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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses

Synthesis and Use of a Trifluoromethylated Azomethine Ylide Precursor: Ethyl 1-Benzyl-*trans*-5-(trifluoromethyl)pyrrolidine-3-carboxylate

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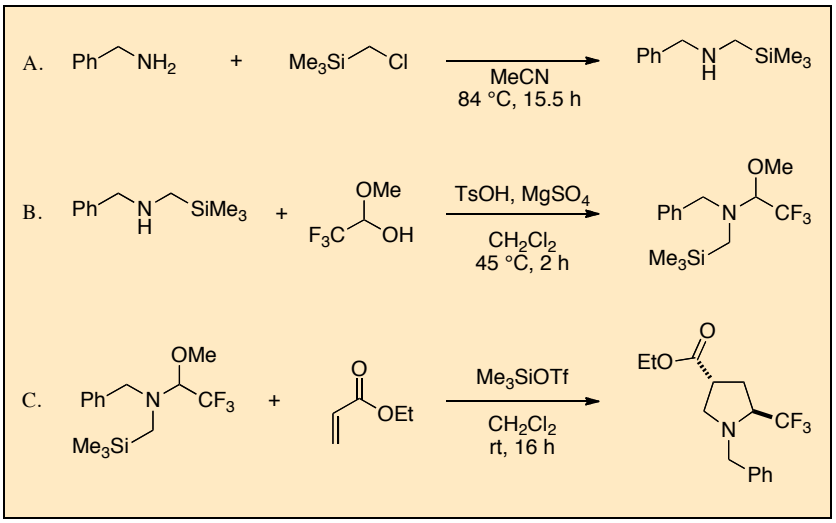

Procedure

A. *N-Benzyl-1-(trimethylsilyl)methanamine.*[2] A dry 2-L, three-necked, round-bottomed flask equipped with a 7.5-cm Teflon-coated magnetic stir bar, a rubber septum, an internal thermometer and a reflux condenser fitted with a nitrogen inlet (Note 1, Note 2) is charged with acetonitrile (500 mL). The stirring is started and benzylamine (43.7 mL, 42.9 g, 400 mmol, 2.0 equiv) is added *via* syringe, followed by (chloromethyl)trimethylsilane

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(27.9 mL, 24.5 g, 200 mmol, 1.0 equiv) *via* syringe over 5 min (Note 3). The mixture is heated on a 2000-mL hemispherical Glas-Col heating mantle using a J-Kem temperature controller until an internal reaction temperature of 84 °C is achieved (ΔT = 95 °C per hour, 40 min total time). After 20 min at this temperature, the mixture begins to precipitate a white crystalline solid (Note 4). The reaction is maintained at this temperature for 15.5 h and is monitored by TLC analysis on silica gel with 20% EtOAc/hexanes as eluent and visualization with acidic ammonium molybdate and ultraviolet radiation (254 nm) (Note 5). The benzylamine starting material has R_f = 0.00–0.21 (blue, UV active), while the product has R_f = 0.08–0.40 (weak to no stain, UV active).

The reaction is cooled to room temperature by allowing reaction mixture to cool slowly over 90 min, vacuum filtered through a one-half inch pad of Celite on a 60 mL medium porosity sintered filtration funnel and rinsed with 100 mL of hexane before being concentrated by rotary evaporation (35 °C, 75 mmHg) to a volume of *ca*. 100 mL (Note 6). The resulting liquid is suspended between hexane (250 mL) and water (250 mL) and transferred to a 1-L separatory funnel. The organic phase is removed and the aqueous phase is extracted with hexane (2 × 250 mL). The combined organic phases are washed with saturated aqueous sodium chloride (100 mL), dried over anhydrous magnesium sulfate (*ca* 20 g) and filtered through a one-half inch pad of Celite on a 60 mL medium porosity glass filtration funnel. The solvent is removed by rotary evaporation (35 °C, 15 mmHg) leaving a pale yellow liquid, which is transferred to a 50-mL one-neck round-bottomed flask and purified by fractional vacuum distillation (bp 84–94 °C/5 mmHg) over a still head apparatus featuring a 6-cm water-cooled condenser set at 4 °C, a ground glass joint thermometer and a cow collection adapter to give *N*-benzyl-1-(trimethylsilyl)methanamine (21.0–26.1 g, 54–67%) as a colorless liquid (Notes 7 and 8).

B. *N-Benzyl-2,2,2-trifluoro-1-methoxy-N-((trimethylsilyl)methyl)ethan-1-amine.* A 250-mL, three-necked, round-bottomed flask equipped with a 3.5-cm Teflon-coated magnetic stirbar, a rubber septum, an internal thermometer and a reflux condenser fitted with a nitrogen inlet (Note 1) is charged with anhydrous magnesium sulfate (12.0 g, 100 mmol, 1.0 equiv) and *p*-toluenesulfonic acid (860 mg, 5.0 mmol, 0.05 equiv) *via* powder addition funnel followed by dichloromethane (45 mL) and trifluoroacetaldehyde methyl hemiacetal (41.9 mL, 52.0 g, 400 mmol, 4.0 equiv) *via* syringe (Note 9). The vessel is then heated on a 250-mL

hemispherical Glas-Col heating mantle using a J-Kem temperature controller until an internal reaction temperature of 55 °C was achieved (ΔT over 15 min). *N*-Benzyl-1-(trimethylsilyl) methanamine (21.9 mL, 19.3 g, 100 mmol, 1.0 equiv) is added dropwise *via* syringe over 10 min at 45 °C internal temperature. The suspension is maintained at this temperature for 2 h and is monitored by ^{1}H NMR (400 MHz, $CDCl_3$), observing the disappearance of a peak at 2.07 ppm, corresponding to the amine starting material. The reaction is cooled to room temperature by removal of the heating mantle, vacuum filtered through a one-half inch pad of Celite on a 30 mL medium porosity glass filtration funnel and rinsed with 50 mL of dichloromethane before being concentrated by rotary evaporation (50 °C, 15 mmHg) (Note 10). The resulting pale yellow liquid is dissolved in 5% EtOAc/hexane (1 mL per g) (Note 5) and applied to 200 g of Merck neutral alumina 90 packed in a 5-cm diameter column with a 2 cm sand layer on top. The product is eluted with 1 L of 5% EtOAc/hexane (Note 5) collecting 50 mL fractions to afford 23.9-24.3 g, (78-80%) of a colorless liquid, consisting mainly (78-81%) of *N*-benzyl-2,2,2-trifluoro-1-methoxy-*N*-((trimethylsilyl)methyl)ethan-1-amine, which is sufficiently pure for further synthetic use (Note 11).

An analytically pure sample may be prepared *via* flash column chromatography by dissolving the crude liquid in 1% EtOAc/hexanes (1 mL per g) (Note 5) and applying it to Sigma-Aldrich Merck grade 9385 60 Å (230-400 mesh) silica gel (10 g per g of crude material) packed in a 10-cm diameter column with a 2 cm sand layer on top. The product is eluted with 1% EtOAc/hexanes (Note 5) to afford *N*-benzyl-2,2,2-trifluoro-1-methoxy-*N*-((trimethylsilyl)methyl) ethan-1-amine as a colorless liquid (bp 100–104 °C/5 mmHg) (Note 12).

C. *Ethyl 1-benzyl-trans-5-(trifluoromethyl)pyrrolidine-3-carboxylate.* A 250-mL three-necked round-bottomed flask equipped with a 3.5-cm Teflon-coated magnetic stirbar, a rubber septum, internal thermocouple and a nitrogen inlet (Note 1) is charged with dichloromethane (105 mL). *N*-Benzyl-2,2,2-trifluoro-1-methoxy-*N*-((trimethylsilyl)methyl)ethan-1-amine (12.8 g, 41.9 mmol, 1.2 equiv) and ethyl acrylate (3.8 mL, 3.5 g, 35.0 mmol, 1.0 equiv) are then added *via* syringe. Trimethylsilyl trifluoromethanesulfonate (1.3 mL, 1.6 g, 7.0 mmol, 0.2 equiv) is added dropwise *via* syringe (Note 13). The reaction is stirred at room temperature for 16 h and is monitored by TLC analysis on silica gel with 5% EtOAc/hexane as eluent and visualization with potassium permanganate (Note 4). The hemiaminal starting material has R_f = 0.75 (yellow), while the

product has R_f = 0.31 (yellow). The reaction is quenched at room temperature by addition of saturated aqueous $NaHCO_3$ (100 mL) from a measuring cylinder and is transferred to a 500-mL separatory funnel (Note 14). The organic phase is removed and the aqueous phase is extracted with dichloromethane (2 × 100 mL). The combined organic phases are dried over anhydrous magnesium sulfate (*ca* 10 g) and filtered through a one-half inch pad of Celite on a 30 mL medium porosity glass filtration funnel (Note 10). The solvent is removed by rotary evaporation (35 °C, 15 mmHg) leaving a pale yellow liquid which is dissolved in 1% EtOAc/hexane (1 mL per g) (Note 5) and applied to 500 g of Sigma-Aldrich Merck grade 9385 60 Å (230-400 mesh) silica gel packed in a 10-cm diameter column. The product is eluted with 2 L of 1% EtOAc/hexanes followed by 5 L of 2% EtOAc/hexane (Note 5) to afford ethyl 1-benzyl-*trans*-5-(trifluoromethyl) pyrrolidine-3-carboxylate (3.54–4.93 g, 34–47%) as a colorless liquid (bp 104–108 °C/5 mmHg) (Notes 15, 16 and 17).

Notes

1. All glassware is oven-dried at 200 °C overnight and allowed to cool to ambient temperature under nitrogen, which is maintained throughout the course of the reaction.
2. A glass inlet is recommended. Use of a septum and needle resulted in corrosion of the needle and incorporation of red color in the reaction mixture, due to evolution of hydrochloric acid during the reaction.
3. Water content in acetonitrile (EMD, HPLC grade, 99.9%) was measured by Karl Fisher titration prior to use, found to contain 50-80 ppm water, and was used as received. Benzylamine (99.5+%) was obtained from Sigma-Aldrich and used as received. Chloromethyltrimethylsilane (98%) was obtained from Oakwood Products Inc. and used as received.
4. Agitation must be sufficient to prevent precipitated solids from sticking to internal thermocouple. Significant aggregation of solids was found to result in overall lower yield (64-70% crude weight-adjusted yield as measured by Quantitative-NMR versus benzyl benzoate internal standard).
5. Hexane (Sigma-Aldrich, HPLC >98.5%) and EtOAc (Sigma-Aldrich, anhydrous 99.8%) were used as received with no further purification.

6. Celite 545 filter agent (Sigma-Aldrich) wetted with *ca.* 20 mL hexane prior to filtration.
7. Distillation was performed by warming the reaction mixture using a bath composed of Aluminum beads at bath temperature of 130–170 °C; the collection flasks were cooled to 0 °C. Desired product was observed to distill at head temperature of 84–94 °C; residual solvent (hexane) was observed in early fractions and was discarded. The distillation was stopped after six hours, leaving some residual product behind (7-12% by Quantitative-NMR versus benzyl benzoate internal standard, observed in all experiments). Total isolated yield is variable, dependent on apparatus and total distillation time.
8. The compound displays the following physical and spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 9 H), 1.17 (br, 1 H), 2.07 (s, 2 H), 3.82 (s, 2 H), 7.24–7.28 (m, 1 H), 7.31–7.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –2.6, 39.5, 58.1, 126.8, 128.1, 128.3, 140.6; FTIR (neat, υ_{max} cm^{-1}) 3028 (w), 2954 (w), 2894 (w), 2780 (w), 1490 (w), 1450 (m), 1355 (w), 1250 (s), 1181 (w), 1102 (w), 1075 (w), 1030 (w), 850 (s), 836 (s), 765 (w), 734 (s), 694 (s), 670 (w); R_f 0.10–0.40 (20% EtOAc/hexane); HRMS (ESI+) calculated for $C_{11}H_{20}NSi$ $[M+H]^+$ 194.1365, found 194.1364. Anal. Calcd. for $C_{11}H_{19}NSi$: C 68.33, H 9.90, N 7.24, Si 14.52; found C 68.29, H 9.87, N 7.17, Si 14.47.
9. Dichloromethane (Sigma-Aldrich, HPLC grade ≥99.9%) was measured by Karl Fisher titration prior to use, found to contain <50 ppm water, and was used as received. Trifluoroacetaldehyde methyl hemiacetal (technical grade, >90% by ^{1}H NMR) was purchased from Oakwood Products Inc. and was used as received. *p*-Toluenesulfonic acid monohydrate (>98.5%) was purchased from Sigma-Aldrich and was dried by Dean-Stark azeotropic distillation in toluene prior to use (after treatment, contains 1.7% water by Karl Fisher titration using Metrohm KF oven). Magnesium sulfate (laboratory reagent grade) was purchased from Fisher scientific and dried in an oven at 200 °C overnight prior to use (after treatment, contains <0.1% water by dry Karl Fisher titration using Metrohm KF oven).
10. Celite 545 filter agent (Sigma-Aldrich) wetted with *ca.* 5 mL dichloromethane prior to filtration.
11. Submitters isolated higher purity product (>90%) in overall lower yield (65-71%) indicating variability in retained versus discarded fractions and efficiency of chromatography. Crude weight-adjusted reaction

yield is 69-75% as measured by Quantitative-NMR analysis versus benzyl benzoate internal standard.

12. Purification on silica gel gives analytically pure product, but lower recovery of material (less than can be accounted for by simply removing the impurities), suggesting that the compound may be unstable to silica chromatography. The product proved intractable to distillation and co-distills with byproducts observed in the crude material. The compound displays the following physical and spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 9 H), 2.30 (d, *J*=15.1 Hz, 1 H), 2.38 (d, *J* = 15.1 Hz, 1 H), 3.48 (s, 3 H), 3.81 (d, *J* = 13.9 Hz, 1 H), 3.94 (d, *J* = 13.9 Hz, 1 H), 4.15 (qd, *J* = 5.7, 1.5 Hz, 1 H), 7.28–7.31 (m, 1 H), 7.33–7.37 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –1.4, 40.0, 56.4, 57.6, 89.5 (q, *J* = 30.4 Hz), 124.1 (q, *J* = 290.0 Hz), 127.3, 128.5, 128.7, 138.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –76.0 referenced externally to CF_3-toluene; the submitters report a chemical shift of –73.3 ppm; FTIR (neat, υ_{max} cm^{-1}) 2954 (w), 2830 (w), 1490 (w), 1455 (w), 1373 (w), 1268 (m), 1245 (m), 1150 (s), 1121 (s), 1089 (s), 1071 (s), 1024 (w), 990 (w), 968 (w), 837 (s), 763 (w), 739 (m), 721 (w), 697 (s); R_f 0.75 (5% EtOAc/hexanes); HRMS (ESI+) calculated for $C_{14}H_{23}NOF_3Si$ $[M+H]^+$ 306.1501, found 306.1515. Anal. Calcd. for $C_{14}H_{22}NOF_3Si$: C 55.06, H 7.26, N 4.59, F 18.66, Si 9.20; found C 54.82, H 6.98, N 4.78, F 17.83, Si 9.14.
13. Dichloromethane (Sigma-Aldrich, HPLC grade ≥99.9%) was measured by Karl Fisher titration prior to use, found to contain <50 ppm water, and was used as received. Ethyl acrylate (99% with 10-20 ppm MEHQ as inhibitor) was obtained from Sigma-Aldrich and was used as received. Trimethylsilyl trifluoromethanesulfonate (99%) was obtained from Fluka (Sigma-Aldrich) and was used as received.
14. During quench with aqueous sodium bicarbonate a small exotherm was observed, reaching maximum temperature of 23 °C.
15. Weight-adjusted crude yield before chromatography is 5.17-6.67 g (49-64%) as measured by Quantitative-NMR versus benzyl benzoate internal standard. Submitters' isolated yield was 5.01-5.48 g (47-52%).
16. After using 5 L of 2% EtOAc/hexane, impure fractions containing product continued to elute from the chromatography column. Discrepancies in yield may be due to variability in discarded versus retained fractions, or due to the volatility of the desired product.
17. A small fraction of the desired product is recovered as a mixture with other diastereo-/regio-isomers, which may be re-purified to improve the isolated yield. The isomers form in a 30:5:5:1 ratio (2,4 anti : 2,4 syn :

2,3 anti : 2,3 syn) as previously reported.[3] The compound displays the following physical and spectral properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, *J* = 7.1 Hz, 3 H), 2.23 (ddd, *J* = 13.4, 7.9, 2.9 Hz, 1 H), 2.35 (m, 1 H), 2.59 (app t, *J* = 9.3 Hz, 1 H), 3.13 (m, 1 H), 3.20 (app t, *J* = 7.7 Hz, 1 H), 3.45 (dqd, *J* = 10.3, 7.0, 3.1 Hz, 1 H), 3.64 (d, *J* = 13.3 Hz, 1 H), 4.13 (app qd, *J* = 7.1, 2.1 Hz, 2 H), 4.20 (d, *J* = 13.2 Hz, 1 H), 7.28 (t, *J* = 4.2 Hz, 1 H), 7.33–7.34 (app d, *J* = 4.5 Hz, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 29.4 (q, *J* = 2.0 Hz), 42.2, 56.2, 59.5, 60.9, 63.2 (q, *J* = 29.4 Hz), 126.8 (q, *J* = 280.3 Hz), 127.3, 128.4, 128.5, 138.4 (C4), 173.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ: –78.8 (CF_3); FTIR (neat, υ_{max} cm^{-1}) 2980 (w), 2814 (w), 1730 (s), 1455 (w), 1390 (w), 1373 (w), 1279 (m), 1139 (s), 1110 (m), 1028 (m), 925 (w), 860 (w), 742 (m), 699 (s); R_f 0.47 (10% EtOAc/hexanes); HRMS (ESI+) calculated for $C_{15}H_{19}NO_2F_3$ $[M+H]^+$ 302.1368, found 302.1378. Anal. Calcd. for $C_{15}H_{18}NO_2F_3$: C 59.79, H 6.02, F 18.92, N 4.65, found C 59.53, H 5.95, F 19.80, N 4.79.

Handling and Disposal of Hazardous Chemicals

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Discussion

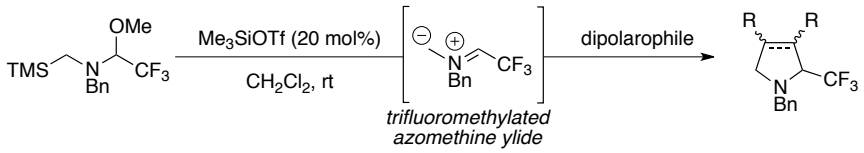
The introduction of fluorine into molecular scaffolds targeted by the pharmaceutical, agrochemical and materials chemistry sectors can confer

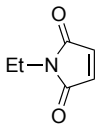
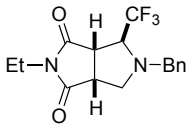
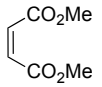
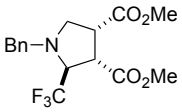
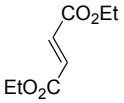
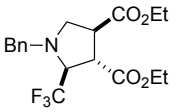
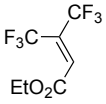
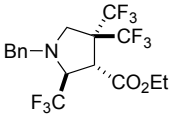
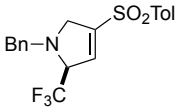
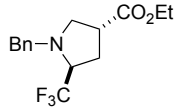
superior property profiles compared to their non-fluorous congeners.[4] The unison of methods generating rapid complexity with simple fluorinated starting materials is a strategy that offers the potential to deliver interesting building blocks.[5] Furthermore, the presence of fluorine in such complexity-generating reactions provides an interesting means to control chemo-, regio-, diastereo- and even enantioselectivities through steric and electronic effects.

With regard to azomethine ylides[6] bearing a trifluoromethyl group, few approaches are known. Those that are present in the literature are generally not shown to be broad of scope and suffer from longevity of starting material preparation. Meffert reports trapping of a geminally disubstituted trifluoromethylated azomethine ylide derived from a parent azlactone with dimethylacetylenedicarboxylate.[7] Tanaka *et al* report a thermal ring opening/1,3 dipolar cycloaddition approach from acyl-trifluoromethylated aziridines. [8] While Viehe assessed 1,3 dipolar cycloadditions of ylides derived from trifluorothioacetamides;[9] a process which Domingo later studied computationally.[10]

The ylide precursor reported here is prepared in a straightforward fashion in two synthetic steps from bulk, readily available starting materials. Furthermore it has been shown to perform well in cycloaddition reactions with a set of dipolarophiles that are typically used in these types of processes, including mono-, di- and tri-substituted alkenes, alkynes and diimides. Seemingly, the CF_3 group helps impart useful levels of regio- and diastereo-control, with a clear preference for the least sterically encumbered transition state; leading to the 2,4 anti pyrrolidines and 2,4 substituted 3-pyrrolines as the major isomers which are generally isolable from the mixture by flash column chromatography.[2]

Table 1. Examples of the substrate scope of 1,3 dipolar cycloaddition reactions using the trifluoromethylated azomethine ylide

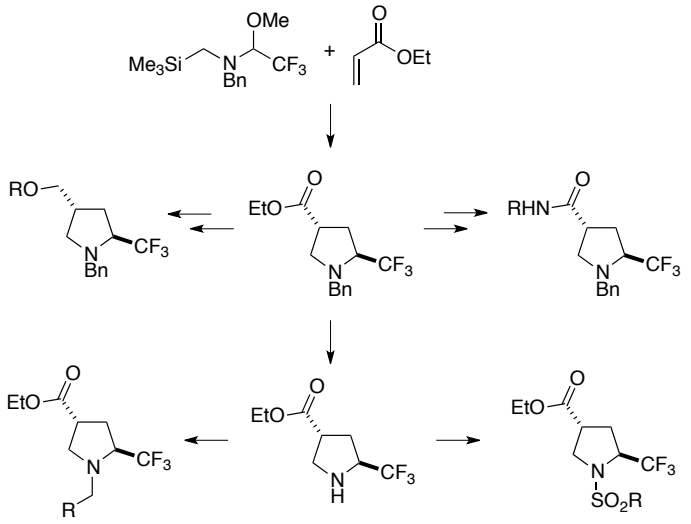


dipolarophile	major product	yields and selectivities
		83% yield *1 diastereomer*
		83% yield 1 diastereomer
		74% yield 6:1 dr
		65% yield 1 regioisomer 22:1 dr
		74% yield 7:2 regioselectivity
		58% yield 6:1 regioselectivity 30:5:5:1 dr

yield corresponds to clean samples of major isomers shown
dr reported as *2,4* anti: *2,4* syn: *2,3* anti: *2,3* syn

The cycloadducts may be *N*-debenzylated without incident and the 3-pyrrolines oxidized to the corresponding pyrroles with manganese dioxide. The ester described herein is also synthetically versatile, undergoing hydrolysis, reduction and hydrogenolysis under standard conditions in high yields. The adducts may be further functionalized using standard procedures for amide coupling, tosylation/displacement, reductive

amination and sulfonylation chemistry in high yield and without erosion of relative stereochemistry.[11]



Scheme 1. Synthetic uses of ethyl 1-benzyl-*trans*-5-(trifluoromethyl) pyrrolidine-3-carboxylate[11]

References

1. Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK, CB2 1EW. e-mail: dma33@cam.ac.uk. DMA acknowledges financial support from Pfizer.
2. This is an adaptation of a procedure reported by Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526–2529.
3. Tran, G.; Meier, R.; Harris, L.; Browne, D. L.; Ley, S. V. *J. Org. Chem.* **2012**, *77*, 11071–11078.
4. (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (b) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589. (c) Kirsch P.; Bremer, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4216–4235.
5. (a) Wilson, P. G.; Percy, J. M.; Redmond, J. M.; McCarter, A. W. *J. Org. Chem.* **2012**, *77*, 6384–6393. (b) Kyne, S. H.; Percy, J. M.; Pullin, R. D. C.; Redmond, J. M.; Wilson, P. G. *Org. Biomol. Chem.* **2011**, *9*, 8328–8339. (c)

Audouard, C.; Garayt, M. R.; Kérourédan, E.; Percy, J. M.; Yang, H. *J. Fluor. Chem.* **2005**, *126*, 609–621.
6. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–910. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2810. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484–4517.
7. Burger, K.; Meffert, A.; Bauer, S. *J. Fluor. Chem*. **1977**, *10*, 57–62.
8. Tanaka, K.; Nagatani, S.; Ohsuga, M.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 589–591.
9. (a) Laduron, F.; Ates, C.; Viehe, H. G. *Tetrahedron Lett.* **1996**, *37*, 5515–5518. (b) Laduron, F.; Viehe, H. G. *Tetrahedron* **2002**, *58*, 3543–3551.
10. Domingo, L. R. *J. Org. Chem.* **1999**, *64*, 3922–3929.
11. Allwood, D.M.; Ley, S.V., Unpublished results.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(Chloromethyl)trimethylsilane; (2344-80-1)
Benzenemethanamine; (100-46-9)
Benzenemethanamine, *N*-[(trimethylsilyl)methyl]-; (53215-95-5)
Ethanol, 2,2,2-trifluoro-1-methoxy-; (431-46-9)
Benzenesulfonic acid, 4-methyl-; (104-15-4)
Sulfuric acid magnesium salt (1:1); (7487-88-9)
Benzenemethanamine, *N*-(2,2,2-trifluoro-1-methoxyethyl)-*N*-[(trimethylsilyl)methyl]; (1415606-26-6)
2-Propenoic acid, ethyl ester; (140-88-5)
Methanesulfonic acid, 1,1,1-trifluoro-, trimethylsilyl ester; (27607-77-8)
3-Pyrrolidinecarboxylic acid, 1-(phenylmethyl)-5-(trifluoromethyl)-, ethyl ester, (3*R*,5*S*)-*rel*-; (1415606-48-2)

Steven V. Ley received his PhD from Loughborough University in 1972, after which he carried out post-doctoral research with Professor Leo Paquette at Ohio State University, followed by Professor Derek Barton at Imperial College London. In 1975, he joined that Department as a lecturer and became Head of Department in 1989. In 1992, he moved to the 1702 BP Chair of Organic Chemistry at the University of Cambridge and became a Fellow of Trinity College. He was elected to the Royal Society in 1990 and was President of the Royal Society of Chemistry (RSC) 2000-02. Steve has been the recipient of many prizes and awards including the Yamada-Koga Prize, Nagoya Gold Medal, ACS Award for Creative Work in Synthetic Organic Chemistry and the Paul Karrer Medal.

Daniel M. Allwood was born in 1986 in Mansfield, England. He completed his undergraduate degree in chemistry at the University of Warwick in 2008. Following this, he joined Prof. Steven V. Ley's group at the University of Cambridge as a Ph.D. student, where he worked on the design, biological evaluation and asymmetric synthesis of novel non-peptidomimetic XIAP inhibitors. Currently, he is a postdoctoral research associate in the Ley group, investigating various areas of synthetic methodology.

Duncan L. Browne was born in 1983 in Dunstable, England. He graduated with a Masters degree in chemistry in 2006 from the University of Sheffield and with a Ph.D. in Organic Synthesis in 2009 from the same institution (with Joseph P. A. Harrity). Following this, he was awarded a one year Doctoral Prize Fellowship from the EPSRC. In 2010 he moved to the ITC and Whiffen Laboratories at the University of Cambridge as a Postdoctoral Research Associate with Steven V. Ley, where he has been developing new flow chemistry tools, techniques and synthetic methods.

Hannah E. Peterlin is currently a fourth year student at Northeastern University working toward a B.S. degree in chemistry. She has participated in the cooperative education program through Northeastern and has held various positions within the field of chemistry. Her latest internship was in the Chemical Process R&D group at Amgen Inc. Upon graduation from Northeastern University, she plans to pursue a career in the pharmaceutical industry.

A native of Massachusetts, Neil Langille attended Rochester Institute of Technology, receiving his B.S. degree in Chemistry. He then pursued his Ph. D. at Boston University under the guidance of James Panek; his graduate research focused on hydrometalations and transition metal mediated cross-coupling reactions applied toward natural product synthesis. Following completion of his Ph.D. in 2005, Neil performed post-doctoral studies in Timothy Jamison's laboratory at MIT, applying cascade reactions toward natural product targets. In 2007, Neil joined the Chemical Process R&D department at Amgen in Cambridge, MA. Since joining Amgen, Neil has had the privilege of working on small molecule projects in oncology and neuroscience therapeutic areas.

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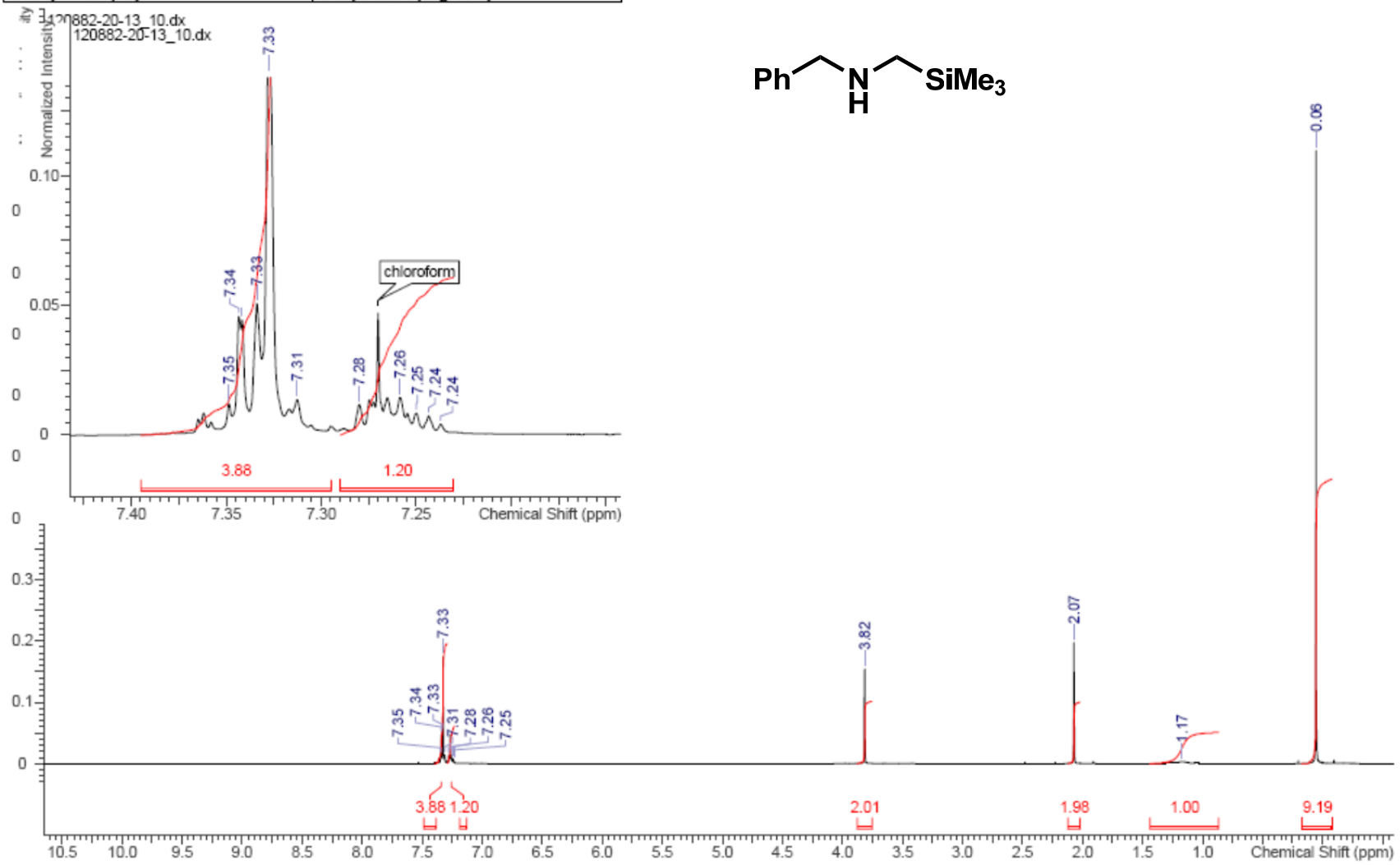

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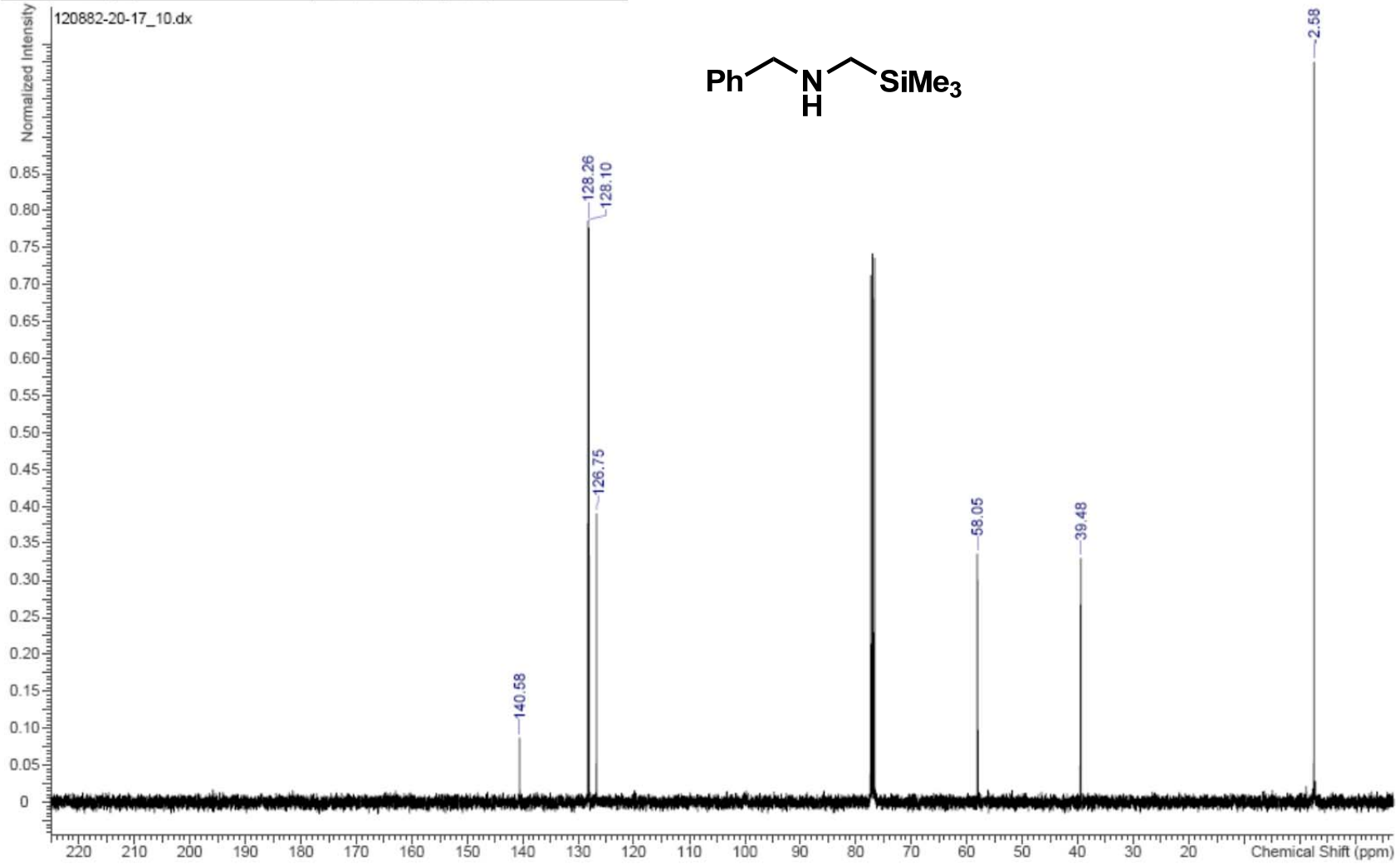

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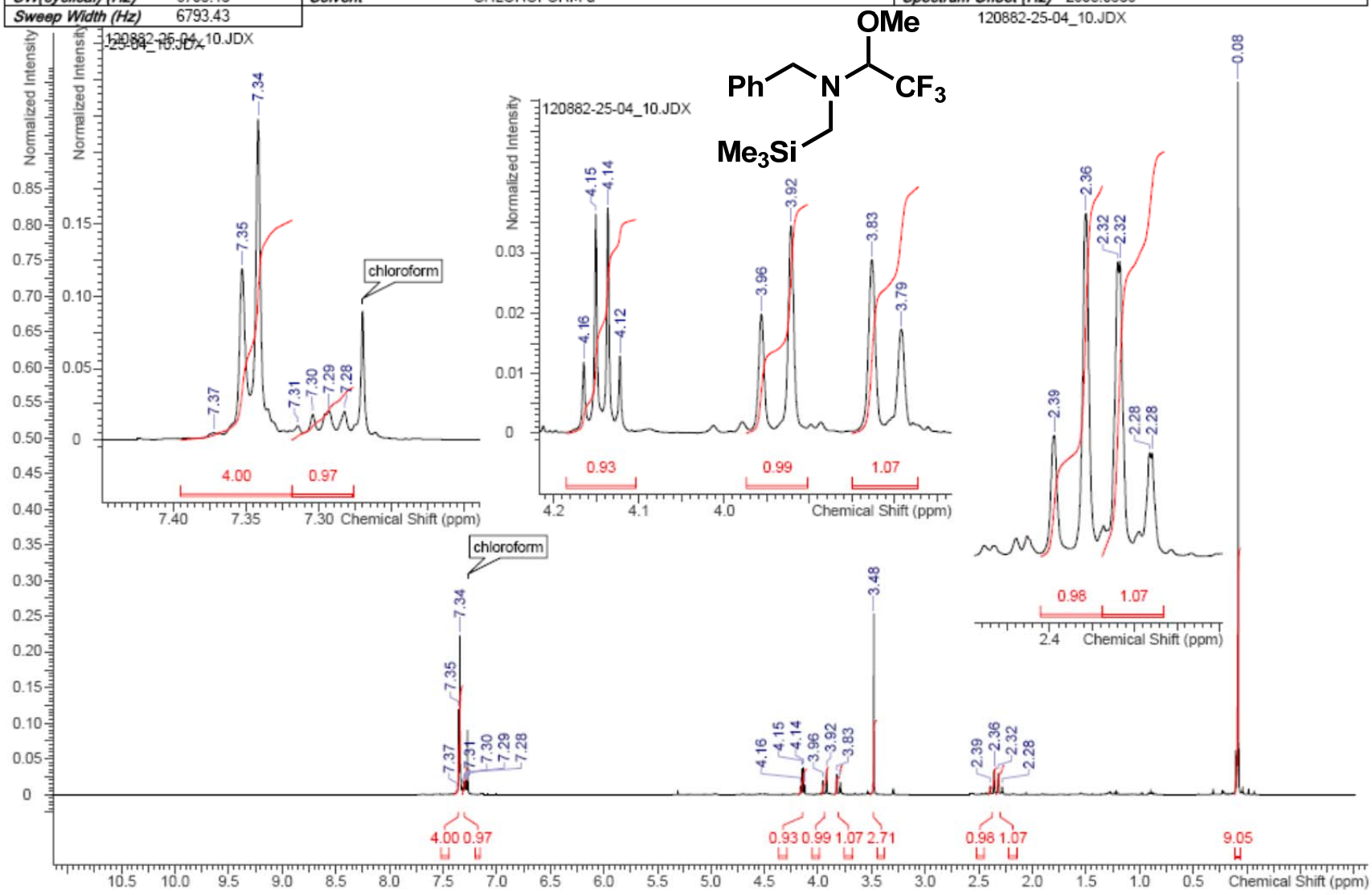

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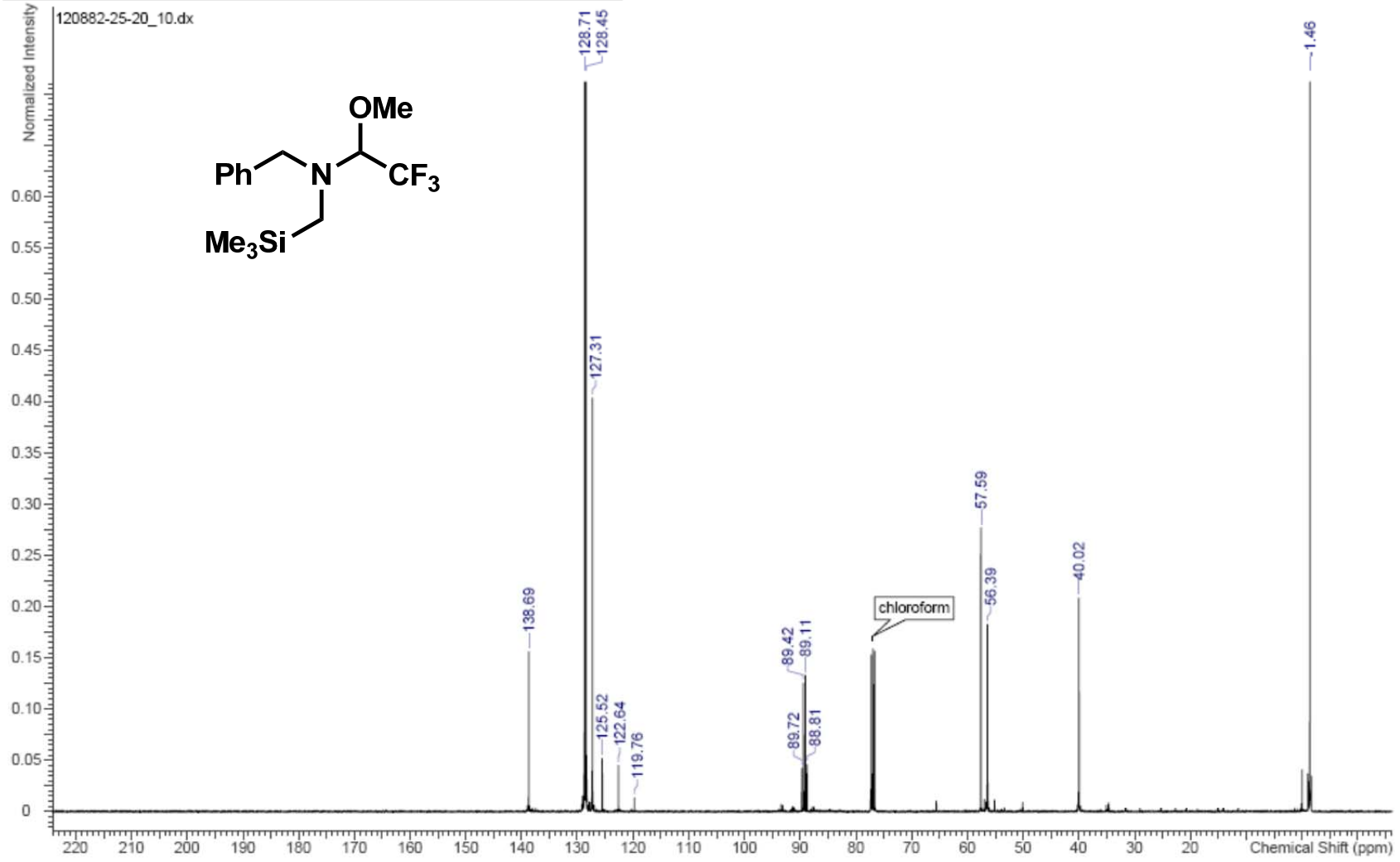

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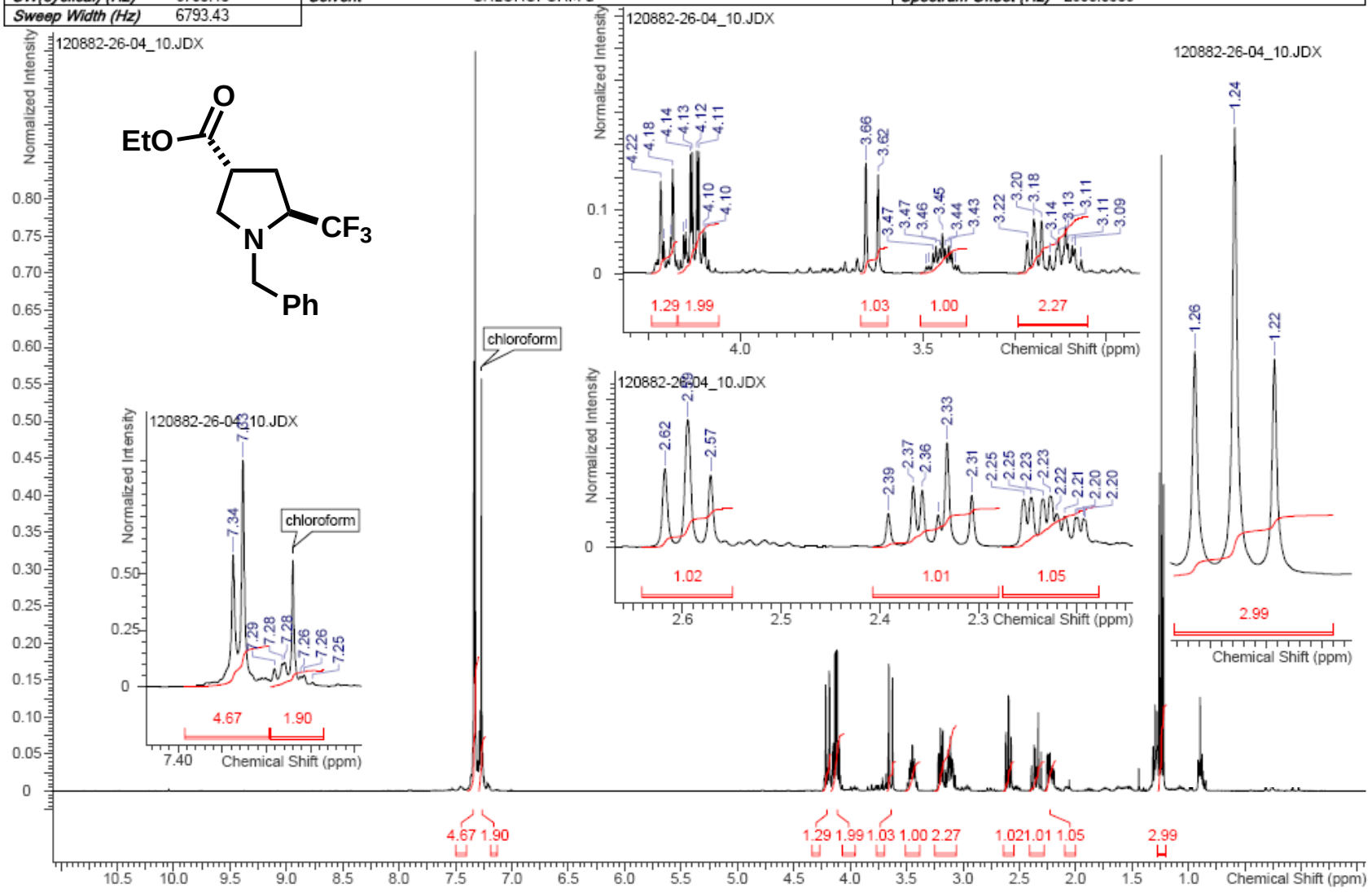

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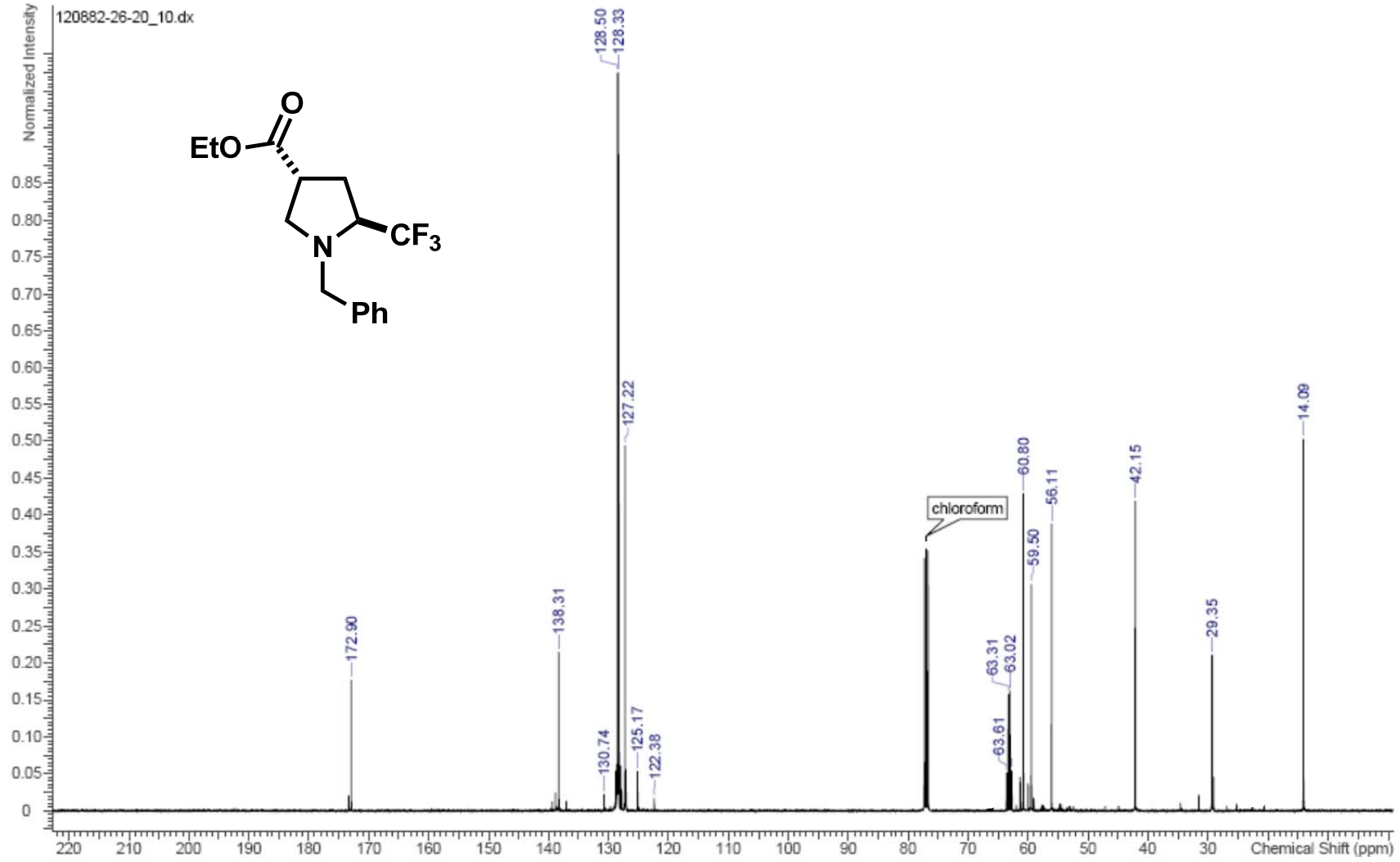

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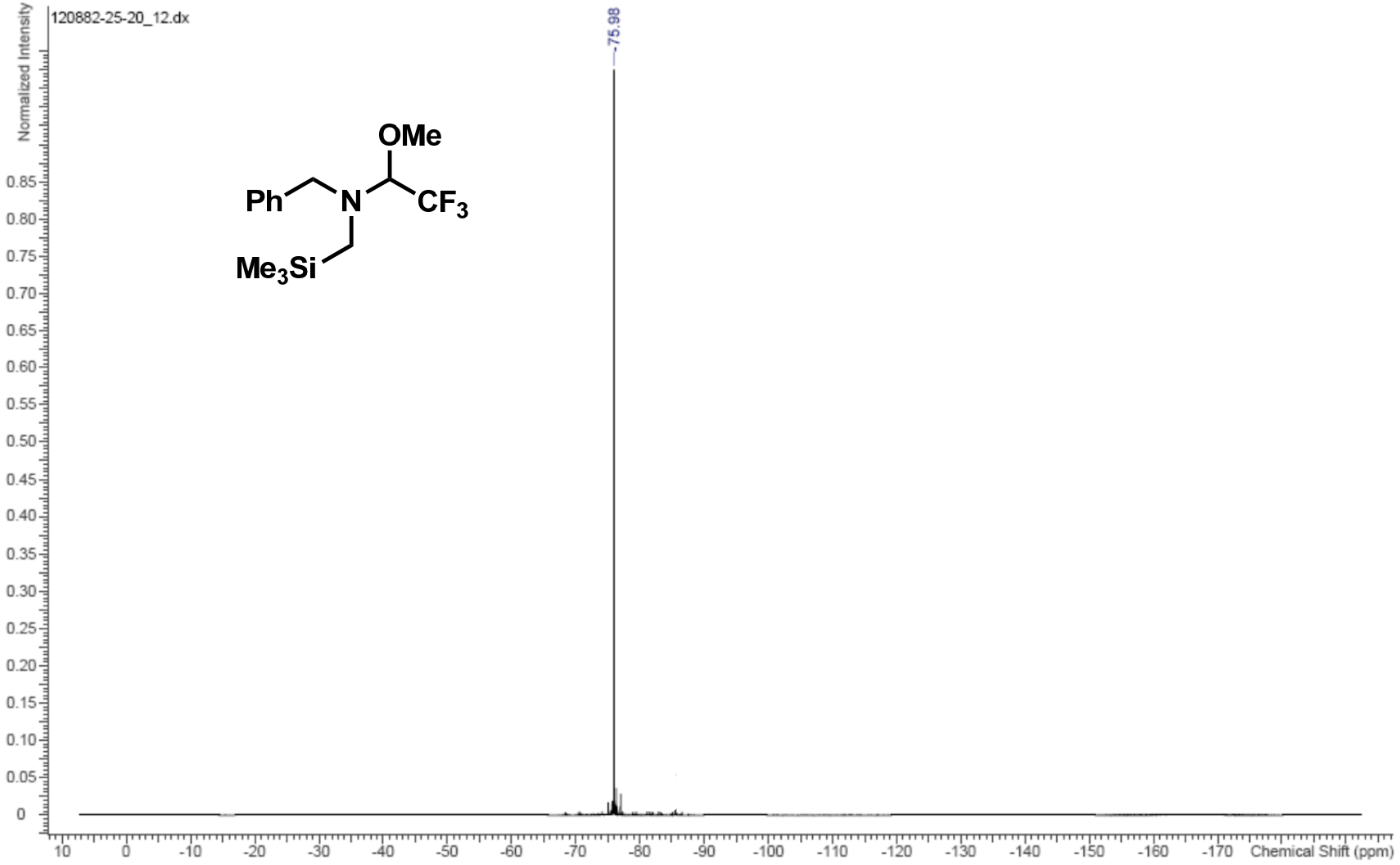

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