Organic Syntheses

Large Scale Epoxide Opening by a Pendant Silanol

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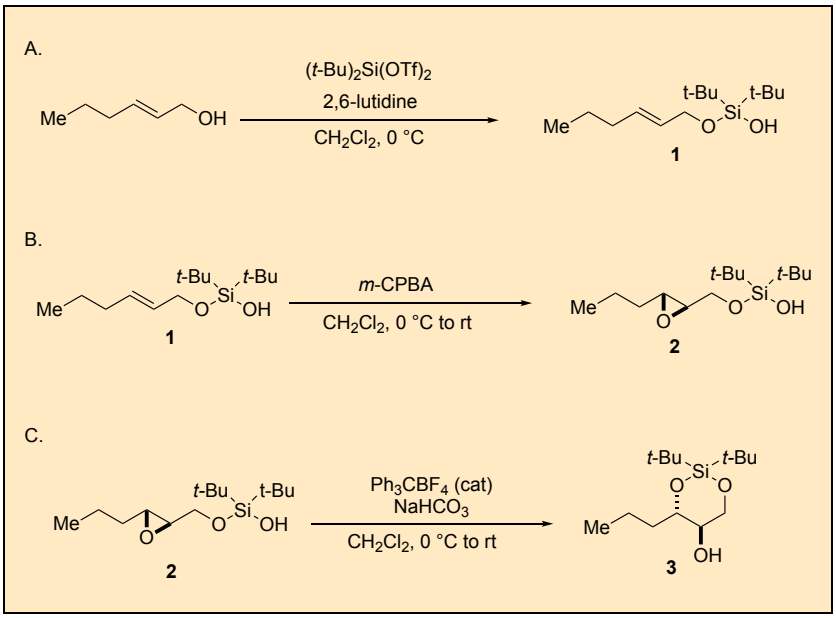
Checked by Alex Kwok Hei Chu and Pauline Chiu



Procedure (Note 1)

A. *(E)-Di-tert-butyl(hex-2-en-1-yloxy)silanol (**1**).* An oven-dried, single-necked (24/40 joint) 500 mL round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4.0 cm x 1.0 cm, oval) and septum. The vessel is purged with argon from a Schlenk line using a 20G inlet and a 20G exit needle connected to an oil bubbler for 30 min (Figure 1A) (Note 2). The flask is then charged with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (20.4 mL,

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62.6 mmol, 1.25 equiv) (Note 3), using a plastic syringe fitted with a 20G needle, and CH_2Cl_2 (200 mL) (Note 4), using a plastic syringe fitted with a 20G needle. The reaction flask is then placed in an ice-water bath. After ten minutes, 2,6-lutidine (14.6 mL, 125 mmol, 2.5 equiv) (Note 5) is added dropwise over 10 min using a plastic syringe fitted with a 20G needle. After the reaction mixture is stirred (250 rpm) for 15 min at 0 °C, *trans*-2-hexen-1-ol (5.9 mL, 50 mmol, 1 equiv) (Note 6) is then added dropwise using a plastic syringe fitted with 20G needle over 10 min, and the solution is stirred (250 rpm) at 0 °C for 1 h (Figure 1B). The progress of the reaction is monitored

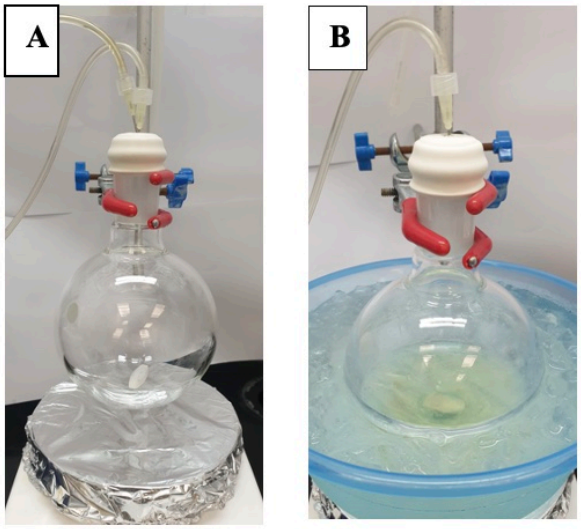


Figure 1. Reaction set-up for Step 1. (A) Reaction flask purging under argon (B) After addition of 2,6-lutidine and *trans*-2-hexen-1-ol to di-*tert*-butylsilyl bis(trifluoromethanesulfonate) in CH_2Cl_2 at 0 °C. (Photos provided by checkers)

by thin-layer chromatography (TLC) (Notes 7 and 8) and *trans*-2-hexen-1-ol is consumed approximately after 1 h following addition (Figure 2). The reaction is quenched at 0 °C by careful, portion-wise addition of saturated aqueous $NaHCO_3$ solution (50 mL in 3 portions) (Note 9). The reaction mixture is then transferred to a 1 L separatory funnel. The organic layer is separated and washed with additional portions of saturated, aqueous

Figure 2. TLC of the crude reaction mixture, stained with ceric ammonium molybdate stain. Mobile phase: 10 % EtOAc in hexanes. Note: S = starting material, C = co-spot lane, R = reaction mixture. Starting material *trans*-2-hexen-1-ol (R_f = 0.17), product 1 (R_f = 0.54) (Photo provided by checkers)

$NaHCO_3$ solution (3 x 75 mL). The organic layer is then washed with 1 M aqueous HCl solution (2 x 75 mL) (Note 10). The organic layer is separated and dried over anhydrous $MgSO_4$ (5 g) (Note 11), filtered under house vacuum (~75 mm Hg) through a 60 mL sintered glass funnel (50 mm frit, coarse) into a 500 mL round-bottomed flask, then concentrated under reduced pressure using a rotary evaporator (Note 12). The resulting residue (Figure 3A) is purified by flash column chromatography on silica gel (Notes 13, 14, 15 and 16). The fractions containing the product (Figure 3B) are combined and concentrated under reduced pressure on a rotary evaporator (Note 17) followed by high vacuum (20 °C, <1 mmHg) for 2 h, to give **1** as a colorless oil (8.67 g, 33.5 mmol, 67%) (Figure 4) (Notes 18 and 19).

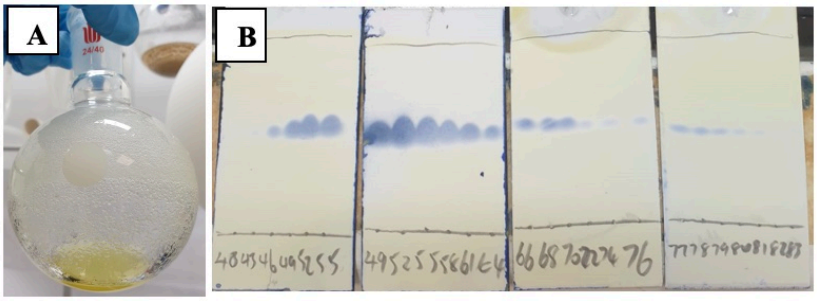


Figure 3. (A) Product before purification. (B) Compound 1 is found in fractions 46-81 (Photos provided by checkers)

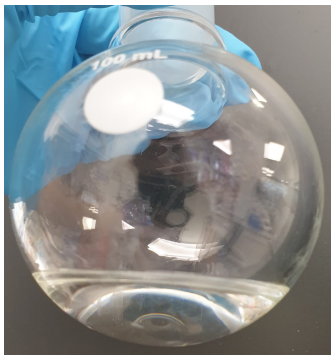


Figure 4. (*E*)-Di-*tert*-butyl(hex-2-en-1-yloxy)silanol (1) is a colorless oil (Photo provided by checkers)

B. *Di-tert-butyl(((2R*,3R*)-3-propyloxiran-2-yl)methoxy)silanol* (**2**). A 250 mL Erlenmeyer flask is equipped with a Teflon-coated magnetic stir bar (3.5 cm x 0.5 cm, rod-shaped). The flask is charged with (*E*)-di-*tert*-butyl(hex-2-en-1-yloxy) silanol (**1**) (7.03 g, 27.1 mmol, 1 equiv), using a 1 mL glass pipette, and CH_2Cl_2 (110 mL), using a 250 mL glass graduated cylinder. The reaction flask is then placed in an ice-water bath (Figure 5A). *m*-Chloroperoxybenzoic acid (9.40 g, ~37.9 mmol, ~1.4 equiv) (Note 20) is added to the flask portion-wise over 10 min. The flask is capped with

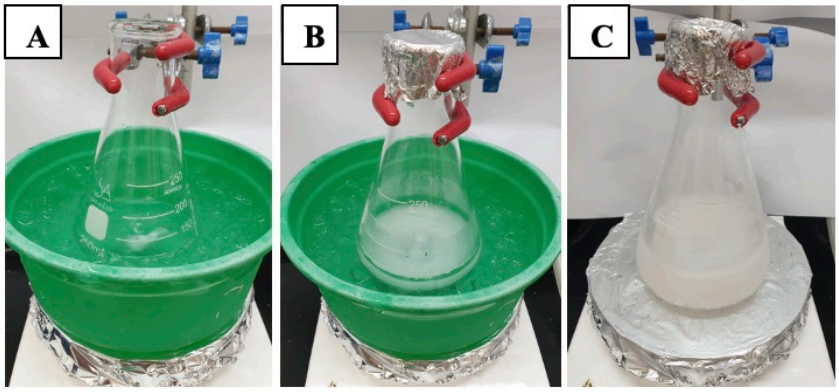


Figure 5. (A) Reaction mixture cooled to 0 °C using an ice-water bath prior to the addition of *m*CPBA. (B) Directly after addition of *m*CPBA. (C) After warming to room temperature (20 °C) , close to reaction completion. (Photos provided by checkers).

aluminum foil (Figure 5B). The reaction mixture is stirred (500 rpm) for 5 min at 0 °C, then the ice-water bath is removed. The reaction mixture is allowed to warm to room temperature (20 °C) with stirring over a period of 3 h (Figure 5C). The progress of the reaction is monitored by TLC (Figure 6). After full consumption of the starting material (~3 h), the reaction is cooled

Figure 6. The progress of the reaction is monitored by TLC analysis on silica gel plates using 10% EtOAc in hexanes as the eluent. TLC spots are visualized by staining with ceric ammonium molybdate stain. Note: S = starting material, C = co-spot lane, R= reaction mixture; Compound 1 (R_f = 0.54), epoxide product 2 (R_f = 0.42) (Photo provided by checkers)

to 0 °C using an ice-water bath and quenched by slowly adding saturated aqueous sodium thiosulfate solution (50 mL) (Note 21). The reaction mixture is then transferred to a 1 L separatory funnel. The reaction flask is rinsed with diethyl ether (75 mL), which is added to the separatory funnel. (Note 22) (Figure 7). The aqueous layer is separated, and the organic layer is washed with 1 M aqueous NaOH solution (3 x 75 mL) (Note 23). The organic layer is dried over anhydrous $MgSO_4$ (5 g), filtered through a 60 mL sintered glass funnel (50 mm frit, coarse) under house vacuum (~75 mm Hg) into a 500 mL round-bottomed flask and concentrated under reduced pressure using a rotary evaporator (Note 12). The residue is purified by flash column chromatography (Figure 8) (Note 24) on silica gel. The fractions containing pure product are combined and concentrated under reduced pressure on a rotary evaporator (Note 17), followed by high vacuum (20 °C, <1 mmHg) for 2 h to afford **2** (Figure 9) as a colorless oil (6.85 g, 24.9 mmol, 92%) (Notes 25 and 26).

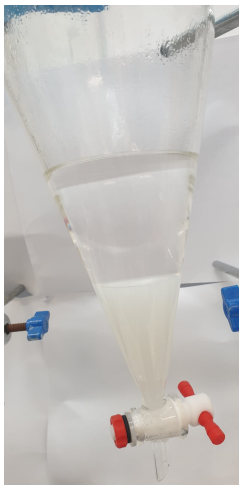


Figure 7. Reaction mixture after quenching with saturated aqueous $Na_2S_2O_3$ solution and diluting with Et_2O (Photo provided by checkers)

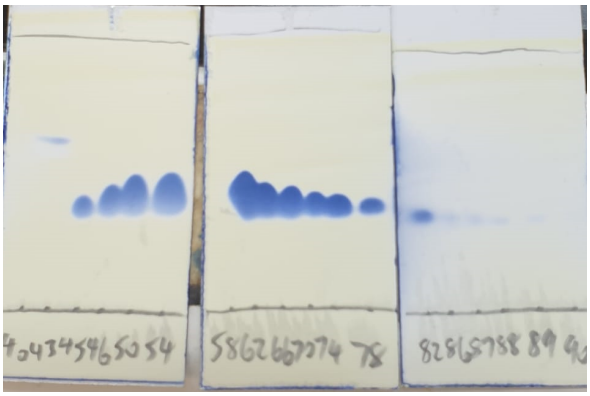


Figure 8. Pure compound 2 is found in fractions 45-89 (Photo provided by checkers)

Figure 9. Di-*tert*-butyl(((2*R,3*R**)-3-propyloxiran-2-yl)methoxy)silanol (2) is a colorless oil (Photo provided by checkers)**

C. (4S,5R*)-2,2-Di-tert-butyl-4-propyl-1,3,2-dioxasilinan-5-ol (**3**).* An oven-dried, single-necked (24/40 joint) 500 mL round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4.0 cm x 1.0 cm, oval) and septum, and purged for 30 min with argon via a 20G inlet from a Schlenk line and a 20G exit needle connected to an oil bubbler (Figure 1A). The flask is then charged with di-*tert*-butyl(((2*R**,3*R**)-3-propyloxiran-2-yl)methoxy)-silanol (**2**) (5.84 g, 21.3 mmol, 1 equiv), and CH_2Cl_2 (200 mL) using a plastic syringe fitted with 20G needle (Note 4). Sodium bicarbonate (1.85 g, 22.0 mmol, 1 equiv) (Note 27) is added in one portion (Figure 10A). Stirring (250 rpm) is commenced. The reaction flask is then placed in an ice-water bath (Figure 10B). After 10 min, Ph_3CBF_4 (1.06 g, 3.21 mmol, 0.15 equiv) (Note 28) is added in three approximately equal portions over 5 min (Figure 10C).

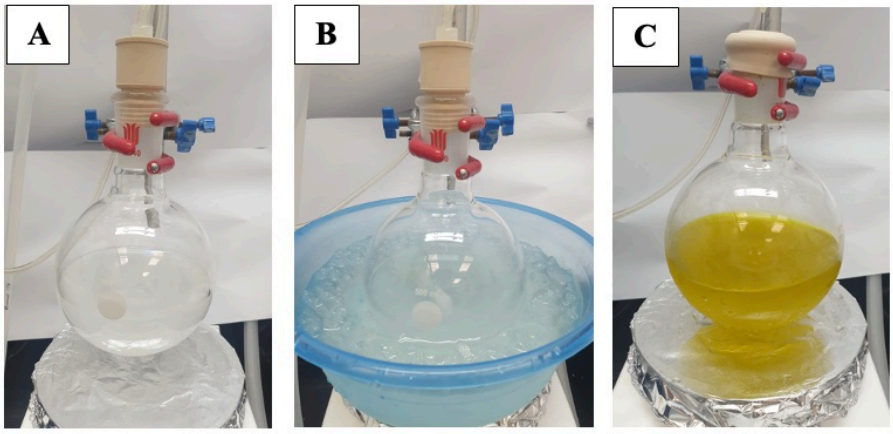


Figure 10. (A) After addition of $NaHCO_3$. (B) The reaction is cooled to 0 °C prior to addition of Ph_3CBF_4. (C) After addition of Ph_3CBF_4 (at 0 °C), the reaction mixture turns bright yellow, and this color persists even after warming to room temperature (20 °C) (Photos provided by checkers)

The ice-water bath is removed, and the reaction mixture is allowed to warm to room temperature (20 °C). The progress of the reaction is monitored by TLC (Figure 11). After the consumption of starting material (~ 2 h after addition of Ph_3CBF_4), the reaction is cooled again using an ice-water bath. The reaction is quenched by adding saturated aqueous $NaHCO_3$ solution (50 mL) (Note 9) and further diluted with an additional 20 mL of CH_2Cl_2 (Figure 12A). The reaction mixture is transferred to a 1 L separatory funnel (Figure 12B). The aqueous layer is removed, and the organic layer is washed with saturated aqueous $NaHCO_3$ solution (2 x 50 mL). The organic layer is dried over anhydrous $MgSO_4$ (5 g) and filtered through a 60 mL sintered glass funnel (50 mm frit, coarse) under house vacuum (~75 mmHg) into a 500 mL round-bottomed flask. After concentrating under reduced pressure on a rotary evaporator (Note 12), the residue is purified by flash column chromatography on silica gel (Notes 29 and 30). The fractions containing pure product **3** are combined (Figure 13) and concentrated under reduced pressure on a rotary evaporator (Note 12) followed by high vacuum (20 °C, <1 mmHg) for 2 h to give **3** as a white solid (Figure 14A) (4.85 g, 17.7 mmol, 83%) (Notes 31 and 32).

Figure 11. The progress of the reaction is monitored by TLC analysis on silica gel with 2% acetone in CH_2Cl_2 as the eluent (Note 25). Spots are visualized after the plate is dipped in ceric ammonium molybdate stain and heated. Note: S = starting material (2), C = co-spot lane, R = reaction mixture containing catalyst (R_f = 0.86, yellow spot) and product 3. Compound 2 (R_f = 0.46), Compound 3 (R_f = 0.44) (Photo provided by checkers).

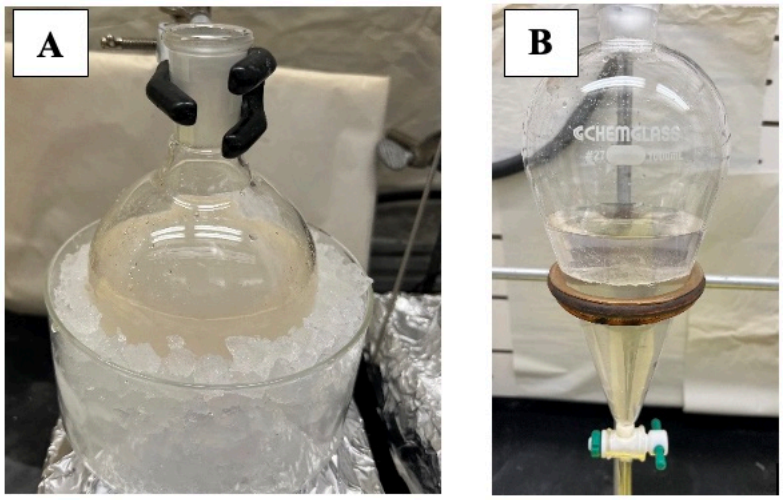


Figure 12. (A) Reaction mixture becomes pale yellow after quenching with saturated aqueous $NaHCO_3$ solution. (B) After partitioning aqueous and organic layers in a 1 L separatory funnel (photos provided by submitters)

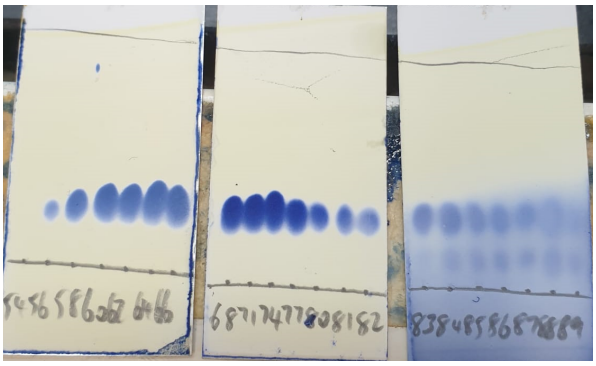


Figure 13. Pure compound 3 is found in fractions 56-82 (Photo provided by checkers)

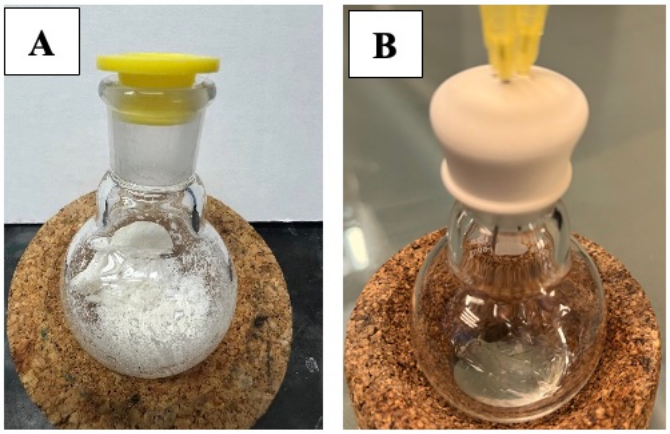


Figure 14. (A) (4*S,5*R**)-2,2-Di-*tert*-butyl-4-propyl-1,3,2-dioxasilinan-5-ol (3) is a white solid after purification. (B) Crystals suitable for X-ray diffraction analysis are grown by slow evaporation from hexanes (photos provided by submitters**

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/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.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 di-*tert*-butylsilyl bis(trifluoromethanesulfonate), *m*-chloroperoxybenzoic acid, diethyl ether, acetone, toluene, CH_2Cl_2, *trans*-2-hexen-1-ol, 2,6-lutidine, concentrated hydrochloric acid, magnesium sulfate, silica gel, hexanes, acetone, concentrated sulfuric acid, sodium bicarbonate, sodium thiosulfate pentahydrate, sodium hydroxide, ammonium molybdate, and ceric ammonium molybdate.

2. The submitters used a nitrogen balloon instead of an argon line.
3. Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) was purchased from Combi-Blocks (96% purity), which was used as received. The checkers purchased di-*tert*-butylsilyl bis(trifluoromethanesulfonate) from Shanghai Macklin Biochemical Technology Co., Ltd (97% purity), which was used as received.
4. CH_2Cl_2 was purchased from Sigma-Aldrich (≥99.5%, ACS reagent grade) and was used as received. The checkers purchased CH_2Cl_2 from Anaqua Global International Inc. Ltd (≥99.5%, ACS reagent grade) which was used as received.
5. 2,6-Lutidine was purchased from TCI America (purity > 98 %) and was used as received. The checkers purchased 2,6-lutidine from TCI China (purity > 98 %) which was used as received.
6. *Trans*-2-hexen-1-ol was purchased from TCI America (purity > 95 %) and used as received. The checkers purchased *trans*-2-hexen-1-ol from TCI China (purity > 95 %) which was used as received.
7. Thin layer chromatography (TLC) was performed on silica gel 60 F254 (aluminum TLC plates). The progress of the reaction is monitored by

TLC analysis eluting with 10% EtOAc in hexanes. Spots are visualized after the plate is dipped in ceric ammonium molybdate stain and heated.

8. Ceric ammonium molybdate stain was prepared by dissolving 12 g of ammonium molybdate, 0.5 g of ceric ammonium molybdate, and 15 mL of concentrated H_2SO_4 in 235 mL water. The checkers prepared ceric ammonium molybdate stain by dissolving 5 g of ammonium molybdate, 1 g of cerium sulfate, and 10 mL of concentrated H_2SO_4 in 90 mL water.
9. The checkers purchased sodium bicarbonate (AR grade) from Dieckmann (Hong Kong) Chemical Industry Co. Ltd., which was used as received.
10. Hydrochloric acid (Certified ACS Plus, 36.5 to 38%) was purchased from Fisher Chemical. A 1 M HCl aqueous solution was prepared by adding 83 mL of th4 concentrated HCl to 917 mL of deionized water. The checkers purchased hydrochloric acid (AR grade, 37%) from RCI Labscan Ltd.
11. Magnesium sulfate (anhydrous) was purchased from Fisher Scientific and used directly. The checkers purchased magnesium sulfate (AR grade, anhydrous) from Dieckmann (Hong Kong) Chemical Industry Co. Ltd., which was used directly.
12. The checkers used a Heidolph Hei-VAP Core Rotovap with a bath temperature of 25 °C and at a vacuum of 200 mmHg.
13. The checkers purchased ethyl acetate from Duksan Pure Chemicals Co. Ltd. (GR grade), which was used as received.
14. Hexanes (>98.5%) was purchased from Fisher Scientific and used as received. The checkers purchased hexanes (ACS grade, >99.5%) from SK Chemicals Co. Ltd., which was used as received.
15. Silica Gel (grade 60, 230-400 mesh) was purchased from Fisher Scientific. The checkers purchased silica gel (0.040-0.063 mm) from Merck KGaA, which was used as received.
16. For flash column chromatography, a 30 cm (L) x 5 cm (W) glass column is charged with 170 g of silica gel and is flushed with 750 mL of 2% EtOAc in hexanes. The height of the silica gel is 16 cm. The crude product is dissolved in 20 mL of 2% EtOAc in hexanes and loaded onto the column. After full adsorption, the top of the silica gel is layered with sand (2 cm). The column was eluted using 500 mL of 2% EtOAc in hexanes, 500 mL of 4% EtOAc in hexanes, then 1 L of 6% EtOAc in hexanes. Fractions of 20 mL were collected. Fractions were checked using TLC (10% EtOAc in hexanes) and visualized by ceric ammonium molybdate stain.

17. The checkers used a Heidolph Hei-VAP Core Rotovap with a bath temperature of 30 °C and a vacuum at 100 mmHg.
18. Analytical data for *(E)*-di-*tert*-butyl(hex-2-en-1-yloxy)silanol (**1**): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.67 (dtt, *J* = 14.7, 6.6, 1.4 Hz, 1H), 5.56 (dtt, *J* = 15.3, 5.3, 1.3 Hz, 1H), 4.29 (dq, *J* = 5.3, 1.2 Hz, 2H), 2.07 – 1.96 (m, 2H), 1.85 (s, 1H) 1.40 (h, *J* = 7.4 Hz, 2H), 1.02 (s, 18H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 131.3, 129.6, 64.3, 34.4, 27.6, 22.5, 20.6, 13.8; IR (ATR) ν 3418, 2962, 2933, 2859, 1683, 1470, 138, 1364, 1104, 1062, 1012, 969, 826, 648, 442 cm^{-1}. HRMS (ESI) *m*/*z* = [M+ Na^{+}] calculated for $C_{14}H_{30}O_2Si$ 281.1913, Found 281.1915. The purity of **1** was determined to be 99.0% by qNMR using 4-nitrotoluene (purity 99.5%, purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.) as the internal standard.
19. A second reaction performed by the checkers on half scale provided 4.43 g (67% yield) of compound **1**.
20. *m*-Chloroperoxybenzoic acid (70-75% purity, with the balance being 3-chlorobenzoic acid and water) was purchased from Thermo Scientific and was used without purification.
21. Sodium thiosulfate pentahydrate (>99%) was purchased from Fisher Scientific and used as received. The checkers purchased sodium thiosulfate pentahydrate (> 99%) from TCI China which was used as received.
22. Diethyl ether (Laboratory grade) was purchased from Fisher Scientific and used as received. The checkers purchased Et_2O (AR grade) from RCI Labscan Ltd. and used the solvent as received.
23. Sodium hydroxide pellets were purchased from Acros Organics. A 1 M NaOH solution was prepared by dissolving 20 g of NaOH pellets in 500 mL deionized water. The checkers purchased sodium hydroxide pellets (AR grade) from Dieckmann (Hong Kong) Chemical Industry Co. Ltd., which was used as received.
24. For flash column chromatography, a 30 cm (L) x 5 cm (W) glass column is charged with 160 g of silica gel and is flushed with 500 mL of 95:5 hexanes/EtOAc. The height of the packed silica gel is 15 cm. The crude product is dissolved in 15 mL of 5% EtOAc in hexanes and loaded onto the column. After full adsorption, the top of the silica gel is layered with sand (2 cm). The column is eluted with 5% EtOAc in hexanes (500 mL), 12% EtOAc in hexanes (500 mL), then 15% EtOAc in hexanes (250 mL). Fraction of 20 mL were collected. Fractions were checked using

TLC (10% EtOAc in hexanes) (Figure 8) and visualized by ceric ammonium molybdate stain.

25. Analytical data for *di-tert-Butyl(((2R*,3R*)-3-propyloxiran-2-yl)methoxy)silanol* (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.12 (ddd, *J* = 12.4, 2.4, 1.1 Hz, 1H), 3.71 (dd, *J* = 12.3, 5.8 Hz, 1H), 2.93 (tq, *J* = 4.7, 2.4 Hz, 2H), 1.61 – 1.37 (m, 4H), 1.03 (s, 9H), 1.01 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 64.1, 59.3, 57.0, 33.7, 27.5, 20.74, 20.67, 19.4, 14.0; IR (ATR) ν 3419, 2963, 2933, 2859, 1471, 1387, 1364, 1242, 1129, 1095, 1012, 939, 851, 827, 772, 649, 442 cm^{-1}.; HRMS (ESI) *m*/*z* = [M + Na^{+}] calculated for $C_{14}H_{30}O_3Si$ 297.1862, Found 297.1865. The purity of **2** was determined to be 99.5% by qNMR using 4-nitrotoluene (purity 99.5%, purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.) as the internal standard.
26. A second reaction performed by the checkers on half scale provided 3.48 g (94%) of compound **2**.
27. Sodium bicarbonate (ACS reagent grade) was purchased from Oakwood Chemical and used as received. The checkers purchased sodium bicarbonate (AR grade) from Dieckmann (Hong Kong) Chemical Industry Co. Ltd., which was used as received.
28. Triphenylcarbenium tetrafluoroborate (Ph_3CBF_4) was purchased from Alfa Aesar (97%) and used as received. The checkers purchased triphenylcarbenium tetrafluoroborate (Ph_3CBF_4) from TCI China (98%) which was used as received.
29. For flash column chromatography, a 30 cm (L) x 5 cm (W) glass column is charged with 160 g of silica gel and is flushed with 500 mL of CH_2Cl_2. The height of the silica gel is 15 cm. The crude product is dissolved in 10 mL of CH_2Cl_2 and loaded onto the column. After full adsorption, the top of the silica gel is layered with sand (2 cm). The column is eluted with CH_2Cl_2 (500 mL), then 2% acetone in CH_2Cl_2 (500 mL) (Note 30), 4% acetone in CH_2Cl_2 (250 mL), and 6% acetone in CH_2Cl_2 (500 mL). Fractions of 20 mL were collected. Fractions were checked using thin-layer chromatography (2% acetone in CH_2Cl_2) and visualized using ceric ammonium molybdate stain (Figure 13).
30. Acetone (Tech Grade) was purchased from Dah Fat Chemical International Ltd. and used as received.
31. Analytical data for (*4S*,5R*)-2,2-di-tert-butyl-4-propyl-1,3,2-dioxasilinan-5-ol*: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.84 – 3.72 (m, 2H), 3.53 (td, *J* = 9.3, 4.5 Hz, 1H), 1.83 – 1.70 (m, 1H), 1.67 – 1.32 (m,

4H), 1.04 (s, 9H), 1.00 – 0.93 (m, 12H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ: 78.1, 70.8, 68.8, 36.8, 27.7, 27.2, 22.8, 20.2, 18.1, 14.2. IR (ATR) ν 3409, 2960, 2934, 2861, 1471, 1387, 1365, 1236, 1215, 1155, 1117, 1080, 1065, 1053, 1040, 1025, 1010, 1000, 938, 895, 825, 787, 769, 756, 727, 651, 598, 460, 440 cm^{-1}; HRMS (ESI) *m*/*z* = [M + Na^+] calculated for $C_{14}H_{30}O_3Si$ 297.1862, Found 297.1861. mp 67–69 °C. The purity of **3** was determined to be 97.3% by qNMR using 4-nitrotoluene (purity 99.5%, purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.) as the internal standard. Single crystals of **3** suitable for X-ray diffraction analysis were grown by dissolving 1 gram of **3 (**obtained from chromatographic purification) in 5 mL of hexanes in a 25 mL round-bottomed flask (Figure 14B). This mixture was heated in a 60 °C oil bath for one min, then cooled to room temperature (20 °C) over 5 min. The flask was sealed with a rubber septum and kept in the refrigerator (~4 °C) for two days. The septum was pierced with two 20G vent needles and left on the benchtop at ambient temperature for one day. Over this time, needle-like, colorless crystals formed in the flask. X-ray diffraction analysis of one of these crystals (CCDC 2245378) unambiguously confirmed the identity and relative stereochemistry of **3**.

32. A second reaction performed by the checkers on half scale provided 2.45 g (84%) of compound **3**.

Working with Hazardous Chemicals

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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant

hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

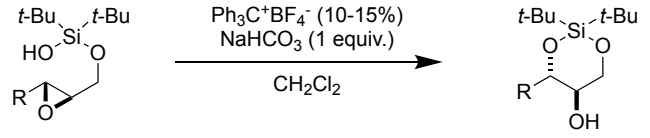
Our laboratory[1] has a programmatic focus on the development of the di-*tert*-butyl silanol functional group into a synthetically useful auxiliary. Prior to our laboratory's interest in this area, silanols only sporadically appeared in the organic synthesis literature. Gevorgyan and co-workers demonstrated that silanols are excellent directing groups for Pd-catalyzed C–H functionalization reactions.[2,3] Lee and co-workers developed a gold-catalyzed cyclization of silanols onto pendant alkynes; these heterocycles serve as versatile precursors for Mukaiyama-type aldol condensations.[4]

Our laboratory developed the first alkene functionalization reaction of silanols; we found that when treated with $Hg(OTf)_2$ and $NaHCO_3$, alkenyl silanols readily cyclize into dioxasilinane organomercury compounds.[5] In the presence of Brønsted acids, these molecules rearrange in a variety of ways.[6,7] We have also explored cyclization reactions of alkenyl silanols in the presence of I^+ and Se^+ electrophiles.[8,9]

As part of this line of inquiry, we were very interested in using tethered silanols to cleave stable electrophiles. As epoxides are very versatile and ubiquitous intermediates in organic synthesis,[10-12] we targeted developing a silanol-tethered ring opening of epoxides as a first step in this direction.[13] Our ring-opening reaction (the scale-up of which is the focus of this *Org. Synth.* contribution) is general for a variety of silanol epoxides derived from *trans*-allylic alcohols, *cis*-allylic alcohols, *trans*-homoallylic alcohols, and *cis*-homoallylic alcohols (Table 1 and Table 2). We applied this method in a short

preparation of protected D-arabitol (Scheme 1). Based on these results, we believe that this methodology is quite general and scalable.

Table 1. Substrate scope with alkyl epoxides



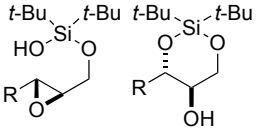
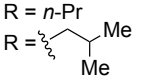
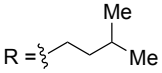
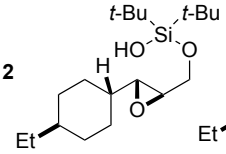
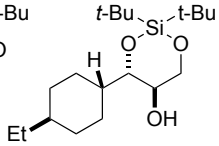
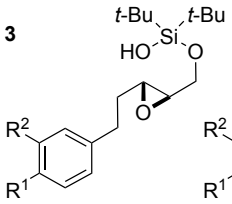
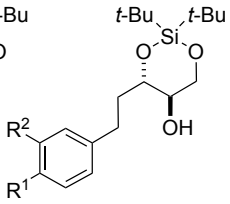
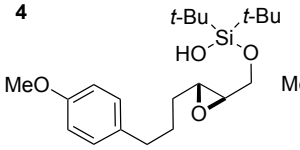
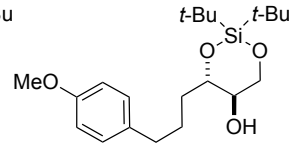
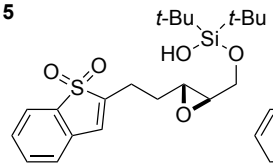
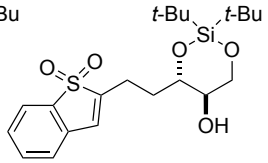
entry	substrate	product	isolated yield
1			R = *n*-Pr **80%** R =  **74%** R =  **83%** R = *i*-Pr **71%** R =  **52%**
2			**71%**
3			R^1 = F, R^2 = H **72%** R^1 = Br, R^2 = H **70%** R^1 = H, R^2 = CF_3 **87%**
4			**70%**
5			**81%**

Table 1 (continued). Substrate scope with alkyl epoxides

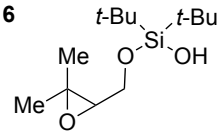
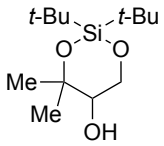
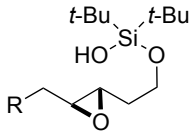
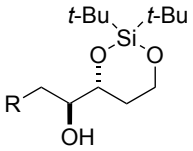
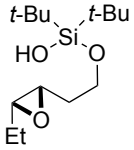
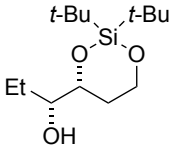
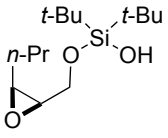
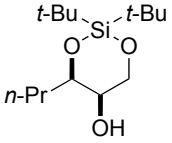
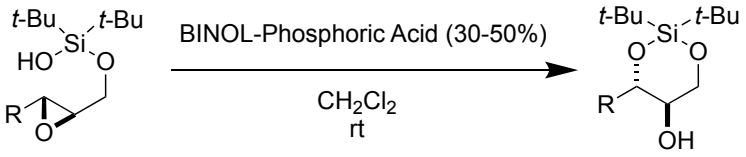
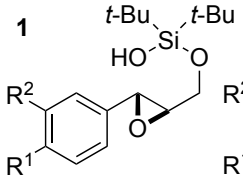
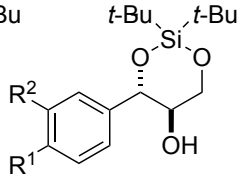
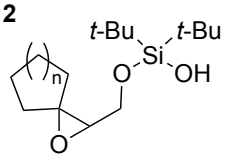
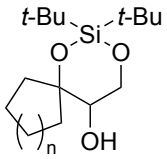
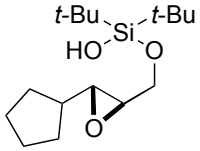
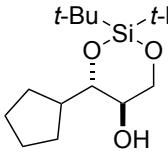
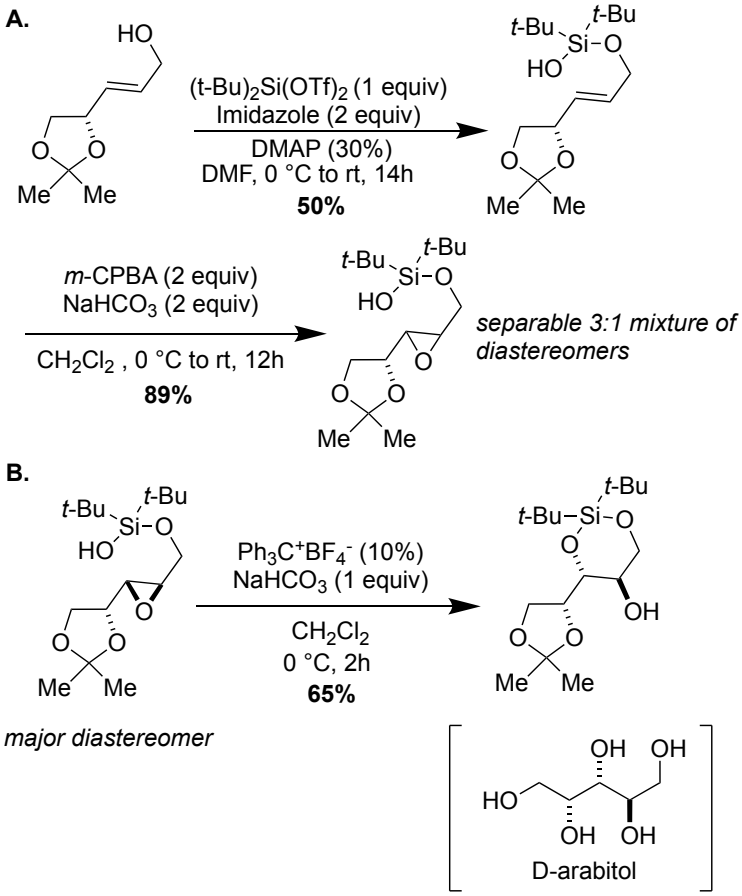
entry	substrate	product	isolated yield
6			**74%**
7			R = Me **65%** R = c-Hex **50%**
8			**60%**
9			**40%**

Table 2. Substrate scope with BINOL-phosphoric acid conditions



entry	substrate	product	isolated yield
1			R^1 = H, R^2 = H **80%** R^1 = F, R^2 = H **63%** R^1 = Br, R^2 = H **85%** R^1 = Cl, R^2 = H **82%** R^1 = H, R^2 = Br **85%**
2			n = 1 **54%** n= 2 **60%**
3			with 10-CSA **43%** with BINOL-PA **50%**[a]

[a]Yield estimated by ^{1}H NMR integration against an internal standard; 30% recovered starting material also noted.



Scheme 1. A short preparation of protected D-arabitol

References

1. Corresponding author: Shyam Sathyamoorthi, ssathyam@ku.edu; https://orcid.ord/0000-0003-4705-7349. Address of all authors: Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66047. Funding: This work was supported by National Institutes of Health Grant R35GM142499.
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13. Nagamalla, S.; Mague, J. T.; Sathyamoorthi, S. Ring Opening of Epoxides by Pendant Silanols. *Org. Lett.* **2022**, *24*, 939–943.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

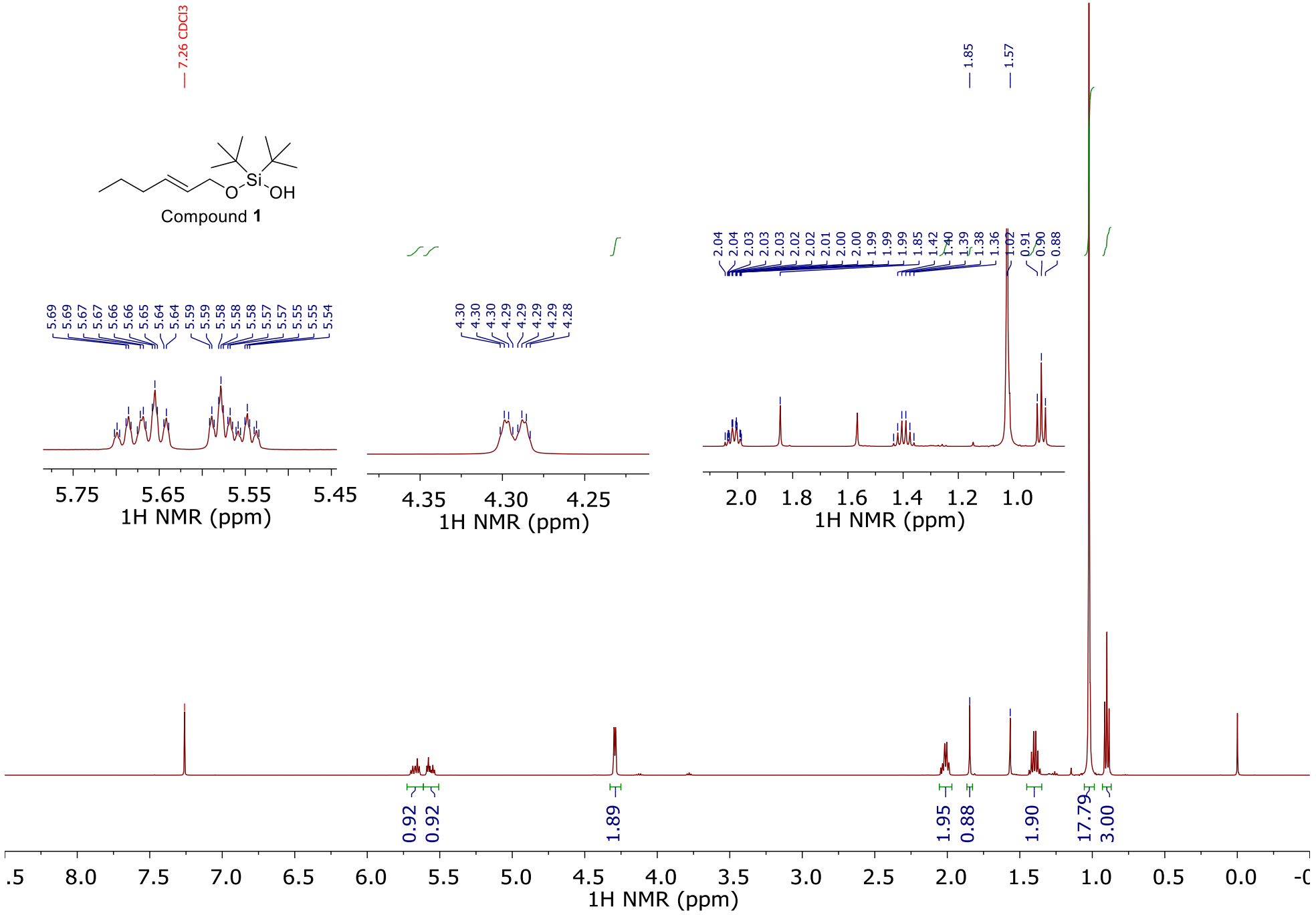
Di-*tert*-butylsilyl bis(trifluoromethanesulfonate), 85272-31-7
2,6-Lutidine, 108-48-5
meta-Chloroperoxybenzoic acid, 937-14-4
Triphenylcarbenium tetrafluoroborate, 341-02-6
Sodium bicarbonate, 144-55-8
trans-2-Hexen-1-ol, 928-95-0

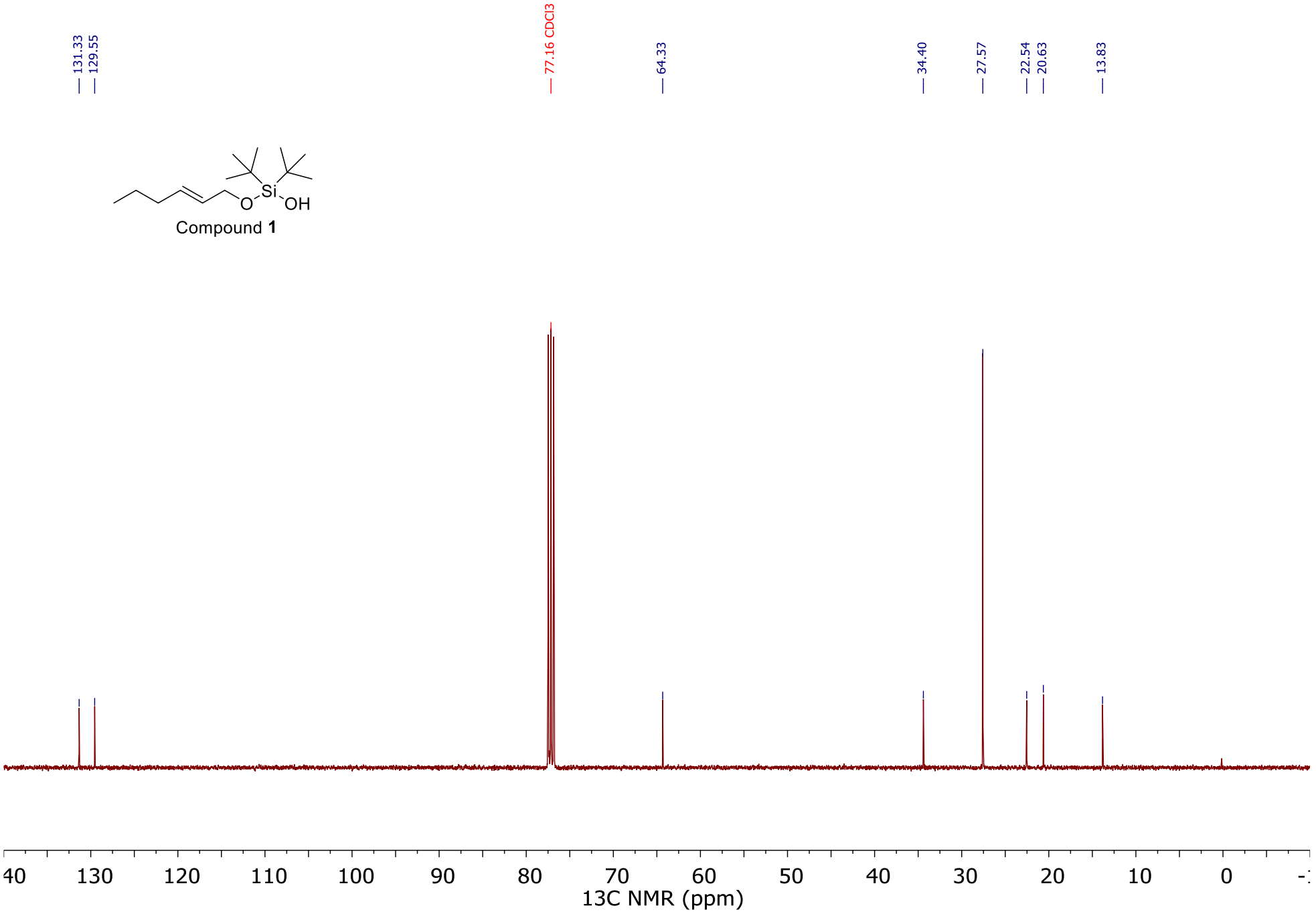
Annu Anna Thomas completed her BS and MS in Chemistry from IIRBS Mahatma Gandhi University Kerala, India in 2018. She then joined Dr. Satyamoorthi's group as a graduate student in the Department of Medicinal Chemistry, University of Kansas in 2020. Her research interests are in developing new methodologies for alkene functionalization.

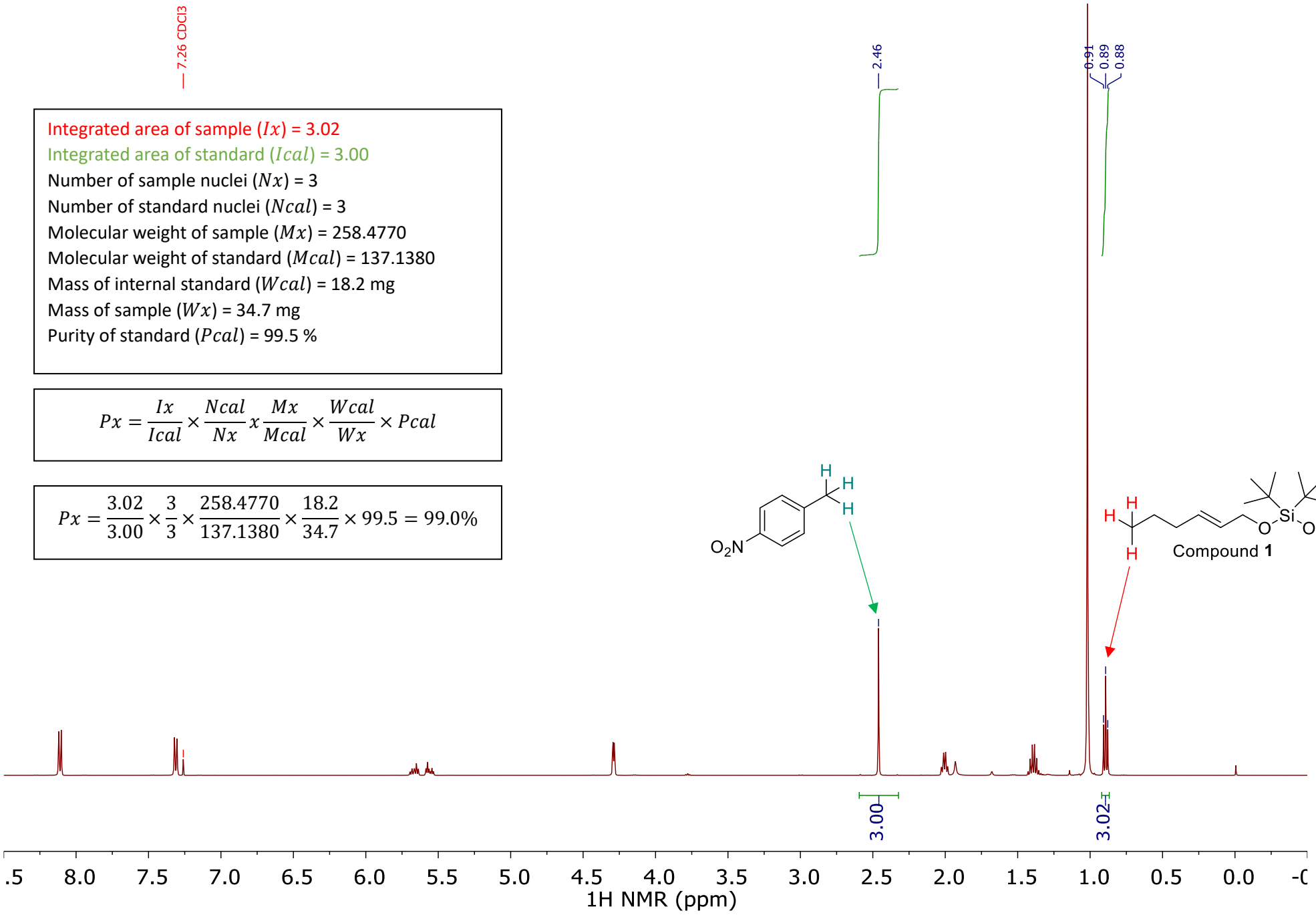
Someshwar Nagamalla received his B.Sc. from Kakatiya University and M.Sc. (Organic Chemistry, 2009) from Osmania University, India. He completed his Ph. D (Organic Chemistry, 2017) at Pondicherry University, India, under the guidance of Dr. C. R. Ramanathan. Following this, he worked as a scientist in a pharmaceutical company, Chemveda Life Sciences (2019), Hyderabad, India. Since December 2019, he has been working as a Postdoctoral Fellow with Professor Shyam Sathyamoorthi in the department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA.

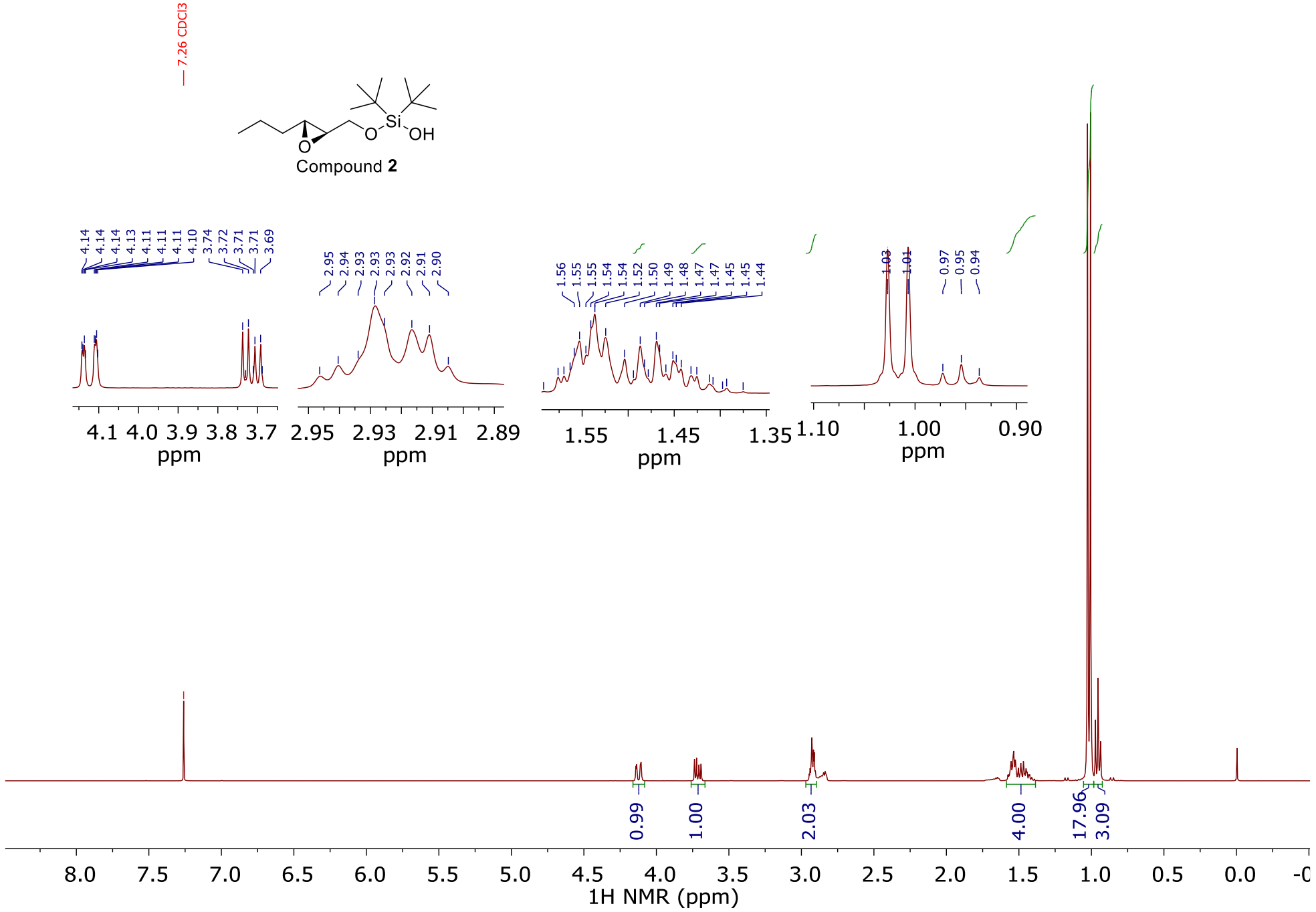
Shyam Sathyamoorthi completed a B.S. degree in Cell and Molecular Biology with a minor in Chemistry at Tulane University, New Orleans, Louisiana, where he worked in the labs of Professor Ken Muneoka and Professor Robert A. Pascal, Jr. He then completed a Ph.D. in chemistry at Stanford University under the guidance of Professor Richard N. Zare (2018), as well as a Doctor of Medicine degree at the Stanford University School of Medicine (2019). Since July 2019, he is an Assistant Professor in the Department of Medicinal Chemistry at the University of Kansas, Lawrence, KS, USA.

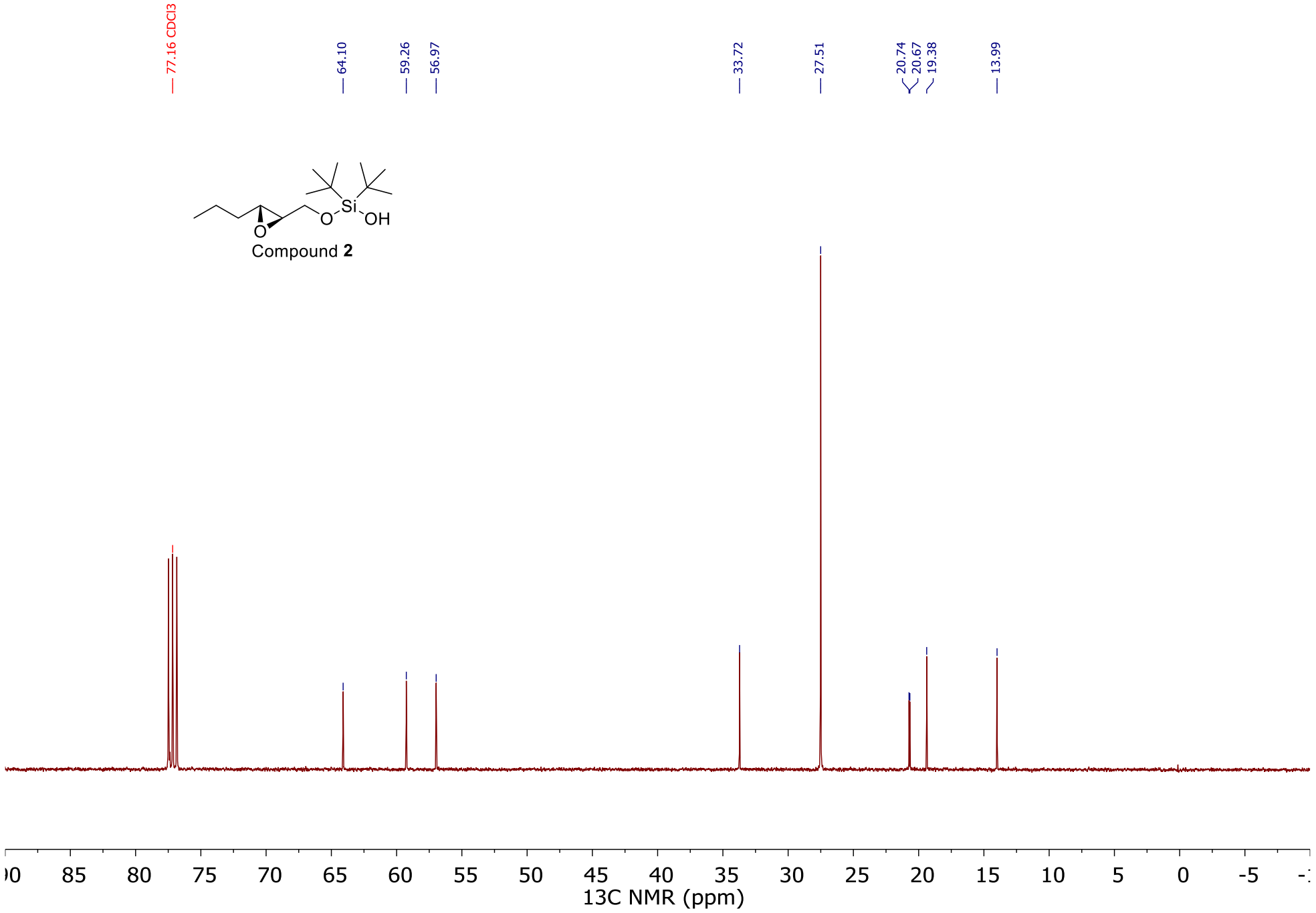
Alex Kwok Hei Chu completed his M.Sci degree in Chemistry at University College London in 2022. Since 2022, he has been studying for a Ph.D. at the University of Hong Kong in the group of Professor Pauline Chiu. In his spare time, he enjoys playing football, basketball and board games.

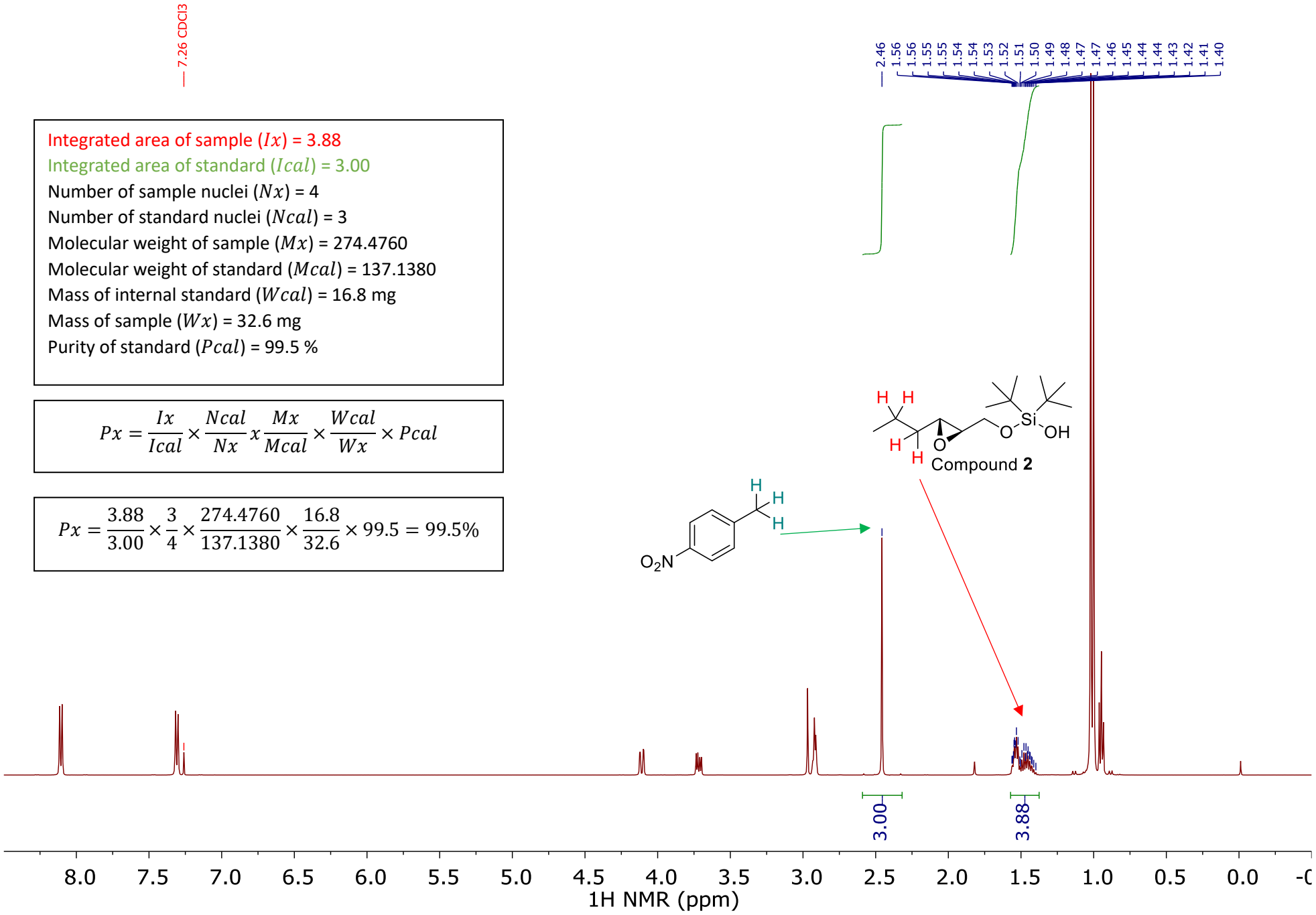

7.26 CDCl3
Si
O
OH
Compound 1
1.85
1.57
1H NMR (ppm)
0.92
0.92
1.89
1.95
0.88
1.90
17.79
3.00

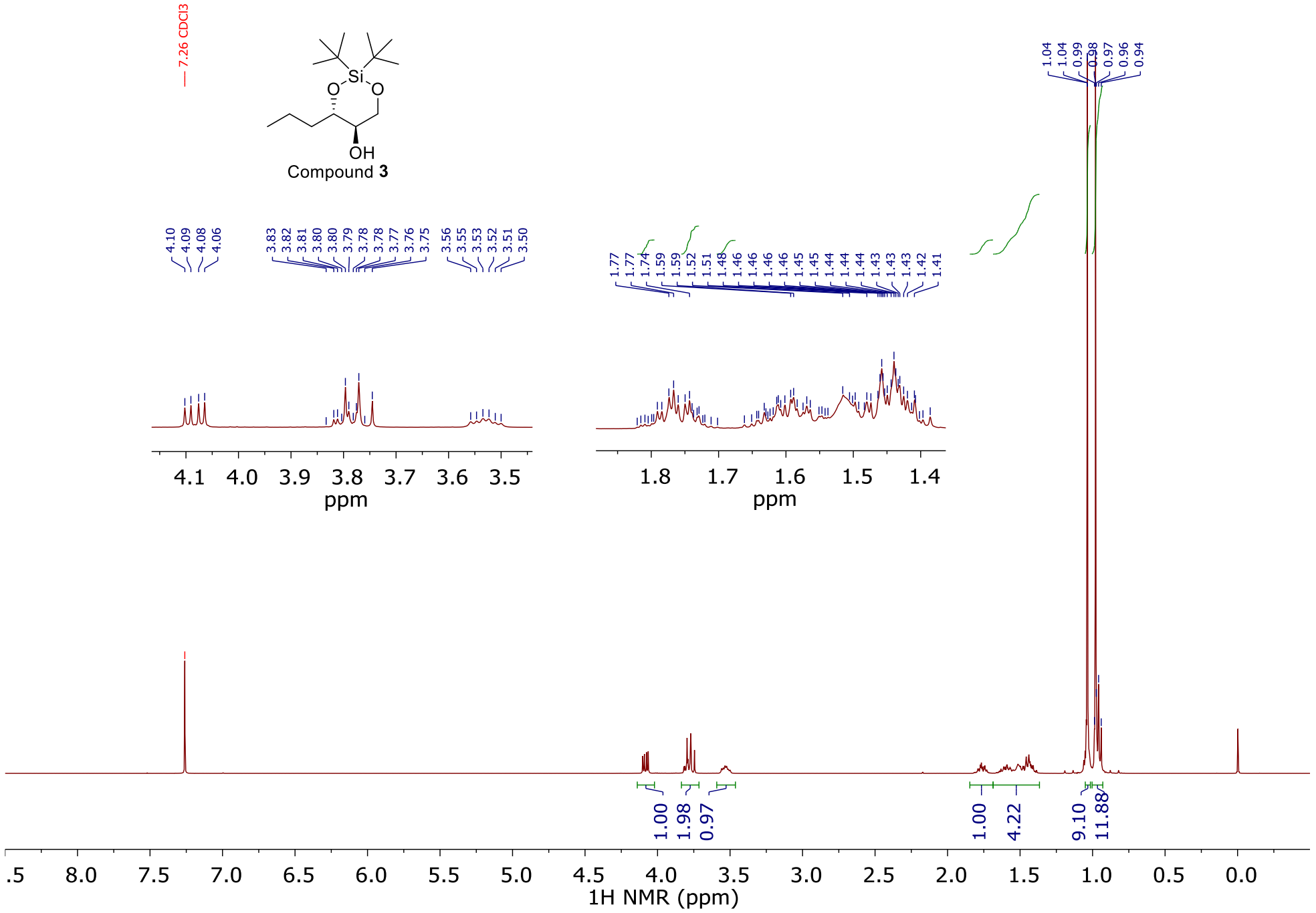

131.33
129.55
77.16 CDCl3
64.33
34.40
27.57
22.54
20.63
13.83
Si
O
OH
Compound 1
40
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C NMR (ppm)

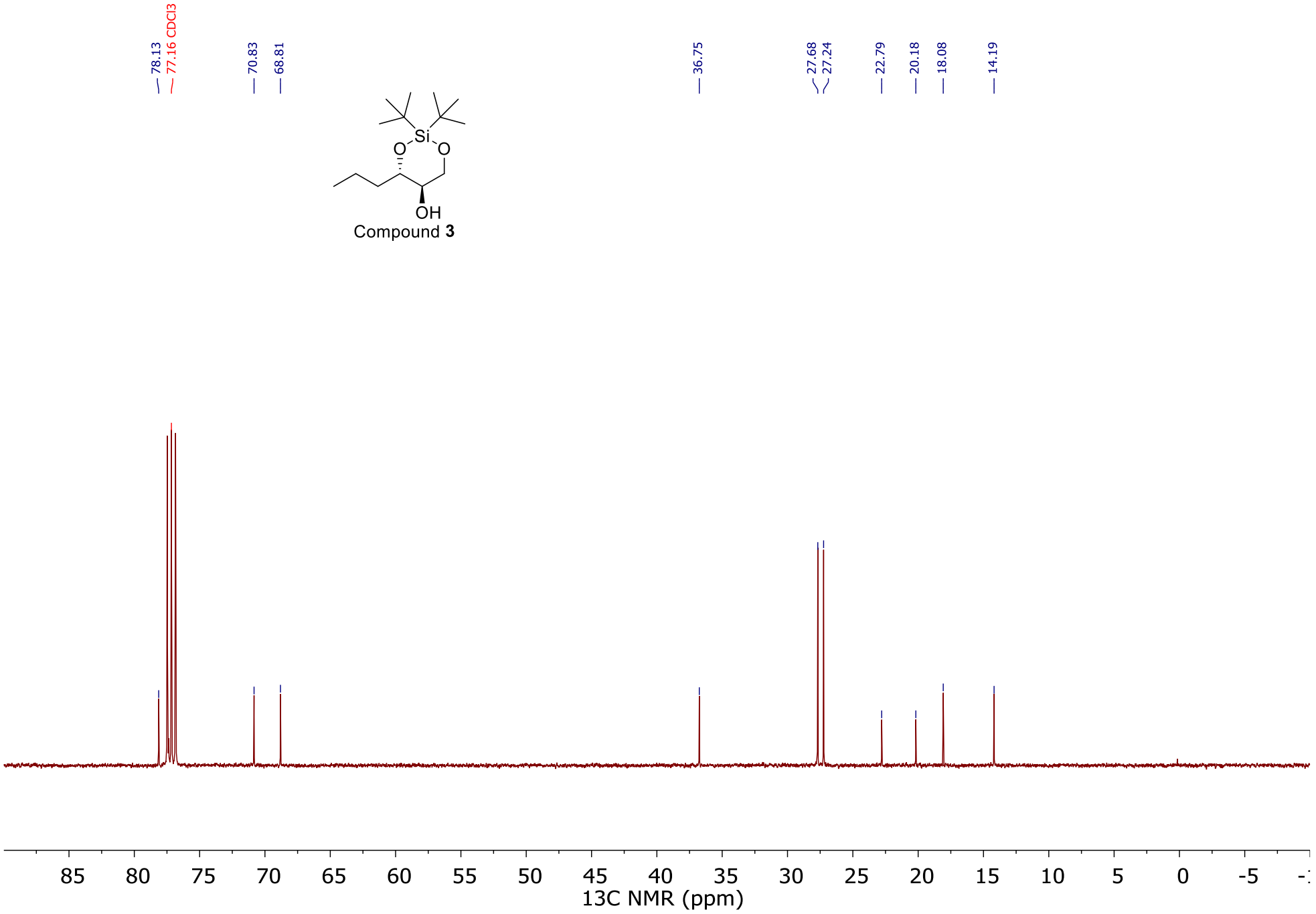

7.26 CDCl3
2.46
0.91
0.89
0.88
Integrated area of sample (Ix) = 3.02
Integrated area of standard (Ical) = 3.00
Number of sample nuclei (Nx) = 3
Number of standard nuclei (Ncal) = 3
Molecular weight of sample (Mx) = 258.4770
Molecular weight of standard (Mcal) = 137.1380
Mass of internal standard (Wcal) = 18.2 mg
Mass of sample (Wx) = 34.7 mg
Purity of standard (Pcal) = 99.5 %
$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} x \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$
$Px = \frac{3.02}{3.00} \times \frac{3}{3} \times \frac{258.4770}{137.1380} \times \frac{18.2}{34.7} \times 99.5 = 99.0\%$
O2N
Si
OH
Compound 1
3.00
3.02
1H NMR (ppm)

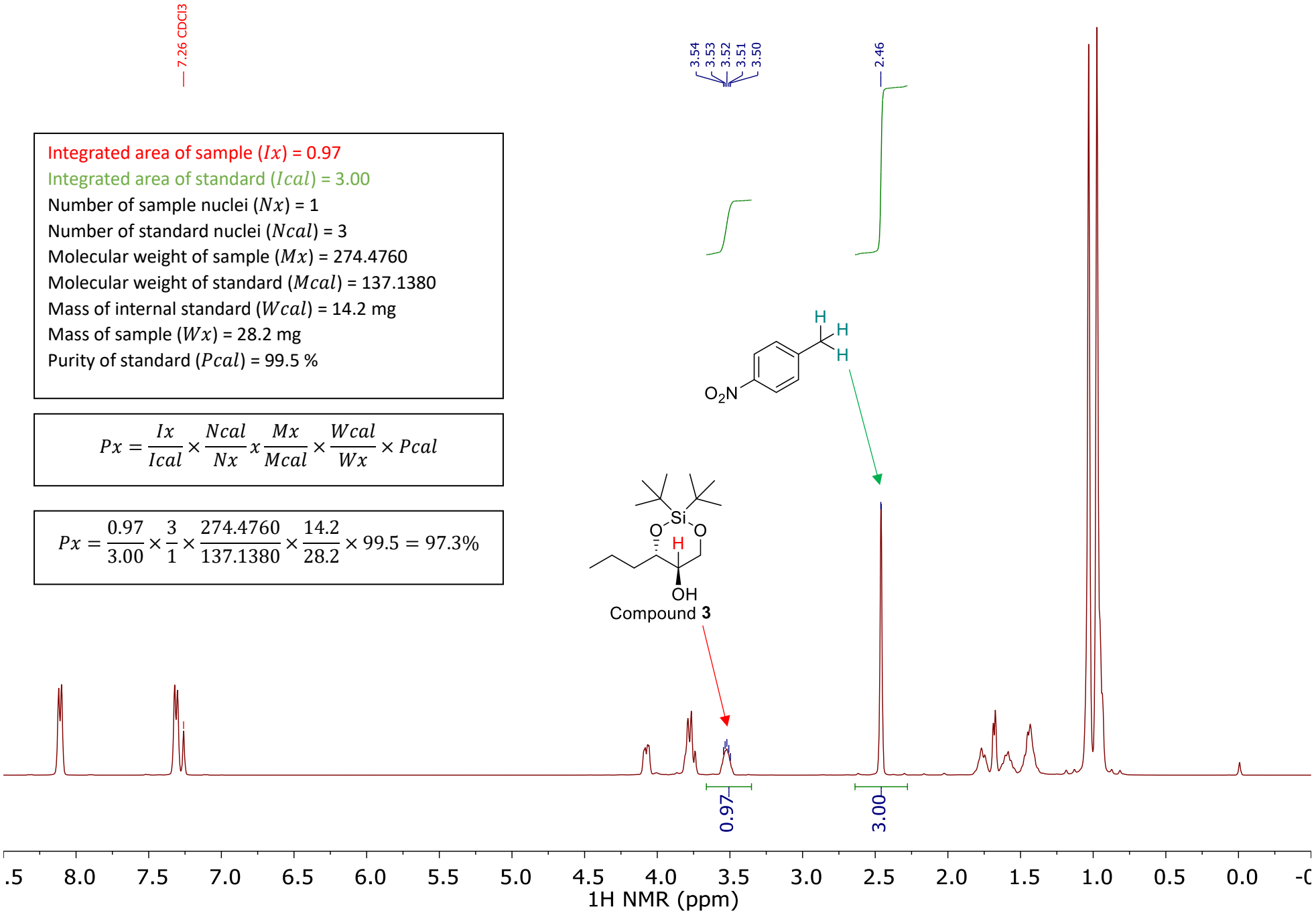

7.26 CDCl3
Si
O
OH
O
Compound 2
4.14
4.14
4.14
4.13
4.11
4.11
4.11
4.10
3.74
3.72
3.71
3.71
3.69
4.1 4.0 3.9 3.8 3.7
ppm
2.95
2.94
2.93
2.93
2.93
2.92
2.91
2.90
2.95 2.93 2.91 2.89
ppm
1.56
1.55
1.55
1.54
1.54
1.52
1.50
1.49
1.48
1.47
1.47
1.45
1.45
1.44
1.55 1.45 1.35
ppm
1.03
1.01
0.97
0.95
0.94
1.10 1.00 0.90
ppm
0.99
1.00
2.03
4.00
17.96
3.09
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1H NMR (ppm)


77.16 CDCl3
64.10
59.26
56.97
33.72
27.51
20.74
20.67
19.38
13.99
Si
O
OH
O
Compound 2
13C NMR (ppm)


7.26 CDCl3
2.46
1.56
1.56
1.55
1.55
1.54
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.47
1.47
1.46
1.45
1.44
1.44
1.43
1.42
1.41
1.40
Integrated area of sample (Ix) = 3.88
Integrated area of standard (Ical) = 3.00
Number of sample nuclei (Nx) = 4
Number of standard nuclei (Ncal) = 3
Molecular weight of sample (Mx) = 274.4760
Molecular weight of standard (Mcal) = 137.1380
Mass of internal standard (Wcal) = 16.8 mg
Mass of sample (Wx) = 32.6 mg
Purity of standard (Pcal) = 99.5 %
$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} x \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$
$Px = \frac{3.88}{3.00} \times \frac{3}{4} \times \frac{274.4760}{137.1380} \times \frac{16.8}{32.6} \times 99.5 = 99.5\%$
H H
H H
O
Si
O
OH
Compound 2
H
H
H
O_2N
3.00
3.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR (ppm)


7.26 CDCl3
Si
O
O
OH
Compound 3
4.10 4.09 4.08 4.06
3.83 3.82 3.81 3.80 3.80 3.79 3.78 3.78 3.77 3.76 3.75
3.56 3.55 3.53 3.52 3.51 3.50
4.1 4.0 3.9 3.8 3.7 3.6 3.5
ppm
1.77 1.77 1.74 1.59 1.59 1.52 1.51 1.48 1.46 1.46 1.46 1.46 1.45 1.45 1.44 1.44 1.44 1.43 1.43 1.43 1.42 1.41
1.8 1.7 1.6 1.5 1.4
ppm
1.04 1.04 0.99 0.98 0.97 0.96 0.94
1.00 1.98 0.97
1.00 4.22
9.10 11.88
.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1H NMR (ppm)


78.13
77.16 CDCl3
70.83
68.81
36.75
27.68
27.24
22.79
20.18
18.08
14.19
Si
O
O
OH
Compound 3
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
13C NMR (ppm)


7.26 CDCl3
3.54
3.53
3.52
3.51
3.50
2.46
Integrated area of sample (Ix) = 0.97
Integrated area of standard (Ical) = 3.00
Number of sample nuclei (Nx) = 1
Number of standard nuclei (Ncal) = 3
Molecular weight of sample (Mx) = 274.4760
Molecular weight of standard (Mcal) = 137.1380
Mass of internal standard (Wcal) = 14.2 mg
Mass of sample (Wx) = 28.2 mg
Purity of standard (Pcal) = 99.5 %
$Px = \frac{Ix}{Ical} \times \frac{Ncal}{Nx} x \frac{Mx}{Mcal} \times \frac{Wcal}{Wx} \times Pcal$
$Px = \frac{0.97}{3.00} \times \frac{3}{1} \times \frac{274.4760}{137.1380} \times \frac{14.2}{28.2} \times 99.5 = 97.3\%$
H
H
H
O_2N
Si
O
O
H
OH
Compound 3
0.97
3.00
.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR (ppm)