Synthesis of Fluorine-Containing Analogues of 1-Lysoglycerophospholipids via Horner-Wadsworth-Emmons Reaction

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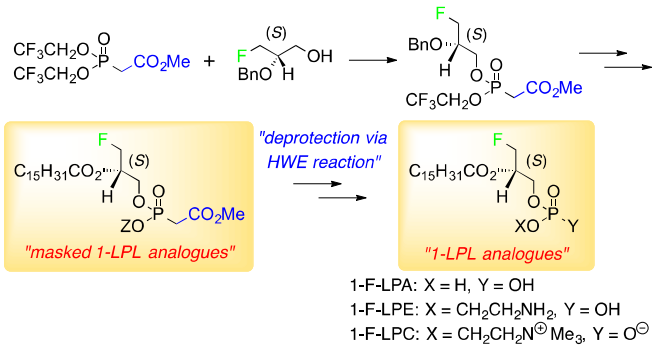

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Abstract This article describes an efficient method of synthesizing fluorine-containing analogues of 1-lysoglycerophospholipids (1-LPLs) by introducing a palmitoyl moiety starting from bis(2,2,2-trifluoroethyl)phosphonoacetate (Still-Gennari reagent). Our method effectively employs Horner-Wadsworth-Emmons reagents as masked 1-LPL derivatives to prepare a series of analogues of 1-lysophosphatidic acid (1-LPA), 1-lysophosphatidylethanolamine (1-LPE), and 1-lysophosphatidylcholine (1-LPC).

Key words lysoglycerophospholipid, Horner-Wadsworth-Emmons reaction, fluorine, lysophosphatidic acid, lysophosphatidylethanolamine, lysophosphatidylcholine

Lysoglycerophospholipids (LPLs), in which only one acyl chain is attached to the glycerol moiety at the *sn*-2 position (1-LPL) or *sn*-1 position (2-LPL), are of considerable current interest as important signaling molecules in living biological systems.[1] Intramolecular acyl chain migration is known to give an equilibrium mixture of 1-LPL and 2-LPL under physiological conditions; the equilibrium generally favors 2-LPL, as shown in Figure 1.[2] On the other hand, fluorine is the most electronegative element of the periodic table and can be considered a reasonable surrogate of a hydroxy group.[3] Thus, replacement of a hydroxy group of 1-LPL by a fluorine atom is an important strategy for blocking the acyl migration of 1-LPL to 2-LPL.[4] In this context, we have been intrigued with *sn*-2 palmitoyl 1-F-LPA (**1**), 1-F-LPE (**2**), and 1-F-LPC (**3**), which are fluorine-containing analogues of 1-lysopohophatidic acid (1-LPA), 1-lysophosphatidylethanolamine (1-LPE), and 1-lysophosphatidylcholine (1-LPC), respectively. However, the literature contains only one report on the synthesis of **1**, by Prestwich et al.,[4b] and there are no reports on the synthesis of **2** or **3**.

Recently, we reported a novel approach to synthesizing glycerophospholipids (PLs) based on the Horner-Wadsworth-Emmons (HWE) reaction of easily handled mixed phosphonoacetate, which serves as a masked precursor of PLs.[5] Herein we describe the facile synthesis of fluorine-containing analogues **1**-**3** using HWE reagent **6** as a key intermediate, which was derived from methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (Still-Gennari reagent, **4**)[6,7] and fluorine-containing chiral alcohol **5** as shown in Figure 1.

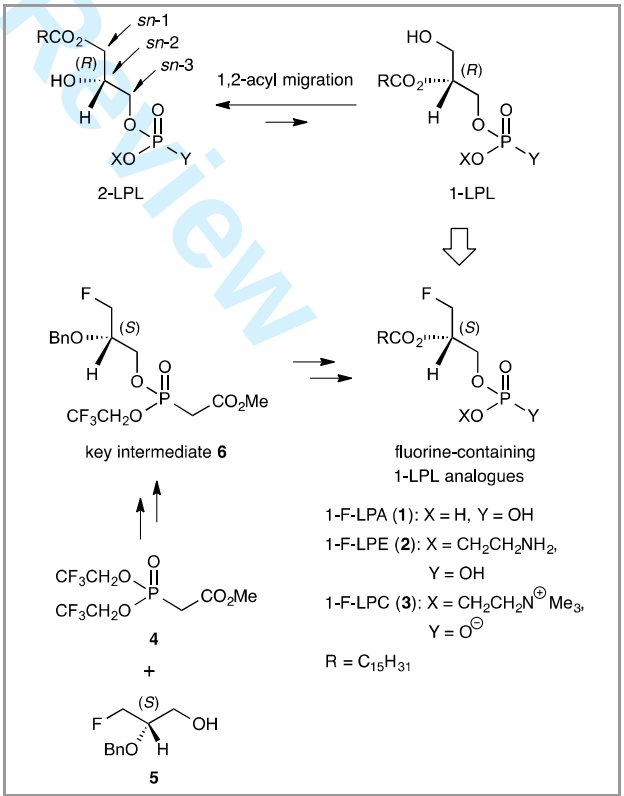
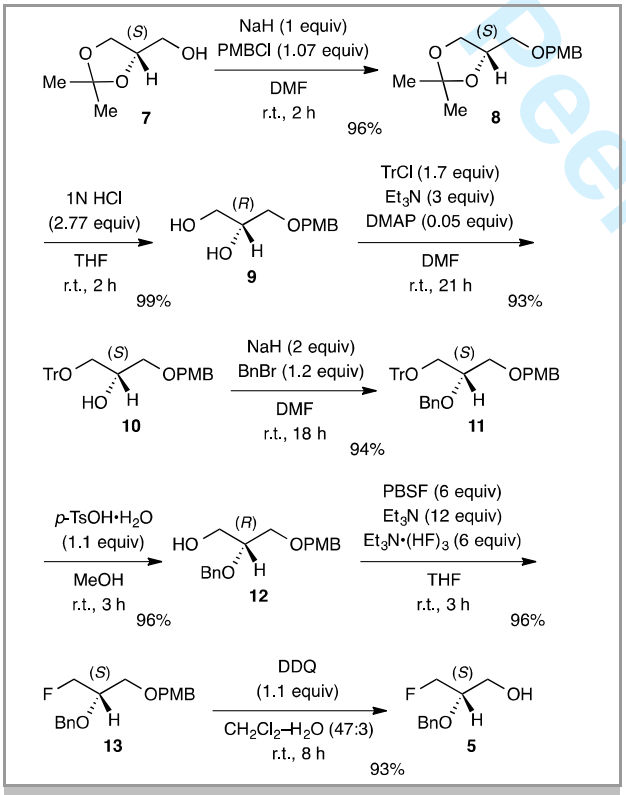


Figure 1 Fluorine-containing analogues **1**-**3** of 1-LPLs

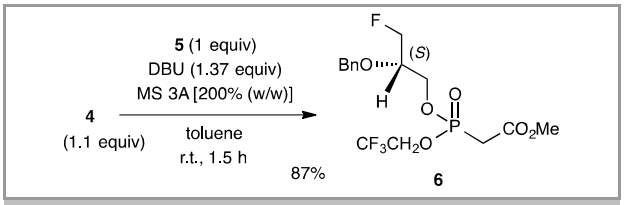
In the synthesis of **5**, (*S*)-2,2-dimethyl-1,3-dioxolan-4-methanol [(*S*)-solketal, **7**][8] was chosen as the starting material (Scheme 1). The *p*-methoxybenzylation of **7** with *p*-methoxybenzyl chloride (PMBCl) in the presence of sodium hydride in DMF provided **8** in 96% yield. Deprotection of the acetonide of **8** under acidic conditions afforded diol **9** in 99% yield. Selective protection of the primary hydroxy group of diol **9** with triphenylchloromethane (TrCl) in the presence of triethylamine and *N*,*N*-dimethylaminopyridine (DMAP) gave secondary alcohol **10** in 93% yield. Benzylation of **10** with benzyl bromide in the presence of sodium hydride in DMF resulted in the formation of **11** in 94% yield. Selective removal of the triphenylmethyl group of **11** was easily performed with *p*-toluenesulfonic acid in methanol to afford primary alcohol **12** in 96% yield. Deoxyfluorination of alcohol **12** by a combination of perfluoro-1-butanesulfonyl fluoride (PBSF), triethylamine, and triethylamine trihydrofluoride provided the corresponding fluoride **13** in 96% yield.[9] The desired chiral alcohol **5** was obtained in 93% yield by oxidative cleavage of the PMB ether of **13** using 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ) as an oxidant in a dichloromethane/water mixed solvent system.[10]



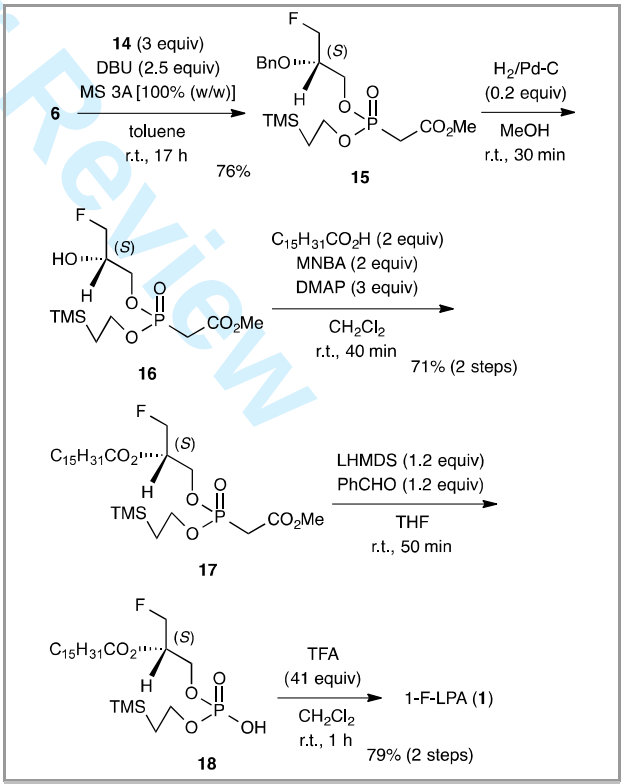
Scheme 1 Synthesis of chiral alcohol **5**

Nucleophilic substitution of the chiral alcohol **5** at the phosphorous center of Still-Gennari reagent (**4**) in the presence of 1.37 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and molecular sieves (type 3A) furnished the key intermediate **6** as an inseparable diastereomeric mixture (ca. 1:1) in 87% yield as shown in Scheme 2.[5,11]

1-F-LPA (**1**), the fluorine-containing analogue of 1-lysophosphatidic acid (1-LPA), was prepared using an HWE reaction of mixed phosphonoacetate **17** with benzaldehyde as the key reaction as shown in Scheme 3. The nucleophilic substitution of 2-(trimethylsilyl)ethanol (**14**)[12] at the phosphorus center of the key intermediate **6** in the presence of excess amounts of **14** and DBU gave phosphonoacetate **15** in 76% yield. After removal of the benzyl group of **15** by hydrogenolysis using a palladium on carbon (Pd-C) catalyst, palmitic acid was incorporated into the resultant secondary alcohol **16** with 2-methyl-6-nitrobenzoic anhydride (MNBA)[13,14] and DMAP to afford **17** in 71% yield (two steps). The HWE reaction of **17** with benzaldehyde in the presence of lithium hexamethyldisilazide (LHMDS) provided the expected phosphodiester **18**, then deprotection of the 2-(trimethylsilyl)ethyl group of the resultant **18** furnished 1-F-LPA (**1**) in 79% yield (two steps). In the synthetic strategy, HWE reagent **17** should be regarded as the masked precursor of *sn*-2 palmitoyl 1-F-LPA (**1**). Compounds **15**-**17** were all obtained as inseparable diastereomeric mixtures (ca. 1:1), similar to the key intermediate **6**.



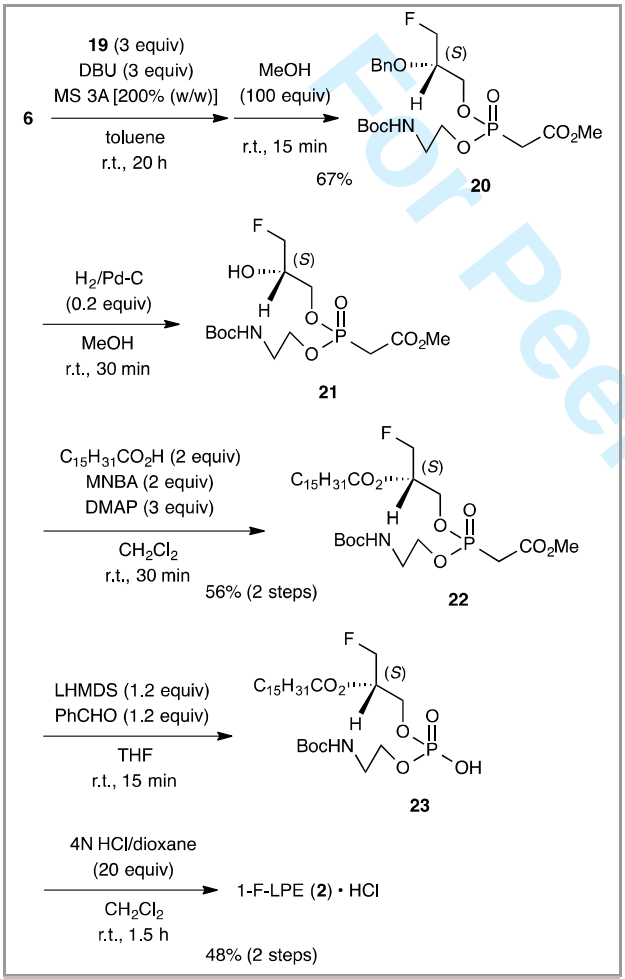
Scheme 2 Synthesis of key intermediate **6**



Scheme 3 Synthesis of 1-F-LPA (**1**)

Subsequently, we explored the preparation of 1-F-LPE (**2**) and 1-F-LPC (**3**) based on the synthetic route of 1-F-LPA (**1**) through **6** as the common key intermediate. The divergent synthesis of

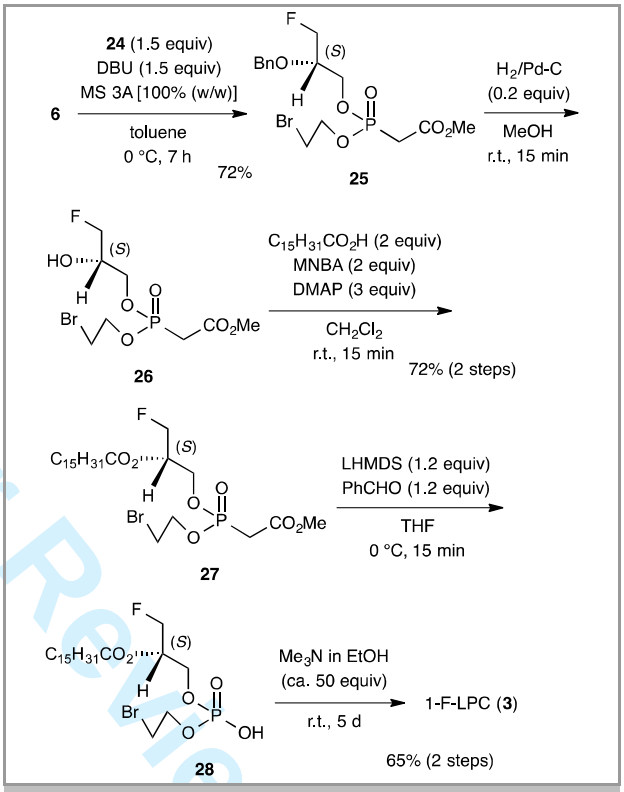
1-F-LPE (**2**), fluorine-containing analogues of 1-lysophosphatidylethanolamine (1-LPE), is shown in Scheme 4. The substitution of *tert*-butyl (2-hydroxyethyl)carbamate (*N*-BOC-ethanolamine, **19**) instead of **14** at the phosphorus center of **6** afforded phosphonoacetate **20** in 67% yield. Hydrogenolysis of **20** using a Pd-C catalyst, followed by condensation of **21** with palmitic acid in the presence of MNBA and DMAP, gave **22** in 56% yield (two steps). The HWE reaction of **22** with benzaldehyde in the presence of LHMDS, followed by deprotection of the Boc group of the resultant phosphodiester **23** under acidic conditions using hydrogen chloride in 1,4-dioxane, afforded 1-F-LPE (**2**) as hydrochloride salt in 48% yield (two steps).



Scheme 4 Synthesis of 1-F-LPE (**2**)

Furthermore, Scheme 5 shows the synthesis of 1-F-LPC (**3**), a fluorine-containing analogue of 1-lysophosphatidylcholine (1-LPC). 2-Bromoethanol (**24**) was used in the reaction with the key intermediate **6** to afford the corresponding phosphonoacetate **25** in 72% yield in a manner similar to that described for the reaction of **6** with **14** and **19**. After hydrogenolysis of **25** using a Pd-C catalyst, condensation of the resultant **26** with palmitic acids using MNBA and DMAP provided **27** in 72% yield (two steps). The HWE reaction of **27** with benzaldehyde in the presence of LHMDS gave phosphodiester **28**, then amination of the resultant **28** in the presence of excess amounts of trimethylamine in ethanol furnished 1-F-LPC (**3**) in 65% yield (two steps).[15]

In conclusion, we have described a novel and efficient method of synthesizing *sn*-2 palmitoyl 1-F-LPA (**1**), 1-F-LPE (**2**), and 1-F-LPC (**3**) as 1,2-acyl migration-blocked analogues of 1-LPLs. Considering the operational ease based on the use of HWE reagents as fluorine-containing masked analogues of 1-LPLs *via* the common key intermediate **6**, we believe this synthetic strategy will be valuable for the chemistry and biochemistry of phospholipids classified as glycerophospholipids (PLs) and sphingophospholipids (SPLs).



Scheme 5 Synthesis of 1-F-LPC (**3**)

The experimental section has no title; please leave this line here.

All melting points were determined on a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AV500 spectrometer. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. ESI-MS were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a J-SCIENCE LAB JM10. Optical rotations were recorded on a P-2200 JASCO digital polarimeter. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Silica Gel 60N (Kanto Chemical) or COSMOSIL 75 SL-II-PREP (Nacalai Tesque)]. Anhydrous THF, CH_2Cl_2, DMF, and toluene were used as purchased from Kanto Chemical. DBU and Et_3N were distilled prior to use. All other reagents were used as purchased.

(*S*)-4-{[(4-Methoxybenzyl)oxy]methyl}-2,2-dimethyl-1,3-dioxolane (8)[16]

To a suspension of NaH (50–72% in mineral oil, 187 mg, 3.90–5.61 mmol) in anhydrous DMF (10 mL) was added **7** (0.5 mL, 4.05 mmol), and

the reaction mixture was stirred at 0 °C for 30 min under argon. After the addition of PMBCl (0.58 mL, 4.28 mmol), the mixture was allowed to warm to r.t. and then stirred for 2 h under argon. H_2O (10 mL) was added to the reaction mixture, and then extracted with EtOAc–*n*-hexane (1:1) (50 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (4:1)] to afford **8** (986 mg, 96%) as a colorless oil; $[\alpha]_D^{24}$ +22.5 (*c* 1.01, $CHCl_3$).

IR (neat): 2986, 2935, 2865, 1613, 1514, 1457, 1371, 1249 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2H), 6.90–6.85 (m, 2H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.28 (quint, *J* = 6.2 Hz, 1H), 4.04 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.80 (s, 3H), 3.72 (dd, *J* = 8.3, 6.3 Hz, 1H), 3.53 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.42 (dd, *J* = 9.8, 5.7 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 130.1, 129.3, 113.8, 109.4, 74.8, 73.2, 70.8, 67.0, 55.3, 26.8, 25.4.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_4Na$: 275.1259; found: 275.1238.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.35; H, 8.08.

(*R*)-3-[(4-Methoxybenzyl)oxy]propane-1,2-diol (9)[16,17]

A mixture of **8** (912 mg, 3.61 mmol) and aq 1 M HCl (10 mL, 10 mmol) and THF (10 mL) was stirred at r.t. for 2 h. Then, aq sat. $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with EtOAc (70 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (15:1)] to afford **9** (760 mg, 99%) as a white solid; mp 37.5–39 °C (white powder, $CHCl_3$–*n*-hexane); $[\alpha]_D^{25}$ –2.2 (*c* 1.23, $CHCl_3$).

IR (KBr): 3330, 2934, 2870, 1612, 1514, 1250 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 2H), 6.90–6.86 (m, 2H), 4.47 (s, 2H), 3.90–3.84 (m, 1H), 3.80 (s, 3H), 3.71–3.65 (m, 1H), 3.63–3.57 (m, 1H), 3.55–3.48 (m, 2H), 2.85 (br s, 1H), 2.41 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 129.8, 129.5, 113.9, 73.3, 71.5, 70.7, 64.1, 55.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{16}O_4Na$: 235.0946; found: 235.0924.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.95; H, 7.61.

(*S*)-1-[(4-Methoxybenzyl)oxy]-3-(trityloxy)propan-2-ol (10)[17]

To a solution of **9** (1.34 g, 6.31 mmol) in anhydrous DMF (10 mL) were added Et_3N (2.63 mL, 18.9 mmol), DMAP (38 mg, 0.311 mmol), and TrCl (3.06 g, 11.0 mmol) at r.t. under argon. The reaction mixture was stirred for 21 h. Then, H_2O (10 mL) was added to the reaction mixture and extracted with EtOAc–*n*-hexane (1:1) (50 mL x 3). The organic layer was washed with H_2O (30 mL), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1 to 4:1)] to afford **10** (2.67 g, 93%) as a yellow oil; $[\alpha]_D^{28}$ -0.6 (*c* 1.01, $CHCl_3$).

IR (neat): 3454, 3058, 3032, 2932, 2870, 1612, 1513, 1448, 1249 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 6H), 7.30–7.20 (m, 11H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.96 (sept, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 3.57 (dd, *J* = 9.7, 4.3 Hz, 1H), 3.52 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.22 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.19 (dd, *J* = 9.4, 5.3 Hz, 1H), 2.39 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 143.8, 130.0, 129.3, 128.6, 127.8, 127.0, 113.7, 86.6, 73.0, 71.2, 69.9, 64.5, 55.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{30}H_{30}O_4Na$: 477.2042; found: 477.2047.

(*S*)-{{2-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]propoxy}methanetriyl}tribenzene (11)

To a solution of **10** (1.70 g, 3.74 mmol) and benzylbromide (533 µL, 4.48 mmol) in anhydrous DMF (8 mL) was added NaH (50–72% in mineral oil; washed with several portions of anhydrous *n*-pentane, 179 mg, 7.46 mmol) at 0 °C under argon. The mixture was stirred at r.t. for 18 h under argon. Then, H_2O (10 mL) was added to the reaction mixture and extracted with EtOAc–*n*-hexane (1:1) (50 mL x 3). The organic layer was washed with H_2O (30 mL x 2), dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (8:1 to 10:1)] to afford **11** (1.91 g, 94%) as a yellow oil; $[\alpha]_D^{23}$ –6.8 (*c* 0.88, $CHCl_3$).

IR (neat): 3060, 3031, 2931, 2868, 1612, 1513, 1449, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 6H), 7.36–7.15 (m, 16H), 6.85–6.81 (m, 2H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 3.77 (s, 3H), 3.79-3.72 (m, 1H), 3.63 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.59 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.29-3.22 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 144.1, 138.7, 130.5, 129.1, 128.7, 128.3, 127.7, 127.4, 126.9, 113.7, 86.6, 77.7, 72.9, 72.2, 70.3, 63.6, 55.2.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{37}H_{36}O_4Na$: 567.2511; found: 567.2511.

(*R*)-2-(Benzyloxy)-3-[(4-methoxybenzyl)oxy]propan-1-ol (12)[18]

To a solution of **11** (100 mg, 0.184 mmol) in MeOH (1.8 mL) was added *p*-toluenesulfonic acid monohydrate (39 mg, 0.205 mmol) at r.t. The reaction mixture was stirred for 3 h. Then, aq 5N NaOH (1 mL) was added to the reaction mixture and extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1)] to afford **12** (53.2 mg, 96%) as a colorless oil; $[\alpha]_D^{23}$ +17.8 (*c* 0.98, $CHCl_3$).

IR (neat): 3440, 3031, 2868, 1612, 1514, 1455, 1248 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5H), 7.26–7.22 (m, 2H), 6.89–6.85 (m, 2H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 3.80 (s, 3H), 3.77–3.71 (m, 1H), 3.70–3.63 (m, 2H), 3.62–3.54 (m, 2H), 2.16 (br t, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 138.2, 130.0, 129.3, 128.4, 127.8, 113.8, 78.0, 73.2, 72.1, 69.9, 62.9, 55.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{22}O_4Na$: 325.1416; found: 325.1416.

(*S*)-1-{[2-(Benzyloxy)-3-fluoropropoxy]methyl}-4-methoxybenzene (13)

To a solution of **12** (1.14 g, 3.77 mmol) in anhydrous THF (10 mL) were added Et_3N (6.24 mL, 45.0 mmol), $Et_3N \cdot (HF)_3$ (3.66 mL, 22.5 mmol), and PBSF (3.96 mL, 22.5 mmol) at r.t. under argon. The reaction mixture was stirred for 3 h. Then, H_2O (10 mL) was added to the reaction mixture and extracted with $CHCl_3$ (50 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (7:1)], then again by column chromatography [*n*-hexane–EtOAc (10:1)] to afford **13** (1.10 g, 96%) as a colorless oil; $[\alpha]_D^{24}$ +13.4 (*c* 1.02, $CHCl_3$).

IR (neat): 2865, 1613, 1514, 1455, 1249 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5H), 7.25–7.21 (m, 2H), 6.89–6.85 (m, 2H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.55 (ddd, $^2J_{H,F}$ = 47.3 Hz, $^2J_{H,H}$ = 9.8 Hz, $^3J_{H,H}$ = 3.7 Hz, 1H), 4.47–4.45 (m, 2H), 4.51 (ddd, $^2J_{H,F}$ = 47.5 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.5 Hz, 1H), 3.80 (s, 3H), 3.86–3.78 (m, 1H), 3.60–3.53 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 138.2, 130.0, 129.3, 128.4, 127.8, 127.7, 113.8, 83.5 (d, $^1J_{C,F}$ = 170.8 Hz), 76.6 (d, $^2J_{C,F}$ = 19.0 Hz), 73.2, 72.4, 68.4 (d, $^3J_{C,F}$ = 8.0 Hz), 55.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{21}FO_3Na$: 327.1372; found: 327.1374.

(*S*)-2-(Benzyloxy)-3-fluoropropan-1-ol (5)[19]

To a solution of **13** (1.40 g, 4.60 mmol) in CH_2Cl_2 (47 mL)–H_2O (3 mL) was added DDQ (1.15 g, 5.07 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 8 h. Then, aq sat. Na_2CO_3 (10 mL) was added to the reaction mixture and extracted with $CHCl_3$ (50 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:1)] to afford **5** (791 mg, 93%) as a colorless oil; $[\alpha]_D^{24}$ +14.8 (*c* 1.01, $CHCl_3$).

IR (neat): 3416, 2953, 2885, 1455, 1348, 1209, 1119, 1060 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.53 (ddd, $^2J_{H,F}$ = 47.2 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.4 Hz, 1H), 4.51 (ddd, $^2J_{H,F}$ = 47.3 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.2 Hz, 1H), 3.78–3.70 (m, 2H), 3.67–3.60 (m, 1H), 2.12 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 128.6, 128.0, 127.9, 82.8 (d, $^1J_{C,F}$ = 170.8 Hz), 77.9 (d, $^2J_{C,F}$ = 19.1 Hz), 72.5, 61.4 (d, $^3J_{C,F}$ = 7.4 Hz).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{10}H_{13}FO_2Na$: 207.0797; found: 207.0784.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy](2,2,2-trifluoroethoxy)phosphoryl}acetate (6)

A solution of alcohol **5** (607 mg, 3.30 mmol) in anhydrous toluene (120 mL) was added to a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**4**) (773 µL, 3.62 mmol), DBU (673 µL, 4.51 mmol), and molecular sieves 3A (1.28 g) in anhydrous toluene (44 mL) at r.t. under argon. After the reaction mixture was stirred at r.t. for 1.5 h, aq 1 M HCl (10 mL) was added to it and then extracted with $CHCl_3$ (50 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **6** (diastereomeric mixture, 1.16 g, 87%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 4.70 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.67 (dd, *J* = 11.6, 2.3 Hz, 1H), 4.53 (ddd, $^2J_{H,F}$ = 46.9 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.9 Hz, 1H), 4.51 (ddd, $^2J_{H,F}$ = 46.9 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.2 Hz, 1H), 4.43–4.31 (m, 3H), 4.25–4.15 (m, 1H), 3.89–3.81 (m, 1H), 3.74/3.73 (s x 2, 3H), 3.08 (br dd, 0.94H for one diastereomer), 3.06 (d, $^2J_{H,P}$ = 21.4 Hz, 1.06H for one diastereomer).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5 (d, $^2J_{C,P}$ = 5.4 Hz), 137.4, 137.3, 128.6, 128.13, 128.10, 128.00, 127.96, 122.7 (qd, $^1J_{C,F}$ = 277.6 Hz, $^3J_{C,P}$ = 8.3 Hz), 81.6 (d, $^1J_{C,F}$ = 172.3 Hz), 75.66, 75.65, 75.62, 75.6, 75.5, 75.49, 75.46, 75.44, 72.44, 72.43, 64.65, 64.59, 64.53, 64.47, 62.7 (qd, $^2J_{C,F}$ = 37.8 Hz, $^2J_{C,P}$ = 5.3 Hz), 52.82, 52.8, 33.9 (d, $^1J_{C,P}$ = 141.8 Hz for one diastereomer), 33.8 (d, $^1J_{C,P}$ = 141.5 Hz for one diastereomer).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{19}F_4O_6PNa$: 425.0753; found: 425.0747.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy][(2-trimethylsilyl)ethoxy]phosphoryl}acetate (15)

DBU (283 µL, 1.90 mmol) was added to a solution of **6** (300 mg, 0.746 mmol), 2-(trimethylsilyl)ethanol (**14**) (319 µL, 2.24 mmol), and molecular sieves 3A (300 mg) in anhydrous toluene (10 mL) at r.t. under argon. After the reaction mixture was stirred at r.t. for 17 h, aq 1 M HCl (10 mL) was added to it and then extracted with $CHCl_3$ (50 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **15** (diastereomeric mixture, 240 mg, 76%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.56 (ddd, $^2J_{H,F}$ = 47.0 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 4.6 Hz, 1H), 4.53 (ddd, $^2J_{H,F}$ = 47.0 Hz, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 5.3 Hz, 1H), 4.36–4.29 (m, 1H), 4.26–4.13 (m, 3H), 3.90–3.81 (m, 1H), 3.723/3.715 (s x 2, 3H), 3.05–2.93 (m, 2H), 1.12–1.06 (m, 2H), 0.03/0.02 (s x 2, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (d, $^2J_{C,P}$ = 4.7 Hz), 137.62, 137.59, 128.5, 127.96, 127.95, 127.9, 127.8, 82.0 (d, $^1J_{C,F}$ = 171.7 Hz), 76.0, 75.9, 75.81, 75.76, 72.34, 72.32, 65.62, 65.56, 65.5, 65.4, 64.13, 64.08, 64.03, 63.97, 63.91, 63.85, 52.58, 52.55, 34.2 (d, $^1J_{C,P}$ = 136.1 Hz for one diastereomer), 34.1 (d, $^1J_{C,P}$ = 135.3 Hz for one diastereomer), 19.80, 19.76, –1.52, –1.53.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{18}H_{30}FO_6PSiNa$: 443.1431; found: 443.1431.

(2*S*)-1-Fluoro-3-{{(2-methoxy-2-oxoethyl)[2-(trimethylsilyl)ethoxy]phosphoryl}oxy}propan-2-yl Palmitate (17)

A mixture of **15** (43 mg, 0.102 mmol) and 10% Pd-C (21 mg, 0.0197 mmol) in MeOH (1 mL) was stirred at r.t. for 30 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **16**. A solution of **16** in anhydrous CH_2Cl_2 (3 mL) was added to a solution palmitic acid (52 mg, 0.203 mmol), 2-methyl-6-nitrobenzoic anhydride (70 mg, 0.203 mmol), and DMAP (37 mg, 0.303 mmol) in anhydrous CH_2Cl_2 (10 mL) at r.t. under argon. The reaction mixture was stirred for 40 min. Aq 1 M HCl (2 mL) was added to the reaction mixture and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (3:2)] to afford **17** (diastereomeric mixture, 41 mg, 71%, two steps) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.26–5.16 (m, 1H), 4.64–4.60 (m, 1H), 4.55–4.51 (m, 1H), 4.38–4.16 (m, 4H), 3.74 (s, 3H), 3.00 (d, $^2J_{H,P}$ = 21.6 Hz, 1H for one diastereomer), 2.98 (d, $^2J_{H,P}$ = 21.5 Hz, 1H for one diastereomer), 2.37 (br td, 2H), 1.67–1.59 (m, 2H), 1.34–1.22 (m, 24H), 1.11 (t, *J* = 8.6 Hz, 2H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.047/0.045 (s x 2, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.83, 172.82, 165.9 (d, $^2J_{C,P}$ = 6.2 Hz), 80.8 (d, $^1J_{C,F}$ = 172.8 Hz for one diastereomer), 80.7 (d, $^1J_{C,F}$ = 173.4 Hz for one diastereomer), 70.3, 70.23, 70.18, 70.13, 70.07, 70.0, 65.7, 65.6, 63.33, 63.28, 63.22, 63.17, 52.6, 34.14, 34.11 (d, $^1J_{C,P}$ = 136.1 Hz for one diastereomer), 34.07 (d, $^1J_{C,P}$ = 135.4 Hz for one diastereomer), 31.9, 29.7, 29.69, 29.66, 29.6, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 19.83, 19.82, 19.79, 19.77, 14.1, –1.51.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{27}H_{54}FO_7PSiNa$: 591.3258; found: 591.3248.

(*S*)-1-Fluoro-3-(phosphonooxy)propan-2-yl Palmitate [1-F-LPA (1)][4b]

To a solution of **17** (70 mg, 0.123 mmol) in anhydrous THF (1.26 mL) was added LHMDS (1.1 mol/L in *n*-hexane, 137 µL, 0.151 mmol) and the solution was stirred at 0 °C for 5 min under argon. After the addition of benzaldehyde (15 µL, 0.147 mmol), the mixture was allowed to warm to r.t. and then stirred for 50 min under argon. Aq 1 M HCl (2 mL) was added to the reaction mixture and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The crude **18** was dissolved in anhydrous CH_2Cl_2 (1.25 mL), and TFA (385 µL, 5.03 mmol) was added. After being stirred at r.t. for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 6:1)] to afford 1-F-LPA (**1**) (39.9 mg, 79%, two steps) as a white solid; mp 80–93 °C); $[\alpha]_D^{27}$ +4.8 (*c* 0.79, $CHCl_3$).

IR (KBr): 2918, 2849, 1729, 1468, 1179 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.23 (br d, 1H), 4.93 (br s, 2H), 4.58 (br d, 2H), 4.23–4.10 (m, 2H), 2.44–2.31 (m, 2H), 1.68–1.55 (m, 2H), 1.40–1.10 (m, 24H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 80.8 (d, $^1J_{C,F}$ = 173.5 Hz), 70.6 (d, $^2J_{C,F}$ = 17.3 Hz), 64.0, 34.2, 31.9, 29.74, 29.72, 29.69, 29.68, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 14.1.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{19}H_{37}FO_6P$: 411.2312; found: 411.2310.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy]{2-[(*tert*-butoxycarbonyl)amino]ethoxy}phosphoryl}acetate (20)

To a solution of **6** (53.4 mg, 0.133 mmol), *tert*-butyl (2-hydroxyethyl)carbamate (**19**) (64.2 mg, 0.398 mmol), and molecular sieves 3A (107 mg) in anhydrous toluene (2 mL) was added DBU (59.4 µL, 0.398 mmol) at r.t. under argon. After being stirred at r.t. for 20 h, MeOH (537 µL, 13.3 mmol) was added and stirred at r.t. for another 15 min. The reaction mixture was filtered and added 1/15 M phosphate buffer (pH 7.4, 10 mL) and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (1:2 to 1:3)] to afford **20** (diastereomeric mixture, 41.3 mg, 67%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 5.15 (br s, 1H), 4.70 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.61–4.54 (m, 1H), 4.51–4.45 (m, 1H), 4.38–4.28 (m, 1H), 4.23–4.05 (m, 3H), 3.89–3.81 (m, 1H), 3.74/3.73 (s x 2, 3H), 3.43–3.28 (m, 2H), 3.08–2.96 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (d, $^2J_{C,P}$ = 3.6 Hz for one diastereomer), 166.0 (d, $^2J_{C,P}$ = 2.9 Hz for one diastereomer), 155.8, 137.42, 137.41, 128.5, 128.07, 128.05, 127.95, 127.94, 81.7 (d, $^1J_{C,F}$ = 171.7 Hz), 79.6, 75.81, 75.76, 75.75, 75.70, 75.65, 75.60, 75.59, 75.54, 72.4, 72.3, 66.21, 66.17, 64.5, 64.4, 64.38, 64.35, 64.30, 64.2, 52.74, 52.71, 41.0, 33.9 (d, $^1J_{C,P}$ = 137.3 Hz for one diastereomer), 33.8 (d, $^1J_{C,P}$ = 137.1 Hz for one diastereomer), 28.4.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{31}FNO_8PNa$: 486.1669; found: 486.1647.

(2*S*)-1-{{{2-[(*tert*-Butoxycarbonyl)amino]ethoxy}(2-methoxy-2-oxoethyl)phosphoryl}oxy}-3-fluoropropan-2-yl Palmitate (22)

A mixture of **20** (54.3 mg, 0.117 mmol) and 10% Pd-C (24.9 mg, 0.0234 mmol) in MeOH (1 mL) was stirred at r.t. for 30 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **21**, which was used in the next reaction without further purification. To a solution of palmitic acid (60 mg, 0.234 mmol), 2-methyl-6-nitrobenzoic anhydride (80.6 mg, 0.234 mmol), and DMAP (42.9 mg, 0.351 mmol) in anhydrous CH_2Cl_2 (3 mL) was added a solution of **21** in anhydrous CH_2Cl_2 (2 mL) at r.t. under argon. The reaction mixture was stirred for 30 min. 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the reaction mixture, and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (1:1)] to afford **22** (diastereomeric mixture, 40.2 mg, 56%, two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26–5.14 (m, 2H), 4.65–4.59 (m, 1H), 4.55–4.49 (m, 1H), 4.38–4.10 (m, 4H), 3.76 (s, 3H), 3.48–3.35 (m, 2H), 3.04 (d, $^2J_{H,P}$ = 21.6 Hz, 0.97H for one diastereomer), 3.02 (br dd, 1.03H for one diastereomer), 2.37 (t, *J* = 7.6 Hz, 2H), 1.67–1.60 (m, 2H), 1.45 (s, 9H), 1.34–1.23 (m, 24H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.89, 172.88, 165.9 (d, $^2J_{C,P}$ = 5.8 Hz), 155.8, 80.7 (d, $^1J_{C,F}$ = 173.3 Hz for one diastereomer), 80.6 (d, $^1J_{C,F}$ = 173.4 Hz for one diastereomer), 79.6, 70.16, 70.11, 70.06, 70.00, 69.95, 69.90, 66.41, 66.36, 63.6, 63.53, 63.48, 63.43, 63.38, 52.8, 41.04, 41.01, 34.1, 33.8 (d, $^1J_{C,P}$ = 137.3 Hz for one diastereomer), 33.7 (d, $^1J_{C,P}$ = 137.1 Hz for one diastereomer), 31.9, 29.71, 29.69, 29.66, 29.62, 29.5, 29.4, 29.3, 29.1, 28.4, 24.8, 22.7, 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{29}H_{55}FNO_9PNa$: 634.3496; found: 634.3470.

(2*S*)-1-{[(2-Aminoethoxy)(hydroxy)phosphoryl]oxy}-3-fluoropropan-2-yl Palmitate Hydrochloride [1-F-LPE (2) · HCl]

To a solution of **22** (69.2 mg, 0.113 mmol) in anhydrous THF (1 mL) was added LHMDS (1.02 mol/L in *n*-hexane, 133 µL, 0.136 mmol) and the solution was stirred at 0 °C for 5 min under argon. After adding benzaldehyde (13.9 µL, 0.136 mmol), the mixture was allowed to warm to r.t. and stirred for 15 min under argon. 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the reaction mixture, and then concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 2:1)] to afford **23**, which was used in the next reaction without further purification. A mixture of **23** and 4 M HCl in 1,4-dioxane (0.57 mL, 2.26 mmol) in CH_2Cl_2 (1 mL) was stirred at r.t. for 1.5 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (2:1)] to afford 1-F-LPE (**2**) · HCl (26.6 mg, 48%, two steps) as a white solid; mp 188–191 °C; $[\alpha]_D^{27}$ +9.7 [*c* 0.55, $CHCl_3$/MeOH (2:1)].

IR (KBr): 2920, 2851, 1741, 1467, 1252, 1225, 1082 cm^{-1}.

^{1}H NMR [500 MHz, $CDCl_3$/CD_3OD (2:1)]: δ = 5.23–5.13 (m, 1H), 4.61 (dd, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,H}$ = 4.1 Hz, 2H), 4.07–3.99 (m, 4H), 3.13–3.09 (m, 2H), 2.39–2.34 (m, 2H), 1.67–1.58 (m, 2H), 1.36–1.22 (m, 24H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR [125 MHz, $CDCl_3$/CD_3OD (2:1)]: δ = 173.9, 81.5 (d, $^1J_{C,F}$ = 171.8 Hz), 71.3 (dd, $^2J_{C,F}$ = 19.4 Hz, $^3J_{C,P}$ = 8.4 Hz), 62.8 (dd, $^3J_{C,F}$ = 7.4 Hz, $^2J_{C,P}$ = 5.2 Hz), 61.8 (d, $^2J_{C,P}$ = 5.2 Hz), 40.8 (d, $^3J_{C,P}$ = 5.4 Hz), 34.4, 32.2, 29.92, 29.89, 29.8, 29.7, 29.6, 29.5, 29.3, 25.1, 22.9, 14.2.

HRMS (ESI): *m/z* [M – H – HCl]$^-$ calcd for $C_{21}H_{42}FNO_6P$: 454.2734; found: 454.2732.

Anal. Calcd for $C_{21}H_{44}ClFNO_6P$: C, 51.26; H, 9.01; N, 2.85. Found: C, 51.23; H, 8.85; N, 2.98.

Methyl 2-{[(*S*)-2-(Benzyloxy)-3-fluoropropoxy]{2-bromoethoxy)phosphoryl}acetate (25)

To a solution of **6** (50 mg, 0.124 mmol), 2-bromoethanol (**24**) (13 µL, 0.186 mmol), and molecular sieves 3A (50 mg) in anhydrous toluene (0.8 mL) was added DBU (28 µL, 0.186 mmol) at 0 °C under argon. After being stirred at 0 °C for 7 h, the reaction mixture was added 1/15 M phosphate buffer (pH 7.4, 3 mL), filtered, and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The oily residue was purified by column chromatography [Silica Gel 60N: *n*-hexane–EtOAc (2:3) to afford **25** (diastereomeric mixture, 38.4 mg, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5H), 4.71 (dd, *J* = 11.7, 1.2 Hz, 1H), 4.68 (dd, *J* = 11.7, 2.8 Hz, 1H), 4.62–4.55 (m, 1H), 4.53–4.45 (m, 1H), 4.41–4.30 (m, 3H), 4.25–4.17 (m, 1H), 3.91–3.81 (m, 1H), 3.74/3.73 (s x 2, 3H), 3.50/3.48 (t x 2, *J* = 6.2, 6.1 Hz, 2H), 3.06/3.04/3.03 (dd, $^2J_{H,P}$ = 21.9 Hz, $^2J_{H,H}$ = 14.8 Hz, dd, $^2J_{H,P}$ = 21.5 Hz, $^2J_{H,H}$ = 14.8 Hz, d, $^2J_{H,P}$ = 21.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8 (d, $^2J_{C,P}$ = 5.9 Hz), 137.5, 128.5, 128.0, 127.94, 127.91, 81.8 (d, $^1J_{C,F}$ = 172.1 Hz), 75.8, 75.7, 75.63, 75.59, 72.4, 72.3, 65.9, 65.8, 65.79, 65.74, 64.47, 64.42, 64.37, 64.34, 64.29, 64.23, 52.72, 52.70, 34.0 (d, $^1J_{C,P}$ = 138.9 Hz for one diastereomer), 33.9 (d, $^1J_{C,P}$ = 138.0 Hz for one diastereomer), 29.9, 29.83, 29.79, 29.7.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{21}BrFO_6PNa$: 449.0141; found: 449.0145.

(2*S*)-1-{[(2-Bromoethoxy)(2-methoxy-2-oxoethyl)phosphoryl]oxy}-3-fluoropropan-2-yl Palmitate (27)

A mixture of **25** (61.2 mg, 0.143 mmol) and 10% Pd/C (30 mg, 0.0282 mmol) in MeOH (1 mL) was stirred at r.t. for 15 min under H_2 atmosphere. The reaction mixture was filtered and concentrated in vacuo to afford **26**, which was used in the next reaction without further purification. To a solution of palmitic acid (73 mg, 0.286 mmol), 2-methyl-6-nitrobenzoic anhydride (99 mg, 0.286 mmol), and DMAP (52 mg, 0.426 mmol) in anhydrous CH_2Cl_2 (6 mL) was added a solution of **26** in anhydrous CH_2Cl_2 (4 mL) at r.t. under argon. The reaction mixture was stirred for 15 min. 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the reaction mixture, and then extracted with $CHCl_3$ (10 mL x 3). The organic layer was dried (anhyd $MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography [Silica Gel

60N: *n*-hexane–EtOAc (1:1)] twice to afford **27** (diastereomeric mixture, 59.6 mg, 72%, two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.27–5.17 (m, 1H), 4.64–4.61 (m, 1H), 4.55–4.51 (m, 1H), 4.45–4.24 (m, 4H), 3.76 (s, 3H), 3.55/3.54 (t x 2, *J* = 6.2, 6.1 Hz, 2H), 3.06 (d, $^2J_{H,P}$ = 21.5 Hz, 1H for one diastereomer), 3.05 (d, $^2J_{H,P}$ = 21.5 Hz, 1H for one diastereomer), 2.37 (t, *J* = 7.6 Hz, 2H), 1.68–1.59 (m, 2H), 1.35–1.20 (m, 24H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 165.7 (d, $^2J_{C,P}$ = 5.4 Hz), 80.7 (d, $^1J_{C,F}$ = 173.3 Hz for one diastereomer), 80.6 (d, $^1J_{C,F}$ = 172.9 Hz for one diastereomer), 70.12, 70.08, 70.06, 70.02, 69.95, 69.91, 69.86, 66.0, 65.97, 65.95, 65.92, 63.7, 63.63, 63.58, 63.53, 63.5, 63.4, 52.8, 34.14, 34.12, 33.94 (d, $^1J_{C,P}$ = 138.7 Hz for one diastereomer), 33.89 (d, $^1J_{C,P}$ = 138.2 Hz for one diastereomer), 31.9, 29.7, 29.69, 29.66, 29.65, 29.62, 29.5, 29.4, 29.3, 29.1, 24.8, 22.7, 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{24}H_{45}BrFO_7PNa$: 597.1968; found: 597.1911.

(*S*)-3-Fluoro-2-(palmitoyloxy)propyl [2-(Trimethylammonio)ethyl] Phosphate [1-F-LPC (3)]

To a solution of **27** (68.6 mg, 0.119 mmol) in anhydrous THF (1 mL) were added LHMDS (1.02 mol/L in *n*-hexane, 140 µL, 0.143 mmol) and benzaldehyde (14.6 µL, 0.143 mmol) at 0 °C under argon. The mixture was stirred for 15 min under argon. 1/15 M phosphate buffer (pH 7.4, 3 mL) was added to the reaction mixture, and then concentrated in vacuo. The residue was purified by column chromatography [COSMOSIL 75 SL-II-PREP: $CHCl_3$–MeOH (100:1 to 3:1)] to afford **28**, which was used in the next reaction without further purification. A mixture of **28** and trimethylamine (ca. 3 mol/L in EtOH, 2 mL, ca. 6 mmol) was stirred at r.t. for 5 d. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (3:1) to $CHCl_3$–MeOH–H_2O (5:5:1)] to afford 1-F-LPC (**3**) (38.7 mg, 65%, two steps) as a white solid; mp 65–67 °C; $[\alpha]_D^{27}$ +9.8 (*c* 1.09, $CHCl_3$).

IR (KBr): 2918, 2850, 1737, 1468, 1247, 1093 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (br d, 1H), 4.69–4.52 (m, 2H), 4.35–4.26 (m, 2H), 3.98–3.91 (m, 2H), 3.82–3.76 (m, 2H), 3.36 (s, 9H), 2.35–2.28 (m, 2H), 1.64–1.54 (m, 2H), 1.34–1.20 (m, 24H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 82.0 (d, $^1J_{C,F}$ = 171.8 Hz), 71.2 (dd, $^2J_{C,F}$ = 19.6 Hz, $^3J_{C,P}$ = 9.1 Hz), 66.2, 62.4, 59.6, 54.6, 34.3, 32.0, 29.78, 29.77, 29.71, 29.66, 29.5, 29.4, 29.2, 25.0, 22.7, 14.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{24}H_{49}FNO_6PNa$: 520.3179; found: 520.3178.

Acknowledgment

Click here to insert acknowledgment text.

Supporting Information

Is there **Supporting Information** to be published? Click here to indicate YES or NO (text and links will be updated prior to publication).

Primary Data

Is there **Primary Data** to be associated with this manuscript? Click here to indicate YES or NO (text and links will be updated prior to publication).

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Supporting Information

for

Synthesis of Fluorine-Containing Analogues of 1-Lysoglycerophospholipids via Horner-Wadsworth-Emmons Reaction

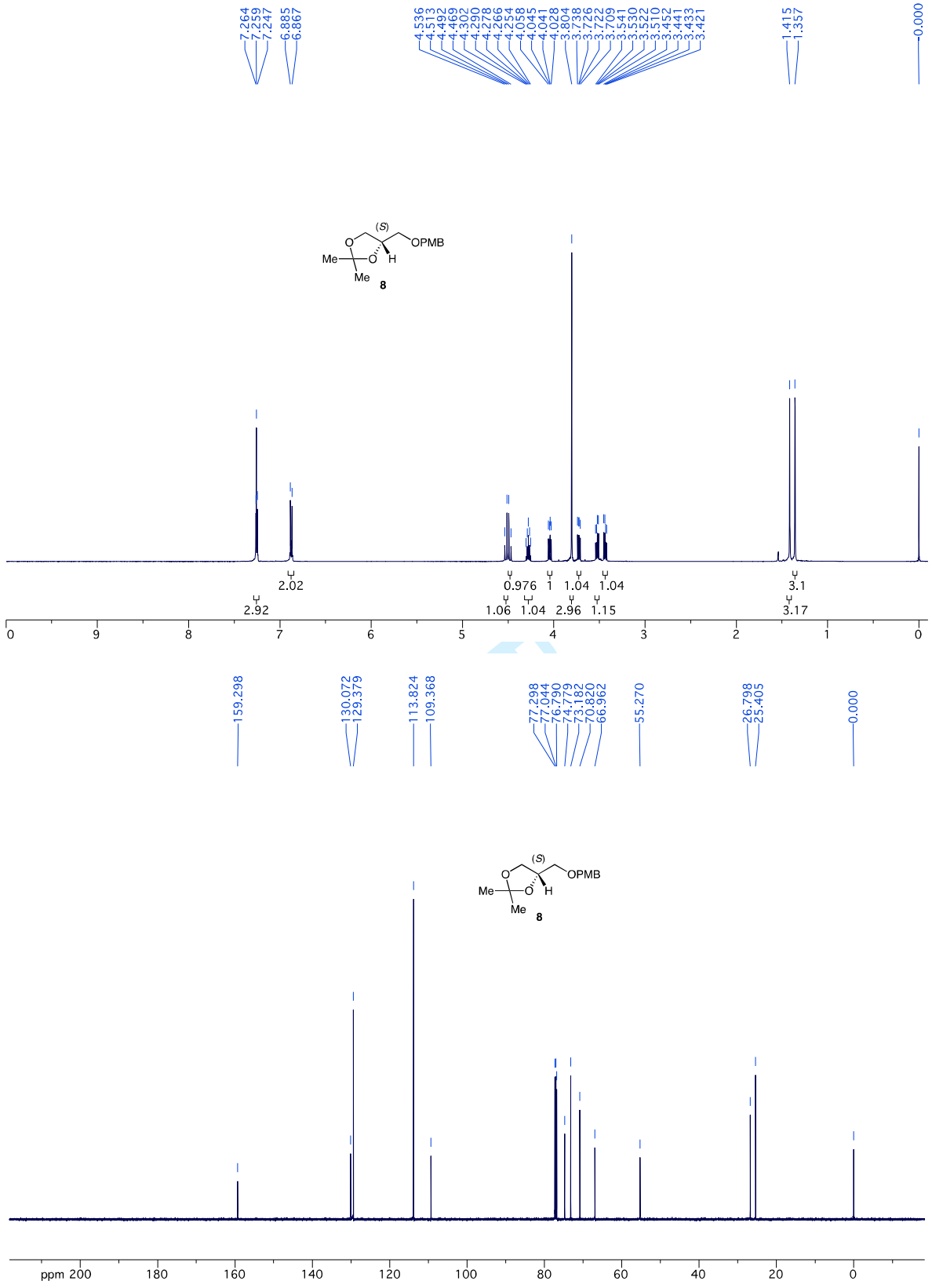
Michiyasu Nakao, Kazue Tanaka, Syuji Kitaike, and Shigeki Sano*

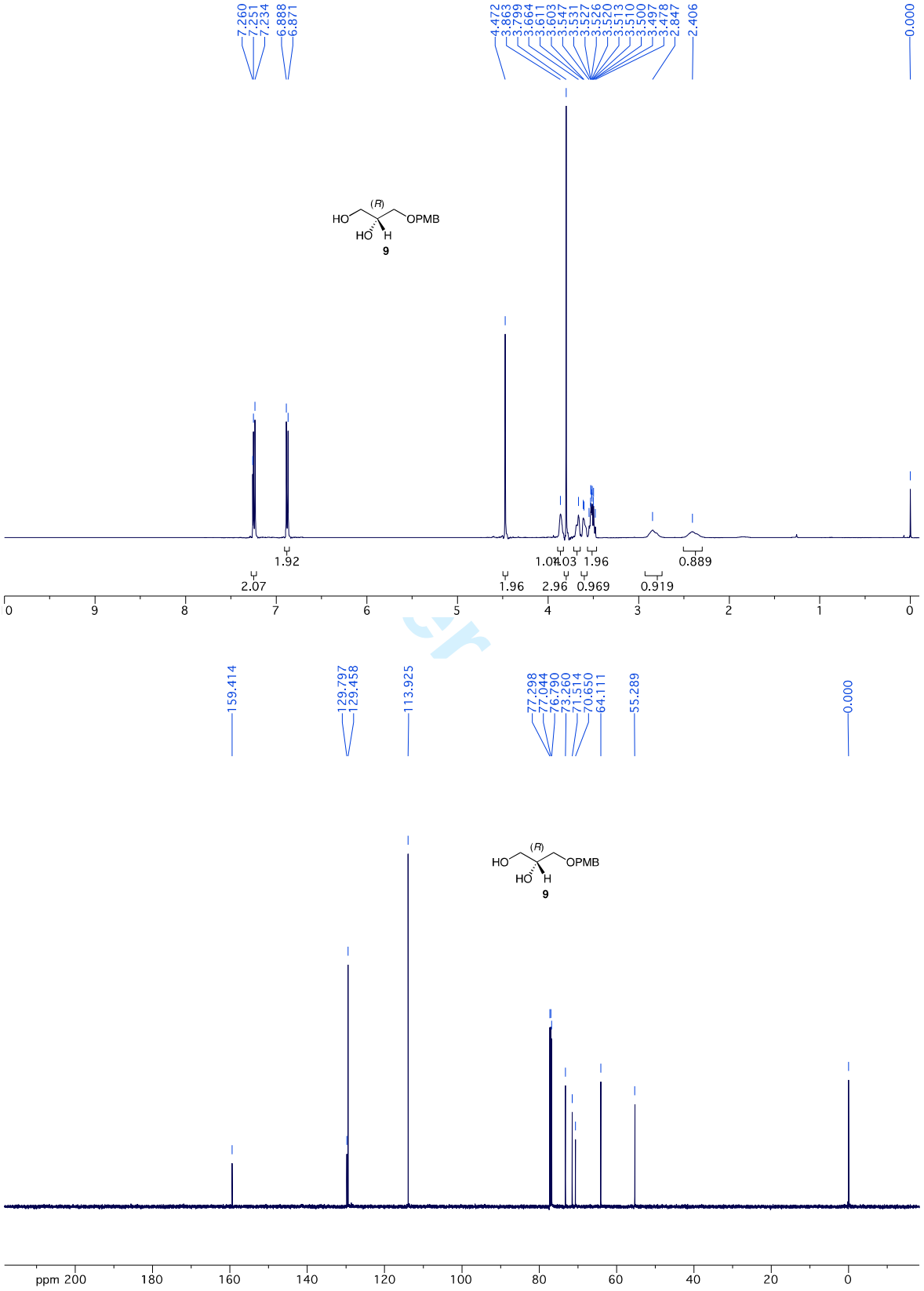
Graduate School of Pharmaceutical Sciences, Tokushima University

Sho-machi, Tokushima 770-8505, Japan

^{1}H and ^{13}C NMR spectra

^{1}H and ^{13}C NMR spectra

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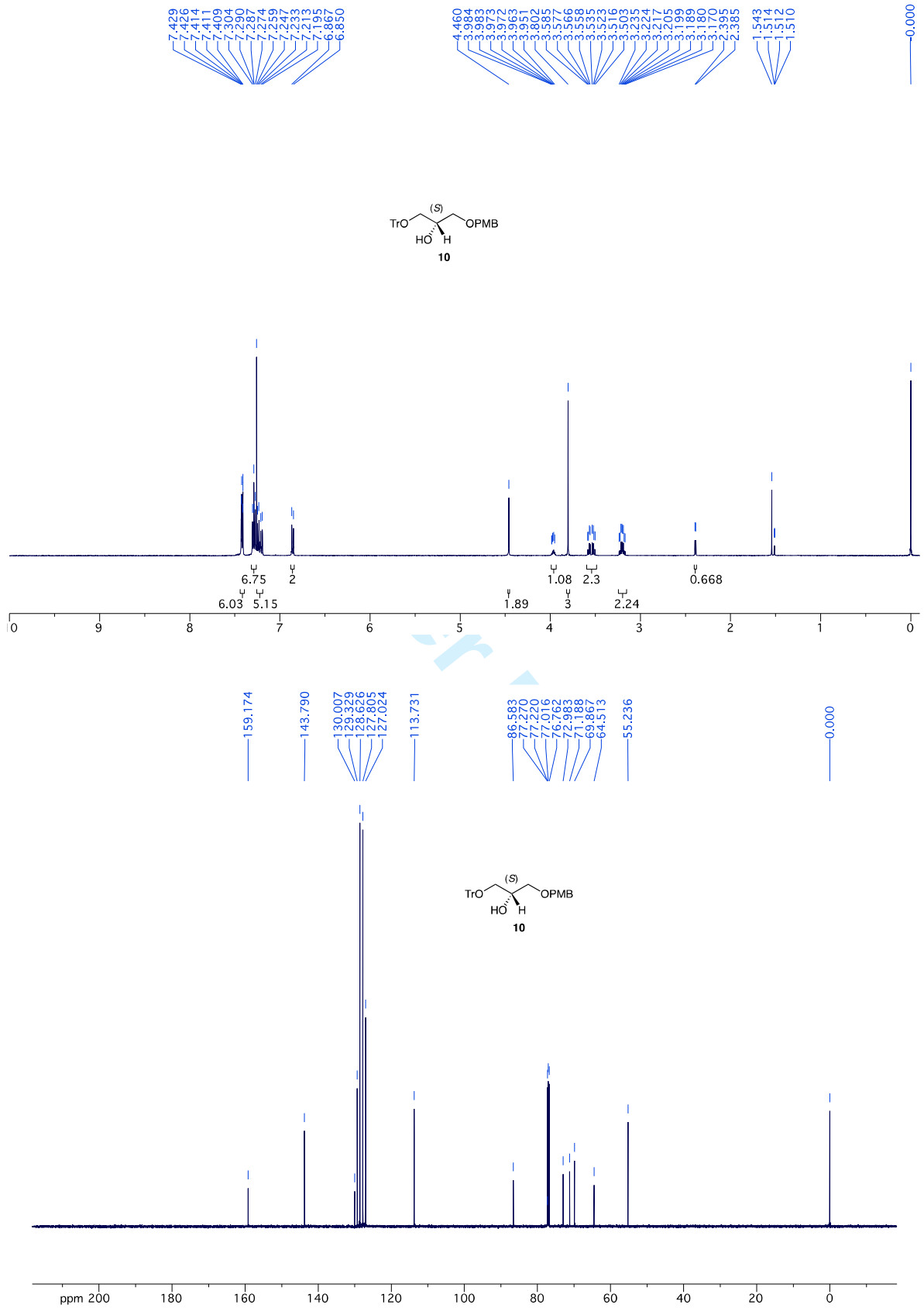
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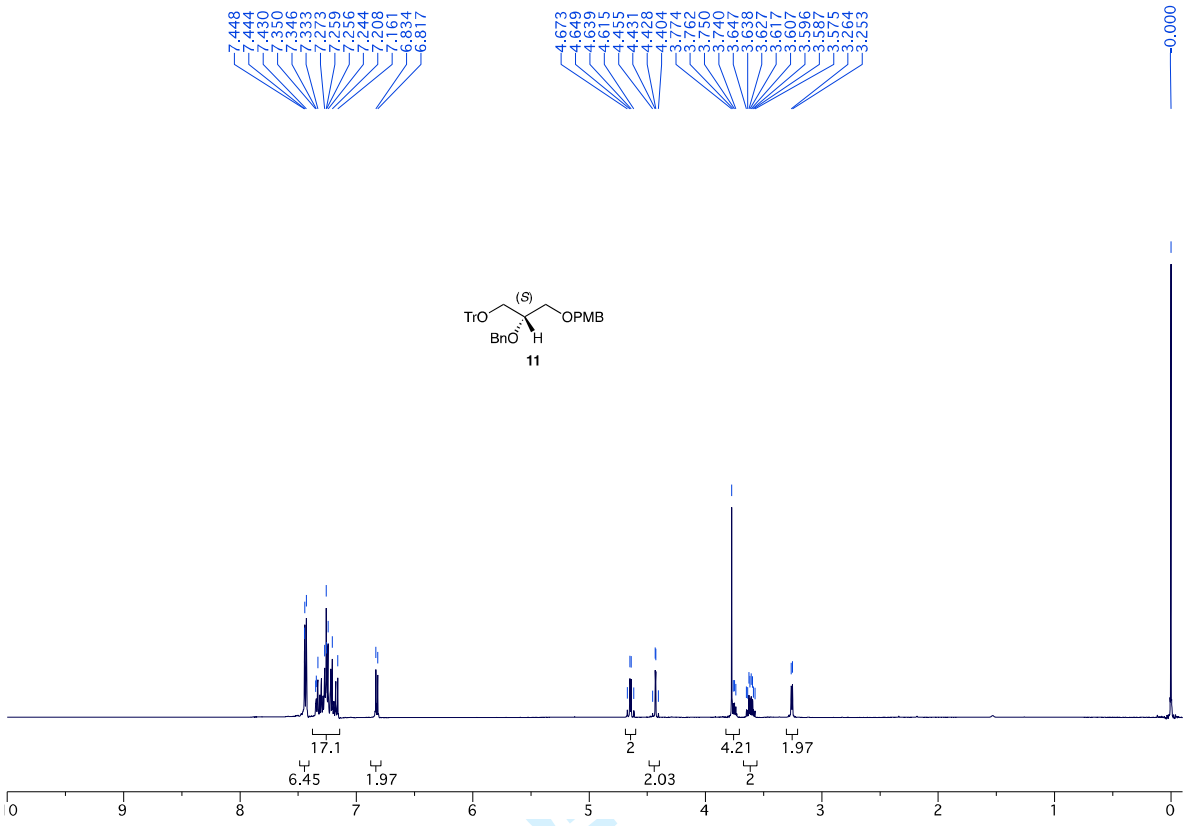
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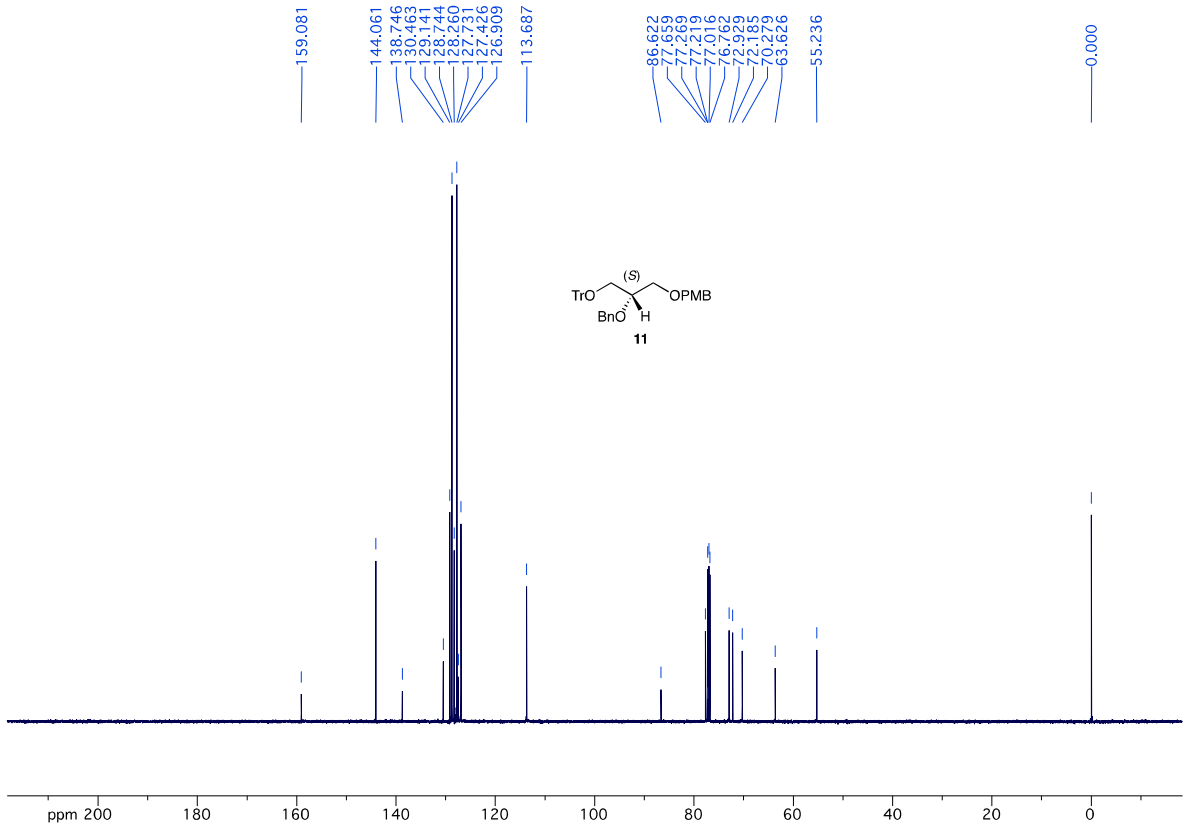
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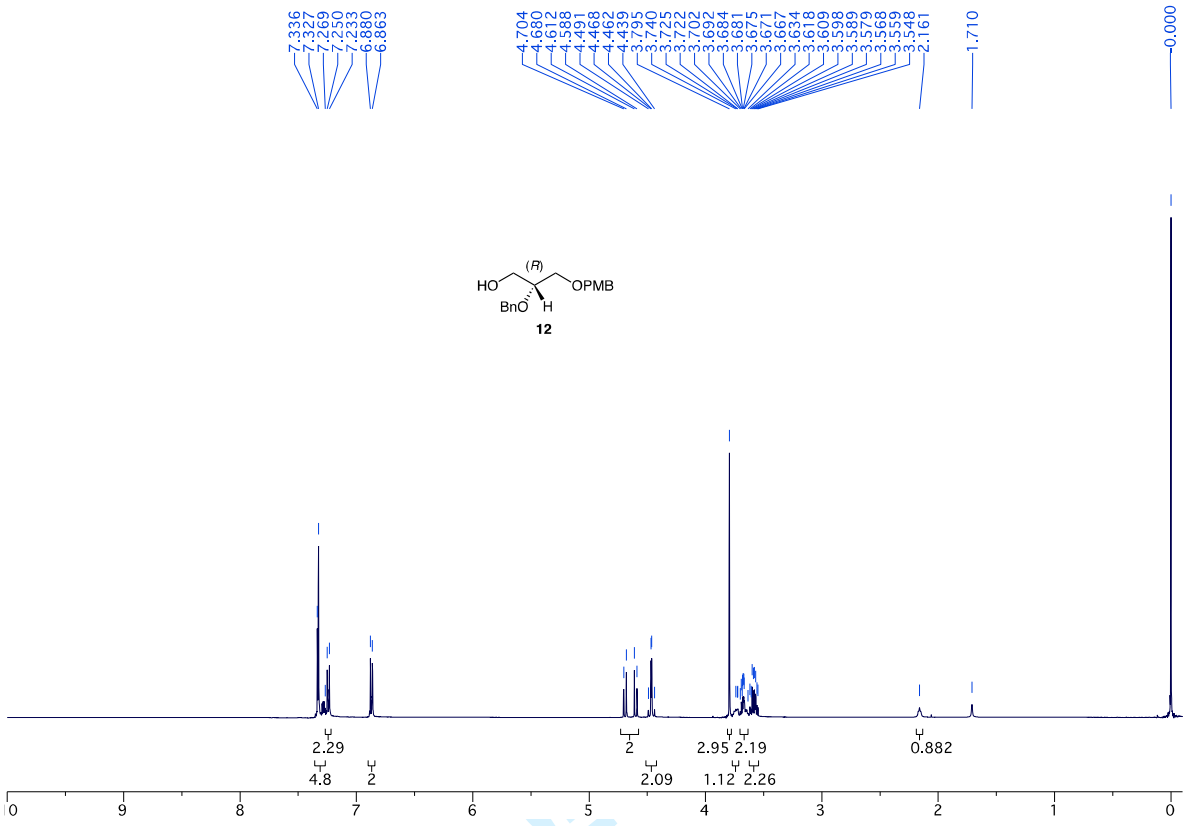
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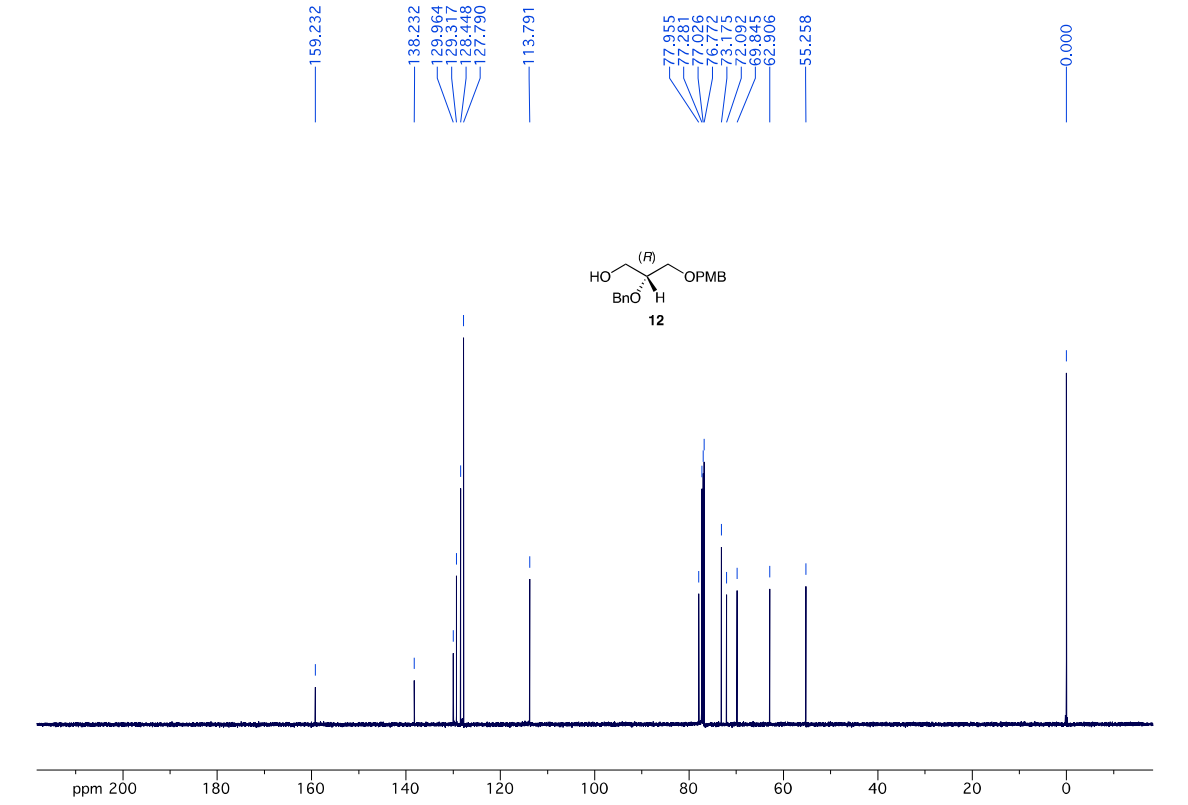
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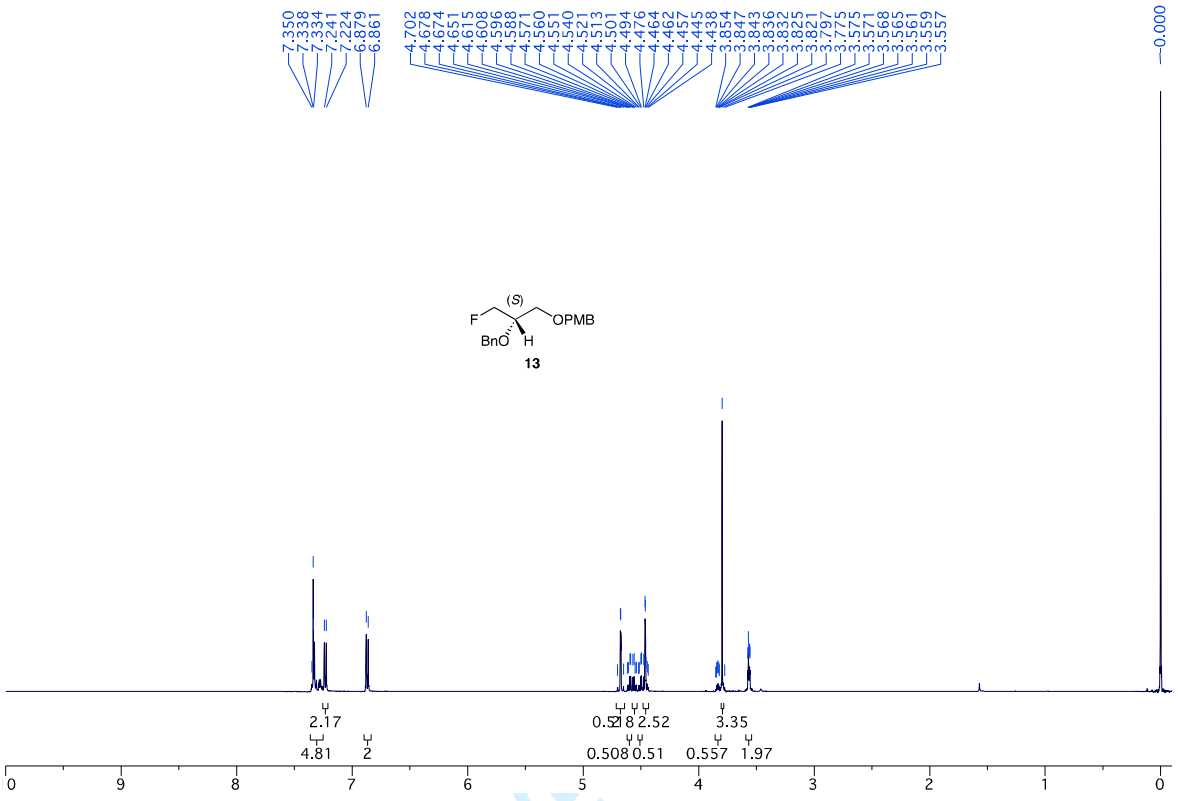
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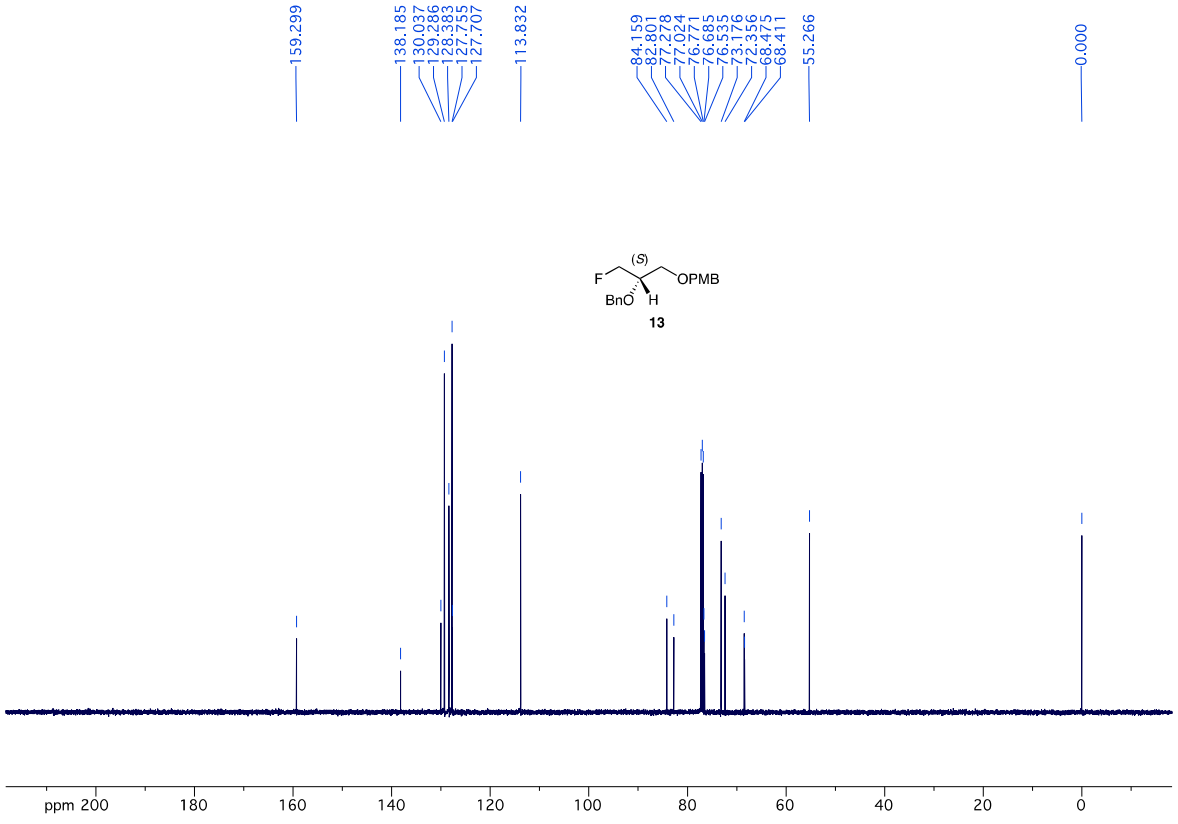
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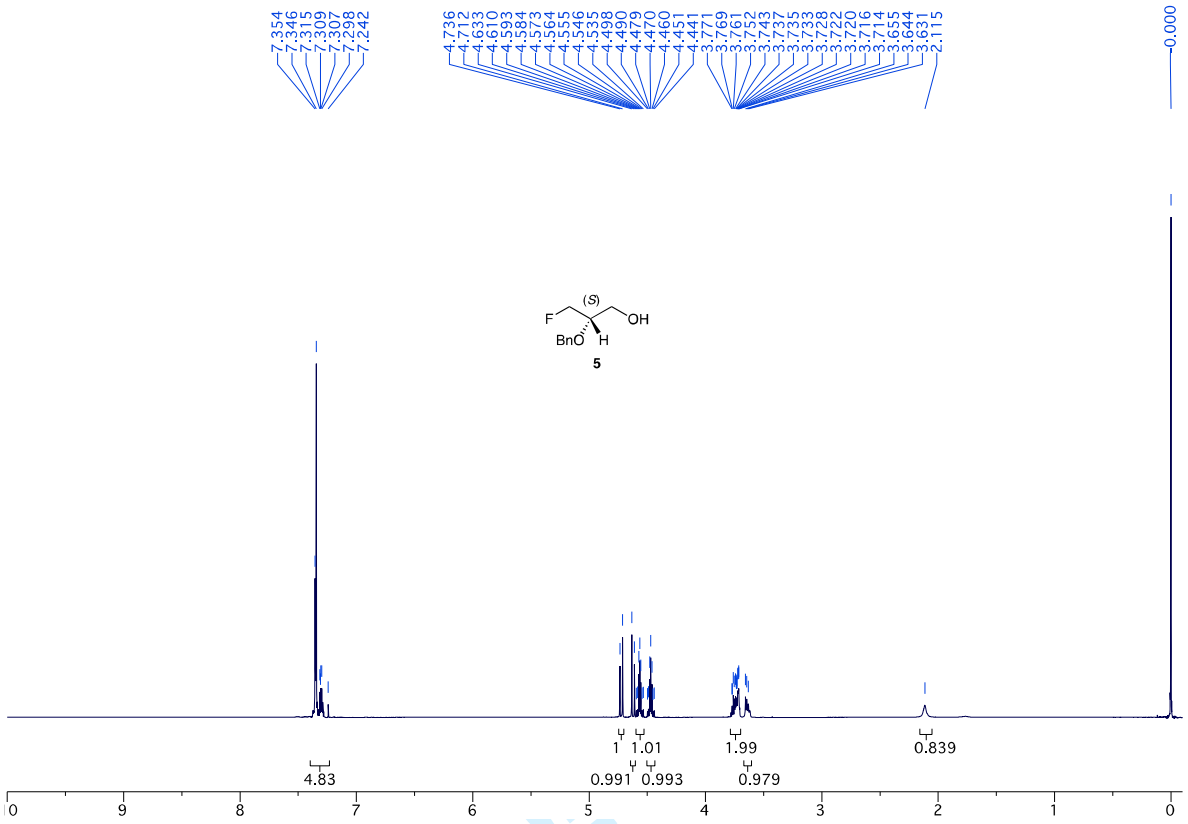
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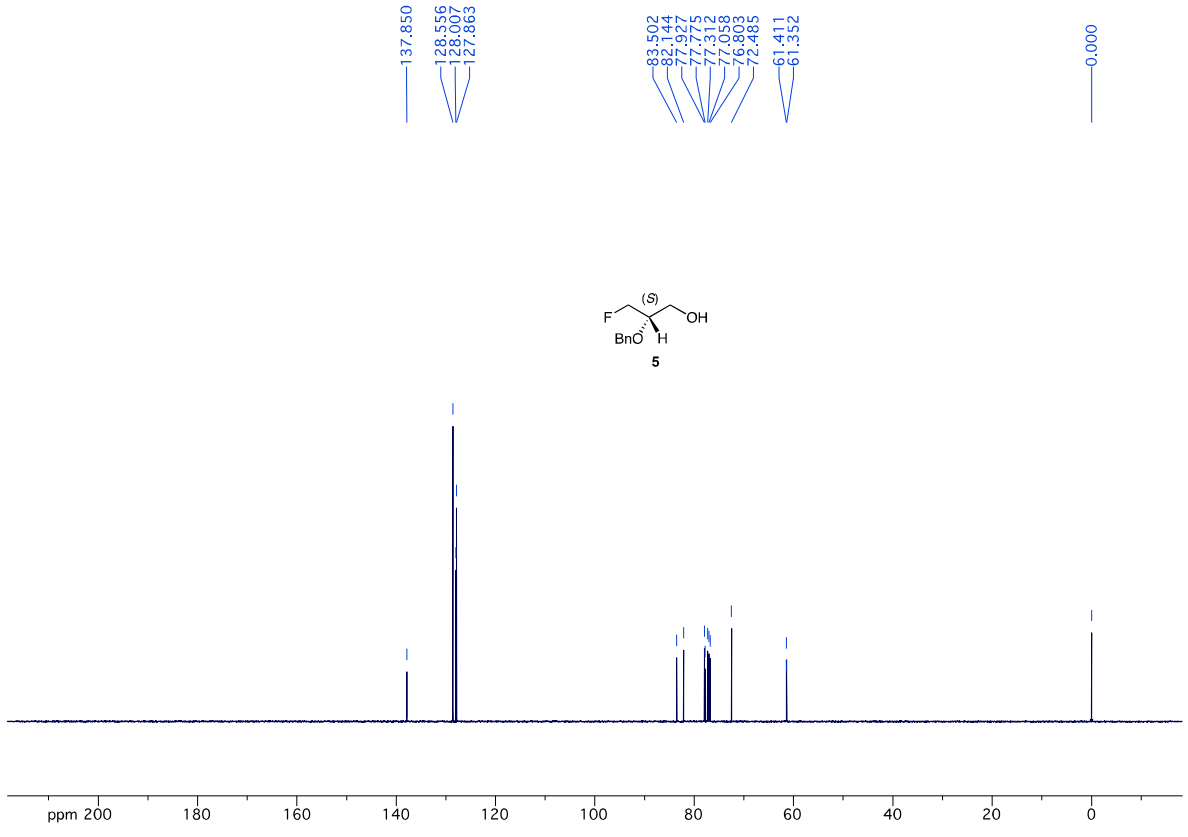
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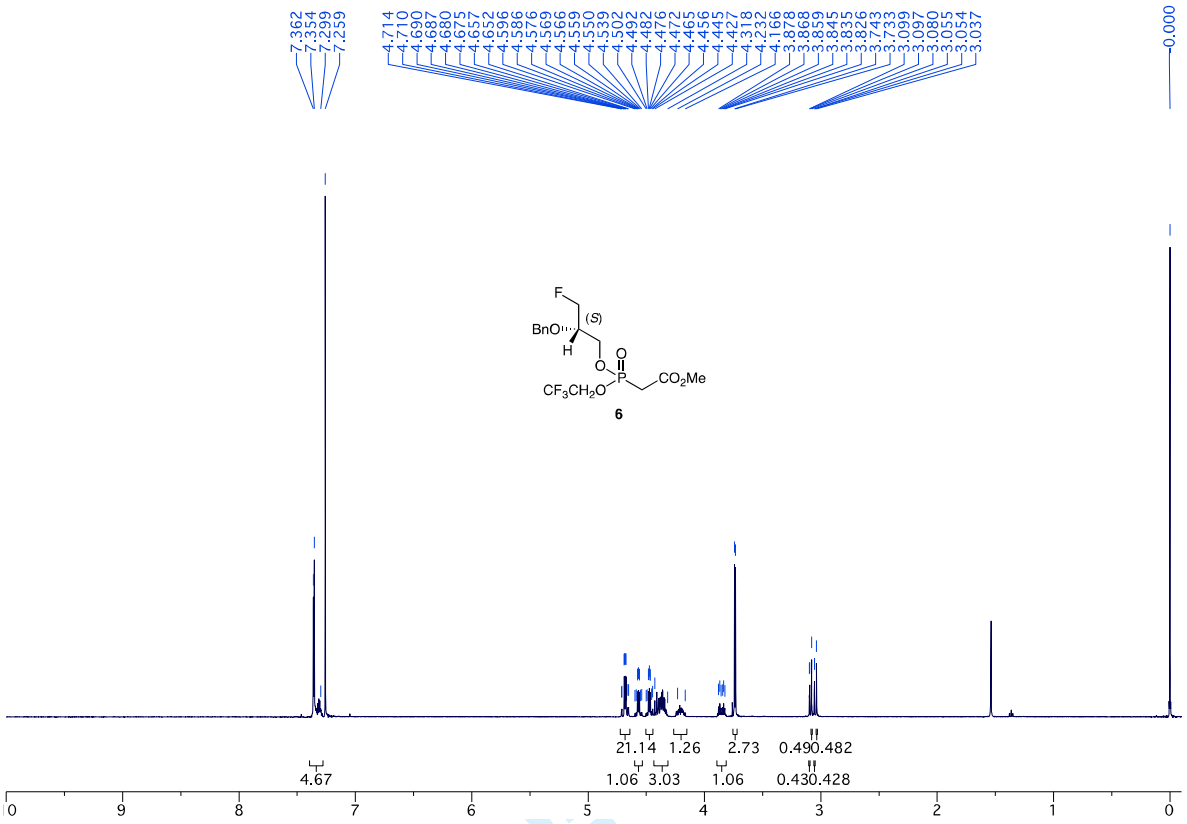
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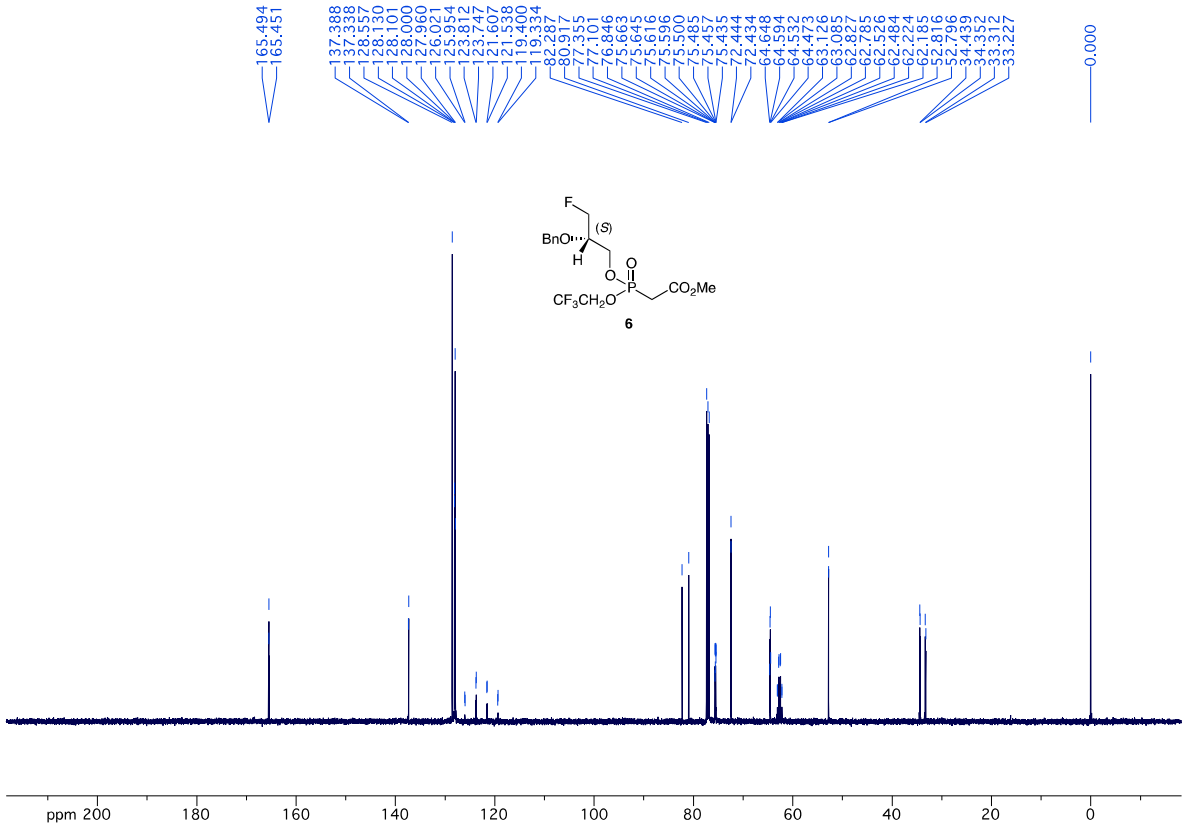
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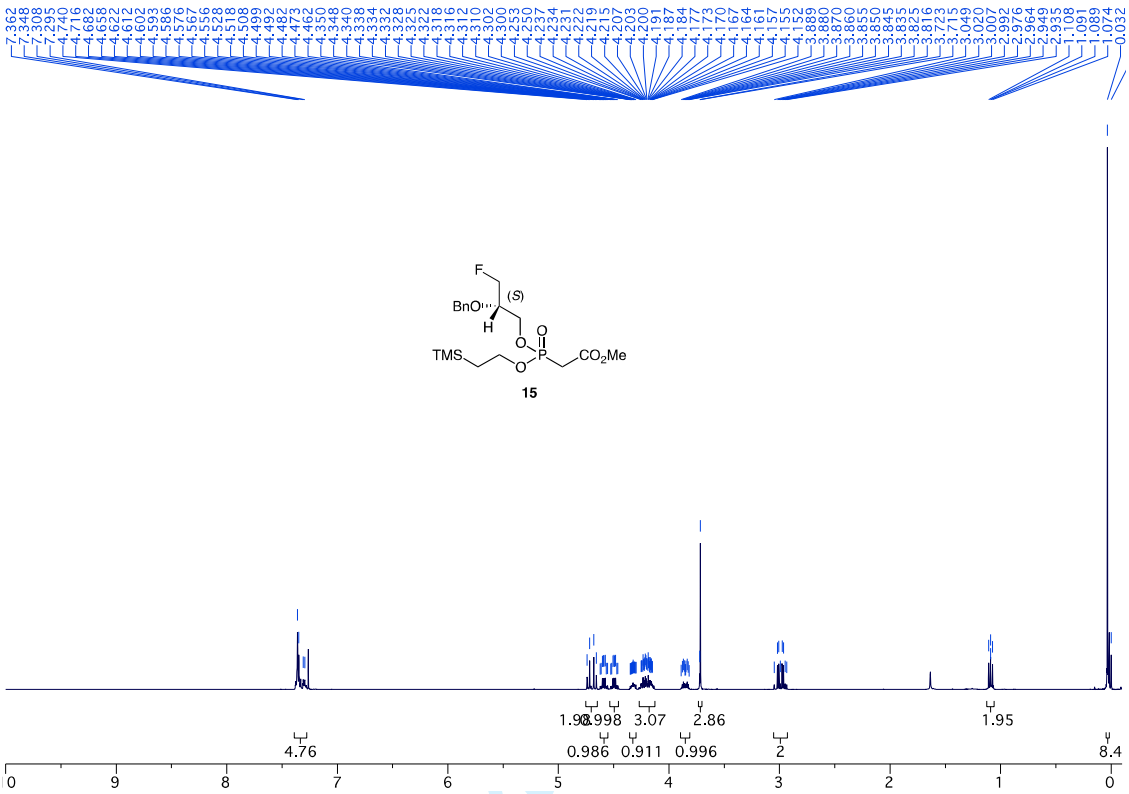
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2.949
2.935
1.108
1.091
1.089
1.074
0.032
F
(S)
BnO
H
O
O
P
O
TMS
CO2Me
15
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0.998
3.07
2.86
1.95
4.76
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0.996
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7
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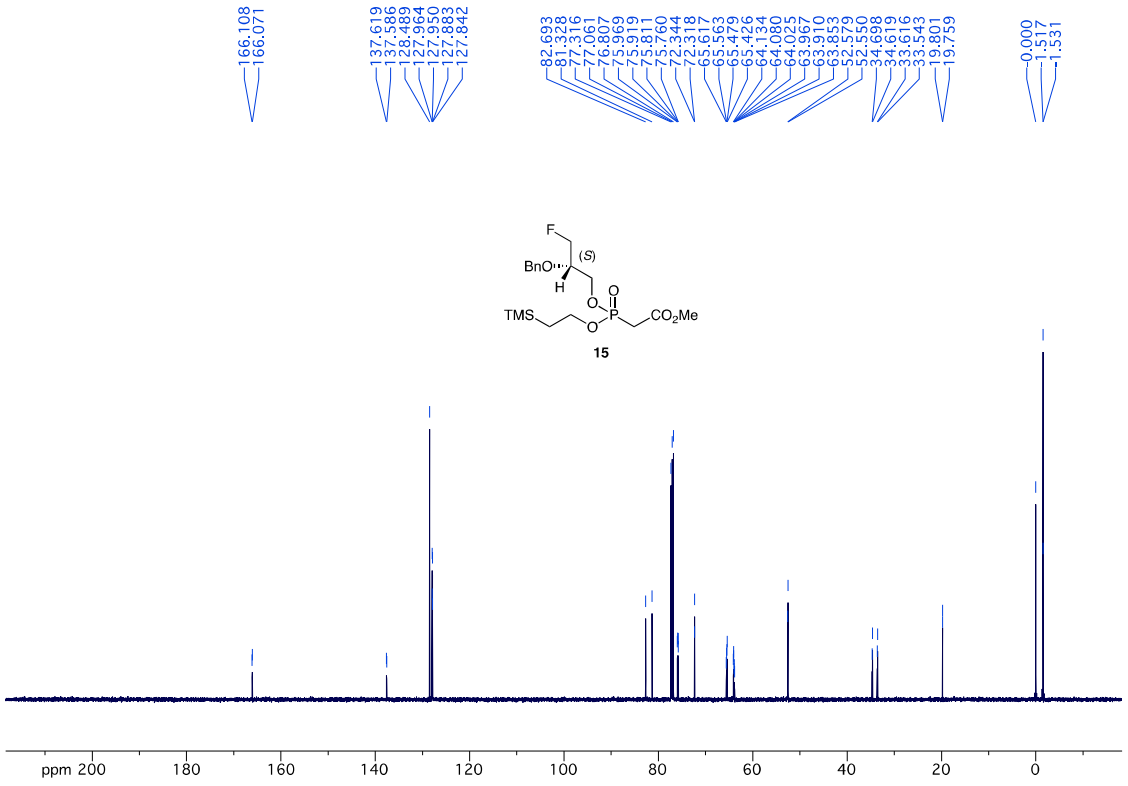
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75.969
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75.760
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72.318
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65.563
65.479
65.426
64.134
64.080
64.025
63.967
63.910
63.853
52.579
52.550
34.698
34.619
33.616
33.543
19.801
19.759
0.000
-1.517
-1.531
F
(S)
BnO
H
O
O
P
O
TMS
CO2Me
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ppm 200
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140
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20
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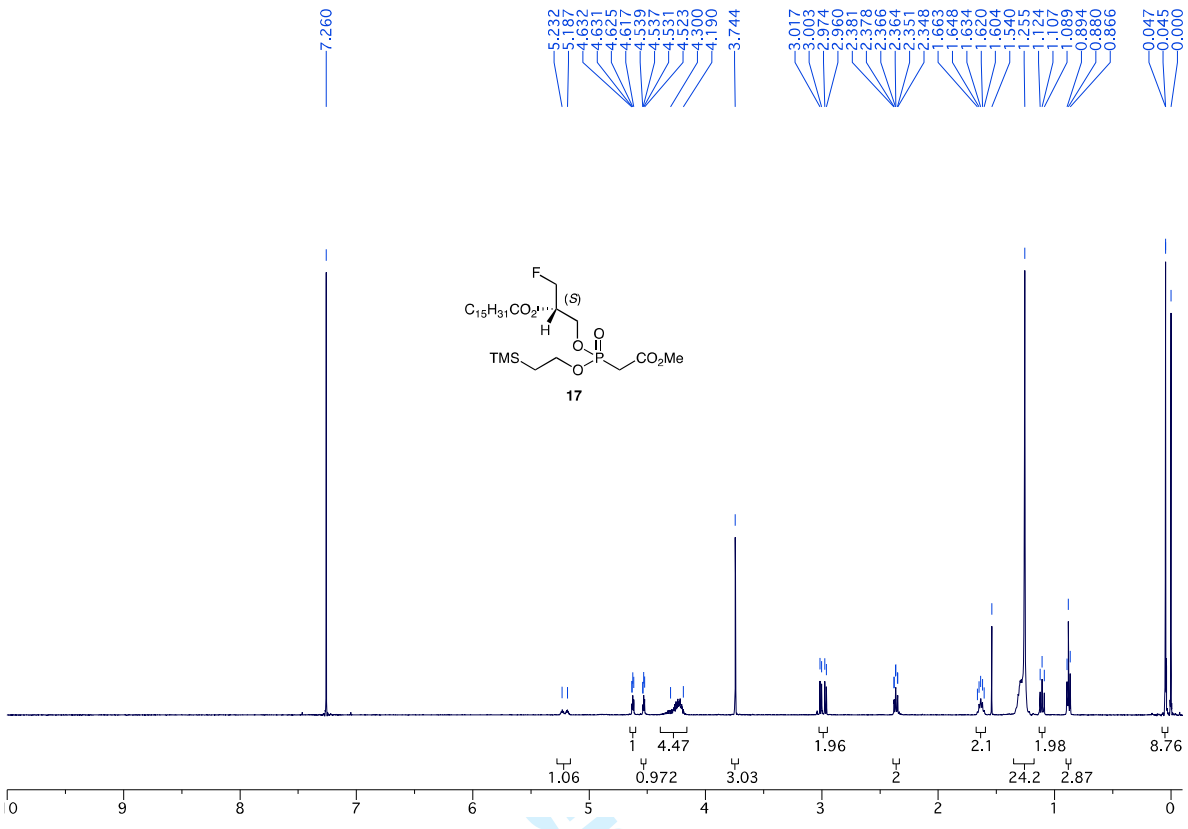
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5.187
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4.625
4.617
4.539
4.537
4.531
4.523
4.300
4.190
3.744
3.017
3.003
2.974
2.960
2.381
2.378
2.366
2.364
2.351
2.348
1.663
1.648
1.634
1.620
1.604
1.540
1.255
1.124
1.107
1.089
0.894
0.880
0.866
0.047
0.045
0.000
F
(S)
C15H31CO2
H
O
O
P
TMS
O
CO2Me
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1
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2.1
1.98
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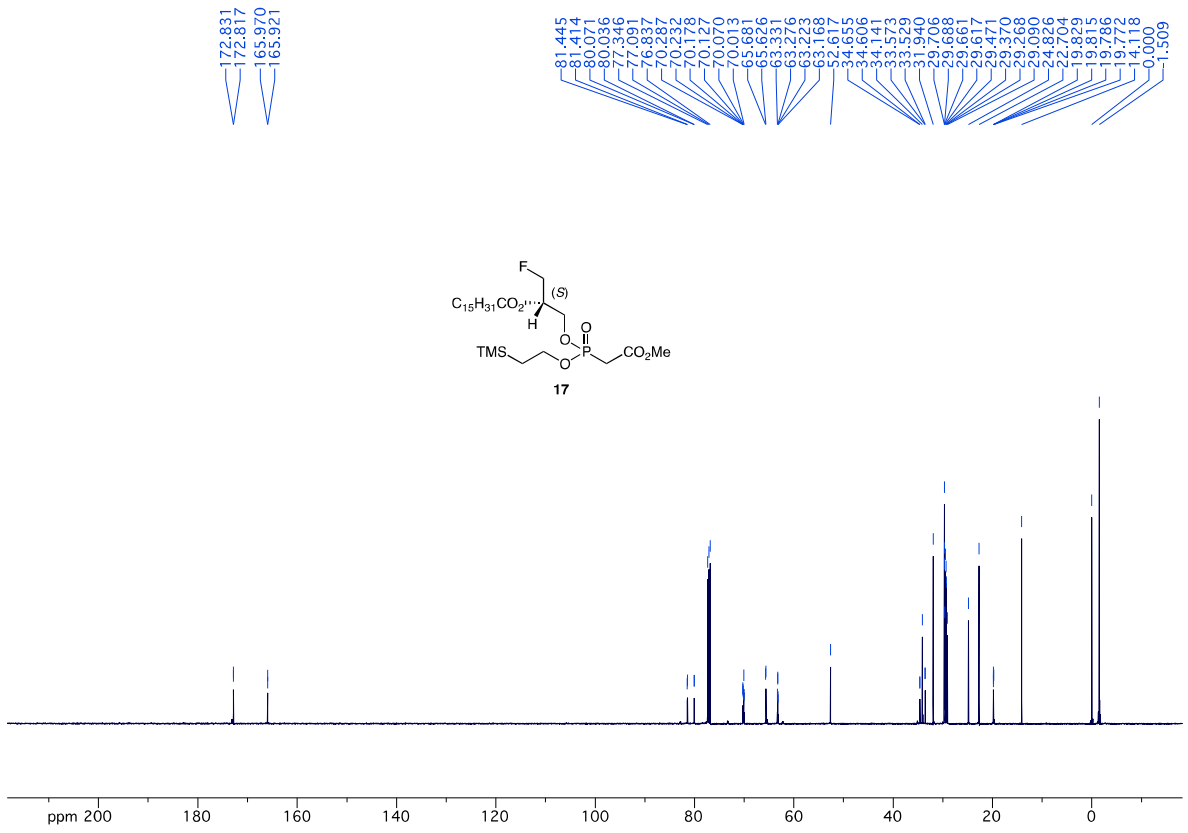
3.03
2
24.2
2.87
0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70.127
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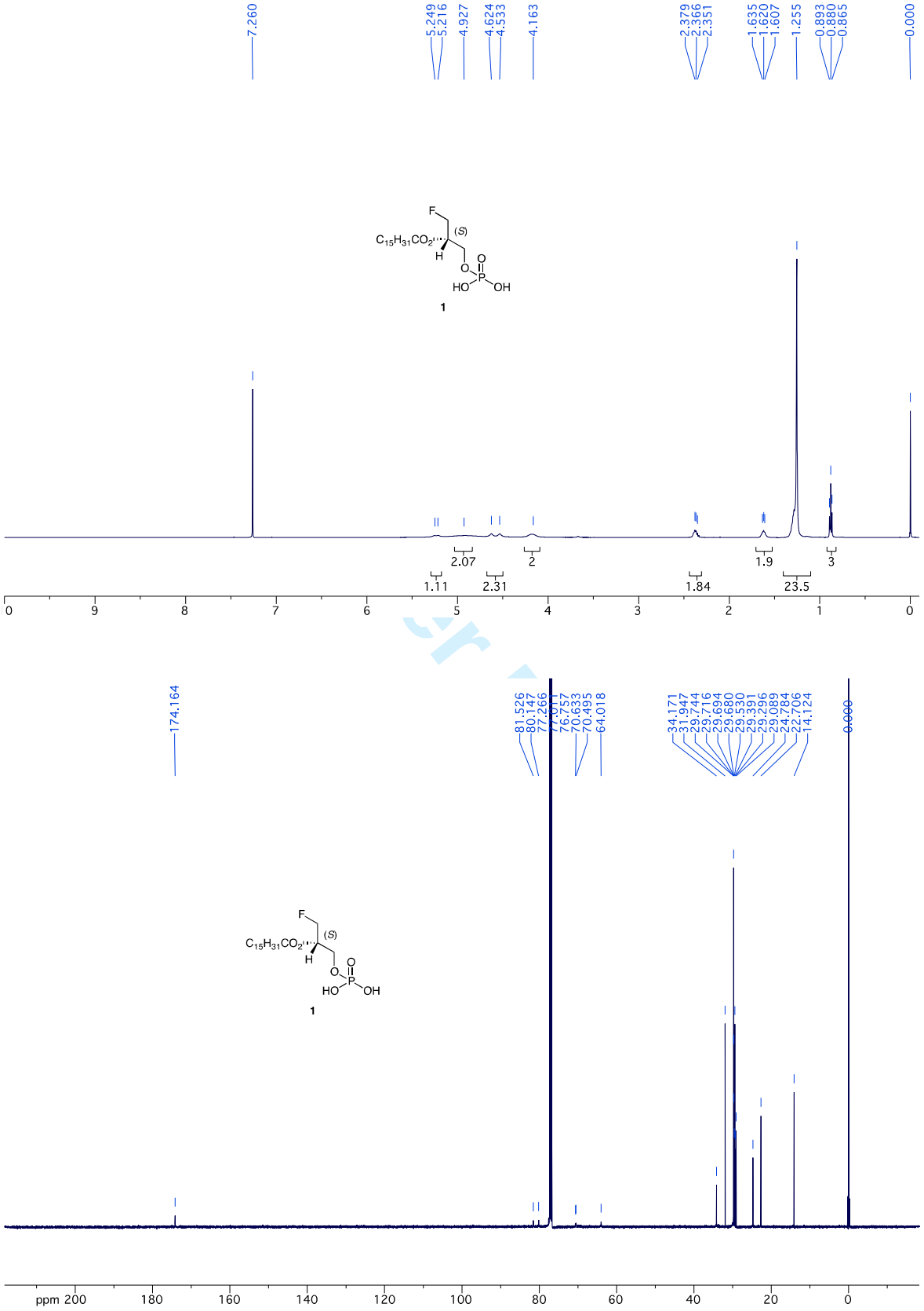
70.013
65.681
65.626
63.331
63.276
63.223
63.168
52.617
34.655
34.606
34.141
33.573
33.529
31.940
29.706
29.688
29.661
29.617
29.471
29.370
29.268
29.090
24.826
22.704
19.829
19.815
19.786
19.772
14.118
0.000
1.509
F
(S)
C15H31CO2
H
O
O
P
TMS
O
CO2Me
17
ppm 200
180
160
140
120
100
80
60
40
20
0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5.216
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4.624
4.533
4.163
2.379
2.366
2.351
1.635
1.620
1.607
1.255
0.893
0.880
0.865
0.000
F
(S)
$C_{15}H_{31}CO_2$
H
O
O
P
HO
OH
1
2.07
2
1.9
3
1.11
2.31
1.84
23.5
174.164
81.526
80.147
77.266
76.757
70.633
70.495
64.018
34.171
31.947
29.744
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29.680
29.530
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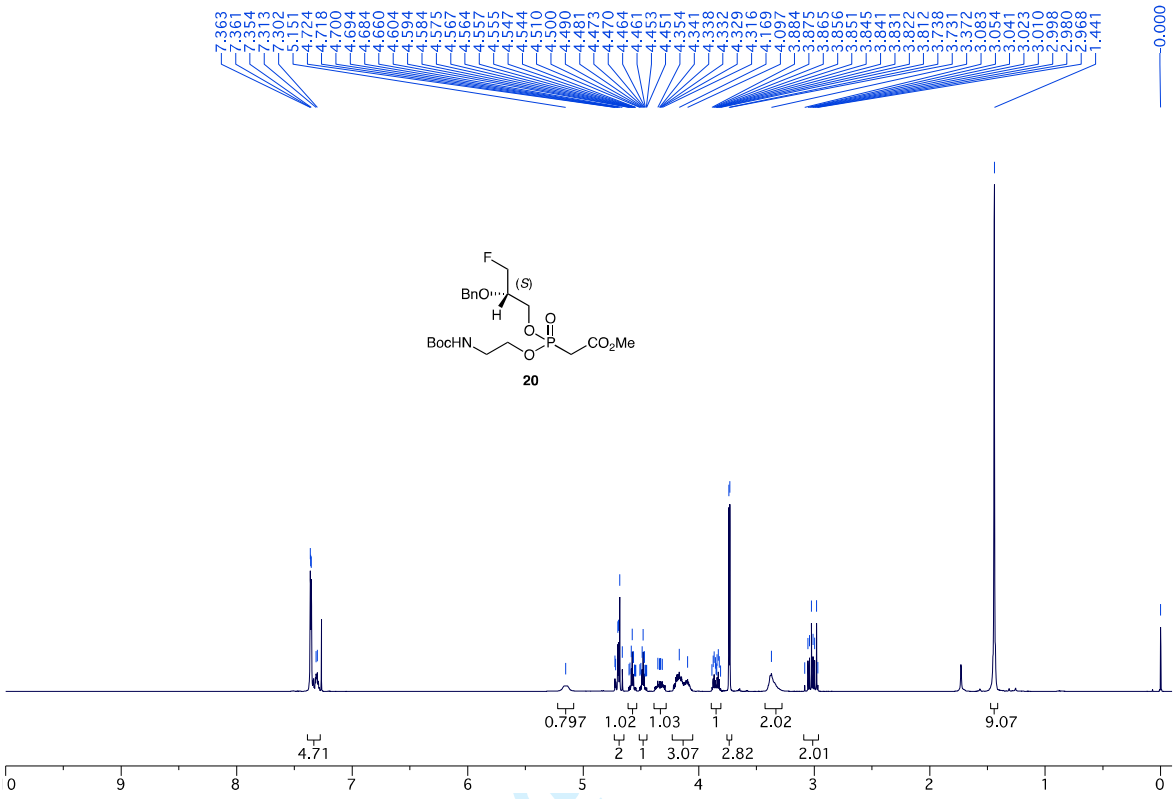
ppm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7.354
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5.151
4.724
4.718
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4.694
4.684
4.660
4.604
4.594
4.584
4.575
4.567
4.564
4.557
4.555
4.547
4.544
4.510
4.500
4.490
4.481
4.473
4.470
4.464
4.461
4.453
4.451
4.354
4.341
4.338
4.332
4.329
4.316
4.169
4.097
3.884
3.875
3.865
3.856
3.851
3.845
3.841
3.831
3.822
3.812
3.738
3.731
3.372
3.083
3.054
3.041
3.023
3.010
2.998
2.980
2.968
1.441
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F
(S)
BnO
H
O
O
P
O
BocHN
CO2Me
20
0.797
1.02
1.03
1
2.02
9.07
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3.07
2.82
2.01
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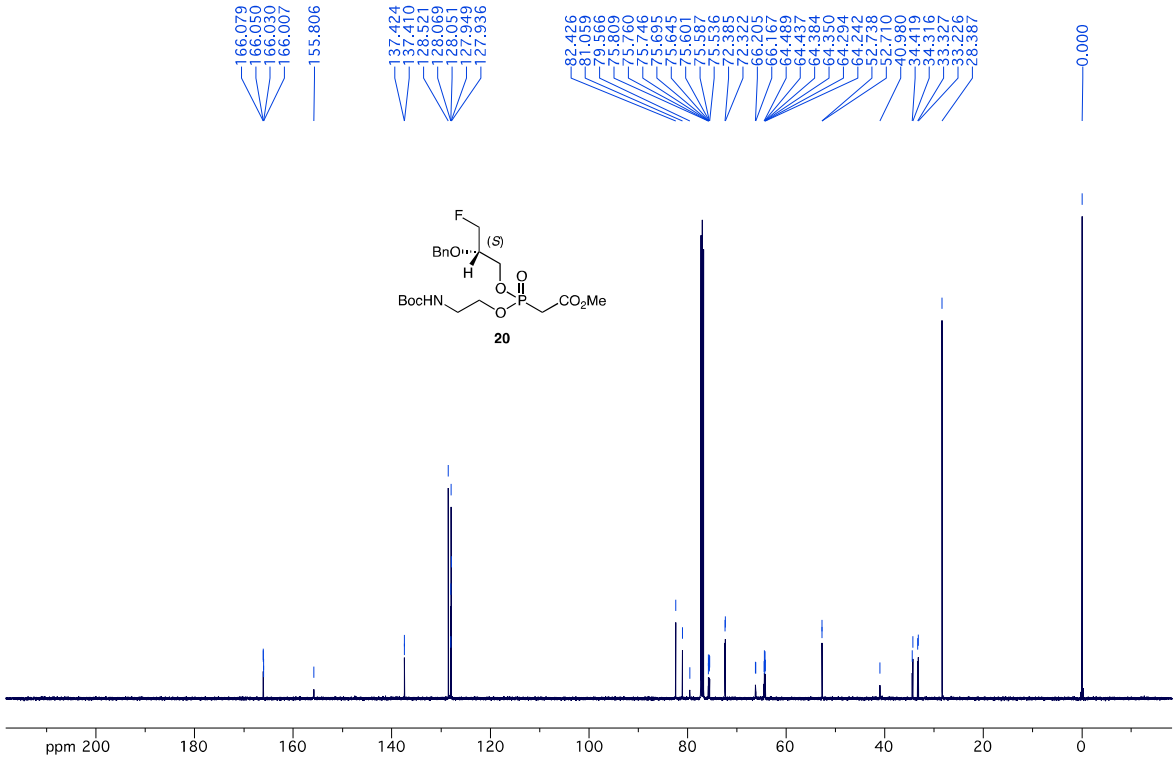
7
6
5
4
3
2
1
0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81.059
79.566
75.809
75.760
75.746
75.695
75.645
75.601
75.587
75.536
72.385
72.322
66.205
66.167
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64.384
64.350
64.294
64.242
52.738
52.710
40.980
34.419
34.316
33.327
33.226
28.387
0.000
F
(S)
BnO
H
O
O
P
O
BocHN
CO2Me
20
ppm 200
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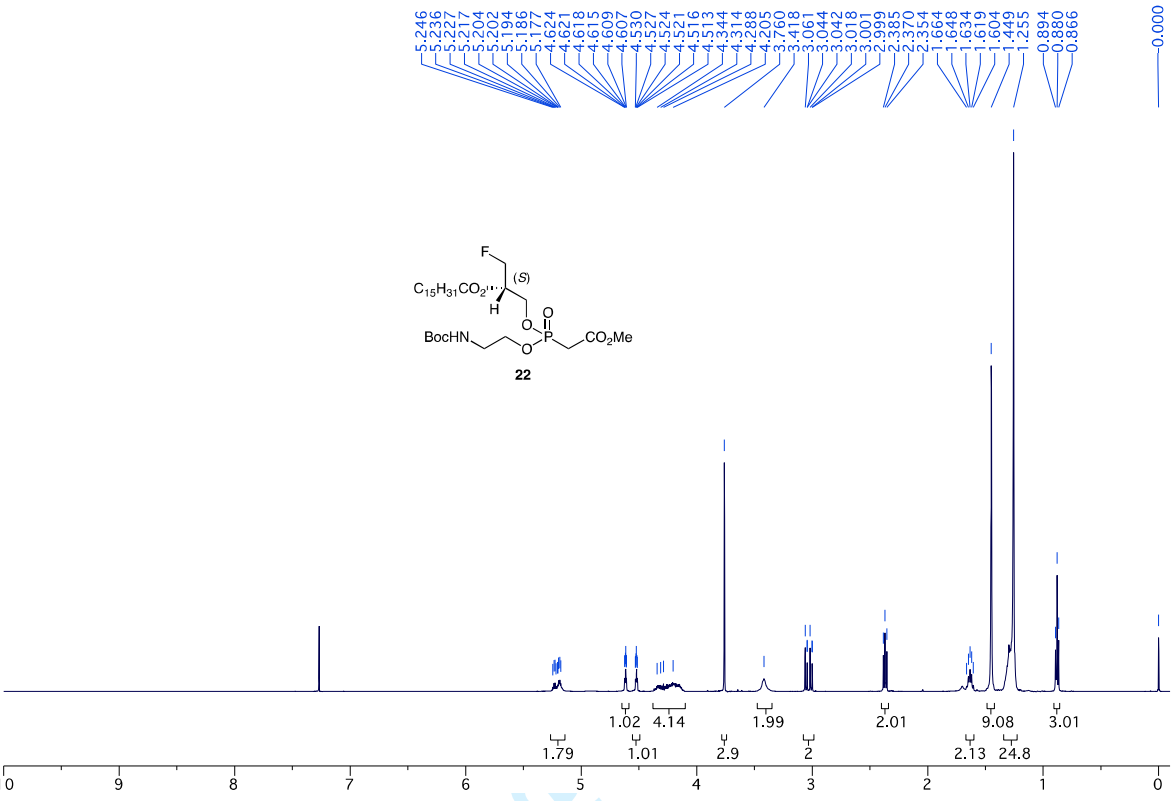
160
140
120
100
80
60
40
20
0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5.204
5.202
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5.186
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4.624
4.621
4.618
4.615
4.609
4.607
4.530
4.527
4.524
4.521
4.516
4.513
4.344
4.314
4.288
4.205
4.200
3.418
3.061
3.044
3.042
3.018
3.001
2.999
2.385
2.370
2.354
1.664
1.648
1.634
1.619
1.604
1.449
1.255
0.894
0.880
0.866
0.000
F
(S)
$C_{15}H_{31}CO_2$
H
O
O
P
BocHN
CO_2Me
22
1.02
4.14
1.99
2.01
9.08
3.01
1.79
1.01
2.9
2
2.13
24.8
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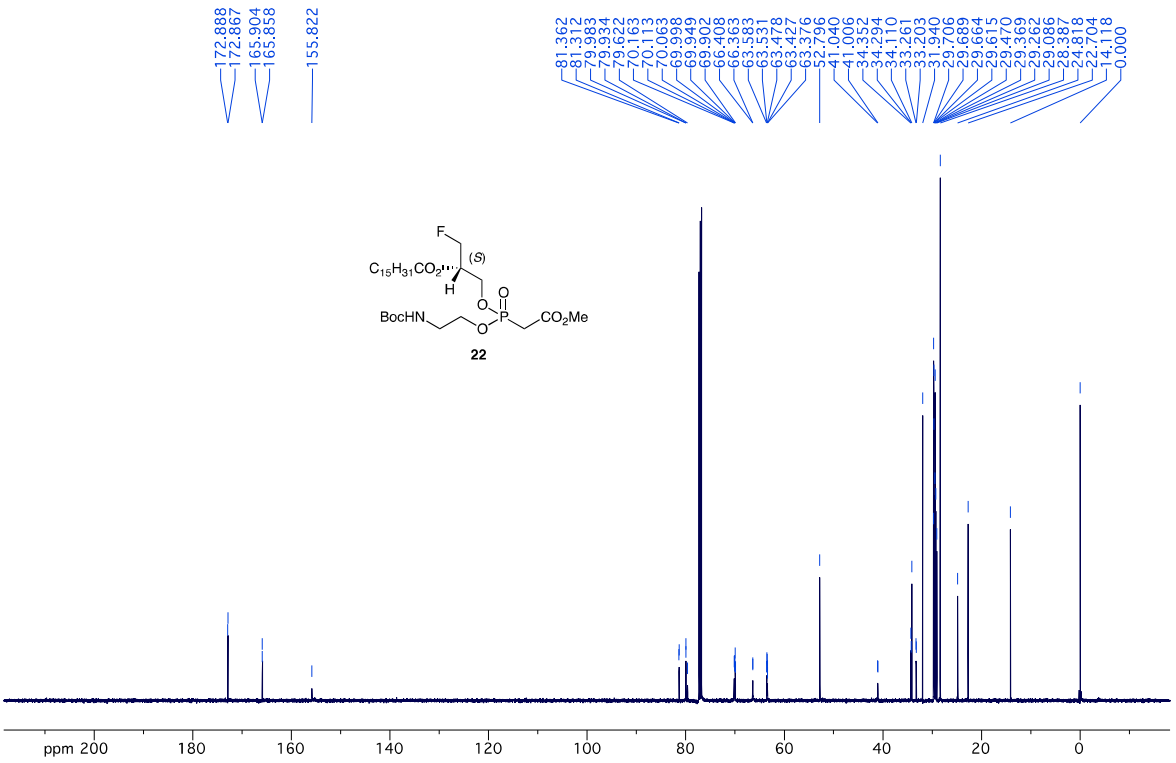
9
8
7
6
5
4
3
2
1
0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70.113
70.063
69.998
69.949
69.902
66.408
66.363
63.583
63.531
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63.427
63.376
52.796
41.040
41.006
34.352
34.294
34.110
33.261
33.203
31.940
29.706
29.689
29.664
29.615
29.470
29.369
29.262
29.086
28.387
24.818
22.704
14.118
0.000
F
(S)
$C_{15}H_{31}CO_2$
H
O
O
P
BocHN
CO_2Me
22
ppm 200
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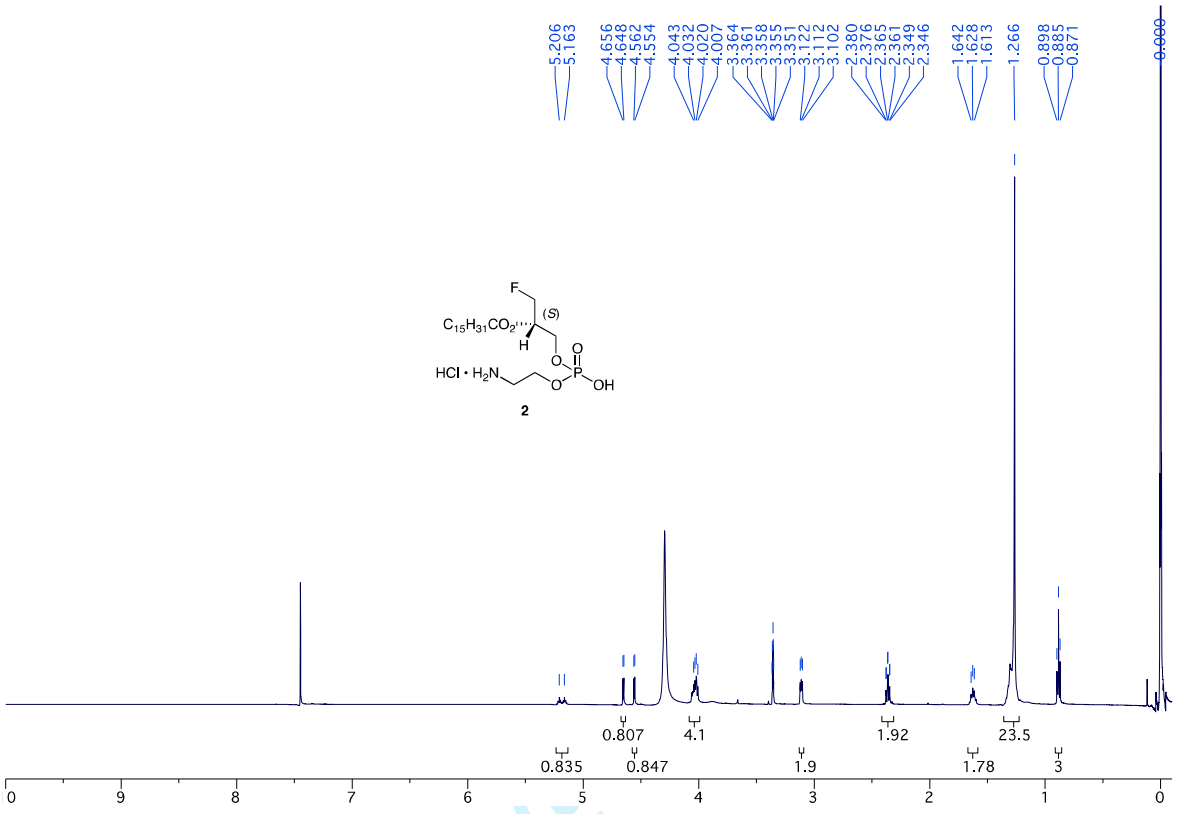
160
140
120
100
80
60
40
20
0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4.007
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3.361
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3.355
3.351
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3.112
3.102
2.380
2.376
2.365
2.361
2.349
2.346
1.642
1.628
1.613
1.266
0.898
0.885
0.871
0.000
F
(S)
H
O
O
P
OH
HCl • H2N
2
0.807
4.1
1.92
23.5
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3
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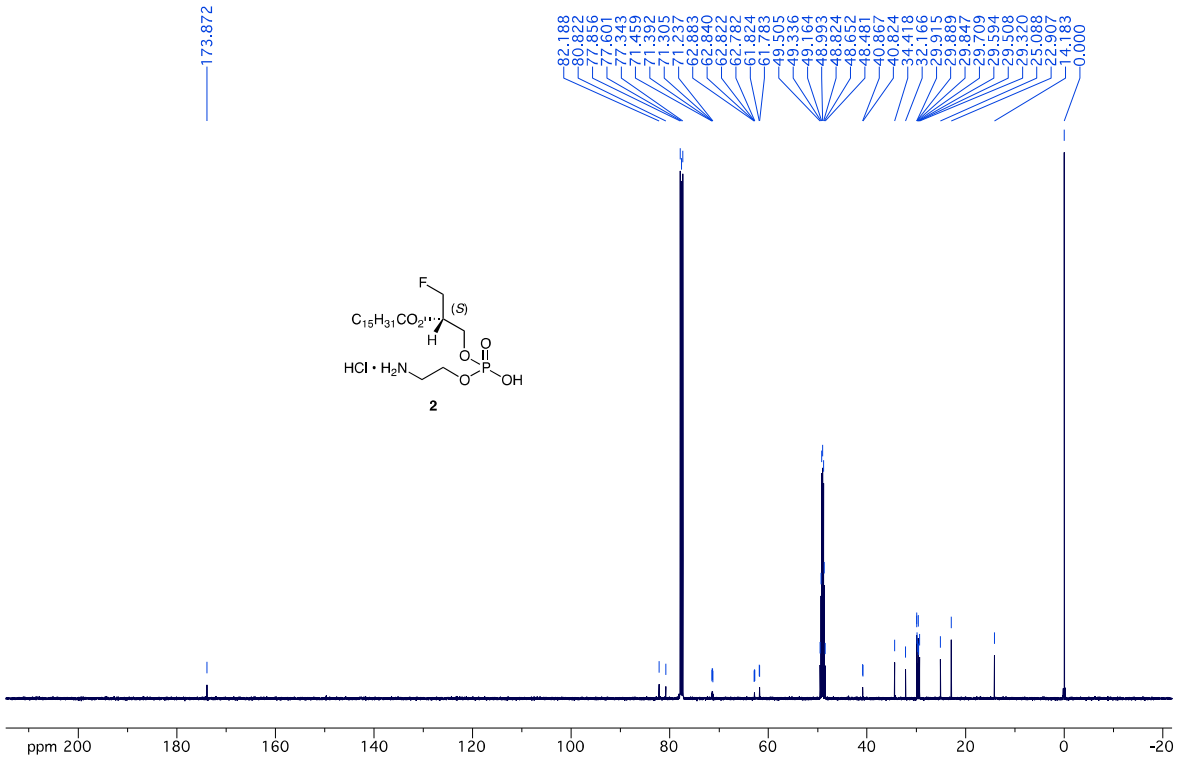
7
6
5
4
3
2
1
0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62.822
62.782
61.824
61.783
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48.481
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40.824
34.418
32.166
29.915
29.889
29.847
29.709
29.594
29.508
29.320
25.088
22.907
14.183
0.000
F
(S)
H
O
O
P
OH
HCl • H2N
2
ppm 200
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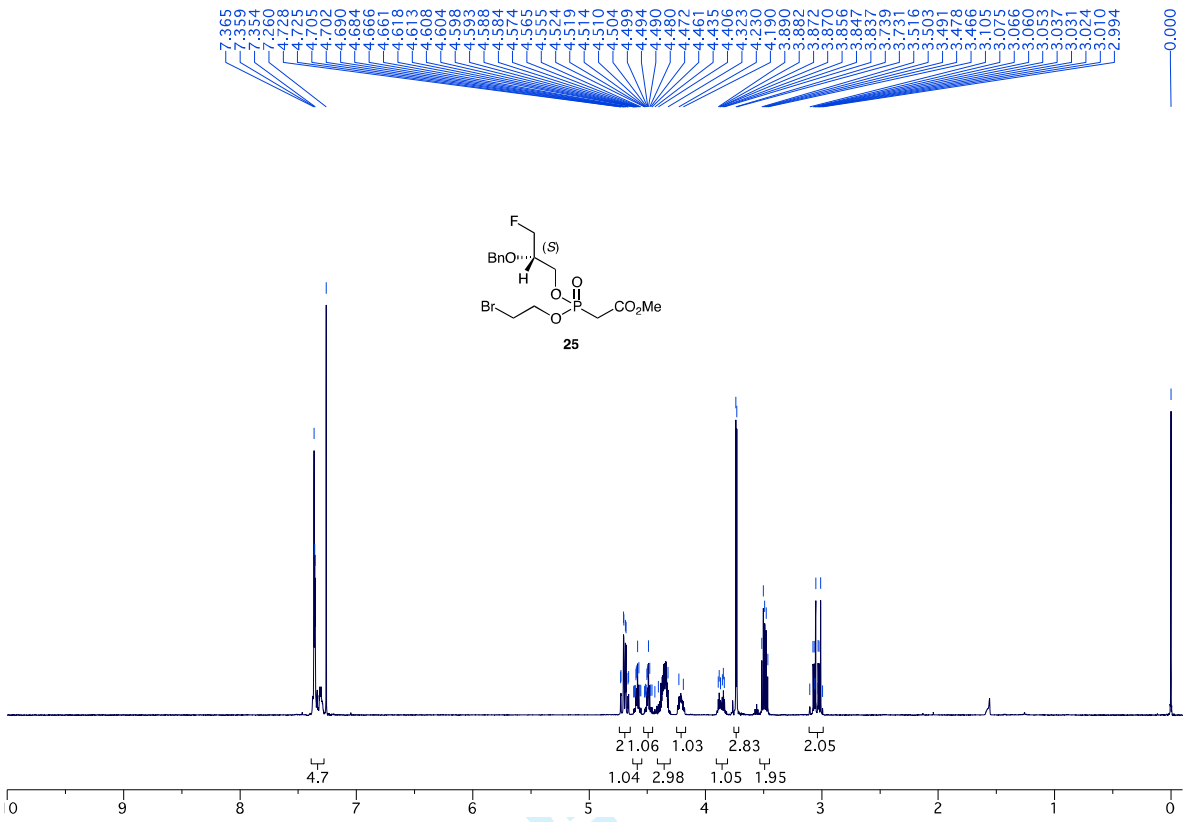
160
140
120
100
80
60
40
20
0
-20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4.618
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4.604
4.598
4.593
4.588
4.584
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4.565
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4.524
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4.514
4.510
4.504
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4.230
4.190
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3.731
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3.075
3.066
3.060
3.053
3.037
3.031
3.024
3.010
2.994
0.000
F
BnO
(S)
H
O
O
P
Br
O
CO2Me
25
4.7
2
1.06
1.03
2.83
2.05
1.04
2.98
1.05
1.95
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7
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4
3
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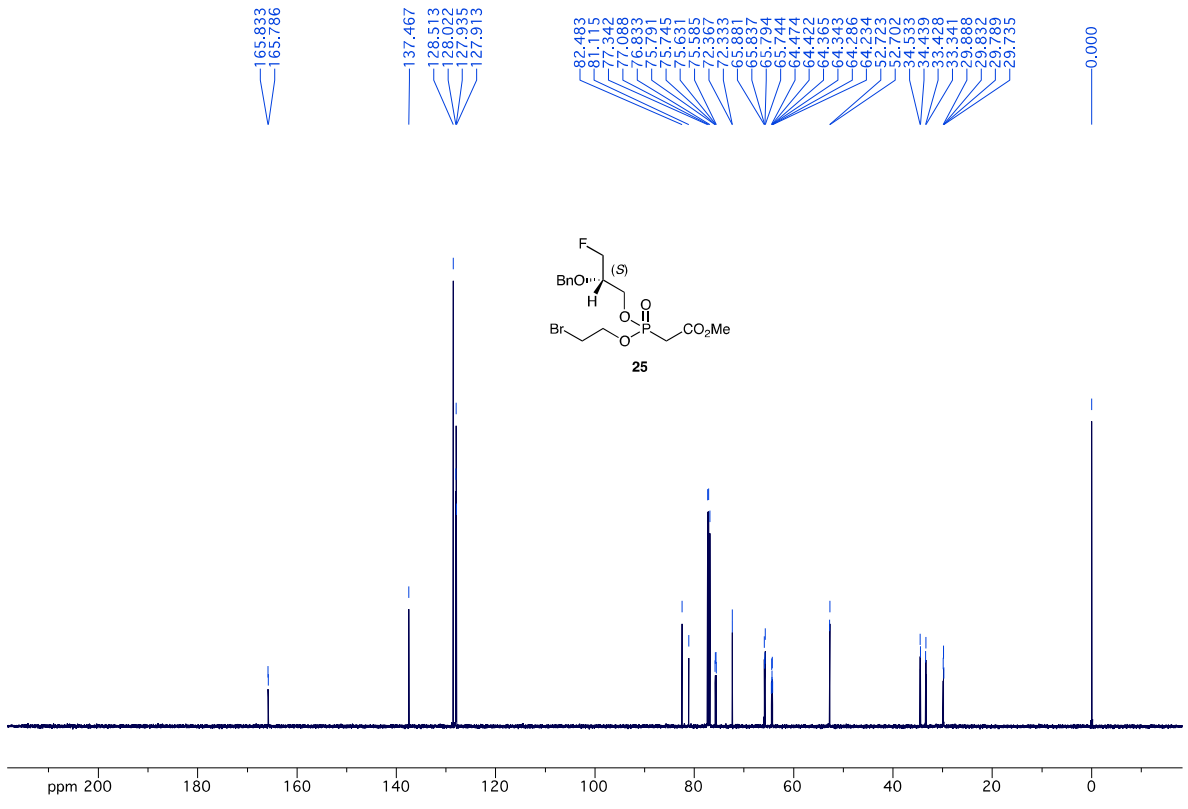
1
0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75.791
75.745
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75.585
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72.333
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65.794
65.744
64.474
64.422
64.365
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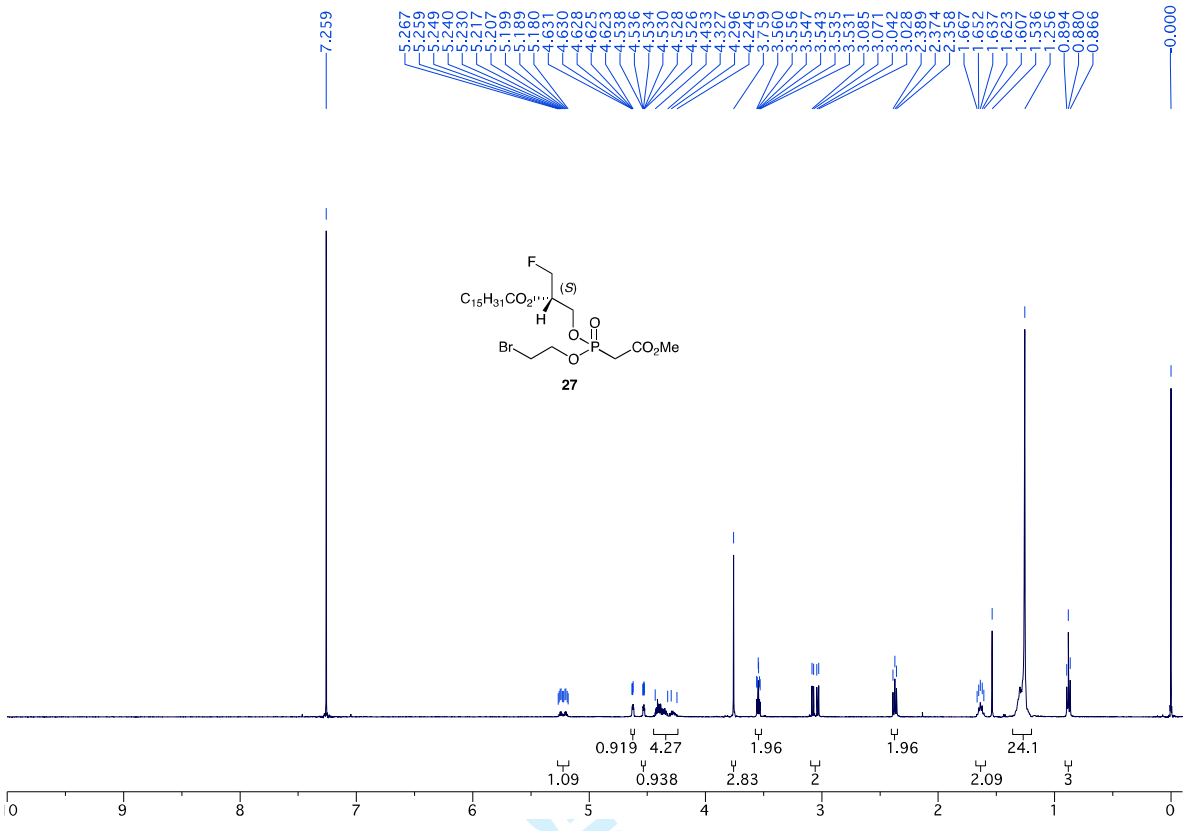
64.234
52.723
52.702
34.533
34.439
33.428
33.341
29.888
29.832
29.789
29.735
0.000
F
BnO
(S)
H
O
O
P
Br
O
CO2Me
25
ppm 200
180
160
140
120
100
80
60
40
20
0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5.259
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5.207
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5.189
5.180
4.631
4.630
4.628
4.625
4.623
4.538
4.536
4.534
4.530
4.528
4.526
4.433
4.327
4.296
4.245
3.759
3.560
3.556
3.547
3.543
3.535
3.531
3.085
3.071
3.042
3.028
2.389
2.374
2.358
1.667
1.652
1.637
1.623
1.607
1.536
1.256
0.894
0.880
0.866
0.000
F
(S)
C15H31CO2
H
O
O
P
Br
O
CO2Me
27
0.919
4.27
1.96
1.96
24.1
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2
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7
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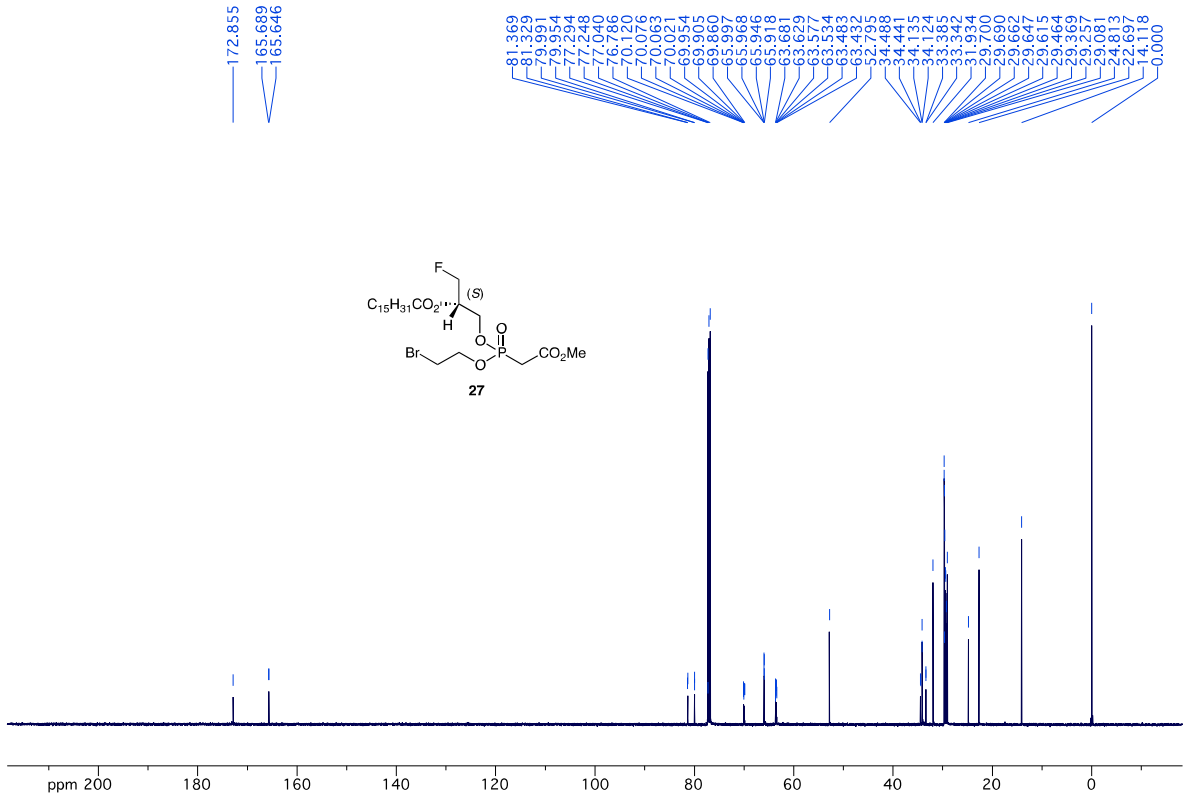
4
3
2
1
0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69.860
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29.700
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29.647
29.615
29.464
29.369
29.257
29.081
24.813
22.697
14.118
0.000
F
(S)
C15H31CO2
H
O
O
P
Br
O
CO2Me
27
ppm 200
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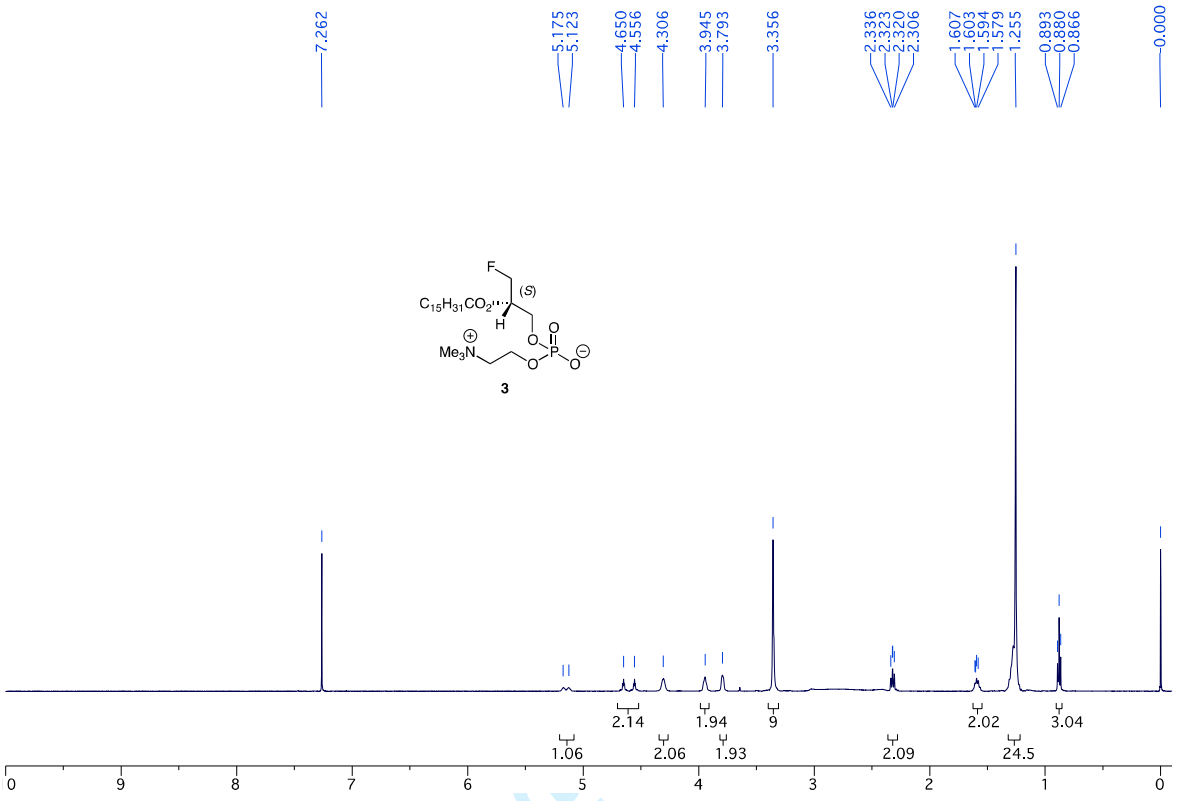
160
140
120
100
80
60
40
20
0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4.306
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3.793
3.356
2.336
2.323
2.320
2.306
1.607
1.603
1.594
1.579
1.255
0.893
0.880
0.866
0.000
F
(S)
$C_{15}H_{31}CO_2$
H
Me_3N
O
P
3
2.14
1.94
9
2.02
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7
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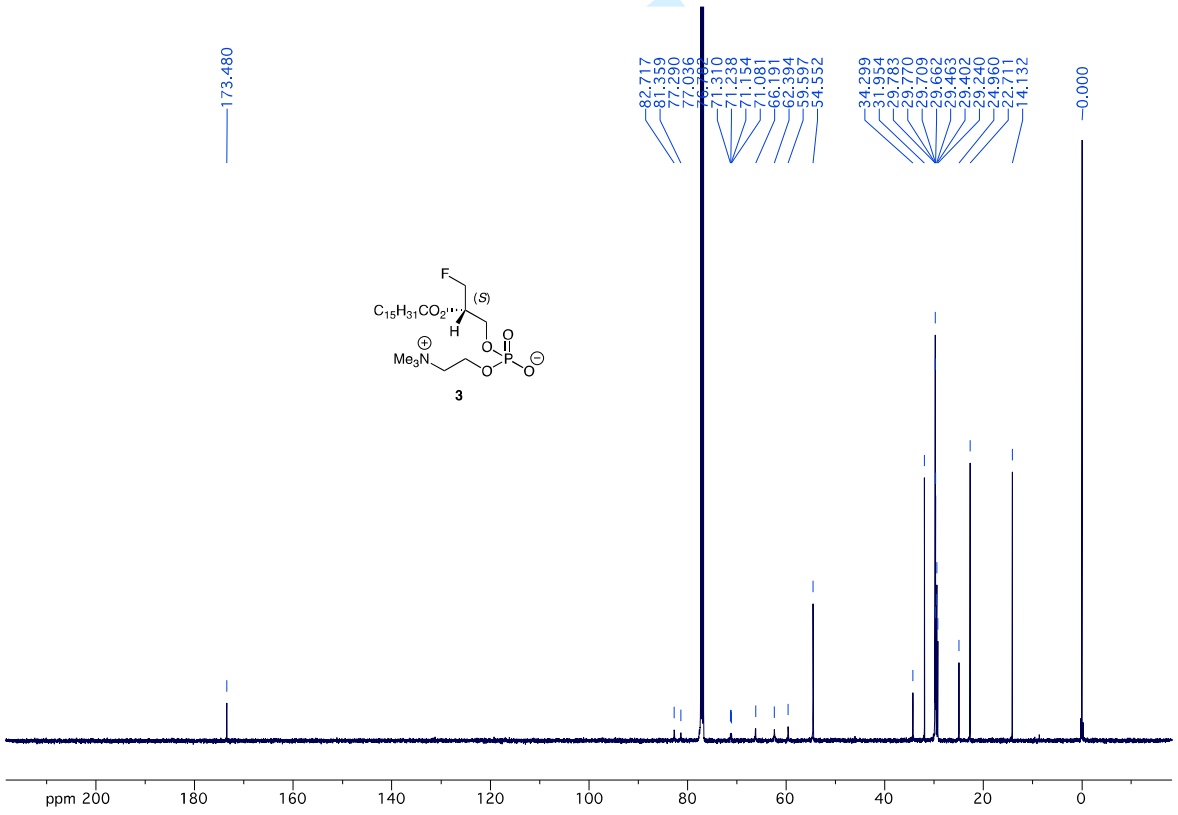
2
1
0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34.299
31.954
29.783
29.770
29.709
29.682
29.463
29.402
29.240
24.960
22.711
14.132
0.000
F
(S)
$C_{15}H_{31}CO_2$
H
Me_3N
O
P
3
ppm 200
180
160
140
120
100
80
60
40
20
0