Organic Syntheses

(*S*)-1,1-Diphenylprolinol Trimethylsilyl Ether

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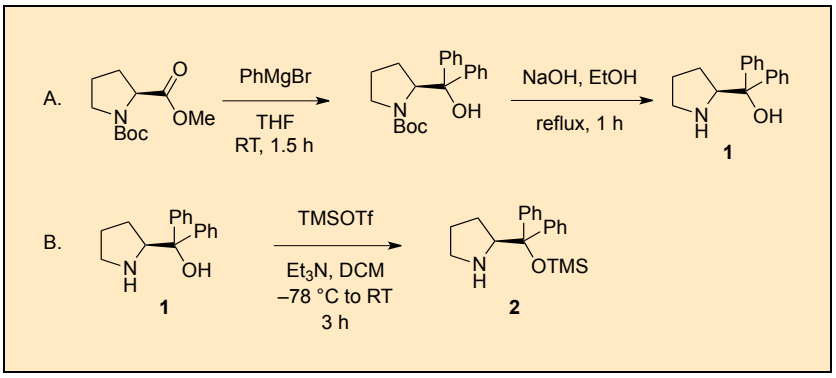
Checked by Eduardo V. Mercado-Marin and Richmond Sarpong



Procedure

A. *(S)-1,1-Diphenylprolinol (**1**).* A 1-L 24/40 three-necked round-bottomed flask is equipped with an egg-shaped, Teflon-coated, magnetic stir bar (15 x 32 mm). The left neck is capped with a rubber septum, the center neck is fitted with a Friedrich's condenser with an inert gas inlet connected to a dry nitrogen source and a bubbler, and the right neck with a 250-mL pressure equalizing addition funnel also capped with a rubber septum (Note 1). The flask is charged by syringe with 250 mL (0.25 mol, 2.5 equiv) of a 1M solution of phenylmagnesium bromide in tetrahydrofuran (THF) (Note 2). A solution of N-Boc-L-proline methyl ester (22.9 g, 100 mmol, 1.00 equiv) (Note 3) in THF (200 mL) (Note 4), is charged to the dropping funnel via syringe and added dropwise to the solution of the Grignard reagent via the addition funnel over 45 min. The reaction is stirred at ambient temperature for 90 min, and then cooled to 0 °C in an ice

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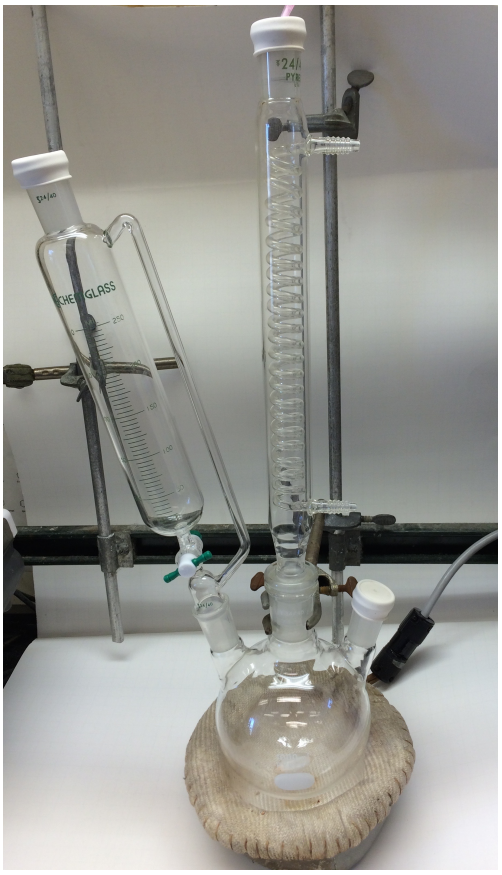

Figure 1. Glassware Assembly for Step A

water bath. The reaction is quenched over 5 min by the controlled addition of a saturated aqueous solution of ammonium chloride (150 mL) via addition funnel. The biphasic mixture is transferred to a 2-L separatory funnel and diluted with water (150 mL). The layers are separated, and the aqueous layer is extracted with diethyl ether (3 x 150 mL). The combined organic layers are dried over sodium sulfate (15 g) and gravity filtered through a large powder funnel equipped with a conical medium porosity filter paper into a 1-L single-necked (24/40) round-bottomed flask. The solvent is removed from the filtrate by rotary evaporation (30 mmHg) at room temperature, providing a clear colorless residue.

The flask containing the residue is equipped with an egg-shaped, Teflon-coated magnetic stir bar (15 x 32 mm). Ethanol (500 mL) (Note 5) is

added to the flask, followed by sodium hydroxide (40.0 g, 1.00 mol, 10.0 equiv) (Note 6) and stirring is initiated. The flask is fitted with a Friedrich's condenser open to the atmosphere. The flask is heated to reflux using a 1-L electric heating mantle and allowed to stir at reflux for 1 h. Heating is discontinued, the Friedrich's condenser removed, and the reaction is concentrated by rotary evaporation using a 50 °C water bath (30 mmHg), providing a light yellow amorphous solid. The residue is dissolved in water (200 mL) and diethyl ether (200 mL), and the resulting biphasic mixture is transferred to a 1-L separatory funnel. The layers are separated and the aqueous layer is extracted with diethyl ether (2 x 200 mL). The combined organic layers are washed successively with water (200 mL) and a saturated aqueous solution of sodium chloride (200 mL). The organic layer is dried over sodium sulfate (15.0 g), and filtered through a large powder funnel containing a conical medium porosity filter paper into a 1-L round-bottomed flask. The solution is concentrated by rotary evaporation (50 mmHg) at room temperature to afford a light yellow solid. The solid is dissolved in 200 mL of boiling hexanes, 2.5 g decolorizing carbon is added, and the solution is filtered hot through a large powder funnel equipped with a conical medium porosity filter paper into a 500 mL Erlenmeyer flask, submerged in a water bath heated to 70 °C, that contains refluxing hexanes (30 mL). Once the filtration is complete, the flask is cooled to 0 °C and kept at 0 °C for 1 h, which results in crystallization (Note 7). The hexanes are decanted and the white crystals are washed with cold (0 °C) hexanes (3 x 20 mL), and the hexanes washes are successively decanted. The resulting moist crystalline solid is transferred to a 250-mL 24/40 single-necked round-bottomed flask that is then fitted with a vacuum adaptor and dried on a vacuum pump (0.15 mmHg) overnight (14 h) to provide 14.04–15.64 g (55–62%) of *(S)-1,1-diphenylprolinol* (**1**) as white crystals (Notes 8 and 9). A second crop of crystals can be obtained by concentrating the mother liquor and hexanes washes by rotary evaporation (30 mmHg) to dryness, dissolving the residue in 50 mL boiling hexanes, then cooling the solution to 0 °C and ageing the solution for 1 h at 0 °C. After decanting the hexanes, the resulting crystalline solids are washed with cold hexanes (3 x 10 mL), isolated by decantation, and dried under vacuum (0.15 mmHg) overnight (14 h) to give 3.09–4.44 g (12–18%) (Note 8) of white crystals of comparable purity to the first crop. The total yield is 17.44–19.16 g (69–76%) (Note 10) of *(S)-1,1-diphenyl-prolinol* (**1**) with a melting point of 73–74 °C.

B. *(S)-1,1-Diphenylprolinol trimethylsilyl ether (**2**)*. A 1-L 24/40 single-necked round-bottomed flask is equipped with an egg-shaped, Teflon-

coated magnetic stir bar (15 x 32 mm) and a 60 mL pressure equalizing addition funnel fitted with a nitrogen inlet. The flask is placed under an atmosphere of nitrogen and flame dried. After cooling to ambient temperature, the flask is charged with a solution of *(S)-1,1-diphenylprolinol* (**1**) (17.7 g, 70.0 mmol, 1.00 equiv) in dichloromethane (350 mL) (Note 11). The solution is cooled to –78 °C in a dry ice and acetone bath, followed by addition of triethylamine (12.7 mL, 9.20 g, 91.0 mmol, 1.30 equiv) (Note 12) in one portion by syringe. Trimethylsilyl trifluoromethanesulfonate (16.5 mL, 20.2 g, 91.0 mmol, 1.30 equiv) (Note 13) is added dropwise via the addition funnel over 30 min. The reaction mixture is stirred and allowed to warm to 0 °C over 2 h. The cooling bath is removed and the reaction mixture is allowed to warm to ambient temperature over 1 h. The reaction is quenched by addition of a solution of sat aq. sodium bicarbonate (100 mL) over 0.5 min. The mixture is diluted with water (100 mL) and transferred to a 1-L separatory funnel. The phases are separated, and the aqueous phase is extracted with dichloromethane (3 x 100 mL). The combined organic phases are dried over anhydrous sodium sulfate (15 g), then gravity filtered through a powder funnel equipped with a medium porosity conical filter paper. The filtrate is concentrated by rotary evaporation (30 mmHg) to afford the impure product as an orange oil. Purification by column chromatography with elution by 60% diethyl ether/hexanes yields 17.51–17.60 g (77–78%) of *(S)-1,1-diphenylprolinol trimethylsilyl ether* (**2**) as a light yellow oil (Note 14).

Notes

1. The submitters recommend that the apparatus be assembled under an atmosphere of nitrogen and flame dried.
2. The Grignard reagent was prepared using the following procedure: A 24/40 1-L three-necked round-bottomed flask equipped with an egg-shaped Teflon coated magnetic stir bar (15 x 32 mm), a Friedrich's condenser with an inert gas inlet in the middle neck, 250-mL pressure equalizing addition funnel capped with a rubber septum in the right neck. Magnesium turnings (6.7 g, 275 mmol, 2.75 equiv) are added to the flask through the remaining open neck. The flask is sealed by capping the open neck with a rubber septum and stirring is initiated. The apparatus is placed under an atmosphere of nitrogen and flame

dried. After allowing the apparatus to cool to ambient temperature, a crystal of iodine (50 mg, 0.2 mmol) is dissolved in 125 mL of anhydrous THF (Note 3) and added via syringe, resulting in a light brown transparent solution. Bromobenzene (26.3 mL, 39.3 g, 250 mmol, 2.5 equiv) is added to the addition funnel, and one quarter of the volume is added to the flask over a one minute period. The flask is heated by a 1-L electric heating mantle until the iodine color dissipates (~45 °C). Heating is stopped, and 125 mL of anhydrous THF is added to the addition funnel to dilute the bromobenzene. The bromobenzene solution is then added dropwise to the flask at a rate sufficient to maintain reflux in the flask (added over 20 min). The clear solution becomes cloudy and brown during the addition. When the addition is complete, heat is reapplied using a 1 L electric heating mantle and the flask is allowed to stir at reflux for 1 h. Heating is discontinued, and the brown cloudy reaction mixture containing unused magnesium is cooled to ambient temperature and used as obtained.

3. *N-(tert-Butoxycarbonyl)-L-proline methyl ester* was prepared by methyl esterification of *N-(tert-butoxycarbonyl)-L-proline.* A 2-L (24/40), single-necked round-bottomed flask, fitted with a 100 mL pressure equalizing addition funnel capped with rubber septum, and egg-shaped Teflon-coated magnetic stir bar (15 x 32 mm) is charged with a solution of *N*-(*tert*-butoxycarbonyl)-*L*-proline (110 g, 0.52 mol, 1 equiv) (prepared from *L*-proline, which was obtained from Spectrum Chemical and used as received, according to the procedures: Keller, O.; Keller, W. E.; van Look, G.; Wersin, G., *Org. Synth.* **1985**, *63*, 160.) in 1.33 L of dimethylformamide (≥99.8%, obtained from Sigma-Aldrich and used as received) and potassium carbonate (obtained from Spectrum Chemical and used as received) (78.4 g, 0.57 mol, 1.1 equiv). Stirring is initiated and the suspension is cooled to 0 °C in an ice water bath and methyl iodide (64.0 mL, 1.03 mol, 2.0 equiv) (99%, obtained from Sigma-Aldrich and used as received) is added dropwise via addition funnel over a period of 10 min. After the addition is complete, the reaction is allowed to warm to ambient temperature and stirring is continued for 15 h. The reaction mixture is filtered through a bed of 15 g of Celite® in a 100-mL coarse fritted funnel and the filter cake is washed with diethyl ether (750 mL). The filtrate is transferred to a 4-L separatory funnel, diluted with of water (750 mL) and extracted with diethyl ether (3 x 375 mL). The combined organic phases are washed successively with water (3 x 750 mL) and sat brine (750 mL), dried over magnesium sulfate

(25.0 g), and vacuum filtered. The filtrate is concentrated *in vacuo* using a 30 °C water bath (30 mmHg) providing the crude product ester (109 g, 92%) as a yellow oil which is used without further purification.

4. Tetrahydrofuran (inhibitor free, Optima®, 99.9%) was obtained from Fisher Scientific and degassed by argon-bubbling for 1 h before being passed through an activated alumina column using a GlassContour solvent system. The solvent is withdrawn from the receiver flask with a syringe.
5. Ethanol (anhydrous) was obtained from Spectrum Chemical and used as received.
6. Sodium Hydroxide (pellets, certified ACS) obtained from Spectrum Chemical and used as received.
7. In the event that crystallization did not occur, the solution was transferred to an etched 500 mL round-bottomed flask cooled to 0 °C and aged for 1 h at 0 °C, which resulted in crystallization.
8. Step A was checked three times, and the yields represent the range of the three trials.
9. Physical properties of *(S)-1,1-diphenylprolinol* (**1**): ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.52–1.82 (m, 5H), 2.89–2.99 (m, 1H), 2.99–3.10 (m, 1H), 4.26 (t, *J* = 7.7 Hz, 1H), 4.65 (s(br)), 1H), 7.11–7.23 (m, 2H), 7.24–7.36 (m, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 25.6, 26.4, 46.9, 64.6, 77.2, 125.7, 126.0, 126.5, 126.6, 128.1, 128.3, 145.6, 148.3. IR (neat): 3354, 3057, 3024, 2945, 2870, 1597, 1491, 1448, 1397, 1171, 991, 746, 696, 659, 634 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{20}NO$ [M+H$^+$] 254.1539; Found: 254.1535. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.64; H, 7.63; N, 5.43.
10. Step A was checked three times with the following results. Run A: 1st Crop: 14.04 g; 2nd Crop: 4.44 g; Total: 18.48 g. Run B: 1st Crop: 15.64 g; 2nd Crop: 3.52 g; Total: 19.16 g. Run C: 1st Crop: 14.35 g; 2nd Crop: 3.09 g; Total: 17.44 g.
11. Dichloromethane (Methylene Chloride, HPLC grade) was obtained from Fisher Scientific and was distilled over calcium hydride prior to use.
12. Triethylamine (HPLC grade, 99%) was obtained from Fisher Scientific and used as received.
13. Trimethylsilyl trifluoromethanesulfonate (99%) was obtained from Oakwood Chemical and used as received.
14. TMS Prolinol **2** is purified on a column (9 x 55 cm) packed with 200 g of silica (obtained from EMD Millipore, 60Å pore size, 230 - 400 mesh) in

30% diethyl ether/hexanes. Fraction collection (500 mL fractions) begins immediately; the column is eluted with 1.5 liters 30% diethyl ether/hexanes, 2 liters 60% diethyl ether/hexanes, then flushed with 1.5 liters of diethyl ether. Fractions 2-7 are pooled and contain the desired product. The product has an R_f of 0.06 in ether but will streak up the plate significantly if concentrated. Physical properties of *(S)-1,1-diphenylprolinol trimethylsilyl ether* (**2**) are: ^{1}H NMR (600 MHz, $CDCl_3$) δ: –0.09 (s, 9H), 1.31 – 1.42 (m, 1H), 1.50 – 1.63 (m, 3H), 1.69 (s(br)), 1H), 2.75 – 2.82 (m, 1H), 2.82 – 2.88 (m, 1H), 4.03 (t, J = 7.0 Hz, 1H), 7.19 – 7.30 (m, 6H), 7.35 (d, J = 6.9 Hz, 2H), 7.46 (d, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 2.3, 25.2, 27.7, 47.3, 65.6, 83.3, 126.9, 127.0, 127.65, 127.72, 127.74, 128.6, 145.9, 147.0. IR (neat): 3059, 3025, 2953, 1492, 1446, 1402, 1313, 1100, 1069, 877, 833, 749, 698 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{28}NOSi$ $[M+H^+]$ 326.1935; Found: 326.1927. Anal. Calcd for $C_{20}H_{27}NOSi$: C, 73.79, H, 8.36, N, 4.30, found: C, 73.82, H, 8.33, N, 4.26.

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

The proline based catalyst (*S*)-1,1-diphenylprolinol trimethylsilyl ether (**2**) has been used extensively in organic chemistry to successfully affect a variety of reactions, including α, β, and even γ-activation of aldehydes by enamine and iminium-ion chemistry.[2] The robustness of this catalyst system is demonstrated by its application to multicomponent cascades to form highly substituted piperidines,[3] cyclohexenes,[4] and hydropyrans.[5]

(*S*)-1,1-Diphenylprolinol trimethylsilyl ether (**2**) is readily prepared by the silylation of (*S*)-1,1-diphenylprolinol (**1**), however, commercial sources of diphenylprolinol can be prohibitively expensive, and current methods for the synthesis of diphenylprolinol and its derivatives are low yielding, practically challenging on scale, or include hazardous reagents such as phosgene.[6] Because of the prevalence of the diphenylprolinol catalysts and the lack of a practical synthesis, we desired an efficient, scalable synthesis of diphenylprolinol (**1**) and its derivatives.

The method reported provides access to diphenylprolinol (**1**) in two steps from the Boc-protected methyl ester of proline, and the trimethylsilyl ether of diphenylprolinol (**2**) via a single transformation from diphenyl prolinol (**1**).

References

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Phenylmagnesium bromide solution; (100-58-3)
N-Boc-L-proline methyl ester; (59936-29-7)
(S)-1,1-Diphenylprolinol: (*S*)-(−)-2-(Diphenylhydroxymethyl)pyrrolidine; (112068-01-6)
Triethylamine; (121-44-8)
Trimethylsilyl trifluoromethanesulfonate; (27607-77-8)
(S)-1,1-Diphenylprolinol trimethylsilyl ether: (S)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether; (848821-58-9)
Magnesium turnings; (7439-95-4)
Bromobenzene; (108-86-1)
N-(*tert*-Butoxycarbonyl)proline; (15761-39-4)
Methyl iodide: Iodomethane; (74-88-4)

Robert K. Boeckman, Jr. received his Bachelors of Science degree in Chemistry in 1966 from Carnegie Institute of Technology (now Carnegie Mellon University). He moved on to Brandeis University where he received the Ph.D. degree under the supervision of James B. Hendrickson and Ernest Grunwald in 1971. He joined the research group of Gilbert Stork in 1970 as an NIH postdoctoral fellow. He began his academic career at Wayne State University in 1972, where he rose to the rank of Professor in 1979. In 1980, he joined the faculty of the University of Rochester where he is currently Marshall D. Gates Jr. Professor of Chemistry. His research interests lie primarily in the area of synthetic organic chemistry, both the development of new synthetic methodology and the total synthesis of complex substances of biological interest.

Douglas J. Tusch received his Bachelors of Science degree in Biochemistry from the Rochester Institute of Technology in 2010 where he researched alkaloid natural product synthesis under the guidance of Professor Jeremy Cody. He then joined the group of Professor Robert Boeckman at the University of Rochester and earned his M.S. in chemistry in 2012. He is currently pursuing a Ph.D. in Professor Boeckman's group studying the areas of total synthesis and organocatalysis.

Kyle F. Biegasiewicz received his Bachelors of Science in Chemistry from Niagara University in 2010, completing undergraduate research with Professor Ronny Priefer. He is currently a chemistry graduate student at the University of Rochester working under the tutelage of Professor Robert K. Boeckman, Jr. His graduate research areas include the total synthesis of natural products and organocatalysis.

Eduardo V. Mercado-Marin received his Bachelors of Science in Chemistry from the University of California, Santa Barbara in 2011, completing undergraduate research under the guidance of Professor Thomas R. R. Pettus. He is currently a chemistry graduate student at the University of California, Berkeley working with Professor Richmond Sarpong. His graduate research is focused on a unified approach to the total syntheses of prenylated indole alkaloid natural products.

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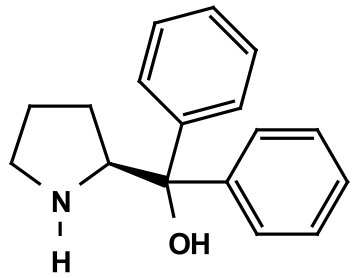

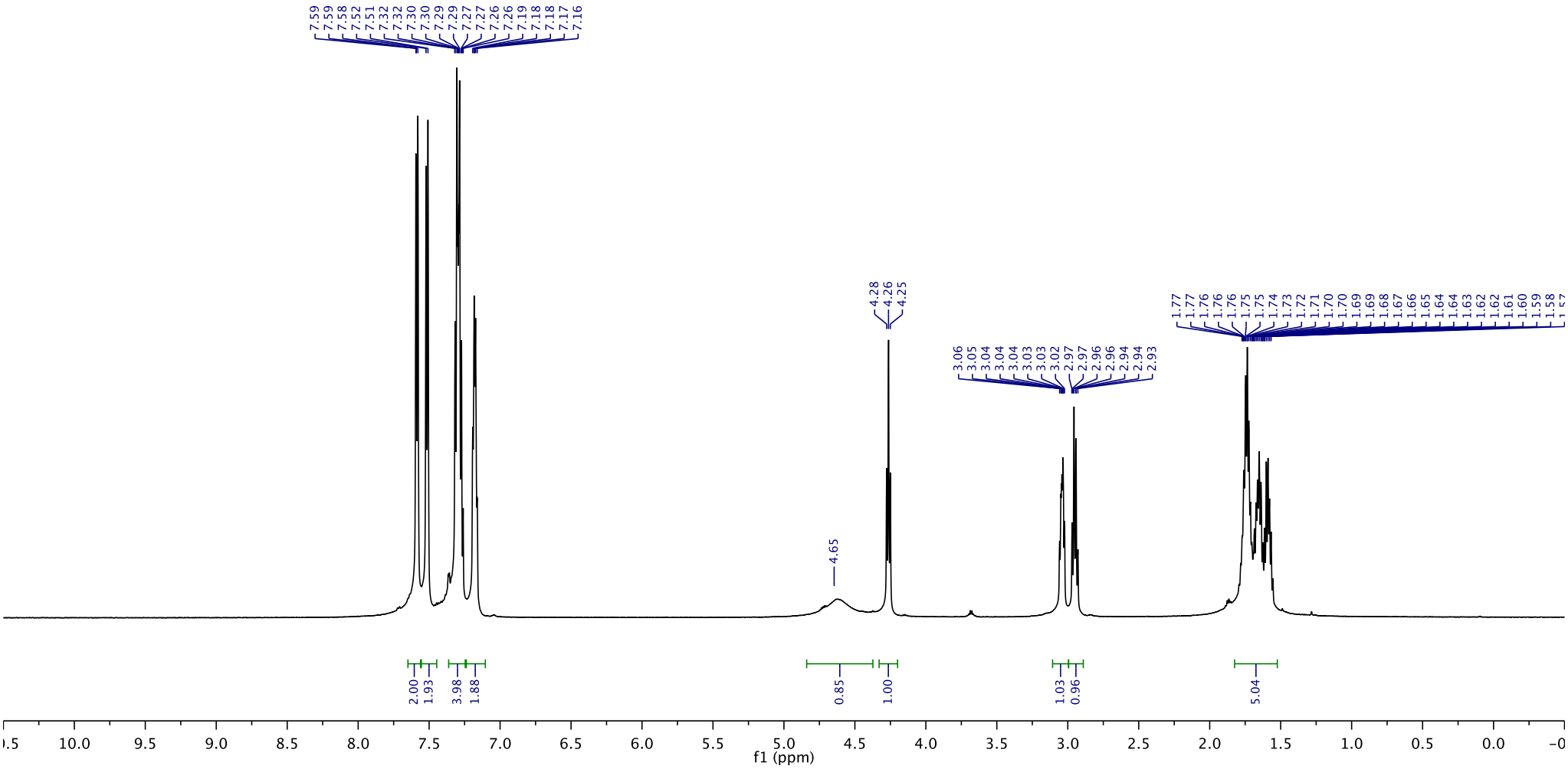

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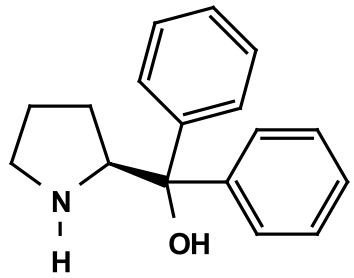

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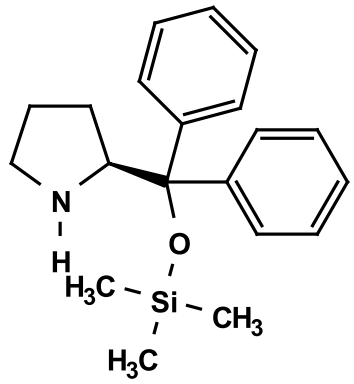

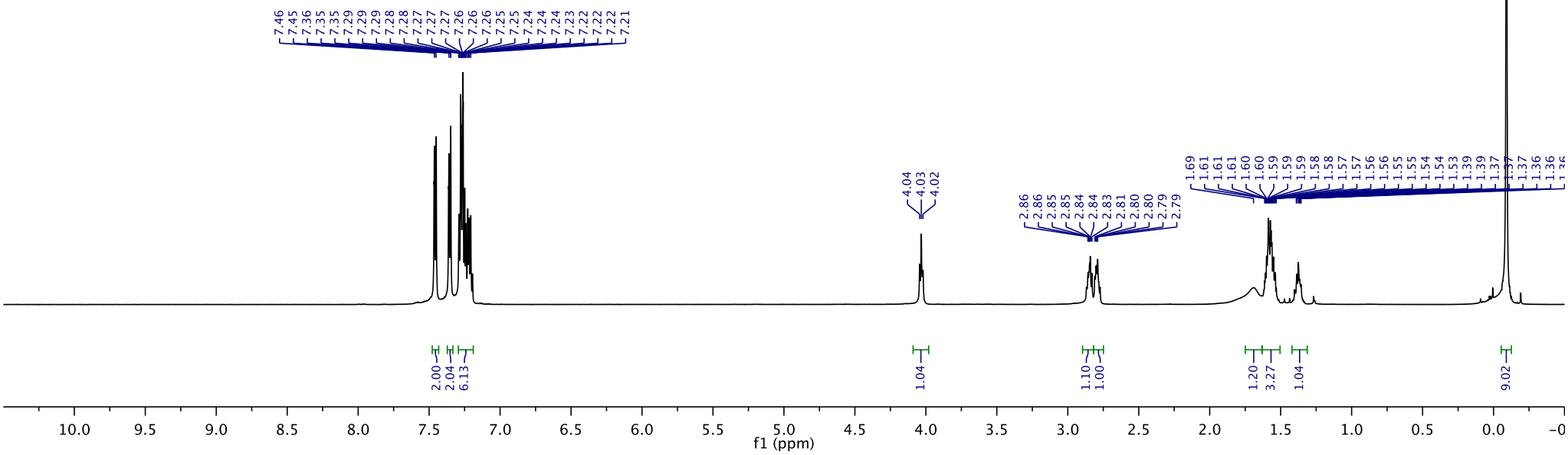

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