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for the Preparation  
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## Working with Hazardous Chemicals

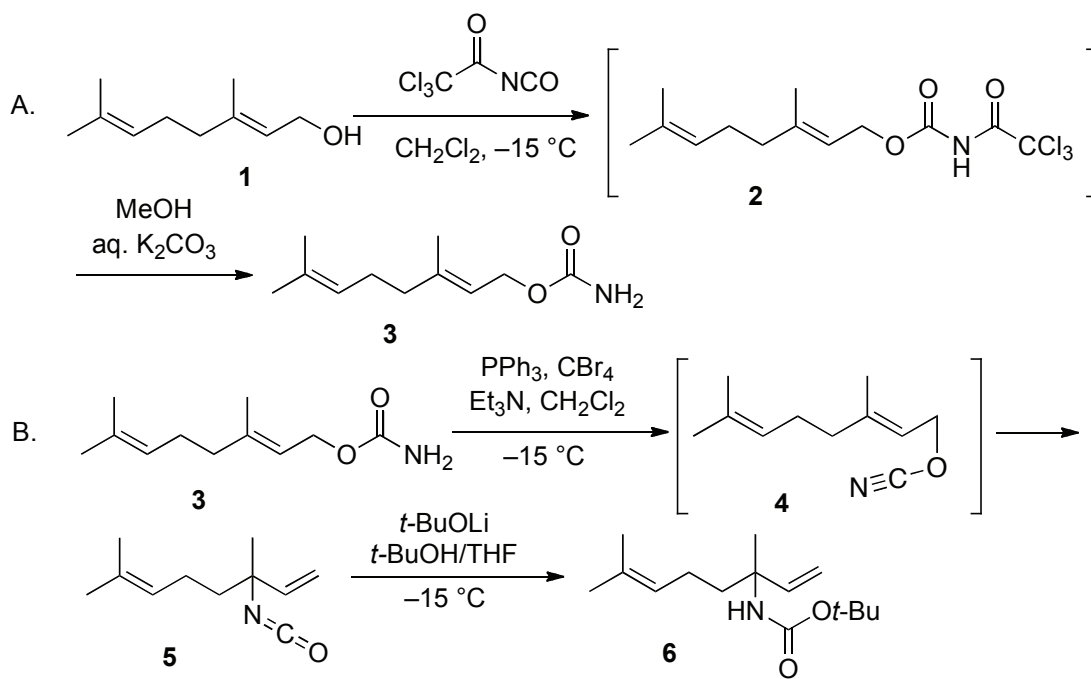
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

## Allyl Cyanate-To-Isocyanate Rearrangement: Preparation of *tert*-Butyl 3,7-Dimethylocta-1,6-dien-3-ylcarbamate



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Checked by Eiji Yoshida and Tohru Fukuyama.

### 1. Procedure

A. (*E*)-3,7-Dimethylocta-2,6-dien-1-ylcarbamate (**3**): An oven-dried 500-mL, three-necked, round-bottomed flask (Note 1) equipped with a magnetic stir bar (8 × 30 mm), a thermometer with a Teflon holder, a rubber septum and an inlet adapter with a three-way stopcock fitted with an argon inlet is charged with geraniol (**1**) (11.0 g, 71.3 mmol, 1.0 equiv) (Note 2) and dry dichloromethane (180 mL) (Note 3). The flask is immersed in a sodium chloride/ice bath (internal temperature  $-15\text{ }^\circ\text{C}$ ). Trichloroacetyl isocyanate (9.30 mL, 14.7 g, 78.0 mmol, 1.10 equiv) (Note 4) is added slowly via a syringe through the rubber septum over a 10 min period at a rate to maintain the internal temperature below  $-10\text{ }^\circ\text{C}$ . After stirring at  $-15\text{ }^\circ\text{C}$  (internal temperature) for 20 min (Note 5), methanol (0.90 mL, 0.71 g, 22 mmol, 0.30 equiv) (Note 6) is added via a syringe inserted through the rubber

septum to quench excess trichloroacetyl isocyanate (Note 7). The solution is transferred to a 1-L recovery flask with the aid of dichloromethane (15 mL), and then concentrated by rotary evaporation (200 mmHg, water bath temperature 40 °C) and dried under vacuum (1.0 mmHg) (Note 8) to yield trichloroacetyl carbamate **2** as a pale yellow oil (25.9 g). The crude **2** in the 1-L recovery flask is dissolved in methanol (240 mL) (Note 6) and a magnetic stir bar (8 × 30 mm) is placed in the flask. Aqueous K<sub>2</sub>CO<sub>3</sub> (2 M, 140 mL) is added to the stirred mixture in portions at room temperature over a 10 min period, resulting in formation of a cloudy solution (Note 9). After stirring at room temperature for 3 h while checking the consumption of trichloroacetyl carbamate **2** by TLC analysis (Note 5), the reaction mixture is concentrated by rotary evaporation (70 mmHg, water bath temperature 40 °C) to about half the original volume. The resulting cloudy solution is transferred to a 1-L separatory funnel and extracted with diethyl ether (3 × 50 mL) (Note 10). The combined organic extracts are washed with water (50 mL) and brine (50 mL), dried over anhydrous MgSO<sub>4</sub> and filtered through cotton. After removal of the solvent by rotary evaporation (70 mmHg, water bath temperature 40 °C), the oily residue is dried under vacuum (1.0 mmHg) (Note 8) to constant weight, affording crude carbamate **3** (13.93 g, 99%) (Note 11) as a white solid, which is used in Step B without further purification.

*B. t-Butyl 3,7-dimethylocta-1,6-dien-3-ylcarbamate (6).* The crude carbamate **3** (13.93 g, 70.6 mmol, 1.0 equiv) in a 300-mL recovery flask is dissolved in toluene (10 mL) (Note 12) and the solvent is removed azeotropically by rotary evaporation (70 mmHg, 50 °C). After repeating this procedure once more followed by drying under vacuum (1.0 mmHg) (Note 8) for 30 min, crude **3** is dissolved in dry dichloromethane (2 × 10 mL) and transferred by a pipette to a 500-mL three-necked, round-bottomed flask equipped with a stir bar (8 × 30 mm), a thermometer with a Teflon holder, a 50-mL pressure-equalizing addition funnel with a rubber septum, and an inlet adapter with a three-way stopcock fitted with an argon inlet. The flask is charged with dry dichloromethane (180 mL), triphenylphosphine (28.0 g, 107 mmol, 1.5 equiv) (Note 13) and triethylamine (20.0 mL, 14.5 g, 143 mmol, 2.0 equiv) (Note 14). The flask is cooled with a sodium chloride/ice bath (internal temperature –15 °C). Carbon tetrabromide (37.8 g, 114 mmol, 1.6 equiv) (Note 15) in dry dichloromethane (20 mL) is added via the dropping funnel over a 30 min period, maintaining the internal temperature below –10 °C. The dropping funnel is rinsed with dry

dichloromethane (5 mL). After stirring at  $-15$  to  $-10$  °C (internal temperature) for 20 min (Note 16), the cooling bath is removed and the yellow reaction mixture is diluted with *n*-hexane (150 mL) (Note 17). After stirring at room temperature for 30 min, the light-brown solution is poured into aqueous  $\text{KHSO}_4$  (1 M, 300 mL) in a 1-L Erlenmeyer flask equipped with a stir bar ( $8 \times 30$  mm). The three-necked flask is rinsed with *n*-hexane ( $2 \times 10$  mL). After stirring vigorously for 30 min, the solution is transferred into a 1-L separatory funnel. The Erlenmeyer flask is rinsed with *n*-hexane ( $2 \times 10$  mL). The organic layer is separated, washed with water (200 mL), saturated aqueous  $\text{NaHCO}_3$  (100 mL) and brine (200 mL), dried over anhydrous  $\text{MgSO}_4$  and filtered through cotton. Concentration by rotary evaporation (200 mmHg, 40 °C) gives a crude mixture containing allyl isocyanate **5** and triphenylphosphine oxide as a yellow solid (72.8 g), to which is added *n*-hexane (200 mL). The resulting mixture is swirled in a sonicator for 5 min to form a suspension. After filtration through a pad of Celite (Note 18) and washing the filter cake with *n*-hexane ( $3 \times 50$  mL), the combined golden yellow filtrate is concentrated by rotary evaporation (90 mmHg, water bath temperature 40 °C), and then dried under vacuum (1.5 mmHg) for 30 min to provide crude isocyanate **5** (25.4 g) as a pale yellow oil (Notes 19 and 20).

An oven-dried 1-L, three-necked, round-bottomed flask equipped with a stir bar ( $8 \times 30$  mm), a thermometer with a Teflon holder, a 100-mL dropping funnel with a rubber septum, and an inlet adapter with a three-way stopcock fitted with an argon inlet is charged with dry tetrahydrofuran (280 mL) (Note 21) and *tert*-butyl alcohol (68.0 mL, 52.3 g, 711 mmol, 10.0 equiv) (Note 22). After cooling to 0 °C in an ice bath, lithium hexamethyldisilazide (1 M solution in tetrahydrofuran, 71.3 mL, 71.3 mmol, 1.0 equiv) (Notes 23 and 24) is added via the dropping funnel over a 10 min period, maintaining the internal temperature below 5 °C. The cooling bath is removed and the solution is stirred at room temperature for 30 min. The dropping funnel is quickly replaced with a 50-mL dropping funnel and the solution of lithium *t*-butoxide is cooled with a sodium chloride/ice bath (internal temperature  $-15$  °C). A solution of crude **5** (25.4 g) in dry tetrahydrofuran (15 mL) is added through the dropping funnel over a 10 min period, keeping the internal temperature below  $-10$  °C. After rinsing the dropping funnel with dry tetrahydrofuran (5 mL), the reaction mixture is stirred below  $-10$  °C for 20 min (Note 25). Saturated aqueous  $\text{NH}_4\text{Cl}$  (100 mL) and water (100 mL) are added to quench the reaction and the

mixture is transferred into a 1-L separatory funnel. The separated aqueous layer is extracted with diethyl ether ( $2 \times 100$  mL). The combined organic layers are washed with water ( $2 \times 100$  mL), brine (200 mL), and dried over anhydrous  $\text{MgSO}_4$ , filtered through cotton, and then concentrated by rotary evaporation (70 mmHg, water bath temperature  $40^\circ\text{C}$ ) to afford crude carbamate **6**, which is dried under vacuum (0.3 mmHg) to constant weight (21.15 g) (Note 26). The residual orange liquid is subjected to silica gel chromatography (Note 27). The combined fractions are concentrated by rotary evaporation (70 mmHg, water bath temperature  $40^\circ\text{C}$ ) and dried under vacuum (1.0 mmHg) (Note 8) to furnish Boc-carbamate **6** as a light-yellow oil (12.44 g, 69% overall yield from **1**) (Notes 28 and 29).

## 2. Notes

1. All glass apparatus was dried in an oven at  $120^\circ\text{C}$  for 2 h and cooled in a drying desiccator.

2. Geraniol (**1**) (97%) was purchased from Wako Pure Chemical Industries, Ltd. and used directly without purification.

3. The submitters purchased dichloromethane from Wako Pure Chemical Industries, Ltd. and dried over  $4\text{\AA}$  molecular sieves. The water content determined by Karl-Fischer titration was  $<10$  ppm. The molecular sieves were activated in a round-bottomed flask by heating in a household microwave oven (500 W) at full power for 5 min, and then cooled to room temperature under vacuum (1.8 mmHg) for 10 min. This procedure was repeated 3 times. The checkers purchased dichloromethane from Kanto Chemicals Co., Inc. and purified by a Glass Contour Solvent Dispensing System. The water content by Karl-Fischer titration was  $<10$  ppm.

4. Trichloroacetyl isocyanate (97%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.

5. The progress of the reaction was monitored by thin-layer chromatography (TLC) using E. Merck pre-coated 0.25 mm thick silica gel 60 F254 plates. The plates were eluted with v/v 3:1 *n*-hexane/ethyl acetate and visualized with 254 nm UV light followed by dipping in a phosphomolybdic acid solution (w/v 3:20 in ethanol) and heating on a hot plate. The product trichloroacetyl carbamate **2** had an  $R_f = 0.58$  and the starting material geraniol (**1**) an  $R_f = 0.33$ . Trichloroacetyl carbamate **2** undergoes gradual hydrolysis to carbamate **3** on TLC resulting in formation of a new spot with an  $R_f = 0.29$ .

6. Methanol (99.8%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
7. A slight temperature increase (ca 1–2 °C) was observed.
8. The submitters dried the material at 0.3 mmHg on a vacuum line.
9. After stirring at room temperature for 15 min, the solution became clear.
10. When using ethyl acetate instead of diethyl ether, the crude product contained some byproducts, which were detrimental in step B.
11. An analytically pure sample was obtained by dissolving the crude carbamate **3** (8.35 g) in *n*-hexane (50 mL) and cooling in an ice bath for one hour. The precipitated white solid was quickly filtered and washed with chilled *n*-hexane to provide pure carbamate **3** (4.63 g 55%). (*E*)-3,7-Dimethylocta-2,6-dien-1-ylcarbamate (**3**) exhibits the following properties: mp 30–31 °C; IR (NaCl): 3464, 3346, 2921, 1712, 1602 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.59 (s, 3 H), 1.69 (s, 3 H), 1.71 (s, 3 H), 2.05–2.12 (m, 4 H), 4.56 (br s, 2 H), 4.59 (d, *J* = 6.9 Hz, 2 H), 5.09 (br t, *J* = 6.4 Hz, 1 H), 5.36 (br t, *J* = 6.9 Hz, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 16.3, 17.6, 25.6, 26.2, 39.4, 61.8, 118.4, 123.6, 131.7, 142.0, 157.4; Anal. calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>: C, 66.97; H, 9.71; N, 7.10. Found C, 66.90; H, 9.48; N, 7.10; HRMS (ESI): *m/z* calcd for C<sub>11</sub>H<sub>20</sub>NO<sub>2</sub> (M+H<sup>+</sup> 198.1494, found 198.1495.
12. Toluene (99.5%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
13. Triphenylphosphine (Extra Pure grade), purchased from Kanto Chemical Co., Inc., was dried in a desiccator over phosphorus pentoxide under vacuum (ca. 20 mmHg) prior to use.
14. Triethylamine, purchased from Wako Pure Chemical Industries, Ltd., was distilled from CaH<sub>2</sub> and stored over potassium hydroxide pellets.
15. Carbon tetrabromide (99%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received.
16. The reaction was monitored by TLC. Carbamate **3** has an R<sub>f</sub> = 0.29 eluting with v/v 3:1 *n*-hexane/ethyl acetate and isocyanate **5** has an R<sub>f</sub> = 0.40 (*n*-hexane) and 0.80 (*n*-hexane/diethyl ether 20:1).
17. *n*-Hexane (95%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
18. A porcelain Büchner funnel (4 cm diameter × 5 cm height) filled with 20 g of Celite was employed.
19. The submitters found that crude **5** can be purified by dissolution in

*n*-hexane followed by passing the solution through a short column of silica gel. After elution with *n*-hexane followed by collecting and concentrating the fractions, isocyanate **5** was obtained as an oil, which was distilled using a Kugelrohr (0.83 mmHg, 50–55 °C). Although the resulting clear oil was homogeneous according to proton and carbon NMR spectroscopy, a correct elemental analysis could not be achieved. Spectral data for 3-isocyanato-3,7-dimethylocta-1,6-diene (**5**) are as follows: IR (NaCl): 2977, 2931, 2257 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.41 (s, 3 H), 1.56–1.64 (m, 2 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.98–2.07 (m, 2 H), 5.05–5.08 (m, 1 H), 5.10 (d, *J* = 10.6 Hz, 1 H), 5.27 (d, *J* = 17.0 Hz, 1 H), 5.75 (dd, *J* = 17.0, 10.5 Hz, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 17.6, 23.1, 25.6, 29.2, 42.8, 62.2, 112.8, 122.9, 123.1, 132.3, 141.9; HRMS (DART): *m/z* calcd for C<sub>11</sub>H<sub>18</sub>NO (M+H)<sup>+</sup> 180.1388, found 180.1385.

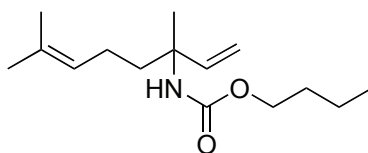
20. <sup>1</sup>H NMR analysis of the crude oil showed a small signal corresponding to the bromoform proton appearing at δ 6.83. Bromoform does not affect the subsequent step.

21. The submitters purchased dry tetrahydrofuran (anhydrous, 99+%) from Kanto Chemical Co., Inc. and used as received. The water content was 1 ppm by Karl-Fischer titration. The checkers purchased dry tetrahydrofuran from Kanto Chemicals Co., Inc., and purified by a Glass Contour Solvent Dispensing System. The water content was 9.5 ppm by Karl-Fischer titration.

22. *t*-Butyl alcohol, purchased from Wako Pure Chemical Industries, Ltd., was distilled from CaH<sub>2</sub> and stored over 4Å molecular sieves.

23. Lithium hexamethyldisilazide (1 M solution in tetrahydrofuran) was purchased from Sigma-Aldrich Chemical Company and used as received.

24. Initially, the submitters employed lithium *t*-butoxide prepared by the reaction of *n*-butyllithium with *t*-butanol in THF. In large-scale experiments, problems were sometimes encountered with the formation of a side product having a similar R<sub>f</sub> value to that of Boc-carbamate **6**. Further exploration showed that the side product was the *n*-butyl carbamate as shown below.



Although this problem could be avoided by using freshly opened *n*-butyllithium coupled with rigorous degassing of *t*-butanol by freeze-thaw cycles immediately before use, lithium hexamethyldisilazide was ultimately

selected as the base to obtain reproducible product purity and yields.

25. Reaction progress was monitored by TLC. The isocyanate starting material **5** has an  $R_f = 0.40$  (*n*-hexane) and the Boc-carbamate product **6** has an  $R_f = 0.47$  (v/v 7:1 *n*-hexane/ethyl acetate).

26. It is important to remove bromoform at this stage because it coelutes with Boc-carbamate **6** during chromatographic purification.

27. The checkers purchased 'Silca Gel 60 (spherical)' (particle size 63–210  $\mu\text{m}$ ) from Kanto Chemical Co., Inc. The crude product was transferred to a column (8  $\times$  30 cm, 100 g of silica gel) with a minimum amount of *n*-hexane and eluted with 400 mL of *n*-hexane. Elution was continued with 1.5 L of *n*-hexane:ethyl acetate (v/v 20:1) and fraction collection (100-mL) was begun. Fractions 4–10 were combined and concentrated by rotary evaporation.

28. The submitters reported purity of 97% by GC analysis using an Agilent 6890N instrument equipped with an Agilent J&W DB-5 column (30.0 m  $\times$  0.25 mm) and a flame ionization detector using a method of 160 °C isotherm for 10 min, then ramp 20 °C/min to 300 °C, then 300 °C isothermal for 8 min with flow rate 30 cm/sec He carrier gas. The retention time for the product was 6.9 min with unidentified small peaks having retention times 1.7–6.4 min.

29. Kugelrohr distillation of carbamate **6** (oven temperature 130–135 °C at 1.0 mmHg) afforded an analytically pure sample. Spectral data for *t*-butyl 3,7-dimethylocta-1,6-dien-3-ylcarbamate (**6**): IR (NaCl): 3277, 2975, 2929, 1717, 1698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.37 (s, 3 H), 1.43 (s, 9 H), 1.60 (s, 3 H), 1.65–1.69 (m, 2 H), 1.68 (s, 3 H), 1.94 (q,  $J = 7.3$  Hz, 2 H), 4.61 (br s, 1 H), 5.05–5.12 (m, 3 H), 5.89 (dd,  $J = 17.4, 10.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 17.5, 22.5, 24.7, 25.6, 28.4, 39.5, 56.1, 78.8, 111.9, 124.0, 131.8, 143.5, 154.2; Anal. calcd for  $\text{C}_{15}\text{H}_{27}\text{NO}_2$ : C, 71.10; H, 10.74; N, 5.53. Found C, 70.71; H, 10.76; N, 5.53; HRMS (DART):  $m/z$  calcd for  $\text{C}_{15}\text{H}_{28}\text{NO}_2$  ( $\text{M}+\text{H}$ ) $^+$  254.2120, found 254.2117.

### Handling and Disposal of Hazardous Chemicals

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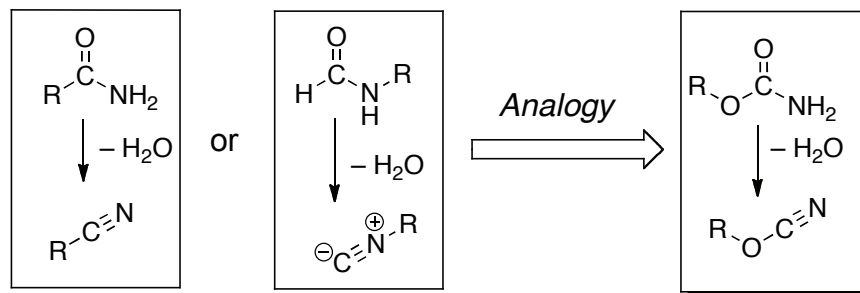
www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In the development and checking of these procedures, every effort has been made to identify and minimize potentially hazardous steps. The Editors believe that the procedures described in this article can be carried out with minimal risk if performed with the materials and equipment specified, and in careful accordance with the instructions provided. However, these procedures must be 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.

### 3. Discussion

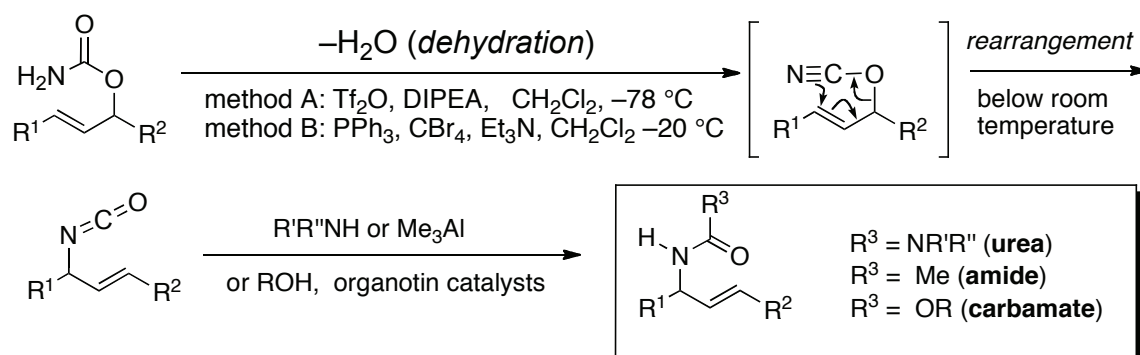
Allyl cyanates generated under several reaction conditions are considered to be possible transient intermediates, which undergo instantaneous rearrangement below ambient temperature to afford allyl isocyanates.<sup>2</sup> Historically, the first attempts to synthesize allyl cyanates dates back to a report in 1970 by Holm, who employed a cheletropic reaction of allyl thiazoles and found that only rearranged allyl isocyanates were isolated.<sup>3</sup> In 1978, Overman examined the synthesis of allyl cyanates by using the reaction of cyanogen chloride with the lithium salts of allyl alcohols and observed formation of a mixture of allylically rearranged isocyanates and dimeric carbamates.<sup>4</sup> Although these two pioneering reports support the belief that rearrangement of presumed allyl cyanates occurs below room temperature, development of an allyl cyanate-to-isocyanate rearrangement as a synthetic method for preparation of allyl amines is hampered by obstacles associated with preparation of cyanates (esters of cyanic acid: R-OCN).<sup>5</sup> Moreover, no mechanistic investigation had been undertaken to determine if the reaction proceeds via an ionic or concerted mechanism.<sup>6</sup>

In 1991, Ichikawa introduced a new synthetic method for the preparation of allyl cyanates which involves *dehydration reactions of allyl carbamates*.<sup>7</sup> This approach is quite reasonable considering the analogous methods to form carbon-nitrogen triple bonds, such as dehydration reactions of amides or formamides to produce nitriles or isonitriles, respectively (Scheme 1).<sup>8</sup>



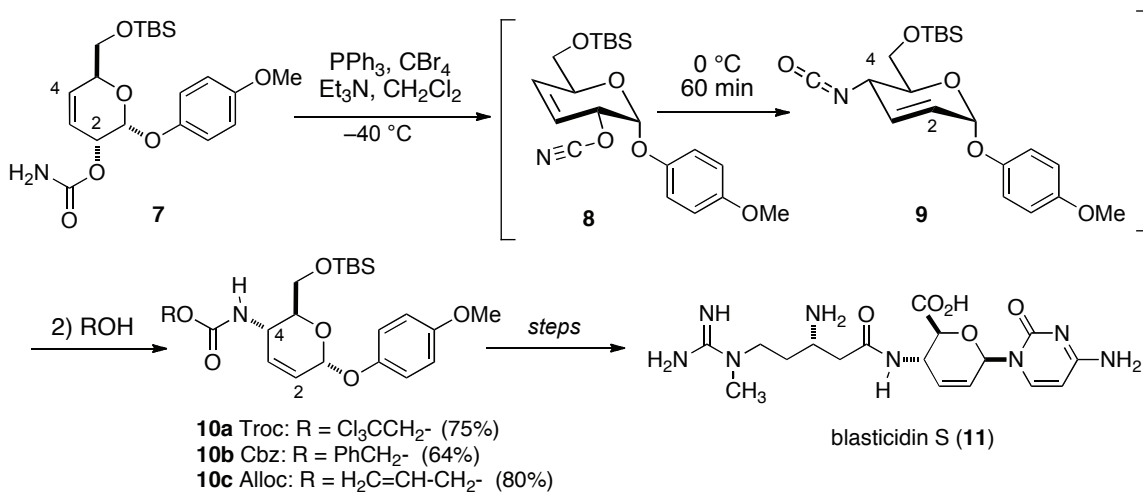
**Scheme 1.** Retrosynthetic analysis of cyanates by analogy

Ichikawa examined several dehydration conditions of allyl carbamates and found that trifluoromethanesulfonic anhydride ( $\text{Tf}_2\text{O}$ ) and diisopropylethylamine (DIPEA) in dichloromethane at  $-78\text{ }^\circ\text{C}$  (method A)<sup>9</sup> and triphenylphosphine, carbon tetrabromide and triethylamine (TEA) in dichloromethane at  $-20\text{ }^\circ\text{C}$  (method B)<sup>10</sup> accomplish the transformation to form allyl cyanates (Scheme 2). It should be noted that these two dehydration methods were originally reported as procedures for the preparation of isocyanides from formamides. Although method B produces triphenylphosphine oxide as co-product, which is often difficult to remove, we preferred method B over method A owing to its experimental simplicity. Furthermore, the reaction conditions employed in method B are sufficiently mild to tolerate a wide range of functional groups. One of the important features of this rearrangement reaction is that the allyl isocyanate products can be flexibly transformed to a variety of allyl amine derivatives. For example, addition of amines, trimethylaluminum or alcohols to the reaction mixture containing the allyl isocyanate affords the respective ureas, acetamides<sup>11</sup> or carbamates.<sup>12</sup>



**Scheme 2.** Allyl cyanate-to-isocyanate rearrangement for the synthesis of allyl amine derivatives

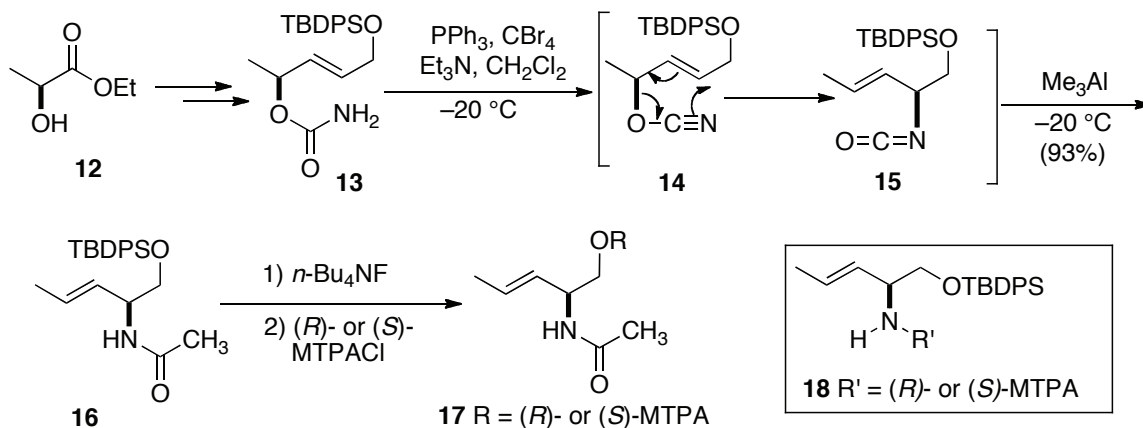
The advantageous feature of the transformation of allyl isocyanates to allyl amine derivatives is demonstrated in synthetic studies of the nucleoside antibiotic, blasticidin S (**11**) (Scheme 3).<sup>13</sup> In the route to this target, transformation of hex-3-enopyranose **7** to 4-amino-hex-2-enopyranose (**10a–c**) was carried out by utilizing an allyl cyanate-to-isocyanate rearrangement (**8**→**9**). Treatment of the produced allyl isocyanate **9** with 2,2,2-trichloroethanol, benzyl alcohol or allyl alcohol furnished the respective Troc (**10a**), Cbz (**10b**) and Alloc carbamate (**10c**) derivatives. After considerable experimentation with these three carbamates to determine the best choice of protecting group, the Troc carbamate (**10a**) was selected as a key intermediate, which led to the first total synthesis of blasticidin S. In addition, it is noteworthy that the intermediate allyl cyanate **8**, having the cyanate group at the pseudo-equatorial position, underwent smooth rearrangement even at 0 °C.<sup>14</sup>



**Scheme 3.** The key step in the total synthesis of blasticidin S.

The stereochemistry of allyl cyanate-to-isocyanate rearrangement was examined using chiral allyl carbamate **13**, which was prepared from ethyl (*S*)-lactate (**12**) (Scheme 4).<sup>15</sup> Dehydration of **13** followed by treatment of the resulting allyl isocyanate **15** with trimethylaluminum furnished amide **16** in a good yield. The enantiomeric purity of the rearranged product **16** was determined to be 98% by analysis of the corresponding MTPA esters **17**. The absolute stereochemistry of the formed stereogenic center in **16** was determined by analysis of the MTPA amides **18** using the Kusumi method for elucidation of the absolute configuration of primary amines.<sup>16</sup> The results of these studies led to the

conclusion that the rearrangement of allyl cyanates proceeds via a concerted mechanism resulting in [1,3]-chirality transfer with a high level of stereoselectivity.



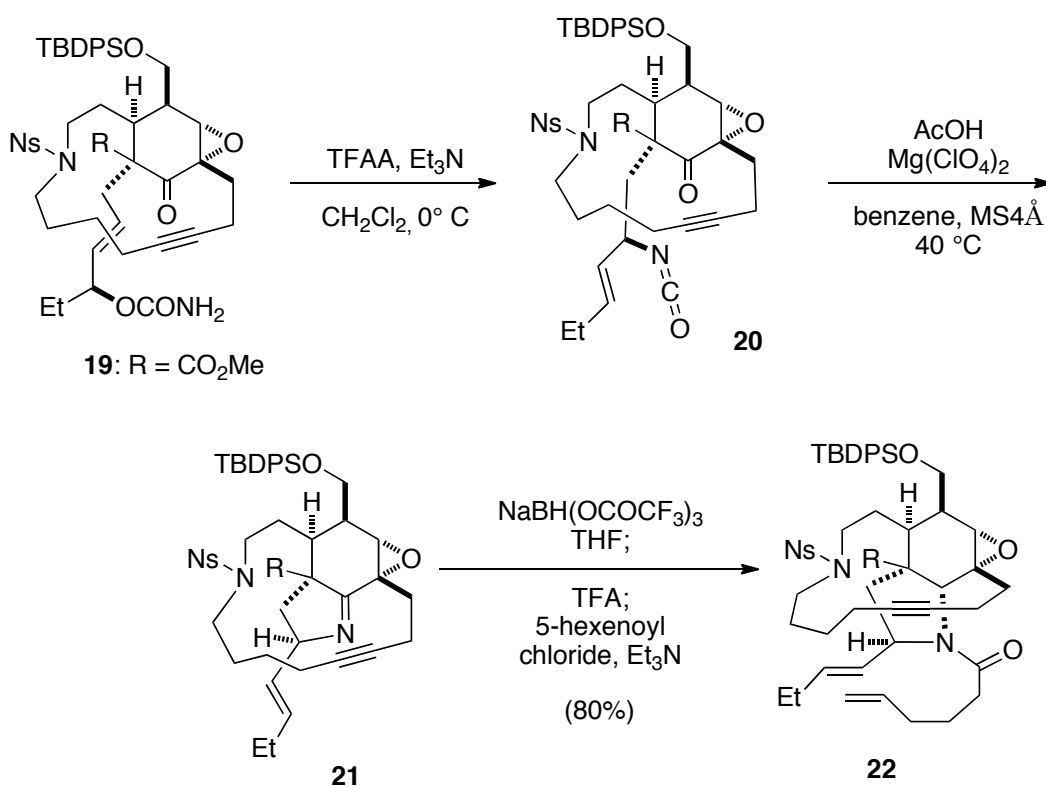
**Scheme 4** Examination of stereochemistry in allyl cyanate-to-isocyanate rearrangement.

The availability of a reliable method for the preparation of allyl cyanates through dehydration of allyl carbamates coupled with the stereoselective nature of the rearrangement established that allyl cyanate-to-isocyanate rearrangement is a useful method for the enantioselective synthesis of allyl amine derivatives. As a result, a number of organic chemists have employed this reaction for the syntheses of nitrogen-containing bioactive compounds.<sup>17</sup>

The procedure described herein, highlighting the allyl cyanate-to-isocyanate rearrangement, serves as an efficient method for the preparation of allyl amines as Boc-carbamate derivatives starting from allyl alcohols. This is exemplified by conversion of geraniol (**1**) to the Boc-carbamate **6**. Carbamoylation of **1** is carried out by treatment with trichloroacetyl isocyanate followed by hydrolysis of the trichloroacetyl group of **2** with potassium carbonate in aqueous methanol to provide allyl carbamate **3** in excellent yield (Step A).<sup>18</sup> Although trichloroacetyl isocyanate is an expensive and moisture-sensitive liquid that causes difficulties in handling, it is an ideal reagent for this transformation due to its high reactivity, clean reaction, and excellent yields.<sup>19</sup>

Dehydration of allyl carbamate **3** generates allyl cyanate **4**, which undergoes spontaneous rearrangement to afford allyl isocyanate **5** (Step B). Although the dehydration conditions are mild enough to tolerate a wide

range of functional groups, one drawback is the formation of the co-product triphenylphosphine oxide. In the present case, dissolution of the crude reaction mixture in hexane results in precipitation of triphenylphosphine oxide, which is easily removed by filtration. In smaller scale experiments, it is more convenient to purify the product directly by chromatographing the crude mixture rather than by precipitation and filtration. When the product has the same or similar  $R_f$  value as triphenylphosphine oxide, tributylphosphine can be used as an alternative.<sup>12</sup> Other dehydration methods, which circumvent problems associated with triphenylphosphine oxide, utilize either  $\text{Tf}_2\text{O}/\text{DIPEA}$ <sup>7</sup> or trifluoroacetic anhydride (TFAA)/TEA.<sup>20</sup> In particular, in their total synthesis of manzamine A, Fukuyama and co-workers employed TFAA/TEA for dehydrating the functional group-rich carbamate **19** (Scheme 5).<sup>21</sup> It should be noted that use of the TFAA/TEA procedure was originally described as a synthetic method for the preparation of nitriles from amides by Casini.<sup>22</sup>



**Scheme 5** The key step in the total synthesis of manzamine A

Transformation of the sterically crowded isocyanate **5** to the Boc-carbamate **6** was performed by reaction with lithium *t*-butoxide. Since lithium *t*-butoxide is a strong base, we cannot employ these conditions with isocyanates containing base-sensitive functional groups or epimerization-prone stereogenic centers. In these cases, it is recommended that related procedures be used to transform hindered isocyanates into carbamates under Lewis or Brønsted acid conditions using titanium tetra-*t*-butoxide<sup>23</sup> or trimethylsilyl chloride<sup>24</sup> or molybdenum (VI) dichloride dioxide.<sup>25</sup>

In summary, the transformation of geraniol (**1**) to Boc-carbamate **6** exemplifies a useful synthetic method for the construction of quaternary carbons bearing nitrogen substituents.<sup>26</sup>

1. Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520 Japan; E-mail: ichikawa@kochi-u.ac.jp.
2. (a) Banert, K.; Groth, S. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 866. (b) Banert, K.; Melzer, A. *Tetrahedron Lett.* **2001**, *42*, 6133.
3. Christophersen, C.; Holm, A. *Acta Chem. Scand.* **1970**, *24*, 1512.
4. Overman, L. E.; Kakimoto, M. *J. Org. Chem.* **1978**, *43*, 4564.
5. (a) Grigat, E.; Pütter, R. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 206. (b) Jensen, K. A.; Holm, A. In *The Chemistry of Cyanates and Their Thio Derivatives Part 1*, Chapter 16, p. 569; Patai, S., Ed.; Wiley-Interscience: New York, **1977**. (c) Grashey, R. In *Comprehensive Organic Synthesis*, Vol. 6, p. 225; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**.
6. Alkyl cyanate-to-isocyanate isomerization reactions are known to proceed via an ionization-recombination pathway. See, Martin, D.; Niclas, H-J.; Habisch, D. *Liebigs Ann. Chem.* **1969**, 727, 10.
7. Ichikawa, Y. *Synlett* **1991**, 238.
8. Y. I. gives thanks to the late Professor Toshio Goto at Nagoya University for his suggestion of this simple and brilliant idea of synthesizing cyanates, described in the following reference: Ichikawa, Y. *Synlett* **2007**, 2927.
9. Baldwin, J. E.; O'Neil, I. A. *Synlett* **1990**, 603.
10. Ichikawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2135.
11. Ichikawa, Y.; Yamazaki, M.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429.
12. Ichikawa, Y.; Osada, M.; Ohtani, I. I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449.

13. (a) Ichikawa, Y.; Hirara, K.; Ohbayashi, M.; Isobe, M. *Chem.–Eur. J.* **2004**, 3241. (b) Ichikawa, Y.; Kobayashi, C.; Isobe, M. *J. Chem. Soc., Perkin Trans. I* **1996**, 377.
14. For a related synthesis of 4-amino-hex-2-enopyranose using the Overman rearrangement, a high temperature (165 °C in *o*-dichlorobenzene) was necessary to promote the rearrangement. (a) Dyong, I.; Weigand, J.; Merten, H. *Tetrahedron Lett.* **1981**, 22, 2965. (b) Dyong, I.; Weigand J.; Thiem, J. *Liebigs Ann. Chem.* **1986**, 577.
15. Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. I* **1994**, 2791.
16. Kusumi, T. Fukushima, T.; Ohtani, I.; Kakisawa, K. *Tetrahedron Lett.* **1991**, 32, 2939.
17. (a) Kapferer, P.; Sarabia, F.; Vasella, A. *Helv. Chim. Acta.* **1999**, 82, 645. (b) Roulland, E.; Monneret, C.; Florent, J-C.; Bennejean, C.; Renard, P.; Leonce, S. *J. Org. Chem.* **2002**, 67, 4399. (c) Yokoyama, T.; Yokoyama, R.; Nomura, S.; Matsumoto, S.; Fujiyama, R.; Kiyooka, S.-i. *Bull. Chem. Soc, Jpn.* **2009**, 82, 1528. (d) Arbour, M.; Roy, S.; Godbout, C.; Spino, C. *J. Org. Chem.* **2009**, 74, 3806. (e) Yokoyama, R.; Matsumoto, S.; Nomura, S.; Higaki, T.; Yokoyama, T.; Kiyooka, S.-i. *Tetrahedron* **2009**, 65, 5181. (f) Gagnon, D.; Spino, C. *J. Org. Chem.* **2009**, 74, 6035. (g) Yamashita, M.; Yamashita, T.; Aoyagi, S. *Org. Lett.* **2011**, 13, 2204. (h) Liu, Z.; Bittman, R. *Org. Lett.* **2012**, 14, 620. (i) Boyd, D. R.; Sharma, N. D.; Kaik, M.; McIntyre, P. B. A.; Stevenson, P. J.; Allen, C. C. R. *Org. Biomol. Chem.* **2012**, 10, 2774.
18. (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, 104, 1109. (b) Hiram, M.; Uei, M. *Tetrahedron Lett.* **1982**, 23, 5307.
19. For other carbamoylation processes, see: Ichikawa, Y.; Morishita, Y.; Kusaba, S.; Sakiyama, N.; Matsuda, Y.; Nakano, K.; Kotsuki, H. *Synlett* **2010**, 1815, and references therein.
20. Roy, S.; Spino, C. *Org. Lett.* **2006**, 8, 939.
21. Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, 132, 10233.
22. Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 18, 1813.
23. C. Spino, C.; Joly, M-A.; Godbout. C.; Arbour, M. *J. Org. Chem.* **2005**, 70, 6118.
24. (a) Ichikawa, Y.; Okumura, K.; Matsuda, Y.; Hasegawa, T.; Nakamura, M.; Fujimoto, A.; Masuda, T.; Nakano, K.; Kotsuki, H. *Org. Biomol. Chem.* **2012**, 10, 614. (b) Benalil, A.; Roby, P.; Carboni, B.; Vaultier, M. *Synthesis* **1991**, 787.

25. Stock, C.; Brückner, R. *Synlett* **2010**, 2429.
26. (a) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotech. Biochem.* **2005**, *69*, 939. (b) Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011**, 47, 4624.

### Appendix

#### Chemical Abstracts Nomenclature; (Registry Number)

(*E*)-3,7-Dimethylocta-2,6-dien-1-ylcarbamate; (16930-44-2)

Geraniol; (106-24-1)

Trichloroacetyl isocyanate; (3019-71-4)

*tert*-Butyl 3,7-dimethylocta-1,6-dien-3-ylcarbamate; (1354913-05-5)

Triphenylphosphine; (603-35-0)

Triethylamine; (121-44-8)

Carbon tetrabromide; (558-13-4)

Lithium hexamethyldisilazide; (4039-32-1)



Yoshiyasu Ichikawa was born in Gamagori, Aichi in 1958. He completed his undergraduate studies and PhD at Nagoya University. After postdoctoral studies in the Dyson Perrins Laboratory at Oxford, UK he joined the faculty of Mie University where he pursued his interests in the synthesis of marine natural products based upon the sigmatropic rearrangements. He moved to Nagoya University in 1992 and emigrated to Kochi University in 2004. His research interests are in the area of synthesis of natural products and carbohydrate chemistry.

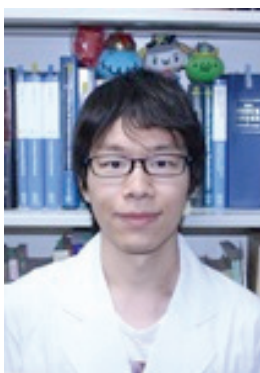


Noriko Kariya was born in 1986 in Kochi, Japan. She carried out her undergraduate research with Professor Yoshiyasu Ichikawa at Kochi University where she received her MS degree in 2012.

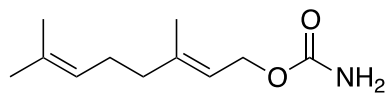




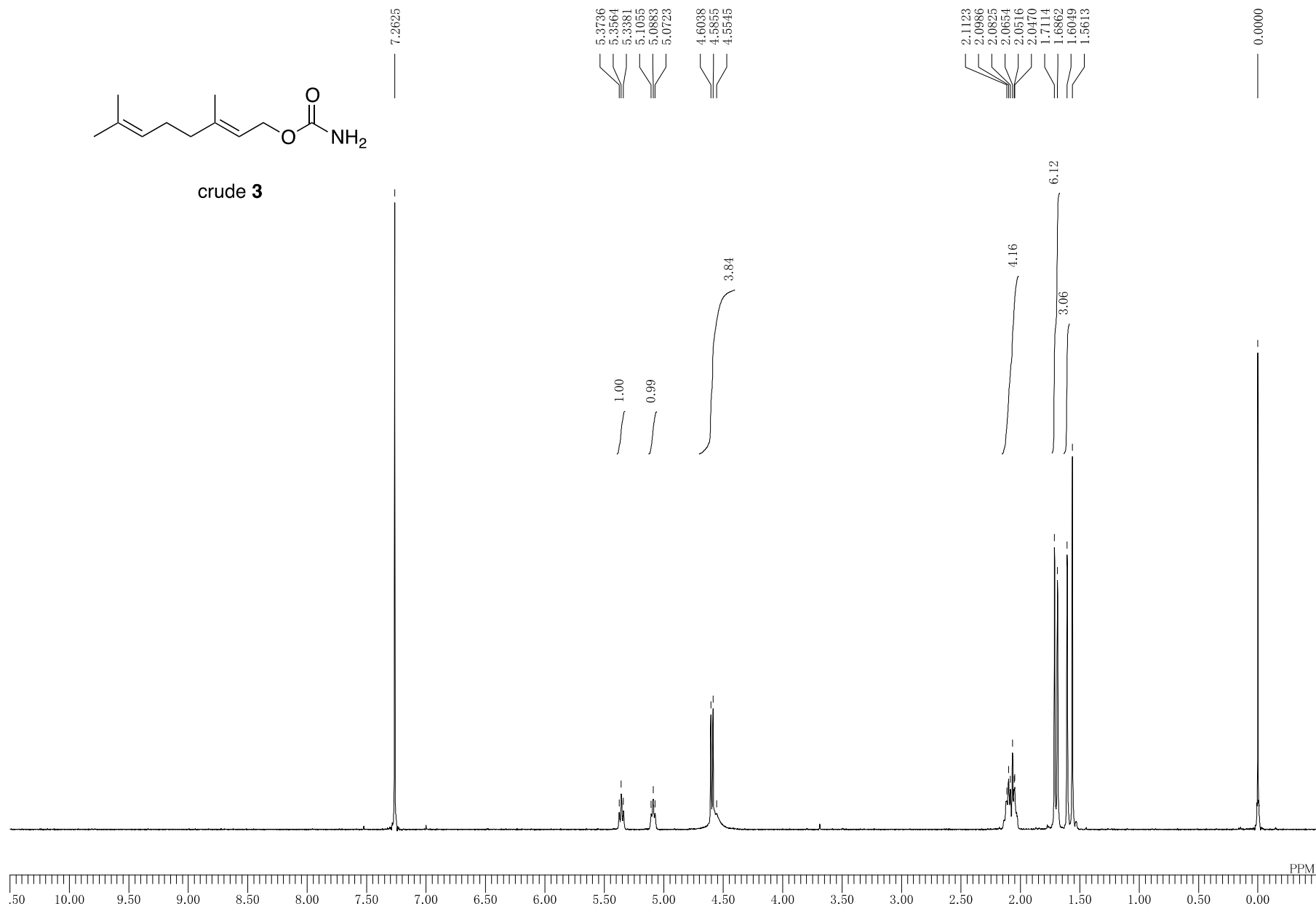
Tomoyuki Hasegawa was born in 1988 in Shizuoka, Japan. He pursued his undergraduate studies with Professor Yoshiyasu Ichikawa at Kochi University where he received his MS degree in 2013.

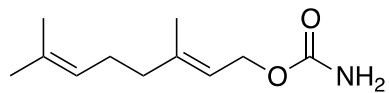


Eiji Yoshida was born in Ann Arbor, Michigan in 1989. He received his B.S. in 2012 from the University of Tokyo. In the same year, he began his graduate studies at the Graduate School of Pharmaceutical Sciences, the University of Tokyo, under the guidance of Professor Tohru Fukuyama. His research interests are in the area of the total synthesis of natural products.

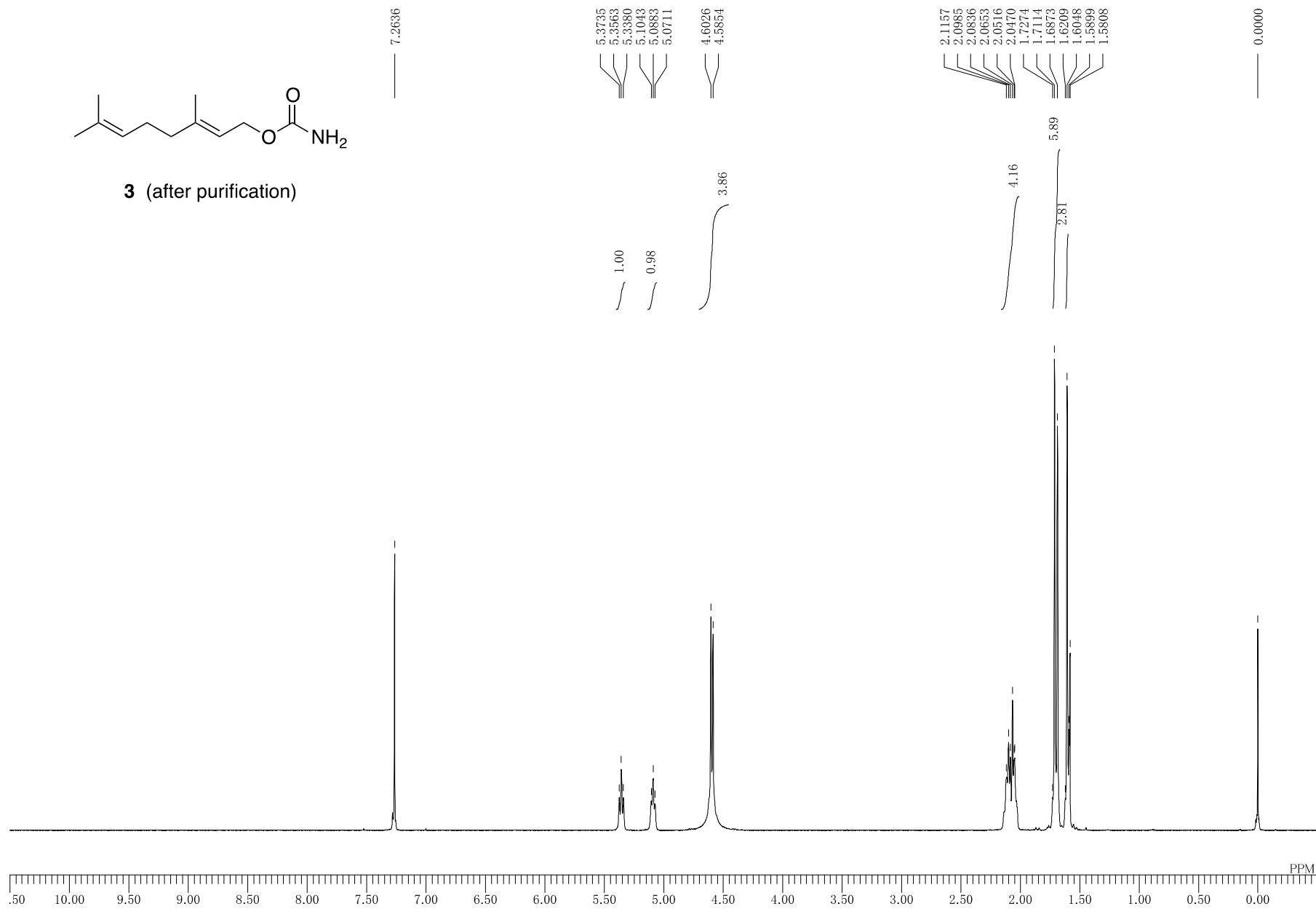


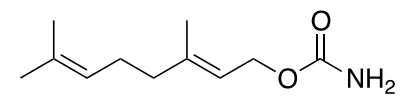
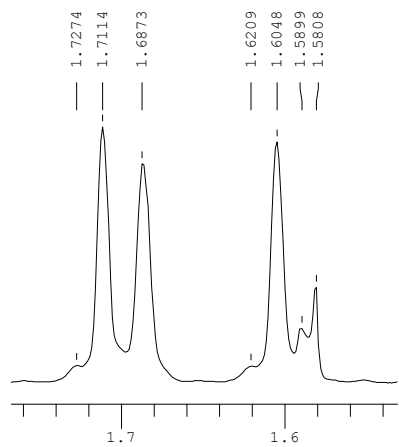
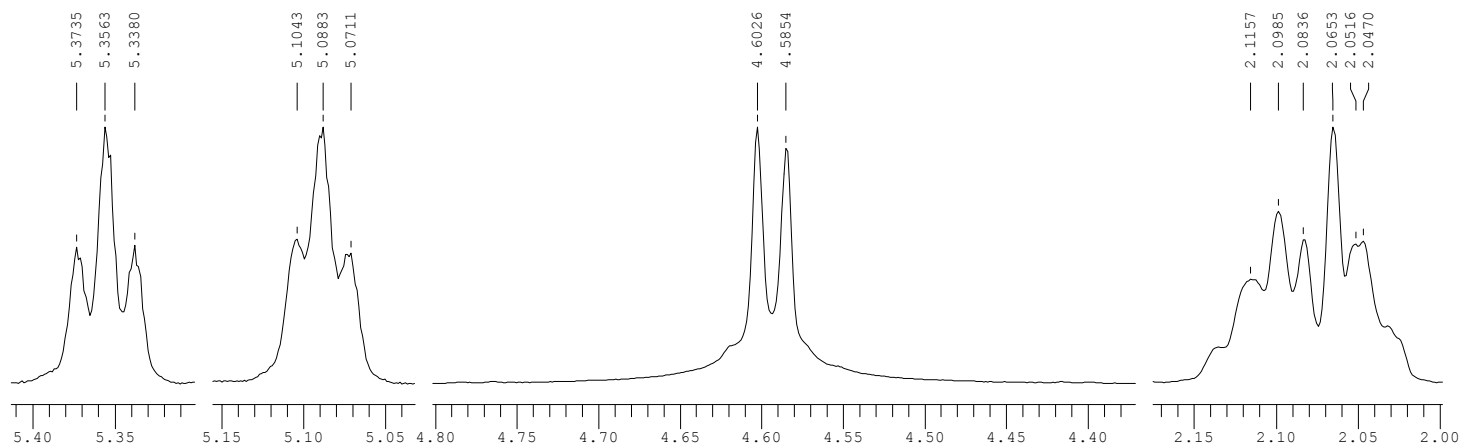
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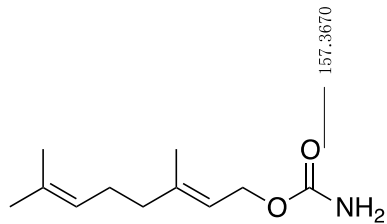


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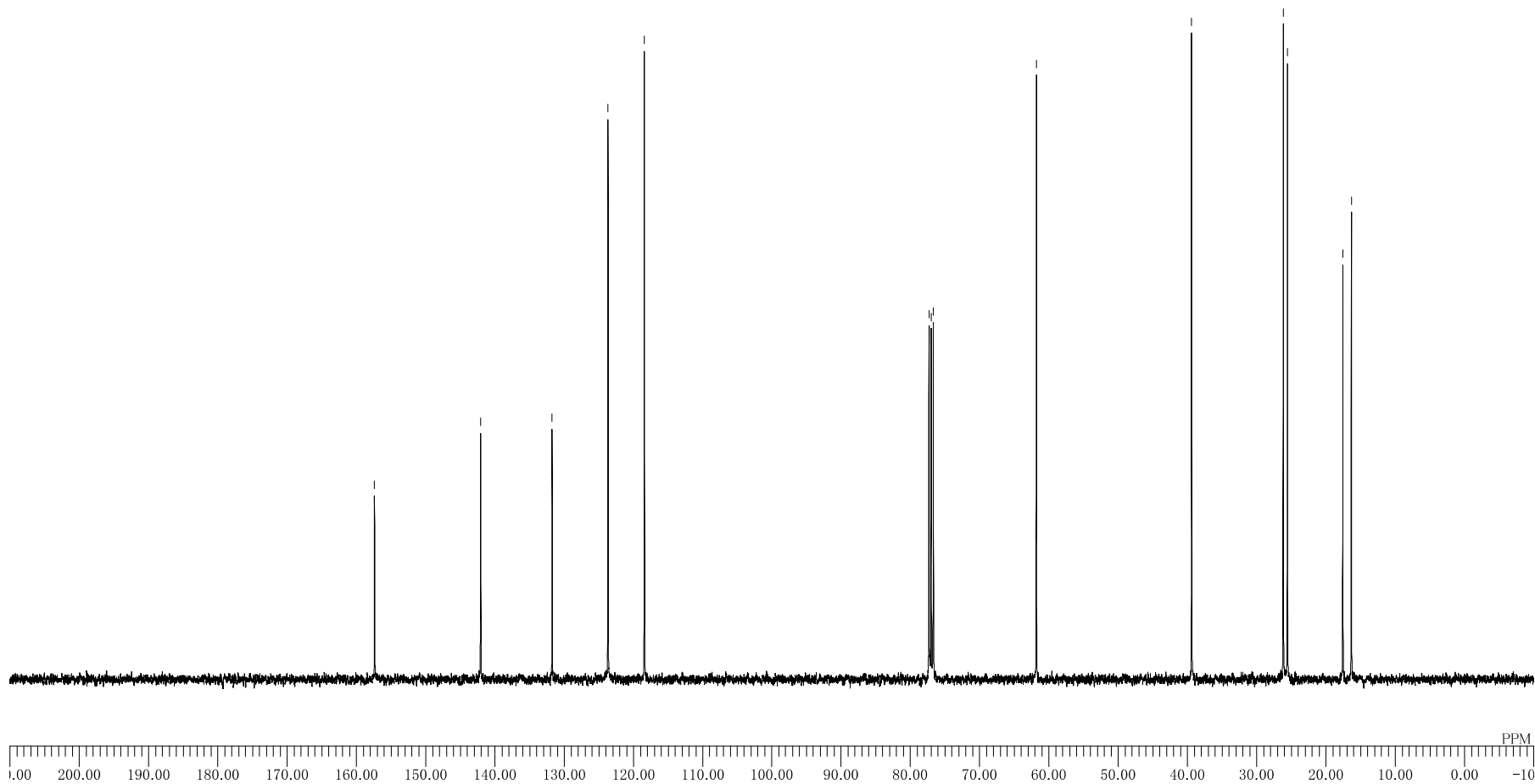
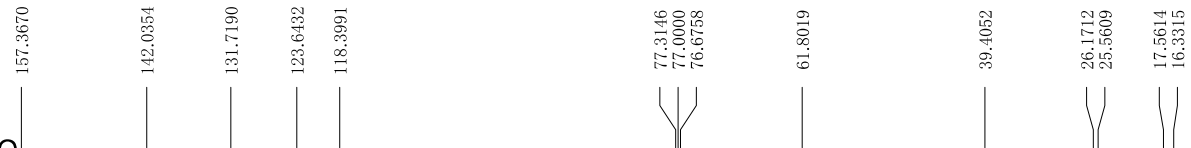


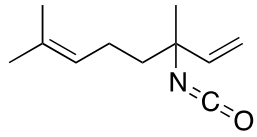


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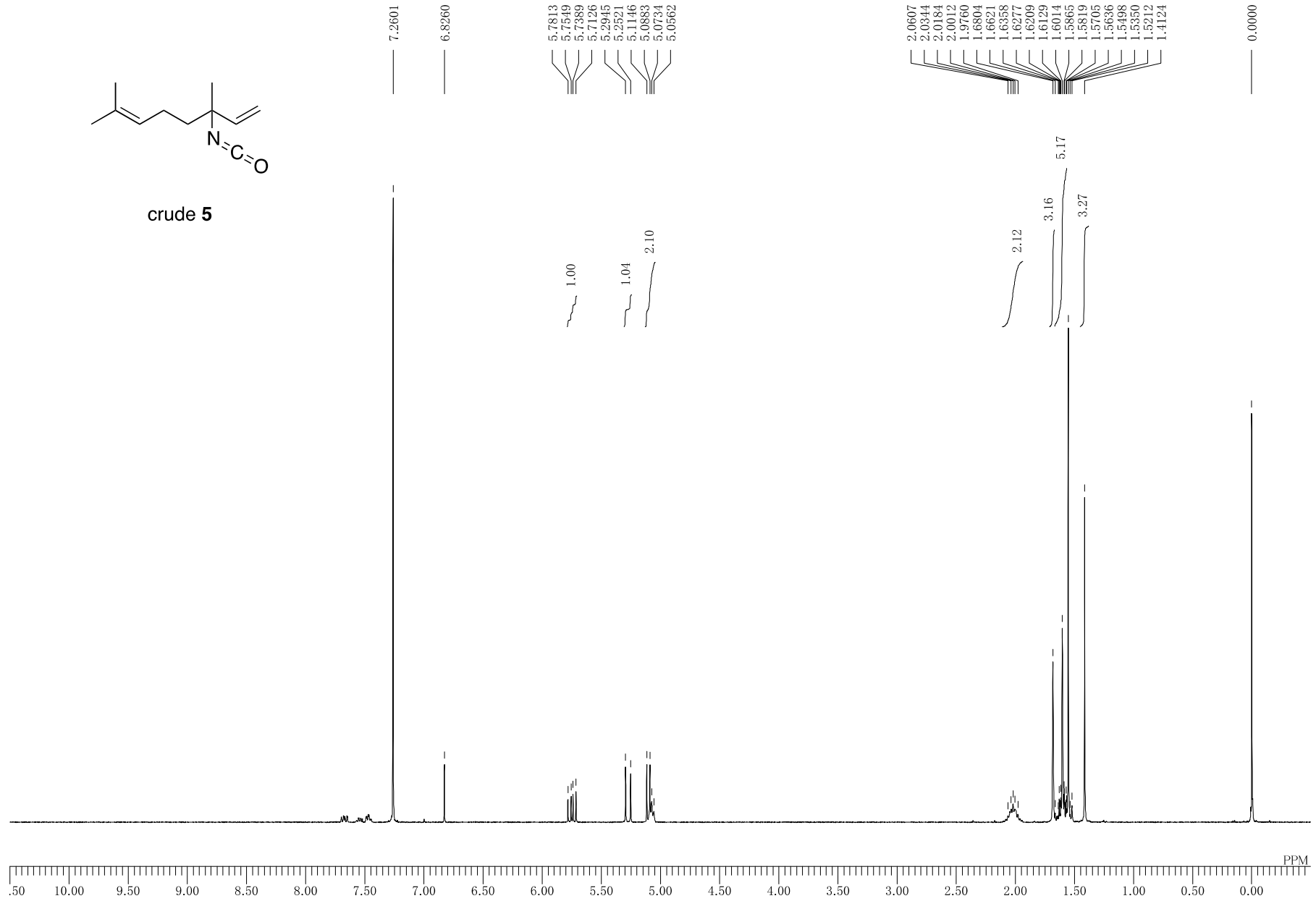


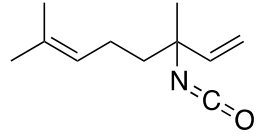
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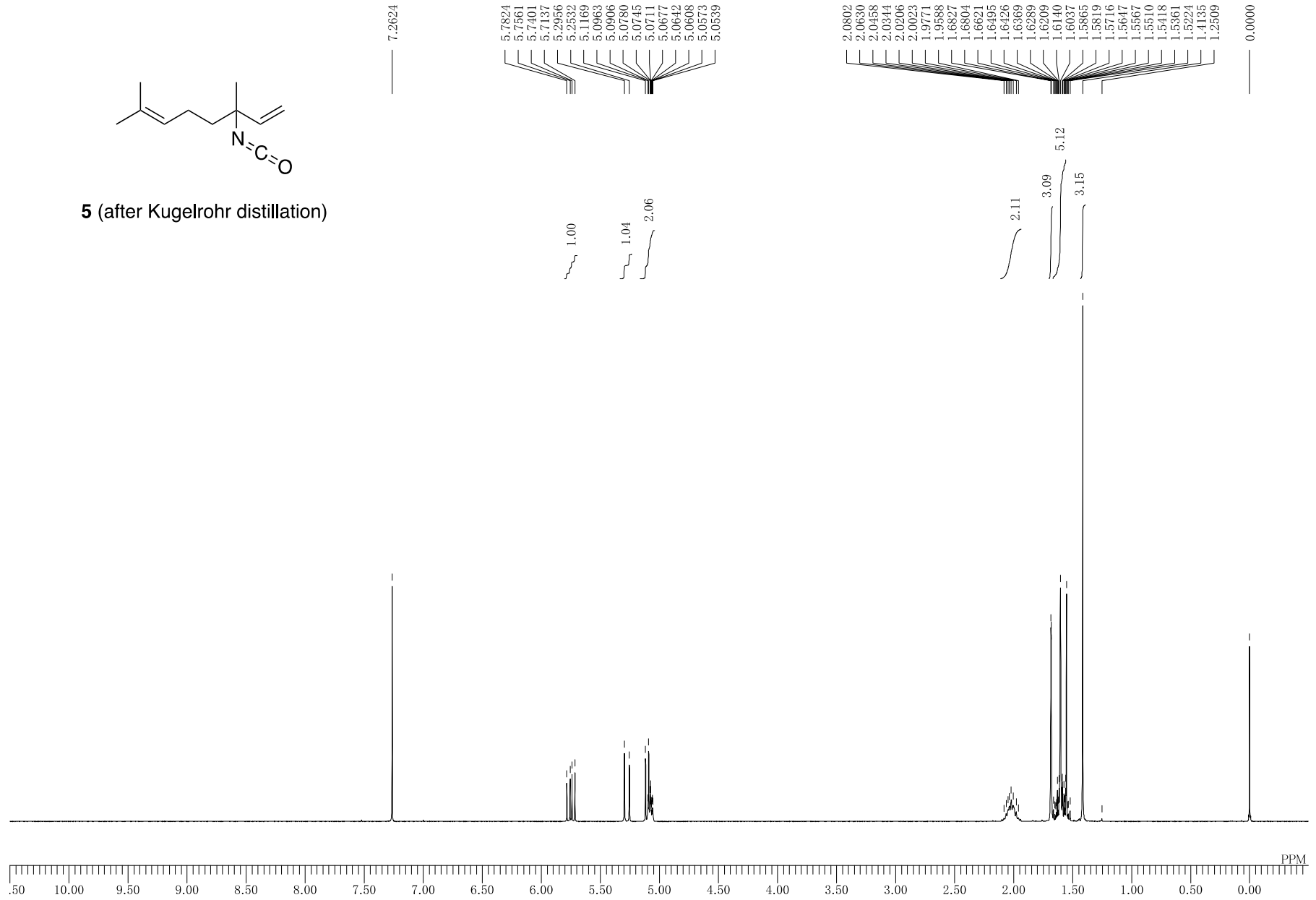


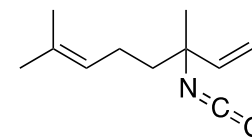
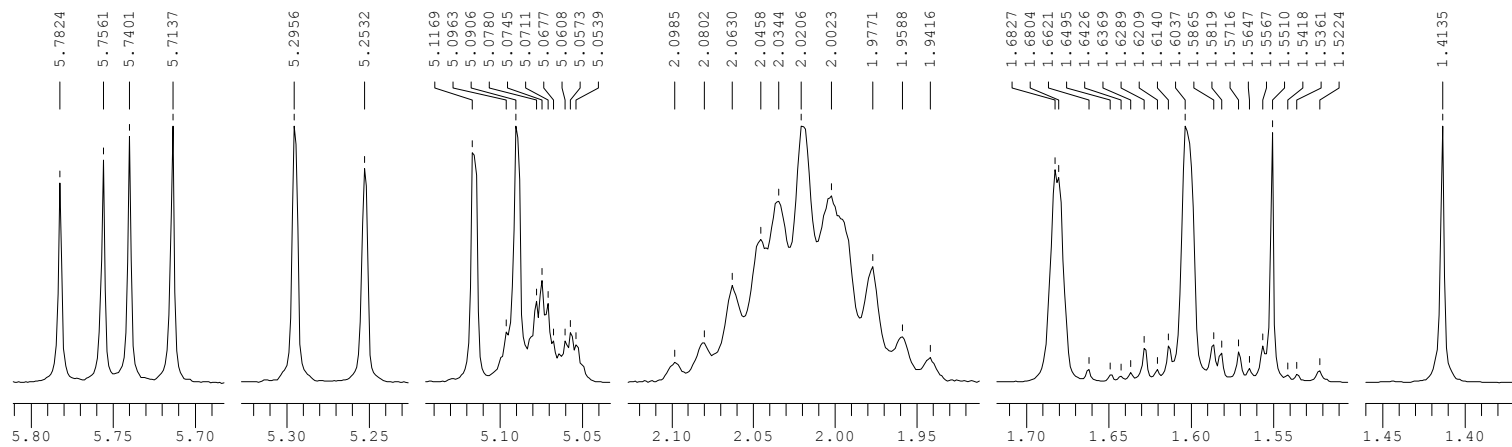
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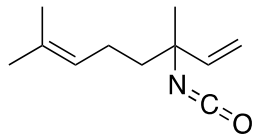




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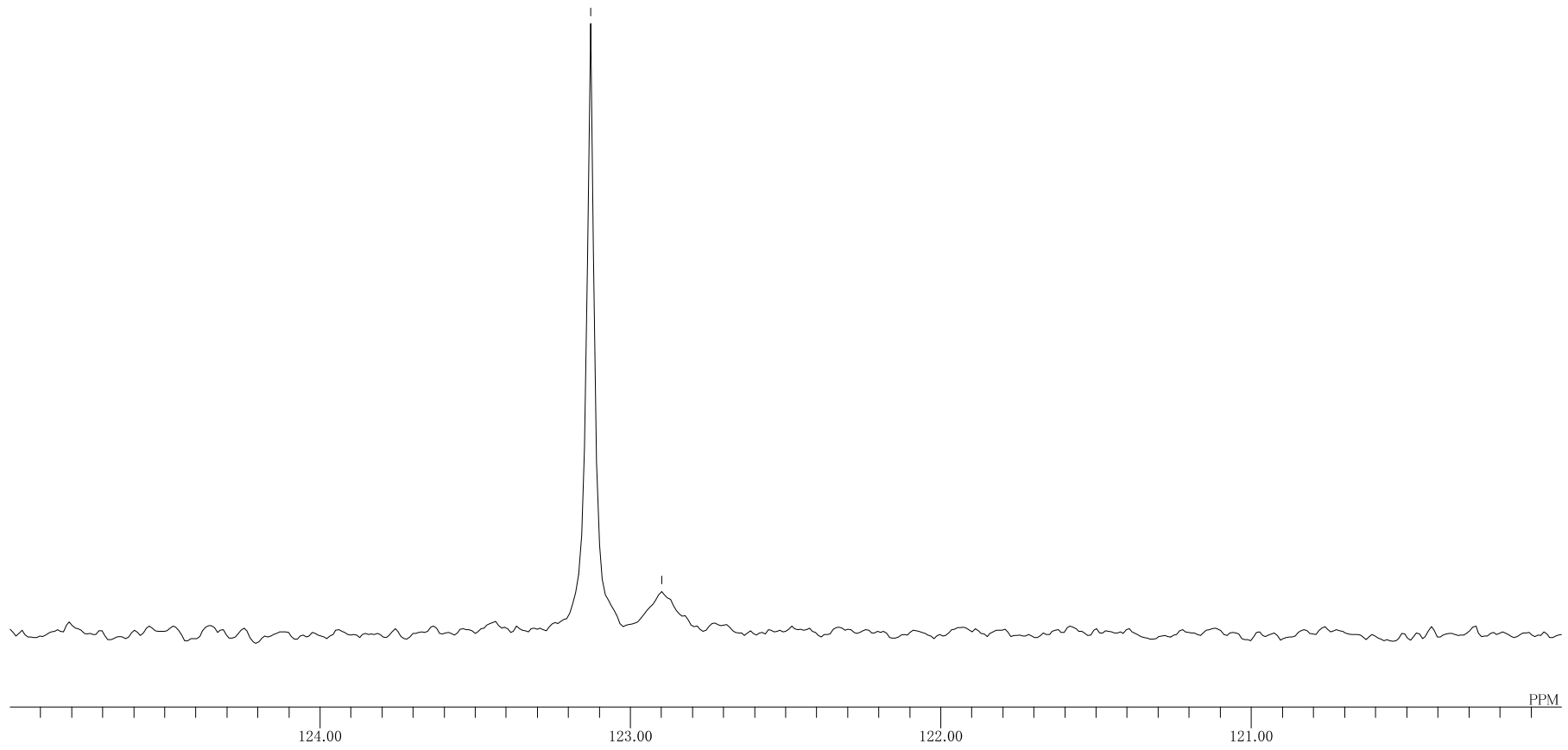


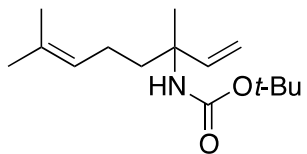




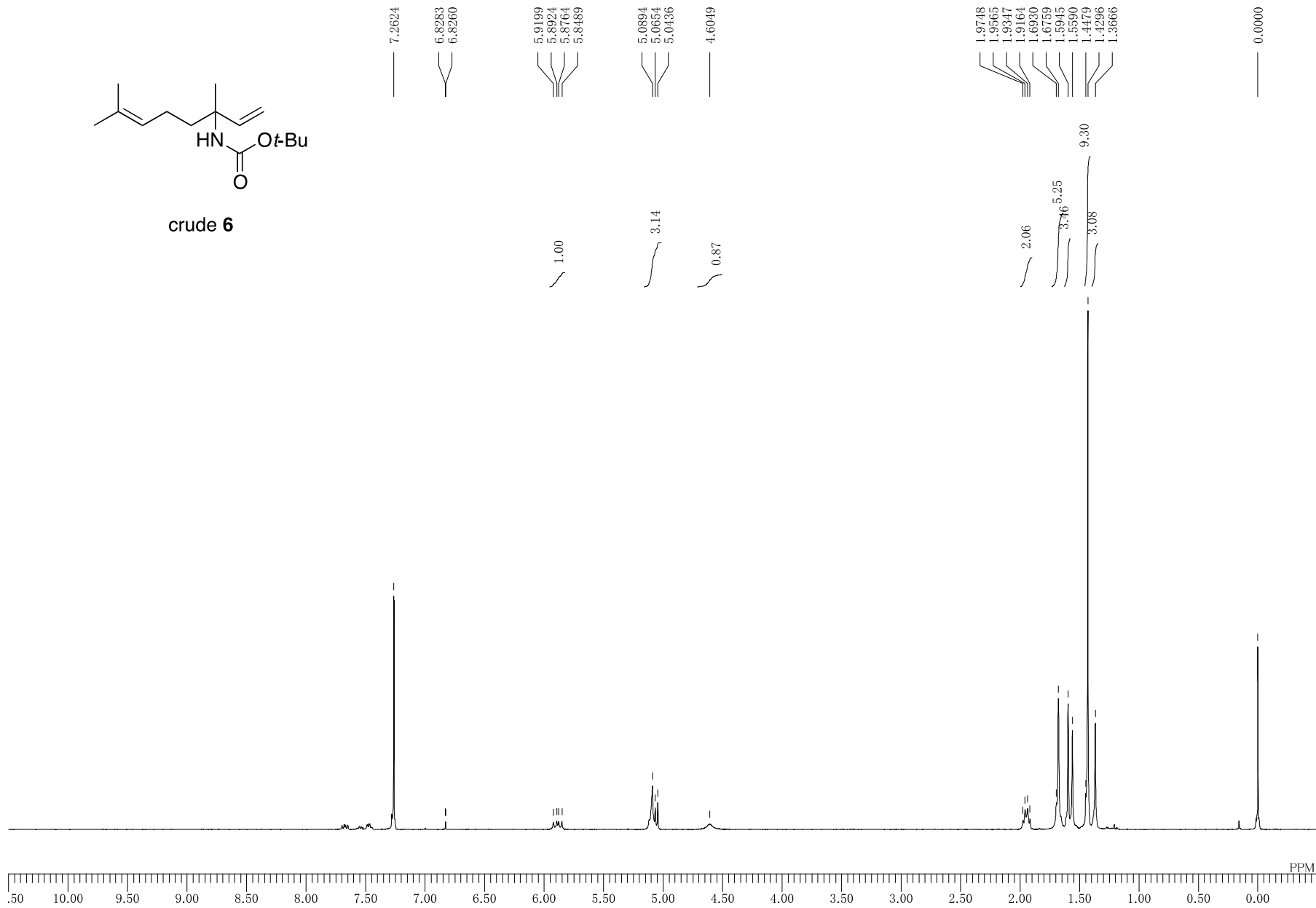
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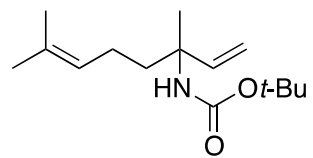
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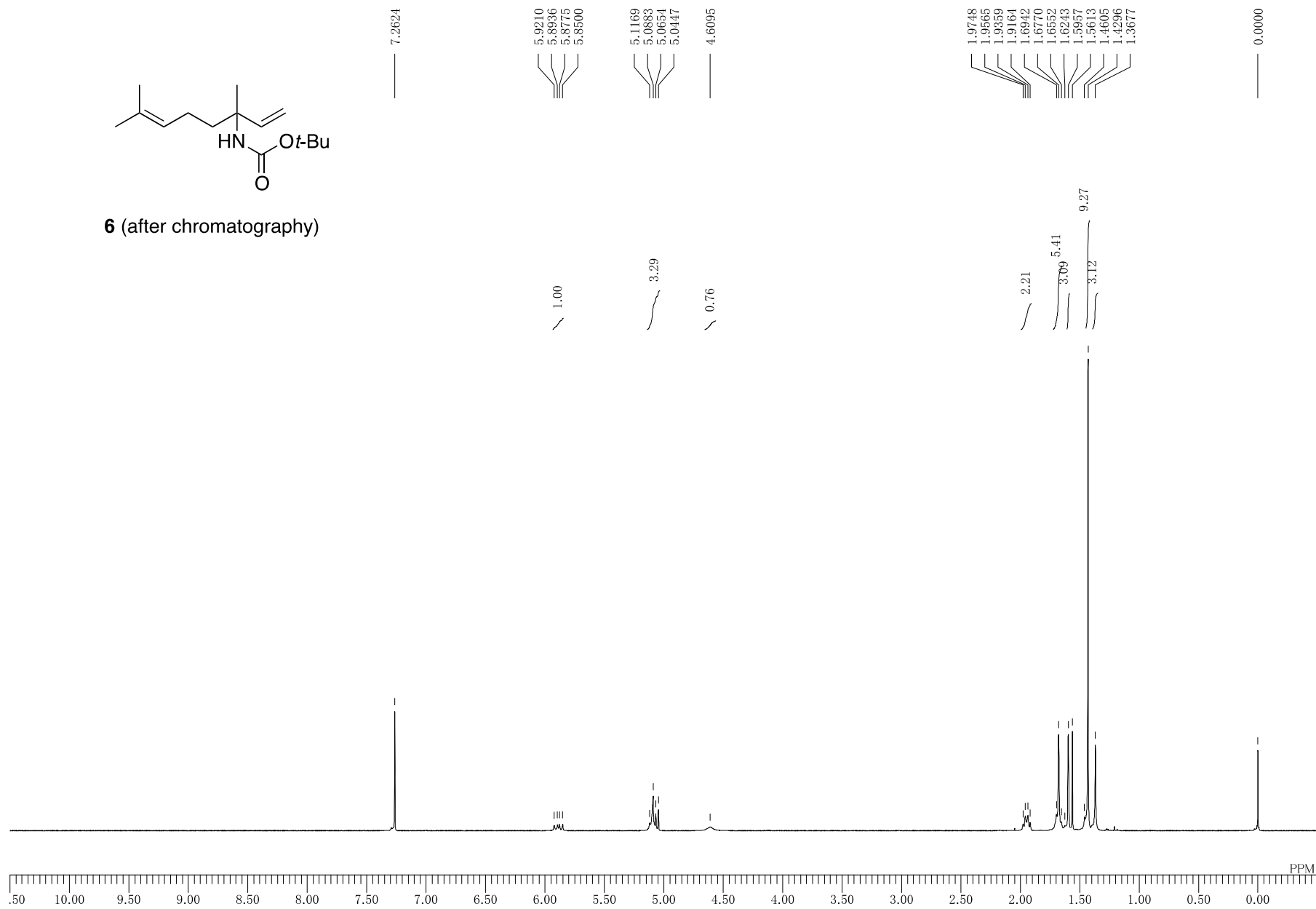


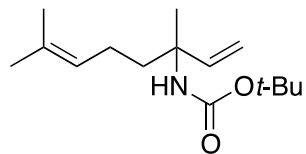
crude 6



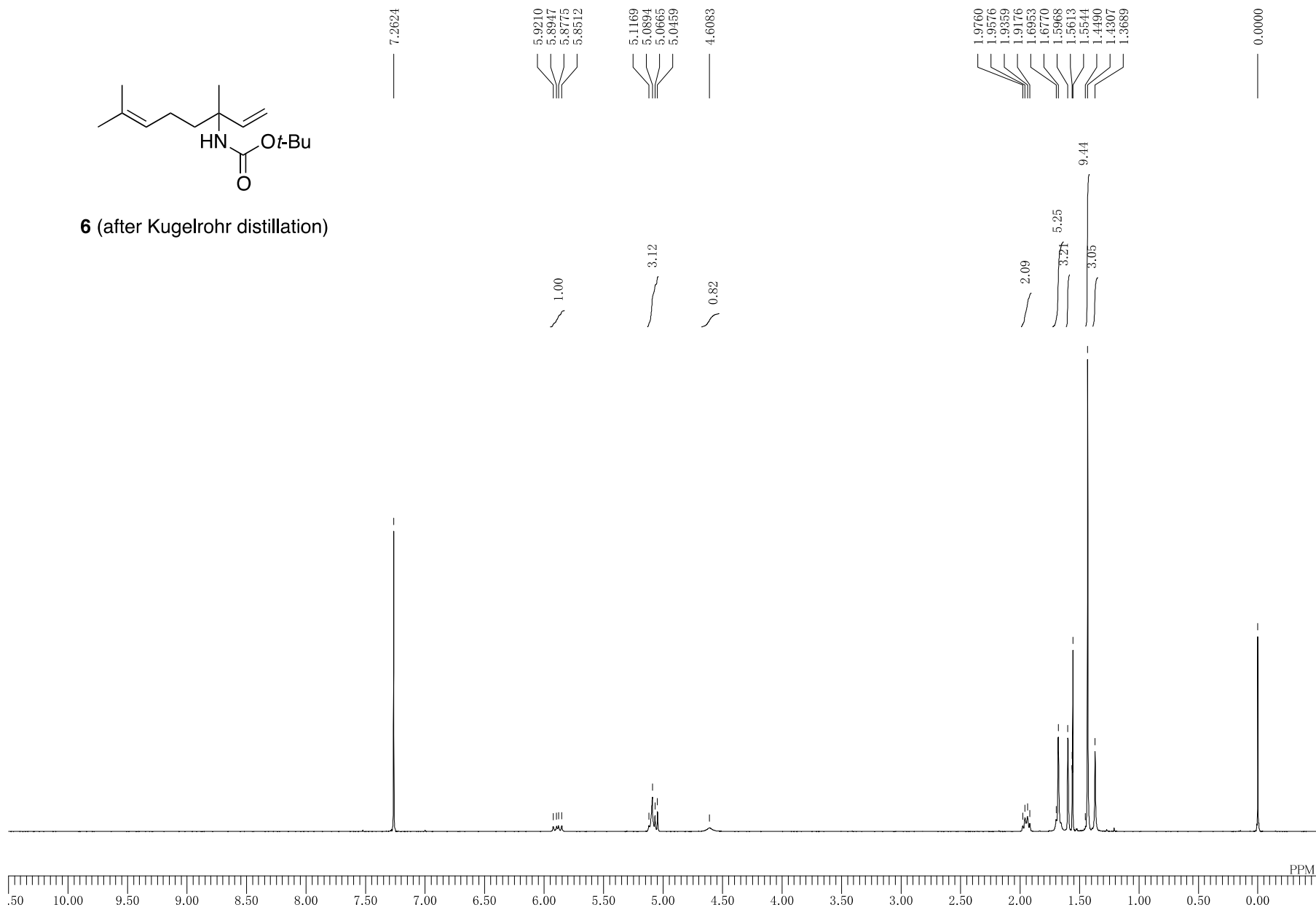


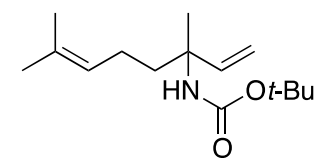
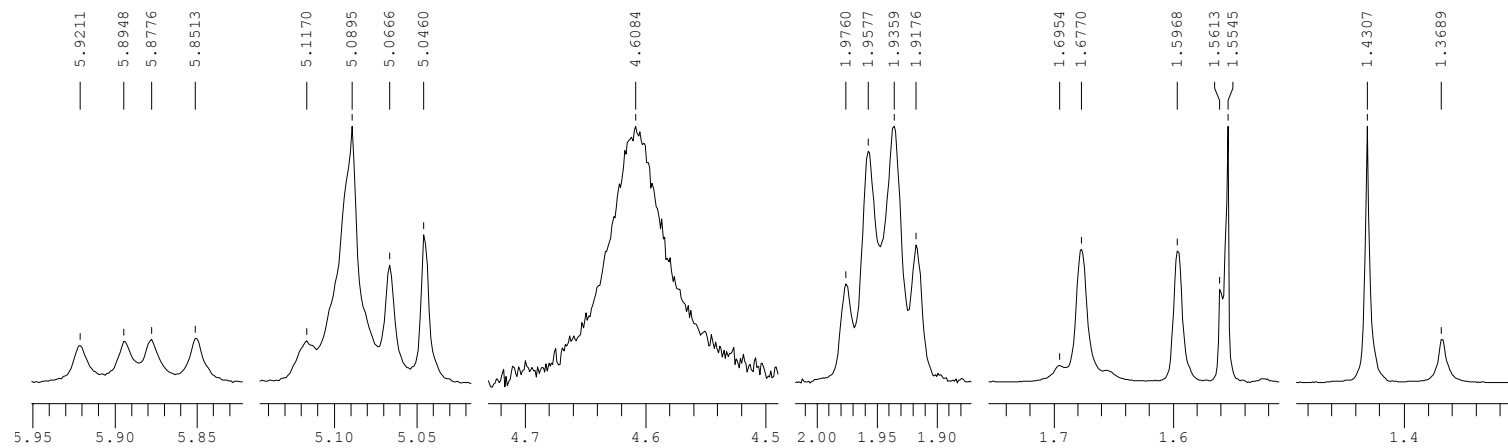
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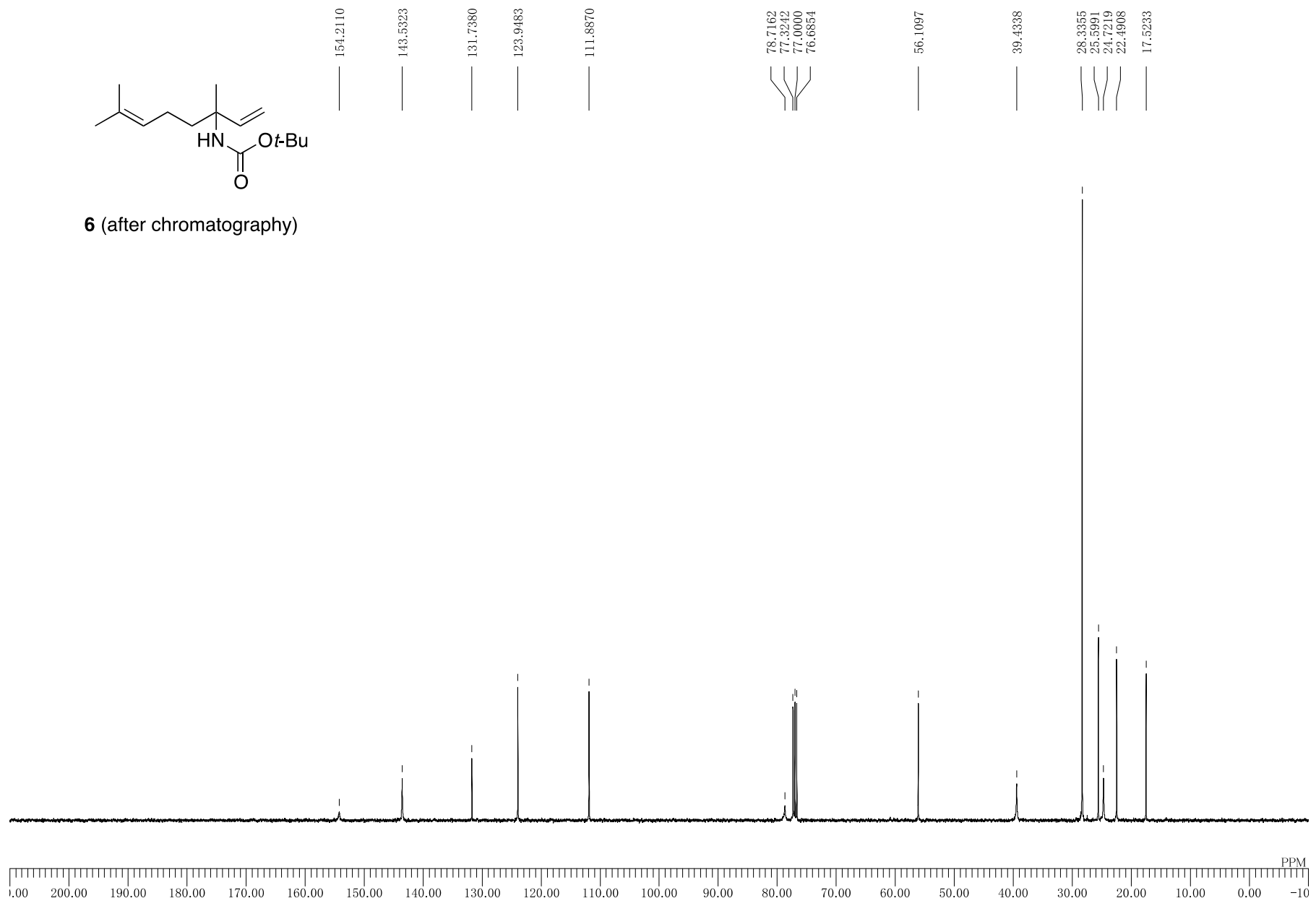




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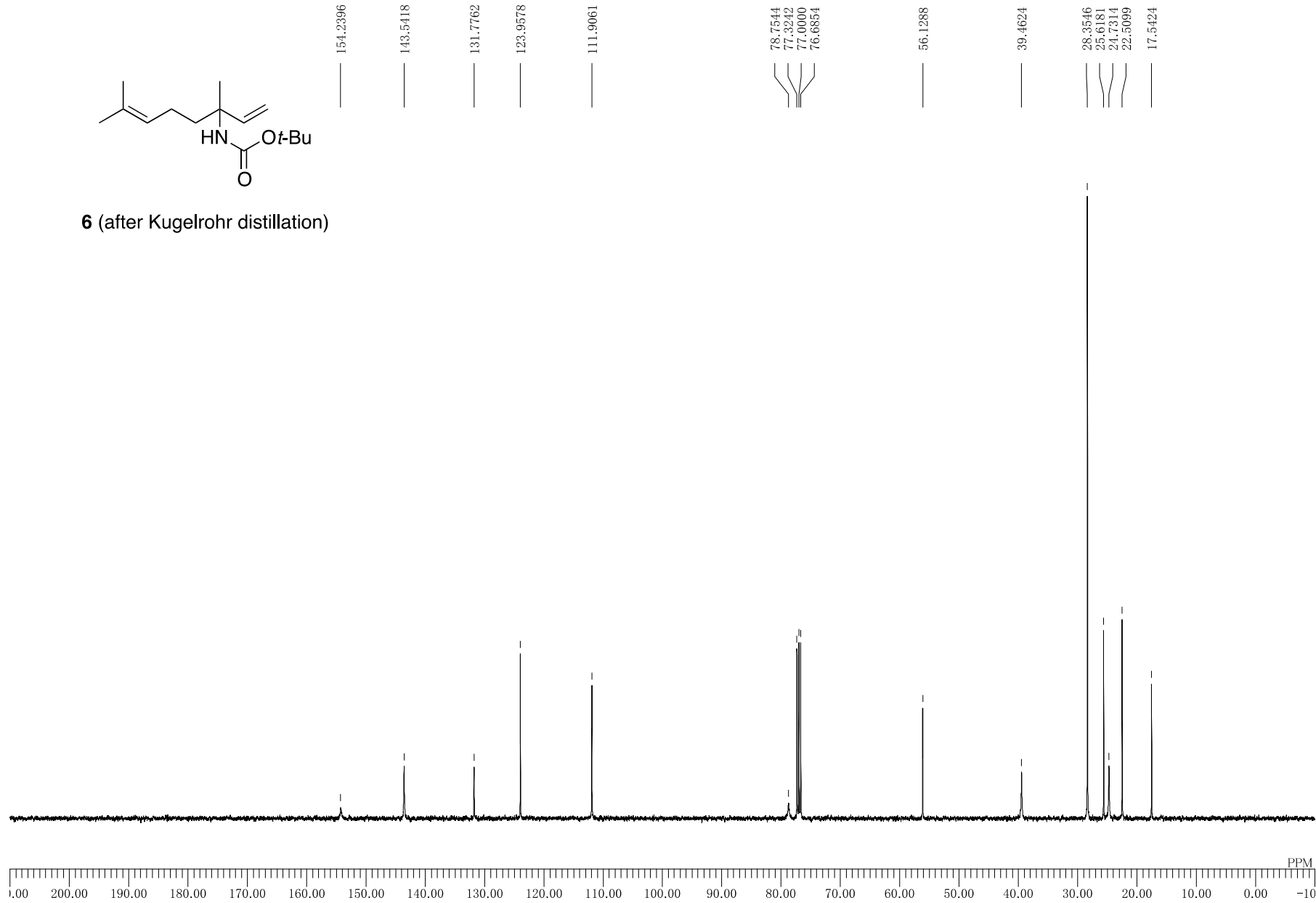


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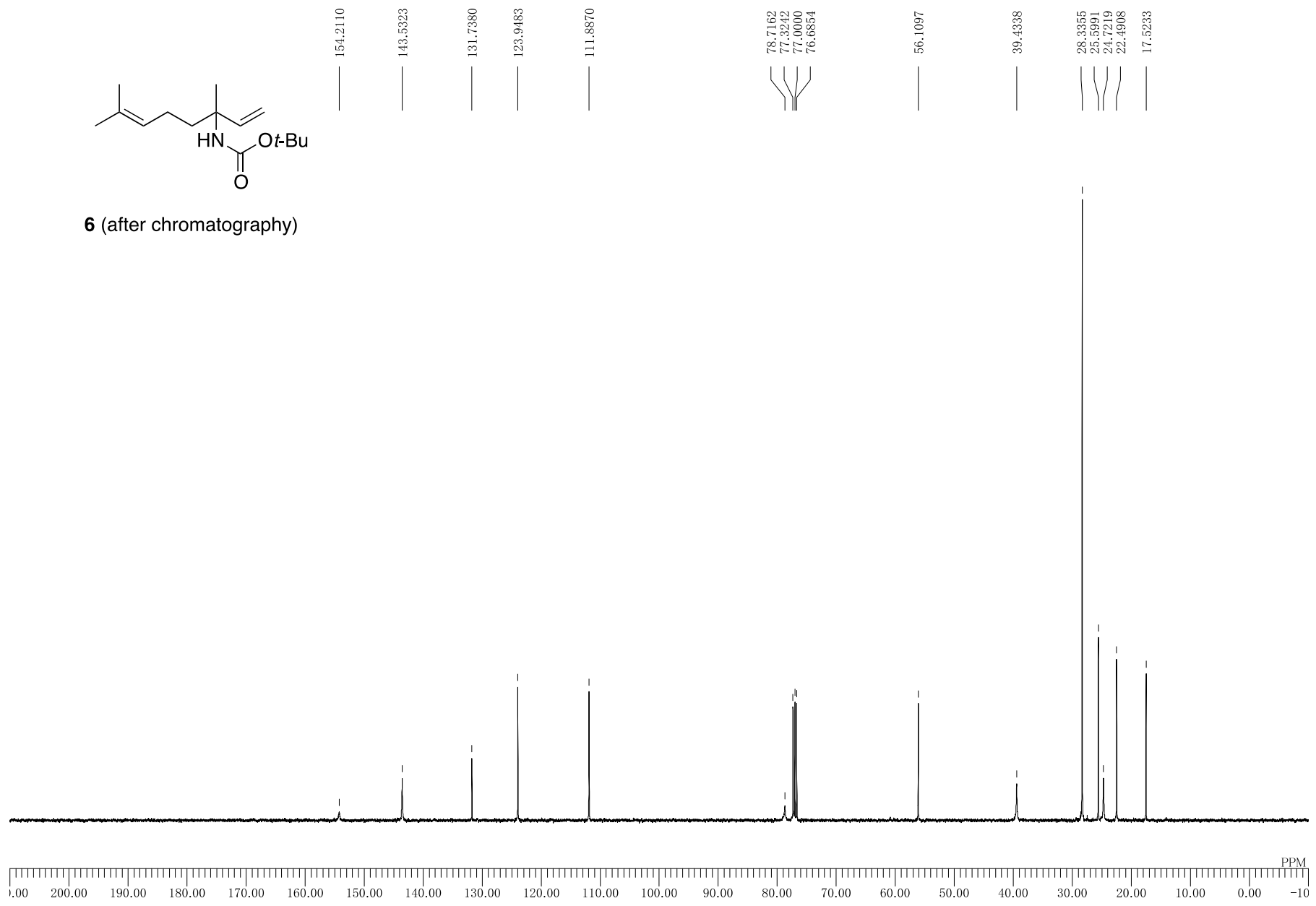
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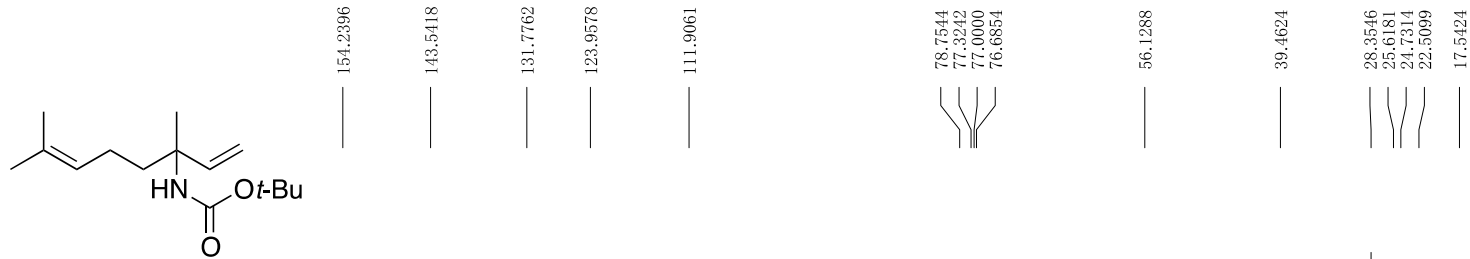






6 (after chromatography)





6 (after Kugelrohr distillation)

