Organic Syntheses

Preparation of *N*-(Boc)-Allylglycine Methyl Ester Using a Zinc-mediated, Palladium-catalyzed Cross-coupling Reaction

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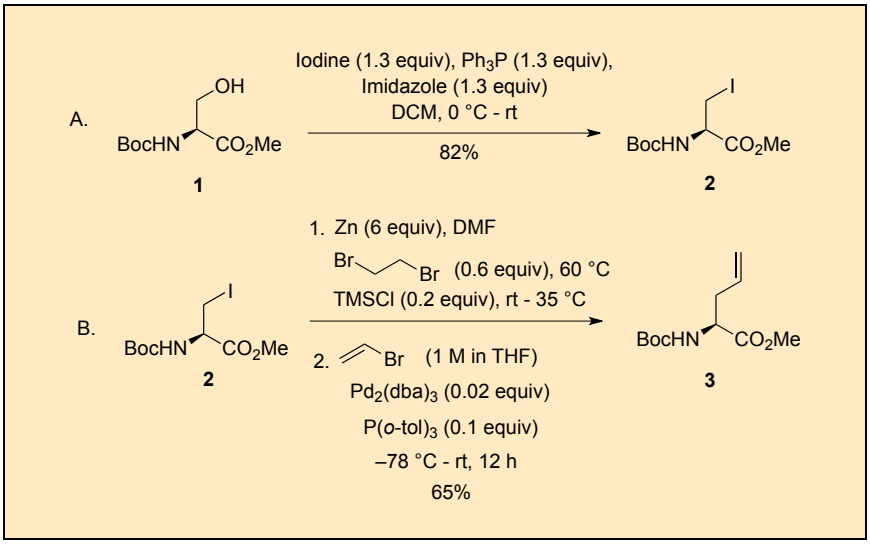

Procedure

A. *tert-Butyl (R)-1-(methoxycarbonyl)-2-iodoethylcarbamate* (**2**). An oven-dried 1000-mL, three-necked, round-bottomed flask containing an egg-shaped Teflon®-coated magnetic stir bar (7 cm long) is equipped with a rubber septum with a thermometer, a 125 mL addition funnel and an argon inlet adaptor. The apparatus is purged with argon (Note 1). Keeping a

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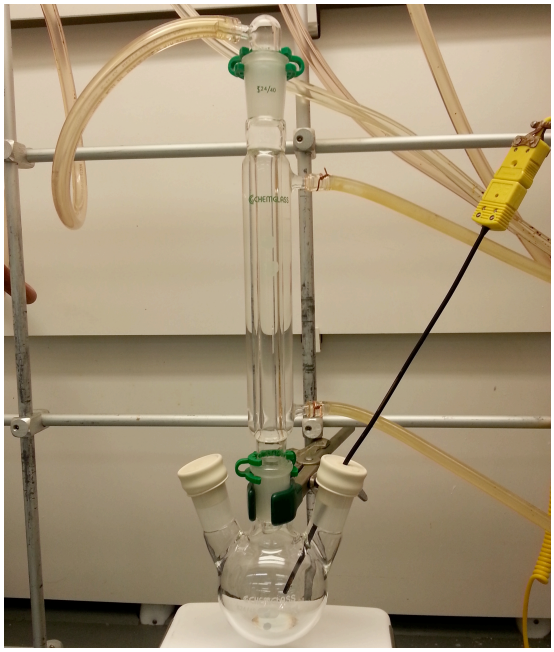
positive flow of argon, the septum is removed temporarily and the flask is charged with triphenylphosphine (Note 2) (32.66 g, 124.5 mmol, 1.3 equiv) and 400 mL of dichloromethane (Note 3). The solution is stirred at room temperature and imidazole (8.47 g, 124.5 mmol, 1.3 equiv) (Note 2) is added in one portion. The resulting mixture is stirred at room temperature for 10 min until full dissolution of imidazole is observed. The solution is cooled in an ice bath to 0 °C and maintained at that temperature during the addition of iodine (31.60 g, 124.5 mmol, 1.3 equiv) (Note 2) in four portions over a period of 20 min. The reaction mixture is stirred in the dark. The solution is warmed to room temperature, stirred for 10 min, and cooled to 0 °C. The septum is replaced with a dropping funnel (see photo), which is charged with *tert*-butyl (S)-1-(methoxycarbonyl)-2-hydroxyethylcarbamate (**1**, 21.00 g, 95.8 mmol) (Note 4) in 100 mL of dichloromethane. To the

reaction mixture at 0 °C, the solution of alcohol **1** in dichloromethane is added drop-wise over 60 min. The resulting slurry is stirred at 0 °C for 1 h, allowed to warm up to room temperature over 1 h, and stirred at that temperature for 1.5 h (Note 5). The reaction mixture is filtered through 150 g of silica gel dry-packed in a 9 cm column using 50:50 ether:hexanes (~700 mL) as eluent and concentrated under reduced pressure to give 32.5 g of brown oil, which is purified by column chromatography (Note 6). Evaporation of the collected fractions provides a colorless oil (26.1 g, 82%) (Notes 7 and 8), which converts to a white solid in the freezer at –20 °C.

B. *tert-Butyl (S)-1-(methoxycarbonyl)but-3-enylcarbamate* (**3**). An oven dried 250-mL three-necked, round-bottomed flask containing an egg-shaped Teflon®-coated magnetic stir bar (4 cm long) is equipped with a reflux condenser fitted with an argon inlet adaptor, a thermometer and a rubber septum (Note 1) (see photo). The apparatus is purged with argon. Keeping a positive flow of argon, the septum is removed temporarily and the flask is charged with zinc dust (11.92 g, 182.3 mmol, 6 equiv) (Note 9).



Dry DMF (20 mL) (Note 10) is then added to the flask via a syringe. 1,2-Dibromoethane (1.57 mL, 3.42 g, 18.2 mmol, 0.6 equiv) (Note 11) is added

next to the stirred suspension via a syringe. The mixture is stirred and heated to 60 °C and stirred at 60 °C for 45 min (Note 12). The mixture is cooled to room temperature. Chlorotrimethyl silane (TMS-Cl; 0.77 mL, 6.0 mmol) (Note 13) is added via a syringe to the slurry, which is stirred for 40 min at room temperature (Note 14). A solution of *tert*-butyl (*R*)-1-(methoxycarbonyl)-2-iodoethylcarbamate (**2**, 10 g, 30.39 mmol) (Note 15) in dry DMF (20 mL) is added via a syringe (Note 16) to the room temperature mixture of activated zinc, which is then heated in a 35 °C oil bath and stirred for 60 min. The zinc insertion was judged complete by TLC analysis (Note 17). After complete zinc insertion, the reaction mixture is cooled to room temperature, and charged with $Pd_2(dba)_3$ (779 mg, 0.85 mmol, 0.028 equiv) (Note 18) and tri(*o*-tolyl)phosphine (925 mg, 3.03 mmol, 0.1 equiv) (Note 19). The resulting mixture is cooled to –78 °C. A solution of vinyl bromide (1 M in THF, 42.5 mL, 42.5 mmol, 1.4 equiv, Note 20) is added drop-wise via a cannula to the stirred –78 °C suspension. After the addition of the vinyl bromide is complete, the cold bath is removed and the reaction mixture is allowed to warm to room temperature with stirring for 12 h (Note 21). The reaction mixture is diluted with ethyl acetate (200 mL) and transferred to a 1 L Erlenmeyer. Water (200 mL) is added and the resulting mixture is filtered through a pad of 35 g of Celite™ in a 6 cm diameter filter funnel. The pad is washed with ethyl acetate (300 mL). The filtrate and washings are combined and transferred to a separating funnel. The organic layer is separated. The aqueous layer is extracted with ethyl acetate (2 x 200 mL). The combined organic layers are washed with brine (400 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 8.2 g of brown oil, which is purified by column chromatography (Note 22). Evaporation of the collected fractions yields 4.50 g (65%) of a brown oil (Notes 23 and 24).

Notes

1. The submitters conducted this procedure under an atmosphere of argon.
2. Triphenylphosphine (99 %), imidazole (purity ≥99 %), and iodine (purity ≥99.9%) were obtained from Aldrich and used as provided. An exotherm of Δ 7 °C per added portion of iodine was observed by the checkers.

3. The submitters used dry dichloromethane from a solvent filtration system (Glass Contour, Irvine, CA). The checkers used anhydrous dichloromethane under inert atmosphere with a sure seal bottle from Aldrich chemical company, Inc.
4. The checkers purchased *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester (**1**) from Sigma-Aldrich. The material was prepared by the submitters according to the procedure reported by Trost, et al.[2.]
5. TLC analysis was performed on Merck Aluminum silica gel plates 60 F_{254}. Reaction conversion was ascertained using the following procedure. The reaction mixture was spotted directly on the TLC plate, which was eluted with (4:1) hexanes/ethyl acetate, and visualized with 254 nm UV light and $KMnO_4$ stain after heating: starting material **1** (R_f = 0.075, a UV inactive and $KMnO_4$ active spot); iodide **2** (R_f = 0.55, a UV active and $KMnO_4$ active spot).
6. Iodoalanine **2** is purified on a silica column in a dark place. The crude residue is absorbed onto 70 g of silica gel, and added to a column (18.4 cm diameter x 20 cm length), which is packed with a slurry of 360 g of silica (high purity grade Silica gel particle size 230-400 mesh ASTM, Merck Ltd.) in hexanes (700 mL). An eluent of 5% diethyl ether in hexanes (~1000 mL) is first flushed through the column to remove the less polar spot *tert*-butyl 1-(methoxycarbonyl)vinylcarbamate. The eluent is switched to 10% diethyl ether/hexanes (~2500 mL) to elute the iodide (R_f = 0.55, 4:1 hexanes/ethyl acetate, visualized with 254 nm UV light and KMnO4 stain on heating).
7. The reaction performed at half scale provided product in 79% yield.
8. Iodide **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9 H), 3.51–3.59 (m, 2 H), 3.78 (s, 3 H), 4.48–4.53 (m, 1 H), 5.32–5.38 (broad d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.9, 28.4, 53.10, 53.8, 80.6, 154.9, 170.1; IR (film): 3346.6, 2981.6, 1731.6, 1688.9, 1521.4, 1438.3,1312.9, 1273.2, 1248.4, 1155.9, 1140.3, 1032.4, 1009.5, 862.9 cm^{-1}. HRMS calcd for $C_9H_{16}NIO_4$ [M+1]: 330.0124. Found: 330.0197. $[\alpha]_D$ +42.0 (*c* 1.0, $CHCl_3$). Calcd for $C_9H_{16}NIO_4$: C, 32.84; H, 4.90; N, 38.56. Found: C, 33.06; H, 4.82; N, 4.28. The enantiomeric purity of compound **2** was >98 % by SFC (eluent 10 % MeOH, pressure 150 bar, flow rate 3 mL/min, injection volume 25 μL into a 20 μL loop, column AD-H, 25 cm x 5 μm, column temp. 35 °C, t_r = 1.68 min); injection of a sample containing an incremental addition of 0.1 mg of the *R*-isomer (t_r = 2.25 min) into 10 mg of *S*-**2** established the limits of detection to be at least 1:99.

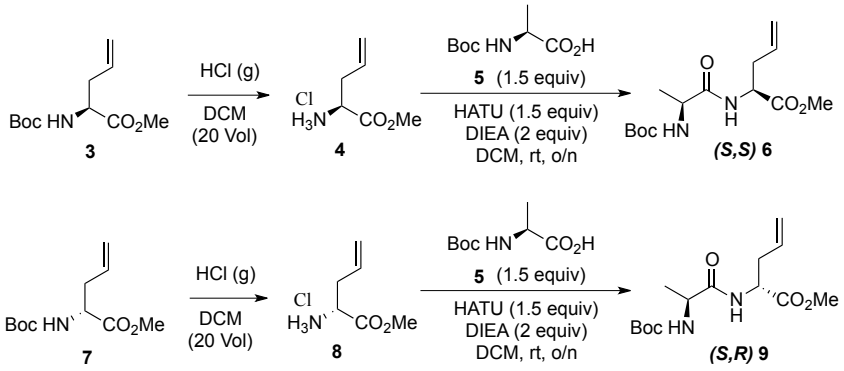
9. Zinc dust (particle size <10 μm, >98 %) was purchased and used as received from Aldrich chemical company.
10. The submitters used dry DMF from a solvent filtration system (Glass Contour, Irvine, CA). The checkers used anhydrous DMF under inert atmosphere with a sure seal bottle from Aldrich chemical company.
11. 1,2-Dibromoethane was purchased from Baker Chemicals and used as received. The checkers purchased 1,2-dibromoethane from Aldrich Chemical Company, Inc. An exotherm of Δ 35 °C and gas evolution were observed by the checkers after addition was completed.
12. The submitters used an oil bath kept at 60 °C external temperature once the exotherm stopped.
13. TMS-Cl (purity ≥97%) was purchased from Aldrich chemical company and used as received.
14. Evolution of gas was observed after the addition of TMS-Cl.
15. During addition of iodide **2**, the round-bottomed flask was covered with aluminum foil and stirred in the dark until the reaction was complete, because iodide **2** is light sensitive.
16. The time for reagent addition varied with reaction scale. In the reported experiment, the addition was completed over 25 min in order to maintain the internal temperature below 35 °C.
17. TLC analysis was performed on Merck Aluminum silica gel plates 60 F_{254}. Reaction conversion was monitored by spotting the reaction mixture on a TLC plate and eluting with 2:1 hexanes/ethyl acetate. Using 254 nm UV light, consumption of starting material (R_f = 0.7) and another spot slightly above the base line were visualized.
18. $Pd_2(dba)_3$ (purity 97%) was purchased from Aldrich chemical company and used as received.
19. Tri(*o*-tolyl)phosphine (purity ≥97%) was purchased from Aldrich chemical company and used as received.
20. Anhydrous THF (50 mL) in a flame-dried measuring cylinder fitted with a septum was cooled to –78 °C. On cooling, the volume of the THF contracted to 45 mL. Vinyl bromide gas was bubbled into the THF until the total volume rose from 45 mL to 48.1 mL yielding a 1M solution. Employment of vinyl bromide solutions of >1 molar augmented formation of methyl *N*-(Boc)alaninate and diminished iodide yield. Checkers used commercially available 1 M vinyl bromide in THF from Aldrich chemical company. Methyl *N*-(Boc)alaninate is removed by chromatography: TLC R_f = 0.21 (9:1 hexanes/ethyl acetate), visualized as a UV inactive and $KMnO_4$ active spot. The checkers stopped the

positive flow of argon after the addition was completed in order to avoid any loss of vinyl bromide. Excess pressure is released through a bubbler connected to the argon inlet adapter. Submitters used a balloon connected to a three-way stopcock to contain the excess pressure of vinyl bromide.

21. Reaction conversion is ascertained on an aliquot of the reaction mixture (100 μL), which was partitioned between ethyl acetate (200 μL) and water (500 μL). The ethyl acetate layer was analyzed by TLC using 9:1 hexanes/ethyl acetate as eluant, and the plate was visualized with 254 nm UV light as well as with $KMnO_4$ stain after heating: methyl *N*-(Boc)alaninate (R_f = 0.21, a UV inactive and $KMnO_4$ active spot); iodide **2** (R_f = 0.29, a UV and $KMnO_4$ active spot); olefin **3** (R_f = 0.29, a UV inactive and $KMnO_4$ active spot).
22. Olefin **3** is purified on a silica column. The residue is absorbed onto 30 g of silica gel. The column (18.4 cm diameter) is packed with slurry of 250 g of silica (high purity grade Silica gel particle size 230-400 mesh ASTM, Merck Ltd.) in hexanes (1000 mL). Elution with 2% ethyl acetate/hexanes removes first all non-polar spots. Switching to 7% ethyl acetate in hexanes (~1500 mL) elutes the product (TLC R_f = 0.29, 9:1 hexanes/ethyl acetate), which is visualized as a UV inactive and KMnO4 active spot on heating.
23. The reaction performed at half scale provided product in 64% yield.
24. *N*-(Boc)Allylglycine methyl ester (**3**): $[\alpha]_D$ +20.2 (c 1.5, $CHCl_3$); lit.[3] $[\alpha]_D$ +18.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (s, 9 H), 2.41–2.53 (m, 2 H), 3.70 (s, 3 H), 4.32–4.38 (m, 1 H), 5.04 (br s, 1 H), 5.08 (s, 1 H), 5.10–5.12 (m, 1 H), 5.62–5.71 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.37, 36.86, 52.29, 53.0, 79.94, 119.12, 132.42, 155.27, 172.62; IR (film): 3359.0, 2978.3, 1745.9, 1715.7, 1505.7, 1437.9, 1366.3, 1249.9, 1162.6, 1051.2, 1022.7, 920.6 cm^{-1}; HRMS calcd for $C_{11}H_{19}NO_4$ [M+1]: 230.1314; Found: 230.13867. In lieu of combustion analysis the checkers determined the purity of *N*-(Boc)allylglycine methyl ester (98.1%) by quantitative ^{1}H NMR assay using dimethyl fumarate as a standard.
    Attempts to ascertain the enantiomeric purity of olefin **3**, as well as the hydrochloride obtained on treating **3** with HCl gas in dichloromethane, both were unsuccessful using SFC on a chiral column. To assess enantiomeric purity, diastereomeric amides were synthesized using respectively Boc-L-Ala (1.5 equiv), *i*-Pr_2NEt (2 equiv), HATU (1.5 equiv) (Note 25). The residue was examined by ^{1}H NMR spectroscopy in CD_3CN at 700 MHz and 400 MHz. Incremental addition of (*S*,*S*)-**6** into

(*S*,*R*)-**9** (Note 25) and observation of the methyl ester singlets at 3.691 and 3.697 ppm demonstrated the diastereomers were of >99:1 dr. Hence, olefin **3** is assumed to be of >98% enantiomeric purity.

25. Synthetic procedure for making diastereomers (*S*,*S*)- **6** and (*S*,*R*)-**9**:



(*S*)-Methyl 2-aminopent-4-enoate hydrochloride (**4**). Dry HCl gas was bubbled into a stirred solution of *tert*-butyl (*S*)-1-(methoxycarbonyl)but-3-enylcarbamate (**3,** 70 mg, 0.30 mmol) in dry dichloromethane at room temperature. Consumption of SM was observed after 3h (TLC). The resulting solution was concentrated under reduced pressure to give (*S*)-**4** as a brown solid: ^{1}H NMR (400 MHz, CD_3OD) δ: 2.68-2.75 (m, 2 H), 3.86 (s, 3 H), 4.16-4.19 (m, 1 H), 5.27-5.33 (m, 2 H), 5.77-5.81 (m, 1 H). (R)-Methyl 2-aminopent-4-enoate hydrochloride *R*-**8** was made by an analogous method as that used to prepare *S*-**4**.

(*S*)-Methyl 2-((*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)pent-4-enoate (*S*,*S*-**6**). A stirred solution of Boc-L-Ala (**5**, 85.1 mg, 0.45 mmol, 1.5 equiv) in DCM (5 mL) was treated with amine hydrochloride (*S*)-**4** (50 mg, 0.30 mmol, 1 equiv), DIEA (77.5 mg, 0.6 mmol, 2 equiv), and HATU (171.1 mg, 0.45 mmol, 1.5 equiv), stirred at room temperature for 16 h, diluted with DCM (~10 mL) and washed with saturated aqueous $NaHCO_3$. The layers were separated. The aqueous layer was extracted with DCM (~10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (*S*,*S*)-**6** as brown oil, which was analyzed without further purification. This following spectral data was provided by the submitters. (*S*,*S*)-**6**: ^{1}H NMR (400 MHz, CD_3CN) δ: 1.27–1.28 (d, *J* = 7.2, 3 H), 1.44 (s, 9 H), 2.43–2.51 (m, 1 H), 2.53–2.60 (m,

1 H), 3.70 (s, 3 H), 4.06–4.10 (m, 1 H), 4.44–4.49 (m, 1 H), 5.10–5.19 (m, 2 H), 5.63 (br s, 1 H), 5.72–5.82 (m, 1 H), 6.91 (br s, 1 H); (*S*,*R*)-**9** was made by the analogous method used to prepare (*S*,*S*)-**6** using *R*-**8**: (*S*,*R*)-**9**: ^{1}H NMR (400 MHz, CD_3CN) δ: 1.26–1.28 (d, J = 7.2, 3 H), 1.44 (s, 9 H), 2.42–2.50 (m, 1 H), 2.53–2.60 (m, 1 H), 3.70 (s, 3 H), 4.05–4.09 (m, 1 H), 4.44–4.49 (m, 1 H), 5.10–5.18 (m, 2 H), 5.62 (br s, 1 H), 5.68–5.81 (m, 1 H), 6.90 (br s, 1 H).

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

In the field of peptide chemistry, unsaturated amino acids and their esters are useful starting materials for the synthesis of amino acids, constrained peptides and peptide mimics. Allylglycine esters have been used as versatile building blocks for the synthesis of macrocyclic dipeptide □-turn mimics,[4] azabicyclo[X.Y.0]alkanone amino acids,[5] the key intermediate of diaminopimelate metabolism L-tetrahydrodipicolinic acid,[6] potent macrocyclic HCV NS3 protease inhibitors,[7] bicyclic amino acid substrates for intramolecular Pauson-Khand cyclizations,[8] and anti-bacterial cyclic peptides.[9] The double bond of the unsaturated amino acid has been functionalized by various chemical processes, including Diels–Alder reactions,[10] and cycloadditions,[11] cross-metathesis,[12] as well as Heck[13] and Suziki-Miyaura cross coupling reactions.[14]

Although a variety of methods have provided allylglycinates in enantiomerically enriched forms,[3,15-25] they require often longer reaction sequences. Diastereoselective syntheses of allylglycinate have been achived using chiral auxiliaries which may be removed or destroyed,[23] such as ephedrine-derived imidazolidinone glycinimides,[22] menthone-derived nitrones,[18] and camphor-derived glycine derivatives.[17,20,24] Enantioselective approaches to allylglycinate have featured allylation of ketoester oximes employing chiral bis(oxazoline) ligands,[21] and allylation of *tert*-butyl glycinate using tartrate-derived and Cinchona alkaloid-derived quaternary ammonium phase-transfer catalysts.[19,28] In addition, allylglycinates have been prepared from amino acids as chiral educts. For example, glutamate served as starting material for the syntheisis of allyl 2-(Boc)amino-4-triphenylphosphonium butanoate, which reacted with various aldehydes and paraformaldehyde in Wittig-Horner-Wadsworth-Emmons reactions to yield unsaturated amino acids.[16] Similarly, ylide from methyltriphenylphosphonium bromide reacted with α-*tert*-butyl *N*-(PhF) aspartate β-aldehyde to provide protected allylglycinate.[4] In the context of our research in peptide mimicry,[4,5] we required an efficient, atom economical route to enantiomerically pure allylglycine analogues. Building on the established precedent of zinc-mediated, palladium-catalyzed cross-coupling reactions of commercially available and inexpensive *tert*-butyl (*R*)-1-(methoxycarbonyl)-2-iodoethylcarbamate,[2,15,26,27,29] this extension employs

vinyl bromide to give effective access to allylglycine in enantiomerically pure form on multi-gram scale.

The zinc insertion reaction of the alininyl iodide **2** are typically performed in DMF to thwart the chelation of the ester and carbamate functions with zinc, which has been suggested to promote β-elimination to the corresponding amino acrylate, particulary when performed in THF.[26] The organozinc intermediate is relatively stable towards air and moisture. Attempts to perform the related Kumuda coupling using vinylmagnesium bromide were unsuccessful and resulted in β-elimination affording amino acrylate. Negishi cross coupling of the alininyl zinc intermediate with vinyl bromide is effectively mediated by $Pd_2(dba)_3$ and tri-(*o*-tolyl)phosphine and has been examined at lower temperature to give the *N*-(Boc)-allylglycine methyl ester **3** with improved yield.

References

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2. Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003,** 5, 4599.
3. Collier, P. N.; Campbell, A. D.; Patel, I.; Taylor, R. J. *Tetrahedron* **2002**, 58, 6117.
4. Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem*. **2005**, 70, 3838.
5. Surprenant, S.; Lubell, W. D. *Org. Lett*. **2006**, 8, 2851.
6. Caplan, J. F.; Sutherland, A.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2217.
7. Nair, L. G.; Bogen, S.; Bennett, F.; Chen, K.; Vibulbhan, B.; Huang, Y.; Yang, W.; Doll, R. J.; Shih, N.-Y.; Njoroge, F. G. *Tetrahedron Lett.* **2010**, 51, 3057.
8. Bolton, G. L.; Hodges, J. C.; Ronald Rubin, J. *Tetrahedron* **1997**, 53, 6611.
9. Boyle, T. P.; Bremner, J. B.; Coates, J.; Deadman, J.; Keller, P. A.; Pyne, S. G.; Rhodes, D. I. *Tetrahedron* **2008**, 64, 11270.
10. Kotha, S. *Acc. Chem. Res*. **2003,** 36, 342.

11. Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M. *Org. Lett.* **2005,** 7, 3597.
12. Wang, Z. J.; Jackson, W. R.; Robinson, A. J. *Org. Lett.* **2013**, 15, 3006.
13. Collier, P. N.; Patel, I.; Taylor, R. J. *Tetrahedron Lett.* **2002**, 43, 3401.
14. Krebs, A.; Ludwig, V.; Pfizer, J.; Dürner, G.; Göbel, M. W. *Chem-Eur. J.* **2004**, 10, 544.
15. A synthesis of methyl *N*-(Cbz)allylglycinate without experimental procedure is reported in: Olsen, J. A.; Severinsen, R.; Rasmussen, T. B.; Hentzer, M.; Givskov, M.; Nielsen, J. *Bioorg. Med. Chem. Lett.* **2002**, 12, 325.
16. Rémond, E.; Bayardon, J.; Ondel-Eymin, M.-J. l.; Jugé, S. *J. Org. Chem.* **2012,** 77, 7579.
17. Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005,** 127, 1066.
18. Katagiri, N.; Okada, M.; Morishita, Y.; Kaneko, C. *Tetrahedron* **1997,** 53, 5725.
19. Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, 60, 7743.
20. Yeh, T.-L.; Liao, C.-C.; Uang, B.-J. *Tetrahedron* **1997**, 53, 11141.
21. Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996,** 37, 8997.
22. Guillena, G.; Nájera, C. *J. Org. Chem*. **2000**, 65, 7310.
23. Myers, A. G.; Gleason, J. L. *Org. Synth*. **1999**, 76, 57.
24. Xu, P.-F.; Lu, T.-J. *J. Org. Chem*. **2003,** 68, 658.
25. Kitagawa, O.; Hanano, T.; Kikuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1993**, 34, 2165.
26. Jackson, R. F.; Moore, R. J.; Dexter, C. S.; Elliott, J.; Mowbray, C. E. *J. Org. Chem.* **1998,** 63, 7875.
27. Carrillo-Marquez, T.; Caggiano, L.; Jackson, R. F.; Grabowska, U.; Rae, A.; Tozer, M. *J. Org. Biomol. Chem*. **2005**, 3, 4117.
28. Bojan, V.; Maja, G. –P.; Radomir, M.; Radomir, N. S. *Org. Lett.* **2014**, 16, 34.
29. Jackson, R. F.; Perez‐Gonzalez, M. *Org. Synth.* **2005**, 77–88.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

1,2-Dibromoethane; (106-93-4)
Chlorotrimethylsilane; (75-77-4)

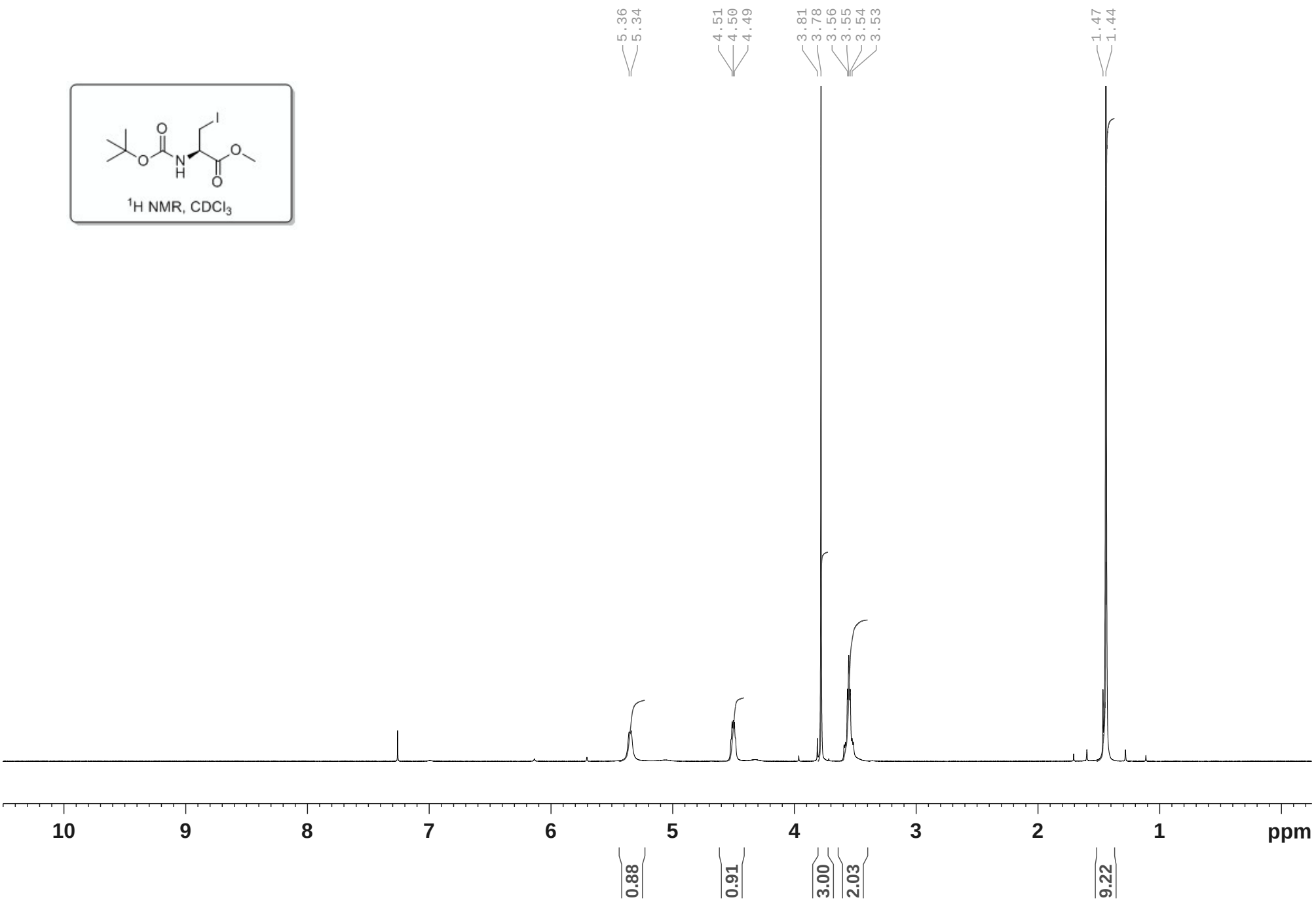
Vinyl bromide; (593-60-2)
Tris(dibenzylideneacetone)dipalladium(0); (51364-51-3)
Tri(o-tolyl)phosphine; (6163-58-2)
Zinc dust (particle size <10 μm); (7440-66-6)
Triphenylphosphine; (603-35-0)
Imidazole; (288-32)
Iodine; (7553-56-2)

N. D. Prasad Atmuri was born in India, in 1984. After receiving his M.Sc. degree in Organic Chemistry from Nagarjuna University in 2006, he worked 4.6 years as an Associate Scientist for Syngene International Ltd, India. In 2013, he began graduate studies at the Université de Montréal under the direction of Professor William D. Lubell. His current research focuses on the development of methods for synthesizing azabicyclo[X.Y.0]alkanones by way of ring closing metathesis and transannular cyclization with specific interest on novel indolizidinone modulators of the prostaglandin F2□ receptor to develop improved therapeutics for preventing preterm labor.

Dr. William D. Lubell obtained his Ph.D. in 1989 from the University of California, Berkeley under the supervision of Professor Henry Rapoport, and studied as a postdoctoral fellow with Professor Ryoji Noyori at Nagoya University, Japan. In 1991, he joined the Chemistry Department of the Université de Montréal, where he is Full Professor. Advancing applications of peptides in drug discovery, Lubell has innovated methods for constraining amino acids and peptides to study structure-activity relationships and evolve peptidomimetic drug candidates with enhanced pharmacokinetic properties, including submonomer azapeptide synthesis, aminolactam scanning and azabicycloalkane amino acid libraries.

Jean-Nicolas (Nick) Desrosiers received his bachelor degree University of Montreal in 2003. He obtained his Ph.D. in 2008 under the supervision of Prof. André Charette, with whom he performed studies on enantioselective processes catalyzed by chiral bisphosphine monoxide copper complexes. In 2008, he joined the research group of Prof. Eric N. Jacobsen at Harvard University as a NSERC postdoctoral fellow. His postdoctoral research mainly focused on silyl ketene acetals acylation through anion-binding catalysis. He is currently working in the Chemical Development department of Boehringer-Ingelheim, Ridgefield, CT.

Dr. Nizar Haddad was born and raised in Israel. He received his B.A. degree (1984) and D.Sc. degree in chemistry (1988, Professor D. Becker) from the Technion, Israel Institute of Technology. After his postdoctoral research at the University of Chicago with Professor J. D. Winkler and additional postdoctoral work at Harvard University with Professor Y. Kishi, he joined the faculty in the Chemistry Department at the Technion, Israel in 1991. Following one-year sabbatical leave with Professor K. C. Nicolaou at the Scripps Research Institute, he joined Boehringer Ingelheim Pharm. Inc. in 1998 where he gained wide experience in process research, process development and scale up operations. Currently, as Senior Principal Scientist, he is heading the Chemical Catalysis group since 2007. His research interests include the development and application of catalytic asymmetric reactions and the application of lab automation in the development of new and economical processes.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5.34
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3.81
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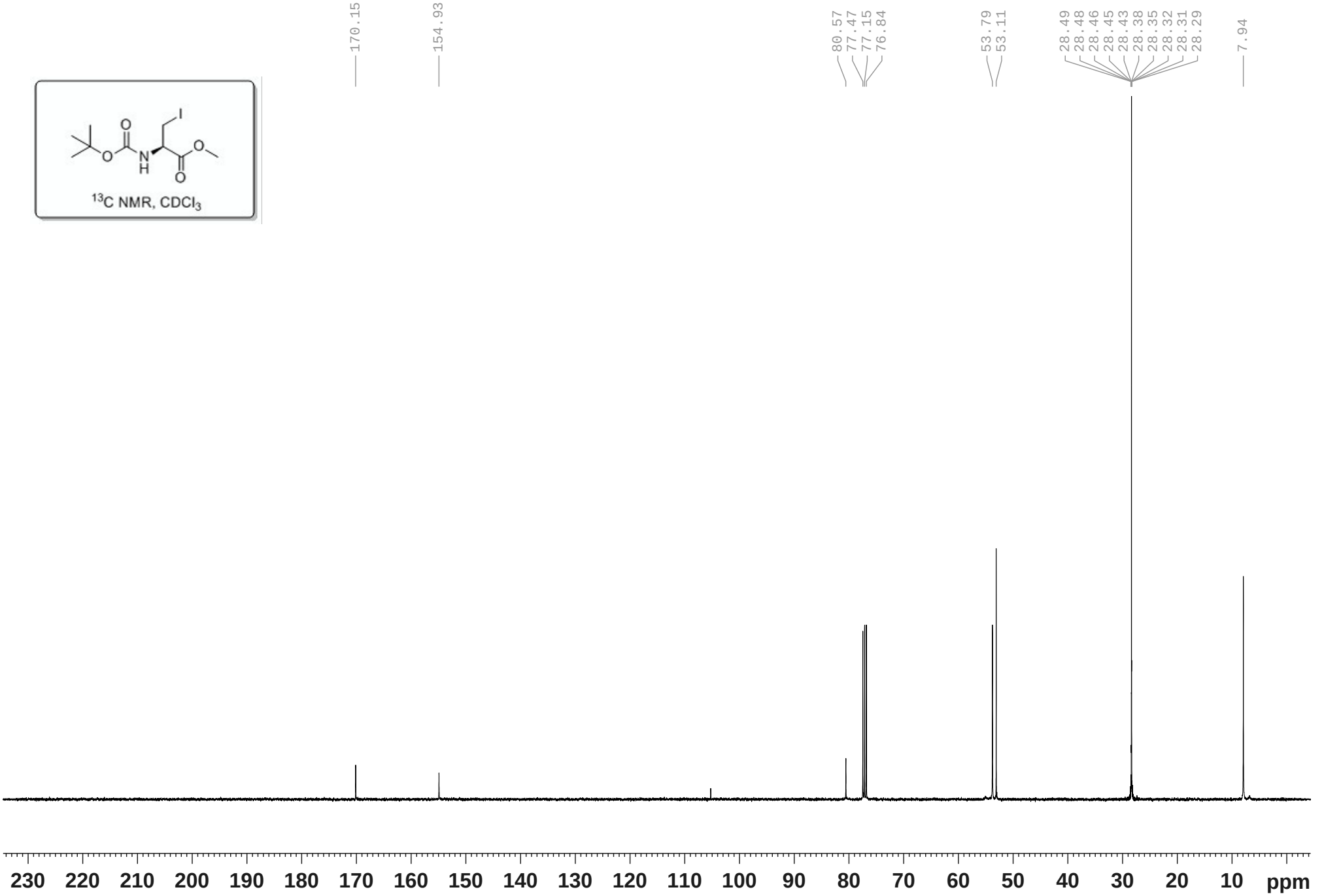
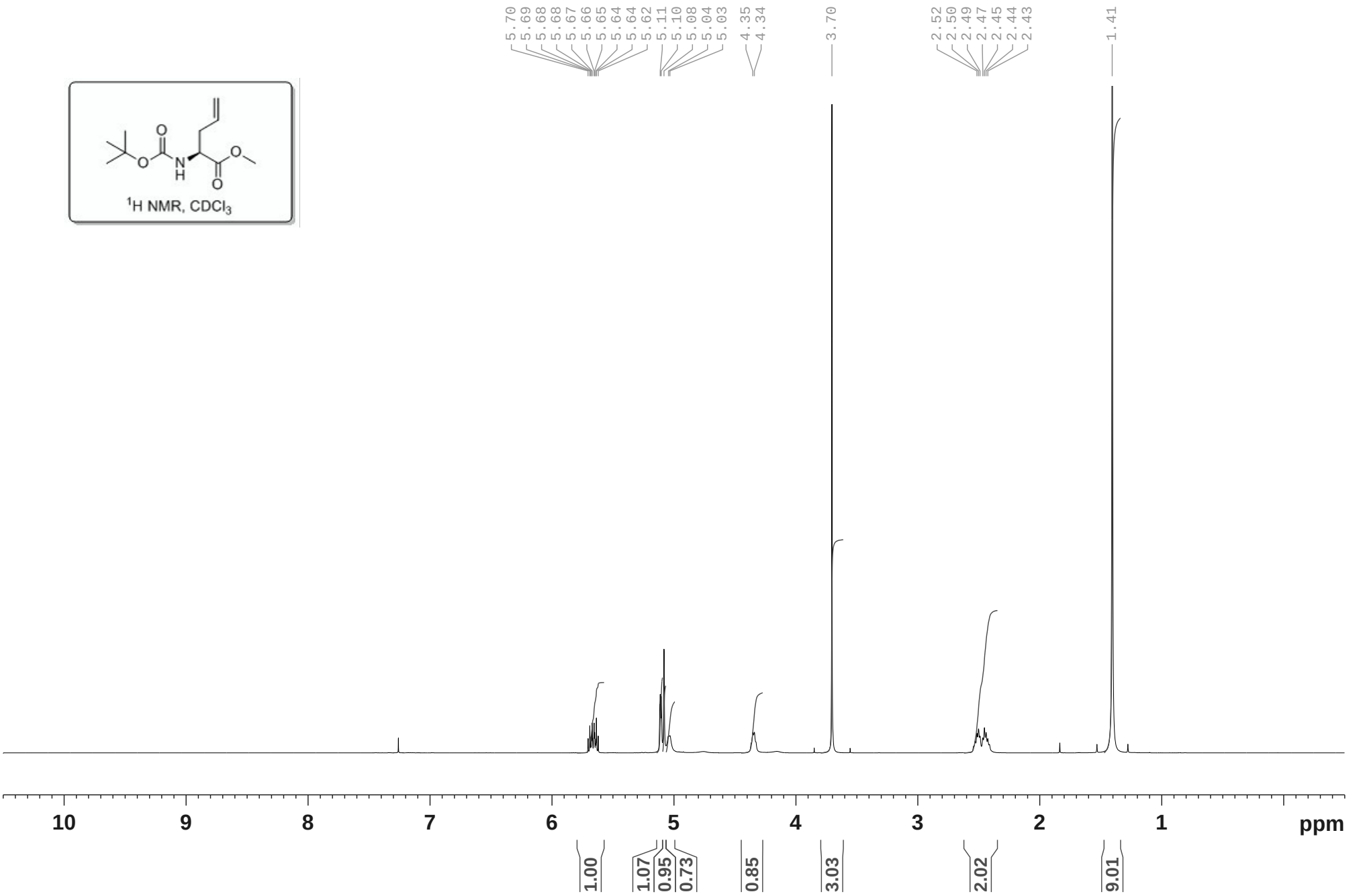
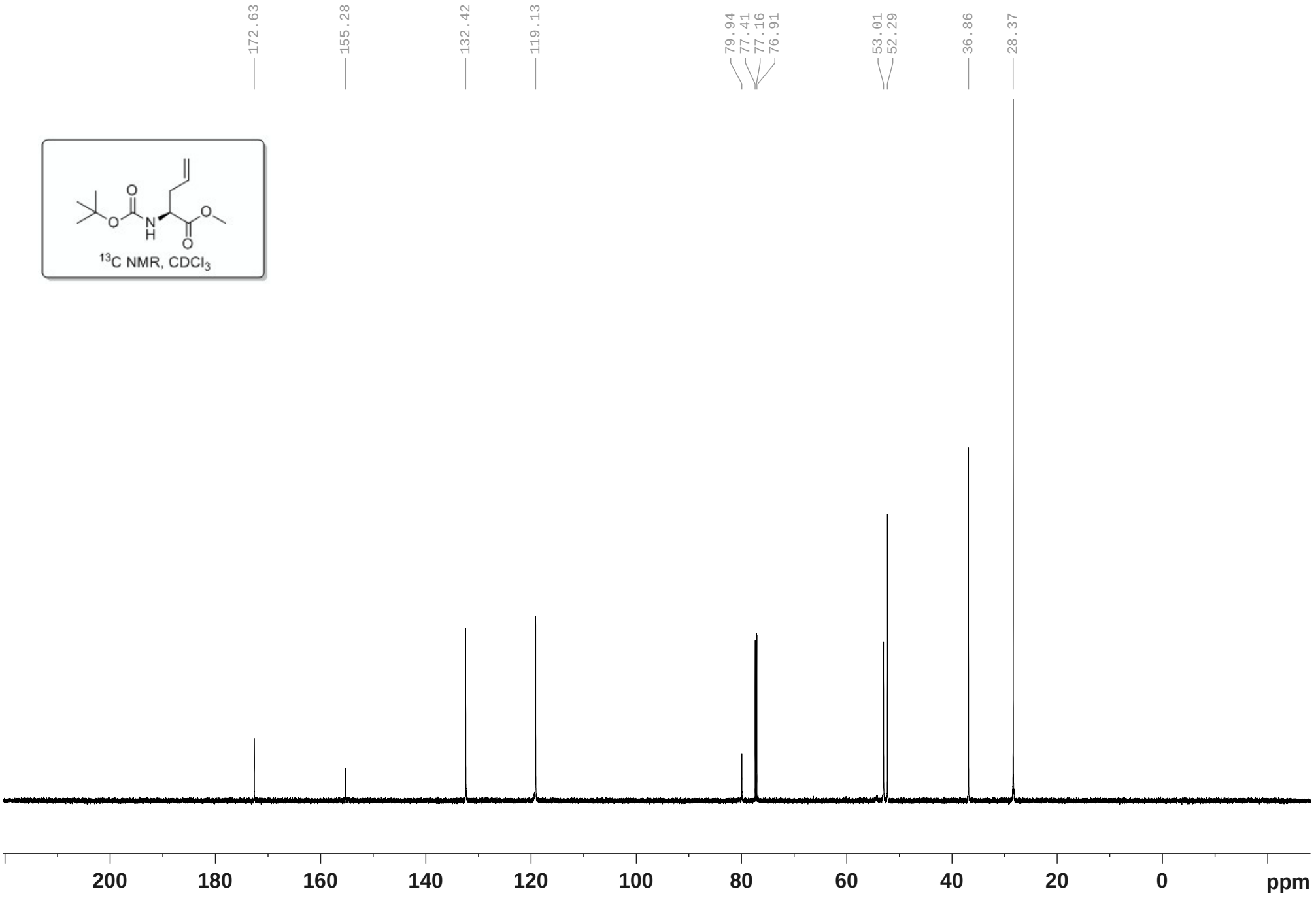
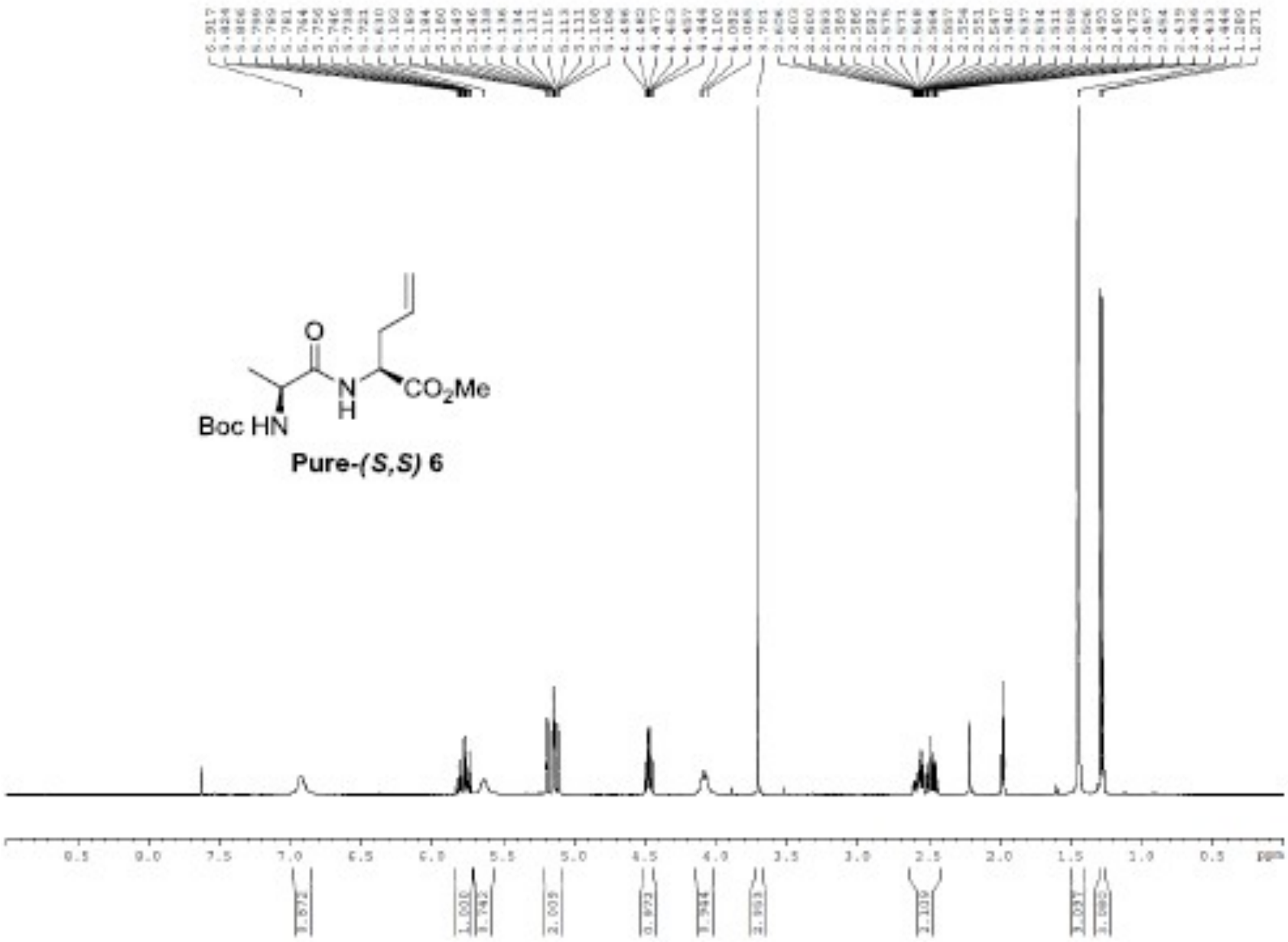
3.54
3.53
1.47
1.44
O
I
O
N
H
O
O
^{1}H NMR, $CDCl_3$
10
9
8
7
6
5
4
3
2
1
ppm
0.88
0.91
3.00
2.03
9.22

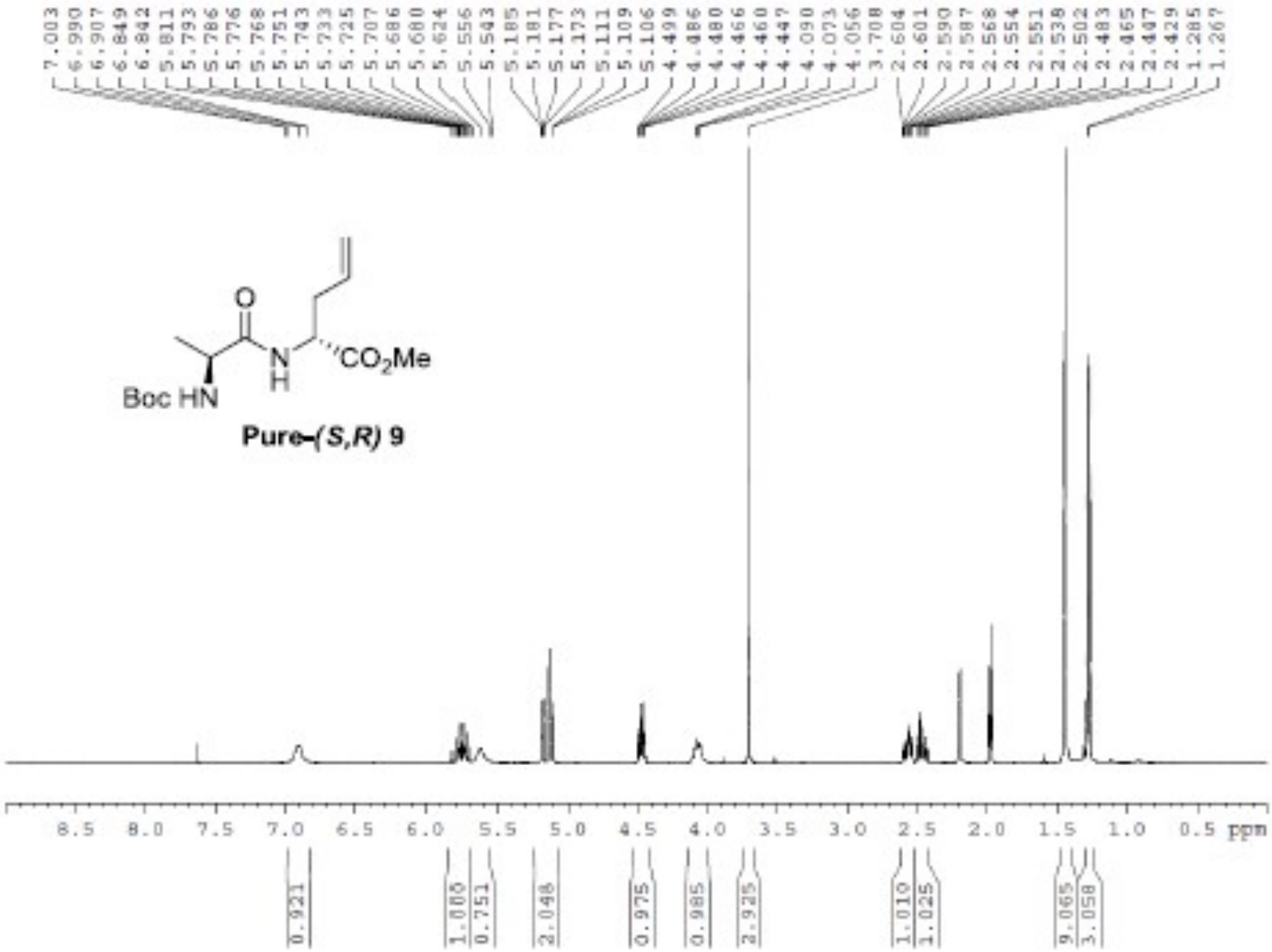

170.15
154.93
80.57
77.47
77.15
76.84
53.79
53.11
28.49
28.48
28.46
28.45
28.43
28.38
28.35
28.32
28.31
28.29
7.94
^{13}C NMR, $CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


5.70
5.69
5.68
5.68
5.67
5.66
5.65
5.64
5.64
5.62
5.11
5.10
5.08
5.04
5.03
4.35
4.34
3.70
2.52
2.50
2.49
2.47
2.45
2.44
2.43
1.41
^{1}H NMR, $CDCl_3$
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.07
0.95
0.73
0.85
3.03
2.02
9.01


172.63
155.28
132.42
119.13
79.94
77.41
77.16
76.91
53.01
52.29
36.86
28.37
^{13}C NMR, $CDCl_3$
200
180
160
140
120
100
80
60
40
20
0
ppm



Pure-*(S,S)* 6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5.776
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5.733
5.725
5.707
5.686
5.680
5.624
5.556
5.543
5.185
5.181
5.177
5.173
5.111
5.109
5.106
4.499
4.486
4.480
4.466
4.460
4.447
4.090
4.073
4.056
3.708
2.604
2.601
2.590
2.587
2.568
2.554
2.551
2.538
2.502
2.483
2.465
2.447
2.429
1.285
1.267
O
N
H
CO2Me
Boc HN
Pure-(S,R) 9
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.921
1.000
0.751
2.048
0.975
0.985
2.925
1.010
1.025
9.065
3.058