 100 MHz, $CDCl_3$
TBDPS
O_2N
(S)-14
ppm

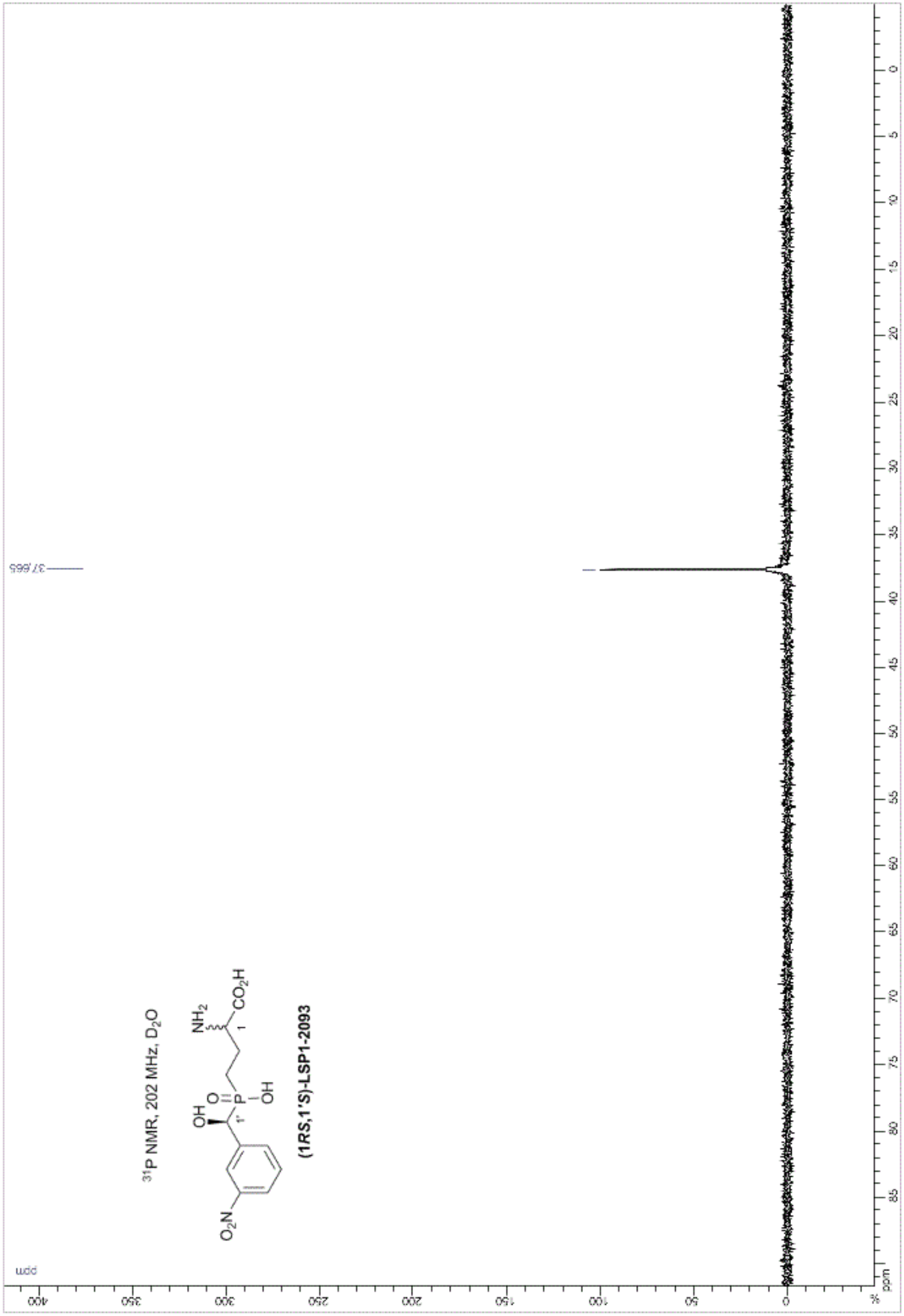


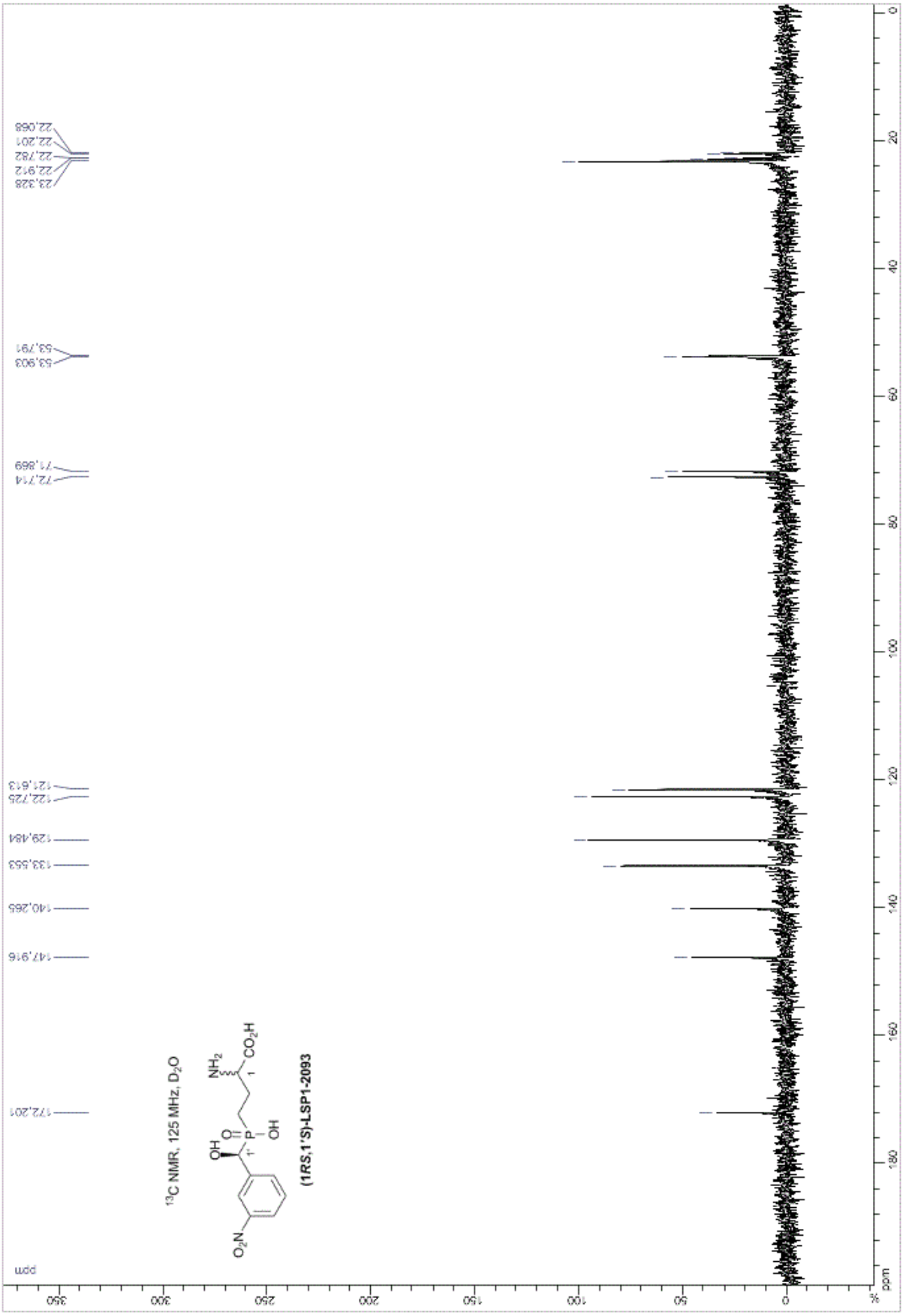
^{1}H NMR, 500 MHz, D_2O
(1RS,1'R)-LSP1-2093
8,234
8,144
8,128
7,770
7,756
7,581
7,566
7,550
4,956
4,937
4,780
3,994
3,980
2,107
2,100
2,090
1,737
1,726
1,713
ppm


ppm
38,046
^{31}P NMR, 202 MHz, D_2O
OH
O
NH_2
O_2N
1'
P
1
CO_2H
OH
(1*RS*,1'*R*)-LSP1-2093
35,1
%
ppm
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0


^{13}C NMR, 125 MHz, D_2O
(1*RS*,1'*R*)-LSP1-2093
172,071
147,880
140,193
133,524
133,499
129,469
122,714
121,580
72,653
71,804
53,762
53,660
23,266
22,837
22,710
22,122
21,995
ppm

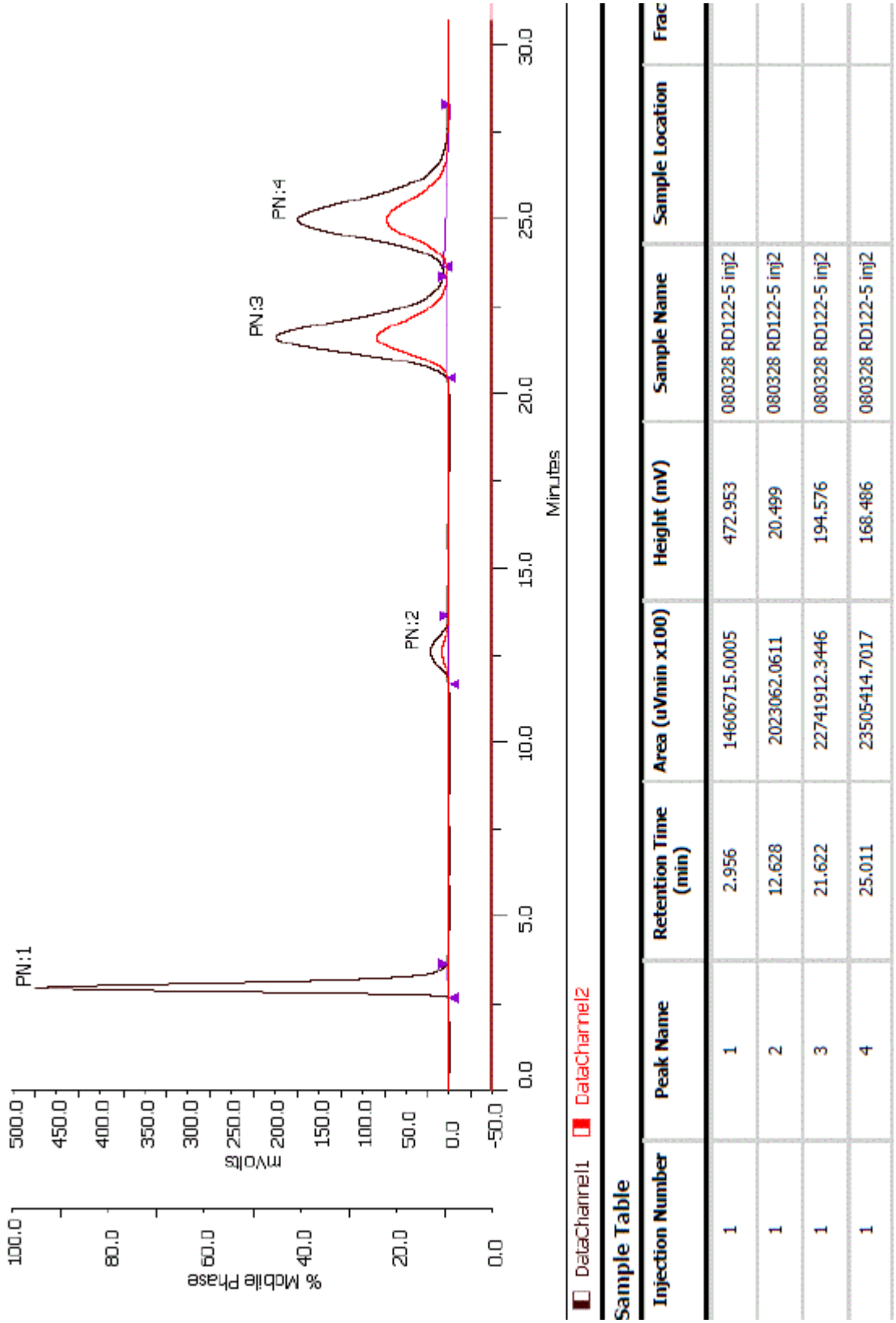

1H NMR, 500 MHz, D2O
(1RS,1'S)-LSP1-2093
8,144
8,054
8,038
7,681
7,666
7,492
7,476
7,460
4,863
4,844
4,611
4,606
3,883
2,010
1,628
1,0
1,0
0,9
0,9
0,8
0,8
2,1
2,1
ppm


37.665
ppm
400
350
300
250
200
150
100
50
0
^{31}P NMR, 202 MHz, D_2O
(1*RS*,1'*S*)-LSP1-2093


^{13}C NMR, 125 MHz, D_2O
(1*RS*,1'*S*)-LSP1-2093
172,201
147,916
140,265
133,563
129,484
122,725
121,613
72,714
71,869
53,903
53,791
23,328
22,972
22,782
22,201
22,068
ppm

5. HPLC Crownpak spectra

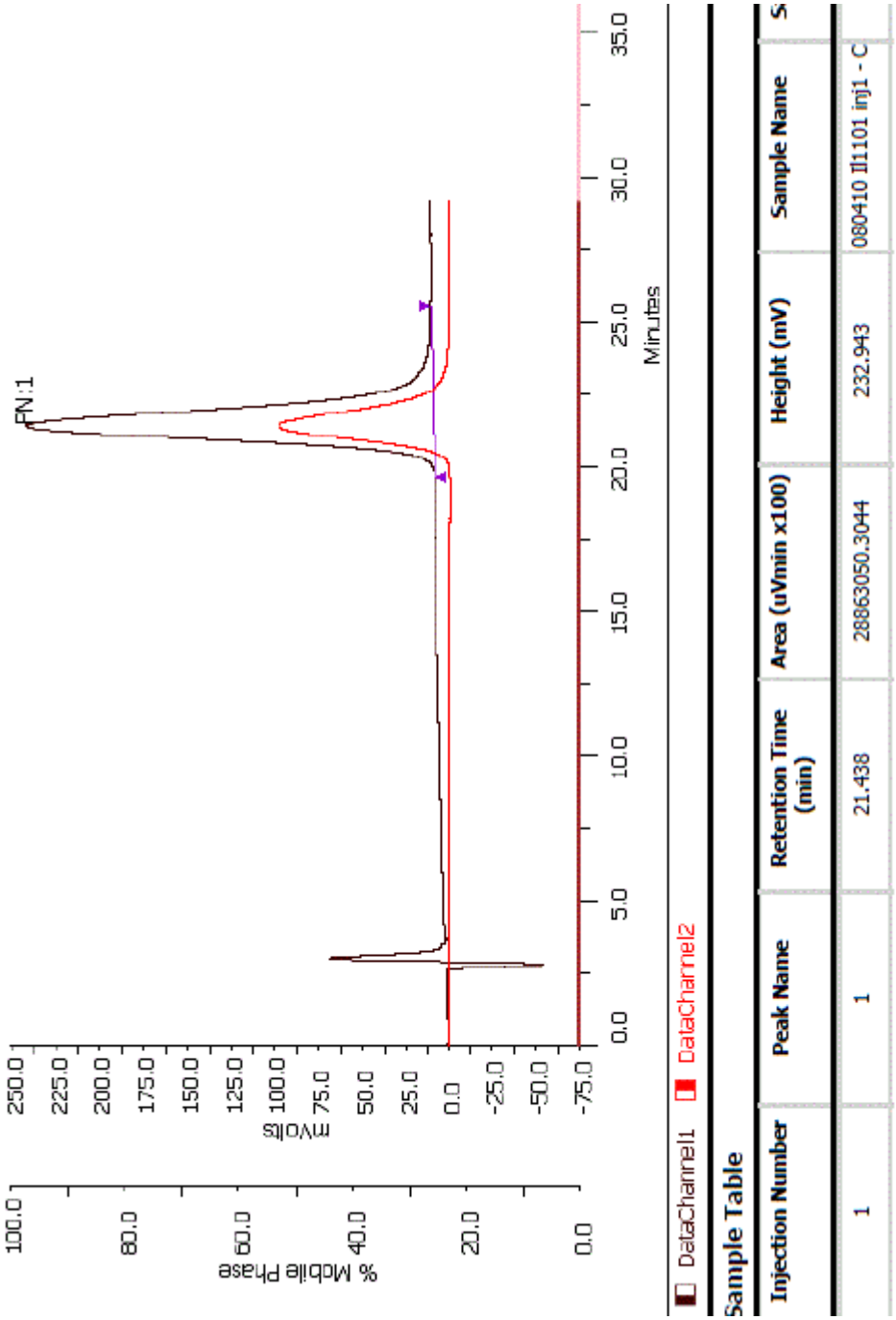
HPLC Crownpak : LSP1-2111 Mixture of 2 diastereomers



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sample Location	Frac
1	1	2.956	14606715.0005	472.953	080328 RD122-5 inj2		
1	2	12.628	2023062.0611	20.499	080328 RD122-5 inj2		
1	3	21.622	22741912.3446	194.576	080328 RD122-5 inj2		
1	4	25.011	23505414.7017	168.486	080328 RD122-5 inj2		

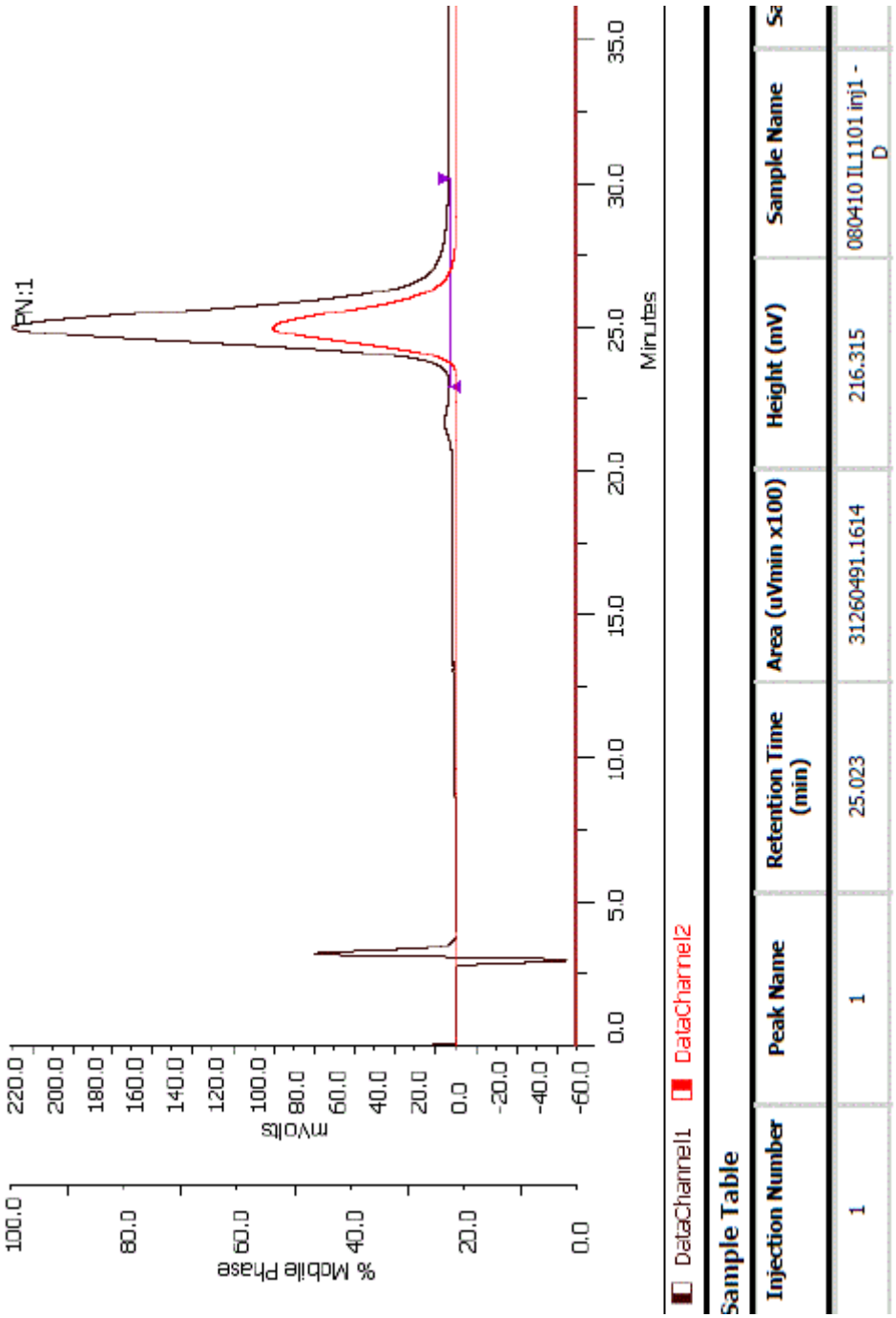
HPLC Crownpak : LSP1-2111 Dia I



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	S
1	1	21.438	28863050.3044	232.943	080410 Il1101 inj1 - C	

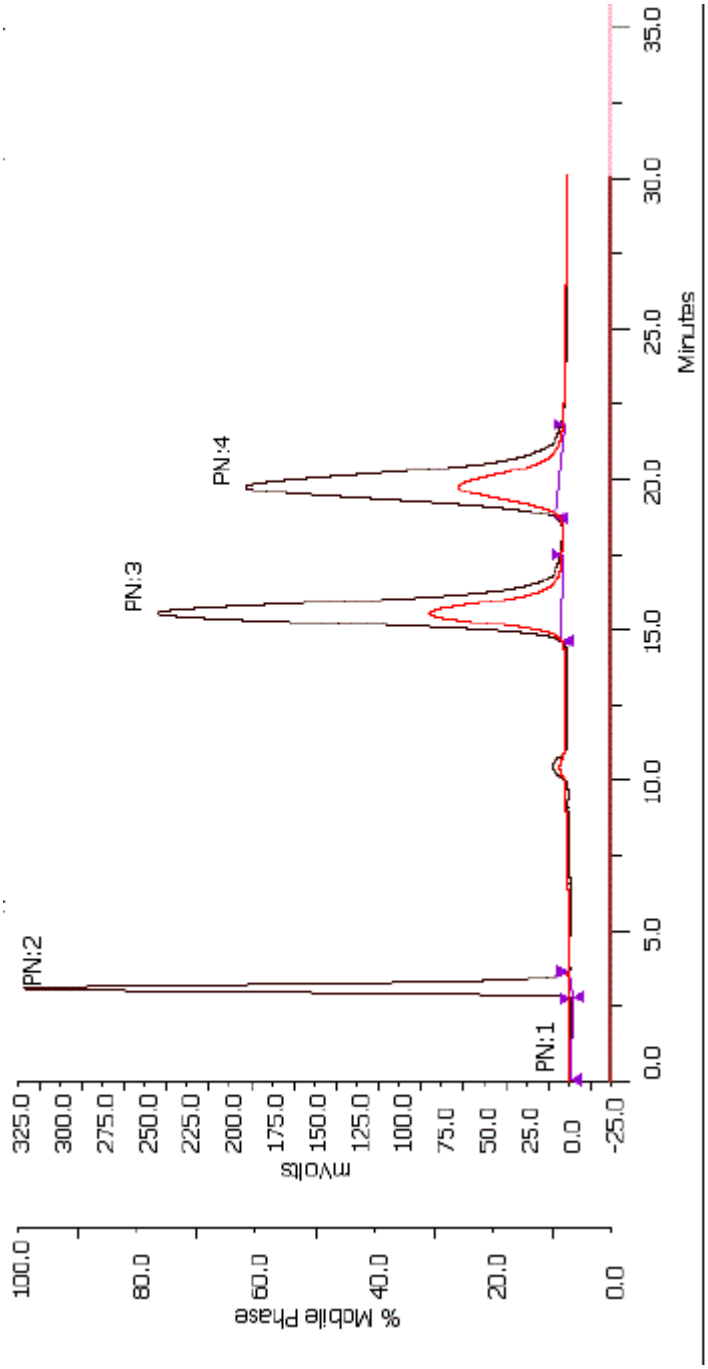
HPLC Crownpak : LSP1-2111 Dia II



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sa
1	1	25.023	31260491.1614	216.315	080410 IL1101 inj1 - D	

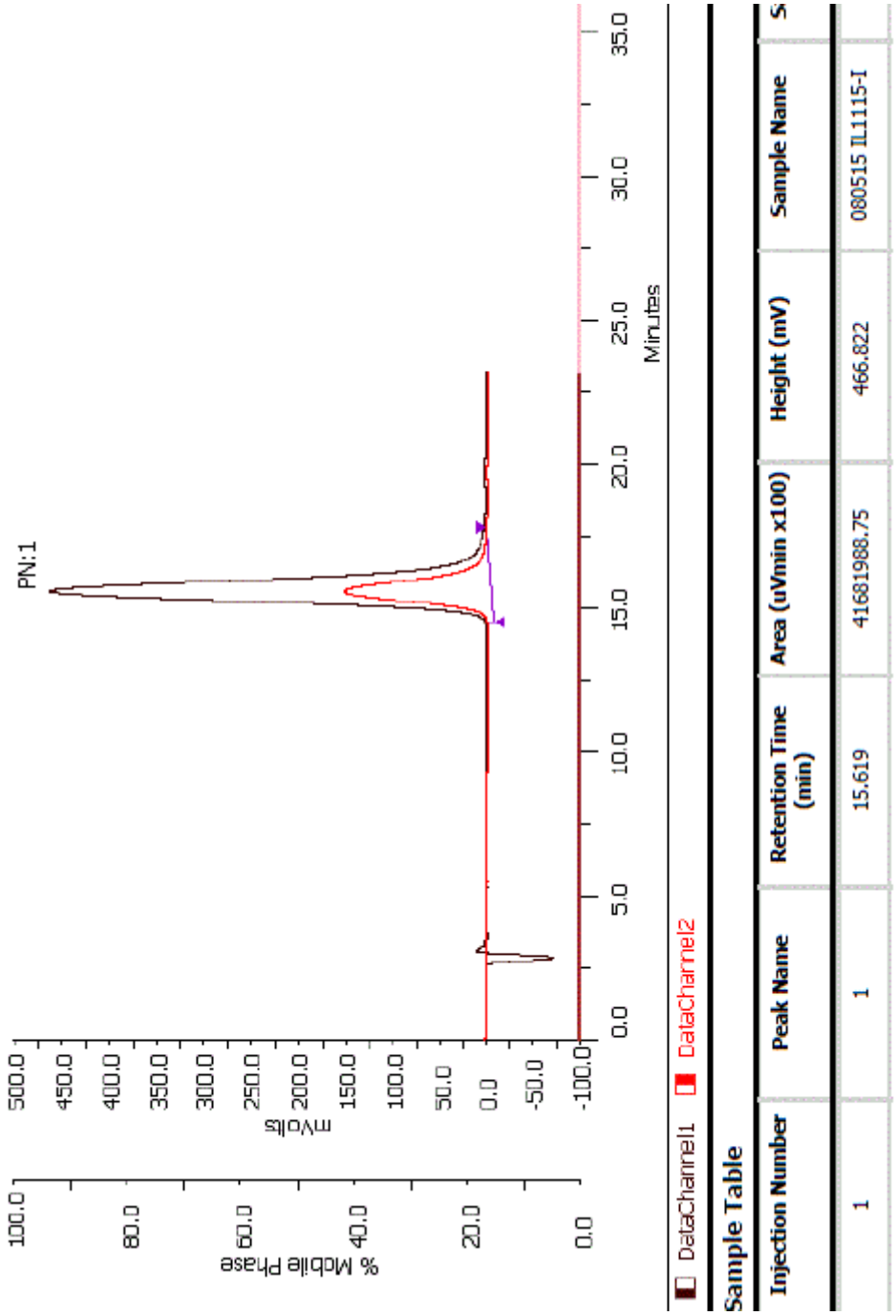
HPLC Crownpak : LSP1-2093 Mixture of 2 diastereomers



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name
1	1	2.69	213158.3376	1.106	080515 IL1113A
1	2	3.117	9087339.1643	321.987	080515 IL1113A
1	3	15.587	20601260.1754	238.421	080515 IL1113A
1	4	19.785	19687298.1025	185.323	080515 IL1113A

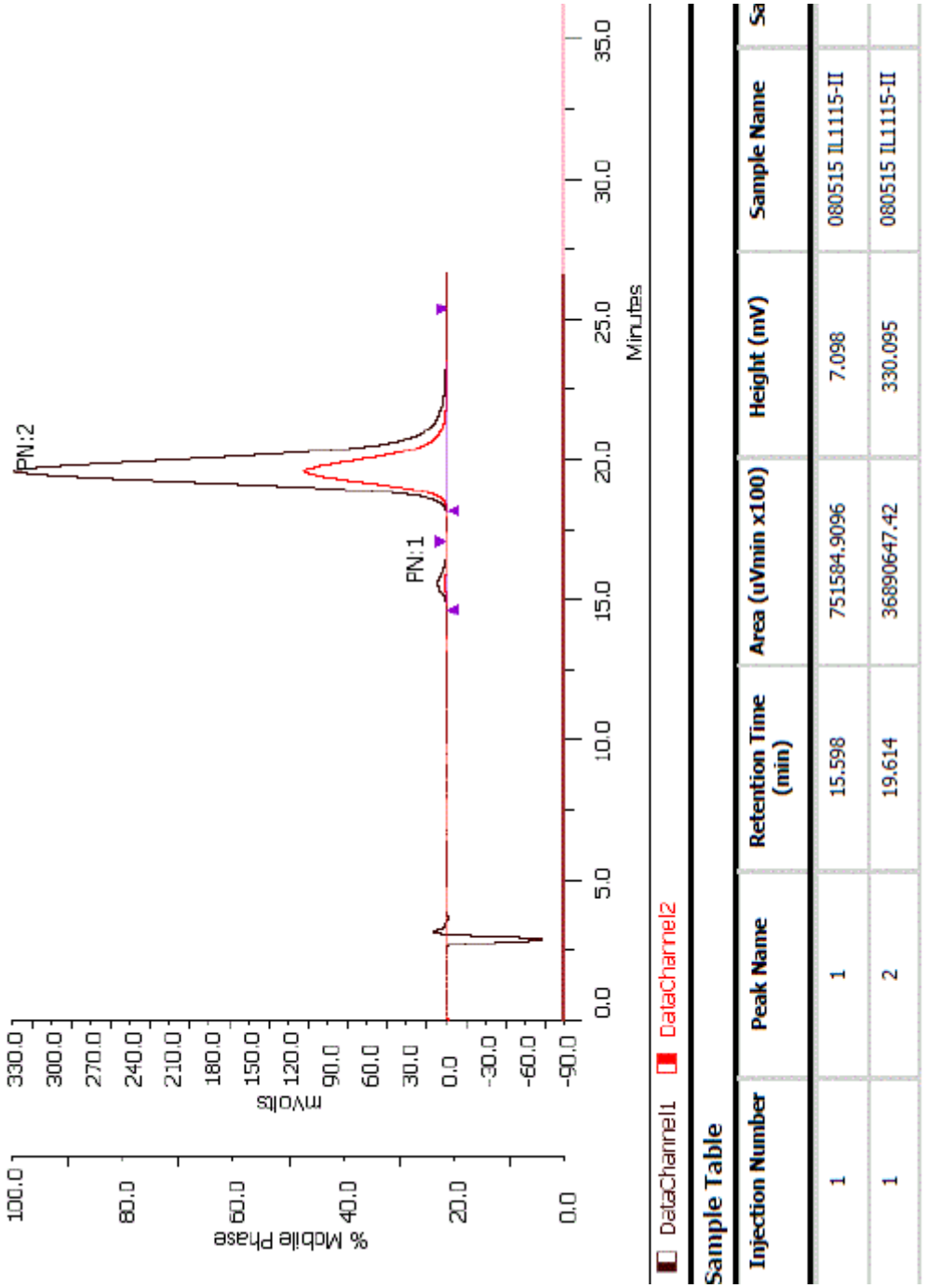
HPLC Crownpak : LSP1-2093 Dia I



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	S
1	1	15.619	41681988.75	466.822	080515 IL1115-I	

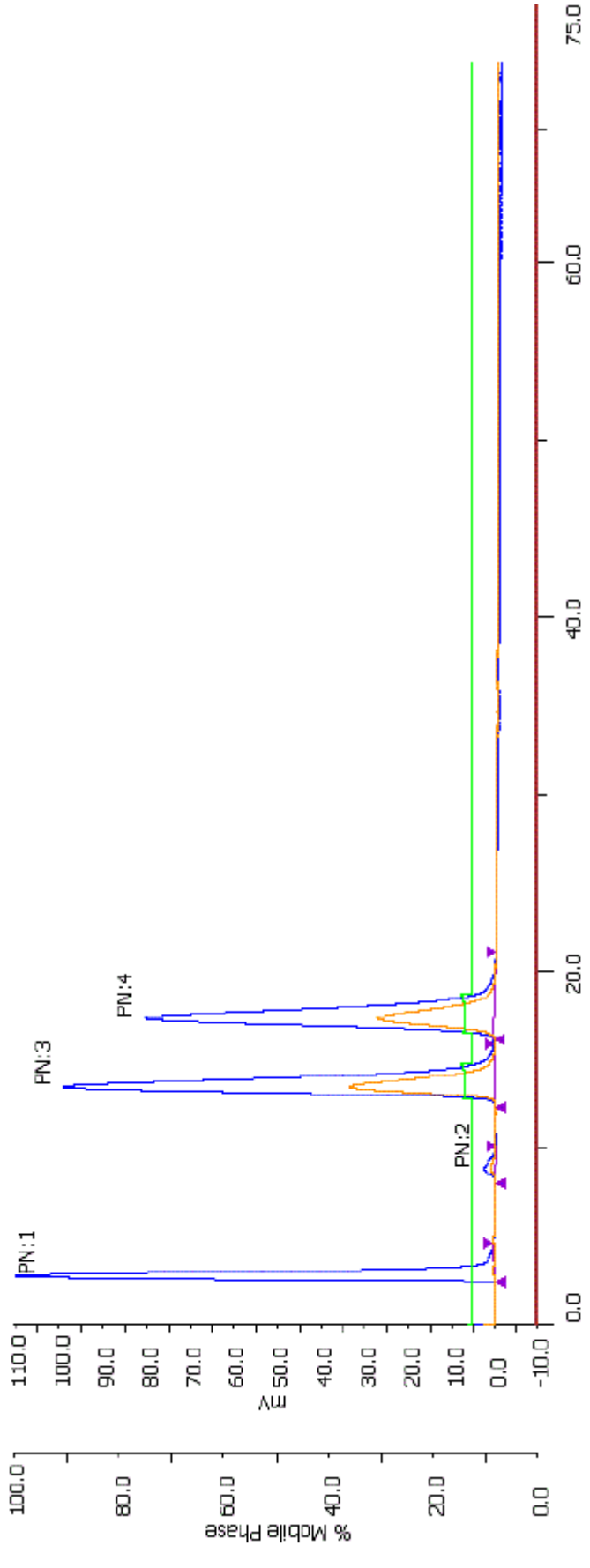
HPLC Crownpak : LSP1-2093 Dia II



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area (uVmin x100)	Height (mV)	Sample Name	Sa
1	1	15.598	751584.9096	7.098	080515 IL1115-II	
1	2	19.614	36890647.42	330.095	080515 IL1115-II	

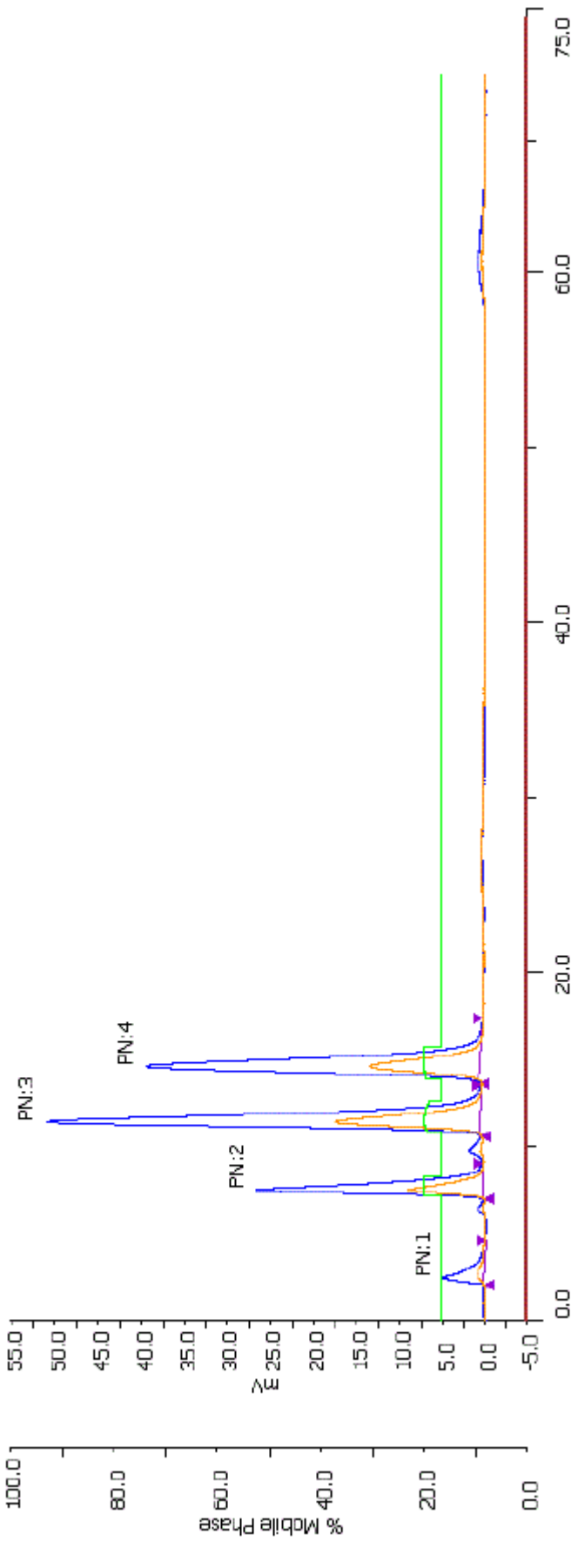
HPLC Crownpak : LSP1-2093 Mixture of 2 diastereomers



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area %	Sample Name	Sample Location	Fraction Site(s)	Area (mVmin /10)
1	1	2.752	22.773	IL1090A	Sample Zone->1		5314020.8509
1	2	8.825	0.97	IL1090A	Sample Zone->1		226277.4963
1	3	13.459	38.905	IL1090A	Sample Zone->1		9078449.1236
1	4	17.329	37.353	IL1090A	Sample Zone->1		8716407.3065

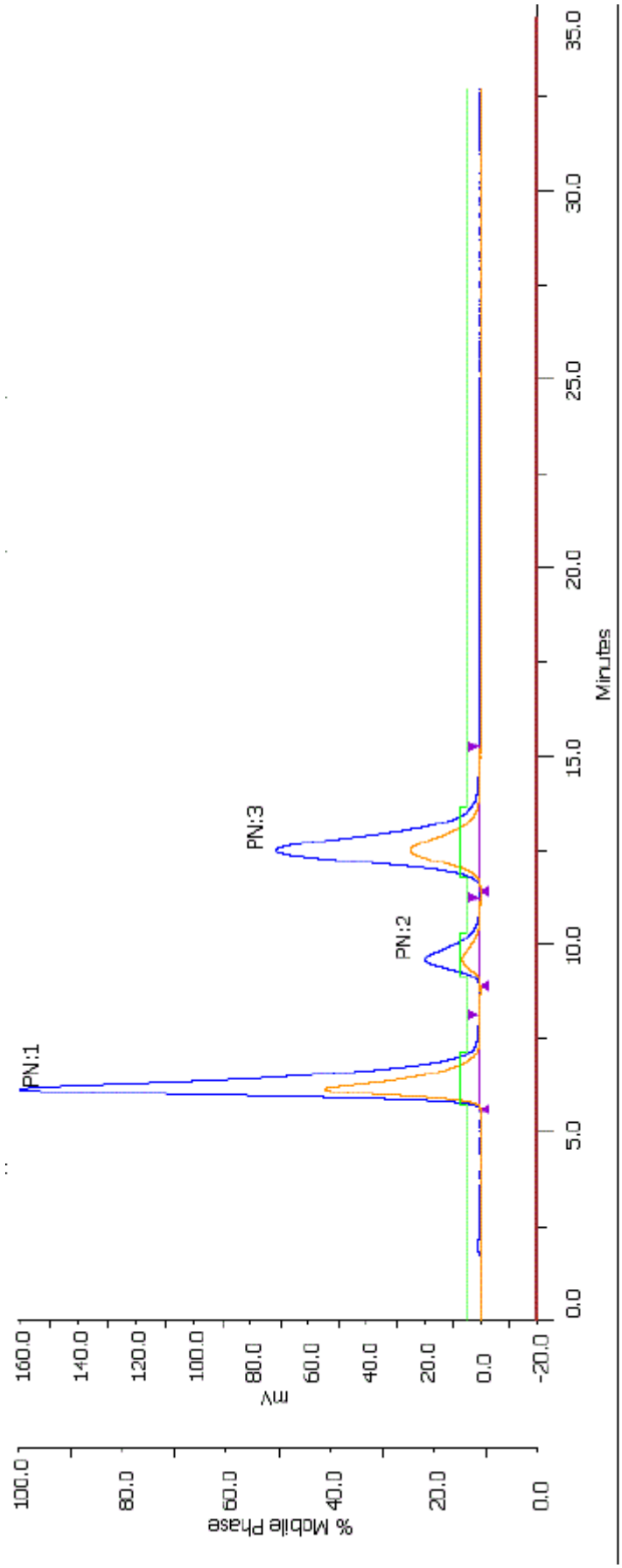
HPLC Crownpak : (1*RS*, 1'*RS*)-LSP1-2093



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area %	Sample Name	Sample Location	Fraction Site(s)	Area (mVmin /10)
3	1	2.498	3.872	RD14176	Sample Zone->3		373888.6375
3	2	7.504	17.652	RD14176	Sample Zone->3		1704528.2335
3	3	11.406	41.413	RD14176	Sample Zone->3		3999075.6709
3	4	14.584	37.063	RD14176	Sample Zone->3		3578984.3938

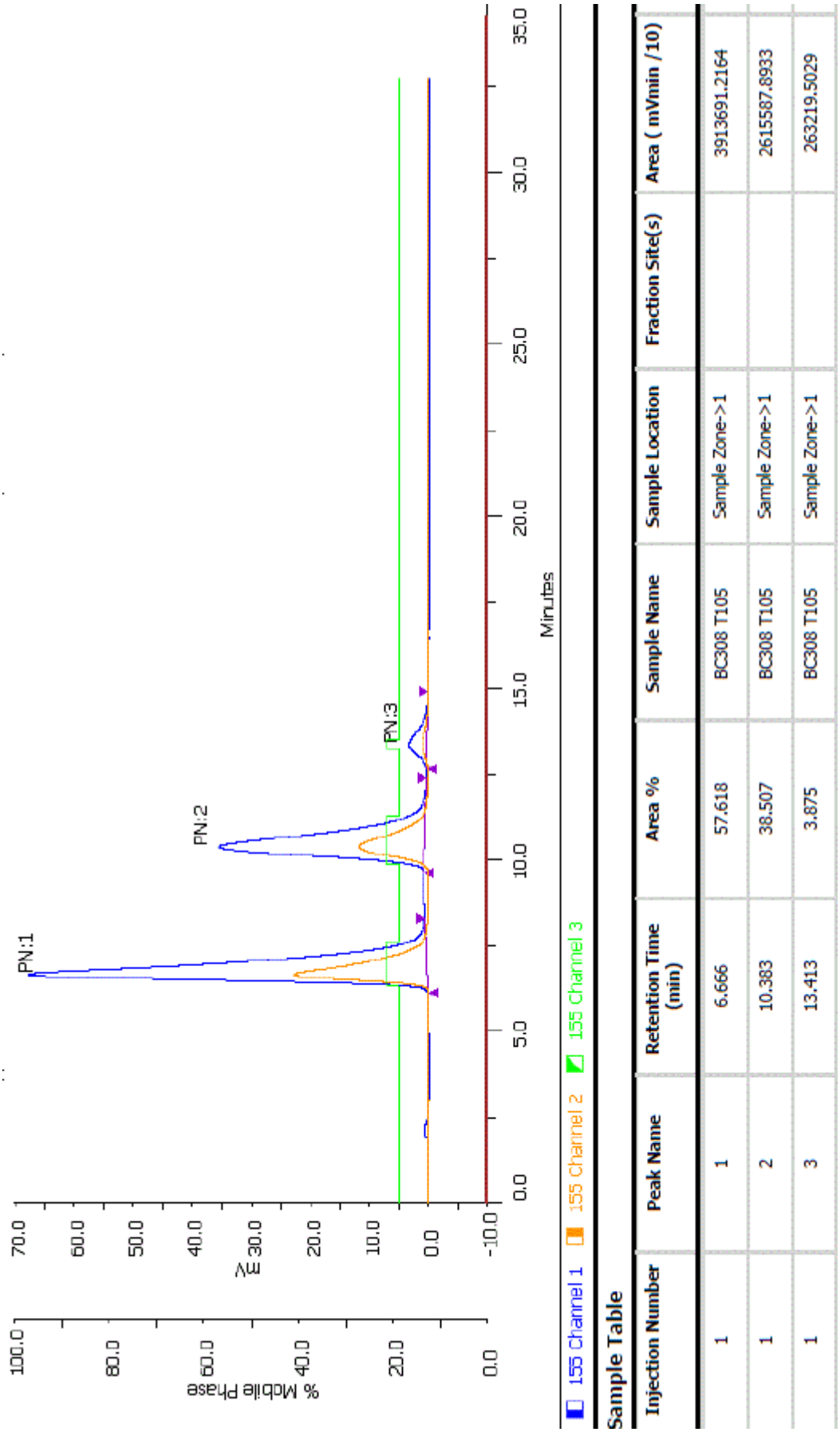
HPLC Crownpak : (1*RS*, 1'*R*)-LSP1-2093



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area %	Sample Name	Sample Location	Fraction Site(s)	Area (mVmin /10)
1	1	6.155	53.359	BC345-F2	Sample Zone->1		8462472.6393
1	2	9.596	8.398	BC345-F2	Sample Zone->1		1331837.7977
1	3	12.502	38.243	BC345-F2	Sample Zone->1		6065188.0336

HPLC Crownpak : (1*RS*, 1'*S*)-LSP1-2093



Sample Table

Injection Number	Peak Name	Retention Time (min)	Area %	Sample Name	Sample Location	Fraction Site(s)	Area (mVmin /10)
1	1	6.666	57.618	BC308 T105	Sample Zone->1		3913691.2164
1	2	10.383	38.507	BC308 T105	Sample Zone->1		2615587.8933
1	3	13.413	3.875	BC308 T105	Sample Zone->1		263219.5029

6. Crystallographic data (CCDC 1016374)

Data were collected with a Bruker SMART APEX CCD diffractometer (Mo-Kα radiation graphite-monochromated radiation, λ = 0.71073 Å) controlled by APEX2 software package.[1] Data integration and global cell refinement were performed with the program SAINT.[2] Data were corrected for absorption by the multiscan semiempirical method implemented in SADABS.[3] The structure was solved by direct methods using SHELXS 97.[4] Refinement, based on F2, was carried out by full matrix least squares with SHELXL-97 software.[5] Non hydrogen atoms were refined anisotropic thermal parameters. The hydrogen atoms were placed in their geometrically generated positions and allowed to ride on their parent atoms with an isotropic thermal parameter 20 % higher to that of the atom of attachment or located in difference Fourier maps, and their positions and isotropic thermal parameters were refined.

(1) *APEX2. Data Collection Software*, Bruker AXS Inc.: Madison, Wisconsin, USA, 2007.

(2) Bruker *SAINT*, Bruker AXS Inc: Madison, Wisconsin, USA, 2007.

(3) *SADABS.2008/1*, Bruker AXS Inc.: Madison, Wisconsin, USA, 2007.

(4) Sheldrick, G. M. *SHELXS-97, Program for crystal structure solution*, University of Gottingen,

Germany, 1997.

(5) Sheldrick, G. M. *SHELXR-97, Program for crystal structure refinement*, University of Gottingen,

Germany, 1997.

Table 1 - Crystal data and structure refinements

Formula	$C_7H_7NO_5P$, $C_8H_{12}N$
Fw	338.29
T(K)	293(2)
wavelenght (Å)	0.71073

crystal system	monoclinic
space group	P21
unit cell dimension	
a (Å)	12.2471(6)
b (Å)	5.6271(3)
c (Å)	13.2223(6)
α (°)	90
β (°)	112.390(2)
γ(°)	90
V (Å^3)	842.53(7)
Z	2
d(calc) (Mg/m^3)	1.333
abs coeff (mm^{-1})	0.189
crystal size (mm^3)	0.15x0.08x0.02
crystal color	Colourless
θ range [deg]	1.67-28.73
index ranges	-16<h<16
	-7<k<7
	-17<l<17
no. of reflns collected	46232
no. of indep reflns	4377
R(int)	0.033
GOF on F^2	1.106
R1/wR2[a,b],[I>2σ(I)]	0.0351/0.0870
R1/wR2[a,b], all data	0.0576/0.1123
largest diff peak and hole [e.Å^{-3}]	0.212and -0.305

[a]R1 = Σ||*Fo*| – |*Fc*||/Σ|*Fo*|. [b] wR2 = {Σ[w($F_O^2 - F_c^2$)^2]/ Σ [w(F_O^2)2] ; where w = $q/\sigma^2(F_O^2) + (qp)^2 + bp$. GOF = S = {Σ[w($F_O^2 - F_c^2$)^2]/ (n – p)$^{1/2}$.