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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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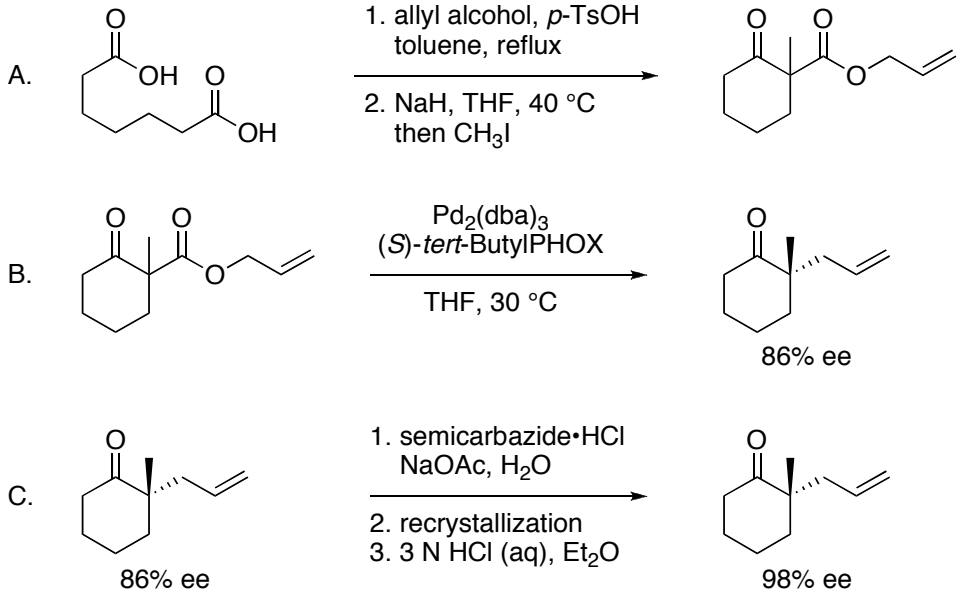
DOI:10.15227/orgsyn.086.0194

PREPARATION OF (*S*)-2-ALLYL-2-METHYLCYCLOHEXANONE
(Cyclohexanone, 2-methyl-2-(2-propen-1-yl)-, (2*S*)-)



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Checked by Christian Ebner and Andreas Pfaltz.
Discussion Addendum *Org. Synth.* **2018**, 95, 439

1. Procedure

Caution! This procedure should be carried out in an efficient fume hood due to the evolution of hydrogen gas during the reaction. Appropriate precautions should be taken to avoid inhalation or direct contact with iodomethane or allyl alcohol. The former is a known carcinogen, and the latter is a potent toxin due to its in vivo metabolism to acrolein, a known carcinogen.

A. 1-Methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester. A 500-mL, single-necked, round-bottomed flask equipped with a large magnetic stir bar (38 x 8 mm) is charged with 50.0 g of pimelic acid (313 mmol, 1.00 equiv), 156 mL of toluene, and 63.9 mL of allyl alcohol (939 mmol, 3.00 equiv) (Note 1). The mixture is stirred vigorously to create a uniform suspension, and 297 mg of *p*-toluenesulfonic acid monohydrate (1.57 mmol, 0.005 equiv) is added. A Dean–Stark trap and a water-cooled condenser with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2) are affixed to the flask, and the resulting

Org. Synth. **2009**, *86*, 194-211
Published on the Web 2/10/2009

suspension is heated to reflux (120 °C oil bath temperature). The mixture in the flask soon became homogeneous. After 16 h at reflux, approximately 11 mL of water had accrued in the Dean–Stark trap. The vessel is cooled to ambient temperature and the solution is transferred to a separatory funnel (500 mL). The organic solution is washed successively with saturated aqueous sodium bicarbonate (3 x 15 mL) and brine (2 x 15 mL) and then dried over anhydrous magnesium sulfate (6 g). After filtration through cotton, the organic solution is concentrated by rotary evaporation under vacuum (60 °C, 15 mmHg) and then the last traces of solvent are removed under high vacuum (0.15 mmHg) to yield 72.3–74.6 g of diallyl pimelate (301–311 mmol, 96–99% yield) as a slightly yellow-colored, free-flowing liquid. GC analysis indicated >99% purity (Note 3).

A flame-dried, three-necked, 1-L flask equipped with a glass stopper, a water-cooled reflux condenser with a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2), a rubber septum, and a magnetic stir bar is charged with 13.2 g of 60% sodium hydride (331 mmol, 1.10 equiv) and tetrahydrofuran (250 mL) (Note 1). The flask is immersed in a water bath (22 °C) and a solution of 72.2 g of crude diallyl pimelate (301 mmol, 1.00 equiv) in 50 mL of tetrahydrofuran is added in a steady stream via cannula during the course of 5 min. Some moderate bubbling (hydrogen evolution) of the reaction mixture is observed during the addition. Following the addition, the suspension is heated to 40 °C and then stirred for 10 h (Note 4) whereupon the reaction mixture turned to a clear, yellowish solution. Once the starting material is consumed (based on TLC, Note 5), 24.3 mL of neat iodomethane (391 mmol, 1.30 equiv) (Note 1) is added to the mixture, which became a white suspension. After an additional 15 h at 40 °C, the mixture is cooled to ambient temperature (22 °C) and water (60 mL) is added carefully via syringe over the course of 9 min to obtain a clear, yellowish solution. The mixture is transferred to a 1-L, single-necked, round-bottomed flask, the THF is removed by rotary evaporation under vacuum (40 °C, 150 mmHg) (Note 6), and the remaining solution is transferred to a separatory funnel (500 mL) and diluted with ethyl acetate (100 mL). The phases are separated and the aqueous phase is extracted with ethyl acetate (3 x 75 mL). The combined organic extracts are washed with brine (1 x 50 mL) and dried over anhydrous magnesium sulfate (5 g). After filtration through cotton, the organic solution is concentrated by rotary evaporation under vacuum (40 °C, 75 mmHg) to yield a yellow liquid. The material is purified by short-path distillation until the first drop of the

distillate turned yellow to give 52.9–53.0 g (270 mmol, 90% yield) (Note 7) of a clear, colorless liquid boiling from 69–72 °C/0.08 mmHg. GC analysis found >99% product purity (Note 8).

B. (2S)-2-Methyl-2-(2-propen-1-yl)-cyclohexanone. A flame-dried, 50-mL, conical flask equipped with a rubber septum is charged with a portion of 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester, placed under vacuum (0.06 mmHg) for 60 min to remove any dissolved gases, and then backfilled with argon. A 1-L, three-necked, round-bottomed flask is equipped with a stir bar, two rubber septa, and a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2). The apparatus is flame-dried under vacuum and backfilled with dry argon (three cycles). After cooling the flask to ambient temperature, 435 mL of anhydrous tetrahydrofuran (Notes 1 and 9) is added and the flask is immersed in a 30 °C water bath. A twelve-inch needle is inserted through one of the septa and used to bubble dry argon gas through the liquid for 30 min. The needle is removed and then 1.02 g of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 1.11 mmol, 0.0125 equiv) and 1.03 g of (*S*)-*tert*-ButylPHOX (2.67 mmol, 0.030 equiv) (Note 1) are added. The mixture immediately became opaque and took on a golden-brown color. This mixture is stirred at 30 °C for 30 min (Note 10). Subsequently, neat 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester (17.5 g, 89.03 mmol, 1.00 equiv) from the conical flask is added via syringe in a dropwise fashion to the catalyst mixture over the course of 10 min.

When the transfer is complete, the syringe is rinsed successively with two 5 mL portions of anhydrous tetrahydrofuran into the reaction mixture. Upon addition of the substrate to the catalyst mixture, the color changed to olive green. The mixture is maintained at 30–32 °C for 22–23 h (Note 11), when TLC indicated complete consumption of the starting material (Note 12). The olive green-colored mixture is then passed through a pad of silica gel (5 cm diameter x 5 cm height) and rinsed with diethyl ether (200 mL). The bright yellow filtrate is concentrated by rotary evaporation under vacuum (150 mmHg, 40 °C) (Note 13). The liquid is then transferred to a 50-mL round-bottomed flask and distilled through a short path apparatus into a receiving flask immersed in an ice water bath to provide 11.5–12.8 g (75.7–84.2 mmol, 85–95% yield) of (*S*)-2-allyl-2-methylcyclohexanone as a clear, colorless liquid boiling from 91–93 °C/16 mmHg that is analytically pure based on standard techniques (Note 14). Analysis of this material by

GC on a chiral stationary phase found 86–87% enantiomeric excess (Note 15). In a reaction that gave 85% yield after distillation, additional product was obtained by subjecting the material remaining in the distillation pot to flash chromatography on silica gel (Notes 16 and 17), which provided an additional 1.14 g of product (7.50 mmol, 8% yield), also of 86% ee, for a combined yield of 12.64 g (83.2 mmol, 93% yield) (Note 18).

C. Enrichment of (2S)-2-methyl-2-(2-propen-1-yl)-cyclohexanone via (2E)-2-[(2S)-2-methyl-2-(2-propenyl)cyclohexylidene]-hydrazinecarboxamide. Into a 250-mL, pear-shaped flask is added 5.58 g of sodium acetate (68.0 mmol, 1.00 equiv), 8.38 g of semicarbazide hydrochloride (74.8 mmol, 1.10 equiv), 75 mL of purified water (Note 1), and a large magnetic stir bar. The solution is stirred until all of the solids dissolved. At this point, 10.34 g of neat 2-allyl-2-methylcyclohexanone (68.0 mmol, 1.00 equiv) is added via syringe. When the addition is complete, a two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold (Note 2) is attached and the mixture is heated to 60 °C for 14 h (Note 19). The thick slurry is vacuum filtered (water aspirator) directly through filter paper on a porcelain Büchner funnel and rinsed with water (2 x 20 mL). The white solid is dried for 30 min on the funnel, transferred to a 250-mL round-bottomed flask, which then is immersed in a 50 °C water bath. The white solid is dried under vacuum (0.3 mmHg) until a constant mass of 12.2 g (58.3 mmol, 86% yield) is achieved (about 8 h). At this point, the semicarbazone is found to have 90–91% ee (measured by reverting to the ketone, Note 20).

A stir bar is added to the flask and the solids are suspended in 150 mL of toluene with mixing at approximately 400 rpm. After a water-cooled reflux condenser is attached to the flask, the mixture is then heated to 110 °C (bath temperature) in an oil bath. After a few minutes at this temperature, the solids dissolve completely to afford a clear colorless solution (Note 21). Heating is discontinued and the stirred mixture is allowed to cool to ambient temperature (20 °C) overnight while still immersed in the oil bath (Note 22). The cooled heterogeneous mixture is vacuum filtered (water aspirator) through filter paper on a porcelain Büchner funnel. The solids are rinsed with toluene (2 x 10 mL) and then dried on the filter for 15 min (Note 23). The solids are transferred to a 250-mL pear-shaped flask and dried under vacuum (0.3 mmHg) until a constant mass of 10.8–10.9 g (51.7–52.2 mmol, 76–77% yield, 89–90% recovery) is observed. This material is found to have

98–99% enantiomeric excess (measured by reverting to the ketone, Note 20).

A 250-mL pear-shaped flask containing a magnetic stir bar and 10.5 g of semicarbazone (50.2 mmol) and 40 mL of diethyl ether is stirred to suspend the solids. To the suspension is added 20 mL of 3 N aqueous hydrochloric acid (Note 1). No appreciable heat evolution is observed. The mixture is stirred vigorously for 3 h at ambient temperature (20 °C), at which time all of the solids had disappeared and two clear colorless phases are observed. The biphasic mixture is transferred to a 100-mL separatory funnel and the phases are separated. The aqueous phase is extracted with diethyl ether (3 x 10 mL). The combined organic layers are then washed successively with saturated sodium bicarbonate (2 x 5 mL), water (1 x 5 mL), and brine (2 x 5 mL). The organic phase is dried over anhydrous magnesium sulfate (1 g) and then filtered through cotton and concentrated by rotary evaporation under vacuum (150 mmHg, first at 20 °C, then at 40 °C to remove the last traces of solvent) to provide 7.62–7.63 g (50.1–50.2 mmol, >99% yield) of (*S*)-2-allyl-2-methylcyclohexanone of 98% ee (Notes 14 and 15). GC analysis demonstrates the product is formed in >99% product purity (Note 24).

2. Notes

1. Pimelic acid (≥99%, Fluka), allyl alcohol (≥99%, Sigma-Aldrich), *p*-toluenesulfonic acid monohydrate (ACS reagent, ≥98.5%, Sigma-Aldrich), toluene (Baker ultra resi-analyzed, J.T.Baker), solid sodium bicarbonate (tech grade, Brenntag Schweizerhall AG), magnesium sulfate (tech. grade, Brenntag Schweizerhall AG), sodium hydride (60% dispersion in mineral oil, Acros), iodomethane (Reagent Plus, 99%, Sigma-Aldrich), tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$, Strem), sodium acetate (puriss. p.a., ACS reagent, anhydrous, ≥99.0% (NT), Fluka), semicarbazide hydrochloride (99%, Alfa Aesar), and hydrochloric acid (36–38 wt%, J.T.Baker), were purchased and used as received. Checkers purchased purified water (for HPLC, Fluka), submitters used water purified with a Barnstead NANOpure Infinity UV/UF system. Ethyl acetate (tech. grade, Brenntag Schweizerhall AG) was distilled prior to use, diethyl ether (tech. grade, Brenntag Schweizerhall AG) was distilled and passed through an activated alumina column under nitrogen prior to use,[2] tetrahydrofuran (HPLC grade, Fisher) was distilled from sodium 9-fluorenone ketyl[3] or

passed through an activated alumina column under argon prior to use. The ligand (*S*)-*tert*-ButylPHOX was prepared using our accompanying procedure in *Organic Syntheses*.[4,5]

2. A two-tap Schlenk adapter connected to a bubbler and an argon/vacuum manifold is illustrated in Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Org. Synth.* **2008**, *85*, 64–71.

3. The esterification product, diallyl pimelate, may be distilled (bp 134–135 °C/0.2 mmHg), but this is not necessary for this application. Distillation of a separate sample of diallyl pimelate led to significant loss of material to unidentified polymeric byproducts formed in the distillation flask, and distillation is therefore not recommended. Product purity was measured by GC using a CE Instruments GC 8000 Top equipped with a Restek Rtx-1701 column (30.0 m x 0.25 mm) and a flame ionization detector using a method of 100 °C isothermal for 5 min, then ramp 13 °C/min to 240 °C, then 240 °C isothermal for 5 min with 60 kPa He carrier gas flow. The retention time for the product was 17.85 min. No further signals were observed by the checkers, and therefore a product purity of 98% was assigned with >99% yield. Submitters reported observation of a predominant but unidentified impurity with slightly shorter retention time than the product. The product exhibited the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33–1.40 (m, 2 H), 1.66 (apparent quintet, J = 7.7 Hz, 4 H), 2.34 (t, J = 7.6 Hz, 4 H), 4.57 (apparent dt, J = 5.7, 1.4 Hz, 4 H), 5.23 (apparent dq, J = 10.4, 1.3 Hz, 2 H), 5.30 (apparent dq, J = 17.2, 1.5 Hz, 2 H), 5.91 (ddt, J = 17.2, 10.4, 5.7 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 24.7, 28.7, 34.1, 65.1, 118.3, 132.4, 173.3; IR (neat film, NaCl) 3086, 3025, 2942, 2866, 1733, 1648, 1456, 1421, 1378, 1272, 1173, 1086, 991, 932, 734 cm^{-1}; MS (FAB, NBA) *m/z* (%) 242 (11), 241 (100, $[M+H]^+$), 183 (85), 137 (31), 136 (14), 125 (53), 77 (10), 69 (12), 41 (59), 39 (12); HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_4$ $[M]^+$: 240.1362, found 240.1355; TLC (Hex/EtOAc = 4:1) R_f = 0.46. Anal calcd for $C_{13}H_{20}O_4$: C 64.98, H 8.39, found C 65.28, H 8.38.

4. Submitters reported 7 h at 22 °C and an additional 4 h at 40 °C until all starting material was consumed. After this time the checkers did not observe full conversion by TLC analysis using the TLC method described in Note 5.

5. The progression of the cyclization may be monitored by TLC analysis using 20% ethyl acetate in hexanes as eluent with $KMnO_4$ staining (submitters used *p*-anisaldehyde staining): R_f diallyl pimelate = 0.46, R_f

cyclized intermediate = 0.58–0.77 (broad, also UV active), R_f alkylation product = 0.56. The detection of diallyl pimelate is often obscured by the cyclized intermediate.

6. Following the submitters' procedure, THF was not removed before diluting with ethyl acetate. In the checkers' hands no phase separation took place under these conditions.

7. Submitters reported 67% yield and 92% purity.

8. Using the GC method described in Note 3, 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester has a retention time of 14.77 min. The distilled material contains a small amount (<1% by GC) of uncyclized pimelate and <1% of an unidentified byproduct (retention time of 14.61 min). Submitters report observation of 6% of uncyclized diallyl pimelate and 2% of unidentified byproduct, which does not significantly affect the subsequent step. Out of this mixture analytically pure material may be obtained by flash chromatography on silica gel using a gradient of 1.5 → 4% diethyl ether in hexanes as eluent. GC response factors between 1-methyl-2-oxo-cyclohexanecarboxylic acid 2-propenyl ester and diallyl pimelate were determined with purified products to confirm these ratios, however assuming a 1:1 response factor gave the same ratios. The product showed the following characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (s, 3 H), 1.43–1.50 (m, 1 H), 1.59–1.78 (m, 3 H), 1.98–2.05 (m, 1 H), 2.42–2.54 (m, 3 H), 4.58–4.66 (m, 2 H), 5.24 (dd, *J* = 10.4, 0.8 Hz, 1 H), 5.31 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.83–5.93 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.4, 22.7, 27.6, 38.3, 40.8, 57.3, 65.9, 119.0, 131.6, 172.9, 208.2; IR (neat film, NaCl) 3442, 3082, 2939, 2866, 1719, 1648, 1452, 1377, 1336, 1301, 1259, 1212, 1160, 1121, 1084, 1062, 1038, 977, 936, 854, 816, 767, 668, 599 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 196 (26, $[M]^+$), 168 (18), 139 (12), 138 (23), 137 (26), 127 (44), 111 (27), 110 (14), 109 (48), 83 (30), 82 (23), 81 (100), 69 (34), 67 (16), 55 (56), 43 (22), 41 (85), 39 (24); HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096; TLC (Hex/EtOAc = 4:1) R_f = 0.56. Anal calcd for $C_{11}H_{16}O_3$: C 67.32, H 8.22, found C 67.17, H 8.15.

9. The substrate concentration (0.2 M) described herein yields product of slightly lower enantiomeric excess (about 1% lower) than the previously reported, optimized conditions (0.033 M in substrate). For smaller scale where overall quantity of solvent is less important, the lower substrate concentration is recommended.

10. The complexation time prior to adding substrate is important to the overall reaction. Shorter or longer complexation times led to lower product yield and incomplete substrate conversion.

11. Submitters reported 26 h reaction time.

12. Although the reaction produces an equivalent of carbon dioxide, the evolution of this byproduct is not visually apparent during the reaction. The reaction is readily evaluated by TLC analysis using 10% diethyl ether in pentane as eluent with $KMnO_4$ staining (submitters used *p*-anisaldehyde staining): R_f dibenzylideneacetone = 0.24 (also UV active), R_f β-ketoester = 0.33, R_f product = 0.46.

13. Care should be taken to ensure that the moderately volatile product is not lost during concentration of the filtrate. However, if a substantial amount of solvent remains, distillation of the product does not occur smoothly. At 150 mmHg and 40 °C, tetrahydrofuran and diethyl ether are easily removed and product is not lost.

14. The distilled material showed the following analytical data: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.54–1.61 (m, 1 H), 1.65–1.90 (m, 5 H), 2.23 (apparent ddt, *J* = 13.9, 7.3, 0.9 Hz, 1 H), 2.33–2.40 (m, 3 H), 5.01–5.06 (m, 2 H), 5.69 (apparent ddt, *J* = 16.6, 11.1, 7.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.2, 22.8, 27.5, 38.7, 38.9, 42.1, 48.6, 118.0, 133.9, 215.5; IR (neat film, NaCl) 3393, 3076, 2933, 2864, 1706, 1451, 1124, 995, 913 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 152 (31, $[M]^+$), 137 (36), 123 (29), 109 (60), 108 (27), 95 (33), 94 (21), 93 (69), 83 (49), 82 (16), 81 (31), 79 (21), 69 (14), 68 (17), 67 (66), 55 (100), 53 (13), 41 (50), 39 (25); HRMS (EI) *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; TLC (Pentane/Et_2O = 9:1) R_f = 0.46. Anal calcd for $C_{10}H_{16}O$: C 78.90, H 10.59, found C 78.86, H 10.48; optical rotation following enrichment (Part C): $[\alpha]_D^{21.0}$ –47.0 (*c* 2.30, dichloromethane, 98% ee).

15. GC analyses were performed with a Fisons Instruments HRGC Mega2 series equipped with a Chiraldex G-TA column (30.0 m x 0.25 mm) and a flame ionization detector. The assay conditions for 2-allyl-2-methylcyclohexanone are 100 °C isothermal, 60 kPa H_2 carrier gas flow, retention times: major (*S*) enantiomer = 14.15 min, minor (*R*) enantiomer = 17.09 min. The absolute configuration was established by X-ray crystallographic analysis of a semicarbazone derivative bearing a substituent with known absolute configuration.[6]

16. Column chromatography: 5 cm diameter x 10 cm height, eluting with 10% diethyl ether in pentane, 100 mL forerun, collecting 30 mL

fractions. Product appeared in fractions 9–20. See Note 12 for TLC conditions. For smaller scale preparations, it is often convenient to perform chromatography directly rather than distilling the product.

17. In the reaction that gave 95% yield after distillation, TLC (see Note 12) of the distillation residue showed only traces of product. Therefore no flash chromatography was performed.

18. Submitters reported 76% yield after distillation and an additional 11% from flash chromatography for an overall yield of 87%.

19. Semicarbazone formation begins before the addition of ketone is complete, although conversion at room temperature is sluggish.

20. To ensure an accurate ee value, the powder was mixed thoroughly prior to measurement. The enantiomeric excess was determined by suspending a small amount of semicarbazone (approximately 10 mg) in a biphasic mixture of diethyl ether (1 mL) and 2 N aqueous hydrochloric acid (1 mL) at ambient temperature. After 30 min of stirring, all of the solids had dissolved and the organic layer was separated, dried briefly over anhydrous magnesium sulfate, filtered through cotton, and the filtrate concentrated by rotary evaporation. The residue was then dissolved in *tert*-butyl methyl ether and analyzed by GC (see Note 15 for separation conditions). The semicarbazone was homogeneous according to the proton and carbon NMR spectra, and appears to be a single geometric isomer. However a correct elemental analysis could not be achieved. The following properties were observed: mp 190–191 °C (toluene, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 3 H), 1.41–1.48 (m, 1 H), 1.53–1.71 (m, 5 H), 2.14–2.25 (m, 2 H), 2.32–2.39 (m, 2 H), 5.00 (apparent d, J = 3.5 Hz, 1 H), 5.03 (s, 1 H), 5.68–5.9 (m, 1 H), 8.29 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.2, 22.9, 24.7, 26.1, 38.7, 41.6, 43.1, 117.3, 134.9, 157.3, 158.7; IR (neat film, NaCl) 3465, 3243, 3198, 3074, 2967, 2860, 1695, 1665, 1567, 1477, 1374, 1111, 1078, 991, 909 cm^{-1}; MS (EI, 70 eV) *m/z* (%) 209 (35, $[M]^+$), 194 (44), 168 (15), 165 (100), 151 (33), 150 (70), 149 (23), 148 (10), 135 (48), 134 (28), 125 (95), 108 (36), 107 (15), 98 (35), 96 (21), 95 (18), 93 (33), 91 (18), 82 (12), 81 (63), 80 (14), 79 (30), 77 (12), 67 (42), 55 (30), 53 (17), 44 (11), 41 (48), 39 (14); HRMS (CI, CH_4) *m/z* calc'd for $C_{11}H_{20}N_3O$ $[M + H]^+$: 210.1606, found 210.1599; $[\alpha]_D^{21.0}$ –50.5 (*c* 1.91, methanol, 98% ee).

21. At the reported concentration, the hot toluene solution is not saturated. The additional solvent helps maintain efficient stirring as the crystallization progresses and the viscosity of the mixture increases. The

additional solvent does not significantly affect the efficiency of product recovery.

22. Stirring during the crystallization process is very important to the efficiency of the ee improvement. For example, two separate 300 mg portions of semicarbazone with 89% ee were recrystallized from hot toluene (about 3 mL) with and without stirring. Although product recovery was comparable for either procedure (81% and 80%, respectively), the unstirred crystallization provided semicarbazone of 93% ee while the stirred crystallization provided semicarbazone of 96% ee. Either procedure yields the product as very fine needles.

23. Concentration of the filtrate by rotary evaporation provided an additional 1.24–1.32 g (10–11% recovery) of semicarbazone. GC analysis of the corresponding ketone found 20–26% ee for this material (see Note 20).

24. Using the GC method described in Note 3, 2-allyl-2-methylcyclohexanone has a retention time of 11.43 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

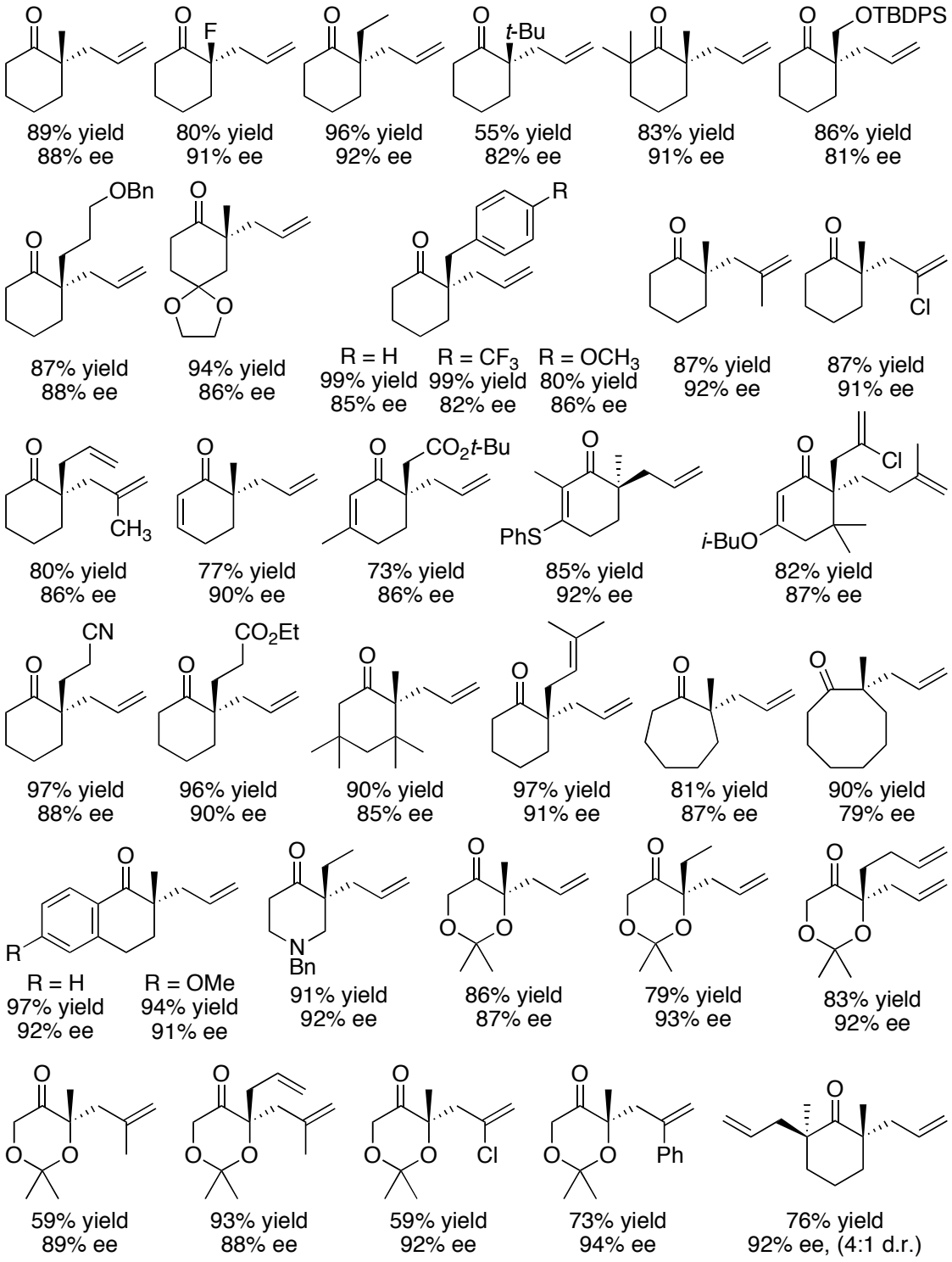
The Dieckmann cyclization protocol employed here is a modification of a similar procedures developed by Tsuji and coworkers[7] and Fuchs and coworkers.[8] This improved procedure allows preparation of racemic allyl β-keto ester substrates in two steps with a single purification. Importantly, the single-pot cyclization/alkylation is an improvement over our previously reported method that required solvent exchange.[9] The Dieckmann protocol is useful for the preparation of a number of substituted allyl β-keto esters by varying the electrophile. Possible substituents include alkyl, benzyl, substituted benzyl, and alkenyl.[9] Other more sensitive substituents may be introduced by quenching the intermediate β-keto ester enolate with aqueous acid and then alkylating the resulting β-keto ester under more mild conditions (e.g., K_2CO_3, acetone, 50 °C).[9] In this manner, the β-keto ester enolate may undergo conjugate addition, aldol, or fluorination reactions with appropriate electrophilic components.[9] The β-keto ester substrates are useful

not only for enantioselective decarboxylative allylation, but also for enantioselective decarboxylative protonation reactions generating α-tertiary cycloalkanones.[10] Alternative methods for synthesis of β-keto ester substrates include acylation of ketones with diallyl carbonates,[9] allyl cyanoformates,[9,11] allyl chloroformates,[12] or allyl 1*H*-imidazole-1-carboxylates.[13]

The enantioselective decarboxylative allylation method from allyl β-keto esters,[9,14] based on non-enantioselective transformations pioneered by Tsuji and Saegusa,[15] represents a substantial advance in asymmetric allylation since prior methods[16] required that the putative prochiral enolate intermediate[17] be stabilized by an electron-withdrawing group (e.g., esters or aryl groups) or contain only a single acidic site.[18,19] To highlight the previous deficiency in the literature, 2-allyl-2-methylcyclohexanone had not been prepared in high enantiomeric excess prior to our work since few alternative synthetic methods are available.[20] Related enantioselective transformations for the conversion of allyl enol carbonates and silyl enol ethers to α-quaternary cycloalkanones, also based on earlier work by Tsuji,[21] have been developed by our group[6,22] and others.[23] However, β-keto ester substrates are often preferable due to the straightforward synthesis and ease of substrate handling. The procedure reported herein has been optimized for large-scale preparation and features lower catalyst loading and higher substrate concentration than our previously reported work. These changes have minimal impact on the efficiency and selectivity observed in the reaction. Improvements to purification include conditions for distillation of the product and an improved protocol for conversion to the corresponding semicarbazone derivative. Conditions for recrystallization of the semicarbazone derivative are also reported, and provide access to highly enantioenriched 2-allyl-2-methylcyclohexanone.

The scope of this transformation[9] and the related transformation of allyl enol carbonates and enol silanes[6,22] has been demonstrated to include alkyl, alkenyl, aryl, ethereal, siloxy, halogen,[24] ketone, ester, and nitrile substituents. Additionally, the ring may be appended, unsaturated, enlarged, or substituted with heteroatoms. The delivered allyl group may be substituted at the internal position. Cascade allylation has also been performed to generate two quaternary stereocenters. Good levels of enantioselectivity are observed throughout these variations and products may be obtained in 55–99% yield and 80–94% ee (Table 1).[6,9,22]

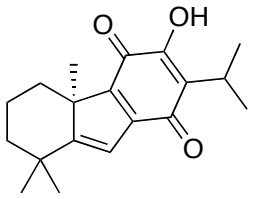
Table 1. Ketones prepared via enantioselective decarboxylative allylation.[6,9,22]



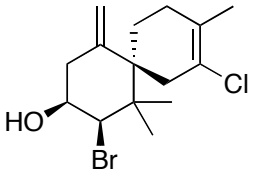
The non-enantioselective Tsuji allylation reaction has been used sparingly in total synthesis efforts.[25] Since the development of asymmetric variants, however, enantioselective decarboxylative allylation has functioned as a key asymmetric step in the synthesis of the natural products (+)-

dichroanone,[26] (+)-elatol,[27] (+)-laurencenone B,[27] (–)-cyanthiwigin F,[28] (+)-carissone,[29] and (+)-cassiol[30] as well as in an approach to the natural product zoanthenol[31] (Table 2). Other useful transformations of the product (*S*)-2-allyl-2-methyl cyclohexanone include elaboration to various [6.5]- and [6.6]-fused bicycles and oxidation to a caprolactone derivative (Table 3a).[6] Spirocyclic systems are accessible by employing Grubbs' olefin metathesis catalysts[32] with α,ω-dienes[18,22,27] (Table 3b). Dioxanone products may be cleaved to access acyclic keto diols and α-hydroxy esters (Table 3c).

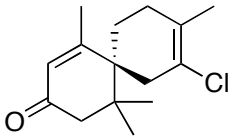
Table 2. Synthetic targets accessed via enantioselective decarboxylative allylation.



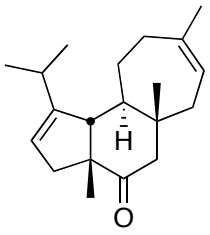
(+)-Dichroanone



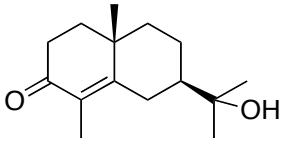
(+)-Elatol



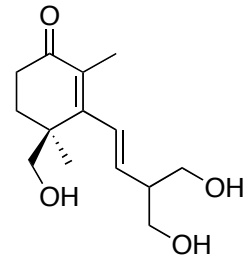
(+)-Laurencenone B



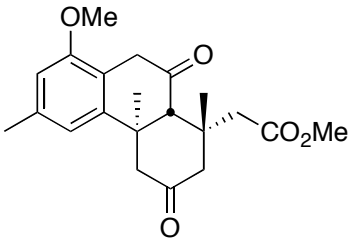
(–)-Cyanthiwigin F



(+)-Carissone

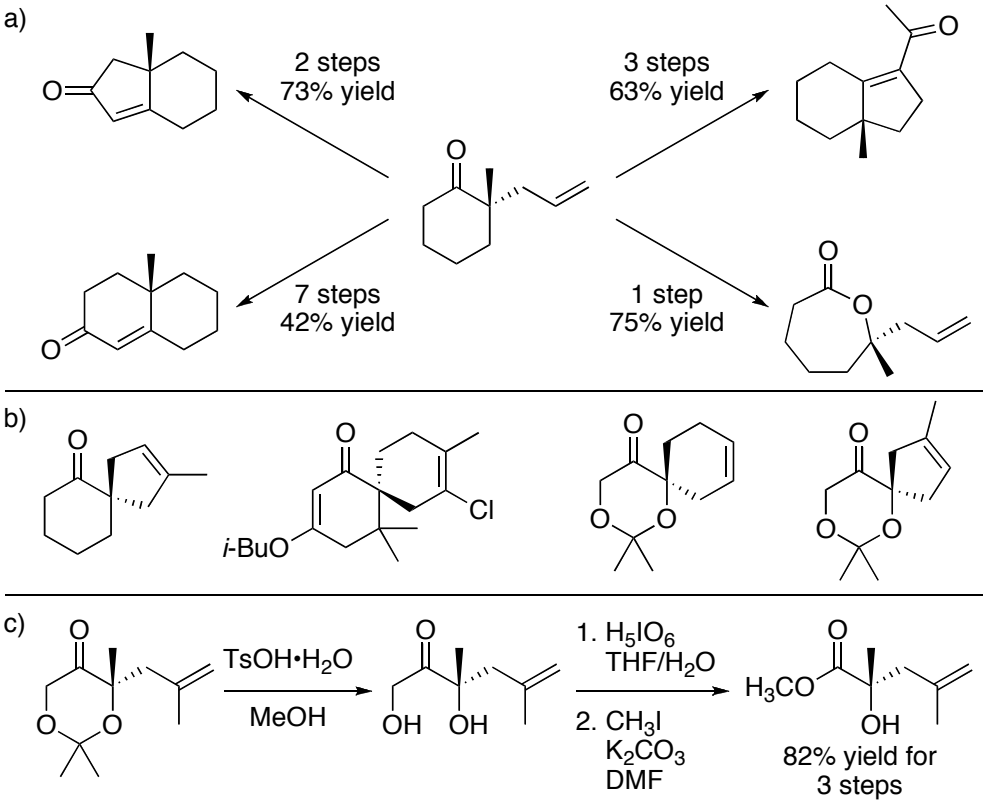


(+)-Cassiol



ABC ring system of Zoanthenol

Table 3. (a) Derivatives of 2-allyl-2-methylcyclohexanone.[6] (b) Spirocycles accessible via ring-closing metathesis.[18,22,27] (c) Cleavage of dioxanones to access acyclic products.[22]



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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

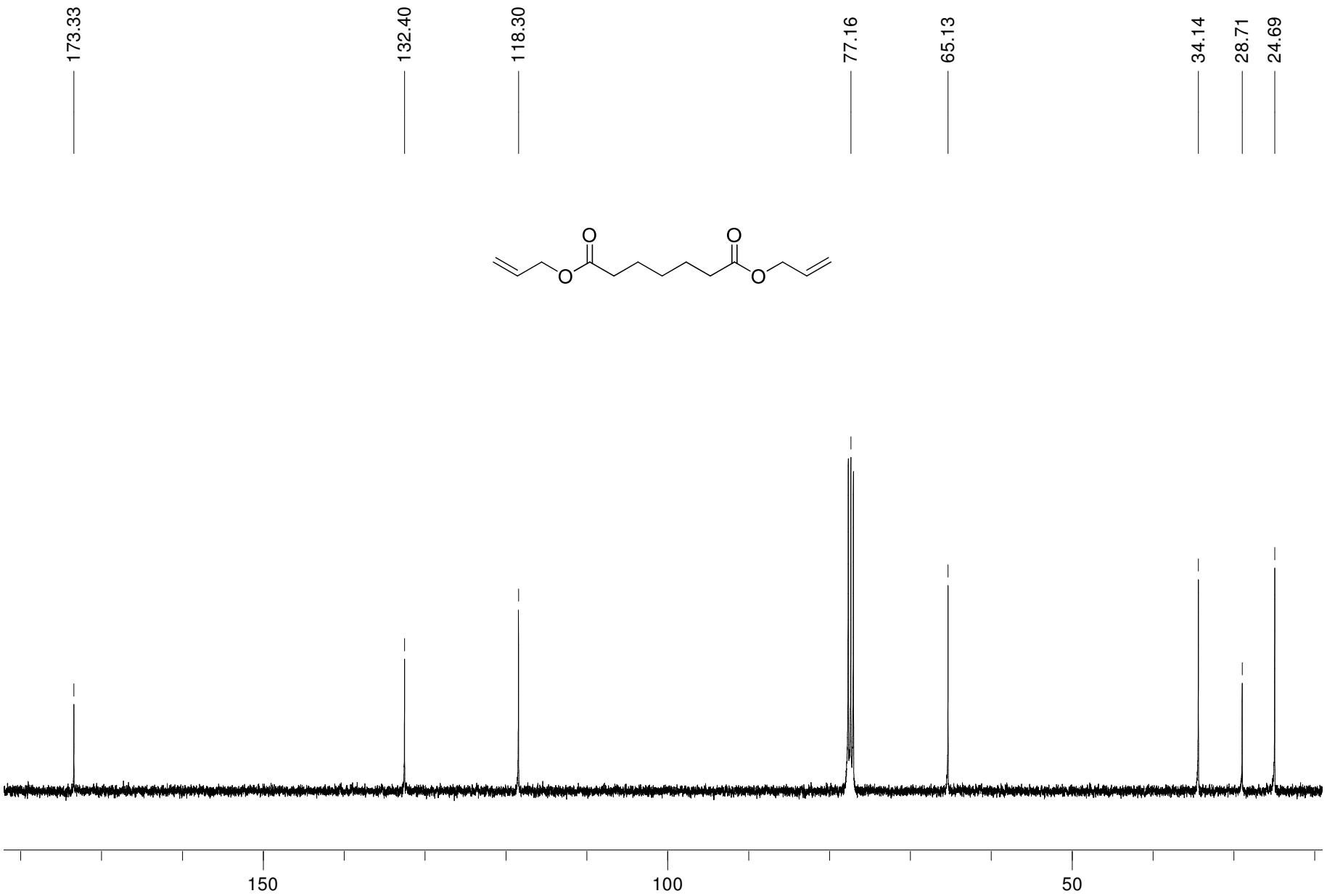
Pimelic acid: Heptanedioic acid; (111-16-0)
Allyl alcohol: 2-Propen-1-ol; (107-18-6)
p-Toluenesulfonic acid monohydrate: Benzenesulfonic acid, 4-methyl-, hydrate (1:1); (6192-52-5)
Diallyl pimelate: Pimelic acid, diallyl ester; (91906-66-0)
Sodium hydride; (7646-69-7)
Iodomethane: Methane, iodo-; (74-88-4)
Allyl 1-methyl-2-oxocyclohexanecarboxylate: Cyclohexanecarboxylic acid, 1-methyl-2-oxo-, 2-propenyl ester; (7770-41-4)
Tris(dibenzylideneacetone) dipalladium(0): Palladium, tris[μ-[(1,2-η:4,5-η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-; (51364-51-3)
(*S*)-*tert*-ButylPHOX: Oxazole, 4-(1,1-dimethylethyl)-2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-, (4*S*)-; (148461-16-9)
(*S*)-2-Allyl-2-methylcyclohexanone: Cyclohexanone, 2-methyl-2-(2-propen-1-yl)-, (2S)-; (812639-07-9)
Sodium acetate: Acetic acid, sodium salt (1:1); (127-09-3)
Semicarbazide hydrochloride: Hydrazinecarboxamide, hydrochloride (1:1); (563-41-7)
(*S*)-2-(2-Allyl-2-methylcyclohexylidene)hydrazinecarboxamide: Hydrazinecarboxamide, 2-[(2*S*)-2-methyl-2-(2-propenyl)cyclohexylidene]-, (2*E*)-; (812639-25-1)

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the labs of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey labs he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry and a KAUST GRP Investigator. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

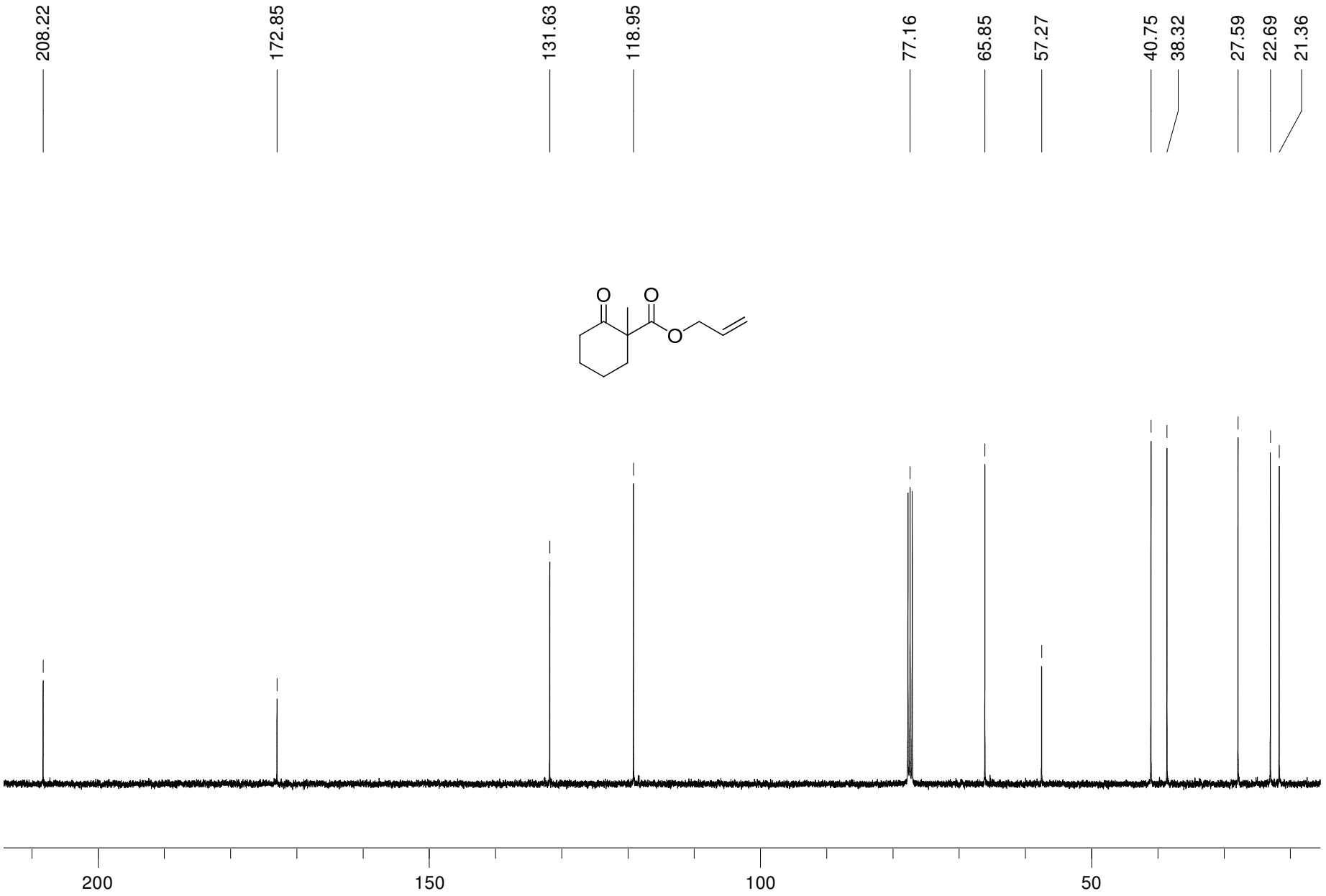
Justin T. Mohr received his A.B. degree in chemistry in 2003 from Dartmouth College where he conducted research with Professor Gordon W. Gribble. He joined the laboratories of Professor Brian M. Stoltz at Caltech in 2003 where he has pursued Ph.D. studies as a Lilly fellow. His research interests include the development of enantioselective reactions and applications in natural product total synthesis.

Michael R. Krout received his B.S. degree in biochemistry from the Indiana University of Pennsylvania in 2002. He then worked in the medicinal chemistry department at Merck Research Laboratories in West Point, PA, where he was involved in the development of non-steroidal selective androgen receptor modulators aimed toward the treatment of osteoporosis. In the fall of 2003, he joined the lab of Professor Brian Stoltz at Caltech where he has worked toward his Ph.D. as a Lilly fellow. His research interests include the development of catalytic, asymmetric methods and their utility in natural product total synthesis.

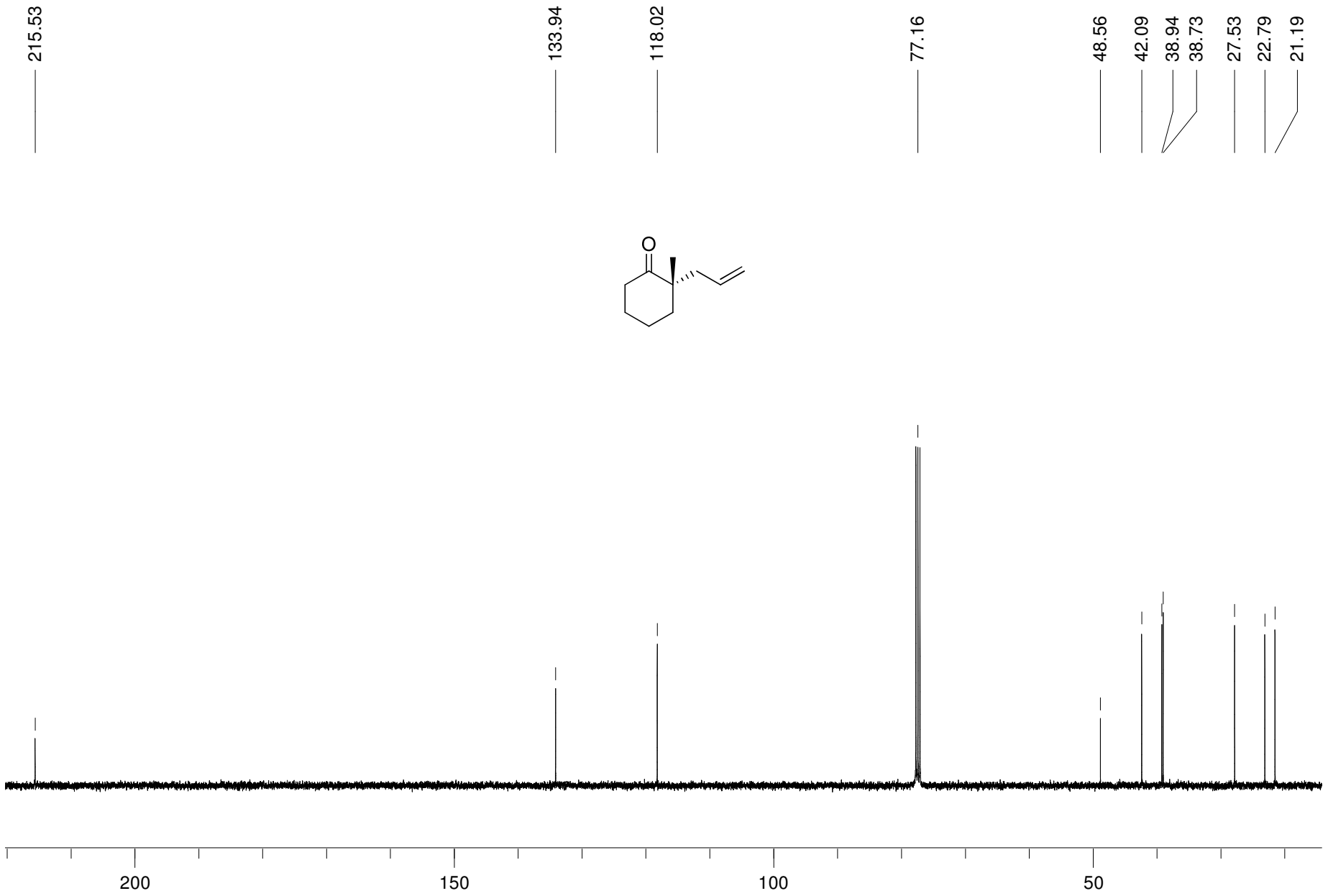
Christian Ebner was born in Mönchengladbach (Germany) in 1984 and did his chemistry studies at the University of Basel (Switzerland). In 2008 he obtained his M.Sc. degree under the supervision of Prof. Andreas Pfaltz, whose group he joined as a Ph.D. student in May 2008. His current work deals with the synthesis of new ligands and the development of a new screening method for palladium-catalyzed reactions.



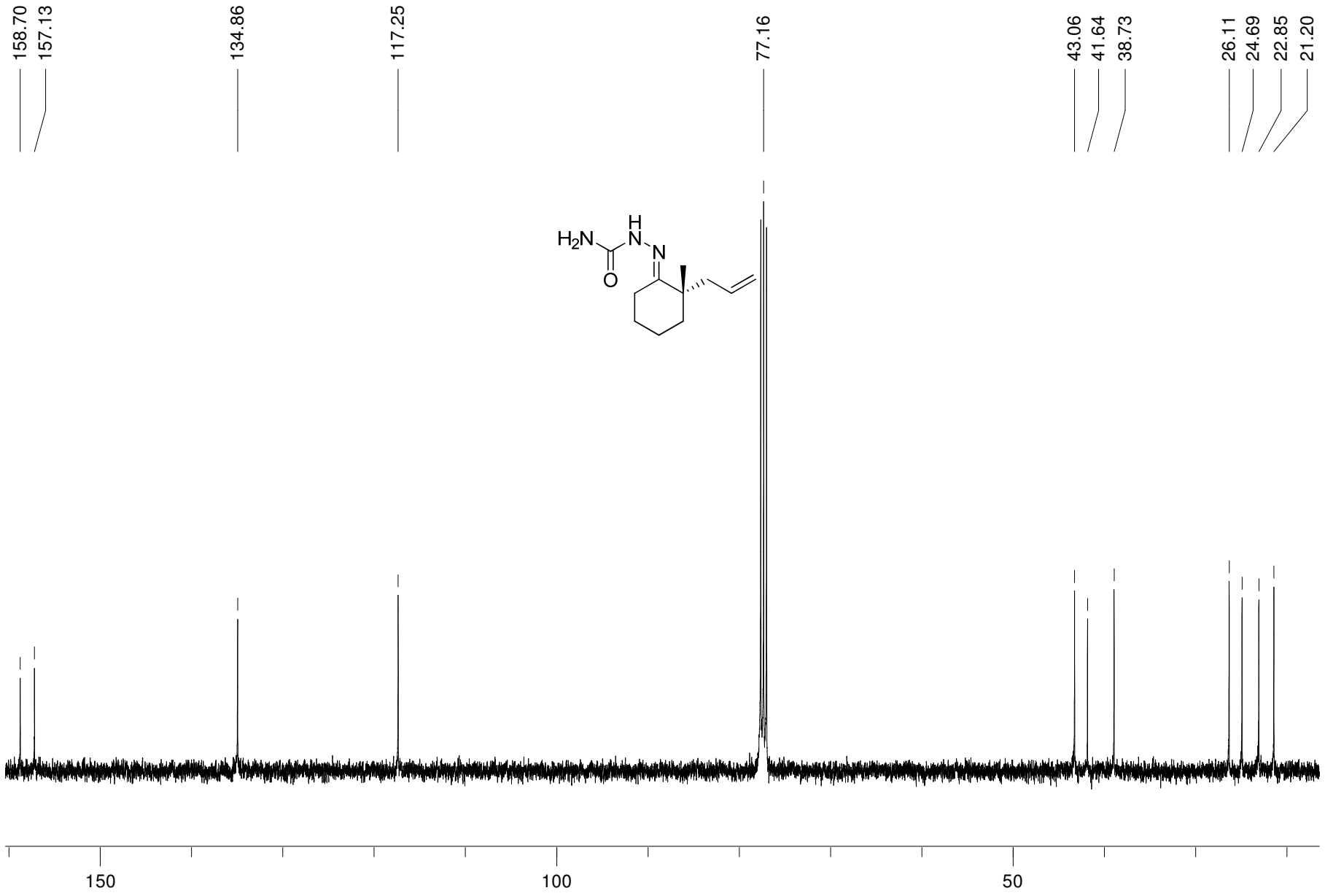
^{13}C NMR Spectrum of diallyl pimelate (101 MHz, $CDCl_3$)



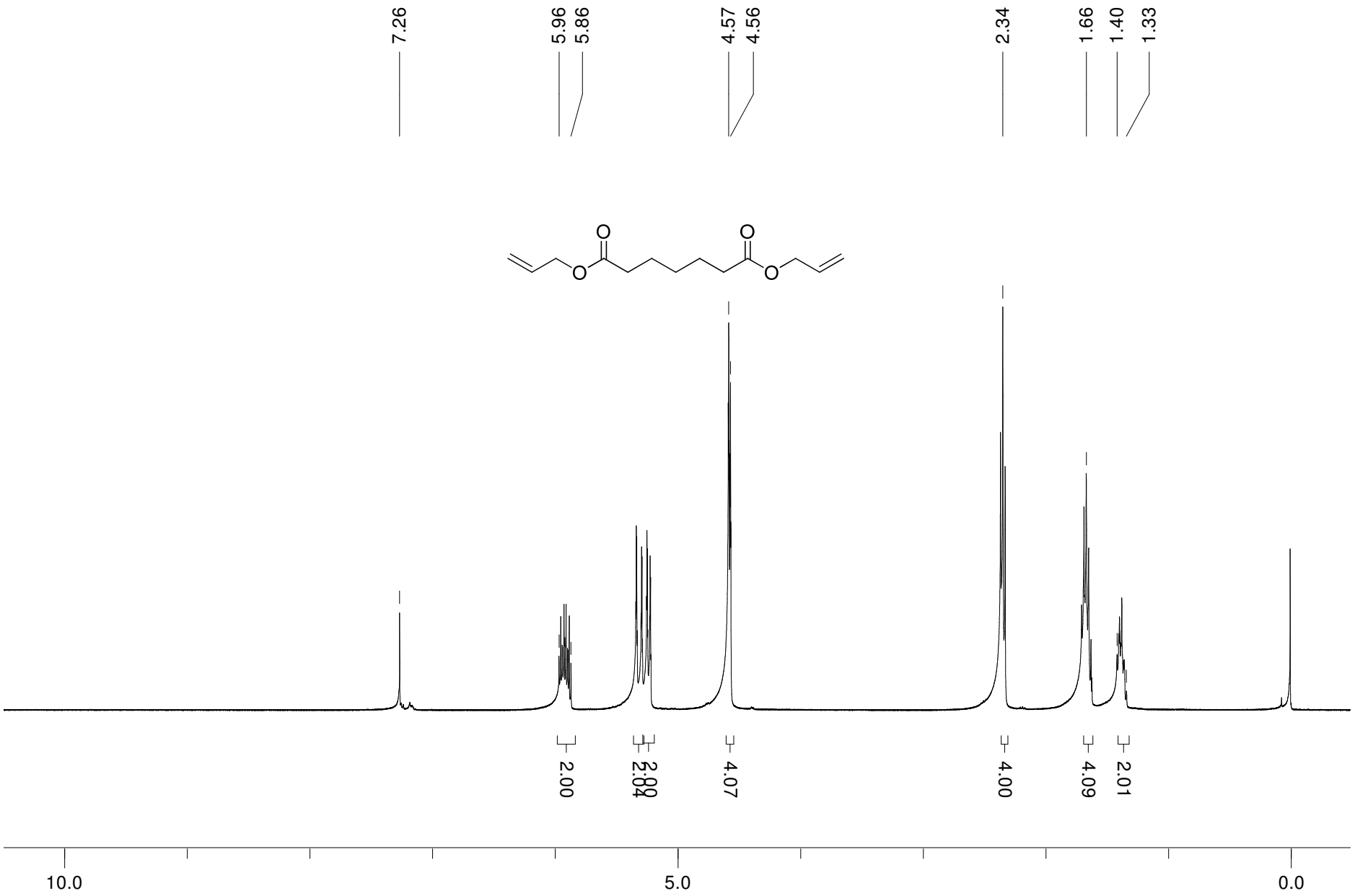
^{13}C NMR Spectrum of 1Methyl-2-oxo-Cyclohexanecarboxylic acid 2-propenyl ester (101 MHz, $CDCl_3$)



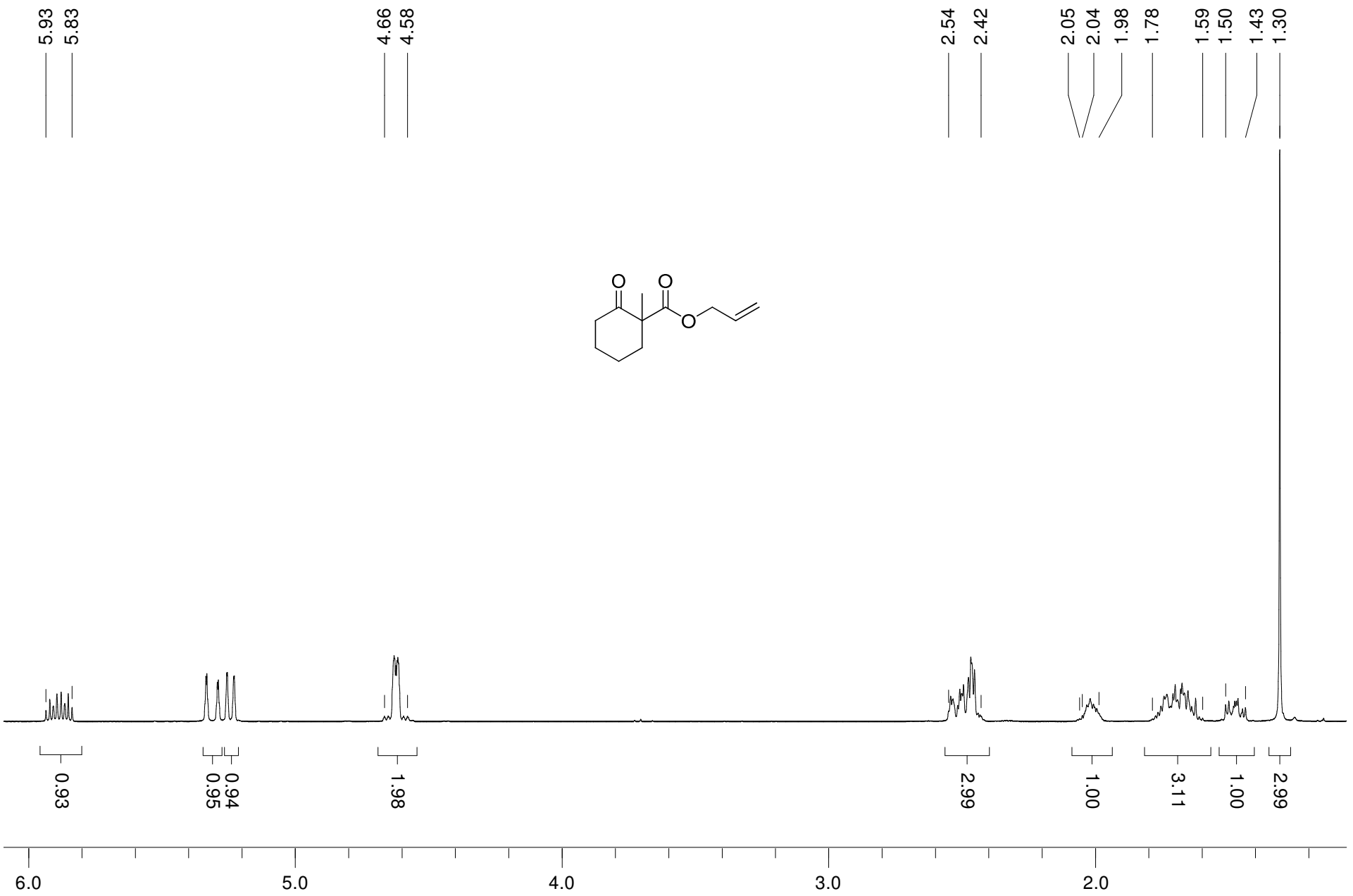
^{13}C NMR Spectrum of (2*S*)-2-Methyl-2-(2-propen-1-yl)-cyclohexanone (101 MHz, $CDCl_3$)



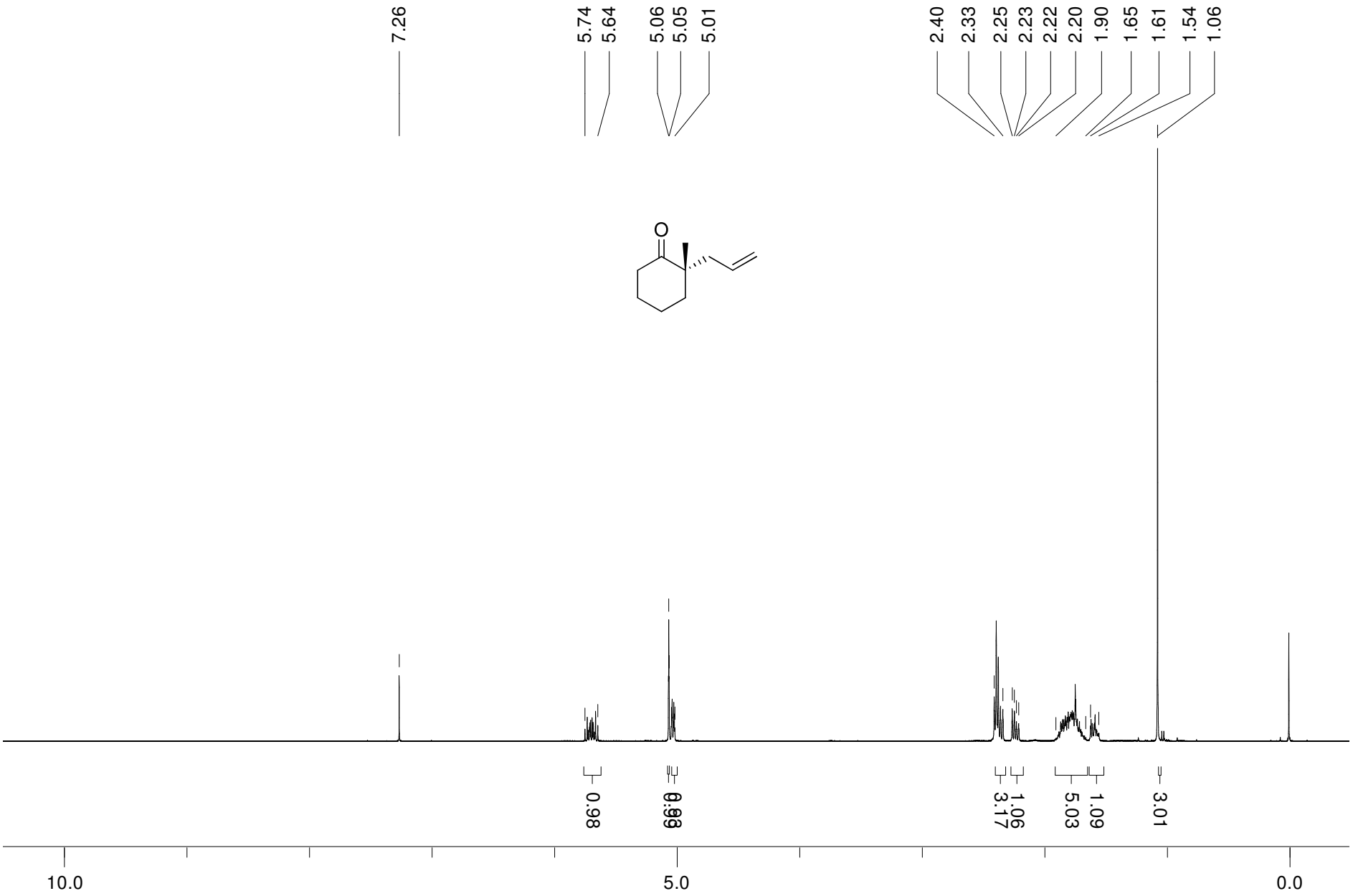
^{13}C NMR Spectrum of (2*E*)-2-[(2*S*)-2-Methyl-2-(2-propen-1-yl)-cyclohexylidene]-hydrazinecarboxamide (101 MHz, $CDCl_3$)



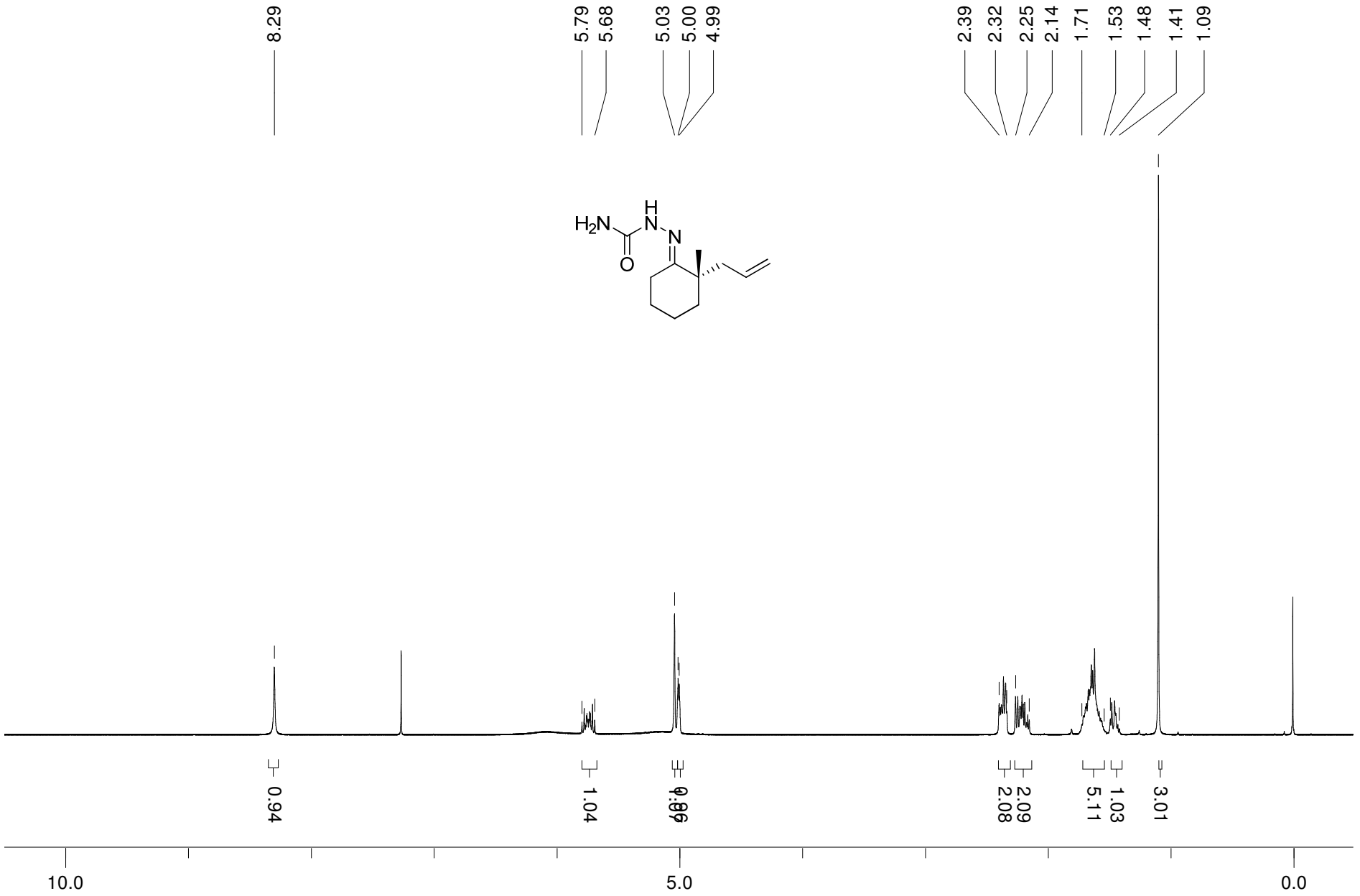
^{1}H NMR Spectrum of diallyl pimelate (400 MHz, $CDCl_3$)



^{1}H NMR Spectrum of 1Methyl-2-oxo-Cyclohexanecarboxylic acid 2-propenyl ester (400 MHz, $CDCl_3$)



^{1}H NMR Spectrum of (2*S*)-2-Methyl-2-(2-propen-1-yl)-cyclohexanone (400 MHz, $CDCl_3$)



^{1}H NMR Spectrum of (2*E*)-2-[(2*S*)-2-Methyl-2-(2-propen-1-yl)-cyclohexylidene]-hydrazinecarboxamide (400 MHz, $CDCl_3$)