A Convergent Triflate Displacement Approach to (α-Monofluoro)alkylphosphonates

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SUPPORTING INFORMATION

Experimental Section

General. All reactions were conducted under argon atmosphere using oven-dried glassware. Methylene chloride and diisopropylamine were distilled from CaH_2. THF and Et_2O were distilled from sodium benzophenone ketyl. HMPA was distilled from Na under reduced pressure. Methanol was distilled from Mg. Potassium bis(trimethyl)silylamide in toluene was purchased from Aldrich. Sodium mercury amalgam (containing 5% sodium) was freshly prepared *(Reagents for Organic Synthesis*, L. F. Fieser & M. Fieser, Vol 1, p. 1030 (1967, Wiley, New York) or purchased from Aldrich. Other reagents were obtained from commercial sources and used without further purification. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded on a Bruker-DRX-Avance-500-GE or Omega-300 instrument with chemical shifts reported relative to residual $CHCl_3$ (7.25 ppm). Proton-decoupled ^{13}C NMR spectra were acquired on a Bruker-DRX-Avance-500 or GE Omega-300 instrument with chemical shifts reported relative to $CDCl_3$ (77.0 ppm). ^{31}P and ^{19}F NMR spectra were recorded on a GE Omega-300 or Bruker-DRX-Avance-500 instrument with chemical shifts reported relative to the internal (capillary) standards triphenylphosphine (-5.80 ppm), and trifluoroacetic acid (-76.5 ppm), respectively. Infrared spectra were obtained using an Analect RFX-65 FTIR spectrometer. Mass spectra were acquired at the Nebraska Center for Mass Spectrometry (University of Nebraska-Lincoln). Elemental analyses were carried out by Midwest Microlab, LLC (Indianapolis, IN).

Diethyl 1-Fluoro-1-phenylsulfonyl-3-methylbutane-1-phosphonate (10a). To a solution of diethyl (α-fluoro-α-phenylsulfonyl)methylphosphonate (**8**, 167 mg, 0.54 mmol) and HMPA (0.3 mL) in 1.1 mL THF cooled to -78°C , was added KHMDS (1.1 mL of a 0.5 M solution in toluene, 0.54 mmol) slowly, down the sides of the flask. Deprotonation was carried out for 5 min at that temperature. Then isobutyl iodide (63 μL, 0.54 mmol) was added and the cold bath was removed in order to allow the reaction to slowly warm. After 1 h of stirring, the reaction was quenched with NH_4Cl (5 mL) and Et_2O (5 mL). The organic layer was further extracted with Et_2O (3 x 3 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (30%→50% EtOAc-hexane) gave **10a** (142 mg, 72%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6 Hz, 3 H), 0.96 (d, *J* = 6 Hz, 3 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.31 (t, *J* = 7 Hz, 3 H), 2.01 (m, 1 H), 2.25 (m, 2 H), 4.19 (m, 4 H), 7.56 (dd, *J* = 7,8 Hz, 2 H), 7.69 (t, *J* = 7 Hz, 1 H), 7.98 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.29 (d, *J* = 5 Hz), 16.32 (d, *J* = 6 Hz), 23.2 (d, *J* = 3 Hz), 24.6, 24.7 (br), 39.0 (d, *J* = 18 Hz), 64.4 (d, *J* = 7 Hz), 64.7 (d, *J* = 7 Hz), 108.8 (dd, *J* = 166, 232 Hz), 128.6, 130.9, 134.5, 135.7; ^{31}P NMR (122 MHz, $CDCl_3$) δ 9.14 (d, *J* = 83 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ -167.03 (ddd, *J* = 18, 34, 82 Hz); HRMS (FAB, 3-NOBA) calcd for $C_{15}H_{25}O_5PFS$ ($M+H^+$) 367.1144, obsd 367.1145.

(*S*)-(+)-Citronellyl iodide (9b). To (*S*)-(+)-citronellyl bromide (500 mg, 2.28 mmol) were added acetone (7 mL) and NaI (1 g, 6.85 mmol; pre-dried in vacuo at 210 °C), and this solution was stirred in the dark for 72 h. The acetone was then evaporated , and the residue was taken up in Et_2O (10 mL) and extracted with $Na_2S_2O_4$ (3 x 10 mL), dried ($MgSO_4$) and evaporated to give the desired product **9b** (550 mg). The iodide was used directly in the next step without further purification: : ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 4 Hz, 3 H), 1.19 (m, 2 H), 1.52 (m, 2H), 1.59 (s, 3 H), 1.69 (s, 3 H), 1.92 (m, 3 H), 3.19 (m, 2 H), 4.97 (m, 1 H).

Diethyl (4S)-4,4-Dimethyl-1-fluoro-1-phenylsulfonyl-7-nonene-1-phosphonate (10b). Following the procedure for the synthesis of **10a**, from diethyl (α-fluoro-α-phenylsulfonyl)methylphosphonate (**8**, 100 mg, 0.32 mmol), KHMDS (0.64 mL of a 0.5 M solution in toluene, 0.32 mmol) and **9b** (129 mg, 0.48 mmol) was obtained **10b** (100 mg, 69%) as a colorless oil, following flash chromatography (10%→50% EtOAc-hexane). ^{31}P NMR of the crude showed that it contained a 1:1 mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$; *resolved peaks*) δ 0.84 (d, *J* = 6 Hz, 3 H; one diastereomer), 0.85 (d, *J* = 6 Hz, 3 H; other diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 108.0 (dd, *J* = 166, 230 Hz; one diastereomer), 108.1 (dd, *J* = 165, 228 Hz; other diastereomer); ^{31}P NMR (122 MHz, $CDCl_3$) δ 9.03, (d, *J* = 82 Hz; one diastereomer), 9.08 (d, *J* = 82 Hz; other diastereomer); ^{19}F NMR (283 MHz, $CDCl_3$) δ -164.2 (m, both diastereomers); HRMS (FAB, 3-NOBA) calcd for $C_{21}H_{35}O_5PFS$ (M+H$^+$) 449.1926, obsd 449.1937; Anal Calcd for $C_{21}H_{34}O_5PFS$: C, 56.25; H, 7.59. Found: C, 56.21; H, 7.49.

α^4,3-*O*-Isopropylidene-α^5-pyridoxyl Chloride. To a solution of α^4,3-*O*-isopropylidenepyridoxine (75 mg, 0.36 mmol), NEt_3 (0.15 mL, 1.0 mmol) and DMAP (13 mg, 0.1 mmol) in CH_2Cl_2 (2.3 mL) at 0 °C, was added methanesulfonyl chloride (31 μL, 0.4 mmol) dropwise, via syringe. After 1 h at 0 °C, the reaction was quenched with water, and extracted with CH_2Cl_2 (3 x 2 mL). The combined organics were then dried ($MgSO_4$), filtered and concentrated to give a clean sample of the desired product, without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 6 H), 2.41 (s, 3 H), 4.46 (s, 2 H), 4.93 (s, 2 H), 7.99 (s, 1 H).

α^4,3-*O*-Isopropylidene-α^5-pyridoxyl Iodide (9d). The crude pyridoxyl chloride (90 mg) and tetrabutylammonium iodide (217 mg, 0.59 mmol) in CH_2Cl_2 (2 mL) were stirred for 1 h in the dark at 0 °C. After quenching with water, and extraction (CH_2Cl_2; 3 x 2 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated. For characterization purposes, the iodide could be purified by chromatography (30%→50% EtOAc-hexane). Iodide **9d** (79 mg, 70%) was obtained as an unstable oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 6 H), 2.38 (s, 3 H), 4.23 (s, 2 H), 4.79 (s, 2 H), 8.01 (s, 1

H); HRMS (FAB, 3-NOBA) calcd for $C_{11}H_{15}NO_2I$ ($M+H^+$) 320.0147, obsd 320.0156. *Note*: In practice, it proved to be much more efficient to generate the iodide **9d**, in situ, from the corresponding chloride (see below).

α^4,3-*O*-Isopropylidene-α^5-deoxy-α^5-[diethyl(1'-fluoro-1'-phenylsulfonyl)phosphonomethyl]pyridoxine (10d). To a solution of (α-fluoro-α-phenylsulfonyl)methylphosphonate (**8**, 183 mg, 0.59 mmol) and HMPA (0.7 mL) in THF (2 mL) cooled to -78°C , was added KHMDS (1.18 mL of a 0.5 M solution in toluene, 0.59 mmol). After allowing for deprotonation for 5 min, a solution of pyridoxyl chloride (90 mg crude) and tetrabutylammonium iodide (217 mg, 0.59 mmol) at -78°C in THF (0.9 mL)/ CH_2Cl_2 (0.3 mL) was added, via cannula. The cold bath was then removed. After 90 min total reaction time, NH_4Cl (satd. aq., 3 mL) and Et_2O (4 mL) were added. The organic layer was further extracted with Et_2O (3 x 4 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. Flash chromatography (50% EtOAc/hexane→100% EtOAc) gave **10d** (108 mg, 60% over 2 steps) as a pale brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7 Hz, 3 H), 1.22 (t, J = 7 Hz, 3 H), 1.49 (s, 6 H), 2.34 (s, 3 H), 3.44 (m, 2 H), 3.88 (m, 1 H), 4.00 (m, 1 H), 4.14 (m, 2 H), 4.80 (s, 2 H), 7.53 (t, J = 8 Hz, 2 H), 7.67 (dd, J = 7, 8 Hz, 1 H), 7.95 (d, J = 7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 (d, J = 6 Hz), 16.1 (d, J = 6 Hz, 2 C), 18.3, 24.3, 24.9, 29.7 (d, J = 19 Hz), 60.0 (d, J = 6 Hz), 64.4 (d, J = 7 Hz), 64.9 (d, J = 7 Hz), 99.6, 107.1 (dd, J = 166, 233 Hz), 121.2, 126.9, 128.6 (2C), 130.8 (2 C), 134.8, 135.2, 142.8, 145.7, 146.8; ^{31}P NMR (122 MHz, $CDCl_3$) δ 7.45 (d, J = 80 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ -164.4 (ddd, J = 21, 29, 82 Hz); HRMS (FAB, 3-NOBA) calcd for $C_{22}H_{30}O_7PFSN$ ($M+H^+$) 502.1464, obsd 502.1487.

General Procedure A. Diethyl 1-Fluoro-1-phenylsulfonyl-3,4-(*O*-isopropylidene)-3,4-dihydroxybutylphosphonate (10c). To a solution of diethyl (α-fluoro-α-phenylsulfonyl)methylphosphonate (**8**, 763 mg, 2.46 mmol) in HMPA (1.7 mL)/THF(7 mL) at -78°C, was added KHMDS (4.9 mL of a 0.5 M solution in toluene, 2.46 mmol). Following deprotonation (5 min at -78°C), a solution of **9c**[15] (325 mg, 1.23 mmol) in THF (3 mL) at -78°C was added, via cannula. The cold bath was then removed, and after 20 min, the reaction was quenched with NH_4Cl (5 mL) and Et_2O (5 mL). [For triflates, in general, displacement reactions were complete after 10-20 min total reaction time as judged by TLC (eluent typically 50% EtOAc-hexane)]. The organic layer was further extracted with Et$_2$O (3 x 10 mL). The combined organics were dried (MgSO$_4$), filtered and evaporated. ^{19}F and ^{1}H NMR of the crude showed that it contained a 3:1 mixture of diastereomers. Flash chromatography (10%→50% EtOAc-hexane) gave **10c** (355 mg, 68%,) as a colorless oil containing a mixture of diastereomers: ^{1}H NMR (300 MHz, CDCl$_3$; *resolved peaks*) δ 3.53 (dd, *J* = 7, 8 Hz, 1 H; major), 3.62 (dd, *J* = 7, 8 Hz, 1 H; minor); ^{13}C NMR (125 MHz, CDCl$_3$) δ 16.1 (t, *J* = 5 Hz, 2 C), 25.37 (minor), 25.39 (major) , 26.60 (major), 26.63 (minor), 35.4 (d, *J* = 20 Hz; major), 35.5 (d, *J* = 20 Hz; minor), 64.6 (d, *J* = 7 Hz), 64.9 (d, *J* = 6 Hz), 69.4 (d, *J* = 4 Hz; major), 69.8 (d, *J* = 3 Hz; minor), 71.1 (br; minor), 71.4 (br; major), 105.9 (dd, *J* = 166, 229 Hz; major), 106.3 (dd, *J* = 166, 229 Hz; minor), 108.4 (major), 108.6 (minor), 128.6, 130.69 (minor), 130.73 (major), 134.6 (minor), 134.7 (major), 134.8 (major), 135.2 (minor); ^{31}P NMR (202 MHz, CDCl$_3$) δ 7.88 (d, *J* = 81 Hz; both diastereomers); ^{19}F NMR (283 MHz, CDCl$_3$) δ 166.7 (ddd, *J* = 15, 37, 81 Hz; major), -167.1 (app dt, *J* = 24, 82 Hz; minor); HRMS (FAB, 3-NOBA/NaI) calcd for $C_{17}H_{26}O_7PFSNa$ (M+Na$^+$) 447.1018, obsd 447.1027.

Benzyl 6-Deoxy-6-diethyl-(1’-fluoro-1’-phenylsulfonyl)phosphonomethyl-2,3,4-tri-*O*-benzyl–β-D-glucopyranoside (10e). Following general procedure A, **9e**^{15} (136 mg, 0.2 mmol),) afforded the desired product **10e** (100 mg, 60%) as a white solid (1:1 mixture of diastereomers as determined from ^{31}P NMR): ^{1}H NMR (500 MHz, CDCl$_3$; *resolved peaks*) δ 7.47 (t, *J* = 8 Hz, 2 H; one diastereomer), 7.53 (t, *J* = 8 Hz, 2 H; other diastereomer), 7.62 (t, *J* = 7 Hz, 1 H; one diastereomer), 7.68 (t, *J* = 9 Hz, 1 H; other diastereomer), 7.96 (d, *J* = 8 Hz, 2 H; one diastereomer), 7.98 (d, *J* = 9 Hz, 1 H; other diastereomer); ^{13}C NMR (125 MHz, CDCl$_3$) δ 33.2 (d, *J* = 19 Hz; one diastereomer), 33.5 (d, *J* = 19 Hz; other diastereomer), 74.6 (d, J = 13 Hz; one diastereomer), 74.8 (d, J = 13 Hz; other diastereomer), 102.0 (one diastereomer), 102.1 (other diastereomer), 130.85 (one diastereomer), 130.92 (other diastereomer); ^{31}P NMR (202 MHz, CDCl$_3$) δ 7.78 (d, *J* = 83 Hz; one diastereomer), 8.16 (d, *J* = 83 Hz; other diastereomer); ^{19}F NMR (470 MHz, CDCl$_3$) δ -166.3 (ddd, *J* = 16, 36, 83 Hz; one diastereomer), -166.5 (dt,

J = 23, 82 Hz; other diastereomer); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{45}H_{50}O_{10}SPFLi$ (M+Li$^+$) 839.3006, obsd 839.3037.

3-*O*-Benzyl-5-deoxy-5-diethyl(1'-fluoro-1'-phenylsulfonyl)phosphonomethyl-1,2-*O*-isopropylidene-α-D-ribofuranoside (10f). From **9f**[15] (235 mg, 0.55 mmol) following general procedure A, was obtained **10f-***first eluting diastereomer* (135 mg), as a white solid, and **10f-***second eluting diastereomer* (110 mg), as a colorless oil. Total yield was 78% (245 mg -1:1.2 ratio of diastereomers, as determined from integration of characteristic signals in the crude ^{19}F NMR): **10f**-*first eluting diastereomer***:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (overlapping t, J = 7 Hz, 6 H), 1.33 (s, 3 H), 1.57 (s, 3 H), 2.33 (m, 1 H), 2.69 (ddd, J = 4, 15, 42 Hz, 1 H), 3.36 (dd, J = 4, 9 Hz, 1 H), 4.22 (m, 4 H), 4.50 (t, J = 4 Hz, 1 H), 4.53 (d, J = 12 Hz, 1 H), 4.57 (t, J = 9 Hz, 1 H), 4.80 (d, J = 12 Hz, 1 H), 5.71 (d, J = 4 Hz, 1 H), 7.35 (m, 5 H), 7.51 (app dd, J = 7, 8 Hz, 2 H), 7.66 (t, J = 7 Hz, 1 H), 7.97 (d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3 (t, J = 7 Hz; 2C), 26.68, 26.73, 33.8 (d, J = 20 Hz), 64.7 (d, J = 7 Hz), 65.1 (d, J = 8 Hz), 72.1, 73.7, 76.1, 82.4, 104.4, 113.0, 127.9, 128.0, 128.4, 128.5, 131.2, 134.5, 135.1, 137.4; ^{31}P NMR (122 MHz, $CDCl_3$) δ 7.54 (d, J = 84 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ -165.2 (ddd, J = 12, 43, 85 Hz); HRMS (FAB, 3-NOBA) calcd for $C_{26}H_{34}O_9SPFLi$ (M+Li$^+$) 579.1805, obsd 579.1794.

10f -*second eluting diastereomer* **:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (dt, J = 3, 7 Hz, 6 H), 1.32 (s, 3 H), 1.51 (s, 3 H), 2.48 (m, 1 H), 2.77 (ddd, J = 2, 15, 21 Hz, 1 H), 3.31 (dd, J = 4, 9 Hz, 1 H), 4.21 (m, 5 H), 4.49 (t, J = 4 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.76 (d, J = 12 Hz, 1 H), 5.70 (d, J = 4 Hz, 1 H), 7.34 (m, 5 H), 7.49 (app dd, J = 7, 8 Hz, 2 H), 7.65 (t, J = 7 Hz, 1 H), 7.99 (d, J = 8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3 (t, J = 5 Hz; 2C), 26.67, 26.73, 34.2 (d, J = 19 Hz), 64.8 (d, J = 7 Hz), 65.0 (d, J = 7 Hz), 72.0, 72.8 (br), 76.2, 82.0, 104.1, 112.9, 128.0, 128.04, 128.5, 128.6, 131.0, 134.6, 135.6, 137.4; ^{31}P NMR (122 MHz, $CDCl_3$) δ 7.99 (d, J = 79 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ -167.2 (dt, J = 21, 79 Hz).

3,5-Bis-*O*-allyl-6-deoxy-6-diethyl(1'-fluoro-1'-phenylsulfonyl)phosphonomethyl-1,2-*O*-isopropylidene-α-D-glucofuranoside (10g). From **9g**[15] (236 mg, 0.44 mmol) following general procedure A, was obtained **10g** (201 mg, 66%; 1:0.4 ratio of diastereomers as determined from integration of the characteristic signals in the crude ^{19}F NMR spectrum) as a colorless oil: ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 34.5 (d, *J* = 20 Hz; minor), 35.0 (d, *J* = 20 Hz; major), 115.7 (major), 115.9 (minor), 117.1 (major), 117.3 (minor); ^{31}P NMR (122 MHz, $CDCl_3$) δ 8.67 (d, *J* = 82 Hz; both diastereomers); ^{19}F NMR (283 MHz, $CDCl_3$) δ -166.7 (ddd, *J* = 9, 42, 82 Hz; major), -169.4 (ddd, *J* = 12, 27, 81 Hz; minor); HRMS (FAB, 3-NOBA) calcd for $C_{26}H_{39}O_{10}SPF$ ($M+H^+$) 593.1985, obsd 593.1990.

General Procedure B. Diethyl 1-Fluoro-3-methylbutane-1-phosphonate (11a). To a stirred suspension of **10a** (129 mg, 0.35 mmol) and anhydrous NaH_2PO_4 (293 mg, 2.45 mmol) in THF (0.35 mL) and MeOH (2.1 mL) at rt was added fresh 5% Na(Hg) (810 mg, 1.76 mmol) in one portion. The reaction proceeded to completion in 10 min and was quenched by adding CH_2Cl_2 (3 mL) and 1 N HCl (3 mL). Following filtration and further extraction with CH_2Cl_2 (3 x 3 mL), the organics were dried ($MgSO_4$), filtered and evaporated to dryness. Flash chromatography (30%→100% EtOAc-hexane) afforded the desired product, **11a** (63 mg, 79%), as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6 Hz, 3 H), 0.97 (d, *J*= 6 Hz, 3 H), 1.35 (t, *J* = 7 Hz, 6 H), 1.59 (m, 1 H), 1.91 (m, 2 H), 4.19 (dq, *J* = 7, 14 Hz, 4 H), 4.79 (dddd, *J* = 3, 4, 11, 47 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4 (d, *J* = 5 Hz), 16.5 (d, *J* = 4 Hz), 21.3, 23.1, 24.6 (dd, *J* = 2, 14 Hz) 38.5 (d, *J* = 20 Hz), 62.7 (d, *J* = 7 Hz), 63.1 (d, *J* = 7 Hz), 87.4 (dd, *J* = 171, 179 Hz); ^{31}P NMR (122 MHz, $CDCl_3$) δ 18.6 (d, *J* = 75 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ –209.7 (ddt, *J* = 15, 46, 75 Hz); HRMS (FAB, 3-NOBA/LiI) calcd for $C_9H_{20}O_3PFLi$ ($M+Li^+$) 233.1294, obsd 233.1292.

Diethyl (4S)-4,4-Dimethyl-1-fluoro-7-nonene-1-phosphonate (11b). From **10b** (87 mg, 0.19 mmol) following general procedure B, was obtained **11b** (47 mg, 80%; 1:1 diastereomeric mixture as judged by ^{31}P NMR) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$; *resolved peaks*) δ 0.88 (d, *J* = 6 Hz, 3 H; one diastereomer), 0.89 (d, *J* = 6 Hz, 3 H; other diastereomer) (See Supporting Information for a copy of the entire NMR spectrum); ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 32.3 (dd, *J* = 3, 12 Hz; one diastereomer), 32.5 (dd, *J* = 3, 12 Hz; other diastereomer), 89.2 (dd, *J* = 170, 180 Hz; one diastereomer), 89.4 (dd, *J* = 170, 180 Hz; other diastereomer); ^{31}P NMR (122 MHz,

$CDCl_3$) δ 18.2 (d, *J* = 76 Hz; one diastereomer), 18.3 (d, *J* = 76 Hz; other diastereomer); ^{19}F NMR (283 MHz, $CDCl_3$) δ -209.6 (m, both diastereomers); HRMS (FAB, 3-NOBA) calcd for $C_{15}H_{31}O_3PF$ (M+H$^+$) 309.1994, obsd 309.2000.

Diethyl 1-Fluoro-3,4-(*O*-isopropylidene)-3,4-dihydroxybutylphosphonate (11c). From **10c** (79 mg, 0.19 mmol) following general procedure B, was obtained **11c** (47 mg, 89%) as a colorless oil and a (1:1 mixture of diastereomers as judged by ^{31}P NMR): ^1H NMR (500 MHz, $CDCl_3$*; resolved peaks*): δ 3.56 (app t, *J* = 8 Hz, 1 H; one diastereomer), 3.61 (app t, *J* = 8 Hz, 1 H; other diastereomer) [See Supporting Information for a complete NMR spectrum]; ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 85.5 (d, *J* = 173 Hz; one diastereomer), 86.9 (d, *J* = 172 Hz; other diastereomer); ^{31}P NMR (122 MHz, $CDCl_3$) δ 16.82 (d, *J* = 75 Hz; one diastereomer), 17.12 (d, *J* = 75 Hz; other diastereomer); ^{19}F NMR (470 MHz, $CDCl_3$): δ -207.3 (m; one diastereomer), -212.3 (m; other diastereomer); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{11}H_{22}O_5PFLi$ (M+Li$^+$) 291.1348, obsd 291.1351.

α^4,3-*O*-Isopropylidene-α^5-deoxy-α^5-[diethyl(1'-fluoro)phosphonomethyl]pyridoxine (11d). From **10d** (36 mg, 0.07 mmol) following general procedure B, but allowing for 30 min reaction time, was obtained **11d** (18 mg, 71%), after flash chromatography (50%-EtOAc/hexanes→10% MeOH-EtOAc): ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7 Hz, 6 H), 1.52 (s, 3 H), 1.54 (s, 3 H), 2.40 (s, 3 H), 3.02 (m, 2 H), 4.19 (dq, *J* = 7, 14 Hz, 4 H), 4.78 (m, 1 H), 4.82 (dd, *J* = 16, 27 Hz, 2 H), 7.95 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.45 (br, 2 C), 17.6, 24.3, 25.0, 29.6 (d, *J* = 21 Hz), 58.9 (br), 63.2 (d, *J* = 7 Hz), 63.6 (d, *J* = 7 Hz), 88.6 (dd, *J* = 170, 184 Hz), 100.1, 125.7, 127.5, 138.9, 146.1, 146.4; ^{31}P NMR (122 MHz, $CDCl_3$) δ 16.1 (d, *J* = 75 Hz); ^{19}F NMR (283 MHz, $CDCl_3$) δ –207.4 (app ddt, *J* = 6, 27, 47 Hz); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{16}H_{25}NO_5PFLi$ (M+Li$^+$) 368.1614, obsd 368.1628.

Benzyl 6-Deoxy-6-diethyl(1'-fluoro)phosphonomethyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (11e). From **10e** (85 mg, 0.10 mmol) following general procedure B, was obtained a **11e**, as two readily separable diastereomers (60 mg, 85%; 1:1 ratio of diastereomers as determined by ^{31}P NMR). Flash chromatography (10%→50% EtOAc-hexane) afforded the individual diastereomers separately. The stereochemistry was determined as previously described:[8] **11e**-7R diastereomer (*first-eluting*): $[\alpha]^{22}_{D}$ –6.82 (*c* 0.8, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.35 (app dt, *J* = 7, 8 Hz, 6 H), 2.39 (m, 2 H), 3.47 (t, *J* = 9 Hz, 1 H), 3.56 (m, 2 H), 3.65 (t, *J* = 9 Hz, 1 H), 4.21 (m, 4 H), 4.56 (d, *J* = 8 Hz, 1 H), 4.66 (d, *J* = 11 Hz, 1 H), 4.70 (d, *J* = 12 Hz, 1 H), 4.75 (d, *J* = 11 Hz, 1 H), 4.72 (d, *J* = 11 Hz, 1 H), 4.77 (d, *J* = 11 Hz, 1 H), 4.88 (d, *J* = 11 Hz, 1 H), 4.89 (d, *J* = 12 Hz, 1 H), 4.80 (d, *J* = 11 Hz, 1 H), 4.93 (d, *J* = 11 Hz, 1 H), 4.95 (d, *J* = 12 Hz, 1 H), 4.96 (d, *J* = 11 Hz, 1 H), 4.99 (d, *J* = 11 Hz, 1 H), 5.12 (dddd, *J* = 3, 5, 9, 47 Hz), 7.34 (m, 20 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 16.4 (br, 2 C), 32.1 (d, *J* = 18 Hz), 63.0 (dd, *J* = 7, 31 Hz, 2 C),71.2, 71.4 (dd, *J* = 4, 11 Hz), 74.8, 75.0, 75.6, 81.2, 82.4, 84.7, 86.1 (dd, *J* = 171, 180 Hz), 102.5, 127.6 (2 C), 127.7, 127.74, 127.80, 127.9 (2 C), 128.0, 128.3, 128.32 (2 C), 128.4, 137.3, 138.1, 138.4, 138.5; ^{19}F NMR (470 MHz, CDCl$_3$) δ -205.5 (dddd, *J* = 18, 32, 47, 73 Hz); ^{31}P NMR (202 MHz, CDCl$_3$) δ 17.22 (d, $J_{F,P}$ = 73 Hz); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{39}H_{46}O_8PFLi$ (M+Li$^+$) 699.3062, obsd 699.3058.

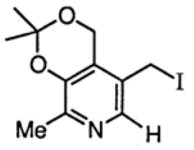
11e-7S diastereomer (*second-eluting*): mp 75-76°C; $[\alpha]^{22}_{D}$ +12.1 (*c* 1.00, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.35 (app dt, *J* = 7, 5 Hz, 6H), 1.79 (br app dt, *J* = 13, 44 Hz, 1 H), 2.47 (m, 1H), 3.28 (t, *J* = 9 Hz, 1H), 3.5 (dd, *J* = 8, 9 Hz, 2 H), 3.65 (t, *J* = 9 Hz, 1 H), 4.18 (app quintet, *J* = 7.5 Hz, 4 H), 4.52 (d, *J* = 8 Hz, 1 H), 4.61 (d, *J* = 11 Hz, 1 H), 4.69 (d, *J* = 12 Hz, 1 H), 4.72 (d, *J* = 11 Hz, 1 H), 4.77 (d, *J* = 11 Hz, 1 H), 4.88 (d, *J* = 11 Hz, 1 H), 4.89 (d, *J* = 12 Hz, 1 H), 4.92 (d, *J* = 11 Hz, 1 H), 4.94 (app ddt, *J* = 2, 13, 47 Hz, 1 H), 4.95 (d, J = 11 Hz, 1 H), 7.31 (m, 20 H); 13C NMR (125 MHz, CDCl3) _ 16.45 (br, 2 C), 32.6 (br), 63.0 (br, 2 C), 69.4 (d, J = 11 Hz), 71.6, 74.9, 75.1, 75.7, 81.5, 82.4, 84.7, 102.6, 127.6 (2 C), 127.8, 127.89, 127.92, 127.98, 128.0, 128.1, 128.3, 128.36, 128.41, 128.5, 137.2, 137.9, 138.4, 138.5; 19F NMR __ -214 (dddd, J = 12, 44, 46, 73 Hz); 31P NMR (202 MHz, CDCl3) _ 17.47 (d, J F,P =73 Hz); IR (ATR) 2905, 1261, 1071, 1017 cm-1; HRMS (FAB, 3-NOBA/NaI) calcd for C39H46O8PFNa (M+Na+) 715.2812, obsd 715.2816.

3-O-Benzyl-5-deoxy-5-diethyl(1'-fluoro)phosphonomethyl-1,2-O-isopropylidene-_-D-ribofuranoside (11f). From 10f (50 mg, 0.08 mmol) following general procedure B, was obtained 11f (30 mg, 80%; 1:1 ratio of diastereomers as determined from the crude 31P

NMR spectrum) as a white solid. The diastereomers were separated on an analytical chiral HPLC column [Chiracel OD-from Chiral Technologies Inc. (Daicel)] with isocratic elution (10% i-PrOH-hexane): 11f-First eluting diastereomer 1H NMR (300 MHz, CDCl3) _ 1.35 (m, 9 H), 1.53 (s, 3 H), 1.85 (dddt, J = 2, 4, 15, 46 Hz, 1 H), 2.31 (m, 1 H), 3.43 (dd, J = 4, 9 Hz, 1 H), 4.20 (m, 5 H), 4.55 (d, J = 12 Hz, 1 H), 4.57 (t, J = 4 Hz, 1 H), 4.77 (d, J = 12 Hz, 1 H), 4.97 (dddd, J = 2, 3, 12, 47 Hz, 1 H), 5.71 (d, J = 4 Hz, 1 H), 7.36 (m, 5 H);); 19F NMR (470 MHz, CDCl3) __-212 (m); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.41 (d, *J* = 73 Hz); **11f**-*Second eluting diastereomer* : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (app t, *J* = 7 Hz, 6 H), 1.52 (s, 6 H), 2.27 (m, 2 H), 3.60 (dd, *J* = 4, 9 Hz, 1 H), 4.19 (m, 5 H), 4.52 (t, *J* = 4 Hz, 1 H), 4.57 (d, *J* = 12 Hz, 1 H), 4.75 (d, *J* = 12 Hz, 1 H), 5.01 (m, 1 H), 5.73 (d, J = 4 Hz, 1 H), 7.32 (m, 5 H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -207.9 (m); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.19, (d, *J* = 76 Hz); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{20}H_{30}O_7PFLi$ (M+Li$^+$) 439.1872, obsd 439.1873.

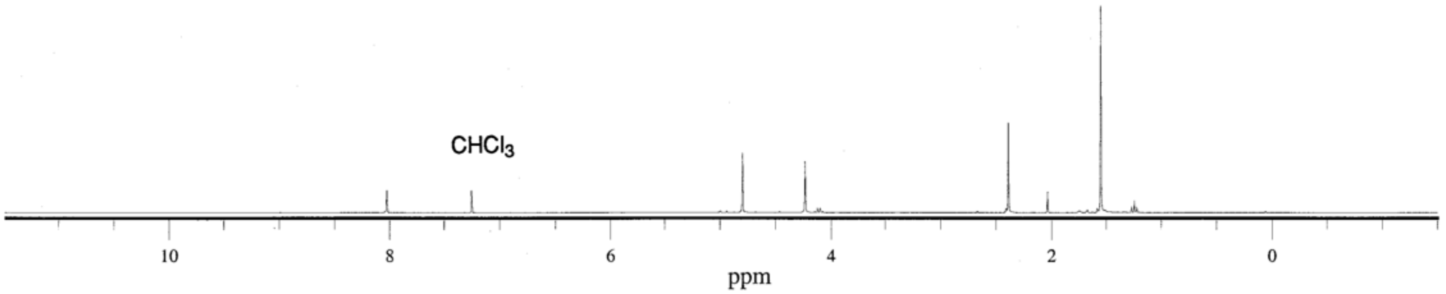
3,5-O-allyl-6-deoxy-6-diethyl(1'-fluoro)phosphonomethyl-1,2-O-isopropylidene-α-D-glucofuranoside (11g). From **10g** (102 mg, 0.17 mmol) following general procedure B, was obtained **11g** (60 mg, 78%; 1:0.8 ratio of diastereomers as determined from the crude ^{31}P NMR spectrum) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) *See Supporting Information* ; ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 16.5 (d, *J* = 5 Hz, 2 C), 26.2, 26.5, 26.7, 26.8, 31.9 (d, *J* = 20 Hz; one diastereomer), 33.8 (d, *J* = 20 Hz; other diastereomer), 85.3 (dd, *J* = 172, 178 Hz; one diastereomer), 85.8 (dd, *J* = 171, 180 Hz; other diastereomer), 104.8 (one diastereomer), 105.1 (other diastereomer); ^{31}P NMR (122 MHz, $CDCl_3$) δ 18.0 (d, *J* = 76 Hz; one diastereomer), 18.2 (d, *J* = 76 Hz; other diastereomer); ^{19}F NMR (283 MHz, $CDCl_3$) δ -209.0 (m, one diastereomer), -212.3 (m, other diastereomer); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{20}H_{34}O_8PFLi$ (M+Li$^+$) 459.2146, obsd 459.2156.

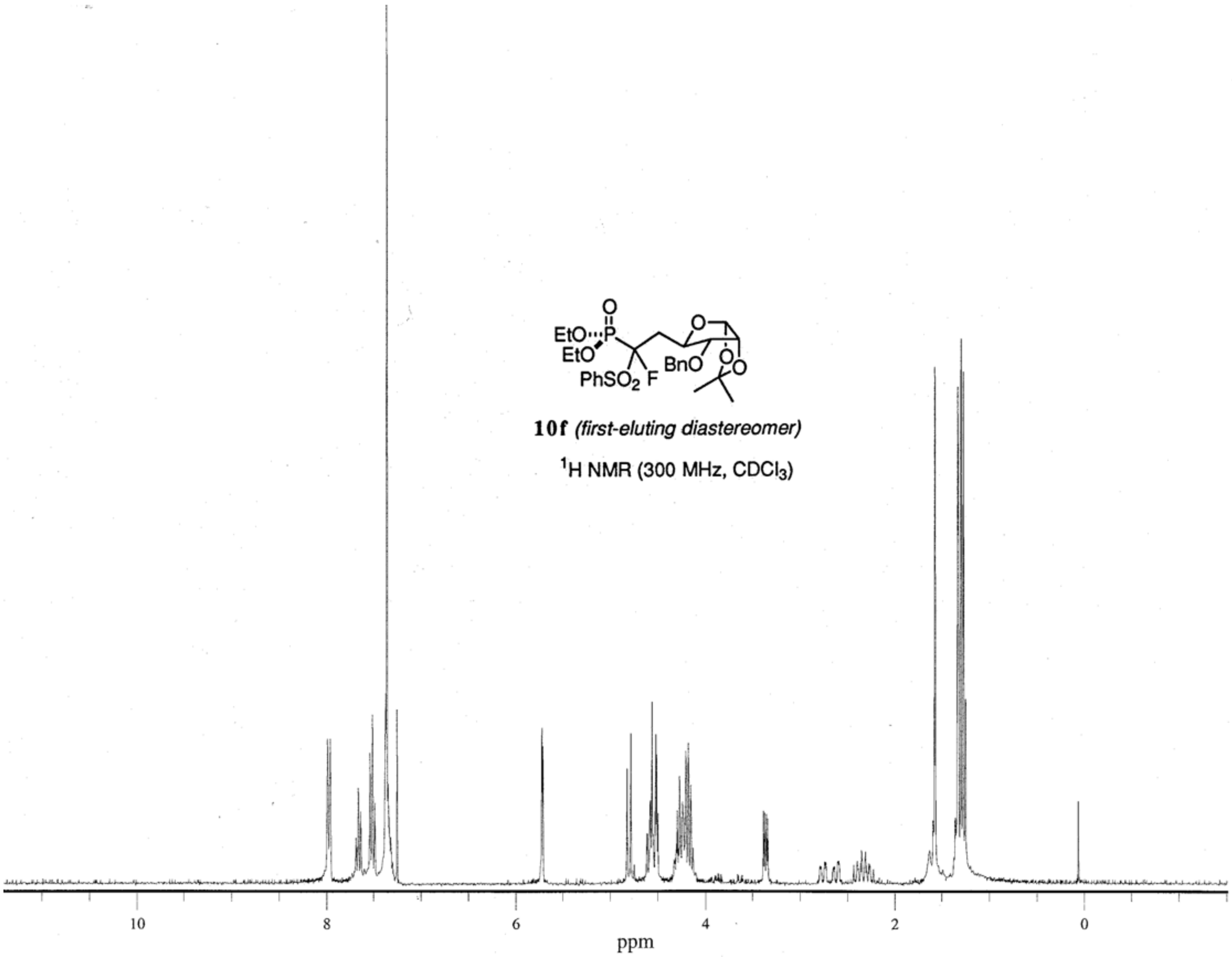
Benzyl 6-Deoxy-6-(1'-fluoro)phenylsulfonylmethyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (12e). To a solution of **10e** (45.5 mg, 0.06 mmol) in benzene (0.3 mL) was added Bu_3SnH (0.03 mL, 0.11 mmol) and AIBN (catalytic amount), and this solution was bubbled with Ar for 10 min. The mixture was then refluxed for 6 h, until no starting material remained, as judged by TLC. After partitioning between water (2 mL) and EtOAc (3 x 2 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (50% EtOAc-hexanes) afforded **12** (29 mg, 71%) as a white solid : ^1H NMR (500 MHz, $CDCl_3$; *resolved peaks*) δ 4.45 (d, J = 8 Hz, 1 H; one diastereomer), 4.51 (d, J = 8 Hz, 1 H; other diastereomer), 5.15 (ddd, J = 2, 12, 49, 1 H; one diastereomer), 5.39 (app dq, J = 5, 46 Hz, 1 H; other diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$; *resolved peaks*) δ 99.3 (d, J = 219 Hz; one diastereomer), 100.2 (d, J = 219 Hz; other diastereomer), 102.7 (one diastereomer), 103.0 (other diastereomer); ^{19}F NMR (283 MHz, $CDCl_3$): δ -176.6 (dq, J = 15, 46 Hz; one diastereomer), -183.4 (ddd, J = 9, 39, 49 Hz; other diastereomer); HRMS (FAB, 3-NOBA/LiI) calcd for $C_{41}H_{41}O_7FSLi$ ($M+Li^+$) 703.2717, obsd 703.2748.



9d

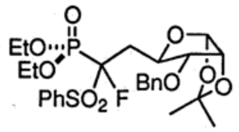
^{1}H NMR (300 MHz, $CDCl_3$)





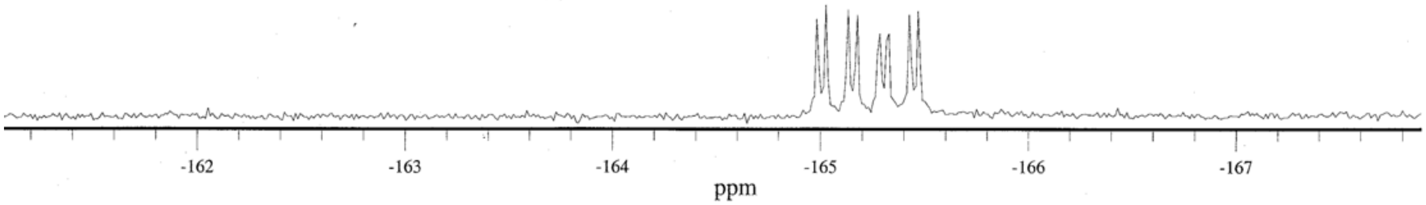
10f *(first-eluting diastereomer)*

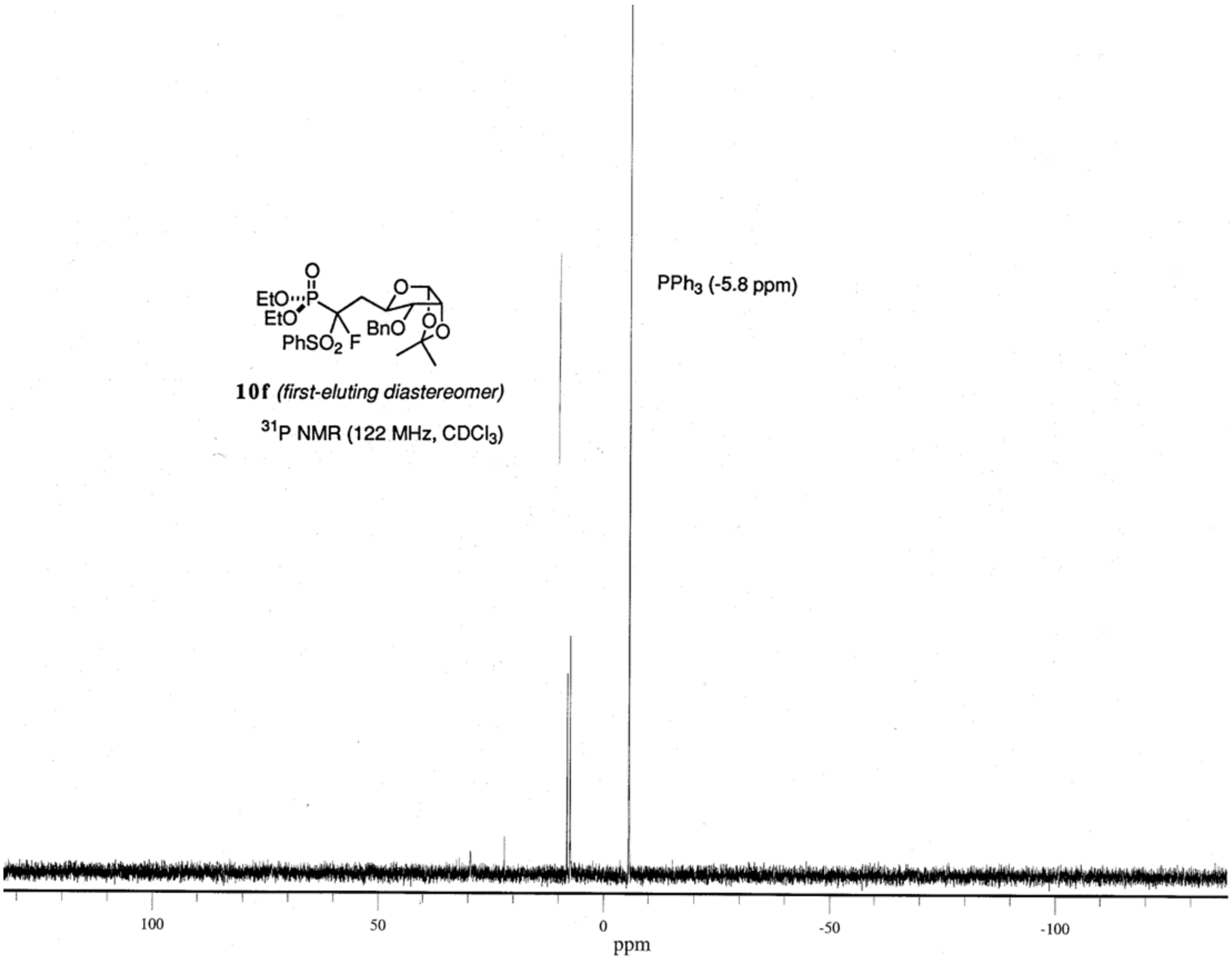
^{1}H NMR (300 MHz, $CDCl_3$)



10f *(first-eluting diastereomer)*

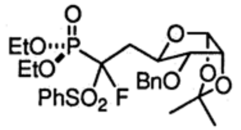
^{19}F NMR (283 MHz, $CDCl_3$)





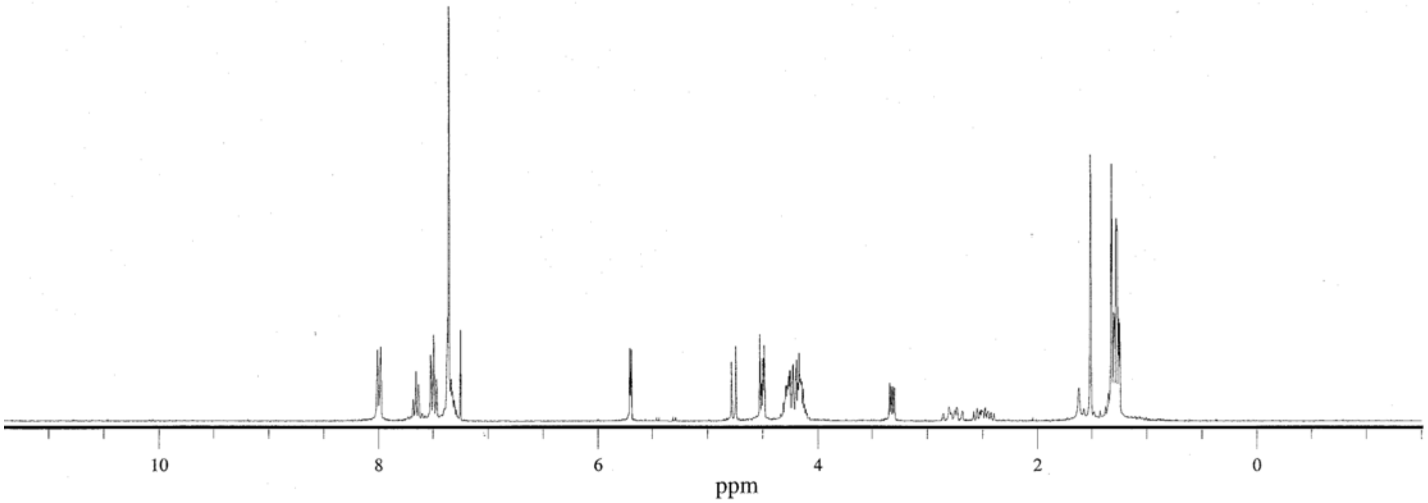
10f *(first-eluting diastereomer)*

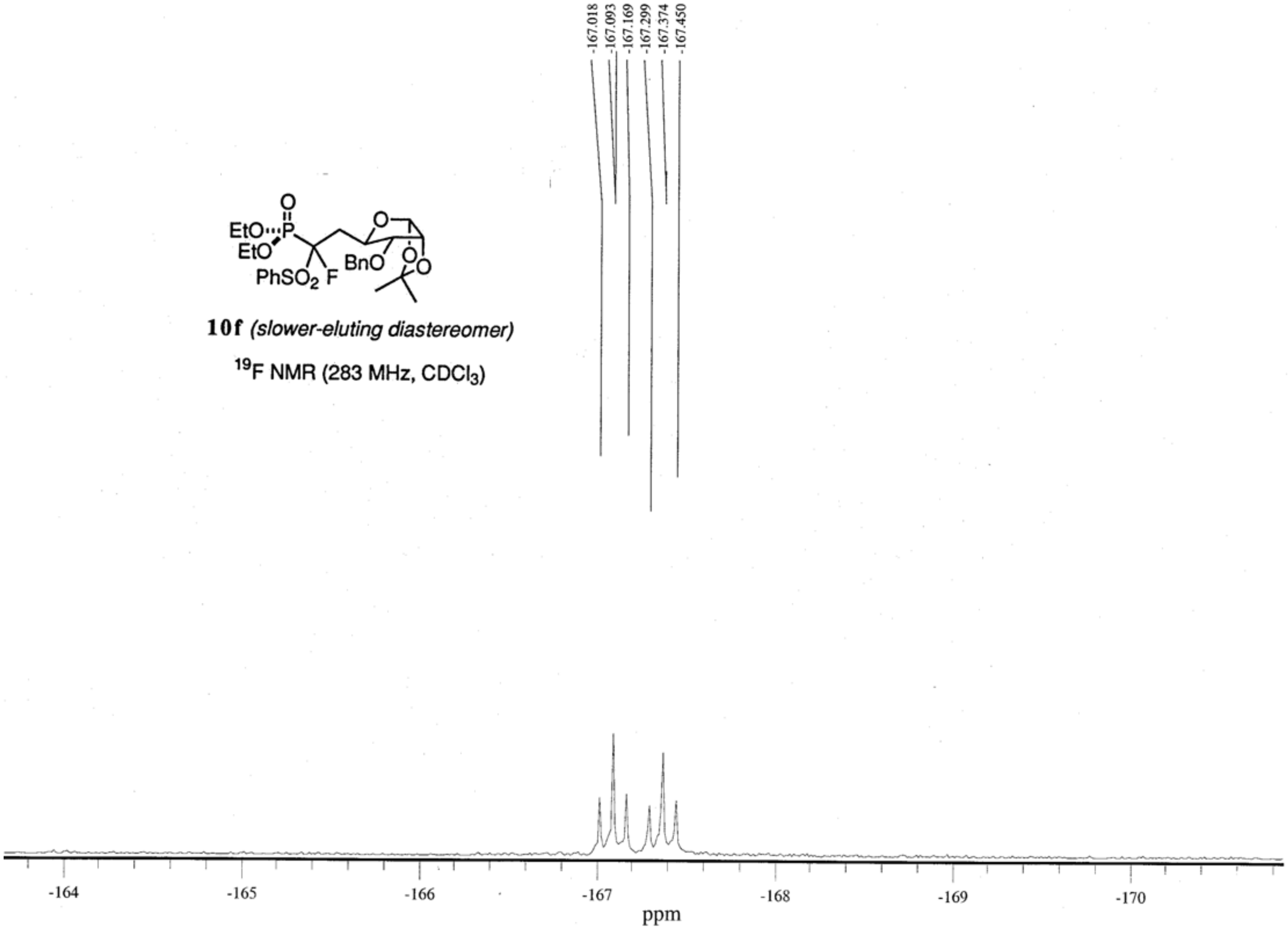
^{31}P NMR (122 MHz, CDCl$_3$)



10f *(slower-eluting diastereomer)*

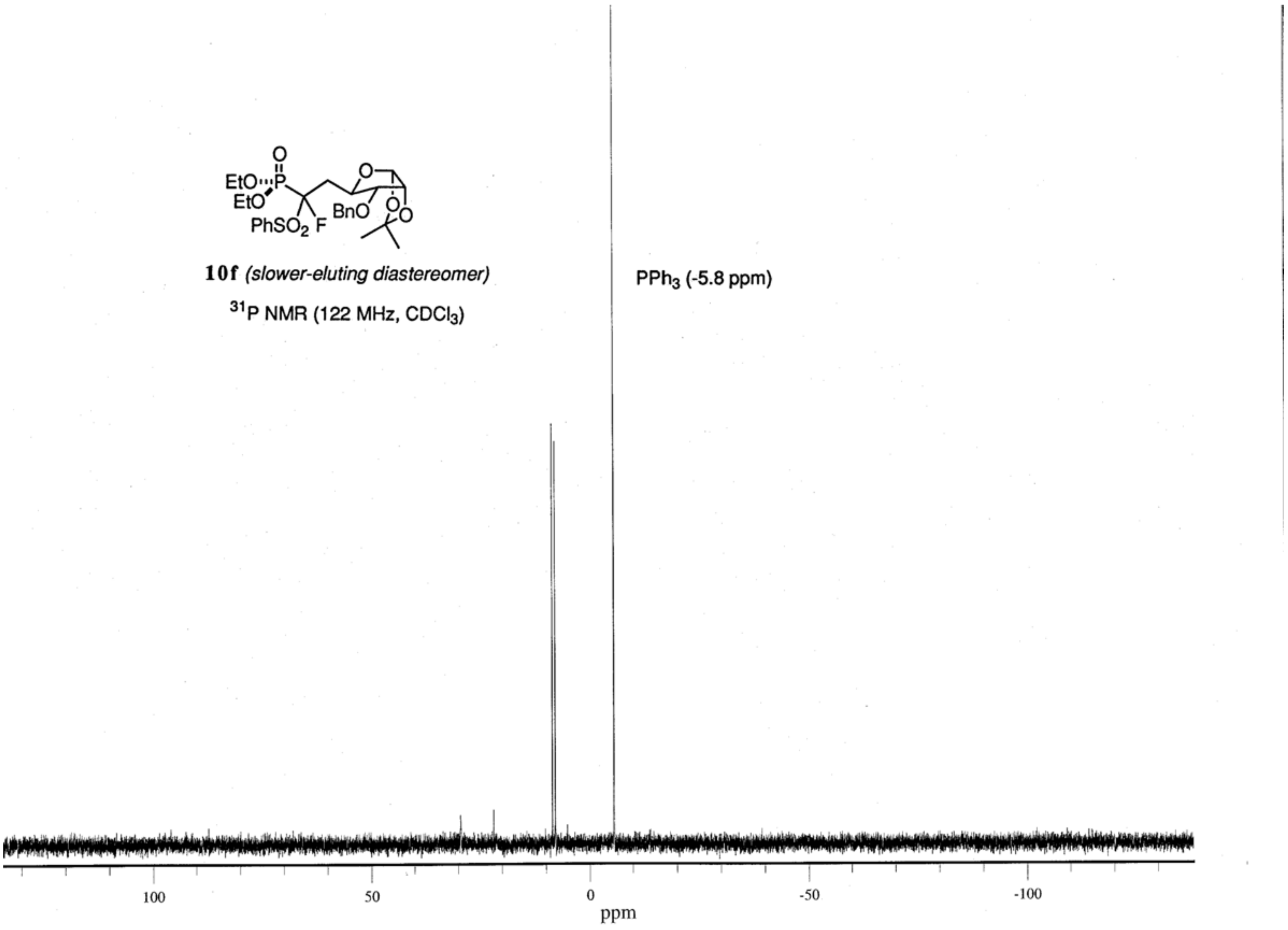
^{1}H NMR (300 MHz, CDCl$_3$)





10f *(slower-eluting diastereomer)*

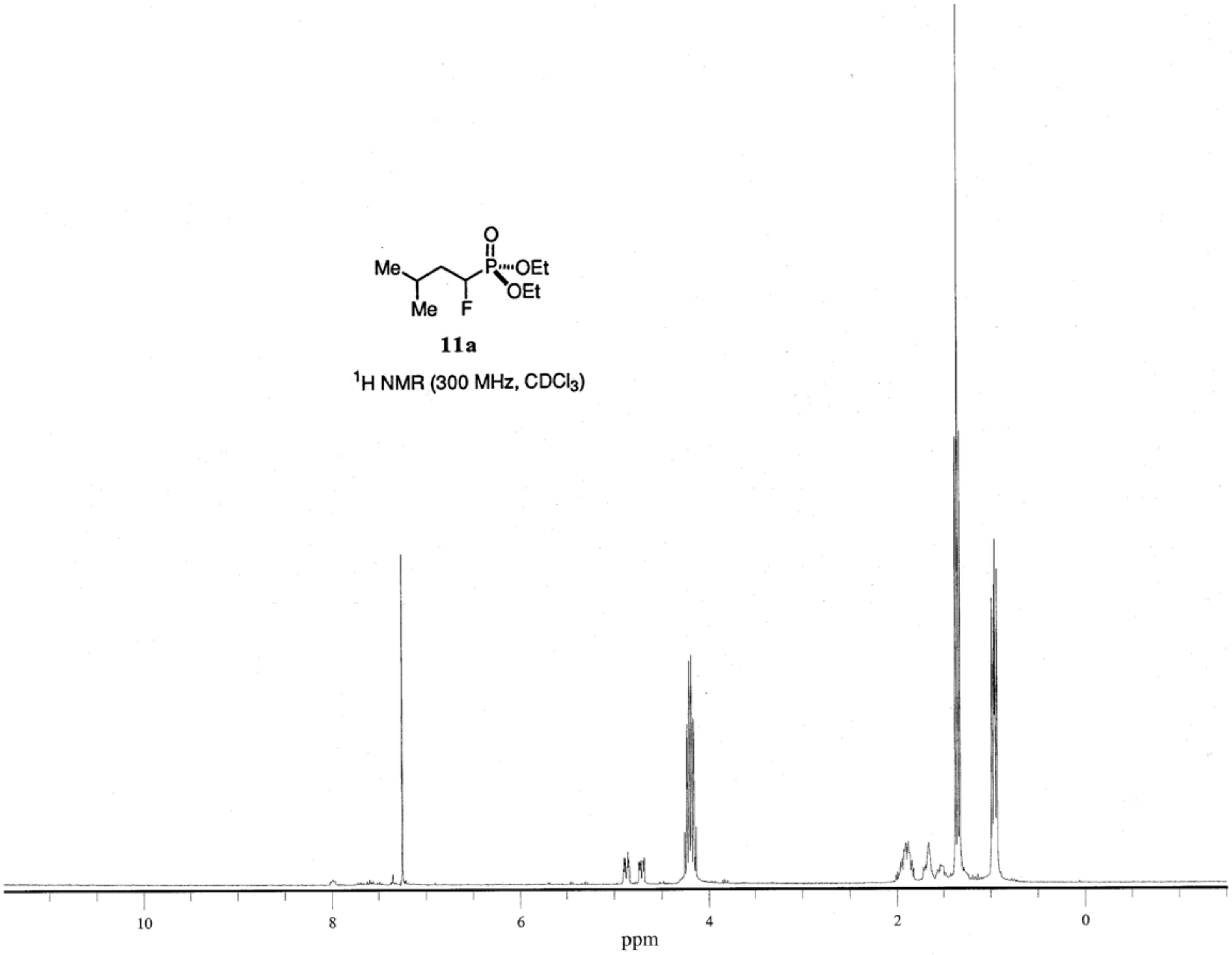
^{19}F NMR (283 MHz, $CDCl_3$)



10f *(slower-eluting diastereomer)*

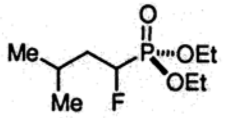
^{31}P NMR (122 MHz, CDCl$_3$)

PPh$_3$ (-5.8 ppm)



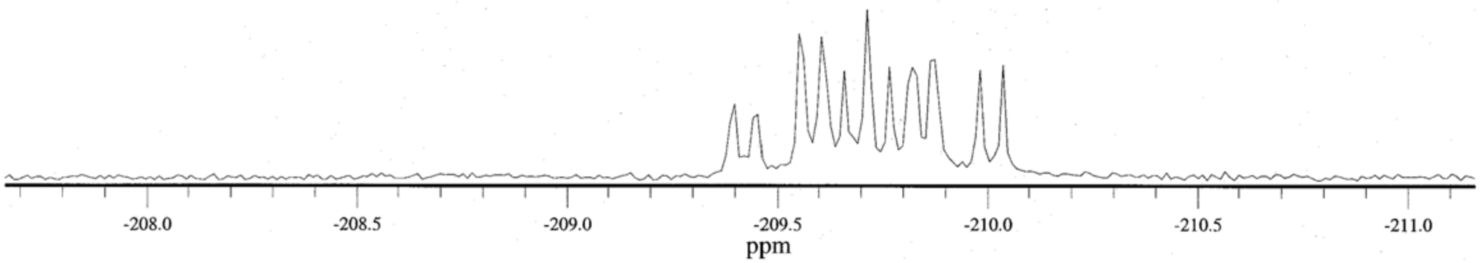
11a

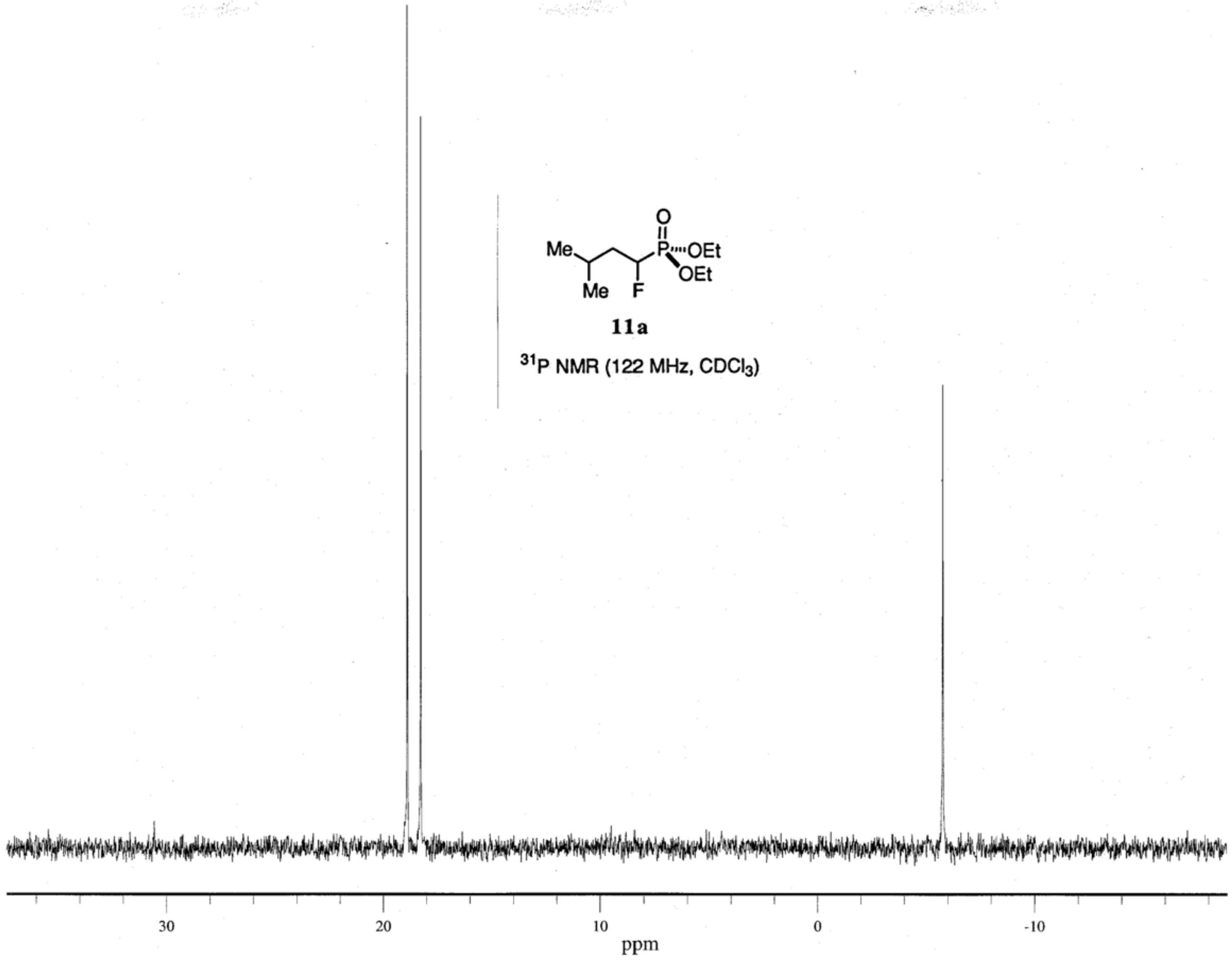
^{1}H NMR (300 MHz, CDCl$_3$)



11a

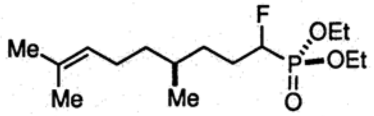
^{19}F NMR (283 MHz, CDCl$_3$)





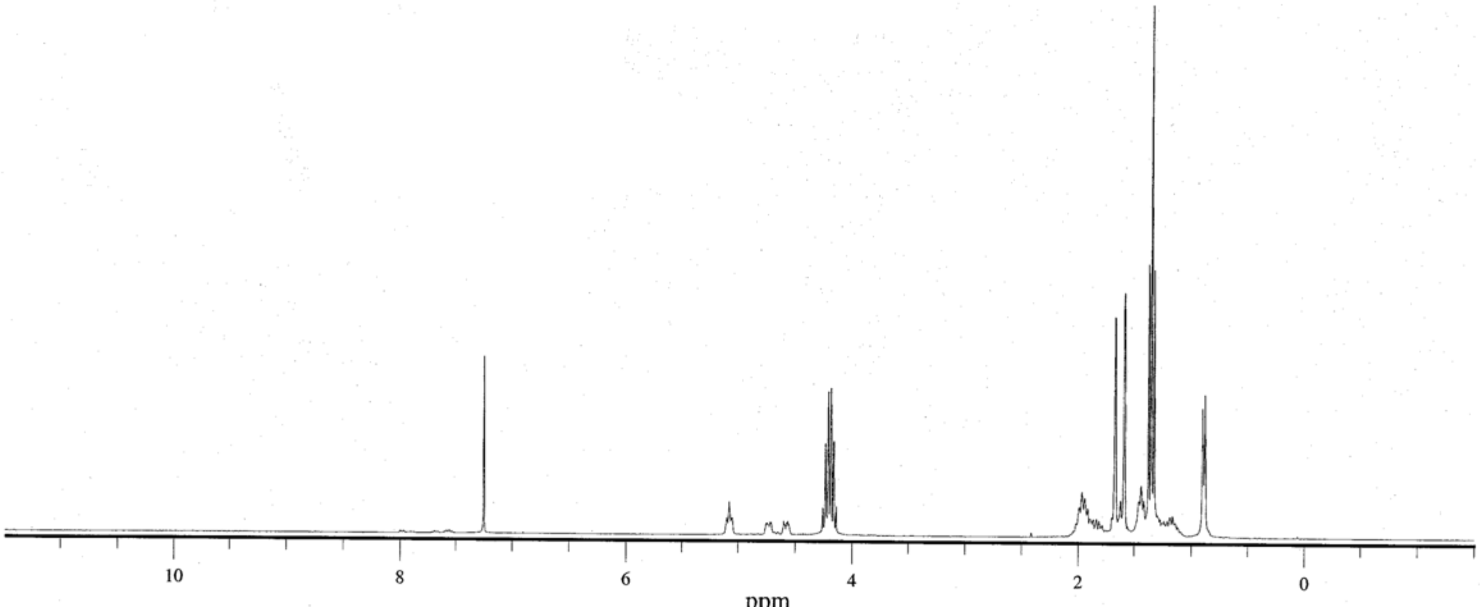
11a

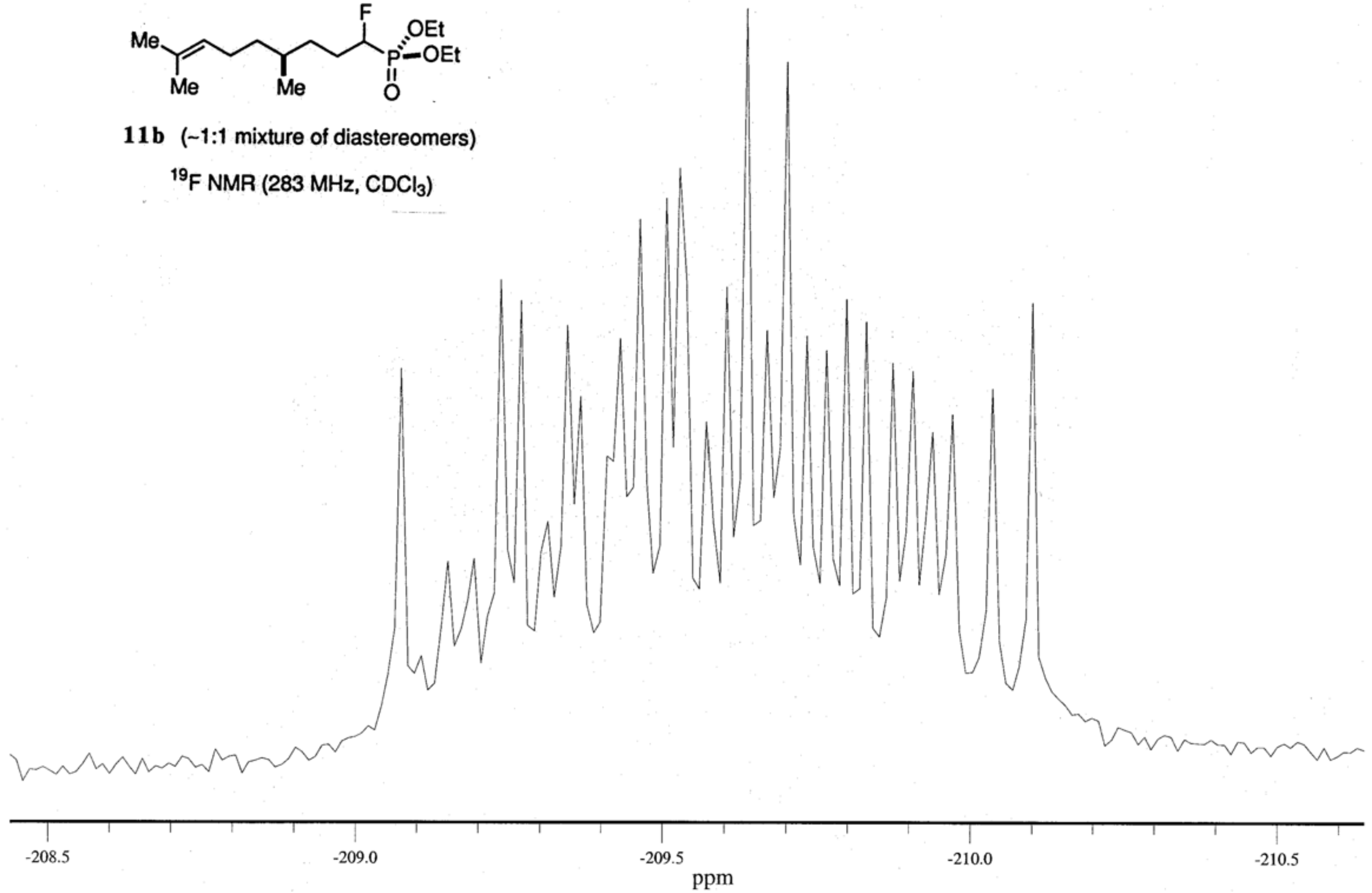
^{31}P NMR (122 MHz, $CDCl_3$)



11b (~1:1 mixture of diastereomers)

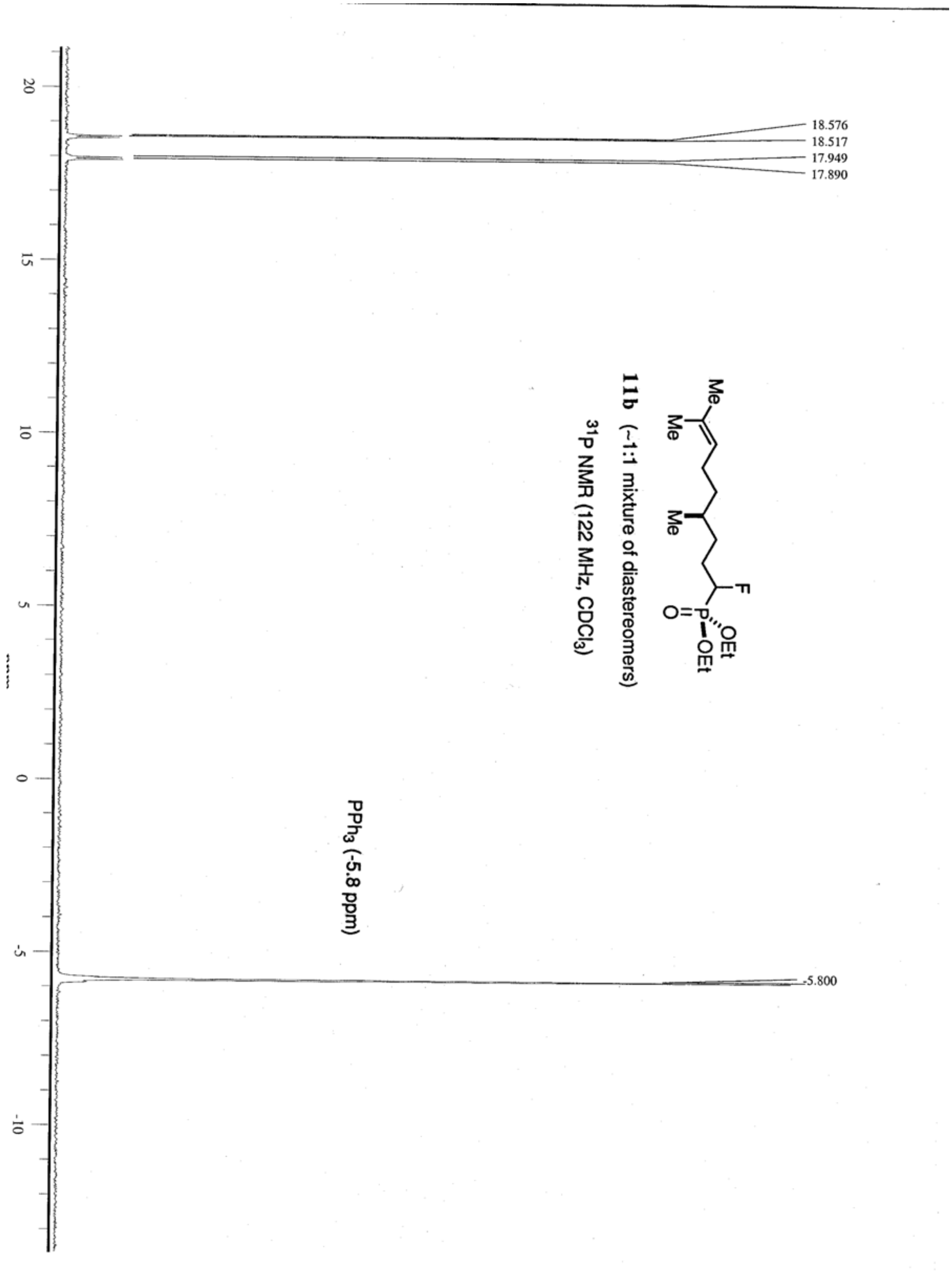
^{1}H NMR (300 MHz, CDCl$_3$)





11b (~1:1 mixture of diastereomers)

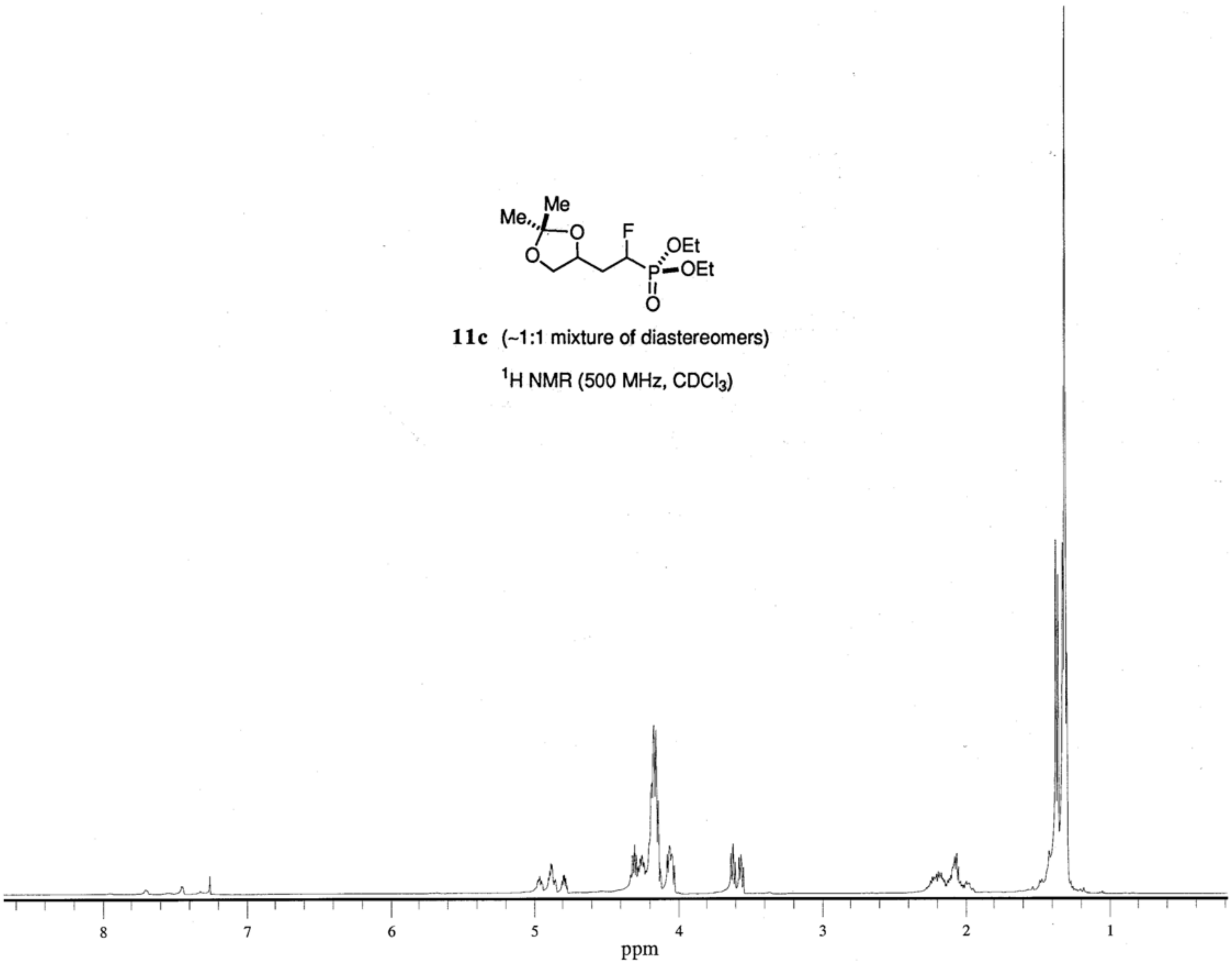
^{19}F NMR (283 MHz, CDCl$_3$)



11b (~1:1 mixture of diastereomers)

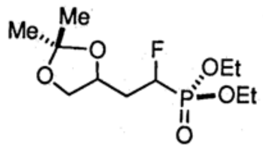
^{31}P NMR (122 MHz, CDCl$_3$)

PPh$_3$ (-5.8 ppm)



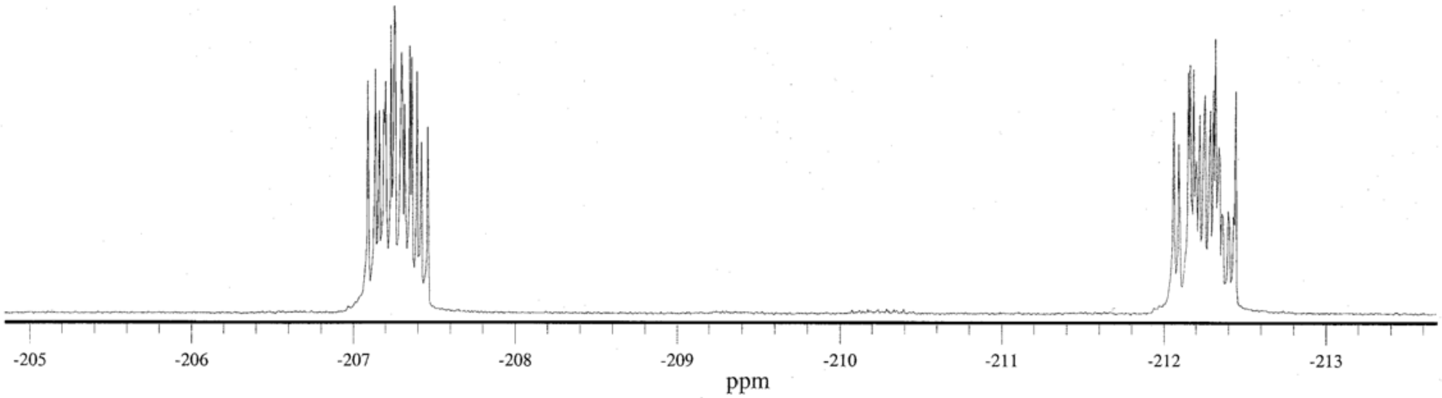
11c (~1:1 mixture of diastereomers)

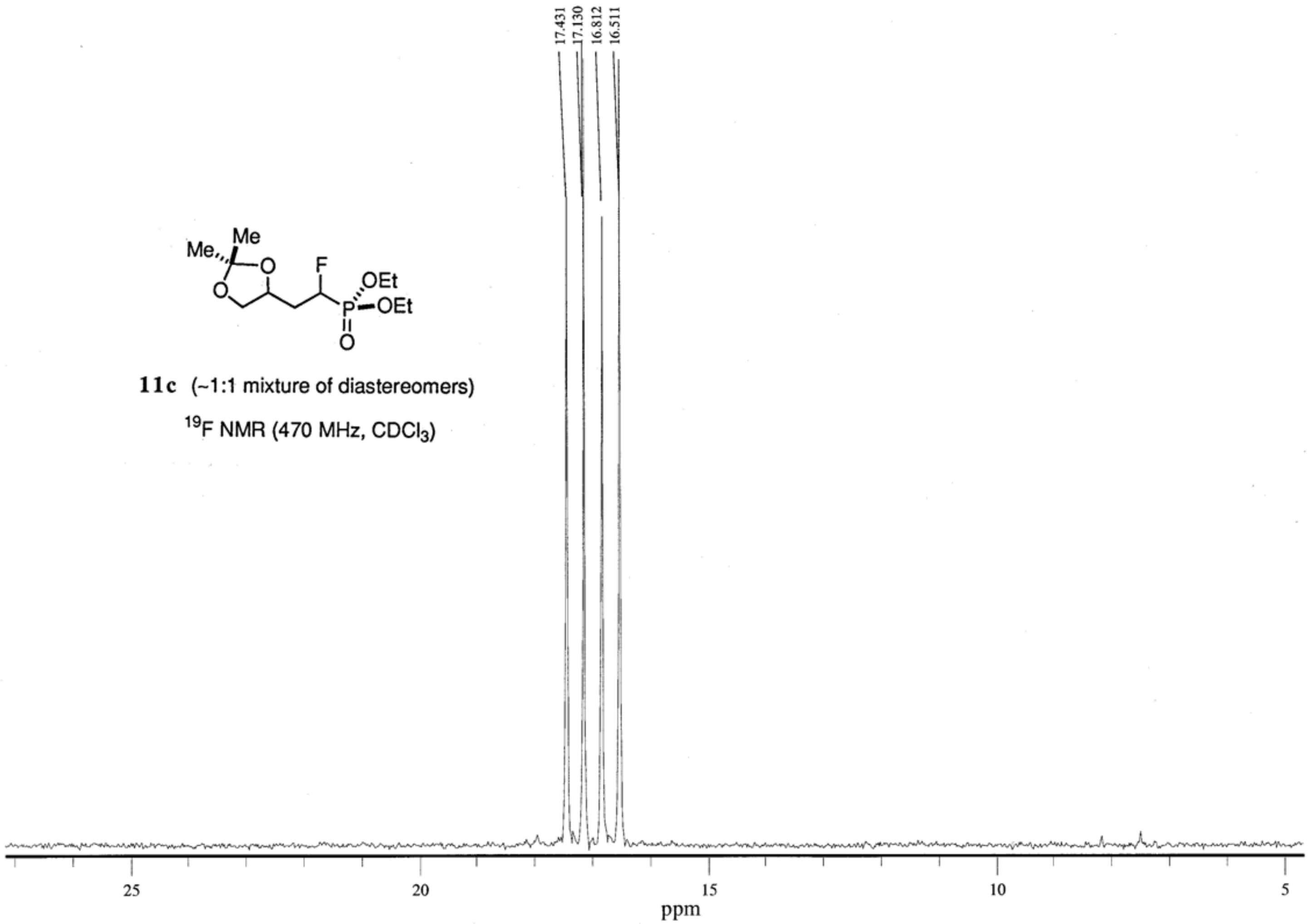
^{1}H NMR (500 MHz, $CDCl_3$)



11c (~1:1 mixture of diastereomers)

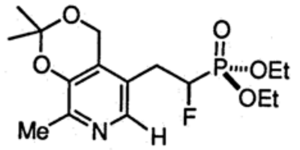
^{31}P NMR (122 MHz, CDCl$_3$)





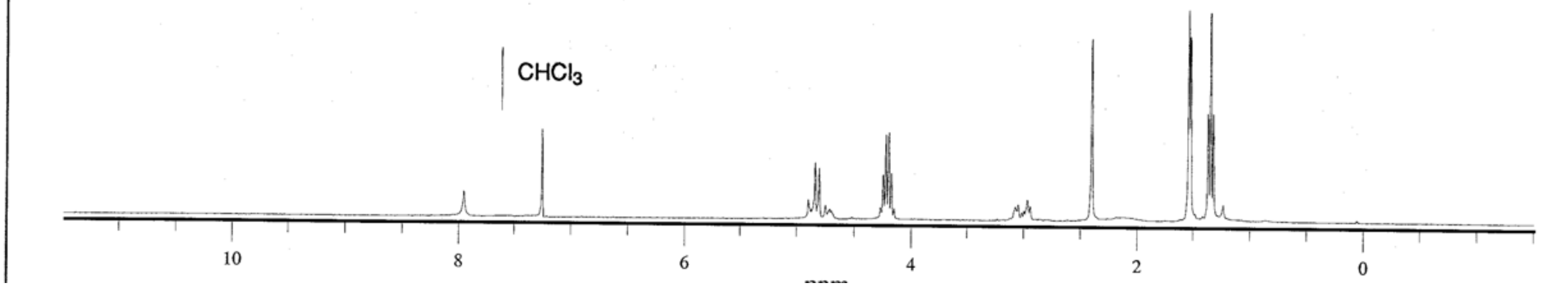
11c (~1:1 mixture of diastereomers)

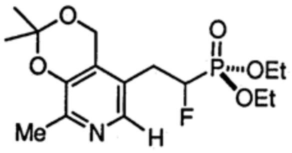
^{19}F NMR (470 MHz, $CDCl_3$)



11d

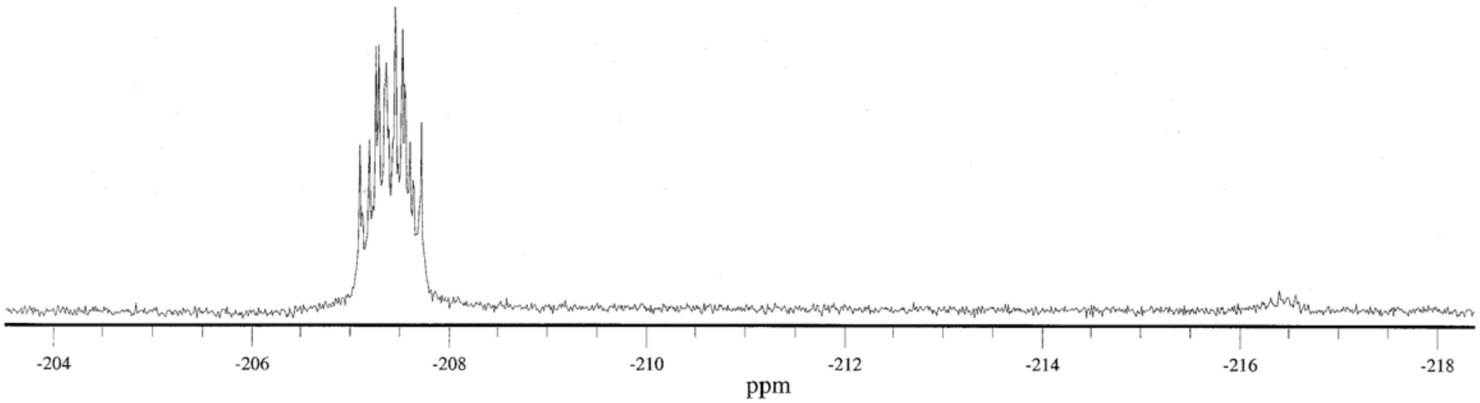
^{1}H NMR (300 MHz, CDCl$_3$)

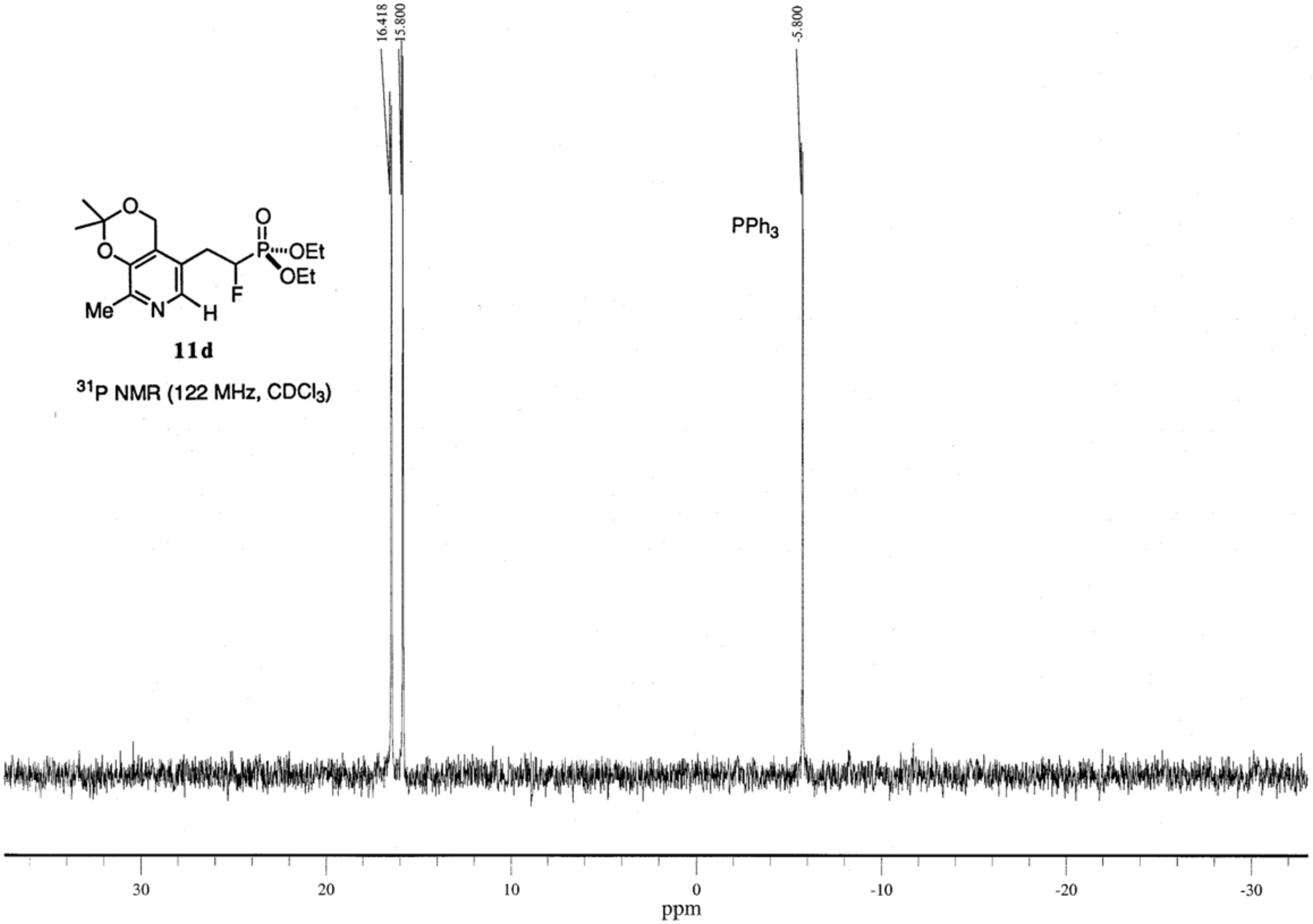




11d

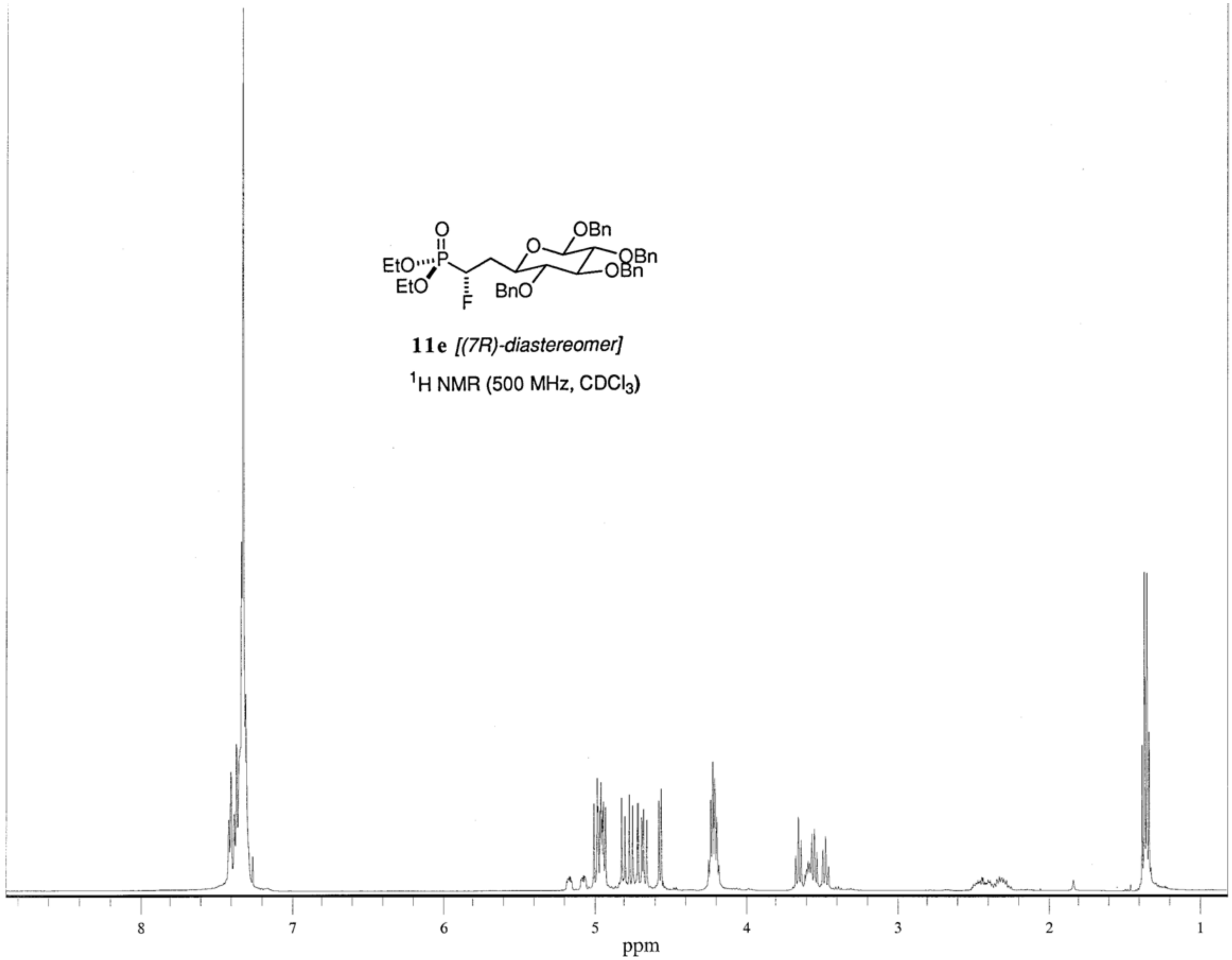
^{19}F NMR (283 MHz, CDCl$_3$)





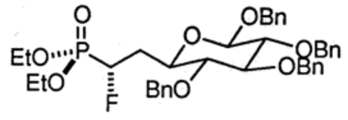
11d

^{31}P NMR (122 MHz, CDCl$_3$)



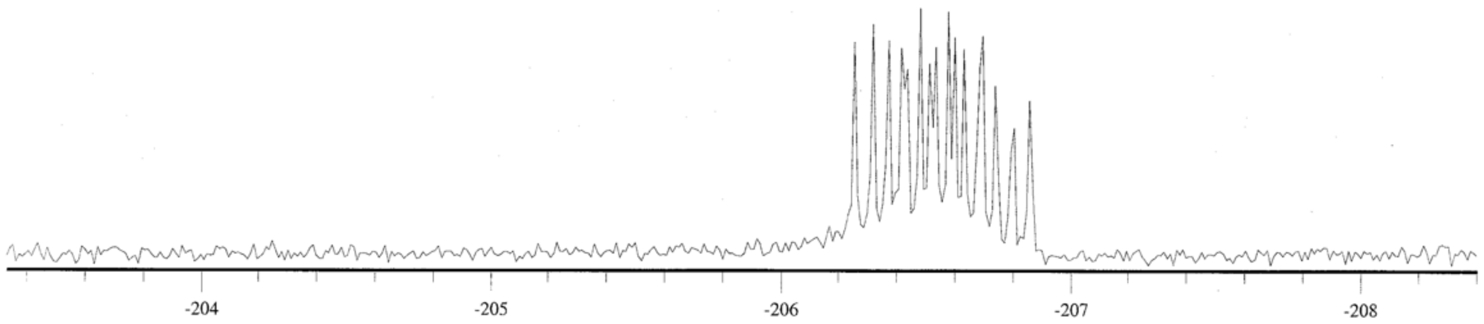
11e *[(7R)-diastereomer]*

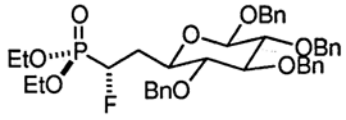
^{1}H NMR (500 MHz, CDCl$_3$)



11e *[(7R)-diastereomer]*

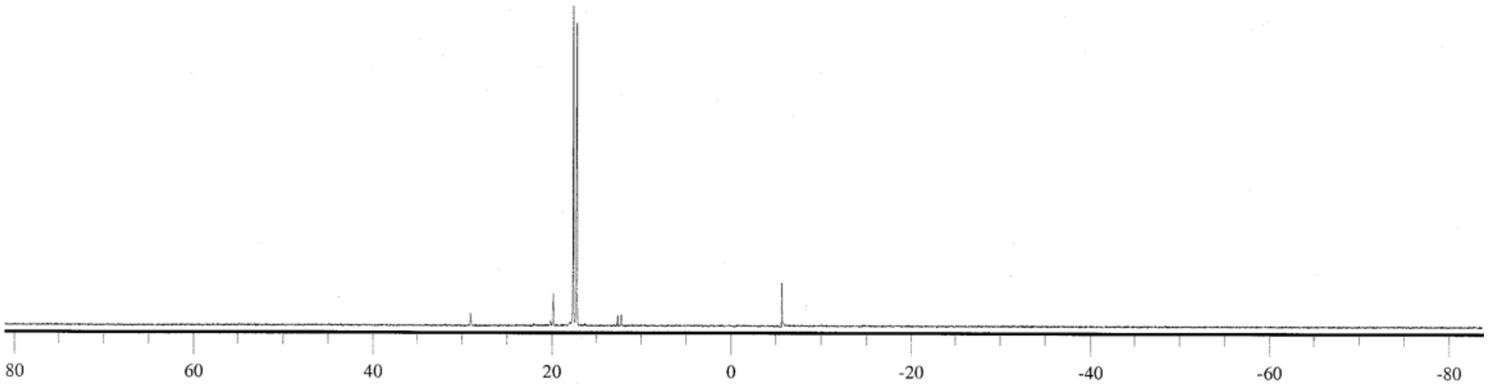
^{19}F NMR (283 MHz, CDCl$_3$)

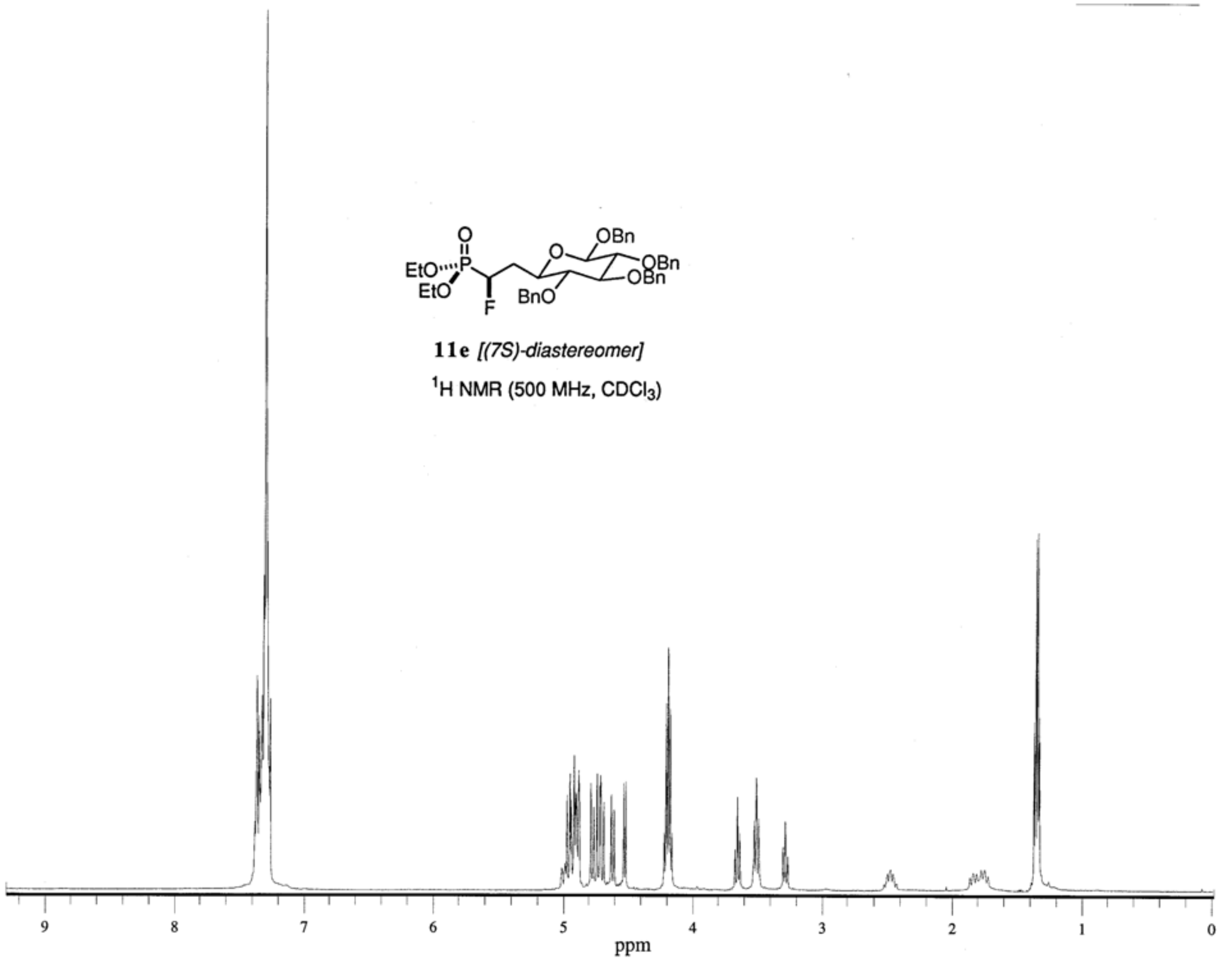




11e *[(7R)-diastereomer]*

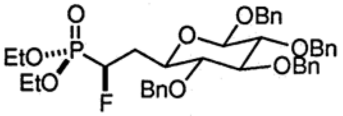
^{31}P NMR (202 MHz, CDCl$_3$)





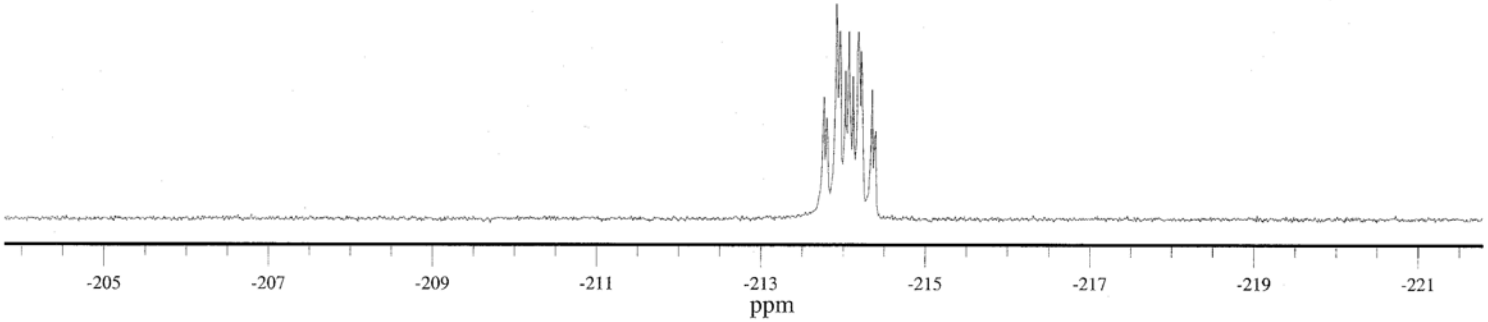
11e *[(7S)-diastereomer]*

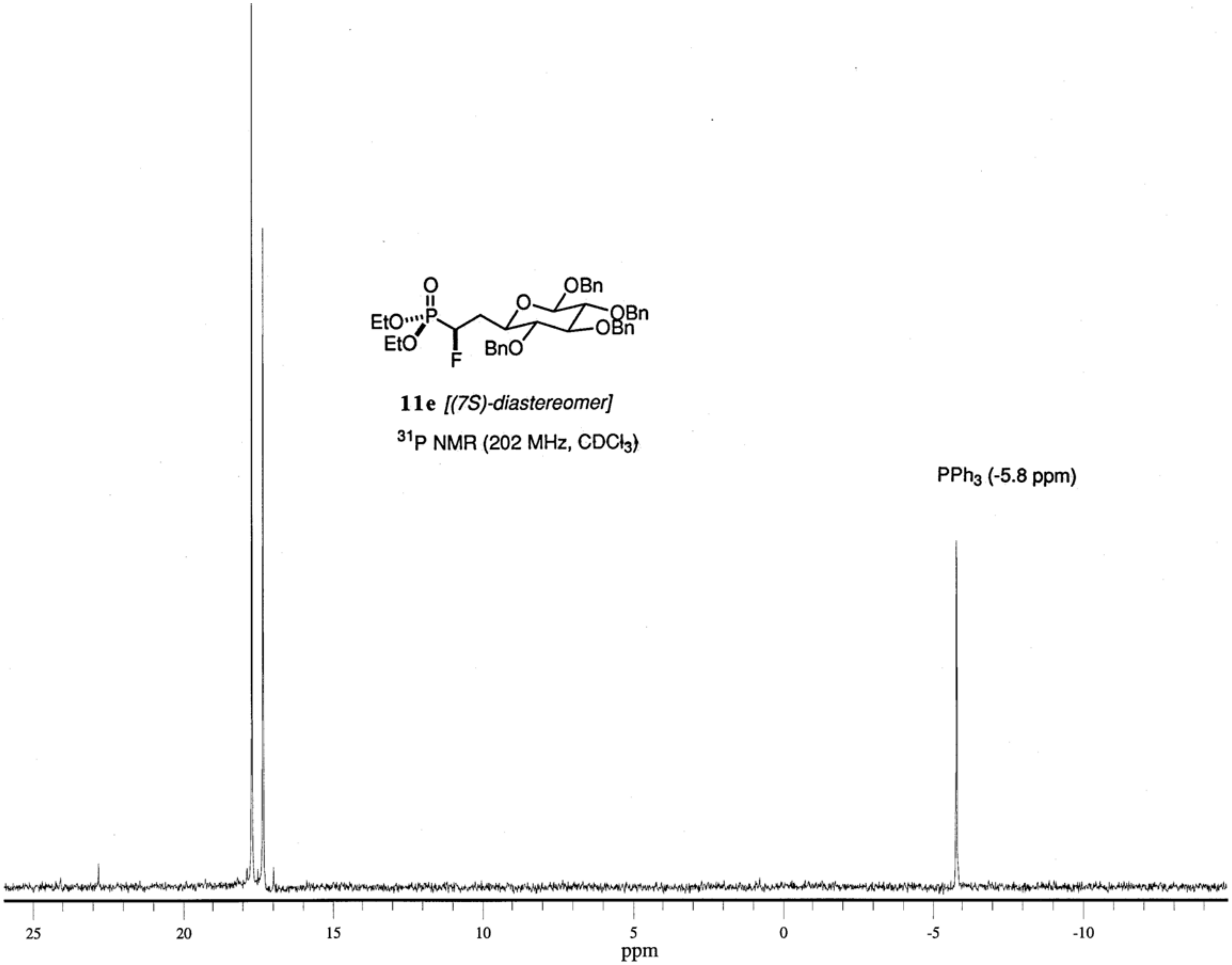
^{1}H NMR (500 MHz, $CDCl_3$)



11e *[(7S)-diastereomer]*

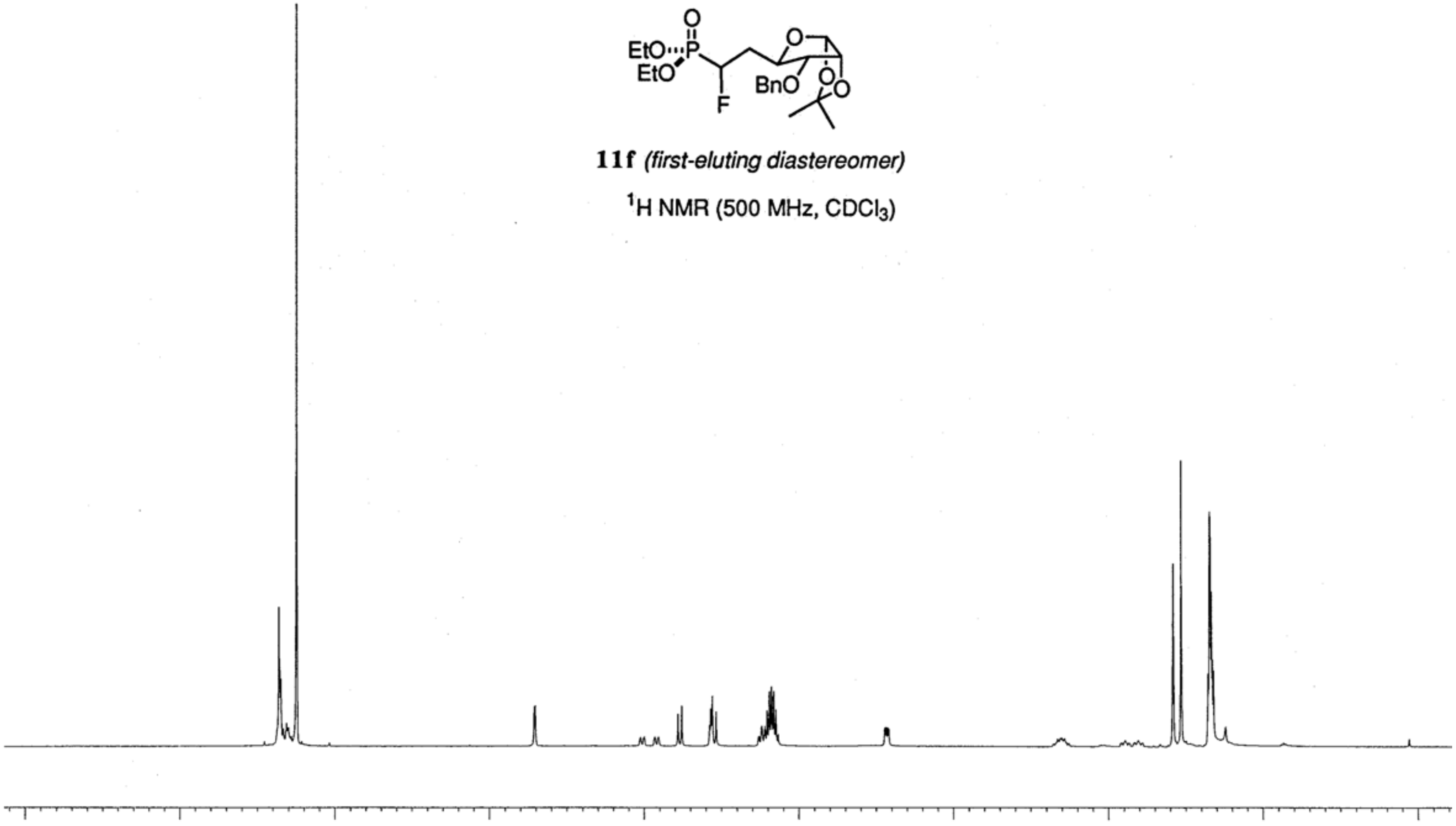
^{19}F NMR (283 MHz, CDCl$_3$)





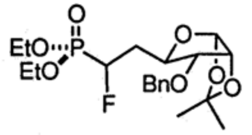
11e *[(7S)-diastereomer]*

^{31}P NMR (202 MHz, CDCl$_3$)



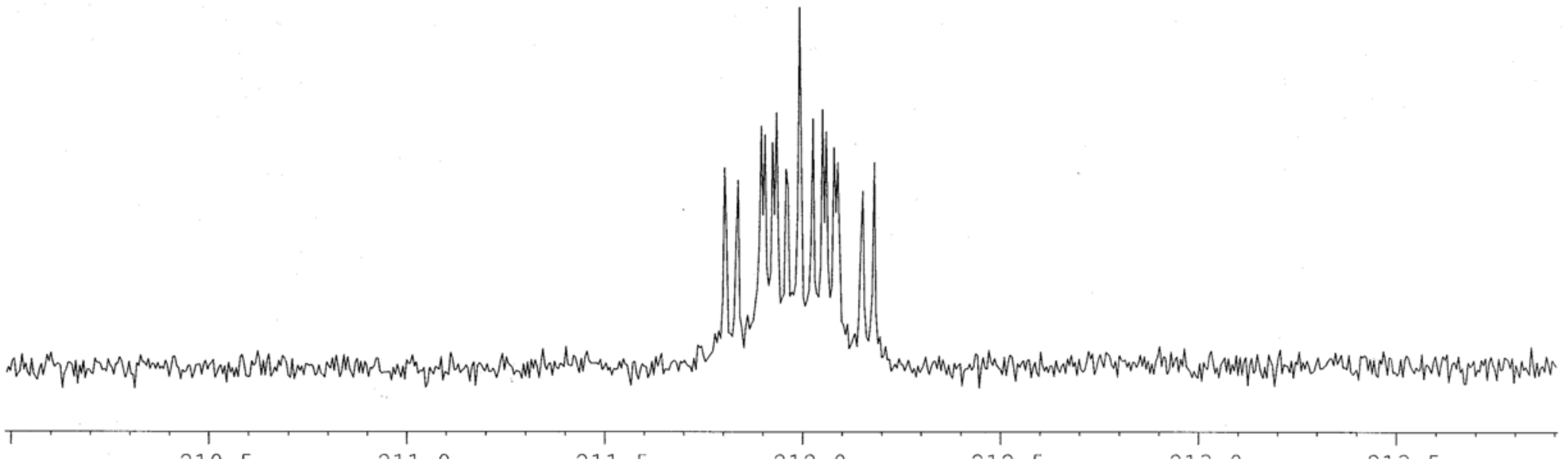
11f *(first-eluting diastereomer)*

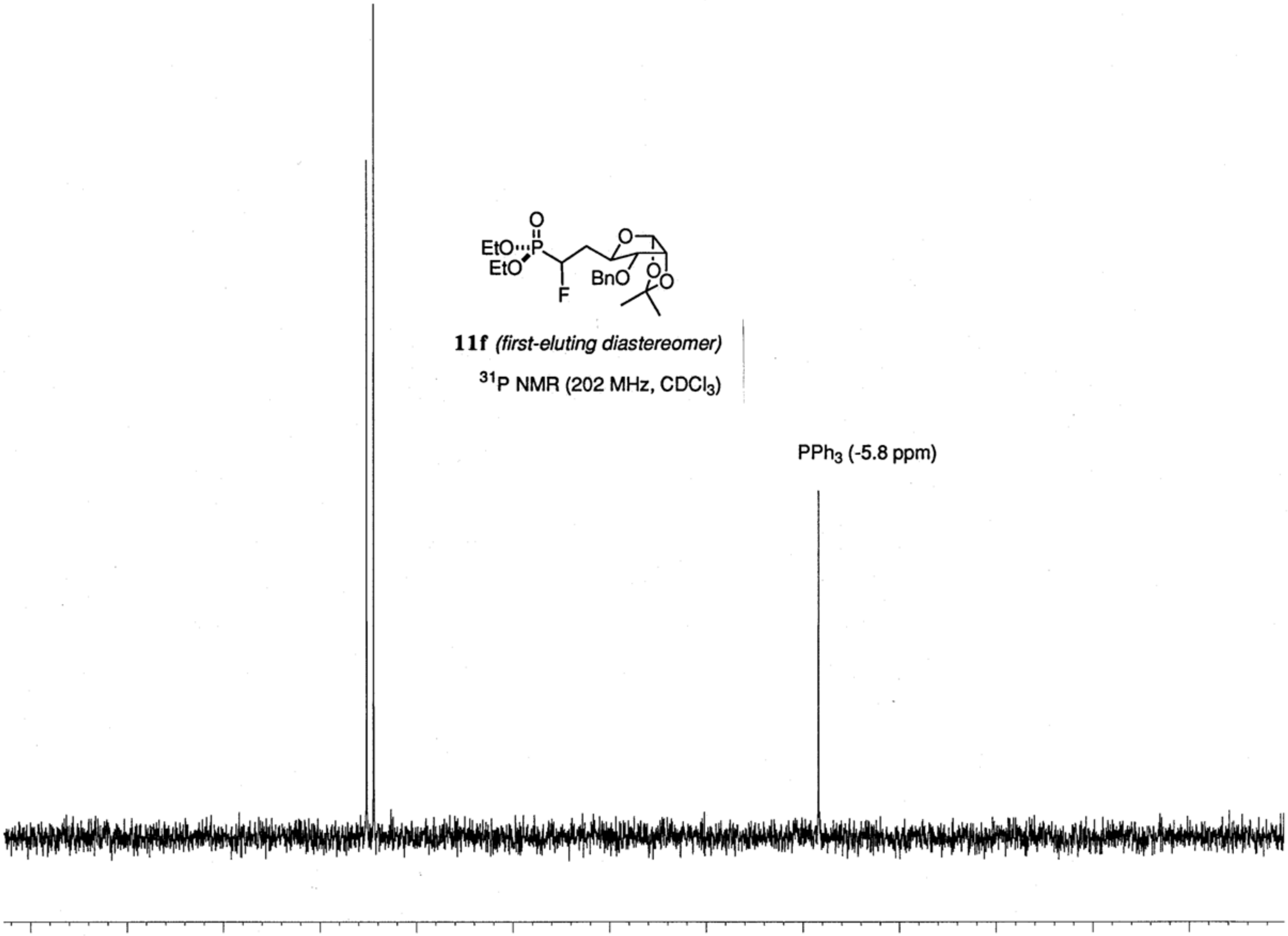
^1H NMR (500 MHz, $CDCl_3$)



11f *(first-eluting diastereomer)*

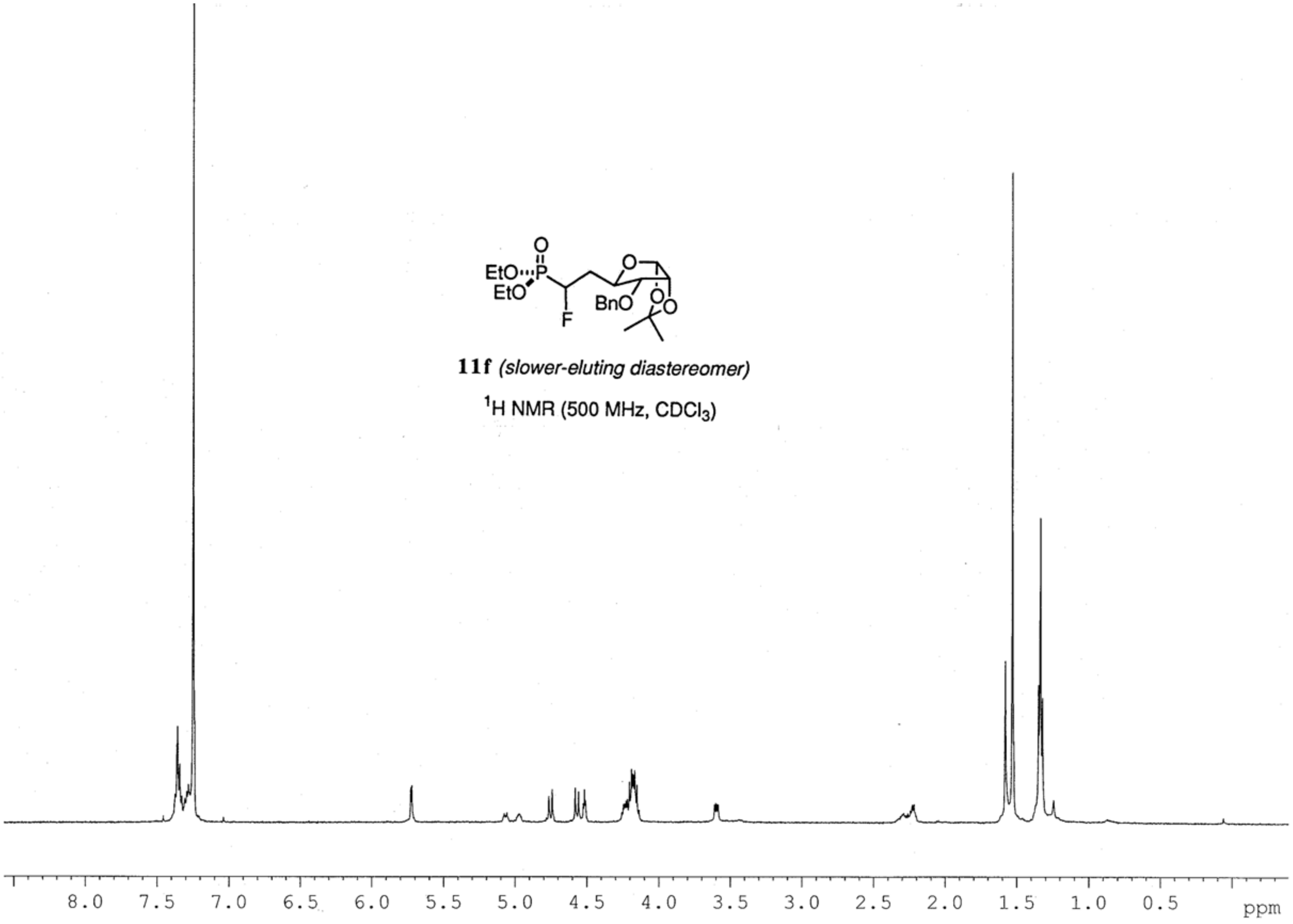
^{19}F NMR (470 MHz, CDCl$_3$)





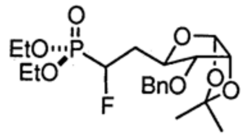
11f *(first-eluting diastereomer)*

^{31}P NMR (202 MHz, CDCl$_3$)



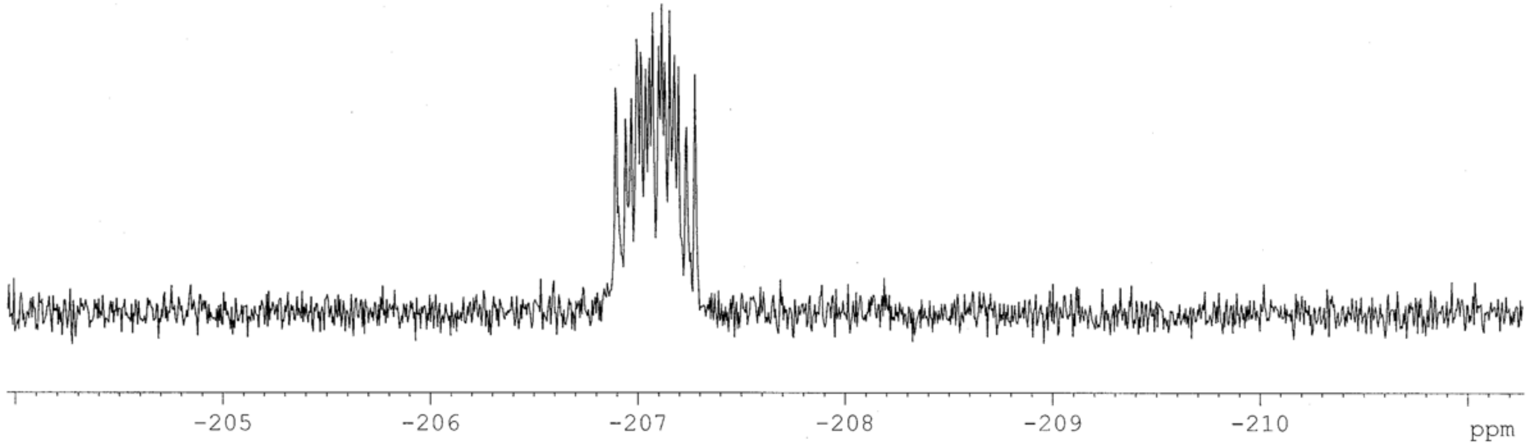
11f *(slower-eluting diastereomer)*

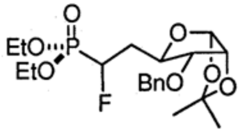
^{1}H NMR (500 MHz, CDCl$_3$)



11f *(slower-eluting diastereomer)*

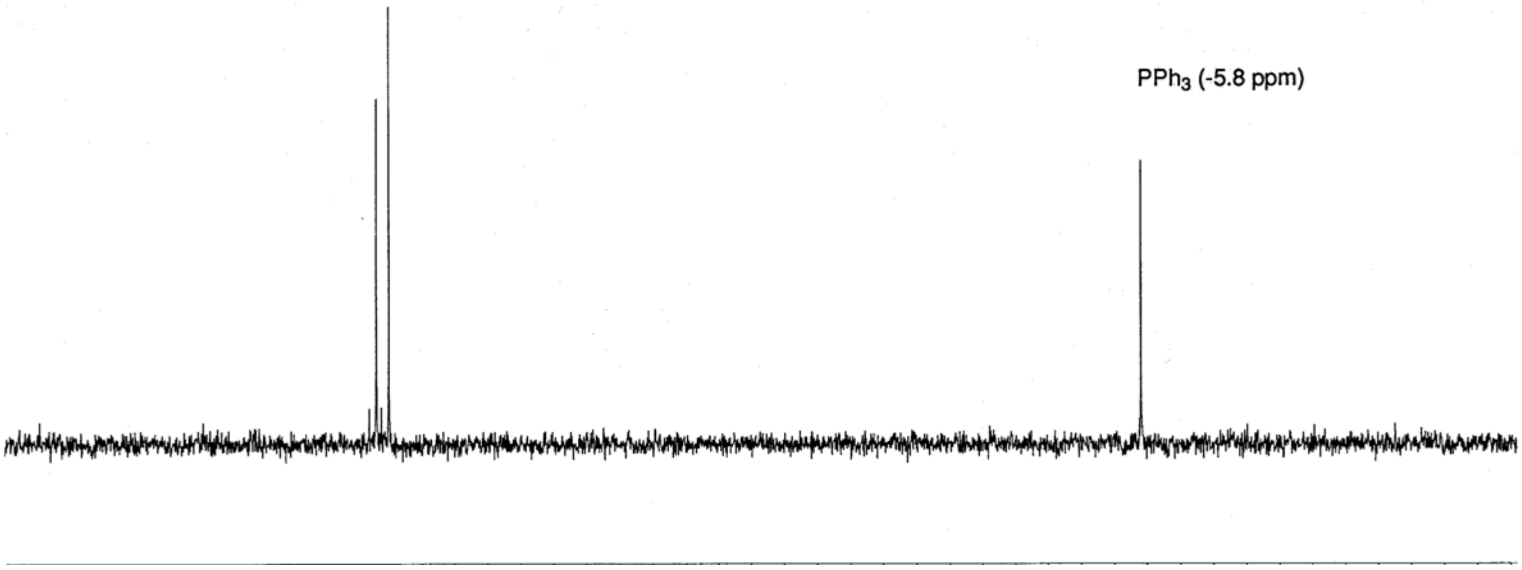
^{19}F NMR (470 MHz, CDCl$_3$)

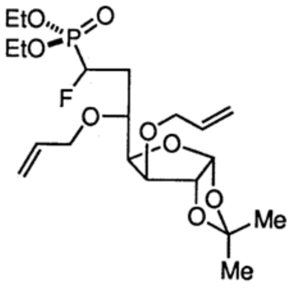




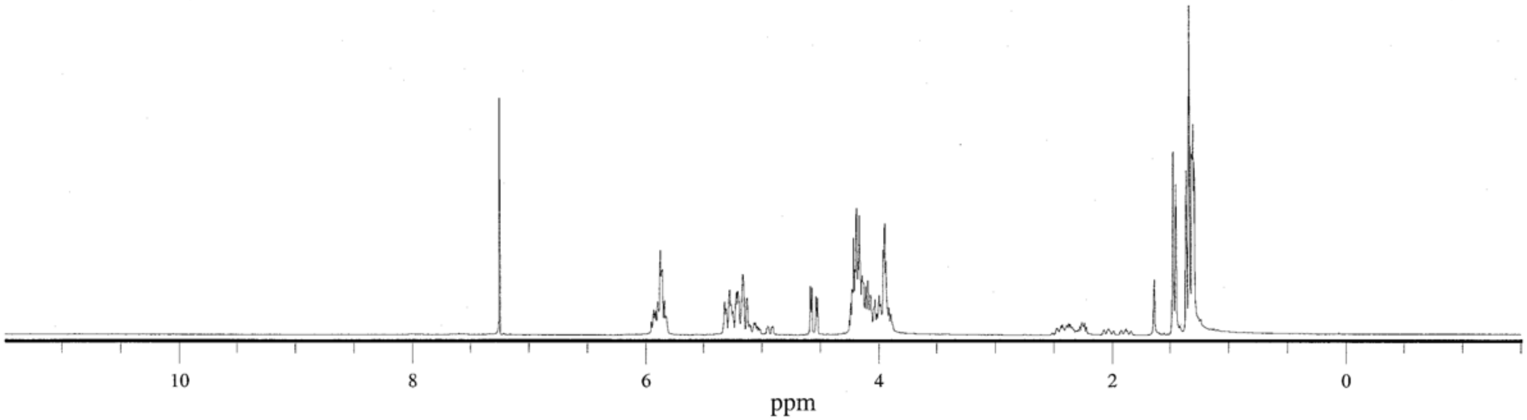
11f *(slower-eluting diastereomer)*

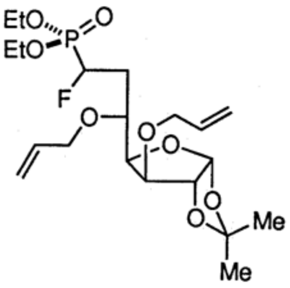
^{31}P NMR (202 MHz, CDCl$_3$)





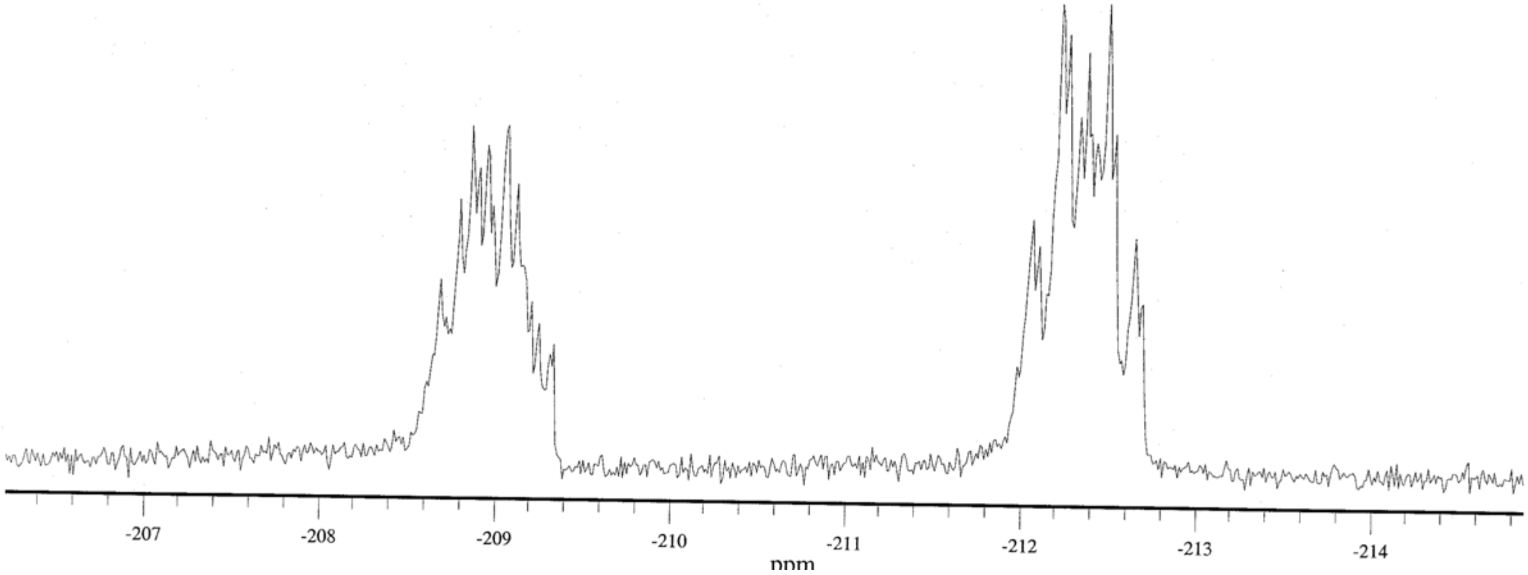
11g (~1:1 mixture of diastereomers)
^{1}H NMR (300 MHz, $CDCl_3$)

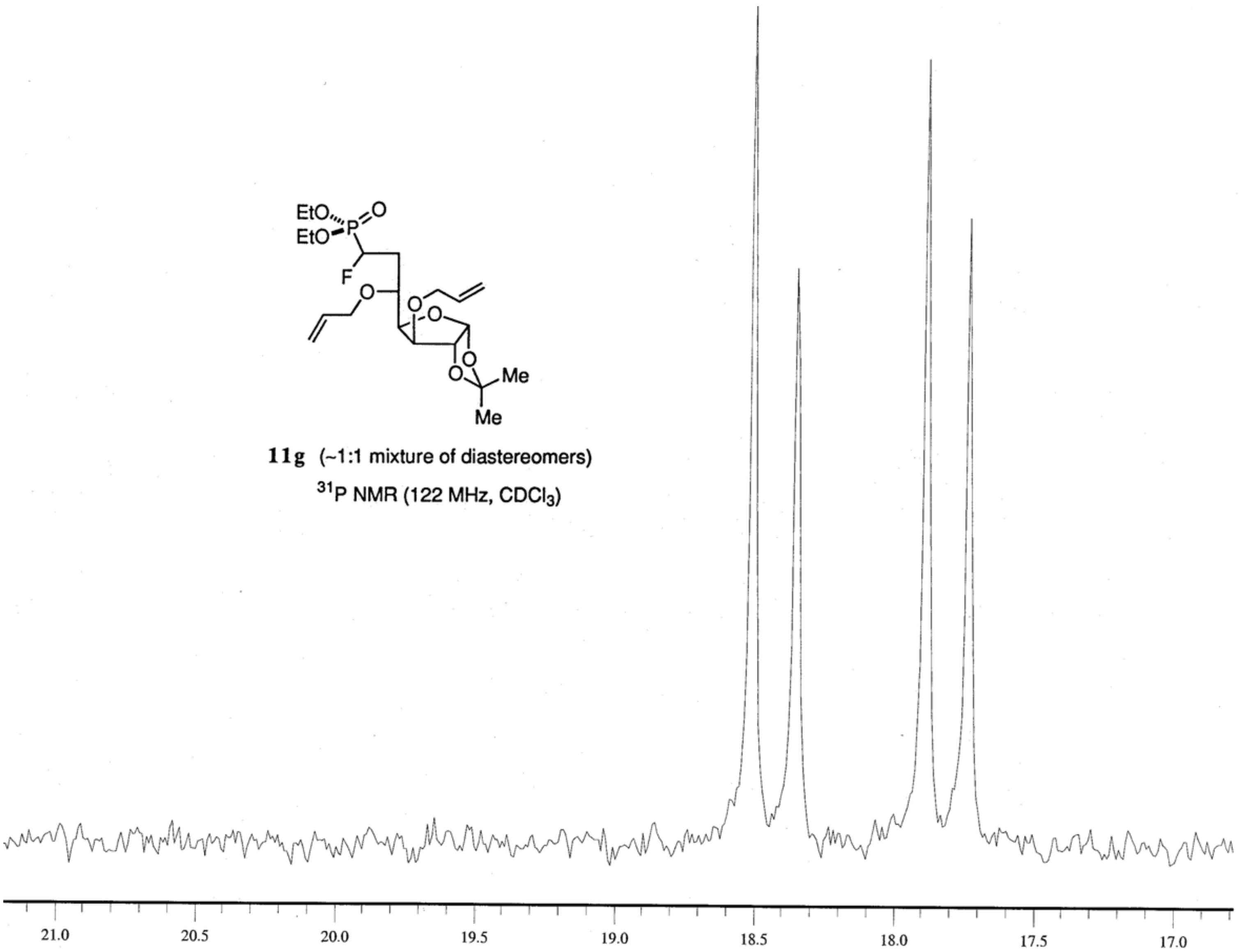




11g (~1:1 mixture of diastereomers)

^{19}F NMR (283 MHz, CDCl$_3$)





11g (~1:1 mixture of diastereomers)
^{31}P NMR (122 MHz, $CDCl_3$)