



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

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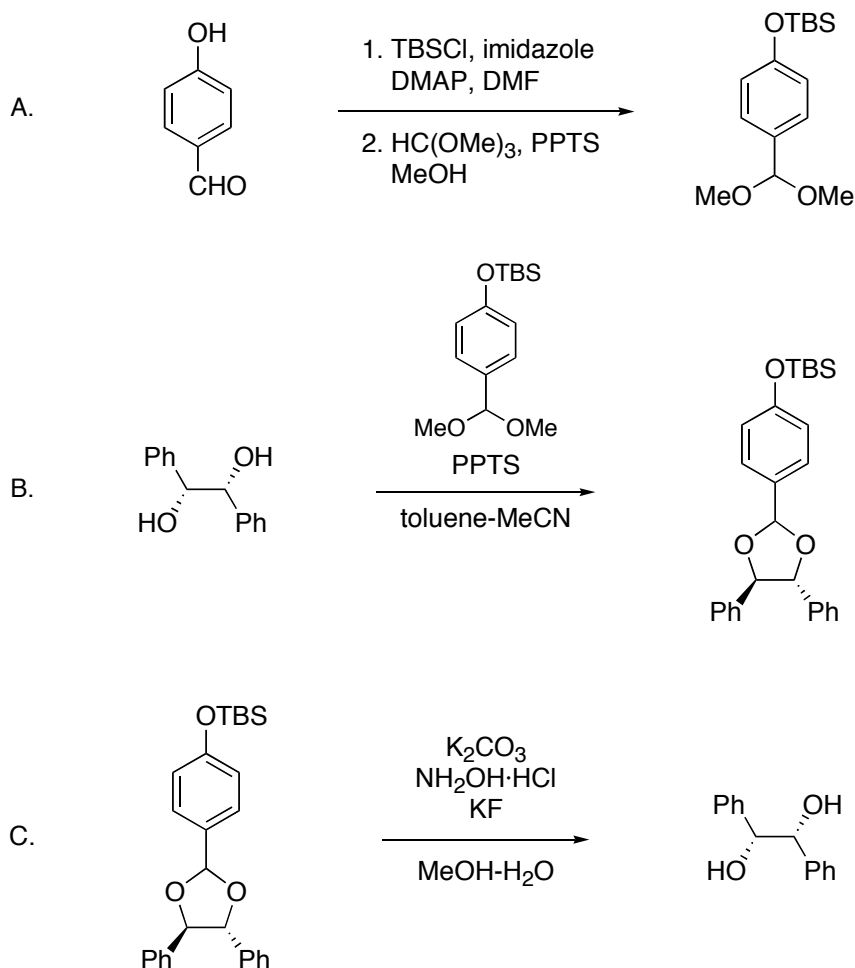
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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**PROTECTION OF DIOLS WITH  
4-(*tert*-BUTYLDIMETHYLSILOXY)BENZYLIDENE ACETAL  
AND ITS DEPROTECTION:  
(4-(((4*R*,5*R*)-4,5-DIPHENYL-1,3-DIOXOLAN-2-YL)PHENOXY))(*tert*-  
BUTYL)DIMETHYLSILANE**



Submitted by Hiroyuki Osajima,<sup>1</sup> Hideto Fujiwara,<sup>2</sup> Kentaro Okano,<sup>2</sup> Hidetoshi Tokuyama,<sup>2</sup> and Tohru Fukuyama.<sup>1</sup>

Checked by Scott E. Denmark and Wen-Tau T. Chang.

## 1. Procedure

*A. (4-(Dimethoxymethyl)phenoxy)(tert-butyl)dimethylsilane.* A 100-mL oven-dried, three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum, a thermocouple and an argon gas inlet is charged with *tert*-butylchlorodimethylsilane (6.08 g, 40.3 mmol) (Note 1) and DMF (20 mL) (Note 2). To the mixture are added

4-hydroxybenzaldehyde (4.92 g, 40.3 mmol) (Note 3), imidazole (4.12 g, 60.5 mmol) (Note 4), and 4-dimethylaminopyridine (0.248 g, 2.02 mmol) (Note 5) in separate portions with stirring. After being stirred for 2 h (Note 6) at ambient temperature (19 °C), the reaction mixture is poured into water (30 mL) in a 500-mL separatory funnel and the suspension is extracted with EtOAc (2 x 25 mL). The combined organic extracts are diluted with EtOAc (50 mL), and then washed with 5% aq. NaCl solution (100 mL), water (4 x 100 mL), and sat. aq. NaCl solution (100 mL), then are dried over anhydrous MgSO<sub>4</sub> (1.6 g), filtered, and concentrated on a rotary evaporator (20 °C, 30 mmHg). The residue is dissolved with toluene (50 mL) and the resulting solution is concentrated on a rotary evaporator (40 °C, 30 mmHg) (Note 7) to give a pale yellow oil (9.43 g) (Note 8). The crude product is used in the next step without further purification (Note 9).

A 500-mL, oven-dried, three-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a rubber septum, a thermocouple and an argon gas inlet is charged with the crude product prepared above (9.43 g), MeOH (60 mL) (Note 10), and trimethyl orthoformate (40 mL) (Note 11). To the mixture is added pyridinium *p*-toluenesulfonate (1.01 g, 4.03 mmol) (Note 12). After being heated in a 50 °C oil bath (internal temperature: 43 °C) for 3.5 h (Note 13), the solution is cooled to ambient temperature and is poured into sat. aq. NaHCO<sub>3</sub> solution (100 mL) in a 1-L separatory funnel. The two-phase mixture is extracted with EtOAc (3 x 100 mL) and the combined organic extracts are washed with sat. aq. NaCl solution (2 x 100 mL), then are dried over Na<sub>2</sub>SO<sub>4</sub> (2.2 g), filtered, and concentrated on a rotary evaporator (20 °C, 30 mmHg). The residue is dissolved with toluene (50 mL) and the resulting solution is concentrated on a rotary evaporator (40 °C, 30 mmHg) (Note 7) to give a yellow oil (10.07 g). The oil is purified by silica gel column chromatography (elution with hexanes/EtOAc, 20:1) (Notes 14, 15) to yield (4-(dimethoxymethyl)phenoxy)(*tert*-butyl)dimethyl silane (9.66 g, 85%) (Note 16).

*B. (4-((4R, 5R)-4,5- Diphenyl-1,3- dioxolan-2-yl) phenoxy) (tert-butyl)dimethylsilane.* A 500-mL, oven-dried, three-necked round-bottomed flask equipped with a reflux condenser (fitted with an argon gas inlet), a Teflon-coated magnetic stir bar, a rubber septum, and a thermocouple is charged with (1*R*,2*R*)-1,2-diphenylethane-1,2-diol (6.43 g, 30.0 mmol) (Note 17), toluene (96.0 mL) (Note 18), MeCN (32.0 mL) (Note 19), and (4-(dimethoxymethyl)phenoxy)(*tert*-butyl)dimethylsilane (9.27 g, 32.8 mmol). After stirring the solution for 3 min, pyridinium *p*-toluenesulfonate (2.26 g,

9.0 mmol) (Note 11) is added. The reaction mixture is heated in a 50 °C oil bath (internal temperature: 45 °C) and is stirred for 1 h (Note 20). The mixture is cooled to ambient temperature and then is poured into sat. aq. NaHCO<sub>3</sub> solution (100 mL) in a 1-L separatory funnel, and the suspension is extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with sat. aq. NaCl solution (2 x 100 mL), then are dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (20 g), filtered, and concentrated on a rotary evaporator under reduced pressure to give a yellow, viscous oil. The residue is purified by silica gel column chromatography (elution with hexanes/CH<sub>2</sub>Cl<sub>2</sub>, 7:3) (Notes 21, 22) to give a colorless, viscous oil (12.33 g) (Note 23) which is triturated with MeOH to yield (4-((4*R*,5*R*)-4,5-diphenyl-1,3-dioxolan-2-yl)phenoxy) (*tert*-butyl)dimethylsilane as a white solid (11.51 g, 89%) (Note 24).

*C. (1*R*,2*R*)-1,2-Diphenylethane-1,2-diol.* A 500-mL, three-necked round-bottomed flask equipped with a reflux condenser (fitted with an argon inlet), a Teflon-coated magnetic stir bar, a rubber septum, and a thermocouple is charged with (4-((4*R*,5*R*)-4,5-diphenyl-1,3-dioxolan-2-yl) phenoxy) (*tert*-butyl)dimethylsilane (10.8 g, 25.0 mmol), K<sub>2</sub>CO<sub>3</sub> (17.3 g, 125 mmol) (Note 25), MeOH (200 mL) (Note 9), and water (50 mL). After addition of KF (1.46 g, 25.0 mmol) (Note 26) and stirring for 5 min followed by addition of NH<sub>2</sub>OH·HCl (8.69 g, 125 mmol) (Note 27), the reaction mixture is heated in an 85 °C oil bath (internal temperature: 69 °C) and is stirred for 37 h (Note 28). The reaction mixture is cooled to ambient temperature and is decanted (Note 29) into sat. brine (150 mL) in a 1-L separatory funnel and is extracted with EtOAc (3 x 200 mL). The combined organic extracts are washed with 3 M NaOH (3 x 100 mL), H<sub>2</sub>O (100 mL), and brine (100 mL), and then are dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (20 g), filtered, and concentrated on a rotary evaporator (21 °C 30 mmHg) to afford 5.40 g of the crude diol as a white solid. Purification by recrystallization yields (1*R*,2*R*)-1,2-diphenylethane-1,2-diol as white crystals (4.65 g, 87%) (Notes 30, 31).

## 2. Notes

1. *tert*-Butylchlorodimethylsilane (97%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
2. DMF (99.9%, water content: < 0.02%) was purchased from Fisher Scientific and used as received without further purification.
3. 4-Hydroxybenzaldehyde (98%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.



4. Imidazole (99%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
5. 4-Dimethylaminopyridine (99%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
6. The reaction typically requires 2 h to go to completion and is monitored by  $^1\text{H}$  NMR spectroscopy. A small aliquot of the reaction mixture is removed and is treated with brine. The organic layer is separated and concentrated under reduced pressure (30 °C, 30 mmHg) to afford the NMR sample. Stirring is stopped when the ratio of the signal for the formyl proton of the alcohol ( $\delta$  9.85, 1 H) to that of the TBS ether ( $\delta$  9.89, 1 H) is less than 0.10.
7. Azeotropic removal of water was carried out with toluene ( $\geq 99.5\%$ , water content:  $< 0.030\%$ ) purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
8. The ratio of the alcohol ( $\delta$  9.85, 1 H) to the TBS ether ( $\delta$  9.89, 1 H) is 0.06.
9. The compound exhibits the following physicochemical properties:  $R_f = 0.61$  (hexanes/EtOAc, 4:1; Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with an ethanol solution of  $\text{Ce}_2(\text{SO}_4)_3$  and phosphomolybdic acid (Ce-PMA)); IR (neat)  $\text{cm}^{-1}$ : 2956, 2930, 2859, 1701, 1599, 1576, 1508, 1274, 1211, 1156, 909, 841, 800, 783, 705;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.25 (s, 6 H), 0.99 (s, 9 H), 6.94 (d,  $J = 8.5$  Hz, 2 H), 7.79 (d,  $J = 8.5$  Hz, 2 H), 9.89 (s, 1 H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.4, 18.2, 25.5, 120.4, 130.4, 131.9, 161.5, 190.9.
10. Methanol ( $\geq 99.8\%$ , water content:  $< 0.100\%$ ) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
11. Trimethyl orthoformate (99%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
12. Pyridinium *p*-toluenesulfonate (98%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
13. The reaction typically requires 3.5 h to go to completion and is monitored by  $^1\text{H}$  NMR spectroscopy. A small aliquot of the reaction mixture is removed and treated with brine. The organic layer is concentrated under reduced pressure (30 °C, 30 mmHg) to afford the NMR sample. Heating and stirring is stopped when the ratio of the signal of the aldehyde ( $\delta$  9.89, 1 H) to that of the dimethyl acetal ( $\delta$  5.33, 1 H) is less than 0.05 for maximizing the yield and reproducibility.

14. Silica gel (grade 9385, 60 Å) was purchased from Merck (230–400 mesh).
15. The crude material is dissolved in eluent (5 mL) and then is charged onto a column (diameter = 5 cm, height = 5 cm) of 42 g of silica gel (slurry packed). The column was eluted with hexanes/EtOAc, 20:1 and 50-mL fractions were collected. Fraction 2-7 were combined and concentrated on a rotary evaporator under reduced pressure (30 °C, 30 mmHg).
16. The compound exhibits the following physicochemical properties:  $R_f$  = 0.71 (hexanes/EtOAc, 4:1; Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with Ce-PMA)); IR (neat)  $\text{cm}^{-1}$ : 2955, 2931, 2896, 2858, 1610, 1511, 1472, 1362, 1264, 1165, 1099, 1056, 915, 840, 805, 781;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.19 (s, 6 H), 0.98 (s, 9 H), 3.31 (s, 6 H), 5.34 (s, 1 H), 6.83 (d,  $J$  = 8.5 Hz, 2 H), 7.30 (d,  $J$  = 8.5 Hz, 2 H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.5, 18.2, 25.6, 52.6, 103.1, 119.8, 127.8, 130.9, 155.8; MS (EI)  $m/z$  (relative intensity): 282.1 (9), 251.1 (100), 225.0 (24), 195 (6), 179 (6), 151 (4), 137 (3), 97 (4), 75 (39); Anal. Calcd for  $\text{C}_{15}\text{H}_{26}\text{O}_3\text{Si}$ : C, 63.78; H, 9.28. Found: C, 63.50; H, 9.64.
17. (1*R*,2*R*)-1,2-Diphenylethane-1,2-diol (99%, 98% ee) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
18. Toluene ( $\geq 99.5\%$ , water content:  $< 0.030\%$ ) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.
19. MeCN ( $\geq 99.9\%$ , water content:  $< 0.01\%$ ) was purchased from Fisher Scientific and used as received without further purification.
20. The reaction typically requires 1 h to go to completion and is monitored by  $^1\text{H}$  NMR spectroscopy. A small aliquot of the reaction mixture is removed and treated with brine. The organic layer is separated and concentrated under reduced pressure (30 °C, 30 mmHg) to afford the NMR sample. Heating and stirring is stopped when the signal for the dimethyl acetal ( $\delta$  5.33, 1 H) is fully converted to the signal for the diphenylethane acetal ( $\delta$  6.36, 1 H).
21. The crude material is dissolved in eluent (5 mL) and then is charged onto a column (diameter = 6 cm, height = 22 cm) of 345 g of silica gel (slurry packed). The column was eluted with hexanes/ $\text{CH}_2\text{Cl}_2$ , 7:3 and 50-mL fractions were collected. Fractions 17-53 were combined and concentrated on a rotary evaporator under reduced pressure (30 °C, 30 mmHg).

22. Alternatively, the conversion to (4-((4*R*,5*S*)-4,5-diphenyl-1,3-dioxolan-2-yl)phenoxy)(*tert*-butyl)dimethylsilane could be carried out following the method of Noyori<sup>3</sup> using (4-(dimethoxymethyl)phenoxy)-(*tert*-butyl)dimethylsilane and the bis(trimethylsilyl) ether.

23. The checkers found that the product can be crystallized by addition of methanol (10 mL) followed by sonication for 15 min. The murky solution is cooled to -27 °C for 1 h to induce precipitation and the white solid is collected by filtration (10.79 g). A second crop (0.72 g) is obtained by sonicating the concentrated mother liquor in MeOH (5 mL) for 1 min and cooling to -27 °C for 1 h.

24. The compound exhibits the following physicochemical properties:  $R_f$  = 0.20 (hexanes/CH<sub>2</sub>Cl<sub>2</sub>, 7:3; Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with Ce-PMA)); mp 46–47 °C (MeOH); IR (film) cm<sup>-1</sup>: 2955, 2929, 2884, 2857, 1610, 1513, 1264, 1108, 1088, 1071, 1013, 913, 839, 803, 781, 762, 698; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 0.23 (s, 6 H), 1.01 (s, 9 H), 4.96 (s, 2 H), 6.36 (s, 1 H), 6.92 (d,  $J$  = 8.5 Hz, 2 H), 7.30–7.39 (m, 10 H), 7.56 (d,  $J$  = 8.5 Hz, 2 H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ: -4.4, 18.2, 25.7, 85.2, 87.1, 104.8, 120.1, 126.3, 126.9, 128.09, 128.12, 128.50, 128.54, 128.57, 130.9, 136.6, 138.4, 156.7; MS (ESI)  $m/z$  433.3; MS (EI)  $m/z$  (relative intensity): 326.2 (100), 297.2 (79), 269.1 (54), 241.1 (11), 220.1 (21), 179.1 (16), 149.0 (9), 91.1 (19), 73.1 (27); Anal. Calcd for C<sub>27</sub>H<sub>32</sub>O<sub>3</sub>Si: C, 74.96; H, 7.46. Found: C, 74.69; H, 7.52.

25. Potassium carbonate (98%, powdered, 325 mesh) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.

26. Potassium fluoride (99%) was purchased from Alfa-Aesar and used as received without further purification.

27. Hydroxylamine hydrochloride (98%) was purchased from Aldrich Chemical Company, Inc. and used as received without further purification.

28. The reaction typically requires 26–37 h to go to completion and is monitored by <sup>1</sup>H NMR spectroscopy. A small aliquot of the reaction mixture is removed and treated with brine. The organic layer is separated and concentrated under reduced pressure (30 °C, 30 mmHg) to afford the NMR sample. Heating and stirring is stopped when the ratio of the signal for the protected diol (δ 4.96, 2 H) to that for the starting diol (δ 4.70, 2 H) is less than 0.05 to maximize the yield and reproducibility.

29. The salt generated in the reaction causes some emulsion during the extraction.

30. To crystallize the product, the residue is dissolved in hot EtOAc/hexanes, 3:2 (100 mL). The solution is then cooled to room temperature and left in a freezer at  $-27\text{ }^{\circ}\text{C}$  for 2 h. The colorless crystals are collected by filtration (4.01 g). A second crop of crystals (0.64 g) is obtained by dissolving the concentrated mother liquor in hot EtOAc/hexanes, 3:2 (13 mL) followed by the same cooling procedure.

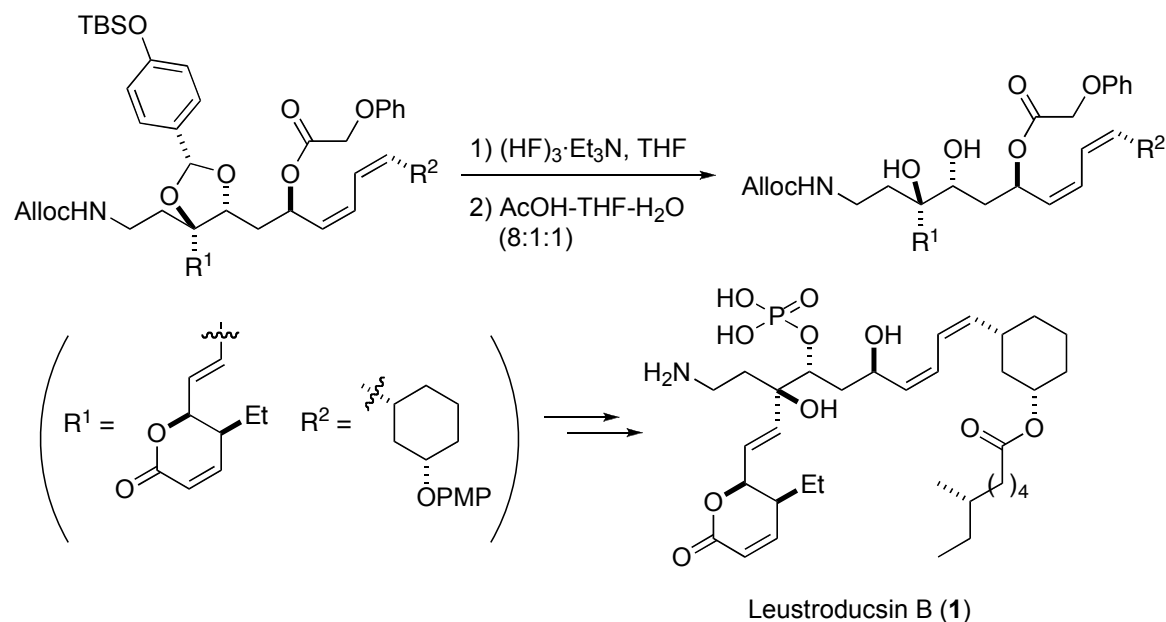
31. The compound exhibits the following physicochemical properties:  $R_f = 0.52$  (hexanes/EtOAc, 1:1; Merck silica gel 60F-254 plate (visualized with 254 nm UV lamp and stained with Ce-PMA)); mp  $146\text{--}147\text{ }^{\circ}\text{C}$  (hexane/EtOAc); IR (KBr)  $\text{cm}^{-1}$ : 3499, 3393, 2895, 1452, 1385, 1198, 1178, 1045, 1013, 846, 777, 747, 705, 695;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.92 (s, 2 H), 4.70 (s, 2 H), 7.10–7.14 (m, 4 H), 7.21–7.25 (m, 6 H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 79.1, 126.9, 127.9, 128.1, 139.8; MS (EI)  $m/z$  (relative intensity): 214.1 ( $< 0.5\%$ ), 107.0 (100), 79.1 (81); Anal. Calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_2$ : C, 78.48; H, 6.59. Found: C, 78.56; H, 6.66.

### Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academic Press; Washington, DC, 1995.

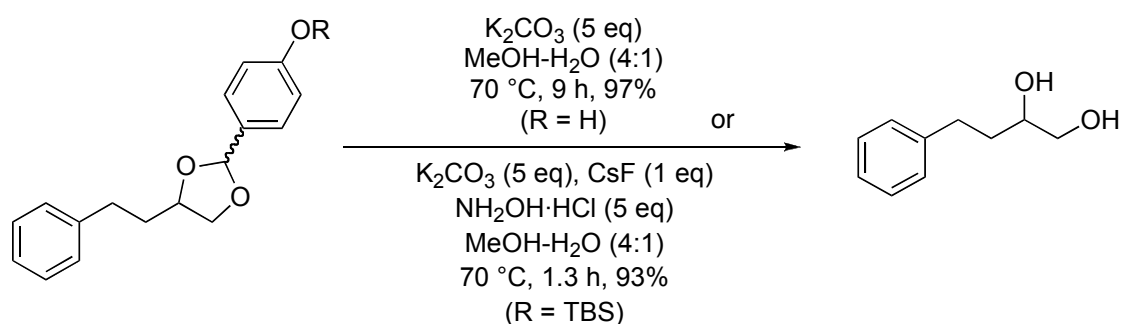
### 3. Discussion

Protection and deprotection of functional groups play a critical role in successful synthesis of multifunctionalized, complex molecules. Among a variety of protecting groups on 1,2-diols,<sup>3</sup> the most frequently used ones are cyclic acetals and ketals. However, since their deprotections generally require strongly acidic conditions, these protecting groups are generally incompatible with acid-labile functional groups. During the course of synthetic studies on leustroducsin B<sup>4</sup>, we devised a novel benzylidene-type protecting group, *p*-(*tert*-butyldimethylsilyl-oxy)benzylidene group<sup>5</sup> (Scheme 1). This protecting group could be removed under a mild two-step sequence, desilylation of the phenolic hydroxyl group with  $(\text{HF})_3\cdot\text{Et}_3\text{N}$  and the subsequent treatment with weakly acidic conditions (AcOH-THF- $\text{H}_2\text{O}$ ). Exploitation of this protective group was the key to achieve the total synthesis of leusroducsin B bearing highly acid-sensitive functionalities.



**Scheme 1.** Mild Acidic Deprotection of a Novel Benzyldiene-Type Protecting Group.

Further investigations on the utility of this newly developed protective group revealed that this group could also be removed in a single step under mild basic conditions (Scheme 2). Thus, treatment of the *p*-hydroxybenzyldiene acetal with  $K_2CO_3$  in MeOH- $H_2O$  at 70 °C gave the corresponding diol in almost quantitative yield. Furthermore, addition of  $NH_2OH \cdot HCl$  and CsF dramatically facilitated the deprotection process and the single-step deprotection of the TBS ether took place smoothly. Trapping of the liberated *p*-hydroxybenzaldehyde with hydroxylamine would accelerate the deprotection process under the equilibrium conditions.

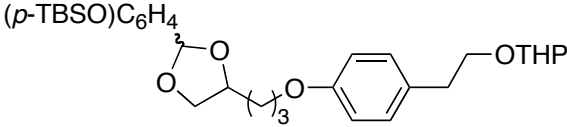
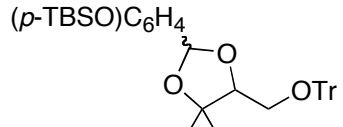
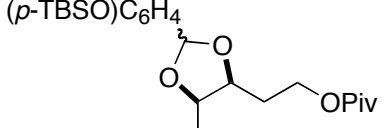
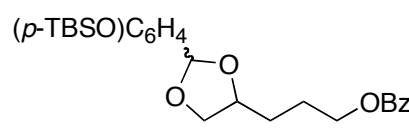


**Scheme 2.** Single-Step Deprotection under Basic Conditions

As shown in Table 1, acid-labile functional groups such as the THP ether and triphenylmethyl group were unaffected during the deprotection process. While benzyl ester could not tolerate these basic conditions, more

robust pivaloyl ester survived.

**Table 1.** Chemoselective Deprotection of the Benzylidene-Group under Basic Conditions<sup>a</sup>

|   |   |
|---|---|
| <br>2.5 h, 93% | <br>21 h, 91%               |
| <br>3.5 h, 92% | <br>1.5 h, 29% <sup>b</sup> |

<sup>a</sup>Conditions: K<sub>2</sub>CO<sub>3</sub> (5 equiv), NH<sub>2</sub>OH·HCl (5 equiv), CsF (1 equiv), MeOH-H<sub>2</sub>O (4:1), 70 °C. <sup>b</sup>Hydrolysis of benzoyl group occurred.

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3. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley & Sons: New York, **2006**; p 321.
4. Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048-4049.
5. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley & Sons: New York, **2006**; p 339. (b) Kaburagi, Y.; Osajima, H.; Shimada, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron Lett.* **2004**, *45*, 3817-3821.

## Appendix

### Chemical Abstracts Nomenclature; (Registry Number)

*tert*-Butyldimethylsilyl chloride: Silane, chloro(1,1-dimethylethyl)dimethyl-; (18162-48-6)

4-Hydroxybenzaldehyde: Benzaldehyde, 4-hydroxy-; (123-08-0)  
Imidazole: 1*H*-Imidazole; (288-32-4)  
4-(Dimethylamino)pyridine: 4-Pyridinamine, *N,N*-dimethyl-; (1122-58-3)  
Trimethyl orthoformate: Methane, trimethoxy-; (149-73-5)  
Pyridinium *p*-toluenesulfonate: Benzenesulfonic acid, 4-methyl-, compd. with pyridine (1:1); (24057-28-1)  
(1*R*,2*R*)-1,2-Diphenylethane-1,2-diol: 1,2-Ethanediol, 1,2-diphenyl-, (1*R*,2*R*)-; (52340-78-0)  
Potassium fluoride: Potassium fluoride (KF); (7789-23-3)  
Potassium carbonate: Carbonic acid, potassium salt (1:2); (584-08-7)  
Hydroxylamine hydrochloride: Hydroxylamine, hydrochloride (1:1); (5470-11-1)



Tohru Fukuyama received his Ph.D. in 1977 from Harvard University with Yoshito Kishi. He remained in Kishi's group as a postdoctoral fellow until 1978 when he was appointed as Assistant Professor of Chemistry at Rice University. After seventeen years on the faculty at Rice, he returned to his home country and joined the faculty of the University of Tokyo in 1995, where he is currently Professor of Pharmaceutical Sciences. He has primarily been involved in the total synthesis of complex natural products of biological and medicinal importance. He often chooses target molecules that require development of new concepts in synthetic design and/or new methodology for their total synthesis.



Hiroyuki Osajima was born in Nishio, Aichi in 1978. He received his B.S. in 2003 and M.S. in 2005 from the University of Tokyo under the direction of Professor Tohru Fukuyama. During his M.S. studies, he worked on the development of the new benzylidene-type protecting group and synthetic studies toward pyrroloacridine alkaloid, plakinidines. Currently, he works for Tokyo CRO, Inc. as a CMC regulatory consultant.



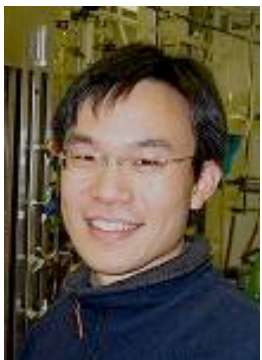
Hideto Fujiwara was born in Iwate, Japan in 1984. He received his B.S. in 2007 from Tohoku Pharmaceutical University, where he carried out undergraduate research in the laboratories of Professor Yasuyuki Endo. In the same year, he started his doctoral studies at Graduate School of Pharmaceutical Sciences, Tohoku University under the supervision of Professor Hidetoshi Tokuyama. His current research interest is total synthesis of natural products.



Kentaro Okano was born in Tokyo in 1979. He received his B.S. in 2003 from Kyoto University, where he carried out undergraduate research under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama, the University of Tokyo and started his Ph.D. research on synthetic studies toward antitumor antibiotic yatakemycin by means of the copper-mediated aryl amination strategy. In 2007, he joined the faculty of Tohoku University, where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. His current research interest is natural product synthesis based on the development of new synthetic methodologies.



Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a postdoc with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed as Associate Professor in 2003. In 2006, he moved to Tohoku University, where he is currently Professor of Pharmaceutical Sciences. His research interest is on the development of synthetic methodologies and total synthesis of complex natural products.



Wen-Tau T. Chang obtained his BSc (Hon.) from the University of Auckland, New Zealand in 2005. Under the guidance of Assoc. Prof. Brent Copp, he investigated compounds with 4-thiazolidinone scaffold against the cell growth of *Mycobacterium tuberculosis*. In 2006, he began his graduate studies at the University of Illinois at Urbana-Champaign and joined the research group of Prof. Scott Denmark. His research interests include the transition-metal catalyzed transformation of organosilanol(ate)s.



TC-5-96-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

Ambient temperature

User: 1-14-87

File: TC-5-96-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec

Pulse 65.9 degrees

Acq. time 1.086 sec

Width 30165.9 Hz

402 repetitions

OBSERVE C13, 125.6473175 MHz

DECOUPLE H1, 499.6923275 MHz

Power 44 dB

continuously on

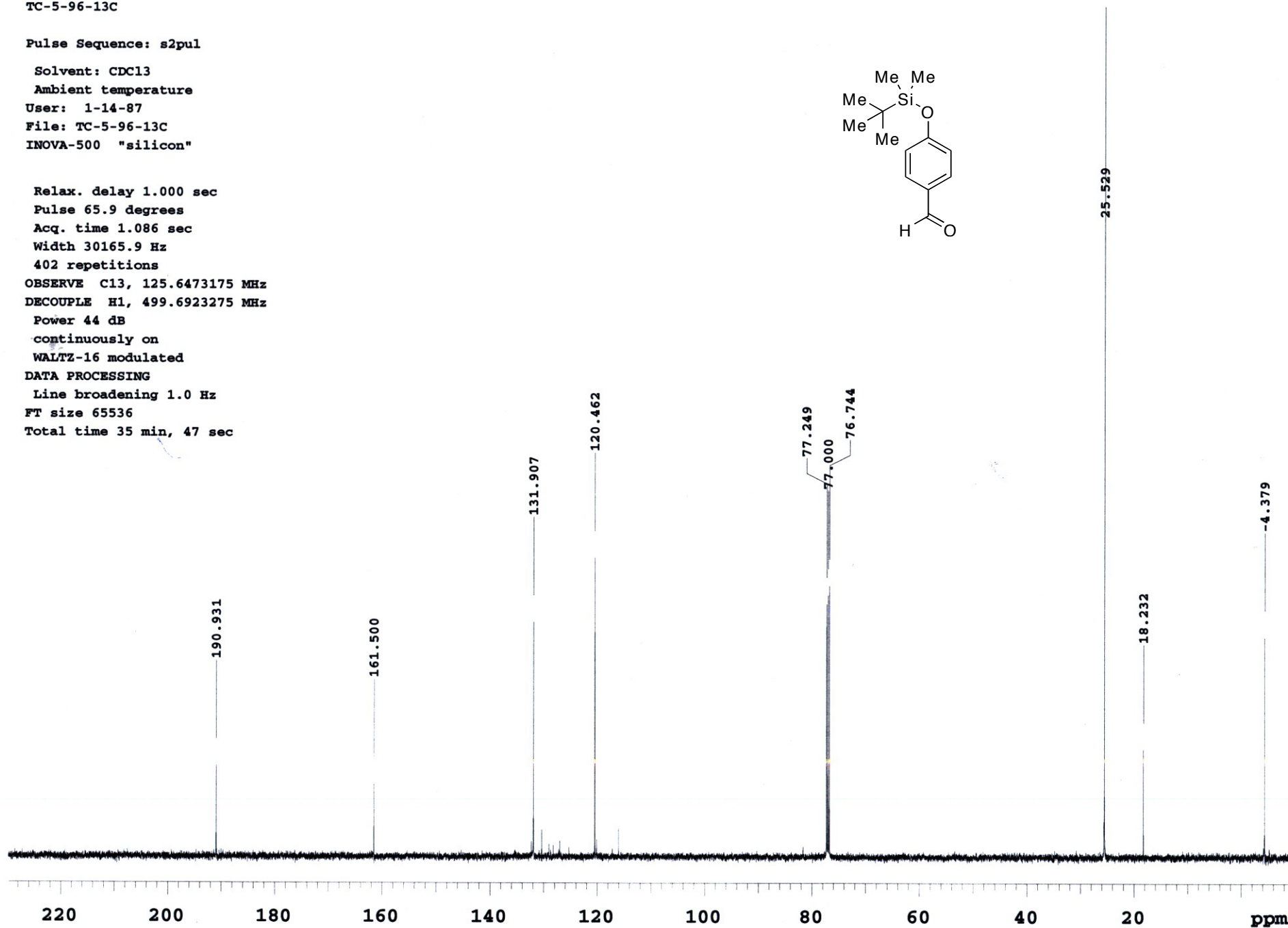
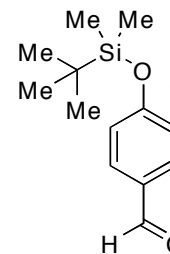
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 35 min, 47 sec



TC-5-97-c1-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

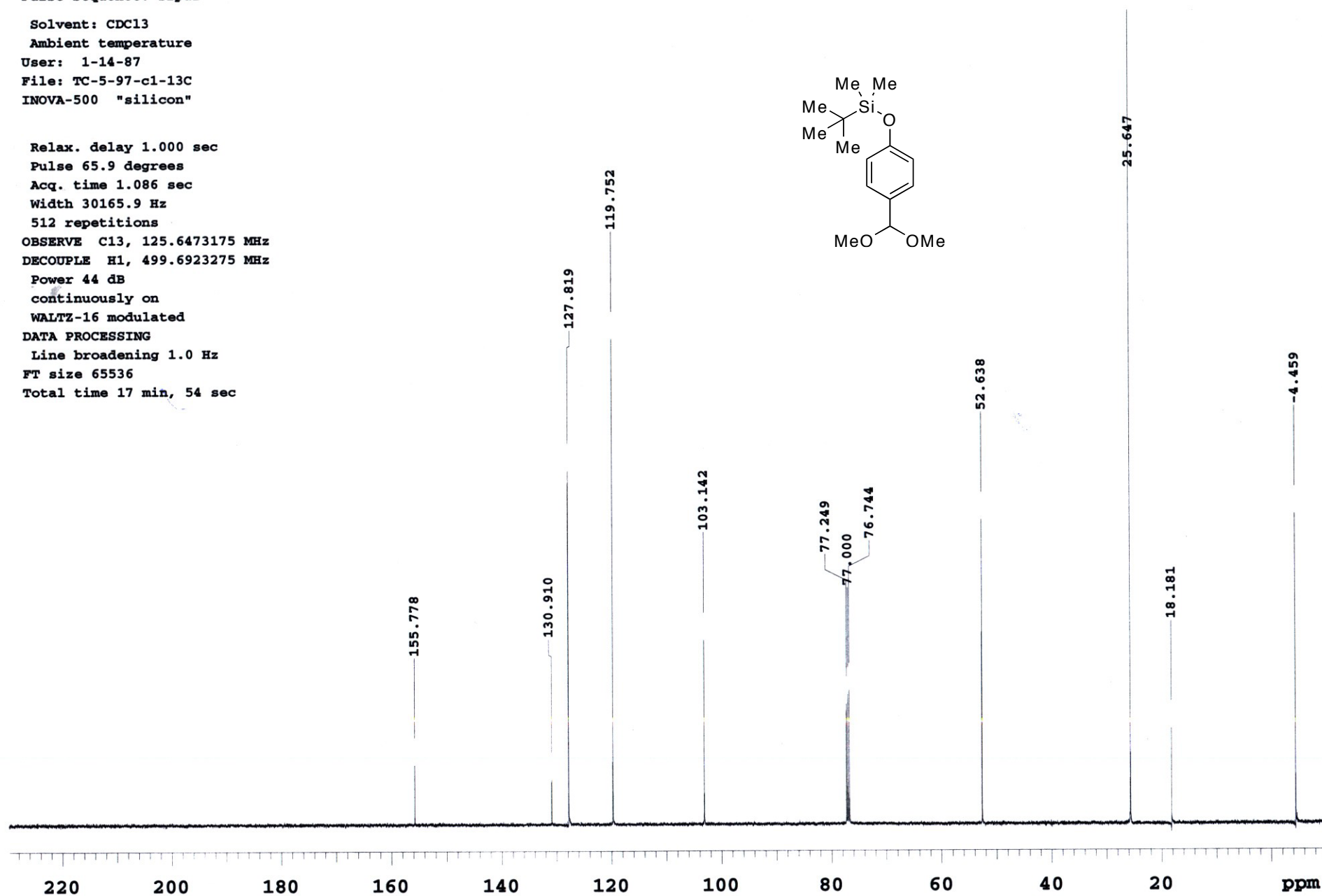
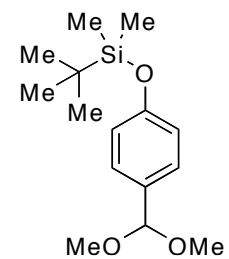
Ambient temperature

User: 1-14-87

File: TC-5-97-c1-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec  
Pulse 65.9 degrees  
Acq. time 1.086 sec  
Width 30165.9 Hz  
512 repetitions  
OBSERVE C13, 125.6473175 MHz  
DECOUPLE H1, 499.6923275 MHz  
Power 44 dB  
continuously on  
WALTZ-16 modulated  
DATA PROCESSING  
Line broadening 1.0 Hz  
FT size 65536  
Total time 17 min, 54 sec



TC-6-7-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

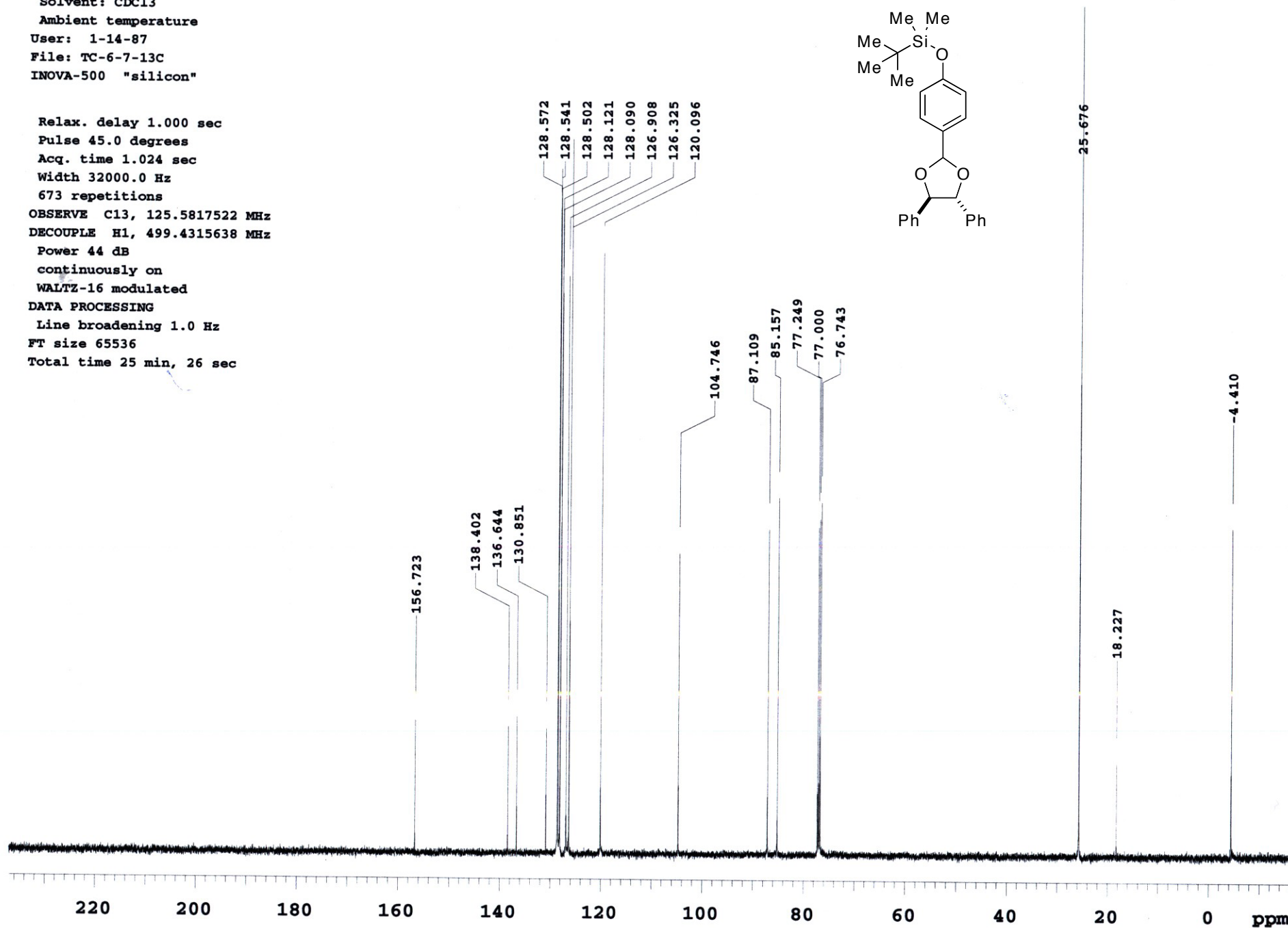
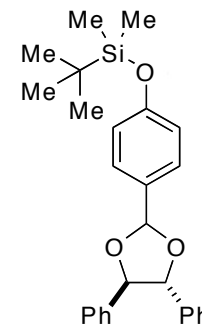
Ambient temperature

User: 1-14-87

File: TC-6-7-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 1.024 sec  
Width 32000.0 Hz  
673 repetitions  
OBSERVE C13, 125.5817522 MHz  
DECOUPLE H1, 499.4315638 MHz  
Power 44 dB  
continuously on  
WALTZ-16 modulated  
DATA PROCESSING  
Line broadening 1.0 Hz  
FT size 65536  
Total time 25 min, 26 sec



TC-6-7-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

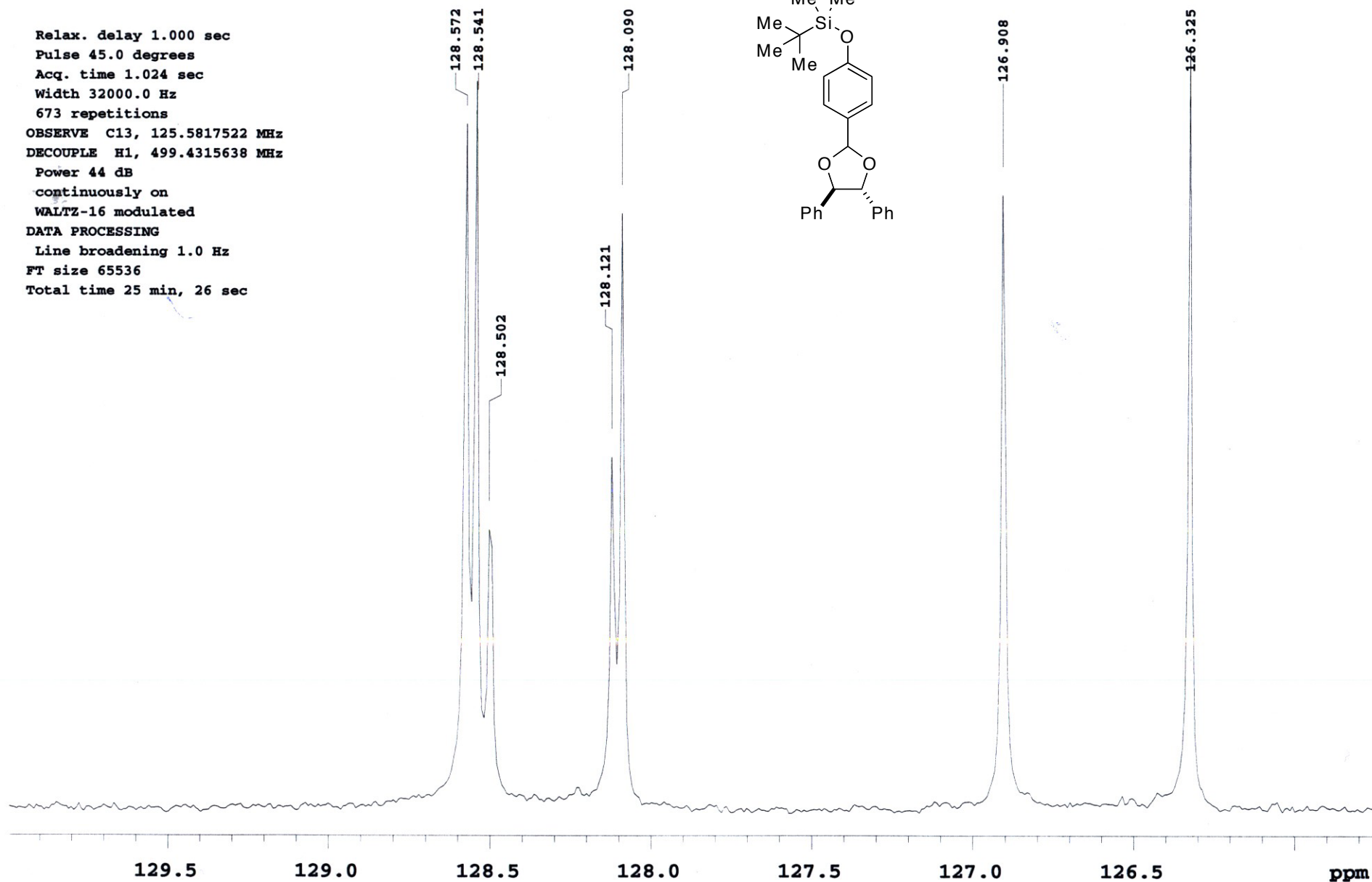
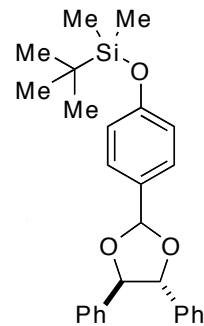
Ambient temperature

User: 1-14-87

File: TC-6-7-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 1.024 sec  
Width 32000.0 Hz  
673 repetitions  
OBSERVE C13, 125.5817522 MHz  
DECOUPLE H1, 499.4315638 MHz  
Power 44 dB  
continuously on  
WALTZ-16 modulated  
DATA PROCESSING  
Line broadening 1.0 Hz  
FT size 65536  
Total time 25 min, 26 sec



TC-6-16-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

Ambient temperature

User: 1-14-87

File: TC-6-16-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.024 sec

Width 32000.0 Hz

548 repetitions

OBSERVE C13, 125.5817512 MHz

DECOUPLE H1, 499.4315638 MHz

Power 44 dB

continuously on

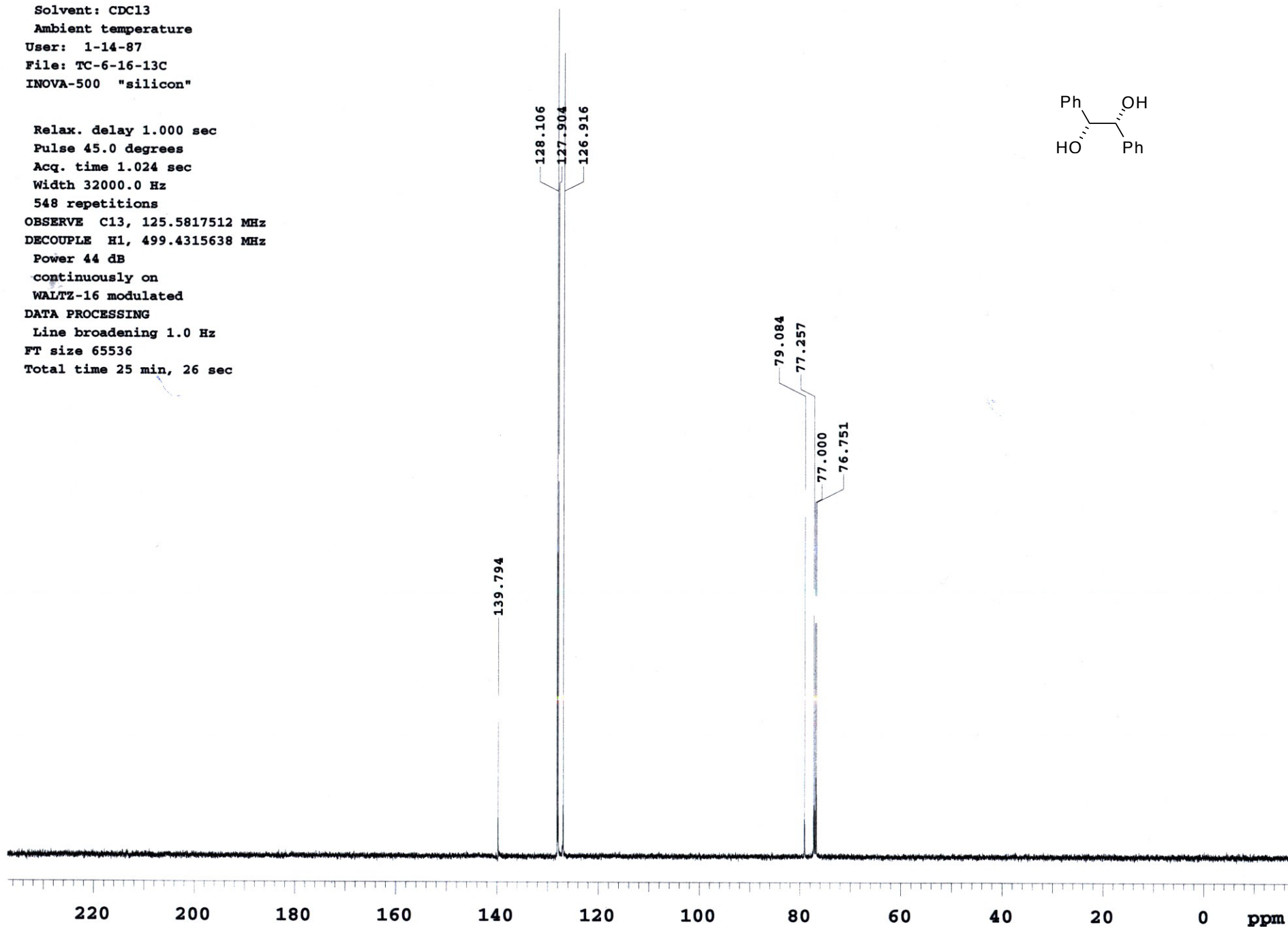
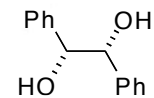
WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 25 min, 26 sec



TC-5-96-1H

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

File: TC-5-96-1H

INOVA-500 "silicon"

Relax. delay 8.000 sec

Pulse 61.6 degrees

Acq. time 4.665 sec

Width 7024.9 Hz

8 repetitions

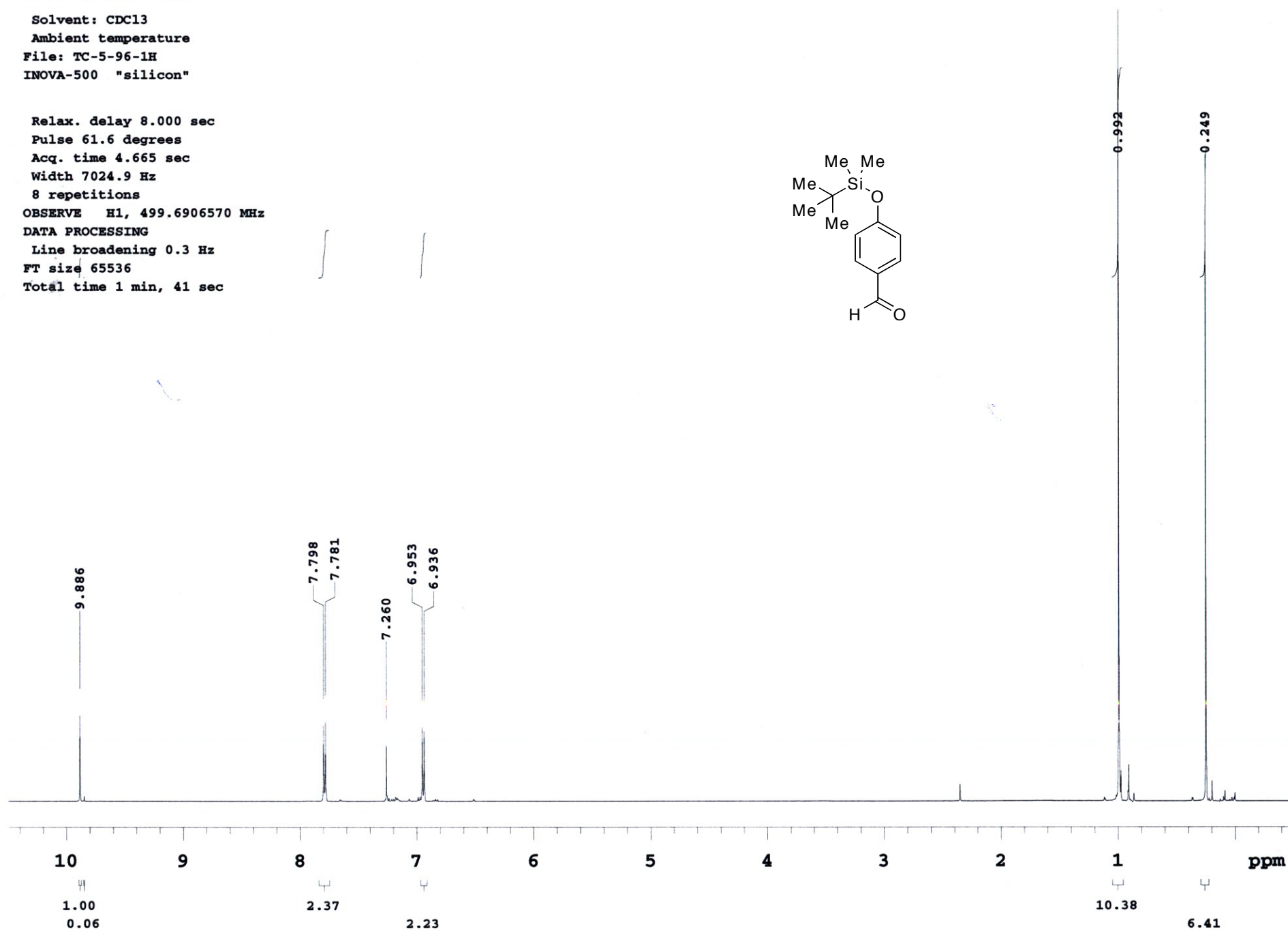
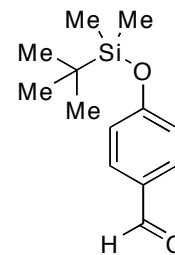
OBSERVE H1, 499.6906570 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 1 min, 41 sec





TC-5-97-cl-1H

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

Ambient temperature

File: TC-5-97-cl-1H

INOVA-500 "silicon"

Relax. delay 8.000 sec

Pulse 61.6 degrees

Acq. time 4.665 sec

Width 7024.9 Hz

8 repetitions

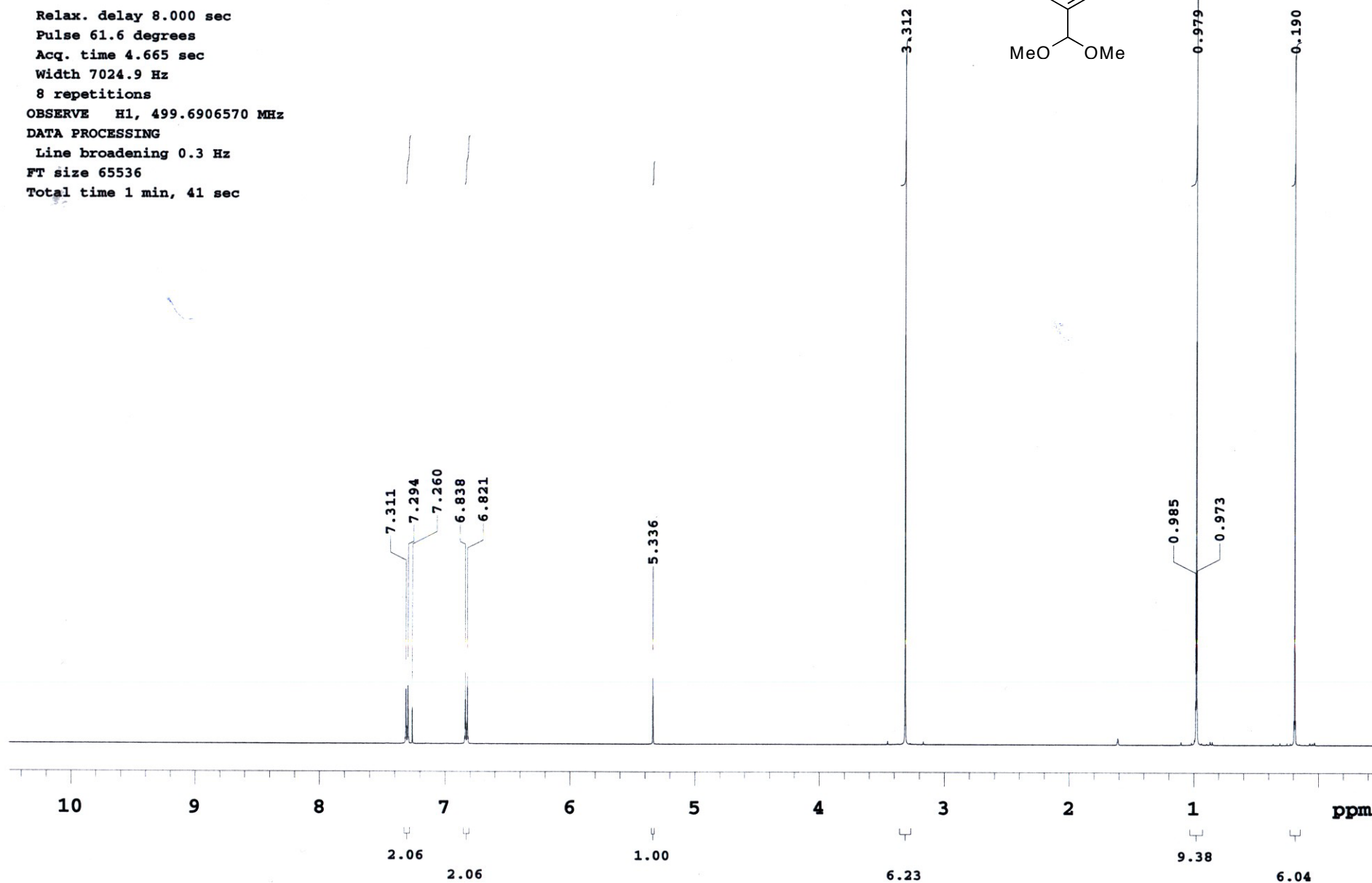
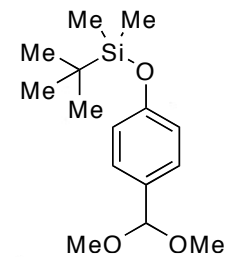
OBSERVE H1, 499.6906570 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 1 min, 41 sec



TC-5-97-cl-1H

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

Ambient temperature

File: TC-5-97-cl-1H

INOVA-500 "silicon"

Relax. delay 8.000 sec

Pulse 61.6 degrees

Acq. time 4.665 sec

Width 7024.9 Hz

8 repetitions

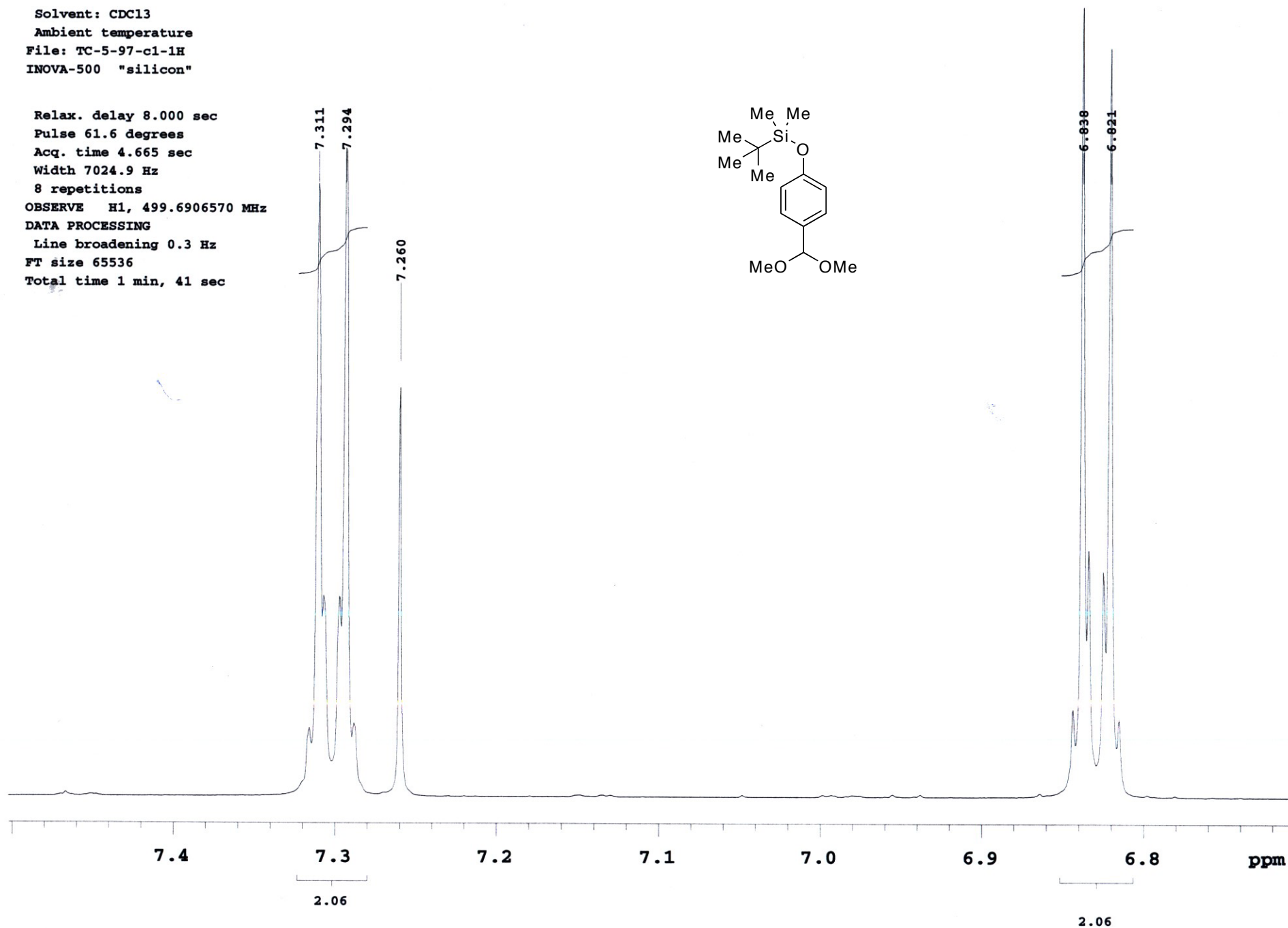
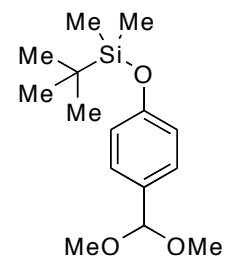
OBSERVE H1, 499.6906570 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 1 min, 41 sec





TC-6-7-1H

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

File: TC-6-7-1H

INOVA-500 "silicon"

Relax. delay 10.000 sec

Pulse 45.0 degrees

Acq. time 4.096 sec

Width 8000.0 Hz

16 repetitions

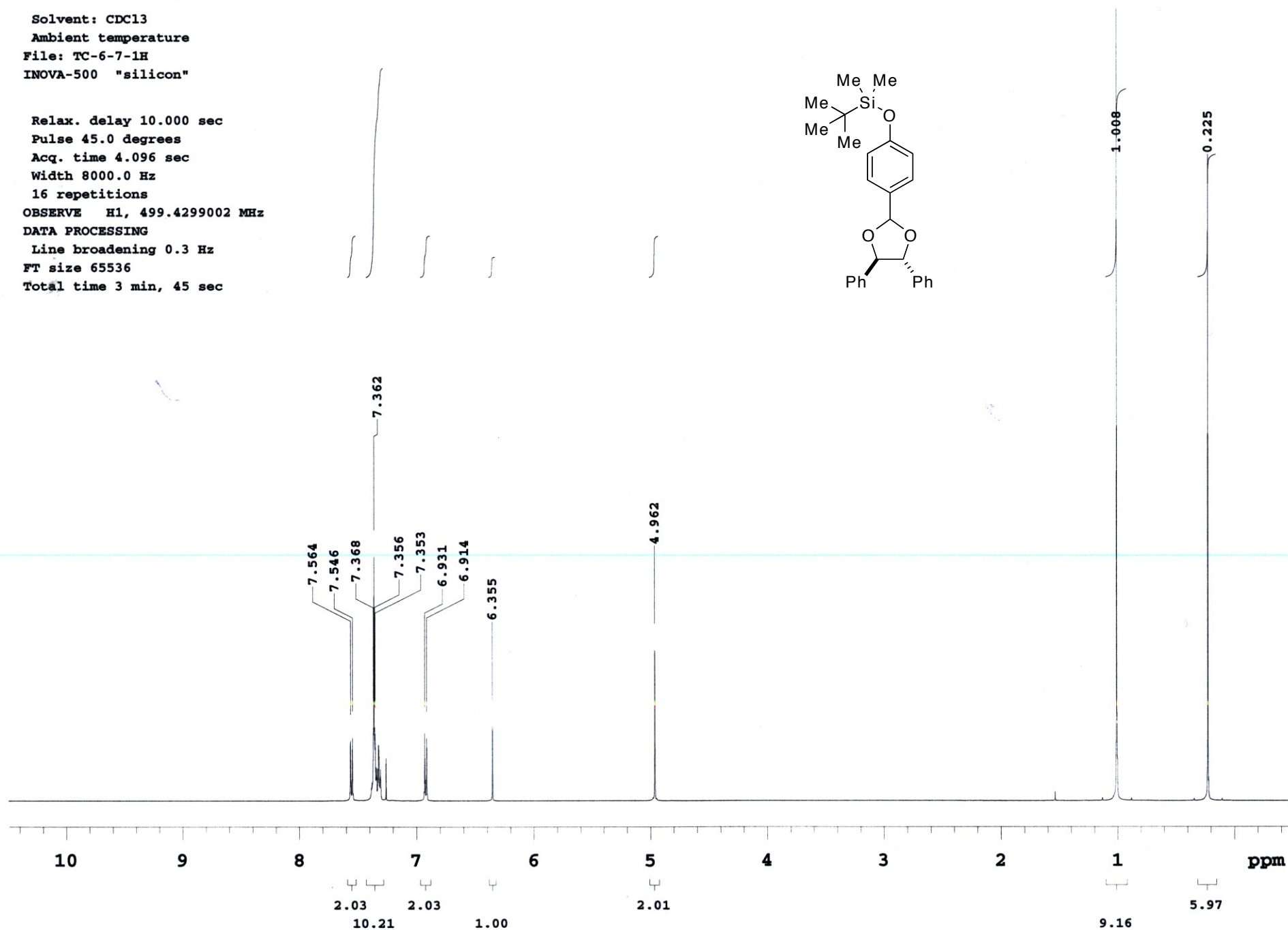
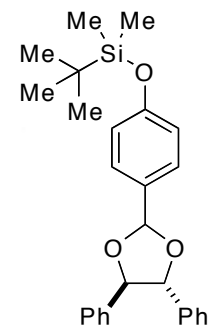
OBSERVE H1, 499.4299002 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 3 min, 45 sec



TC-6-7-13C

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

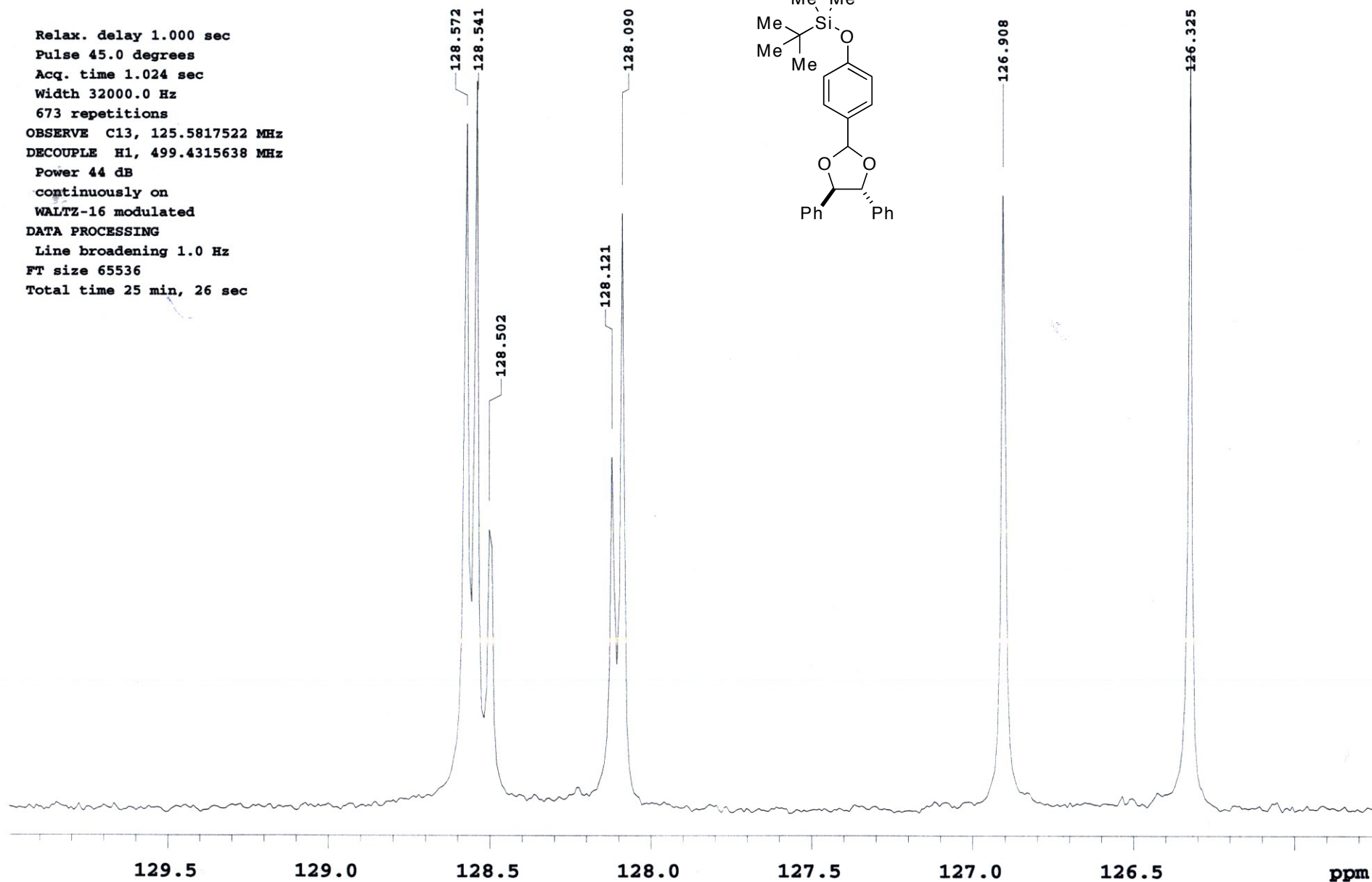
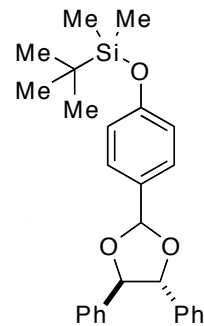
Ambient temperature

User: 1-14-87

File: TC-6-7-13C

INOVA-500 "silicon"

Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 1.024 sec  
Width 32000.0 Hz  
673 repetitions  
OBSERVE C13, 125.5817522 MHz  
DECOUPLE H1, 499.4315638 MHz  
Power 44 dB  
continuously on  
WALTZ-16 modulated  
DATA PROCESSING  
Line broadening 1.0 Hz  
FT size 65536  
Total time 25 min, 26 sec



TC-6-16-1H

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

File: TC-6-16-1H

INOVA-500 "silicon"

Relax. delay 10.000 sec

Pulse 45.0 degrees

Acq. time 4.096 sec

Width 8000.0 Hz

16 repetitions

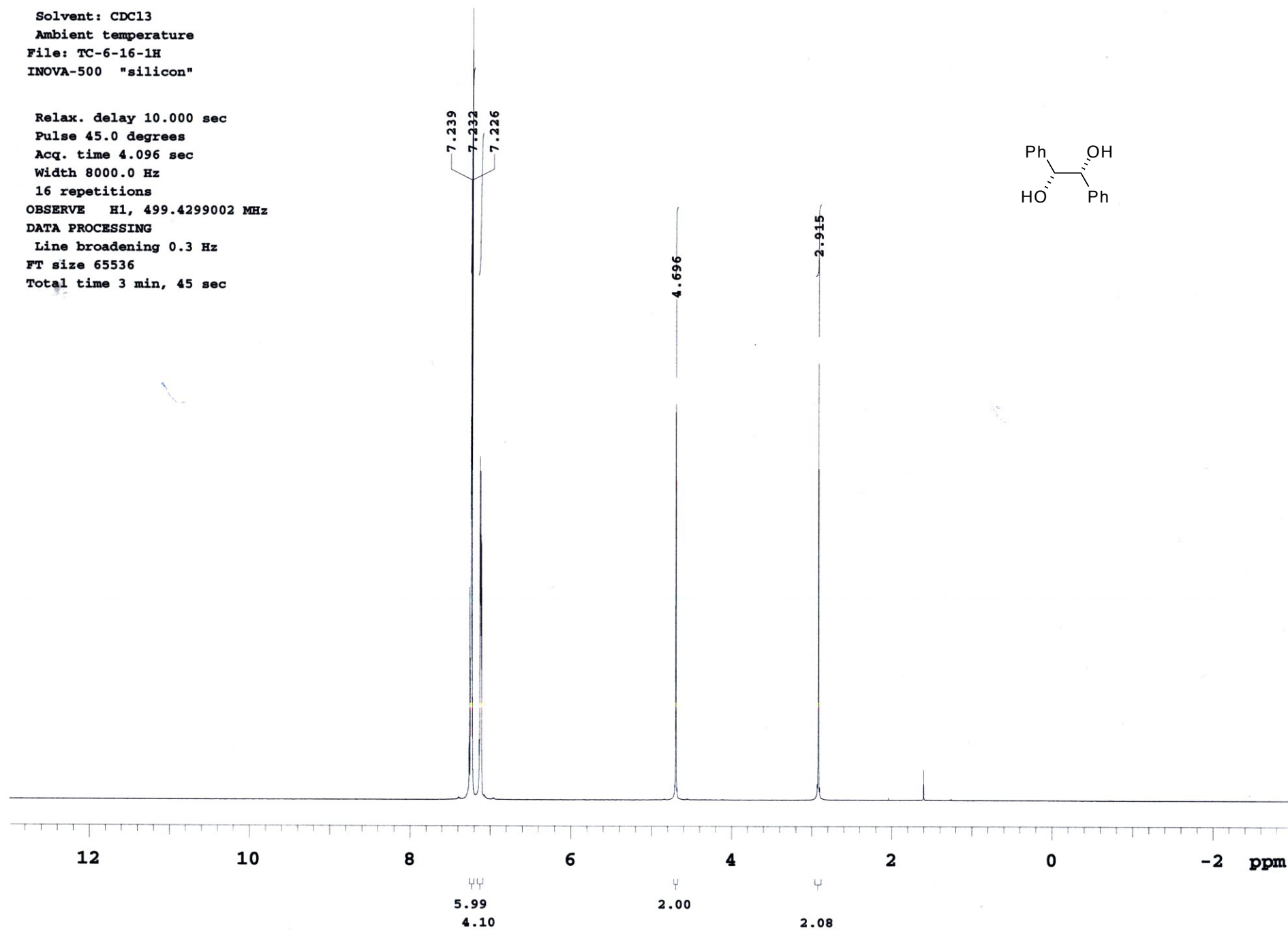
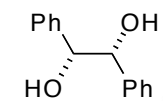
OBSERVE H1, 499.4299002 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 3 min, 45 sec



TC-6-16-1H

Pulse Sequence: s2pul

Solvent: CDCl<sub>3</sub>

Ambient temperature

File: TC-6-16-1H

INOVA-500 "silicon"

Relax. delay 10.000 sec

Pulse 45.0 degrees

Acq. time 4.096 sec

Width 8000.0 Hz

16 repetitions

OBSERVE H1, 499.4299002 MHz

DATA PROCESSING

Line broadening 0.3 Hz

FT size 65536

Total time 3 min, 45 sec

