

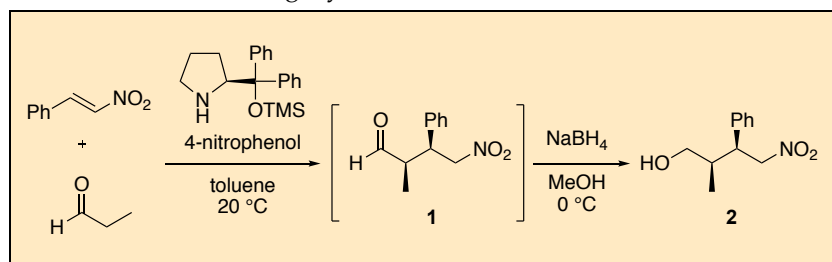
Asymmetric Michael Reaction of Aldehydes and Nitroalkenes

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Procedure (Note 1)

A. (2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanol (**2**). A 500-mL three-necked round-bottomed flask is equipped with an egg-shaped, Teflon-coated, magnetic stir bar (8 x 32 mm), an internal thermometer, a two-way stopcock with a hose (central neck), and a three-way stopcock connected to a nitrogen inlet hose (Figure 1). The flask is charged with a solution of trans-β-nitrostyrene (10.00 g, 67.0 mmol, 1.0 equiv) (Note 2) in toluene (60 mL) (Note 3). The stirred solution is immersed in a water bath in order to cool the internal temperature to 16 °C (Note 4), followed by addition of propanal (5.8 g, 7.2 mL, 100 mmol, 1.5 equiv) (Note 5) and 4-nitrophenol (466 mg, 3.4 mmol, 0.05 equiv) (Note 6). (*S*)-1,1-Diphenylprolinol trimethylsilyl ether (1.09 g, 3.4 mmol, 0.05 equiv) (Note 7) in toluene (7 mL) (Note 3) is added over 0.5 min. After the reaction mixture is stirred at 16 ~ 20 °C (Notes 4 and 8) for 30 min, the internal temperature is cooled down to 0 ~ 3 °C with an ice bath. Methanol (134 mL) (Note 9) is added to the reaction mixture and then NaBH₄ (3.80 g, 100.5 mmol) (Note 10) is slowly added (Note 11) over

30 min, while maintaining the internal temperature at 0 ~ 15 °C. After addition, the reaction mixture is stirred at 0 °C for 1 h, then quenched with 1M aqueous HCl (50 mL) over 1 min. The solution is partially concentrated by the removal of MeOH (115–130 mL) under reduced pressure (30 °C, 120–50 mmHg). The resulting yellow solution is diluted with CH₂Cl₂ (150 mL) and washed with H₂O (100 mL). The aqueous layer is extracted with CH₂Cl₂ (2 x 150 mL). The organic layers are combined, dried over Na₂SO₄ (20 g) and gravity filtered through a filter paper. Dichloromethane (70 mL) is used to wash the Na₂SO₄. The combined filtrate is transferred to a round-bottomed flask and concentrated by rotary evaporation (30 °C, 200–15 mmHg) to afford the crude product. Purification by flash column chromatography with elution by 33% ethyl acetate / hexanes (Note 12) provides alcohol **2** (12.76–12.97 g, 91–93% yield, > 20:1 dr, 98% ee) as a yellow oil (Notes 13, 14, and 15).



Figure 1. Glassware assembly for reaction

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with β -nitrostyrene, toluene, propanal, (S)-1,1-diphenylprolinol trimethylsilyl ether, 4-nitrophenol, sodium borohydride, methanol, dichloromethane, sodium sulfate, hexanes, ethyl acetate, silica gel, and aqueous hydrochloric acid.
2. *trans*- β -Nitrostyrene (98.0%) was obtained from TCI and used as received.
3. Toluene (99.5%, dehydrated) was obtained from Wako and used as received.
4. The internal temperature was carefully maintained. When the reaction temperature exceeded 25 °C, the diastereoselectivity decreased.
5. Propanal (>95%) was obtained from TCI and was distilled before use.
6. 4-Nitrophenol (>99.0%) was obtained from TCI and used as received.
7. The checkers used commercial (S)-1,1-diphenylprolinol trimethylsilyl ether (95.0%, Sigma-Aldrich). The submitters used (S)-1,1-diphenylprolinol trimethylsilyl ether that was prepared by the method reported in a previous *Org. Synth.* article.²
8. TLC analysis was performed on silica gel with 33% ethyl acetate/hexanes (visualized by UV, KMnO₄). The spot of *trans*- β -nitrostyrene (R_f = 0.67) completely disappeared and the Michael adduct **1** was formed (R_f = 0.43). The submitters report that the Michael adduct

- 1 can be purified by column chromatography; however, column purification on a large scale can be slow resulting in a decrease in diastereoselectivity being observed. Physical properties of Michael adduct **1** as reported by Submitters are: ^1H NMR (300 MHz, CDCl_3) δ : 1.01 (d, $J = 7.2$ Hz, 3H), 2.72–2.83 (m, 1H), 3.77–3.85 (ddd, $J = 5.6, 9.4, 9.4$ Hz, 1H), 4.64–4.71 (dd, $J = 9.2, 12.8$ Hz, 1H), 4.77–4.83 (dd, $J = 5.7, 12.6$ Hz, 1H), 7.15–7.36 (m, 5H), 9.72 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ : 12.2, 44.1, 48.5, 78.2, 128.1, 129.1, 136.7, 202.5.
9. MeOH (99.8%, dehydrated) was obtained from Wako Pure Chemical Industries, Ltd. and used as received.
 10. Sodium borohydride (NaBH_4) was obtained from Wako Pure Chemical Industries, Ltd. and used as received.
 11. The internal temperature rapidly increased to 15 °C even though the flask was in a cold bath (0 °C). Hydrogen gas was evolved and constantly removed from the system.
 12. Alcohol **2** is purified on a column (7 x 30 cm) packed with 190 g of silica gel 60 N (obtained from Wako Pure Chemical Industries, Ltd., 100–210 μm) with 33% ethyl acetate / hexanes. Fraction collection (100 mL fractions) begins immediately and fractions 15–41 were pooled, which contain the desired product. The product (**2**) has a R_f of 0.17 in 33% ethyl acetate / hexanes (visualized by UV, KMnO_4).
 13. Physical properties of alcohol **2** are: ^1H NMR (600 MHz, CDCl_3) δ : 0.82 (d, $J = 6.9$ Hz, 1H), 1.50 (s, 1H), 2.04–1.99 (m, 1H), 3.49 (dd, $J = 6.9, 10.8$ Hz, 1H), 3.60 (dd, $J = 10.8, 4.6$), 3.66 (dt, $J = 9.5, 6.6$ Hz, 1H), 4.76 (dd, $J = 9.6, 12.6$ Hz, 1H), 4.90 (dd, $J = 6.2, 12.6$ Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR (150 MHz, CDCl_3) δ : 14.1, 38.4, 46.2, 65.7, 78.8, 127.6, 128.3, 128.7, 137.7; IR (neat): 3395, 3031, 2967, 2924, 2882, 1603, 1552, 1495, 1455, 1434, 1381, 1204, 1140, 1031, 983, 911, 846, 756, 703, 626, 553 cm^{-1} . HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_3$ [$\text{M}+\text{H}^+$] m/z 210.1051; found m/z 210.1054. [α] $_D^{20} = -16.4$ ($c = 1.03$, acetone).
 14. Diastereomeric ratio was determined by ^1H NMR analysis of the purified product. The methyl resonance of the minor diastereomer is $\delta = 1.04$, and the corresponding resonance of the major diastereomer is $\delta = 0.82$.
 15. Enantiomeric excess was determined to be 98% by HPLC using the following conditions: Chiralcel OD-H column (particle size: 5 μm ; dimensions: ϕ 4.6 mm x 250 mm), 90% hexanes/10% isopropanol, 1.0 mL/min. Retention times are: 12 min (minor), 14 min (major). Detection: 254 nm.

Working with Hazardous Chemicals

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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are 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.

Discussion

The asymmetric Michael reaction of aldehydes and nitroalkenes catalyzed by diphenylprolinol trimethylsilyl ether affords the Michael adduct in a good yield with excellent diastereoselectivity and enantioselectivity.³ The reaction was greatly accelerated in the presence of acid.⁴ This Michael reaction is a powerful method, which has already been successfully employed in the synthesis of biologically active compounds.⁵

References

1. Department of Chemistry, Graduate School of Science, Tohoku University, 6-3 Aramaki-Aza, Aoba, Aoba-ku, Sendai 980-8578, Japan. E-mail: yhayashi@m.tohoku.ac.jp We thank JSPS KAKENHI Grant Number JP16H01128 in Middle Molecular Strategy for support of this work.
2. Boeckman, Jr., R. K.; Tusch, D. J.; Biegasiewicz, K. F. *Org. Synth.* **2015**, 92, 309–319.
3. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, 44, 4212–4215.
4. Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, 94, 719–745.
5. Hayashi, Y. *Chem. Sci.* **2016**, 7, 866–880.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

trans- β -Nitrostyrene; (5153-67-3)

Propanal: propionaldehyde; (123-38-6)

4-Nitrophenol; (100-02-7)

(S)-1,1-Diphenylprolinol trimethylsilyl ether: (S)-(-)- α , α -Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether; (848821-58-9)

Sodium borohydride: Borate(1-), tetrahydro-, sodium (1:1); (16940-66-2)



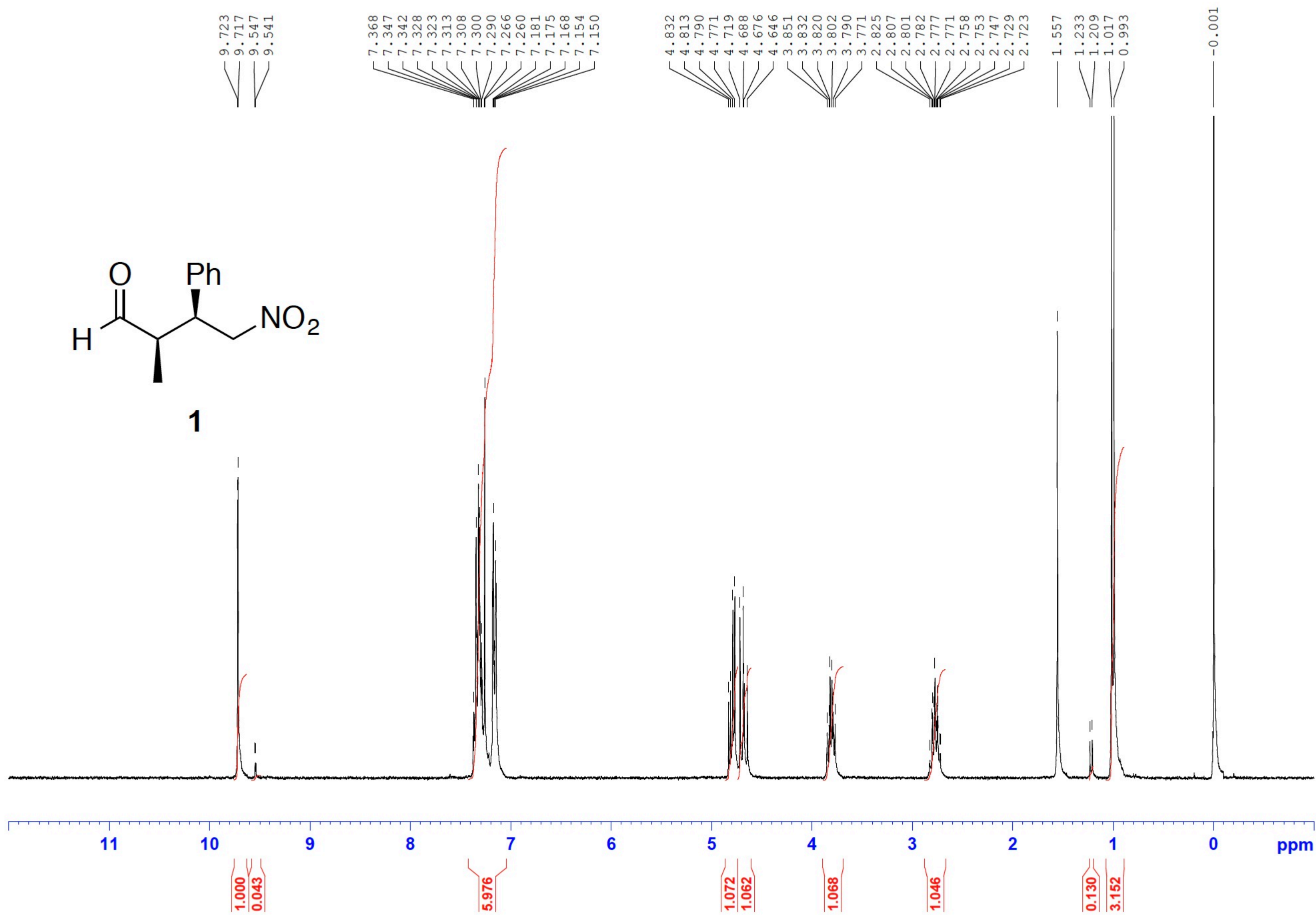
Yujiro Hayashi received a Ph. D. from The University of Tokyo. He was appointed as an assistant professor at The University of Tokyo (1987). He moved to Tokyo University of Science as an associate professor (1998), was promoted to full professor (2006), and moved to Tohoku University (2012). He undertook postdoctoral study at Harvard University (Prof. E. J. Corey). He was awarded with an Incentive Award in Synthetic Organic Chemistry, Japan, SSOCJ Daiichi-Sankyo Award for Medicinal Organic Chemistry and the Chemical Society of Japan Award for Creative Work for 2010. He received a Novartis Chemistry Lectureship Award and Inoue Prize for Science.

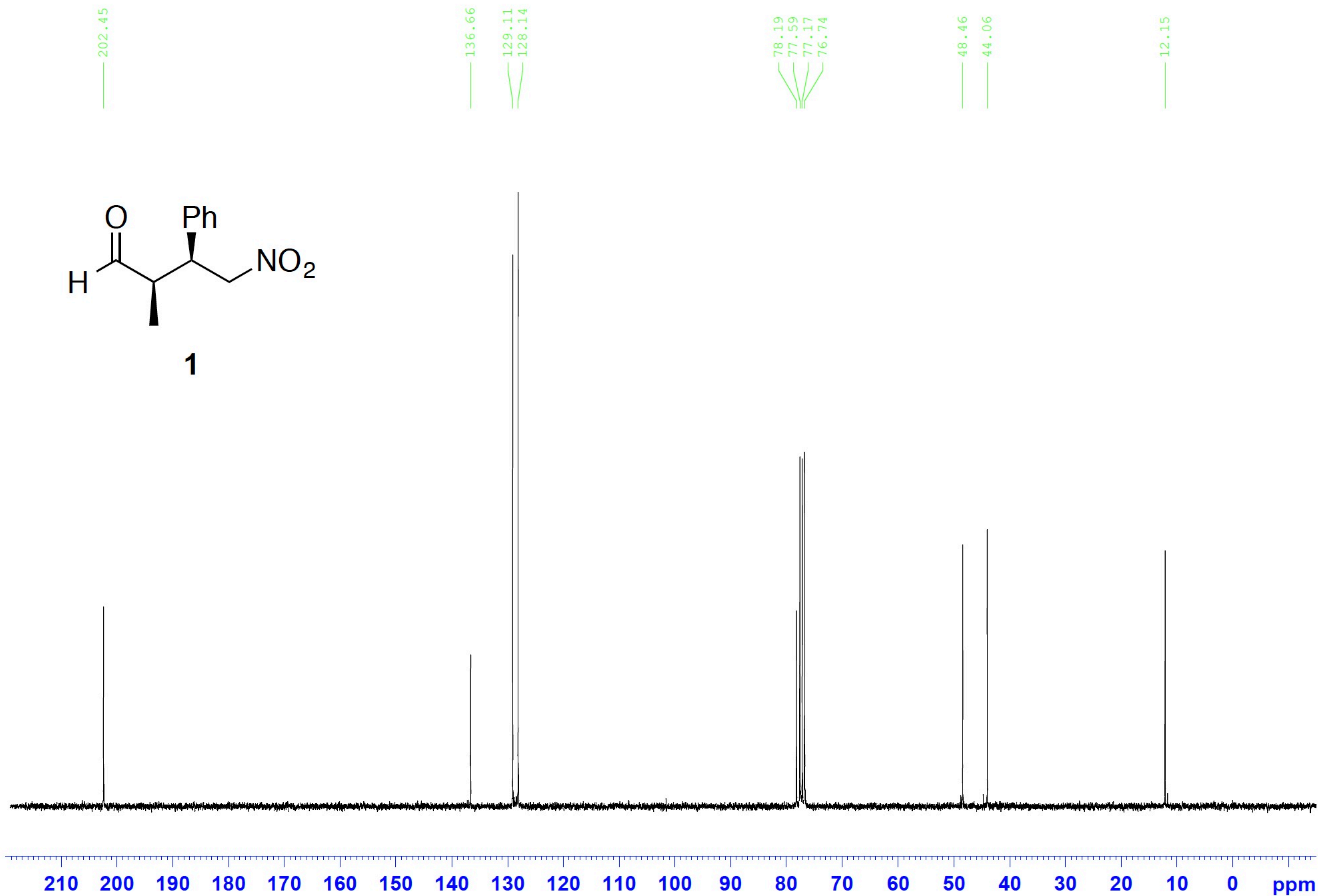
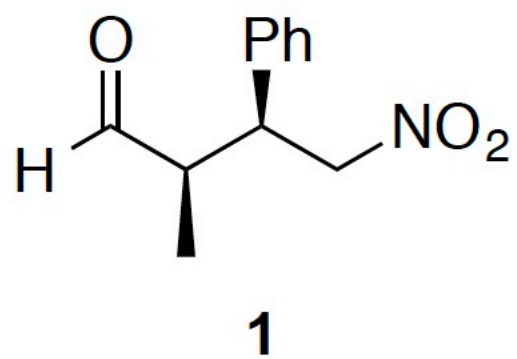


Shin Ogasawara was born in Kyoto, Japan in 1983. He received his M.S. degree in 2009 from Osaka Prefecture University. Since 2009, he has been working as a process chemist at department of manufacturing process development in Otsuka Pharmaceutical Co., Ltd. He completed his Ph.D. under the supervision of Prof. Yujiro Hayashi at Tohoku University in 2016.



Yasuyuki Ueda was born in 1992 in Nagano, Japan. He received his B.Sc. degree in 2015 at Tokai University under the supervision of Prof. Mikio Watanabe. In the same year, he joined the research group of Prof. Keisuke Suzuki at Tokyo Institute of Technology. In 2017, he received his M.Sc., and is currently pursuing his Ph.D.





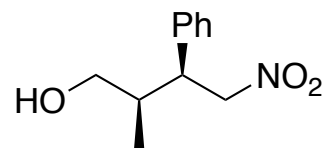


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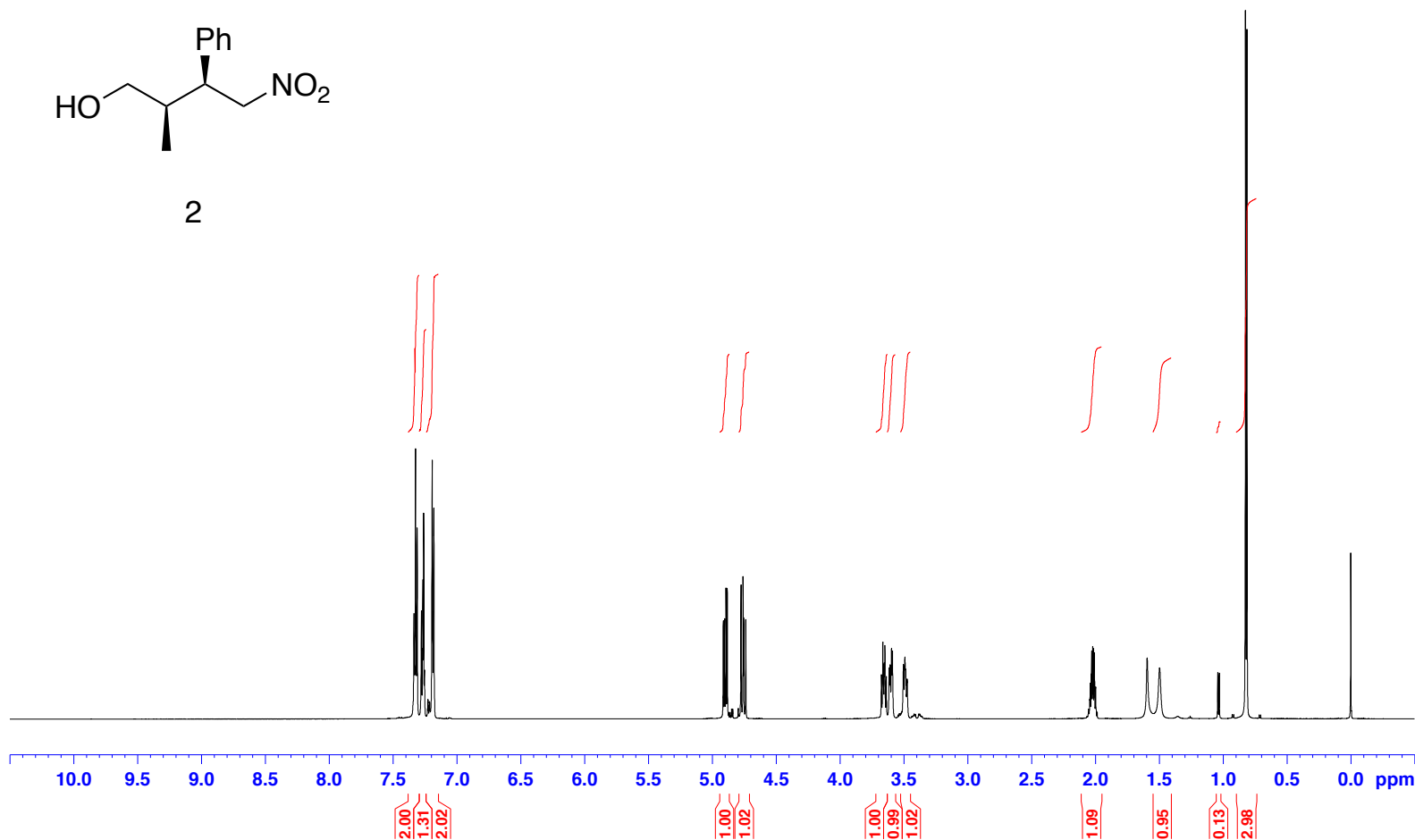
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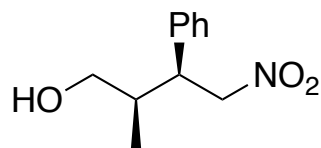


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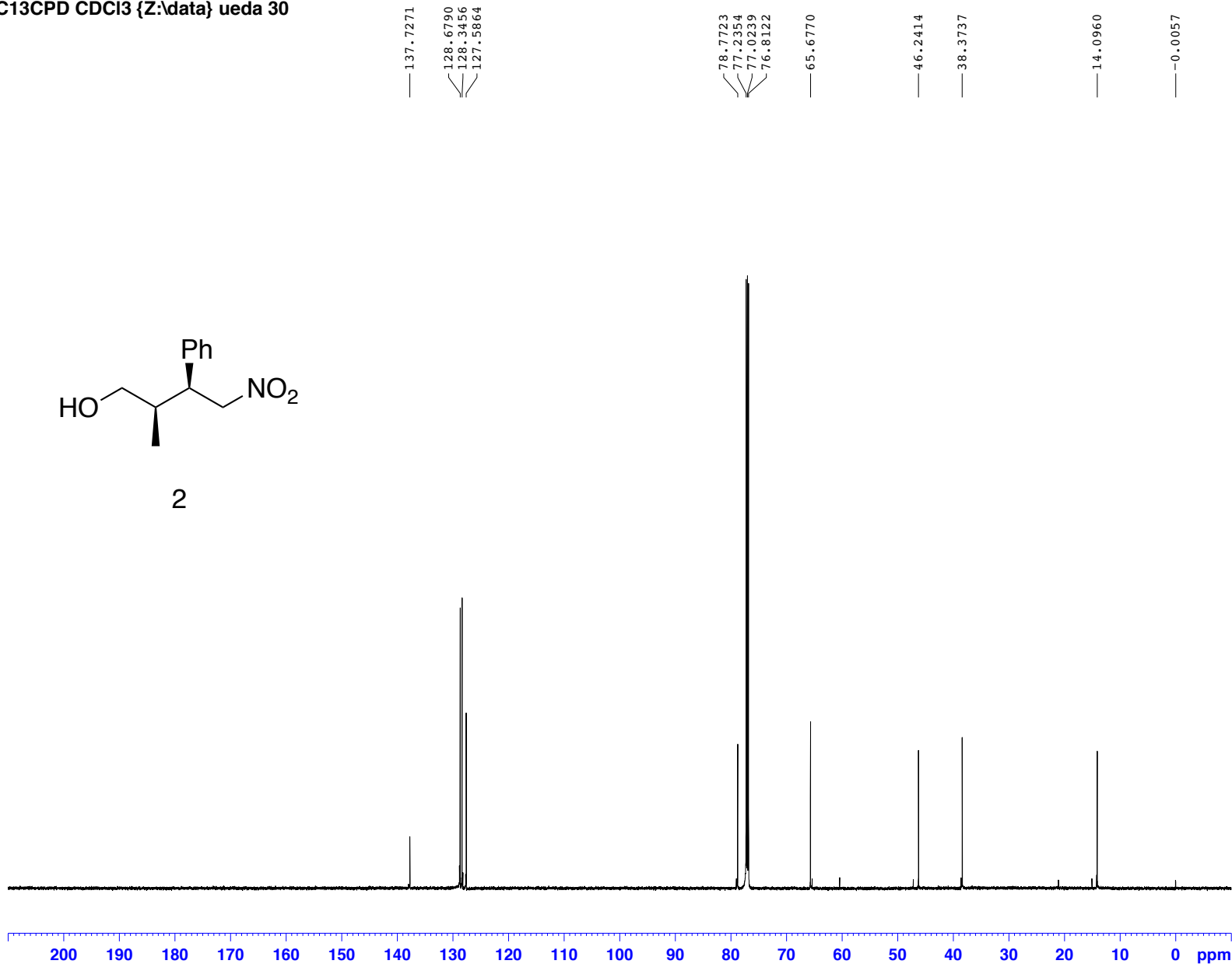


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