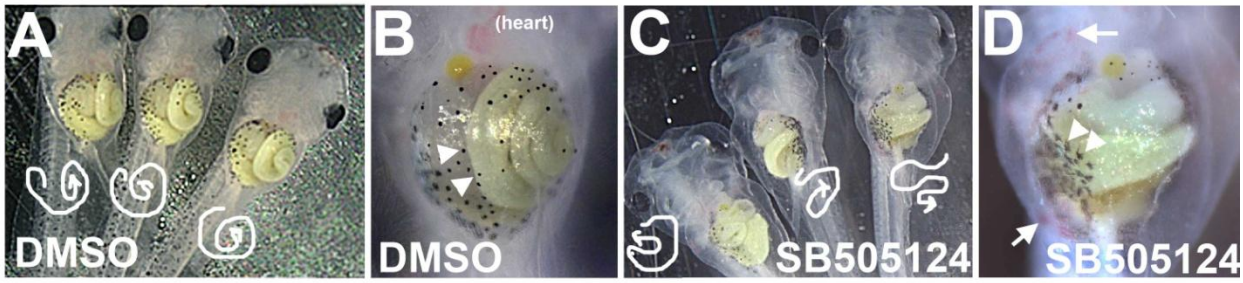
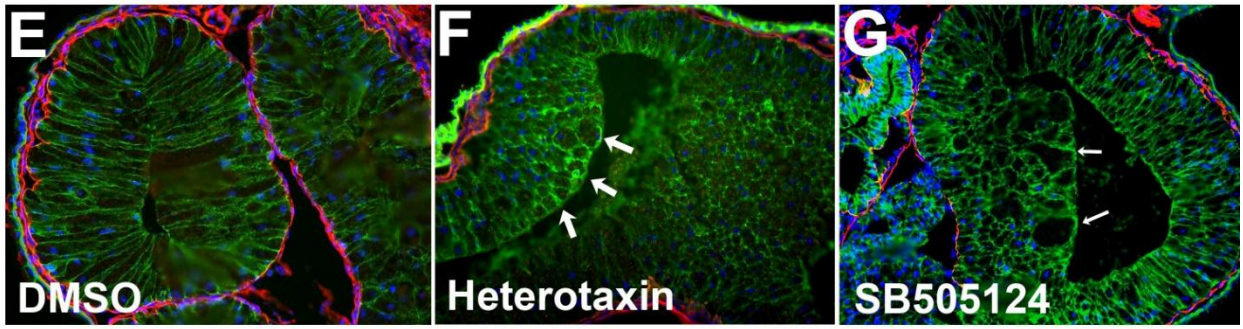
Supplemental Data:

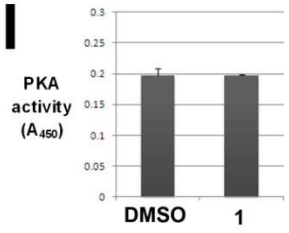
Figure S1, related to Figure 4. The phenotypic profile of the known TGF-β inhibitor, SB-505124, mimics heterotaxin's profile (see Figure 4). SB-505124 causes a left-right asymmetry phenotype (C). For example, compared to the normal CCW coiling of controls (A; see free-hand arrows), gut coiling in SB505124 embryos is severely disrupted (C, see free-hand arrows). In addition, SB-505124 also induces a melanogenesis phenotype. For example, compared to the rounded pigment cells seen in DMSO controls (A; B, arrowheads), the melanocytes in SB-505124-treated embryos (C; D, arrowheads) are more dendritic. Moreover, SB-505124 also disrupts vasculogenesis/angiogenesis, as evinced by obvious hemorrhaging throughout the ventral regions of the embryo (D, arrows), while blood can only be seen in the ventricle of the heart (indicated) in the DMSO control (B). (E-G) Finally, SB-505124 impedes cell migration. Immunohistochemical staining for E-cadherin (green), laminin (red) and nuclei (blue; DAPI) reveals a similar disruption of the cell rearrangements necessary for gut epithelial morphogenesis in frontal sections through the gut tube of embryos treated with heterotaxin (F; 100μM) and SB-505124 (G; 12.5μM), compared to DMSO controls (E). H) Time course studies reveal the sensitivity of each phenotype to SB-505124 exposure. "Left-right asymmetry" = reversal of heart looping, foregut looping, and/or intestinal rotation; Vasculogenesis/Angiogenesis" = hemorrhaging or enlarged blood vessels; "Melanogenesis" = decreased number and increased dendricity of melanocytes; "migration" = perturbed cell rearrangement, indicated by shortening of the primitive gut tube. "+" indicates that at least 75% of embryos exhibited the phenotype in two or more independent trials; "+/-" indicates that at least 50% of embryos exhibited the phenotype in two or more independent trials. ND, not determined. **Heterotaxin does not affect PKA or PKC signaling.** (I-J) Embryos were exposed to DMSO or 50μM heterotaxin (**1**) for 48 hrs. Extracts from exposed embryos were assayed in triplicate using a PKA (I) or PKC (J) assay kit (MBL International) according to manufacturer protocol. Heterotaxin does not significantly affect PKA or PKC signaling ($p>0.05$).





H

Stage of exposure	Phenotypic Profile SB-505124			
	Left-right asymmetry	Vasculogenesis/ Angiogenesis	Melanogenesis	Migration
10-46	+	ND	+	+
18-46	+	ND	+	+
26-46	+/-	+/-	+	+
32-46	-	+	+	+/-



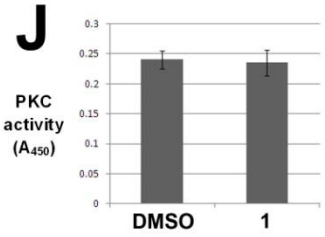


Figure S2, related to Figure 6. Heterotaxin inhibits the expression of the nodal target gene *Xantivin*. . *In situ* hybridization for the *Xenopus lefty* homologue (*Xantivin*) gene was performed on DMSO- (A, B) and heterotaxin-treated (C,D) embryos. The expression (arrows) is shown for both the left (A, C) and right (B, D) sides (stage 24). **Heterotaxin inhibits non-Smad-dependent TGF-β signaling via PI3K/Akt.** (E) Western blotting of A549 cells exposed to 10ng/ml TGF-β1 and DMSO, 100-200μM **1** or **32** for 1 hr**.** TGF-β1-induced phosphorylation of Akt, an indication of PI3K activation, is inhibited by **1**, but not **32**. β-actin is total protein control.

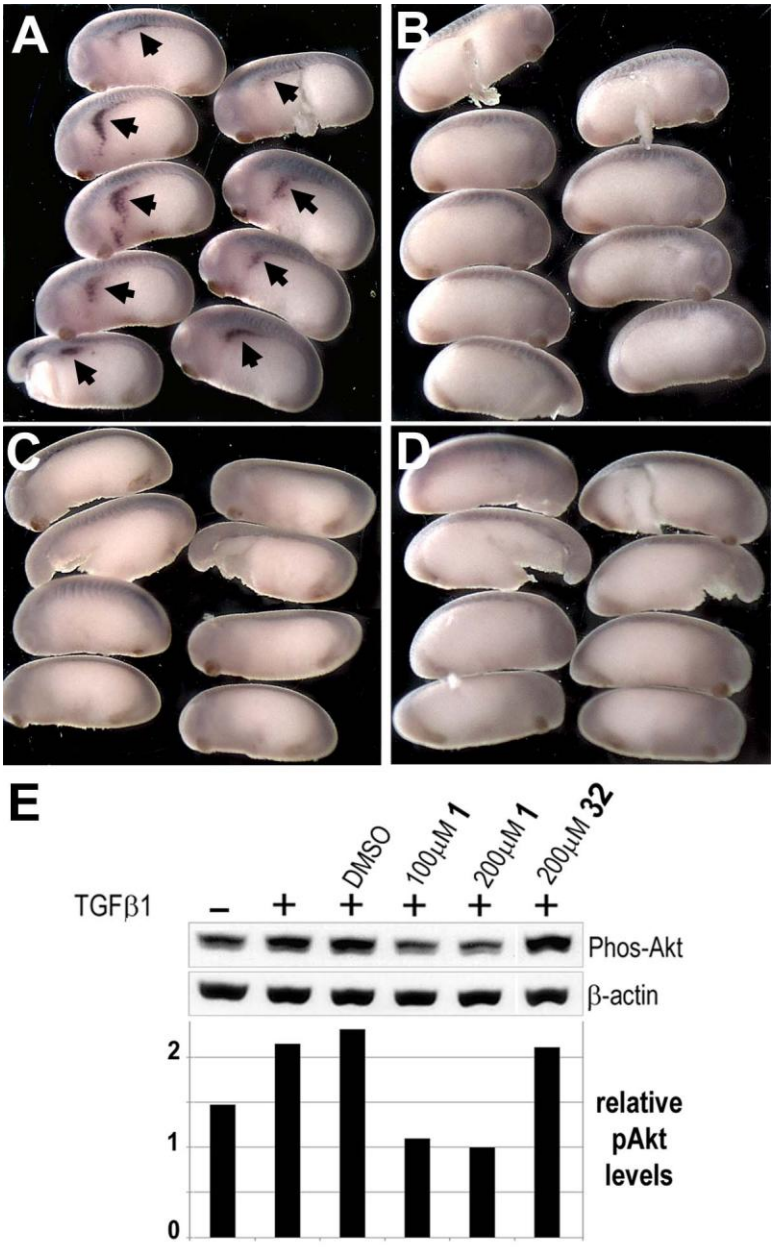
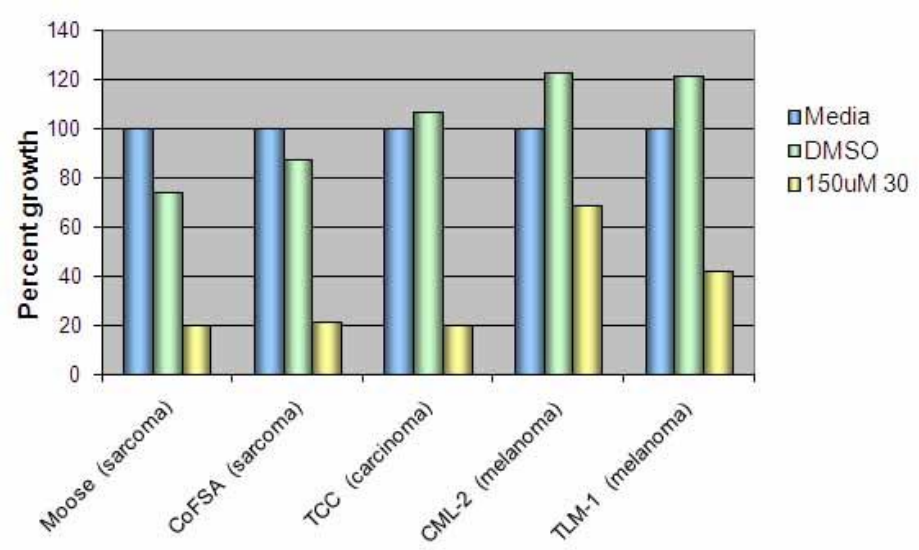
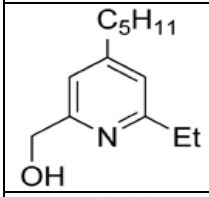
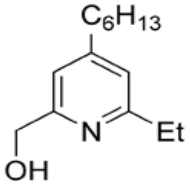
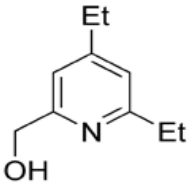
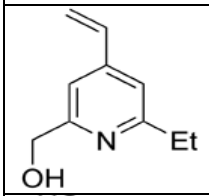
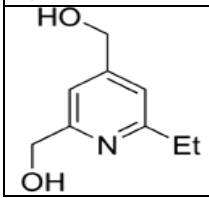


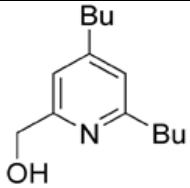
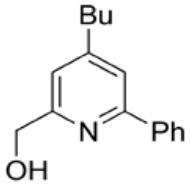
Figure S3, related to Figure 7. Heterotaxin analog 30 inhibits the growth of mammalian tumor cell lines. Five canine tumor cell lines*, including two sarcoma cell lines (Moose/MBSa and CoFSA), one carcinoma cell line (TCC) and two melanoma cell lines (CML-2 and TLM-1), were placed in a 96-well plate at cell densities sufficient to achieve approximately 75% confluence in 3 days. In addition to the cells, test wells received DMSO or 150μM heterotaxin analog **30**. After 3 days of incubation under standard conditions, 10μL WST-1 reagent (Roche) was added to the wells according to the manufacturer's instructions. Absorbance of each well at 450 nm was determined after a 4 h incubation period. Cell proliferation was calculated as a percent of the control wells.

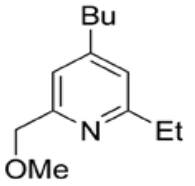
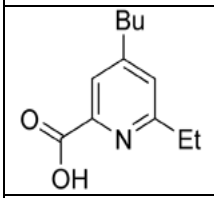
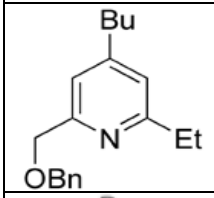
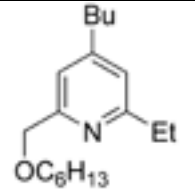


**Canine melanoma cell lines, TLM-1 and CML-2, were the kind gifts of Drs. Jaime Modiano and Lauren Wolfe, respectively. Dr. Deborah Knapp gifted us the canine transitional carcinoma cell line, TCC. CoFSA is a canine oral fibrosarcoma cell line produced by Dr. Melanie Wergin, while Moose/MBSa is a canine oral fibrosarcoma cell line produced in the author's (M. Hauck) laboratory.*

Table S1, related to Figure 5. Structure-activity relationships of heterotaxin analogs. *Xenopus* embryos were exposed to analogs from gastrulation through organogenesis (st 10-45; Nieuwkoop and Faber, 1994), at a range of concentrations (10-200μM). If a specific phenotype was observed, the dosing regimen was repeated at least once with oocytes obtained from a different female to confirm specificity. The minimum concentration at which at least 50% of embryos exhibited a specific phenotype (EC_{50}) is indicated for each analog. Phenotypes were scored as in Figure 4. Phenotype severity is indicated by: "+/-" (mild), "+" (obvious), "++" (severe). If a phenotype was not observed in any category in at least 50% of embryos exposed to a given analog, or if a compound induced non-specific toxicity (gastrulation defects, generalized edema), a "--" is shown. In the case of toxicity, the concentration at which at least 50% of embryos died is indicated as LC_{50}.

Structure	Cmpd #	Phenotypes				EC_{50}
		Left-right	Vasculogenesis	Melanogenesis	Migration	
R^2 substituents						
	**28**	**+**	**+**	**+/-**	**+**	50μM
	**29**	**--**	**--**	**--**	**--**	Toxic LC_{50}= 100μM
	**27**	**--**	**--**	**--**	**--**	n/a
	**33**	**--**	**--**	**--**	**--**	Toxic LC_{50}= 50μM
	**32**	**--**	**--**	**--**	**--**	n/a

R^1 substituents						
	**31**	**+/-**	**+**	**+**	**+**	10μM
	**30**	**+**	**+**	**+**	**+**	50μM

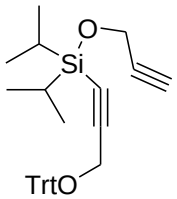
CH_2OH group modifications						
	**34**	+	+	+/-	++	100μM
	**38**	+	+/-	+	++	200μM
	**35**	+	+	+	+/-	10μM
	**36**	+	+	++	+	200μM

Supplemental Experimental Procedures:

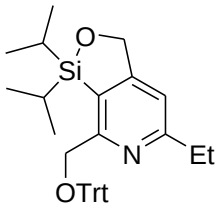
Separation of regioisomers

Heterotaxin regioisomers were separated by silica gel chromatography (hexanes/ethyl acetate 3:1-1:1). The fractions were analyzed by ^{1}H NMR and GC-MS on an HP 5890 Series II G1800 A gas chromatograph (analyses used helium gas at 1.0 mL/min) and a J&W scientific DB-5MS capillary column (length 30 m, i.d. 0.25 mm, film thickness 0.25 µm); inlet temperature: 300°C; oven temperature: 60°C held for 5 min, followed by a 20°C/min increase to a final temperature of 325°C held for 1.8 min).

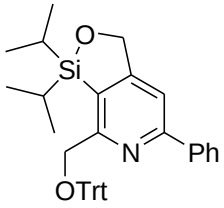
Synthetic Protocols:



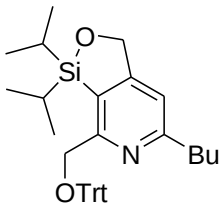
Diisopropyl(prop-2-ynyloxy)(3-(trityloxy)prop-1-ynyl)silane (5): To a cooled (−78°C) solution of **2** (597 mg, 2 mmol) in 2 mL of THF was added dropwise 857 µL of *n*-BuLi (2.45 M in hexanes, 2.1 mmol). After being stirred 15 minutes at this temperature, 410 µL of chlorodiisopropylsilane (**3**) (2.4 mmol) was added and the reaction mixture was warmed to room temperature. The solution was then diluted in Et_2O (7 mL), washed with saturated solution of NH_4Cl (5 mL), brine (5mL), dried over MgSO4, filtered, and concentrated to dryness. The residue was purified by flash silica gel chromatography, eluting with hexanes to give **4** (627 mg, 76%) as a colorless oil and used without further characterization. To a solution of **4** (518 mg, 1.2 mmol) in 5.5 mL of CH_2Cl_2 was added slowly 214 mg of NBS (1.2 mmol). The mixture was stirred until completion of the reaction by TLC (hexanes) and then this solution was transferred into a solution of propargyl alcohol (62 mg, 1.1 mmol), 153 µL of TEA (1.1 mmol) and 15 mg of DMAP (0.12 mmol) in 5.5 mL of CH_2Cl_2. After completion of the reaction by TLC (9:1, hexanes/EtOAc), the mixture was concentrated to dryness and the residue was purified by flash silica gel chromatography, eluting with 9:1 EtOAc/hexanes to give **5** (437 mg, 85%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 6H), 7.39 – 7.22 (m, 9H), 4.45 (d, *J* = 2.4 Hz, 2H), 3.82 (s, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 1.16 – 0.98 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.79, 128.83, 128.17, 127.43, 105.59, 88.02, 84.20, 73.15, 54.03, 52.94, 17.27, 17.15, 13.19; HRMS (ESI^+) calcd for $C_{31}H_{34}NaO_2Si$ $(M+Na)^+$ 489.22258, found 489.22218.



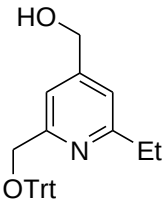
5-Ethyl-1,3-dihydro-1,1-diisopropyl-7-((trityloxy)methyl)-[1,2]oxasilolo[3,4-c]pyridine (6): Compound **5** (496 mg, 1.06 mmol) was dissolved in 26 mL xylenes in a flame dried 50 mL round bottom flask. Propionitrile (585 mg, 10.6 mmol) was added to the solution followed by $CpCo(CO)_2$ (12.2 µL, 0.106 mmol) and the solution was irradiated at 300W for 90 min. in a CEM Discover microwave synthesizer under open vessel conditions. The mixture was concentrated and the residue was purified by flash silica gel chromatography, eluting with 9:1 hexanes/EtOAc to give **6** (545 mg, 98%) as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.53 (m, 6H), 7.39 – 7.17 (m, 10H), 5.04 (s, 2H), 4.11 (s, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 1.47 (t, *J* = 7.6 Hz, 3H), 1.05 – 0.88 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.69 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.06, 161.43, 160.78, 144.31, 129.24, 128.56, 127.95, 127.13, 124.18, 114.45, 87.61, 71.78, 70.46, 31.57, 17.39, 17.12, 13.52, 13.38; HRMS (ESI^+) calcd for $C_{34}H_{40}NO_2Si$ $(M+H)^+$ 522.228228, found 522.28168.



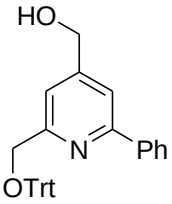
1,3-dihydro-1,1-diisopropyl-5-phenyl-7-((trityloxy)methyl)-[1,2]oxasilolo[3,4-c]pyridine (7): Compound **7** was synthesized using benzonitrile following a similar procedure for **6** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.75 – 7.62 (m, 5H), 7.62 – 7.42 (m, 5H), 7.40 – 7.20 (m, 9H), 5.15 (s, 2H), 4.20 (s, 2H), 1.04 – 0.92 (m, 2H), 0.89 (d, *J* = 6.5 Hz, 6H), 0.72 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.17, 161.23, 157.64, 144.29, 139.50, 132.94, 132.36, 129.41, 129.25, 128.94, 127.98, 127.29, 127.17, 125.99, 112.26, 98.82, 87.60, 71.94, 70.32, 17.33, 17.07, 13.37; ESI-MS calcd for $C_{38}H_{40}NO_2Si$ $(M+H)^+$ 570.3, found 570.3.



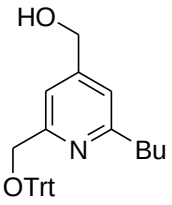
5-Butyl-1,3-dihydro-1,1-diisopropyl-7-((trityloxy)methyl)-[1,2]oxasilolo[3,4-c]pyridine (8): Compound **8** was synthesized using valeronitrile following a similar procedure for **6** in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.56 (m, 6H), 7.41 – 7.20 (m, 9H), 6.96 (s, 1H), 5.05 (s, 2H), 4.12 (s, 2H), 2.98 – 2.84 (m, 2H), 1.99 – 1.86 (m, 2H), 1.62 – 1.41 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.99 – 0.89 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 6H), 0.70 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.14, 161.33, 160.77, 144.32, 129.22, 128.87, 128.12, 127.91, 127.34, 127.10, 124.11, 115.00, 87.58, 71.72, 70.37, 38.18, 31.66, 22.76, 17.35, 17.07, 14.31, 13.35; ESI-MS calcd for $C_{36}H_{43}NO_2Si$ $(M+H)^+$ 550.3, found 550.4.



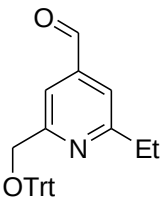
(2-Ethyl-6-((trityloxy)methyl)pyridin-4-yl)methanol (9): To a solution of **6** (869 mg, 1.66 mmol) in THF (41.5 mL) was added TBAF (1M solution in THF, 5 mL, 5mmol). The mixture was refluxed until the completion of the reaction by TLC (3:2, hexanes/EtOAc). The mixture was concentrated and the residue was purified by flash silica gel choromatography, eluting with 3:2 hexanes/EtOAc to give **9** (679 mg, 99%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.44 (m, 7H), 7.38 – 7.18 (m, 9H), 7.06 (s, 1H), 4.77 (s, 2H), 4.35 (s, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.25, 159.20, 144.14, 128.94, 128.13, 127.31, 117.84, 115.52, 87.52, 67.29, 64.34, 31.53, 14.31; HRMS (ESI$^+$) calcd for $C_{28}H_{28}NO_2$ $(M+H)^+$ 410.21200, found 410.21209.



(2-Phenyl-6-((trityloxy)methyl)pyridin-4-yl)methanol (10): Compound **10** was synthesized following the same procedure as for **9** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.85 (m, 2H), 7.62 (s, 1H), 7.61 – 7.50 (m, 7H), 7.50 – 7.18 (m, 12H), 4.79 (s, 2H), 4.46 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.59, 157.11, 151.41, 144.05, 139.49, 129.04, 128.90, 128.83, 128.11, 127.31, 127.19, 116.73, 116.60, 87.51, 67.31, 64.17; HRMS (ESI$^+$) calcd for $C_{32}H_{28}NO_2$ $(M+H)^+$ 458.2120, found 458.2133.

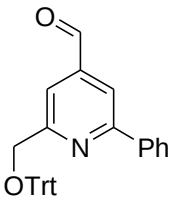


(2-Butyl-6-((trityloxy)methyl)pyridin-4-yl)methanol (11): Compound **11** was synthesized following the same procedure as for **9** in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.43 (m, 6H), 7.41 – 7.21 (m, 9H), 7.05 (s, 1H), 4.76 (s, 2H), 4.36 (s, 2H), 2.81 – 2.57 (m, 2H), 1.73 – 1.55 (m, 2H), 1.45 – 1.21 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.21, 159.17, 150.83, 144.14, 128.94, 128.13, 127.31, 118.51, 115.49, 87.52, 67.29, 64.25, 38.31, 32.43, 22.76, 14.15; HRMS (ESI$^+$) calcd for $C_{30}H_{32}NO_2$ $(M+H)^+$ 438.2433, found 438.2441.

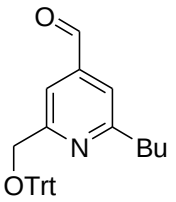


2-Ethyl-6-((trityloxy)methyl)pyridine-4-carbaldehyde (12): A solution of DMSO (30 µL, 0.427 mmol) in DCM (200 µL) was added dropwise to a solution of oxalyl chloride (75µL, 0.855 mmol) in DCM (1 mL) at −60°C and stirred for 15 min. Compound **9** was dissolved in DCM (1 mL) and

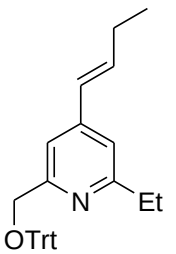
DMSO (10 µL) and the solution was added to the oxalyl chloride solution at −60°C and stirred at this temperature for 45 min. TEA (206 µL, 1.46 mmol) was then added slowly and the mixture was allowed to warm to room temperature and stirred until complete as indicated by TLC (3:2, hexanes/EtOAc). The solution was extracted with 2 mL H_2O, 2 mL sat. $NaHCO_3$, and 2 mL brine and the organic layer was dried over Na2SO4, filtered, and concentrated to dryness. The residue was purified by flash silica gel chromatography, eluting with 4:1 hexanes/EtOAc to give **12** (89 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.95 (s, 1H), 7.65 – 7.49 (m, 6H), 7.45 (s, 1H), 7.40 – 7.18 (m, 9H), 4.45 (s, 2H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.52, 164.56, 161.08, 143.84, 142.94, 128.83, 128.17, 127.39, 118.62, 117.32, 87.68, 66.97, 31.43, 14.02; Due to the instability of the aldehyde, no HRMS was obtained.



2-Phenyl-6-((trityloxy)methyl)pyridine-4-carbaldehyde (13): Compound **13** was synthesized following the same procedure as for **12** in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.08 (s, 1H), 8.06 – 7.99 (m, 3H), 7.61 (d, *J* = 7.9 Hz, 6H), 7.54 – 7.42 (m, 3H), 7.41 – 7.24 (m, 9H), 4.60 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.18, 161.53, 158.11, 143.83, 143.31, 138.33, 129.68, 128.98, 128.82, 128.15, 127.39, 127.13, 118.37, 117.06, 87.70, 67.11; Due to the instability of the aldehyde, no HRMS was obtained.

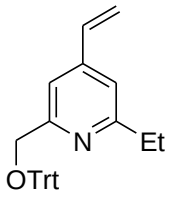


2-Butyl-6-((trityloxy)methyl)pyridine-4-carbaldehyde (14): Compound **14** was synthesized following the same procedure as for **12** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.99 (s, 1H), 7.65 – 7.51 (m, 6H), 7.45 (s, 1H), 7.41 – 7.21 (m, 9H), 4.51 (s, 2H), 2.94 – 2.78 (m, 2H), 1.84 – 1.62 (m, 2H), 1.54 – 1.32 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.38, 163.51, 161.01, 143.80, 142.75, 128.77, 128.09, 127.31, 119.23, 117.18, 87.63, 66.96, 38.07, 32.05, 22.55, 14.03; Due to the instability of the aldehyde, no HRMS was obtained.

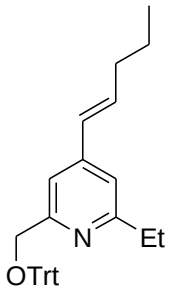


4-((E/Z)-But-1-enyl)-2-ethyl-6-((trityloxy)methyl)pyridine (15): *n*-BuLi (252 µL, 2.5 M in hexanes) was added dropwise over 30 min. to a suspension of triphenylpropylphosphonium bromide (323 mg, 0.839 mmol) in THF (21 mL) at 0°C and stirred for 1 hour at this temperature.

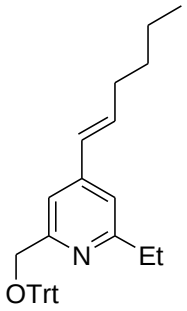
Compound **12** (171 mg, 0.420 mmol) dissolved in THF (10.5 mL) was added to this mixture over 1 hour at 0°C and allowed to warm to room temperature until the reaction was complete as indicated by TLC (10% EtOAc/hexanes). The mixture was filtered over celite, washed with EtOAc (15 mL), and the solution was concentrated to dryness. The residue was purified by flash silica gel chromatography, eluting with 10% EtOAc/hexanes to give **15** (141.6 mg, 78%) as a clear yellow oil, which was a mixture of E/Z isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.52 (dd, *J* = 7.0, 1.6 Hz, 6H), 7.40 – 7.18 (m, 9H), 6.90 (s, 1H), 6.39 (d, *J* = 11.6 Hz, 1H), 5.97 – 5.77 (m, 1H), 4.35 (s, 2H), 2.82 – 2.66 (m, 2H), 2.55 – 2.39 (m, 2H), 1.33 – 1.21 (m, 3H), 1.16 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.83, 158.89, 146.36, 144.21, 138.54, 128.93, 128.11, 127.29, 127.14, 120.22, 117.61, 87.40, 67.20, 31.53, 22.60, 14.55, 14.35; HRMS (ESI$^+$) calcd for $C_{31}H_{31}NO$ $(M+H)^+$ 434.24839, found 434.24798.



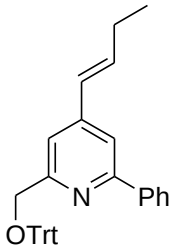
2-Ethyl-6-((trityloxy)methyl)-4-vinylpyridine (16): Compound **16** was synthesized using methyltriphenylphosphonium bromide following the same procedure as for **15** in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.56 – 7.48 (m, 6H), 7.39 – 7.19 (m, 9H), 7.04 (s, 1H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.03 (d, *J* = 17.6 Hz, 1H), 5.50 (d, *J* = 10.8 Hz, 1H), 4.35 (s, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.29, 159.41, 146.01, 144.19, 135.81, 128.96, 128.14, 127.32, 118.24, 117.51, 115.29, 87.53, 67.25, 31.51, 14.33.



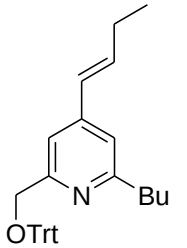
2-Ethyl-4-((E/Z)-pent-1-enyl)-6-((trityloxy)methyl)pyridine (17): Compound **17** was synthesized using *n*-butyltriphenylphosphonium bromide following the same procedure as for **15** in 74% yield as a mixture of E/Z isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.55 – 7.45 (m, 6H), 7.39 – 7.14 (m, 9H), 6.89 (s, 1H), 6.41 (d, *J* = 11.5 Hz, 1H), 5.96 – 5.81 (m, 1H), 4.34 (s, 2H), 2.82 – 2.62 (m, 2H), 2.55 – 2.36 (m, 2H), 1.63 – 1.48 (m, 2H), 1.24 (td, *J* = 7.6, 3.0 Hz, 3H), 1.06 – 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.81, 158.84, 146.45, 144.20, 136.91, 128.93, 128.11, 127.73, 127.29, 120.25, 117.64, 87.42, 67.23, 31.52, 31.29, 23.28, 14.36, 14.12; HRMS (ESI$^+$) calcd for $C_{32}H_{34}NO$ $(M+H)^+$ 448.26404, found 448.26252.



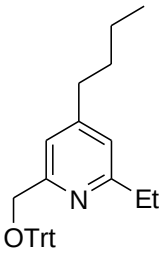
2-Ethyl-4-((E/Z)-hex-1-enyl)-6-((trityloxy)methyl)pyridine (18): Compound **18** was synthesized using amyltriphenylphosphonium bromide following the same procedure as for **15** in 63% yield as a mixture of E/Z isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.62 – 7.50 (m, 6H), 7.41 – 7.26 (m, 9H), 6.94 (s, 1H), 6.45 (d, *J* = 11.9 Hz, 1H), 6.02 – 5.85 (m, 1H), 4.40 (s, 2H), 2.87 – 2.69 (m, 2H), 2.63 – 2.41 (m, 2H), 1.62 – 1.48 (m, 2H), 1.49 – 1.36 (m, 2H), 1.29 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.70, 158.75, 146.39, 144.10, 137.05, 128.83, 128.04, 127.48, 127.21, 120.18, 117.57, 87.33, 67.12, 32.18, 31.45, 28.91, 22.61, 14.33, 14.13; HRMS (ESI^+) calcd for $C_{33}H_{36}NO$ $(M+H)^+$ 462.27969, found 462.27930.



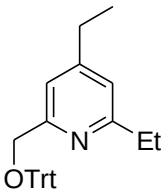
4-((E/Z)-But-1-enyl)-2-phenyl-6-((trityloxy)methyl)pyridine (19): Compound **19** was synthesized following the same procedure as for **15** in 76% yield as a mixture of E/Z isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 – 7.90 (m, 2H), 7.74 (s, 1H), 7.66 – 7.55 (m, 5H), 7.53 – 7.24 (m, 14H), 6.52 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.97 (dt, *J* = 11.7, 7.4 Hz, 1H), 4.51 (s, 2H), 2.67 – 2.49 (m, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.45, 156.94, 146.62, 144.11, 139.81, 138.80, 128.88, 128.82, 128.78, 128.09, 127.28, 127.15, 127.02, 119.11, 118.77, 87.37, 67.25, 22.63, 14.57; HRMS (ESI^+) calcd for $C_{35}H_{32}NO$ $(M+H)^+$ 482.2484, found 482.2490.



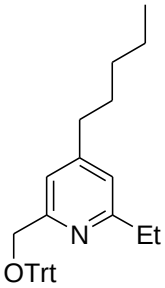
4-((E/Z)-But-1-enyl)-2-butyl-6-((trityloxy)methyl)pyridine (20): Compound **20** was synthesized following the same procedure as for **15** in 58% yield as a mixture of E/Z isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.60 – 7.51 (m, 6H), 7.40 – 7.25 (m, 9H), 6.91 (s, 1H), 6.41 (d, *J* = 11.7 Hz, 1H), 5.90 (dt, *J* = 11.7, 7.4 Hz, 1H), 4.39 (s, 2H), 2.72 (dd, *J* = 13.8, 5.8 Hz, 2H), 2.58 – 2.43 (m, 2H), 1.78 – 1.59 (m, 2H), 1.47 – 1.31 (m, 2H), 1.19 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.71, 158.81, 146.11, 144.10, 138.49, 128.84, 128.06, 127.23, 127.04, 120.88, 117.46, 87.30, 67.09, 38.30, 32.47, 22.73, 22.58, 14.55, 14.15; HRMS (ESI^+) calcd for $C_{33}H_{36}NO$ $(M+H)^+$ 462.2797, found 462.2809.



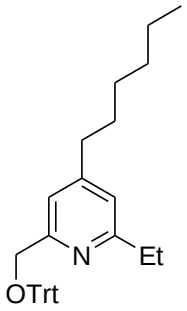
4-Butyl-2-ethyl-6-((trityloxy)methyl)pyridine (21): A mixture of **15** (53 mg, 0.122 mmol) and Pd/C (8 mg, 15% wt.) in EtOH (1.5 mL) was stirred under 1 atm of H_2 for 24 hours. The mixture was filtered through celite and concentrated to give **21** (53 mg, 100%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.46 (m, 6H), 7.41 (s, 1H), 7.37 – 7.18 (m, 9H), 6.85 (s, 1H), 4.32 (s, 2H), 2.80 – 2.58 (m, 4H), 1.75 – 1.59 (m, 2H), 1.50 – 1.32 (m, 2H), 1.29 – 1.17 (m, 3H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.61, 158.63, 152.94, 144.20, 128.92, 128.06, 127.23, 120.48, 118.20, 87.42, 67.28, 35.43, 32.73, 31.37, 22.57, 14.37, 14.11; HRMS (ESI^+) calcd for $C_{31}H_{34}NO$ $(M+H)^+$ 436.2640, found 436.2641.



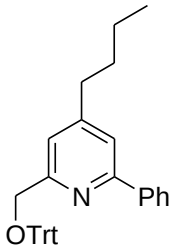
2,4-Diethyl-6-((trityloxy)methyl)pyridine (22): Compound **22** was synthesized following the same procedure as for **21** in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 6H), 7.45 (s, 1H), 7.37 – 7.14 (m, 9H), 6.89 (s, 1H), 4.35 (s, 2H), 2.81 – 2.59 (m, 4H), 1.40 – 1.12 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.68, 158.69, 154.18, 144.16, 128.89, 128.34, 128.05, 127.51, 127.21, 119.90, 117.62, 87.39, 67.25, 31.40, 28.67, 14.71, 14.38; HRMS (ESI^+) calcd for $C_{29}H_{30}NO$ $(M+H)^+$ 408.23274, found 408.23239.



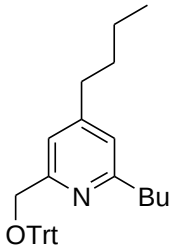
2-Ethyl-4-pentyl-6-((trityloxy)methyl)pyridine (23): Compound **23** was synthesized following the same procedure as for **21** in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.3 Hz, 6H), 7.49 (s, 1H), 7.43 – 7.21 (m, 9H), 6.92 (s, 1H), 4.43 (s, 2H), 2.83 – 2.74 (m, 2H), 2.72 – 2.65 (m, 2H), 1.79 – 1.62 (m, 2H), 1.50 – 1.35 (m, 4H), 1.28 (t, *J* = 7.6 Hz, 3H), 0.98 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.27, 158.32, 153.56, 144.08, 128.87, 128.04, 127.22, 120.62, 118.35, 87.46, 66.90, 35.68, 31.59, 31.01, 30.15, 22.64, 14.27, 14.14; HRMS (ESI^+) calcd for $C_{33}H_{38}NO$ $(M+H)^+$ 450.27969, found 450.27838.



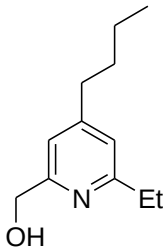
2-Ethyl-4-hexyl-6-((trityloxy)methyl)pyridine (24): Compound **24** was synthesized following the same procedure as for **21** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 6H), 7.42 (s, 1H), 7.36 – 7.17 (m, 9H), 6.87 (s, 1H), 4.33 (s, 2H), 2.80 – 2.58 (m, 4H), 1.78 – 1.57 (m, 2H), 1.36 (bs, 6H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.97 – 0.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.23, 158.26, 144.05, 128.85, 128.31, 128.05, 127.52, 127.23, 126.70, 120.64, 118.36, 87.44, 66.81, 35.74, 31.80, 30.97, 30.46, 29.10, 22.73, 14.31, 14.25; HRMS (ESI$^+$) calcd for $C_{33}H_{38}NO$ $(M+H)^+$ 464.29534, found 464.29471.



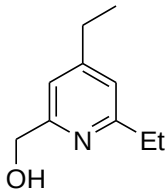
4-Butyl-2-phenyl-6-((trityloxy)methyl)pyridine (25): Compound **25** was synthesized following the same procedure as for **21** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.7 Hz, 2H), 7.70 – 7.54 (m, 7H), 7.54 – 7.18 (m, 13H), 4.57 (s, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 1.87 – 1.65 (m, 2H), 1.58 – 1.39 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.93, 156.35, 154.13, 144.04, 129.10, 128.88, 128.82, 128.08, 127.38, 127.28, 119.77, 87.53, 66.92, 35.63, 34.16, 32.68, 22.52, 14.10; HRMS (ESI$^+$) calcd for $C_{35}H_{34}NO$ $(M+H)^+$ 484.2640, found 484.2647.



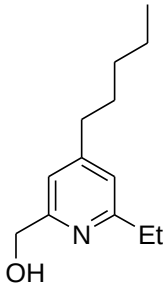
2,4-Dibutyl-6-((trityloxy)methyl)pyridine (26): Compound **26** was synthesized following the same procedure as for **21** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 6H), 7.46 (s, 1H), 7.36 – 7.19 (m, 9H), 6.92 (s, 1H), 4.50 (s, 2H), 2.84 – 2.73 (m, 2H), 2.73 – 2.62 (m, 2H), 1.75 – 1.58 (m, 4H), 1.51 – 1.28 (m, 4H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.34, 157.48, 143.77, 128.73, 128.50, 128.21, 128.02, 127.24, 121.74, 118.83, 87.58, 65.82, 36.74, 35.42, 32.42, 32.24, 22.54, 22.40, 13.99, 13.98; HRMS (ESI$^+$) calcd for $C_{33}H_{38}NO$ $(M+H)^+$ 464.2953, found 464.2961.



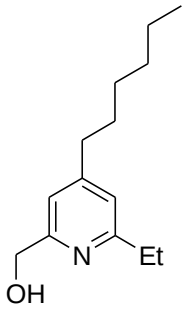
(4-Butyl-6-ethylpyridin-2-yl)methanol (Heterotaxin 1): Acetyl chloride (100 µL) was added slowly to a solution of MeOH (2mL) and DCM (3 mL) at 0°C. Compound **21** (81.5 mg, 0.187 mmol) was dissolved in this solution and allowed to stir at room temperature until the reaction was complete (30 min.) as indicated by TLC (10% EtOAc/hexanes). The solution was concentrated to dryness and the residue was dissolved in 4 mL DCM and extracted with 2 mL 1M NaOH. The aqueous layer was extracted with DCM (3×3 mL) and the organic layers were combined, dried over Na2SO4, filtered, and concentrated to dryness. The residue was purified by flash silica gel chromatography, eluting with 0.1% TEA/EtOAc to give **1** (36 mg, 100%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.85 (s, 1H), 4.68 (s, 2H), 2.78 (q, *J* = 7.6 Hz, 2H), 2.64 – 2.50 (m, 2H), 1.69 – 1.52 (m, 2H), 1.42 – 1.32 (m, 2H), 1.29 (t, *J* = 7.6 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.31, 158.23, 153.43, 121.10, 118.26, 64.07, 35.19, 32.65, 30.93, 22.49, 14.02; HRMS (ESI^+) calcd for $C_{12}H_{20}NO$ $(M+H)^+$ 194.15449, found 194.15415.



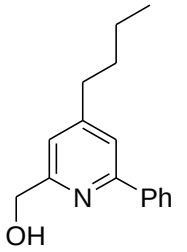
(4,6-Diethylpyridin-2-yl)methanol (27): Compound **27** was synthesized following the same procedure as for **1** in 71% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 2H), 4.68 (s, 2H), 4.26 (bs, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.38 – 1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.42, 158.27, 154.45, 120.52, 117.44, 64.08, 31.11, 28.42, 14.56, 13.97; HRMS (ESI^+) calcd for $C_{10}H_{16}NO$ $(M+H)^+$ 166.12319, found 166.12235.



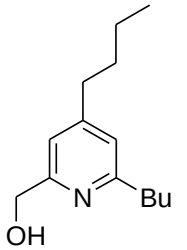
(6-Ethyl-4-pentylpyridin-2-yl)methanol (28): Compound **28** was synthesized following the same procedure as for **1** in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 4.68 (s, 2H), 4.49 (bs, 1H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.63 – 2.48 (m, 2H), 1.71 – 1.50 (m, 2H), 1.40 – 1.19 (m, 7H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.30, 158.15, 153.24, 121.03, 117.99, 64.05, 35.47, 31.60, 31.08, 30.25, 22.62, 14.14, 14.01; HRMS (ESI^+) calcd for $C_{13}H_{22}NO$ $(M+H)^+$ 208.17014, found 208.16936.



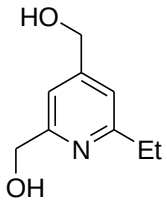
(6-Ethyl-4-hexylpyridin-2-yl)methanol (29): Compound **29** was synthesized following the same procedure as for **1** in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 4.68 (s, 2H), 4.13 (bs, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.64 – 2.48 (m, 2H), 1.67 – 1.48 (m, 2H), 1.42 – 1.18 (m, 9H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.36, 158.19, 153.23, 121.04, 117.93, 64.08, 35.53, 31.80, 31.14, 30.54, 29.12, 22.73, 14.22, 13.98; HRMS (ESI$^+$) calcd for $C_{14}H_{24}NO$ $(M+H)^+$ 222.18579, found 222.18569.



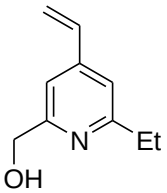
(4-Butyl-6-phenylpyridin-2-yl)methanol (30): Compound **30** was synthesized following the same procedure as for **1** in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 – 7.93 (m, 2H), 7.54 – 7.36 (m, 4H), 6.99 (s, 1H), 4.78 (s, 2H), 2.75 – 2.59 (m, 2H), 1.76 – 1.57 (m, 2H), 1.50 – 1.28 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.62, 156.11, 153.55, 139.20, 129.12, 128.82, 127.07, 119.66, 119.03, 64.06, 35.36, 32.70, 22.49, 14.04; ESI-MS calcd for $C_{16}H_{20}NO$ $(M+H)^+$ 242.2, found 242.2.



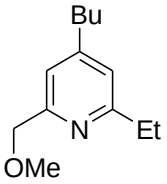
(4,6-Dibutylpyridin-2-yl)methanol (31): Compound **31** was synthesized following the same procedure as for **1** in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.84 (s, 1H), 4.67 (s, 2H), 4.24 (bs, 1H), 2.84 – 2.64 (m, 2H), 2.63 – 2.47 (m, 2H), 1.76 – 1.50 (m, 4H), 1.45 – 1.23 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.29, 158.19, 152.99, 121.67, 117.91, 64.06, 37.83, 35.16, 32.68, 32.09, 22.66, 22.49, 14.12, 14.03; ESI-MS calcd for $C_{14}H_{24}NO$ $(M+H)^+$ 222.2, found 222.2.



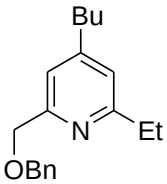
(6-Ethylpyridine-2,4-diyl)dimethanol (32): Compound **32** was synthesized from **9** following the same procedure as for **1** in 66% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.30 (s, 1H), 7.10 (s, 1H), 4.59 (d, *J* = 3.6 Hz, 4H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.18, 161.81, 154.77, 119.39, 116.85, 65.59, 63.85, 31.86, 14.85; HRMS (ESI^+) calcd for $C_9H_{14}NO_2$ $(M+H)^+$ 168.10245, found 168.10209.



(6-Ethyl-4-vinylpyridin-2-yl)methanol (33): Compound **33** was synthesized from **16** following the same procedure as for **1** in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 2H), 6.65 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.95 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 10.8 Hz, 1H), 4.72 (s, 2H), 2.93 – 2.71 (m, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.99, 158.79, 146.17, 135.21, 118.71, 118.14, 114.88, 64.10, 31.21, 13.93; HRMS (ESI^+) calcd for $C_{10}H_{14}NO$ $(M+H)^+$ 164.1075, found 164.1069.

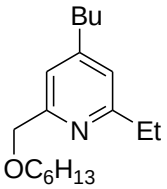


4-Butyl-2-ethyl-6-(methoxymethyl)pyridine (34): To a suspension of 60% NaH (4.08 mg, 0.102 mmol) in THF (100 µL) at 0°C was added compound **1** (16.5 mg, 0.0854 mmol) dissolved in THF (100 µL). This mixture was allowed to stir for 1 hour at 0°C before MeI (36.4 mg, 0.256 mmol) was added. The mixture was allowed to warm to room temperature and stirred until the reaction was complete as indicated by TLC (EtOAc). NH_4Cl (1.5 mL) was added to the reaction mixture and was extracted with EtOAc (2 mL). The organic layer was washed with H_2O (2 mL), brine (2 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash silica gel chromatography, eluting with 4:1 hexanes/EtOAc to give **34** (15.3 mg, 86%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.87 (s, 1H), 4.53 (s, 2H), 3.47 (s, *J* = 0.5 Hz, 3H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.64 – 2.50 (m, 2H), 1.67 – 1.53 (m, 2H), 1.44 – 1.27 (m, 5H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.11, 157.62, 153.08, 120.96, 118.85, 75.97, 58.95, 35.33, 32.75, 31.46, 22.58, 14.39, 14.06; HRMS (ESI^+) calcd for $C_{13}H_{22}NO$ $(M+H)^+$ 208.17014, found 208.16923.

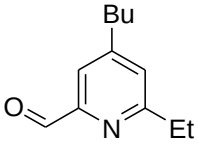


2-((Benzyloxy)methyl)-4-butyl-6-ethylpyridine (35): Compound **35** was synthesized using benzyl bromide following the same procedure as for **34** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H), 7.14 (s, 1H), 6.88 (s, 1H), 4.69 – 4.61 (m, 4H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.64 – 2.52 (m, 2H), 1.68 – 1.54 (m, 2H), 1.44 – 1.32 (m, 2H), 1.31 – 1.25 (m, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.97, 157.78, 153.03, 138.33, 128.59, 128.08,

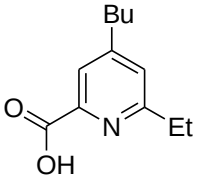
127.87, 120.91, 118.87, 73.53, 73.12, 35.34, 32.76, 31.47, 22.59, 14.43, 14.09; ESI-MS calcd for $C_{19}H_{26}NO$ $(M+H)^+$ 284.2, found 284.2.



4-Butyl-2-ethyl-6-((hexyloxy)methyl)pyridine (36): Compound **36** was synthesized using 1-bromohexane following the same procedure as for **34** in 42% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.86 (s, 1H), 4.58 (s, 2H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.64 – 2.53 (m, 2H), 1.76 – 1.53 (m, 5H), 1.47 – 1.22 (m, 10H), 0.96 – 0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.96, 158.32, 152.96, 120.79, 118.72, 74.14, 71.43, 35.36, 32.74, 31.92, 31.49, 29.94, 26.09, 22.84, 22.60, 14.41, 14.23, 14.07.; ESI-MS calcd for $C_{18}H_{32}NO$ $(M+H)^+$ 278.2, found 278.3.

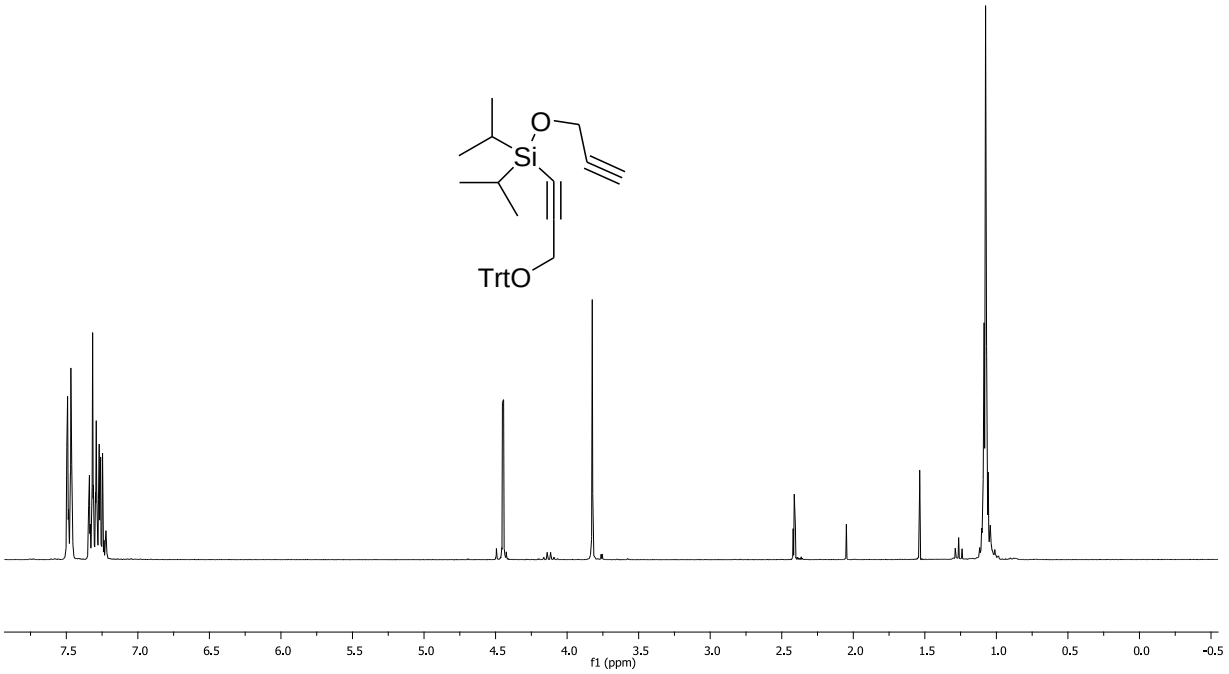


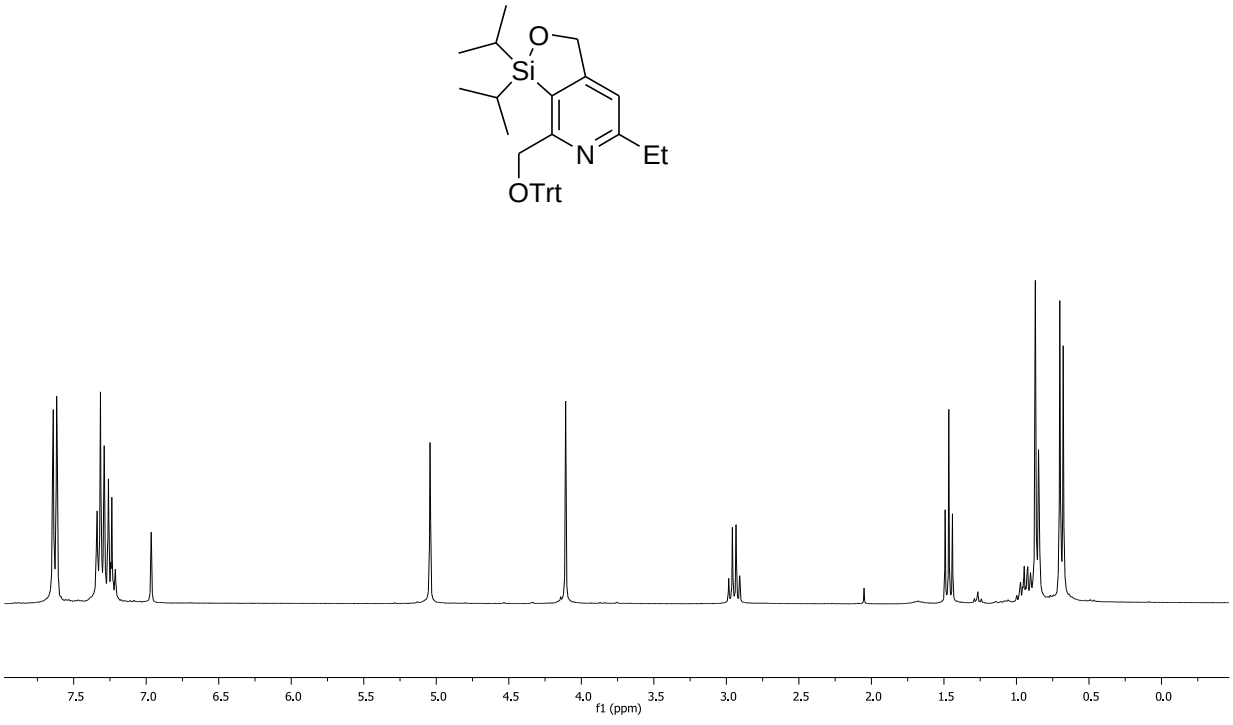
4-Butyl-6-ethylpyridine-2-carbaldehyde (37): MnO_2 (425 mg) was added in 5 portions over 24 hours to a solution of **1** (34 mg, 0.176 mmol) in DCM (2 mL) until the reaction was complete as indicated by TLC (EtOAc). The reaction mixture was filtered through celite, and the solution was evaporated to dryness to give **37** (17.2 mg, 51%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, *J* = 0.7 Hz, 1H), 7.61 (s, 1H), 7.19 (s, 1H), 2.87 (q, *J* = 7.6 Hz, 2H), 2.74 – 2.54 (m, 2H), 1.73 – 1.52 (m, 2H), 1.43 – 1.27 (m, 5H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.41, 164.41, 153.56, 152.66, 126.78, 119.51, 35.11, 32.54, 31.29, 22.46, 14.06, 13.99; ESI-MS calcd for $C_{12}H_{18}NO$ $(M+H)^+$ 192.1, found 192.1.

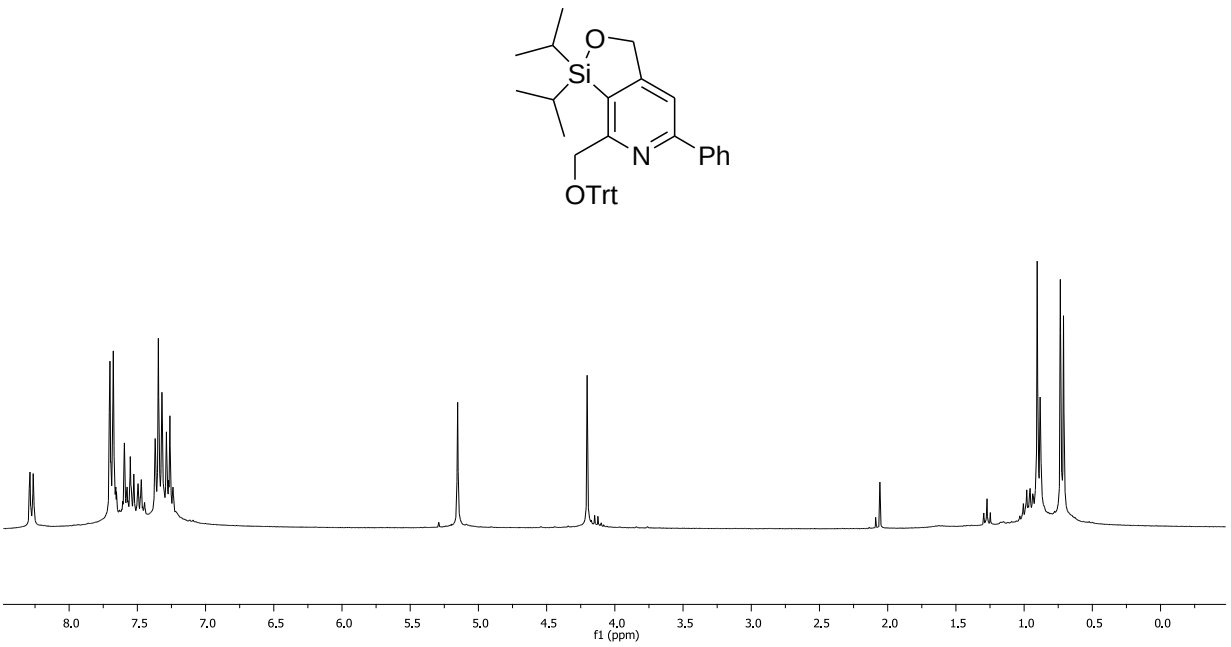


4-Butyl-6-ethylpyridine-2-carboxylic acid (38): Compound **37** (15.9 mg, 0.0831 mmol) was dissolved in 1:1 H_2O/*t*-BuOH (1 mL) then NaH_2PO_4 (50 mg, 0.416 mmol) and 2-methyl-2-butene (1 mL) were added. $NaClO_2$ (38 mg, 0.416 mmol) was added in three portions over one minute and the mixture was stirred (2 hr) until the reaction was complete as indicated by TLC (EtOAc). The mixture was diluted with H_2O (2 mL) and extracted with DCM (4×3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness to give **38** (15.3 mg, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.23 (s, 1H), 2.95 – 2.78 (m, 2H), 2.75 – 2.62 (m, 2H), 1.73 – 1.54 (m, 2H), 1.43 – 1.27 (m, 5H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.92, 162.43, 155.58, 145.64, 126.89, 121.38, 35.21, 32.48, 30.59, 22.44, 13.97, 13.58; HRMS (ESI^+) calcd for $C_{12}H_{18}NO_2$ $(M+H)^+$ 208.1338, found 208.1333.

^{1}H NMR spectra of new compounds (300 MHz, $CDCl_3$):



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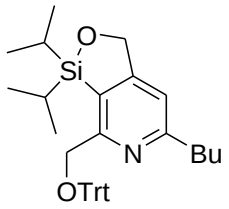
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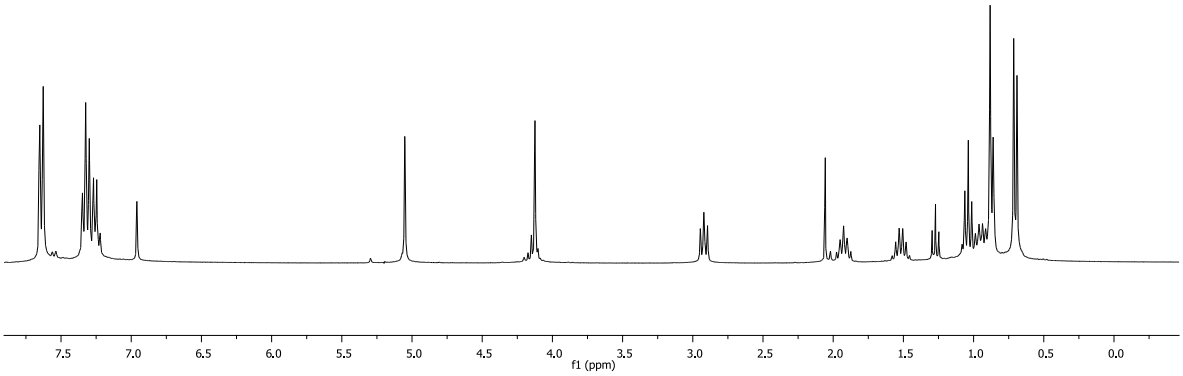
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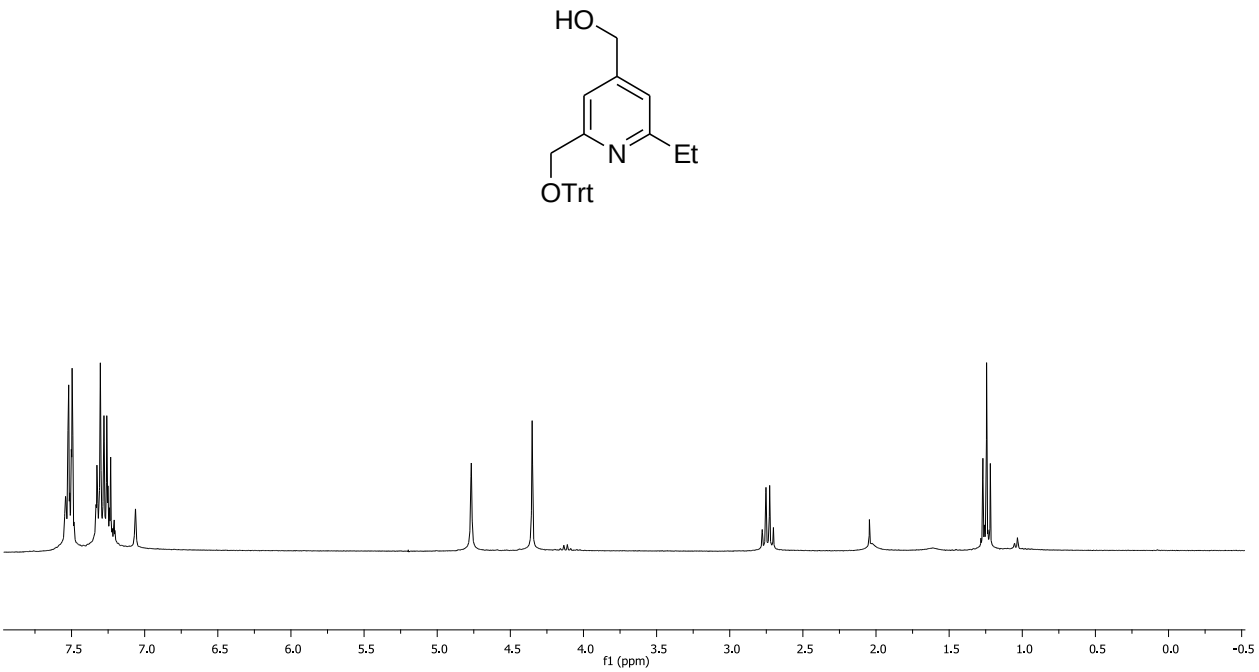
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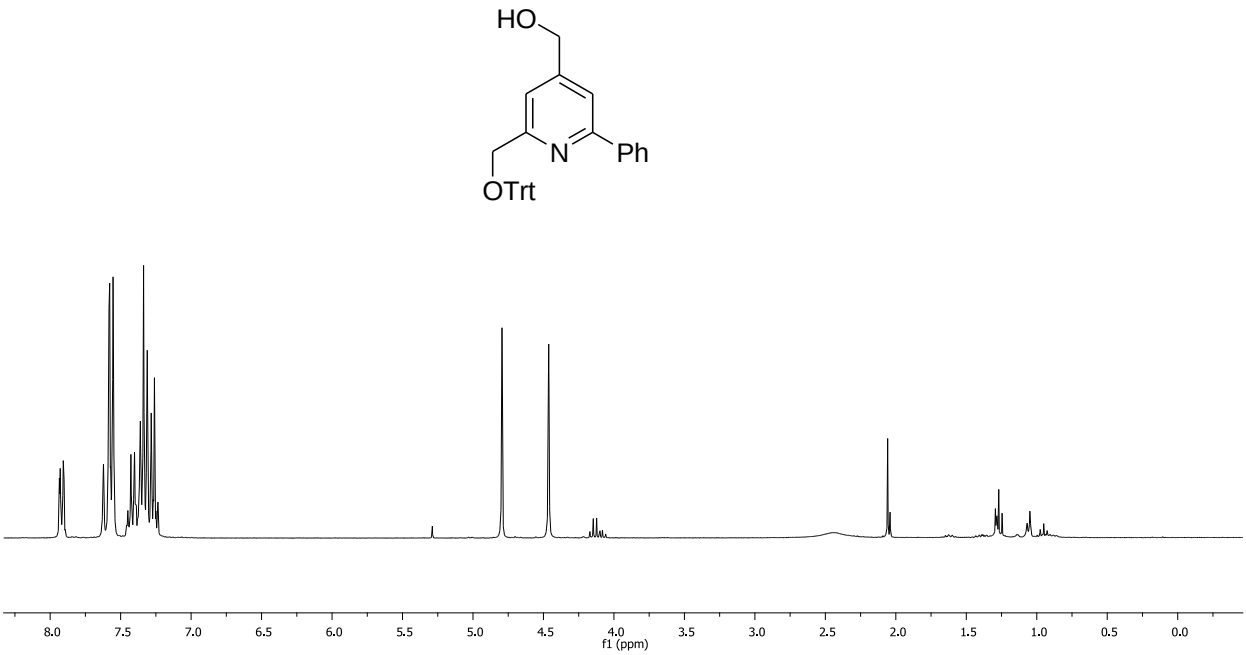
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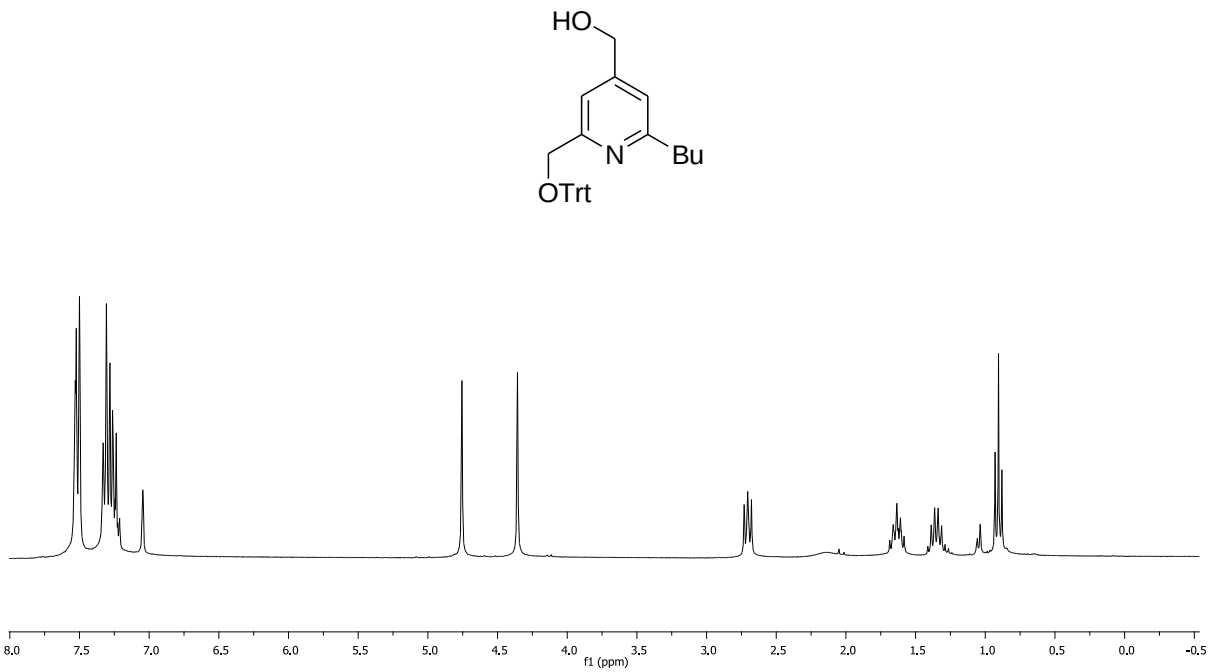
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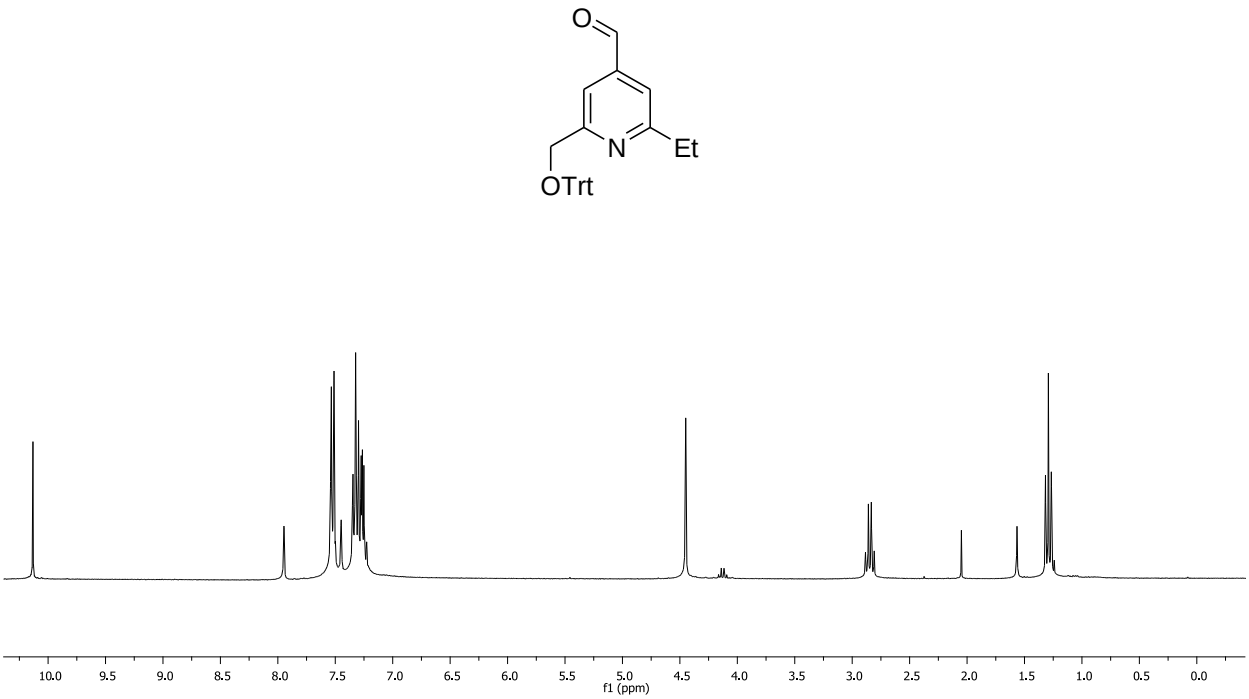
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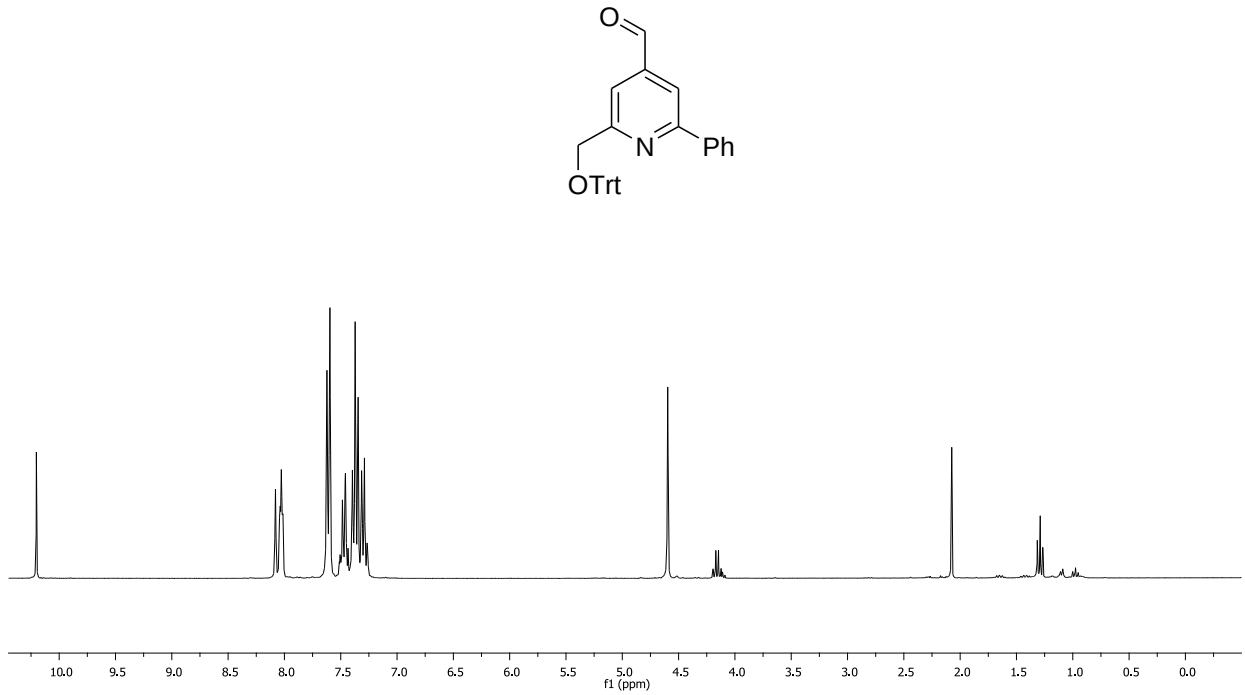
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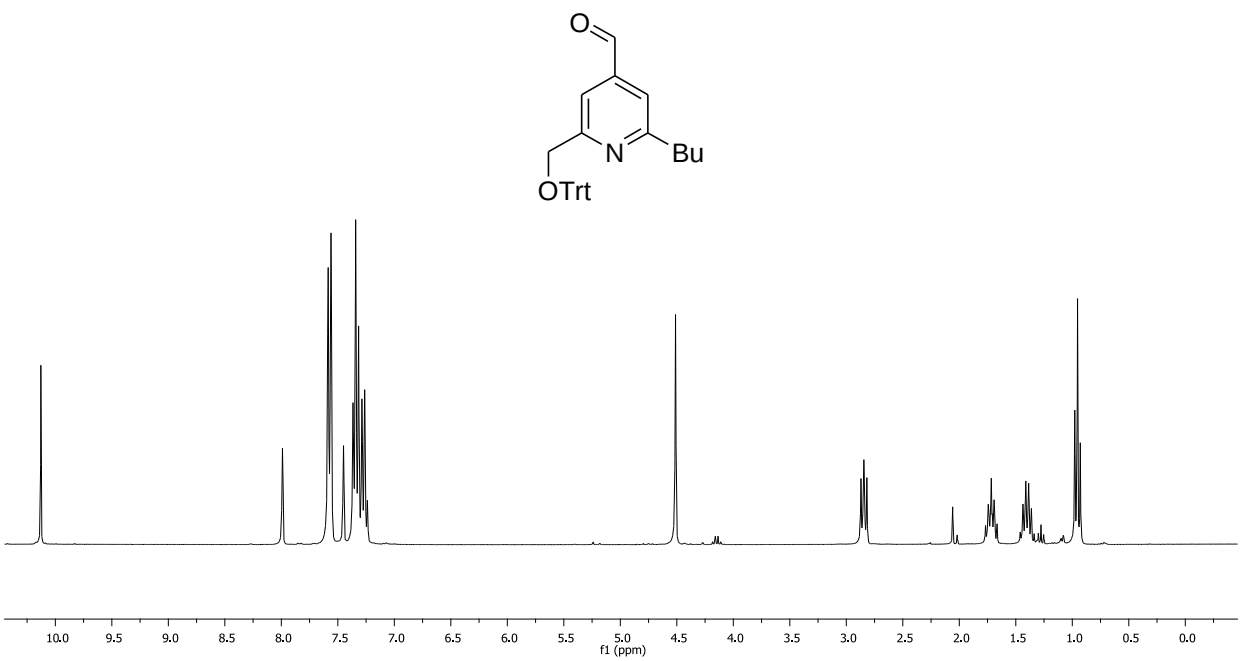
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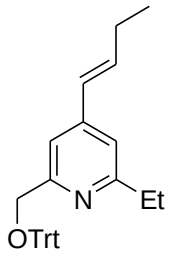
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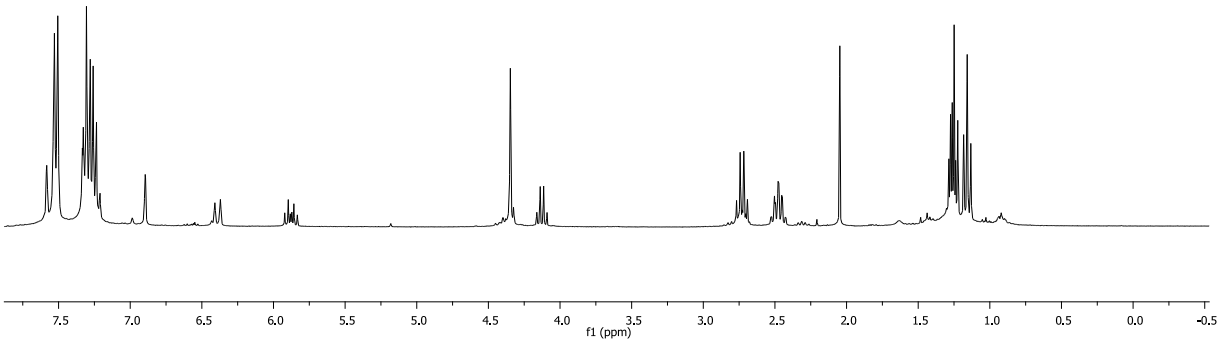
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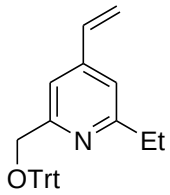
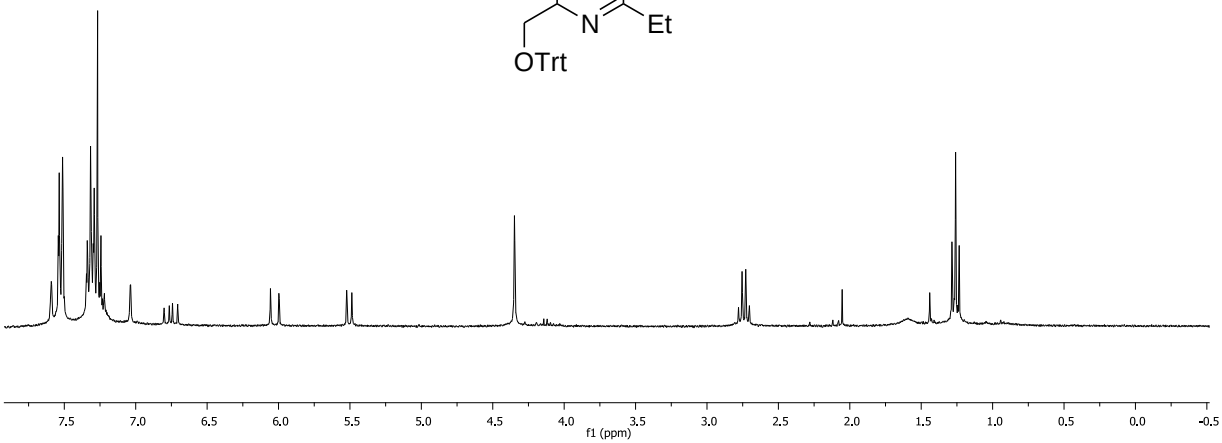
f1 (ppm)


N
Et
OTrt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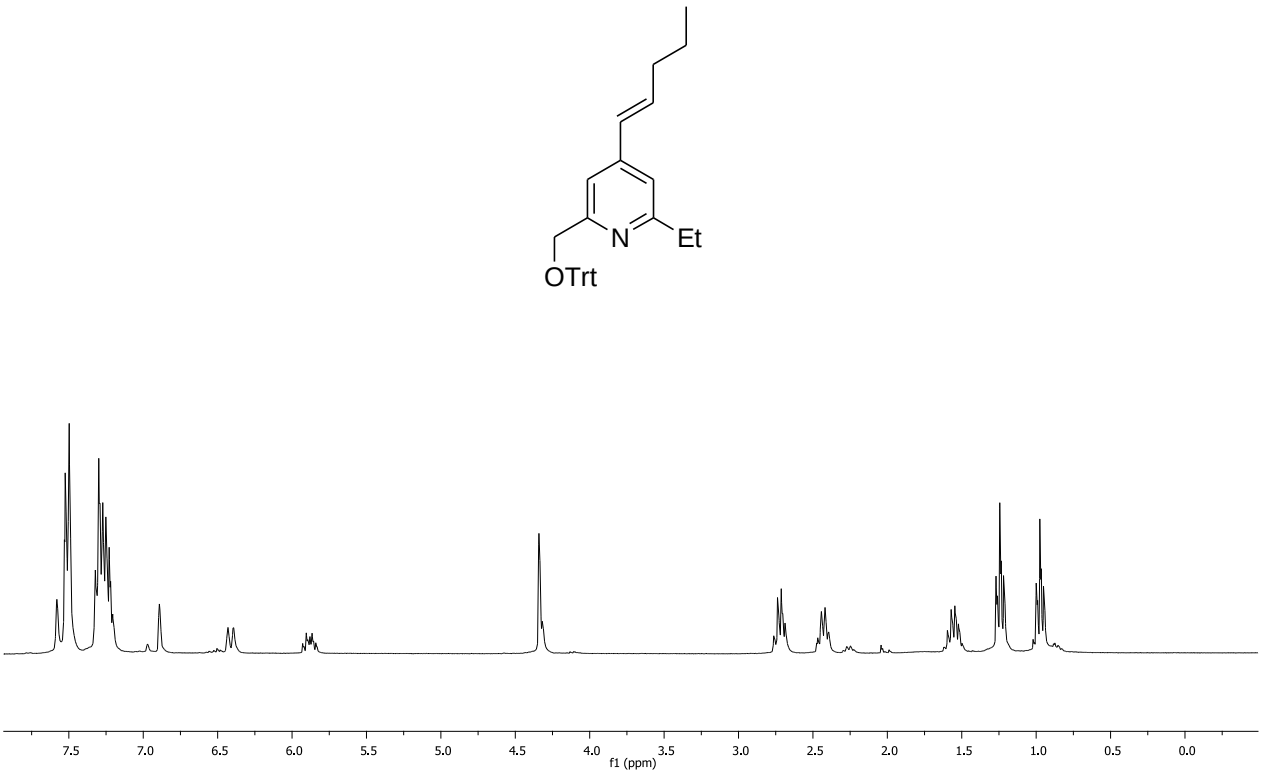
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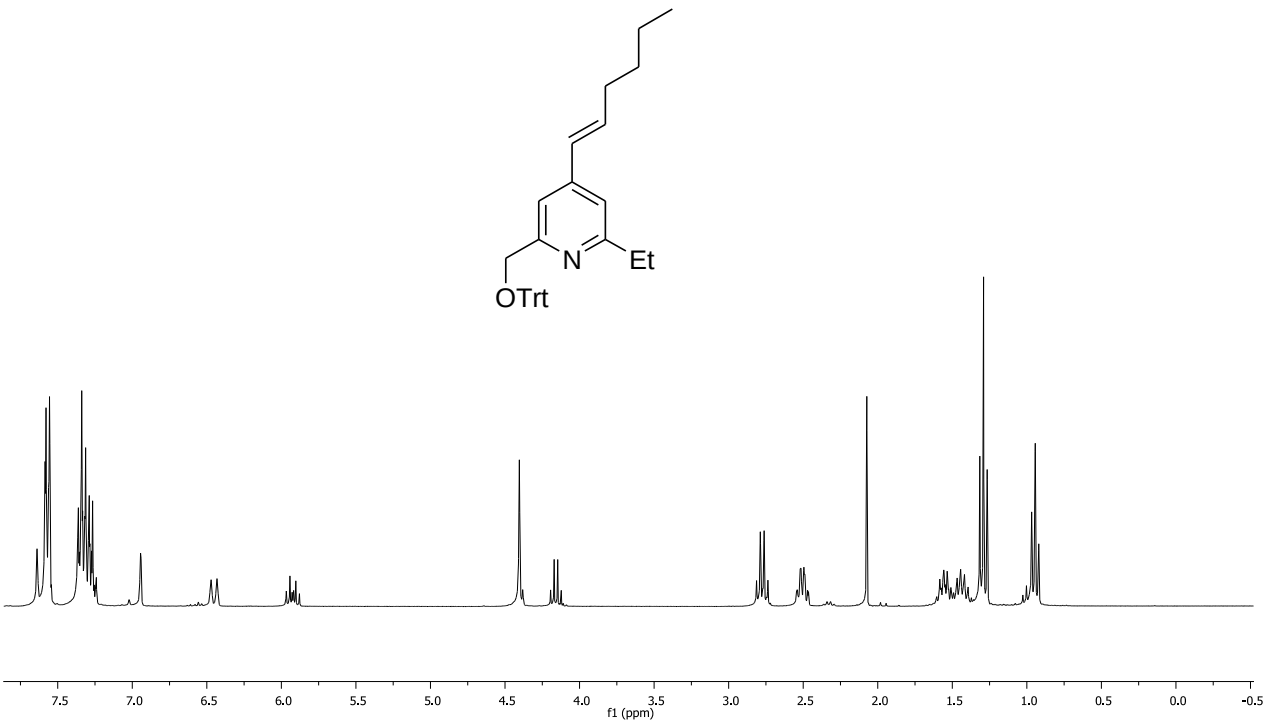
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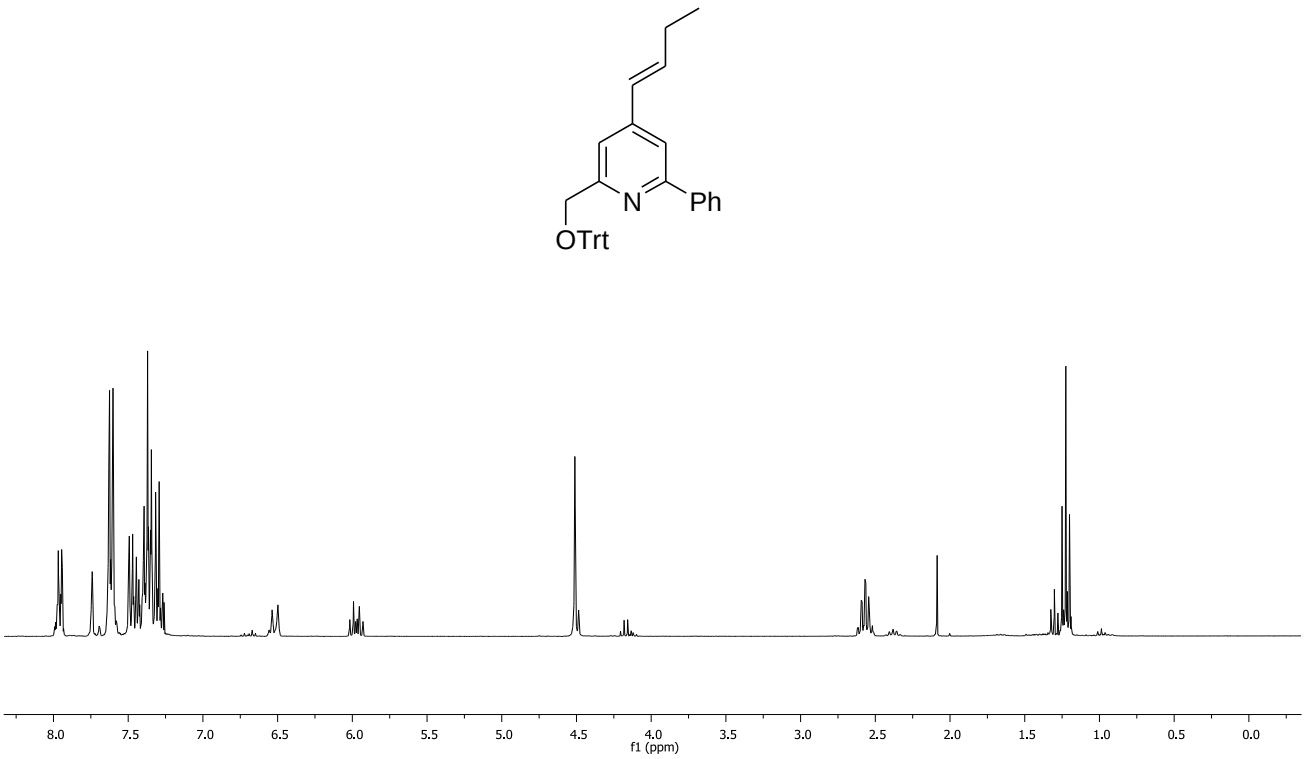
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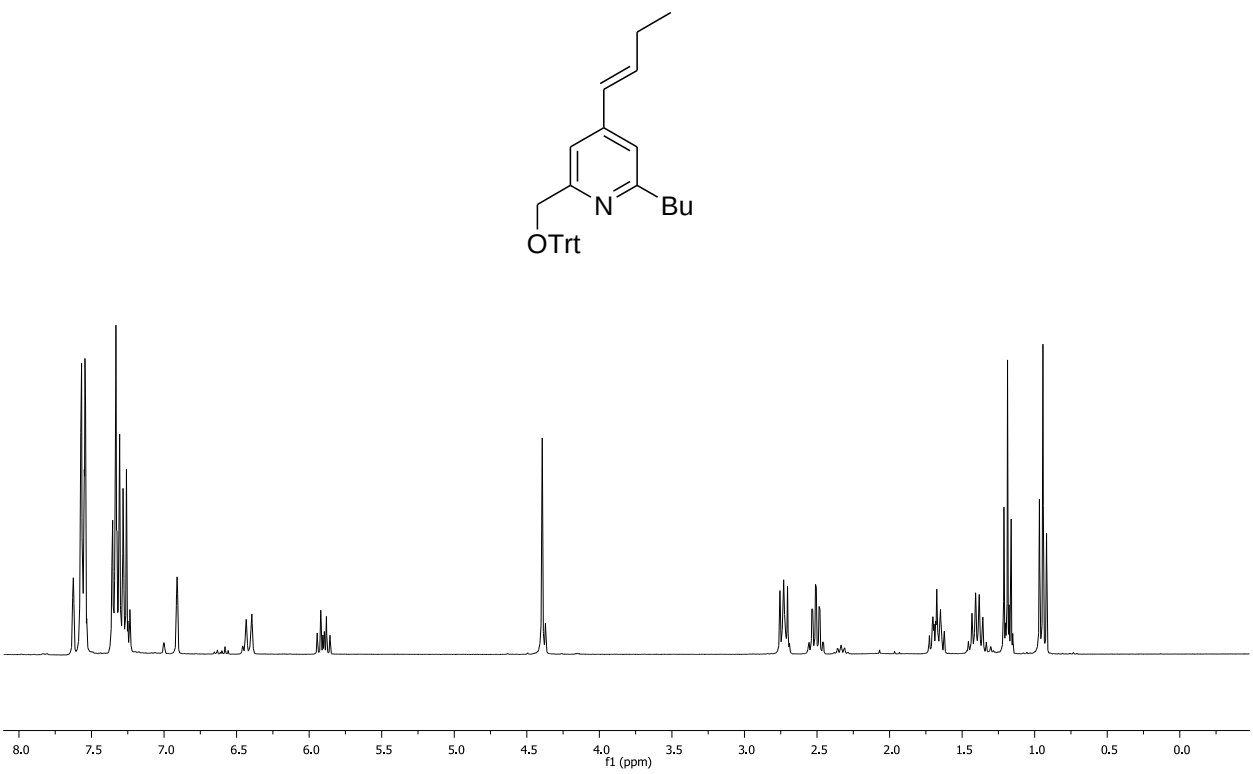
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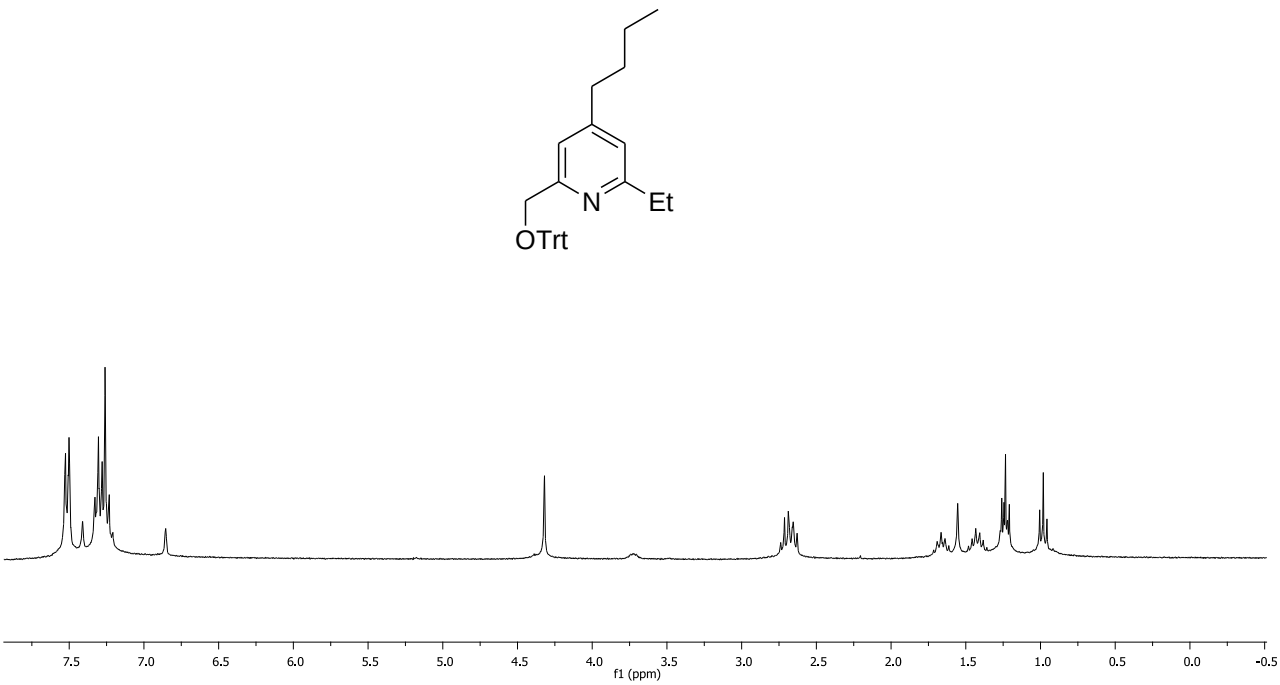
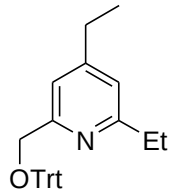
Supplemental Text and Figures (Part 2)

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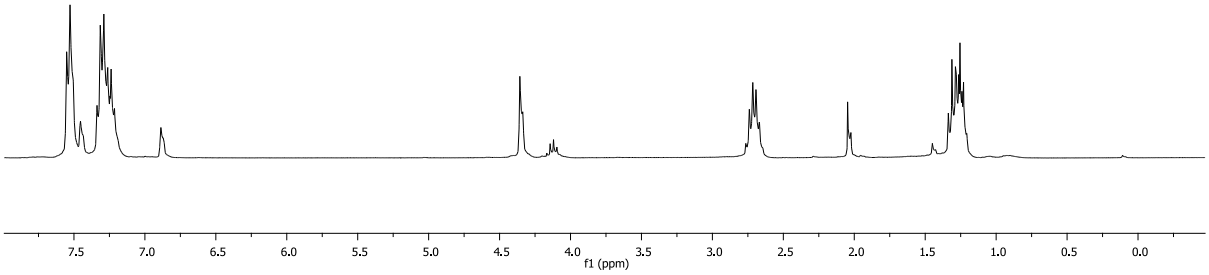
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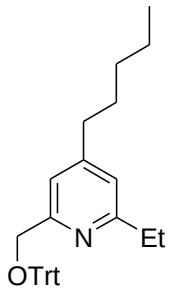
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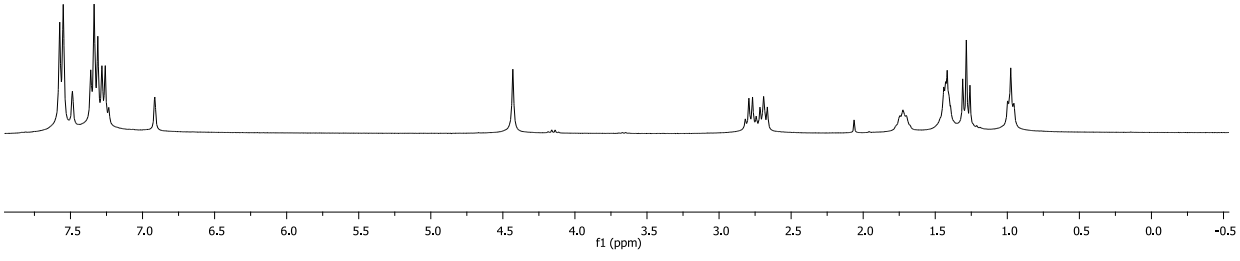
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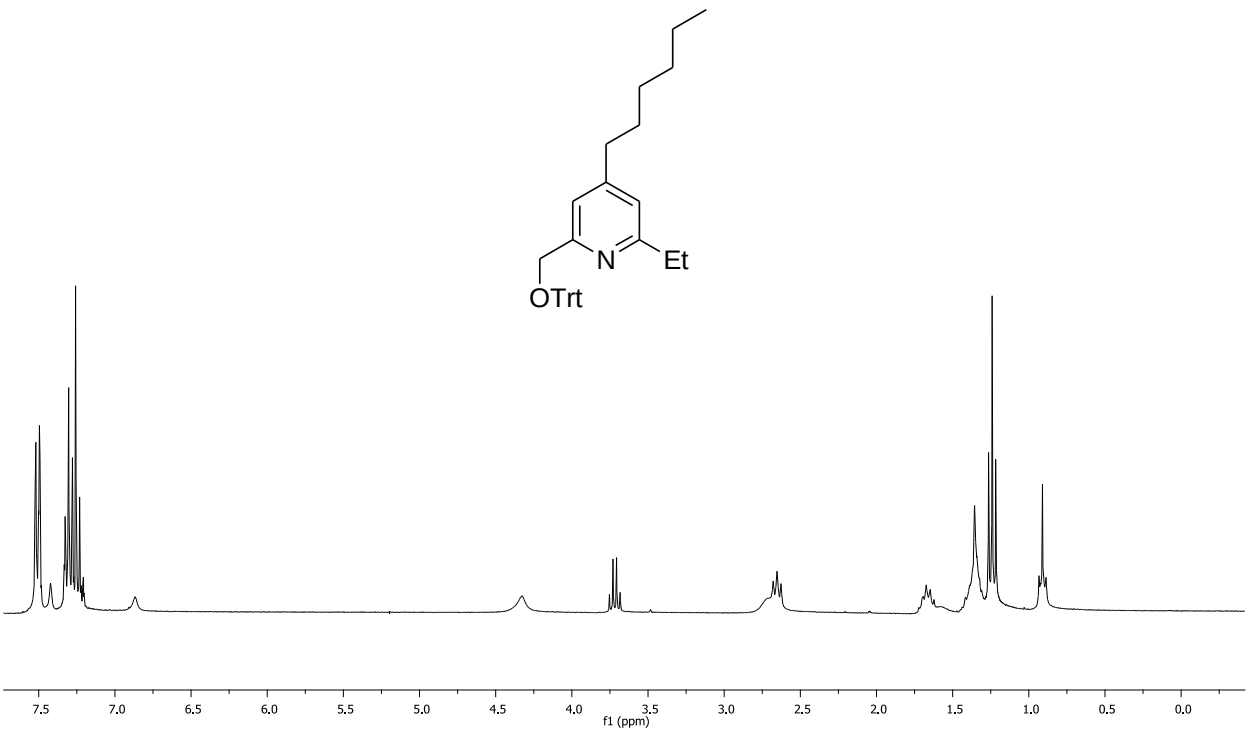
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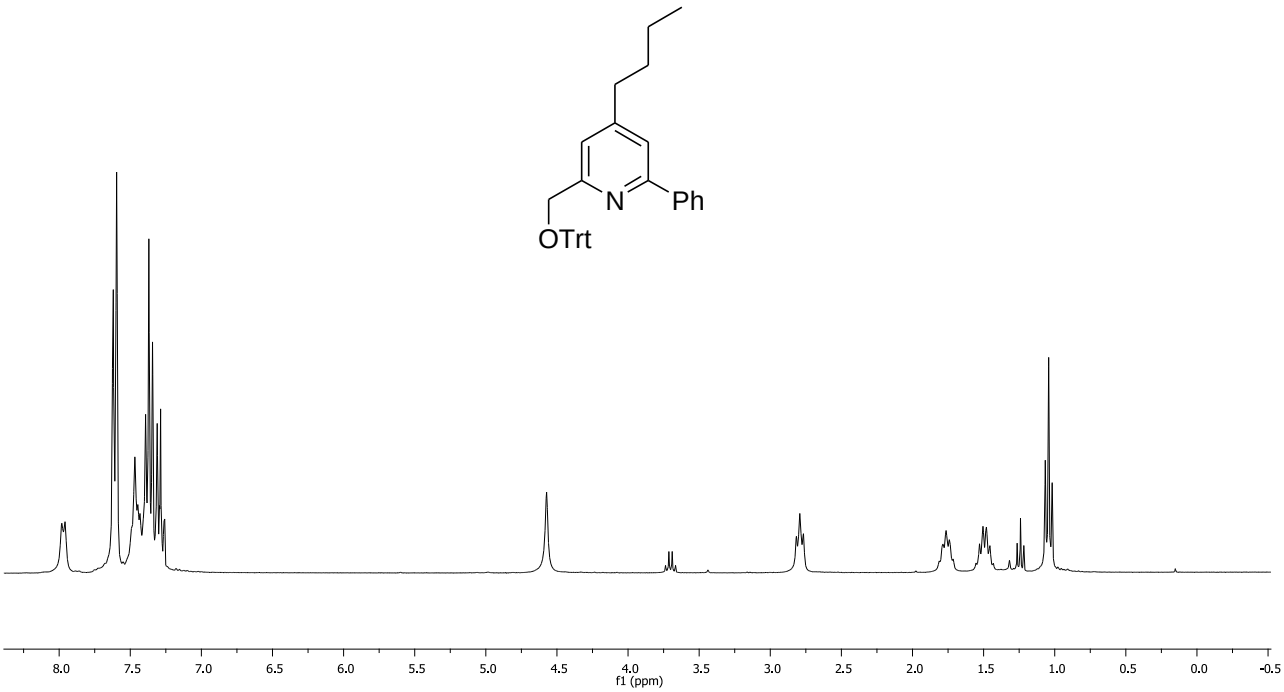
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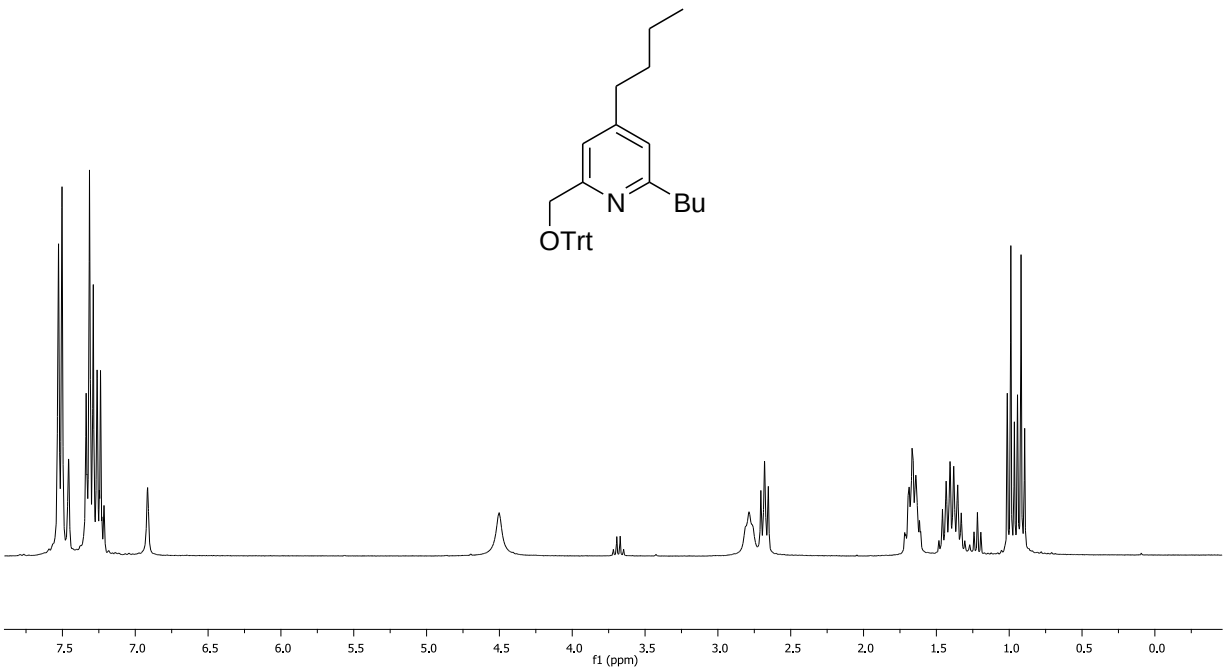
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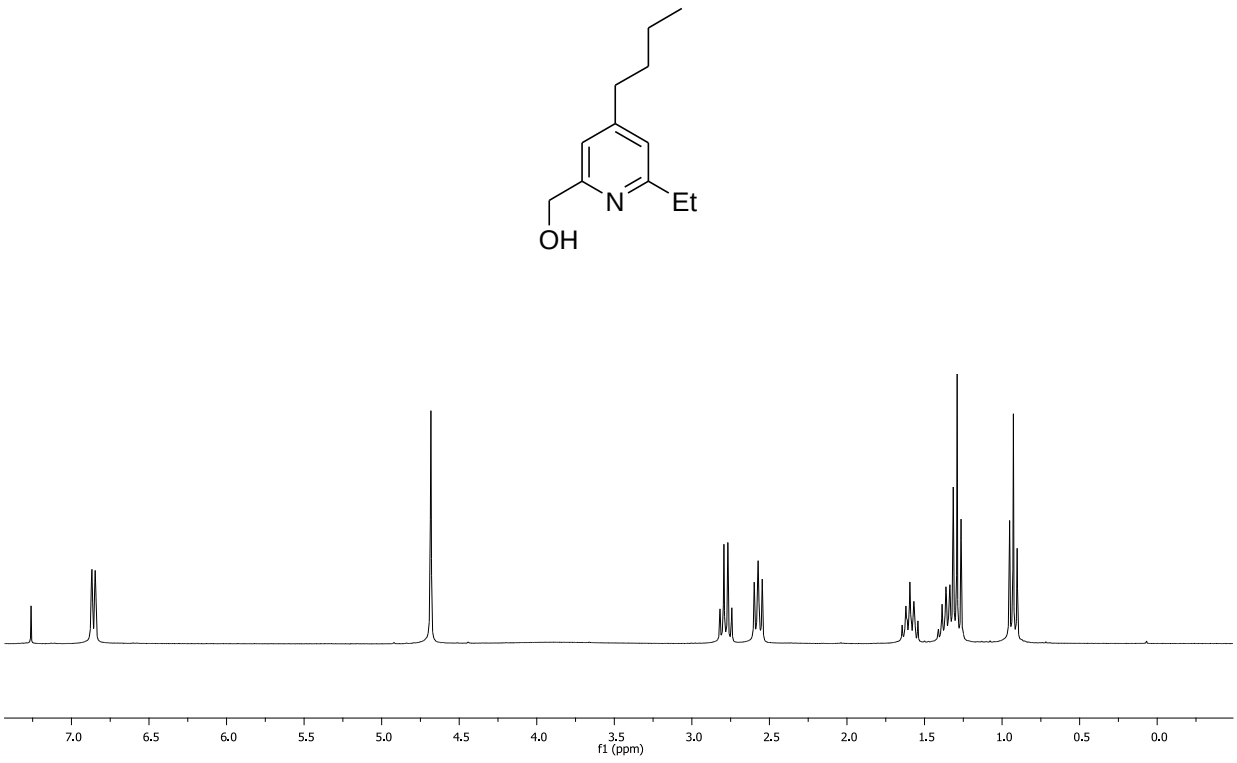
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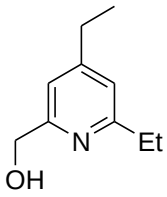
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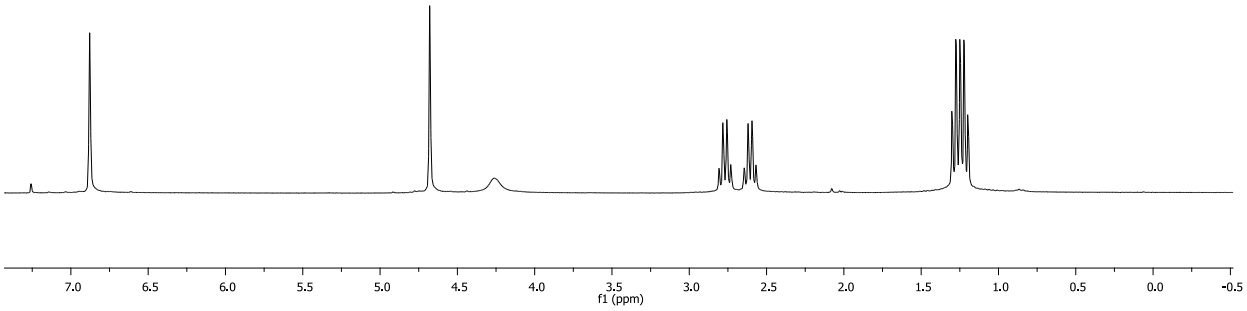
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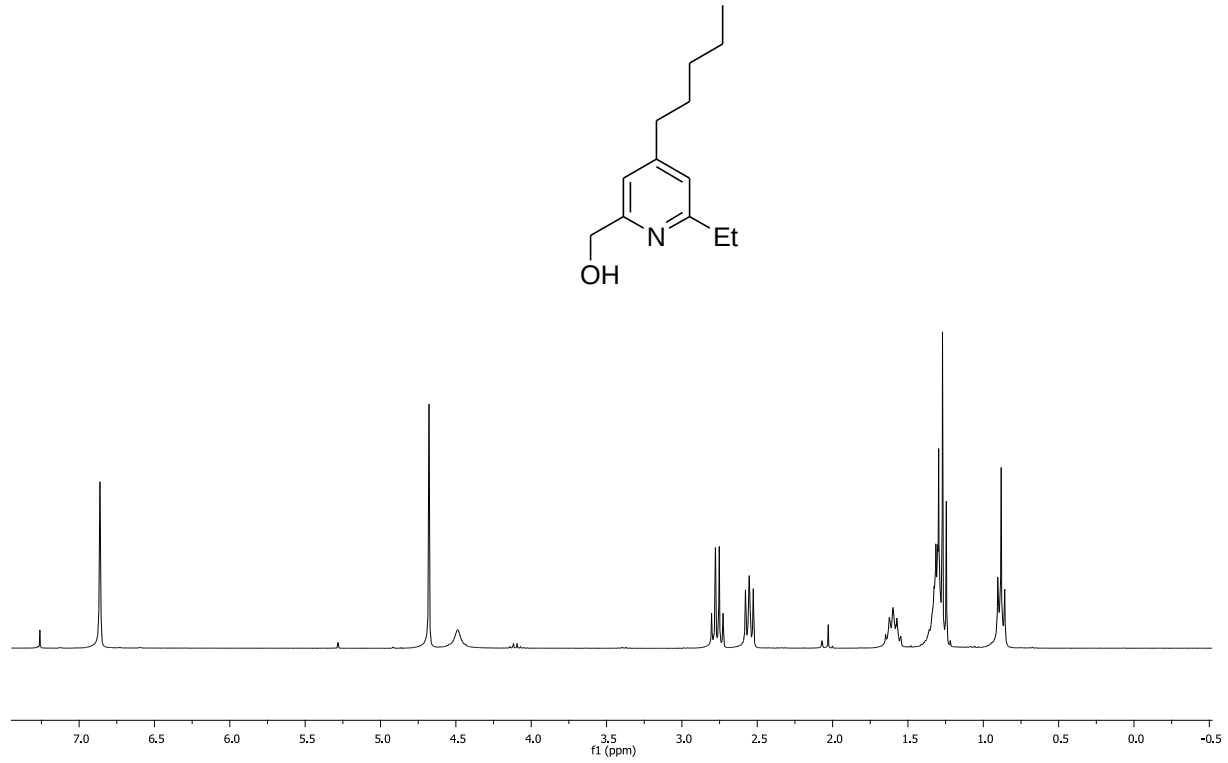
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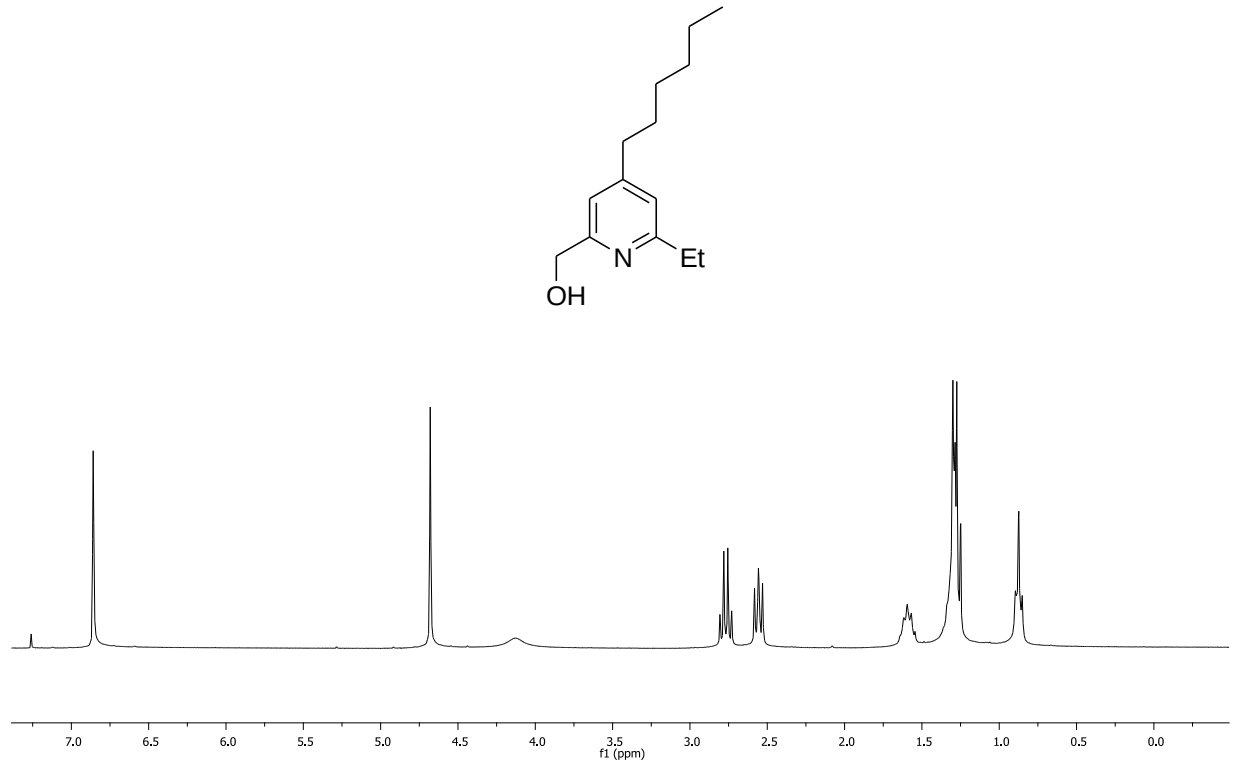
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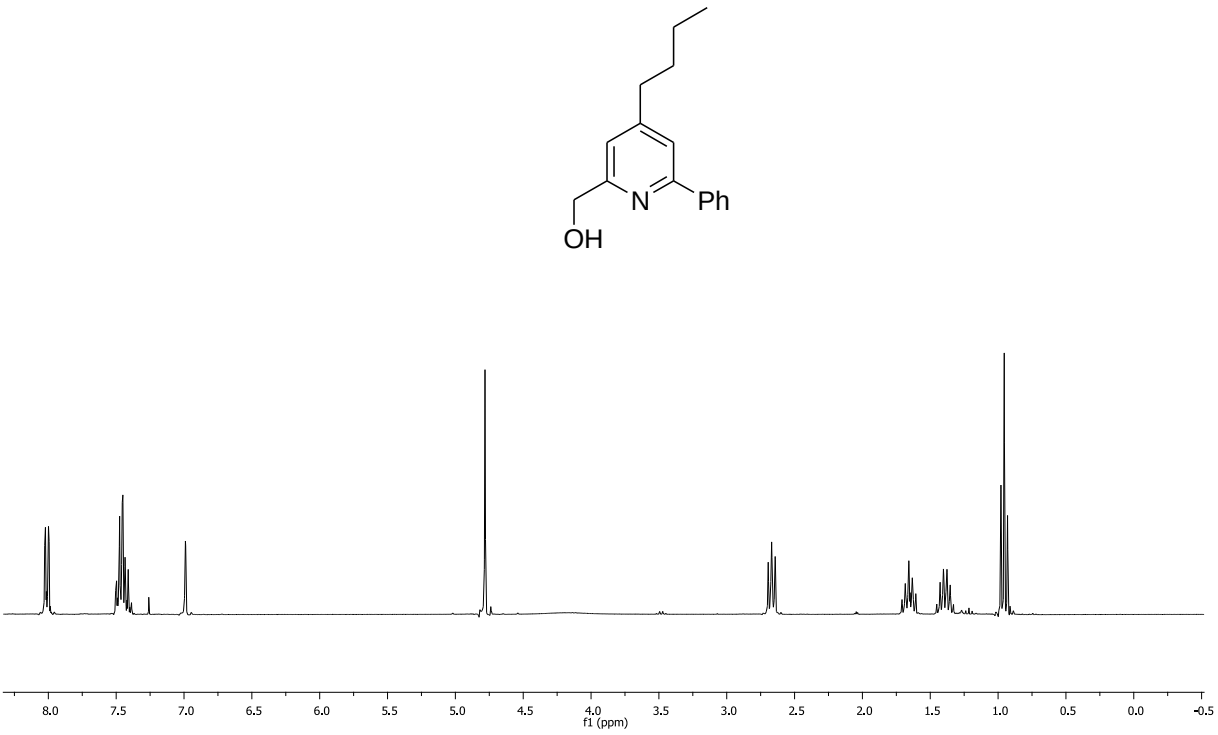
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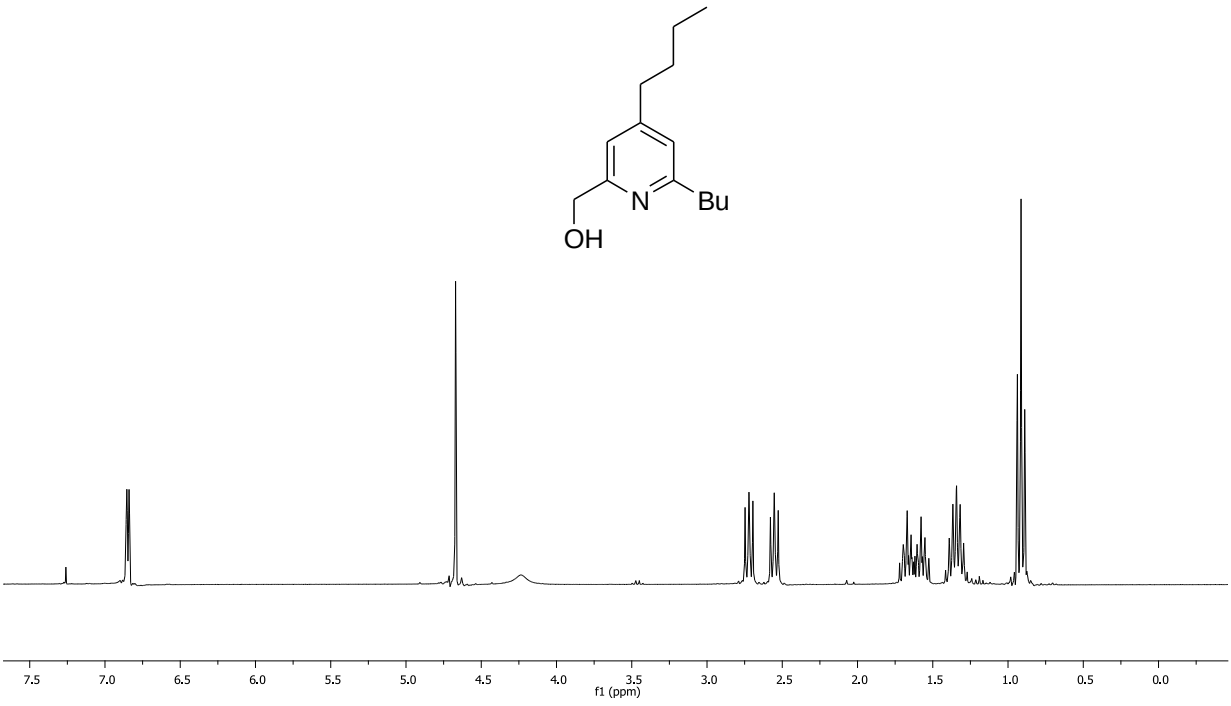
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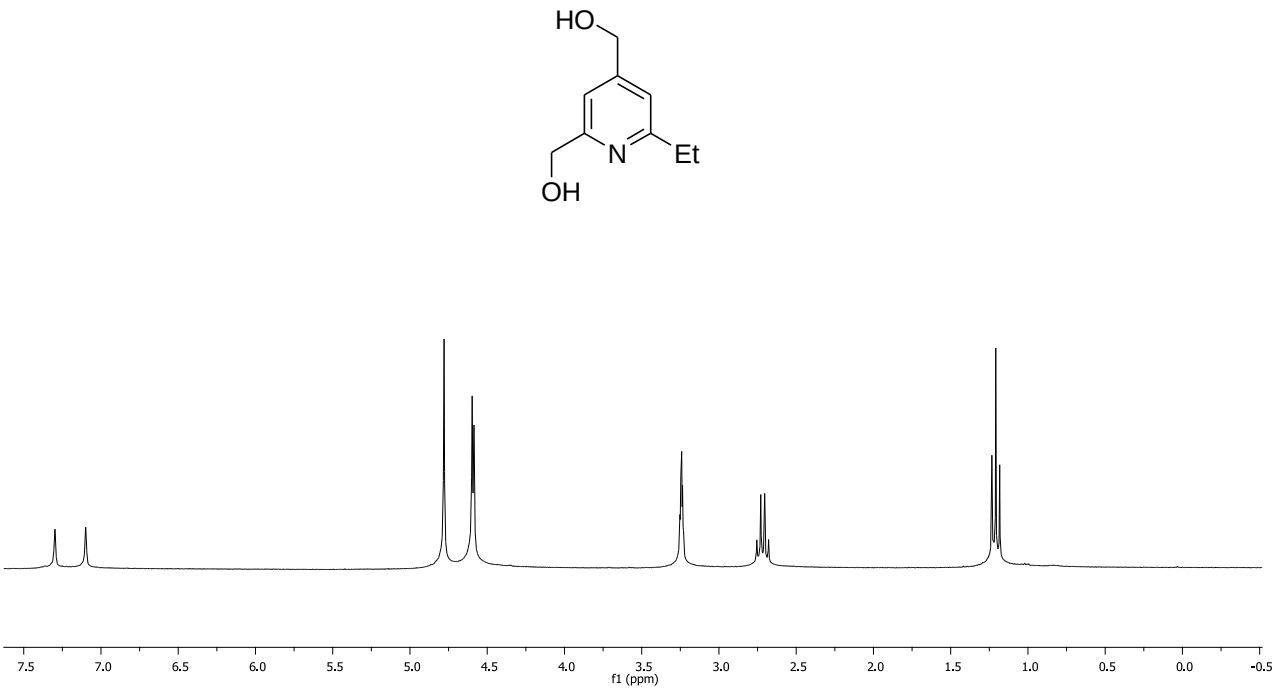
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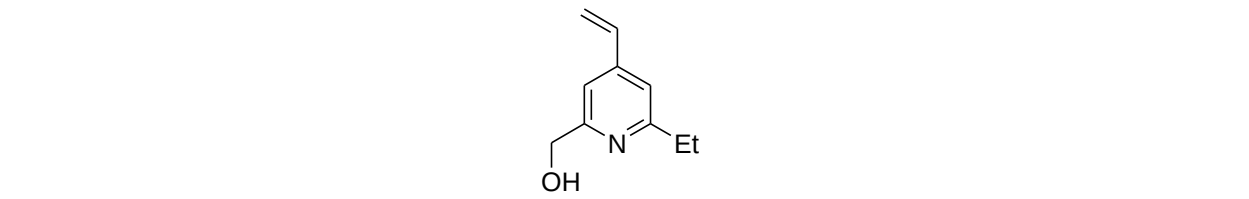
f1 (ppm)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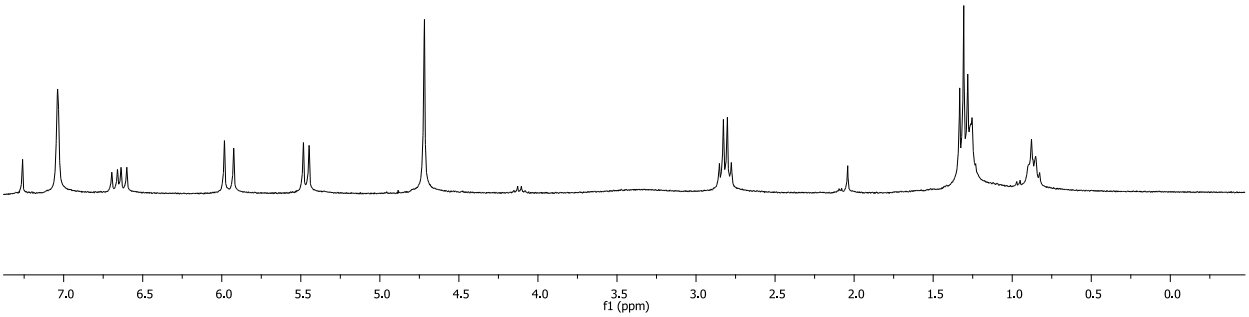
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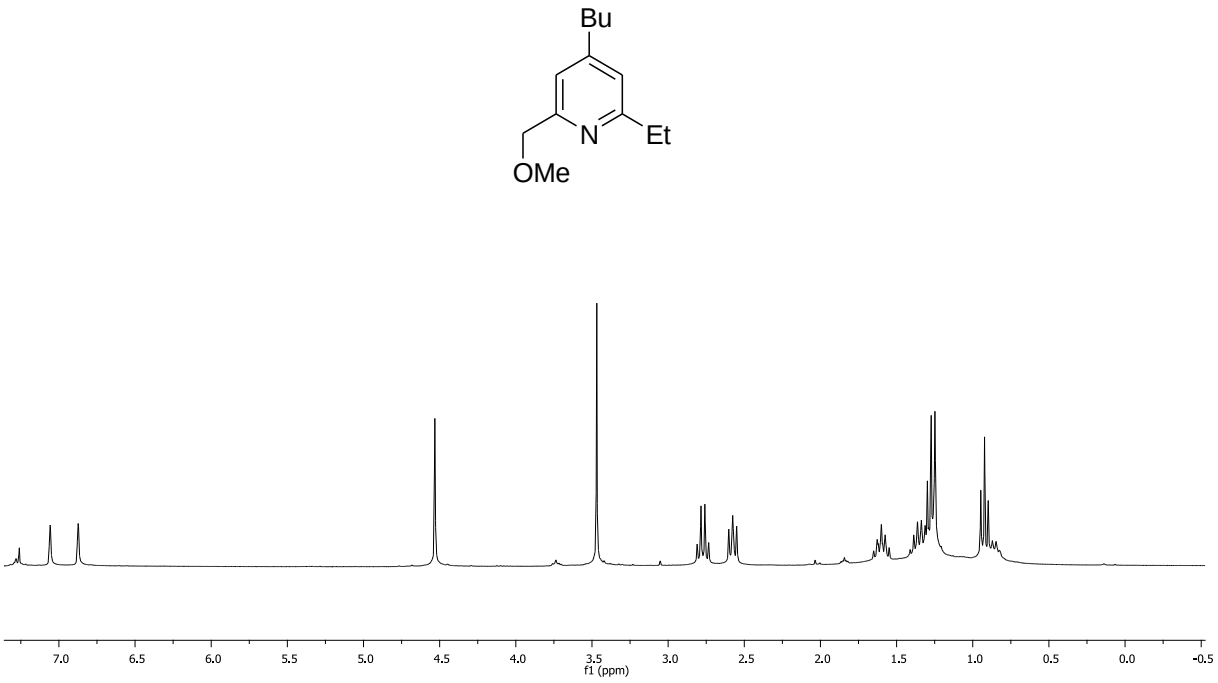
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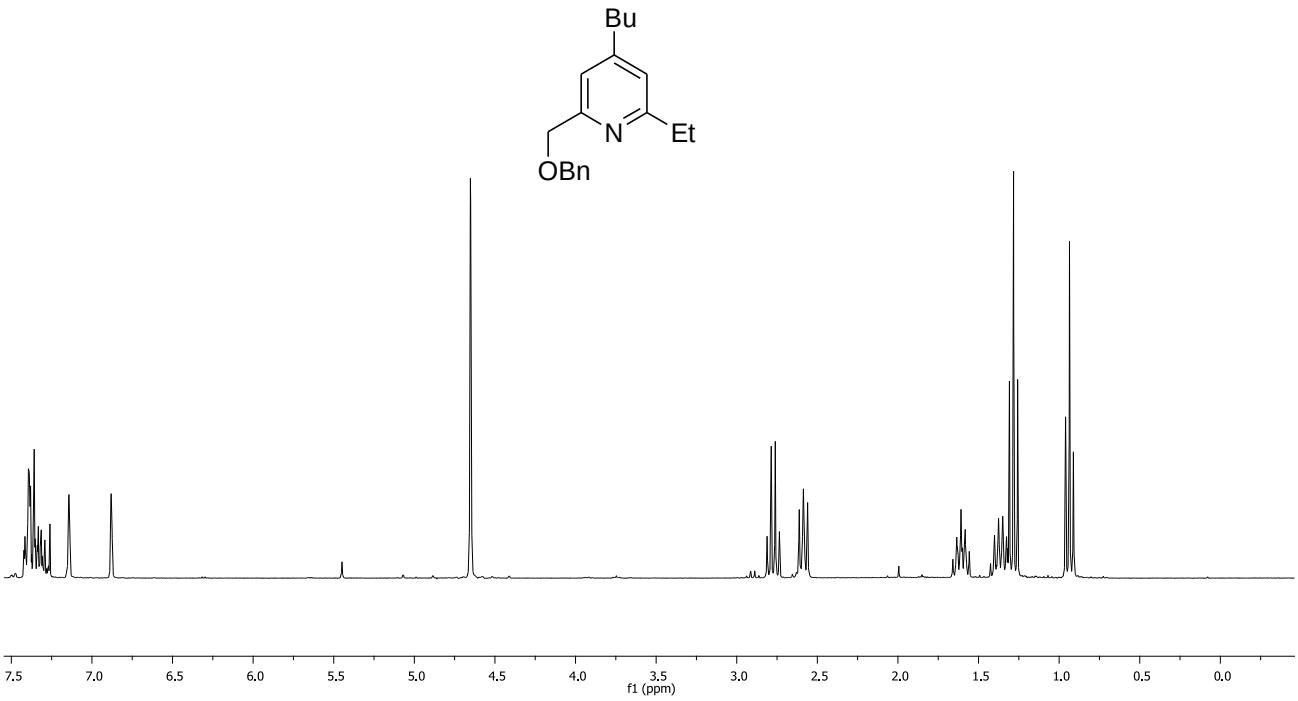
f1 (ppm)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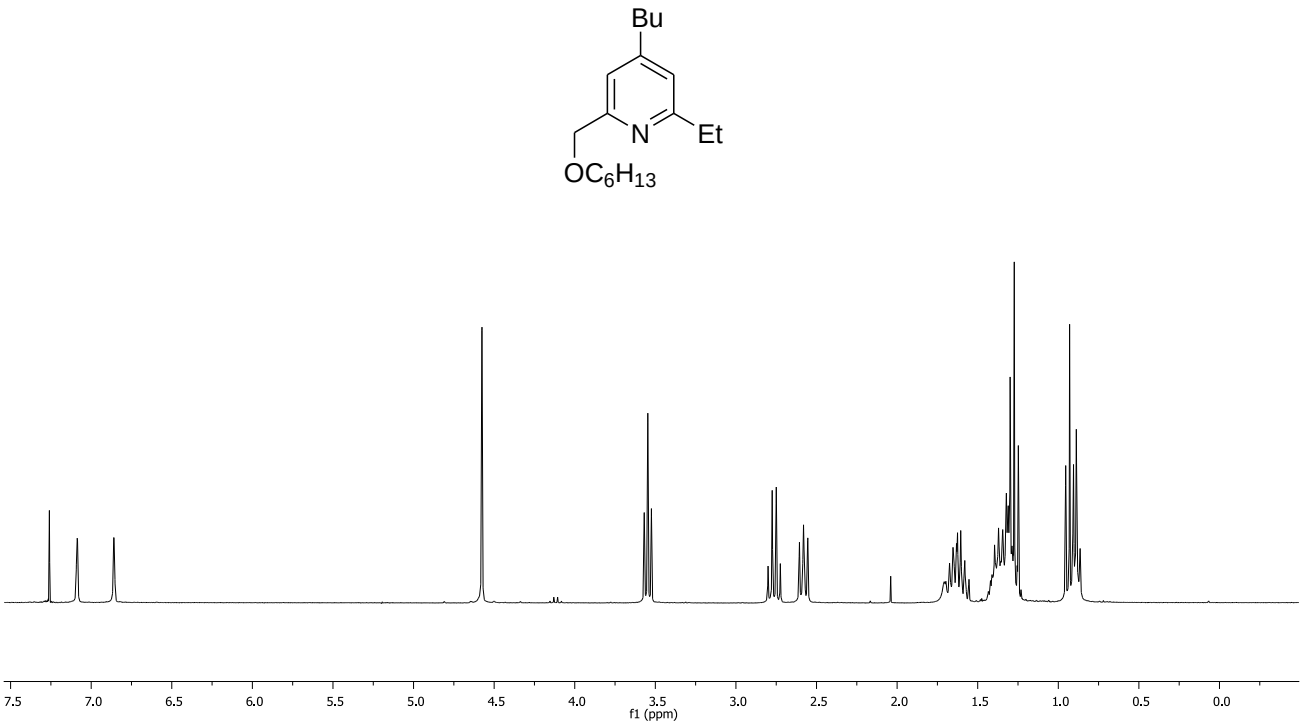
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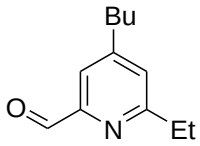
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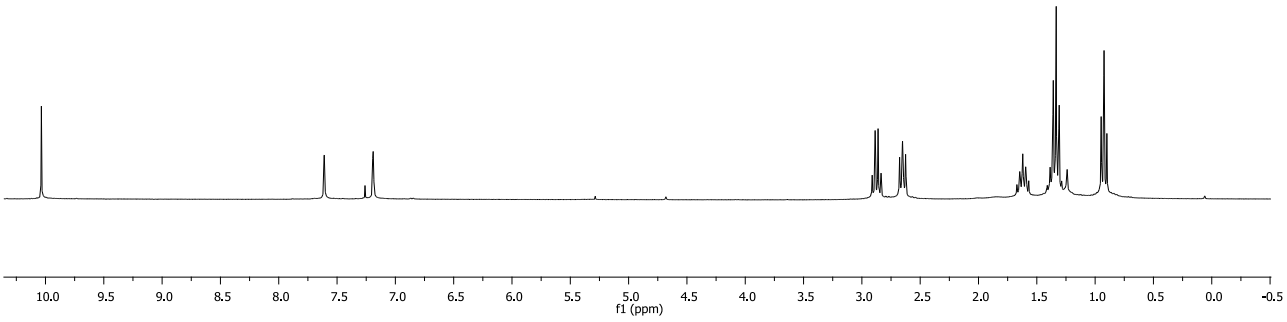
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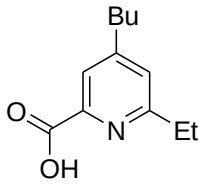
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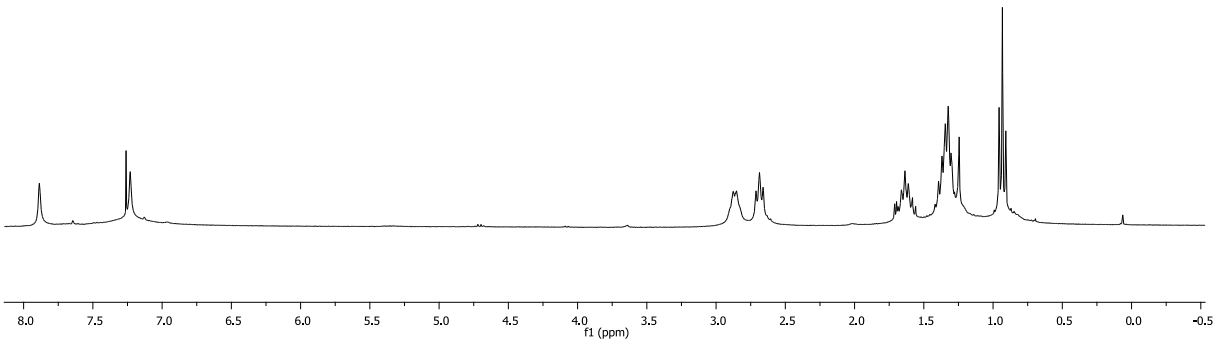
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f1 (ppm)