Organic Syntheses

Simplified Preparation of the (1*R*,2*S*)-Berkessel salalen Ligand from *cis*-1,2-Diaminocyclohexane (*cis*-DACH)

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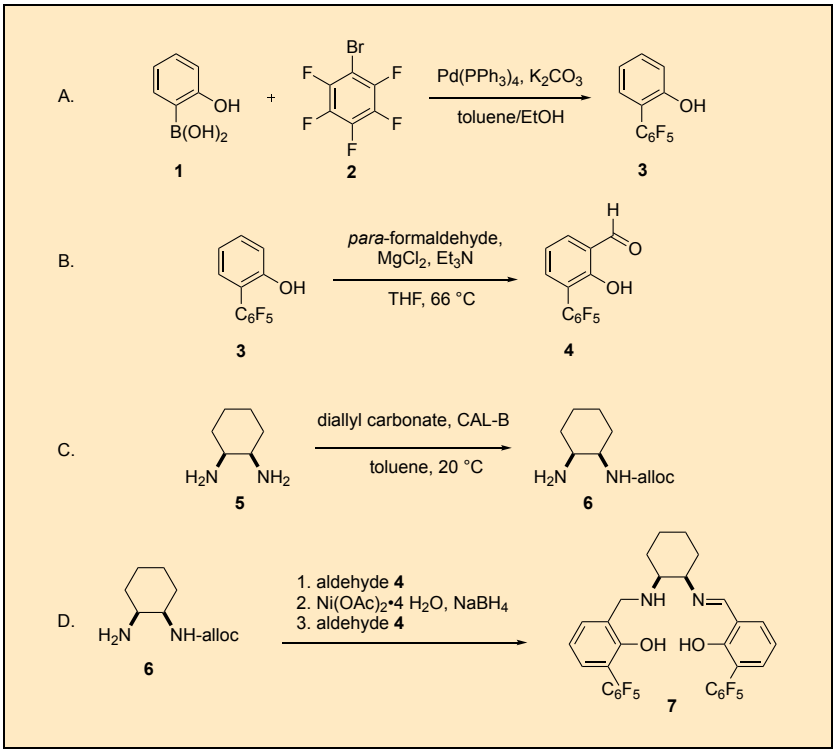

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Procedure (Note 1)

A. *2′,3′,4′,5′,6′-Pentafluoro-2-hydroxy-(1,1′-biphenyl) (**3**).* A 250-mL three-necked-flask is equipped with a rod-shaped Teflon-coated magnetic stir bar (3-cm) and a reflux condenser connected to the middle neck. The two remaining necks of the flask are closed with glass stoppers. The apparatus is flushed with argon, evacuated and dried with a heat gun three times. Mild positive argon pressure is ensured by means of an argon bubbler on top of the reflux condenser. The 2-hydroxyphenyl boronic acid **1** (8.18 g, 59.3 mmol, 1.2 equiv) and potassium carbonate (14.8 g, 108 mmol, 2.1 equiv) are placed in the flask. One of the glass stoppers on the reaction flask is exchanged for a rubber septum. Absolute EtOH (60 mL, not stored under argon (Note 2)) and 70 mL toluene are added (Notes 3 and 4) using 60-mL plastic syringes and 100-mm syringe needles. For the deoxygenation of the reaction mixture, a 2-mL plastic syringe is cut in half, and the front part is inserted into a tube connected to the argon line. A syringe needle (180 mm) is inserted into the reaction mixture through the septum, and connected to the syringe (Figure 1). The other argon connection of the apparatus (argon bubbler on top of the reflux condenser) is closed, and a short needle is pierced through the same septum as argon outlet (Figure 1). While stirring, argon is bubbled through the mixture for 5 min.

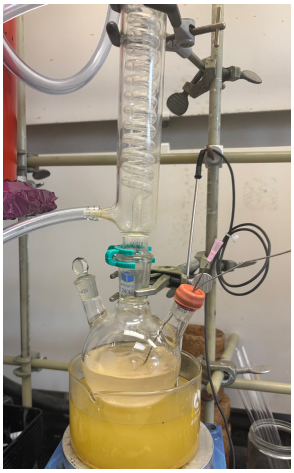


Figure 1. Set up for the deoxygenation; Bubbling during the deoxygenation with stirring. (Photos provided by the checkers)

The syringe needles used as argon inlet and outlet are removed, and mild positive argon pressure is maintained by means of the argon bubbler on top of the reflux condenser. Then, $Pd(PPh_3)_4$ (0.63 g, 0.54 mmol, 1 mol%) is added as solid in one portion under positive pressure followed by pentafluorobromobenzene (**2**) (6.3 mL, 50.1 mmol, 1.0 equiv) using a 12-mL plastic syringe and a needle (22G × 4''). The rubber septum is replaced by a glass stopper, and the reaction mixture is refluxed overnight with an oil bath (16 h, oil bath temperature 120 °C) (Notes 4, 5 and 6). The flask is allowed to cool to room temperature (18-22 °C), and the ethanol is removed by means of a rotary evaporator (115 mmHg, 40 °C). The remaining solution is cooled to 0 °C by means of an ice bath, and 200 mL HCl (1 M) are added over 20 min *via* a 250-mL dropping funnel, with stirring (Figure 2). The phases are separated in a 500-mL separatory funnel, and the aqueous phase is extracted with dichloromethane (DCM) (3 × 150 mL).

Figure 2. Set up for HCl dropwise addition in step A. (Photo provided by the checkers)

The combined organic phases are dried over Na_2SO_4 (45 g), and the solvent is removed under reduced pressure (600 mmHg to 7.5 mmHg, 40 °C). The crude product, 19.3g, is dissolved in 100 mL EtOAc and 20 g of silica gel (Note 7) are added. The solvent is removed by means of a rotary evaporator (150 mmHg to 7.5 mmHg, 40 °C). The crude product, adsorbed on silica gel,

is purified by column chromatography (*c*-hex:EtOAc = 9:1, R_f = 0.21 for the product phenol **3**) (Notes 5, 7 and 8). The product is obtained as a 5:1 mixture of **3** (9.46-9.62 g, 36.9-40.0 mmol, 73-74%) and phenol as an off white solid (total mass: 10.1-10.3 g) (Note 9).

B. *2-Hydroxy-3-(2',3',4',5',6'-pentafluorophenyl)-benzaldehyde (**4**).* A 250-mL three-necked-flask is equipped with a rod-shaped Teflon-coated magnetic stir bar (3-cm) and a reflux condenser connected to the middle neck. The two remaining necks of the flask are closed with glass stoppers. The apparatus is flushed with argon, evacuated, and dried with a heat gun three times. The flask is charged with the mixture of compound **3** (7.08 g of the mixture, 25.0 mmol, 1.0 equiv), *para*-formaldehyde (4.71 g, 157 mmol, 5.8 equiv), and magnesium dichloride (5.51 g, 57.9 mmol, 2.1 equiv) (Note 10) under positive pressure. The apparatus is evacuated once more (without heating) and flushed with argon. Mild positive argon pressure is maintained by means of an argon bubbler on top of the reflux condenser. One of the glass stoppers is exchanged for a rubber septum. Absolute THF (100 mL) is added using a 60-mL plastic syringe and a 100-mm syringe needle followed by dry Et_3N (7.7 mL, 55.0 mmol, 2.0 equiv) using a 12-mL plastic syringe and a needle (22G × 4''). The rubber septum is exchanged for a glass stopper, and the reaction mixture is refluxed overnight in an oil bath (16 h, oil bath temperature 80 °C) (Figure 3) (Notes 5 and 11). The flask is allowed to cool to room temperature (18-22 °C), and the solvent is removed under reduced pressure (175 mmHg, 40 °C) (Note 12).

Figure 3. Reflux setup in step B. (Photo provided by the checkers)

To the bright yellow residue, 220 mL aq. HCl (1 M) are added over 10 min by means of a 250-mL dropping funnel, with stirring (no cooling bath applied). The mixture is stirred until the yellow color disappeared (ca. 10 min, see Figure 4). The mixture is then extracted with DCM (3 × 80 mL) using a 500-mL separatory funnel. The combined organic phases are dried over anhydrous Na_2SO_4 (35 g) and the solvent is removed under reduced pressure, by means of a rotary evaporator (600 mmHg to 225 mmHg to 7.5 mmHg, 40 °C). The crude product is dissolved in EtOAc (50 mL) and 8 g of silica gel (Note 7) are added. The solvent is removed by means of a rotary evaporator (150 mmHg to 7.5 mmHg, 40 °C). The crude product adsorbed on silica gel is purified by column chromatography (toluene:*c*-hex 1:2 to 1:1) (Notes 7 and 13). For the final recrystallization, the material obtained by chromatography is dissolved, at reflux temperature (oil bath set to 85 °C), in the minimal amount of *c*-hex necessary for full dissolution (ca. 20 mL). After cooling to room temperature (18-22 °C) and after completion of the crystallization, the crystals of **4** are isolated by suction filtration using a 60-mL medium-porosity Büchner funnel and dried in vacuo (< 1 mmHg), affording the salicylic aldehyde **4** as pale-yellow needles (4.76-4.86 g, 16.5-16.9 mmol, 61-62%) (Note 14).

Figure 4. Appearance/color of the reaction mixture: A. before addition of 1 M HCl; B. after addition of HCl in step B. (Photos provided by the authors)

C. *Allyl (1R,2S)-2-aminocyclohexyl carbamate (**6**).* To a flame-dried 250-mL Schlenk flask with a rod-shaped Teflon-coated magnetic stir bar (3-cm) is added *Candida antarctica* lipase B (CAL-B, 3.93 g, ca. 10 kU) immobilized on polystyrene. The flask is evacuated and flushed with argon three times. Abs. toluene (100 mL) is added (Figure 5 and Notes 15, 16) under positive pressure using a 60-mL plastic syringe and a 100-mm syringe needle, followed by *cis*-1,2-diaminocyclohexane (**5**) (3.6 mL, 30 mmol, 1.0 equiv) and diallyl carbonate (4.7 mL, 33 mmol, 1.1 equiv) using 6-mL plastic syringes and needles (22G × 4''). The flask is closed with a glass stopper and the suspension is stirred at room temperature (18-22 °C) for 7 d (Notes 17 and 18). After 7 d, if a substantial amount of **5 is** still present, (Note 19) additional CAL-B (2.50 g, ca. 5 kU) is added under positive pressure, and the reaction is stirred for another 3 d. After a total of 10 d, methanol (50 mL) is added (measured using a graduate cylinder), and the immobilized enzyme is filtered off by suction filtration through a 60-mL medium-porosity Büchner funnel.

Figure 5. Experimental set up used in step C. (Photo provided by the authors)

The filter cake is washed with toluene (200 mL). The solvent of the filtrate is removed by means of a rotary evaporator (250 mmHg to 60 mmHg to 7.5 mmHg, 50 °C), and the residue is purified by column chromatography [DCM:MeOH (saturated with NH_3) = 95:5) (Notes 7 and 20] to give a dark brown, viscous oil (5.13-5.19 g, 26.1-26.2 mmol, 86-87%) (Note 21 and 22).

D. *2′,3′,4′,5′,6′-Pentafluoro-3-({(E)-[(1R,2S)-2-{[(2′,3′,4′,5′,6′-pentafluoro-2-hydroxy-[1,1′-biphenyl]-3-yl)methyl]amino}cyclohexyl]imino}methyl)-[1,1′biphenyl]-2-ol* (**7**), *"(1R,2S)-Berkessel ligand."* An open 250-mL round-bottomed flask (Note 23), equipped with a rod-shaped Teflon-coated magnetic stir bar (2-cm), is charged with allyl (1*R*,2*S*)-2-aminocyclohexyl carbamate (**6**) (981 mg, 4.95 mmol, 1.0 equiv) using a glass pipet. Methanol (10 mL) is then added using a 12-mL plastic syringe and a needle (22G × 4") at room temperature (18-22 °C) under air. 2-Hydroxy-3-(2',3',4',5',6'-pentafluorophenyl)-benzaldehyde (**4**) (1.40 g, 4.85 mmol, 0.98 equiv) is added with stirring (500 rpm) and the yellow solution (Figure 6A and Note 24) is continued to stir. After 3 h (Note 25), nickel(II)acetate tetrahydrate (Note 26) (123 mg, 0.495 mmol, 0.1 equiv) is added in one portion. Upon dissolution of the nickel salt, the mixture adopts a greenish-yellow color (Figure 6B).

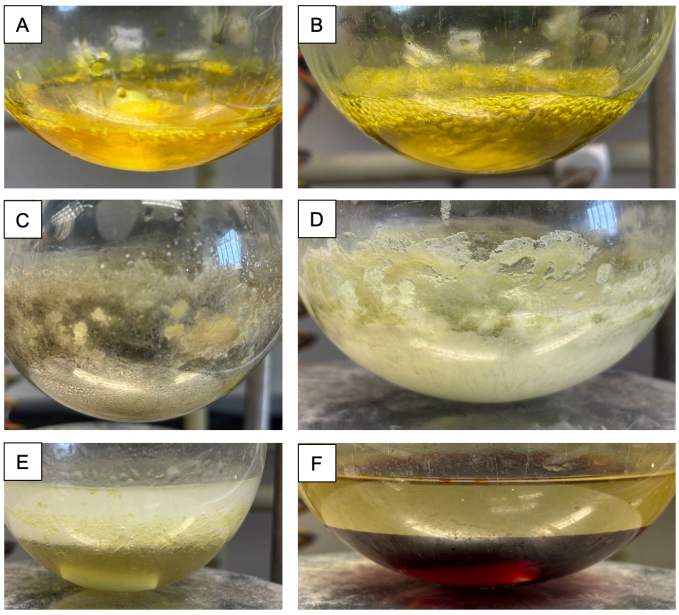


Figure 6. Appearance /color of the reaction mixture: A. after the addition of benzaldehyde (4) to allyl (1*R*, 2*S*)-2-aminocyclohexyl-carbamate (6) in methanol; B. after the addition of $Ni(OAc)_2{\cdot}4\ H_2O$; C. vigorous reaction/evolution of gas upon addition of $NaBH_4$; D. after addition of water; E. two layers form upon addition of DCM; F. after completion of the second condensation step; top layer: aqueous phase; bottom layer: organic phase. (Photos provided by the checkers)

Sodium borohydride (1.03 g, 27.2 mmol, 5.5 equiv) is then added in one portion, with rapid stirring. Upon addition of the sodium borohydride, the reaction mixture turned dark, and an exothermic reaction with vigorous evolution of gas started immediately (Note 27). After ca. 20 min, the color of the reaction mixture again changes to yellowish-green (Figures 6C and 6D) (Note 28). Water (40 mL) is added dropwise over 5 min *via* a 100-mL dropping funnel (Note 29), and the reaction mixture is stirred for another 10 min at regular speed (500 rpm). The addition of water results in the precipitation of a greenish solid (Figure 6E). DCM (25 mL) is added using a 24-mL plastic syringe. Two layers form, and the precipitate dissolves (Figure 6F). 2-Hydroxy-3-(2',3',4',5',6'-pentafluorophenyl)benzaldehyde (**4**) (1.43 g, 4.95 mmol, 1.0 equiv) is added, and the reaction mixture is stirred for another 3 h at room temperature (18-22 °C). The upper layer turns yellow, and the bottom layer turns from dark orange to red over the course of the reaction (Figure 6G). The two layers are separated in a 250-mL separatory funnel, and the aqueous layer is extracted with DCM (3 × 20 mL). The combined organic layers are dried over anhydrous magnesium sulfate, filtered, and the solvents are removed under reduced pressure (600 mmHg to 20 mmHg, 40 °C) by means of a rotary evaporator. The crude product (Note 30) is purified by column chromatography on silica gel (*c*-hex:ethyl acetate, 4:1; R_f(ligand **7**) = 0.38) (Notes 7 and 31). For the final recrystallization, the yellow solid obtained by chromatography is dissolved, at reflux temperature (85 °C), in *c*-hex (ca. 180 mL). After cooling to room temperature (18-22 °C), and after completion of the crystallization, the crystals of **7** are isolated by suction filtration using a 60-mL medium-porosity Büchner funnel and dried *in vacuo* (< 1 mmHg). Bright yellow crystals (1.32-1.45 g, 2.0-2.2 mmol, 41-43%) of mp 167 °C and ≥99 % ee of the ligand **7** are obtained (Note 32 and 33).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington,

D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/about/governance/committees/chemical-safety.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 2-hydroxyphenyl boronic acid, potassium carbonate, ethanol, toluene, $Pd(PPh_3)_4$, pentafluorobromobenzene, HCl (1M), dichloromethane, anhydrous sodium sulfate, ethyl acetate, silica gel, cyclohexane, *para*-formaldehyde, magnesium chloride, tetrahydrofuran, triethylamine, *Candida antarctica* lipase B (CAL-B) immobilized on polystyrene, *cis*-1,2-diaminocyclohexane, diallyl carbonate, methanol, ammonia, nickel(II)acetate tetrahydrate, sodium borohydride, and anhydrous magnesium sulfate, as well as hazards associated with nickel hydride reductions, *i.e.* sodium borohydride reductions carried out in the presence of catalytic amounts of nickel salts.

2. The checkers used both absolute ethanol stored under inert atmosphere (anhydrous) and absolute ethanol (HPLC grade) stored under air without distillation. Both gave the product mixture in the same yields (74%).
3. The authors obtained absolute toluene (99.85%) and THF (99.5%, stabilized) from Arcos Organics (extra dry over molecular sieves, AcroSeal grade). Absolute ethanol (99.8%) was purchased from Fisher Scientific. All other solvents were obtained in technical grade and were distilled (no inert gas and no drying agents applied) prior to use. The checkers purchased absolute toluene (anhydrous, 99.8%) from Alfa Aesar and ethanol (anhydrous, ≥99.5%) from Sigma Aldrich and both were used as purchased; absolute THF was purchased from VWR and then degassed and stored under argon and molecular sieves prior to use; methanol (ACS grade) and DCM (ACS grade) used in step D were purchased from VWR and Fisher Chemical, respectively, and used as received. Solvents for work-ups and purifications were obtained in ACS grade and used as received.
4. The authors purchased reagents used in step A from the following companies: boronic acid **1** (98%) and pentafluorobromobenzene (**2**, 98%): BLDPharm; K_2CO_3 (anhydrous, 99%): Fisher Chemical; $Pd(PPh_3)_4$:

Carbolution (no purity given, product number: CCC03013). Checkers purchased boronic acid **1** (98%) from Ambeed, pentafluorobromobenzene (**2**, >99%) from TCI, K_2CO_3 (anhydrous, 99%) from Alfa Aesar, and $Pd(PPh_3)_4$ (99%) from Strem.

5. For TLC analysis, VWR TLC aluminium-backed plates Silica F254 (200 μm layer thickness) 20x20 cm were used and cut to appropriate size. For the elution of the plates, standard TLC chambers were used. Eluent compositions and detection methods are stated in the *Notes* for all individual experimental procedures.
6. TLC of the reaction mixture [*c*-hex/EtOAc 9:1, UV light (λ = 254 nm)/$KMnO_4$ dye: 3 g $KMnO_4$, 20 g K_2CO_3 , 5 mL 5% NaOH solution and 300 mL water].

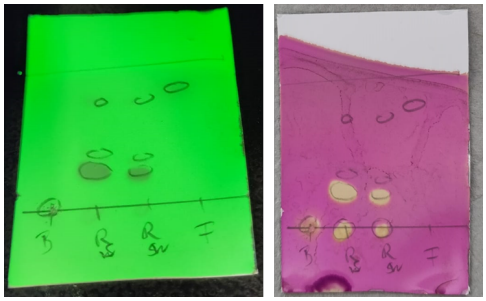


Figure 7. TLC of the reaction mixture. B: boronic acid 1, R: reaction mixture in two different concentrations, F: pentafluorobromobenzene (2) (Photos provided by the authors)

7. Silica gel for column chromatography (0.035-0.07 mm) was purchased from Acros.
8. Column size: 8x11 cm, 270 g of silica gel, elution with ca. 500 mL of solvent, then collection of fractions (50 mL each) was started. Checkers collected fractions 7-30.
9. The phenol by-product can be removed by recrystallisation from *c*-hex. However, it is more convenient to continue on with the mixture, and to perform the purification after the formylation step. The phenol impurity is readily detected in the mixture by its characteristic ^{1}H-NMR signals: (300 MHz, $CDCl_3$) δ (ppm) = 7.29 – 7.23 (m, 2H), 6.99 – 6.91 (m, 1H), 6.90 – 6.82 (m, 2H), 5.52 (bs, 1H, OH). See below for the analytical data of the pure, recrystallized 2',3',4',5',6'-pentafluoro-2-hydroxy-(1,1'-biphenyl) (**3**). For the recrystallization, the 5:1 mixture of **3** with phenol was

dissolved, at reflux temperature, in the minimal amount of *c*-hex necessary for full dissolution. After cooling to room temperature and after completion of the crystallization, the colorless crystals of **3** were isolated by suction filtration using a 60-mL medium-porosity Büchner funnel and dried *in vacuo* (ca. 1 mbar) at room temperature (18-22 °C). Checkers obtained white crystals which became a powder *in vacuo*; percent of recovery was 41%.

Analytical data of recrystallized **3**: mp. 100 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 5.06 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 144.6 (d, *J* = 248 Hz, 2C), 140.9 (d, *J* = 254 Hz), 137.8 (d, *J* = 252 Hz, 2C), 132.1, 131.3, 121.3, 116.3, 113.7, 112.2 (d, *J* = 4 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ -139.83 (dd, *J* = 23.0, 8.1 Hz), -155.21 (t, *J* = 20.8 Hz), -162.45 (td, *J* = 22.1, 8.2 Hz); HRMS $[M\bullet]^+$ calculated for $C_{12}H_5F_5O$: 260.0261, found: 260.0271; IR (ATR): 3513, 1485, 1444, 1059, 982, 870, 757 cm^{-1}; The analytical data are in agreement with the literature.[3] The purity of recrystallized **3** was determined to be 98.7 wt% as determined by qNMR using methyl 3,5-dinitrobenzoate (99%, Sigma-Aldrich) as an internal standard.

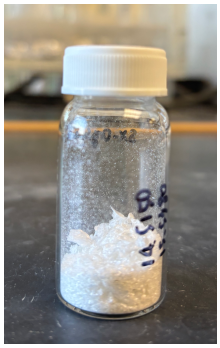


Figure 8. Pure compound 3 after recrystallization. (Photo provided by the checkers)

10. The authors obtained reagents used in step B from the following companies: *para*-formaldehyde (≥95%) and $MgCl_2$ (≥98%, anhydrous, reagent grade): Sigma Aldrich; Et_3N (≥99%, laboratory reagent grade): Fisher Scientific. Checkers purchased *para*-formaldehyde (≥90.0%) from TCI, $MgCl_2$ (97.5%, 2% max H_2O) from Strem, and Et_3N (anhydrous, ≥99.5%) from Sigma Aldrich.

11. Crude TLC of the reaction was performed using two concentrations of unpurified reaction mixture [*c*-hex/EtOAc 9:1, UV light (λ = 254 nm)].

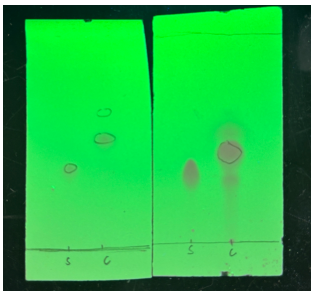


Figure 9. TLC of the reaction mixture of step B. S: starting material 3, C: crude mixture (Photos provided by the checkers)

12. Checkers transferred the reaction mixture to a one-neck flask before concentration with a rotary evaporator and continued with the same flask for HCl dropwise addition.
13. Column size: 13x5.5 cm, 170 g of silica gel; 600 mL of a 2:1 mixture of *c*-hex/toluene, followed by 500 mL of a 1:1 mixture was used as eluent. Ca. 250 mL of solvent were eluted, then collection of fractions (50 mL each) was started. Product: fractions 4 to 18. Checkers used ca. 200 g silica gel with 650 mL of 2:1 mixture of hexanes/toluene then 1:1 mixture; checkers collected fractions 9 to 21.

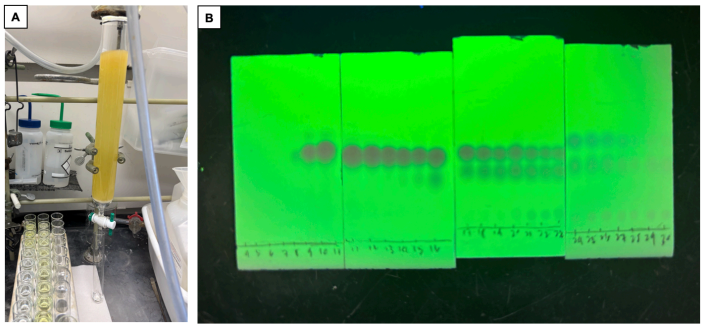


Figure 10. A. Column chromatography; B. TLCs of the collected fractions [1:1 hexanes/toluene]. (Photos provided by the checkers)

14. Analytical Data of **4**: mp. 117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.45 (s, 1H), 9.98 (d, *J* = 1.0 Hz, 1H), 7.73 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.52 (d, *J* = 7.6

Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ 196.5, 159.5, 144.6 (d, J = 252 Hz, 2C), 141.2 (d, J = 254 Hz, 2C), 139.0, 137.8 (d, J = 251.2 Hz), 135.5, 121.1, 120.0, 115.7, 110.7; ^{19}F NMR (565 MHz, CDCl3) δ -139.56 (dd, J = 23.0, 8.3 Hz), -154.30 (td, J = 21.2, 8.5 Hz), -162.22 (td, J = 21.5, 8.1 Hz); HRMS $[M\bullet]^+$ calculated for $C_{13}H_5F_5O_2$: 288.0210, found: 288.0210; IR (ATR): 3031, 2363, 1647, 1490, 989, 962, 739, 666 cm^{-1}; The analytical data are in agreement with the literature.[3] The checkers determined the purity of recrystallized **4** to be 100 wt% as determined by qNMR using methyl 3,5-dinitrobenzoate (99%, Sigma-Aldrich) as an internal standard. The authors confirmed the purity by elemental analysis: Anal. Calcd for $C_{13}H_5F_5O_2$: C 54.18, H 1.78; Found: C 54.57, H 1.85.

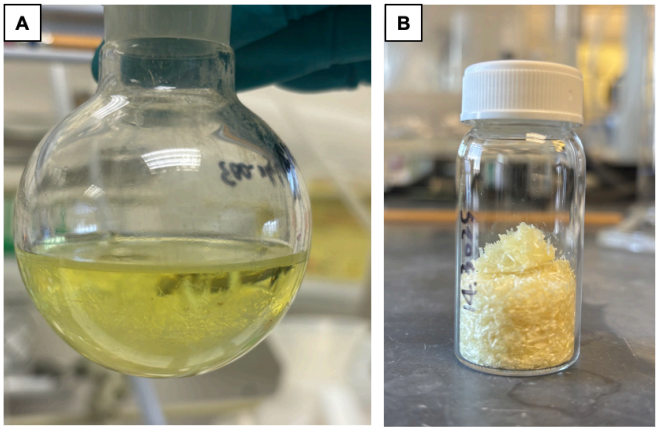


Figure 11. A. Formation of needle shaped crystals from cyclohexane in a 100 mL RBF; B. Pure compound 4 after recrystallization. (Photos provided by the checkers)

15. The reagents used by both authors and checkers in step C were purchased from the following companies: *cis*-DACH (98%): BLDPharm; diallyl carbonate (99%) and CAL-B (product number 52583, *Candida antarctica* lipase B, recombinant from yeast, immobilized on Immobead 150, ≥ 2000 U/g): Sigma Aldrich.
16. The authors did not dry or evacuate the flask prior to flushing with argon. However, because anhydrous toluene and inert atmosphere were employed by the authors, checkers decided to flame dry the flask and exchange atmosphere with argon.

17. After reaction setup, checkers closed the outlet of the Schlenk flask and stirred the reaction under inert atmosphere without active flow of argon. The authors stirred the reaction under a constant flow of argon. Checkers noticed the occurrence of a suspended white material on day 2 of stirring..
18. The original procedure from the authors was a 4-day reaction. But checkers observed much slower reactivity. After communication with the authors, the procedure was modified.
19. TLC was performed using an aliquot of the reaction mixture (obtained under positive pressure) after stirring for 7 days. $KMnO_4$ was used for detection [95:5 DCM:7M NH_3 in MeOH] (see Note 6 and 20).

Figure 12. TLC of the reaction mixture after staining with $KMnO_4$. SM: starting material 5, C: crude mixture (Photo provided by the checkers)

20. Column size: 16x5 cm, 200 g of silica gel. Ca. 150 mL of solvent were passed through the column, then collection of fractions (50 mL each) was started. Product: fractions 16 to 32. $KMnO_4$ was used for detection (see Note 6). The authors saturated MeOH through bubbling NH_3 for 3 h at 0 °C. Checkers purchased 7M NH_3 in MeOH from Oakwood Chemicals. For collection of the product, checkers collected fractions 10 to 24.

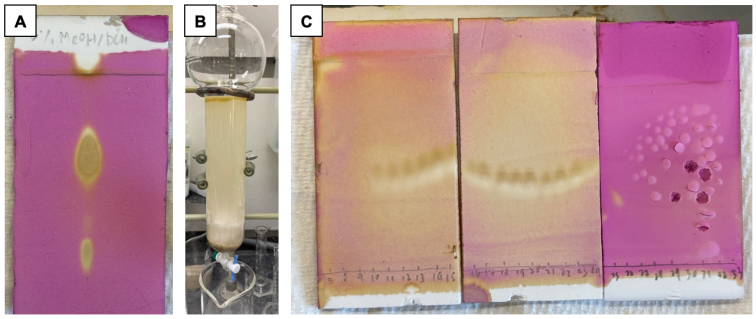


Figure 13. A. TLC of the reaction mixture of step C after stirring for 10 d; B. Column chromatography; C. TLCs of the collected fractions [95:5 DCM:7M NH_3 in MeOH]. (Photos provided by the checkers)

21. Analytical data of **6**: $[\alpha]_D^{20}$ 4.3 (c 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 – 5.83 (m, 1H), 5.34 – 5.22 (m, 2H), 5.20 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.54 (d, *J* = 5.7 Hz, 2H), 3.74 – 3.54 (m, 1H), 3.01 (dt, *J* = 6.9, 3.8 Hz, 1H), 1.71 – 1.57 (m, 2H), 1.56 – 1.26 (m, 8H); ^{13}C NMR (126 MHz, CDCl3) δ 156.1, 133.2, 117.7, 65.5, 52.2, 49.9, 32.3, 28.1, 23.1, 20.8; HRMS $[M+Na]^+$ calculated for $C_{10}H_{18}N_2O_2Na$: 221.1266, found: 221.1265; IR (ATR): 3326, 2929, 2858, 2362, 1698, 1522, 1236, 1040 cm^{-1}; The analytical data are in agreement with the literature.[4] Please note the authors reported the clean product (based on both NMR analysis and elemental analysis; Anal. Calcd for $C_{10}H_{18}N_2O_2$: C 60.58, H 9.15, N 14.13; Found: C 60.50, H 9.05, N 14.16) as a pale yellow oil. However, the checkers obtained **6** as a dark brown oil with a purity of only 89.2 wt% by qNMR using methyl 3,5-dinitrobenzoate (99%, Sigma-Aldrich) as an internal standard. The peak for the unidentifiable impurity was at δ 3.62 ppm in the ^{1}H NMR (overlapped with **6**) and δ 70.8 ppm in the ^{13}C NMR.
22. The checkers determined the enantiomeric excess to be >99 % by HPLC analysis (Figure 14). For this purpose, the product **6** was derivatized with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene: 0.20 g (1.0 mmol, 1.0 equiv) of sample was dissolved in 2.2 mL THF in a flame-dried 10 mL round-bottomed flask under Ar. The isothiocyanate (0.18 mL, 1.0 mmol, 1.0 equiv) was added and the reaction was stirred overnight at room temperature. After removing solvent, the derivatized product (**S1**) was purified through column chromatography (1% MeOH/DCM) as a yellow solid (96%). 2 mg of **S1** was dissolved in *i*-PrOH and submitted to HPLC analysis. The column temperature was set to 19 °C. Diode array detection

(DAD) was used, and λ = 230 nm was chosen for peak integration. HPLC: τ_R [min] = 3.8 (minor; 1*S*,2*R*), 4.7 (major; 1*R*,2*S*) (Diacel Chiralpak AD-H (5 μm, 4.6x100 mm), *n*-hex/*i*-PrOH, 95:5; flow rate = 0.8 ml/min). For preparation of racemic **S1**, **5** (0.20 g, 1.8 mmol, 1.0 equiv) was dissolved in DCM (8.8 mL) followed by addition of Et_3N (0.29 mL, 2.1 mmol, 1.2 equiv) and Alloc-Cl (0.19 mL, 1.8 mmol, 1.0 equiv). The reaction was stirred overnight at room temperature and then the solvent was removed. The racemic **S1** was purified through the same conditions (see Note 20) and then further derivatized as stated above.

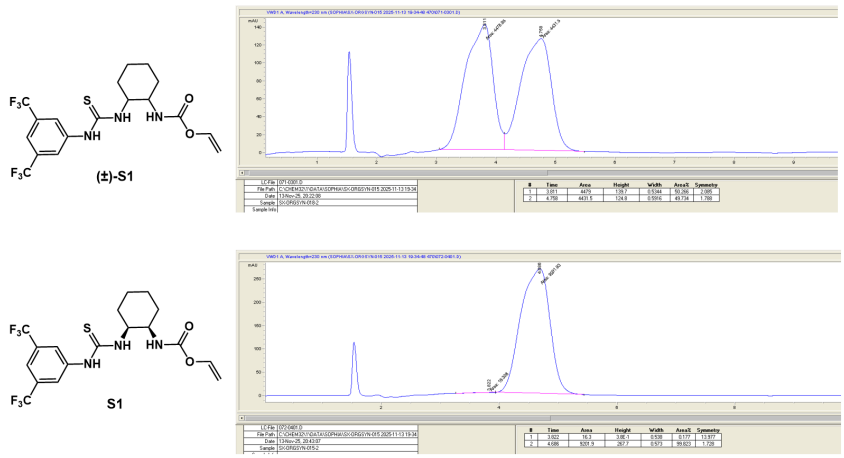


Figure 14. HPLC Comparison of racemic and enantiomerically pure 6 after derivatization.

The authors determined the enantiomeric excess of **6** to be 97% by capillary GC on chiral stationary phase. For this purpose, the product was derivatized with trifluoroacetic anhydride: 5 mg of sample were dissolved in 1.0 mL DCM in a 2-mL GC-vial. 0.5 mL sat. K_2CO_3 solution and a 3 mm rod-shaped Teflon-coated magnetic stir bar were added. While stirring, 3 drops of trifluoroacetic anhydride were added. The solution was stirred at room temperature for 30 min. The organic phase was then separated with a pipette, and filtered through anhydrous Na_2SO_4 (in a pipette with a cotton plug and a layer of Na_2SO_4 on top) into another GC-vial. The vial was filled up with DCM and submitted to GC analysis. τ_R = 31.5 min (major; 1*R*,2*S*), 33.9 (minor, 1*S*,2*R*); CP-Chirasil-

Dex CB 0.25 µm, 25 m × 0.25 mm ID; 19.78 psi N_2 gas; 60 °C, 10 °C/min to 150 °C (30 min).

23. This procedure can just as well be performed in an equally sized beaker (250 mL).
24. The authors reported a colorless-to-yellow color change when adding **6**. Since the checkers used the dark brown oil of **6**, the solution was yellow to start with and no color change was observed when adding aldehyde **4**.
25. The authors reported completion of the consumption of aldehyde **4** by TLC (*c*-hex/ethyl acetate, 3:1; R_f (aldehyde **4**) = 0.59, detection with $KMnO_4$ solution and UV light (λ = 254 nm) (see Note 6). Because checkers were not able to obtain highly pure **6**, aldehyde **4** was not fully consumed, even with extended reaction time (4.5 h) so stirring for this step was only kept at 3 h.

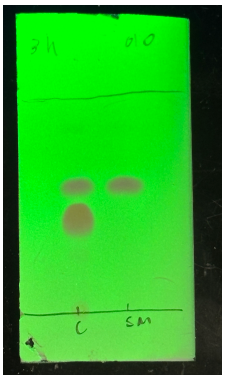
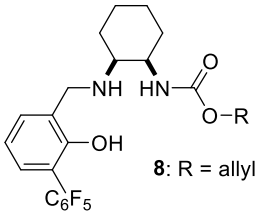


Figure 15. TLC of the reaction mixture before addition of $Ni(OAc)_2$ [*c*-hex/ethyl acetate, 3:1]. C: crude mixture; SM: starting material 4 (Photo provided by the checkers)

26. The authors obtained the reagents used in step D from the following company: nickel(II) acetate tetrahydrate (≥99%) and $NaBH_4$ (≥98%): Sigma Aldrich. Checkers purchased nickel(II) acetate tetrahydrate (99%) from thermo scientific and $NaBH_4$ (≥98%) from Sigma Aldrich.
27. The evolution of hydrogen makes the excess of $NaBH_4$ necessary.
28. If a greenish solid precipitated after the color change to yellowish-green, it was dissolved by addition of more MeOH (up to ca. 10 mL).
29. The authors used a pipet to add the water.
30. A dark orange oil. TLC analysis of the crude product showed two spots [*c*-hex/ethyl acetate, 4:1; detection with $KMnO_4$ solution and UV light (λ

= 254 nm) (see note 5)]: R_f = 0.38 (ligand **7**) and R_f = 0.20 [inseparable mixture of the non-deprotected intermediate **8** and its reduction product (R = *n*-propyl)]). Checkers' crude TLC showed four to five spots [hexanes/ethyl acetate, 4:1; detection with UV light (λ = 254 nm)] with the largest one being the ligand **7**.



8: R = allyl

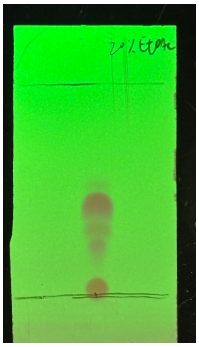


Figure 16. TLC of the reaction mixture of step D. (Photo provided by the checkers)

31. Column size: 12x5.5 cm, 160 g of silica gel, elution with ca. 150 mL of solvent, collection of fractions (50 mL each) was started when the eluent turned yellow. Product: fractions 2 to 10 (colored yellow). Checkers collected fractions 3 to 12. The product from the column became a yellow foam *in vacuo*.

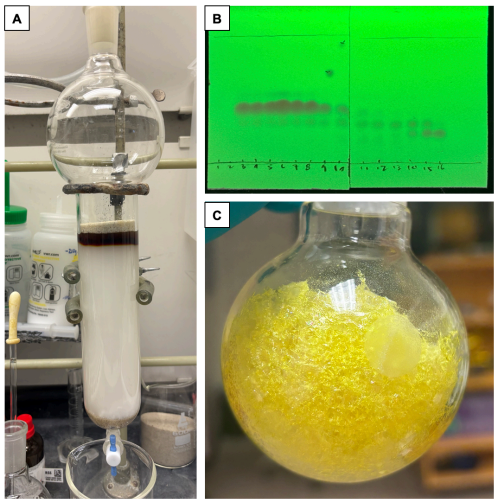


Figure 17. A. Column chromatography; B. TLC of the collected fractions; C. Appearance of the product from the column *in vacuo*. (Photos provided by the checkers)

32. The final recrystallization from *c*-hex is necessary to obtain the ligand **7** in analytically pure form and with ≥ 99 % ee. The ligand **7** displays the following physical and spectroscopic properties: bright yellow crystals; mp. 167 °C (163 °C reported by the authors); $[\alpha]_D^{20}$ -94.3 (c 1.2, $CHCl_3$); the authors reported $[\alpha]_D^{20}$ -181.9 (c 1.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.01 (s, 1H), 8.53 (s, 1H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.09 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 4.14 (d, *J* = 14.2 Hz, 1H), 4.03 (d, *J* = 14.2 Hz, 1H), 3.72 (q, *J* = 3.4 Hz, 1H), 2.81 (dt, *J* = 11.4, 3.6 Hz, 1H), 2.01 – 1.33 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 159.5, 156.6, 145.6, 143.6 (2C), 141.6, 139.9, 138.8 (2C), 136.8 (2C), 134.8, 133.4, 130.9, 130.0, 122.9, 119.2, 119.0, 118.7, 115.0, 114.2, 112.9, 112.0, 68.1, 57.2, 49.4, 33.1, 27.6, 24.9, 20.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -139.34 – -139.47 (m), -139.47 – -139.59 (m), -139.88 (dd, *J* = 23.5, 8.1 Hz), -140.05 (dd, *J* = 23.5, 8.2 Hz), -155.50 (t, *J* = 20.9 Hz), -156.46 (t, *J* = 20.9 Hz), -162.70 (td, *J* = 23.2, 8.3 Hz), -162.88 – -163.46 (m); HRMS $[M+Na]^+$ calculated for $C_{32}H_{22}F_{10}N_2O_2Na$: 679.1419, found: 679.1443; IR (ATR): 2939, 2864, 2358, 1628, 1520, 1495, 1447, 981 cm^{-1}.

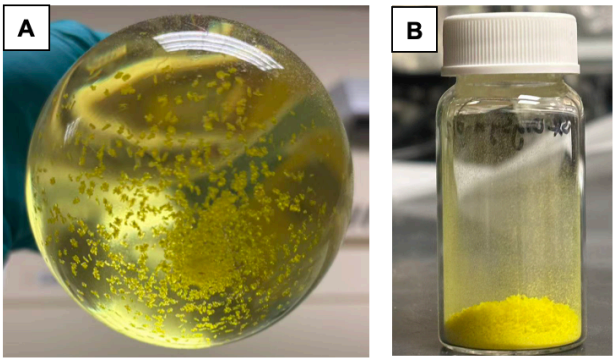


Figure 18. A. Formation of crystals of 7 from cyclohexane (after 1 week); B. Appearance of the final recrystallized ligand 7. (photos provided by the checkers)

33. The checkers determined the purity of recrystallized **7** to be 100 wt% as determined by qNMR using methyl 3,5-dinitrobenzoate (99%, Sigma-Aldrich) as an internal standard. The authors confirmed the purity by elemental analysis (Anal. Calcd for $C_{32}H_{22}F_{10}N_2O_2$: C, 58.54; H, 3.38; N, 4.27. Found: C, 58.74; H, 3.47; N, 4.09.). HPLC: τ_R [min] = 9.0 (major, **7**), 13.1 (minor, *ent*-**7**) (Diacel Chiralpak OD-H (5 μm, 4.6x100 mm), *n*-hex/*i*-PrOH, 95:5; flow rate = 0.5 ml/min). For the determination of enantiomeric purity, ca. 1 mg of the solid ligand **7** was placed in a 2 mL vial and was dissolved in ca. 0.4 mL *i*-PrOH. If necessary, ultra-sonication at ca. 20 °C can be applied. Upon complete dissolution of the solid, 1.5 mL *n*-hex was added and the solution was submitted to HPLC-analysis (auto-injection). The column temperature was set to 19 °C. Diode array detection (DAD) was used, and λ = 254 nm was chosen for peak integration. For HPLC assay, checkers received a racemic sample of **7** from the authors. The authors reported the preparation was done following step D with racemic **6** (Figure 19).

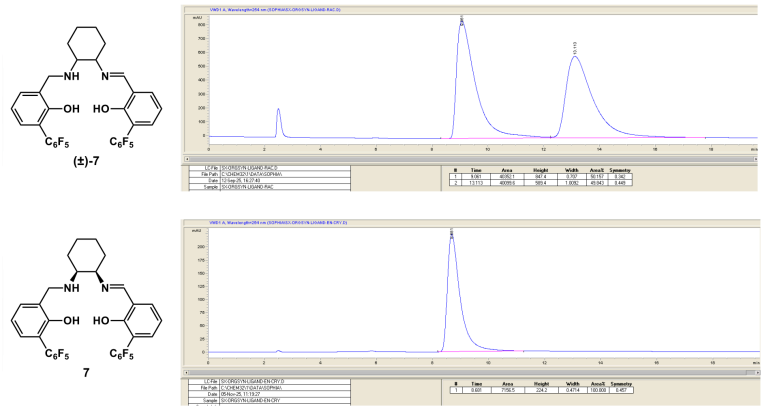


Figure 19. HPLC Comparison of racemic and enantiomerically pure 7

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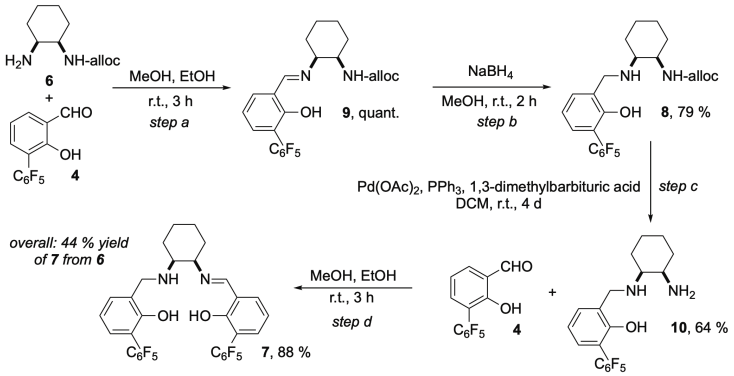
Discussion

The catalytic asymmetric epoxidation of terminal, non-conjugated olefins has been a long-standing problem in asymmetric synthesis. In 2005, Katsuki *et al.* discovered that titanium salalen-complexes derived from *trans*-DACH can catalyze the asymmetric epoxidation of terminal and other non-activated olefins with hydrogen peroxide.[5] Based on this seminal discovery, our own group has developed a modular synthesis of salalen ligands such as **7** based on *cis*-DACH.[6-9] This switch to *cis*-DACH as the chiral building block has proven highly advantageous both in terms of enantioselectivity and catalyst stability. Further optimization identified the *bis*-pentafluorophenyl substituted ligand **7** ("Berkessel ligand") as highly effective and enantioselective[8].

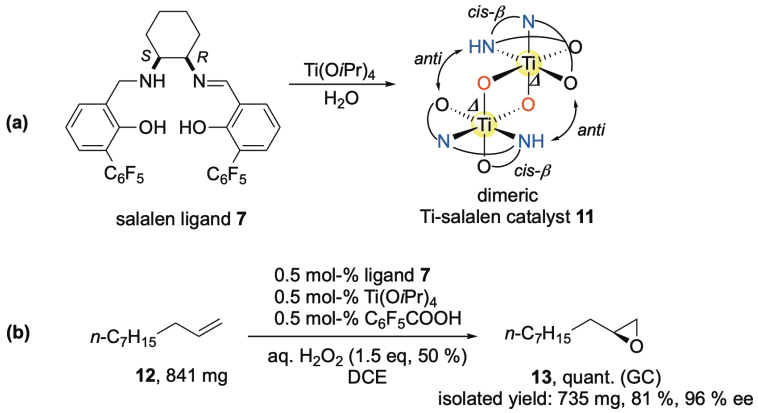
Our original modular four-step synthesis of the enantiopure salalen-ligand **7** is summarized in Scheme 1.[8] As in the case of the simplified procedure presented herein, enantiopure (1*R*,2*S*) mono-alloc *cis*-DACH (**6**) served as the starting material. The latter building block is readily available, in large quantities, by enantioselective mono-alloc protection of *cis*-DACH with diallyl carbonate. Our procedure employs commercially available *Candida antarctica* lipase B (CAL-B) as the chiral acyl transfer catalyst.[4] In the first step of the ligand synthesis (step a), the mono-alloc protected *cis*-DACH **6** was condensed with one equivalent of the salicylic aldehyde **4**,which is readily prepared following literature procedures,[3,10] affording the cor-



Scheme 1. Stepwise synthesis of the *cis*-DACH salalen ligand 7[8]

responding imine **9** in quantitative yield. Subsequent reduction with $NaBH_4$ gave the benzylic amine **8** in 79 % yield (step b). Pd-catalyzed alloc-deprotection (step c) liberates the primary amine **10**, albeit at a moderate yield of 64%, and requiring long reaction times of ca. 4 d. A final condensation with a second equivalent of the salicylic aldehyde **4** (step d) completes the ligand synthesis. After column chromatography and recrystallization, the salalen ligand **7** was obtained in 88% yield and > 98 %*ee*. Note that the enantiomeric ligand *ent*-**7** is also available, albeit requiring two additional steps, *via* the (1*S*,2*R*) BOC-monoprotected pseudo-enantiomer of the (1*R*,2*S*) alloc-monoprotected *cis*-DACH **6**.[4]

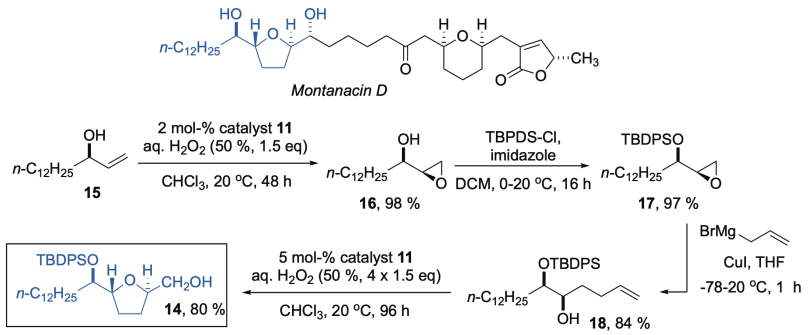
The above reaction sequence gave an overall 44% yield of the ligand **7** (based on the mono-alloc *cis*-DACH **6**) over four linear steps. Of the latter, the Pd-catalyzed alloc-deprotection (step c) was typically the "bottleneck", plagued with varying reaction rates, and yields typically not exceeding ca. 65 %. While working on the improvement of this step, our attention was drawn to a protocol by Yin *et al*. for the reductive cleavage of allyl esters, employing sodium borohydride in the presence of a catalytic amount of nickel chloride.[11] We reasoned that the Yin procedure may be adapted to the alloc-deprotection mentioned above. We were delighted to find that alloc-deprotection indeed proceeded smoothly in the presence of $NaBH_4$/ $Ni(OAc)_2 \bullet 4H_2O$. In methanol as solvent, complete consumption of the N-alloc *cis*-DACH **8** was achieved, with 10 mol-% of $Ni(OAc)_2 \bullet 4H_2O$, within 10 min (instead of 4 d). Further experimentation showed that using the above deprotection procedure, all four reaction steps can be carried out in the one-pot fashion described herein. As the result, the overall time necessary for the preparation of the ligand **7** (≥ 99 % ee) from mono-alloc *cis*-DACH **6** could be shortened from ca. 5 d to 7 h, while improving the overall yield from 44 % to 52 %.



Scheme 2. (a) Self-assembly of the dimeric Ti-epoxidation catalyst 11 from the *cis*-DACH salalen ligand 7 and Ti(O*i*Pr)$_4$; (b) asymmetric epoxidation of 1-decene (12) using the *in situ* generated catalyst 11

As shown in Scheme 2a, the ligand **7** spontaneously forms the dimeric Ti-epoxidation catalyst **11** ("Berkessel-Katsuki catalyst") when combined with Ti(O*i*Pr)$_4$.[8] With aqueous hydrogen peroxide as oxidant, in particular terminal, non-conjugated olefins are smoothly transformed by catalyst **11** to their epoxides, in high yields and enantiopurity. For example, 1-decene (**12**) is converted to its (*S*)-epoxide **13** in 81 % isolated yield and 96 % ee by using just 0.25 mol-% of the dimeric catalyst **11**, prepared *in situ* from 0.5 mol-% of both ligand **7** and Ti(O*i*Pr)$_4$ (Scheme 2b).[8,9] Similarly, O-benzyl protected 8-nonenol was converted by catalyst **11** to its (*S*)-epoxide in 77 % yield and 94 % ee, as a part of the synthesis of the macrolide *Rickiol E3* by Kalesse, Stadler *et al.*[12]

Furthermore, the Berkessel-Katsuki-catalyst **11** allows the highly selective (d.r. typically ≥ 99:1) *syn*-epoxidation of chiral terminal allylic alcohols (and allylic ethers) - it is thus complementary to the Sharpless catalyst which provides the *anti*-epoxy alcohols.[13] Scheme 3 shows the structure of the annonaceous acetogenine *Montanacin D* harboring a *syn-trans-syn* THF unit, together with that of its "western" building block **14**. Our synthesis of the *syn-trans*-building block **14** comprises two epoxidation steps effected by catalyst **11**. Starting from enantiopure (*R*)-pentadec-1-en-3ol (**15**), epoxidation with catalyst **11** afforded the pure *syn*-epoxy alcohol (**16**) in almost quantitative yield. After TBDPS-protection, Cu(I)-catalyzed epoxide



Scheme 3. Synthesis of the enantiopure *syn-trans*-THF building block 14 of *Montanacin D*, involving two epoxidation steps catalyzed by the dimeric Ti-complex 11 of the *cis*-DACH salalen ligand 7[13]

opening of **17** with allyl magnesium bromide provided the terminal olefin **18**. The (*S*)-selective epoxidation of the latter was again carried out with catalyst **11**. The cyclization of the intermediate (S)-epoxide occured spontaneously, and the purely *syn-trans*-configurated THF building block **14** was isolated in 80 % yield, on gram scale.[13] For further applications of our *cis*-DACH derived Ti-salalen catalysts in natural product syntheses in other laboratories, see refs. 12, 14-16. We could recently show that the Berkessel-Katsuki catalyst **11** also effects the highly enantioselective hydroxylation of benzylic C-H bonds.[17] Another recent study of ours elucidated the intriguing mechanism by which the dimeric Berkessel-Katsuki Ti-catalyst **11** activates hydrogen peroxide for electrophilic oxygen transfer.[18]

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17. Wartmann, C.; Nandi, S.; Neudörfl, J.-M.; Berkessel, A. Titanium Salalen Catalyzed Enantioselective Benzylic Hydroxylation. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306584. DOI: 10.1002/anie.202306584.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

2-Hydroxy-3-(2',3',4',5',6'-pentafluorphenyl)-benzaldehyde (**4**); (1256351-24-2)
Allyl (1*R*,2*S*)-2-aminocyclohexyl-carbamate (**6**);(1261082-38-5)
2 ,3',4',5',6'-Pentafluoro-3-({(E)-[(1R,2S)-2-{[(2',3',4',5',6'-pentafluoro-2-hydroxy-[1,1'-biphenyl]-3-yl)methyl]amino}cyclohexyl]imino}methyl)[1,1' -biphenyl]-2-ol (**7**);(2055467-90-6)
2-Hydroxyphenyl boronic acid (89466-08-0)
Pentafluorobromobenzene (344-04-7)
cis-1,2-Diaminocyclohexane(694-83-7)

Diallyl carbonate (15022-08-9)
Nickel(II)acetate tetrahydrate (6018-89-9)
Sodium borohydride (16940-66-2)

Christina Wartmann was born in Cologne, Germany. She started her chemistry studies at the University of Cologne in 2014, where she received both her B. Sc. in Chemistry in 2017 and her M. Sc. in 2020 with Prof. Dr. Albrecht Berkessel. In July 2023 she completed her Ph.D. studies with Prof. Berkessel, and joined the group of Prof. Guy Lloyd-Jones in Edinburgh as a post-doctoral researcher in 2024. Her research interests center around structural, mechanistic and synthetic aspects of both metal- and organocatalysis.

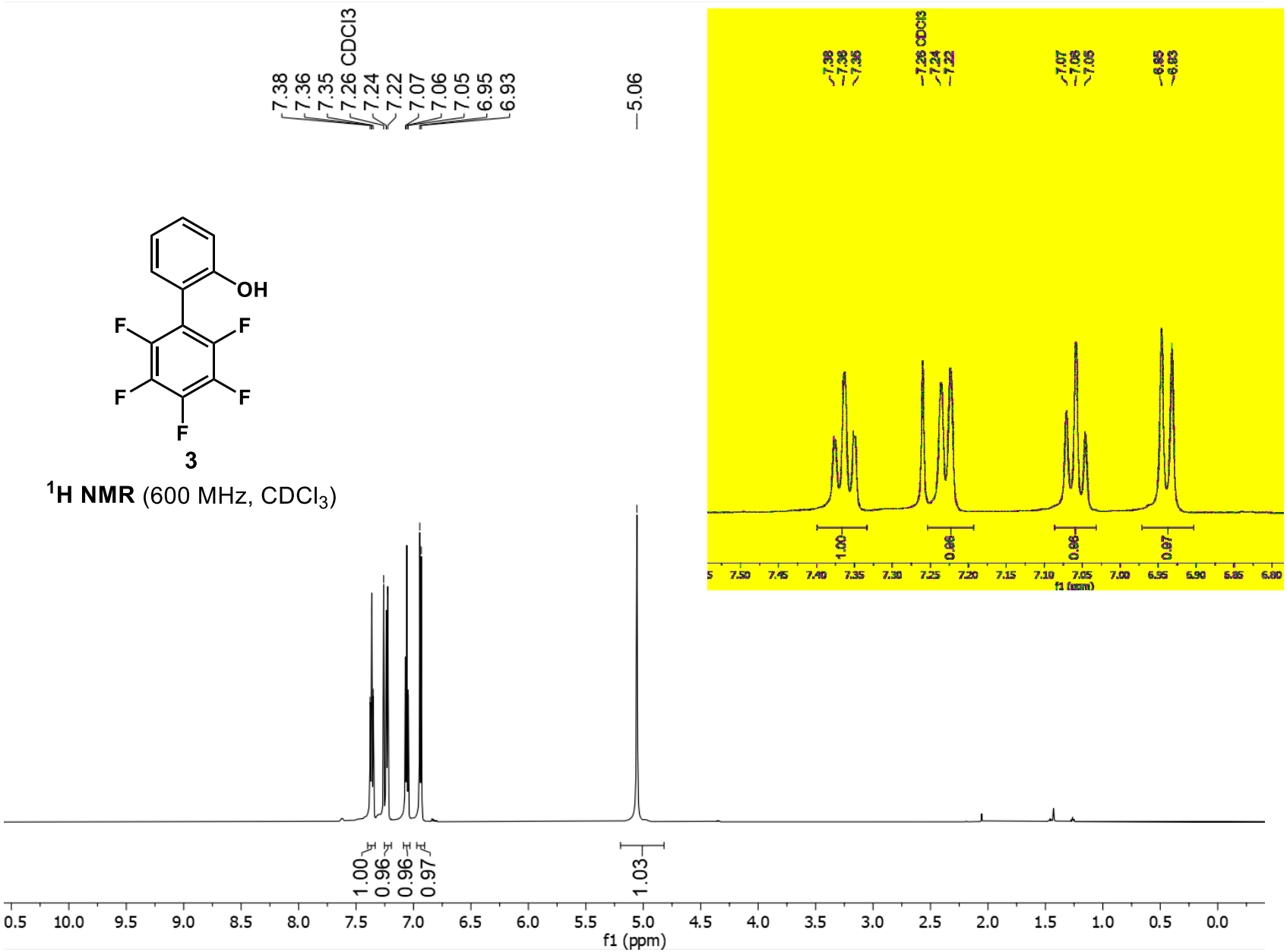
Tobias M. Leuther was born in Solingen, Germany in 1990. He studied chemistry at Cologne University and earned his B. Sc. in 2013 with Prof. Dr. Ralf Giernoth. For his Master's studies, he moved to Freiburg, Germany, where he completed his M.Sc. in 2015 with PD Dr. Jan Streuff. Back to Cologne, he finished his Ph.D. studies in the group of Prof. Berkessel in 2019. His research focused on catalytic asymmetric epoxidation with titanium salalen complexes.

Hauke Engler was born in Münster, Germany in 1987. He studied chemistry at the University of Göttingen and obtained his B.Sc. in 2011, and his M.Sc. in 2013, both in the group of Prof. Dr. Franc Meyer. After a short internship at the Max- Planck Institute for Coal Research, Mülheim in 2013, he started his Ph.D. in the group of Prof. Berkessel at the University of Cologne in 2014. The focus of his Ph.D. studies, which were completed in 2018, was on mechanistic aspects of the Ti-salalen-catalysed epoxidation of terminal olefins.

Albrecht Berkessel obtained his Ph.D. with Professor Waldemar Adam at Würzburg University in 1985. Later on, he joined the research group of Professor Ronald Breslow at Columbia University, New York. His habilitation at the University of Frankfurt/Main (associated to Professor Gerhard Quinkert) was completed in 1990. In 1992, he became Associate Professor at Heidelberg University. From 1997 to his retirement in 2021, he has served as Full Professor of Organic Chemistry at Cologne University. His research interests center around many aspects of catalysis, such as mechanism and method development, both in metal- and organocatalysis, as well as biomimetic and medicinal chemistry.

Mengei (Sophia) Xu was born in Shanghai, China. She moved to the U.S. for high school and obtained her B. S. in chemistry in 2022 from Emory Univerity, working with Prof. Simon Blakey. She then began her Ph.D. studies at UC Irvine and joined Prof. Vy Dong's group. Her doctoral work includes transition-metal catalyzed asymmetric hydrofunctionalizations and Pd-photocatalytic three component coupling.

Vy Dong received her Ph.D. from UC Berkeley/Caltech in 2004 under Professor David MacMillan. She then returned to UC Berkeley, working with Professors Robert Bergman and Kenneth Raymond as an NIH Postdoctoral Fellow. In 2006, she began her independent career at the University of Toronto and was appointed the Adrian Brook Distinguished Professor in 2011. She later relocated to UC Irvine, where she is now a Chancellor's Professor. Her research program spans complex molecule synthesis, asymmetric catalysis, mechanistic investigations, and pioneering photocatalysis and electrocatalysis.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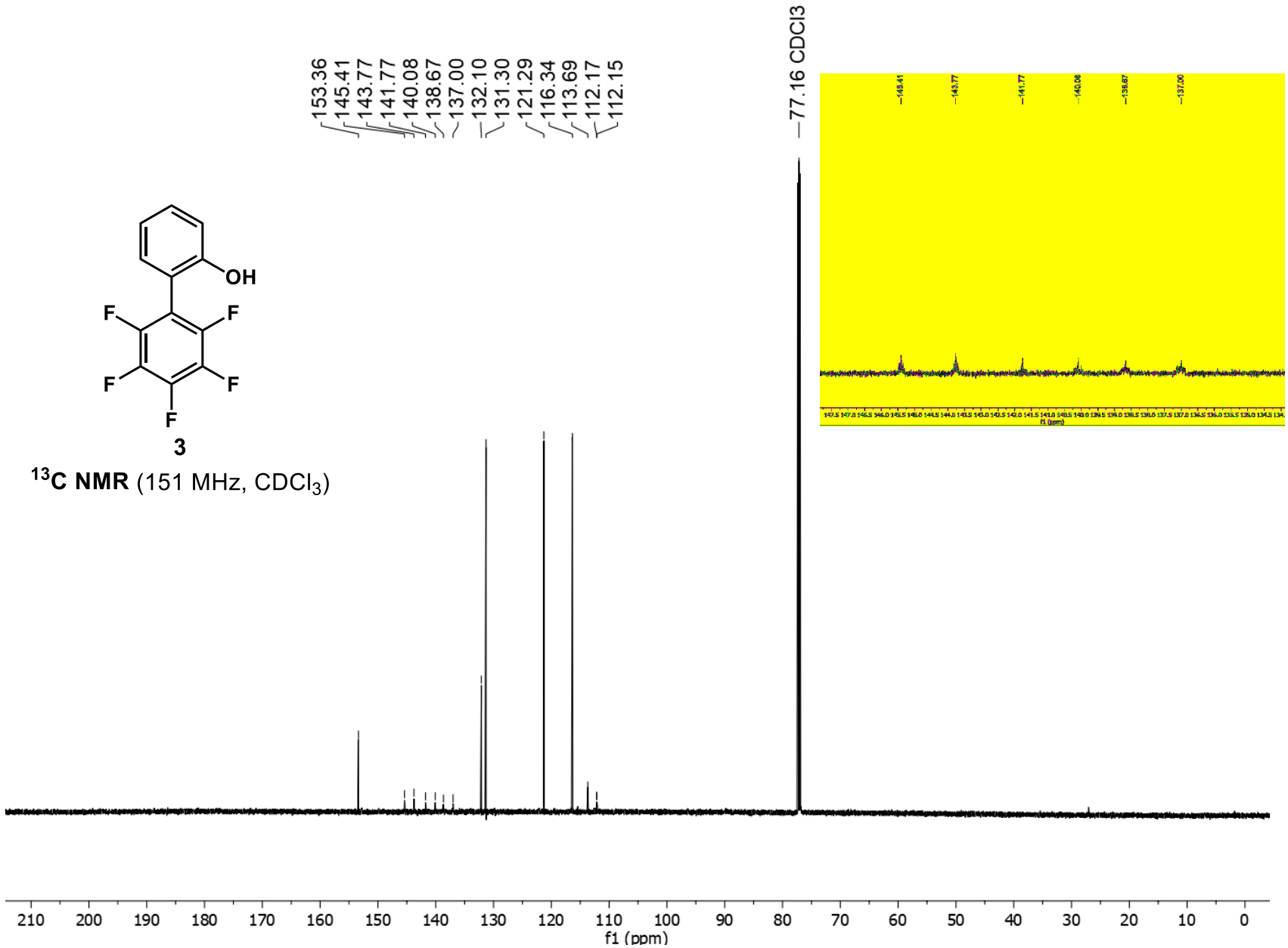
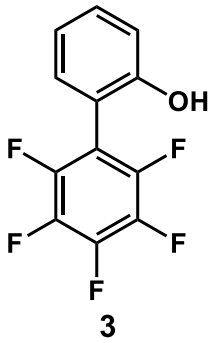
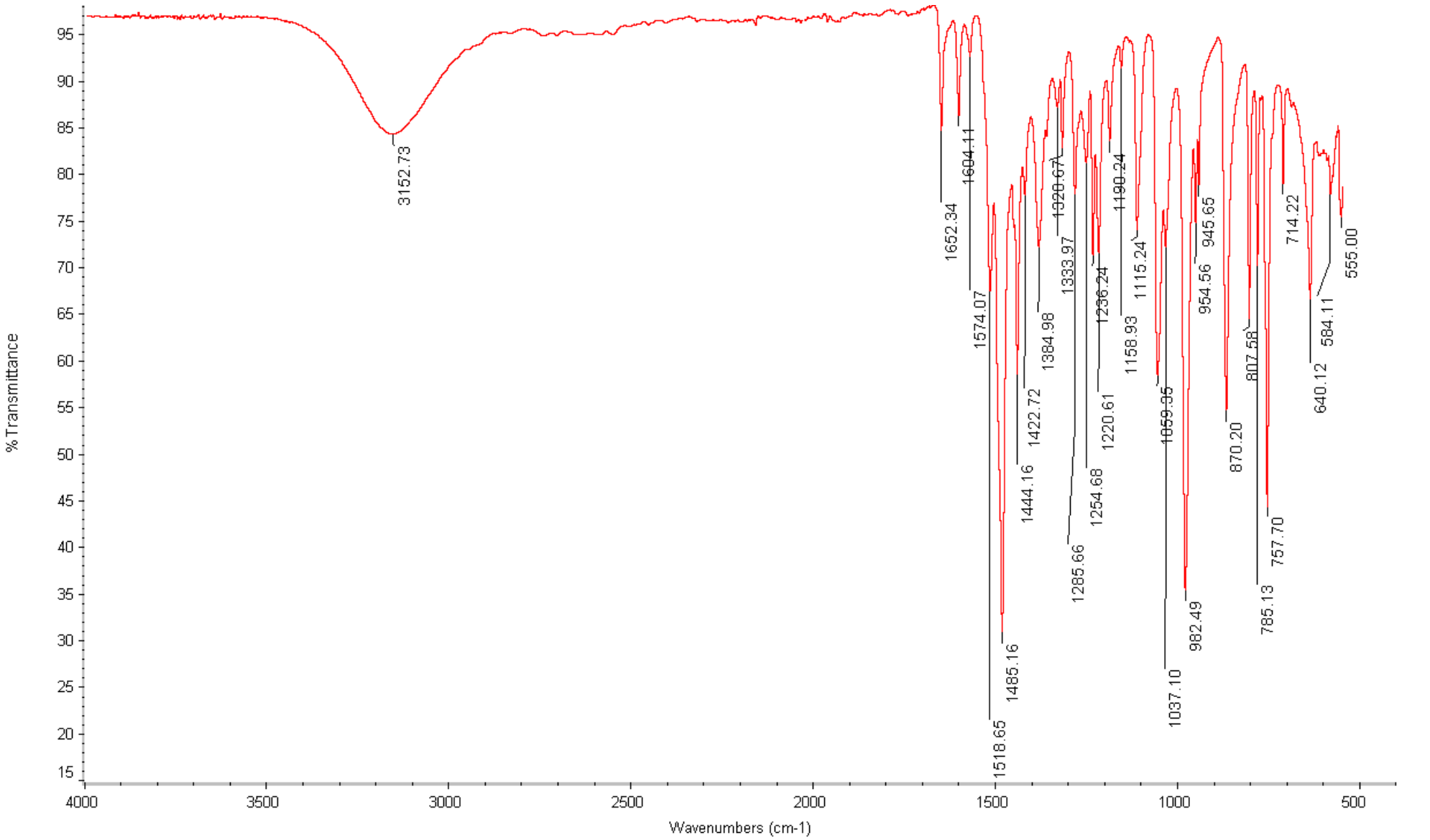
7.36
7.35
7.26 CDCl3
7.24
7.22
7.07
7.06
7.05
6.95
6.93
5.06
OH
F
F
F
F
F
3
1H NMR (600 MHz, CDCl3)
1.00
0.96
0.96
0.97
1.03
f1 (ppm)


153.36
145.41
143.77
141.77
140.08
138.67
137.00
132.10
131.30
121.29
116.34
113.69
112.17
112.15
77.16 CDCl3
OH
F
F
F
F
F
3
13C NMR (151 MHz, CDCl3)
f1 (ppm)



3

^{19}F NMR (565 MHz, $CDCl_3$)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Wavenumbers (cm-1)
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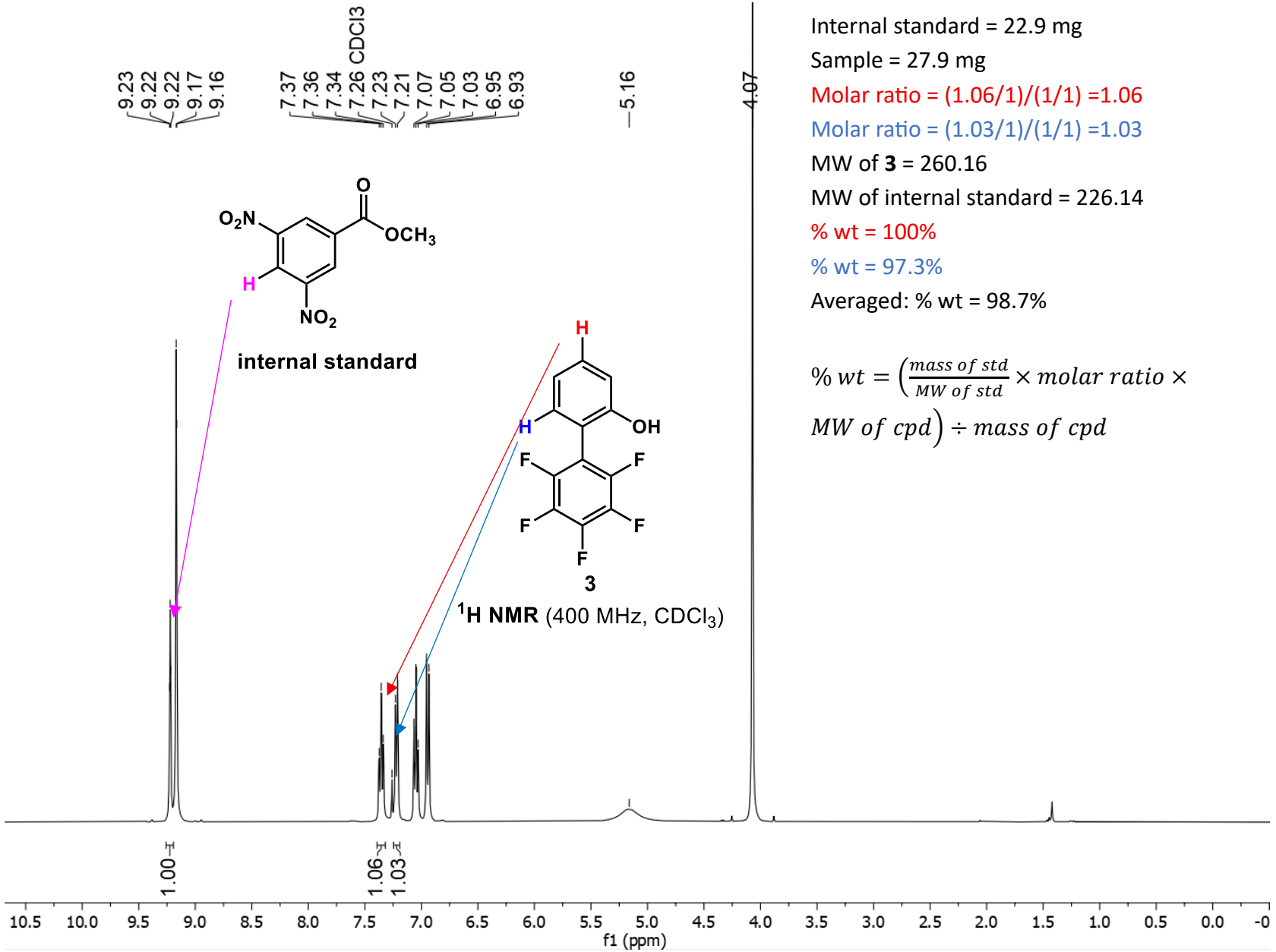
1604.11
1574.07
1518.65
1485.16
1444.16
1422.72
1384.98
1333.97
1320.07
1285.66
1254.68
1236.24
1220.61
1190.24
1158.93
1115.24
1059.95
1037.10
982.49
954.56
945.65
870.20
807.58
785.13
757.70
714.22
640.12
584.11
555.00



Internal standard = 22.9 mg

Sample = 27.9 mg

Molar ratio = (1.06/1)/(1/1) =1.06

Molar ratio = (1.03/1)/(1/1) =1.03

MW of **3** = 260.16

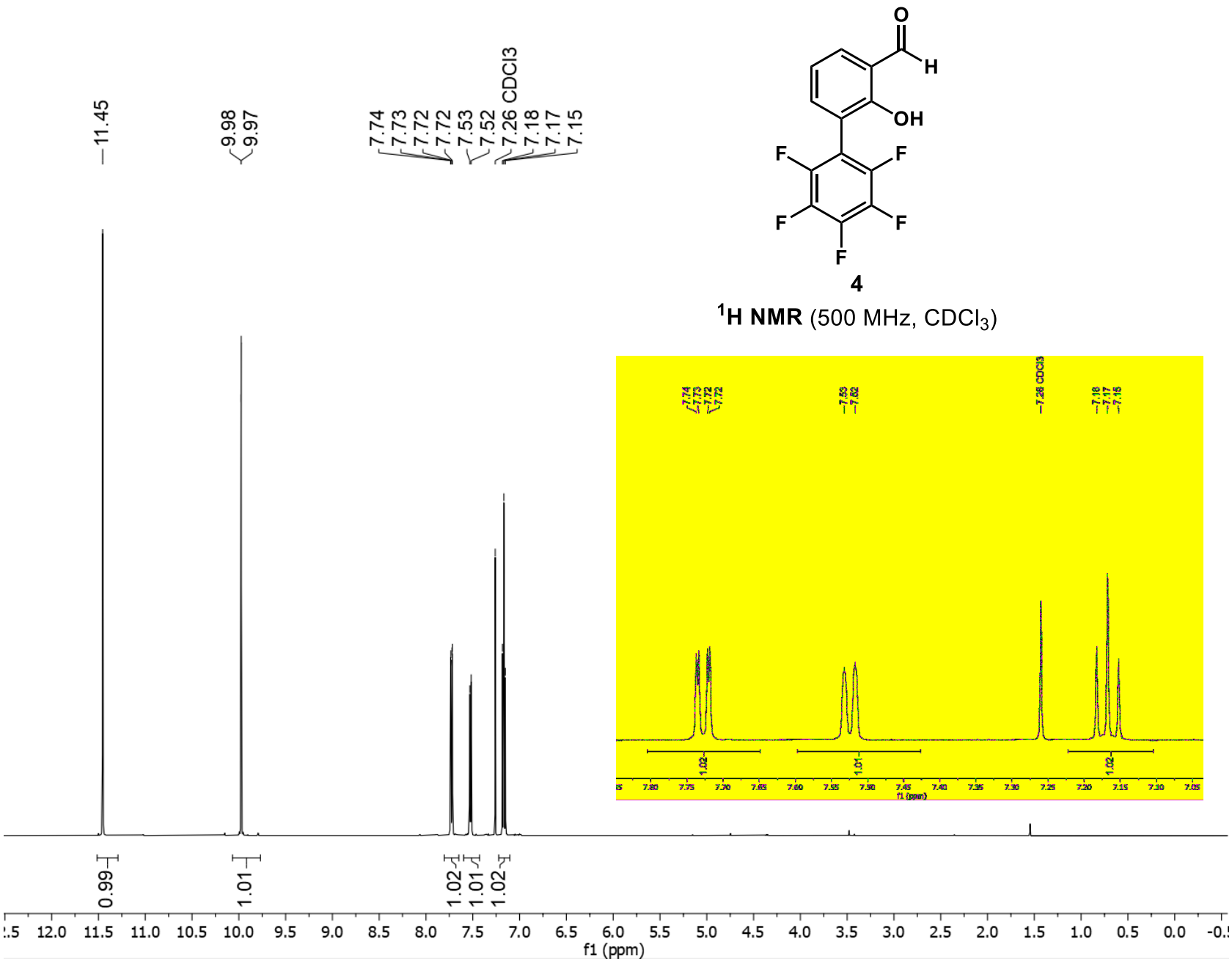
MW of internal standard = 226.14

% wt = 100%

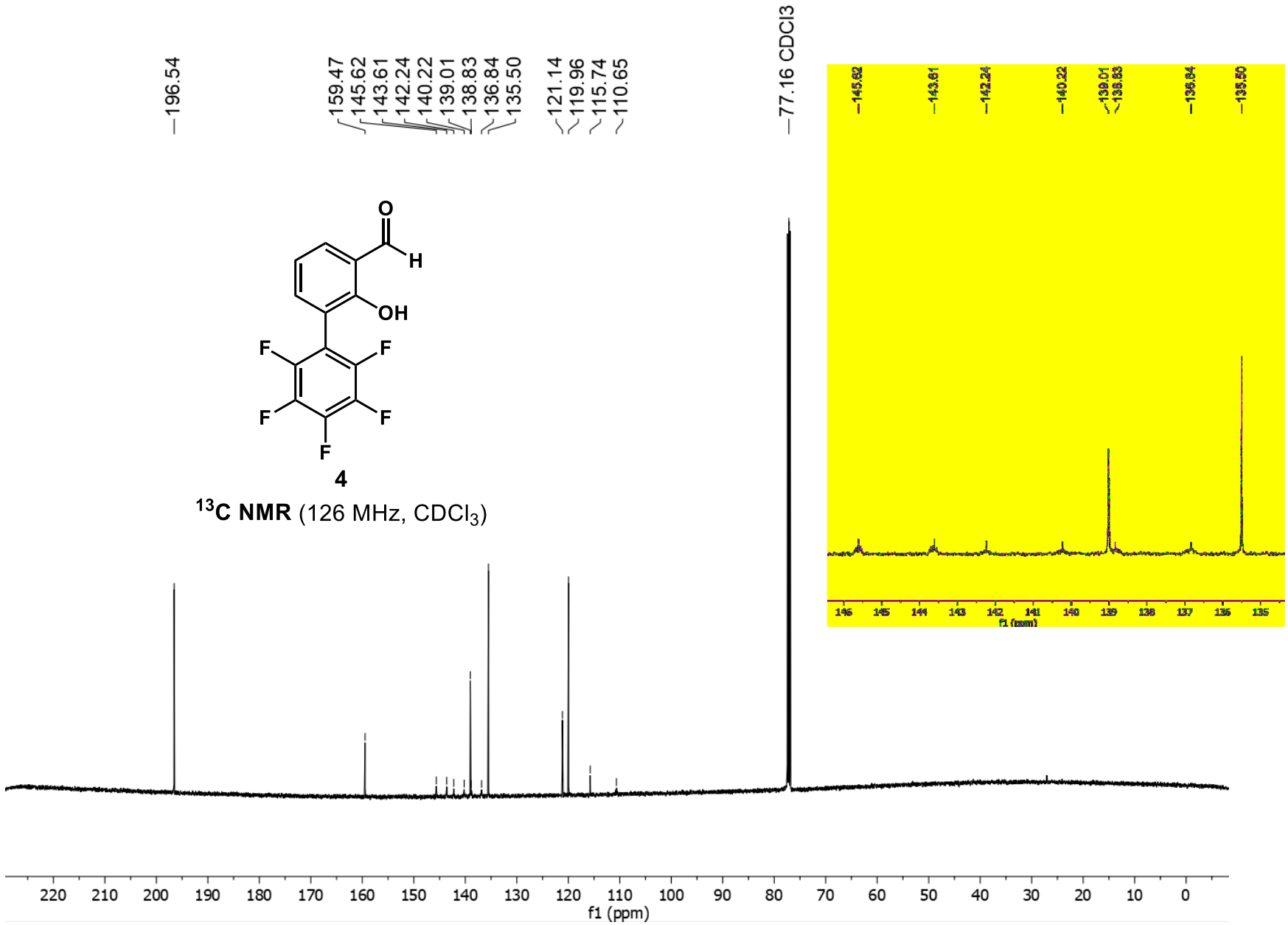
% wt = 97.3%

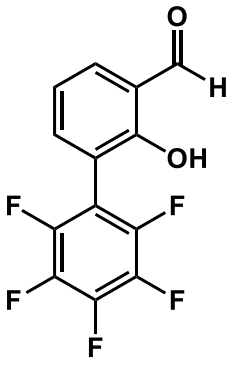
Averaged: % wt = 98.7%

$$\%\, wt = \left(\frac{mass\ of\ std}{MW\ of\ std} \times molar\ ratio \times MW\ of\ cpd\right) \div mass\ of\ cpd$$



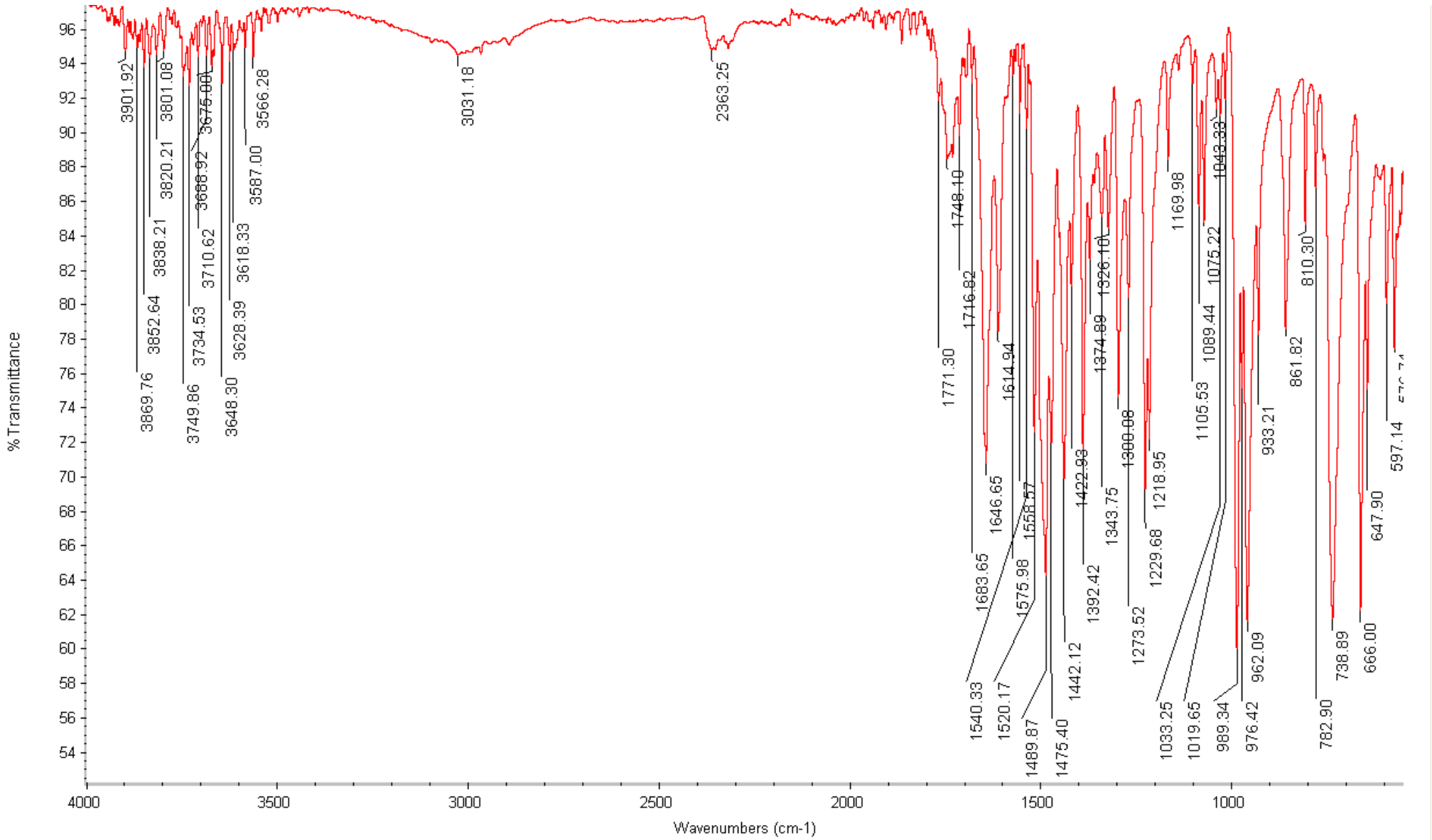
^{1}H NMR (500 MHz, $CDCl_3$)

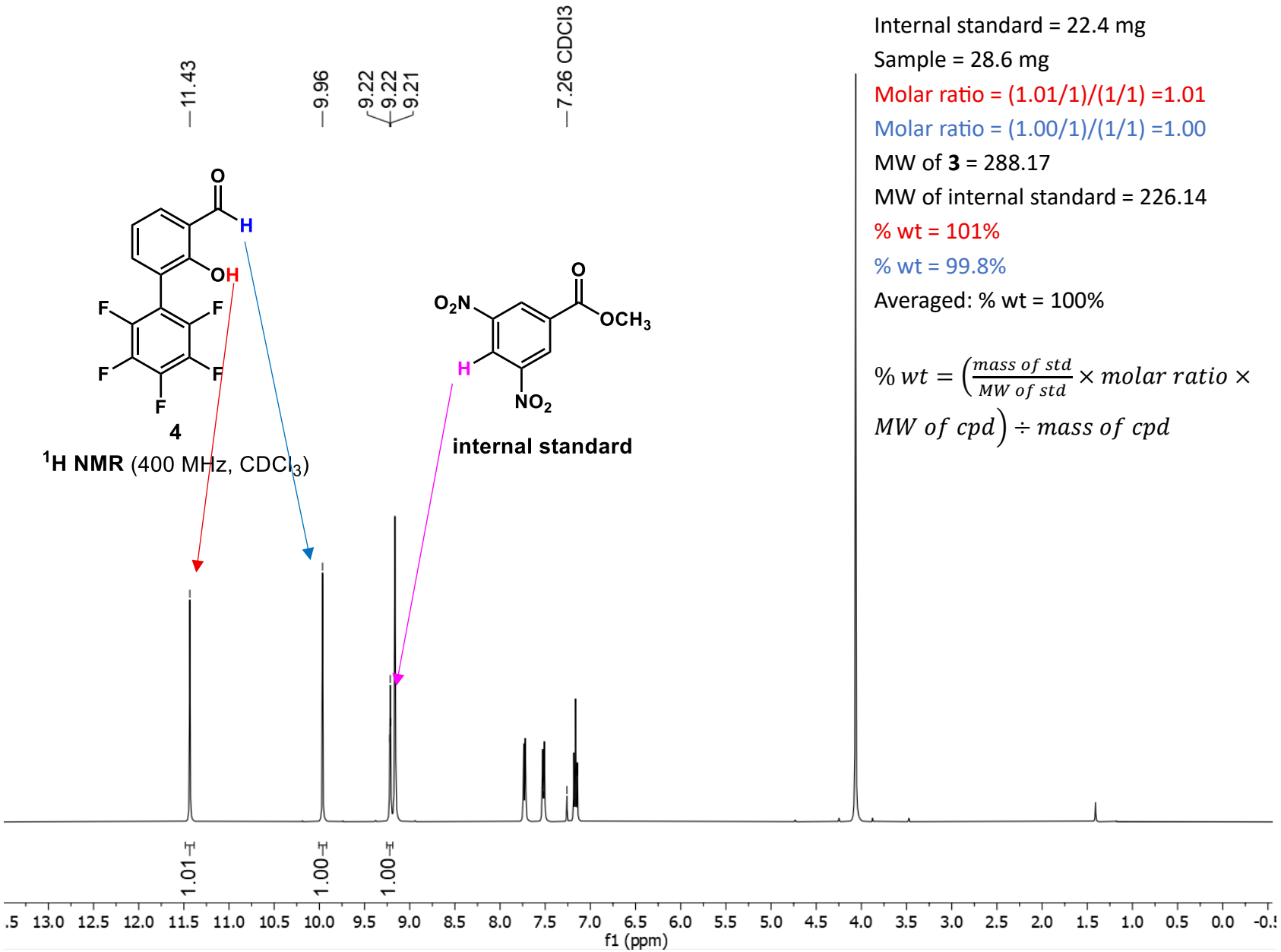

196.54
159.47
145.62
143.61
142.24
140.22
139.01
138.83
136.84
135.50
121.14
119.96
115.74
110.65
77.16 CDCl3
O
H
OH
F
F
F
F
F
4
13C NMR (126 MHz, CDCl3)
f1 (ppm)



4

^{19}F NMR (565 MHz, $CDCl_3$)


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
96
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
3901.92
3869.76
3852.64
3838.21
3820.21
3801.08
3749.86
3734.53
3710.62
3688.92
3675.00
3648.30
3628.39
3618.33
3587.00
3566.28
3031.18
2363.25
1771.30
1748.10
1716.82
1683.65
1646.65
1614.94
1575.98
1558.57
1540.33
1520.17
1489.87
1475.40
1442.12
1422.98
1392.42
1374.89
1343.75
1326.10
1300.08
1273.52
1229.68
1218.95
1169.98
1105.53
1089.44
1075.22
1043.33
1033.25
1019.65
989.34
976.42
962.09
933.21
861.82
810.30
782.90
738.89
666.00
647.90
597.14



Internal standard = 22.4 mg

Sample = 28.6 mg

Molar ratio = (1.01/1)/(1/1) =1.01

Molar ratio = (1.00/1)/(1/1) =1.00

MW of **3** = 288.17

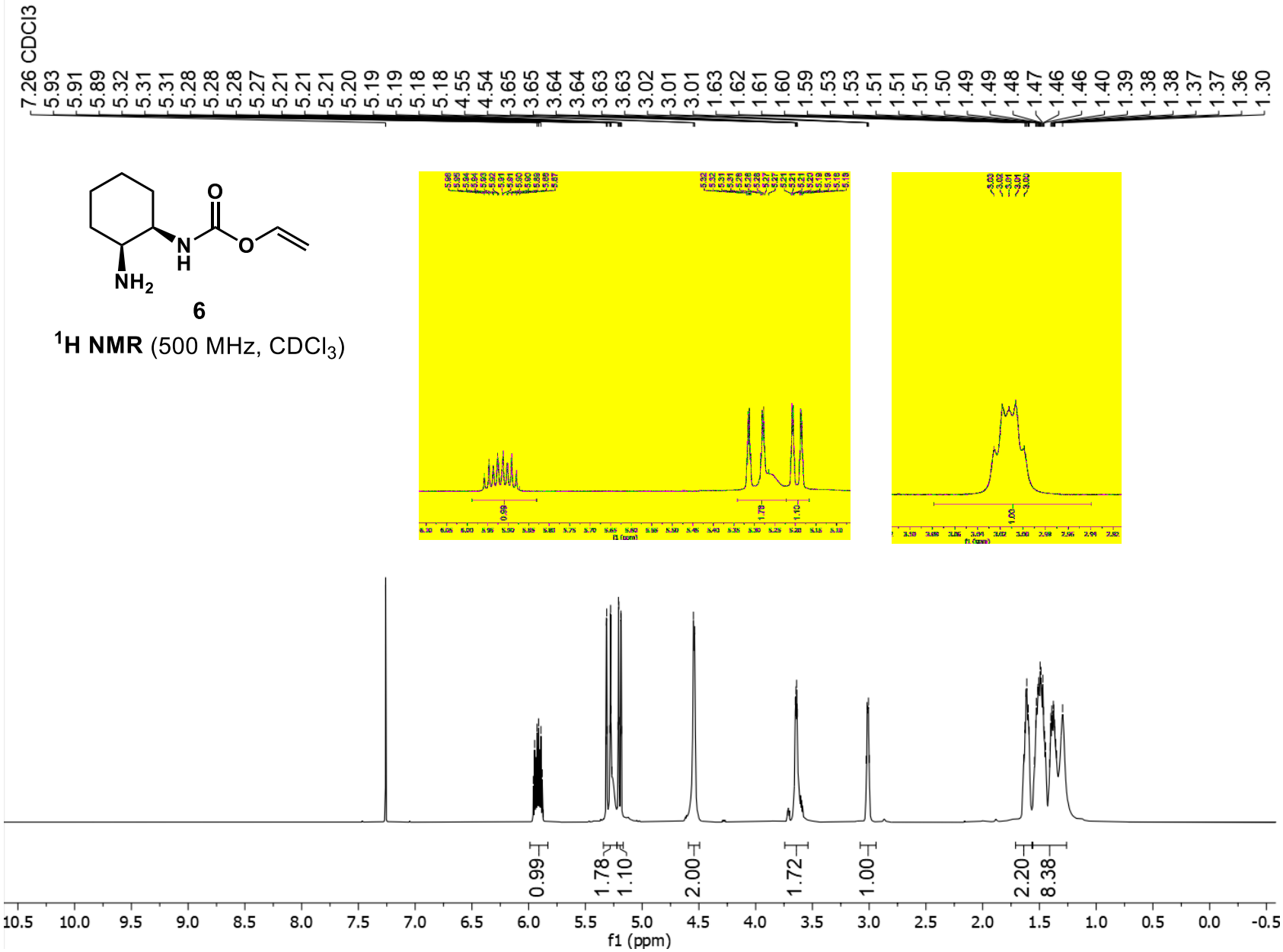
MW of internal standard = 226.14

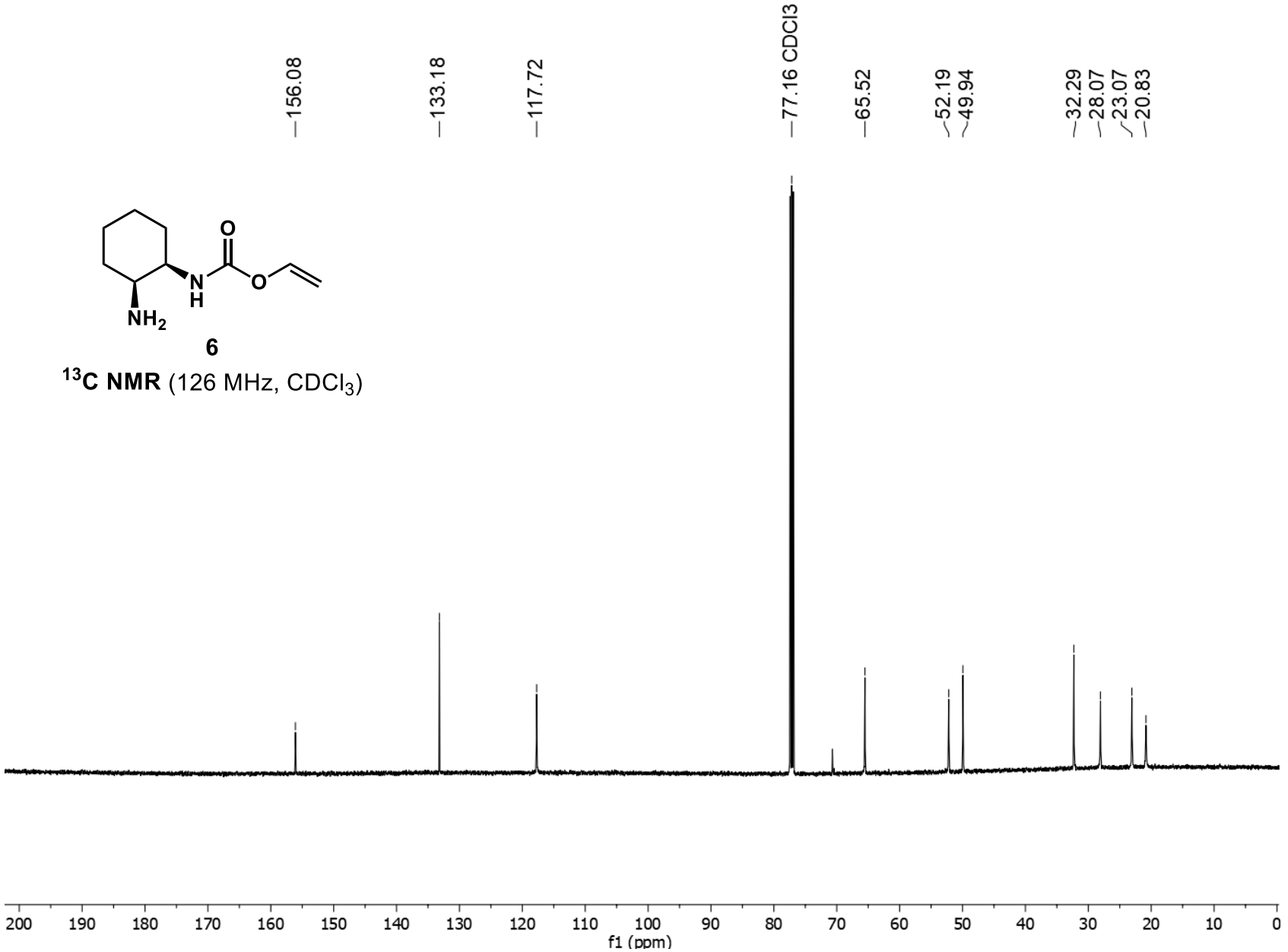
% wt = 101%

% wt = 99.8%

Averaged: % wt = 100%

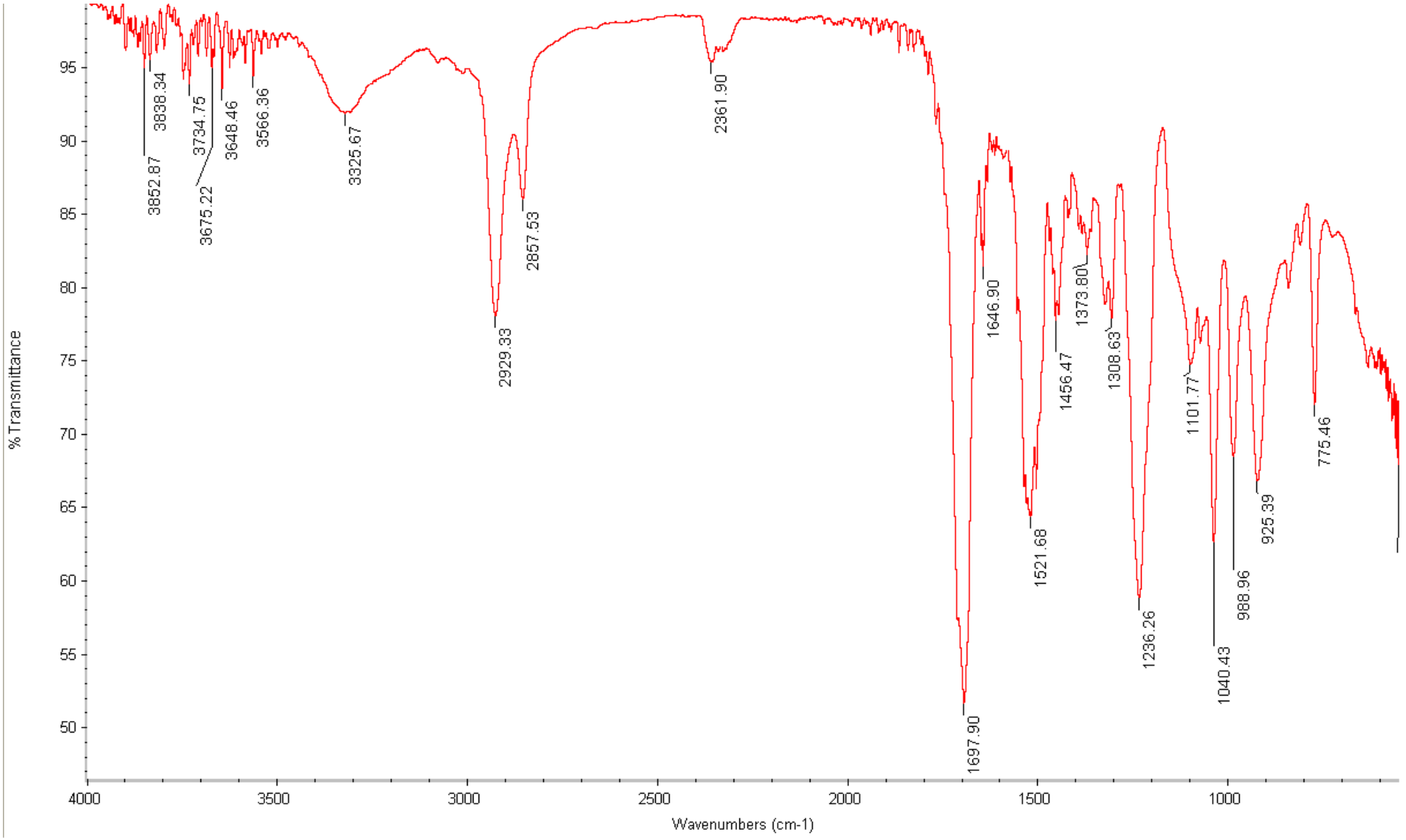
$$\%\ wt = \left(\frac{mass\ of\ std}{MW\ of\ std} \times molar\ ratio \times MW\ of\ cpd\right) \div mass\ of\ cpd$$

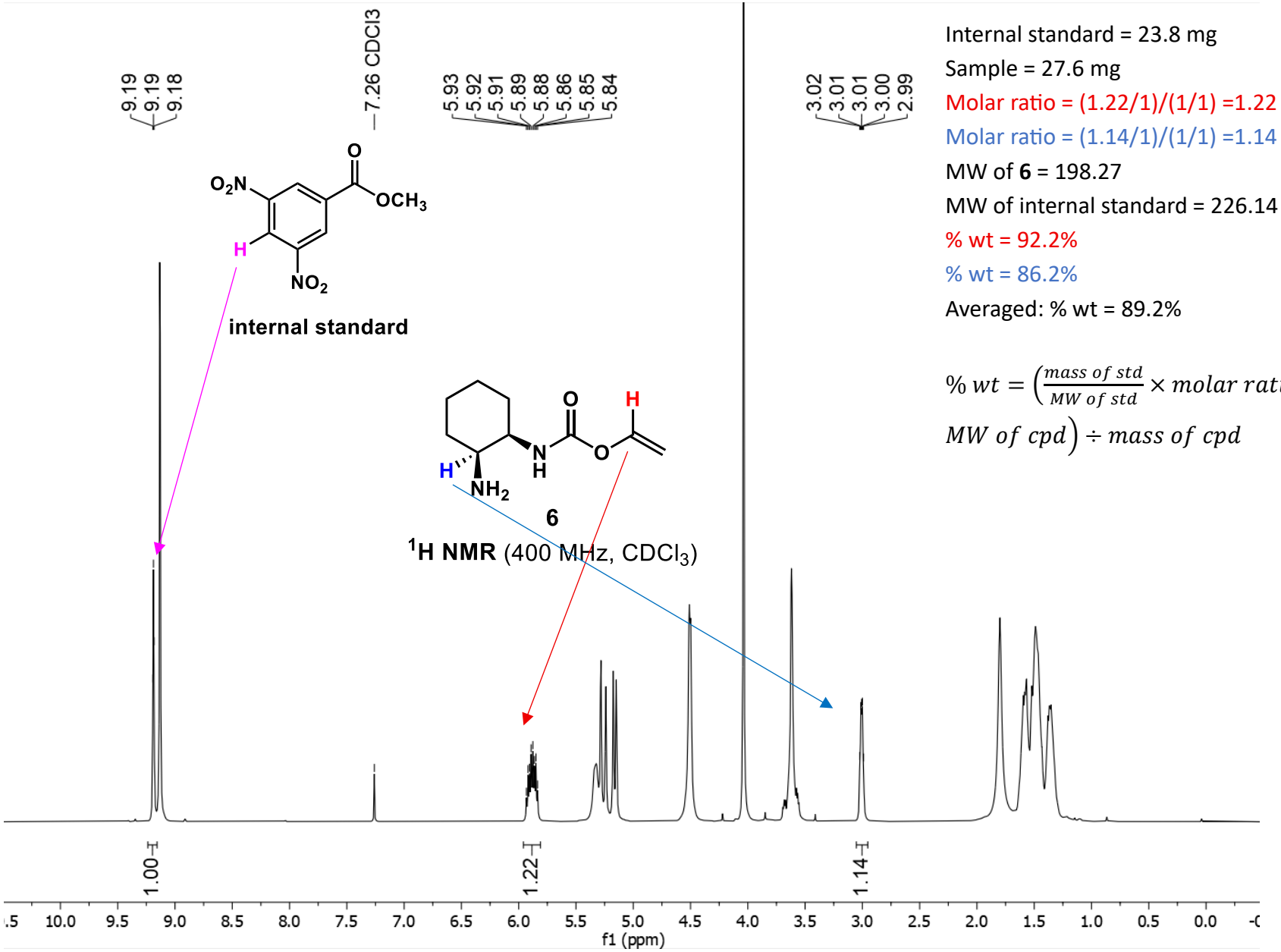

7.26 CDCl3
5.93 5.91 5.89 5.32 5.31 5.31 5.28 5.28 5.28 5.27 5.21 5.21 5.21 5.20 5.19 5.19 5.18 5.18 4.55 4.54 3.65 3.65 3.64 3.64 3.63 3.63 3.02 3.01 3.01 1.63 1.62 1.61 1.60 1.59 1.53 1.53 1.51 1.51 1.51 1.50 1.49 1.49 1.48 1.47 1.46 1.46 1.40 1.39 1.38 1.38 1.37 1.37 1.36 1.30
O
N
H
O
NH2
6
1H NMR (500 MHz, CDCl3)
0.99
1.78
1.10
2.00
1.72
1.00
2.20
8.38
f1 (ppm)



6

^{13}C NMR (126 MHz, $CDCl_3$)


% Transmittance
95
90
85
80
75
70
65
60
55
50
3852.87
3838.34
3734.75
3675.22
3648.46
3566.36
3325.67
2929.33
2857.53
2361.90
1697.90
1646.90
1521.68
1456.47
1373.80
1308.63
1236.26
1101.77
1040.43
988.96
925.39
775.46
4000
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



Internal standard = 23.8 mg

Sample = 27.6 mg

Molar ratio = (1.22/1)/(1/1) =1.22

Molar ratio = (1.14/1)/(1/1) =1.14

MW of **6** = 198.27

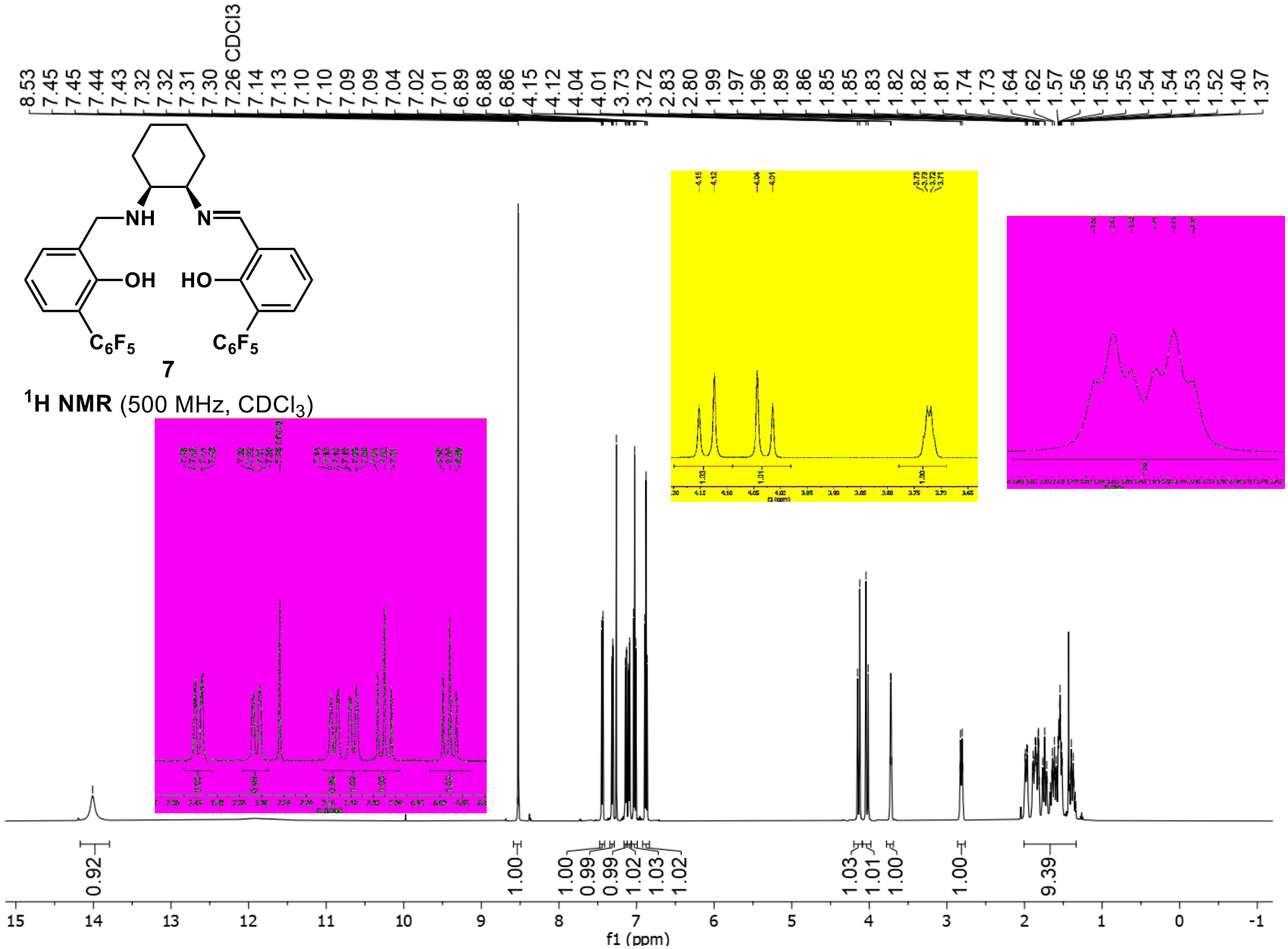
MW of internal standard = 226.14

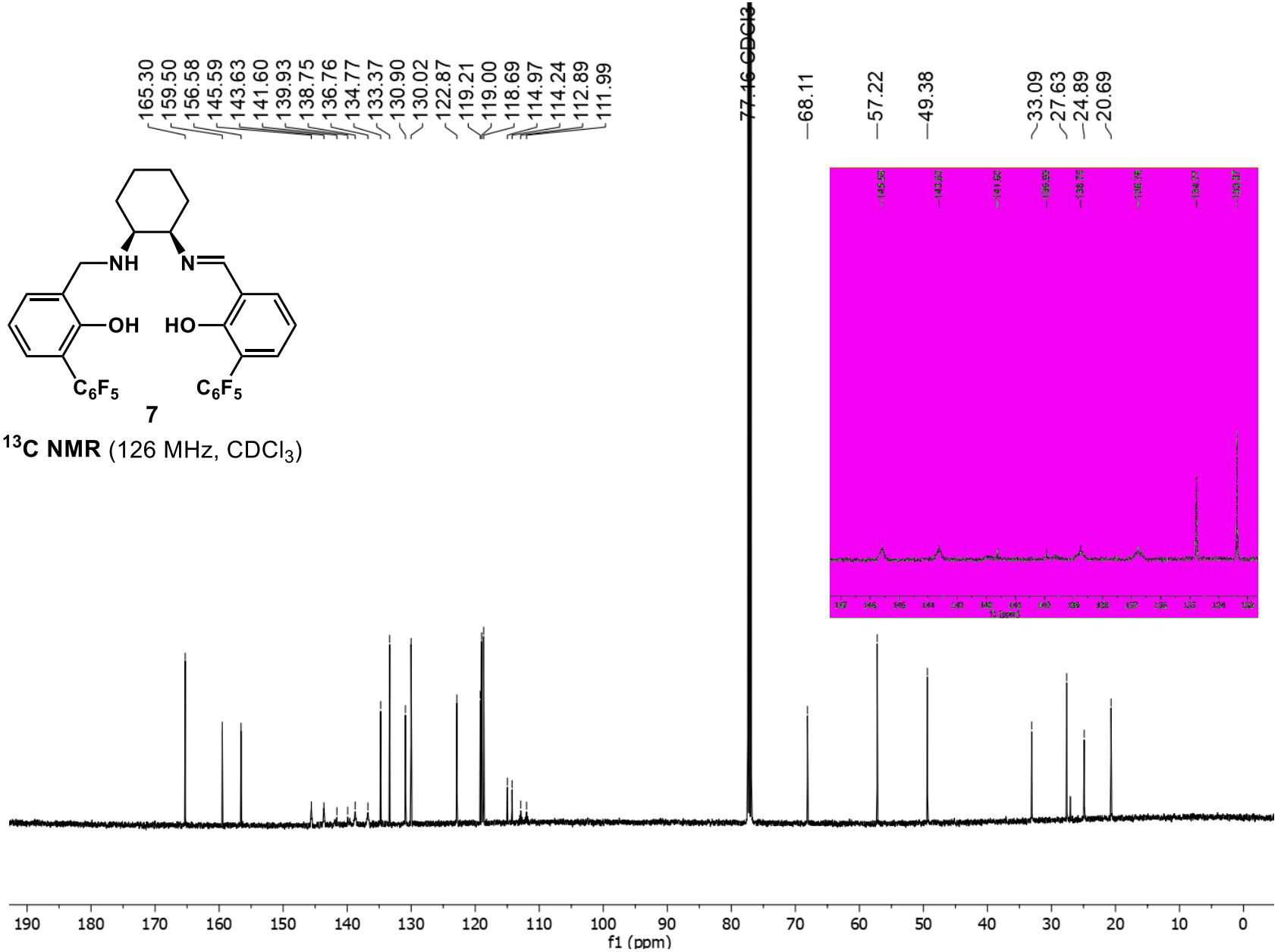
% wt = 92.2%

% wt = 86.2%

Averaged: % wt = 89.2%

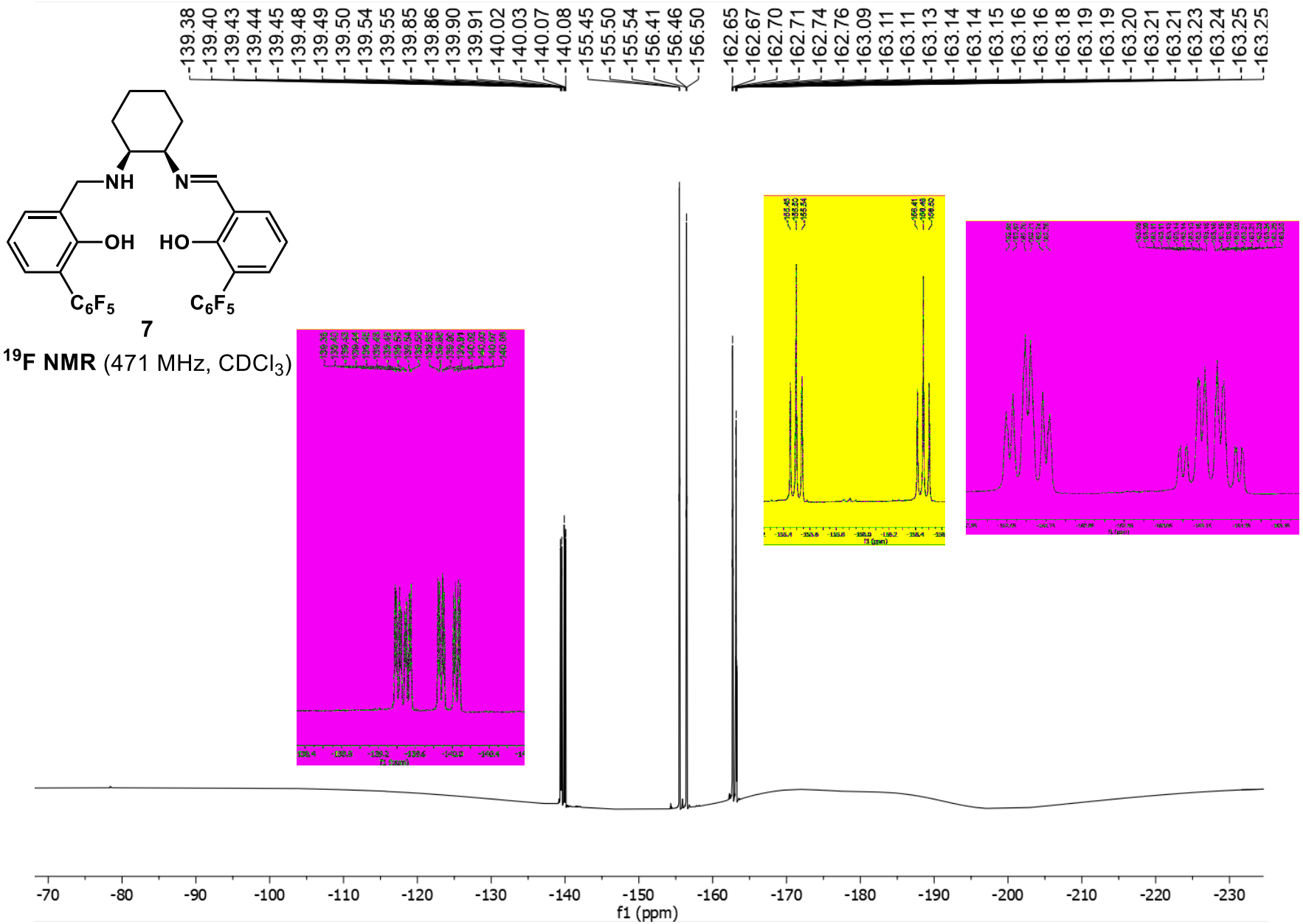
$$\%\, wt = \left(\frac{mass\ of\ std}{MW\ of\ std} \times molar\ ratio \times MW\ of\ cpd\right) \div mass\ of\ cpd$$

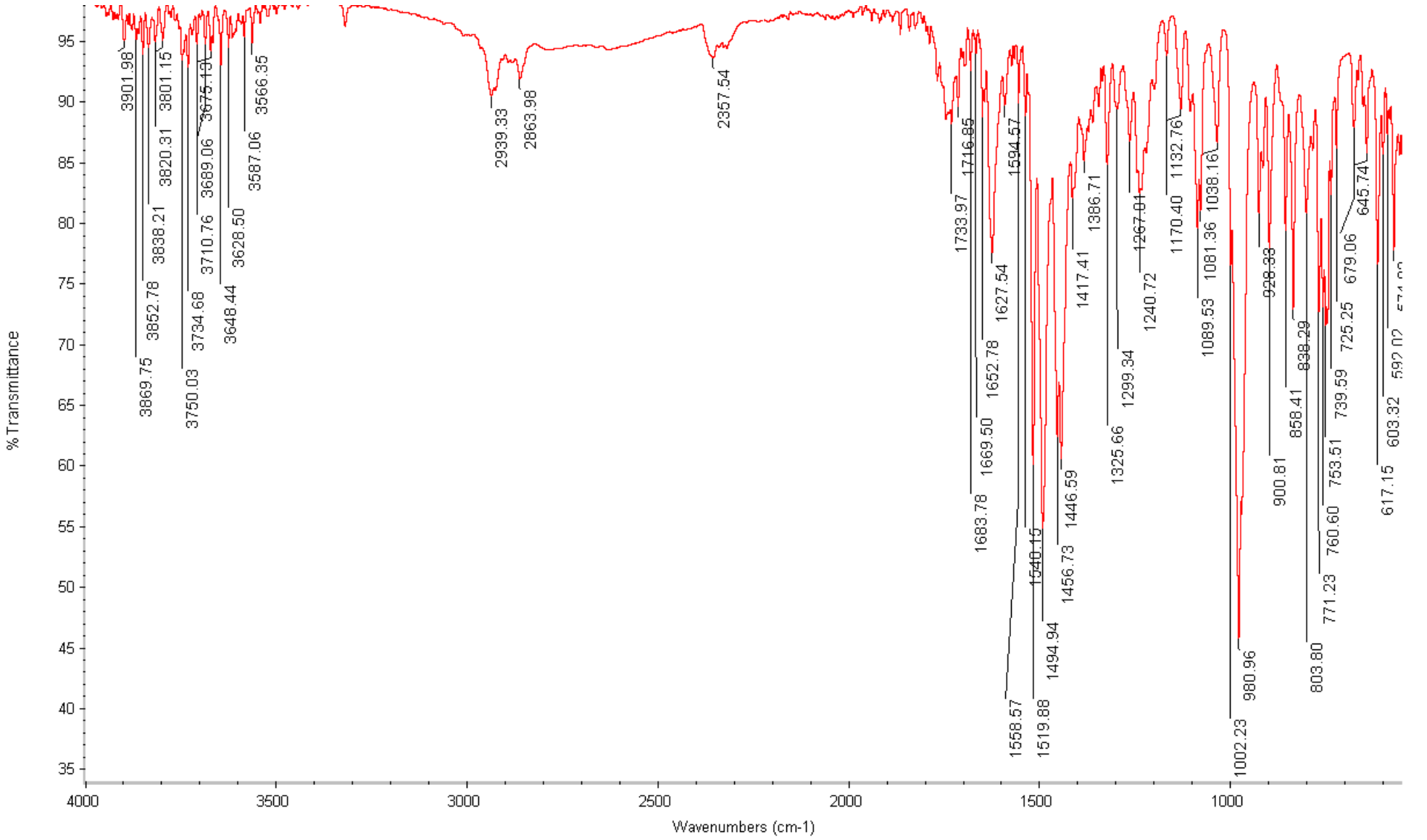

8.53 7.45 7.45 7.44 7.43 7.32 7.32 7.31 7.30 7.26 CDCl3 7.14 7.13 7.10 7.10 7.09 7.09 7.04 7.02 7.01 6.89 6.88 6.86 4.15 4.12 4.04 4.01 3.73 3.72 2.83 2.80 1.99 1.97 1.96 1.89 1.86 1.85 1.85 1.83 1.82 1.82 1.81 1.74 1.73 1.64 1.62 1.57 1.56 1.56 1.55 1.54 1.54 1.53 1.52 1.40 1.37
NH
N
OH
HO
C6F5
C6F5
7
1H NMR (500 MHz, CDCl3)
0.92
1.00
1.00
0.99
0.99
1.02
1.03
1.02
1.03
1.01
1.00
1.00
9.39
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)



7

^{13}C NMR (126 MHz, $CDCl_3$)


NH
N
OH
HO
C6F5
C6F5
7
19F NMR (471 MHz, CDCl3)
f1 (ppm)


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
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90
85
80
75
70
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3901.98
3869.75
3852.78
3838.21
3820.31
3801.15
3750.03
3734.68
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3689.06
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2939.33
2863.98
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900.81
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725.25
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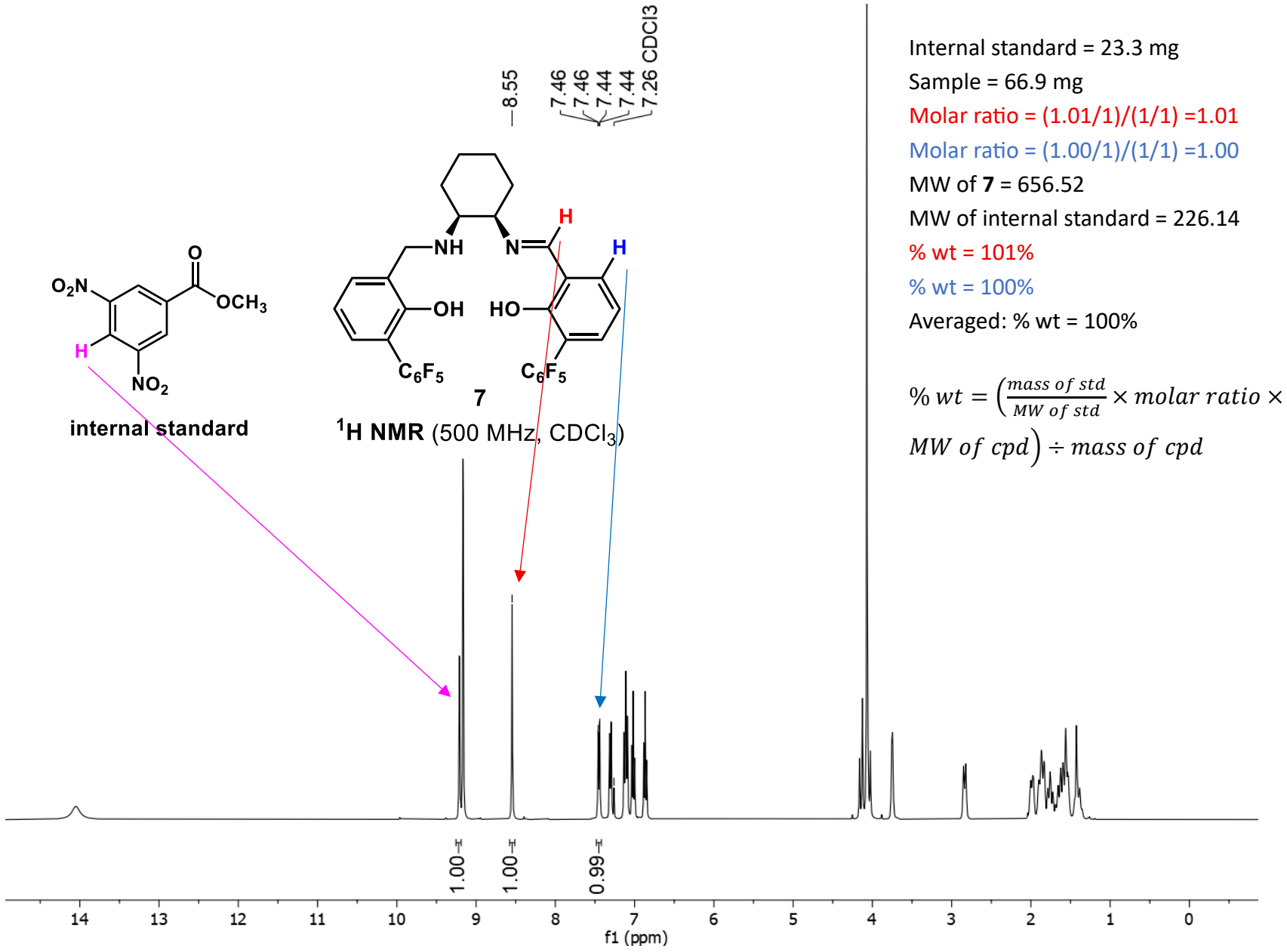
617.15
603.32



Internal standard = 23.3 mg

Sample = 66.9 mg

Molar ratio = (1.01/1)/(1/1) =1.01

Molar ratio = (1.00/1)/(1/1) =1.00

MW of **7** = 656.52

MW of internal standard = 226.14

% wt = 101%

% wt = 100%

Averaged: % wt = 100%

$$\%\ wt = \left(\frac{mass\ of\ std}{MW\ of\ std} \times molar\ ratio \times MW\ of\ cpd\right) \div mass\ of\ cpd$$