



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

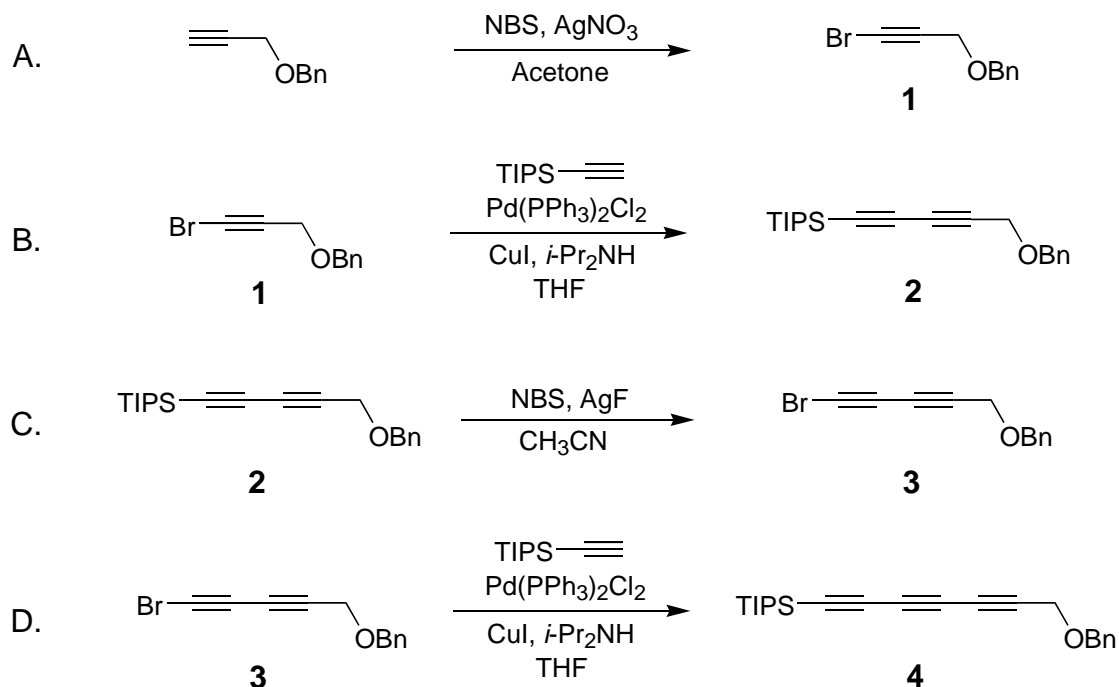
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

**SYNTHESIS OF POLYYNES BY IN SITU DESILYLATIVE  
BROMINATION AND PALLADIUM-CATALYZED COUPLING: (7-  
(BENZYLOXY)HEPTA-1,3,5-TRIYNYL)TRIISOPROPYLSILANE**



Submitted by Soonho Hwang, Hee Ryong Kang, and Sanghee Kim.<sup>1</sup>  
Checked by Olesya Haze and Rick L. Danheiser.

### 1. Procedure

A. *((3-Bromoprop-2-ynyloxy)methyl)benzene (1)*. A 500-mL, three-necked, round-bottomed flask (Note 1) equipped with a magnetic stir bar, two glass stoppers, and an argon inlet adapter is charged with benzyl propargyl ether (11.2 g, 76.6 mmol, 1.0 equiv) (Note 2), 150 mL of acetone (Note 3), and *N*-bromosuccinimide (15.0 g, 84.3 mmol, 1.1 equiv) (Note 2). To the resulting yellow solution, silver(I) nitrate (1.30 g, 7.65 mmol, 0.1 equiv) (Note 2) is added, and the cloudy-grey reaction mixture is stirred at 24 °C for 30 min (Notes 4, 5). The reaction mixture is transferred to a 1-L separatory funnel containing 100 mL of saturated aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and diluted with 200 mL of Et<sub>2</sub>O and 200 mL of pentane (Note 6). The organic layer is separated and washed with two 200 mL portions of brine, dried over MgSO<sub>4</sub> (5 g), filtered, and concentrated by rotary evaporation (20 °C, 20 mmHg) to give 18 g of an orange oil. This material is purified by silica gel

column chromatography (Note 7) to afford 14.8–15.4 g (86–89%) of bromoacetylene **1** as a light yellow oil (Note 8).

*B. (5-(Benzyloxy)penta-1,3-diynyl)triisopropylsilane (2).* A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, glass stopper, rubber septum, and an argon inlet adapter is charged with bromoacetylene **1** (7.60 g, 33.8 mmol, 1.0 equiv), 230 mL of tetrahydrofuran (Note 3), and (triisopropylsilyl)acetylene (9.10 mL, 7.40 g, 40.5 mmol, 1.2 equiv) (Note 2). Dichlorobis(triphenylphosphine)palladium(II) (0.478 g, 0.68 mmol, 0.02 equiv) (Note 2) and copper(I) iodide (0.130 g, 0.68 mmol, 0.02 equiv) (Note 2) are added in one portion, and diisopropylamine (10.0 mL, 7.16 g, 70.8 mmol, 2.1 equiv) (Note 2) is added by syringe over 2 min. The resulting yellow slurry is stirred at 24 °C for 5 h, during which time the color of the slurry darkened progressively to brown (Note 9, 10). Saturated aq NH<sub>4</sub>Cl solution (25 mL) is then added, and the resulting mixture is diluted with 250 mL of Et<sub>2</sub>O and transferred to a 1-L separatory funnel. The organic layer is separated and washed with two 250 mL portions of brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> (15 g, 10 min), filtered, and concentrated by rotary evaporation (25 °C, 20 mmHg) to give 13 g of viscous brown oil. Column chromatography on silica gel (Note 11) yields 8.13–8.41 g (74–76%) of TIPS-diyne **2** as a yellow oil (Note 12).

*C. ((5-Bromopenta-2,4-diynyloxy)methyl)benzene (3).* A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper and an argon inlet adapter is charged with TIPS-diyne **2** (8.79 g, 26.9 mmol, 1.0 equiv), 135 mL of freshly distilled acetonitrile (Note 3), *N*-bromosuccinimide (5.75 g, 32.3 mmol, 1.2 equiv) and silver(I) fluoride (4.10 g, 32.3 mmol, 1.2 equiv) (Note 2). The reaction flask is fitted with a mechanical stirrer (Note 13) and wrapped in aluminum foil. The heterogeneous reaction mixture is stirred at 22–25 °C for 2 h (Note 14). The reaction mixture is filtered through a pad of 20 g of Celite with the aid of 100 mL of Et<sub>2</sub>O (Note 6). The filtrate is diluted with 100 mL of Et<sub>2</sub>O, transferred to a 1-L separatory funnel, washed with two 200 mL portions of brine, dried over Na<sub>2</sub>SO<sub>4</sub> (15 g, 10 min), filtered, and concentrated by rotary evaporation (25 °C, 20 mmHg) to give 8.3 g of an orange oil. Column chromatography on silica gel (Note 15) gives 6.124 g (91%) of bromo diyne **3** (Note 16) as an orange oil (Note 17).

*D. (7-(Benzyloxy)hepta-1,3,5-triynyl)triisopropylsilane (4).* A 500-mL, two-necked, round-bottomed flask equipped with a stir bar, rubber septum, and argon inlet adapter is charged with alkynyl bromide **3** (5.90 g,

23.7 mmol, 1.0 equiv), 240 mL of tetrahydrofuran, and (triisopropylsilyl)acetylene (6.40 mL, 5.20 g, 28.5 mmol, 1.2 equiv). Dichlorobis(triphenylphosphine)palladium(II) (0.500 g, 0.71 mmol, 0.03 equiv) and copper(I) iodide (0.136 g, 0.71 mmol, 0.03 equiv) (Note 18) are added in one portion, and diisopropylamine (7.00 mL, 5.01 g, 49.5 mmol, 2.0 equiv) is added by syringe over 1 min. The resulting yellow slurry is stirred at 24 °C for 5 h, during which time the slurry darkens progressively to a deep brown color (Note 19). Saturated aq NH<sub>4</sub>Cl solution (20 mL) is then added, and the resulting mixture is transferred to a 1-L separatory funnel and diluted with 250 mL of Et<sub>2</sub>O. The organic layer is washed with two 250 mL portions of brine, dried over Na<sub>2</sub>SO<sub>4</sub> (20 g, 10 min), filtered, and concentrated by rotary evaporation (rt, 20 mmHg) to give 5 g of a viscous black oil. Column chromatography on silica gel (Note 20) affords 3.19 g (38%) (Note 21) of triyne **4** as a brown oil (Note 22).

## 2. Notes

1. The checkers used flame-dried glassware and carried out the reaction under an atmosphere of argon. The submitters dried their apparatus in an oven at 80 °C for 8 h and performed the reaction under an atmosphere of nitrogen.

2. Benzyl propagyl ether (98.0%) was purchased from Acros Organics. *N*-Bromosuccinimide (99%) and silver(I) nitrate (99+%, ACS reagent) were purchased from Aldrich Chemical Co., Ltd. (Triisopropylsilyl)acetylene (98.0+%) was purchased from Fluka. Copper(I) iodide (99.999%), diisopropylamine (99.5%), and silver(I) fluoride (99%) were purchased from Aldrich Chemical Co., Ltd. The checkers purchased dichlorobis(triphenylphosphine)palladium(II) (99.99%) from Aldrich Chemical Co., Ltd. while the submitters obtained this catalyst (>98.0%) from Tokyo Chemical Industry Co., Ltd.

3. The checkers used acetone (HPLC grade, J. T. Baker) that was distilled under argon after drying over anhydrous K<sub>2</sub>CO<sub>3</sub>. The checkers purchased tetrahydrofuran (HPLC grade) from J.T. Baker and purified it by pressure filtration under argon through activated alumina. The checkers purchased acetonitrile (ChromAr grade) from Mallinckrodt and distilled it from CaH<sub>2</sub>. The submitters employed acetone, tetrahydrofuran, and acetonitrile that was purchased from Burdick & Jackson and dried by distillation from anhydrous K<sub>2</sub>CO<sub>3</sub>, sodium/benzophenone ketyl, and CaH<sub>2</sub>,

respectively. The submitters used tetrahydrofuran after bubbling nitrogen through it for 15 min.

4. Because of the photosensitivity of NBS, AgF, and the brominated product, the reaction was protected from light by wrapping the flask with aluminum foil.

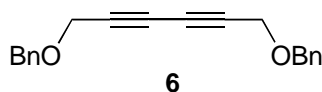
5. The progress of the reaction was monitored by TLC analysis on EMD (Merck) pre-coated glass-backed silica gel 60 F-254 250  $\mu\text{m}$  plates. The plates were eluted twice with 20:1 hexanes:EtOAc, and visualized by UV absorbance at 254 nm or with  $\text{KMnO}_4$ , PMA, or *p*-anisaldehyde stain. Benzyl propargyl ether has  $R_f = 0.4$ , and bromoacetylene **1** has  $R_f = 0.5$ .

6. Diethyl ether was obtained by the checkers from Mallinckrodt (anhydrous, stabilized, AR<sup>®</sup>, ACS grade) and by the submitters from SK chemicals. The checkers purchased  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  (ACS grade,  $\geq 99.5\%$ ) from Mallinckrodt.

7. Flash column chromatography was carried out using Sorbent Technologies Standard Grade 60 $\text{\AA}$  230–400 mesh silica gel. A glass column (6 x 40 cm) was slurry-packed with 300 g of silica gel. The compound was loaded in a solution of 20:1 hexanes/EtOAc. The column was eluted with 20:1 hexanes:EtOAc, collecting an initial 300 mL fraction, and then 30 mL fractions. The fractions containing the desired product were combined and concentrated by rotary evaporation at room temperature (20 mmHg).

8. The submitters report obtaining 16.19 g (94%) of bromoacetylene **1** as a colorless oil. Characterization data for ((3-bromoprop-2-ynyloxy)methyl)benzene (**1**): IR (film): 3065, 3031, 2853, 2214, 1497, 1454, 1353, 1091, 1029, 738, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.22 (s, 2H), 4.61 (s, 2H), 7.28–7.38 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 46.8, 58.2, 71.9, 76.4, 128.2, 128.3, 128.7, 137.3; Anal. calcd for  $\text{C}_{10}\text{H}_9\text{BrO}$ : C, 53.36; H, 4.03. Found: C, 53.27; H, 3.91.

9. When the reaction temperature was maintained at 30  $^\circ\text{C}$ , the reaction was completed within 1 h. However, the formation of homocoupling product **6** increased significantly from 1 to 8%.



10. The progress of the reaction was monitored by TLC analysis (two elutions with 50:1 hexanes/EtOAc). Under these conditions (triisopropylsilyl)acetylene  $R_f = 0.88$ , TIPS-diyne **2**  $R_f = 0.44$ ,

bromoacetylene **1**  $R_f = 0.35$ , and the homocoupling product **6**  $R_f = 0.26$ .

11. A glass column (6 x 40 cm) was slurry-packed with 300 g of silica gel. The product was loaded as a solution in 50:1 hexanes/EtOAc. The column was eluted with 50:1 hexanes:EtOAc, collecting an initial 500 mL fraction, and then 30-mL fractions. The fractions containing the desired product were combined and concentrated by rotary evaporation at room temperature (20 mmHg).

12. The submitters reported carrying out the reaction at 20 °C for 2 h, and obtained 8.50 - 9.10 g (77-83%) of TIPS-diyne **2** as a yellow oil. Characterization data for (5-(benzyloxy)penta-1,3-diyne)triisopropylsilane (**2**): IR (film): 3066, 3032, 2944, 2891, 2866, 2105, 1497, 1462, 1384, 1352, 1241, 1073, 997, 883, 796, 736, 697, 665  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.10 (s, 21H), 4.26 (s, 2H), 4.63 (s, 2H), 7.28-7.38 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.4, 18.7, 57.8, 71.9, 72.0, 73.1, 84.6, 89.2, 128.2, 128.3, 128.6, 137.3; UV ( $\text{CH}_3\text{OH}$ )  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ): 243 (760), 255 (810), 269 (480); MS (EI)  $m/z$  (rel int) 326 ( $\text{M}^+$ , 1); HRMS (EI) calcd for  $\text{C}_{21}\text{H}_{30}\text{OSi}(\text{M}^+)$  326.2066, found 326.2066; Anal. calcd for  $\text{C}_{21}\text{H}_{30}\text{OSi}$ : C, 77.24; H, 9.26. Found: C, 77.09; H, 9.37. The purity of TIPS-diyne **2** was determined by the submitters to be 97% according to HPLC analysis. HPLC analysis was performed on a Agilent 1200 series with YMC-Pack SIL column (250 x 4.6 mm), elution with EtOAc/hexane (gradient, 20% EtOAc/hexane, 25 min) at 1 mL/min while monitoring at 300 nm. The retention time of the TIPS-diyne **2** was 13.9 min.

13. The checkers found that vigorous stirring is critical to obtain consistently high yields. With magnetic stirring the checkers observed that longer reaction times (6–7 h) were required and the reaction proceeded in lower yield (30–40%). Silver(I) fluoride does not completely dissolve in the reaction mixture and without efficient stirring forms a sticky mass at the bottom of the reaction flask.

14. The progress of the reaction was monitored by TLC analysis (one elution with 20:1 hexanes/EtOAc; TIPS-diyne **2**  $R_f = 0.44$ , bromo diyne **3**  $R_f = 0.36$ ).

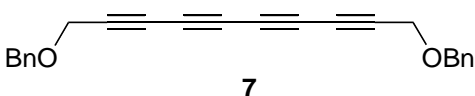
15. A glass column (6 x 40 cm) was slurry-packed with 260 g of silica gel. The product was loaded as a solution in 20:1 hexanes/EtOAc. The column was eluted with 20:1 hexanes:EtOAc, collecting an initial 400 mL fraction, and then 225 mL fractions. The fractions containing the desired product were combined and concentrated by rotary evaporation (during concentration the colorless product slowly became yellow-orange).

16. When the reaction was carried out at half this scale (13.5 mmol) with magnetic stirring, the checkers obtained the bromo diyne in somewhat lower yield (2.83 g, 84%). The submitters report obtaining 5.91-6.24 g (88–93%) of bromo diyne **3** as a yellow oil. Bromo diyne **3** is stable to storage in a freezer (-20 °C) for at least a week. However, prolonged exposure to air and light at room temperature caused slow decomposition.

17. Characterization data for ((5-bromopenta-2,4-dinyloxy)methyl)benzene (**3**): IR (film): 3031, 2862, 2236, 2142, 1497, 1454, 1351, 1258, 1192, 1073, 1028, 905, 738, 697, 665 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.24 (s, 2H), 4.62 (s, 2H), 7.28-7.39 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 41.6, 57.6, 65.1, 71.61, 71.63, 72.0, 128.3, 128.4, 128.7, 137.1; UV (CH<sub>3</sub>OH) λ<sub>max</sub>, nm (ε): 212 (1300), 265 (3000), 304 (800); HRMS (EI) calcd for C<sub>12</sub>H<sub>9</sub>BrO (M<sup>+</sup>) 247.9837, found 247.9839. The purity of bromo diyne **3** was determined by the submitters to be 98% by HPLC analysis. HPLC analysis was performed on a Agilent 1200 series with YMC-Pack SIL column (250 x 4.6 mm), elution with EtOAc/hexane (gradient, 15% EtOAc/hexane, 25 min) at 1 mL/min while monitoring at 300 nm. The retention time of the bromo diyne **3** was 9.0 min.

18. The checkers found that when grey CuI (99.999%, from Aldrich Chemical Co., Ltd) was used as received, the product was obtained in lower yield (30-33%) and the reaction was not complete after 6 h. Improved results were obtained (38-45% yield, reaction complete within 5 h) by using white CuI obtained by purification by Soxhlet extraction with THF followed by drying at 0.05 mmHg for 24 h.

19. The progress of the reaction was monitored by TLC analysis (one elution with 20:1 hexanes/EtOAc; (triisopropylsilyl)acetylene R<sub>f</sub> = 0.86, triyne **4** R<sub>f</sub> = 0.41, bromo diyne **3** R<sub>f</sub> = 0.36, and homocoupling product **7** R<sub>f</sub> = 0.17).



20. A glass column (6 x 40 cm) was slurry-packed with 270 g of silica gel. The product was loaded as a solution in 5 mL of 50:1 hexanes/EtOAc. The column was eluted with 50:1 hexanes/EtOAc, collecting an initial 600 mL fraction, and then 30 mL fractions. The fractions containing the desired product were combined and concentrated by rotary evaporation at room temperature (20 mmHg).

21. When the reaction was carried out at half this scale (11.8 mmol), the checkers obtained diyne **3** in improved yield (1.88 g 45%). The submitters obtained 3.65–4.15 g (44–50%) of triyne **4** as a deep brown oil and report that the yield of the reaction decreases considerably as the scale increases (0.3 g scale : 75%; 1.5 g scale = 67%; 5.0 g scale = 50%).

22. Characterization data for (7-(benzyloxy)hepta-1,3,5-triynyl)triisopropylsilane: IR (film): 3032, 2944, 2891, 2866, 2164, 2078, 1497, 1462, 1384, 1350, 1282, 1075, 1018, 997, 883, 736, 697, 678, 665  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.108–1.113 (m, 21H), 4.26 (s, 2H), 4.62 (s, 2H), 7.28–7.38 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 11.4, 18.7, 57.7, 60.3, 63.9, 71.7, 72.0, 74.5, 85.5, 89.7, 128.25, 128.34, 128.7, 137.0; UV ( $\text{CH}_3\text{OH}$ )  $\lambda_{\text{max}}$ , nm ( $\epsilon$ ): 222 (75000), 285 (1000), 303 (1200), 354 (600); MS (EI)  $m/z$  (rel int) 350 ( $\text{M}^+$ , 2); HRMS (EI) calcd for  $\text{C}_{23}\text{H}_{30}\text{OSi}$  ( $\text{M}^+$ ) 350.2066, found 350.2063; Anal. calcd for  $\text{C}_{23}\text{H}_{30}\text{OSi}$ : C, 78.80; H, 8.63. Found: C, 78.67; H, 8.43. The purity of triyne **4** was determined to be 96% by HPLC analysis under the conditions described in Note 17 (retention time of **4** was 13.9 min).

### Safety and Waste Disposal Information

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

### 3. Discussion

Unsymmetrically substituted conjugated diyne and polyne units continue to attract widespread interest because of their unusual electrical, optical, and structural properties.<sup>2</sup> Consequently, the development of efficient synthetic approaches toward these rigid units remains an important challenge to synthetic organic chemists.<sup>2–4</sup>

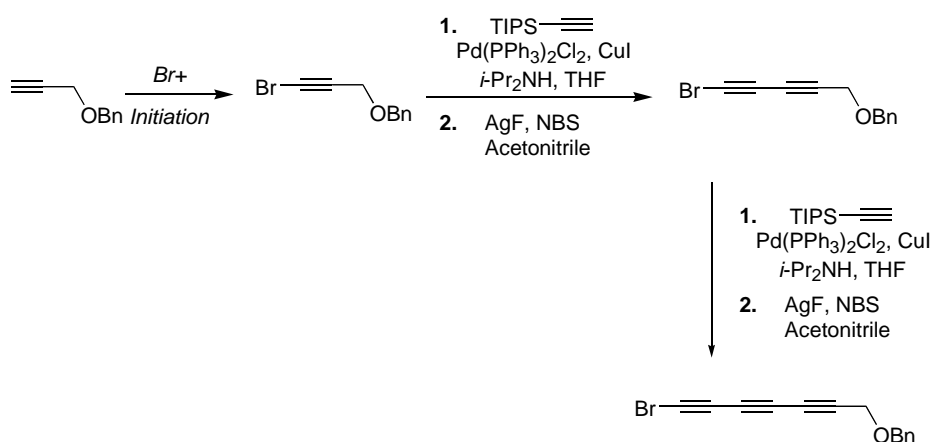
The method most commonly used for the preparation of unsymmetrical diyne and polyne compounds is the Cadiot-Chodkiewicz coupling reaction,<sup>5</sup> the metal-catalyzed cross-coupling of a 1-haloalkyne with a terminal alkyne. The major limitation of this coupling reaction, however, is that terminal diynes and higher polyynes required as coupling partners or precursors of 1-haloalkynes are often unstable.<sup>2,3,6</sup> To overcome this challenge, many elegant alternative methods have been explored.



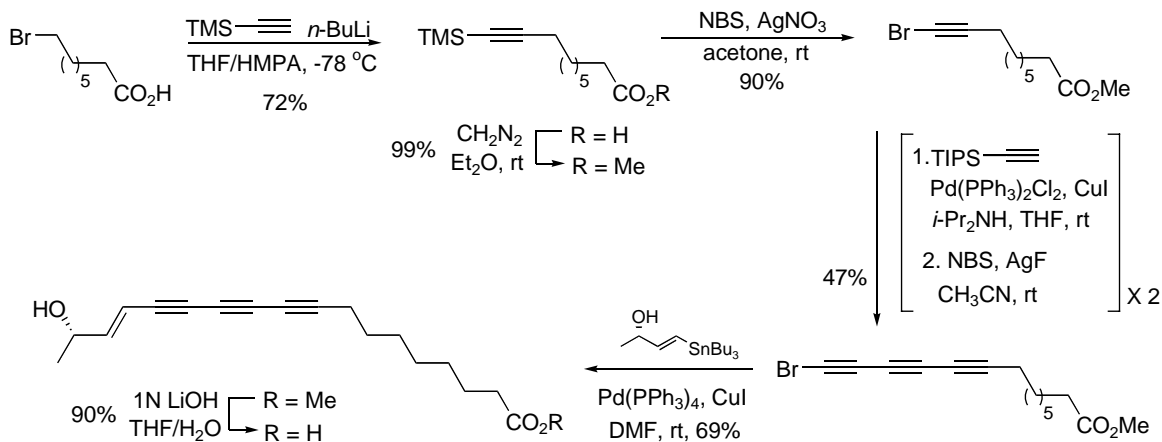
We have developed an iterative strategy for the synthesis of unsymmetrically substituted polyynes as shown in Scheme 1. The key to the success of this iterative method lies in the *in situ* one-pot desilylative bromination, which avoids the complication encountered with the isolation of sensitive terminal alkynes.

In this process, the starting terminal alkyne was first converted to bromoalkyne under standard NBS/AgNO<sub>3</sub> conditions.<sup>7</sup> At this point, we employed TIPS-acetylene as a cross-coupling partner for the homologation reactions because it had previously been reported that TMS-acetylene decomposes under the basic conditions of the coupling reaction such that no desired cross-coupling product can usually be isolated.<sup>8</sup> When we used TIPS-acetylene, the desired cross-coupling product was obtained in good yield under the modified Sonogashira conditions. Our initial attempts to effect the *in situ* one-pot desilylative bromination of TIPS-diyne used the standard NBS/AgNO<sub>3</sub> conditions developed by Isobe and co-workers for the conversion of TMS-protected acetylenes to bromoacetylenes.<sup>9</sup> Unfortunately, these conditions led only to the recovery of the starting material. On the other hand, when we employed AgF instead of AgNO<sub>3</sub>, we could obtain the desired bromo diyne in high yield. Repeating the two-step acetylene homologation sequence on this bromo diyne then generated the expected bromo triyne readily in good overall yield.

**Scheme 1.** General Iterative Protocol for Synthesis of Unsymmetrical Polyynes.



**Scheme 2.** Total synthesis of (*S*)-(*E*)-15,16-dihydrominuartynoic acid.



By employing our new iterative strategy, we accomplished the total synthesis of (*S*)-(*E*)-15,16-dihydrominuartynoic acid from a simple starting material in a high overall yield (Scheme 2).<sup>10</sup> In addition, we have developed a facile solid-phase synthetic pathway to generate a library of natural product-like polyynes.<sup>11</sup> These results demonstrate that our approach can be applied efficiently to the synthesis of various unsymmetrical polyynes.

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- (a) Ginsburg, E. J.; Gorman, C. B.; Grubbs, R. H. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988.
- For recent papers that include a discussion of this topic, see: (a) Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883–2886. (b) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339–1347.
- For reviews, see: (a) Hartung, R. E.; Paquette, L. A. *Chemtracts* **2002**, *15*, 106–116. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632-2657.
- Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed., Marcel Dekker: New York, 1969; pp. 597–647.
- (a) Haley, M. M.; Bell, M. L.; English, J. J.; Johnson, C. A.; Weakley,

- T. J. R. *J. Am. Chem. Soc.* **1997**, *119*, 2956–2957. (b) Patel, G. N.; Chance, R. R.; Turi, E. A.; Khanna, Y. P. *J. Am. Chem. Soc.* **1978**, *100*, 6644–6649. (c) Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. *Tetrahedron Lett.* **1997**, *38*, 7483–7486.
7. Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 727–729.
8. (a) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844. (b) Eastmond, R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 4591–4599. (c) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1965**, *4*, 217–228.
9. Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485–486.
10. Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601–3604.
11. Lee, S.; Lee, T.; Lee, Y. M.; Kim, D.; Kim, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8422–8425.

## Appendix

### Chemical Abstracts Nomenclature; (Registry Number)

Benzyl propargyl ether; (4039-82-1)  
*N*-bromosuccinimide: NBS; (128-08-5)  
Silver nitrate; (7761-88-8)  
(Triisopropylsilyl)acetylene: Ethynyltriisopropylsilane; (89343-06-6)  
Dichlorobis(triphenylphosphine)palladium(II):  
    Bis(triphenylphosphine)palladium(II) Dichloride; (13965-03-2)  
Copper(I) iodide: Cuprous iodide; (7681-65-4)  
Diisopropylamine: DIPA; (108-18-9)  
Silver(I) fluoride; (7775-41-9)



Sanghee Kim received his B.S. degree in pharmacy from Seoul National University in 1988, where he also obtained his M.S. degree in medicinal chemistry in 1990. After finishing military service as a lieutenant, he worked for a year as an assistant researcher at the Korea Institute of Science and Technology. In 1992, he joined Prof. Jeffery Winkler's group at the University of Pennsylvania and earned his Ph.D. in organic chemistry in 1997. After two years as a postdoctoral fellow with Prof. K.C. Nicolaou, at The Scripps Research Institute, he worked at Abbott Laboratories as a research scientist. He moved to Seoul National University in 1999, where he is currently a professor of college of pharmacy teaching various advanced courses in the field of medicinal and synthetic chemistry.



Soonho Hwang was born in 1983 in Daejeon, Korea and received his B.S. degree in pharmacy from Wonkwang University in 2007. In 2007, he began his graduate studies at the Seoul National University, under the guidance of Prof. Sanghee Kim. His research focuses on the total synthesis of natural products, mainly based on the palladium-catalyzed cross-coupling and [3,3]-sigmatropic Claisen rearrangement.



Hee Ryong was born in 1979 in Yesan, Korea. After finishing military service, he received his B.S. degree in chemistry from Kongju University in 2005. He completed his M.S. degree in 2007 at Seoul National University, where he worked on "Signal Regulator Synthesis Laboratory" under the supervision of Prof. Sanghee Kim. His thesis included discussions of the utilities of trialkylsilyl acetylene and AgF system. Currently, he works at the pharmaceutical company Chong Kun Dang as a medicinal chemist.



Olesya Haze graduated from the University of Rochester in 2006 with a B.S. degree in Chemistry and a B.A. degree in Mathematics. As an undergraduate she studied silane cation radical fragmentations and bonded exciplexes under the guidance of Professor Joseph Dinnocenzo. Currently Olesya is a graduate student at the Massachusetts Institute of Technology where she is developing photochemical benzannulation reactions for the synthesis of highly substituted heteroaromatic compounds in the laboratory of Professor Rick Danheiser.

137.32  
128.66  
128.29  
128.15

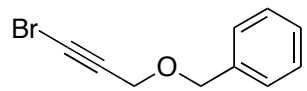
77.55  
77.23  
76.91  
76.38  
71.89

58.23

46.37

F2 - Acquisition Parameters

Date\_ 20080911  
Time\_ 22.49  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 128  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 1625.5  
DW 20.850 usec  
DE 6.00 usec  
TE 292.2 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TD0 1

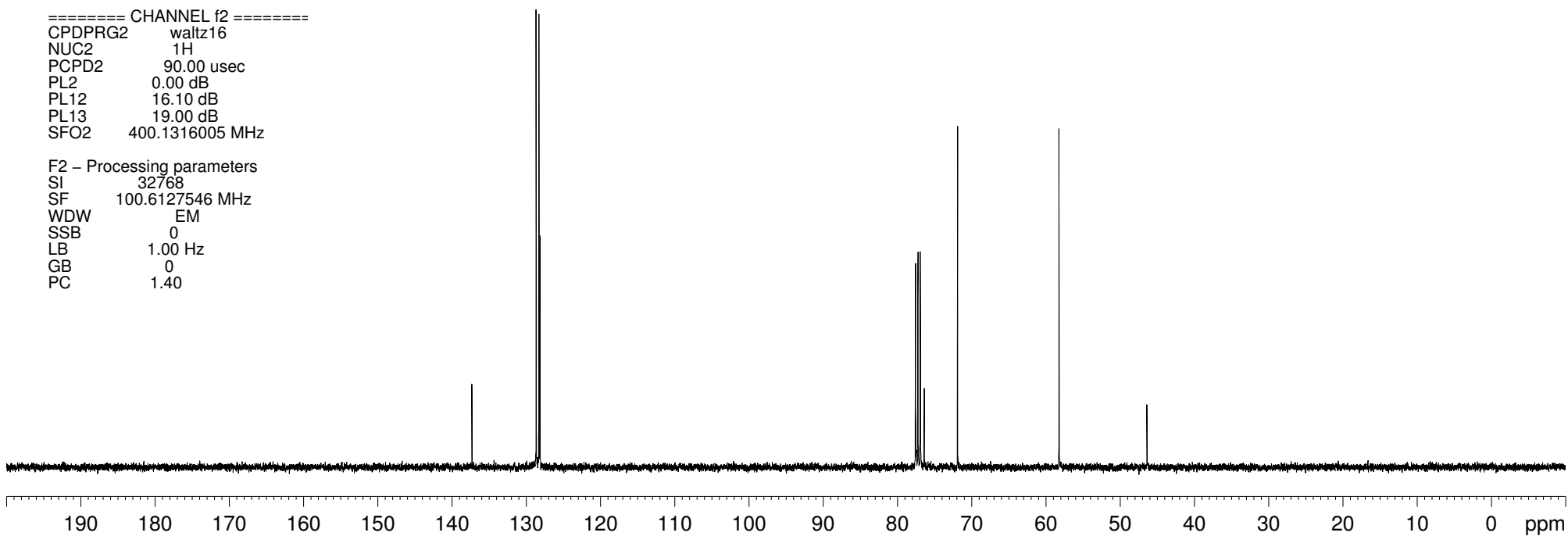


1

===== CHANNEL f1 =====  
NUC1 13C  
P1 9.38 usec  
PL1 0.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 90.00 usec  
PL2 0.00 dB  
PL12 16.10 dB  
PL13 19.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127546 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



F2 - Acquisition Parameters

Date\_ 20090106  
 Time 19.06  
 INSTRUM spect  
 PROBHD 5 mm BBO BB-1H  
 PULPROG zgpg30  
 TD 65536  
 SOLVENT CDCl3  
 NS 80  
 DS 2  
 SWH 23980.814 Hz  
 FIDRES 0.365918 Hz  
 AQ 1.3664756 sec  
 RG 7298.2  
 DW 20.850 usec  
 DE 6.00 usec  
 TE 293.2 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 DELTA 1.89999998 sec  
 TD0 1

===== CHANNEL f1 =====

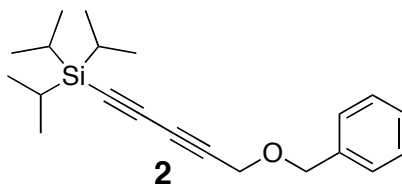
NUC1 13C  
 P1 8.75 usec  
 PL1 -3.00 dB  
 SFO1 100.6228298 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16  
 NUC2 1H  
 PCPD2 90.00 usec  
 PL2 -1.00 dB  
 PL12 14.52 dB  
 PL13 18.00 dB  
 SFO2 400.1316005 MHz

F2 - Processing parameters

SI 65536  
 SF 100.6127560 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40



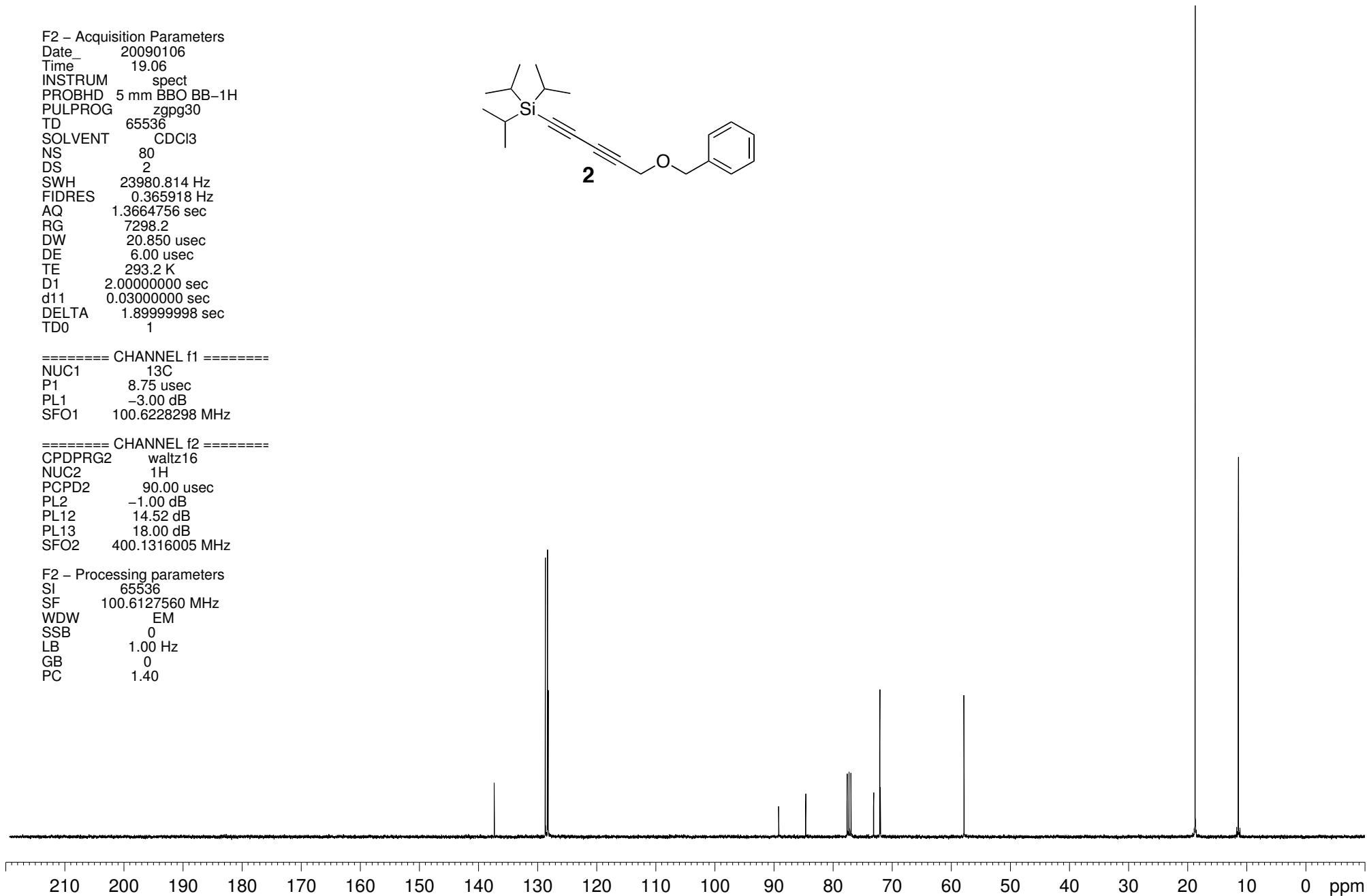
137.28  
 128.64  
 128.27  
 128.15

89.15  
 84.57  
 77.55  
 77.23  
 76.91  
 73.07  
 72.03  
 71.92

57.77

18.70

11.40



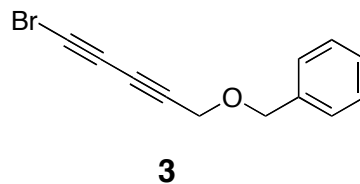
137.13  
128.71  
128.37  
128.26

77.55  
77.23  
76.91  
72.00  
71.63  
71.61  
65.06  
57.58

41.56

F2 - Acquisition Parameters

Date\_ 20090106  
Time\_ 19.16  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 128  
DS 2  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 8192  
DW 20.850 usec  
DE 6.00 usec  
TE 293.2 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TD0 1



===== CHANNEL f1 =====

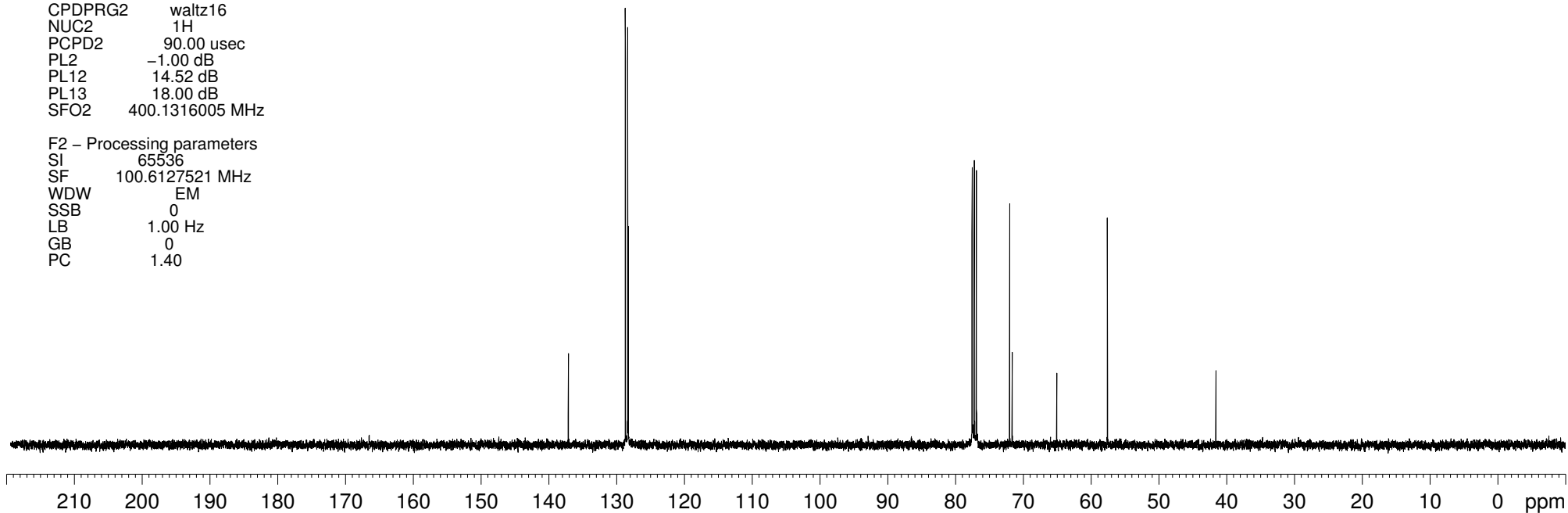
NUC1 13C  
P1 8.75 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16  
NUC2 1H  
PCPD2 90.00 usec  
PL2 -1.00 dB  
PL12 14.52 dB  
PL13 18.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters

SI 65536  
SF 100.6127521 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



F2 - Acquisition Parameters

Date\_ 20090106  
Time\_ 19.36  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 81  
DS 2  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 14596.5  
DW 20.850 usec  
DE 6.00 usec  
TE 293.2 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TD0 1

===== CHANNEL f1 =====

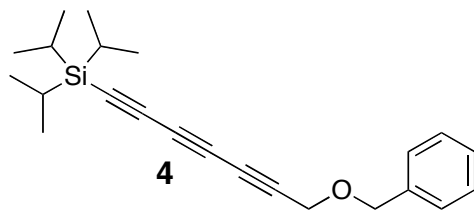
NUC1 13C  
P1 8.75 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====

CPDPRG2 waltz16  
NUC2 1H  
PCPD2 90.00 usec  
PL2 -1.00 dB  
PL12 14.52 dB  
PL13 18.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters

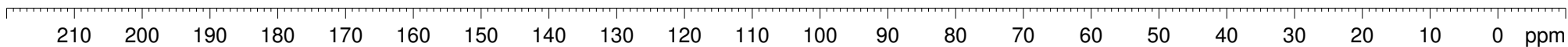
SI 65536  
SF 100.6127573 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40



137.03  
128.68  
128.34  
128.25

89.67  
85.48  
77.55  
77.23  
76.91  
74.50  
71.99  
71.67  
63.90  
60.31  
57.69

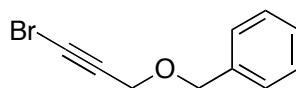
18.68  
11.41





7.380  
7.378  
7.368  
7.270

4.613  
4.216

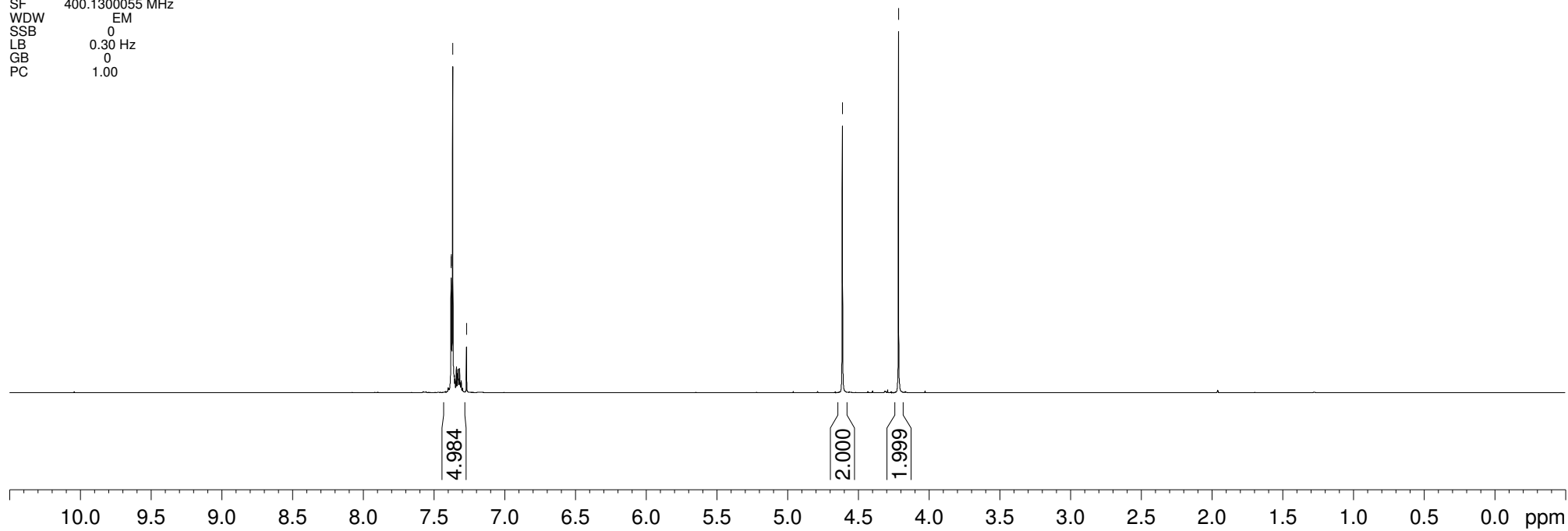


1

F2 - Acquisition Parameters  
Date\_ 20081117  
Time 13.13  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zg30  
TD 65536  
SOLVENT  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 128  
DW 60.400 usec  
DE 6.00 usec  
TE 293.2 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 15.07 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

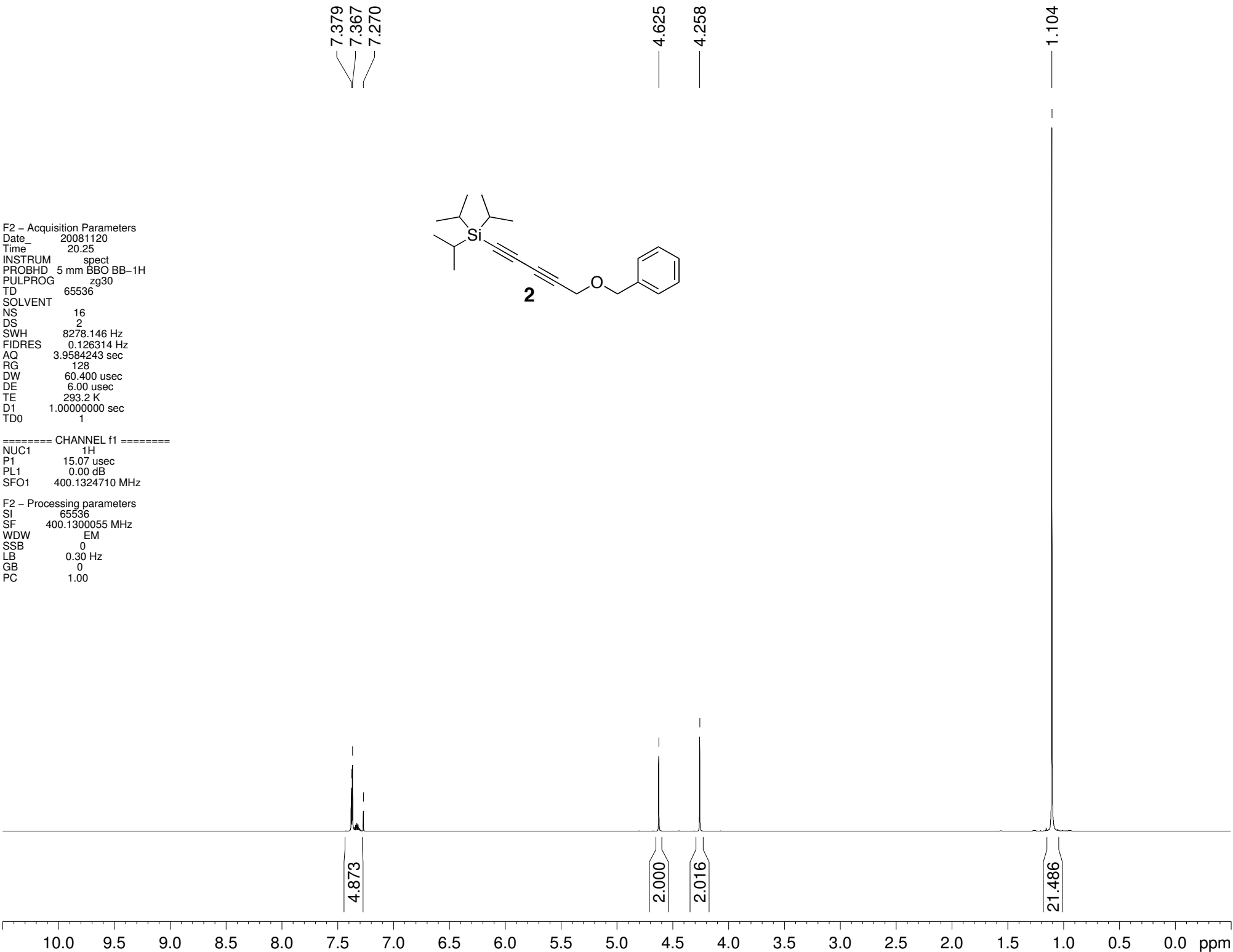
F2 - Processing parameters  
SI 65536  
SF 400.1300055 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



F2 - Acquisition Parameters  
Date\_ 20081120  
Time 20.25  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zg30  
TD 65536  
SOLVENT  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 128  
DW 60.400 usec  
DE 6.00 usec  
TE 293.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 15.07 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

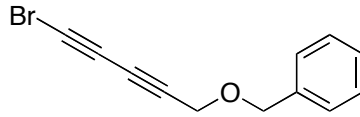
F2 - Processing parameters  
SI 65536  
SF 400.1300055 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



7.379

4.622

4.242

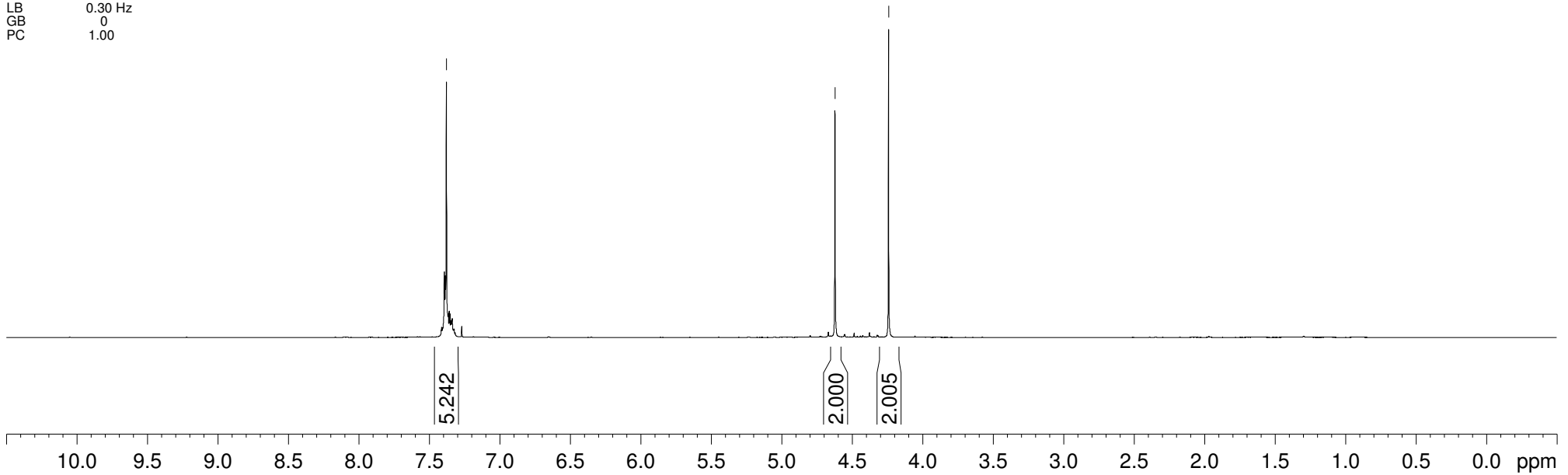


3

F2 - Acquisition Parameters  
Date\_ 20081002  
Time 16.25  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 128  
DW 60.400 usec  
DE 6.00 usec  
TE 291.2 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 14.00 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 65536  
SF 400.1300054 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



7.369

4.616

4.264

1.113  
1.108

F2 - Acquisition Parameters  
Date\_ 20081202  
Time 19.38  
INSTRUM spect  
PROBHD 5 mm QNP 1H/13  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 57  
DW 60.400 usec  
DE 6.00 usec  
TE 291.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 14.00 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 65536  
SF 400.1300054 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

